Chemical Science Review and Letters ISSN 2278-6783

Research Article

Synthesis, Spectroscopic Characterization and Antimicrobial Screening of Aluminium(III) porphyrin Complexes containing Substituted Salicylates

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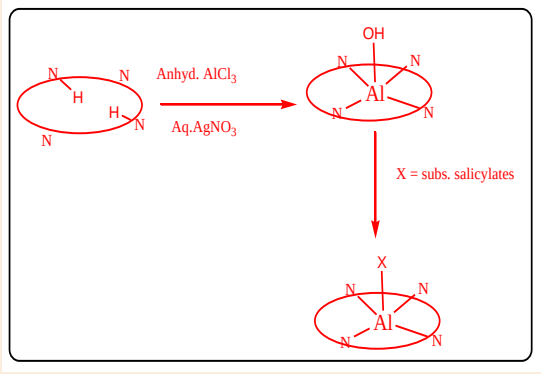
Abstract

A series of aluminium(III)meso-tetraphenylporphyrin(TPP-Al(III)) containing axially coordinated salicylate anion [TPP-Al-X)], where X=salicylate(SA), 4-Chlorosalicylate(4-CSA), 5-Chlorosalicylate(5-CSA), 5-Flourosalicylate(5-FSA), 4-Aminosalicylate(4-ASA), 5-Aminosalicylate(5-ASA), 5-Nitrosalicylate(5-NSA) and 5-sulfosalicylate(5-SSA)] have been synthesized and characterized by various spectroscopic techniques including ultraviolet-visible(UV-Vis), infrared(IR) spectroscopy, proton nuclear magnetic resonance (^{1}H NMR) spectroscopy, ^{27}Al, ^{19}F, ^{13}C NMR and Mass studies. The complexes were also screened for their bacterial activity.

Keywords: meso-tetraphenylporphyrin(TPP); Salicylic acid; Substituted salicylic acid; Biological activity



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Introduction

Salicylic acid (SA) and its derivatives are biologically important ligands. These are widespread in nature and are of considerable relevance in medicinal chemistry [1, 2]. Its well known and most widely used drug aspirin reduces the risk of many diseases associated with aging and is also used in the treatment of rheumatic fever, pain and for the prevention of thrombosis in the vascular system. In the search of literature, it was revealed that there are many studies which deal with salicylic acid complexes of various metal ions [3-14] but only few examples of metalloporphyrins coordinated to salicylic acid derivatives were seen. As far as aluminium is concerned being a non-essential metal, it may be involved in the action of enzymes such as succinic dehydrogenase and d-aminolevulinate dehydrase (involved in porphyrin synthesis). Moreover aluminium hydroxide is used as an antacid in the treatment of gastric ulcers and as a phosphate binder in cases of long-standing renal failure. Also, aluminium compounds are used in antiperspirants, antiseptics solutions and as adjuvant in vaccines.

Considering all these biological applications of salicylic acid derivatives, aluminium and tetraphenyl porphyrin, we have synthesized and characterized aluminium(III)-meso-tetraphenylporphyrins (TPP-Al-X) complexes axially bonded to substituted salicylate anions and screened all these synthesized compounds for their antibacterial activity.

Experimental

Materials and Instruments

Pyrrole (Fluka, Switzerland) was distilled over KOH pellets under reduced pressure before use. Benzaldehyde was procured from Aldrich, USA. Anhydrous sodium sulphate (Na_2SO_4) was procured from Ranbaxy Labs. Ltd. (India). Anhydrous aluminium (III)chloride, Benzonitrile and various salicylic acid were purchased from Alfa Asear, Japan.

Benzonitrile was dried and vacuum distilled before use. The optical absorption spectrum of the compounds was recorded on a T90+ UV/VIS spectrophotometer using a pair of matched quartz cells of 10mm path length at an ambient temperature. The ^{1}H NMR ^{13}C NMR, ^{19}F NMR spectra were recorded on a Bruker Avance III (400 MHz) in Deutrated DMSO using tetramethylsilane as an internal standard. IR spectra were recorded in the Department of Chemistry, University of Jammu on Shimadzu spectrophotometer. Mass spectra were recorded on Bruker Daltonics spectrophotometer and the spectra were recorded at room temperature using methanol as solvent, from Indian Institute of Integrative Medicine (IIIM) Jammu.

Antibacterial Activity

Qualitative screening of the synthesized complexes for antibacterial activity was carried out by agar well diffusion assay against seven different Gram positive and Gram negative strains (9). Bacterial strains used are *Bacillus Klebsiella pneumoniae cereus, Bacillus subtilis, Alcalygenes denitrifican, Staphylococcus aureus, Klebsiella pneumoniae, Micrococcus luteus and Campylobactor coli*. Sterilized nutrient agar (20ml) was inoculated with 100µl bacterial suspension (10^8 CFU/ml) and poured into a sterilized petriplates. Plates were allowed to solidify and a well of 6mm was aseptically bored into the agar plate by using a cork borer. Axially ligated aluminium(III)complexes were added into each well. Finally the plates were kept for incubation at 37°C for 24h. Chloramphenicol(10µg) was used as positive reference.

Synthesis of Complexes
meso-tetraphenylporphyrin [TPP]

The metal free-base H_2TPP was synthesized by the conventional method of condensation of benzaldehyde with pyrrole by modified Adler method [15]. The purified porphyrin was obtained in ›20% yields. (UV-Vis spectra: λ_{max},(nm) in $CHCl_3$ 418, 515, 548, 590, 646.

meso-(tetraphenylporphinato)aluminium(III)chloride [TPP-Al-Cl]

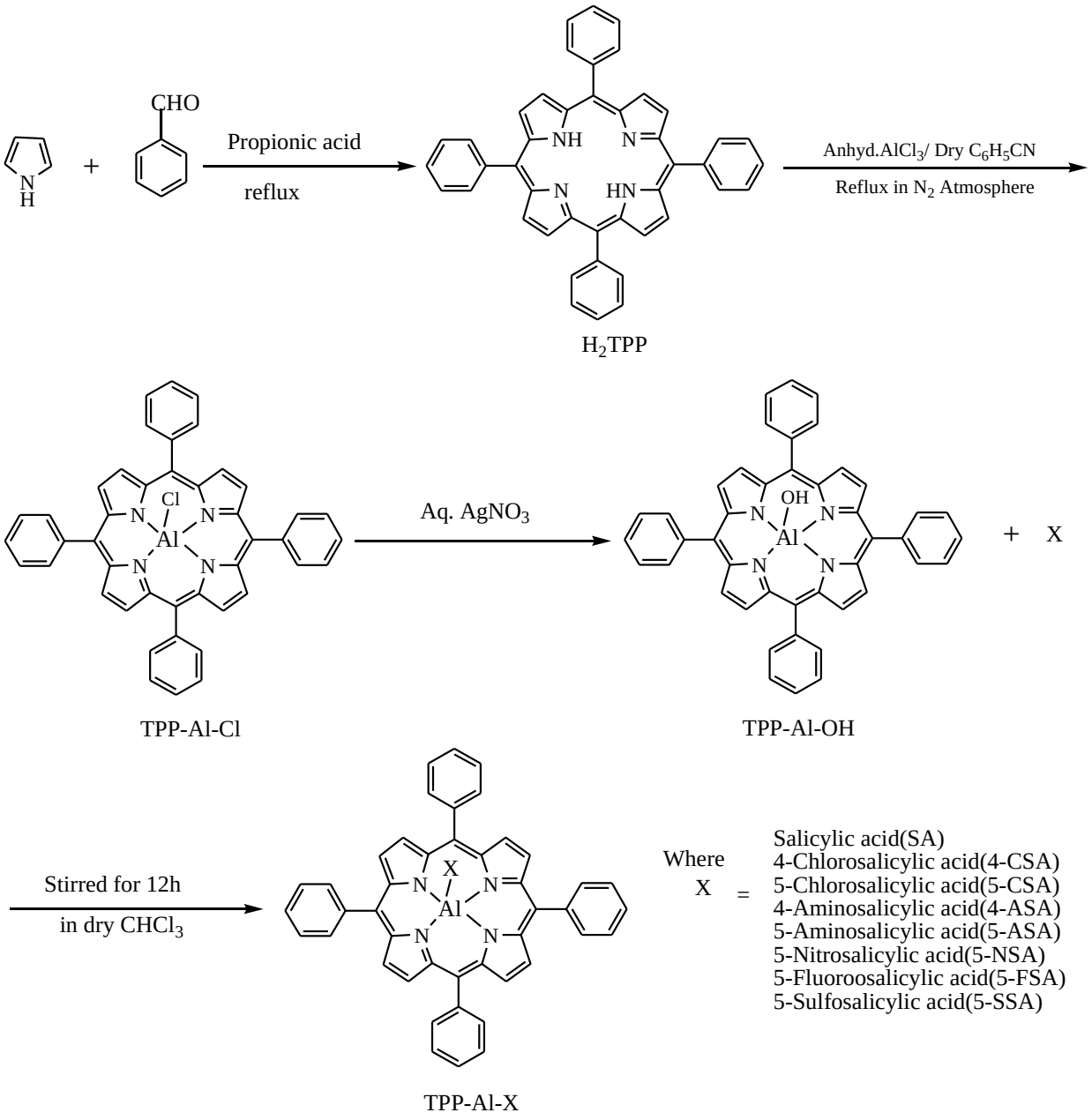
H_2TPP (0.1g) was refluxed with anhydrous $AlCl_3$ (0.1g) in dry benzonitrile (16ml) for 1-3hrs. The reaction course was monitored by absorption spectra of the reaction mixture. The refluxing was stopped when the absorption bands of H_2TPP disappeared. The reaction mixture was filtered to remove the presence of excess $AlCl_3$. To the filtrate excess hexane was added for complete precipitation of the complex. The precipitates were washed with hexane and dissolved in methanol. A 3N HCl solution was added to precipitate the complex which was then recrystallized from the solution of acetone and hexane. Reddish purple crystals thus obtained were of TPP-Al-Cl. $4H_2O$. More reddish crystals of TPP-Al-Cl.H_2O were obtained by drying TPP-Al-Cl. $4H_2O$ at 110-120°C for 2hrs.

Meso-(tetraphenylporphinato)aluminium(III)hydroxide [TPP-Al-OH]

TPP-Al-Cl.H_2O (0.1 mg) was dissolved in a mixture of $CHCl_3$ and MeOH in 10:1 ratio. The solution was shaken with 0.1% $AgNO_3$ solution and the $CHCl_3$ layer was separated. The process was repeated until no further precipitates of AgCl separated out. Finally, the solution was passed through Na_2SO_4 and dried to obtain purple crystals of TPP-Al-OH.

Axially coordinated meso-(tetraphenylporphyrinato)aluminium(III)-salicylate [TPP-Al-X]

To a solution of 5,10,15,20-tetraphenylporphyrinaluminium(III)hydroxide (0.020g, 0.03mmol) in 10ml $CHCl_3$ was added , as a solid, 5 equiv. of salicylic acid (SA) (0.15nmol). The resulting solution was stirred at room temperature for 12 h, at which time it was filtered to remove excess acid. The solution was evaporated to yield purple colored complex(92%). Similar procedure was followed with all other substituted salicylic acids. The purified axially ligated aluminium porphyrin complexes were obtained in yields of 80-85% (**Scheme 1**).



Scheme 1 General Synthetic route for the synthesis of axially coordinated meso-(tetraphenylporphyrinato) aluminium(III) salicylate [X-Al-TPP]

Results and Discussion

^{1}H NMR

^{1}H NMR spectra of all the synthesized complexes were recorded in DMSO. The resonance positions and the morphology of the of porphyrin ring protons are similar to those of other metalloporphyrins. The presence of axially ligated Al(III) metal in the porphyrins ring results in the shift of the β-resonance to the downfield accompanied by marginal changes in the pattern where as the signals of axial ligand protons are shifted to higher field in comparison to the signals of Porphyrin-protons.

The ^{1}H NMR spectra of 5-SSA-Al-TPP showed two double signals at 6.98 and 7.01 ppm and the singlet at 7.8 ppm for protons 3, 4 and 6 of the axial ligand, respectively. The singlet at 9.1ppm is assigned as H_{β}, the singlet at 8.8 ppm is assigned as ortho $H_{o,}$ another singlet at 7.8ppm is assigned as meta H_{m} and multiplet at 8.2 ppm is assigned as para H_{p} on meso-aryl group. Similar results are observed in case of other complexes also with slight variation resulting from the presence of electron donating and electron withdrawing groups present on the axial ligand. In case of electron-donating groups such as chloro, amino the resonances are shifted up field whereas in case of electron withdrawing groups such as fluoro, nitro and sulfo the resonances are shifted downfield.

Aluminium-27(^{27}Al NMR) Spectroscopy

It has been known that the signals of ^{27}Al NMR are observed in different regions of chemical shifts depending on the coordination number of the aluminium atom. Benn et al studied the ^{27}Al NMR of 50 aluminium compounds and their adducts with base, and found an experimental rule that 4-coordinated Al shows its chemical shift (δ / ppm) signal between 180 ppm and 125 ppm (relative to $Al(NO_3)_3$ in D_2O); for instance(δ) 153 ppm for $(Me_3Al)_2$ and (δ)182 ppm for $Me_3Al(THF)$.On the other hand, $AlCl_3(THF)_2$ shows its signal at (δ) 63.0 ppm in CH_2Cl_2/THF. Also, Koester et al reported another example i.e., $Cl_2AlOXOAl(Cl)OXOAlCl_2$ [X=B(Ph)OB(Ph)], in which central Al atom is 5-coordinated by four oxygen atoms and one Chlorine atom, showing its ^{27}Al NMR signal at(δ) 43 ppm in toluene-*d8*. Koester's complex is unique in the respect that the central Al atom is tetragonal pyramidal in the structure determined by the X-ray diffraction analysis. These examples shows that the chemical shift(δ) in ^{27}Al NMR do not always correspond to the coordination number of Aluminium atom, but Aluminium complexes of similar structures show their signals in a similar region. It was strongly suggested that between capped Aluminium(III)-meso-tetraphenyl porphyrin [(capP)] and Aluminium(III)-meso-tetraphenylporphyrin [Al(TPP)], no great difference in their mode of ligand coordination exist. In case of axially ligated aluminium(III) complexes, ^{27}Al NMR spectra of 5-CSA-Al-TPP was recorded and exhibit a sharp peak at 73.69 ppm.

^{19} F NMR

Fluorine -19 NMR has been extremely helpful in ascertaining both the identity and purity of the compound. The 100% natural abundance of spin ½ 19F and its high gyromagnetic ratio allow ^{19}F NMR spectra to be obtained readily. Since the complex 5-FSA-Al-TPP contains single fluorine atom, so single peak without any splitting is observed at -126.845 ppm.(**Figure 1**)

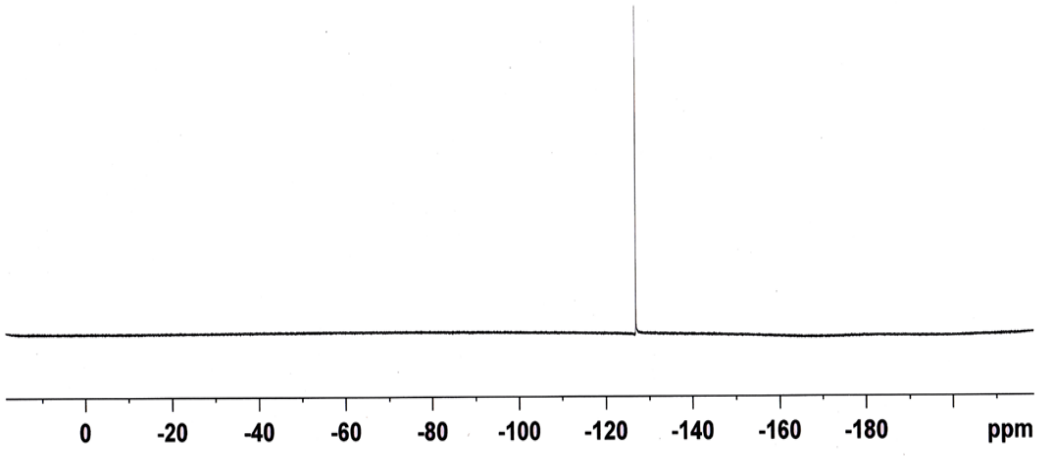


Figure 1 ^{19}F NMR spectra of 5-FSA-Al-TPP

^{13}C NMR

^{13}C NMR signals are spread in a 200 ppm region. Two major groups for carbon frequencies were distinguished by the performance of ^{13}C NMR. The aromatic carbons of meso-tetraphenylporphyrin ring resonate between 130-170 ppm and the methinic carbons in the region of 90-120 ppm.[1] The ^{13}C NMR spectra of axially ligated complex of aluminium(III) porphyrin i.e. 5-SSA-Al-TPP, display signals at 126.77 ppm corresponding to C_{meso}. Similarly, signals observed at 147.84 ppm for $C_{\alpha,}$ 128.77, 131.97, 132.72, 134.08, 141.96 ppm for porphine core and aryl rings shifted downfield in comparison with the corresponding signals of the ligand. Also, the carbons of the salicylate group has resonances 111.789, 163.14, 115.76, 133.60, 116.80, 131.97 and 171.58 ppm for C_1, $C_{2,}$ $C_{,3,}$ C_4 , $C_{,5}$, C_6 and COO respectively. The chemical data does not present any unexpected information in respect to other metalloporphyrinic derivatives.

Infra-red spectroscopy

The IR spectra of all synthesized complexes exhibit vibrational bands typical of the porphyrin ligand. Two moderately strong absorptions in the far-IR region at 350–250 cm^{-1} assigned to the symmetric and antisymmetric M–Cl modes are absent. In the IR spectrum of the complex 5-CSA-Al-TPP, (Al-O) and Al-N bands are observed at 528.33 and 72527 cm^{-1}. The absorptions assigned to the stretching vibration -(C=O) occur at 1720–1700 cm^{-1}, -(C–O) at 1220–1200 cm^{-1} and -(O–H) at 3600–3550 cm^{-1} appear. For 5-SSA-Al-TPP**,** bands of the SO_2 group are present at 1250–1160 cm^{-1} (as(SO_2)) and 1035–995 cm^{-1} (sym(SO_2)), and the triplet of the stretching vibrations (S–O) is at 670–570 cm^{-1}. Characteristic IR absorption bands of symmetric and asymmetric stretching vibrations of the C–O bond of the carboxylate group bonded to the central metal ion are in the range 1640–1430 cm^{-1}.

Absorption Spectroscopy

The electronic absorption spectra of aquo-meso-tetra-phenyl porphyrinatoaluminium(III) [(OH)(H_2O)AlTPP] shows bands at 404.0, 425.0, 516.0, 556.0, 569.0 nm. As a consequence of the coordination of aluminium(III) ion, both the Soret bands (at 350 nm - 450 nm) and the Q bands (at 500 nm - 700 nm) were found to be red-shifted in all compounds. The red shift of absorption can be attributed to that the metal orbitals are closer in energy to the antibonding π^* molecular orbitals (lowest unoccupied molecular orbitals, LUMOs) than to the bonding orbitals (highest occupied molecular orbital, HOMO) of porphyrin, so that the perturbation they cause decreases the energy of the LUMOs more than that of the HOMO, resulting in the bathochromic effect of $\pi \rightarrow \pi^*$ transitions. Not only metallation of the free base porphyrin but also axial coordination is accompanied by red shifts of the characteristic absorption bands. Thus, it is clear that [(OH)(H_2O)AlTPP] shows bathochromic shift when compared to the respective free-base porphyrin (H_2TPP) due to the incorporation of metal ion in the porphyrin ring. On the other hand the axially ligated metalloporphyrin undergoes changes in both the wavelength and relative intensities of the absorption bands as compared to the respective metalloporphyrin.

Table 1 Optical Absorption data of axially ligated aluminium(III) porphyrin in $CHCl_3$

Porphyrins	**λ_{max}, nm**		
	B(0,0)	Q(1,0)	Q(0,0)
SA- Al-TPP	427.00	562.00	602.00
4-CSA – Al-TPP	428.00	564.00	604.00
5-CSA- Al-TPP	428.00	570.00	605.00
4-ASA- Al-TPP	426.00	559.00	596.00
5-ASA- Al-TPP	426.00	566.00	609.00
5-FSA- Al-TPP	423.00	556.00	599.00

5-NSA- Al-TPP	422.00	554.00	593.00
5-SSA- Al-TPP	422.00	555.00	600.00

It is observed that the Soret bands and the visible bands of axially ligated Al(III) porphyrin with different salicylates are red shifted as compared to the respective [(OH)Al(III)TPP] (**Table 1**).

Mass Spectroscopy

The mass spectra axially ligated Al(III) metalloderivatives have been obtained by mass spectroscopy technique. The mass spectra of these complexes show molecular ion peak which is in good agreement with the structure suggested by various spectroscopic studies. The mass spectrum of SA-Al-TPP shows the molecular ion peak(m/z) at 779.35 ($C_{51}H_{33}AlN_4O_3$; calc.= 776.24).

Antibacterial Studies

The results of antibacterial activity of the complexes are depicted in **Table 2.** All the complexes were examined by agar well diffusion assay against various bacterial strains and inhibitory activity was determined by zone of inhibiion. All the complexes except 5-SSA-Al-TPP showed potential inhibitory activity against *Campylobactor coli* i.e SA-Al-TPP(15 mm), 5-CSA-Al-TPP(14 mm) 5-ASA-Al-TPP(12.5 mm), 5-FSA-Al-TPP(21 mm) 5-NSA-Al-TPP(12 mm).

Table 2 *In vitro* antibacterial evaluation of free base porphyrin and the corresponding aluminium(III) porphyrin complexes.

S. No.	**Bacterial Strain**	**SA-Al-TPP**	**5-CSA-Al-TPP**	**5-ASA-Al-TPP**	**5-FSA-Al-TPP**	**5-NSA-Al-TPP**	**5-SSA-Al-TPP**	***Control***
1.	*Bacillus cereus*	-	-	-	9	-	-	21
2.	*Bacillus subtilis*	7	12	7	-	-	-	23
3.	*Alcalygenes denitrifican*	13	11	11	8.5	10.6	-	19
4.	*Staphylococcus aureus*	10	6.5	8.5	9.5	10	-	16
5.	*Klebsiella pneumonia*	-	9.5	8.2	8	19	-	22
6.	*Micrococcus leuteus*	-	-	-	75	-	-	23
7.	*Campylobactor coli*	15	14	12.5	21	12	-	17.5

Control Used : Chloramphenicol (antibiotic)

Conclusion

In this article, we have described the synthesis of free base porphyrin and their subsequent reactions with Anhy.$AlCl_3$ and salicylic acid derivatives so as to get axially ligated Al(III) porphyrins. The structures of above porphyrin compounds were characterized by UV-Vis, IR, ^{1}H NMR, ^{13}C NMR and elemental analysis. In axially ligated aluminium(III) porphyrin complexes, bands showed slight red shift corresponding to the structural distortion in the porphyrin macrocycle, and concomitant electronic coupling of the metalloporphyrin to the salicylate mediated by the

aluminium metal ion. The Infra-red spectra of these compounds showed that salicylate groups axially ligated to aluminium(III) porphyrins to form five-coordinate complexes of Al(III) porphyrins. Additionally, the ^{1}H NMR spectral study of these compounds showed that signals of axial ligand protons are shifted to higher field in comparison to the signals of porphyrin protons. The mass spectroscopy provided the information regarding the appearance of the molecular ion peak (m/z).

Acknowledgement

The authors would like to thank University Grants Commisssion for financially supporting this work sanctioned vide F.No.41-242/2012 (SR) dated 13 Jul 2012.

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Publication History
Received 01st Nov 2014
Revised 19th Nov 2014
Accepted 12th Dec 2014
Online 30th Dec 2014