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Original article

Efficient synthesis of hexahydroindenopyridines and their potential as melatoninergic ligands

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ABSTRACT

Hexahydroindenopyridine (HHIP) is an interesting tricyclic piperidine nucleus that is structurally related to melatonin, a serotonin-derived neurohormone. Melatonin receptor ligands have applications in several cellular, neuroendocrine and neurophysiological disorders, including depression and/or insomnia. We report herein an efficient two-step method to prepare new HHIP via enamine *C*-alkylation-cyclization. The influence of substituents on the benzene ring and the nitrogen atom on melatoninergic receptors has been studied. Among the 25 synthesized HHIPs, some of them containing methylenedioxy (series 2) and 8-chloro-7-methoxy substituents (series 4) on the benzene ring revealed affinity for the MT_1 and/or the MT_2 receptors within the nanomolar range or low micromolar. Similar activities were also encountered for those presenting urea (**4g**), *N*-aryl (**2e**) and *N*-alkyl (**2f**) acetamide functions. Therefore, new synthesized compounds with a HHIP nucleus have emerged as new promising leads towards the discovery of melatoninergic ligands which could provide new therapeutic agents.

1. Introduction

Melatonin (*N*-acetyl-5-methoxytryptamine) is a serotonin-derived neurohormone of long-standing interest found in some algae and higher animals, including humans. The pineal gland produces melatonin under the influence of the suprachiasmatic nucleus of the hypothalamus by a circadian rhythm of secretion, with peak levels occurring during darkness [1]. Melatonin (MLT) participates in a variety of cellular, neuroendocrine and neurophysiological processes. It is involved in the modulation of the cardiovascular and immune systems, as well as in the glucose metabolism and hormone secretion. For this reason, a disturbance in melatonin rhythm and secretion is involved in the development of neurodegenerative diseases, cancer, stroke, thermoregulation and sleep disorders [2–7]. Melatonin exerts its effects by several molecular mechanisms, including via high-affinity G-protein-coupled receptors. Indeed, it activates MT_1 and MT_2 receptors, at nanomolar concentrations, and also binds with a lower affinity to the third putative isoform MT_3 receptor, which is the intracellular protein quinone reductase 2 [8,9].

Since both MT_1 and MT_2 receptors are widely distributed in different areas of the brain and extracerebral organs, multiple functional roles for melatonin have been suggested. However, considerable attention has been paid to melatonin receptor ligands in recent years given their applications in insomnia and depression. Among the melatoninergic drugs, agomelatine is a commercialized antidepressant (Laboratoires Servier, valdoxan® and thymanax®) that stands out for its interesting properties as a potent agonist of MT_1 and MT_2 receptors (Fig. 1) [10,11].

Hexahydroindenopyridine (HHIP) is an intriguing heterocyclic framework that provides a new class of compounds with potential use as therapeutic agents. HHIPs possess a tricyclic ring system that contains a constrained indeno-piperidine pharmacophoric nucleus. This class of compounds displays several biological activities, including antidepressant [12–14], serotoninergic [15,16],

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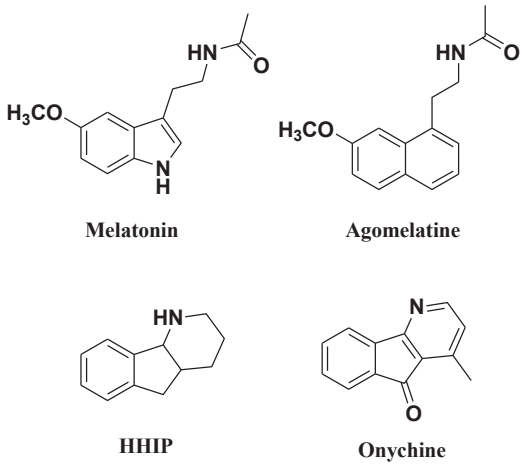


Fig. 1. Melatonin, agomelatine, HHIP and onychine.

antipsychotic [17], antispermatogenic [18] and inhibition of the 11β-hydroxysteroid dehydrogenase enzyme [19]. Furthermore, HHIPs have attracted our interest as potential melatoninergic ligands thanks to their original melatonin-related structure (Fig. 1).

The literature has described different synthetic methods to obtain this type of molecules. In this regard, Augstein et al. prepared 5-phenyl-HHIPs from a cyanoethyl phenylindanone in two steps, but obtained low yields [12]. Some authors achieved the synthesis of HHIPs via a tricyclic lactam intermediate. Kunstmann et al. carried out the synthesis through the condensation of aldehydes and 6-phenyl-3,4-dihydropyridin-2-ones which were prepared from 5-oxo-5-phenylvaleronitriles [13]. Van Emelen et al. did so by an intramolecular Ritter reaction of a hydroxynitrile [20] whereas Hong et al. obtained 4-azafluorenes, onychine-type (Fig. 1), through a hetero Diels–Alder cycloaddition of indenes with 1,3-azabutadienes [21].

In this work, we decided to use a new method which allowed us to easily obtain the HHIP framework in very few steps and with good yields [22]. We evaluated the influence of different substituents in the nitrogen atom and at the C-7 and C-8 positions of the benzene ring of the synthesized HHIPs on their affinity towards melatoninergic receptors. To this end, we have prepared four sets of differently substituted HHIPs (series 1–4) and their affinity towards MT_1 and MT_2 receptors was tested to establish a chemical structure-activity relationship (SAR).

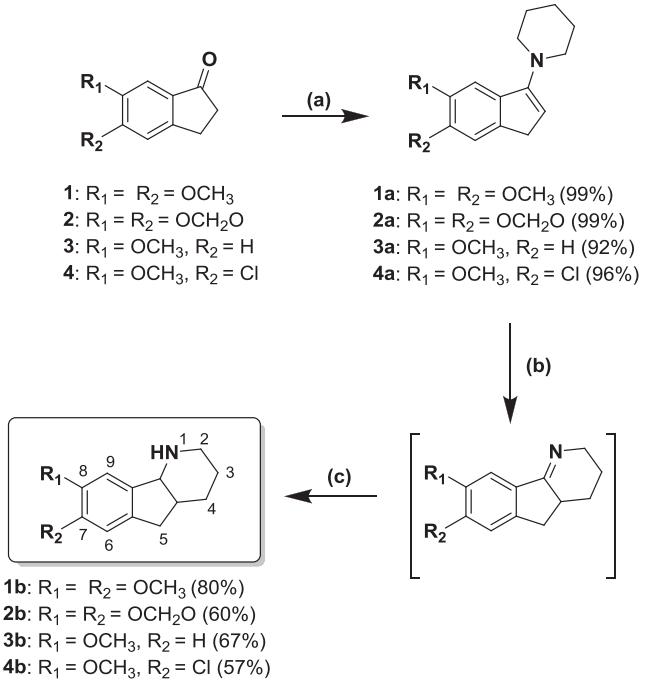
2. Results and discussion

2.1. Chemistry

The synthesis of HHIP has been accomplished as outlined in Schemes 1–6. We have prepared four series of compounds (series 1–4) in accordance with the starting material. Therefore, we synthesized the following parent compounds: 7,8-dimethoxy-2,3,4,4a,5,9b-hexahydro-1*H*-indeno[1,2-*b*]pyridine (series 1) (Schemes 1 and 3); 7,8-methylenedioxy-2,3,4,4a,5,9b-hexahydro-1*H*-indeno[1,2-*b*]pyridine (series 2) (Schemes 1 and 4); 8-methoxy-2,3,4,4a,5,9b-hexahydro-1*H*-indeno[1,2-*b*]pyridine (series 3) (Schemes 1 and 5); and 7-chloro-8-methoxy-2,3,4,4a,5,9b-hexahydro-1*H*-indeno[1,2-*b*]pyridine (series 4) (Schemes 1 and 6).

The first step consisted in preparing the appropriate enamine (**1a**–**4a**) from a commercially available 1-indanone (**1**–**4**), using piperidine in the presence of $TiCl_4$ which acts as both Lewis acid catalyst and water scavenger. As starting materials, we employed: 5,6-dimethoxy-1-indanone (**1**, series 1), 5,6-methylenedioxy-1-indanone (**2**, series 2), 6-methoxy-1-indanone (**3**, series 3) and 5-chloro-6-methoxy-1-indanone (**4**, series 4). This reaction took place at room temperature in toluene for 3 days. Next, and with no further purification, the enamine (**1a**-**4a**) was treated with 3-bromopropylamine hydrobromide in DMF under reflux to give the tricyclic ring system with an imine function, which was reduced with $NaBH_4$ in ethanol to obtain the expected HHIP nucleus (Scheme 1) [22–25].

Parcell and Hauck [25] proposed that this reaction worked via an iminium ion in which, firstly the 3-bromopropylamine would attack the iminium tautomeric form of the enamine, followed by the piperidine elimination to give a new imine. This imine would be in equilibrium with an enamine form, and its double bond could react with the bromopropylamine chain (SN2) to displace the bromine anion with intramolecular cyclization. However, this mechanism shows some inconsistencies and the more feasible reaction mechanism would be the well-known C-alkylation reaction



Scheme 1. Synthesis of HHIPs **1b**–**4b** (series 1–4). Reagents and conditions: (a) piperidine, $TiCl_4$, toluene, N_2 atmosphere, r.t., 3 days; (b) 3-bromopropylamine hydrobromide, DMF, N_2 atmosphere, reflux, 8 h; (c) $NaBH_4$, EtOH, rt, 16 h.

of enamines with alkyl halides (Scheme 2) [22].

Synthesis of compounds of the series 1 (Scheme 3): 7,8-dimethoxy-2,3,4,4a,5,9b-hexahydro-1*H*-indeno[1,2-*b*]pyridine (**1b**) was *N*-methylated with formaldehyde and formic acid, followed by reduction with $NaBH_4$ to obtain **1c**. When **1b** and **1c** were O-demethylated after the treatment with BBr_3, catecholic HHIPs **1d** and **1e**, were respectively prepared. The N-acetylation of **1b** with Ac_2O and pyridine allowed us to attain **1f**. When **1b** was treated with an isothiocyanate reagent, such as 1-(2-isothiocyanatoethyl) piperidine and 1,2,3-trifluoro-4-isothiocyanatobenzene, the corresponding thiourea derivatives **1g** and **1h**, were respectively obtained.

Synthesis of compounds of the series 2 (Scheme 4): 7,8-methylenedioxy-2,3,4,4a,5,9b-hexahydro-1*H*-indeno[1,2-*b*]