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Review: Bismuth complexes: synthesis and applications in biomedicine

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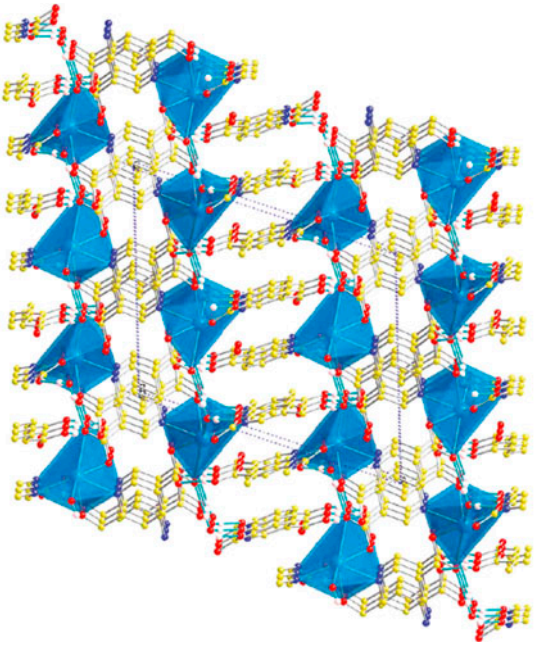

This paper reviews the synthesis and biomedical applications of bismuth complexes with unusually low toxicity and excellent clinical performances, summarizes their main synthesis methods, and biomedical applications as drugs for the therapeutic treatment of gastrointestinal disease, *Helicobacter pylori* infection, and various cancers; especially, describes the development of bismuth-based MOFs in the drug delivery and potential application in cancer treatment.

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A variety of bismuth complexes have been extensively explored in biomedical applications. The well-known low toxicity and environmental friendliness of bismuth salts make them valuable for large-scale synthesis of various bismuth-based complexes, which become more significant as active pharmaceutical ingredients of medical products. Bismuth complexes have been widely and preferably used in biomedicine with satisfactory therapeutic effect, which is highlighted in this review. However, their synthesis methods have been scarcely summarized. The classification of the main synthesis methods of bismuth complexes has been done here, followed by updates of the relevant advances concerning applications in biomedicine such as therapeutic effect on gastrointestinal diseases, antimicrobial, and anticancer activities, and the description of the side effect and biotoxicity resulting from long-term use of bismuth as well. Bismuth containing metal–organic frameworks, newly developed bismuth-based materials, are also discussed here, becoming a hot research topic recently. An outlook for future study on the potential use of bismuth complexes in biomedicine is provided in the end.

Keywords: Bismuth complexes; Synthesis methods; MOFs; Biomedical application

1. Introduction

Bismuth, known since ancient times, is a heavy metal element, as shown in the periodic table of elements (figure 1), which had been confused with lead and tin for centuries owing to its special location in the periodic table horizontally and diagonally, respectively, thus leading to some similar properties among these three metals. What completely differs from toxic lead and tin is that bismuth has unusually low toxicity [1]. The toxicity of most bismuth compounds is less than sodium chloride [2]. So both metal bismuth and its compounds are commonly considered biologically safe and nontoxic. Researchers attribute such remarkably low toxicity of bismuth compounds to their insolubility in neutral aqueous solutions like biological fluids and inhibition of pathogenic bacteria such as *Helicobacter pylori* (*H. pylori*) [3], a spiral-shaped micro-aerophilic gram-negative bacterium, which can cause various gastric diseases, including gastritis, peptic ulcerations, gastric carcinoma, and mucosa-associated lymphoid tissue lymphoma. Most likely, the synthesis of soluble bismuth complexes may provide evidence to explain the exact reason about the nontoxicity of bismuth-containing compounds.

Due to these attractive characteristics, fundamental research of bismuth chemistry has been prompted in several fields including use in organic syntheses, industrial use as precursors in advanced materials science, sensing applications [4–6], bioactivity like treatment of a variety of gastrointestinal disorders, antitumor, antimicrobial, and antibacterial activities [7]. The first bismuth-containing medicine reported in 1786 for the treatment of dyspepsia was marked as the beginning of the medical use of bismuth complexes [8]. Afterwards, more and more bismuth complexes were explored in the treatment of various gastrointestinal disorders and microbial infections, including syphilis, diarrhea, gastritis, and colitis, where good and desirable efficacy and unexpectedly low toxicity in the therapy were always received. Use of radioisotope ^{212}Bi and ^{213}Bi compounds as targeted radio-therapeutic agents for cancer therapy has indicated the anticancer activities of bismuth complexes [9]. The biological activities of bismuth complexes are believed to rely on both the ligand and the coordination geometry of the complexes.

The ground-state electron configuration of bismuth $4f^{14}5d^{10}6s^26p^3$ is usually stable and the three 6*p* electrons are responsible for bond formation during coordination. Thus, in the majority of Bi containing complexes, bismuth exhibits an oxidation state of +3. The coordination number is irregular ranging from 3 to 10. In some cases, the two 6*s* electrons can also be shared with ligand for bond formation in five-coordinate bismuth complexes where

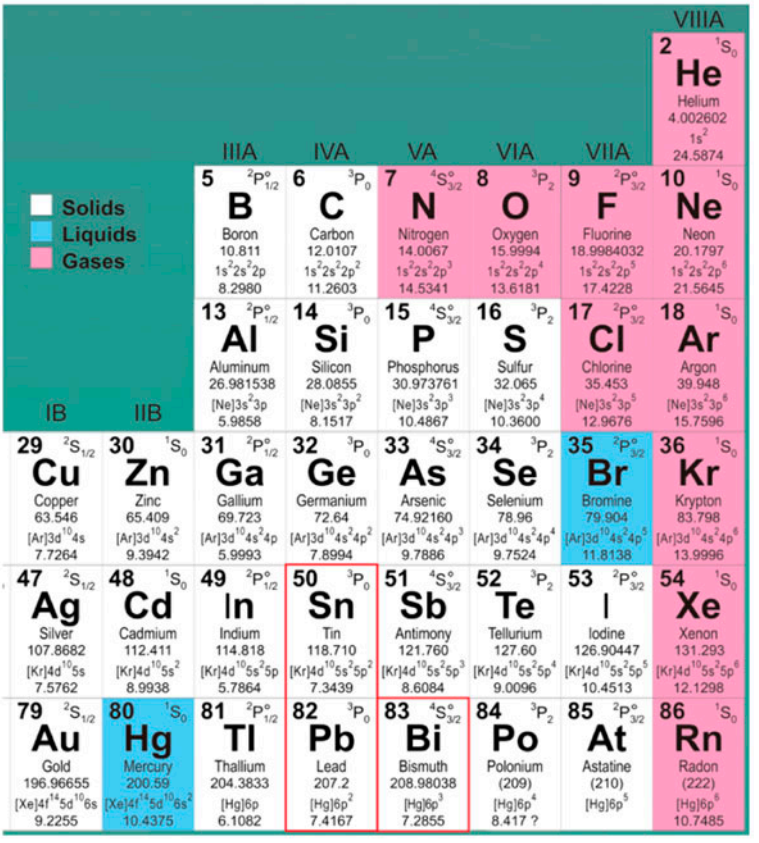

Figure 1. The periodic table of elements with Bi, Sn, and Pb highlighted in red squares (see http://dx.doi.org/10.1080/00958972.2014.999672 for color version).

bismuth shows oxidation state of +5. The higher valent state makes Bi(V) complexes strongly oxidative and unstable and thus Bi(V) complexes are mainly applied in arylation and oxidation reactions. This is why the existing Bi(V) complexes are less available than Bi (III) ones.

Structural patterns in organometallic and inorganic Bi(III) or Bi-transition metal derivatives have been observed. For biomedical applications, organometallic Bi(III) complexes make major contributions to therapeutic treatments. Organobismuth compounds with a large variety of ligands and coordination environments had been synthesized for biological evaluation [7, 10]. Nevertheless, few reports concern synthetic methods. Bismuth metal–organic frameworks (MOFs) have not been discussed in previous reviews. MOFs, porous organic–inorganic hybrid materials with intriguing structural topologies, are regarded as a subclass of coordination polymers and becoming one of the most rapidly developing fields in chemical and material sciences due to their potential functional materials in structure-dependent applications, e.g. gas storage and separation, sensing, and drug delivery [11–13]. For medical purposes, Bi-MOFs take full advantage of their delivery function of drugs into living environments without obvious bio-toxic effects caused to the human body. As a result, more efforts have been made to develop various Bi-MOFs. Therefore, in this review, the

synthesis methods, recent advances of bismuth complexes (especially Bi-MOFs) as well as the utilization of their antiulcer, antimicrobial, and anticancer activities in biomedicine will be reviewed, accompanied by description of side effects and biotoxicity as well as the outlook of future perspectives of bismuth complexes.

2. Synthesis methods of bismuth complexes

2.1. *Hydrothermal synthesis*

Hydrothermal synthesis, a method to synthesize single-crystals, includes various techniques of crystallizing substances from high temperature aqueous solutions at high vapor pressures. The crystal growth is commonly performed in an apparatus consisting of a Teflon-lined steel pressure autoclave, where an insoluble or poorly soluble reactant is supplied along with water. A gradient of temperature is necessarily maintained at opposite ends of the growth chamber where the reactant dissolves in the hotter end and seeds precipitated for additional crystal growth in the cooler end. The factors affecting crystal growth mainly involve temperature, heating, agitation rate as well as response time. Such method has been applied to produce bismuth complexes.

Through hydrothermal synthesis, He *et al.* prepared well-dispersed bismuth-asparagine coordination polymer spheres (BACP-2) with an average diameter of 800 nm via aqueous reaction of $Bi(NO_3)_3{\cdot}5H_2O$ and asparagine at 80 °C for 24 h [figure 2(A)] [14]. Using Ti $(C_4H_9)_4$ and $Bi(NO_3)_3{\cdot}5H_2O$ as raw materials, potassium bismuth titanate ($K_{0.5}Bi_{0.5}TiO_3$) nanoparticles with about 50–100 nm diameter were prepared in alkaline solution at 160–200 °C, having tetragonal crystal structure and good dispersibility but greatly affected by alkaline concentration and temperature of solutions [15]. via a copolymer of phosphono and carboxylic acid mediated hydrothermal method, carboxyl-capped YVO_4 : Eu,Bi nanoparticles with average diameter of about 10 nm were synthesized by Luo *et al.*, where magnetic stirring of the mixed $Bi(NO_3)_3YCl_3$, $EuCl_3$, phosphono, and carboxylic acid solutions was necessary before the mixture was transferred into a Teflon-lined stainless steel autoclave for reaction in NaOH media at 180 °C for 24 h [16]. The small particle size, good dispersibility in water solution, and good crystal quality (figure 3) facilitated carboxyl-capped YVO_4 : Eu, Bi nanoparticles flowing on the nitrocellulose membrane under capillary force in immunochromatographic test strip assay applications. Bismuth-amino acid coordination polymers (BACPs) with different morphologies scaling from nano to microsize were prepared just by heating the aqueous reacting solution of $Bi(NO_3)_3{\cdot}5H_2O$ and asparagine at different temperatures for certain periods, a facile, green, and mild hydrothermal synthesis method [figure 2(B)] [17], and the prepared BACPs exhibited unique biological properties and potential application in bio-medicine. By mixing bismuth nitrate, an excess of pyridine-2,5-dicarboxylic acid (H_2pydc) and 4,4′-bipyridine or KOH in deionized water within a sealed Teflon-lined bomb, Wibowo *et al.* synthesized stable Bi(pydc)(Hpydc)(H_2O), Bi-MOFs nanoparticles at 140 °C for 3 days as shown in figure 4 [18].

2.2. *Solvothermal synthesis*

Solvothermal synthesis commonly used to produce chemical compounds is very similar to the hydrothermal route, but, solvothermal synthesis is carried out in organic media. Since the solvothermal route gains benefits from both the sol–gel [19] and hydrothermal routes

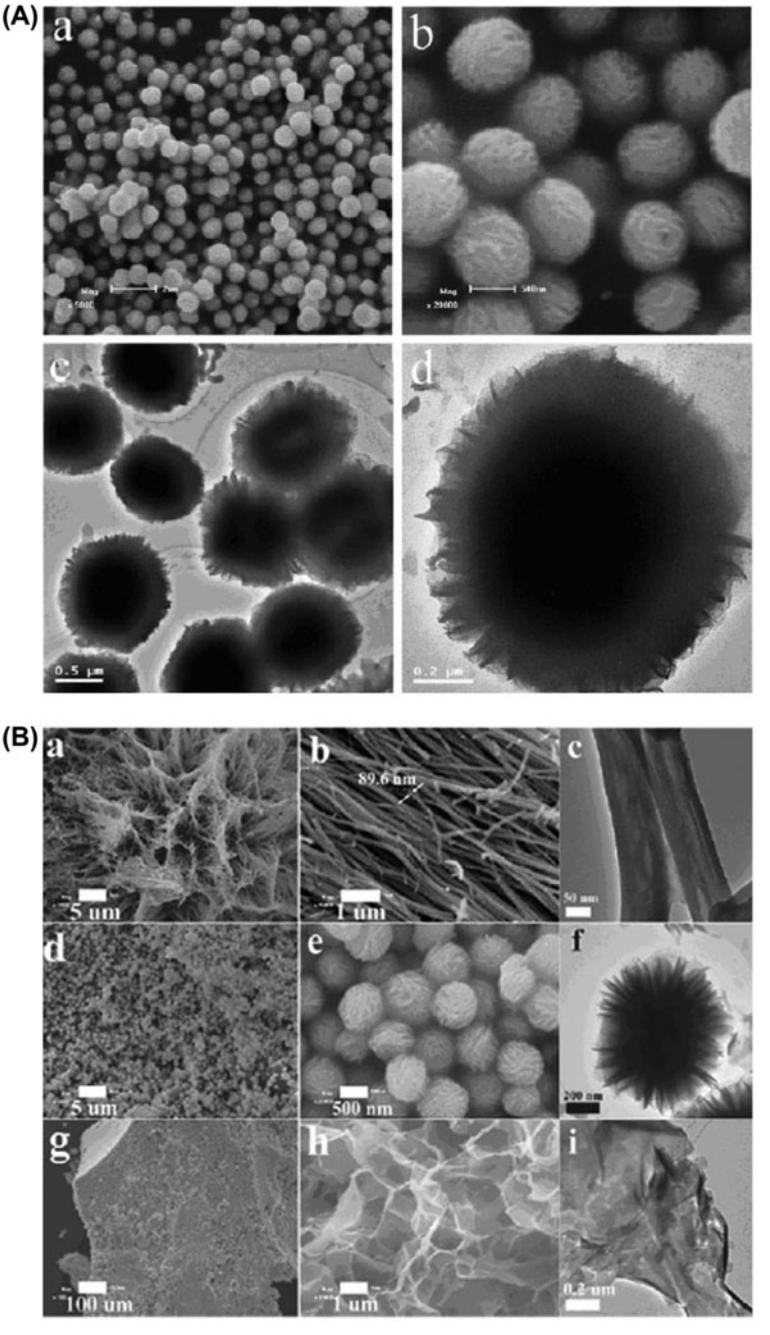

Figure 2. Morphological images of (A) BACP-2 as acquired by SEM (a,b) and TEM (c,d) [14]; (B) SEM and TEM images of (a–c) BACP-1 obtained at 10 °C (d and e), BACP-2 obtained at 80 °C and (g–i) BACP-3 obtained at 160 °C [17].

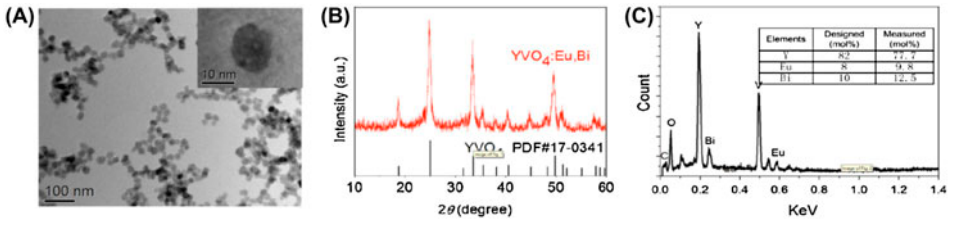

Figure 3. TEM images (A), XRD spectrum (B) and EDX analysis spectrum (C) of carboxyl-capped YVO_4:8% Eu, 10%Bi nanoparticles. The line spectrum in (B) corresponds to the literature data of bulk YVO_4 [16].

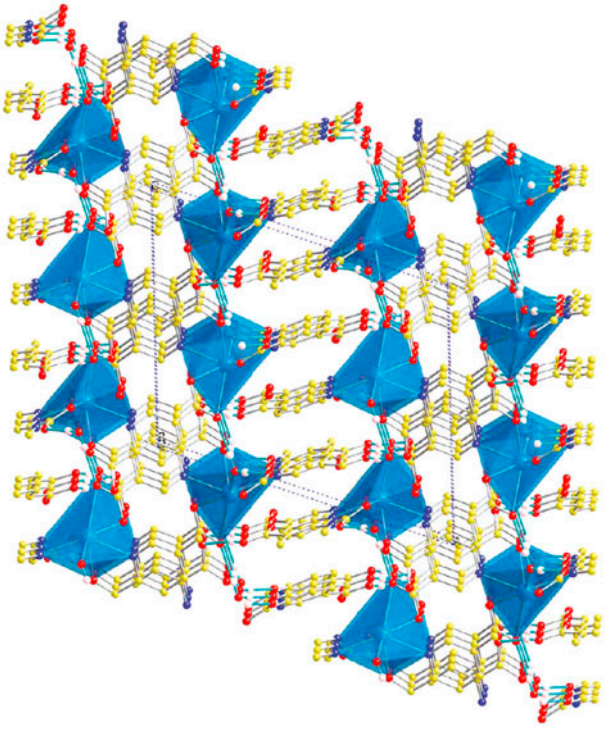

Figure 4. 3-D structure of Bi-MOFs. The 1-D chains connect via hydrogen bonding (light blue lines) in the *x*- and the *y*-direction. Blue: Bi; Red: O; Dark blue: N; Yellow: C; Pink: H [18] (see http://dx.doi.org/10.1080/00958972.2014.999672 for color version).

[20], control over the size, shape distribution, and crystallinity of metaloxide nanoparticles or nanostructures is thus allowed by changing experimental parameters, including reaction temperature, reaction time, solvent type, surfactant type, and precursor type.

Li *et al.* reported solvothermal synthesis of $Bi(L)(NO_3)_2(CH_3OH)$ in CH_3OH/HNO_3 media through reaction at 70 °C for 0.5 h, where HL = 2-acetylpyrazine *N*(4)-phenylthiosemicarbazone, and L^- was used as complexing ligand [21]. As shown in figure 5, the 3-D molecular structure of $Bi(L)(NO_3)_2(CH_3OH)$ is a monomeric, seven-coordinate distorted pentagonal bipyramidal geometry with the pentagonal plane defined by the tridentate N_2S thiosemicarbazone, one electron pair ($6s^2$) of the Bi(III) and monodentate methanol,

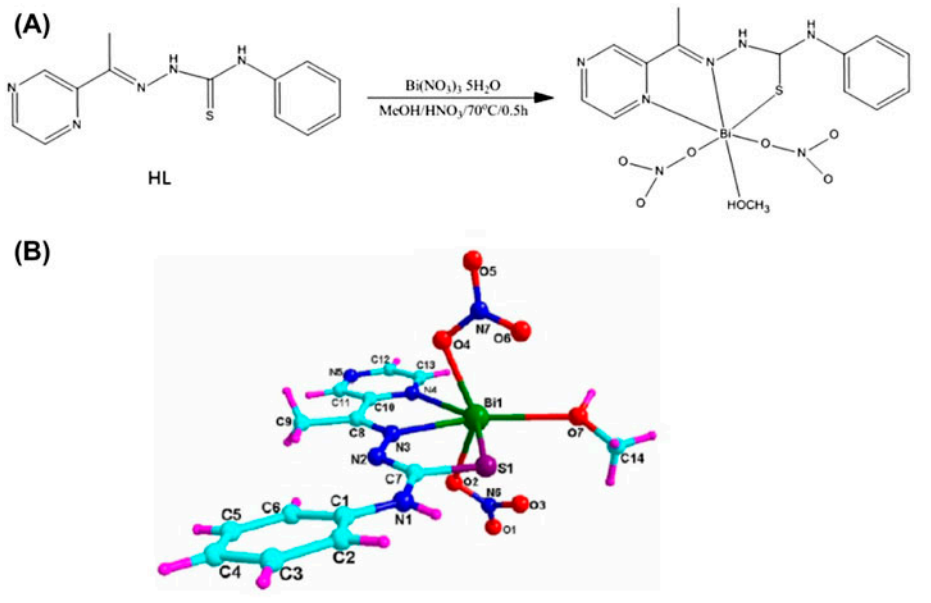

Figure 5. (A) The reaction scheme for the synthesis and (B) 3-D molecular structure of $Bi(L)(NO_3)_2(CH_3OH)$ with atom numbering [21].

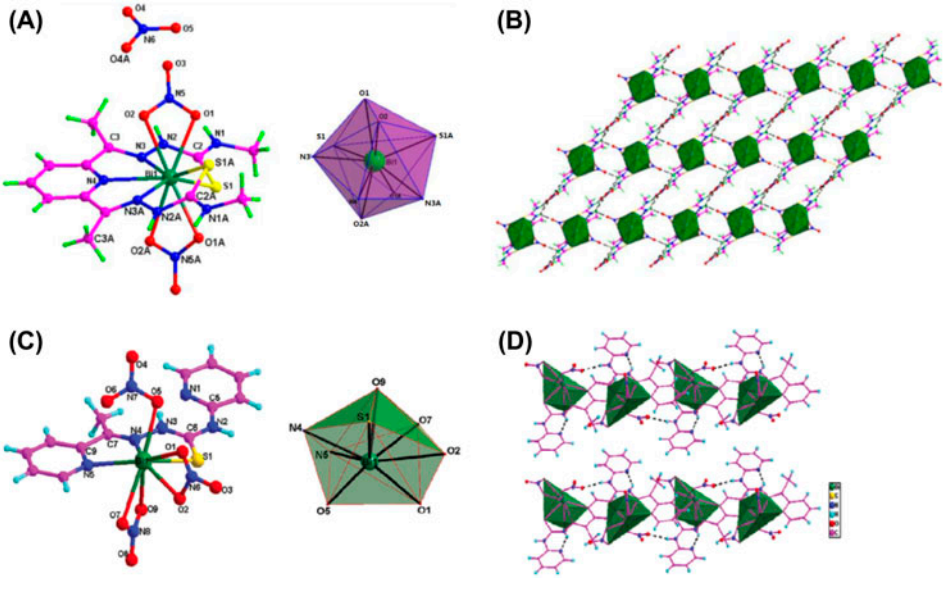

Figure 6. (A) Structure of $(Bi(H_2L)(NO_3)_2)NO_3$ with atom numbering scheme and polyhedron showing distorted geometry around bismuth. (B) Molecular packing projected along the *b* axis of the crystals. (C) Structure of $Bi(HL)(NO_3)_3$ with atom numbering scheme and polyhedron showing dodecahedral geometry around bismuth of the asymmetric unit. (D) The molecular packing projected along the *a* axis of complex [22, 23].

whereas axial positions are occupied by two monodentate NO_3^- ions. The tridentate deprotonated thiosemicarbazone coordinates to bismuth with its imine nitrogen, thiol sulfur, and pyrazine nitrogen, forming two five-membered chelate rings [figure 5(B)]. Using similar method, a nine-coordinate Bi(III) complex, $(Bi(H_2L)(NO_3)_2)NO_3$ [figure 6(A) and (B)], with H_2L = 2,6-diacetylpyridine bis(^{4}*N*-methylthiosemicarbazone), and a dodecahedral Bi (III) complex, $Bi(HL)(NO_3)_3$ [figure 6(C) and (D)] (HL = 2-acetylpyridine *N*(4)-pyridylthiosemicarbazone), were prepared in methanol by Li *et al.* [22, 23]. Andrews and co-workers developed two new bis-carboxylate Bi(III) complexes, $PhBi(o\text{-}MeOC_6H_4CO_2)_2(bipy)\cdot 0.5EtOH$ and $PhBi(C_9H_{11}N_2O_3CO_2)_2(H_2O)\cdot 6H_2O$, nonsteroidal anti-inflammatory drugs, through reactions in a Schlenk flask after refluxing in ethanol for 10–12 h [24] (bipy refers to 1,2′-bipyridine). Another two $BiBr_3$ supramolecular complexes, $[Bi(2\text{-}bpmp)Br_{2.06}Cl_{0.94}]$ and $[Bi(4\text{-}H_2bpmp)Br_{4.29}Cl_{0.71}]\cdot H_2O$ {2-bpmp = N,N -bis(2-pyridylmethyl)piperazine and 4-bpmp = N,N′-bis(4-pyridylmethyl) piperazine}, were prepared by Khanjani *et al.* [25] through reaction of bismuth(III) chloride and potassium bromide with two nitrogen donor ligands in methanol under thermal gradient conditions, where a branched tube was used with ligand-containing arm immersed in an oil bath at 60 °C and the other arm kept at ambient temperature. After 7–10 days reaction, the two $BiBr_3$ supramolecular complexes were obtained with their supramolecular networks caused by extensive hydrogen-bonding interactions.

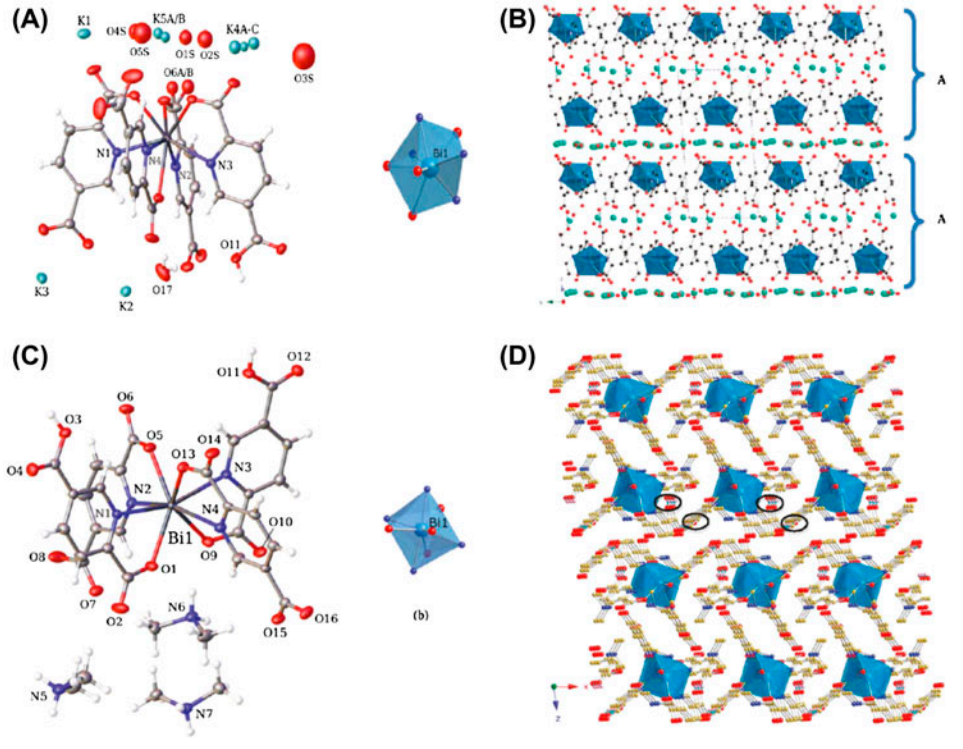

Figure 7. (A) Asymmetric unit and (B) view along the *x*-direction of $K_4Bi(pydc)_3(Hpydc)(H_2O)_{3.3}$ showing *hydrogen bonded anionic layer A* counter balanced by potassium cations; (C) asymmetric unit and (D) the 1-D supramolecular structure of $(DMA^+)_3Bi(pydc)_2(Hpydc)_2$ created via hydrogen bonding along the *x*-direction [18].

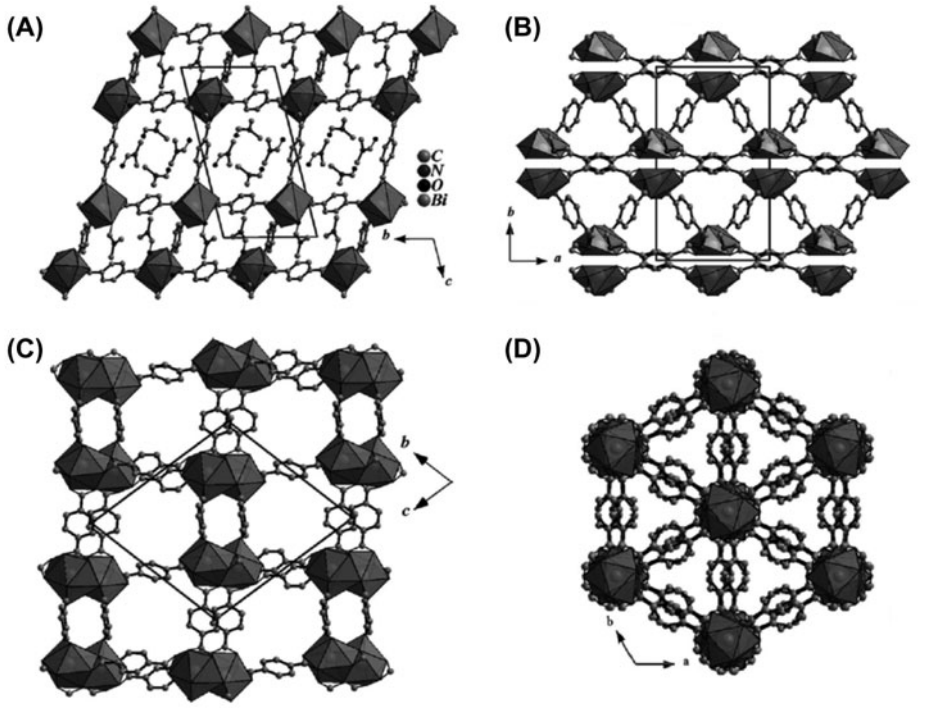

Figure 8. The view of the 3-D structures in MOFs (A) 1, (B) 2, (C) 3, and (D) 4 down *a*, *c*, *a*, and *c* axis, respectively [26].

The solvothermal method is more popularly used to prepare bismuth-based MOFs. For example, Wibowo and co-workers reported the synthesis of two Bi-MOFs, $K_4Bi(pydc)_3(H\text{-}pydc)(H_2O)_{3.3}$ [figure 7(A) and (B)] and $(DMA^+)_3Bi(pydc)_2(Hpydc)_2$ [figure 7(C) and (D)], through reaction of $Bi(NO_3)_3{\cdot}5H_2O$ with dicarboxylic acid (H_2pydc) in a Teflon-lined bomb using K(Na(OH)/DMF as reaction media at 100 and 140 °C for 3 days, respectively [18]. Using benzenedicarboxylic acid as complexing ligand, four anionic MOFs containing bismuth, $Bi(1,4\text{-}bdc)_2(dmf)]{\cdot}(dma)(dmf)_2$ (1), $Bi(1,4\text{-}bdc)_2{\cdot}(dma)(dmf)$ (2), $Bi4(1,4\text{-}bdc)_7(HIm){\cdot}(dma)_2(dmf)_2$ (3) and $Bi(1,4\text{-}bdc)_2{\cdot}(dma)$ (4) (dma = dimethyl ammonium cation, HIm = imidazole and dmf = dimethylformamide), were produced in a stainless steel reactor at 100 °C for 3 days [26], where Bi-MOF (1) has a layer structure and Bi-MOFs (2–4) a 3-D structure, as shown in figure 8. Preparation of higher or lower valent state of Bi-MOFs has also been achieved. For instance, Kumar and Mishra synthesized a new MOF of $Bi^V(L)OClO_3$ (L = 2-(4,6-diamino-3-(3-amino-6-(1-methyamino-ethyl)tetrahydropyran-2-yl)oxy-2-hydroxy- cyclohexoxy)-5-methyl-4-methylamino-tetrahydropyran-3,5-diol) by dissolving sodium bismuthate in 1 : 1 $HClO_4$ and HCl to obtain Bi(V) and refluxing reaction mixture of Bi(V) and complexing ligand in CH_3OH at ~85 °C for several hours (figure 9) [27]. A low-valence Bi(II) trifluoroacetate, the first inorganic salt of bismuth in oxidation state +2, was also obtained in its pure, unstabilized form through comproportionation between bismuth metal and bismuth(III) trifluoroacetate ($Bi(O_2CCF_3)_3$ in a sealed, evacuated glass ampule heated at 110 °C for 2 days [28]. The obtained Bi(II) compound is decomposed by the majority of common solvents, but can be stabilized and crystallized as

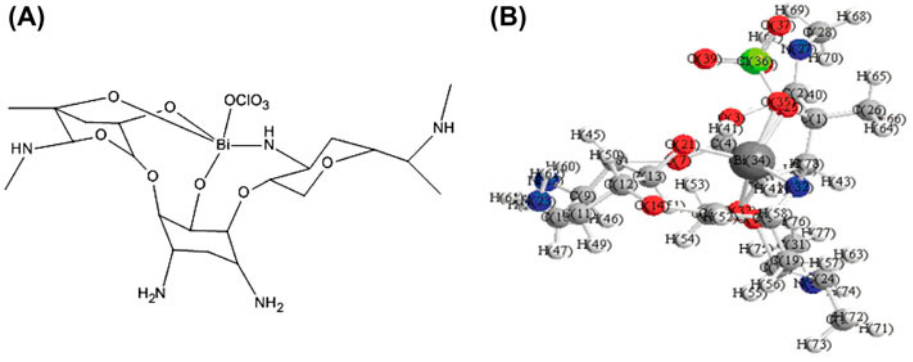

Figure 9. Chemical structure (A) and ball shape structure (B) of Bi(V)L($OClO_3$). Color code: Bi, dark gray; O: red; C, light gray [27] (see http://dx.doi.org/10.1080/00958972.2014.999672 for color version).

π-adducts with arenes in aromatic solvents, such as $Bi_2(O_2CCF_3)_4{\cdot}(C_6H_5Me)$ and $Bi_2(O_2CCF_3)_4{\cdot}(1,4\text{-}C_6H_4Me_2)_2$.

2.3. *Microwave synthesis*

Currently, microwave irradiation (MWI) is an efficient and environmentally benign method to accomplish various inorganic syntheses to afford products in higher yields within shorter reaction times [29–35]. However, only a few bismuth complexes synthesized by MWI have been reported, which has proved that the synthesis reaction time of bismuth MOFs can be reduced from 12 h to 20 min or shorter using MW-assisted synthesis instead of conventional heating [36]. For example, Baczkowicz *et al.* reported the synthesis of Bi(III)-starch complexes with microwave of 800 W within 15 min and Bi(V)-starch complexes by heating mixtures of starch (16.2 g) and 28, 54, and 82 g of $NaBiO_3$ in the microwave oven (800 W) for 5, 10, and 15 min [37]. The coordination behaviors of bismuth(III) compounds with benzothiazoline were investigated by Mahajan *et al.* [38, 39], where the reaction mixtures were irradiated inside a microwave oven at 700 W for 4–7 min. All the results provide evidence that MWI is more effective than traditional methods and thus should be recommended for the preparation of bismuth-based complexes including Bi-MOFs.

2.4. *Routine solution synthesis*

Besides the aforementioned three synthesis methods, some other simple approaches (routine solution syntheses) have been applied for preparation of bismuth complexes as well, one of which is stirring preparation of organic and/or inorganic compounds of bismuth. Solid diclofenac-bismuth complexation was attempted by mixing diclofenac sodium and bismuth subcitrate aqueous solutions and stirring for 1 h at room temperature [40]. Murafuji and coworkers prepared a series of heterocyclic organobismuth(III) (ClBi(5-R-$C_6H_{3\text{-}2}$-SO_2C_6H4-1′-):R = Me, Ph, MeO, Cl, H, *t*-Bu, CF_3, F, Me_2 N). A solution of 2,2′-dilithiated diphenyl sulfone generated from diphenyl sulfone and butyllithium in THF was added dropwise at −40 °C to a suspension of dichloro(4-methylphenyl)bismuthane in ether and the resulting mixture was stirred for 3 h to reach ambient temperature [41]. The synthesis of nine

new tris-substituted Bi(III) aminoarenesulfonates, $Bi(O_3S\text{-}R^N)_3$ (R^N = o-aminophenyl, *m*-aminophenyl, 6-amino-3-methoxyphenyl, *p*-aminophenyl, 2-pyridyl, *o*-amino-naphthyl, 5-aminonaphthyl, 4-amino-3-hydroxynaphthyl and 5-isoquinolinyl), was well described by Busse *et al.* just by stirring the reaction mixtures for different time periods like 16, 24, or 36 h at room temperature [42]. Unfortunately, the long reaction time weakens the advantages of this method.

3. Biomedical applications

3.1. *Therapeutic effect on gastrointestinal disease*

H. pylori plays an important role in development of chronic gastritis and peptic ulcers and has been closely linked to the pathogenesis of gastric cancer [43–45], hence therapeutic treatment is usually recommended once *H. pylori* infection is diagnosed. *H. pylori* is susceptible to several antibiotics such as clarithromycin, amoxicillin, metronidazole, tetracycline, rifabutin, and fluoroquinolones [46, 47], and is inherently resistant to many other antibiotics like bacitracin, vancomycin, trimethoprim, polymyxins, and nalidixic acid [48, 49]. This bacterial infection, however, has proven challenging to cure. The loss of eradication efficacy has been currently explained from several aspects, and the key factor for treatment failure is its antibiotic resistance [50]. As the resistance rate varies in different geographic areas, it is necessary to make adjustments for the selection of therapeutic regimes according to local resistance pattern [51, 52]. The general use of antibiotics in the region is majorly responsible for *H. pylori*'s antibiotic resistance in various regions [53, 54]. With the aim to decrease antibiotic resistance, bismuth compounds have been utilized to treat gastrointestinal disorders and ulcers with well-known inhibition activity against *H. pyloi* [7]. Among those bismuth-containing pharmaceuticals, bismuth subsalicylate (BSS) colloid, bismuth subcitrate, and ranitidine bismuth citrate are the most widely selected to inhibit the growth or spread of *H. pylori* [55–60]. Especially, the replacement of traditional triple therapy by bismuth-containing quadruple rescue therapy performs strong eradication of *H. pylori* [61–67]. A complex of bismuth with *d*-polygalacturonic acid, usually called colloidal bismuth pectin, has been approved for clinical use in China [8].

Generally, the antiulcer activity of bismuth-containing medicines is explained by simple precipitation of bismuth within the ulcer crater, resulting in formation of a glycoprotein-bismuth complex as a protective coating which contributes to the healing of the lesion [8]. The exact molecular mechanisms describing the anti *H. pylori* activity of bismuth compounds have not been fully understood, but the biological targets are clearly related to several proteins and enzymes of *H. pylori*. As noted, oxidative stress in *H. pylori* cells could be induced by bismuth treatment leading to inhibition of overall protease activities [68]. Moreover, the inhibition of important enzymes against *H. pylori* like urease has also been found to be directly related to the anti *H. pylori* activity of bismuth compounds [8]. The development of bismuth-containing nanostructures with potent activities against *H. pylori* is currently an interesting trend for the design of novel pharmaceutical preparations of bismuth compounds [69, 70]. Some commercial medicines with therapeutic effect on gastrointestinal disease are summarized in table 1, in which a bismuth-containing complex is the main ingredient.

Table 1. List of some commercial bismuth-containing medicines with therapeutic effect on gastrointestinal disease.

Medicine name	Bismuth complex
Compounds Bismuth Aluminate Tablets, Debitai	Bismuth Aluminate
Veytalo Tablet, Cascara	Basic bismuth nitrate
Colloidal bismuth petin	Colloidal bismuth petin
Weishusan	Bismuth subcarbonate
Oxybuprocaine Hydrochloride Gel	Bismuth carbonate
Ranitidine	Bismuth citrate
Tripotassium dicitratobismuthate	Bismuth subcitrate
Livzon Dele, Bielomatik	Bismuth potassium citrate

3.2. *Antimicrobial activity*

A number of bismuth complexes developed over the years have been accessed for other antibacterial and antifungal activities. For instance, the antibacterial activity of a new bismuth(III)-sulfapyridine complex was evaluated as several times more potent than that of the single sulfapyridine against *Salmonella typhimurium*, *Staphylococcus aureus*, *Shigella dysenteriae*, *Shigella sonnei*, *Pseudomonas aeruginosa*, and *Escherichia coli* [71]. Hernandez-Delgadillo *et al.* synthesized aqueous colloidal bismuth oxide nanoparticles ($B_{i2}O_3$ NP) and analyzed their fungicidal activity against *Candida albicans* and antibiofilm capabilities [72], where the obtained $B_{i2}O_3$ NP displayed better antimicrobial activity against *C. albicans* growth (reducing colony size by 85%) and more complete inhibition of biofilm formation (figure 10) than those obtained with chlorhexidine, nystatin, and terbinafine, the most effective oral antiseptic and commercial antifungal agents. These results suggest that colloidal $B_{i2}O_3$ NP could be a very interesting candidate as a fungicidal agent to be incorporated into an oral antiseptic. Most surprisingly, Alharbi *et al.* study showed that the growth of the pathogenic yeast could be inhibited by bismuth compounds which stimulated the growth of filamentous fungi instead [73]. A series of new cyclic organobismuth compounds bearing a nitrogen or sulfur as an additional ring member were synthesized with their antibacterial activities against five strains of gram-negative and gram-positive bacteria assessed [74]. It was found that the eight-membered ring compounds exhibited MICs less than 0.5 μg mL^{-1} against *S. aureus* and were more active than the six-membered ones. The gram-positive bacteria (*S. aureus*, *Bacillus subtilis*, and *Enterococcus faecalis*) were more susceptible to both types of ring compounds than the gram-negative ones (*E. coli* and *P. aeruginosa*). The antimicrobial potency could be increased by mixing bismuth(III) complexes containing pyrazoline and salicylate or acetate moieties as well [75]. Recently, Andrews and co-workers tested their library of *tris*-carboxylate bismuth(III) complexes derived from common NSAIDs against the parasite *Leishmania major* promastigotes [24]. The NSAID free acids and their bismuth derivatives show negligible antileishmanial activity at concentrations 1.95–250 μg mL^{-1} against the promastigotes of *L. major*. Meanwhile, several bis-carboxylate phenylbismuth(III) and *tris*-carboxylate bismuth(III) complexes were synthesized from the corresponding substituted benzoic acid derivatives [24], showing significant *antiLeishmanial* activity against the promastigotes of *L. major* V121 at very low concentrations, while their respective free carboxylic acids display no activity. These bismuth(III) complexes also inhibited the growth of the human fibroblast cells at all concentrations studied (1.95–500 μg mL^{-1}). Bi(III) alone is not responsible for high toxicity, which has been evidenced by the low toxicity of both $BiCl_3$ and $Bi(NO_3)_3$ against human fibroblast cells. Thus, the overall toxicity of bismuth(III) complexes toward the parasite and mammalian

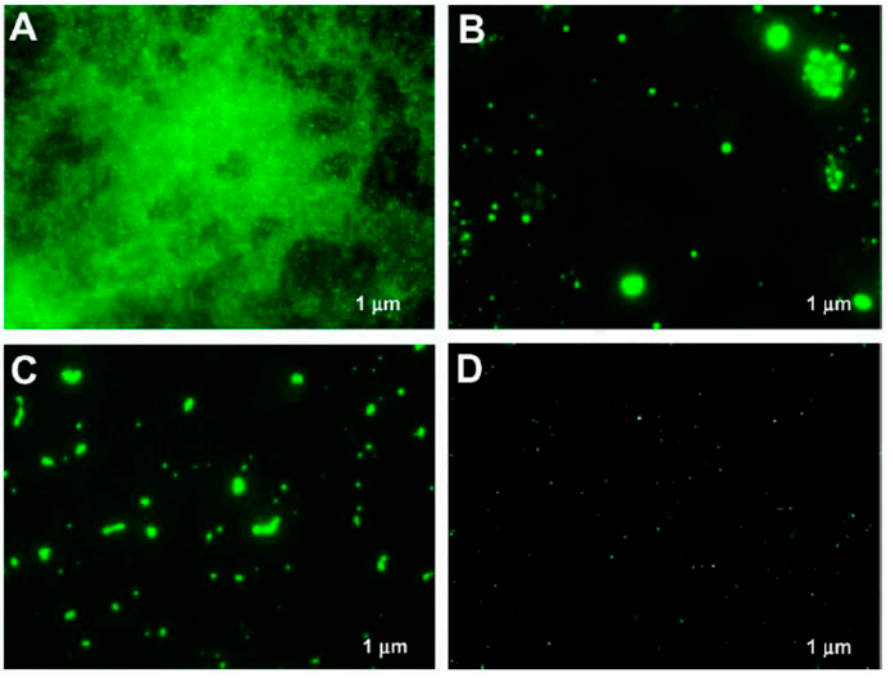

Figure 10. Inhibition of *Candida albicans* biofilm detected by fluorescence microscopy after 24 h. As a growth control, *C. albicans* was added to culture media; 2% chlorhexidine and 1% terbinafine were employed as positive inhibition controls. (A) Growth control; (B) chlorhexidine; (C) terbinafine; and (D) Bi_2O_3 NPs [72].

Table 2. List of bismuth complexes inhibiting micro-organisms.

Micro-organism	Bismuth complex
S. aureus	BisTOL [73], BisPYR [73]
E. coli, S. aureus	$BiC_9H_9ON_4SCl_2$ [34], $BiC_{18}H_{14}O_2N_8S_2Cl$ [34]
P. aeruginosa, E. coli, Legionella pneumophilo	BisBAL [73]
P. aeruginosa, Legionella pneumophilo	$Bi(NO_3)_3$ [73]
E. coli, S. aureus, P. aeruginosa, S. typhimurium, S. sonnei, S. dysenteriae	$Bi(^*sp)_3Cl_3$ [8]
E. coli, S. aureus, P. aeruginosa, Staphyococcus epidermidis	$C_{32}H_{49}BiC_{15}N_7O_{29}$ [72]
C. Albicans	Bi_2O_3 nanoparticles [72]
E. coli, Pseudomonas aeruginosa	$BiCl(O^{\cap}N^{\cap}S)$ [33], $BiCl_3{\cdot}(HO^{\cap}N^{\cap}SH)$ [33]
Pseudomonas aeruginosa	LiBiEDT-TOB [72]
Leishmanial major	$Bi\{(CH_3CONH)_2C_6H_3CO_2\}_3(H_2O)_3$ [24], $PhBi(o\text{-}NO_2C_6H_4CO_2)_2$ [24], $PhBi(o\text{-}MeOC_6H_4CO_2)_2(bipy)$ [24], $PhBi(m\text{-}MeOC_6H_4CO2)_2(H_2O)_2$ [24], $PhBi(C_9H_{12}N_2O_3CO_2)_2(H_2O)$ [24]
Staphyococcus epidermidis, S. aureus	BisEDT [73]
Staphyococcus epidermidis, Bacillus subtilis, C. Albicans, E. coli	bismuth salicylate [69]
Fusarium oxysporum, Alternaria alternate	$BiCl(O^{\cap}N^{\cap}S)$ [33], $BiCl_3{\cdot}(HO^{\cap}N^{\cap}SH)$ [33]
Streptococcus mutans	Zero-valent bismuth nanoparticles [75]
Macrophomina phaseolina, Fusarium oxysporum	$BiC_9H_9ON_4SCl_2$ [34], $BiC_{18}H_{14}O_2N_8S_2Cl$ [34]

Note: *sp=sulfapyridine.

cells is dependent on both ligand and metal [24]. Although the antimicrobial activities of bismuth compounds and their nanoparticles have been reported (table 2), the micro-organism inhibition of bismuth-based MOFs was rarely involved.

3.3. *Antitumor activity*

The main targets for biocoordination of bismuth compounds are nonDNA sites, offering new opportunities for novel mechanisms of action in bismuth-containing compounds for treatment of cancer [57, 76]. Several synthetic bismuth molecules including organo- and in-organo-bismuth derivatives have been prepared by a number of research groups and evaluated in their *in vitro* cytotoxic or antiproliferative activities against various cancer cell lines. Bismuth compounds containing the anion derived from 6-mercaptopurine were among the first antitumor trials, motivated by the known antileukemic activity of the thiol. These studies demonstrate that the presence of bismuth was essential for activity of the compounds containing anions derived from 8-hydroxyquinoline and 2-methyl-8-hydroxyquinoline. The bismuth derivatives also included bismuth dithiolates and dithiocarbamates, a water-soluble bismuth macrocycle complex, heterocyclic organobismuth derivatives, triarylbismuth bis (carboxylates), tris(2-(*N*,*N*-dimethylaminomethyl)phenyl) bismuth, and bismuth 8-quinolin-ethiolates [57, 76].

Compared with classical anticancer agents, several bismuth compounds mentioned above were verified to exhibit more potent antiproliferative effects. Recently, some new bismuth complexes have been clinically explored and assessed in cytotoxic or antitumor activity. For example, a new bismuth(III)-sulfapyridine complex was synthesized by Marzano and co-workers, which inhibited the growth of chronic myelogenous leukemia cells with an IC_{50} value of 44 μM, implying more potent anticancer effects than the free ligand [71]. A nine-coordinate bismuth(III) complex derived from pentadentate 2,6-diacetylpyridine bis (^{4} *N*-methylthiosemicarbazone) was first synthesized by Li *et al.* [22] and showed much higher antibacterial and anticancer activities than its parent ligand during *in vitro* biological studies, especially with MIC = 10.66 μM against *Bacillus cereus* and *S. typhimurium* and IC_{50} = 26.8 μM against K562 leukemia cells. It also evidently inhibited H22 xenograft tumor growth on tumor-bearing mice. These results indicate that coordination with bismuth (III) might be an interesting strategy in the discovery of new anticancer drug candidates. Li and co-workers also developed another nine-coordinate dodecahedral bismuth(III) complex and carried out *in vitro* biological studies against four human cancer cells which exhibited prominent inhibition against the growth of HCT-116 cell (human colorectal cancer), Hela cell (human cervical carcinoma), and HepG2 cell (human hepatocellular carcinoma) [23].

Bismuth(III) complexes with thiosemicarbazones have been comparatively rare. A seven-coordinate bismuth(III) complex, $[Bi(L)(NO_3)_2(CH_3CH_2OH)]$ (HL = 2-acetylpyridine *N*(4)-phenylthiosemicarbazone), has been synthesized (figure 11) with higher *in vitro* anti-proliferative activity in four human cancer cells tested. It's possible apoptotic mechanism reveals that the obtained compound promoted a dose-dependent apoptosis in HepG2 cells and the apoptosis was associated with an increase in intracellular reactive oxygen species production and reduction of mitochondrial membrane potential [77]. Although a number of bismuth complexes with anticancer activity have been reported, it is clear that the exploration of the anticancer activity of bismuth complexes is relatively undeveloped, especially the study of anticancer activity about bismuth MOFs. Among the compounds evaluated for cytotoxicity or antitumor activity, bismuth compounds seem promising and deserve more

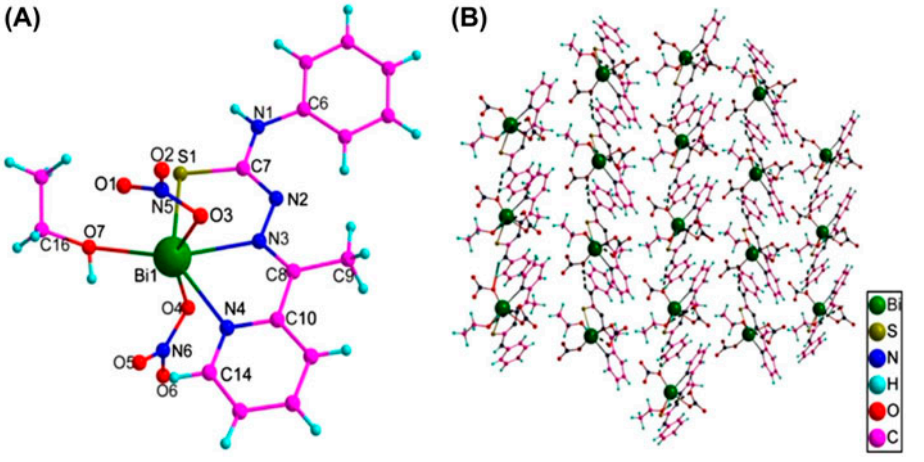

Figure 11. (A) Structure of complex with atom numbering scheme; (B) hydrogen bond in dashed lines [77].

Table 3. List of bismuth complexes with antitumor activities toward certain cancer cells.

Cancer cell line	Bismuth complex
K562	$Bi(L)NO_3(CH_3OH)$ [21], $BiCl_3(C_{11}H_{11}N_3O_2S)_3$ [71]
H22, K562	$[Bi(H_2L)(NO_3)_2]NO_3$ [22]
HCT-116, Hela, K562, HepG2	$Bi(HL)(NO_3)$ [23]
HepG2	$Bi(L)(NO_3)(CH_3CH_2OH)$ [77]
NHI 3T3	Bismuth-asparagine coordination polymers [17]
IGROV, MCF-7, A498, EVSA-T, M19, WIDR, H226	$Bi(S_2CNR_2)_3$ [78]
HL-60, Molt-4, U937, H226, A549, H596, MG-63, K562, HT1080, KATO3, MIA paca, NB4, MDA-MB-4355, Colo201, DLD-1, SK-N-SH	N-tert-butyl-bi-chlorodibenzo[c,f][1, 5]azabismocine [79], bi-chlorodibenzo [c,f][1, 5] thiabismocine [79], bi-chlorophenothiabismin-S,S-dioxide [79]
MGC-803	$C_{14}H_{12}BiClS$ [80], $C_{35}H_{31}BiGeO_2S$ [80], $C_{20}H_{17}BiClN$ [80], $C_{41}H_{36}BiGeNO_2$ [80], $C_{20}H_{23}BiClN$ [80], $C_{41}H_{42}BiGeNO_2$ [80]

research so as to offer potential and preferable applications in clinical therapy. Table 3 lists some bismuth complexes showing proven antitumor activity toward certain cancer cell lines.

4. Side effects and toxicity

Although bismuth complexes have been widely applied against *H. pylori* infection in peptic ulcer and exhibited inhibition, some side effects have been reported, including disturbances of taste, dizziness, abdominal pain, and mild diarrhea in some patients [81, 82], and a small number of patients with parageusia and glossitis [82], but no statistically significant difference in the incidence of side effects was found among the standard triple, bismuth pectin quadruple, and sequential therapies [82]. Also, Iuchi *et al.* reported heterocyclic organobismuth(III) compounds 1#, 3# and 5# (figure 12) had cytotoxicity for normal human cell

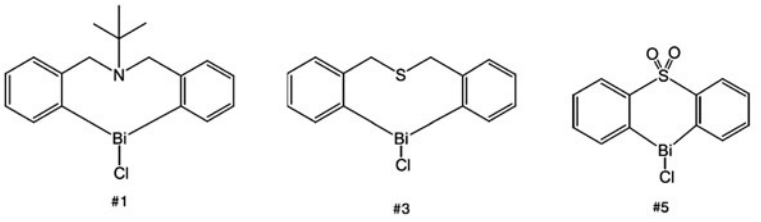

Figure 12. Chemical structures of cyclic organobismuth(III) compounds [79].

fibroblasts [79]. The cytotoxicity for normal human cell fibroblasts showed no difference in fibrosarcoma, gastric cancer, cervical cancer, and lung cancer cell lines, but displayed significant difference in leukemia cell line. This might indicate that some heterocyclic organobismuth compounds are harmful to the human body as well. So, the side effects like abdominal pain and mild diarrhea might be relative to the cytotoxicity caused to fibroblasts.

However, those side effects are characteristic of self-elimination once the therapy is terminated [82]. Being safe in the majority of patients, bismuth could cause a well-described toxic state marked by progressive neurological decline. For instance, a rare cause of neurologic dysfunction of bismuth complexes has been reported by Reynolds *et al.* which could be hardly distinguished from other causes of progressive neurologic dysfunction [83]. Also, confusion, postural instability, myoclonus as well as problems with language have been reported to be features of bismuth toxicity. According to the statistical analysis, 99% of ingested bismuth is not absorbed by the human body but passes unaltered through the feces. A small amount of the absorbed bismuth is eliminated from the body via renal or hepatic processes, not metabolism, with possibility of causing harm to kidney or liver, so bismuth encephalopathy may result from a long-term ingestion of BSS [84]. Since the main ingredient in common bismuth-containing stomach medicines is BSS with less side effects, bismuth as a cause of neurologic dysfunction may be ignored. Bismuth toxicity is usually difficult to diagnose owing to its low incidence [79], and the mechanism of bismuth toxicity has not been described, so both the intake control of the bismuth compounds and the shorter treatment period may be primary tools to reduce bismuth toxicity. Even so, bismuth complex drugs are considered safer than other compounds as drugs in biomedical applications.

5. Conclusion and outlook

Because of the low toxicity of bismuth(III) salts, more and more applications of bismuth (III) salts in the synthesis of active pharmaceutical ingredients are expected in the coming years. Benign chemical processes and products demand safer reagents for design of new reactions. In drug therapy, metal-based compounds may offer advantages over pure organic compounds. Since the toxicity of the metal is mainly responsible for the side effects and toxicity of metal-based therapy, a good choice may be provided by the low toxicity of bismuth for the use of bismuth salts to synthesize various complexes/medicines to treat gastrointestinal diseases, such as dyspepsia or eradication of *H. pylori*, or other cancers. Moreover, bismuth compounds such as bismuth subnitrate have been recently found to be

capable of reducing the side effects of cisplatin, a well-known anticancer metal-based drug. Although ^{213}Bi compounds have been used for their extraordinary antitumor ability in radiotherapy and already under Phase I/II clinical trials for non-well-recognized cancers, the high costs, unresolved chemical problems, radiologic side effects as well as the rare availability hinder their further development in radiotherapeutic treatment of cancer. Accordingly, extensive work on exploration of new bismuth complexes has been carried out with their *in vitro* and *in vivo* biological evaluation assessed, which includes bismuth-fluoroquinolone complexes as antibacterial agents, dithiocarbamates, and dibenzo azabismocine derivatives as interesting antitumor compounds [85]. Several bismuth MOFs have been synthesized with their structures characterized, which have displayed great potential and promising applications in drug delivery, but their biological evaluation has been scarcely reported. This is considered as an interesting area certainly deserving more research effort, particularly in applications of cancer treatment.

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