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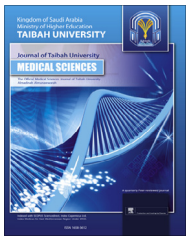

Experimental Study

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

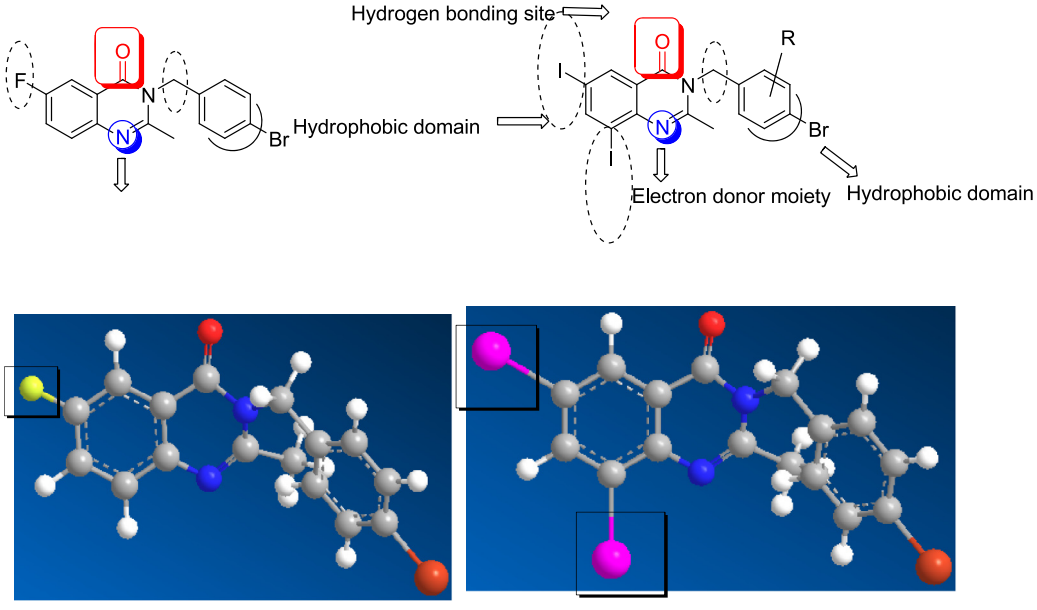


Figure 1: Structural similarities, pharmacophoric features and atomic size variation between iodine and fluorine atoms. The right side compound contains diiod atoms represented by pink color while the left side compound contains fluro atom represented by yellow color on the quinazolinone moiety.

calculate the ClogP values of the newly synthesized compounds to reflect their overall lipophilicity.

Materials and Methods

Synthesis

The strategy used to synthesize the compounds is shown in Scheme 1. It comprises two simple reactions. Acetylation or benzoylation followed by ring closure produced 2-amino-5-fluoroobenzoic acid (1). This compound was refluxed with acetic anhydride for 1 h and converted to benzoxazinone (2), which afforded a quantitative yield of 6-fluoro-2-methyl-4*H*-benzo[*d*][1,3]oxazin-4-one (2). The second reaction is nucleophilic displacement of the oxygen of benzoxazinone with the nitrogen of the amino group upon treatment with amine derivatives, performed by refluxing compound (2) with the appropriate amine under dry conditions for 6 h to give amine derivatives of 6-fluoro-2-methyl-quinazolinone (4–11) in variable yields of 60–71%. The reacted amines were selected by a manual method of the Hansch approach to drug design suggested by Topliss.[16] In this procedure, an initial small group of compounds is selected, tested and ordered according to potency. The compounds were designed to contain unsubstituted, monosubstituted and disubstituted aromatic rings with different types of halogen and other hydrophobic and hydrophilic groups of either electronic-rich or electronic-deficient groups in order to study the structure–activity relations of these compounds and to compare their anticonvulsant activity.

Chemistry

The compounds were analyzed at the Analytical Center, College of Science, Cairo University, Egypt. Melting-points were measured on a Griffin apparatus and are uncorrected. The ^{1}H NMR spectra were run with TMS as the internal standard (Sigma–Aldrich) on a Varian Mercury VXr-300 NMR spectroscope. Mass spectra were obtained on a JEOL-SX-102 instrument by electron impact ionization. Elemental analyses (C, H, N) were performed on a Perkin-Elmer 240C analyser. All values were within ±0.4% of the theoretical values. All chemicals used for synthesis were purchased from Sigma–Aldrich.

Experimental

6-Fluoro-2-methyl-4H-benzo[d][1,3]oxazin-4-one (2)

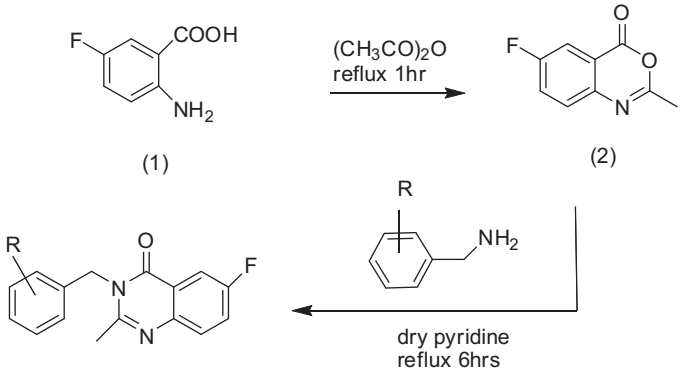
Compound (2) was prepared by refluxing 1.55 g (0.01 mol) of 2-amino-5-fluorobenzoic acid (1) with an appropriate amount of acetic anhydride for 1 h. The residue obtained was evaporated to complete dryness, left to cool, washed many times with petroleum ether, collected, filtered and dried in the absence of moisture. The yield was 88%; melting-point, 123–125 °C; ^{1}H NMR (DMSO-d_6), δ 1.51(s, 3H, CH_3) 7.22–7.98 (m, 3H, Ar–H). Calculated analysis for $C_9H_6FNO_2$ (179.04): C, 60.34; H, 3.38; N, 7.82. Found: C, 26.32; H, 1.01; N, 3.74. MS (EI) *m*/*z*: 179 [M].

General method for preparation of test compounds (4–11)

Compounds (4–11) were prepared by mixing 1.79 g (0.01 mol) of compound (2) with 0.01 mol of amine derivatives in 100 ml dry pyridine, refluxing for 6 h, cooling, treatment with a small amount of 10% hydrochloric acid and pouring onto crushed ice. The crystals obtained were collected by filtration and recrystallized from ethanol or glacial acetic acid.

3-Benzyl-6-fluoro-2-methylquinazolin-4(3H)-one (4)

Yield, 71%; melting-point, 285–287 °C; ^{1}H NMR (DMSO-d_6), δ 2.54 (s, 3H, CH_3), 5.41 (s, 2H, CH_2), 7.12–8.17 (m, 8H,



(3)

4) R = H
5) R = 4Cl
6) R = 4F
7) R = 4I
8) R = 4Br
9) R = $3NO_2$
10) R = $4OCH_3$
11) R = $3,5Cl_2$

Scheme 1: Synthesis of the target compounds (4–11).

Ar–H). Calculated analysis for $C_{16}H_{13}FN_2O$ (268.1): C, 71.63.27; H, 4.88; N, 10.44. Found: C, 71.81; H, 4.68; N, 10.63. MS (EI) *m/z* 269.1 [M + 1].

3-(4-Chlorobenzyl)-6-fluoro-2-methylquinazolin-4(3H)-one (5)

Yield, 69%; melting-point, 320–322 °C; ^{1}H NMR (DMSO-d_6), δ 2.61 (s, 3H, CH_3), 5.59 (s, 2H, CH_2), 7.01–8.23 (m, 7H, Ar–H). Calculated analysis for $C_{16}H_{12}ClFN_2O$ (302.06): C, 63.48; H, 4.00; N, 9.25. Found: C, 63.61; H, 3.91; N, 9.41. MS (EI) *m/z* 302.06 [M].

3-(4-Fluorobenzyl)-6-fluoro-2-methylquinazolin-4(3H)-one (6)

Yield, 67%; melting-point, 292–294 °C; ^{1}H NMR (DMSO-d_6), δ 2.63 (s, 3H, CH_3), 5.57 (s, 2H, CH_2), 7.13–8.43 (m, 7H, Ar–H). Calculated analysis for $C_{16}H_{12}F_2N_2O$ (286.09): C, 67.13; H, 4.23; N, 9.79. Found: C, 67.31; H, 4.37; N, 9.84. MS (EI) *m/z* 287.09 [M + 1].

3-(4-Iodobenzyl)-6-fluoro-2-methylquinazolin-4(3H)-one (7)

Yield, 65%; melting-point, 350–352 °C; ^{1}H NMR (DMSO-d_6), δ 2.58 (s, 3H, CH_3), 5.72 (s, 2H, CH_2), 7.18–8.13 (m, 7H, Ar–H). Calculated analysis for $C_{16}H_{12}FIN_2O$ (394): C, 48.75; H, 3.07; N, 7.11. Found: C, 48.92; H, 3.23; N, 7.37. MS (EI) *m/z* 394 [M].

3-(4-Bromobenzyl)-6-fluoro-2-methylquinazolin-4(3H)-one (8)

Yield, 64%, melting-point, 352–354 °C; ^{1}H NMR (DMSO-d_6), δ 2.56 (s, 3H, CH_3), 5.86 (s, 2H, CH_2), 7.01–8.13 (m, 7H, Ar–H). Calculated analysis for $C_{16}H_{12}BrFN_2O$ (346.01): C, 55.35; H, 3.48; N, 8.07. Found: C, 55.56; H, 3.61; N, 8.14. MS (EI) *m/z* 346.01 [M].

3-(3-Nitrobenzyl)quinazolin-6-fluoro-2-methyl-4(3H)-one (9)

Yield, 60%; melting-point, 342–344 °C; ^{1}H NMR (DMSO-d_6), δ 2.66 (s, 3H, CH3), 5.52 (s, 2H, CH_2), 7.24–8.11 (m, 7H, Ar–H). Calculated analysis for $C_{16}H_{12}FN_3O_3$ (313.09): C, 61.34; H, 3.86; N, 13.41. Found: C, 61.41; H, 3.94; N, 13.59. MS (EI) *m/z* 313.09 [M].

3-(4-Methoxybenzyl)-6-fluoro-2-methylquinazolin-4(3H)-one (10)

Yield, 66%; melting-point, 324–326 °C; ^{1}H NMR (DMSO-d_6), δ 2.62 (s, 3H, CH_3), 3.48 (s, 3H, OCH_3), 5.62 (s, 2H, CH_2), 7.13–8.33 (m, 7H, Ar–H). Calculated analysis for $C_{17}H_{15}FN_2O_2$ (298.11): C, 68.45; H, 5.07; N, 9.39. Found: C, 68.21; H, 5.23; N, 9.42. MS (EI) *m/z* 298.11 [M].

3-(3,5-Dichlorobenzyl)-6-fluoro-2-methylquinazolin-4(3H)-one (11)

Yield, 60%; melting-point, 360–362 °C; ^{1}H NMR (DMSO-d_6), δ 2.54 (s, 3H, CH_3), 5.72 (s, 2H, CH_2), 7.03–8.21 (m, 6H, Ar–H). Calculated analysis for $C_{16}H_{11}Cl_2FN_2O$ (336.02): C, 56.99; H, 3.29; N, 8.31. Found: C, 57.07; H, 3.42; N, 8.19. MS (EI) *m/z* 336.02 [M].

Animals

Swiss mice of both sexes, 8–10 weeks old and weighing about 25–30 g were procured from the Animal House, College of Pharmacy, King Abdulaziz University, Saudi Arabia, and were maintained in polypropylene cages (six animals per cage) at 25 ± 2 °C, relative humidity of 45–55%, under 12 h light and dark cycles. They were fed standard animal feed and acclimatized for 1 week before use. The protocol was approved by the institutional animal ethics committee (Approval No: 3006/434), and all experiments were carried out according to internationally valid guidelines.

Biological screening

The newly synthesized compounds (4–11) were screened to evaluate their anticonvulsant activity and their neurotoxicity. Preliminary screening was performed with 100 mg/kg of each compound given intraperitoneally after electrical induction of convulsions with maximal electroshocks (MES).[11] The MES model has been used to identify anticonvulsants that are functionally similar to phenytoin, and activity in this model appears to be highly predictive of the ability to protect against generalized tonic–clonic seizures. The anticonvulsant activity of the newly synthesized compounds was compared to that of phenytoin as the reference drug at the same dose, 100 mg/kg. Neurological toxicity was determined in the rotarod test as described elsewhere.[17]

Anticonvulsant activity

To determine anticonvulsant activity, the animals were divided randomly into 10 groups of six animals. One group served as the vehicle control group and received 10% DMSO solution (10 ml/kg) 30 min before seizure induction; eight groups received the test compounds dissolved in 10% DMSO; and a reference group received phenytoin (100 mg/kg). The electrical stimulus produced from the electroconvulsiometer was 150 mA. Current was applied for 0.2 s via auricular electrodes. Protection against the spread of MES-induced seizures was identified by abolition of the hind leg and tonic maximal extension component of the seizure.[18] Seizures, tonic–clonic convulsions, hypnosis and death were recorded.

Neurological toxicity

Neurotoxicity was determined by the rotarod test in mice by the method of Dunham and Miya.[17] Briefly, 10 groups of four animals were trained to balance on a rotating rod (3 cm diameter and 6 rpm speed) and allowed three attempts to remain on the rod for 20 s. Eight groups of trained animals were treated with the test compounds, a positive control group was treated with phenytoin, and a negative control group was treated with saline (10 ml/kg). The test compounds were considered to be neurotoxic at a particular dose if the trained animal showed lack of rolling roller performance. The animals were tested in this manner 30 min and 4 h after drug administration, and the neurotoxic effect was recorded and compared with that of the control group treated with saline.

Statistical analysis

Data obtained are expressed as means. Statistical differences between treated and control groups in screening for anticonvulsant

Table 1: Anticonvulsant activity of the target compounds in the maximal electroshock seizure test.

Compound ID	%Protection	ClogP
10% DMSO (control)	0	–
4	50.16	3.07035
5	71.98[c]	3.78335
6	70.34[b]	3.21335
7	69.48[b]	4.19335
8	73.07	3.93335
9	53.91[c]	2.81335
10	25.51[b]	2.98935
11	30.08	4.49636
Phenytoin (standard)	78.12	2.085

Values are expressed as means, $n = 6$ animals in each group. [b]$p < 0.05$, [c]$p < 0.01$ when compared to control.

Table 2: Neurotoxicity screening of the target compounds.

Compound ID	2 h	4 h
Normal saline (control)	0/4	0/4
4	0/4	0/4
5	0/4	0/4
6	0/4	0/4
7	1/4*	1/4*
8	0/4	0/4
9	0/4	1/4*
10	0/4	1/4*
11	1/4*	1/4*
Phenytoin (standard)	0/4	0/4

Statistical significance test for comparison of test with control was done using the "Chi-square test". *$p < 0.05$, $n = 4$.

activity were evaluated by one-way analysis of variance (ANOVA), followed by Tukey's test (Sigma Stat version 3; SPSS Inc.). Neurotoxicity was analyzed with the chi-squared test. A p value < 0.05 was considered statistically significant.

Results

Compounds 4–11 were synthesized according to the reaction sequence illustrated in Scheme 1. The structures of the compounds were deduced from ^{1}H NMR, IR and mass spectra and their composition by elemental analysis. The chemical shift and multiplicity patterns correlated well with the proposed structures, and the elemental analysis showed good agreement between experimentally determined and theoretically calculated values.

Screening of compounds 4–11 for anticonvulsant activity showed that compounds 5–8 had significant activity against MES-induced seizures (Table 1), indicating the ability of these compounds to prevent seizure spread. Compounds 4, 9 and 11 showed medium activity, and compound 10 had the least activity. The most active compounds were 5–8, which gave 69.5–73.1% protection, compound 8 conferring 73% protection. Compound 4 reduced the MES effect by 50%, while compounds 4, 9 and 11 gave 30.1–53.9% protection.

No neurotoxicity was seen with the test compounds at 0.5 and 1 h. Compounds with 4-iodo and 3,5-dichlorosubstituents showed 25% more neurotoxicity than the standard 2 h after administration (Table 2), and compounds 7, 9, 10 and 11 showed 25% more neurotoxicity 4 h after administration. Compounds 4, 5, 6 and 8 showed no toxicity.

The value for the ClogP correlation was greater than 2 for all the tested compounds, indicating that they can all cross the blood–brain barrier efficiently. No specific relation was found between biological activity and ClogP values, except for a relation with neurotoxicity in the case of compounds 7 and 11, which had the highest ClogP values (4.19 and 4.49, respectively) and the greatest neurotoxicity.

Discussion

The active compounds tested in this study had all the requisites of anticonvulsant activity. The commonest structural element of older-generation anticonvulsants is a nitrogen hetero-atomic system bearing one or two phenyl rings and at least one carbonyl group.[6] The definition suggests the presence of an aryl hydrophobic binding site, a hydrogen bonding domain, an electron donor group and another hydrophobic–hydrophilic site controlling the pharmacokinetics of the anticonvulsant.[10,11] Thus, our newly proposed pharmacophore model includes all the factors important for anticonvulsant activity (Figure 1).

The results of biological screening of the synthesized analogues led to understanding of the structure–activity relations of these compounds. Inspection of their chemical structure suggests that they can be divided into two parts: a quinazolinone and an amine part. The quinazolinone part has been reported to have significant broad-spectrum anticonvulsant activity.[12] The presence of a halogen substituent at the sixth position from the distal aromatic ring of the quinazolinone moiety greatly enhanced the anticonvulsant activity of the newly synthesized compounds when compared with other compounds. Compounds 4–11 exhibited promising anticonvulsant activity, indicating that different substitution on the aromatic ring varies anticonvulsant activity. Compounds 5–8, which have mono halogen substituents at the para position from the distal aromatic ring of the quinazolinone moiety gave maximum protection against seizures induced by MES. Compound 8, which contains a mono bromo substitution, was the most active, while compounds 10 and 11, which contain an electron donating group (methoxy) and 3,5 dichloro substitution, had the least anticonvulsant activity. Substitution of the aromatic ring of the quinazolinone system by electron donating or electron withdrawing groups may thus play a key role in their anticonvulsant activity.

Conclusion

Eleven novel 3-substituted-6-fluro-2-methyl-quinazolin-4(3H)-one derivatives were synthesized and tested for anticonvulsant activity. All the newly synthesized compounds had significant anticonvulsant activity. Three compounds showed promising activity, while the other five compounds had moderate activity. All compounds tested for neurotoxicity showed a good safety margin.

Conflict of interest

The author of the paper "New fluorinated quinazolinone derivatives as anticonvulsant agents" discloses any commercial associations that might pose a conflict of interest in connection with the submitted manuscript such as employment, consult-

ancies, paid lecturing, financial involvement, patent ownership, etc.

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