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Synthesis and Pharmacology of Seleninic Acid Analogues of the Inhibitory Neurotransmitter γ-Aminobutyric Acid

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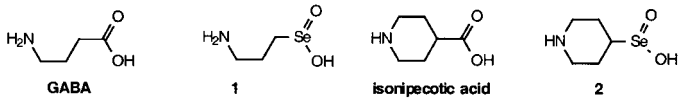
ABSTRACT



The first seleninic acid analogues of γ-aminobutyric acid (GABA) and of the specific $GABA_A$ agonist piperidine-4-carboxylic acid (isonipecotic acid), 1 and 2, respectively, have been synthesized and shown to be potent agonists at the GABA receptors.

The concept of bioisosteric replacement 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.[1] A number of acidic groups have been shown to be useful carboxyl group bioisosteres, although different biological systems frequently show markedly different bioisosteric tolerance. The 3-isoxazolol group has been successfully used in the synthesis of analogues of the central inhibitory neurotransmitter γ-aminobutyric acid (GABA).[2] Recently the phosphinic acid[3] and the sulfinic acid[4] groups have been explored in the preparation of bioisosteres of GABA. However, the bioisosteric potential of the seleninic acid group has, so far, not been investigated, although it has structural and protolytic properties similar to those of the carboxyl group. 2-Aminoethaneseleninic acid has previously been synthesized,[5] and we now report the synthesis and in vitro pharmacology of the seleninic acid analogues of GABA and of the specific $GABA_A$ agonist piperidine-4-carboxylic acid (isonipecotic acid), **1** and **2**, respectively.

Of the four organic acids of selenium (selenol and selenenic, seleninic, and selenonic acids), the seleninic acid group is the most stable. Seleninic acids can be prepared in several ways, e.g., by hydrolysis of trihalogeno alkylselanes,[6] oxidative hydrolysis of selenocyanates,[7] and controlled

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Scheme 1. Syntheses of Amino Seleninic Acids **1** and **2**

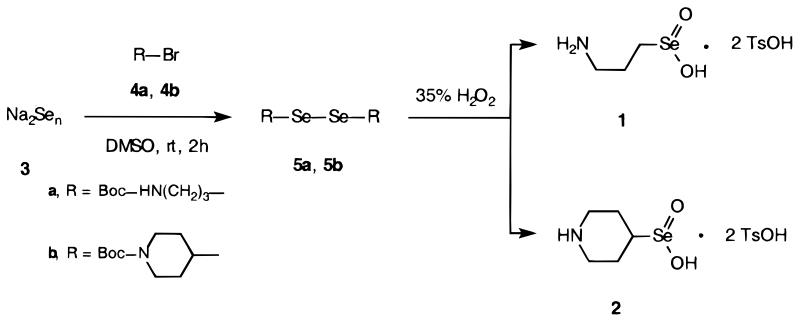

Table 1. $GABA_A$ and $GABA_B$ Receptor Effects of the Dihydrotosylate Salts of **1** and **2**

compd	binding at rat $GABA_A$ receptors (IC_{50}, μM)[a]	binding at rat $GABA_B$ receptors (IC_{50}, mM)[a]	potency at human $GABA_A$ receptors (EC_{50}, μM)[b]	maximum response at human $GABA_A$ receptors (% relative to maximum GABA)
GABA	0.128	0.025	15	100
1	2.0	0.08	350	30
isonipecotic acid	0.33[14]	>1000	400	60
2	4.0	>100	200	3

[a] In vitro inhibition of GABA receptor binding in rat brain synaptosomes using a previously described method.[15] [b] Activities at human $GABA_A$ receptors expresed in Xenopus oocyces using the method previously described.[16]

oxidation of selenols,[8] but are most frequently and readily prepared by oxidative cleavage of organodiselenides by aqueous HNO_3,[9] aqueous H_2O_2,[10] aqueous Br_2,[11] or ozone.[12] Our approach was to utilize a method for the ready and reliable generation of a sodium polyselenide **3** solution in DMSO (Scheme 1),[13] which reacts with Boc-protected 3-bromopropylamine **4a** or Boc-protected 4-bromopiperidine **4b** to give bis(3-*N*-*tert*-butoxycarbonylaminopropyl)diselenide **5a** and bis(*N*-*tert*-butoxycarbonyl-4-piperidyl)diselenide **5b**, respectively. The diselenides **5a** and **5b** were extracted from the reaction mixture with ether upon dilution with water. Although the diselenides could also be synthesized without amino protecting group, the resulting bisaminoalkyl diselenides were not easily purified. After removal of the Boc groups of **5a** and **5b** by treatment with *p*-toluenesulfonic acid in hot acetic acid, followed by dilution of the reaction mixture with dichloromethane, the seleninic acids were prepared by gentle oxidation of the diselenides with 35% aqueous H_2O_2 at room temperature. This procedure caused the dihydrotosylate salts of **1** and **2** to precipitate from the reaction mixture as colorless crystalline salts, which were purified by recrystallization from water−acetic acid. Notably, both compounds were shelf-stable for several months. Bicarbonate solutions of **1** and **2** were stable for weeks at room temperature.[19,20] The preparation and isolation of **1** was relatively straightforward, as compared with the procedures described for several alkane-1-seleninic acids, including 2-aminoethaneseleninic acid. The finding that **2** could be isolated as a stable material is quite remarkable, since, to the best of our knowledge, this is the first example of a compound with a seleninic acid situated at a secondary carbon atom.

The affinity for the $GABA_A$ and $GABA_B$ receptors of the dihydrotosylate salts of **1** and **2** as well as their functional (agonist/antagonist) properties were characterized in binding studies, guinea pig ileum, and cloned $GABA_A$ receptors (Table 1). It has been experimentally established, that there is a high correlation between binding data obtained in cell lines expressing human GABA receptors[17] and rat brain homogenates,[18] reflecting that the inter species homology in $GABA_A$ receptor sequence and structure is very high. The 3-aminopropaneseleninic acid **1** was shown to be a potent and relatively selective $GABA_B$ agonist. At cloned human $GABA_A$ receptors **1** was a medium potent partial agonist with a maximum response of 30% relative to GABA. In contrast, the piperidine-4-seleninic acid **2** was shown to be a potent and selective partial $GABA_A$ agonist with a

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maximum response of 3% of that of GABA. Quite surprising, whereas the seleninic acid analogue **1** of GABA activates the $GABA_A$ receptor with a potency 20 times lower than that of GABA, the seleninic acid analogue **2** is differing in potency by a factor of 2 as compared with isonipecotic acid but produces a maximum reponse of only 3% as compared to 60% for isonipecotic acid.

In conclusion, we have synthesized the first bioactive seleninic acid analogues **1** and **2**, of GABA and shown them to be potent $GABA_B$ and $GABA_A$ agonists, respectively.

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(19) **3-Aminopropaneseleninic Acid Dihydrotosylate (1).** A solution of sodium tetraselenide was prepared in the following manner: To a stirred solution of sodium methoxide (3.38 g, 63 mmol) and 95% aqueous hydrazine (0.5 g, 16 mmol) in DMSO (80 mL) was added selenium (9.87 g, 125 mmol) in small portions during a 5 min period under vigorous stirring. The reaction mixture was further stirred at room temperature for 30 min under nitrogen. Di-*tert*-butyl dicarbonate (10.9 g, 50 mmol) and 3-bromopropylamine hydrobromide (10.9 g, 50 mmol) in triethylamine−THF (1:4, 125 mL) was stirred for 4 h at room temperature. The reaction mixture containing **4a** was filtered directly into the sodium tetraselenide solution. The resulting black reaction mixture was stirred at room temperature under nitrogen for 2 h, diluted with water (400 mL), and extracted with ether (3 × 125 mL). The combined ether phases were washed with water (2 × 50 mL), dried (Na_2SO_4), filtered, and evaporated in vacuo to give the crude diselenide **5a** as a yellow oil. *p*-Toluenesulfonic acid monohydrate (19.0 g, 0.1 mol) in glacial acetic acid (0.3 L) was added, and the resulting solution was heated (100 °C) for 30 min (to ensure complete removal of the Boc-group). After cooling to 0 °C in an ice bath dichloromethane (0.15 L) was added. The solution was dropwise titrated (yellow to colorless) with 35% aqueous hydrogen peroxide during a 10 min period. During the reaction the product was formed as a white precipitate, which was filtered off and dissolved in water−glacial acetic acid (1:9, 0.1 L) at 60 °C. Glacial acetic acid (0.1 L) was added and the flask left at room temperature overnight. Filtration and drying (vacuum oven, 45 °C) gave **1** (5.75 g, 22%) as white flakes: mp 126−130 °C (dec). $C_{17}H_{25}NO_8S_2Se$: found C 39.71, H 4.66, N 2.70, S 12.43; calcd C 39.69, H 4.90, N 2.72, S 12.46. ^{1}H NMR (D_2O) δ: 1.91−1.95 (2 H, t, J = 7.7 Hz), 2.02 (6 H, s), 2.80−2.85 (4 H, m), 4.70 (5 H, s), 6.99 (4 H, d, J = 7.9 Hz), 7.41 (4 H, (d) ppm. ^{77}Se NMR (D_2O) δ: 1224 ppm.

(20) **Piperidine-4-seleninic Acid Dihydrotosylate (2).** The product was prepared from 4-bromopiperidine hydrobromide in analogy with the synthesis of 3-aminopropaneseleninic acid dihydrotosylate. Purification was achieved by dissolving the product in the minimum amount of water−glacial acetic acid (1:7) at 60 °C followed by addition of the same volume of glacial acetic acid. Upon cooling the precipitate was filtered off and dried (vacuum oven, 45 °C) to give **2** (15%) as white flakes: mp 162−164 °C (dec). $C_{19}H_{27}NO_8S_2Se$: found C 42.19, H 4.86, N 2.52, S 11.99; calcd C 42.22, H 5.03, N 2.59, S 11.86. ^{1}H NMR (D_2O) δ: 1.70−1.89 (2 H, m), 2.06−2.12 (2 H, m), 2.18 (6 H, s), 2.85−2.95 (2 H, m), 3.04−3.16 (1 H, m), 3.37−3.43 (2 H, m), 4.70 (4 H, br s), 7.15 (4 H, d, J = 8.0 Hz), 7.41 (4 H, d) ppm. ^{77}Se NMR (D_2O) δ: 1225 ppm.