

**SYNTHESIS AND ANTIFUNGAL ACTIVITY OF 6-BROMO-2[(4-(2,3-DICHLOROPHENYL)) PIPERAZINE-1-YL)METHYL]-3-[8-HYDROXY QUINOLINE -5-YL]-3-QUINAZOLIN -4-ONE LIGAND AND ITS TRANSITION METAL CHELATES**

R.T. Vashi\*, C. D. Shelat & Himanshu Patel

\*Department of Chemistry, Navyug Science College, Rander Road, Surat-395009, India

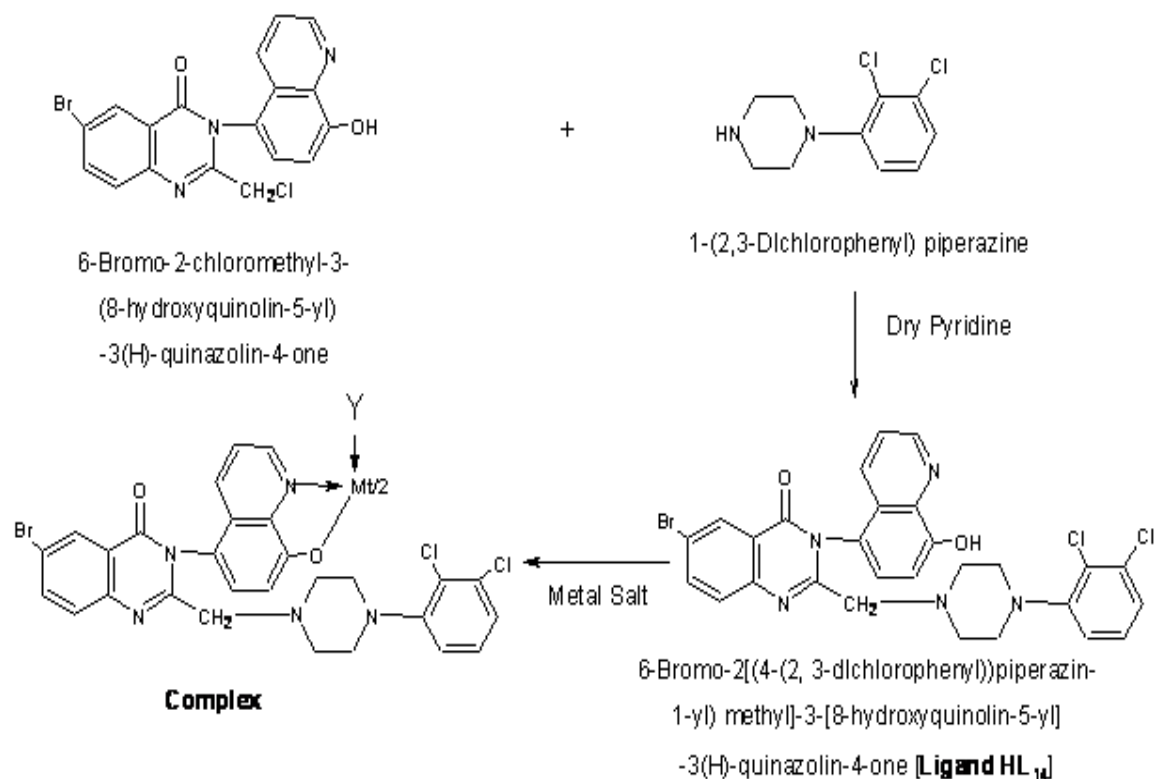
**ABSTRACT:** The present investigation involved the synthesis of novel ligand HL<sub>14</sub> and its chelate complexes with Cu(II), Ni(II), Co(II), Mn (II) and Zn(II). The characterization studies of chelates were conducted using various physicochemical methods such as elemental analysis, conductometric studies, magnetic susceptibility, FT-IR, NMR and electronic spectral data. The stoichiometry of the complex has been carried out and found to be 1: 2 (Metal: ligand). An octahedral geometry around Co (II), Ni (II) and Mn (II), distorted octahedral geometry around Cu (II) and tetra hedral geometry around Zn(II) have been proposed. The antifungal activity of ligand and its metal chelates was performed against various fungi.

**Key Words:** 8-Hydroxy quinoline ligand, Complexes, Electronic, NMR spectral studies, Antifungal activity

## INTRODUCTION

The unique heterocyclic nitrogen compounds especially quinazolinone derivatives are employed in many biological processes and as synthetic drugs (Patel N.B. et al., 2006).The Quinazolin-4-one derivative is exploited in biological activities such as antifungal (Vashi, R.T., et al., 2010, Vashi, R.T. et al., 2009, Vashi, R.T. et al., C.D. 2010). A 8-hydroxyquinoline and quinazolin-4-one molecules into one molecule have not received any attention in spite of well-defined applications of both the molecules. Hence it was thought to explore the study of qunazolin-4- one 8-hydroxyquinoline merged molecules as ligand HL<sub>14</sub> with their complexes with Cu (II), Ni (II), Co (II), Mn (II) and Zn (II) metal ion. Antifungal activities of the ligand and its metal chelates have also been studied.

General structure of formation of chelate was shown in scheme-I.



Mt: Cu<sup>2+</sup>, Mn<sup>2+</sup>, Co<sup>2+</sup>, Ni<sup>2+</sup>, Zn<sup>2+</sup> Y = H<sub>2</sub>O

### Scheme I

## MATERIALS AND METHODS

All the chemicals used were of pure grade (Merck and B.D.H). Double distilled water was used throughout the experiment. The melting point of ligand was determined by open capillary method and was uncorrected.

**Synthesis of BPMHQ ligand (HL<sub>14</sub>):** 6-bromo-2-chloromethyl-3-(8-hydroxy quinolin-5-yl)-3(H)-quinazolin-4-one from 5-bromoanthranilic acid was prepared according to previous literature (Vashi, R.T. et al., 2010). A mixture of 6-bromo-2-chloromethyl-3-(8-hydroxy quinolin-5-yl)-3(H)-quinazolin-4-one (0.01 mole) and 1-Cyclohexyl piperazine (20 ml.) in dry pyridine (20 ml.) was refluxed for 12 hrs. Pyridine was distilled off as much as possible and the residue was poured into little crushed ice with stirring. The product, HL<sub>14</sub> i.e. 6-Bromo-2-((4-(2,3-dichlorophenyl))piperazin-1-yl)methyl-3-[8-hydroxyquinolin-5-yl]-3(H)-quinazolin-4-one ligand was separated out, filtered and washed with water and finally with ethanol. The air dried product was quantitative. Melting point for HL<sub>14</sub> > 230 °C.

**Synthesis of Chelates:** A dried ligand sample HL<sub>14</sub> (0.01 M) was stirred in 85 % (v/v) formic acid and then it was diluted by water until complete dissolution. The resultant solution was designated as reagent solution. This solution was used for preparation of chelates with particular ligand with transition metal ions. The formic acid solution of ligand was added drop-wise to a solution of Cu(NO<sub>3</sub>)<sub>2</sub>.6H<sub>2</sub>O, Ni(NO<sub>3</sub>)<sub>2</sub>.6H<sub>2</sub>O, Co(NO<sub>3</sub>)<sub>2</sub>.6H<sub>2</sub>O, MnCl<sub>2</sub>.6H<sub>2</sub>O, Zn(NO<sub>3</sub>)<sub>2</sub>.6H<sub>2</sub>O (0.005 mole) in 100 ml of water with constant stirring. The resultant pH 4.5 [for Cu(II)], pH 6.0 [for Ni(II) and Co(II)] and pH 5.6 [for Mn(II) and Zn(II)] were maintained by addition of sodium acetate. A dark colored solid precipitated out. It was allowed to settle and digested on water bath at 70 °C for about 2 h. The solid mass was filtered, washed with 1:1 mixture of water-ethanol and finally with acetone then dried. The percentage yield of chelates was in the range of 69-82 %. All the chelates were powdered well and dried at 70 °C over a period of 24 h.

The C, H and N contents of metal chelates were determined on elemental analyzer Thermofinigan 1101 Flash EA. The metal contents were estimated using standard methods (Vogel A.I., 1978). The molar conductance of the complexes in DMF (10<sup>-3</sup> M) solutions were measured at room temperature using Systronics model 305 direct reading conductivity bridge. <sup>1</sup>H NMR spectra of ligand was recorded on Bruner NMR spectrophotometer. PMR chemical shifts were recorded in δ – value using TMS as an internal standard in CDCl<sub>3</sub> /D<sub>6</sub>- DMSO. The IR spectra (KBr) were recorded in the range 4000-600 cm<sup>-1</sup> on a Nicolet -760 Spectrophotometer. Electronic spectra of the metal chelates were recorded on a Beckman – DK-2A spectrophotometer using MgO as reference.

Magnetic susceptibility ‘ $\chi_m$ ’ was measured by Gouy’s method (Lewis, J. and Wilkins, R.G. 1964) at room temperature (300 K) using Hg [Co(CNS)<sub>4</sub>] as calibrant (Figgis, B.N. et al., 1960), and the effective magnetic moment from relation,  $\mu_{\text{eff}} = 2.84 \sqrt{\chi_m \times T}$ , where T is the absolute temperature (Williams J.O., 1978). Diamagnetic corrections were made by using Pascal’s constants.

The ligand and its metal chelates were screen at 1000 ppm concentration in vitro for their antifungal activity against five fungi viz. *Botrydepladia thiobromine*, *Nigrospora sp.*, *Rhizopus nigricans*, *Aspergillus fumigatus* and *Candida albicans*. The antifungal activity of the compounds was measured by plate method (Barry, A.L. 1996). Five days old cultures were suspended in potato dextrose agar (PDA) medium and autoclaved at 1200 °C for 15 minutes at 15 atmospheric pressure. The percentage inhibition of fungi was calculated after 5 days using the formula given below:

$$\text{Percentage of inhibition} = 100 (X-Y) / X$$

Where X= area of colony in control plate (without sample) and Y = area of colony in test plate.

## RESULTS AND DISCUSSION

The complexes are microcrystalline colored powders having melting points higher than the ligand. They are stable in air at room temperature. All compounds gave satisfactory elemental analysis, suggesting 1:2 (metal: ligand) stoichiometry. Elemental and molar conductance data were shown in Table-1. The result indicates that they are less molar in DMF. The molar conductance values found to be 29.68, 10.02, 7.98, 9.68 and 10.11 ohm<sup>-1</sup>cm<sup>2</sup>mol<sup>-1</sup> for Co(II), Ni(II), Zn(II), Cu(II) and Mn(II) respectively. So, the electrical conductivity of these chelates was found in the decreasing order: Co > Mn > Ni > Zn > Cu. The very low values of chelates indicates that they are non-electrolytic (Geary W.J., 1971) and monomeric in nature. The low conductance values may be attributed to the large cations (Upadhyay R.K., 1977).

**Infrared spectra:** The basic features of FT-IR spectra of ligand HL<sub>14</sub> was depicted in table 2, which indicates the attachment of 1-Pyridininenyl piperazine into 6-bromo-2-chloromethyl-3-(8-hydroxy quinolin-5-yl)-3(H)-quinazolin-4-one.

**Table 1 Analytical and physical data of ligand and its metal chelates**

Ligand / Mol. Formula	M. W. (g/mole)	Yield (%)	Elemental Analysis (%) Found (Calcd.)					Observed $\mu_{\text{eff}}$ (B.M) (Expected)	$\Lambda_M$ ( $\text{Ohm}^{-1} \text{cm}^2$ $\text{mol}^{-1}$ )
			C	H	N	Br	M		
HL <sub>14</sub> C <sub>28</sub> H <sub>22</sub> N <sub>5</sub> O <sub>2</sub> BrCl <sub>2</sub>	611.0	79	54.80 (54.99)	3.50 (3.60)	11.30 (11.45)	-	-	-	-
(HL <sub>14</sub> ) <sub>2</sub> Cu <sup>2+</sup> C <sub>56</sub> H <sub>46</sub> N <sub>10</sub> O <sub>6</sub> Cu <sup>2+</sup> Br <sub>2</sub> Cl <sub>4</sub>	1319.54	75	48.20 (48.29)	3.20 (3.30)	10.00 (10.06)	11.30 (11.35)	4.50 (4.56)	2.00 (1.7-2.2)	9.68
(HL <sub>14</sub> ) <sub>2</sub> Ni <sup>2+</sup> C <sub>56</sub> H <sub>46</sub> N <sub>10</sub> O <sub>6</sub> Ni <sup>2+</sup> Br <sub>2</sub> Cl <sub>4</sub>	1314.69	82	51.10 (51.11)	3.30 (3.49)	10.50 (10.64)	12.00 (12.01)	4.30 (4.46)	3.12 (2.9-3.4)	10.02
(HL <sub>14</sub> ) <sub>2</sub> Co <sup>2+</sup> C <sub>56</sub> H <sub>46</sub> N <sub>10</sub> O <sub>6</sub> Co <sup>2+</sup> Br <sub>2</sub> Cl <sub>4</sub>	1314.90	69	51.00 (51.10)	3.40 (3.49)	10.60 (10.64)	12.00 (12.01)	4.70 (4.72)	4.89 (4.4-5.2)	29.68
(HL <sub>14</sub> ) <sub>2</sub> Mn <sup>2+</sup> C <sub>56</sub> H <sub>46</sub> N <sub>10</sub> O <sub>6</sub> Mn <sup>2+</sup> Br <sub>2</sub> Cl <sub>4</sub>	1370.90	79	51.20 (51.26)	3.40 (3.50)	10.60 (10.67)	12.00 (12.05)	4.10 (4.14)	5.91 (5.2-6.0)	10.11
(HL <sub>14</sub> ) <sub>2</sub> Zn <sup>2+</sup> C <sub>56</sub> H <sub>46</sub> N <sub>10</sub> O <sub>6</sub> Zn <sup>2+</sup> Br <sub>2</sub> Cl <sub>4</sub>	1321.39	80	50.80 (50.85)	3.40 (3.48)	10.50 (10.59)	11.90 (11.95)	5.50 (5.52)	-	7.98

**NMR spectra:** The main chemical shifts and its respective probable functional group of Ligand, HL<sub>14</sub> are mentioned in table 3. The chemical shift confirmed the formation of HL<sub>14</sub> i.e. 6-Bromo-2[(4-(2,3-dichlorophenyl)piperazin-1-yl)methyl]-3-[8-hydroxyquinolin-5-yl]-3(H)-quinazolin-4-one.

**Table 2: FT-IR spectroscopic data of HL<sub>14</sub> and its justification**

S. No.	Group Frequency ( $\text{cm}^{-1}$ )	Probable functional group/ Assignment
1	3400 to 2600	Phenolic group bonded to N atom of 8-hydroxy quinoline moiety (Syamal, A., et al, 1987)
2	2923, 2852 and 1470	Aromatic CH and methylene group of bridge and piperazine ring (Singh, D.P., et al.,1997)
3	1710	C=O of quinazolinone moiety
4	1500-1400	Aromatic breathing
5	1580-1600	Nitrogen in the chelate formation (Syamal, A., et al, 1987, Reddy, P.S.N., and Agarwal, B.V. 1987)
6	1095	New C-O-M bond formation
7	840-830	Coordinated water

**Table 3: <sup>1</sup>H NMR data of HL<sub>14</sub> and its justification**

Sr. No.	Chemical Shift ( $\delta$ ppm)	Probable Functional group
1	3.47	CH <sub>2</sub> bridge
2	3.44 to 3.52	Triplet -CH <sub>2</sub> of piperazine
3	4.82	Singlet of phenolic -OH
4	7.1 to 8.84	Multiplet, quinazolinone

### Magnetic moment and Electronic spectra:

The magnetic moment and molar conductance of complexes were depicted in table 1. The electronic spectral data were shown in table-4. At room temperature the magnetic moment ' $\mu_{\text{eff}}$ ' values for the Co (II) complex is 4.89 B.M suggest high spin octahedral geometry, which is further supported by the electronic spectral data. The value of transition ratio  $\nu_2 / \nu_1$  was 2.22 providing further evidences for octahedral geometry for the Co (II) complexes.

**Table 4: Magnetic moment and electronic spectra of complexes of ligand HL<sub>14</sub>**

Samples	Electron Transition	Absorption band (cm <sup>-1</sup> )	$\nu_2/\nu_1$
(HL <sub>14</sub> ) <sub>2</sub> Co <sup>2+</sup>	<sup>4</sup> T <sub>1g</sub> (F) ----> <sup>4</sup> T <sub>1g</sub> (F)	8479	2.21
	<sup>4</sup> T <sub>1g</sub> (F) ----> <sup>4</sup> A <sub>2g</sub> (F)	18799	
	<sup>4</sup> T <sub>1g</sub> (F) ----> <sup>4</sup> T <sub>1g</sub> (P)	24523	
(HL <sub>14</sub> ) <sub>2</sub> Ni <sup>2+</sup>	<sup>3</sup> A <sub>2g</sub> (F) ----> <sup>3</sup> T <sub>1g</sub> (F)	14990	1.58
	<sup>3</sup> A <sub>2g</sub> (F) ----> <sup>3</sup> T <sub>1g</sub> (P)	23696	
(HL <sub>14</sub> ) <sub>2</sub> Cu <sup>2+</sup>	<sup>2</sup> B <sub>1g</sub> ----> <sup>2</sup> A <sub>1g</sub>	15500	1.53
	Charge Transfer Transition	23698	
(HL <sub>14</sub> ) <sub>2</sub> Mn <sup>2+</sup>	<sup>6</sup> A <sub>1g</sub> ----> <sup>4</sup> T <sub>1g</sub> ( <sup>4</sup> G)	15856	-
	<sup>6</sup> A <sub>1g</sub> ----> <sup>4</sup> T <sub>2g</sub> ( <sup>4</sup> G)	18755	
	<sup>6</sup> A <sub>1g</sub> ----> <sup>4</sup> E <sub>g</sub> , <sup>4</sup> T <sub>1g</sub> ( <sup>4</sup> G)	24548	

In the Ni (II) complex,  $\mu_{\text{eff}}$  value at room temperature is observed to be 3.12 B.M. as expected for six coordinated spin free Ni (II) species. The  $\nu_2/\nu_1$  ratio for the chelate was 1.57 occurs in the usual range (1.60–1.82) for octahedral Ni (II) chelates (Syamal A. et al., 1986). The spectral bands are well within the range observed for hexacoordinate octahedral complexes reported earlier (Singh D.P. et al., 1997).

The Cu (II) complex exhibit normal magnetic moments (2.00 B.M.) indicating the distorted octahedral geometry, which is in agreement with data reported by several research worker (Reddy P.S.N. et al., 1987). These complex show broad asymmetric bands in the region at 15500 and 23698 cm<sup>-1</sup> assignable to <sup>2</sup>B<sub>1g</sub> ----> <sup>2</sup>A<sub>1g</sub> and charge transfer transition respectively (Chaudhary G.L. et al., 1997). These results reveal the distorted octahedral geometry for these complexes. The former band may be due to <sup>2</sup>E<sub>g</sub> ----> <sup>2</sup>T<sub>2g</sub> accounted due to Jahn Teller effect suggesting thereby a distorted octahedral geometry for these complexes (Satapathy K.C. et al., 1989). The value of transition ratio  $\nu_2/\nu_1$  was 1.53.

Zn(II) complex is diamagnetic as expected for d<sup>10</sup> systems and may have tetrahedral geometry (Yidliz M. et al., 2004). The observed magnetic moment (5.00 B.M.) for Mn(II) complex indicates high spin octahedral environment (Sahu B.K. et al., 1979).

**Antifungal activity:** The ligand and chelates were used for their antimicrobial studies by means of fungi, such as *Candida Albicans*, *Botrydepladia Thibromine*, *Nigrospora Sp*, *Aspergillus Fumigatus* and *Rhizopus Nigricums*. Antifungal activity of ligand and its metal chelates shown in Table-5 inhibition of fungal in following decreasing order:

HL<sub>14</sub>>Co(II) > Cu(II) > Zn(II) > Mn(II) > Ni(II).

The substitutions of phenyl rings by chlorine have much more effect on the fungicidal activity. The results suggest that variation in structure on coordination affects the growth of micro organisms and may result in to inhibitory or reduction in toxicology of metal ions towards some organisms (Patel M.M. et al., 1996).

**Table 5: Antifungal activity of ligand HL<sub>14</sub> and its metal chelates**

Samples	Zone of inhibition at 1000 µm (%)				
	CA	BT	NS	AF	RN
HL <sub>14</sub>	91	90	90	89	91
(HL <sub>14</sub> ) <sub>2</sub> Cu <sup>2+</sup>	79	75	78	79	76
(HL <sub>14</sub> ) <sub>2</sub> Ni <sup>2+</sup>	69	62	63	63	65
(HL <sub>14</sub> ) <sub>2</sub> Co <sup>2+</sup>	80	82	84	81	87
(HL <sub>14</sub> ) <sub>2</sub> Mn <sup>2+</sup>	66	65	68	67	68
(HL <sub>14</sub> ) <sub>2</sub> Zn <sup>2+</sup>	77	72	75	77	79

CA: *Candida Albicans*, BT: *Botrydepladia Thibromine*, NS: *Nigrospora Sp.*,  
AF: *Aspergillus Fumigatus*, RN: *Rhizopur Nigricums*

## CONCLUSION

The ligand molecule acts as a hexadentate ligand in all the studied cases of complex. Bonding either among N (4) depending upon the nature of the metal ions. Octahedral structures for Ni (II), Co (II) and Mn (II) complexes, tetrahedral polymeric structure for Zn (II), and distorted octahedral for Cu (II) complex have been tentatively proposed. Present work will contribute in the field of new antifungal for some plant pathogenic organisms.

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## REFERENCES

- Barry, A.L. (1996) Antibiotics in Laboratory Medicine, Williams & Wilkins, Baltimore, 3<sup>rd</sup> Ed.  
 Chaudhary, G.L., Prasad, S.R. and Rahman, B.M. (1997) Synthesis, Magnetic and Spectral studies of some Schiff base chelates of Iron, Cobalt, Nickel, Zinc, Cadmium and Mercury (II), J. Ind. Chem. Soc., 4, 683-685.  
 Figgis, B.N., and Lewis, J. (1960) The Magneto Chemistry of Chelates in Modern Coordination Chemistry, Interscience, New York.  
 Geary, W.J. (1971) The use of conductivity measurements in organic solvents for the characterization of coordination compounds. Coord. Chem. Rev., 7:81-122.  
 Lewis, J., and Wilkins, R.G. (1964) Modern Coordination Chemistry, Newscience, New York.  
 Patel, M.M. and Patel, H.R., (1996) Synthesis, Spectral, Thermal, Electrical and Antimicrobial studies of some complexes derived from 7- (α -phenyl -α m/p- nitroanilinomethyl) -8- quinolinol, J. Ind. Chem Soc., 73, 313-317.  
 Patel, N.B., and Chaudhari, R.C. (2006) Quinazolin-4(3H)-ones of 2-[2-(2,6-dichlorophenyl)amino]phenyl acetic acid with substituted aryl acetamide and their microbial studies. J Ind. Chem. Soc., 83, 838-841.

- Reddy, P.S.N., and Agarwal, B.V. (1987) Synthesis and Characterization of New Schiff Base Complexes of 2-Pyridinecarboxaldehyde and Thiosemicarbazides, *Syn. React. Inorg. Metal-Org. Chem.*, (17)6, 585 – 594.
- Sahu, B.K. and Mahapatra, B.K., (1979) *J. Ind. Chem. Soc.*, 56, 825.
- Satapathy, K.C., Dash, D.C., Pradhan, G.C. and Naik, A. (1989) *J. Ind. Chem. Soc.*, 66, 292.
- Singh, D.P., Shishodia, N., Yadav, B.P. and Rana, V.B. (1997) Synthesis and characterization of bivalent metal complexes of a tetradentate N6 macrocyclic ligand, *Polyhedron*, 16(13), 2229-2232.
- Syamal, A., Maurya, M.R., Dooms, E., and McLean Jr. J.A. (1986) Synthesis and Characterization of Nickel (II), Cobalt (II), Copper(II), Manganese (II), Zinc (II), Zirconium (IV), Oxomolybdenum (V), and Dioxouranium (VI) Complexes of the Schiff Base Derived from Salicylaldehyde and Thiophene-2-Carboxylic Acid Hydrazide. *Synth. React. Inorg. Metal-Org. Chem.*, 16(1), 39 – 60.
- Upadhyay, R.K. (1977) Chemistry of mixed ligand complexes of copper (II) involving ketoanil and thiourea, ammonia or anionic ligands. *J. Ind. Chem. Soc.*, 74, 535-537.
- Vashi, R.T., Patel, S.B. and Kadiya, H.K. (2010) Synthesis and characterization of 2-[(8-hydroxyquinolinyl)-5-aminomethyl]-3-(4-methoxyphenyl)-3(H)-quinazolin-4-one and its metal complexes with Cu(II), Ni(II), Mn(II), Co(II) and Zn(II) ions. *Der Pharma Chemica*, 2(1), 109-116.
- Vashi, R.T., and Patel, S.B. (2009) Synthesis, Characterization and Antifungal Activity of Novel Quinazolin-4-one Derivatives Containing 8-Hydroxyquinazoline Ligand and its Various Metal Complexes. *E-J. Chem.*, 6 (S1), S445-S451
- Vashi, R.T., and Shelat, C.D. (2010) Transition Metal Complexation Studies on Heterocyclic Ligands. *Asian J. Chem.* 22(3), 1745-1750.
- Vashi, R.T., Shelat, C.D., Patel, H.J. (2010a) Synthesis and antifungal activity of 6-bromo-2[(4-phenyl)-1-yl) methyl]-3-[8-hydroxy quinoline -5-yl]-3-quinazolin -4-one ligand and its metal chelates, *Int. J. current Pharm. Res.*, 2(3), 57-60.
- Vogel, A.I. (1978) *A Text book of Quantitative Inorganic Analysis*, 3<sup>rd</sup> Ed, ELBS, London.
- Williams, J.O. (1978) Electrical Conduction in Organic Solids, *Adv. Phys. Org. Chem.*, 16, 159-237
- Yidliz, M., Dulger, B., Yancu, S.Y.K., and Yanpici, B.M. (2004) Synthesis and antimicrobial activity of bis(imido) Schiff bases derived from thiosemicarbazide with some 2-hydroxyaldehydes and metal complexes. *J. Ind. Chem. Soc.*, 81, 7-12.

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