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Preliminary Studies on a New Group of Imidazole Derivatives with Anticonvulsant Activity

Antikonvülzan Aktivite Gösteren İmidazol Türevi Yeni Bir Grup Madde ile Yapılan Ön Çalışmalar

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SUMMARY

In a preliminary study, the anticonvulsant profiles of three compounds having the basic structures w-(l H-l-imidazolyl)-N-(p-substituted phenyl) acetamide, propionamide and butiramide with methyl substituents on the para position of benzene ring have been evaluated in mice in comparison with the standart antiepileptic drug, phenobarbital. The anticonvulsant activities of these compounds against maximal electroshock induced seizures were comparable to or less than that of phenobarbital. Further studies on the anticonvulsant activities and the toxicological characteristics of these compounds are now in progress in our department.

ÖZET

Benzen halkasının para pozisyonunda metil sübstitüentleri taşıyan w-(lH-l-imidazolil)-N-(p-sübstitüefenil) asetamid, propioamid ve bütiramid yapısındaki üç bileşiğin antikonvülzan aktiviteleri standart antiepileptik bir ilaç olarak seçilen fenobarbitalle karşılaştırmalı olarak bir ön çalışma halinde araştırılmıştır. Antikonvülzan aktivitenin araştırılmasında maksimal elektroşok testi kullanılmış ve elektroşokla oluşturulan konvülziyonlara karşı sentezlenen bileşiklerin fe-

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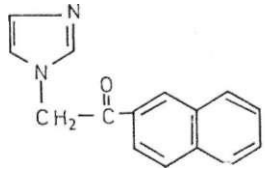
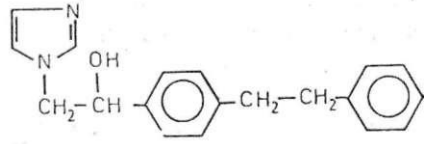
nobarbitalle karşılaştırılabilir düzeyde antikonvülzan aktivite gösterdikleri belirlenmiştir. Sözkonusu bu bileşiklerin antikonvülzan aktiviteleri ve toksikolojik özellikleri ile ilgili daha ileri araştırmalar laboratuvarlanmızda sürdürülmektedir.

Key Words: 2-(1H-1-imidazolyl)-N-(p-tolyl) acetamide, 3-(1H-1-imidazolyl)-N-(p-tolyı) propionamide, 4-(1H-1-imidazolyl)-N- (p-tolyl) butiramide, anticonvulsant activity

Several antiepileptic drugs are present for the treatment of convulsive diseases but in spite of this, many patients suffer from both the inadequate control of seizures and the toxic side effects of anticonvulsant drugs (1-4). The research for new antiepileptic drugs with more selective anticonvulsant effects and /or lower toxicity is therefore essential. In this study, the synthesis of a new group of compounds were accomplished(5) and their anticonvulsant activities have been investigated. The aim of our study is to develope new antiepileptic compounds with more selective anticonvulsant activities and less toxic side effects. The new drugs NMI and denzimol, which had been previously selected for advanced clinical studies for their potent anticonvulsant activities against maximal electroshock seizures (MES) have been chosen as our model compounds (Figure 1), for synthesis (6,7).



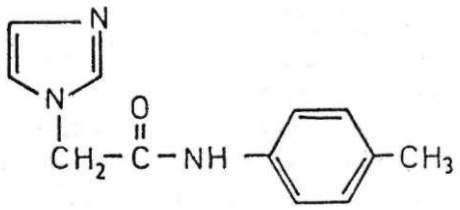
NMI



DENZİMOL

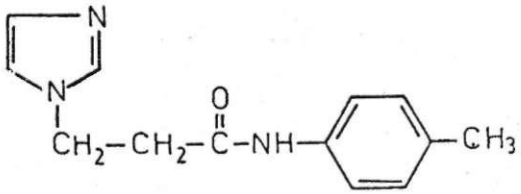
Figüre 1

2-(1H-1-imidazolyl)-N-(p-tolyi) acetamide (Compound I), 3-(1H-1-imidazolyl)-N-(p-tolyl) propionamide (Compound II) and 4-(1H-1-imidazolyl)-N-(p-tolyl) butiramide (Compound III) were synthesized in our laboratories. In this preliminary study the anticonvulsant activity of these compounds were evaluated and compared with phenobarbital (Figure 2).



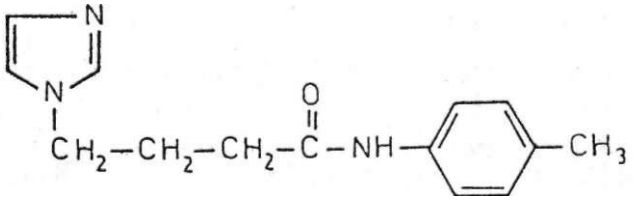
2-(1H-1-**imidazolyl)-N-(p-tolyt) acetamide**

(Compound I)



3_(1H-1-imidazolyl)-**N**-(p-tolyOpropionamide

(Compound II)



4-(1H-1-**imidazolyl)-N-(p-tolyl)**butiramide

(Compound III)

Figüre 2

EXPERIMENTAL

Materials:

Male albino mice of 20-25 g were used. The animals were housed in colony cages having free access to food and water and were maintained with natural lightdark cycle at room temperature. Experimental groups were chosen by means of a completely randomized schedule and tests were conducted between 8.30 and 13.00 a.m.. Phenobarbital-Na was obtained from commercial source (Sigma) and hydrochloride salts of Compound I, Compound II and Compound III were synthesized in our laboratory. All drugs were dissolved in physiological saline and the doses are quaoted in terms of the hydrochloride salts.

Methods:

Maximal Electroschock Seizure Assay (MES):

The anticonvulsant activity was evaluated using the method of Graziani, G. et al(7) which is a modified method of Swinyard et al(8). in groups of 8 mice for each dose level. The animals were subjected to 60 Hz alternating current of 25 m A delivered 0.2 sec. via corneal electrodes. The pretreatment time was 30 minutes following i.p. administration. The abolition of tonic extansor sezizures indicated proctecting activity. Median effective dose (ED 50 %) which prevented seizures in 50 % of animals, was calculated.

Effects On Motor Movements:

Male albino mice were trained to do coordinated motor movements continuously for 10 minutes on a rotarod, 3 cm in diameter - 2.3 rpm (7). Impairment of the coordinated motor movements was defined as inability of the animals to retain on the rotarod for a 5 minutes test period. Rotarod performance was tested after 30 minutes following i.p. administration in mice.

Statistical Analyses:

Median effective doses, i.e. ED 50% values of each drug and their 95 % confidence limits were calculated by the method of Litchfield and Wilcoxon(9).

RESULTS AND DISCUSSION

The results reported in Table 1 clearly indicate that Compound 1, Compound II and compound III administered i.p. in mice, exerted a protective action against maximal electroshock seizures, but the standart drug phenobarbital was the most potent compound (ED 50 =9.69 mg/kg). After i.p. administration, Compound I (ED 50 = 15.62 mg/kg) was the most potent among the three compounds under trial. Compound II (ED 50 = 30.72 mg /kg) and Compound III (ED 50 = 30.84 mg/kg) were equally active against maximal electroschock seizures.

Table 1

Compound number	Anticonvulsant activity (MES) of the compounds and standart drug phenobarbital in mice after i.p. administration (ED 50 in mg /kg and 95 % confidence limits)
I	15.62 (14.29 - 17.06)
II	30.72 (23.81 - 39.63)
III	30.84 (18.01 - 52.78)
Phenobarbital	9.69 (6.73 - 13.95)

Although median neurotoxic dose (NTD 50%), the dose which made 50 % of animals fall from the rotarod were not determined, at the tested i.p. doses of Compound I, Compound II and Compound III for the anticonvulsant activity, no difference at the motor movements were observed.

Previous studies proved that the presence of a small oxygen-containing substituent in the alkylene bridge, particularly carbonyl, hydroxy, methoxy or ethylenedioxy, associates to the anticonvulsant properties of the imidazole-containing anticonvulsant agents(10) and branching or lengthening of the aliphatic chain between imidazole and aryl moieties in some derivatives exerts no important effect on the anticonvulsant activity(ll). On the other hand it is known that some of the anticonvulsant drugs in use contain amid structures with acid characteristics. On the basis of this general knowledge and findings we selected NM1 and denzimol as model compounds for our study. These compounds which were imidazole derivatives containing different functional groups in the alkylene bridge, showed anticonvul-

sive activity. Our synthesis program was initiated by keeping in mind the following three points:

1. Increasing the acidity of the compound by substituting a phenyl ring to the amide hydrogen,

2. Substituting a methyl group to the para position of the phenyl ring to modify the interaction of the phenyl ring with the macromolecules of the organism,

3. Lengthening the aliphatic chain between the imidazole and amide function (up to 3 carbons) to determine possible changes at the anticonvulsant activity.

The three compounds thus synthesized with w-(1H-1-imidazolyl-N-(p-substituted phenyl) basic structure displayed anticonvulsant activity against electroshock induced seizures. The anticonvulsant activity of Compound I was comparable to phénobarbital. Compounds II and III were also active but their activities were less than the anticonvulsant effect of phenobarbital. This result is in consistance with the findings of Niardi et al(10) for N-(p-tolyl) derivatives as well.

Although the definite value of a compound can be assessed only by clinical trials, further studies on the anticonvulsant activities and toxic properties of these compounds are in progress with the aim of developing a compound with an enhanced therapeutic index.

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