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Original article

Design, synthesis, anticonvulsant, and antiarrhythmic properties of novel *N*-Mannich base and amide derivatives of β-tetralinohydantoin

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ABSTRACT

Background: 5,5-Diphenylhydantoin (Phenytoin) is a well-known anticonvulsant and antiarrhythmic drug which may cause unwanted side effects. In order to avoid the adverse effects of phenytoin, especially on the central nervous and cardiovascular systems, two small series of amine derivatives (Mannich bases) and amide ones were designed containing β-tetralinohydantoin system. In preliminary studies, some of arylpiperazinylmethyl derivatives with a β-tetralinohydantoin moiety were effective in screening anticonvulsant tests in mice.

Methods: These new amine and amide derivatives of β-tetralinohydantoin were evaluated in standard anticonvulsant screens (maximal electroshock (MES) or pentylenetetrazole (scPTZ) seizure tests) and their neurotoxicity was assessed in standardized rotarod tests. Additionally, due to structural features (a hydantoin ring), influence on antiarrhythmic activity, electrocardiogram components and blood pressure was tested in rats.

Results: The new *N*-Mannich bases were effective in maximal electroshock or pentylenetetrazole seizures screens; and the most interesting compound **4** (1-{[4-(1-phenyethyl)-piperazin-1-yl]methyl}-3′,4′-dihydro-1′H,2H,5H-spiro[imidazolidine-4,2′-naphthalene]-2,5-dione) displayed anticonvulsant activity in both the aforementioned tests. Furthermore, compound **6**, an amide derivative of β-tetralinohydantoin, displayed significant antiarrhythmic activity in a barium chloride-induced arrhythmia model (ED_{50} 16.3 mg/kg), but it was devoid of anticonvulsant protection. None of the tested compounds affected the electrocardiogram components or blood pressure in normotensive rats.

Conclusion: All new *N*-Mannich bases containing the β-tetralinohydantoin system and 1-phenylalkylpiperazine were classified to Anticonvulsant Screening Program 1st class. In contrast, our results suggested that the introduction of an amide bond in the alkyl side chain of the β-tetralinohydantoin system abolished the anticonvulsant activity, but not the antiarrhythmic one. However, further studies are required for a definitive conclusion.

Introduction

Basic structural requirements for compounds with anticonvulsant activity have been created in recent decades. The most important fragments of anticonvulsants are the heterocyclic system, and at least one carbonyl group and the phenyl or alkyl groups attached to the heterocyclic system [1]. This template is present in the structures of 5,5-diphenylhydantoin (5,5-diphenylimidazolidine-2,4-dione, Dilantin, Phenytoin, DPH) (Fig. 1). Introduced originally for the control of convulsive disorders, DPH has long been recognized as an antiarrhythmic agent [2,3], affecting sodium channel modes in a manner characteristic for antiarrhythmics belonging to class Ib according to the Vaughan Williams classification [4]. This class of antiarrhythmic agents interfere with the sodium channel and are defined as membrane stabilizing agents. Modulation of voltage-dependent sodium channels is also one of the mechanisms of pharmacological action of a potential new anticonvulsant. This type of activity leads to stabilization and regulation of the excitability of neurons within the central nervous system [5].

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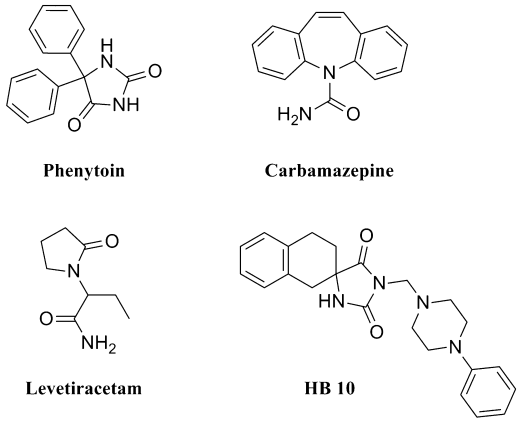

Fig. 1. Structures of well-known anticonvulsant and the lead structure (**HB 10**).

Previous studies have identified differently substituted imidazolidine-2,4-diones as a new antiepileptic group of compounds [6,7]. Imidazolidine-2,4-diones containing the β-tetralinohydantoin system (3′,4′-dihydro-1′*H*,2*H*,5*H*-spiro[imidazolidine-4,2′-naphthalene]-2,5-dione) and a 4-arylpiperazine or 4-benzyl-piperazine moiety connected to the imide N3 atom by the methylene spacer (Mannich bases) were effective in the maximal electroshock (MES) and/or subcutaneous pentylenetetrazole (scPTZ) screen. The most active compound was HB10 (Fig. 1), (1-[(4-phenylpiperazin-1-yl)methyl]-3′,4′-dihydro-1′H,2H,5H-spiro[imidazolidine-4,2′-naphthalene]-2,5-dione), with an ED_{50} value of 1.88 mg/kg in the MES test (Fig. 1). To explore this group of compounds more deeply, a small, diverse series of β-tetralinohydantoin derivatives carrying either a phenylalkylpiperazine fragment (Mannich bases) or an N-benzylacetamide moiety (amide analogs) have been design. In the Mannich bases, the distance between the aromatic ring and piperazine moiety was elongated to check the impact of such modification on anticonvulsant activity. Furthermore, the amide bond in the alkyl side chain was introduced with the aim of verifying whether it affects both anticonvulsant and arrhythmic activity. An amide function was chosen owing to its presence in many classical and new anticonvulsants [8], for example carbamazepine, valproic acid, and levetiracetam (Fig 1), as well as in antiarrhythmic agents, for example lidocaine, mexiletine and tocainide. Additionally, we wanted to establish which of the aforementioned structural modifications will help to avoid adverse effects to the central nervous and cardiovascular system.

New compounds were tested for their anticonvulsant activity within the Antiepileptic Drug Development (ADD) Program in Epilepsy Branch, Neurological Disorders Program, National Institute of the Neurological and Communicative Disorders and Stroke (NIH/NINDS), Rockville, MD, USA.

Due to their mode of action, the investigated compounds derived from hydantoin may exhibit not only anticonvulsant but also antiarrhythmic activity; therefore, they were tested in an animal model of arrhythmia induced by barium hydrochloride. Furthermore, in order to verify the cardiac safety profile of β-tetralinohydantoin derivatives, the affinity for α_1, α_2 and β_1 receptors was evaluated and their electrocardiographic activity was tested. Then, the influence of the tested hydantoin compounds on the blood pressure in anesthetized rats was also investigated.

Materials and methods

Chemistry

All the chemicals and solvents were purchased from Merck (Darmstadt, Germany) and were used without further purification. Melting points (mp) were determined in open capillaries on an Electrothermal 9300 apparatus and were uncorrected. The purity of the compounds was confirmed by the thin-layer chromatography (TLC) performed on Merck silica gel 60 F_{254} aluminum sheets (Merck; Darmstadt, Germany), using the developing systems: S_1 – benzene/ethyl acetate/acetone (10:5:1 *v/v/v*), S_2 – acetone/isopropanol/chloroform (20:10:1 *v/v/v*) and S_3 – methanol: ammonia 25% (9:0.2 *v/v*). Spots were detected by their absorption under UV light (λ = 254 nm). The structures were confirmed by spectral (^{1}H NMR) and elemental (C, H, N) analysis. Nuclear magnetic resonance spectra were obtained in a Varian Mercury spectrometer (Varian Inc., Palo Alto, CA, USA), in $CDCl_3$, operating at 300 MHz. Chemical shifts were expressed in δ (ppm) and the coupling constants *J* in Hertz. Signal multiplicities are represented by the following abbreviations: s (singlet), br s (broad singlet), d (doublet), t (triplet), q (quartet), m (multiplet). Elemental analysis for C, H, and N were carried out by a micro method using the elemental Vario EI III Elemental analyser (Hanau, Germany). The results of elemental analyses were within ±0.4% of the theoretical values.

The starting β-tetralinohydantoin (**1**), was obtained by the method described previously [9].

*General procedure for the synthesis of compounds **2–4***

To a solution of β-tetralinohydantoin (0.005 mol) in 20 mL 99% ethanol, 0.005 mol of arylpiperazine and 0.015 mol 36% formaldehyde solution were added, then the reaction mixture was refluxed for 24 h. After cooling, the precipitate was filtered, dried and recrystallized form anhydrous ethanol.

*1-{[4-(4-chlorobenzyl)-piperazin-1-yl]methyl}-3′,4′-dihydro-1′H,2H,5H-spiro[imidazolidine-4,2′-naphthalene]-2,5-dione (**2**)*

White powdery crystals. Yield 88%; mp 188–191 °C; TLC: R_f = 0.78 (S_2), 0.86 (S_3); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.86–2.01 (m, 2H, cyclohexene), 2.22–2.35 (m, 2H, cyclohexene), 2.46 (br s, 4H, piperazine), 2.69 (br s, 4H, piperazine), 2.93–3.14 (m, 2H, cyclohexene), 3.49 (s, 2H, CH_2-Ar), 4.50 (s, 2H, N3-CH_2), 5.63 (s, 1H, hydantoin), 7.07–7.32 (m, 8H, ArH). Anal calcd for $C_{24}H_{27}N_4O_2$ (438.95): C, 65.67; H, 6.20; N, 12.76; found: C, 65.97; H, 6.30; N, 12.76.

*1-{[4-(2-phenyethyl)-piperazin-1-yl]methyl}-3′,4′-dihydro-1′H,2H,5H-spiro[imidazolidine-4,2′-naphthalene]-2,5-dione (**3**)*

White powdery crystals. Yield 77%; mp 165–167 °C; TLC: R_f = 0.68 (S_2), 0.73 (S_3); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.87–2.01 (m, 2H, cyclohexene), 2.21–2.37 (m, 2H, cyclohexene), 2.59–2.61 (br s, 6H, piperazine, CH2-piperazine), 2.77–2.89 (br s, 6H, piperazine, CH2-Ar), 2.93–3.13 (m, 2H, cyclohexene), 4.54 (s, 2H, N3-CH2), 5.72 (s, 1H, hydantoin), 7.08–7.32 (m, 9H, Ar). Anal calcd for C25H30N4O2 (418.52): C, 71.74; H, 7.22; N, 13.39; found: C, 71.70; H, 7.16; N, 13.23.

*1-{[4-(1-phenyethyl)-piperazin-1-yl]methyl}-3′,4′-dihydro-1′H,2H,5H-spiro[imidazolidine-4,2′-naphthalene]-2,5-dione (**4**)*

White powdery crystals. Yield 65%; mp 139–141 °C; TLC: R_f = 0.78 (S_2), 0.86 (S_3); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.35–1.37 (d, 3H, *J* = 7.2, CH3), 1.84–2.00 (m, 2H, cyclohexene), 2.20–2.37 (m, 2H, cyclohexene), 2.38–2.58 (br s, 4H, piperazine), 2.59–2.75 (br s, 4H, piperazine), 2.83–3.13 (m, 2H, cyclohexene), 3.35 (s, 1H, CH-Ar), 4.48 (s, 2H, N3-CH2), 5.67 (s, 1H, hydantoin), 7.07–7.30 (m, 9H, Ar). Anal calcd for C25H30N4O2 (418.52): C, 71.74; H, 7.22; N, 13.39; found: C, 71.66; H, 7.40; N, 13.08.

*General procedure for the preparation of ethyl-(2,5-dioxo-3′,4′-dihydro-1*H,*1′*H-spiro[imidazolidine-4,2′-naphthalen]-1-yl)acetate (**5**)*

To a suspension of 0.05 mol of β-tetralinohydantoin (**1**) and 0.055 mol potassium carbonate in 100 mL of acetone, ethyl