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Fosmidomycin analogues with *N*-hydroxyimidazole and *N*-hydroxyimidazolone as a chelating unit†

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Fosmidomycin has been reported to have many biological activities as an antibacterial and antimalarial, along with being a herbicidal agent. Its unique mode of action involves the inhibition of a key step of the non mevalonate pathway by blockade of a crucial enzyme, the 1-deoxy-D-xylulose 5-phosphate reductoisomerase (DXR), whose expression is present in bacteria, plasmodium parasites and higher plants, but not in mammals. Herein we report the development of fosmidomycin and of FR-900098 constrained analogues belonging to an unusual heterocyclic based complexing subunit involving *N*-hydroxyimidazoles and cyclic *N*-hydroxyureas.

Introduction

During the late 1970s, fosmidomycin **1a**, also known under the acronym FR-31564, was isolated from *Streptomyces lavendulae* and first evaluated as a natural antibiotic in an early phase II study for the management of bacterial infections.[1] In an *in vitro* assay with the purified recombinant *E. coli* DXR, Seto *et al.* showed that a crucial enzyme of the initial step of the mevalonate-independant pathway of isoprenoid biosynthesis,[2] 1-deoxy-D-xylulose 5-phosphate reductoisomerase (DXR), was inhibited by fosmidomycin in a dose-dependent manner with an IC_{50} value of 8.2 nM.[3] Later, the natural antibiotic **1a** and its methyl derivative FR-900098 **1b** have been reported for their *in vitro* antimalarial activity against *Plasmodium falciparum* and *in vivo* in mice against *Plasmodium vinckei*.[4] The efficiency of both compounds against *Plasmodium falciparum* on human has been proved after the latter cured uncomplicated malaria.[5] Nevertheless, in human a high rate of recrudescence has been observed, which coupled to a moderate gastrointestinal absorption rate (20 to 40% after administration of an oral dose of 7.5 mg kg^{-1} of **1a**) and a short half-life *per os* (~2 h) has probably precluded fosmidomycin as a monotherapeutic agent towards malaria.[6] On the other hand, two other clinical trials using a combination of fosmidomycin–clindamycin gave promising results for a possible new treatment against malaria.[7] But at the best of our knowledge, no therapy using these two compounds has been commercialized yet and this prompted the search for better effective inhibitors.[8] This phosphonic acid antibiotic, also proved to be effective against the DXR enzyme of higher plants,[9] and its herbicide activity has even been patented.[10] The combined low mammalian toxicity (LD_{50} rats, oral > 8 g kg^{-1})[4] and high hydrophilic properties of the fosmidomycin **1a** and its acetyl analogue **1b** present a great interest to discover a novel class of compounds for herbicide applications. Consequently, both structures have been seen as valuable leads for the preparation of new inhibitors of DXR in higher plants. Due to considerable conformational rearrangement of DXR upon formation of the DXR–fosmidomycin complex, two sites are of a crucial importance for tight binding, selectivity and for the development of effective molecules.[11] The positively charged pocket binds the phosphonate group of fosmidomycin with a high specificity whereas an amphipathic region binds the hydroxamic acid through complexation with a divalent cation, generally magnesium. The hydrophobic region of the carbon backbone is considered as a modulatory region and is exploited by different classes of fosmidomycin-like inhibitors. Then, modulation of the cation-complexing unit along with the modulatory region offers fine-tuning possibilities.[12]

In this context, the 5-acyl-*N*-hydroxyimidazoles **2** were perceived as molecules having a highly potent complexing unit by comparison with the parent molecules **1a–b** (Fig. 1). Chelation based on acyl-*N*-hydroxyimidazoles **2** has without ambiguity interesting features.

First of all, the complexing moiety can be seen as a close pharmacophore of the bioactive metabolite, diketonitrile (DKN) which is referred to be an iron complexing agent and an inhibitor of the 4-hydroxyphenylpyruvate dioxygenase (HPPD), a ferrous iron metalloenzyme. DKN is generated by conversion in plants from isoxaflutole herbicide,[13] and the presence of a

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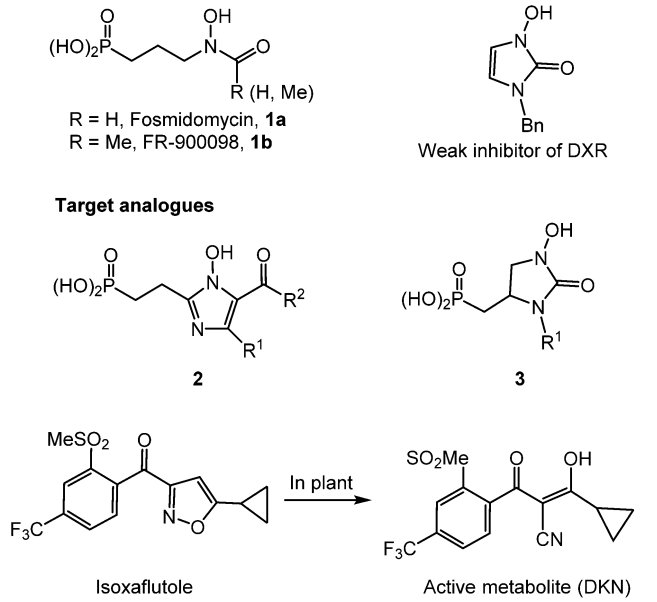
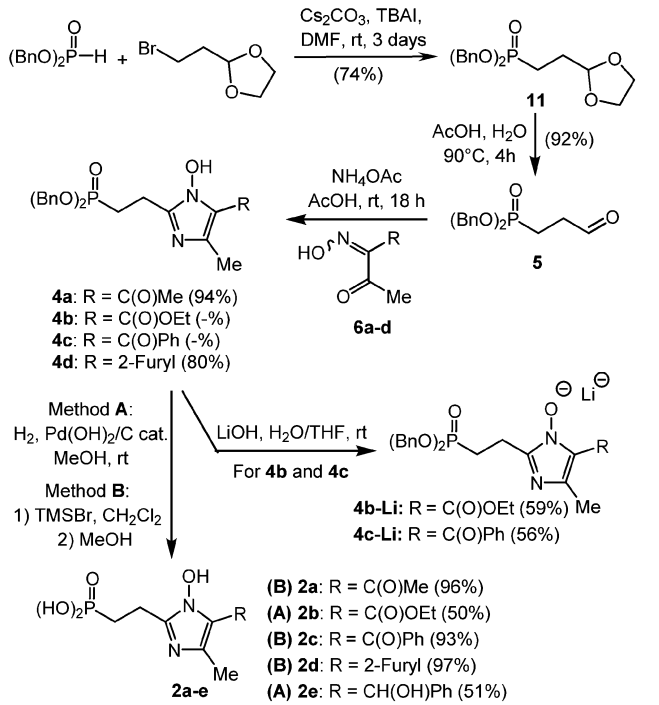


Fig. 1 Fosmidomycin **1a**, FR-900098 **1b** and a weak inhibitor of DXR. Sterically strained analogues **2** and **3**. Isoxaflutole and its active metabolite (DKN).

β-(1,3)-diketone moiety permits the creation of a stable ion–dipole interaction in the active enzyme active site (Fig. 1). Secondly, conformational restriction due to imidazole ring, constituted another feature justifying the preparation of acyl-*N*-hydroxyimidazoles **2**. In the same way, *N*′-benzyl-*N*-hydroxyurea was already reported as a modest of DXR (Fig. 1).[14] Nevertheless, the targeted cyclic *N*-hydroxyureas **3** can be considered as closer and conformationally modified fosmidomycin **1a** analogues. These original structures are fully different from those previously tested and could be present interesting features for the development of new herbicides. *N*-Hydroxyimidazoles **2** were obtained from the phosphonate **4**. The key step of the chemical pathway was a three-component cyclisation of substituted α-ketooximes **6** (ref. 15 and 16) with the 3-phosphonopronionaldehyde **5** (ref. 17) and ammonia (Fig. 2). In the other side, *N*-hydroxyurea derivatives **3** were intended to be synthesized by a 5-*exo*-trig cyclization according to the Baldwin rules of compound **8** coming from the phosphonoallylamine **9** by reaction with an isocyanate. The *O*-benzylhydroxyamino group should be accessible from reductive oximination of the β-phosphonoacrolein **10**. The last steps of the synthesis of **3** are the cleavage of the phosphonic ester functions and a critical hydrogenolysis of the *O*-benzyl protective group without cleavage of the N–O bond.

Results and discussion

The 4-dibenzylphosphono-propionaldehyde **5** was an expected intermediate for the preparation of the *N*-hydroxyimidazolyl derivatives **2** (Scheme 1). It was accessible by adapting a two-step sequence which started from the Michaelis–Becker reaction of dibenzyl phosphite with bromoethyldioxolane promoted by caesium carbonate (Cs_2CO_3) instead of sodium hydride. The resulting dibenzyl (2-(1,3-dioxolane-2-yl)ethylidene)phosphonate **11** was obtained in 74% yield. An acidic work-up using acetic acid in water gave almost quantitatively the aldehyde **5** without hydrolysis of the phosphonic ester function (Scheme 1).[17] In parallel, substituted ketooximes **6a–d** were prepared according to the reaction of the corresponding ketone



Scheme 1 Synthesis of hydroxyimidazoles **4a–d** and **2a–e**.

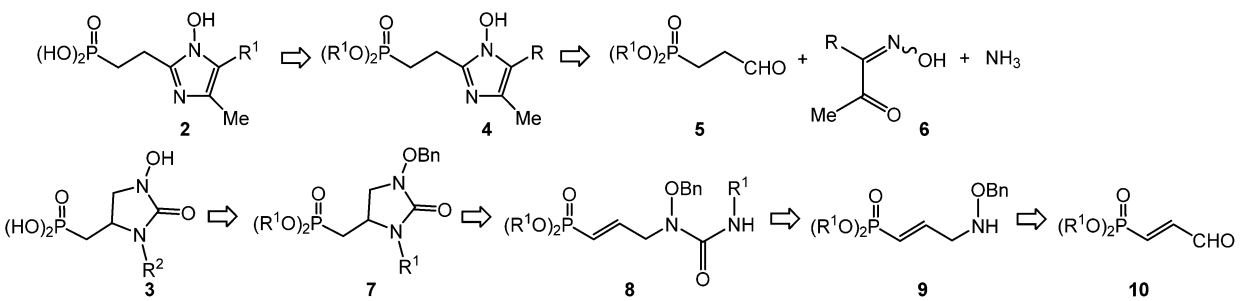


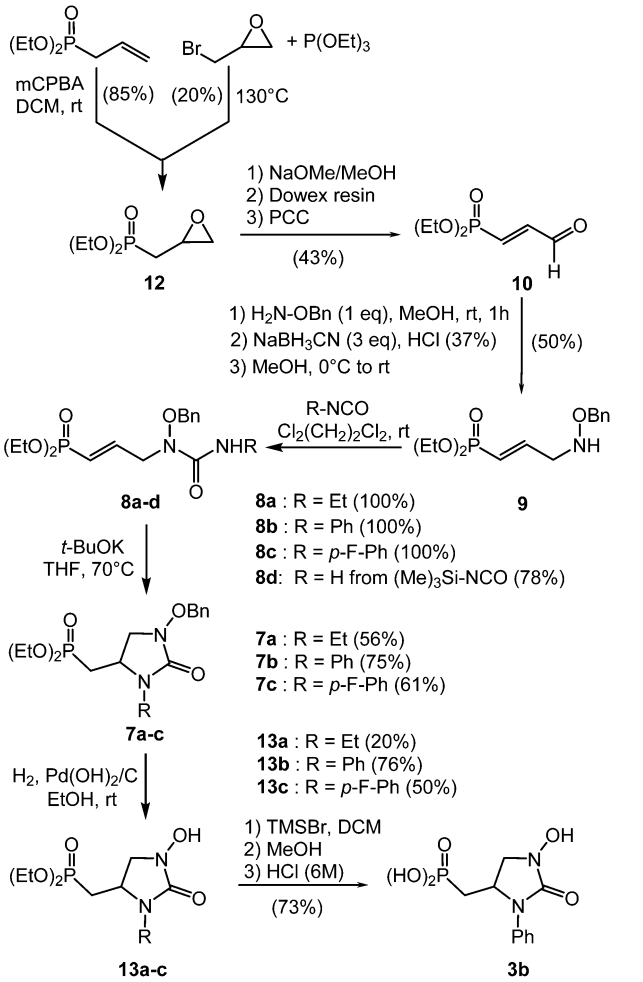
Fig. 2 Retrosynthetic pathways for targeted hydroxyimidazoles **2** and hydroxyimidazolones **3**.

with a hydrochloric solution of sodium nitrite in 41% to 86% yields.[15,16] The reaction of cyclisation between aldehyde **5** and α-hydroxyiminocarbonyl derivatives **6a–d** was performed in mild conditions using ammonium acetate as a source of ammonia in acetic acid at room temperature.[18] The desired products **4a–d** were obtained after flash chromatography in isolated yield ranging from 56% to 94%. Interestingly, when unsymmetrical diketone such as 2-hydroxyimino-1-phenyl-butane-1,3-dione **6c** was used, a full regioselectivity was observed, only affording the phenylketo-hydroxyimidazole **4c**. The benzyl protected phosphonic esters were not stable on storage for a long period of time giving products resulting from an internal nucleophilic substitution and forming a *N*-benzyloxyimidazolyl phosphonic acid monoester. Then reaction of **4b** and **4c** by addition of one equivalent of lithium hydroxide in a mixture water–THF (1 : 1) gave the stable lithium salts. An acid-base titration with a diluted aqueous solution of hydrogen chloride permitted to determine a pK_a around 5.5 for these products **4b**-Li and **4c**-Li. Several catalysts were tested for the cleavage of benzyl group of phosphonate **4a–d** (Pd/C, $Pd(OH)_2$/C and $Pd/BaSO_4$) keeping in mind to minimize the cleavage of the sensitive N–O bond.[19,20] The best results were observed with $Pd(OH)_2$/C in methanol at room temperature with hydrogen at 1.0 bar pressure (Scheme 2). Then, phosphonic acid **2b** was obtained after recrystallization in 50% yield. In the same conditions, the reaction on **4c** gave the alcohol **2e** in 51% yield by reduction of the ketone concomitantly with the cleavage of the benzyl group. To circumvent this side-reaction, bromo trimethylsilane has been used for **4a**, **4c** and **4d**, affording after solvolysis in methanol the desired phosphonic acids **2a**, **2c** and **2d**.

Slow crystallisation of the three final products into water gave single crystals which were analysed by X-ray experiments, confirming thus each structure (Fig. 3).[21] These compounds **2a–b** and **2d** existed as zwitterionic imidazoliums by protonation of nitrogen in position 3.

The molecular packing in the single crystals showed intermolecular hydrogen bonding between the *N*-hydroxy group and an oxygen atom of the phosphonic acid group. Surprisingly, no intramolecular hydrogen bonding between the *N*-hydroxy group and heteroatom on the substituent in position 5 was highlighted. The *N*-hydroxyimidazole **2b** crystallized with one molecule of water in a *P*21/*n* crystal cell. On the contrary *N*-hydroxyimidazole **2a** and **2d** crystallized without water and presented a crystal cell with *Pn* and *P*21/*n* space group symmetry, respectively.

For the second series of fosmidomycin analogues **3**, the 3-phosphonoacrolein intermediate **10** was obtained from oxiranylmethylphosphonate **12** (Scheme 2). For that purpose, two different methodologies have been tested. The first one was an Arbuzov reaction between epichlorhydrin and triethyl phosphite, nevertheless the reaction revealed unsuccessful forming diethyl methylphosphonate. When using epibromohydrin, oxiranylmethyl phosphonate **12** was isolated only in a low yield (20%, litt.[22] 61.9%). Therefore, another way using oxidation of commercial allylphosphonate with *m*-CPBA in dichloromethane has been preferred and furnished the expected epoxide **12** in multigram scale (Scheme 2).[23] The 3-phosphonoacrolein **10**



Scheme 2 Synthesis of protected *N*-benzyloxyimidazolones **7a–c** and **3c**.

synthesis was achieved according to a three-step sequence involving a treatment by sodium methoxide, followed by an elimination mediated by Dowex resin and subsequent oxidation of the resulting alcohol with PCC.[24] A reductive amination was finally performed using *O*-benzyl hydroxylamine in methanol and sodium cyanoborohydride. After flash chromatography, the phosphonoallyl benzyloxyamine **9** was isolated in 50% yield. The chemical diversity was introduced at the following step, by reaction of different isocyanates affording *N*-hydroxybenzylureas **8a–d** (78–100%). A favourable 5-*exo*-trig intramolecular Michael addition has been led with success, using potassium *tert*-butoxide (20 mol%) in tetrahydrofuran at 70 °C overnight. Cyclic imidazolones **7a**, **7b** and **7c** were isolated in 56 to 75% yields. For **7d** (R = H), two unidentified products were observed by ^{31}P NMR with an identical ratio, but none of them was separable by column chromatography on silica or by preparative HPLC, and therefore imidazolone **7d** characterization revealed unsuccessful. The deprotection of the benzyl group of **7a–c** was first tested by hydrogenolysis with palladium hydroxide in ethanol at room temperature and overnight. For all the reactions, we observed the cleavage of the N–O bond. For phenyl **7b** and *p*-fluorophenyl **7c** derivatives, the expected imidazolones

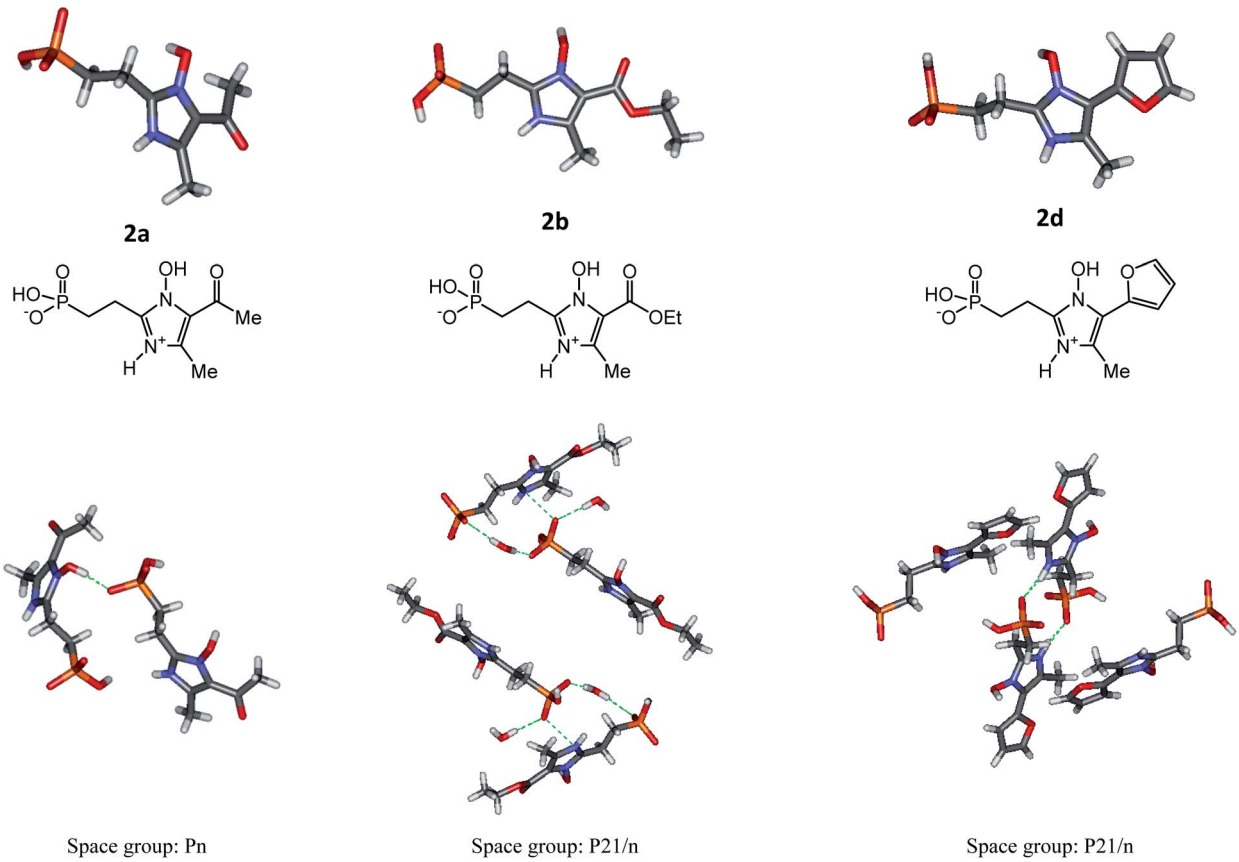


Fig. 3 Conformations adopted in the crystal for phosphinic acids **2a**, **2b** and **2d** and their crystal packing.

13b–c were obtained in 76% and 50% yields, respectively. Compound **13a** was successfully obtained by modification of the reaction conditions, using palladium hydroxide on charcoal in ethanol for only three hours. Nevertheless, only low yield (20%) of deprotected imidazolone **13a** was obtained after purification. Then, a final removal of both ethyl groups was performed on **13b** by treatment with trimethylsilyl bromide, followed by methanolysis. Nevertheless, despite a large excess of trimethylsilyl bromide (12 eq.) the reaction never reached the completion. Then a solution of hydrochloric acid (6 M) was added and the mixture was refluxed. After one night, fully deprotected phosphinic acid **3b** was obtained in 73% yield.

Experimental

General information

All air and/or water sensitive reactions were carried out under a nitrogen atmosphere. The solvents were dried using standard methods, distilled and stored under nitrogen. Reactions were monitored by ^{31}P NMR using DMSO-d_6 as internal references. Chromatography columns were performed on silica gel (Merck 60 AC. 35–70 μm). All NMR spectra were recorded on a BRUKER Ultra shield 400 plus instrument at 161.99 MHz for ^{31}P, 376.50 MHz for ^{19}F, 400.13 MHz for ^{1}H and 100.61 MHz for ^{13}C. The spectrometer used for low and high mass resolution spectra was electrospray ionization (ESI) WATERS Micromass Q-Tof spectrometer with as internal reference H_3PO_4 (0.1% in water–acetonitrile, 1 : 1).

Preparation of precursor

Dibenzyl (3-oxopropyl)phosphonate (5). Dibenzyl (3-oxopropyl)phosphonate (**5**)was prepared in two steps from dibenzylphosphite according to the procedure already described.[17] Nevertheless for the first step, cesium carbonate in the presence of iodide tetrabutylammonium has been used instead of sodium hydride.

Preparation of precursors

α-Ketooximes (6)

*3-Hydroxyimino-pentane-2,4-dione (**6a**) (ref. 15a and b)* At −5 °C, a solution of nitrite sodium (7.1 g, 0.10 mol) in water (20 mL) was added dropwise to a solution of acetyl acetone (10 g, 0.10 mol) in hydrochloric acid (50 mL, 2 M), and the mixture was allowed to stand for 20 min. The mixture was extracted with ethyl acetate (3 × 40 mL), then combined organic layers were dried over magnesium sulfate and concentrated under vacuum. The crude was purified by recrystallization from chloroform affording the expected compound as a white solid. Yield: 86% (11.1 g).

General procedure for 6b–d

At −10 °C, a solution of nitrite sodium (1.26 g, 1.77 mmol) in water (20 mL) was added dropwise over 30 min to a solution of ketone (1.61 mmol) in acetic acid (15 mL). The mixture was allowed to stand at room temperature for 2 h. Then, the product

was extracted with ethyl acetate (3 × 70 mL), combined organic layers were dried over magnesium sulfate and concentrated *in vacuo*. After purification, the compound was used directly in the next step because of its low stability.

Ethyl 2-(hydroxyimino)-3-oxobutanoate (6b) (ref. 15a and c) The purification by recrystallization from toluene afforded the expected compound. Yield: 74% (0.19 g).

2-(Hydroxyimino)-1-phenylbutane-1,3-dione (6c) (ref. 16) The purification by recrystallization from toluene afforded the expected compound. Yield: 62% (0.19 g).

1-(Furan-2-yl)-2-(hydroxyimino)butane-1,3-dione (6d) (ref. 16) The purification by recrystallization from toluene afforded the expected compound. Yield: 41% (0.12 g). ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 2.44 (s, 3H), 6.48 (dd, $^3J_{HH}$ = 3.1 Hz, $^3J_{HH}$ = 1.4 Hz, 1H), 7.28 (d, $^3J_{HH}$ = 3.1 Hz, 1H), 7.51 (d, $^3J_{HH}$ = 1.4 Hz, 1H). ^{13}C NMR (100.61 MHz, $CDCl_3$) δ 28.65, 112.62, 118.5, 147.31, 150.34, 156.67, 197.65, 200.39.

General procedure

***N*-Hydroxyimidazoles (4a–d).** A solution containing dibenzyl (3-oxopropyl)phosphonate (**5**, 1.0 g, 3.15 mmol), α-ketooxime (**6a–d**, 4.7 mmol) and ammonium acetate (315 mg, 4.1 mmol) in acetic acid (50 mL) was stirred at room temperature for 12 h. Water (40 mL) was poured into the reaction mixture and the mixture was extracted with ethyl acetate (80 mL). The combined organic layers were dried over magnesium sulfate and concentrated *in vacuo*.

Dibenzyl (2-(5-acetyl-1-hydroxy-1*H*-imidazol-2-yl)ethyl)phosphonate (4a). The resulting residue was purified by column chromatography (silica, EtOAc–EtOH (100 : 0 to 70 : 30)), to afford the desired product. Yield: 94% (1.26 g). ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 2.14–2.22 (m, 2H), 2.34 (s, 3H), 2.38 (s, 3H), 2.89–2.97 (m, 2H), 4.88 (dd, $^2J_{HH}$ = 11.8 Hz, $^3J_{HP}$ = 8.0 Hz, 2H), 4.95 (dd, $^2J_{HH}$ = 11.8 Hz, $^3J_{HP}$ = 8.8 Hz, 2H), 7.19–7.27 (m, 10H). ^{13}C NMR (100.61 MHz, $CDCl_3$) δ 16.60 (s), 18.53 (d, $^2J_{CP}$ = 3.6 Hz), 22.97 (d, $^1J_{CP}$ = 141.3 Hz), 28.19 (s), 67.41 (d, $^2J_{CP}$ = 6.1 Hz), 122.27 (s), 127.87 (s), 128.47 (s), 128.61 (s), 136.04 (d, $^3J_{CP}$ = 6.6 Hz), 141.66 (d, $^3J_{CP}$ = 15.3 Hz), 190.88 (s). ^{31}P NMR (161.97 MHz, $CDCl_3$) δ 31.14 (s). HRMS (ESI) *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{26}N_2O_5P$ 429.1579, found 429.1577.

Lithium 2-(2-(bis(benzyloxy)phosphoryl)ethyl)-5-(ethoxycarbonyl)-1*H*-imidazol-1-olate (4b-Li). The resulting residue was purified by column chromatography (silica, EtOAc–EtOH 100 : 0–70 : 30) to afford the *N*-hydroxyl intermediate **4b** (0.85 g, 1.85 mmol). **4b** was dissolved in tetrahydrofuran (10 mL) and a solution of lithium hydroxide monohydrate (0.078 g, 1.85 mmol) in water (5 mL) was slowly added. The resulting mixture was stirred for an additional 1 h. After concentration *in vacuo*, the lithium salts **4b**-Li was obtained. Yield: 59% (0.86 g). ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.26 (t, $^3J_{HH}$ = 7.0 Hz, 3H), 2.18–2.30 (m, 2H), 2.21 (s, 3H), 2.75–2.81 (m, 2H), 4.19 (q, $^3J_{HH}$ = 7.0 Hz, 2H), 4.98 (dd, $^2J_{HH}$ = 12.1 Hz, $^3J_{HP}$ = 7.4 Hz, 2H), 5.03 (dd, $^2J_{HH}$ = 12.1 Hz, $^3J_{HP}$ = 8.3 Hz, 2H), 7.19–7.27 (m, 10H). ^{13}C NMR (100.61 MHz, DMSO-d_6) δ 14.26 (s), 16.87 (s), 18.76 (d, $^2J_{CP}$ = 2.9 Hz), 21.95 (d, $^1J_{CP}$ = 136.8 Hz), 59.26 (s), 66.25 (d, $^2J_{CP}$ = 5.6 Hz), 115.42 (s), 127.60 (s), 128.04 (s), 128.40 (s), 136.71 (d, $^3J_{CP}$ = 6.6 Hz), 138.98 (s), 141.18 (d, $^3J_{CP}$ = 19.0 Hz), 163.13 (s). ^{31}P NMR (161.97 MHz, DMSO-d_6) δ 32.44 (s). HRMS (ESI) *m*/*z* [M + H]$^+$ calcd for $C_{23}H_{27}LiN_2O_6P$ 465.1767, found 465.1778.

Lithium 5-benzoyl-2-(2-(bis(benzyloxy)phosphoryl)ethyl)-1*H*-imidazol-1-olate (4c-Li). The resulting residue was purified by column chromatography (silica, EtOAc–EtOH 100 : 0–70 : 30) to afford the *N*-hydroxyl intermediate **4c** (0.87 g, 1.76 mmol). **4c** was dissolved in tetrahydrofuran (10 mL) and a solution of lithium hydroxide monohydrate (0.074 g, 1.76 mmol) in water (5 mL) was slowly added. The resulting mixture was stirred for an additional 1 h. After concentration *in vacuo*, the lithium salts was obtained. Yield: 56% (0.88 g). ^{1}H NMR (400.13 MHz, DMSO-d_6) δ (ppm) 1.69 (s, 3H), 2.28–2.36 (m, 2H), 2.86–2.93 (m, 2H), 5.06 (dd, $^2J_{HH}$ = 12.1 Hz, $^3J_{HP}$ = 7.5 Hz, 2H), 5.1 (dd, $^2J_{HH}$ = 12.1 Hz, $^3J_{HP}$ = 8.2 Hz, 2H), 7.34–7.62 (m, 15H). ^{13}C NMR (100.61 MHz, DMSO-d_6) δ 17.42 (s), 18.74 (d, $^2J_{CP}$ = 2.9 Hz), 22.68 (d, $^1J_{CP}$ = 138.3 Hz), 66.32 (d, $^2J_{CP}$ = 5.8 Hz), 125.27 (s), 127.63 (s), 128.04 (s), 128.07 (s), 128.24 (s), 128.41 (s), 136.69 (d, $^3J_{CP}$ = 6.6 Hz), 140.45 (s), 141.41 (s), 142.72 (d, $^3J_{CP}$ = 18.3 Hz). ^{31}P NMR (161.97 MHz, DMSO-d_6) δ 32.37 (s). HRMS (ESI) *m*/*z* [M + H]$^+$ calcd for $C_{27}H_{27}LiN_2O_5P$ 497.1818, found 497.1817.

Dibenzyl (2-(5-(furan-2-carbonyl)-1-hydroxy-1*H*-imidazol-2-yl)-ethyl)phosphonate (4d). The resulting residue was purified by column chromatography (silica, EtOAc–EtOH (100 : 0–70 : 30)) to afford the desired product. Yield: 80% (1.14 g). ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 2.11–2.19 (m, 2H), 2.30 (s, 3H), 2.89–2.98 (m, 2H), 4.91 (dd, $^2J_{HH}$ = 11.9 Hz, $^3J_{HP}$ = 8.0 Hz, 2H), 4.96 (dd, $^2J_{HH}$ = 11.9 Hz, $^3J_{HP}$ = 9.3 Hz, 2H), 6.37 (dd, $^3J_{HH}$ = 3.3 Hz, $^3J_{HH}$ = 1.76 Hz, 1H), 6.72 (d, $^3J_{HH}$ = 3.3 Hz, 1H), 7.19–7.27 (m, 11H). ^{13}C NMR (100.61 MHz, $CDCl_3$) δ 13.13 (s), 17.66 (s), 23.29 (d, $^1J_{CP}$ = 140.5 Hz), 67.73 (d, $^2J_{CP}$ = 6.6 Hz), 107.13 (s), 110.99 (s), 119.29 (s), 127.93 (s), 128.61 (s), 128.66 (s), 135.76 (d, $^3J_{CP}$ = 5.8 Hz), 141.13 (s), 144.18 (s). ^{31}P NMR (161.97 MHz, $CDCl_3$) δ 32.79 (s). HRMS (ESI) *m*/*z* [M + H]$^+$ calcd for $C_{24}H_{26}N_2O_5P$ 453.1579, found: 453.1582.

Deprotection reaction

N-Hydroxyimidazoles

Method A. In a Schlenck tube was introduced palladium dihydroxyde on charcoal (10%), dibenzyl phosphonate (**4b** or **4c**) and degassed ethanol. Three vacuum (until solvent bubbling)/nitrogen, two vacuum/hydrogen were performed on the system. After vigorously stirring at room temperature for 24 h (**4b**) or 40 °C for 36 h (**4c**), the reaction mixture was filtered on celite and the filtrate was concentrated *in vacuo*.

(2-(5-(Ethoxycarbonyl)-1-hydroxy-1*H*-imidazol-2-yl)ethyl)phosphonic acid (2b). From palladium dihydroxide on charcoal (65 mg), **4b** (0.65 g, 1.42 mmol) and ethanol (10 mL), the desired product was obtained. Yield: 50% (0.20 g). ^{1}H NMR (400.13 MHz, D_2O): δ 1.23 (t, $^3J_{HH}$ = 7.0 Hz, 3H), 1.96–2.04 (m, 2H), 2.38 (s, 3H), 3.05–3.14 (m, 2H), 4.27 (q, $^3J_{HH}$ = 7.0 Hz, 2H). ^{13}C NMR (100.61 MHz, DMSO-d_6): δ 8.13 (s), 10.51 (s), 15.09 (d, $^2J_{CP}$ = 3.7 Hz), 20.06 (d, $^1J_{CP}$ = 136.8 Hz), 59.96 (s), 115.32 (s), 132.00 (s), 140.96 (d, $^3J_{CP}$ = 13.9 Hz), 156.08 (s). ^{31}P NMR (161.97 MHz, D_2O) δ 25.67 (s). HRMS (ESI) *m*/*z* [M + H]$^+$ calcd for $C_9H_{16}N_2O_6P$ 279.0746, found: 279.0739.

(2-(1-Hydroxy-5-(hydroxy(phenyl)methyl)-1*H*-imidazol-2-yl)-ethyl)phosphonic acid (2e). From palladium dihydroxide on charcoal (100 mg), **4c** (0.80 g, 1.68 mmol) and ethanol (30 mL), the desired product was obtained. Yield: 51% (0.27 g). ^{1}H NMR (400.13 MHz, D_2O) δ 1.21–1.27 (m, 1H), 1.84–1.92 (m, 2H), 2.01 (s, 3H), 2.96–3.03 (m, 2H), 6.04 (s, 1H), 7.29–7.38 (m, 5H). ^{13}C NMR (100.61 MHz, D_2O) δ 9.05 (s), 17.94 (d, $^2J_{CP}$ = 3.6 Hz), 24.38 (d, $^1J_{CP}$ = 134.6 Hz), 65.11 (s), 123.52 (s), 126.02 (s), 127.50 (s), 128.23 (s), 128.78 (s), 139.37 (s), 140.71 (d, $^3J_{CP}$ = 14.6 Hz). ^{31}P NMR (161.97 MHz, D_2O) δ 21.47 (s). HRMS (ESI) *m*/*z* $[M + H]^+$ calcd for $C_{13}H_{18}N_2O_5P$ 313.0953, found 313.0955.

Method B. At 0 °C, trimethylsilylbromide (1.27 mL, 10 mmol) was added to a solution of benzyl phosphonate (**4a**, **4c** and **4d**, 1 mmol) in dichloromethane (10 mL). The reaction mixture was allowed to stand up at room temperature and stirred for 14 h. After concentration to dryness under vacuum, methanol (10 mL) was added and the resulting mixture was stirred at room temperature for 2 h, thus concentrated *in vacuo*. Further purification was not required.

(2-(5-Acetyl-1-hydroxy-1*H*-imidazol-2-yl)ethyl)phosphonic acid (2a). Yield 96% (0.24 g). ^{1}H NMR (400.13 MHz, D_2O) δ 2.00–2.09 (m, 2H), 2.41 (s, 3H), 2.48 (s, 3H), 3.07–3.14 (m, 2H). ^{13}C NMR (100.61 MHz, D2O) δ 11.52 (s), 17.67 (d, $^2J_{CP}$ = 3.6 Hz), 23.17 (d, $^1J_{CP}$ = 137.5 Hz), 29.58 (s), 125.20 (s), 134.54 (s), 142.96 (d, $^3J_{CP}$ = 14.6 Hz), 190.80 (s). ^{31}P NMR (161.97 MHz, D_2O) δ 24.08 (s). HRMS (ESI) *m*/*z* $[M + H]^+$ calcd for $C_8H_{14}N_2O_5P$ 249.0640, found 249.0637.

(2-(5-Benzoyl-1-hydroxy-1*H*-imidazol-2-yl)ethyl)phosphonic acid (2c). Yield: 93% (0.29 g). ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.98–2.06 (m, 2H), 2.13 (s, 3H), 2.96–3.03 (m, 2H), 7.56–7.66 (m, 2H), 7.68–7.76 (m, 1H), 7.76–7.82 (m, 2H). ^{13}C NMR (100.61 MHz, DMSO-d_6) δ 14.00 (s), 18.75 (s), 24.78 (d, $^1J_{CP}$ = 135.4 Hz), 125.11 (s), 128.46 (s), 129.03 (s), 132.90 (s), 137.82 (s), 144.51 (d, $^3J_{CP}$ = 15.4 Hz), 184.73 (s). ^{31}P NMR (161.97 MHz, DMSO-d_6) δ 23.58 (s). HRMS (ESI) *m*/*z* $[M + H]^+$ calcd for $C_{13}H_{16}N_2O_5P$ 311.0797, found: 311.0797.

(2-(5-(Furan-2-carbonyl)-1-hydroxy-1*H*-imidazol-2-yl)ethyl)-phosphonic acid (2d). Yield: 97% (0.25 g). ^{1}H NMR (400.13 MHz, D_2O) δ 1.97–2.06 (m, 2H), 2.30 (s, 3H), 3.05–3.12 (m, 2H), 6.49 (dd, $^3J_{HH}$ = 3.1 Hz, $^3J_{HH}$ = 1.0 Hz, 1H), 6.78 (d, $^3J_{HH}$ = 3.1 Hz, 1H), 7.55 (d, $^3J_{HH}$ = 1.0 Hz, 1H). ^{13}C NMR (100.61 MHz, D_2O) δ 9.57 (s), 17.71 (d, $^2J_{CP}$ = 3.7 Hz), 23.61 (d, $^1J_{CP}$ = 136.1 Hz), 111.04 (s), 111.39 (s), 119.29 (s), 123.32 (s), 141.23 (d, $^3J_{CP}$ = 14.6 Hz), 144.10 (s), 145.38 (s). ^{31}P NMR (161.97 MHz, D_2O) δ 24.01 (s). HRMS (ESI) *m*/*z* $[M + H]^+$ calcd for $C_{10}H_{14}N_2O_5P$ 273.0640, found 273.0640.

Synthesis of diethyl (oxiran-2-ylmethyl)phosphonate (12) and diethyl (E)-(3-oxoprop-1-en-1-yl)phosphonate (10). Starting materials **12** (ref. 23) and **10** (ref. 24) were prepared respectively according to procedure described in literature.

Diethyl (*E*)-(3-((benzyloxy)amino)prop-1-en-1-yl)phosphonate (9). (*E*)-diethyl (3-oxoprop-1-en-1-yl)phosphonate (15.2 g, 78.2 mmol, 1 eq.) was dissolved in MeOH (25 mL) and *O*-benzyl hydroxylamine (8.19 mL, 78.2 mmol, 1 eq.) was added at 0 °C. The mixture was stirred for 1 h at room temperature. After addition of MeOH (300 mL), $NaBH_3CN$ (14.8 g, 230 mmol, 3 eq.) was added by small portions. After 30 min at room temperature, concentrated HCl (46 mL, 37%) was added slowly at 0 °C. Then, a new portion of $NaBH_3CN$ (3.5 g, 54 mmol) was added at room temperature and one more time after 2 hours (7.0 g, 109 mmol). The reaction was stirred overnight and then concentrated under reduced pressure. An aqueous solution of KOH (10%) was added until pH = 10 and then the product was extracted three times with CH_2Cl_2 (100 mL). Organic layers were combined, dried over $MgSO_4$ and concentrated under reduced pressure. The resulting crude was purified by column chromatography (silica heptane–AcOEt 60 : 40–0 : 100) to afford the desired product. Yield: 50% (11.8 g). ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 1.34 (t, $^3J_{HH}$ = 7.1 Hz, 6H), 3.68–3.71 (m, 2H), 4.06–4.14 (m, 4H), 4.73 (s, 2H), 5.85–5.96 (ddt, $^2J_{PH}$ = 20.3 Hz, $^3J_{HH}$ = 17.2 Hz, $^4J_{HH}$ = 3.2 Hz, 1H), 6.77–6.89 (ddt, $^3J_{PH}$ = 27.8 Hz, $^3J_{HH}$ = 17.4 Hz, $^3J_{HH}$ = 5.5 Hz, 1H), 7.33–7.37 (m, 5H). ^{13}C NMR (100.61 MHz, $CDCl_3$) δ 16.36 (d, $^3J_{CP}$ = 6.4 Hz), 54.21 (d, $^3J_{CP}$ = 23.2 Hz), 61.77 (d, $^2J_{CP}$ = 5.6 Hz), 77.33 (s), 119.11 (d, $^1J_{CP}$ = 187.8 Hz), 127.96 (s), 128.42 (s), 137.53 (s), 148.55 (d, $^2J_{CP}$ = 4.9 Hz). ^{31}P NMR (161.97 MHz, $CDCl_3$) δ 17.84 (s).

General procedure

***N*-hydroxybenzylureas.** Under N_2, compound **9** (1.5 g, 5 mmol) was dissolved in dichloroethane (25 mL) and isocyanate (2, 3 or 6 eq.) was added. The reaction mixture was stirred at room temperature for 3 h (overnight for 8 days). The solution was concentrated *in vacuo* and the resulting crude was used for the next step without further purification.

(*E*)-Diethyl (3-(1-(benzyloxy)-3-ethylureido)prop-1-en-1-yl)-phosphonate (8a). From ethylisocyanate (1.2 mL, 15 mmol), the desired product was obtained. Yield: 100% (1.8 g). ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 1.03 (t, $^3J_{HH}$ = 7.3 Hz, 6H), 1.33 (t, $^3J_{HH}$ = 7.2 Hz, 3H), 3.15–3.22 (m, 2H), 4.05–4.12 (m, 4H), 4.23–4.25 (m, 2H), 4.80 (s, 2H), 5.68 (t, $^3J_{HH}$ = 5.5 Hz, 1H), 5.87 (ddt, $^2J_{PH}$ = 19.6 Hz, $^3J_{HH}$ = 17.2 Hz, $^4J_{HH}$ = 1.4 Hz, 1H), 6.72–6.84 (m, 1H), 7.36–7.41 (m, 5H). ^{13}C NMR (100.61 MHz, $CDCl_3$) δ 15.07 (s), 16.33 (d, $^3J_{CP}$ = 6.4 Hz), 34.94 (s), 54.22 (d, $^3J_{CP}$ = 24.5 Hz), 61.80 (d, $^2J_{CP}$ = 5.6 Hz), 77.41 (s), 120.21 (d, $^1J_{CP}$ = 186.9 Hz), 128.79 (s), 129.01 (s), 129.31 (s), 135.14 (s), 146.89 (d, $^2J_{CP}$ = 5.0 Hz), 159.62 (s). ^{31}P NMR (161.97 MHz, $CDCl_3$): δ 17.24 (s). HRMS (ESI) *m*/*z* $[M + H]^+$ calcd for $C_{17}H_{28}N_2O_5P$ 371.1740, found: 371.1736.

(*E*)-Diethyl (3-(1-(benzyloxy)-3-phenylureido)prop-1-en-1-yl)-phosphonate (8b). From phenylisocyanate (1.0 mL, 10 mmol), the desired product was obtained. Yield: 100% (2.1 g). ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 1.32 (t, $^3J_{HH}$ = 7.0 Hz, 6H), 4.05–4.12 (m, 4H), 4.33–4.35 (m, 2H), 4.91 (s, 2H), 5.88–5.97 (m, 1H), 6.76–6.89 (m, 1H), 7.26–7.31 (m, 5H), 7.41–7.47 (m, 5H), 7.60 (s, 1H). ^{13}C NMR (100.61 MHz, $CDCl_3$) δ 16.33 (d, $^3J_{CP}$ = 6.6 Hz), 51.72 (d, $^3J_{CP}$ = 24.9 Hz), 61.87 (d, $^2J_{CP}$ = 5.9 Hz), 77.95 (s), 119.31 (s), 120.70 (d, $^1J_{CP}$ = 186.6 Hz), 123.74 (s), 128.93 (s), 129.02 (s), 129.37 (s), 129.44 (s), 134.71 (s), 137.53 (s), 146.22 (d, $^2J_{CP}$ = 5.1 Hz), 156.68 (s). ^{31}P NMR (161.97 MHz, $CDCl_3$) δ 16.99 (s). HRMS (ESI) *m*/*z* $[M + H]^+$ calcd for $C_{21}H_{28}N_2O_5P$ 419.1736, found 419.1736.

(*E*)-Diethyl (3-(1-(benzyloxy)-3-(4-fluorophenyl)ureido)prop-1-en-1-yl)phosphonate (8c). From 4-fluorophenylisocyanate (1.2 mL, 10 mmol), the desired product was obtained. Yield: 100%

(2.1 g). ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 1.32 (t, $^3J_{HH}$ = 7.0 Hz, 6H), 4.05–4.13 (m, 4H), 4.32–4.35 (m, 2H), 4.90 (s, 2H), 5.88–5.97 (m, 1H), 6.76–6.88 (ddt, m, 1H), 6.95–7.01 (m, 2H), 7.20–7.23 (m, 2H), 7.35–7.44 (m, 5H), 7.51 (s, 1H). ^{13}C NMR (100.61 MHz, $CDCl_3$) δ 16.32 (d, $^3J_{CP}$ = 5.8 Hz), 51.67 (d, $^3J_{CP}$ = 24.9 Hz), 61.96 (d, $^2J_{CP}$ = 5.9 Hz), 77.88 (s), 115.51 (d, $^2J_{CF}$ = 22.7 Hz), 120.54 (d, $^1J_{CP}$ = 187.4 Hz), 121.18 (d, $^3J_{CF}$ = 7.3 Hz), 129.03 (s), 129.40 (s), 129.47 (s), 133.46 (d, $^4J_{CF}$ = 2.2 Hz), 134.71 (s), 146.27 (d, $^2J_{CP}$ = 5.1 Hz), 156.82 (s), 159.15 (d, $^1J_{CF}$ = 243.0 Hz). ^{31}P NMR (161.97 MHz, $CDCl_3$) δ 17.02 (s). HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{21}H_{27}FN_2O_5P$ 437.1642, found 437.1642.

(*E*)-Diethyl (3-(1-(benzyloxy)-3-ureido)prop-1-en-1-yl)phosphonate (8d). From trimethylsilyl isocyanate (4 mL, 30 mmol), followed by a column chromatography (silica), the desired product was obtained. Yield: 78% (1.3 g). ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 1.31 (t, $^3J_{HH}$ = 7.0 Hz, 6H), 4.03–4.10 (m, 4H), 4.22–4.23 (m, 2H), 4.83 (s, 2H), 5.49 (bs, 2H), 5.81–5.90 (m, 1H), 6.68–6.80 (m, 1H), 7.36–7.28 (m, 5H). ^{13}C NMR (100.61 MHz, $CDCl_3$) δ 16.35 (d, $^3J_{CP}$ = 6.6 Hz), 51.21 (d, $^3J_{CP}$ = 24.9 Hz), 61.85 (d, $^2J_{CP}$ = 5.9 Hz), 77.42 (s), 120.25 (d, $^1J_{CP}$ = 187.3 Hz), 128.82 (s), 129.10 (s), 129.25 (s), 134.73 (s), 146.31 (d, $^2J_{CP}$ = 5.1 Hz), 160.21 (s). ^{31}P NMR (161.97 MHz, $CDCl_3$) δ 17.17 (s). HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{15}H_{24}N_2O_5P$ 343.1417, found 343.1423.

General procedure

***N*-benzyloxyimidazolones.** Under N_2, **8a–c** (1 eq.) was dissolved in THF (0.1 mol L^{-1}) and *t*-BuOK (20 mol%) was introduced. The reaction was heated at reflux for 48 h and the mixture was concentrated under reduced pressure. Water (10 mL) was added and extracted with EtOAc (3 × 25 mL), organic layers were combined, dried over magnesium sulfate and concentrated under reduced pressure. The resulting residue was purified by column chromatography (silica, heptane–AcOEt 50 : 50–0 : 100).

(±)-Diethyl ((1-(benzyloxy)-3-ethyl-2-oxoimidazolidin-4-yl)-methyl)phosphonate (7a). From **8a** (1.2 g, 3.24 mmol), the desired product was obtained. Yield: 56% (0.67 g). ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 1.12 (t, $^3J_{HH}$ = 7.2 Hz, 3H), 1.32 (t, $^3J_{HH}$ = 7.1 Hz, 3H), 1.33 (t, $^3J_{HH}$ = 7.1 Hz, 3H), 1.79 (ddd, $^2J_{HP}$ = 17.1 Hz, $^2J_{HH}$ = 14.8 Hz, $^3J_{HH}$ = 10.7 Hz, 1H), 2.19 (ddd, $^2J_{HP}$ = 21.5 Hz, $^2J_{HH}$ = 15.0 Hz, $^3J_{HH}$ = 2.9 Hz, 1H), 3.02 (dq, $^2J_{HH}$ = 14.2 Hz, $^3J_{HH}$ = 7.0 Hz, 1H), 3.14 (dd, $^2J_{HH}$ = 8.2 Hz, $^3J_{HH}$ = 6.6 Hz, 1H), 3.46–3.50 (m, 1H), 3.56 (dq, $^2J_{HH}$ = 14.7 Hz, $^3J_{HH}$ = 7.3 Hz, 1H), 3.71–3.78 (m, 1H), 4.04–4.14 (m, 4H), 4.97 (d, $^2J_{HH}$ = 11.4 Hz, 1H), 5.02 (d, $^2J_{HH}$ = 11.4 Hz, 1H), 7.33–7.46 (m, 5H). ^{13}C NMR (100.61 MHz, $CDCl_3$) δ 12.55 (s), 16.38 (d, $^3J_{CP}$ = 5.9 Hz), 16.44 (d, $^3J_{CP}$ = 5.9 Hz), 28.66 (d, $^1J_{CP}$ = 138.8 Hz), 35.81 (s), 46.73 (s), 53.57 (d, $^3J_{CP}$ = 1.4 Hz), 61.95 (d, $^2J_{CP}$ = 6.6 Hz), 62.06 (d, $^2J_{CP}$ = 6.6 Hz), 77.88 (s), 128.23 (s), 128.36 (s), 129.08 (s), 136.72 (s), 162.04 (s). ^{31}P NMR (161.97 MHz, $CDCl_3$) δ 26.10 (s). HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{17}H_{28}N_2O_5P$ 371.1736, found 371.1736.

(±)-Diethyl ((1-(benzyloxy)-3-phenyl-2-oxoimidazolidin-4-yl)-methyl)phosphonate (7b). From **8b** (1.5 g, 3.6 mmol), the desired product was obtained. Yield: 75% (1.13 g). ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 1.31 (t, $^3J_{HH}$ = 7.0 Hz, 3H), 1.32 (t, $^3J_{HH}$ = 7.0 Hz, 3H), 1.85 (ddd, $^2J_{HP}$ = 16.7 Hz, $^2J_{HH}$ = 15.2 Hz, $^3J_{HH}$ = 11.1 Hz, 1H), 2.25 (ddd, $^2J_{HP}$ = 21.1 Hz, $^2J_{HH}$ = 15.2 Hz, $^3J_{HH}$ = 2.0 Hz, 1H), 3.36 (dd, $^2J_{HH}$ = 8.2 Hz, $^3J_{HH}$ = 5.3 Hz, 1H), 3.63–3.67 (m, 1H), 4.03–4.15 (m, 4H), 4.36–4.44 (m, 1H), 5.05 (s, 2H), 7.17–7.20 (m, 5H), 7.36–7.50 (m, 5H). ^{13}C NMR (100.61 MHz, $CDCl_3$) δ 16.39 (d, $^3J_{CP}$ = 5.9 Hz), 28.48 (d, $^1J_{CP}$ = 138.3 Hz), 48.05 (d, $^2J_{CP}$ = 1.5 Hz), 52.62 (s), 61.01 (d, $^2J_{CP}$ = 6.6 Hz), 62.06 (d, $^2J_{CP}$ = 6.6 Hz), 77.98 (s), 121.33 (s), 125.02 (s), 128.41 (s), 128.43 (s), 129.22 (s), 129.26 (s), 136.41 (s), 136.73 (s), 159.84 (s). ^{31}P NMR (161.97 MHz, $CDCl_3$) δ 26.06 (s). HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{21}H_{28}N_2O_5P$ 419.1724, found 419.1736.

(±)-Diethyl ((1-(benzyloxy)-3-(4-fluorophenyl)-2-oxoimidazolidin-4-yl)methyl)phosphonate (7c). From **8c** (1.6 g, 3.6 mmol), the desired product was obtained. Yield: 61% (0.97 g). ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 1.31 (t, $^3J_{HH}$ = 7.0 Hz, 6H), 1.82 (ddd, $^2J_{HP}$ = 16.9 Hz, $^2J_{HH}$ = 15.2 Hz, $^3J_{HH}$ = 11.1 Hz, 1H), 2.18 (ddd, $^2J_{HP}$ = 17.2 Hz, $^2J_{HH}$ = 15.2 Hz, $^3J_{HH}$ = 2.1 Hz, 1H), 3.34 (dd, $^2J_{HH}$ = 8.2 Hz, $^3J_{HH}$ = 5.8 Hz, 1H), 3.64–3.68 (m, 1H), 4.04–4.12 (m, 4H), 4.29–4.36 (m, 1H), 5.04 (s, 2H), 7.08–7.12 (m, 2H), 7.36–7.49 (m, 7H). ^{13}C NMR (100.61 MHz, $CDCl_3$) δ 16.40 (d, $^3J_{CP}$ = 6.0 Hz), 28.54 (d, $^1J_{CP}$ = 138.9 Hz), 48.43 (d, $^2J_{CP}$ = 1.5 Hz), 52.72 (s), 62.02 (d, $^2J_{CP}$ = 6.6 Hz), 62.12 (d, $^2J_{CP}$ = 6.6 Hz), 78.03 (s), 116.11 (d, $^2J_{CF}$ = 22.7), 123.53 (d, $^3J_{CF}$ = 8.0 Hz), 128.45 (s), 129.24 (s), 132.68 (s), 136.35 (s), 159.94 (s), 160.05 (d, $^1J_{CF}$ = 245.9 Hz). ^{31}P NMR (161.97 MHz, $CDCl_3$) δ 25.83 (s). HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{21}H_{27}FN_2O_5P$ 437.1649, found 419.1642.

General procedure

***N*-Hydroxyimidazolones.** In a Schlenk tube and under N_2, the appropriate amount of $Pd(OH)_2$/C (10%) was introduced and two vaccum-nitrogen sequences were performed. Then, the 5-membered ring derivative (1 eq.) in EtOH was added and the mixture was then let under hydrogen atmosphere overnight at room temperature (3 h for **7a**). The mixture was then filtered through a celite pad, and ethanol was removed under vacuum. The resulting crude was purified by column chromatography (silica, heptane–AcOEt–EtOH 90 : 18 : 2–0 : 90 : 10).

(±)-Diethyl ((1-hydroxy-3-ethyl-2-oxoimidazolidin-4-yl)-methyl)phosphonate (13a). From **7a** (0.07 g, 0.19 mmol) and $Pd(OH)_2$/C (10%, 0.007 mg) in ethanol (2.5 mL), the desired product was obtained. Yield 20% (0.01 g). ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 1.12 (t, $^3J_{HH}$ = 7.1 Hz, 3H), 1.36 (t, $^3J_{HH}$ = 7.0 Hz, 3H), 1.90 (ddd, $^2J_{HP}$ = 17.4 Hz, $^2J_{HH}$ = 15.0 Hz, $^3J_{HH}$ = 10.7 Hz, 1H), 2.25 (ddd, $^2J_{HP}$ = 21.3 Hz, $^2J_{HH}$ = 14.8 Hz, $^3J_{HH}$ = 2.7 Hz, 1H), 3.05 (dq, $^2J_{HH}$ = 14.2 Hz, $^3J_{HH}$ = 7.1 Hz, 1H), 3.34 (dd, $^2J_{HH}$ = 8.2 Hz, $^3J_{HH}$ = 6.6 Hz, 1H), 3.49–3.58 (m, 1H), 3.73–3.77 (m, 1H), 3.82–3.88 (m, 1H), 4.11–4.16 (m, 4H), 8.46 (bs, 1H). ^{13}C NMR (100.61 MHz, $CDCl_3$) δ 12.59 (s), 16.44 (d, $^3J_{CP}$ = 5.9 Hz), 16.46 (d, $^3J_{CP}$ = 5.9 Hz), 28.70 (d, $^1J_{CP}$ = 139.1 Hz), 36.12 (s), 47.00 (s), 54.28 (d, $^4J_{CP}$ = 1.5 Hz), 62.10 (d, $^2J_{CP}$ = 6.6 Hz), 62.24 (d, $^2J_{CP}$ = 6.6 Hz), 163.96 (s). ^{31}P NMR (161.97 MHz, $CDCl_3$) δ 26.15 (s). HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{10}H_{22}N_2O_5P$ 281.1266, found 281.1257.

(±)-Diethyl (((1-hydroxy-3-phenyl)-2-oxoimidazolidin-4-yl)-methyl)phosphonate (13b). From **7b** (1.1 g, 2.6 mmol) and $Pd(OH)_2$/C (10%, 0.11 g) in ethanol (30 mL), the desired product was obtained. Yield 76% (0.66 g). ^{1}H NMR (400.13 MHz, $CDCl_3$)

δ 1.35 (t, $^3J_{HH}$ = 7.0 Hz, 3H), 1.36 (t, $^3J_{HH}$ = 7.1 Hz, 3H), 1.95 (ddd, $^2J_{HP}$ = 17.1 Hz, $^2J_{HH}$ = 15.2 Hz, $^3J_{HH}$ = 11.1 Hz, 1H), 2.28 (ddd, $^2J_{HP}$ = 21.2 Hz, $^2J_{HH}$ = 15.0 Hz, $^3J_{HH}$ = 2.2 Hz, 1H), 3.61 (dd, $^2J_{HH}$ = 8.4 Hz, $^3J_{HH}$ = 5.8 Hz, 1H), 3.88–3.92 (m, 1H), 4.08–4.20 (m, 4H), 4.46–4.55 (m, 1H), 7.19–7.24 (m, 1H), 7.39–7.44 (m, 4H). ^{13}C NMR (100.61 MHz, $CDCl_3$) δ 16.40 (d, $^3J_{CP}$ = 6.6 Hz), 28.52 (d, $^1J_{CP}$ = 139.0 Hz), 48.34 (s), 53.44 (s), 62.24 (d, $^2J_{CP}$ = 6.6 Hz), 62.25 (d, $^2J_{CP}$ = 6.6 Hz), 121.90 (s), 125.31 (s), 129.30 (s), 136.60 (s), 161.93 (s). ^{31}P NMR (161.97 MHz, $CDCl_3$) δ 26.12 (s). HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{14}H_{22}N_2O_5P$ 329.1272, found 329.1266.

(±)-Diethyl ((1-hydroxy-3-(4-fluorophenyl)-2-oxoimidazolidin-4-yl)methyl)phosphonate (13c). From **7c** (0.15 g, 0.35 mmol) and $Pd(OH)_2/C$ (10%, 0.015 g) in ethanol (4 mL), the desired product was obtained. Yield 50% (0.06 g). ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 1.32 (t, $^3J_{HH}$ = 7.0 Hz, 3H), 1.33 (t, $^3J_{HH}$ = 7.0 Hz, 3H), 1.92 (ddd, $^2J_{HP}$ = 17.2 Hz, $^2J_{HH}$ = 15.2 Hz, $^3J_{HH}$ = 11.1 Hz, 1H), 2.21 (ddd, $^2J_{HP}$ = 17.4 Hz, $^2J_{HH}$ = 15.0 Hz, $^3J_{HH}$ = 2.2 Hz, 1H), 3.54 (dd, $^2J_{HH}$ = 8.5 Hz, $^3J_{HH}$ = 6.5 Hz, 1H), 3.87–3.91 (m, 1H), 4.04–4.17 (m, 4H), 4.37–4.46 (m, 1H), 7.06–7.10 (m, 2H), 7.32–7.37 (m, 2H). ^{13}C NMR (100.61 MHz, $CDCl_3$) δ 16.40 (d, $^3J_{CP}$ = 5.8 Hz), 28.60 (d, $^1J_{CP}$ = 139.1 Hz), 48.77 (s), 53.47 (s), 62.27 (d, $^2J_{CP}$ = 6.6 Hz), 62.36 (d, $^2J_{CP}$ = 6.6 Hz), 116.18 (d, $^2J_{HF}$ = 22.7), 124.18 (d, $^3J_{HF}$ = 8.8 Hz), 132.51 (d, $^4J_{HF}$ = 2.9 Hz), 161.98 (s), 160.25 (d, $^1J_{CF}$ = 245.2 Hz). ^{31}P NMR (161.97 MHz, $CDCl_3$) δ 26.06 (s). HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{14}H_{21}FN_2O_5P$ 347.1180, found 347.1172.

(±)-(1-Hydroxy-3-phenyl-2-oxoimidazolidin-4-yl)methylphosphonic acid (3b). At 0 °C and under nitrogen, trimethylsilylbromide (0.47 mL, 3.65 mmol, 6 eq.) was added to a solution of **13b** (200 mg, 0.61 mmol) in dichloromethane (10 mL). The reaction was stirred at room temperature overnight and concentrated in vacuum to dryness. Then, methanol was added (10 mL) and the mixture was stirred at room temperature for one hour, and then solvent was evapored. The crude was diluted in a hydrochloride solution (6 M) and the mixture was heated at reflux for 4 hours. After evaporation, the pure product was obtained without further purification. Yield: 73% (0.12 g). ^{1}H NMR (400.13 MHz, D_2O) δ 1.69–1.91 (m, 2H), 3.26–3.30 (m, 1H), 3.64–3.68 (m, 1H), 4.15–4.24 (m, 1H), 7.04–7.09 (m, 3H), 7.18–7.22 (m, 2H). ^{13}C NMR (100.61 MHz, D_2O) δ 28.93 (d, $^1J_{CP}$ = 133.9 Hz), 49.63 (d, $^2J_{CP}$ = 1.5 Hz), 53.52 (s), 124.64 (s), 127.07 (s), 129.48 (s), 135.36 (s), 162.64 (s). ^{31}P NMR (161.97 MHz, D_2O) δ 24.25 (s). HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{10}H_{14}N_2O_5P$ 273.0639, found: 273.0640.

Conclusions

N-Hydroxyimidazoles **2a–d** and cyclic *N*-hydroxyureas **13a–c**, both rigidified analogues of fosmidomycin have been successfully prepared as potential inhibitors of DXR. Compounds **2a–d** have been prepared by a three-component reaction through the condensation-cyclization sequence between dibenzyl (3-oxopropyl)phosphonate **5**, α-ketooximes **6** and ammonium acetate. The five-membered ring hydroxyureas derivatives have been synthesized from an unusual intramolecular Michael addition leading to the desired structures.

In vivo evaluations as herbicides for compounds **4a–d**, **2a–e**, **13a–c** and **3c** were conducted by spraying on different cultures of interest belonging to monocotyledons or dicotyledons. Unfortunately, no biological activity was seen in this preliminary screening. Nevertheless other *N*-hydroxyurea analogues are expected and will be evaluated in due course.

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