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SYNTHESIS OF HETREROCYCLIC LIGANDS :SYNTHESIS,CHARACTERIZATION AND ANTIMICROBIAL ACTIVITY

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Abstract: A heterocyclic Ligand Prepared from 1,3,4-thiadiazole moiety in alcoholic medium. Synthesized heterocyclic ligand is characterized quantitatively and qualitatively by using elemental analysis, UV–Vis, FT-IR spectroscopy, mass spectroscopy, ^{1}H NMR &^{13}C-NMR, and molar conductance measurement. The preliminary *in vitro* antibacterial and antifungal activity showed that heterocyclic ligand show the moderate activity against tested bacterial Strains *S. aureus* and *B. subtilis* and fungal strains of *F. Oxysporum*and, *A. Niger* using Kirby-Bauer disc diffusion method.

Keywords: Heterocyclic ligand 1,3,4 Thiadiazole,MetalComplexes,.Antibacterial activity

Introduction:

Schiff bases synthesized from an amino and carbonyl compound are significant class of ligands that coordinate to metal ions by azomethine group and had been studied broadly[i].In azomethine derivatives, the -C=N- linkage is important for biological activity, a lot of azomethine had been reported to possess remarkable antibacterial, antimalarial,antifungal, and anticancer activities[ii].1,3,4-Thiadiazole is heterocyclic compound was first described in 1882 by Fischer farther it has been developed by Bush and his groups .Goerdler in 1956 has demonstrated the true nature, of the ring system in[iii].1,3,4-Thiadiazole derivatives have interesting biological activity probably due to strong aromaticity of this ring system, which leads to great in vivo stability and generally, a deficient in toxicity for higher vertebrates, including humans. When diversified functional groups that interact with biological receptors that attached to this ring, compounds possessing outstanding properties are access. Except for some antibacterial sulfonamides (albucid and globucid), is no longer used clinically, but which having historical importance, the most interesting and important examples is constituted by 5-amino-l,3,4-thiadiazole-derivatives[iv].Farther addition, the chemistry and the applications of these novel Schiff bases thiadiazoles group containing moieties derivatives could be extensively studied by coordinating to various metal ions. As a result, the structural activity relationship study of 1,3,4-thiadiazoles could be enlarge in the future development[v-xi].

Present study the synthesis and characterization of new heterocyclic ligand 4-bromo-2-(((5-mercapto-1,3,4-thiadiazol-2-yl)imino)methyl)-6-methoxyphenol.Moreover ,the preliminary *in vitro* antibacterial and antifungal screening activities of the ligand are carried out and the results are reported herein.

Materials and methods:

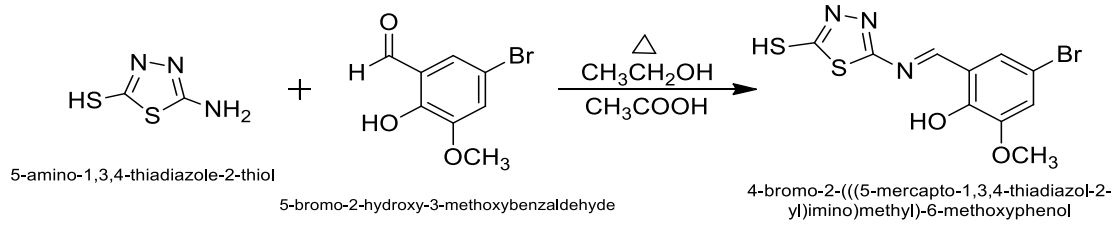
Experimental:

All chemical of analytical grade. 5-bromo-2-hydroxy-3-methoxybenzaldehyde and 5-amino-1,3,4-thiadiazole-2-thiol from Sigma- Aldrich and Alfa Aesar used without further purification. Dist. Ethanol used for synthesis of ligand, diethyl ether (Sigma-Aldrich). IR Spectra recorded on Perkin Elmer Spectrometer in range 4000-400 cm-1 KBr pellets.^{1}H and ^{13}CNMR Spectra were recorded on BRUKER AVANCE III HD NMR 500 MHz spectrophotometer. The C,H and N analyses were carried out using a Euro-E 3000.Magnetic susceptibility measurements for the synthesized complexes were obtained at room temperature using Room Temperature magnetic moments by Guoy's method in B.M.Electronic Spectra using DMSO on Varian Carry 5000 Spectrometer.Mass Spectra were recorded on Bruker IMPACT HD.

Biological Activity:

Schiff Base ligand evaluated in vitro their antibacterial activity against two bacteria,viz, *B. Subtilis*; *S. aureus*,Two fungi strains *A. niger and F. oxysporum*by Kirby-Bauer disc method[xii].The fungal and bacterial strains subcultured on PDA media and Nutrient Agar media. The stock solution was prepared in DMSO (1 mg mL^{-1}) solution for test. The stock solution again diluted using sterilized water to dilute to 500 ppm. The bacteria were subculture in agar medium and disc were kept incubated for 37^{o}C at 30 hrs. The standard for antibacterial activity is Ciprofloxacin and antifungal activity is Miconazole was also screen under same condition for comparison of bioactivity. Activity was measure and calculated by zone of inhibition in mm surrounding the discs. The experimental value compare with standard drug value of ligand.

Synthesis of Schiff base Ligand: The mixture of 1:1 5-bromo-2-hydroxy-3-methoxybenzaldehyde (2.31g,0.01mol) with 5-amino-1,3,4-thiadiazole-2-thiol (1.33 g, 0.01 mol) dissolved in ethanol. Then add Few drops of glacial acetic acid was added .The resultant mixture stirred for 4-5 hrs the yellowish colored precipitate of Ligands was obtained. Wash with Ethanol recrystalised with Ethanol and Ether then dried. The purity of compound was checked by TLC using Silica Gel method (Scheme.1).



Scheme.1 Synthesis of ligands

Results and Discussion: The ligand (Fig.1) 4-bromo-2-(((5-mercapto-1,3,4-thiadiazol-2-yl)imino)methyl)-6-methoxyphenol is stable at room temperature in solid state. The ligand is soluble in organic solvent likeDMSO,DMF.The physical and analytical data shown in Table. 1.Spectral evaluation shows formation of ligand.

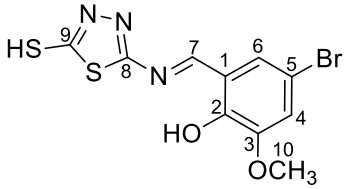


Figure1: Structure of Schiff base Ligands(L).

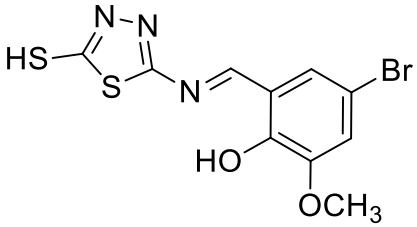
Entry	Products	Time (h)	Yield (%)	M.P (°C)
L	 L	4-5	72	230

Table 1.Structure of Heterocyclic Ligands

Characterization data of Heterocyclic Ligands 4-bromo-2-(((5-mercapto-1,3,4-thiadiazol-2-yl)imino)methyl)-6-methoxyphenol (Table.1,L): Dark Yellow;M.F. $C_{10}H_8BrN_3O_2S_2$;Yield : 72% ; M.P.230°C;Molar Cond.(DMSO 1×10^{-3}conc., ohm^{-1} cm^2 mol^{-1}):6.62; UV(DMSO, cm^{-1}): 282 ($\pi\rightarrow\pi^*$ tran. of benzene ring), 368 ($n\rightarrow\pi^*$ azomethine moieties and phenolic -OH.); IR(KBr Cm^{-1}) : ν =3323 (O-H str. in aromatic ring),ν= 1633 (C=N azomethine), ν=1493 (-C=N-N=C str.in Thiadiazole ring), ν=1268 (C-O Phenolic), ν=1026 (N-N Thiadiazole ring), ν=756 (C-S-C str.in thiadiazole ring) ; ^{1}H NMR (400 MHZ.DMSO d_6) δ ppm: δ = 11.23(s,1H,Ar-OH), δ =8.80 (s,1H,CH=N), δ = 7.10-7.56(s,2H,Ar-CH), ; ^{13}C NMR (DMSO-d_6, 400 MHZ,) δ ppm : δ =150.6-121.6 (C_1-C_6 Aromatic), δ =161.7 (C_7,-C=N-Azomethine), δ =155.6 (C_8Thiadiazole ring), δ = 181.3 (C_9 Thiadiazole ring), δ = 52.2 (C_{10} – OCH_3–).; MS (70 eV) m/z :347 [M+H,100%],Anal.Calcd.For$C_{10}H_8BrN_3O_2S_2$:C, 34.69; H, 2.33;N, 12.14;S, 18.52.Found : C, 34.60; H, 2.31;N, 12.02;S, 18.46.

Results and Discussion:

The IR spectra of 4-bromo-2-(((5-mercapto-1,3,4-thiadiazol-2-yl)imino)methyl)-6-methoxyphenol Schiff base Heterocyclicligand and its complexes are listed in Table 2. The Infrared Spectra of the free ligands are compared with the metal complexes in order to determine the coordination sites that may be involved in a chelation. There are important peaks in the spectra of the ligand, which is different in complexes helps to Confirm the formation of metal complexes IR spectra of 4-bromo-2-(((5-mercapto-1,3,4-thiadiazol-2-yl)imino)methyl)-6-methoxyphenol ligand HL Schiff base Heterocyclicligand most characteristic bands at 3318-3335 cm^{-1} ν(O-H), 1628-1645 cm^{-1} ν(C=N, azomethine) and 1262-1269 cm^{-1} ν(C-O). The Heterocyclicligand spectra showed bands at 3314-3340 cm^{-1} and 1333-1350 cm^{-1} due to the deformation and stretching of the phenolic –OH[xiii].The band 1628-1645 cm^{-1} due to the azomethine (-C=N-)group of the Schiff bases Heterocyclicligand[xiv-xv].The phenolic λ(C–O) stretching vibration that appeared band at 1262-1269 cm^{-1} in ligands. The band of ν(C–S–C) at 751–756 cm^{-1} of the Thiadiazole ring of ligand[xvi].The ^{1}H-NMR spectra of Heterocyclic ligand were recorded in Dimethyl Sulphoxide solution using TMS as a standard.The spectra of

Heterocyclic ligand shows singlet at δ7.10-7.56 ppm due to aromatic proton. while azomethine (-C=N-) proton resonate at singlet δ8.80 ppm the phenolic-OH has signal singlet at δ11.23 ppm and Thiadiazole containing (–SH) group shows singlet at δ13.40 ppm[xvii].^{13}C-NMR of Heterocyclic Ligand**,** peak appeared at δ152-160 ppm imine group (-C=N-),peak 180-182 ppm Due to carbon sulphur C-SH bonding in Thiadiazole.120-136 ppm because of aromatic carbon,155-172 ppm peak because of (Table. 4) Ar-OH group[xviii].Mass Spectra of Heterocyclic ligand shows the peak at m/z 347 which is M+H peak at 100% intensity this peak support to the structure formation of ligand.Molar conductance of Heterocyclic ligand were observed at room temperature at 1×10^{-3}M DMSO Solution. The studies show imperceptible molar conductance value is 6.62 $ohm^{-1}cm^2mol^{-1}$results shows in table 5.it is observed that all ligand was non-electrolytic in nature[xix-xx].The electronic absorption spectral data of the Heterocyclic ligands is taken in DMSO as a solvent.The band appearing at 225-321 is due to transition of benzene ring of the ligand. The other band due to free ligands 321-373 nm due to transition for azomethine groups and phenolic -OH[xxi].

Antimicrobial activity

The antimicrobial activity on two gram positive bacteria i.e *S. aureus and B.Subtlis*two fungi i.e *A. niger*and *F.Oxysporum*was taken.The synthesized Heterocyclic ligand show good biological activity against microorganism. The bactericidal and fungicidal analysis of the compounds are given in Tables 2.[xxii-xxiv]

Compounds	**Antibactrial Activity**		**Antifungal Activity**	
	S.aureus	***B.subtilis***	***A.niger***	***F.oxysporum***
	Diameter of inhibition Zone in mm	**Diameter of inhibition Zone in mm**	**Diameter of inhibition Zone in mm**	**Diameter of inhibition Zone in mm**
	500ppm	**500ppm**	**500ppm**	**500ppm**
Ligands(HL)	18	18	14	22
Ciprofloxacin(Standard)	34	33	---	---
Miconazole(Standard)	---	---	31	27

Table 2. Antimicrobial activity of Heterocyclic ligand

Conclusion

The Novel Synthesis, characterization, and antimicrobial activity of 4-bromo-2-(((5-mercapto-1,3,4-thiadiazol-2-yl)imino)methyl)-6-methoxyphenol(L) by conventional method. The antimicrobial activity data show heterocyclic ligand (L) is biologically potent to all pathogenic microorganisms. These type of study helps to decrease emerging problems in drug resistance microorganism in health sciences.

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