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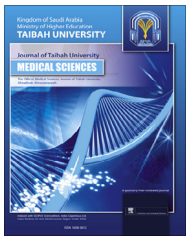

Experimental Study

New fluorinated quinazolinone derivatives as anticonvulsant agents

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الملخص

أهداف البحث: تتناول هذه الدراسة تحضير بعض مركبات الفلورو كوينازولينون الجديدة لاختبارها كمضادات للصرع مع اختبار سميتها العصبية.

طرق البحث: تم اختبار المركبات كمضادات للصرع عن طريق اختبار الصدمة الكهربائية القصوى وذلك باستخدام عشرة مجموعات من الفئران السويسرية تحتوى كل مجموعة على ستة فئران، ثمانية منهم لاختبار المركبات بتركيز مائة ملجرام لكل كيلوجرام، ومجموعة أخرى للمركب المعار (فنيتوين بتركيز مائة ملجرام لكل كيلوجرام)، ومجموعة أخرى محكمة 10 مل (محلول دمسو 10% لكل كيلوجرام). بينما تم اختبار السمية العصبية عن طريق اختبار الاتزان الدائري في الفئران السويدية باستخدام عشرة مجموعات من الفئران تحتوى كل مجموعة على أربعة فئران ثمانية منهم لاختبار المركبات بتركيز مائة ملجرام لكل كيلوجرام، ومجموعة أخرى للمركب المعار (فنيتوين بتركيز مائة ملجرام لكل كيلوجرام)، ومجموعة أخرى محكمة (10مل محلول ملح لكل كيلوجرام) وكمحاولة لإيضاح النتائج التي تم الحصول عليها، قمنا بدراسة العلاقة بن التركيب الكيميائي والنشاط الحيوي للمركبات كما قمنا بدراسة بعض الخصائص المفسرة لها.

النتائج: معظم هذه المركبات أعطت نتائج جيدة كمضادات للصرع مع مستوى أقل من السمية العصبية.

الاستنتاجات: هذه النوعية من المركبات الجديدة تصلح أن تكون نواة مستقبلية لإعداد أدوية جديدة كمضادات للصرع، أكثر نشاطا وأقل سمية عصبية.

الكلمات المفتاحية: كوينازولينون; مضاداتللصرع; الأمينات; السمية العصبية; فلورو; تصنيع

Abstract

Objectives: The aim of the present work was to synthesize some novel fluorinated quinazolinones and to evaluate them for anticonvulsant activity and neurotoxicity.

Methods: Eight compounds were synthesized. Their anticonvulsant activity was evaluated from maximal electroshock-induced seizures in eight groups of six Swiss mice given the test compounds (100 mg/kg intraperitoneally), one control group given 10% DMSO (10 ml/kg) and one given the reference compound phenytoin (100 mg/kg). Neurotoxicity was evaluated by the rotarod test in eight groups of four Swiss mice given the test compounds (100 mg/kg), one given saline (10 ml/kg) and one given phenytoin (100 mg/kg). The structure–activity relations of the compounds and ClogP correlations were determined to explain the results.

Results: Four compounds showed significant anticonvulsant activity with low neurotoxicity when compared with the reference drug.

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Conclusion: The newly designed compounds could be useful templates for the design and optimization of more active analogues as anticonvulsant agents with low neurotoxicity.

Keywords: Anticonvulsant; Amines; Fluoro; Neurotoxicity; Synthesis; Quinazolinone

Introduction

"Epilepsy" is in fact several disorders characterized by neuronal hyperexcitability and neuronal firing. It affects up to 1% of the world's population.[1] The anticonvulsants used to treat this condition are known as antiepileptic drugs[2] and are among the most widely used drugs for the treatment of central nervous system disorders.[3] Many effective antiepileptic drugs are available on the market[4] and include phenobarbital, phenytoin, carbamazepine and valproic acid.[5] About 70% of people with epilepsy achieve some improvement, with satisfactory seizure control, with the available antiepileptic drugs.[6] As these drugs have many side-effects, like drowsiness, ataxia, gastrointestinal disturbances, megaloblasticanaemia and hirsutism,[7,8] however, it is essential to find other chemical entities for the treatment of epilepsy with less toxicity and fewer side-effects.

We previously reported that some heterocyclic derivatives could be used as anticonvulsant agents.[9,10] Some of these derivatives include a quinazolinone ring system,[11–13] which is an important scaffold embedded in a variety of medicinal agents.[12] Quinazolinones have various biological activities, including anticonvulsant,[11] antibacterial,[12] psychosedative,[13] anticancer[14] and antihypertensive activities.[15] Quinazolinone derivatives have therefore been widely used in the production of various drugs.[11–15] In view of the wide applications of the quinazolinone molecule in medicinal chemistry, we synthesized a number of substituted amine derivatives with a fluorinated quinazolinone moiety as antiepileptic agents.

In our previous studies,[11] we reported that some derivatives of 6,8-diiodo-2-methyl-3-substitutedquinazolin-4(3H)-ones had good anticonvulsant activities (Figure 1). These derivatives were hybrid molecules that included diiodoquinazolinone as a fixed moiety with different substituted amines. Iodine atoms at positions 6 and 8 of the quinazolinone moiety have larger atomic size, atomic radius, atomic covalent bond and van der Waal radius than other halogens such as fluorine.[14] The large size of iodine atoms could cause repulsive, hydrophobic interactions, which would negatively affect the binding of iodinated derivatives to their biological target.[15] Fluorine atoms are, however, more reactive than iodine because they are much smaller and hence react easily, and they are more electronegative. Furthermore, some iodinated compounds have been reported to have idiosyncratic side-effects.[12,16] We therefore decided to synthesize some novel fluorinated quinazolinone with the same structure as our previously reported compounds but replacing iodine by fluorine at position 6 of the quinazolinone moiety. Figure 1 shows the structural similarities and the atomic size variation between iodine and fluorine atoms in the previously reported diiodoquinazolinone compounds and the newly synthesized derivatives. The present study is thus a continuation of our attempt to find new, safe, and effective antiepileptic agents.

In order for antiepileptics to be effective, they must cross the blood–brain barrier.[11] Highly lipophilic substances can permeate the brain interstitium relatively easily.[15] Determination of brain–blood partitioning in vitro is difficult, time-consuming, expensive, not always available and not suitable for screening a large number of new chemicals.[11] We therefore used an alternative method based on computerized models to

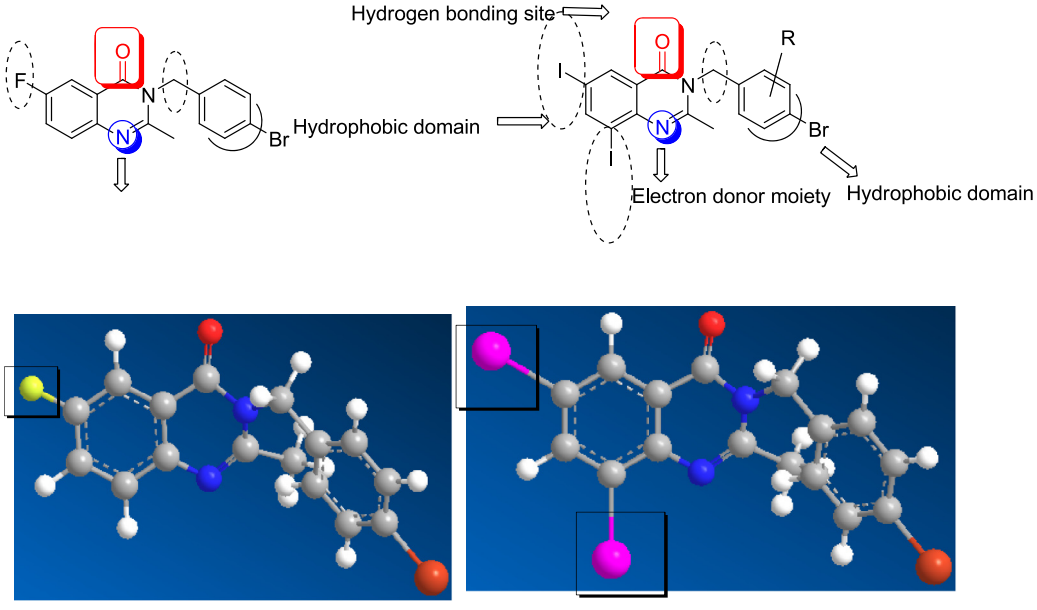

Figure 1: Structural similarities, pharmacophoric features and atomic size variation between iodine and fluorine atoms. The right side compound contains diiod atoms represented by pink color while the left side compound contains fluro atom represented by yellow color on the quinazolinone moiety.