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Synthesis, Spectroscopic characterization and biological evaluation studies of Schiff base ligand derived from 3-amino-5-bromobenzofuran-2-carboxamide and 3-formyl-2-mercaptoquinoline and its metal complexes

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ABSTRACT

A protocol for the synthesis of 3-((2-mercaptoquinolin-3-yl)methyleneamino)-5-bromobenzofuran-2-carboxamide has been developed by the condensation of 3-amino-5-bromobenzofuran-2-carboxamide with 3-formyl-2-mercaptoquinoline. Metal complexes of the Schiff base were prepared from their chloride salts of Co(II), Ni(II), Cu(II), Cd(II), Zn(II) and Hg(II) in ethanol. The prepared Schiff bases and chelates have been characterized by elemental analysis, molar conductance, magnetic susceptibilities, FTIR, ^{1}HNMR, electronic spectral studies, ESR and mass. The molar conductance studies show non-electrolytic behavior of the complexes. The ligands and their metal complexes has been screened for their antibacterial and antifungal activities and its activity increases on complexation.

Keywords: Benzofuran Schiff base; Metal complexes; Quinoline; Spectral studies; Biological activity.

INTRODUCTION

The structural and therapeutic diversity tied with commercial viability of heterocyclic molecules with sulfur atom has captivated organic and medicinal chemists. The benzo[*b*]furan ring is often incorporated in pharmaceutical agents as a core structural motif, and thus it continues to attract extensive synthetic efforts. They have found applications in agrochemicals, pharmaceuticals, physiological and cosmetics and as a result, there is ongoing interest in their chemical synthesis. (1) Schiff bases derived from 3-formyl-2-mercaptoquinoline has also proven to be important pharmaceutical agents. Metal complexes of quinoline derivatives has proven their significance in diagnosis of diseases like heart disease, brain disorder, cancer, diabetics and tissue hypoxia, and to detect multi-drug resistance.(2) Thus with an effort to capitalize the pharmacological potential of the heterocyclic compound and to improve the efficiency, output, and quality of the process, the present investigation cope with the synthesis, characterization, and biological studies of Schiff base obtained by the condensation of 3-amino-5-bromobenzofuran-2-carboxamide with 3-formyl-2-mercaptoquinoline.

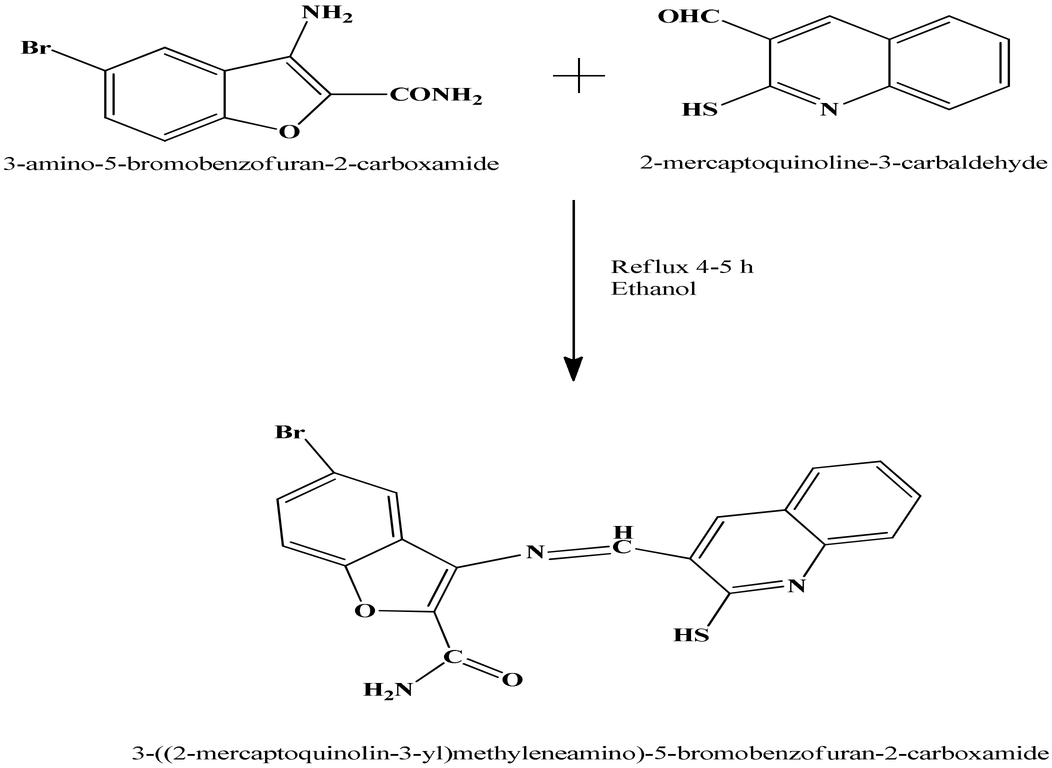
MATERIALS AND METHODS

All chemicals used were of analytical reagent grade.3-amino-5-bromobenzofuran-2-carboxamide and 3-formyl-2-mercaptoquinoline were synthesized according to the literature procedure [3, 4]. The metal and chloride contents were determined as per Vogel's procedure [5]. Elemental analysis (C, H and N) were estimated out on a Perkin Elmer 240C model at the Central Drug Research Institute (CDRI), Lucknow. Infrared spectra were recorded in the spectral range of 4000-350 cm^{-1} using Perkin Elmer Spectrum-one FT-IR spectrometer. The ESR spectrum of the Cu(II) complex in the polycrystalline state was recorded on a Varian-E-4X band EPR spectrophotometer using TCNE as the 'g' marker (g = 2.00277) at room temperature. Mass spectra were recorded with a JEOL LC MATE II

LC-MS mass spectrometer. Molar conductivity measurements were recorded on a ELICO CM-180 conductivity bridge in DMF (10^{-3} M) solution using a dip-type conductivity cell fitted with a platinum electrode and the magnetic susceptibility measurements were made at room temperature on a Gouy balance using $Hg[Co(NCS)_4]$ as the calibrant.

Preparation of 3-((2-mercaptoquinolin-3-yl)methyleneamino)-5-bromobenzofuran-2-carboxamide

An equimolar mixture of 3-amino-5-bromobenzofuran-2-carboxamide (2.55 g, 0.01 mol) and 3-formyl-2-mercaptoquinoline (1.89 g, 0.01 mol) in ethanol (25 mL) with catalytic amount of acetic acid were reflux for about 4-5 h on a water bath. The progress of the reaction was checked by TLC. The light yellowish colored solid separated on partial evaporation of solvent was filtered, washed with warm ethanol and recrystallized from hot ethanol.



Scheme 1: Synthesis of 3-((2-mercaptoquinolin-3-yl)methyleneamino)-5-bromobenzofuran-2-carboxamide

Synthesis of metal complexes.

Hot ethanolic solution (15 mL) of Schiff base (2 mmol) and metal chlorides (1 mmol) were refluxed on water bath for 3 h. Then, sodium acetate has been added to the reaction mixture to adjust the pH to 6.0–7.0, after which immediately solid, intense colored complexes precipitated out. The volume of the reaction mixture was reduced to one-half by evaporation of solvent. Metal chelates separated were collected by filtration, washed thoroughly with water and little warm ethanol, and finally dried in a desiccators over fused $CaCl_2$.

BIOLOGICAL ACTIVITIES

In vitro antimicrobial bioassay:

The antimicrobial activities of the newly synthesized Schiff base ligand and its complexes were studied by well diffusion method [6].

Antibacterial activity:

Media used: Peptone 10 g, NaCl 10 g and yeast extract 5 g, Agar 20 g in 1000mL of distilled water. For the antibacterial screening of newly synthesized compounds, 18 hours old bacterial inoculums containing approximately 10^4–10^6 colonies forming units (CFU)/mL were used. The wells were dug in the media with the help of a sterile metallic borer with centers at least 6 mm. Recommended concentration (100 µL) of the test sample was introduced in the respective wells. The plates were incubated immediately at 37 °C for 24 h. Activity was determined by measuring the diameter of zones showing complete inhibition (mm). The antibacterial activity of a common standard antibiotic *Gentamicine* was also recorded using the same procedure as above at the same concentrations and solvent.

Antifungal activity:
The antifungal activities of test compounds against fungal strains were evaluated by using Potato Dextrose Agar (PDA) media having the composition 250 g of peeled potato were boiled for 20 min and squeezed and filtered. To this filtrate 20 g of dextrose was added and the volume was made up to 1000mL by distilled water.

Initially, the stock cultures of *Aspergillus Niger* and *Aspergillus flavus* were revitalized by inoculating in broth media and grown at 27 °C for 48 h. The agar plates of the above media were prepared as well as the wells were made in the plate. Each plate was inoculated with 16 h old cultures (100 µl 10^4 CFU) and broadens uniformly on the plate. After 15 min, the wells were filled with different concentrations of test samples. Furthermore, all the plates were incubated at 27 °C and the linear growth of the fungus was recorded by measuring the diameter of the fungal colony after 48 h. The antifungal activity of a common standard antibiotic *Fluconazole* was also recorded using the same procedure as above at the same concentrations and solvent.

RESULTS AND DISCUSSION

The analytical data and physical properties showed that, the Schiff base and its complexes were light in color, stable and non hygroscopic at room temperature (table 1). The complexes were sparingly soluble in common organic solvents, but are readily soluble in strong coordinating solvents like DMF and DMSO. Measured molar conductance values are very low to account for dissociation of the complexes in DMF, indicating the non electrolytic nature of the complexes [7]

Table 1. Elemental analysis, magnetic susceptibility and molar conductance data of Schiff base and its metal complexes

Compounds	Mol. Wt. (g/mol)	Mp. (˚C)	Elemental analysis found and (calculated) %				μ_{eff} (BM)	$\Lambda_m{}^*$
			C	H	N	M		
$C_{19}H_{12}BrN_3O_2S$	427.30	272	53.15 (53.53)	2.59 (2.84)	12.24 (9.86)	-	-	-
$[CO(C_{19}H_{11}BrN_3O_2S)_2]$	909.49	>300	50.00 (50.18)	2.21 (2.44)	11.23 (9.24)	6.25 (6.48)	4.81	14.26
$[Ni(C_{19}H_{11}BrN_3O_2 S)_2]$	909.25	>300	50.05 (50.20)	2.24 (2.44)	11.30 (6.46)	6.18 (6.46)	2.89	15.53
$[Cu(C_{19}H_{11}BrN_3O_2S)_2]$	914.10	>300	49.53 (49.93)	2.14 (2.43)	11.30 (9.19)	6.45 (6.95)	1.92	18.12
$[Cd(C_{19}H_{11}BrN_3O_2S)Cl]$	573	>300	47.20 (47.40)	2.10 (2.30)	11.36 (8.73)	11.36 (11.67)	-	16.06
$[Zn(C_{19}H_{11}BrN_3O_2S)Cl]$	526	290	49.51 (49.83)	2.16 (2.42)	9.48 (9.18)	7.01 (7.14)	-	14.82
$[Hg(C_{19}H_{11}BrN_3O_2S)Cl]$	661	297	43.22 (43.42)	2.5 (2.11)	7.95 (8.00)	19.00 (19.08)	-	12.33

* *Molar conductance values in* $Ohm^{-1}cm^2\,mol^{-1}$

IR spectral studies:
The IR spectra of the prepared Schiff base ligand and its metal complexes exhibited characteristic bands of the expected functional groups (table 2).

The IR spectrum of the free Schiff base ligand showed a broad band at 2531 cm^{-1} which was assigned to the phenolic ν(SH) stretching [8]. The band at 3146 cm^{-1} are assigned to NH_2 stretching vibrations of primary amide group in Schiff base, which was practically remain unchanged in the spectra of its complexes suggesting nonparticipation of NH_2 group on chelation [3]. A high intensity strong band observed at 1635cm^{-1} in the Schiff base due to ν(C=O) stretching vibration of the carbonyl group. This band shifted to a lower wave number side in all the complexes indicates the involvement of the carbonyl oxygen in bonding with metal ions [9].Further, a medium-to-strong intensity band at 1584 cm^{-1} in the Schiff base ligand attributed to ν(C=N) stretch of the azomethine group. Coordination of the Schiff base to the metal ions through the nitrogen atom was expected to reduce electron density in the azomethine link and lower the ν(C=N) absorption frequency. Hence, this band shifted to a lower wave number side in all the complexes indicates the participation of the azomethine nitrogen in coordination with metal ions [10]. Furthermore, the ν(C–O–C) stretch was observed at 1205 cm^{-1}, which remains unaltered in the metal complexes, indicating non-participation of the furan ring oxygen atom in the bonding with metal ions in accordance with previous reports [11]. The weak intensity non-ligand bands observed in the region of 455-434 and 560-540 cm^{-1} in the spectra of the complexes are assigned to stretching frequencies of ν(M–N) and ν (M–O) stretching bands, respectively which further support the coordination of the Schiff base with metal ions via carbonyl oxygen and azomethine nitrogen [12]. Hence IR spectral data evidently confirms the coordination of the Schiff base ligand with different metal ions.

Table 2. The infrared frequencies (cm^{-1}) of the Schiff base ligand and its complexes

Ligand / Complex	ν_{SH}	$\nu_{C=O}$	$\nu_{C=N}$	ν_{M-O}	ν_{M-N}
$C_{19}H_{12}BrN_3O_2S$	2531	1635	1584	-	-
$[Co(C_{19}H_{11}BrN_3O_2S)_2]$	-	1612	1567	547	434
$[Ni(C_{19}H_{11}BrN_3O_2S)_2]$	-	1610	1560	540	438
$[Cu(C_{19}H_{11}BrN_3O_2S)_2]$	-	1604	1540	552	447
$[Cd(C_{19}H_{11}BrN_3O_2S)Cl]$	-	1620	1564	551	448
$[Zn(C_{19}H_{11}BrN_3O_2S)Cl]$	-	1618	1557	547	440
$[Hg(C_{19}H_{11}BrN_3O_2S)Cl]$	-	1608	1547	560	455

^{1}HNMR spectral studies.

The ^{1}HNMR spectrum of the ligand displayed distinct singlets at δ (11.23) (s, 1H, SH) assigned to phenolic proton of (–SH) and the signal at δ (9.14) (s, 1H, >CH=N) due to azomethine proton, δ (5.82) (s, 2H, NH_2) due to amine respectively.

Upon Zinc complex formation, the absence of characteristic proton resonance signals at δ 11.23 (s, 1H, SH) of the Schiff base . The downfield shift of azomethine proton from δ 9.14 (s, 1H, >CH=N) of the Schiff base to δ 9.54 (s, 1H, >CH=N) in complexes, indicate the involvement of >CH=N nitrogen. The aromatic protons at δ (6.86–8.51) (m, 8H) shifted downfield in the complexes. Hence, the ^{1}H NMR spectral data of Schiff base and its complexes confirm the formation of complex with ligand.

Mass spectral studies:

A mass spectrum was performed to determine molecular weight. The LC–MS mass spectrum of the Schiff base showed a molecular ion peak at *m/z* 427, which is equivalent to its total molecular weight.

ESR spectrum of the Cu(II) complex:

The analysis of spectrum gives following data $g_{||}$ = 2.214, $g_{\perp}$ = 2.051, g_{av} = 2.105 and g_{iso} = 2.17. The observed $g_{||}$ value for the Cu (II) complex was less than 2.3 was in agreement with the covalent character of the metal ligand bond. The spectra show asymmetric band with observed values of $g_{||} > g_{\perp} > 2.00277$ indicating that the unpaired electrons lay predominantly in the in $d_{x^2-y^2}$ orbital with possible mixing of d_{z^2} because of low symmetry [13].

According to Hathaway, the value of 'G' was determined as $G = (g_{||} - 2.00277) / (g_{\perp} - 2.00277) = 4.38$ which is more than 4 suggesting that there is negligible or no interaction between the copper centers which measures the negligible exchange interaction between the metal centers in polycrystalline solid [14].

Electronic spectral studies:

The electronic absorption spectra of the Co(II), Ni(II) and Cu(II) complexes are presented in table 3. The electronic spectrum of Co(II) complex displayed bands at 15702 and 20640 cm^{-1}, assignable to $^4T_{1g}$ (F) → $^4A_{2g}$ (F) (ν_2) and $^4T_{1g}$ (F) → $^4T_{2g}$ (P) (ν_3) transitions respectively, in an octahedral environment [15]. The ν_1 band was calculated using the band fitting procedure suggested by Underhill and Billing [16]. The electronic spectrum of Ni(II) complex exhibited two absorption bands, at 14285 and 23809 cm^{-1}. These two bands are assignable to $^3A_{2g}$ (F) → $^3T_{1g}$ (F) (ν_2) and $^3A_{2g}$(F) → $^3T_{1g}$ (P) (ν_3) transitions, respectively, in an octahedral environment.

The light green colored Cu(II) complex exhibited low intensity single broad asymmetric band at 13352-17473 cm^{-1}. The broadness of the band indicates the three transitions $^2B_{1g}$ → $^2A_{1g}$ (ν_1), $^2B_{1g}$ → $^2B_{2g}$ (ν_2) and $^2B_{1g}$ → ^2E_g (ν_3), which are of similar in energy and give rise to only one broad absorption band. The broadness of the band may be due to dynamic Jahn–Teller distortion. All of these data suggested a distorted octahedral geometry around the Cu(II) ion [17]. The octahedral geometry was further supported by the values of ligand field parameters, such as the Racah inter electronic repulsion parameter (B′), ligand field splitting energy (10 Dq), nephelauxetic parameter (β) and ligand field stabilization energy (LFSE) [18]. The (B′) values for the complexes were lower than the free ion values, which indicate the orbital overlap and delocalization of d-orbitals. The (β) values obtained were less than unity, suggesting a considerable amount of covalency for the metal–ligand bonds. Further, the (β) value for the Ni(II) complex was less than that of the Co(II) complex, indicating the greater covalency of the M–L bond .

Table 3. Electronic spectral data and ligand field parameters of Co(II), Ni(II) and Cu(II) Complexes

Complexes	Absorption bands(cm^{-1})			Dq (cm^{-1})	B′ (cm^{-1})	β	β%	$\nu_{2/}\nu_1$	LFSE (Kcal)
	ν_{1*}	ν_2	ν_3						
Co(II)	7102	15702	20640	760	902	0.92	7.01	2.21	13.0
Ni(II)	8790	14285	23809	879	779	0.74	25.01	1.62	30.16
Cu(II)	13352-17473			1538	-	-	-	-	26.36

**Calculated values.*

Biological activity results

Antimicrobial activity:

In the present study, the in vitro antibacterial results indicates that the Schiff base and its complexes were found to be more active against *E. coli* and moderately active against *B. subtilis* as shown in table 3.

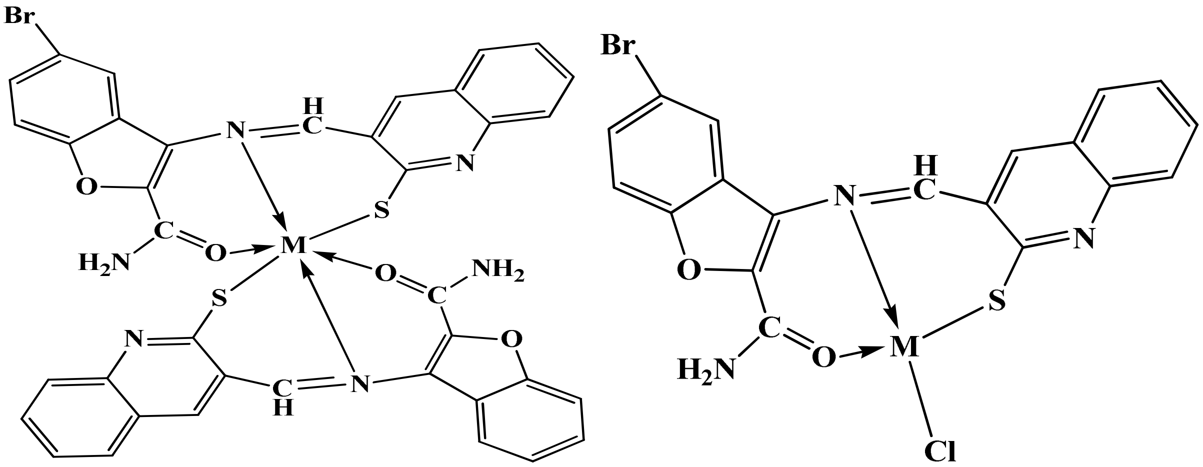
In case of antifungal activity, the Schiff base and its complexes exhibit good activity against *A. flavus than A. niger* Hence, the comparative study of in vitro antimicrobial activity of the Schiff base and its Co(II), Ni(II), Cu(II), Zn(II), Cd(II) and Hg(II) complexes indicate that all the metal complexes show promising activity than the corresponding Schiff base. In other word the antimicrobial activity of the Schiff base was enhanced upon complex formation with different metal ions.

TABLE 4: Antimicrobial activity results of the Schiff base ligand and its metal complexes

Compound	**Concentration (μgmL^{-1})**	**Zone of Inhibition against bacteria (mm)**		**Zone of Inhibition against fungi (mm)**	
		B. subtilis	*E. coli*	*A. flavus*	*A. niger*
$C_{19}H_{12}BrN_3O_2S$	50	7	8	8	6
	100	10	10	11	11
	200	12	12	13	12
$[Co(C_{19}H_{11}BrN_3O_2S)_2]$	50	11	10	11	9
	100	14	11	14	11
	200	19	12	16	16
$[Ni(C_{19}H_{11}BrN_3O_2S)_2]$	50	8	9	9	8
	100	12	14	13	11
	200	17	18	18	17
$[Cu(C_{19}H_{11}BrN_3O_2S)_2]$	50	12	13	12	11
	100	17	17	16	14
	200	**22**	**19**	**21**	**18**
$[Cd(C_{19}H_{11}BrN_3O_2S)Cl]$	50	12	12	10	8
	100	16	13	13	12
	200	**22**	**21**	**20**	**19**
$[Zn(C_{19}H_{11}BrN_3O_2S)Cl]$	50	14	12	12	12
	100	16	11	17	16
	200	**21**	**19**	**18**	**20**
$[Hg(C_{19}H_{11}BrN_3O_2S)Cl]$	50	13	17	13	13
	100	16	19	16	15
	200	**20**	**21**	**20**	**19**
Gentamicine	200	27	30	-	-
Fluconazole	200	-	-	25	23

CONCLUSION

The newly synthesized Schiff base ligand behaves as tridentate ONS donor. The DNA cleavage results revealed that the metal complexes showed good efficiency towards DNA cleavage. The antimicrobial activity results revealed that all complexes were superior to the free ligand as the process of chelating dominantly affects the overall biological behavior of the compounds. Hence based on physicochemical and spectroscopic methods the structure of the metal complexes has been proposed (figure 1).



Where M= Co(II), Ni(II) and Cu(II). **Where M= Cd(II), Zn(II) and Hg(II).**

Figure 1: Proposed Structures of Complexes

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