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Studies On Some New Flavone Derivatives Possessing Spasmolytic Avtivity IV

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Summary : It is aimed to investigate the spasmolytic activity of some new flavone derivatives which contain both flavone and benzodioxane ring systems. The spasmolytic activity of the water soluble flavone derivatives synthesized in our laboratory were tested against agonists such as acetylcholine, histamine and $BaCl_2$ by using «Flavoxate HCl» as reference compound. The activity tests were performed on guinea-pig ileum in the isolated organ bath. The results indicate that the compounds II, III and IIIa were more active on histamine contractions than «Flavoxate HCl».

BAZI YENİ FLAVON TÜREVLERİ ÜZERİNDE SPAZMOLİTİK ETKİ ÇALIŞMALARI IV

Özet : Bu çalışmada flavon ve benzodioksan çekirdeklerini birarada içeren yeni bazı flavon türevlerinin spazmolitik etkilerinin incelenmesi amaçlanmıştır. Suda çözünür türevler elde edildikten sonra, asetilkolin, histamin ve $BaCl_2$ agonistlerine karşı, «Flavoxate HCl» bileşiği referans alınmak suretiyle incelenmiştir. Aktivite testleri izole organ banyosunda kobay ileumu ile yapılmıştır. Elde edilen sonuçlar II, III ve IIIa bileşiklerinin, histamin kontraksiyonlarına karşı, «Flavoxate HCl» den daha aktif olduğunu göstermektedir.

Key Words : Spasmolytic Activity, Flavoxate HCl, % Spasmolytic Inhibition Flavone Derivatives.

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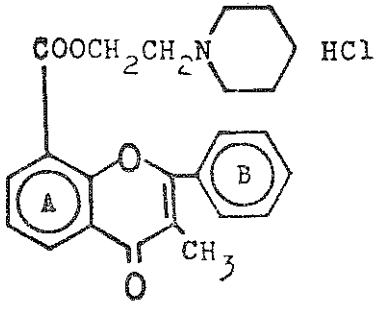
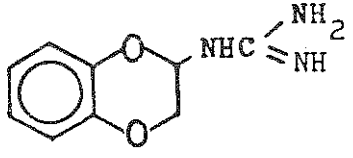
INDRODUCTION

In our previous study (1), some flavone derivatives containing ring systems of «Flavoxate HCl» and «Guanoxan», which are known as spasmolytic and α-adrenergic receptor blocker, respectively, were synthesized. Their platelet aggregation inhibitory effect was investigated, because recently it has been shown that some flavonoid derivatives possess platelet aggregation inhibitory activity (2, 3). Since the compounds synthesized were insoluble in water, their expected spasmolytic activity could not be determined. Therefore it was planned to prepare a new series of water soluble flavone derivatives with the same ring structure. So, thus eight new compounds were synthesized which have not appeared in the literature before and their chemical structures were elucidated by their spectral data (4). Moreover, platelet aggregation inhibitory effect of these compounds were investigated. This part will be published later.



Flavoxate HCl



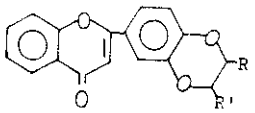
Guanoxan

MATERIAL and METHOD

Eight compounds which have been synthesized are shown in Table 1.

Baker - Venkataraman method (5) which is the general procedure for the preparation of flavones, was chosen for the synthesis of the compound. Then, benzodioxane ring system was closed by using the phenol functions of the ring B. Because the ring B, being non-symmetrical, two positional isomers were formed, and the main product, 2-ethoxycarbonyl derivative, was seperated by fractional crystallization. The ester function of the isomer mentioned above was changed to amide form using several substituted amine derivatives (4, 6). The HCl salts formed were purified by crytallisation from EtOH - Ether. The salts of

TABLE 1. The formulas of chemical compounds.



No	R	R'	Chemical Name
I	$CONHCH_2CH_2NH_2$	H	2-[2-[N-(Aminoethyl)carboxamido]-1,4-benzodioxane-6-yl]-4H-1-benzopyran-4-one
II	$CONHCH_2CH_2N(Me)_2$	H	2-[2-[N^2-(N^1,N^1-Dimethylaminoethyl)-carboxamido]-1,4-benzodioxane-6-yl]-4H-1-benzopyran-4-one
III	$CONHCH_2CH_2N(Et)_2$	H	2-[2-[N^2-(N^1,N^1-Diethylaminoethyl)-carboxamido]-1,4-benzodioxane-6-yl]-4H-1-benzopyran-4-one
IIIa	H	$CONHCH_2CH_2N(Et)_2$	2-[2-[N^2-(N^1,N^1-Diethylaminoethyl) -carboxamido]-1,4-benzodioxane-7-yl]-4H-1-benzopyran-4-one
IV	$CONH(CH_2)_3N(Et)_2$	H	2-[2-[N^3-(N^1,N^1-Diethylaminopropyl) carboxamido]-1,4-benzodioxane-6-yl]-4H-1-benzopyran-4-one
V	$CONHCH_2$-(4-pyridyl)	H	2-[2-[N-(4-Pyridinylmethyl)carboxamido]-1,4-benzodioxane-6-yl]-4H-1-benzopyran-4-one
VI	$CONHCH_2$-(3-pyridyl)	H	2-[2-[N-(3-Pyridinylmethyl)carboxamido]-1,4-benzodioxane-6-yl]-4H-1-benzopyran-4-one
VII	CON(piperazinyl)-CH_2CH_2OH	H	2-[2-[[4-(2-Hydroxyethyl)-1-piperazinyl]-carbonyl]-1,4-benzodioxane-6-yl]-4H-1-benzopyran-4-one

pyridine derivatives were not prepared, but dissolved by Eq. HCl in water.

The spasmolytic activity of water soluble flavone derivatives obtained were tested against acetylcholine, histamine and $BaCl_2$ by using Flavoxate HCl (7) as a reference. The experiments were carried out in isolated organ bath at concentrations given in Table 2. The activity tests were performed on guinea-pig ileum. Strips of the terminal ileum were obtained from guinea-pigs, weighing 400-500 g of either sex. The contractions were recorded on a kymograph.

In order to determine the percentage inhibition, first the maximum contractions with the agonists (Ach, His and $BaCl_2$) were obtained, and then, the antagonis-

TABLE 2.

Agonist / [a] Antagonist	% INHIBITION		
	Acetylcholine[b]	Histamine[c]	$BaCl_2$[d]
Flavoxate HCl	84.4[e] ± 2.26[f] (74.7-94.1)[g] (3)[h]	64.3 ±4.09 (51.3-77.3) (4)	80.5 ±8.20 (54.4-106.5) (4)
I	72.9* ± 2.12 (63.8-81.9) (3)	44.3* ±3.19 (36.1-52.5) (6)	86.4 ±3.81 (70.0-102.8) (3)
II	65.1* ± 5.38 (48.0-82.2) (4)	84.4◉ ± 3.35 (75.8-92.9) (6)	70.8 ±3.23 (56.9- 84.7) (3)
III	81.6 ± 0.75 (79.2-84.1) (4)	97.9◉ ± 0.63 (95.9-99.9) (4)	94.7 ±1.69 (90.0- 99.4) (5)
IIIa	82.7 ± 1.18 (77.6-87.8) (3)	97.1◉ ±1.09 (92.4-101.8) (3)	90.7 ±2.95 (78.0-103.4) (3)
IV	76.3 ± 2.25 (66.6-86.0) (3)	75.6 ±4.59 (63.8-87.4) (6)	75.8 ±2.19 (66.4- 85.2) (3)
V	35.7* ± 3.18 (22.0-49.4) (3)	25.4* ±1.16 (21.7-29.1) (4)	25.3* ±3.60 (9.80- 40.9) (3)
VI	43.6* ± 4.09 (26.0-61.2) (3)	21.4* ±2.73 (9.66-33.1) (3)	25.8* ±3.56 (10.5- 41.2) (3)
VII	22.9* ± 2.13 (16.1-29.7) (4)	15.4* ±2.21 (8.37-22.4) (4)	19.0* ±3.86 (2.40- 35.6) (3)

[a]Conc. against Ach and $BaCl_2$=3.27x10^{-8}mol/ml ; His=2.18x10^{-8} mol/ml : [b]Con.= 0.64 µg/ml : [c]Conc=0.1 µg/ml [d]Conc.=200 µg/ml : [e]X=aritmetic mean : [f]Standart error of the mean : [g]Confidence limits tx(S.E.M) (Tabled t value for 95 % probability and n-1 degrees of freedom : [h]No. of exp. : * $p < 0.05$: ◉more active than the reference compound : Student's t test for paired differences has been used when applicable.

tic effects of the compounds were tested. The results are shown in Table 2.

Since compound III was found the most active among the other derivatives (Table 2), compound IIIa was prepared to investigate the influence of positional isomerism on the pharmacological activity.

RESULTS and DISCUSSION :

The results are given in Table 2. The aim of this study was to compare the spasmolytic activity of the newly synthesized flavone derivatives with Flavoxate HCl (URISPAS®), which has been used as spasmolytic in some urogenital disorders. These derivatives contain a flavone nucleus, with a high spasmolytic effect, and 1,4-benzodioxane nucleus which is also found in some anti-adrenergics.

According to results obtained :

1. Antagonistic activity of the compounds II, III and IIIa against histamine were increased, due to substituted ethylenediamine side chain.
2. Compared with the percentage inhibition of Flavoxate HCl, compounds II, III and IIIa, were also found more active on histamine contractions ($p<0.05$). On the other hand, the antagonistic effects of these compounds were not found significantly different from Flavoxate HCl on acetycholine and $BaCl_2$ contractions.
3. It was also observed that there was no difference in pharmacological activity between the positional isomers III and IIIa, on the contractions of all the agonists.
4. Since it was found that compound III and IIIa were more active than the reference compound, these derivatives may be considered worthy of further pharmacological tests

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