التخليق والتقييم الفارماكولوجي الأولي لبعض مشتقات الترايزول

سلسل كمال عبد الرحمن
كلية بغداد للصيدله –باب المعظم

الخلاصة

اعتمادا على نتائج المعلومات السابقة التي تم الحصول عليها من الدراسة النظرية للأدوية التي لها فعالية بيتا – ادرينيرجيه حضرت سلسله من مشتقات 2–بروبانول امين تحتوي على حلقة ترايازول وتم تقييم فعالية وتأثير هذه المشتقات في أوعية القلب . وهذه المركبات اختبرت على ادينات القلب النابضة المأخوذه من الجرذان البيضاء .

Synthesis and Preliminary Pharmacological Evaluation of Some New Triazole Derivatives

S . K Abdul-Rahmann

Baghdad college of pharmacy —Baghdad- bab almoadam

Abstract

On the basis of the results which was previously obtained from the structural and the theoretical studies on ~-adrenergic drugs, a series of 2-propanolamine derivatives containing triazole moiety have been prepared and evaluated for their cardiovascular activity . These derivatives were tested by using spontaneously-beating right atria of albino rats.

Introduction

1,2,4 —Triazole is one of a class of organic heterocyclic compounds containing a five member di-unsaturated ring structure composed of three nitrogen atoms and two ton odjacent carbon atoms.

The 1,2,4- Triazole derivatives are known in the specific literature for their wide pharmacological activity (5,7). Main types of their activity are antibacterial and antifungal activities (4, 8 & 11). Which led to an intensive research on their synthesis

The incentive for the present work was thus devoted to the synthesis of certain arylthiopropanolamine series.

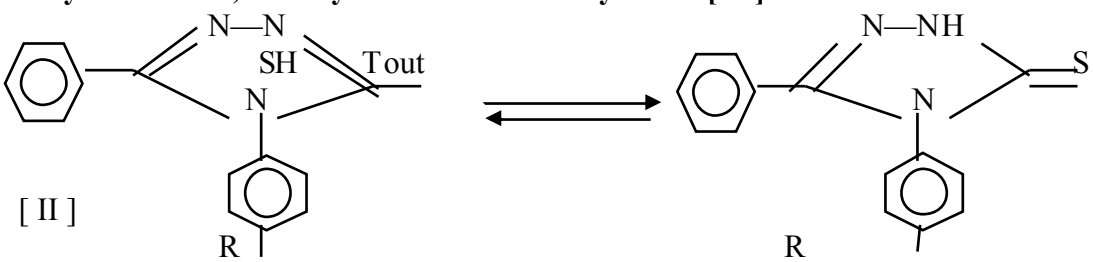
4,5-Diaryls-1,2,4-triazole [II] was synthesized by the oxidative cyclization of appropriate 1-substituted-4-arylthiosemicarbozide [1] ,, scheme (1) .

A series of 2-propanolamine derivatives containing triazole moiety [III – IX] have been prepared ,, table (1), investigated and evaluated for their cardiovascular activity in rats, table (2)inorder to study their effect on blood pressure and heart rate . The basic requirement to have cardiovascular and β -adrenergic blocking effect in the propanolamine moiety besides the aromatic moiety is attached by the ethereal linkage as it has previously shown in literature (1-5 & 8,9).

Experimental

Chemical part

Synthesis of 4, 5-diaryls-1. 2. 4-triazole-3yl-thiol [II]



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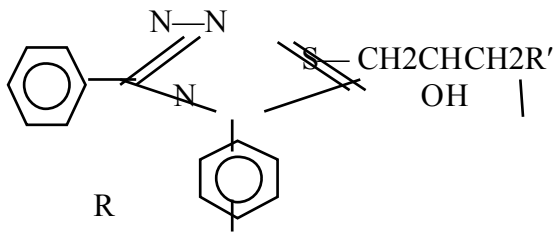
A mixture of 1-substituted-4-arylthiosemicarbazide [I], 8% sodium hydroxide in ethanol was heated under reflex for 5hr. After concentration and cooling the solution was filtered and neutralized with 10% acetic acid solution (8) The solid.product that formed was filtered and recrystallized from ethanol.

Synthesis of 1,2,4-triazole derivatives [III – IX]



[III—IX]

General procedure

A mixture of 4,5-diaryls-1,2,4-triazol-3y1-thiol [II], potassium hydroxide (1mM) in 80% ethanol (10 ml) andN-3 (chloro-2-hydroxypropyl) substituted amine (1mM) with a continuous stirring and was left for 24hr at room temperature. The residual solution was concentrated in vacuo and the product was precipitated by agradual addition of water. The precipitate was filtered, washed with water, dried and recrystallized from methanol/water .Table (1) showed the physical properties of the products.

Pharmacological part:

(a) **Animals being used**

In these experiments adult albino rats of either sex [300—400 gm] were used. The animals were housed as apair in a cage in an environmentally controlled room at 21-23^{o}C temperature, with lighting on from 6 a.m. to 5p.m.

They were fed adlibitum , a local pelleted diet containing by dry weight 56% carbohydrate , 20% protein , 5% fat & 10% of salt, vitamins & cellulose .

(b) **Spontaneously-beating right atria.**

Rats were stunned & hearts were quickly removed . Right atria were dissected out & were suspended in a 20 ml, double jacketed organ bath containing krebs physiological solution of the following composition [gm/I]: NaC1 5.5, KCI 0.35 , $MgSO_4$, 7 H_20 0.11 ,$CaCL_2$ 0.14, KH_2P0_4 0.16 ,$NaHCO_3$ 2.10 , glucose 2.0 , PH 7.4 maintained at 37^{0}C±1 ^{0}C & continuously bubbled with a stream of 5% CO_2-95% O_2 mixture.

Initial tension [Resting tension] of 1.0gm was applied, the tissue was allowed to equilibrate for a period of 45-60 min .and during this time, the bathing fluid was changed every 15 min(9), spontaneous contractions of the right atria were isometrically recorded by using a force transducer [UFI], , coupled to lectromed recorder physiographe. The results were registered at least 3 in 6 different experiments & in different preparations.

Results and Discussion

Triazoles play an important role among the heterocyclic compounds. By keeping this in view, it was considered desirable to synthesis the title compound with the hope that the inner in corporation of l,2,4-triazole ring might enhance the biological activity of the original synthesized compound .

4,5-diaryls-l,2,4-triazole [II] was obtained by the oxidative cyclization appropriate l-substitited-4-

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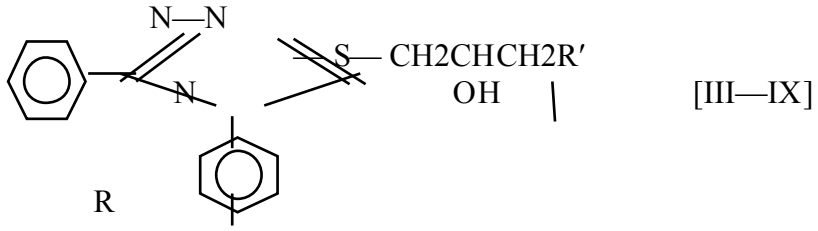
The new 1.2. 4-triazole derivative [III – IX]



[III—IX]

They were synthesized by stirring aqueous methanolic solution 80% (10m1) with 4,5-diaryle-1,2,4-triazole[II] and N-(3-chloro-2-hydroxypropyl) substituted amine (1 mM) for 24hr at room temperature .The product was recrystallized from methanol/water.
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Pharmacological results:

Experiments were carried .Several & different concentrations of compounds [III—IX] were tested on the spontaneous contractions of the right atria of albino rats to detect their behavior & to determine the median effective dose of each compound . Compounds with concentration 1 mg/ml showed anegative inotropic effect on the right atria except compounds [IV & VIII] which needed more concentration to produce asimilar activity. The increasing of the concentrate in organ bath of these experiments showed calcium antagonistic activity. The median effective dose of compounds[III-- IX] on the spontaneous contractions of the right atria of albino rats,is shown in table (2)
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Reference

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Table 2

Compound	Median effective dose ED_{50}
III	2mg / ml ($5.4x10^{-3}$ M)
IV	1mg / ml ($2.7x10^{-3}$M)
V	1mg / ml ($2.6x10^{-3}$ M)
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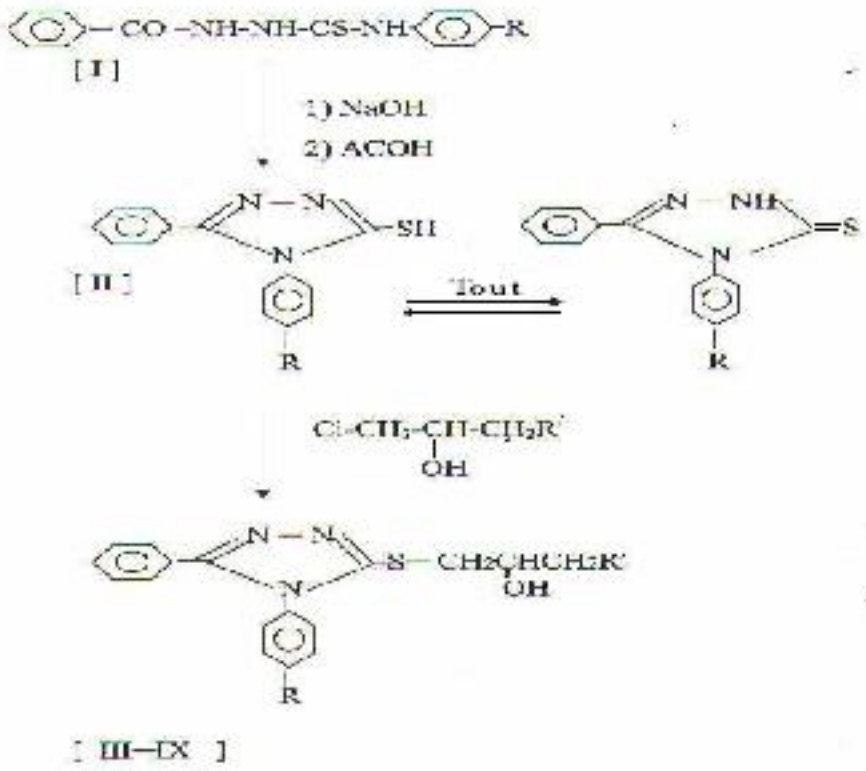

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Scheme (1)

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مجلة ابن الهيثم للعلوم الصرفة والتطبيقية المجلد22 (3) 2009

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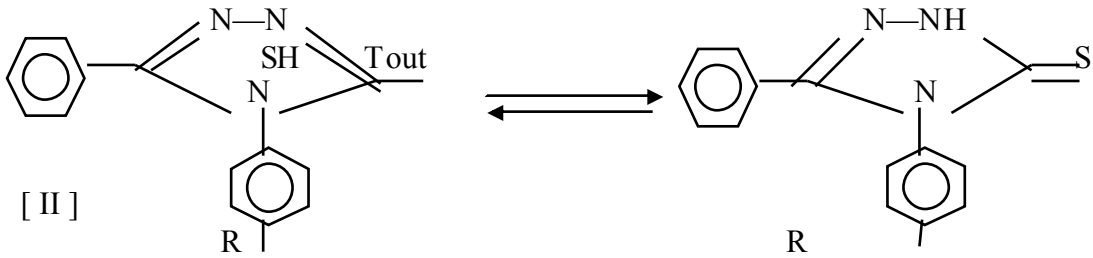

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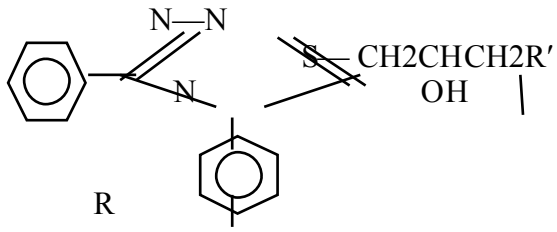

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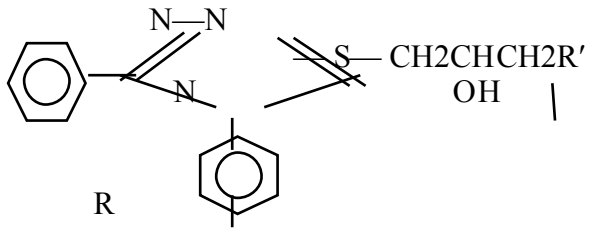

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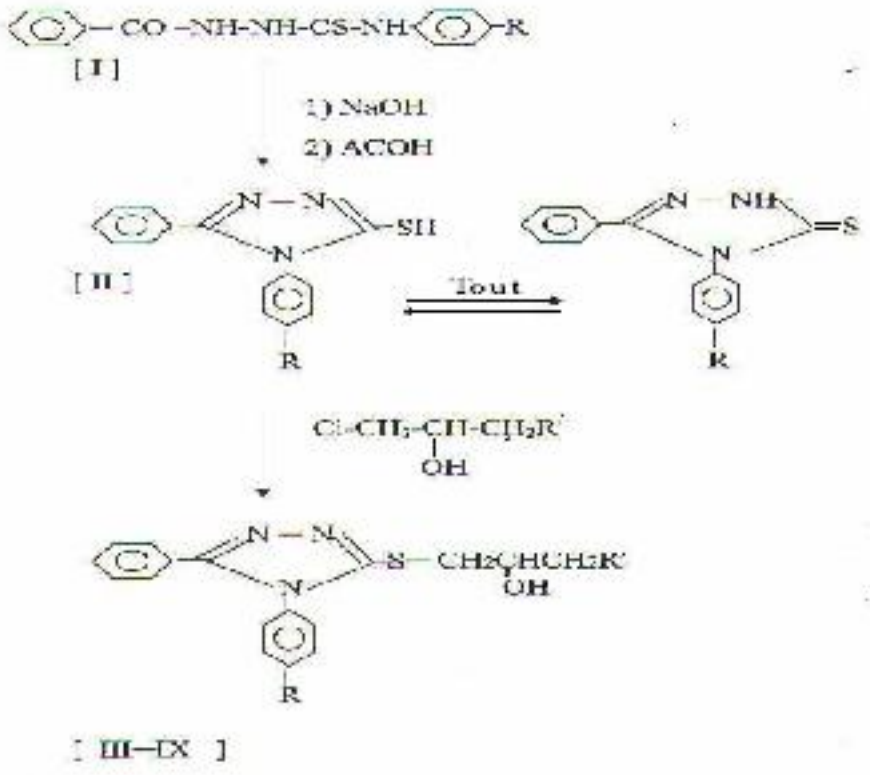

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