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Synthesis and characterization of copper-specific tetradendate ligands as potential treatment for Alzheimer's disease

Synthèse et caractérisation de ligands tétradentes du cuivre, à visée thérapeutique pour la maladie d'Alzheimer

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ABSTRACT

To regulate copper homeostasis for the therapy of Alzheimer's disease, a series of "tetradendate monoquinoline" (TDMQ) ligands consisting of an 8-aminoquinoline nucleus with a bidentate amine side chain attached at the C2 position of the quinoline moiety, both parts being able to take part in copper chelation, were designed. These TDMQ ligands are potentially able to provide the square planar tetradentate coordination sphere, which is preferred for the extraction of copper(II) from amyloids, with a lower as possible molecular weight, to optimize the passage through different physiological barriers.

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RÉSUMÉ

La perturbation de l'homéostasie du cuivre dans le cerveau des patients atteints de la maladie d'Alzheimer est un phénomène majeur de la pathologie. Cette communication présente la synthèse et la caractérisation de ligands de type TDMQ (= tétradente monoquinoléine), conçus pour rétablir cette homéostasie, et donc jouer un rôle thérapeutique. Ces ligands sont constitués d'un cycle 8-aminoquinoléine et d'une chaîne polyamine bidente liées en position C2 de la quinoléine. Les propriétés stériques et électroniques de ces ligands doivent leur permettre de chélater le cuivre(II) dans un environnement plan carré, avec une forte affinité, ce qui est requis pour extraire efficacement le cuivre lié aux amyloïdes dans le cerveau. De plus, leur faible poids moléculaire est favorable à un passage efficace des différentes barrières physiologiques.

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1. Introduction

Alzheimer's disease (AD) is the main cause of neurodegenerative disorders. Today, dementia is estimated to affect more than 46 million people worldwide, with the number doubling every 20 years, and the World Health Organization estimates that the number may reach 131 million by 2050 [1]. The profound irreversible memory loss and progressive cognitive dysfunction, together with impaired language skill and personality changes, make AD a terrible disease for patients and their families, and render it a potential social and economic crisis of 21st century [2].

Currently, the approved drugs (four acetylcholine inhibitors and memantine, a noncompetitive antagonist of *N*-methyl-D-aspartate receptor) are weakly effective and their efficiency/cost ratios are questionable. Therefore, the design of new efficient drugs to stop AD evolution at the early stages has become one of the most important challenges in medicinal chemistry.

A normal brain requires metal ions for a number of important cellular processes. As such, the brain contains relatively high concentrations of transition metals, especially Fe, Zn, and Cu, that take part in the neuronal activity within the synapses (Zn(II) in particular) and ensure the function of various metalloproteins and metalloenzymes. However, the accumulation of Cu, Fe, and Zn within senile plaques reaches 400, 950, and 1100 μM, respectively, three to five times the concentration observed in a normal brain [3]. The strong affinity of these metal ions for Aβ amyloids promotes Aβ aggregation [4], which is considered as a main factor for amyloid toxicity in AD or other pathological condition [5]. Moreover, the activation of copper−amyloid by an endogenous reductant is probably at the origin of the redox stress tightly correlated with AD pathogenesis [6]. Iron−amyloids are weaker promoters of an oxidative stress, mainly due to iron precipitation [7]. Consequently, we focused our attention on the design of specific copper chelators to restore metal homeostasis in AD brain by extraction of copper ions from pathological sinks (amyloids being the major one) and transfer them to copper-carrier proteins, to recycle them in their physiological role [8]. On the basis of such hypothesis, we designed a series of ligands that are expected to (1) extract Cu(II) from the Cu−Aβ complex, (2) release the copper ion under physiological conditions, and (3) inhibit the production of reactive oxygen species induced by Cu−Aβ in the presence of a physiological reductant. Therefore, they may be able to regulate copper homeostasis and reduce the oxidative stress in AD brain. These ligands must be selective for copper with respect to zinc chelation, to avoid the depletion of zinc proteins by an exogenous ligand as potential drug candidate. In fact, the lack of selectivity for copper and the coordination of zinc by clioquinol and PBT2 might be at the origin of their failure in clinical trials [9]. On the basis of our knowledge on tetradendate ligand PA1637, which suffer from a low solubility [10], we decided to design new tetradentate copper ligands based on a mono-8-aminoquinoline motif to reduce the size and the molecular weight of the ligands and consequently facilitate their passage through the blood−brain barrier.

Here, we report the syntheses and the characterization of prototype ligands of this new series, named TDMQ (tetradendate monoquinolines). For the sake of stability, these ligands were prepared as hydrochloric salts. In a preliminary study of complexation, TDMQ5 was found to efficiently chelate copper(II) as a 1/1 metal/ligand complex, whereas zinc(II) was not chelated in the same conditions.

2. Results and discussion

These TDMQ ligands consist of an 8-aminoquinoline nucleus and a bidentate amine side-chain attached at C2 of the quinoline moiety, both fragments taking part in copper chelation to provide the square planar tetradentate coordination sphere, which is preferred for efficient chelation and selectivity for copper(II).

2.1. Syntheses

Structural modulations of the 8-aminoquinoline series were carried out by preparing compounds having (1) different substituents on the quinoline nucleus, a chlorine atom at C5 and C7 positions for TDMQ5 and TDMQ20, or CF_3 group at C6 for TDMQ16 and TDMQ22, and (2) a side chain of variable length: one methylene group in the proximal part of the side chain for TDMQ5 and TDMQ16, or two methylenes for TDMQ20 and TDMQ22. The structures of these ligands are summarized in Scheme 1.

2.1.1. Synthesis of TDMQ5 and TDMQ16 (short side chain, n = 1)

TDMQ5 was prepared starting from 3,5-dichloroaniline as presented in Scheme 2 (A = 3,5-dichloro-2-nitroaniline). The quinoline ring was synthesized in the presence of acetaldehyde in hydrochloric acid to yield 5,7-dichloro-2-methylquinoline (B). Nitration of B in a mixture of HNO_3/H_2SO_4 produced 8-nitro-5,7-dichloro-2-methylquinoline (D). Reduction of the nitro group was achieved by iron/acetic acid in ethanol. After protection of the amino group, the 2-methyl substituent was oxidized by selenium dioxide, and the side chain was introduced by reductive amination of the aldehyde function by *N,N*-dimethyl-1,2-ethanediamine in the presence of triacetoxyborohydride. The resulting ligand was then protonated in a diethyl ether solution of hydrochloric acid.

TDMQ16 was synthesized starting from 2-nitro-4-(trifluoromethyl)aniline (C, Scheme 2), and the quinoline ring was synthesized as described above for TDMQ5, then providing 2-methyl-8-nitro-6-(trifluoromethyl)quinoline (D). The following steps of the synthesis of TDMQ16 were the same as for TDMQ5 (reduction of 8-nitro, protection of amino group, oxidation of 2-methyl, introduction of the side chain, and protonation). The overall yields were 7% and 13% for TDMQ5 and TDMQ16, respectively, from commercially available starting materials.

2.1.2. Synthesis of TDMQ20 and TDMQ22 (long side chain, n = 2)

TDMQ20 was synthesized starting from 5,7-dichloro-2-methyl-8-nitroquinoline (D, Scheme 3). Subsequent

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