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Synthesis of 2-pyridones as tissue factor VIIa inhibitors

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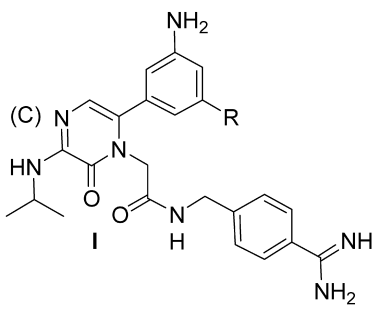
Abstract—2-Pyridones were prepared from 2,6-dibromopyridine via a multi-step synthesis. A variety of chemical transformations, including regioselective nucleophilic addition and selective nitrogen alkylation, afforded the penultimate intermediate **9**. A combination of two-dimensional NMR techniques to unequivocally assign the structure of **9** is described. Compound **9** was then used in a Suzuki coupling and further derivatized to afford the targeted tissue Factor VIIa inhibitors. These compounds were tested in several serine protease enzyme assays with biological activity reported.

Cardiovascular disease consisting of unstable angina, myocardial infarction and sudden death, are the most frequent cause of mortality in the United States and Western countries.[1] The disease is associated with acute thrombus formation, often as the result of a plaque rupture. Thrombosis also occurs in transient ischemic attack, stroke, peripheral occlusive arterial disease, deep vein thrombosis, pulmonary embolism, abrupt closure following angioplasty, and the disseminated intravascular coagulation associated with sepsis and certain cancers. Effective and safe antithrombotics are needed to combat these diseases. Most research has focused on thrombin and Factor Xa inhibitors as potentially valuable therapeutic agents for these diseases.[2] More recently, small molecule inhibitors of tissue Factor (TF) VIIa have been the point of much research effort because of their potential to inhibit the coagulation cascade while lessening the risk of bleeding side effects.[3] The extrinsic coagulation cascade is triggered by the binding of Factor VIIa to cell surface TF. This cascade is critical in normal hemostasis, but is also involved in the pathogenesis of various thrombotic diseases. Under normal conditions, TF expressed in the sub-endothelium of healthy blood vessels is not exposed to blood. However, in disease or injury, vessel wall or plaque TF is exposed and complexes with its cofactor Factor VIIa, leading to the activation of Factors IX and X. The complex of Factor Xa and Factor Va on a membrane surface converts prothrombin to thrombin, leading to fibrin formation, deposition, and subsequent thrombus formation.[4]

We previously reported the preparation of pyrazinone analogs as noncovalent tissue Factor VIIa inhibitors.[5] These pyrazinone compounds are active-site inhibitors for Factor VIIa exhibiting potency at the single-digit nanomolar level (IC_{50}) with excellent selectivity over thrombin (IIa) and Factor Xa. In an effort to increase the potency and influence the pharmocokinetic properties, other heterocyclic ring systems were evaluated. Depicted in Figure 1 is the lead pyrazinone core structure **I**. Focusing on the central ring, one of the exercises was to replace the nitrogen at the 4-position in the pyrazinone ring with carbon, resulting in a pyridone heterocycle as the core ring.[6] Other groups have disclosed the pyridone template in the design of human leukocyte elastase (HLC) inhibitors[7] and thrombin inhibitors.[8] We too were motivated by the attractiveness of the pyridone template and the fact that it has not been reported as a TF/VIIa inhibitor. Based on the structure activity relationship established with the previously prepared pyrazinone analogs, two targeted pyridone analogs were selected for preparation. Herein, we describe their synthesis and biological activity.

Several commercially available substituted pyridines were evaluated in terms of potential starting material for the



I

Figure 1.

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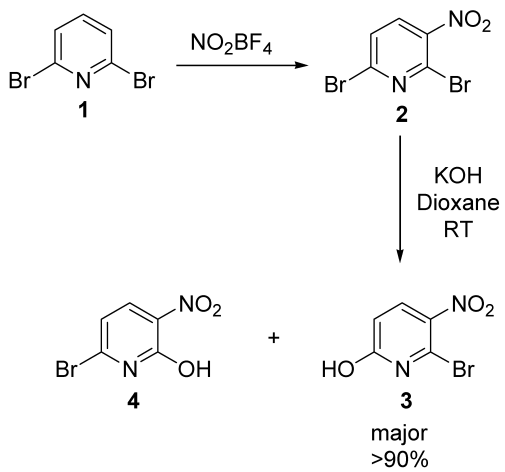
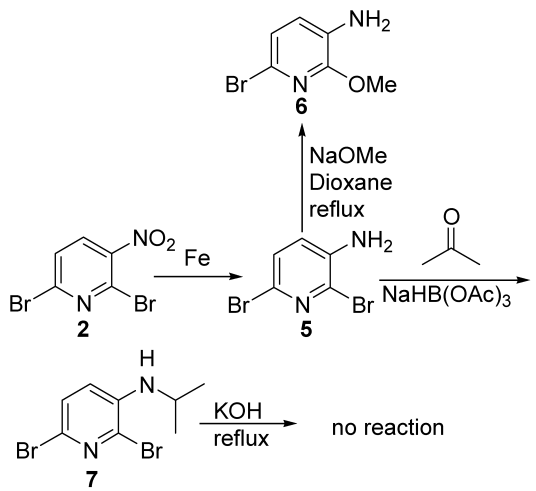


Scheme 1.

synthesis. It was decided to proceed with the synthesis using readily available, inexpensive 2,6-dibromopyridine **1** as the starting material shown in Scheme 1. The dibromopyridine **1** was nitrated according to the literature procedure to afford 2,6-dibromo-3-nitropyridine **2**.[9] Several conditions were attempted to selectively displace the 2-bromo with hydroxide. At room temperature, incomplete reaction occurred or when heat was applied, nonregioselective displacement at both the 2- and 6-position occurred. Complete conversion of the starting material to a mono-substituted pyridine was accomplished using two equivalents of potassium hydroxide in dioxane at room temperature disappointingly resulting in the wrong regioisomer, 6-hydroxypyridine **3**, as the major product.

In an effort to reduce the potential steric crowding at the 2-position and the electronic nature of the pyridine ring, the nitro group of compound **2** was reduced with iron to afford the 3-amino-2,6-dibromopyridine **5** (Scheme 2). Next, reductive amination of the nitrogen followed by nucleophilic displacement of the 2-bromo was attempted. The reductive amination of 3-amino-2,6-dibromopyridine **5** with acetone using sodium triacetoxyborohydride afforded the 3-isopropylamino-2,6-dibromopyridine **7**. Reaction of 3-isopropylamino-2,6-dibromopyridine **7** with potassium hydroxide at reflux in dioxane/water resulted in no reaction,



Scheme 2.

affording only starting material. However, reacting the unsubstituted 3-amino-2,6-dibromopyridine **5** with sodium methoxide in dioxane at reflux afforded exclusively the desired regioisomer, 3-amino-6-bromo-2-methoxypyridine **6**. The proton and carbon NMR of compound **6** was in agreement with the predicted proton and carbon NMR calculated by ACD[10] with significant differences between the two regioisomers evident in the proton NMR. It was decided to fully characterize and conclusively determine the structure at a later point in the synthesis, after alkylation, allowing one set of experiments to determine the correct isomer from a potential set of four isomers.

Thus with the key precursor **6** in hand, the synthesis of the desired targets was conducted as shown in Scheme 3. Several reductive amination conditions were surveyed. The preformation of the imine using titanium tetrachloride with acetone followed by reduction with sodium cyanoborohydride afforded cleanly the 6-bromo-2-methoxy-3-isopropylaminopyridine **8**.[11] The methyl ether **8** was cleaved using boron tribromide to afford the hydroxypyridine **9**. Alkylation of the hydroxypyridine **9** with *t*-butylbromoacetate using calcium hydride as the base afforded a single isomer **10**. While alkylation could occur on either the nitrogen or the oxygen, only one regioisomer was isolated. At this point of the synthesis, compound **10** could be one of four possible isomers **10**, **16**, **17**, and **18** as shown in Figure 2. Compounds **10** and **16** would result from methoxide displacement of 2,6-dibromopyridine **5** (Scheme 2) at the 2-position, suggested by the proton and carbon data, but not definitively determined. Methoxide displacement at the 6-position of 2,6-dibromopyridine **5** would ultimately result in compounds **17** and **18**. Each of these substituted hydroxypyridines could undergo alkylation of the nitrogen or oxygen, affording the potential combination of all regioisomers depicted in Figure 2.

A considerable amount of data was collected, including proton, carbon, HSQC, Inadequate, and a HMBC experiment to fully characterize and definitively assign a structure. The proton NMR spectrum was relatively simple and easy to assign by inspection. The only minor point was to assign each aromatic proton and that was determined from a combination of HSQC and Inadequate data. The various carbon assignments were determined from the HSQC and HMBC spectra. One of the key correlations in this spectrum was the one connecting carbons 2 and 3 (Fig. 3). This piece of data was critical to provide definitive proof of the structure. Also important was to identify the other carbonyl

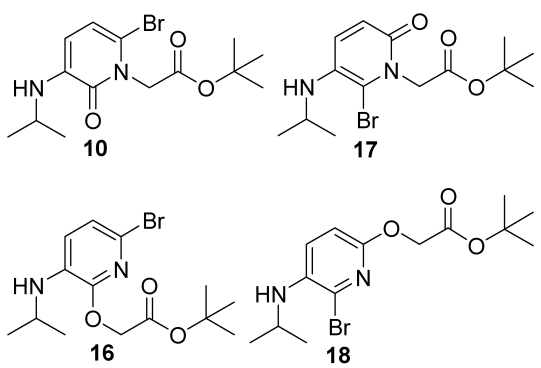
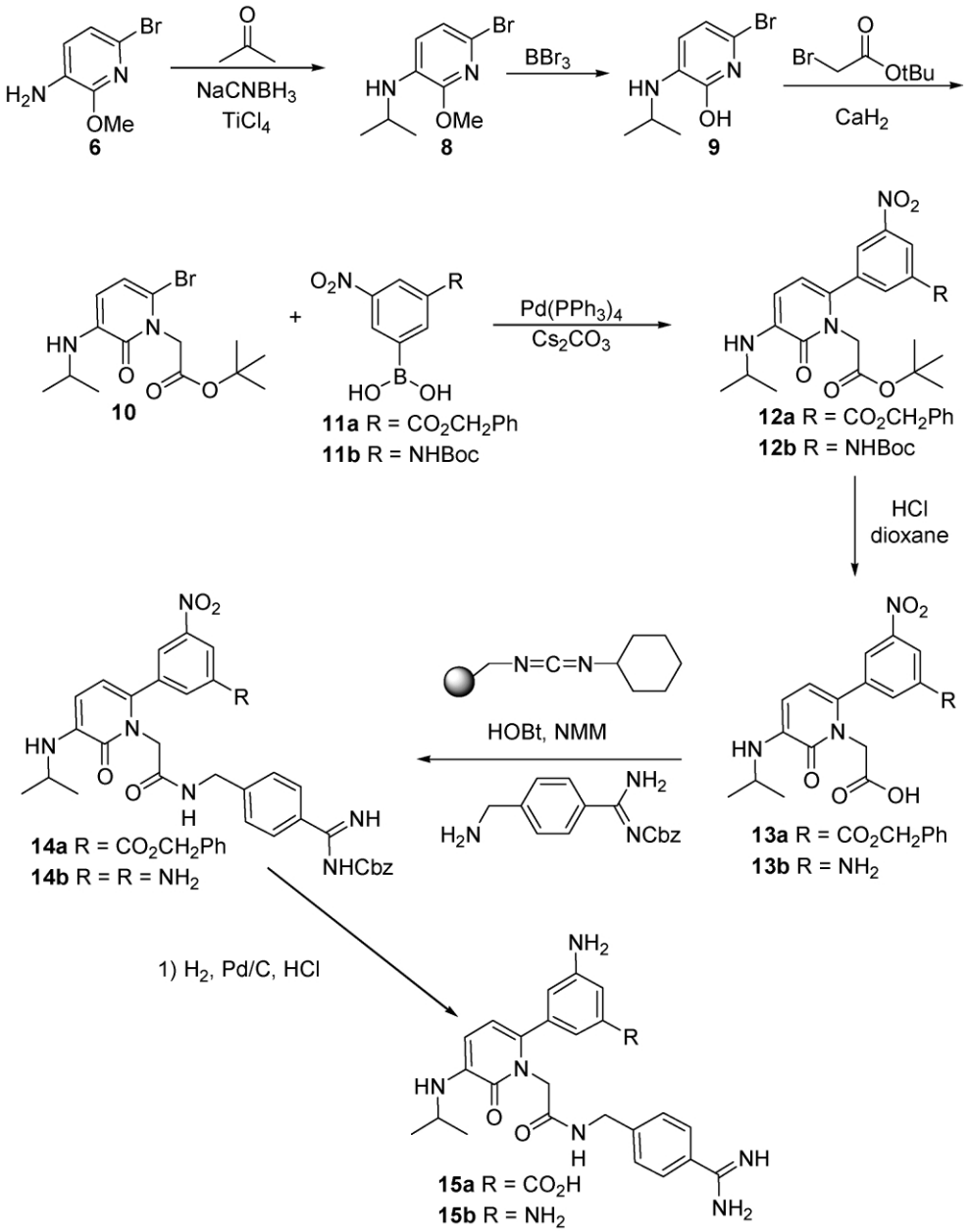


Figure 2. All possible regioisomers.



Scheme 3.

carbon as carbon 8 by its correlation to carbon 7. In addition to the previously mentioned data, there were other key pieces of information that were critical for determining the structure. There were two long-range correlations for the H15/H20 and H14 protons to carbon 3 (136.8 ppm) and in the Inadequate spectrum there was a correlation from this same carbon (C3) to the carbonyl carbon (C2). This data taken together is definitive proof of the structure. The key correlations and carbon–carbon connections obtained from the data are shown in Figure 3.

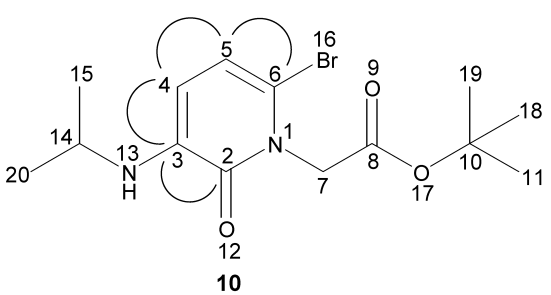


Figure 3. Key correlations.

The completion of the targeted pyridones in Scheme 3 was carried out by performing Suzuki couplings of the *N*-alkylated bromopyridone **10** with the boronic acids **11**, affording the biaryl compounds **12**. Selective hydrolysis of the *t*-butyl ester with hydrochloric acid afforded the carboxylic acids **13**. [Note: Using heat during the evaporation of the solvent in the workup of acid **13a** led to decarboxylation to afford the *N*-methyl derivative (benzyl 3-[5-(isopropylamino)-1-methyl-6-oxo-1,6-dihydropyridin-2-yl]-5-nitrobenzoate). As a result, evaporation of the solvent was conducted using a stream of nitrogen to afford the acids

Table 1. IC_{50} values

Compound	IC_{50} (uM)		
	VIIa	Xa	Thrombin
15a	0.118	>30	>30
15b	0.052	>30	>30

13.] The carboxylic acids **13** were coupled with benzyl amino[4-(aminomethyl)phenyl]methylenecarbamate using polymer-bound carbodiimide, hydroxybenzotriazole, and *N*-methylmorpholine as base to afford the desired products **14**. Concomitant deprotection of the Cbz (and benzyl ester with compound **14b**) and reduction of the nitro group was accomplished using hydrogen with palladium on carbon to afford the desired target compounds **15**.

The target compounds **15a** and **15b** were screened for potency on TF/VIIa and for other enzymes affecting coagulation to determine specificity (Table 1). Each enzyme assay consists of the specific enzyme and chromogenic substrate for that enzyme. Enzyme activity was determined by monitoring the increase in absorbance at 405 nm caused by the release of *p*-nitroaniline when the substrate is hydrolyzed. Inhibition of the enzyme reduces the change in absorbance with the data reported as IC_{50} values. Compounds **15a** and **15b** are both active against TF/VIIa with an IC_{50} of 118 and 52 nM, respectively. Both compounds are selective over thrombin and Factor Xa. However, both pyridones **15a** and **15b** are approximately 5X less potent against TF/VIIa than their corresponding pyrazinone analogs.[5]

In summary, targeted pyridones were successfully prepared via multi-step synthesis using various transformations and regioselective additions with a pyridine nucleus to afford novel pyridone derivatives. The analogs were tested against TF/VIIa but were less potent than their corresponding pyrazinone analogs. With no improved potency and a lack of favorable pharmacokinetics, further syntheses using the pyridone as the core ring were not pursued.

1. Experimental

1.1. General

^1H and ^{13}C NMR spectra were recorded using a 300 and 400 MHz NMR spectrometer. Sample purities were determined by HPLC analysis equipped with a mass spec detector using a C18 3.5 mm 30×2.1 mm column, eluting with a gradient system of 5:95 to 95:5 acetonitrile/water with a buffer consisting of 0.1% TFA over 6 min at 1 mL/min and detected by UV at 254 and 210 nm using a diode array detector. Column chromatography was performed on a preparative liquid chromatography instrument using silica gel columns and on a HPLC system using a 15um 100A, C18 column (25 mm ID×100 mm L). Reported yields are not optimized with emphasis on purity of products rather than quantity.

1.1.1. 2-Bromo-6-hydroxy-3-nitropyridine (3). A solution of 2,6-dibromo-3-nitropyridine (**2**) (3.9 g, 14 mmol) and potassium hydroxide (1.6 g, 28 mmol) in water (30 mL) and dioxane (20 mL) was stirred at room temperature for 20 h. The solution was diluted with 2N hydrochloric acid and extracted with ether. The organic layer was washed with water, brine, dried over magnesium sulfate, and filtered. The solvent was removed by evaporation to afford 2.97 g (97%) of a white solid of product **3**; ^1H NMR ppm (deuteriomethanol): 6.61 (d, 1H, J=8.4 Hz), 8.10 (d, 1H, J=8.4 Hz); ^{13}C NMR ppm (deuteriomethanol): 112.8, 133.6, 137.1, 145.7, 163.7; HPLC purity (retention time): 90% (1.67 min); HRMS calcd for $C_5H_3Br_1N_2O_3$ (M^++H) 217.9327, found 217.9324.

1.1.2. 3-Amino-2,6-dibromopyridine (5). 2,6-Dibromo-3-nitropyridine **2** (6.8 g, 24.3 mmol) was stirred in glacial acetic acid (30 mL). Powdered iron (6.7 g, 119 mmol) was added and the solution was heated to 80°C with vigorous stirring. The solution was stirred at 80°C for 15 min at which point the iron had turned gray. The reaction mixture was filtered through celite and the solid was washed with ether and ethyl acetate. The resultant organic layer was washed with water, brine, dried over magnesium sulfate, and filtered. The solvent was removed to afford the crude product. The product was purified by column chromatography (20% ethyl acetate–hexane) to afford 5.26 g (87%) of a white solid of product **5**; ^1H NMR ppm (deuteriochloroform): 3.89 (s, 2H), 6.89 (d, 1H, J=8.4 Hz), 7.10 (d, 1H, J=8.4 Hz); ^{13}C NMR ppm (deuteriochloroform): 124.8, 125.7, 126.9, 127.7, 141.8; HPLC purity (retention time): >99% (2.95 min); HRMS calcd for $C_4H_4Br_2N_2$ (M^++H) 252.8799, found 252.8779.

1.1.3. 6-Bromo-2-methoxypyridin-3-amine (6). A solution of 2,6-dibromo-3-aminopyridine **5** (10.4 g, 41.5 mmol) and sodium methoxide (15.7 g, 290 mmol) in dioxane (50 mL) was heated to reflux for 48 h. The brown reaction was allowed to cool to room temperature and diluted with saturated solution of ammonium chloride. The solution was extracted with ether and the organic layer was washed with water, brine, dried over magnesium sulfate, and filtered. The solvent was removed by evaporation to afford the crude product. The product was purified by column chromatography (20% ethyl acetate–hexane) to afford 7.1 g (84%) of a red solid of product **6**; ^1H NMR ppm (deuteriochloroform): 3.94 (s, 3H), 6.71 (d, 1H, J=6.0 Hz), 6.83 (d, 1H, J=6.0 Hz); ^{13}C NMR ppm (deuteriochloroform): 67.2, 120.4, 122.5, 124.1, 130.3, 152.4; HPLC purity (retention time): 94% (2.92 min); HRMS calcd for $C_6H_7Br_1N_2O$ (M^++H) 204.9800, found 204.9769.

1.1.4. 2,6-Dibromo-3-isopropylaminopyridine (7). Sodium triacetoxyborohydride (5.5 g, 25.9 mmol) was added to a solution of the aminopyridine **5** (1.6 g, 6.5 mmol), acetone (5.0 mL, excess), and a drop of acetic acid in a tetrahydrofuran-dichloromethane (1:1) solution (50 mL). After stirring at room temperature for 18 h the reaction was heated to reflux for 24 h. The solution was diluted with ether and water. The organic layer was washed with brine, dried over magnesium sulfate, and filtered. The solvent was removed by evaporation to afford the crude product. The product was purified by column chromatography (20% ethyl acetate–hexane) to afford 0.56 g (30%) of a yellow oil of product **7**; ^1H NMR ppm

(deuteriochloroform): 1.27 (d, 6H, J=4.8 Hz), 3.58 (septet, 1H, J=4.8 Hz), 6.74 (d, 1H, J=8.4 Hz), 7.26 (d, 1H, J=8.4 Hz); ^{13}C NMR ppm (deuteriochloroform): 22.7, 44.7, 120.2, 123.9, 127.6, 128.1, 141.3; LRMS for $C_{10}H_{10}N_1Br_2$ (ES, m/z) 293 (M+H).

1.1.5. 6-Bromo-*N*-isopropyl-2-methoxypyridin-3-amine (8). A solution of titanium tetrachloride 1 M in dichloromethane (37 mL, 37 mmol) was added to a solution of 6-bromo-2-methoxypyridin-3-amine **6** (6.8 g, 33.6 mmol) and acetone (3.3 mL, 44.9 mmol) in dichloromethane (100 mL). After stirring at room temperature for 3 h, sodium cyanoborohydride (6.3 g, 100 mmol) was added and the solution stirred at room temperature for 14 h. The solution was diluted with ether and water. The organic layer was washed with brine, dried over magnesium sulfate, and filtered. The solvent was removed by evaporation to afford the crude product. The product was purified by column chromatography (5% ethyl acetate–hexane) to afford 5.7 g (69%) of a red oil of product **8**; ^{1}H NMR ppm (deuteriochloroform): 1.20 (d, 6H, J=4.8 Hz), 3.51 (septet, 1H, J=4.8 Hz), 3.95 (s, 3H), 6.62 (d, 1H, J=6.0 Hz), 6.88 (d, 1H, J=6.0 Hz); HPLC purity (retention time): 95% (3.97 min); HRMS calcd for $C_9H_{13}Br_1N_2O$ (M^++H) 245.0289, found 245.0240.

1.1.6. 6-Bromo-3-(isopropylamino)pyridin-2-ol (9). A solution of boron tribromide 1 M in dichloromethane (46.0 mL, 46 mmol) was added to a solution of 6-bromo-*N*-isopropyl-2-methoxypyridin-3-amine **8** (5.6 g, 0.23 mmol) in dichloromethane (150 mL) at −10°C. The solution warmed to room temperature and stirred for 16 h. The reaction mixture was diluted with water, neutralized with a saturated sodium bicarbonate solution, and extracted with ether. The organic layer was washed with water, brine, dried over magnesium sulfate, and filtered. The solvent was removed by evaporation to afford the crude product. The product was purified by column chromatography (40% ethyl acetate–hexane) to afford 4.12 g (78%) of a white solid of product **9**; ^{1}H NMR ppm (deuteriochloroform): 1.22 (d, 6H, J=4.8 Hz), 3.49 (septet, 1H, J=4.8 Hz), 6.20 (m, 1H), 6.88 (d, 1H, J=6.0 Hz); ^{13}C NMR ppm (deuteriochloroform): 22.3, 44.1, 110.0, 128.6, 132.2, 136.4, 160.0; HPLC purity (retention time): 94% (2.45 min); HRMS calcd for $C_8H_{11}Br_1N_2O$ (M^++H) 231.0133, found 231.0130.

1.2. *tert*-Butyl [6-bromo-3-(isopropylamino)-2-oxopyridin-1(2*H*)-yl]acetate (10)

A suspension of calcium hydride (1.7 g, 40.3 mmol) in tetrahydrofuran (20 mL) was added to 6-bromo-3-(isopropylamino)pyridin-2-ol **9** (4.2 g, 18 mmol) in tetrahydrofuran (200 mL) dropwise via an addition funnel. The resulting suspension was heated to reflux for 30 min. To the mixture was then added a solution of *tert*-butyl bromoacetate (2.9 mL, 19.6 mmol) in tetrahydrofuran (2.3 M). Refluxing of the mixture was continued for 18 h. The reaction mixture was allowed to cool to room temperature, and quenched with an ice water mixture. The aqueous layer was extracted with diethyl ether. The organic layer was washed with water, brine, dried over magnesium sulfate, and filtered. The solvent was removed by evaporation to afford the crude product. The product was purified by column chromatography (10% ethyl acetate–hexane) to afford 4.1 g (66%) of a white solid of product **10**; ^{1}H NMR ppm (deuteriochloroform): 1.08 (H20,H15) (d, 6H, J=6.4 Hz), 1.37 (H11,18,19) (s, 9H), 3.42 (H14) (dsept, 1H, J=6.4, 8.4 Hz), 4.81 (H7) (s, 2H), 5.05 (NH13) (d, 1H, J=8.4 Hz), 6.13 (H4) (d, 1H, J=7.9 Hz), 6.46 (H5) (d, 1H, J=7.9 Hz); ^{13}C NMR ppm (DMSO): 22.3 (C15,C20), 28.2 (C11,18,19), 43.6 (C14), 50.7 (C7), 82.5 (C10), 107.0 (C4), 107.8 (C6), 111.8 (C5), 136.8 (C3), 158.4 (C2), 167.1 (C8); HPLC purity (retention time): 98% (4.63 min); HRMS calcd for $C_{14}H_{21}Br_1N_2O_3$ (M^++H) 345.0814, found 345.0827.

1.3. Benzyl 3-[1-(2-*tert*-butoxy-2-oxoethyl)-5-(isopropylamino)-6-oxo-1,6-dihydropyridin-2-yl]-5-nitrobenzoate (12a)

Tetrakis(triphenylphosphine)palladium(0) (0.20 g, 0.17 mmol) was added to a solution of compound **10** (0.60 g, 1.7 mmol), boronic acid **11a** (0.68 g, 2.3 mmol), and cesium carbonate (2.2 g, 6.7 mmol) in anhydrous dioxane (18 mL). The resulting mixture stirred for at 80°C for 16 h. The reaction mixture was allowed to cool to room temperature and was diluted with water and extracted with diethyl ether. The organic layer was washed with water, brine, dried over magnesium sulfate, and filtered. The solvent was removed by evaporation to afford the crude product. The product was purified by column chromatography (25% ethyl acetate–hexane) to afford 0.70 g (78%) of a red solid of product **12a**; ^{1}H NMR ppm (deuteriochloroform): 1.24 (d, 6H, J=4.8 Hz), 1.39 (s, 9H), 3.57 (septet, 1H, J=4.8 Hz), 4.41 (s, 2H), 5.39 (s, 2H), 6.14 (d, 1H, J=5.7 Hz), 6.40 (d, 1H, J=5.7 Hz), 7.40 (m, 6H), 8.35 (m, 1H), 8.42 (m, 1H), 8.85 (m, 1H); HPLC purity (retention time): >99% (5.70 min); HRMS calcd for $C_{28}H_{31}N_3O_7$ (M^++H) 522.2240, found 522.2242.

1.4. *tert*-Butyl [6-{3-[(*tert*-butoxycarbonyl)amino]-5-nitrophenyl}-3-(isopropylamino)-2-oxopyridin-1(2*H*)-yl]acetate (12b)

Following the same procedure described for **12a**, tetrakis (triphenylphosphine)palladium(0) (0.33 g, 0.28 mmol), compound **10** (1.0 g, 2.9 mmol), boronic acid **11b** (1.3 g, 4.6 mmol), and cesium carbonate (3.7 g, 11.3 mmol) were used to give 0.57 g (39%) of an orange solid of product **12b**; ^{1}H NMR ppm (deuteriochloroform): 1.24 (d, 6H, J=4.8 Hz), 1.40 (s, 9H), 1.49 (s, 9H), 3.67 (septet, 1H, J=4.8 Hz), 4.43 (s, 2H), 6.14 (m, 2H), 7.20 (m, 1H), 7.64 (m, 1H), 7.82 (m, 1H), 8.35 (m, 1H); HPLC purity (retention time): 96% (5.37 min); LRMS for $C_{25}H_{34}N_4O_7$ (ES, m/z) 503 (M^++H).

1.5. [6-{3-[(Benzyloxy)carbonyl]-5-nitrophenyl}-3-(isopropylamino)-2-oxopyridin-1(2*H*)-yl]acetic acid 13a

The *tert*-butyl ester **12a** (0.60 g, 1.1 mmol) was dissolved into 4N hydrochloric acid in dioxane (3 mL) and stirred at room temperature for 22 h. The solvent was removed under a stream of nitrogen (NOTE! heating the acid results in decarboxylation to afford the *N*-methyl derivative, benzyl 3-[5-(isopropylamino)-1-methyl-6-oxo-1,6-dihydropyridin-2-yl]-5-nitrobenzoate) to afford a red gum of product **13a**; ^{1}H NMR ppm (deuteriochloroform): 1.53 (d, 6H, J=4.8 Hz),

3.86 (septet, 1H, *J*=4.8 Hz), 4.55 (s, 2H), 5.39 (s, 2H), 6.42 (d, 1H, *J*=5.4 Hz), 7.39 (m, 5H), 8.29 (d, 1H, *J*=5.7 Hz), 8.37 (m, 1H), 8.44 (m, 1H), 8.94 (m, 1H); HPLC purity (retention time): 78% (4.67 min); HRMS calcd for $C_{24}H_{23}N_3O_7$ (M^++H) 466.1614, found 466.1625.

1.6. [6-(3-Amino-5-nitrophenyl)-3-(isopropylamino)-2-oxopyridin-1(2*H*)-yl]acetic acid 13b

Following the same procedure described for **13a**, *tert*-butyl ester **12b** (0.50 g, 0.10 mmol), was used to afford a yellow solid of product **13b**; ^{1}H NMR ppm (deuteriomethanol): 1.38 (d, 6H, *J*=4.8 Hz), 3.87 (septet, 1H, *J*=4.8 Hz), 4.63 (s, 2H), 6.48 (d, 1H, *J*=5.4 Hz), 7.42 (m, 1H), 7.82 (m, 2H), 7.82 (m, 1H), 8.00 (m, 1H); HPLC purity (retention time): 90% (2.72 min); HRMS calcd for $C_{16}H_{18}N_4O_5$ (M^++H) 347.1350, found 347.1334.

1.7. Benzyl 3-[1-(2-{[4-((*E*)-amino{[(benzyloxy)-carbonyl]imino}methyl)benzyl]amino}-2-oxoethyl)-5-(isopropylamino)-6-oxo-1,6-dihydropyridin-2-yl]-5-nitrobenzoate (14a)

Polystyrene–carbodiimide (2.3 g, 2.3 mmol) (1.00 mmol/g) was added to a slurry of the acid **13a** (0.53 g, 1.1 mmol), 1-hydroxybenzotriazole (0.16 g, 0.71 mmol), benzyl amino[4-(aminomethyl)phenyl]methylcarbamate (0.44 g, 1.3 mmol), and *N*-methylmorpholine (1.3 mL, 11.8 mmol) in a dichloromethane-*N*,*N*-dimethylformamide (3:1) solution (100 mL) and the suspension was agitated for 13 h. Upon completion of the reaction, the polyamine resin (2.81 mmol/g) (5.6 mmol) and polymer-bound aldehyde (2.3 mmol/g) (2.30 mmol) were added and the suspension was agitated for 1 h. The solution was filtered and the polymer was rinsed with *N*,*N*-dimethylformamide and dichloromethane until no more UV activity was seen in the dichloromethane washing. The solvent was removed by evaporation to afford the crude product. The product was purified by reverse-phase chromatography to afford 0.73 g (87%) of an orange solid of product **14a**; ^{1}H NMR ppm (deuterioacetone): 1.19 (d, 6H, *J*=4.8 Hz), 3.48 (septet, 1H, *J*=4.8 Hz), 4.41 (d, 2H, *J*=9.3 Hz), 4.63 (s, 2H), 5.18 (s, 2H), 5.48 (s, 2H), 6.23 (d, 1H, *J*=5.4 Hz), 6.31 (d, 1H, *J*=5.4 Hz), 7.40 (m, 12H), 7.99 (m, 2H), 8.18 (bt, 1H), 8.58 (m, 1H), 8.68 (m, 1H), 8.78 (m, 1H); HPLC purity (retention time): 90% (4.50 min); HRMS calcd for $C_{40}H_{38}N_6O_8$ (M^++H) 731.2829, found 731.2853.

1.8. Benzyl (1*E*)-amino{4-[({[6-(3-amino-5-nitrophenyl)-3-(isopropylamino)-2-oxopyridin-1(2*H*)-yl]acetyl}-amino)methyl]phenyl}methylidenecarbamate (14b)

Following the same procedure described for **14a**, polystyrene–carbodiimide (2.0 g, 2.0 mmol) (1.00 mmol/g), acid **13b** (0.34 g, 3.4 mmol), 1-hydroxybenzotriazole (0.14 g, 1.0 mmol), benzyl amino[4-(aminomethyl)phenyl]-methylcarbamate (0.38 g, 1.2 mmol), and *N*-methylmorpholine (1.1 mL, 10 mmol) was used to afford 0.24 g (39%) of a yellow solid of product **14b**; ^{1}H NMR ppm (deuteriodimethylformamide): 1.36 (d, 6H, *J*=4.5 Hz), 3.70 (septet, 1H, *J*=4.5 Hz), 4.56 (d, 2H, *J*=4.2 Hz), 4.75 (s, 2H), 5.33 (s, 2H), 6.25 (d, 1H, *J*=5.4 Hz), 6.43 (d, 1H, *J*=5.4 Hz), 7.53 (m, 8H), 8.06 (m, 4H), 8.57 (bt, 1H), 11.16 (bs, 1H); HPLC purity (retention time): 80% (3.41 min); HRMS calcd for $C_{32}H_{33}N_7O_6$ (M^++H) 612.2565, found 612.2521.

1.9. 3-Amino-5-[1-[2-({4-[amino(imino)methyl]benzyl}amino)-2-oxoethyl]-5-(isopropylamino)-6-oxo-1,6-dihydropyridin-2-yl]benzoic acid (15a)

A catalytic amount of palladium on carbon (10%) in methanol (5 mL) was added to compound **14a** (0.33 g, 0.45 mmol) in methanol (20 mL) and the mixture was stirred under a balloon of hydrogen at room temperature for 6 h. The mixture was filtered through celite and the solvent was evaporated to afford the product. The product was purified by reverse-phase chromatography to afford 0.28 g (88%) of a yellow solid of product **15a**; ^{1}H NMR ppm (deuteriomethanol): 1.26 (d, 6H, *J*=5.1 Hz), 3.63 (septet, 1H, *J*=5.1 Hz), 4.44 (d, 2H, *J*=4.2 Hz), 4.65 (d, 2H, *J*=7.2 Hz), 6.27 (dd, 1H, *J*=0.6, 5.7 Hz), 6.78 (dd, 1H, *J*=5.7, 13.8 Hz), 7.62 (m, 9H); HPLC purity (retention time): >99% (2.39 min); HRMS calcd for $C_{25}H_{28}N_6O_4$ (M^++H) 477.2250, found 477.2253.

1.10. *N*-{4-[Amino(imino)methyl]benzyl}-2-[6-(3,5-diaminophenyl)-3-(isopropylamino)-2-oxopyridin-1(2*H*)-yl]acetamide (15b)

Following the same procedure described for **15a**, compound **14b** (0.20 g, 0.32 mmol) was used to afford the product. The product was purified by reverse-phase chromatography to afford 0.24 g (39%) of a brown solid of product **15b**; ^{1}H NMR ppm (deuteriomethanol): 1.26 (d, 6H, *J*=4.8 Hz), 3.63 (septet, 1H, *J*=4.8 Hz), 4.44 (s, 2H), 4.65 (s, 2H), 6.27 (d, 1H, *J*=5.7 Hz), 6.57 (d, 1H, *J*=5.7 Hz), 6.65 (m, 3H), 7.55 (d, 2H, *J*=6.0 Hz), 7.77 (d, 2H, *J*=6.0 Hz); HPLC purity (retention time): >99% (2.39 min); HRMS calcd for $C_{24}H_{29}N_7O_2$ (M^++H) 448.2456, found 448.2447.

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