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Non-imidazole histamine H_3 receptor ligands incorporating antiepileptic moieties

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ABSTRACT

A small series of histamine H_3 receptor (H_3R) ligands (**1**–**5**) incorporating different antiepileptic structural motifs has been newly synthesized. All compounds exhibited moderate to high *in vitro* hH_3R affinities up to a sub-nanomolar concentration range with pK_i values in the range of 6.25–9.62 with varying preferences for this receptor subtype. The compounds (**1**–**5**) were further investigated *in vivo* on anticonvulsant effects against maximum electroshock (MES)-induced and pentylenetetrazole (PTZ)-kindled convulsions in rats having phenytoin (PHT) as the reference antiepileptic drug (AED). Surprisingly, animals pretreated with 1 mg/kg, i.p. of 5,5-diphenyl-3-(3-(piperidin-1-yl)propyl)imidazolidine-2,4-dione (**4**) were only moderately protected and no protection was observed for compounds **1**–**3** and **5** in three different doses (1 mg, 5 mg, and 10 mg/kg i.p.). Compound **4** (1 mg/kg, i.p.) failed to modify PTZ-kindled convulsion. However, a dose of 10 mg/kg significantly reduced convulsions in both models. In contrast, 5,5-diphenyl-3-(4-(3-(piperidin-1-yl)propoxy)benzyl)imidazolidine-2,4-dione (**5**) (1, 5, and 10 mg/kg, i.p.) showed proconvulsant effects in the MES model with further confirmation of these results in the PTZ model as no protection was observed against convulsion in the doses tested (1 and 10 mg/kg). In addition, compound **4** (10 mg/kg, i.p.) significantly prolonged myoclonic latency time and shortened total convulsion duration when compared to control, PHT or standard H_3R inverse agonist/antagonist pitolisant (PIT). Our results showed that H_3R pharmacophores could successfully be structurally combined to antiepileptic moieties, especially phenytoin partial structures, maintaining the H_3R affinity. However, the new derivatives for multiple-target approaches in epilepsy models are complex and show that pharmacophore elements are not easily pharmacologically combinable.

1. Introduction

Epilepsy is one of the most common disorders of the human brain, affecting more than 60 million individuals worldwide [1–3]. Phenytoin (PHT) and recent antiepileptic drugs (AEDs), e.g. remacemide, loreclezole and safinamide are only effective within a maximum of 60–80% of patients and are accompanied with unwanted side-effects, such as headache, nausea, anorexia, ataxia, hepatotoxicity, drowsiness, gastrointestinal disturbance, gingival hyperplasia, attention deficit, and cognitive problems (Fig. 1) [4–8]. In many cases the clinical use of AEDs is restricted by their side-effects. Therefore, a continuous need remains to discover new chemical entities for the development of effective and safer AEDs. Among the mentioned side-effects, cognitive impairment especially is commonly seen in patients subjected to chronic AED therapy and for many patients this may be more debilitating than the actual convulsions themselves contributing to a worse quality of life.

The role of central histamine being involved in epilepsy is compelling because of growing evidence from experimental results showing that histamine regulates in some animal models convulsion predisposition and, consequently, acts as an anticonvulsant neurotransmitter in electrically- (as well as chemically-) induced convulsion models [9,10]. Moreover, experimental and pharmacological results are also in agreement with histamine being associated with epileptic convulsion pathophysiology as animals lacking

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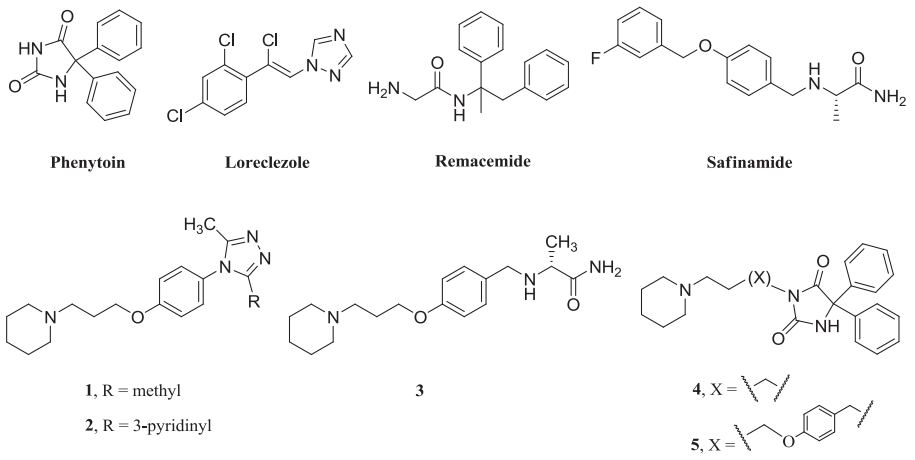

Fig. 1. Structures of considered AEDs and of newly designed final compounds **1**–**5**.

histidine decarboxylase and histamine H_1 receptors (H_1R) were more prone to development of convulsions [11].

The histamine H_3 receptor subtype (H_3R) acts as a presynaptic auto- and heteroreceptor primarily in the central nervous system (CNS) controlling the synthesis as well as the release of histamine and modifying the release of several other neurotransmitters, e.g. dopamine, serotonin, γ-aminobutyric acid, noradrenalin, and acetylcholine. H_3R antagonists have shown distinct pharmacological actions in preclinical and clinical trials revealing their importance for diverse CNS-related therapeutic applications such as depression, schizophrenia, sleep-wake disorders, dementia, or epilepsy [12,13]. In fact, H_3R antagonists/inverse agonists showed significant inhibitory activity in several rodent models of epilepsy, a disease in which high doses of several centrally-acting H_1 receptor (H_1R) antagonists used as anti-allergic drugs have been found occasionally to encourage the development of convulsions in healthy young children, especially those taking antihistamines for a long time [14–17]. Previously, the only success story in man was reported on pitolisant (PIT), one of the most advanced H_3R drugs in clinical development against different sleep disorders (narcolepsy) and Parkinson disease. Recently, significant and imposing efficacy of PIT has been demonstrated on photoepileptic patients with previously unsuccessful standard AEDs co-medication [18].

Supported by the abovementioned results, we used the multiple-target approach involving the designed structural overlap of H_3R pharmacophore with main structural elements of different AEDs on the market. A related approach has previously been realized by linking the known antagonist H_3R pharmacophore (3-piperidinopropoxy)aryl to known neuroleptics [19–22]. Moreover, recent studies have suggested that this multi-targeting approach can successfully be applied to afford dual serotonin transporter/H_3R ligands [23,24]. Therefore, and as a part of our continuous search for potential anticonvulsant drug candidates, the objective of the present study was to link the H_3R pharmacophores, namely 3-piperidinopropan-1-ol and (4-(3-(piperidin-1-yl)propoxy)phenyl)methanol, with several antiepileptic moieties to explore the most relevant substitution pattern combining high H_3R antagonist affinity with potent anticonvulsant activity. Consequently, a series of compounds (**1**–**5**) incorporating hydantoin, aminopropanamide, and 4-(1,2,4-triazole-4-yl)phenol present in phenytoin (PHT), safinamide, and loreclezole, correspondingly, has been synthesized and examined on its *in vitro* antagonistic binding affinities at hH_3Rs. Since antagonism of H_1Rs has been linked to convulsion, and in order to support the receptor-subtype selectivity, the *in-vitro* binding affinities of new compounds **1**–**5** at hH_1Rs have further been tested. Moreover, the *in-vitro* affinities of **1**–**5** at H4Rs have been investigated as H_4Rs were found, amongst H_1R–H_4R, to display the highest receptor homology to H_3Rs. Also, the *in vivo* anticonvulsant effects against maximum electroshock (MES)-induced and pentylenetetrazole (PTZ)-kindled convulsions in Wistar rats were examined.

2. Results and discussion

2.1. Chemistry

Heterocyclic antiepileptic precursors **PI**, **PIV** and **PV** containing hydantoin and 1,2,4-triazole, respectively, were prepared according to previously described methods [25,26]. The precursors **PVII**, **PVIII**, **PX**, and **PXI** containing the 1-(3-phenoxypropyl)piperidine as H_3R pharmacophore elements were prepared as described previously [27–31]. The heterocyclic antiepileptic precursors **PIV** and **PV** were used in the reaction with H_3R pharmacophore element **PVIII** to obtain the final products **1** and **2**, respectively, whereas **PI** was used in the reaction with **PVII** and **PX** to prepare the final products **4** and **5**, respectively. In addition, the H_3R pharmacophore element **PXI** was the starter precursor to obtain the final product **3**.

2.2. Pharmacology

All of the new multiple-target compounds **1**–**5** were first tested for their H_3R activity obtained by [^{3}H]N^{α}-MeHA binding assay on HEK-293 cell membrane preparation stably expressing hH_3R. To expand their pharmacological profile, their binding affinities in competition-binding experiments with seven-point measurements in at least duplicates ($n \geq 2$) were also investigated. Displacement assays were carried out using membrane suspension of cell lines stably expressing the hH_1R (CHO) with [^{3}H]pyrilamine. Moreover, binding assay on Sf9 cells transiently expressing hH_4R was used to examine their affinities at hH_4R (Table 1).

The H_3R affine pharmacophore 1-(3-phenoxypropyl)piperidine present in all compounds is the receptor-binding domain of many H_3R antagonists/inverse agonists and integrates the most substantial structural features that ensure receptor interactions, namely the tertiary amine and, in a certain distance, a polar moiety coupled to an aryl group. In the [^{3}H]N^{α}-MeHA displacement assay, **1**–**5** exhibited moderate to high *in vitro* affinities in the nanomolar as well as sub-nanomolar concentration range with pK_i values in