European Journal of Medicinal Chemistry 45 (2010) 256–263

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Original article

Sigma-1 ligands: Tic-hydantoin as a key pharmacophore

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ARTICLE INFO

Article history:
Received 26 May 2009
Received in revised form
10 August 2009
Accepted 1 October 2009
Available online 9 October 2009

Keywords:
Sigma receptor
Hydantoin
Tetrahydroisoquinoline

ABSTRACT

Sigma-1 receptors are involved in numerous pathological dysfunctions and the synthesis of selective ligands is of interest. We identified a fused tetrahydroisoquinoline-hydantoin (Tic-hydantoin) structure with high affinity and selectivity for these receptors. We report here our efforts towards the pharmacomodulation of this substructure, the synthesis of 9 analogs with stereochemistry inversion, opening of isoquinoline ring, removal of isoquinoline nitrogen, replacement of isoquinoline by pyridine, of Tic-hydantoin moiety by quinazolinedione heterocycle. All these analogs provided a loss in the affinity for the sigma-1 receptor. The present work underlines the real importance of the Tic-hydantoin moiety for the obtainment of high affinity ligands.

1. Introduction

Sigma receptors were first described by Martin et al. in 1976 [1]. They are now classified into two distinct subtypes denoted σ_1 and σ_2 [2]. These subtypes display a different tissue distribution and a distinct physiological and pharmacological profile in the central and peripheral nervous system. Based on the predicted 223 amino acid sequence, sigma-1 receptor shares no homology with any mammalian proteins. Homology analysis of the amino acid sequence has suggested that the sigma-1 receptor has two transmembrane segments, resulting in an extracellular loop of approximately 50 amino acids and an intracellular C-terminus of approximately 125 amino acids [3,4]. According to this model, the N-terminus is very short and also localised intracellularly. The ligand binding region together with the second hydrophobic region has been suggested to be important for the binding of ligands [5] but the exact binding site has still to be elucidated. σ_1 receptors were described to modulate the transmission of neurotransmitters such as norepinephrine, dopamine, serotonin, acetylcholine and glutamate as well as the activity of opiate receptors [6]. Consequently, they are associated with some functions or disorders such as nociception [7], cocaine addiction [8–10], mnesic disorders [11], depression [12], anxiety, epilepsy [13] and are implicated in neuroprotection [14,15]. Furthermore, σ_1 proteins are over expressed in tumor cells, which make them a possible target for cancer treatment [16].

Previous studies in our laboratory evidenced the affinity of compound **1** (Fig. 1) containing the tetrahydroisoquinoline-hydantoin structure towards sigma-1 receptors [17] and a chemical approach to this structure was developed [18]. This compound was first optimized modifying in parallel the Tic-hydantoin structure and the amino side chain to provide a first lead **2** (Fig. 1). The modification of the Tic-hydantoin part consisted in substitution of the aromatic nucleus, aromatic deletion, reduction of the size of the central quinoline ring, reduction of the hydantoin ring and formation of a thiohydantoin [17]. The modification of the amino side chain took advantage of Glennon and Ablorpeddey model [19,20]. The optimal chain was elected as $n = 3$ and $m = 1$, regarding several criteria such as sigma-1 affinity (IC_{50} guinea pig = 3.9 nM), selectivity towards sigma-2 receptor ($IC_{50} > 500$ nM), a limited number of free rotation bond and a very low cytotoxicity providing a high selectivity index (ratio CC_{50}/IC_{50}) greater than 50,000 [21].

In this paper, we report our continuing efforts towards the modulation of Tic-hydantoin core of the lead compound **2** ($n = 3$, $m = 1$) and complete our previous study. Obviously, we decided to evaluate different changes in the substructure (Fig. 2). We focused

Abbreviations: P_{HPLC}, Purity determined by HPLC; TLC, Thin-layer chromatography; t_R, HPLC retention time; CDI, 1,1′-Carbonyldiimidazole; tCDI, 1,1′-Thiocarbonyldiimidazole; EP, Petroleum ether; AcOEt, Ethyl acetate; Hex, *n*-Hexane; Cyh, Cyclohexane; DCM, Dichloromethane; CAN, Acetonitrile; THF, Tetrahydrofuran; IsoQ, Isoquinoline; Pyr, Pyridine; DIEA, Diisopropylethylamine; TFA, Trifluoroacetic acid; PTSA, Paratoluenesulfonic acid; HBTU, 2-(1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate; HOBt, 1-Hydroxybenzotriazole; aro, Aromatic.

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doi:10.1016/j.ejmech.2009.10.004

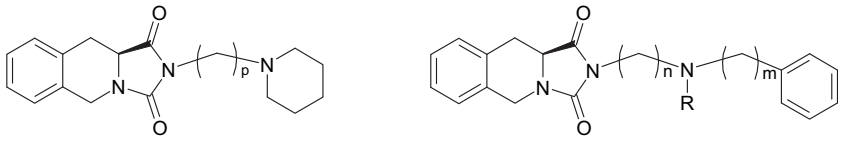

Fig. 1. Structure of compounds **1** and **2**.

our work on the importance of the stereochemistry, the synthesis of thiohydantoin, moderate modifications that were shown to be effective in our last work. To evaluate the importance of the constrained structure, we designed an open quinoline ring. The major changes were introduced with the deletion of the nitrogen atom, the deletion of the central ring with the dance of the nitrogen atom and the extension of the hydantoin ring.

2. Chemistry

N-methyl-*N*-benzyl-1,3-diamine **3** was synthesized according to our previously described procedure [21,22]. Slightly unstable and difficult to purify, it is conserved as its Boc protected form **4**. The synthesis of enantiomer compound **5** follows the same synthetic strategy as compound **2** and is described in Scheme 1. The starting material was commercial Boc-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid **6** (Boc-D-Tic-OH) whose secondary amine function was protected using Boc_2O. Amine **3** was preliminary deprotected by a TFA/CH_2Cl_2 1:1 treatment and followed by a large excess of DIEA (15 equiv), then coupled with acid **6** using HOBt/EDCI activation and an excess of DIEA to yield intermediate **7**. After deprotection of the secondary amino group, evaporation, and addition of THF and DIEA, 1,1′-carbonyldiimidazole (CDI) was added to yield hydantoin **5**. Both enantiomers are chemically and enantiomerically stable. The enantiomeric purity of both enantiomers was evaluated higher than 98% (chiral HPLC). The optical rotation of the two compounds are $[\alpha] = +132.0$ at 28 °C for compound **2** and $[\alpha] = -132.1$ at 28 °C for **5**. Preliminary study showed that those compounds were stable under acidic or neutral solution for more than 48 h.

Synthesis of thiohydantoin analog **8** was similar, starting from L-Tic-OH **9**. The cyclisation step was performed using thiocarbonyldiimidazole (Scheme 2). This thiohydantoin revealed a low chemical stability. Furthermore, HPLC experiments showed a complete racemisation of the compound. After preparative separation of both enantiomers, each compound showed a complete racemisation in ethanol after 30 min at 50 °C. Further details of the racemisation process will be published elsewhere.

The synthesis of analog **11** (Scheme 3) necessitates the preparation of N-Boc-N-methylphenylalanine **12** according to published method [23].

In order to obtain the analog compound **15** without the quinoline nitrogen, a Diels Alder cycloaddition of maleimide **13** and orthoquinodimethane was envisaged. Though modest, the higher yields were obtained according to the synthetic pathway described in Scheme 4. Maleimide **13** was synthesized from amine **3** and maleic anhydride in two steps. Intermediate orthoquinodimethane was obtained from sultine **14** easily prepared from α,α′-dichloro-*o*-xylene [24]. Pyridine analogs **16** and **17** were synthesized according to the same methodology starting from pyridine-2,3-dicarboxylic anhydride for **16** and pyridine-3,4-dicarboxylic anhydride for **17** (Scheme 5). The poor yields were due to the instability of the final compounds towards nucleophiles (methanol for instance) and the difficulty to take them out of silica.

Quinazolinedione analogs **23**–**25** were synthesized in two steps starting from isatoic anhydrides (Scheme 6). These latter compounds were either commercially available or synthesized according to Carter et al. [25] (compounds **18**, **19**).

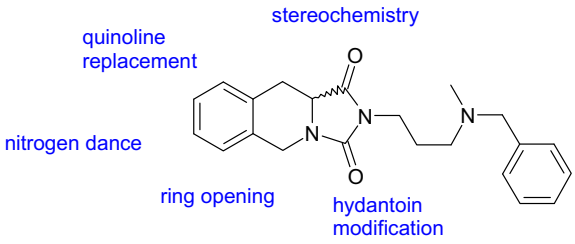

Fig. 2. Pharmacomodulations around the Tic-hydantoin core.

3. Biological results and discussion

All the compounds were evaluated in binding assays on human cerebral cortex σ_1 receptor using haloperidol as reference compound [26]. For compounds showing high σ_1 affinity, binding assays were also performed on rat σ_2 receptor [27]. The specific ligand binding to the receptors is defined as the difference between the total binding and the non-specific binding determined in the presence of an excess of unlabelled ligand. The biochemical results are presented as IC_{50} value, concentration causing a half-maximal inhibition of control specific binding (Table 1) [28].

The lead compound **2** has a high affinity for σ receptors and good σ_1 versus σ_2 selectivity. The configuration of the asymmetrically substituted carbon seems to have an interesting influence on the affinity for σ_1 receptor resulting in a slight increase for the (*R*)-enantiomer **5**, while the selectivity versus σ_2 receptor is preserved.

Replacement of urea by thiourea in compound **8** increased the affinity, as we already described [17] but in this case the results have to take into account the chemical and enantiomeric unstability of the compound. Moreover, thiourea-containing compounds often show many adverse reactions, while in many cases the corresponding urea compounds do not cause similar toxicity [29].

Concerning the modifications of the Tic core, the opening of the isoquinoline ring in amine **11** causes a dramatic loss of affinity, highlightening the importance of a constrained structure whereas the elimination of the isoquinoline nitrogen in compound **15** results in a 6.5-fold decrease in affinity.

The replacement of the Tic core by a more polar pyridine nucleus core provides complete loss of σ_1 affinity for compounds **16** and **17**, which is consistent with Glennon's model.

As our lead compound **2** does not fit exactly with this model because of a too big distance between hydrophobic Tic substructure and central nitrogen atom, the replacement of Tic-hydantoin structure by quinazolinedione heterocycles should be of interest. In our case, non polar substituents were introduced on the aromatic ring providing in all examples an important decrease of affinity at least 10-fold.