DOCTORAL DISSERTATION ABSTRACTS

SYNTHESIS OF NEW NITROETHANE DERIVATIVES, FROM 2-AMINOTHIOPHENOL AND β-NITROSTYRENES, INVESTIGATIONS OF THEIR REACTIONS AND ANTIMICROBIAL ACTIVITIES

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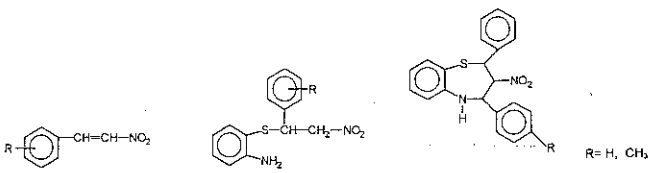
β-Nitrostyrene **1** derivatives have diverse pharmacological activities. Particularly antibacterial and antifungal activities have been scrutinized intensively. Also saturated dervatives β-nitrostyrenes posses similar activities. The common property of these molecules is that carry good leaving groups. Based on this idea it has been planet to obtain the products of addition on the active double bonds of β-nitrostyrenes that would have good leaving group characteristics and to compare their activities with the respective β-nitrostyrenes and thus attaining to compounds of better activity.

For this purpose, 1-[(2-aminophenyl) thio]-1-phenyl - 2 - nitroethane **2** derivatives have been synthesized as addition products of 2-aminothiophenol and β-nitrostyrenes.



1 **2** **3**

Gram (+) bacteria such as *Stafilacoccus aureus, Bacillus subtilis* and Gram (-) bacteria such as *Klebsiella pneumoniae* and *Escherichia coli* were used for antibacterial activity testing. Whereas *Candida albicans, Candida stellatoidea, Candida parapsilosis, Candida pseudotropicalis* were used for antifungal activity testing. Microdilution method was employed for antibacterial activity studies and MIC (Minimal Inhibitory Concentration) values are given as μM/ml. Ampicillin sodium and Clotrimazol have been used as standards for antibacterial and antifungal activity studies respectively.

Antibacterial activities of **2** have been compared with those of **1**. It has been found out **1** and **2** showed weak antibacterial activity, but some the derivatives of **1** and **2** had significant antifungal activity, and **1** were more than active in general.

After synthesis of title compounds 1-[(2-aminophenyl) thio]-1-phenyl-2-nitroethane derivatives cyclization of these compounds to 1,5-benzothiazepine **3** derivatives bearing nitro group at the position three has been tried, which have not been seen in the literature so far.

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

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In this work, the new spectrophotometric methods were developed for the simultaneous determination of active ingredients in three binary mixtures and a ternary mixture containing atropine sulfate: atropine sulfate - diphenoxylate hydrochloride, atropine sulfate - morphine hydrochloride, atropine sulfate - papaverine hydrochloride and atropine sulfate - papaverine - phenobarbital.

In atropine sulfate - diphenoxylate hydrochloride mixture, the drugs were simultaneously determined by two methods; in the first, the determination diphenoxylate hydrochloride was performed by selective precipitation with picric acid in methanolic solution and by reading absorbance value of the solution of this precipitate in acetone at 257.7 nm than, the quantation of atropine sulfate in the mixture was made by measuring dhe $dA/d\lambda$ values at 236.2 nm in the first derivative spectra of the remaining solution after precipitation. In the second, simultaneous determination of these drugs was realized by using ratio spectra derivative spectrophotometry. In this procedure signals were measured at 271.0 nm for atropine sulfate and 262.2 nm for diphenoxylate hydrochloride in the first derivative spectra of the spectra ratio spectrum obtained by using their spectra as divisor. All these methods were applied to a pharmaceutical preparation containing this mixture.

In atropine sulfate - morphine hydrochloride mixture, active components were simultaneously determined by three methods. In the first, Vierordt's method, simultaneous determination of drugs was realized by using A^1_1 values at 257.3 nm and 284.4 nm, λmax of their solution in distilled water, and dissolving two equations with two unkown. In the second, modified Vierordt's method, the determination of the co-existing compounds by using same parameters and solving the equations required in this method. In the third, the quantitation of atropine sulfate and morphine hydrochloride in their binary mixtures was made by using spectra ratio derivative spectrophotometry. In this method, signals were read at 255.870 nm for atropine sulfate and at 273.623 nm for morphine hydrochloride in the first derivative of the ratio spectra obtained by using their solutions in distilled water as divisor.

In atropine sulfate-papaverine hydrochloride mixture, active ingredients were determined by two spectrophotometric methods. In the first, derivative spectrophotometry, $dA/d\lambda$ values were measured at 305.5 nm for atropine sulfate and at 329.8 nm for papaverine hydrochloride in the first derivative spectra of the mixture in methanol - 0.1N NaOH. In the second, these drugs were simultaneously determined by spectra ratio derivative spectrophotometry. In this method, signals were measured at 256.651 nm for atropine sulfate and at 270.546 nm in the first derivative of the ratio spectra obtained by using their solutions in methanol - 0.1N NaOH as divisor.

In atropine sulfate - papaverine hydrochloride - phenobarbital mixture, the quantitation of these drugs were performed by reading the $da/d\lambda$ values simply at 305.5 nm for atropine sulfate, at 329.8 nm for papaverine hydrochloride and at 261.1 nm for phenobarbital in the first derivative spectra of the mixture in methanol - 0.1N NaOH.

In all the methods, mean recoveries and relative standard deviations of the methods, correlation coefficients in regression equations and the concentration ranges in which the Beer's law was valid were determined.

DESIGN AND PREPARATION OF INTRAVAGINAL CONTROLLED RELEASE SYSTEMS

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New delivery routes have been investigated for the drugs which caused problems when used orally. Vaginal mucosa is also one of the new routes being investigated for the drug delivery. Drug administration via vaginal route has the advantage of bypassing the hepatic first past metabolism. Hormones, antimicrobic drugs, vaccines and some proteins and peptides have been administrated by vaginal mucosa. These materials are slowly, but completely absorbed through the vaginal mucosa.

Bromocriptine, a semisynthetic ergot alkaloid, which is a dopamine agonist was chosen as the model drug in this study. It also inhibits release of prolactin hormone and it has been frequently used for the treatment of diseases caused by hyperprolactinemia and for some neurological disorders as a dopamin agonist in clinical trials. Many patients have complained that the oral treatment with bromocriptine has been quitted, due to its side effects on GI tract. It is also subject to hepatic first pass effect and hence, oral bioavailability of bromocriptine is reduced.

The design and development of the intravaginal controlled release dosage form of bromocriptine mesilate with a ring shape was attempted in this study.

Silicon elastomers, MDX-4-4210 and A-2186, were chosen as polymer materials. The release of bromocriptine mesilate from silicone matrices was enhanced by the aid of some liquid and solid excipients. For this purpose, propylene glycol, lactose, NaCl, citric acid, gelatine and low molecular weight gelatine were used. The compatibility of these materials with silicone polymers have been investigated with preliminary experiments. Gelatine and low-molecular weight gelatine were the most effective materials for the enhancement of the release of bromocriptine mesilate in vitro. Propylene glycol was also useful for the increase of release. The release profile of the formulation which contained MDX-4-4210, 10 percent of propylene glycol and the kneading mixture of drug: low molecular-weight gelatine in the ratio of 1:3 was in most agreement with the target profile. The effect of this formulation which was prepared with a ring shape, on plasma prolactine level was investigated in rabbits. The results were compared with control and placebo groups. Plasma prolactin levels were measured by RIA method. It was observed that the plasma prolactin level of test group was significantly decreased ($p<0.05$) compared with control and placebo group. This decrease was maintained for 10 days.

It was concluded that, bromocriptine mesilate was absorbed from rabbit vagina and the controlled release intravaginal ring of bromocriptine mesilate was effective on decrease of plasma prolactin level for ten days.

THE ROLE OF ALPHA-1-PROTEINASE INHIBITOR AND ALPHA-2-MACROGLOBULIN IN PROTEINASE INHIBITION

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α_1-Proteinase inhibitor (α_1-PI) and α_2-macroglobulin (α_2-M) are two plasma proteins responsible for the control of proteases of tissue origin. The question of whether or not data acquired with purified α_1-PI and α_2-M in isolation are applicable to their mixtures has been examined, using bovine pancreatic trypsin as the target proteinase. Tryptic activity was inhibited totally by α_1-PI. Entrapment in α_2-M increased esteratic activity by 12%. Experiments done using mixtures of inhibitors showed that α_1-PI was more effective in mixtures than in isolation; alternatively, α_2-M had inferior activity in mixed protein populations: Titrations of trypsin with mixtures of α_1-PI and α_2-M showed that the effective ratio of rate constants for the association of enzyme with the two inhibitors ($k_M/k_{PI}=10\pm1.5$) was different from that inferred from the individual second-order rate constants (k_{ass}) reported earlier ($k_M/k_{PI}=30$). The effect of the redox state of α_1-PI on inhibitory activity was examined: The titrations were repeated using mixtures of α_2-M with oxidized and reduced α_1-PI (0% and 60% SH content, respectively). The results obtained with mixtures containing oxidized α_1-PI were similar to those obtained with plasma, and k_M/k_{PI} was lower than the literature value. In contrast, k_M/k_{PI} observed in mixtures with reduced α_1-PI was higher than expected. This suggested that k_{ass} for α_1-PI might be different for the two forms of the inhibitor. To check this possibility, k_{ass} values for different redox forms of α_1-PI were determined. The SH content of α_1-PI did not change the type of inhibition. Oxidized and reduced α_1-PI yielded k_{ass} values ($k_{ass}=2.7\pm0.3\times10^5$ $M^{-1}sec^{-1}$) which were similar and did not differ from the value reported in literature. The results suggested that α_1-PI and α_2-M might interact with each other.