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Heterocycle-to-Heterocycle Route to Quinoline-4-amines: Reductive Heterocyclization of 3-(2-Nitrophenyl)isoxazoles

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Abstract

A variety of quinoline-4-amines were synthesized from substituted 3-(2-nitrophenyl)isoxazoles utilizing Zn⁰ or Fe⁰ dust and HOAc via a reductive heterocyclization process. The starting isoxazoles were synthesized from readily available starting materials. A brief survey of functional groups tolerated in this reductive heterocyclization was performed and several 10-amino-3,4-dihydrobenzo[b][1,6]naphthyridin-1(2H)-one and 9-amino-3,4-dihydroacridin-1(2H)-one examples were synthesized.

Keywords

Heterocycle; Fused-ring systems; Diversity Oriented Synthesis; Reduction; Heterocyclization

Introduction

In addition to the importance of isoxazoles as biologically active compounds, some of which are found in nature,¹ isoxazoles are also useful intermediates in the synthesis of complex targets as demonstrated by Suzuki in a synthesis of Seragakinone A where an isoxazole was employed as a 1,3-diketone equivalent.² Indeed, isoxazoles can serve as masked building blocks for other heterocycles, fused rings, aldols, and related compounds.³ For example, the N-O bond of the isoxazole ring can be reductively cleaved by catalytic hydrogenation or by metal carbonyl complexes [for example, Fe(CO)₅ or Mo(CO)₆ in moist acetonitrile] to enamino ketones, which can subsequently be converted to 1,3-diketones, α,β -unsaturated ketones, or β -ketoamides.³ In this context, an isoxazole ring can be considered a protecting group – one that is stable to many synthetic transformations – that is easily transformed to these various functionalities under appropriate reaction conditions.

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Supporting Information (see footnote on the first page of this article): Copies of ¹H and ¹³C NMR spectra of all compounds.

We previously reported cleavage of the amide moiety in isoxazolopiperidones as a route to orthogonally protected diamino acids (Figure 1A).⁴ We have also recently shown that substituted isoxazoles undergo reductive heterocyclization in M/HOAc (M = Zn⁰ or Fe⁰) when a 2-nitrophenyl group is appended to the 3-, 4- or 5-position of the isoxazole ring (Figure 1B).⁵ In continued exploration of these heterocycle-to-heterocycle strategies,⁶ we report here on the utility and limitations of 3-(2-nitrophenyl)isoxazole reductive heterocyclizations in obtaining quinoline-4-amines. We also report a brief survey of functional group compatibility with these reductive heterocyclizations conditions.

It is also noteworthy that quinoline-4-amines – the product of the isoxazole-based heterocycle-to-heterocycle chemistry reported here – have anti-malarial properties⁷ with Chloroquine (CQ) being the drug of choice for the treatment of malaria. Unfortunately, rising resistance to CQ suggests new drugs are needed (Figure 2). Quinoline-4-amines are also useful in the treatment of Alzheimer's Disease (AD) by way of inhibition of acetylcholinesterase (AChE).⁸ Tacrine was the first approved drug for the treatment of AD, but has limited use due to hepatotoxicity. Additionally, (–)-huprine X and (–)-huprine Y, analogs of the natural alkaloid (–)-huperazine A, are among the most potent AChE inhibitors.⁹ For these reasons, we were also interested in synthesizing analogs of these biologically active compounds utilizing the chemistry developed herein.

Results and Discussion

The requisite 3-(2-nitrophenyl)isoxazoles are easily synthesized from α -chlorooximes and 1,3-carbonyls or terminal alkynes in moderate to good yields following established literature procedures.^{5,6} In this work, we report that Zn⁰ or Fe⁰ in HOAc are suitable metal reductants for the conversion of both nitro ($\rightarrow$ amine) and isoxazole ($\rightarrow$ β -keto imine) moieties with subsequent heterocyclization to the targeted quinoline-4-amines. Batra et al.¹⁰ reported the reductive heterocyclization of 2-nitrophenyl isoxazoles using H₂/Pd•C – conditions that do not allow, for example, C=C and C $\equiv$ N functional groups in the substrate. In contrast, using Fe⁰/H⁺ in the reductive heterocyclization tolerates many functional groups, including C=C and C $\equiv$ N (*vide infra*).

As outlined in Table 1, a collection of substituted 3-(2-nitrophenyl)isoxazoles (**1a–d**) were synthesized by the reaction of *in situ* generated enolates or terminal alkynes with (2-nitrophenyl)nitrile oxide. With these representative 3-(2-nitrophenyl)isoxazoles in hand, it was found that a keto-substituted isoxazole readily accommodates these reductive heterocyclization conditions (Table 1, **1a** $\rightarrow$ **2a** in 90% yield). In contrast, an ester appended at C4 of the isoxazole ring gives the targeted quinoline-4-amine **2b** in only 6% yield, with the major product being the carboxylic acid analog (**2b'**; R² = CO₂H) of isoxazole **2b** (e.g., ester hydrolysis). Current work has revealed that substituting HOAc with the weaker acid aq. NH₄Cl can improve the yield of the desired reductive heterocyclization product. For example, the yield for **1b** $\rightarrow$ **2b** improved from 6% in HOAc to 22% in aq. NH₄Cl, but the carboxylic acid analog of **2b** was still the major product in 39% yield.

Interestingly, a nitrile group at C4 tolerates these reductive heterocyclization conditions well, giving quinoline-4-amine **2c** in 76% yield. The yield decreases to 36% under aq.

NH_4Cl conditions. Quinoline-4-amine **2d** was obtained from **1d** (prop-1-en-2-yl substituent at C5) under the $\text{Fe}^0/\text{aq. NH}_4\text{Cl}$ in 51% yield, while Fe^0/HOAc failed to deliver the targeted product. In general, substitution at C5 of the isoxazole did not give satisfactory results under Fe^0/HOAc conditions, but changing the acid source to aq. NH_4Cl gave the quinoline-4-amine product in low to good yields. This brief survey demonstrates that these sensitive functional groups generally survive well the metal-mediated ($\text{M}^0 \rightarrow \text{M}^{+1}$) reductive heterocyclization conditions.

With these calibrating Table 1 results in hand, attention was turned to the synthesis of 10-amino-3,4-dihydrobenzo[*b*][1,6]-naphthyridin-1(2*H*)-one and 9-amino-3,4-dihydroacridin-1(2*H*)-one analogs of the previously mentioned pharmaceuticals (Figure 1) from piperidine-2,4-dione or 1,3-cyclohexanone starting materials. The route to piperidine-2,4-diones (Scheme 1) commenced with Boc protection of β -alanine **3a/b** following a modified literature procedure.¹¹ The resulting *N*-protected amino acid **4a/b** was then used to *C*-acylate Meldrum's acid under standard EDC/DMAP coupling conditions.⁴ Subjecting these resulting Meldrum's acid analogs to refluxing EtOAc ($\rightarrow$ acyl-ketene intermediate) yielded the targeted piperidine-2,4-diones **5a/b** in 85–90% yield over 2 steps. Piperidine-2,4-diones **5a/b** or cyclohexane-1,3-dione were then reacted with NaH in dry THF followed by the slow addition of α -chlorobenzaldoximes **6** to give 6,7-dihydroisoxazolo[4,5-*c*]pyridin-4(5*H*)-one **7a–d** and 6,7-di-hydrobenzo[*d*]isoxazol-4(5*H*)-one **7e** in 43–89% yield (Table 2).¹²

Previous studies have established that zinc and iron dust are both effective reductants.¹³ This, in conjunction with the results outlined in Table 1, led us to undertake several experiments with dihydroisoxazolopyridinone **7a** using Zn^0/HOAc as the reductant. At 120° C, **7a** decomposed (Table 3, entry 1) with loss of the Boc protecting group (detected by LCMS). Fortunately, lowering the reaction temperature to 80 °C (entry 2; or even 22 °C = entry 3) overnight gave us the desired dihydrobenzonaphthyridinone **9a** in good yield. In an effort to obtain intermediate **8a** (Table 3) and provide insight into the order of events, the reduction was stopped after 1 h at 0 °C. Under these conditions, starting material **7a** and aniline **8a** (nitro reduced) were obtained in an ~2:1 ratio, respectively, and dihydrobenzonaphthyridinone **9a** was obtained in 7% yield. This result suggests that the nitro moiety of **7a** is reduced before reduction of the isoxazole *N,O*-bond and, once the isoxazole *N,O*-bond in intermediate **8a** is reduced, heterocyclization proceeds to give product **9a**. Indeed, when isolated aniline **8a** was resubmitted to Zn^0/HOAc at 22 °C, it was cleanly converted to dihydrobenzonaphthyridinone **9a** in quantitative yield,

Dihydroisoxazolopyridinones **7a–d** as well as dihydrobenzoisoxazolone **7e** (Scheme 2) were subjected to reductive heterocyclization under these optimized Zn^0/HOAc conditions (22 °C, 18 h) to give 10-amino-3,4-dihydrobenzo[*b*][1,6]naphthyridin-1(2*H*)-one **9a–d** in 33–89% yield and 9-amino-3,4-dihydroacridin-1(2*H*)-one **9e** in 80% yield (Scheme 2). To further expand the scope of this work, the Boc moiety in 6,7-dihydroisoxazolo[4,5-*c*]pyridin-4(5*H*)-one **7a** was deprotected (TFA in CHCl_3 at 0° C, 30 min.) to give the free amide, which was subsequently treated with NaH in dry THF followed by *p*-bromobenzyl

bromide to give **7f** in 40% overall yield. This *N*-alkylated isoxazole (**7f**) was then subjected to the reductive heterocyclization reaction to yield **9f** in 22% yield.

Finally, to demonstrate that the 4-aminoquinoline moiety of **9** can also be diversified by *N*-alkylation, conversion **9a** → **10** was investigated. It was found that phase transfer *N*-alkylation conditions (DCM:1M aq. NaOH + TBAB) using benzyl bromide yielded **10** in 69% yield (Scheme 3). In contrast, reacting the 4-aminoquinoline moiety of **9a** with benzaldehyde under reductive amination conditions failed (in the condensation step).

Conclusions

Various quinoline-4-amines were synthesized utilizing Zn⁰ or Fe⁰ and HOAc from substituted 3-(2-nitrophenyl)-isoxazoles via reductive heterocyclization. Aqueous ammonium chloride also worked well in some cases as an acid source. The requisite starting isoxazoles were easily synthesized from readily available starting materials. A survey of functional group tolerance for these conditions revealed that alkenes, nitriles, ketones, amides, and tert-butyl carbamates are stable to this heterocycle-to-heterocycle reductive heterocyclization, whereas esters were found to partially hydrolyze. A few examples of 10-amino-3,4-dihydrobenzo[b][1,6]naphthyridin-1(2H)-ones were also synthesized and diversified.

Experimental Section

General

All chemicals were purchased from commercial suppliers and used without further purification. Analytical thin layer chromatography was carried out on pre-coated plates (silica gel 60 F254, 250 μm thickness) and visualized with UV light. Flash chromatography was performed using 60 Å, 32–63 μm silica gel (Scientific Adsorbents). Concentration *in vacuo* refers to rotary evaporation under reduced pressure. The chemical purity of all compounds was determined by HPLC and HRMS or LC–MS and confirmed to be 95%. ¹H NMR spectra were recorded at 300 MHz, 400 MHz, 600 MHz or 800 MHz at ambient temperature with Acetone-*d*₆, DMSO-*d*₆, CDCl₃, CD₃CN, or CD₃OD as solvents. ¹³C NMR spectra were recorded at 75 Hz, 100 MHz, 150 MHz or 200 MHz at ambient temperature with Acetone-*d*₆, DMSO-*d*₆, CDCl₃, CD₃CN, or D₃OD as solvents. Chemical shifts are reported in parts per million (ppm) relative to the residual solvent peak. Infrared spectra were recorded on an ATI-FTIR spectrometer. The specifications of the Waters LC/MS are as follows: electrospray (+) ionization, mass range 100 – 1500 Da, 20 V cone voltage, and Xterra® MS C18 column (2.1 mm × 50 mm × 3.5 μm), 0.2 mL/min, eluents were water/0.1% HCOOH and MeCN/0.1% HCOOH in gradient, and Waters 996 PDA. Preparative HPLC specifications are as follows: 15 mL/min flow rate, Xterra Prep MS C18 OBD column (19 mm × 100 mm), eluents were water/0.1% HCOOH and MeCN/0.1% HCOOH in gradient, and dual wavelength absorbance detector. High-resolution mass spectra were acquired on an LTQ Orbitrap XL mass spectrometer equipped with an electrospray ionization source (ThermoFisher, San Jose, CA), operating in the positive ion mode. Samples were introduced into the source via loop injection at a flow rate of 200 ul/min, in a solvent system of 1:1 acetonitrile:water with 0.1% formic acid. Mass spectra were

acquired using Xcalibur, version 2.0.7 SP1 (ThermoFinnigan). The spectra were externally calibrated using the standard calibration mixture, and then calibrated internally to <2 ppm with the lock mass tool.

General Procedure A; Reduction with HOAc

The specific isoxazole (1 eq, 1 mmol), acetic acid (~88 eq, 5.0 mL), and iron powder (18 eq, 1.0 g) were combined and heated at 80 – 120 °C overnight. The reaction mixture was filtered, rinsed with DCM (10 mL), diluted with DCM (75 mL), washed with sat. NaHCO₃ (25 mL) and dried over Na₂SO₄. The organics were concentrated under reduced pressure and flash column chromatography yielded the products.

General Procedure B; Reduction with NH₄Cl

The specific isoxazole (1 eq, 1 mmol) and NH₄Cl (18 eq) were dissolved in tBuOH:H₂O (20 mL/mmol) and iron powder (18 eq) was added. The mixture was heated at 80 °C overnight. The reaction was filtered and the filter cake was rinsed with EtOAc. H₂O (30 mL) was added, the mixture was extracted with EtOAc (3 × 40 mL), and dried over Na₂SO₄. The organics were concentrated under reduced pressure and flash column chromatography yielded the products.

1-(5-Methyl-3-(2-nitrophenyl)isoxazol-4-yl)ethan-1-one (1a)

Pen-tane-2,4-dione (1.03 mL, 10 mmol) was dissolved in dry THF (20mL) and cooled in an ice bath. 60% dispersed in mineral oil NaH (0.44 g, 11 mmol) was added portionwise and stirred for 5 minutes. N-Hydroxy-2-nitrobenzimidoyl chloride (2.2 g, 11 mmol) was dissolved in dry THF (20 mL) and added dropwise to the slurry and stirred overnight at rt. Equal volumes of water and EtOAc (40 mL total) were added, organics separated, and aqueous layer extracted with EtOAc (20 mL). The combined organics were washed with brine, dried over Na₂SO₄, and concentrated *in vacuo*. Column chromatography yielded a pale yellow solid (2.21 g, 90% yield). ¹H NMR (600 MHz, Chloroform-*d*) δ 8.16 (d, *J* = 8.2 Hz, 1H), 7.68 (t, *J* = 7.4 Hz, 1H), 7.63 (t, *J* = 7.8 Hz, 1H), 7.44 (d, *J* = 7.5 Hz, 1H), 2.73 (s, 3H), 2.17 (s, 3H). ¹³C NMR (150 MHz, Chloroform-*d*) δ 191.2, 173.7, 160.4, 148.4, 133.6, 132.0, 130.9, 125.0, 124.8, 117.2, 29.8, 14.1. HRMS *m/z* calculated for C₁₂H₁₁N₂O₄ [M + H]⁺ 247.0713, found: 247.0717.

Methyl 5-methyl-3-(2-nitrophenyl)isoxazole-4-carboxylate (1b)

Following the procedure for **1a**, except using methyl 3-oxobutanoate (1.30 g, 10 mmol), gave **1b** as a yellow solid (0.127 g, 46% yield). ¹H NMR (600 MHz, Chloroform-*d*) δ 8.17 (d, *J* = 8.1 Hz, 1H), 7.66 (t, *J* = 7.5 Hz, 1H), 7.60 (t, *J* = 7.8 Hz, 1H), 7.47 (d, *J* = 7.5 Hz, 1H), 4.03 (q, *J* = 7.1 Hz, 2H), 2.69 (s, 3H), 1.02 (t, *J* = 7.1 Hz, 3H). ¹³C NMR (150 MHz, Chloroform-*d*) δ 175.3, 161.2, 160.8, 148.3, 133.4, 132.2, 130.7, 124.9, 124.5, 108.8, 60.8, 13.6, 13.3. HRMS *m/z* calculated for C₁₃H₁₃N₂O₅ [M + H]⁺ 277.0819; found: 277.0827.

3-(2-Nitrophenyl)-5-phenylisoxazole-4-carbonitrile (1c)

Following the procedure for **1a**, except using 3-oxo-3-phenylpropanenitrile (0.576 g, 4.0 mmol), gave **1c** as a yellow solid (0.372 g, 64% yield). ¹H NMR (600 MHz, Chloroform-*d*)

δ 8.27 (d, J = 8.1 Hz, 1H), 8.11 (d, J = 7.3 Hz, 2H), 7.82 (t, J = 7.5 Hz, 1H), 7.77 (d, J = 7.8 Hz, 1H), 7.68 (d, J = 7.5 Hz, 1H), 7.67 – 7.57 (m, 3H), ; **^{13}C NMR** (150 MHz, Chloroform- d) δ 174.3, 161.6, 147.9, 134.0, 133.0, 132.2, 129.5, 126.9, 125.5, 124.6, 121.4, 111.4, 89.1. **HRMS** m/z calculated for $\text{C}_{16}\text{H}_{10}\text{N}_3\text{O}_3$ $[\text{M} + \text{H}]^+$ 292.0717; found: 292.0722.

3-(2-Nitrophenyl)-5-(prop-1-en-2-yl)isoxazole (1d)

Following the procedure for **1a**, except using 2-methylbut-1-en-3-yne (0.66 g, 10 mmol), gave **1d** as a yellow solid (0.177 g, 77%); while none of the regioisomeric isoxazole was detected, a small amount of isoxazolino-isoxazole (i.e., bis cycloadduct; ~10% yield) was obtained. **^1H NMR** (600 MHz, Chloroform- d) δ 7.89 (d, J = 7.6 Hz, 1H), 7.63 – 7.61 (m, 2H), 7.55 (ddd, J = 8.2, 5.4, 3.6 Hz, 1H), 6.29 (s, 1H), 5.77 (s, 1H), 5.29 (s, 1H), 2.04 (s, 3H). **^{13}C NMR** (150 MHz, Chloroform- d) δ 170.9, 160.0, 148.6, 132.9, 131.5, 130.6, 130.4, 124.4, 124.2, 117.6, 100.5, 19.5. **HRMS** m/z calculated for $\text{C}_{12}\text{H}_{11}\text{N}_2\text{O}_3$ $[\text{M} + \text{H}]^+$ 231.0764; found: 231.0763.

1-(4-Amino-2-methylquinolin-3-yl)ethan-1-one (2a)

General procedure A with **1a** (0.246 g, 1.0 mmol) yielded **2a** as a white solid (0.180 g, 90%). **^1H NMR** (600 MHz, Chloroform- d) δ 7.85 (d, J = 8.4 Hz, 1H), 7.76 (d, J = 8.4 Hz, 1H), 7.65 (dd, J = 8.3, 7.0 Hz, 1H), 7.39 (dd, J = 8.3, 7.0 Hz, 1H), 7.08 (s, 2H), 2.79 (s, 3H), 2.62 (s, 3H). **^{13}C NMR** (150 MHz, Chloroform- d) 203.4, 157.7, 151.5, 147.3, 131.2, 128.9, 125.0, 120.8, 117.2, 112.8, 33.1, 27.7. **HRMS** m/z calculated for $\text{C}_{12}\text{H}_{13}\text{N}_2\text{O}$ $[\text{M} + \text{H}]^+$ 201.1022; found: 201.1027.

Methyl 4-amino-2-methylquinoline-3-carboxylate (2b)

General procedure A with **1b** (0.277 g, 1.0 mmol) yielded **2b** as a white solid (14 mg, 6%), ester hydrolysis (**2b'**) was the major product in 63% yield, see below. General procedure B with **1b** (0.277 g, 1.0 mmol) yielded **2b** as a white solid (51 mg, 22%). **^1H NMR** (600 MHz, Chloroform- d) δ 7.85 (d, J = 8.4 Hz, 1H), 7.75 (d, J = 7.4 Hz, 1H), 7.64 (t, J = 7.6 Hz, 1H), 7.38 (t, J = 7.6 Hz, 1H), 7.08 (s, 2H), 4.40 (q, J = 7.1 Hz, 2H), 2.81 (s, 3H), 1.42 (t, J = 7.1 Hz, 3H). **^{13}C NMR** (150 MHz, Chloroform- d) δ 169.5, 159.5, 153.7, 147.4, 131.2, 1289.0, 124.8, 120.6, 117.0, 102.4, 60.9, 28.0, 14.3. **HRMS** m/z calculated for $\text{C}_{13}\text{H}_{15}\text{N}_2\text{O}_2$ $[\text{M} + \text{H}]^+$ 231.1128; found: 231.1131. **4-Amino-2-methylquinoline-3-carboxylic acid (2b')**: Isolated a white powder (0.145 g, 63%). **^1H NMR** (600 MHz, DMSO- d_6) δ 10.88 (s, 1H), 10.77 (s, 1H), 8.42 (s, 1H), 8.13 (d, J = 8.1 Hz, 1H), 7.53 (t, J = 7.7 Hz, 1H), 7.21 (d, J = 8.2 Hz, 1H), 7.13 (t, J = 7.6 Hz, 1H), 2.58 (s, 3H). **^{13}C NMR** (150 MHz, DMSO- d_6) δ 200.9, 162.9, 158.7, 140.1, 133.4, 124.5, 121.5, 115.9, 113.0, 101.6, 33.5. **HRMS** m/z calculated for $\text{C}_{11}\text{H}_{11}\text{N}_2\text{O}_2$ $[\text{M} + \text{H}]^+$ 203.0815; found: 203.0823.

4-Amino-2-phenylquinoline-3-carbonitrile (2c)

General procedure A with **1c** (0.245 g, 1.0 mmol) yielded **2c** as a yellow solid (0.186 g, 76%). General procedure B with **1c** (0.245 g, 1.0 mmol) yielded **2c** as a yellow solid (88 mg, 36%) **^1H NMR** (600 MHz, Chloroform- d) δ 8.08 (d, J = 8.8 Hz, 1H), 7.92 (d, J = 6.5 Hz, 2H), 7.83 – 7.76 (m, 2H), 7.59 – 7.44 (m, 4H), 5.76 (s, 2H). **^{13}C NMR** (150 MHz, DMSO-

d_6) 159.2, 155.2, 148.5, 138.8, 132.5, 130.8, 129.9, 128.9, 128.7, 126.4, 120.3, 117.5, 115.2, 86.3. **HRMS** m/z calculated for $C_{16}H_{12}N_3$ $[M + H]^+$ 246.1026; found: 246.1032.

2-(Prop-1-en-2-yl)quinolin-4-amine (2d)

General procedure A with **1d** (0.230 g, 1.0 mmol) yielded no product (0.0 g, 0%). General procedure B with **1d** (0.230 g, 1.0 mmol) yielded **2d** as a yellow solid (94 mg, 51%). **¹H NMR** (600 MHz, DMSO- d_6) δ 7.58 (d, J = 7.8 Hz, 1H), 7.18 (s, 1H), 7.13 (t, J = 7.6 Hz, 1H), 6.81 (d, J = 8.2 Hz, 1H), 6.61 (dd, J = 7.9, 7.1 Hz, 1H), 6.25 (s, 2H), 5.77 (s, 1H), 5.39 (s, 1H), 2.10 (s, 3H). **¹³C NMR** (150 MHz, Chloroform- d) δ 172.4, 168.8, 163.7, 147.3, 131.0, 129.8, 117.4, 116.3, 115.9, 110.3, 100.4, 19.7. **HRMS** m/z calculated for $C_{12}H_{13}N_2$ $[M + H]^+$ 185.1073; found: 185.1069.

tert-Butyl 3-(2-nitrophenyl)-4-oxo-6,7-dihydroisoxazolo[4,5-c]pyridine-5(4H)-carboxylate (7a)

tert-Butyl 2,4-dioxopiperidine-1-carboxylate (4.00 g, 18.8 mmol) was dissolved in dry THF (100 mL) and cooled to 0 °C. NaH (0.450 g, 18.8 mmol) was added to the solution over a 5 min period. N-Hydroxy-2-fluorobenzimidoyl chloride (2.71 g, 15.6 mmol) was added dropwise over 1 hour and stirred for 4 hours from 0 °C to rt. The reaction mixture was concentrated in vacuo, dissolved in ethyl acetate (75 mL), and an equal volume of water was added. The organic layer was separated and aqueous layer extracted additional times with ethyl acetate (2 $\times$ 75 mL). The combined organics were washed with brine, dried over sodium sulfate, and concentrated in vacuo. The residue was purified by crystallization from EtOAc to yield a colorless solid (0.239 g, 68%). **¹H NMR** (600 MHz, Chloroform- d) δ 8.25 (d, J = 8.1 Hz, 1H), 7.73 (t, J = 7.5 Hz, 1H), 7.69 (t, J = 8.1 Hz, 1H), 7.61 (d, J = 7.5 Hz, 1H), 4.20 (t, J = 6.5 Hz, 2H), 3.19 (t, J = 6.5 Hz, 2H), 1.56 (s, 9H). **¹³C NMR** (150 MHz, Chloroform- d) δ 176.0, 159.7, 152.4, 148.5, 133.7, 132.4, 131.5, 131.5, 125.3, 123.2, 111.0, 83.8, 44.4, 28.2, 23.5. **HRMS** m/z calculated for $C_{17}H_{17}N_3NaO_6$ $[M + Na]^+$ 382.1010; found: 382.1011.

tert-Butyl 3-(5-chloro-2-nitrophenyl)-4-oxo-6,7-dihydroisoxazolo[4,5-c]pyridine-5(4H)-carboxylate (7b)

Followed the same procedure as **7a**, except N-Hydroxy-5-chloro-2-nitrobenzimidoyl chloride (0.230 g, 0.977 mmol) was added. The reaction was purified by column chromatography to yield a colorless solid (0.192 g, 50%). **¹H NMR** (600 MHz, Chloroform- d) δ 8.24 (d, J = 8.7 Hz, 1H), 7.66 (dd, J = 8.8, 2.3 Hz, 1H), 7.61 (d, J = 2.3 Hz, 1H), 4.22 (t, J = 6.5 Hz, 2H), 3.21 (t, J = 6.5 Hz, 2H), 1.51 (s, 9H). **¹³C NMR** (150 MHz, Chloroform- d) δ 175.9, 159.2, 158.6, 152.2, 146.6, 140.0, 132.1, 131.2, 126.5, 124.7, 110.8, 83.8, 44.1, 28.0, 23.3. **HRMS** m/z calculated for $C_{17}H_{16}ClN_3NaO_6$ $[M + Na]^+$ 416.0620; found: 416.0621.

tert-Butyl 6-methyl-3-(2-nitrophenyl)-4-oxo-6,7-dihydroisoxazolo[4,5-c]pyridine-5(4H)-carboxylate (7c)

Followed the same procedure as **7a**, except tert-butyl 2-methyl-4,6-dioxopiperidine-1-carboxylate (0.250 g, 1.1 mmol) was used. The reaction was purified by column

chromatography to yield a colorless solid (0.201 g, 54%). **¹H NMR** (600 MHz, Chloroform-*d*) 8.24 (d, *J* = 8.0 Hz, 1H), 7.71 (t, *J* = 7.5 Hz, 1H), 7.66 (t, *J* = 7.8 Hz, 1H), 7.61 (d, *J* = 7.5 Hz, 1H), 4.92 (p, *J* = 6.8 Hz, 1H), 3.41 (dd, *J* = 17.5, 6.5 Hz, 1H), 2.97 (d, *J* = 1.3 Hz, 1H), 1.47 (s, 9H), 1.40 (d, *J* = 6.8 Hz, 3H). **¹³C NMR** (150 MHz, Chloroform-*d*) δ 174.4, 159.4, 158.8, 152.2, 148.2, 133.5, 132.2, 131.2, 125.1, 123.0, 110.0, 83.5, 51.6, 29.2, 28.0, 20.2. **HRMS** *m/z* calculated for C₁₈H₂₀N₃O₆ [M + H]⁺ 374.1347; found: 374.1365.

***tert*-Butyl 3-(5-chloro-2-nitrophenyl)-6-methyl-4-oxo-6,7-dihydroisox-azolo[4,5-c]pyridine-5(4H)-carboxylate (7d)**

Followed the same procedure as **7a**, except *tert*-butyl 2-methyl-4,6-dioxopiperidine-1-carboxylate (0.250 g, 1.1 mmol) was used and N-Hydroxy-5-chloro-2-nitrobenzimidoyl chloride (0.215 g, 0.917 mmol) was added to yield a colorless solid (0.161 g, 43%). **¹H NMR** (600 MHz, Chloroform-*d*) δ 8.25 (d, *J* = 8.7 Hz, 1H), 7.66 (dd, *J* = 8.7, 2.3, 1H), 7.64 (d, *J* = 2.3 Hz, 1H), 4.97 (m, 1H), 3.46 (dd, *J* = 17.5, 6.5 Hz, 1H), 3.00 (dd, *J* = 17.5, 1.2 Hz, 1H), 1.52 (s, 9H), 1.44 (d, *J* = 6.8 Hz, 3H). **¹³C NMR** (150 MHz, Chloroform-*d*) δ 174.6, 158.7, 158.5, 152.1, 146.6, 140.1, 132.1, 131.1, 126.6, 124.8, 110.1, 83.6, 51.7, 29.2, 28.0, 20.3. **HRMS** *m/z* calculated for C₁₈H₁₉ClN₃O₆ [M + H]⁺ 408.0957; found: 408.0978.

3-(2-Nitrophenyl)-6,7-dihydrobenzo[d]isoxazol-4(5H)-one (7e)

Followed the same procedure as **7a**, except 1,3-cyclohexadione (1.12 g, 10 mmol) was used. The reaction was purified by column chromatography to yield a colorless solid. **¹H NMR** (600 MHz, Chloroform-*d*) δ 8.23 (d, *J* = 8.0 Hz, 1H), 7.71 (td, *J* = 7.4, 1.4 Hz, 1H), 7.66 (td, *J* = 7.8, 1.6 Hz, 1H), 7.60 (dd, *J* = 7.3, 1.6 Hz, 1H), 3.07 (t, *J* = 6.3 Hz, 2H), 2.52 – 2.44 (t, *J* = 6.4 Hz, 2H), 2.24 (p, *J* = 6.4 Hz, 2H). **¹³C NMR** (150 MHz, Chloroform-*d*) δ 192.2, 180.9, 157.8, 148.4, 133.5, 132.2, 131.2, 125.0, 123.4, 114.4, 37.6, 23.1, 22.1. **HRMS** *m/z* calculated for C₁₃H₁₁N₂O₄ [M + H]⁺ 259.0713; found: 259.0721.

5-(4-Bromobenzyl)-3-(2-nitrophenyl)-6,7-dihydroisoxazolo[4,5-c] pyridin-4(5H)-one (7f)

Isioxazole **7a** (0.826 g, 1.93 mmol) was boc deprotected and N-alkylated following literature procedures^{5,14} to yield **7f** as a white powder (0.321 g, 39%) over two steps. **¹H NMR** (600 MHz, Chloroform-*d*) δ 8.25 (d, *J* = 8.1 Hz, 1H), 7.74-7.72 (m, 1H), 7.70-7.66 (m, 2H), 7.45 (d, *J* = 8.4 Hz, 2H), 7.12 (d, *J* = 8.4 Hz, 2H), 4.56 (s, 2H), 3.60 (t, *J* = 7.2 Hz, 2H), 3.14 (t, *J* = 7.2 Hz, 2H); **¹³C NMR** (150 MHz, Chloroform-*d*) δ 173.3, 160.9, 159.0, 149.0, 135.8, 133.4, 132.2, 131.9, 131.1, 129.7, 125.0, 123.2, 121.7, 109.5, 48.4, 45.2, 22.7. **HRMS** *m/z* calculated for C₁₉H₁₅BrN₃O₄ [M + H]⁺ 428.0240; found: 428.0255.

***tert*-Butyl 3-(2-aminophenyl)-4-oxo-6,7-dihydroisoxazolo[4,5-c]pyri-dine-5(4H)-carboxylate (8a)**

General procedure A with **7a** (0.359 g, 1.0 mmol) and zinc powder (1.2 g, 18 mmol) gave **8a** as a white solid (95 mg, 29%). **¹H NMR** (600 MHz, Chloroform-*d*) δ 7.79 (dd, *J* = 7.9 and 1.5 Hz, 1H), 7.19 (td, *J* = 7.7 and 1.5 Hz, 1H), 6.79 (t, 7.7 Hz, 1H), 6.736 (d, 8.2 Hz, 1H), 4.83 (s, 2H), 4.15 (t, *J* = 6.4, 2H), 3.09 (t, *J* = 6.4 Hz, 2H), 1.52 (s, 9H). **¹³C NMR** (150 MHz, Chloroform-*d*) δ 176.9, 160.9, 159.7, 152.9, 146.0, 132.8, 131.6, 117.6, 116.6, 111.0,

110.6, 83.8, 44.0, 28.3, 23.6. **HRMS** m/z calculated for $C_{17}H_{19}N_3NaO_4$ $[M + Na]^+$ 352.1268; found: 352.1268.

***tert*-Butyl 10-amino-1-oxo-3,4-dihydrobenzo[b][1,6]naphthyridine-2 (1H)-carboxylate (9a)**

General procedure A with **7a** (0.359 g, 1.0 mmol) and zinc powder (1.2 g, 18 mmol) gave **9a** as a yellow solid (0.278 g, 89%). **¹H NMR** (600 MHz, DMSO- d_6) δ 9.39 (bs, 1H), 8.32 (d, J = 8.3 Hz, 1H), 7.69 – 7.67 (m, 2H), 7.44 – 7.41 (m, 1H), 3.86 (t, J = 6.2 Hz, 2H), 3.02 (t, J = 6.2 Hz, 2H), 1.49 (s, 9H). **¹³C NMR** (150 MHz, DMSO- d_6) δ 167.6, 159.9, 155.9, 153.1, 148.4, 132.4, 129.0, 125.1, 123.8, 118.7, 99.8, 82.7, 43.9, 33.3, 28.4. **HRMS** m/z calculated for $C_{17}H_{20}N_3O_3$ $[M + H]^+$ 314.1499; found: 314.1514.

***tert*-Butyl 10-amino-8-chloro-1-oxo-3,4-dihydrobenzo[b][1,6] naphth-yridine-2(1H)-carboxylate (9b)**

General procedure A with **7b** (0.393 g, 1.0 mmol) and zinc powder (1.2 g, 18 mmol) gave **9b** as a yellow solid (0.247 g, 71%). **¹H NMR** (600 MHz, Chloroform- d) δ 7.82 (d, J = 2.2 Hz, 1H), 7.80 (d, J = 8.8 Hz, 1H), 7.64 (dd, J = 8.8 and 2.2 Hz, 1H), 4.04 (t, J = 6.4 Hz, 2H), 3.18 (t, J = 6.4 Hz, 2H), 1.62 (s, 9H). **¹³C NMR** (150 MHz, Chloroform- d) δ 167.5, 159.5, 154.0, 152.2, 146.6, 132.4, 130.8, 130.7, 120.4, 118.8, 101.0, 83.4, 43.5, 33.0, 29.7. **HRMS** m/z calculated for $C_{17}H_{19}ClN_3O_3$ $[M + H]^+$ 348.1109; found: 348.1131.

***tert*-Butyl 10-amino-3-methyl-1-oxo-3,4-dihydrobenzo[b][1,6] naphth-yridine-2(1H)-carboxylate (9c)**

General procedure A with **7c** (0.373 g, 1.0 mmol) and zinc powder (1.2 g, 18 mmol) gave **9c** as a yellow solid (0.216 g, 58%). **¹H NMR** (600 MHz, Chloroform- d) δ 7.86 (dd, J = 8.4, 1.2 Hz, 1H), 7.83 (dd, J = 8.3, 1.3 Hz, 1H), 7.69 (ddd, J = 8.3, 6.9, 1.3 Hz, 1H), 7.43 (ddd, J = 8.2, 6.9, 1.3 Hz, 1H), 4.70 – 4.64 (m, 1H), 3.46 (dd, J = 16.0, 5.7 Hz, 1H), 2.93 (dd, J = 16.0, 2.1 Hz, 1H), 1.59 (s, 9H), 1.29 (d, J = 6.7 Hz, 3H). **¹³C NMR** (150 MHz, Chloroform- d) δ 167.0, 157.7, 154.6, 152.3, 148.4, 131.9, 129.1, 125.2, 121.0, 118.1, 100.2, 83.2, 50.1, 39.0, 28.2, 19.1. **HRMS** m/z calculated for $C_{18}H_{22}N_3O_3$ $[M + H]^+$ 328.1656; found: 328.1674.

***tert*-Butyl 10-amino-8-chloro-3-methyl-1-oxo-3,4-dihydrobenzo[b] [1,6]naphthyridine-2(1H)-carboxylate (9d)**

General procedure A with **7d** (0.361 g, 1.0 mmol) and zinc powder (1.2 g, 18 mmol) gave **9d** as a yellow solid (0.119 g, 33%). **¹H NMR** (600 MHz, DMSO- d_6) δ 7.83 (d, J = 2.2 Hz, 1H), 7.82 (d, J = 8.8 Hz, 1H), 7.65 (dd, J = 8.8 and 2.2 Hz, 1H), 4.73 – 7.68 (m, 1H), 3.49 (dd, J = 16.2 and 5.7, 1H), 2.95 (dd, J = 16.1 and 2.2 Hz, 1H), 1.62 (s, 9H), 1.32 (d, J = 6.8 Hz, 3H). **¹³C NMR** (150 MHz, DMSO- d_6) δ 166.7, 157.9, 153.5, 152.2, 146.9, 132.3, 130.8, 130.7, 120.5, 118.9, 100.6, 83.3, 50.0, 38.9, 28.1, 19.1. **HRMS** m/z calculated for $C_{18}H_{21}ClN_3O_3$ $[M + H]^+$ 362.1266; found: 362.1289.

9-Amino-3,4-dihydroacridin-1(2H)-one (9e)

General procedure A with **7e** (0.139 g, 0.57 mmol) gave **9e** as a white solid. (91 mg, 80%). **¹H NMR** (600 MHz, Chloroform- d) δ 10.24 (s, 1H), 7.85 (d, J = 8.4 Hz, 1H), 7.82 (d,

$J = 8.5$ Hz, 1H), 7.68 (t, $J = 7.7$ Hz, 1H), 7.40 (t, $J = 7.6$ Hz, 1H), 6.17 (s, 1H), 3.11 (t, $J = 6.4$ Hz, 2H), 2.72 (t, $J = 6.5$ Hz, 2H), 2.14 (p, $J = 6.5$ Hz, 2H). ^{13}C NMR (150 MHz, Chloroform- d) δ 201.6, 163.8, 154.4, 148.2, 132.0, 129.18, 124.8, 120.9, 117.6, 106.5, 39.9, 34.6, 21.6. HRMS m/z calculated for $\text{C}_{13}\text{H}_{13}\text{N}_2\text{O}$ $[\text{M} + \text{H}]^+$ 213.1022; found: 213.1028.

10-Amino-2-(4-bromobenzyl)-3,4-dihydrobenzo[b][1,6]naphthyridin-1(2H)-one (9f):)

General procedure A with **7f** (0.428 g, 1.0 mmol) gave **9f** as a yellow solid (84 mg, 22%). ^1H NMR (600 MHz, DMSO- d_6) δ 7.88 (d, $J = 8.4$ Hz, 1H), 7.83 (d, $J = 8.4$ Hz, 1H), 7.7. (ddd, $J = 8.4$, 6.8, and 1.3 Hz, 1H), 7.50 (d, $J = 8.4$ Hz, 2H), 7.46 (ddd, $J = 8.4$, 6.9, 1.3 Hz, 1H), 7.25 (d, $J = 8.4$ Hz, 2H), 4.75 (s, 2H), 3.57 (t, $J = 6.7$ Hz, 2H), 3.16 (t, $J = 6.7$ Hz, 2H). ^{13}C NMR (150 MHz, DMSO- d_6) δ 167.5, 158.5, 153.3, 148.2, 136.4, 131.9, 131.3, 129.6, 129.1, 124.8, 121.5, 120.7, 118.2, 100.6, 49.7, 44.7, 32.8. HRMS m/z calculated for $\text{C}_{19}\text{H}_{17}\text{BrN}_3\text{O}$ $[\text{M} + \text{H}]^+$ 382.0550; found: 382.0573.

tert-Butyl 10-(benzylamino)-1-oxo-3,4-dihydrobenzo[b][1,6] naphth-yridine-2(1H)-carboxylate (10)

9a (50 mg, 0.15 mmol), was dissolved in DCM and 1M NaOH (3:2, 5 mL). TBAB (40 mg, 0.12 mmol) and benzyl bromide (29 mg, 0.17 mmol), were added sequentially and stirred overnight. Water (10 mL) and DCM (10 mL) were added, the organics separated, washed with brine, dried over Na_2SO_4 . Column chromatography yielded yellow powder (42 mg, 69% yield). ^1H NMR (600 MHz, Chloroform- d) δ 10.95 (s, 1H), 8.11 (d, $J = 8.7$ Hz, 1H), 7.84 (d, $J = 8.4$ Hz, 1H), 7.64 (t, $J = 7.6$ Hz, 1H), 7.45 – 7.36 (m, 4H), 7.32 (t, $J = 7.2$ Hz, 1H), 7.24 (d, $J = 8.4$ Hz, 1H), 5.01 (d, $J = 6.1$ Hz, 2H), 3.99 (t, $J = 6.4$ Hz, 2H), 3.18 (t, $J = 6.4$ Hz, 2H), 1.57 (s, 9H). ^{13}C NMR (150 MHz, Chloroform- d) δ 168.1, 158.6, 158.5, 152.1, 138.0, 131.8, 129.0, 128.6, 127.8, 127.0, 126.3, 123.7, 118.8, 110.0, 102.3, 83.2, 52.3, 43.5, 33.0, 28.1. HRMS m/z calculated for $\text{C}_{24}\text{H}_{26}\text{N}_3\text{O}_3$ $[\text{M} + \text{H}]^+$ 404.1969; found: 404.1990.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1.

(a) Ring opening of isoxazolopiperidinone to give orthogonally protected diamino acids. (b) 2-Nitrophenylisoxazoles undergo reductive heterocyclizations to quinoline-4-amines, 3-acyl-(1*H*)-indoles, and quinolin-4(1*H*)-ones.

Figure 2.

Quinoline-4-amine pharmaceuticals in comparison to the new cyclic quinoline-4-amines reported here.

Scheme 1.

Reduction of heterocyclic 3-(2-nitrophenyl)isoxazole. Reagents and conditions: i. Zn^0 dust, HOAc, $0 - 120^\circ\text{C}$, 1 or 18 hrs (see table).

Scheme 2.

Reductive heterocyclization (Zn⁰ dust, HOAc, 22 °C, overnight) of (a) 6,7-dihydroisoxazolo[4,5-c]pyridin-4(5H)-ones and (b) 6,7-dihydrobenzo-[d]isoxazol-4(5H)-one.

Scheme 3.
N-Alkylation of the 4-aminoquinoline amine.

Table 1

Synthesis and reduction of 3-(2-nitrophenyl)isoxazoles – a functional group screen.

1	R¹(C5)	R²(C4)	2/HOAc^[b]	2/NH₄Cl^[b]
a	Me	C(=O)Me	90%	ND
b	Me	CO ₂ Et	6%/63% ^[c]	22%/39% ^[c]
c	Ph	C ≡ N	76%	36%
d	(C=CH ₂)Me	H	0%	51%

^[a] No regioisomeric isoxazoles were detected in these cycloadditions.

^[b] Isolated yields.

^[c] Major product is ester hydrolysis (**1b** → **2b**/R² = CO₂H).

Table 2

Cycloaddition of α -chlorobenzaldoxime-driven nitrile oxides onto piperidine-2,4-diones and cyclohexane-1,3-dione.

7	X	R ¹	R ²	Yield ^[a]
a	NBoc	H	H	89
b	NBoc	H	5-Cl	71
c	NBoc	Me	H	58
d	NBoc	Me	5-Cl	43
e	CH ₂	H	H	57

^[a] Isolated yields.

Table 3

Reductive heterocyclizations – temperature and time dependence.

entry	time	temperature	7a:8a:9a	9a yield ^[a]
1	18 h	120 °C	0:0:0	0
2	18 h	80 °C	0:0:1	81
3	18 h	22 °C	0:0:1	89
4	1 h	0 °C	9.5:4.4:1	7 ^[b]

^[a] Isolated yields.^[b] Recovered **7a** (63%) and intermediate aniline **8a** (29%).