Synthesis and biological evaluation of potential bisubstrate inhibitors of protein farnesyltransferase. Design and synthesis of functionalized imidazoles†

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A novel series of compounds, derived from 2,5-functionalized imidazoles, have been synthesized as potential bisubstrate inhibitors of protein farnesyltransferase (FTase) using structure-based design. These compounds have a 1,4-diacid chain and a tripeptide connected by an imidazole ring. The synthetic strategy relies on the functionalization at the C-2 position of the heterocycle with the diacid side chain and peptide coupling at the C-5 position. Several new compounds were synthesized in good yields. Kinetic experiments on the most active compounds revealed different binding modes depending on the diacid chain length.

Introduction

Since its identification, the protein farnesyltransferase (FTase) has emerged as a promising target in cancer therapy.[1] Recently, it has also appeared as a potential target for the treatment of parasitic diseases.[2] FTase is a zinc metalloenzyme[3] that catalyses the addition of the lipid 15-carbon isoprenyl farnesyl moiety from farnesylpyrophosphate (FPP) to a sulfhydryl of a cysteine residue embedded in the C-terminal CaaX sequence motif of cellular signal transduction proteins.[4] The CaaX box is defined by an invariant cysteine residue (C), two aliphatic residues (aa) and the C-terminal residue (X), which contributes to substrate specificity. The farnesylation reaction is part of a series of modifications necessary for plasma membrane association, extracellular signal transmission and cell proliferation.[4,5]

A broad range of FTase inhibitors (FTIs) that mimic the C-terminal CaaX tetrapeptide and the farnesylpyrophospate (FPP) have been already described,[6] however only a few compounds designed to mimic both substrates have been reported so far.[7] This kind of compound is classified as a bisubstrate derivative, which is expected to exhibit better specificity and affinity for the enzyme than either substrate alone due to its similarity with the transition state of FTase.

In this paper, we wish to report our initial results on the synthesis and the biological evaluation of higher-substituted imidazoles with the aim of obtaining a novel class of FTIs. Based on the studies reported by the Fierke,[8] Poulter[9] and Beese[10] groups on the transition state **1** of this enzyme, we designed a new class of compounds with the general structure **2** outlined in Fig. 1 in order to connect the CaaX- and pyrophosphate-binding sites.

The principal scaffold of our analogues is the imidazole ring. In spite of the difficulty of working with this heterocycle due to its particular reactivity, imidazole is a very important moiety of FTIs because of the strong interaction of its basic nitrogen with the zinc atom in the FTase catalytic binding site. Numerous FTIs bear an imidazole ring such as tipifarnib[11] and BMS-214662,[12] which are under clinical trials against cancer. It has been shown by X-ray crystallography of these anticancer candidates complexed with FTase that the imidazole is effectively bound to the zinc atom.[13] A 1,4-diacid was chosen to go into the pyrophosphate binding site because FPP competitive inhibitors bearing a 1,4-diacid, such as chaetomellic acid A, have shown very good affinities for the enzyme.[14] Finally, the peptidic side chain is believed to function as a mimic of the CaaX box. In order to obtain better interaction with the enzyme, the chain length between the heterocycle and the diacid has been varied.

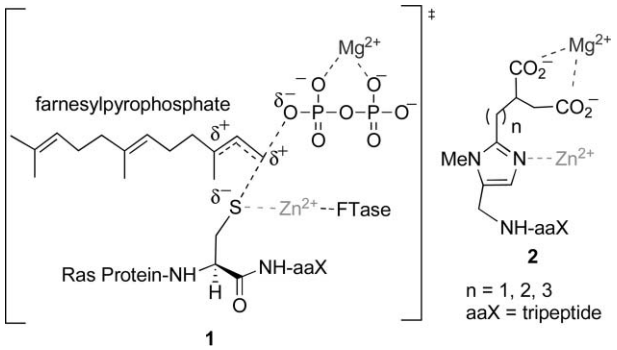

Fig. 1 Transition state of FTase (**1**) and our design of transition state analogues (**2**).

The originality of these compounds relies on the 1,4-diacid scaffold as well as the highly functionalized imidazole ring. In fact, all the described imidazole-containing FTIs are either monosubstituted in the C-4/5 position (like BMS-214662) or disubstituted in the N-1 and C-5 positions (like tipifarnib). To the best of our knowledge, no compound with a structure related to our general model **2** has been described to date. Finally, this work could also provide additional information about the exact transition state of this enzyme that remains currently unknown.

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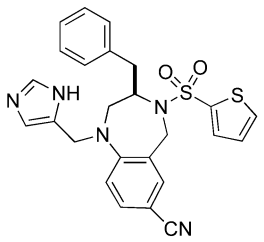
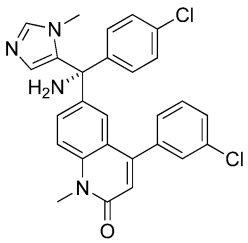
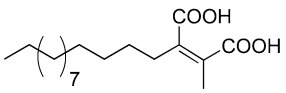


BMS-214662



Tipifarnib
(Zarnestra®)



Chaetomellic acid A

This article describes the synthesis and the biological activity of the first compounds of this new class of FTIs with the peptide chain linked at the C-5 position of the imidazole ring.

Results and discussion

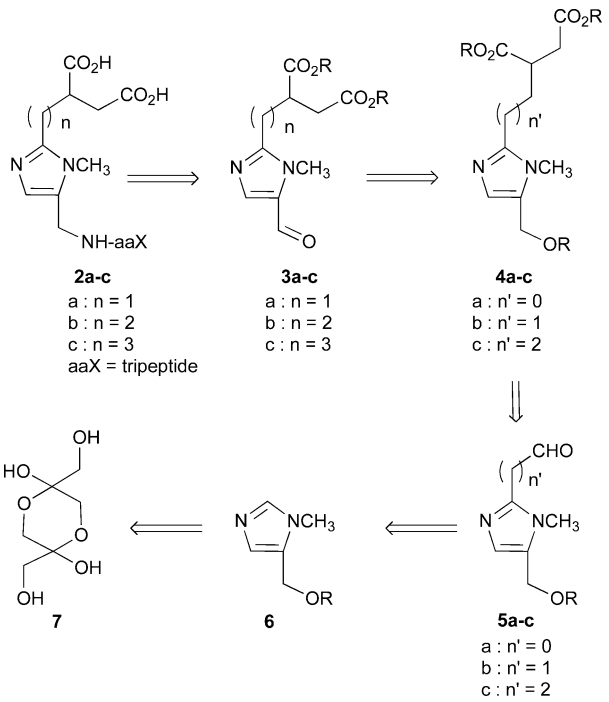
1. Chemistry

Our first approach relied on the introduction of the diacid side chain at the C-2 position of the imidazole moiety followed by the coupling of the peptide at the C-5-substituted position. Among the reactions of 2-lithioimidazoles with electrophiles,[15] only a few methods have so far been described for the direct introduction of a functionalized alkyl chain at the C-2 position of this heterocycle.[16] In fact, our initial efforts to execute the C-2 functionalization by reaction between 2-lithioimidazole and bromoesters were unsuccessful. Therefore, we looked into palladium-catalyzed coupling reactions with 2-iodoimidazole derivatives under Heck conditions. No C-2-substituted compound could be isolated under these conditions, but these attempts allowed us to find a new way to synthesize imidazoisoindole derivatives, and this new reaction has been the subject of another study reported elsewhere.[17]

Therefore, we planned another retrosynthetic route, depicted in Scheme 1. The peptide chain could be introduced at the end of the syntheses by reductive amination of the aldehydes **3** obtained after deprotection and oxidation of the C-5 hydroxymethyl moiety of compounds **4**. The key step of the syntheses is the introduction of the 1,4-diester moiety by a Horner–Wadsworth–Emmons reaction on the aldehydes **5** obtained by functionalization at the C-2 position of the 1-methyl-5-hydroxymethylimidazole derivative **6** synthesized from 1,3-dihydroxyacetone dimer **7**.

Starting from the commercially available 1,3-dihydroxyacetone dimer **7**, the *N*-methyl-5-(hydroxymethyl)imidazole **8** was readily obtained in two steps (47% overall yield) using the Marckwald[18] procedure slightly modified by Rapoport[19] and Collman[20] (Scheme 2). Compound **8** was easily converted into aldehyde **5a** ($n' = 0$) *via* TBS-protection followed by formylation[21] of the C-2 position (75% yield after two steps). Next, this compound **5a** was used as a common intermediate for the syntheses of all our analogues.

With aldehyde **5a** in hand, we started the synthesis of the intermediate **4a** bearing only one carbon between the imidazole



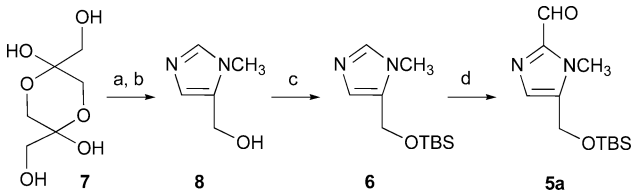
2a-c
a : n = 1
b : n = 2
c : n = 3
aaX = tripeptide

3a-c
a : n = 1
b : n = 2
c : n = 3

4a-c
a : n' = 0
b : n' = 1
c : n' = 2

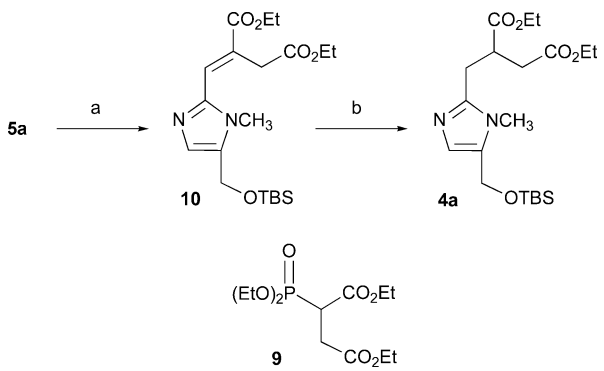
5a-c
a : n' = 0
b : n' = 1
c : n' = 2

Scheme 1 Retrosynthetic analysis.



Scheme 2 *Reagents and conditions*: a) KSCN, CH_3NH_2·HCl, AcOH, 1-butanol, RT, 3 days, 62%; b) 2.4 N HNO_3, $NaNO_2$ cat., RT, 6 h, 75%; c) TBDMSCl, imidazole, DMF, RT, 2 h, 91%; d) *n*BuLi, THF, −78 °C, 45 min, then DMF, −78 °C → RT, 2 h 30 min, 83%.

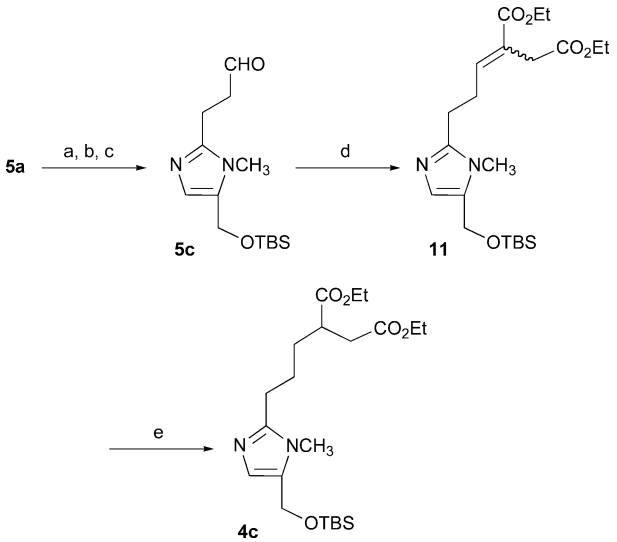
core and the 1,4-diester chain. Our approach was accomplished by using a Horner–Wadsworth–Emmons reaction[22] involving a phosphonosuccinic ester followed by the hydrogenation of the double bond (Scheme 3). The 2-(diethoxyphosphoryl)succinic acid diethyl ester **9** has previously been synthesized in one step using a slightly modified Linke protocol.[23] Under typical Horner–Wadsworth–Emmons conditions, compound **10** was obtained in



Scheme 3 *Reagents and conditions*: a) **9**, NaH, THF, RT, 2 h, (100% *E* isomer), 69%; b) H_2 (1 atm), Pd/C (10%), EtOAc, RT, 4 h, 100%.

69% yield, and following catalytic hydrogenation gave the expected compound **4a** in quantitative yield.

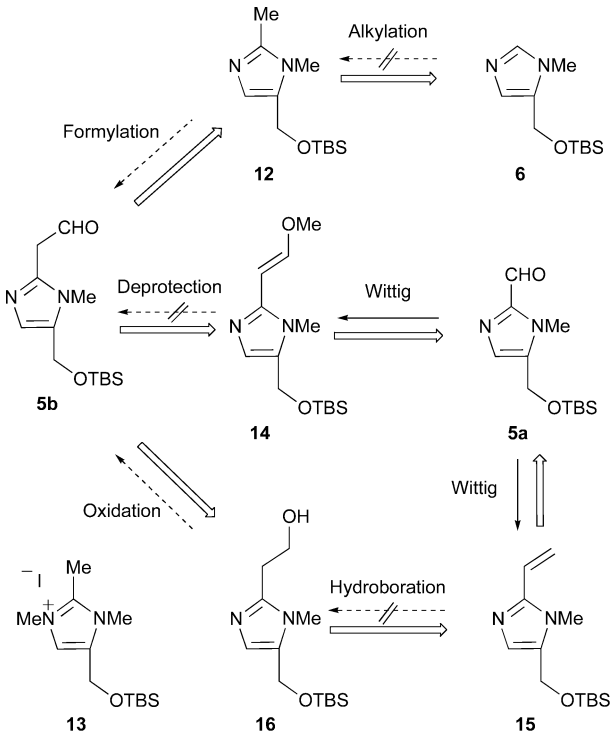
With **4a** synthesized, we turned our attention to the intermediate **4c** with a three-carbon chain between the imidazole ring and the 1,4-diester part (Scheme 4). The aldehyde **5a** was submitted to Horner–Wadsworth–Emmons olefination with triethyl phosphonoacetate. The double bond of the resulting ester was then hydrogenated and the ester was reduced to the corresponding aldehyde **5c** ($n' = 2$). An additional Horner–Wadsworth–Emmons olefination with **9** afforded the required compound **11** in 70% yield, which was further hydrogenated to give the analogue **4c** in 92% yield.



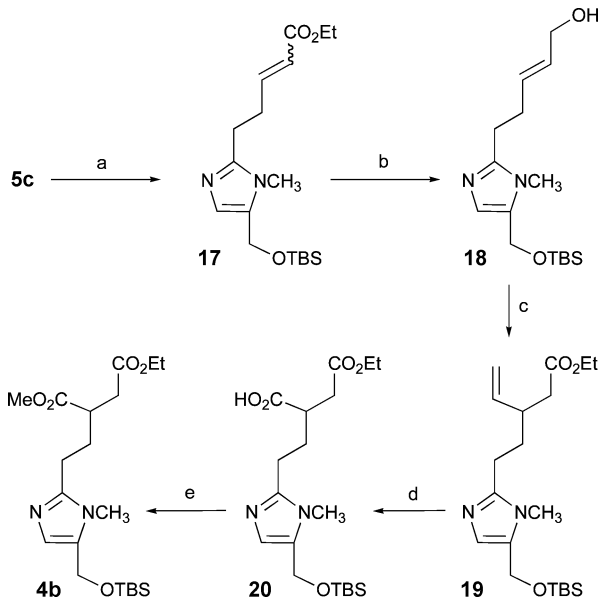
Scheme 4 *Reagents and conditions*: a) $(EtO)_2P(O)CH_2CO_2Et$, NaH, THF, 0 °C → RT, 3 h, (*E*/*Z* 9 : 1), 77%; b) H_2 (1 atm), Pd/C (10%), EtOAc, RT, 3 h, 100%; c) DIBAL-H, CH_2Cl_2, −78 °C, 2 h, 82%; d) **9**, NaH, THF, 0 °C → RT, 1 h 40 min, (*E*/*Z* 4 : 1), 70%; e) H_2 (1 atm), Pd/C (10%), EtOAc, RT, 3 h, 92%.

Whereas the syntheses of the intermediates **4a** and **4c** were quite straightforward by application of the Horner–Wadsworth–Emmons procedure with **9**, it was more troublesome to obtain compound **4b**. In fact, all our attempts to synthesize the aldehyde **5b** ($n' = 1$) were unsuccessful (Scheme 5). The alkylation–formylation sequence[24] failed because methylation of **6** afforded only compound **13**. Though the formation of the enol ether **14** was straightforward, no reaction or decomposition of the starting material was observed when compound **14** was submitted to different deprotection conditions.[25] Finally, the hydroboration of the vinyl derivative **15**, easily obtained by Wittig condensation on **5a**, was unsuccessful whatever the conditions employed. Though the formation of the organoborane was observed, the following addition of $NaOH/H_2O_2$ gave back the starting material, likely by simple deprotonation and elimination of the borane, since **15** is strongly stabilized by the conjugation of the double bond with the imidazole ring. Following these results, we changed our strategy and investigated a novel way to synthesize compound **4b**.

Finally, compound **4b** was successfully obtained using a Johnson–Claisen rearrangement[26] (Scheme 6). Starting from the aldehyde **5c**, a Horner–Wadsworth–Emmons reaction led to the α,β-unsaturated ester **17** in 94% yield. After reduction to the corresponding allylic alcohol **18**, a Johnson–Claisen rearrangement afforded compound **19** in 91% yield. Application of the Sharpless procedure[27] ($RuCl_3 \cdot nH_2O$ and a catalytic amount of $NaIO_4$) on compound **19** provided the expected acid **20** in very low yield. Then compound **19** was submitted to Lemieux–von Rudloff conditions[28] following the Hesse and Detterbeck protocol[29] with $NaIO_4$ and a catalytic amount of $KMnO_4$. By application of these conditions,



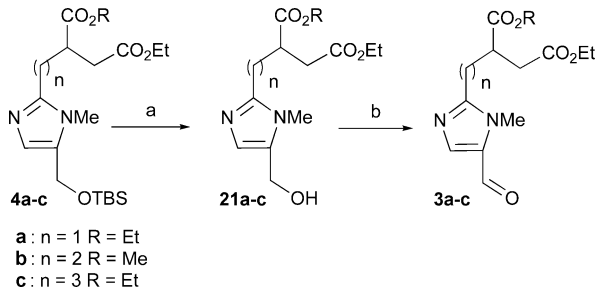
Scheme 5 Attempts at the synthesis of aldehyde **5b**.



Scheme 6 *Reagents and conditions*: a) $(EtO)_2P(O)CH_2CO_2Et$, NaH, THF, 0 °C → RT, 2 h 40 min, 94%; b) DIBAL-H, CH_2Cl_2, −78 °C, 4 h, 79%; c) $H_3CC(OEt)_3$, H^+, 140 °C, 1 h, 91%; d) $KMnO_4$, $NaIO_4$, K_2CO_3, *t*BuOH–H_2O, RT, 26 h, 53% at 68% conversion; e) $TMSCHN_2$, MeOH, 0 °C, 2 h, 72%.

the acid **20** was isolated in 53% yield at 68% conversion of the starting material. Esterification of **20** with $TMSCHN_2$[30] in MeOH afforded the intermediate **4b** required for the synthesis of the $n = 2$ analogue.

Having synthesized compounds **4a–c**, the corresponding aldehydes **3a–c** were prepared using a TBS-deprotection–oxidation sequence (Scheme 7). Two tripeptides were chosen as the aaX part of our new derivatives **2**. Valine-phenylalanine-methionine (VFM) is the aaX part of CVFM, a highly active FTI, and valine-isoleucine-alanine (VIA) is the C-terminal part of yeast H-Ras protein.[1a] These two tripeptides were synthesized in very good overall yields according to the classical peptide chemistry using EDCI and HOBt peptide coupling reactions.[31]



Scheme 7 *Reagents and conditions*: a) TBAF, THF, 0 °C → RT, 30 min (**21a**: 85%, **21b**: 80%, **21c**: 83%); b) MnO_2, $CHCl_3$, reflux, 32–48 h (**3a**: 86%, **3b**: 92%, **3c**: 97%).

Having successfully prepared the required aldehydes **3a–c** and the protected tripeptides **22** and **23**, reductive amination followed by saponification of the ester functions was performed, giving our target molecules **2a–f** (Scheme 8). The reductive amination was carried out with $NaBH_3CN$,[32] and the saponification was performed with $LiOH{\cdot}H_2O$ in THF–MeOH–H_2O mixture, leading to the expected 2,5-difunctionalized imidazoles in very good yields.

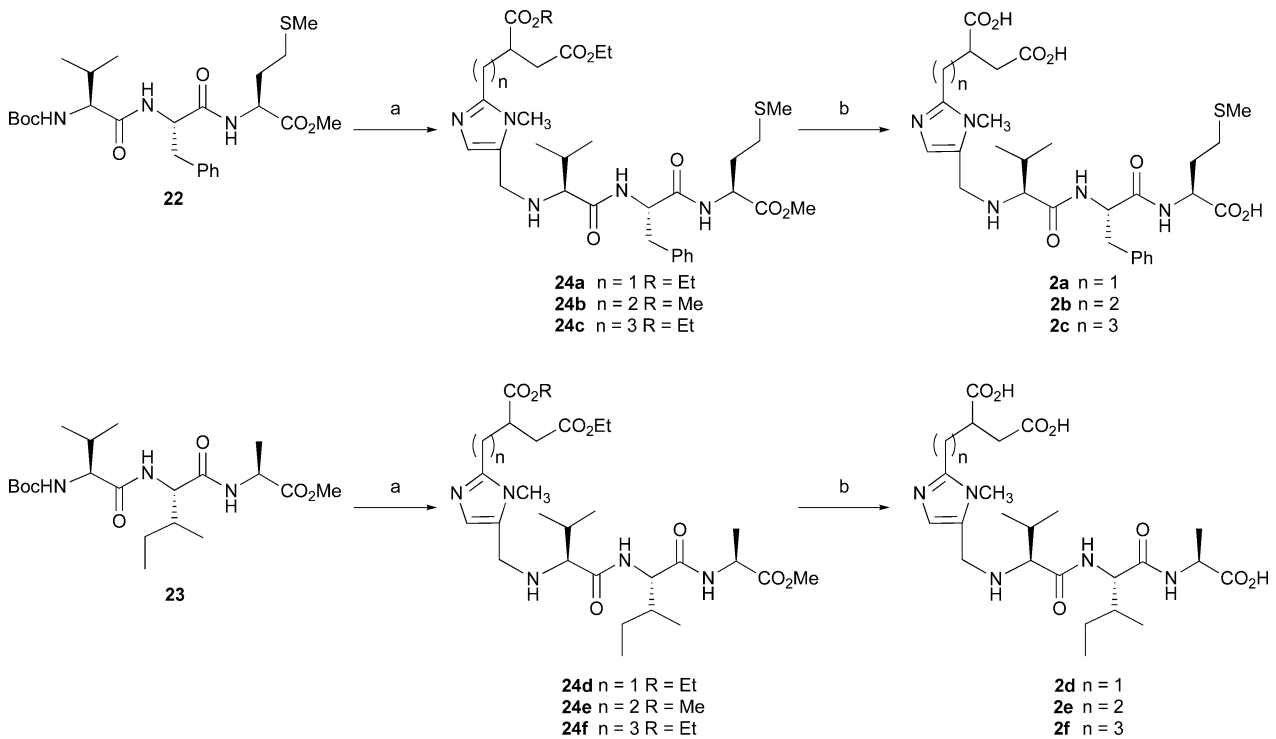
2. Biological evaluation

Compounds **24a–f** and **2a–f** were evaluated for their inhibitory activity against recombinant yeast FTase[33] using a fluorescent-based assay[34] and adapted to 96-well plate format. Results are reported in Table 1.

Generally, VFM-bearing compounds are more active than VIA-containing imidazoles. In the VIA series, the acids **2d–f** are all more active than the corresponding esters **24d–f**, and the most active compound in this series is **2e** bearing 2 carbons between the imidazole ring and the succinic moiety. In the VFM series,

Table 1 Activity on yeast FTase

Compound	*n*	Peptide	IC_{50}/μM
24a	1	VFM	>1000
24b	2	VFM	190 ± 20
24c	3	VFM	35 ± 3
24d	1	VIA	Inactive
24e	2	VIA	>1000
24f	3	VIA	340 ± 10
2a	1	VFM	150 ± 5
2b	2	VFM	400 ± 10
2c	3	VFM	80 ± 5
2d	1	VIA	270 ± 10
2e	2	VIA	80 ± 15
2f	3	VIA	180 ± 20



Scheme 8 *Reagents and conditions*: a) i) TFA–CH_2Cl_2, 0 °C, 20 min, ii) 4 Å MS, CH_2Cl_2–MeOH, RT, 10 min, then aldehyde **3a–c**, iii) $NaBH_3CN$, MeOH–AcOH (10 : 1), RT (**24a**: 94%, **24b**: 77%, **24c**: 79%, **24d**: 56%, **24e**: 80%, **24f**: 72%); b) $LiOH{\cdot}H_2O$, THF–MeOH–H_2O, 0 °C → RT, 2–18 h (**2a**: 86%, **2b**: 82%, **2c**: 82%, **2d**: 89%, **2e**: 75%, **2f**: 85%).

the results are quite different. Except for $n = 1$, the esters are more active than the corresponding acids, and the best activity is obtained for compound **24c** with $n = 3$. In order to understand these differences and to check if these new compounds were bisubstrate inhibitors, the most active derivatives, **24c** (IC_{50} = 35 μM), **2c** (IC_{50} = 80 μM) and **2e** (IC_{50} = 80 μM), were subjected to kinetic studies. The ester derivative **24c** is noncompetitive to both substrates whereas compound **2c** is competitive to the peptide but not to FPP. The inhibition constant of compound **2c** (K_i = 60 μM) was deduced from these kinetic experiments. Surprisingly, compound **2e** exhibits a different binding mode. It appears to be noncompetitive to the peptide substrate and uncompetitive to FPP, suggesting that it binds at a location that does not prevent FPP binding.

Some known inhibitors bearing a 1,4-diacid moiety are competitive to FPP.[14] However, in contrast to our designed compounds, they all bear an aliphatic chain that mimics the farnesyl moiety. The lack of interaction of our imidazole derivatives with the FPP binding site may be due to the absence of such a hydrophobic chain in that part of the molecule.

The difference of activity between the VFM- or VIA-derivatives **2b–c** and **2e–f** is surprising. However it is known that CVFM adopts a binding conformation in the FTase active site different from that of the other peptides (like CVIM) due to the presence of the phenyl ring.[35] Because of this aromatic ring, it can similarly be assumed that the VFM-containing compounds **2b–c** adopt a different conformation than the VIA-derivatives **2e–f**, and that the length of the diacid chain is more or less detrimental to binding according to the conformational behaviour of these derivatives.

In contrast to most of the reports on FTIs, our biological results are based on the determination of the inhibitor binding mode. In our case, these experiments have allowed us to demonstrate different binding modes (dependent on the nature of the tripeptide and of the carbon chain carried by the imidazole ring) that were hardly foreseeable on the basis of the IC_{50} values.

Conclusions

In summary, we have synthesized different higher-substituted imidazoles with a succinic acid unit at C-2 and a tripetide at C-5 of this heterocycle. The key transformation of our C-2 functionalisation sequence was a Horner–Wadsworth–Emmons reaction that permitted us to achieve our syntheses in good overall yields. This protocol was discovered following the failure of a more traditional alkylation and of palladium-catalyzed reactions due to the particular reactivity of the imidazole ring. The target compounds were obtained from the commercially available 1,3-dihydroxyacetone dimer **7** in a linear sequence with 14.5% and 9.0% (**2a** and 2**d**, $n = 1$, 10 steps), 2.4% and 2.4% (**2b** and **2e**, $n = 2$, 16 steps), 7.6% and 7.2% (**2c** and **2f**, $n = 3$, 13 steps) yields with VFM and VIA tripeptides respectively. Investigations of the biological profile of our target compounds have shown that VFM-containing compounds are generally more active than VIA derivatives, and that the carbon chain length has an influence on the activity. However, the kinetic experiments have demonstrated that 2,5-disubstituted imidazoles are not bisubstrate analogues, and only compound **2c** is competitive to the CaaX motif.

The aim of this work was to create new inhibitors that can bind to both CaaX and pyrophosphate binding sites. The failure of our first 2,5-disubstituted imidazoles to fit this requirement could be due to the relative position of the succinic acid and of the peptide. Furthermore, a hydrophobic alkyl chain might be needed to mimic the farnesyl group and to position the acid moiety in the pyrophosphate binding site. Therefore, we are pursuing our investigation into highly substituted imidazoles by the synthesis of 1,2- and 2,4-disubstituted imidazoles as well as compounds bearing a hydrophobic chain near the 1,4-diacid moiety.

Experimental

General method

Unless otherwise indicated, all reactions were carried out with magnetic stirring and, in the case of air- or moisture-sensitive compounds, reactions were carried out in oven-dried glassware under argon. Syringes were used to transfer the reagents and the solvents were purged with argon prior to use. Tetrahydrofuran (THF) was distilled over sodium/benzophenone. Dichloromethane (CH_2Cl_2), triethylamine (Et_3N), diisopropylamine and toluene were distilled over calcium hydride. *N*,*N*′-Dimethylformamide (DMF) was dried over $MgSO_4$ followed by distillation under reduced pressure. Analytical thin-layer chromatography was carried out on precoated silica gel glass plates (Merck TLC plates, silica gel $60F_{254}$). The silica gel (silica gel 60 (35–70 μm)) used for column chromatography was purchased from SDS. ^1H and ^{13}C NMR spectra were recorded on Bruker AC-250/300 and DPX-300 spectrometers at 250 and 300 MHz. ^1H chemical shifts are reported in delta (δ) units in parts per million (ppm) relative to the singlet at 7.26 ppm for *d*-chloroform (residual $CHCl_3$) and the singlet (0.00 ppm) for TMS. ^{13}C Chemical shifts (δ) are reported in ppm relative to the central line of the triplet at 77.0 ppm for *d*-chloroform. Splitting patterns are designated as: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; b, broad and combinations thereof. Coupling constants *J* are reported in hertz (Hz). Melting points were measured on a Büchi b-450 apparatus and are uncorrected. IR spectra were recorded with an FTIR Perkin-Elmer Spectrum BX spectrometer. Low- and high-resolution mass spectra were recorded by a navigator LC/MS (source AQA) instrument for electron spray ionisation (ESI – base resolution) and electron ionisation (EI – high resolution). Optical rotations were measured with a JASCO 1010 polarimeter in a 1 dm cell using the sodium D line (589 nm) at the temperature, solvent, and concentration indicated. Elemental analyses were performed by the Microanalytical Laboratory of the ICSN-Gif-sur-Yvette.

5-(*tert*-Butyldimethylsilanyloxymethyl)-1-methyl-1*H*-imidazole (6)

To a stirred solution of **8** (1.70 g, 15.2 mmol) in DMF (17 mL) were added imidazole (3.10 g, 45.5 mmol) and *tert*-butyldimethylchlorosilane (2.50 g, 16.7 mmol). The reaction mixture was stirred for 2 h at room temperature. Then, the reaction was quenched with H_2O (30 mL) and extracted with Et_2O (3 × 40 mL). The combined organic layers were dried over $MgSO_4$. Concentration followed by column chromatography on silica gel (EtOAc–MeOH 9.5 : 0.5) afforded **6** (3.13 g, 91%) as an amorphous colorless solid. ^1H NMR data identical to those previously reported[36]; ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 138.3,

130.5, 127.3, 54.6, 31.1, 25.3 (3C), 17.7, −5.8 (2C); IR (KBr) 1061, 1256, 1471 cm^{-1}; HRMS calcd for $C_{11}H_{23}N_2OSi$ $[M + H]^+$: 227.1580; found: 227.1547.

5-(*tert*-Butyldimethylsilanyloxymethyl)-1-methyl-1*H*-imidazole-2-carbaldehyde (5a)

n-Butyllithium (17.6 mL, 28.2 mmol, 1.6 N in hexane) was added dropwise to a solution of **6** (5.30 g, 23.5 mmol) in THF (60 mL) at −78 °C. After 40 min at this temperature, DMF (5.60 mL, 70.5 mmol) was added. The reaction mixture was allowed to warm to room temperature and after 2 h 30 min, CH_2Cl_2 (90 mL) was added. The organic phase was successively washed with brine (80 mL) and H_2O (80 mL), and dried over $MgSO_4$. Concentration afforded the crude product as a yellow oil that was purified by column chromatography on silica gel (heptane–EtOAc 3 : 2) followed by crystallization (heptane) to afford the required aldehyde **5a** (5.00 g, 83%) as white crystals. Mp 60.7–62.5 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 9.77 (s, 1H), 7.16 (s, 1H), 4.72 (s, 2H), 4.01 (s, 3H), 0.89 (s, 9H), 0.08 (s, 6H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 182.3, 144.3, 137.4, 130.4, 55.0, 32.1, 25.7 (3C), 18.1, −5.5 (2C); IR (KBr) 1072, 1256, 1484, 1689 cm^{-1}; MS (ESI+): *m*/*z* 255 $[M + H]^+$; Elemental analysis calcd (%) for $C_{12}H_{22}N_2O_2Si$: C 56.65, H 8.72, N 11.01; found: C 56.52, H 8.69, N 11.04.

2-[5-(*tert*-Butyldimethylsilanyloxymethyl)-1-methyl-1*H*-imidazol-2-ylmethylene]succinic acid diethyl ester (10)

A suspension of sodium hydride (0.54 g, 13.4 mmol) in THF (5 mL) was treated with triethyl phosphonosuccinate **9**[27] (3.66 g, 11.8 mmol) at 0 °C. The solution was stirred for 30 min at room temperature before addition of the aldehyde **5a** (2.55 g, 10.0 mmol) in THF (10 mL). After 3 h at room temperature, the reaction mixture was diluted with CH_2Cl_2 (40 mL) and extracted with brine (30 mL) and H_2O (30 mL). The organic layer was dried over $MgSO_4$ and concentrated. The crude product was purified by column chromatography on silica gel (heptane–EtOAc 4 : 1) to afford **10** (2.00 g, 69%, only the *E* isomer as determined by NOE experiments) as white crystals. Mp 52.2–53.9 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.58 (s, 1H), 7.05 (s, 1H), 4.66 (s, 2H), 4.28 (s, 2H), 4.26 (q, J = 7.0 Hz, 2H), 4.13 (q, J = 7.0 Hz, 2H), 3.72 (s, 3H), 1.31 (t, J = 7.0 Hz, 3H), 1.23 (t, J = 7.0 Hz, 3H), 0.88 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 171.4, 167.5, 144.0, 132.9, 129.2, 127.4, 124.0, 61.2, 60.6, 55.3, 33.6, 30.6, 25.8 (3C), 18.2, 14.2 (2C), −5.3 (2C); IR (KBr) 1062, 1268, 1463, 1637, 1709, 1736 cm^{-1}; MS (ESI+): *m*/*z* 411 $[M + H]^+$, 433 $[M + Na]^+$. Elemental analysis calcd (%) for $C_{20}H_{34}N_2O_5Si$: C 58.51, H 8.35, N 6.82; found: C 58.21, H 8.26, N 6.75.

2-[5-(*tert*-Butyldimethylsilanyloxymethyl)-1-methyl-1*H*-imidazol-2-ylmethyl]succinic acid diethyl ester (4a)

Pd/C (0.10 g) was added to a solution of **10** (1.00 g, 2.44 mmol) in EtOAc (15 mL). The mixture was allowed to react at room temperature under hydrogen atmosphere (1 atm) for 4 h. The reaction was filtered through a pad of Celite with EtOAc and the filtrate was concentrated to give **4a** (0.97 g, 100%) as a yellowish oil. ^{1}H NMR (250 MHz, $CDCl_3$) δ 6.80 (s, 1H), 4.62 (s, 2H), 4.13 (m, 4H), 3.59 (s, 3H), 3.36 (m, 1H), 3.13 (dd, J = 6.0, 15.0 Hz, 1H), 2.88 (dd, J = 6.0, 15.0 Hz, 1H), 2.74 (m, 2H), 1.23 (td, J = 1.5, 7.5 Hz, 6H), 0.88 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ173.7, 171.7, 146.4, 131.0, 126.3, 60.9, 60.6, 55.5, 39.9, 35.3, 30.3, 28.3, 25.8 (3C), 18.2, 14.1 (2C), −5.3 (2C); IR (KBr) 1057, 1256, 1472, 1736 cm^{-1}; HRMS calcd for $C_{20}H_{37}N_2O_5Si$ $[M + H]^+$: 413.2472; found: 413.2460.

(*E*,*Z*)-3-[5-(*tert*-Butyldimethylsilanyloxymethyl)-1-methyl-1*H*-imidazol-2-yl]acrylic acid ethyl ester

A suspension of sodium hydride (1.29 g, 32.1 mmol) in THF (15 mL) was treated with triethyl phosphonoacetate (6.00 mL, 30.1 mmol) at 0 °C. The solution was stirred for 30 min at room temperature before addition of the aldehyde **5a** (2.55 g, 10.0 mmol) in THF (10 mL). After 3 h at room temperature, the reaction mixture was diluted with CH_2Cl_2 (30 mL) and extracted with brine (20 mL) and H_2O (20 mL). The organic layer was dried over $MgSO_4$ and concentrated. The crude product was purified by column chromatography on silica gel (heptane–EtOAc 7 : 3) to afford (*E*,*Z*)-3-[5-(*tert*-Butyl-dimethylsilanyloxymethyl)-1-methyl-1*H*-imidazol-2-yl]acrylic acid ethyl ester (2.40 g, 77%, *E*/*Z* 9 : 1) as a white amorphous solid. ***E* isomer**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 (d, J = 15.5 Hz, 1H), 7.03 (s, 1H), 6.82 (d, J = 15.5 Hz, 1H), 4.67 (s, 2H), 4.27 (q, J = 7.0 Hz, 2H), 3.73 (s, 3H), 1.32 (t, J = 7.0 Hz, 3H), 0.88 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.1, 144.2, 133.9, 129.4, 128.7, 120.7, 60.7, 55.4, 30.6, 25.7 (3C), 18.3, 14.4, −5.2 (2C); IR (KBr) 1036, 1279, 1469, 1631, 1706, 3058 cm^{-1}; HRMS calcd for $C_{16}H_{29}N_2O_3Si$ $[M + H]^+$: 325.1947; found: 325.1927. ***Z* isomer**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61 (d, J = 12.5 Hz, 1H), 6.97 (s, 1H), 6.28 (d, J = 12.5 Hz, 1H), 4.73 (s, 2H), 4.32 (q, J = 7.0 Hz, 2H), 3.86 (s, 3H), 1.34 (t, J = 7.0 Hz, 3H), 0.91 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.7, 144.7, 135.4, 129.6, 128.9, 120.1, 60.8, 55.7, 31.0, 25.7 (3C), 18.4, 14.1, −5.3 (2C); IR (KBr) 1040, 1245, 1466, 1617, 1695, 3377 cm^{-1}; HRMS calcd for $C_{16}H_{28}N_2O_3SiNa$ $[M + Na]^+$: 347.1767; found: 347.1755.

3-[5-(*tert*-Butyldimethylsilanyloxymethyl)-1-methyl-1*H*-imidazol-2-yl]propionic acid ethyl ester

Pd/C (0.21 g) was added to a solution of (*E*,*Z*)-3-[5-(*tert*-butyldimethylsilanyloxymethyl)-1-methyl-1*H*-imidazol-2-yl]acrylic acid ethyl ester (2.10 g, 6.73 mmol) in EtOAc (15 mL). The mixture was allowed to react at room temperature under hydrogen atmosphere (1 atm) for 3 h. The reaction was filtered through a pad of Celite with EtOAc and the filtrate was concentrated to give 3-[5-(*tert*-butyldimethylsilanyloxymethyl)-1-methyl-1*H*-imidazol-2-yl]propionic acid ethyl ester (2.10 g, 100%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.82 (s, 1H), 4.61 (s, 2H), 4.15 (q, J = 7.0 Hz, 2H), 3.59 (s, 3H), 2.90 (m, 4H), 1.25 (t, J = 7.0 Hz, 3H), 0.88 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.9, 147.9, 131.0, 126.1, 60.6, 55.5, 31.7, 30.2, 25.9 (3C), 22.1, 18.2, 14.2, −5.3 (2C); IR (KBr) 1057, 1256, 1472, 1736 cm^{-1}; MS (ESI+): *m*/*z* 327 $[M + H]^+$.

3-[5-(*tert*-Butyldimethylsilanyloxymethyl)-1-methyl-1*H*-imidazol-2-yl]propionaldehyde (5c)

Diisobutylaluminium hydride (5.99 mL, 5.99 mmol, 1 N in heptane) was added to a solution of 3-[5-(*tert*-butyldimethylsilanyloxymethyl)-1-methyl-1*H*-imidazol-2-yl]propionic acid

ethyl ester (1.30 g, 3.99 mmol) in CH_2Cl_2 (12 mL) at −78 °C. The reaction was stirred at this temperature for 2 h, and 3 drops of MeOH were added to neutralize the excess of diisobutylaluminium hydride. The mixture was warmed to room temperature and quenched with a saturated aqueous solution of potassium sodium tartrate (20 mL). After stirring for 30 min, the mixture was filtered through a pad of Celite. The organic layer was separated, washed with brine (10 mL) and H_2O (10 mL), dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography on silica gel (EtOAc–MeOH 9.7 : 0.3) to give **5c** (0.93 g, 82%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.87 (s, 1H), 6.76 (s, 1H), 4.59 (s, 2H), 3.56 (s, 3H), 2.97 (m, 4H), 0.85 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.1, 147.6, 131.2, 125.9, 55.5, 40.8, 30.2, 25.8 (3C), 19.4, 18.2, −5.3 (2C); IR (KBr) 1077, 1248, 1479, 1679 cm^{-1}; MS (ESI+): *m*/*z* 283 $[M + H]^+$, 315 $[M + H + MeOH]^+$.

2-{3-[5-(*tert*-Butyldimethylsilanyloxymethyl)-1-methyl-1*H*-imidazol-2-yl]propylidene}succinic acid diethyl ester (11)

A suspension of sodium hydride (0.16 g, 3.94 mmol) in THF (10 mL) was treated with triethyl phosphonosuccinate **9**[27] (1.02 g, 3.28 mmol) at 0 °C. After stirring for 30 min at room temperature, the aldehyde **5c** (0.93 g, 3.28 mmol) in THF (3 mL) was added. After stirring for 1 h 40 min at room temperature, the reaction mixture was diluted with CH_2Cl_2 (15 mL) and extracted with H_2O (10 mL). The organic layer was dried over $MgSO_4$ and concentrated. The crude product was purified by column chromatography on silica gel (EtOAc–MeOH 9.8 : 0.2) to give **11** (1.00 g, 70%, *E*/*Z* 8 : 2) as a colorless oil. ***E* isomer**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.97 (t, J = 7.0 Hz, 1H), 6.77 (s, 1H), 4.57 (s, 2H), 4.15 (t, J = 7.0 Hz, 2H), 4.08 (q, J = 7.0 Hz, 2H), 3.54 (s, 3H), 3.32 (s, 2H), 2.75 (m, 2H), 2.66 (m, 2H), 1.23 (t, J = 7.0 Hz, 3H), 1.20 (t, J = 7.0 Hz, 3H), 0.84 (s, 9H), 0.03 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.8, 166.8, 147.9, 143.5, 131.1, 126.9, 126.1, 60.8 (2C), 55.5, 32.4, 30.2, 26.9, 25.9, 25.8 (3C), 18.2, 14.3 (2C), −5.3 (2C); IR (KBr) 1076, 1256, 1487, 1643, 1706, 1735 cm^{-1}; HRMS calcd for $C_{22}H_{39}N_2O_5Si$ $[M + H]^+$: 439.2628; found: 439.2627. ***Z* isomer**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.80 (s, 1H), 6.17 (t, J = 7.0 Hz, 1H), 4.61 (s, 2H), 4.20 (q, J = 7.0 Hz, 2H), 4.13 (q, J = 7.0 Hz, 2H), 3.55 (s, 3H), 3.25 (s, 2H), 2.97 (m, 2H), 2.82 (m, 2H), 1.35 (t, J = 7.0 Hz, 3H), 1.32 (t, J = 7.0 Hz, 3H), 0.88 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.4, 166.3, 148.4, 145.2, 130.9, 126.7, 126.4, 60.5 (2C), 55.5, 40.2, 30.3, 27.6, 26.5, 25.8 (3C), 18.2, 14.2 (2C), −5.3 (2C); IR (KBr) 1062, 1259, 1471, 1648, 1706, 1735 cm^{-1}; HRMS calcd for $C_{22}H_{39}N_2O_5Si$ $[M + H]^+$: 439.2628; found: 439.2632.

2-{3-[5-(*tert*-Butyldimethylsilanyloxymethyl)-1-methyl-1*H*-imidazol-2-yl]propyl}succinic acid diethyl ester (4c)

Pd/C (95.0 mg) was added to a solution of **11** (950 mg, 2.17 mmol) in EtOAc (15 mL). The mixture was allowed to react at room temperature under hydrogen atmosphere (1 atm) for 3 h. The reaction was filtered through a pad of Celite with EtOAc and the filtrate was concentrated. The residue was purified by column chromatography on silica gel (EtOAc–MeOH 9.8 : 0.2) to give **4c** (875 mg, 92%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.75 (s, 1H), 4.57 (s, 2H), 4.10 (m, 4H), 3.51 (s, 3H), 2.82 (m, 1H), 2.63 (m, 3H), 2.41 (dd, J = 5.0, 16.0 Hz, 1H), 1.73 (m, 3H), 1.59 (m, 1H), 1.21 (m, 6H), 0.85 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.8, 172.0, 148.9, 130.8, 126.0, 60.7 (2C), 55.6, 41.1, 36.2, 31.6, 30.3, 26.9, 25.9 (3C), 25.1, 18.3, 14.3 (2C), −5.2 (2C); IR (KBr) 1055, 1258, 1472, 1735 cm^{-1}; HRMS calcd for $C_{22}H_{41}N_2O_5Si$ $[M + H]^+$: 441.2785; found: 441.2822.

4-(*tert*-Butyldimethylsilanoxymethyl)-1,2,3-trimethyl-3*H*-imidazol-1-ium iodide (13)

n-Butyllithium (4.31 mL, 6.90 mmol, 1.6 N in hexane) was added dropwise to a solution of **6** (1.30 g, 5.75 mmol) in THF (15 mL) at −78 °C. After stirring for 45 min at this temperature, iodomethane (0.55 mL, 8.63 mmol) was added. After stirring for 2 h at this temperature and for 1 h at room temperature, CH_2Cl_2 (20 mL) was added. The organic phase was successively washed with a saturated aqueous solution of $Na_2S_2O_3$ (15 mL), brine (15 mL), H_2O (15 mL), and dried over $MgSO_4$. Removal of the solvent afforded the crude product as a yellow solid. The residue was purified by crystallization (pentane–EtOAc 4 : 1) to afford **13** (1.50 g, 68%) as a yellowish solid. Mp 122.1–124.8 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.44 (s, 1H), 4.70 (s, 2H), 3.97 (s, 3H), 3.86 (s, 3H), 2.87 (s, 3H), 0.90 (s, 9H), 0.13 (s, 6H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 145.3, 132.6, 120.4, 54.8, 36.6, 33.7, 25.8 (3C), 18.2, 12.4, −5.3 (2C); MS (ESI+): *m*/*z* 255 $[M]^+$.

5-(*tert*-Butyldimethylsilanoxymethyl)-2-(2-methoxyvinyl)-1-methyl-1*H*-imidazole (14)

To a suspension of (methoxymethyl)triphenylphosphonium chloride (1.14 g, 3.33 mmol) in THF (6 mL) at 0 °C potassium *tert*-butoxide (5.54 mL, 5.54 mmol, 1 N in THF) was added dropwise. After stirring for 30 min at this temperature, a solution of the aldehyde **5a** (705 mg, 2.77 mmol) in THF (8 mL) was added slowly to the suspension. After 5 h at room temperature, H_2O (3 mL) was added and the reaction mixture was concentrated. The residue was diluted with CH_2Cl_2 (20 mL) and washed with H_2O (15 mL). The organic phase was separated, dried over $MgSO_4$ and concentrated. The phosphine oxide formed was crystallized (heptane–EtOAc 4 : 1) and filtered. Then, the residue was purified by column chromatography on silica gel (CH_2Cl_2–MeOH 9.5 : 0.5) to give **14** (0.61 g, 78%) as a yellowish oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 (d, J = 12.0 Hz, 1H), 6.80 (s, 1H), 5.61 (d, J = 12.0 Hz, 1H), 4.61 (s, 2H), 3.69 (s, 3H), 3.54 (s, 3H), 0.88 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.3, 145.9, 131.5, 126.6, 92.4, 57.3, 55.4, 30.1, 25.8 (3C), 18.2, −5.3 (2C); IR (KBr) 1054, 1231, 1469, 1642, 3072 cm^{-1}; HRMS calcd for $C_{14}H_{27}N_2O_2Si$ $[M + H]^+$: 283.1842; found: 283.1855.

5-(*tert*-Butyldimethylsilanoxymethyl)-1-methyl-2-vinyl-1*H*-imidazole (15)

To a suspension of sodium hydride (173 mg, 4.33 mmol) in THF (20 mL), methyltriphenylphosphonium bromide (1.41 g, 3.94 mmol) was added at room temperature. After stirring for 2 h at this temperature, a solution of the aldehyde **5a** (1.00 g, 3.94 mmol) in THF (10 mL) was added. The mixture was refluxed for 5 h followed by 14 h of stirring at room temperature. Then, the reaction mixture was filtered, washed with ether (3 × 15 mL) and concentrated. The phosphine oxide formed was crystallized

(heptane–EtOAc 4 : 1) and filtered. Then, the residue was purified by column chromatography on silica gel (ether) to afford **15** (715 mg, 72%) as a white amorphous solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.91 (s, 1H), 6.60 (dd, J = 11.0, 17.0 Hz, 1H), 6.17 (dd, J = 1.5, 17.0 Hz, 1H), 5.41 (dd, J = 1.5, 11.0 Hz, 1H), 4.64 (s, 2H), 3.64 (s, 3H), 0.88 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.4, 131.6, 127.5, 122.8, 118.1, 55.4, 30.3, 25.8 (3C), 18.2, −5.3 (2C); IR (KBr) 1038, 1257, 1468, 1625, 3096 cm^{-1}; HRMS calcd for $C_{13}H_{25}N_2OSi$ [M + H]$^+$: 253.1736; found: 253.1765.

5-[5-(*tert*-Butyldimethylsilanyloxymethyl)-1-methyl-1*H*-imidazol-2-yl]pent-2-enoic acid ethyl ester (17)

To a suspension of sodium hydride (341 mg, 8.53 mmol) in THF (10 mL), triethyl phosphonoacetate (1.50 mL, 7.26 mmol) was added at 0 °C. After stirring for 30 min at room temperature, the aldehyde **5c** (1.85 g, 6.60 mmol) in THF (5 mL) was added. After stirring 2 h 40 min at room temperature, the reaction mixture was diluted with CH_2Cl_2 (20 mL) and washed with brine (15 mL) and H_2O (15 mL). The organic layer was dried over $MgSO_4$ and concentrated. The crude product was purified by column chromatography on silica gel (EtOAc–MeOH 9.8 : 0.2) to give **17** (2.15 g, 94%) as a white amorphous solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.04 (m, 1H), 6.81 (s, 1H), 5.89 (d, J = 16.0 Hz, 1H), 4.62 (s, 2H), 4.18 (q, J = 7.0 Hz, 2H), 3.55 (s, 3H), 2.66–2.84 (m, 4H), 1.28 (t, J = 7.0 Hz, 3H), 0.88 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.5, 147.8, 147.4, 131.0, 126.2, 122.2, 60.3, 55.5, 30.2, 29.9, 25.8 (3C), 25.6, 18.2, 14.3, −5.3 (2C); IR (KBr) 1049, 1253, 1471, 1655, 1715, 3385 cm^{-1}; HRMS calcd for $C_{18}H_{33}N_2O_3Si$ [M + H]$^+$: 353.2260; found: 353.2267.

5-[5-(*tert*-Butyldimethylsilanyloxymethyl)-1-methyl-1*H*-imidazol-2-yl]pent-2-en-1-ol (18)

Diisobutylaluminium hydride (18.3 mL, 18.3 mmol, 1 N in heptane) was added to a solution of **17** (2.15 g, 6.10 mmol) in CH_2Cl_2 (20 mL) at −78 °C. The reaction was stirred at this temperature for 4 h, and 5 drops of MeOH were added to neutralize the excess of diisobutylaluminium hydride. The mixture was warmed to room temperature and quenched with a saturated aqueous solution of potassium sodium tartrate (50 mL). After stirring for 1 h, the mixture was filtered through a pad of Celite. The organic layer was separated, washed with brine (20 mL) and H_2O (20 mL), dried over $MgSO_4$ and concentrated. The crude product was purified by column chromatography on silica gel (heptane–EtOAc 9 : 1) to afford **18** (1.50 g, 79%) as white crystals. Mp 74.3–77.5 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.79 (s, 1H), 5.73 (m, 2H), 4.61 (s, 2H), 4.08 (d, J = 5.5 Hz, 2H), 3.55 (s, 3H), 2.96 (sl, 1H), 2.76 (t, J = 7.0 Hz, 2H), 2.47 (q, J = 7.0 Hz, 2H), 0.87 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.7, 130.8, 130.6, 130.5, 125.8, 63.2, 55.6, 30.2, 30.1, 26.8, 25.8 (3C), 18.2, −5.3 (2C); IR (KBr) 1054, 1249, 1471, 1645, 3175 cm^{-1}; HRMS calcd for $C_{16}H_{31}N_2O_2Si$ [M + H]$^+$: 311.2155; found: 311.2140.

3-{2-[5-(*tert*-Butyldimethylsilanyloxymethyl)-1-methyl-1*H*-imidazol-2-yl]ethyl}pent-4-enoic acid ethyl ester (19)

The allylic alcohol **18** (1.50 g, 4.84 mmol) was heated at 140 °C in the presence of triethyl orthoacetate (6.20 mL, 33.9 mmol) and propionic acid (22.0 µL, 0.29 mmol) with concomitant removal of ethanol. The solution was refluxed for 3 h, and then the triethyl orthoacetate was evaporated. The mixture was diluted with EtOAc (15 mL) and filtered through a pad of Celite (EtOAc–MeOH 9.5 : 0.5). The organic layer was evaporated and the residue was purified by column chromatography on silica gel (heptane–EtOAc 1 : 9) to afford **19** (1.66 g, 91%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.77 (s, 1H), 5.66 (m, 1H), 5.08 (m, 2H), 4.69 (s, 2H), 4.10 (q, J = 7.5 Hz, 2H), 3.51 (s, 3H), 2.62 (m, 3H), 2.38 (m, 2H), 1.93 (m, 1H), 1.76 (m, 1H), 1.23 (t, J = 7.5 Hz, 3H), 0.87 (s, 9H), 0.03 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.2, 149.1, 140.2, 130.7, 126.0, 116.0, 60.3, 55.5, 40.4, 40.1, 32.0, 30.1, 25.8 (3C), 24.7, 18.2, 14.3, −5.3 (2C); IR (KBr) 1052, 1252, 1471, 1640, 1731, 3079 cm^{-1}; HRMS calcd for $C_{20}H_{37}N_2O_3Si$ [M + H]$^+$: 381.2573; found: 381.2546.

2-{2-[5-(*tert*-Butyldimethylsilanyloxymethyl)-1-methyl-1*H*-imidazol-2-yl]ethyl}succinic acid 4-ethyl ester (20)

To a solution of **19** (1.00 g, 2.63 mmol) in *t*BuOH (4.3 mL) were added an aqueous solution of K_2CO_3 (1.09 g in 8.7 mL of H_2O, 7.89 mmol), $NaIO_4$ (1.69 g, 7.89 mmol) and $KMnO_4$ (333 mg, 2.10 mmol). After stirring for 48 h at room temperature, the mixture was extracted with EtOAc (6 × 5 mL). The combined organic layers were filtered through a pad of Celite (EtOAc–MeOH 9 : 1) and concentrated. The residue was purified by column chromatography on silica gel (EtOAc then EtOAc–MeOH–AcOH 8.5 : 1.5 : 0.1) to afford **20** (0.37 g, 53% at 68% conversion) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.53 (bs, 1H), 6.87 (s, 1H), 4.61 (s, 2H), 4.12 (q, J = 7.0 Hz, 2H), 3.59 (s, 3H), 2.90 (m, 4H), 2.42 (m, 1H), 2.16 (m, 1H), 1.88 (m, 1H), 1.24 (t, J = 7.0 Hz, 3H), 0.88 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.9, 172.6, 148.5, 131.2, 122.8, 60.5, 55.2, 40.9, 36.8, 30.4, 29.4, 25.8 (3C), 24.6, 18.2, 14.2, −5.3 (2C); IR (KBr) 1024, 1253, 1453, 1723, 3373 cm^{-1}; HRMS calcd for $C_{19}H_{35}N_2O_5Si$ [M + H]$^+$: 399.2315; found: 399.2329.

2-{2-[5-(*tert*-Butyldimethylsilanyloxymethyl)-1-methyl-1*H*-imidazol-2-yl]ethyl}succinic acid 4-ethyl ester 1-methyl ester (4b)

To a solution of **20** (0.20 g, 0.50 mmol) in MeOH (4 mL) was added trimethylsilyldiazomethane (0.75 mL, 1.50 mmol, 2 N in ether) at 0 °C. After stirring for 2 h at this temperature, the reaction mixture was concentrated and the residue was purified by column chromatography on silica gel (heptane–EtOAc 1 : 9 → EtOAc) to afford **4b** (0.15 g, 72%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.78 (s, 1H), 4.60 (s, 2H), 4.12 (q, J = 7.0 Hz, 2H), 3.70 (s, 3H), 3.54 (s, 3H), 2.95 (m, 1H), 2.65–2.82 (m, 3H), 2.52 (dd, J = 16.5, 5.0 Hz, 1H), 2.07 (m, 2H), 1.24 (t, J = 7.0 Hz, 3H), 0.87 (s, 9H), 0.03 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.8, 171.6, 148.1, 131.0, 125.8, 60.7, 55.4, 51.9, 40.7, 36.2, 30.2, 29.4, 25.8 (3C), 24.6, 18.2, 14.2, −5.3 (2C); IR (KBr) 1051, 1253, 1471, 1731 cm^{-1}; HRMS calcd for $C_{20}H_{37}N_2O_5Si$ [M + H]$^+$: 413.2472; found: 413.2477.

General procedure A: Deprotection of the TBS group

A solution of tetrabutylammonium fluoride (1 N in THF) was added to a THF solution of compounds **4a–c** at 0 °C. After stirring for 30 min at room temperature, the reaction mixture was

evaporated. The residue was purified by column chromatography on silica gel to afford the required primary alcohols **21a–c**.

2-(5-Hydroxymethyl-1-methyl-1*H*-imidazol-2-ylmethyl)succinic acid diethyl ester (21a). Prepared according to general procedure A on compound **4a** (1.00 g, 2.42 mmol) in THF (12 mL) with TBAF (4.85 mL, 4.85 mmol). After work-up and column chromatography (EtOAc–MeOH 9.5 : 0.5), **21a** (617 mg, 85%) was isolated as a white amorphous solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.68 (s, 1H), 4.54 (s, 2H), 4.11 (m, 4H), 3.62 (s, 3H), 3.30 (m, 1H), 3.11 (dd, J = 7.0, 15.0 Hz, 1H), 2.85 (dd, J = 7.5, 15.0 Hz, 1H), 2.69 (m, 2H), 1.23 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.6, 171.7, 146.3, 131.9, 126.0, 61.0, 60.7, 54.1, 39.9, 35.3, 30.3, 28.2, 14.2, 14.1; IR (KBr) 1487, 1726, 3139 cm^{-1}; MS (ESI+): m/z 299 [M + H]$^+$, 321 [M + Na]$^+$; Elemental analysis calcd (%) for $C_{14}H_{22}N_2O_5$: C 56.36, H 7.43, O 26.81; found: C 56.12, H 7.37, O 26.76.

General procedure B: Oxidation of the primary alcohol

Manganese dioxide (6.5 equiv.) was added to a $CHCl_3$ solution of **21a–c**. The mixture was refluxed for 32–48 h. After cooling to room temperature, the reaction was filtered through a pad of Celite (EtOAc) and concentrated. The residue was purified by column chromatography to afford the required aldehydes **3a–c**.

2-(5-Formyl-1-methyl-1*H*-imidazol-2-ylmethyl)succinic acid diethyl ester (3a). Prepared according to general procedure B on compound **21a** (350 mg, 1.18 mmol) in $CHCl_3$ (15 mL) with MnO_2 (671 mg, 7.67 mmol). After refluxing for 48 h, filtration followed by column chromatography (CH_2Cl_2–MeOH 9.9 : 0.1) afforded **3a** (300 mg, 86%) as a yellowish amorphous solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.66 (s, 1H), 7.68 (s, 1H), 4.13 (m, 4H), 3.91 (s, 3H), 3.44 (m, 1H), 3.18 (dd, J = 7.0, 15.0 Hz, 1H), 2.96 (dd, J = 7.0, 15.0 Hz, 1H), 2.77 (m, 2H), 1.23 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.0, 173.1, 171.4, 153.3, 143.0, 132.0, 61.2, 60.8, 39.4, 34.5, 32.3, 27.7, 14.2, 14.1; IR (KBr) 1469, 1657, 1725 cm^{-1}; HRMS calcd for $C_{14}H_{20}N_2O_5Na$ [M + Na]$^+$: 319.1270; found: 319.1251.

Boc-valinyl-phenylalaninyl-methionine methyl ester (22)

To a solution of Boc-L-phenylalanine (1.99 g, 7.51 mmol) in CH_2Cl_2 (25 mL) were added at room temperature L-methionine methyl ester (1.50 g, 7.51 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.72 g, 9.00 mmol), 1-hydroxybenzotriazole hydrate (1.20 g, 9.00 mmol) and *N*-methylmorpholine (1.00 mL, 7.51 mmol). After stirring for 2 h 30 min, the reaction was quenched with water (25 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography on silica gel (heptane–EtOAc 3 : 2) followed by crystallization (heptane–EtOAc 9 : 1) to afford the required dipeptide BocPhe-Val-OMe (2.92 g, 95%) as white crystals. BocPhe-Val-OMe (1.34 g, 3.27 mmol) was deprotected with a solution of 75% TFA–CH_2Cl_2 (8 mL) at 0 °C for 20 min. Evaporation with ether gave the required deprotected dipeptide as a white solid, which was diluted in CH_2Cl_2 (25 mL) and treated with Boc-L-valine (0.71 g, 3.27 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (748 mg, 3.92 mmol), 1-hydroxybenzotriazole hydrate (523 mg, 3.92 mmol) and *N*-methylmorpholine (0.40 mL, 3.27 mmol). After stirring for 2 h 30 min at room temperature, the reaction was quenched with water (20 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried over $MgSO_4$ and concentrated. The residue was purified by crystallization (MeOH) to give **22** (1.33 g, 80%) as white crystals. Mp 161.8–163.7 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.15–7.34 (m, 5H), 6.70 (bs, 1H), 6.61 (bd, J = 7.5 Hz, 1H), 4.95 (bd, J = 7.0 Hz, 1H), 4.72 (m, 1H), 4.60 (m, 1H), 3.91 (m, 1H), 3.70 (s, 3H), 3.09 (m, 2H), 2.40 (t, J = 7.5, 2H), 2.13 (m, 2H), 2.05 (s, 3H), 1.92 (m, 1H), 1.42 (s, 9H), 0.92 (d, J = 7.0 Hz, 3H), 0.82 (d, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.7, 171.6, 170.6, 156.0, 136.4, 129.4, 128.9 (2C), 127.3 (2C), 80.4, 60.4, 54.3, 52.6, 51.8, 38.1, 31.5, 30.6, 30.0, 28.4 (3C), 19.4, 17.5, 15.5; MS (ESI+): m/z 532 [M + Na]$^+$.

Bocvalinyl-isoleucinyl-alanine methyl ester (23)

Prepared according to the protoco1 used for **22** with Boc-L-isoleucine (2.15 g, 9.31 mmol), CH_2Cl_2 (35 mL), L-alanine methyl ester (1.30 g, 9.31 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (2.12 g, 11.2 mmol), 1-hydroxybenzotriazole hydrate (1.48 g, 11.2 mmol) and *N*-methylmorpholine (1.25 mL, 9.31 mmol). After work-up, column chromatography on silica gel (heptane–EtOAc 7 : 3) followed by crystallization (heptane–EtOAc 9 : 1) BocIle-Ala-OMe (2.21 g, 75%) was isolated as white crystals. Deprotection of BocIle-Ala-OMe (1.12 g, 3.54 mmol) was carried out with 75% TFA–CH_2Cl_2 (10 mL) at 0 °C for 20 min. Reaction with Boc-L-valine (769 mg, 3.54 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (807 mg, 4.25 mmol), 1-hydroxybenzotriazole hydrate (563 mg, 4.25 mmol) and *N*-methylmorpholine (0.48 mL, 3.54 mmol) afforded after work-up and crystallization (pentane–EtOAc 9 : 1) compound **23** (1.20 g, 82%) as white crystals. Mp 176.9–180.2 °C; $[\alpha]_D^{23}$ −42.6 (c 1.22 $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.90 (bd, J = 7.5 Hz, 1H), 6.81 (bd, J = 7.5 Hz, 1H), 5.26 (bd, J = 7.5 Hz, 1H), 4.56 (m, 1H), 4.35 (m, 1H), 3.96 (m, 1H), 3.74 (s, 3H), 2.11 (m, 1H), 1.90 (m, 1H), 1.44 (s, 9H), 1.39 (d, J = 7.0 Hz, 3H), 0.91 (m, 14H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.1, 172.0, 170.7, 156.1, 80.1, 60.4, 57.8, 52.5, 48.2, 37.1, 30.8, 28.6 (3C), 24.9, 19.4, 18.2, 18.1; 15.5, 11.4; MS (ESI+): m/z 438 [M + Na]$^+$; Elemental analysis calcd (%) for $C_{20}H_{37}N_3O_6$: C 57.81, H 8.98, N 10.11, O 23.10; found: C 57.69, H 8.79, N 10.05, O 23.13.

General procedure C: Reductive amination

Tripeptides **22** and **23** (1.00 mmol) were deprotected with a solution of 75% TFA–CH_2Cl_2 at 0 °C for 20 min. Evaporation with ether gave the required deprotected tripeptide as a white solid which was diluted in MeOH–CH_2Cl_2 and treated with powdered 4 Å molecular sieves and triethylamine (1 equiv.). After stirring for 10 min at room temperature, a solution of **3a–c** in MeOH–CH_2Cl_2 was added to the mixture. After 4 h, a solution of sodium cyanoborohydride (1.5–2 equiv.) in MeOH–AcOH (1 : 0.1) was added. The solution was stirred for 18 h at room temperature. Then, the mixture was filtered through a pad of Celite (CH_2Cl_2) and concentrated. The mixture was taken into H_2O and extracted with CH_2Cl_2 (3×). The combined organic layers were dried over

$MgSO_4$ and concentrated. The residue was purified by column chromatography on silica gel to afford compounds **24a–f**.

Compound 24a. Prepared according to general procedure C. Deprotection: **22** (200 mg, 0.39 mmol) in a solution 75% TFA–/CH_2Cl_2 (3 mL). Reductive amination: To a solution of the deprotected tripeptide in MeOH–CH_2Cl_2 1 : 1 (4 mL) were added: powdered 4 Å molecular sieves (450 mg) and triethylamine (55.0 µL, 0.39 mmol), **3a** (116 mg, 0.39 mmol) and a solution of sodium cyanoborohydride (50.0 mg, 0.79 mmol). After work-up the residue was purified by column chromatography on silica gel (CH_2Cl_2–MeOH 9.5 : 0.5) to afford **24a** (225 mg, 94%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.18–7.42 (m, 6H), 6.82 (bs, 1H), 6.74 (s, 1H), 4.78 (m, 1H), 4.62 (m, 1H), 4.13 (m, 4H), 3.73 (s, 3H), 3.63 (s, 3H), 3.60 (d, J = 14.0 Hz, 1H), 2.93–3.49 (m, 6H), 2.80 (m, 3H), 2.45 (t, J = 7.0 Hz, 2H), 2.11 (m, 1H), 2.06 (s, 3H), 1.96 (m, 2H), 1.24 (m, 6H), 0.85 (d, J = 7.0 Hz, 3H), 0.80 (d, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.9, 173.0, 171.9, 171.6, 171.0, 146.2, 130.6, 136.5, 129.3 (2C), 128.8 (2C), 127.1, 122.6, 67.6, 61.4, 61.0, 54.0, 52.6, 51.6, 42.2, 40.0, 38.0, 35.4, 31.6, 31.3, 31.0, 29.8, 27.4, 19.4, 18.2, 15.4, 14.2, 14.1; HRMS calcd for $C_{34}H_{52}N_5O_8S$ $[M + H]^+$: 690.3537; found: 690.3521.

General procedure D: Saponification

To a solution of **24a–f** in THF–MeOH–H_2O 1 : 1 : 1 was added lithium hydroxide monohydrate (3.6 equiv.) at 0 °C. After 1–2 h at this temperature and 1–16 h at room temperature, Amberlite IRC 50 resin (H^+) was added and the mixture was stirred until pH = 7.0. Then, the reaction was filtered and the resin was washed with MeOH (3×). Evaporation of the solvents afforded the target compounds **2a–f**.

Compound 2a. Prepared according to general procedure D. **24a** (90.0 mg, 0.13 mmol) in THF–MeOH–H_2O 1 : 1 : 1 (1.5 mL) and lithium hydroxide monohydrate (20.0 mg, 0.47 mmol) at 0 °C for 1 h and at room temperature for 1 h. After work-up, **2a** (69.5 mg, 86%) was isolated as a colorless foam. ^{1}H NMR (250 MHz, CD_3OD) δ 7.13–7.38 (m, 5H), 6.68 (s, 1H), 4.86 (m, 1H), 4.33 (m, 1H), 3.67 (s, 3H), 3.61 (d, J = 14.0 Hz, 1H), 2.89–3.34 (m, 6H), 2.74 (m, 3H), 2.49 (t, J = 8.0 Hz, 2H), 2.16 (m, 1H), 2.07 (s, 3H), 1.98 (m, 2H), 0.85 (m, 6H); ^{13}C NMR (62.5 MHz, CD_3OD) δ 181.6, 180.0, 177.9, 176.6, 172.8, 149.2, 138.0, 132.2, 130.5 (2C), 129.7 (3C), 122.3, 68.7, 55.7, 45.3, 42.2, 41.3, 38.7, 34.1, 32.8, 31.7, 31.2, 29.5, 28.0, 20.2, 19.4, 15.4; HRMS calcd for $C_{29}H_{42}N_5O_8S$ $[M + H]^+$: 620.2754; found: 620.2762.

Yeast FTase assay

Assays were carried out on 96-well plates, prepared with Biomek NKMC and Biomek 3000 from Beckman Coulter and read on Wallac Victor fluorimeter from Perkin-Elmer. In each well, 20 µL of farnesyl pyrophosphate (10 µM) was added to 180 µL of a solution containing 2 µL of varied concentrations of **24a–f** and **2a–f** (dissolved in DMSO) and 178 µL of a solution composed of 0.1 mL of partially purified recombinant yeast FTase (2.2 mg mL^{-1}) and 7.0 mL of Dansyl-GCVLS peptide (in the following buffer: 5.8 mM DTT, 12 mM $MgCl_2$, 12 µM $ZnCl_2$ and 0.09% (w/v) CHAPS, 53 mM Tris·HCl, pH 7.5). Then the fluorescence development was recorded for 15 min (0.7 seconds per well, 20 repeats) at 30 °C with an excitation filter at 340 nm and an emission filter at 486 nm. Each measurement was performed twice as duplicate or triplicate.

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