Synopsis

This thesis is divided into two parts: Part-A and Part-B. Part-A deals with (a) novel bismuth pyridine-carboxylates (coordination polymers and monomeric/dimeric structures) using bismuth nitrate or ammonium bismuth citrate, (b) phenylbismuth heterocyclic carboxylates using BiPh$_3^-$ secondary bonding interactions in the products, and (c) synthesis and characterization of BiVO$_4$. In Part-B, (a) synthesis and structural characterisation of lanthanide oxopyridinium/dipicolinate complexes, (b) anticancer activity of gadolinium dipicolinate so obtained, and (c) synthesis of lanthanide(III)-zinc(II) pyrophosphates Ln$_2$/3ZnP$_2$O$_7$ are discussed. Each part is subdivided into three chapters: (a) Introduction (literature survey), (b) Results and Discussion, and (c) Experimental Section. The compounds obtained in the present study are, in general, characterised by mp, IR and UV-Vis (solid/solution), NMR ($^1$H) and TGA techniques followed by elemental analyses and single crystal X-ray structure determination, where possible. References are compiled at the end of each part.

PART-A

In Chapter 1, a review of literature on aspects relevant to this part is presented. In Chapter 2, the results obtained on these aspects are discussed while in Chapter 3, the experimental details are presented. Important results of this part are outlined here.

(i) Synthesis and structures of bismuth carboxylates from bismuth nitrate

In an attempt prepare the alternatives to bismuth metal based drugs available in the market, we made an attempt to synthesise three bismuth carboxylates [Bi(2-O$_2$C-C$_3$H$_4$N)$_3$]$_n$ (1), {Bi[(2,6-O$_2$C)$_2$C$_2$H$_5$N][(2-HO$_2$C-6-O$_2$C)C$_2$H$_5$N].H$_2$O}$_n$ (2) and Bi(O$_2$CC$_9$H$_6$N)$_2$(O$_3$N)(O$_2$CC$_9$H$_6$NH).2H$_2$O (3) [Fig. 1] by treating bismuth nitrate with the appropriate ligand in 1:3 molar ratio.
Figure 1. Structural drawings of 1-3 highlighting the coordination around bismuth atoms [water molecules are not shown].

Compound 1 crystallised in the space group $P2_1/n$. The central bismuth has a tricapped trigonal prismatic coordination [Fig. 2]. The lone pair of electrons on bismuth appears to be stereochemically inactive. Overall, the compound is a coordination polymer with three bridging oxygen atoms between adjacent bismuth centres.

Figure 2. X-ray structure of 1. Asymmetric unit showing the coordination around bismuth and polyhedron showing tricapped trigonal prismatic bismuth centre.

Compound 2 [Fig. 3] is also a coordination polymer but the structural motif is quite different from that observed in 1. Although there are two distinct bismuth atoms in the asymmetric unit, both exhibit eight coordination with dodecahedral geometry. A major difference between the two bismuth atoms lies in the longest
bond length: While for Bi(1), it is the coordinate bond to the carboxylic acid C=O [i.e. Bi(1)-O(6)], for Bi(2) it is a bridging oxygen of the [Bi₂O₂] skeleton [Bi(2)-O(2)]. Also, two Bi(1) and only one Bi(2) form a larger ring as mentioned before.

Figure 3. Drawings representing the X-ray structure of 2. Left: Asymmetric unit along with parts of other units to show the overall skeleton. Right: Polyhedra showing dodecahedral geometry around the two bismuth atoms of the asymmetric unit.

Unlike 1 and 2, compound 3 is monomeric [Fig. 4], most likely because of the sterically bulkier quinoline carboxylate moiety not permitting the oligomerization/polymerization. The distortion in geometry from the more regular dodecahedron may, at least in part, be due to the lone pair of electrons on bismuth.

Figure 4. Drawings representing the X-ray structure of 3. Left: asymmetric unit. Right: polyhedron showing slightly distorted dodecahedral geometry.

The TGA data show that compound 1 is perfectly stable up to ~360 °C, while compound 2 behaves differently, with the non-coordinated water molecules coming
off before the decomposition sets in. Compound 3 shows a more interesting behaviour with its melting point almost coinciding with decomposition/sublimation at ca ~220 °C (consistent with its lower melting point). Decomposition of all the compounds leads to Bi$_2$O$_3$.

(ii) **Bismuth- dipicolinate prepared from ammonium bismuth citrate**

The reaction of ammonium bismuth citrate with dipicolinic acid in water led to compound {[Bi((2,6-O$_2$C)$_2$C$_5$H$_3$N)((2-HO$_2$C-6-O$_2$C)C$_5$H$_3$N)(H$_2$O)]$_2$.5H$_2$O}$_n$ (5) which is different from {Bi[(2,6-O$_2$C)$_2$C$_5$H$_3$N)][(2-HO$_2$C-6-O$_2$C)C$_5$H$_3$N].H$_2$O}$_n$ (2) obtained by using bismuth nitrate pentahydrate and dipicolinic acid. Compound 2 is a coordination polymer while 5 is a dimeric molecule. The structural drawings for the dimeric unit in 5 are given in Figure 5. In 5, the coordination number at bismuth is nine and the geometry can be described as distorted tricapped trigonal prism.

![Molecular structure of the dimeric unit in 5](image)

**Figure 5.** Left: Molecular structure of the dimeric unit in 5. Right: Polyhedron showing the distorted tricapped trigonal prismatic geometry at bismuth.

(iii) **Synthesis and structures of bismuth- pyridine carboxylates from BiPh$_3$**

The reaction of BiPh$_3$ with 3-hydroxy picolinic acid (1:3 molar ratio) in ethanol resulted in [PhBi(2-O$_2$C-3-(OH)C$_5$H$_3$N)$_2$(2-O$_2$C-3-OHC$_5$H$_3$NH)] (6). Compound 6 is monomeric in bismuth having a BiN$_2$O$_4$ skeleton with a pentagonal pyramidal geometry as shown in Figure 6. A closer look at the structure reveals that there is an additional weak but discernible secondary interaction between the coordinated O7 and bismuth atom of a second molecule [distance 3.449(5)Å, sum of van der Waals distances 3.9 Å], in the direction of the lone pair, leading to a weakly held dimer as shown in Figure 6 (right). Use of pyridine as the solvent in the 1:3 stoichiometric reaction of BiPh$_3$ and 3-hydroxy picolinic acid at room temperature resulted in an entirely different product, [Bi(2-O$_2$C-3-
The coordination number around bismuth is eight and we may describe the geometry as distorted dodecahedron as shown in Figure 7.

**Figure 6.** Left: Molecular structure of compound 6. Right: Structure of 6 showing weak dimer formation via additional Bi…O interactions. The Bi-O8 distance is 4.592 (6) Å.

**Figure 7.** Left: Molecular structure of the anion in compound 8. Right: Intramolecular O-H…O hydrogen bonding is also shown.

The compound [PhBi(2-O2C-C4H3N2)2(2-O2C-C4H4N2).H2O] (9) was obtained by the 1:3 reaction of BiPh3 and pyrazine-2-carboxylic acid in refluxing ethanol. To our knowledge, this is the first structural report on bismuth pyrazine-2-carboxylate. Taking into consideration only the stronger interactions, the geometry at bismuth may still be treated as pentagonal pyramid [Fig. 8]. What is unique in the system however, is that the bismuth atoms of two molecules come close to N2’ of a second molecule [distance 3.509(8) Å; sum of van der Waals distances 4.0 Å]
resulting in a weak dimer. Although this distance is not in the realm of any significant bonding interactions, the fact that the nitrogen atom is located on the same side as the expected region for the lone pair of electrons on bismuth is unusual.

**Figure 8.** Left: Molecular structure of compound 9. Right: Dimer formation via weak Bi–N interaction in 9.

Quinoline-2-carboxylic (quinaldic) acid is expected to react in a manner analogous to picolinic acid. However, the 1:3 stoichiometric reaction of BiPh₃ with this acid, conducted in refluxing ethanol afforded the bis-carboxylated product [PhBi(2-O₂C-C₉H₆N)₂.H₂O] (10). The primary coordination number of bismuth is 5 [Fig. 9]. This basic geometry can be construed as square pyramid with quinaldate N/O at the base of the pyramid. Curiously though, compound 10 forms a weakly held dimer with two additional Bi-O interactions involving O₃ and O₄ [Bi...O₃’ 3.347(5)Å; Bi...O₄’ 3.495(7) Å; symm. equiv.: –x, 1-y, 2-z] in the direction of the lone pair of electrons, as shown in Figure 9.

**Figure 9.** Molecular structure of compound 10 excluding the non-coordinated water molecule.
To our knowledge, structural chemistry of Bi(III) compounds of furan-2-carboxylic (furoic) acid and thiophene-2-carboxylic acids is not reported prior to our work. We have isolated crystalline \([\text{Ph}_2\text{Bi(O}_2\text{C-C}_4\text{H}_3\text{O})]\) (11) by the reaction of BiPh\(_3\) and 2-furoic acid (used 1:3 molar ratio) in ethanol at room temperature (25 °C). Bismuth-thiophene carboxylates \([\text{Ph}_2\text{Bi(O}_2\text{C-C}_4\text{H}_3\text{S})]\) (12) and \([\text{PhBi(O}_2\text{C-C}_4\text{H}_3\text{S})_2]\) (13) were obtained from a procedure similar to that for compound 11.

In compound 11 [Fig. 10], primary coordination number of bismuth can be considered to be five with the longest Bi-O1’ bond being 2.981(5)Å. Excluding the weaker Bi...O3 interaction [3.32(2) Å] to the furoate oxygen, the geometry at bismuth can be considered to square pyramidal with C7 as the apical bond and the remaining atoms C1, O1, O1’ and O2’ at the base. It can be noted that the carboxylate acts as both a bridging and a chelating ligand. The resulting entity is a coordination polymer. Unlike compound 11, compound 12 was obtained only in trace quantities in a pure state. There are three molecules in the asymmetric unit (not shown here). As observed in the structure of 11, the carboxylate moiety acts both as a chelating and as a bridging ligand leading to a polymeric chain. The coordination geometry at bismuth in 12 is rather irregular, but may be approximated as square pyramid with C1 (for Bi1), C8 (for Bi2) and C41 (for Bi3) at the apices of the corresponding bismuth atom.

![Figure 10](image)

**Figure 10.** Left: Molecular structure of compound 11, showing the weaker Bi...O interaction also. Right: The polymeric chain in 11.
Compound 13 compound has two carboxylates per bismuth. One carboxylate is purely chelating while the other is involved in both chelation and bridging [Fig. 12]. The molecule thus can be considered to be a dimer of [PhBi(O_2C-C_4H_3S)_2]. The primary coordination sphere around bismuth has five oxygen atoms and one carbon atom but the geometry is non-octahedral. The overall geometry involving these groups is pentagonal pyramid [Fig. 12, right]; however there are interesting secondary Bi…S interactions in the structure (not shown here).

![Figure 12. Molecular structure of compound 13. Left: labelled structure showing the dimeric unit. Right: Polyhedra depicting the primary coordination sphere of pentagonal pyramid around bismuth.](image)

The TGA data of compound 6 is stable up to ~210 °C and complete decomposition occurs near to 400°C. For compound 8 at 150 °C, pyridine and protonated pyridine are eliminated. Remaining decomposition pattern is similar to 6. Compound 9 behaves differently, with the non-ordinated water molecules coming off and decomposition for this molecule starts at 270 °C and completes at 350 °C. In all the cases the final product of decomposition is most likely Bi_2O_3.

(iv) Bismuth vanadate (BiVO_4): A new simple synthetic route

Bismuth vanadate (BiVO_4; 14) is prepared from bismuth nitrate and ammonium (14a) or sodium vanadate (14b) in water under reflux conditions. The phase purity of the sample was confirmed by powder X-ray (Fig. 13, left). The energy-dispersive X-ray spectrum (EDS) analysis confirms the formation of the
stoichiometric BiVO₄. The Raman spectra of the compounds between 10 and 1400 cm⁻¹ are shown in Figure 13 (right). Each spectrum is dominated by an intense Raman band at 828 cm⁻¹ assigned to $\nu_\text{s}(\text{V–O})$, along with other peaks. Both the materials 14a and 14b are found to have nearly same $E_g$ of 2.58 eV [calculated using the plot of $\alpha h\nu^2$ vs. photon energy ($h\nu$)] which is slightly higher than 2.4 eV reported from other groups.

![Figure 13](image)

**Figure 13.** Left: Powder X-ray pattern, Right: Raman Spectra of BiVO₄ (14a and 14b)

**PART-B**

Chapter 4 pertains to the literature on lanthanide oxopyridinum/ dipicolinate complexes. Chapter 5 describes the results obtained in the present study. Chapter 6 is the experimental section. Important results are outlined below.

(i) **Synthesis and spectral data of lanthanide-4-hydroxy pyridine complexes**

Synthesis of the lanthanide hydroxypyridine compounds $[\text{M(4-O-C₆H₄NH)}₃(\text{NO₃})₂(\text{H₂O})₂][\text{NO₃}] \{\text{M = La (3), Ce (4), Pr (5), Nd (6), Eu (7) and Gd (8)}\}$ was accomplished by the simple reaction of the corresponding nitrates with three mole equivalents of 4-hydroxypyridine in ethanol or water. All the compounds 3-8 crystallized in the chiral space group $P2₁2₁2₁$. Molecular structures of the representative compounds 6 and 7 are shown in Figure 14. One of the interesting features in these structures is the reversal of stereochemistry between the structures of the neodymium compound 6 and the europium compound 7 (as well as 3-5) [Fig. 14, bottom]. Since each of these structures is in a chiral space group, this result
appears to be a case of spontaneous resolution. As per TGA, complete removal of organic residues did not occur till 400 °C.

Figure 15. Top: Molecular structures of the cationic part in 6 and 7; the anion is nitrate (not shown). Bottom: Polyhedral representation around the central atom in 6 and 7 showing the opposite stereochemistry.

(ii) Lanthanide dipicolinates: Simplified synthetic route and X-ray structures

As a continuation of our studies on bismuth dipicolinates, which also has a large size and exhibits +3 oxidation state, we became interested in lanthanide dipicolinates of the formula \{Ln[(2-HO$_2$C-6-O$_2$C)C$_5$H$_3$N]$_3$\}$_{1.5}$H$_2$O \[Ln = $^{(9)}$Sm, $^{(10)}$Gd, $^{(11)}$Eu, $^{(12)}$Dy, $^{(13)}$Tb and $^{(14)}$Tm\}. These were synthesized by the reaction of Ln(NO$_3$)$_3$.$x$H$_2$O with pyridine-2,6-dicarboxylic acid in water under reflux conditions for 4 h. All these compounds crystallize in the same space group ($P1\bar{1}$) with essentially the same structure and for this reason; we shall concentrate on only the gadolinium complex 10. There are two molecules in the asymmetric unit. In each case, gadolinium ion is surrounded by three dipicolinate ligands (Fig. 16). The ligand coordinates to the gadolinium ion through pyridine nitrogen and carboxylate oxygen in a five-membered chelating manner such that coordination number of lanthanide ion is 9. The bulk purity of the crystals obtained is compared by single crystal data and powder data thus obtained are in good agreement with each other.
(iii) **Antitumor activity of the Gadolinium dipicolinate (compound 10)**

Preliminary screening was done on cancer cell lines of different origins. Compound 10 showed significant effect on the proliferation of Hepatocellular carcinoma cells (HepG2). HepG2 cells were treated with 10 (10, 25, 50, 100, 250, 500, 1000 μM) for 48 h and cell proliferation was determined by the MTT assay. A 50% inhibition in HepG2 cell proliferation was observed at 250 μM concentration of 10 in 48 h.

Western-blot analysis was performed with cytoplasmic extracts devoid of mitochondria, with anti-cytochrome c mouse monoclonal antibodies to detect cytochrome c release. We observed a time dependent increase in cytochrome c release in the cells treated with 10 (250 μM) and no release was observed in control cells (Fig. 17a). Upon treatment with 10 (250 μM) changes in the expression of Bcl-2 and BAX were observed. Bcl-2 protein expression decreased and pro-apoptotic protein BAX levels increased in a time dependent manner in 10 treated cells compared with the untreated controls (Figures 17b, 17c). Increase in the cell number in sub G0/G1 phase with treatemnt is characteristic feature of apoptosis induction. HepG2 cells treated with 10 (100 and 250 μM) for 48 h were analysed on FACS for the cell cycle alterations. Typical sub-diploid apoptotic peaks were observed in 10 treated cells. Control cells showed a G1, followed by S and G2/M-phases. Only 1.17% of the control cells showed hypodiploid DNA (Fig. 18a). Cells with hypodiploid DNA increased in 10 treated cells. Hypodiploid cells were 23.96% in 100 μM and 47.76% 250 μM in treated cells (Figures 18b and 18c). Thus this gadolinium dipicolinate compound has shown promising effect on the proliferation of hepatocellular carcinoma cells.
Figure 17. Time dependent expression of proteins involved in cell death process in compound 10 treated HepG2 cells (Western blot analysis)

Figure 18. Cell cycle alterations of 10 treated HepG2 cells (see txt for details).

(iv) Attempted preparation of lanthanide zinc pyrophosphates, Ln$_{2/3}$ZnP$_2$O$_7$ [Ln = Pr (15), Sm (16), Nd (17), Dy (18) and Gd (19)]

In our earlier experiments using domestic microwave oven, we were able to obtain pure samples of Ln$_{2/3}$ZnP$_2$O$_7$ [Ln = Pr (15), Sm (16), Nd (17), Dy (18) and Gd (19)] by treating Na$_2$ZnP$_2$O$_7$ with the *in situ* prepared lanthanide chlorides. However, since the microwave oven used was a domestic one, for reproducibility, later investigations were performed by using a muffle furnace [600 °C/ 6 h]. To our dismay, the results obtained using the microwave were not very much reproducible by using the furnace in terms of the purity of the samples as evidenced by powder X-ray for the samples.