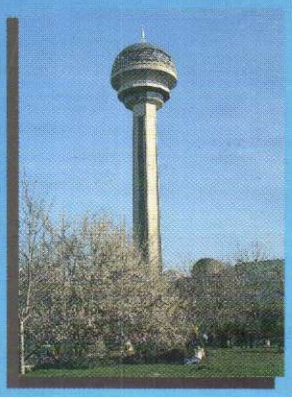
5th INTERNATIONAL SYMPOSIUM ON PHARMACEUTICAL SCIENCES (ISOPS-5)

ANKARA UNIVERSITY, FACULTY OF PHARMACY
ANKARA, 24-27 JUNE 1997



ABSTRACTS

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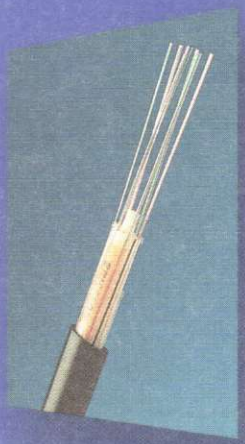

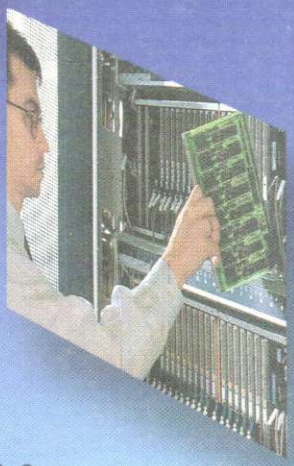

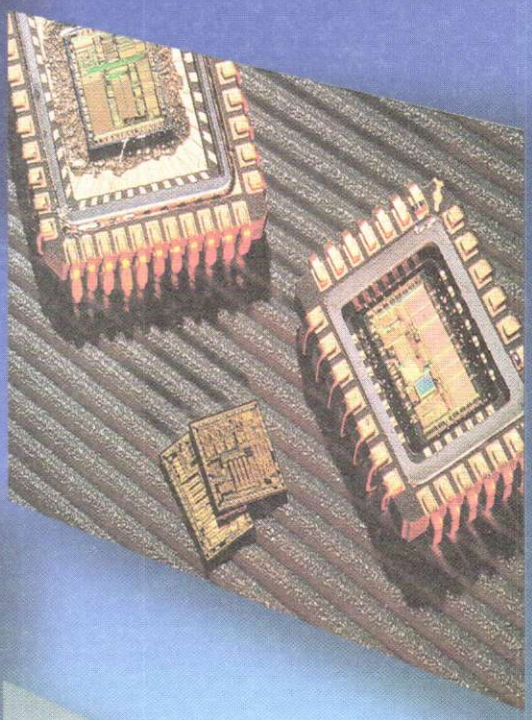

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5th INTERNATIONAL SYMPOSIUM on PHARMACEUTICAL SCIENCES (ISOPS5)

ANKARA UNIVERSITY
FACULTY of PHARMACY

ABSTRACTS

24-27 June, 1997
ANKARA

The Congress has been generously supported by

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Dear Participants,

It is a pleasure to welcome you to the University of Ankara, Faculty of Pharmacy for the 5th International Symposium on Pharmaceutical Sciences (ISOPS5).

Eight years ago, the First Symposium on the Pharmaceutical Sciences in Ankara was realized and the efforts of our Faculty to promote this Symposium, was based on a belief to scientific research and the exchange ideas within the international pharmaceutical research community. In June 1989, the concept of increasing necessity for pharmaceutical researchers to consider their research in a more international context, became visible for the first time at the European level.

With this Fifth Symposium on Pharmaceutical Sciences in Ankara, we also believe that certain milestones will be passed and undoubtedly, there is an honorable evidence which shows that researchers from different countries are enthusiastic and motivated about the impression of participating such a Pharmaceutical Symposium in Ankara, Turkey. This interest will particularly be promising at a time when the drug industry in Turkey are involved with research and development like those found in most countries which in the pharmaceutical industry is fully occupied with research and related problems resulting from ongoing changes in health.

I would like to congratulate the Committees for their fine efforts in organizing the ISOPS5. There are 310 scientists from several countries participating this Symposium. With this book, you will find abstracts of 32 plenary lectures and approximately 150 oral and poster presentations which we believe that the abstracts introduce the fact that these studies contribute to the concept of a globalization of the pharmaceutical sciences. In addition to general sessions and poster displays, the exibition of scientific and educational equipment from several companies will provide other highlights for the Symposium.

Please feel free to use computers in the enterence of the Conference Hall or Computer room at the third floor, to get an access to Internet and to send e-mails.

As you participate in our Faculty's programs, we hope you will take some time to investigate the resources which Ankara city can offer you. We also hope that the next International Symposium on Pharmaceutical Sciences (ISOPS6) will be realized with more participating in numbers and with more specific topics included, in 1999.

Finally, we wish you a succesful and productive meeting in which mutual relations can be strengthened and scientific expectations met.

Sincerely,

Seçkin ÖZDEN,
President of ISOPS5

Honorary President of the Symposium
Prof.Dr. Günal AKBAY
President of Ankara University

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PLENARY LECTURES

NEW TRENDS IN CHIRAL HPLC SEPARATION TECHNIQUES

Hassan Y. Aboul-Enein

Bioanalytical and Drug Development Laboratory, Biological and Medical Research Department (MBC-03), King Faisal Specialist Hospital and Research Centre, P.O. Box 3354, Riyadh 11211, Saudi Arabia

Optical activity and asymmetry is widespread in nature. Most of the biochemical processes are stereochemically controlled and it is therefore not surprising that the optical isomers of xenobiotics and chiral bioactive compounds can behave differently in terms of pharmacodynamics, pharmacokinetics, and even toxicological activity. However, most synthetic drugs are still administered as a racemic mixture, mainly due to claimed cost benefits.

The explosive development of enantioselective HPLC methodology over the last decade has rendered the analysis of chiral drugs in bulk, pharmaceutical dosage forms and in biological fluids an easy task. Enantioselective bioassays of drugs and their optical purity are becoming important issues both scientifically as required by the drug regulatory authorities.

In order to design direct enantioselective chromatographic systems one needs a chiral selector which is covalently or adsorptively bonded to a support surface (e.g. silica gel) or a chiral polymer gel. These stationary phases must have the ability to form physicochemically transient diastereomeric molecular complexes with the individual analyte enantiomers. The magnitude of the intermolecular interactions of chiral selector and analyte enantiomers will result in retention, and the spatial orientation of the chiral substituents in the diastereiomeric molecule complex will allow for enantioselectivity. The intermolecular binding and driving forces forming the "transition" complexes can be coulombic, dipole-dipole, charge transfer, hydrogen bonding, and or hydrophobic in character.

Based on this concept, over 100 specialized chiral stationary phases (CSPs) have been developed and are commercially available. An overview of the various types of these CSPs including the recent ones are presented.

PL-2

MASS SPECTROMETRY IN CLINICAL AND FORENSIC TOXICOLOGY

D. Fompeydie

University of Paris V, Faculty of Pharmacy, Department of Analytical Chemistry, 75270 Paris cedex 06 and Hospital Fernand Widal, Department of Biochemistry and Toxicology 75045 Paris cedex 10.

Since devices easy to use are available, GC-MS can be applied to screen drugs and toxic. It permits the unequivocal identification of drugs. Protocol for its use for illicit products is classical but in biological material, matrix and drug metabolism require special protocol:

* hydrolysis (acid, basic or enzymatic) to dissociate conjugates
* separation of the drug and its metabolites by extraction (liquid-liquid or liquid-solid)
* derivatization to convert polar groups into non polar derivative to improve chromatography and increase sensitivity.

The sample is then submitted to chromatographic separation and mass analysis.

The answer can be done by comparison of retention time and mass spectrum stored in library with reference standard.

Quantitative analysis using an internal standard can be made by SIM acquisition.
We present some results of analysis done in our laboratory .

SEQUENTIAL INJECTION EXTRACTION WITHOUT PHASE SEPARATION FOR SAMPLE PREPARATION AND DRUG ANALYSIS

Gary D. Christian

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Solvent extraction is a powerful technique for sample pretreatment for drug analysis. Analytes may be separated by classes of compounds to improve selectivity, separated from the sample matrix to eliminate matrix effects, or preconcentrated to improve sensitivity. Conventional solvent extraction is time consuming and labor intensive, and generates large amounts of solvent waste. We have combined the technique of sequential injection analysis (SIA) with a thin-film extraction method to perform automated sequential injection extraction (SIE). SIA is an intermittent flow technique in which microliter volumes sample zone and organic solvent zone are sequentially injected next to one another. The organic solvent plug deposits as a thin film on a Teflon tube as it is pushed by the aqueous sample plug, and the sample pushes through the solvent, causing the analyte to extract into the thin film. The flow is reversed and a second extraction step occurs. The process may be repeated with a fresh injected aqueous buffer zone to back extract the analyte. The analyte, in either the organic or aqueous phase, may be transported to a flow cell for direct measurement, or it may be collected for analysis by, e.g., chromatography. The SIE technique has been demonstrated for the extraction and back extraction of barbiturates (acid/neutral compounds) or seratonin reuptake inhibitors (basic compounds), as classes of compounds, for analysis by HPLC. SIE is demonstrated for direct photometric measurement of the extracted analyte, for the determination of molybdenum, vanadium (IV) and (V), and chromium (III) and (VI).

PHYSIOLOGICAL CHEMISTRY OF α, β ANOMERS AND ITS ALDEHYDE FORM OF D-GLUCOSE

Jun Okuda, Ichitomo Miwa

Faculty of Pharmacy, Meijo University, Nagoya 468, Japan

D-Glucose equilibrates among the α–, β–anomers and its aldehyde form in water. The authors first devised the enzymic determination of α– and β–anomers of D-glucose by using β–D-glucose oxidase and mutarotase. Then, the half life of the equilibrium was estimated to be only 2.3 min at 37℃ in blood. Concerning to anomeric preferences of D-glucose-metabolizing enzymes, it became clear that hexokinase types I, II, III prefer to phosphorylate β–D-glucose to D-glucose 6-phosphate, while glucokinase prefers α–D-glucose. Aldehyde form of D-glucose is specifically reduced to sorbitol by aldose reductase. In the study of immunohistochemistry of glucokinase and mutarotase, it is revealed that glucokinase exists in nuclei of rat liver at low glucose concentration and diffuses to cytoplasm at high glucose concentration. Glucokinase exists in cytoplasm of rat Langerhans islets. Mutarotase localizes in nuclei of rat kidney and liver. α–D-Glucose preferentially stimulates insulin secretion from Langerhans islets, compared with β–D-Glucose. β–D-Glucose suppresses afferent activity of hepatic vagus nerve filaments of the guinea pig, and decreases stomach motility in the rat.

PHARMACEUTICAL EDUCATION AND ACCREDITATION IN THE USA

Daniel A. Nona

American Council on Pharmaceutical Education, Chicago, IL 60610, USA

The objectives for this presentation are to trace the historical development of pharmaceutical education in the United States during this century and to discuss changes occurring and contemplated as we enter the 21st century. The perspective for this discussion will be the accreditation program of the American Council on Pharmaceutical Education, the agency for the accreditation of professional degree programs in pharmacy and providers of continuing pharmaceutical education. To develop this perspective, the background, value and purpose of accreditation are sketched, and the procedures and process for setting standards for accreditation are outlined. The progressive development of pharmaceutical education is related to major studies presenting the need for changes and their influence upon the adoption of accreditation standards and their subsequent implementation. A possible model for the establishment and administration of international educational and competence standards based upon adoption of the principles of accreditation is suggested.

CONTROL OF LIPOGENESIS

David M. Gibson

Department of Biochemistry and Molecular Biology, Indiana University School of Medicine, Indianapolis, Indiana, 46202-5122, USA

This review of the central themes in the control of lipogenesis in mammals emphasizes the maintenance of caloric homeostasis during the diurnal feed-fast cycle. Long-term regulation is executed principally by the hormones insulin and glucagon (during feeding and starvation respectively) by signalling induction and repression of a set of lipogenic enzymes catalyzing the synthesis of fatty acids and fat (triacylglycerol or TAG) from precursors that can form acetyl CoA. Short-term control mediated by insulin and glucagon affects the state of phosphorylation of a second (overlapping) set of enzymes through the action of protein kinases and protein phosphatases. In general, feeding and the accompanying release of insulin bring about the dephosphorylated mode of this enzyme set thereby promoting the flux of organic precursors into the major storage metabolic fuels: glycogen in liver and TAG in liver and adipose tissue. In progressive starvation, the phosphorylated enzyme mode is established causing the release of glucose from glycogen, lipolysis of TAG (release of free fatty acids) and gluconeogenesis from amino acids (in liver). The roles of cyclic AMP protein kinase and the recently characterized 5'AMP-activated protein kinase are discussed vis-à-vis protein phosphatases in mediating glucagon and insulin signalling, in particular, the key enzymes acetyl CoA carboxylase (fatty acid synthesis) and HMG CoA reductase (cholesterol synthesis). Newly described feedback controls of appetite and uncoupled metabolic fuel expenditure by adipose tissue further limit TAG accumulation.

ANTIBIOTIC RESISTANCE: A WORLDWIDE PROBLEM

H. Erdal Akalın

Pfizer Drug Inc., Ortakoy, Istanbul, Turkey

Since their discovery, antibiotics have proved to be effective for the control of many bacterial infectious diseases. However, it was soon evident that bacteria rapidly became resistant to antibiotics. For the first time since antibiotics were introduced about 50 years ago, antibiotic resistance has become a global problem of vast scope and complexity.

The variety of infections that demonstrate antibiotic resistance is striking, ranging from community-acquired pathogens such as Shigella spp., and *Haemophilus influenzae* to hospital-acquired infections due to *Staphylococcus aureus* and Enterobacter spp. The problem has appeared worldwide, both in developed and developing nations.

VANADIUM: A POTENTIAL THERAPEUTIC AGENT FOR DIABETES

J.H. McNeill and S. Verma

Faculty of Pharmaceutical Sciences, The University of British Columbia, Vancouver, B.C., CANADA V6T 1Z3

We demonstrated in 1985 that vanadium administered in the drinking water to streptozotocin (STZ) diabetic rats restored elevated blood glucose to normal. Subsequent studies have shown that vanadyl sulfate can lower elevated blood glucose, cholesterol and triglycerides in a variety of diabetic models including the STZ diabetic rat, the Zucker fatty rat and the Zucker diabetic fatty rat. Long-term studies of up to one year did not show toxicity in control or STZ rats administered vanadyl sulfate in doses that lowered elevated blood glucose. In the BB diabetic rat, a model of insulin-dependent diabetes, vanadyl sulfate lowered the insulin requirement by up to 75%. Vanadyl sulfate is effective orally when administered by either single dose or chronic doses. It is also effective by the intraperitoneal route. We have also been able to demonstrate marked long-term effects of vanadyl sulfate in diabetic animals following treatment and withdrawal of vanadyl sulfate. Because vanadyl sulfate is not well absorbed we have synthesized and tested a number of organic vanadium compounds. One of these, bis(maltolato)oxovanadium(IV) (BMOV), has shown promise as a therapeutic agent. BMOV is 2-3x more potent than vanadyl sulfate and has shown less toxicity. The mechanism of action of vanadium is currently under investigation. Several studies indicate that vanadium is a phosphatase inhibitor and vanadium can active serine/threonine kinases distal to the insulin receptor presumably by preventing dephosphorylation due to inhibition of phosphatases. Short-term clinical trials using inorganic vanadium compounds in diabetic patients have been promising.

MOLECULAR MECHANISMS OF INSULIN RESISTANCE. STRUCTURE AND SYNTHESIS OF A NOVEL INOSITOL-GLYCAN PSEUDO-DISACCHARIDE FROM BEEF LIVER WITH INSULIN-LIKE BIOACTIVITY *IN VITRO* AND *IN VIVO*.

J. Larner[1], G.S. Rule[2], J.D. Price[1], T. Piccariello[1], S. Abe[1], M. Sleevi[3], G. Allan[3] and L.C. Huang[1]

[1]Department of Pharmacology, University of Virginia School of Medicine, Charlottesville, Virginia 22908. [2]Department of Biochemistry, University of Virginia School of Medicine, Charlottesville, Virginia 22908. [3]Insmed Pharmaceuticals, Inc., Richmond, Virginia 23219.

We isolated a putative insulin mediator or mimetic from beef liver by methods scaled up from rat liver where we had identified D-chiro-inositol and galactosamine as components. Structure was determined by degradative chemistry and 1 and 2 D NMR as a pseudo-disaccharide of pinitol (3-0-methyl D-chiro-inositol) and galactosamine chelated to a metal likely manganese. When infused, it effectively decreases hyperglycemia in diabetic rats to euglycemia in 60 min equally to a comparable dose of insulin without producing hypoglycemia. Two members of a family of Mg^{++} requiring phosphatases PDH and 2C are activated by left shifting the Mg^{++} dose response. Thus, two rate-limiting enzymes of non-oxidative and oxidative glucose disposal are activated by dephosphorylation, glycogen synthase and PDH. A decrease of chiro-inositol in urine and tissues in type II diabetic subjects and 1st degree relatives as well as in monkeys correlates with the degree of insulin resistance.

STUDIES ON NATURALLY OCCURRING SUBSTANCES FOR INHIBITORS OF GLYCOSIDASES

Genjiro Kusana

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Inhibition of glycosidases has been of a number of potential therapeutic uses, including the treatment of cancer, diabetes and AIDS. We have attributed primarily to screening of the inhibitory activities with hot water extracts of plants and crude drugs to α-glucosidase (α-glu). After the isolation and the structural elucidation of the principles, we have bioassayed secondarily the inhibitory activities to other glycosidases such as β-glucosidase (β-glu), (α/β-man). Several examples of new active substances are as follows: broussonetinine **A** (IC_{50}, 16 nM to β-gal), 0.3 μM to α-man), **B** (11 nM to β-gal, 0.29 μM to α-man), broussonetinine **C** (36 nM to β-gal, 0.32 μM to β-man), **D** (29 nM to β-gal, 0.34 nM to β-man, **E** (3.3 μM to α-glu), 55 nM to β-glu), 2 nM to β-gal, 23 nM to β-man), **F** (1.5 μM to α-glu, 10 nM to β-glu, 4 nM to β-gal, 28 nM to β-man), others isolated from Broussonetia kazinoki and B. papyrifera (Moraceae). Other new substances from several plants will be also reported.

MEANING OF GENERALLY EXISTING NATURAL COMPOUNDS

Yukio Ogihara, Makoto Inoue and Mitsuhiko Nose

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Kampo medicine, a boiling water extract of several kinds of herbal medicines, has been widely used for clinical treatments in Japan. This medicine was created in China and brougth to Japan via Korean peninsula at 5th Century and has followed an independent course of development in Japan. But, a scientific knowledge of Kampo medicine is still lacking, so this precious properties is slighted by modern doctors.

Last twenty years, we have investigated the Kampo medicine chemically and pharmacologically to change this situation. In this report, I will discuss on the chemical properties of Kampo medicine, especially focused on generally existing compounds such as polysaccarides and gallic acid.

QUALITY CONTROL AND STANDARDIZATION OF PHYTOPHARMACA

Otto Sticher
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The interest in complementary therapies has considerably increased in the last decade. Among them, phytotherapy plays an important role and phytomedicines make a remarkable contribution to the total pharmaceutical market. Preparations based on garlic, ginkgo, ginseng, and hawthorn are leading phytomedicines in various countries of central Europe. In Germany, the market share of phytomedicines is about 6%. Phytomedicines are well-established in the OTC market and they are often prescribed by general practitioners. As a consequence, they must comply with the same requirements as all other drugs; that is to say their effectiveness, safety and pharmaceutical quality have to be demonstrated and documented. Unlike synthetic drugs, plant-derived preparations represent multicomponent drugs which make great demands on the analyst. In the case of garlic, ginkgo, and hawthorn, quality control is especially demanding because the constituents are complex in chemical structure, number, and in the special case of garlic, also concerning stability. This presentation deals with some general aspects of quality requirements as well as with analytical methods related to research topics covered by our work. The quality of phytomedicines as well as that of the crude plant material used for the production of extracts has to be guaranteed, because lack of quality can lead to under- and overdosage or to side effects due to contaminations, impurities, or falsifications. Quality control of phytomedicines comprises the following three subjects:

- clear botanical identification of the plant material used
- proof of absence or of contents below official limiting values of undesired toxic components and toxicologically significant impurities such as heavy metals, pesticides, radioactivity, bacteria, or fungi
- quantitative determination of active components or lead compounds

In addition, a demand for validation and control of all steps of the production process are indispensable in order to guarantee a high quality of the resulting products. It has to be demonstrated that new analytical methods meet the requirements of internationally accepted quality control guidelines. The great variability of composition and concentrations of compounds in plant material, caused by different plant species, different climate, light and soil conditions, harvesting of different parts of the plant or at different stages of development, or by different drying and storage methods, have to be taken into consideration. Different industrial processing leads to further alterations of the final products. As a consequence, standardization of the plant material, in-process controls and final product controls are essential, and a clear and detailed declaration of the product is necessary. Standardization makes possible the production of a homogenous preparation from heterogenous starting material. Since it ensures a steady content within a given range, it plays an important role for reproducibility of therapeutic effectiveness from batch to batch. The concentration of compounds in a standardized extract is fixed by official monographs or by the manufacturers themselves; therefore, standardization of plants with known active compounds is not problematic. For plants of which the active principles are not yet known or plants containing constituents with low stability, such as garlic, standardization is made on lead compounds, but this is only a temporary solution.

Sulfur containing L-cysteine derivatives have been reported to be characteristic, genuine constituents of various Allium species. The S-alk(en)yl-L-cysteine sulfoxides, especially (+)-S-allyl-L-cysteine sulfoxide (alliin), are precursors of a variety of more lipophilic products derived from enzymatic conversion, e.g. alliin to allicin by the alliinase after cell rupture and further transformation to ajoenes, vinyldithiins or sulfides. Most of the previous chromatographic analyses tended to concentrate on the latter compounds because they are considered to be associated with the biological activity of garlic. In this case, the genuine cysteine sulfoxides and probably also the g-glutamyl peptides act as prodrugs. The quantitation of these genuine compounds for the quality control is reasonable. Depending on the processing technique, various pharmaceutical products such as garlic powders, dry extracts, oil-macerates, or steam distillates arise. Their constituents represent the lipophilic conversion products mentioned above which complicate or even disable a rational quality control.

Other plants, such as ginkgo or hawthorn can raise problems since in both plants, two groups of constituents, namely flavonoids and terpene lactones or procyanidins, respectively, are considered to be the active principles. Therefore, it has to be decided on which group of components the extract shall be standardized. Standardization on different compounds can make a comparison of different products difficult or even impossible. Nevertheless, standardization is nowadays done on flavonoids and terpene lactones, such as in lthe case of ginkgo. With this approach the number and the variety of chemical structures are the limiting factor. HPLC methods requiring hydrolysis of the flavonoid glycosides have been, therefore, elaborated. This hydrolysis step is necessary due to the great number of flavonoid glycosides found in these plants. As a result we can propose simple and reproducible methods which allow us to quantify the corresponding aglycones. In the case of ginkgo extracts the main aglycones kaempferol, quercetin and isorhamnetin are determined; in the case of hawthorn extracts, quercetin and vitexin are determinded. For the quantification of the terpene lactones in ginkgo, HPLC and GC methods are available while the assay of procyanidins in hawthorn remains still an unresolved problem.

COMPLEX TETRA AND PENTACYCLIC COUMARIN DERIVATIVES FROM THE GENUS *ERIOSTEMON* (RUTACEAE)

Peter G. Waterman, Mohammad A. Rashid and Satyajit D. Sarker

Phytochemistry Research Laboratories, Department of Pharmaceutical Sciences, University of Strathclyde, Glasgow G1 1XW, Scotland, U.K.

A phytochemical investigation of the west Australian species *Eriostemon brucei* (Rutaceae) yielded 15 complex coumarins based on a 6-(or 8)-C-geranyl-5,7-dihydroxycoumarin precursor. Four of these compounds were confirmed as the previously reported bruceol, deoxybruceol, eriobrucinol and hydroxyeriobrucinol. Among the 11 novel compounds were 6, named the protobruceols, which probably represent an intermediate (tricyclic) state in the formation of the more complex coumarins. Of the remaining 5, two were regioisomers of eriobrucinol and another an isomer of hydroxyeriobrucinol. The final two compounds, named the pseudobruceols, represent new cyclisation patterns for the geranyl side-chain. Critical factors in the identification of these compounds are discussed. Subsequent studies on an east Australian species, Eriostemon myoporoides revealed a series of 7 further coumarins of this class based on a 2'-deoxybruceol skeleton and formed from a 6-C-farnesyl-5,7-dihydroxycoumarin precursor. At this point these compounds and unique to these two species.

THE QUANTIFICATION OF STERIC EFFECTS IN QSAR BY THE SEGMENTAL METHOD

Marvin Charton

Chemistry Department, School of Liberal Arts and Sciences, Pratt Institute, Brooklyn, NY 11205, USA.

The segmental method of quantifying steric effects has been previously applied to the determination of quantitative structure property relationships (QSPR) for chemical reactivities (rate and equilibrium constants), partition coefficients, cohesive energy densities, and chromatographic properties. It is here applied to bioactivities ranging from enzyme kinetic quantities to insect tissues and spinach chloroplasts. The mehod determines the locus of the steric effects in a substituent.

ASYMMETRIC SYNTHESIS OF CARBOHYDRATES

John M. Gardiner and Martin Penny

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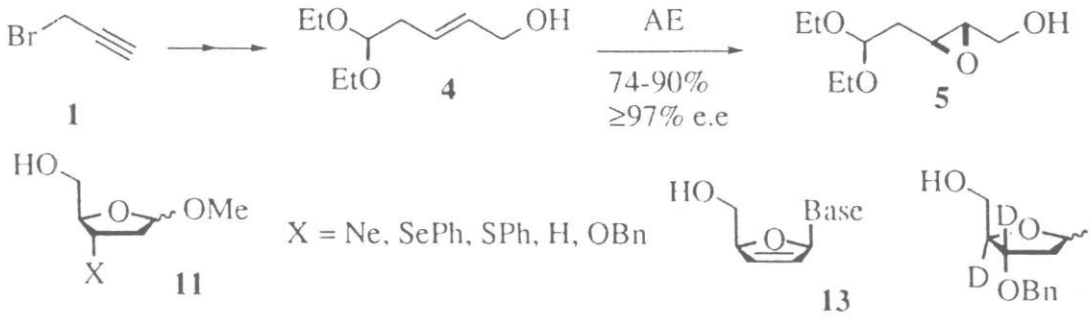
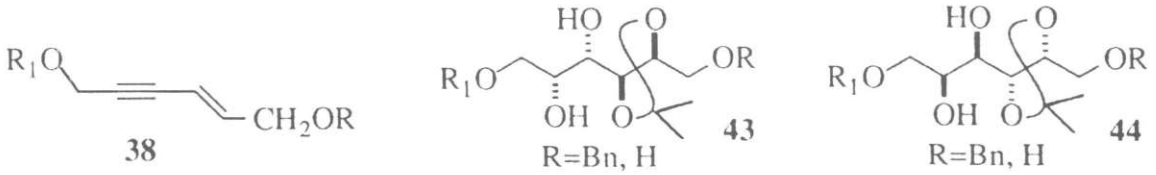
We have been developing practicable methods for the asymmetric synthesis of C5 and C6 sugars. These methodologies are applicable to introduction of stable (NMR) labels to ultimately provide new labelled nucleosides and monosaccharides for NMR conformational and dynamic studies of biological interactions of oligonucleotides and oligosaccharides.



We have developed *de novo* asymmetric routes to 2-deoxyfuranosides **11** (as precursors to nucleosides and modified nucleosides) as well as d4 systems **13**, using methodology which can allow for introduction of specific deuterium (e.g. **14**) and ^{13}C labels. We have also recently developed a *de novo* asymmetric method for the synthesis of six-carbon sugars. Specifically, an enantioversatile route to D- and to L-galactal (protected as **43** and **44**), precursors to both D-galactose and L-fucose, by a *de novo* synthesis, using ethylbromoacetate (and its derived Wittig reagent), methylene Wittig, and DMF or paraformaldehyde, as sole carbon sources, *via* eneynes of type **38**. The route is thus completely versatile with respect to introduction of any number and combination of ^{13}C labels, since all these materials are commercially available labelled. Synthesis of an advanced intermediate di-^{13}C labelled is demonstrated. Additionally, the chemistry developed is designed to also allow for flexible introduction of regiospecific ^{2}H labels. Our methodology should now allow for the targeted synthesis of specific ^{13}C labelled monosaccharides for inclusion in target oligosaccharides, which will be useful for developing NMR techniques in the study of biologically important/therapeutically relevant carbohydrate-protein complexes.



NEW PERSPECTIVES FOR THE TREATMENT OF HIV INFECTION (AIDS)

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The recent launching of several new inhibitors of Human Immunodeficiency Virus (HIV) targeted at the HIV reverse transcriptase (RT) or HIV protease has led to the design of two-, three- or even four-drug combination trials. Initial evaluations have revealed marked reductions of viral load in patients receiving a triple combination of two nucleoside RT inhibitors with either a non-nucleoside RT inhibitor or protease inhibitor. However, whether the long-lasting suppression of viral replication will ultimately result in clinical improvement and prolonged survival, remains to be resolved. Namely, it is presently unclear whether multidrug-resistant HIV mutants will emerge after prolonged combination therapy. Cell culture studies should be useful to guide clinicians in choosing the optimal drug combinations. Also, inhibitors that are targeted at virus adsorption or fusion, or HIV integrase, have not yet been explored in clinical practice. Drug development is often complicated by a number of pharmaceutical drawbacks, namely: oral bioavailability, drug interactions, ease or cost of chemical synthesis, and convenience (and compliance) of the drug treatment regimens. It is concluded that all possible modalities to improve existing HIV therapies should be explored.

DESIGN AND SYNTHESIS OF TRICYCLIC NUCLEOSIDES (DIMENSIONAL PROBES) AS ANALOGS OF CERTAIN ANTIVIRAL POLYHALOGENATED BENZIMIDAZOLE NUCLEOSIDES.

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Structure activity relationship studies involving nucleosides that are structurally related to 2,5,6-trichloro-1-(b-D-ribofuranosyl)benzimidazole are presented. The relationship between these studies and the rationale for the design and synthesis of naptho[2,3-*d*]imidazole nucleosides are also presented. Several retro-synthesis of the requisite heterocyclic compounds as well as the corresponding nucleosides are described. Studies involved in the assignment of regiochemistry as well as stereochemistry is presented for all of the target (2-chloro, 2-benzylthio, 2-hydrogen) naptho[2,3-*d*]imidazole nucleosides. All of the target nucleosides have been evaluated for their anti-viral activity against human cytomegalovirus and toxicity against human foreskin fibroblasts cells.

IN VITRO TESTING PROCEDURES FOR LOCALLY APPLIED/LOCALLY ACTING PRODUCTS - SUBSTITUTE FOR BIOAVAILABILITY/BIOEQUIVALENCE STUDIES?

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Locally applied/locally acting products are products that are applied locally and are intended to have their effect at the application site. Any systemic action is an undesired reaction. The active ingredient(s) of locally applied/locally acting products penetrate(s) the skin after release from the formulation and cause(s) a pharmaceutical response.

The efficacy and/or safety of these products depends on the active ingredient(s) *and* the excipient(s). Every change in the components and composition could alter the extent of the penetration of the drug substance.

The regulatory requirements are defined in the "note for guidance on clinical requirements for locally applied, locally acting products containing known constituents" and in the draft of the SUPAC-SS Guidance. In vitro release tests in the pharmacopoeias are performed for tablets, vaginal preparations, rectal preparations and transdermal patches.

For locally applied/locally acting products no detectable blood levels are expected. Therefore, the performance of in vitro tests leads to results that cannot predict bioavailability or bioequivalence.

With sufficient characterization of the test performance of the in vitro testing procedure for locally applied/locally acting products, these tests can be used for batch release purposes. Changes with regard to the SUPAC-SS Guidance can be monitored.

REGULATORY REQUIREMENTS OF NOVEL DOSAGE FORMS

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In today's health care environment there is an increasing need to develop, register and market drugs with more advanced delivery systems and packaging 1, 2. For the registration of novel dosage forms a number of dedicated guidelines have been published in the areas of chemistry/pharmacy, toxicology, clinic, and pharmaco-economy. In this overview emphasis has been placed on those guidelines referring to in-vitro drug release and on the establishment of in-vivo/in-vitro correlations, on the toxicological consequences of the use of non-established excipients, and on the biopharmaceutical and therapeutical validation of extended-release preparations for well-known drug substances. The EC suplementary guideline "Clinical testing of prolonged action forms with special reference to extended-release-forms" of July 1990 [3], defines the studies to be conducted in man, which are specific to new extended-release forms containing recognised active and safe drug substances so as to ensure a more prolonged action than the conventional pharmaceutical already marketed. Finally pharmaco-economical guidelines are considered, since the often higher price for the new delivery systems should be justified. Controlled-release systems can add economic value to drugs by simplifying drug regimens and by controlling the rate of drug input. Programmed or pulsatile drug release taking into account the body's day/night rhythm may be more advantageous for the patient. Targeted release directing drugs to the diseased organs or sites, thereby avoiding as much as possible other places, may lower safety problems and enhance the effectiveness of the treatment. Countries that have developed Health Economic guidelines are Australia, Canada, Italy, Spain, the United Kingdom and the United States [4].

[1] A.P. Sam., J.G. Fokkens, The expanding role of drug delivery systems in modern health care. In: Innovations in Drug Delivery, Impact on Pharmacotherapy, eds. A.P. Sam, J.G. Fokkens, Anselmus Foundation, 2nd edition, 1996.

[2] A.P. Sam., J.G. Fokkens., The drug delivery system, a key factor in adding therapeutic and economic value to pharmacotherapy. I and II. Pharmaceutical Technology Europe, Voleme 8 (May, June, 1997).

[3] Clinical testing of prolonged action forms with special reference to extended-release dosage forms, Addendum (July 1990) to: The rules governing medicinal products in the European Community, Vol. III.

[4] L.A. Gensudo, J.G. Kotsanos, Review of health economic guidelines in the form of regulations, principles, policies, and positions, Drug Information Journal 30, 1003-1016 (1996).

MODERN TABLET EXCIPIENTS: PRESENT STATUS AND TRENDS

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Besides the active principle a tablet formulation for direct compression normally contains a filler, a binder, a disintegrant, a glidant and a lubricant. During the last two decades materials were developed having filler/binder and e. g. disintegrating properties facilitating the development and production of tablets.

Three different materials, Ludipress®, consisting of α-lactose monohydrate 93 %, soluble povidone 3.5 % and crosslinked povidone 3.5 %, Avicel PH 200®, a granulated microcrystalline cellulose and Cellactose®, a combination of α-lactose monohydrate 75 % and powdered cellulose 25 %, were characterized by their powder properties and investigated for their compression behaviour alone and in combination with ascorbic acid as an example for a high dosed and highly water soluble drug and paracetamol as a high dosed and sparingly water soluble one. The three multi purpose excipients showed similar compressional pressure/hardness profiles but while the disintegration times of Ludipress® and Avicel PH 200® tablets were low and nearly independent over a compressional pressure range from 50 to 250 MPa, Cellactose® exhibited a tremendous increase in disintegration time above 100 MPa.

In direct compression the main problem with low dosed drugs is the content uniformity. By the formation of interactive mixtures using glibenclamide as a model drug it was shown that the coefficient of variation of glibenclamide content of the tablets was in the range of 1 % indicating excellent content uniformity. Differences were found in the dissolution behaviour of Ludipress® and Cellactose®·corresponding to the disintegration behaviour of the tablets.

THE ROLE OF THE HEME OXYGENASE SYSTEM IN THE MOLECULAR DYNAMICS OF MAMMALIAN GASEOUS MONOXIDE CELL SIGNALING

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The heme molecule plays a pivotal role in generation and function of the gaseous heme ligands, carbon monoxide (CO) and nitric oxide (NO) which are now recognized as important cell signals in a variety of organ systems. In turn, the heme oxygenase [HO] system [EC 1.14.99.3] which catalyzes oxidation of heme to produce CO plays a central role in CO-based cell signaling, as well as regulation of the hemeoproteins, nitric oxide synthase and soluble guanylate cyclase. The microsomal HO system consists of two forms identified to date: the oxidative stress-inducible protein HO-1 [HSP32] and the constitutive isozyme HO-2. These proteins differ in tissue distribution, primary structure, and regulation. This review highlights the current information on molecular and biochemical properties of HO-1 and HO-2 and their potential role(s) in the molecular dynamics of gaseous second messengers.

THE EMERGENCE OF PHARMACOEPIDEMIOLOGY AS A DISCIPLINE

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Pharmacoepidemiology is a hybrid scientific discipline drawing upon the foundations of both pharmacology, the study of drugs; and epidemiology, the study of disease. These disciplines have been closely aligned since the first part of this century, when many pharmaceutical products emerged, and the occurrence and causation of many diseases was fully explored. The importance of a complete analysis of the outcomes of drug therapy, either positive or negative, has become a global and crucial concern as more and more drugs with a narrow therapeutic window have entered the international marketplace. Just as a new therapeutic agents must have a complete chemical, pharmacological, pharmacokinetic, and clinical profile before market entry; so must a complete examination of the outcomes (clinical, economic, humanistic) of the product after market entry proceed. In addition, drugs of abuse or social drugs (alcohol, tobacco, etc.) can be examined from a pharmacoepidemiologic standpoint so as to assess the negative effects of continued use. Pharmacoepidemiology encompasses the reviewal of clinical trials, case control studies, cohort studies, voluntary adverse drug reaction and adverse drug effects, and postmarketing assessments. Pharmacoepidemiology holds great promise and potential to further aid in the assessment of outcomes of pharmacotherapeutic treatments. In order to reach its full potential, pharmacoepidemiology must assume a global, transcontinental focus which encompasses ready and facile communication across disciplines, linked databases; and provide for an enhanced communication of research findings.

FORMATION OF HETEROCYCLES IN THE MASS SPECTROMETER

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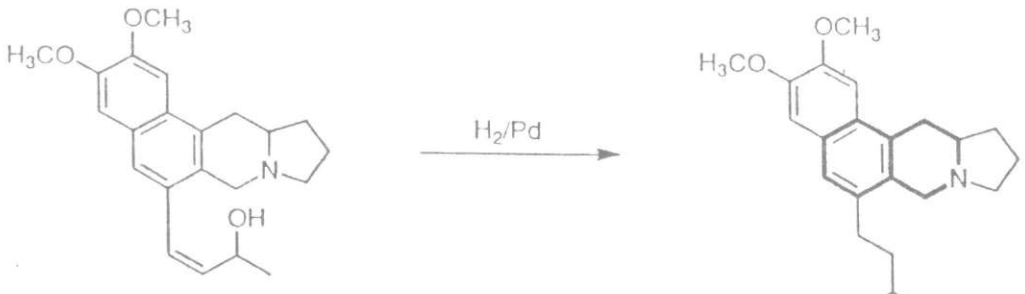
It was misleading situation which stood at the beginning of our research on the formation of heterocycles in the mass spectrometer (Fig. 1). We had found traces of a naphthoindolizidine alkaloid in the asclepiadaceae plany cynanchum vincetoxicum, which shows a cis-configurated double bond in its ^{1}H-NMR spectrum. Hydrogenation afforded a dihydro derivatives which loses a four C-unit from the side chain, seemingly pointing towards benzylic of a C_4-side chain. This interpretation, however, was wrong. The combination of all the spectroscopic data showed that the complete side chain had bee lost - against the fragmentation rules of mass spectrometry which "prohibit" a C-C cleavage at an aromatic C-atom, characterized by sp^2 hybridization.



Vincetene

Fig. 1

TRADITIONAL FOLK MEDICINES & NATURAL RESOURCES FOR ADULT-DISEASE PREVENTION

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Prevention of disease in adults is now the most urgent public health problem. In Japan, the death rate from heart failure and brain failure have decrease, however, the death rate from cancer has increased year by year. It has become apparent that environmental factors play an important role both in causing and in preventing adult diseases such as human cancer and diabetes, which is assocaiated with a variety of vascular complications such as cataracts, neuropathy and retinopathy.

Now, we are surveying ways to evaluate the prevention on Bovine Lens Aldose Reductase inhibitory activity, hematological activity and antitumor-promoting activity in vitro and in vivo systems for two-stage mouse lung, skin and colon carcinogenesis using under the materials;

I. Umbelliferous plants and isolated coumarin, flavonoid and etc.
  I-1 Crude drugs in China and in Japan
    Qian-Hu: Peucedanum praeruptorum, P. decursivum
    Angelicae Radix: Angelica acutiloba var. sugiyamae
  I-2 Edible plant in Japan
    Water dropwort (Seri in Japanese)
    Ashita-Ba in Japanese: Angelica keiskei
  I-3 Traditional folk medicine in Egypt and in Turkey
    Ferula elaeactytis; Ferulago trachycarpa; Frangos platychaena

II. Species and Allium genus as edible plant and crude drug and isolated chalcone, saponin and etc.
  II-1 Spices
  II-2 Xiebai: the bulbs of Allium chinense

These materials suggest that not only coumarins, but also natural chalcones may play an important role in cancer chemoprevention.

METABOLISM OF ANANDAMIDE, AN ENDOGENOUS LIGAND FOR CANNABINOID RECEPTORS

Natsuo Ueda[1], Kazuhisa Katayama[2], Yuko Kurahashi[1], Mitsujiro Suzuki[1], Hiroshi Suzuki[1], Shozo Yamamoto1, and Itsuo Kato[2]

Departments of [1] Biochemistry and [2] Cardiovascular Surgery, Tokushima University, School of Medicine, Tokushima 770, Japan

Anandamide (arachidonylethanolamide) is an endogenous ligand for cannabinoid receptors, and its biological activities are lost by its enzymatic hydrolysis to arachidonic acid and ethanolamine. We partially purified "anandamide amidohydrolase" from the microsomes of porcine brain to a specific activity of 0.37 mmol/min/mg protein by hydrophobic chromatography. The enzyme preparation catalyzed not only the hydrolysis of anandamide but also its synthesis by the reverse reaction. Several lines of enzymological evidence suggested that the two reactions were catalyzed by a single enzyme protein. This finding was confirmed with a recombinant enzyme transiently expressed in COS-7 cells by the use of the recently cloned cDNA for the rat enzyme hydrolyzing oleamide. We also examined the tissue distribution of the enzyme in rat. Liver showed by far the highest activities of anandamide synthase and hydrolase. We noted that the hydrolase activity was much lower than the synthase activity in small intestine. However, the low activity was attributable to inhibition by endogenous lipids, and after removal of lipids by acetone extraction the hydrolase activity in small intestine was as high as the synthase activity. Furthermore, by Northern blot analysis an intense band of the anandamide amidohydrolase mRNA was detected in small intestine and stomach as well as liver. These results demonstrated the presence of a considerable amount of the enzyme in small intestine.

BIOSENSORS: NEW TOOLS FOR PHARMACOLOGICAL AND DRUG ANALYSIS

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Biosensors are analytical devices which combine, in close connection, a physical transducer and a biological element. Typical physical transducers are electrodes (Pt,Au,C,Glass...), optical fibres, piezoelectric elements, thermistors ... and the biological elements are proteins (enzymes, antibodies, peptides ...), nucleic acids (DNA ..), bacteria, tissues and lipids from cell membranes.

The unique design of biosensors allows application in wider domains than the classical analytical techniques. Similarly to the latter, biosensors may be used in clinical laboratories for the analysis of physiological parameters such as glucose, lactate, creatine, urea, uric acid... with however the advantage of requiring a minimum sample treatment. This is offered thanks to the elaborated sensing tip of the biosensor which combines, in addition to the biological layer, one or two membranes which protect the biosensor from fouling and which, relatively selectively, extract the analyte of interest from its complex environment. Ideal biosensors are reagentless and smart because auto-calibrated. Over classical analytical methods, biosensors offer improvements in rapidity of the analysis allowing on-site control and quantification of vital parameters such as in hospital emergency situations (surgery, drug intoxication, addiction...).

Thanks to the immobilized biological elements, biosensors can be advantageously applied in drug toxicity/activity test screening. Some biosensors may be applied as detection systems combined to separation techniques (HPLC). Currently efforts are dealing with the development of DNA based sensors for the detection of DNA damage or for the sequence-specific hybridization detection of various viral or bacterial DNA (e.g., HIV-1,TB) and for drug - DNA interaction studies.

Immunosensors are available for on-line monitoring of antigen-antibody reactions and are especially useful in affinity studies and screening of antibodies. New efforts, at a molecular level, are oriented towards the reconstitution of the biological element natural environment at the sensing tip for improved stability and optimum activity/affinity.

PLANT IMMUNOSTIMULANTS

Recent Results

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Our screening program which has spanned more than 10 years with a battery of *in vitro*- and *in vivo* systems has revealed a great number of potential low- and high molecular compounds from plants with immunostimulating activity (alcaloids, terpenoids, quinones, polysacchar-ides). Of these, the macrocyclic **bryostatins** from the marine organism *Budula neritina*, the **polysaccharides** of *Echinacea purpurea* cell cultures and **lectins** from *Urtica dioica* root and *Viscum album* (mistletoe) respectively occupy the first place. The bryostatins showed a maximal stimulating effect of the phagocytosis and lymphocyte proliferation in a conc. range of 1 µM to 10 µM (*in vitro*) and 50 - 100 g (*in vivo*). At the same time they can mimic many effects of the multipotential recombinant human granulocyte-macrophage colony stimulating factor (HGM-CSF), but lack complete tumor promoting potential. The novel observation that bryostatins and many other naturally occuring and also synthetic antitumoral agents (e.g., vincristin, plumbagin, podophyllotoxin, Taxol) - which are known for their cytotoxic or immunosuppressive activity at high doses - show a reversal immunostimulating effect at very low doses, opens a new therapeutic concept for cancer treatment. Bryostatins show also a dose dependent modulating effect on the release of arachidonic metabolites from neutrophils (PMNL) suggesting at least in part an antitumor promoting effect. As the complement act-ivating potential of low molecular weight compounds is concerned, beside rosmarinic acid and a few flavonol-acyl-glycosides as well as some triterpenoid acids (*i.e.* boswellic acid) were found to inhibit the classical way of the complement cascade. An acidic **arabino-glactan** from the tissue culture of *Echinacea purpurea* was found to stimulate macrophages *in vitro* and *in vivo* to produce TNF-α, IL1, interferone-β_2 , and oxygen radicals. The same *Echinacea* polysaccharide, administered prophylactically to mice, is able to give 60 - 100% protection to lethal *Leishmania enriettii* and *Candida albicans* infections and is now considered for clinical trials. The N-acetylglucosamine specific lectin of *Urtica dioica* (m.w. 9500 D) binds to EGF-receptors of prostate cells and blocks cell proliferation, whereas the galactoside specific mistletoe lectin of *Viscum album* is able to activate tumorcidal effector mechanisms such as TNF, Nk-cells, apoptosis.

DEEVELOPMENT OF A CLINICAL PHARMACY CURRICULUM: ITS INTEGRATION WITH PHARMACEUTICAL SCIENCES

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The University of Tennessee College of Pharmacy is rated as one of the top 7 colleges of pharmacy in the United States. This is due to its educational, research and service programs. Clinical pharmacy education has been a major focus of the pharmacy program at Tennessee since 1969. The success of the Tennessee educational program can be traced to the relationships that exist between the pharmaceutical, medical and clinical sciences. Clinical pharmacists must possess a strong background in the basic medical sciences of anatomy, physiology, pathology, immunology, microbiology and biochemistry as well as a sound background in general and organic chemistry. These serve as the building blocks for the pharmacutical sciences. For a clinical pharmacist to be succesful, they must have a firm background in the pharmaceutical and medical basic sciences. Clinical education must likewise be integrated into the total curriculum and not added on the end. Clinical skills development must begin early in the cirriculum and can enhance the student's understanding of the relevance of the basic sciences. This presentation will focus on the curriculum at Tennessee and how the integration of the clinical and pharmaceutical sciences have strenght the educational programs of the college. One result has been the development of a Pharm. D./Ph. D. program which has attracted pharmacists into the pharmaceutical sciences graduate program. Another result of this integration has been collaborative research between the clinical and basic sciences.

PL-29

A LOGICAL APPROACH FOR STRUCTURE ELUCIDATION OF NEW NATURAL PRODUCTS

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In continuation of our interest on the bioactive principles from the medicinal plants of Pakistan, Turkey, Jordan and Mongolia, we have so far isolated over 200 novel and new compounds and elucidated their structures. In the process, we have developed a logical protocol for structyre elucidation of novel and new natural products. The protocol allows a rapid structure determination with no chances of incorrect structure. The isolation and chemical structures of new triterpenoids, steroidal lactones, lignans, counmarins and steroidal and indole alkaloids found in plants (Withania somnifera, Delphinium denudatum, Murraya paniculata, Podophyllum emodi, Veratrum album, Fritillaria imperialis, Rhazya stricta, etc.) and their biological activity (cytotoxic, anifungal, antibacterial nematicidal, anti-cholinergic, hypotensive, etc.) will be discussed. Recent structural studies on new bioactive marine natural products will also be presented. Modern NMR, Mass and X-ray diffraction have been employed to elucidate the structures of the complex organic molecules isolated.

IMPROVING PHARMACISTS INFORMATION ON GENERAL ASPECTS OF COSMETICS AND PERSONAL CARE PRODUCTS AND CONSUMER COUNSELING MATTERS

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In the Colleges of Pharmacy in the USA, the Pharmaceutical Education is continuously being modified according to the changing needs of immediate health, and political environments. During the last decade, the emerging new subjects were emphasized and replaced several topics from the Pharmacy Curricula which were traditionally taught to the pharmacy students around the world. Cosmetics and some dermatologicals were among them. Presently, very few pharmacy students are interested in taking the cosmetic courses as electives. Meanwhile, the chemistry, biology, and chemical engineering departments are emphasizing their teaching and research activities on cosmetics and health care products related topics and, their students are encouraged to take cosmetic courses at undergraduate level. In Europe, a few pharmacy colleges in Italy and France and all Pharmacy Colleges in Turkey offer cosmetic courses at undergraduate and graduate levels as compulsory and elective courses.

In the USA, the public with low and middle-level income, purchase the inexpensive but functional brands of cosmetics and self-care products mainly from the pharmacies and the supermarkets. Some of the products that are classified as cosmetics in the European Union (EU), which include antiperspirants, hair dyes, antidandruff and shaving preparations, certain products for mouth and tooth care, sunscreen and suntan products and products for skin blanching, are classified as Over the Counter (OTC) drugs. Although, cosmetics are not taught among compulsory courses, the cosmetics that are classified under OTC drugs are offered as at least 3 credits. Therefore, the American Pharmacy Students are expected to be familiar with related products in the market, their function, use and side effects caused by them. However, the preliminary research carried out by the students who took cosmetic courses as electives indicated that, in addition to the OTC course, cosmetic courses improved their understanding toward the functions, physiology and biochemistry of skin, hair and nails and improved their comprehension of appropriate use of dermatologicals and cosmetics. They felt more competent in advising to the consumer in a cosmetic or dermatological related matter. According to the consumers, the pharmacists knowledge prevailed in medication field, not necessarily in the cosmetics. The dermatologists, via telephone interviews, indicated that they would prefer advising to the patient about cosmetics and matters related to the dermatologicals themselves.

Compared to the vital drug-related matters that they are expected to manage, the pharmacists should not lose their share in the field of cosmetics and dermatologicals neither should they reflect disinterested or incompetent attitude toward cosmetics related inquiries coming from the consumer. If they loose their competency in the eye of the public and the dermatologists, it would be very difficult to regain their trust in a field which is within the pharmacists specialization since the days of Galenus.

THE HISTAMINE H_3 RECEPTOR, MOLECULAR PHARMACOLOGY, SELECTIVE LIGANDS AND PERSPECTIVES FOR THERAPY

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Histamine receptors have since long been the target for drugs. The Histamine H_1 blockers are effective anti-allergics and the H_2 antagonists are very successful medicaments against gastric ulcers.

It took long before the important role of histamine in the Central Nervous System was accepted. Currently, the H_3 receptor constitutes an interesting target for new medicins.

The H_3 receptor is a presynaptic one, occurring both as an auto- and as a heteroreceptor, thereby controling the homeostasis of several neurotransmittors. Several selective ligands have been found, both H_3 agonists and antagonists.

In this lecture the role of the H_3 system will be briefly reviewed. Several classes of selective ligands will be discussed. Finally, the perspectives for therapeutic uses will be introduced; most emphasis will be on CNS applications, as it has been found that in degenerative diseases (Alzheimer), but also in Schizophrenia, normal histamine patterns are disturbed.

ORAL PRESENTATIONS

ANTIVIRAL ACTIVITIES OF MEDICINAL PLANTS: HOW DO WE EXPLAIN THEM?

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In our studies on medicinal plants from various parts of the world, we have found numerous phytochemicals that possess impressive bioactivities against several animal viruses (Adirect@ antiviral activities). These chemicals include a range of structurally distinct compounds such as alkaloids, polyynes, sulfur-containing heterocycles, furyl derivatives and complex quinones. Many of them are also photosensitizers, and in these cases their antiviral activities are dependent upon, or augmented by, the appropriate wavelength of light. This requirement for light may explain the importance of sunlight in certain traditional applications of such plant materials.

Because of the many types of phytochemicals that possess antiviral activity, and the frequent requirement for light, we have found it necessary to modify and expand our test procedures so as to permit detection of compounds with many different properties, and to accommodate distinct modes of action of an antiviral phytochemical, since the activity could result from virucidal action (direct killing of the virus particles) or from an interference in virus replication, or both. In addition to these phytochemicals with Adirect@ antiviral activities, beneficial effects of extracts may also be due to compounds - or combination of compounds - with Aindirect@ antiviral activities, such as immuno-modulators.

Virologists and microbiologists have recently characterised various human defence mechanisms that counteract infectious disease through a network of immuno-modulatory cytokines, as well as other physiologically important molecules. We now know that many viruses and microbes can cause disease by perturbing this cytokine network and thus give rise to an imbalanced immune system. It is possible that many phytochemicals, including some of the so-called immuno-modulators of plant origin, might work by stimulating or inhibiting specific cytokines in such a way as to restore a properly balanced immune system. In addition, recent work has indicated that some phytochemicals can interact with certain components of signal transduction pathways. This could help to explain the apparent multiple activities of materials such as *Hypericum* extracts. The total benefit of a medicinal plant extract may therefore be due in part or in whole to such compounds acting together with the Adirect@ antivirals and other Adirect@ antimicrobials. The challenge is to design relevant and simple bioassays to look for these Aindirect@ activities.

ENT-KAURENE DITERPENES FROM *SIDERITIS ATHOA*

G. Topçu[1], A.C. Gören[2], G. Tümen[3], Y.K. Yıldız[2]

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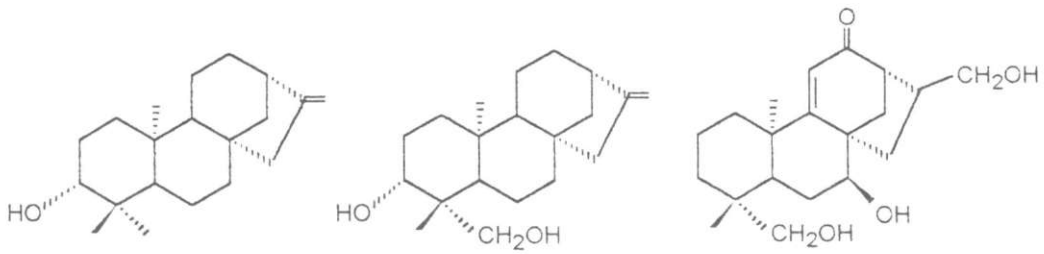
From *Sideritis athoa*, ten ent-kaurene diterpenes, five of them being new, were isolated. The known compounds were identified as linearol,19-deacetylinearol, sidol, ent-3β,7α-di-hydroxykaur-16-ene, ent-3β,19-dihydroxykaur-16-ene and ent-3α-hydroxykaur-16-ene. The structures of the new ones are under investigation, three of them were established as ent-3β-hydroxykaur-16-ene (**1**) ent-3β,19-dihydroxykaur-16-ene (**2**) and ent-7α,17,19-tri-hydroxy-kaur-9(11)-ene-12-one (**3**) by spectroscopic (IR, UV, NMR and MS) and chemical means.



1 **2** **3**

NSAIDs AS GUESTS IN CYCLODEXTRIN INCLUSION: PHYSICOCHEMICAL AND STRUCTURAL CHARACTERISATION OF SOLID INCLUSION COMPLEXES

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Encapsulation of poorly soluble drugs in cyclodextrins (CyDs) significantly improves their performance by rendering them more soluble and hence increasing their bioavailability [1]. For non-steroidal anti-inflammatory drugs (NSAIDs), an additional advantage of CyD-inclusion is the reduction of gastric side effects [2]. We report the preparation of several CyD inclusion complexes with NSAIDs of the salicylate, fenamate and profen classes as guests and their characterisation by thermal analysis (TGA, DSC, HSM), UV spectrophotometry and X-ray diffraction. The objective was to determine the chemical compositions (Host H: Guest G: Water W stoichiometric ratios) as well as demonstrate the integrity of the crystalline products as true inclusion complexes, which is important if application in solid dosage drug development is intended. Table 1 lists the complexes, their stoichiometries, crystal space groups determined by single crystal X-ray diffraction analysis, and the number of complex units in each crystal unit cell.

Table 1.

Complex	H	G	H:G:W	Space group	Z
1	β-CyD	diflunisal	1:1:13.0	$P2_12_12_1$	8
2	β-CyD	tolfenamic acid	1:1:14.2	$P2_1$	6
3	β-CyD	meclofenamate sodium	1:1:16.0	$P2_12_12_1$	4
4	β-CyD	ibuprofen	1:1:12.0	C2	4
5	γ-CyD	ibuprofen	1:1:18.3	$P42_12$	2
6	DIMEB	ibuprofen	1:1:1.0	$P2_12_12_1$	4

Formation of inclusion complexes was demonstrated by various methods including suppression of drug fusion endotherms in DSC traces, comparison of X-ray data with those for known complexes and, for complexes 3 and 4, by complete three-dimensional X-ray analysis. The latter showed that the drug in 3 has its phenylcarboxylate ring inserted in the host cavity from the primary hydroxyl side with the dichloromethylphenyl moiety protruding from the cavity, analogous to the inclusion of diclofenac sodium in β-CyD [3]. Crystallographic evidence for ibuprofen inclusion in complex 4 was unequivocal, but the guest is so severely disordered even at -50°C, that its modelling was not feasible. In contrast, the inclusion of ibuprofen in trimethylated β-CyD (TRIMEB) is well defined [4].

1. J. Szejtli: **Cyclodextrin Technology**. Kluwer Academic Publishers (1988).
2. J. Szejtli: **Controlled drug bioavailability**, Vol.3, J. Wiley and Sons, New York, p.1 (1985).
3. M.R. Caira, V.J. Griffith, L.R. Nassimbeni, B. van Oudtshoorn: **J. Chem. Soc. Chem. Commun.**, 1061, (1994).
4. G.R. Brown, M.R. Caira, L.R. Nassimbeni, B. van Oudtshoorn: **J. Incl. Phenom.** 26, 281, (1996).

A NONHUMAN PRIMATE STUDY ON THE EFFECT OF THE HALOPERIDOL TETRAHYDROPYRIDINE METABOLITE, HPTP ON DOPAMINE RECEPTOR AND TRANSPORTER BINDING.

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Researching the activities and toxicities of metabolites of drugs is of growing importance and has received increasing attention during the last decade in order to gain a better understanding of the efficacy and safety profile of drugs in clinical use. HPTP, 4-(4-chlorophenyl)-1-[4-(fluorophenyl)-4-oxobutyl]-1,2,3,6-tetrahydropyridine, the tetrahydropyridine metabolite of the classical neurolepticum, haloperidol, has recently been the focus for further understanding the well-known side effect profile of haloperidol.

The current study was aimed at investigating the effect of HPTP treatment on dopamine receptor and transporter binding in the nonhuman primate, i.e. the baboon *Papio ursinus*. The study was performed using the dopamine receptor ligand, ^{123}I-iodobenzamide (IBZM) and the dopamine transporter ligand, [^{123}I]2ß-carbomethoxy-3ß-(4-iodophenyl)tropane (ß-CIT) in planar scintigraphy and single photon emission computed tomographic (SPECT) protocols. Dopamine receptor binding in the striatum was measured from the time activity curves by calculating the IBZM ratios of the basal ganglia to frontal cortex and of the basal ganglia to cerebellum. ^{99m}Tc-HMPAO (hexamethylpropylene amine oxime) SPECT detected no changes in striatal perfusion during HPTP treatment. The transporter binding was measured by dynamic imaging of the basal ganglia, frontal cortex and cerebellum using ß-CIT.
IBZM dopamine receptor binding is initially (as measured after 18 weeks treatment) decreased by HPTP treatment in the basal ganglia, frontal cortex (not significantly) and cerebellum but reversed to control values in the frontal cortex, as measured after 58 weeks treatment with HPTP. The binding to the basal ganglia and to a lesser degree the cerebellum is still affected after 58 weeks treatment with HPTP but indicates a tendency to return towards the control values. The results of the planar dynamic study with ß-CIT indicate a decrease in the ß-CIT binding to the dopamine transporters in the basal ganglia and to a lesser extent the cerebellum as measured by the time activity and percentage washout rate of the ß-CIT in the HPTP treated baboons. The effect of HPTP on the serotonin transporters appears to be minimal as observed from the results obtained from the frontal cortex. These results indicate that HPTP influences both presynaptic and postsynaptic dopaminergic neurones.

THE HISTORY OF QSAR

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The history of quantitative structure activity relationships (QSAR) is conveniently divided into three components:

1. The development of structure activity relationships, SAR,
2. The discovery of qualitative relationships between physicochemical quantities (QlSAR) and biological activity; and
3. The development of quantitative relationships between physicochemical parameters and biological activities, QSAR.

SAR was the first of these components to emerge. This began with the work of Crum-Brown and Fraser and continues to the present. QlSAR first appeared in the work of Richet (solubility). Overton, Meyer, and Traube soon followed.with the identification of partition coefficients, surface tension, and osmotic pressure as physicochemical parameters related to bioactivity. Moore reported that toxicity of some substandes to insects was related to boiling point. .

A major influence on QSAR came from the development of quantitative chemical reactivity-structure relationships (QSCR). As rate and equilibrium constants accumulated in the literature, qualitative efforts were made to relate them to molecular structure. This produced SCR. Structural effects were first parameterized by Derrick. Later work modeled the observation of linear plots of one set of chemical reactivities against another. With the introduction of the Hammett equation in 1937, QSCR appeared as did the use of regression analysis for fitting the data to the model. Another contibution is the study of structural effects on physical properties.

In 1962 these various threads were brought together in the works of Hansch and his coworkers who developed a Hammett-type model based on lipophilicity (or hydrophobicity) using Hammett substituent constants as parameters.

O-6

INCREASING OF DISSOLUTION RATES OF TABLETS CONTAINING NAPROXEN USING LYOTROPIC LIQUID CRYSTALS

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The aim of this study is to increase dissolution rates of naproxen (NAP) tablets prepared by coating with lyotropic liquid crystals. Lyotropic liquid crystals were prepared using sodium lauryl sulfate, water and liquid vaseline. Appropriate proportions of these substances were mixed at room temperature. NAP was coated by mixing liquid crystals. NAP tablets were prepared by press. The codes and constituents of formulations were shown in Table1.

Table 1 Codes and constituents of formulations

Code	Substances (mg)					
	NAP	Liquid Crystal A	Liquid Crystal B	Ac-Di-Sol	Avicel pH 101	Mg-stearat %
NP	250	-	-	10	100	1
NP-1A	250	12.5	-	10	100	1
NP-2A	250	25	-	10	100	1
NP-3A	250	37.5	-	10	100	1
NP-1B	250	-	12.5	10	100	1
NP-2B	250	-	25	10	100	1
NP-3B	250	-	37.5	10	100	1

* Codes in table belongs to powder formulations. Formulations added P to these codes describes tablet formulations

The effects of liquid crystal ratios and liquid crystal formulations were investigated on release rate of active substance from NAP tablets. In-vitro release experiments were carried out according to USP XXIII Method II. The ratios of liquid crystals in tablets were 5%, 10% and 20% respectively. The liquid crystals were determined by polarized light microscopy and X-ray powder diffractometry. As shown in Figure 1, dissolution rates of NAP were increased depended on ratios of liquid crystals in tablets.

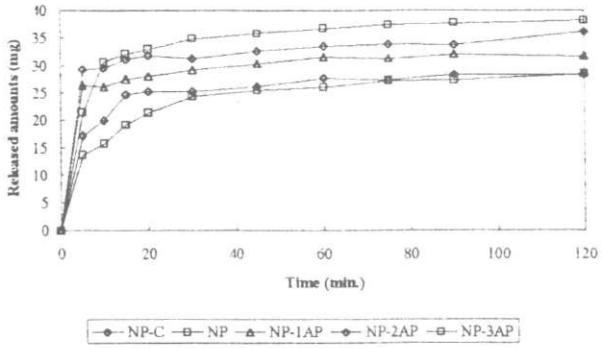

Figure 1. Release profiles of naproxen from tablet formulations prepared by liquid crystal A

CHEMOMETRIC METHODS IN ANALYTICAL CHEMISTRY

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Modern instruments are currently coupled with computers. This allows to store a large number of experimental data, to transform them for improving their guality and to use them for gualitative and guantitative determinations. We will show some examples of applications (smoothing of data, multicomponent analysis, identification of compounds...). These chemometric methods can help analytical chemists in their work but must be used with precautions to control that the mathematical formula used for this purpose are compatible with the experimental conditions.

ELECTRONIC POSTERS

PHARMACOPHORE STUDIES FOR ANTAGONISTS AT α_{1A} AND α_{1B} ADRENERGIC RECEPTOR SUBTYPES

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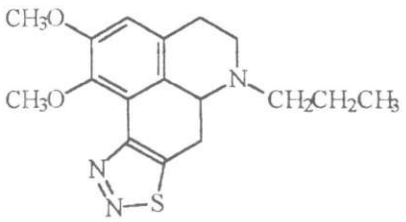
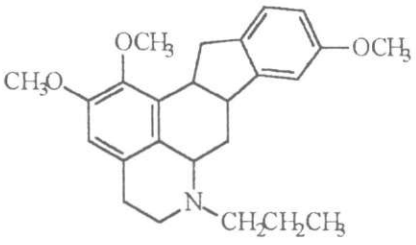
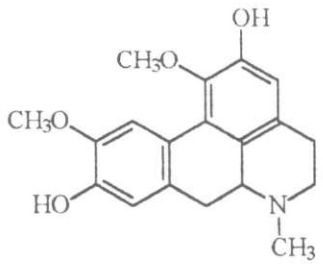
The α_{1A} adrenergic receptor subtype could play a role in the treatment of benign prostatic hyperplasia. In order to design subtype selective antagonists, pharmacophores for selective affinity for α_{1A} and α_{1B} adrenergic receptors have been investigated by using the Apex-3D and Catalyst packages (independently) by Molecular Simulations, Inc. (formerly Biosym Technologies, San Diego, CA, U.S.A.). Aporphine analogues were analysed and new structural changes predicted according to the pharmacophore models. Thiadiazole (1) was predicted to be selective for α_{1A} and IQC (2) was predicted to be somewhat selective for the α_{1B} subtype according to the Apex-3D package. Both compounds were expected to show affinity in the pK_i= 8 range. However, ligand binding studies on cloned receptors show that 2 is selective for α_{1A} (pK_i= 8.2) and 1 has much lower affinity and is only slightly selective for the α_{1A} subtype. These results agree to a certain extent with the pharmacophores developed by the Catalyst package. Boldine (3) and its derivatives were also investigated. In these cases, the Apex-3D pharmacophores correctly predict the α_{1A} selectivity and reasonable affinity, whereas the Catalyst pharmacophores predict low affinity and no selectivity.



Thiadiazol (1)



IQC (2)



Boldine (3)

BASIC HYDROLYSIS OF CRYSTAL VIOLET IN CICLODEXTRINS AND MICELLES/CYCLODEXTRINS MIXED SYSTEMS.

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The Cyclodextrins (CD) are Cyclic oligomers of alfa-D-glucose joined at the alfa(1,4) position. Their shape is generally described as a torus, with its cavity one of its most important characteristics. This cavity enables them to form inclusion complexes in solution. In this way, they can act as hosts for small organic molecules of an adequate size and polarity.

The possibility to use the CD as enzymatic models has resulted in a great number of studies of this kind in the literature. Because of their ability to form inclusion complexes, the CDs can influence the course of chemical reactions with respect to the rate and/or product selectivity (1). In recent years, the CD complexation with surfactants is a particular case that has been widely studied. The addition of CD to surfactant aqueous solutions greatly affects the physico-chemical properties of the solution (2). These changes are due to the ability of the CD to screen the hydrophobic groups of surfactants molecules from contact with the aqueous medium forming inclusion complexes in which the surfactant hydrophobic chain is inserted in CD cavity. As a consecuence, surfactants are ideal guests that allow study of CD complexation, because its hydrophilic and hydrophobic groups can change sistematically. The influence of cyclodextrins and mixed systems Cyclodextrin-CTACl upon the reaction of basic hydrolysis of Crystal Violet have been studied.

In presence of only cyclodextrins we have observed a catalytic effect due the formation of a complex between Crystal Violet and CD. The equilibrium constant for the formation of the Crystal Violet-CD complex and the reactivity constant have been obtained.

The results obtained in presence of a mixed system Cyclodextrin-CTACl are interpreted considering the surfactant monomers complexation with CD. The micellar pseudophase model has been extended, with ionic exchange for these mixed systems. This complexation causes a increase in the apparent "cmc". This increase depends upon the CD concentration. The apparent "cmc" has been defined as the sum of the cmc and the surfactant monomer-cyclodextrin complex concentration. The reactivity constant and the binding constants of Crystal Violet - CTACl micelles and Crystal Violet - Cyclodextrin have been obtained.

[1] O.S. Tee, Adv.Phys.Org.Chem. 29, 1 (1994).
[2] H. Mwakibite, D.M. Cristantino, W. Bloor, J.F. Holzwarth, Langmuir, 11, 57 (1995).

ESTIMATION OF TOXIC EFFECTIVE DOSE OF THE ELEMENTS BY USE OF ARTIFICIAL NEURAL NETWORK

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In this study, application of artificial neural networks (ANNs) in toxicology is investigated. ANNs are used to estimation of toxic effective dose (TED) of the elements. Data were taken from "The Elements" (J.Emsley,1991). NNMODEL (version 1.4, Neural Fusion) was used for the data analysis. A data matrix contains 25 variables of 19 elements (B, Al, K, V, Cr, Fe, Co, Cu, Se, Br, Mo, Ag, In, Sn, Sb, Te, Ba, Hg, Pb). 3 variables was selected for inputs: electronegativites (Pauling), effective nuclear charge (Clementi), heat conduction. The output variable is Ln(10*TED). The ANN includes 3 inputs, 4 hidens and 1 output. The test matrix contains 4 elements. The results are on the table.

Element	Estimation of TED (mg)	TED (Emsley,1991) (mg)
Li	142.4	92-200
Zn	347.7	150-600
As	11.4	5-50
Cd	25.2	3-330

All 4 predicted values are at the appropriate intervals. The estimations of TED for the others elements are on the next table. The results of this study indicate that the ANN based technology may be useful for QSAR approach in toxicology.

Element	Mn	Ni	Rb	Nb	Rh	Ta	W
Estimation of TED (mg)	0.4	115.3	1746.6	98.4	3.6	137.9	3069.9

POSTER PRESENTATIONS

INFORMATION THEORY AND ITS USE IN ANALYTICAL CHEMISTRY

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Information theory is used to optimize the process of obtaining the necessary output from a given set of inputs in a system. Analytical Chemistry is a system in which the process of extracting information about the composition of a sample is realized.

It has therefore become ever more important to determine the optimum amount of sample used in the analytical process for gaining maximum information.

Information theory helps us to optimize the process by its tools and technique.

DETERMINATION OF GUAIFENESIN (GLYCEROL GUAIACOLATE) AND CODEINE PHOSPHATE IN COMBINATION USING HIGH-PERFORMANCE LIQUID CHROMATOGRAPHY (HPLC)

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Guaifenesin and codeine phosphate are two active ingredients that have expectorant and antitussive activity, respectively. Due to their pharmacological effects, they are used in pharmaceutical preparations used for cold-catching. A reversed-phase HPLC method has been developed for the simultaneous determination of guaifenesin and codeine phosphate in the tablet dosage form. Guaifenesin and codeine phosphate were analyzed and quantified by an isocratic HPLC apparatus (Waters 510 HPLC pump, Waters 717 Plus Autosampler, Waters 996 Photodiode Array Detector). A C_{18} Bondapak column (10 µ, 3.9x300 mm) was used. The mobile phase was methanol-water (50:50) at 1.8 ml/min rate flow, and chromatogram was monitored at 221.5 nm. Identification was based on retention time and quantification was performed by automatic peak area determination, corrected for the internal standard.

QUANTITATION OF ACETAMINOPHEN AND 4-AMINOPHENOL USING HIGH-PERFORMANCE LIQUID CHROMATOGRAPHY

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Acetaminophen (paracetamol) is currently one of the most commonly used analgesic and antipyretic. It is often used as an alternative to aspirin and available without a prescription. Its determination in pharmaceutical dosage forms (quality control) and in biological fluids (overdose monitoring) remains great interest. Many methods (spectrophotometric, non aqueous titration, polarographic, chromatographic, fluorometric, and derivative spectrophotometric) have been reported for the determination of acetaminophen and/or 4-aminophenol as an impurity in acetaminophen (1,2). Most of these methods are not suitable for simultaneous determination of acetaminophen and 4-aminophenol with the presence of preservatives, colorants and flavors commonly added to liquid formulations. Among the various analytical techniques, high-performance liquid chromatography (HPLC) constitutes the most popular chromatographic method for separating mixtures of drugs and their degradation products. In this study, a reversed-phase high-performance liquid chromatographic method has been developed for the quantitation of acetaminophen as well as its degradation product, 4-aminophenol. The method is specific for detection and determination of these compounds in a complex mixture, without pretreatment. A C_{18} stationary phase is used with a methanol-water (1:2, v/v) mixture at 1.78 ml/min flow rate and spectrophotometric detection at 193.3 nm, at which 4-aminophenol shows maximum absorbance. Sulphamethoxazole is used as an internal standard and the analysis is completed within 5 minutes. The detection limit of the method is 0.015 µg/ml for 4-aminophenol. This method is sensitive for detecting small concentrations of 4-aminophenol in acetaminophen dosage forms and could be applied to quality and stability monitoring of paracetamol.

1. Ammer, B.; Greenblatt, D.J.; Divoll, M.; Abernethy, D.R. and Shargel, J., **J. Chromatogr.**, 226, 224, 1981.
2. Street, K.W. and Schenk, G.H., **J. Pharm. Sci.**, 68, 1306, 1979.

A SIMPLE METHOD FOR DETERMINATION OF TRETINOIN IN MINOXIDIL-TRETINOIN SOLUTION BY HIGH PERFORMANCE LIQUID CHROMATOGRAPHY

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A Simple high-performance liquid chromatography (HPLC) method for the quantification of tretinoin in minoxidil-tretinoin solution is described. Cyanocobalamin was used as internal standard. The chromatographic seperation was accomplished with an isocratic mobile phase cosnsiting of methanol-water (75:25, v/v) at a flow rate of 1.3 ml/min. The HPLC column was novapak C18 and the detector ultraviolet at 366 nm was used. In addition in this method tretinoin was separated efficiently from isotretinin, therefore been used for kinetic study of tretinoin. The precision linearity and limit of quantification of this method were within acceptable limits.

P-5

APPLICATION OF THE RATIO SPECTRA DERIVATIVE SPECTROPHOTOMETRY AND VIERORDT'S METHOD TO QUANTITATIVE ANALYSIS OF PARACETAMOL AND METAMIZOL IN A PHARMACEUTICAL FORMULATION

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Two new spectrophotometric methods, ratio spectra derivative spectrophotometry and Vierordt's method for the determination of paracetamol and metamizol in a mixture were described. These procedures do not require any separation step. In the first method, derivative amplitudes were measured in their first derivative of the ratio spectra of their mixture solution in 0.1N HCl at 222.6 or 252.4 nm for paracetamol and at 263.8 or 279.5 nm for metamizol. Calibration graphs were linear in the range 8–40 µg/ml for paracetamol and 12–48 µg/ml for metamizol. In the method, the relative standard deviations were found as 0.25 % and 0.23 % for paracetamol and metamizol, respectively. In Vierordt's method, $A\,{}^{1}_{1}$ (% 1, 1 cm) values for paracetamol and metamizol were determined at 242.7 nm and 258.4 nm in their zero–order spectra in 0.1N HCl. The amounts of both compounds were calculated by means of equations with two unknowns using the A^{1}_{1} (%1, 1 cm) values. The relative standard deviations in Vierordt's method for paracetamol and metamizol were found to be 0.43 % and 0.60 %, respectively. The methods were successfully applied to a pharmaceutical formulation for the determination of these compounds.

SPECTROPHOTOMETRIC SIMULTANEOUS ANALYSIS OF LISINOPRIL - HYDROCHLOROTHIAZIDE MIXTURE IN TABLETS

N. Erk

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Two new spectrophotometric methods for the simultaneous determination of lisinopril (**I**) and hydrochlorothiazide (**II**) in their binary mixture are proposed. In the first method, derivative spectrophotometry, $dA/d\lambda$ values ere measured at 271.615 nm for (**I**) and 258.504 nm for (**II**) in the first derivative spectra of the solution of their mixture in 0.1 N HCl: methanol (1:1). Relative standard deviations of the method were found to be 0.95 % and 1.36 % for (**I**) and (**II**) respectively. In the second method, absorbancy ratio method , absorbances of the solution of this mixture in 0.1 N HCl: methanol (1:1) were measured at 258.504 nm (λ_{max} of lisinopril), at 271.330 nm (λ_{max} of hydrochlorothiazide) and at 263.634 nm (λ_{iso}). Relative standard deviations of the method were found to be 1.06 % for (**I**) and 1.58 % for (**II**) .

Mean recoveries of the drugs in these two methods were well agreed with each other. The concentrations of the compounds for Beer's law compliance were also determined in the methods. These methods were successfully applied to a tablet marketing in Turkey.

SIMULTANEOUS DETERMINATION OF EPHEDRINE HYDROCHLORIDE AND THEOPHYLLINE IN TABLETS BY SPECTROPHOTOMETRIC METHODS

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In this study, three new spectrophotometric methods were used for the simultaneous determination of ephedrine hydrochloride (I) and theophylline (II) in their binary mixture.In the first method,derivative spectrophotometry,$dA/d\lambda$ values were measured at 241,0 nm and 284,1nm for (I) and (II) respectively in the first derivative spectra of their combination. The relative standard deviation of the method was found to be 0,78 % for (I) and 1,30 % for (II). In the second, absorbancy ratio method, the quantification of ephedrine hydrochloride and theophylline was performed by using the absorbances read at 257,2 nm, 264,9 nm and 271,0 nm in the zero - order spectra of their mixture. Relative standard deviation of the method was found to be 1,05 % and 0,68 % for (I) and (II) respectively. In the third, gravimetry + derivative spectrophotometry, the quantification of ephedrine hydrochloride and theophylline was realized by precipitating ephedrine hydrochloride with ammonium reineckate at pH : 6 selectively and by reading the absorbance of the solution of the precipitate in acetone at 524,8 nm for (I) and by measuring the $dA/d\lambda$ values at 253,6 nm in the first derivative spectra of the remaining solution for (II).The relative standard deviation of the method was found to be 1,73 % for (I) and 0,15 % for (II). Recoveries were found to be 99,4 % and 99,8 % for (I) and (II) respectively. These three methods have been successfully applied to a tablet containing these drugs.

FLOW-THROUGH SPECTROPHOTOMETRIC DETERMINATION OF OMEPRAZOLE IN PHARMACEUTICAL PREPARATIONS CONTAINING ENTERIC COATED PELLETS

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Omeprazole is a benzimidazole derivative which inhibits gastric acid secretion. Flow-through systems are widely used as a tool to solve analytical problems and have many advantages in the subject of pharmaceutical applications. Besides, the system is a promising technique used for the test of kinetic experiments and dissolution tests. In this study, a flow-through spectrophotometric method for the analysis of omeprazole is described. Since stability of omeprazole is very poor in acid media, the standard and sample solutions were prepared in 0.1 M NaOH. The detector was adjusted to 305 nm and each of the solutions were pumped through the capillary for 2 min. The baseline was almost stable. The calibration curve was fitting the equation [signal (mAU) = 0.192 +53313 C (M); r^2 = 0.9998]. Detection limit was calculated to be $8x10^{-6}$ M at the signal to noise ratio is equal to 3. UV-spectrophotometry was chosen as a comparison technique. The experiments were performed at 305 nm and a calibration equation was found as [A = 0.02 + 15373 C (M); r^2 = 0.9997] in the concentration range of 9.810^{-6} and $4.9.10^{-5}$ M. The flow-through spectrophotometric technique has been applied to determine omeprazole in capsules containing coated pellets. It was found that the matrix of pellets does not alter the results. The results were evaluated statistically by comparing it to the results of the UV-spectrophotometric method. Insignificant differences were found at a 95 % probability level between the techniques according to the statistical evaluations. The proposed technique may be promising for certain purposes. It may be applied to the routine analysis employing very small volumes such as 20 µL. The technique is accurate, practical and reproducible for the analysis of omeprazole.

THE FLOW-INJECTION ANALYSIS OF AMBROXOL IN PHARMACEUTICAL TABLETS

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Ambroxol is a new mucolytic drug that is used for the treatment of lung disease. A flow-injection analysis of ambroxol and the application of the technique to the pharmaceutical tablets containing ambroxol is described in this study. Distilled water was used as the suitable solvent for ambroxol during the experiments. Coil length and flow rate could not be varied because of lacking of instrumentation. The maximum absorbances of ambroxol were obtained at 209 and 244 nm. Better results were also obtained at 209 nm while the determination was performing by means of flow-injection analysis.

The injection time corresponds to injection volume was tested in the range of 1-5 seconds and it was determined that a straight line passes through origin was observed between 1 and 4 seconds. The concentration effect on the signals, at injection time of 2 seconds and 209 nm was examined and an equation corresponds to [signal(mV or mAU) = 0.01 + 10582.5 C(M) ; r=0.9998] was calculated in the 1.03×10^{-4} - 5.15×10^{-4} M concentration range. Reproducibility was found to be around 1.5 percent and detection limit was calculated to be 2.5×10^{-5} M at the criteria of signal to noise ratio is 3. This study was applied to ambroxol tablets. The results of the assays were statistically evaluated by comparing them with those of UV-spectrophotometry. According to the t- and F-tests, the differences between the two methods were found to be insignificant at 95 % probability level. Flow-injection analysis has also an advantage regarding to analysis number in a unit time. It can perform at least fifty injections in an hour that it is very appreciable number as routine analysis laboratories. Therefore, it is concluded that the method proposed with this study is rapid, practicable, accurate and for routine analysis of ambroxol.

A CAPILLARY ELECTROPHORETIC METHOD FOR THE EXAMINATION OF SALICYLATE ION TO DETERMINE HYDROXYL FREE RADICAL

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A CE technique which can be applied to determine the level of hydroxyl free radical in living organism exposed under certain circumstances is described in this study. MEKC technique was used during the study. A buffer system consisting of 20 mM borate and 25 mM SDS at pH 8.5 was the best solution to solve each component within fifteen minutes. 2 minutes vacuum injection and 30 kV potential were applied for the CE analysis. Luminal was a good internal standard for this analysis. The most available wavelength was 200 nm for four compounds. Standard sample of DHBA's were prepared by addition of ascorbic acid to protect their further oxidation. The compounds appeared in the electropherograms and their migration times are minutes for luminal (8.5), 2,5-DHBA (10.4), salicylic acid (11.5) and 2,3-DHBA (12.6) respectively. Well-correlated calibration equations which almost passes through origin were obtained for the subjected materials as ratio values (signal of material/signal of internal standard) against concentration of related compound. The detection limit was 1.68 ng for salicylate (S/N= 3). To check the course of the reaction and confirm the validity of the method progressed in this study, a salicylate and hydrogen peroxide solution was exposed to UV radiation and the decrease of salicylate, increase of 2,5-DHBA and 2,3-DHBA were clearly observed and it was also additional two peaks appeared. These two peaks have been attributed to the formation of oxidation product of 2,5-DHBA and 2,3-DHBA. The amount of the compounds were determined to be thirty-three percent of salicylate was changed into hydroxylated forms. All of the results showed that the method is very cheap among the other sophisticated methods. The method is also selective, accurate and practical. Therefore, it is a promising method for the examination hydroxylation of salicylic acid and the determination of hydroxyl free radical.

ZEEMAN BACKGROUND CORRECTED GRAPHITE FURNACE ATOMIC ABSORPTION SPECTROPHOTOMETRIC DETERMINATION OF SELENIUM IN BIOLOGICAL MATERIALS

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Selenium is an essential trace element for organism. Since the range between the essential and toxic levels of selenium is very narrow, the analysis of this element at ppb level in biological material is being important.

The analysis of selenium in biological material such as serum, plasma, erythrocyte, whole blood and breast milk were performed by Zeeman Background Corrected Graphite Furnace Atomic Absorption Spectrophotometry. The optimum matrix modifier was found as $Pd+Mg(NO_3)_2$, the pyrolysis and atomization temperatures were determined as 1200°C and 2200 °C, respectively. Drying step was achieved by three steps as 70, 120 and 250 °C with temperature ramping program. Stabilized Temperature Platform Furnace conditions were applied in analysis.

Since the calibration curves of direct calibration and standard addition methods were found in parallel, direct calibration method was preferred in the analysis. Detection limit, linearity and average recovery were found as 4.9 ppb up to 98 ppb and 103.63%, respectively.

At the end of this study it is shown that the quantitative results obtained by the developed method could be an important step in the detection of liver cirrhosis, infertility, cardiovascular disease and different types of cancer, which is caused by deficiency of selenium. Additionally, it was suggested that the reliable analysis of selenium by this method in the biological material might be an effective index during the treatment stage of these diseases.

URINARY EXCRETION OF EPHEDRINE AFTER ORAL ADMINISTRATION

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Ephedrine is a drug that has clinical use in illnesses like rhinitis, colds, sinusitus. It's also one of substances abused in sports. A capillary gas chromatographic method with Mass Selective Detector and Nitrogen-Phosphorus Detector has been used for measuring ephedrine and its major metabolite norephedrine in urine after solvent extraction. The extraction procedure and the temperature programme used has been developed by us. The urinary excretion of ephedrine was studied after the oral intake of ephedrine hydrochloride.

DETECTION OF METHYLTESTOSTERONE FROM URINE BY USING HPLC PURIFICATION PRIOR TO GC-MS ANALYSIS

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Methyltestosterone (MT), as an anabolic agent is widely abused in sports and is encountered as a doping agent.The determination of trace amounts of analytes in biological samples is a well-known problem. So in order to reduce the effect of interfering components and to enrich the analytes of interest, sample pretreatment is necessary in most cases. The situation for MT is the same. Although several gas chromatographic methods are available for the detection of MT, because of the lack of purification, it is difficult to go down to very low detection limits. In this study, HPLC is used as a purification method for lowering the detection limit of MT. In the analysing procedure, firstly, known amounts of MT are spiked in urine. These samples are then applied to HPLC. MT is collected from HPLC between 7.1-8.1 min. (Rt=7.6 min). Norethandrolone as internal standard is then added to these samples. After that the samples are evaporated to dryness and then silylated. Finally the samples are applied to capillary GC-MS.

HPLC conditions:

Flow rate: 1.5 ml/min. Solvent A: H_2O , Solvent B: Acetonitril

Gradient: Starting with B (0 %) and linear increase within 3.01 min. to 60 % of B and linear increase within 8.01 min. to 80 % of B.

DAD monitoring: 246 nm.

Column: ODS Hypersil 5 µm, 200x4.6 mm.

GC conditions:

Column: Fused silica capillary column (dimethylpolysiloxan; 17m, 0.2mm, 0.11µm)

Carrier gas: He (0.882 ml/min)

Split ratio: 1/10

MS conditions:

Ionization : Electron Impact

Mode: Selected Ion Monitoring (SIM)

Analyzer: Quadropole

Electron energy: 70 eV

Eventually we have found that by using HPLC purification prior to GC-MS analysis, it is possible to lower the detection limit to about 10 ng/ml urine which is better than the results with GC-MS.

THE DIFFERENTIAL PULSE POLAROGRAPHIC DETERMINATION OF PRAZOSIN HYDROCHLORIDE IN PHARMACEUTICAL TABLETS

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Prazosin HCl is a new quinazoline derivative that, like doxazosin has selectivity for postsynaptic α_1 -adrenergic receptors. It has an effective first-line therapy in the treatment of essential hypertension. The optimum polarographic conditions for the determination of prazosin and the application of method to the pharmaceutical preparations containing active material is described in this study. The variation of the limiting current was examined in a wide pH range and the most beautiful polarograms were appeared in the 0.5 M H_2SO_4 solution containing 5 percent (v/v) methanol. It was found that the system controlling the polarographic current was totally diffusional. Under these conditions the process was found to be irreversible. The stability of prazosin in methanolic HCl was examined and encountered that it is stable at least one week. The calibration studies were performed using differential pulse polarography and the variation of prazosin concentration versus the peak current at -1.02 V was found to be a straight line which corresponds to[$i(\mu A) = -2x10^{-4} + 1550\ C(mol.L^{-1})$; r= 0.9997 equation. The validity of the method was examined applying to the pharmaceutical preparation of prazosin in the optimum analytical and polarographic conditions. The determination of prazosin was also realized by UV-spectrophotometry which were admitted as comparison method. All the results of the assays were statistically evaluated using t- and F-test, respectively.

According to the statistical results, high reproducibility was observed and insignificant differences were found between the differential pulse polarographic technique and UV-spectrophotometry at the 95 % probability level. As a conclusion, the method proposed in this study is accurate, precise and rapid. Therefore, it can be suggested for the routine analysis of prazosin in the field of pharmaceutical controls.

A VOLTAMMETRIC DETERMINATION OF NISOLDIPINE IN PHARMACEUTICAL PREPARATIONS AND BODY FLUIDS

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Nisoldipine is a new dihydropyridine derivative and a potent calcium channel bloker which is specifically used in the treatment of angina pectoris and hypertension. A differential pulse voltammetric method is described for the determination of nisoldipine based on the oxidation of dihydropyridine group on the surface of rotating glassy carbon disk electrode. The experiments were carried out in the supporting electrolyte consisting of 0.2 M KCl and 0.1 M phosphate buffer solution containing 30 percent ethanol (v/v) during the investigation of pH effect. The maximum signal to noise ratio and the most symmetrical peaks were obtained in the use of the supporting electrolyte solution containing 0.1 M H_2SO_4 in 30 percent ethanol (v/v) and initial potential of +300 mV. The factor affecting the voltammetric current was diffusional in the range of 200-2000 rpm and up to $1x10^{-4}$ M nisoldipine concentration. Detection limit were calculated to be $8x10^{-6}$ M for the concentration of $7.8x10^{-5}$ M nisoldipine, accepting the ratio of signal to noise (S/N) equal to 3 and reproducibility was ±0.9 % for five successive experiments in the same conditions. The DP voltammetric determination of nisoldipine in film coated tablets and in human serum was realized in the optimum rotating conditions. According to the statistical evaluations acceptable results were obtained in both application. Therefore, the method proposed in this study is practical, sensitive and accurate for the analysis of nisoldipine preparations in the quality control laboratories.

THE VOLTAMMETRIC DETERMINATION OF AMLODIPINE IN PHARMACEUTICAL TABLETS BY DIFFERENTIAL PULSE VOLTAMMETRY

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Amlodipine is a new dihydropyridine derivative and a potent calcium channel bloker which is specifically used in the treatment of angina pectoris and hypertension. A differential pulse voltammetric study and the determination of amlodipine in tablets have been carried out based on the fact that the oxidation of dihydropyridine group on the surface of glassy carbon electrode in the stationary and rotating conditions occurs. A supporting electrolyte consisting of 0.2 M KCl and 0.1 M phosphate buffer solution in 10 percent (v/v) methanol was employed during the investigation of initial potential and pH effects. No adsorption effect was observed during use of initial potential of 0 mV and the most symmetrical peaks were obtained at pH 5.5 for both stationary and rotating conditions. In the range of 200-1000 rpm rotation and up to $1.0x10^{-4}$ M amlodipine concentration the factor affecting the voltammetric current was diffusional. The effect of rate of potential was tested between 2 and 20 mV for the stationary condition and the species of current was found to be diffusional up to $5x10^{-4}$ M. The voltammetric determination of amlodipine in tablets was realized in the optimum rotating system conditions and depending on the statistical evaluations acceptable results were obtained. Therefore, the method proposed in this study is practical, sensitive and accurate for the analysis of amlodipine preparations in the quality control laboratories.

A RAPID METHOD FOR THE DETERMINATION OF PIROXICAM IN RAT PLASMA USING HIGH-PERFORMANCE LIQUID CHROMATOGRAPHY

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Piroxicam, a non-steroidal anti-inflammatory (NSAID) drug that is used in the treatment of rheumatoid arthritis and osteoarthritis. Severalhigh-performance liquid chromatographic (HPLC) methods have been developed for measurement of piroxicam in human plasma. However, few methods are presented for detection of piroxicam in rat. The sample preparation involved liquid extraction, centrifugation and evaporation. Separation of piroxicam from internal standard (tenoxicam) occurred on a reversed phase C18 column with a mobile phase consisting of methanol-phosphate buffer (45:55, pH 2). The detection limit of the assay was 0.02-20 fg/ml. The assay linearity was good (typically r=0.9992).

The present paper reports a sensitive, rapid and accurate high-performance liquid chromatographic method for determination of piroxicam in rat plasma after single oral dose of 2mg/kg of piroxicam.

VOLTAMMETRIC DETERMINATION OF DOXAZOSIN IN TABLETS USING ROTATING PLATINUM ELECTRODE

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Doxazosin is a new postsynaptic a-1 adrenoreceptor antagonist that is used to regulate the blood tension. This study describes the voltammetric behavior of doxazosin molecule based on the oxidation on the surface of platinum electrode in the stationary and rotating conditions and to determine doxazosin in the tablets by differential pulse technique at only rotating condition. The experiments were carried out in the supporting electrolyte consisting of 0.2 M KCl and 0.2 M buffer solution in 10 percent (v/v) ethanol. The effect of initial potential was investigated and no adsorption effect was observed during use of initial potential of +500 mV. The influence of pH on the peak current and peak potential was examined and the most symmetrical peaks were obtained at 0.5 M H_2SO_4 for rotating conditions. In the rotation range of 50-1000 rpm and up to $1.0x10^{-5}$ M doxazosin concentration the factor affecting the voltammetric current was diffusional. The effect of rate of potential was tested between 2 and 20 mV for the stationary condition and the species of current was found to be diffusional up to $3x10^{-5}$ M concentration of doxazosin solution. The voltammetric determination of doxazosin in tablets was realized in the optimum rotating system conditions. Using the statistical evaluations acceptable results were obtained. Therefore, the method proposed in this study is practical, sensitive and accurate for the analysis of doxazosin for the quality control laboratories.

VOLTAMMETRY OF TRAZODONE BY PLATINUM ELECTRODE AND ITS DETERMINATION IN TABLETS IN THE ROTATING CONDITIONS

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Trazodone is a new drug used for the treatment of depressive behavior. The voltammetric behavior of trazodone based on its oxidation on the surface of platinum electrode in the stationary and rotation conditions and its determination in tablets by DP rotating conditions are described, in this study. The experiments were conducted in the supporting electrolyte consisting of 0.2 M KCl and 0.2 M acetate or phosphate buffer solution to investigate the initial potential and pH effects. No adsorption effect was observed in use of initial potential of +300 mV and a supporting electrolyte solution having pH 5.5 both stationary and rotating conditions. The factor affecting the voltammetric current was diffusional in the range of 200-2000 rpm and $1x10^{-5}$ -$5x10^{-5}$ M for rotating ; 2-10 mV rate of potential for stationary conditions. The voltammetric determination of trazodone in tablets was realized in the optimum rotating system conditions and according to the statistical evaluations acceptable results were obtained. Therefore, the method proposed in this study is practical, sensitive and accurate for the analysis of trazodone preparations in the quality control laboratories.

THE ANALYSIS OF DIFLUNISAL TABLETS WITH DIIFERENTIAL PULSE POLAROGRAPHY, SECOND DERIVATIVE SPECTROSCOPY AND HIGH PERFORMANCE LIQUID CHROMATOGRAPHY

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Diflunisal (2',4'-difluoro-4-hydroxy-3-biphenyl carboxylic acid) is a salysilic acid derivative with analgesic and antiinflammatory activity. Because it is a relatively new drug, few procedures for its determination have been reported. After the electrochemical optimization studies, not only the instrumental parameters were determined, but also pH:4.82 acetate buffer was chosen as the supporting electrolyte among the ones tried. The peak potential was found as -0.35 V vs. Ag/AgCl and the current-concentration relation at this voltage and between 10-150 ppm was decided to be linear. After the application of second derivative spectroscopy to the methanolic solutions of diflunisal (N=8) the calibration was found to be linear between 10-150 ppm. The differential pulse polarographic and second derivative spectroscopic results were compared with high performance liquid chromatography results. The mobile phase used was: 50% MeOH + 33.3% 0.1 M H_3PO_4 + 16.7% tetrahydrofuran (pH:3.0). The retention time of diflunisal was 12.336 min, while the retention time of the internal standard sodium naproxen was 5.357 min. The linearity limits were 1-150 ppm. Eventually, the applicability of all the three methods to the tablet dosage forms of pharmaceutical preperations of diflunisal (Dolphin®) were shown.

DIFFERENTIAL PULSE ADSORPTIVE STRIPPING VOLTAMMETRIC DETERMINATION OF FAMOTIDINE IN A BIOLOGICAL MATERIAL

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Famotidine is a potent H_2 -receptor antagonist used for the treatment of peptic ulcer disease, gastroesophageal reflux, esophagitis and pathological hypersecretory conditions in adults. This drug was determined by using the adsorption related polarographic peak obtained by the method of adsorptive stripping voltammetry. Peak currents were measured with hanging mercury drop electrode at -1.26 V vs. Ag/AgCl reference electrode in 0.01 M aqueous tetramethylammoniumtetrafluoro borate solution as a supporting electrode. The biopsy samples from the different parts of the stomach were analyzed with adsorptive stripping voltammetry after liquid-liquid extraction.

DIFFERENTIAL PULSE POLAROGRAPHIC DETERMINATION OF TENOXICAM IN PHARMACEUTICALS

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A new polarographic method was developed for determination of tenoxicam. Electrochemical reduction of the substance was studied in various supporting electrolytes in the range of pH 1.4 to 9.0. The best defined polarograms were obtained in phosphate buffer pH 5.3. Peak currents were measured with static mercury drop electrode. Direct Current (DC), Pulse (P), and Differential Pulse Polarographic (DPP) techniques were applied. In DPP technique, which was the most sensitive, the best defined peaks were observed with a peak potential of -1.33 V vs.Ag / AgCl reference electrode in the phosphate buffer pH 5.3. The reversibility test was performed by using DC polarography. A linear relationship was observed between log [(id-i) / i] and E, the regression equation of this curve was y = 0.044 x - 1.39. The reduction of tenoxicam in selected supporting electrolyte was irreversible and diffusion controlled. The quantitative evaluation is based on the dependence peak current on tenoxicam concentration. The linear calibration range was 0.025 - 20.000 ppb. Developed Differential Pulse Polarographic method for tenoxicam was applied to two different commercial preparations. There is no need any extraction procedure before polarographic analysis.

VOLTAMMETRIC DETERMINATION OF CEFTRIAXONE

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Ceftriaxone is a member of the third generation cephalosporin antibiotics. Microbiological, colorimetric, chromatographic (especialy HPLC) , spectroscopic, fluorimetric and enzimatic methods were reported in literature for the determination of cephalosporins in simple solutions or in body fluids.The technique of voltammetry has sofar been little applied to these compounds, the few studies carried out in this context have contributed no data of kinetic or analytical interest as they included no thorough study of the experimental conditions and hence gave rise to irreproducible results.These arose mainly from the strong adsorption of these substances at the electrode.

In this work electrooxidation of ceftiaxone using platinum, specially activated glassy carbon electrode and carbon paste electrode and polymer - modified carbon paste electrode was investigated. The effects of supporting electrolite, pH and scan rate on the electrooxidation were shown.

The data revealed that;

Pt electrode was not convenient for the electrooxidation of ceftriaxone as the electrode became inactive because of the strong adsorption of the substance.

The shapes of the voltammograms and the numbers of the oxidation steps changed depending on the nature of the electrode.

With glassy carbon electrode in 0.5 M H_2SO_4 peak current and ceftriaxone concentration relationship showed two linear sections the first one was in the range of 2.10^{-5} - 1.10^{-4} M and the second one was in the range of 1.10^{-4} - 6.10^{-4} M.

In 0.2 M H_3PO_4 and in acetate buffer of pH 3.5 also linear relationships were observed.Also with carbon paste electrode in 0.5 M H_2SO_4 and in 0.2 M H_3PO_4 solutions linear peak current - concentration relationships were obtained. But statistical evalution of the data revealed that the most suitable electrode for the quantitative determination of ceftriaxone was specially activated glassy carbon electrode.

VOLTAMMETRIC OXIDATION AND DETERMINATION OF TRAZODONE

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Trazodone, 2- { 3 - [4 - (m - chlorophenyl) -1- piperazinyl] propyl}-1,2,4-triazolo-[4,3a]pyridine-3(2H)-one, is a triazolopyridine derivative with antidepressant and anxiolytic activity.

In this study, the voltammetric characteristics of the compound were investigated in aqueous media as a function of pH by linear sweep and cyclic voltammetry at the platinum and activated glassy carbon electrodes. Between pH 1.5 and 11.0, trazodone was characterized by a single oxidation step at both electrodes. Cyclic voltammetric measurements showed an irreversible behavior in the range of scan rates comprised of between 10 and 100 mVs^{-1} and in the entire pH range investigated. The anodic process was diffusion controlled at the two types of the electrodes used. The procedure gave linear concentration ranges of $1x10^{-5}$ to$1x10^{-3}$ M and $8x10^{-6}$ to $6x10^{-4}$ M at platinum and activated glassy carbon electrode, respectively, in 0.2 M sulphuric acid.

Based on this study, a simple, rapid and inexpensive voltammetric method was developed for the determination of the drug in tablets.

VOLTAMMETRIC DETERMINATION OF TINIDAZOLE IN TABLETS

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Tinidazole is a 5-nitroimidazole derivative with a strong activity against anaerobic or microaerophilic bacteria and protozoa.

Several works on the polarograhic and voltammetric reduction of tinidazole have been published. However, no attempt has been made to study the electrochemical reduction of tinidazole at carbon based electrodes.

In this work,the optimum voltammetric conditions for the determination of tinidazole were described based on the reduction at activated glassy carbon electrode. A single voltammetric peak, which is due to the four-electron reduction of the nitro group to the corresponding hydroxylamine, was observed over the pH 1.5-10.5 range. The peak was found to be irreversible and diffusion controlled at scan rates from 10 mVs^{-1} to 100 mVs^{-1}.

The quantitative determination of tinidazole was performed in Britton-Robinson buffer pH9,where the peak current reached the highest value.The peak current was linear with tinidazole concentration in the range $2x10^{-6}$- $8x10^{-4}$ M with a slope of 2.49 $\mu A/10^{-5}M$, intercept of 8.66μA and correlation coefficient of 0.998 by linear sweep voltammetry at activated glassy carbon electrode.

The proposed method was applied to the determination of tinidazole in tablets.Furthermore, results obtained by the proposed method have been compared with the HPLC [1] with UV detection. The voltammetric method presented in this study can be concluded to be used accurate, simple and practical in the determination of tinidazole in tablets.

[1] Menouer,M., Guermouche, S., Guermouche, M.H., **J.Pharm.Belg.**,42, 243, 1987.

ELECTROCHEMICAL OXIDATION OF THE SYMPATHOMIMETIC AGENT TERBUTALINE SULFATE

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Terbutaline sulfate [1-(3,5-dihydroxyphenyl)-2-t-butylaminoethanol sulfate], is a β_2-adrenoceptor agonist, primarly used in the treatment of asthma, bronchitis and emphysema.

To the best of our knowledge, the voltammetric characteristics of this drug have not yet been reported.

This study describes the electrooxidation of terbutaline sulfate at the platinum and activated glassy carbon electrode. The compound was oxidized irreversibly at high positive potentials at both electrodes. The response was evaluated with respect to pH, scan rate, nature of the buffer and other variables.

From a quantitative point of view, the glassy carbon electrode was well suited for the sensitive determination of this drug in phosphate buffer pH 6 at scan rate of 0.1 Vs^{-1}. The peak current at about 0.8 V vs SCE was proportional to the concentration in the range of 8.10^{-6} to 8.10^{-4} M. The activation of the glassy carbon surface by applying a new pretreatment [1] allowed a higher sensitivity compared with the non-activated surface.This pretreatment resulted in limit of detection for the compound down to 6.10^{-6} M.

The proposed method was readily applied to the determination of terbutaline sulfate in tablets and syrups without any preceding and time-consuming separation.

[1] Özkan, S., Biryol, İ., Şentürk,Z., **Turkish J. Chem.**, 18, 34, 1994.

DETERMINATION OF FURAZOLIDONE IN TABLETS BY REDUCTION AT ACTIVATED GLASSY CARBON ELECTRODE

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Furazolidone, a nitrofuran derivative with a nitro group at the 5-position on the furan ring, has been used as an antibacterial and bactericidal agent.

The electrochemical reduction of furazolidone at mercury or solid electrodes is a classical voltammetric behavior. However, up to date, none of these voltammetric methods at solid electrodes has been applied for the determination of furazolidone in pharmaceutical formulations.

In this work, the electrochemical reduction of furazolidone at a glassy carbon electrode activated by applying a new pretreatment was studied to carry out its direct determination in tablets.

The voltammetric reduction of furazolidone was found to give rise to a single well defined peak in the pH range 1.5-12.0. Quantitative measurements were made in 0.2 M H_2SO_4 and phosphate buffer pH 7, because of the best peak definition and the highest signal. Voltammograms recorded at scan rate of 100 mVs^{-1} showed that furazolidone can be determined in the entire concentration range $6x10^{-6}$ to $6x10^{-4}$ M (i [µA]= 14.92 + $2.63x10^5$ C [M] r=0.999) with a detection limit of $5x10^{-6}$ M and $4x10^{-6}$ to $6x10^{-4}$ M (i [µA]= 27.49 + $3.57x10^5$ C [M] r=0.998) with a detection limit of $2x10^{-6}$ M in H_2SO_4 and phosphate buffer, respectively. The suitability of the proposed method was illustrated by determining furazolidone in tablets. The results obtained by the proposed method were compared with USP XXIII procedure which involves a spectrophotometric method.

INVESTIGATION OF THE OXIDATION MECHANISM OF BAMIPINE

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Studies of the electrochemical oxidation of bamipine [4-(N-benzylanilino)-1-methylpiperidine], which is used as an antihistaminic drug, have been limited to its voltammetric investigation at platinum(1) and carbon fiber (2) electrodes.

The aim of this work was to determine the redox behavior of this drug at a glassy carbon electrode and to compare the results with those of carbon paste and platinum electrodes. The influence of pH, various electrolytes, concentration, scan rate and presence of surfactant was carefully examined by linear scan and cyclic voltammetry.

Using differential pulse voltammetry, the drug yielded a well-defined voltammetric response in phosphate buffer pH 7.4, with 20% methanol at +0.74 V (vs Ag/AgCl). Three linear sections with slopes of 9.15 $\mu A/10^{-4}M$, 3.73 $\mu A/10^{-4}M$ and 2.16 $\mu A/10^{-4}M$ were found in the $1x10^{-6}$ to $1x10^{-5}$ M, $1x10^{-5}$ to $1x10^{-4}$ M and $1x10^{-4}$ to $6x10^{-4}$ M concentration ranges, respectively. The reproducible voltammetric signals were obtained with relative standard deviation of 2.4% for 7 replicate measurements of $4x10^{-5}$ M bamipine.

[1] Biryol,İ., Kabasakaloğlu,M., Şentürk,Z., **Analyst**, 114, 181, 1989.
[2] Surmann,P., Peter,B., **Electroanalysis**, 8, 692, 1996.

MEMBRANE THIOL OXIDATION IN PATIENTS WITH DILATED CARDIOMYOPATHY

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Thiol (SH) oxidation is one of the important indicators of oxidative stress in the body. There is high incidence of fatal arrhythmias and sudden cardiac death among the patients with dilated cardiomyopathy. Increased oxidative stress may be responsible for high arrhytmia and sudden death rate in these patients. From this point of view, we aimed to investigate membrane thiol oxidation by measuring thiol status of red blood cell membranes (RBCM) obtained from the patients with dilated cardiomyopathic heart failure and from healthy subjects. A total of 23 patients with heart failure, 16 men and 7 women, ranging in age from 31 to 66 years, were studied. Causes of heart failure were idiopathic dilated cardiomyopathy (IDC) in 12 patients (8 men and 4 women, aged from 31-66 years), and ischemic heart failure (ischemic dilated cardiomyopathy: ISCDC) in 11 patients (8 men and 7 women, aged from 32-65 years). Twenty-one healthy normal volunteers, 12 men and 9 women, aged from 25 to 67 years, were also included in the study. Red blood cell membranes were isolated according to Hanahan and Ekholm (1). Free SH groups in the membrane preparations were determined by dithiobis nitrobenzoic acid according to the method of Habeeb (2). Thiol levels of RBCM were calculated by the use of molar absorbtivity of thionitrobenzoate anion, the reaction product. Results were expressed as µmol SH / mg membrane protein. Protein measurements in membrane preparations were carried out by a modification of Lowry procedure (3). Statistical significance between the groups was determined by Mann - Whitney U Test. Scatter plot of the RBCM SH status of IDC, ISCDC and control groups is shown in Figure 1. There was no statistically significant difference between the RBCM SH levels of two patient groups (P>0.05). But SH content of RBCM of the ISCDC and IDC groups were significantly decreased as compared with healthy controls (P=0.0008 and P=0.0173, respectively). In conclusion, increased membrane SH oxidation due to oxidative stress may increase the incidence of arrhthmia and sudden death in patients with dilated cardiomyopathy.

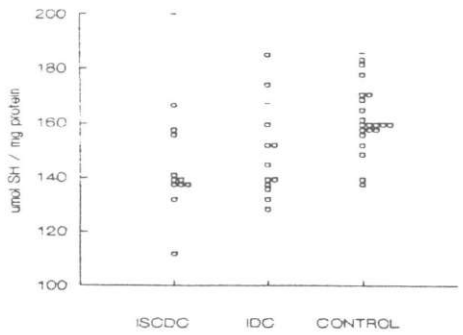

Figure 1. Scatter plot of RBCM SH content of the groups.

References

1. Hanahan DJ, Ekholm EJ. **Methods Enzymol** 1974;31:168 - 72.
2. Habeeb AFSA. **Methods Enzymol** 1972;25:457 - 64.
3. Markwell MA, Haas SM, Tolbert NE, Bieber LL. **Methods Enzymol** 1981;72:296 - 303.

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LIPID PEROXIDATION IN PATIENTS WITH BREAST CANCER

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Many studies have implicated lipid peroxidation in aging and several diseases such as cancer, atherosclerosis, rheumatoid arthritis, inflammation, reperfusion injury, lupus. Therefore, it would be desirable to detect lipid peroxidation breakdown products in biological materials. MDA is one of the final decomposition products of lipid peroxidation.

In this study, the levels of serum MDA were determined in 59 breast cancer patients and 59 healthy controls. The average MDA levels of patient group was estimated to be 6.82 µmol/L and that of normal subjects 3.65 µmol/L. The MDA levels in breast cancer patients were significantly higher than that in normal subjects ($p<0.001$).

There was no significant difference between serum triglycerides levels of controls and those of cases ($p>0.05$) but cholesterol levels of controls were found significantly higher than those in cases ($p<0.001$). There was correlation between serum levels of MDA and triglycerides and cholesterol levels in both groups ($r= -0.2938$ $p< 0.001$, $r= -0.4661$ $p <0.001$, respectively).

There was no statistically difference between controls and cases in terms of uric acid levels ($p>0.05$) but albumin levels of controls were found higher than those in cases ($p<0.05$). There was correlation between serum levels of MDA and albumin levels in controls and cases ($r=-0.1995$, $p< 0.05$).

The effects of factors such as age, menopausal status, menopausal age, quetelet index (kg/m^2), age at first birth, suckling period, inherited cancer history, metastasis, chemotherapy, smoking status, drinking habits, dietary habits, dietary fat consumption on serum MDA levels were evaluated statistically.

EFFECTS OF PYRIDINE ON RABBIT LIVER AND LUNG DRUG METABOLIZING ENZYMES: *p*- NITROPHENOL HYDROXYLASE, ETHYLMORPHINE N-DEMETHYLASE AND 7-ETHOXYRESORUFIN O -DEETHYLASE

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The aim of this study was to determine the *in vivo* effects of pyridine treatment on P450 dependent drug metabolizing enzymes; *p*- nitrophenol hydroxylase, ethylmorphine N- demethylase and 7- ethoxyresorufin *O*- deethylase in liver and lung.

Adult male New Zealand white rabbits were injected three times intraperitoneally on day 1, 5 and 8 with 250 mg/kg body weight of reagent grade pyridine as a 20% solution. Controls were administrated with saline. Liver and lung microsomes were prepared from control and pyridine treated rabbits. The cytochrome P450 contents and microsomal drug metabolizing enzyme activities were determined (1).

Results suggested that, pyridine treatment of rabbits caused 4.4- fold increase in *p*-nitrophenol hydroxylase activity of rabbit liver microsomes but it did not alter the activity of enzyme in lung. No significant change was observed in the activity of ethylmorphine N-demethylase in liver but the enzyme activity was enhanced 1.8-fold in lung microsomes. Pyridine treatment caused 6.9- and 3.2- fold increases in liver and lung 7-ethoxyresorufin O-deethylase activity, respectively.

P450 contents of liver and lung were also enhanced by pyridine treatment by 2.0 - and 1.4 - fold, respectively. Induction of P450 isozymes was observed with the high intensity bands corresponding to Mr of 51000 and 53000 in the SDS- PAGE profile of liver microsomes from pyridine treated rabbits.

Administration of pyridine markedly enhanced hydroxylation rates of *p*- nitrophenol which is a specific substrate for cytochrome P4502E1. Ethylmorphine is not a specific substrate for cytochrome P4502E1 thus, as expected liver microsomal ethylmorphine N- demethylase activity was not altered upon pretreatment of rabbits with pyridine.The increase in lung ethylmorphine N- demethylase activity was found statistically insignificant. However, 7- ethoxyresorufin *O*- deethylase activity was enhanced by pyridine treatment in both organs and this increase is known to be associated with cytochrome P4501A1 induction.

[1] Arınç E., Adalı O., İşcan M., Güray T., **Arch. Toxicol.**, 65, 186- 190, 1990.

SERUM FREE CARNITINE AND LIPID LEVELS IN PEDIATRIC PATIENTS UNDERGOING HEMODIALYSIS OR CONTINUOUS AMBULATORY PERITONEAL DIALYSIS

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Lipid and lipoprotein abnormalities have long been recognized in uremic patients treated with hemodialysis (HD) and peritoneal dialysis (PD) (1). The causes of these abnormalities are still remain unclear, but are probably multifactorial (2). Some studies have suggested that carnitine deficiency resulting from the loss of carnitine during dialysis may also be a contributing factor since this low molecular weight substance is necessary for mitochondrial fatty acid oxidation (3, 4). However, there are conflicting reports related with serum carnitine levels in undialyzed and dialyzed patients with chronic renal failure. We, therefore, aimed to evaluate serum free carnitine levels in undialyzed and dialyzed pediatric patients with end-stage renal failure, and in their age-matched healty controls. Dialyzed patients were treated with hemodialysis (HD) or continuous ambulatory peritoneal dialysis (CAPD).

We also determined serum total cholesterol (TC), triglyceride (TG), high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C) and very low density lipoprotein cholesterol (VLDL-C) levels. In statistical evaluation, TC and LDL-C levels in CAPD treated patients; TG and VLDL-C levels in undialyzed, HD and CAPD treated patients were significantly higher than those of controls. In HD patients HDL-C levels were found to be significantly lower compared to controls. Although serum free carnitine levels in dialyzed patients lower than those of controls, the difference was not statistically significant.

[1] Appel, G., **Kidney International**, 39, 169-183, 1991.
[2] Wanner, C., Frommherz, K., and Hörl, W.H., **Cardiology**, 78, 202-217, 1991.
[3] Wanner, C., Forster-Wanner, S., Shaeffer, G., Schollmeyer, P., Hörl, W.H., **Am. J. Nephrol.**, 6, 206-211, 1986.
[4] Murakami, R., Momota, T., Yoshiya, K., Yoshikawa, N., Nakamura, H., Honda, M., and Ito, H., **J. Pediatric Gastroenterelogy and Nutrition**, 11, 371-374, 1990.

DETERMINATION OF ASCORBIC ACID LEVELS WITH HPLC IN LUNG CANCER

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Ascorbic acid is the most effective, a water soluble, chain-breaking antioxidant that reacts directly with free radicals, but also it can act as a prooxidant. Ascorbic acid can act as a sinergist with tocopherol in lipid peroxidation. On the other hand. it can be protected by urate in biological fluids. Recent studies have suggested that there is an important releationship between vitamin C and cancer.

We aimed to measure the levels of ascorbic acid with HPLC that can have effective functions in prophylaxis and treatment of cancer.

In our study, serum vitamin C, uric acid, and albumin, cholesterol and triglyceride levels of 30 patients diagnosed as primary lung cancer and 45 healthy subjects were measured. The effects of factors suggest cell type of cancer, age, quetelet index, dietary habits, drinking habits and smoking on serum vitamin C levels were evaluated statistically. A significant difference was found when the average vitamin C levels of patient group (0.112±0.112mg/dl) compared with control group (0.394±0.200 mg/dl) ($p<0.05$).

Our data indicate that there are no statistically significant reletionship between serum ascorbic acid levels and above factors. There wasn't found correlation between serum vitamin C levels of patients with lung cancer and uric acid, albumin, cholesterol and triglyceride levels (respectively, $r= -0.144$; $r= 0.047$; $r= 0.075$; $r= -0.09$).

A STUDY ON DISTRIBUTION OF PHARMACIES IN Turkey FOR THE PERIOD OF 1990-1996

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There are seven Faculty of Pharmacy in Turkey. Some of the graduates from these faculties work in state instutions and hospitals, some of them work in pharmaceutical industry and universities but most of them establish a pharmacy or work in a pharmacy.
In this study, the distribution of the pharmacies, and ratio of pharmacy/ population have been invesigated for the period of 1990-1996.

Data of this study have been collected by reviewing of the records of the pharmacies in the Pharmacy Licence Branch of the General Directory of Drug and Pharmacy of the Ministry of Health. These data have been evaluated together with the knowledge obtained from the State Institute of Statistics Prime Ministry of Republic of Turkey.

As a result of the study, the estimated population of Turkey is 62.697.000 and there are 16.716 pharmacies in 80 cities at the end of 1996. According to these data, there is one pharmacy for 3747 persons in Turkey.

The data of this study have been compared with data of the previous studies and some evaluations have been carried out.

A STUDY ON THE KNOWLEDGE LEVELS OF PATIENTS ABOUT MEDICINES ADDRESSING COMMUNITY PHARMACIES IN TWO DIFFERENT REGIONS OF ANKARA

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The responsibility of the public in rational use of medicine is conscious consumption. In fact, this responsibility is shared among public, medical staff and media communication.

This research has been made in the aim of determining the consciousness and knowledge levels of patients going to pharmacies in two different domicile areas of socio-economical and cultural differences.

The research is made between the dates 1 June - 30 August 1996 in Ankara.

The survey is applied to 500 patients with a face to face meeting who had gone to a pharmacy in order to buy medicine in Küçükesat district in Çankaya county having high socio-economical condition and in Esertepe district in Keçiören county having a lower socio-economical level. After a code key is formed by the survey technical using the data gathered; statistical evaluations are done in computer conditions by using SPSS program.

In the study significance tests, khi-square tests, log-linear analysis and percentage importance tests are used.

At the end of the study it is observed that people living in Küçükesat according to their physical specifications are more capable of buying conscious medicine than the public of Esertepe.

A RESEARCH ABOUT THE ATTITUDES OF THE COMMUNITY PHARMACISTS, WORKING IN THE ANKARA MUNICIPALITY BORDERS, TOWARDS THE ETHICAL PROBLEMS THEY ENCOUNTERED

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Although pharmacy ethics is a new field for Turkey, many researches were made about this subject in the last years.

Pharmacy ethics investigates how a pharmacist should behave in a particular situation by adopting the ethical rules and principles to the pharmacy practice.

In this study, an inquiry has been carried out to 408 pharmacists. They are choosen among 1052 community pharmacists, who are registered to the Ankara Pharmacists Chamber at the end of 1995 and working in 8 regions, by Random Sampling Method. The data collected by interviews and questionnaires is coded and statistically analyzed. The statistical analysis is accomplished by the utilization of SPSS (ver.2.0) software programme and x^2 (khi-square) test is applied.

Some of the findings of this study are as follows: 79.1 % of the pharmacists that the questionnaire applied indicated that patient counselling is always important. And 61.1% of these pharmacists indicated that they are against the advertisement of drugs and 77.5% of them indicated that the distrubition of OTC drugs should be made only from the pharmacies.

By the application of this questionaire the attitudes of community pharmacists are tried to be determined and the different aspects of the subject have been discussed.

ANTIMICROBIAL SUSCEPTIBILITY PATTERNS OF RECENTLY ISOLATED OXALATE UTILIZING BACTERIA

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Oxalic acid and its sodium, potassium, ammonium, or calcium salts occur in tissues of many species of plants and algae and is ingested with the plant material by man and animals. In humans, oxalate is present in the blood, in urine, and kidney stones. There is an interesting phenomenon that treatment of kidney stones could probably be attempted with oxalate degrading enzymes from oxalate-utilizing bacteria. Several species of aerobic bacteria are known to be able to grow with oxalate. But their antibiotic susceptibility patterns have not been reported yet.

In this paper, susceptibilities of eight strains of aerobic, oxalate-utilizing bacteria and two oxalate-utilizing reference strains *Pseudomonas oxalaticus* DSM 1105 and *Methylobacterium extorquens* DSM 1337 to 18 antimicrobial agents were determined by the National Committee for Clinical Laboratory Standarts (NCCLS) disk diffusion method. All strains were sensitivity towards Carbenicillin and resistant to Rifampicin. Penicillinase production was detected in 80% of all strains tested.

The results show that in addition to the normal determination methods it is possible to separate some of the strains of these oxalate utilisers with the help of antimicrobial susceptibility patterns.

INVESTIGATIONS ON THE RHIZOMES OF *CNIDIUM SILAIFOLIUM* (Jacq.) Simonkai subsp. *ORIENTALE* (Boiss.) Tutin

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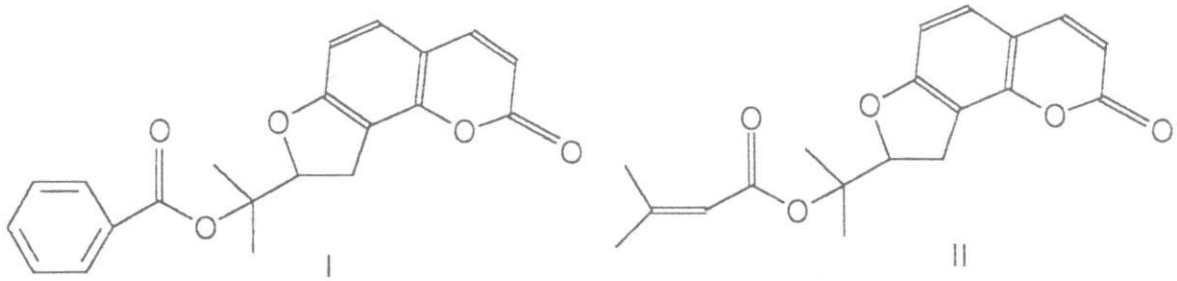
The genus *Cnidium* is represented by one species in Turkey. Here we report coumarins from the rhizomes of *Cnidium silaifolium* ssp. *orientale*. Rhizomes of *Cnidium* species are used for sedative, antiallergic and antiinflamatory effects in Japan and some far - east countries[1]. Apart from these activity their antitumoral, antimutagenic and anticomplementary effects were also determined[2].

The plant material was collected from Kastamonu- Tosya. The rhizomes were extracted with Et_2O and concentrated. The dried extract was applied to column chromotography over silica gel eluting with n- hexan: EtOAc with increasing concentrations of EtOAc. The obtained fractions were either rechromotographed or applied to prep. HPLC, yield : Benzoiloxy Columbianetin (compound **I**) and O- Senecioiloxy Columbianetin (compound **II**). The structures of compounds were based on their spectral analysis (MS, ^1H -^{13}C- and 2D - NMR). **I** is a new compound and reported for the first time.



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References

[1] LEE, S.Y., KIM, M.J., YIM, D.S., KIM, H.Y. : Phythalide Content of Cnidium rhizome. **Saenyak Hakhoechi**. 21 (1) : 69-73, 1990, **Ref. C.A.** 113 : 217923 q , 1990.

[2] OKUYAMA, T., TAKATA, M., NISHINO, H., NISHINO, A., TAKAYASU, J., WASHIMA, A. : Studies on the Antitumor Promoting Activitiy of Naturaly Occurring Substances. II . İnhibition Tumor - Promoter- Enhanced Phospholipid Metabolism by Umbelliferous Materials. **Chem. Pharm. Bul**. 38 (4) : 1084-1086, 1990.

FATTY-ACID COMPOSITION OF THE SESAME OILS PREPARED BY TWO DIFFERENT METHODS

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Sesamum indicum L.(Sesame, Pedaliaceae family) is cultivated especially in Aegean and Mediterrenean regions of Turkey(1).

In this study , sesame oil is extracted from sesame seeds by two different extraction methods; namely, by soxhelet extraction and by percolation at room temperature(2) Amount and fatty-acid composition of the two oils are determined by capillary GLC method.

Sesame oil is methylated by the method given by Metcalfe -1966 (3) and fatty-acid methyl ester composition of the saponified fraction is analysed on OV-1 column by capillary GLC.

The results indicate that fatty-acid composition of the two oils prepared by different methods is somewhat different from each other. (Table 1)

Table 1: Fatty-acid Composition of the Sesame Oils Prepared by Two Different Methods

Sesame oil	Amount of Sesame oils (a/a)	Palmitic acid	Stearic acid	Oleic acid	Linoleic acid	Arachidic acid
Soxhelet extraction	52.1 %	9.7570	5.7779	39.6219	44.3110	0.5319
Percolation at room	48.9 %	10.3063	6.1239	42.6410	40.5299	0.5644

REFERENCES

[1] Baytop,A: Farmasötik Botanik. Baha matbası,Istanbul,1967.

[2] Hudson,B.J.F: Evening Primrose (Oenothera spp.) Oil and Seed. The American Oil Chemists' Society Journal. 61(3), 540-543,1983.

[3] Metcalfe,L.D., Schimita,A.A., Pelka,J.R: Rapid Preparation of Fatty Acid Esters From Lipids for Gas Chromatographic Analysis. Analytical Chemistry, 38(3), 514-515,1966.

FLAVONOID COMPOUNDS FROM *Ballota saxatilis* subsp. saxatilis

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Ballota species have been known since the Dioscorides and the infusions prepared from from the leaves are reported to possess antiulcer, antispasmodic and sedative activities (1). Diterpenoids and flavonoids in plant are active compounds. In this work, the flavonoidal compouns of *Ballota saxatilis* subsp. saxatilis were investigated. The aerial parts of *Ballota saxatilis* sabsp. saxatilis were extracted with Me_2CO and chromatographed on a Silica gel column and eluted with Petroleum ether-EtOAc mixtures. the Petroleum ether- EtOAc (90:10, 80:20) fractions eluted Compound **1,2,3,4.** The structures have been elucidated by spectroscopic methods (UV, EI-MS, ^{1}H-NMR, ^{13}C-NMR) in comparison with previously reported data (2,3). These data allowed us to identificate compounds as **6, hydroxy kaempferol 7,4' dimethyl ether, Qercetin 3,7,3',4' tetra methyl ether, 6, hydroxy apigenin 7,4' dimethyl ether, Kaempferol 3,7,4' trimethyl ether**.

[1] Meriçli, A.H, Meriçli, F., Tuzlacı, E., **Acta Pharmaceutica Turcica**, 30, 143-144 (1988).

[2] Ferreres, F.A., Tomas-Barberan, F., **Journal of Natural Products**, 49 (3) 554-55 (1986).

[3] Tomas-Barberan, F., Gil, I.M., **Phytochemistry**, 31 (9), 3097-3102, (1992).

DITERPENOIDS FROM *Ballota saxatilis* subsp. saxatilis

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Ballota L. is a wide spread genus of the Lamiaceae family. In Turkey, *Ballota* genus is represented by eleven species, six subspecies, ten of which are endemic (1). The leaves and the tops of the plant are used for the treatment of colic, astma, influenza, insomnia and haemorrhoids (2). Ballota saxatilis subsp. saxatilis is distributed in Central Anatolia and has not been investigated before. The present work reports the isolation of diterpenoids from this plant. The aerial parts of *Ballota saxatilis* subsp. saxatilis were extracted with Me_2CO and chromatographed on a Silica gel column and eluted with petroleum ether-EtOAc mixtures. The petroleum ether-EtOAc (98:2, 90:10) fractions eluted compounds **1, 2, 3**. The structures have been elucidated by spectroscopic methods (EI-MS, ^{1}H-NMR, ^{13}C-NMR) in comparison with previously reported data(3,4). These data allowed us to identificate compounds as **Hispanolone**, **Dehydrohispanolone** and **Ballonigrine**.

[1] Davis, P.H., **Flora of Turkey and the East Aegean Islands**, 7, Edinburg Univ. Press, Edinburg, 1972.
[2] Meriçli, A.H., Meriçli, F., Tuzlacı, E., **Acta Pharmaceutica Turcica**, 30, 143-144 (1988).
[3] Savona et al., **Phytochemistry**, 31(1), 344-346 (1992).
[4] Savona et al., **J. Chem. Soc. Perkin Trans.** 1, 322-324 (1977).

COUMARINS OF DAPHNE PONTICA L. : I-DETERMINATION OF UMBELLIFERONE AND DAPHNORETIN

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Daphne pontica L. (Thymelaeaceae), which is called in Turkish as sırımağı, sırımbağı, kurtbağı, karaot regionally; is widespread along the coast of Blacksea Region and also grows up Marmara and Middle Anatolian Region. This plant which grows underneath of forest is a species of *Daphne*(1,2). According to literature (3,4) and our studies it was undestood that this plant contains mainly coumarins.

Methanol and chloroform extracts of the leaves have been examined by TLC separately. And chloroform extracts of the stems and also the leaves have been applied to silica gel column chromatography and eluted by increasing eluting power of petroleum ether: chloroform: methanol. Umbelliferone has been determined in fraction (79-118) eluted by benzen:chloroform (70 : 30) from the column and daphnoretin has been also determined in initial chloroform and methanol extracts of the leaves by TLC developing with benzen:buthanol (95:5) and toluen:ether (saturated by 10 % acetic acid) on silica gel. Then the presence of these two coumarins have been proved by comparing Rf values and the UV spectrums of the samples that were isolated with the authentic samples (5).

As a result, it was determined that the leaves of *Daphne pontica* L. also contain umbelliferone and daphnoretin in the free state like stems of this plant. Especially, existance of umbelliferone in the leaves of this plant have been observed for the first time.

1. KARAMANOĞLU, K.: Türkiye Bitkileri. I. Cilt, A. Ü. Ecz. Fak. Yayınları, Sayı 32, Ankara, 1974.
2. BAYTOP, A.: Farmasötik Botanik Ders Kitabı, İst. Üniv. Basımevi, Üniv. Yayın No:3637, Fak. Yayın No:58, İstanbul, 1991.
3. ERGENÇ, N. : The Daphnin and Daphnetin of *Daphne pontica* L.. İstanbul Ecz. Fak. Mec. 4, 72-76, 1968.
4. DOĞANCA, S. : *Daphne pontica* L. Üzerinde Fitokimyasal Araştırmalar II.. Mar. Üniv. Ecz Der., 3 (1): 69-70, 1987.
5. YAMAGUCHI, K. : Spectral Data of Natural Products. Vol. 1, Elvesier Publishing Company, New York, 1970.

RECENT STUDIES ON THE TRITERPENIC GLYCOSIDES OF CIMICIFUGA SPECIES

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The rhizomes of several species of *Cimicifuga* genus are used for treatment of an anti-inflammatory, antipyretic and analgesic remedy in traditional chinese medicines. So far many kinds of the constituents such as caffeic acid congeners, chromones, isoflavones, a carbazole alkaloid, indolinones, and cycloartane triterpenic congeners and their glycosides.

We have investigated the constituents of Japanese *Cimicifuga* species and reported the structures of 25 triterpenic glycosides. Now we report the isolation of new glycosides named cimiaceroside, cimicifugoside S-1, S-2, and S-3 from *C. simlex* and *C. acerina* and the structural elucidation on the basis of spectral data, the absolute stereostructure of cimicifugoside determined by the X-ray analysis and the CD of the reaction products, and biological activities of the glycosides obtained so far, aglycones and reaction products, such as antimalaria, inhibition of thymidine transport and antilipemic effects.

ALKALOIDS OF *GONOCYTISUS PTEROCLADUS*

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Gonocytisus pterocladus (Boiss.) Spach is an errect shrub up to 5m. In this research, the alkaloids of *G. pterocladus* which have not been studied before were investigated. The alkaloids of different organs (roots, stems, leaves, flowers, pods and seeds) of the plant collected in the vicinity of Hatay, Turkey were isolated and identified on the basis of their R_f values, Mps., IR and Mass spectral characteristics and in comparison with published data.

IRIDOID AND PHENYLPROPANOID GLYCOSIDES OF *PHLOMIS PUNGENS* var. *PUNGENS*

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As a part of our continuing studies on the secondary metabolites of the *Phlomis* species (1-4) which are used as tonic and stimulant in Anatolia (5), now we report the constituents of *Phlomis pungens* Willd. var. *pungens* (Labiatae).

The plant material was collected from Çorum, Boğazkale,Hattuşaş, Turkey. Air-dried aerial parts of the plant were extracted with MeOH. This crude extract was concentrated in vacuo to dryness. Its water soluble part was extracted with petroleum ether and then the aqueous phase was concentrated and chromatographed over poliamide eluting with H_2O, followed by increasing concentrations of MeOH. The fraction eluted with H_2O was chromatographed over silica gel by stepwise elution with $CHCl_3$-MeOH-H_2O (80:20:2 → 60:40:4) and then rechromatographed over Sephadex LH-20 with MeOH to give compound **1**(Iridoid glucoside).

The fractions eluted with H_2O-MeOH (50:50, 25:75) from the poliamide column, rich in phenylpropanoid glycosides applied to Medium Pressure Liquid Chromatography (MPLC) by using reversed-phase column. Eluting with increasing amounts of MeOH (20 → 60%) yielded compounds **2-4**.
The fraction eluted with MeOH from the poliamide column rich in flavonoids has still been under the investigation.

Structures of the isolated compounds **[1-4]** were established by spectroscopic (UV, IR, FAB-mass, ^{1}H-NMR, ^{13}C-NMR, 2D-NMR) methods and determined as lamiide **[1]** (6), forsythoside B **[2]** (7), alyssonoside **[3]** (8, 9) and leucosceptoside B **[4]** (10).

Alyssonoside and leucosceptoside B were isolated for the first time from a *Phlomis* species.

1. Çalış, İ., Başaran, A.A., Saracoğlu, İ., Sticher, O., Rüedi, P., Phytochemistry, **29**, 1253 (1990).
2. Çalış, İ., Başaran, A.A., Saracoğlu, İ., Sticher, O., Rüedi, P., Phytochemistry, **30**, 3073 (1991).
3. Başaran, A.A., Saracoğlu, İ.,Çalış, İ., Hacettepe University, Journal of The Faculty of Pharmacy **11**, 81 (1991).
4. Saracoğlu, İ., Inoue, M., Çalış, İ., Ogihara, Y., Biol. Pharm. Bull., **18**, 1396 (1995).
5. Baytop, T., Therapy with Medicinal Plants in Turkey (Past and Present), İstanbul, Publications of Istanbul University, No: 3255 (1984).
6. Bianco, A., Bonini, C., Guiso, M., Iavarone, C., Tragola, C., Gazz. Chim. Ital., **107**, 67 (1977).
7. Endo, K., Takahashi, K., Abe, T., Hikino, H., Heterocycles, **19**, 261 (1982).
8. Çalış, İ., Hosny, M., Khalifa,T., Rüedi, P., Phytochemistry, **31**, 3624 (1992).
9. Warashina, T., Miyase, T., Ueno, A., Phytochemistry, **31**, 961 (1992).
10. Miyase, T., Koizumi, A., Ueno, A., Noro,T., Kuroyanagi, M., Fukushima, S., Akiyama, Y., Takemoto, T., Chem. Pharm. Bull., **30**, 2732 (1982).

THE COMPARATIVE STUDIES ON TWO VARIETIES OF *PHLOMIS PUNGENS* BY HPLC, I.

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There are 34 *Phlomis* species growing in Turkey (1) and some of them are used as tonic and stimulant in Anatolia under the traditional name of "Çalba, Şalba" (2).In our previus researches we studied on *Phlomis linearis* and *P. armeniaca* (3-6). In addition to this species, in this study we have investigated two varieties of *P. pungens* Willd.

Phlomis pungens Willd. var. *pungens* and *P. pungens* Willd. var. *hirta* Velen. were collected from Çorum, Boğazkale, Hattuşaş, Turkey. Air-dried aerial parts of two plants were extracted with MeOH. H_2O-soluble part of methanolic extract was cromatographed over poliamide eluting with H_2O, followed by increasing concentrations of MeOH to yield three main fractions for each plant. Fr. A eluted with H_2O was rich in iridoid glucosides, Fr. B eluted with aqueous MeOH was rich in phenylpropanoid glycosides and Fr. C eluted with MeOH was rich in flavonoids.

Total extracts and Frs. A-B of two plants were applied to HPLC separately. All analysis were carried out on a Waters 510, Millipore HPLC system equipped with a Waters 996 Photodiode Array Detector set at 220, 254, 330, 366 nm and 3.9×300 mm, 10µm µBondapak C_{18} column by using, MeOH : H_2O (30:70) mobile phase, the flow rate was 1 ml/min.

Authentic substances : Lamiide, forsythoside B, alyssonoside and leucosceptoside B were isolated from *P. pungens* var *pungens* of which isolations and structure elucidations were presented as another poster at this meeting.

By compairing the retention times of the eluted peaks of Frs. A and B with the ones of the authenthic substances it was possible to identify the following compounds for *P. pungens* var. *hirta* and *P. pungens* var *pungens*. The output order was lamiide, forsythoside B, alyssonoside and leucosceptoside B.

The HPLC studies on the Fr.C have still been continuing. According to the results obtained, there were no significant differences between *P. pungens* var. *pungens* and *P. pungens* var. *hirta* from the point of view of iridoid and phenylpropanoid glycosides.

References

1.Davis, P. H., Flora of Turkey and East Aegean Islands, Vol. **7**, University Press, Edinburgh (1982).
2. Baytop, T., Therapy with Medicinal Plants in Turkey (Past and Present), İstanbul, Publications of Istanbul University, No: 3255 (1984).
3. Çalış, İ., Başaran, A.A., Saracoğlu, İ., Sticher, O., Rüedi, P., Phytochemistry, **29**, 1253 (1990).
4. Çalış, İ., Başaran, A.A., Saracoğlu, İ., Sticher, O., Rüedi, P., Phytochemistry, **30**, 3073 (1991).
5. Başaran, A.A., Saracoğlu, İ.,Çalış, İ., Hacettepe University, Journal of The Faculty of Pharmacy **11**, 81 (1991).
6. Saracoğlu, İ., Inoue, M., Çalış, İ., Ogihara, Y., Biol. Pharm. Bull., **18**, 1396 (1995).

IRIDOID GLYCOSIDES AND A PHENYLPROPANOID GLYCOSIDE FROM *NEPETA UCRAINICA*

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There are 33 *Nepeta* species growing in Turkey and 16 of them are endemic(1). The infusions of most of the species are used as stimulant and in gastric disorders in folk medicine of Turkey(2).

It is reported that caffeic acid esters are important substances from the point of view of chemotaxonomic studies and their distribution in Lamiaceae family at generic level has considerable value(3). Thus, in our department many plants from Labiatae have been studied to find out their chemical content. Leonosides A and B from *Leonurus glaucescens*(4), Phlinosides A, B and C from *Phlomis linearis*(5), Lavandulifolioside from *Stachys lavandulifolia*(6) are the examples of caffeic acid esters isolated from the plants studied from Lamiaceae. To continue investigations, *Nepeta ucrainica* (Lamiaceae) is studied which was collected from Kazakistan where it is used as a herbal tea.

The aerial parts of the plant were extracted with methanol. After evaporation under vacuum to dryness, water was added and then extracted with petroleum ether, chloroform and n-buthanol respectively. By using chromatographic methods, the n-buthanol extract was fractionated. 2 iridoid glycosides and a phenylpropanoid glycoside were isolated and their structures were elucidated by spectral (UV, FT-IR, ^{1}H-NMR, ^{13}C-NMR) and chemical (acidic hydrolysis) methods.

References

1. Davis, P. H., **Flora of Turkey and East Aegian Islands**, Vol. 7, University Press,Edingburg (1982).
2. Baytop, T., **Therapy with Medicinal Plants in Turkey (Past and Present)**, Istanbul, Publications of The Istanbul University, No:3225 (1984).
3. Harborne, J. B., **Z. Naturforsch. Teil** B **21**, 604 (1966).
4. Çalış, İ., Ersöz, T., Taşdemir, D., Rüedi, P., **Phytochemistry 31**, 1 (1992).
5. Çalış, İ., Başaran, A. A., Saracoğlu, İ., Sticher, O., Rüedi, P., **Phytochemistry 29**, 4 (1990).
6. Başaran, A. A., Çalış, İ., Anklin, C., Nishibe, S., Sticher, O., **Helvetica Chimica Acta 71** (1988).

ALKAN, SESQUITERPEN and DITERPENOIDS from *ABIES NORDMANNIANA* subsp. *BORNMUELLERIANA*

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Abies nordmaniana subsp *bornmuelleriana*, growing in North Anatolia of Turkey, is an endemic plant. *Abies* resin is used for the treatment of catarrh and is applied as a poultice to help arthritis, cuts and bruises and gargles for sore throats.

The aim of present study is the isolation and structure elucidation of alkan, sesquiterpen and diterpenoids from the leaves and cones of *A. nordmanniana* subsp. *bornmuelleriana* and the evaluation of the results of Brine Shrimp lethality bioassay of 11-eudesmen -4-ol.

An alkan n-nonacosanol and a sesquiterpenoid 11-eudesmen-4-ol were isolated from chloroform extract of leaves whereas diterpenoids were isolated from petroleum extract of cones.

All of the compounds were identified by chemical and spectroscopic methods (UV, IR, ^{1}H-NMR, ^{13}C-NMR) and co-chromatography on TLC.

11-eudesmen-4-ol showed moderate lethality in the Brine Shrimp test (LC_{50} =31ppm)

PYRROLIZIDINE ALKALOIDS from *Heliotropum ramossimum*

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As part of our investigation on pyrrolizidine alkaloids (PAS), we have been studied the isolation and identification of PAS from H. ramossimum. The plant was collected from Saleh-Abad, a suburb of Tehran. A voucher specimen is deposited in the herbarium of Tehran Faculty of Pharmacy.

The methanolic perculated extract of the entire plant was partitioned between EtOAc and 1% HCl in water. The aqueous layer was defatted with petroleum ether and the alkaloids were extracted by $CHCl_3$.

Isolation of the alkaloids was performed by column chromatography on silica gel using different concentrations of $CHCl_3$-MeOH as eluent system. Further isolation was carried out by TLC.

The structures of isolated alkaloids were confirmed by means of IR, ^{1}H, ^{13}C NMR and MS spectra. The following alkaloids were identified:
Heliotrine, Heliotrine N-oxide, Helurine, Helurine N-oxide.

A COPARATIVE STUDY OF THE ESSENTIAL OILS OF TWO IRANIAN NEPETA SPECIES

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The chemical compositions of the Essential oils of the aerial parts of two Iranian *Nepeta* species; *N. cephalotes* Boiss. and *N. meyeri* Benth. were determined by means of GC, GC/MS and high- resolution ^{1}H-NMR for the main compounds.

1,8- Cineol 11.4 % and 4.8 % and nepetalactone 35.1 % and 2.4 % constituted of the oils of *N. cephalotes* and *N.meyeri* respectively. The other major components of the essential oil of *N. cephalotes* were a -pinene (2.1 %), sabinen (2 %), ϖ-pinene (18.2 %), p-cymene (2.3 %), trans-pinocarevol (2.1 %), nopinone (2.6 %) and thuj-3-en-10-al (1.6 %). On the other hand 1,4-hexadiene, 2,3,4,5- tetramethyl (4.8 %) and epinepetalactone (65.1 %) were found as the main components of N.Meyeri.

CYTOTOXIC ACTIVITY OF IRANIAN SOLANUMS

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This is a first report of "cytotoxic activity of Iranian solanums" under a joint project between the Faculty of Pharmacy, Tehran University of Medical Sciences and Tokyo College of Pharmacy. Solanums are very well-known plants which have beeen used for treatment of various diseases. As a first phase of the project, seven samples of solanum species were collected from different regions of Iran in 1989, 1990 and 1991.

A voucher specimen of this plant were kept at the Herbarium of Faculty of Pharmacy. The whole parts of plants were ground and then extracted with ethanol and chloroform. The ethanolic and chloroformic extrat were tested on V79 cells for probable cytotoxic activity.

The results of this investigation will be presented at the Symposium.

ESSENTIAL OIL COMPOSITION OF TWO ENDEMIC *SIDERITIS* SPECIES FROM TURKEY

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Sideritis phlomoides Boiss. & Bal. and *S. vulcanica* Hub.-Mor. are endemic *Sideritis* species in Turkey. Water distilled essential oils from the aerial parts of these plants were analysed by GC/MS. The oils from two samples of *Sideritis phlomoides* were found to contain β-caryophyllene (11% and 30%) and α-bisabolol (14% and 16%) as major constituents. β-caryophyllene (9%) was found as the major component also in the oil of *Sideritis vulcanica*.

COMPOSITION OF THE ESSENTIAL OILS OF *THYMUS PSEUDOPULEGIOIDES* KLOKOV ET DES.- SHOST

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Water distilled essential oils from aerial parts of *Thymus pseudopulegioides* collected from three different localities in Turkey were analysed by GC/MS. One hundred and four compounds were identified representing 97.5 to 99.5% of the total components dedected in thymol/carvacrol (50.1/10.7%), thymol/linalool (23.1/20.2%), linalool/α-terpinyl acetate/geraniol (21.6/16.7/11.2%) rich oils.

THE COMPOSITION OF THE ESSENTIAL OIL OF *BIFORA RADIANS* BIEB.

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Aerial parts of *Bifora radians* herb collected in the vicinity of Eskişehir were water distilled to yield 0.42% oil. The oil was analysed by GC/MS. Aldehydes were found to be the main components. Twenty nine components were characterized representing 99.6% of the oil with (E)-2-tridecenal (47.2%) and (E)-2-tetradecenal (23.4%) as major constituents.

GC/MS ANALYSIS OF THE ESSENTIAL OIL OF *ORIGANUM HAUSSKNECHTII* BOISS. AN ENDEMIC SPECIES IN TURKEY

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Origanum haussknechtii Boiss. is an endemic species in Turkey. Water distilled essential oil from the herbal parts of this plant was analysed by GC/MS. One hundred and one components were characterized representing 91.5% of the total components detected. Major constituents of the oil obtained in 0.24% yield were identified as *p*-cymene (15.6%) and borneol (14.2%).

ANTIBACTERIAL ACTIVITY OF *SENECIO* SPECIES GROWING IN Turkey

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Senecio is the largest genus in the family Compositae. In Turkey, *Senecio* is represented with 39 species.

The chemistry of this genus is not uniform. The main compounds are pyrrolizidine alkaloids, furanoeremophilanes, eremophilanes, flavonoids and oplopanes.

Several *Senecio* species growing in Turkey are reported to be highly toxic.

In this study the antibacterial activities of the ethanolic extracts of some *Senecio* species growing in Turkey have been investigated. The antibacterial activities of the extracts are reported against *Bacillus subtilis, Escherichia coli, Escherichia faecalis, Klebsiella pneumoniae, Pseudomonas aeroginosa, Pseudomonas mirabilis, Staphylococcus aureus,* and *Stapylococcus epidermidis.*

GC/MS ANALYSIS OF THE ESSENTIAL OIL OF *ORIGANUM HAUSSKNECHTII* BOISS. AN ENDEMIC SPECIES IN TURKEY

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COMPOSITION OF THE ESSENTIAL OIL OF *NEPETA TRACHONITICA* POST FROM TURKEY

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Water distilled essential oil from the aerial parts of *Nepeta trachonitica* was analysed by GC/MS. Sixty seven components were characterized representing 86.7% of the total components detected with spathulenol (22.16%) as the major constituent.

HIGH PERFORMANCE LIQUID CHROMATOGRAPHIC ANALYSIS OF RUTIN IN SOME PLANTS

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Recently, naturally occurring flavonoids as well as those synthesized are used in modern medicine for various therapeutic effects. Especially in the U.S.A., Western and Central Europe, rutin and its semi-synthetic derivatives have found a wide application area in some veneous diseases. It is reported as an active compound for the treatment of capillary fragility, rheumatic fever of haemorrhagic conditions, the cases of coronary thrombosis, apoplexy, retinal haemorrhage and radiation injuries. A few plants containing rutin, for example *Fagopyrum esculentum, Sophora japonica, Eucalyptus macrorrhynca* are used as the sources for obtaining rutin in some countries.

Rutin is found in varying amounts in some plant species cultivated and growing naturally in Turkey. Most of these plants have been used in traditional folk medicine. In this research, a simple and successful reversed-phase high performance liquid chromatographic method was performed for the analysis of rutin in various parts of some plants. Chromatographic analysis was achieved on a LiChrospher 100 RP18 reversed phase column and using an isocratic mixture of water, methanol and glacial acetic acid (65:30:5) at a flow rate of 0.8 ml/min as a mobile phase. The UV detection was performed at 259 nm.

As a result, the quantity of rutin of methanol extracts of *Forsythia viridissima* (flower), *Hedysarum varium* (flower), *Sophora japonica* (flower), *Sophora japonica* (fruit) and *Viola tricolor* (flower) were determined as 3.08 %, 5.18 %, 6.27 %, 7.03 %, 11.37 %, respectively.

ANTIBACTERIAL ACTIVITY OF *SENECIO* SPECIES GROWING IN Turkey

F.Ergun[1], Ş.Küsmenoğlu[1], B.Şener[1], D.Deliorman[1], A.Velioğlu[2], C.Bozok Johansson[2]

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ANTIMICROBIAL ACTIVITIES OF *GALIUM* SPECIES

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Galium is a genus of Rubiaceae family which spread widely in Turkey and consists of 101 species gathered in 10 sections.

Galium species causes to coagulate the milk because of an enzyme in their chemical composition. For this reason, this plant is called as "Yoğurt herb".

The earlier works on the aerial parts of *Galium* species growing in Anatolia were studied on their flavonoids, iridoids, alkaloids by us.

The present work is concerned with assay of ethanolic extracts of various *Galium* species for their possible antimicrobial activities.

EFFECTS OF IRRIGATION ON THE OIL CONTENT AND FATTY ACID COMPOSITION OF SOME SUNFLOWER *(Helianthus annuus* L.) SEEDS

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The characteristics of vegetable oils depend on the nature of the fatty acid constituents which determine the suitability for edible and industrial uses. The oil of cultivated sunflower ((*Helianthus annuus* L.) is recognized as a high quality edible oil. It contains two main unsaturated fatty acids, oleic acid (18:1) and linoleic acid (18:2) besides two saturated fatty acids, stearic acid (18:0) and palmitic acid (16:0) . There is a strong negative correlation between oleic and linoleic acid. The fatty acid composition of sunflower oil is influenced by different factors such as temperature and genotype.

In this study, the composition of fatty acids in three inbred sunflower lines, the mixture of the lines, synthetic variety, Ekiz 1 and V.8931 were determined. The effects of irrigation and non-irrigation during the development of the plant of sunflower on the amount and content of the oils were also investigated. The fatty acid composition of seed oil was determined by gas chromatography using Ultra 1 column.

Oleic acid content is 29.06-52.20 % in non-irrigated conditions and 24.89-45.34 % in irrigated conditions. Linoleic acid content is 5.60-33.00 % in non-irrigated conditions 2.80-20.07 % in irrigated conditions.

As a result, the amount of fatty acids was increased by irrigation but the content of linoleic and oleic acid was decreased. The oils contain 34.66- 85.20 % oleic and linoleic acids. The negative effect of irrigation on the content of these fatty acids was observed.

AN INVESTIGATION ON *BALLOTA NIGRA* L. SUBSP. *ANATOLICA* P.H. DAVIS

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Ballota genus from Lamiaceae is represented by 11 species and 7 subspecies while 8 species and 2 subspecies are endemic, in Turkey. Among the *Ballota* species, *Ballota nigra* L. consists of 5 subspecies (1).

While in our Country, aerial parts of some subspecies of *B. nigra* L. are used as antienflammatory, antiseptic for wounds and against gastrointestinal disorders (2,3), in European Countries, *B. nigra* L. is especially used as sedative(4). In our previous study, anxiolytic and antidepressant activity of two endemic *Ballota* species were investigated and it has been found that both of these species showed potent activities(5).

In this study, botanical properties were investigated on an endemic subspecies; *Ballota nigra* L. subsp. *anatolica* P.H. Davis. Morphology of the plant has been described and characteristics of the subspecies were explained by the original photographs and drawings. Anatomical properties of leaves and stem of the plant were determined by means of some different techniques. In cytological examination, chromosome shapes were drawn and chromosome numbers were counted.

Therefore, aerial parts of the plant were qualitatively and quantitatively analyzed.

References

1.Davis, P.H., **Flora of Turkey and The East Aegan Islands**, Vol.7, University Press, Edinburg (1982).
2.Yeşilada, E., Honda, G., Sezik, E., Tabata, M., Goto, K., Ikeshiro, Y., Traditional Medicine in Turkey. IV. Folk Medicine in the Mediterranean subdivision, **J. Ethnopharmacology**, 39, 31-8 (1993).
3.Yeşilada, E., Honda, G., Sezik, E., Tabata, M., Fujita, T., Tanaka, T., Takeda, Y., Takaishi, Y., Traditional Medicine in Turkey. V. Folk Medicine in the inner Taurus Mountains, **J. Ethnopharmacology**, 46, 133-52 (1995).
4.Pinkas, M., Bézanger-Beauquesne, L., Torck, M., **Les plantes dans la therapeutique moderne**, 100, Maloine S.A., (Editeur) Paris (1986).
5.Vural, K., Ezer, N., Erol, K., Şahin, F.P., Anxiolytic and Antidepressant Activities of some *Ballota* Species, **J. Fac. Pharm.**, 13(1), 29-32 (1996).

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A TRIP IN INTERNET TO THE BOTANICAL GARDENS

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Internet is a magic word of today to which 160 countries and much more 40 million people are connected has become a view of an ocean which has been getting bigger day by day. The people in all over the world are able to reach to a big data source via Internet which have been being updated. It is possible to connect to the largest dictionary of the world, a big software library, 40 million users and all the subject that you can imagine. One of these subject is botanical gardens.

A lot of botanical garden which is a national herbarium today, provide the information about botany and horticulture for the people. In addition to that, they have been being the tool of the resting and the entertainment. Therefore, they make a light to the culture of the different countries and always save their dynamicism with the social activities.

It is aimed to make a trip to a green voyage via Internet which is the most important technical and social benefit of the knowledge era and to show some botanical gardens from United States of America to Holland, from England to Singapore, Australia and New Zeland and from Russia to Germany, Scotland and Alaska.

The foundation of these botanical gardens, foundational aims, development until today, their herbarium and those which are containing the plants, educational programs, scientific studies, projects and publishes, the other units and social activities will be given with their pictures and Internet adresses.

ANTI-INFLAMMATORY ACTIVITY OF SOME TURKISH *RUBUS* SPEC.

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Rubus spec. (Rosaceae) have been used for the treatment of various ailments, since the time of Dioscorides (1). There are 17 *Rubus* spec., including 8 hybrids in Turkey and mostly called as "Böğürtlen" (2-3). Among these species especially *R. sanctus* and *R. hirtus* have the most widespread utilization. Roots and leaves of these species are frequently used in folk medicine for various purposes; to treat hemorrhoids, against psoriasis and gonorhea, for wound healing, to stop bleeding, to pass kidney stone/or sand, to stop diarrhea, to promote maturation of abscess, and as well as antipyretic, antirheumatic, hypoglycemic and tonic (3-5)

In this study anti-inflammatory activity of the extracts and fractions obtained from the leaves of *Rubus sanctus* Schreber, *Rubus hirtus* Waldst. et Kit., and an hybrid plant of these two species (*R. sanctus* x *R. hirtus*) have been investigated. The activity of the methanolic extracts and fractions obtained by successive solvent extractions (petroleum ether, chloroform, ethyl acetate, n-butanol and remaining aqueous extract) were tested using carrageenan-induced hind paw edema model in mice. Indomethacin was used as a reference compound. Results confirmed the folkloric utilization of these species for the treatment of inflammatory diseases.

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References

1. Fournier, P. **"Le Livre des Plantes Médicinales et Vénéneuses de France"** Vol. III (Ed. Lechevalier,P.), Paris (1948).
2. Davis, P.H. **"Flora of Turkey and the East Aegean Islands"** Vol. 4, University Press, Edinburgh (1972).
3. Baytop, T. **"Therapy with Medicinal Plants in Turkey -Past and Present"** Istanbul University Publ., No 3255, İstanbul (1984).
4. Yeşilada, E., Honda,G., Sezik,E., Tabata, M., Goto,K., Ikeshiro,Y., Traditional Medicine in Turkey IV. Folk Medicine in the Mediterranean Subdivision, **Journal of Ethnopharmacology**, 39, 31-8 (1993).
5. Honda, G., Yeşilada, E., Tabata, M., Sezik,E., Fujita,T., Takeda,Y., Takaishi,Y., Tanaka,T., Traditional Medicine in Turkey VI. Folk Medicine in West Anatolia, **Journal of Ethnopharmacology**, 53, 75-87 (1996).

ALKALOIDS FROM TURKISH *PAPAVER TRINIIFOLIUM*

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The alkaloids of *Papaver triniifolium* Boiss. endemic to Turkey have been investigated (1). Rhoeagenine, narcotine, sinactine and cheilanthifoline have been isolated from the species collected at Beypazarı (Ankara).

In our previous works we showed the existence of chemotypes of this species growing in East Anatolia(2,3). This is the first report on the alkaloids of a sample of *P.triniifolium* obtained from Central Anatolia.

The presence of rhoeagenine has been shown for the first time in the species.

References:

1. Cullen, J. (1965) in: Flora of Turkey and the East Aegean Islands, (Davis P. H., ed.), 1, 227, University Press, Edinburgh.
2. Sarıyar, G. (1983) Planta Med. 49, 43.
3. Sarı, A. (1994) "*Papaver triniifolium* Boiss. Türünün Tersiyer ve Katerner Alkaloitleri Üzerinde Araştırmalar", Dissertation, İstanbul.

ARYLTETRALIN LIGNANS FROM *LINUM CARIENSIS*

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Lignans possess interesting biological activities, their antitumour properties being of the most importance. Podophyllotoxin is a starting compound for the chemical synthesis of antitumour agents Etoposide and Teniposide. Chemical synthesis of podophyllotoxin is possible but both complex and uneconomic. Therefore podophyllotoxin is isolated from plants grown in the Himalayas and converted chemically to the drug. Due to a limited occurence of this species, phytochemical studies have focused on the discovery of podophyllotoxin from other plant species. As already in some *Linum* species, lignans were detected (1-3). Genus Linum belongs to the Fam. Linaceae. This genus contains about 200 species mainly annual or perennial herbs with some small shrubs, and they are distributed all over the world in a very wide variety of habitat. *Linum cariensis* a member of the section Syllinum which is endemic to Turkey.

Podophyllotoxin, 5-methoxypodophyllotoxin a-peltatin and b-peltatin were isolated from ethanolic extract of *L. cariensis*. Their structure were established from spectral data.

Podophyllotoxin glucoside and 5-methoxypodophyllotoxin glucoside were also found in this species.

References

1-Weis,S. G., Tin-Wa, M., Perdue,R. E and Farnsworth, N. R., J. Pharm. Sci. 64, 95-98,(1975).
2- Berlin, J., Wray, V., Mollenschoft, C. and Sasse, F., J. Nat. Prod. 49, 435-438,(1986).
3- Broomhead, A. j and dewick, P. M., Phytochemistry, 29, 3839-3844, (1990).

TOPOLOGY OF THE AGONIST SELF-INHIBITORY LOCUS ON THE NICOTINIC ACETYLCHOLINE RECEPTOR

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The nicotinic acetylcholine receptor (AChR) is the most profusely studied neurotransmitter-gated ion channel. The specific binding of acetylcholine (ACh) in the micromolar concentration produces a conformational change on the receptor that opens the ion channel to allow movement of cations in favour of their electrochemical gradient. The excess of ACh is then hydrolized by the enzyme acetylcholinesterase. However, within a short timespan, the ACh concentration in the synaptic cleft can reach the millimolar range and cause the inhibition of the ion flux previously elicited by the same agonist. This process, named agonist self-inhibition, is belived to be mediated by agonist binding to an inhibitory site located in the channel lumen. However, the occurrence of agonist-induced displacement of quinacrine and ethidium from their nonluminal noncompetitive inhibitor binding sites respectively located at the lipid-protein interface and in the vestibule of the AChR opens the possibility for the location of the agonist self-inhibitory binding site at a nonluminal domain (reviewed in Arias, *J. Neurosci. Res.* **44**, 97-105, 1996). Particularly, the displacement of quinacrine was considered to be specific on the basis of several experimental arguments. For example: **(1)** the existence of a very important difference in the agonist apparent inhibition constants (K_i's) when these constants are obtained either by displacement of quinacrine binding or by displacement of ethidium binding; (Arias and Johnson, *Biochemistry* **34**, 1589-1595, 1995); **(2)** the same sequence order for suberyldicholine, spin-labeled ACh, ACh, and carbamylcholine to displace AChR-bound quinacrine as agonist potencies to inhibit $^{86}Rb^+$ efflux; **(3)** a higher quenching efficiency of spin-labeled ACh on AChR-bound quinacrine fluorescence than AChR-bound ethidium fluorescence, indicating that the agonist-induced displacement of quinacrine binding from its site on the AChR is mediated by a steric mechanism; **(4)** a good correlation between the relative partition coefficient of agonists in AChR-rich membranes and the K_i values obtained by quinacrine displacement, suggesting an agonist membrane partitioning approach mechanism (Arias, *Mol. Membr. Biol.* **12**, 339-347, 1995). Finally, **(5)** by comparing the agonist K_i values, obtained by AChR-bound quinacrine displacement at 4°C and in the presence of 100 mM NaCl, with the ones observed by measuring the agonist concentration that inhibit 50% of the maximum $^{86}Rb^+$ efflux from AChR vesicles (Forman et al., *Biochemistry* **26**, 2807-2814, 1987), a perfect correlation was observed (Arias, *Arch. Biochem. Biophys.* **333**, 1-11, 1996). Taking into account these data, we are able to describe a scenario where the agonist self-inhibitory binding site overlaps with the quinacrine locus. In turn, since the quinacrine binding site is located in a nonluminal domain, the agonist self-inhibition of the AChR migth be mediated by an **allosteric** mechanism.

THERMODYNAMIC OF LIGAND BINDING TO THE NICOTINIC ACETYLCHOLINE RECEPTOR

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The nicotinic acetylcholine receptor (AChR) is a glycoprotein with multiple ligand binding sites. An important question to be answered is how the AChR is modulated upon ligand binding. Among AChR pharmacological properties, the inhibition of the intrisically-coupled cation channel by exogenous and endogenous molecules has deserved special attention. Within this perspective, this work displays and attempt to elucidate the inhibitory mechanism of the AChR by spectroscopic means (Arias, *Arch. Biochem. Biophys.* **333**, 1-11, 1996). Specifically, quantitative fluorescence spectroscopy was used to characterize: (**1**) the mechanism of quinacrine binding to its high-affinity noncompetitive inhibitor binding site located at the lipid-protein interface of the AChR and (**2**) the process by which agonists at high concentrations sterically compete for the quinacrine locus. For the first purpose, we study the temperature and ionic strength dependence of quinacrine binding by measuring the apparent dissociation constant of quinacrine at the temperature range of 4-23°C and in the NaCl concentration order of 0-250 mM. For the second objective, AChR native membranes suspended in buffer 10 mM sodium phosphate, pH 7.4, were preincubated with quinacrine for 2 h. Then, the specific quinacrine fluorescence was monitored while high concentrations of cholinergic agonists such as suberyldycholine, acetylcholine, or carbamylcholine were added to the suspension. By repeating these back titrations at 4, 9, and 15°C in the absence of NaCl, and at 4°C in the presence of 100 mM NaCl, we determined the temperature and ionic strength dependence of agonist binding to the quinacrine domain. Taking into account the enthalpy change (ΔH) and the entropy change (ΔS) values obtained from the van't Hoff plots as well as the free energy change (ΔG) values, the binding of both quinacrine (measured in the temperature range from 15 to 23°C) and agonists at high concentrations (measured in the temperature regime of 4-15°C) are enthalpy-driven processes. Nevertheless, quinacrine binding is exothermic and agonist binding is endothermic. One plausible model to explain our results is that the quinacrine molecule needs first to be sterically well oriented to further enter into its binding site located in a crevice at the lipid-protein interface, whereas agonist moleculas do not. The former model for quinacrine is in agreement with the fact that the quinacrine locus is close to a nonannular lipid domain (Arias, *Biochim. Biophys. Acta*, in press, 1997). Additionally, considering the positive sign of the differential free energy change ($\Delta G_{NaCl} - \Delta G$) values of both quinacrine and agonist binding, a relatively minimal electrostatic component is present in the quinacrine locus.

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LOCALIZATION OF NONCOMPETITIVE INHIBITOR BINDING SITES ON THE NICOTINIC ACETYLCHOLINE RECEPTOR

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The nicotinic acetylcholine receptor (AChR) is the archetype of the ligand-gated ion channel superfamily. A major focus of current research on the AChR has been to determine the structural details of ligand binding sites. For this purpose, we have characterized the binding sites of two high-affinity noncompetitive inhibitors (NCIs), quinacrine and ethidium bromide, by using fluorescence resonance energy transfer (FRET) and steady-state fluorescence quenching approaches (reviewed in Arias, *Mol. Membr. Biol.* **13**, 1-17, 1996). The use of FRET has allowed measurement of the distance between the ethidium (donor) binding site and the hydrophobic probe C_{12}-Texas Red as acceptor at the surface membrane (Johnson and Nuss, *Biochemistry* **33**, 9070-9077, 1994). A transverse distance of ~46 Å was calculated by assuming a model where the donor is attached at a certain distance from the major axis of symmetry. This distance is compatible with the ethidium binding site located at the AChR vestibule wall. Additionally, the FRET measurement between the quinacrine (donor) binding site and the lipophilic acceptors C_{12}-eosin and Di10ASP-PS [*N*-(3-sulfopropyl)-4-(*p*-didecylaminostyryl) pyridiunium] (Valenzuela et al., *J. Biol. Chem.* **267**, 8238-8244, 1992) evidenced that the quinacrine locus is at a distance less than 10 Å apart from the lipid membrane, suggesting that this site should be located at the lipid-protein interface. In agreement with this location, AChR-bound quinacrine fluorescence was quenched by several spin-labeled lipid derivatives (Valenzuela et al., 1992; Arias et al., *J. Biol. Chem.* **268**, 6348-6355, 1993a; *Biochemistry* **32**, 6237-6242, 1993b). Moreover, the efficiency of spin-labeled androstane (ASL) and stearate (5-SAL) to quench the AChR-bound ethidium fluorescence was about 5 times lower than the efficiency to quench AChR-bound quinacrine fluorescence (Arias et al., 1993b). The same 5-SAL derivative and its unlabeled species stearate displaced quinacrine, but not ethidium, from its corresponding binding site (Arias et al., 1993b; Arias, *Biochim. Biophys. Acta*, in press, 1997). A deeper insight into the location of the quinacrine binding site was obtained by using a series of different positional isomers of the fatty acid analogue spin-labeled stearate, namely 5-, 7-, 12- and 16-SAL (Arias et al., 1993a). The elicited 5- and 7-SAL quenching efficiency was two times higher than the one for 12- and 16-SAL, indicating that the quinacrine binding site is located ~7 Å below the aqueous-lipid interface. Finally, by comparing the accessibilty of lipids that probe nonannular lipid domains such as 5-SAL and ASL, and spin-labeled phosphatidylcholine which only binds to the annular lipid domain, the quinacrine binding site was located close to a nonannular lipid domain (Arias, 1997). The noncompetitive inhibition process is considered to be determined by binding of NCI drugs to the channel lumen. However, the existence of nonluminal NCI binding sites (e.g., quinacrine and ethidium) opens the possibility for the regulation of cation permeation by an **allosteric** process.

THE EFFECTS OF EXOGENOUS MELATONIN AND AGE-RELATED CHANGES IN MALONDIALDEHYDE AND GLUTATHIONE LEVELS OF GASTRIC MUCOSA OF THE RATS

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Free radical levels and antioxidant capacity of the stomach with increasing age and the role of melatonin are not known well[1,2]. In this experimental study, we aimed to study the age-related changes of malondialdehyde (MDA), a lipid peroxidation product, levels of plasma and gastric mucosa, and GSH levels of gastric mucosa and the effects of short term exogenous melatonin on these parameters in the rats.

There were significant differences in the levels of plasma MDA, gastric MDA between the control groups of young and old rats (1.32±0.19 vs. 4.89±1.19 nmol/ml, p=0.024; 23.63±3.81 nmol/g stomach vs. 49.45±5.93 nmol/g stomach, p=0.006, respectively). While plasma MDA levels were significantly lower in the melatonin group of old rats when compared to the control group (1.61±0.33 vs. 4.89±1.19 nmol/ml, p=0.020) gastric MDA and GSH levels did not differ significantly (p=0.465 and p=0.882, respectively). There were no significant differences in the levels of measured parameters between the groups of young rats.

In conclusion, our results suggest that decreased gastric mucosal defense system of elderly patients may be related with an increase in free radical levels, and exogenous melatonin may not have a role on mucosal defense by means of its actions on oxidative stress.

References:

1. Szabo S: Mechanisms of gastric mucosal injury and protection. J Clin Gastroenterol 13 (Suppl. 1): S21-S34, 1991
2. Poeggeler B, Reiter RJ, Tan D-X, Chan L-D, Manchester LC: Melatonin, hydroxyl radical mediated oxidative damage and aging: A hypothesis. J Pineal Res 14:151-168, 1993

EFFECT OF ILOPROST ON HEALING DELAYED COLON ANASTOMOSES WITH INTRAPERITONEAL 5-FLUOROURACIL IN EARLY POSTOPERATIVE RATS

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5-fluorouracil (5-FU) remains the most effective chemotherapeutic agent in the management of patients with systemic colorectal cancer. The studies in recent years put forward the gradually increasing benefits of 5-FU within the adjuvant chemotherapy protocols after complete surgical resections (1). However, many studies also have demonstrate that 5-FU delays wound healing on colonic anastomoses (2). In this experimental study, we examined the influence of intraperitoneal (IP) 5-FU on healing of colonic anastomoses, and also to find out whether or not Iloprost (PGI_2 analogue, a potent vasodilator, with confirmed cytoprotectivity, and inhibitor of thrombocyte aggregation) reverses the delayed wound healing. A total of 80 Wistar-Albino male rats were seperated into 4 groups. From the day of the operation, group A received IP saline solution, group B received IP 20 mg/kg 5-FU, group C received IP 20 mg/kg 5-FU plus 2µg/kg Iloprost, and group D received 2µg/kg Iloprost. Each group were divided into two subgroups and both subgroup were sacrificed on third and seventh postoperative days, respectively. The subject were measured for anastomose bursting pressures, tissue hydroxyproline levels and the wound healing was evaluated histopathologically. The stastistical evaluations among each group were made with Student's-t and Pearson chi square tests. As a result, Iloprost had an accelerating effect on normal colonic anastomose wound healing histopathologically, had no significant difference on breaking strength and hidroxyproline levels, and significantly influenced healing of the delayed healing effect of 5-FU.

1- Grem, J.L. Current treatment approaches in colorectal cancer. Semin. Oncol., Supp. 1:17, 1991.
2- Martens, M.S.W.C., Hendriks, T., Wobbes, T., et al. Intraperitoneal cytocytatics impair early postoperative collagen synthesis in experimental intestinal anastomoses. Br. J. Cancer, 65:694, 1992.

EFFECTS OF TAURINE APPLICATION ON THE PROSTAGLANDIN AND MALONDIALDEHYDE LEVELS IN SKELETAL MUSCLE ATROPHY INDUCED BY DENERVATION

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The effects of taurine as an antioxidant and Ca^{+2} stabilizer on the denervated fast-twitch gastrocnemius and slow-twitch soleus muscles of the rats were investigated. Transport of taurine into skeletal muscle was performed by the intraperitoneal injection of 150 mg/kg/day taurine, beginning 6 hours before neurotomy and lasting 10 days. After 10 days following neurotomy the animals were sacrificed and malondialdehyde (MDA) and prostaglandin E_2 like activity (PGLA) levels of both denervated and non-treated muscle and taurine-treated muscles were measured.

MDA levels (X± SE) of the denervated and taurine-treated gastrocnemius muscles were (17.3 ± 2.2 nmol/g) lower than denervated and non-treated controls (67 ± 4.8 nmol/g). But there were no significant differences between taurine-treated and non-treated soleus muscles. Also the PGLA levels (X± SE) of denervated and taurine-treated gastrocnemius muscles were (24.4± 3 ng/g) lower than denervated and non-treated controls (39.2 ± 4.2 ng/g), but the PGLA levels of denervated and taurine-treated soleus muscles were higher than denervated and non-treated controls (41.1± 6.5; 25.2 ± 3 ng/g respectively).

The protective effects of taurine against lipid peroxidation and PGE_2 production in the denervated muscles were found to be much greater in fast-twitch gastrocnemius muscles than slow-twitch soleus muscles.

EFFECTS OF EGF DOSAGE FORMS ON THE TEAR STRENGTH AND ZINC LEVEL OF SKIN WOUND

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Epidermal growth Factor (EFG) and zinc have been reported to increase the reepithelization and reparative tissue strength through enhanced collagen deposition in the wound site (1). In this study two EGF dosage form were chosen to assess wound healing by wound tissue zinc levels and tearing strengths. Solution form of EGF in 0.9% Nacl w/v and gel form of EGF in 0.2% carbopol 940 polymer (gel) were applied on full-thickness skin wounds of mice at the rate of 5µl twice a day for 7 and 15 days (2).

Wound zinc levels increased in the 7th day compared to15th day, especially in wounds treated with EGF.The wound tear strenght of mice were significantly higher at the 15th day of treatment in the gel-treated group compared with the solution-treated mice and controls. The similarity of zinc level in the wound tissue treated with EGF in 0.2% carbopol at the 15th day of operation with unwounded dermal zinc level and increased wound tear strenght by EGF treatment in gel indicate that sustained release of EGF from bioadhesive polymer accelerates healing of full-thickness skin incision wounds of mice on 15th day.

Table I. The effect of EGF dosage forms on full-thickness incision wounds zinc levels of mice

Dermal tissue zinc level (n: 5)		138 ± 59 µg/g dry Weight	
Application	n	7th day of operation	15th day of operation
Untreated	5	145 ± 36	53 ± 7 ..,...
PS treated	5	166 ± 25	38 ± 13 ..,...
Gel treated	5	177 ± 12	43 ± 13 ..,...
PS + EGF	5	202 ± 53	155 ± 17 .
Gel +EGF	5	234 ± 50 .,...	126 ± 18 .,...

PS: 0.9 % Nacl solution 5 µl twice a day x 15 days
PS+EGF : 100 ng EGF/ml PS 5 µl twice a day x 15 days
Gel: Carbopol 940 (0.2% w/w) 5 µl twice a day x 15 day
* $p<0.05$ difference between untreated controls and treated groups
** $p<0.05$ difference between on the 7th and 15th days zinc levels of wounds
*** $p<0.05$ difference between normal skin and wound tissue zinc levels

References:

1.Laato, M., Niinikoshi, J., Gerdin, b., Lebel, L. (1986) Stimulation of wound healing by epidermal growth factor. Ann. Sur.203 (4), 379-381.
2. Çelebi, N., Erden, N., Gönül, B., Koz, M. (1994) Effects of epidermal growth factor dosage forms on dermal wound strength in mice. J. Pharm. Pharmcol. 46, 386-387

EFFECTS OF EXTRACT *GENTIANA LUTEA* subsp. *SYMPHYANDRA* ROOTS ON THE BILE FLOW IN RATS: A POSSIBLE HEPATOPROTECTIVE ACTIVITY

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There is an increasing demand in the whole world for hepatoprotective (antihepatotoxic) drugs, since epidemiological studies indicate that the incidence of hepatic diseases such as viral hepatitis, cirrhosis, hepatomegaly, hepatocarcinoma has increased. Moreover, living in a world of inadequately controlled environmental pollution and expanding pollution due to therapy with potent drugs, the liver which is the mainstay in metabolism and excretion, is continually exposed to a variety of xenobiotics and therapeutic agents. A number of standardised plant extracts and just a few compounds isolated from plants have been used for the clinical management of liver diseases. However, drugs which have been used in clinics are not quite satisfactory in terms of their efficacy, potency, safety and side effects. Starting point in the development of new hepatoprotective drugs is to study plants having ethnomedical use. As a choleretic agent, *Gentiana lutea* is one of the plants which has been used in the folk medicine for the protection of liver[1]. In the present study, we aimed to investigate possible effects of the extract prepared from *G. lutea* ssp. *symphyandra* roots on the bile production and liver in rats.

With this aim, bile flows of rats which were treated by a single i.p. dose of CCl_4 (0.12 ml/kg) 24 h prior to experiments were measured after the cannulation of bile duct under urethane anaesthesia (375 mg/kg i.p.)[2]. After an equilibration period of 1 h, the lyophilized extract were administered intraduodenally (500 mg/kg i.p.), while control animals received physiological saline only. To monitor the effect of multiple dose therapy, rats received the same dose of *G.lutea* ssp. *symphyandra* extract for 3 days (2 days prior to CCl_4 administration) and their bile flows were measured after the cannulation. In all groups, bile samples were collected for 3 h with 15 min intervals. After the completion of bile flow experiment, rat livers were removed and put in neutral formaldehyde solution (10 %) for the histological examination. According to results obtained, multiple dose treatment of rats with the plant extract was normalized the decreased bile flow due CCl_4, whereas single dose therapy was ineffective on the impaired bile flow. These data indicate that the extract prepared from *Gentiana lutea* ssp. *symphyandra* roots has a hepatoprotective activity.

References

1. Duke, J., Handbook of Medicinal Plants, CRC Press, Boca Raton USA, pp.207-208 (1985)
2. Öztürk, Y., Aydın, S., Başer, K.H.C., Kırımer, N., Kurtar-Öztürk, N., Hepatoprotective activity of *Hypericum perforatum* L. alcoholic extract in rodents. Phytother. Res. 6, 44-46 (1992).

EFFECTS OF GENTIOPICROSIDE, SWERTIAMARINE AND SWEROSIDE FROM *GENTIANA LUTEA* subsp. *SYMPHYANDRA* ROOTS ON CULTURED 3T3 FIBROBLASTS: IMPLICATIONS FOR WOUND HEALING

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Fibroblasts are among the cells which play an important role in wound healing and tissue repair through physiological properties such as migration and proliferation to cover wounded tissue, collagen syntesis to increase the tensile strength of skin etc. *G. lutea* roots have been used in folk medicine for the treatment of skin wounds (1,2). In a preliminary study, we have previously reported that gentiopicroside, sweroside and swertiamarine may be responsible for the wound healing activity of *G. lutea* subsp. *symphyandra* roots (3). The present study has aimed at investigating the effect of these three secoiridoids on 3T3 fibroblast cell lines in order to obtain further experimental evidence for their wound healing activities and approach to their mechanisms of action.

With this aim, 3T3 fibroblast cells were incubated in DMEM (Dulbecco's Modified Eagle's Medium) containing 10% FCS (Fetal Calf Serum) at 37°C gassed with 5% CO_2, cells were "trypsinized" using 2.5% Trypsin in Puck's Saline. Fibroblast cultures (containing approximately $1x10^6$ cells/ml) were rinsed after 24 hr and test compounds gentiopicroside, sweroside and swertiamarine were added into the culture medium. After 24 hr, cells were counted using a cell counter and a microscope (4). Results obtained in 3T3 fibroblast cell culture are discussed, with reference to the published information.

Literatures

1. Baytop, T., Türkiye'de Bitkiler ile Tedavi, İstanbul Üniversitesi Yayınları No:3255, Sanal Matbaacılık, İstanbul, sf.194 (1984)

2. Duke, J., Handbook of Medicinal Plants, CRC Press, Boca Raton USA, pp.207-208 (1985)

3. Korkmaz,S., Öztürk, N., Öztürk,Y., Zeytinoğlu, H., Zeytinoğlu, M., Başer, K.H.C., *G. lutea* subsp. *symphyandra* ekstresinin fibroblast hücre kültürlerindeki etkileri, XIII. Ulusal Farmakoloji Kongresi Program ve Bildiri Özetleri Kitabı, sf.156, Kemer (1996)

4. Korkmaz,S., Fibroblast hücre kültürlerinde yara iyileştirici etkinin araştırılması, Anadolu Üniversitesi Sağlık Bilimleri Enstitüsü Farmakoloji Anabilim Dalı Yüksek Lisans Tezi (1996)

ANALGESIC ACTIVITY OF THE EXTRACT PREPARED FROM *GENTIANA LUTEA* subsp. *SYMPHYANDRA* ROOTS ON MICE

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In the folk medicine, *Gentiana lutea* roots have been used for its analgesic, antipyretic and antiinflammatory properties[1]. There are, however, no experimental evidence for these activities. The purpose of the present study was to investigate possible analgesic activity of the extract prepared from *G. lutea* ssp. *symphyandra* roots. For this purpose, two different doses (250 and 500 mg/kg i.p.) were administered to mice and the analgesic activity was measured by both "tail-clip" and "tail-immersion" methods as described previously[2,3]. Results obtained in these two tests strongly suggested that the plant extract has a weak analgesic activity.

References

1. Duke, J., Handbook of Medicinal Plants, CRC Press, Boca Raton USA, pp.207-208 (1985)

2. Öztürk, Y., Aydın, S., Beis, R., Başer, K.H.C., Berberoğlu, H., Effects of Hypericum perforatum L. and Hypericum calycinum L. extracts on the central nervous system in mice. Phytomedicine 3, 139-146 (1996).

3. Almeida, R.N., Hiruma, C.A., Barbosa-Filho, J.M., Analgesic effect of rotindifolone in rodents. Fitoterapia 67, 334-338 (1996).

RECEPTORS OF PHARMACOLOGICAL AGENTS - NEUROMODULATORS AND ANTIDEPRESSANTS ON HUMAN IMMUNOCOMPETENT CELLS

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Centers of specific binding of antidepressants and biochemical marker imipramine was characterized on immunocompetent cells-lymphocytes from peripheral human blood. As it was shown, receptors of tricyclic antidepressant imipramine are based on mononuclear lymphocytes including monocytes. T- and B- lymphocyte cells are in both active for specific 3H-imipramine binding. Scatchard analysis of binding isotherms showed its non-linear hyperbolic character. Two independent binding sites was identified for imipramine on mononuclear lymphocytes: high affinity binding site is characterized by constant of dissociation of the ligand receptor complex Kd=3íM and maximal concentration of binding sites Bmax=120 fmoles/mln cells for T-lymphocytes and Kd=3,5íM and maximal concentration of binding sites Bmax=97 fmoles/mln cells for B-lymphocytes. Low-affinity binding site for T-lymphocytes is characterized by Kd=43 íM and maximal concentration of binding sites Bmax=1800 fmoles/mln cells. Kd for B-lymphocytes being equal to 52 nM and maximal concentration of binding sites Bmax being equal to 1500 fmoles/mln cells. Analysis of isotherms of binding of quinuclidinil benzilate (from 1 to 100 nM of ligand concentration) using Scatchard plot clears one type of binding sites with Kd=40nM and maximal concentration of binding sites 2100 fmoles/mg protein. Parameters of receptor binding received are in correlation with corresponding parameters for infact B-lymphocytes. Maximal concentration of M-cholinoreceptors on mononuclear lymphocytes is near to maximal concentration of binding sites for low-affinity imipramine binding. Investigation of stability of M-cholinoreceptors on T- and B-lymphocytes shows that freezing of the cells results in lowering of binding level up to 10 folds. As a result of freezing we can notice disappearance of low-affinity imipramine binding. It looks like low-affinity imipramine binding site is cholinergic muscarinic binding site. It was also established that 5-Hydroxytriptaimine (serotomin) binds to mononuclear lymphocytes as a reversible, temperature-dependent receptor-binding agent. Physico-chemical parameters of this reaction was estimated. The role of imipramine receptors and muscarinic cholinergic receptors in the function of human immunocompetent cells is discussed.

BENZODIAZEPINE RECEPTORS ON HUMAN BLOOD CELLS AS A PHARMACOLOGICAL MODEL

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It was shown that benzodiazepine receptors on human leukocytes are of peripheral type according to their pharmacological and biochemical characteristics. Using peripheral type benzodiazepine ligands Ro-5-4864 and PK-11195 physico-chemical parameters of benzodiazepine binding to lymphocytes and platelets from peripheral human blood was estimated. It was shown that the process of binding of peripheral benzodiazepine ligands is in accordance with the model with one type of binding site. Estimated Kd (constants of dissociation of the complex of the ligand and receptor) is 55 íM for lymphocytes and peripheral ligand Ro-5-4864, and 16 íM for 3H-PK-11195. Maximal concentrations of binding sites for 3H-Ro-5-4864 and 3H-PK-11195 are 1400 fmoles/mg protein and 2400 fmoles/mg protein. Corresponding values for membranes of lymphocytes are as follows. For 3H-Ro-5-4864 no binding was discovered; for 3H-PK-11195 - Kd=10nM and maximal concentration of binding sites is 3940 fmoles/mg protein. Investigation of influence of GABA ligands on the binding of peripheral benzodiazepine ligands was carried out with the help of GABA and (+) and (-) baclofen using intact lymphocytes from peripheral human blood. It was shown that 5mM of GABA rises binding of 3H-Ro-5-4864 two fold and decreases the binding of 3H-PK-11195 up to 30%. Stereoisomers of baclofen have no influence on the binding of 3H-PK-11195 with intact lymphocytes, but (+) - baclofen activates binding of 3H-Ro-5-4864 with intact lymphocytes two fold; (-) - baclofen being of no activity. It was assumed that there are two different types of peripheral benzodiazepine binding sites. In accordance with our experimental data binding of peripheral receptors on blood cells corresponds with the model of two independent binding sites for agonist Ro 5-4864 and antagonist PK-11195. The data discussed above are of greate importance for modelling of benzodiazepine drugs both in central and peripheral sites of specific binding.

THE EFFECT OF CHRONIC ALCOHOL AND NICOTINE TREATMENT ON LIPID PEROXIDATION AND GLUTATION LEVELS IN THE LENS

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Increased lipid peroxidation (LPO) are associated with various pathological conditions. As the lens has a rich supply of oxygen and contents a large quantity of polyunsaturated fatty acids, conceivable that lens is susceptible to oxidative damages which lead to LPO.

In the present study we aimed to investigate the effect of alcohol (EtOH) and nicotine (N) treatment on the antioxidant system in the lens. Female Spraque-Dawley rats were divided into four groups. Rats were injected i.p. with 2g/kg EtOH as a 20% solution in saline (EtOH group), 0.75g/kg nicotine bitartarate (N group) and EtOH and N in combination (EtOH + N group) for ten days twice daily. Control were injected saline only. Animals were sacrificed 12 hours after the last injection and eyes were rapidly removed. Lens homogenates were used for malondialdehyde (MDA) levels as index of LPO and GSH levels. MDA and GSH levels were 57.8 pmol/mg tissue and 1.39 nmol/mg tissue in EtOH group, 107 pmol/mg tissue and 2.08 nmol/mg tissue in N group, 159 pmol /mg tissue and 1.65 nmol/mg tissue in EtOH + N group,and 61 pmol/mg tissue and 1.57 nmol/mg tissue in C group respectively.

As a result, EtOH and N treatment seem to have a tendency to exaggerate LPO in rats.

ANTICONVULSANT ACTIVITY OF THIOSEMICARBAZIDE DERIVATIVES AGAINST PENTYLENETETRAZOL SEIZURES

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Thiosemicarbazide derivatives have been synthesized and tested for different pharmacological activities. In particular, the anticonvulsant activity has been reported in the literature. Following these observations, we have designed and synthesized a series of 1,4 disubstituted thiosemicarbazides (dTSCs).These derivatives were evaluated for their anticonvulsant activity.

Numerous chemical compounds may produce generalized seizures when administered systematically. The prototype agent in the class of systemic convulsants is pentylenetetrazol (PTZ). PTZ initially produces myoclonic jerks, which then become sustained and may lead to a generalized tonic-clonic seizure when given by the parenteral route.

In the present study we investigated the anticonvulsant activity of dTSCs on PTZ induced seizures in mice. The test compounds were suspended in 5% aqueous suspension of gum acacia and administered to animals at a dose of 100mg/kg i.p.. Controls animals were injected 5% aqueous suspension of gum acacia. Four hours after the administration mice were injected i.p.with PTZ at a dose of 55mg/kg .The mice were observed for the next 60 min for the occurance of seizures. Following results were obtained .

dTSCs deriv.	seizure latency (min.)*	% protective effect**
$-CH_3$	18	72
$-C_2H_5$	03	10
$-C_3H_7$	03	10
$-CH_2-CH=CH_2$	06	43
$-C_6H_{11}$	04	20
$-C_6H_5$	04	20

*: Seizure latency was defined as the time of first two myoclonic jerks of the forelimbs after PTZ injection.

**: % protective effect was defined as the preventation potential against PTZ induced generalized convulsions.

STUDIES ON THE SYNTHESIS OF SOME IMIDACLOPRID DERIVATIVES AND THEIR INSECTICIDE ACTIVITIES

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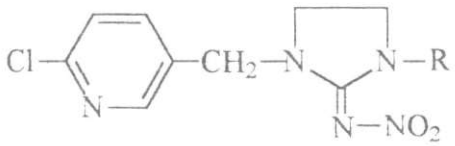
The synthesis of "1H-imidazole-2-amino-1-[(6-chloro-3-pyridinyl)methyl]4,5-dihydro-N-nitro (Imidacloprid)" derivatives were aimed because of their insecticide activities.



General Formula

R=H(Imidacloprid),Me, Et, Pro, Isopro, Bu, Isobu ect.

Significant information about the syntheses and activities of imidacloprid and their derivatives were noted in the literature. According to the new data, imidacloprid and derivatives are very effective insecticide compounds. However, synthesis and activity studies in this field have not been completed. In the present study which aimed to fulfill the gap in the literature, synthesis of mentioned derivatives are going to be realized by starting materials which are cheap and freely available. For this reason, a new method of imidacloprid synthesis was developed. After the determination of acute lethal toxicities and LD_{50} values of all compounds, their activities on some agricultural harmfull insects are going to be investigated. At this stage, equipment and manpower of the Directorship of Anatolia Agricultural Study will be used. At the further step of studies, quantitative structure-activity relationships (QSAR) and the activities will be determined using physicochemical parameters, obtained theoretically and practically.

THE ADDITION PRODUCTS OF β-METHYL-β-NITROSTYRENE DERIVATIVES WITH 2-MERCAPTOMETHYLBENZIMIDAZOLE AND THEIR NMR STUDIES

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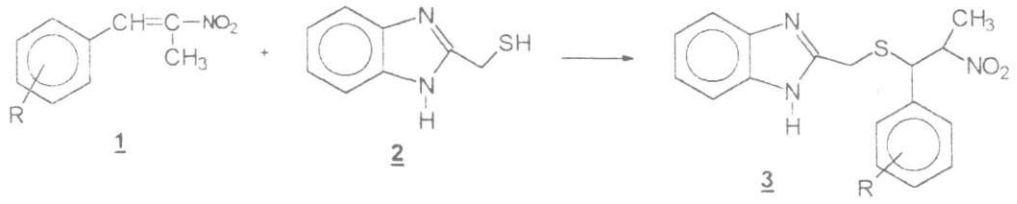
2-[(2-Nitro-1-phenyl-propyl)thiomethyl]benzimidazole **3** derivatives have been synthesized by the addition of appropriate β-methyl-β-nitrostyrenes **1** on 2-Mercaptomethylbenzimidazole **2** in ethanolic solution at room temperature[1,2] (Scheme 1).



R= H, Cl, NO_2, CH_3, OCH_3, OC_2H_5, $N(CH3)_2$

Scheme 1: Synthesis of compound **3**

According to ^{1}H-NMR spectra the addition product is a mixture of two rotamers (**A** and **B**) of the same compound.[3] The signal of the methyl group located at b position to nitro group has been observed as two doublets in the ^{1}H-NMR spectrum and ratio of their intensity was 1:3 at room temperature. By recording the spectra at different temperatures (70°C and 100°C) the ratio of these signals has changed. This observation deliniates that the mixture consists of two rotamers and they can not be considered as stereoisomers because diastereomers can not be converted to each other with heat. Also on the ^{1}H-NMR spectra of other derivatives of type **3** the raito of **A** and **B** rotamers has been determined referring to the intensity of two signals given by the methyl group.

REFERENCES

1. BERÇİN, E., GÖKÇE, M., ABBASOĞLU, U., NOYANALPAN, N.,: **J. Fac. Pharm. Gazi**, 1995, **12** (2), 117.

2. FEDEROV, B.P., MAMEDOV, R.M.: **Izv. Akad. Nouk. SSSR, Old. KhimNouk**, 1962, 1626, Ref: **Chem. Abstr.**, 1962, **58,** 9048g.

3. BERÇİN, E., GÖKÇE, M., ÖZÇELİK, B., YURTSEVER, M., NOYANALPAN, N.: **J. Fac. Pharm. Gazi**, 1995, **12** (2), 173

THE PRODUCTS OF MICHAEL TYPE ADDITION OF 2-MERCAPTOMETHYLBENZIMIDAZOLE ON THE DERIVATIVES OF β-NITROSTYRENE AND THEIR STRUCTURE ELUCIDATION

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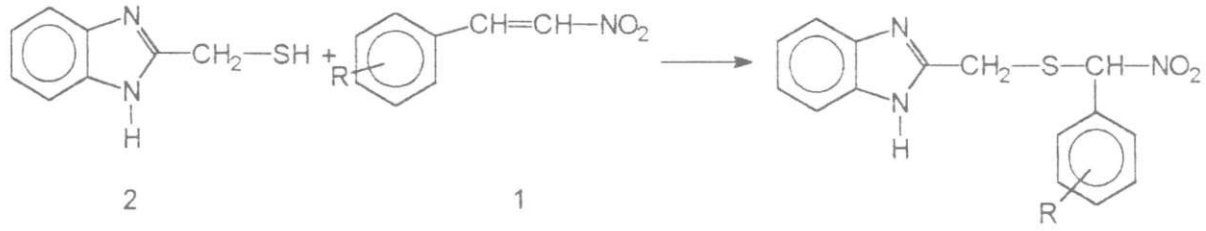
β-Nitrostyrenes **1** are well known broad spectrum antimicrobial activities[1,2,3]. Also their addition products have similar activities. The synthesis and antimicrobial activities different addition products of β-nitrostyrenes and aromatic thiols groups were reported from our earlier studies[4,5,6].

In continuation of our programme we have developed new type addition pruducts of β-nitrostyrenes and 2-mercaptomethylbenzimidazoles **2**. In present investigation have been synthesized 2-[(2-nitro-1-phenyl-ethyl)thiomethyl]benzimidazole **3** derivatives from appropriately

substituted **1** and compound **2** (scheme 1).Their detailed structural analyses have also been eluciated with various NMR technics.



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REFERENCES

1) SCHÖHÖFER, F., SCHOOH, M. , Arzneimittel-Forsch, 1948, 8, 374.
2) SCHALES, O., GRAFEE, H., A., J. Am. Chem Soc., 1952, 74, 4486.
3) XORGE, A. D., JORGE, S. S.. ARTURO, E. , J. Am. Chem Soc., 1953, 75, 4581.
4) BERÇİN, E., GÖKÇE, M., ABBASOĞLU, U., NOYANALPAN, N., J. Fac. Pharm. Gazi, 1995, 12(2), 117.
5) BERÇİN, E., GÖKÇE, M., ÖZÇELİK, B., YURTSEVER, M., NOYANALPAN, N., J. Fac. Pharm. Gazi, 1995, 12(2), 173.
6.) BERÇİN, E., GÖKÇE, M., NOYANALPAN, N., J. Fac. Pharm. Gazi, 1996, 13 (1)

SYNTHESIS OF SOME NEW HYDRAZONES AND 3-ACETYL-2,5-DISUBSTITUTED-1,3,4-OXADIAZOLINES

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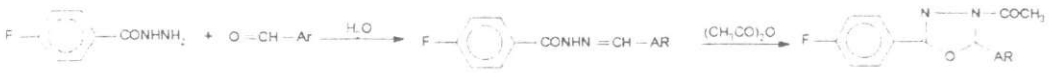
Hydrazones are reported to possess antimicrobial, antitubercular, anticonvulsant and antiinflammatory activities. 3-Acetyl-1,3,4-oxadiazolines are known to exhibit some antibacterial and antifungal activities. These observations prompted us to synthesise some new compounds. In this study, 4-fluorobenzoic acid (substitutedmethylene) hydrazides (2a-d) were prepared by condensation of 4-fluorobenzoic acid hydrazide with appropriate aldehyde. Then, 3-acetyl-2,5-disubstituted-2,3-dihydro-1,3,4-oxadiazoles (3a-d) were synthesised by heating these compounds (2a-d) with acetic anhydride. The structure of synthesised compounds were elucidated using UV, IR, ^{1}H-NMR, ^{13}C-NMR (3b) and Mass (2b,3a) spectroscopic methods besides elemental analyses.



(1) (2a-d) (3a-d)

AR: 

IN VITRO RAT HEPATIC MICROSOMAL METABOLISM OF PHENANTHRIDINE

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Phenanthridine is a fused azaheterocyclic compound which exists in a number of plants. Although its *in vivo* metabolism was previously reported, no work is available in the literature showing any *in vitro* metabolites of this alkaloid formed by experimental animals. The aim of our studies was to answer the question as to whether phenanthridine produces the corresponding N-oxide and lactam as metabolites and the mechanism involved. We now report our preliminary findings using rat hepatic microsomal preparations (control and induced with phenobarbitone) fortified with NADPH as enzyme source.

The potential metabolite, phenanthridine-N-oxide was prepared by m-CPBA oxidation of substrate; the lactam was commercially available. The substrate and its two potential metabolites were then separated using TLC and HPLC. The substrate (2 μmol) was incubated with hepatic washed rat microsomal preparations fortified with NADPH for 1/2 h at 37°C. The substrate and metabolites were extracted with DCM (2x5 mL) after saturating the incubate with NaCl (0.8 g); concentrated under a stream of N_2 at 20°C and analysed by HPLC and TLC. Four metabolites ie the corresponding N-oxide, and lactam and two unknown products were detected. Both N-oxide and the lactam metabolites showed identical chromatographic behaviour and UV spectrum using a multiarray UV detector linked to our HPLC system as the authentic compounds. The unknown metabolites are proposed to be phenolic metabolites because of their chromatographic behaviour in our systems and response to detection reagents. The amount of both metabolites were significantly increased when phenobarbitone induced rat microsomes were used as enzyme source. The results show that both metabolites are formed by phenobarbitone inducible CYP450 isozymes and it may be that the lactam was produced via the N-oxide. Experiments are under way to investigate the proposed pathway.

SYNTHESIS AND ANALGESIC, ANTISPASMODIC ACTIVITY OF SOME NEW N-SUBSTITUTED INDOLE-2-CARBOXYLIC ACIDE ESTERS

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Indole is important heterocylic ring which is exist in different biologically active compounds such as; antihypertansive, analgesic-antiinflammatory, antihistaminic, antitumor, antidepressant, antispasmodic, local anestesic, antibacterial and antiviral etc. In this study, we have aimed especially to prepare new compounds which indicate antispasmodic activity.

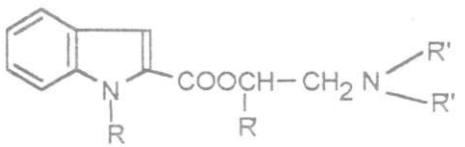
We have synthesised N-sübstituted indole-2-carboxylic acide esters. Their structures are shown below, by the Formula-1. The synthesis of these compounds have been performed in two phases :

1- 1H-indole-2-carboxylic acide was treated with benzyl or phenyl bromide,

2- Esterification of carboxylic acide was realized by the alkylaminoalcoholes in the presence of 1,1'-carbonyldiimidazole.

Structure of these compounds were elucidated and confirmed by UV, IR, ^{1}H-NMR, MASS spectroscopic methods and elementary analysis.

Some of compounds have been assayed for their antispasmodic activity on guinea pig ileum and their analgesic activity have been tested on mice. The results show that ; especially S_{2a} , S_{2b} , S_2 derivatives of the synthetised compounds posses the antispasmodic activity in pharmacological consentrations.



R= H , Ph, CH_2Ph

R= H, CH_3

R',R' = CH_3, C_2H_5, 

Formula-1

SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF SOME 3,4,5-TRISUBSTITUTED-1,2,4- TRIAZOLE AND THEIR SOME POSSIBLE METABOLITES

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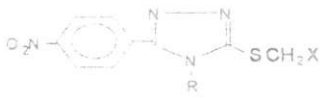
In this study, the synthesis and biological evaluation of 5-(4-nitrophenyl)-4-substituted-3-substitutedthio-4H-1,2,4-triazole are reported. The synthesis of these compounds involved two steps. In the first step, 2a-f were obtained from the sodium salts of 1a and 1b by reaction with benzyl, 4-nitrobenzyl and phenacyl chloride respectively. From the condensation of thioether derivatives (2e-f) with hydroxylamine hydrochloride was also produced corresponding 2g-h derivatives in the alkaline conditions. Afterwards 3a-b were obtained from esterification of the sodium salt of 1a with benzoyl and 4-nitrobenzoyl chloride. In the other part of this resarch, the possible metabolites of the thioethers have been synthesized.

The structure of synthesized compounds were elucidated using UV, IR, ^{1}H-NMR, ^{13}C-NMR (2e) and Mass (2a, 2b,2e, 2f, 2g, 2h) spectroscopic methods besides elemental analyses.

All of the synthesized compounds were tested for their antimictobial activity against S.aureus ATCC 29213, E.coli ATCC 25922, P.aeruginosa ATCC 27853, C.albicans ATCC 2091 and M.fortiutum ATCC 6841. Most of the screened substences were found to be active against C.albicans and M. fortiutum.



2a-h

compounds	R	X
2a	$-CH_2CH=CH_2$	$-C_6H_5$
2b	$-C_6H_5$	$-C_6H_5$
2c	$-CH_2CH=CH_2$	$-C_6H_4NO_2$ (p)
2d	$-C_6H_5$	$-C_6H_4NO_2$ (p)
2e	$-CH_2CH=CH_2$	$-COC_6H_5$
2f	$-C_6H_5$	$-COC_6H_5$
2g	$-CH_2CH=CH_2$	$-CNOHC_6H_5$
2h	$-C_6H_5$	$-CNOHC_6H_5$

3a-b

compounds	R	X
3a	$-CH_2CH=CH_2$	$-C_6H_5$
3b	$-CH_2CH=CH_2$	$-C_6H_4NO_2$ (p)

SOME FACTORS INFLUENCING THE *IN VITRO* METABOLISM OF COMUTAGEN 2-AMINO-3-METHYLPYRIDINE

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2-Amino-3-methylpyridine (2A3MP) is known to be mutagenic towards *Salmonella typhimurium TA98* only in the presence of norharman and a metabolic activating system (S9) (1). In order to investigate the mechanism of comutagenesis we have first examined the metabolism of 2A3MP using fortified hepatic fractions from the rat and rabbit (2). It was shown that 2A3MP was metabolised by both species to yield 2-amino-3-methylpyridine-1-N-oxide (2A3MPNO), 2-amino-3-hydroxymethylpyridine (2A3HMP) and 2-amino-3-methyl-5-hydroxypyridine (2A3M5HP). Metabolic products having the characteristics of 2-hydroxylamino-3-methylpyridine or the corresponding nitroso or nitro compounds have not been conclusively identified (2). As the failure to detect metabolites derived via oxidation of the exo amino group in earlier experiments may have been due to the enzyme source, we carried out incubations using a S9 hepatic fraction derived from arochlor 1254 induced rat in order to mimic conditions usually used to examine compounds for mutagenesis or comutagenesis. In this study, factors affecting the metabolism of 2-amino-3-methylpyridine *in vitro* have been studied and the conditions which allow maximal metabolism established. Ring nuclear and methyl hydroxylation, and 1-N-oxidation of 2A3MP were linear with respect to arochlor 1254 induced rat S9 supernatant (10,000 g fraction) up to 4.86 mg per ml. The results showed that 20 min incubation time was adequate to observe metabolites formed from 2A3MP. The rate of metabolite production increased with increase in substrate concentration up to 2 µmol per incubate. Using the data obtained the apparent K_m and V_{max} values were calculated using Hanes-Wolf and Lineweaver-Burk plot. No N-hydroxylation of the *exo*-amino group was observed.

References:

1-Sugimura T, Nagao M, and Wakabayashi K: Metabolic aspects of the comutagenic action of norharman. ***Adv Exper Med Biol.*** 1982; 136:1011-1025.

2-Altuntas TG, Manson D, Zhao K, and Gorrod JW: Comutagenesis-I:The *in vitro* metabolism of 2-amino-3-methylpyridine. ***Chemical Research in Toxicology***, 1997, submitted.

NEW IMIDAZO[2,1-*b*]THIAZOLE DERIVATIVES : SYNTHESIS AND ANTIFUNGAL ACTIVITY

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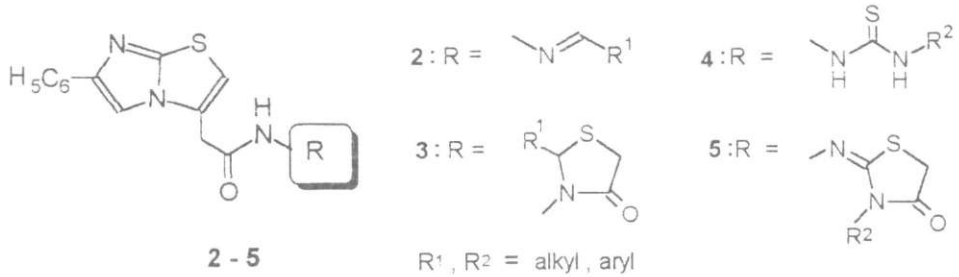
The rapidly expanding population of immunocompromised patients is resulting in corresponding increases in diseases caused by yeasts and other fungi. Although not life-threatening superficial mycosis, infections of keratinized tissues such as skin, nails and hair causes prolonged periods of distress to the infected patient. Dermatophytoses which are most prevalent among superficial mycosis are currently treated by imidazole derivatives, clotrimazole, miconazole, econazole and other azole antifungals. Derivatives of imidazo-fused heterocycles also show antifungal activity (1). To provide further insight into the antifungal properties of compounds carrying imidazo-fused systems, hitherto unreported imidazo[2,1-*b*]thiazole derivatives (**2-5**) have been synthesized from 6-phenylimidazo[2,1-*b*]thiazole-3-acetic acid hydrazide (2) . The compounds are fully characterized by IR, NMR, MS as well as elementary analysis.



All the compounds were evaluated for antifungal activity (3) against three dermatophyte strains *Trichophyton mentagrophytes var. erinacei* NCPF-375, *Trichophyton rubrum* and *Microsporum audounii* using ketoconazole as the standard. Compounds **2b**, **2g**, **2j**, **2k**, **4d** and **5d** were as effective as the standard against *T. rubrum* and *M. audounii* (MIC 6μg/ml) whereas the activity of **2a** against *M. audounii* was superior to the standard (MIC 3μg/ml). **3b** and **3g** showed the highest activity against *T. mentagrophytes var. erinacei* NCPF-375 (MIC 3μg/ml).

References:

1. Cesur N, Cesur Z, Ergenç N, Uzun M, Kiraz M, Kasımoğlu Ö, Kaya D, Arch. Pharm.(Weinheim) 327, 271 (1994).
2. Harraga S, Nicod L, Drouhin JP, Xicluna A, Panouse JJ, Seilles E, Robert JF, Eur. J. Med. Chem., 29, 309 (1994).
3. Granade TC, Artis WM, Antimicrob. Agent Chemother., 17, 725 (1980).

SYNTHESIS AND ANTIBACTERIAL ACTIVITIES OF SOME PYRROLYL-NITROIMIDAZOLE DERIVATIVES

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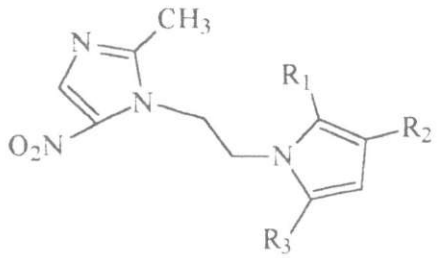
It has been known that the alcoholic function on metronidazole molecule is suitable for various reactions. Hence it is substituted with different groups and other effective nitroimidazole derivatives are obtained.
In this study, the hydroxyl was converted into amino group and some pyrrolyl derivatives were synthesized using this new function.
The expected antibacterial activities for the compounds obtained were tested.



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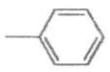
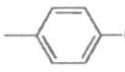
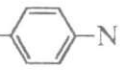
R_2 = H, $COOC_2H_5$
R_3 = H, CH_3,  ,  , 

SYNTHESIS AND STRUCTURAL ELUCIDATION OF SOME 5-ACETYL-3,4-DIHYDRO-6-METHYL-4-(SUBSTITUTED PHENYL)-2(1H)-PYRIMIDINONES

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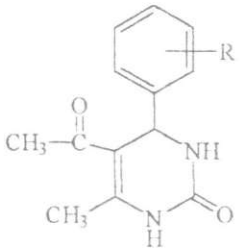
Calcium channel blockers have attained major significance in the therapy for cardiovascular diseases during the past few years (1, 2). It has been reported that some 1,2,3,4-tetrahydro-, 2-oxo- or 2-thioxo-1,2,3,4-tetra-hydropyrimidine derivatives have vasodilator, antihypertensive and calcium channel blocker activities (3, 4). In our previous studies the synthesis and calcium antagonistic activities of some 1,2,3,4-tetrahydro-6-methyl-4-(substituted phenyl)-2-thioxo-5-pyrimidinecarboxylic acid methyl esters have been described (5, 6). In order to acquire further information on the structural characteristics enhancing calcium antagonistic activity in this serie of compounds, we synthesized some new 5-acetyl-3,4-dihydro-6-methyl-4-(substituted phenyl)-2(1H)-pyrimidinone derivatives (I) which we expect to show calcium antagonistic activity.



R: 3-OCH_3; 2-CH_3; 3-CH_3; 4-CH_3; 2-Cl; 3-Cl; 3-Br

(I)

5-Acetyl-3,4-dihydro-6-methyl-4-(substituted phenyl)-2(1H)-pyrimidinone derivatives were prepared in one-step by acid-catalyzed condensation of urea with acetylacetone and various aromatic aldehydes according to the modified Biginelli reaction. The structures of the compounds were determined by examining their UV, IR, ^{1}H-NMR and mass spectral data and elementary analysis. In the UV spectra two absorption maxima were observed in the 218-235 and 299-302 nm regions, respectively. The IR spectra showed strong absorption bands at 1716-1700 cm^{-1} (C=O, acetyl) and 1681-1594 cm^{-1}(C=O, ring). In the ^{1}H-NMR spectra of the compounds the H-4 proton of the ring was seen as a well separated doublet approximately at 5.21-5.63 ppm. The signals of N_1-H and N_3-H protons appeared as a singlet at about 7.74-7.89 and 9.14-9.28 ppm, respectively. In the mass spectra, molecular ion peaks were prominent for all the compounds. All the spectral data are in accordance with the assumed structures and elementary analysis confirm the molecular formulae.

References

1. Bühler, F.R., Hulthén, U.L., Kiowski, W., Muller, F.B., Bolli, P., J. Cardiovasc. Pharmacol. 4, 5350 (1982).
2. Theráux, P., Taeymans, Y., Waters, D., Drugs 25, 178 (1983).
3. Cho, S., Shima, K., Mizuno, A., Takeuchi, Y., Jpn. Kokai Tokkyo Koho JP 61,130,276 [86,130,276] (Cl. C07D239/28), 18 June 1986; ref: CA 106, 5072s (1987).
4. Vitolina, R., Kimenis, A.,Khim.-Farm. Zh. 23(3), 285 (1989); ref: CA 111,188c (1989).
5. Ertan, M., Balkan, A., Saraç, S., Uma, S., Renaud, J.F., Rolland, Y., Arch. Pharm. (Weinheim) 324, 135 (1991).
6. Ertan, M., Balkan, A., Saraç, S., Uma, S., Rübseman, K., Renaud, J.F., Arzneim.-Forsch./Drug Res. 41 (II), 725 (1991).

THE ROLE OF R(I) INDEX, PHYSICOCHEMICAL AND STRUCTURAL PARAMETERS ON BIOLOGICAL ACTIVITY AGAINST CANDIDA PARAPSILOSIS

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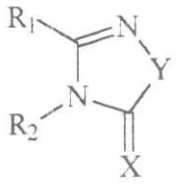
The purpose of this study was to examine the role of certain predictor variables of quantum chemical parameter R(I), hydropobicity predictor π, and structural parameters on the antifungal activities against Candida parapsilosis. The sample consists of a series of 14 compounds having 3,4- disubstituted-1, 2, 4- oxa (thia)- diazole- 5 (4H)- ones (thiones) structure.



The compounds were formerly tested for their antifungal activities against Candida parapsilosis. The quantitative structure- activity relationship (QSAR) of these compounds was studied using the R(I), π, and structural parameters. In this work, the dependent variable (activity) has been defined as log 1/C. C is the molar MIC value of the compounds. R(I) represents the electron density of HOMO at atom 1 that is one of the active sites having the important role in probable chemical reactions. The electron donating and electron - withdrawing groups are presented as the substituents R_1 and R_2 in the compounds. R(I) values were calculated using semiemprical molecular orbital calculations. The physicochemical parameter investigeted included the hydrophobicity of the compounds (π). Values of π for substituents were taken from the Table given by Hansch et al. $\Sigma\pi$ was used for the hydrophobicity of the whole molecule. The structural descriptor I_Y expresses the the replacement of S by the O atoms in position 1. The other structural variable I_X is used to represent the replacement of S by the O which are double bonded to the C atom in position 5. The best fitted equation(s) for the activity against C. parapsilosis was selected using all possible combination techniques of multiple regression analysis under various statistical criteria. The results gave two best equations. The first best equation included only I_Y parameter. The R(I) index ($F= 99.17$, $p=0.0000$, $R^2 =0.89$) was statistically important, and produced a positive effect on the potency. It means that the presence of sulfur atom in position 1 was favored for increasing the activity. The second best fitted equation showed that the predictors R (I), $R(I)^2$, $\Sigma\pi$, and I_X all together explained 93% of the variation in the biological activity data ($F=30.99$, $p=0.0000$). The positive coefficient of $\Sigma\pi$ indicated that the hydrophobicity caused an increase in the activity ($t=3.139$, $p=0.0119$). Besides these features, the equation showed that the structural parameter I_X was also significant ($t=7.757$, $p=0.0000$). The negative coefficient of I_X revealed that S which is double bonded to the C atom in position 5 was not favorable against C. parapsilosis. On the other hand, there was a parabolic relationship between the biological activities and the R(I) index. R(I) ($t=4.925$, $p=0.008$) and its square ($t=4.547$, $p=0.0014$), each made a significant contribution to the variation in the activity.

SYNTHESIS AND ANTIFUNGAL ACTIVITY OF SOME TRIAZOLYL-ACETOPHENONE OXIME-ETHERS

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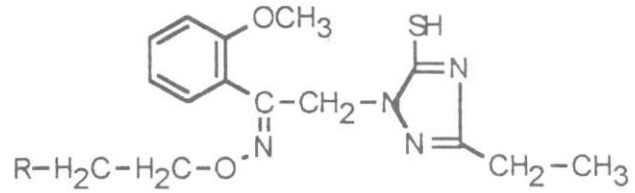
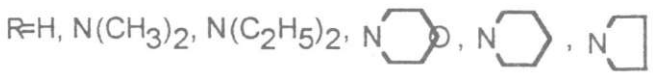
In our previous study we described the synthesis some triazolylacetophenone derivatives possessing antifungal activity(1).
Brain and co-workers have been prepared some oxime-ether derivatives of known antibacterial compound, Eritromycin, and observed good activity compared with Eritromycin(2).
The aim of this study was to synthesize some new compounds belonging to the oxime-ether series of triazolylacetophenone(see formula) which will be obtained by the condensation of α-(3-ethyl-5-mercapto-1,2,4-triazol-1-yl)-o-methoxyacetophenone and substituted amino derivatives($R-CH_2-CH_2-O-NH_2$) in order to improve the antifungal activity.
Chemical structures of the compounds have been identified using IR, ^{1}H-NMR, Mass and elementary analysis.
Studies on the antifungal activity are in progress.





References

1)R. Ertan, G. Ayhan, N. Yuluğ, Y. Rolland; ***Arzneim.Forsh./Drug Res.***, 45(I),620-623(1995)

2)E. G. Brain, A. K. Forrest, E. Hunt, C. Shillingford, J. M. Wilson; ***The Journal of Antibiotics***, XLII(12),1817-1822(1989)

SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF SOME NEW ANILINO BENZIMIDAZOLES

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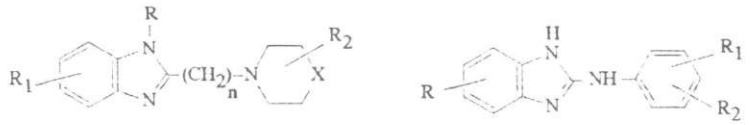
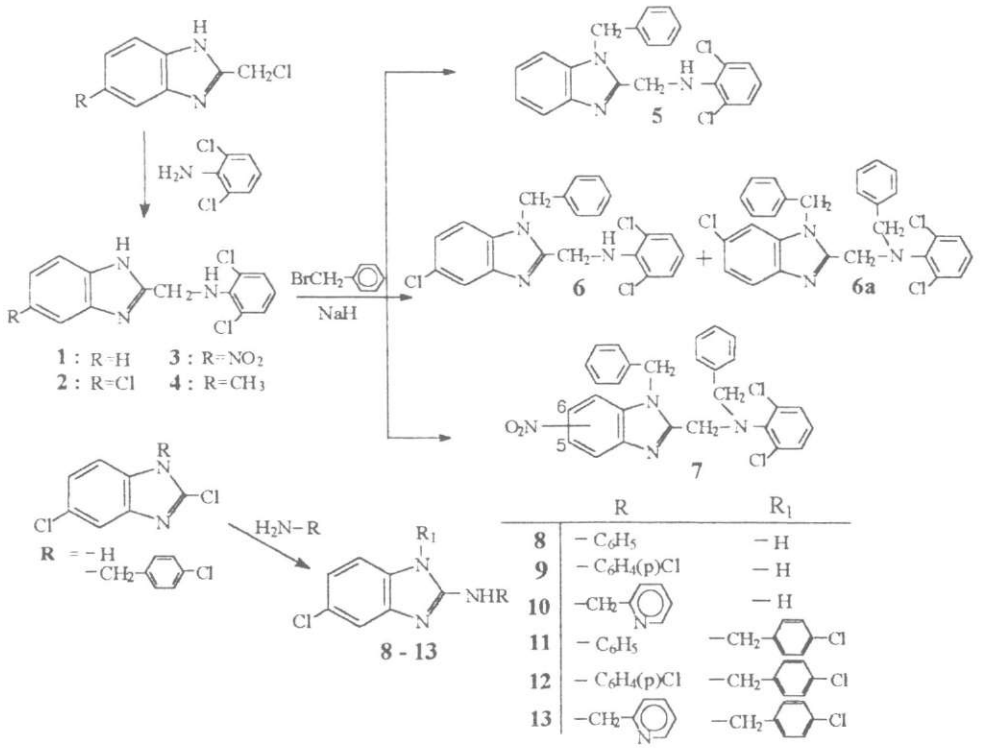
In our previous papers we reported the synthesis and antimicrobial evaluation of 2-(substituted-piperidinyl or piperazinyl)benzimidazoles **I**. As a continuation to our work on these derivatives, we found a patent concerning the synthesis of anilinobenzimidazoles **II** , some of which exhibited potent activity against to *Staphylococcus aureus* by the tube dilution method.



I **II**

This result encouraged us to prepare some new derivatives of **II** and in order to investigate the influence of N^1-alkylation on the antimicrobial activity some N^1-substituted anilino-benzimidazoles were prepared. Synthesized compounds are given in Scheme.



1 : R=H **3** : R=NO_2
2 : R=Cl **4** : R=CH_3

	R	R_1
8	$-C_6H_5$	−H
9	$-C_6H_4$(p)Cl	−H
10	$-CH_2$-(2-pyridyl)	−H
11	$-C_6H_5$	$-CH_2$-(Cl)
12	$-C_6H_4$(p)Cl	$-CH_2$-(Cl)
13	$-CH_2$-(2-pyridyl)	$-CH_2$-(Cl)

The structure elucidation of the **1-13** were achieved by their NMR, Mass and elemental analysis and X-Ray analysis (**1,5,6a**). **1-13** were evaluated for their *in vitro* antimicrobial activity against *Staphylococcus aureus, Escherichia Coli* and *Candida albicans*. **2**, **8** and **9** exhibited best activity.

SYNTHESIS OF SOME NEW BENZIMIDAZOL-CARBOXAMIDES AND EVALUATION OF THEIR ANTIMICROBIAL ACTIVITY

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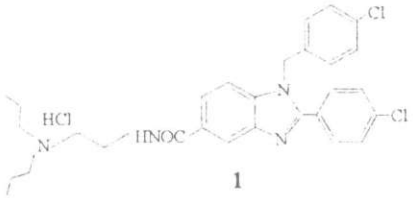
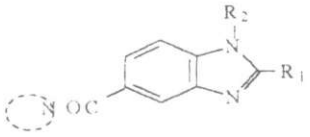
Ankara University , [1]Department of Pharmaceutical Chemistry, [2]Department of Microbiology, Faculty of Pharmacy, 06100-Tandogan Ankara Turkey,

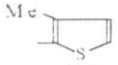
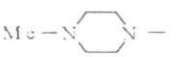
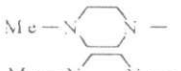
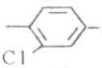
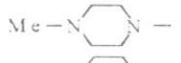
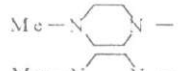
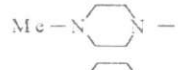
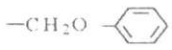
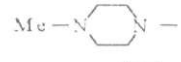
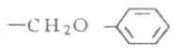
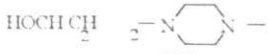
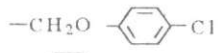
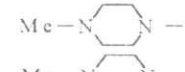
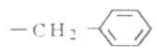
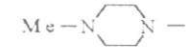
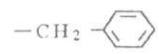
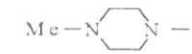
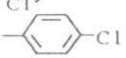
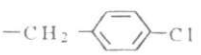
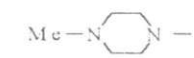
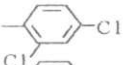
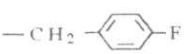
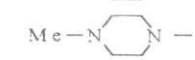
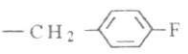
We already reported the synthesis and antimicrobial evaluation of a series N'-(N,N-dialkylaminoethyl)-benzimidazole-5(6)-carboxamides. The study revealed that compounds **1** exhibited potent antimicrobial activity. We planned to modify the structure of compounds **1** in order to find new antimicrobial agents.



1

The newly synthesized compounds are given below. The structure elucidation of **6-18** were achieved by their NMR, Mass and elemental analysis and these compounds were evaluated for their in-vitro antimicrobial activity against *S. aureus, E. Coli and C. albicans.* Compounds **17** and **18** exhibited best activity.



	R_1	R_2	N
6		—H	
7		—H	
8		—H	
9		—H	
10		—H	
11		— H	
12		— H	
13		— H	
14			
15			
16			
17			
18			$(CH_3)_2NCH_2CH_2NH$

SYTHESIS AND ANTIINFLAMMATORY ACTIVITY OF 1-BENZYL-2-(ALKYLTHIO)PYRROLO[2,3-d]IMIDAZOLE-5-CARBOXYLATES

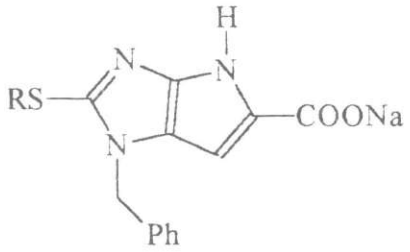
M.A. Ebrahimzad, A. Zarghi, A. Shafiee

Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Medical Sciences, University of Tehran, Tehran, Iran

Based on the structure activity relationships of non steroidal antiinflammatory agents a series of 1-benzyl-2-(alkylthiopyrolo)[2,3-d]imidazole-5-carboxylates were designed and synthesized as antiinflammatory agents. Because of structural similarity with indomethacin, this drug was used as reference drug.

The antiinflammatory activity was assessed in vivo by the carregeenan-induced edema test in the hindpaws of the rat.

Our results demonstrate that these compounds have antiinflammatory activity.



R= Me, Et, Pr, Bn

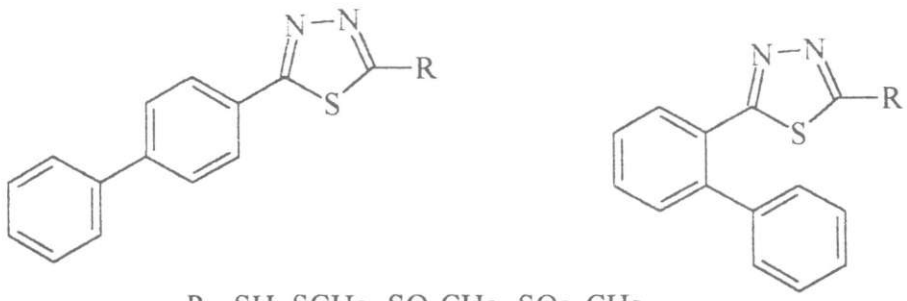
SYTHESIS AND ANTIFUNGAL ACTIVITY OF NEW BIPHENYLYL THIADIAZOLE DERIVATIVES

S.A. Tabatabai, A. Foroumadi, M. Piraii, H. Peyvand, A. Shafiee

Department of Pharmaceutical Chemistry, Faculty of Pharmacy, The Medical Science University of Tehran, Tehran, Iran

New derivatives of biphenylyl thiadiazole were synthesized from the reaction of corresponding phenylbenzoic acids with thiosemicarbazide in the presence of phosphorousoxychloride followed by diazotisation, substitution and oxidation of the mercapto group.

In vitro antifungal activity tests revealed that some derivatives have anti-candida albicans properties comparable to miconazole nitrate.



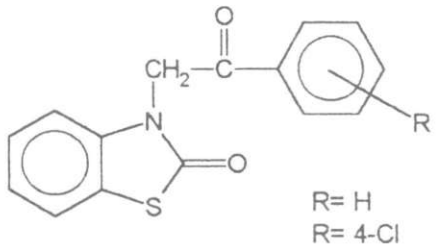
R= SH, SCH_3, SO-CH_3, SO_2-CH_3

3-(BENZOYLMETHYL)BENZOTHIAZOLE-2-ONE DERIVATIVES : SYNTHESIS AND ANTINOCICEPTIVE ACTIVITY

B. Çakır[1], D. S. Doğruer[1], E. Yeşilada[2], M.F. Şahin[1]

Gazi University, Faculty of Pharmacy, [1]Department of Pharmaceutical Chemistry, [2]Department of Pharmacognosy, Etiler, Ankara, Turkey

Five 3-(benzoylmethyl)benzothiazole-3-one (1) derivatives have been synthesized (I). Their structure have been elucidated by IR and NMR spectral data. Antinociceptive activity of the compounds has been investigated by Modified Koster Test.



R= H	Ia
R= 4-Cl	Ib
R= 4-Br	Ic
R= 2-Cl	Id
R= 2-Me	Ie

Compound Id has been found more active than the others the reduction derivatives of I have been being prepared and their antinociceptive activity has also been investigated and the results will be discussed in detail.

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SYNTHESIS AND ANTIMICROBIAL ACTIVITIES OF 2-(p-SUBSTITUTED STYRYL)-5(6)-CHLOROBENZIMIDAZOLES.

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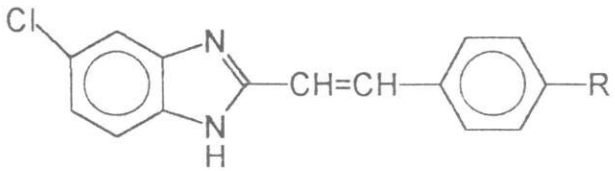
Gazi University, Faculty of Pharmacy, [1]Department of Pharmaceutical Chemistry, [2]Department of Microbiology, Etiler, Ankara, Turkey

Seven 2-(p-substituted styryl)-5(6)-chlorobenzimidazole derivatives have been obtained by refluxing with 2-methyl-5(6)-chlorobenzimidazole and p-substituted arylaldehydes in acetic anhydride for 30 hours[1-3].



R: H, OH, Cl, NO_2, CH_3, OCH_3, OC_2H_5

2-Methyl-5(6)-chlorobenzimidazole as a starting material has been prepared by refluxing 4-chloro-o-phenylenediamine with glacial acetic acid in hydrochloric acid for 6 hours according to the Phillips Method[4].

Antimicrobial activity of the synthesized compounds have been tested against yeast-like fungus such as *Candida albicans* and Gram(+) bacteria such as *Staphylococcus aureus, Streptococcus faecalis* and Gram(-) bacteria such as *Klebsiella oxytoce, Enterobacter aerogines.*

References

1. Sullivan, W.R.: **J. Med. Chem.,** 13(4), 783, (1970).
2. Tosun, A., Ersan,S., Uzunoğlu, Ş., Nacak, S., Şahin, M.F., Özden, T., Abbasoğlu, U.: **J. Fac. Pharm. Gazi**, 12(1), 29, (1995).
3. Tosun, A., Uzunoğlu, Ş., Şahin, M.F., Özçelik, B.: **J. Fac. Pharm. Gazi**, 13(2), 113, (1996).
4. Phillips, M.A.: **J. Chem. Soc.**1143, (1931).

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NEW PLATINUM(II) COMPLEXES OF 5(6),2-DISUBSTITUTED BENZIMIDAZOLE DERIVATIVES AND THEIR IN VITRO ANTIMICROBIAL ACTIVITIES

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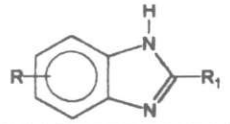
Cisplatin [*cis*-diamminedichloroplatinum(II)] is one of the most commonly used anticancer drugs in the treatment of testicular ovarian, bladder and head and neck cancers. However its more widespread use is limited by inherent resistance by acquired drug resistance and by its major side effects. There is continuing interest in the development of new platinum group transition metal based chemotherapeutic agents which are less toxic and have broder spectrum of activity. Replacement of the NH_3 groups by some cyclic amines generally reduces the toxicity of the platinum compounds. The use of amines more compatible to the human system might possibly be another way of surmounting these problems. For this purpose, we have chosen some benzimidazole derivatives as a carrier ligand since benzimidazole nucleus is known by the human system. In the present study, six 5-non/-methyl-2(-phenyl/-2'-pyridyl/-mercaptomethyl)benzimidazoles and their Pt(II) complexes have been synthesized.The ligands synthesized have been reported in literature before. The Pt(II) complexes are orginal except Comp. 9. Complexes have been obtained by the reaction of the ligands and K_2PtCl_4.
The chemical structures of the Pt(II) complexes have been characterized by their elemental analyses, IR and ^{1}H-NMR spectra compairing with those of the ligands.



Comp. No	R	R_1	Ligand	Comp. No	Complex
1	H	phenyl	L1	7	$[PtL^1{}_2Cl_2]\bullet H_2O$
2	CH_3	phenyl	L2	8	$[PtL^2{}_2Cl_2]\bullet 3H_2O$
3	H	2'-pyridyl	L3	9	$[PtL^3Cl_2]\bullet H_2O$
4	CH_3	2'-pyridyl	L4	10	$[PtL^4Cl_2]\bullet H_2O$
5	H	CH_2SH	L5	11	$[PtL^{5'}Cl_2]^*$
6	CH_3	CH_2SH	L6	12	$[PtL^{6'}Cl_2]^*$

* $L^{5'}$ and $L^{6'}$ are deprotone form of L^5 and L^6 respectively.

Also, in this study in order to investigate the in vitro antimicrobial activity diffecences of the ligands and their Pt(II) complexes,in vitro antibacterial and antifungal activities of the compounds have been tested against gram possitive (S.aureus, S.faecalis) and gram negative (E.coli,P.aeruginosa) bacteria and yeast like fungus (C.albicans) using "Macrodilution Broth Method". The test results have shown that most of the compounds tested had MIC (Minimum Inhibition Concentration) values of 200µg/mL against the microorganisms used. There were no differences between the in vitro antimicrobial activities of the ligands and their Pt(II) complexes. To study on antitumor activities of the Pt(II) complexes have also been planned.

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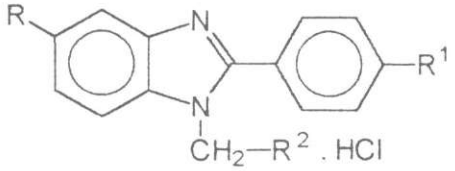
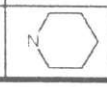
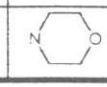
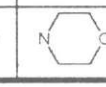
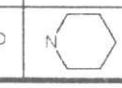
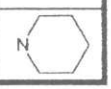
STUDIES ON ANALGESIC AND ANTI-INFLAMMATORY ACTIVITIES OF 1-DIALKYLAMINOMETHYL-2-(P-SUBSTITUTED PHENYL)-5-SUBSTITUTED BENZIMIDAZOLE DERIVATIVES

S. Nacak[1], S. Ersan[1], N. Noyanalpan[1], and E. Yeşilada[2]

University of Gazi, Faculty of Pharmacy, [1]Department of Pharmaceutical Chemistry, [2]Department of Pharmacognosy, Hipodrom-Ankara, Turkey



Comp.	1a	1b	1c	1d	1e	1f	1g	1h	1i
R	CH_3	OCH_3	OCH_3	OCH_3	NO_2	NO_2	NO_2	NO_2	NO_2
R^1	CH_3	OCH_3	CH_3	NO_2	OCH_3	CH_3	Cl	NO_2	OCH_3
R^2					NEt_2	NEt_2	NEt_2	NEt_2	

In this study analgesic and anti-inflammatory activity of 1,2,5-trisubstituted benzimidazole derivatives have been examined. Analgesic activities of these compounds were investigated by a Modified Koster's Test. Among the compounds synthesized especially compound 1g [1-(diethylaminomethyl)-2-(p-chlorophenyl)-5-nitro benzimidazole hydrochlorid] has shown higher activity than acetylsalicylic acid (ASA) and Indomethacin. Compound 1e [1-(diethylaminomethyl)-2-(p-methoxyphenyl)-5-nitro benzimidazole hydrochlorid], 1f [1-(diethylaminomethyl)-2-(p-tolyl)-5-nitro benzimidazole hydrochlorid] and 1i. [1-(piperidinomethyl)-2-(p-methoxyphenyl)-5-nitro benzimidazole hydrochlorid] exhibited as potent as the standard acetylsalicylic acid (ASA). Therefore the compounds (1e, 1f, 1g and 1i) were screened for their anti-inflammatory activities using the carrageenan-induced hind paw edema test. Except 1g all compounds were almost inactive against this model of inflammation compared to Indomethacin.

References

1. Fuveau, S.A. : Ref. C.A., **77**, 118208s (1972).
2. Dol'nikov, Yu. Ya.; Epel'dimov, I.S. : Sb. Rab. Gel'mitol., 129 (1971).
3. Kamissarov, I.V.; Filippov, I.T.; Prokop'eva, T.M.; Dadal, V.; Litvinenko, L.M.; Simonenko, Yu.S.: Khim. Farm. Zh. **16**(5), 570 (1982).
4. Wright, J.B. : J. Amer. Chem. Soc., **71**, 2033 (1949).
5. Bloom, A.; Day, A.R. : J. Org. Chem., **4**, 14 (1939).
6. Koster, R.; Anderson, M.; Debeer, E.J. : Fed. Proc., **18**, 412 (1959).
7. Kasahara, Y.; Hikino, H.; Tsurufuji, S.; Watanabe, M.; Ohuchi, M. : Planta Medica, **51**, 325 (1985).

DNA BINDING STUDIES WITH *cis*-DICHLOROBIS (5(6)-NON/CHLOROSUBSTITUTED-2-HYDROXYMETHYLBENZIMIDAZOLE) PLATINUM (II) COMPLEXES

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Department of Pharmaceutical Chemitry, Faculty of Pharmacy, University of Gazi, 06330-Etiler- Ankara, Turkey

Cisplatin [*cis*-$Pt(NH_3)_2Cl_2$] is a clinically important antitumor drug used in the treatment of testicular, ovarian, bladder and head and neck cancers. However, the drugs wide-spread use is limited by its major side effects which include nephrotoxicity, myelosuppression, ototoxicity and other neurological disorders. The need for cisplatin analogs which are less toxic and have a broader spectrum of activity has led to the synthesis of a large number of platinum complexes over the past two decades. Recently, interest has been directed toward developing cisplatin analogs which have heterocyclic amine ligands coordinated to the cytotoxic platinum (II) moiety. Replacement of the NH_3 groups by cyclic amines (especially those involving large rings) generally reduces the toxicity of the platinum compounds. The benzimidazole nucleus is found in a variety of naturally occuring compounds such as vitamin B_{12} and its derivatives, and it is structurally similar to purine bases. Furthermore, benzimidazoles are known to exhibit a wide variety of pharmacological properties including antitumor activity and inhibition of nucleic acid synthesis. With regard to benzimidazole-platinum complexes, even though the interaction of benzimidazoles with various metal ions has been studied for almost three decades.There are only a few reports on the antitumor activity of benzimidazole-platin complexes. We reasoned that by combining the intrinsic antitumor activity of certain benzimidazoles with that of platinum it might be posible to obtain compounds with superior chemotherapeutic index in terms of increased bioavailability, higher cytotoxicty, and lower side effects than cisplatin. We have chosen Pt(II) complexes of 5(6)-substituted-2-hydroxymethylbenzimidazoles for this purpose. In a previous paper, we described the synthesis and characterization of complexes of the structure, *cis*-[$Pt(L)_2Cl_2$] $\bullet 2H_2O$, where L is 5(6)-non/or -chloro substituted-2-hydroxymethylbenzimidazole (compound I and II). We also evaluated the ability of these compounds to damage DNA or interfere with DNA replication by determining their cytotoxic effects on the repair proficient *E.coli* strain AB1157 (Rec A^+) and the repair deficient mutant AB2463 (Rec A). These preliminary test indicated that even though these two compounds were less effective than cisplatin at equal doses nevertheless exerted strong cytotoxic activity and hence warranted further investigations. In the present study,we have characterized the DNA binding properties of compounds I and II and the affinity of DNA modified by these compounds to the HMG-domain protein, since there is some evidence that binding of these proteins to cisplatin adducted DNA may be an important determinant in cytotoxicity. The DNA platinated with these compounds was specifically recognized by HMG1.

THE MULTIVARIATE QSAR ANALYSIS OF SOME NOVEL SUBSTITUTED BENZOXAZOLES AGAINST *S. aureus* USING THE PLS REGRESSION METHOD

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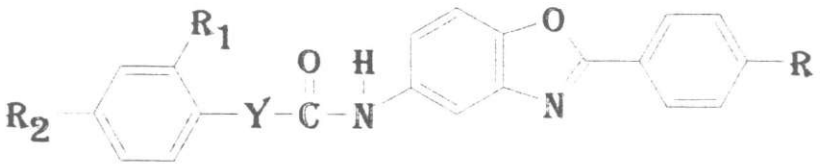
Partial least squares (PLS) regression is a wellknown chemometrical tool in combutatutional chemistry which has many inherent advantages compared to univariate regression. The PLS method has shown to be suitable in QSAR studies aimed at detecting the structural features affecting the biological activity, being free of the pitfalls typical of the widely used multiple regression analysis (MRA) which may lead to unrealible interpretations and predictions.

In this study, the multivariable QSAR analysis of antibacterial active 24 benzoxazoles (Formula I) against the Gram-positive microorganism *S. aureus* was performed by using the PLS regression method.



Formula I

Predictions for the lead optimization in this QSAR analysis have been described by the description of various hydrophobic, electronic, steric and structural parameters related to the positions R, $R_1$and R_2. Cross-validation method was also applied to the data set in order to prove the predictive power by using the SAS statistical software.

The results of our study in these set of compounds can be summarized as follows;

- QSAR analysis reveals that the substitution at position R_2 is found significant rather than the positions R and R_1 to improve the activity.
- Electronic and steric properties of the substituents on position R_2 are detected more indicative than the hydrophobic effect for the antibacterial activity.
- Substituting this position with a group considering the minimal width which reflects the tendency of flexible substituents to change their conformation in a way that minimizes steric interactions together with the positive resonance effect enhances the potency.

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THE ACTIVITY CONTRIBUTION ANALYSIS OF SOME ISOSTERIC POLYSUBSTITUTED HETEROCYCLICS AGAINST A GRAM-POSITIVE ROD USING THE FREE-WILSON APPROACH

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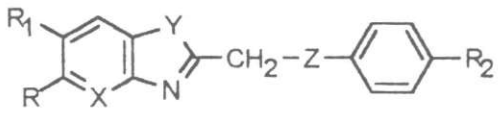
Due to the need of new and different antibacterial agents and many effective antibacterial drugs possess heterocyclic systems, QSAR analysis of some novel isosteric polysubstituted heterocyclic compounds holding benzoxazole, benzimidazole, benzothiazole and oxazolo(4,5-*b*)pyridine fused ring systems were determined for their antibacterial activity against the Gram-positive rod, *Bacillus subtilis*.
Predictions for the lead generation and/or optimization have been described by the results obtained from Free-Wilson approach which is a valuable alternative tool in QSAR analysis. Determination of the activity contributions of the structural descriptors in this homologous series of compounds against *Bacillus subtilis* performed by using the BMDP statistical software. The group activity contributions with the position side values and the statistical parameters are given below;



Position	Group	Activity contributions Position	Group	Position	Group	Activity contributions Position	Group
R		0.281		X		0.002	
	-H		-0.002		-CH=		0.000
	-Cl		0.054		-N=		-0.002
	$-NO_2$		0.069	Y		0.028	
	$-CH_3$		0.013		-O-		-0.001
	$-COOCH_3$		-0.211		-S-		0.024
R_1		0.067			-NH-		-0.004
	-H		-0.009	Z		0.035	
	$-NO_2$		0.058		-O-		-0.009
	$-CH_3$		0.013		-S-		0.020
R_2		0.053			-NH-		-0.008
	-H		-0.007		$-CH_2-$		-0.015
	-Cl		0.046				
Constant contribution (μ)			3.987				
Number of compounds (n)			38				
Square of correlation coefficient (R^2)			0.996				
Standard deviation (s)			0.004				
F value (*F*)			831.5				

SIMULTANEOUS DETERMINATION OF MEDAZEPAM AND HYOSCINE BUTYLBROMIDE IN TABLETS BY SECOND-DERIVATIVE ULTRAVIOLET SPECTROMETRY

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Medazepam **1** is a tranquilizing agent. Several techniques, including spectrophotometric, derivative spectrophotometric[1,2], gas chromotographic, HPLC have been reported for its determination. Hyoscine butylbromide **2** is employed as an antispasmodic drug. Determination of **2** has been accomplished by spectrophotometry, derivative spectrophotometry[3] and HPLC. To date no method for the simultaneous determination of compounds **1** and **2** in pharmaceutical forms has been described. This paper reports a second-derivative UV spectrophotometric method for the analysis of **1** and **2** in tablets without prior separation and the comparison of the results with those of the reference methods[4,5]. In the preparation of calibration graphs of these drugs, aliquots of the stock solutions of **1** (0.05- 0.25 ml) or **2** were transferred separately into 10 ml calibrated flasks and diluted to volume with 0.1 N hydrochloric acid. The derivative absorbance values were measured versus peak to peak amplitudes at 252.6 and 264.8 nm for **1** and zero-crossing amplitude at 212.5 nm for **2**. The amount of **1** and **2** were calculated from the regression equations. Linear relationships were obtained over the ranges of 3.5- 20 μg. ml^{-1} of compounds **1** and **2**. The regression equations were the following $D = 6 \times 10^{-3} C + 3.5 \times 10^{-3}$ with $r = 0.9997$ for **1** and $D = 2.5 \times 10^{-3} C - 2.4 \times 10^{-3}$ with $r = 0.9999$ for **2**.

The proposed method was applied to the determination of **1** and **2** in tablets and the results were compared withe those of the reference methods (Table).

Table: Assay results for **1** and **2** in tablets [a]

Recovery ± standard deviation [b] (%)

Comp.	Derivative method	Reference method
1	102.43 (± 0.56)	102.52 (± 0.23)
2	99.43 (± 0.08)	99.85 (± 0.14) [c]

[a] each tablet contained 10 mg of **1** and **2**, [b] n= 6, [c] n= 5

References

(1) M. E. Abdel-Hamid, M. M. Abdel-Khalek, M. S. Mahrous, *Anal. Lett.*, 17, 1353 (1984).

(2) V. Singh, S. K. Shukla, J. S. Mahanwal, *Indian J. Forensic-Sci.*, 4, 89 (1990).

(3) N. Erk, F. Onur, *Anal. Lett.*, 29, 369 (1996).

(4) *The British Pharmacopoeia*, p. 995, British Pharmacopoeia Commission, London (1993).

(5) C. Silveria, M. T. Barrosa, *Rev. Port. Farm.*, 14, 96 (1964).

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SYNTHESIS AND STRUCTURE ACTIVITY RELATIONSHIPS OF 3-HYDRAZONO-2-INDOLINONES WITH ANTITUBERCULOSIS ACTIVITY

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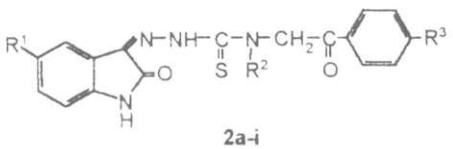
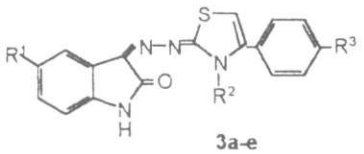
The discovery of the potent antimicrobial activity of 2-indolinones led in the past decade to extensive synthesis of related compounds and as a result, a variety of broad spectrum antimicrobial agents were developed [1,2]. Investigation of the structure activity relationships in a class of 2-indolinones revealed that 5-halogenation, 5-alkylation, N-alkylation, N-acylation and N-Mannich base formation were effective in causing a marked rise in activity against various viruses, bacteria and fungi. In the light of these findings and in continuation of our work on 3-hydrazono-2-indolinones [3,4] two novel series of phenacylthiosemicarbazono-1*H*-2-indolinones and thiazolinehydrazono-1*H*-2-indolinones were synthesized. These new compounds and 3-hydrazono-2-indolinone derivatives which were previously reported were tested for antituberculosis activity to construct the structure activity relationship. The reaction of 3-(4-substituted-3-thiosemicarbazono)-1*H*-2-indolinones (**1a-e**) with 2-bromoaceto-phenone in the presence of anhydrous sodium acetate furnished 3-phenacylthiosemicarbazono-1*H*-2-indolinones (**2a-i**) or 3-(3,4-disubstituted-4-thiazoline)-2-hydrazono-1*H*-2-indolinones (**3a-e**) in good yields. The structure of all the synthesized compounds were determined by the elemental analyses and spectral data (IR, ^{1}H-NMR, EIMS).



2a-i



3a-e

The new hydrazonoindolinones **2a-i** and **3a-e** and other hydrazonoindolinones which were previously reported [3-4] were evaluated for in vitro antituberculous activity against Mycobacterium tuberculosis $H_{37}Rv$. The 3-hydrazono-1*H*-2-indolinones exhibited varying degrees of inhibition in the in vitro primary screening that was conducted at 12 μg/ml against M. tuberculosis $H_{37}Rv$ in BACTEC 12B medium using the BACTEC 460 radiometric system [5]. Rifampin was used as the standard in the tests. **2a**, **2d**, **2g-i**, **3b** and **3e** effecting >90% inhibition in the primary screen at 12 μg/ml were re-tested at lower concentrations against M. tuberculosis $H_{37}Rv$ to determine the actual minumum inhibitory concentration (MIC) in the CABTEC 460. Among **2** and **3**, the R^1 and / or R^3-substituted derivatives were more active than other entries with no substitution. Potency was insensitive to the electronic nature of the substituent at R^1 and R^3, where the most active compounds were R^1 bromine and R^3 bromine, nitro or methoxy substituted derivatives.

References:

[1] Maysinger, D., Movrin, M., Saric, M. M., Pharmazie **35**, 14 (1980)

[2] Varma, R. S., Garg, P. K., Verma, H. N. et al., Arch. Pharm. (Weinheim) **314**, 918 (1981)

[3] Karalı, N., Gürsoy, A., Farmaco **49**, 819 (1994)

[4] Gürsoy, A., Karalı, N., Büyüktimkin, S., et al., ibid. **51**, 437 (1996)

[5] Inderleid, C. B., Antibiotics in Laboratory Medicine, 3rd ed. (Ed: Lorian, V.) Williams and Wilkins, Baltimore, 134-197 (1991).

HIGH-PRESSURE LIQUID CHROMATOGRAPHIC-FLUORIMETRIC DETERMINATION OF AMINOGLUTETHIMIDE WITH DANSYL CHLORIDE

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Aminoglutethimide (AG) is a drug used for the treatment of breast cancer, and Cushing's syndrome related to adrenal tumors. Several HPLC techniques (1-3) for the determination of AG have been reported in the literature. No HPLC method with fluorimetric derivatization has been reported to date.

In this study, AG was reacted with dansyl chloride (DNS-Cl) in the presence of $NaHCO_3$ to furnish AG-DNS, the fluorescent derivative. The structure of the derivative so obtained was elucidated by UV, IR, ^1H and ^{13}C NMR spectroscopy and elemental analysis.

The formation of derivative was quantitative in 1 hour at room temperature in the presence of 0.01M $NaHCO_3$ and 8 fold excess DNS-Cl.

The HPLC apparatus consisted of Waters M6000A pump, U6K injector, a Waters 420 fluorescence detector and HP 3365 Chem Station data handling system. The column was μ-bondapak C18 (300×3.9mm ID). The mobile phase was a mixture of acetonitrile-water (56:44) and the flow rate was 1ml/min. Excitation and emission wavelengths for the fluorimetric detector were optimized at 360 and 530nm respectively.

Aliquots of AG (2-6μg/ml) were taken. Calibration graph was constructed using peak height versus concentration. The results of linear regression analysis were slope 181.0; intercept -27.2 and correlation coefficient r=0.9994 (n=5).

The method was used for the quantitation af AG in tablet formulation. The proposed and the reference method (4) were compared using student's t test of significance and F test of significance.

References:

(1) Robinson, B.A.; Cornell, F.N., *Clin. Chem.* 29/6, 1104 (1983).

(2) Kamblawi, M.O.; Stevens, R.G.; Nicholls, P.J., *J. Chromatogr*, 309, 431 (1984)

(3) Aboul-Enein, H.Y.; Islam, M.R.; *Biomed Chromatogr.*, 5, 74 (1991)

(4) Murray, F.T.; Santner, S.; Samojlik, E.; Santen, R.J., *J. Clin. Pharmacol.* 704-711 (1979).

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SYNTHESIS AND ANTIBACTERIAL ACTIVITY OF SOME 5-ARYL-2-SUBSTITUTEDAMINO-1,3,4-OXADIAZOLES AND 2-SUBSTITUTEDIMINO-5-PHENYL / METHYL-4-THIAZOLIDINONES

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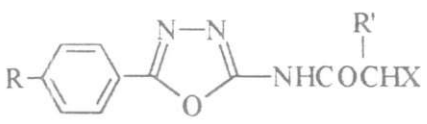
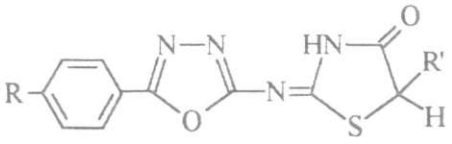
Both 2-amino-1,3,4-oxadiazoles [1] and 4-thiazolidinones [2] show antibacterial activity. In an attempt to obtain compounds with enhanced potency, we synthesized new substances by combining these two structures. Reaction of 5-aryl-2-amino-1,3,4-oxadiazoles, obtained by the oxydative cyclization of aromatic aldehyde semicarbazones [3], with a-chloro-a-phenylacetyl chloride and a-bromopropionyl bromide yielded 5-aryl-2-[(a-chloro-a-phenylacetyl / a-bromopropionyl)amino]-1,3,4-oxadiazoles (Ia-XIIa) [4] Furthermore, Ia-XIIa were refluxed with ammonium thiocyanate to give 5-phenyl / methyl-2-[(5-aryl-1,3,4-oxadiazol-2-yl)imino]-4-thiazolidinones (It-XIIt) [5]. The formulas of the compounds were confirmed by the elemental analyses and their structures were determined by UV, IR, ^{1}H-NMR and EI mass spectral data.



Ia-XIIa



It-XIIt

R=H, CH_3O, Cl, Br, F, CH_3, R =C_6H_5, CH_3.

Our compounds have been tested for *in vitro* antibacterial activity and found highly active against S.aureus, with MIC values ranging from 0.24 to 125 mcg / ml.
LD_{50} of compounds chosen as prototypes was estimated in mice. The results showed that the acute toxicity of thiazolidinones was quite low exhibiting an LD_{50} in excess of 1000 mg / kg.

References :

1) Saikawa I. et al., Japan **11**, 384 (1965), June 7, Appl.Oct.15, 1962.- Ref.C.A.**63**, 13275b (1965).
2) Pujari, H.K. et al., J.Sci.Ind.Research (India) **14B**,448 (1955).- Ref.C.A.**50**, 11317f (1956).
3) Scott, F.L. et al., J.Chem.Soc.Perkin Trans **1(13)**, 1918 (1972).
4) Kauer, K.C.,U.S.Patent 2, 780, 631 (195719.- Ref.C.A.**51**, 10587e (1957).
5) Cesur, Z., Pharmazie **42(11)**, 716 (1987)

STUDIES ON THE SYNTHESIS OF SOME 5-ACETYLINDAN ARYLOXYACETOHYDRAZONE DERIVATIVES

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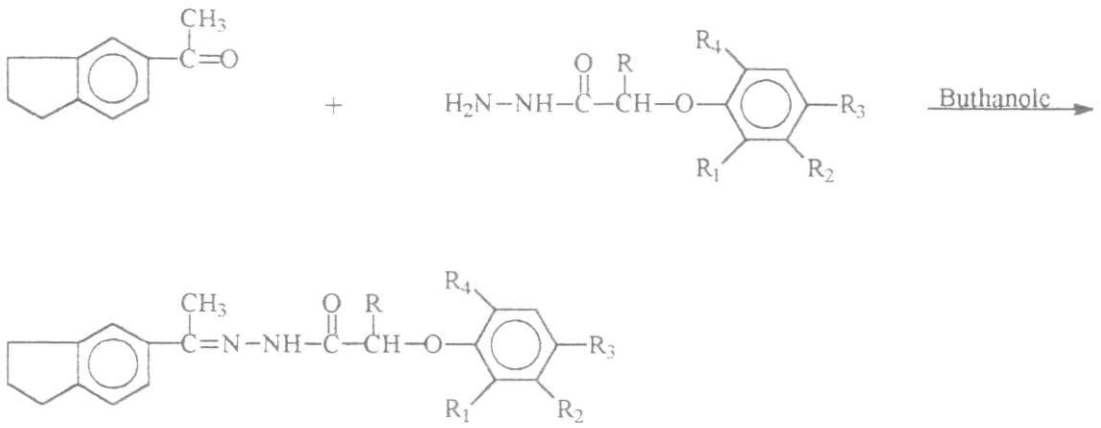
Some 5-acetylindan aryloxyacetohydrazone derivatives were synthesized by reacting 5-acetylindan with aryloxyacetohydrazide derivatives in buthanole. The structure of the compounds obtained were performed by using IR, ^{1}H-NMR and elemental analyses results.



R = H, CH_3
R_1= H, NO_2, Cl, CH_3
R_2= H, NO_2, Cl,
R_3= H, NO_2, Cl, CH_3, OCH_3
R_4= H, CH_3

NEW HISTAMINE H_2- AND H_3- RECEPTOR ANTAGONISTS

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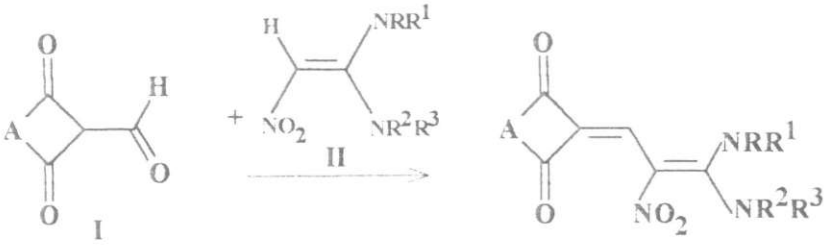
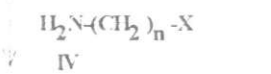
During modification of 1,1-diamino-2-nitroethenes in reactions of their N,N'-substituted derivatives (II) with 2-formyl-1,3-cyclandiones (I) a series of 2-(2-nitro-3,3-diamino-2-propen-1-ilyden)-1,3-cyclandiones (III) exhibiting H_2-receptor antagonist activity was synthesised. X-ray structural investigations revealed that these compounds have betaine III-2 structure.



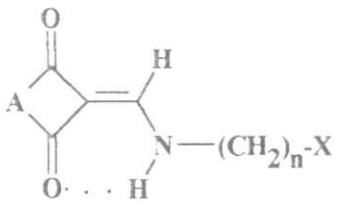
I

II

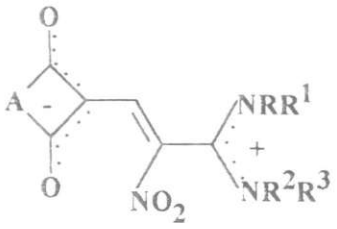
III-1



IV



V



III-2

A=$CH_2C(CH_3)CH_2$, 1,2-C_6H_4. a) R=R^2=CH_3, R^1=R^3=H;
b) R=R^2=CH_2CH_2OH, R^1=R^3=H; c) R=CH_3, R^2=CH_2CH_2OH, R^1=R^3=H;
d) RR^1=R^2R^3=N-morpholyl-, n=2, 3; X=4-morpholyl-, 3-indolyl-, 4-imidazolyl-, 4-oxo-3,4-dihydro-3-quinazolyl, $C_6H_4(OH)$ (4), $C_6H_3(OH)_2$ (3,4).

For the search of new H_3-receptor blocators the corresponding 2-aminomethylen-1,3-cyclandiones (V) were obtained in reactions of I with histamine, tryptamine, tyramine, 3-(2-aminoethyl-4-oxo-3,4-dihydroquinazoline and their homologues (n=3) and evaluated for their antihistaminic activity.

QUANTITATIVE DETERMINATION BY USING HPLC AND GLC METHODS FOR COCAINE HCl IN SYNTHETIC BINEARY MIXTURES WITH PROCAINE HCl, LIDOCAINE HCl AND CAFFEINE

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Cocaine HCl is a substance which creates psychological dependence.Usually it is presented on the market as being diluted by other substances. Local anesthetics, analeptics, C.N.S stimulating agents and some inert subtances were widely used for this purpose.

In this study, HPLC and GLC methods were applied for qualitative and quantitative determinations of synthetic bineary mixtures. In the HPLC method:,μ Bondopack C_{18}10μm. column system, mobile phase consisting of methanol-water-phosphoric acide-1% hexylamine (75:175:250:3,5) and U.V. detection by photodiodearray (196-600 nm) were used. The lineer concentration areas were found in a range of 2.5-25 μg/mL. The R.S.D % for cocaine HCl, procaine HCl, lidocaine HCl and caffeine were found as 0.922 - 0.568 - 1.180 and 1.04 respectivelly.

In the GLC determination: two different column systems were used [2% OV-17-Gas Chrom W-HP 100-200 mesh filled column and 0.25 SE-52 fused silica capillary column (30 m x 0.55 mm)]. Nitrogen and helium were used in filled and capillary column respectively .Mobile phase flow-rates were set as 30 mL/min during the analysis and F.I.D were applied for the detection in both column systems.

The linear concentration intervals were found in a range of 2-25 μg/mL in both methods. R.S.D % for cocaine HCl, procaine HCl, lidocaine HCl, and caffeine were found as 0.907- 0.948- 0.770- 0.901 in filled column. In capillary column; they were found as 0.774 - 0.809 and 0,814 for cocaine HCl , procain HCl and caffein respectively .In quantitative determinations, antipyrine was chosen as internal standard in both methods.

COMPARISON OF VARIOUS GEL BEADS FOR THE IMMOBILIZATION OF RAT PANCREATIC ISLETS

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Since conventional insulin therapy has failed to achieve tigtht glucose control, most of the studies focused on the alternative insulin delivery systems which would by-pass some of unresolved problems associated with mechanical insulin pumps and organ transplantations. Microencapsulation of pancreatic islets (insulin secreting cells) is a potentially effective method to prevent graft rejection in organ transplantations without the need of immunosupression.

This study was undertaken to investigate the encapsulation and the release characteristics of two natural gel polymers , chitosan and sodium-alginate which were used to prepare beads used in immobilization of islet cells. The cells were obtained from Wistar rats and immobilized in chitosan by dropping the mixture into a solution containing tripolyphosphate and sodium alginate ,or in sodium alginate by dropping the gel mixture into a solution containing calcium chloride and chitosan. The droplets formed smooth and spherical gel beads by ionotropic gelation. The mean diameter of sodium alginate and chitosan beads were about 2.5 mm and 1.6 mm respectively.

For *in vitro* release experiments, the beads were maintained in minimal essential medium at 37^{0}C for the three months and the insulin release was measured spectrophotometrically. It has been found that the release was continued for three months without any change on the insulin structure which has been controlled by electrophoretic and chromotographic methods.

The effects of various factors on bead and release properties were also studied. According to the results of this study, sodium alginate induced chitosan beads may be used as an alternative for chitosan reinforced sodium alginate beads to immobilize the pancreatic islet cells.

EVALUATION OF ALGINATE-REINFORCED CHITOSAN BEADS FOR PROTEINS

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Using ionotropic gelation method in the preparation of beads offers the advantage of avoiding harsh organic solvent conditions, which make it possible to incorporate bioactive molecules.

Recently, chitosan beads have been used successfully to encapsulate peptide and proteins. The biodegradibility and biocompability of chitosan also makes this polymer a safe matrix to be used in the body. However, the beads are known to progressively degrade in aqueous media containing ionic compounds. This erosion can be prevented by sodium alginate induction of chitosan beads.

In the present study, an attempt was made to prepare sodium alginate induced chitosan beads for protein encapsulation. Bovine serum albumin was used as a model protein. In standard procedure, sodium alginate were added to tripolyphosphate (TPP) solution; beads were formed by dropwise addition of chitosan solution into this TPP solution. *In vitro* protein release was assayed by incubating beads in PBS at 37°C. At periodic intervals, samples were removed and analysed for protein amount using modified Bradford method. Total protein loading was estimated using the above method after distruption of beads.

Spherical and smooth beads could be formed by this method. The strength of the bead structure was enhanced by adding the alginate to the external phase. Beads size and encapsulation efficiency changed depending on formulation factors. An increase in BSA amount caused a change in encapsulation efficiency.

The effect of various formulation factors such as sodium alginate concentration and protein amount, on protein release properties, was investigated. The amount of BSA also affected the initial protein release.

As a conclusion, alginate-treated chitosan beads may be used as a matrix for sustained release of proteins.

SUSTAINED RELEASE WAX MATRIX FORMULATIONS OF KETOROLAC TROMETHAMINE WITH COMPRITOL 888 ATO AND HD 5 ATO

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Application of a wax matrix dosage form, in which drugs are incorporated into inert water insoluble matrix materials, has been attempted in many types of matrix forms, including granules and tablets, in an effort to obtain an effective sustained release system. In order to examine the function of a wax matrix system as a barrier for the controlled release of oral dosage forms, reservoir devices were prepared and dissolution tests were carried out. It was reported that after dissolution of the active or water-soluble ingredients in a wax matrix, the wax matrix system becomes porous without disintegrating and this porous structure is used as a barrier for control of the drug dissolution rate, as is the insoluble polymer membrane. Tablet matrix systems containing Compritol (Glyceryl Behenate) have been used extensively in experimental formulation for devoloping oral sustained release drug delivery systems. Its compressibility and binding properties as well as its insolubility in water confer Compritol 888 ATO the ability to build matrices when used at appropiriate levels in tablets. It should be bare in mind that the levels recommended for a prolonged release of drugs are much higher that the typical levels preconized for the use of Compritol 888 ATO as lubricant in tablets and hard shell capsules. In this study, wax matrix tablets of Ketorolac Tromethamine were prepared by direct compression technique to achieve this, Compritol 888 ATO and HD 5 ATO have been used to be wax matrix excipients in different concentrations. For the quality control of tablets, weight deviation, hardness, friability, diameter-hight ratio, content uniformity of the active substances and in vitro dissolution techniques were performed. Spectrophotometric method was used for Ketorolac Tromethamine assay. Dissolution profile of each tablet was plotted and evaluated kinetically.

AN EQUATION DEVELOPMENT FOR THE STIMATION OF DRUG RELEASE FROM ETHYL CELLULOSE PELLETS. PART I.

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In recent years, optimization techniques have become more widely used in the pharmaceutical industry. There are many methods that can be used and have been used for optimization; classical and otherwise. The effect on a real system of changing some input (some factor or variable) is observed directly at the output, and that set of real data is used to develop mathematical models. The responses from the predictive models are then used for optimization. Once experimental data are collected and relationships generated by regression analysis, the formulator is able to select the best formulation. The results of an optimization study can enable for product improvement (1-3). In the present study, ethyl cellulose was used to prepare sustained-release oxolamine citrate pellets. The formulations were prepared at 1:1, 1:2 and 1:3 polymer-drug ratios. Dissolution studies were carried out according to rotating paddle at 50 rpm. It was observed that the release of oxolamine citrate was prolonged. The results obtained were examined with simple linear regression equations for slope and intercept values as a function of time. As a result, a regression equation was estimated for the release of oxolamine citrate from pellets. The obtained and predicted drug releases were compared. A good relationship was found. In addition, the predicted drug release values have been successfully validated in the repeated in vitro release studies for three another formulations.

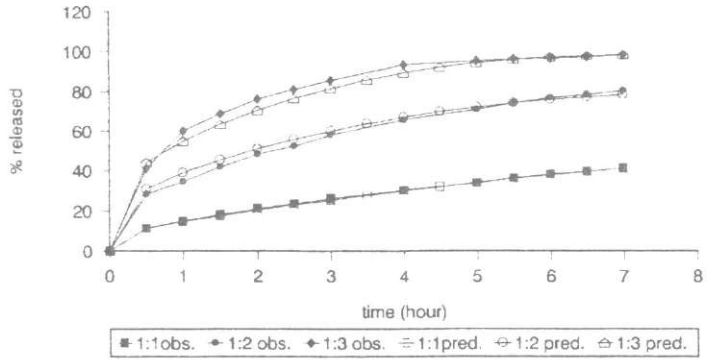

Figure: The comparison of the obtained and predicted release results.

1-SCHWARTZ, J.B., 1990, Optimisation Techniques in Pharmaceutical Formulation and Processing-In: *Modern Pharmaceutics*, edited by Banker G.S, Rhodes C.T (Marcel Dekker, Inc.), pp.803-828.

2-MC GURK, J.G., LENDREM, D.W., POTTER, C.J., 1991, Use of statistical experimental design in laboratory scale. Formulation optimisation and progression in laboratory scale, *Drug Development and Industrial Pharmacy*, **17**, 2341-2358.

3-BOLTON, S., 1990, *Pharmaceutical Statistics. Practical and Clinical Applications* (Marcel Dekker, Inc.), pp. 210-261.

STUDIES ON THE DISSOLUTION OF CHLORZOXAZONE MATRIX TABLETS PREPARED WITH EUDRAGIT ACRYLIC RESINS

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Chlorzoxazone, is one of the derivatives of benzoxazole which is used as a central muscle relaxant (1,2). For the first time, the matrix form of Chlorzoxazone was prepared. Matrix systems are the ones in which the drug is dissolved or dispersed in a solid polymer matrix (3). The primary aim in these pharmaceutical dosage forms; is the sustained release of the active substance also to prevent its side effects on the gastro-intestinal system. The matrix tablets of Chlorzoxazone were prepared by using different Eudragits, dispersing agent(lactose) and lubricant(primojel). We also investigated the effect of content of active substance on the release. Sustained release matrix tablets of Chlorzoaxazone were formulated at different drug: polymer: (lactose) ratios. Different types of Eudragits (Eudragit RL 100, RS 100 and S 100) were added. Direct compression was employed for these tablets. Also some other matrix tablets were formulated at different drug:eudragit:lactose:primojel ratios. Wet granulation was employed for these tablets. The dissolution of prepared tablets were studied by using the USP XXII Paddle Method at 100 rpm in simulated gastric and intestinal media (4). Samples withdrawn at appropriate time intervals were filtered and assayed using a UV-Visible spectrophotometer at 280 nm and 287 nm. To increase the dissolution results of the matrix tablets prepared with Drug:Eudragit RL 100:Lactose, 10 and 20 % of primojel was added to the matrix tablets prepared with Drug:Eudragit RS 100:Lactose. Besides, to obtain better dissolution profiles the amount of Eudragit RS 100 and the pressure applied during the production of the tablets were increased. The release percentages of Chlorzoxazone were found as 92.7% in simulated gastric medium and as 94.7% in intestinal medium.

Referances:

1) Karayalp, O.S., Rasyonel Tedavi Yönünden Tibbi Farmakoloji, Cilt 2, 1985.

2) Martindale The Extra Pharmacopeia, 29th Ed. London, The Pharmaceutical Press, 1989.

3) Gürsoy, A., Piskin, E., Dortunç, B., Peppas, A. N., "Kontrollü Ilaç Serbestletiren Sistemler", Marmara Üniversitesi Eczacilik Fakültesi Yayinlari, No: 469/5, Istanbul,1989.

4) The United States Pharmacopeia XXII, (USP XXII- NF XVII), United States Pharmacopeial Convention, Inc., Rockville, 1990.

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DISSOLUTION CHARCATERISTICS OF PIROXICAM-PHOSPHOLIPID COPRECIPITATES

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The dissolution of poorly water soluble drugs is often a rate-limiting step for absorption. In aqueous media, phospholipids disperse spontaneously to form bilayer structures which have the capacity to entrap or sequester solutes. This behavior may improve bioavailability of drugs. Piroxicam, a non-steroidal anti-inflammatory drug, is practically water insoluble. Solid dispersions of piroxicam and various phospholipids were used to evaluate the effect of phospholipids on the dissolution behavior of the drug. Coprecipitates of piroxicam and phospholipids were prepared by the solvent method. The solvent, chloroform was removed at room temperature under nitrogen. Further drying was accomplished in a vacuum dissector overnight. Coprecipitates were usually tested within 48 hours after preparation. Physical mixtures were prepared by gently triturating appropriate quantities of piroxicam and phospholipid using a mortar and pestle. Both coprecipitates and physical mixtures were passed through an 80-mesh sieve prior to dissolution study. The dissolution study was performed with paddle method (100 rpm) at 37°C using 900 mL of distilled deionized water as the dissolution medium. Sieved samples were sprinkled on the surface of the stirred dissolution medium at the beginning of the study. Samples were taken at different intervals and the concentration of piroxicam was determined using a UV spectrophotometer at wavelength 360 nm. The dissolution of phospholipid coprecipitates of piroxicam was compared with physical mixtures and pure piroxicam. The dissolution of the physical mixtures was similar to the pure drug. Coprecipitates of piroxicam yielded greater initial dissolution rate and a higher limiting concentration after 60 min. Phospholipids with phase transition temperature lower than 37°C (e.g. dimyristoyl phosphatidyl glycerol; DMPG and dimyristoyl phosphatidyl choline; DMPC) increased the dissolution of piroxicam more than those with phase transition temperature higher than the experimental temperature (e.g. dipalmitoyl phosphatidyl choline; DPPC and distearoyl phosphatidyl choline DSPC). Among all the phospholipids tested, DMPG had the greatest effect on both the rate and extent of dissolution of piroxicam. Compared to the pure drug, the piroxicam-DMPG system (weight ratio of 15:1) increased the dissolution at 60 minutes from approximately 16% to 80% of the total drug used. Increasing the DMPG content from 15:1 to 5:1 resulted in only a 9.4% increase in the initial dissolution rate and a further 3.2% increase in the limiting concentration. Thus a small amount of the carrier phospholipid was enough for a dramatic increase in the rate and extent of dissolution. In presence of aqueous medium, phospholipids form liposomal structures as part of rapid, dynamic process of dispersion and effectively increases the saturation concentration of drug in the diffusion layer during the dissolution process. The results suggest that piroxicam undergoes improved dissolution from phospholipid coprecipitates. Phospholipids have the potential in developing formulations which have the dual roles of controlled release and improved bioavailability of drugs.

HOT STAGE MICROSCOPY COMBINED WITH VIDEO PHOTOGRAPHY IN THE STUDY OF THE THERMAL BEHAVIOUR OF PARACETAMOL

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Paracetamol is usually supplied as the monoclinic form. The orthorhombic form of paracetamol has been shown to exhibit greater compressibility and faster dissolution than the monoclinic form. This form is produced by melting of monoclinic crystals of paracetamol followed by cooling at specific rates. Standardizing conditions for prediction of the resulting form remains a problem. Conflicting reports regarding the thermal behaviour of paracetamol exist in the scientific literature. In this investigation an intensive study of the thermal behaviour of the drug was done by conducting several heating and cooling experiments. A novel approach to study the thermal behaviour of paracetamol during the heating and cooling phases was thus developed. The visualization of the process led to a possible explanation of existing discrepancies. To visualize the processes taking place during heating and cooling a video camera was mounted on a hot stage microscope. Changes observed with the microscope complimented and explained results obtained by the use of differential scanning calorimetry. The observed nucleus formation, crystal growth, habit transformation, sublimation and the final melt are shown on snap shots taken from the video.

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THE INVESTIGATION OF CORRELATION BETWEEN THE MICROBIOLOGICAL QUALITY AND PHYSICAL STABILITY IN MULTIPLE EMULSIONS

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Multiple emulsions are emulsions in which one dispersed phase is enclosed in another. As a result of their compound structure multiple emulsions can entrap drug and cosmetic active substances, protect them from degradation and modulate their release rate to improve product efficacy. However, they can easily contaminated with the microorganism. The purpose of the present study is to investigate the microbiological quality control of the samples and to evaluate the results according to the Turkish Cosmetic Regulations (1). The correlation between the microbial contamination and the physical stability were also evaluated.

The w/o/w multiple emulsions were prepared using a two-step process (2). The samples were kept at 4°C, 25°C and 37°C for the storage tests and the pH values were determined during the storage period. All samples were examined for microbial count, yeast and mold count and enterobacteria count were done and inexistence of staphylococcus aureus, Pseudomonas aeroginosa, Escherichia coli, Salmonella species and Candida albicans were confirmed. At the 28th day, 3rd and 6th months, microbial counts of the samples kept at 3 different temperatures (4°C, 25°C, 37°C) were determined.

Microbiological tests results remain within the limits of regulation for the samples which contain preservative. However, we found the total via microorganism count well above the limits of the cosmetic regulations for the samples kept at 22°C and 37° and do not contain preservative . Besides this. significant correlation was not found between the microbiological quality and physical stability data.

As a result, it can be say that, this type cosmetic formulations should contain a proper preservatives.

REFERENCES:

1. Cosmetic Regulations published in the Official Gazette dated 8 April 1994 and numberd 21899.
2. M De Luca, JL Grossiord, JM Medard, C Vaution and M Seiller, A stable w/o/w multiple emulsion, **Cosm. & Toil.** 105 (11) 65-69 (1990).

CORTICOSTERONE PROMOTES INCREASED HEME OXYGENASE-2 PROTEIN AND TRANSCRIPT EXRESSION IN THE NEWBORN RAT BRAIN

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Heme oxygenase (HO-2) is predominant heme oxygenase isozyme in neurons in the brain, the enzymes cleaves the heme molecule at the α-meso carbon bridge to form CO, Fe and biliverdin. Recently, in the promotor region of the HO-2 gene a consensus sequence of the glucocorticoid response elements (GRE) has been identified. Presently, we have investigated the potential relevalence of the GRE to expression of isozyme, at transcript and protein levels, in the 14 day old rat brain, by examining the effect of postparturition corticosterone treatment (4 days, starting 24-36 h after birth) on the developmental pattern of HO-2 expression. Northern blot analysis showed that HO-2 trancripts (~ 1.3 and ~ 1.9 kb) in brain increase with age. In many brain nuclei, HO-2 protein, as visualized by immunohistochemistry, was detected at low levels in neurons in the 14 day old rat brain. Postparturition exposure to corticosterone resulted in marked enhancement of HO-2 immunoreactivity in several neuronal populations, including, among others, the cerebellum, the hippocampal formation, and the oculomotor and red nuclei. The response to elevated levels of corticosterone was particulary striking in Purkinje neurons of cerebellum and the CA3 region of hippocampus. This was linked to an increase in gene transcription, as indicated by in situ hybridization analysis, which revealed an increase in the signal for HO-2 transcripts in these regions. Elevated levels of heme oxygenase activity and HO-2 protein were consistent with an increse in catalytically active protein expression.These data point to the intimate involvement of the adrenal steroids in developmentally-linked HO-2 expession in the neurons involved in motor function and cognition, and hence, identify a potentially important aspect of adrenal steroids' effects on brain growth and differentiation.

ALTERATIONS IN THE CYTOCHROME P450 DEPENDENT AND GLUTATHIONE S-TRANSFERASE ENZYME ACTIVITIES IN MALE AND FEMALE RATS BY CIGARETTE SMOKE

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Although gender dependent different modulations of monooxygenases (MO)s and glutathione S-transferases (GST)s certain xenobiotics have been reported in rodents no information is avaible concerning cigarette smoke (CS) in this regard. Therefore, the effects of CS on hepatic and pulmonary MOs (aniline 4- hydroxylase, AH; aminopyrine N-demethylase, AMND; 7-ethoxyresorufin O- deethylase, EROD; p-nitroanisole O- demethylase, p-NAOD), lipid peroxidation (LP) and reduced glutathione (GSH) levels and GSTs (1-chloro-2,4-dinitrobenzene, CDNB; 1,2-dichloro-4-nitrobenzene, DCNB; ethacrynic acid, EAA; 1,2-epoxy-3-(p-nitrophenoxy)-propane, ENPP) were determined in male and female rats. The animals were exposed to CS five times a day, with one our intervals, for three days in a chamber where smoke and fresh air lead alternatively and were killed 16 hours after last treatments. As compared to controls only the following alterations were noted; CS significantly increased hepatic AMND, EROD and p-NAOD and pulmonary EROD and p-NAOD activities in both genders. Significant increases were noted in pulmonary AH and AMND activities in males and females respectively. Significant decrease was noted in hepatic LP level of males by CS. Pulmonary GSH and LP, and hepatic GSH levels were significantly increased by CS in both genders. In males, hepatic GST activities toward EAA and ENPP significantly increased and decreased, respectively. In females, CS significantly increased hepatic GST activity only toward DCNB. All pulmonary GST activities of males were significantly depressed by CS. In females, however, CS significantly increased pulmonary GST activities toward CDNB and DCNB. These results suggest that gender related differences exist in the modulations of hepatic GST and pulmonary MO and GST activities but not in those of hepatic MO activities by CS in rats. (Supported by Research Fund of Ankara University Grant No: 87-03-00- 04)

GLUTATHIONE AND LIPID PEROXIDATION LEVELS IN HUMAN BREAST TUMOR

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Breast cancer is the most frequent cause of cancer death in women. The lipid peroxidation (LP), a free radical toxicity, is known to be involved in promotion of carcinogenesis. The glutathione (GSH) an important cellular defense mechanism is a well known antioxidant, a free radical scavenger. Although several lines of evidence related to the levels of GSH and LP in tumors of various tissues in humans have been established studies devoted to the breast tumor in this respect are rather rare and contradictory. Therefore, we aimed to investigate the levels of GSH and LP of breast tumor and surrounding tumor free (normal) tissues of 39 breast cancer female patients with infltrating ductal carcinoma and examine whether there exist any relationship between these two parameters. The possible influences of the stage and grade of malignancy, and menopausal status and chemotherapy on GSH and LP levels were also evaluated. Large interindividual variations in the levels of GSH and LP were found in both tumor and tumor free tissues. Nevertheless, most of tumors (33/39, 85 %) had higher GSH levels than those of normal tissues. The mean GSH levels of tumors were significantly higher (about 4.0-fold) than those of normal tissues. This tendency did not change with the stage and grade of the malignancy, menopausal status and chemotherapy. However, although more than half of the tumor samples (23/39, 59 %) had higher LP levels than their corresponding normal tissues no significant difference was noted between the mean LP levels of tumor and tumor free tissues. The stage and grade of the malignancy, and menopausal status and chemotherapy had no impact on LP levels of tumors. These results reveal that the GSH, but not LP, is a good marker of breast malignancy and that there is no relationship between GSH and LP levels in either tumor or tumor free breast tissues in humans (Supported by the Research Fund of Ankara University grant No. 92-30-00-07)

DEVELOPMENT OF RESTRICTION SITE MUTATION TECHNIQUE FOR *ras* ONCOGENE IN THE RAT

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The Restriction Site Mutation (RSM) technique or Restriction Fragment Length Polymorphism / Polymerase Chain Reaction (RFLP/PCR) is a DNA-based method for detecting mutations in animals or cell cultures (1,2). Mutations are determined and identified as alterations (base changes and insertions or deletions) of the DNA sequence at a chosen restriction endonuclease recognition sequence. At the first step of the assay, genomic DNA that is exposed to physical or chemical mutagen is exhaustively digested with the restriction endonuclease without the selection of mutant phenotype. At the second step, resistance sequences containing the mutated target site are specifically amplified using the PCR. In this step, DNA without mutations (wild-type) will be cleaved at the selected restriction endonuclease site and can not be amplified by the PCR. Finally, at the last step, the RSM assay products are subjected to further restriction endonuclease digestion in order to remove any amplified products containing sensitive restriction endonuclease recognition sequences. In contrast to the most of the traditional mutation analyses, the RSM assay does not rely upon the selection of a mutated phenotype and thus is not limited to mutational analysis in only a few genes. The assay allows the isolation of rarely occurring mutated sequences from a vast excess of background unmutated wild-type sequences.

In this study, we have developed protocols to analyse mutations in restriction endonuclease recognition sequences of the *ras* gene of the rat by the RSM assay. The *ras* family of proto-oncogenes play an important role in the development of various human cancers (3). The optimization and validation of the assay have been performed using a variety of tissues from individual laboratory rats. Several suitable restriction endonucleases (*Hind*III, *Cfo*I, *Hin*fI and *Nla*IV) and primer pairs have been identified for detecting mutations in the *ras* proto-oncogene of the rat.

1) Parry, J. M.; Shamsher, M.; Skibinski, D. O. F.; Mutagenesis; 5; 209; 1990.
2) Felley-Bosco, E.; Pourzand, C.; Ziljstra, J.; Amstad, P.; and Cerutti, P.; *Nucleic Acid Research*; **19**; 2913; 1991.
3) Bos, J. L.; *Cancer Research*; **46**; 4682; 1989.

STUDIES CONDUCTED FOR THE QUANTITY DETERMINATIONS OF SYNTHETIC DYES ADDED INTO SOME FOODSTUFFS

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This study has been planned and carried out with a view to discover whether or not those synthetic dyes which are not allowed to be added into the jams, have already been added into the jams and also the quantities of synthetic dyes existing in the puddings, candies and granulated powder drinks which are permitted to be added with such dyes, are also compatible with the quantities specified by the Food Additives Regulation in Turkey.

All samples used during this study, have been obtained from sources of Ankara market and totally 263 samples have been analysed.

The extraction process of all samples, has been performed through the wool coloring method. The extracted dyes have been subjected to the qualitative analysis through the TLC (Thin Layer Chromatography) Method. At the end of qualitative analysis performed on the jams and puddings, it has not been possible to handle the quantitative determinations since no synthetic dye has been found.

The samples of candy and granulated powder drinks, in the contents of synthetic dyes, have determined the use of a single C_{18} Sep-pak Cartridge and also the spectrophotometric method.

Among these synthetic dyes, the average level of Ponceau 4R has been found as 117.45±19.37 mg/kg, in the candies, 294.79±26.21 mg/kg for the granulated powder drinks. The values were not suitable by the Food Additives Regulation.

The average level of Tartrazine has been determined as 147.77±20.50 mg/kg and 201.19±37.16 mg/kg respectively for candies and granulated powder drinks. The level of Tartrazine was in maximum values for granulated powder drinks.

The average levels of Sunset Yellow F.C.F. have been found as 174.58±31.54 mg/kg and 293.31±24.19 mg/kg respectively for candies and granulated powder drinks. The values also had been found over dose.

The average level of azorubine, has been determined as 181.22±20.22 mg/kg for candies and found compatible with those specified by the Food Additives Regulations.

The average value of mixed dyes existing in the granulated powder drinks, has been determined as 241.44±17.67 mg/kg. This value was over the value specified by the Food Additives Regulation.

STUDIES ON THE FATTY ACID AMOUNTS OF OLIVE AND CORN OILS OBTAINED FROM ANKARA LOCAL MARKETS

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This study has been carried out in order to determine the percentage of fatty acids, refractive index and the amount of free fatty acids in the samples of olive and corn oils sold in the local market places of Ankara.

The percentages of fatty acids were determined by applying the gas-liquid chromatography. In the samples, the refractive index was measured at level of 40°C by employing the refractometer. The amounts of free fatty acids were also calculated as oleic acid by the method of titration.

The average values of fatty acid determined in the samples of olive oils are at the levels of 13.423±0.106 %, 0.161±0.008 %, 2.218±0.041 %, 71.506±0.288 %, 11.862±0.208 % and 0.837±0.035 % respectively for palmitic acid, palmitoleic acid, stearic acid, oleic acid, linoleic acid and linolenic acid.

In the olive oil samples, the mean value of the refractive index was measured as 1.4621±0.0001. In these samples, the average value of free acids was determined as 0.206±0.068 %.

The average values of fatty acid determined in tha samples of corn oils are at the levels of 0.054±0.005 %, 11.540±0.059 %, 1.603±0.027 %, 26.520±0.229 %, 59.231±0.221 %, 0.877±0.014 % and 0.107±0.007 % respectively for miristic acid, palmitic acid, stearic acid, oleic acid, linoleic acid, linolenic acid and arachidic acid.

In the corn oil samples, the mean value of the refractive index was measured as 1.4668±0.0001. Also in these samples, the average value of free fatty acid was determined as 0.157±0.005 %.

Consequently, it has been observed that the values of fatty acids determined in the samples of analysed corn and olive oils, were in conformity with the values specified by the T.S. (Turkish Standards) and to the values indicated in the various literatures. It has been found that the values of free fatty acids and refractive indexes determined in the oil samples, were compatible with the acceptable limits specified by the T.S.

THIOCYANATE QUANTITIES AND CHEMICAL QUALITY CONTROLS IN MILKS IN ANKARA REGION

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This study consists of the analysis of the quantities of thiocyanate in raw cow milk samples obtained from three different farms in the vicinity of Ankara, from the point of view of human health and the activation of the lactoperoxidase / thiocyanate / hydrogen peroxide system (LPS). Quantitative chemical analyses for density, fat content, acidity, total solids pH and qualitative chemical analyses for the presence of formaldehide, carbonate and hydrogen peroxide from preservatives were also performed on these raw cow milk samples from the said region.

It was determined that the average amount of thiocyanate in the samples obtained from farm 1was 2.830"0.072 ppm, from farm 2 was 3.190"0.106 ppm and from farm 3 was 3.560"0.085 ppm.

Densities of milk samples of farms 1, 2 and 3 were determined as : 1.0318"0.0002, 1.0318"0.0001, 1.0305"0.0002; average fat percentages : 3.440"0.095, 3.250"0.065,3.060"0.059; average total solids (%) : 12.090"0.123, 11.720"0.080, 11.480"0.081; average pH values : 6.58"0.011, 6.63"0.114, 6.39"0.026; average acidities (SH) : 8.130"0.126, 7320"0.145,8.710"0.233 average fatless total solids (%) : 8.650"0079, 8.470"0.081, 8.400"0.062 respectvvely.

Hydrogen peroxide and formaldehide from preservative materials were not encountered. Sodium carbonate was detected in 1 sample of Farm 1, in none of the samples of Farm2 and in 7 samples of Farm 3.

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A STUDY ON THE ARTIFICIAL SWEETENERS ADDED TO FOODS

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The purpose of this study is to determine whether artificial sweeteners e.g. saccharin, cyclamate and aspartame have been added to foods.

The study was conducted on samples of jam, marmalade, fruit juice, soft drinks, sesame halvah, baklava (sweet pastry) produced by 21 different organizations and sold in the local markets of Ankara. A total of 300 samples were analyzed to detect sweeteners.

None of the samples contained cyclamate and saccharin.

The average amounts of aspartame in soft drinks was determined to be in the range of 219.97±7.07 and 560.16±8.53 mg/lt. It was observed however that the average amount of aspertame in non-dietary soft drinks was at the level of 41.76±3.58 mg/lt.

The aspertame used in the dietary soft drinks did not exceed the limit specified in Turkish Food Additive Regulations. The aspartame content in two products was as indicated on the label, while in other 2 products it was determined that it exceeded the amounts indicated on the label ($p<0.05$).

EFFECTS OF A NEWLY SYNTHESIZED BENZIMIDAZOLE COMPOUND ON MONOOXYGENASE ACTIVITIES

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A retinoid-type benzimidazole compound (benzimidazole-tetranaphthalene, BITN) was synthesized and its effects on hepatic cytochrome P450 (CYP) dependent ethoxyresorufin O-deethylase (EROD) and pentoxyresorufin O-deethylase (PROD) enzyme activities were determined in rats *in vitro* (1, 2). In vitro addition of BITN in 10^{-3} M concentration to the reaction medium caused inhibitions in EROD (94 %) and PROD (82%) activities. With the same concentration (10^{-3}M) *all-trans*-retinoic acid (RA) was able to inhibit EROD activity 65 % and PROD activity 59 % whereas buthylated hydroxytoluen (BHT) inhibited EROD and PROD activities 73 % and 62 %, respectively. The specific inhibitors of EROD activity (caffeine) and PROD activity (SKF 525A) at 10^{-3} M concentration inhibited the corresponding enzymes 33 % and 77 %, respectively. Thus, these results reveal that the BITN has a stronger inhibitory effect than RA, BHT, caffeine and SKF 525 A on the enzyme activities. Since these enzymes (EROD, CYP 1A1/2 and PROD, CYP2B1/2) activate polycyclic hydrocarbons, aromatic amines and aliphatic halogenated hydrocarbons to their ultimate mutagenic or carcinogenic forms, and are effective in producing reactive oxygen species such as superoxide, hydroxyl radical and hydrogen peroxide, the new compound, BITN, appears to have a greater anticarcinogenic and antioxidant potential than RA and BHT.

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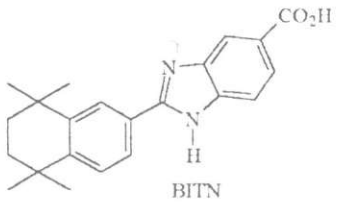

BITN

1. Burke, M. D.; Thompson, S.; Elcombe, C. R.; Halpert, J.; Haaparanta, T.; Mayer, R. T., **Biochem. Pharmacol.**, 34, 3337 (1985).
2. Nedelcheva, V.; Gut, I., **Xenobiotica,** 24, 1151 (1994).

DETERMINATION OF AFLATOXINS IN DRIED RED PEPPER SAMPLES ROVIDED FROM ISTANBUL MARKET

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Aflatoxins (AFLs) are highly toxic, carcinogenic compounds. They are produced by the fungal species *Aspergillus flavus* and *A. parasiticus* which are present in many food supplies, grown in many areas of the world. A variety of techniques have been used for the separation and identification of the four major naturally occuring AFLs namely aflatoxin B_1 , B_2, G_1 and G_2 . In this study, aflatoxins were determined in dried red pepper samples provided from spice-sellers, street bazaars and markets in Istanbul and on the samples from the known origin of Turkey (Urfa, Kahramanmaraş, Kayseri, Silifke) and India. Samples were extracted with methanol/water (85:15) and sample clean-up procedure was performed with disposable SPE (solid-phase extraction) column. The aflatoxins were eluted from the column with chloroform/acetone (9:1) and detected using TLC and HPLC. The highest level of aflatoxin B_1 was determined as 109.7 ppb in the sample from a spice-seller. The results of TLC and HPLC studies were found as comparable. In about 50 % of dried red pepper samples aflatoxin B_1 levels were higher than 5 ppb and total aflatoxin levels were higher than 20 ppb in about 40 % of samples. Aflatoxin contamination does not only concern public health but also stands to be an economic problem. As a result of our study we believe that aflatoxin analysis has to be done and declared to the consumer for food products such as dried red pepper samples that can have a high possibility of aflatoxin contamination in Turkey.

THE CHARACTERISTICS OF THE SEED OF *COLCHICUM* SPECIES

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The bulbs and the seeds of *Colchicum* species are used in the treatment and agriculture because of containing colchicin. The seeds which are obtained from different *Colchicum* species in Turkey are exported. The chemical studies that have been done so far show that these species contain different amounts of colchicine. In these studies the seeds *of Colchicum,*(*C. spesiosum, C. bornmuelleri, C. kotschyi*), that exported and those having a potential to be exported (*C. cilicicum*), are obtained from 4 different species whose morphological and microscopical characteristics are determined. The result was compared with the characteristics of *C. autumnale* which is accepted as an official species.

MODELİNG STUDIES & COMPUTATIONAL ANALYSIS OF INTERACTION BETWEEN HUMAN HISTAMINE-2 RECEPTOR AND ITS ANTAGONISTS

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The Human Histamine-H2 receptor belongs to G-protein coupled receptors. Its antagonists play an important role in the treatment of diseas connected with gastric acid hypersecretion. We undertook this study to characterize the molecular basis of the interaction of antagonists with the human H2-receptor.

Our defined a complete three-dimensional model of the human H2-receptor (including helices, loops and terminals) used to elucidate the interactions of antagonists at the receptor. Using the quantum and molecular mechanic calculations and also conformational analysis and molecular dynamic simulation, we studied antagonists in the isolated and in the complex form with the H2-receptor (with several tautomeric and configuration forms).

We identified the residues likelyto be responsible for receptor-antagonist interactions and receptor suppression. To define the precise receptor-antagonist interactions, several forms of the ***SK&F-92456, Nizatidine, Ranitidine*** and ***Roxatidine*** monocations docked into the binding site. The nature of important physicochemical interactions between antagonists and adjacent amino acids also studied.

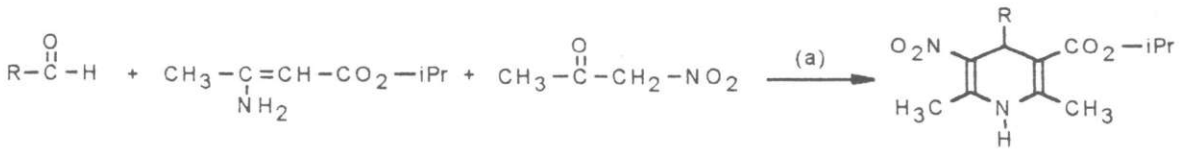
Results on the antagonists demonstrated thet the mode of recognition is similar to the same pattern obtained for agonists, i.e., imidazolium in SK&F-92456, methyl dimethylammonium in Nizatidine and Ranitidine and methyl piperidinium in Roxatidine anchors at the ASP-98, whereas the endgrup (nitrodiaminoethene in SK&F-92456, Nizatidine and Ranitidine and acetyloxy acetamide in Roxatidine) is located between the ASP-186 and THR-190. Results showed that the antagonists interact with amino acids which mostly located in the transmembran helices III, IV, V and VI, small part of second and third extracellular loops. ASP-98 and ASP-186 have an important role in receptor supression. Results demonstrated receptor environment induced isomerization on antagonists.

SYNTHESIS AND CALCIUM CHANNNEI MODULATING EFFECTS OF ISOPROPYL 1,4-DIHYDRO-2,6-DIMETHYL-3-NITRO-4-(THIENYL)-5-PYRIDINE CARBOXYLATES

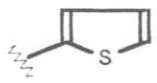
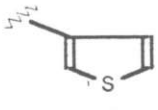
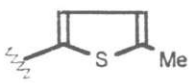
R. Miri*, E.E. Knaus**

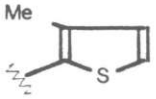
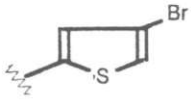
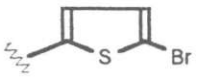
* Faculty of Pharmacy, Medical Sciences, University of Tehran, Tehran, Iran.
** Faculty of Pharmacy Pharmaceutical Sciences, University of Albera, Edmonton, Alberta, Canada.

A group of racemic isopropyl 1,4-dihydro-2,6-dimethyl-3-nitro-4-(thienyl)-5-pyridine carboxylates 1a-f were prepared using a modified Hantzsch reaction that involved the condensation of a thienylcarboxaldehyde 1a-f with isopropyl 3-aminocrotonate 2 and nitroacetone. *In vitro* calcium channel antagonist activities were determined using a guinea pig ileum longitudinal smooth muscle (GPILSM) assay. Compound 4a-f exhibited weaker calcium channel antagonist activity (10^{-5} to 10^{-7} M range) than the refrence drug nifedipine (IC_{50}= 1.43 x 10^{-8} M). The point of attachment of the C-4 thienyl ring system wasa determinant of antagonist activity [3-thienyl (4b) >2-thienyl (4a)]. A 5-substituent in the 2-thienyl moiety influence antagonist activity where the potency order was 5-bromo-2-thienyl 4f ≥ 5-methyl-2-thienyl 4c > 2-thienyl 4a. Although the 5-methyl-2-thienyl 4c and 3-methyl-2-thienyl 4d isomers are equipotent antagonists, the 5-bromo-2-thienyl compound 4f appears to be marginally more active than the 4-bromo-2-thienyl isomer 4e. The 2-thienyl compound 4a, unlike the 3-thienyl isomer 4b, exhibited an agonist effect on GPILSM in the absence of the muscarinic agonist carbachol.



1 2 3 4

1,4 a, R =  b, R =  c, R = 

d, R =  e, R =  f, R = 

(a) Reagents and conditions dry EtOH, reflux 12 h.

OPHTALMOLOGICAL PRODUCTS FROM NATURAL SUBSTANCES

C. Rizescu, C. Cristescu, C. Popescu, L.D. Popescu, C. Rizescu , N. Stoian,
A. Rizescu, D. Bordea, M. Marilena

Biotechnology University, Dimitrie Cantemir, Bucharest, Hungary

I) From the culture plants flowers Tagetes Pathulae which contains helenien (dipalmitic ester of lutein) 1-1,5 g., it prepares the product HELIGAL tablets, smilar to ADAPTINOL BAYER. Extracted helenien associated with total eye bovine extract-obtained tablets growing up to possibility of the eye adoptation from light to dark and can use with good results in hemeralopia, short-sightedness, pigmentar retinitis, in comparison with the product HELİGAL.

II) From Vaccinum myrtillus fruits, it prepares total extract of antacians used in the stimulation and regeneration of the retinal purple, retinal or corticoretinal vascular anxieties, hemeralopia. The product DIBEFON is similar to DIFRAREL. There were studied also the total extracts from: Fructus Rabis nigri, Fructus morus alba, Fructus morus nigra, Fructus cymsboti, Fructus hippophae rhamnoides, Fructus vaccinum myrtilli in different proportions. Chemically it evidenced in the fruits of Ribes nigri, Morus alba, Morus nigra and specilly in Vaccinum myrtillis, glycoside of cyanidol and dolphinidol, vitamins catechic tannins, glucides, carotene, pectines, organic acids. Cymsboti fruits contains a big quantity of vitamin C, and hippophae rhamnoides contains ca. 1500 mg. % ascorbic acid, carotenoid substances, flavones, amino acids, terpenoid substances. Obtained preparations guide to visual acuity rise, action in circulatory anxieties of nervous nature, in microcirculation improvement, protect ocular vascularization, have an activating effect to retinal purple regeneration, sensitive the photoreceivers.

STUDIES ON SPECTROPHOTOMETRIC DETERMINATION OF PARACETAMOL AND MEFENAMIC ACID. I. EFFECT OF pH

C.Yücesoy, K.Tülek

Ankara University, Faculty of Pharmacy, Dept. of Analytical Chemistry, Ankara, Turkey

The binary combination of paracetamol (P) and mefenamic acid (M) is used in analgesic preparations. Both compounds show spectral shifts in acidic and alkaline media, since they possess auxochromic groups. Using this property simultaneous determination of them were performed by difference spectrophotometry. Simultaneous determination of the drugs by derivative spectrophotometry, absorbance ratio and Vierordt method in acidic and alkaline media were also developed. For this purpose solutions of P and M in 0.02 N methanolic HCl and 0.02 N methanolic NaOH were used. The results obtained in acidic and alkaline media using the methods mentioned were compared statistically by Newman-Keuls method. Statistically significant differences between the results were tried to explain.

THE NAME LIST OF PHARMACISTS WERE GRADUATED FROM MEDICAL SCHOOLS IN ISTANBUL IN 19TH CENTURY

Adnan Ataç

Gülhane Military Medical Academy, Department of the History of Medicine Etlik, Ankara, Turkey

Licence education on pharmaceutical was first started to given at "Mekteb-i Tıbbiye-i Adliye-i Şâhâne" in 1840, in Türkish history of pharmacy.

Pharmaceutical department was established in 1827, under the domain of medical school, and it's first alumni was graduated in 1843. Until 1900, 171 pharmacist were graduated from this school.

Another medical school, which belonged to civilions, "Mekteb-i Tıbbiye-i Mülkiye-i Şâhâne" was founded in 1867. First pharmacist was graduated from this school in 1874, and 497 pharmacists were graduated until 1900.

The aim of present study is to find out the names and their graduation years of all graduates of both school and to keep them in a list.

AUTHORS INDEX

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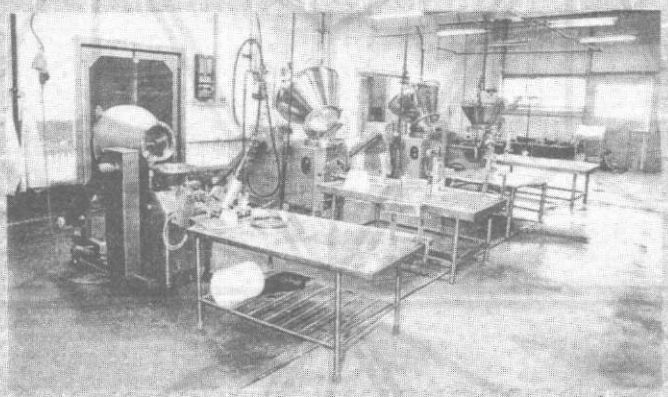

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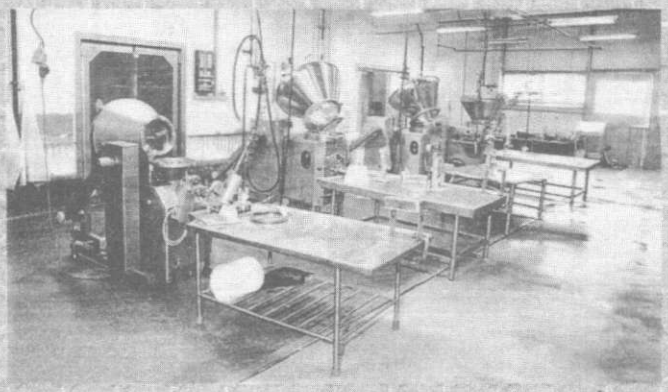

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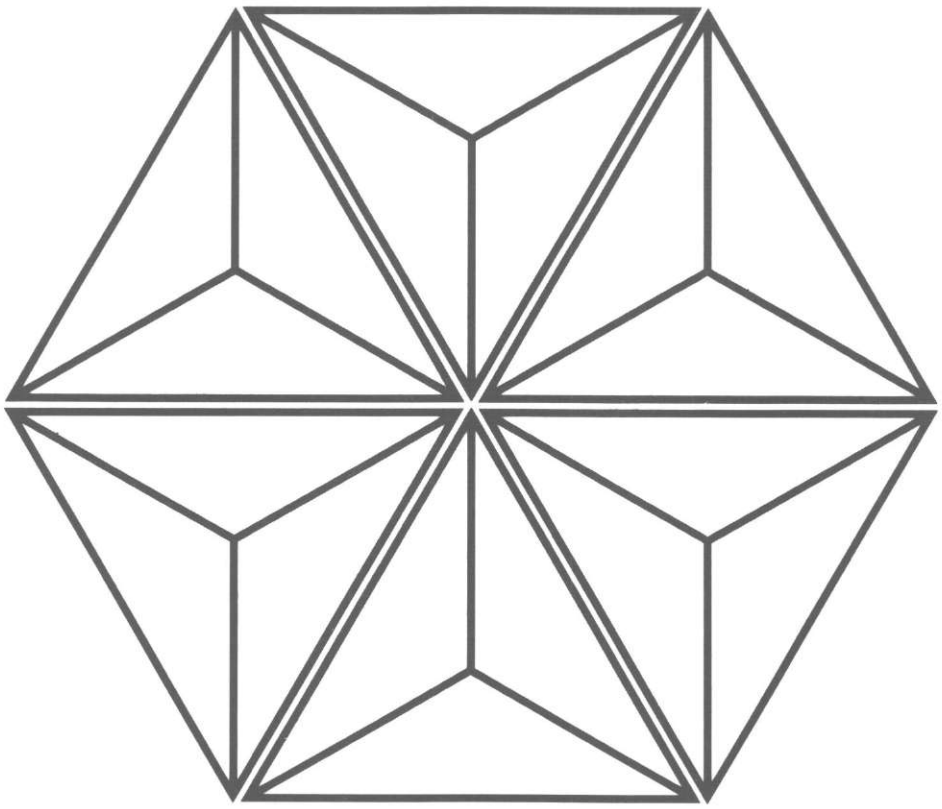

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ENFEKSİYON TEDAVİSİNDE

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PROSPEKTÜS ÖZETİ:
DUOCID® TABLET/SÜSPANSİYON ENDİKASYONLARI: DUOCID® TABLET/SÜSPANSİYON hekimin oral yoldan tedaviyi yeterli ve uygun bulduğu hallerde, sinüzit, otitis media, üst solunum yolu enfeksiyonları, bakteriyel pnömoni, bron üriner sistem enfeksiyonları, gonore, deri ve yumuşak doku enfeksiyonlarında kullanılabilir. Pnömokok, menengekok, A grubu hemolitik streptokok enfeksiyonlarında ampisiline üstünlüğü yoktur. DUOCID® IM/IV ile başlangıç tedavisind sonra sulbaktam/ampisilin tedavisi gerektiren hastalarda da sultamisilin endike olabilir. **KONTRENDİKASYONLARI:** Özgeçmişinde herhangi bir penisiline karşı alerjik reaksiyon bulunan kişilerde bu ilacın kullanılması kontrendikedir. **UYARILA** Penisilin tedavisi yapılan hastalarda ciddi, hatta bazen fatal aşırı duyarlılık (anafilaktik) reaksiyonları bildirilmiştir. Bu reaksiyonlar daha ziyade geçmişinde penisilin ve/veya multipl alerjenlere aşırı duyarlılığı olan kişilerde meydana gelir Anamnezide penisilin duyarlılığı olan kişilerde sefalosporinlerle tedavi edildiğinde, şiddetli reaksiyonlar meydana geldiği bildirilmiştir. Penisilin tedavisinden önce; geçmişte penisilin, sefalosporin ve diğer alerjenlere duyarlılık reaksiyonl olup olmadığının dikkatle soruşturulması tavsiye edilir. Eğer alerjik bir reaksiyon meydana gelirse, ilaç kesilmeli ve uygun tedavi başlatılmalıdır. Ciddi, anafilaktik reaksiyonlar adrenalin ile hemen acil tedavi gerektirir. Oksijen, intraven steroidler ve intübasyon dahil solunum yollarına müdahale gerekli olduğu şekilde uygulanmalıdır. Hamilelikte ve emzirme döneminde kullanım: Hayvanlarda üreme çalışmaları, sultamisiline bağlı olarak hiçbir fertilite bozukluğu veya fetü zarar delili olmadığını göstermiştir. Bununla beraber, insanlarda hamilelikte ve emzirme döneminde kullanım emniyeti henüz saptanmamıştır. **ÖNLEMLER:** Her antibiyotik preparatında olduğu gibi, mantarlar dahil duyarlı olmayan organizmala aşırı üreme belirtileri için devamlı gözlem gereklidir. Süperenfeksiyon olduğunda, ilaç kesilmeli ve/veya uygun tedavi uygulanmalıdır. Uzun süreli tedavilerde, renal, hepatik ve hematopoetik sistemler dahil olmak üzere, organ sistem disfonksiyo yönünden periyodik kontroller tavsiye edilir. **YAN ETKİLER:** Genellikle sultamisilin iyi tolere edilir. Gözlenen yan etkilerin çoğu, hafif ve orta şiddette olup, tedavi süresince normal olarak tahammül edilirler. Gastrointestinal: Diğer ampis sınıfı antibiyotiklerde olduğu gibi, en sık görülen yan etki diyare/yumuşak gaitadır. Bulantı, karın ağrıları/krampları nadiren gözlenmiştir. Epigastrik rahatsızlıklar ve kusma ise enderdir. Deri/Deri Yapıları: Deri döküntüsü ve kaşıntı seyr olarak gözlenmiştir. Muhtelif: Sersemlik/sedasyon, yorgunluk/halsizlik ve baş ağrısı seyrek olarak gözlenmiştir. Ampisilinin kullanımına bağlı yan etkilerin ara sıra gözlenmesi beklenebilir. **DOZAJ VE UYGULAMA:** Erişkinlerde tavsiye edil sultamisilin dozu günde iki defa 375-750 mg'dır. 30 kg'dan daha hafif çocuklardaki enfeksiyonların çoğunluğunda, enfeksiyonun ciddiyetine ve doktorun takdirine bağlı olarak dozaj iki doza bölünmüş olarak 25-50 mg/kg/gün sultamisilin 30 kg ve üstündeki çocuklara yetişkin dozu verilmelidir. Erişkinlerde ve çocuklarda tedavi, genellikle ateş düştükten 48 saat sonraya ve anormal belirtiler kaybolana kadar devam ettirilir. Tedavi normal olarak 5 ila 14 gün süreyle uygula fakat gerekirse tedavi süresi uzatılabilir. Komplikasyonsuz gonore tedavisinde 2.25 g sultamisilin tek oral doz (altı adet 375 mg tablet) olarak verilebilir. Sulbaktam ve ampisilin plazma konsantrasyonlarını uzatmak amacıyla 1.0 g probene beraberce uygulanmalıdır. Şüpheli sifiliz lezyonu bulunan gonore vakalarında, sultamisilin uygulanmadan önce karanlık saha muayeneleri yapılmalı ve asgari dört ay süreyle aylık serolojik testler uygulanmalıdır. Akut mafsal romatizm veya glomerulonefriti önlemek amacıyla, hemolitik streptokoklara bağlı her türlü enfeksiyonların tedavisine en az 10 gün süreyle devam edilmesi tavsiye olunur. Ciddi renal bozukluğu olan hastalarda (kreatinin klirensi < 30 ml/dak) sulbakt ve ampisilinin eliminasyon kinetiği birbirine benzer şekilde etkilenmekte ve birinin diğerine plazma oranları değişmeden kalmaktadır. Sultamisilin dozu bu hastalarda mutat ampisilin uygulanmasında olduğu gibi daha seyrek olarak uygulanmalı Süspansiyon hazırlanırken, şişenin üzerindeki çizgiye kadar (70 ml) kaynamış soğumuş temiz su ilave edilerek iyice çalkalanır. Sulandırılmış oral süspansiyon buzdolabında saklanmalı, 14 gün içinde kullanılmayan kısmı atılmalıdır. **TAKD ŞEKLİ ve SATIŞ FİYATI :** Beheri 375 mg sultamisiline eşdeğer 10 tabletlik şişelerde 2.096.000 TL. Sulandırıldıktan sonra her 5 cc'lik ölçekte 250 mg sultamisilin içeren kuru toz halinde, 70 ml'lik süspansiyon şişelerinde 2.266.000 40 ml'lik pediatrik süspansiyon şişelerinde 1.331.500 TL (Haziran 1997 tarihindeki perakende satış fiyatları esas alınmıştır.)
DUOCID® IM/IV ENDİKASYONLARI: Duyarlı mikroorganizmalara bağlı sinüzit, otitis media, epiglottit, bakteriyel pnömoniler gibi üst ve alt solunum yolları enfeksiyonları; idrar yolları enfeksiyonları ve piyelonefrit, peritonit, kolesistit, endome ve pelvik selülit gibi intraabdominal enfeksiyonlar, bakteriyel septisemi; deri ve yumuşak doku, kemik ve eklem enfeksiyonları ve gonore tedavisi. Abdominal veya pelvik cerrahi müdahalelerde perioperatif olarak ve doğum veya sezar sonrası ameliyat proflaksisi. **KONTRENDİKASYONLARI:** Özgeçmişinde herhangi bir penisiline alerjik reaksiyon bulunan kişilerde. **UYARILAR:** Penisilinlerle tedavide ciddi, bazen fatal anafilaktik reaksiyonlar bildirilmiştir. Penisilin uygulamasın önce geçmişte penisilin, sefalosporin veya diğer alerjenlere duyarlılık olup olmadığı soruşturulmalıdır. Alerjik bir reaksiyon gözlenirse ilaç kesilmeli ve uygun tedavi (adrenalin, O₂ IV steroidler, intübasyon) başlatılmalıdır. Hamilelikte kullan emniyeti henüz tespit edilmemiştir. **ÖNLEMLER:** Süperenfeksiyon gelişirse, ilaç kesilmeli ve uygun tedavi uygulanmalıdır. Uzun süreli tedavilerde, periyodik olarak organ sistem disfonksiyonu kontrolü tavsiye edilir. Bu, yenidoğanlarda özell prematüre ve diğer bebeklerde önemlidir. **YAN ETKİLER:** En sık görülen yan etkiler, enjeksiyon yerinde ağrı ve ampisilin tedavisinde görüldüğü gibi bulantı, kusma ve diyaredir. **DOZAJ VE UYGULAMA:** İntravenöz yolla 3 dakikadan da uzun bir sürede bolüs enjeksiyonu olarak veya 15-30 dakika sürede daha büyük dilüsyonlarda infüzyon halinde verilebilir. Derin intramüsküler enjeksiyon halinde uygulanabilir. Erişkinlerde DUOCID® dozu genellikle 6 ila 8 saatte bir 1. gramdır (0.5-1 g sulbaktam ve 1-2 g ampisilin). Hafif ve orta derecede enfeksiyonlu hastalarda 0.75-1.5 g'lik doz günde iki defa IM olarak uygulanabilir. Günlük maksimum sulbaktam dozu 4 g'dır. Çocuklar, bebekler ve yenidoğanlarda genell dozaj 150 mg/kg/gün'dür. (50 mg/kg sulbaktam ve 100 mg/kg ampisiline tekabül eder.) Ampisilinde olduğu gibi yenidoğan bebeklere dozlar 12 saat ara ile verilmelidir. Tedavi süresi genelde 5 ila 14 gündür. Gerekirse bu süre uzatılır. C renal fonksiyon bozukluğunda (kreatinin klirensi>30 ml/dak) DUOCID® mutat ampisilin uygulamasında olduğu gibi daha seyrek olarak uygulanmalıdır. Sodyum kısıtlaması gereken hastalarda 1.5 g DUOCID®'in 115 mg (5 mmol) sody ihtiva ettiği dikkate alınmalıdır. Ameliyat enfeksiyonları profilaksisinde 1.5-3 g DUOCID® anestezi başlangıcında verilir. 24 saat süre ile bu doz 6-8 saat ara ile tekrarlanabilir. DUOCID® IM/IV 0.25 g: 250 mg ampisilin + 125 mg sulbakt DUOCID® IM/IV 0.5 g: 500 mg ampisilin + 250 mg sulbaktam. DUOCID® IM/IV 1.0 g: 1000 mg ampisilin + 500 mg sulbaktam. DUOCID® IM/IV 2.0 g : 2000 mg ampisilin + 1.0 g sulbaktam. **TAKDİM ŞEKİLLERİ VE SATIŞ FİYATI:** 0.2 IM/IV ve IM Lidokainli 369.500 TL, 0.5 g IM/IV ve IM Lidokainli 606.000 TL, 1 g IM/IV ve IM Lidokainli 1.100.200 TL (Haziran 1997 tarihindeki perakende satış fiyatları esas alınmıştı

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