Water soluble tin(IV) complexes as antibacterial and anticancer agents

Synthesis of new water soluble diorganotin(IV) complexes with hydrazones derived from Girard-T reagent as antibacterial and anticancer agents

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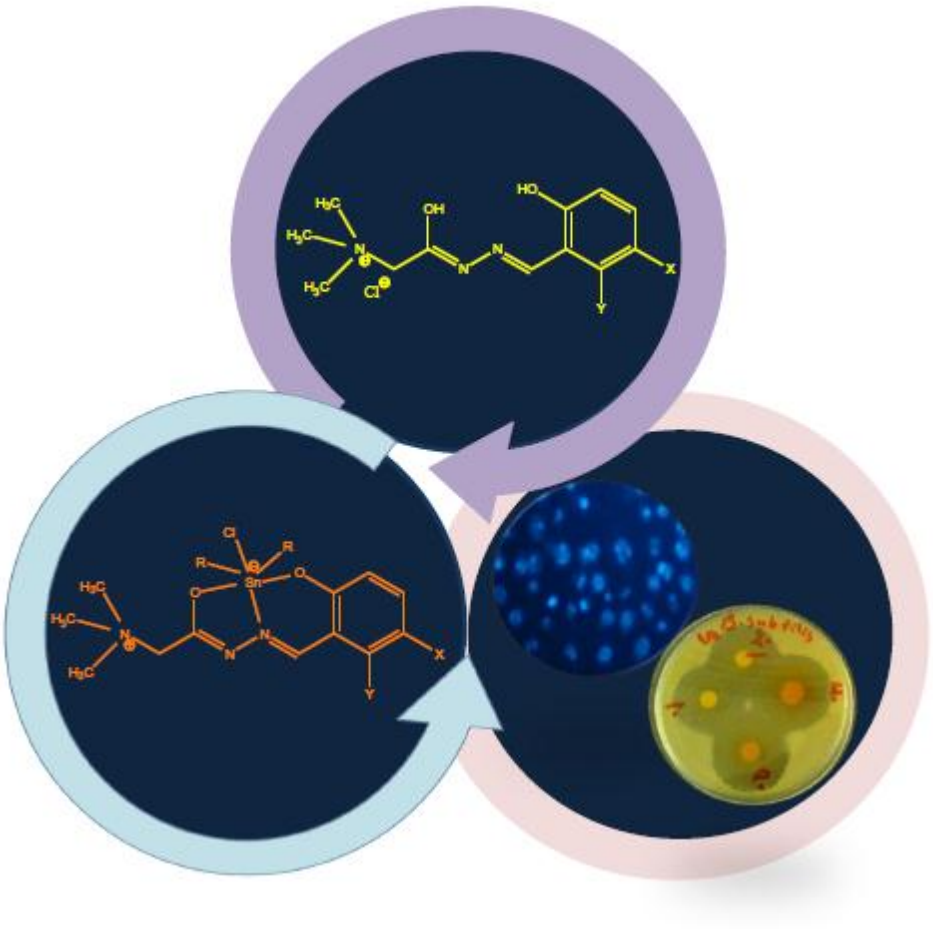
Abstract

Three new water soluble organotin complexes $R_2Sn(5\text{-}BrSalGT)Cl$ [R = Ph, Me] and $Ph_2Sn(2\text{-}OHNaphGT)Cl$ have been synthesized by the reaction of R_2SnCl_2 (R = Ph or Me) with Schiff bases derived from condensation of Girard-T reagent with 5-bromosalicylaldehyde and 2-naphthaldehyde, $(5\text{-}BrH_2SalGT)Cl$ (**1**) and $(2\text{-}OHH_2NaphGT)Cl$ (**2**). The synthesized compounds have been investigated by elemental analysis, conductometric measurements, IR, ^1H NMR, and ^{119}Sn NMR spectroscopy. These data show that the deporotonated ligand is coordinated to Sn(IV) via ONO atoms and six-coordinate zwitterionic complexes are formed. The ligands and their complexes were investigated for their *in vitro* toxicity against Gram-positive (*Bacillus subtilis* and *Staphylococcus aureus*) and Gram-negative (*Escherichia coli* and *Pseudomonas aeruginosa*) bacteria. The results show remarkable antibacterial activity against the studied bacteria. All complexes exhibit more inhibitory effects than the parent ligand. The anticancer activity of all compounds were also performed on HN5 cell line and $(2\text{-}OHH_2NaphGT)Cl$ with

concentration of 1 mg mL^{-1} was found to shows higher anticancer activity than other compounds.



Keywords

Hydrazone, Organotin, Water solubility, Antibacterial activity, Anticancer activity

1. Introduction

During the past decades, the use of organotin compounds has increased dramatically, most likely due to their diverse applications ranging from biological activity to catalysis for technical processes, even though in recent years these have been circumscribed by environmental considerations.[1-3] One of the most interesting research areas in organotin compounds is the investigation of their antitumor activities.[4] Organotin complexes with a variety of ligands, such as Schiff bases, have proven to be active against several tumor cell lines, but most of the compounds reported to date are completely insoluble in water at physiological pH.[5] Thus much effort should be directed to overcome this obstacle. Solubility in water is an important issue, dominating the *in vivo* testing of compounds with promising *in vitro* properties.[6, 7] In addition, organotins would be much more environmental friendly if their aqueous solubility could be increased. Until now a few water soluble organotin compounds have been synthesized and tested *in vitro* against some tumor cell lines. They have displayed significant activities, sometimes much higher than that of cis-platin.[8] During the last few years, condensation of Girard's reagents with ketones or aldehydes forms water-soluble ionic hydrazones represents an interesting research subject and some transition metal complexes with these ligands have been reported.[9-18] However, a survey of literature reveals that no attempt has been made to synthesize organotin(IV) complexes of Girard reagent hydrazones. We have previously reported the first organotin(IV) complexes with this type of ligands.[19] In continuation of our studies, this paper presents synthesis, characterization, anticancer activity, and antibacterial activity of three organotin(IV) complexes with two Girard-T hydrazones, (5-BrH_2SalGT)Cl (1) and (2-OHH_2NaphGT)Cl (2), derived from condensation of trimethylammoniumacetohydrazide

chloride (Girard's T reagent) with 5-bromosalicylaldehyde and 2-hydroxynaphthaldehyde, respectively.

2. Results and Discussion

2.1. Synthesis

The synthesis and crystal structure of (5-BrH_2SalGT)Cl (1) have been reported earlier by Revenko et. al.[17] Herein we have prepared 1 and 2 according to a slightly modified procedure by refluxing a solution of Girard's T reagent and the corresponding aldehyde in 1:1 molar ratio in methanol for 1 h (Figure 1). The organotin(IV) complexes, Ph_2Sn(5-BrSalGT)Cl (3), Me_2Sn(5-BrSalGT)Cl (4) and Ph_2Sn(2-OHNaphSalGT)Cl (5) were synthesized by refluxing a methanolic solution of R_2SnCl_2 (R = Ph and Me) with the corresponding Schiff base in the presence of NEt_3 as a base, in 1:1:2 molar ratio. As shown in Figure 1, the prepared ligands exist in two tautomeric forms due to the ketoamide group in their structure. According to the literature,[17] (5-BrH_2SalGT)Cl (1) in the solid state, is in the keto-amine form and the organic cation is associated with chloride anion through hydrogen bond (Figure 1).

The Schiff bases and their complexes are well soluble in DMSO and DMF, less soluble in EtOH and $CHCl_3$ and insoluble in Et_2O. The compounds 3 and 5 are relatively soluble and the others are readily soluble in water and all of them are air-stable. The molar conductivity of Schiff bases in DMF solutions refers to a 1:1 type electrolytes.[20] The complexes have higher conductivity than non-electrolytes. This can be due partly to solvation of the coordinated chloride.[15] The new compounds have been characterized by spectroscopic methods and our attempts for preparation of crystals suitable for X-ray crystallography were unsuccessful.

2.2. Spectroscopic studies

In the ^{1}H NMR spectrum of 1 in DMSO, two groups of signals were observed that is related to presence of two tautomeric forms in solution. A tautomeric form (I and II in Figure 1) ratio of 75:25 is obtained from the integrals of the signals. The ^{1}H NMR spectrum of 2 is complex due to presence of a mixture of tautomeric forms in solution and confident assignments are difficult. However in the ^{1}H NMR spectra of complexes, the absence of any signals at high frequency assigned to acidic hydrogens suggests complete deprotonation of ligand and coordination of phenolic and enolic oxygens to tin. Appearance of ^{117}Sn satellites around the imine proton signal in the spectra of 3, 4 and 5 with ^{3}J(^{119}Sn-H) coupling 34.0, 31.5 and 39.2 Hz, respectively, indicates the involvment of imine nitrogen atom in the coordination with Sn(IV).

The ^{1}H NMR spectrum of 4 shows a singlet at 1.33 ppm for $SnMe_2$ protons accompanied by satellites due to ^{119}Sn-^{1}H coupling. ^{2}J(^{119}Sn-^{1}H) for this complex (89.6 Hz) is larger than uncomplexed Me_2SnCl_2 (68.7 Hz) indicates the higher coordination number of tin. Substituation of ^{2}J(^{119}Sn-^{1}H) in the Lockhart-Manders equation,[21] gives a value of 144.5° for Me-Sn-Me angle. This value, in agreement with IR data, suggests a non-linear C-Sn-C moiety in the complexes. The ^{119}Sn{^{1}H}NMR spectra of 3-5 show one sharp singlet at -456.3, -241.3 and -445.0 ppm. These chemical shifts are at lower frequency than those of the original $SnPh_2Cl_2$ (-32 ppm) and $SnMe_2Cl_2$ (+137 ppm) and indicate an increase in coordination number of tin. According to the ^{119}Sn chemical shift ranges reported empirically,[22-24] the Sn(IV) atom is six-coordinated in the all synthesized complexes.

In the IR spectra of 1 and 2, a strong band which appeared at 1697 and 1704 cm^{-1}, respectively, is assigned to ν(C = O) and indicates tautomeric form I for these compounds. The IR spectra of complexes do not display this absorption band suggesting that the ligand coordinates with Sn(IV)

in the enol form. The ν(O-H) and ν(N-H) are absent in the spectra of complexes due to deprotonation of the Schiff base on coordination with tin(IV) atom. The new bands in the region 455-461 and 527-572 cm^{-1} in the IR spectra of complexes are assigned to ν(Sn-N) and ν(Sn-O), respectively.[25-27] Presence of both ν_{sym}(Sn-C) and ν_{asym}(Sn-C) at 571 and 642 cm^{-1}, respectively, in the IR spectrum of 4 is consistent with a nonlinear Me-Sn-Me configuration.[28]

Therefore, on the basis of our data and with considering the structure of transition metal complexes with the similar ligands,[9, 15, 17] the formally neutral structure shown in Figure 2 is suggested for complexes.

[Insert Figure 2]

2.3. Antibacterial activity

The antibacterial activity of prepared compounds were assayed against four bacterium (*Bacillus sabtilis*, *Staphylococcus aureus*, *Escherichia coli*, and *Pseudomonas aeruginosa*) under different concentration with respect to Nalidixic acid, penicillin, Gentamycin, Streptomycin, and Vancomycin as standard drugs. The results of the antibacterial activity, MIC, and MBC are presented in Table S 1 and Table S 2 respectively. (Supplemental Materials)

The results showed that the all Schiff bases and their complexes have considerable activities against both Gram-positive and Gram-negative bacteria species. In the most cases, organotin complexes show more inhibitory effects than the parent ligands. It can be explained according to Overton's concept and Tweedy's chelation theory.[29, 30] On the basis of Overton's concept, the lipid membrane that surrounds the cell favors the passage of only the lipid-soluble materials therefore lipo-solubility is an important factor, which controls the antimicrobial activity. According to chelation theory the polarity of metal ions will be reduced due to the overlap of

ligand orbitals and electron delocalization over the whole chelate ring enhances lipophilicity of complexes. The inhibitory effects of complexes may be also related to the intrinsic biological activity effects of organotin moiety. It is interesting that *P. aeruginosa* was remarkably inhibited by all compounds, while many of the standard drugs are ineffective on this microorganism as previously reported.[31] The activity of 1 and its complexes may also be related to presence of bromine in the structure. It agrees with previous reports that the compounds having halogens at the aromatic ring showed a good inhibitory effect on bacterial growth.[32, 33] In the case of antibacterial activity studies it was found that synthesized Girard reagent-based Schiff bases and their Sn(IV) complexes are more active than some non-zwitterionic Schiff bases such as N'-(5-bromo-2-hydroxybenzylidene) isonicotinohydrazide, N'-((2-hydroxynaphthalen-1-yl)methylene) isonicotinohydrazide, (Furan-2-yl)(5-hydroxy-3-methyl-5-phenyl-4,5-dihydro-1*H*-pyrazol-1-yl)methanone and their Sn(IV) complexes that previously reported by our research group.[28, 34] This can be related to various factors such as higher conductivity, solubility in both water and organic solvents, and dipole moment of prepared zwitterionic compounds.

2.4. Anticancer activity

Cell viability

The cytotoxicity assay (MTT assay) was carried out to evaluate the cell viability of cells in culture. An augment in the % growth inhibition with increasing concentration of complexes on HN5 cell line was determined. Cell viability is dependent on the interaction between the cells and the medium culture. The results of MTT assay for 1-day cell cultures are shown in Figure S 1. These results showed that there is significantly higher viability in control samples than cells exposure to the more complexes. (Data for control samples do not show separately in Figure S 1

but it was used to calculate the cell's viability values). It means that these complexes have anticancer activity in tested concentrations. In the following days (Day 2 and Day 3) the viability of treated cells decreased relative to cells cultured in the control samples. In this study the synthesized compounds have been screened for their anticancer activity. The Me_2Sn(5-BrSalGT)Cl (indicated with number of 4 in Figure S 1) exhibited higher cytotoxic activity than its corresponding ligand (indicated with number of 1 in Figure S 1). This may due to the chelation process that increases the lipophilic character of complex and biological activity effects of the organotin moiety.[35, 36] According to our findings, diphenyltin(IV) complexes are less effective for cytotoxic activity than their parent ligands. This is in disagreement with earlier reports on the anticancer activity of similar complexes.[37, 38] This observation can be related to their moderate water solubility. The cell viability data of HN5 cells show that the 0.1 mg mL^{-1}, and 1 mg mL^{-1} doses of (2-OHH_2NaphGT)Cl (more effective component indicated with number of 2 in Figure S 1) resulted in significant reduction in cell viability of approximately 10.7% and 9% respectively as compared to control after 1 d. According to these data we can suggest these complexes as effective components for cancer therapy in future.

Cell death

DAPI is a kind of specific dye for binding DNA. With the process of cell death, the ability of permeability for dye is improved and the dead cells will produce high blue fluorescence. As shown in Figure S 2, in the present investigation after 24 h exposure to the synthesized compounds, the cells exhibited characteristic cell death features in a dose dependent manner such as chromatin condensation and intensely fluorescent nuclear condensation as observed under a fluorescence microscope using DAPI staining. Microscopic observation showed that the normal

cells had normal forms with a round and uniformity nucleus while, dead cells had the round form with chromatin condensation and fragmentation of the nucleus. The treated cells exhibited fragmented and condensed nuclei's showing cellular shrinkage which is a characteristic feature of apoptosis.

3. Conclusion

Three new zwitterionic organotin(IV) complexes, R_2Sn(5-BrSalGT)Cl [R = Ph, Me] and Ph_2Sn(2-OHNaphGT)Cl were synthesized and characterized. On the basis of above disscussion, it is suggested that the coordination number of Sn(IV) is six, involving one ONO tridentate schiff base, two organic groups and one chloride. The Schiff base acts as a double-deprotonated ligand coordinated through phenolic and enolic oxygens and imine nitrogen. The synthesized organotin complexes show remarkable activity against both Gram-positive (*B. subtilis* and *S. aureus*) and Gram-negative (*E. coli* and *P. aeruginosa*) bacterial species. Since most research studies on the new anti-tumor drugs dealing with antibiotics affecting Gram-negative bacteria, it is possible that these new synthesized organotin(IV) complexes have also anti-tumor effects. Although the mechanism of biological action of organotin derivatives is still not clear, in designing new anti-tumor tin compounds it is necessary to individuate a balance between solubility and lipophilicity features in order to achieve ideal efficacy. Cell viability results proposed that treatment of ligand and complexes significantly reduces the cell viability of cancer cell line in a dose dependent manner and these compounds can enhance cytotoxic activities against tumor cell lines. Therefore with due attention to water solubility of synthesized compounds they may be excellent candidates to be used as drugs and have the potential to be a promising alternative to anticancer agents.

4. Experimental

4.1. Materials and methods

All chemicals were obtained from Merck except diphenyltin dichloride and Girard-T reagent which were respectively purchased from Alfa Aesar and Acros Company, and all were used as received. All solvents were of reagent grade and used without further purification. Fourier transform infrared spectra were recorded by a FT BOMEM MB102 spectrophotometer in the 400-4000 cm^{-1} wavenumber range. The ^{1}H and $^{119}Sn\{H\}$ NMR spectra were obtained on a Bruker 400 MHz Avance Ultrashield spectrometer using TMS and $SnMe_4$, as references, respectively. The molar conductivity of 1mM solutions of synthesized compounds in anhydrous dimethylformamide were measured on a METROHM 644 conductometer. The Supplemental Materials contians ^{1}H and ^{119}Sn NMR spectra of the ligands and complexes (Figures S 3 -- S 10)

4.2. Synthesis of ligands and theirs complexes

(5-BrH_2SalGT)Cl (**1**)

(5-BrH_2SalGT)Cl (**1**) was prepared according to a modified procedure described in the literature:[17] 5-bromo-2-hydroxybenzaldehyde (1.005 g, 5 mmol) in methanol (5 mL) was added to a stirring solution of Girard-T (0.838 g, 5 mmol) in methanol (7 mL). This solution was refluxed for 60 min. A white precipitate was formed after slow evaporation of solvent at room temperature. The resulting product was collected and washed with ethanol.

(2-OHH_2NaphGT)Cl (**2**)

This compound was synthesized as described for **(1)** from 2-hydroxynaphthaldehyde (0.861 g, 5 mmol). Yield: 74%; m.p. 198 °C; Anal. Calc. for $C_{16}H_{20}N_3O_2Cl$(%): C, 59.72; H, 6.22; N, 13.06. Found: C, 60.02; H, 5.85; N, 12.76. Λ_M (DMF): 101 S cm^2 mol^{-1}. FT-IR (KBr, cm^{-1}): 3443-3438 br, ν(OH); 3020, 2949, ν(CH); 1704, ν(C = O); 1624, ν(C = N).

Ph_2Sn(5-BrSalGT)Cl (**3**)

Triethylamine (0.28 mL, 2 mmol) was added to a stirring solution of (5-BrH_2SalGT)Cl (0.351 g, 1 mmol) in absolute methanol (7 mL). This solution was stirred for 15 min. Then a solution of Ph_2SnCl_2 (0.340 g, 1mmol) in methanol (3 mL) was added and the solution was refluxed for 120 min at 80 °C. A yellow precipitate was formed after evaporation the solvent at room temperature. This product was collected, washed with cool ethanol and dried in vacuum on $CaCl_2$. Yield: 0.38 g (61%); m.p 298 °C;Anal. Calc. for $C_{24}H_{25}N_3O_2BrClSn$ (%): C, 46.38; H, 4.05; N, 6.76. Found: C, 46.70; H, 4.03; N, 7.20. Λ_M (DMF): 61 S cm^2 mol^{-1}. FT-IR (KBr, cm^{-1}): 1617, ν(C = N); 545, ν(Sn-O); 460, ν(Sn-N). ^{1}H NMR (DMSO-d_6): δ = 8.57 [s, 1H, H_7, $^3J(^{119}Sn\text{-}^1H)$ = 35.0 Hz], 7.63 (s, 1H, H_6), 7.56 [d, 4H, H_o in $SnPh_2$, $^3J_{HH}$ = 6.2, $^3J(^{119}Sn\text{-}^1H)$ = 88.5 Hz], 7.40 (d, 1H, H_4, $^3J_{HH}$ = 8.9 Hz), 7.34-7.27 (m, 6H, $H_{m,p}$ in $SnPh_2$), 6.79 (d, 1H, H_3, $^3J_{HH}$ = 8.9 Hz), 4.14 (s, 2H, CH_2), 3.09 (s, 9H, N-CH_3). $^{119}Sn\{^1H\}$NMR (DMSO-d_6): δ = - 456.3.

Me_2Sn(5-BrSalGT)Cl (**4**)

This complex was synthesized as described for **(3)** from Me_2SnCl_2 (0.219 g, 1 mmol). Yield: 0.26 g (52%); m.p. 280 °C; Anal. Calc. for $C_{14}H_{21}N_3O_2BrClSn$ (%): C, 33.81; H, 4.25; N, 8.45. Found: C, 34.01; H, 4.70; N, 8.83. Λ_M (DMF): 79 S cm^2 mol^{-1}. FT-IR (KBr, cm^{-1}): 1618, ν(C =

N); 571, ν_{sym}(Sn-C); 642,ν_{asym}(Sn-C); 527, ν(Sn-O); 461, ν(Sn-N). ^{1}H NMR (DMSO-d_6): δ = 9.11 [s, 1H, H7, $^{3}J(^{119}Sn\text{-}^{1}H)$ = 31.5 Hz], 8.06 (s, 1H, H_6), 7.97 (d, 1H, H_4, $^{3}J_{HH}$ = 9.0 Hz), 7.21 (d, 1H, H_3, $^{3}J_{HH}$ = 8.9 Hz), 4.60 (s, 2H, CH_2), 3.79 (s, 9H, N-CH_3), 1.33 [s, 6H, Sn-CH_3, $^{2}J(^{119}Sn\text{-}^{1}H)$ = 89.6 Hz]. ^{119}Sn{^{1}H}NMR (DMSO-d_6): δ = - 214.3.

Ph_2Sn(2-OHNaphGT)Cl (**5**)

This complex was synthesized as described for **(3)** from (2-OHNaphSalGT)Cl (0.322 g, 1 mmol). Yield: 0.38 g (64%); m.p. 270 °C; Anal. Calc. for $C_{28}H_{28}N_3O_2ClSn$ (%): C, 56.74; H, 4.76; N, 7.09. Found: C, 56.32; H, 4.60; N, 7.05. Λ_M (DMF): 92 S cm^2 mol^{-1}. FT-IR (KBr, cm^{-1}): 1603, ν(C = N); 572, ν(Sn-O); 455, ν(Sn- N). ^{1}H NMR (DMSO-d_6): δ = 9.40 [s, 1H, H_7, $^{3}J(^{119}Sn\text{-}^{1}H)$ = 39.2 Hz], 8.13 (d, 1H, H_d, $^{3}J_{HH}$ = 8.6 Hz), 7.90 (d, 1H, H_3, $^{3}J_{HH}$ = 9.0 Hz), 7.78 (d, 1H, H_a, $^{3}J_{HH}$ = 7.9 Hz), 7.62 [d, 4H, H_o in $SnPh_2$, $^{3}J_{HH}$ = 7.0, $^{3}J(^{119}Sn\text{-}^{1}H)$ = 88.6 Hz], 7.49 (t, 1H, H_c, $^{3}J_{HH}$ = 8.2 Hz), 7.33-7.25 (m, 6H, $H_{m,p}$ in $SnPh_2$ and H_b), 7.10 (d, 1H, H_4, $^{3}J_{HH}$ = 9.0 Hz), 4.17 (s, 2H, CH_2), 3.15 (s, 9H, N-CH_3). ^{119}Sn{^{1}H}NMR (DMSO-d_6): δ = - 445.0.

.4.3 **Antibacterial tests**

The antibacterial activity of synthesized compounds was investigated *in vitro* against two Gram-positive (*Bacillus subtilis* ATCC 12711 and *Staphylococcus aureus* ATCC 6538) and two Gram-negative (*Escherichia coli* ATCC 11303 and *Pseudomonas aeruginosa* ATCC 27853) bacteria using the paper-disc diffusion method. The results were compared with standard antibacterial drugs, Vancomycin (30 mg/disc), Nalidixic acid (30 mg/disc), Streptomycin (10 mg/disc), penicillin (10 mg/disc), and Gentamicin (10 mg/disc). The solutions of **3** and **5** in DMSO and **1**, **2**, and **4** in H_2O were prepared at 5, 10, 20 and 40 mg mL^{-1} concentration. Basal media for the

assay of the organisms was prepared by using Muller Hinton broth. Lawn culture of all strains (0.5 MacFarland standard) were exposed to paper discs inoculated with 40 μL of test compounds or DMSO as a control. Finally, the plates were incubated at 37 °C for 24 h where inhibition zones diameters around each disc were measured in mm. The value of MIC and MBC for all prepared compounds was also determined.

4.4. Anticancer tests

Cell line culture

HN5 cancer cell line was purchased from Iran Pasteur Institute, Tehran, Iran. Cell line were cultured and maintained in DMEM medium supplemented with 10% FBS, 1% penicillin/streptomycin at 37°C with 5% CO2. HN5 (3×10^6) cells were seeded in T-25 tissue culture flask (Orange Scientific, USA) in 10 ml DMEM medium,10% FBS until confluent. When 90% confluence was obtained, the cells were passaged.

Cell viability analysis

MTT assay

The cell numbers of viable cells in the culture plates were quantitatively assessed with 3-(4,5-dimethylthiazol-2-yl)-diphenyltetrazolium bromide (MTT, Sigma). The solutions of prepared compounds were prepared at 0.1 and 1 mg mL^{-1} concentration in water. After 1, 2 and 3 d of cell culture with the prepared solutions, cells were washed with PBS and incubated with MTT (5 mg mL^{-1}) containing serum free medium. After 3 h of incubation at 37 °C in 5% CO_2, The MTT formazan were dissolved in DMSO (300 mL) and transferred to a 96-well plate. The absorbance

of the content of each well was measured at 570 nm using a spectrophotometric plate reader (Expert 96, Asys Hitch, Ec Austria).

Nuclear morphology assay:

DAPI staining was performed to determine cell death. Briefly the cells were seeded into sterilized 24 well plate for 24 h and treated with the Schiff bases and their complexes for another 24 h. Untreated cells were used as controls. Treated cells and controls were rinsed with phosphate buffered saline (PBS) fixed with paraformaldehyde 4% stained with 1μg mL^{-1} 4,6-diamidino-2-phenylindose (DAPI) for 2 min to reduce the background, the stained cells were washed with PBS and observed under a fluorescence microscope (Olympus, Japan).

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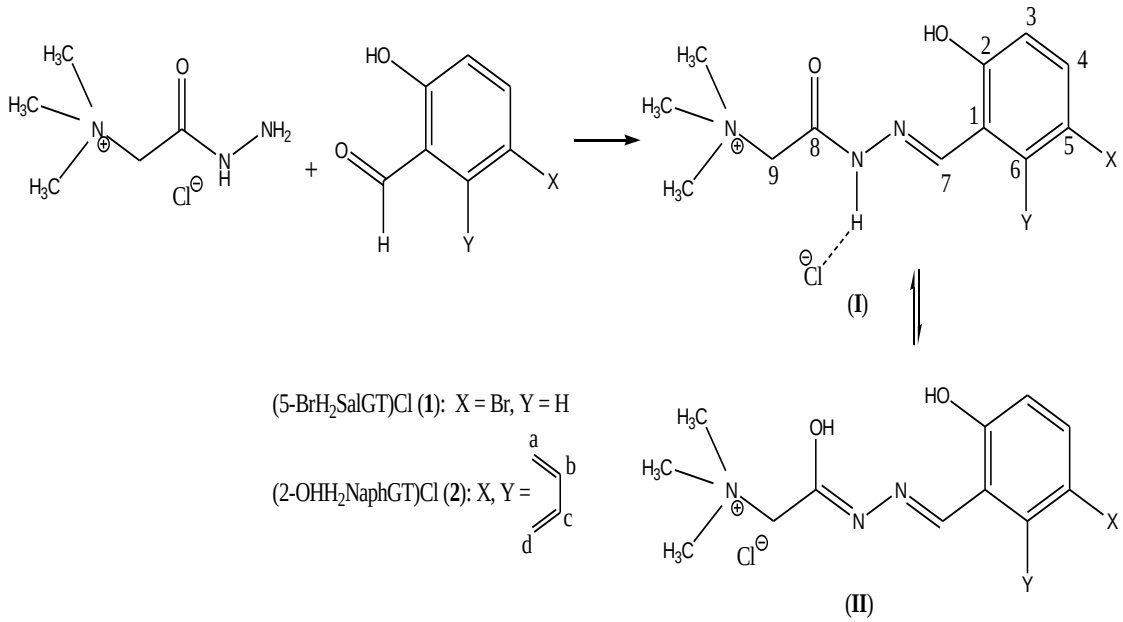

Figure 1 Synthetic pathway and tautomeric forms, keto-amine (I) and enol-imine (II), of Schiff bases.

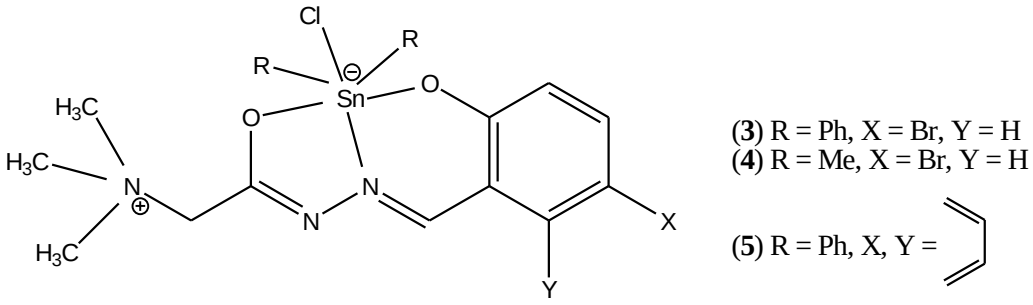

Figure 2 Suggested structure for organotin complexes.