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Synthesis of a Dopamimetic Thionated Dipeptide Prodrug of L-DOPA

Ye WANG, Zhan Zhu LIU*, Shi Zhi CHEN

Institute of Materia Medica, Chinese Academy of Medical Sciences
& Peking Union Medical College, Beijing 100050

Abstract: L-DOPA has gained widespread credit over the past decades as being the mainstay of the pharmacological treatment of Parkinson's disease. However, there are many adverse effects associated with the use of L-DOPA. The prodrug approach is the most promising way to solve the problem. In this article, a thionated dipeptide prodrug of L-DOPA **11** was synthesized *via* 10 steps in a total yield of 26.5% from L-DOPA.

Keywords: Prodrug, dipeptide, Parkinson's disease, L-DOPA

Although a number of innovative anti-Parkinson's agents have been launched and used clinically in the past decades, the classical dopamine-related L-DOPA (levodopa), which was first introduced in the clinical practice in 1960s, remains to be the mainstay of symptomatic treatment of this disease, often leading to more than 50% amelioration of clinical manifestations[1-3]. However, there are a number of therapeutic problems arising from the long-term therapy with L-DOPA. The most serious limitations of L-DOPA can be summarized as follows: poor bioavailability, wide range of interpatient variation of plasma levels, unpredictable therapeutic response, and various side effects[4]. It is known that the physical-chemical properties of L-DOPA are the decisive factor responsible for the above problems: low water solubility resulting in incomplete dissolution at or *prior to* the absorption site, low lipid solubility resulting in unfavorable partition, and high susceptibility of the drug molecule to chemical and enzymatic degradation. The prodrug approach was the most promising way to resolve the dissolution-absorption-metabolism problems prior and during absorption of L-DOPA. A lot of efforts have been made to the structural modifications of L-DOPA, including some possible prodrugs such as aliphatic esters, di- and tripeptides of L-DOPA[5-8].

In order to improve the therapeutic value of L-DOPA, we have carried out a project aimed at searching for a pharmacologically useful prodrug of L-DOPA. Instead of a simple dipeptide derived from the condensation of two molecules of L-DOPA, 7,8-dimethoxy-1, 2, 3, 4-tetrahydroisoquinoline-3-carboxylic acid (Tic), which was synthesized from L-DOPA and formaldehyde through several steps, was used as the substitute of L-DOPA to condense with another molecule of L-DOPA. It is expected that the topographically constrained Tic structural component may stabilize the dipeptide

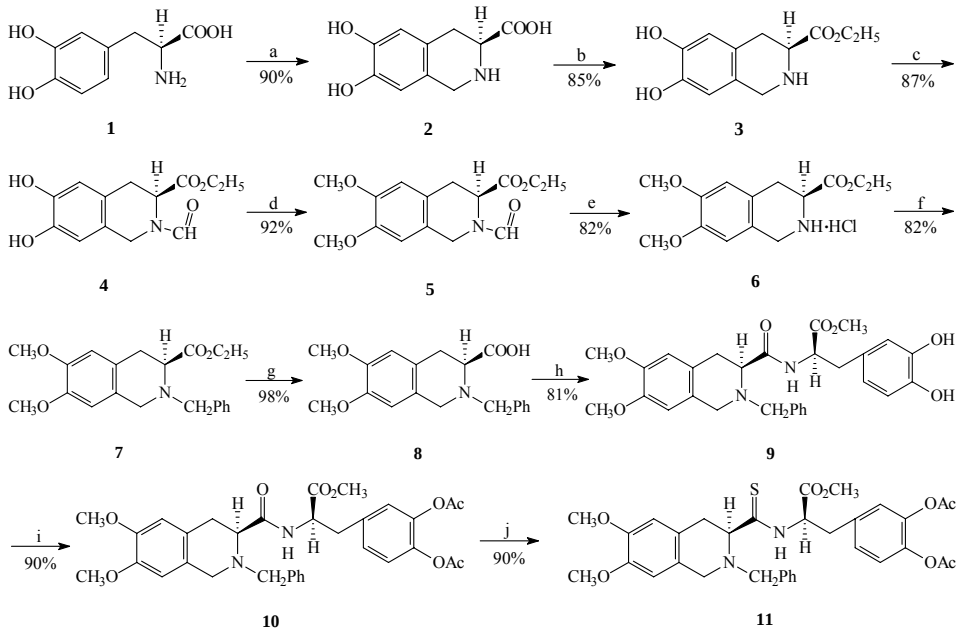
* E-mail: liuzhanzhu@imm.ac.cn

to some extent. Besides, the carbonyl group of the dipeptide was thionated to further stabilize it. Moreover, the carboxyl group was protected as methyl ester, and the hydroxy groups of catechol were protected with two acetyl groups.

Thus, L-DOPA **1** reacted with formaldehyde under acidic condition to give the tetrahydroisoquinoline product **2**. **2** was esterified in refluxing anhydrous ethanol containing HCl to yield ethyl ester **3**. The N-formyl product **4** was obtained through the reaction of **3** with formic acid/acetic anhydride. The phenolic hydroxyl groups in **4** were methylated with dimethyl sulfate in acetone to give **5**, which was N-deprotected under acidic condition to yield **6**. **6** reacted with benzyl chloride in acetone to yield the N-benzyl compound **7**. **7** was saponified with KOH in methanol to give the acid **8**. **8** was coupled with L-DOPA methyl ester under the catalysis of HOSu/DCC in DMF to give the pseudo dipeptide **9**. **9** reacted with acetic anhydride/pyridine to give **10**, which was thionated with Lawesson's regent in refluxing benzene to give **11**. The structure of **11** was confirmed by ^{1}HNMR, ^{13}CNMR, FABMS, HRMS[9].

In summary, we have prepared a thionated pseudo dipeptide in a total yield of 26.5% *via* 10 steps with L-DOPA as the starting material. Further biological test result is in progress and will be reported successively.

Scheme 1



a. $HCHO/H_2SO_4$; b. C_2H_5OH/HCl, reflux; c. $HCOOH/(CH_3CO)_2O$; d. Me_2SO_4/Acetone, r. t.; e. conc. HCl, r. t.; f. $PhCH_2Cl/K_2CO_3$, Acetone; g. KOH/CH_3OH; h. HOSu/DCC, DMF, L-DOPA methyl ester; i. Ac_2O/pyridine; h. Lawesson's reagent, benzene, reflux.

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References and Notes

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9. Data of compound **11**: ^{1}H-NMR (300MHz, $CDCl_3$, δppm): 10.3 (d, 1H, J=2.0Hz, NH), 7.4 (m, 5H, Ar-H), 7.1(m, 3H, Ar-H), 6.7(s, 1H, Ar-H), 6.6(s, 1H, Ar-H), 5.4(d, 1H, J=15Hz, $ArCH_2N$), 3.9(d, 1H, J=12.5Hz), 3.7(s, 3H, OCH_3), 3.65(d, 1H, J=12.5Hz), 3.6(s, 3H, OCH_3), 3.59(s, 3H, OCH_3), 3.35(m, 6H), 3.3(s, 3H, CH_3CO), 3.1(dd, 1H, J=16.5, 8.5Hz), 2.5(s, 3H, CH_3CO); ^{13}C-NMR (DMSO-d_6, δppm): 204.8, 170.2, 168.2, 168.1, 147.4, 147.1, 141.7, 140.8, 138.3, 138.1, 135.4, 135.3, 129.5, 128.9, 127.1, 125.9, 125.1, 124.1, 123.4, 111.4, 111.3, 110.0, 79.2, 70.7, 58.7, 57.7, 55.5, 52.3, 51.6, 35.0, 32.8, 20.3, 20.2; IR (KBr, cm^{-1}): 3199(NH), 1774 (C=O), 1741 (C=O), 1610 (C=S); FAB-MS: 621 (*m+1/z*), 282, 190; HRMS (FAB): Calcd. for $C_{35}H_{37}N_2O_8$ 621.2271, Found 621.2294.

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