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New Antihypertensive Agents. II.[1,2] Studies on New Analogs of 4-Piperidylbenzimidazolinones

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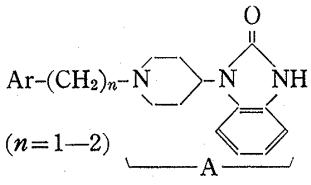
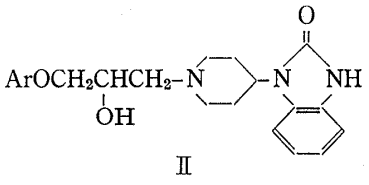
As a part of our search for new antihypertensive agents, several 4-piperidylbenzimidazolinone derivatives (I—III) were synthesized. These compounds showed only moderate antihypertensive activity in three hypertensive rat models.

Keywords——antihypertensive activity; 4-piperidylbenzimidazolinones; methyldopa; peptide bond; structure-activity relationship

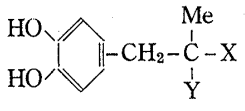
A previous report from our laboratories described the synthesis and biological properties of 4-piperidylbenzimidazolinones as a novel class of compounds with interesting antihypertensive activity.[1] Encouraged by these results, we undertook furter studies to prepare other analogs of general formula I-III.



I



II



III

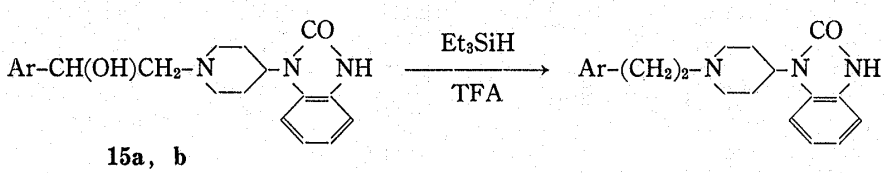
i) X: NH_2, Y:COA, $CONHCH_2COA$
ii) X: COOR(R=H or CH_3),
Y: $NHCOCH_2A$, $NHCO(CH_2)_2COA$

Many compounds having a structure which includes three or four methylene groups between a phenyl ring and the nitrogen atom of a piperidine ring have beer synthesized in attempts to find new neuroleptics. However, only a few examples of type I and II compounds were found in the literature.[3] We also designed compounds of type III on the basis of the following considerations: i) the bioavailability of methyldopa is known to be low[4] and therefore methyldopa derivatives (which are more efficiently absorbed) might show higher antihypertensive potency; ii) methyldopa is widely thought to be a centrally acting antihypertensive agent,[4] and the 4-piperidylbenzimidazolinone group is likely to have high affinity for the central nervous system.[5] Thus, it seemed attractive to synthesize benzimidazolinone derivatives of type III, which contain a methyldopa moiety. This paper describes the synthesis and antihypertensive activity of 4- piperidyl benzimidazolinones of formula I—III.

Chemistry

The ethanamine derivatives **4** and **5** shown in Table I were prepared by ionic hydrogen-

ation (triethylsilyl hydride/trifluoroacetic acid[6]) of **15**, which has already been obtained in high yield.[1]



15a, b

15a: Ar=3,4-methylenedioxyphenyl
15b: Ar=3,4-dimethoxyphenyl

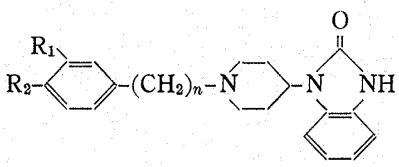
4: Ar=3,4-methylenedioxyphenyl
5: Ar=3,4-dimethoxyphenyl

Compound **1** was prepared by reaction of the benzyl chloride derivative with 4-(1,3-dihydro-2*H*-benzimidazol-2-one-1-yl) piperidine (**16**) in 64.8% yield. Further reduction of the resulting **1** gave **2** in 92% yield. This product was isolated as the dioxane complex.[7]

Compounds **3** was obtained by cleavage of the alkoxy linkage of **4** with BBr_3.[1]

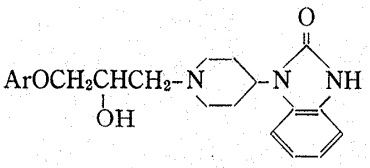
The piperidinyl-aryloxy-propanol derivatives (**6**, **7**) shown in Table II were prepared by reaction of the corresponding 3-aryloxy-1,2-epoxypropane with **16** in ethanol.

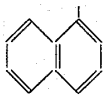
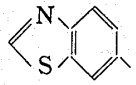
TABLE I.



Compd.	R_1	R_2	n	Form	Crystn. solvent	mp °C	Formula
1	BzlO	BzlO	1	Base	*n*-BuOH	168.5—169.5	$C_{33}H_{33}N_3O_3$
2	OH	OH	1	HCl	*n*-BuOH	179—181	$C_{19}H_{21}N_3O_3 \cdot HCl \cdot \left[\begin{smallmatrix}O\\O\end{smallmatrix}\right]$
3	OH	OH	2	HBr	*n*-BuOH	202—205	$C_{20}H_{23}N_3O_3 \cdot HBr \cdot 1.5H_2O$
4	<O-	O-	2	HCl	MeOH	240—245	$C_{21}H_{23}N_3O_3 \cdot HCl$
5	CH_3O	CH_3O	2	Base	AcOEt	155—157	$C_{22}H_{27}N_3O_3$

TABLE II.

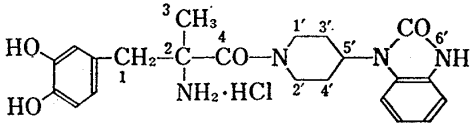
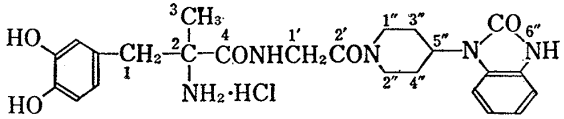
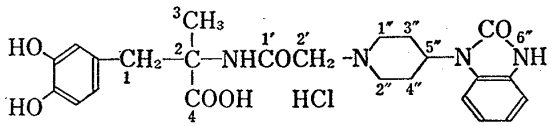
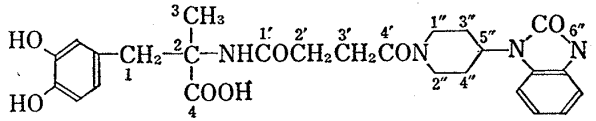
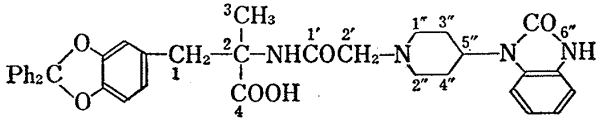
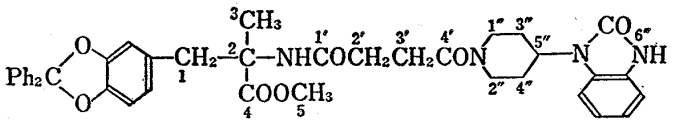
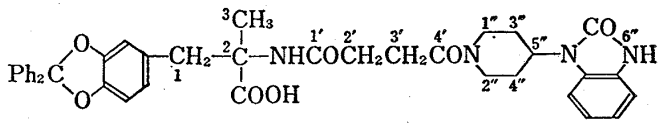


Compd.	Ar	Form	Crystn. solvent	mp °C	Formula
6		HCl	—	Powder	$C_{25}H_{27}N_3O_3 \cdot HCl \cdot 0.5H_2O$
7		Base	MeOH	240—243	$C_{22}H_{24}N_4O_3S$

We investigated the syntheses of a series of 3,4-dihydroxyphenyl-2-methyl-L-alanine (methyldopa, **17**) derivatives of formula III, as summarized in Table III.

The synthesis of compound **8** was carried out as follows. *N*-Benzyloxycarbonyl-3,4-dibenzyloxycarbonyloxyphenyl-2-methyl-L-alanine (Z-methyldopa(Z)$_2$OH, **18**) was obtained in 36.3% yield by a method analogous to that described for 3,4-dihydroxyphenyl-L-alanine

TABLE III. Type III Compounds and Their CMR Spectra

Compd.	Structure	Solv. Ref.	Assignment
8		D_2O Dioxane	22.73(C3), 29.26(C3′, C4′), 42.19(C1), 44.58, 48.92(C1′, C2′), 50.96(C5′), 63.06(C2), 155.73(C6′), 169.32(C4).
9		D_2O Dioxane	21.95(C3), 29.02, 29.51(C3″, C4″), 41.89(C1), 43.06, 51.26(C1″, C2″), 45.26(C1′), 61.74(C2), 155.87 (C6′), 168.65(C2′), 172.19(C4).
10		DMSO-d_6 TMS	22.23(C3), 25.4(C3″, C4″), 46.36, 51.84 (C1″, C2″), 51.84(C5″), 59.33(C2′), 59.10(C2), 153.44(C6″), 163.36 (C1′), 174.21(C4).
11		DMSO-d_6 TMS	22.48 (C3), 27.41 (C2′), 29.06 (C3″, C4″), 30.70 (C3′), 44.59, 49.83(C1″, C2″), 49.83(C5″), 58.48(C2), 153.62, (C6″), 169.88, 171.04(C1′, C4′), 175.06(C4).
12		$CDCl_3$ TMS	23.90(C3), 28.87(C3″, C4″), 41.50(C1), 43.11, 50.57 (C1″, C2″), 50.57(C5″), 61.64(C2′), 62.13(C2), 154.85 (C6″), 169.57(C1′), 178.84(C4).
13		$CDCl_3$ TMS	23.03(C3), 28.08(C2′), 28.93, 29.48(C3″, C4″), 31.67 (C3′), 41.24(C1), 45.08, 50.50(C1″, C2″), 50.50(C5″), 52.45(C5), 60.55(C2), 154.90(C6″), 170.25, 171.83(C1′, C4′), 174.21(C4).
14		$CDCl_3$ TMS	23.09(C3), 28.34(C2′), 28.93, 29.36(C3″, C4″), 31.86 (C3′), 41.18(C1), 45.08, 50.68(C1″, C2″), 50.68(C5″), 60.61(C2), 155.02(C6″), 170.51, 172.51(C1′, C4′), 176.52 (C4).

(dopa).[8] Condensation of **18** with **16** by the use of dicyclohexylcarbodiimide (DCC) in CH_2Cl_2 and purification of the product by SiO_2 chromatography gave the Z-methyldopa$(Z)_2$-piperidine amide derivative (**19**) in 62% yield. Removal of the protective groups on the methyldopa residue by reduction (H_2, Pd on carbon) provided **8** in moderate yield.

The synthetic route to compound **9** is outlined in chart 1. Coupling of Z-glycine with **16** by DCC, followed by hydrogenolysis of resulting Z-glycine piperidinamide derivative (**20**) gave the glycine piperidinamide derivative (**21**) in 78% overall yield. Condensation of **21** with Z-methyldopa$(Z)_2$OH (**18**) by the use of DCC gave **22** in 45% yield after chromatographic purification on SiO_2. Removal of the *N,O,O'*-protective groups of **22** by hydrogenolysis afforded **9** as an amorphous powder in almost quantitative yield.

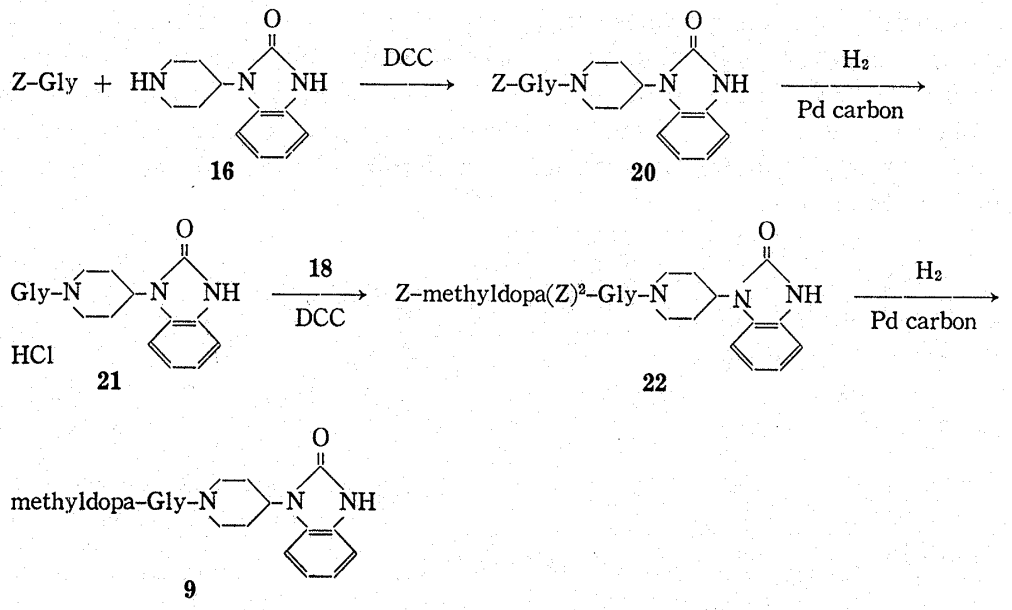


Chart 1

Compound **10** was prepared starting from diphenylmethylenedioxyphenyl-2-methyl-L-alanine (**23**)[9] as outlined in Chart 2. Treatment of **23** with chloroacetyl chloride in the presence of triethylamine (TEA) in the pH range of 9.6—10.0 afforded the *N*-chloroacetyl derivative **24** as a sole product in 47% yield. The structure of **24** was assigned on the basis of elemental

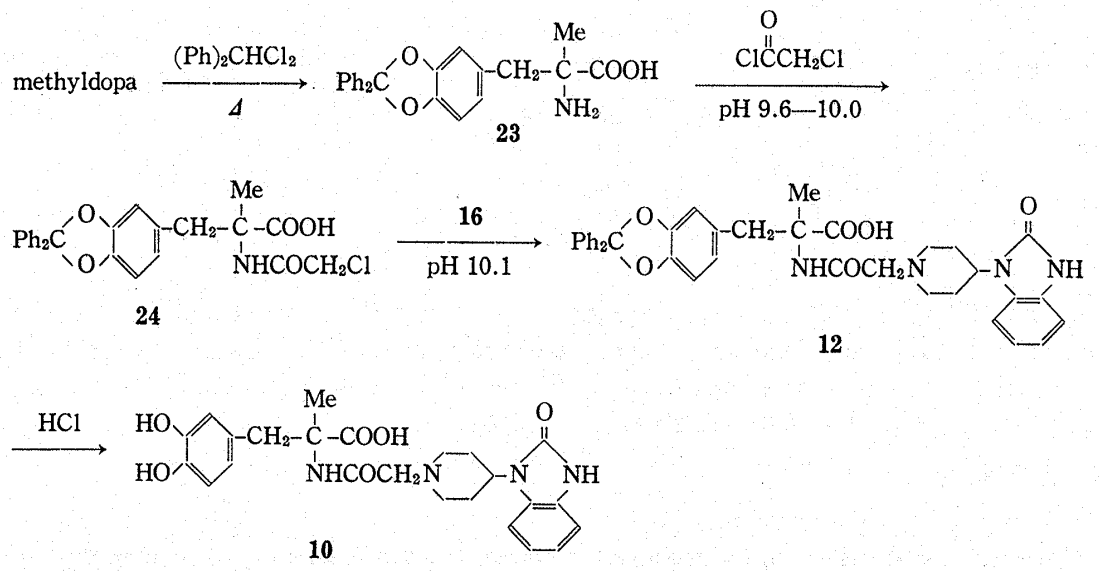
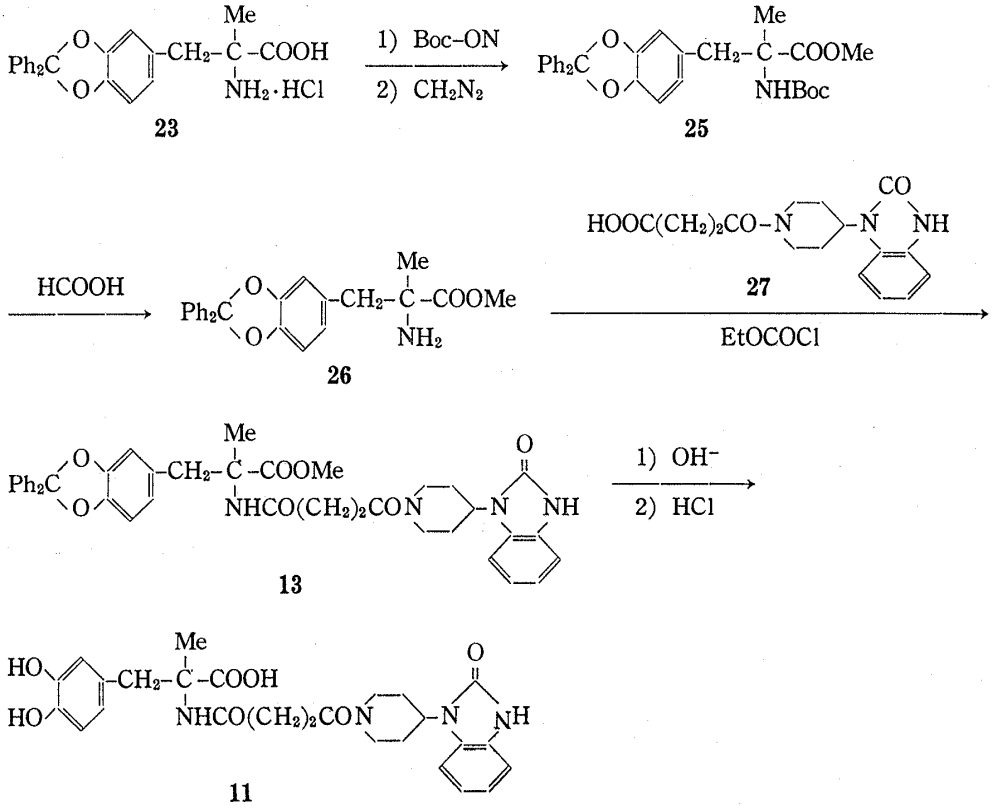


Chart 2

analysis and its proton nuclear magnetic resonance (PMR) spectrum, which exhibited a chloroacetyl methylene signal at δ 4.1. Condensation of **24** with **16** in dioxane–H_2O was carried out at a constant pH of the reaction mixture of pH 10.1. The reaction was complete after 72 h at room temperature, and **12** was obtained in 40.3% yield. Removal of the protective group on **12** by acid treatment (HCl) gave the desired **10** in 63% yield as its hydrochloride.

Compound **11** was synthesized according to the scheme in Chart 3. The starting methyldopa-OMe derivative, whose phenolic groups were protected with a diphenylmethylene group was obtained from **23** *via* three steps. Protection of the amino group[10] on **23** with 2-(*tert*-butoxycarbonyloxyloxyimino)-2-phenylacetonitrile (BOC–ON)[11] and successive esterification of the resulting N-protected derivative of **23** (**24**) with diazomethane in Et_2O gave an ester (**25**) in high yield. Selective removal of the Boc group on **25** with formic acid (10 eq) in AcOEt at 0—20°C afforded **26** in almost quantitative yield. On the other hand, 4-[4-(1,3-dihydro-2*H*-benzimidazol-2-one-1-yl)-piperidin-1-yl]-4-oxo-butanoic acid (**27**) was obtained by the reaction of **16** with succinic anhydride in $CHCl_3$. Condensation of **26** with **27** by the mixed anhydride method (EtOCOCl, —5°C, 24 h) in $CHCl_3$ gave **13** in 43% yield. Treatment of **13** with 3 eq of 1.36 N NaOH in MeOH and successive deprotection of the resulting **14** with HCl in $CHCl_3$ gave **11** in high yield.



23 25 26 27 13 11

Chart 3

In the PMR spectra of the final products (**8**—**11**) and their inthermediates, some proton signals assignable to methylene or methyl of methyldopa were masked by the piperidine ring proton signals, so the structures were confirmed by carbon nuclear magnetic resonance (CMR) spectroscopy. The assignments are shown in Table III.

Biological Results

The compounds were examined for hypotensive activities. In the first step of screening, the hypotensive activities were measured after oral administration of the compounds to unanesthetized animals. For this purpose, spontaneously hypertensive rats (SHR), DOCA

salt hypertensive rats (DHR), and normotensive rats (NTR) were utilized. Rats (male) were anesthetized and a cannula was fixed in the carotid artery of each rat. After the operation (3—4 d), blood was led to the pressure transducer through the cannula and recorded on an ink-writing oscillograph. Animals were not anesthetized and could move freely during the blood pressure measurements. The results from this type of experiments are summarized in Table IV. As is shown in this Table, the hypotensive activities of the compounds tested in the present study were not so remarkable in marked contrast to those of the compounds tested in the previous report.[1] The other difference of the compounds tested in the present study from those in the previous study is that the present compounds did not show hypotensive activities in normotensive rats, although they were more or less hypotensive in SHR and DHR.

Table IV. Hypotensive Activities of the Synthetic Compounds in Unanesthetized Rats

Compounds No.	Animals		
	SHR	DHR	NTR
1		−7.5(50)	0(50)
2		−11.3(50)	0(50)
3		−22.5(50)	0(50)
4	−30(30)	−52.5(13)	0(50)
		−37.5(25)	
		−45 (50)	
5	−61.3(50)		0(50)
6	−25.0(30)	+25.0(50)	0(50)
7		−53.4(50)	0(50)
8	−41.3(30)		0(50)
9			0(50)
10			−20(50)
11			0(50)
12			
13			0(50)
14			0(50)

SHR, DHR, and NTR indicate spontaneously hypertensive rats, DOCA salt hypertensive rats, and normotensive rats, respectively. The numbers and numbers in parentheses represent the maximum decreases in blood pressure (mmHg) and the doses (mg/kg) given orally, respectively.

Table V. Effects of Some Benzimidazolinone Derivatives on the Mean Arterial Blood Pressure and Heart Rate of Anesthetized Rats

Cpd. No.	Dose (mg/kg)	No. of animals	Initial level	Changes in blood pressure (mmHg)				
				30[a]	60[a]	120[a]	180[a]	240[a]
6	300	2	114+6	−35±10	−44±11	−48±15	−43±18	−38±1
10	100	2	121±8	−4±1	−13±5	−27±22	−27±19	−28±13
13	100	2	117±4	−5±4	−18±0	−4±1	−11±3	−14±3

Cpd. No.	Dose (mg/kg)	No. of animals	Initial level (beats/min)	Changes in heart rate (beats/min)				
				30[a]	60[a]	120[a]	180[a]	240[a]
6	300	2	350±20	−105±35	−123±48	−143±43	−145±30	−125±25
10	100	2	373±18	−23±8	−38±8	−43±8	−48±18	−33±23
13	100	2	378±43	−10±0	−18±13	−8±13	−18±23	−23±8

a) Time (min) after the administration of the drugs.
Each compound was administered intraperitoneally.

Among these compounds, three compounds (**6**, **10** and **13**) were tested for hypotensive activities in anesthetized normotensive rats. Male Wistar strain rats weighing 250 to 320 g were anesthetized with urethane 600 mg/kg *i.p.*, and alphachloralose, 60 mg/kg *i.p.* Afterial blood pressure was measured from the left common carotid artery by means of a pressure transducer. Heart rates were also measured with a cardiotachometer triggered by blood pressure pulses. Both parameters were measured on an ink-writing oscillograph for 4 h. The compounds were administered intraperitoneally. The results are summarized in Table V. Large doses were needed to produce a substantial decrease in the blood pressure, and even after the administration of large doses the decrease in blood pressure was only slight. Heart rate was also decreased to some extent after the administration of large doses.

From these results, it can be concluded that the compounds tested in the present study are unlikely to be useful as hypotensive drugs.

Experimental

Melting points were determined with a Mitamura hot-stage apparatus and are uncorrected. Infrared spectra were recorded on a Hitachi 215 grating infrared spectrometer or a Shimadzu IR-27G grating infrared spectrometer. PMR spectra were determined on a Varian T-60, JNM-PFT-100, or JNM-FX-100 spectrometer. Chemical shifts are given in δ values relative to Me_4Si as a standard. CMR spectra were obtained at 25.1 MHz on a JNM-FX-100 spectrometer operating in a Fourier transform mode with Me_4Si as an internal standard. Thin layer chromatography was carried out on silica gel plates (silica gel 60, F_{254}, Merck). *Rf* values refer to the following solvent systems: Rf_1=$CHCl_3$–MeOH–AcOH–H_2O, 10: 10: 1: 10 lower layer, Rf_2=*n*-BuOH–AcOH–H_2O, 4: 1: 1.

Preparation of 1-[2-(3,4-Dimethoxyphenyl)ethyl]-4-(1,3-dihydro-2*H*-benzimidazol-2-one-1-yl)piperidine (**5**)——A mixture of **15b**[1] (1.69 g, 4.25 mmol) and triethylsilyl hydride (1.5 g, 12.9 mmol) in 10 ml of trifluoroacetic acid was stirred vigorously at room temperature for 24 h. The reaction mixture was concentrated *in vacuo* and the residue was dissolved in 10 ml of AcOEt. Then conc. H_2SO_4 was added until no more precipitates appeared. The precipitates were filtered, washed with AcOEt, dried and dissolved in 10 ml of H_2O. The solution was made alkaline and extracted with $CHCl_3$. The extract was washed, dried over Na_2SO_4 and concentrated to dryness to yield crude crystals, which were recrystallized from AcOEt to yield 0.9 g (55.5%) of **5**. IR ν_{max}^{KBr} cm^{-1}: 1700. NMR ($CDCl_3$) δ: 1.6—4.65 (piperidine ring H), 2.74 (ArC<u>H</u>$_2$C<u>H</u>$_2$–N<), 3.86, 3.90 (C<u>H</u>$_3$O), 6.6—7.4 (arom.), 10.3 (N<u>H</u>). *Anal.* Calcd for $C_{22}H_{27}N_3O_3$: C, 69.27; H, 7.13; N, 11.02. Found: C, 69.21; H, 7.02; N, 11.31.

Preparation of 1-(3,4-Dibenzyloxyphenylmethyl)-4-(1,3-dihydro-2*H*-benzimidazol-2-one-1-yl)piperidine (**1**)——A solution of 3,4-dibenzyloxybenzyl chloride[12] (2.0 g, 5.91 mmol), **16** (1.29 g, 5.94 mmol) and triethylamine (0.6 g, 5.93 mmol) in 20 ml of DMF was stirred for 12 h at room temperature. The solution was concentrated *in vacuo* and the residue was dissolved in $CHCl_3$. The solution was washed wtih H_2O and dried. over Na_2SO_4. Removal of the solvent gave crystals, which were recrystallized from *n*-BuOH to obtain 2.0 g (64.8%) of **1**. IR ν_{max}^{KBr} cm^{-1}: 1700. NMR (DMSO-d_6) δ: 3.4 (ArC<u>H</u>$_2$–N<), 5.08, 5.12 (di PhC<u>H</u>$_2$O), 10.77 (N<u>H</u>). *Anal.* Calcd for $C_{33}H_{33}N_3O_3$: C, 76.27; H, 6.40; N, 8.09. Found: C, 76.37; H, 6.40; N, 8.03.

Preparation of 1-(3,4-Dihydroxyphenylmethyl)-4-(1,3-dihydro-2*H*-benzimidazol-2-one-1-yl)piperidine (**2**)——A mixture of **1** (2 g, 3.85 mmol), HCl (0.14 g, 3.84 mmol) and 10% Pd/C (0.4 g) in 50 ml of MeOH was stirred under an H_2 atmosphere at room temperature for 12 h. The catalyst was filtered off and the filtrate was concentrated under reduced pressure. The residue was treated with 60 ml of dioxane and the whole stirred well. The crystals were filtered, washed with dioxane and dried. Yield 1.8 g (91.9%). Rf_1 0.11, Rf_2 0.73 (one spot). IR ν_{max}^{KBr} cm^{-1}: 1712, 1690 (sh.). NMR (CD_3OD) δ: 4.22 (ArC<u>H</u>$_2$N<). *Anal.* Calcd for $C_{19}H_{21}N_3O_3 \cdot HCl \cdot 1.5$  : C, 59.11; H, 6.75; N, 8.27. Found: C, 58.87; H, 6.56; N, 8.17.

Preparation of 1-[2-(3,4-Dihydroxyphenyl)ethyl]-4-(1,3-dihydro-2*H*-benzimidazol-2-one-1-yl)piperidine Hydrobromide (**3**)——To a solution of **4** (2.1 g, 5.23 mmol, as hydrochloride) in 20 ml of $CHCl_3$ was added 3.93 g (15.7 mmol) of BBr_3 with cooling. The mixture was stirred for 24 h at room temperature. The precipitate was filtered, washed with $CHCl_3$ and dried. The crude crystals were washed with H_2O and recrystallized from *n*-BuOH to obtain 1.4 g (60.0%) of **3**. Rf_2 0.66. IR ν_{max}^{KBr} cm^{-1}: 1690 (sh.), 1680. *Anal.* Calcd for $C_{20}H_{23}N_3O_3 \cdot HBr \cdot 1.5H_2O$: C, 53.94; H, 6.11; N, 9.44. Found: C, 53.68; H, 5.89; N, 9.23.

Preparation of 1-[2-Hydroxy-3-(benzothiazol-6-yloxy)-propan-1-yl]-4-(1,3-dihydro-2*H*-benzimidazol-2-one-1-yl)piperidine (**7**)——A solution of 3-(benzothiazol-6-yloxy)-1,2-epoxypropane[13] (1.0 g, 4.82 mmol) and **16** (1 g, 4.61 mmol) in 20 ml of EtOH was heated under reflux for 9 h. The solution was concentrated to *ca.* 5 ml, then the crystals were collecetd by filtration and dried. Recrystallization of the crude product from MeOH gave 0.9 g (46.0%) of **7**. IR ν_{max}^{KBr} cm^{-1}: 1680. *Anal.* Calcd for $C_{22}H_{24}N_4SO_3$: C, 62.24; H, 5.70; N, 13.20. Found: C, 62.13; H, 5.68; N, 13.21.

Preparation of 3,4-Dihydroxyphenyl-2-methyl-L-alanine (1,3-Dihydro-2*H*-benzimidazol-2-one-1-yl)-piperidinamide Hydrochloride (8)——i) Preparation of *N,O,O'*-Tribenzyloxycarbonyl-methyldopa (**18**): A solution of carbobenzoxy chloride (120.2 g, 0.705 mol) in 450 ml of Et_2O and 700 ml of 1 N NaOH were added simultaneously to an ice-chilled solution of methyldopa (45 g, 0.213 mol) in 374 ml of 1 N NaOH and 216 ml of H_2O with vigorous stirring under a stream of nitrogen. The addition was completed within 2 h and stirring was continued for 1 h at 0°C. The aqueous layer was separated, washed three times with Et_2O and acidified to pH 3.5. The mixture was extracted with Et_2O and the extract was washed successively with 0 1 N HCl and H_2O, then dried over Na_2SO_4. Removal of the solvent *in vacuo* gave 47.4 g (36.3%) of **18** as a pale purple oil, Rf_1 0.63. IR ν_{max}^{Neat} cm^{-1}: 1780, 1775, 1730, 1275. NMR ($CDCl_3$) δ: 1.58 (α-C<u>H</u>$_3$), 3.2—3.48 (β-C<u>H</u>$_2$), 5.08 (NCOOC<u>H</u>$_2$Ph), 5.15 (OCOOC<u>H</u>$_2$Ph).

ii) Condensation of **18** with **16**: DCC (0.94 g, 4.56 mmol) was added to a stirred solution of **18** (2.8 g, 4.56 mmol) in 20 ml of CH_2Cl_2 under an N_2 atmosphere with cooling. The mixture was stirred for 1.5 h, then **16** (0.99 g, 4.56 mmol) was added to the reaction mixture with cooling in an ice bath. The mixture was stirred at 0°C for 5 h and the reaction temperature was slowly elevated to room temperature. The precipitate was filtered off and the filtrate was concentrated. The residue was dissolved in AcOEt and the solution was shaken successively with 1 N NaOH, 1.2 N HCl, and H_2O. The solution was dried and concentrated to give 2.8 g of crude *N*-benzyloxycarbonyl-3,4-dibenzyloxycarbonyloxyphenyl-2-methyl-L-alanine [4-(1,3-dihydro-2*H*-benzimidazol-2-one-1-yl)]piperidinamide (**19**), which was purified by chromatography on silica gel with AcOEt to obtain 2.3 g (62.1%) of pure oil, Rf_1 0.73. IR ν_{max}^{Neat} cm^{-1}: 1780, 1725, 1720, 1700, 1270. NMR ($CDCl_3$) δ: 1.4 (α-C<u>H</u>$_3$), 1.0—3.6, 4.0—4.4 (piperidine ring H), 3.3—3.5 (β-C<u>H</u>$_2$), 5.2, 5.25 (Ph-C<u>H</u>$_2$OCO–), 6.65—7.2 (arom. for methyl dopa), 7.25—7.4 (arom. for benzimidazole), 7.35 (arom. for benzyloxycarbonyl).

iii) Removal of Protecting Groups on **19**: A mixture of **19** (2.7 g, 3.32 mmol), HCl (0.12 g, 3.29 mmol) and 10% Pd-carbon (0.5 g) in 20 ml of MeOH was stirred under a hydrogen atmosphere for 3 h. The catalyst was filtered off and the filtrate was concentrated *in vacuo* to give an amorphous powder, which was triturated with AcOEt and filtered to obtain 0.76 g of **8**, in 48.3% yield, *Rf* 0.44 (*n*-BuOH saturated with H_2O). IR ν_{max}^{KBr} cm^{-1}: 1710—1700, 1680—1630. NMR (DMSO-d_6) δ: 0.9—4.4 (piperidine ring protons), 1.75 (α-C<u>H</u>$_3$), β-C<u>H</u>$_2$ signals were buried in the signals due to piperidine ring protons, 6.5—7.0 (arom. for methyldopa), 6.95—7.4 (arom. for benzimidazole), 10.85 (–N<u>H</u> for benzimidazole), *Anal.* Calcd for $C_{22}H_{26}N_4O_4 \cdot HCl \cdot 1.5H_2O$: C, 55.75; H, 6.38; N, 11.82. Found: C, 55.75; H, 6.20; N, 11.88.

Preparation of 3,4-Dihydroxyphenyl-2-methyl-L-alanylglycine [4-(1,3-dihydro-2*H*-benzimidazol-2-one-1-yl)]piperidinamide (9)——i) *N*-Benzyloxycarbonyl-glycine-[4-(1,3-dihydro-2*H*-benzimidazol-2-one-1-yl)]-piperidinamide (**20**): To a suspension of 2.89 g (13.82 mmol) of Z-glycine in 50 ml of CH_2Cl_2, 2.85 g(13.82 mmol) of DCC was added with cooling. After 15 min, a solution of **16** (3.0 g, 13.81 mmol) in 20 ml of CH_2Cl_2 was added to the above mixture. The whole was stirred for 2 h with cooling and then warmed to room temperature. After being stirred for an additional 2 h, the mixture was worked up as described previously. Crude crystals were recrystallized to give 4.5 g (79.8%) of **20**, Rf_1 0.54. mp 131—141°C. IR ν_{max}^{KBr} cm^{-1}: 1720, 1700, 1672. NMR ($CDCl_3$) δ: 1.0—4.9 (piperidine ring H), 4.0—4.2 (ZNHC<u>H</u>$_2$CO), 5.15 (PhC<u>H</u>$_2$OCO), 6.9—7.4 (arom. for benzimidazole), 7.35 (arom. for benzyloxy carbonyl), 10.05 (N<u>H</u> for benzimidazole). *Anal.* Calcd for $C_{22}H_{24}N_4O_4$: C, 64.69; H, 5.92; N, 13.72. Found: C, 64.84; H, 6.18; N, 13.45.

ii) Glycine [4-(1,3-Dihydro-2*H*-benzimidazol-2-one-1-yl)]piperidinamide·hydrochloride (**21**): A mixture of **20** (540 mg, 1.32 mmol), HCl (50 mg, 1.37 mmol), and Pd-carbon (0.5 g) in 30 ml of MeOH was stirred under a hydrogen atmosphere for 4.5 h. The catalyst was removed and the filtrate was concentrated *in vacuo* to give 390 mg (95.1%) of **21** as white crystals which were used in the next reaction without further purification, Rf_2 0.34. mp 256—259°C (dec.). IR ν_{max}^{KBr} cm^{-1}: 1680, 1655. NMR (DMSO-d_6) δ: 1.0—4.8 (piperidine ring H), 6.8—7.4 (arom. for benzimidazole), 11.0 (N<u>H</u> for benzimidazole), CH_2 proton signals for glycine were buried in the piperidine ring proton signals. *Anal.* Calcd for $C_{14}H_{19}ClN_4O_2$: C, 54.11; H, 6.16; N, 18.03. Found: C, 54.10; H, 6.23; N, 18.01.

iii) *N*-Benzyloxycarbonyl-3,4-dibenzyloxycarbonyloxyphenyl-2-methyl-L-alanyl-glycine [4-(1,3-dihydro-2*H*-benzimidazol-2-one-1-yl)]piperidinamide (**22**): DCC (0.8 g, 3.88 mmol) was added with stirring to a cooled solution of **18** (2.37 g, 3.86 mmol) in 50 ml of CH_2Cl_2. The mixture was stirred for 0.5 h with cooling, and then **21** (1.2 g, 3.86 mmol) and triethylamine (0.39 g, 3.86 mmol) were added. Stirring was continued for 1.5 h at 0°C and the mixture was allowed to warm to room temperature. Work-up of the reaction mixture as described above gave a crude product, which was purified by chromatography on silica gel with AcOEt to obtain 1.52 g (45.3%) of **22** as a white powder, Rf_1 0.62. IR ν_{max}^{KBr} cm^{-1}: 1780, 1720, 1700, 1650, 1275. NMR (DMSO-d_6) δ: 1.05—4.7 (piperidine ring H), 1.3 (α-C<u>H</u>$_3$), 3.27 (NHC<u>H</u>$_2$CO), 5.06 (NCOOC<u>H</u>$_2$Ph), 5.21 (OCOOC<u>H</u>$_2$Ph), 6.7—7.3 (arom. for methyldopa), 7.1—7.4 (arom. for benzimidazole), 7.4 (arom. for benzyloxycarbonyl), 10.8 (N<u>H</u> for benzimidazole). *Anal.* Calcd for $C_{48}H_{47}N_5O_{11}$: C, 66.27; H, 5.45; N, 8.05. Found: C, 65.94; H, 5.27; N, 7.82.

iv) Removal of Protecting Groups on **22**: A solution of **22** (1.53 g, 1.76 mmol) and HCl (70 mg, 1.92 mmol) in 20 ml of MeOH was shaken in the presence of 0.3 g of Pd-carbon catalyst under atmospheric pressure of hydrogen. After usual work-up, 830 mg (99.1%) of **9** was obtained as a white powder, Rf_2 0.42. IR ν_{max}^{KBr} cm^{-1}: 1700—1680, 1660—1640. NMR (D_2O) δ: 1.2—4.8, (piperidine ring H), 1.9 (α-C<u>H</u>$_3$), 6.7—7.2 (arom.

for methyldopa), 7.0—7.4 (arom. for benzimidazole).

Preparation of *N*-{1-Oxo-2-[4-(1,3-dihydro-2*H*-benzimidazol-2-one-1-yl)-piperidin-1-yl]ethyl}-3,4-dihydroxyphenyl-2-methyl-L-alanine-hydrochloride (10)——i) *N*-Chloroacetyl-3,4-diphenylmethylenedioxyphenyl-2-methyl-L-alanine (**24**): A solution of chloroacetyl chloride (2.07 g, 18.33 mmol) in 10 ml of dioxane and triethylamine (1.85 g, 18.3 mmol) were added simultaneously to a solution of 3,4-diphenylmethylenedioxyphenyl-2-methyl-L-alanine hydrochloride (**23**) (6.3 g, 15.3 mmol) and triethylamine (3.2 g, 31.6 mmol) in 80 ml of H_2O and 100 ml of dioxane. When the addition was completed, the reaction mixture was stirred for 1 h. The procedure was repeated with chloroacetyl chloride (2.07 g, 18.33 mmol) and triethylamine (1.85 g, 18.3 mmol). The reaction mixture was acidified to pH 4.5 with 0.2 N HCl and extracted with AcOEt. The extract was washed, dried over Na_2SO_4, and concentrated under reduced pressure. The resultant solid was recrystallized from AcOEt–*n*-hexane to give 3.25 g (47%) of **24**, Rf_1 0.62, Rf_2 0.81. mp 195—197°C. IR ν_{max}^{KBr} cm^{-1}: 1730, 1630. NMR ($CDCl_3$) δ: 1.7 (α-C$\underline{H}_3$), 3.28 (β-C$\underline{H}_2$), 4.01 (NCOC$\underline{H}_2$Cl), 6.5—6.9 (arom. for methyldopa), 7.0—7.7 (arom. for diphenylmethylenedioxy). *Anal.* Calcd for $C_{25}H_{22}ClNO_5$: C, 66.45; H, 4.91; N, 3.10. Found: C, 66.17; H, 4.77; N, 3.03.

ii) *N*-{1-Oxo-2-[4-(1,3-dihydro-2*H*-benzimidazol-2-one-1-yl)piperidin-1-yl]ethyl}-3,4-diphenylmethylenedioxyphenyl-2-methyl-L-alanine (**12**): The solution of **24** (2.3 g, 5.09 mmol) and **16** (1.2 g, 5.52 mmol) in 3.6 ml of 1 N NaOH and 36 ml of dioxane was stirred for 72 h at room temperature. In order to maintain the pH of the solution at pH 10—10.1, 1 N NaOH was continuously added during the reaction. When the reaction was completed, the solution acidified to pH 6.5. The precipitate was filtered off, washed and dried. Recrystallization from AcOEt–*n*-hexane gave 1.3 g (40.3%) of **12**, Rf_1 0.56. mp 180—183°C. IR ν_{max}^{KBr} cm^{-1}: 1730, 1700, 1630. NMR (DMSO-d_6) δ: 0.8—4.8 (piperidine ring H), 1.55 (C$\underline{H}_3$), two methylene proton signals (PhC$\underline{H}_2$ and COC$\underline{H}_2$N$<$) were buried in the piperidine ring proton signals, 6.5—7.0 (arom. for methyl dopa), 6.9—7.3 (arom. for benzimidazole), 7.0—7.7 (arom. for diphenylmethylenedioxy), 10.8 (N$\underline{H}$ for benzimidazole). *Anal.* Calcd for $C_{37}H_{36}N_4O_6$: C, 70.24; H, 5.74; N, 8.86. Found: C, 70.11; H, 5.82; N, 8.43.

iii) Removal of Protecting Group on **12**: A solution of **12** (1.3 g, 2.06 mmol) and 120 mg (3.28 mmol) of HCl in 1 ml of MeOH and 5 ml of $CHCl_3$ was stirred for 3 h at room temperature. The precipitates were filtered and washed well with MeOH. The product was purified by reprecipitation from MeOH–DMF. 650 mg (62.5%) of **10** was obtained, Rf_1 0.047, Rf_2 0.52. IR ν_{max}^{KBr} cm^{-1}: 1690, 1660. NMR (DMSO-d_6) δ: 1.27 (α-C$\underline{H}_3$), 1.6—4.8 (piperidine ring H), two methylene protons were buried in the piperidine ring protons, 6.2—6.8 (arom. for methyldopa), 6.8—7.7 (arom. for benzimidazole), 10.95 (N$\underline{H}$ for benzimidazole). *Anal.* Calcd for $C_{24}H_{29}ClN_4O_6 \cdot 0.5H_2O$: C, 56.08; H, 5.88; N, 10.90. Found: C, 56.17; H, 5.85; N, 10.66.

Preparation of *N*-{1,4-Dioxo-4-[4-(1,3-dihydro-2*H*-benzimidazol-2-one-1-yl)piperidin-1-yl]-butan-1-yl}-3,4-dihydroxyphenyl-2-methyl-L-alanine (11)——i) 3,4-Diphenylmethylenedioxyphenyl-2-methyl-L-alanine Methyl ester·hydrochloride (**26**): A solution of **23** (1.2 g, 3.2 mmol), triethylamine (0.5 g, 4.9 mmol), and BOC–ON (0.9 g, 3.65 mmol) in 15 ml of dioxane and 15 ml of H_2O was stirred for 48 h at room temperature. The reaction mixture was concentrated and the residue was diluted with H_2O and extracted with AcOEt. The extract was washed several times with 10% aq. triethylamine solution, dil. AcOH and H_2O. The extract was dried over Na_2SO_4 and concentrated under reduced pressure to obtain 1.0 g (65.6%) of *N-tert*-butoxycarbonyl-3,4-diphenylmethylenedioxyphenyl-2-methyl-L-alanine (**24**) as a white powder, Rf_1 0.55. IR ν_{max}^{KBr} cm^{-1}: 1705, 1650, 1490, 1245. NMR ($CDCl_3$) δ: 1.48 (*tert*-B$\underline{u}$) 1.52 (α-C$\underline{H}_3$), 3.21 (β-C$\underline{H}_2$), 6.5—6.9 (arom. for methyldopa), 7.2—7.72 (arom. for diphenylmethylenedioxy). *Anal.* Calcd for $C_{28}H_{29}NO_6$: C, 70.72; H, 6.15; N, 2.95. Found: C, 70.66; H, 6.39; N, 2.91. An ethereal solution of diazomethane was added to a solution of **24** (0.9 g, 1.89 mmol) in 20 ml of Et_2O under cooling until the color of diazomethane persisted. After additional stirring for 1 h, the solution was worked up as usual to yield 908 mg (98.0%) of *N-tert*-butoxycarbonyl-3,4-diphenylmethylenedioxyphenyl-2-methyl-L-alanine methyl ester (**25**) as an oil, Rf_1 0.86. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1732, 1704, 1490, 1245. NMR ($CDCl_3$) δ: 1.4 (*tert*-B$\underline{u}$), 1.46 (α-C$\underline{H}_3$), 3.13 (β-C$\underline{H}_2$), 3.69 (COOC$\underline{H}_3$), 6.4—6.86 (arom. for methyldopa), 7.1—7.8 (arom. for diphenylmethylenedioxy). A solution of **25** (490 mg, 1.0 mmol) and 1 g of HCOOH in 0.5 ml of AcOEt was stirred for 48 h at room temperature. The solution was concentrated *in vacuo*. The residue was diluted with AcOEt and the solution was mixed with 36.5 mg (1.0 mmol) of HCl in 3 ml of AcOEt. The resulting solution was washed with H_2O, dried, and concentrated to afford 410 mg (96.3%) of **26** as an oil, Rf_1 0.56. IR ν_{max}^{KBr} cm^{-1}: 1750, 1500, 1260, 1220. NMR ($CDCl_3$) δ: 1.8 (α-C$\underline{H}_3$), 3.26 (β-C$\underline{H}_2$), 3.6 (COOC$\underline{H}_3$), 6.5—7.0 (arom. for methyldopa), 7.0—7.8 (arom for diphenylmethylenedioxy). *Anal.* Calcd for $C_{24}H_{24}ClNO_4$: C, 67.68; H, 5.68; N, 3.29. Found: C, 67.66; H, 5.89; N, 3.00.

ii) 4-Oxo-4-[4-(1,3-dihydro-2*H*-benzimidazol-2-one-1-yl)piperidin-1-yl]-butanoic Acid (**27**): A mixture of succinic anhydride (0.92 g, 9.2 mmol) and **16** (2 g, 9.21 mmol) in 10 ml of $CHCl_3$ was stirred for 4 h at room temperature. The crystals were filtered, washed with $CHCl_3$ and dried. Crude **27** (2.85 g, 97.5%) was obtained. It was used in the next reaction without further purification. An analytical sample was recrystallized from MeOH. Rf_1 0.51, Rf_2 0.65. mp 215—216°C. IR ν_{max}^{KBr} cm^{-1}: 1740, 1693, 1635. NMR (DMSO-d_6) δ: 1.4—4.8 (piperidine ring H), 2.57 (COC$\underline{H}_2$C$\underline{H}_2$COOH), 6.8—7.4 (arom. for benzimidazole), 10.8 (N$\underline{H}$ for benzimidazole). *Anal.* Calcd for $C_{16}H_{19}N_3O_4$: C, 60.55; H, 6.04; N, 13.24. Found: C, 60.23; H, 6.01; N, 13.22.

iii) Condensation of **26** with **27**: A solution of ethoxycarbonyl chloride (1.37 g, 12.62 mmol) in 5 ml of $CHCl_3$ was added to a solution of **27** (4.0 g, 12.61 mmol) and triethylamine (1.28 g, 12.65 mmol) in 20 ml of $CHCl_3$ at −5°C. The mixture was stirred for 30 min at the same temperature, then **26** (5.37 g, 12.61 mmol) and triethylamine (1.28 g, 12.65 mmol) were added at −5°C. The mixture was further stirred for 15 h at the same temperature and then allowed to warm to room temperature. The reaction mixture was concentrated and the residue was diluted with H_2O and extracted with AcOEt. The extract was washed sucessively with 10% AcOH, saturated $NaHCO_3$, and H_2O, then dried over Na_2SO_4. Removal of the solvent gave a residue, which was reprecipitated from AcOEt–Et_2O to obtain 3.7 g (42.6%) of *N*-{1,4-dioxo-4-[4-(1,3-dihydro-2*H*-benzimidazol-2-one-1-yl) piperidin-1-yl]-butan-1-yl}-3,4-diphenylmethylenedioxyphenyl-2-methyl–L-alanine methyl ester (**13**), Rf_1 0.68. IR ν_{max}^{KBr} cm^{-1}: 1740, 1700, 1650—1630. NMR (DMSO-d_6) δ: 1.0—4.9 (piperidine ring H), 1.24 (α-C<u>H</u>$_3$), 2.53 (NHCOC<u>H</u>$_2$C<u>H</u>$_2$CO–N<), 3.6 (COOC<u>H</u>$_3$), 6.5—8.1 (arom.), 10.87 (N<u>H</u> for benzimidazole). *Anal.* Calcd for $C_{40}H_{40}N_4O_7 \cdot 0.5H_2O$: C, 68.85; H, 5.92; N, 8.03. Found: C, 68.97; H, 6.06; N, 7.62.

iii) Hydrolysis of **13**: A solution of **13** (4.75 g, 6.81 mmol) in 30 ml of MeOH was treated with 15 ml of 1.36 N NaOH. The solution was stirred for 24 h at room temperature under a stream of nitrogen. The solution was acidified to pH 2.4 and extracted with AcOEt. Usual work-up of the extract gave 3.27 g (71.2%) of *N*-{1,4-dioxo-4-[4-(1,3-dihydro-2*H*-benzimidazol-2-one-1-yl)]butan-1-yl}-3,4-diphenylmethylenedioxyphenyl-2-methyl–L-alanine (**14**) as a powder, Rf_1 0.57. IR ν_{max}^{KBr} cm^{-1}: 1720, 1700, 1650—1630. *Anal.* Calcd for $C_{39}H_{38}N_4O_7 \cdot 0.5H_2O$: C, 68.50; H, 5.75; N, 8.19. Found: C, 68.84; H, 5.72; N, 7.95.

iv) Removal of Protecting Group on **14**: **14** (2.16 g, 3.20 mmol) was treated with HCl (0.35 g, 9.59 mmol) in 8 ml of AcOEt and 20 ml of $CHCl_3$. The mixture was stirred for 1.5 h at room temperature. The precipitates were filtered and washed with AcOEt. The solid was purified by reprecipitation from DMF–AcOEt to obtain 1.6 g of **11** in 97.8% yield, Rf_1 0.18. IR ν_{max}^{KBr} cm^{-1}: 1720, 1700, 1660—1620. NMR (DMSO-d_6) δ: 1.23 (C<u>H</u>$_3$), 1.3—4.9 (piperidine ring H), methylene signals for NCOC<u>H</u>$_2$C<u>H</u>$_2$N were buried in DMSO-d_6, 6.4—7.8 (arom.), 10.8 (N<u>H</u> for benzimidazole). *Anal.* Calcd for $C_{26}H_{30}N_4O_7 \cdot 0.5H_2O$: C, 60.11; H, 6.01; N, 10.78. Found: C, 60.02; H, 5.89; N, 10.53.

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