Doctoral Dissertation Abstracts

DETERMINATION OF ACTIVE INGREDIENTS IN THE MIXTURES CONTAINING CAFFEINE BY USING SPECTROPHOTOMETRIC METHODS AND THE APPLICATION OF THESE METHODS TO PHARMACEUTICAL PREPARATIONS

M. Filiz YURTSEVER, Supervisor: Prof. Dr. Feyyaz ONUR, Department of Analytical Chemistry, Faculty of Pharmacy, Ankara University, 06100, Ankara, Turkey.
Date of examination : March 24, 1998

In this thesis ; the aim was the development of new spectrophotometric methods for the simultaneous determination of active compounds in a ternary mixture (caffeine + analgin + paracetamol) and in three binary mixtures (caffeine + aspirin, caffeine + propyphenazone and caffeine + chlorphenoxamine. HCl) containing caffeine. For the ternary mixture ; two new spectrophotometric methods (ratio spectra derivative spectrophotometry using double divisor and using zero-crossing technique) were developed. For the analysis of caffeine + aspirin and caffeine + propyphenazone mixtures, two new spectrophotometric methods (Vierordt's method and ratio spectra derivative spectrophotometry) were used. For caffeine + chlorphenoxamine. HCl mixture, only one spectrophotometric method (ratio spectra derivative spectrophotometric technique) has been developed. All the methods developed for the same mixture were compared with each other and with the chromatographic methods (TLC and HPLC). All these methods were also applied to the commercial formulations containing these mixtures and marketed in Turkey and were found suitable for the routine analysis of these preparations.

THE SYNTHESIS OF CONDENSED OXAZOLINONE DERIVATIVES EXPECTED TO SHOW ANALGESIC-ANTIINFLAMMATORY EFFECTS AND THE INVESTIGATION OF THE THEIR PHARMACOLOGICAL ACTIVITY

Uzm. Ecz. Nesrin GÖKHAN, Supervisor: Prof. Dr. Hakkı ERDOĞAN, Hacettepe Üniversitesi, Sağlık Bilimleri Enstitüsü, Ankara.
Date of examination : June 3, 1998

In this study, twenty four 3-[2-(2-/4-pyridyl)] ethyl-(5-chloro)-6-(2,5-; 2,3-; 3,4-; 3,5-; 2,6 - difluorobenzoyl) - 2 - benzoxazolinone (A) and 3-[2-(2-/4-pyridyl)] ethyl-(6-bromo) - oxazolo [4,5-b] pyridine - 2 - one (B) were synthesized and screened for their analgesic antiiflammatory activities. Starting compounds having 6-(difluorobenzoyl)-2- benzoxazolinones structure were prepared by reacting 2 - benzoxazolinone with aromatic carboxylic acids in the presence of polyphosphoric acid. Oxazolo [4,5-b] pyridine-2-one was synthesized by reacting 2-amino-3-hydroxypyridine and 1,1'-carbonyldiimidazole. 6-Bromooxazolo [4,5-b] pyridine - 2 - one was also yielded by bromination of the oxazolo [4,5-b] pyridine - 2 - one. Target compounds were obtained by reacting these derivatives with 2-/4-vinylpyridine according to the Michael Reaction.

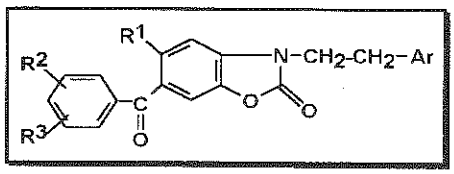
Melting points, percentage yields, crystallization solvent, molecular formula and elemental analyses of the synthesized compounds are given in the table.

The physical properties, R_f values on thin layer chromatography and the UV absorption properties of the compounds were determined. The structures of the compounds were proved by IR, ^{1}H-NMR, ^{13}C-NMR, mass spectroscopy and elemental analysis.

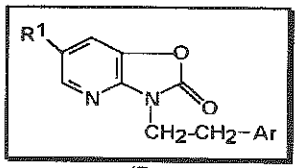
The analgesic activity of the synthesized compounds were tested by modified Koster Test using Aspirin as reference. Analgesic activities of four compounds were higher than that of Aspirin. Among these compounds, analgesic activity of 3-[2-(4-pyridyl)] ethyl-6-(2,5 - difluorobenzoyl) - 2 - benzoxazolinone (Compound 1) (%86.40 $p<0.01$) was higher than those of others.

Antiinflammatory activity of the compounds was tested by carrageenan hind paw edema test. It was found that 3-[2-(2-pyridyl)] ethyl-5-chloro-6- (3,5 - difluorobenzoyl) - 2 - benzoxazolinone (Compound 18) was the most potent compound in this series.

Ulcerogenic activities of some compounds were also studied and no gastrointestinal bleeding was observed at the 100 mg/kg dose level for two compounds of the studied compounds only.



(A)



(B)

Doctoral Dissertation Abstracts

INVESTIGATION OF THE EFFECT OF EPIDERMAL GROWTH FACTOR (EGF) ON GASTROINTESTINAL SYSTEM ULCERS

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Date of examination : June 19, 1998.

It was aimed to develop a microemulsion formulation that will increase the stability of epidermal growth factor (EGF) which is a polypeptide in gastrointestinal system and to examine the effect of intragastric (i.g.) administration of EGF and to provide healing in acute gastric ulcers induced by cold restraint stress in rats in this study.

The microemulsions were prepared by using labrafil M 1944 CS, Arlacel 186 and Brij 35, absolute alcohol and distilled water as oil phase, surfactants, co-surfactant and aqueous phase, respectively. The physical characteristics such as phase separation, turbidity, droplet size, refractive index, density, conductivity, pH and viscosity of microemulsions were measured at different temperatures (4°C, 30°C and 40°C) during 12 months.

The stability of EGF in microemulsion was also investigated at two different storage temperatures (30°C and 40°C) for three months. Amounts of EGF were measured by radioimmunoassay (RIA).

The in vitro release of EGF from microemulsion was carried out using Franz diffusion cell in pH 1.2 gastric medium at 37±0.1°C.

Female Wistar albino rats weighing 189-229 g were used throughout the study. Acute gastric lesions were induced by cold restraint stress for 4 hr in rats. EGF were administered at a dose of 6 $\mu g/kg.day^{-1}$ as i.g. and intraperitonally (i.p.) for seven days. Basal gastric acid secretion ($\mu mol\ H^+$/ 30 min.), ulcer score (mm^2), gastric mucos amount ($\mu g/g$ tissue), mucosal tissue cholesterol (mg/g tissue), EGF levels (pg/g tissue), chymus pH, basal pH and change in weight of stomach were determined.

The change in the mucosa of stomach were examined histologically in all experimental animal groups.

The results indicated that the physical characteristics of the developed microemulsion did not change under different storage temperatures ($p>0.05$). It was observed that the viscosity of microemulsion changed slightly with time at storage temperatures ($p>0.01$).

The results indicate that EGF degrades via first order kinetics at two different storage conditions. The shelf life (t_{90}) of EGF in microemulsions was found to be 7 days at 25°C.

According to the in vitro release study, the release of EGF from microemulsion was found as 85% within 6 hr.

Gastric acid secretion was reduced significantly within 30 min. after administration of EGF microemulsion ($p>0.05$). There were not significant decrease in gastric acid secretion of the IPEGF group when compared with IPPS group ($p>0.05$).

The results indicated that, the ulcer score reduced significantly by IPEGF ($p>0.05$), IG-EGF ($p<0.001$) and ME+EGF ($p<0.001$) treated groups compared to untreated groups.

In the IG-EGF ($p<0.05$) and ME+EGF ($p<0.001$) groups mucus levels were increased remarkably compared to their control groups. In contrast, there was not observe any significant change in mucus levels by i.p. EGF treatment ($p>0.05$).

The mucosal tissue cholesterol levels increased significantly in ME+EGF, IPEGF and IGEGF groups compared to their controls groups ($p<0.05$). On the other hand there were not significant difference in tissue EGF levels and weight changes of stomach in all experimental groups ($p>0.05$).

According to the histological studies, on EGF administered groups it was found that a considerable heal occurred in IG-EGF and IPEGF groups, and the heal in ME+EGF groups were similar to that of healthy rats (CONTROL).

It was concluded that i.g. EGF administration in the microemulsion formulation is effective than EGF solution in water and also it is more effective than i.p. EGF solution in physiologica saline.

PHARMACOGNOSIC INVESTIGATIONS ON THE SPECIES OF THE GENUS *PSORALEA*, GROWING IN TÜRKİYE

Levent ALTUN, Supervisor: Prof. Dr. Nevin TANKER, Department of Pharmacognosy, Faculty of Pharmacy, Ankara University, 06100 Ankara, Turkey.
Date of examination : July 1, 1998

Many phytochemical investigations, pharmacological, microbiological and phytotherapeutical, have been made outside Türkiye on the terpenic compounds, flavonids, calcones, isoflavonoids, compounds with cumestan structure and coumarins of the species of the genus Psoralea.

In our country, the genus Psoralea is represented by 3 species: *P. bituminosa* L., *P. acaulis* Stev. and *P. jaubertina* Fenzl.

In this study we determined the active compounds of aerial parts and roots of *P. bituminosa* and *P. acaulis*. Studies were carried out on the methanolic extracts of the aerial part of *P. acaulis*, as well as isolation of psoralen, a furanocoumarin derivative, daidzin, an isoflavonoid compound has also been isolated from this genus for the first time. The structures of these compounds have been elucidated by UV, IR, Mass, ^1H and ^{13}C NMR spectral methods. We also determined the quantity of these compounds, in the leafy branches, in flowers, fruits and in roots of these two species, by HPLC, using external standardisation method; we found that the psoralen and daidzin contents of the leafy branches of *P. bituminosa* were 0.0673% and 1.6288%, the flowers were 0.1566% and 0.2338%, the fruits were 0.0708% and 0.1510%, the roots were 0.0771% and 0.3789%; and for P. acaulis the contents of these compound were 0.2107% and 1.4877% for the leafy branches, 0.3118% and 1.4976% for the flowers, 0.1641% and 1.3387% for the fruits, 0.1016% and 2.2840% for the roots.

Quantitative analysis of acid insoluble ash and loss on drying the roots and aerial parts of both species gave us the following results as 4.83-4.90% ash, 1.15-1.45% acid insoluble ash, 10.09-10.15% humidity for the aerial part of *P.bituminosa*, and for the roots 4.77-4.91% ash, 0.46-0.57% acid insoluble ash and 4.89-5.16 humidty. For the other species, *P. acaulis*, these values were 4.93-5.23%, 0.35-0.42% and 9.96-10.20% for the aerial part and 3.73-3.95%, 0.55-0.60% and 3.97-4.07% for the roots respectively.

As a result of the previous studies, which indicated that various species of the genus *Psoralea* had strong antistaphylococcus activity, We have made an additional study to determine the antimicrobial activites of these species, on 8 different Gram(+) and Gram(-) bacteria and on 1 fungus, by preparing root and flower extracts with ethanol 70% and petroleum ether. As a result of this work, we found that the extracts prepared with ethanol 70% had no effect, but the ones prepared with petroleum ether had strong activities, especially on *Staphylococcus aureus* in comparison with standardised ampicillin.

Doctoral Dissertation Abstracts

STUDIES ON 2 - SUBSTITUTED - 6, 6 - DIMETHYL - 3-ACYL - 4 - ARYL - 5 - OXO - 1, 4, 5, 6, 7, 8 - HEXAHYDROQUINOLINE DERIVATIVES

Uzm. Ecz. Yeşim ALTAŞ, Supervisor: Prof. Dr. Cihat ŞAFAK, Hacettepe Üniversitesi, Sağlık Bilimleri Enstitüsü, Ankara.
Date of examination : July 3, 1998

In this study, twenty-two new compounds having a 2,6,6-trimethyl-3-acetyl-4-aryl-5-oxo - 1, 4, 5, 6, 7, 8 - hexahydroquinoline structure have been synthesized and screened for their calcium antagonistic activies. The compounds were prepared by the reaction of appropriate aromatic aldehyde, 4,4-dimethyl - 1, 3 - cyclohexanedione and acetylacetone. The melting points and percentage of the yields of the compounds are given below in the table.

The physical properties, R_f values on thin layer chromatography and UV absorption properties of the compounds have been determined. The structures of the compounds have been elucidated by IR, ^{1}H-NMR, mass spectra and elemental analyses.

The calcium antagonistic activities of the compounds were determined by the tests performed on isolated rabbit ileum and lamb carotid artery. According to activity studies, compounds 10 and 12 have been found the most active in this series. Introduction of various substituents to position three of the phenyl ring increases activity, except the 3-boromophenyl derivative. Compounds 15 and 17 have increased the contractions of barium chloride in the intestine at low concentration (10^{-4} M). Therefore, it is thought that these compounds would be agonist/antagonist. However at this concentration, these compounds have not produced any contraction by potassium chloride during inhibition and incubation. For this reason, it is difficult to term (agonist-antagonist) these compounds. The results of activity show that compounds exert similar activity on isolated rabbit ileum and lamb carotid artery.

STUDIES ON THE SYNTHESIS, STRUCTURE ELUCIDATION OF 5-FLUORO-1, 2, 6-TRISUBSTITUTED BENZIMIDAZOLE CARBOXYLATE OR AMIDE DERIVATIVES AND THEIR ANTIMICROBIAL EFFECTS

Canan KUŞ, Supervisor: Prof. Dr. Hakan GÖKER, Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Ankara University, 06100 Ankara, Turkey.
Date of examination : July 24, 1998

In the present work, targeted benzimidazoles involved ten different synthesis steps. At first, 2,5-difluoroacetanilide (2) was obtained by the acetylation of 2,5-difluoroaniline (1), following this, nitritation of 2 afforded 2,5-difluoro-4-nitroacetanilide (3), then acidic hydrolysis of 3 gave the 2,5-difluoro-4-nitroaniline (4). 2,5-difluoro-4-chloro nitro benzene (5) was prepared by the Sandmeyer reaction of 4. Substitution of this compound with cyclopropyl amine and ammonia gave 5-chloro-N-cyclopropyl-4-fluoro-2-nitro aniline (6a) and 5-chloro-4-fluoro-2-nitro aniline (6b), respectively.

1-[5-(Cyclopropylamino)-2-fluoro-4-nitrophenyl) - 4 or 3-substituted piperazines or piperidines (7a-7b) and 4-fluoro-5-(4-substituted piperazine- or piperidine-1-yl)-2-nitro aniline (7c-7f) were prepared by the substitution of 6a-b with several piperazine or piperidine derivatives. Reduction of 7a-f afforded 4,5-disubstituted-o-phenylendiamine derivatives (8a-f).

The final products, benzimidazole carbamate derivatives 9a-e, were prepared by the reaction of 1,3-dialkoxycarbonyl-S-methylisothiourea with 8c-e. On the other hand the reaction of 8a-c,f with ethyl β-amino-β ethoxyacrylate hydrochloride gave the ester derivatives of benzimidazoles 10a-d. Amidification of these esters with several N,N-dialkylaminoethyl or propylamine derivatives gave the acetamidobenzimidazoles 11a-f. Catalytic hydrogenation of 10a, in the presence of palladium on charcoal (Pd/C) and DMF gave 12.

By these reactions, a series of new 23 compounds (8 intermediates and 15 final products) were prepared. The purity of these compounds were controlled by TLC and mps were determined for the unhygroscopic compounds. The chemical structure of the compounds were elucidated by their IR, ^{1}H-NMR, Mass spectral data and their elemental analysis. In addition conformational analysis of 12 was performed with its X-ray crystallography data.

Compounds 9a-e, 10a-d, 11a-f and 12 were evaluated for their in vitro antimicrobial activity against *Bacillus subtilis, Staphylococcus aureus, Escherichia coli* and *Candida albicans* by the paper disk method. All the synthesized compounds showed the growth inhibition zone against *Candida albicans*. Methyl 5-fluoro-6-(4-methyl piperidin-1-yl)-^{1}H-benzimidazole-2-carbamate (9c) had comparable antifungal activity to fluconazole and ketoconazole with a 18 mm diameter inhibition zone . In addition compounds 10a-d, and 11a-f also exhibited comparable inhibition results to ampiciline against *Bacillus subtilis*.

Doctoral Dissertation Abstracts

PHARMACOGNOSTIC INVESTIGATIONS ON CYCLOARTANE TRITERPENE SAPONOSIDES OF SOME *ASTRAGALUS* SPECIES

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Date of examination : August 13, 1998

Many *Astragalus* species are used in folk medicine for their hepatoprotective, antioxidative, immunostimulant and antiviral properties. Three groups of chemicals have been described as pharmacologically activite principles: polysaccharides, saponins and phenolics (RIOS & WATERMAN, 1997).

In this study, *A microcephalus* Willd., *A. brachypterus* Fischer and *A. trojanus* Stev. are studied from the point of view of their cycloartane type saponin contents. Air dried roots of *A. microcephalus*, *A. brachypterus*, *A. trojanus* as well as the overground parts of *A. trojanus* were extracted by 80% EtOH. As a result of the chromatographical studies (VLC, Open Column Chromatography and MPLC) on the water soluble parts of the ethanolic extracts, six cycloartane-type glycocides were isolated from *A. microcephalus* (A. mic 1-6), eight from *A. brachypterus* (A. brac 1-8), twelve from *A. trojanus* (A. tro 1-12) and six from the overground parts of *A. trojanus* (ATH 1-6). In addition, a new oleanane glycoside (A. tro 13), a new tryptophan derivative (A. tro 15), a steroidal glycoside (A. tro 14), and a isoflavonoid (ATH 7) were isolated. The structural analysis of these compounds were carried out by chemical (acetylation) and mainly spectroscopic [UV, IR, FAB-MS, 1D-NMR, (^{1}H-NMR, ^{13}C-NMR), 2D-NMR (DQF-COSY, TOCSY, HOHAHA, HSQC, HMBC and ROESY] a means. Cycloastragenol [20 (R), 24 (S)-epoxy-3β, 6α, 16β, 25-tetrahydroxycycloartane] and cyclocanthogenol [3β, 6α, 16β, 24(S), 25-pentahydorxycycloartane] were found as the sapogenol moiety for a total of nineteen compounds. Among these isolated compounds, cycloastragenol, astragalosides I, II, IV and VII, astrasieversianins I and II, cyclocanthoside E are known saponins, while cyclocephaloside II, brachyosides A-C and trojanosides A-F and H are found to be new compounds for nature and science.

In addition in this study, a new cycloartane type sapogenol for *Astragalus* species (20,25-epoxy-3β, 6α, 16β, 24α-tetrahydroxycycloartane) was also determined as the sapogenol moiety of a new saponin, named cyclocephaloside I, from *Astragalus microcephalus*.

SYNTHESIS, STABILITY AND METABOLISM OF AROMATIC SECONDARY AND TERTIARY AMINES AND THEIR POSSIBLE METABOLIC INTERMEDIATES

İlkay KÜÇÜKGÜZEL, Supervisor: Assoc. Prof. Dr. Mert ÜLGEN, Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Marmara University, 81010 İstanbul, Turkey.
Date of examination : October 5th 1998

An investigation of the metabolic pathways of several tertiary and secondary amines has been carried out using in vitro techniques of drug metabolism. The aim of this study was to establish the factors influencing C- and N-oxygenation of nitrogenous compounds giving rise to a wide variety of metabolic end-products. The main area of our interest was focused on the possible formation of amides or N-oxygenated metabolites from both tertiary and secondary amines depending of their physicochemical nature.

Substrates utilized in the present study could be separated into three groups. Group-1 substrates consisted of aryl of aralkyl substituted tertiary amines, namely, N-ethyldibenzylamine, tribenzylamine, N-benzyl-N-methylaniline, N,N-dibenzylaniline and an amide, N,N-dibenzylbenzamide. Group-2 substrates comprised three N-benzylic heterocyclic amine ie. 1-(2,4,6-trimethylbenzyl)pyrrolidine, 1-(2,4,6-trimethylbenzyl)piperidine and 9-(2,4,6-trimethylbenzyl)-9H-carbazole. N-(4-Chlorobenzyl)-4-chloro-aniline and 4,4'-dichlorodibenzylamine were selected as group-3 substrates, representing the aryl- alkyl and dialkyl secondary amines, respectively. The choice of these model compounds was aimed at providing substrates with different lipofilicity and basicity.

Metabolic studies on these model compounds initially required the synthesis, purification and characterization of certain N-benzylic tertiary and secondary amines and their corresponding N-acyl or N-oxygenated derivatives, together with some other potential metabolites followed by separation of each substrate from its metabolites using thin-layer and reversed-phase high pressure liquid chromatographic methods. The subsequent step of our studies on the metabolism of tertiary and secondary amines involved incubation of the above substrates using rat microsomal preparations fortified with NADPH. The post-incubates were then analyzed by thin-layer and high pressure liquid chromatographic methods.

The results of these metabolic experiments indicated that neither tertiary nor secondary amines produced any metabolites having identical chromatographic properties with the authentic amides. However, incubation of the two alicyclic tertiary amines, 1-(2,4,6-trimethylbenzyl)pyrrolidine and 1-(2,4,6-trimethylbenzyl)-piperidine resulted in the formation of α-oxo derivatives. N-Dealkylation was the common pathway observed with each substrate. It was also observed that N-oxygenation was highly influenced by the pk_a of the parent amine used as substrate. Enzyme induction studies revealed that some dealkylation and aromatic hydroxylation reactions were mediated by phenobarbitone-inducible isoforms of cytochrome P-450. However, N-oxidations of 1-(2,4,6-trimethylbenzyl)-pyrrolidine and 1-(2,4,6-trimethylbenzyl) piperidine seemed not to be affected by phenobarbitone induction, indicating the possible involvement of a different enzyme system independent of cytochrome P-450, such as flavin-containing monooxygenases.

Several p-hydroxylated metabolites were directly detected and corresponded to authentic compounds with N-benzyl-N-methylaniline and N,N-dibenzylaniline. The secondary amines yielded the corresponding N-oxidation products ie. hydroxylamines and nitrones. However, both secondary amines failed to produce the corresponding amides, whilst the parent imine was detected as a metabonate when N-(4-chlorobenzyl)-4-chloroaniline was used as substrate. The nitrones α,N-bis(4-chlorophenyl)nitrone and α-(4-chlorophenyl)-N-(4-chlorobenzyl) nitrone were observed to be unstable under daylight giving several breakdown products such as amides or 4-chlorobenzaldehyde, possibly via the corresponding oxaziridines.

From the above data, it can be concluded that synthesis of amides requires initial nitrone formation which can only be formed from secondary amines. Hydroxylamines are intermediary products giving rise to nitrones. However, the corresponding nitrones were not intermediates leading to amides when the required precautions were taken during extraction and analysis of post-incubates. In the present study, the metabolic N-oxygenation could be considered as a function of substrate basicity and the formation of lactam metabolites from alicyclic tertiary amines is a biphasic process mediated by microsomal and cytosolic enzymes.

Doctoral Dissertation Abstracts

STUDIES ON SOME CHEMICAL COMPOUNDS WITH ANTIDIABETIC ACTIVITY

Oya BOZDAĞ DÜNDAR, Supervisor: Prof. Dr. Rahmiye ERTAN, Department of Pharmaceutical Chemistry, Faculty of Pharmacy Ankara University, 06100 Ankara, Turkey.
Date of examination : October 23, 1998

In this study, it was aimed to investigate the synthesis and the antidiabetic activity of some new flavone derivatives which contain SU compounds moiety at m- position, 2,4-TZD and analog rings at m- or p- position of B ring of flavone nucleus.

Synthesis of the compounds:

For 3'-Flavonyl-SU;

1. 3'-Flavone sulfonamide was synthesized.

2. Starting from this compound 7 original 3'-flavonyl SU derivatives were synthesized.

For flavonyl 3' (or 4')-2,4-TZD and analogs;

1. Flavon-3' (or 4')bromomethyl was synthesized.

2a. The derivatives which contain a methylene link between flavone and 2,4-TZD were synthesized with reaction of this compound and 2,4-TZD ring.

2b. However, after changing the 3' (or 4')-bromomethyl group of this compound to aldehyde group and condensation of this compound with 2,4-TZD, 2,4-imidazolidinedione and 2-thiohydantoine rings by Knoevenagel reaction, the derivatives which contain a methyn link between flavone and these ring systems were synthesized. The reaction of this group of compounds with ethyl or methyl iodide, N-alkyl substituted derivatives were prepared.

By using these 2 different general methods, 20 original compounds were synthesized. 10 of these compounds were from the m- position and 10 of them were from the p- position of the flavone ring.

The purity was controlled by TLC and then melting points were determined. The chemical structure of the synthesized compounds were elucidated by their IR, ^{1}H NMR, Mass and Elementary analysis data.

Conformational structure of compound 3'-flavonesulfonamide which was the starting substance for 3' flavonyl SU group was performed by X-Ray analysis, and interaction of this group compounds with SU receptors was examined. According to this, it was seen that flavonyl SU group compounds interact with A and B site of SU receptors for the biological activity and results of biological assays showed that flavonyl SU group compounds have insulin releasing activity.

SIMULTANEOUS DETERMINATION OF CISPLATIN, TRANSPLATIN AND TRICHLOROAMMINEPLATINATE BY HPLC USING 4-METHYL-2-THIOURACIL AS DERIVATIZING AGENT

Filiz ARIÖZ, Supervisor: Ass. Prof. Dr. Güler YALÇIN, Department of Analytical Chemistry, Faculty of Pharmacy, Marmara University, 81010 İstanbul, Turkey.
Date of examination : December 7, 1998

In this study, a simple, rapid selective and sensitive method has been developed for detecting the antitumour agent cis-diamminedichloroplatinum (II) (cisplatin) (CDDP) and its toxic impurities trans-diamminedichloroplatinum(II) (transplatin) (TDDP) and trichloroammineplatinate anion (TCAP) using HPLC in one run. By using 4-methy-2-thiouracil (MTU) as a derivatizing agent new compounds have been formed from the a. m. Pt compounds.

In this method, a μ-Bondapak C_{18} column (300 x 3.9 mm ID, 10 μM particule size) and 0.02 M sodium acetate and acetic acid running buffer containing 4%, (v/v) methanol, 6 mM tetrabutylammonium hydrogensulfate and 4mM sodium octanesulfonate at pH 3.7 with 1mL min^{-1} flow rate are used. Isocratic elution was performed and detection was carried out at 315 nm.

Reactant concentration, methanol content, pH and reaction time on the yield of derivatives were investigated and the optimum conditions for the detector response were defined. MTU derivatives of each three platinum compounds were formed in the presence of 22 times MTU of total platinum species in an acetate buffer solution containing 40% methanol (v/v) and 0.9% KCl solution at pH 3.7 and ambient temperature, they were stable for one hour. The a.m. method was applied to a formulation of the drug in the market without any pretreatment and no interference from the matrix was investigated.

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Bilimsel Taramalar / Scientific Reviews

Nadeem Irfan BUKHARI, Mahmood AHMAD, Shadab QAMAR : "Effects of Geonetics on the Bioavailabilty and Disposition Kinetics of Mefenamic Acid."

Page 97. The Table 1 was inadvertently omitted during process of printing. We are sory for mishap. Table 1 was presented below.

Sayfa 97. Tablo 1 basımda unutulmuştur. Basım sırasında gözden kaçan bu hata nedeniyle özür dileriz. Tablo 1 aşağıda sunulmuştur.

Table 1. Mean ± SD (n=27) plasma levels and pharmacokinetics parameters of mefenamic acid in rabbits.

Parameters	Time (hrs)	(Mean±SD)
Plasma levels (μg/mL)	0.5	0.68±0.12
	1.0	1.88±0.24
	1.5	2.57±0.26
	2.5	3.37±0.52
	4.0	1.68±0.39
	6.0	1.09±0.27
	8.0	0.59±0.12
	12.0	0.12±0.07
C_{max} (hrs)		3.36±0.55
T_{max} (hrs)		2.50±0.00
$AUC_{0-\infty}$ (μg.hr/mL)		14.9±2.02
$AUMC_{0-\infty}$ (μg.hr^2/mL)		60.9±7.75
MRT (hrs)		4.16±0.26
$t_{1/2abs}$ (hrs)		0.77±0.23
K_{abs}		0.93±0.29
$t_{1/2elim}$ (hrs)		1.93±0.29
K_{elim}		0.36±0.08
Vd (L)		14.5±2.58
Cl_t (mL/min)		86.6±9.67