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RESEARCH ARTICLE

Synthesis of imidazole-containing analogues of farnesyl pyrophosphate and evaluation of their biological activity on protein farnesyltransferase

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Abstract

With the aim of creating new bisubstrate inhibitors of protein farnesyltransferase (FTase), new carboxylic farnesyl pyrophosphate analogues have been designed and synthesized. The original structures are built around three elements: a prenyl moiety, a 1,4-diacid motif and an imidazole ring. All the compounds were evaluated for their ability to inhibit FTase and compared with the corresponding derivatives lacking the imidazole ring, synthesized for that purpose. These new compounds are not bisubstrate inhibitors probably because the imidazole ring is not in the right position to interact with the zinc atom. However these derivatives display FPP competitive inhibition with a good activity in the carboxylic farnesyl pyrophosphate analogues series.

Keywords: *farnesyltransferase inhibitors; imidazole; isoprenyl; inhibitors*

Introduction

The protein farnesyltransferase (FTase) appears to be an important target in anticancer therapy [1] and, recently, in antiviral and antiparasitic fields [2]. FTase catalyzes the farnesylation of many proteins (Scheme 1) and this post-translational modification is a critical step for several proteins involved in the intracellular signal transduction and the cell proliferation. Indeed, the hydrophobic farnesyl group is necessary for membrane targeting and also for protein-protein interactions of these proteins making the farnesylation process a crucial step [1, 3].

FTase is a heterodimeric zinc metalloenzyme [4] which transfers the farnesyl group, a 15-carbon isoprenoid lipid unit, from the farnesyl pyrophosphate (FPP) to the cysteine of the C-terminal CaaX motif (C: cysteine, a: aliphatic amino acid, X: serine or methionine or alanine or glutamine) [3]. All the data concerning FTase catalytic reaction suggest that its mechanism is associative with an "exploded" transition state. [5]

Numerous FTase inhibitors (FTIs) have been developed and reported [6]. Some of them are currently in preclinical or clinical trials and have shown efficacy as anticancer agents alone or in combination with cytotoxic compounds [7]. Most of FTIs are FPP or CaaX competitive inhibitors [8]. However, bisubstrate compounds, *i.e.* able to bind to both FPP and CAAX sites, are expected to have a high affinity and specificity for FTase [9]. Therefore, we focused our interest on the design and the synthesis of potential bisubstrate FTIs and herein our approach and our first results are described.

On the course of our research of original new FTIs, based on the structures of already described FTIs, we designed potential bisubstrate compounds (Figure 1). Our first series of analogues **1** where a 1,4-diacidic moiety was connected to the peptidic chain through an imidazole ring, was unable to bind to the FFP binding site [10]. Therefore to accomplish this binding, we designed a new series **2** composed by three elements: a prenyl moiety, a 1,4-diacid motif and an imidazole ring.

We chose a 1,4-diacid motif to mimic the pyrophosphate of the FPP because this acidic moiety is present in several potent natural FPP competitive inhibitors like chaetomellic acid A (Figure 2) [11]. Concerning the imidazole ring, it is also a common moiety of potent FTIs [12]. By its basic nitrogen, it realizes a strong interaction with the zinc atom in the FTase catalytic binding site. To evaluate the importance of

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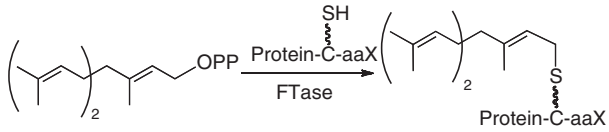


Scheme 1. Protein farnesylation.

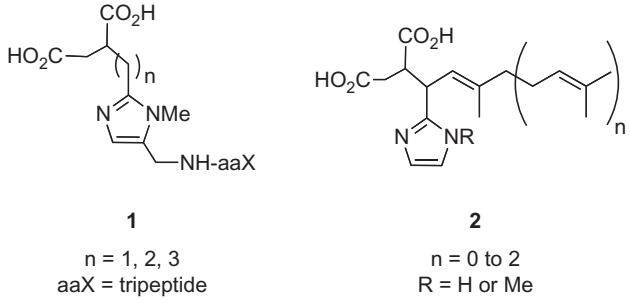


Figure 1. Potential bisubstrate analogues.

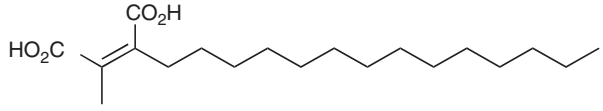


Figure 2. Chaetomellic acid A.

a free NH in these structures, we synthesized and evaluated the structures with a free or a methyl amine.

Experimental protocols

Commercial compounds were used without any further purification. Tetrahydrofuran (THF) was freshly distilled from sodium/benzophenone. Pyridine was stored over KOH and other solvents over 3Å molecular sieves. Column chromatography was performed with silica gel 60 (35-70 µm). Preparative TLC (PLC) was performed on SDS TLC with silica gel 60.

NMR spectra (^{1}H and ^{13}C) were recorded on a Brucker Avance 300 (300 MHz), DRX400 (400 MHz) and Avance 500 (500 MHz). Chemical shifts are given in ppm relative to $CDCl_3$ (^{1}H: 7.27 ppm; ^{13}C: 77.14 ppm), CD_3OD (^{1}H: 3.34 ppm; ^{13}C: 49.9 ppm) or $(CH_3)_4Si$, as an internal standard. Splitting patterns are designed as: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; b, broad and combinations thereof. IR spectra were recorded on a Perkin-Elmer Spectrum BX. Mass spectra were recorded on Thermofinningan Automass with a quadripole detection (IE) and on Thermoquest AQA Navigator with a TOF detection (ESI-HRMS).

Chemistry

General procedure A: Alkylation at C-2 position of the imidazole ring

To a stirred solution of compound **3a-b** in anhydrous THF under argon at -78°C was added *n*-butyllithium (1.6 M in hexane, 1 equiv). After 40-50 min under argon at –78°C, compound **4a-c** (1.5 equiv.) was added dropwise. The solution was stirred 20-150 min under argon at –78°C then it was slowly allowed to warm to room temperature. The reaction mixture was quenched with water and concentrated under reduced pressure. The mixture was diluted with EtOAc washed three times with brine. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel to afford compounds **5a-d**.

*3-Methyl-1-[1-(2-trimethylsilanyl-ethoxymethyl)-1H-imidazol-2-yl]-but-2-en-1-ol (***5a***):* Prepared according to general procedure A on SEM-1*H*-imidazole **3a** [34] (0.29 g, 1.5 mmol) in anhydrous THF (3 mL) with *n*-butyllithium (1.0 mL, 1.6 mmol), 50 min, and 3-methylcrotonaldehyde **4a** (210 µL, 2.2 mmol), 20 min. After column chromatography (CH_2Cl_2/MeOH : 96/4) **5a** was isolated as a yellow wax (0.28 g, 68% yield); IR (CH_2Cl_2) ν : 3400; 3133; 3111; 1679; 1248 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0 (s, 9H); 0.90 (t, 2H, J = 8.0 Hz); 1.80 (bs, 3H); 1.82 (bs, 3H); 3.49 (t, 2H, J = 8.0 Hz); 5.31 (s, 2H); 5.55 (d, 1H, J = 9.0 Hz); 5.61 (dd, 1H, J = 9.0 Hz and J' = 1.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: -1.4 (3C); 17.9; 18.3; 26.0; 63.9; 66.3; 75.1; 120.5; 127.0; 124.4; 137.0; 149.9 ; MS (IE, MeOH) m/z 282 $[M]^{+\cdot}$.

*3-Methyl-1-(1-methyl-1H-imidazol-2-yl)-but-2-en-1-ol (***5b***):* Prepared according general procedure A on N-methyl-1*H*-imidazole **3b** (1.96 g, 23.9 mmol) in anhydrous THF (34 mL) with *n*-butyllithium (18.0 mL, 28.8 mmol), 45 min, and 3-methylcrotonaldehyde **4a** (3.4 mL, 33.5 mmol), 30 min. The crude product was purified by precipitation in ether to afford **5b** as a white powder (2.7 g, 68% yield); IR (CH_2Cl_2) ν: 3073; 2964; 2897; 2825; 1676; 1282 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.76 (bs, 6H); 3.65 (s, 3H); 5.45 (d, 1H, J = 9.0 Hz); 5.56 (bd, 1H, J = 9.0 Hz); 6.77 (bs, 1H); 6.85 (bs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 18.1; 28.7; 32.8; 63.9; 122.6; 123.9; 126.5; 136.7; 149.2; HRMS (ESI, MeOH) calculated for $C_9H_{15}N_2O$ $[M+H]^+$: 167.1184; found 167.1147.

*3,7-Dimethyl-1-(1-methyl-1H-imidazole-2-yl)-octa-2,6-dien-1-ol (***5c***):* Prepared according general procedure A on N-methyl-1*H*-imidazole **3b** (0.35 mL, 4.4 mmol) in anhydrous THF (3.4 mL) with *n*-butyllithium (3.3 mL, 5.3 mmol), 45 min, and geranial **4b** [34] (1.07 g, 7.02 mmol), 2h30. After column chromatography (CH_2Cl_2/MeOH : 96/4) **5c** was isolated as a light yellow oil (1.0 g, 100% yield); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.58 (bs, 3H); 1.66 (bs, 3H); 1.78 (d, 3H, J = 1.0 Hz); 2.09 (m, 4H); 3.63 (s, 3H); 5.06 (m, 1H); 5.49 (m, 2H); 6.79 (d, 1H, J = 1.0 Hz); 6.90 (d, 1H, J = 1.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 16.6; 17.7; 25.7; 26.3; 32.8; 39.6; 64.1; 121.8; 123.8; 123.9; 126.7; 131.8; 140.5; 149.4; HRMS (ESI, MeOH) calculated for $C_{14}H_{23}N_2O$ $[M+H]^+$: 235.1810; found: 235.1799.

*3,7,11-Trimethyl-1-(1-methyl-1H-imidazol-2-yl)-dodeca-2, 6, 10-trien-1-ol (***5d***):* Prepared according general procedure A on N-methyl-1*H*-imidazole **3b** (0.4 mL, 5.0 mmol) in anhydrous THF (4 mL) with *n*-butyllithium (3.75 mL, 6.0 mmol), 40 min, and farnesal **4c** [36] (1.61 g, 7.3 mmol), 2 h. After column chromatography (CH_2Cl_2/MeOH : 95/5) **5d** was

isolated as a light yellow oil (1.45 g, 96% yield); IR (CH_2Cl_2) ν: 3110; 2960; 2913; 2857; 1668; 1279 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 1.58 (bs, 3H); 1.60 (bs, 3H); 1.68 (bs, 6H); 1.80 (bs, 3H); 1.91-2.19 (m, 8H); 3.63 (s, 3H); 5.08 (m, 2H); 5.48 (d, 1H, J = 9.0 Hz); 5.55 (bd, 1H, J = 9.0 Hz); 6.81 (bs, 1H); 6.92 (bs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 16.0; 16.7; 17.7; 25.7; 26.3; 26.7; 32.8; 39.6; 39.7; 64.1; 121.8; 123.6; 123.7; 124.3; 126.8; 131.4; 135.5; 140.8; 149.2 ; HRMS (ESI, MeOH/CH_2Cl_2) calculated for $C_{19}H_{31}N_2O$ $[M+H]^{+:}$ 303.2436; found: 303.2443.

General procedure B. Oxidation of the secondary alcohol

Anhydrous THF was added to manganese dioxide (IV) and the alcohols **5a-d** under argon at 0°C. After stirring 2 h at 0°C, the reaction mixture was filtered over Celite® and concentrated under reduced pressure.

*3-Methyl-1-[1-(2-trimethylsilanyl-ethoxymethyl)-1H-imidazol-2-yl]-but-2-en-1-one (***6a***):* Prepared according to general procedure B on **5a** (152 mg, 0.54 mmol) in anhydrous THF (12 mL) with MnO_2 (0.52 g, 6.0 mmol). **6a** was obtained without purification as a yellow wax (151 mg, 100% yield); IR (CH_2Cl_2) ν: 2952; 1656; 1609; 1247 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ: 0 (s, 9H); 1.03 (t, 2H, J = 8.5 Hz); 2.02 (s, 3H); 2.27 (s, 3H); 3.58 (t, 2H, J = 8.5 Hz); 5.85 (s, 2H); 7.18 (bs, 1H); 7.27 (bs, 1H); 7.29 (s, 1H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ: -1.5 (3C); 17.8; 21.0; 28.2; 66.8; 76.5; 121.2; 124.1; 129.0; 144.4; 158.4; 181.8; HRMS (ESI, EtOAc) calculated for $C_{14}H_{24}N_2O_2SiNa$ $[M+Na]^+$: 303.1505; found: 303.1518.

*3-Methyl-1-(1-methyl-1H-imidazol-2-yl)-but-2-en-1-one (***6b***):* Prepared according to general procedure B on **5b** (0.95 g, 5.7 mmol) in anhydrous THF (40 mL) with MnO_2 (5.9 g, 67.8 mmol). The crude product was purified by column chromatography on silica gel (CH_2Cl_2/EtOAc : 9/1) to afford **6b** as a white solid (0.84 g, 90% yield); IR (CH_2Cl_2) ν: 2939; 1651; 1609 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ : 2.01 (bs, 3H); 2.26 (bs, 3H); 4.04 (s, 3H); 6.98 (bs, 1H); 7.11 (bs, 1H); 7.28 (bs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 21.1; 28.3; 36.5; 121.2; 126.7; 128.6; 144.7; 158.1; 182.0; HRMS (ESI, MeOH) calculated for $C_9H_{13}N_2O$ $[M+H]^+$: 165.1028; found: 165.1005.

*3,7-Dimethyl-1-(1-methyl-1H-imidazole-2-yl)-octa-2,6-dien-1-one (***6c***):* Prepared according to general procedure B on **5c** (1.0 g, 4.3 mmol) in THF (26 mL) with MnO_2 (5.63 g, 64.7 mmol). The crude product was purified by column chromatography on silica gel (Heptane/EtOAc : 8/2) to afford **6c** as a light yellow oil (0.8 g, 80% yield); ^1H NMR (300 MHz, $CDCl_3$) δ: 1.62 (bs, 3H); 1.68 (bs, 3H); 2.27 (m, 7H); 4.04 (s, 3H); 5.12 (m, 1H); 6.99 (bs, 1H); 7.13 (bs, 1H); 7.30 (bs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ : 17.7; 19.7; 25.7; 26.5; 36.4; 42.0; 120.7; 123.2; 126.6; 128.5; 132.4; 144.7; 161.6; 182.2; HRMS (ESI, MeOH/CH_2Cl_2) calculated for $C_{14}H_{21}N_2O$ $[M+H]^+$: 233.1654; found : 233.1650.

*3,7,11-Trimethyl-1-(1-methyl-1H-imidazol-2-yl)-dodeca-2,6,10-trien-1-one (***6d***):* Prepared according to general procedure B on **5d** (1.27 g, 4.2 mmol) in THF (28 mL) with MnO_2 (5.58 g, 64 mmol). The crude product was purified by column chromatography on silica gel (Heptane/EtOAc : 8/2) to afford **6d** as a light yellow oil (1.16 g, 92% yield); IR (CH_2Cl_2) ν: 2960; 2913; 2863; 1656; 1609 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 1.59 (bs, 3H); 1.62 (bs, 3H); 1.67 (bs, 3H); 2.02 (m, 4H); 2.28 (bs, 7H); 4.05 (s, 3H); 5.11 (m, 2H); 6.99 (bs, 1H); 7.13 (bs, 1H); 7.32 (bs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 16.5; 17.7; 19.7; 25.7; 26.4; 26.7; 36.4; 39.7; 42.0; 120.7; 123.1; 124.3; 126.6; 128.5; 131.4; 136.1; 144.7; 161.6; 182.2; HRMS (ESI, MeOH/CH_2Cl_2) calculated for $C_{19}H_{28}N_2ONa$ $[M+Na]^+$: 323.2099; found: 323.2108.

General procedure C. Reformatsky reactions

Anhydrous THF was added to a bromocarboxylic ester, α,β-insaturated ketones **6a-d** and HCl-activated zinc under argon at room temperature. After 5 h in an ultrasound bath (temperature around 40°C), the reaction mixture was filtered over Celite® and concentrated. The crude product was dissolved in ether and washed with 10% HCl, twice with saturated $NaHCO_3$ and once with brine (**a**) or dissolved in EtOAc and washed with KOH 1M (**c-d**). The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel to afford compounds **8**, **10a-d**.

*2-(2-Methyl-propenyl)-5-oxo-2-[1-(2-trimethylsilanyl-ethoxymethyl)-1H-imidazol-2-yl]-tetrahydro-furan-3-carboxylic acid methyl ester (***8***):* Prepared according to general procedure C on **6a** (0.7 g, 2.5 mmol) in anhydrous THF (5 mL) with 2-bromosuccinic acid dimethyl ester **7** [37] (1.13 g, 5.0 mmol), and HCl-activated zinc (0.33 g, 5.0 mmol). After column chromatography on silica gel (CH_2Cl_2/EtOAc : 96/4) **8** was isolated as a colorless oil (0.62 g, 63% yield); IR (CH_2Cl_2) ν: 2950; 1789; 1737; 1248; 1094; 1080 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 0 (s, 9H); 0.92 (m, 2H); 1.34 (bs, 3H); 1.80 (bs, 6H); 2.83 (dd, 1H, J = 8.5 Hz and J' = 17.5 Hz); 3.14 (dd, 1H, J = 10.0 Hz et J' = 17.5 Hz); 3.52 (m, 3H); 3.68 (s, 3H); 5.29 (s, 2H); 5.64 (s, 1H); 6.94 (d, 1H, J = 1.0 Hz); 7.07 (bs, 1H) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ: -1.4 (3C); 18.1; 18.4; 27.5; 32.4; 51.6; 52.3; 66.8; 76.0; 84.7; 121.1; 124.3; 127.6; 139.8; 144.1; 170.1; 173.8; HRMS (ESI, CH_3CN) calculated for $C_{19}H_{30}N_2O_5SiNa$ $[M+Na]^+$: 417.1822; found: 417.1810.

*3-Hydroxy-5-methyl-3-[1-(2-trimethylsilanyl-ethoxymethyl)-1H-imidazol-2-yl]-hex-4-enic acid tert-butyl ester (***10a***):* Prepared according to general procedure C on **6a** (1.95 g, 7.0 mmol) in anhydrous THF (14.2 mL) with bromoacetic acid *tert*-butyl ester **9** (3.1 mL, 21.4 mmol), and HCl-activated zinc (1.44 g, 22.0 mmol). After column chromatography on silica gel (CH_2Cl_2/EtOAc : 9/1) **10a** was isolated as a yellow oil (1.4 g, 51% yield); IR (CH_2Cl_2) ν: 3418; 2952; 2916; 1702; 1697; 1367; 1352; 1153 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ: 0 (s, 9H); 0.91 (t, 2H, J = 8.5 Hz); 1.27 (bs, 3H); 1.46 (s, 9H); 1.67 (bs, 3H); 2.70 (d, 1H, J = 16.5 Hz); 3.26 (d, 1H, J = 16.5 Hz); 3.48 (t, 2H, J = 8.5 Hz); 5.38 (d, 1H, J = 10.0 Hz); 5.43 (d, 1H, J = 10.0 Hz); 5.49 (s, 1H); 6.89 (bs, 1H); 7.04 (bs, 1H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ: -1.3 (3C); 17.4; 18,2; 27.1; 28.1 (3C); 44.0; 66.3; 72.4; 76.0; 81.8; 119.8; 126.6; 128.7; 135.2; 150.0; 173.4; HRMS (ESI, MeOH) calculated for $C_{20}H_{36}N_2O_4SiNa$ $[M+Na]^+$: 419.2342; found: 419.2347.

*3-Hydroxy-5-methyl-3-(1-methyl-1H-imidazol-2-yl)-hex-4-enoic acid tert-butyl ester (***10b***):* Prepared according to general procedure C on **6b** (786 mg, 4.8 mmol) in anhydrous THF (10 mL) with bromoacetic acid *tert*-butyl ester **9** (2.1 mL, 14.6 mmol), and HCl-activated zinc (0.97 mg, 14.9 mmol). After column chromatography on silica gel (Heptane/EtOAc : 7/3) **10b** was isolated as a yellow oil (1.0 g, 74 % yield); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.21 (bs, 3H); 1.46 (s, 9H); 1.69 (bs, 3H); 2.69 (d, 1H, J = 16.0 Hz); 3.25 (d, 1H, J = 16.0 Hz); 3.66 (s, 3H); 5.38 (s, 1H); 5.46 (s, 1H); 6.78 (bs, 1H); 6.83 (bs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 17.2; 27.3; 28.3 (3C); 34.3; 44.1; 72.6; 81.9; 122.6; 126.1; 128.3; 134.9; 149.9; 173.7; HRMS (ESI, MeOH) calculated for $C_{15}H_{24}N_2O_3Na$ $[M+Na]^+$: 303.1685; found: 303.1691.

*3-Hydroxy-5,9-dimethyl-3-(1-methyl-1H-imidazol-2-yl)-deca-4,8-dienoic acid tert-butyl ester (***10c***):* Prepared according to general procedure C on **6c** (764 mg, 3.3 mmol) in anhydrous THF (6.6 mL) with bromoacetic acid *tert*-butyl ester **9** (1.5 mL, 10.3 mmol), and HCl-activated zinc (0.65 mg, 10.0 mmol). After column chromatography on silica gel (CH_2Cl_2/EtOAc : 95/5) **10c** was isolated as a yellow oil (0.91 g, 79 % yield); ^{1}H NMR (300 MHz, $CDCl_3$): 1.19 (d, 3H, J = 1.1 Hz); 1.48 (s, 9H); 1.58 (bs, 3H); 1.67 (bs, 3H); 2.01 (m, 4H); 2.68 (d, 1H, J = 16.5 Hz); 3.26 (d, 1H, J = 16.5 Hz); 3.66 (s, 3H); 5.05 (m, 1H); 5.42 (s, 1H); 5.47 (bs, 1H); 6.78 (d, 1H, J = 1.0 Hz); 6.83 (d, 1H, J = 1.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 15.2; 17.7; 25.7; 26.5; 28.1 (3C); 34,0; 40.8; 43.7; 72.3; 81.7; 122.4; 123.8; 125.8; 128.3; 131.8; 138.1; 149.7; 173.5; HRMS (ESI, MeOH/CH_2Cl_2) calculated for $C_{20}H_{33}N_2O_3$ $[M+H]^+$: 349.2491; found: 349.2502.

*3-Hydroxy-5,9,13-trimethyl-3-(1-methyl-1H-imidazol-2-yl)-tetradeca-4,8,12-trienoic acid tert-butyl ester (***10d***):* Prepared according to general procedure C on **6d** (1.0 g, 3.3 mmol) in anhydrous THF (6.8 mL) with bromoacetic acid *tert*-butyl ester **9** (1.5 mL, 10.3 mmol), and HCl-activated zinc (0.65 mg, 10.0 mmol). After column chromatography on silica gel (CH_2Cl_2/EtOAc : 95/5) **10d** was isolated as a pale yellow oil (1.0 g, 74 % yield); IR (CH_2Cl_2) *ν*: 3110; 2975; 2927; 1698; 1367; 1349; 1152 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.21 (bs, 3H); 1.48 (s, 9H); 1.58 (bs, 3H); 1.60 (bs, 3H); 1.68 (bs, 3H); 1.92-2.12 (m, 8H); 2.69 (d, 1H, J = 16.5 Hz); 3.27 (d, 1H, J = 16.5 Hz); 3.67 (s, 3H) 5.08 (m, 2H); 5.41 (bs, 1H); 5.49 (bs, 1H); 6.78 (bs, 1H); 6.84 (bs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 15.2; 16.0; 17.7; 25.7; 26.5; 26.7; 28.1 (3C); 34.1; 39.7; 40.8; 43.6; 72.3; 81.7; 122.3; 123.6; 124.,3; 125.8; 128.2; 131.5; 135.5; 138.1; 149.7; 173.5; HRMS (ESI, MeOH) calculated for $C_{25}H_{41}N_2O_3$ $[M+ H]^+$: 417.3117; found: 417.3102.

General procedure D. Dehydration

To a stirred solution of hydroxyesters **10a-d** in pyridine under argon at 0°C $POCl_3$ was added dropwise. After stirring 14 hours at room temperature, the reaction mixture was diluted with ether and quenched carefully with water. The solution was basified with KOH 10M then extracted with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel to afford compounds **11a-d**.

*5-Methyl-3[1-(2-trimethylsilanyl-ethoxymethyl)-1H-imidazol-2-yl]-hexa-2,4-dienoaic acid tert-butyl ester (***11a***):* Prepared according general procedure D on **10a** (1.03 g, 2.6 mmol) in pyridine (6.5 mL) with $POCl_3$ (1.2 mL, 12.9 mmol). After column chromatography (Heptane/EtOAc : 6/4) **11a** was isolated as a yellow oil (737 mg, 75% yield); IR (CH_2Cl_2) *ν*: 2953; 1704; 1627; 1248; 1147 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0 (s, 9H); 0.88 (t, 2H, J = 8.0 Hz); 1.33 (s, 9H); 1.36 (bs, 3H); 1.85 (bs, 3H); 3.47 (t, 2H, J = 8.0 Hz); 5.09 (s, 2H); 6.00 (d, 1H, J = 1.0 Hz); 6.04 (bs, 1H); 7.09 (bs, 1H); 7.13 (bs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: -1,1 (3C); 18.2; 19.4; 28.3 (3C); 28.6; 67.0; 75.8; 80.7; 119.4; 124.9; 125.6; 129.2; 141.6; 144.3; 144.7; 165.0; HRMS (ESI, EtOAc) calculated for $C_{20}H_{35}N_2O_3Si$ $[M+H]^+$: 379.2417; found: 379.2422.

*5-Methyl-3-(1-methyl-1H-imidazol-2-yl)-hexa-2,4-dienoic acid tert-butyl ester (***11b***):* Prepared according to procedure D on **10b** (0.82 g, 3 mmol) in pyridine (7.5 mL) with $POCl_3$ (1.4 mL, 15.2 mmol). After column chromatography (Heptane/EtOAc : 1/1) **11b** was isolated as a yellow oil (646 mg, 82% yield); IR (CH_2Cl_2) *ν*: 2976; 2933; 1698; 1145 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.20 (bs, 3H); 1.85 (bs, 3H); 1.33 (s, 9H); 3.47 (s, 3H); 6.03 (s, 2H); 6.91 (bs, 1H); 7.09 (bs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 18.5; 28.2 (3C); 28.5; 32.9; 80.4; 120.4; 125.4; 125.9; 128.6; 141.6; 144.2; 144.7; 165.0; HRMS (ESI, EtOAc) calculated for $C_{15}H_{23}N_2O_2$ $[M+H]^+$: 263.1760; found: 263.1733.

*5,9-Dimethyl-3-(1-methyl-1H-imidazol-2-yl)-deca-2,4,8-trienoic acid tert-butyl ester (***11c***):* Prepared according to procedure D on **10c** (0.79 g, 2.3 mmol) in pyridine (5.7 mL) with $POCl_3$ (1.06 mL, 11.4 mmol). After column chromatography (Heptane/EtOAc : 6/4) **11c** was isolated as a yellow oil (613 mg, 82% yield); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.20 (d, 3H, J = 1.0 Hz); 1.32 (s, 9H); 1.59 (bs, 3H); 1.68 (bs, 3H); 2.11 (m, 4H); 3.45 (s, 3H); 5.06 (m, 1H); 6.00 (bs, 1H); 6.04 (bs, 1H); 6.90 (d, 1H, J = 1.0 Hz); 7.08 (d, 1H, J = 1.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 16.7; 17.7; 25.7; 26.5; 28.0 (3C); 32.7; 42.0; 80.3; 120.2; 123.4; 124.9; 126.2; 128.6; 132.1; 141.5; 144.8; 147.4; 164.9; HRMS (ESI, MeOH/CH_2Cl_2) calculated for $C_{20}H_{31}N_2O_2$ $[M+H]^+$: 331.2386; found: 331.2386.

*5,9,13-Trimethyl-3-(1-methyl-1 H-imidazol-2-yl)-tetradeca-2,4,8,12-tetraenoic acid tert-butyl ester (***11d***):* Prepared according to procedure D on **10d** (2.16 g, 5.2 mmol) in pyridine (16 mL) with $POCl_3$ (2.41 mL, 25.9 mmol). After column chromatography (CH_2Cl_2/EtOAc : 9/1) **11d** was isolated as a yellow oil (1.77 g, 85% yield); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.17 (bs, 3H); 1.29 (s, 9H); 1.57 (bs, 6H); 1.65 (bs, 3H); 1.90-2.02 (m, 4H); 2.09 (bs, 4H); 3.42 (s, 3H); 5.05 (m, 2H); 5.92 (bs, 1H); 6.01 (bs, 1H); 6.87 (d, 1H, J = 1.0 Hz); 7.04 (d, 1H, J = 1.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 16.4; 17.1; 18.0; 26.0; 26.8; 27.0; 28.3 (3C); 33.0; 40.0; 42.3; 80.6; 120.5; 123.6; 124.6; 125.2; 126.4; 128.8; 131.7; 136.1; 141.8; 145.0; 147.8; 165.2; HRMS (ESI, MeOH/CH_2Cl_2) calculated for $C_{25}H_{39}N_2O_2$ $[M+ H]^+$: 399.3012; found: 399.3024.

General procedure E. Reduction of the conjugated double bond

Anhydrous methanol was added to the conjugated alkenes **11a-d** and magnesium turnings under argon at room temperature. After controlling the temperature with an ice bath at the beginning, the reaction mixture was stirred for 3 h and quenched with 3N HCl. The solution was basified with 3M KOH, the formed gel was filtered and the filtrate was extracted with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel to afford compounds **13a-d**.

*5-Methyl-3[1-(2-trimethylsilanyl-ethoxymethyl)-1H-imidazol-2-yl]-hex-4-enoic acid tert-butyl ester (***13a***):* Prepared according to general procedure E on **11a** (327 mg, 0.87 mmol) in anhydrous methanol (7 mL) with Mg (0.32 g, 13.3 mmol). After column chromatography (Heptane/EtOAc : 6/4) **13a** was isolated as a yellow oil (205 mg, 62% yield); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0 (s, 9H); 0.89 (dd, 2H, J = 7.5 Hz and J' = 9.0 Hz); 1.38 (s, 9H); 1.69 (bs, 3H); 1.77 (bs, 3H); 2.59 (dd, 1H, J = 7.5 Hz and J' = 15.0 Hz); 2.92 (dd, 1H, J = 8.0 Hz and J' = 15.0 Hz); 3.45 (dd, 2H, J = 7.5 Hz and J' = 9.0 Hz); 4.23 (m, 1H); 5.23 (bs, 1H); 5.24 (s, 2H); 6.88 (bs, 1H); 6.95 (bs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: -1.1 (3C); 18.2; 18.6; 26.1; 28.4 (3C); 33.6; 40.9; 66.3; 75.1; 80.6; 119.8; 125.0; 127.8; 133.4; 150.4; 171.7; HRMS (ESI, MeOH) calculated for $C_{20}H_{36}N_2O_3SiNa$ $[M+Na]^+$: 403.2393; found: 403.2388.

*5-Methyl-3-(1-methyl-1H-imidazol-2-yl)-hex-4-enoic acid tert-butyl ester (***13b***):* Prepared according to general procedure E on **11b** (434 mg, 1.66 mmol) in anhydrous methanol (9.6 mL) with Mg (0.51 g, 21.2 mmol). After column chromatography (ether) **13b** was isolated as a yellow oil (352 mg, 80% yield); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.36 (s, 9H); 1.68 (bs, 3H); 1.75 (bs, 3H); 2.56 (dd, 1H, J = 7.5 Hz and J' = 16.0 Hz); 2.92 (dd, 1H, J = 8.0 Hz and J' = 16.0 Hz); 3.54 (s, 3H); 4.07 (ddd, 1H, J = 7.5 Hz, J' = 8.0 Hz and J" = 10.0 Hz); 5.13 (bd, 1H, J = 10.0 Hz); 6.21 (d, 1H, J = 1.0 Hz); 6.88 (d, 1H, J = 1.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 18.5; 26;9; 28.2 (3C); 32.7; 33.4; 40.4; 80.5; 120.7; 124.5; 127.2; 133.1; 149.7; 171.7; HRMS (ESI, EtOAc) calculated for $C_{15}H_{24}N_2O_2Na$ $[M+Na]^+$: 287.1735; found: 287.1719.

*5,9-Dimethyl-3-(1-methyl-1H-imidazol-2-yl)-deca-4,8-dienoic acid tert-butyl ester (***13c***):* Prepared according to general procedure E on **11c** (488 mg, 1.48 mmol) in anhydrous methanol (12.5 mL) with Mg (0.73 g, 30.4 mmol). After column chromatography (CH_2Cl_2/EtOAc : 8/2) **13c** was isolated as a yellow oil (347 mg, 71% yield); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.37 (s, 9H); 1.55 (bs, 3H); 1.64 (bs, 3H); 1.76 (d, 3H, J = 1.5 Hz); 2.01 (m, 4H); 2.57 (dd, 1H, J = 7.0 Hz and J' = 16.0 Hz); 2.97 (dd, 1H, J = 8.0 Hz and J' = 16.0 Hz); 3.54 (s, 3H); 4.09 (m, 1H); 5.02 (m, 1H); 5.13 (bd, 1H, J = 10.0 Hz); 6.73 (d, 1H, J = 1.0 Hz); 6.89 (d, 1H, J = 1.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 16.4; 17.7; 25.7; 26.5; 28.0 (3C); 32.4; 33.1; 39.5; 40.0; 80.2; 120.5; 123.2; 123.9; 127.0; 131.6; 136.5; 149.5; 171.5; HRMS (ESI, MeOH/CH_2Cl_2) calculated for $C_{20}H_{33}N_2O_2$ $[M+H]^+$: 333.2542; found: 333.2511.

*5,9,13-Trimethyl-3-(1-methyl-1 H-imidazol-2-yl)-tetradeca-4,8,12-trienoic acid tert-butyl ester (***13d***):* Prepared according to general procedure E on **11d** (1.4 g, 3.5 mmol) in anhydrous methanol (28 mL) with Mg (1.77 g, 74 mmol). After column chromatography (CH_2Cl_2/EtOAc : 8/2) **13d** was isolated a yellow oil (1.0 g, 71% yield); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.34 (s, 9H); 1.53 (bs, 3H); 1.55 (bs, 3H); 1.63 (bs, 3H); 1.73 (bs, 3H); 1.86-2.11 (m, 8H); 2.54 (dd, 1H, J = 7.0 Hz and J' = 16.0 Hz); 2.95 (dd, 1H, J = 8.0 Hz and J' = 16.0 Hz); 3.51 (s, 3H); 4.06 (m, 1H); 5.02 (m, 2H); 5.11 (d, 1H, J = 10.0 Hz); 6.68 (d, 1H, J = 1.0 Hz); 6.85 (d, 1H, J = 1.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 16.3; 16.7; 18.0; 26.0; 26.7; 27.0; 28.3 (3C); 33.7; 33.3; 39.8; 39.9; 40.2; 80.5; 120.7; 123.9; 124.4; 124.6; 127.2; 131.5; 135.5; 136.8; 149.7; 171.7; HRMS (ESI, MeOH) calculated for $C_{25}H_{41}N_2O_2$ $[M+H]^+$: 401.3268; found: 401.3169.

General procedure F. Succinic moiety building

n-Butyllithium (1.6 M in hexane) was added to a cooled (-78°C) solution of diisopropyl amine in anhydrous THF (1.6 mL) under argon at -78°C. After 35 min, a solution of the saturated esters **13a-d** in anhydrous THF was added dropwise under argon at -78°C. After 35 min at -78°C, bromoacetic acid *tert*-butyl ester **9** was added dropwise under argon. The solution was stirred for 4 h at -78°C and was slowly allowed to warm to room temperature. The reaction mixture was quenched with water, poured in EtOAc and washed three times with brine. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel to afford compounds **15a-d**.

*2-{3-Methyl-1-[1-(2-trimethylsilanyl-ethoxymethyl)-1H-imidazol-yl]-but-2-enyl} succinic acid di-tert-butyl ester (***15a***):* Prepared according to general procedure F on **13a** (303 mg, 0.8 mmol) in anhydrous THF (1 mL) with in situ prepared LDA (*n*-Butyl lithium (595 µL) and diisopropyl amine (134 µL), 0.95 mmol) in anhydrous THF (1.6 mL) and **10** (140 µL, 0.95 mmol). After column chromatography (Heptane/ EtOAc : 8/2) **15a** was isolated as a pale yellow oil (0.23 g, 72% yield with 81% conversion). We evaluated the diastereomeric rate by HPLC on Symmetry® column 250x4.6mm with H_2O/MeOH 20/80, flow: 1 mL/min (t_r= 24.94 min for the diastereoisomer **15aA**, 47% and 29.57 min for the diastereoisomer **15aB**, 53 %); ^{1}H NMR (300 MHz, $CDCl_3$) δ: Compound **15aA**: 0 (s, 9H); 0.90 (t, 2H, J = 8.0 Hz); 1.38 (s, 9H); 1.40 (s, 9H); 1.69 (bs, 6H); 2.25 (dd, 1H, J = 4.0 Hz and J' = 11.0 Hz); 2.56 (m, 1H); 3.32 (m, 1H); 3.44 (t, 2H, J = 8.0 Hz); 4.00 (m, 1H); 5.21 (s, 2H); 5.37 (d, 1H, J = 10.0 Hz); 6.86 (bs, 1H); 6.98 (bs, 1H); Compound **15aB**: 0 (s, 9H); 0.88 (m, 2H); 1.28 (s, 9H); 1.41 (s, 9H); 1.69 (bs, 3H); 1.71 (bs, 3H); 2.56 (m, 2H); 3.19 (m, 1H); 3.43 (t, 2H, J = 8.5 Hz); 4.12 (t, 1H, J= 10.5 Hz); 5.12 (d, 1H, J = 11.0 Hz); 5.35 (d, 1H, J = 10.5 Hz); 5.37 (d, 1H, J = 11.0 Hz); 6.83 (bs, 1H); 6.94 (bs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: Compound **15aA**: -0.3 (3C); 18.1; 18.6; 26.2; 28.2 (3C); 28.4 (3C); 36.6; 39.0; 47.1; 66.3; 75.1; 80.6; 80.7; 119.9; 123.7; 128.1; 133.9; 148.9; 171.4; 173,3; Compound **15aB**: -0.8 (3C); 18.1; 18.8; 26,3; 28.1 (3C); 28.4 (3C); 35.6; 37.9; 47.3; 66.2; 75.1; 80.7; 80.8; 119.5; 122.6; 127.8;

135.2; 149.5; 171.5; 173.3; HRMS (ESI, MeOH) calculated for $C_{26}H_{47}N_2O_5Si$ $[M+H]^+$: 495.3254; found: 495.3253.

*2-[3-Methyl-1-(1-methyl-1H-imidazol-2-yl)-but-2-enyl]-succinic acid di-tert-butyl ester (***15b***):* Prepared according to general procedure F on **13b** (327 mg, 0.86 mmol) in anhydrous THF (1.2 mL) with in situ prepared LDA (*n*-Butyl lithium (700 µL) and diisopropyl amine (155 µL), 1.1 mmol) in anhydrous THF (1.9 mL) and **9** (160 µL, 1.1 mmol). After column chromatography (Heptane/ EtOAc : 4/6) **15b** was isolated as a pale yellow oil (223 mg, 76% yield, 91% conversion); ^{1}H NMR (300 MHz, $CDCl_3$) δ : 1.29 (s, 9H); 1.42 (s, 9H); 1.70 (bs, 3H); 1.72 (bs, 3H); 2.57 (m, 2H); 3.20 (td, 1H, J = 5.0 Hz and J' = 9.0 Hz); 3.60 (s, 3H); 4.01 (dd, 1H, J = 9.0 Hz and J' = 10.5 Hz); 5.30 (bd, 1H, J = 10.5 Hz); 6.71 (d, 1H, J = 1.0 Hz); 6.91 (d, 1H, J = 1.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 18.4; 25.9; 27.7 (3C); 28.1 (3C); 32.6; 35.3; 37.6; 46.6; 80.5 (2C); 120.1; 122.3; 127.2; 134.7; 148.7; 171.2; 173.0; HRMS (ESI, EtOAc) calculated for $C_{21}H_{35}N_2O_4$ $[M+H]^+$: 379.2597; found: 379.2610.

*2-[3,7-Dimethyl-1-(1-methyl-1H-imidazole-2-yl)-octa-2,6-dienyl]-succinic acid di-tert-butyl ester (***15c***):* Prepared according to general procedure F on **13c** (230 mg, 0.69 mmol) in anhydrous THF (1.0 mL) with in situ prepared LDA (*n*-Butyl lithium (600 µL) and diisopropyl amine (125 µL), 0.96 mmol) in anhydrous THF (1.5 mL) and **9** (130 µL, 0.89 mmol). After column chromatography (Heptane/ EtOAc : 6/4) **15c** was isolated as a pale yellow oil (128 mg, 42% yield); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.29 (s, 9H); 1.43 (s, 9H); 1.57 (bs, 3H); 1.65 (bs, 3H); 1.69 (d, 3H, J = 1.0 Hz); 2.05 (m, 4H); 2.52 (dd, 1H, J = 9.5 Hz and J' = 16.0 Hz); 2.65 (dd, 1H, J = 4.0 Hz and J' = 16.0 Hz); 3.22 (td, 1H, J = 4.0 Hz and J' = 9.5 Hz); 3.59 (s, 3H); 4.01 (dd, 1H, J = 9.5 Hz and J' = 10.5 Hz); 5.03 (m, 1H); 5.28 (bd, 1H, J = 10.5 Hz); 6.70 (d, 1H, J = 1.0 Hz); 6.91 (d, 1H, J = 1.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 16.7; 17.7; 25.7; 26.3; 27.8 (3C); 29.1 (3C); 32.6; 35.4; 37.5; 39.7; 46.6; 80.5 (2C); 120.1; 122.6; 123.9; 127.2; 131.8; 138.1; 148.8; 171.3; 173.0; HRMS (ESI, MeOH) calculated for $C_{26}H_{43}N_2O_4$ $[M+H]^+$: 447.3223; found: 447.3235.

*2-[3,7,1-Trimethyl-1-(1-methyl-1H-imidazol-2-yl)-dodeca-2,6,10-trienyl]-succinic acid di-tert-butyl ester (***15d***):* Prepared according to general procedure F on **13d** (200 mg, 0.5 mmol) in anhydrous THF (1.2 mL) with in situ prepared LDA (*n*-Butyl lithium (410 µL) and diisopropyl amine (91 µL), 0.65 mmol) in anhydrous THF (1.5 mL) and **9** (95 µL, 0.65 mmol). After column chromatography (Heptane/ EtOAc : 8/2) **15d** was isolated as a pale yellow oil (124 mg, 48% yield); ^{1}H NMR (300 MHz, $CDCl_3$) δ : 1.29 (s, 9H); 1.43 (s, 9H); 1.57 (bs, 3H); 1.59 (bs, 3H); 1.67 (bs, 3H); 1.70 (bs, 3H); 1.90-2.13 (m, 8H); 2.53 (dd, 1H, J = 9.0 Hz and J' = 16.0 Hz); 2.66 (dd, 1H, J = 4.0 Hz and J' = 16.0 Hz); 3.18-3.31 (m, 1H); 3.60 (s, 3H); 4.05 (dd, 1H, J = 9.5 Hz and J' = 10.5 Hz); 5.05 (m, 2H); 5.31 (d, 1H, J = 10.5 Hz); 6.71 (bs, 1H); 6.92 (bs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 16.4; 17.1; 18.0; 26.0; 26.7; 27.1; 28.1 (3C); 28;4 (3C); 32.4; 35.7; 37.7; 40.0; 46.9; 80.8 (2C); 120.4; 122.7; 124.1; 124.7; 127.4; 131.6; 135.8; 138.7; 149.2; 171.6; 173.3; HRMS (ESI, MeOH/ CH_2Cl_2) calculated for $C_{31}H_{51}N_2O_4$ ($[M+H]^+$: 515.3849; found: 515.3834.

General procedure G. Deprotection of SEM-compounds

TFA (3.6 mL) was added drop by drop to a stirred solution of ester (0.24 mmol) in dichloromethane (1.8 mL) at room temperature. After 5 hours, the solvent was evaporated. The crude product was precipitated to afford the expected acid **12a**, **14a** or **2a**.

*3-(1H-imidazol-2-yl)-5-methyl-hexa-2,4-dienoic acid (***12a***):* General procedure G on **11a** (91 mg, 0.24 mmol) afforded **12a** as a white powder after precipitation with ether in methanol (27 mg, 36% yield); IR (CH_2Cl_2) *ν*: 3148; 3121; 2916; 1557; 1346 cm^{-1}; ^{1}H NMR (300 MHz, CD_3OD) δ: 1.73 (bs, 3H); 1.95 (bs, 3H); 6.08 (bs, 1H); 6.11 (bs, 1H); 7.40 (bs, 2H); ^{13}C NMR (75 MHz, CD_3OD) δ: 20.5; 27.3; 122.5; 123.1 (2C); 130.1; 134.2; 145.3; 145.4; 171.9; HRMS (ESI, MeOH) calculated for $C_{10}H_{12}N_2O_2Na$ $(M+Na)^+$: 215.0796; found: 215.0802.

*3-(1H-imidazol-2-yl)-5-methyl-hex-4-enoic acid (***14a***):* General procedure G on **13a** (108 mg, 0.28 mmol) afforded **14a** as a white powder after precipitation with acetone (41 mg, 49% yield); IR (CH_2Cl_2) *ν*: 3147; 2978; 2916; 1666; 1180; 1137 cm^{-1}; ^{1}H NMR (300 MHz, CD_3OD) δ: 1.57 (bs, 3H); 1.60 (bs, 3H); 2.63 (dd, 1H, J = 6.5 Hz and J' = 17.0 Hz); 2.75 (dd, 1H, J = 7.7 Hz and J' = 17.0 Hz); 4.25 (m, 1H); 5.11 (d, 1H, J = 9.5 Hz); 7.23 (bs, 2H); ^{13}C NMR (75 MHz, CD_3OD) δ: 19.0; 26.7; 35.3; 39.7; 120.8 (2C); 121.6; 141.0; 151.6; 174.5 ; HRMS (ESI, MeOH) calculated for $C_{10}H_{15}N_2O_2$ $[M+H]^+$: 195.1134, found: 195.1149.

*2-[1-(1H-imidazol-2-yl)-3-methyl-but-2-enyl]-succinic acid (***2a***):* General procedure G on **15a** (57 mg, 0.11 mmol) afforded **2a** as a pale yellow oil (44 mg, 100% yield). HPLC on a Symmetry® column 150 x 4.6 mm, elution with a gradient 100% H_2O, 1% TFA to 100% CH_3CN, 1% TFA; t_r= 10.1 min for the diastereoisomer **2aA** and 10.7 min for the diastereoisomer **2aB**; IR (CH_2Cl_2) *ν*: 3154; 2976; 2915; 1666; 1190 cm^{-1}; ^{1}H NMR (300 MHz, CD_3OD) δ: **diastereoisomer 2aA:** 1.50 (bs, 3H); 1.66 (bs, 3H); 2.25 (dd, 1H, J = 6.5 Hz and J' = 17.0 Hz); 2.56 (dd, 1H, J = 8.0 Hz and J' = 17.0 Hz); 3.12 (m, 1H); 4.16 (dd, 1H, J= 6.0 Hz and J' = 10.0 Hz); 5.19 (d, 1H, J = 10.0 Hz); 7.22 (bs, 1H); 7.23 (bs, 1H); **diastereoisomer 2aB:** 1.55 (bs, 3H); 1.60 (bs, 3H); 2.46 (dd, 1H, J = 5.0 Hz and J' = 17.0 Hz); 2.56 (dd, 1H, J = 7.0 Hz and J' = 17.0 Hz); 3.12 (m, 1H); 4.26 (t, 1H, J= 10.0 Hz); 5.06 (d, 1H, J = 10.0 Hz); 7.22 (bs, 2H); ^{13}C NMR (75 MHz, CD_3OD) δ: **diastereoisomer 2aA:** 19.2; 26.9; 36.1; 39.9; 47.3; 118.4; 121.0 (2C); 142.3; 150.6; 175.6 (2C); **diastereoisomer 2aB :** 19.1; 26.7; 35.4; 40.1; 47.1; 120.5; 120.8 (2C); 143.5; 150.9; 175.6; 176.3; HRMS (ESI, MeOH) calculated for $C_{12}H_{17}N_2O_4$ $[M+H]^+$: 253.1144; found: 253.1167.

General procedure H. Deprotection of the N-methyl-isoprenyl-compounds

Formic acid (5 mL) was added to ester (0.25 mmol) at room temperature. After 19 hours, the solvent was evaporated to afford the corresponding acid **12b**, **14b** or **2b**.

*5-Methyl-3-(1-methyl-1H-imidazol-2-yl)-hexa-2,4-dienoic acid (***12b***):* General procedure H on **11b** (66 mg, 0.25

mmol) afforded **12b** as a pale orange oil (52 mg, 100% yield). IR (CH_2Cl_2) ν: 3396; 2970; 2920; 2852; 1698; 1600; 1265 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ: 1.25 (bs, 3H); 1.90 (bs, 3H); 3.60 (s, 3H); 6.13 (bs, 1H); 6.39 (bs, 1H); 7.40 (bs, 1H); 7.46 (bs, 1H); 8.20 (s, 1H); ^{13}C NMR (75 MHz, CD_3OD) δ: 18.6; 28.3; 34.6; 122.3; 124.0; 124.1; 132.9; 133.3; 145.5 (2C); 169.4; HRMS (ESI, MeOH) calculated for $C_{11}H_{14}N_2O_2Na$ $[M+Na]^+$: 229.0953; found: 229.0924.

*5-Methyl-3-(1-methyl-1H-imidazol-2-yl)-hex-4-enoic acid (***14b***):* General procedure H on **13b** (60 mg, 0.23 mmol) afforded **14b** as a pale yellow powder (47 mg, 100% yield); IR (CH_2Cl_2) ν: 3375; 2960; 2915; 2857; 1713; 1274 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ: 1.56 (bs, 3H); 1.58 (bs, 3H); 2.56 (dd, 1H, J = 6.0 Hz and J' = 16.5 Hz); 2.74 (dd, 1H, J = 9.0 Hz and J' = 16.5 Hz); 3.66 (s, 3H); 4.25 (m, 1H); 5.01 (bd, 1H, J = 9.5 Hz); 7.16 (bs, 2H); 8.04 (s, 1H); ^{13}C NMR (75 MHz, CD_3OD) δ: 17.0; 24.5; 32.2; 33.5; 38.3; 119.1; 119.9; 122.6; 137.5; 149.3; 165.3; 173.5; HRMS (ESI, MeOH) calculated for $C_{11}H_{16}N_2O_2Na$ $[M+Na]^+$: 231.1109; found: 231.1078.

*2-[3-Methyl-1-(1-methyl-1H-imidazol-2-yl)-but-2-enyl]-succinic acid (***2b***):* General procedure H on **15b** (88.5 mg, 0.23 mmol) afforded **2b** as a pale yellow oil (54 mg, 87% yield); IR (CH_2Cl_2) ν: 3376; 1572; 1567; 1557; 1385 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ: 1.29 (bs, 3H); 1.30 (bs, 3H); 2.29 (d, 2H, J = 5.5 Hz); 2.84 (td, 1H, J = 5.5 Hz and J' = 10.5 Hz); 3.43 (s, 3H); 4.05 (t, 1H, J = 10.5 Hz); 4.77 (d, 1H, J = 10.5 Hz); 6.96 (s, 2H); 7.64 (s, 1H); ^{13}C NMR (75 MHz, CD_3OD) δ: 19.5; 26.7; 35.4; 36.1; 38.2; 46.6; 120.3; 120.4; 125.0; 142.5; 150.8; 165.8; 175.7; 176.4; HRMS (ESI, MeOH) calculated for $C_{13}H_{19}N_2O_4$ $[M+H]^+$: 267.1345; found: 267.1318.

General procedure I. Deprotection of the N-methyl-geranyl and N-methyl-farnesyl compounds

The ester in toluene (3 mL) with silica gel (35-70 μm) was refluxed with vigorous agitation for 14 hours. After cooling, the reaction mixture was filtered over Celite®, washed with CH_2Cl_2/MeOH 8/2 and concentrated. The crude product was purified by preparative TLC to afford the corresponding acid **12c-d**, **14c-d** or **2c-d**.

*5,9-Dimethyl-3-(1-methyl-1H-imidazol-2-yl)-deca-2,4,8-trienoic acid (***12c***):* Prepared according general procedure I on **11c** (36 mg, 0.11 mmol) with SiO_2 (550 mg). After preparative TLC (CH_2Cl_2/MeOH : 9/1) **12c** was isolated as an orange oil (18 mg, 60% yield) ; IR (CH_2Cl_2) ν: 3127; 2960; 2925; 2857; 1591; 1373 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$/Pyridine-d_5 1/1) δ: 0.96 (bs, 3H); 1.29 (bs, 3H); 1.38 (bs, 3H); 1.81 (m, 4H); 3.17 (s, 3H); 4.81 (m, 1H); 5.76 (bs, 1H); 6.05 (bs, 1H); 6.66 (bs, 1H); 6.85 (bs, 1H); ^{13}C NMR (125 MHz, $CDCl_3$/Pyridine-d_5 1/2) δ: 16.7; 17.8; 25.7; 26.8; 33.0; 41.8; 121.2; 124.0; 125.4; 127.7; 128.1; 131.8; 146.1; 149.0; HRMS (ESI, MeOH) calculated for $C_{16}H_{21}N_2O_2$ $[M-H]^-$: 273.1603; found: 273.1619.

*5,9-Dimethyl-3-(1-methyl-1H-imidazol-2-yl)-deca-4,8-dienoic acid (***14c***):* Prepared according general procedure I on **13c** (38 mg, 0.11 mmol) with SiO_2 (575 mg). After preparative TLC (CH_2Cl_2/MeOH : 9/1) **14c** was isolated as a colorless oil (18 mg, 58% yield); IR (CH_2Cl_2) ν: 3392; 2960; 2915; 2857; 1574; 1392 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$/Pyridine-d_5 1/1) δ: 1.52 (bs, 3H); 1.62 (bs, 3H); 1.79 (s, 3H); 1.95-2.09 (m, 4H); 2.85 (dd, 1H, J = 6.0 Hz and J' = 16.0 Hz); 3.32 (dd, 1H, J = 8.0 Hz and J' = 16.0 Hz); 3.50 (s, 3H); 4.30 (m, 1H); 5.03 (m, 1H); 5.27 (bd, 1H, J = 9.5 Hz); 6.76 (d, 1H, J = 1.0 Hz); 6.98 (d, 1H, J = 1.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$/Pyridine-d_5 1/1) δ: 16.3; 17.6; 25.6; 26.5; 32.2; 33.1; 39.5 (2C); 120.8; 124.1; 124.6; 126.7; 131.3; 136.5; 150.0; 174.4; HRMS (ESI, MeOH) calculated for $C_{16}H_{23}N_2O_2$ $[M-H]^-$: 275.1760; found: 275.1743.

*2-[3,7-Dimethyl-1-(1-methyl-1H-imidazole-2-yl)-octa-2,6-dienyl]-succinic acid (***2c***):* Prepared according general procedure I on **15c** (55 mg, 0.12 mmol) with SiO_2 (620 mg). After preparative TLC (CH_2Cl_2/MeOH : 85/15) **2c** was isolated as a colorless oil (13.5 mg, 34% yield); IR (CH_2Cl_2) ν: 3396; 2970; 2927; 2852; 1715; 1614; 1395; 1264 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$/Pyridine-d_5 1/1) δ: 1.53 (bs, 3H); 1.64 (bs, 3H); 1.79 (bs, 3H); 2.15-2.02 (m, 4H); 3.10 (m, 2H); 3.62 (s, 3H); 3.88 (m, 1H); 4.54 (m, 1H); 5.06 (m, 1H); 5.55 (bd, 1H, J = 10.5 Hz); 6.82 (bs, 1H); 7.04 (bs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$/Pyridine-d_5 1/1) δ: 16.5; 17.7; 25.6; 26.4; 32.8; 34.3; 37.0; 39.7; 46.0; 120.8; 122.4; 124.1; 125.3; 131.4; 138.6; 149.5; 174.6; 175.4; HRMS (ESI, MeOH) calculated for $C_{18}H_{27}N_2O_4$ $[M+H]^+$: 335.1971; found: 335.1940.

*5,9,13-Trimethyl-3-(1-methyl-1H-imidazol-2-yl)-tetradeca-2,4,8,12-tetraenoic acid (***12d***):* Prepared according general procedure I on **11d** (32.5 mg, 0.08 mmol) with SiO_2 (400 mg). After preparative TLC (CH_2Cl_2/MeOH : 9/1) **12d** was isolated as a white powder (16.5 mg, 59% yield); IR (CH_2Cl_2) ν: 3353; 2960; 2922; 2846; 1693; 1253 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$/Pyridine-d_5 1/1) δ: 1.29 (bs, 3H); 1.60 (bs, 3H); 1.61 (bs, 3H); 1.67 (bs, 3H); 1.97-2.05 (m, 2H); 2.05-2.18 (m, 6H); 3.50 (s, 3H); 5.14 (m, 2H); 6.12 (bs, 1H); 6.36 (bs, 1H); 7.00 (bs, 1H); 7.17 (bs, 1H); ^{13}C NMR (125 MHz, $CDCl_3$/Pyridine-d_5 1/1) δ: 16.0; 16.8; 17.7; 25.7; 26.5; 26.8; 33.1; 39.8; 41.8; 121.1; 123.7; 124.5; 125.3; 126.2; 127.9; 131.1; 135.7; 144.6; 144.8; 146.8; 167.6; HRMS (ESI, MeOH) calculated for $C_{21}H_{31}N_2O_2$ $[M+H]^+$: 343.2386; found: 343.2372.

*5,9,13-Trimethyl-3-(1-methyl-1 H-imidazol-2-yl)-tetradeca-4,8,12-trienoic acid (***14d***):* Prepared according general procedure I on **13d** (50 mg, 0.125 mmol) with SiO_2 (680 mg). After preparative TLC (CH_2Cl_2/MeOH : 9/1) **14d** was isolated as a colorless oil (29.0 mg, 67% yield); IR (CH_2Cl_2) ν: 3390; 2965; 2916; 2857; 1714; 1383 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$/Pyridine-d_5 1/1) δ: 1.53 (bs, 3H); 1.55 (bs, 3H); 1.63 (bs, 3H); 1.78 (bs, 3H); 1.90-2.11 (m, 8H); 2.86 (dd, 1H, J = 5.5 Hz and J' = 16.0 Hz); 3.42 (dd, 1H, J = 8.5 Hz and J' = 16.0 Hz); 3.55 (s, 3H); 4.33 (m, 1H); 5.08 (m, 2H); 5.34 (d, 1H, J = 9.5 Hz); 6.82 (bs, 1H); 7.01 (bs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$/Pyridine-d_5 1/1) δ: 16.2; 16.5; 17.8; 25.9; 26.6; 26,9; 32.9; 33.1; 39.7; 39.9 (2C); 121.1; 124.0; 124.1; 124.7; 125.5; 131.2; 135.3; 137.3; 150.0; 174.3; HRMS (ESI, MeOH) calculated for $C_{21}H_{31}N_2O_2$ $(M-H)^-$: 343.2386; found: 343.2380.

*2-[3,7,1-Trimethyl-1-(1-methyl-1H-imidazol-2-yl)-dodeca-2,6,10-trienyl]-succinic acid (***2d***):* Prepared according general procedure I on **15d** (41 mg, 0.08 mmol) with SiO_2 (420 mg). After preparative TLC (EtOAc/MEK/HCO_2H/H_2O :

5/5/0.3/0.3) **2d** was isolated as a colorless oil (14.5 mg, mixture of 2 diastereoisomer couples, 45% yield); IR (CH_2Cl_2) ν : 3428; 2922; 2852; 1722; 1712; 1384; ^{1}H NMR (300 MHz, $CDCl_3$/Pyridine-d_5 1/1) δ: **2dA**: 1.50 (bs, 3H); 1.53 (bs, 3H); 1.61 (bs, 3H); 1.76 (bs, 3H); 1.88-2.08 (m, 8H); 2.74 (dd, 1H, J = 7.0 Hz and J' = 17.0 Hz); 3.16 (dd, 1H, J = 7.0 Hz and J' = 17.0 Hz); 3.60 (s, 3H); 3.75 (m, 1H); 4.36 (dd, 1H, J = 4.5 Hz and J' = 10.5 Hz); 5.05 (m, 2H); 5.43 (d, 1H, J = 10.5 Hz); 6.96 (bs, 1H); 7.04 (bs, 1H); **2dB**: 1.54 (bs, 3H); 1.55 (bs, 3H); 1.63 (bs, 3H); 1.77 (bs, 3H); 1.90-2.16 (m, 8H); 3.19 (m, 2H); 3.82 (s, 3H); 4.15 (m, 1H); 4.81 (m, 1H); 5.09 (m, 2H); 5.76 (d, 1H, J = 10.5 Hz); 7.16 (bs, 2H); ^{13}C NMR (75 MHz, $CDCl_3$/Pyridine-d_5 1/1) δ: **2dA**: 16.2; 16.9; 17.9; 25.9; 26.7; 27.0; 33.5; 35.2; 37.4; 39.8; 39.9; 45.7; 119.8; 122.1; 123.9; 124.1; 124.7; 131.1; 135.8; 141.3; 149.2; 174.6; 174.9; **2dB**: 16.2; 16.8; 17.7; 25.7; 25.8; 26.9; 33.9; 34.2; 35.1; 39.7; 39.8; 45.3; 120.4; 121.1; 121.6; 123.6; 124.7; 131.1; 135.5; 141.1; 150.3; 174.7; 175.8; HRMS (ESI, MeOH) calculated for $C_{23}H_{33}O_4N_2$ $[M-H]^-$: 401.2440; found : 401.2444.

*Synthesis of (2E,4E,8E)-ethyl 5,9,13-trimethyltetradeca-2,4,8,12-tetraenoate (***21***):* Triethyl phosphonoacetate **20** (674 µL, 3.4 mmol, 1.5 equiv.) was added to a cooled (0°C) suspension of NaH (60% in oil, 155 mg, 3.9 mmol, 1.7 equiv.) in anhydrous THF (28 mL) under argon. After 10 min at 0°C and 30 min at room temperature, a solution of farnesal **4c** (504 mg, 2.3 mmol) in anhydrous THF (4.5 mL) was added. The reaction was stopped after stirring 4h30 at room temperature by addition of HCl 10%. After standard work-up, the residue was purified by column chromatography on silica gel (Heptane/CH_2Cl_2 : 7/3) to afford **21** (482 mg, 74% yield) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.28 (t, 3H, J = 7.0 Hz) ; 1.59 and 1.67 (bs, 6H) ; 1.59 (bs, 3H) ; 1.89 (bs, 3H) ; 1.93-2.11 (m, 4H) ; 2.15 (m, 4H) ; 4.19 (q, 2H, J = 7.0 Hz) ; 5.07 (m, 2H) ; 5.77 (d, 1H, J = 15.0 Hz) ; 5.98 (d, 1H, J = 11.5 Hz) ; 7.57 (dd, 1H, J = 11.5 Hz and J' = 15.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 14,7; 16,3; 17,7; 18.0; 26.0; 26.5; 27.0; 40.0; 40.6; 60.4; 119.1; 123.6; 124.5; 131.7; 136.2; 141.3; 150.0; 168.0. HRMS (ESI, MeOH-CH_2Cl_2) calculated for $C_{19}H_{30}O_2Na$ $[M+Na]^+$: 313.2144; found : 313.2122.

*Synthesis of (4E,8E)-ethyl 5,9,13-trimethyltetradeca-4,8,12-trienoate (***24***):* Ethyl acetate (0.8 mL, 8.2 mmol, 2.05 equiv.) was added to a cooled (-110°C) suspension of CuI (3.2 g, 16.8 mmol, 4.2 equiv.) in THF (30 mL) under argon. After few minutes, a LDA solution (0.82 M in THF, 8.2 mmol, 2.05 equiv.) previously prepared at -78°C, was added dropwise. After stirring 2h at -110°C, farnesyl bromide **23** (1.08 mL, 4 mmol) was added and the reaction mixture was stirred 2 h at -110°C. The reaction was quenched by saturated ammonium chloride. After standard work-up with heptane, the residue was purified by column chromatography on silica gel (Heptane/EtOAc : 97/3 then Heptane/CH_2Cl_2, 3/7) to afford **24** (642 mg, 69% yield) as a yellowish oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.25 (t, 3H, J = 7.1 Hz); 1.59 and 1.68 (bs, 6H); 1.59 (bs, 3H); 1.62 (bs, 3H); 1.92-2.12 (m, 8H); 2.31 (m, 4H); 4.12 (q, 2H, J = 7.0 Hz); 5.10 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 14.6; 16.3; 18.0 ; 26.0; 23.9; 26.9 ; 27.1; 34.9; 40.0; 60.5; 122.7; 124.4 ; 124.7; 131.5; 135.3; 136.8; 173.7. HRMS (ESI, MeOH-CH_2Cl_2) calculated for $C_{19}H_{32}O_2Na$ $[M+Na]^+$: 315.2300; found: 315.2299.

*Synthesis of (E)-diethyl 2-((2E,6E)-3,7,11-trimethyldodeca-2,6,10-trienylidene) succinate (***26***):* A solution of diethyl 2-(diethoxyphosphoryl)succinate **25** (500 mg, 1.6 mmol, 1.5 equiv.) in anhydrous THF (0.7 mL) was added to a cooled (0°C) suspension of NaH (60% in oil, 155 mg, 3.9 mmol, 1.7 equiv.) in anhydrous THF (0.7 mL) under argon. After 10 min at 0°C and 30 min at room temperature, a solution of farnesal **4c** (234 mg, 1.1 mmol) in anhydrous THF (2.2 mL) was added. The reaction was stopped after stirring 4h30 at room temperature by addition of HCl 10%. After standard work-up, the residue was purified by column chromatography on silica gel (Heptane/CH_2Cl_2 : 4/6) to afford **26** (271 mg, 66% yield) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.24 (t, 3H, J = 7.0 Hz); 1.28 (t, 3H, J = 7.0 Hz); 1.59 (bs, 3H); 1.59 and 1.66 (bs, 6H); 1.91 (bs, 3H); 1.96 (m, 2H); 2.04 (m, 2H); 2.17 (m, 4H); 3.42 (s, 2H); 4.13 (q, 2H, J = 7.0 Hz); 4.21 (q, 2H, J = 7.0 Hz); 5.08 (m, 2H); 6.06 (d, 1H, J = 12.0 Hz); 7.64 (d, 1H, J = 12.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 14.5; 14.6; 16.4; 17.9; 18.0; 26.0; 26.7; 27.0; 32.8; 40.0; 41.1; 61.0; 61.1; 120.3; 122.2; 123.6; 124.6; 131.7; 136.2; 137.2; 151.0 168.1; 171.4. HRMS (MALDI-TOF, CH_2Cl_2) calculated for $C_{23}H_{37}O_4$ $[M+H]^+$: 377.2691; found : 377.2701.

*Synthesis of diethyl 2-((2E,6E)-3,7,11-trimethyldodeca-2,6,10-trienyl)succinate (***28***):* Prepared according to general procedure E on **26** (60 mg, 0.16 mmol) in anhydrous methanol (1.3 mL) with Mg (67 mg, 2.8 mmol). After preparative TLC (Heptane/EtOAc : 9/1) **28** was isolated as a colorless oil (21 mg, 38% yield) as a mixture of ethyl-methyl and dimethyl esters (13 and 25% respectively); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.26 (t, 3H, J = 7.0 Hz); 1.60 (bs, 18H); 1.69 (bs, 18H); 1.95-2.10 (m, 24H); 2.27 (dt, 3H, J= 8.0 and 14.5 Hz); 2.37 (dt, 3H, J= 6.5 and J' = 14.5 Hz); 2.45 (m, 3H); 2.66-2.73 (m, 3H); 2.81-2.92 (m, 3H); 3.67 (s, 9H); 3.70 (s, 6H); 4.16 (q, 2H, J = 7.0 Hz); 5.09 (m, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 14.5; 16.3; 16.4; 16.5; 18.0; 26.0; 26.9; 27.1; 30.4; 35.2; 35.3; 40.1; 41.8; 41.9; 52.0; 52.2; 52.4; 60.9; 120.3; 120.4; 124.3; 124.7; 131.6; 135.6; 138.8; 138.9; 172.9; 173.0; 174.9; 175.4. HRMS (ESI, MeOH-CH_2Cl_2) calculated for $C_{21}H_{34}O_4Na$ $[M+Na]^+$: 373.2355; found : 373.2335 for the dimethyl ester.

General procedure J. Saponification of the farnesyl pyrophosphate analogues

A solution of sodium hydroxide 2M (1.25 mmol, 1.6 equiv.) was added to the ester in ethanol (3 mL) and the reaction mixture was heated at 70°C for 14 hours. After cooling, the reaction mixture was acidified with HCl 1M and extracted twice with ethyl acetate. The organic layers were pooled, washed with brine, dried and concentrated. The crude product was purified by reverse phase (C18) column chromatography (H_2O/CH_3CN : 80/20 to 0/100) to afford the corresponding acid **16**, **17**, **18** and **19**.

*(2E,4E,8E)-5,9,13-trimethyltetradeca-2,4,8,12-tetraenoic acid (***16***) :* Prepared according general procedure J on **21** (230 mg, 0.79 mmol). Compound **16** (86.9 mg, 42% yield)

was obtained after purification as a colorless oil; ^{1}H NMR (300 MHz, CD_3OD) δ: 1.62, 1.64 and 1.69 (bs, 9H); 1.93 (bs, 3H); 1.97-2.14 (m, 4H); 2.22 (m, 4H); 5.12 (m, 2H); 5.78 (bd, 1H, J = 15.0 Hz); 6.07 (d, 1H, J = 11.5 Hz); 7.62 (dd, 1H, J = 11.5 Hz and J' = 15.0 Hz). ^{13}C NMR (75 MHz, CD_3OD) δ: 17.0; 18.2; 18.6; 26.8; 28.1; 28.6; 41.7; 42.1; 120.9; 125.4; 125.5; 126.2; 133.0; 137.7; 143.5; 151.9; 172.0. HRMS (MALDI-TOF, CH_3OH-CH_2Cl_2) calculated for $C_{17}H_{26}O_2Na$ $[M+Na]^+$: 285.1830; found : 285.1839.

*(4E,8E)-5,9,13-trimethyltetradeca-4,8,12-trienoic acid (***17***) :* Prepared according general procedure J on **24** (253 mg, 0.87 mmol). Compound **17** (38.9 mg, 17% yield) was obtained after purification as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.60 (bs, 6H); 1.69 (bs, 3H); 1.69 (bs, 3H); 1.93-2.14 (m, 8H); 2.28-2.44 (m, 4H); 5.11 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 16.4; 18.0; 26.0; 26.3; 26.9; 27.1; 34.6; 40.0; 40.1; 122.3; 124.4; 124.7; 131.6; 135.5; 137.4; 180.0. HRMS (ESI, CH_3OH) calculated for $C_{17}H_{27}O_2$ $[M-H]^-$: 263.2011; found : 263.1971.

*(E)-2-((2E,6E)-3,7,11-trimethyldodeca-2,6,10-trienylidene) succinic acid (***18***) :* Prepared according general procedure J on **26 (**52 mg, 0.14 mmol). Compound **18** (29.6 mg, 67% yield) was obtained after purification as a white amorphous solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.60 (bs, 3H); 1.61 (bs, 3H); 1.69 (bs, 3H); 1.95 (bs, 3H); 1.97-2.09 (m, 4H); 2.13-2.27 (m, 4H); 3.47 (s, 2H); 5.09 (m, 2H); 6.10 (bd, 1H, J = 12.0 Hz); 7.78 (d, 1H, J = 12.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 16.4; 17.0; 18.1; 26.0; 26.7; 27.0; 33.3; 40.0; 41.2; 120.2; 120.6; 123.5; 124.6; 131.7; 136.4; 139.9; 153.4; 173.9; 178.0. HRMS (ESI, CH_3OH) calculated for $C_{19}H_{27}O_4$ $[M-H]^-$: 319.1909; found : 319.1895.

*2-((2E,6E)-3,7,11-trimethyldodeca-2,6,10-trienyl)succinic acid (***19***) :* Prepared according general procedure J on **28** (20 mg, 0.06 mmol). Compound **19** (4.6 mg, 25% yield) was obtained after purification as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.63 (bs, 6H); 1.66 (bs, 3H); 1.70 (bs, 3H); 1.98-2.17 (m, 8H); 2.31-2.41 (m, 2H); 2.46 (dd, 1H, J = 5.0 Hz and J' = 16.5 Hz); 2.61 (dd, 1H, J = 9.0 Hz and J' = 16.5 Hz); 2.75-2.82 (m, 1H); 5.10-5.20 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 17.0; 17.2; 18.6; 27.7; 28.4; 28.7; 32.0; 37.5; 41.7; 41.8; 44.3; 123.0; 126.2; 126.4; 133.0; 137.0; 139.9; 178.1; 180.1. HRMS (ESI, CH_3OH-CH_2Cl_2) calculated for $C_{19}H_{29}O_4$ $[M-H]^-$: 321.2066; found : 321.2045.

Biological assays

Yeast FTase assay

Assays were realized on 96-well plates, prepared with Biomek NKMC and Biomek 3000 from Beckman Coulter and read on Wallac Victor fluorimeter from Perkin-Elmer. Per well 20 µL of farnesyl pyrophosphate (10 µM) was added to 180 µL of a solution containing 2 µL of varied concentrations of **11-15a-d**, **2a-d** and **16-19** (dissolved in DMSO) and 178 µL of a solution composed by 0.1 mL of partially purified recombinant yeast FTase (2.2 mg/mL) and 7.0 mL of Dansyl-GCVLS peptide (in the following buffer: 5.8 mM DTT, 6 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 s per well, 20 repeats) at 30 °C with an excitation filter at 340 nm and an emission filter at 486 nm. Each measurement was realized twice as duplicate or triplicate.

Production of recombinant human FTase

To obtain recombinant heterodimeric human FTase in *Escherichia Coli*, the two subunits were expressed as a translationally coupled operon under transcriptional control by the bacteriophage T7 in the plasmid pET-DUET-1 (Novagen). Translational coupling was achieved by placing the alpha subunit coding sequence upstream of the ß subunit coding sequence. A $(His)_6$-tag was fused to the C-terminal part of the alpha subunit, allowing affinity purification of the heterodimer from *E. Coli* extracts.

The transformed strain BL21 RIL(DE3) was grown at 37°C in 14 liters of LB-rich medium with 50 µg.mL^{-1} ampicillin and induced at a cell density of 0.6 A_{600} with 1 mM isopropyl-ß-D-thiogalactopyranoside. After 12-15 h, the cells were collected by centrifugation. A fraction (22.5 g) was diluted in 50 mL buffer A (25 mM Tris,HCl pH 7.4, 0.5 M NaCl) plus protease inhibitors and lysed with Dyno mill (0.2 mm) 25 times for 30 s at 4 °C, 4500 rpm. The lysate solution and rinsing (60 mL) were pooled and centrifuged at 10000 rpm (JA 25 50) for 20 min. The supernatant was loaded on a His crude column, (5 mL, Amersham) and eluted stepwise with buffer A and buffer B (25 mM Tris,HCl pH 7.4, 0.5 M NaCl, 0.5M imidazole): 0-4%B, 4-25%B, 25-100%B. The most active fractions (~80% pure) eluted at 25% buffer B were pooled, concentrated by ultrafiltration (YM30 filter) and stored in buffer A with 5% glycerol at 4°C.

Human FTase assay

Assays were realized on 96-well plates, as described for yeast FTase but Octyl-D-glucopyranoside (0.18%) was used instead of CHAPS and the solution contains 5 µL of partially purified human FTase (1.5 mg/mL) in 1 mL peptide solution.

The kinetic experiments have been realized under the same conditions either with FPP as varied substrate with constant concentration of Dns-GCVLS of 2 µM or with Dns-GCVLS as varied substrate with constant concentration of FPP of 5 µM. Non linear regression were made by KaleidaGraph 4.03 software.

Assay for in vitro inhibition of *P. falciparum* growth

The chloroquine-resistant strain FcB1/Colombia of *Plasmodium falciparum* was maintained *in vitro* on human erythrocytes in RPMI 1640 medium supplemented by 8% (v/v) heat-inactivated human serum, at 37°C, under an atmosphere of 3% CO_2, 6% O_2, 91% N_2 [38]. *In vitro* drug susceptibility assays were performed using a modification of the semi-automated microdilution technique of Desjardins *et al.* [39]. Drugs were prepared in DMSO at a 10 mM concentration. Compounds were serially diluted two-fold with 100 µL culture medium in 96-well plates. Asynchronous parasite cultures (100 µL, 1% parasitaemia and 1% final hematocrite) were then added to each well and incubated for 24 h at 37°C

prior to the addition of 0.5 μCi of [^{3}H]-hypoxanthine (GE Healthcare, France, 1 to 5 Ci·mmol/mL) per well. After a further incubation of 24 h, plates were frozen and thawed. Cell lysates were then collected onto glass-fiber filters and counted in a liquid scintillation spectrometer. The growth inhibition for each drug concentration was determined by comparison of the radioactivity incorporated in the treated culture with that in the control culture maintained on the same plate. The concentration causing 50% growth inhibition (IC_{50}) was obtained from the drug concentration-response curve and the results were expressed as the mean values ± standard deviations determined from several independent experiments.

Results and discussion

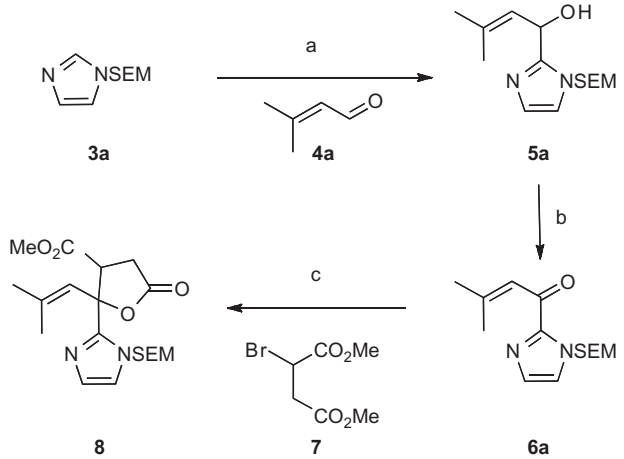
Chemistry

A convergent synthesis consisting on the addition of the succinic moiety to the imidazole ring branched with the prenyl group has first been explored (Scheme 2). The synthetic pathway was undertaken for compound **2a** with one isoprenyl unit (n = 0) and a free amine. Our starting material was the N-SEM-imidazole **3a**, easily obtained by classical protection of the N-1 imidazole with SEM-Cl.[13]

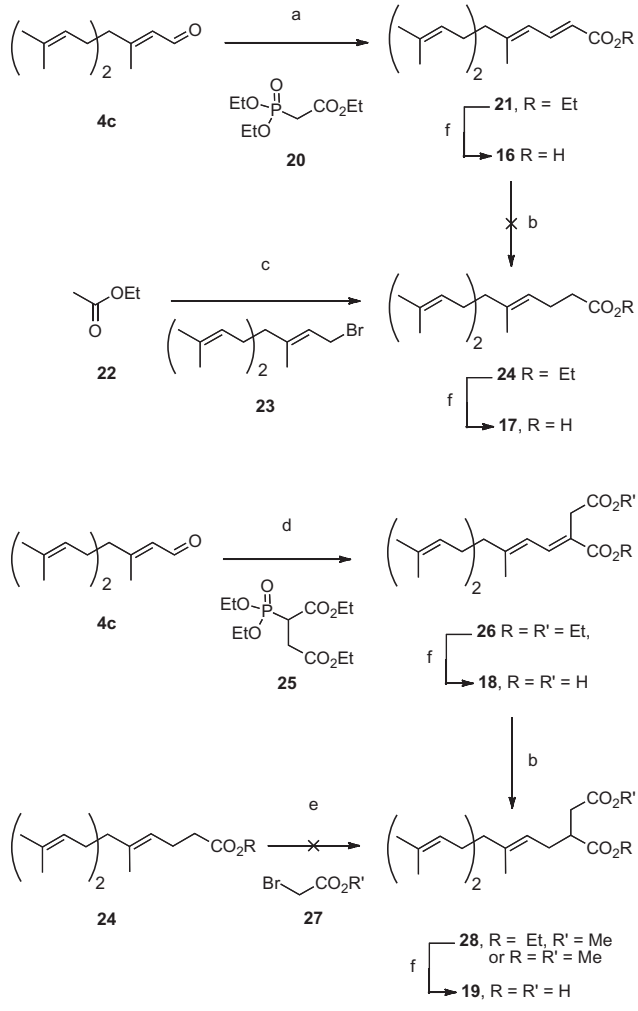
The deprotonation with *n*BuLi of the N-1 protected imidazole ring **3a** [14] followed by the addition on the 3-methylcrotonaldehyde **4a** led to the allylic alcohol **5a** which was easily oxidized by MnO_2 [15]. The direct addition of the carbanion on the methyl ester of 3-methylcrotonic acid was considered but the high reactivity of the formed ketone **6a** to nucleophilic addition led to a mediocre yield (26%). To introduce the succinic moiety two reaction types were applied. In the classic Horner-Wadsworth-Emmons procedure, the diethyl phosphonosuccinic acid diethyl ester [16] didn't react with the α,β-insaturated ketone **6a**. Whereas the Reformatsky reaction between the 2-bromo-succinic acid dimethyl ester **7** and the α,β-insaturated ketone **6a** in presence of activated zinc in an ultrasound bath [17] led to the lactone **8**. This lactone resulted from the attack of the alcoholate formed during the Reformatsky reaction [18]. Our efforts to avoid the formation of the lactone **8** or to open it were unsuccessful.

Therefore, we decided to build up the succinic motif from two acetic units (Scheme 3). The first unit was introduced by a Reformatsky reaction between the ketones **6a-d** and the *tert*-butyl bromoacetate **9**. Then, $POCl_3$ in pyridine [19] dehydrated efficiently the tertiary hydroxyesters **10a-d** to the corresponding conjugated Z-alkenes **11a-d** which were regioselectively reduced by magnesium in dry methanol [20] in good yields. Finally, the second acetic unit was introduced by alkylation at the α-position of the saturated esters **13a-d** using LDA and the *tert*-butyl bromoacetate **9**.

The deprotection step of **11a-d**, **13a-d** and **15a-d** appeared more complex than expected. Indeed, the final double bond of the prenyl group presented a higher reactivity in the case of the geranyl (n = 1) and farnesyl (n = 2) moieties. TFA [21] and formic acid [22] provided the expected deprotected



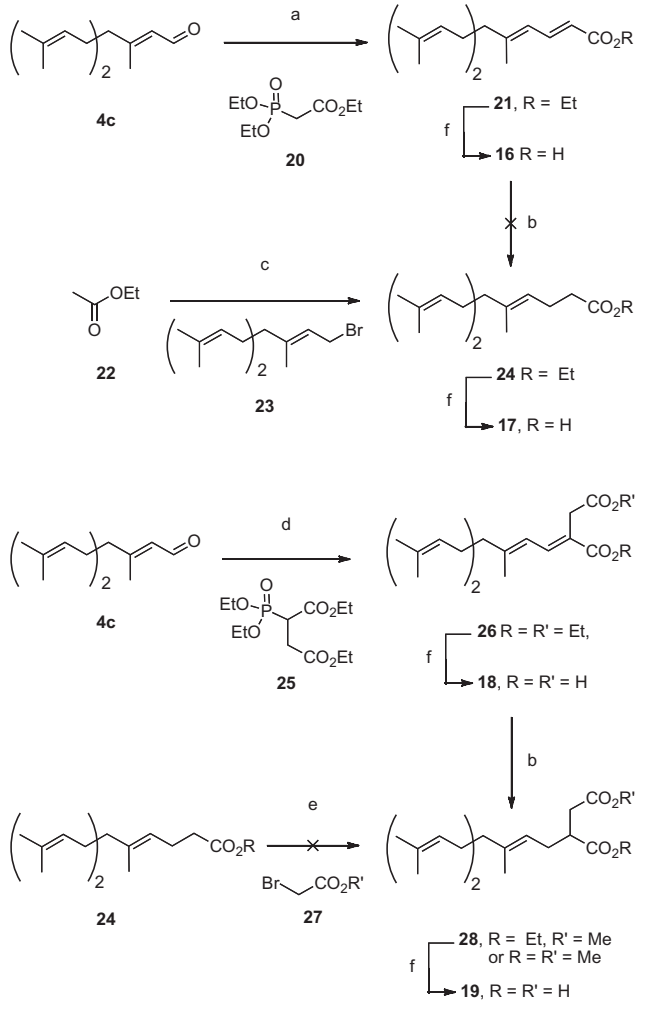
Scheme 2. Convergent synthesis pathway. a) *n*BuLi, THF, –78°C, 50 min then addition of **4a**, –78°C, 20 min to RT 1h (68%); b) MnO_2, THF, 0°C, 2h (100%); c) **7**, THF, Zn, ultrasounds, 40°C, 4h30 (63%).



Scheme 3. Synthesis of farnesyl acids. a) NaH and **20**, THF, 0°C, 10 min then 30 min RT, then addition of **4c**, RT, 4h30 (74%); b) Mg, MeOH, RT, 4h (38%); c) CuI, LDA, THF, 2h, -110°C, then addition of **23**, -110°C, 2h (69%); d) NaH and **25**, THF, 0°C, 10 min then RT, 40 min, then addition of **4c**, RT, 2h15 (66%); e) LDA, THF, –78 °C, 35 min then addition of **27**, –78°C; f) NaOH 2M, EtOH, 70 °C, 15h (77-100%).

compounds **12a-b**, **14a-b** and **2a-b** from the compounds **a** (R = SEM, R' = *tBu*, n = 0) and **b** (R = CH_3, R' = *tBu*, n = 0) respectively. However, in the case of the compounds **c** (R = CH_3, R' = *tBu*, n = 1) and **d** (R = CH_3, R' = *tBu*, n = 2), only silica in refluxing toluene [23] provided the desired compounds **12c-d**, **14c-d** and **2c-d**. In the TFA and formic acid conditions, we observed the addition of the carboxylate group of the acidic reagent on the terminal double bond of compounds **c** and **d** [24].

To study the influence of the imidazole ring on the activity of compounds **2d**, **12d** and **14d**, we also synthesized the corresponding FPP analogues **16**, **17**, **18** and **19** according the synthetic pathway described in Scheme 4. Compound **21** was obtained by a Horner-Wadsworth-Emmons reaction with triethylphosphonoacetate **20** on the aldehyde **4c**. Reduction of the double bond with magnesium in dry methanol did not afford the desired compound **24** in sufficient yield. This derivative was finally obtained by a SN_2 reaction of the anion of ethyl acetate **22** on farnesyl bromide **23** [26]. Contrary to compounds **13**, it was impossible to obtain compound **28** by alkylation of **24** with bromo acetate. Therefore we synthesized compound **26** by a Horner-Wadsworth-Emmons reaction with tetraethylphosphonosuccinate **25** [10] and reduced the conjugated double bond by magnesium in dry methanol. As observed with compound **21**, the yield was moderate and we obtained a mixture of transesterified compounds **28**. It is likely that the presence of the imidazole ring in compounds **12** favored the reduction of this double bond by additional conjugation. Compounds **21**, **24**, **26** and **28** were saponified in warm sodium hydroxide in ethanol to afford the corresponding acids **16**, **17**, **18** and **19** in good to excellent yields.



Scheme 4. Second synthetic pathway. a) *n*BuLi, THF, –78°C, 45 min then addition of **4a-c**, –78°C, 20 min to 2h30 to RT 1h (68-100%); b) MnO_2, THF, 0°C, 2h (80-100%); c) **9**, THF, Zn, ultrasounds, 40°C, 5h (51-79%); d) $POCl_3$, Pyridine, 0°C to RT 14h (75-85%); e) for **a** (R = SEM, n = 0) TFA, CH_2Cl_2, RT, 5h, for **b** (R = CH_3, n = 0) HCO_2H, RT, 19h and for **c** (R = CH_3, n = 1) and **d** (R = CH_3, n = 2) SiO_2, toluene, reflux, 14h; f) Mg, MeOH, RT, 3h (62-80%); g) LDA, THF, –78°C, 35 min then addition of **9**, –78°C, 4h (42-72%).

Biological Evaluation

Inhibitory activity of compounds **11d**, **12a-d**, **13d**, **14a-d**, **15d** and **2a-d** was evaluated in a fluorescence-based assay [27] against yeast and human recombinant FTases [28, 29]. Results are summarized in Tables 1 and 2. The inhibition rate was measured at 10^{-3}M for the **a** and **b** series (Table 1) and IC_{50} was estimated for compounds which presented measurable activities in the **c** and **d** series and compared with the chaetomellic acid A activity measured under our conditions (Table 2).

The very similar results obtained in both **a** and **b** series (Table 1) indicate that the presence of a hydrogen or a methyl on the N-1 position of the imidazole ring does not change the interaction with FTase. Therefore, only the N-methylimidazole derivatives of the **c** and **d** series were studied. As expected, the farnesyl compounds (series **d**) are much more active than their geranyl analogues (series **c**). Indeed, they are able to realize more interactions with the hydrophobic pocket. Concerning the acidic part, the succinic moiety (**2d**) shows its superiority to mimic the FPP pyrophosphate compared to a monoacid unit (**12d**, **14d**). Generally, the presence of the free carboxylic acid (**12d**, **14d** and **2d**) led to a better inhibition. Concerning the ester analogues (**11d**, **13d** and **15d**) it is surprising that the unsaturated monoester **11d** is the most active compound whereas the corresponding acid **12d** is less active than the succinic analogue **2d**. However, the ester activities are weak and it would not be meaningful to draw conclusions from these results. The activity of compounds **16-19** also shows that a

Table 1. Activity on yeast FTase of **a** and **b** compounds (n = 0).

Compounds	R	Inhibition at 10^{-3}M	Compounds	R	Inhibition at 10^{-3}M
12a	H	8%	**12b**	Me	8%
14a	H	21%	**14b**	Me	25%
2a	H	Inactive	**2b**	Me	Inactive

Table 2. Activity on recombinant yeast and human FTase of **c** and **d** compounds (R = CH_3 and FPP analogues).

Compounds	n	IC_{50}yeast FTase	IC_{50}human FTase
Chaetomellic acid[a]		0.34 ± 0.03 μM	0.175 ± 0.01μM
11d	2	600 ± 100 μM	300 ± 60 μM
12c	1	inactive	ND[b]
12d	2	130 ± 15 μM	175 ± 15 μM
13d	2	inactive	inactive
14c	1	inactive	ND
14d	2	700 ± μM	500 ± 40 μM
15d	2	ND	700 ± 65 μM
2c	1	850 ± 50 μM	590 ± 45 μM
2d	2	28 ± 3 μM	12 ± 0.8 μM
16	2	40 ± 5 μM	130 ± 15 μM
17	2	42 ± 7 μM	170 ± 20 μM
18	2	16 ± 1.2 μM	6.5 ± 1.0 μM
19	2	2.5 ± 0.5 μM	5.4 ± 0.9 μM

a: IC_{50} measured under our conditions.
b: not determined.

diacid is more active than a monoacid but here the presence of the double bond has little influence on the activity even if the more active compound is the succinic acid **19**. Finally, these results show that the presence of the imidazole ring unexpectedly does not enhance the activity.

In order to explain this result, kinetic studies were performed with compound **2d** to precise the binding mode of our imidazole containing compounds.

As shown in Figure 3, compound **2d** is competitive to FPP (K_i^{app} = 10.5 μM) like chaetomellic acid A (K_i^{app} = 0.19 μM measured in our assay conditions) and uncompetitive to the peptidic substrate DnsGCVLS (K_i^{app} = 160 μM). Therefore, our imidazole containing compounds are unable to bind to the peptide binding site. The imidazole ring apparently can not interact efficiently with the zinc atom as was initially planned. This explains the similar activity we observed for the succinic analogues **2d** and **19**.

Two reasons can be put forward: firstly, the distance between the farnesyl moiety and the imidazole ring is too

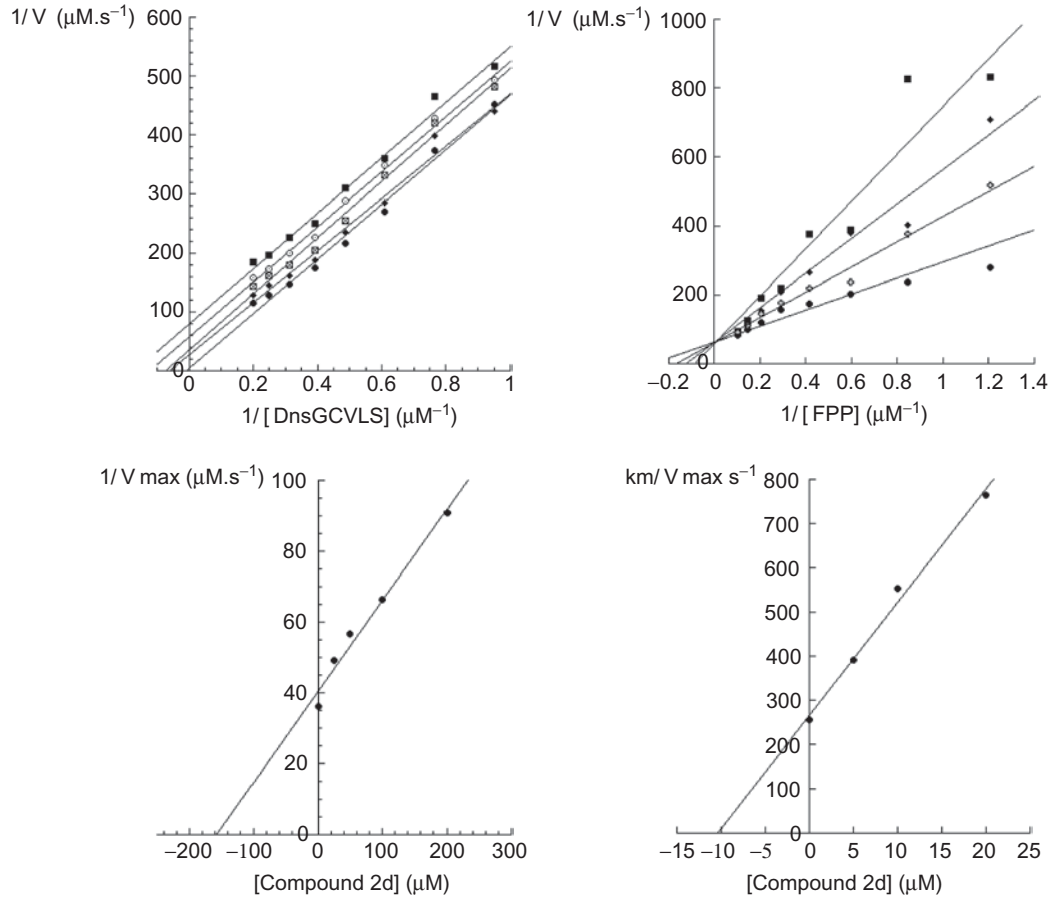


Figure 3. Kinetic experiments on compound **2d**. a) double reciprocal with DnsGCVLS as the varied substrate and fixed concentration of FPP. Concentrations of **2d** were: 200μM (■), 100μM (⊙), 50μM (⊠), 25μM (◆), 0μM (●); b) double reciprocal with FPP as the varied substrate and fixed concentrations of DnsGCVLS. Concentrations of **2d** were: 20μM (■), 10μM (◆), 5 μM (+), 0μM (●); c) K_i^{app} measured from competition with DnsGCVLS; d) K_i^{app} measured from competition with DnsGCVLS; d) $K_{i,}^{app}$ measured from competition with FPP.

short to allow zinc binding or/and the imidazole ring might not be well oriented to achieve this interaction with the zinc atom. Thus, to improve the activity of compound **2d**, the imidazole ring could be attached further from the farnesyl group or/and functionalized on another position.

Though less active than chaetomellic acid A, we have synthesized new succinic analogues of FPP with IC_{50} and K_i in the micromolar range. When compared to the other dicarboxylic analogues of FPP described in the literature, these compounds are among the most active ones [30-33].

All our derivatives of the **d** series were evaluated for their ability to block the *in vitro* growth of the intraerythrocytic form of *Plasmodium falciparum*. Only compound **15d** displayed activity against *P. falciparum* (IC_{50} = 30 ± 2 μM). It is generally observed that the esters are more active than the corresponding acids in cellular assays, because of differences in cell penetration. These results are in good agreement with the enzymatic assays where the succinyl derivative displayed the best activity.

Conclusion

We have synthesized twelve new compounds (type **2**) formed by an imidazole ring, a prenyl group and an acidic moiety. Some of them revealed encouraging inhibitory activities in the micromolar range against human or yeast FTase as well as against the growth of *Plasmodium falciparum*. Four analogues devoid of the imidazole ring have also been synthesized and evaluated showing a similar activity on FTase. These derivatives are not able to bind to both substrate binding sites but they are competitive FPP inhibitors with a rather good activity in this field. The structural difference with Chaetomellic acid A, relies on the absence of a double bond between the two carboxyl groups and a methyl on this double bond. It would be worth investigating other modifications on these analogues to find new more potent FPP inhibitors.

In our course of designing bisubstrate inhibitors, we have synthesized two series of compounds. The first series of compounds (type **1**) were only CaaX inhibitors and the series reported herein are only FPP inhibitors. Therefore a combination of both series would likely lead to the expected bisubstrate inhibitors. This is currently under investigation as well as modifications of the connecting position on the imidazole ring and of the length between the imidazole moiety and the FPP analogue part of the molecule.

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***Declaration of interest*:** The authors report no conflicts of interest.

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