EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 7
Issue: 4
242-249
Year: 2020

ANTIBACTERIAL AND ANTIFUNGAL STUDY ON NOVEL $Ag^{(I)}$-15C5 COMPLEXES

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Article Received on 30/01/2020 **Article Revised on 20/02/2020** **Article Accepted on 10/03/2020**

ABSTRACT

Crown ether is a general name given to macrocyclic polyethers containing ethylene bridges separating electronegative oxygen atoms. They typically contain central electron rich hydrophilic cavity with diameter varying from 1.2-6.0 Å. Crown ethers have been used for the various studies pertaining to extraction equilibrium constant, stability constant and for determination of some of the alkali and alkaline earth elements and other elements from p, d and f-block elements. Crown ethers have a significant coordination power towards silver ion. The present paper describes synthesis, characterization and antimicrobial study of novel Ag(I) complexes synthesized by 15-crown-5 ether. The organic salts used for complexation were salts of nitrophenols. Products were isolated from silver salts of all the three nitrophenols, 2-nitrophenol(ONPH), 2,4-dinitrophenol(DNPH) and 2,4,6-trinitrophenol(TNPH), having general formula of [Ag.L](Pic^-), where L = 15C5 and Pic^- = Picrate anion. Elemental analysis, molar conductivity, UV-Vis, IR, and ^{1}H-NMR spectral analysis were performed for establishment of the structure of synthesized complexes. Antibacterial activities of the synthesized complexes were determined by using Kirby Bauer disc diffusion method. Antibacterial and antifungal activity of the prepared complexes were determined and recorded by zone inhibition method.

KEYWORDS: 15C5, ONPH, DNPH, TNPH.

INTRODUCTION

Crown ethers[1,2] have many applications in catalysis, organic synthesis, biochemistry, microbiology, and material science. Their applications in biology include, the ability to regulate enzyme activity, interact with DNA,[3] and act as antimicrobial agents. Simple crown compounds such as 15-crown-5 and 18-crown-6 have the ability to interact with enzymes.[4] This interaction increases the activity of enzymes when used in organic solvents.[5] Numerous enzymes experience increased activity from the presence of crown ethers.[6-8] Crown ethers principally interact with lysine ammonium groups. These complexes inhibit the formation salt bridges, forming a more thermodynamically stable and catalytically active enzyme. Crown ether compounds have been designed and synthesized to interact with DNA.[9] Crowns may be synthesized to inhibit cell proliferation, and new systems are being exploited to kill microbial organisms. The interest in crown ethers in both biological science and industry is growing.[10] Five types of pathogenic bacteria and one fungi were used in this work which includes four gram positive bacteria, staphylococcus aureus, E. faecalis, lactobacillus, B. subtilis; one gram negative bacteria Escherichia coli and one fungi C. albicans. All the used ligands showed very small activity against the tested bacteria and fungi while all the prepared complexes showed very good results. Table shows the inhibition zones of the ligands and the prepared complexes. All the prepared complexes gave good inhibition zones. These fungi and bacteria are known for its resistance to most of the developed antibiotics and is known to be the major cause of many health issues and infections.[11-13]

Coordination chemistry of macrocyclic ligands with silver ion has been a fascinating area of current research interest to the modern chemists all over the world.[14-15] Interest and quest in designing new macrocyclic ligands is due to their potential use in biological systems: as synthetic ionophores, as therapeutic reagents for the treatment of metal intoxication, as cyclic antibiotics, to study the biological guest-host interactions, in solvent extraction and in catalysis.[16-22]

MATERIALS AND METHODS

The nitrophenols and crown ethers used were of E. Merck and S. Aldrich respectively. The commercially available regents of AR grade were used without further purification. Results of elemental analysis of synthesized compounds agreed with required value within experimental error. IR spectra were recorded by Perkin Elmer RX1 (4000-450 cm^{-1}) at SAIF-CDRI. UV-visible spectral data were recorded through Systronic double beam spectrophotometer-2203 (600-200 nm). The ^1H−NMR spectra of ligands and synthesized complexes were recorded in $CDCl_3$ by Bruker DRX-300 at SAIF-CDRI.

EXPERIMENTAL

Preparation of silver salt of nitrophenols; Ag(ONP), Ag(DNP) and Ag(TNP)

About 4 mmol(0.644 gm) of sodium salt of 2-nitrophenol was taken in a conical flask and 25 ml of 95% ($^V/_V$) ethanol was added to it. The ethanolic solution of sodium salt of 2-nitrophenol was heated on a water bath and continuously shaken till gets completely dissolved and the solution becomes homogeneous. Then, 4 mmol of $AgNO_3$ (0.68 gm) was dissolved in 25 ml of 95% ($^V/_V$) ethanol and continuously shaken till the silver nitrate gets completely dissolved. The freshly prepared ethanolic solution of silver nitrate was slowly added to the ethanolic solution of sodium salt of 2-nitrophenol and continuously shaken. On adding the ethanolic solution of silver nitrate, brownish orange coloured silver salt of 2-nitrophenol (AgONP) precipitated out.[23] The mixture was continuously stirred on hot plate equipped with magnetic stirrer for 45 minutes to ensure complete precipitation.

Similarly, silver salt of 2,4-dinitrophenol(AgDNP), and 2,4,6-trinitrophenol (AgTNP) were prepared by taking 4 mmol of appropriate sodium salt and using the above described procedure. Some physical properties of synthesized silver salts are given in table-1.

Table 1: Physical properties of silver salts.

Compound	Colour	Melting point (^0C)	% Nitrogen
AgONP	Brownish orange	270^d	5.69
AgDNP	Yellow	265^d	9.62
AgTNP	Yellowish Brown	245^e	12.51

d – decomposition temp, e – explosion temp

Preparation of adducts of 15-crown-5 ether with silver salts of 2-nitrophenol, 2,4-dinitrophenol and 2,4,6-trinitrophenol

The dried organic salt (0.002 mol) was suspended in 50 ml dry methanol and heated it with constant stirring to get a clear solution. Stoichiometric proportion of 15-crown-5 ether (0.002 mol) was added in that and then the reaction mixture was refluxed in an inert medium on a hot plate equipped with magnetic stirrer at 50-55^{0}C. A clear solution was formed. It was filtered and concentrated to half of its bulk. On cooling this solution, solid crystalline product began to precipitate. The product was separated out and allowed to stand overnight then filtered on a buchner funnel. The compound was washed with few drops of dry methanol and dried over KOH desiccator.

15C5.Ag(ONP) : $C_{16}H_{24}NO_8Ag$
15C5.Ag(DNP) : $C_{16}H_{23}N_2O_{10}Ag$
15C5.Ag(TNP) : $C_{16}H_{22}N_3O_{12}Ag$

Table 2: Percentage composition of silver-crown ether complexes.

Compound	% C	% N	% O	% Ag
15C5.Ag(ONP)	42.36	2.74	28.22	21.13
15C5.Ag(DNP)	38.93	5.04	31.69	19.42
15C5.Ag(TNP)	36.01	7.00	34.65	17.96

RESULT AND DISCUSSION

UV-Visible study

Electronic absorption spectra of synthesized compounds provide small but significant evidence of bonding in complexes. Saturated crown ethers do not show any absorption above 220 nm. The electronic spectral studies of synthesized complexes shows only some deviation of π - π^*, n - π^*, σ - π^* and σ - σ^* transitions due to shifting of electron density from donor atoms to cationic species. The slight change in spectral band position is usually taken as either solvent effect or interaction of electron cloud of donor atom of ligand with silver ion. The bond energy in organic compound possess energy equivalent to absorption energy of ultraviolet or visible radiation as they form bonds by ion-dipole interactions and/or involvement of non-bonding electrons with central metal ions.[24-26] The n - σ^* transition of phenolic (C–O) group is observed at high energy and phenyl ring π - π^*, σ - σ^* transitions between 180–250 nm region. The antibonding orbitals σ^* and π^* are quantized energy level of higher energies. Besides bonding electronic transitions, intermolecular transition known as charge transfers (C–T) transitions of high intensity are usually observed in dyes and coordination complexes.[27]

FTIR study

The infrared spectra of aromatic as well as aliphatic crown ether shows the presence of ether linkages by a strong broad band around 1230 cm^{-1} for aromatic-O-aliphatic and a band at 1100 cm^{-1} for aliphatic-O-aliphatic group. The 15C5 crown ethers in uncoordinated state display ν(C–O–C) stretching vibration band near 1100±22 cm^{-1}. This ν(C–O–C) vibration band shifted to lower frequency by 10-15 cm^{-1} in almost all complexes suggesting crown ether's oxygen interaction with silver ion.[28] The ν(O–H) stretching vibration in almost all nitrophenols are observed as very broad and medium band in the region 3150–3320 cm^{-1} which almost disappears in their salts. The disappearance of ν(O–H) band suggests bonding of phenolic oxygen with metal ions on deprotonation of phenolic –OH group. The ν(C–O) band shifts to higher frequency due to acquiring higher (C–O) bond order on deprotonation in silver metal salts. This increase is attributed to bonding of phenolic oxygens (C–O) in all complexes. The stretching bands of $–NO_2$ in AgONP, AgDNP and AgTNP are at around 1605 cm^{-1}, 1618±5 cm^{-1} and 1642±5cm^{-1}. These bands shifted to lower frequency in complexes. The $\nu(NO_2)$ located near 845±10 cm^{-1} also shifted to the lower vibrational frequency in the complexes. The FTIR band observed near 740–780 cm^{-1} is attributed to phenyl ring ν(C–H) out of plane bending vibration. The 15-crown-5 ether display $\nu(–CH_2–)$ stretching vibrations at 2920±10 cm^{-1} and these are little affected on bonding with silver ion in complexes. Some hygroscopic complexes in their FTIR spectrum displays a broad band around 3352–3420 cm^{-1}, with maxima near 3405±10 cm^{-1}.[29,30] In the far-IR region new bands, absent in the spectrum of the free ligands, are found in the 470–590 cm^{-1} region, which may be assigned to the $\nu(Ag–O_{crown})$ stretching frequency.[31-33] Some FTIR-spectrum of the synthesized complexes are shown in figure 1.1–1.3. Since nature of FTIR peaks are almost similar thus, spectrum of only three complexes, $[Ag^+.15C5](ONP^–)$, $[Ag^+.15C5](DNP^–)$ and $[Ag^+.15C5](TNP^–)$ are shown. Thus FTIR studies of the complexes also suggest bonding of silver salt of nitrophenols with crown ether oxygen atoms.

^{1}H-NMR Study

Information on some crown ether interactions leading to supramolecule formation is available from detailed measurements of the chemical shift variations of protons of the crown ethers as a function of the concentration of the silver-metal ion with the crown ether.[34] The conformation and the binding of small-ring dibenzo crown ethers with small cations in solution have been previously investigated.[35] The ^{1}H-NMR study of synthesized crown ether complexes provides useful information regarding structure of complexes.[36] The chemical shift of proton in 15C5 (figure 2) shows solvent dependent chemical shift and feels noticeable shifts change upon complexation. After formation of the complex $[Ag.L](Pic^-)$, the ethereal proton chemical shift $\delta(–CH_2–O–)$ shows downfield shift $[\Delta\delta(–CH_2–O–)]$ by 0.08–0.25 ppm, showing metal-crown ether bond formation.[37-39] The relative change in the downfield shift shows the relative strength of the synthesized complexes.[40,41] In all cases, the exchange between free and complexed crown was fast on the ^{1}H-NMR time scale and only a single population average ^{1}H-signal was observed. The ^{1}H-NMR spectrum of 15C5 shows peaks at, δ(1H)=3.920–3.926 (20H, 5 $–CH_2CH_2O–$), in $CDCl_3$. The shift of $–CH_2–$ signals in complexes from free crown ether suggested the coordination of crown ether oxygen of 15C5[42] with silver ion.[43-45] One ^{1}H-NMR spectrum of the synthesized complex along with 15C5 are shown in figure 3. Since the nature of ^{1}H-NMR peaks are almost similar thus, spectrum of only one compound is shown. Figure-4 shows proposed structures of complexes $[M^+.L](Pic^–)$, where M = Ag^+, L = 15C5 and OX = $ONP^–$/ $DNP^–$/$TNP^–$ based on all reported evidences.

Antibacterial and antifungal activity of the prepared complexes

Crown ethers have many applications in catalysis, organic synthesis, biochemistry, microbiology, and material science. Their applications in biology include the ability to regulate enzyme activity, interact with DNA, and act as antimicrobial agents. Simple crown compounds such as 18-crown-6 and 15-crown-5 have the ability to interact with enzymes.

Antimicrobial test was performed using Kirby Bauer disc diffusion method.[46,47] Five bacterial isolates, Escherichia coli, Staphylococcus aureus, E. faecalis, B-Subtilis, Lactobacillus and one fungal isolate of C. albicans were used in this work. The isolates were planted on the surface of an agar on petriplates incubated at 37°C for 24 hrs and stored at 4°C for the later use. Sterile filter paper dishes are placed in 4-5 places on the petriplates. The test compound was then added at the centre of each paper. The plates are inverted and then incubated for 16 hrs. After incubation depending on the strain and chemical complex inhibition zones were developed around each test sample. The diameter of the zone of inhibition around each disc was measured to the nearest millimeter.[48,49] Controlled experiments were performed and only equivalent volume of solvents were added and applied on the paper discs. The antimicrobial activities were expressed as minimum inhibitory concentration (MICS) values[50,51] corresponding to the lowest concentration of the compound that produces a measureable zone of inhibition. All the used ligands showed very less activity against the tested bacteria and fungi while all the prepared complexes showed very good results. Table shows the inhibition zones of the prepared complexes. All the prepared complexes gave good inhibition zones. Results of antimicrobial tests of synthesized complexes are listed in table-3.

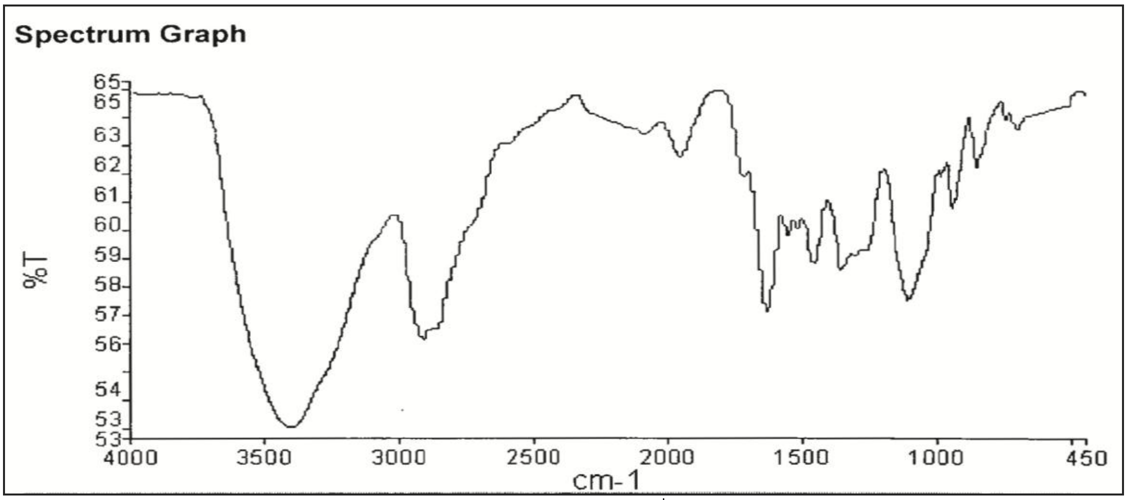

Fig. 1.1: FTIR Spectrum of [Ag^+.15C5](ONP^-).

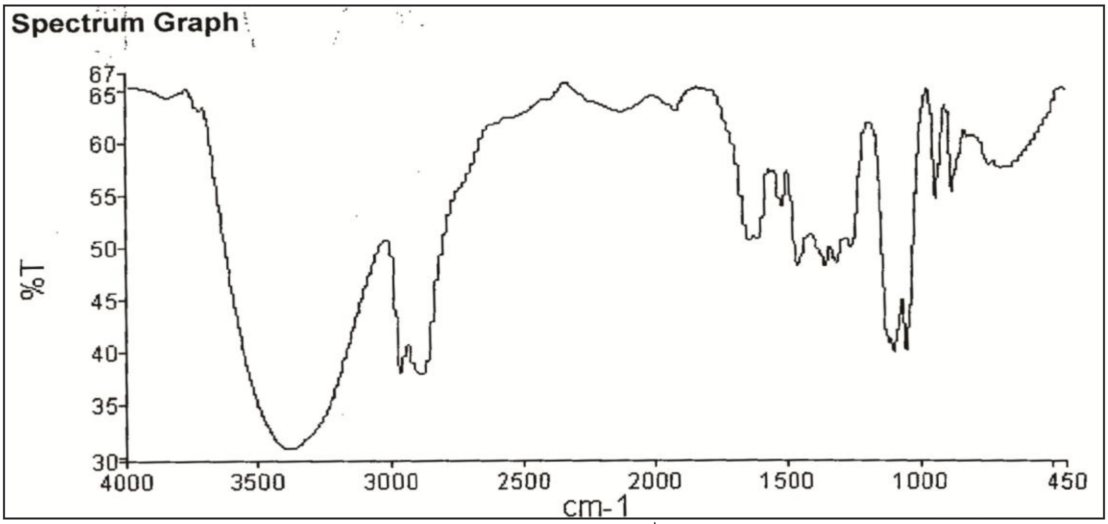

Fig. 1.2: FTIR Spectrum of [Ag^+.15C5](DNP^-).

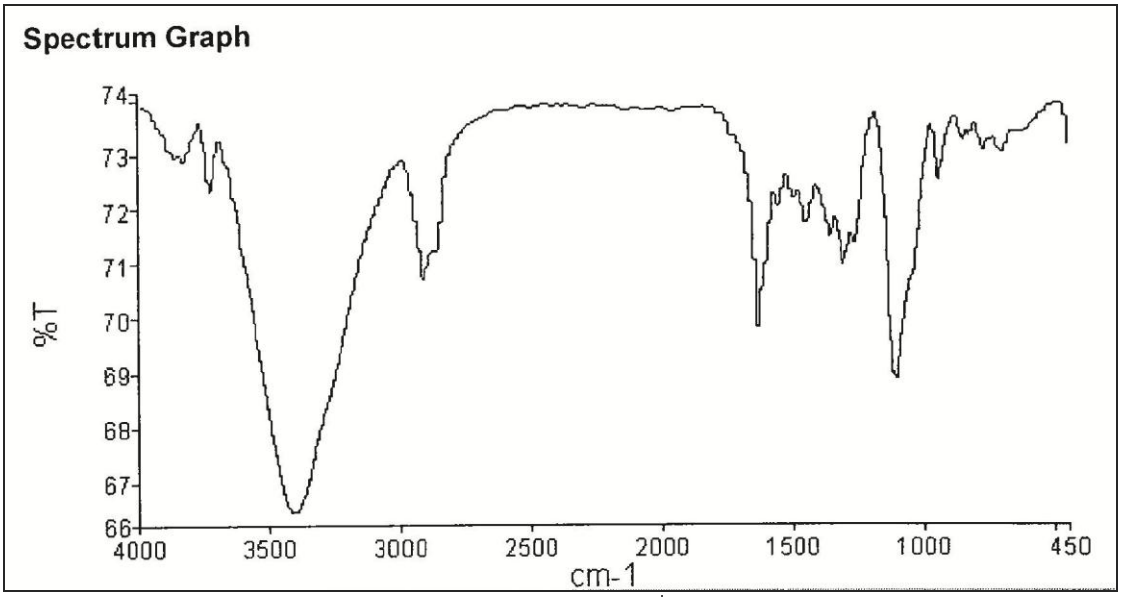

Fig. 1.3: FTIR Spectrum of [Ag^+.15C5](TNP^-).

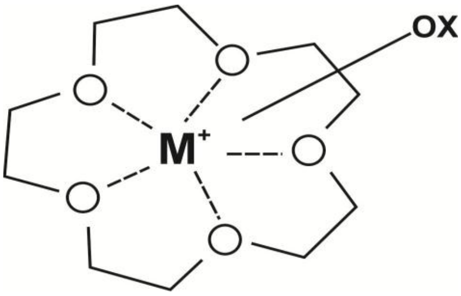

Fig. 3: Proposed structures of complexes [M^+.L](Pic^-), where M = Ag^+, L = 15C5 and OX = ONP^-/ DNP^-/ TNP^-.

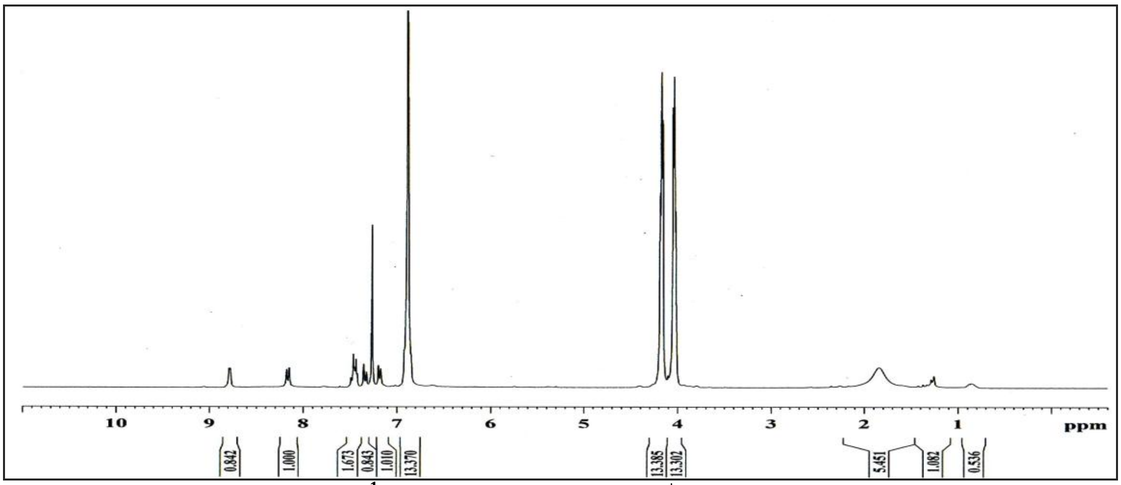

Fig. 2: ^{1}H-NMR Spectrum of [Ag^+.15C5](TNP^-).

Table 3: Prominent FTIR bands of silver-crown ether complexes (in cm^{-1})

Compound	ν_s(C-O-C)	ν_1(-NO_2), ν_3(-NO_2)	ν_s(C-H)bending ν_{as}(-CH_2-)bending
AgONP15	1102.76	1632.53, 833.28	1454.68, 1355.74
AgDNP15	1093.54	1645.09, 879.94	1454.01, 1357.12
AgTNP15	1099.12	1633.89, 870.01	1452.05, 1303.52

Table 4: Prominent FTIR bands of silver-crown ether complexes (in cm^{-1}).

Compound	ν(M-O) / ν(M-O_{crown})	ν (N=O)$_{str}$ in C-NO_2
AgONP15	480	1250
AgDNP15	510, 525	1257.16
AgTNP15	470, 598	1280

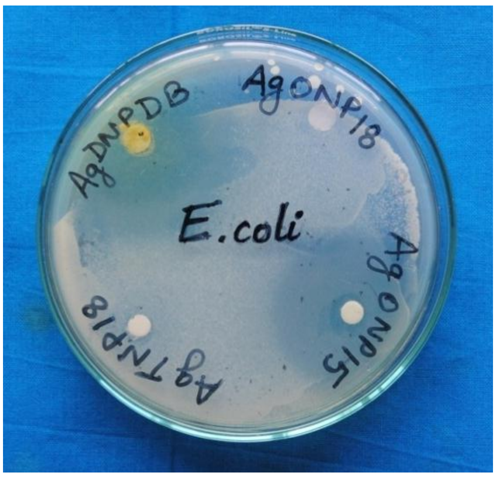

Fig. 4.1: Microbial study against E. coli.

Fig. 4.2: Microbial study against E. coli.

Fig. 5: Microbial study against Lactobacillus.

Fig. 5: Microbial study against S. aureus.

Table 3: Zone of inhibition along the diameter.

Samples	E. coli (gram -ve)	Lactobacillus (gram +ve)	S. aureus (gram +ve)	E. coli (gram -ve)	Lactobacillus (gram +ve)	S. aureus (gram +ve)
AgONP15	30 mm	6 mm	6 mm	24 mm	8 mm	6 mm
AgDNP15	34 mm	30 mm	6 mm	28 mm	6 mm	14 mm
AgTNP15	6 mm	6 mm	6 mm	6 mm	6 mm	18 mm

ACKNOWLEDGEMENT

We are thankful to the Head, SAIF, CDRI, Lukhnow, for providing FTIR-spectra, [1]H-NMR spectra and necessary facilities.

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