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Synthesis, Characterization, Molecular Docking, Thermal Degradation Studies and Biological Screening of N-{[2-(Pyridin-4-ylcarbonyl)hydrazinyl]carbonothioyl}furan-2-carboxamide and its Mn(II), Ni(II), Co(II), Cu(II) and Zn(II) Complexes

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N-{[2-(Pyridin-4-ylcarbonyl)hydrazinyl]carbonothioyl}furan-2-carboxamide and its complexes with Ni(II), Co(II), Cu(II), Zn(II) and Mn(II) ions have been synthesized. The structure of the synthesized compounds was elucidated by elemental analysis, conductivity measurements, UV-visible, FT-IR, ^{1}H NMR, powder XRD and thermal analysis studies. Most of metal complexes have exhibit thermal degradation between 80-750 °C and the powder X-rays diffraction data suggest that all the synthesized metal complexes were in nano crystalline phase. The computational molecular docking has been studied using Hex molecular modeling package version 8.2. The three dimensional structure of *E. coli* MurBenzyme (PDB code 2MBR) was used in microbial activity. The metal complexes showed comparable E total values with the standard drug tetracycline. The antioxidant and antimicrobial activity of prepared compounds indicate agreeable results *versus* bacterial strains three Gram-positive bacteria; *S. aureus*, *S. pyogenes* and *P. acnes* and three Gram-negative bacteria; *E. coli*, *K. terrigena* and *K. pneumonia*. The antifungal activity gave good results against fungal strains *C. albicans, C. neoformans* and *Trichosporon.*

Keywords: Thiosemicarbazone, Transition metal(II) complexes, Antioxidant, Molecular docking.

INTRODUCTION

Thiosemicarbazone derivatives are of wide interest because of their diverse biological activity and clinical applications. For some time, semi-and thiosemicarbazones have been a subject of interest in different profiles, *i.e*., they form complexes with many metal ions which would exhibit a diverse chemical, physical and structural properties [1]. Many of these compounds and their metal complexes have shown a wide spectrum of biological activity [2]. Therefore the design and synthesis of thiosemicarbazone derivatives and their metal complexes are of particular interest to have increased drug activity and to decrease their toxicity of metal ions. Thus these compounds used for a variety applications including clinical biology, analytical and in industries [3,4]. Thiosemicarbazone derivatives complexes have also been used as anticancer, antituberculer, antibacterial, antifungal, hypertensive and hypothermic reagents [5,6]. It has been suggested that thiosemicarbazone drugs may act to inhibit viruses by binding to copper ions, which are the constituents of the virus [7-9]. In addition, thiosemicarbazone derivatives exhibits enhanced thermodynamic and kinetic stabilities due to their modied complexation properties relative to the corresponding simple molecular precursor [10]. These properties of thiosemicarbazones and their metal complexes have become a subject of intense research. Based on the above advantages, we report the synthesis and characterization of thiosemicarbazone and their metal complexes. Also, all the synthesized complexes were investigated for molecular docking and the *in vitro* antioxidant activity.

EXPERIMENTAL

Elemental analyses was obtained from Perkin-Elmer 2400 II CHNS/O rapid analyzer and metal analyses were carried out by standard methods**.** The elemental analysis (C, H, N, S) was performed using Perkin-Elmer 2400 II CHNS/O Elemental analyzer. Melting point of the ligand and their metal complexes was measured by using melting point apparatus model code NAMPA/045 and are uncorrected. UV-visible spectra were measured in DMSO on an ocean optics USB 4000USA spectrophotometer, using 1 cm path length cuvette at room temperature. Infrared spectra were recorded using FT-IR 8400s Shimadzu spectrometer with KBr pellets in the range of 4000-400 cm^{-1}. The molar conductance data was measured using

freshly prepared DMF solutions (10^{-3} M) at 25 °C with a EQUIP-TRONICS model-660A instrument. The ^{1}H NMR spectra have been recorded as 400 MHz Varian-AS NMR spectrometer in DMSO-d_6 using tetramethylsilane (TMS) as the internal standard. The thermal analysis (DTA and TGA) were carried out on a Shimadzu DT-30 and TG-50 thermal analyzers in the range 27-800 °C at the heating rate of 10 °C min^{-1} in nitrogen atmosphere. The magnetic susceptibility measured at the room temperature using the Gouy method with mercuric tetrathiocyanatocobaltate(II) as the standard. Mass spectra was recorded using the instrument Code; SC/AD/10-014.

The chemicals furan-2-carbonyl chloride, NH_4SCN and acetone were purchased from the Sigma Aldrich, Laboratory chemicals, Bangalore, Karnataka, India. Nickel(II) chloride hexahydrate, cobalt(II) chloride hexahydrate, copper(II) chloride dehydrate, anhydrous zinc(II) chloride and manganese(II) chloride were purchased from MERCK, Sudha Traders, Shivamogga, Karnataka, India. The metal chlorides were used in their hydrated form. The ethanol, methanol, acetone and dimethylformamide were used before distilled and dried by following the reported method [11].

Synthesis of (N-{[2-(pyridin-4-ylcarbonyl)hydrazinyl]-carbonothioyl}furan-2-carboxamide) (IF): A solution of furan-2-carbonyl chloride (2.61 g, 0.02 mol) in 20 mL dry acetone was mixed to a solution of ammonium thiocyanate (1.90 g, 0.025 mol) in 10 mL dry acetone in a round bottom flask. The reaction mixture was stirred on magnetic stirrer for 8 h at 35 °C. After the reaction completed, the white solid of NH_4Cl was removed by filtration. The filtrate furan-2-carbonyl isothiocyanate (3.06 g, 0.02 mol) was added to the solution of isonicotinic acid hydrazide (3.42 g, 0.025 mol) in 20 mL dry acetone with constant stirring. The mixture was refluxed at the same temperature for 6 h. The progress of the reaction was monitored by TLC (chloroform:methanol in the ratio 0.9:0.1). After the reaction, the reaction product was poured into ice cold water when the cream coloured precipitate obtained was filtered, washed with ice cold water and recrystallized from the methanol (**Scheme-I**). m.f. $C_{16}H_{13}N_5O_5S$: Yield: 88 %; Colour: Cream; m.p.: 160-162 °C; m.w.: 290.29; Anal. calcd. and found (%): C; 49.65 (49.75), H; 3.47 (3.62), N; 19.30 (19.42), S; 11.05 (11.32): IR (KBr, ν_{max}, cm^{-1}): 3222 (N^4-H), 2953 (N^2-H), 2753 (N^1-H), 2656 (Ar-C-H), 1667 (C^6=O), 1578 (C^1=O), 1009 (N-N), 849 (C=S). ^{1}H NMR (DMSO-d_6, 400 MHz): δ ppm 12.09 (s, 1H, N^4H), 11.58 (s, 1H, N^2H), 11.41 (s,1H, N^1H), 6.77 (t, 1H, 2-furan), 7.86-7.81 (s, 2H, 2-furan), 8.08-8.07 (s, 2H, 4-phyridine), 8.80-8.79 (s, 2H, 4-phyridine). ^{13}C NMR (100 MHz, DMSO-d_6): δ ppm 180.79 (C=S), 163.21 (C^6=O), 157.03 (C^1=O), 150.34, 148.46, 144.48, 139.28 (5C, 4-pyridine), 121.46, 118.84, 112.47 (4C, 2-furan). Mass spectrum (M^+) at *m/z*: 290.9.

Synthesis of the metal complexes: A solution of nickel(II) chloride hexahydrate (0.713 g, 0.003 mol), cobalt(II) chloride hexahydrate (0.713 g, 0.003 mol), copper(II) chloride dehydrate (0.511 g, 0.003 mol), zinc(II) chloride (0.408 g, 0.003 mol) and manganese(II) chloride tetrahydrate (0.593 g, 0.003 mol) in ethanol was added to a solution of the parent ligand (IF) (1.741 g, 0.003 mol) in ethanol to obtain corresponding metal complexes. The resulting reaction mixture was refluxed for 8 h. The solid product was collected by filtration and washed with 4-5 mL of hot methanol and dried in a vacuum over anhydrous calcium chloride in a desiccator. The obtained metal complexes were characterized by melting point, molar conductance and spectral techniques.

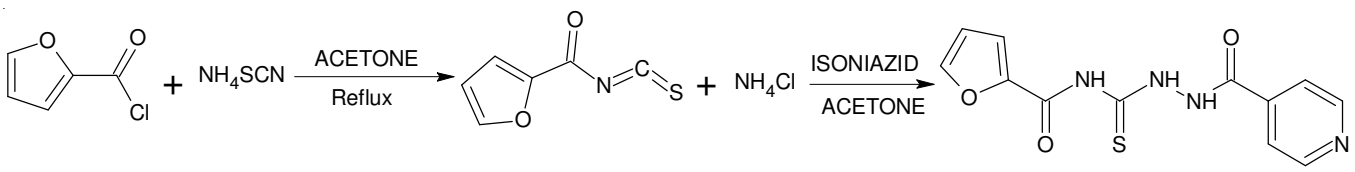
$[NiCl_2(L)_2]H_2O$ complex (IF_1): $C_{24}H_{18}N_8O_6S_2NiCl_2$; Yield: 68 %; Colour: Brown; m.p: 278-270 °C; m.w.: 726.18; Anal. calcd. and found (%): C; 40.70 (41.43), H; 2.56 (2.83), N; 15.82 (15.85), S; 9.06 (9.67), Ni; 8.29.. IR (KBr, ν_{max}, cm^{-1}): 3456 ν(H_2O), 3370 (N^4-H), 3141 (N^1-H), 1595 (C=N), 1527 (C^1=O), 1010 (N-N), 862 (C=S), 464 (M-O), 412 (M-S). Molar conductance: 24.67 ohm^{-1} cm^2 mol^{-1}. Mass spectrum (M^+) at *m/z*: 730.10.

$[CoCl_2(L)_2]$ complex (IF_2): $C_{24}H_{18}N_8O_6S_2CoCl_2$; Yield: 64 %; Colour: Green; m.p: 300-302 °C; m.w.: 708.42; Anal. calcd. and found (%): C; 40.69 (40.99), H; 2.56 (2.65), N; 15.82 (15.90), S; 9.05 (9.11) Co ; 8.32. IR (KBr, ν_{max}, cm^{-1}): 3445 ν(H_2O), 3312 (N^4-H), 3230 (N^1-H), 1614 (C=N), 1579 (C^1=O), 1043 (N-N), 837 (C=S), 458 (M-O), 414 (M-S); Molar conductance: 36.51 ohm^{-1} cm^2 mol^{-1}. Mass spectra (M^+) at *m/z*: 712.39.

$[Cu(L)_2]Cl_2$ complex (IF_3): $C_{24}H_{18}N_8O_6S_2CuCl_2$; Yield: 68 %; Colour: Brown; m.p: 270-272 °C; m.w.: 713.03; Anal. calcd. and found (%): C; 40.43 (40.52), H; 2.54 (2.71), N; 15.72 % (15.69), S; 8.99 (found 9.10), Cu; 8.91. IR (KBr, ν_{max}, cm^{-1}): 3475 ν(H_2O), 3366 (N^4-H), 3178 (N^1-H), 1595 (C=N), 1493 (C^1=O), 1011 (N-N), 857 (C=S), 465 (M-O), 413 (M-S). Molar conductance: 145.61 ohm^{-1} cm^2 mol^{-1}.

$[ZnCl(L)_2]Cl$ complex (IF_4): $C_{24}H_{18}N_8O_6S_2ZnCl_2$; Yield: 72 %; Colour: Orange; m.p: 309-310 °C; m.w.: 714.89; Anal. calcd. and found (%): C; 40.32 (40.83), H; 2.54 (2.62), N; 15.67 (15.70), S; 8.97 (9.22), Zn; 9.15. IR (KBr, ν_{max}, cm^{-1}): 3447 ν(H_2O), 3329 (N^4-H), 3229 (N^1-H), 1612 (C=N), 1549 (C^1=O), 1008 (N-N), 878 (C=S), 467 (M-O), 415 (M-S); ^{1}H NMR (DMSO-d_6, 400 MHz): δ ppm 12.10 (s, 2H, N^4H), 11.58-11.42 (s, 2H, N^1H), 6.80-6.76 (t, 2H, 2-furan), 7.86-7.77 (s, 4H, 2-furan), 8.08-7.78 (s, 4H, 4-pyridine), 8.80-8.75 (s, 4H, 4-phyridine). Molar conductance: 90.61 ohm^{-1} cm^2 mol^{-1}.

$[MnCl_2(L)_2]$ complex (IF_5): $C_{24}H_{18}N_8O_6S_2MnCl_2$. Yield: 74 %; Colour: Light yellow; m.p: 295-297 °C; m.w.: 704.42; Anal. calcd. and Found (%): C; 40.92 (40.99), H; 2.58 (2.79), N; 15.91 (15.96), S; 9.10 (9.43), Mn; 7.80. IR (KBr, ν_{max}, cm^{-1}): 3461 ν(H_2O), 3312 (N^4-H), 3104 (N^1-H) 1616 (C=N), 1518



Scheme-I: Synthesis of IF ligand

(C^1=O), 1062 (N-N), 832 (C=S), 463 (M-O), 414 (M-S). Molar conductance: 42.02 ohm^{-1} cm^2 mol^{-1}.

RESULTS AND DISCUSSION

The metal complexes are stable and non-hygroscopic in nature. The elemental analyses indicating the IF_1 to IF_5 metal complexes have been 1:2 stoichiometry. The molar conductance values of IF_1, IF_2 and IF_5 complexes were too low to account for any dissociation of the complexes in DMF, indicating the non-electrolytic bivalent nature, while in the case of IF_3 and IF_4 complexes were higher molar conductance values suggest that the complexes are uni-bivalent in nature. It is observed higher molar conductance values for some complexes due to partial dissociation of complexes in their solution

NMR studies: In the case of ^{1}H NMR spectrum of the ligand (IF), the signals at 12.09, 11.58 and 11.41 ppm (s, 3H, NH) is assigned to NH protons of thioamide and another signal observed at 7.86, 7.81 (s, 2H, Ar-H) and 6.77 ppm (t, 1H, Ar-H) are due to 2-furan ring protons. In addition, the singlet signals around 8.07-8.80 ppm (s, 4H, Ar-H) are ascribed to 4-pyridine ring protons.

^{13}C NMR spectrum of the ligand (IF) exhibited signals at 150.34, 163.21 and 180.79 ppm assigned to two (C=O) and one (C=S) groups, respectively. 2-Furan and 4-pyridine moieties exhibited peaks in the region 112.67-121.46 and 139.28-150.28 ppm, respectively.

FT-IR spectral studies: The main IR frequencies exhibited by ligand IF and its metal complexes IF_1-IF_5 were given as earlier assignments. The IR spectrum of IF showed a strong intensity band at 3222, 2953 and 2753 cm^{-1} assignable to ν(NH) of thioamide group, respectively. In the case of IR spectra of metal complexes, the band due to thioamide one NH group has disappeared, indicating enolization of the C=S of thioamide during complexation and subsequent coordination of the carbonyl oxygen *via* deprotonation [12]. The band appeared at 1667 cm^{-1} in the ligand due to ν(C=O) has been disappeared in all the metal complexes, confirm enolization of thioamide function during complexation which is evident by the appearance of a new band in the region 1616-1592 cm^{-1} due to the formation of >C=N–N< azine moiety [13-15]. The new bands appeared in this region indicating the involvement of thioamide sulphur in the complexation with metal ions [16]. The appearance of new bands in the region 3475-3445 cm^{-1} for metal complexes, indicate the presence of coordinated or lattice water in these complexes [17]. Appearance of a new set of bands in all the complexes, due to ν(M–O) and ν(M–S) vibrations and is the direct evidence for complexation. The bands of complexes IF_1 to IF_5 observed in the region 465 to 458 and 415 to 412 cm^{-1} are assigned to ν(M–O) and ν(M–N), respectively [18].

Magnetic measurements: The magnetic parameters were recorded by Gouy method using a $Hg[Co(CNS)_4]$ as standard. The IF_3 shows magnetic moment of 1.92 BM, which indicates the presence of in distorted tetrahedral geometry. The magnetic moments of IF_1 and IF_2 were 3.31 and 4.81 BM, respectively. These results suggested that octahedral geometry [19].

Electronic absorption spectra: The solution of IF_2 electronic spectrum exhibited absorption bands 13,513, 15,151 and 17,241 cm^{-1} due to the $^4T_{1g}(F) \rightarrow {}^4T_{2g}(F)$ (ν_1), $^4T_{1g}(F) \rightarrow {}^4A_{2g}(F)$ (ν_2) and $^4T_{1g}(F) \rightarrow {}^4T_{1g}(P)$ (ν_3) transitions, respectively [20,21]. The green coloured of IF_3 are three bands corresponding to octahedral geometry. The IF_1 displayed an electronic spectrum with transitions at 13,333 and 15,151 cm^{-1}, respectively. These bands may be assigned to the transitions $^3A_{2g}(F) \rightarrow {}^3T_{2g}(F)$ (ν_1) and $^3A_{2g}(F) \rightarrow {}^3T_{1g}(F)$ (ν_2), respectively [22,23]. The brown colour of IF_1 exhibit two bands are due to octahedral geometry [23]. The IF_3 showed band at 14,925 cm^{-1}, which may be assigned to the transitions $^2B_{1g} \rightarrow {}^2A_{1g}(d^2x - y_2 \rightarrow d^2z)$ (ν_1) [24]. The broad band of dark brown coloured IF_3 indicative of distorted tetrahedral geometry. The comparison study of UV-spectra of IF and IF_1-IF_3 is presented in Fig. 1.

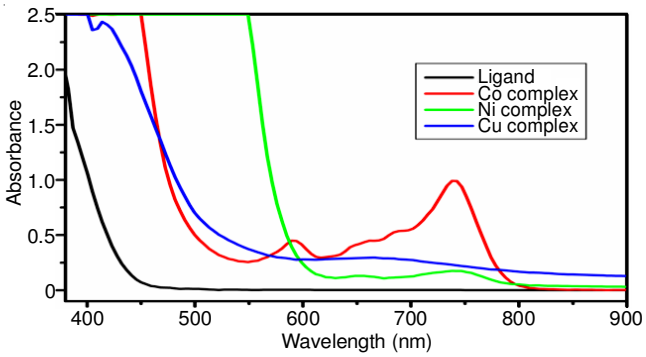


Fig. 1. Electronic spectra of the ligand and its metal complexes

Thermal analyses studies of metal complexes: Thermal stability and thermal behaviour of all the metal complexes were studied by thermogravimetric analyses (TGA) in the temperature range 25-900 °C. The thermogram of the IF_1 shows a mass loss of 3.01 % (calcd. 2.47 %) in the temperature range 98-105 °C indicates the loss of one Lattice water molecule. The second step of the decomposition from 140-240 °C, with a mass loss of 9.51 % (calcd. 9.77 %) corresponds to loss of the coordinated two chlorine atoms, the third step involves in the dissociation at the temperature of 260-400 °C with weight loss of 35.66 % (calcd. 28.99 %) corresponds to the decomposition of furan moiety [25,26]. The fourth step at 410-690 °C with weight loss of found 42.79 % (calcd. 49.07 %) is referring to the removal of pyridine moiety and at the end, left behind stable residue NiO 9.09 % (calcd. 10.28 %) at 690-740 °C. Similarly, the TG curve of the IF_2 to IF_5 shows three-steps of decomposition. The first step at 190-240, 130-210, 180-270 and 170-260 °C with weight loss of 10.71, 9.45, 9.99 and 10.18 %, respectively (calcd. 10.02, 9.95, 9.95 and 10.07 %) is attributed to the loss of two chlorine atoms, the second step with weight loss of 33.95, 35.79, 34.61 and 35.98 % (calcd. 36.33, 36.43, 36.24 and 36.12 %) at 260-300, 230-300, 280-390 and 240-380 °C was corresponding to the removal of furan group from the coordinated ligand. The third step at 320-700, 340-680, 400-710 and 390 °C with weight loss of 42.75, 42.87, 42.41 and 42.18 %, respectively (calcd. 42.90, 42.55, 42.41 and 43.02 %) is referring to the removal of pyridine moiety. The mass of the final residue 13.06, 11.88, 12.47 and 10.94 % (calcd. 10.59, 11.15, 11.38 and 10.16 %) at 710-740, 700-750, 720-750 and 690-750 °C corresponded to stable CoO, CuO, ZnO and MnO, respectively [27]. The results well agreed with the decomposition of the metal complexes. The nature of decomposition curves of complexes IF_1, IF_3 and IF_4 are represented in Fig. 2.

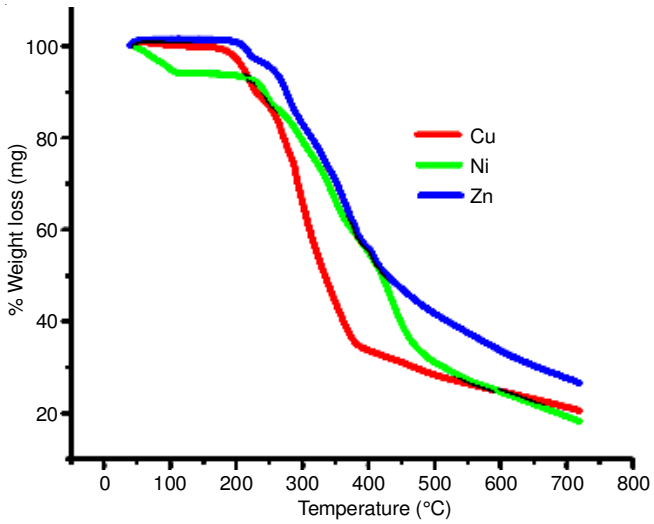


Fig. 2. TGA thermogram curves of IF_1, IF_3 and IF_4

DPPH free radical scavenging activity: Antioxidant activity of different concentration of complexes in DMF and ascorbic acid in terms of free radical scavenging ability was evaluated using DPPH free radical assay [28,29]. The compounds exhibited marked antioxidant activity by scavenging DPPH* (free radical) and converting into DPPH and the activity was found to be dose dependent. The complexes IF_1-IF_5 found to be more potent than the IF. The results were described in Table-1.

Antibacterial activity: A cup plate method using Hi-Media agar medium was employed to study the antibacterial activity of the synthesized compounds against three Gram-positive bacteria, *Staphylococcus aureus*, *Streptococcus pyogenes* and *Propionibacterium acnes* and three Gram-negative bacteria, *Escherichia coli*, *Klebsiella terrigena* and *Klebsiella pneumoniae*. Preparation of nutrient broth, sub-culture, base layer medium, agar medium and peptone water was done as per the standard procedure [30]. The results of the study are summarized in Table-2. The tested compound showed slight to moderate antibacterial activity compared to the standard drugs against all microorganisms.

TABLE-1
DPPH FREE RADICAL SCAVENGING ACTIVITY OF IF AND ITS METAL COMPLEXES

Compounds	DPPH radical scavenging activity (%) of different concentrations (µg/mL) of compounds		
	50	100	200
IF	69.22	73.05	78.71
IF_1	93.91	96.11	89.22
IF_2	84.96	87.14	90.14
IF_3	92.06	93.56	93.54
IF_4	67.07	70.95	69.44
IF_5	67.07	66.89	68.64
Standard	93.13	95.18	97.11

Antifungal activity: The antifungal activity of the synthesized compounds was tested against three different fungi, *i.e. C. albicans, C. neoformans* and *Trichosporon* by a filter paper disc technique [31,32]. The concentration of test compounds was 100 µg/mL. After 48 h treatment, zone of inhibition produced by each compound was measured in mm. Fluconozole was used as the standard antifungal agent and DMF as a control. Moreover, the microbial data revealed that the complexes were superior to the free ligand in the inhibition of the tested bacteria and fungi. It is noticed that the concentration play a vital role in increasing the degree of inhibition, *i.e.*, the activity increased with increasing concentration of the complexes. The results are given in Table-2.

TABLE-2
ANTIBACTERIAL AND ANTIFUNGAL ACTIVITIES OF IF AND ITS METAL COMPLEXES

Compounds	Conc. (µg/mL)	Zone of inhibition (mm)								
		Antibacterial activity						Antifungal activity		
		Gram-positive bacteria			Gram-negative bacteria					
		S. aureus	*S. pyogenes*	*P. acnes*	*E. coli*	*K. terri*	*K. pneumoniae*	*C. albican*	*C. neoformans*	*Trichosporon*
IF	50	21	13	20	11	12	15	11	10	11
	100	19	15	21	12	12	13	13	12	13
	200	18	17	14	17	13	17	14	15	14
IF_3	50	11	11	10	12	12	12	11	11	12
	100	14	12	11	18	13	14	14	14	14
	200	14	13	15	15	13	16	17	15	15
IF_2	50	12	11	11	11	14	12	12	11	11
	100	16	12	12	15	10	11	16	14	12
	200	11	13	10	14	12	15	18	17	14
IF_1	50	13	12	10	18	11	10	13	12	10
	100	12	13	12	13	11	14	15	13	12
	200	12	15	12	18	13	14	15	15	16
IF_4	50	15	16	10	11	11	13	14	13	10
	100	15	15	10	12	12	16	15	16	11
	200	17	14	13	13	13	18	17	18	15
IF_5	50	12	11	13	11	13	16	12	11	13
	100	18	14	10	12	14	10	16	14	14
	200	13	12	10	13	11	13	17	16	16
Control (DMF)		00	00	00	00	00	00	00	00	00
Tetracycline	10	23	21	19	24	23	22	–	–	–
Fluconozole	10	–	–	–	–	–	–	25	23	24

Molecular docking studies: Molecular docking work was performed with the Hex molecular modeling package version 8.2. The three dimensional crystal structure of *E. coli* MurBenzyme (PDB code 2MBR) was downloaded from protein data bank. The synthesized compounds were converted to 2D and 3D structures and were used for converting to protein data base (pdb) formats and visual conformation by using Discovery Studio 3.1 Client (Accelrys, USA). The *E. coli* MurB enzyme (PDB code: 2MBR) which is known to be responsible for causing antimicrobial infections. In the present work, an attempt was made to evaluate their antibacterial properties, so we target *E. coli* MurBenzyme receptor throughout docking study. Tetracycline drug was used as the standard. The obtained docking scores are tabulated in Table-3. The metal complexes IF_1-IF_5 exhibited almost similar binding interaction energy with the lowest docking score compared to the standard drug Tetracycline. Among all the synthesized compounds docked, complexes IF_1-IF_3 showed more negative E-total values -329.45, -331.67 and -343.62, kcal/mol compared with the standard drug Tetracycline (E-total value -266.34 kcal/mo1) and had a significantly better inhibiting ability towards the *E. coli* MurB enzyme receptor, which binds to the active site of receptors through hydrogen bonds and other interactions with a variety of amino acids of the active site, thereby potentially inhibiting the bacterial infection-causing property of the receptor. While, the compounds IF_4, IF_5 and ligand showed more negative E total values-319, -312 and -209.40 kcal/mol compared with the standard drug Tetracycline (E-total-266.34 kcal/mol). Furthermore, the docking studies of the ligand molecules with *E. coli* MurBenzyme revealed that all the compounds exhibited bonding with various amino acids in the active pockets. The estimated binding affinity of compounds IF_1-IF_5 with the receptor a hydrogen network with a plethora of amino acids includes GLN120, ARG159, ASN121, ARG159, TYR158, VAL326, ILE122, PRO111, SER50, SER116, GLU325, VAL326, LEU109, ILE110, PRO111, PRO118, LEU129, *etc*., being present in the active sites and gives a clue about the importance of hydrogen bond formation for effective enzyme binding, thereby potentially inhibiting the bacterial infection-causing property of the receptor. The obtained results may provide a sufficient explanation and good compromise between docking scores and *in vitro* results of antibacterial activity. All compounds in the series have got three dimensional (3D) and two dimensional (2D) interactions with active site of receptor 2MBR as shown in Figs. 3-5.

Powder XRD studies: Powder X-ray diffraction of the complexes was recorded over the $2\theta = 0\text{-}80^\circ$ ranges, the diffractograph of the complexes are displayed in Fig. 6. The major

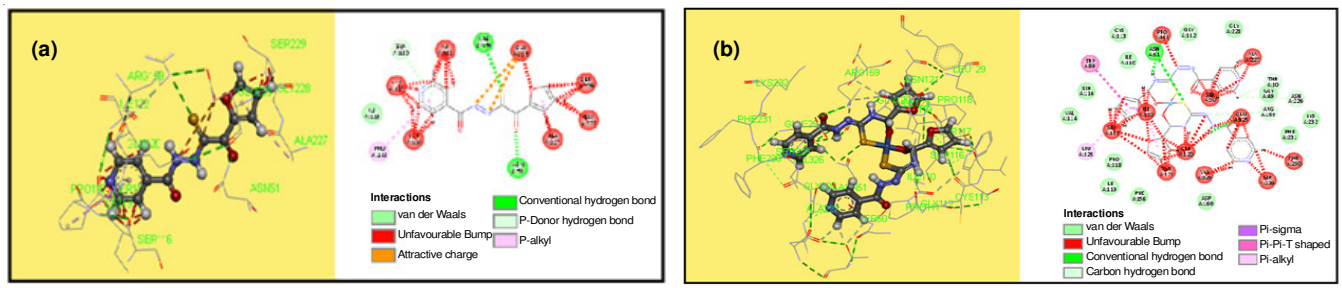


Fig. 3. Three dimensional (3D) and two dimensional (2D) interaction of compounds (a) IF and (b) IF_1 with active site of receptor 2MBR

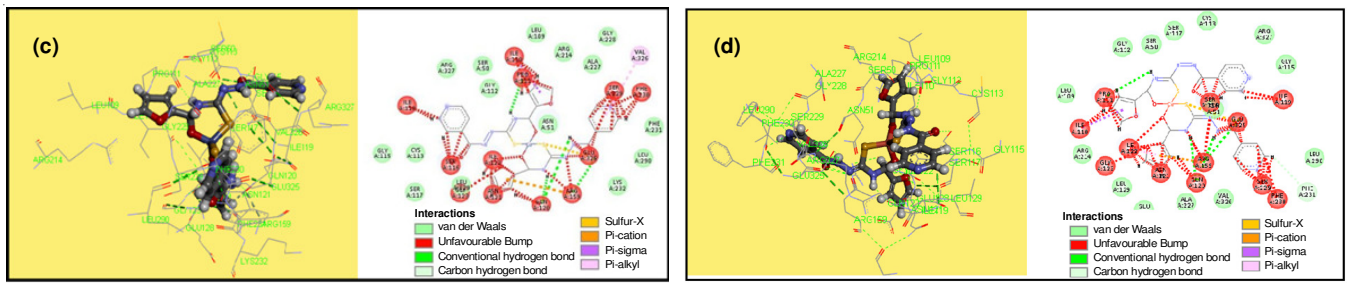


Fig. 4. Three dimensional (3D) and two dimensional (2D) interaction of compounds (c) IF and (d) IF_1 with active site of receptor 2MBR

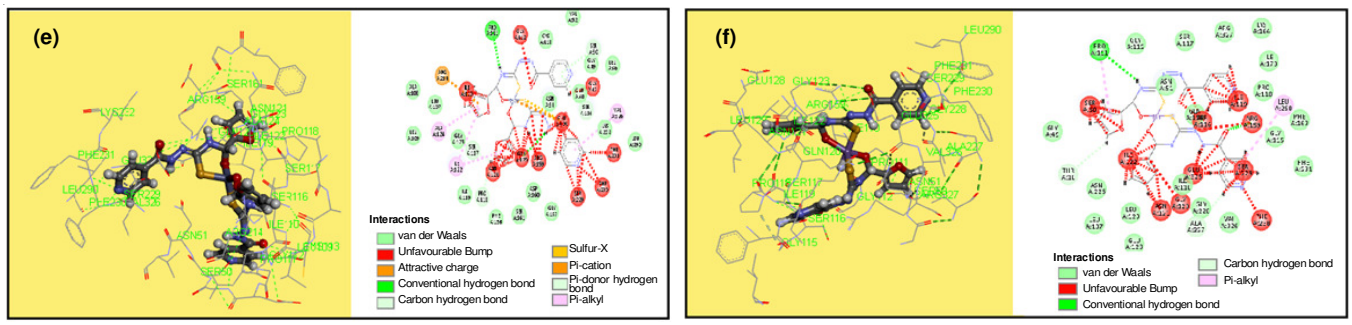


Fig. 5. Three dimensional (3D) and two dimensional (2D) interaction of compounds (e) IF and (f) IF_1 with active site of receptor 2MBR

TABLE-3
MOLECULAR DOCKING STUDIES OF IF AND IF_1-IF_5

Compounds	Receptor PDB code	ΔG (Kcal/mol) with MurBenzyme
IF	2MBR	-209.40
IF_1	2MBR	-329.45
IF_2	2MBR	-331.67
IF_3	2MBR	-343.17
IF_4	2MBR	-312.36
IF_5	2MBR	-319.44
Tetracycline	2MBR	-266.34

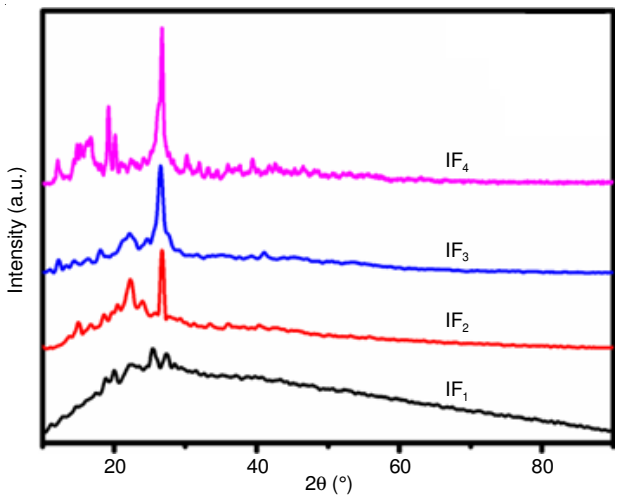


Fig. 6. Powder X-ray diffraction spectra of IF_1-IF_4 metal complexes

peaks of relative intensity greater than 10 % were indexed using a computer program. The diffraction data like angle (2θ), inter planar spacing (d) and the relative intensity (%) have been summarized in Table-4. From the data, all the metal complexes (IF_1-IF_4) show sharp crystalline peaks, indicating their crystalline nature. The powder-XRD patterns of all the metal complexes are very similar and suggest that the complexes have similar structure. The average crystallite size of the complexes were calculated using the Sherrer formula [33]. The complexes IF_1-IF_4 have a crystallite size of 19.998, 11.242, 31.980 and 20.299 nm, respectively, suggesting that the complexes are in a nano crystalline phase.

TABLE-4
POWDER XRD SPECTRAL DATA OF IF_1-IF_4 COMPLEXES

Complexes	2θ	d (Å)	ESD	Full width at half maximum
IF_1	25.321	3.514	19.998	0.326
IF_2	26.661	3.340	11.242	0.272
IF_3	26.528	3.357	31.980	0.811
IF_4	26.695	3.336	20.299	0.474

Conclusion

A new compound N-{[2-(pyridin-4-ylcarbonyl)hydrazinyl]-carbonothioyl}furan-2-carboxamide and series of its metal complexes from IF_1 to IF_5 have been synthesized. These compounds have been characterized by various physico-chemical techniques. The TGA/DTA data indicate stepwise degradation. The obtained results are in good agreement with the proposed structure. The ligand evidenced by IR coordinated through two donor sulphur and oxygen atoms. The electronic transitions found to agree with the expected transitions for octahedral geometry for most of the complexes excepting copper complex which tentatively proposed to have distorted tetrahedral geometry (Fig. 7). The newly synthesized IF_1-IF_5 exhibited moderate antibacterial activity against *S. aureus*, *S. pyogenes*, *P. acnes, E. coli*, *K. terrigena* and *K. pneumoniae* and significant antifungal activity against *C. albicans, C. neoformans* and *Trichosporon.* The complexes also exhibited good results towards molecular docking.

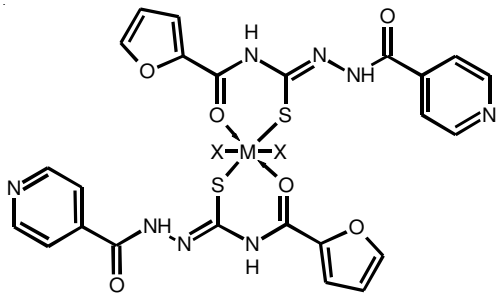


Fig. 7. Proposed structure of metal complex (M = Ni(II), Co(II), Cu(II), Zn(II) and Mn(II), x = Cl, H_2O.

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