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HEAD QUARTERS - Bangalore

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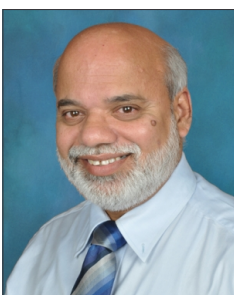
INSERTIONS

- Collectors Album
- Continuing Education

Dear APTI Members,

APTI Headquarters has been changed to 620/D, 35th Cross, 2nd Block, ESI Hospital, Between Variar Bakery and RTO Office, Rajajinagar, Bangalore- 560 010, for further communication Please contact our new address.

OFFICIAL DESK



Dear Pharmacy Teachers,

On behalf of newly elected team of APTI Central as well as State Branch, let me thank everybody for giving overwhelming support during online election of APTI for various posts which has created history in Pharmacy Profession and Strengthen the foundation of democracy in India. This technology of online election and communication through e-mails and mobiles will give the opportunity for any common teacher to utilize his/her dynamism at various receptors of APTI and also bring all of us together to build Pharmacy Profession through faster communication and actions.

Our team is committed to bring **Change** and **Progress** to benefit every Pharmacy Teacher to make his life comfortable and satisfied. Our team proposes following changes and progress to achieve milestone of **2020 Pharma Super Power** a dream set by his Excellency Ex. President of India Dr. A.P.J. Abdul Kalam.

Change

1. By Increasing **Academy – Industry Interaction** and suggesting change in **curriculum to make student competent** to take challenges in **Pharma Industries** and **Health Care profession**.
2. Involvement of **State Branches** in various **Professional Activities** and making funds available to them to carryout programmes to build the **brand of APTI**.
3. Making Various Committees of **Active Teachers** with agenda and responsibilities to give **Solutions to Common Teachers**.
4. Representing to **Government** and **Regulatory Bodies** on continuous basis to **protect the rights of pharmacists** emphasizing **Pharmacy Teachers**.

Progress

1. World – Class Pharmacy Teachers Training **Institute to develop** Competent Teachers **to build** Competent Pharmacists.
2. Organizing **International Convention** and doing **Faculty Exchange Programme** to develop **Global Competency**.
3. Creating awareness of **Career Opportunities in Pharmacy** to increase **Influx of Students towards Pharmacy** and creating **APTI Placement Cell for Quality Jobs**.
4. Making APTI a platform for solutions to give **Status, Stability, Security, Scale** ultimately to build **Pharmacy Profession and Education**.

All our APTI team will put passion, zeal and enthusiasm to achieve this mission in a span of 36 months given to us.

Thanking you and looking forward to meet you at various platforms during APTI programs.

Dr. Mahesh Burande
President Elect.
2013-2016

INSTITUTIONAL NEWS



21st & 22nd December, 2013.



A two day National Seminar on “Discovery, Strategies and Challenges in Pharmaceutical harmonization” begins at Vignan Pharmacy College.

A Souvenir was released on the occasion.

Dr. M. Venkat Reddy, Ex-Director, Druga Control Administration, inaugurated the function and stated his views on pharmacy education. He

said that pharmacy is the only profession which is not effected by recession.

Mrs. Harita Vasireddy, VIMTA Labs, shared her views on Industry trends and challenges and the various opportunities in the health care sector. The concepts pertaining to intellectual property rights and regulatory affairs were explained to students by resource person Dr. S. Padmaja. She advised the young pharmacists to have work satisfaction and to imbibe commitment towards their profession.

Dr. L. Rathaiah, Chairman, Vignan Group of Institutions, spoke on this occasion and stated that the students should build up their inner talents and such interaction sessions would be a platform to explore their capabilities.

Dr. V. Nagalakshmi discussed on the value of harmonization and integration and the importance of communicative skill.

Dr. P. Srinivasa Babu, Principal of the college appreciated the participants who came from distant colleges to attend the seminar.

21st January 2013

K T Patil College of Pharmacy, Osmanabad, organised a guest lecture session on 21st January 2013.

On this occasion, the first lecture was delivered by Dr A M Deshmukh, Head Dept of Microbiology, Dr Babasaheb Ambedkar Marathwada University, Aurangabad, Sub-Centre Osmanabad, on **Intellectual Property Rights**. Dr Deshmukh emphasized the importance of patents in present global competitional era. He motivated research students to file patent on their original research work, and prove their innovative research skills for international recognition.

Second lecture was delivered by Dr D V Kulkarni, Professor, Govt Ayurvedic College and Hospital, Osmanabad, on **Novel Approaches in Handling Bronchial Asthma**. He presented new clinical methods for treating asthma. The session was presided by Dr Shivanand Patil, Administrative Officer and felicitation was given by him. Principal Dr Arunadevi .S Birajdar was also present. Inaugural speech was presented by Mr. Shaikh Gazi, Head Dept of Pharmaceutical Chemistry and Scientific Co-ordinator. Votes of thanks were given by Mr. Ulhas Surwase.

22nd - 23rd Feb, 2013

The Department of Pharmacy Sumandeep Vidyapeeth organized the aforementioned seminar at the SBKS MIRC auditorium on 22nd & 23rd Feb 2013. The inaugural function was started at 10 am and after the invocation Dr. A. K. Seth HOD Pharmacy gave a welcome address. The Honorable Chancellor Dr. Mansukhbhai Shah presided over the function and conveyed his best wishes for the seminar. Honorable Vice -Chancellor Dr.



J. R. Patel was the guest of honor for the function and he delivered a speech in which he also wished a grand success of the seminar. The chief guest Dr. A. K. Shukla COO Vovantis Pharmaceutical spoke about the challenges of the pharmaceutical industries and advised the youngsters to update the knowledge to face the challenges. Mr. J. J. Chaudhari Director Operation GLPL gave a keynote address in which he talked about Novel Drug Delivery system. The inaugural function ended with the vote of thanks by Prof. R. Balaraman.

Prof. M. R. Yadav, Prof. Rajni Giridhar, Prof. K. K. Sawant, Prof. Rakesh Shrivastava Prof. Naresh Kumar M S University Baroda, Dr. Vikas Shrishath, Piramal health care, Chennai Prof. M. C. Gohel School of Life Sciences Ahmadabad University Prof. Mourya Principal, Govt. Pharmacy College, Prof Tejal Gandhi, Principal, Anand College of pharmacy. Mr. Santosh Savarkar Alembic Pharmaceutical Ltd. Vadodara Dr. Prateek Patel, Vasu Research Centre Baroda. Mr. Sandhip Andhari, A plus Pharmaceutical consultancy, Vadodara and Mrs Anagha Maharao, Institute of Pharmaceutical Management, Mumbai delivered plenary lectures on advances in research in the field of pharmaceutical sciences. There were 75 posters and 15 oral presentations by PG and research students from several institutes. About 300 delegates all over countries participated in this seminar.

Finally a valedictory function was held at 6 pm on the second day Dr. Seth gave a welcome address to our chief guest Dr. Jayshreeben Mehta the Formal Vice- Chancellor, Sumandeep Vidyapeeth. She presided over the function and gave away the prizes to the winners of the first best and second best posters and oral session respectively. The function was ended by the vote of thanks from the organizing secretary Dr. R. Balaraman.

2nd March 2013

Department of Pharmacology, Sinhgad Institute of Pharmacy, Narhe, Pune-41 organized one day workshop on "Hands on Experimental Pharmacology" on 2nd March 2013. Fifty delegates from various colleges actively participated.

The program was started with launching of operation table attached to camera for a live demonstration of laboratory animal surgery (VJ



Instrument) by guest of honor and developer Mr. Vivek Deoda. The real time display of cannulation and aortic banding techniques were done using the operation table. Demonstration of surgery to 50 delegates at once was done using single animal, advocating the 3 R principle of CPCSEA. The other important techniques viz. surgical induction of neuropathy, ICV administration using stereotaxi, reproductive surgeries, kidney ligation techniques and GLP while handling of animals were demonstrated by the students of M. Pharm (Pharmacology).

Mrs. Rima Joshi, Team Leader, Clinical data management, SPARK, Dr. (Mrs.) Urmila Aswar, Convener of the workshop, Dr. P. A. Thakurdesai, Manager, Scientific affairs, Indus Biotech. enlightened the young pharmacologists regarding various avenues in Pharmacology and available job opportunities. The workshop was successfully coordinated under the kind guidance of Dr K.G. Bothra, Principal and Prof M.K. Aswar, HOD, Pharmacology department.

17th March 2013



Department of Pharmacy, Govt. Polytechnic, Amravati organized An AICTE Sponsored One Day National Symposium on "Recent Advances in Pharmaceutical Research" on 17th March 2013 at Govt. Polytechnic, Amravati, (Maharashtra).

Dr.S.S.Toshniwal was the Chief Guest of the function. He emphasized the need of registering the patent for the research in pharmacy field by researchers or academicians. Dr. K.S.Laddha, Institute of Chemical Technology, Mumbai delivered the keynote address. He enlightened the audience on "Phytochemical Reference Substances - Extraction, Isolation and Applications in Herbal Analysis" in his effective presentation.

The function was presided over by Shri D.N.Shingade, Principal, Govt. Polytechnic, Amravati. Dr. S.D.Wakode, Delhi Institute of Pharmaceutical Sciences and Research, New Delhi delivered lecture on Animal House Management. Dr.V.K.Mourya, Principal, Govt. College of Pharmacy, Amravati addressed the audience on Changing Role of Pharmacist in New Millennium.

Prof. Shrikant V. Kalikar, Head of Department of Pharmacy, Govt. Polytechnic, Amravati was Chief Coordinator and Prof. G.J. Deshmukh was Coordinator of the symposium. Dr. Ku. R.D.Chakole, Prof. R.P.Umbarkar, Prof. Ku. V.V. Gawande contributed as organizing committee members.

About 360 researchers, academicians and students from different states participated in the symposium. 216 research papers were presented in poster presentation.

The programme was attended by large gathering of teachers and students of Pharmacy faculty in the region.

20th -21st March, 2013



Sinhgad College of Pharmacy (SCOP) Vadgaon (Bk) had organized two days National level seminar on “Pharmacovigilance: Ensuring the safe Use of Medicines” From 20th March to 21st March 2013. This seminar was sponsored by University of Pune. Ms. V. M. Shende, Co-ordinator of the seminar & Dr. K. N. Gujar, Principal SCOP and Convener of the Seminar, welcomed dignitary and all the delegates.

Being a responsible Pharma Professional Dr. K. N. Gujar, has organized this seminar for creating awareness and providing knowledge of the Pharmacovigilance to the budding pharmacist for monitoring adverse drug reactions and ensuring the safe use of medicines in the society.

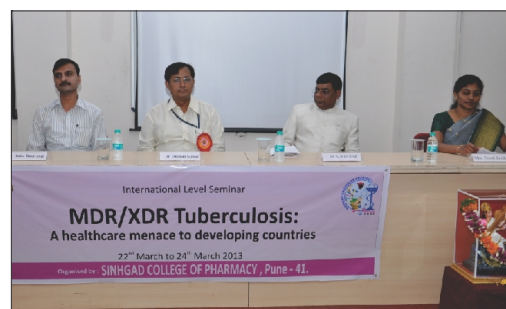
Dr. Padmakar Pandit, Professor & Head Department of Pharmacology, B. J. Medical College, Pune inaugurated the seminar and explained basic concepts of Pharmacovigilance and emphasized on the need of Pharmacovigilance centers in India. He made it clear that Physician and Pharmacist as members of healthcare team are responsible for monitoring adverse drug reactions and ensuring the drug safety.

Eminent speakers from B.J. Medical College, D. Y. Patil Medical College and professors from various Pharmacy Colleges were invited to deliver the lectures. Topic such as Signal detection in Pharmacovigilance and details of suspected adverse drug reactions form, Risk-benefit Assessment in Pharmacovigilance, Drug development & importance of Pharmacovigilance, impact of Drug & Cosmetics (1st Amendment) Rules, 2013 on Clinical Research with respect to Pharmacovigilance and Role of Pharmacist in drug safety, were discussed in depth.

Ms. R. S. Sahane, Assistant Professor at SCOP proposed Vote of thanks. Around 80 students representing state and national institutes were present.

The seminar evoked great response from the students and boosted the knowledge of Pharmacovigilance and created awareness for monitoring adverse drug reactions and ensuring the safe use of medicines.

22nd - 24th March, 2013



Sinhgad College of Pharmacy (SCOP) Vadgaon (Bk) had organized three days International seminar on “MDR / XDR Tuberculosis: A healthcare menace to developing countries” From 22nd March to 24th March. This seminar was sponsored by University of Pune.

Tuberculosis, one of the dreaded diseases today, especially in the background of AIDS has been declared as a global emergency. In view of world TB day on 24th March and to take few initial steps towards the stop TB programme Dr. K. N. Gujar, Principal SCOP has taken the initiative to bring together all healthcare professional on a common platform and exchange the ideas to fight the problem together.

Dr. Dhiman Sarkar Scientist from National chemical laboratory NCL inaugurated the seminar and briefed about Anti-tubercular research and Drug discovery initiatives in India to overcome the problem of multidrug resistance (MDR) and extensive drug resistance (XDR).

Eminent speakers from Indian institute of science education and research (IISER), B.J. Medical College, and professors from various institutions were invited to deliver the lectures. Topic such as new drug discovery, Novel formulation approaches, microbiological aspects, diagnosis of TB, patient related issues, TB HIV co infection, causes and remedies of TB and how the menace can be talked were discussed in depth.

Mrs. Priti Jamkar Professor at SCOP and coordinator of the programme proposed the vote of thanks. Around 100 students and faculty representing national and international institutes were present.

The seminar created awareness amongst all the delegates as well as the invitees towards stop TB mission.

15th - 27th April, 2013



PDEA's Seth Govind Raghunath Sable College of Pharmacy, Saswad organized AICTE sponsored two week Faculty Development Programme on 'Innovations in Pharmaceutical Teaching and Research' from 15th to 27th April 2013.

The topic of this programme was selected with the aim of training the teachers and professionals in innovative teaching methodologies for effective teaching as well as research methodologies for undertaking systematic research.

The programme was inaugurated at the auspicious hands of Dr. Megha Uplane, Associate Professor, Department of Education and Extension, University of Pune, Pune and Dr. P. D. Chaudhari, Dean, Faculty of Pharmaceutical Sciences and Principal, Modern College of Pharmacy, Nigdi. Dr. P. D. Chaudhari delivered a keynote address, appreciating the theme of the faculty development programme in view of its urgency in the current time. An eminent speaker Dr. Megha Uplane, in her lecture explained different strategies of Innovative teaching focusing on pedagogic principles in a very lucid manner. Dr. P. D. Chaudhari enlightened us on active passive learning concept, Z-A approach of pedagogy in his elaborative speech on 'Teaching methods, skills, strategies and innovations to enhance creativity'. The programme included lectures by eminent speakers, Industrial visit and demonstration of various advanced instrumental techniques. Total 59 participants from different colleges attended the programme. Principal and convener Dr. Ashok Bhosale played key role in the successful organization of programme. Prof. Dr. Meenakshi Deodhar and Mrs. Rajashree Chavan coordinated the programme.

15th to 17th April, 2013

Dr. Wafa. Y. Dahdal, Director of International Programs and Associate Director of Professional Development, American Colleges of Clinical



Pharmacy, Kansas, USA, visited Faculty of Pharmacy, Sri Ramachandra University on 2nd June 2013. She visited various departments of Sri Ramachandra Medical Center and the Drugs and Poisons Information Center of the Department of Pharmacy Practice. She discussed on the topic "Advances in Pharmacy Practice across the globe" with the Pharm D students and the faculty of the Department of Pharmacy Practice. Dr.D.Chamundeeswari, Principal, Dr. K. Chitra, Vice-Principal, Faculty of Pharmacy, SRU, and Dr. S. Rajendiran, Professor, Dept. of Pathology, SRU, felicitated Dr. Wafa and participated in the interactions.

29th - 30th April, 2013



The Dept. of Pharmacy Practice, Faculty of Pharmacy, Sri Ramachandra University, organized a two days program on "SRU's hands-on workshop on basic PK/PD modeling" at SRU on 29th and 30th April 2013. Dr.D.Chamundeeswari, Principal, Faculty of Pharmacy, welcomed the gathering. Dr. S.P.Thyagarajan, Professor of Eminence & Dean (Research), SRU, inaugurated the workshop. Dr. K.V. Somasundaram, Dean of Faculties, SRU, released the workshop manual and delivered the presidential address.

The chief guest Dr.S. D. Rajendran, Head, Medical Affairs Division, Sristek, Hyderabad, delivered the Keynote address. Dr.G.Kannan, Assistant Professor, Dept. of Pharmacy Practice, Faculty of Pharmacy, SRU, the convener of the program, presented the overview of the workshop. Dr.K.Chitra, Vice Principal, Faculty of Pharmacy, Sri Ramachandra University, proposed the vote of thanks. The highlights of the workshop were lectures on basic PK/PD modeling by legends like Dr.Surulivel Rajan, Assistant Professor, Dept. of Pharmacy Practice, Manipal College of Pharmaceutical Sciences, Manipal University,

Karnataka; Dr. Venkateswari Muthukrishnan, Application Scientist, Certara; Dr. N. Fakrudeen Ali Ahamed, Deputy Manager and In-Charge, DMPK - Bioanalytical Department, Orchid Research Laboratories Ltd., Chennai, and Dr. S. Seethalakshmi, Professor and Head, Dept. of Pharmacology, Sri Ramachandra Medical College & RI, Chennai, and hands on training by experts using Phoenix WinNonlin software. 52 delegates from academic institutions and pharma industries of South India participated. Valedictory was held on 30th April 2013.

6th May, 2013



The Pharmacy Education Unit, Faculty of Pharmacy, Sri Ramachandra University, organized a Faculty Development Program on "Quality Indicators for Andragogues" at SRU on 6th May 2013. Dr. D.Chamundeswari, Principal, Faculty of Pharmacy, welcomed the gathering. Dr. K .V. Somasundaram, Dean of Faculties, Sri Ramachandra University, inaugurated the program and Dr. P. V. Vijayaraghavan, Director (Academic Administration)Dean (Education), Sri Ramachandra University, delivered the presidential address. Dr.K. Sujatha, Professor, Dept. of Pharmaceutical Chemistry, Faculty of pharmacy, SRU, and the Secretary of Faculty Development Committee presented the overview of the program. Dr. K.Chitra, Vice Principal, Faculty of Pharmacy, Sri Ramachandra University, proposed the vote of thanks. Highlights of the program included a lecture by Dr. S.P. Thyagarajan, Professor of Eminence & Dean (Research), SRU, on " Academic Performance Indicators(API)" followed by a hands on training on API. A colloquy was also conducted on the topic "Managing students effectively-need of the hour -- A congenial teacher Vs commanding teacher". The Moderator was Dr.A. Rekha, Associate Dean of Students, SRU. There was a session on teaching methodologies for Pharm D Curriculum. 39 faculty members of Faculty of Pharmacy, SRU and 11 participants from Pharmacy colleges in and around Chennai participated.

8th May, 2013

Sri Venkateswara College of Pharmacy, RVS Nagar, Chittoor, Andhra Pradesh organized a Special Lecture on "Role of Dissolution & *In Vitro* Release in Regulating Pharmaceuticals" on 8th May 2013 by Dr. Vinod P.



Shah, Ex. US FDA, Pharmaceutical Consultant. The Special Lecture was presided by the Principal, Dr. K. Bhaskar Reddy. The lecture was aimed about recent updates and challenges on dissolution testing. More than 200 Delegates participated including faculties, under graduate, post graduate students and research scholars. An interactive session was held with faculties and students regarding dissolution testing. Dr. R. Meenakshi Sundaram, Director (R&D) and Principal felicitated Dr. Vinod P. Shah.

11th May, 2013



Amar Shaheed Baba Ajit Singh Jujhar Singh Memorial College of Pharmacy, Bela, Ropar, Punjab, successfully organized a one-day Symposium on the theme "Management of Experimental Animals and Alternatives" on May 11, 2013. The symposium was organised with 2 objectives: to familiarise participants with ethical and humane care of experimental animals and to make participants aware about alternative non-animal training methods. The symposium was formally inaugurated by Sh. S.S.Dhillon, Director, MSME, Ludhiana, (an enterprise of Govt of India) as Chief guest and Sh. Sangat Singh Longia Sr. Vice President and Sh. Devender Singh, Secretary, ASBASJSM by lighting the lamp.

Dr. S.S. Sharma, Dr. (Mrs) Kanwalit Chopra, Dr. Pawan Krishan, Dr. P.D.Juyal and Dr. Neeraj Khatri delivered the scientific presentation during the symposium. More than 200 delegates from Punjab, Himachal Pradesh, Rajasthan, M.P., Chandigarh and adjoining states participated in the symposium. Dr. G.D. Gupta, Director, welcomed all the participants and put light on the objective of conducting this type of symposium in present scenario of Biomedical research. Dr. Nitin Bansal, Organising secretary, cordially thanked all the speakers and participants to make this symposium a

successful event. Prof. Gupta wished that all the participants would share the gained knowledge and experience of this symposium with colleagues and students in their respective parent institution. The stage and venue symposium was smoothly organized by Dr. Shailesh Sharma Dr. Rajeev Garg and Ms. Vandana Kharb.

25th May, 2013



Sri Adichunchanagiri College of Pharmacy, B G Nagara, Karnataka organized a mega event, a national level inter-college cultural competition programme named 'BGS GALA-13' the festival. The BGS GALA-13 was organized by the SAC college of Pharmacy at BGS Auditorium, BG Nagara with the support of Sri Adichunchanagiri Sikshana Trust and sponsors.

The BGS GALA-13 was inaugurated by Sri Sri Sri Niramalanandanatha Maha Swamiji on 25th May, 2013. Kannada film actor Mandya Ramesh was the chief guest. Dr. Ramesh B, Principal of Sri Adichunchanagiri College Of Pharmacy, Dr. Shivaramu, Principal Sri Adichunchanagiri Medical College and Dr. Narendra, Principal BGSIT, BG Nagara were also present.

Various events organized during the two days of BGS GALA-13 were group Dance Traditional, Solo Singing, Group Singing, Solo Western Dance, Face Painting, War of Bands, Solo Dance Traditional, Fashion Show and Group Dance Western.

The participants from various colleges of Karnataka participated in the events and received prizes. The Judges for the competitions were Mr. Chandan Shetty, Singer, lyrics writer and Music director, Bangalore, Mr. Narendra, Veena artist, Hassan, Vidvan Unnath, Principal and Director, Natyakalanivas, Hassan. SJB College of Nursing, Bangalore received the champion's trophy.

IPA Pune Local Br in association with Nirali Prakashan Pune organized open discussion on "Generic drugs", where "Generic Aushadhe: Samaj-Gairsamaj" a Marathian book authored by Dr. Atmaram Pawar, President IPA Pune Br was released by Shri Satej Patil Minister for



State FDA Maharashtra. Dr. Himadri Sen Chairman Pharma group Steer World, Arunkumar Khanna Executive Director Emcure Pharma, Dr. Mrs Maya Tulpule President IMA Pune Br shared the views. Hon. Minister felicitated Vijay Patil President MSPC Maharashtra, Dr. Pravin Choudhari Dean Pharmacy Pune University and Shridhar Joshi of JB Chemicals for their contribution in respective field. Sachin Itkar Secretary IPA Pune was the convener and Dr. Neeraj Vyavhare was the coordinator of the programme.



Dayanand College of Pharmacy, Latur, has achieved grand success in National Level (GPAT-2013) examination conducted by AICTE New Delhi for M.Pharm admission. This is grand success for the institute. Eight (8) students are qualified in GPAT-2013 from pioneer batch.

Qualified students are namely Kazi Nishat, Shaikh Heena, More Datta, Sujalegaonkar Anagha, Mandhane Padma, Yelmate Archana, Bhosale Priya & Vidhate Bhagvat felicitated by Mr. Laxmireman Lahoti (President), Mr. Arvindrao Sonvane (Vice-President) Mr. Ramesh Biyani (Secretary), Dayanand Education Society, Latur. These students had valuable guidance from Dr. Dhanraj Jadge, Principal & other faculty members, Dayanand College of Pharmacy, Latur.

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Ph.D AWARDEES



Dr. Ajay Dinkar Shinde, working as Asst. Professor, at SVPM' S College of Pharmacy, Malegaon (Bk), Dist: Pune, Maharashtra, was awarded the degree of Doctor of Philosophy (Ph.D) by Shivaji University, Kolhapur, Maharashtra, under the faculty of Pharmacy on 4th May 2013 for research entitled, "Development of Novel Drug Delivery System for Optimization of Pharmacokinetics of

Insulin". The research work was carried out at Govt. College of Pharmacy, Karad, under the guidance of Dr. S.B. Bhise, Principal Sinhgad Institute of Pharmaceutical Sciences, Lonawala, Pune.

He has published 4 International papers and presented several research articles in National, International and State level conferences. He is presently involved in Anti-Diabetic and NDDS research. Presently he is guiding 7 M. Pharmacy students in Pharmaceutics Faculty. He has 13 years teaching experience for undergraduate and post-graduate pharmacy students.

He acknowledges Management, Shivnagar Vidya Prasarak Mandal, Malegaon (Bk), Principal Prof. R.N. Patil, SVPM'S College of Pharmacy, Malegaon (Bk) and Dr. S.R. Chaphalkar, Director, VSBT School of Biotechnology, Baramati for help extended in research work.



Dr. K. Saravana Kumar working as Associate Professor in Sree Vidyanikethan College of Pharmacy, A. Rangampet, Tirupati, Andhra Pradesh, completed Doctor of Philosophy (Ph.D) in Pharmaceutical Sciences (Pharmaceutics) by Jawaharlal Nehru Technological University Anantapur(JNTUA), Anantapur, Andhra Pradesh in May

2013, thesis entitled "Preparation and Evaluation of Mucoadhesive Microspheres by using different polymers for few Candidate Drugs". The work was carried out under the guidance of Prof. K.B. Chandra Sekhar, Jawaharlal Nehru Technological University Anantapur (JNTUA), Anantapur, Andhra Pradesh and Dr.P.Jayachandra Reddy, Principal in Krishnateja Pharmacy College, Tirupati, Andhra Pradesh.

He has published 20 International papers and attended 20 conferences.



Mr. Ashish Kumar Manigauha, Associate Professor, Dept. of Pharmacology, Technocrats Institute of Technology – Pharmacy (TIT-Pharmacy), Bhopal has been awarded the degree of Doctor of Philosophy (Ph. D) in Pharmaceutical Sciences by Dr. Hari Singh Gour University, Sagar, Madhya Pradesh (A Central University), on the topic entitled "Exploring Tumor Inhibition Potential of

Ipomoea pes-caprae Linn" on 21st June 2013. His research work was carried out under the Supervision of Dr. M. D. Kharya, Professor, Dept. of Pharmaceutical Sciences, Dr. Hari Singh Gour University, Sagar and Co-Supervision of Dr. N. Ganesh, Head & Senior Scientist, Dept. of Research Jawaharlal Nehru Cancer Hospital and Research Center, Bhopal. The outcome of the research revealed potential antioxidant and anti-tumor properties.

He has over 8 years of teaching and research experience. He has published 18 research and 4 review articles in various journals of national/international repute. He has also presented various research papers in national/international conferences, seminars, symposia and workshops and won awards. He is reviewer of 4 national/international journals. He is a life member of various professional bodies like IPS, IPA, APTI, APP and Registered Pharmacist in State Pharmacy Council.



Mr. Maulikkumar R. Amin working as an Assistant Professor in Department of Pharmaceutical Chemistry, Kalol Institute of Pharmacy, Kalol, Gujarat has been recently awarded Doctor of Philosophy (Ph.D) in Pharmaceutical Analysis by Ganpat University, Kherva, Mehsana in May-2013 for thesis entitled "Stability indicating simultaneous determination of new muscle relaxant drugs by chromatographic methods".

The Research work was carried out under the guidance of Dr.P.U.Patel, Professor & Head, Department of Pharmaceutical Quality Assurance, Shree S.K.Patel College of Pharmaceutical Education & Research, Ganpat University, Mehsana-384012.

Dr. Amin has more than six years of teaching/research and industry experience. He has published 6 research papers and 7 poster presentations

in various national and international Journals. Furthermore, he has published two books entitled, "Method development and validation of anti-histaminic drug in plasma" and "Simultaneous estimation of anti-diabetic drugs by HPLC" respectively. Dr. Amin has received St.John's Pharmacy College Award for Best Paper in Pharmaceutical Analysis for the research article "Quantitative determination of fexofenadine in human plasma by UPLC" by Indian Journal of Pharmaceutical Education and Research at APTI-16th Annual National Convection, Moga, Punjab on 7-9th October 2011.

He is registered pharmacist of Gujarat State Pharmacy Council, life member (GU/LM-252) of APTI and Indian Chemical Society, Kolkata. (LM-F/7486)



M. Prince Francis, M.Pharm, Ph.D Associate Professor Department of Pharmaceutical Chemistry, has 8 years of teaching & research experience in his field. Awarded PhD in Pharmaceutical Chemistry, from Dr. M.G.R Medical University, Chennai, Tamilnadu. He has published 06 scientific research and review papers in reputed national & international journals and presented more than 11 research reports and abstracts at national and international scientific conferences in the area of Pharmaceutical Chemistry. Currently working on research activity for Natural Products, Analytical and bio-analytical Method Development. Research activities in the area of Quality control and Quality Assurance.



S. Muthukumar , Associate professor, has 8 years of teaching & research experience in Pharmacy field. He has done his under graduation & Post graduation from M.G.R Medical University, Chennai, Tamilnadu and Submitted thesis for PhD in Pharmaceutical Chemistry, Karpagam University, Coimbatore, Tamilnadu. He has published 19 scientific research and review papers in national & international journals

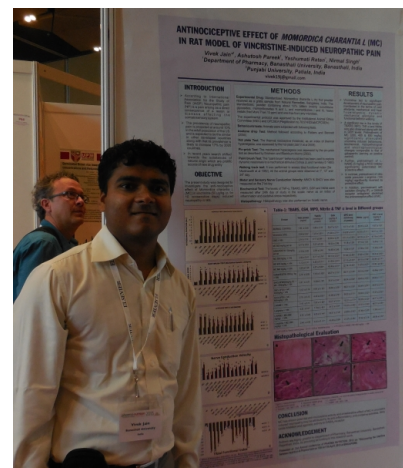
and presented more than 11 research reports and abstracts at national and international scientific conferences in the area of Pharmaceutical Chemistry. Currently working on research activity for drug design & molecular modeling in synthetic chemistry, clinical trials, & bio analytical studies.

Dr.Srinivas Reddy. Karka, Associate Professor, Vaagdevi College of Pharmacy, Hanamkonda, Warangal has been awarded the degree of Doctor of Philosophy (Ph.D) in Pharmacognosy and Phytochemistry by Andhra University, Visakhapatnam for thesis entitled "Phytochemical and Biological Studies on the Traditional Medicines used by Folklore in the region of Deccan Plateau" under the guidance of Prof.S.Ganapaty, Principal, University College of Pharmaceutical Sciences, Andhra University, Visakhapatnam.

He has 3 years of industrial, 6 years of teaching experience and presented 20 publications in national & international journals and presented many papers in national seminars to his credit and being a life member of APTI.

He acknowledges Secretary, CH. Devender Reddy, Principal, Dr. Challa Srinivas Reddy, all teaching and non teaching staff of Vaagdevi College of Pharmacy.

KUDOS



Mr. Vivek Jain Assistant Professor (Pharmacology), Department of Pharmacy, Banasthali University, Banasthali , Rajasthan has attended 2nd Annual conference of Pharma Nutrition, 2013 on "Discovering the interface between Nutrition & Pharma held on 15th to 17th April, 2013 at Singapore and presented a research paper entitled "Antinociceptive effect of Momordica charantia I (MC) in rat model of Vincristine induced neuropathic pain". He is thankful to Department of Science and Technology, New Delhi for considering him as Young Scientist and for providing the financial support for presenting in the conference, he is also grateful to Banasthali University for financial support. The paper presented in the conference was co-authored by Dr. Nirmal Singh, Department of Pharmaceutical sciences & Drug Research, Punjab University Patiala,

Ashutosh Pareek and Yashumati Ratan, Department of Pharmacy, Banasthali University.



Dr. Prashant R. Murumkar, Assistant Professor, Department of Pharmaceutical Chemistry, Sinhgad Institute of Pharmacy, Narhe, Pune has attended 245th American Chemical Society National Meeting & Exposition held at New Orleans, LA, USA held during 7-11th April 2013 and presented his research work entitled "CoMSIA studies on a novel series having tartarate diamides as TACE inhibitors". Dr.

Prashant has been awarded International Travel Grant from Indian Council of Medical Research (ICMR) as well as Council of Scientific & Industrial Research (CSIR), New Delhi to attend the ACS Meet.

During this trip to USA Dr. Prashant has visited Penn State Hershey Cancer Institute, Hershey, Pennsylvania where he has interacted with Dr. Shantu Amin who is a Director of Organic Synthesis Core at Penn State Hershey Cancer Institute and also with other scientists including Dr. Jong Yun and Dr. Shen-shu Sung on the recent development in the drug discovery research. Presently Dr. Prashant is a member of American Chemical Society, Washington DC, USA. In his research career Dr. Prashant has co-authored two book chapters and published around 20 research papers in peer reviewed international journals and has also applied for one Indian patent.



Dr. Papiya Bigoniya, working as Principal in Radharaman College of Pharmacy, Ratibad, Bhopal, M.P. (Affiliated To Rajiv Gandhi Prodyogiki Vishwavidyalaya, Bhopal) has participated and presented a scientific research paper entitled "Phytopharmacological screening of *Lepidium sativum* seeds total alkaloid: Hepatoprotective, anti-diabetic and *in-vitro* antioxidant activity along with identification by LC/MS/MS" in 2nd

international conference on "Pharma-Nutrition 2013" organized by Elsevier in Max Atria Singapore Expo, Singapore from April 15th -17th 2013.

She is thankful to Department of Science and Technology, Government of India, for providing financial assistance as international travel grant for presenting this research paper.

Dr. P. Bigoniya is a life member of APTI (MP / LM-099), IPA, IPS, InPharm and Drug Discovery Network. She has 15 years of professional experience with more than 60 research publications in peer reviewed national and international journals and presented more than 45 papers in various conferences, SDPs and workshops. She has also completed research projects funded by AICTE, New Delhi and DRDE, Gwalior. She is reviewer of esteemed scientific publishers like Elsevier, Taylor and Francis, Academic Journals, Science alert and Biomed Central and also in advisory board of four reputed journals.



Prof. Dr. P. Selvam, M. Pharm; Ph.D.; FNABS; Principal, Nova College of Pharmaceutical Education & Research, Jupudi, Krishna Dt, A.P affiliated to JNTU, Kakinada, participated and presented research papers in 26th International Conference on Antiviral Research (ICAR) organized by International Society for Antiviral Research (ISAR) at San Francisco, California, U.S.A. May 11th-15th, 2013, He presented research papers entitled "Design, Synthesis of Novel Inhibitors of HIV Integrase/LEDGF (P-75) interactions" and "Inhibition of HIV-Integrase/LEDGF interactions by compounds isolated from ethanolic extract of *Morinda citrifolia*, L. Noni fruit". He also visited Dept of Pharmaceutical Chemistry and Small Molecule Drug Discovery Centre (SMDDC), School of Pharmacy, University of California, San Francisco. He received international travel grant from Indian Council for Medical Research, New Delhi, also financial support from World Noni Research Foundation, Chennai and Bharat Ratna Kamarajar Liver Hospital & Research Centre, Madurai. He published more than 50 Research papers in indexed journals and presented more than 100 Research presentations in National and International Conferences in the area of Anti-viral drug Design and Development. He is a life member of professional societies like APTI, NABS, ISNS, NMRS and ISAR. He visited U.S.A., Belgium, Canada, Japan & Bulgaria for presentation of research papers and research collaboration. Mr. M. Krishna Rao, Secretary, Nova educational society appreciated his achievements

ACHIEVEMENTS



Mr. Y. Karthik, Research Scholar, Department of Pharmaceutical Analysis, JSS College of Pharmacy, Udthagamandalam, Tamil Nadu received first prize as best scientific poster presentation award in the section of pharmaceutical Analysis at 5th Indian Pharmaceutical Association Student Congress organized by Indian Pharmaceutical Association - Nilgiris Local Branch, JSS College of Pharmacy, Udthagamandalam and jointly organized by JSS University, Mysore held during 26-27th April, 2013. Currently he is pursuing his Ph.D under the supervision of Dr. S.N.Meyyanathan, Professor and Head, Department of Pharmaceutical Analysis at JSS College of Pharmacy, Udthagamandalam.



Dr. Kunal Roy, Associate Professor in the Department of Pharmaceutical Technology, Jadavpur University, Kolkata, has received Marie Curie International Incoming Fellowship funded by the European Union. He will carry out research work in the University of Manchester, UK for two years. Dr. Roy is an Associate Editor of Molecular Diversity, Springer and also a member of the Editorial Advisory Board,

European Journal of Medicinal Chemistry, Elsevier. Dr. Roy is actively engaged in research in the area of Quantitative structure-activity relationships (QSAR) and he has to his credit more than 190 research publications in peer reviewed journals. Dr. Roy has been a former Commonwealth Academic Staff Fellow in the year 2007-08 and a recipient of different awards including Bioorganic and Medicinal Chemistry Most Cited Paper 2003-2006, 2004-2007 and 2006-2009 awards from Elsevier.

Amar Shaheed Baba Ajit Singh Jujhar Singh Memorial College of Pharmacy, Bela got Best Performing Institution of the Year Award during 4th International Achievers Summit on "Generating Global Partnerships" on 22nd June, 2013 at Bangkok, Thailand. The award was given by International Achievers Conference (IAC). IAC is the Association of



Economical, Political, Business, Professional and other leaders of the Indian community which defines and discusses the key issues of Indian economy. Prof. G.D. Gupta, Director, received the prize on behalf of the institution was delighted to achieve this milestone and told that this is due to the hardwork, dedication and professional commitment of all the faculty members and students. He also thanked the management committee for providing excellent facilities necessary for smooth running of the Institution. S. Rajbans Kaur, President of the Institution expressed her satisfaction and congratulated the entire staff members and students for their great accomplishment.



Dr.Sathiyarayanan, Associate Professor, Bharati Vidyapeeth Deemed University-Poona College of Pharmacy has been conferred with Best Researcher Award- for the year 2012-13 by Bharati Vidyapeeth Deemed University Pune. Bharati Vidyapeeth Deemed University awards best researchers every year during the foundation day to researchers who excelled in their field of research at University level. This year Dr.Sathiyarayanan L from Poona College of Pharmacy received this award at the hands of Hon'ble Mr. Justice Chandrashekar Dharmadhikari, Former Judge, Bombay High Court in the august presenece of Hon.ble Dr. Patangrao Kadam, Founder - Chancellor, Bharati Vidyapeeth University and Minister for Forests, Rehabilitation, Relief Work & Earthquake Rehabilitation, Government of Maharashtra and Hon'ble Dr. Shivaji Rao Kadam, Vice Chancellor, Bharati Vidyapeeth University. Dr.Sathiyarayanan L has

published around 40 papers in peer reviewed international and national journals, filed 01 patent and presented 25 papers in various conferences. He is the recipient of AICTE-CAYT award, UGC travel grant, AICTE-ED cell grant, UGC Major Research project and AICTE-National level Seminar grant. Presently he is the Associate Editor of 'Pharm.Methods' journal from Elsevier Publication and was the member of editorial board in Pharmacomag and Pharmacogreviews journals. He has visited international universities such as university of oxford, School of Pharmacy UCL, London, University of Wolverhampton, University of Strathclyde and University of Bradford. He also visited Switzerland and Germany. He is the member of Board of Studies, Bharati Vidyapeeth University, Pune and life member of APTI. He is the approved research guide of Bharati Vidyapeeth University, Pune and reviewer for several referred journals. Dr. K.R. Mahadik, Principal and faculty members of Bharati Vidyapeeth Deemed University-Poona College of Pharmacy appreciated Dr.Sathyanarayanan for the achievement.

Mr. Aditya Ganeshpurkar, currently working as Assistant Professor of Pharmacology at Shri Ram Institute of Technology-Pharmacy, Jabalpur, M.P., India, successfully completed Post Graduate Diploma in Pharmaceutical Sales Management from Indira Gandhi Open National University (IGNOU), New Delhi and secured first rank all over the



India. He was awarded with gold medal in 26th convocation held at Jabalpur Regional Centre at Xavier Institute of Management, Jabalpur. He also expressed his thoughts regarding the course at the main convocation centre at IGNOU, New Delhi, through audio video conferencing.

Mr. Aditya Ganeshpurkar has previously been secured merit position in B.Pharm and M.Pharm. He is recipient of Junior Scientist Award by SBAM, RD University, Jabalpur. He has authored and coauthored 18 research papers. He is life member of APTI, SBCI and STOX-India.

APTI Headquarters: 620/D, 35th Cross, 2nd Block, ESI Hospital, Rajaji Nagar, Bangalore- 560 010

M: +91 98440 23000 / 99647 37136, Tele: 91 80 23325094

Email: aptibulletinalerts@gmail.com, aptienquiry@gmail.com Home page: <http://www.aptiindia.org>

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ASSOCIATION OF PHARMACEUTICAL TEACHERS OF INDIA (APTI)



APTI Headquarters: 620/D, 35th Cross, 2nd Block,

ESI Hospital, Rajaji Nagar, Bangalore- 560 010, Karnataka

M: +91 98440 23000 / 99647 37136

Tele: 91 80 23325094

Email: aptibulletinalerts@gmail.com, aptienquiry@gmail.com

Home page: <http://www.aptiindia.org>

COLLECTOR'S ALBUM



Percy LeBaron Spencer

(9 July 1894 – 8 September 1970)

was an American engineer and inventor. He became known as the inventor of the microwave oven

Contributed by
Kuntal Das, Asst. Professor
St. John's Pharmacy College,
Vijayanagar, Bangalore.

Ribonuclease H Inhibitors: From Bench to Clinic

Ranganathan Balasubramanian

Department of Pharmaceutical Chemistry, Amrita School of Pharmacy, Amrita Vishwa Vidyapeetham University, Health Sciences Campus, Kochi - 682041, Kerala

ABSTRACT

Much research has been done in the realm of antiretroviral (ARV) drugs since the discovery of human immunodeficiency virus (HIV) as the causative agent of acquired immunodeficiency syndrome (AIDS), wherein the progressive breakdown of the immune system helps life-threatening opportunistic infections and cancers to thrive. In spite of stumbling blocks to the development of an effective vaccine against HIV, the last 25 years have witnessed tremendous positive strides in the identification of viable therapeutic strategies to counter the virus. As a result of this sustained effort, about 25 compounds are currently in clinical use. However, newer anti-HIV drugs are required given the persistence of viral replication reservoirs, the selection and spreading of resistant mutants and the occurrence of side effects with the existing medications. Ideally, these newer drugs should target viral features that have not yet been inhibited by the current treatments. The present review briefly addresses one such offbeat target ribonuclease H (RNase H) and summarizes the development of potential RNase H inhibitors (RNHIs).

Keywords: Antiretroviral drugs, Ribonuclease H, Drug resistance, Reverse transcription

INTRODUCTION

In 1983, findings from two independent research investigations led by Robert Gallo¹ and Luc Montagnier² established HIV as the etiological agent of AIDS. HIV, an enveloped and roughly spherical lentivirus possesses single-stranded positive RNA [ss (+) RNA] as its genetic material. Belonging to the family retroviridae, the virus replicates through the process of reverse transcription catalyzed by the enzyme reverse transcriptase (RT). This enzyme has been the main target for discovery of ARVs. This is corroborated by the fact that almost 50% of the anti-AIDS drugs currently in the market are RT inhibitors (RTIs). Two types of HIV have been characterized – (a) HIV-1 that is more virulent, infective, widespread and responsible for the AIDS pandemic and (b) HIV-2 which exhibits a lower virulence, infectivity, capacity for transmission and is largely confined to West Africa³.

Structurally, HIV-1 RT is an extended, asymmetric heterodimer comprising a 560-residue catalytic p66 subunit and a smaller 440-residue p51 subunit having a structural role⁴. The enzyme has three sequential biochemical activities: (a) RNA-dependent DNA polymerase, (b) RNase H and (c) DNA-dependent DNA polymerase, all of which are absolutely required for the successful completion of reverse transcription, and consequently, viral replication. A full turnover of this enzyme results in the copying of ss (+) RNA of the viral genome into double-stranded complementary DNA (ds cDNA) that can integrate into the host genome leading to a long-term, difficult-to-treat viral infection. The two RT-associated functions i.e., the DNA polymerase activity and RNase H activity are carried out by distinct catalytic sites, both of which are housed within the p66 subunit and separated from each other by approximately 40 Å⁴.

RNase H structure and function

The HIV-1 RT-associated RNase H activity has until recently been largely unexplored and offers an attractive non-traditional target for drug development. RNase H functions as a non-specific endonuclease that selectively degrades the RNA strand of RNA:DNA hybrids. RNases H can exist both as a free enzyme (human and *E. coli* RNase H1) and as a domain of a larger enzyme as in HIV-1 RT. In the case of HIV-1 RT, this domain is located at the C-terminus of the p66 subunit while possessing an asymmetric arrangement of five-stranded mixed beta-sheet flanked by four alpha helices and eight connecting loops⁵. It is structurally homologous to other retroviral RNases H [like murine leukemia virus (MLV)⁶ and avian sarcoma leukemia virus (ASLV)]. A series of about a dozen residues, rich in positively charged amino acids, referred to as the basic loop is thought to serve as a handle that aids substrate binding⁷.

The RNA hydrolysis catalyzed by HIV-1 RNase H may occur in concert with or be completely independent of DNA synthesis. Whatever be the mode of cleavage, the two catalytic sites of HIV-1 RT are temporally coordinated and interdependent; with mutations in one domain affecting the other activity⁸. Although both the enzymatic activities are absolutely necessary for successful replication of the virus; prior to every catalytic event, RT makes a decision of whether to bind as a polymerase or an RNase H based on the structure and composition of the nucleic acid substrate⁹.

The active site of the HIV-1 RNase H domain contains a highly conserved DEDD motif with mutations in any of the D443, E478, D498 and D549 residues abolishing enzymatic activity. Proper enzyme function associated with this domain needs magnesium ions; however, it seems to tolerate manganese and cobalt ions as well¹⁰. In fact, the crystal structure of this domain has indicated the need for two divalent cations, an evidence that has now led to the general acceptance of a “two-metal-ion mechanism” for retroviral RNase H hydrolysis¹¹. These two metal ions are optimally coordinated at a distance of

3.5 to 4 Å from each other by the four aforementioned active site carboxylates to facilitate phosphodiester hydrolysis¹². This three-dimensional spatial arrangement is recently being exploited in the design of putative small molecule RNHIs.

Inhibitors of HIV-1 RNase H activity

It is now firmly established that abolition of RNase H activity of RT stops HIV-1 replication and therefore, can serve as a viable strategy for anti-AIDS drug development. However, there has been an extreme bias thus far of drugs towards the inhibition of RT-associated polymerase activity. This could be mainly attributed to the flat surface topography of the RNase H domain owing to lack of deep, mobile, often hydrophobic pockets that serve as convenient footholds for small molecules during the inhibitor design process. Another factor that slowed down the development of RNHIs was the time-consuming radioactivity-based assay methodology needed to assess RNase H activity. As a result, RNHIs are yet to reach the clinical development stage. Lately, however, this has attracted attention as a promising target and a number of compounds with anti-HIV-1 RNase H activity have been reported. Biochemically, these compounds utilize the cation-chelating mechanism as their mode of inhibition (active site inhibitors) or inhibit HIV-1 RNase H allosterically. Based on their origin and chemical structure, they can be divided into many classes.

N-hydroxyimides. Developed from a successful influenza inhibitor program at Roche¹³, these were among the first series of compounds that provided proof-of-concept for metal-chelating active site RNHIs. These molecules feature the 3-oxygen pharmacophore wherein three oxygen atoms present in the inhibitor moiety are arranged so as to mimic the transition state of the two-metal-ion-mediated phosphodiester cleavage. This binding orientation was confirmed after obtaining a crystal structure of the isolated RNase H domain with a bound N-hydroxyimide inhibitor in the presence of Mn²⁺. Though these compounds show decent activity, their antiviral effect is probably thought to arise due to their inhibition of HIV integrase (IN) enzyme rather than RNase H¹⁴.

Diketo acid derivatives. The diketo acid (DKA) motif that arose from the Merck IN inhibitor program presents an alternative 3-oxygen pharmacophore. Early DKA derivatives showed almost equal ability to inhibit RNase H domain as well as HIV-1 IN¹⁵. Moreover, they did not block viral replication in cell-based assays. Subsequently, an Italian group reported a reversible, non-competitive DKA-based compound 6-[1-(4-fluorophenyl)methyl-1H-pyrrol-2-yl]-2,4-dioxo-5-hexenoic acid ethyl ester (RDS 1643, **1**, Fig. 1) that specifically inhibited only HIV-1 RNase H activity at essentially the same levels in vitro and in MT-4 cell-based assays. A noteworthy fact about RDS 1643 is its ability to inhibit the replication of three HIV-1 non-nucleoside RT inhibitor (NNRTI)-resistant viral mutants¹⁶.

N-hydroxynaphthyridinones. Another scaffold derived as an offshoot of the Merck IN inhibitor program, compounds belonging to this structural class exhibit active site-directed inhibition of HIV-1 RNase H with greater potency than DKAs¹⁷. However, their ability to inhibit IN enzyme in vitro and lack of antiviral activity in cell cultures hindered their further development.

Hydroxylated tropolones. A targeted high-throughput screen of a library of natural products performed at the American National Cancer Institute (NCI)

led to β -thujaplicinol containing yet another 3-oxygen pharmacophore in the form of a hydroxylated tropolone¹⁸. Although this compound is a very specific HIV-1 RNHI, it lacks antiviral activity in cell culture.

Pyrimidinol carboxylic acid derivatives. Recently, this class of compounds was designed at Gilead Sciences Inc. from structural analysis of the other known metal-chelating RNHI scaffolds described above¹⁹. Mode of inhibition of this representative of the 3-oxygen pharmacophore was established after successful crystallographic studies of one such inhibitor in complex with isolated HIV-1 RNase H domain in the presence of Mn²⁺. Members of this class were selective for the viral enzyme compared to human RNase H1 but were not pursued actively due to their apparent lack of antiviral activity in cultures.

Quinones and naphthoquinones. Illimaquinone, a sesquiterpenoid isolated as a secondary metabolite from marine red sea sponge is the prototypical member of this pharmacophoric class of RNHIs. Although it was selective for inhibition of HIV-1 RNase H activity over RNA-dependent DNA polymerase (RDDP) activity, it exhibited equipotent ability to inhibit HIV-1 RNase H and *E. coli* RNase H1²⁰. Moreover, the mechanism and reversibility of inhibition remains unclear.

Nucleotides and dinucleotides. An intriguing feature of HIV-1 reverse transcription was the fact that monophosphates of 3'-azido-3'-deoxythymidine (AZT), 2',3'-dideoxyadenosine and 2',3'-dideoxyguanosine as well as the nucleotide dimer diguanosine slightly inhibited the RT-associated RNase H activity. The potency and mechanism of inhibition were dependent on the nucleic acid substrate composition and the type of catalytic divalent metal ion. Their precise mode of action has not been understood yet.

Naphthalene sulfonic acid derivatives. These constitute a class of RNHIs which prevent retroviral RT interaction with the hydrolysis substrate without interacting with the RNase H site. First generation of these compounds exhibited low anti-HIV-1 RNase H activity and were subsequently replaced by nanomolar inhibitors obtained via a combinatorial medicinal chemistry approach²¹. Unfortunately, their effect on viral replication is 100-fold lower than the one observed on enzyme activity.

Mappicine analogs. Efficient academia-industry collaboration between University of Pittsburgh and Fluorous Technologies, Inc. has resulted in the identification of some active leads after screening a 560-member library of mappicine analogs²². These lead compounds exemplified by **2** (Fig. 1) are active in isolated RNase H enzyme assays, cell-based assays, are effective against NNRTI-resistant HIV-1 mutant strains and seem poised for further preclinical development²³.

1,2,4-triazoles. Identified as RNHIs through a high-throughput screening (HTS) initiative at Wyeth, the antiviral activity of these compounds is not attributed to their interaction with RNase H domain of RT. Rather, computational as well as crystallographic studies indicate that these triazoles bind in the NNRTI binding pocket of HIV-1 – a non-ideal scenario as they would then antagonize NNRTI binding and preclude the utility of an entire class of clinical ARVs²⁴. Further, resistance to the triazoles, which would definitely involve mutations in the NNRTI binding pocket, would most likely confer cross-resistance to the current NNRTI class.

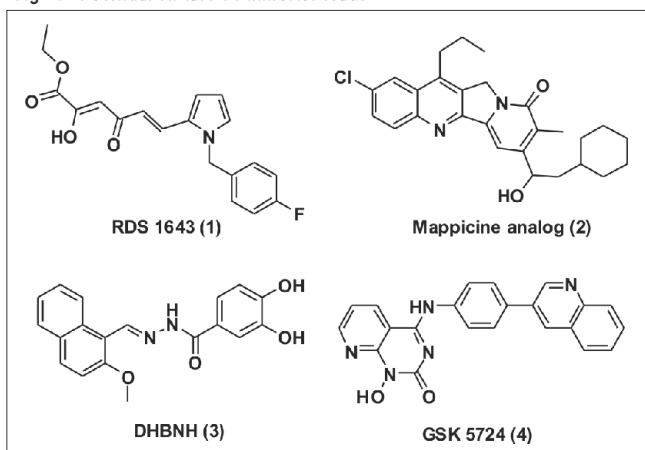
Thiocarbamates. This is another lead series derived from the primary screen of

500,000 compounds in the Wyeth corporate database followed by secondary screen of the 1500 hits subsequently obtained²⁵. Although they exhibited good selectivity over the polymerase activity of RT as well as the related human and *E. coli* RNases H, their low potency put an end to their further development.

Vinylogous ureas. This group of allosteric inhibitors was identified by screening a 230,000-membered library of natural as well as synthetic compounds at NCI²⁶. Their binding site on HIV-1 RT was precisely determined by a combination of protein footprinting, mutagenesis and mass spectrometry experiments²⁷. More biochemical investigations on kinetics and mode of inhibition are underway.

N-acyl hydrazones. These molecules represented the first set of allosteric RNHIs. Early series of these compounds were dual function inhibitors that inhibited both the RT-associated functions. Careful iterative structural manipulations resulted in a potent and selective compound dihydroxybenzoyl naphthyl hydrazone (DHBNH, **3**, Fig. 1), which, after co-crystallization with HIV-1 RT, has been shown to bind to a novel site on the enzyme, greater than 60 Å away from the RNase H active site, and near both the polymerase active site and NNRTI binding site²⁸.

Fig. 1: Potential RNase H inhibitor leads



Conclusion and future perspective

Most anti-HIV drug development programs move directly to phase I human safety trials because robustness of animal models for prediction of clinical efficacy of HIV-1 therapies is still highly debatable. Given the nature of the infection, ability of the test compound to be utilized as a component of combination drug therapies with the clinical anti-HIV agents should be rigorously evaluated. The pace with which small molecule “drug-like” RNHIs have been identified has steadily increased with the development of a robust fluorescence-based assay, amenable to robotic HTS²⁹. For instance, the compound GSK 5724 (**4**, Fig. 1) developed by structure-based drug design and containing pyrido-pyrimidinone scaffold³⁰ was revealed as an exciting candidate for further development a few months ago.

Although a number of inhibitors of HIV-1 RNase H activity are now reported,

their exact biochemical mechanism of inhibition is poorly understood. Active site-directed RNHIs would likely retain potency against drug-resistant HIV-1 variants because there have been no major mutations conferring resistance to ARV drugs reported within the RT RNase H domain. Studies however suggest that active site-directed inhibitors that effectively bind the RNase H domain may have difficulty accessing this site during transcription when RT is bound to an RNA template³¹. Therefore, it is important that inhibitors that do not bind in the active site of HIV-1 RNase H should also be explored.

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