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Synthesis and anti-diabetic activity of new *N*,*N*-dimethylphenylenediamine-derivatized nitrilotriacetic acid vanadyl complexes

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ABSTRACT

Vanadium compounds are promising anti-diabetic agents. However, reducing the metal toxicity while keeping/improving the hypoglycemic effect is still a big challenge towards the success of anti-diabetic vanadium drugs. To improve the therapeutic potency using the anti-oxidative strategy, we synthesized new *N*,*N*-dimethylphenylenediamine (DMPD)-derivatized nitrilotriacetic acid vanadyl complexes ([VO(dmada)]). The in vitro biological evaluations revealed that the DMPD-derivatized complexes showed improved antioxidant capacity and lowered cytotoxicity on HK-2 cells than bis(maltolato)oxidovanadium (IV) (BMOV). In type II diabetic mice, [VO(p-dmada)] (0.15 mmol kg^{-1}/day) exhibited better hypoglycemic effects than BMOV especially on improving glucose tolerance and alleviating the hyperglycemia-induced liver damage. These insulin enhancement effects were associated with increased expression of peroxisome proliferator-activated receptor α and γ (PPARα/γ) in fat, activation of Akt (v-Akt murine thymoma viral oncogene)/PKB (protein kinase-B) in fat and liver, and inactivation of c-Jun NH_2-terminal protein kinases (JNK) in liver. Moreover, [VO(p-dmada)] showed no tissue toxicity at the therapeutic dose in diabetic mice and the oral acute toxicity (LD50) was determined to be 1640 mg kg^{-1}. Overall, the experimental results indicated that [VO(p-dmada)] can be a potent insulin enhancement agent with improved efficacy-over- toxicity index for further drug development. In addition, the results on brain Tau phosphorylation suggested necessary investigation on the effects of vanadyl complexes on the pathology of the Alzheimer's disease in the future.

1. Introduction

The prevalence of diabetes mellitus is increasing at an alarming rate [1]. It is an arduous task for pharmaceutical workers to find effective drugs for diabetes mellitus. In previous efforts, vanadium compounds have been synthesized and shown to have comprehensive anti-diabetic activities in vitro and in vivo [2–6]. Oral administration of vanadium compounds could ameliorate insulin resistance and reduce hyperglycemia both in diabetic mice and in limited human studies [5,7–10]. Since the failure of bis(ethylmaltolato)oxidovanadium(IV) (BEOV) in phase II clinical trial due to the renal side effect, the challenge for anti-diabetic vanadium drug discovery has been on how to develop highly active vanadium complexes with balanced drug toxicity, especially on the renal side effect [11–15].

Based on the known molecular mechanism of pharmacological and toxicological effects of vanadium complexes, the strategy for controlling vanadium toxicity has been proposed by utilizing antioxidant bifunctional ligands [14,16–18]. Accordingly, we previously prepared two series of vanadyl complexes, e.g. bis((5-hydroxy-4-oxo-4H-pyran-2-yl)methyl-2-hydroxybenzoatato)-oxidovanadium (IV) (BSOV) and vanadyl *N*-(*p*-hydroxyphenylcarbamoylmethyl)iminodiacetate ([VO(phpada)]) [14,18]. [VO(phpada)] produced more stable hypoglycemic effect than BMOV (the methyl analog of BEOV) in *db/db* mice. Both BSOV and [VO(phpada)] exhibited reduced oral acute toxicity and in vitro cytotoxicity on kidney cells. After a long term (7 months) treatment, BSOV caused much lower incidence of renal interstitial edema than BMOV [19].

In the present work, we describe the synthesis and evaluation of vanadyl complexes conjugated with *N*,*N*-dimethylphenylenediamine (DMPD), which is an antioxidant capable of capturing a variety of free radicals. In addition, DMPD was shown to mitigate metal-free β-amyloid (Aβ) and metal-Aβ induced cytotoxicity in vitro and reduced cerebral Aβ plaques, as well as to significantly improve cognitive defects in 5 × FAD mice of Alzheimer's disease (AD) [20]. The dimethylamino functional group was important in targeting and modulating Aβ aggregation pathways and scavenging free radicals [20]. Considering the

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close connection of AD with diabetes in pathological processes, especially the deposition of amyloidogenic proteins (i.e. Aβ peptides and islet amyloid polypeptide) [21–24] and protection of vanadyl complexes on neural cells under βamyloid burden [25], we expected the incorporation of DMPD moiety into vanadyl complexes to improve the anti-diabetic potency as well as potential anti-senile dementia.

2. Materials and methods

2.1. Materials

N,*N*-dimethylphenylenediamines were from Alfa Aesar (Alfa Aesar Chemical Co. Ltd., USA). Vanadium (IV) oxide sulfate hydrate was from Sigma-Aldrich (St. Louis, MO, USA). L-Ascorbic acid was from Beijing Chemical Reagent Company (Beijing, China). Antibodies for peroxisome proliferator-activated receptor γ (PPARγ), phosphorylated c-Jun NH_2-terminal protein kinases (p-JNK), Akt (v-Akt murine thymoma viral oncogene)/PKB (protein kinase-B) and glyceraldehyde-3-phosphate dehydrogenase (GAPDH) were from Santa Cruz Biotechnology (Santa Cruz, CA, USA). Antibody for PPARα was purchased from Cell Signaling Technology (Cell Signaling Technology, Inc. Beverly, MA, US). Antibody for p-Tau231 was obtained from Abcam (Abcam, UK). Dulbecco's Modified Eagle's medium (DMEM) was purchased from Hyclone (Fisher Scientific International Inc., USA) and fetal bovine serum (FBS) was obtained from Gibco (Gibco BRL Co. Ltd., USA). 3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium (MTS) was from Promega (Promega Co., USA). All other chemicals were of analytic grade unless specified statement.

2.2. Synthesis

The synthesis route is illustrated in Scheme 1:

2.2.1. Synthesis of ligands (*3a,b,c*)

The compounds were synthesized according to the reference [26] with modification. Briefly, under the protection of nitrogen, 20 mmole nitrilotriacetic acid in 50 mL of anhydrous pyridine was placed in a 100 mL round bottom flash. Then 22 mmole acetic anhydride was added under constant stirring for 1 h at 110 °C. After cooling to 50 °C, 22 mmole of *N*,*N*-dimethylphenylenediamine was added and stirred for 1 h at 50 °C. Pyridine was removed by vacuum distillation. The residue was dissolved in a minimal amount of aqueous ammonia and then the product was precipitated by dropwise addition of hydrochloride to pH 4–5. The final product was collected by filtration, washed with anhydrous alcohol, and further purified by recrystallization in ethanol-water. The purity was assessed by HPLC (> 97%). Finally, the samples were characterized by IR absorption (Nicolet Instruments, USA), ESI-MS (Applied Biosystems, USA) and ^{1}H NMR spectra (Bruker, USA).

3a (*p*-H_2dmada): White; Yield 88.3%; IR (cm^{-1}): 1600 cm^{-1}, 905 cm^{-1} (ring $\nu_{C=C}$); 1620 cm^{-1} ($\nu_{as(COO)}$); 1397 cm^{-1} ($\nu_{s(COO)}$); ^{1}H NMR (δ): 7.33 (s, 2H), 7.02 (s, 2H), 4.03 (s, 2H), 3.66 (s, 4H), 2.83 (s, 6H); ESI-MS: *m/z* 310 $[M + H]^+$; MW calc. ($C_{14}H_{19}O_5N_3$) 309.13.

3b (*m*-H_2dmada): White; Yield 72.1%; IR (cm^{-1}): 1556 cm^{-1}, 898 cm^{-1} (ring $\nu_{C=C}$); 1626 cm^{-1} ($\nu_{as(COO)}$); 1353 cm^{-1} ($\nu_{s(COO)}$); ^{1}H NMR (δ): 7.33 (t, J = 7.9 Hz, 2H), 7.03 (t, J = 7.9 Hz, 2H), 4.10 (m, 2H), 3.69 (s, 4H), 2.91 (s, 6H); ESI-MS: *m/z* 310 $[M + H]^+$; MW calc. ($C_{14}H_{19}O_5N_3$) 309.13.

3c (*o*-H_2dmada): White; Yield 48.5%; IR (cm^{-1}): 1599 cm^{-1}, 904 cm^{-1} (ring $\nu_{C=C}$); 1647 cm^{-1} ($\nu_{as\ (COO)}$); 1398 cm^{-1} ($\nu_{s(COO)}$); ^{1}H NMR (δ): 7.52–7.20 (m, 4H), 4.11 (s, 2H), 3.72 (s, 4H), 2.77 (s, 6H); ESI-MS: *m/z* 310 $[M + H]^+$; MW calc. ($C_{14}H_{19}O_5N_3$) 309.13.

2.2.2. Synthesis of vanadyl complexes (*4a,b,c*)

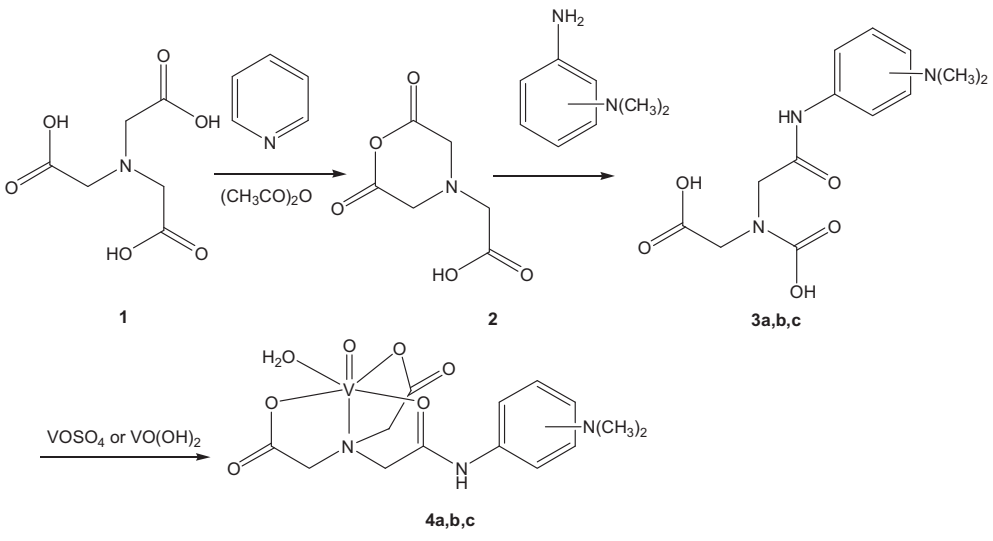
For preparation of **4a**, 10 mmole **3a** was dissolved in 20 mL of deionized water. The solution was adjusted to pH 7–8 with 0.5 M NaOH. Under stirring, 20 mL of vanadyl sulfate (10 mmole) was added dropwise, resulting in formation of a dark green precipitate. The product was collected by centrifugation (5000 rpm) and further purified by recrystallization in DMSO-water.

For preparation of **4b** (or **4c**), **3b** (or **3c**) (1 mmole) was dissolved in 50 mL of deionized water. Then freshly prepared vanadyl(IV) hydroxide (~2 mmole) was added and the solution was left with stirring for 2 h at room temperature. The unreacted vanadyl (IV) hydroxide was removed by filtration. The product was obtained by vacuum distillation and purified by recrystallization in water. Finally, the vanadyl complexes were characterized by IR absorption (Nicolet Instruments, USA), elemental analysis (Elementar, DEU), UV–Vis (Cary-300, USA), ESI-MS (Applied Biosystems, USA) and EPR spectrometry (Bruker-ESP300, DEU).

4a [VO(p-dmada)]: Green; Yield 81.2%; IR (cm^{-1}): 1600 cm^{-1}, 910 cm^{-1} (ring $\nu_{C=C}$); 1624 cm^{-1} ($\nu_{as(COO)}$); 1297 cm^{-1} ($\nu_{s(COO)}$); 971 cm^{-1} ($\nu_{V=O}$); ESI-MS: *m/z* 393 $[M + H]^+$; Elemental Analysis (%): Found: C 42.62; N 10.80; H 4.91; Anal. Calc. $C_{14}H_{19}N_3O_7V$ (%): C 42.87; N 10.71; H 4.88.

4b [VO(m-dmada)]: Dark blue-gray; Yield 67.6%; IR (cm^{-1}): 1521 cm^{-1}, 909 cm^{-1} (ring $\nu_{C=C}$); 1627 cm^{-1} ($\nu_{as(COO)}$); 1390 cm^{-1} ($\nu_{s(COO)}$); 988 cm^{-1} ($\nu_{V=O}$); ESI-MS: *m/z* 393 $[M + H]^+$; Elemental Analysis (%): Found: C 43.02; N 10.61; H 4.82; Anal. Calc. $C_{14}H_{19}N_3O_7V$ (%): C 42.87; N 10.71; H 4.88.

4c [VO(o-dmada)]: Dark blue-gray; Yield 73.1%; IR (cm^{-1}):



Scheme 1. The synthesis route for vanadyl *N*-(*N*,*N*-dimethylaminophenylcarbamoylmethyl) iminodiacetate ([VO(dmada)]).

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