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Preparation of 3-benzyloxy-2-pyridinone functional linkers: tools for the synthesis of 3,2-hydroxypyridinone (HOPO) and HOPO/hydroxamic acid chelators

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ABSTRACT

In contrast to 2,3-dihydroxypyridine, the 3-benzyloxy protected derivative, **2**, undergoes facile alkylation at ambient temperatures with a variety of functionalized alkyl halides in good yields. This alkylation has been used to prepare a number of linkers that permit the attachment of 3,2-HOPO moieties onto various scaffolds using a wide range of coupling methods. The Mitsunobu reaction of **2** with representative alcohols was found to be of limited value due to competing O-alkylation that led to product mixtures. The phthalimide **3j** can be converted in two steps to HOPO isocyanate **6** in excellent yields. Isocyanate **6** can be coupled to amines at room temperature or to alcohols in refluxing dichloroethane to obtain the corresponding urea or carbamate linked ligand systems. The coupling of isocyanate **6** with TREN followed by deprotection gave the tris-HOPO **10**, an interesting target as it has both cationic and anionic binding sites. The HOPO hydroxylamine linker **11** was shown to be especially valuable as its coupling with carboxylic acids proceeds with the concomitant generation of an additional hydroxamate ligand moiety in the framework. The utility of this linker was shown by the preparation of two mixed HOPO-hydroxamate chelators, **16** and **19**, based on the structure of desferrioxamine, a well-known trihydroxamate siderophore.

1. Introduction

Siderophores are low molecular weight molecules with high affinity for iron (III) that are produced by bacteria and fungi to sequester iron from their environment. Structures of natural siderophores can be quite diverse and the ligand groups involved in the complexation of iron vary. Desferrioxamine, DFO is a trihydroxamate that was first isolated from *Streptomyces pilosus* in 1950 and is probably the most widely studied siderophore in terms of therapeutic potential. DFO is used for the treatment of iron overload in patients with β-thalassemia.[1] It is one of the rare siderophores to have a functional group (amine) available for subsequent modification.[2] This fact has facilitated the preparation of a number of DFO-conjugates for various biochemical studies.[3] Enterobactin is a siderophore of enterobacteria in which three catecholate groups anchored to a cyclic serine trimer backbone are used to bind the ferric iron in an hexadentate manner.[4] Many analogs of both DFO and enterobactin have been synthesized and examined for iron coordination and potential biomedical applications (Fig. 1).[5]

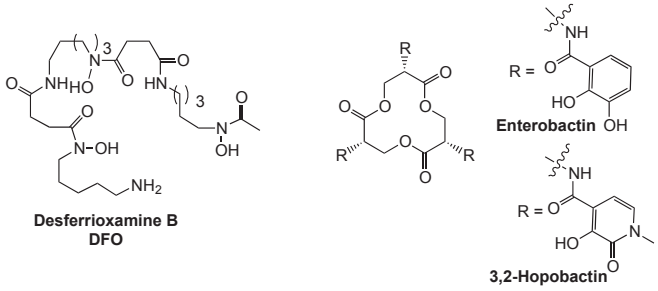

Fig. 1. Structures of desferrioxamine, enterobactin and 3,2-hopobactin.

Hydroxypyridinones, HOPOs, are powerful chelating groups for hard metal ions (Fig. 2). As chelating groups, one could view HOPOs as monobasic pyridine analogs of catechols in which bidentate coordination occurs through both oxygens. There has been much interest in the incorporation of this ligand onto various platforms to prepare new generations of synthetic siderophores. The use of hydroxypyridinones as 'privileged' structures for the design of medicinal drugs has been recently reviewed.[6] As therapeutic agents, the 3,4-HOPO, *deferiprone,* is used for in vivo iron clearance

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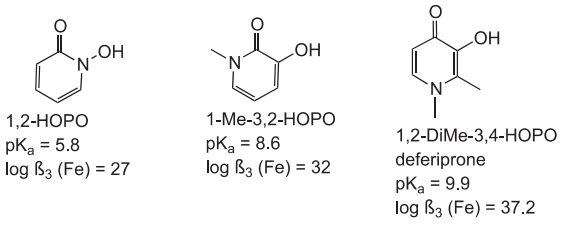


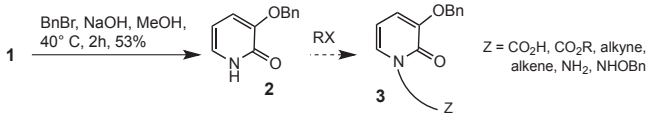
Fig. 2. Hydroxypyridinone chelators for Fe(III).[16]

(Fig. 2).[7] HOPO compounds have also been evaluated for cancer treatment[8] and as novel antibacterial compounds.[9,10] HOPO siderophores have been studied in a variety of diagnostic applications including as MRI contrast agents[11,12] and in positron emission tomography (PET).[13,14] It is important to mention that hydroxypyridinones for selective actinide binding and remediation of transuranic waste is an active area of interest.[15]

Methods to introduce hydroxypyridinones onto scaffolds and for its conjugation into biomolecules are limited both in terms of number and flexibility. One popular approach to introduce the 3,2-HOPO ligand, developed by Raymond and co-workers, involves acylation of an activated HOPO carboxylic acid substrate (**C**, Scheme 1) with various amines. Reagent **C** is available in four steps from commercially available 2,3-dihydroxypyridine, DHP, **1**. The key step in this sequence involves carboxylation at the 4 position of the pyridinone ring of **A** using Kolbe–Schmitt conditions to get **B**. This reaction is limited in terms of substrate tolerance and works best when there is either a methyl or ethyl group on the nitrogen of the pyridinone ring. The activated ester **C** is prepared in two steps from **B** and can be coupled to a polyamine such as tris(2-amino)ethylamine, TREN (Scheme 1) to obtain the hexadentate siderophore, **TRENHOPO**, after deprotection.[17] The method developed by Hider and co-workers for tethering HOPO to amine backbones involves the use of an activated acyl derivative introduced on the nitrogen of the pyridinone ring. The sequence begins with the alkylation of **1** with excess ethyl bromoacetate at refluxing temperature to give **D**. The workup for the reaction involves removing the excess ethyl bromoacetate, a potent lachrymator, by distillation. Subsequently, ester **D** is converted in two steps to NHS ester, **E**, for acylation with amines. Coupling with an amine, for example, TREN, followed by deprotection gives **CP-130**.[18] The serious drawback to this approach is that the alkylation of **1** is a poor reaction with most electrophiles. Both of the protocols described above, involve attachment of the HOPO moiety via an amide linkage.

Our group has published methods for the attachment of the 3,2-HOPO ligand onto scaffolds without concomitant formation of an amide bond. The goal has been to prepare less structurally rigid ligands with greater water solubility. In one method, ester **D** was converted into electrophilic imidate salt, **F**, which reacts readily with secondary amines and phenols. For example, salt **F**, was reacted with 1,4,7-triazacyclononane, to give tris HOPO ligand, **TACN-3,2-HOPO**, after deprotection.[19]

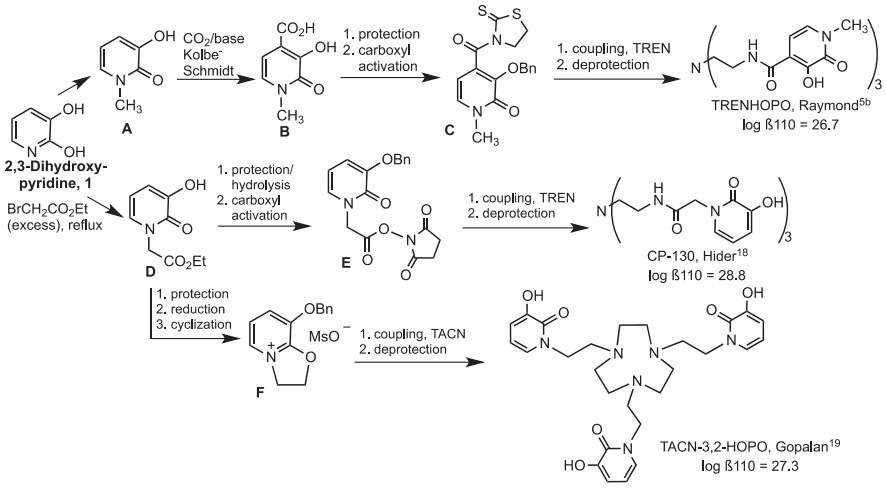
Given the interest in siderophores for various applications, synthetic methods that would allow the introduction/tethering of 3,2-HOPO onto a variety of scaffolds are of value. However, as discussed, current methods to introduce 3,2-HOPO ligands to prepare a variety of targets are limited. There is a need for functional 3,2-HOPO linkers, **3**, that can be readily conjugated/tethered to polymers, biomolecules and antibacterial drugs (Scheme 2). Further, functional linkers, **3**, could be used to prepare new classes of siderophores including those that have mixed ligands and analogs essential for structure activity relationships. It is important that the functional groups, Z, on the HOPO linker can be varied to accommodate the proposed coupling method to the substrate of interest.



Scheme 2.

The major impediment to prepare 3,2-HOPO linkers has been limitations on the alkylation of 2,3-dihydroxypyridine, **1**. In this paper, we report that *O*-benzyl protected HOPO, **2**, is a good nucleophile and can be readily alkylated to give access to a variety of functional HOPO linkers, **3**. The synthetic utility of the linkers prepared in this study has been demonstrated by the preparation of a urea linked tris-3,2-HOPO attached to a TREN backbone. It is also noteworthy that this study gives access to a new class of HOPO linkers that can be coupled to acids with concomitant generation of a hydroxamate bond. To demonstrate the value of this class of linkers, two new mixed ligand hydroxamate-HOPO siderophores, which are modeled on DFO, have been prepared.

We began with a systematic study of the alkylation of 3-benzyloxy-2-pyridinone, **2**, which is readily prepared by O-benzylation of **1** (Scheme 2).[20] There have been some isolated examples in the literature of *N*-alkylation of protected 3-alkoxy-2-



Scheme 1.

pyridinones, such as **2**.[21] However, the reaction has not been well studied. Further, the relative reactivity of the *O*-protected derivative of 2,3-dihydroxypyridine, **2**, relative to the parent, **1**, in alkylation reactions has not been evaluated. It is known that protection of the 3-hydroxy group of both 3,2 and 3,4-HOPOs has a large impact on the observed regioselectivity of aminomethylation (Mannich reaction) compared to the corresponding unprotected parents.[22] Hence, a potential concern was the possibility of competing O-alkylation with the desired N-alkylation of the substrate and how that might impact the utility of this reaction.

2. Results and discussion

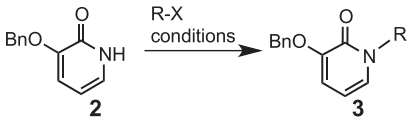
2.1. Alkylation of 2

It is known that the alkylation of **1** with ethyl bromoacetate can be carried out using large excess of the alkylating agent under reflux conditions. To determine the effect of protecting the 3-hydroxy group, the alkylation of **2** with ethyl bromoacetate (1 equiv) using sodium hydride in DMF was investigated. The reaction was facile and the desired *N*-alkylated product was isolated in 93% yield after only 2 h (Table 1, entry 1). The ease of this reaction compared to the direct alkylation of **1** was remarkable. Further, the product from O-alkylation was not observed.

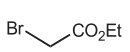
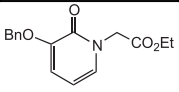
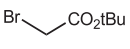
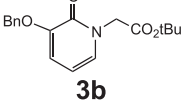
The positive results from this initial reaction led us to study the alkylation of **2** with *tert*-butyl bromoacetate (Table 1, entry 2) under a variety of conditions. Treatment of **2** with sodium hydride (1.1 equiv) in DMF followed by addition of *tert*-butyl bromoacetate (1.1 equiv), gave the desired product in 80% yield after chromatographic purification. The reaction could be carried out in either DMF or THF though the reaction was much faster in DMF as expected. When the alkylation was carried out using potassium fluoride on alumina as the base in acetonitrile solvent, the product was isolated in 73% yield after purification. Although the KF/alumina is somewhat expensive, the simple filtration work-up and avoiding DMF (easier for workup) is an advantage. The product from O-alkylation was not observed in either the sodium hydride or KF/alumina reactions. The reaction was also investigated using either DBU or K_2CO_3 as the base in DMF. In both cases, the product formation was very slow, making it an unattractive reaction.

The alkylation study was then expanded to include a variety of functionalized alkyl halides (Table 2). In the case of reactive allyl bromide (Table 2, entry 1), excellent yields of the desired *N*-alkylated product could be obtained using either sodium hydride in DMF or KF/alumina. In general, the yields of the alkylation reaction were higher when sodium hydride in DMF was used instead of KF/alumina. In a few cases, some of the corresponding *O*-alkylated product, **4**, was also formed (Table 2, entries 2, 4, 8, 9, 11). The O-alkylation products were much less polar than the desired product of N-alkylation and were easily removed by chromatography.

Table 1
Alkylation of 3-benzyloxy-2-pyridinone, **2**, with α-bromoesters



2 **3**

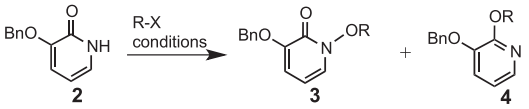
Entry	R-X	Product, 3	Conditions	Yield 3 (%)
1		 **3a**	A	93
2		 **3b**	A B	80 73

Conditions: A. NaH, DMF, 0 °C to rt, N_2, 2 h.
B. KF/alumina, CH_3CN, rt, 24 h.

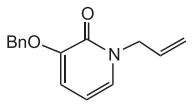
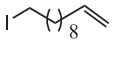
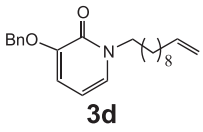
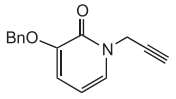
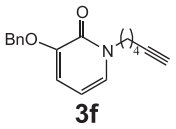
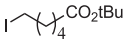
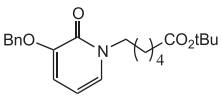
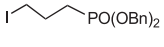
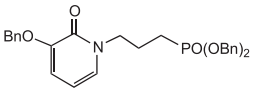
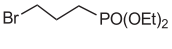
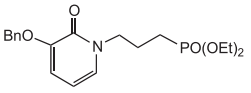
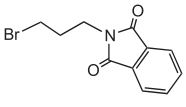
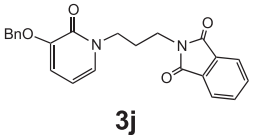
2.2. Alkylation of 2 with alcohols

Because functionalized alcohols are readily available starting materials, the Mitsunobu reaction of **2** using allyl alcohol as a model was investigated. Reaction of HOPO **2** with allyl alcohol in the

Table 2
Alkylation of 3-benzyloxy-2-pyridinone, **2**, with alkyl halides

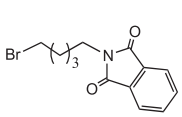
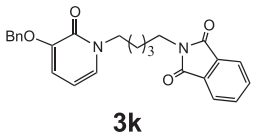
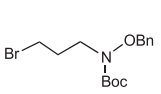
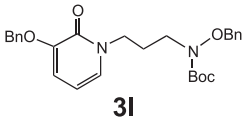
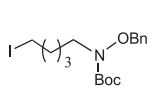
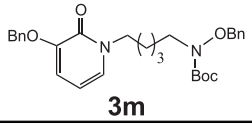


2 **3** **4**

Entry	R-X	Product, 3	Conditions	Yield 3 (%)
1		 **3c**	A B	88 90
2		 **3d**	A	79[a]
3		 **3e**	A B	81 63
4		 **3f**	A B	75[a] 49
5		 **3g**	A	75
6		 **3h**	A	77
7		 **3i**	A	80
8		 **3j**	A	82[a]

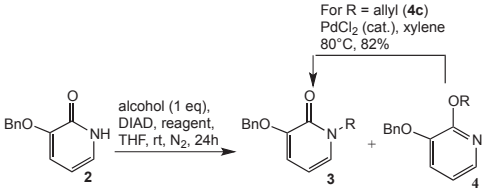
(*continued on next page*)

Table 2 (*continued*)

Entry	R-X	Product, 3	Conditions	Yield 3 (%)
9		 **3k**	A	69[a]
10		 **3l**	A	86
11		 **3m**	A	81[a]

Conditions: A. NaH, DMF, 0 °C to rt, N_2, 24 h.
B. KF/Al_2O_3, CH_3CN, rt, 24 h.
[a] 10–15 % yield of the corresponding *O*-alkylated product **4** was isolated.

presence of diisopropyl azodicarboxylate (DIAD) and polystyrene-supported triphenylphosphine in THF gave predominantly the product of N-alkylation, **3c**, along with 20% of the product from O-alkylation, **4c** (Table 3, entry 1) (Scheme 3). It is noteworthy that the *O*-allyl product, **4c**, can be easily rearranged to the *N*-allyl product, **3c**, in xylene at 80 °C in the presence of a catalytic amount of $PdCl_2$ (see 4.6). When the Mitsunobu reaction of **2** was carried out with 11-decen-1-ol under the same conditions, the desired product of N-alkylation, **3d**, was obtained in only 27% yield along with 20% yield of the corresponding *O*-alkylated product, **4d** (Table 3, entry 2). To



Scheme 3.

Table 3
Reaction of **2** with alcohols under Mitsunobu conditions

Entry	ROH	Reagent	Product, yield %	Product, yield %
1	Allyl alcohol	PS-PPh_3	**3c**, 47	**4c**, 20
2	11-Undecen-1-ol	PS-PPh_3	**3d**, 27	**4d**, 20
3	11-Undecen-1-ol	PPh_3	**3d**, 26	**4d**, 51

improve the reaction yield, the reaction was performed using triphenylphosphine in place of PS-PPh_3 (Table 3, entry 3). In this case, the product of O-alkylation, **4d**, was the major product and was isolated in 51% yield. While it is interesting to note that alkylation of **2** directly with alcohols is feasible under Mitsunobu conditions, there is significant and undesirable competition with O-alkylation.

2.3. Applications of functional HOPO linkers

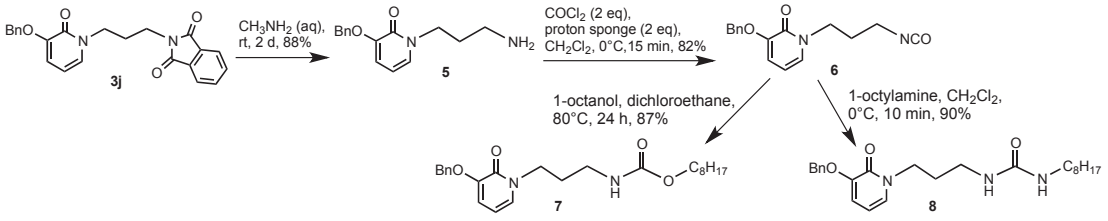
2.3.1. Tethering of 3,2-HOPO via carbamate and urea linkages. The N-alkylation of **2** provides easy access to a variety of HOPO linkers differing in functional groups. The phthalimide products, **3j** and **3k**, are precursors to the corresponding amines, **5**. This was demonstrated by the conversion of phthalimide, **3j**, to amine, **5**, using aqueous methylamine in 90% yield (Scheme 4). Amine **5** has been prepared by an alternate route and successfully coupled with acid chlorides and sulfonyl chlorides.[23]

The conversion of the HOPO amine **5** to the corresponding isocyanate provides a reactive linker for coupling with amines and alcohols. Treatment of amine **5** with a solution of phosgene in toluene in the presence of proton sponge in dichloromethane gave the corresponding isocyanate **6** in 82% yield. The isocyanate was of sufficient purity to use without further purification. The reaction of HOPO isocyanate was then examined with alcohols and amines. As an example, reaction of isocyanate, **6**, with 1-octanol proceeded cleanly in dichloroethane at 80 °C to give carbamate linked HOPO, **7**. As expected, the reaction of 1-octylamine with isocyanate, **6**, in dichloromethane at 0 °C was faster and gave excellent yield of the corresponding HOPO urea, **8**, after chromatographic purification.

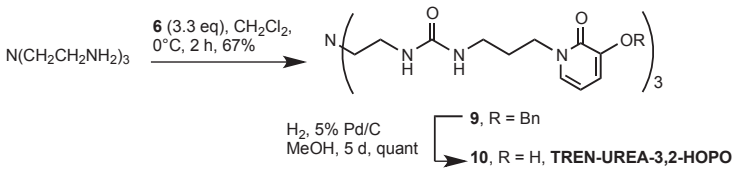
*2.3.2. Synthesis of urea-linked tris-HOPO chelator, **10**.* Ion pair recognition is an emerging area in supramolecular chemistry.[24] There has been much interest in the design of ditopic chelators capable of simultaneous complexation of both anions and cations in their scaffolds. It has been hypothesized that the binding of the cation could preorganize the receptor for enhanced binding of the anion.[25] TREN based urea receptors have been shown to be effective for the binding of oxyanions and to facilitate their encapsulation.[26] TREN has been a highly used tripodal platform to prepare hydroxamates and hydroxypyridinones that show strong binding to iron.[27]

A TREN tris-urea HOPO ditopic chelator was a tempting target to demonstrate the utility of the new HOPO isocyanate linker **6**. Reaction of TREN with a slight excess of isocyanate **6**, in dichloromethane at 0 °C gave the protected HOPO, **9**, in 67% yield after chromatographic purification (Scheme 5). Debenzylation of **9** using a hydrogen balloon and 5% Pd on carbon gave the desired urea-linked tris-HOPO chelator, **10**, in quantitative yield.

2.3.3. Synthesis of mixed HOPO/hydroxamate analogs of desferrioxamine, DFO. In DFO and enterobactin, iron complexation is achieved by three hydroxamate or three catecholate ligands, respectively. There are also many natural siderophores where the ferric ion is complexed by a mixed ligand system. For example, *Mycobacterium tuberculosis* produces a suite of siderophores called



Scheme 4.



Scheme 5.

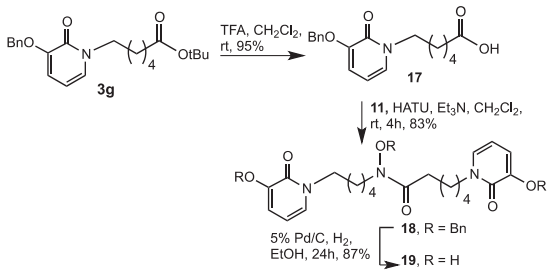
carboxymycobactins to sequester iron to support its growth.[29] The coordination of iron is accomplished by a cyclic hydroxamic acid, a hydroxamic acid and a phenolate oxazoline. In aerobactin, one of the siderophores of pathogenic *Escherichia coli*, the complexation of iron is achieved by two hydroxamic acids and a citrate moiety.[28]

While mixed ligand chelators occur widely in natural siderophores,[29] synthetic analogs have not been as widely studied perhaps due to greater difficulty in their syntheses. An interesting example of the use of mixed ligands is the recent publication of a biscatecholate–monohydroxamate conjugated to an antibiotic to generate a new drug candidate that is selective against *A. baumannii*.[30] A recent review on sequestering agents for actinides documents several synthetic mixed ligand 3,2-HOPO chelators.[15] Our own group has published the synthesis of mixed ligand 3,2-HOPO/hydroxamic acid and 3,2-HOPO/carboxylic acid and 3,2-HOPO mixed chelators on polyphenol platforms.[31]

The HOPO linkers developed in this study are convenient intermediates for the synthesis of HOPO mixed ligand systems that have not been hitherto examined. We envisioned using the bifunctional linkers to prepare mixed HOPO/hydroxamic acid ligands inspired by the structure of the siderophore, desferrioxamine, DFO. The protected HOPO-hydroxylamine linker **11** is a useful tool as it provides a novel advantage. After deprotection of **3m** to the corresponding hydroxylamine **11**, it can be coupled to a carboxylic acid. This coupling reaction generates a hydroxamic acid linkage, resulting in a mixed hydroxamate-HOPO mixed ligand system.

The first DFO analog to be prepared was the HOPO/dihydroxamate mixed ligand, **15**, in which one hydroxamic acid of DFO is replaced with a 3,2-HOPO ligand (Scheme 6). The protected hydroxylamine HOPO, **11**, was coupled to the functionalized carboxylic acid, **12**, using HATU in the presence of triethylamine in dichloromethane to give **13**. It is pleasing to note that this key step, in which the hydroxamic acid bond is formed, proceeded in good yield. Removal of the Boc protecting group of **13** using TFA gave the free hydroxylamine **14**, in 77% yield after chromatographic purification. Hydroxylamine, **14**, was coupled with acetyl chloride in the presence of triethylamine in dichloromethane to generate the fully protected mixed ligand **15**. Global deprotection of the benzyl protecting groups using 5% Pd on carbon gave the mixed dihydroxamic acid/HOPO ligand, **16**, in excellent yield. It is important to point out that the chain lengths of both linkers **11** and **12** can be readily varied. Also, a variety of acid chlorides can substitute for acetyl chloride in the preparation of **15**, making this synthetic approach highly flexible.

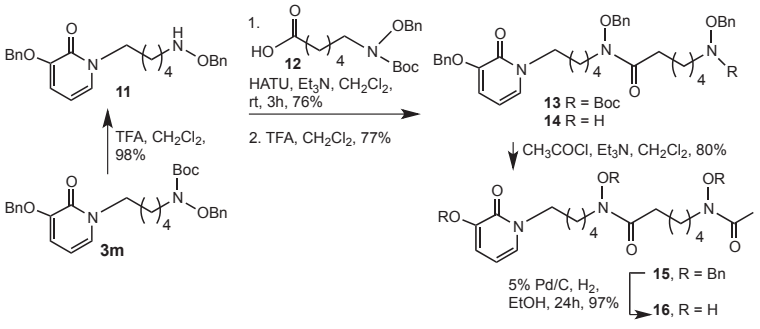
The next target to be prepared was the diHOPO/hydroxamate mixed ligand, **19**, in which two hydroxamic acids of DFO are replaced with 3,2-HOPO ligands (Scheme 7). It is interesting to note that the chemistry uses two HOPO linkers produced from this work to create the mixed ligand siderophore. Hydrolysis of t-butyl ester, **3g**, using TFA in dichloromethane gave the HOPO acid, **17**, in 95% yield. HATU mediated coupling of HOPO acid, **17**, with HOPO hydroxylamine, **11**, generated the fully protected mixed ligand, **18**, in 83% yield after purification. Global deprotection of the benzyl groups was accomplished using 5% Pd/C in ethanol to give the diHOPO/hydroxamate mixed ligand DFO analog, **19**, in 87% yield.



Scheme 7.

3. Conclusions

The hydroxypyridinone ligand has become an integral part in the design of new classes of synthetic siderophores targeted towards therapeutic and diagnostic applications. In particular, HOPO and HOPO/terephthalamide (mixed ligand) chelators have been widely studied as MRI contrast agents.[11] Hence, synthetic methods that give access to new generations of HOPO chelators as well as those that allow the conjugation of this ligand to existing platforms are important. The functional HOPO linkers reported in this study allow its attachment to various platforms



Scheme 6.

via a number of coupling protocols. For instance, the HOPO alkynes from this study are potential partners for both click chemistry with azides[32] and Sonogashira coupling[33] with aryl halides. The ability to alkylate 3-benzyloxy-2-pyridinone, **2**, with a variety of functionalized alkylating agents in good yields and under mild conditions (sodium hydride in DMF at room temperature) removes a serious hurdle faced by researchers in this area by greatly improving the availability of HOPO coupling agents. In the case of more active alkylating agents, such as allyl bromide, the alkylation can be performed using potassium fluoride on alumina. This protocol offers simplicity in the product isolation. In most cases, O-alkylation of **2** was a minor pathway and posed no problems.

It is interesting to note that **2** can function as a partner in Mitsunobu reactions with primary alcohols. To our knowledge, this reaction has not been studied before.[34] Unfortunately, under the reaction conditions both *O* and *N*-alkylated products of **2** are formed with low selectivity, limiting the usefulness of this approach.

Particularly useful HOPO linkers to emerge from this work are the isocyanate **6** and the HOPO-hydroxylamine, **11**. HOPO isocyanate, **6**, should be a highly desirable partner for bioconjugation where an amine is available for coupling. This reagent also allows the preparation of new classes of potential ditopic receptors as demonstrated by the preparation of **TREN-UREA-3,2-HOPO, 10**. The syntheses of mixed HOPO/hydroxamate ligands, **16** and **19**, exemplifies the special advantages of linkers such as **11**. The tethering of an HOPO moiety with concomitant generation of a hydroxamate binding site in the skeleton is novel. In addition, ligands **16** and **19** are the first examples of mixed hydroxamate/HOPO analogs of DFO in which the HOPO moiety is part of the backbone and not just appended to the terminal amine of DFO. This new coupling protocol should greatly enhance the ability to synthesize mixed HOPO-hydroxamate mixed ligands for therapeutic and diagnostic studies.

4. Experimental

4.1. General methods

Melting points were measured in capillary tubes and are uncorrected. Infrared spectra were recorded on an FT-IR Spectrometer. NMR spectral samples were prepared using $CDCl_3$ unless otherwise indicated. All chemical shifts are reported in parts per million (ppm) relative to the deuterated solvent or an internal tetramethylsilane (TMS) reference. High resolution mass spectral analyses were obtained using electrospray ionization with the samples dissolved in either chloroform or methanol. Analytical thin layer chromatography was performed on silica 60/F254 plastic plates. Column chromatography was done using silica gel (60–200 mesh or 200–400 mesh) unless otherwise indicated. Radial chromatography was conducted using a centrifugal thin-layer chromatograph and plates were prepared using silica gel 60 containing gypsum. Polystyrene-triphenylphosphine (PS-PPh_3) had a loading capacity of 1.88 mmol/g. Sodium hydride (NaH) was obtained as a 57–63% mineral oil dispersion. Potassium fluoride on alumina (KF/Al_2O_3) was 40% by weight KF. Phosgene was obtained as a 20% solution in toluene. 3-(Benzyloxy)pyridin-2(1*H*)-one, **2**, was prepared according to literature procedure.[20]

4.2. Representative procedure A for the alkylation of 3-(benzyloxy)pyridin-2(1*H*)-one, 2, using sodium hydride

*4.2.1. Synthesis of ethyl 2-(3-(benzyloxy)-2-oxopyridin-1(2H)-yl)acetate (**3a**).* To a solution of **2** (0.20 g, 0.99 mmol) in anhydrous DMF (3 mL) under N_2 at 0 °C was added NaH (0.044 g, 1.09 mmol). The mixture was warmed to rt and stirred for 30 min. After cooling back to 0 °C, ethyl bromoacetate (0.12 mL, 1.09 mmol) was added and the mixture stirred at rt for 2 h. The reaction was quenched with saturated NH_4Cl (10 mL) and the product extracted into ethyl acetate (3×30 mL). The combined organic extract was dried (Na_2SO_4) and the solvent removed in vacuo. Excess DMF was removed by Kugelrohr distillation. The crude product was purified by radial chromatography (hexane/ethyl acetate gradient) to give ester **3a** (0.26 g, 93%) as a white solid: mp 114–115 °C; IR (neat) 2986, 1751 (C=O), 1654 (HOPO C=O), 1598 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.43–7.36 (m, 2H), 7.34–7.21 (m, 3H), 6.87 (dd, *J*=6.9, 1.6 Hz, 1H), 6.64 (dd, *J*=7.4, 1.6 Hz, 1H), 5.99 (dd, *J*=7.4, 6.9 Hz, 1H), 5.04 (s, 2H), 4.62 (s, 2H), 4.18 (q, *J*=7.1 Hz, 2H), 1.23 (t, *J*=7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.7, 158.1, 148.6, 136.2, 129.6, 128.4, 127.9, 127.3, 116.1, 104.8, 70.6, 61.6, 50.6, 14.1. HRMS [M+H$^+$] *m*/*z* calcd for $C_{16}H_{18}NO_4$ 288.1236, found 288.1230.

4.3. Representative procedure B for the alkylation of 2 using KF/Al_2O_3

*4.3.1. Synthesis of tert-butyl 2-(3-(benzyloxy)-2-oxopyridin-1(2H)-yl)acetate (**3b**).* To a suspension of **2** (0.20 g, 0.994 mmol) in CH_3CN (17 mL) was added *tert*-butyl bromoacetate (0.22 mL, 1.49 mmol) and KF/Al_2O_3 (1.73 g, 11.9 mmol) and the mixture was stirred at rt for 24 h. The solids were filtered off and rinsed with ethyl acetate. The solvent was removed in vacuo and the crude product was purified by radial chromatography (hexane/ethyl acetate gradient) to give ester **3b** (0.23 g, 73%) as a white solid. Using representative procedure A, **3b** was isolated in 80% yield: mp 130–131 °C; IR (neat) 2975, 1743 (C=O), 1655 (HOPO C=O), 1602 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.44–7.37 (m, 2H), 7.36–7.23 (m, 3H), 6.84 (dd, *J*=7.2, 1.7 Hz, 1H), 6.64 (dd, *J*=7.2, 1.7 Hz, 1H), 6.02 (t, *J*=7.2 Hz, 1H), 5.09 (s, 2H), 4.57 (s, 2H), 1.47 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 166.8, 158.1, 148.8, 136.3, 129.5, 128.5, 127.9, 127.3, 115.9, 104.6, 82.6, 70.7, 51.0, 28.0. HRMS [M+H$^+$] *m*/*z* calcd for $C_{18}H_{22}NO_4$ 316.1549, found 316.1537.

4.4. Synthesis of functional HOPO linkers, 3

*4.4.1. 1-Allyl-3-(benzyloxy)pyridin-2(1H)-one (**3c**).* Representative procedure A was followed using allyl bromide in place of ethyl bromoacetate and the reaction mixture was stirred 24 h to give alkene **3c** as a yellow solid in 88% yield. Using representative procedure B, **3c** was isolated in 90% yield. mp 51–52 °C; IR (neat) 3033, 1652 (HOPO C=O), 1602 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.47–7.40 (m, 2H), 7.40–7.24 (m, 3H), 6.88 (dd, *J*=6.9, 1.7 Hz, 1H), 6.64 (dd, *J*=7.4, 1.7 Hz, 1H), 6.03 (dd, *J*=7.4, 6.9 Hz, 1H), 5.99–5.87 (m, 1H), 5.27–5.15 (m, 2H), 5.12 (s, 2H), 4.61 (dt, *J*=5.9, 1.5 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 157.9, 148.8, 136.3, 132.5, 128.5, 128.5, 127.9, 127.2, 118.3, 115.6, 104.7, 70.6, 51.0. HRMS [M+H$^+$] *m*/*z* calcd for $C_{15}H_{16}NO_2$ 242.1181, found 242.1172.

*4.4.2. 3-(Benzyloxy)-1-(undec-10-enyl)pyridin-2(1H)-one (**3d**).* Representative procedure A was followed using 11-bromoundec-1-ene in place of ethyl bromoacetate and the reaction mixture was stirred 24 h to give alkene **3d** as a yellow oil in 79% yield. The corresponding *O*-alkylated product **4d** was also isolated in 12% yield. **3d**: IR (film) 2926, 1655 (HOPO C=O), 1606 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.46–7.38 (m, 2H), 7.36–7.22 (m, 3H), 6.87 (dd, *J*=7.1, 1.7 Hz, 1H), 6.62 (dd, *J*=7.1, 1.7 Hz, 1H), 5.97 (t, *J*=7.1 Hz, 1H), 5.87–5.70 (m, 1H), 5.08 (s, 2H), 5.04–4.86 (m, 2H), 3.92 (t, *J*=7.4 Hz, 2H), 2.03 (q, *J*=6.8 Hz, 2H), 1.81–1.65 (m, 2H), 1.43–1.19 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.01, 148.83, 139.04, 136.43, 129.06, 128.42, 127.81, 127.25, 115.52, 114.13, 104.34, 70.63, 49.80, 33.76, 29.37, 29.34, 29.19, 29.10, 29.04, 28.86, 26.61.

HRMS [M+H$^+$] *m*/*z* calcd for $C_{23}H_{32}NO_2$ 354.2433, found 354.2430. **4d**: IR (film) 2926, 1595, 1449, 1201 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.73 (dd, *J*=5.0, 1.6 Hz, 1H), 7.46–7.23 (m, 5H), 7.04 (dd, *J*=7.7, 1.6 Hz, 1H), 6.74 (dd, *J*=7.7, 5.0 Hz, 1H), 5.90–5.70 (m, 1H), 5.14 (s, 2H), 5.04–4.86 (m, 2H), 4.38 (t, *J*=6.9 Hz, 2H), 2.04 (q, *J*=6.8 Hz, 2H), 1.85 (quintet, *J*=7.2 Hz, 2H), 1.57–1.18 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.3, 143.1, 139.2, 138.0, 136.8, 128.6, 127.9, 127.2, 120.9, 116.4, 114.1, 71.0, 66.3, 33.8, 29.6, 29.5, 29.4, 29.2, 29.1, 29.0, 26.1. HRMS [M+H$^+$] *m*/*z* calcd for $C_{23}H_{32}NO_2$ 354.2433, found 354.2433.

*4.4.3. 3-(Benzyloxy)-1-(prop-2-ynyl)pyridin-2(1H)-one (**3e**).* Representative procedure A was followed using propargyl bromide in place of ethyl bromoacetate and the reaction mixture was stirred for 24 h to give alkyne **3e** as a light yellow oil in 81% yield. Using representative procedure B, **3e** was isolated in 63% yield: IR (neat) 3217, 2121 (C≡C), 1652 (HOPO C=O), 1602 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45–7.38 (m, 2H), 7.37–7.25 (m, 3H), 7.21 (dd, *J*=7.2, 1.7 Hz, 1H), 6.63 (dd, *J*=7.2, 1.7 Hz, 1H), 6.05 (t, *J*=7.2 Hz, 1H), 5.09 (s, 2H), 4.77 (d, *J*=2.6 Hz, 2H), 2.47 (t, *J*=2.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.6, 148.5, 136.2, 128.5, 127.9, 127.3, 127.2, 115.6, 105.0, 77.1, 75.0, 70.7, 37.5. HRMS [M+H$^+$] *m*/*z* calcd for $C_{15}H_{14}NO_2$ 240.1025, found 240.1022.

*4.4.4. 3-(Benzyloxy)-1-(hex-5-ynyl)pyridin-2(1H)-one (**3f**).* Representative procedure A was followed using 6-iodo-1-hexyne in place of ethyl bromoacetate and the reaction was stirred for 24 h to give alkyne **3f** as a light brown solid in 75% yield. The corresponding *O*-alkylated product **4f** was isolated in 10% yield. Representative procedure B was followed using 6-iodo-1-hexyne in place of *tert*-butyl bromoacetate to give **3f** in 49% yield. **3f**: mp 41–43 °C; IR (neat) 3232, 2952, 2111 (C≡C), 1651 (HOPO C=O), 1592 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46–7.38 (m, 2H), 7.38–7.22 (m, 3H), 6.89 (dd, *J*=6.9, 1.7 Hz, 1H), 6.63 (dd, *J*=7.4, 1.7 Hz, 1H), 6.01 (dd, *J*=7.4, 6.9 Hz, 1H), 5.10 (s, 2H), 3.98 (t, *J*=7.2 Hz, 2H), 2.24 (td, *J*=7.0, 2.7 Hz, 2H), 1.96 (t, *J*=2.7 Hz, 1H), 1.91–1.83 (m, 2H), 1.62–1.50 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 158.1, 148.9, 136.4, 128.9, 128.5, 127.9, 127.3, 115.5, 104.6, 83.7, 70.7, 68.9, 49.1, 28.2, 25.4, 18.1. HRMS [M+H$^+$] *m*/*z* calcd for $C_{18}H_{20}NO_2$ 282.1494, found 282.1484.

*4.4.5. tert-Butyl 6-(3-(benzyloxy)-2-oxopyridin-1(2H)-yl)hexanoate (**3g**).* Representative procedure A was followed using *tert*-butyl 6-iodohexanoate in place of ethyl bromoacetate and the reaction mixture was stirred for 24 h to give ester **3g** as a light brown oil in 75% yield: IR (film) 2935, 1729 (C=O), 1652 (HOPO C=O), 1606 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46–7.36 (m, 2H), 7.36–7.20 (m, 3H), 6.88 (dd, *J*=7.1, 1.7 Hz, 1H), 6.63 (dd, *J*=7.1, 1.7 Hz, 1H), 5.98 (t, *J*=7.1 Hz, 1H), 5.08 (s, 2H), 3.93 (t, *J*=7.3 Hz, 2H), 2.20 (t, *J*=7.4 Hz, 2H), 1.75 (quintet, *J*=7.5 Hz, 2H), 1.61 (quintet, *J*=7.5 Hz, 2H), 1.42 (s, 9H), 1.38–1.29 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.8, 158.0, 148.8, 136.4, 129.1, 128.4, 127.8, 127.2, 115.5, 104.4, 79.9, 70.6, 49.5, 35.2, 28.7, 28.1, 26.0, 24.6. HRMS [M+H$^+$] *m*/*z* calcd for $C_{22}H_{30}NO_4$ 372.2175, found 372.2166.

*4.4.6. Dibenzyl 3-(3-(benzyloxy)-2-oxopyridin-1(2H)-yl)propylphosphonate (**3h**).* Representative procedure A was followed using dibenzyl 3-iodopropylphosphonate in place of ethyl bromoacetate to give **3h** as a yellow oil in 77% yield IR (film) 3033, 1656 (HOPO C=O), 1606 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48–7.21 (m, 15H), 6.77 (dd, *J*=7.2, 1.6 Hz, 1H), 6.60 (dd, *J*=7.2, 1.6 Hz, 1H), 5.93 (t, *J*=7.2 Hz, 1H), 5.07 (s, 2H), 5.06–4.90 (m, 4H), 3.96 (t, *J*=7.0 Hz, 2H), 2.10–1.94 (m, 2H), 1.80–1.68 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.0, 148.8, 136.4, 136.2 (d, J_{PC}=5.6 Hz), 129.0, 128.6, 128.5, 128.5, 128.0, 127.9, 127.3, 115.4, 104.6, 70.7, 67.3 (d, J_{PC}=6.7 Hz), 49.4 (d, J_{PC}=15.7 Hz), 22.9 (d, J_{PC}=141.9 Hz), 22.0 (d, J_{PC}=5.1 Hz). HRMS [M+H$^+$] *m*/*z* calcd for $C_{29}H_{31}NO_5P$ 504.1940, found 504.1927.

*4.4.7. Diethyl 3-(3-(benzyloxy)-2-oxopyridin-1(2H)-yl)propylphosphonate (**3i**).* Representative procedure A was followed using diethyl 3-bromopropylphosphonate in place of ethyl bromoacetate to give **3i** as a yellow oil in 80% yield: IR (film) 2983, 1654 (HOPO C=O), 1604 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48–7.23 (m, 5H), 6.95 (dd, *J*=7.2, 1.8 Hz, 1H), 6.65 (dd, *J*=7.2, 1.8 Hz, 1H), 6.0 (t, *J*=7.2 Hz, 1H), 5.11 (s, 2H), 4.20–3.95 (m, 6H), 2.21–1.98 (m, 2H), 1.88–1.64 (m, 2H), 1.32 (t, *J*=7.0 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.1, 148.9, 136.3, 129.0, 128.5, 128.0, 127.3, 115.5, 104.8, 70.7, 61.7 (d, J_{PC}=6.5 Hz), 49.6 (d, J_{PC}=16.8 Hz), 22.6 (d, J_{PC}=142.4 Hz), 22.2 (d, J_{PC}=4.6 Hz), 16.5 (d, J_{PC}=6.1 Hz). HRMS [M+H$^+$] *m*/*z* calcd for $C_{19}H_{27}NO_5P$ 380.1627, found 380.1628.

*4.4.8. 2-(3-(3-(Benzyloxy)-2-oxopyridin-1(2H)-yl)propyl)isoindoline-1,3-dione (**3j**).* Representative procedure A was followed using *N*-(3-bromopropyl)phthalimide in place of ethyl bromoacetate and the reaction mixture was stirred for 24 h to give phthalimide **3j** as a light yellow solid in 82% yield. The corresponding *O*-alkylated product **4j** was also isolated in 10% yield. **3j**: mp 102–103 °C; IR (neat) 2937, 1702 (C=O), 1650 (HOPO C=O), 1595 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87–7.77 (m, 2H), 7.76–7.64 (m, 2H), 7.46–7.39 (m, 2H), 7.38–7.22 (m, 3H), 7.03 (dd, *J*=7.1, 1.6 Hz, 1H), 6.64 (dd, *J*=7.1, 1.6 Hz, 1H), 6.03 (t, *J*=7.1 Hz, 1H), 5.09 (s, 2H), 4.02 (t, *J*=6.9 Hz, 2H), 3,75 (t, *J*=6.9 Hz, 2H), 2.17 (quintet, *J*=6.9 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.2, 157.9, 148.8, 136.3, 134.0, 131.9, 129.2, 128.4, 127.9, 127.3, 123.2, 115.5, 104.7, 70.6, 47.5, 35.3, 28.2. HRMS [M+H$^+$] *m*/*z* calcd for $C_{23}H_{21}N_2O_4$ 389.1501, found 389.1490.

*4.4.9. 2-(5-(3-(Benzyloxy)-2-oxopyridin-1(2H)-yl)pentyl)isoindoline-1,3-dione (**3k**).* Representative procedure A was followed using *N*-(5-bromopentyl)phthalimide in place of ethyl bromoacetate and the reaction mixture was stirred for 24 h to give phthalimide **3k** as a yellow solid in 69% yield. The corresponding *O*-alkylated product **4k** was also isolated in 12% yield. **3k**: mp 123–124 °C; IR (neat) 2938, 1704 (C=O), 1651 (HOPO C=O), 1595 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85–7.75 (m, 2H), 7.73–7.62 (m, 2H), 7.46–7.38 (m, 2H), 7.37–7.21 (m, 3H), 6.89 (dd, *J*=7.1, 1.7 Hz, 1H), 6.63 (dd, *J*=7.1, 1.7 Hz, 1H), 5.98 (t, *J*=7.1 Hz, 1H), 5.08 (s, 2H), 3.94 (t, *J*=7.4 Hz, 2H), 3.67 (t, *J*=7.2 Hz, 2H), 1.81 (quintet, *J*=7.4 Hz, 2H), 1.17 (quintet, *J*=7.2 Hz, 2H), 1.47–1.30 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.3, 158.0, 148.8, 136.4, 133.9, 132.0, 129.0, 128.4, 127.8, 127.3, 123.1, 115.5, 104.5, 70.6, 49.5, 37.6, 28.5, 28.1, 23.8. HRMS [M+H$^+$] *m*/*z* calcd for $C_{25}H_{25}N_2O_4$ 417.1814, found 417.1816.

*4.4.10. tert-Butyl benzyloxy(3-(3-(benzyloxy)-2-oxopyridin-1(2H)-yl)propyl)carbamate (**3l**).* Representative procedure A was followed using *tert*-butyl benzyloxy(3-bromopropyl)carbamate[35] in place of ethyl bromoacetate and the reaction mixture was stirred for 24 h to give **3l** as a light brown oil in 86% yield: IR (film) 2980, 1695 (C=O), 1652 (HOPO C=O), 1606 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45–7.37 (m, 4H), 7.37–7.22 (m, 6H), 6.85 (dd, *J*=6.9, 1.7 Hz, 1H), 6.61 (dd, *J*=7.3, 1.7 Hz, 1H), 5.95 (dd, *J*=7.3, 6.9 Hz, 1H), 5.06 (s, 2H), 4.85 (s, 2H), 3.96 (t, *J*=6.8 Hz, 2H), 3.48 (t, *J*=6.8 Hz, 2H), 2.05 (quintet, *J*=6.8 Hz, 2H), 1.49 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.0, 156.4, 148.8, 136.4, 135.4, 129.4, 129.3, 128.5, 128.5, 128.4, 127.9, 127.3, 115.5, 104.5, 81.5, 77.0, 70.7, 47.7, 47.0, 28.3, 26.8. HRMS (M+Na$^+$) *m*/*z* calcd for $C_{27}H_{32}N_2NaO_5$ 487.2209, found 487.2207.

*4.4.11. tert-Butyl benzyloxy(5-(3-(benzyloxy)-2-oxopyridin-1(2H)-yl)pentyl)carbamate (**3m**).* Representative procedure A was followed using *tert*-butyl benzyloxy(5-iodopentyl)carbamate[35] in place of ethyl bromoacetate and the reaction mixture was stirred for 24 h to give **3m** as a yellow oil in 81% yield. The corresponding

O-alkylated product **4m** was also isolated in 12% yield. **3m**: IR (film) 2938, 1694 (C=O), 1652 (HOPO C=O), 1606 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.45–7.19 (m, 10H), 6.81 (dd, J=7.1, 1.7 Hz, 1H), 6.60 (dd, J=7.1, 1.7 Hz, 1H), 5.94 (t, J=7.1 Hz, 1H), 5.05 (s, 2H), 4.80 (s, 2H), 3.89 (t, J=7.3 Hz, 2H), 3.40 (t, J=7.1 Hz, 2H), 1.72 (quintet, J=7.5 Hz, 2H), 1.61 (quintet, J=7.4 Hz, 2H), 1.49 (s, 9H), 1.38–1.23 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.9, 156.4, 148.7, 136.4, 135.6, 129.3, 129.0, 128.4, 128.3, 127.8, 127.2, 115.5, 104.4, 81.0, 76.7, 70.5, 49.5, 49.2, 28.7, 28.3, 26.6, 23.7. HRMS ($M+Na^+$) m/z calcd for $C_{29}H_{36}N_2NaO_5$ 515.2516, found 515.2521.

4.5. Representative procedure for the Mitsunobu reaction of 2 with alcohols

*4.5.1. Synthesis of **3c**.* To a suspension of **2** (0.20 g, 0.994 mmol) in anhydrous THF (9 mL) under N_2 was added PS-PPh_3 (1.06 g, 1.99 mmol) followed by DIAD (0.39 mL, 1.99 mmol). After 5 min, allyl alcohol (0.068 mL, 0.994 mmol) was added and the mixture stirred at rt for 24 h. The PS-PPh_3 was filtered off and the solvent removed in vacuo. The crude product was purified by radial chromatography (hexane/ethyl acetate gradient) to give **3c** (0.11 g, 47%) (see 4.4.1) and **4c** (0.047 g, 20%) as a light yellow oil. **4c**: IR (film) 3066, 2933, 1595 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.72 (dd, J=5.0, 1.5 Hz, 1H), 7.45–7.23 (m, 5H), 7.05 (dd, J=7.8, 1.5 Hz, 1H), 6.75 (dd, J=7.8, 5.0 Hz, 1H), 6.23–6.07 (m, 1H), 5.42 (dq, J=17.2, 1.5 Hz, 1H), 5.25 (dq, J=10.4, 1.5 Hz, 1H), 5.14 (s, 2H), 4.95 (dt, J=5.4, 1.5 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.4, 143.0, 137.7, 136.6, 133.6, 128.6, 128.0, 127.2, 120.7, 117.3, 116.8, 70.9, 66.6. HRMS [$M+H^+$] m/z calcd for $C_{15}H_{16}NO_2$ 242.1181, found 242.1180.

*4.5.2. Synthesis of **3d**.* Using representative procedure for the Mitsunobu alkylation, the *N*-alkylated product **3d** was obtained in 27% yield and the *O*-alkylated product **4d** was obtained in 20% yield. When triphenylphosphine was used in place of PS-PPh_3, and the crude reaction mixture purified by column chromatography on neutral alumina (hexane/ethyl acetate gradient), **3d** was obtained in 26% yield and **4d** was obtained in 51% yield.

4.6. Synthesis of 3c via rearrangement of 4c

To a solution of **4c** (0.039 g, 0.162 mmol) in xylene (1 mL) under N_2 was added $PdCl_2$ (0.0028 g, 0.0162 mmol) and the mixture was heated at 80 °C for 3 h. After cooling, the catalyst was removed by filtration through a short silica gel column rinsing with $CHCl_3$. The solvent was removed in vacuo and the crude product was purified by radial chromatography to give **3c** (0.032 g, 82%) (see 4.4.1).

4.7. 1-(3-Aminopropyl)-3-(benzyloxy)pyridin-2(1*H*)-one (5)

The phthalimide **3j** (1.83 g, 4.71 mmol) was suspended in 40% aqueous methylamine (23 mL, 0.30 mol) and the mixture stirred for 2 days until all of the phthalimide had dissolved. The reaction mixture was diluted with water (20 mL) and the product extracted into $CHCl_3$ (3×30 mL), dried ($MgSO_4$) and the solvent removed in vacuo to give the known HOPO amine **5**.[31b] (1.07 g, 87.7%). ^1H NMR (300 MHz, $CDCl_3$) δ 7.45–7.33 (m, 5H), 6.92 (dd, J=6.9, 1.8 Hz, 1H), 6.63 (dd, J=6.9, 1.8 Hz, 1H), 6.03 (t, J=7.3 Hz, 1H), 5.12 (s, 2H), 4.09 (t, J=6.9 Hz, 2H), 2.72 (t, J=6.5 Hz, 2H), 1.89 (quintet, J=6.8 Hz, 2H).

4.8. 3-(Benzyloxy)-1-(3-isocyanatopropyl)pyridin-2(1*H*)-one (6)

A solution of **5** (0.20 g, 0.77 mmol) and 1,8-bis(dimethyl)aminonaphthalene (0.36 g, 1.54 mmol) in CH_2Cl_2 (5 mL) was added dropwise to a solution of phosgene (0.79 mL, 1.54 mmol) in toluene at 0 °C and the reaction mixture was stirred for 15 min. The solvents were removed in vacuo and the residue was dissolved in CH_2Cl_2 (15 mL) and washed with 1M HCl (15 mL). The aqueous layer was again extracted with CH_2Cl_2 (15 mL×2) and the combined organic layers were dried (Na_2SO_4) and the solvent was removed in vacuo. The product was further dried under high vacuum to give the isocyanate **6** as a pale yellow oil (0.18 g, 82%), which was used without further purification: IR (neat) 2952, 2278 (NCO), 1652 (HOPO C=O), 1606 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.18–7.45 (m, 5H), 6.89 (dd, J=6.8, 1.5 Hz, 1H), 6.65 (dd, J=7.4, 1.4 Hz, 1H), 6.05 (t, J=7.1 Hz, 1H), 5.11 (s, 2H), 4.07 (t, J=6.8 Hz, 2H), 3.40 (t, J=6.3 Hz, 2H), 2.04–2.13 (quintet, J=6.6 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.3, 149.2, 136.4, 128.7, 128.6, 128.2, 127.5, 122.0, 115.7, 105.2, 70.9, 47.5, 40.4, 30.2. Anal. Calcd $C_{16}H_{16}N_2O_3$: C, 67.59; H, 5.67; N, 9.85; Found: C, 67.81, H, 5.84, N, 9.86.

4.9. Octyl-3-(3-(benzyloxy)-2-oxopyridin-1(2*H*)-yl)propylcarbamate (7)

A solution of **6** (0.34 g, 0.18 mmol) and 1-octanol (0.043 mL, 0.27 mmol) in anhydrous 1,2-dichloroethane (2.5 mL) was heated at reflux for 1 day under N_2. After cooling, the reaction mixture was diluted with CH_2Cl_2 (5 mL) and washed with saturated NH_4Cl (15 mL), saturated NaCl (15 mL), dried (Na_2SO_4) and the solvents removed in vacuo. Excess octanol was removed by Kugelrohr distillation to give the carbamate **7** as a pale yellow oil (0.065 g, 87%): IR (neat) 3317 (NH), 2928, 2856, 1714 (C=O), 1652 (HOPO C=O), 1601 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.30–7.44 (m, 5H), 6.89 (dd, J=6.8, 1.2 Hz, 1H), 6.67(dd, J=7.5, 1.6 Hz, 1H), 6.07 (t, J=7.1 Hz, 1H), 5.76 (br s, 1H), 5.12 (s, 2H), 4.00–4.09 (m, 4H), 3.13 (dt, J=6.4, 5.7 Hz, 2H), 1.86–1.95 (m, 2H), 1.52–1.65 (m, 2H), 1.27 (br s, 10H), 0.88 (t, J=6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.9, 157.4, 149.0, 136.4, 128.9, 128.8, 128.3, 127.6, 115.7, 105.7, 71.1, 65.1, 46.4, 37.2, 32.1, 30.2, 29.46, 29.3, 26.1, 22.9, 14.4.

4.10. 1-(3-(3-(Benzyloxy)-2-oxopyridin-1(2*H*)-yl)propyl)-3-octylurea (8)

A solution of 1-octylamine (0.03 mL, 0.21 mmol) in CH_2Cl_2 (2 mL) was added to isocyanate **6** (0.04 g, 0.141 mmol) at 0 °C and stirred for 10 min. The reaction mixture was diluted with CH_2Cl_2 (5 mL) and washed with saturated NH_4Cl (15 mL), saturated NaCl (15 mL), dried (Na_2SO_4) and the solvents removed in vacuo. The crude product was purified using radial chromatography (ethyl acetate) to give urea **8** as a pure white solid (0.05 g, 90%): mp 93–94 °C; IR (KBr) 3335 (NH), 2925, 2854, 1656 (HOPO C=O), 1621 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.33–7.43 (m, 5H), 6.90 (dd, J=6.7, 1.7 Hz, 1H), 6.67 (dd, J=7.5, 1.6 Hz, 1H), 6.11 (t, J=7.2 Hz, 1H), 5.76 (t, J=5.7 Hz, 1H), 5.13 (s, 2H), 4.37 (m, 1H), 4.09 (t, J=6.1 Hz, 2H), 3.12–3.20 (m, 4H), 1.85–1.93 (m, 2H), 1.43–1.49 (m, 2H), 1.27 (br s, 10H), 0.88 (t, J=6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.9, 149.0, 136.3, 129.1, 128.9, 128.4, 127.6, 115.9, 106.0, 71.1, 46.7, 40.8, 36.4, 32.1, 30.6, 30.5, 29.7, 27.2, 23.0, 14.4.

4.11. 1,1′,1″-(2,2′,2″-Nitrilotris(ethane-2,1-diyl))tris(3-(3-(3-(benzyloxy)-2-oxopyridin-1(2*H*)-yl)propyl)urea) (9)

A solution of tris-(2-aminoethyl)amine (0.040 g, 0.24 mmol) in CH_2Cl_2 (2 mL) was added to isocyanate **6** (0.21 g, 0.80 mmol) at 0 °C and stirred for 2 h at 0 °C. The solvent was removed in vacuo and the crude product was purified using silica gel chromatography (methanol) to give urea **9** as a white solid (0.16 g, 67%): mp 65–67 °C; IR (KBr) 3366 (NH), 3063, 2922, 2852, 1651 (HOPO C=O), 1598 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.29–7.39 (m, 15H), 6.94 (dd, J=6.9, 1.6 Hz, 3H), 6.64 (dd, J=7.4, 1.4 Hz, 3H), 6.16 (br s, 3H), 6.04 (t, J=7.1 Hz, 3H), 5.95–6.05 (m, 3H), 5.02 (s, 6H), 3.99 (t, J=6.5 Hz, 6H), 3.06–3.14 (m, 12H), 2.49–2.52 (m, 6H), 1.79–1.88 (m,

6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.6, 158.5, 148.8, 136.3, 129.5, 128.8, 128.4, 127.7, 115.7, 105.6, 71.0, 55.8, 47.1, 39.0, 36.8, 30.3; HRMS [M+H$^+$] *m*/*z* calcd for $C_{54}H_{67}N_{10}O_9$ 999.5087, found 999.5105.

4.12. 1,1′,1″-(2,2′,2″-nitrilotris(ethane-2,1-diyl))tris(3-(3-(3-hydroxy-2-oxopyridin-1(2*H*)-yl)propyl)urea (10)

A suspension of **9** (0.07 g, 0.07 mmol) and 5% Pd/C (0.08 g) in methanol was stirred under H_2 balloon for four days. The catalyst was removed by the filtration through a 0.45 μm nylon filter rinsing with methanol. The solvents were removed in vacuo and the product was dried under high vacuum to give urea **10** as a viscous brown oil (0.059 g, quant.): IR (neat) 3334 (NH), 1646 (br) (C=O) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.09–7.11 (d, *J*=5.13 Hz, 3H), 6.79–6.82 (d, *J*=7.2 Hz, 3H), 6.20–6.25 (m, 3H), 4.04 (unres t, 6H), 3.17 (unres t, 12H), 2.61 (t, *J*=5 MHz, 6H), 1.89 (unres t, 6H); ^{13}C NMR (75 MHz, CD_3OD) δ 161.3, 160.1, 148.4, 129.2, 117.0, 108.5, 56.1, 48.5, 39.6, 38.2, 31.3; HRMS [M+H$^+$] *m*/*z* calcd for $C_{33}H_{49}N_{10}O_9$ 729.3679, found 729.3709.

4.13. Representative procedure for hydrolysis of Boc protecting group

*Synthesis of 3-(benzyloxy)-1-(5-(benzyloxyamino)pentyl)pyridin-2(1H)-one (**11**).* A solution of **3m** (0.695 g, 1.41 mmol) in 1:1 TFA/CH_2Cl_2 (12 mL) was stirred at rt for 2.5 h. The solvent was removed in vacuo and the residue was adjusted to pH 10 using 1 N NaOH. The product was extracted into CH_2Cl_2 (3×50 mL) and the extract was dried (Na_2SO_4). The solvent was removed in vacuo to give **11** (0.442 g, 98%) as a brown oil, which was used without purification: IR (neat) 3249, 2937, 1652 (HOPO C=O), 1606 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46–7.37 (m, 2H), 7.37–7.19 (m, 8H), 6.82 (dd, *J*=7.1, 1.3 Hz, 1H), 6.60 (dd, *J*=7.1, 1.3 Hz, 1H), 5.96 (t, *J*=7.1 Hz, 1H), 5.52 (br s, 1H), 5.06 (s, 2H), 4.66 (s, 2H), 3.90 (t, *J*=7.3 Hz, 2H), 2.88 (t, *J*=7.0 Hz, 2H), 1.73 (quintet, *J*=7.5 Hz, 2H), 1.52 (quintet, *J*=7.3 Hz, 2H), 1.40–1.25 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.0, 148.8, 138.0, 136.4, 129.0, 128.4, 128.3, 128.3, 127.8, 127.7, 127.2, 115.4, 104.4, 76.1, 70.6, 51.8, 49.6, 28.9, 27.0, 24.2.

4.14. 6-(Benzyloxy(*tert*-butoxycarbonyl)amino)hexanoic acid (12)

To a solution of *tert*-butyl benzyloxycarbamate (4.02 g, 18.0 mmol) in anhydrous DMF (60 mL) under N_2 at 0 °C was added NaH (1.51 g, 37.8 mmol). The mixture was warmed to rt and stirred for 30 min. After cooling back to 0 °C, 6-bromohexanoic acid (3.86 g, 19.8 mmol) was added and the mixture was stirred at rt for 1 h and then heated at 70 °C for 18 h. The reaction mixture was cooled and quenched with saturated NH_4Cl (50 mL) and the aqueous layer acidified to pH 2 with conc. HCl. The product was extracted into ethyl acetate (3×50 mL), dried (Na_2SO_4) and the solvent was removed in vacuo. The crude product was dissolved in 1M NaOH and impurities removed by extraction with ethyl acetate (2×20 mL). The aqueous later was then acidified with conc. HCl, and the product extracted into ethyl acetate (3×30 mL), dried (Na_2SO_4) and the solvent removed in vacuo to give acid **12** (4.27 g, 70%) as an oil, which was used in the next step without further purification. A portion of **12** was purified by preparative chromatography for characterization: IR (film) 2937, 1705 (C=O) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.2–10.85 (br s, 1H), 7.46–7.28 (m, 5H), 4.82 (s, 2H), 3.40 (t, *J*=7.1 Hz, 2H), 2.32 (t, *J*=7.5 Hz, 2H), 1.73–1.54 (m, 4H), 1.50 (s, 9H), 1.40–1.23 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.7, 156.6, 135.7, 129.4, 128.5, 128.4, 81.3, 76.9, 49.4, 34.0, 28.3, 26.7, 26.2, 24.4. HRMS (M+Na$^+$) *m*/*z* calcd for $C_{18}H_{27}NO_5Na$ 360.1781, found 360.1777.

4.15. *tert*-Butyl benzyloxy(6-(benzyloxy(5-(3-(benzyloxy)-2-oxopyridin-1(2*H*)-yl)pentyl)amino)-6-oxohexyl)carbamate (13)

To a solution of acid **12** (0.134 g, 0.398 mmol) in anhydrous CH_2Cl_2 (1.5 mL) under N_2 at 0 °C was added triethylamine (0.076 mL, 0.543 mmol) followed by HATU (0.151 g, 0.398 mmol) and **11** (0.142 g, 0.362 mmol). The mixture was stirred at rt for 3 h. The reaction mixture was diluted with CH_2Cl_2 (30 mL) and washed with 2 N HCl (2×15 mL), saturated $NaHCO_3$ (2×15 mL), saturated NaCl (15 mL) and dried (Na_2SO_4). The solvent was removed in vacuo and the crude product was purified by radial chromatography (hexane/ethyl acetate gradient) to give **13** (0.195 g, 76%) as a colorless oil: IR (film) 2937, 1698, 1655 (HOPO C=O), 1607 cm$^{-1;}$ ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47–7.25 (m, 15H), 6.84 (dd, *J*=7.1, 1.4 Hz, 1H), 6.62 (dd, *J*=7.1, 1.4 Hz, 1H), 5.97 (t, *J*=7.1 Hz, 1H), 5.08 (s, 2H), 4.81 (s, 2H), 4.76 (s, 2H), 3.92 (t, *J*=7.3 Hz, 2H), 3.62 (t, *J*=6.8 Hz, 2H), 3.40 (t, *J*=7.2 Hz, 2H), 2.36 (t, *J*=7.5 Hz, 2H), 1.83–1.69 (m, 2H), 1.69–1.53 (m, 6H), 1.49 (s, 9H), 1.40–1.23 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.6, 158.0, 156.5, 148.9, 136.4, 135.6, 134.5, 129.3, 129.1, 129.0, 128.9, 128.7, 128.5, 128.4, 128.4, 127.8, 127.3, 115.5, 104.5, 81.0, 76.8, 76.3, 70.7, 49.6, 49.4, 45.0, 32.2, 28.6, 28.3, 26.9, 26.6, 26.4, 24.3, 23.7. HRMS [M+H$^+$] *m*/*z* cald for $C_{42}H_{54}N_3O_7$ 712.3962, found 712.3965.

4.16. *N*-(Benzyloxy)-*N*-(5-(3-(benzyloxy)-2-oxopyridin-1(2*H*)-yl)pentyl)-6-(benzyloxyamino)hexanamide (14)

Following the representative procedure for hydrolysis of Boc group, and substituting **13** for **3m**, the protected hydroxylamine **14** was obtained in 77% yield as a yellow oil after radial chromatography (hexane/ethyl acetate gradient then 10% methanol/ethyl acetate). IR (film) 3436 (NH), 2939, 1653 (HOPO C=O), 1605 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46–7.38 (m, 2H), 7.38–7.20 (m, 13H), 6.82 (dd, *J*=6.9, 1.6 Hz, 1H), 6.60 (dd, *J*=7.4, 1.6 Hz, 1H), 6.01–5.91 (m, 1H), 5.09 (s, 2H), 4.76 (s, 2H), 4.68 (s, 2H), 3.90 (t, *J*=7.3 Hz, 2H), 3.69–3.55 (m, 2H), 2.90 (t, *J*=7.0 Hz, 2H), 2.36 (t, *J*=7.4 Hz, 2H), 1.79–1.70 (m, 2H), 1.68–1.55 (m, 4H), 1.55–1.44 (m, 2H), 1.37–1.25 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.7, 158.0, 148.8, 138.0, 136.4, 134.5, 129.1, 129.0, 128.8, 128.7, 128.4, 128.3, 127.8, 127.7, 127.2, 115.6, 104.6, 76.2, 76.1, 70.7, 51.9, 49.6, 45.0, 32.2, 28.5, 27.1, 26.9, 26.4, 24.4, 23.7. HRMS [M+H$^+$] *m*/*z* calcd for $C_{37}H_{46}N_3O$ 612.3437, found 612.3443.

4.17. *N*-(Benzyloxy)-*N*-(5-(3-(benzyloxy)-2-oxopyridin-1(2*H*)-yl)pentyl)-6-(*N*-(benzyloxy)acetamido)hexanamide (15)

To a solution of **14** (0.305 g, 0.499 mmol) in anhydrous CH_2Cl_2 (2 mL) under N_2 at 0 °C was added triethylamine (0.10 mL, 0.748 mmol) followed by acetyl chloride (0.039 mL, 0.548 mmol). The reaction mixture was stirred at rt for 24 h. The reaction mixture was diluted with CH_2Cl_2 (30 mL) and washed with 2 N HCl (2×15 mL), saturated $NaHCO_3$ (2×15 mL), saturated NaCl (15 mL) and dried (Na_2SO_4). The solvent was removed in vacuo and the crude product was purified by radial chromatography (hexane/ethyl acetate gradient then 10% methanol/ethyl acetate) to give **15** (0.279 g, 86%) as a yellow oil: IR (film) 2939, 1651 (HOPO C=O), 1606 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46–7.22 (m, 15H), 6.85 (dd, *J*=7.2, 1.7 Hz, 1H), 6.62 (dd, *J*=7.2, 1.7 Hz, 1H), 5.97 (t, *J*=7.2 Hz, 1H), 5.07 (s, 2H), 4.78 (s, 2H), 4.76 (s, 2H), 3.91 (t, *J*=7.3 Hz, 2H), 3.61 (t, *J*=6.8 Hz, 4H), 2.36 (t, *J*=7.4 Hz, 2H), 2.07 (s, 3H), 1.75 (quintet, *J*=7.5 Hz, 2H), 1.69–1.54 (m, 6H), 1.39–1.22 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.6, 172.0, 158.0, 148.8, 136.4, 134.5, 129.1, 128.8, 128.6, 128.4, 127.8, 127.2, 115.5, 104.4, 76.2, 76.1, 70.6, 49.5, 45.1, 32.1, 28.6, 26.7, 26.5, 26.4, 24.2, 23.7, 20.5. HRMS [M+H$^+$] *m*/*z* calcd for $C_{39}H_{48}N_3O_6$ 654.3543, found 654.3553.

4.18. *N*-Hydroxy-*N*-(5-(3-hydroxy-2-oxopyridin-1(2*H*)-yl)pentyl)-6-(*N*-hydroxyacetamido)hexanamide (16)

To a solution of **15** (0.377 g, 0.577 mmol) in EtOH (5 mL) was added 5% Pd on carbon (0.123 g, 0.0577 mmol) and the mixture was stirred at rt under a H_2 balloon for 24 h. The catalyst was removed by centrifugation followed by filtration. The filtrate was concentrated in vacuo to give **16** (0.215 g, 97%) as a light brown oil: IR (neat) 3176, 2937, 1600 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 7.10 (d, J=6.8 Hz, 1H), 6.83 (d, J=6.8 Hz, 1H), 6.24 (d, J=6.8 Hz, 1H), 4.96 (br s, 3H), 4.00 (t, J=7.0 Hz, 2H), 3.64–3.56 (m, 4H), 2.47 (t, J=7.2 Hz, 2H), 2.09 (s, 3H), 1.82–1.72 (m, 2H), 1.71–1.55 (m, 6H), 1.40–1.27 (m, 4H); ^{13}C NMR (75 MHz, CD_3OD) δ 175.8, 173.4, 159.8, 148.2, 129.2, 117.1, 108.4, 50.7, 48.8, 48.7, 33.2, 29.9, 27.5, 27.2, 25.6, 24.5, 20.4. HRMS [M+H^+] m/z calcd for $C_{18}H_{30}N_3O_6$ 354.2129, found 384.2138.

4.19. 6-(3-(Benzyloxy)-2-oxopyridin-1(2*H*)-yl)hexanoic acid (17)

Following the representative procedure for hydrolysis of Boc group, **3g** was hydrolyzed to give acid **17** in 95% yield as a light brown solid: mp 104–105 °C; IR (neat) 2943, 1723 (C=O), 1639 (HOPO C=O), 1579 cm-1; ^1H NMR (300 MHz, $CDCl_3$) δ 7.46–7.39 (m, 2H), 7.39–7.24 (m, 3H), 6.89 (dd, J=7.2, 1.6 Hz, 1H), 6.67 (dd, J=7.2, 1.6 Hz, 1H), 6.50 (t, J=7.2 Hz, 1H), 5.06 (s, 2H), 3.95 (t, J=7.3 Hz, 2H), 2.28 (t, J=7.3 Hz, 2H), 1.75 (quintet, J=7.5 Hz, 2H), 1.62 (quintet, J=7.5 Hz, 2H), 1.45–1.28 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.6, 158.2, 148.8, 136.2, 128.9, 128.5, 127.9, 127.4, 115.6, 105.3, 70.7, 49.8, 33.9, 28.7, 26.0, 24.3. HRMS [M+H^+] m/z calcd for $C_{18}H_{22}NO_4$ 316.1549, found 316.1540.

4.20. *N*-(Benzyloxy)-6-(3-(benzyloxy)-2-oxopyridin-1(2*H*)-yl)-*N*-(5-(3-(benzyloxy)-2-oxopyridin-1(2*H*)-yl)pentyl)hexanamide (18)

To a solution of acid **17** (0.127 g, 0.404 mmol) in anhydrous CH_2Cl_2 (1.5 mL) under N_2 at 0 °C was added triethylamine (0.077 mL, 0.550 mmol) followed by HATU (0.153 g, 0.404 mmol) and **11** (0.144 g, 0.367 mmol). The reaction mixture was stirred at rt for 4 h. The reaction mixture was diluted with CH_2Cl_2 (30 mL) and washed with 2 N HCl (2×15 mL), saturated $NaHCO_3$ (2×15 mL), saturated NaCl (15 mL) and dried (Na_2SO_4). The solvent was removed in vacuo and the crude product was purified by radial chromatography (hexane/ethyl acetate gradient then 10% methanol/ethyl acetate) to give **18** (0.209 g, 83%) as a yellow oil: IR (film) 2942, 1660, 1652 (HOPO C=O), 1606 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.45–7.40 (m, 4H), 7.37–7.23 (m, 11H), 6.89–6.82 (m, 2H), 6.63 (d, J=7.5 Hz, 1H), 6.62 (d, J=7.5 Hz, 1H), 5.98 (t, J=7.1 Hz, 1H), 5.97 (t, J=7.1 Hz, 1H), 5.08 (s, 4H), 4.78 (s, 2H), 3.93 (t, J=7.3 Hz, 2H), 3.92 (t, J=7.3 Hz, 2H), 3.61 (br t, J=6.8 Hz, 2H), 2.36 (t, J=7.4 Hz, 2H), 1.85–1.70 (m, 4H), 1.69–1.54 (m, 4H), 1.41–1.23 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.5, 158.0, 148.9, 136.4, 134.5, 129.1, 129.1, 128.9, 128.7, 128.5, 127.9, 127.3, 115.49, 115.48, 104.5, 104.4, 76.3, 70.7, 49.6, 45.1, 32.1, 28.9, 28.6, 26.5, 26.3, 24.1, 23.7. HRMS [M+H^+] m/z calcd for $C_{42}H_{48}N_3O_6$ 690.3543, found 690.3526.

4.21. *N*-Hydroxy-6-(3-hydroxy-2-oxopyridin-1(2*H*)-yl)-*N*-(5-(3-hydroxy-2-oxopyridin-1(2*H*)-yl)pentyl)hexanamide (19)

To a solution of **18** (0.208 g, 0.302 mmol) in EtOH (3 mL) was added 5% Pd on carbon (0.064 g, 0.0302 mmol) and the mixture stirred at rt under a H_2 balloon for 24 h. The catalyst was filtered off using diatomaceous earth and the filtrate was concentrated in vacuo to give **19** (0.110 g, 87%) as a light brown solid: mp 40–46 °C (del); IR (neat) 3130, 2932, 1647, 1585 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 7.08 (d, J=6.8 Hz, 2H), 6.82 (d, J=6.8 Hz, 2H), 6.22 (d, J=6.8 Hz, 2H), 4.86 (br s, 3H), 4.00 (t, J=7.0 Hz, 4H), 3.60 (t, J=6.7 Hz, 2H), 2.47 (d, J=7.2 Hz, 2H), 1.82–1.70 (m, 4H), 1.70–1.56 (m, 4H), 1.44–1.26 (m, 4H); ^{13}C NMR (75 MHz, CD_3OD) δ 175.8, 160.0, 159.9, 148.3, 129.3, 129.2, 116.9, 116.9, 108.3, 108.3, 50.9, 50.7, 48.7, 33.1, 30.1, 30.0, 27.4, 27.3, 25.6, 24.6. HRMS [M+H^+] m/z calcd for $C_{21}H_{30}N_3O_6$ 420.2135, found 420.2133.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2015.10.028. These data include MOL files and InChiKeys of the most important compounds described in this article.

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