International Conference

on

Drug Discovery: Perspectives and Challenges

(Including Symposium on infectious diseases)

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And

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on
Medicinal Plants and Functional foods in the management of Diabetes, Obesity and Cardiovascular Diseases

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Indian Society of Chemists & Biologists,India

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P-1

MEDICINES DISCOVERY IN THE 21ST CENTURY:FOR WHAT AND FORWHOM?

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To deny that advances in health delivery and research, including therapeutic medicines during the past sixty years, have not been of significant benefit to mankind is to deny reality. Equally, few will deny that the future should not be one of at least equal promise. Children will be born with their genes profiled, "personalized" medicines will be a reality, gene and stem cell therapies will be mature disciplines and with major implications for the degenerative disorders of an aging world. This new world will be one of artificial cells and machines, many specifically created de novo with an expanded genetic code and that will execute specific tasks, including the disease- and site-specific delivery of drugs, genes and gene repair instructions to DNA-based computers. These advances will have been made possible by a remarkable three decades of scientific research, culminating in the reading of several genomes, including the human genome.

The transition from phenotype-based to genotype-based drug discovery has brought with it the realization that biology is governed by a set of basic principles – diversity, replication, evolution and self-organization – that are now recognized as generally applicable in disciplines from anthropology to zoology, including engineering and synthetic organic chemistry, and that are linked intimately through the process of biological recognition. The application of these principles to three fundamental steps in drug discovery and development – finding the target, finding the molecule, and delivering the molecule – will be illustrated with specific examples.

These developments will, however, be naught for our comfort if the division between the rich and the poor worlds continues. Science has delivered for the rich world, but party and politics have blinded our eyes and have limited the participation of the poor world. Progress will not be possible until the cycle of poverty and poor health is broke. This will not occur with a free market Darwinism model of economic development favored by the United States.

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PL-2

"NM283, the first nucleoside analog with selective anti-HCV activity. Phase IIb clinical trial results" Paolo La Clla, – University of Cagliari - ITALY

There are approximately 170 million people worldwide with chronic hepatitis C virus (HCV) infection, of which approximately 2.7 million are in the United States. Chronic HCV infection accounts for 40 percent of end-stage cirrhosis, 60 percent of liver cancer and 30 to 40 percent of liver transplants in the United States and other industrialized countries. Responses to current treatment options are frequently inadequate due to the inability of some patients to tolerate these treatments and by their limited effectiveness, particularly in patients infected with HCV genotype 1. The genotype 1 strain of HCV is the most treatment-resistant HCV genotype and is estimated to cause more than 70 percent of the reported cases of hepatitis C in the U.S. and Japan, and more than 65% of the reported cases of hepatitis C in Western Europe.

Valopicitabine (NM283) is an oral, novel nucleoside analog that is currently being developed in combination with pegylated interferon for use in both treatment refractory and treatment naive patient populations in an FDA in an FDA-approved trial.

Valopicitabine combined with pegylated interferon demonstrated significantly greater viral suppression after 12 weeks of treatment compared to re-treatment with ribavirin plus pegylated interferon in chronic hepatitis C, genotype 1 patients who were non- responders to previous therapy. Data will be presented from this phase IIb clinical trial.

P:3 Discovery and Development of Drugs for Leishmaniasis

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Leishmaniasis is a worldwide parasitic disease. Current therapies include pentavalent antimonial drugs and the polyene antibiotic amphotericin B. One new drug, miltefosine has recently been registered for treatment and two others, the aminoglycoside paromomycin and the 8-aminoquinoline sitamaquine are on clinical trial. There are four features of leishmaniasis that are germane to development of novel drugs: (i) the disease is caused by an intracellular protozoan parasite that survives and divides in phagolyosomal compartments of macrophages, (ii) there are 17 different species of *Leishmania* that infect humans, with variation in drug sensitivity, (iii) three of these species cause visceral leishmaniasis (VL) while the others cause cutaneous

leishmaniasis (CL), which imposes different pharmacokinetic requirements on drugs, and (iv) activity of most drugs is influenced by host immune status.

The drug discovery and development process has taken many interesting routes in leishmaniasis; several will be illustrated in this presentation. For example, research on the isoprenoid biosynthetic pathway has identified several target enzymes. One of these, farnesylpyrophosphate synthase, is inhibited by phosphonate analogues including some developed for osteoporosis. One of these, risedronate, proved highly effective against experimental visceral leishmaniasis. Other compounds, for example, miltefosine, were discovered by serendipity. This alkylphosphocholine is now registered for treatment of VL and CL, but there are concerns about resistance. Treatment of leishmaniasis has also benefited from improved formulations. In particular liposomal amphotericin B has proved to be a highly effective treatment for VL, whilst topical formulations of another antibiotic, paromomycin, have been developed for CL. Immunotherapy has also featured in treatment of both forms of this disease. Recently, a topical formulation of imiquimod, a compound that activates macrophages, has proved to be an interesting adjunct to treatment of CL.

Most of the compounds used or on clinical trial for leishmaniasis were initially developed for other disease indications. The new product development public-private-partnerships, such as DNDi and IOWH, aim to bring new specific treatments for leishmaniasis through partnerships with academic, commercial and international organisations.

P:4 Chemical and Enzymatic Tools for Carbohydrate Chemistry:Underpinning Anti-Microbial Drug Discovery

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Recent advances in chemical and enzymatic carbohydrate chemistry make access to complex glycoconjugates much more practical. Examples of enzymatic methods to probe substrate recognition and enzyme/gene function will be presented, along with manipulation of antibiotic glycosylation and hence biological acitivity. In addition, recent work on chemical and enzymatic synthesis of bacterial LPS and parasite mucin glycans will be illustrated.

Chemical methodology:

From solution phase to 'on-column' glycosylation: trichloroacetimidate-based glycosylation promoted by perchloric acid-silica. B. Mukhopadhyay, S. V. Maurer, N. Rudolph, R. M. van Well, D. A. Russell, R. A. Field, *J. Org. Chem.*, 2005, 70, 9059-9062

Iodine promoted glycosylation with glycosyl iodides: α-glycoside synthesis. R. M. van Well, K. P. R. Kartha, R. A. Field, *J. Carbohydr. Chem.*, 2005, 24, 463-474.

Glycosylation reactions with 'disarmed' thioglycoside donors promoted by *N*-iodosuccinimide and $HClO_4$-silica. B. Mukhopadhyay, B. Collet, R. A. Field, *Tetrahedron. Lett*., 2005, 46, 5923-5925.

Enzymology and enzymatic synthesis:
Characterisation of *Streptomyces spheroides* NovW and revision of its functional assignment. to a dTDP-6-deoxy-D-*xylo*-4-hexulose 3-epimerase, M. Tello, P. Jakimowicz, J. C. Errey, C. L. Freel Meyers, C. T. Walsh, M. J. Buttner, D M. Lawson, R. A. Field, *Chem. Commun*., submitted.

The 1.5 Å resolution crystal structure of NovW: a 4-keto-6-deoxy sugar epimerase from the novobiocin biosynthetic gene cluster of *Streptomyces spheroides*. P. Jakimowicz, Tello, C. L. Freel Meyers, C. T. Walsh,M. J. Buttner, R. A. Field, D. M.Lawson, *Proteins: Structure, Function and Bioinformatics*, in press.

Probing the specificity of macrolide glycosyltransferases: *in vitro* remodelling of a polyketide antibiotic creates active bacterial uptake and enhances potency. M. Yang, M. R. Proctor, D. N. Bolam, J. C. Errey, R. A. Field, H. J. Gilbert, B. G. Davis, *J. Am. Chem. Soc*., 2005, 127, 9336-9337.

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The position of a key tyrosine in dTDP-4-keto-6-deoxy-D-glucose-5-epimerase (EvaD) alters the substrate profile for this RmlC-like enzyme. A. B. Merkel, L. L. Major, J. C. Errey, M. D. Burkart, R. A. Field, C. T. Walsh, J. H. Naismith, *J. Biol. Chem*., 2004, 279, 32684–32691.

The structural basis of the mechanism of bacterial sugar-nucleotide modifying enzymes. R.A. Field, J.H. Naismith, *Biochemistry*, 2003, 42, 7637-7647.

PL-5:
PROBING THE PARASITE TARGETS WITH NOVEL NATURAL PRODUCT ANTIPARASITIC PHARMACOPHORES

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Leads from the natural products have provided some of the most valuable drugs for treatment of parasitic diseases, the major global heath problem. However, emergence of resistance against currently used drugs demands identification of novel antiparasitic pharmacophores. Some novel natural products have been identified with highly potent antiparasitic activities *in vitro* as well as promising efficacy *in vivo*. Distinctive pharmacophore structures of these agents offer new antiparasitic drugs leads and therefore have been employed as the tools to probe the parasite targets and pathways. Manzamine A, a □-carboline alkaloid antibiotic isolated from a marine sponge, has shown activities against wide range of *Plasmodium falciparum* strains resistant to pyrimethamine, chloroquine, quinine, sulfadoxine and cycloguanil. It also cures malaria infection in mice. Besides predominant toxicity against ring stage of the parasite cells, manzamine A also caused selective impairment of the pathways related to the parasite invasion into the host's erythrocytes. Treatment with manzamine A produced unique metabolic response in the malaria parasite, as determined by global gene expression profiling. The most predominant response was in protein synthesis, indicated by the repression of ribosomal protein mRNAs, translation initiation factors and translation elongation factors. A few genes associated with glycolysis were also down regulated, including phosphofructokinase, fructose-bisphosphate aldolase and glucose-6-phosphate isomerase. Natural compounds derived from specific chemical classes could also be employed for validation of the parasite targets. Terpenoids and isoprenoids highly abundant in natural resources, which may target the unique non-mavelonate pathway of isoprenoids biosynthesis, sterol biosynthesis & protein prenylation functions of parasitic protozoa, were found to be useful sources of antiparasitic agents. The natural and semisynthetic organosulfur compound libraries, selected as the potential inhibitors of glutathione and cysteine dependent antioxidant defense functions have also yielded potential antiparasitic lead molecules. Novel natural products therefore offer promising leads for target identification, validation and new antiparasitic drug discovery.

PL-6.**Title AWAITED**

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PL-7
Title : AWAITED

Prof. Mukund S. Chorghade

PL8

Database Mining for efficient, modern Organic Synthesis: case studies to prepare antiviral and anti-Alzheimer compounds

2. Synthesis of Second-Generation Galanthamine-type Anti-Alzheimer Drugs

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PL 9 : HEPATITIS C VIRUS - HOST CELL INTERACTION: IDENTIFICATION OF CELLULAR FACTORS INTERACTING WITH HCV 3' NON TRANSLATED REGIONS

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Chronic infection by Hepatitis C virus (HCV) is the leading cause of severe hepatitis which often develops into liver cirrhosis and hepatocellular carcinoma. The molecular mechanisms underlying HCV replication and pathogenesis are poorly understood. Similarly, the role(s) of host factors in the replication of HCV remain undefined. Based on our knowledge of other RNA viruses, it is likely that a number of cellular factors may be involved in facilitating HCV replication. It has been demonstrated that elements within the 3' nontranslated region (3'NTR) of the (+) strand HCV genome are essential for initiation of (-) strand synthesis. The RNA signals within the highly conserved 3' NTR may be the site for recruiting cellular factors which mediate virus replication/pathogenesis. However, the identities of putative cellular factors interacting with these RNA signals have been unknown. In this report, we demonstrate that an RNA affinity capture system developed in our lab used in conjunction with LC/MS/MS mass spectrometry has allowed us to positively identify a number of cellular proteins that

specifically interact with the 3'NTR (+) of HCV. The binding of these cellular proteins could not be competed out by a 10-fold excess of nonspecific competitor RNA. With few exceptions, all of the identified cellular proteins are RNA binding proteins whose reported cellular functions provide unique insights into host cell-virus interactions and possible mechanisms influencing HCV replication and HCV-associated pathogenesis.

P-10 Design and Investigation of a New Class of Acyclic Pyrimidine Nucleosides as Potential Anti-hepatitis B Virus Agents

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Hepatitis B virus (HBV) infection is one of the leading causes of death due to infectious disease worldwide. There are approximately 400 million people with chronic HBV infection, with an annual global death toll of 1.2 million per year. In fact, chronic HBV infected people are 10 times more numerous than HIV (human immunodeficiency virus) patients. New infection with HBV can be prevented by vaccination. However, the present vaccination is not effective for 400 million chronic carriers worldwide. It has been observed that suppression of the replication of HBV in the liver leads to improved liver pathology and decreased progression to liver cirrhosis and hepatocellular carcinoma. Antiviral therapy can be aimed to clear the virus load in body fluids of the infected people and therefore reduce the risk of viral transmission to others. The major clinical limitations of current antiviral drugs for HBV are the emergence of drug-resistant viral strains and/or toxicity upon prolonged therapy. Molecular modeling studies have suggested that acyclic nucleosides provide torsional flexibility and shorter chain connecting the base and the sugar moiety as compared to anti-HBV drug lamivudine. Further, the dNTP binding pocket of HBV DNA pol containing M204V/I+L180M (also referred to as M552V/I+L528M) mutations is more constrained and crowded, allowing smaller acyclic nucleoside analogs to be accommodated more effectively than bulkier oxathiolane of lamivudine. Therefore, nucleoside analogs which have sugar ring systems that are modified or acyclic, may retain activity against lamivudine-resistant mutants.

A group of 5- and/or 6-substituted acyclic pyrimidine nucleosides with various open chain moieties were designed, synthesized and investigated for antiviral activities. Among the compounds tested 5-(1-azidovinyl)-, 5-(1-azido-2-haloethyl)-, 5-vinyl-, 5-chloro-, and 5-bromo analogs possessing acyclic glycosyl moieties were found to be active antiviral agents in the *in*

vitro assays against wild-type duck HBV and human HBV. Intriguingly, this class of compounds was also found to retain sensitivity against lamivudine-resistant HBV containing single mutation (M204I) and double mutations (L180M/M204V). The compounds investigated did not show cytotoxicity to host HepG2 and Vero cells, upto the highest concentration tested. Our studies show the potential of acyclic pyrimidine nucleosides as a new class of anti-HBV agents against both wild-type and drug-resistant mutant HBV.

PL-11 **PRODRUG DESIGN STRATEGY TO IMPROVE CHEMOTERAPEUTIC DRUG EFFECTIVENESS**

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Although there are more than 7 000 drugs for most of the diseases, many physico-chemical, pharmacokinetic, pharmacological, and toxicological besides organoleptic unwanted properties can be barriers for their clinical use. With the aim of optimizing mainly the physico-chemical properties of a drug, which reflex in its poor pharmacokinetic characteristics, the latentiation process, much currently known as prodrug design, is a good alternative [1]

The interest in prodrug design as an alternative to improve drug effectiveness has been increased. For example, among the blockbusters drugs in the pharmaceutical market, five – lovastatin, sinvastatin, omeprazole, acyclovir, and enalapril – are prodrugs [1]. Prodrug design is a molecular modification process proposed by Harper, in 1959, that comprehends the transformation of a drug in an inactive transport form that *in vivo*, through chemical or enzymatic reactions, releases the drug either at or near the site of action (Fig. 1).

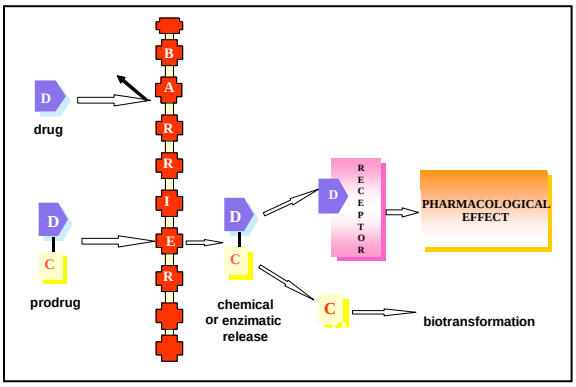

Figure 1. Prodrug approach

Fig. (1). Prodrug concept . D – drug. C- carrier.

There are many reasons that justify the need for drug molecular modification through prodrug design, as follows [2]: *pharmaceutical problems*, as low solubility, low chemical stability, undesirable taste, odor, high irritation and pain; *pharmacokinetic problems*, as low oral absorption, high rate of presystemic metabolism, low absorption by non-oral routes, low time profile, and low selectivity in organ/tissue active agent delivery, and *pharmacodynamic problems*, as low therapeutic index and lack of selectivity in the action site.

The studies on advanced systems of prodrug design have been concentrated in cancer field, due to the urgent need for selective antineoplastic drugs. Neverthless, it is of utmost importance to extend those modern approaches to infectious diseases, as tropical endemies and tuberculosis, for instance. These diseases affect mainly poor people of undeveloped countries and new and better drugs must be searched. We have been working on prodrug design with some antimalarial, antileishmanial, anti-chagas´ disease and tuberculostatic agents with the objective of improving their activity and obtaining selective systems derived.

Chung, [3] sinthesized mutual prodrugs of primaquine and nitrofurazone using dipeptides as spacer groups. These peptides are selectively cleaved by cruzipain, a cysteinyl-protease found only in *t. Cruzi*. The rational for this approach was the mechanism of the drugs: while primaquine increases the oxidative stress into the parasite, nitrofurazone, as a trypanothione reductase inhibitor, do not allow the protective action of the enzyme, provoking the increase in the intracellular oxidative stress. The compound in which lys-arg was the spacer group has been the most active dipeptide prodrugs of primaquine as synthesis intermediates also showed to be active in cell cultures infected with *t. Cruzi*.

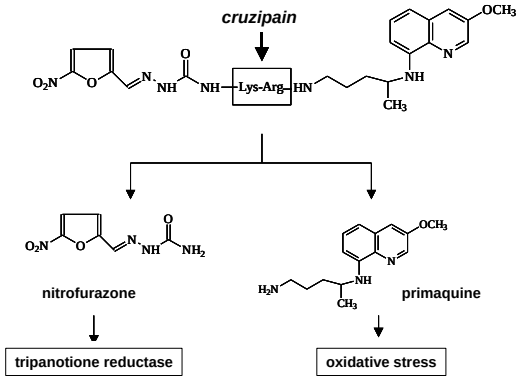

FIG. (2). **MUTUAL PRODRUG OF PRIMAQUINE AND FURAZONE WITH LYS-ARG AS SPACER GROUP.**

Using the same approach, scarlato *et al*. [4] synthesized potentially antimalarial targeted drugs of primaquine with selective hepatic delivery. the synthesis followed in which tiogalactopyranoside and succinyl/carboxymethyl dextrans are firstly and separately synthesized. the director group is linked through ethylenediamine spacer group. Succynildextran-galactopyranoside-primaquine showed to be promising in tests with mice infected with *p. berghei*, increasing the efficacy and decreasing the toxicity of the drug. This potential targeted drug has significantly decreased the parasitemia in the nineth/eleventh day of parasite inoculation and drug administration to mice. while primaquine lead to 25% of mice mortality, its targeted drug did not cause any death in the tested animals**.**

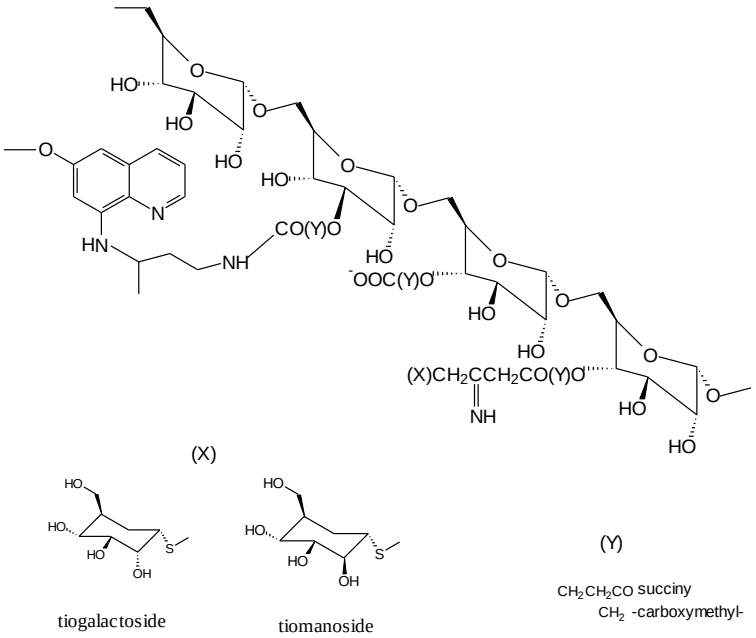

FIG. (3). POTENTIALLY ANTIMALARIAL DRUG TARGETED OF PRIMAQUINE

the advance in cloning methods and gene controlled expression in mamal cells has allowed the elucidation of enzymes and membrane transporters tridimensional structure, making possible the rational design of highly selective targeted drugs [2] like adept approaches (*antibody-directed enzyme prodrug therapy*).

adept approach by definition involves a non existant enzyme in the body, coupled to a monoclonal antibody, in order to activate the prodrug, selectivity cleaved by this enzyme [1] (fig. 4). the monoclonal antibody-enzyme conjugate is administered at first, and the antigen-antibody interaction occurs. Prodrug is then administered and the enzyme from the complex enzyme-antibody-antigen selectively cleaves the carrier-drug linkage, releasing the drug, responsible for the action against either the pathogenic organism (bacteria, helminth or protozoa) or the tumour cell.

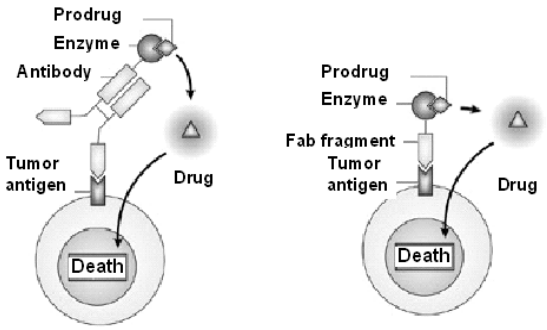

FIG. (4). **ADEPT WITH FULL ANTIBODY AND WITH FAB FRAGMENT.**

Cephalosporin may be a carrier to be used in adept approach. The prodrugs (cephalosporins substituted at the c-3' position) are activated after antibody-beta-lactamase conjugate hydrolysis, releasing the active drug to the target. The chemotherapy for cancer and

protozoiasis success may be limited by several drawbacks, including low concentrations in target cells, systemic toxicity, lack of selectivity for target cells over normal cells and the appearance of drug-resistance. Adept is a promising strategy with two steps to increase selectivity the drug to the target. Prodrugs of cephalosporin and primaquine have been also synthesized by blau (2005) in order to be used in adept approach to the treatment of chagas'disease [5].

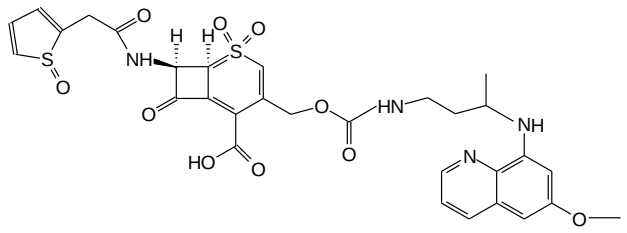

FIG (5). PRODRUG CEPHALOSPORIN-PRIMAQUINE FOR USING IN ADEPT APPROACH

CONCLUSION

Prodrug approach has been useful for the treatment of many diseases, either infectious or provoked by normal physiology disturbance. It has been an important, rational and possible alternative to introduce better drugs in therapy, due to fast advance in biotechnology field and in organic compounds identification.

In spite of using – and also for this very reason – generally simple synthetic routes, the modern systems that have been used for prodrug design deserve more and more interest, mainly because they allow to obtain highly selective compounds potentially useful for therapeutic purposes.

The studies on advanced systems of prodrug design have been concentrated in cancer field, due to the urgent need for selective antineoplastic drugs. Neverthless, it is of utmost importance to extend those modern approaches to infectious diseases, as tropical endemies and tuberculosis, for instance. These diseases affect mainly poor people of undeveloped countries and new and better drugs must be searched. We have been working on prodrug design with some antimalarial,

antileishmanial, anti-Chagas´ disease and tuberculostatic agents with the objective of improving their activity and obtaining selective systems derived.

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P-15 The Vision and Impact of Life Styles on Health and Disease

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"yat\ ipNDo td\ ba`mhaMDo" – "That which is in the microcosm of the body is also in the macrocosm of the universe". This is one of the fundamental and revolutionary discoveries of Bharat's Rishis. The impact of this formulation can be even greater than that of Einstein's $E=mc^2$, leading to nuclear chain reaction. It was in the quest of a harmony of the organism with its universe that Bharatiya Vidya – Para and Apara – evolved. Human development, sankaras, life-habits, social happiness and longevity were spun by this vision of harmony. Healthy life-styles were a consequence of such an all-encompassing vision, in India. Ayurveda, Yoga and Upasana emphasized that Pragnya was central to human health and happiness and Pragnyaparadha was the major culprit leading to disharmony and diseases.

Under the sheep's skin of globalization the wolf of western wasteful habits are invading the orient. The six enemies of man are being deified by the materialistic ethos. The quick and indulgent life-styles are engulfing the globe. Let us recall what the great seer of India–Sri Aurobindo said, "We are the pioneers hewing our way through the jungle of the lower Prakriti: It will not do for us to be cowards and shirkers and refuse the burden, to clamour for everything to be made quick and easy for us. Alone all things I demand from you endurance, firmness and heroism – the true spiritual heroism. I want strong men. I do not want emotional children."

What are the so-called major life-style diseases? How can we correlate these diseases with Ayurvedic Samprapti and Shat-kriya-kala? The focus can be on the major epidemics on-going in India. India has got a dubious distinction of being the diabetes capital of the world! What can Ayurveda offer to the nation and the world that would control and retreat the epidemic of diabesity. The practices of Dina-charya, Ritu-charya, Ahara-Vihara and Achara-rasayana along with Shrodhan–Shaman can offer unique modalities for prevention and treatment of diabesity. CSIR-NMITLI project has very interesting and novel findings already. Dealing with insulin resistance and visceral obesity are the main targets being addressed.

South Asians, including Indians, are very prone to atherosclerosis and coronary heart disease. Dean Ornish took inspiration for "Reversing Heart Disease", from Indian seers viz Swami Sachidananda. The appropriate and individualized programme to prevent and treat heart diseases involves major changes in life-style as to diet, exercise and stress. There are several studies, in India, supporting benefits of such interventions, based on Ayurveda and the current knowledge. The need for a national consensus on integrative care of heart diseases is vital. CCRAS, ICMR and CSIR have already taken up the Golden Triangle Approach for coronary heart disease and hyperlipidemia.

For Life-styles to be followed with a Life long compliance, the school health education has to incorporate the basics of Ayurveda and Swasthavritta in the curriculum. The media and the opinion-leaders have to criticise the wrong Lie-styles and encourage creatively healthy Life-styles. Bharat can be a world number for healthy Life-styles.

PL-16 The impact of obesity on Women's health and life-styles".

Dr. (Mrs) Rama Vaidya, SPARC, President of AIIRO,

PL **-17 The epidemiology and profile of diabetes in India".**

Dr. V. Mohan, MDRF, Chennai. "

PL-18
Development of a functional antirabies vaccine using viral coat protein expressed in plant leaves

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The production of pharmaceutical and industrial recombinant proteins is carried out traditionally in bacterial, yeast or animal cell lines. However, a majority of the pharmaceutical and bioactive proteins have to be made through expensive technologies using mammalian and human cell lines due to incorrect folding of proteins or the lack of -or unsuitable - post translationational modifications in simpler systems. High cost of the eukaryotic cell – based technologies limits the upscaling of the biopharmaceuticals manufacture inspite of serious short supply of some of these even in the US. High costs further limit their accessibility in developing world. Besides cost limitations, biosafety of serum or animal cell derived products has made the current approaches increasingly questionable. Among the several alternatives that are currently available, transgenic plants or *in vitro* grown plant cell, tissue or organ based technologies are emerging as the most preferred approaches to manufacture bioactive proteins of interest to

pharmaceutical and industrial sectors. In order for the plant based recombinant proteins to become a commercial reality, several challenging issues need to be addressed. Some of these are: *in vitro* methods in plant and cell tissue culture, high level expression of proteins in the targeted tissue or organ, correct conformational folding of proteins, genetic engineering of plants to achieve animal – like post translational modification of proteins, biosafety and environmental safety of the engineered plants, innovative approaches to protein purification, delivery systems for effective and safe release of target proteins through parenteral, mucosal or edible routes etc. Plant cells have been demonstrated to express, process, fold and assemble a variety of complex proteins in biologically active forms. The essential principles have been established in case of more than fifty proteins, using nuclear and chloroplast transformation of plant cells. We have examined some of these issues, taking antirabies and anticholera proteins as representative examples. Some of the recent findings will be discussed during the presentation. One of the recent research papers published by our group may be referred to in Journal of Biotechnology (2005), volume 119, pp 1-14.

Synthetic genes coding for the cholera toxin B and surface glycoprotein (G protein) of rabies virus were strategically designed to achieve high-level expression in transgenic plants. The native signal peptides were replaced by that of the pathogenesis related protein, PR-S of *Nicotiana tabacum*. An endoplasmic reticulum retention signal was included at C-terminus of the G protein. Tobacco plants were genetically engineered by nuclear transformation. Selected transgenic lines expressed the cholera toxin at nearly 1% and the chimeric G protein at about 0.2 to 0.4% of the total soluble leaf protein. Mice immunized intraperitoneally with the G protein purified from tobacco leaf microsomal fraction elicited high level of immune response as compared to the inactivated commercial viral vaccine. The plant-derived G protein induced complete protective immunity in mice against intracerebral lethal challenge with live rabies virus. The results establish that plants can provide a safe and effective production system for the expression of immunoprotective rabies virus surface protein. Details related to the development of systems for high-level expression of genes in plants will be discussed.

PL-19 Novel 2-thiazolylamino-5-aryliden-thiazole-4-ones with COX inhibitory activity.

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Non-steroidal anti-inflammatory drugs (NSAIDs) exhibit anti-inflammatory effects by reducing prostaglandin synthesis through the inhibition of COX-1 and COX-2 activity. Most NSAIDs inhibit both COX isoenzymes. As COX–2 was found to be mainly induced during inflammation, COX-2 selective inhibitors have been designed in order to reduce gastrointestinal irritation and other undesired side effects, coming from COX-1 inhibition. However, COX-2 selective inhibition resulted in increased cardiovascular events induced by uncontrolled platelet aggregation, as COX-2 is the dominant source of prostacyclin production from the endothelium. Research on optimal anti-inflammatory drugs discovery continues.

Besides, a trend to design multifunctional drugs for fighting multifuctorial diseases has been immerged.

In the present study we evaluated the COX inhibitory activity of new compounds designed to have antimicrobial activity. Antiinflammatory activity of the designed compounds was predicted by computer program PASS and was experimentally verificated. The new compounds, containing a 5-substituted thiazole-4-one ring connected to a thiazolyl ring via an amine bridge, were found to differ in COX inhibitory activity depending on the thiazolyl ring substitution.

Antiinflammatory activity was evaluated using the carrageneen induced mouse paw edema test. The COX-1 and COX-2 activity was measured using ovine COX-1 and human recombinant COX-2 enzymes included in the "COX Inhibitor Screening Assay" kit provided by Cayman (Cayman Chemical Co., Ann Arbor, MI, USA).

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PL-20 Dr.B.B.LOHRAY

ZYDUS CADILLA , Ahemdabad

IN-1

Bisphosphonates and Novel Related Structural Classes for Bone Resorption Disorder,

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IN-2

Synthesis and structure activity relationship of novel quinolones against Gram positive bacteria

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Gram-positive bacteria are responsible for a wide range of diseases, and rising antibiotic resistance in this group is causing increasing concern. The quinolones are widely used in the treatment of bacterial infections and exert their antibacterial activtiy by interfering with the function of two essential bacterial enzymes, DNA gyrase and topoisomerse IV.

A major recent focus of quinolone antibacterials has been the development of agents with enhanced activity against Gram-positive bacteria. Despite limited activity of ciprofloxacin against these bacteria, subsequently developed and marketed quinolones - including sparfloxacin, levofloxacin, trovafloxacin, grepafloxacin, gemifloxacin, gatifloxacin, and moxifloxacin - had increased activity against Gram-positive bacteria and received regulatory approvals for treatment of patients with various gram positive infections.

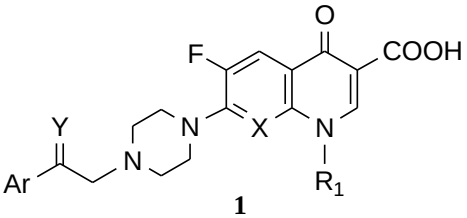
The 1,4- dihydro-4-oxopyridine-3-carboxylic acid associated with a 5,6-fused aromatic ring is the common chemical feature of quinolones. The nitrogen at N-1 is almost indispensable for activity and the carboxylic acid at position 3 and the carbonyl group at position 4 are considered critical for binding to DNA. Since position 2 is very close to the binding site, it is believed that any added bulk inhibits access and results in a lower level of activity.

Much of the improved potency of modern quinolones against Gram-positive microorganisms has been achieved by tinkering with the N-1, C-5, C-6, C-7, and C-8 substituents on the quinolone ring system.

The 7-cyclic amine moiety of quinolones possesses enough structural flexibility to allow product optimization. In addition, a position on the quinolone molecule, where substitutions of bulky groups are permitted, is C-7 position. Accordingly, we described a number of *N*-substituted piperazinyl quinolones (**1-3**) containing certain bulky substituent in the piperazine unit of 7-

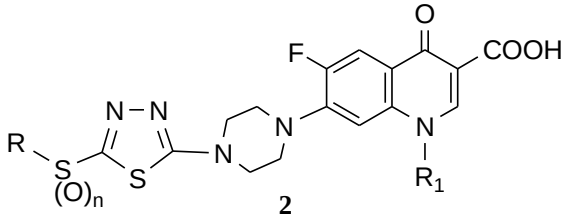
piperazinyl quinolones, to identify a particular chemical modification that allows manipulation of potency particularly in Gram-positive bacteria. Some of these derivatives exhibit high activity against staphylococci more potent than their parent *N*-piperazinyl quinolones.

Although the nature of the C-7 substituent is known to influence quinolone activity, but improvement of anti-Gram-positive activity in this type of *N*-substituted piperazinyl quinolones may be due to more favorable accumulation in Gram-positive bacteria.



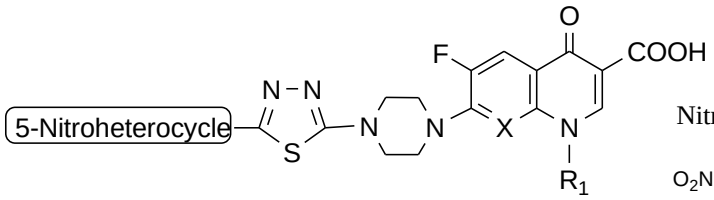
1

X= CH, N
R_1= Et, c-Pr
Ar= substituted phenyl, thiophene, furan
Y= O, NOH, NOR



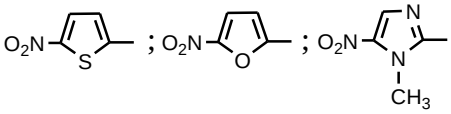
2

R_1= Et, c-Pr
R= benzyl, nitrobenzyl
n = 0, 2



3

Nitroheterocycle:



I-3 SYNTHESIS AND CYTOTOXIC EVALUATION OF NEW 2-OXO-ACETAMIDES AND 4*H*-1,3-BENZODIOXINES

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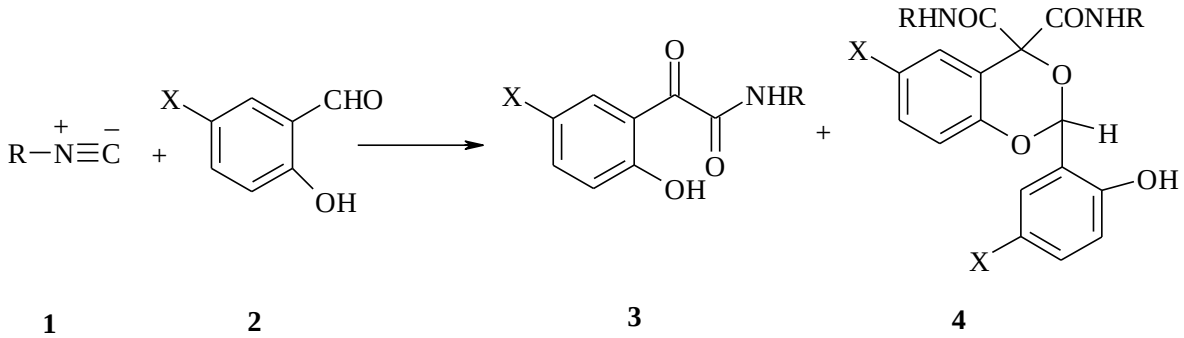
Some 2-oxoacetamides were found to have 5-HT_3 receptor partial agonist activities.[1] *1*H*-1,3-benzodioxine moiety has been used as building blocks for oligonucleotide synthesis. This work, aims at presenting a new method of synthesis of 2-(2-hydroyphenyl)-2-oxoacetamides 1*H*-1,3-benzodioxine derivatives. Another objective of the study reported in this paper was to evaluate the cytotoxicity properties of these species against some cancer cell lines including K562, HL60, MCF-7, and PC12. The results compare with the cytotoxic effect of the agents against a normal human cell line, HFFF-P16. In addition, their antifugul activities have been studied against some candid species including* C. glabrata, C. parapsilosis, C. tropicalis *and* C. dubliansis.

The reaction between alkyl isocyanides ***1***[2,3] *and 2-hydroxybenzaldehyde or 2-hydroxy-5-nitrobenzaldehyde in CH_2Cl_2, leads to 2-oxoacetamides* ***3*** *and 4*H*-1,3-benzodioxine derivatives* ***4*** *in moderate yields. The products were characterized on the basis of their spectroscopic data, and a single-crystal X-ray diffraction of* ***4*** *(R = $Me_3CCH_2CMe_2$, X = H).*



1 **2** **3** **4**

X = H; NO_2

R = *t*-Bu; Cyclohexyl; Bn; 2,6-Dimethylphenyl; 1,1,3,3-Tetramethylbutyl

In vitro activity against murine and human cancer cell lines

The growth-inhibitory properties of 2-(2-hydroyphenyl)-2-oxoacetamide were examined in various murine (PC12) and human (HL60, K562, and MCF-7) cancer cell lines, using the MTT assay following 72 h of drug exposure. HFFF-P16 cells were used as non-malignant control. A cytotoxic index was calculated for each agent as IC_{50} of the test compound against HFFF-P16 divided by its IC_{50} against cancer cell line. This cytotoxic index could give an indication of the preferential effects of the test compound on cancer cell lines compared with non-malignant cells.

It was found that *N_2,N_4*-di-*tert*-butyl-2-(2-hydroxy-5-nitrophenyl)-6-nitro-4*H*-1,3-benzodioxine-2,4-dicarboxamide (**4c**) showed the greatest absolute and preferential cytotoxicity against all examined cell lines. The IC_{50} values for this agent ranged from 34-781 ng/ml, whereas those for Doxorubicin (used as a positive control) ranged from 18-110 ng/ml. Although *N'*-cyclohexyl-2-(2-hydroy-5-nitrophenyl)-2-oxoacetamide and *N'*-cyclohexyl-2-(2-hydroyphenyl)-2-oxoacetamide

exhibited a similar cytotoxic effect against all cell lines. In all cell lines, the growth inhibitory potencies of the former was found to be lowest, giving IC_{50} values of 9 µg/ml.

In vitro antifungal activity

2-oxoacetamide derivatives were tested against *C. parapsilosis*, *C. albicans*, *C. tropicalis* and *C. dubliansis*. It was found that any compound of the 2-oxoacetamide series displayed antifungal activity at the MIC range of 1.9 to 125 µg/ml. Of all fungi species, *C. tropicalis* showed the most sensitivity to 2-oxoacetamide derivatives. *N*'-(*tert*-butyl)-2-(2-hydroxy-5-nitrophenyl)-2-oxoacetamide showed a significant activity against all species specially *C. tropicalis*. Its MIC values was significantly lower than Ketokonazole. *N*'-Cyclohexyl-2-(2-hydroyphenyl)-2-oxoacetamide (**3b**) and *N*'-cyclohexyl-2-(2-hydroy-5-nitrophenyl)-2-oxoacetamide (**3d**) showed the same antifungal effect. The most and least sensitive strains of candida, towards Ketoconazole were *C. parapsilosis* and *C. tropicalis* with MIC values 0.5 and 16 mg/ml.

Conclusions

Comparison of the cytotoxic effects of the four synthesized oxoacetamides suggests that the presence or absence of the N_2O group on the meta position of the benzene ring has little effect on the activity of the compound. Also, replacing the cyclohexyl group with the *tert*-butyl moiety decreases the cytotoxicity of the compound. Compound **4c** showed the greatest activity against the cancer cell lines tested. However, as the structure of **4c** is substantially different from all the other compounds tested in this work, it is difficult to draw any conclusions on the SAR of this molecule.

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I-4 $BF_3.Et_2O$ MEDIATED SYNTHESIS OF PHARMACEUTICALLY USEFUL HETEROCYCLES

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Metals and metal halides have earlier been used by us for synthesis of NO donors.[1,2] We have successfully employed $BF_3.Et_2O$ for synthesis of Oxadiazoles,[3] Benzimidazoles,[4] Benzoxadiazepines, Benzoxaazepines, Quinoxalines, Benzoxazoles and Benzothiazepines.

The pharmaceutical utility of these heterocycles shall be discussed.

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I-4

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I-6: Single Electron Transfer Process for *in situ* Thiolate Anion Generation: Applications in Organic Synthesis

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Functional group transformation is an unavoidable exercise in organic synthesis of any length. The prevalence of phenolic and carboxylic acid moieties in wide ranges of biological active compounds necessitates synthetic manipulation of these functional groups through protection and deprotection. Various methodologies involving 'electrophilic activation,'[1] and 'dual activation'[2] strategies have been developed in this laboratory for masking hydroxyl groups. The regeneration of the parent phenol/carboxylic acid involves nucleophilic cleavage and thiolate anions are popular choice for the desired transformation. To this effect, a novel concept of 'demand based

thiolate anion generation' was developed in this laboratory for chemo-selective functional group transformations.[3] However, dealing with thiols often becomes a least favourable option due to potential health hazard, obnoxious smell and prone to form disulfides by aerial oxidation. In the present deliberation, single electron transfer process for *in situ* thiolate anion generation will be discussed for achieving efficient methodologies for deportection of phenols and carboxylic acids in chemo- and regio-selective fashion.[4]

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I-7 Interaction of *Mycobacterium tuberculosis* with macrophages: some *in vitro* protective effects of serum amyloid P-component

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The acute-phase proteins (APPs) are evolutionarily highly conserved proteins and constitute important components of innate immunity. Soon after an infection or injury, the blood levels of APPs, C-reactive protein (CRP; a prototype human APP) and serum amyloid P-component (SAP; a major mouse APP) increase greatly. During acute-phase of both human and murine TB, the blood levels of CRP and SAP are known to increase rapidly, respectively, and this apparent paradox prompted us to study the effects of SAP, *in vitro*. Dose-dependent quantities of purified mouse SAP inhibited *Mycobacterium tuberculosis* Erdman uptake by mouse alveolar macrophages (AMs), *in vitro*; 10-15 μg/ml appeared optimal. This diminished *M. tuberculosis* uptake was invariably associated with reduced intramacrophage mycobacterial growth as

determined by plating. *N*-glycanase, and not *O*-glycanase, deglycosylation of purified SAP resulted in the loss of its ability to inhibit mycobacterial uptake. Further, the SAP-inhibition of mycobacterial uptake by AMs appeared to be pH and cation-dependent, and was blocked by mannose-based simple sugars. Furthermore, purified SAP, in a concentration-dependent manner, activated mouse AMs for augmented *M. tuberculosis* killing, *in vitro*; 10-15 μg/ml SAP exerted maximum effect. Nitric oxide-appeared to be the effector molecule for intra-AM mycobacterial killing as both aminoguanidine and N^G-monomethyl-L-arginine annulled it, and SAP treated infected AMs elaborated significant nitrite. Because innate immunity is known to play important roles in TB, these *in vitro* activities of SAP appeared to be consistent with its pro-inflammatory host defence functions. Detailed investigation along these lines, especially those using SAP knockout mice, are most definitely warranted.

I-8
Ethnopharmacology and Drug Discovery

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I-7 Design and synthesis of pyrazolo[3,4-*d*]pyrimidine core based flexible compounds for studying 'arene interactions'

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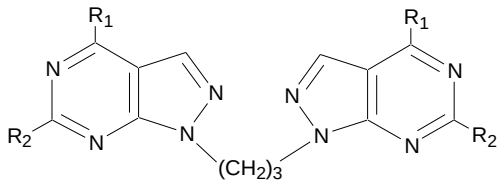
Arene interactions are known to play an important role in molecular recognition, stabilization of DNA/RNA structures, crystal engineering, foldamers, molecular tweezers/clips and drug development. Since Hunter and Sanders paper (*JACS*, **1990**, *112*, 5525) this area has witnessed hectic activity, however, the nature of π–π interactions is still not well understood. The offset stacked geometry is the most common geometry for **arene interactions**, but the least well studied (*JACS*, **2002**, *124*, 1860). As their strength is much less than that of H-bond in water they are quite difficult to study.

In **1995**, we started, for the first time, use of pyrazolo[3,4-*d*]pyrimidine core, which is isomeric with biologically significant purine system, for studying **arene interactions**. Thus, we reported first synthesis of 1,3-bis(4,6-dimethylsulfanyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)propane (**1a**, Fig. 1) in order to develop new flexible model for studying *intramolecular* aromatic π–π interactions. X-Ray crystallographic studies on **1a** confirmed *intramolecular stacking* and in addition revealed *intermolecular stacking*. Robustness of the unusual **U-motif** in compound **1a**



1a: $R_1 = R_2 =$ SMe;
1b: $R_1 = R_2 =$ SEt;
1c: $R_1 = R_2 =$ S-iso-Pr;
1d: $R_1 =$ OEt, $R_2 =$ SMe;
1e: $R_1 =$ O-iso-Pr, $R_2 =$ SMe

formed due to *intramolecular stacking* has been further demonstrated in ethyl- (**1b**) and iso-propyl- (**1c**) analogs by X-ray crystallography. Symmetrical structures (**1d** & **1e**; Fig. 1) related to **1a** but having 4-alkoxy group in place of 4-methylsulfanyl group, also show similar folded conformation (*JMS*, **2005**, *750*,179).

Figure 1

Protein and Peptide Drug Delivery

Dr N.Udupa,Principal,MCOPS,Manipal

Recent advances in pharmaceutical technology have led to an inflow of new protein and peptide drugs in the market. However, its application is limited because of their physical and chemical instability and lack of desirable delivery systems for adequate absorption and distribution. Many methods were used to devise peptide and protein drugs delivery system. Because of their relatively large size, they have low transdermal bioavailabilities. Carrier system such as microspheres, liposomes and nanoparticles can improve oral absorption of peptides and protein drugs. However, the drugs need to be protected from the harsh environment in the stomach facilitating the absorption of the drug through the intestinal walls. Protein drugs when encapsulated may denature within the polymer matrix causing a loss of biological activity and possible changes in immunogenicicty. The unique requirements of peptides and proteins in

designing delivery systems, and the unprecedented recent growth in the field, have driven a great deal of research into novel means of drug delivery. The search for approaches that provide formulations that are stable, bioavailable, readily manufacturable, and acceptable to the patient, has led to major advances in development of nasal and controlled release technology. The field of parenteral solution technology has also seen some new demands made of it, and what was formerly a conventional area of formulation technology has made scientific advances to meet the needs of these compounds. At the same time, strides are being made in fundamental research in areas including oral delivery, transdermal delivery, and pulsatile and 'on demand' delivery of peptides and proteins.

Insulin therapy is the cornerstone of the treatment for the diabetic patients and there have been many trials to develop an ideal insulin delivery system, which mimic the physiologic pattern of insulin secretion. Until now the most effective way to keep the blood glucose concentration close to normal is multiple subcutaneous insulin injection. However this is not practical for most patients and attended with the risk of life threatening hyperglycemia.

I-9 Ayurvedic Medicinal Plants and Management of Adult Obesity

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Submitted to the International Satellite Symposium on Medicinal Plants and Functional foods in Diabetes, Obesity & CVS Diseases

While obesity has been described as Medorog in Ayurvedic classics, its etiology and pathogenesis have several features common to our modern day understanding of this complex multifactorial disease. Both the systems recognize the role of physical activity and diet regulation but the role of fat (Meda) in obstructing the channels (Srotasas) vis-à-vis the metabolism of adipose tissue and the role of hypothalamus through the endocrine system show differences in the perception of the disease and its management.

Though the genetic predisposition of obesity is similar to the disposition of kaphaj prakruti persons to obesity, associated social and behavioral factors also influence the outcome of obesity management. While lipolytic statins are the only major modern drugs currently used in the management of obesity, regulation of eating behaviour has been shown to be influenced by GI humour factors viz. cholecystokinin and bombesin etc. The use of Triphala and Trikatu in the management of digestive system to regulate obesity needs to be thus carefully examined. The role of other Ayurvedic Deepan-Pachak medicines like Chitrak, Hingu, Shigru, etc. also needs to be examined in this light as well as the role of neuro-endocrine factors.

Ayurveda also recommends local application of lepas (ointments) containing Shalmali, Vasak, Bilva, Shireesh and Chandan etc. and medicated oils, which could play an important yet harmless role of influencing the adipocytes as an endocrine gland or liposuction promoted by cosmetic surgery with known adverse risks. The likely convergence of the approaches used by Ayurveda shall be examined in this paper in light of our increased understanding of molecular mechanisms of neuro-endocrine and gastro-intestinal regulation of obesity. This integrated approach may also open up new vistas in the management of associated risk factors and other serious comorbidities associated with obesity.

I-10

Dr. MUTHUSAMY, CSMCRI, Bhavnagar

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Oral-1

SYNTHESIS & ANTIMICROBIAL STUDIES OF

NEW 5-N^2-[{SUBSTITUTED BENZOTHIAZOLYL}SULFONAMIDO]-2-METHOXY-N^3-[2-{(4-HYDROXY) PHENYL}-4-OXO-THIAZOLIDINO]CARBOXAMIDE

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5-N^2-[{Substituted benzothiazolyl}sulfonamido]-2-methoxy-N^3-[2-{(4-hydroxy)phenyl}-4-oxo-thiazolidino]carboxamide $\mathbf{5_{a\text{-}l}}$ have been synthesized by the cyclization of Schiff bases $\mathbf{4_{a\text{-}l}}$ with thioglycolic acid from corresponding 5-N^2-[{substituted benzothiazolyl}sulfonamido]-2-methoxy benzoyl hydrazine $\mathbf{3_{a\text{-}l}}$. Compounds $\mathbf{3_{a\text{-}l}}$ in turn were prepared by dehydroxyhalogenation followed by condensation with hydrazine hydrates of 5-N^2-[{substituted benzothiazolyl}sulfonamido]-2-methoxy benzoic acids $\mathbf{2_{a\text{-}l}}$. Compounds $\mathbf{2_{a\text{-}l}}$ in turn were prepared by chlorosulfonation followed by condensation with substituted 2-amino benzothiazoles of acid **1**. Final compounds have been characterized by their element analysis, IR, ^1H-NMR. All the synthesized compounds have been screened for their antimicrobial activity. Some of them show good activity.

Oral-2

EXPERIMENTAL AND QSAR STUDIES ON ANTIFUNGUL COMPOUNDS

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Inhibition activity of a large number of organic compounds (benzene and salicylic acid derivatives and large organic molecules) towards two fungi *Aspergillus niger* and *Fusarium Rosium* were studied in the wet lab. The extent of inhibition of the organic compounds was determined by measuring the decrease in percentage turbidity at a transmission at 660 nm. Quantitative structure activity relationships (QSAR) were developed relating the antifungul activity with the structural descriptors of these molecules.

The minimum energy conformations of the molecules were determined using Molecular Mechanics (MM+) in conjugation with Quantum mechanics technique (PM3). Steric, electronic, topological, constitutional, aromatic and thermodynamic descriptors for these molecules were evaluated and the best descriptors were selected from this list and correlated with the antifungul activity. Dipole moment of the molecule was correlated with the antifungul activity (~ 0.6) for both the fungi. For *Fusarium Rosium* X4 (connectivity index chi-4)and Jhetv (Balaban-type index from van der Waals weighted distance matrix, topological descriptor) had high correlation with the antifungul activity (correlation coefficients of 0.7 an d-0.66 respectively). While for *Aspergillus niger* TIC1 (total information content index with neighborhood symmetry of 1-order) and SPI (superpendentic index, topological descriptor) were highly correlated with antifungul activity (correlation coefficients of -0.67 and -0.74 respectively). Linear regression models were developed relating the observed antifungul activity as the dependent variable and various descriptors as the independent variable.

Oral-3

TOTAL SYNTHESIS OF A NOVEL CYCLIC HEXAPEPTIDE OF NATURAL ORIGIN

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Abstract :

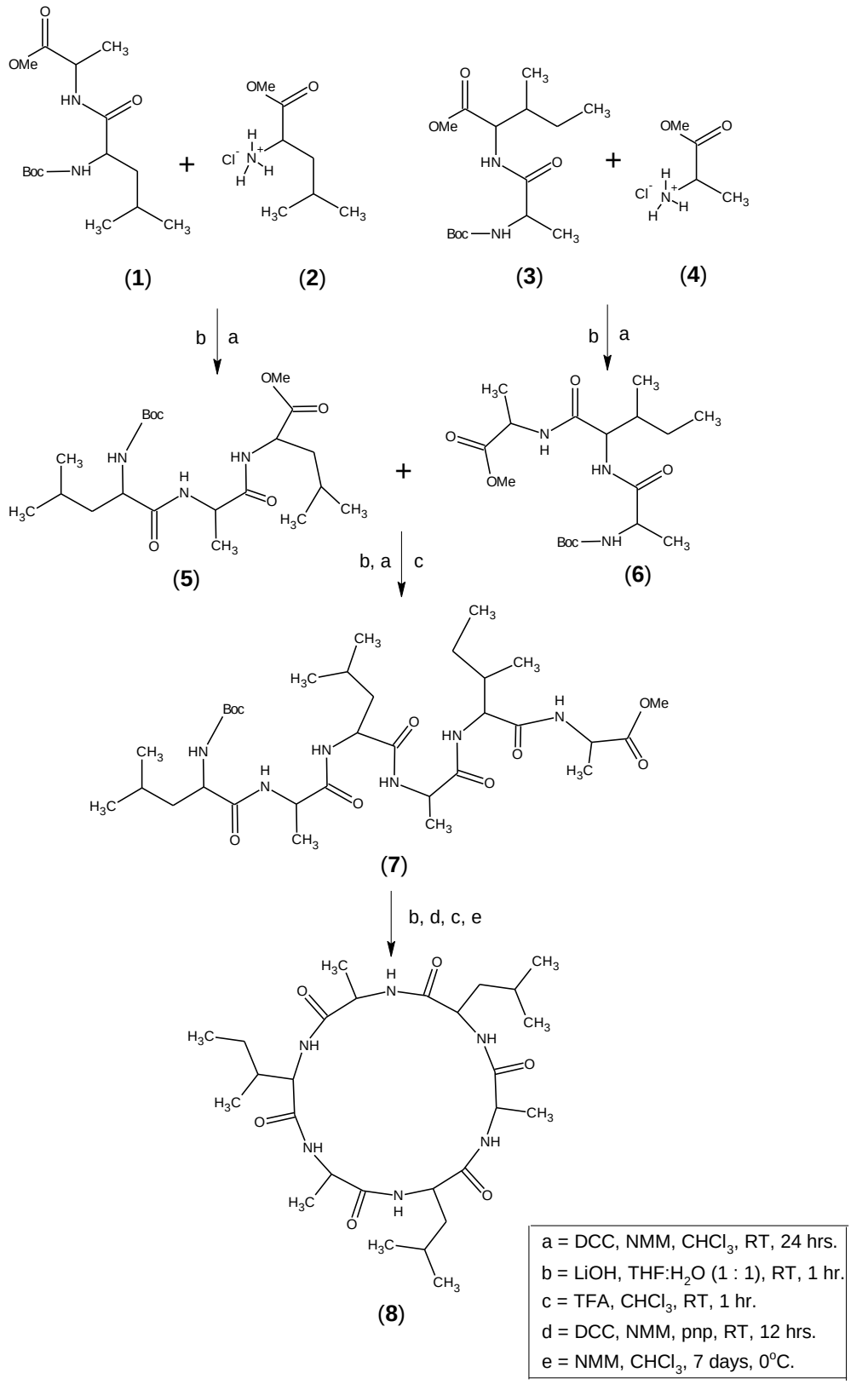
Antimicrobial peptides have played a crucial role in the pharmaceutical research as biomedically useful agents or as lead compounds for drug development. As part of ongoing efforts towards finding novel antifungal and antibacterial agents, a new alanine-rich cyclic hexapeptide has been synthesized by solution phase technique which was isolated from the marine sediment-derived bacterial strain *Halobacillus litoralis* YS3106. In order to carry out the synthesis of halolitoralin A (**8**), two dipeptide units and two amino acid units were coupled:

a) Boc-Leu-Ala-OMe (**1**) b) Leu-OMe.HCl (**2**)

c) Boc-Ala-Ile-OMe (**3**) d) Ala-OMe.HCl (**4**)

The ester group of dipeptide Boc-Leu-Ala-OMe (**1**) was removed by alkaline hydrolysis with LiOH and the deprotected unit was coupled with amino acid methyl ester hydrochloride Leu-OMe.HCl (**2**) to get tripeptide unit Boc-Leu-Ala-Leu-OMe (**5**). Similarly, dipeptide unit (**3**) after deprotection at carboxyl end, was coupled with (**4**) to obtain another tripeptide unit Boc-Ala-Ile-Ala-OMe (**6**). Then, the ester group of (**5**) was removed using LiOH and Boc group of (**6**) was removed using TFA. Both deprotected units were now coupled using DCC and NMM to get linear hexapeptide Boc-Leu-Ala-Leu-Ala-Ile-Ala-OMe (**7**) which was finally cyclized by keeping the whole contents at 0°C for 7 days in alkaline conditions to get halolitoralin A (**8**) (**Scheme A**).

The structure of peptide was characterized by FTIR, ^{1}H NMR, ^{13}C NMR, FAB MS spectral data as well as elemental analyses. The newly synthesized peptide was also screened for its antimicrobial activities against eight microorganisms and found to exhibit potent antifungal activity against pathogenic fungi *Candida albicans* and *Trichophyton mentagrophytes* along with potent antibacterial activity against gram negative bacteria *Pseudomonas aeruginosa* and *Escherichia coli*.


(1)
(2)
(3)
(4)
b a
(5)
(6)
b, a c
(7)
b, d, c, e
(8)
a = DCC, NMM, CHCl3, RT, 24 hrs.
b = LiOH, THF:H2O (1 : 1), RT, 1 hr.
c = TFA, CHCl3, RT, 1 hr.
d = DCC, NMM, pnp, RT, 12 hrs.
e = NMM, CHCl3, 7 days, 0°C.

Scheme A

Oral-4

STUDIES ON ACUTE TOXICITY AND ANTIINFLAMMATORY POTENTIALITY OF THE METHANOLIC EXTRACT OF *Grewia asiatica* LEAVES

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The present study has been carried out on the methanol extract obtained from the leaves of *Grewia asiatica*, a plant commonly used in the treatment of pain and rheumatism in the folklore. The study of anti-inflammatory activity was carried out on Wister rats at three different doses (50,100 and 150 mg/kg body weight) using different phlogistic agents like carragenin and the percentage inhibition of edema were calculated. The extract was found to show significant anti-inflammatory activity in a dose dependant way. On phytochemical screening the extract was found to possess steroid, alkaloid and tannin. The anti-inflammatory activity was found to be due to the presence of β-sitosterol. Acute toxicity study had revealed that the extract was safe even up to 1000 mg/kg body weight. The observation of the present study scientifically validated the traditional claim of the plant as an anti-inflammatory agent.

Oral--5

EMERGENCE OF *AEGLE MARMELOS* (CORREA) LINN. FRUIT EXTRACT AS A POTENT ANTIDIARRHOEAL AGENT

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Chloroform extract of *Aegle marmelos* (Correa) Linn. fruit (AMFE) was studied for its *in vitro* effect on organisms causing diarrhoea and also for its *in vivo* antidiarrhoeal potential in mice. The *in vitro* antimicrobial activity was studied following agar dilution and disc diffusion techniques. The extract was tested for its minimum inhibitory concentrations (MIC) against 35 various pathogenic strains of *Shigella* spp., *Escherichia coli* and *Vibrio cholerae* followed by comparative antimicrobial assay of the extract and standard antibacterial agent, ciprofloxacin, against selected sensitive bacterial strains. The extract was then studied for its *in vitro* mode of antibacterial function. The extract was found to be mostly active against the strains *of V. cholerae*, followed by *E. coli* and *Shigella* spp. The *in vitro* antimicrobial activity was found to be comparable to that of ciprofloxacin and the extract was proved to be bactericidal in its action.

Further, AMFE treated mice showed significant inhibitory activity against castor oil induced diarrhoea. The results so obtained thus establish the efficacy of AMFE as an effective antidiarrhoeal agent.

O-6

EVALUATION OF ANTITYPHOID POTENTIALITY OF *Phyllanthus amarus* AGAINST ANTIBIOTIC RESISTANT SALMONELLA ISOLATES: A STUDY *INVITRO*

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There are a large number of plants that are well known today for their various medicinal uses. One such plant is *Phyllanthus amarus* belonging to the family Euphorbiaceae used mainly by the tribals of Chotanagpur region in the treatment of typhoid. The whole plant has already been reported to be very effective in the treatment of liver damage and infections caused by hepatitis B virus. Presently an attempt was made to justify its folklore claim by evaluating its antityphoid potentiality against some clinical isolates of *Salmonella* spp characterized by routine bacteriological evaluation and showing high degree of antibiotic resistance on screening. The methanol extract of the whole plant was found to possess alkaloid, tannin and flavanoid as phytoconstituents on preliminary phytochemical screening. The extract was found to possess significant antityphoid activity as all strains showing resistance to the commonly used antibiotics including ciprofloxacin, penicillin, tetracycline and cephalexin reference standard in our laboratory were found to be inhibited at a very low concentration of the extract when tested by agar dilution technique. The extract was found to show a very large diameter of zone of inhibition when tested by disc diffusion technique against the strains causing

typhoid. Further the extract was found to reveal bactericidal effect in its mode of action thereby justifying its traditional claim.

Oral-7

Pharmacokinetic Studies on CDRI 85/92 (an antiulcer pharmacophore) and its ester form as prodrug.

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Oral administration is considered to be the best mode of drug administration. Quite a number of drugs experience setback in spite of having good efficacy due to less bioavailability.

Hence, there is need to improve the oral bioavailability by improving the oral absorption and/or decreasing its presystemic metabolism. Prodrugs offer a viable strategy in this regard. Compound CDRI-85/92 (5-styryl-4, 5-cis-1, 3-oxazl-2-one-4-carboxylic acid) is a new antiulcer pharmacophore with potent proton pump inhibition profile. The compound selectively and competitively inhibits the gastric proton pump making it the drug of choice for the treatment of patients with acid related diseases. In this study, the comparative pharmacokinetics of CDRI 85/92 and its ester derivative were evaluated in male *Sprague-Dawley* rats in order to find out whether the later can be used as a potential prodrug of CDRI-85/92.

The compound and its ester derivative were separately administered orally at 20 mg/kg to male *Sprague-Dawley* rats and blood samples were withdrawn upto 48 h. Serum concentration-time profile of CDRI-85/92 was determined using LC-UV method and the pharmacokinetic parameters were calculated by subjecting the concentration-time data to non-linear regression analyses using WinNonlin software.

In both the studies, peak concentrations (C_{max}) of CDRI-85/92 were observed at 15 min post administration but the C_{max} after oral dose of the ester derivative was higher (956 ng/ml) than that after the compound (469 ng/ml). Following oral dose of the ester derivative, the rate of elimination of the compound was lower ($t_{1/2}$, 17.5 h) than that after the compound ($t_{1/2}$, 6.3 h). There was 4.0-fold enhancement in the AUC (3263ng.h/ml) of the prodrug as compared to CDRI-85/92 (892 ng.h/ml).

In conclusion, the prodrug (hydrophobic) has improved pharmacokinetics (higher C_{max} and AUC and sustained release) as compared to the hydrophilic CDRI-85/92.

O-8 Serine hydroxymethyltransferase inhibiotors as antileishmanial agent

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A biochemical pathway that has been exploited in the past for the treatment of infectious diseases is the folic acid biosynthetic pathway. Dihydrofolate reductase (DHFR) and thymidylate synthase (TS), together with serine hydroxymethyltransferase (SHMT) are essential for replication in virtually all organisms. Of the trio of enzymes involved in the thymidylate

synthase cycle, SHMT is the only enzyme yet to be studied clinically as a target for leishmanial chemotherapy. Serine hydroxymethyltransferase, a member of the alpha class of the pyridoxal-5'-phosphate (PLP)-dependent enzymes, is ubiquitous for generating one carbon fragments for the synthesis of nucleotides, methionine, thymidylate, choline, etc. SHMT inhibitors like D-cyclo serine, Aminoxy acetic acid, Hydroxylamine and Methoxyamine were never tried as antileishmanial agent. We have studied the effect of these SHMT inhibitors on leishmanial growth. In this study we have tested the efficacy of these compounds alone or in combination with some known anti leishmanial drugs such as pentamidine, amphotericin B and miltefosine. We found that SHMT inhibitors are effective against both promastigote and amastigote form of *Leishmania donovani* when used alone or in combination with known antileishmanial drugs.

O-9

MICROARRAY OF LEISHMANIA DONOVANI: A ROLE IN DRUG DISCOVERY AND DEVELOPMENT

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Leishmaniasis is a worldwide parasitic disease affecting 12 million people in 88 countries including India with 500 new cases every year. There is no vaccine in routine use and appearance of resistance against the currently available drugs has raised the pressing need for discovery of new genes essential for parasite survival that could represent for the development of new drugs and vaccines. To identify such genes, we used DNA microarrays for measuring changes in transcript abundance that occur as *Leishmania donovani* promastigotes transform into amastigotes. Microarrays of 2204 PCR amplified DNA fragments from genomic library of *L.donovani* were probed with fluorescent cDNA generated from total RNA of promastigotes and amastigotes. Data was normalized for background and relative abundance of RNA for each spot was calculated. Out of 21 DNA fragments, that were consistently up-regulated in amastigotes, one exhibited significant homology (>92%) with *L.major* annotated genome sequence for putative dipeptidyl carboxypeptidase. Subsequentely, complete coding sequence was amplified, cloned and sequenced. Both RNA and protein levels of LdDCP are higher in axenic amastigotes compared to promastigotes. LdDCP is an exopeptidase, belonging to the zinc metallopeptidase family and cleaves cleaves Hip-His-Leu, a substrate for mammalian peptidyl dipeptidase A also known as angiotensin converting enzyme (ACE). Further, captopril, an ACE specific inhibitor was able to inhibit significantly both the LdDCP enzyme activity as well as promastigote growth. The data strongly suggests that this newly identified DCP could serve as drug target in *Leishmania*

O-10

Structure based drug design of inhibitors targeting recombinant pteridine reductase1 from *Leishmania donovani* clinical isolate

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*presenting author
oral presentation; in International symposium on drug discovery: perspectives and challenges.
Sub area: Combinatorial chemistry, high throughput screening and drug discovery

Pteridine reductase 1 (PTR1) is part of a novel metabolic pathway in *Leishmania* associated with folate metabolism. Its main function is to salvage pterins but a second one is to reduce folates. The novelty and possible uniqueness of the pathway in which PTR1 is involved opens the possibility of developing specific inhibitors, which in combination with dihydrofolate reductase inhibitors could be highly effective against *Leishmania.* In order to increase our understanding of this putative important chemotherapeutic target, we carried out the cloning, overexpression and purification of this enzyme from a clinical isolate of *Leishmania donovani* causing kala azar in India. This recombinant enzyme has been used in structure based drug design and high throughput screening. The ultimate aim is to identify target based compounds worthy of development for the chemotherapy of visceral leishmaniasis. An effective system of compound evaluation utilizing rapid, economical and target based biological screening and testing has also been developed.

O-11

Synthesis of some new heterocyclic compounds, for antiplasmid activity"
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O-12

Glyco-quantum dots: self-luminescent multivalent carbohydrate display for detection of bacteria

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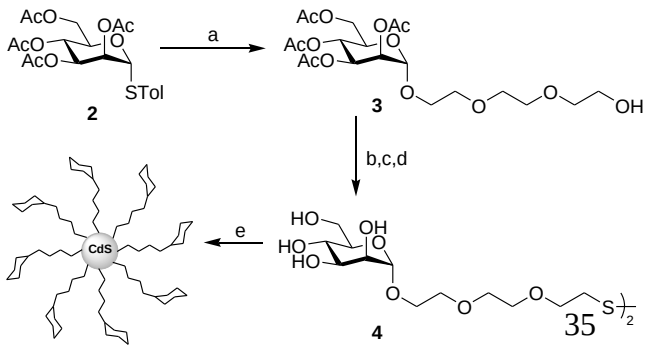
Modified semiconductor nanoparticles (quantum dots) for multivalent display of various types of biomolecules have earned a great interest due to powerful fluorescence properties. Quantum dots (QD) are 100 times more stable against photo-bleaching than organic dyes and therefore very much attractive for designing effective fluorescence probes for *in vitro* or *in vivo* cellular imaging.[1] Reports on bio-conjugated QDs with peptides and proteins,[2] DNA,[3] antibodies[4] and other molecules[5] are available in the literature and well recognized as efficient biological markers.



However, carbohydrate functionalized QDs have not been reported until very recently by Penadés.[6] But the application of carbohydrate-conjugated QDs in biological assays has not yet been explored. A single QD with large surface volume is ready for the covalent attachment of multiple ligands that provides a great possibility for enhanced carbohydrate-pathogen interactions. Moreover, depending on the size of the dots they emit light at a variety of precise wavelength that can be utilized for developing a library of glyco-QDs fabricated with different carbohydrate ligands emitting different colours. Such library could be used for the detection of specific bacteria in a mixture. The present poster will demonstrate the potential application of mannose conjugated QD (ManQD, **1**) for the detection of bacteria involving specific lectin-carbohydrate interaction.

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O-13Modern Methods in Drug Designing

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Abstract
Traditionally, the process of drug development has revolved around a screening approach and trial-and-error method, as no body knew which compound or approach could serve as a drug or therapy. This discovery process was very time consuming and laborious and discovery of a new drug used to take around 8-14 years and costs about $ 800 million. In order to minimize the time and cost in this drug discovery process, scientists around the world contributed tremendously and come up with a modern drug-designing program. The beauty of this modern drug designing is that now we can tailor the drug with desired combinations. In this review, the new drug designing methods will be discussed.
1. Introduction
2. What is a drug?
3. Mechanism of drug action
3.1 By interfering with the biological functions of viruses, bacteria or parasites 3.2 By blocking interaction of viruses, bacteria or parasites with our systems 3.3 By interfering with or enhancing or controlling our own biological function(s)
4. Discovery of drugs
4.1 Drug discovery process 5. Need of drug design? 6. Modern drug designing
6.1 What is a "Lead Molecule"?
6.1.1 Lead identification

6.1.2 Lead Optimization
6.2 Refining drug activity
6.2.1 Combinatorial chemistry
6.2.2 Structure-based design
6.2.2.1 Drug Design Using Known Receptor Structures
6.2.2.2 Docking
6.2.2.2.1 Docking software
6.2.2.2.2 Docking applications
6.2.2.3 Drug Design Using Known ligand Structures
6.3 Quantitative Structure-Activity Relationships (QSAR)
6.4 Criteria of a good drug
6.5 ADME properties
7. Drug testing
8. Formulation
9. Production
10. Application of computers in drug designing

O-14

SYNTHESIS AND CYTOTOXIC ACTIVITY OF NEW LUPANE TYPE DERIVATIVES

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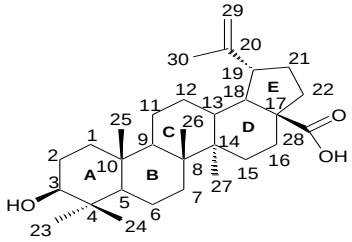
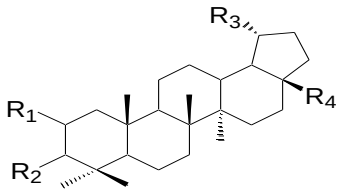
Betulinic acid **(1)**, 3β-hydroxy-lup-20(29)-en-28-oic acid, a naturally occurring pentacyclic lupane type triterpene, is widely distributed through out the tropics. Betulinic acid was recognized for its anticancer and anti-HIV activities. Previous reports revealed that betulinic acid is a melanoma specific cytotoxic agent. Recent evidence indicated that betulinic acid also possesses a broader spectrum of cytotoxic activity against other cancer cell lines. Betulinic acid has shown to function through the induction of apoptosis irrespective of the cells p-53 and CD-95 status. Some experimental reports indicated that betulinic acid acts through the mitochondrial pathway, though the precise molecular target and mechanism of action are not yet clear and is now the focus for number of ongoing research programs. As far as toxicity of betulinic acid is concerned, it has been found highly safe even at the dose of 500 mg/Kg body weight. Therefore, these findings and favorable therapeutic index, made betulinic acid a very attractive agent for the clinical treatment for various types of cancer [1].





2

The C-1, C-2, C-3, C-4, C-20, C-28, A-ring, D-ring and E-ring are the sites for diversification in betulinic acid. Hundreds of derivatives have been prepared and tested for their cytotoxic activity [2-4]. In our laboratory, a series of betulinic acid derivatives (prototype **2**) have been synthesized and screened for *in vitro* cytotoxic activity on human cancer cell lines. A number of derivatives have shown better cytotoxicity than betulinic acid. The synthesis, and cytotoxic activity of these derivatives will be presented.

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O-15

PHARMACEUTICAL STANDARDIZATION OF KAPARDIKA BHASMA

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Bhasma is a unique dosage form of Ayurveda, which is prepared after very individualized calcination / incineration of metal and minerals including same substances in calcium compound.Kapardika Bhasma (marine shell) is wiedly used in Ayurvedic therapeutics to treat elements of various systems specifically gastrointestinal tract (GIT) disorders. Pharmaceutical standardization of Kapardika Bhasma has been done in order to established temperature range and duration for production of Kapardika Bhasma.

To establish standards for maintaining the quality of Kapardika Bhasma comparative analytical study of genuine laboratory sample and three market samples according to Ayurveda such as organoleptic characters and other physical and chemical parameters have been performed. As well as analytical parameters such as Ash value, Acid insoluble Ash, Calcium estimation, invitro antacid activity, trace elements, durg toxicity study, UV spectrophotometric analysis, Nephelometry, Turbidimetry and Powder crystallography study have also been done.On the basis of pharmaceutical and analytical study, it can be observed that Kapardika Bhasma may be

prepared in this temperature range having above quoted analytical value.Details of the observations of the present study will be given in the full paper at the time of scientific session.

O-16 DASHAN SAMSKAR CHURNA – From Raw Materials To Finished Products

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A widely used Ayurvedic preparation DASHAN – SAMSKAR CHURNA has been prepared using various authentic raw drugs. For individual raw material powder microscopy and various pharmacognostical tests have been performed. Each drug (powder) has been evaluated for their physicochemical characteristics and phytochemical composition by implementing various analytical parameters such as ash value, acid insoluble ash, extractive values (water, alcohol), tannin and calcium estimation for specific drugs.

Later on a detailed comparative study of genuine laboratory sample with two market samples have been done complying the same physicochemical and phytochemical parameters. Along with these GC-MS, UV-spectrophotometric analysis & TLC patterns have been developed for individual drugs as well as the finished products and are reported here to assist in regulatory analysis and surveillance of indigenous medicines. A spectrum of parameters necessary to establish identity, strength and purity of market samples have also been proposed.

An additional effort for more acceptability of the formulation is done by designing formulae for dental paste of the same. Antimicrobial and bactericidal tests of the paste have been performed.

Detailed laboratory investigations of the study will be presented in the full paper at the time of scientific session.

O-17 Novel activity of certain bioactive medicinal plant extracts against multiple drug resistant bacteria

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Emergence and dissemination of multidrug resistant bacteria (MDRB) all over the world has triggered immense interest in the new drugs or preparations from the natural sources including plants to combat infectious diseases. Problematic groups of MDRB include methicillin resistant *Staphylococcus aureus* (MRSA), Vancomycin resistance enterococci (VRE), β-lactamases producing bacteria including extended and more extended spectrum beta lactamases (ESβL) and multi drug resistance encoding R-plasmids in Gram-negative bacteria (*E. coli, Salmonella, Klebsiella* and *Shigella* spp.) and *Mycobacterium tuberculosis*.

In the present study, we report here the effect of alcoholic extracts of four plants namely *Acorus calamus* (Rhizome), *Hemidesmus indicus* (Stem) , *Holarrhena antidysenterica* (Bark) and *Plumbago zeylanica* (Root) on selected isolates of MDR bacteria, R-plasmid conjugation frequency and plasmid curing property.

Above plant extracts demonstrated broad-spectrum activity against isolates of MRSA, ESβL producing enteric bacteria. R-plasmid transfer from *E. coli* Rp_4 and EC-38 to recipient *E. coli* K-12 strain, conjugation experiments was conducted in the presence and absence of plant extracts. Significant decrease in conjugation frequency of Rp4 and EC-38 plasmids in recipient *E. coli* K-12 strain was observed by norfloxacin, ciprofloxacin and crude extract of *Acorus calamus, H. indicus* and *P. zeylanica* at sub MIC concentrations. Similarly Rp4 plasmid was eliminated by acridine orange and pefloxacin from 33.0% to70% of the treated host bacterial cells. Plasmid curing ability could be demonstrated by the extract of *H. indicus* (25%), *H. antidysenterica* (15%) and *P. zeylanica* (32%). Such curing ability of crude extracts at sub-MIC concentration indicated their possible interference with plasmid maintenance property and requires further in-depth investigation to identify antibacterial and anti-plasmid active phytocompounds.

O-18 Enhanced Antioxidant Activity of Hesperetin – Phospholipid Complex: A Value Added Formulation Approach

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Hesperetin, a naturally occurring flavanone, is known to possess varieties of biological activities. Due to its rapid elimination from body, hesperetin needs frequent administration to maintain effective plasma concentration. The aim of present study was to evaluate the therapeutic potential of hesperetin - phospholipid complex in oxidative stress condition so as to compare the effect to that of free hesperetin. Hesperetin - phospholipid complex was prepared and assessed for antioxidant activity in carbon tetrachloride intoxicated rats at a dose level of 100 mg/kg, p.o. Liver function tests were studied by assessing serum glutamate oxaloacetate transaminase (SGOT), serum glutamate pyruvate transaminate (SGPT), serum alkaline phosphatase (SALP) and total bilirubin. Marker enzymes of liver namely glutathione peroxidase (GPX), superoxide dismutase (SOD), catalase (CAT) and thiobarbituric acid reactive substances (TBARS) were measured to evaluate the antioxidant potential at the same dose level. Plasma concentration of hesperetin also measured. The results of this study show that hesperetin – phospholipid complex enhanced the antioxidant activity of the biomolecule and protected the liver significantly ($P < 0.05$ and < 0.01) for a longer period of time as compared to free hesperetin at the same dose level. It suggests that phospholipid complex of hesperetin produced better antioxidant activity than free drug and the effect persisted for a longer period of time, which may be helpful in reducing the early elimination of the molecule from the system.

KEYWORDS. Hesperetin - phospholipid complex, oxidative stress, antioxidant, free radicals, sustained release.

POSTER

PO-1 : QSAR studies of COX-2 inhibitors of commercial interest

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Quantitative structure activity relationship (QSAR), binding studies and drug likeliness property estimation on selective COX-2 inhibitors of commercial interest (drugs in market and some on clinical trials) was preformed. Molecular Mechanics (MM+) in conjugation with Molecular Dynamics (PM3) techniques was utilized for determining the minimum energy conformation of the molecules. The COX-2 inhibitory activity (pIC_{50}= -logIC_{50}) of these twelve compounds was correlated with nineteen descriptors including steric, electronic and constitutional parameters. pIC_{50} activity showed highest positive correlation with both volume and HOMO (Highest occupied molecular orbital). A multiple linear regression model was developed to describe the pIC_{50} with these two descriptors as the independent variables (R^2 of the model = 0.82). The predictive ability of the QSAR equation is estimated to be q^2= 0.66, which is satisfactory to utilize it to design newer templates or modification of earlier existing templates. The inhibitory activity increased with decrease in binding energy (or interaction energy) between the commercial compounds with COX-2 enzyme (correlation coefficient = -0.65). Drug-likeliness properties such as logBB (measure of brain permeability of drugs), log P (octonol-water partition), P_{eff} (effective permeability through intestine) and HBD (number of hydrogen bond donors) relate the biological activity, absorption, side effects and the interaction energy. Calculated values showed that they are in the acceptable range. Cluster analysis based on dendrogram (relative distance between inhibitory concentrations) showed about four different clusters in which Nimuselide was separate from other compounds.

P-2 STUDIES ON CHEMICAL SYNTHESIS OF PEPTIDOMIMETICS: PROTECTED *B*-AMINO CARBAMATE MOIETIES INTO PEPTIDES

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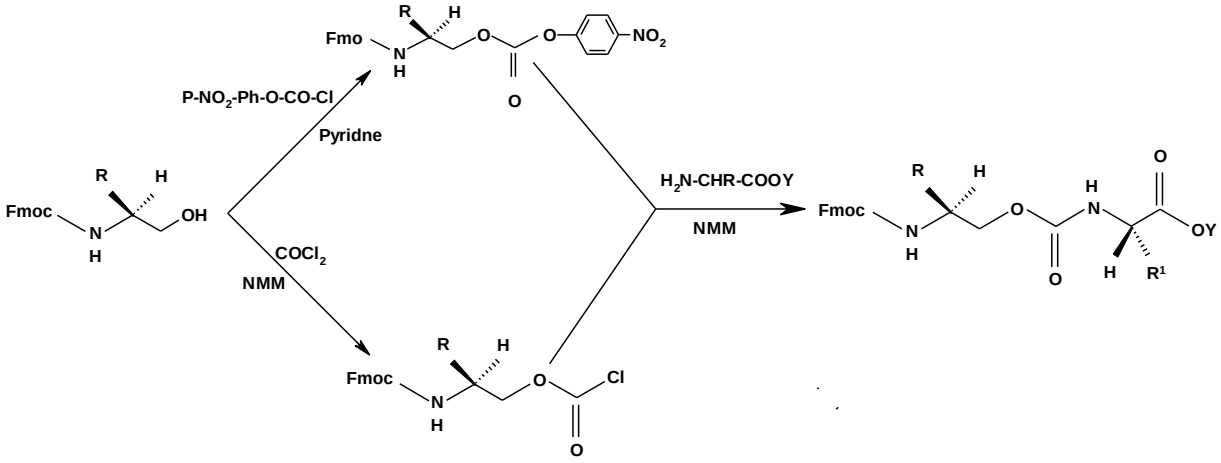
Peptides are short, sequence and length-specific oligomers composed of amino acids. Unfortunately, peptides themselves are inferior as drug candidates because of their low oral bioavailability, potential immunogenicity and poor metabolic stability *in vivo*. A recent effort to ameliorate disadvantageous peptide characteristics, and thus generate viable modifications of the native peptide backbone to generate peptidomimetic oligomers is gaining significance. The 'unnatural biopolymers' of the type oligopeptide carbamates consists chiral amino carbonate monomers linked via a carbamate backbone. Such peptidomimetics are often protease resistant, and may have reduced immunogenicity and improved bioavailability the properties of which may modify their pharmacological and folding properties relative to peptide analogues.

In the present paper the solution phase synthesis of monomeric building blocks N^{α}-Fmoc-β-amino alkoxy carbonyl chlorides (Fmoc-NH-CHR-CH_2-O-CO-Cl) and N^{α}-Fmoc- β -amino alkoxy carbonates (Fmoc-NH-CHR-CH_2-O-CO-O-C_6H_5) as well as synthesis of oligocarbamates and oligocarbonates is delineated.



P-3

Biopharmaceutics Classification System : A Scientific and Regulatory Tool in Drug Development Process

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Several newer concepts and technologies have been developed during the recent past in the science of biopharmaceutics. The Biopharmaceutics Classification System (BCS) is one such new concept that allows estimation of contributions of three major factors - dissolution, solubility and intestinal permeability for controlling rate and extent of drug absorption. BCS classifies drug substances into four groups according to their solubility and permeability properties. According to this class boundary, a drug substance is considered highly soluble when the highest dose strength is soluble in ≤ 250 ml of water over a pH range of 1 to 7.5 and a drug substance is considered highly permeable when the extent of absorption in humans is determined to be ≥ 90 % of an administered dose, based on mass balance or in comparison to an intravenous reference dose. Class I consists of drugs (Propranolol, Metoprolol, Diltiazem) having high solubility and high permeability exhibiting very rapid dissolution and bioavailbility. Class II exhibits drugs (Ketoconazole, Nifedipine, Mefenemic acid) having low solubility and high permeability. Class III drugs (Acyclovir, Captopril, Alendronate) show high solubility and low permeability whereas Class IV drugs (Tobramycin, Furosemide, Cefuroxime) exhibits low solubility and low permeability which may be the cause of poor and variable bioavailability. BCS also plays a very significant role for the formulation pharmacist in the task of developing a new dissolution method during early investigational stages of formulation design and optimization. Furthermore, BCS based biowaiver can be requested by the sponsor during ANDAs, INDs/NDAs or for significant post approval changes. The BCS enables pharma manufacturers to reduce the cost of approving scale-up and post approval changes (SUPAC) to certain oral drug products.

P-4

Potential of Biostatistics in Pharmaceutical Field

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Statistical techniques have been widely used in many diverse areas of scientific investigations. The topics which find particular application to pharmaceutical research include estimation, decision making and testing of hypotheses. Factorials designs are used in experiments/research where the effects of different factors or conditions on experimental results are to be elucidated. Moreover, factorial designs are the designs of choice for simultaneous determination of the effects of several factors and their interactions. In recent years, factorial designs including modified factorials and simplex lattice designs have been successfully applied to pharmaceutical formulation optimization to attain an acceptable performance of all relevant attributes and to prepare and evaluate the predicted optimal formulations. Biostatistics can be successfully used to analyze and validate data from the experimental designs. Analysis of variance (ANOVA) is the most powerful tool to compare two or more group means. Well-designed experiments are usually optimal with respect to meeting study objectives. ANOVA includes very simple statistical designs such as t-test and one-way ANOVA or other complex designs viz. Tukey's multiple range test, two way ANOVA, Scheffe's method, Dunnett's test as well as some non-parametric tests such as Kruskal-Wallis test, Sign test, Friedman test and Wilcoxon signed rank test that are widely used for the comparison of two treatments in a paired design. When ANOVA is violated, then non-parametric confidence interval for cross-over studies are used. Another widely used concept in estimation and hypothesis testing in the pharmaceutical field is the confidence interval which plays an important role in the evaluation of drugs and drug products as the statement statistical significance is one of supporting data for drug efficacy to the FDA and other regulatory authorities.

P -5 QSAR studies of microtubule stabilizing agents

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Microtubules, major structural components in cells, are the target of a large and diverse group of anticancer drugs. Their inefficacy on certain resistant cells and toxic side effects have led to search of new drugs. In this paper a QSAR model on antitumor drugs, those that stabilize microtubule, is discussed.

IC_{50} or EC_{50} activity data of compounds belonging to the family of microtubule stabilizing agents were collected from the literature. These compounds showed activity towards five cancer cell lines namely, parental ovarian cell line (1A9), two of its mutants that are taxol resistant (1A9PTX10 and 1A9PTX22), drug sensitive human breast cancer cell line MCF-7 and its drug resistant cell line MCF7-ADR. The molecular structures were built and their minimum energy conformation was determined using both Molecular mechanics (MM+) and Semiempirical Quantum mechanics (PM3) methods. A set of 14 molecular descriptors was calculated for each compound. Linear regression models and neural network models were developed for the five data sets individually with the highly correlated descriptors.it was found that the molecular descriptor lumo (lowest unoccupied molecular orbital) correlated (> 0.75) well with the anticancer activity for the cell lines 1a9, 1a9ptx10 and 1a9ptx22 (ovarian cells), whereas logp exhibited good correlation (~ 0.75) with activity on the mcf-7 and mcf7-adr cells (breast cancer cells). lumo is an indication of the electronic feature of the molecule and logp is an indication of its hydrophylic-liphophylic nature. a back propagation neural network model gave good data fitting and good model predictions when compared to liner regression models.

P -6

A Facile Microwave Induced Synthesis of Heterocyclic Compound and dialdehyde from Naturally Occurring Limonoids under Solvent – Free Condition

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Paniculatin (I) (6□-acetoxyazadirone), a naturally occurring meliacin was subjected to chemical transformations under microwave irradiation to give heterocyclic compound and also dialdehyde derivative. These includes 2-methyl oxazolo [4,5-d][1,2,20,21,22,23-hexahydro] paniculatin (4), 2-methyl oxazolo [4,5-d][6□-,7□-dihydroxy- 1,2,20,21,22,23 – hexahydro] paniculatin (5) and

dialdehyde (9) derivatives of paniculatin . These reactions give excellent yields in a very short time when carried out under microwave irradiation under solvent-free condition.

P-7

Marine Sponges : Rich Sources for Bioactive Cyclic Peptides

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The marine environment is a rich source of both biological and chemical diversity that provides unique chemical compounds with the potential for industrial development as pharmaceuticals, cosmetics, nutritional supplements, molecular probes, fine chemicals and agrochemicals. To date, researchers have isolated around 7000 marine natural products, 33 percent of which are from sponges. Marine sponges are well recognized for their ability to produce a wide array of natural peptides which exhibit their bioactivities through binding to corresponding acceptor molecules (receptors or enzymes) that allow them to act as therapeutic agents. Among various sponges, sponges of order 'Lithistida' especially those belonging to 'Theonella' genera have received special attention in providing cyclic polypeptides ranging from depsipeptides to large-ring bicyclic peptides (glycopeptidolipids) with anticancer, antifungal, inhibitory activity against thrombin, trypsin, Ca^{2+}-ATPase and superoxide generation. Other interesting bioactivities associated with these cyclic congeners include antibacterial, anti-inflammatory, anthelmintic, anti-HIV and inhibitory activity against protein phosphatases 1 and 2A. Marine sponge derived cyclic peptides are characterized by unique structures with unusual amino acids such as formyl-leucine, chloroisoleucine, bromotryptophan, Adha, isoserine and heterocyclic moieties viz. imidazole and (O-methylseryl)thiazole. Although there are only a few marine-derived products currently on the market, several robust new peptides derived from the natural products are now in the clinical pipeline with more development and are currently in Phase-I and II clinical trials as anticancer agents. While the marine world offers an extremely rich resource for novel peptides, it also represents a great challenge that requires inputs from various scientific areas to bring the marine chemical diversity up to its therapeutic potential.

P-8

Combinatorial Chemistry and Its Impact on Pharmaceutical and Allied Industrie

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Drug discovery is a complex never-ending process which utilizes conventional as well as novel approaches. Among new strategies used in drug discovery process, solid and liquid phase combinatorial chemistry have emerged as powerful tools for identifying pharmacologically active compounds and optimizing the biological activity of lead compound. Instead of synthesizing single compound, the novel technology of combinatorial chemistry exploits automation and miniaturization to synthesize libraries of chemical compounds. During the last decade, there has been an explosion in the exploration and adoption of combinatorial chemistry techniques and still it continues to expand with new chemistries and represents an area of massive growth for future. Recent developments in this field include oligosaccharide-based libraries, applicability to supercritical fluid chromatography and nuclear receptors as well as emergence of microwave-assisted combinatorial chemistry. Combinatorial chemistry is now set to become a core technology for pharmaceutical, biotechnology and agrochemical industries. In combination with other technologies such as high throughput screening, robotics, advanced softwares and genetics, this field has the ability to shorten the time to market for new drugs and make drug discovery a less costly process. Solid phase combinatorial chemistry has also proven a paradigm shift for the chemistry community as it is majorly practiced currently in the synthesis of biopolymers, natural products, catalyst selection, chemical ligation and materials development. Moreover, this technique offers better drugs of significant therapeutic and commercial value, new semiconductors and an artificial nose, all with a one-thousand-fold increase in productivity. Overall, the rapidly growing methodology of combinatorial chemistry represents a broad spectrum of techniques that are increasingly becoming a standard part of the medicinal chemists' and industrial tool kit.

P-9

Marine Sponges : Rich Sources for Bioactive Cyclic Peptides

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The marine environment is a rich source of both biological and chemical diversity that provides unique chemical compounds with the potential for industrial development as pharmaceuticals, cosmetics, nutritional supplements, molecular probes, fine chemicals and agrochemicals. To date, researchers have isolated around 7000 marine natural products, 33 percent of which are from sponges. Marine sponges are well recognized for their ability to produce a wide array of natural peptides which exhibit their bioactivities through binding to corresponding acceptor molecules (receptors or enzymes) that allow them to act as therapeutic agents. Among various sponges, sponges of order 'Lithistida' especially those belonging to 'Theonella' genera have received special attention in providing cyclic polypeptides ranging from depsipeptides to large-ring bicyclic peptides (glycopeptidolipids) with anticancer, antifungal, inhibitory activity against thrombin, trypsin, Ca^{2+}-ATPase and superoxide generation. Other interesting bioactivities associated with these cyclic congeners include antibacterial, anti-inflammatory, anthelmintic, anti-HIV and inhibitory activity against protein phosphatases 1 and 2A. Marine sponge derived cyclic peptides are characterized by unique structures with unusual amino acids such as formyl-leucine, chloroisoleucine, bromotryptophan, Adha, isoserine and heterocyclic moieties viz. imidazole and (O-methylseryl)thiazole. Although there are only a few marine-derived products currently on the market, several robust new peptides derived from the natural products are now in the clinical pipeline with more development and are currently in Phase-I and II clinical trials as anticancer agents. While the marine world offers an extremely rich resource for novel peptides, it also represents a great challenge that requires inputs from various scientific areas to bring the marine chemical diversity up to its therapeutic potential.

P-10

Soft Drugs: Powerful Tool for Drug Development

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Soft drugs are biologically active, therapeutically useful synthetic compounds that are characterized by a predictable and controllable *in vivo* metabolism to inactive, nontoxic and readily excretable metabolites after achieving their therapeutic role. Soft drugs are designed to

overcome the physicochemical limitation in the delivery of a drug into a target organ. The ideal soft drug should combine stability in the target tissue with very rapid inactivation in the blood stream. A true soft drug acts locally and is devoid of systemic toxicities. In soft drug design, the goal is not to avoid metabolism but rather to control and direct it. Among various approaches for soft drug design, inactive metabolite-based soft drugs and soft analogs strategies have been the most useful and successful for designing safe and selective drugs. Soft drugs are 'ante' to prodrugs (e.g. Hetacillin, Rolitetracycline) which are usually designed as a means of abrogating pharmaceutical shortcomings of the parent drugs. Soft drugs or antedrugs (e.g. Celecoxib, Lotepredol etabonate) also differs from nonmetabolizable hard drugs (e.g. Lisinipril, Cetyl pyridinium chloride) which are designed to contain the structural characteristics necessary for pharmacological activity but in a form that is not susceptible to metabolic or chemical transformation. Now a days, the soft drug and pro-soft drug concepts are developed extensively to overcome the physical and pharmacological shortcomings of various therapeutic classes of agents especially in anti-inflammatory steroid (glucocorticoid) therapy. Furthermore, the cost, complexity, adverse drug reactions and potential risk factors causing withdrawal of drugs from market have made the approach of soft drug design unique and attractive to the scientists involved in drug design. In fact, an increased therapeutic index is the aspiration for this approach in drug designing as well as evaluation criteria.

P-11

Pro-Prodrugs: An Approach to Improve Biopharmaceutical and Pharmacokinetic Complications

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A pro-prodrug is a biologically inactive molecule which is transformed *in vivo* enzymatically and/or chemically in two steps to the active species. In many cases, it is difficult to obtain a prodrug having proper combination of adequate stability *in vitro* and high susceptibility to regenerate the parent drug *in vivo*. A promising means of solving these shortcomings involves the use of cascade latentiation or pro-prodrugs which utilizes only enzymatic conversion to prodrug that further cleave enzymatically/chemically to release the active principle. Pro-prodrugs also allow some controlled delivery of various prodrug compounds. If a prodrug shows site-

specific activation but has poor transport properties or stability problems, it can be converted to a pro-prodrug that transports better or is more stable. This is particularly seen in case of carrier type prodrugs which are required to be formulated as ophthalmic, parenteral or oral liquid preparations where conversion to active drug is chemically trigerred by a change in pH. Pro-prodrugs improve the poor oral absorption and some of them have been developed as direct inhibitor of thrombin and platelet aggregation Ximelagatran, antiherpetic agent 6-Deoxyacyclovir, platelet glycoprotein IIb/IIIa antagonist Sibrafiban, dipivalate ester of 6-Deoxyganciclovir useful for human cytomegalovirus infections and conjugates of 8-Quinolinamines which are useful as antimalarial agents. Furthermore, double ester approach can be utilized to ease the hydrolysis of simple alkyl and aryl esters of β-lactam antibiotics, in gene therapy using *E. Coli* cytosine deaminase (CD) – HSV1-thymidine kinase fusion gene (CD/TK) for treatment of different tumors. Additional efforts on new ways to approach the toxicokinetic and the clinical pharmacokinetics of prodrugs and their active counterparts are of paramount importance for pro-prodesign to become an important part for research and development of new therapeutic agents.

P-12

Effect of Sanjeevani Vati on *Salmonella Typhi*: *Invitro* studies

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Typhoid, an infectious disease caused by *Salmonella typhi*, strikes about 21 million people around the world and kills about 2,00,000 every year. Modern system of medicine has recommended a number of chemotherapeutic agents for treatment but associated with untoward side effects. Hence, there is an immense need to develop an ayurvedic approach to cure infectious disease like typhoid. Present investigation was focussed to evaluate the antimicrobial property of Sanjeevani Vati, an ayurvedic formulation containing ten herbal drugs. Subsequently, the crude drugs were processed and tablets were prepared by Compression method. Physicochemical parameters like moisture content, total ash, pH value, disintegration time and dissolution time were considered for standardization of Sanjeevani Vati. Furthermore, aqueous and methanolic extracts of Sanjeevani vati were prepared for antimicrobial evaluation against *Salmonella typhi* (MTCC NO.733) by Disc Diffusion Method. Results indicated that methanolic extract of Sanjeevani Vati significantly inhibited the growth of microorganism (Zone of

inhibition is 10-13 mm) in comparison of aqueous extract exhibited no zone of inhibition in any of the plate.

P-13

***In silico* model for identifying HERG inhibitors**

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The cause of 25% of the total drugs withdrawal can be implicated upon their risk ofcausing cardiac arrythmias and 2 to 3% of all drug prescriptions involve medications,that may unintentionally cause the long QT syndrome. Virtually all these cases can betraced to drug interaction with a particular cardiac ion channel known as HERG (humanether-a-go-go related gene). We have developed a predictive 2D-QSAR model usingvarious descriptors such as topological descriptors (Kier's shape indices), thermodynamicdescriptors (AlogP), electrotopological state indices and ADMET descriptors for 56structurally diverse HERG inhibitors. The robustness of QSAR model was characterizedby the values of the internal leave one out cross-validated r2 (q2) for the training set andexternal predictive r2 for the test set consisting of 13 molecules. The significance of thetraining set models was confirmed by statistically higher values of r2 for the original data
set as compared to r2 values for the same data set with randomly shuffled activities. The present QSAR model has a q2 and predictive r2 value of 0.78 and 0.70 respectively. All the above mentioned analysis was performed using QSAR modules available in Cerius24.10. The performance of our 2D QSAR model is comparable with an already reported CoMFA model1. QSAR model developed in this study shall aid in future screening of novel HERG inhibitors.

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P-14: Pharmacoinformatics study in the design of Selective iNOS inhibitors

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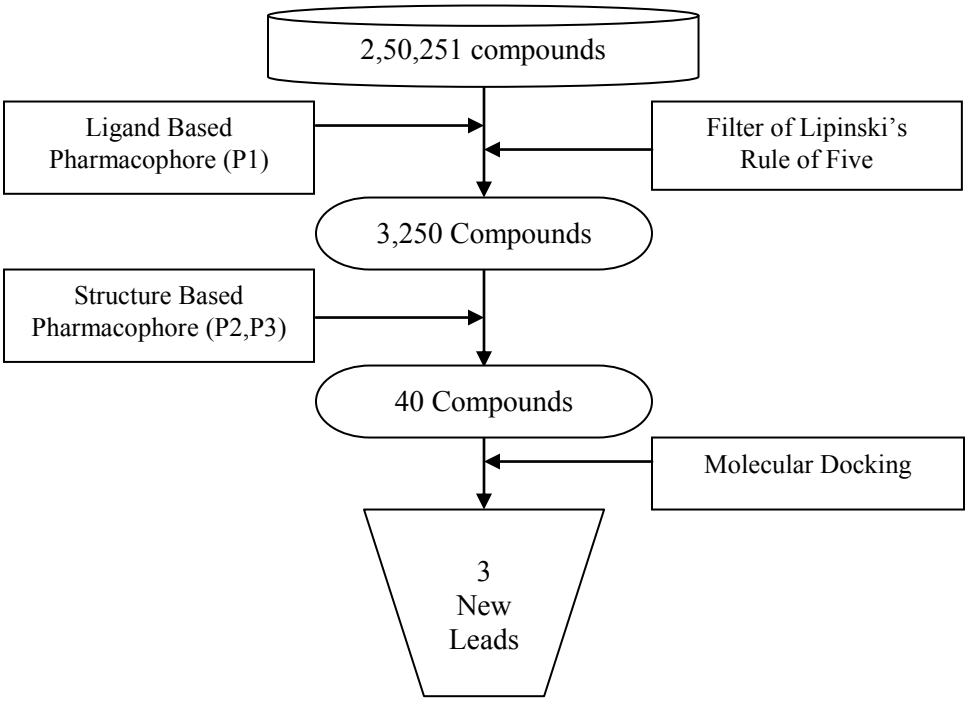
Selective inhibition of inducible Nitric Oxide Synthase is a challenging problem. Several new compounds are being suggested for selective iNOS inhibition. But the final acceptability of these systems remains to be poor. In this work we report pharmacophore mapping and molecular docking analysis to perform virtual screening of a large databank of known chemicals to identify

new leads which may potentially show selective iNOS inhibition. DISCO based pharmacophore mapping methods followed by receptor-based pharmacophore mapping methods were employed in screening the molecules from NCI databank. The primarily screened molecules were docked using FlexX based molecular docking methodology. The final selection of the compounds was made on the basis of selective binding in iNOS.



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P-15

SYNERGISM OF EUGENOL WITH ANTIBIOTICS AGAINST SELECTED BACTERIAL SPECIES

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The problem of microbial resistance is growing and the outlook for the use of antimicrobial drugs in the future is still uncertain. Therefore research is focused towards controlling the use of antibiotics as well as developing new drugs. Interactions between antimicrobial agents provide clues as to their mechanisms of action and influence the combinations chosen for therapy of infectious diseases. The synergistic effect from the association of antibiotic with plant extracts against resistant bacteria has shown to lead to new choices for the treatment of infectious diseases. Eugenol is a major component (approximately 85%) of clove oil and has been reported to possess antibacterial and antifungal activity. In the present study, it has been shown experimentally that eugenol acted in synergism (using the FIC index-fractional inhibitory concentration) when combined with antibiotics such as penicillin, ampicillin, tetracycline and erythromycin against bacteria such as *Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae* and *Bacillus subtilis*. The minimum concentration of the drug that inhibits the complete growth of the microorganism is measured by liquid dilution method using a spectrophotometer. The experiments have shown to reduce the concentration of the antibiotics used by a factor of 2 to 10. This indicates that if this strategy is followed the development of antibiotic resistance could be reduced. The mechanism of action of synergy is probably because of damage in the cell membrane or blocking the production of extracellular enzymes. The damage to the cell wall can assessed by the release of cellular components using spectrophotometric techniques.

P-16

SYNTHESIS OF SOME SUBSTITUTED PHENOTHAZINE VIA SMILES REARRANGEMENT

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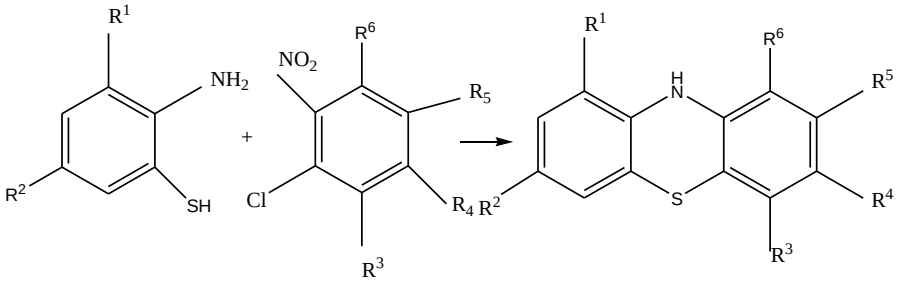
Nitrogen and sulphur containing heterocycles playa major role in the history of medicinal chemistry. Phenothiazines possess a wide spectrum of pharmacological and biological activities. They have been used as tranquilizers, anti-emetics, anthelmintics, anti-inflammatory, diuretics, antihystamins, sedatives, fungicides, bactericide, insecticide and etc. Phenothiazines have been synthesized via smiles rearrangement involving condensation of substituted 2-amino benzene-thiols with halonitrobenzenes. Halonitrobenzens containing nitro group at ortho positions to halogen yield phenothiazines in single steps as smiles rearrangement occurs in situ. Halonitrobenzens having a nitro group at ortho to halogen give substituted 2-amino-2'-nitrodiphenyl sulphides which on formulation with 90% formic acid yield substituted 2-formamido-2'-nitrodiphenyl sulphides which undergo smiles rearrangement to provide phenothiazine. The products have been elucidated by elemental analysis and spectral data.



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P-17

***In vitro* Studies on the Protection of DNA from Reactive Oxygen Species**

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Oxygen is an essential component of living organisms. The generation of reactive oxygen species (ROS) such as superoxide anion, hydrogen peroxide, hydroxyl radical and singlet oxygen are inevitable in aerobic metabolism of the body. ROS are also generated as a result of energy production from mitochondria during the electron transport chain, as part of an antimicrobial or antiviral response, as well as detoxification reactions carried out by the cytochrome P-450 system diseases. Free radicals or ROS can cause oxidation of lipids, proteins, DNA strand break, base modification and modulation of gene expression. An imbalance between ROS and antioxidants may cause mutagenic changes and adversely affect immune functions resulting in several degenerative diseases. To control the level of ROS and to protect cells under stress condition, living tissues contain several enzymes and chemicals capable in scavenging ROS. Catalase, peroxidase and phytochemicals like ascorbates, glutathione, polyphenols, tocopherols act as antioxidants. Polyphenols are present in vegetables, fruits, grains, seeds, leaves, flowers, and barks are responsible for their color. They also work as antioxidants by scavenging free radicals and play a key role to reduce the risks of cancer, cardiovascular diseases, asthma, dermatitis, aging and other related diseases.Therefore, in order to find potential sources of antioxidants some selected plants were studied for their total phenolic contents (TPC) and free radical scavenging activity (FRSA). The TPC varied from 9.8 to 134 mg/g gallic acid equivalent (GAE), antioxidant activity 16.9 to 88.6% and FRSA showed wide range in terms of IC_{50} (inhibitory concentration) from 0.1 to 21.32 mg/ml, EC_{50} (efficiency concentration) from 6.95 to 826.59 mg/mg DPPH and ARP (antiradical power) 0.12 to 29.38. The concentration dependent effect of H_2O_2 in causing DNA damage and scavenging effects of various plant extracts were studied *in vitro* to identify antioxidants suitable for the protection or repair of DNA. The control and experimental plasmid and calf thymus DNA exposed to Fenton reagent with and without antioxidants were studied by using 1% & 0.7% agarose gel electrophoresis respectively. The

plant extracts of *Allium cepa, Glycine max, Momordica charantia, Pterocarpus marsupium, Trigonella foenum-graecum* and *Cinnamomum tamala* showed significant protection of DNA damage against ROS at a concentration of ranging from 5 to 20 µg/ml. The experimental evidence showed that these plants due to their antioxidant and free radical scavenging activities may be helpful in the prevention or treatment of oxidative stress and associated diseases.

P-18:

Ellagic acid: Antioxidant, free radical scavenging activities and sources

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Polyphenols are one of the most widely distributed groups of non-nutritive phytochemicals. They range from simple phenolics to highly polymerized tannins with molecular weight greater than 30000 DA and are generally present in plants as glycoside conjugates. This form of polyphenols are most common where various sugar molecules, organic acids and lipids are linked with phenolic ring structure. In nature a major class of phenols is phenolic acids where a large number of them have been identified. They play an important role in human nutrition and are implicated with numerous biological properties including antioxidant, anti-inflammatory, anticancer and antiatherosclerotic activities. Among these phytochemicals, ellagic acid (EA), is a phenolic bislactone (flavonoid) dimeric derivative of gallic acid, occurs in some vegetables, fruits and nuts such as strawberries, raspberries, grapes, black currants and walnuts in either its free form, as EA-glycosides, or bound as ellagitannins (ETs). It has antimutagenic and anticarcinogenic properties, inhibits *in vitro* and *in vivo* genotoxicity of a variety of chemical carcinogens, including polycyclic aromatic hydrocarbons, N-nitroso compounds, aromatic amines and mycotoxins. It has also been found to cause apoptosis in cancer cells. In order to find promising natural sources of ellagic acid different parts of certain plants like fruit coat and aerial parts of *Trapa bispinosa*, fruits and leaves of *Lagestroemia speciosa*, fruits and bark of *Terminalia arjuna, T. muellaria* and *T. chebula* were studied for their total phenolic content (TPC) antioxidant (AOA) and free radical scavenging activities (FRSA), composition of phenols through HPLC and LC-MS/MS. These plants were found to have very good antioxidant activity and free radical scavenging activity. Variation of TPC in crude fractions was from 43.0 to 167.8 mg/g GAE (gallic acid equivalent), AOA 33 to 98 % and FRSA measured by DPPH in terms of inhibitory concentration (IC_{50}), efficiency concentration (EC_{50}) and antiradical power (ARP). Most of the plants showed strong FRSA as evident by their lower IC_{50} varying from 0.01 to 0.30 mg/ ml, EC_{50} from 0.67 to 13.04 mg/ mg DPPH and high ARP from 9.04 to 148.3 as compared to standard quercetin. The amounts of ellagic acid were found to vary from 0.24 mg/g to 926.0 mg/g in different parts of these plant extracts. Gallic, ferulc, caffiec, and protocatechuic acids were also present in low quantities.

P-19:Nutraceutical potential and free radical scavenging activity of some agri-wastes

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The word nutraceutical combines 'nutrition' and 'pharmaceutical' to mean that food can be used as preventive drugs. The novelty of this concept is the added knowledge through science about the disease preventing phytochemicals or phytonutrients present in foodstuffs. They play a key role in their efficacy for the prevention or treatment of diseases and have tremendous impact on the health care system. The main groups of phytochemicals with nutraceutical properties include terpenes, phytosterols, phenols and thiols. The selection is based on the protective functions, physical and chemical characteristics of the molecules. Epidemiological data as well as *in vitro* studies strongly suggest that foods containing phytochemicals with antioxidant properties have strong protective effects against major health related risks like cancer and cardiovascular diseases. Reactive oxygen species (ROS) are produced in the cells by cellular metabolism and some other exogenous environmental agents. They can cause damage to cellular bio-molecules like DNA, RNA, proteins, lipids, carbohydrates, proteins and enzymes. Oxidation of bases in DNA may adversely affect immune functions resulting in mutagenic changes and a variety of diseases. Antioxidants offer protection against several degenerative diseases. Carotenoids, ascorbates, tocopherols and polyphenols are major phytochemicals with antioxidant potential and are capable to inactivate ROS.

Crop production generates considerable amounts of agricultural residues that can be potential sources of phytochemicals of nutraceutical importance with health protective and disease preventive properties. In order to find potential sources of antioxidants, the residual parts, waste or byproducts of agri-crops were studied for total phenolic content, antioxidant, free radical scavenging and their composition. The amount of phenols varied from 15.9 to 98.7 mg/g gallic acid equivalent (GAE) and antioxidant activity (AOA) from 28.7 to 85.6%. In general AOA was found to be higher in the seed coats as compared to their total seeds. Samples with promising phenolic contents and AOA were further subjected for free radical scavenging activity (FRSA) by DPPH assay method in terms of IC_{50}, EC_{50} and anti radical power (ARP). The selected promising samples were analyzed by HPLC and LC-MS/MS for specific polyphenolic composition like gallic acid, caffeic acid, chlorogenic acid, ferulic acid and flavonoids.

P-20:
Phytochemicals and antioxidant status of *Celosia argentea*

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Celosia argentea L. Syn *C. margaritacea* L (Cockscomb or Quail grass) family Amaranthaceae is used in traditional system of medicine for sores, ulcers, and skin eruptions. Its seeds are used medicinally as an ophthalmic antiphlogistic and astringent, in cough, as eye-wash in conjunctivitis or retinal haemorrhage and flowers as astringent, haemostatic, in dysentery, enterorrhagia, metrorrhagia and epipstaxis. In Chinese system of medicine its decoction is used to stop nose bleeding, internal use in heat, swollen eyes, superficial visual obstruction and cataracts caused by wind-heat, bleeding in hemorrhoids, diarrhea, bleeding in menopause, yeast infections and various types of bleeding. Two isoflavones, 5-methoxy-6, 7-methylenedioxy-2'-hydroxyisoflavone and 2', 5-dimethoxy-6, 7-methylenedioxyisoflavone, cholesterylpalmitatie, 3,4-dihydroxylbenzaldehyde, p-hydroxylbenzoic acid, 3,4-

dihydroxybenzoic acid, and *n*-butyl-β-D-frucose glycoside were isolated from the aerial part and a series of celogentins A–J as well as moroidin were reported from the seeds.

C. argentea is a troublesome weed in flax fields, but its leaves and shoots are gathered and consumed as a vegetable. Polyphenols are non-nutritive phytochemicals with antioxidant property that contain protective and disease-preventing agents. They act as potential free radical scavengers and are capable to reduce the risks of cancer and cardiovascular diseases. In order to find its utility the leaves and flowers were studied for total phenolic contents (TPC) and antioxidant activity (AOA). The TPC in leaves and flowers varied from 7.1 to 23.4 mg/gm gallic acid equivalent (GAE) and AOA 29.2 to 77.5%.

P-21

Systems biology of Stem cells

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Stem cells continue to be of enormous scientific and clinical interest, due to the myriad therapeutic possibilities promised by their use. It has already yielded key insights into the elusive biology of human development and has great potential for increasing our understanding of devastating human diseases like diabetes, cancer, Parkinson's disease and other neurodegenerative diseases The initial excitement generated by identification of novel stem cell populations has given way to more focused effort on methods to manipulate their differentiation and self-renewal capacities. A number of genome-scale studies are now underway to catalog stem cell gene expression.

Systems biology, which treats biology as an informational science and attempts to solve fundamental problems in biology and medicine by taking more of a big picture approach.
It is the study of living organisms in terms of their underlying network structure rather than simply their individual molecular components. It's those new properties that arise when you go from the molecule to the system.

It is our basic understanding that cells interact and communicate via chemical signaling, and possibly through contact. In general, the fate of a cell is determined by its internal state, and by its perception of its own local state, and by the local state of the environment itself Using a systems approach to understand the multiplicity of choices that a stem cell makes in going down its pathway to differentiation studying stem cells in the bone marrow, hematopoietic stem cells. Applying systems approaches toward looking at issues of genetic predisposition to disease, one can move toward more of a predictive kind of medicine. And then ultimately, to take genes that predispose to disease, put them in the context of the systems in which they operate using the systems approaches, and learn how to circumvent whatever limitations they impose.

This paper reviews all that has been done and all that can be done in unraveling the mystery of stem cell systems biology.

P-22:

Saponins: Potential as Contraceptive Microbicide

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Trichomoniasis is an important anti-viral sexually transmitted disease (STD) caused by the protozoan *Trichomonas vaginalis*, and has been associated with increased HIV incidence. Classical treatment involves drugs of nitro-imidazole family. However, in addition to being toxic/associated side effects, resistance to these classical drugs is on the increase, thus emphasizing the need for development of effective novel anti-*trichomonas* agents. Saponins, a component of CDRI herbal local contraceptive CONSAP, have been established to have *in vitro* spermicidal activity at a concentration of 0.05%. In the present study, the anti-*trichomonas* activity of saponins has been demonstrated.

Using *in vitro* susceptibility assay the minimum lethal concentration of saponins for *Trichomonas vaginalis* was found to be ten-folds lower than its effective spermicidal concentration. *T. vaginalis* adheres to the cervical epithelial cells involving surface expressed adhesins (APs) and cysteine proteases (CPs). Cytoadherence is a key step in establishment of infection. Saponins inhibit by ~50% the ability of the parasites to cytoadhere to HeLa cervix cells when compared to untreated control cells. Also, substrate gel electrophoresis shows that 4h treatment with saponins inhibits the proteolytic activity of CPs. The hemolytic activity of the parasite is also highly diminished on treatment with saponins for 3h. Besides, effect of saponins at the genomic level was studied. *T. vaginalis* specific TvCP2 and AP-65 expression was significantly decreased at a concentration of 0.005% while at sub-lethal concentration (0.002%) the expression was similar to that of untreated control. Further, saponins also inhibited the host immune system evasion exhibited by *T. vaginalis* as evidenced by consistent up-regulation of IL-8 expression upto 6h. Preliminary results of scanning electron microscopy have revealed effect on membrane ruffling and reduction in phagocytic ability.

P-23

NEW THIOZOLIDINYL QUINAZOLINONES AND THEIR ANTIBACTERIAL ACTIVITY

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3-[4$^{|}$-(2-Monosubstituted phenyl-4-oxothiozolidinyl)-2-[(2$^{|}$-6$^{|}$-dichloro phenyl)amino]phenylmethyl-7-chloroquinazolin-4(3*H*)-ones **IV$_{a-j}$** have been synthesized by the cyclization with thioglycolic acid of Schiff bases **III$_{a-j}$** via 3-[4$^{|}$-aminophenyl]-2-[(2$^{|}$-6$^{|}$-dichlorophenyl)amino]phenylmethyl-7-chloro- quinazolin-4(3*H*)-one **II** of benzoxazine derivative **I**. All the final compounds were characterized by spectral (IR and ^{1}H-NMR) data and elemental analysis. Their antibacterial activity against both gram positive and gram negative bacteria as well as antifungal activity at two different concentrations have been studied.

P-24

SYNTHESIS AND ANTIMICROBIAL STUDY OF 1-ETHYL-6-HYDROXY-4-OXO-PYRIDO[2,3-h]-3[(SUBSTITUTED ARYL UREIDO)CARBONYL]- QUINOLINES

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Reduction of 8-hydroxy-5-nitroquinoline **I** with Sn/Hcl gave 8-hydroxy 4-aminoquinoline hydrochloride which was dissolved in 50 ml water and adjust pH 8 to 9 with dil. $NaHCo_3$ gave 8-hydroxy-5-amino quinoline **II**, which on condensation with diethyl ethoxymethylene malonate (EMME)gave diethyl-N-(8-hydroxy-5-quinolinyl)aminoethylelemalonate **III**. Compound **III** was thermally cyclized in presence of diphenylether gave **IV**. Ethylation of **IV** and hydrolysis of **V** gave the desired product **VI** in good yield.

Condensation of **VI** with different aryl urea gave title compounds $\mathbf{VIII_{1-12}}$. All the synthesized compounds have been characterized by means of their elemental analysis, IR & ^{1}H NMR. Their antibacterial and antifungal activities have also been evaluated. The results found were moderate to good compare to standard drugs.

P-25

NEW PYRIDOQUINOLONES AND THEIRMICROBIAL STUDIES

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An amide derivatives of pyridoquinolones are synthesized by using N^1-substituted phenyl sulfanilamides, phenyl thioureas and phenyl amines at C-3 position of 1-hydroxyethyl-6-chloro-4-oxo-pyrido[2,3-h]quinoline-3-carboxylic acid **XIII**. And we get substituted 1-hydroxyethyl-6-

chloro-4-oxo-pyrido[2,3-h]-3-{N^4-[N^1-(substituted phenyl)sulfanilamido]carbonyl} quinoline **XV_{1-12},** 1-hydroxyethyl-6-chloro-4-oxo-pyrido[2,3-h]-3-[N-(substituted phenyl thioureido) carbonyl]quinoline **XV_{13-24}** & 1-hydroxyethyl-6-chloro-4-oxo-pyrido[2,3-h]-3-[N-(substituted phenylamino) carbonyl]quinoline **XV_{25-36}**. Synthesized compounds are characterized by elemental analysis and spectral data. All the new compounds have been screened for antibacterial and antifungal activity at 100 μg/ml & 200 μg/ml concentrations using cup-plate method and we found some of the compounds exhibit appreciable activity.

P-26

Antimicrobial activity of isolated constituents and plant extract of *Piper longum Linn.*

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The diverse behavior of bacteria has always put a challenge in the treatment of infections caused by them. the cost, toxicity and the resistance of the bacteria to the present antibacterial agents has emerged the need for the discovery of new less toxic antibacterial agents. the aim of the present study was to evaluate the antibacterial activity of the isolated constituents and extracts from the roots of the plant *piper longum linn.* (family: piperaceae) the constituents were isolated by column chromatographic method. the isolated constituents, pet ether extract and aqueous extract were tested against two gram positive and six gram negative bacteria. the structures of the isolated constituents were confirmed by spectral analysis. The isolated constituents, pet ether extract were found to show the antimicrobial activity against the two gram positive and six gram negative bacteria. However the aqueous extract did not show any activity against all of the tested microorganisms. The isolated constituents were found to show better activity profile than the pet ether extract which shows that the isolated constituents are mainly responsible for the antibacterial activity.

P-27

Nutraceutical potential of underutilized parts of some plants.Avantina Sharma* and H.B. Singh ,Plant Pathology Division,National Botanical Research Institute, Lucknow-226001, **avantina_sharma@yahoo.com**

There is an old Chinese proverb, which states that medicine should be used only when food fails to heal. It underlines the importance of food as a therapeutic agent. Working on the same principle are nutraceuticals, which effectively utilise the natural potential of food for the prevention or treatment of specific disease. Carotenoids, phenols, vitamins C and E are some phytochemicals with antioxidant properties. Antioxidants are known to scavenge the free radicals and are helpful in protection against cancer and other degenerative diseases. Carotenoids are sources of pro-vitamin A and also possess anti-oxidant activity and are mainly composed of lutein, zeaxanthin, lycopene, cryptoxanthin, alpha and beta-carotene. Carotenoids with provitamin A activity are generally considered as safe because they are not associated with specific adverse health effects. Phytoesterogens, carotenoids, lutein, lycopene and tocopherols have therapeutic potential and are being used as nutraceuticals.

Taking a queue from "Best out of waste", the under or un-utilised parts of some plants were investigated to explore their nutraceutical potential. The leaves of pigeon pea (*Cajanus cajan*), drumstick (*Moringa oleifera*), sugar cane (*Saccharum officinarum*), cauliflower (*Brassica oleracea*), Jatropha (*Jatropha curcas*), kamrakh (*Averrhoa carambola*), curry leaves (*Murraya koenigii*) and betel (*Piper betle*) were investigated for total carotenoids, antioxidant (AOA) and free radical scavenging activities. The amount of carotenoids varied from 0.41 to 5.3 mg/100 g and AOA ranged from 35.6 to 52.3%. Its highest quantity was found in pigeon pea followed by cauliflower leaves (5.2 mg/100g). The studies are of significant importance to identify the suitable source(s) of carotenoids with promising potential as antioxidant and health protective benefits.

P-28

Natural compound from Boswellia serrata exhibits potential anti-inflammatory effect-An in vitro target based study

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Plants have formed the basis for traditional medicinal systems for thousands of years. Today approximately 80 percent of the world's population relies on traditional plant-based medicines for primary health care. The synergistic components found in botanical mixtures represent a largely untapped source of new pharmaceutical products with novel and multiple mechanisms of action. Pharmaceutical industry has heavily relied and researched on traditionally used natural products to increase their lead molecule database, for use as a template in the development of new drugs. This along with the simultaneous improvement in sensitivity of chemical and biological screening techniques has greatly improved prospects of finding new drugs. There are many reports that traditional medicinal herbs extract enhances various types of immune response. Diseases such as rheumatoid arthritis and Crohn's disease are characterized by chronic inflammation leading to destruction of normal tissue integrity. Mediators released during inflammatory diseases activate intracellular signaling cascades regulated by kinase and phosphatase enzymes. The mitogen- activated protein kinases (MAPKs) are part of such signaling cascades at which diverse extracellular stimuli converge to initiate inflammatory cellular responses.

The objective of this study is based on the potential intervention between the effective traditional medicine and the concept-based approach of modern sciences, with the interplay of chemistry and biology. In this context, the anti-inflammatory potential of the plant *Boswellia serrata* was studied on human PBMCs and mouse macrophages to study its effect on potent mediators on inflammation such as proinflammatory cytokines (**TNF, IL-1, IFN and IL-12**), pro-inflammatory mediators (COX**-2, Nitric oxide, 5-LO**) and the active lead was isolated and structural characterization performed. The effect of the crude extract and the lead molecule were studied on **MAP kinases** which play a major role in the regulation of a variety of inflammatory mediators to understand the mechanism of action. This study will bridge this gap by giving us useful leads and insights on various signaling aspects of inflammatory disease and the use of traditional medicinal plants for inflammatory disorders. The purified active lead may thus:

Serve as the source of a drug that is extracted and purified from the plant.Serve as the starting aterial for the synthesis of other drugs. Serve as the model of the synthesis of novel new drugs. Research efforts could thus be directed for a number of diseases for which suitable drugs are not available in the modern system of medicine and where herbal drugs have a possibility of offering new drugs.

P-29

Insights Into Protection Of Test Data

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With the rapid advances made by India in various fields, the Protection of Test Data has gained momentum especially when India has a rich technological research base. A basic element of data protection is the obligation imposed on third parties not to disclose the data. It differs from patenting and both are distinct forms of protection, independent of the each other. The clinical test data is not protected by the way of patent. According to Article 1.2 of the TRIPS Agreement, the protection of test data is a category of "intellectual property" and its protection is provided under Article 39.3, which should be read in the light of Article 39.1 of the TRIPS Agreement and Article *10bis* of the Paris Convention.

Nature of protection:

- No protection of the data.
- Article 39.3 prohibits only unfair commercial use.
- Mandates protection only when the process of obtaining the data involves "a considerable effort".

Issues of concern:

- No proper definition of data.
- Undermines the right to information.
- Non-disclosure, at times, facilitates the circulation and use of sub-standard drugs.
- Unnecessarily adds burden on the D.C.G.Is.

Recommended strategies:

- Power of D.C.G.Is. to demand undisclosed information for drug approval from the manufacturer/importer.
- Limit the data requirement to new drugs not introduced elsewhere.
- Obligation to declare the status and nature of information that needs protection.

In sum, the above said regulations should be enacted in a manner that encourages legitimate competition and facilitates access to drugs, while respecting the interests of the originators of data in accordance with the standards of protection established by the TRIPS Agreement.

P-30
HEALING POTENTIAL OF *CELOSIA ARGENTEA* FOR DERMAL WOUNDS

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Wounds are physical injuries that result in an opening or breaking of the skin. Proper healing of wounds is essential for the restoration of disrupted anatomical continuity and disturbed functional status of the skin. *Celosia argentea* L. (Amaranthaceae) is used in traditional medicine for sores, ulcers, and skin eruptions. Wound healing potential of ethanolic extract of aerial part of *C. argentea* for treatment of dermal wounds in rats was studied on excision and incision wounds models. Various parameters of incision wound viz. epithelization period, scar area, tensile strength and hydroxyproline measurements along with wound concentration were used to evaluate the effect of *C. argentea* on wound healing. The result showed that *C. argentea* accelerates the wound healing process by decreasing the surface area of the wound, epithelization period along with increasing the tensile strength and hydroxyproline content compared to the control group and comparable to Nitrofurazone group.

Wound healing involves different phases as contraction, epithelization, granulation, colangenation, etc. Aerial parts of *C. argentea* have been found to contain phenolic acid which works as antioxidant. Since the role of free radicals and antioxidants in wound healing are very clearly defined, wound healing potential of *C. argentea* may be partly due to the potential antioxidant activity of the plant.

Key words: *Celosia argentea*, wound healing activity.

P-31
1,3,4-Oxadiazoles: Synthesis And Biological Activities

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1,3,4-Oxadiazole find a unique place in the medicinal chemistry. This moiety has been found to have some remarkable biological activities such as anti-inflammatory, analgesic, antimicrobial, antitumor, anticonvulsant etc. We had synthesized a number of 1,3,4-oxadiazoles and tested them for their anti-inflammatory activity in our lab, the results were encouraging[1]. With this point in mind we have synthesized some newer 1,3,4-oxadiazole derivatives as non-steroidal non-acidic anti-inflammatory agents with lesser ulcerogenic effect.

2-Substituted aryl-5-(2,4,6-trichlorophenoxymethyl)-1,3,4-oxadiazole (IIIa-f) was synthesized by refluxing 2,4,6-Trichlorophenoxyacetic acid hydrazide (II) with aromatic acid/arylalkonic acid in phosphorous oxychloride. Compound (II) was prepared by the by two-step process from 2,4,6-trichlorophenol (I).Fig-1.

The structure of synthesized compounds was assigned on the basis of elemental analysis and spectral data (IR, ^{1}HNMR and Mass). Anti-inflammatory activity was evaluated as described by Winter *et al* (1962), the ulcerogenic effect was determined by the method of Cioli *et al* (1979) and lipid peroxidation activity was performed by Ohkawa *et al* (1979) in Wistar rats.

Compound IIId and IIIf showed the maximum anti-inflammatory activity. Tested compounds showed a significant reduction in ulcerogenic property with the severity index ranging from 0.417 to 0.667, where as the standard drug Ibuprophen showed severity index of 2.00. All the synthesized compounds with less ulcerogenic property also showed a reduced lipid peroxidation, suggesting that the tested compounds have inhibited induction of gastric lesions which might be the result of inhibition of lipid peroxidation in the gastric mucosa.

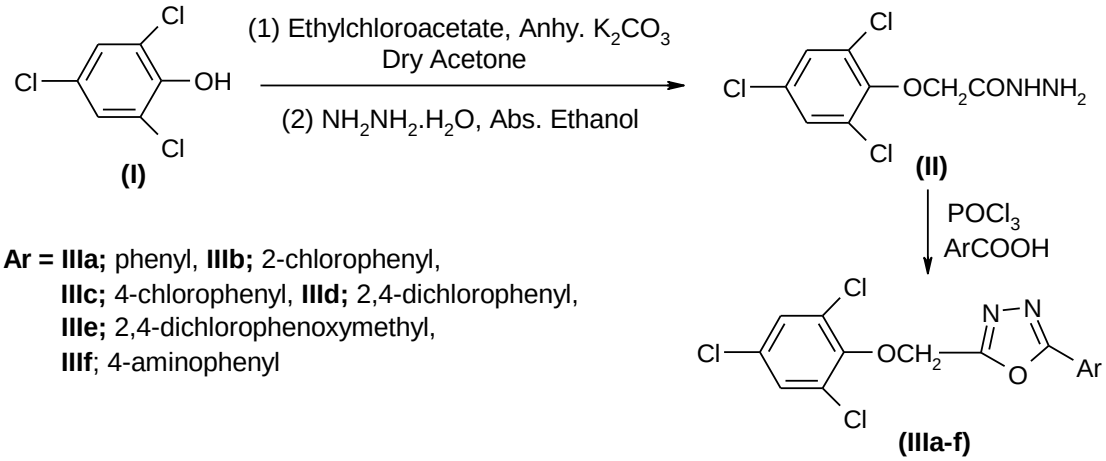

Fig-1

[1]M. Amir and S. Kumar, synthesis of some new 2-(2-fluoro-4-biphenylyl)propionic acid derivatives as potential anti-inflammatory agents, Pharmazie, 60 (2005) 175-180.

P-32

HEALING POTENTIAL OF *CELOSIA ARGENTEA* FOR DERMAL WOUNDS

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Wounds are physical injuries that result in an opening or breaking of the skin. Proper healing of wounds is essential for the restoration of disrupted anatomical continuity and disturbed functional status of the skin. *Celosia argentea* L. (Amaranthaceae) is used in traditional medicine for sores, ulcers, and skin eruptions. Wound healing potential of ethanolic extract of aerial part of *C. argentea* for treatment of dermal wounds in rats was studied on excision and incision wounds models. Various parameters of incision wound viz. epithelization period, scar area, tensile strength and hydroxyproline measurements along with wound concentration were used to evaluate the effect of *C. argentea* on wound healing. The result showed that *C. argentea* accelerates the wound healing process by decreasing the surface area of the wound, epithelization period along with increasing the tensile strength and hydroxyproline content compared to the control group and comparable to Nitrofurazone group.

Wound healing involves different phases as contraction, epithelization, granulation, colangenation, etc. Aerial parts of *C. argentea* have been found to contain phenolic acid which works as antioxidant. Since the role of free radicals and antioxidants in wound healing are very clearly defined, wound healing potential of *C. argentea* may be partly due to the potential antioxidant activity of the plant.

Key words: *Celosia argentea*, wound healing activity.

P-33

Synthesis and Antidepressant Activity of Some Thiosemicarbazones of Acetophenones

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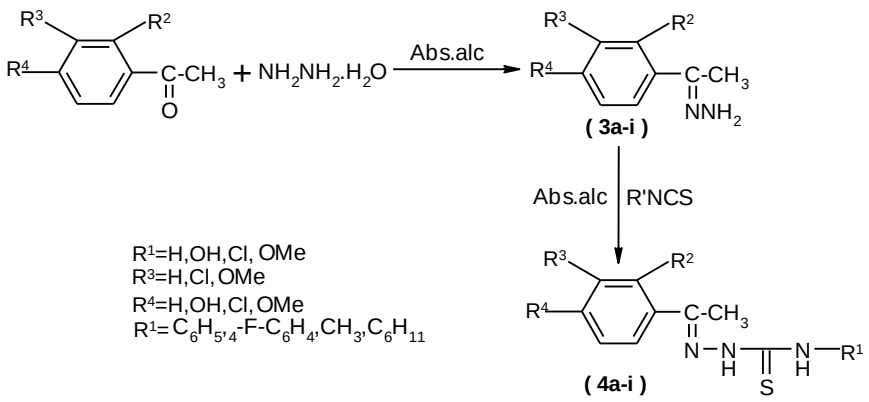
Medicinal Chemistry is the discipline concerned with the determining the influence of chemical structure on biological activity. The extensive properties of sulphur atom led to the development of a large variety of compounds having sulphur atom like thiosemicarbazones. In recent years a great deal of research has been developed to the synthesis of certain thiosemicarbazones and to the investigation of their various pharmacological properties[1-3]. In view of these observations and in continuation of our research on thiosemicarbazones of pharmacological significance it was contemplated to synthesize some new thiosemicarbazones of acetophenones with a view to evaluate their possible antidepressant activity.

A series of acetophenone derivatives **(3a-i)** were synthesized by preparing their hydrazones, which were refluxed with different aryl/alkyl isothiocynates to form corresponding thiosemicarbazones **(4a-i)** shown in **Scheme1**.



Scheme 1

Structures of all the compounds were established by FTIR, ^{1}H NMR and mass spectroscopy.

All the compounds were screened for antidepressant activity by forced swimming test (FST) method[4] using fluoxetine (30 mg/kg) as standard drug. Compound **4c, 4f, 4g, 4h, 4i, 4j and 4k** showed significant results comparable to the standard drug. compound **4g** was found to be most potent but less active than the standard fluoxitine. The 4-N-aryl/alkyl thiosemicarbazones of acetophenones synthesized promised newer antidepressants.

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P-34

SYNTHESIS & BIOLOGICAL ACTIVITIES OF BUT-3-EN-4-OLIDES

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Klobb introduced the term "butenolide". Butenolides consist of α,β-unsaturated lactones, and may be regarded as furan derivatives. They are also termed as furanones, a ubiquitous chemical moiety found in many natural products. This moiety has been found to have some remarkable activities[1] such as anti-inflammatory, analgesic, antimicrobial, antitumor, anticonvulsant etc.

We had examined in our laboratories the anti-inflammatory activity of a number of 2-arylidene-4-substituted phenyl butenolides and the results obtained were encouraging [2,3]. Thus,

it would be worthwhile to synthesize a series of 2-arylidene-4-(4-chlorophenyl) but-3-en-4-olides (IIIa-f) from 3-(4-chloro-benzoyl) propionic acid (II) for their anti-inflammatory with reduced ulcerogenic adverse effect.

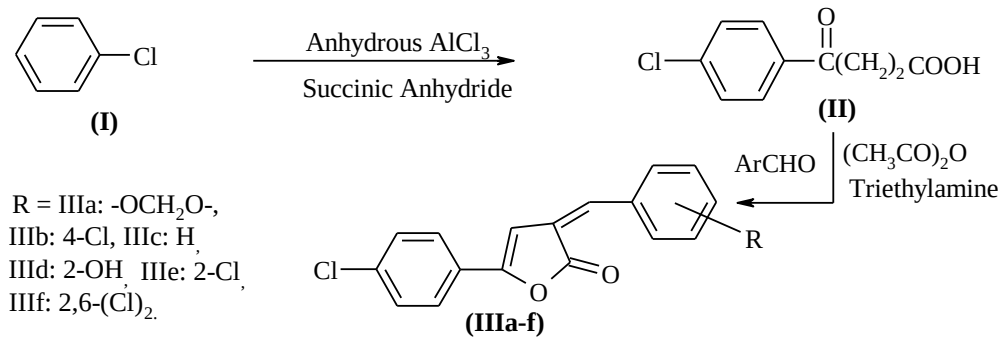

Fig-1: Scheme for synthesis

The structure of the various compounds synthesized was assigned on the basis of elemental analysis as well as IR, ^{1}H NMR and Mass spectral data. Anti-inflammatory activity was evaluated by carragenan-induced hind paw edema method as described by *Winter et al (1962)* and the ulcerogenic effect was determined by *Cioli et al* (1979) method in Wistar rats.

Anti-inflammatory activity results showed that the compound (IIIf) exhibited maximum activity (60.16%) and its activity was comparable with the standard drug indomethacin (69.23%). Marked reduction was observed in the severity index of ulcerogenic activity, which ranged from 0.422 ± 0.07 to 0.657 ± 0.11. SAR showed that substitution of one or more electron-withdrawing group in arylidene moiety enhanced the anti-inflammatory activity. Compounds having disubstitution were found to have better anti-inflammatory activity as compared to monosubstituted one.

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P-35

Synthesis and microbial studies of 2-[(3^{l}-trifluoromethylphenyl)amino]-3-[n^{1}-(substituted benzothiazolyl)carbonyl] pyridines

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2-[(3^{l}-Trifluoromethylphenyl)amino]-3-[N^{1}-(substitutedbenzothiazolyl)carbonyl] pyridine derivatives $\mathbf{V_{a-m}}$ prepared by three steps. The preparation of 2-amino substituted benzothiazole $\mathbf{II_{a-m}}$ by the cyclization of substituted aniline **I** with ammonium thiocynate in the first step, the second step was the preparation of 2-[(3^{l}-tri fluoromethylphenyl)amino]pyridine-3-carbonylchloride **IV** from 2-[(3^{l}-trifluoro- methylphenyl)amino]pyridine-3-carboxylic acid **III** and the formation of third step $\mathbf{V_{a-m}}$ from $\mathbf{II_{a-m}}$ and **IV**. The structures of new compounds have been established on the basis of elemental analysis, IR and ^{1}H-NMR spectral data. The antibacterial and antifungal activity was screened for all the synthesized compounds.

P-36

Enhanced Dose Dependent lipolytic activity of WY14643 in Dyslipidimis Diabetic hamster

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Dyslipidimia,a major risk factor for diabetes and the syndrome is directly link to altered lipid-glucose homeostasis. We have developed an appropriate model in hamster that has shown diabetes as well as dyslipidemia. Ten days of high fat feeding has significantly increased basal plasma lipids and glucose levels. Treatment with WY14643, produced a Dose dependent decrease bin plasma lipid levels.lmprove high dencity lipoprotein with significant lowering of very low density lipoproteins.Diabetic conditions were significantly improved by WYl4643with normalizationof glucose levels. Beside this, it also enhanced the lipolysis by activating the lipases for effective catabolism oflipids. WY14643 Found to reduced the rate of body weight gain and highest dose of300umol/kg WY14643 was found to reduced the diet intake significantly, during the entire course of study. These data suggests that wy14643 may correct the diabetes and dyslipidimia conditions effectively. We are using this protocol for development of drug and the model for understanding the stages involved in the metabolic dosorder.

P-37

Application of computer in Modern drug discovery Programme

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Computer aided drug design (CADD) also called computer assisted molecular design (CAMD), represent more recent applications of computers as tools in the drug design process.
CADD is a powerful tool of drug research and development.

Computer aided drug design is a specialized discipline that uses computational methods to stimulate drug-receptor interactions. CADD methods are heavily dependent on databases and their applications.

It has wide range of applications such as:

- vHTS-Virtual High-throughput screening
- Sequence analysis
- Homology modeling
- Similarity search
- Drug lead optimization
- Physicochemical modeling
- Drug bioavailability and bioactivity
- De-novo design

CADD is no longer merely a promising technique. It is a practical and realistic way of helping the medicinal chemist. It has extensive impact in the area of drug design. Computational tools have become increasingly important in the drug discovery and design processes.

Computer aided drug discovery reduces the cost and time of a new drug to many folds and also give new insights.

In this conference we would like to discuss various applications of computer in modern drug discovery programme.

P-37 A

DEVELOPMENT OF A DATABASE FOR ANTICANCER DRUGS & TARGETS

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[2]Biological Sciences Group, Birla Institute of Science and Technology (BITS),

Pilani-333031, Rajasthan, India,The aim of pharmaceutical research and development is to ensure a continuing pipeline of new chemical entities (NCEs). Failure of promising lead candidates late in drug discovery process is regarded as commercially unacceptable. Even the existing marketed drugs have problems in one form or other like stability, bioavailability, toxicity etc. Advances in drug design and new computational methods are leading to new paradigm shift towards *in silico* drug discovery research. It is well known that biological activity whether therapeutically desirable or undesirable (toxicity), mainly depend on the chemical structure of the molecule. There is huge and diverse amount of data related to different aspects of drugs (or drug like molecules) which can be utilized for new drug discovery research. The

potential of new lead compound can be predicted at very early stage for drug likeness on the basis of experimental data available. Proper management of data by developing database with user friendly Graphics User Interface is necessary to employ Pharmainformatics tools efficiently. Present work reports building a consolidated database for anticancer drugs, their appropriate targets and other relevant information collected from various resources. Database with graphical user interface has been created which includes mainly query page, containing molecule name, NSC number, CAS number, molecular formula, its structure, mechanism of action and resistance, Pharmacokinetic profile, T_{max}, $T_{1/2}$, Indications, dosage range, dosage forms available, Drug interactions, special considerations, Toxicities, chemical and biological classification, brand name, major manufacturer etc. At present more than 100 anticancer drugs which are already being marketed has been included in the database along with their nomenclature, structure, physico-chemical properties, Lipinski's parameters filter, its biological activity and other relevant experimental data. This database will be utilized for *in silico* drug discovery endeavors. Database would be regularly updated as and when new drugs discovered.

P-38

Synthesis and antileishmanial profile of some novel terpenyl pyrimidone derivatives

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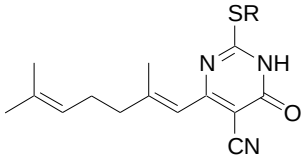
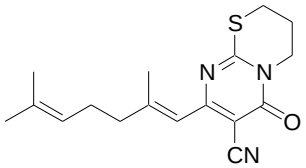
Visceral leishmaniasis (VL) or Kala-azar caused by *Leishmania donovani* is one of the major public health problems in many tropical countries of the world and about 1.5 to 2.0 million new cases arise every year. Around 90 % of total VL cases occur in India ,Nepal, Bangladesh & Sudan.[1] The control of VL remains a challenging problem because no vaccine exists and the available chemotherapeutics have serious side effects and require long-term treatment. The emergence of antimonial resistance, and rise in Leishmania-HIVco-infections necessitates the search for new antileishmanials.[1] Natural product based new leads are proving quite useful in this area and lichochalcone A, curcumin and quinoline alkaloids are showing promise as new leads. In our institute's ongoing programme on chemotherapy of leishmaniasis we have been engaged in the synthesis and bioevaluation of novel natural product based heterocycles.[2,3] In continuation of these studies we synthesized some novel pyrimidone derivatives **1** and **2** using commercially available citral.



1



2

a) R = Me

b) R = $CH_2CH{=}CH_2$

These compounds were screened for their antileishmanial activity profile in *Leishmania donovani*/hamster model at 50 mg/kg x 5 days (i.p) dose level. Some of the compounds showed moderate inhibitory activity. The results will be discussed.

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P-38A

Synthesis and antileishmanial profile of novel dipyridyl /dipyridoyl alkanes

S.Pandey[1], M.Verma[1], Ramesh[2], Nishi[2], S.N.Suryawanshi[1] and Suman Gupta[2]

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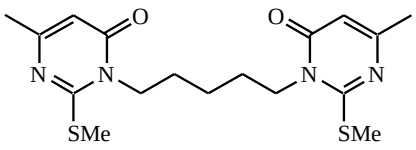
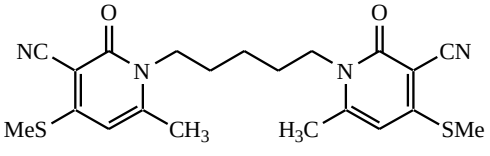
Leishmaniasis is estimated to afflict 12 million people worldwide, causing disease ranging from skin lesions in cutaneous leishmaniasis to a progressive and fatal hepatosplenomegaly in visceral leishmaniasis. The visceral form of leishmaniasis, commonly known as kala-azar is caused by the parasite *Leishmania donovani*, which affects 61 out of the 88 countries worldwide.The current chemotherapy for leishmaniasis is limited. Pentavalent antimonials have been the recommended drugs for the treatment of both Visceral (VL) and Cutaneous leishmaniasis(CL) for more than 50 years, but long courses, toxicity ,and resistance in India limit their use. New drugs have become available in recent years for the treatment of VL, including highly efficacious but expensive lipid amphotericin-B formulations, of which AmBisome is only one widely available. Oral miltefosine has recently been licensed for use in India for treatment of VL. Miltefosine is an alkylphosphocholine, initially developed as an anticancer agent that also shows selective activity against *Leishmania.* Miltefosine has undergone successful clinical trials for anthroponotic VL in Bihar state, India, with 94% cure rate, including antimony-resistant cases, and is currently in Phase IV trials in India and Nepal. However, clinical trials have identified gastrointestinal toxicity and teratogenicity in association with this drug .Therefore, the development of new antiprotozoal compounds with improved pharmacological properties is imperative.

In continuation of our studies on novel antileshmanial agents[1-3] we have successfully synthesized dipyridyl/dipyridoyl alkanes as possible antileishmanial agents as shown in figure 1. The compounds were screened for their *in-vitro* and *in-vivo* antileishmanial activity. Some of them showed encouraging activity profile. The leads generated are under investigation.





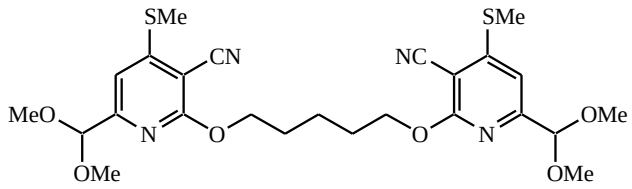


Fig. 1

References:

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P-39

LIPID LOWERING ACTIVITY OF ANTHOCEPHALUS INDICUS (KADAM)

* AK. KHANNA, * * VISHNU KUMAR, *M.M. KHAN, *RAMESH CHANDER, **K. JAW AD , *J.K. SAXENA and ***R.K. SINGH

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Anthocephalus indicus ; kadam (a.indicus) family Rubiaceae has been reported for the treatment of wounds, ulcer, pain, swelling, vomiting, oedema and cough. However no information is available regarding its hypolipidemic property. The present study is planned to investigate the hypolipidemic activity of A.indicus (root) in triton induced hypolipidemic rats.

Hypolipidemia was induced in Charles Foster rats (200-250 gm) by injecting triton wr-1339 (400mg/kg) intraperitonally and treating simultaneously with alcoholic extract of root of A indicus at a dose of 500mg/kg orally. After 18 hours, blood was withdrawn and Serum Total Cholesterol (TC), phospholipid (PL) and tryglyceride (Tg) and post heparin lipolytic activity (PHLA) were estimated by Standard Spectrophotometric methods. A marked increase in Serum levels of TC(22 fold), PL(2.7 fold), TG(2.4 fold) following inhibition of PHLA (30%) respectively were noticed as a result of triton induced hyperlipidemia in rats. However animals treated with the alcoholic extract of root A indicus showed significant lowering of lipids by decreasing TC 23%, PL 22%, TG 20% respectively. The treatment of extract also reactivated PHLA by 21 %. It is suggested that A indicus showing lipid lowering activity may be a drug of choice to fulfill the present demand for development of lipid lowering drugs.

P-40

SYNTHESIS AND BIOLOGICAL EVALUATION OF COSCINAMIDE AND SYNTHETIC ANALOGS

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Several interesting biologically active bisindole alkaloids have been reported from marine organisms over the past few decades. As part of our interest in the synthesis of biologically active marine natural products, we undertook a synthesis of coscinamides (bisindole enamide) and synthetic analogs using tryptamine to explore the biological potential.

Key Words: Conscinamide, bisindole enamide, Tryptamine

P-41
Sequence analysis, Homology modeling, Molecular Docking to identify ROR Ligands

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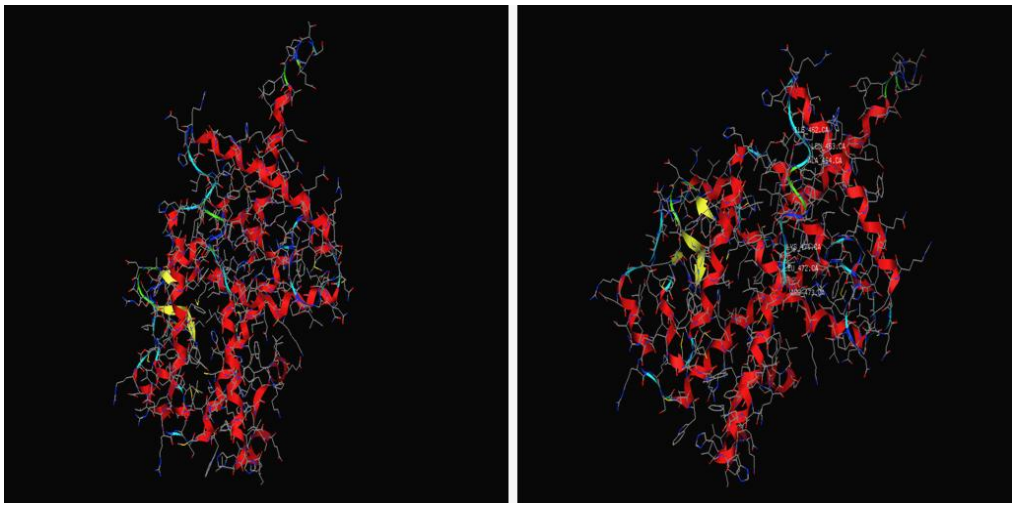
ROR is one of the nuclear hormone receptors whose ligands have not yet been identified. Moreover the crystal structure of ROR has not yet been solved till present. Pairwise sequence comparison between PPAR and ROR using NCBI protein databank showed that there is 27 % identity and 50 % similarity. Further sequence analysis indicated that the sequence identity and sequence similarities in the ligand binding domain of PPAR and ROR respectively are 30% and 53%. Since this similarity is high enough it is hypothesized that the ligands binding at PPAR may bind to ROR also. This is further supported by the fact that ROR is expressed in skeletal muscles and its expression is induced in adipocyte differentiation. Moreover, ROR maps to human chromosome 1q21-q23 which is a region of linkage to diabetes in some humans races. Homology Modeling of ROR with the help of the ROR as the template was carried out using the MOE software. Ligands acting at PPAR have been docked in the active site using the MOE software. Ligands acting at PPAR have been docked in the active site of ROR . Based on the molecular docking patterns, docking scores, partial de-novo design has been carried out to identify ligands for ROR . The results are presented in this paper.



(a) (b)

Fig. a) RORγ model obtained from homology modeling b) 3D structure of RORγ after refinement

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P-42

New CNS depressant Cardenolide from the roots of *Nerium Oleander*

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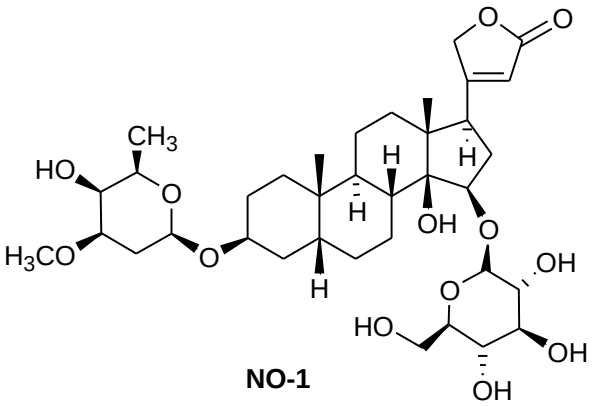
A bioassay guided fractionation of the aqueous alcoholic (95%) extract of the fresh dried roots of *Nerium oleander* showing Central Nervous System (CNS) depressant effect in swiss mice was under taken. As a result, one new cardenolide named nerioleanderoside (**NO-1)** exhibiting CNS depressant activity in mice at the dose of 50mg/kg was isolated from the n-butanolic fraction of the alcoholic extract. The structure of nerioleanderoside was elucidated as 3□-*O*-(D-diginosyl)-15□-*O*-(D-glucopyranosyl)-14□-hydroxy-card-20(22)-enolide using spectroscopic methods including ^{1}HNMR, ^{13}C DEPT NMR spectral studies and comparison of its data with similar type of compounds reported in the literature.



NO-1

3β -*O*-(D-diginosyl)-15β-*O*-(D-glucopyranosyl) -14β-hydroxy-card-20(22)-enolide

P-43

Neutrophil responses under hypertensive condition: a perception from spontaneously hypertensive rats (SHR)

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Neutrophils are forerunners in the innate immune response against foreign intrusion, endowed with several cytotoxic properties. Competent in production of nitric oxide (NO), these granulocytes profoundly influence the hemostasis of cardiovascular physiology. The present study was undertaken to evaluate modulation of NO generation and neutrophil functions in four months old male SHR.

Phagocytosis, respiratory burst, surface expression of CD 11 b and NO generation in neutrophils were assessed by flow cytometry, hydrogen peroxide (H_20_2) and peroxynitrite (ONOO-) generation by fluorimetry, Myeloperoxidase (MPO) activity was evaluated biochemically, and NO synthesis was measured as total nitrite content.

Phagocytic potential was unaffected in SHR as compared to control but an augmentation in the free radical generation capacity was evidenced by enhanced NADPH oxidase activity substantiated from the increased generation of superoxide. This correlated to increased generation of both H202 and ONOO-. MPO activity remained unaffected in resting neutrophils from SHR thereby ruling out the participation of hypochlorous acid in the amplified DCF response. We also observed a trend of increase in NO production in neutrophils from SHR which

could be a compensatory mechanism to maintain vascular tone or prevent endothelium-neutrophil association in excess under conditions of reduced NO generation by the endothelium itself. CD 11 b expression, a marker of secretory vesicle secretion, was elevated in resting as well as stimulated neutrophils following phagocytosis; implicating a more activated state of neutrophils from the hypertensive group.

The results obtained suggest that circulating neutrophils in SHR seems to be activated which might contribute to the oxidative stress during hypertension.

P-44

SSRI Antidepressants As Possible Dual-Function Spermicides

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The study investigated the spermicidal and antitrichomonas activity of SSRI antidepressants with a view to generate a new lead for development of dual-function spermicidal contraceptives, which is an urgent global need. Fluoxetine, sertraline and fluvoxamine exhibited both spermicidal and antitrichomonas activity *in vitro*, whereas paroxetine and citalopram showed only spermicidal activity. Fluoxetine had better activity profile than the other antidepressant drugs with its spermicidal and anti-trichomonas activities being comparable to the OTC contraceptive, N-9. The non-detergent nature of fluoxetine and a much superior spermicidal ED_{50} value may add considerably to its merit as a candidate for microbicidal contraceptive. Thus the antidepressants exhibiting both the spermicidal and antitrichomonas activities might provide useful lead for the development of novel, dual-function spermicidal contraceptives.

P-47

SYNTHESIS AND HYPOTENSIVE ACTIVITY OF NOVEL 1- AND 2- SUBSTITUTED AMINOALKOXY NAPHTHALENES

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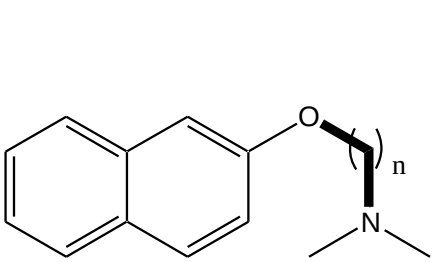
1-Substituted aminoalkoxy naphthalenes **1** and 2-substituted aminoalkoxy naphthalenes **2** were synthesized from 1- and 2- naphthols, **3** and **4** which on further conversion into corresponding naphthoxyalkanoic acids and their Mannich reaction with appropriate secondary amines and *p*-formaldehyde resulted in the formation of corresponding aminoalkoxy naphthalenes **1** and **2**. The

hypotensive activity of **1** and **2** was compared with reference compound Propranolol **5**. Some of these derivatives show better hypotensive activity when compared with Propranolol in cats.



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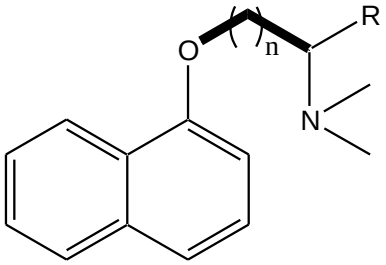

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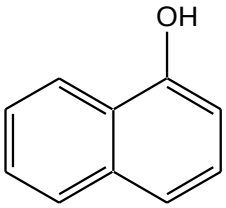

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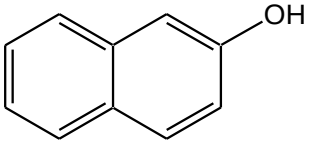

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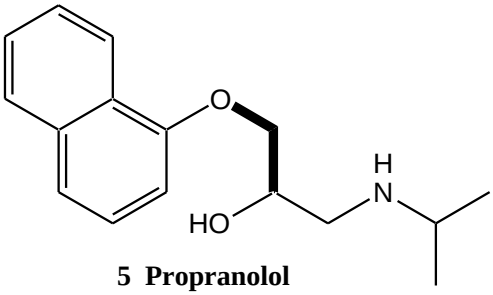

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P-48

Antioxidant and free radical scavenging activities of some agri-wastes

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Antioxidants are widely needed to prevent deterioration of various oxidisable goods, such as foods, cosmetics, pharmaceuticals and plastics etc. Reactive oxygen species (ROS) the by-product of cell metabolism are also produced in the body on exposure various environmental pollutants. They can damage to cellular bio-molecules like DNA, RNA, proteins, lipids, carbohydrates and consequently may adversely affect immune system resulting in a variety of diseases. Antioxidants play a key role to inactivate ROS and are associated with reduced risk of cardiovascular diseases and cancer. Carotenoids, ascorbates, tocopherols and polyphenols are major plant antioxidants with biological properties like anti-carcinogenic, anti-mutagenic, anti-allerginic and anti ageing etc. Their presence has been extensively reported in various parts of plants. Agricultural and industrial residues are attractive sources of natural antioxidants.

To find potential natural sources of antioxidants, the extracts of some selected agricultural residues such as total aerial parts, leaves, pod hull, seed coat, stem and roots of leguminous plants like *Arachis hypogaea, Cajanus cajan, Cicer arietinum, Glycine max, Phaseolus mungo* and *P. radiatus* were studied for their total phenolic content, antioxidant and free radical scavenging activities. The amount of total phenols in extracts of various plants varied from 2.1 (*Glycine max*, pod hull) to 59.3 mg/g gallic acid equivalent (*Cajanus cajan*, seed coat) and antioxidant activity (AOA) 12.5 to 70.1 %. Parts with high AOA were studied for their free radical scavenging activity (FRSA) in terms of IC_{50} (inhibitory concentration), EC_{50} (efficiency concentration), ARP (antiradical power) and reducing power etc. Promising plants were further assayed for their specific phenolic composition through HPLC and LC-MS/MS. The studies are of significant importance to identify the potential natural sources of phenols with promising antioxidant and free radical scavenging activities to develop nutraceuticals fortified with suitable phytochemicals.

P-49

Prevalence and antibiotic susceptibility of bacterial species causing Neonatal Septicemia in Neonatal Intensive Care Units

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Septicemia in neonates refers to the generalized bacterial infection documented by a positive blood culture in first four weeks of life and is one of the fourth leading causes of neonatal mortality in India. Prior to the antibiotic era, the mortality of septicemia was 90%, but it declined to 24-58% after antibiotics came into use. The clinical microbiology laboratory plays a significant role in the management of patients with Septicemia. Culturing a pathogenic microorganism from blood is a highly specific indicator of septicemia, and performance of antimicrobial susceptibility testing may assist in the appropriate use of antimicrobial therapy for neonates with septicemia. Furthermore, early and rapid administration of antimicrobial therapy to neonates with septicemia has been shown to reduce mortality. The study was undertaken to evaluate major bacterial isolates from neonatal septicemia cases, the association between positive blood culture reported by the Neonatal Intensive Care Units (NICU) and the antimicrobial susceptibilities of the bacterial isolates. Of the 50 episodes of septicemia characterized in the study, prematurity was found to be the major factor of neonatal septicemia. The six most common isolated bacterial species were *Staphylococcus aureus* (33%), *Escherichia coli* (19%),

coagulase-negative staphylococci (18%), *Enterococci* (6%), *Pseudomonas aeruginosa* (9%), *Morexella sp.* (5%). MIC values for most commonly used antibiotics like ciprofloxacin, ceftrioxime, ceftizidime, Netilmicin, gentamicin and tobramycin were determined against isolated bacterial strains and it was found that Netilmicin was most effective against all bacterial species isolated.

P-50

1-Aryloxy-2-substituted aminomethyltetrahydronaphthalenes: rigid analogues of fluoxetine as selective and potent appetite suppressant

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Obesity is the most common metabolic disease in developed nations[1] and effective treatment is challenging. Obesity is associated with an increased mortality rate and risk factors such as hypertension, hyperlipidemia and diabetes mellitus.[2] Prevention of obesity is extremely important though difficult. Since obesity is the storage of excess energy, increasing satiety or altering the dietary preferences for complex carbohydrates relative to fat rich food can decrease the energy intake. Agents, which reduce body weight, have been actively sought after for many decades. Most marketed antiobesity drugs are appetite suppressants.[3] The appetite suppressants or anorectics act directly on the CNS and decrease food consumption by altering central adrenergic[4] or serotonergic[5] system. Activation of serotonergic system either by direct activation of serotonergic receptor or by inhibiting serotonin reuptake (SSRIs) has proved successful in suppressing appetite. Fluoxetine[6,7], a selective serotonin reuptake inhibitor, provided an important lead to develop SSRIs. The massive use of this drug as an antidepressant and its adverse effects of appetite suppression[8, 9] and concurrent loss of body weight indicated its use for the treatment of obesity.[11] This prompted us to synthesize conformationally rigid analogues of fluoxetine that are devoid of antidepressant effect. Thus we herein report the synthesis, pharmacological evaluation and SAR studies of 1-aryloxy-2-substituted aminomethyltetrahydronaphthalene derivatives as conformationally rigid analogues of fluoxetine.

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P-51 SYNTHESIS, CHARACTERIZATION, AND THERMAL REACTIVITY OF CYCLIC/ACYCLIC ENEDIYNES

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The novel chemical framework, and potent antitumor activity of the enediyne natural products such as calicheamicin, dynemicin, esperamicin, and neocarzinostatin has fostered interest in the development of simple enediynes with low thermal cyclization temperature to the formation of cytotoxic 1,4-benzenoid diradical intermediate. of Thermal reactivity modulation of an enediyne via various approaches has been the subject of intense study since last one decade. To understand the role of electronic effect, and size of the ring on enediyne cyclization, we have synthesized cyclic/acyclic enediynes, and their characterization and thermal reactivity will be presented.

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P-52

PRODUCTION OF β-GALACTOSIDASE BY

Kluyveromyces lactis

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Key words: lactose hydrolysis, lactase, enzyme activity, and fermentation.

Lactose, the major carbohydrate component of milk, is of limited availability because of low solubility and indigestibility in many individuals. For this reason lactose is often hydrolyzed before use with the help of β-galactosidase (lactase) enzyme. Microbial hydrolysis of lactose to glucose has enough commercial potential and different strains of various microorganisms are employed for this purpose. Biocatalytic hydrolysis of lactose has been studied in relation to the

cell density with the cells of *Kluyveromyces lactis* (MTCC-117) substrate concentration, pH, buffer and trace elements. The effect of pH on enzyme activity has been studied and it has been found that the optimal pH and molarity of the phosphate buffer was 6.8 and 50 mM respectively. pH over 6.8 cause a significant decrease in enzyme activity and lactose hydrolysis. In this pH value at 0.3 molarity enzyme activity was 5.3 times less. One unit of enzyme activity (U) corresponds to the amount of enzyme that liberates a micromole of glucose per minute in reaction conditions. Addition of trace elements has also been studied. Presence of Mn^{++} ions (0.5mg/L) increases the enzyme activity.

P-53

BIOTRANSFORMATION OF BENZALDEHYDE TO PRODUCE L-PAC BY YEAST CELLS

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Key words- fermentation, acetoin activity, L-PAC, L-ephedrine, Optical
Rotation, biotransformation

L-ephedrine hydrochloride is an ingredient of pharmaceutical products used as antiasthmatics and decongestants. The plant Ephedra is major source for this compound, which is rare in occurrence currently. Alternatively L-ephedrine may be prepared from an intermediate compound, L-phenylacetyl carbinol (L-PAC). L-PAC is an optically active compound obtained by the microbial bioconversion of the substrate benzaldehyde in presence of pyruvate, the co-substrate, generated during the cell growth. Bioconversion of benzaldehyde to L-phenylacetyl carbinol (L-PAC) was studied with growing and harvested free and immobilised cells of *Saccharomyces cerevisiae* under various growth and biotransformation conditions. Production of L-PAC with high optical rotation depended strongly on the cell density and carbon sources.Biotransformation of L-PAC from benzaldehyde was carried out in medium containing glucose, sucrose, molasses and jaggery separately. Yield of L-PAC (as observed by the optical rotation) varied substantially with these substrates. Different sucrose concentrations (0.2, 0.3, 0.4 M) were tried for benzaldehyde bioconversion; with 0.3 M of sucrose optical rotation of L-PAC

was found to be–112.5˚.However, with jaggery L-PAC of -125^0C rotation was observed. The paper presents the scope for increasing the yield of L-PAC.

P-53A

Screening, isolation and taxonomic characterization of antibiotic producing microorganism

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Department of fermentation Technology,Central Drug Research Institute,Lucknow-226001, INDIA

During extensive programme of screening and isolation of biologically active organisms from nature several microbial strains were isolated that showed broad spectrum antimicrobial activity. One of the very active isolates was studied in detailed for characterization and purification, isolation and chemical characterization of the active compound produced during fermentation. Producer organism was identified as *Streptomyces rochei* at Micribial Type Culture Collection (MTCC), Chandigarh, India. The strain was cultivated in a production medium, active compound was extracted from the fermentation broth, purified by HPLC and chemically characterized by UV, IR, NMR and Mass spectra. The active compound was turned out to be borrelidin. Borrelidin is angiogenesis inhibitor, shows strong antitumor activity and is being illustrated as strong anticancer lead compound. It is reported to show antimalarial activity also. Borrelidin is produced by *S. rochei*, *S. parvulus*, other *Streptomyces* spp. and complete chemical synthesis of this compound is reported.

We have attempted to optimize the yield of borrelidin by growing the producer organism under different nutritional conditions. Supplementation of various organic and inorganic nitrogen and carbon sources in the growth medium has ushered significant influence on the production of borrelidin *S. rochei* is reported to produce other antibacterial and antifungal antibiotics also. We have studied antimicrobial activity profile of the crude extract of fermentation broth of our strain. Activity of the broth crude extract against *Candida albicans*, *Staphylococcus epidermis, Enterobacter cloaceae, Pseudomonas aeruginosa, Streptococcus faecalis, Streptococcus pneumoniae* and *Clostridium perfringens* are worth mentioning. In this paper we are reporting the isolation, characterization and optimum fermentation conditions for *S. rochei* cultivation for borrelidin production.

P-54

Production of antimicrobial compounds by the natural isolate of *Streptomyces* sp.

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An antibiotic producing microbial strain was isolated from the soil samples collected from the hilly areas. Taxonomic and biochemical characterization of the strains revealed that the isolated strain belonged to the genus *Streptomyces*. Antibacterial and antifungal activity profile of the extracted crude was studied against various multi drug resistant strains such as *S.typhii*, *B.subtilis, S.cerevasiae, C.terreus, C.albicans, B.nivea and T.rubrum.* Nutritional requirement of the strain was also studied. The experiments were carried out in shake flasks level under the controlled experimental conditions. The fermentation medium consisted of glycerol and soybean meal as the main carbon and nitrogen source respectively.

Partial purification of the active compound was done by sephadex LH-20 and HPLC. During purification it was observed that the crude contains two major active compounds. The paper presented here describes isolation, characterization and nutritional requirements of the antibiotic producing soil isolate of *Streptomyces* sp. Simultaneously the partial purification of the compound is also discussed.

Key words : ***Antibiotic, fermentation,*** Streptomyces

P-55

Title –Synthesis and Pharmacological Evaluation of SYP-17, a Selective Adenosine A_{2A} Antagonist, as Anit-Parkinsion Agent.

Swapnil Gulabrao Yerande*, Hardik Thakar, Gajanan Inamdar, Rajan S. Giri Kamala K Vasu, and V. Sudarsanam

Parkinson's disease (PD) is a neurodegenerative disease of the substantia nigra. Damage to neurons in the substantia nigra causes a dopamine deficiency in the striatum, resulting in disturbed motor functioning. The current management of PD is based on the dopaminergic therapy aimed at reversing the effects of striatal dopamine depletion induced by the destruction of nigrostriatal pathways. However, the introduction of dopaminergic drugs is associated with acute side effects, such as hypotension, and series of long term related complications that increases in severity with disease progression. These include loss of drug efficacy, the on set of dyskinesia, and the occurrence of psychosis.

There is growing evidence suggesting that the A_{2A} receptor is a potential target for the novel non dopaminergic antiparkinsionian therapy.

In the present study we have synthesized thiazole derivative to be adensoine antagonist. All the synthesised compounds were characterized by IR, NMR,MASS.

The best compound of the series SYP-17, an adenosine A_{2A} antagonist, ((Ki-0.103 μM) was tested in the e N- Methyl-4- Phenyl-Tetrahydro Pyridine (MPTP) model of Parkinson Disease.

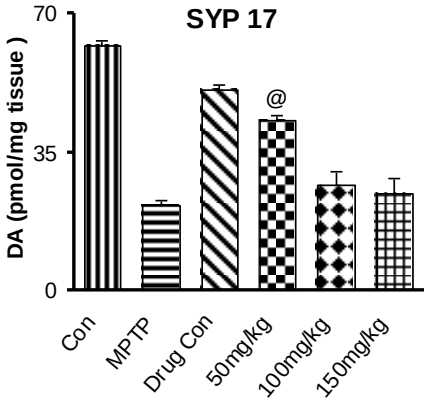


Fig-1. Effects of SYP-17 on the dopamine depletion caused by MPTP in striatum of Balb/c mice.

SYP-17 which has affinity in the *in vitro* radioligand binding assays for adenosine A_{2A} receptor (Ki-103 nM) and negligible affinity for Dopamine D_2 receptors (17.59 % displacement @ 1μM) showed protection against MPTP induced dopamine depletion in the Balb/c mice. (Fig-1)

SUMMARY

Introduction

Parkinson's disease (PD) is a neurodegenerative disease of the substantia nigra, a brain area that projects to the striatum, which together form the nigrostriatal dopaminergic pathways. There is growing evidence suggesting that the A_{2A} receptor is a potential target for the novel non dopaminergic antiparkinsionian therapy.

Experimental work done.

SYP-17 was tested in the adenosine A_1, A_{2A} and A_3 receptor and Dopamine D_2 receptor radioligand binding assays. The MPTP model of Parkinson was done as per previously reported protocols. Behavioral Pharmacology was done using the conventional protocols.

Result and Discussion.

SYP-17 has high affinity for adenosine A_{2A} receptor (Ki-103 nM) and negligible affinity for Dopamine D_2 receptors (18 % displacement @ 1 μM). (Table-1 and 2)

Table-1- Affinities of SYP-17 at human adenosine A_1, A_{2A} and A_3 receptors expressed as Ki values (in μM ±SEM, n=3) or percentage displacement at 1 μM.

K_i in nM or % displacement at 1 мM			
Code	**Human A_1 receptor**	**Human A_{2A} receptor**	**Human A_3 receptor**
SYP 17	35.5%	**0.103 ± 0.015**	17.1 %

Ki determined if displacement is >50%

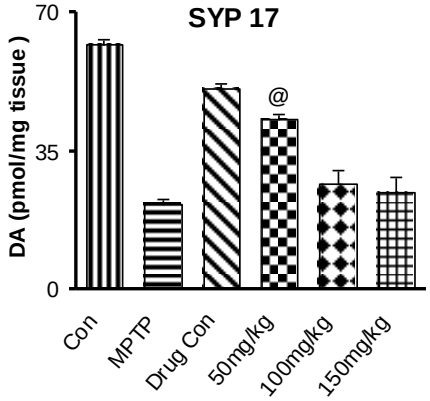
Table-2 Binding affinities of SYP-17 at Dopamine D_2 receptor expressed as percentage displacement (n=3).

Sr.no	Code	Concentration	3H-spiperone binding (% inhibition)
1	**SYP-17**	10^{-6} M	17.59%
2	Haloperidol	10^{-6} M	82%

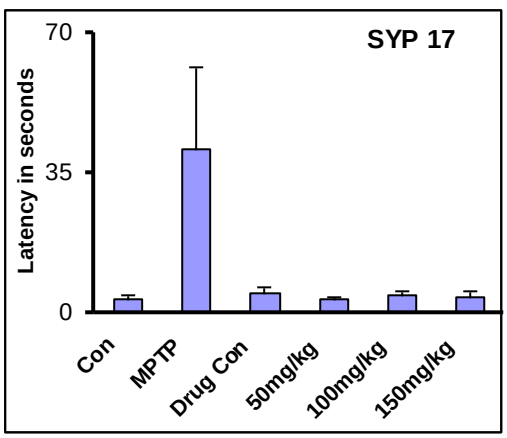
The SYP-17 reversed the akinesia and catalepsy caused by MPTP in the Balb/c mice. It also showed protection in MPTP induced dopamine depletion in Balb/c mice at dose of 50 mg/kg, p.o., but didn't showed comparable protection at 100mg and 150 mg dose. (Fig-1)

The loss of selectivity by SYP-17 for adenosine A_{2A} receptor at higher doses may be the one possible reason for the activity of SYP-17 at lower dose (50 mg/kg, p.o).

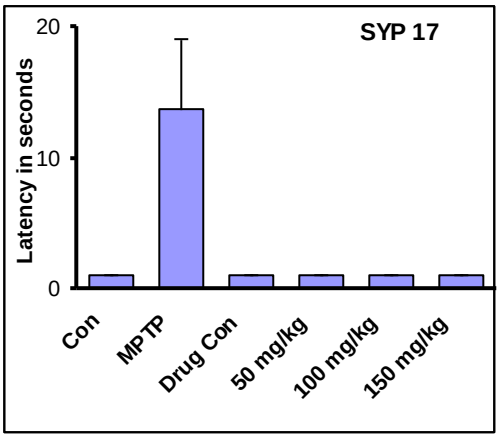
Fig (1) – (A) Effects of SYP-17 on the dopamine depletion caused by MPTP in striatum of Balb/c mice. (B) Effects of SYP-17 in the MPTP induced Akinesia model, (C) Effects of SYP-17 in the MPTP induced Catalepsy model.



(**A)**



(B)



(C)

Conclusion

SYP-17 which has high affinity for adenosine A_{2A} adenosine receptor (Ki-103 nM) and negligible affinity for Dopamine D_2 receptors (17.59 % displacement @ 1μM) showed protection against MPTP induced dopamine depletion in the Balb/c mice.

Future plans

SYP-17 is further planned to be tested at lower doses in MPTP model and 6-OH Dopamine model of parkinson disease.

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P-55A SYNTHESIS AND BIOLOGICAL SCREENING OF SOME NEW 3-SUBSTITUTED INDOLO [2,3] IMIDAZOLES

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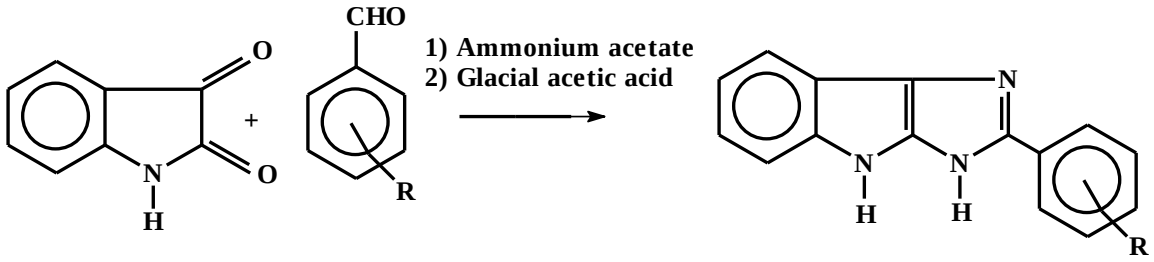
Isatin and Imidazoles are important class of compounds which posses immense pharmacological activities[1-3]. In the present study, the title compounds have been synthesized by combining both isatin and imidazole moiety. The synthesized compounds were evaluated for their anti-inflammatory activity. As both indole and imidazole moieties are very reactive and posses different biological activities. It was considered worthwhile to synthesize the drug having biological activity of derivative of both moieties in a single molecule. This concept has dual advantage in the sense that it will not only reduce number of drug to be taken at a time but also reduce the side effect due to multi drug therapy.

3-Substituted indolo[2,3] imidazoles **(Ia-g)** were obtained by condensing isatin (1*H*-indole2, 3-dione) **(I)** with substituted aryl aldehyde **(a-g)** in presence of glacial acetic acid and

ammonium acetate. After refluxing for 6-8 hrs. on water bath, reaction mixture was poured in to water and ammonia is added, solid which was separated out was recrystallized with appropriate solvent (**Fig-1)**.

Purity of compounds is checked by TLC. ^{1}H NMR, MASS and IR spectroscopy confirms the structure of the synthesized compounds.



(I) **(a-g)** **(Ia-g)**

R ⇒ H, 2-Cl, 3-Cl, 4-Cl, 2-NO_2, 3-NO_2, 4-NO_2.

Fig -1

Newly synthesized compounds were screened for their anti-inflammatory activity by using carrageenan induced rat hind paw oedema method[4]. The compound having chloro substitute at 3rd or 4th position showed comparable anti-inflammatory activity to the standard i.e. indomethacin.

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P-56

An antibacterial proteinaceous compound from *Streptomyces fulvissimus* MTCC 7336

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A screen of bioactive secondary metabolites producing actinomycetes identified *Streptomyces fulvissimus* MTCC 7336 as a producer of an antibacterial compound with high level of activity against MRSA (Methicillin resistant *Staphylococcus aureus*). Active compound was recovered from the culture supernatant through ammonium sulphate saturation that indicated it's proteinaceous nature. SDS PAGE analysis of the active compound revealed a major component with an estimated size of 63kDa along with few other minor bands, identification of the candidate peptide is yet to be ascertained. The current strain with antiMRSA activity may have a future prospect to control other microbial infections.

P-57

EVALUATION OF NOVEL PLATABILITY OF *Arachis hypogea* POLYMER.

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A novel biopolymer is isolated by simple innovative method using milk separated from *Arachis hypogea* seeds. The isolated polymer is subjected for characterization by evaluating suitable analytical method and found that it is protein polymeric in nature. The current aim of our research work is to evaluate the platability of the above isolated polymer by formulating plates loaded with gentamicin by extrusion method. The plates were subjected for various physicochemical characteristics like thickness, breakability, content uniformity, weight variation, surface pH, swelling index and in vitro release studies. These studies showed that the polymer is feasible for preparing gentamicin plates. Finally the conclusion was drawn that the polymer exhibits a novel inbuilt platability and suitability characters for delivering gentamicin through trans-soft palatal route.

P-58

PREPARATION AND CHARACTERIZATION OF SODIUM SALT OF *Musa paradisiaca* POLYMER

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A novel mucoadhesive biopolymer is isolated from *Musa paradisiaca* fruit by a simplified economic novel method. It was characterized for its nature by performing various analytical studies. Our studies revealed that the isolated polymeric material consists of hydroxyl and carboxylic groups. The mucoadhesivity of the above said polymer was studied using ex vivo mucoadhesivity method. From the experimental outcoming, it was revealed that it possesses a novel mucoadhesive character. This character is due to the presence of hydroxyl and carboxylic functional groups in the polymeric structure.

The current aim of our research work is to enhance the mucoadhesivity of the polymer by preparing sodium salt by a simplified method using monochloroacetic acid and sodium hydroxide. The prepared sodium salt of *Musa paradisiaca* polymer is subjected for confirmation of sodium salt formation by subjecting the sample for FTIR studies.

It is evaluated for its mucoadhesivity by *ex-vivo* method.

From our experimental data the conclusions were drawn that the novel synthesized sodium salt of *Musa paradisiaca* polymer also possesses a promising mucoadhesive characters. Hence it can be also used as a mucoadhesive material for preparing mucoadhesive formulations.

P-59

***In vitro* cultivation of *Plasmodium falciparum*: Studies with modified media supplemented with albumax and hypoxanthine.**

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The success of *in vitro* cultivation of malaria parasite (Trager and Jensen, 1976) has come up as an easily approachable method to screen compounds against the target parasite. However risk associated with good quality human serum has been the major drawback which was over come by use of 0.5% albumax, a lipid rich bovine serum albumin. Recently a combination of RPMI-1640, NCTC-135 and IMDM (RPNI) found supportive for long term continuous cultivation of *P. falciparum* in the presence of 10% bovine calf serum (BCS). The present study was carried out to observe the growth pattern of *P. falciparum* in RPNI after supplementation with albumax, used at different concentrations and hypoxanthine. The laboratory maintained 3D7 strain of *P. falciparum* was used and initial culture suspension contained ~0.5% parasitaemia and 6% haematocrit. The experiments were carried in 24 well plate and cultures were maintained static in candle jar at 37^0C. The spent culture medium was replaced once in every 48hrs. The results revealed identical growth of *P. falciparum* in particular medium supplemented with either BCS or different concentrations of albumax. The maximum parasitaemia ranged between 22 & 24% in RPNI medium and 10 & 12% in RPMI-1640. Addition of hypoxanthine in RPMI-1640 caused an increase in % parasitaemia whereas in medium RPNI no extra advantage could be seen.

P-60

***In vitro* cultivation of *Plasmodium falciparum* in modified media with various sera supplements**

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RPNI, a combination of three commercially available growth media (RPMI-1640, NCTC-135 and IMDM) found supportive for long term continuous cultivation of *P. falciparum* in the

presence of 10% bovine calf serum (Srivastava and Puri 2004). This medium is rich in nutrients such as Co-enzymes, nucleic acid derivatives, ascorbic acid, Glutathione, glucose, amino acids & vitamins. The present study was under taken to observe the suitability of RPNI medium for the development of *P. falciparum* in the presence of horse, goat and rabbit sera. The laboratory maintained 3D7 strain of *P. falciparum* was used for study. The cultures at 6% haematocrit were maintained using the candle jar protocol. The spent culture medium was replaced once in 24hrs and parasitaemia was monitored daily till day 7 except in horse serum the observation continued upto day 60. The parasitaemia was monitored microscopically for which a drop of culture from the settled layer was spread into thin film. It was air dried, fixed in methanol, stained with Giemsa stain.

The results revealed that horse, goat and rabbit sera supported the development of *P. falciparum* and horse serum in RPNI medium supported the continuous culture upto day 60 of observation period. In RPMI-1640 medium maximum parasitaemia was observed in the presence of rabbit serum. Details of findings will be discussed.

P-61

In vitro cultivation *of Plasmodium falciparum: Studies with modified media* supplemented with albumax and hypoxanthine

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Division of Parasitology, Central Drug Research Institute, Lucknow, India

The success of *in vitro* cultivation of malaria parasite (Trager and Jensen, 1976) has come up as an easily approachable method to screen compounds against the target parasite. However risk associated with good quality human serum has been the major drawback which was over come by use of 0.5% albumax, a lipid rich bovine serum albumin. Recently a combination of RPMI-1640, NCTC-135 and IMDM (RPNI) found supportive for long term continuous cultivation of*P. fa/ciparum in the presence of 10% bovine calf serum (BCS). The present study was carried* out to observe the growth pattern of *P. fa/ciparum* in RPNI after supplementation with albumax, used at different concentrations and hypoxanthine. The laboratory maintained 3D7 strain of *P falciparum was used and initial culture suspension contained -0.5% parasitaemia and 6%* haematocrit. The experiments were carried in 24 well plate and cultures were maintained static in candle jar at 37°C. The spent culture medium was replaced once in every 48hrs. The resultsrevealed identical growth of *P. fa/ciparum* in particular medium supplemented with either BCS or different concentrations of albumax. The maximum parasitaemia ranged between 22 & 24% in RPNI medium and 10 & 12% in RPMI-I640. Addition of hypoxanthine in RPMI-1640 caused an increase in % parasitaemia whereas in medium RPNI no extra advantage could be seen.

P-62

***In vitro cultivation of Plasmodium falciparum in modified media with various* sera supplements**

Kumkum Srivastava, Shubhra Singh, Prathibha Singh and S. K. Puri
Division of Parasitology, Central Drug Research Institute, Lucknow, India

RPNI, a combination of three commercially available growth media (RPMI-1640, NCTC-135and IMDM) found supportive for long term continuous cultivation of *P. falciparum* in the presence of 10% bovine calf serum (Srivastava and Poo 2004). This medium is rich in nutrientssuch as Co-enzymes, nucleic acid derivatives, ascorbic acid, Glutathione, glucose, amino acids &vitamins. The present study was under taken to observe the suitability of RPNI medium for thedevelopment of *P. falciparum* in the presence of horse, goat and rabbit sera. The laboratorymaintained 3D7 strain of *P. falciparum* was used for study. The cultures at 6% haematocrit were maintained using the candle jar protocol. The spent culture medium was replaced once in 24hrsand parasitaemia was monitored daily till day 7 except in horse serum the observation continued upto day 60. The parasitaemia was monitored microscopically for which a drop of culture from the settled layer was spread into thin film. It was air dried, fixed in methanol, stained with Giemsa stain.The results revealed that horse, goat and rabbit sera supported the development of *P. falciparum* and horse serum in RPNI medium supported the continuous culture upto day 60 of observationperiod. In RPMI-1640 medium maximum parasitaemia was observed in the presence of rabbit serum. Details of findings will be discussed.

P-63

Synthesis of Oligosaccharides Analogs Present in Cardiac Glycosides

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Department of Chemistry, Lucknow University, Lucknow 226007

Cardiac glycosides are one of the oldest therapeutic agents which are clinically used as inotropic drugs to improve the myocardial contractibility in the treatment of congestive heart failure. These glycosides also exhibit cytotoxic, macrofiliariae, anticancer, anti depressant, and antitumor activities. The biological activities of these glycosides depend on the structure of aglycon and the oligosaccharides present therein. The role of oligosaccharides in the biological activity of the compound is very decisive as it provides solubility to the compound for the penetration of the drug. Owing to this biological importance of the oligosaccharides different trisaccharide have been synthesized and glycosidically linked to the different naturally occurring cardiotonic agents viz strophanthidin and digitoxigenin. For this purpose 2-Deoxy glucose, L-fucose and L-rhamnose were converted into suitable acceptor synthons and celliobiose and gentibiose were converted into suitable donors using the protection and deprotection strategies which were

glycosidically linked using TMS-OTf to obtain their respective trisaccharides. The trisaccharides were then finally linked to digitoxigenin and strophanthidin to obtain biologically active cardiac glycosides.

P-64

SYNTHESIS AND BIOLOGICAL ACTIVITY OF SOME NEW PYRAZOLINES CONTAINING IODO NUCLEUS

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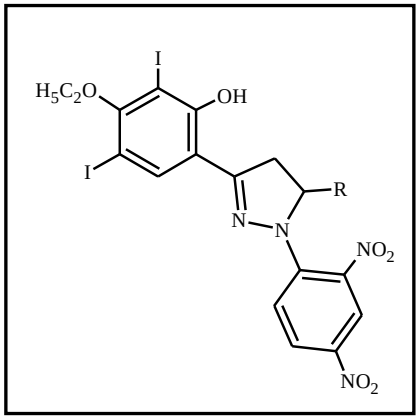
Smt. S. M. Panchal Science College, Talod - 383 215,
Hemchandracharya North Gujarat University, Patan (Gujarat) India.

We are engaged in a program to explore novel heterocyclic entities in ordered to studying their pharmacological profile**.**The chemistry of heterocyclic compounds has attained greater interest because of its useful application in medicine, agriculture and industrial chemistry. Amongst them nitrogen containing five members heterocycles such as pyrazolines have proved to be the most active nucleus. due to their wide range of pharmacological activities such as antimicrobial, analgesic, antipyretic, antiallergic, insecticidal and cardiovascular.



The structural assignment of the compounds was based on elements analysis and IR, ^{1}H NMR and Mass spectral data. All the synthesized compounds have been screened for their antimicrobial activity to gram-positive and gram-negative bacterial strains and antifungal activity. The antimicrobial activities of the synthesized compounds have been compared with standard drugs like Amoxycillin, Ciprofloxecine and Griseofulvin. The purity of synthesized compounds have been checked by TLC.

P-65

SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF AURONE QUINOXALINES

V. M. Barot and T. M. Upadhyay

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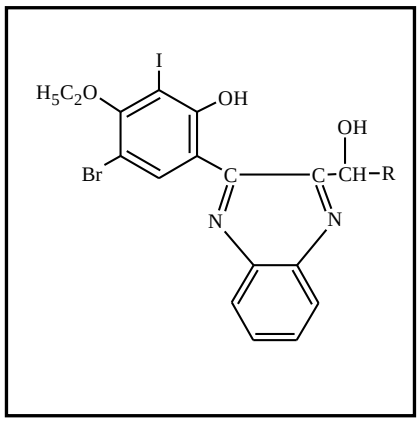
Interesting biological activities of a novel heterocycles like aurone quinoxalines have been extensively explored for their applications in the field of medicine. Antimicrobial agents are

continuously in the process of modification to exhibit broader spectrum, greater potency and lesser toxicity. Significant biological properties assocated with quinoxaline derivatives have focused considerable interest to design the compounds in which quinoxaline ring system is incorporated.



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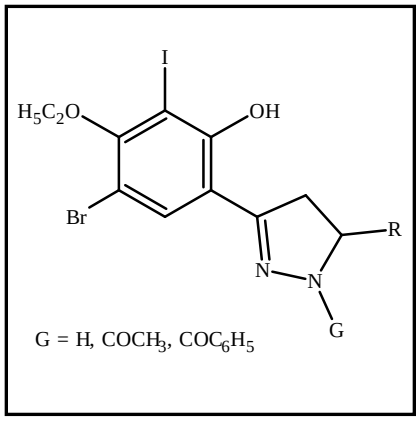
P-66
SYNTHESIS AND BIOLOGICAL EVALUATION OF SOME NEW PYRAZOLINE

V. M. Barot and S. D. Desai

P.G. Centre of Chemistry, Smt. S. M. Panchal Science College, Talod - 383 215, Hemchandracharya North Gujarat University, Patan (Gujarat) India.

In continuation of our earlier work on the synthesis heterocyclic compounds which were found to possess multifarious antimicrobial activity. Substituted pyrazoline have drown considerable attention due to their wide range of pharmacological activities such as antimicrobial, anti inflammatory, analgesic and anthelmintic. In view of this we now report the synthesis of some new heterocycles viz. 2-pyrazoline and their derivatives.



The structural assignment of the compounds was based on elements analysis and IR, ^{1}H NMR and Mass spectral data. All the synthesized compounds have been screened for their antimicrobial activity to gram-positive and gram-negative bacterial strains and antifungal activity. The antimicrobial activities of the synthesized compounds have been compared with standard drugs like Amoxycillin, Ciprofloxecine and Griseofulvin. The purity of synthesized compounds have been checked by TLC.

P-67
SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF NEW AURONE DERIVATIVES.

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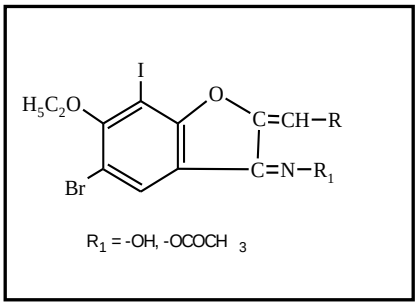
Among a wide variety of heterocycles that have been explored for developing pharmaceutically important molecule, aurone oxime and N-acetyl aurone oxime are one of them. Several nitrogen and oxygen containing heterocycles compounds are useful in pharmaceutical chemistry. The structural assignment of the compounds was based on elements analysis and IR, ^{1}H NMR and Mass spectral data. All the synthesized compounds have been screened for their antimicrobial activity to gram-positive and gram-negative bacterial strains and antifungal activity. The antimicrobial activities of the synthesized compounds have been compared with standard drugs like Amoxycillin, Ciprofloxecine and Griseofulvin. The purity of synthesized compounds have been checked by TLC.



P-65

Evaluation of *In vitro* Antimicrobial Activity of Methanol Extract from *Manilkara hexandra* (Roxb.) Dubard Leaf against Human Pathogens

Jigna Parekh and Sumitra Chanda*

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The methanol extract of *Manilkara hexandra* (Roxb.) Dubard leaf was evaluated for antimicrobial activity at two different concentrations against some human pathogens. The antimicrobial activity was determined by agar disc diffusion method. All the microorganisms exhibited concentration dependent activity at different levels. The inhibitory effect of the extract was compared with standard antimicrobics. The minimum inhibitory concentration (MIC) was also determined.

P-66

EVALUATION OF SOME MEDICINAL PLANTS FOR ANTI-INFLAMMATORY POTENCY

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NSAID's currently used have severe side and toxic effects, so there is high need for an alternate source of anti-inflammatory drugs from traditional source. In the present investigation *Scindap officinalis, Merremia turpentum* and *Gymnema sylvestre* were screened for their chronic anti-inflammatory activity. Cotton pellet induced granuloma method was used to study the chronic anti-inflammatory activity of the 3 plants. Albumin, protein, acid phosphatase (ACP) and alanine transaminase (ALT) level were also investigated from the serum. Drug dose used for the above study was 300mg/kg. Standard drug Indomethacin 2.5mg/kg was used for comparative study. All the data were statistically evaluated by Student's t-test and ANOVA. This kind of screening work will lead us to create baseline information in obtaining new pharmaceuticals from natural products.

P-67

DEMAND OF HERBAL HEPATOPROTECTIVE FORMULATIONS IN LUCKNOW.

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According to early VADIC literature, Ayurvada was supposedly first passed on by Lord Brahma to sage Bharadvaja. Bharadwaja in turn taught it to other sages like punarvasu atreya. He taught Ayurveda to his 6 disciples namely, *AGNIVASHA* , *BHELA*, *JATUKARANA* , *PRASARA*, *HARITA* and *KSHARA PANI* .These disciples, on the basis of their own knowledge of the subject, composed these works and blessed the authors. The treatises became popular and proved helpful in mitigating the human sufferings.

Our investigation was concerned on herbal hepatoprotective formulations which are used to treat acute and chronic hepatic disorders in the population ofLucknow. The aim of our studies were on

the commercial preparation and components, dosage thereof widely used as liver protective. The study was initiated from primary data collection through the convenient sampling.

It was found that 70 % of patients suffering form liver disorders belonging to the age group of 25 to 40 years prefer herbal formulations as compared to allopathic drugs. The main ingredient used in these formulations are *bhringraj*, *kalmegh*, *punarnava*, *kutaki*, *kasani*, etc. and it was found that the amount of bhringraj is more than other ingredients. Most of the preparations are present in liquid dosage forms. The major companies which are involved in manufacture of these herbal formulations are HIMALAYA, CHARAK, DABUR, DHANWANTI pharmacy, etc. The side effects in these herbal formulations are negligible.

P-68

TRADITIONAL PREPARATION HAVING NUTRACUTICAL IMPORTANCE

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"HEALTH FOR ALL" means that the health is to be brought with in the reach of each and everyone. This is only possible when there is a proper integration of herbal drugs with modern medicine. There are various plants which were used to cure and prevent the diseases from ancient time, but most of them lost there credential in present time due to the lack of proper knowledge of pharmaceutical supplements. The language happened to be an other barrier for the popularity of our ancient knowledge. That was general population could not easily understand the meaning of these sanskritised knowledge and uses of plants. So this is one of the major limitations for popularity of Ayurvedic system of medicine. In rural areas widely growing plants are used but the product of those plants could not be commercialized.

Our main aim is to find out some of the plants which were reported in Vedas and puranas

to determine pharmacological activity and if possible to formulate it in the form of suitable pharmaceutical preparations.

P-69

The Nutraceutical revolution: its impact on R&D

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The nutraceutical revolution began in the early 1980s, which has generated a fresh interest on plant based medicines. A few years ago Stephen L.Defelic coined the term “nutraceutical” in order to give a much needed identity and legitimacy to this amorphous area.

Nutraceuticals can be defined in two ways (i) potential nutraceutical and (ii) established nutraceuticals. A potential nutraceutical is one that holds a promise of a particular health or medical benefit and such a potential nutraceutical becomes an established one, after there are sufficient clinical data to demonstrate such a benefit.

It is believed that the market of potential nutraceutical will be substantially higher in coming years as the awareness on the benefits and safety of plant based medicines is growing, substantially.

P-70

THE NUTRCEUTICAL BENEFIT OF FEW PLANTS

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A recent survey in UK, Germany, and France concluded that diet is one of the highly rated factors among the human population as compared to other factors for maintaining good health.

Nutraceuticals are the fastest growing segment of today's food industry. A market estimate suggested it to reach up to $60 billion, growing at 5 % per annum. "Functional foods," "nutraceuticals," "pharmaconutrients,"and dietary ingredients" are all terms used indiscriminately for nutrients or nutrient-enriched foods that can prevent or treat diseases.

Nutraceuticals are clearly not drugs,. A nutraceutical or pharmaconutrient is surely a nutrient that maintains, supports, and normalizes any physiologic or metabolic function, but can also potentiate, antagonize, or otherwise modify physiologic or metabolic functions. A nutraceutical may be a single natural nutrient in powder or tablet form, not necessarily a complete food and not a drug.

The evolving concept of nutraceuticals and functional foods raises exciting prospects for future nutrition research associated with health benefits for the general population.

P-71

Strategic Visioning for Vaccine Development Vac 1.0: ***Advancing Knowledge. Transforming Lives***

Vipin Dwivedi, Vinod Kumar, [1]Deepak Deka, [1]**Dr.** P.N. Dwivedi, [2]Dr. V. Raina
Biosoftware Development Centre 1Dept. of Veterinary Sciences 2Dept. of Molecular Biology
Bioinformatics Institute of India Punjab Agricultural University Indraprashta Apollo Hospitals

The confluence of two "Vaccine Development " and "Bioinformatics" each of which has benefited from Major conceptual and technical advances, coupled with the recent surge in data and research Results from variety of stages, provides an unparalleled opportunity to develop new vaccines for diseases with no conventional treatments. Vaccine development and research is still relatively naïve however, and number of challenges need to be addressed as a prelude to clinical application and development. We has already taken the initiative by establishing a co-ordinated multidisciplinary programme of research, developing a national resource much needed to underpin the discovery science, and build capacity in Vaccine research and development.Today we stand at the dawn of the Information Age, in life science. What was once intractable and unthinkable is now becoming mundane. The use of informationtechnology in the field of molecular biology has grown steadily Information technologyis revolutionizing all aspects of our world at unimaginable and unprecedented rates. Inthis IT era although information's are available about vaccines and infectious organisms but, there is no single platform which can help to design an effective vaccine and also provide precise information related to vaccines. So, this will be our attempt to providesolution and knowledge to the people who have interest in this field.This tool (VAC 1.0)

will help to gain knowledge about different aspects to be consideredfor an effective vaccine development like infectious nature of the agent, virulencegene(s), neutralizing epitopes, important gene sequences, protein profiles, protein threedimensional structures, already available vaccines and other molecular biology information's. It will directly help the scientific group for designing and development of effective vaccines and indirectly it'll help to control the infectious diseases of both animal and human populations. Thus it'll help to improve the health status of the both animal and human population as well as it'll also help to acquire knowledge in this field.This shall enable the research community an access to unified vaccine related information, tools and techniques. VAC 1.0 contains necessary information related tovaccine on every aspects that is required for R & D. VAC 1.0 is in Development stage

P-72

Antioxidant activity and antimutagenicity of some bioactive plant extracts

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Antioxidant activity of methanol extracts of *Acorus calamus* (rhizome), *Holarrhena antidysenterica* (bark) was characterized by the DPPH scavenging activity. The results were compared with commercially available known antioxidant like BHT, BHA and ascorbic acid. Extracts of both plants showed concentration dependent activity ranging from 1.09 to 20.88% decolourization at 25, 50 and 100 µg/ml concentrations. *A calamus* extract showed relatively higher activity as compared to *H. antidysentrica*. On comparison with control their activity was weak. The extracts from *Acorus calamus,Hemidesmus indicus, Holarrhena antidysenteruica* and *Plumbago zeylanica* were tested for *in vitro* toxicity to sheep erythrocytes and their possible antimutagenic potential. These extracts could not demonstrate toxicity to sheep erythrocytes as well as genotoxicity in Ames *Salmonella* test strains (TA97a, TA100, TA102 and TA104). However, these extracts showed sign of antimutagenic activity against sodium azide and MMS induced mutagenicity in above test strains of *Salmonella typhimurium* by pre-incubatio test method. The present investigation demonstrated that the above traditionally used Indian medicinal plants are non-toxic and exhibited promising antimutagenic activity**.**

P-73

A **semi-parametric approach to outlier detection for *in vitro* NMR data of metabolites**

M. Srivastava, M. Abbas, Raja Roy*, Ankita Pandey*
*Biometry and Statistics Division; * SA/F ,COR/, Lucknow*

In vitro NMR spectroscopic examination of tissue extracts can be combined with appropriate multivariate techniques to monitor the characteristic metabolic differences between different types of tumors. In general NMR descriptors are constructed as a data matrix with samples along the rows and the descriptors comprising the columns. This matrix is used to set threshold for the differential diagnosis of breats tumors with a special reference to fibroadenoma and ductal carcinoma. For many reasons, some observations appeared to be inconsistent with the remainder of the collected data which influences the threshold levels. The number of outlier

cases may become large due to the involvement of several metabolites. On the omission of such wild cases, we may land-up with inadequate sample size, and we may loose some valuable information in the form of governing pattern. This could also lead to personal bias. Therefore, such outlier cases should be restricted to minimum. To support a scientific basis to detect outlier we propose a graphical method which can help to look into some influencing metabolites. It is based upon the Normal distribution plot of variables. First the standard Gaussian distribution curve was plotted for each metabolite jointly for two conditions benign and malignant.Metabolites with lesser overlapping region were targeted for detecting outliers. Plotting suggests that in general mean of the malignant is lower than the benign group. Cases showing observations beyond 99% limit in a large number of metabolites have been considered as outliers. After the exclusion of outlier cases, the univariate prediction of percent correct classification has improved form 4 to 16 percent. The joint prediction of tumor using Glycine and Choline was more efficient by 11 % after excluding the outliers.

P-74

Efficacy of *Myristica fragrans* Houtt.and *Cassia tora* Linn. with modern drug in Triton WR 1339 induced hyperlipidaemia in rats.

Shweta Singh, Sasikumar Menon*, Dr.Sunita Shailajan & Dr. Jaripatke K.K.
*Animal Testing Unit, S.P.Mandali's, Ramnarain Ruia College, Matunga, Mumbai-400019, India.

Several plants have been identified for their therapeutic use as hypolipidaemic agents. In the present study a mixture of slurry of *Myristica fragrans* and *Cassia tora* (seed powders) were evaluated and compared with modern drug for their efficacy in the treatment of triton WR 1339 induced hyperlipidaemia in rats. Blood and tissue biochemical parameters were measured. The potential of *Myristica fragrans* and *Cassia tora* as hypolipidaemic agents is discussed.

P-75

Efficacy of *Eugenia jambolana* and *Anacardium occidentale* in treatment of alloxan induced diabetes in rat.

Priyaj Mhatre, Dr.Sasikumar Menon*, Dr. Sunita Shailajan
& Dr. Jaripatke K.K. S.P.Mandali's, Ramnarain Ruia College, Matunga, Mumbai-400019, India.,*Therapeutic Drug Monitoring Laboratory (TDML), Sion (E), Mumbai-400022, India.

Several plants have been identified for therapeutic use as antidiabetic agents. In the present study slurry of *Eugenia jambolana* (seeds powder) and *Anacardium occidentale* (leaves powder) were evaluated for their efficacy in the treatment of alloxan induced diabetes in rats. Blood glucose level was measured using GOD-POD method after treatment with the combination of slurry of *Eugenia jambolana* seeds and extract of *Anacardium occidentale* leaves. The efficacy of the

treatment was evaluated using various biochemical parameters. The potential of using *Eugenia jambolana* seeds and *Anacardium occidentale* leaves to control glucose levels in diabetes has been discussed.

P-76

Studies on *Trigonella foenum graceum* with modern drug in alloxan induced diabetic rat model.

Neeta Kadam, Dr.Sasikumar Menon*. Dr. Sunita Shailajan & Dr. Jaripatke K.K.
Animal Testing Unit, S.P.Mandali's, Ramnarain Ruia College, Matunga,
Mumbai-400019, India.,*Therapeutic Drug Monitoring Laboratory (TDML), Sion (E),
Mumbai-400022, India.

Several plants have been identified for therapeutic use with antidiabetic properties. In the present study slurry of *Trigonella foenum graceum* (leaf extact) alongwith modern drug was evaluated for its efficacy in the treatment of alloxan induced diabetes in rats. Blood glucose level was measured using GOD-POD method for the evaluation. The slurry of *Trigonella foenum graceum* leaf extract with modern drug was studied in alloxan induced diabetic rats. The efficacy was evaluated using biochemical observations. The results discuss the potential use of *Trigonella foenum graceum* for an adjunct therapy with a modern antidiabetic agent to control glucose levels in the long-term management of diabetes.

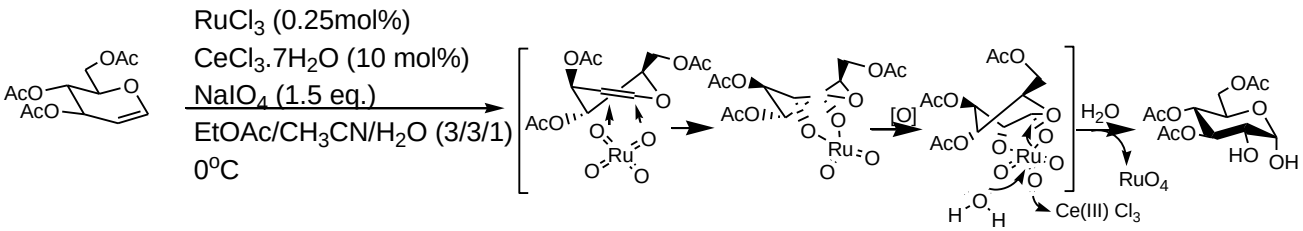
P-77

An efficient stereoselective dihydroxylation of glycals using a bimetallic system, $RuCl_3/CeCl_3/NaIO_4$

Pallavi Tiwari, Anup Kumar Misra
Medicinal and Process Chemistry Division, Central Drug Research Institute,
Lucknow-226 001, India

Suitably protected 1,2-dihydroxy carbohydrate derivatives are useful synthetic intermediates in several organic transformations such as, in the synthesis of polyhydroxylated chiral natural products, O-glycosides and C-glycosides syntheses. They have also been used in the O-glycosylations involving intramolecular aglycon delivery. Conventionally, sugar derived 1,2-diols are prepared using the reaction sequence of conversion of acetobromosugars to the corresponding sugar orthoesters followed by hydrolysis of orthoesters to the sugar 1,2-diols. Although, this method has been used widely, use of excess *s*-collidine as solvent during the formation of orthoesters is a serious drawback of this protocol. Other reported methods for the preparation of sugar 1,2-diols include (a) osmium-catalyzed (OsO_4, AD-mix$_\alpha$ and AD-mix$_\beta$)

dihydroxylation of glycals; (b) Conversion of glycals to 1,2-glycal epoxides using dimethyldioxirane followed by hydrolytic opening of 1,2-glycal epoxides; (c) reaction of glycals with oxone in acetone. There are several drawbacks in the above-mentioned methods, which include the use of very expensive and toxic reagents, difficulties in removing the Osmium salt from the products, use of very unstable epoxidation reagent, and formation of C-2 epimer. We are disclosing our findings for the use of $RuCl_3/CeCl_3.7H_2O/NaIO_4$, a bimetallic reagent system for the dihydroxylation of glycals to prepare only sugar 1,2- *cis*-diols (Scheme 1).



Scheme 1

P-78

Oxidation of thioglycosides to glycosyl sulfoxies and sulphones

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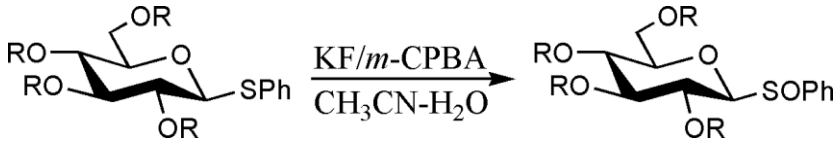
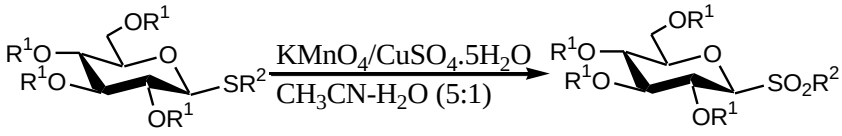
Glycosyl sulfoxides deserve a distinct position in the synthetic carbohydrate chemistry in synthesizing oligosaccharides and glycoconjugates. They are used to generate glycosyl carbanions towards the synthesis of *C*-glycosides and for the preparation of 2-hydroxy glycals. Several oxidizing agents have been employed for the selective oxidation of thioglycosides into corresponding glycosyl sulfoxides. However, most of the reported methods suffer from a number

of shortcomings including requirement of strict control of temperature (below –38°C), anhydrous reaction conditions, over-oxidation to sulfone, partial solubility and difficulty in removing of the by product from the sulfoxides.

Glycosyl sulfones are important class of synthetic intermediates used for the formation of C-C bond and a number of biologically important *C*-glycosides. The oxidation of thioglycosides to sulfones has been achieved most successfully using *m*-CPBA. However, this method suffers from a number of shortcomings as mentioned in the case of sulfoxide preparations. In this endeavor, we are disclosing our findings on the treatment of KF/*m*-CPBA combination with thioglycosides for rapid generation of glycosyl sulfoxides with high selectivity and efficiency (Scheme 1) and oxidation of thioglycosides to glycosyl sulfones using $KMnO_4/CuSO_4.5H_2O$ under neutral condition (Scheme 2).



Scheme 1



Scheme 2

P-79

Synthesis of thio- and selenoglycosides by cleavage of dichalconides in the presence of zinc/zinc chloride and reaction with glycosyl bromides

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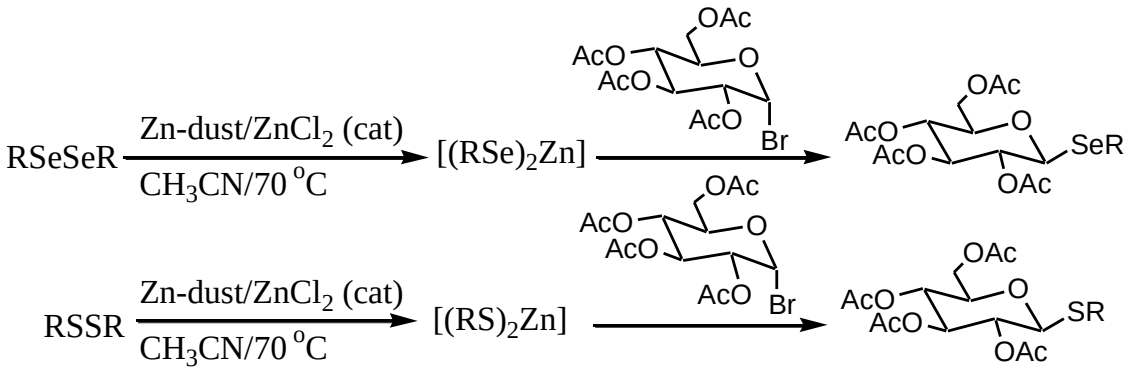
Thio- and selenoglycosides have found versatile applications in the field of carbohydrate chemistry as very effective and stable glycosyl donors. They are useful intermediates for the

preparation of functionalized glycals, glycosyl fluorides, sulfoxides and sulfones etc., which are used as glycosyl donors for *O*- and *C*-glycosylation. There are a number of reports in the literature for the preparation of thio- and selenoglycosides. The most often employed protocol for the thioglycoside preparation is the treatment of glycosyl acetates with malodorous and toxic alkyl/aryl thiols or selenols in the presence of a Lewis acid. In both the cases, there are similar drawbacks including the use of malodorous reagents and incompatibility of base labile protecting groups etc. Therefore, there is an urgent need to develop an odorless convenient and general reaction protocol for the preparation thio- and seleno glycosides. In this endeavor, we wish to report our findings on treatment of zinc with disulfides/diselenides followed by reaction of thiolate/selenide anions formed *in situ* with glycosyl bromides to furnish thio- and selenoglycosides in an odorless generalized one-pot reaction conditions with high stereoselectivity.



Scheme 1

Reference

Mukherjee, C.; Tiwari, P.; Misra, A. K. *Tetrahedron Lett* (**2005**) accepted, in press.

P-80

Synthesis of substituted 4*H*-1,4 Benzothiazines

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4*H*-1,4-Benzothiazines possess a wide spectrum of pharmacological activities similar to phenothiazines due to the presence of a fold along the nitrogen sulphur axis which is one structural specificity to impart similar biological activities.

The present work comprise with synthesis of substituted phenylthiourea by condensation between substituted aromatic amines and potassium thiocyanate, which on cyclization with sulphuryl chloride afforded substituted 2-amino benzo thiazoles, the later on ring cleavage with alkali results substituted 2-amino thiophenols. Condensation between substituted 2-amino thiophenols with different 1,3-diketones yields substituted 4*H*-1,4 Benzothiazines. A series of substituted 3-methyl- 4*H*-1,4-benzothiazine was synthesized using different substituents. The present route provides an edge over other classical synthetic procedures.

Purity of all the synthesized compounds was confirmed by Thin Layer Chromatography. The structure of the synthesized compounds were confirmed by IR, ^{1}H NMR, and MASS spectrometry.

P-81

Synthesis, Structural Modifications and Biological evaluation of 1, 4-diphenyl substituted-1,4,5,6-tetrahydropyridine

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Synthesis of 2-pyridone derivatives are of significant interest in current medicinal chemistry due to the number of biological activities shown by this entity. Natural compounds with this structure have emerged as potent antitumor, antifungal, antiviral, and psychotherapeutics.

The present work deals with a preparation of pyridine derivatives possessing an acetyl, amino, cyano and carboxylate functionalities along with a phenyl ring attached to pyridine. They have been prepared by Knoevenagel type cross-condensation of (un)substituted aldehyde, cyanoacetamide and β-dicarbonyl compounds with basic catalyst. A small library of 5-acetyl-2-amino-6-oxo-1,4-di(un)substituted phenyl-1,6-dihydropyridine-3-carbonitrile has been synthesized by using various substrates. The reaction conditions for such substrates are studied and optimized. The structure of the synthesized compounds were confirmed by spectral analysis like IR, ^{1}H NMR, and MASS spectrometry. The preliminary biological screening results will be presented.

P-82

Synthesis and Crystal Structure of Dimethyl 2,6-dimethyl-4-(2-nitrophenyl)-N-(2-methoxyphenyl-1,4-dihydropyridine-3,5-dicarboxylate

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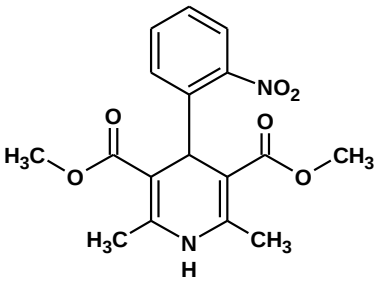
Research on the 1, 4-dihydro pyridine (1,4-DHP) moiety is of deep interest because of its recognition as a core structure in calcium channel antagonists, chemotherapeutic agent such as multi drug resistance (mdr) reversal in tumor cells, potent immunomodulating and antitubercular agent. Currently most widely used antihypertensive drug Nifedipine, is highly sensitive to aerial oxidation and therefore it's impurity profile was also very important to study from the stability point of view.

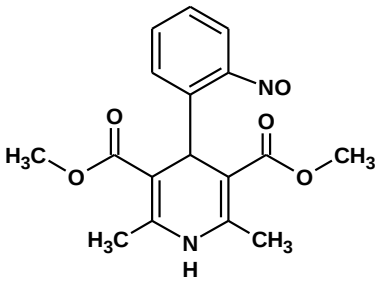
The stability of N-phenylsubstituted DHP is very interesting with compare to the nifedipine under UV irradiation. Present molecule is more stable and the 2-NO_2 phenyl ring is stabilized. So as to avoid the nitrososation under exposure of air. The structure is used for pharmacophoric requirement other than cardiovascular.

Our present work exhibits the synthesis as well as X-ray crystallographic study of dimethyl-2,6-dimethyl-4-(2-nitrophenyl)-N-(2-methoxyphenyl-1,4-dihydro pyridine -3,5-dicarboxylate.

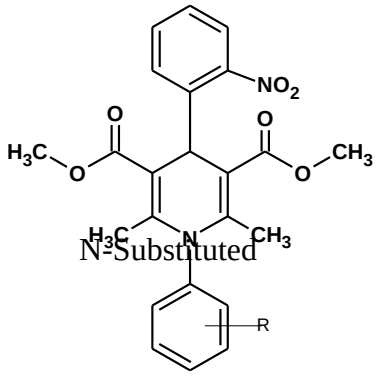
Purity of synthesized compound was checked by TLC. Characterization of newly synthesized compound was done by FT-IR, ^{1}H NMR and Mass spectral interpretation.



Nifedipine



Nitroso Impurity



N-Substituted DHP

P-83

Synthesis and Biological activity of some Pyrano[2',3':4,5]Pyrano[3,2-c] Quinoline-2-Carbonitriles

Hrishikesh Acharya, Nikhil Vekariya, Jalpa Trivedi, Arun Mishra, Dinesh Manvar, Denish Karia, Nimish Mungara and Anamik Shah

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The biological activity of 2-amino-4-aryl-3-carbonitrile -4Hnaptho[1,2-b] pyran has raised a renewed interest for reactivity of poly functionalized 2-amino-4H-pyran which prompted to synthesize some potential pharmacologically active analogues as anti HIV and anticancer agents. Pyrano fused heterocycles are important for diversed biological spectrum like antibacterial, antihistamines, antimicrobials, enzyme substrates and alkaloids. Benzofuro[2,3-c] quinolines and benzofuro[3,2-c]quinolines were studied as anticancer agents.

Thus, condensation of 1:2 mole proportion of appropriate aromatic amine and Diethyl malonate afford 4-hydroxy-6-methyl-2*H*-pyrano [3, 2-*c*] quinoline-2, 5(6*H*)-dione (A). Condensation of (A) with cinnamonitrile derivatives in the presence of basic organic catalyst gives title compound 3-Amino-1-(Substituted Phenyl) -6-Methyl-5,12-Dioxo-6,12-Dihydro-1H,5H-Pyrano[2',3':4,5] Pyrano [3,2-c] Quinoline-2-Carbonitriles. A small library of 3-Amino-1-(Substituted Phenyl) -6-Methyl-5,12-Dioxo-6,12-Dihydro-1H,5H-Pyrano[2',3':4,5] Pyrano [3,2-c] Quinoline-2-Carbonitriles were prepared by using various substrates. The structure of the synthesized compounds were confirmed by spectral analysis like IR, ^{1}H NMR, and MASS spectrometry.

P-84

Search towards synthetic modulators of malarial Glutathione-S-transferase

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Search is on towards the identification of novel biochemical targets for antimalarial drug design. Given the inexorable spread of drug resistance and until the development of an effective antimalarial vaccine, search for effective, safe and affordable drugs for malaria is one of the most pressing health priorities worldwide. The area of glutathione (GSH) metabolism provides a number of promising chemotherapeutic targets. Glutathione-S-transferase(s); GSTs (E.C.2.5.1.18) have been investigated in parasitic protozoans with respect to their biochemistry and they have been identified as potential vaccine and drug candidates in protozoan parasites. GST activity was determined in various subcellular fractions of malaria parasites *Plasmodium yoelii* and was found to be localized mainly in the cytosolic fraction. The specific activity of the enzyme in cytosolic fraction was determined to be around 0.058 ± 0.016 µmol/min/mg protein. Hemin, a known inhibitor of mammalian GST, maximally inhibited this enzyme from *P. yoelii* to nearly 86%. In a search towards synthetic modulators of malarial GST, 575 compounds belonging to various chemical classes were screened for their effect on crude GST from *P. yoelii* and 92 compounds belonging to various chemical classes were studied on recombinant GST from *P. falciparum* respectively. Among all the compounds screened, several compounds inhibited/stimulated the enzyme to the extent of 40% or more. Noteworthy in this connection are ten compounds i.e. 645 and 646 (glycosylated hydroxamic acids), 360, 361, 362, 363 and 376 (isoxazole and substituted isoxazole derivatives), 580, 582 and 620 (nucleosides and C-nucleosides) which showed simultaneous stimulation (40% or more) on *P. yoelii* and *P. falciparum* GST.

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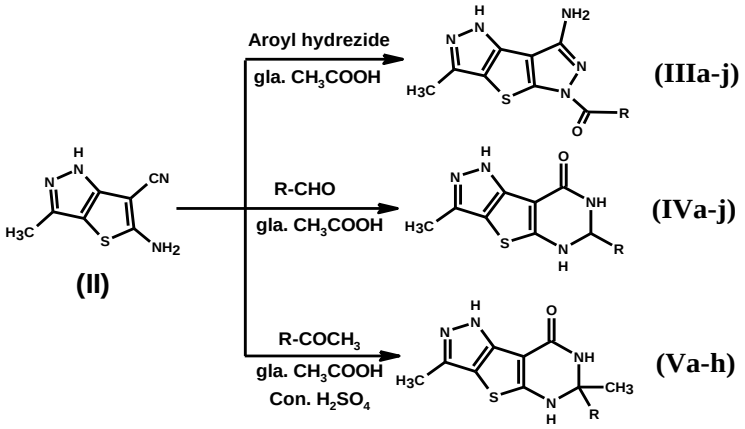
P-85

Synthesis and biological evaluation of pyrazolo[3',4';4,5]thieno[2,3-c]pyrazoles, pyrazolo [3',4';4,5]thieno[2,3-d]pyrimidin-8-ones derivatives via Gewald reaction.

H. V. Mathukiya, S. J. Vaghasia and V. H. Shah*

Chemical Research Laboratory,Department of Chemistry, Saurashtra University, Rajkot, Gujarat-INDIA-360005

The chemoselective heterocyclisation of (5-Methyl-2,4-dihydro-3H-pyrazol-3-ylidin)-malononitrile **(I)** has been accomplished via Gewald reaction to afford 3-methyl-5-amino-6-cyano-1H-thieno[3,2-c]pyrazole**(II)**. The **(II)** on action of aroyl hydrazides, aromatic aldehydes and aromatic acetophenones afford pyrazolo [3',4';4,5]thieno[2,3-c]pyrazoles **(IIIa-j)**, 3-methyl-pyrazolo[3',4';4,5]thieno[2,3-d] pyri- midin-8-ones **(IVa-j)** and 3,6-dimethyl-pyrazolo[3',4';4,5]thieno[2,3-d] pyrimidin-8-ones**(Va-h)** respectively.



The constitutions of the products have been delineated by elemental analyses, IR, PMR and Mass spectral data.

The products were assayed for their *in vitro* biological assay like antibacterial activity towards *S. pyogens* MTCC-442 and *S. aureus* MTCC-96 (Gram positive) and *E. coli* MTCC-443 and *B. subtillis* MTCC-441 (Gram negative) bacterial strain and antifungal activity towards *Aspergillus niger* MTCC-282 and *Candida albicans* MTCC-227 at different concentrations (µg/ml) : 0 (control), 5, 10, 25, 50, 100, 200, 500 for their MIC (Minimum Inhibitory Concentration) values. The biological activities of the synthesized compounds were compared with standard drugs.

P- 86

***Plasmodium yoelii nigeriensis* infection in db/+ mice: Development of a novel model for maintenance of *in vivo* malaria infection**

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Division of Biochemistry, Central Drug Research Institute, Lucknow (India)

The development and *in vivo* testing of potential antimalarial compounds is complicated by the fact that the causative agent *Plasmodium falciparum* only infects humans and some higher

order primates. Several animal models have been developed as alternatives using other species of parasite from the *Plasmodium* genus. One of the most common approaches is using strains of parasites like *Plasmodium berghei* and *Plasmodium yoelii* that cause malaria-like infection in rodents. The study for the first time reports the db/+ mouse as an alternative experimental host to Swiss albino mice for the maintenance of *Plasmodium yoelii nigeriensis* infection. The background for the db/+ mouse is the C57BL/Ks strain in which one of the alleles is defective while the other is normal. A progressive increase in % parasitaemia has been observed in infected Swiss mice, with a maximum of 44 % parasitaemia by day 8 and % mortality has been found to be maximum by day 10 (75 %). A similar increase in % parasitaemia was observed in infected db/+ mice as in routinely used Swiss albino mice, with a maximum of 49 % parasitaemia by day 5. The % mortality was found to be maximum by day 5 (50 %). The db/+ mouse-*P. yoelii nigeriensis* infection was found to be responsive to the antimalarial drug mefloquine (Mf). Results obtained show that Mf cured the infection of mice by the 5^{th} day. Menadione, a standard mammalian glutathione depletor and antimalarial drug, caused a slight delay in the rise of infection in this model, but could not cure the mice. The possibility of the development of synthetic compounds that target glutathione (GSH) metabolism of the parasite has also been discussed in this new model. The present study also attempts to measure the levels of GST(s), the major GSH utilizing, drug metabolizing and detoxifying enzymes in liver, kidney and spleen of *P. yoelii nigeriensis* infected db/+ mice and in the same tissues after treatment with known antimalarial drugs.

P-87

Evaluation of Analgesic Potentials of Indian Hypericum Species

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In Indian System of Medicines [ISM] numbers of plants are used for their biological potentials and many of them are screened on scientific basis. Indian biodiversity presents wide versatility where many plants which are not mentioned in the ancient text of ISM but still they are used in the folklore systems of medicines. Under present studies *Hypericum mysorense* and *Hypericum hookerianum* which are commonly found at the higher altitude in India were evaluated for their analgesic potentials. *Hypericum perforatum* a well known species of *Hypericum* is reported to posses many CNS potentials. By tapping the ethnomedicinal knowledge and potentials reported for *Hypericum perforatum,* attempt has been made to estimate the analgesic potentials of Indian *Hypericum* species.

A standardized 80% methanolic extracts of *Hypericum mysorense* and *Hypericum hookerianum* were subjected for the evaluation of analgesic potentials by using animal models. Based on the toxicity profile doses of 100 and 200 mg/kg body wt. of extract were used in the experiment. Dose dependant analgesic effect was observed on administration of *H. mysorense* methanol extract in thermal (50% and 84.37 %) and chemical (49.9% and 54.8%) induced pain behavior. As well as dose dependant analgesic effect was also observed in *H. hookerianum* methanol extract in chemical induced algesia, where pain inhibition was found to be up to 47.29% and 53.60%. The activity was found to be comparable with the standard drug Acetyl salicylic acid.

P-88

QSAR STUDIES ON MODELING OF DIURETIC ACTIVITY OF BENZENE SULFONAMIDES

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This is the first report on the use of valence force constant as a molecular descriptor for modeling diuretic activity of benzene sulfonamides. We have shown that carbonic anhydrase inhibitory activities of benzene sulfonamides can be excellently modeled using distance-based topological indices, information theoretic indices, ad hoc parameters along with some spectro-photometric parameters such as ^{13}C NMR chemical shifts. This introduction prompted as to undertake the present investigations, in that we have modeled diuretic activity of benzene sulfonamides using valence force constant as a molecular descriptors. For this modeling, we have used both regular as well as robust–regression analysis giving encouraging results.

Employing maximum R^2 method and stepwise regression analysis, we have first attempted two variable regression analysis. Out of the several such modeling one with force constant, f(S=O), and the indicator parameter Ipy is found the best :

log(1/C) = 0.8102 (± 0.2802) f(S=O) – 0.7314 (± 0.1618) Ipy – 7.5952 (± 2.7400) ……..(1)

n = 19, CV = 1.025, R = 0.7754, R^2_A = 0.5517, F = 12.066

Here, and hereafter n is the number of compounds, CV–is the coefficient of variance, R–is the multiple correlation coefficient, R^2_A– is the adjustable R^2 and F–is the F-statistics.

Successive regression indicated that addition of IP_3 to the above model expressed by eq. (2) increases the statistics slightly.

log(1/C) = 0.8251 (± 0.2962) f(S=O)– 0.7406 (± 0.1717) IP_4 – 0.0386 (± 0.1698) IP_3

– 7.733 (± 2.8900)…….. ……..(2)

n = 19, CV = 1.1367, R = 0.7763, R^2_A = 0.5232, F = 7.584

Interestingly, we observed that there is decrease in the magnitude of R^2_A, as we pass from two variables to three variable models. Therefore, that in the present case regular multiple regression analysis failed to give excellent models. In view of this, we have attempted robust multiple regression analysis.

Robust regression provides an alternative to least-square regression that works with less restrictive assumptions. We have, therefore, carried out robust regression analysis following Huber's method because Huber's method is currently the most frequently recommended in the regression texts.

log(1/C) = 1.1682 (± 0.3298) f(S=O) – 11.1627 (± 3.2215) …… (3)

n = 19, CV = 0.9340, R = 0.6518, R^2_A = 0.3918, F = 12.545

In an attempt to obtain still better models, we have followed step-wise regression analysis. The results have shown that there is large improvement. In the statistics, as we pass from one variable to two variable modeling. Out of the several two variable modeling attempted, the one contains f(S=O) and IP_4 as the correlating parameter was found the best :

log(1/C) = 0.8389 (± 0.2513) f(S=O) – 0.6235 (± 0.1325) IP_4 – 7.8989 (± 2.4565) ……(4)

n = 19, CV = 0.8755, R = 0.8168, R^2_A = 0.6255, F = 16.034

Successive robust regression analysis yielded a three variable model with slightly better statistics. This model contained f(S=O), IP_3 and IP_4 as the correlating parameters and is found as :

log(1/C) = 0.8682 (± 0.2688) f(S=O) – 0.0224 (± 0.1305) IP_3– 0.6181 (± 0.1377) IP_4

$$- 8.1759 (\pm 2.6202) \ldots\ldots\ldots\ldots\ldots\ldots (5)$$

$n = 19$, $CV = 0.8807$, $R = 0.8215$, $R^2_A = 0.6098$, $F = 10.3700$

Thus, like regular multiple regression analysis, the two variable model is more significant in robust multiple regression analysis also. Of course, the results obtained in robust regression analysis are considerably better than the regular regression analysis.

P-89

Antihyperglycemic effects of rhizomes of *Curculigo orchioides* Gaertn.

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Diabetes mellitus is hereditary metabolic disorder characterized by hyperglycemia, glycosuria, hunger, thirst and gradual loss of weight. Side effects associated with the use of insulin and oral hypoglycemic agents, there is an increasing demands of patients to use natural products. World Health Organization has recommended that use of natural products should be encouraged specially in countries where access to the conventional treatment of diabetes is not adequate. The aim of this study is to evaluate the extract of *Curculigo orchioides* claimed to have potential anbtidiabetic effect according to Unani system of Medicine.

Ethanolic extract (100mg/kg, p.o.) of *Curculigo orchioides* are screened against normal and Oral glucose tolerance test models for their Antihyperglycaemic effect and extract activity is compared with standard Glimeperide (500 μg/kg, p.o.) solution. Results indicated that serum glucose level on normal rats reduces to 16.39% and 20.68% after 30 and 90 minutes. The extract and standard have prevented the increase in blood glucose level significantly ($P<0.001$) after glucose administration; the maximum glucose tolerance was observed at the 30 minutes. The ethanolic extract of Curculigo orchioides rhizomes, given orally at a dose of 100mg/kg, possesses significant hypoglycemic in both normal and glucose loaded rats.

The result presented here may help to establish a scientific basis for the utility of *Curculigo orchioides* the treatment of diabetes. Preliminary phytochemical investigation showed that the presence of triterpenoid saponins, glycoside and tannin may be responsible for the antidiabetic activity.

P-90

Antihyperglycemic effect of leaves of *Cinnamomum tamala* Nees

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Natural Products Research Laboratory, Department of Pharmaceutical Sciences, Dr. Hari Singh

Gour Vishwavidyalaya, Sagar (M.P.)

Diabetes mellitus is the commonest endocrine disorder that affects more than one hundred million people worldwide and increasing in prevalence. Plants represent a major potential source of drugs for dealing with hyperglycemia. Traditionally the medicinal plants are being used very often in the form of powder, paste, decoction and infusion of crude herbs. The leaves of *Cinnamomum tamala* Nees (Family Lauraceae) have claimed to be effective in management of diabetes but sufficient data is not available to support this statement. In the present investigation the aqueous extracts of leaves of *Cinnamomum tamala* (CT) was evaluated for 15 days in alloxan induced diabetic rats. Alloxan (120 mg/kg) was used as diabetogenic agent and the animals with blood glucose level of more than 250mg/dl were considered for the experiment. The aqueous extracts of CT were orally feeded at a dose of 125 mg/kg and 250mg/kg every day until 15 day while control and diabetic controls did not receive plant extracts. Blood glucose levels were monitored on every 5^{th} day during the treatment. Oral feeding of plant extracts of two doses for 15 days produced a significant fall in the blood glucose level to 16.57% and 32.28% respectively in comparison with the 48 hrs level. The maximum reduction in blood glucose level was seen in animal receiving aqueous extract of CT at dose of 250mg/kg P.O. The results clearly indicated that the aqueous extract of CT at dose of 250mg/kg P.O. exhibited significant blood glucose lowering activity in alloxan induced diabetic rats.

P-91

CONTROLLED RLEASE OF A NEOPLASTIC AGENT FROM CALCIUM PECTINATE BEADS FOR COLON SPECIFIC DRUG DELIVERY

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Ulcerative colitis, if not treated, leads to colon cancer. Colorectal cancer is the second leading cause of cancer deaths in United States and more than 66,000 cancer of colon cancer are reported to occur every year in India. In the present work the polysaccharide pectin is selected as a drug carrier for colon-specific delivery of drugs based on its specific biodegradability by pectinase, the enzyme secreted by the colonic bacteria. It is used as its calcium salt to overcome solubility problems in physiological environment of upper GIT.

Calcium Pectinate gel beads of 5FU were prepared using the inotropic gelation method. The concentration of drug was investigated on the percentage of drug entrapped, size distribution and drug release from the beads. Beads were characterized for their size, entrapment efficiency, and swellability. In-vitro and In-vivo drug release studies were performed to assess the suitability of the delivery system for the colorectal cancer.

The smooth spherical beads bearing 5 FU were prepared while little rough surface was imparted after coating with Eudragit S100. The mean diameter of 5FU loaded CPG beads ranges between 1.55-1.90 mm while CPG beads without drug had diameters of 1.12-1.32 mm. It was observed that about 90% of drug was released from the beads after 8 hr in the colon. Results of studies indicate that calcium pectinate offered a high degree of protection from premature drug release in simulated upper GIT conditions and delivers its most of the drug load in colon and thus offers a good choice for the administration of anticancer drug to the colon.

P-92

Planar Chromatographic Analysis of Oil and Extract of *Acorus calamus* Linn. Rhizomes using β-Asarone as Marker.

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Acorus calamus Linn. belonging to the family Araceae, commonly known as sweet flag is an aromatic herb indigenous to Central Asia and Eastern Europe. The rhizomes of the plant have been bestowed with much therapeutic potential in Ayurveda such as epilepsy, depression and other mental disorders, bronchitis, cough, gout, inflammation, tumors, haemorrhoids, skin diseases, numbness and general debility. Nevertheless, the occurrence of potentially carcinogenic β-Asarone [(Z)-1, 2, 4-trimethoxy-5-prop-1-enyl-benzene], limits its therapeutic use. A rapid and accurate method with Planar Chromatography has been developed to quantify β-Asarone in the oil and extract of *Acorus calamus* L. rhizomes (Tetraploid variety). The R_f of β-Asarone was found to be 0.46 with densitometric scanning at 254 nm, using toluene and ethyl acetate in 93:7 ratio by volume as the mobile phase. The correlation coefficient 0.99 was indicative of good linear dependence of peak area on concentration. The β-Asarone content in methanol extract and oil of Acorus rhizomes were found to be 8.29 % and 87.94 % w/w respectively. The proposed method permits reliable quantitative monitoring of the negative marker β-Asarone in Acorus rhizomes.

P-93

Synthesis and antimicrobial properties of trialkylsilyl ethers of alkanolamine methiodides

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A number of compounds belonging to the series of O-trialkyl(aryl)silyl ethers of dialkylaminoethanol methiodides of formula: $[R^1R^2R^3SiOCH_2CH_2NR_2Me]^+I^-$ (R^1,R^2,R^3 = CH_3, C_2H_5, C_3H_7, C_4H_9, C_6H_5, C_6H_{13}, C_7H_{15}, C_8H_{17}, $C_{10}H_{21}$, $C_{11}H_{23}$, $C_{16}H_{33}$; R = CH_3, C_2H_5) have been synthesized by the dehydrocondensation reaction of dialkylaminoethanols with various trialkyl(aryl) hydrosilanes in the presence of catalyst and subsequent reaction with methyl iodide. The compounds synthesized have been characterized by multinuclear NMR and chromatomass-spectroscopy and their antifungal and antibacterial activity on gram positive and gram negative bacteria using agar ditch diffusion method has been studied.

The antibacterial and antifungal activity of new compounds in comparison with unsilylated one has been investigated in dimethyl sulfoxide against *Proteus mirabilis* NCIM 2241, *Staphylococcus aureus* ATCC 25923, *Bacillus cereus* ATCC 11778, *E. coli* ATCC 25922, *Candida tropicalis* ATCC 4563 and *Candida albicans* ATCC 2091.

It has been found that silylation increases the antimicrobial activity of aminoalkanols and biological activity increases with the lipophilicity increase of the compound tested. In some cases the antibacterial activity of compounds synthesized was higher in comparison with known antibacterial agents.

P-94

Evaluation for antihyperglycaemic activity in some terrestrial flora

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In recent years, there has been renewed interest in herbal medicine for the treatment of diabetes and many other diseases as herbal drugs are generally considered economic and out of toxic effect. According to the latest estimate there is existence of about 300000 angiosperm plants and over 250000 lower plants (pteridophytes, bryophytes, lichens, algae and fungi) on the earth and hardly 0.1% of these have been scientifically investigated for their medicinal properties .Many of these plants, particularly those found in tropics and subtropics exhibit extensive intra specific variability, which account for new drugs to treat diabetes mellitus seems to very promising. In the present study antihyperglycemic activity in ethanolic extract of some of the collected terrestrial plants was evaluated in validated animal models of diabetes. The test extracts were administered orally at 250 mg/kg body weight to the overnight fasted male albino rats and

their oral glucose tolerance was followed till two hours. The variance analysis regarding the area under the curve during the glucose tolerance test showed that out of 100 plant extracts evaluated, around 30% plant extracts showed statistically significant ($p<0.05$) inhibition on postprandial hyperglycaemia. However, when these extracts were subjected to streptozotocin-induced diabetic rats, very few among them showed either very slight decline or no change in blood glucose levels of these hyperglycaemic rats. Noteworthy, in this connection are the extracts of *Nymphaea rubra, Jatropha gossypifolia, Prunus cerasoides, Verbascum thapus, Polygonum barbatum, Premna mucronata, Grewia optiva, Strobilanthes canaricus, Moringa oleifera, Saussurea lappa, Euphorbia prostrata, Alocasia indica, and Dioscorea glabra* irrespective of their significant inhibition on postprandial hyperglycaemia in normal rats.

P-95

Evaluation of biological activities of some Schiff bases and metal complexes

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Some Schiff bases were synthesised from sulphonamide and race acetophenone. The characterisation was done by CHN analysis, IR and NMR spectral data. These Schiff bases were evaluated for their antimicrobial activity against some gram positive and gram negative bacteria and fungi. The antibacterial activity was studied against *B. mega, E. coli, B. substilis, P. fluorescences* and anti fungal activity against *A. awamori*. Further, copper, nickel, cobalt and iron complexes of two Schiff bases were also synthesised. Their structure characterisation was done by CHN analysis and IR spectral data and their antibacterial and anti fungal activities was also evaluated. The comparison of activities of ligand and complexes shows that presence of metal causes more inhibition i.e., more activity. Out of four metals studied, cobalt and iron are found to be more active.

Key words: Antibacterial activity, metal complexes, Schiff bases.

P-96

Evaluation of antibacterial activity of some Schiff bases

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From 4-amino phenol, some Schiff bases were synthesized. By IR and NMR spectral data, the structure characterization of these synthesized compounds were done. The antibacterial activity of all these synthesized Schiff bases was studied against *B. cereus-ATCC 11778, P. aero-ATCC 27853, E. coli-ATCC 25922, K. pneu- NClM 2719 and S. aureus-ATCC 25923* by agar ditch method. For this, two solvents dimethylformamide and dimethyl sulfoxide were selected. It is observed that antibacterial activity depends on the molecular structure of Schiff base, solvent used and bacterial strain under consideration. Out of two solvents studied, dimethyl formamide is proved to be best and salicyldehyde as side chain to 4-amino phenol could be used as lead molecule in drug designing i.e., in inhibiting above bacterial strains.

Keywords: Schiff bases, antibacterial activity.

P-97

A Multicomponent Reaction: Efficiently furnishing Phenylmethylene-2-thiohydantoin with some unusual consequences.

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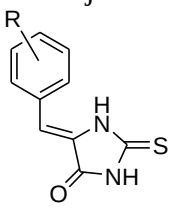
ρ For crystallography queries.

Current problem of synthetic enterprise is its resource intensive nature. Serial reactions and purifications require massive amount of solvents and materials. The average pharmaceutical synthesis yields 25-100 kg (including solvents) of waste per kilogram of product
One way to create synthetic routes with excellent atom efficiency or E-factor each to increase the number of reactions performed per pot in the same way that metabolic pathways run many reactions in the same environment.
Two specific terms are used for multicomponent reactions one is domino or cascade reaction and other is sequential reaction. Domino reactions describe closely coupled reactions where intermediates are inseparable, while in sequential reactions intermediates are separable.

In sequential reaction we design the reaction sequence so that the first step creates the conditions to trigger the next stage and that in turn sets up the third reactions, and so on, chemist can put all the ingredients in together at beginning. The main goal is to create a reaction that not only be selective but also highly efficient, saving time, energy and raw materials and also cope with one of major concern of the pharmaceutical industry getting shape right.



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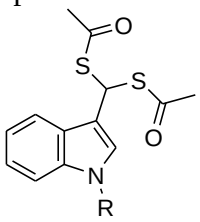

(2)

We describe here a multicomponent reaction that converts aryl aldehydes efficiently to phenylmethylene-2-thiohydantoin(1). But 3-formylindole behaves erratically and gem-dithioacyl protection (hitherto unreported protection for aldehyde function) occurs by this muticoponent reaction(2). Mechanistic study of this unusual behavior of indole for finding some clues to generalize this protection method, is described.

P-98

ELUCIDATION OF PHYSICOCHEMICAL CHARACTERISTICS OF A NOVEL MATERIAL ISOLATED FROM *Arachis hypogea*

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Arachis hypogea seed is gifted by the nature with a powerful stabilizer for stabilizing the oil content. The current aim of our research work is to characterize its novel physicochemical properties. The stabilizer was subjected to elemental analysis, solubility, pH incompatibility, dissociation constant, melting point UV, IR, NMR, Mass spectral analysis, and SEM analysis. Finally, the results of the studies were interpreted and found that it possesses novel polymeric character. Hence, the novel biomaterial can be used as an excipient in the pharmaceutical formulations.

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CHARACTERIZATION OF NOVEL SURFACTABALITY OF A BIOPOLYMER ISOLATED FROM *Cocos nucifera*

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Surfactant plays a vital role in the pharmaceutical formulations by its inbuilt capability of reducing the interfacial tension between two phases.

The current aim of our research worm is to characterize the surfactability of a novel biopolymer which is isolated from fresh kernels of ***Cocos nucifera***. The polymer is subjected for determining its conductivity by preparing in various concentrations like 0.005%, 0.1%, 0.2%, 0.3%, 0.4%, 0.5% and 0.6% and the surface tension of the above same solutions were also determined in triplicates. Apart from this the polymer is subjected for determining HLB value.

Our results reveal that the polymer solution showed a constant conductivity and drop in surface tension at a specific concentration which concludes that the polymer is having ability to form the micelles, which is an ideal characteristic feature of a surfactant. From these studies the conclusion was drawn that the ***Cocos nucifera*** biopolymer possesses an inbuilt novel surfactability character.

P-100

Facile synthesis of pyrazolo[3,4-*d*]pyrimidine and pyrimido [4,5-*d*]pyrimidin-4-one derivatives

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Pyrazolopyrimidine and primidopyrimidine derivatives have shown wide range of biological activities such as A_1 adenosine receptors, KDR, Src, EGFR, antiproliferative, DHFR, antimicrobial, antifungal and lipid peroxidation. Due to wide range of activities we have synthesized pyrazolo[3,4-*d*]pyrimidine and pyrimido[4,5-*d*]pyrimidin-4-one derivatives.