Doctoral Dissertation Abstract...

INVESTIGATION OF SYNTHESIS AND ANALGESIC ACTIVITY OF SOME TIARAMIDE DERIVATIVES

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Date of examination:October 16, 1998

Synthesis of derivatives of tiaramide (4-[(5-chloro-2-benzothiazolinone-3-yl)acetyl]-1-piperazine ethanole) and 6-benzoyl-2-benzothiazolinone, whose analgesic activity is reported was aimed in the study. Twenty-one benzothiazolinone derivatives were, thus, obtained.

Chemical structures of the compounds synthesized were elucidated by their IR, ^{1}H-NMR and ^{13}C-NMR spectral data and elemental analyses. Six of the compounds were reported in the literature before.

Antinociceptive activity of the compounds were tested by Modified Koster Test employing aspirin and tiaramide as the references. Seven of the compounds, 1-[-2-(5-chloro-2-benzothiazolinone-3-yl)acetyl]-4-(4-flourophenyl)piperazine, 1-[-2-(5-chloro-2-benzothiazolinone-3-yl)acetyl]-4-(4-chloro phenyl)piperazine, 1-[-2-(5-chloro-2-benzothiazolinone-3-yl)acetyl]-4-hydroxypiperidine, 2-[-2-(5-chloro-2-benzothiazolinone-3-yl)acetyl]amino-4,6-dimethylpyridine, 6-(4-chlorocinnamoyl)-3-methyl-2-benzothiazolin-one, 6-(4-methylcinnamoyl)-3-methyl-2-benzothiazolinone and 6-(4-methoxycinnamoyl) -3-methyl-2-benzothiazolinone were found more active than aspirin and tiaramide.

In addition, statistical correlation between the biological activity and some structural parameters of the compounds such as log P, parachor, molar refractivity and molecular connectivity indices have been investigated. Linear regression analysis indicated that there is reverse correlation between the biological activity and liposolubility. There is a linear correlation between second and third degree molecular connectivity indices and the biological activity.

In conclusion, it is likely that the more water soluble compounds are the more active ones.

THE RHYTHMIC ROLE OF L-ARGININE - NO/cGMP PATHWAY IN THE ANALGESIC EFFECT PATTERN OF ANTIHISTAMINIC-MEPYRAMINE

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Date of Examination: October 28, 1998.

In this study, it is aimed to investigate the following items by p-BQ-induced abdominal constriction pain model in mice: 1) The involvement of L-arginine/NO/cGMP pathway in H_1-receptor antagonist mepyramine-induced antinociception; 2) The chronorhythmic profiles of all agents administered individually and concomitantly; 3) The 24-h temporal variation of control serum nitrite levels as an NO_x indicator with respect to the concomitant administration of mepyramine and L-arginine/NO cascade component agents.

Recently it has been shown by us that mepyramine profiled an antinociceptive pattern in p-BQ-induced mouse writhing test without a time dependency. In this study, mepyramine portrayed circadian antinociceptive fluctuations. The agents involved in L-arginine/NO/cGMP cascade such as enzymatic and non-enzymatic precursors, NOS and NOS+sGC inhibitors displayed significant temporal variations when interacted with mepyramine. The serum nitrite levels of all the agents studied exhibit similar temporal fluctuations. The conclusions of the study: 1) the antinociceptive activity pattern obtained for mepyramine exhibit daily variations; 2) L-arginine and L-NAME display a chrononociceptive dual pattern as antinociception and nociception; 3) MM and SNP only possess a circadion antinonciceptive activity; 4) concomitant administrations of L-arginine/NO cascade agents with mepyramine induce an involvement both rhythmically and nociceptive processing activity; 5) control serum nitrite levels of mouse show a lack of temporal existence; 6) however, serum nitrite levels of single or cotreatment administrations of mepyramine and cascade agents exhibit daily fluctuations; 7) the overall results confirm the dual pattern of L-arginine/NO pathway by this novel chronergic protocol, and shed light on the complex pattern of NO both centrally and peripherally in nociceptive processing.

RESEARCHES ON TAXANE DERIVATIVE COMPOUNDS FROM TAXUS BACCATA L. GROWING IN TURKEY

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Taxol, a diterpenoid with a taxane-type structure was first isolated from the bark of the Pacific Yew Tree (*Taxus brevifolia* L.) and was found to be a new class of microtubule-stabilizing anticancer agent used in chemotherapy. The wood of thick branches of the European Yew Tree (*Taxus baccata* L.) growing in Turkey was found to be richer in taxoid content than the other parts of the plant. Investigation of the taxane-type constituents of *Taxus baccata* L. (Taxaceae) recorded in the Flora of Turkey, collected from Rize-Çamlıhemşin is presented.

As a result of the isolation and purification procedures, 14 compounds were obtained and their structures were elucidated by extensive spectroscopic analysis primarily by two-dimensional NMR techniques. They are; **10-Deacetylbaccatin III*, Baccatin III, Baccatin VI** and **Taxol** from the oxetane-bearing; **2α, 5α, 10β-Triacetoxy-14β-(2-methyl)-butryloxy-4 (20), 11-taxadiene** and **Taxusin** from the exocylic-containing; and **1β-Hydroxybaccatin I** from the epoxide-bearing taxoids were determined from the wood of thick branches of T. *baccata* L. growing in Turkey. Among these, taxusin and baccatin III were found to be major compounds.

In addition, six phenolic compounds, namely, **3-Methoxy-4-hydroxycinnamaldehyde, Lariciresinol, 3'-Demethyllariciresinol, Isolariciresinol, 3'-Demethylisolariciresinol-9'-hydroxyisopropylether** and **3-Demethylisolariciresinol** were also isolated along with taxoids. During phytochemical studies, **β-sitosterol** was also obtained.

This is the first report of the taxoid content of the wood of the European Yew Tree (T. *baccata* L). Apart from the presence of the above mentioned phenolic compounds except isolariciresinol in the genus, *Taxus* is being investigated for the first time in this research, as well as their extensive spectroscopic data.

*It was obtained from the fleshy barks of the thick branches of T. *baccata* L.

PHARMACOGNOSTICAL COMPARISONS ON *Viscum album* L. subspecies

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Viscum L. is a semi-parasitic genus growing on various host plants, such as trees and shrubs. The plant is known as "Ökse Otu" in Turkey. In our country, *Viscum* L. is represented by one species and 3 subspecies. These subspecies are V.*album* ssp. *album*, V.*album* ssp. *abietis*, V.*album* ssp. *austriacum*. Continuing our researches on these subspecies, comparative investigations were carried out with especially the phenylpropanoid glycosides of the subspecies of V.*album* in this study.

The leaves and stems of the samples belonging to three subspecies were dried and powdered, then extracted with ethanol at room temperature. The concentrated extracts were dissolved in water and extracted with petroleum ether (40-60°C), diethyl ether, ethylacetate and n-butanol/H_2O, respectively. The yield of the fractions of *V.album* ssp. album was, higher than the others. With the controls carried out by thin layer chromatography it was determined that the contents of the extracts of n-butanol and ethylacetate were richer than the others. Therefore these extracts were selected for the further investigations.

As a conclusion, the phenylpropanoid glycosides named syringin, coniferin, and kalopanaxin D were obtained from V.*album* ssp. *album*. The structures of all the compounds were elucidated by means of spectral evidence (UV, IR, ^{1}H-, ^{13}C-NMR, FAB-MS). Additionally, the phenolic compounds named 5,7-dimethoxy - flavanone - 4' - O - [β - D-apiofuranosyl(1→2)]-β-D-glucopyranoside, 5,7 - methoxy - flavanone - 4' - O - β - D - glucopyranoside, 5,7-dimethoxy-flavanone-4'-O-[2''-O-(5'''-O-trans-cinnamoyl)-β-D-apiofuranosyl]-β-D - glucopyranoside, 2'-hydroxy-4',6'-dimethoxy-chalcone-4-O-[-D-glucopyranoside and 2'-hydroxy-4',6'-dimethoxy-chalcone-4-O-[2''-O-(5'''-O-trans-cinnamoyl)-β-D-apiofuranosyl]-β-D-glucopyranoside were also isolated from V.*album* ssp. *album*.

During the chromatographical studies (MPLC, CC) on the n-butanol extract, 2,6-dimethyl-2,7-octadien-1,6-diol-6-O-[6'-O-β-D-apiofuranosyl]-β-D-glucopyranoside and 5,7-dimethoxy-flavanone-4'-O-[β-D-apiofuranosyl(1→2)]-β-D-glucopyranoside were isolated from V.*album* ssp. *album* and found to be new compounds for this subspecies.

As a result of the chromatographical studies (MPLC, CC) on the n-ethylacetate extract, 5,7-dimethoxy-flavanone-4'-O-[2''-O-(5'''-O-trans-cinnamoyl)-β-D-apiofuranosyl]-β-D-glucopyranoside, and 2'-hydroxy-4',6'-dimethoxy-chalcone-4-O-[2''-O-(5'''-O-trans-cinnamoyl)-β-D-apiofuranosyl]-β-D-glucopyranoside were isolated from V.*album* ssp. *album*. This is the first report of these compounds found in the *Viscum* genus.

Qualitative and quantitative determinations of the phenylpropanoid glycosides of three V.*album* subspecies were made using High Performance Liquid Chromatography (HPLC). However, flavanon and chalcon contents of the plant were not studied using HPLC due to the isomerisation problems.

In the biological activity studies the vasoactive effect of the n-butanol extract of V.*album* ssp. *album*, as well as the fractions and the phenolic compounds isolated from these fractions were studied using rat thoracic aorta.

"INVESTIGATION OF URİC ACİD - ALLANTOIN RATIO AS A POTENTIAL MARKER IN LUNG CANCER CASES"

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Free radicals have been implicated in the cause or pathology of cancer, aging, heart disease, chronic inflammation, and parasitic infections. Due to the fact that lungs are regularly exposed to volatile toxins and oxygen, free radicals have been gaining increasing importance in the pathology of lung cancer. At the same time, lungs have developed specific antioxidant defense systems against free radical reactions. Uric acid is one of the important intra- and extra-cellular antioxidants because it is found in plasma in higher concentrations than other antioxidants and because of its ability to react with such strong oxidants as HO., HOCl.. If the urate radical which results from the reaction of uric acid and free radicals cannot be reconverted to uric acid through reduction, it is converted to such products of oxidation as allantoin (found in the highest concentration), oxonic acid, oxaluric acid and glioxilic acid.

In this study the serum allantoin and uric acid levels for patients diagnosed with lung cancer (n=70) and control group members (n=75) were measured and the ratios were calculated. The mean allantoin and uric acid levels and ratios in the patients group were 61.18, 3.21 μM, 291.66 7.87 μM, 21.90 and 1.24, while in the control group they were 36.63 1.38 μM, 294.6, 7.23 μM 13.29 and 0.69, respectively. A statistically significant relation was found between the serum allantoin levels and ratios of the patient and control groups ($p<0.001$), but no statistically significant relation was found in the uric acid levels ($p>0.05$). The effects on serum allantoin and uric acid levels of the patient and control groups of sex, age, quetelet index, smoking, alcohol intake, diet, and fat consumption, metastasis, history of cancer in the family, and the type of lung cancer were studied.

In order to determine the effect of free radicals on uric acid in lung cancer, rats were injected with 20-methylcholantrene. With the exception of one of them, rats did not develop lung cancer, but pneumonia was observed in all of them. The allantoin and uric acid levels in the serum samples of 11 patients and 11 control rats were 148.67 ± 24.55 M, 150.27 ± 30.70 M and 138.94 ± 9.60 M, 154.47 ± 22.02 M, respectively. The ratios of patients and control rats were 112.93 ± 11.03 and 106.00 ± 17.06, respectively. A statistically significant relation was found between the serum allantoin and uric acid levels and ratios of the patient and control rats ($p<0.001$).

"9th INTERNATIONAL SYMPOSIUM ON RECENT ADVANCES IN DRUG DELIVERY SYSTEMS" TOPLANTISININ ARDINDAN

The University of Utah Center for Controlled Chemical Delivery tarafından düzenlenen "9th International Symposium on Recent Advances in Drug Delivery Systems" isimli toplantı 22-25 Şubat 1999 tarihleri arasında Salt Lake City, Utah'da yapılmıştır. Bu yılki simpozyumun özelliği; Wisconsin Üniversitesi, Eczacılık Fakültesi, Farmasötik Bölümü öğretim üyelerinden Prof. Dr. Joseph R. Robinson'un onuruna düzenlenmiş olmasıdır. J.R. Robinson, özellikle kontrollu salım sistemleri, biyoadhezyon, peptit ve protein tipi ilaçların mukozal uygulamaları konularında pek çok sayıda araştırma yapmış, bu konuların duayeni olma özelliğini taşıyan bir bilim adamıdır.

İki yılda bir aynı merkez tarafından düzenlenen bu simpozyumun genel amacı; farmasötik bilimler, polimer bilimi, hücre ve moleküler biyoloji ve tıp alanlarındaki araştırıcıları biraraya getirecek konuları ortak bir platformda tartışmaktır.

Bu yılki simpozyuma 20 ülkeden yaklaşık 350 araştırıcı katılmıştır. Simpozyumda 3.5 gün boyunca 36 sözlü ve 56 poster tebliği sunulmuştur. Sunulan bildiriler genel olarak yeni ilaç taşıyıcı sistemler, peptit ve proteinlerin oral, mukozal, oküler uygulamaları, ilaç hedefleme, oral aşılar, hidrojeller, dendrimerler, gen tedavisi, biyolojik olarak parçalanabilen polimerler, yeni biyoadhesif polimerler, transdermal ilaç sistemleri konularını içermekteydi.

İlaç ve ilaç taşıyıcı sistemlerle ilgili olarak son yeniliklerin üst düzeyde tartışıldığı bu simpozyumdan yeni bilgilerle donanmış olarak ayrıldık.

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