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Brief Articles

Codrugs Linking L-Dopa and Sulfur-Containing Antioxidants: New Pharmacological Tools against Parkinson's Disease

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A series of multifunctional codrugs (**1**−**6**) were synthesized to overcome the pro-oxidant effect associated with L-dopa (LD) therapy. Target compounds release LD and dopamine (DA) in human plasma after enzymatic hydrolysis, displaying an antioxidant effect superior to that of *N*-acetylcysteine (NAC). After intracerebroventricular injection of codrug **4**, the levels of DA in the striatum were higher than those in LD-treated groups, indicating that this compound has a longer half-life in brain than LD.

Introduction

Parkinson's disease (PD[a]) is a progressive disabling neurodegenerative disorder characterized by severe difficulties with body motions and associated with autonomic dysfunction, depression, and dementia.[1,2] Increasing evidence suggests that oxidative stress may play an important role in the pathogenesis of PD.[3] In particular, the reduced mitochondrial complex I activity in substantia nigra seems to be implicated in energy impairment and increased reactive oxygen species (ROS) generation that could lead to a signal mediated apoptotic process.[4] This hypothesis postulates that LD and DA can induce the degeneration of cultured dopaminergic neurons, enhancing oxidative stress and accelerating the degenerative process of residual cells in patients with PD.[5−7] Thus the inhibition of nonenzymatic oxidation of DA and the inhibition of ROS formation are important strategies for preventing the age-related neurodegenerative disease, and any novel antioxidant molecule proposed as potential neuroprotective treatment should meet the prerequisite of being able to cross the BBB after systemic administration. This objective has been achieved through the targeted prodrug approach and also through the multitarget-directed drug design strategy to obtain promising multifunctional drugs for the treatment of PD and Alzheimer's disease (AD).[8−10] More recently, several dual acting codrugs in which LD and DA are linked covalently to an antioxidant molecule have been shown to provide sustained release in rat striatum and seem to protect against the oxidative stress deriving from autoxidation of DA.[11−13] Sulfur-containing compounds have earned great attention due to the profound role played by intracellular GSH in antioxidant cell defense and redox regulation. Compounds such as NAC and methionine can raise the intracellular concentration of GSH, strengthening the natural cellular antioxidant system, and methionine and bucillamine may protect PC 12 cells against DA-induced nigral cell loss in PD by binding to oxidative metabolites of DA.[14−19] If oxidative stress plays a major role in the pathogenesis of PD, then compounds with antioxidant efficacy could be utilized for neuroprotective therapy. Recent evidence has indicated that LD-GSH codrugs are useful anti-Parkinson agents devoid of the pro-oxidant effects associated with LD therapy; they are able to induce sustained delivery of DA in rats, restoring the GSH depletion evidenced in SNpc of PD patients.[8,12]

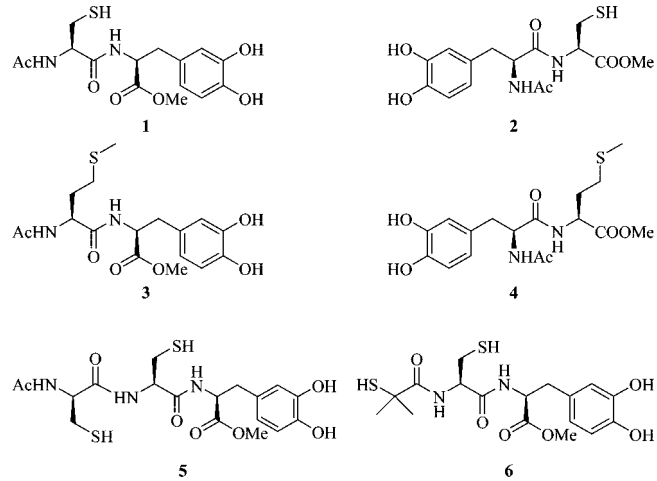

Figure 1. Chemical structures of multifunctional codrugs **1**−**6**.

The present investigation was focused on providing new anti-Parkinson codrugs in which LD is linked to cysteine, methionine, and bucillamine. These multifunctional codrugs **1**−**6** (Figure 1) containing sulfur antioxidants could prove to be useful agents against PD by preventing DA-induced cell death through direct

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[a] Abbreviations: ANOVA, analysis of variance; DA, dopamine; LD, L-dopa; BBB, blood−brain barrier; PD, Parkinson's disease; AD, Alzheimer's disease; AUC, area under the curve; AUMC, area under the first moment curve; MRT, mean residence time; ROS, reactive oxygen species; SGF, simulated gastric fluid; SNpc, substantia nigra pars compacta; NAC, *N*-acetylcysteine; GSH, glutathione; UV-DAD, ultraviolet diode array detection; EC, electrochemical detection.

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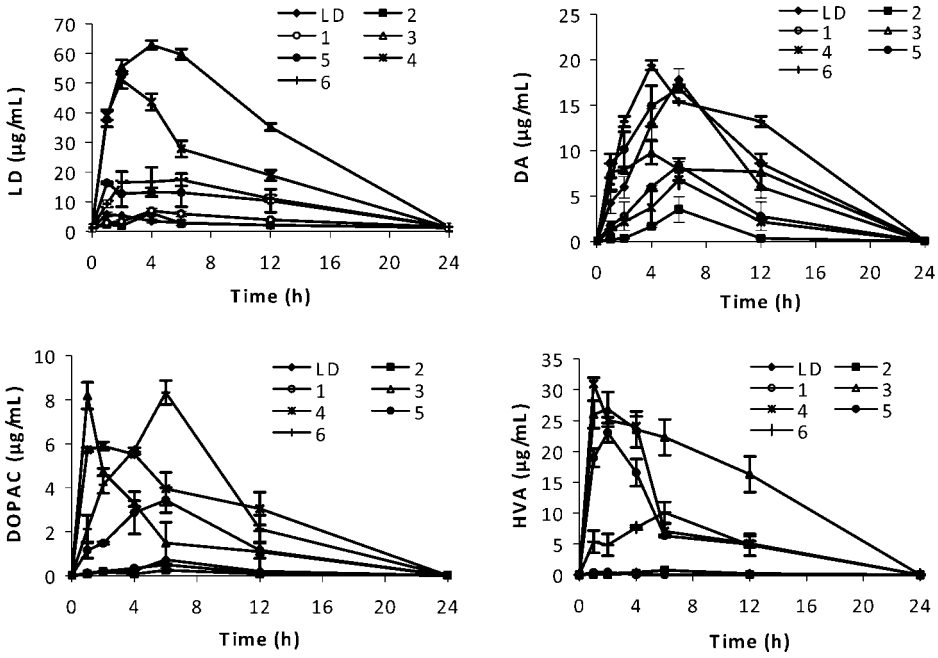

Figure 2. Plasma concentration profile of LD, DA, DOPAC, and HVA after oral administration of LD and **1**−**6** in rats. Data are expressed as mean ± SE. Each experiment was performed in triplicate.

antioxidant effects and via the stimulation of GSH synthesis. We hypothesize that treatment with codrugs linking LD and sulfur-containing antioxidants may also provide a new therapeutic strategy for PD by ameliorating the dissolution profile, gastrointestinal absorption, nigrostriatal bioavailability, and metabolism problems of LD.

Specifically, this work includes synthesis of codrugs **1**−**6** and evaluation of their physicochemical and biological properties. The pharmacological "in vivo" behavior of these new compounds as anti-Parkinson agents is also discussed.

Results and Discussion

Coefficient partition (log *P*) of conjugates **1**−**6** was determined in *n*-octanol/phosphate buffer (pH 7.4) by the saturated shake-flask method.[11] The concentration of codrugs was evaluated using an HPLC apparatus (peaks visualization were performed by ultraviolet diode array detection (UV-DAD)). The same method was employed for the evaluation of solubility in water and in buffer solutions at pH 1.3, 5.0, and 7.4. The lipophilicity of codrugs **1**−**6** was also calculated using the ACD LogP software package, version 4.55 (Advanced Chemistry Development Inc., Toronto, Canada). All the new codrugs showed high lipophilicity when compared to the parent drug LD (log $P = -2.39$).[20] In particular, compounds **3** and **6** showed the logP of 0.38 and 0.92, respectively; these values, together the good water solubility (about 100 mg/mL for compound **3**), are near the optimum for good intestinal absorption.[21] The lipophilicity of new compounds were also estimated using reverse-phase chromatographic retention times (RT);[22] log capacity factor (log *K*) values were determined using octadecyl silica columns and are strictly correlated to logP and clogP. Stability studies were performed in isotonic sodium phosphate buffer (pH 7.4) and simulated gastric fluid (SGF, pH 1.3) at 37 °C; the disappearance of the codrugs was monitored by the HPLC UV-DAD method.[23] Bioconversion of codrugs into LD was assessed at 37 °C in rat and human plasma diluted to 80% with isotonic sodium phosphate buffer (pH 7.4) as previous described.[11−13] Pseudo-first-order hydrolysis rate constants for the chemical and enzymatic hydrolysis were calculated from the slopes of linear plots of the logarithm of residual codrugs **1**−**6** against time. Under buffer solutions the new compounds showed a great chemical stability. The stability observed at pH 1.3 ($t_{1/2} > 290$ h) implies that compounds **1**−**6** are potentially able to pass unhydrolyzed through the stomach after oral administration; at pH 7.4, the compounds are stable enough ($t_{1/2} > 21$ h) to be absorbed intact from the intestine. In rat plasma, a quantitative conversion to LD was observed. The reported bioconversion was demonstrated by liquid chromatography/mass spectrometry (LC/MS) and NMR analysis. The formation of LD from human plasma proceeds more slowly; the faster hydrolysis in rat than in human plasma may be ascribed to the different enzyme systems, more efficient in rat plasma.[24] In particular, the bioconversion to LD of compounds **3** and **4** proceeds more slowly than the other codrugs. The antioxidant activity of codrugs **1**−**6** was assessed by using chemiluminescent (CL) assay.[25] In our evaluation, lucigenin was employed to amplify the signal due to superoxide anions generated by xanthine/xanthine oxidase system, while luminol was used to measure the level of hydrogen peroxide.[26] We found that, in comparison with NAC, the superoxide and peroxide scavenger activity was elevated for all synthesized compounds. These results may be related to the synergic scavenging activity of LD and antioxidant moiety (NAC, bucilamine, and methionine). In particular LD, NAC, bucilamine, and methionine were found to be effective antioxidants in different "in vitro" assays including antilipid peroxidation and superoxide anion radical scavenging.[27] The antioxidant activities of codrugs **1**−**6** could be highly controlled by the presence of free catechol groups.[28] In our study, male Sprague−Dawley rats were used for the "in vivo" absorption experiments. Figure 2 shows LD plasma concentration trends obtained in rats over time following the oral administration of codrugs **1**−**6** and of LD at doses of 0.332 mmol/kg. The noncompartimental pharmacokinetic parameters are presented in Table 1 (C_{max}, T_{max}, AUC, AUMC, and MRT). The mean plasma concentrations and C_{max} for codrugs **3** and **4** were significantly larger than those of the other compounds, and a large difference was also observed between the AUC values. Peak plasma concentrations of codugs **3** and **4** were

Table 1. Noncompartimental Pharmacokinetic Parameters of Codrugs **1**−**6**

compd	T_{max} (h)[a]	C_{max} (μg/mL)[a]	AUC (μg/(mL h))[a]	AUMC (μg/(mL h^2))[a]	MRT (h)[a]
LD	1.03 (±0.05)	5.63 (±0.75)	117.73 (±15.68)	1053.92 (±140.40)	8.95 (±1.56)
1	4.05 (±0.12)	6.91 (±0.97)	179.06 (±25.13)	1673.20 (±234.88)	9.34 (±1.31)
2	4.11 (±0.16)	6.19 (±1.21)	110.62 (±21.62)	1053.36 (±205.91)	9.52 (±1.86)
3	4.22 (±0.21)	62.87 (±1.51)	1624.91 (±39.03)	12319.3 (±295.88)	7.58 (±0.18)
4	2.25 (±0.04)	51.07 (±2.95)	984.01 (±56.84)	6844.84 (±395.38)	6.96 (±0.40)
5	1.55 (±0.04)	16.31 (±0.37)	432.20 (±36.51)	3608.38 (±304.82)	8.35 (±0.71)
6	6.04 (±0.18)	17.41 (±2.03)	493.29 (±57.52)	4056.32 (±472.97)	8.22 (±1.81)

[a] Values are means of three experiments, standard deviation is given in parentheses.

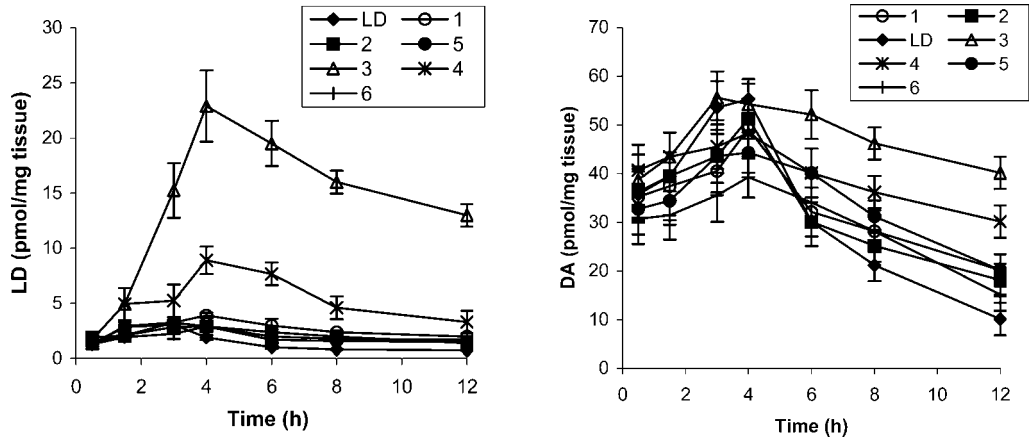

Figure 3. Rat striatal levels of LD and DA after oral administration of LD, and **1**−**6**. Data are expressed as mean ± SE. Each experiment was performed in triplicate.

reached about 4 and 2 h respectively after oral dosing. A slow decrease of plasmatic levels for codrug **3** was observed only 6 h after administration; in this case, the plasma concentration was still elevated after 8 h (53 μg/mL). Human and animal biochemical investigations clearly confirm that wearing-off phenomenon or end-of-dose deterioration is directly related to LD plasma level fluctuation after long-term treatment of PD with chronic LD therapy.[29,30] For these reasons, it can be asserted that codrug **3** is able to prolong plasma LD levels and could be beneficial in the treatment of motor fluctuation. The bioavailability of the new synthesized compounds was also evaluated by comparing neostriatal LD and DA levels after administration of codrugs **1**−**6** and LD. A previously reported HPLC method with electrochemical detection (EC) was utilized.[31] The LD and DA striatal level profiles are shown in Figure 3. Among the studied compounds, only codrugs **3** and **4** are of particular interest, as they were able to induce sustained delivery of both LD and DA in rat striatum with respect to equimolar doses of LD; the striatal levels of LD and DA were still elevated after 6 h; in particular, 18 pmol/mg of LD for compounds **3** and 8 pmol/mg of LD for compound **4** were observed. In the light of the physicochemical and pharmacokinetic properties and persistent high levels of LD delivery in the plasma and striatum even after 12 h from the administration, it could be suggested that codrugs **3** and **4** could enter intact into the brain and be available to elicit a pharmacological response. As affirmed by some authors, lipid-soluble molecules with a molecular weight under 500 Dalton threshold gain access to brain by free diffusion.[32] With the hypothesis that residues of intact codrugs **3** and **4** pass the BBB, these codrugs were delivered by daily intraventricular infusion in order to determine their metabolism in the central nervous system, in particular in the striatum. As shown in Table 2, higher striatal levels of DA were observed in rats after 1 week intracerebroventricular (icv) administration of codrug **4** (1 μmol/kg) compared to equimolar doses of **3** and LD ($P < 0.05$). No significant differences were found among LD striatal levels of rats after 1 week icv administration of codrugs **3**, **4**, and LD.

Table 2. Rat Striatal Levels of LD and DA, after 1 Week icv Administration of LD, **3**, and **4** (1 μmol/kg) in Rats[a]

compd	LD[b] (pmol/mg tissue)	DA[b] (pmol/mg tissue)
LD	3.36 (±1.18)	0.07 (±0.01)
3	4.03 (±0.65)	0.09 (±0.01)
4	2.13 (±0.37)	0.22 (±0.04)*

[a] Data are expressed as mean ± SE. Each experiment was performed in triplicate. *$P < 0.05$ compared to **3**- and LD-treated groups. [b] Values are means of three experiments, standard error is given in parentheses.

To evaluate the dopaminergic activity of equimolar doses of these compounds, the effects of codrugs **1**−**6** were studied on spontaneous locomotor activity, grooming, and rearing of rats in an open field apparatus in comparison with LD-treated animals. An hour and a half after drug administration by gavage, the treated groups showed a decreased pattern of these behaviors compared to the control group, which received vehicle only ($P < 0.05$). With regard to animals treated with **3**, locomotion, grooming, and rearing episodes were significantly ($P < 0.05$) decreased compared to the LD-treated group. Similar results were obtained after treatment with **4** on grooming and rearing episodes compared to the LD-treated group ($P < 0.05$). In addition, compounds **3**−**6** induced a significant decrease of rearing compared to LD treatment ($P < 0.05$). The performance in open field may provide a good measure of the animal's reaction toward novelty, which is usually exploration. When a treatment has a stimulant effect, the animals engage in increased locomotion, grooming, and rearing as they explore the open field, and when a treatment using a high dose of a drug has a sedative effect, the animals exhibit fewer of these behaviors as they explore.[33] As seen in previous experiments by our group, oral administration of LD with benserazide induces peripheral effects that reduce locomotor activities and thus has a sedative effect.[11,12] In the present case, it seems that, compared to LD treatment, codrugs **3** and **4** induce greater sedative effects and

thus impair explorative behavior. This may be related to the increased potency of codrugs used at the same molar doses as the LD treatment. As observed for explorative activity, treatment with LD and codrugs **2**−**6** also influenced anxiety-like behavior (fewer entries in the center of arena), leading to a pattern of behavioral depression compared to the behavior of the control group ($P < 0.05$). No significant modifications were revealed in anxiety-like activities among the five groups treated with LD and **2**−**6**. Table 2 shows that the levels of DA in the striatum of rats injected intracerebroventricularly for one week with 1 μmol/kg of codrug **4** were higher than the values of both **3**- and LD-treated groups ($P < 0.05$), indicating that this compound has a longer half-life in the brain. These data were correlated in part with the neuropharmacodynamic profiles of drug action. An increase of locomotion and % ambulatory episodes of rats treated with **3** and **4** was observed when compared with rats LD-treated from the first to the fourth day of the experiment. In particular, after treatment with codrug **4**, animals show a high number of rearings compared with LD-treated rats ($P < 0.05$). High locomotion, rearing, and % ambulatory episodes in the middle field are commonly interpreted as low emotionality (low fear)/high exploratory behavior.[34] These behavioral changes as well are correlated with increase of DA concentration in the brain.[35] Surprisingly, administration of LD on the first and second days induced a strong decrease of locomotion, rearing, and % ambulatory episodes, a trend that reversed on the third day, with increased locomotion, rearing, and % ambulatory episodes. We presumed that this behavior was linked to the dose of LD, which in a short time induced a high release of DA, which stimulates presynaptic autoreceptors. It is likely that the endogenous DA release is reduced, with consequent impairment of locomotor activity. We decided to repeat the experiment using low dosages (0.1 μmol/kg) of the compounds. The data show that our idea was correct: low doses of LD increase all exploratory parameters on the first and second days of injection. In addition, it was seen that not only treatment with LD but also that with codrugs **3** and **4** increases the trend of exploratory behavior (locomotion, % ambulatory, and % rearing episodes) of rats compared with that of control group ($P < 0.05$). Some differences in behavior were observed among treated groups: icv administration with codrug **4** proved more effective in increasing % ambulatory and % rearing episodes in the center of the open field between the first and third days of treatment ($P < 0.05$). The results obtained after repeated icv administrations confirm the higher bioavailibility of codrug **4** with respect to the others compounds.

In conclusion, we designed and synthesized a series of potential anti-Parkinson codrugs in which LD is linked to cysteine, methionine, and bucillamine. Our findings indicate that codrugs **1**−**6** show a good radical scavenging activity when compared to NAC. In rat and human plasma, the new derivatives undergo bioconversion to LD; in particular, hydrolysis in human plasma of compounds **3** and **4** proceeds more slowly than the other codrugs and thus these compounds are potentially able to reduce LD plasma fluctuation. The bioavailability of the new synthesized compounds was evaluated by comparing neostriatal LD and DA levels after oral administration by intragastric tube. The LD and DA striatal level profiles indicate that, among the studied compounds, codrugs **3** and **4** are of particular interest because they were able to induce sustained delivery of both LD and DA in rat striatum with respect to equimolar doses of LD; furthermore, the levels of DA in the striatum of rats injected intracerebroventricularly with codrug **4** were higher than those of the LD-treated groups, indicating that this compound has a longer half-life in brain, an observation that corresponds well with the neuropharmacodynamic profile of drug action. Taken together, these results indicate that codrug **4** may offer benefits in the treatment of PD; this novel compound has the potential to provide an alternative to LD therapy in order to avoid nigrostriatal oxidative degeneration; furthermore, the sustained striatal concentration of **4** may offer a new therapeutic strategy for preventing long-term motor complication associated with chronic LD therapy.

Experimental Section

The synthesis of **1**−**6** was performed according to Schemes **1**−**4** in Supporting Information. We describe herein the general procedure for the preparation of the final products.

General Procedure for the Preparation of Compounds 1, 2, 5, and 6. A solution of the foregoing full protected di- or tripeptide methyl ester **9**−**10**, **17**, or **19** (7.6 mmol) in a mixture of *n*-PrOH/H_2O (2:1) (105 mL) was brought to pH 8.5 with 25% aqueous NH_3 and flushed with nitrogen. After 30 min, tri-*n*-butylphosphine (9.1 mmol) was added and the stoppered flask stirred at room temperature. After 1.5 h, the reaction mixture was concentrated and subjected to column chromatography on silica gel using $CHCl_3$:MeOH as eluant to afford the corresponding reduced di- or tripeptide methyl ester.

Ac-Cys-LD-OMe (1). Yield: 66%; $R_f = 0.28$, $CHCl_3$:MeOH (9:1). ^{1}H NMR ($CDCl_3$): 1.60 (1H, t, SH), 1.97 (3H, s, AcNH), 2.69−2.82 (2H, m, Cys β-CH_2), 2.85−3.02 (2H, m, LD β-CH_2), 3.70 (3H, s, OMe), 4.59 (1H, m, Cys α-CH), 4.70 (1H, m, LD α-CH), 6.38−6.68 (3H, m, ArH), 6.77 (1H, d, $J = 8.36$ Hz, Cys NH), 6.91 (1H, d, $J = 7.47$ Hz, LD NH). ^{13}C NMR ($CDCl_3$) δ: 23.27 (Cys Ac), 26.86 (Cys β-CH_2), 36.78 (LD β-CH_2), 52.98 (Cys α-CH), 53.95 (OMe), 54.78 (LD α-CH), 115.59−144.09 (LD Ar), 170.04, 171.93, and 171.97 (3 × CO). MS (ESI) *m*/*z* 355 $(M - H)^-$. Anal. ($C_{15}H_{20}N_2O_6S$) C, H, N, S.

Ac-LD-Cys-OMe (2). Yield: 69%; $R_f = 0.22$, $CHCl_3$:MeOH (9:1). ^{1}H NMR ($CDCl_3$) δ: 1.60 (1H, t, SH), 1.74 (3H, s, AcNH), 2.48−2.53 (2H, m, Cys β-CH_2), 2.74−2.81 (2H, m, LD β-CH_2), 3.61 (3H, s, OMe), 4.41−4.44 (2H, m, Cys α-CH and LD α-CH), 6.48−6.61 (3H, m, ArH), 8.02 (1H, d, $J = 8.35$ Hz, Cys NH), 8.39 (1H, d, $J = 7.91$ Hz, LD NH). ^{13}C NMR ($CDCl_3$) δ: 23.16 (LD Ac), 25.94 (Cys β-CH_2), 37.63 (LD β-CH_2), 52.78 (Cys α-CH), 54.81 (OMe), 55.16 (LD α-CH), 115.79−145.44 (LD Ar), 169.80, 171.19, and 172.53 (3 × CO). MS (ESI) *m*/*z* 355 $(M - H)^-$. Anal. ($C_{15}H_{20}N_2O_6S$) C, H, N, S.

Ac-Cys-Cys-LD-OMe (5). Yield: 62%; R*f* = 0.15, $CHCl_3$:MeOH (97:3); ^{1}H NMR (DMSO-d_6) δ: 1.86 (3H, s, Cys Ac), 2.21 and 2.32 (2H, 2*t*, Cys SH), 2.66−2.78 (6H, m, 2 × Cys β-CH_2 and LD β-CH_2), 3.56 (3H, s, OMe), 4.31−4.38 (3H, m, 2 × Cys α-CH and LD α-CH), 6.39−6.60 (3H, m, ArH), 8.12 (1H, t, $J = 7.50$ Hz, Cys NH), 8.29 (1H, d, $J = 7.80$, Cys NH), 8.74 (1H, d, $J = 13.80$, LD NH). ^{13}C NMR (DMSO-d_6) δ: 23.20 (Cys Ac), 26.78 and 27.01 (2 × Cys β-CH_2), 36.79 (LD β-CH_2), 52.49 and 54.84 (2 × Cys α-CH), 55.62 (OMe), 55.79 (LD α-CH), 116.08−145.68 (LD Ar), 170.27, 170.33, 170.74 and 172.48 (4 × CO). MS (ESI) *m*/*z* 458 $(M - H)^-$. Anal. ($C_{18}H_{25}N_3O_7S_2$) C, H, N, S.

Buc-LD-OMe (6). Yield: 70%; $R_f = 0.35$, $CHCl_3$:MeOH (97:3). ^{1}H NMR ($CDCl_3$) δ: 1.61 (1H, t, Buc SH), 1.65 and 1.68 (6H, 2*s*, Buc CH_3), 2.06 (1H, s, Buc SH), 2.75−3.0.5 (4H, m, Buc β-CH_2 and LD β-CH_2), 3.75 (3H, s, OMe), 4.61 (1H, m, LD α-CH), 4.78 (1H, m, Buc α-CH), 6.42−6.75 (3H, m, ArH), 6.96 (1H, d, $J = 7.8$ Hz, LD NH), 7.82 (1H, d, $J = 8.40$ Hz, Buc NH). ^{13}C NMR ($CDCl_3$) δ: 26.99 (Buc β-CH_2), 30.14 and 30.18 (Buc 2 × CH_3), 36.81 (LD β-CH_2), 47.52 (Buc $C(CH_3)_2$), 52.96 (OMe), 53.95 (LD α-CH), 54.97 (Buc α-CH), 115.61−144.01 (LD Ar), 169.85, 172.04, and 176.78 (3 × CO). MS (ESI) *m*/*z* 415 $(M - H)^-$. Anal. ($C_{17}H_{24}N_2O_6S_2$) C, H, N, S.

General Procedure for the Preparation of Compounds 3 and 4. Saturated $NaHCO_3$ (74 mL) was added to a solution of dipeptide methyl ester **13** or **14** (4.3 mmol) in MeOH (144 mL)

and H_2O (71 mL), and the solution was stirred for 1 h at room temperature. The reaction mixture was quenched by dropwise addition of HCl (2.0 M) until the solution was slightly acidic. The aqueous layer was extracted with EtOAc, and the combined organic layer was washed with brine, dried, concentrated in vacuo, and then chromatographed on silica gel using $CHCl_3$:MeOH (9:1) as eluant to afford the corresponding deprotected dipeptide methyl ester.

Ac-Met-LD-OMe (3). Yield: 75%; $R_f = 0.27$, $CHCl_3$:MeOH (9:1). ^{1}H NMR ($CDCl_3$) δ: 1.90−2.05 (2H, m, Met β-CH_2), 1.96 (3H, s, Met Ac), 2.04 (3H, s, Met CH_3), 2.50−2.55 (2H, m, Met γ-CH_2), 2.91−3.04 (2H, m, LD β-CH_2), 3.76 (3H, s, OMe), 4.64 (1H, m, Met α-CH), 4.77 (1H, m, LD α-CH), 6.44−6.75 (3H, m, ArH), 6.95 (1H, d, $J = 8.24$ Hz, LD NH), 7.10 (1H, d, $J = 8.52$ Hz, Met NH). ^{13}C NMR ($CDCl_3$) δ: 15.47 (Met CH_3), 23.15 (Met Ac), 30.26 and 31.46 (Met β- and γ-CH_2), 36.83 (LD β-CH_2), 52.68 (Met α-CH), 52.86 (OMe), 53.94 (LD α-CH), 115.42−144.26 (LD Ar), 171.60, 171.85, and 172.10 (3 × CO). MS (ESI) *m*/*z* 383 (M − H)$^-$. Anal. ($C_{17}H_{24}N_2O_6S$) C, H, N, S.

Ac-LD-Met-OMe (4). Yield: 65%; $R_f = 0.27$, $CHCl_3$:MeOH (95:5). ^{1}H NMR ($CDCl_3$) δ: 1.90−2.05 (2H, m, Met β-CH_2), 1.98 (3H, s, LD Ac), 2.06 (3H, s, Met CH_3), 2.53−2.55 (2H, m, Met γ-CH_2), 2.90−3.03 (2H, m, LD β-CH_2), 3.71 (3H, s, OMe), 4.60 (1H, m, Met α-CH), 4.65 (1H, m, LD α-CH), 6.55 (1H, d, $J = 8.10$ Hz, LD NH), 6.65−6.85 (3H, m, ArH), 7.15 (1H, d, $J = 8.32$ Hz, Met NH). ^{13}C NMR ($CDCl_3$) δ: 15.54 (Met CH_3), 23.17 (LD Ac), 30.06 and 31.42 (Met β- and γ-CH_2), 38.22 (LD β-CH_2), 52.04 (Met α-CH), 52.95 (OMe), 55.23 (LD α-CH), 117.42−144.45 (LD Ar), 171.51, 171.84, and 172.24 (3 × CO). MS (ESI) *m*/*z* 383 (M − H)$^-$. Anal. ($C_{17}H_{24}N_2O_6S$) C, H, N, S.

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Supporting Information Available: Chemistry; Schemes **1**−**4**; experimental conditions and spectral data of all intermediates (**9**, **10**, **13**, **14**, **16**, **17**, and **19**); tables of elemental analysis and physicochemical and pharmacokinetic properties of codrugs **1**−**6**; figures of antioxidant and dopaminergic behavior of final porducts. This material is available free of charge via the Internet at http://pubs.acs.org.

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