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Synthesis of 61-bis(1-adamantylcarbamoyl)-1,2-methano[60]fullerene and its antagonistic effect on haloperidol-induced catalepsy in mice

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Abstract—The 61-bis(1-adamantylcarbamoyl)-1,2-methano[60]fullerene was synthesized from *N*,*N*′-di(1-adamantyl)malondiamide and C_{60} in the presence of 1,8-diazabicyclo[5,4,0]-7-undecene. The intraperitoneal administration of this fullerene derivative (10 mg/kg) caused an antagonistic effect on haloperidol-induced catalepsy in mice.

1. Introduction

Since fullerene was discovered in 1985,[1] the biological activities of its derivatives have been focused on in the field of medicinal chemistry. Photodriven DNA cleavage,[2,3] antioxidant activity,[4] the inhibition activity of HIV protease,[5,6] antibacterial activity[7] and the neuron protection effect[8] of the fullerene derivatives have been reported. Furthermore, the fullerene derivative was not mutagenic and cell toxic without photoirradiation.[9,10] These results indicated that fullerene derivatives were useful compounds for developing medicines against various diseases.

Parkinson's disease is a basal ganglia denaturation disease with an extrapyramidal function abnormality.[11] The characteristic conditions of Parkinson's disease are tremors, rigidity and akinesia.[12,13] The dopamine cell is damaged by oxidative stress because superoxide and hydrogen peroxide are produced by the autoxidation of dopamine or the oxidation of dopamine by monoamine oxidase.[14] Catalepsy is the rigid state of a part or all of the muscle, and is induced by the dopamine D_2 receptor block of haloperidol.[15] The catalepsy can be considered to represent an animal model for Parkinson's disease or for neuroleptic-induced parkinsonism in humans.[15] Amantadine is a dopamine releasing medicine,[16] and inhibits the uptake of dopamine to the synaptic vesicle in the corpus striatum[17] and monoamine oxidase activity.[18]

The fullerene molecule can pass through the blood–brain barrier.[19] Carboxymethylenefullerene has an antioxidant effect and neuron protection effect.[8] More recently, it was reported that fullerene C_{60} and ascorbic acid protect cultured chromaffin cells against levodopa toxicity.[20] From these studies, the fullerene derivatives, which can pass through the blood–brain barrier, release dopamine, and have an antioxidant activity and neuron protection effect, might be a medicine against Parkinson's disease. Thus we synthesized 61-bis(1-adamantylcarbamoyl)-1,2-methano[60]fullerene, which might be hydrolyzed to carboxymethylenefullerene and amantadine by an amidase, such as anandamine aminohydrolase (fatty acid amide hydrolase, EC 3.5.1.4), which hydrolyzed anandamine to ethanolamine and arachidonic acid in the human brain.[21,22] The antagonistic effect on haloperidol-induced catalepsy in mice was then evaluated.

2. Results and discussion

N,*N*′-Di(1-adamantyl)malondiamide (**1**) was synthesized by the reported method.[23]

Keywords: Fullerene; Catalepsy.
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2.1. Preparation of 61-bis(1-adamantylcarbamoyl)-1,2-methano[60]fullerene (2) (Fig. 1)

To a stirred solution of C_{60} fullerene (purity of 99.5%, SES Research, Houston, TX, USA, 435 mg, 0.60 mmol) in toluene (200 mL) was added **1** (330 mg, 0.89 mmol) and carbontetrabromide (300 mg, 0.90 mmol). To this mixture was dropwise added 1,8-diazabicyclo[5,4,0]-7-undecene (0.9 mL, 6.0 mmol) for over 10 min and then the reaction solution was stirred for 27 h at ambient temperature. The resulting solution was filtered and the crude product was purified by column chromatography (silica gel, toluene–chloroform = 1:1, v/v) to give **2** (55.4 mg, 8.48% yield, mp > 300 °C) (Fig. 1). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.24 (8H, s), 1.74 (8H, d, J = 6.5 Hz), 2.16 (12H, s), 2.97–3.02 (2H, m), 6.73 (2H, s). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 29.48, 29.69, 36.24, 41.31, 53.72, 138.01, 140.96, 142.20, 142.27, 142.92, 142.99, 143.07, 143.76, 144.40, 144.69, 144.77, 145.14, 145.18, 145.40, 146.11, 161.86. HRFAB-MS m/z = 1089.2538 (error, +0.07).

2.2. Antagonistic effect

Three ddY male mice (8 weeks, 34–38 g) were used for each dose plan. Amantadine was dissolved in 0.9% (w/v) saline. Compound **2** was suspended in a 10% (v/v) aqueous dimethylsulfoxide (DMSO) solution. The amantadine (10 or 32 mg/kg) and **2** (10 or 32 mg/kg) were intraperitoneally administered to the mice. After 30 min, haloperidol (2 mg/kg) in 0.9% (w/v) saline was intraperitoneally administered. The antagonistic effect of the amantadine and **2** was evaluated by a bar test at 0.5, 1, 2 or 4 h after the haloperidol administration.[24]

The administration of amantadine (10 or 32 mg/kg) caused an antagonistic effect on the haloperidol-induced catalepsy. However, the antagonistic effect was not proportional to the administered amount of amantadine (Fig. 2). The administration of **2** (10 mg/kg) caused an antagonistic effect on the haloperidol-induced catalepsy. However, the administration of **2** (32 or 100 mg/kg) did not cause the effect. It was reported that 1-adamantanyl-arachidonylamide inhibited the fatty acid amide hydrolase (IC_{50}, 37.4 ± 8.6 μM).[25] Thus, it is possible that the administration of **2** (32 or 100 mg/kg) caused inhibition of the fatty acid amide hydrolase as stated above, and **2** was not hydrolyzed in the mice brain, and consequently, no antagonistic effect was observed. In the study of the central nervous system effects of DMSO, Braude and Monroe reported that the intraperitoneal administration of 1.25 g/kg of DMSO to mice did not produce a decrease in the spontaneous motor activity.[26] In this study, 1.1 g/kg of DMSO was administered to the mice. Therefore, it was thought that the administered dose of DMSO did not affect the central nervous system.

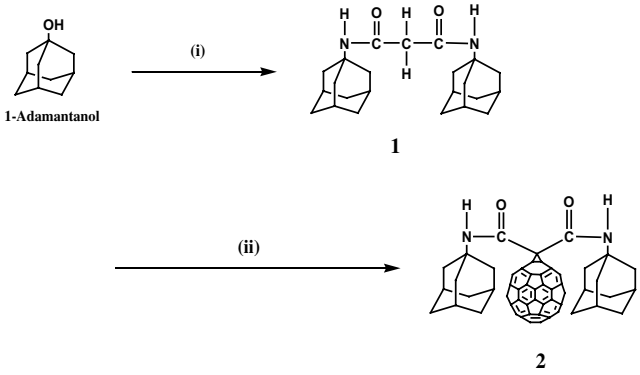

Figure 1. Synthesis of **2**: (i) cyanoacetamide, trifluoroacetic acid; (ii) C_{60}, 1,8-diazabicyclo[5,4,0]-7-undecene, CBr_4, toluene.

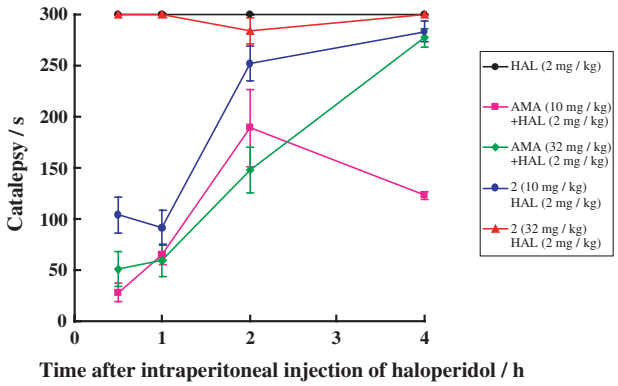

Figure 2. Antagonistic effect on amantadine and **2** for haloperidol-induced catalepsy in mice. HAL: haloperidol; AMA: amantadine; values represent mean ± SE.

In conclusion, we found that the intraperitoneal administration of the fullerene derivative (10 mg/kg) caused an antagonistic effect on haloperidol-induced catalepsy in mice.

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