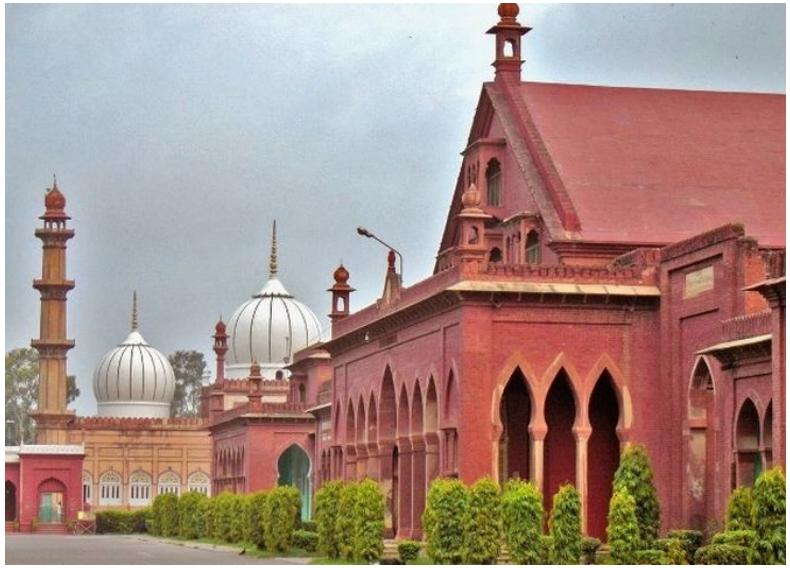
Global Contribution of Women in Science

علم الانسان ما لم يعلم

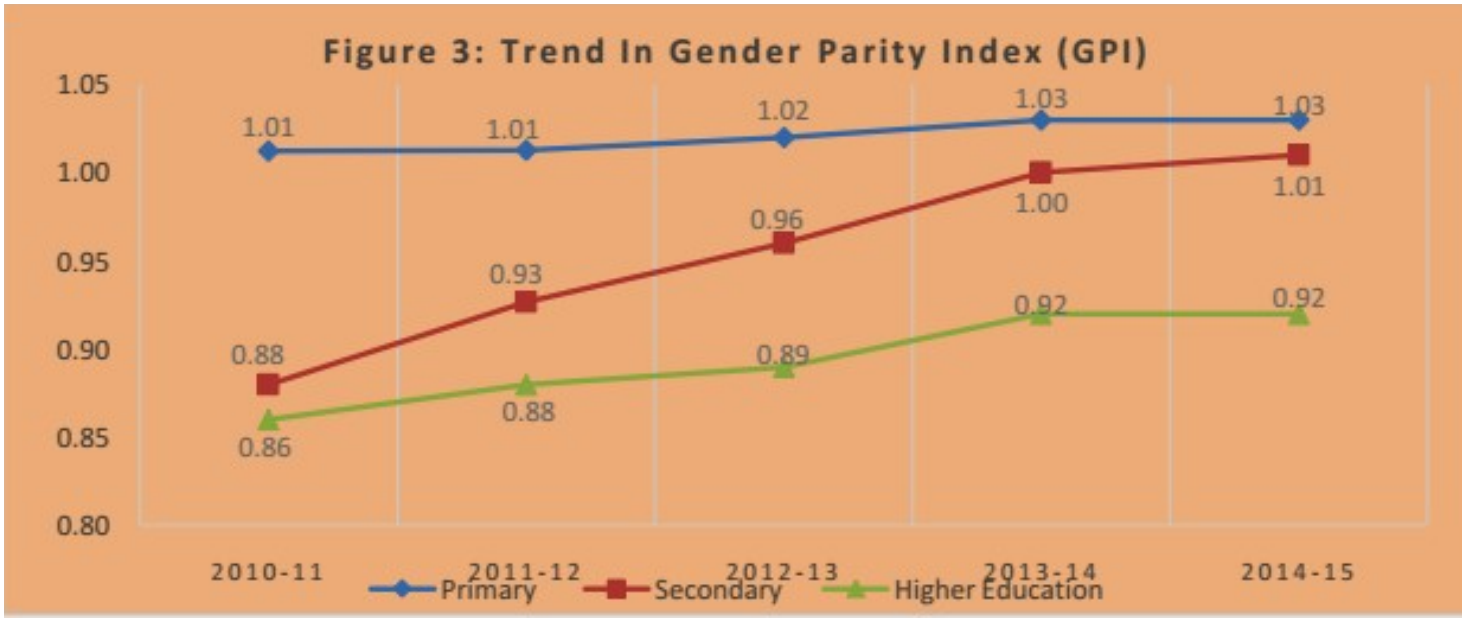
Allama al-insān mā lam y'alam

Taught man what he did not know (Qur'an 96:5)

Farukh Arjmand
Professor
Department of Chemistry
Co-Director, A.P.J. Abdul Kalam STEM-ER Center
Aligarh Muslim University



Education is the single most important factor to ensure gender equality and empowerment. The Gender Parity Index (GPI) is the ratio of the number of female students enrolled at primary, secondary and tertiary levels of education to the corresponding number of male student in each level. Thus GPI (based on GER) which is free from the effects of the population structure of the appropriate age group, provides picture of gender equality in education. During 2005-06 to 2014-15, substantial progress has been achieved towards gender parity in education as revealed by GPI in the following figure:



Present Scenario of Women's Education in Science

- **Recently, India is getting close to gender parity in the classroom as women have outnumbered men in education.**
- **This is the silver lining in the latest education trend in the country after the narrowing of gender gap with more girls now opting for college.**
- **The All India Survey on Higher Education (AISHE) has shown that India has now registered its best performance on the Gender Parity Index (GPI) in the last seven years- from 0.86 in 2010-11 to 0.94 in 2016-17.**
- **The girls-to-boys ratio in primary classes is already 1.02 while that in secondary school is 0.94. "In fact, India is predicted to be the only country in South and West Asia to have an equal ratio of girls to boys in both primary and secondary education.**
- **More women are educated than men in Goa, Himachal Pradesh, Meghalaya, J&K, Nagaland, Sikkim and Kerala In fact, in 2015.**

India was predicted to be the only country in South and West Asia to have an equal ratio of girls to boys in both primary and secondary education.

Women in STEM in India 2018

The current status of women in higher education has been described in the **All India Survey on Higher Education (AISHE 2014-2015)** (Ministry of Human Resource Development of Higher Education, New Delhi, 2016).

Muslims constitute 14.5% of the Indian population, only 4.5 % are enrolled in higher education (male and female), as compared to other social groups. The Muslim female proportion in STEM is likely to be less than 1%, despite their overall population in India of 7.5%.

- Women in STEM fields lag far behind their male counterparts, the problem is particularly **acute for women from minorities and disadvantaged groups.**

- The primary reasons are the deeply regressive socioeconomic and cultural factors in the lives of women from minority and/or poor backgrounds.

- As young girls they are discouraged and systematically discriminated against in favor of males from similar backgrounds, and lack the support necessary to remain in environments that may be otherwise conducive to the advancement of women.

APJ Abdul Kalam Center for STEM Education and Research

- The STEM Center for education and research at Aligarh Muslim University has been established in collaboration between Aligarh Muslim University and The Ohio State University, USA in November 2013.
- The initiative aims to strengthen collaboration and build partnerships between American and Indian institutions of higher education. Each project received an award of approximately $250,000 that was utilized to train eight AMU students in a batch of two(4+4).


AND RESEARCH
ALIGARH MUSLIM UNIVERSITY
&
THE OHIO STATE UNIVERSITY


INTERDISCIPLINARY

OSU Governing Board

Director: Prof. Anil Pradhan (Astronomy, Chemical Physics, Biophysics)
Co-Director: Prof. Sultana Nahar (OSU astronomy, Adjunct Professor AMU Physics)
Co-Director: Prof. Karen Irving (Education, Stem Faculty Training Program Coordinator)

AMU Governing Board

Director: Prof. Tauheed Ahmad, Department of Physics
Co-Director: Prof. (Mrs) Farukh Arjmand, Department of Chemistry.

Members

Prof. Karen Irving (Education)
Mr. Chirostopher Carey (OIA)
Prof. Altaf Wani (Medicine)
Prof. Syed Rizvi (OSU, Lima)

Associate Members

Dr. Asim Rizvi (Biochemistry)
Dr. (Ms.) Hala Noman (Physics)
Mr. Malik Azeem (Zoology)
Ms. Nida Rehmani (Biochemistry)
Mr. Parvez Alam (Biotechnology)
Ms. Sabiha Parveen (Chemistry)
Mr. Taqseer Khan (Mathematics)
Ms. Swaleha Naseem (Nanotechnology)

- Seek external funds for self sustaining operation of the centre.
- Participation by STEM departments and Interdisciplinary Institutes.
- Funds for the STEM faculty training at OSU and AMU in accordance with USIEF-OSU-AMU.
- Participation from selected Indian and US universities from Indo-US Consortium for STEM education and Research.
- Facilitate outreach activities for STEM education of primary and secondary students, focusing on disadvantage and minority groups.
- Collaboration with other Indian and US Universities for joint STEM education and Research Programs.
- Establish a technology incubator unit for sponsorship of specific research projects.

Women in STEM Roadshow

Indo-US Collaboration: STEM Educational and Research Opportunities for Women from Minorities and Disadvantaged Groups

Goal: To encourage and provide information about education and professional opportunities in science, technology, engineering and mathematics (STEM) fields for girls and young women through roadshow workshops in Delhi, Hyderabad, Kolkata, Aligarh, Patna and Kurnool in February 2018. The workshops will also highlight STEM educational opportunities at U.S. institutions of higher learning and introduce participants to EducationUSA.

OBJECTIVES

- Strengthen people-to-people ties between the United States and India through exchanges of information, experiences and expertise
- Support economic growth and development by creating awareness for girls and young women on higher education opportunities in STEM fields
- Encourage more Indian students to consider higher education opportunities in the United States by interacting with U.S. university alumni in India and promoting EducationUSA

PARTICIPATION

- 25 to 27 female students in STEM fields from colleges and universities
- Five to seven teachers from colleges, universities and high schools
- Three to four alumni from U.S. universities in the STEM fields

WORKSHOP OVERVIEW

- Nine workshops, each will be one and a half days in length; two in Delhi-NCR, Hyderabad and Kolkata and one in Aligarh, Patna and Kurnool
- Each workshop will be three sessions of three hours each. The first two sessions will comprise of lectures on STEM fields from international and local experts, training on teaching and learning pedagogies, feedback and Q&A. The third session will be a hands-on electronic experience including information on EducationUSA programs, connections to Roadshow Network for reporting, interactions, social media, etc
- Certificates to all participants will be awarded during a ceremony following the third session
- Light breakfast, lunch and tea and coffee breaks will be provided and internet, A/V facilities will be available

THE OHIO STATE UNIVERSITY

EXPECTATIONS

- Students will prepare themselves to study in the STEM fields and seek opportunities within U.S. universities and professional work in India
- Mentors will promote and motivate female students to be involved in STEM fields
- Alumni mentors will interact with high school students in three two hour sessions in each of the three U.S. consular districts of Delhi, Hyderabad and Kolkata
- Administrative officials of participating institutions are especially encouraged to select students and teachers from minorities and disadvantaged groups

GRANT OPPORTUNITIES AND ASSESSMENT

- Selected STEM Mentor Fellowships will be awarded in each workshop
- A limited number of travel grants for out-of-town participants will be available
- All monitoring and evaluations, follow-up sessions and final outcomes will be conducted through the Indo-U.S. APJ Adbul Kalam STEM Education and Research Center of The Ohio State University-Aligarh Muslim University where participants will report their progress

APPLICATION

Applicants should submit a brief resume to local contacts:

- Dr. Noor-e-Zahra, Delhi, noor_zahra_india@yahoo.co.in
- Madiha Ahmed, Kolkata, ahmedmadiha11@gmail.com
- Nida Mir, Hyderabad and Kurnool, nidamir78@gmail.com
- Syed Hasnain, Patna, syedhasanain@gmail.com
- Dr. Farukh Arjmand, Aligarh, farukh_arjmand@yahoo.com
- Sabiha Parveen, Aligarh, sabihap1@gmail.com
- Swaleha Naseen, Aligarh, nswaleha@gmail.com

CONTACT

Officials and International Experts

- Dr. Sultana N. Nahar, Program Director, professor, The Ohio State University
- Dr. Karen Irving, professor, The Ohio State University
- Dr. Nasreen Haque, President and CEO, Intalage Inc.

Visit go.osu.edu/womenstemroadshow

Objectives of Women in STEM Roadshow

- To encourage and provide information about education and professional opportunities in STEM fields for girls and young women through roadshow workshops in Delhi, Hyderabad, Kolkata, Aligarh, Patna and Kurnool in February 2018. The workshops will also highlight STEM educational opportunities at U.S. institutions of higher learning and introduce participants to Education USA.
- Strengthen people-to-people ties between the United States and India through exchange of information, experiences and expertise.
- Support economic growth and development by creating awareness for girls and young women on higher education opportunities in STEM fields.
- Encourage more Indian students to consider higher education opportunities in the United States by interacting with U.S. university alumni in India and promoting Education USA.
- To implement a STEM Roadshow in selected cities to women to pursue opportunities in encourage girls and young the fields STEM.

Juxtapose this to Hillary Clinton, who ran for President of the U.S. in 2008 and noted in her concession speech, **“I am a woman and, like millions of women, I know there are still barriers and biases out there, often unconscious, and I want to build an America that respects and embraces the potential of every last one of us.”**

.

- In recent years, due to the global socio-political scenario, the phrase "Muslim woman" represents an image of a suppressed un-empowered woman.
- Interestingly, this image is not what our history records or what our present women reflects
- There are many prominent Muslim women who hold key positions like current Prime Ministers of Bangladesh (**Sheikh Hasina Wazed**) and Mali (**Cissé Mariam Kaïdama Sidibé**) Similarly, President of Kosovo, **Atife Jahjaga,** is the world's youngest female president, as well as her country's first female Muslim president.

Since 1988, Bangladesh, Indonesia, Mali, Pakistan, Kosovo, Kyrgyzstan, Senegal and Turkey have been led, at some point, by a Muslim woman president or prime minister.

Contribution of prominent women to Science

Shirin Ebadi (Iran, 1947-Present)

In 2003, **Shirin** became the first Muslim woman to receive the **Nobel Peace Prize**. As a judge in Iran, she was the first woman to achieve **Chief Justice status**.

However, she was dismissed from this position after the 1979 Revolution. As a lawyer, Shirin has taken on many controversial cases and in result, has been arrested numerous times. Her activism has been predicated on her view that, ***"An interpretation of Islam that is in harmony with equality and democracy is an authentic expression of faith. It is not religion that binds women, but the selective dictates of those who wish them*** **cloistered."**

Kalpana Chawla

Kalpana Chawla (March 17, 1962 – February 1, 2003) was an American astronaut and the first woman of Indian origin in space.

She first flew on Space Shuttle *Columbia* in 1997 as a mission specialist and primary robotic arm operator.

In 2003, Chawla was one of the seven crew members who died in the Space Shuttle *Columbia* disaster when the craft disintegrated during its re-entry into the Earth's atmosphere.

Chawla was posthumously awarded the Congressional Space Medal of Honor,and several streets, universities, and institutions have been named in her honor.

Sunita PandyaWilliams

Sunita Pandya Williams (born September 19, 1965) is an American astronaut and United States Navy officer of Indo-Slovenian descent.

She formerly held the records for total spacewalks by a woman (seven) and most spacewalk time for a woman (50 hours, 40 minutes).

Sunita was assigned to the International Space Station as a member of Expedition and Expedition.

In 2012, she served as a flight engineer on Expedition and then commander of Expedition

Anousheh Ansari (USA, 1966-Present)

In 2006, **Anousheh** became the first Muslim woman in **space**., "*I hope to inspire everyone - especially young people, women and young girls all over the world and in Middle Eastern countries that do not provide women with the same opportunities as men -- to not give up their dreams and to pursue them*.... It may seem impossible to them at times. But I believe they can realize their dreams if they keep it in their hearts, nurture it, and look for opportunities and make those opportunities happen."

Maryam Mirzakhani

Maryam Mirzakhani 3 May 1977 – 14 July 2017) was **an Iranian mathematician and a professor of mathematics at Stanford University, USA.**

In 2014, **Mirzakhani** was honored with the **Fields Medal,** the most prestigious award in mathematics. Thus, she became both the first woman and the first Iranian to be honored with the award.

I don't have any particular recipe [for developing new proofs] ... It is like being lost in a jungle and trying to use all the knowledge that you can gather to come up with some new tricks, and with some luck, you might find a way out.

Professor Sultana Nahar, Department of Astronomy, The Ohio State University, USA, is a subject expert in **astrophysics area of research**, In addition as she's worked to bring higher science education to women and children in underdeveloped countries.
Dr. Nahar also founded the **International Society of Muslim Women in Science** to give Muslim women from developing countries exposure to Western science.

Sultana Nahar started programs to encourage the international involvement of scientists in developing countries. Since then she has connected people from 22 countries to the American Physical Society who otherwise may not have had access.
In addition, she has created programs to link emerging research professionals in developing countries **(Bangladesh, Egypt, India** and **Palestine**) with universities in the United States, including OSU. The group encourages women to pursue a career in science despite outside pressure.
"***We have a brain like any man and we are supposed to learn,"*** she said. ***"God has given you a brain. It doesn't mean you have to waste your dream to do other things."***

Dr Ameenah Gharib Fakim: Mauritius

Fakim is the current (and first female) **President of Mauritius**. She obtained her PhD degree in Organic Chemistry from Exeter University. She is known for having finished the first full inventory of Mauritius and Rodriguez Island's aromatic and medicinal plants. **She has penned more than 28 scientific books, which have sold worldwide and are used as reference books by students and researchers worldwide.**

The goal of my research is to produce safe plant-based medicines to combat everyday ailments and to help children who are suffering in the Indian Ocean region, and also in Africa."

Aisha Elsafty: Egypt

Elsafty is a Computer Scientist at the University of Cambridge. She specialises in **'AdHoc networking**,' the connecting of **computational devices via wireless technology that are used to establish networks in disaster areas and developing countries.**

My faith inspires my work in many different ways.

Sameena Shah: India

Shah is a Senior Research Scientist at **Thomson Reuters, New York.** She is the winner of the **2009 Google India Women in Engineering Award.** Shah works extensively in Artificial Intelligence. She presented an algorithm in computerized cognitive leaning that she and a team of colleagues developed at IIT Delhi, India.

I love research in Computer Science because it satiates my inherent desire to understand the logic behind things.

Professor Khatijah Mohammad Yousoff

After receiving her early education in Penang, Malaysia, she won a Colombo Plan Scholarship to La Trobe University, Australia for Tertiary Education, where she graduated with a degree in Microbiology. Her current research is on the development of therapeutic and diagnostic reagents from NDV (Newcastle Disease Virus), a contagious and fatal viral disease affecting most species of birds.

She was accorded **UNESCO's Carlos Finlay Prize for microbiology in 2005,** the second Asian scientist to receive such an honour. She was earlier honoured by the Houghton Trust to deliver the 3rd Houghton Lecture at the XIIth World Veterinary Poultry Association (WVPA) Congress in 2002 for her contributions to the poultry industry, the first Asian scientist to be bestowed such an honour. In 2008, she received the **Distinguished Alumni Award from her alma mater, La Trobe University**, the ninth person to receive this honour from over its 120,000 alumni.

Strong believer in the need to translate science into tangible benefits for people around the world.

Dr Ismahane Elouafi: Morocco/Canada

Elouafi was awarded a PhD in Genetics from Cordoba University .
She is currently the Director General of ICBA, a leading research facility that aims to help poor farmers in places where water is scarce. Prior to her appointment as head of the ICBA, she held a number of positions in the Canadian Food Inspection Agency.

She believes that Science has to be the basis of decisions and development plans in order to achieve efficiency and alleviate discrimination and poverty.

I have reached where I am today not because I'm a woman but in spite of being a woman."

Professor Dr. Bina Shaheen Siddiqui: Pakistan

Shaheen Siddiqui holds a PhD in Organic Chemistry from the University of Karachi. She has made significant contributions to medicine and agriculture through her study and classification of indigenous plant materials.

Siddiqui has written more than **250 research articles a**nd has been honoured with several prestigious awards, including **the Khwarizmi International Award of Iran and Salam Prize in Chemistry.**

Dr Rim Al Turkmani: Syria/UK

Dr Turkmani is a Syrian born astrophysicist. She gained her BSc in Electrical Engineering from the University of Damascus before moving to Sweden to study her Masters and then her PhD in Astrophysics. Dr Turkmani works on the physics of the solar corona – the halo around the sun – and through the use of computer simulation, observations and theoretical modelling, she tries to understand the dynamics of energy release in solar surface explosions, known as solar flares.

My faith is important to me and I was always taken by verses in the Qur'an which ask people to ponder the universe.

Dr. Hayat Al Sindi: Saudi Arabia

Dr. Hayat Sindi is a Saudi Biotechnologist from Makkah. She was the first woman from the Middle East to hold a PhD in Biotechnology. She was also head hunted to join George Whitesides' famous laboratory. Sindi co-founded '**Diagnostics-For-All,**' which aims to bring easier technology to developing countries. She raised money for the project by winning the prestigious Harvard Enterprise Competition and the $100,000 MIT award, attracting a further $10m from Bill Gates.

Do not let people belittle your dreams, if you believe in who you are, go for it."

Dr. Maryam Matar: United Arab Emirates

Born in 1975, **Dr. Matar** holds a B.A. in Medicine and Surgery and a degree from the Family Medicine Residency Program with distinction. She is the founder and Executive Director of two non-profit civil associations, "**UAE Down's Syndrome Association**" and "**UAE Genetic Diseases Association**," which support families from 17 different nationalities.

Being a woman is very challenging, but anything is possible to achieve with dedication, a clear goal and teamwork

Research scholars under my Supervision
Total 14 = 11 Girls + 3 Boys

Dr. Fareeda Athar

Dr. Mala Chauhan

Dr. Jamsheera

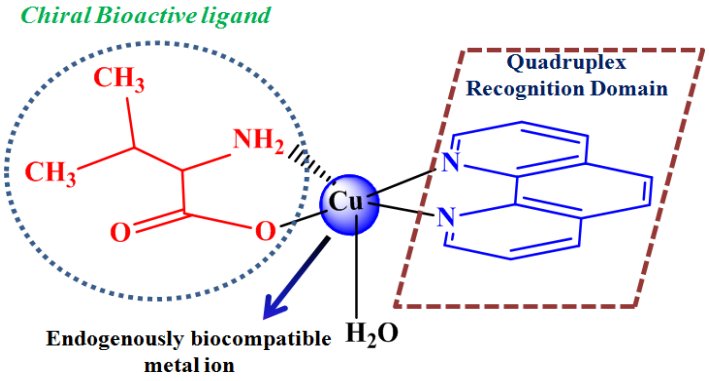
Dr. Shazia Parveen

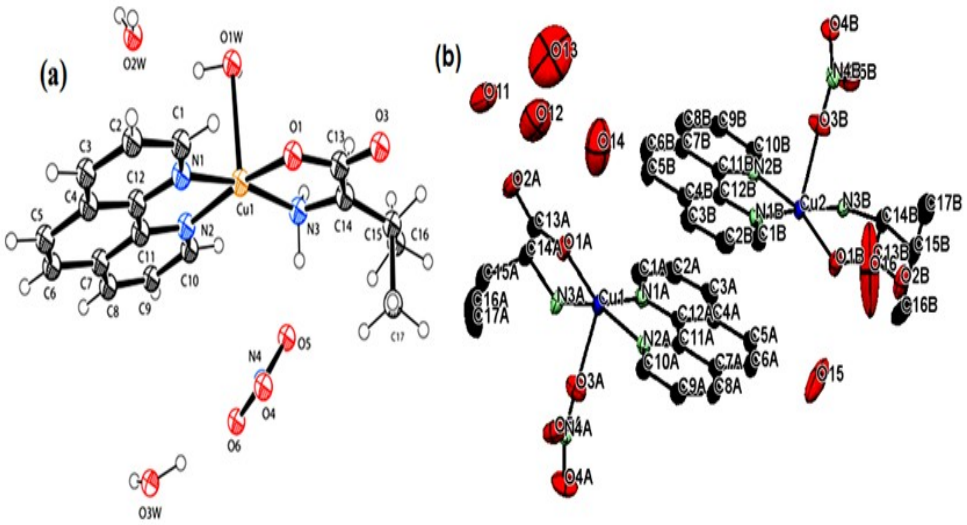
Sabiha Parveen

Surbhi Sharma

Siffeen Zehra

Zeenat Afshan





Complex	1a	1b
Formula	$C_{17}H_{24}CuN_4O_8$	$C_{34}H_{46\cdot50}Cu_2N_8O_{15.50}$
Fw (g mol^{-1})	505.96	942.37
crystal system	Monoclinic	Monoclinic
space group	P 21	C2
a (Å)	5.74690(10)	24.605
b (Å)	20.6365(2)	7.348
c (Å)	9.28010(10)	26.014
α (deg)	90	90
β(deg)	98.2040(10)	119.52
γ (deg)	90	90
U (Å^3)	1089.32(2)	4092.7
Z	2	4
ρ_{calc} (mg/cm^3)	1.543	1.529
μ (mm^{-1})	1.871	1.967
F(000)	522	1954
Temp (K)	150(2)K	100(2)K
Indep reflns	3741	3579
GOF[a]	1.080	1.065
R[b][I>2σ(I)]	0.0253	0.0452
wR_2[b] (all data)	0.0775	0.1280

Smart Metal Based Drug Entity – SMBDE 6

Table. The relative IC_{50} values for complexes 1a and 1b in different human cancer cell lines

Compound	MCF7	BxPC3	AsPC1	Huh7
	Breast cancer	Pancreatic cancer	Pancreatic cancer	Liver
L–complex, 1a	2.15 ± 0.04	2.46 ± 0.22	2.29 ± 0.19	1.44 ± 0.05
D–complex, 1b	2.52 ± 0.12	2.23 ± 0.60	1.95 ± 0.10	1.43 ± 0.08

❖Complexes **1a** and **1b** exhibited significant cytotoxic activity against all four tested cell lines with IC_{50} values in the range of 1–3 μM.

❖The experimental results with remarkably low IC_{50} values validate the potential of chiral complexes **1a** and **1b** to act as promising anticancer drug agents and warrants further *in vivo* investigations.

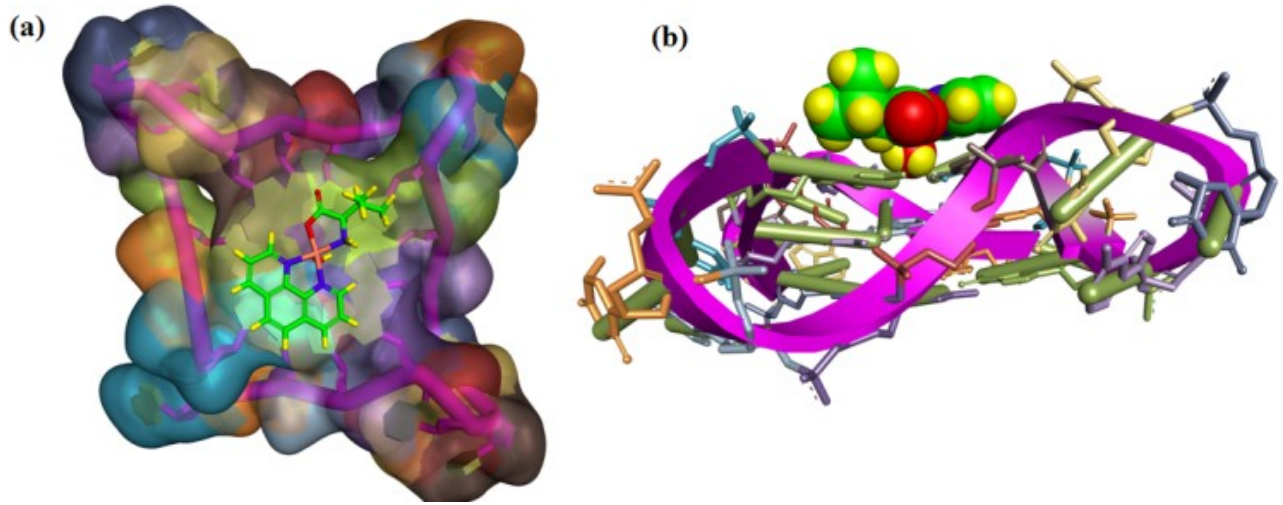


Fig. Top view and **(b)** side view of the docked pose of complex **1a** with parallel quadruplex G4 structure (PDB ID: 1KF1). The G4 surface structure is represented as ribbon and the complex **1a** as CPK and sticks.

PCCP

COMMUNICATION

Vibrational dynamics (IR, Raman, NRVS) and a DFT study of a new antitumor tetranuclearstannoxane cluster, Sn(IV)-oxo-{di-*o*-vanillin} dimethyl dichloride†

F. Arjmand,*[a] S. Sharma,[a] M. Usman,[a] B. M. Leu,*[b] M. Y. Hu,[b] L. Toupet,[c] D. Gosztola[d] and S. Tabassum[a]

Cite this: *Phys. Chem. Chem. Phys.*, 2016, **18**, 17805

Received 30th April 2016,
Accepted 8th June 2016

DOI: 10.1039/c6cp02914k

www.rsc.org/pccp

The vibrational dynamics of a newly synthesized tetrastannoxane was characterized with a combination of experimental (Raman, IR and tin-based nuclear resonance vibrational spectroscopy) and computational (DFT/B3LYP) methods, with an emphasis on the vibrations of the tin sites. The cytotoxic activity revealed a significant regression selectively against the human pancreatic cell lines.

The resurgence of organotin(IV) as active metallopharmaceuticals in cancer oncology is well recognized[1,2] and much attention is being devoted to the design and synthesis of therapeutically active compounds of organotin(IV) embedded in organic frameworks with N-O, O-O, N-N donor atoms.[3,4] *o*-Vanillin, 2-hydroxy-3-methoxy benzaldehyde is a useful drug precursor that has been used for the preparation of many Schiff base complexes and conjugate supramolecular motifs that display exceptional biological activities *viz.*, anti-inflammatory, antibacterial, antiviral and antitumor.[5] Organotin(IV) compounds possessing ligand skeletons with Sn–N, Sn–S and Sn–O bonds are considered to be therapeutically potent, and it was observed that the organotin complexes which have covalent bonds between the Sn and O atoms are very active compounds compared to those which have coordinate bonds between them. Furthermore, it was observed that amongst the organotin(IV) compounds, the activity of diorganotin(IV) was highest for most of the human cancer cell lines.[6] Previous literature reports reveal that the biological activity of diorganotin compounds, R_2SnX_2, is determined by the R organic group which exercises control on the cytotoxic activity, while X groups control the delivery of the active R_2Sn^{2+} species.[7]

Many studied organotin(IV) complexes are mononuclear,[1c] although tetranuclear or polymeric species have also been investigated.[8] Since metal nuclearity plays a key role in imparting pharmacological responses to drug entities, many organotin(IV) complexes that are polynuclear or have an appropriate coordination number were found to exhibit a better biological activity as compared to mononuclear derivatives. Recently, X. Shang *et al.* reported ladder-like tetraorganostannoxane complexes formulated as $[R_8Sn_2(C_6H_{11}COO)(\mu_3\text{-}O)(\mu\text{-}OH)]_2$ (R = Et, ^{n}Bu, ^{n}Oct and Ph) possessing a Sn_4O_4 core. The therapeutic potential of these complexes was assessed by their cytotoxic activity against the human tumor cell lines, *viz.*, HL-60, BGC-823 and KB with cisplatin as a control.[9] The IC_{50} values (μM) of these complexes showed good antitumor activity. Several other organooxotin clusters have also been synthesized[10] and chemically modified by organic ligands using selective spacers or tailed groups, such as carboxylic acids, phosphonic acid, phosphinic acid and arsonates.[11]

Organooxotin clusters are considered a new class of pharmaceutical drug motifs owing to their remarkable structural diversity[12] and exceptional biological applications.[13] Recently, organooxotin clusters with methylresorcin[4]arene cavitands were found to be suitable for drug delivery at the target site with specificity.[14] It was further revealed that the organic substituent attached to tin atoms through an oxo bridge in stannoxane complexes could be responsible for good anticancer activities. Furthermore, probing vibrations coupled to localized electronic excitations during chemical reactions could be crucial for depicting the interactions at the active site at the molecular level.[15] The experimental identification of in-plane and out-of-plane vibrational modes could significantly contribute to understand binding interactions with biological molecules and their reaction dynamics.[16] In tetraorganostannoxane, the presence of four tin atoms contributes to a larger molecular system and therefore, many vibrational frequencies that could be responsible for more intimate binding emerge. Among the out-of-plane vibrations, the most significant modes in the low frequency region are

[a] *Department of Chemistry, Aligarh Muslim University, Aligarh 202002, India. E-mail: farukh_arjmand@yahoo.co.in; Tel: +91 5712703893*
[b] *Advanced Photon Source, Argonne National Laboratory, Argonne, Illinois 60439, USA. E-mail: leu@aps.anl.gov; Tel: +1 630 252 8821*
[c] *Institut de Physique de Rennes, UMR 625, Université de Rennes 1, Campus de Beaulieu Bat. 11 A, 263 av. Général Leclerc, 35042 Rennes Cedex, France*
[d] *Center for Nanoscale Materials, Argonne National Laboratory, Argonne, Illinois, USA*

† Electronic supplementary information (ESI) available: Detailed experimental procedures and characterisation; additional biophysical data. CCDC 1403573. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c6cp02914k

Inorganica Chimica Acta 458 (2017) 8–27

Contents lists available at ScienceDirect

Inorganica Chimica Acta

journal homepage: www.elsevier.com/locate/ica

Review article

Chiral transition metal complexes: Synthetic approach and biological applications

Surbhi Sharma [a], Mala Chauhan [b], A. Jamsheera [c], Sartaj Tabassum [a], Farukh Arjmand [a,*]

[a] *Department of Chemistry, Aligarh Muslim University, Aligarh 202002, India*
[b] *Chinmaya Degree College, H.N.B., Garhwal University, Srinagar, Garhwal, India*
[c] *Department of Chemistry, NIT Aizawal, Mizoram, India*

ARTICLE INFO

Article history:
Received 26 September 2016
Received in revised form 6 December 2016
Accepted 9 December 2016
Available online 20 December 2016

Keywords:
Chirality
Transition metal complexes
Molecular recognition
Pharmaceuticals
Biomimetic enzyme models
Nucleic acid probes

ABSTRACT

Chiral metal complexes render new breakthroughs in chemical sciences by providing stereoselective, robust and enantiomerically pure compounds and their applications as pharmaceuticals, diagnostic agents, in supramolecular assemblies, enzyme catalysis, biomimetic model systems and as nucleic acid probes. Recent progress in interdisciplinary research has motivated researchers to look for innovative measures to improve the quality of life and spurred various efforts directed towards the creation of molecularly engineered novel synthetic agents. The use of food additives, flavors, agrochemicals, pharmaceuticals and new medical diagnostic agents is indispensible in modern era, therefore to foster this concept, synthetic methodologies have to be monitored carefully. The growth of this core technology has given rise to enormous economic potential in the manufacture of pharmaceuticals, fungicides, flavors, and fragrances. As this subject is an essential component of molecular science, this review deals with the most representative contributions in the field of chiral transition metal complexes, their synthetic methodology and biological applications.

Contents

1. Introduction

Chirality is an intrinsic universal feature of various levels of matter [1]. Molecular chirality plays an important role in science and technology. Life depends on molecular chirality as many biological

* Corresponding author.
E-mail address: farukh_arjmand@yahoo.co.in (F. Arjmand).

http://dx.doi.org/10.1016/j.ica.2016.12.011
0020-1693/

[170] (a) M.L. Leiserowitz, Nature 296 (1982) 21–26; (b) L. Addadi, E. Gati, M. Lahav, J. Am. Chem. Soc. 103 (1981) 1251–1252; (c) L. Addadi, J. van Mil, M. Lahav, J. Am. Chem. Soc. 103 (1981) 1249–1251.
[171] R.A. Hegstrom, D.K. Konepudi, Sci. Am. (1990) 108.
[172] A.N. Collins, G.N. Sheldrake, J. Crosby, Chirality in Industry (Wiley and Sons, Chichester, 1992, vol. 1 and 1997, vol. 2.
[173] J. Chin, S.S. Lee, K.J. Lee, S. Park, D.H. Kim, Nature 401 (1999) 254.
[174] (a) M.C.-L. Yeung, V.W.-W. Yam, Chem. Soc. Rev. 44 (2015) 4192; (b) S. Leininger, B. Olenyuk, P.J. Stang, Chem. Rev. 100 (2000) 853.
[175] G.F. Swiegers, T.J. Malefetse, Chem. Rev. 100 (2000) 3483.
[176] R.M. Izatt, J.D. Lamb, N.E. Izatt Jr., J. Am. Chem. Soc. 101 (1979) 6273.
[177] R.M. Izatt, K. Pawlak, J.S. Bradshaw, R.L. Bruening, Chem. Rev. 91 (1991) 1721.
[178] L.A. Nguyen, H. He, C. Pham-Huy, Int. J. Biomed. Sci. 2 (2006) 85–100.
[179] H. Ali, J.E. van Lier, Chem. Rev. 99 (1999) 2379.
[180] A.Y. Louie, T.J. Meade, Chem. Rev. 99 (1999) 2711.
[181] W.A. Volkert, T.J. Hoffman, Chem. Rev. 99 (1999) 2269.
[182] R. Onfelt, P. Lincoln, B. Norden, J. Am. Chem. Soc. 123 (2001) 3630.
[183] F.M. Foley, F.R. Keene, J.G. Collins, J. Chem. Soc. Dalton Trans. (2001) 2968.
[184] K.E. Erkkila, D.T. Odom, J.K. Barton, Chem. Rev. 99 (1999) 2777.
[185] S.J. Franklin, J.K. Barton, Biochemistry 37 (1997) 16093.
[186] C.V. Christodoulou, A.G. Eliopoulos, L.S. Young, L. Hodgkins, D.R. Ferry, D.J. Kerr, Br. J. Cancer 77 (1998) 2088.
[187] M. Guo, H. Sun, S. Bihari, J.A. Parkinson, R.O. Gould, S. Parsons, P.J. Sadler, Inorg. Chem. 39 (2000) 206.
[188] P. Yang, M. Guo, Met.-Based Drugs 5 (1998) 41.
[189] K. Radtke, F.A. Lorenitzo, R.W. Byrnes, W.E. Antholine, D.H. Petering, Biochem. J. 301 (1994) 655.
[190] S.J. Brown, X. Tao, T.A. Wark, D.W. Stephan, P.K. Mascharak, Inorg. Chem. 27 (1988) 1581.
[191] H. Kurosaki, K. Hayashi, Y. Ishikawa, M. Goto, K. Inada, I. Tanigushi, M. Shionaya, E. Kimura, Inorg. Chem. 38 (1999) 2824.
[192] J.D. Tan, S.E. Hudson, S.J. Brown, M.M. Olmstead, P.K. Mascharak, J. Am. Chem. Soc. 114 (1992) 3841.
[193] E. Farinas, J.D. Tan, N. Baidya, P.K. Mascharak, J. Am. Chem. Soc. 115 (1993) 2996.
[194] H. Kuramochi, K. Takahashi, T. Takita, H. Umezawa, J. Antibiot. 34 (1981) 578.
[195] H. Kurosaki, K. Hayashi, Y. Ishikawa, M. Goto, Chem.lett. (1995) 691.
[196] T.E. Lehmann, L.J. Ming, M.E. Rosen Jr., Biochemistry 36 (1997) 2807.
[197] A. Mukherjee, S. Dhar, M. Nethaji, A.R. Chakravarty, Dalton Trans. (2005) 349.
[198] M.C. Biagini, M. Ferrari, M. Lanfranchi, L. Marchio, M.A. Pellinghelli, J. Am. Chem. Soc. Dalton Trans. (1999) 1575.
[199] G.P. Moss, Pure Appl. Chem. 68 (1996) 2193.
[200] N. Farrell, D.M. Kiley, W. Schmidt, M.P. Hacker, Inorg. Chem. 29 (1990) 397.
[201] A. Rodger, K.K. Patel, K.J. Sanders, M. Datt, C. Sacht, M.J. Hannon, J. Chem. Soc. Dalton Trans. (2002) 3657.
[202] C. Sacht, M.S. Datt, S. Otto, A. Roodt, J. Chem. Soc. Dalton Trans. (2000) 727.
[203] V. Schurig, F. Betschinger, Chem. Rev. 92 (1992) 873.
[204] M.M. Aly, J. Coord. Chem. 43 (1998) 89.
[205] C.J. Jones, Chem. Soc. Rev. 27 (1998) 289.
[206] R. Breslow, Acc. Chem. Res. 28 (1995) 146.
[207] F.C.J.M. van Veggel, W. Verboom, D.N. Reinhoudt, Chem. Rev. 94 (1994) 279.
[208] D.H. Busch, N.W. Alcock, Chem. Rev. 94 (1994) 585.
[209] P.A. Vigato, S. Tamburini, D.E. Fenton, Coord. Chem. Rev. 106 (1990) 25.
[210] A.J. Kirby, Angew Chem. In. Ed. Engl. 35 (1996) 707.
[211] R. Hage, Recl. Trav. Chem. Pays-Bas 115 (1996) 385.
[212] M.A. Halcrow, G. Christou, Chem. Rev. 94 (1994) 2421.
[213] Z. Li, C. Jablonski, Inorg. Chem. 39 (2000) 2456.
[214] Z.Y.L. Ojima, in: R.D. Adams, F.A. Cotton (Eds.), Catalysis by di and Polynuclear Metal Cluster Complexes, Wiley-VCH, Stony Brook, NY, 1998, p. 307.
[215] R. Breslow, X. Zhang, R. Xu, M. Maletic, R. Merger, J. Am. Chem. Soc. 118 (1996) 11678.
[216] M. Shibasaki, H. Sasai, T. Arai, Angew Chem. Int. Ed. Egl. 36 (1997) 1237.
[217] R.G. Konsler, J. Karl, E.N. Jacobsen, J. Am. Chem. Soc. 120 (1998) 10780.
[218] R.L. Feringa, O.J. Gelling, M.T. Rispens, M. Lubben, in: L. Fabbrizzi, A. Poggi (Eds.), Transition Metals in Supramolecular Chemistry, Kluwer Press, Amsterdam, 1994, p. 171.
[219] D.R. Smith, Chem. Rev. 164 (1997) 575.
[220] A. Volbeda, A. Lahm, F. Sikiyama, D. Suck, EMBO J. 10 (1991) 1607.
[221] E. Hough, L.K. Henson, B. Birkens, K. Jynes, S. Hansen, A Hordvik, C. Little, E. Dodson, Z. Derewenda, Nature 338 (1989) 357.
[222] S.K. Burley, P.R. David, R.M. Sweet, A. Taylor, W.N. Lipscomb, J. Mol. Biol. 224 (1992) 113.
[223] E.E. Kim, H.W. Wyckoff, J. Mol. Biol. 218 (1991) 449.
[224] E.C. Fusch, B.J. Lippert, J. Am. Chem. Soc. 116 (1994) 7204.
[225] R.L. Paul, A.J. Amoroso, P.L. Jones, S.M. Couchman, Z.R. Reeves, L.H. Rees, J.C. Jeffery, J.A. McCleverty, M.D. Ward, J. Chem. Soc. Dalton Trans. (1999) 1563.
[226] A. Bilyk, A.K. Hall, J.M. Harrow field, M.W. Hosseini, G. Mislin, B.W. Skelton, C. Taylor, A.H. White, Eur. J. Inorg. Chem. (2000) 823.
[227] Y. Yoshikawa, E. Ueda, K. Kawabe, H. Miyake, H. Sakurai, Y. Kojima, Chem. Lett. (2000) 874.
[228] Y. Yoshikawa, E. Ueda, Y. Suzuki, N. Yanagihara, H. Sakurai, Y. Kojima, Chem. Pharm. Bull. 49 (2001) 652.
[229] Y. Yoshikawa, E. Ueda, H. Miyake, H. Sakurai, Y. Kojima, Biochem. Biphys. Res. Commun. 281 (2001) 1190.
[230] Y. Yoshikawa, E. Ueda, H. Miyaka, H. Sakurai, Y. Kojima, Elements 11 (2000) 349.
[231] R. Ren, P. Yang, W. Zhang, Z. Hua, Inorg. Chem. 39 (2000) 5454.
[232] X.S. Tan, Y. Fujii, T. Sato, Y. Nakano, M. Yashiro, Chem. Commun. (1999) 881.
[233] V. Beudny, O. Vrana, F. Gaucheron, V. Kleinwachter, M. Leng, V. Brabec, Nucleic Acids Res. 20 (1992) 267.
[234] K. Vickery, A.M. Bonin, R.R. Fenton, S. O'Mara, P.J. Russell, L.K. Webster, T.W. Hambley, J. Med. Chem. 36 (1993) 3663.
[235] R.R. Fenton, W.J. Easdale, H.M. Er, S.M. O'Mara, M.J. McKeage, P.J. Russell, T.W. Hambley, J. Med. Chem. 40 (1997) 1090.
[236] K. Naing, M. Takahashi, M. Taniguchi, A. Yamagishi, Inorg. Chem. 34 (1995) 350.
[237] D. Baker, R.J. Morgan, T.C. Strekas, J. Chem. Soc. Chem. Commun. (1992) 1099.
[238] J.K. Barton, U.S. Pat. 4699978, 1987.

Prof. (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. Sheworks 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 112 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 12 Ph.D and 4 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, Institut de Physique de Rennes-UMR 6251,université de Rennes 1, France and Advanced Photon Source, Argonne National Laboratory, Argonne, Illinois 60439,United States.

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 105 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 16 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.

Ms. Surbhi Sharma is presently pursuing Ph.D under the supervision of Prof. (Mrs.) Farukh Arjmand in the Department of Chemistry, Aligarh Muslim University, Aligarh. She was awarded prestigious UGC Basic Science Research (BSR) fellowship in 2015. Her research topic includes 'Synthesis, characterization of new metal-based antitumor chemotherapeutic compounds and their biological evaluation". She has published 2 research articles in the peer reviewed journals (PCCP and Rsc advances) of international repute.

RSC Advances

PAPER

Cite this: RSC Adv., 2017, 7, 6587

Synthesis of chiral *R*/*S*-pseudopeptide-based Cu(II) & Zn(II) complexes for use in targeted delivery for antitumor therapy: enantiomeric discrimination with CT-DNA and pBR322 DNA hydrolytic cleavage mechanism†

Sabiha Parveen, Sartaj Tabassum and Farukh Arjmand*

Received 5th October 2016
Accepted 2nd January 2017

DOI: 10.1039/c6ra24770a

www.rsc.org/advances

Chiral pseudopeptide Cu(II) and Zn(II) complexes ($1_{S/R}$ and $2_{S/R}$, respectively), were obtained by a *de novo* synthetic strategy employing pseudopeptide synthons derived from *R*/*S*-2-amino-2-phenylethanol and *N*-methyliminodiacetic acid. The complexes were thoroughly characterized by elemental analysis, mass spectrometry, and IR; the $2_{S/R}$ complexes were further characterized by ^{1}H, ^{13}C NMR, whereas $1_{S/R}$ complexes were studied by EPR spectroscopy. *In vitro* DNA binding studies were carried out by UV-Vis, fluorescence, thermal denaturation and circular dichroic techniques. The experimental results revealed that the complexes strongly bind to DNA *via* electrostatic interaction. The extent of binding was quantified by computing their intrinsic binding constant (K_b) and binding constant (*K*) values, which showed that the *S*-enantiomers of both complexes 1 and 2 exhibited higher binding propensities as compared to their *R*-enantiomeric analogs, and followed the trend $1_S > 2_S > 1_R > 2_R$. Thermal denaturation studies of complexes in the absence and presence of CT-DNA have been carried out and the calculated ΔT_m was found to be 1–3 °C, depicting the electrostatic mode of binding, which corroborated the results of the UV-Vis, fluorescence and other optical methods. The cleavage efficiencies of 1_S and 2_S with pBR322 DNA were evaluated by gel electrophoretic assay. *S*-Enantiomers of both Cu(II) and Zn(II) complexes were found to be efficient cleaving agents and cleavage reactions were mediated by hydrolytic pathways, which were further validated by relegation experiments using the T4 ligase enzyme. The cytotoxic activity of 1_S and 2_S showed pronounced GI_{50} values <10 μg mL^{-1} in the case of the HeLa cancer cell line, whereas for other cell lines, *viz.* MCF7, Hep-G2 and MIA-Pa-Ca-2, moderate activity was observed, which implicated the selective response of drug entities towards different cancer phenotypes.

Introduction

Cancer or malignant neoplasm is a complex class of diseases that are difficult to treat due to various phenotypes being derived from numerous organs/tissues with multiple etiologies and endless combinations of genetic and epigenetic alterations.[1] It is said that we have entered "the age of cancer", with 6.5 million cancer deaths in 2003, reaching 12 million in 2013, and predication of 22 million deaths by 2030, which may exponentially increase to 35 million by 2050.[2] Although much innovation in drug design strategies has been carried out in the past decades and a large number of new chemical entities (NCEs) and screenable drug targets have been synthesized, only a few of them were found to be efficacious against various cancers.[3] Over 40% of marketed drug candidates have been terminated because of the undesirable biological consequences of drug metabolism, toxicity and dose-limiting side effects. In light of the above, tremendous efforts have been made in the recent past toward the development of targeted chemotherapy. In "targeted" therapy, a drug is developed to target a specific cellular signalling pathway on which cancer cells depend for growth, metastasis, or angiogenesis.[4] Targeted therapy focuses on the development of selective therapeutics, whereas classical therapy focuses on the development of increasingly cytotoxic compounds. Targeted chemotherapy thus holds the enormous potential to combat severe side effects and acquired resistance associated with classical chemotherapeutics.[5]

The incorporation of chiral centers in either metal complexes or ligand scaffolds plays a critical role in the regulation of stereoselectivity at the target site and in the enhancement of the pharmacological behavior of metal complexes due to complementarity with chiral biotargets.[6] As such, there is an increasing demand for enantiomeric pharmaceuticals that

Department of Chemistry, Aligarh Muslim University, Aligarh 202002, India. E-mail: farukh_arjmand@yahoo.co.in; Tel: +91 5712703893

† Electronic supplementary information (ESI) available. See DOI: 10.1039/c6ra24770a

RSC Advances

PAPER

Cite this: RSC Adv., 2016, 6, 79372

Synthesis, characterization, and crystal structure of RNA targeted L- and D-phenylalanine-(1,10-phen)–copper(II) conjugate complexes: comparative *in vitro* RNA binding profile of enantiomers and their biological evaluation by morphological studies and antibacterial activity†

Surbhi Sharma,[a] Loic Toupet,[b] Musheer Ahmad[c] and Farukh Arjmand*[a]

Received 4th June 2016
Accepted 9th August 2016

DOI: 10.1039/c6ra14503e

www.rsc.org/advances

New ternary chiral Cu(II) complexes **1a** and **b** derived from L- and D-phenylalanine and 1,10-phenanthroline were synthesized and characterized thoroughly by single crystal X-ray diffraction and other spectroscopic techniques *viz.* UV-vis, IR, EPR, ESI-MS and elemental analysis. The complexes crystallized in the monoclinic *P*21 space group, possessing the lattice parameters a = 5.74690(10) Å, b = 20.6365(2) Å, c = 9.28010(10) Å, $\alpha = \gamma = 90°$, and β = 98.2040(10) in complex **1a** and a = 5.728(5) Å, b = 20.587(5) Å, c = 9.252(5) Å, $\alpha = \gamma = 90°$, and β = 98.308(5) in complex **1b** per unit cell, respectively. Comparative *in vitro* RNA binding studies of the L- and D-enantiomeric complexes, **1a** and **b**, were carried out by a variety of optical spectroscopy techniques *viz.* UV-vis, fluorescence, and circular dichroism. Because copper is a redox metal ion, cyclic voltammetry was employed to evaluate the enantioselective RNA binding of the complexes. The results demonstrated that the L-enantiomer of Cu(II) complex, **1a**, binds more strongly to the t-RNA motif than the D-enantiomer, thereby underlining the differential disposition of the enantiomers and the site preference of RNA for the L-enantiomer over the D-enantiomer. Furthermore, the comparative K_b, K and K_{sv} values of the L- and D-complexes demonstrated significant increases for the L-enantiomer of the copper complex, **1a**, in comparison to its D-enantiomeric form, **1b**. SEM analysis divulged surface morphological alteration of complexes **1a** and **b**, evidenced by the formation of hollow tubes and a concrete-like structure with the RNA condensate, which was less pronounced in SEM micrographs of the complex **1b** condensate. Complexes **1a** and **b** were evaluated by the agar well diffusion method and demonstrated significant antibacterial activity.

Introduction

The interaction of transition metal complexes with nucleic acids is one of the most interesting areas of bioinorganic chemistry and medicinal chemistry owing to the possible applications of these complexes as therapeutic agents for drug design,[1,2] nucleic acid structural probes[3] and artificial nucleases.[4–6] Nucleic acids, particularly DNA and RNA, are primary targets for most drugs for treating infectious diseases,[7,8] *viz.*, HIV, AIDS, hepatitis C and cancer.[8] RNA, particularly microRNA (miRNA), plays an indispensable role in various biological processes, including development, cell proliferation, differentiation and apoptosis. Thus, altered miRNA expression is likely to contribute to many human diseases, including cancer.[10–12] RNA differs from CT-DNA not only in the composition of the bases but also in structure. CT-DNA has a B-form double-helical configuration with a wide major groove and a relatively narrow minor groove, while yeast t-RNA has an A-form conformation with an L-shaped tertiary structure (mainly unispiral), a deep major groove, and a wide, shallow minor groove. These differences are expected to lead to different binding modes and affinities.[13,14]

The *in vivo* structures of DNA and RNA are very different; whereas DNA typically remains in the helical double stranded form, RNA folds into diverse structures, adopting folds that are similar to proteins; this is responsible for its diverse functions in cells.[15] The specific recognition of pockets available in RNA by suitable ligands, involving non-covalent binding usually

[a]Department of Chemistry, Aligarh Muslim University, Aligarh 202002, India. E-mail: farukh_arjmand@yahoo.co.in; Tel: +91 5712703893
[b]Institut de Physique de Rennes, UMR 625, Université de Rennes 1, Campus de Beaulieu Bat. 11 A, 263 av. Général Leclerc, 35042 Rennes Cedex, France
[c]Department of Applied Chemistry, Aligarh Muslim University, Aligarh 202002, India

† Electronic supplementary information (ESI) available. CCDC 1405339 and 1472957. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c6ra14503e

Dalton Transactions

PAPER

View Article Online
View Journal | View Issue

Cite this: Dalton Trans., 2015, 44, 10330

Mechanistic insights into a novel chromone-appended Cu(II) anticancer drug entity: *in vitro* binding profile with DNA/RNA substrates and cytotoxic activity against MCF-7 and HepG2 cancer cells†

Imtiyaz Yousuf,[a] Farukh Arjmand,*[a] Sartaj Tabassum,[a] Loic Toupet,[b] Rais Ahmad Khan[c] and Maqsood Ahmad Siddiqui[d]

Received 22nd February 2015,
Accepted 22nd April 2015

DOI: 10.1039/c5dt00770d

www.rsc.org/dalton

A new chromone-appended Cu(II) drug entity (**1**) was designed and synthesized as a potential anticancer chemotherapeutic agent. The structural elucidation was carried out thoroughly by elemental analysis, FT-IR, EPR, ESI-MS and single crystal X-ray crystallography. Complex **1** resulted from the *in situ* methoxylation reaction of the 3-formylchromone ligand and its subsequent complexation with the copper nitrate salt in a 2 : 1 ratio, respectively. **1** crystallized in the monoclinic $P2_1/c$ space group possessing the lattice parameters, a = 8.75 Å, b = 5.07 Å, c = 26.22 Å, $\alpha = \gamma = 90°$, β = 96.3° per unit cell. Furthermore, *in vitro* interaction studies of **1** with ct-DNA and tRNA were carried out which suggested more avid binding propensity towards the RNA target *via* intercalative mode, which was reflected from its K_b, K and K_{sv} values. The gel electrophoretic mobility assay was carried out on the pBR322 plasmid DNA substrate, to ascertain the cleaving ability and the mechanistic pathway in the presence of additives, and the results revealed the efficient cleaving ability of **1** *via* the oxidative pathway. *In vitro* cell growth inhibition *via* the MTT assay was carried out to evaluate the cytotoxicity of complex **1** and IC_{50} values were found to be in the range of 5–10 μg mL^{-1} in HepG2 and MCF-7 cancer cell lines, which were found to be much lower than the IC_{50} values of previously reported similar Cu(II) complexes. Additionally, in the presence of **1**, reactive oxygen species (ROS) and thiobarbituric acid reactive substance (TBARS) levels in the tested cancer cell lines increased significantly, coupled with reduced glutathione (GSH) levels. Thus, our results suggested that ROS plays an important role in cell apoptosis induced by the Cu(II) complex **1** and validates its potential to act as a robust anticancer drug entity.

Introduction

Cancer or malignant neoplasm is a complex class of disease in which a group of cells divide uncontrollably beyond the normal limit, subsequently intruding into the near or distant tissues (metastasis), ultimately causing cell death. There are more than 100 phenotypes of cancers derived from numerous organs or tissues with multiple etiologies and endless combinations of genetic and epigenetic alterations.[1,2] The primary treatment modalities include surgery, chemotherapy, radiation, immunotherapy, *etc.*[3] However, the mainstay treatment is based on chemotherapy involving various natural and synthetic compounds that have potential to kill or check the unwanted proliferation of cancerous cells. Metal-based drugs offer much promise for cancer chemotherapy, which gained momentum after the serendipitous discovery of cisplatin, *cis*-diamminedichloroplatinum(II), an antitumor drug used clinically for the treatment of solid malignancies.[4] Nevertheless, the issues of systemic toxicity, drug resistance and limited therapeutic window have motivated researchers to look for targeted cancer therapies.

Targeted cancer therapy involves the use of drugs or other natural compounds that block the growth and spread of can-

[a]Department of Chemistry, Aligarh Muslim University, Aligarh 202002, India. E-mail: farukh_arjmand@yahoo.co.in
[b]Institut de Physique de Rennes, UMR 625, Université de Rennes 1, Campus de Beaulieu Bat. 11 A, 263 av. Général Leclerc, 35042 Rennes Cedex, France
[c]Department of Chemistry, College of Science, King Saud University, Riyadh, Kingdom of Saudi Arabia
[d]Department of Zoology, College of Science, King Saud University, Riyadh, Kingdom of Saudi Arabia

† Electronic supplementary information (ESI) available. CCDC 977911. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c5dt00770d

www.nature.com/scientificreports

SCIENTIFIC REPORTS

OPEN

Heteroleptic Copper(I) Complexes of "Scorpionate" Bis-pyrazolyl Carboxylate Ligand with Auxiliary Phosphine as Potential Anticancer Agents: An Insight into Cytotoxic Mode

Received: 13 December 2016
Accepted: 21 February 2017
Published: 24 March 2017

Rais Ahmad Khan[1], Mohammad Usman[2], Rajakumar Dhivya[3], Perumalsamy Balaji[3], Ali Alsalme[1], Hamad AlLohedan[1,*], Farukh Arjmand[2], Khalid AlFarhan[1], Mohammad Abdulkader Akbarsha[3], Fabio Marchetti[4], Claudio Pettinari[4] & Sartaj Tabassum[1,2,*]

New copper(I) complexes $[CuCl(PPh_3)(L)]$ (1: L = L_A = 4-carboxyphenyl)bis(3,5-dimethylpyrazolyl) methane; (2: L = L_B = 3-carboxyphenyl)bis(3,5-dimethylpyrazolyl)methane) were prepared and characterised by elemental analysis and various spectroscopic techniques such as FT-IR, NMR, UV–Vis, and ESI-MS. The molecular structures of complexes 1 and 2 were analyzed by theoretical B3LYP/DFT method. Furthermore, *in vitro* DNA binding studies were carried out to check the ability of complexes 1 and 2 to interact with native calf thymus DNA (CT-DNA) using absorption titration, fluorescence quenching and circular dichroism, which is indicative of more avid binding of the complex 1. Moreover, DNA mobility assay was also conducted to study the concentration-dependent cleavage pattern of pBR322 DNA by complex 1, and the role of ROS species to have a mechanistic insight on the cleavage pattern, which ascertained substantial roles by both hydrolytic and oxidative pathways. Additionally, we analyzed the potential of the interaction of complex 1 with DNA and enzyme (Topo I and II) with the aid of molecular modeling. Furthermore, cytotoxic activity of complex 1 was tested against HepG2 cancer cell lines. Thus, the potential of the complex 1 is promising though further *in vivo* investigations may be required before subjecting it to clinical trials.

Cancer is ranked the second most common cause of death, only after cardiovascular diseases. Hepatocellular carcinoma or hepatic/liver cancer is the sixth most widespread cancer and the third leading cause of cancer-associated deaths[1]. In the year 2016, in the USA alone, new cases and deaths due to liver/intrahepatic bile duct cancer were found to be 39230 (incidence) and 27170 (mortality)[2]. Several research efforts have been made to deal with liver cancer, which include the area of metal-based drugs for cancer chemotherapy. The field of metallodrugs came to be recognized after the foundation laid by the serendipitous discovery of cisplatin (cis-diamminedichloroplatinum(II)). Cisplatin exhibited wide applications as a chemotherapeutic agent, but it has also been found to produce severe side effects[3,4]. Since then there has been a hectic search for better metal-based cancer chemotherapeutic drugs. The unique properties of metal ions can be taken to advantage in

[1]Department of Chemistry, College of Science, King Saud University, Riyadh 11451, Saudi Arabia. [2]Department of Chemistry, Aligarh Muslim University, Aligarh-202002, India. [3]National Center for Alternatives for Animal Experiments, Bharathidasan University, Tiruchirappalli, 620024, India. [4]Surfactant Research Chair, College of Science, King Saud University, Riyadh 11451, Saudi Arabia. [5]Dipartimento di Scienze Chimiche, Universita' degli Studi di Camerino, via S. Agostino 1, 62032 Camerino, Macerata, Italy. Correspondence and requests for materials should be addressed to S.T. (email: tsartaj62@yahoo.com)

NJC

PAPER

Check for updates

Cite this: *New J. Chem.*, 2018, 42, 506

Single X-ray crystal structure, DFT studies and topoisomerase I inhibition activity of a tailored ionic Ag(I) nalidixic acid–piperazinium drug entity specific for pancreatic cancer cells†

Imtiyaz Yousuf,[a] Mohammad Usman,[a] Musheer Ahmad,[b] Sartaj Tabassum[a] and Farukh Arjmand[a]

Received 21st September 2017,
Accepted 22nd November 2017

DOI: 10.1039/c7nj03602g

rsc.li/njc

Novel ionic Ag(I)–piperazinium nalidixic acid conjugate 1 was synthesized as a potential antitumor agent and was thoroughly characterized by elemental analysis, FT-IR, ^{1}H and ^{13}C NMR and single X-ray crystal diffraction studies. Complex 1 crystallized in the triclinic space group *P*1 and comprises a dipiperazinium–Ag(I) cationic unit, two nalidixate (nal^-) anionic moieties and a nitrate ion. The Ag(I) ion adopted a linear configuration upon coordination with two nitrogen atoms of piperazinium cations ($pipzH^+$) arranged in a trans fashion. The density functional theory (DFT) studies of 1 revealed the HOMO and LUMO to be localized on the metal center *viz.*, the $d_{x^2-y^2}$ orbital and partially localized on the C27, C28, C29, C30, C31, C32, N7 and N6 atoms of the piperazinium moiety. Non covalent interaction (NCI) calculations were carried out to identify the weak non-covalent interactions from the topological analysis and reduced gradient of the electron density of complex 1. Our results revealed significant inter- and intramolecular non-covalent interactions between the nal^- and $[Ag(pip)_2]^{2+}$ units. Furthermore, an analysis of Hirshfeld surfaces and fingerprint plots were carried out to ascertain a comparison between intermolecular interactions which provide interesting supramolecular architectures involving combinations of N–H···O, O–H···O and C–H···O linkages into a two-dimensional framework. *In vitro* binding studies of 1 with ct-DNA and tRNA revealed higher binding propensity for tRNA which was evidenced from its higher intrinsic binding constant, K_b and binding constant, *K* values and the mode of binding was found to be groove binding in nature. The catalytic activity of topoisomerase I enzyme in the presence of complex 1 was ascertained by gel electrophoretic assay which demonstrated significant inhibitory effects at a low concentration of 25 μM. The cytotoxicity activity of 1 was determined by SRB assay on MIA-PA-CA-2, HepG2, HeLa and MCF7 human cancer cell lines; these results exhibited specific and selective antitumor activity for the MIA-PA-CA-2 cancer cell line with a GI_{50} value <10.

Introduction

Pancreatic cancer is the most aggressive form of cancer characterized by early metastasis, and poor prognosis with an exceptionally high mortality rate.[1,2] Being one of the four most common cancer phenotypes in developing countries with a marginal 5 year survival rate of less than 5%, there is serious concern regarding the cure and prevention of these cancers.[3] Although general factors (long standing diabetes, alcohol consumption, *etc.*) pose high risk for developing pancreatic cancer, most of the cancer cases are known to occur by somatic mutations.[4,5] Regarding the treatment modalities, surgery at an earlier stage in combination with chemotherapy and radiotherapy may help to shrink the tumor cells enough so that they can be removed by other invasive methods. The chemotherapeutic intervention for pancreatic cancers involves drugs *viz.*, Nab-paclitaxel (Abraxane),[6] oxaliplatin (Eloxatin)[7] and fluorouracil (5-FU)[8] *etc.* which are used alone or in combination. Despite enormous research efforts undertaken to improve the clinical responses of these drugs towards pancreatic cancers, no substantial success has been achieved so far. Furthermore, adverse side effects, *viz.*, peripheral neuropathy, gastrointestinal problems, mouth sores, vomiting, diarrhoea, and loss of appetite and patient compliance, often arise.[9] To overcome such issues, extensive efforts are being undertaken to develop and design transition

[a]Department of Chemistry, Aligarh Muslim University, Aligarh 202002, Uttar Pradesh, India. E-mail: farukh_arjmand@yahoo.co.in
[b]Department of Applied Chemistry, Aligarh Muslim University, Aligarh 202002, Uttar Pradesh, India

† Electronic supplementary information (ESI) available. CCDC 1547115. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c7nj03602g

Conclusions

Until the middle of nineteenth century, girls and women were educated only for traditional household works. Now, the society is witnessing changes in the role-status of women. There is greater emphasis on education of girls and women in the same way as we educate boys and men. The modern-day parents want to fulfil the aspiration of their children without gender parity.

Dr. (Mrs) Farukh Arjmand was 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 **122** 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**. Her present citations are **2472** and h-index is **26**. She has contributed a chapter ''Antitumor activity of tin complexes'' to Encyclopedia of Metalloproteins (Springer, 2012). Dr. Arjmand has successfully guided **12 + 1 Ph.D** and **4 M. Phil** students. She has run **05 major research projects** as PI on the design of metal-based drug candidates awarded by TWAS, Italy, 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, ACTREC, Mumbai (India) USTC, China, USM, Malaysia, Materials Chemistry Laboratory Oujda, Morocco and Institut de Physique de Rennes – UMR 6251,universite de Rennes 1, France and National Laboratory Advanced Photon Source, 9700 S. Cass Avn., Bldg 437 E004, ARGONNE, IL 60439,USA. She is the member of prestigious societies in chemical science: ICC (Indian council of chemists), ISCB (Indian society of chemist and biologists) and ACS (American Chemical Society). She has been awarded **Distinguished women scientist award 2016** in chemical science by ISCB in addition to various other awards *viz.,* **Young Scientist 2005, ICC, Mumbai**, **Shiksha Rattan Puraskar 2010, IFSI New Delhi.** Recently in 2016, her Ph.D scholar Ms. Sabiha Parveen has completed research training of five months in **The Ohio State University OSU (USA)** under **INDO-US STEM-ER programme** with Prof. James A. Cowan. Presently, Prof. Farukh is serving as the **Co-director** of APJ Abdul Kalam STEM-ER centre for education and research which is a joint venture between OSU and AMU.

Thank You.....