



A New Type of Carboxypeptidase A Inhibitors Designed Using an Imidazole as a Zinc Coordinating Ligand

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Abstract—2-(4-Imidazolyl)hydrocinnamic acid (**1**) and its congeners (**2–4**) having different length of alkyl chain spacers between the imidazole ring and the α -carbon to the carboxylate of **1** have been designed, synthesized and evaluated as inhibitors for carboxypeptidase A to show that they are competitive inhibitors for the enzyme. Inhibitor **1** was most potent having the K_i value of 0.8 μ M. The present study demonstrates that imidazole ring is an effective zinc coordinating ligand that can be useful for the design of inhibitors for zinc proteases. © 1997 Elsevier Science Ltd.

Introduction

Enzyme inhibitors are receiving increasing attention as tools for the study of mechanism of enzyme reaction and more importantly as potential therapeutic agents. Over the past few years we have been involved in the study of the development of novel design principles for enzyme inhibitors, especially of an irreversible type using well-characterized proteases such as carboxypeptidase A and α -chymotrypsin as model target enzymes.¹ The design principles developed with these enzymes bear special importance because they can be translated to zinc proteases of medicinal value, leading to the discovery of potential lead compounds for drug development. In this paper we wish to report the synthesis and evaluation of a novel type of competitive inhibitors for carboxypeptidase A, which we have designed using a route suggested by nature.

Zinc proteases which are differentiated from other proteases by having a catalytically essential zinc ion at the active site constitute an important class of proteolytic enzymes.² They are widely distributed throughout a variety of tissues and play key roles in numerous physiological processes.² These enzymes are thus important from the viewpoint of developing new therapeutic agents as was demonstrated with angiotensin converting enzyme³ and matrix metalloproteases.⁴ The active site zinc ion of these enzymes is coordinated to His, Glu, Asp, or Cys. The water molecule is the fourth and universal ligand. Of the amino acid residues, His is by far the most frequently used zinc ligand. Apparently, the zinc ion at the active site of these enzymes prefers the imidazolyl nitrogen for coordination. However, the imidazole ring has received only scant attention in the design of inhibitor for zinc proteases.⁵

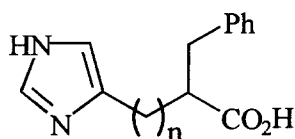
Carboxypeptidase A (CPA) is a leading prototypical enzyme for these zinc proteases.⁶ This zinc protease hydrolyzes peptide bonds at the C-terminus of substrates. The C-terminal amino acid residue having a hydrophobic side-chain such as Phe is preferably cleaved from the substrate. The zinc ion at the active site of carboxypeptidase A is coordinated to two imidazole rings of His-69 and His-196, the carboxylate of Glu-72, and a water molecule. In the catalytic reaction the zinc ion is thought to coordinate to the carbonyl oxygen of the scissile peptide bond of substrate thus to activate the scissile bond for hydrolytic cleavage. It is thus conceivable that substrate analogues which bear a moiety having a high binding affinity for the zinc ion such as imidazole would serve as inhibitors for the enzyme by binding to the enzyme at the active site in competition with substrate.

Results

Chemistry

Four compounds, **1–4** were synthesized as potential inhibitors for CPA for the present study. The synthesis of **1** (Scheme 1) commences with triflation of an imidazole nitrogen of methyl imidazole acetate followed by an introduction of a benzyl group at the α -position. After alkaline hydrolysis of the methyl ester, the trityl protecting group was removed under acidic conditions to afford **1** as a hydrochloride salt.

Synthetic route for the preparation of **2** is shown in Scheme 2. 4-*N*-tritylimidazolcarbaldehyde (**9**) that was prepared using the method described in the literature⁷ was subjected to the Horner–Wittig condensation with **10** prepared from trimethylphosphonoacetate and benzyl bromide in the presence of sodium hydride to afford **11**. Catalytic hydrogenation and subsequent



1 : $n = 0$

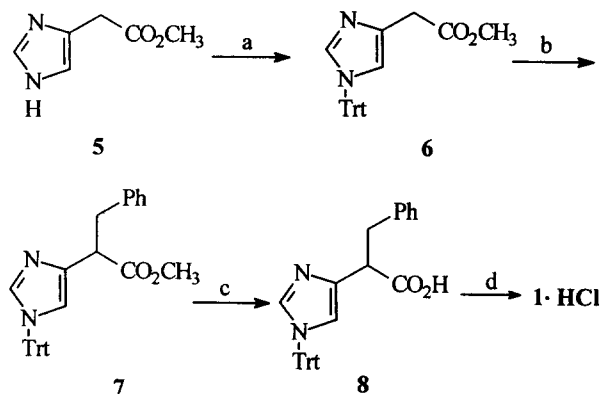
2 : $n = 1$

3 : $n = 2$

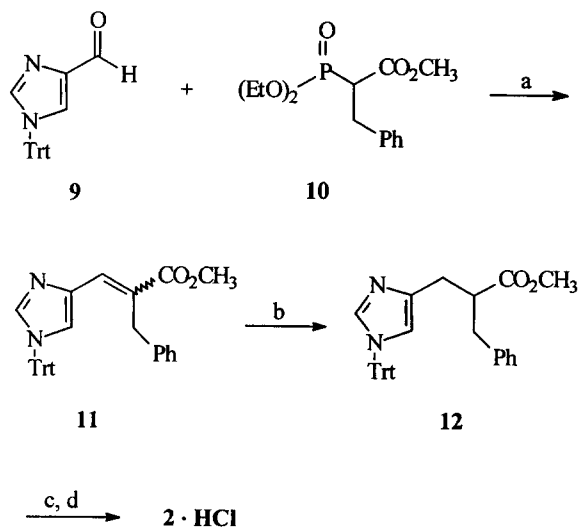
4 : $n = 3$

hydrolysis of the ester moiety followed by deprotection of the trityl group afforded **2**. An alternative synthetic path of shorter steps for **2** starts with urocanic acid methyl ester (Scheme 3).

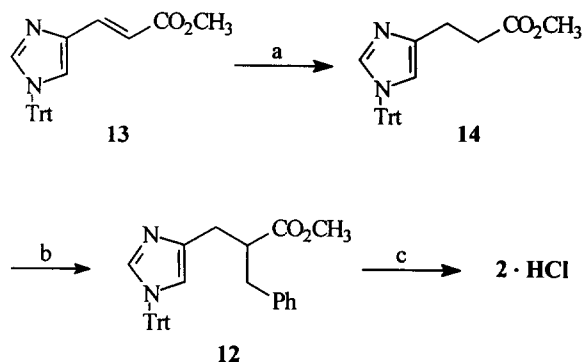
Protection of urocanic acid methyl ester with trityl chloride was followed by catalytic hydrogenation and



Scheme 1. Reagents, conditions and yields: (a) TrtCl, Et₃N, DMF, rt, 67%; (b) LDA, -78 °C, benzyl bromide, THF, 61%; (c) 10% NaOH, MeOH, 95%; (d) 3 N HCl, dioxane, reflux, 55%.



Scheme 2. Reagents, conditions and yields: (a) NaH, THF, 50 °C, 81%; (b) H₂, Pd-C, MeOH-CH₂Cl₂, 1 atm, 92%; (c) 10% NaOH, MeOH, 94%; (d) 3 N HCl, dioxane, reflux, 65%.



Scheme 3. Reagents, conditions and yields: (a) H₂, Pd-C, 1 atm, CH₂Cl₂-EtOH, 59%; (b) LDA, -78 °C, benzyl bromide, THF, 58%; (c) 10% NaOH, MeOH; 3 N HCl, dioxane, reflux, 65%.

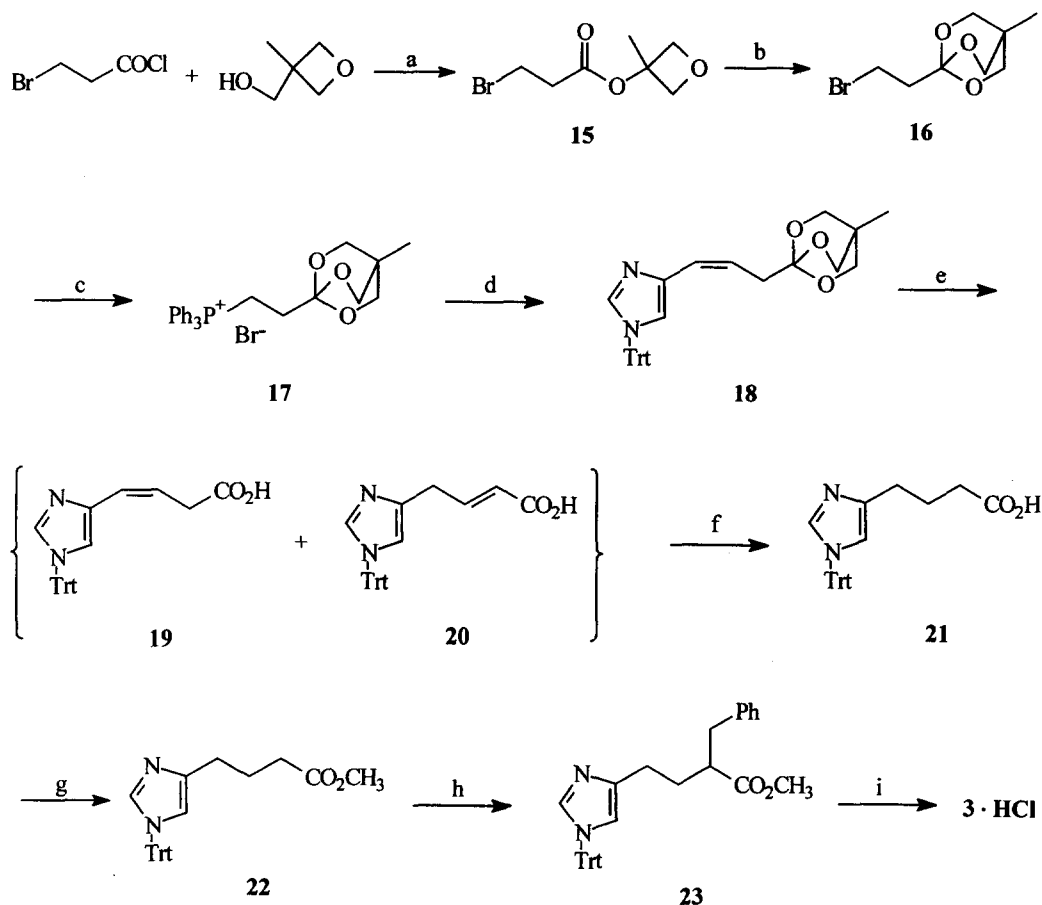
subsequent benzylation at the α -position using LDA and benzyl bromide to afford **12** which was converted into **2·HCl** as described above.

Compound **3** was prepared by two different routes as shown in Schemes 4 and 5. The Wittig reagent, prepared from an alkyl bromide (**16**), having a latent carboxylate functionality as a bridged carboxylic ortho ester,⁸ was condensed with aldehyde **9** in the presence of dimethyl sodium in DMSO to give **18**. Compound **16** was prepared from 3-hydroxymethyl-3-methyloxetane and 3-bromopropionyl chloride according to the literature method.⁹ Treatment of **18** with 0.3 N sulfuric acid followed by neutralization converted the bridged carboxylic acid ortho ester to a free carboxylic functionality, giving the corresponding carboxylic acid as a mixture of **19** and **20**. Catalytic hydrogenation of the regioisomeric mixture followed by esterification afforded **22** which was transformed into a hydrochloride salt of **3** in a manner analogous to that used for the preparation of **1**. In the alternative synthetic path, **24** was brominated with *N*-bromosuccinimide to give **25** which was then converted into phosphonium salt **26** by allowing to react with triphenylphosphine. The condensation of **26** with aldehyde **9** under the Wittig conditions using *n*-butyl lithium and subsequent catalytic hydrogenation yielded **23** which was converted into **3·HCl** as was described in Scheme 4.

The synthesis of **4** is outlined in Scheme 6. *N*-protected urocanic acid methyl ester (**13**) was reduced with lithium aluminum hydride at 0 °C to give **28**. Oxidation of **28** with manganese dioxide followed by reaction with **10** under the Horner-Wittig conditions using sodium hydride in THF produced **30**. Catalytic hydrogenation of **30** and subsequent hydrolysis of the ester moiety and detritylation yielded **4** which was isolated as a hydrochloride salt.

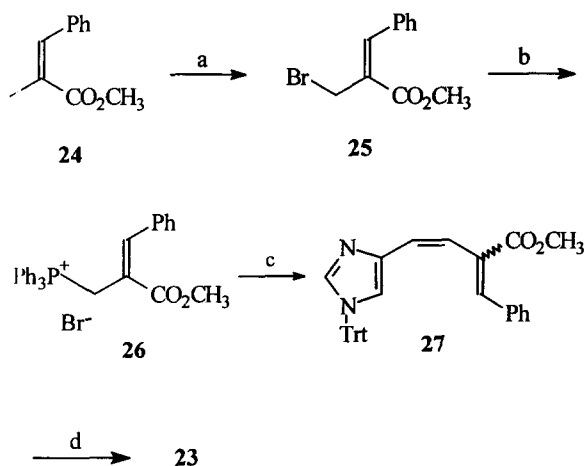
Biological properties

Compounds **1–4** were tested as hydrochloride salts for their inhibitory activities towards CPA by measuring spectrophotometrically the CPA-catalyzed hydrolysis of hippuryl-L-phenylalanine (substrate) in the presence of

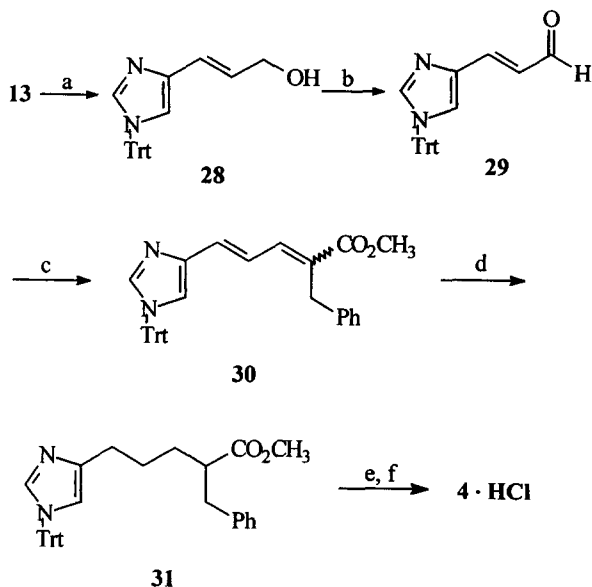


Scheme 4. Reagents, conditions and yields: (a) Pyridine, THF, 0 °C, 71%; (b) BF_3 etherate, CH_2Cl_2 , 0 °C, 76%; (c) Ph_3P , NaHCO_3 , CH_3CN , reflux, 85%; (d) **9**, NaH , DMSO, 50 °C, 48%; (e) 0.3 N H_2SO_4 , MeOH, 20 min; 1 N NaOH , 92%; (f) H_2 , Pd-C, 1 atm, 95%; (g) K_2CO_3 , CH_3I , DMF, 81%; (h) LDA, -78 °C, benzyl bromide, THF, 61%; (i) 10% NaOH , MeOH; 3 N HCl , dioxane, reflux, 60%.

each inhibitor at 25 °C in 0.05 M Tris buffer (pH 7.5)–0.5 M NaCl solution. They were shown to be competitive inhibitors for CPA as indicated by the Lineweaver–Burk plots. The Lineweaver–Burk plot for **3** (Fig. 1) is exemplary.



Scheme 5. Reagents, conditions and yields: (a) NBS, cat. AIBN, CCl_4 , reflux, 92%; (b) Ph_3P , CH_3CN , rt, 63%; (c) *n*-BuLi, THF/DMSO then **9**, THF, 78%; (d) H_2 , Pd-C, 1 atm, ethanol, 91%.



Scheme 6. Reagents, conditions and yields: (a) LiAlH_4 , THF, 0 °C, 15 min, 57%; (b) MnO_2 , dioxane, 80 °C, 30%; (c) **10**, NaH , THF, 43%; (d) H_2 , Pd-C, 1 atm, CHCl_3 -MeOH, 92%; (e) 10% NaOH , MeOH, 97%; (f) 3 N HCl , dioxane, reflux, 65%.

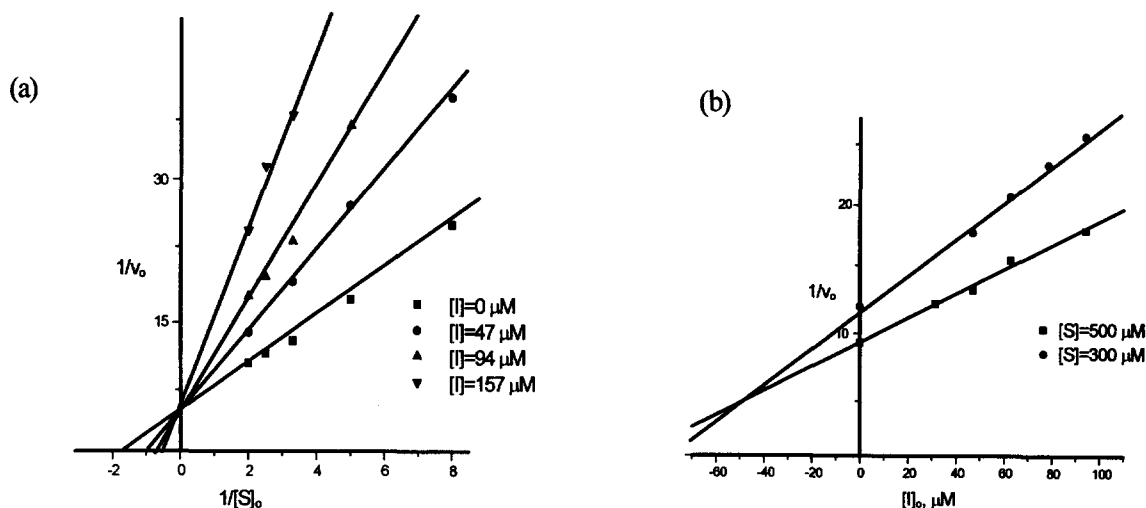


Figure 1. The Lineweaver-Burk (a) and Dixon (b) plots for the inhibition of CPA-catalyzed hydrolysis of hippuryl-L-phenylalanine (substrate) by **3** at $[\text{CPA}] = 7.80 \times 10^{-7} \text{ M}$.

The K_i values for these inhibitors were determined from the respective Dixon plot¹⁰ and are listed in Table 1.

Discussion

Inhibitors **1–4** have been designed as substrate analogue inhibitors for CPA. The rationale for designing them as CPA inhibitors is illustrated in Figure 2. As substrate analogues the carboxylate in the inhibitors would form hydrogen bonds with the guanidinium moiety of Arg-145 and the benzyl group would be accommodated in the primary substrate recognition pocket.^{1a} The imidazole ring would then be rested at a position proximal to the active site zinc ion, thereby forming a coordinative bond with the metal ion. Zinc ion is known to form complexes with the nitrogen of imidazole readily, as reflected by zinc enzymes in which the zinc ion is coordinated to His, Glu, Asp, or Cys having a binding frequency of $\text{His} \gg \text{Glu} > \text{Asp} = \text{Cys}$.¹¹ Accordingly, the substrate analogues bearing an imidazole ring would bind to the enzyme at the active site in competition with substrate to function as inhibitors. Indeed, they were shown to be competitive inhibitors for CPA in kinetic analysis (Fig. 1).

Inhibitor **1** is most potent with the K_i value of $0.8 \mu\text{M}$, which compares favorably with the K_i value of $1.1 \mu\text{M}$ reported for 2-benzylsuccinic acid,¹² a prototypic competitive inhibitor of CPA. However, **1** is much less

potent than *N*-[[[(benzyloxycarbonyl)amino]methyl]hydroxyphosphinyl]-L-phenylalanine, dilithium salt (ZG^oP), a representative transition state analogue inhibitor, the K_i of which was reported to be $0.09 \mu\text{M}$.¹³

As the spacer alkyl chain between the imidazole and the α -carbon to the carboxylate is lengthened, the K_i values increases rapidly, indicating that the imidazole ring in **1** is optimally rested for coordination to the zinc ion, and as the alkyl spacer is lengthened, the imidazole ring is too far distanced from the zinc ion for coordination. It is, however, interesting to note that inhibitor **3** in which the alkyl spacer consists of two methylene units is 3.5-fold more potent than inhibitor **2** having one methylene unit. The reason for this unexpected decrease in the K_i value in the case of **3** is not immediately apparent. The inhibitory constants reported in this study were determined with racemic mixtures and thus it is expected that if they are resolved the inhibitory potency of enantiomers possibly of the L-series would be

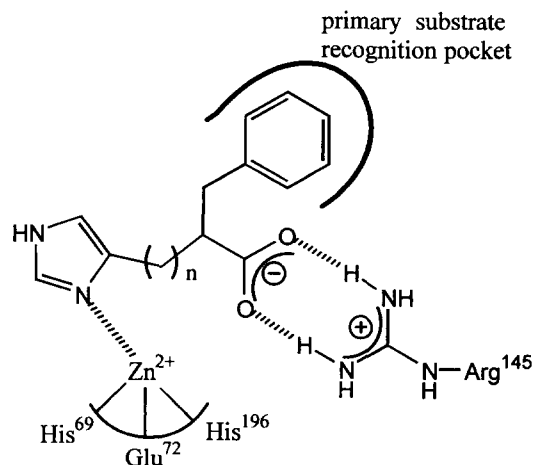


Figure 2. Schematic representation showing binding of 2-benzyl-2-(4-imidazolyl)alkylacetic acid to the active site of CPA.

Table 1. Inhibition constants (K_i s) of imidazole containing inhibitors in the inhibition of CPA

Inhibitor No. ^a	K_i (μM)
1	0.8
2	190
3	55
4	1410

^aInhibitors **1–4** were tested as hydrochloride salt.

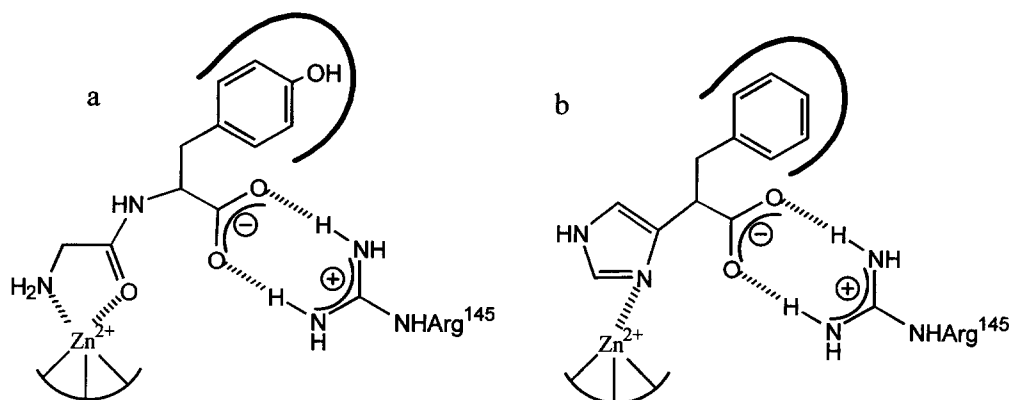


Figure 3. Diagram that illustrates binding of Gly-Tyr (a) and 2-benzyl-2-(4-imidazolyl)acetic acid (**1**) (b) to the active site of CPA. The amide carbonyl oxygen of Gly-Tyr and the N_1 of imidazole ring of **1** rest at a nearly identical position, liganding to the active site zinc ion.

improved. In general, in the case of competitive inhibitors of CPA, inhibitors which belong to the L-series were shown to be more potent than their enantiomers.^{12,14}

The design rationale and inhibitory activities found with compounds **1–4** suggest that a coordinative bond formation occurs between the imidazole ring of the inhibitors and the active site zinc ion when the inhibitors bind the enzyme, and the carboxylate of the inhibitors forms hydrogen bonds with the guanidinium moiety of Arg-145 and the phenyl ring fits in the primary substrate recognition pocket of the enzyme. This mode of binding is reminiscent to complexing of peptide substrate to the enzyme with the scissile peptide carbonyl oxygen being ligated to the zinc ion as revealed by the X-ray structure of CPA complexed with slowly hydrolyzing substrate, Gly-Tyr (Fig. 3a).¹⁵ It may be inferred from the X-ray structure that of the two nitrogen atoms in the imidazole ring of **1** the N_1 is most likely the site of ligation (Fig. 3b), and the proposition is consistent with the conclusion derived from the analysis of the Cambridge Structural Database that in the interaction of zinc ion with an imidazole ring the metal ion prefers the nitrogen having the sp^2 lone electron pair.¹⁶

Conclusion

Histidine is frequently found as a zinc coordinating ligand in metalloenzymes. Apparently, nature often utilizes the imidazole ring for ligating the metal ion in these enzymes. In spite of the obvious interest of using the imidazole ring as a ligand to the active site zinc ion in the design of inhibitors for the metalloenzymes, only scant examples have been reported. In this study we have demonstrated using CPA as a model enzyme that the imidazole ring is an effective zinc coordinating functionality that can be useful in the design of inhibitors for zinc containing proteases. Imidazole ring is an attractive substitute for the widely used thiol zinc ligand as seen in many of angiotensin converting

enzyme inhibitors³ in view of the fact that the thiol confers the disadvantage of being rapidly oxidized.

Experimental

General remarks and materials

¹H NMR and ¹³C NMR spectra were recorded on a Bruker AM 300 (300 MHz) instrument using tetramethylsilane as the internal standard. IR spectra were recorded on a BOMEM FT IR M100-C15 spectrometer. Mass spectra were obtained with KRATOS MS 25 RFA spectrometer. High-resolution mass spectra were recorded on a JEOL JMX-HX110/110A by the Korea Basic Science Center, Taejeon, Korea. Flash chromatography was performed on silica-gel 60 (230–400 mesh) and thin-layer chromatography (TLC) was carried out on silica-coated glass sheets (Merck silica-gel 60 F-254). Melting points were taken on a Thomas-Hoover capillary melting point apparatus and were uncorrected. Elemental analyses were performed at the Basic Science Center, Kyungbook National University, Taegu, Korea. A Perkin-Elmer Lambda 15 UV-Vis spectrometer was used in enzyme inhibition studies.

Kinetic studies

All solutions were prepared by dissolving in doubly distilled, deionized water. Stock assay solutions were filtered before use. CPA (EC 3.4.17.1) was purchased from Sigma Chemical Co. (Allan form, twice crystallized, from bovine pancreas, aqueous suspension.) The hydrolysis of hippuryl-L-phenylalanine by CPA was measured spectrophotometrically at 25 °C in 50 mM Tris buffer–0.5 M NaCl adjusted to pH 7.5 at 254 nm. Enzyme concentrations were estimated from the absorbance at 278 nm ($\epsilon_{278} = 64,200$). Initial velocities were calculated from the linear initial slopes of the change in absorbance where the amount of substrate consumed was less than 10%. K_i values were determined according to the method of Dixon.¹⁰

4-Imidazoleacetic acid methyl ester (5). A mixture of imidazoleacetic acid hydrochloride (1 g, 6.2 mmol), 20 mL of anhydrous methanol and 0.5 mL of concentrated sulfuric acid was heated at 65 °C overnight. Ammonia water (28%, 2 mL) was added to the reaction mixture and was concentrated under reduced pressure. To the residue was added water (30 mL) and extracted with ethyl acetate (20 mL $\times$ 5). The combined extract was dried (MgSO_4) and evaporated to give the product as a yellow oil (0.52 g, 48%). ^1H NMR (CDCl_3) δ 3.71 (s, 3H), 3.78–3.85 (s, 2H, methylene), 7.0 (s, 1H), 7.37 (s, 1H, H-5), 7.66 (s, 1H, H-2).

4-(*N*-triphenylmethyl)imidazole acetic acid methyl ester (6). To a stirred mixture of **5** (2.0 g, 14.2 mmol), 30 mL of DMF, and 3.6 g (35.5 mmol) of Et_3N under N_2 was added a solution of triphenylmethyl chloride (4.4 g, 15.6 mmol) in 90 mL of DMF. The mixture was stirred at room temperature overnight, then 200 mL of water was added to the reaction mixture. The precipitate that separated was collected, washed with water and triturated with ether to give the product as a white solid (1.8 g, 67%). mp 140–142 °C; ^1H NMR (CDCl_3) δ 3.65 (s, 2H, methylene), 3.72 (s, 3H, methyl ester), 6.80 (s, 1H, H-5 of imidazole), 7.14–7.40 (m, 16H, H-2 and aromatic).

2-(*N*-triphenylmethylimidazol-4-yl)hydrocinnamic acid methyl ester (7). To a solution of diisopropyl amine (0.36 g, 3.8 mmol) in 1.6 mL of THF under N_2 at 0 °C was added a *n*-BuLi (1.6 M in *n*-hexane, 2.45 mL, 3.9 mmol) by a microsyringe. It was stirred for 15 min at that temperature and cooled to –78 °C. Then a solution of **6** (1.25 g, 3.26 mmol) in 10 mL of THF was added slowly to the LDA solution and stirred for additional 1 h. Benzyl bromide (0.43 mL, 3.8 mmol) was added to the reaction mixture at –78 °C and warmed to 0 °C slowly and stirred for 2 h at 0 °C. To the reaction mixture was added saturated aqueous ammonium chloride solution (50 mL), extracted with chloroform (50 mL $\times$ 3), washed with brine (30 mL $\times$ 2), dried (MgSO_4) and evaporated. The residue was purified by column chromatography (ethyl acetate:*n*-hexane = 2:1) to give the product as a yellow oil (0.93 g, 61%). IR 1725, 1440, 1490 cm^{-1} ; ^1H NMR (CDCl_3) δ 3.20–3.36 (m, J = 6 Hz, 2H, benzyl), 3.66 (s, 3H), 3.90–3.99 (t, J = 6.5 Hz, 1H, 2-H), 6.62 (s, 1H, H-5 of imidazole), 7.08–7.40 (m, 21H, H-2 of imidazole and aromatic); ^{13}C NMR (CDCl_3) δ 38.5, 47.8, 52, 119.8, 126.3–139.6, 143, 174.

2-(*N*-triphenylmethylimidazol-4-yl)hydrocinnamic acid (8). A mixture of **7** (0.6 g, 1.27 mmol), 10% NaOH (4 mL) and MeOH (20 mL) was heated at 50 °C for 1 h. The solvent were removed by evaporation in vacuo and the residue was diluted in water and adjusted to pH 1–2 by the addition of 10% HCl. This solution was extracted with chloroform (20 mL $\times$ 3), dried (MgSO_4) and evaporated to give the product as a yellow fluffy solid (0.55 g, 95%). IR 3300–3500, 1720, 1440, 1490 cm^{-1} ; ^1H NMR (CDCl_3) δ 3.08–3.16

(dd, J = 6 Hz, 1H, benzyl), 3.43–3.49 (dd, J = 6 Hz, 1H, benzyl), 3.98–4.13 (m, 1H, 2-H), 6.40 (s, 1H, H-5 of imidazole), 6.95–7.63 (m, 20, aromatic), 7.80 (s, 1H, H-2 of imidazole), 8.82 (br, 1H, COOH).

2-(4-Imidazolyl)hydrocinnamic acid hydrochloride (1-HCl). To the suspension of **8** (0.4 g, 0.87 mmol) in dioxane (10 mL) was added concentrated HCl (0.5 mL) and the mixture was refluxed for 1.5 h. The solvents were removed in vacuo and the residue was diluted in water (20 mL). This solution was washed with ether (10 mL $\times$ 4) and concentrated under reduced pressure. The residue was triturated with isopropyl alcohol/ether, and the supernatant layer was decanted to give the hygroscopic product as a pale yellow solid (0.13 g, 55%). IR (thin film) 3500–2400, 1710, 1610 cm^{-1} ; ^1H NMR (D_2O) δ 3.04–3.11 (dd, J = 6 Hz, 1H, benzyl), 3.27–3.34 (dd, J = 6.6 Hz, 1H, benzyl), 4.10–4.17 (m, 1H, 2-H), 7.05–7.33 (m, 6H, H-5 of imidazole and aromatic), 8.48 (s, 1H, H-2 of imidazole); ^{13}C NMR (D_2O) δ 37, 44, 107, 117, 127–137, 175; HRMS (FAB $^+$) calcd for: ($\text{C}_{12}\text{H}_{12}\text{N}_2\text{O}_2\text{HCl} - \text{Cl}^-$): 217.0977; found: 217.0980.

4-(*N*-triphenylmethyl)imidazolecarboxaldehyde (9). A mixture of 4-(*N*-triphenylmethyl)imidazol-methanol 7 (7 g, 20.6 mmol), activated MnO_2 (17.3 g, 200 mmol) and dioxane (200 mL) was refluxed for 5 h. The hot reaction mixture was filtered through a celite pad and washed with dioxane (50 mL $\times$ 3). The filtrate was evaporated and the white solid was dried in vacuo at 110 °C. The crude product was recrystallized from ethanol: yield, 6.8 g (95%). An analytical sample was further recrystallized from ethyl acetate. Mp 203–205 °C (literature: 7 197–199 °C); IR 1684 cm^{-1} ; ^1H NMR (CDCl_3) δ 7.09–7.13 (m, 6H), 7.33 (q, 9H), 7.52 (d, 1H, 5-H), 7.60 (d, 1H, 2-H), 9.88 (s, 1H, CHO); anal. calcd for $\text{C}_{23}\text{H}_{18}\text{N}_2\text{O}$: C, 81.63; H, 5.36; N, 8.28; found: C, 81.40; H, 5.57; N, 8.30.

Trimethyl-2-benzylphosphonoacetate (10). To a suspension of NaH (60%, 1.2 g, 30 mmol) in 80 mL of anhydrous dimethoxyethane was added a solution of trimethylphosphonoacetate (5.0 g, 27.5 mmol) in 10 mL of dimethoxyethane. After 1 h at room temperature, benzyl bromide (3.9 mL, 33 mmol) was introduced by a syringe and the mixture was heated at 65 °C for 2 h. Ice was poured onto the reaction mixture and extracted with ethyl acetate (50 mL $\times$ 3) and the combined extract was dried (MgSO_4), and evaporated. The residue was purified by column chromatography (EtOAc :*n*-hexane = 1:3 $\rightarrow$ EtOAc) to give the product as a colorless oil (4.1 g, 55%). ^1H NMR (CDCl_3) δ 3.22–3.34 (m, 2H), 3.55 (d, 1H), 3.66 (s, 3H), 3.82 (s, 3H), 3.85 (s, 3H), 7.19–7.30 (m, 5H).

2-Benzyl-3-(*N*-triphenylmethylimidazol-4-yl)-2-propenoic acid methyl ester (11). To a suspension of NaH (60%, 0.43 g, 10.7 mmol, washed with *n*-hexane three times) in 4 mL of dried THF under N_2 was added **10** (2.91 g, 10.7 mmol). The mixture was heated at 50 °C for 30 min and cooled to room temperature. To this

solution was added slowly a solution of **9** (3.0 g, 8.88 mmol) in dried THF (20 mL). The mixture was heated at 50 °C for 3 h, then diluted with aqueous ammonium chloride solution (100 mL), extracted with ethyl acetate (60 mL $\times$ 3), dried (MgSO₄) and evaporated. The crude product was purified by column chromatography (ethyl acetate:*n*-hexane = 1:3) to give the product as a colorless oil (81%). IR (neat) 1709 cm⁻¹; ¹H NMR (CDCl₃) δ 3.51 (s, 3H), 3.69 (s, 2H, benzyl), 6.61 (s, 1H, $-\text{CH}=\text{C}-$), 7.36–7.11 (m, 22H, Hs of imidazole and aromatic); MS (EI, *m/z*) 484 (M⁺).

3-(*N*-triphenylmethylimidazol-4-yl)-2-propenoic acid methyl ester (13). To a stirred mixture of urocanic acid methyl ester (2.0 g, 13.1 mmol), 30 mL of DMF, and 3.3 g (32.75 mmol) of Et₃N under N₂ at 0 °C was added a solution of triphenylmethyl chloride (4.03 g, 14.4 mmol) in 50 mL of DMF. The mixture was stirred at room temperature for 3 h. Crushed ice was added portionwise to the reaction mixture. The precipitate that separated was collected, washed with water, and recrystallized from ethanol to give the product as a off-white solid (3.6 g, 70%). Mp 214–216 °C; IR (thin film) 1700, 1640, 1480, 1440 cm⁻¹; ¹H NMR (CDCl₃) δ 3.77 (s, 3H), 6.56 (d, *J* = 15.5 Hz, 1H), 7.04 (s, 1H, H-5 of imidazole), 7.05–7.76 (m, 17H).

3-(*N*-triphenylmethylimidazol-4-yl)-2-propanoic acid methyl ester (14). A solution of **13** (2.4 g, 6.08 mmol) in CH₂Cl₂:ethanol (40:80 mL) was hydrogenated (55 psi) in the presence of 10% Pd–C (0.4 g) at room temperature for 5 h. The reaction mixture was filtered through a celite pad and washed with dichloromethane. The filtrate was concentrated and the residue was purified by column chromatography (ethyl acetate:*n*-hexane = 2:1) to give the product as a white solid (1.4 g, 59%). An analytical sample was recrystallized from ethyl acetate (20% *n*-hexane). Mp 158–159 °C; IR (KBr pellet) 1725, 1440, 1480 cm⁻¹; ¹H NMR (CDCl₃) δ 2.65–2.70 (t, *J* = 5.5 Hz, 2H), 2.87–2.92 (t, *J* = 6.0 Hz, 2H), 3.64 (s, 3H), 6.57 (s, 1H, H-5 of imidazole), 7.11–7.37 (m, 16H, H-2 of imidazole and aromatic); anal. calcd for C₂₆H₂₄N₂O₂: C, 78.76; H, 6.10; N, 7.06; found: C, 78.78; H, 6.36; N, 7.05.

2-Benzyl-3-(*N*-triphenylmethylimidazol-4-yl)propanoic acid methyl ester (12). From **11**: a mixture of **11** (2.0 g, 4.24 mmol) in CH₂Cl₂:ethanol (60:40 mL) was hydrogenated (55 psi) in the presence of 10% Pd–C (0.2 g) at room temperature for 7 h. The reaction mixture was filtered through a celite pad and washed with dichloromethane. The filtrate was concentrated and the residue was purified by column chromatography (ethyl acetate:*n*-hexane = 1:3) to give the product as a colorless oil (1.9 g, 92%). IR (neat) 1732 cm⁻¹; ¹H NMR (CDCl₃) δ 2.70–3.07 (m, 4H, 2 $\times$ CH₂), 3.14 (m, 1H, α -H), 3.49 (s, 3H), 6.57 (s, 1H, H-5 of imidazole), 7.15–7.40 (m, 21H, H-2 of imidazole and aromatic); ¹³C NMR (CDCl₃) δ 38.4, 41.3, 48.2, 51.7, 75.6, 119.3, 126.7–142.8, 176; MS (EI) *m/z* 486 (M⁺).

From **14**: to a solution of diisopropyl amine (0.96 g, 9.43 mmol) in THF (5 mL) under nitrogen atmosphere at 0 °C was added *n*-BuLi (1.6 M in *n*-hexane, 6.44 mL, 9.5 mmol) by a microsyringe. The mixture was stirred for 15 min at that temperature and cooled to –78 °C. To this solution was added slowly a solution of **14** (3.4 g, 8.57 mmol) in 30 mL of THF and stirred for an additional 1 h at –78 °C. Benzyl bromide (1.1 mL, 9.4 mmol) was added to the reaction mixture at –78 °C and warmed to 0 °C slowly and stirred at that temperature for 5 h. To the reaction mixture was added aqueous ammonium chloride solution (150 mL), extracted with chloroform (100 mL $\times$ 3), washed with brine (50 mL $\times$ 2), dried (MgSO₄) and evaporated. The residue was purified by column chromatography (ethyl acetate:*n*-hexane = 2:1) to give the product as a yellow oil (2.4 g, 58%), which was identical with that obtained from **11**.

2-Benzyl-3-(4-imidazolyl)propanoic acid hydrochloride (2·HCl). A mixture of **12** (1.52 g, 3.21 mmol), 10% NaOH (7 mL) and MeOH (30 mL) was heated at 50 °C for 1 h, then evaporated under reduced pressure. The residue was diluted in water and the pH of solution was adjusted to about 1 by the addition of 10% HCl. This solution was extracted with chloroform (20 mL $\times$ 3), dried (MgSO₄) and evaporated to give 2-benzyl-3-(*N*-triphenylmethylimidazol-4-yl)propanoic acid as a yellow fluffy solid (1.44 g, 94 %). IR (thin film) 3200–3400, 1700, 1590, 1440, 1480 cm⁻¹; ¹H NMR (CDCl₃) δ 2.62–2.88 (m, 3H), 3.07–3.16 (m, 2H), 6.52 (s, 1H, H-5 of imidazole), 7.05–7.38 (m, 20H, aromatic), 7.56 (s, 1H, H-2 of imidazole), 9.1 (br, 1H, COOH).

To the suspension of 2-benzyl-3-(*N*-triphenylmethylimidazol-4-yl)propanoic acid (0.8 g, 1.69 mmol) in dioxane (15 mL) was added concentrated HCl (1.0 mL) and the mixture was refluxed for 1.5 h, then evaporated under reduced pressure and the residue was diluted in water (30 mL). This solution was washed with ether (20 mL $\times$ 4) and concentrated under reduced pressure. The residue was triturated with isopropyl alcohol/ether, and the supernatant layer was decanted to give the hygroscopic product as a pale yellow solid (0.27 g, 65%). IR (neat) 2500–3500 (br, –OH), 1720, 1600 cm⁻¹; ¹H NMR (D₂O) δ 2.77–3.03 (m, 5H), 7.09–7.25 (m, 6H, H-5 of imidazole and aromatic), 8.41 (s, 1H, H-2 of imidazole); ¹³C NMR (D₂O) δ 26.3, 37.8, 47.3, 115.9, 126–139, 178.8; HRMS (FAB⁺) calcd for (C₁₃H₁₄N₂O₂, HCl – Cl[–]): 231.1134, found: 231.1139.

3-Bromopropionate ester of 3-methyl-3-hydroxy-methyloxetane (15). To the solution of 3-methyl-3-hydroxymethyloxetane⁹ (3.6 g, 35.3 mmol) and pyridine (3.0 mL, 35.3 mmol) in dried THF (70 mL) at 0 °C was added slowly a solution of 3-bromopropionyl chloride (6.2 g, 35.5 mmol) which was prepared from 3-bromopropionic acid and thionyl chloride prior to use in THF (50 mL). The mixture was stirred for 1 h at that temperature then diluted with water (100 mL) and extracted with dichloromethane (100 mL $\times$ 3). The organic extract

was washed with water, dried (MgSO_4) and concentrated to give the product as a pale yellow oil (5.92 g, 71%). Because this compound undergoes HBr elimination to produce the corresponding acrylic ester upon chromatography, it was used in the subsequent reaction without further purification. ^1H NMR (CDCl_3) δ 1.37 (s, 3H), 2.93–3.0 (m, 2H), 3.55–3.66 (m, 2H), 4.22 (s, 2H), 4.41–4.44 (m, 2H), 4.51–4.56 (m, 2H).

1-(2-Bromoethyl)-4-methyl-2,6,7-trioxabicyclo[2,2,2]octane (16). Compound **15** (3.0 g, 12.65 mmol) was dissolved in CH_2Cl_2 (15 mL), cooled to 0 °C and treated with freshly distilled BF_3 -etherate (0.37 mL, 3.16 mmol). The resulting mixture was stirred for 3.5 h at 0 °C. The mixture was quenched with triethylamine (1.93 mL, 13.9 mmol), then was added ether (15 mL) and stirred for 20 min. The precipitate was filtered and the filtrate was concentrated to give the product as an oily yellow solid. It was purified on a short silica-gel column eluting with *n*-hexane (pretreated with 5% triethylamine) to give 2.3 g (76%) of product as a pale yellow crystals. Mp 71 °C (literature:⁹ 72 °C); ^1H NMR (CDCl_3) δ 0.82 (s, 3H), 2.23–2.29 (m, 2H), 3.40–3.45 (m, 2H), 3.89 (s, 6H); ^{13}C NMR (CDCl_3) δ 14.4, 26, 30, 41, 73, 118.8.

1-(2-Triphenylphosphoniummethyl)-4-methyl-2,6,7-trioxabicyclo[2,2,2]octane bromide (17). A mixture of **16** (2.3 g, 9.7 mmol), triphenylphosphine (12.7 g, 48.5 mmol) and sodium bicarbonate (0.9 g, 10.7 mmol) in acetonitrile (25 mL) was refluxed for 20 h. The mixture was cooled to room temperature, diluted with methylene chloride and filtered through a celite pad to remove the inorganic salts. Removal of the solvent under reduced pressure afforded a brown gummy solid. Trituration with ether gave the product as a yellow solid which was dried over P_2O_5 under vacuum (4.11 g, 85%). Mp 205–208 °C; ^1H NMR (CDCl_3) δ 0.82 (s, 3H), 1.96–2.00 (m, 2H), 3.28–3.52 (m, 2H), 3.87 (s, 6H), 7.67–7.89 (m, 15H); ^{13}C NMR (CDCl_3) δ 13.8, 17.5, 29.1, 29.8, 72.2, 106.8, 116.8, 130.3, 132.7, 135.

1-((*N*-triphenylmethylimidazol-4-yl)propyl-2-enyl)-4-methyl-2,6,7-trioxabicyclo[2,2,2]octane (18). The mixture of NaH (60%, 0.12 g, 4.4 mmol, washed with *n*-hexane three times) in 5 mL of dried DMSO was heated at 75–80 °C for 30 min. A solution of **17** (1.18 g, 2.2 mmol) in 8 mL of DMSO was added and heated at 70 °C for 1 h. Then a solution of **9** (0.4 g, 1.1 mmol) in 15 mL of DMSO was added and the resulting mixture was heated at 50 °C for 24 h. The mixture was diluted with aqueous ammonium chloride solution, extracted with chloroform (50 mL $\times$ 3), dried (MgSO_4) and evaporated in vacuo. The residue was purified by column chromatography (ethyl acetate:chloroform:Et₃N = 10:5:0.5) to give the product as a yellow oil (0.25 g, 48%). ^1H NMR (CDCl_3) δ 0.81 (s, 3H), 2.92 (d, J = 6.9 Hz, 1H), 3.89 (s, 6H), 5.66–5.72 (m, 1H), 6.4 (d, J = 12 Hz, 1H), 6.85 (s, 1H), 7.13–7.70 (m, 16H).

4-(*N*-triphenylmethylimidazol-4-yl)-3-butenic acid (19) and 4-(*N*-triphenylmethylimidazol-4-yl)-2-butenic acid (20). Compound **18** (480 mg, 0.96 mmol) was treated with methanolic sulfuric acid (0.3 N, 3.4 mL) for 20 min. NaOH, 1 N (5 mL) was added to the mixture and stirred overnight at room temperature. The mixture was dissolved in water and acidified with 3 N HCl, then extracted with chloroform (20 mL $\times$ 3). The combined extract was dried (MgSO_4) and concentrated. The crude product was purified by column chromatography (CHCl_3 :MeOH = 10:1) to give **19** (180 mg, 47%, R_f = 0.4) and **20** (170 mg, 45%, R_f = 0.2). IR 1709 cm^{-1} (**19**), 1726 cm^{-1} (**20**); ^1H NMR (CDCl_3): for **19**, δ 3.16 (d, J = 6 Hz, 2H), 6.23 (d, J = 9 Hz, 1H), 6.64 (m, 1H), 7.11–7.34 (m, 16H), 7.6 (s, 1H, H-2 of imidazole); for **20**, δ 3.43 (d, J = 9 Hz, 2H), 5.8–5.9 (m, 1H), 6.43 (d, J = 9 Hz, 1H), 7.13 (s, 1H, H-4 of imidazole), 7.31–7.70 (m, 16H); MS (EI) m/z 394 (M^+).

4-(*N*-triphenylmethylimidazol-4-yl)-butanoic acid (21). A solution of **19** and **20** (360 mg, 0.9 mmol) in ethyl acetate/ethanol (15/6 mL) was hydrogenated in the presence of 10% Pd-C (100 mg) at atmospheric pressure for 1 h. The reaction mixture was filtered (celite pad), washed with chloroform and the filtrate was concentrated to give the product as a pale yellow solid (340 mg, 95%), which was used without further purification in the subsequent reaction. ^1H NMR (CDCl_3) δ 1.95 (t, J = 7.2 Hz, 2H), 2.38 (t, J = 7 Hz, 2H), 2.69 (t, J = 7.5 Hz, 2H), 6.57 (s, 1H), 7.11–7.66 (m, 16H).

4-(*N*-triphenylmethylimidazol-4-yl)-butanoic acid methyl ester (22). To a mixture of **21** (0.47 g, 1.18 mmol) and K_2CO_3 (0.2 g, 1.4 mmol) in DMF (20 mL) was added methyl iodide (0.33 g, 2.4 mmol) at room temperature and stirred overnight. The mixture was diluted with ethyl acetate and filtered. The organic layer was washed with water, dried (MgSO_4), and evaporated. The residue was purified by column chromatography (ethyl acetate:*n*-hexane = 2:1) to give the product as a yellow oil (0.38 g, 81%). IR (neat) 1755 cm^{-1} ; ^1H NMR (CDCl_3) δ 2.04 (t, J = 7.2 Hz, 2H), 2.39 (t, J = 7 Hz, 2H), 2.77 (t, J = 7.5 Hz, 2H), 3.77 (s, 3H), 6.63 (s, 1H), 7.07–7.44 (m, 16H).

2-Bromomethylcinnamic acid methyl ester (25). A mixture of 2-methylcinnamic acid methyl ester (4.37 g, 24.8 mmol), *N*-bromosuccinimide (4.86 g, 27.3 mmol) and AIBN (40 mg) in carbon tetrachloride (55 mL) was refluxed for 7 h. The mixture was filtered to remove succinimide that was formed and the filtrate was evaporated in vacuo. The residue was purified by column chromatography (ethyl acetate:*n*-hexane = 1:3) to give the product as a yellow liquid (5.8 g, 92%). IR (neat) 1720 cm^{-1} ; ^1H NMR (CDCl_3) δ 3.72 (s, 3H), 4.42 (s, 2H), 7.40–7.61 (m, 5H), 7.85 (s, 1H).

Methyl-2-(triphenylphosphoniummethyl)cinnamate, bromide (26). A mixture of **25** (5.8 g, 22.7 mmol), triphenyl phosphine (11.9 g, 45.4 mmol) and

acetonitrile (220 mL) was stirred at room temperature for 6 h. The mixture was then concentrated and the resulting gummy solid was purified by column chromatography ($\text{CHCl}_3 \rightarrow 15\% \text{ MeOH in } \text{CHCl}_3$) to give the product as a pale yellow solid (7.4 g, 63%). An analytical sample was recrystallized from ethyl acetate. Mp 165–170 °C; $^1\text{H NMR}$ (CDCl_3) δ 3.4 (s, 3H), 4.97 (d, $J = 14.7$ Hz, 2H), 7.26–7.93 (m, 20H), 7.94 (d, $J = 5.1$ Hz, 1H); anal. calcd for $\text{C}_{29}\text{H}_{26}\text{BrO}_2\text{P}$: C, 67.32; H, 5.07; found: C, 67.06; H, 5.46.

1-Phenyl-2-carbomethoxy-4-(*N*-triphenylmethylimidazol-4-yl)-1,3-butadiene (27). To a solution of **26** (2.14 g, 4.14 mmol) in THF/DMSO (50/5 mL) was added *n*-BuLi (2.5 M in *n*-hexane, 2.6 mL, 4.2 mmol) at 0 °C and stirred at room temperature for 1 h. To this ylide solution was added a solution of **9** (0.7 g, 2.1 mmol) in THF (5 mL) and stirred overnight at room temperature. To the resulting mixture was added aqueous ammonium chloride solution (100 mL), then extracted with chloroform (50 mL $\times$ 3), dried (MgSO_4) and evaporated. The residue was purified by column chromatography (ethyl acetate:*n*-hexane = 2:1) to give the product as a yellow solid (0.8 g, 78%). Mp 133–135 °C; IR (thin film) 1718, 1440, 1480 cm^{-1} ; $^1\text{H NMR}$ (CDCl_3) δ 3.84 (s, 3H), 6.86 (s, 1H), 7.15–7.49 (m, 23H), 7.51 (s, 1H).

2-Benzyl-4-(*N*-triphenylmethylimidazol-4-yl)butanoic acid methyl ester (23). From **27**: a solution of **27** (0.85 g, 1.71 mmol) in ethanol (40 mL) was hydrogenated (55 psi) in the presence of 10% Pd–C (0.1 g) at room temperature for 6 h. The reaction mixture was filtered (celite pad) and washed with chloroform. The filtrate was concentrated and the residue was purified by column chromatography (ethyl acetate:*n*-hexane = 2:1) to give the product as a colorless oil (0.78 g, 91%). IR (neat) 1730, 1590, 1490, 1440 cm^{-1} ; $^1\text{H NMR}$ (CDCl_3) δ 1.92–2.07 (m, 2H), 2.55–2.96 (m, 5H), 3.6 (s, 3H), 6.53 (s, 1H, H-5 of imidazole), 7.12–7.37 (m, 21H); $^{13}\text{C NMR}$ (CDCl_3) 26.7, 32.2, 38.9, 47.5, 51.8, 75.5, 118.4; MS (EI) m/z 500 (M^+).

From **22**: to a solution of diisopropyl amine (0.096 g, 0.94 mmol) in THF (3 mL) under nitrogen atmosphere at 0 °C was added *n*-BuLi (1.6 M in *n*-hexane, 0.64 mL, 0.95 mmol) by a microsyringe. The mixture was stirred for 15 min at that temperature and cooled to –78 °C. A solution of **22** (0.34 g, 0.86 mmol) in 5 mL of THF was added slowly to the prepared LDA solution and stirred for additional 1 h at –78 °C. Benzyl bromide (0.11 mL, 0.94 mmol) was added to the reaction mixture at –78 °C and warmed to 0 °C slowly and stirred for 5 h at 0 °C. To the reaction mixture was added aqueous ammonium chloride solution (15 mL), extracted with chloroform (20 mL $\times$ 3), washed with brine (20 mL $\times$ 2), dried (MgSO_4) and evaporated. The residue was purified by column chromatography (ethyl acetate:*n*-hexane = 2:1) to give the product as a yellow oil (0.26 g, 61%), which was identical with that obtained from **27**.

2-Benzyl-4-(4-imidazolyl)butanoic acid hydrochloride (3·HCl). To the suspension of 2-benzyl-4-(*N*-triphenylmethylimidazol-4-yl)butanoic acid (0.2 g, 0.4 mmol) in dioxane (10 mL) was added concentrated HCl (1.0 mL) and the mixture was refluxed for 2 h, then evaporated in vacuo and the residue was diluted in water (20 mL). This solution was washed with ether (20 mL $\times$ 4) and concentrated under reduced pressure. The residue was triturated with isopropyl alcohol/ether, and the supernatant layer was decanted to give the product as a hygroscopic pale yellow solid (70 mg, 60%). IR (thin film) 2500–3500, 1710, 1610 cm^{-1} ; $^1\text{H NMR}$ (D_2O) δ 1.75–1.93 (m, 2H), 2.54–2.84 (m, 3H), 7.04 (s, 1H), 7.09–7.25 (m, 5H), 8.05 (s, 1H); $^{13}\text{C NMR}$ (D_2O) δ 22.2, 30.1, 38.1, 47.2, 116.0, 126–139.3, 180.1; HRMS (FAB^+) calcd for ($\text{C}_{14}\text{H}_{16}\text{N}_2\text{O}_2$, $\text{HCl} - \text{Cl}^-$): 245.1290, found: 245.1288.

3-(*N*-triphenylmethylimidazol-4-yl)-2-propen-1-ol (28). To the suspension of lithium aluminum hydride (0.29 g, 7.6 mmol) in dried tetrahydrofuran (50 mL) was added slowly **13** (1.5 g, 3.8 mmol) in tetrahydrofuran (30 mL) at 0 °C and stirred for 15 min. The mixture was diluted with ethyl acetate (100 mL) and the excess lithium aluminum hydride was destroyed by the addition of water (4 mL) and 3 N NaOH (4 mL). The organic extract was dried (MgSO_4) and evaporated to give the product as a white solid (0.8 g, 57%). Mp 171–173 °C; IR 3500 cm^{-1} ; $^1\text{H NMR}$ (CDCl_3) δ 4.25 (d, $J = 4$ Hz, 2H), 6.46 (m, 2H), 6.48 (s, 1H), 6.77–7.42 (m, 16H).

3-(*N*-Triphenylmethylimidazol-4-yl)-2-propenaldehyde (29). To a warmed solution of **28** (1.0 g, 2.7 mmol) in dioxane (30 mL) was added manganese dioxide (2.4 g, 27 mmol) and the resulting mixture was heated at 80 °C for 2 h. The mixture was filtered on a sintered glass and the filtrate was concentrated in vacuo. The residue was triturated with ether/ethyl acetate to give the product as a white solid (0.15 g, 30%). IR 1680 cm^{-1} ; $^1\text{H NMR}$ (CDCl_3) δ 6.77 (q, $J = 7.8$ Hz, 1H), 7.08–7.38 (m, 17H), 7.53 (s, 1H), 9.60 (d, $J = 7.8$ Hz).

2-Benzyl-5-(*N*-triphenylmethylimidazol-4-yl)-2,4-pentadienic acid methyl ester (30). To a suspension of NaH (60%, 0.062 g, 2.5 mmol, washed with *n*-hexane $\times$ 3) in 4 mL of dried THF under N_2 was added trimethyl-2-benzylphosphono acetate (**10**, 0.68 g, 2.5 mmol). The mixture was heated at 50 °C for 20 min and cooled to room temperature. To this solution was added a solution of **29** (0.61 g, 1.67 mmol) in dried THF (10 mL). The mixture was heated at 50 °C for 6 h, then diluted with aqueous ammonium chloride solution (30 mL), extracted with ethyl acetate (20 mL $\times$ 3), dried (MgSO_4) and evaporated in vacuo. The residue was purified by column chromatography (ethyl acetate:*n*-hexane = 1:1) to give the product as a colorless solid (43%). Mp 120–122 °C; *E*-form: $R_f = 0.8$; *Z*-form: $R_f = 0.7$. $^1\text{H NMR}$ (CDCl_3): for *E*-form, δ 3.72 (s, 3H), 3.86 (s, 2H), 6.80 (d, $J = 15$ Hz, 1H), 6.94 (s, 1H, H-5 of imidazole), 7.03–7.51 (m, 23 H); for *Z*-

form, δ 3.56 (s, 3H), 3.85 (s, 3H), 6.56 (dd, J = 11.7, 10.2 Hz, 1H), 6.94 (s, 1H), 7.02–7.46 (m, 23H).

2-Benzyl-5-(*N*-triphenylmethylimidazol-4-yl)pentanoic acid methyl ester (31). A mixture of **30** (0.54 g, 1.06 mmol) in chloroform:methanol (20:10 mL) was hydrogenated (55 psi) in the presence of 10% Pd–C (0.12 g) at room temperature for 2 h. The reaction mixture was filtered (celite pad) and the filtrate was concentrated. The residue was purified by column chromatography (ethyl acetate:*n*-hexane = 2:1) to give the product as a colorless oil (0.50 g, 92%). IR (neat) 1728 cm^{-1} ; ^1H NMR (CDCl_3) δ 1.53–1.73 (m, 3H), 1.89 (m, 1H), 2.51–2.78 (m, 4H), 2.89–2.96 (m, 1H), 3.57 (s, 3H), 6.51 (s, 1H), 7.13–7.36 (m, 21H).

2-Benzyl-5-(4-imidazolyl)pentanoic acid hydrochloride (4·HCl). A mixture of **31** (0.37 g, 0.72 mmol), 10% NaOH (3 mL) and MeOH (10 mL) was heated at 50 °C for 3 h, then evaporated in vacuo. The residue was dissolved in water and adjusted to pH 1 by the addition of 10% HCl. This solution was extracted with chloroform (20 mL $\times$ 3), dried (MgSO_4) and evaporated to give the 2-benzyl-5-(*N*-triphenylmethylimidazol-4-yl)pentanoic acid as a yellow fluffy solid (0.35 g, 97%). IR (thin film) 3300–3500, 1715, 1490, 1440 cm^{-1} ; ^1H NMR (CDCl_3) δ 1.44–1.83 (m, 4H), 2.63–2.89 (m, 4H), 2.90–2.99 (m, 1H), 6.62 (s, 1H), 6.91–7.42 (m, 20H), 8.10 (s, 1H).

To a suspension of 2-benzyl-5-(*N*-triphenylmethylimidazol-4-yl)pentanoic acid (0.31 g, 0.62 mmol) in dioxane (10 mL) was added concentrated HCl (1.0 mL) and the mixture was refluxed for 2 h, then evaporated in vacuo. The residue was dissolved in water (20 mL). This solution was washed with ether (20 mL $\times$ 4) and concentrated under reduced pressure. The residue was triturated with isopropyl alcohol/ether, and the supernatant layer was decanted to give the product as a hygroscopic pale yellow solid (0.12 g, 65%). IR (thin film) 2500–3500, 1720, 1610 cm^{-1} ; ^1H NMR (D_2O) 1.42–1.63 (m, 4H), 2.53–2.82 (m, 6H), 3.30–3.55 (m, 1H), 7.07 (s, 1H), 7.11–7.26 (m, 5H), 8.42 (s, 1H); ^{13}C NMR (D_2O) δ 23.7, 25.7, 30.4, 38.0, 47.5, 115.6, 126.3–139.6, 180.7; HRMS (FAB^+) calcd for ($\text{C}_{15}\text{H}_{18}\text{N}_2\text{O}_2$, $\text{HCl} - \text{Cl}^-$): 259.1447; found: 259.1441.

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