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Fosmidomycin Analogues with N-Hydroxyimidazole and N-Hydroxyimidazolone as Chelating Unit

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Fosmidomycin has been reported to have many biological activities as antibacterial, antimalarial, along with 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 parasite 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. 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-independent pathway of isoprenoid biosynthesis, 1-deoxy-D-xylulose 5-phosphate reductoisomerase (DXR), was inhibited by fosmidomycin in a dose-dependent manner with an IC50 value of 8.2 nM. 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. The efficiency of both compounds against Plasmodium falciparum on human has been proved after the latter cured uncomplicated malaria. 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. On the other hand, two other clinical trials using a combination of fosmidomycin-clindamycin gave promising results for a possible new treatment against malaria. 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. This phosphonic acid antibiotic, also proved to be effective against the DXR enzyme of higher plants, and its herbicidal activity has even been patented. The combined low mammalian toxicity (LD50 rats, oral > 8 g.kg-1) and high hydrophilic properties of the fosmidomycin 1a and its acetyl analogue 1b present a great interest to develop a new 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. 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.

Cite this: DOI: 10.1039/x0xx00000x

www.rsc.org/

Received 00th September 2013, Accepted 00th September 2013.

DOI: 10.1039/x0xx00000x
based on acyl-N-hydroxyimidazoles 2 has without ambiguity interesting features.

Figure 2. Retrosynthetic pathways for targeted hydroxyimidazoles 2 and hydroxyimidazolones 3.

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 4-hydroxyphenylpyruvate dioxygenase (HPPD), a ferrous iron complexing agent and an inhibitor of Isoxaflutole herbicide, and the presence of a β(1,3)-diketone moiety permits the creation of a stable ion-dipole interaction in the active enzyme active site (Figure 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 (Figure 1). 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-ketoimines 6 with the 3-phosphonopronionaldehyde 5 and ammonia (Figure 2). In the other side, N-hydroxyurea derivatives 3 were intended to be synthesized by a 5-endo-trig cyclization according to the Baldwin rules of the 3-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-benzoylimidazolyl 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 pKa 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/BaSO4) keeping in mind to minimize the cleavage of the sensitive N-O bond. 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.

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 phosphate with bromoethyldioxolane promoted by caesium carbonate (Cs2CO3) 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). In parallel, substituted ketoimines 6a-d were prepared according to the reaction of the corresponding ketone with a hydrochloric solution of sodium nitrite in 41% to 86% yields. 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. 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-benzoylimidazolyl 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 pKa 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/BaSO4) keeping in mind to minimize the cleavage of the sensitive N-O bond. 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.
Scheme 1. Synthesis of hydroxyimidazoles 4a-d and 2a-e.

Slow crystallisation of the three final products into water gave single crystals which were analysed by X-ray experiments, confirming thus each structure (Figure 3). 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-hydroxyimidazolide 2b crystallized with one molecule of water in a P21/n crystal cell. On the contrary N-hydroxyimidazolide 2a and 2d crystallized without water and presented a crystal cell with Pn and P21/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 for forming diethyl methylphosphonate. When using epibromohydrin, oxiranylmethyl phosphonate 12 was isolated only in a low yield (20%, litt. 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). The 3-phosphonoacrolein 10 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. A reductive amination was finally performed using O-benzyl hydroxylamine in methanol and sodium cyanoborohydride. After flash chromatography, the phosphonoallyl benzoxylamine 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

Figure 3. Conformations adopted in the crystal for phosphinic acids 2a, 2b and 2d and their crystal packing.
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-e 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 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, despite a large excess of hydrochloric acid (6 M) was added 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.

![Scheme 2. Synthesis of protected N-benzzyloximidazolones 7a-c and 3e.](image)

**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. 35-70µm). 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$_2$PO$_4$ (0.1 % in water/acetonitrile, 1:1).

**Preparation of precursor.**

Dibenzy1 (3-oxopropyl)phosphonate (5) was prepared in two steps from dibenzy1phosphinate according to the procedure already described. Nevertheless for the first step, cesium carbonate in the presence of iodide tetrabutylammonium has been used instead of sodium hydride.

**Preparation of precursors. α-Ketoxoximes (6)**

3-Hydroxyiminono-pentane-2,4-dione (6a). 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 x 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 x 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-(hydroxyiminono)-3-oxobutanoate (6b).** The purification by recrystallization from toluene afforded the expected compound. Yield: 74% (0.19 g).

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

1-(Furan-2-yl)-2-(hydroxyiminono)butane-1,3-dione (6d). 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, $^3$J$_{HH} = 3.1$ Hz, $^3$J$_{HH} = 1.4$ Hz, 1H), 7.28 (d, $^3$J$_{HH} = 3.1$ Hz, 1H), 7.51 (d, $^3$J$_{HH} = 1.4$ 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 dibenzy1 (3-oxopropyl)phosphonate (5, 1.0 g, 3.15 mmol), α-ketoxoxime (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.

**Dibenzy1 (2-(5-acetyl-1-hydroxy-1H-imidazol-2-yl)ethyl)phosphonate (4a).** The resulting residue was purified by column chromatography (silica, EtOAc/EtOH 1:100 to 70:30) to afford the desired product. Yield: 80% (1.4 g). 1H NMR (400.13 MHz, CDCl3) δ 2.11–2.19 (m, 2H), 2.30 (s, 3H), 2.89–2.98 (m, 2H), 4.91 (dd, J2H1 = 11.9 Hz, J1P2 = 8.0 Hz, 2H), 4.96 (dd, J2H1 = 11.9 Hz, J2H2 = 9.3 Hz, 2H), 6.37 (dd, J2H1 = 3.3 Hz, J2H2 = 1.76 Hz, 1H), 6.72 (d, J2H2 = 3.3 Hz, 1H), 7.19–7.27 (m, 11H). 13C NMR (100.61 MHz, CDCl3) δ 13.13 (s), 17.66 (s), 23.29 (d, J2C1 = 140.5 Hz), 67.73 (d, J2CP = 6.6 Hz), 107.13 (s), 110.99 (s), 119.29 (s), 127.93 (s), 128.61 (s), 128.66 (s), 135.76 (d, JCP = 5.8 Hz), 141.13 (s), 144.18 (s). 31P NMR (161.97 MHz, CDCl3) δ 32.79 (s). HRMS (ESI) m/z [M+H]+ calculated for C22H20N2O3P 429.1579, found 429.1577.

**Deprotection reaction. N-hydroxyimidazoles.** Method A: In a Schlenck tube was introduced palladium dihydroxide 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-Ethoxy carbonyl)-1-hydroxy-1H-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). 1H NMR (400.13 MHz, D2O): δ 1.23 (t, J2H1 = 7.0 Hz, 3H), 1.96–2.04 (m, 2H), 2.38 (s, 3H), 3.05–3.14 (m, 2H), 4.27 (q, J2H1 = 7.0 Hz, 2H). 13C NMR (100.16 MHz, DMSO-d6): δ 8.13 (s), 10.51 (s), 15.09 (d, JCP = 3.7 Hz), 20.06 (d, JCP = 136.8 Hz), 59.96 (s), 115.32 (s), 132.00 (s), 140.96 (d, JCP = 13.9 Hz), 156.08 (s). 31P NMR (161.97 MHz, D2O) δ 25.67 (s). HRMS (ESI) m/z [M+H]+ calculated for C9H9N2O3P 279.0746, found 279.0739.

(2-(1-Hydroxy-5-(hydroxyphenyl)methyl)-1H-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). 1H NMR (400.13 MHz, D2O): 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). 13C NMR (100.61 MHz, D2O) δ 9.05 (s), 17.94 (d, JCP = 3.6 Hz, 24.38 (d, JCP = 134.6 Hz), 65.11 (s), 123.52 (s), 127.50 (s), 128.23 (s), 128.78 (s), 139.37 (s), 140.71 (d, JCP = 14.6 Hz). 31P NMR (161.97 MHz, D2O) δ 21.47 (s). HRMS (ESI) m/z [M+H]+ calculated for C15H16N3OP 313.0953, found 313.0955.

Method B: At 0°C, trimethylsilyl bromide (1.27 mL, 10 mmol) was added to a solution of benzyl phosphonate (4a, 4b or 4c, 1 mmol) in dichloromethane (10 mL). The reaction mixture was stirred 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-1H-imidazol-2-yl)ethyl)phosphonic acid (2a). Yield 96% (0.24 g). 1H NMR (400.13 MHz, D2O) δ 2.00–2.09 (m, 2H), 2.41 (s, 3H), 2.48 (s, 3H), 3.07–3.14 (m, 2H). 13C NMR (100.61 MHz, D2O) δ 11.52 (s), 17.67 (d, JCP = 3.6 Hz), 23.17 (d, JCP = 137.5 Hz), 29.58 (s), 125.20 (s), 134.54 (s), 142.96 (d, JCP = 14.6 Hz), 190.80 (s). 31P NMR (161.97 MHz, D2O) δ 24.08 (s). HRMS (ESI) m/z [M+H]+ calculated for C15H16N3OP 249.0640, found 249.0637.

(2-(5-Benzonyl-1-hydroxy-1H-imidazol-2-yl)ethyl)phosphonic acid (2c). Yield: 93% (0.29 g). 1H NMR (400.13 MHz, DMSO-d6) 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). 13C NMR (100.61 MHz, DMSO-d6) δ 14.00 (s), 18.75 (s), 24.78 (d, JCP = 135.4 Hz), 125.11 (s), 128.46 (s), 129.03 (s), 137.82 (s), 144.51 (d, JCP = 15.4 Hz), 184.73 (s). 31P NMR (161.97 MHz, DMSO-d6) δ 23.58 (s). HRMS (ESI) m/z [M+H]+ calculated for C15H15N2O3P 311.0797, found 311.0797.
(2-((Furan-2-carbonyl)-1-hydroxy-1H-imidazol-2-yl)ethyl)phosphonic acid (2d). Yield: 97% (0.25 g). 1H NMR (400.13 MHz, CDCl3) δ 1.32 (t, JHH = 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). 13C NMR (100.61 MHz, CDCl3) δ 16.33 (d, JCP = 6.6 Hz), 51.72 (d, JCP = 24.9 Hz), 61.87 (d, JCP = 5.9 Hz), 77.95 (s, 1H), 119.31 (s), 120.70 (d, JCP = 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, JCP = 5.1 Hz), 156.68 (s). 31P NMR (161.97 MHz, CDCl3) δ 16.99 (s). HRMS (ESI) m/z [M+H]+ calculated for C12H18F2N2O3P 437.1642, found 437.1642.

(E)-Diethyl (3-(1-benzoxyl)-3-(4-fluorophenyleureido)prop-1-en-1-yl)phosphonate (8c). From 4-fluorophenylisocyanate (1.2 mL, 10 mmol), the desired product was obtained. Yield: 20% (2.1 g). 1H NMR (400.13 MHz, CDCl3) δ 1.32 (t, JHH = 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), 6.76–6.89 (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). 13C NMR (100.61 MHz, CDCl3) δ 16.32 (d, JCP = 5.8 Hz), 51.67 (d, JCP = 24.9 Hz), 61.96 (d, JCP = 5.9 Hz), 77.88 (s), 115.51 (d, JCP = 22.7 Hz), 120.54 (d, JCP = 187.4 Hz), 121.18 (d, JCP = 7.3 Hz), 129.03 (s), 129.40 (s), 134.97 (s), 133.46 (d, JCP = 2.2 Hz), 134.71 (s), 146.27 (d, JCP = 5.1 Hz), 156.82 (s), 159.15 (d, JCP = 243.0 Hz). 31P NMR (161.97 MHz, CDCl3) δ 17.02 (s). HRMS (ESI) m/z [M+H]+ calculated for C21H27F2N2O3P 543.1417, found 543.1423.

General Procedure. N-phenylisooxazoliones. Under N2, 8a-c (1 eq) was dissolved in THF (0.1 mol/L) and Bu2OK (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-phenyl-2-oximidazolidin-4-yl)methylphosphonate (7b). From 8b (1.5 g, 3.6 mmol), the desired product was obtained. Yield: 75% (1.13 g). 1H NMR (400.13 MHz, CDCl3) δ 1.31 (t, JHH = 7.0 Hz, 3H), 1.32 (t, JHH = 7.0 Hz, 3H), 1.85 (ddd, JHP = 16.7 Hz, JHH = 15.2 Hz, JHH = 11.1 Hz, 1H), 2.25 (ddd, JHP = 21.1 Hz, JHH = 15.2 Hz, JHH = 2.0 Hz, 1H), 3.36 (dd, JHH = 8.2 Hz, JHH = 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, 7H). 13C NMR (100.61 MHz, CDCl3) δ 16.39 (d, JCG = 5.9 Hz, 28.48 (d, JCG = 138.3 Hz), 48.05 (d, JCG = 15.0 Hz), 52.62 (s), 61.01 (d, JCG = 6.9 Hz), 72.62 (d, JCG = 6.6 Hz), 77.98 (s), 121.33 (s), 125.02 (s), 128.41 (s), 128.43 (s), 129.02 (s), 136.26 (s), 136.41 (s), 136.73 (s), 159.84 (s). 31P NMR (161.97 MHz, CDCl3) δ 26.06 (s). HRMS (ESI) m/z [M+H]+ calcd for C24H22N3O4P 419.1724, found 419.1736.

(+)-Diethyl ((1-benzyloxy)-3-(4-fluorophenyl)-2-oximidazolidin-4-yl)methylphosphonate (7e). From 8c (1.6 g, 3.6 mmol), the desired product was obtained. Yield: 61% (0.97 g). 1H NMR (400.13 MHz, CDCl3) δ 1.31 (t, JHH = 7.0 Hz, 6H), 1.82 (ddd, JHP = 16.9 Hz, JHH = 15.2 Hz, JHH = 11.1 Hz, 1H), 2.18 (ddd, JHP = 17.2 Hz, JHH = 15.2 Hz, JHH = 2.1 Hz, 1H), 3.34 (dd, JHH = 8.2 Hz, JHH = 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). 13C NMR (100.61 MHz, CDCl3) δ 16.40 (d, JCG = 6.0 Hz, 28.54 (d, JCG = 138.9 Hz), 48.43 (d, JCG = 15.0 Hz), 52.72 (s), 62.02 (d, JCG = 6.6 Hz), 62.12 (d, JCG = 6.6 Hz), 78.03 (s), 116.11 (d, JCG = 22.7), 123.53 (d, JCG = 8.0 Hz), 128.45 (s), 129.24 (s), 132.68 (s), 136.35 (s), 159.94 (s), 160.05 (d, JCG = 245.9 Hz). 31P NMR (161.97 MHz, CDCl3) δ 25.83 (s). HRMS (ESI) m/z [M+H]+ calcd for C26H23F3N3O6P 473.1649, found 419.1642.

General Procedure. N-Hydroxyimidazolones. In a schlenk tube and under N2, the appropriate amount of Pd(OH)2/C (10%) was introduced and two vacuum-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 (3h 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-oximidazolidin-4-yl)methylphosphonate (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). 1H NMR (400.13 MHz, CDCl3) δ 1.12 (t, JHH = 7.1 Hz, 3H), 1.36 (t, JHH = 7.0 Hz, 3H), 1.90 (ddd, JHP = 17.4 Hz, JHH = 15.0 Hz, JHH = 10.7 Hz, 1H), 2.25 (ddd, JHP = 21.3 Hz, JHH = 14.8 Hz, JHH = 2.7 Hz, 1H), 3.05 (dq, JHH = 14.2 Hz, JHH = 7.1 Hz, 1H), 3.34 (dd, JHH = 8.2 Hz, JHH = 6.6 Hz, 1H), 3.49–3.58 (m, 1H), 3.73–3.77 (m, 1H), 3.82–3.88 (m, 4H), 4.11–4.16 (m, 4H), 8.46 (bs, 1H). 13C NMR (100.61 MHz, CDCl3) δ 12.59 (s), 16.44 (d, JCG = 5.9 Hz), 16.46 (d, JCG = 5.9 Hz), 28.70 (d, JCG = 139.1 Hz), 36.12 (s), 47.00 (s), 54.28 (d, JCG = 1.5 Hz), 62.10 (d, JCG = 6.6 Hz), 62.24 (d, JCG = 6.6 Hz), 163.96 (s). 31P NMR (161.97 MHz, CDCl3) δ 26.15 (s). HRMS (ESI) m/z [M+H]+ calcd for C10H12N2O4P 281.1266, found 281.1257.

(+)-Diethyl ((1-hydroxy-3-phenyl)-2-oximidazolidin-4-yl)methylphosphonate (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). 1H NMR (400.13 MHz, CDCl3) δ 1.35 (t, JHH = 7.0 Hz, 3H), 1.36 (t, JHH = 7.1 Hz, 3H), 1.95 (ddd, JHP = 17.1 Hz, JHH = 15.2 Hz, JHH = 11.1 Hz, 1H), 2.28 (ddd, JHP = 21.2 Hz, JHH = 15.0 Hz, JHH = 2.2 Hz, 1H), 3.61 (dd, JHH = 8.4 Hz, JHH = 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). 13C NMR (100.61 MHz, CDCl3) δ 16.40 (d, JCG = 6.6 Hz), 28.52 (d, JCG = 139.0 Hz), 48.34 (s), 53.44 (s), 62.24 (d, JCG = 6.6 Hz), 62.25 (d, JCG = 6.6 Hz), 121.90 (s), 125.31 (s), 129.30 (s), 136.60 (s), 161.93 (s). 31P NMR (161.97 MHz, CDCl3) δ 26.12 (s). HRMS (ESI) m/z [M+H]+ calcd for C26H22N3O4P 399.1722, found 399.1722.

Conclusion

N-Hydroxyimidazoles 2a-d and cyclic N-hydroxyureas 13a-e, 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-oxopropanyl)phosphate 5, α-ketoaminoximes 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.

Acknowledgements

Dr. Camille Midrier and Dr. Sonia Montel were supported in part by grants from Bayer CropScience AG and from the Agence Nationale de la Recherche et de la Technologie.
(ANRT) and the Centre National de la Recherche Scientifique (CNRS).

Notes and references


Crystal single structures were deposited at the Cambridge Crystallographic Data Centre and referenced with numbers: CCDC 959100 (2a); CCDC 959101 (2b) and CCDC 959102 (2d). All crystallographic data are free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

