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Review

Organo-tin antitumor compounds: Their present status in drug development and future perspectives

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ABSTRACT

Toxicity-related problems, drug resistance and broad spectrum of action have hindered the success pathway of platinum antitumor chemotherapeutic drugs, although the survival rates for patients suffering from solid cancers treated by platinum drugs, notably 'cisplatin' is considerably high. Therefore, many non-platinum metal-based chemical entities are gaining attention and have also entered preclinical testing and clinical trails, yet at a later stage they fail to qualify as drugs and consequently, there is lot of setback to pharmaceutical R&D's. Thus, there is a quest for the design of novel metal-based efficacious cancer chemotherapeutics exhibiting a different mode of action of cell death at the molecular level. Among the non-platinum metal-based drugs, organotin compounds have proven their worth in effective management of toxicity issues and specific targeted drug uptake only by the cancerous cells leaving the healthy cells unaffected (apoptosis). Herein, we reflect the progress made in the past decade by organotin compounds as antitumor chemotherapeutic agents (it was observed that more than 50% of organotin compounds show high cytotoxic activity but surprisingly have not entered clinical trails) and explore the landmarks for their future projections in drug industry.

Dr (Mrs) Farukh Arjmand, born in November, 1964, currently working as Professor of Chemistry, Aligarh Muslim University, Aligarh, India since 2009. She has completed her masters and Ph.D in chemistry from Aligarh Muslim university, Aligarh and has vast research experience of 24 years in the specialization area of bioinorganic chemistry . Her research focus is on medicinal inorganic chemistry. She works on "Design and Synthesis of chiral metal-based antitumor chemotherapeutic drug entities" and in vitro interaction studies of metal-based compounds with biomolecules viz, DNA, RNA and nucleotides. She has published more than 102 research articles pertinent to her specialization area in the peer reviewed journals of international repute , has contributed 42 articles to conferences/symposium and has two patents. She has contributed a chapter "Antitumor activity of tin complexes" to Encyclopedia of Metalloproteins (Springer, 2012). Dr. Arjmand has successfully guided 9 Ph.D and 2 M. Phil students and has run five major research projects as PI on the design of metal-based drug candidates awarded by UGC, CSIR and DBT, Govt of India (2001–09) and has visited many countries(China,USA,Egypt) for academic pursuits. She has joint research collaborations with national and international research institutes, IIT Kharagpur, IICT , Hyderabad and ACTREC, Mumbai (India) USTC, China, USM, Malaysia and Materials Chemistry Laboratory Oujda, Morocco and Institut de Physique de Rennes – UMR 6251,université de Rennes 1,France.

Abbreviations: Smac, second mitochondria-derived activator of caspases; TPT-$CuCl_2$, triphenyltinbenzimidazolethiol copper chloride; IV, intravenous therapy; Topo I, topoisomerase I.

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Sabiha Parveen received her B.Sc (Hons.) degree in Chemistry from Aligarh Muslim University in 2009. She earned her Master's Degree in Inorganic Chemistry from the same institution in 2011. Presently, she is pursuing Ph.D under the supervision of Prof.(Mrs.) Farukh Arjmand on research area "Design, synthesis and characterisation of chiral transition metal complexes and their enantiomeric discrimination with biological agents".

Prof. Sartaj Tabassum is working as Professor in the Department of Chemistry, Aligarh Muslim University, Aligarh. He was awarded Senor Research Fellowship (1988) and Research Associateship (1991) by CSIR New Delhi and in 1994 he was appointed as lecturer in the department of chemistry, Aligarh Muslim University. He has published 96 papers in the journals of international repute. He has presented his research work and delivered invited lectures in conferences/symposia. He is a life member of ICC, CRSI, ISCB, DNA Society of India and American Nano Society. He has successfully guided 15 Ph.D and 4 M.Phil students. He has successfully completed many research projects granted by TWAS, Italy, CSIR, UGC, New Delhi, DBT, Govt. of India. As a distinguished Scientist, Prof. Tabassum was awarded Overseas Associateship award in 2005 by DBT, Govt of India. He has signed several MoU and joint research collaboration with University of Camerino UNICAM, Italy, USM Malaysia and USTC Hefei, China. He has visited many countries for academic pursuit particularly, China, USA, Italy as fellow, visiting Professor and for the international conferences. Prof. Tabassum is working in the area of medicinal inorganic chemistry and his main focus is the design and synthesis of heterobimetallic complexes which have potential to act as cancer chemotherapeutics.

Prof. Claudio Pettinari was born in Camerino in 1964. He received his Laurea in Chemistry cum laude, from the University of Camerino in 1989 and he is currently full Professor of General and Inorganic Chemistry at the same University. Author of more than300papers-published on international journals, 160 communications presented at national and international congresses, 4 patents. Winner of the "Bonati" prize in 1998 for Young Researcher in Organometallic Chemistry (Italian Chemical Society), and of the "Nasini" Medal in 2004 for Inorganic Chemists (Italian Chemical Society). Doctor Honoris Causa from University of Galati in 2012. On 2008 he published the book: Scorpionates II. "Chelating Borate Ligands". Guest editor for special issues on Inorganica Chimica Acta and J. Organometallic Chemistry, chairman of the International School of Organometallic Chemistry. His main scientific interestis in the field of organometallic chemistry with N-donor ligands: in particular, the design and synthesis of new scorpionates and their organometallic derivatives (Ru, Pd, Pt, Sn, Rh, Ir, Hg, Zn, Cu) as new catalysts, biological models, and functional materials, their characterization by use of combined techniques (NMR, IR, UV–Vis, ESI, FAB, X-ray, TGA) and study of the irreactivity toward small molecules.

Contents

1. Introduction

The serendipitous discovery of cisplatin by Barnett Rosenberg in 1960s, and later its approval by FDA in 1976 as antitumor drug [1,2] for treating solid malignancies stimulated research interest in medicinal inorganic chemistry using other metal complexes as new therapeutic agents in the treatment of various chronic diseases. The impact of cisplatin has been nothing short of phenomenal. It is effective against a spectrum of human tumors, particularly testicular cancer (against which it is 100% curative if cancer is detected early), ovarian cancer, lung, head and neck and advanced bladder cancers [3]. In spite of therapeutic success, its clinical use is severely hindered by adverse side effects, systemic toxicity and intrinsic resistance [4]. Although the second generation platinum complexes with fewer side effects viz., carboplatin, nedaplatin and lobaplatin (more recently oxaliplatin is found to be first-line treatment for colorectal cancer) were introduced [5], nevertheless, two major challenges for platinum drugs still remained (i) severe side effects that were typical of heavy metal toxicity, and (ii) the development of drug tolerance by the tumors [6]. With the aim to improve the problems associated with the use of platinum compounds as therapeutic agents, a substantial investigation of other non-platinum metals (Au, Ag, Cu, Ti, Ga, Co, Ru and Sn) was undertaken [7]. In a study conducted by National Cancer Institute, NCI, with respect to cytotoxicity tests of metal-based compounds against leukemias P388 and L1210; tin-containing compounds