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Organotin(IV) complexes and DNA interaction: A promising future for tin based metallodrugs

Nitesh Jaiswal

Department of Chemistry, University of Allahabad, Allahabad-211002,India.

Abstract : The growing development in field of biotechnology and genetic engineering is pushing researcher to develop DNA-targeted drugs for treatment of complex disease like cancer. Organotin based agents proving their potency in solving many biological problems. Organotin complexes containing O-, S- and N- derivative ligands has paid significant attention due to their structural feature and cytotoxic property required for biocompatibility and DNA cleavage. This review aims to provide a comprehensive, fruitful insight about tin base metallodrugs and their interaction and effect to biological system, for this purpose we tried to track recent development happened in last ten year.
Keywords : Organotin, Schiff base, DNA interaction, metallodrugs, cancer.

Introduction

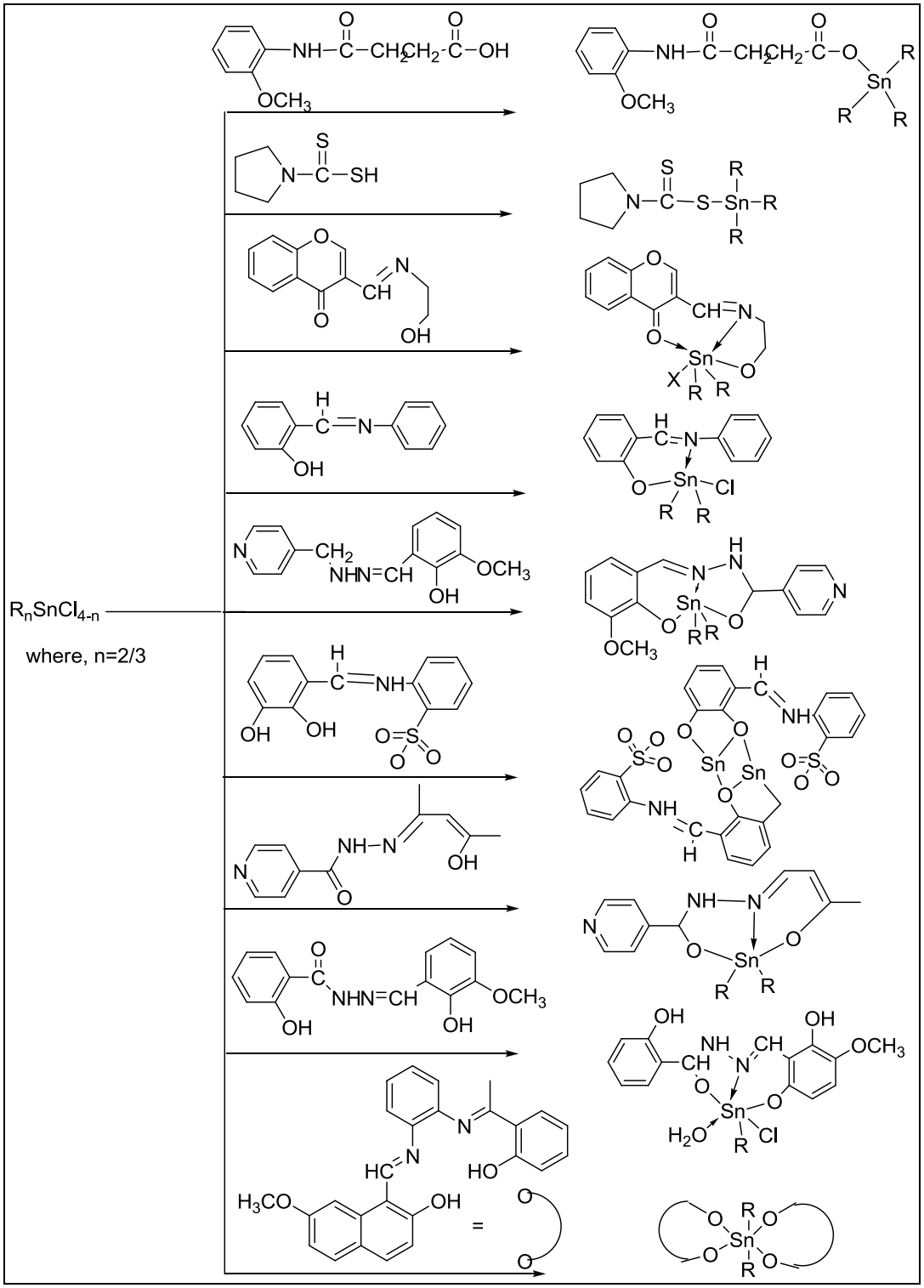
After discovery of cisplatin, new frontier has been opened in research area of inorganic medicinal chemistry for development of metal-based pharmaceutical agents [1-2]. Instead of being toxic in bulk, tin complexes at molecular level in trace amount play very crucial role in biological system [3]. The molecular architecture based design of small tin complexes makes its more effective than cisplatin in vitro tests against human cell line. [4-5]. Orgnotin complexes earned significant attention due to their biocidal activities [6-8]. In the last decades, considerable amounts of organotin(IV) compounds, focused on cancer chemotherapeutics, have been synthesized and studied. Among them, diorganotin (IV) complexes with the derivatives of salicyaldehydes derivative exhibited impressive antitumor activity [9-13]. A large number of organotin(IV) compounds [21-29] have shown efficient cytotoxic activities against panels of human cancer cell lines both *in vitro* and *in vivo*. Among the organic ligands, Schiff bases are most privileged ligands owing to their versatile synthesis, metal binding domain, and novel structural features. Schiff base can prove to be an ideal functional pharmacophore for tin-based drug design [14-16].

Metal complexes are versatile molecules due to the intrinsic characteristics of both metal centers and ligands, providing for a wide range of reactional properties [17]. Thus the choice of choosing medicinal valued ligand to organotin enhances properties of synthesized complex as well as incorporation of other metal along tin to get site specific targeting substructures. Metal centers are prone to participate in nucleophilic substitution reactions due to their cationic nature, targeting amino acids and nucleotides, and thus making proteins and nucleic acids important cellular targets.

Organotin complexes:

Generally all type of organotin (mono-, di- and tri-) complexes more or less show biological activities with specific ligands. The role of ligands is of considerable importance in tuning the cytotoxic characteristics of the complex. Ligands can modify the reactivity, lipophilicity, oral/systematic bioavailability of metal ions,

stabilization of the oxidation state and substitutional inertness depending on the requirements for chemotherapy. Keeping all this fact in mind researcher are continuously working to develop more effective and less side effect metallodrugs.



Scheme 1. Synthetic route for some organotin complexes under different specific condition(which is not mention here)

Hazra and group [26] synthesized and characterized diphenoxo-bridged diorgano dinuclear Sn(IV) compounds derived from the Schiff base 2-[(2,3- dihydroxyphenyl) methylideneamino] benzenesulfonic acid trihydrate and synthesized compounds act as effective cytotoxic (in vitro) agents on all the cell lines tested.

Diorganotin(IV) complexes derived from the isonicotinohydrazide derivative ligand were synthesized by Yadav and her co-workers [27] exhibited a high propensity for DNA binding via electrostatic modes.

Hong and co-workers [25] synthesized and characterized diorganotin(IV) complexes with 2-hydroxy-N'-[(2-hydroxy-3-methoxyphenyl)methylidene]-benzohydrazone and screened positive against CT-DNA with intercalation binding mode and their in vitro cytotoxicity determination reveals that all compounds exhibit good activity toward three cisplatin-resistant human cancer cell lines: A549cisR, HeLacisR and MCF-7cisR cell lines.

Javed et al [31] reported dithiocarbonates derivative of organotin(IV) complexes bind to DNA via intercalative interactions and also shown promising results for antileishmanial activity in vitro.

Mechanism of interaction of DNA with metal complexes

Since DNA is sole responsible for many biological activities at cellular levels and is the most important target for antitumorals because of its central role on replication and transcription, it's becomes inevitable for chemist to get insight about the molecular chemistry and mechanism [31-32] of DNA interaction with metal for developing effective metallodrugs. Therefore, it is necessary to investigate the in-depth interaction mechanism between the drug molecules and DNA, which could lead to the design of novel DNA targeted drugs.

Watson and Crick suggested that, in DNA, the two helical chains were joined together in pairs, a single base from one being hydrogen bonded to a single base from the other chain and, using Chargaff's rule, that one base had to be a purine (A or G) and the other a pyrimidine (T or C) [33]. Furthermore, the normal pairings of bases are adenine with thymine and guanine with cytosine. The pairs of bases, being planar, can be stacked one above the other. The molecule is therefore represented as a spiral staircase with the base pairs forming the steps. DNA exists in biological systems mainly in so-called B-form which is a right-handed helical structure where the base pairs are perpendicular to the helix axis. Under idealised conditions, the diameter of the B-DNA helix is 2 nm, its pitch (the distance a helix rises along its axis per turn) is 3.4 nm and since there are 10 base pairs in each turn of the helix, there is a distance of 0.34 nm between each base pair. The double helix structure of DNA contains voids or groove. These voids are adjacent to the base pairs and may provide a binding site. As the strands are not directly opposite each other, the grooves are unequally sized. One groove, the major groove, is 22 Å wide and the other, the minor groove, is 12 Å wide [33].

The general notion about the interaction mechanism between small molecules and DNA is that it occurs mainly through three non-covalent modes: intercalative binding, groove binding and electrostatic binding [34]. The most important binding mode is intercalative binding in which intercalator binds to DNA by insertion of a planar, aromatic substituent between base pairs, simultaneously lengthening and unwinding the helix [35]. The activity of the compound is mainly dependent on the method and intensity of interaction between DNA and compound.

Spectroscopic and other techniques helps in finding indicate that what mode of binding or interaction is involved between tin complexes and DNA. These techniques include UV-Vis absorption, fluorescence, DNA melting studies, viscosity measurements and molecular docking for investigating the interaction of small molecules and DNA.

Conclusion: way ahead

This review helps in understanding the increasing molecular-level knowledge about how the binding agents bind to DNA and this insight further used in design of new effective tin complexes to combat with cancer.

Functionalizing organotin(IV) complexes with tailored ligand scaffold could yield molecules with altered pharmacological properties, such as improved biocompatibility, minimal systemic toxicity, target specificity and selectivity, which provide a substantial opportunity for the identification of promising cancer

chemotherapeutics. Organotin(IV) complexes in cell biology offer diverse opportunities for manipulating biological processes**.** Identification of novel molecules that can selectively inhibit the growth of tumor cells, avoid causing side effects to patients and acquired resistance, usually associated with common chemotherapeutic agents, is of utmost importance. Novel solutions for the active targeting of tin compounds may provide an increased trend of therapeutic potential reducing toxicity towards normal cells.

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