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ORIGINAL ARTICLE

Design and synthesis of some novel 2-(3-methyl-2-oxoquinoxalin-1(2*H*)-yl)-*N*-(4-(substituted)phenyl) acetamide derivatives for biological evaluation as anticonvulsant agents

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KEYWORDS

2-(3-Methyl-2-oxoquinoxalin-1(2*H*)-yl)acetamide;
Quinoxaline;
Acetamide;
Anticonvulsant agent

Abstract A new series of 2-(3-methyl-2-oxoquinoxalin-1(2*H*)-yl)-*N*-(4-substitutedphenyl)acetamides (**2**–**15**$_{a–c}$) were designed and synthesized in order to evaluate their anticonvulsant activity. The structure of the synthesized compounds was confirmed by elemental analysis and spectral data (IR, ^{1}H NMR and Mass). The data obtained from biological screening revealed that; compounds **9**$_c$ and **8**$_c$ showed the highest anticonvulsant activities in experimental mice.

1. Introduction

Epilepsy, a common chronic neurological disorder that is characterized by recurrent unprovoked seizures, inflicts more than 60 million people worldwide according to epidemiological studies.[1]

Every year approximately 250,000 new cases are added to this figure. It is roughly estimated that 28–30% of patients are resistant to the available medical therapies.[2] It is important to emphasize that epileptic patients should use the anticonvulsant drugs continuously for years. Hence the chronic toxicity of such a long term is of particular importance.[3] The goal of an anticonvulsant is to suppress the rapid and excessive firing of neurons that start a seizure.[4]

Despite the development of several new anticonvulsants, the treatment of epilepsy remains still inadequate, and the patients suffer from a lot of specific problems like neurotoxicity, depression and other CNS related diseases. Moreover many antiepileptic drugs have serious side effects and lifelong medication may be required. Therefore, it is essential to search for newer and potent chemical entities for the treatment of epilepsy.[5]

Drugs in each therapeutic classification frequently show some common basic chemical structure, it is the hope of the chemist that, by the addition of various side chains or a combination of side chains or by somewhat altering the basic

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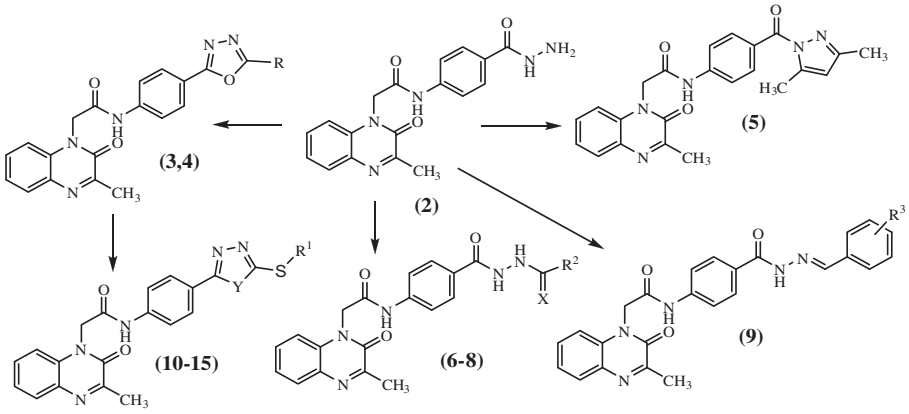

structure itself, he will find compounds better suited for therapeutic use.

Quinoxaline derivatives have received much attention in recent years due to their biological significance and pharmaceutical applications.[6–8] Many quinoxaline derivatives have been reported to possess anticonvulsant activity.[9,10] Some quinoxaline derivatives showed a highly significant effect as an anticonvulsant in comparing to diazepam as a reference drug.[9,11] Many currently prescribed antiepileptic drugs (AEDs) act via voltage-gated sodium channels, voltage-gated calcium channels, voltage-gated potassium channels, activation of γ-aminobutyric acid (GABA) receptor, or by inhibition of the glutamate receptor.[12,13] Glutamate receptors are classified into two major subtypes, *N*-methyl-D-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) receptors. AMPA receptor antagonists may have greater potential clinical utility than do the NMDA antagonists[14] due to the fact that the latter may produce schizophrenia-like symptoms.[15]

Extensive studies have been conducted on quinoxaline derivatives to possess central nervous system (CNS) depressant action with potent (AMPA) receptor antagonist activity, which in some cases inhibit AMPA-induced lethal convulsions in mice.[10,11,16–18] Several members of this family were found to exhibit moderate to significant anticonvulsant activity in comparing to Phenobarbital as the standard drug.[17,18] Furthermore, Compound I (Figure 1) was reported as a potent AMPA receptor antagonist.[16]

On the other hand it has been reported that a lot of compounds containing acid, ester, amide, acid hydrazide,[17–21] oxadiazole, pyrazole,[20,21] semicarbazide, thiosemicarbazide[20] and/or arylidene[17–21] moieties possess good anticonvulsant activity.

Stimulated by the successful applications of quinoxaline derivatives as anticonvulsant agents, our objective was to synthesize novel derivatives of quinoxaline endowed with the previously mentioned moieties, hoping that the hybrid of these pharmacophoric features would produce enhanced anticonvulsant activity and compare the difference in the pharmacological effect.

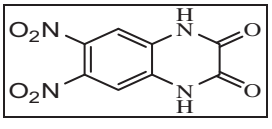

Figure 1 Compound I potent AMPA receptor antagonist.

Therefore a new series of 2-(3-methyl-2-oxoquinoxalin-1(2*H*)-yl)-*N*-(4-(substituted)phenyl)-acetamides were designed and synthesized starting with ortho-phenylenediamine by its reaction with sodium pyruvate to afford 3-methylquinoxalin-2(1*H*)-one which underwent different reactions following the reported procedures[17–26] to afford ethyl ester (**1**), acid hydrazide (**2**), 5-sulphanyl-oxadiazole (**3**), 5-phenyl-oxadiazole (**4**$_{a–c}$), pyrazole (**5**), acetyl (**6**), semicarbazide (**7**$_{a–c}$), thiosemicarbazide (**8**$_{a–c}$), Schiff's bases (**9**$_{a–e}$), triazole (**10**), S-alkyl (**12**$_{a–f}$), S-acetic acid (**13**), S-alkyl acetate (**14**$_{a–g}$) and thioester (**15**$_{a–c}$) derivatives in order to explore the influence of incorporating these groups on the anticonvulsant activity.

The data obtained from the biological screening of the synthesized compounds revealed that; the incorporation of Schiff's bases (compound **9**$_{c}$), thiosemicarbazide (compound **8**$_{c}$), semicarbazide (compounds **7**$_{b}$ and **7**$_{c}$) and 5-benzylsulphanyloxadiazole (compound **12**$_{f}$) moieties exhibited the highest anticonvulsant potency in comparing to Phenobarbital sodium as the reference drug (Table 1).

2. Chemistry

The sequence of reactions followed in the syntheses of the target compounds is illustrated in Schemes 1–3.

A new series of 2-(3-methyl-2-oxoquinoxalin-1(2*H*)-yl)-*N*-(4-(substituted)phenyl)acetamides were designed and synthesized starting with ortho-phenylenediamine by its reaction with sodium pyruvate to afford 3-methylquinoxalin-2(1*H*)-one, following the reported procedures,[22–26] which was then treated with alcoholic potassium hydroxide to afford the corresponding potassium salt.[13] Heating of the obtained potassium salt with ethyl-4-(2-chloroacetamido)-benzoate afforded the corresponding ethyl ester (**1**). The reaction of (1) with hydrazine hydrate afforded the intermediate compound *N*-(4-(hydrazinecarbonyl)phenyl)-2-(3-methyl-2-oxoquinoxalin-1(2*H*)-yl)acetamide (**2**) which underwent cyclization by refluxing with carbon disulfide in the presence of alcoholic potassium hydroxide followed by acidification with hydrochloric acid to give the corresponding 5-sulfanyloxadiazole (**3**) (Scheme 1).