Synthesis and biological evaluation of metal based complexes with the medicinal drug paroxetine hemihydrates

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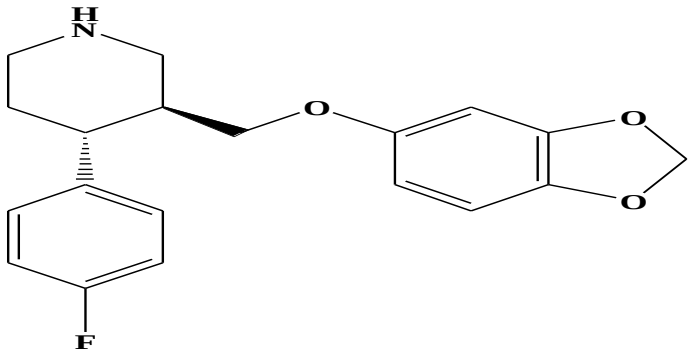
Abstract
Paroxetine is a medicinal drug used to treat various disorders. In the present investigation, Ni(II) and Co(II) metal complexes with medicinal drug Paroxetine has been synthesized and characterized using IR, elemental analysis and magnetic susceptibility. Synthesized compounds were screened against the microorganism including *Escherichia coli, Staphylococcus aureus, Candida albicans* and *Candida glabrata* using Agar well diffusion method. It has been observed that the metal complexes show moderate to higher microbial activities.
Keywords: 1. Paroxetine, 2.metal complexes, 3.microbial activity, 4.agar well diffusion method.

Introduction

A medicinal drug Paroxetine is an antidepressant counted in selective serotonin reuptake inhibitor (SSRI) class, developed by Smithkline beecham[1-2] and used to treat Obsessive compulsive disorder, significantly utilized in the treatment of various types of disorders such as, obsessive compulsive disorder, social anxiety disorder, generalized anxiety disorder, post traumatic stress disorder, premenstrual dysphoric disorder, and many more. Paroxetine sold under the brand name Aropax, Paxil, Pexeva, Seroxat, Sereupin and Brisdelle. Commonly, Paroxetine is benzodioxole trans(−)-3-[(1,3-benzodioxol-5-yloxy)methyl]-4-(4-fluorophenyl) piperidine[3-10].

Paroxetine has been used as an active ingredient in anti-depressant drugs in the form of paroxetine hydrochloride (paroxetine HCl) crystals. Paroxetine Hydrochloride is the hydrochloride salt form of paroxetine.



3-(Benzo[1,3]dioxol-5-yloxy methyl)-4-(4-fluoro-phenyl)-piperidine

In essence, paroxetine is a benzodioxole that contains a piperidine ring containing the 1,3-benzodioxol-5-yloxy)methyl and 4-fluorophenyl substitutes at positions 3 and 4 respectively; the (3S,4R)-diastereomer. Paroxetine is a highly potent and selective 5-HT inhibitor which can bind with high affinity to the serotonin transporter.

Paroxetine is a phenylpiperidine derivative. It is formulated using a secondary amine attached with the piperidine ring, which in turn is associated with the benzodioxol and fluorophenyl groups[11-14]. Chemically, paroxetine is enantiomerically pure, (−)-(3S,4R)-3-[(2H-1,3-benzodioxol-5-yloxy)methyl]-4-(4-fluorophenyl)piperidine hydrochloride hemihydrate with empirical formula of $C_{19}H_{20}FNO_3 \cdot HCl \cdot ½H_2O$. Paroxetine hydrochloride (paroxetine HCl), is a class II drug in a Biological Classification System (BCS). It is freely soluble in methyl alcohol, ethyl alcohol and slightly soluble in water. Paroxetine hydrochloride is an odorless, off-white powder, having a melting point range of 120° to 138°C[15-17].

According to the literature survey, far fewer studies have come across on this particular drug, this is why we are drawn towards the synthesis of the metallic complexes of paroxetine and studied for its biological activity[18-20].

Experimental

The metal complexes have been prepared by the interaction of ligand with the corresponding metal salt in the water soluble form under various conditions after refluxing for the appropriate time. The products were obtained majorly through filtration, washing and re-crystallization.

All the chemicals and metal salts used under the present investigation i.e. $NiCl_2.6H_2O$ & $CoCl_2.6H_2O$ were from Aldrich chemicals of AR grade and commercially available, used without further purification. Metal salt solutions were prepared according to previously reported method.

Nickel(II), Copper(II) complexes of Paroxetine were prepared by mixing of 1 mmol of metal salt and the corresponding amount of 1 mmol of Paroxetine ligand and equivalent of ammonia solution required to neutralize the released protons. The metal chloride and ligand were dissolved in ethanol and ammonia solution. The resultant mixture then refluxed for 4-5 hours. The formed solid complexes were separated by filtration wash many times with water. Solid complexes were dried and used for further analysis. The complexes are soluble in DMSO.

The synthesized metal complexes were investigated for further study. IR spectra of the synthesized complexes were recorded on Bruker. Elemental analysis was carried out on Thermofinnigan. Magnetic susceptibility were measured on Sherwood Scientific Magnetic Susceptibility balance[21-22]. Synthesized complexes were study for their microbial activity by Agar well diffusion method. The agar plate surface is inoculated by spreading a known volume of the microbial inoculums over the entire agar plate surface. A hole of 6 to 8 mm diameter is punched aseptically with a sterile cork borer or a tip, and a volume (20–100 µL) of the antimicrobial extract solution at desired concentration is introduced into the well. Agar plates are then incubated under suitable conditions depending on the test microorganism. The antimicrobial agent diffuses in the agar medium and inhibits the growth of the microbial strain tested.

In nature, many biological systems make extensive use of metallic ions, such as zinc and copper, which are crucial for the normal functioning of organisms. Metals have unique features that include redox activity, coordination site and responsiveness to the organic group. Excessive concentration of metal ions is associated with many pathological side effects that lead to cancer. For these reasons, metal coordination complexes like drugs are becoming very attractive and interesting areas of medical chemistry[23].

Result and discussion

The interaction of Paroxetine with metal chloride [Ni(II), Co(II)] in a 1:1 [M:L] molar ratio under reflux condition gives the solid product. The formations of these complexes were confirmed on the basis of IR, Elemental analysis & Magnetic susceptibility. The solid complexes are air stable. The complexes are coloured and are insoluble in H_2O and other common organic solvents and soluble in dimethyl sulfoxide (DMSO) only. All the metal complexes have high melting point that is greater than 250^0C. The complexes are decomposed without melting at this temperature.

Paroxetine composed of secondary amine which occupied by piperidine ring connected to benzodiaxol and flurophenyl group. By comparing with the literature, in IR spectra of paroxetine show symmetric stretching of ether (C-O-C) appear at 1041 cm^{-1}, in complex which appear at 1031 cm^{-1} in Co(II) and that for Ni(II) is appear at 1035 cm-1, aromatic (C-H) stretching appear at 863 cm^{-1} in Co(II) and peak appear at 666 cm^{-1} is assigned for (M-O) stretching in Co(II) and in Ni(II) (M-O) stretching is appear at 649 cm^{-1} in complex compound, indicating that the formation of Paroxetin-Co(II) metal complexes.
Elemental analysis data shows that the 23.047% of Carbon atom, 3.128% of Hydrogen and 1.111% of Nitrogen found in the complexes indicating the formation of complex through Ether (C-O-C) and aromatic (C-H) group. Magnetic moment 6.46 and 5.29 BM for Ni(II) & Co(II) complexes respectively suggesting that high spin octahedral geometry for the present complexes[20-21].

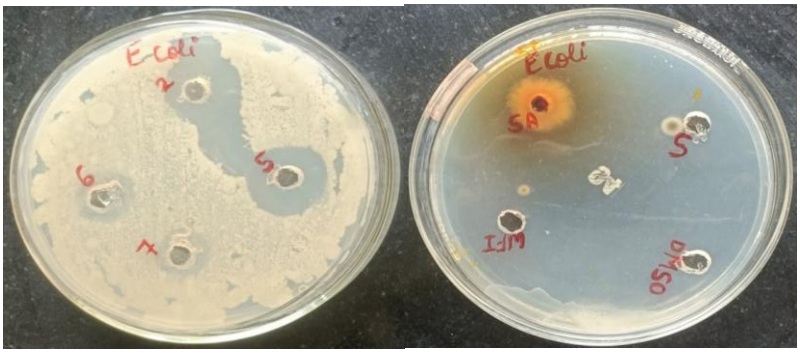
Compound	Melting point	% analysis Experimental(calculated)			μ_{eff} (B.M.)
		C	H	N	
$[Co(C_{19}H_{20}FNO_3 \cdot HCl)]$	< 250	23.04	3.128	1.111	5.29
$[Ni(C_{19}H_{20}FNO_3 \cdot HCl)]$	< 250	23.18	3.205	1.201	6.46

Biological activity
Synthesized paroxetin metal complexes were test for the microbial activity(sample 2). They were tested against the bacterial and fungal strain. For this study, Streptomycin is used as standard bacterial stain and Clotrimazole is used as standard fungal strain. These complexes were tested against two bacterial stains i.e. *Escherichia coli* and *Staphylococcus aureus.* In addition, *Candida albicans* and *Candida glabrata* used as fungal strain. After microbial evaluation it is found that the highest activity was reported with Ni(II) complexes with 26 mm growth inhibition for E. Coli and no activity was reported for S. aureus. Also, *C. albicans* shows the equal inhibitory activity with 13 mm and *C. glabrata* shows the highest inhibitory activity with 21 mm zone of inhibition..

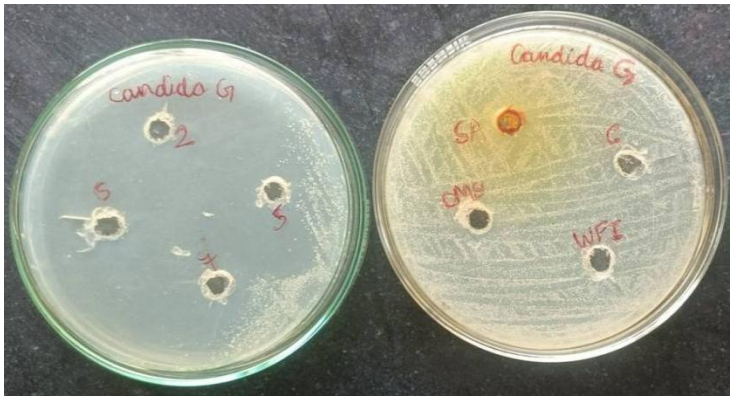
Strains	Zone of inhibition (mm)		
	PC	NC (DMSO)	Sample No 2
Bacterial	ST		
Escherichia coli	26	25	26
Staphylococcus aureus	10	0	0
Fungal	CT		
Candida albicans	10	13	13
Candida glabrata	0	0	21

PC: Positive control; ST: Streptomycin; CT: Clotrimazole; NC: Negative control

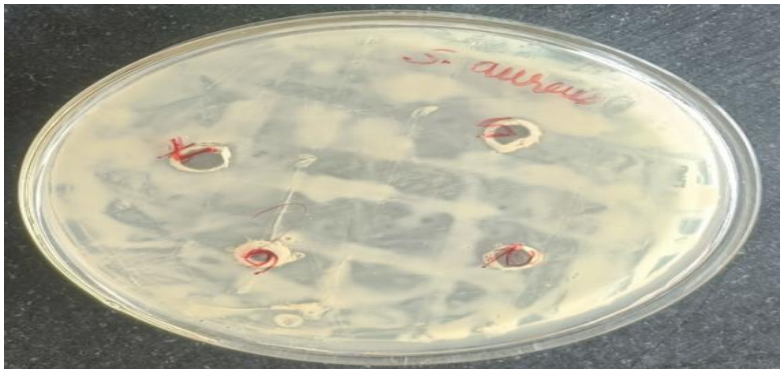
Escherichia coli:



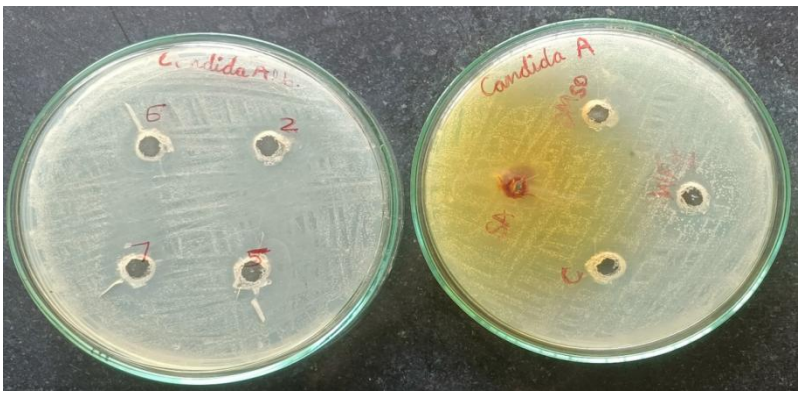
Candida albicans



Candia glabrata



S. aureus



Conclusion

Paroxetine metal complexes were successfully synthesized and characterized by IR, elemental analysis, magnetic susceptibility. From the IR spectra it is clear that metal binds with ligand through oxygen binding site. Magnetic moment 6.46 and 5.29 BM for Ni(II) and Co(II) complexes respectively suggesting that high spin octahedral geometry. From all the data, it is concluded that paroxetine metal complexes were synthesized and characterized successfully.

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