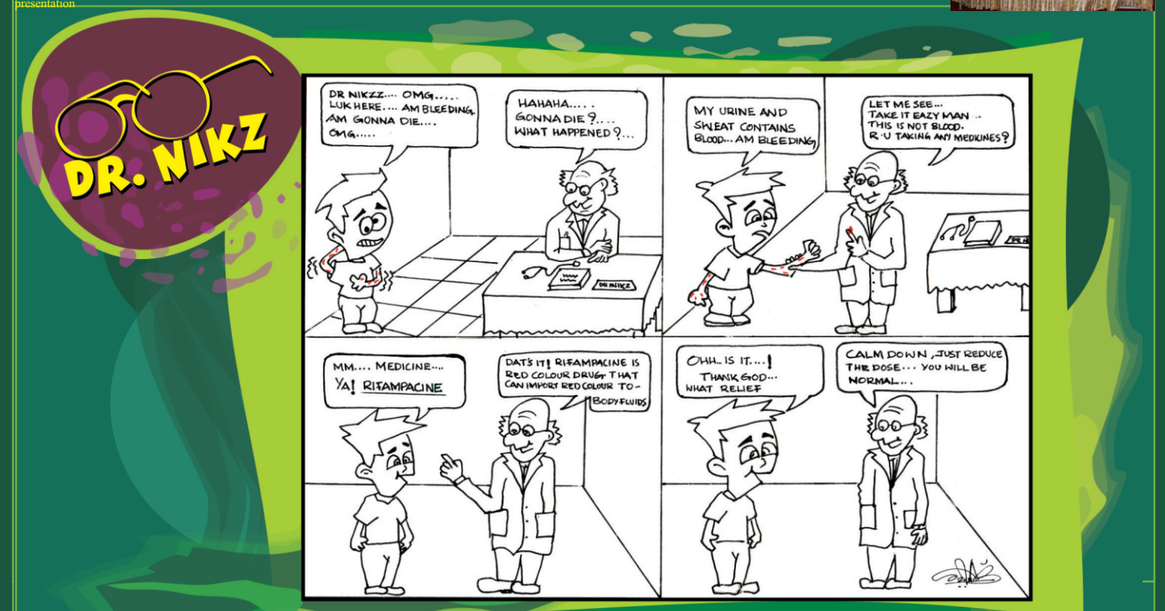
SHIFA CHEMPHARM
The journey of life through chemistry

"National level Workshop Cum Seminar on Laboratory animals in Biomedical research and Ethics"

Department of Pharmacology of Al Shifa college of Pharmacy organized a two days "National level Workshop Cum Seminar on Laboratory animals in Biomedical research and Ethics", which was held on 30th and 31st January 2015. The workshop was inaugurated by Mr.P.Unnen, Managing Trustee, Al Shifa College of Pharmacy, and felicitated by Prof.(Dr) TNK Suriyaprakash, Principal, Al Shifa College of Pharmacy, followed by Mr.Suhail Hamza, General Manager, Shifa institute of Medical sciences. . Resource persons for workshop cum seminar were Dr.Harikrishnan, Scientist, Sri Chitra Tirunal Institute of Medical Sciences & Technology, Trivandrum. Dr. K.R Chandramohan, Senior Scientific Officer, Govt. Medical College, Trivandrum. Dr. K. Nandakumar, Associate Professor, Dept of Pharmacology, MCOP, Manipal. Dr. K. T Manisenthil, Professor & HOD, KMCH COP, Coimbatore . Dr. K. Ashokkumar K, Professor & HOD, Dept of Pharmacology, SRIPMS, Coimbatore. Dr.Sibi P.I, Professor & HOD, Dept of Pharmacology, MG University, Kottayam. Dr.Santhosh, Rajiv Gandhi Institute of Biotechnology, Trivandrum. Dr.V.Ipe Varghese, Registrar, Kerala University of health science appeared as chief guest in the valedictory function.Department of Pharmaceutical Chemistry launched the first eNewsletter in valedictory function in the presence of the Chief Guest Dr.V. Ipe Varghese ,

One Day National Level Seminar and Poster Competition On Recent Trends &Practices in Drug Delivery (Pii-2015)

Al Shifa College of Pharmacy, **DEPARTMENT OF PHARMACEUTICS**, organized a One Day National Level Seminar and Poster Competition on "**Recent Trends & Practice in Drug Delivery**" on 28th April 2015. Prof **Dr. M. K. C.NAIR** (Honourable Vice Chancellor, Kerala University of Health Sciences) was the chief guest of the seminar. Guest of Honor was **Mr.P.UNNEEN**, Managing Trustee ,Alshifa College of Pharmacy. The seminar was honoured by the orator of our invited speaker **Dr.K.L.K Paranjothi. Prof Dr.TNK Suriyaprakash** (Principal, Alshifa College of Pharmacy), **Mr.Suhail Hamza** (General Manager -SIMS)and Prof **Junise.V** (HOD, Department of Pharmaceutics) graced the inaugural function. First Plenary lecture on 'Microneedles on transdermal drug delivery system' was given by Dr.K.L.K Paranjothi. He explained in detail about the importance of micro-needles delivery on transdermal, methods and utilization. Second plenary lecture was given by Dr.A.B.Rema Shree on 'Quality evaluation & standardization of herbal drugs' and revealing about different aspects of herbal drugs. Third plenary lecture was delivered by Dr.Kaladhar Kamalasanan, on 'Nanomedicine' and gave information about different features and its application. The various posters are presented in the poster presentation



For suggestions and feed backs please write to

AL SHIFA COLLEGE OF PHARMACY
Kizhattur, Poonthavanam. P.O., Perinthalmanna, Malappuram Dist., Kerala - 679325
e-mail : shifachempharm@gmail.com

SHIFA CHEMPHARM
The journey of life through chemistry

From Managing Trustee's Desk

I am very happy to note that Department of Pharmaceutical Chemistry, Al Shifa College of Pharmacy, Perintalmanna is releasing the second issue of a newsletter, Shifa ChemPharm, first of its kind in Kerala, for sharing their ideas with their peers all over.

I would like to appreciate the efforts of Dr. Arun Rasheed, HOD, Department of Pharmaceutical Chemistry and Mr. Mansoor K.P., Executive Editor for taking steps to release this newsletter. I am also very happy to see that many faculties, Dr. Arun Rasheed, Dr. Balan P, Prof. S.S Prasanth, Dr. Sanal Dev, Mrs. Neethu Varghese, of the department have written articles which show the calibre of the faculty of Al Shifa College of Pharmacy.

And Dr. R.S.K Vijayan, Rutgers University, New Jersey, USA has contributed a very good article in this newsletter. I appreciate the editorial team for their efforts to get an article from such an eminent person.

The editors have great plans for this newsletter which would be very much useful to the faculties, scientists and peers of other colleges and industries. I appreciate the efforts of Prof. (Dr.) T.N.K. Suriyaprakash M.Pharm., PhD, Principal, for taking the initiatives and his whole team behind the effort for bringing out this informative newsletter.

Mr. P. Unneen

Managing Trustee, Al Shifa College of Pharmacy

From Director, Editorial Board's Desk

Dear healthcare professionals,

It is great pleasure to release the second issue of ShifaChemPharm from the Al Shifa College of Pharmacy, a one and the only of its kind in India. The first issue received rave reviews and accolades from healthcare professionals all over. This is the second newsletter from the repertoire of Al Shifa College of Pharmacy. In ShifaChemPharm, all the faculties of the department contribute something new and also one article from outside expert.

Dr. RSK Vijayan of Rutgers University, USA, has contributed an article titled 'Fragment-based drug discovery Designing Drugs Piece by Piece'. It is a new approach in developing new drugs, instead of High Throughput Screening where bigger molecules which were difficult to be identified and by fragmenting the molecule it is easier to identify each and every entity. Hopefully this approach should reduce the time taken to release new drug into the market since conception. In turn it will reduce the cost of drug discovery which will help in a long run for affordable drug price. Dr. P. Balan, recently joined in Al Shifa family has given basics about HPLC technique, which still is the most sought after instrument in colleges in India. Ms.Neethu Varghese, discussed about serine protease inhibitor for the treatment of liver disorders. It is a novel and smart way in dealing with liver disorder. Chief Editor of ShifaChemPharm, Dr.ArunRasheed, Head, Department of Pharmaceutical Chemistry has published lot of papers in pro drugs in many peer reviewed journals. In this issue, he discussed about the insight in treatment of cancer using prodrug approach, a timely article!

Prof. SS. Prasanth, one of the senior editors of Shifa ChemPharm, has lot of experience in handling FT-IR, HPLC and UFLC instruments, and in fact recently he completed one industrial project on method development and validation of combination of drug under GLP protocol. Here in this issue, he analysed the presence of steroids in herbal formulations, which public thinks safe without being checked thoroughly. I also acknowledge the contribution of Dr.Jemi Jacob, Associate Professor, titled 'Targeted therapy Monoclonal antibodies', who is incidentally our director of Shifa Consultancy Centre of Al Shifa College of Pharmacy, Ms. Sunisha K. S., Assistant Professor, discussed about the drug 'nintedanib' and Ms. S. Karthika, Assistant Professor, described about Click Chemistry which is another approach for quick drug discovery. Dr.SanalDev, joined back to Al Shifa family after completing his PhD under QIP programme has reproduced one of his publications. One of our PharmD (PB) students has also chipped in with an article on deadly Ebola virus. We could see the presence of Mr.Mansoor K.P., Assistant Professor, and Executive Editor, Shifa ChemPharm, in the preparation of this newsletter and is the backbone for this venture.

This is the second Newsletter from this prestigious institution with ShifaClinPharm already in circulation for the past nearly three year published without interruption. These ventures show the depth of faculty strength and their willing and active participation for the benefit of the public and pharmaceutical professionals at large. This is all possible in this institution because of the inspiring leadership of our beloved Mr. P. Unneen, Managing Trustee, who immediately accepted and encouraged to share the Chemistry knowledge with the peers in other colleges and industries. We are also indebted to Mr.Suhail Hamza, General Manager, Shifa Institute of Medical Sciences for his support. We expect contributions from peers and criticism for improving the quality of this newsletter. "The good physician treats the disease; the great physician treats the patient who has the disease" William Osler

Prof. (Dr.) T.N.K. Suriyaprakash. M.Pharm., PhD.,

Principal.

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a quarterly publication from

AL SHIFA COLLEGE OF PHARMACY
Kizhattur, Poonthavanam. P.O., Perinthalmanna,
Malappuram Dist., Kerala - 679325

Message from Chief Editor's Desk

Dear Readers,
The launch of the first Quarterly News letter was on 31st January 2015 at the National Level workshop cum symposium on 'Laboratory Animal handling in biomedical research and ethics' organized by our college. It received positive feedbacks and encouragement from the academia and industrial society of Pharmacy. Following that, we are happy to receive many scientific articles and innovative thoughts from renowned scientists all over the world. This issue got such an article titled 'Fragment-based drug discovery – Designing Drugs Piece by Piece' by Dr. R.S.K.Vijayan, Center for Biophysics and Computational Biology, Temple University, Philadelphia, USA. As ShifaChemPharm is into the second issue, we would like to encourage all to participate more actively by sending your comments, proposing topics and providing us with information important to the field, so that we can fulfill our aim of promoting exchange of ideas, thoughts, and visions for the future of Pharmaceutical Chemistry research.

Our faculty and students were active in various scientific conferences, seminars and research publications in peer reviewed journals. I extend my heartfelt congratulations for each one of them. The success of our News letter is only because of the dedication of our faculty members, unconditional support from our Principal, Prof. (Dr.) T.N.K. Suriyaprakash M.Pharm., PhD., Managing Trustee, Mr. P. Unneen and General Manager Mr. Suhail Hamza.P., We put forth this issue of our News letter which includes thought provoking articles from experts in the field of Pharmaceutical Chemistry. I welcome you all!

FRAGMENT-BASED DRUG DISCOVERY –DESIGNINGDRUGS PIECE BY PIECE

Traditional High Throughput Screening (HTS) has been the mainstay paradigm for discovering small molecules in pharmaceutical drug discovery. Despite its central role in early phase drug discovery, it has failed to deliver on its promise of increasing the numbers and quality of new drugs entering clinical trials. It is in this context, Fragment-based drug discovery (FBDD) emerged as an alternative and complementary technique for hit identification over the past decade1. Paradoxically, FBDD entails the use of various biophysical methods like NMR1 and X-ray crystallography2 for identifying fragments (MW< 200 Da) that bind weakly (<1 mM) to the target of interest.

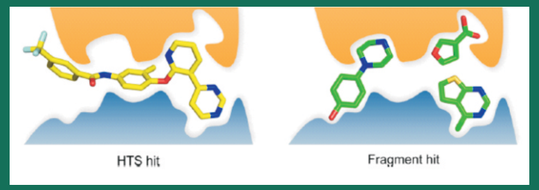


Fig 1: Comparison of hits identified using HTS and Fragment based screening approach: Figure adapted form Biochemistry. 2012 Jun 26;51(25):4990-5003.

These low affinity fragments are subsequently optimized (growing, merging or linking) for affinity and selectivitybased on structure guided design principles to obtainmolecules with higher affinity2.

A primary rationale for screening fragments is the enhanced coverage of the chemical space, achieved using a relatively small screening library of the size (~ 103) fragments. This improves the likelihood of finding new hits even against many previously intractable drug targets, in particular protein–protein interfaces.

The other significant advantages that works in favor of fragment-based screening is that less complex molecules (fragments) display higher hit rates (Hann's Molecular complexity)3 and the concept of additive binding effects observed when linking fragments (Jenck's additivity)4.

Traditionally, affinity has been the sine qua non fortriaging hits and in guiding lead optimization. However, affinity alone can be misleading as binding affinity increases withmolecular size (Hann's – Molecular Obesity)5. Remember, excessivelipophilicity is the antithesis of solubility and is an anathema forgood drug like property. Hence, FBDD employs the concept of 'minimal hydrophobicity' to guide selection and optimization of fragments. Metrics like "Ligand efficiency"whichdefines binding affinity per heavy atom in the molecule6serves as guide post to identify fragment hits withgood binding efficiency and tocontrol lipophilicity during optimization.Akin to Lipinski's famous Rule of 5, scientists from Astex came out with an equivalent rule for fragments, termed as the Rule of 3 (MW <300, cLogP ≤3, number of hydrogen bond donors is ≤3 and the number of hydrogen bond acceptors is ≤3)7. It is now increasingly being used for designing and assemblingfragment libraries.FBDD reached a newmilestone in Aug 2011, with FDA announcing the approval of Zelboraf (vemurafenib), for the treatment of BRAF mutated metastatic melanoma8. Discovered by scientists from Plexxikon (Now acquired by Daiichi Sankyo), is considered to be the first drug derived from an FBDD approach. Success storyof vemurafenib bears testimony to the fact that drugs can be designed piece by piece.

References:

1) Shuker SB, Hajduk PJ, Meadows RP, Fesik SW. Discovering high-affinity ligands for proteins: SAR by NMR. Science. 1996 Nov 29;274(5292):1531-4.

2) Bauman JD, Patel D, Baker SF, Vijayan R.S.K, Xiang A, Parhi AK, Martínez-Sobrido L, LaVoie EJ, Das K, Arnold E.Crystallographic fragment screening and structure-based optimization yields a new class of influenza endonuclease inhibitors. ACS Chem Biol. 2013 Nov 15;8(11):2501-8.

3) Hann MM, Leach AR, Harper G. Molecular complexity and its impact on the probability of finding leads for drug discovery.J Chem Inf Comput Sci. 2001 May-Jun;41(3):856-64.

4) Jencks WP. On the attribution and additivity of binding energies.Proc Natl Acad Sci US A. 1981 Jul;78(7):4046-50.

5) Hann, M. M. Molecular obesity, potency and other addictions in

about the AUTHOR

R.S.K.Vijayan received his Ph.D in Pharmacy from Indian Institute of Chemical Biology, Kolkata, India, in 2011. Thereafter he conducted post-doctoral research at the biomolecular crystallography laboratory in Rutgers University, New Jersey, USA, working on anti-viral drug discovery program employing fragment based drug discovery approach. Currently, he is a post-doctoral associate in the Center for Biophysics and Computational Biology, Temple University, Philadelphia, USA. Author can be reached at

DESIGN AND DEVELOPMENT OF ANALYTICAL METHOD USING HPLC TECHNIQUES

Dr. P. Balan.,Associate Professor,Department of Pharmaceutical Chemistry, Al Shifa College of Pharmacy,

Development of analytical method using High Performance Liquid Chromatography (HPLC) for drug products containing more than one active ingredient plays a significant role in ensuring the identity, purity, potency and performance of drug products. Most of the drugs in multicomponent dosage forms can be analyzed by HPLC method because of its advantages like rapidity, specificity, accuracy, precision and ease of automation. It also eliminates tedious extraction and isolation procedures.

The methods for analyzing drugs in multicomponent dosage forms can be developed by knowing the nature of the sample, namely, its molecular weight, polarity, ionic character and the solubility parameter. It involves considerable trial and error procedures. Usually, the most difficult problem is where to start, what type of column is worth trying with what kind of mobile phase. In general one begins with reversed phase chromatography, when the compounds are hydrophilic in nature.

The organic phase concentration required for the mobile phase can be estimated by gradient elution method. For aqueous sample mixtures, the best way to start is with gradient reversed phase chromatography. Gradient can be started with 5–10% organic phase in the mobile phase and the organic phase concentration (methanol or acetonitrile) can be increased up to 100% within 30–45min. Separation can then be optimized by changing the initial mobile phase composition and the slope of the gradient according to the chromatogram obtained from the preliminary run. The initial mobile phase composition can be estimated on the basis of where the compounds of interest were eluted, namely, at what mobile phase composition. Changing the polarity of mobile phase can alter elution of drug molecules. The elution strength of a mobile phase depends upon its polarity; the stronger the polarity, higher is the elution.

Ionic samples (acidic or basic) can be separated, if they are present in undissociated form. Dissociation of ionic samples may be suppressed by the proper selection of pH. The pH of the mobile phase has to be selected in such a way that the compounds are not ionized. If the retention times are too short, the decrease of the organic phase concentration in the mobile phase can be in steps of 5%. If the retention times are too long, an increase of the organic phase concentration is needed.

In UV detection, good analytical results are obtained only when the wavelength is selected carefully. This requires knowledge of the UV spectra of the individual components present in the sample. If analyte standards are available, their UV spectra can be measured prior to HPLC method development.

The molar absorbance at the detection wavelength is also an important parameter. When peaks are not detected in the chromatograms, it is possible that the sample quantity is not enough for the detection. An injection of volume of 20 µl from a solution of 1 mg/ml concentration normally provides good signals for UV active compounds around 220 nm. Even if the compounds exhibit higher λ_{max}, they absorb strongly at lower wavelength. When acceptable peaks are detected on the chromatogram, the investigation of the peak shapes can help further method development. The addition of peak modifiers to the mobile phase can affect the separation of ionic samples. For examples, the retention of the basic compounds can be influenced by the addition of small amounts of triethylamine (a peak modifier) to the mobile phase. Similarly for acidic compounds small amounts of acids such as acetic acid can be used. This can lead to useful changes in selectivity.

When tailing or fronting is observed, it means that the mobile phase is not totally compatible with the solutes. In most case the pH is not properly selected and hence partial dissociation or protonation takes place. When the peak shape does not improve by lower (1–2) or higher (8–9) pH, then ion-pair chromatography can be used. For acidic compounds, cationic ion pair molecules at higher pH and for basic compounds, anionic ion-pair molecules at lower pH can be used. For amphoteric solutes or a mixture of acidic and basic compounds, ion-pair chromatography is the method of choice.

The low solubility of the sample in the mobile phase can also cause improper peak shapes. It is always advisable to use the same solvents for the preparation of sample solution as the mobile phase to avoid precipitation of the compounds in the column or injector.

TREATMENT OF LIPID DISORDERS BY PCSK9 INHIBITION

ethu Varghese, Asst.Professor.,Dept.of Pharmaceutical Chemistry. Al Shifa College of Pharmacy, Perinthalmanna

PCSK9 (proprotein convertase subtilisin-kexin type 9) is a serine protease inhibitor mainly expressed in liver and intestine. Lower density lipoprotein receptors (LDLR) present on surface of liver cell acts as a binding site and mediate the endocytosis of LDL cholesterol (LDLC).During this process PCSK9 also binds with LDLR and when it does so the receptor is destroyed along with LDL. Thus the drugs which can inhibit PCSK9 can lower the level of circulating cholesterol. The animal studies revealed three main approaches for PCSK inhibition. A peptide which mimics the interaction domain of the LDLR with PCSK9 can inhibit binding to LDLR and prevents its degradation.PCSK9 has also been inhibited In vivo using antisense oligonucleotides or small interfering RNA (siRNA).An Anti –PCSK9 antibody and an anti PCSK9 antigen binding fragment disrupts the interaction between PCSK9 and LDLR thus restoring cellular LDL uptake. Based on the latter idea self-injectable monoclonal antibodies such as Alirocumab (Aventis/Regeneron), Evolocumab (Amgen) and bococizumab were developed. They underwent Phase III clinical trials in 2014.The trial reports concluded that LDL reduction up to 70% was achieved without any side effects. The companies expect to win FDA approval this year and Alirocumab will be made available in the market by July 2015 followed by Evolocumab in August. The drugs are likely to be used for patients with genetically high

Refernces

1) Tavori, Hagai; Giunzioni, Ilaria; Fazio, Sergio. PCSK9 inhibition to reduce cardiovascular disease risk: recent findings from the biology of PCSK9 Current Opinion in Endocrinology, Diabetes & Obesity: – April 2015 – Volume 22 – Issue 2 – p 126132

2) Robinson JP, Farnier M, Krempf M, et al. Efficacy and safety of Alirocumab in reducing lipids and cardiovascular events. The new England journal of medicine, published march 15, 2015 at nejm.org

3) Omar N. Akram, Adeline Bernier, Francine Petrides, Gida Wong, Gilles Lambert. Beyond LDL Cholesterol, a New Role for PCSK9.Arterioscler Thromb Vasc Biol. 2010; 30:1279–1281.

EBOLA– DISEASE FROM A RIVER BANK

Gladson SkariaFirst year Pharm.D (P.B)

The world is now in the fear of EBOLA. Till now 2200 deaths, 4000 affected....and till now its not controlled.... Ebola was first reported in the bank of river EBOLA in the year 1976 of CONGO. So its named as ebola. There are differrent types of ebola viruses–bundhibeygo virus,sudan virus,thay forest virus,ebola virus are the 4 dangerous viruses and the fifth virus restone virus is not threat to humans.

Ebola Virus Disease is a disease caused by one of five different representatives of the Ebolavirus genus; the Ebola virus is a severe infectious disease that can prove fatal in up to 90% of cases. Since its discovery, outbreaks have been sporadic and have been concentrated in the remote regions of Central and West Africa. It is likely, although not verified, that the virus is zoonotic and that the natural host of the virus is fruit bats.

Ebola is a severe and acute viral illness that first presents with the sudden onset of fever, intense weakness, sore throat, headache and muscle pain. Vomiting, diarrhoea, rash, impaired organ function and, in the worst cases, internal and external haemorrhaging follow. The incubation period of the virus can be between 2–21 days and it is only infectious once the patient has begun presenting with symptoms. Skin manifestations may include a maculopapular rash (in about 50% of cases). Early symptoms of Ebola virus disease (EVD) may be similar to those of malaria, dengue fever or other tropical fevers, before the disease progresses to the bleeding phase.In 40–50% of cases, bleeding from puncture sites and mucous membranes (e.g. gastrointestinal tract, nose, vagina and gums) has been reported. In the bleeding phase, which typically starts 5 to 7 days after first symptoms internal and subcutaneous bleeding may present itself through reddening of the eyes and bloody vomit.Bleeding into the skin may create petechiae, purpura, ecchymoses and hematomas. If the infected person does not recover, death due to multiple organ dysfunction syndrome occurs within 7 to 16 days (usually between days 8 and 9) after first symptoms.

It is not entirely clear how Ebola is spread. EVD is believed to occur after an ebola virus is transmitted to an initial human by contact with an infected animal's body fluids. Human–to–human transmission can occur via direct contact with blood or bodily fluids from an infected person (including embalming of an infected dead person) or by contact with contaminated medical equipment, particularly needles and syringes. The potential for widespread EVD infections is considered low as the disease is only spread by direct contact with the secretions from someone who is showing signs of infection. The quick onset of symptoms makes it easier to identify sick individuals and limits a person's ability to spread the disease by traveling. Because dead bodies are still infectious local traditional burial rituals may spread the disease. Semen may be infectious in survivors for up to 50 days.

No ebolavirus–specific treatment exists.Treatment is primarily supportive in nature and includes minimizing invasive procedures, balancing fluids and electrolytes to counter dehydration, administration of anticoagulants early in infection to prevent or control disseminated intravascular coagulation, administration of procoagulants late in infection to control bleeding, maintaining oxygen levels, pain management, and the use of medications to treat bacterial or fungal secondary infections. Early treatment may increase the chance of survival. A number of experimental treatments are being studied. Experimental drugs are made available for use only with the approval of regulatory agencies under named patient programs, known in the US as "expanded access". The FDA has allowed two drugs, Z Mapp and an RNA interference drug called TKM–Ebola, to be used in people infected with Ebola under these programs during the 2014 outbreak.

Whatever may be, there are many critisizations about WHO and other health care teams that they are increasing the fear of peoples on Ebola, like bird flu. some medical experts says that its actually a crooked play of the pharma companies to increase their turn over in the area of vaccination.

Surely ebola is a disease which needs better care and treatment. Instead of fear the methods to increase the immunity power towards the viruses and proper counselling to prevent the disease is needed.

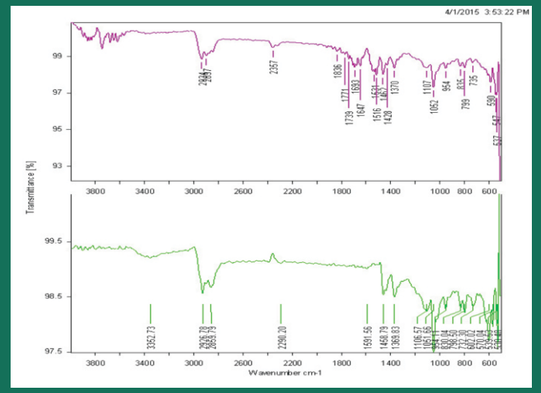
STEROID MOIETY FOUND IN A HERBAL FORMULATION

Mr.S.S. Prasanth.Associate Professor,
Dept.of Pharmaceutical Chemistry

A Female patient aged 52 was admitted in Alshifa hospital with odema, pain in joints,palpitation and some variations in ECG and when enquired it was found that she was taking some herbal capsules for last two months.The physician suspected something in the tablet and was send to Al shifa college of Pharmacy for analysis.

Drugs are often a mixture of active compounds and excipients, and on rare occasion, contaminants.Pharmaceutical mixture deconvolution is thus an attractive application area for spectrum analysis. In this case study, a simple database search of an IR spectrum of a mixture of three steroids was performed.Attenuated Total Reflectance (ATR) is a special IR sampling technique. Its sample preparation is much simpler than that of traditional FT–IR. In recent years, it has been applied in many sample analysis areas..

Here also the sample herbal tablet was subjected to FTIR(ATR) analysis.We got



IR spectra resulting in Cholestrol (first hit) at the top of the hit list followed by ethisterone as the fourth hit. Epiandrosterone (3–β–Hydroxyl–5–α–adrostan–17–one) was at the ninth position

In the software of Mixture Analysis, the percentage match (% Match) shows the quality of each composite spectrum (100% is a perfect match). This example shows that the first composite spectrum closely matched the query spectrum . The individual component is presented in the smaller boxes at the right. The residual, the difference between the composite spectrum and the query spectrum, is available for review in a separate tab. A user can drill down from the link of the individual compound to see the complete structure and property information.

Conclusion: Plant steroids can be isolated through a tedious process lasting three to four days and the yield is very poor in nanograms level. But I wonder here it was in grams level and I suspect it was intentionally added synthetic steroid

Steroids are dangerous drugs, and when used inappropriately, they can cause a host of severe, long–lasting, and often irreversible negative health consequences. These drugs can stunt the height of growing adolescents, masculinize women, and alter sex characteristics of men. Anabolic steroids can lead to premature heart attacks, strokes, liver tumors, kidney failure and serious psychiatric problems. In addition, because steroids are often injected, users risk contracting or transmitting HIV or hepatitis.

RESEARCH ON PRODRUG BASED CANCER THERAPY: RECENT TRENDS

Compiled and Reviewed by Dr. Arun Rasheed

1.New Insights into the Molecular and Epigenetic Effects of Antitumor Pt(IV)–Valproic Acid Conjugates in Human Ovarian Cancer Cells

Substitutionally inert Pt(IV) prodrugs, combining bioactive axial ligands with Pt(IV) derivatives of antitumor Pt(II) compounds, represent a new generation of anticancer drugs. The rationale behind these prodrugs is to release, by reductive elimination inside the cancer cell, an active Pt(II) drug which binds nuclear DNA as well as bioactive ligands that may potentiate toxic effects of the Pt(II) drugs by an independent pathway. Platinum prodrugs, such as Pt(IV) derivatives of cisplatin containing axial valproic acid (VPA) ligands, destroy cancer cells with greater efficacy than conventional cisplatin. The study demonstrated that (i) treatment of the cells with these prodrugs resulted in enhanced histone H3 acetylation and decondensation of heterochromatin markedly more effectively than free VPA; (ii) of the total Pt inside the cells, a considerably higher fraction of Pt from the Pt(IV)–VPA conjugates is bound to DNA than from the conjugates with biologically inactive ligands. The results indicate that the enhanced cytotoxicity of the Pt(IV)–VPA conjugates is a consequence of several processes involving enhanced cellular accumulation, down regulation of HDACs and yet other biochemical processes (not involving HDACs) which may potentiate antitumor effects.

Ref: Novohradsky V, Zerzankova L, Stepankova J, Vrana O, Raveendran R, Gibson D, Kasparkova J, Brabec V. Biochem Pharmacol. 2015, S0006–2952(15)00196–3.doi: 10.1016/j.bcp.2015.04.003.

2. Current strategies for targeted delivery of bio–active drug molecules in the treatment of brain tumo

Brain tumor is one of the most challenging diseases to treat. The major obstacle in the specific drug delivery to brain is blood–brain barrier (BBB). Mostly available anti–cancer drugs are large hydrophobic molecules which have limited permeability via BBB. Therefore, it is clear that the protective barriers confining the passage of the foreign particles into the brain are the main impediment for the brain drug delivery. Hence, the major challenge in drug development and delivery for the neurological diseases is to design non–invasive nanocarrier systems that can assist controlled and targeted drug delivery to the specific regions of the brain. The study involved the treatment of brain tumor by various strategies such as intracerebral implants, BBB disruption, intraventricular infusion, convection–enhanced delivery, intra–arterial drug delivery, intrathecal drug delivery, injection, catheters, pumps, microdialysis, RNA interference, antisense therapy, gene therapy, monoclonal/cationic antibodies conjugate, endogenous transporters, lipophilic analogues, prodrugs, efflux transporters, direct conjugation of antitumor drugs, direct targeting of liposomes, nanoparticles, solid–lipid nanoparticles, polymeric micelles, dendrimers and albumin–based drug carriers.

Ref: Garg T, Bhandari S, Rath G, Goyal AK. J Drug Target. 2015 Apr 2:1–23

CLICK CHEMISTRY – A NEW APPROACH FOR DRUG DISCOVERY

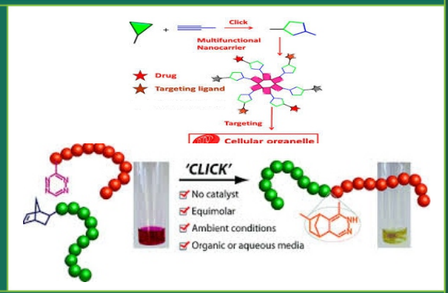
Ms.Karthika.S. Asst Professor Alshifa college of Pharmacy

Introduction

Click chemistry is a chemical philosophy introduced by K. Barry Sharpless of The Scripps Research Institute, in 2001 who got NOBEL prize in the same year. As defined by K. B. Sharpless "Click chemistry is a set of powerful, virtually 100% reliable, selective reactions for the rapid synthesis of new compounds via heteroatom links (C–X–C)..." It describes chemistry tailored to generate substances quickly and reliably by joining small units together. Click chemistry is a modular approach that uses only the most practical and reliable chemical transformations.

The Click Chemistry Approach

Click chemistry does not replace existing methods for drug discovery. It works well in conjunction with structure–based design and combinatorial chemistry techniques, and, through the choice of appropriate building blocks, can provide derivatives or mimics of 'traditional' pharmacophores, drugs and natural products. However, the real power of click chemistry lies in its ability to generate novel structures that might not necessarily resemble known pharmacophores.



Click Chemistry Reaction

Despite many successes, it simplifies compound synthesis, providing faster lead discovery and optimization. A click reaction must be of wide scope, giving consistently high yields with a variety of starting materials. It must be

- Easy to perform.
- Be insensitive to oxygen or water, and use only readily available reagents.
- Reaction work–up and product isolation must be simple, without requiring chromatographic purification.
- Uses carbonheteroatom bond–forming connection chemistry.

The Click Chemistry Universe

A concerted research effort in laboratories and industries has yielded a set of extremely reliable processes for the synthesis of building blocks and compound libraries: Cycloaddition reactions, especially from the 1,3–dipolar family but also hetero–Diels–Alder reactions. Nucleophilic ring–opening reactions, especially of strained heterocyclic electrophiles, such as epoxides, aziridines, cyclic sulfates, cyclic sulfamidates, aziridinium ions and episulfonium ions. Carbonyl chemistry of the non–aldol type (e.g. the for–mation of oxime ethers, hydrazones and aromatic hete–rocycles). Addition to carboncarbon multiple bonds; particularly oxidation reactions, such as epoxidation, dihydrox–ylation , aziridination , and nitrosyl and sulfenyl halide additions [13], but also certain Michael addition reactions. It is the azide alkyne Huisgen cycloaddition using a Copper (Cu) catalyst at room temperature. Although the Cu(I)–catalyzed variant was first reported by Meldal and co–workers for the synthesis of peptidotriazoles on solid support, these authors did not recognize the potential of the reaction and did not make a connection with the click chemistry concept. Sharpless and Fokin independently described it as a reliable catalytic process offering "an unprecedented level of selectivity, reliability, and scope for those organic synthesis endeavors which depend on the creation of covalent links between diverse building blocks."

Conclusions

Click chemistry has proven to be a powerful tool in biomedical research, ranging from combinatorial chemistry and target–templated in situ chemistry for lead discovery, to bioconjugation strategies for proteomics and DNA research. The click chemistry in general, promise to accelerate both lead finding and lead optimization, due, above all, to its great scope, modular design, and reliance on extremely short sequences of near–perfect reaction.

References

1) Kolb, H.C. et al. (2001) Click chemistry: diverse chemical function from a few good reactions. Angew. Chem. Int. Ed. Engl. 40, 20042021. 2) Sneader, W. (1996) Drug Prototypes and Their Exploitation, John Wiley & sons. 3) Bemis, G.W. and Murcko, M.A. (1996) The properties of known drug 1. Molecular frameworks. J. Med. Chem. 39, 28872893. 4) Bohacek, R.S. et al. (1996) The art and practice of structure–based drug design: a molecular modeling perspective. Med. Res. Rev. 16, 350. 5) Newman, D.J. et al. (2003) Natural products as sources of new drugs over the period 1981–2002. J. Nat. Prod. 66, 10221037.

New to market – NINTEDANIB

Mrs.Sunisha.K.S., Asst.Professor.,Dept.of Pharmaceutical Chemistry

Nintedanib (formerly BIBF 1120) marketed under the brand names Ofev and Vargatef is used along with other medications to treat some types of non-small-cell lung cancer and for idiopathic pulmonary fibrosis (IPF).
It is a small molecule tyrosine-kinase inhibitor, targeting vascular endothelial growth factor receptor (VEGFR), fibroblast growth factor receptor (FGFR) and platelet derived growth factor receptor (PDGFR) being developed by Boehringer Ingelheim. Nintedanib was approved for idiopathic pulmonary fibrosis on Oct 15, 2014 by the FDA

MEDICAL USES

IDIOPATHIC PULMONARY FIBROSIS

Nintedanib is used for idiopathic pulmonary fibrosis. Results from randomized controlled trials look promising as of 2014

LUNG CANCER

It may also be used along with docetaxel as a second line agent for certain types of non-small-cell lung cancer

ADVERSE EFFECTS

The most common side effects observed with nintedanib were reversible elevation in liver enzymes (10–28% of patients) and gastrointestinal disturbance (up to 50%). Nintedanib inhibits the growth and reshaping of blood vessels which is also an essential process in normal wound healing and tissue repair

MECHANISM OF ACTION

Nintedanib is an indolinone-derived drug that inhibits the process of blood vessel formation (angiogenesis). Angiogenesis inhibitors stop the formation and reshaping of blood vessels in and around tumours, which reduces the tumour's blood supply, starving tumour cells of oxygen and nutrients leading to cell death and tumour shrinkage. Unlike conventional anti-cancer chemotherapy which has a direct cell killing effect on cancer cells, angiogenesis inhibitors starve the tumour cells of oxygen and nutrients which results in tumour cell death. One of the advantages of this method of anti-cancer therapy is that it is more specific than conventional chemotherapy agents, therefore results in fewer and less severe side effects than conventional chemotherapy.
The process of new blood vessel formation (angiogenesis) is essential for the growth and spread of cancers. It is mediated by signaling molecules (growth factors) released from cancer cells in response to low oxygen levels. The growth factors cause the cells of the tumour's blood vessel to divide and reorganize resulting in the sprouting of new vessels in and around the tumour, improving its blood supply.
Angiogenesis is a process that is essential for the growth and spread of all solid tumours, blocking it prevents the tumour from growing and may result in tumour shrinkage as well as a reduction in the spread of the cancer to other parts of the body. Nintedanib exerts its anti-cancer effect by binding to and blocking the activation of cell receptors involved in blood vessel formation and reshaping (i.e. VEGFR 1-3, FGFR 1-3 AND PDGFR□ and □). Inhibition of these receptors in the cells that make up blood vessels (endothelial cells, smooth muscle cells and pericytes) by Nintedanib leads to programmed cell death, destruction of tumor blood vessels and a reduction in blood flow to the tumour. Reduced tumour blood flow inhibits tumor cell proliferation and migration hence slowing the growth and spread of the cancer.

CURRENT CLINICAL TRIALS

A phase III clinical trial was underway examining the safety and efficacy of nintedanib on patients with the non-cancerous lung condition idiopathic pulmonary fibrosis.Nintedanib, under the brand name Ofev, was approved by the FDA for treatment of idiopathic pulmonary fibrosis on 15 Oct 2014.

References

1. Ahluwalia, N; Shea, BS; Tager, AM (15 October 2014). "New therapeutic targets in idiopathic pulmonary fibrosis. Aiming to rein in runaway wound-healing responses.".American journal of respiratory and critical care medicine 190 (8): 867–78.PMID 25090037
2. Popat, S; Mellemgaard, A; Fahrbach, K; Martin, A; Rizzo, M; Kaiser, R; Griebsch, I; Reck, M (5 December 2014). "Nintedanib plus docetaxel as second-line therapy in patients with non-small-cell lung cancer: a network meta-analysis.". Future oncology (London, England): 1–12. PMID 25478720.

COMBINATORIAL LIBRARY DESIGN, SYNTHESIS AND IN-VITRO EVALUATION OF 2- AMINO-3 CYANOPYRIDINE ANALOGUES AS POTENTIAL ANTICANCER AGENTS.

Sunil.R.Dhaneshwar[a] and Sanal Dev[b]

a. Professor & Chairperson, Department of Pharm.Chemistry, Ras Al Khaimah Medical and Health Sciences University, College of Pharmaceutical Sciences, Ras Al Khaimah, P.O.Box 11172, U.A.E.

b. Research Scholar, Department of Pharmaceutical Chemistry, B.V.D.U Poona College of Pharmacy, Pune, Maharashtra, India.

Topoisomerase IIα enzymes are known to be an important target in anticancer drug development. A small virtual combinatorial library of compounds has been prepared and performed structure based virtual screening studies for the identification of lead compound with Topoisomerase IIα inhibitory activity. The common structural core selected for the design was 2-amino-3-cyano pyridine and various substitutions at 4 and 6th position of the pyridine ring were made using Combiglide module of Schrodinger suite 2013. The generated small molecule library was docked against ATP binding site of DNA topoisomerase-IIα (PDB:1ZXM).Top five compounds having better binding affinity were selected and synthesized by a one pot reaction using microwave irradiation. We noticed that one pot synthesis of the target compounds from malononitrile, aromatic aldehyde, methyl ketone and ammonium acetate under microwave irradiation is a successful method. The reaction time is significantly reduced when compared to the conventional method. Completion of the reaction was accomplished in 12 min with high degree of purity. Mild reaction condition, reproducibility, minimal use of solvent and excellent yield in short reaction time are the notable advantages of this method. The structures of all the compounds were established on the basis of analytical and spectral data. Synthesized compounds were screened for anticancer activity on MCF-7 (Breast cancer) and A549 (Lung cancer) cell lines. Among the tested compounds CG-5 demonstrated the best inhibitory potential against both the cell lines, activity of compound CG-5 was comparable to the standard drug adriamycin in the study against MCF-7 cell line with GI50 value of <0.1.The same compound was also found to be effective against A549 cancer cell line . This skeleton can be used as a novel anticancer scaffold for further modification and design of novel potent compounds. The reported method is useful to identify potent compounds using simple building blocks, limited number of synthesis and minimal experimental effort.

TARGETED THERAPY- MONOCLONAL ANTIBODIES

Dr.Jemi Jacob. Assistant Professor., Dept.of Pharmaceutical Chemistry

Monoclonal antibodies are antibody produced by a single clone of cells or cell line and consisting of identical antibody molecules. Monoclonal antibodies are used as "targeted" therapy for treating various diseases.
Antibodies are part of the immune system. Normally, the body creates antibodies in response to an antigen entering the body. The antibodies attach to the antigen in order to mark the antigen for destruction by the body's immune system. In the laboratory specific antigens are analyzed and special antibody that will attach to the target antigen is created and synthesized. An antibody will attach to a matching antigen like a key fits a lock. This technology allows treatment to target specific cells, causing less toxicity to healthy cells.
Monoclonal antibodies recognize and attach to specific proteins produced by cells. Each monoclonal antibody recognizes one particular protein. They work in different ways depending on the protein they are targeting. So different monoclonal antibodies have to be made to target different types of diseases. Many different monoclonal antibodies are already available to treat various diseases. Some are licensed to treat particular types of cancer/autoimmune disease. Some newer types are still in clinical trials.

Types of Monoclonal Antibodies

There are 3 main types of monoclonal antibodies. They work in slightly different ways. They may

- Trigger the immune system to attack cancer cells
- Block signals telling cancer cells to divide
- Carry cancer drugs or radiation to cancer cells

Application of Monoclonal Antibodies as Targeted Therapy

- Diagnostic tests Once monoclonal antibodies for a given substance have been produced, they can be used to detect the presence of this substance. The Western blot test and immuno dot blot tests detect the protein on a membrane.
- Therapeutic treatment Therapeutic monoclonal antibodies act through a number of mechanisms, such as blocking of targeted molecule functions, inducing apoptosis of cells which express the target, or by modulating signalling pathways.

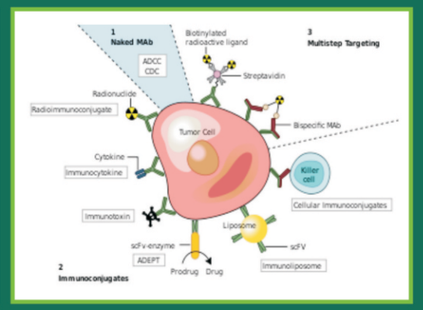
a) Cancer treatment –One possible treatment for cancer involves monoclonal antibodies that bind only to cancer cell-specific antigens and induce an immunological response against the target cancer cell.

b) Treatment of Autoimmune diseases-Monoclonal antibodies used for autoimmune diseases include infliximab and adalimumab, which are effective in rheumatoid arthritis, Crohn's disease, ulcerative Colitis and ankylosing spondylitis by their ability to bind to and inhibit TNF-α. Basiliximab and daclizumab inhibit IL-2 on activated T cells and thereby help prevent acute rejection of kidney transplants. Omalizumab inhibits human immunoglobulin E (IgE) and is useful in moderate-to-severe allergic asthma.

Examples of Therapeutic Monoclonal Antibodies

Some examples of clinically important monoclonal antibodies.

Name	Use	Target
Infliximab / Adalimumab	rheumatoid arthritis, crohn's disease, ulcerative colitis, ankylosing spondylitis	Inhibits tnf-α
Basiliximab / Daclizumab	Acute rejection of kidney transplants	Inhibits il-2 on activated t cells
Omalizumab	Moderate-to-severe allergic asthma	Inhibits immunoglobulin e (ige)
Gemtuzumab	Relapsed acute myeloid leukemia	Targets myeloid cell surface antigen cd33 on leukemia cells
Alemtuzumab	b cell leukemia	Targets an antigen cd52 on t- and b-lymphocytes
Rituximab	non-hodgkin's lymphoma	Targets phosphoprotein cd20 on b lymphocytes
Trastuzumab	Breast cancer with her2/neu overexpression	Targets the her2/neu receptor
Nimotuzumab	Squamous cell carcinomas, glioma	egfr inhibitor
Cetuximab	Squamous cell carcinomas, colorectal carcinoma	egfr inhibitor
Bevacizumab	Anti-angiogenic cancer therapy	Inhibits vegf
Bavituximab	Cancer, viral infections	phosphatidylserine
Palivizumab	rsv infections in children	Inhibits an rsv fusion (f) protein
Abciximab	Prevent coagulation in coronary angioplasty	Inhibits the receptor gpiib/iiia on platelets



References

http://en.wikipedia.org/wiki/Monoclonal_antibody, http://www.chemocare.com/chemotherapy, http://www.cancerresearchuk.org