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Research paper

Multifunctional diamine AGE/ALE inhibitors with potential therapeutical properties against Alzheimer's disease

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ABSTRACT

An important part of pathogenesis of Alzheimer's disease (AD) is attributed to the contribution of AGE (Advanced Glycation Endproducts) and ALE (Advanced Lipid peroxidation Endproducts). In order to attenuate the progression of AD, we designed a new type of molecules that consist of two trapping parts for reactive carbonyl species (RCS) and reactive oxygen species (ROS), precursors of AGE and ALE, respectively. These molecules also chelate transition metals, the promoters of ROS formation. In this paper, synthesis of the new AGE/ALE inhibitors and evaluation of their physicochemical and biological properties (carbonyl trapping capacity, antioxidant activity, Cu^{2+}-chelating capacity, cytotoxicity and protective effect against *in vitro* MGO-induced apoptosis in the model AD cell-line PC12) are described. It is found that compounds **40b** and **51e** possess promising therapeutic potentials for treating AD.

1. Introduction

Alzheimer's disease (AD) is the most common neurodegenerative disease that leads to memory loss and progressive cognitive impairment. Two neuropathological hallmarks resulting from abnormal protein deposits are identified in AD brains as extracellular amyloid β (Aβ) plaques and intracellular tau-associated neurofibrillary tangles (NFT) [1]. A critical imbalance between cerebral reactive oxygen species (ROS) production and endogenous antioxidant capacities associated with biometal dyshomeostasis has been suggested to be a driving force for AD onset and progression [2–4]. Indeed, Aβ-oligomers induce oxidative stress whereas transition metals (Zn^{2+}, Cu^{2+} and Fe^{3+}) stimulate Aβ aggregation and APP (amyloid precursor protein) processing [2–4]. Besides these various triggering factors at the early stages of AD, advanced glycation endproducts (AGE) induced by oxidative stress exacerbation are now considered to play an important role at the late stages of pathogenesis [2]. Non-enzymatic condensation of reducing carbohydrates (mainly glucose) with free nucleophilic functional groups of proteins such as amino and guanidino groups of lysine and arginine, respectively, provides labile Schiff bases that in turn rearrange to more stable α-ketoamines called Amadori products [5]. Oxidation of Amadori products results in the formation of very reactive α-oxoaldehydes, called as reactive carbonyl species (RCS), such as glyoxal (GO), methylglyoxal (MGO) and 3-deoxyglucosone (3-DG). This process is known as “Maillard reaction”. Condensation of resulting α-oxoaldehydes with nucleophilic groups of proteins or of nucleic acids further leads to structural rearrangements to provide various products bearing nitrogen- and oxygen-containing heterocycles and representing the

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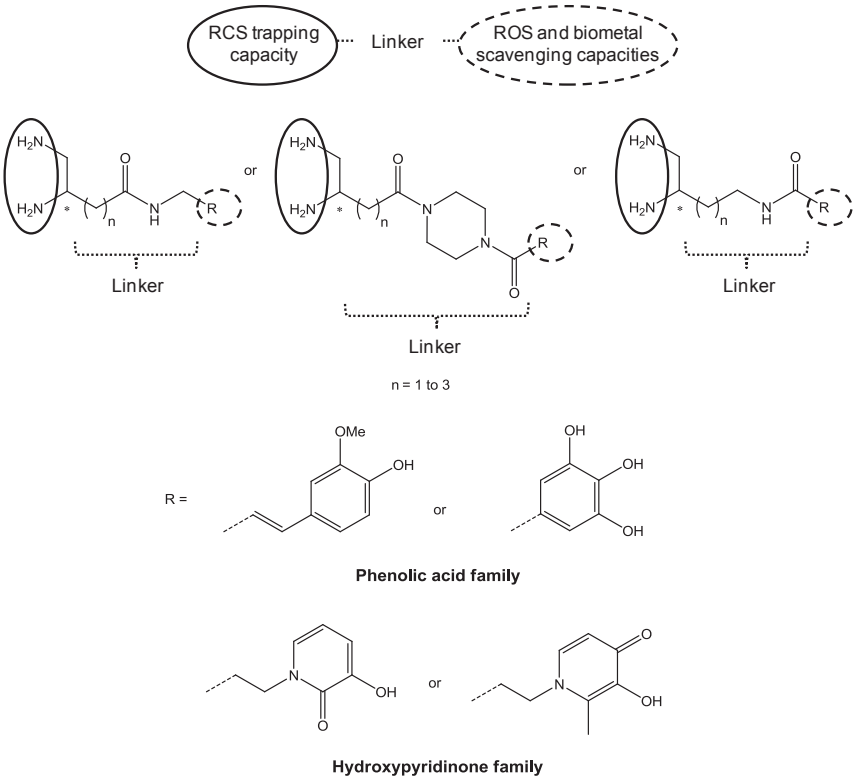

Fig. 1. New multifunctional diamine AGE/ALE inhibitors.

heterogenous variety of AGE [6]. The slow oxidative degradation of monosaccharides like triose-phosphate intermediates in glycolytic pathway also forms the corresponding α-oxoaldehydes [7]. ALE (Advanced Lipid peroxidation Endproducts) correspond to the formation of similar irreversible covalent adducts. The lipid peroxidation of polyunsaturated fatty acids leads to the production of α,β-unsaturated aldehydes such as acrolein, malondialdehyde (MDA) and 4-hydroxy-2-nonenal (4-HNE) [5,7,8]. Michael addition of nucleophilic groups of biomolecules to thus formed RCS induces the formation of ALE. AGE/ALE formation plays an important role in age-related tissue and cell dysfunction As toxic mediator and oxidative stress promoter [6], carbonyl stress is also implicated in the pathogenesis of diabetic microvascular complications (nephropathy, retinopathy and neuropathy) [9], atherosclerosis [10], cardiovascular and neurodegenerative diseases [8]. In order to prevent and treat these pathologies, several AGE inhibitors have already been reported including aminoguanidine, pyridoxamine, carnosine, 2,3-diaminophenazine, tenilsetam and OPB-9195. However, clinical trials of these AGE inhibitors have been suspended up to date [8,11]. In AD, extensive AGE/ALE accumulation linked to enhanced RCS level has been reported in senile plaques and NFT [2,12]. The overproduction of MGO is due to the progressive decrease in efficacy of carbonyl-detoxification systems (glyoxalases), but also to a dysfunction of glycolytic pathway [12,13]. Furthermore, Aβ-mediated membrane lipid peroxidation intensifies 4-HNE, acrolein and MDA synthesis [2,14]. Consequently, RCS accumulation takes part in the vicious downward redox amyloid spiral leading to neurodegeneration. AGE/ALE contribute to AD pathogenesis through three main mechanisms. First, glycated Aβ cross-linking promotion accelerates its deposition and its protease resistance [12]. Secondly, AGE/ALE formation not only accelerates tau hyperphosphorylation, disturbs the neuronal membrane depolarization process and the glucose transport but also exacerbates glutamate-mediated excitotoxicity [12,13]. Thirdly, AGE promote *via* their receptors RAGE oxidative stress and inflammation as well as cell apoptosis [5,12,13].

New treatments are urgently needed since current AD therapies offer only short-term benefits to patients by transiently improving the cognitive symptoms [15]. Considering the multifactorial pathogenesis of AD, an attractive strategy has recently emerged favoring the design of multifunctional drugs [1]. With this in mind and as a continuation of our effort in developing efficient AGE/ALE inhibitors [16,17], we have designed a new type of molecules that are simultaneously able to trap RCS as well as ROS and transition metals (Fig. 1).

Previously, we have successfully demonstrated the efficacy of 2,3-diaminopropionic acid (Dap) derivatives to trap MGO and MDA (Fig. 2). In this paper, we report the synthesis of new AGE/ALE inhibitors and the evaluation of these molecules in terms of their capacities to trap RCS, ROS, and Cu^{2+} as well as their cytotoxicity and their protective effect against *in vitro* MGO-induced apoptosis in the model AD cell-line PC12.

2. Results and discussion

2.1. Chemistry

As shown in Scheme 1, our synthetic strategy involves: i) the transformation of α-carbonyl group of easily available amino acids

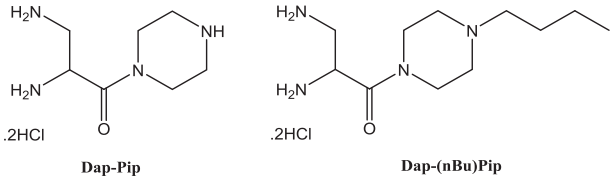

Fig. 2. Dap derivatives of previous AGE/ALE inhibitor series.