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Novel sulfamides and sulfamates derived from amino esters: Synthetic studies and anticonvulsant activity

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ABSTRACT

We report herein the design and optimization of a novel series of sulfamides and sulfamates derived from amino esters with anticonvulsant properties. The structures were designed based on the pharmacophoric pattern previously proposed, with the aim of improving the anticonvulsant action. The compounds were obtained by a new synthetic procedure with microwave assisted heating and the use of adsorbents in the isolation process. All the derivatives showed protection against the maximal electroshock seizure test (MES test) in mice at the lowest dose tested (30 mg/kg) but they did not show significant protection against the chemical induced convulsion by pentylenetetrazole. These results verify the ability of the computational model for designing new anticonvulsants structures with anti-MES activity. Additionally, we evaluated the capacity of the synthesized structures to bind to the benzodiazepine binding site (BDZ-bs) of the γ-aminobutiric acid receptor ($GABA_A$ receptor). Some of them showed medium to low affinity for the BDZ-bs.

1. Introduction

Epilepsy is not one condition, but a complex set of cerebral disorders that have in common the occurrence and recurrence of seizures (Fisher et al., 2014). About 65 million people worldwide currently live with epilepsy, and only 70% of them control the seizures with the available medication (Moshé et al., 2015), at expenses of the significant adverse side effects that increase their toxic actions when a lifelong medication is required (Bialer et al., 2013; Löscheran and Schmidt, 2011). The remaining one third of the patients are still resistant to the current anticonvulsant drugs, condition known as refractory epilepsy (French, 2007). Under this scenario, there is a genuine need for new antiepileptic compounds with more efficacy and safety.

Research from our group and others has focused on sulfamide derivatives as new targets of anticonvulsant drugs. (Gavernet et al., 2009, 2007a, 2007b; McComsey et al., 2013). Particularly, our previous findings allowed us to define a new pharmacophoric pattern for amino acid derived sulfamides (Fig. 1) (Gavernet et al., 2009), with anticonvulsant action evidenced in the Maximal electroshock seizure test in mice (MES test, Porter et al., 1984).

The most promising compounds were two β-Alanine sulfamide derivatives: the methyl [N-(N′-2-propylpentyl)-sulfamoyl]-β-alaninate and the methyl [N-(N′butyl)-sulfamoyl]-β-alaninate (compounds 1 and 2, Fig. 2). They exhibit some structural similarities with the anticonvulsant drug Valrocemide (Isoherranen et al., 2001), a valproic acid derivative with a glycinamide moiety linked to the valpromide function (compound 3, Fig. 2).

We report herein the synthesis and anticonvulsant activity of a new set of β-alanine derived sulfamides (compounds 4–9, Fig. 3). Additionally, we replaced β-alanine moiety of Methyl [N-(p-fluorobenzyl)-sulfamoyl] β-alaninate (compound 9, Fig. 3) by L-valine and L-phenyl alanine skeleton (compounds 10 and 11, Fig. 3). As will be explained in Section 4, compound 9 showed promising anticonvulsant action, so we synthesized structures 10 and 11 in order to explore the influence of other amino acid chains to the activity.

To obtain the new structures we design here a new synthetic protocol by using microwave assisted synthesis. As will be described in the next section, the synthetic routes of sulfamides involved the previous preparation of ester sulfamates. Sulfamates also comply with the pharmacopohore requirements for the polar

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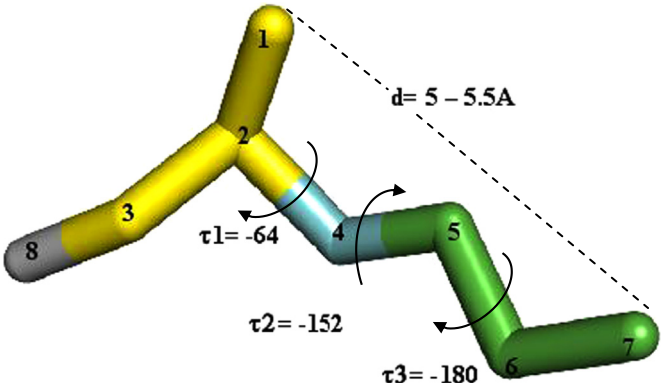

Fig. 1. Pharmacophoric pattern proposed by Gavernet et al. (2009). The anti-MES requirements can be summarized as: (1) a polar moiety (atoms 1–3, in yellow), (2) a hydrophobic chain (atoms 5–7 in green) placed in a conformation defined by *t*1, *t*2, *t*3 and *d*, and connected to the polar moiety through a link atom (atom 4, in cyan), (3) any group attached to atom 3 should be non polar or H.

group and they present a similar electronic distribution than sulfamides (Gavernet et al., 2007a). In fact, the anticonvulsant drug Topiramate presents this function into its chemical structure. For that reason we included the sulfamates showed in Fig. 4 in the protocols for biological assays.

It is worth mentioning that sulfamides and sulfamates are versatile functions that have been employed in medicinal chemistry to construct active compounds with different applications. These functionalities interact with molecular targets of several diseases, such as aspartic proteases (HIV-1 protease, γ-secretase), serine proteases, metalloproteinases, steroid sulfatases and 5-HTID Receptors among others (Nussbaumer and Billich, 2005; Reitz et al., 2009; Winum et al., 2006). They have also successfully tested as carbonic anhydrase inhibitors due to their bioisosteric correspondence with sulfonamide, the classical functional group that inhibit the active isoforms through its direct interaction with the active site (Gavernet et al., 2013; McKenna and Supuran, 2014).

2. Materials and methods

2.1. Chemistry

In previous investigations we synthesized amino acid derived sulfamides by modifying the synthesis of aril/alkyl sulfamides via catechol sulfate (DuBois and Stephenson, 1980). Catechol sulfate (prepared with catechol and sulfuryl chloride) reacts with the salt of the amino ester under controlled conditions, to yield a sulfamate ester derivative (Scheme 1). Then, the resulting sulfamate reacts with the alkyl/aryl amine to yield the amino acid derived sulfamide (Scheme 1, Gavernet et al., 2009). Unlike previous methodologies, we employed here microwave assisted synthesis in both steps of the reaction. With this method, we incorporated reactions under solvent free conditions, which is more benign to the environment than the use of the traditional reaction media.

The synthetic route outlined in Scheme 1 was employed for the synthesis of β-Alanine methyl ester sulfamides. However, our attempts to obtain the corresponding sulfamates from L-valine methyl ester and L-phenylalanine methyl ester were not successful, even when traditional heating and different catechol/amino ester ratio were used.

Particularly, the synthesis of the sulfamate of L-valine methyl ester (compound 13) with the traditional heating gave the N,N′-disubstituted sulfamide, the N,N′-Sulfonyl bis-L-valine dimethyl ester (Gavernet et al., 2009), as the main product of the reaction; and small quantities of compound 13 (which was purified and tested). This result is consistent with the analysis of the products obtained from the synthesis of other alkyl and aryl sulfamates (DuBois and Stephenson, 1980). Finally, we prepared the sulfamides 10 and 11 by inverting the synthetic route: first we obtained the sulfamate of p-fluorobenzyl amine and then we added the corresponding amino ester (Scheme 2).

The synthetic methods outlined in Schemes 1 and 2 involve the production of equimolar quantities of sulfamide and catechol. In our experience, the isolation and purification of the sulfamide from the relative large amounts of catechol causes difficulties during the work up process. Traditionally, we washed the crude product and then we performed at least one column chromatography process, which require large amounts of silica gel and dichloromethane as the elution solvent (Gavernet et al., 2009). In this investigation we replaced the standard work up process by an heterogeneous filtration process. We directly added to the reaction mixture an insoluble inorganic compound with the capacity to absorb selectively catechol and then filtered the solid.

Details about the synthesis of the new sulfamides and sulfamates, their physicochemical characteristics and their spectroscopic characterization are summarized next.

2.1.1. General information

Melting points were determined using capillary tubes with an electrothermal melting point apparatus and were uncorrected. Thin-layer chromatography (TLC) was performed with aluminum backed sheets with silica gel 60 F254 (Merck, ref 1.05554), and the spots were visualized with 254 nm UV light and 5% aqueous solution of ammonium molybdate (VI) tetrahydrate. Column chromatography was performed on silica gel 60 (70–230 mesh, Merck, ref 1.07734.2500). ^{1}H and ^{13}C NMR spectra were recorded for compounds 3, 4 and 6 on a Varian Gemini 200 spectrometer at 200 and 50 MHz; whereas we employed a BRUKER AVANCE II 500 spectrometer at 500 and 126 MHz for the rest of the structures. The chemical shifts were reported in ppm (δ scale) relative to internal TMS, and coupling constants were reported in Hertz (Hz). FTIR spectra were performed using a Bruker EXINOX 55 equipment. Spectra were recorded at room temperature in the 4000–400 cm^{-1} range, and the samples were prepared in form of wafers with KBr. Absorption values were expressed as wavenumbers (cm^{-1}) and only significant absorption bands are given. Analytical grade solvents were employed for crystallization, while pure solvents were used for the reactions, extractions and column chromatography. Commercial amines were distilled prior to their

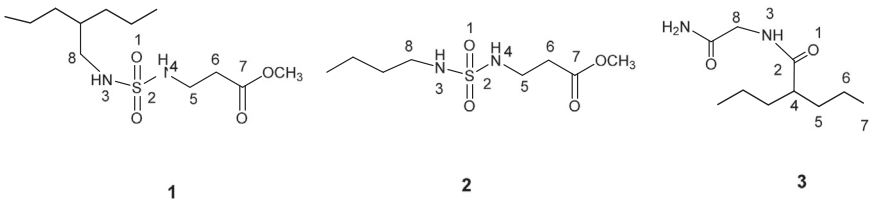

Fig. 2. Compounds with anticonvulsant properties analyzed in previous investigations by Gavernet et al. (2009). Atoms are numbered for the centers that define the pharmacophoric pattern shown in Fig. 1.