European Journal of Medicinal Chemistry 81 (2014) 218–226

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

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

Original article

New developments in redox chemical delivery systems by means of 1,4-dihydroquinoline-based targetor: Application to galantamine delivery to the brain

Mihaela-Liliana Ţînţaş [a], Lénaïg Foucout [a], Sylvain Petit [a], Sylvain Oudeyer [a], Fabienne Gourand [b,c,d], Louisa Barré [b,c,d], Cyril Papamicaël [a,*], Vincent Levacher [a,*]

[a] Normandie Univ, COBRA, UMR 6014 et FR 3038, Univ Rouen, INSA Rouen, CNRS, IRCOF, 1 Rue Tesnière, 76821 Mont Saint Aignan Cedex, France
[b] CEA, DSV/I2BM, LDM-TEP Group, GIP Cyceron, Bd Henri Becquerel, BP 5229, 14074 Caen Cedex, France
[c] Université de Caen Basse-Normandie, Caen, France
[d] CNRS, UMR ISTCT 6301, LDM-TEP Group, GIP Cyceron, Caen, France

ARTICLE INFO

Article history:
Received 22 October 2013
Received in revised form
5 May 2014
Accepted 5 May 2014
Available online 6 May 2014

Keywords:
Redox chemical delivery system
Blood brain barrier (BBB)
Acetylcholinesterase (AChE) inhibitors
Galantamine

ABSTRACT

The therapeutic efficiency of palliative treatments of AD, mostly based on acetylcholinesterase (AChE) inhibitors, is marred by serious adverse effects due to peripheral activity of these AChE inhibitors. In the literature, a redox-based chemical delivery system (CDS) has been developed to enhance drugs distribution to the brain while reducing peripheral side effects. Herein, we disclose two new synthetic strategies for the preparation of 1,4-dihydroquinoline/quinolinium salt redox-based systems particularly well designed for brain delivery of drugs sensitive to alkylation reactions. These strategies have been applied in the present case to the AChE inhibitor galantamine with the aim of alleviating adverse effects observed with cholinergic AD treatment. The first strategy is based on an intramolecular alkylation reaction as key step, whilst the second strategy relies on a useful coupling between galantamine and quinolinium salt key intermediate. In the course of this work, polymer-supported reagents and a solid-phase synthesis approach revealed to be highly helpful to develop this redox-based galantamine CDS.

1. Introduction

Alzheimer's disease (AD) is a multi-factorial disorder clinically characterized by several bio-chemical and pathological events: low concentrations of the neurotransmitter acetylcholine (ACh) in the central nervous system (CNS) [1], interneuronal deposits of aberrant proteins like β-amyloid plaques [2,3] and intraneuronal deposits of *tau*-proteins (neurofibrillary tangles) [4], oxidative stress [5] and dys-homeostasis of biometals [6]. Although different strategies are explored to prevent AD progression, only palliative treatments based on increasing ACh levels in the CNS by means of acetylcholinesterase (AChE) inhibitors are presently available along with memantine; a NMDA (*N*-methyl-D-aspartate) receptor antagonist [7]. Although AChE inhibitors have clearly demonstrated improved cognitive function in Alzheimer's patients, many side effects (*eg.* gastrointestinal events, nausea, vomiting, diarrhoea, dizziness) mainly associated with their peripheral AChE inhibitory activity, strongly impact on the patient's quality of life and may lead to treatment discontinuation [8]. Among the various strategies investigated to improve the transport and distribution of drugs into the brain, the redox-based chemical delivery system (CDS) developed by N. Bodor [9] appears as an appealing chemical tool to reach this goal. However, the use of lipophilic carriers derived from 1,4-dihydropyridines is prone to electrophilic attack on the enamine 5,6-double bond [10] and may severely impede the development of this CDS strategy. To circumvent this issue, our group has recently developed new lipophilic carriers in 1,4-dihydroquinoline series, in which the enamine character of the double bond is masked [11]. In this context, we sought to develop a new brain-targeting galantamine CDS based on 1,4-dihydroquinoline/quinolinium salt redox carrier. The delivery system for galantamine is depicted in Fig. 1.

After crossing the lipoidal blood brain barrier (BBB), the galantamine covalently-bound to 1,4-dihydroquinoline undergoes enzymatic oxidation to give rise to the corresponding quinolinium salt which is sequestered in the CNS. Sustained release of galantamine and elimination of the quinolinium salt take place through enzymatic hydrolysis in the CNS. According to this scenario, this

* Corresponding authors.
E-mail addresses: cyril.papamicael@insa-rouen.fr (C. Papamicaël), vincent.levacher@insa-rouen.fr (V. Levacher).

http://dx.doi.org/10.1016/j.ejmech.2014.05.022
0223-5234/

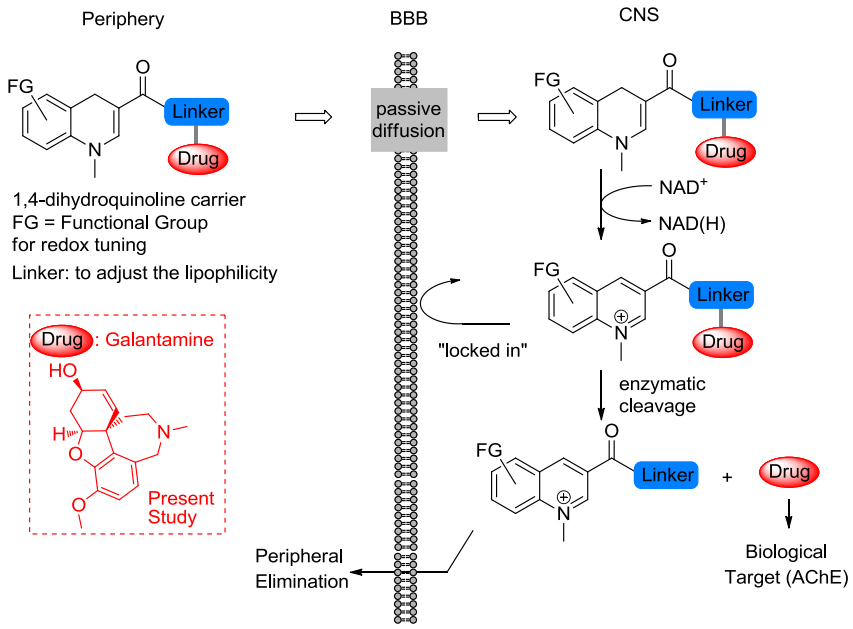

Fig. 1. Brain-targeting galantamine CDS by means of 1,4-dihydroquinoline carriers.

CDS strategy is intended to reduce peripheral levels of galantamine while improving its CNS delivery and should therefore attenuate side-effects associated with current AChE inhibitor treatments. It is worth mentioning that annelation of the 1,4-dihydropyridine ring is not only intended to protect the enamine 5,6-double bond towards electrophilic attack, but can also provide an easy way to tune the redox properties of the carrier by introducing various electron-donating and -withdrawing functional groups (FG) at the phenyl moiety to reach a good compromise between peripheral stability of the carrier and its oxidation in the CNS.

2. Results and discussion

2.1. Chemistry

The design of a brain-targeting galantamine CDS based on 1,4-dihydroquinoline is not as straightforward as it might appear, due to the presence of a tertiary nitrogen atom in galantamine which may compete during the required quaternization step of the quinoline moiety. Two main approaches have been considered to address this issue while providing general solution for targeting drugs sensitive to alkylation reactions by these redox CDSs. The first approach implements an intramolecular quaternization, as key step, ensured by a properly functionalized alkyl chain at C-2 of the quinoline ring. The originality of this strategy consists in the use of a suitable protecting group which, after galantamine coupling with the carrier, would be easily converted into a leaving group able to promote smooth cyclization to form the desired quinolinium salt (Scheme 1a). A solid-phase variant of this intramolecular quaternization strategy is also reported (Scheme 1a). Last but not least, the second approach will consider the formation of the quinolinium salt prior to drug introduction, thus avoiding any problem of quaternization of the drug. To this end, it will be necessary to implement a challenging coupling between galantamine and an activated carboxylic acid at C-3 of the quinolinium salt (Scheme 1b).

First, we focused on the development of the intramolecular quaternization strategy. The required quinoline precursor **3a** was prepared through a Borsche modification of the Friedländer methodology [12] from imine **1** [13] and β-ketoester **2**. A brief screening of the conditions revealed that the reaction could be conducted under neat conditions in the presence of piperidine leading to the quinoline **3a** in 85% isolated yield. On the other hand, compound **2** was synthesized by treatment of γ-butyrolactone with lithio ethyl acetate, following a literature procedure previously reported with δ-valerolactone [14]. Hydroxy β-ketoester **2** was obtained in equilibrium with its cyclic hemiketal form (ratio 1:2) in 94% overall yield. With quinoline **3a** in hand, we then undertook the protection of the alcohol chain at C-2 with 3,4-dihydro-2*H*-pyran under acidic conditions leading to THP ether derivative **3b** in 90% yield. Among the plethora of alcohol protecting groups available in the literature, THP protecting group was selected not only because of its high stability under basic conditions that will be further required for ester hydrolysis at C-3, but also because of numerous literature reports that describe its straightforward one-step conversion into various leaving groups [15–17]. As laid down, hydrolysis of quinoline ester **3b** could be performed under alkaline conditions, without altering THP ether at C-2, affording quinoline carboxylic acid **3c** in 70% yield (Scheme 2).

At this stage and before undertaking the tricky coupling between the resulting quinoline carboxylic acid **3c** and galantamine, we sought to validate our intermolecular quaternization approach from quinoline **3b**. Thus, according to a procedure reported by Sonnet [16], quinoline **3b** was reacted with PPh_3/Br_2 in CH_2Cl_2 to give the expected bromide derivative. We actually determined by ^1H NMR analysis that, in the present case, the quinoline was *N*-protonated and upon addition of DIEA, quaternized quinoline **4a** could be obtained within 5 min with 82% overall yield from quinoline **3b**. We also obtained quinolinium salt **4a** in the same yield following the method described by Miokowski [17] which suggests an alternative procedure using a mixture of PPh_3 and CBr_4.

Having validated the crucial cyclization step from quinoline **3b**, we then investigated the coupling reaction between quinoline **3c** and galantamine by screening various coupling agents such as DCC/DMAP, FEP/DIEA and PyBOP/DIEA. However, ^1H NMR analysis of the crude reactions could not be conclusive regarding the formation of the desired compound **3d**. Tedious purifications resulting from