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Original article

Newer GABA derivatives for the treatment of epilepsy including febrile seizures: A bioisosteric approach

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Abstract

The present study aims at design and synthesis of newer γ-aminobutyric acid (GABA) derivatives with the combination of thiosemicarbazone and GABA pharmacophores in order to develop newer anticonvulsants. The reported compounds were designed as bioisosteric analogues of GABA semicarbazones. The structures of the synthesized compounds were confirmed by the use of their spectral data besides elemental analysis. Initial anticonvulsant screening was performed using intraperitoneal (i.p.) maximal electroshock-induced seizure (MES), subcutaneous pentylenetetrazole (scPTZ), subcutaneous strychnine (scSTY), and subcutaneous picrotoxin (scPIC)-induced seizure threshold tests. A model involving 22-day old rat pups was also employed to further screen the effects of the test compounds against hyperthermia-induced febrile seizures. Only compounds **1** and **11** were found to be active in the MES test. Most of the compounds were found to be effective in the scPIC and febrile seizure models and very few compounds showed protection in scPTZ and scSTY models. This is the first report on these new GABA derivatives effective in the treatment of febrile seizures.

Keywords: Thiosemicarbazones; Anticonvulsants; GABA; Pentylenetetrazole; Picrotoxin; Strychnine; Febrile seizures

1. Introduction

Epilepsy is the most common primary neurological disorder known, affecting 0.4–0.8% of the population and up to 50 million people worldwide [1,2]. Epilepsy is the tendency to experience seizures-intermittent, usually unprovoked and stereotyped episodes that result from abnormal, paroxysmal electrical discharge of neurons of the cerebral cortex [3]. 4-Aminobutyric acid (GABA) is the principal inhibitory neurotransmitter in the mammalian brain [4,5]. It is well documented that attenuation of GABAergic neurotransmission is involved in the pathophysiology of several central nervous system (CNS) disorders in humans, namely anxiety, pain, and epilepsy [6–8]. The peripheral administration of GABA cannot be usefully performed since this neurotransmitter is able to cross the blood–brain diffusion barrier (BBB) only when extremely high doses are applied, which produce severe adverse side effects [9]. Hence, over the past few decades, research aimed at achieving successful delivery of GABA into the CNS has resulted in the discovery of various GABA analogues with improved pharmacological activities [10]. Recently, we reported the anticonvulsant properties of variously substituted *N*,*N*-phthaloyl GABA amides and acid hydrazones [11]. One of the approaches to analog-based drug discovery is the concept of bioisosteric replacement (Fig. 1), which continues to play an important role in bioorganic and medicinal chemistry in the design of novel pharmacological tools as well as new therapeutic agents with optimal pharmacological profile and improved pharmacokinetic properties [12]. In the past decade, aryl semicarbazones had been designed that were structurally dissimilar from many common anticonvulsants containing the dicarboximide function (CONRCO), which may contribute to

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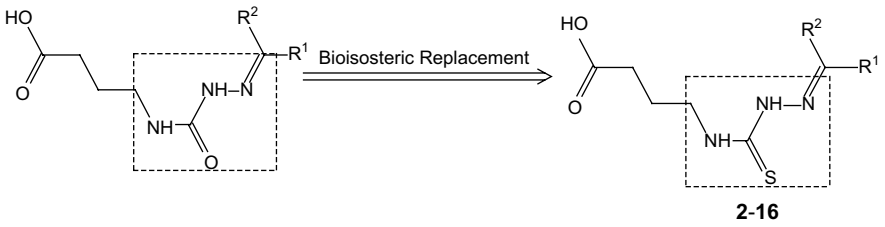
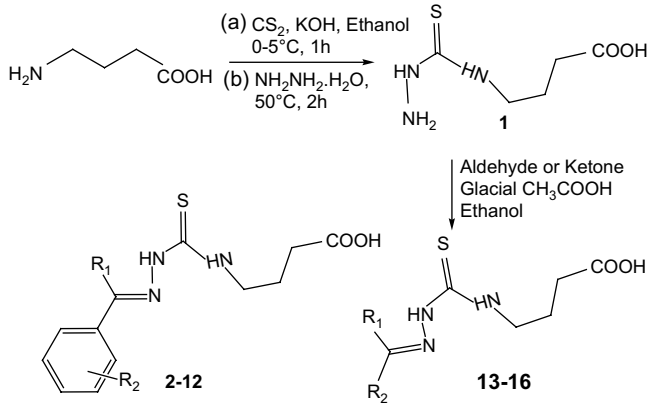


Fig. 1. Anticonvulsant compounds designed by bioisosteric replacement.

toxic side effects [13]. Consistent advances in the design of novel anticonvulsant agents have been obtained through the works of Dimmock and his colleagues [14], which included various aryl semicarbazones and (aryloxy) aryl semicarbazones. Recently, we reported the anticonvulsant and antinociceptive activities of GABA semicarbazones designed as pharmacophoric hybrids [15]. Moreover, various aryl thiosemicarbazides and thiosemicarbazones have also been reported by our group to exhibit anticonvulsant activity in maximal electroshock seizure (MES) and subcutaneous pentylenetetrazole (scPTZ) tests. These agents were also found to block the expression of fully kindled seizures [16]. Hence, given the promising biological profile of GABA derivatives, aryl semicarbazones/thiosemicarbazones, we initiated a drug discovery program focusing on the design and synthesis of newer GABA thiosemicarbazones as bioisosteric analogues of GABA semicarbazones. These GABA thiosemicarbazones were found to exhibit anticonvulsant activity in various animal models of seizure including the febrile seizure model with lesser neurotoxicity.

2. Synthesis

The synthesis of GABA thiosemicarbazones was accomplished as per earlier reported procedure [17,18] and presented in Scheme 1. The 4-(hydrazine carbothioamido)butanoic acid (**1**) was synthesized from 4-aminobutanoic acid via a one-pot procedure. 4-Aminobutanoic acid on treatment with carbon disulphide in the presence of potassium hydroxide in ethanol gave the potassium salt of the corresponding 4-dithiocarbamate derivative, which on reaction with hydrazine hydrate yielded 85% of **1**. Finally the required thiosemicarbazones (**2**–**16**) were prepared by the reaction between appropriate aryl/alkyl aldehydes or ketones and 4-(hydrazine carbothioamido)butanoic acid in the presence of glacial acetic acid in ethanol. The yields ranged from 45% to 78%. The purity was assessed by TLC; and the assignments of the structures were based on elemental and spectroscopic methods. The physical properties of the synthesized compounds are presented in Table 1. The chemical shifts obtained from ^{1}H NMR spectra supported the proposed structures. The ^{1}H NMR spectrum revealed that the hydrazino proton (=N–NH) showed a singlet at $\delta = 11.27$–11.68 ppm and the alkyl NH at 1.99–2.03 ppm both of which were D_2O exchangeable. All of the compounds (**2**–**16**) showed a characteristic D_2O exchangeable singlet due to OH proton of the acid function at $\delta = 12.3$–12.36 ppm. The aryl ring protons resonated at $\delta = 6.9$–8.41 ppm. The singlet due to 1H of carbimino proton was observed at $\delta = 8.0$–8.2 ppm and the singlet due to 3H of carbimino CH_3 was observed at $\delta = 0.91$ ppm.



Scheme 1. Synthetic route to GABA thiosemicarbazones.

3. Results and discussion

The synthesized compounds (**1**–**16**) were evaluated at dose levels of 30, 100 and 300 mg/kg intraperitoneally in mice for anticonvulsant activity. In our anticonvulsant drug development program, our approach was to test the new compounds preliminarily in two standard models MES and scPTZ (at NIH) for their ability to reduce seizure spread and to elevate seizure threshold, respectively. Further to understand the mechanistic aspects, we undertook testing in the other two models scSTY and scPIC in our laboratory. From our initial screening results we found that some compounds showed broad spectrum anticonvulsant activity, which prompted us to evaluate their efficacy in a stress-induced febrile seizure model. Table 2 lists the results obtained from the initial anticonvulsant evaluation of the synthesized compounds compared to the clinically proven antiepileptics such as phenytoin and ethosuximide. The acute neurological toxicity was determined by the rotorod test.

Two compounds (**1** and **11**) showed activity in the MES screen at 300 mg/kg with a shorter duration of action (0.5 h) indicative of their ability to prevent seizure spread. In the scPTZ screen, a test used to identify compounds that elevate seizure threshold, six compounds (**2**, **4**, **5**, **7**, **15**, and **16**) showed protection. Compound **16** was the most effective in this model exhibiting protection at 30 mg/kg for a shorter