JOC Notes

Unique Tandem Heck-Lactamization Naphthyridinone Ring Formation between Acrylanilides and Halogenated Pyridines

Raymond J. Cvetovich,* Robert A. Reamer, Lisa DiMichele, John Y. L. Chung, and Jennifer R. Chilenski

Merck Research Laboratories, Merck & Co., Inc., P.O. Box 2000, Rahway, New Jersey 07065

raymond_cvetovich@merck.com

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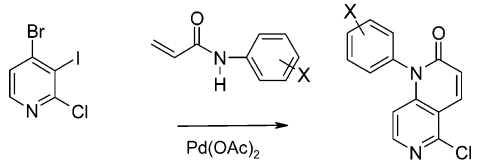
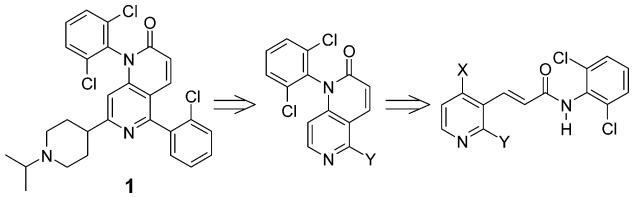


The Heck coupling of acrylanilides with 4-bromo-2-chloro-3-iodo-pyridine using palladium acetate can produce bis-Heck products or undergo an unusual tandem Heck-lactamization ring formation to generate 5-chloro-1-aryl-1,6-naphthyridin-2(1*H*)-ones.

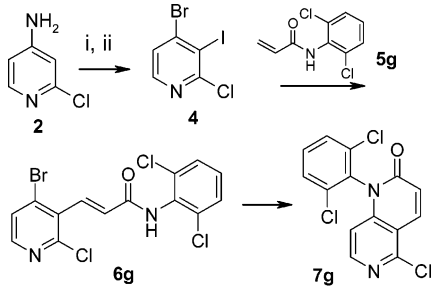
Discussion

p38 Mitogen-activated protein (MAP) kinase inhibitors are known to positively regulate the release of tumor necrosis factor-α (TNF-α) and interleukin-1 (IL-1) in response to stress. Therapeutic strategies to target these cytokines have been clinically validated with biological agents that sequester TNF-α, resulting in efficacy in the treatment of rheumatoid arthritis (RA), Crohn's disease, and psoriasis.[1] *N*-aryl-1,6-naphthyridin-2(1*H*)-ones, exemplified by structure **1**, have been reported to be potent p38 MAP kinase inhibitors.[2] A synthetic strategy toward *N*-arylnaphthyridinones such as **1** could progress from the Heck coupling of acrylanilides with halo-substituted pyridines, followed by cyclization (see Scheme 1). The use of acrylanilides in Heck coupling reactions has received little attention in the literature,[3] although acrylamide has been successfully coupled with aryl iodides using palladium acetate,[4a] immobilized palladium,[4b,c] cyclopalladated ferrocenylimines,[4d] and tetrazole-ligand Pd(II),[4e] as well as with aryl bromides using palladacycle.[5] 1,6-Naphthyridin-2(1*H*)-ones have been successfully synthesized by Hunt,[2] Savarin,[6a] Larock,[6b] Erian,[6c] and Chung.[6d] Separately, 1,8-,[7a,b] 1,5-,[7b] and 1,7- [7b] naphthyridinones have been synthesized utilizing a number of different approaches.

SCHEME 1. Potential Route to p38 Kinase Inhibitor Naphthyridinones



SCHEME 2. Potential Synthetic Route to Naphthyridinone 7g[a]



[a] (i) $NaNO_2$, 48% HBr, H_2O, 25 °C; (ii) LDA, THF, −70 °C, I_2.

Trihalopyridine **4** provides a useful substitution pattern about the pyridine ring to allow the Heck coupling with 2′,6′-dichloroacrylanilide (**5g**) at the 3-iodo position to form **6** which would then be ring closed to synthesize 2-chloro-*N*-aryl-naphthyridinone **7**. Trihalopyridine **4** was readily synthesized (see Scheme 2) from 4-amino-2-chloropyridine (**2**) via Sandmeyer reaction with $NaNO_2$/aq HBr/KBr at 25 °C (in the absence of copper catalysts) to make 4-bromo-2-chloropyridine (**3**)[8] in >98% yield. Deprotonation/iodination using LDA/I_2 in THF at −70 °C produced trihalopyridine **4** in 69% isolated yield as a crystalline solid.

When acrylanilide **5g** reacted with trihalopyridine **4** in DMAC at 120 °C, in the presence of $Pd(OAc)_2$ and DIPEA, a slow

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reaction ensued. Multiple products were formed but a minor product was isolated in ~10% yield that was identified by NMR and MS analysis as 2-chloro-naphthyridinone **7g**, the structure of which was confirmed by single-crystal X-ray analysis. Small amounts of Heck product **6g** were found in the reaction mixture as well as bis-Heck analogue **8g**. No known precedents for this tandem Heck cyclization are known, although intramolecular cyclization of benzamides have been reported by Buchwald et al. using palladium catalysis[9] and Hunt[2] has successfully cyclized dichloroanilides onto bromopyridines using copper catalysis,[2] with neither procedure involving the use of α,β-unsaturated amides.

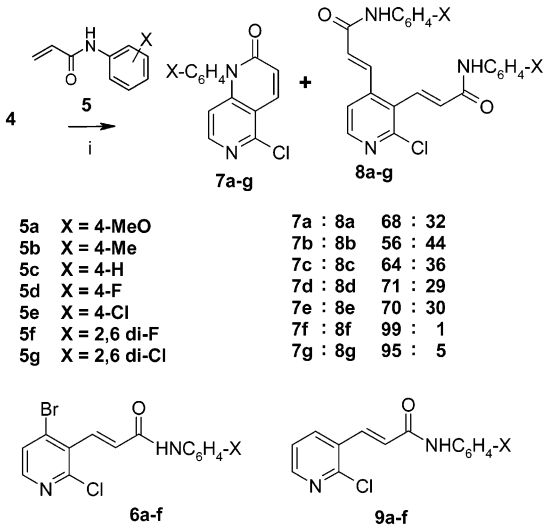
Optimization of reaction conditions led to the use of ethylene carbonate (EC) as solvent in the presence of dichloroacrylanilide (2 equiv), $Pd(OAc)_2$ (3 mol %), sodium acetate (3 equiv), potassium bromide (6 equiv) and water (10 v%). Among the solvents screened (DMF, DMAC, DMSO, toluene, water, alcohols, gycol), ethylene carbonate was superior in increasing the reaction rate, especially in combination with KBr and water which allowed reaction completion in 3 h at 90 °C and produced naphthyridinone **7g** in yields of up to 85%. The use of other salts, such as LiBr, CsBr, tetrabutylammonium bromide, and tetrabutylammonium iodide were compared. While some minor rates differences were observed, the best additive was KBr, with yield and reaction rate favored with the use of 6−10 equiv of KBr. The presence of phosphine ligands or the attempted use of Hermann's catalyst led to polymerization of di-chloro-acrylanilide with the formation of little or no desired product. The use of nonphosphine ligands, such as neocuproine (2,9-dimethyl-1,10-phenanthroline) did not result in useful rates but did favor the production of mono-Heck coupling to give **6g** as the major product. No discernible deviation was observed when using either a nitrogen atmosphere or allowing exposure to air.

The extension of this unique tandem Heck-lactamization cyclization reaction to acrylanilides bearing differing aryl substitution was then examined (see Scheme 3). The series of acrylanilides **5a**−**g** was prepared by stirring the corresponding aniline in DMAC and adding acryloyl chloride, followed by crystallization with water.[10] In this way each acrylanilide was prepared in 85−95% yield. Each acrylanilide (2 equiv) was then heated with trihalopyridine **4** using the conditions described above.

The Heck reaction with acrylanilides **5a**−**g** showed a clear reaction rate difference that was dependent on the electron donating/withdrawing ability of the substituents with the fastest rates of the Heck reaction achieved with electron donating groups attached to the aryl ring. In most cases two major products (see Scheme 4) were identified: 2-chloro-naphthyridinone **7a**−**g** and bis-Heck product **8a**−**g**. The selectivity was observed to vary, with the highest conversions to naphthyridinone **7** occurring with the stronger electron withdrawing groups of acrylanilide **5f** and **5g**, and bis-Heck byproduct formation being significant with acrylanilides **5a**−**e**.

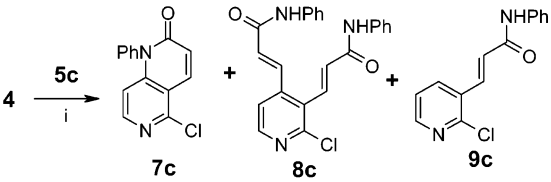
When the stoichiometry of the acrylanilide **5a**−**f** was decreased to 1.1 equiv, yields declined and other byproducts were identified, particularly mono-Heck products **6a**−**f** as well as very small amounts of debrominated mono-Heck products **9a**−**f** (proposed structure based on LCMS of reaction mixtures). With difluoroacrylanilide **5f** and dichloroacrylanilide **5g**, the yields of naphthyridinone **7f** and **7g** decreased, but remained the major products.

SCHEME 3. Acrylanilide 5a−g Products[a]



[a] (i) Ethylene carbonate, NaOAc, KBr, H_2O, $Pd(OAc)_2$, 90 °C.

SCHEME 4. Effect of Base on Product Formation[a]



	4	7c	8c	9c
NaOAc	34	28	56	
Na_2CO_3	12	55	8	
NaOH		80	8	
Cs_2CO_3		58	0	40
K_2CO_3		87	6	
KOH		88	4	

[a] (i) Ethylene carbonate, base, KBr, H_2O, $Pd(OAc)_2$, 90 °C, 2 h.

The effect of base strength was examined in the reaction of acrylanilide **5c** with trihalopyridine **4**, using NaOAc, Na_2CO_3, K_2CO_3, Cs_2CO_3, NaOH, and KOH. Rates and selectivity differences were readily observed by varying the choice of base (see Scheme 4). Sodium acetate gave the slowest rate of consumption of trihalopyridine **4** and produced the greatest amount of bis-Heck product **8c**. Sodium carbonate was faster than sodium acetate and produced less bis-Heck product. But potassium carbonate was much faster than sodium carbonate producing mostly naphthyridinone **7c**, similar to NaOH and KOH. The effect of sodium versus potassium was also seen between NaOH and KOH, with KOH producing less bis-Heck coupling and an 88% yield of naphthyridinone **7c**. Cesium carbonate was quite different. Reactions with cesium carbonate produced naphthyridinone **7c** along with a large amount of debrominated mono-Heck **9c**. The variation of base in the reaction of acrylanilide **7g** with trihalopyridine **4** showed little or no effect, presumably owing to its higher acidic strength and the effectiveness of NaOAc as a base in that reaction.

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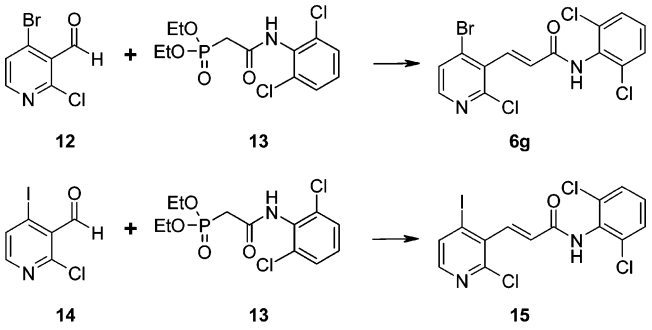
SCHEME 5. Formation of Aryl Acrylanilide 6g and 15



Unsaturated anilide **6g** was prepared by the Emmon−Wadsworth condensation (see Scheme 5) of aldehyde **12** with phosphonate **13** then resubjected to the Heck reaction conditions, but no desired cyclization product was detected. Instead, a slow steady degradation took place in the absence of acrylanilide **5g**, and bis-Heck products were formed in its presence. In a similar fashion, the iodoanalogue **15** was prepared from aldehyde **14**.[11] It likewise failed to cyclize to naphthyridinone **7g** when subjected to the Heck cyclization conditions described above. In each case, prolonged heating led to unidentified degradates.

While no definitive mechanism can be deduced from the data available, it appears that following the initial Heck coupling at the pyridyl iodide position a nondisassociated palladium intermediate is involved in the subsequent ring closure onto the bromide position.

Summary

A unique tandem Heck-lactamization ring formation of naphthryidinones in the reaction of acrylanilides with 4-bromo-2-chloro-3-iodo-pyridine catalyzed by $Pd(OAc)_2$ was discovered and optimized to produce 5-chloro-1-aryl-1,6-naphthyridin-2(1*H*)-ones in good to excellent yields. The effects of solvents, ring substitution, additives, and choice of base were examined in optimizing the reaction for reaction rates and yield.

Experimental Section

4-Bromo-2-chloropyridine (3).[8d] 4-Amino-2-chloropyridine (25.0 g, 194 mmol) was dissolved in 48% HBr (170 mL) and water (180 mL) and cooled to 2 °C. A solution of sodium nitrite (22.7 g, 330 mmol) in water (125 mL) was added dropwise over 1 h, then KBr (25 g, 210 mmol) was added. The heterogeneous mixture was allowed to warm to 22 °C and stirred overnight. After the mixture was cooled to 2 °C, the pH was adjusted to 10 using 50% sodium hydroxide solution (80 g, 1 mol), and MTBE (300 mL) was added. The organic phase was separated and evaporated *in vacuo*, and a slightly yellow oil was obtained (38.0 g).

4-Bromo-2-chloro-3-iodo-pyridine (4). A solution of *n*-butyllithium (2.5 M, 82 mL) was added to diisopropylamine (30.1 mL, 215 mmol) in THF (100 mL) that was cooled to −40 °C. After the mixture was cooled to −70 °C, a solution of 4-bromo-2-chloropyridine (36.5 g, 190 mmol) in THF (100 mL) was added over 2.5 h, and the mixture was stirred a further 2 h at −70 °C. A solution of iodine (50.6 g, 200 mmol) in THF (100 mL) was added over 2 h, while maintaining the reaction temperature at less than −65 °C. This mixture was stirred a further 30 min, then poured into a mixture of 5% sodium thiosulfate (500 mL) and IPAc (500 mL). The organic phase was washed with water then evaporated *in vacuo* to a dark brown solid (55.4 g). This was crystallized from methanol (150 mL) by the addition of water (50 mL) to give 41.91 g of tan solids (69% isolated yield). ^{1}H NMR (400.25 MHz) $CDCl_3$: δ 8.13 (d, J = 5.1 Hz, 1H), 7.45 (d, J = 5.1 Hz, 1H). ^{13}C NMR (100.65 MHz) $CDCl_3$: δ 156.6, 148.6, 143.1, 126.5, 104.1.

Diethyl{2-[(2,6-dichlorophenyl)amino]-2-oxoethyl}phosphonate (13). To a solution of diethylphosphonoacetic acid (2 mL, 11.9 mmol) in dichloromethane (10 mL) was added oxalyl chloride (2.2 mL, 23.9 mmol) at 22 °C under nitrogen. The mixture was stirred overnight and then concentrated. The brown oil was stirred under house vacuum for 1 h and then diluted with dichloromethane (10 mL), followed by the addition of 2,6-dichloroaniline (1.97 g, 11.9 mmol). Pyridine (2.0 mL, 23.9 mmol) was slowly added over 10 min, maintaining <35 °C using a water bath. After stirring for 4−5 h, the reaction mixture was quenched with 1.5 N HCl (16 mL) and brine (20 mL) and extracted with EtOAc (60 mL). The mixture was filtered to facilitate phase separation. The organic layer was washed with brine (15 mL), dried (Na_2SO_4), and evaporated to dryness to give 4 g of oil. Purification by flash chromatography (50 to 100% EtOAc/heptane) afforded 2.42 g (60%) of pure product as a white solid. ^{1}H NMR (400.25 MHz) $CDCl_3$: δ 8.84 (1H), 7.29 (d, J = 8.1, 2H), 7.12 (t, J = 8.1, 1H), 4.21−4.14 (om, 4H), 3.09 (d, J = 20.9, 2H), 1.33 (t, J = 7.1, 6H). ^{13}C NMR (100.65 MHz) $CDCl_3$: δ 162.4 (J = 3.7), 133.8, 132.2, 128.6, 128.5, 63.07 (J = 6.5), 35.05 (J = 31.0, 16.45 (J = 6.3). LCMS: $C_{12}H_{16}Cl_2NO_4P$; *m*/*e* 362.0 (10) = M + Na. HRMS (ES+): calcd for $C_{12}H_{17}Cl_2NO_4P$ (M + 1), 340.02668; found, 340.02755; calcd for $C_{12}H_{16}Cl_2NO_4PNa$ (M + Na), 362.00862; found, 362.00889.

(2*E*)-3-(4-Bromo-2-chloropyridin-3-yl)-*N*-(2,6-dichlorophenyl)acrylamide (6 g). Potassium *tert*-butoxide (1 M) in THF (11.5 mL) was added over 5 min to a solution of phosphonoanilide **13** (3.40 g, 10.0 mmol) cooled at 0 °C. The solution was stirred for 1.5 h, then pyridylaldehyde **12** (2.67 g, 10 mmol) as a solid was added. The resulting solution was warmed to 22 °C and stirred for 2.5 h. Water (125 mL) was added to form a precipitate which was filtered and washed with water (3 × 50 mL). The product was dried *in vacuo* at 55 °C to give 3.7 g of crystalline white product (93% yield). ^{1}H NMR (400.25 MHz) d_6-DMSO: δ 10.37 (1H), 8.26 (d, J = 5.2, 1H), 7.88 (d, J = 5.2, 1H), 7.59−7.55 (om, 3H), 7.39 (t, J = 8.1, 1H), 6.99 (d, J = 6.1, 1H). ^{13}C NMR (100.65 MHz) d_6-DMSO: δ 162.3, 149.5, 149.2, 135.1, 134.8, 133.4, 132.6, 130.7, 129.7, 129.4, 128.6, 128.2. LCMS: $C_{14}H_8BrCl_3N_2O$; *m*/*e* 406.9 (100) = M + 1, 408.9 (65), 405.0 (45). HRMS (ES+): calcd for $C_{14}H_9BrCl_3N_2O$ (M + 1), 404.89584; found, 404.89640.

(2*E*)-3-(2-Chloro-4-iodopyridin-3-yl)-*N*-(2,6-dichlorophenyl)-acrylamide (15). Potassium *tert*-butoxide (1 M) in THF (11.5 mL) was added over 5 min to a solution of phosphonoanilide **13** (3.40 g, 10.0 mmol) cooled at 0 °C. The solution was stirred for 1.5 h, then pyridylaldehyde **14** (2.67 g, 10 mmol) was added as a solid. The resulting solution was warmed to 22 °C and stirred for 2 h to give a precipitate. Water (60 mL) was added, and the precipitate was filtered and washed with a 1/1 mixture of THF/water (40 mL). The product was dried *in vacuo* at 55 °C to give 3.8 g of crystalline white product (83.9% yield). ^{1}H NMR (400.25 MHz) d_6-DMSO: δ 10.33 (br s, 1H), 8.05 (d, J = 5.0, 1H), 8.00 (d, J = 5.0, 1H), 7.57 (d, J = 8.1, 2H), 7.50 (d, J = 16.0, 1H), 7.38 (t, J = 8.1, 1H), 6.85 (d, J = 16.0, 1H). ^{13}C NMR (100.65 MHz) d_6-DMSO: δ 162.3, 148.8, 147.5, 138.9, 134.3, 134.1, 133.5, 132.6, 129.4, 129.3, 128.5, 113.6. LCMS: $C_{14}H_8Cl_3IN_2O$; *m*/*e* 452.8 (100), 454.8 (90). HRMS (ES+): calcd for $C_{14}H_9Cl_3IN_2O$ (M + 1), 452.88197; found, 452.88388; calcd for $C_{14}H_9Cl_3IN_2ONa$ (M + Na), 474.86391; found, 474.86351.

Heck Reactions. General Procedure. A mixture of acrylanilide (2.0 mmol), 4-bromo-2-chloro-3-iodopyridine (1.0 mmol), sodium acetate (3.0 mmol), potassium bromide (6.0 mmol), ethylene carbonate (12 g), water (1.2 mL), and palladium acetate (0.03 mmol) was heated to 90 °C for 3−12 h. The mixture was poured into water (25 mL) and toluene (25 mL), the phases were separated,

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and the aqueous phase was re-extracted with toluene (25 mL). The combined toluene phases were washed with water (3 × 25 mL). The mixture of phases required filtration to isolate the bis-Heck product which was insoluble. The Heck-cyclization product, contained in the toluene extract, can be purified via column chromatography (silica gel 60, ethyl acetate/hexanes). The bis-Heck product can be purified by applying a THF dissolved sample to silica gel 60 and eluting with ethyl acetate.

5-Chloro-1-(4-methoxyphenyl)-1,6-naphthyridin-2(1*H*)-one (7a). ^{1}H NMR (400.25 MHz) $CDCl_3$: δ 8.19 (dd, J = 10.0, 0.7 Hz, 1H), 8.13 (d, J = 5.9 Hz, 1H), 7.18−7.08 (m, 4H), 6.87 (d, J = 10.0 Hz, 1H), 5.56 (dd, J = 5.9, 0.7 Hz, 1H), 3.89 (s, 3H). ^{13}C NMR (100.65 MHz) $CDCl_3$: δ 162.0, 160.4, 151.0, 148.5, 148.2, 136.3, 129.5 (2C), 128.8, 124.5, 115.9 (2C), 114.5, 110.4, 55.8. LCMS: $C_{15}H_{11}ClN_2O_2$; *m/e* 287.0 = M + 1. HRMS (ES+): calcd for $C_{15}H_{12}ClN_2O_2$ (M + 1), 287.05818; found, 287.06099.

(2*E*,2′*E*)-3,3′-(2-Chloropyridine-3,4-diyl)bis[*N*-(4-methoxyphenyl)acrylamide] (8a). ^{1}H NMR (400.25 MHz) d_6-DMSO: δ 10.29 (s, 1H), 10.26 (s, 1H), 8.45 (d, J = 5.2 Hz, 1H), 7.70−7.68 (m, 7H), 6.97 (d, J = 15.6 Hz, 1H), 6.94−6.89 (m, 4H), 6.49 (d, J = 15.8 Hz, 1H), 3.74 (s, 3H), 3.73 (s, 3H). ^{13}C NMR (100.65 MHz) d_6-DMSO: δ 161.9, 161.6, 155.6 (2C), 150.5, 148.9, 144.3, 134.9, 133.2, 132.21, 132.00, 131.97, 129.7, 129.2, 120.9 (2C), 120.8 (2C), 120.7, 114.0 (4C), 55.1 (2C). LCMS: $C_{25}H_{22}ClN_3O_4$; *m/e* 486.1 = M + Na.

5-Chloro-1-(4-methylphenyl)-1,6-naphthyridin-2(1*H*)-one (7b). ^{1}H NMR (400.25 MHz) $CDCl_3$: δ 8.17 (dd, J = 10.0, 0.6 Hz, 1H), 8.09 (d, J = 5.9 Hz, 1H), 7.39 (m, 2H), 7.11 (m, 2H), 6.84 (d, J = 10.0 Hz, 1H), 6.52 (dd, J = 5.9, 0.6 Hz, 1H), 2.44 (s, 3H). ^{13}C NMR (100.65 MHz) $CDCl_3$: δ 161.6, 150.7, 148.1, 148.0, 139.8, 136.1, 133.5, 131.1 (2C), 128.0 (2C), 124.3, 114.2, 110.2, 21.3 LCMS: $C_{15}H_{11}ClN_2O$; *m/e* 271.0 = M + 1. HRMS (ES+): calcd for $C_{15}H_{12}ClN_2O$ (M + 1), 271.06327; found, 271.06531.

(2*E*,2′*E*)-3,3′-(2-Chloropyridine-3,4-diyl)bis[*N*-(4-methylphenyl)acrylamide] (8b). ^{1}H NMR (400.25 MHz) d_6-DMSO: δ 10.40 (s, 1H), 10.33 (s, 1H), 8.44 (d, J = 5.1 Hz, 1H), 7.71−7.57 (m, 7H), 7.18−7.10 (m, 4H), 7.04 (d, J = 15.6 Hz, 1H), 6.51 (d, J = 15.8 Hz, 1H), 2.26 (s, 3H), 2.25 (s, 3H). ^{13}C NMR (100.65 MHz) d_6-DMSO: δ 162.1, 161.9, 150.5, 148.9, 144.3, 136.4, 136.3, 135.0, 133.4, 132.7 (2C), 132.2, 129.7, 129.2 (5C), 120.7, 119.4 (2C), 119.3 (2C), 20.5 (2C). LCMS: $C_{25}H_{22}ClN_3O_2$; *m/e* 454.1 = M + Na.

5-Chloro-1-phenyl-1,6-naphthyridin-2(1*H*)-one (7c). ^{1}H NMR (400.25 MHz) $CDCl_3$: δ 8.20 (dd, J = 10.0, 0.6 Hz, 1H), 8.12 (d, J = 6.0 Hz, 1H), 6.66−7.53 (om, 3H), 7.26−7.22 (om, 2H), 6.87 (d, J = 10.0 Hz, 1H), 6.49 (dd, J = 6.0, 0.6 Hz, 1H). ^{13}C NMR (100.65 MHz) $CDCl_3$: δ 161.6, 151.0, 148.2, 148.1, 136.4 (2C), 130.6 (2C), 129.8, 128.5 (2C), 124.5, 114.4, 110.2. LCMS: $C_{14}H_9ClN_2O$; *m/e* 257.0 = M + 1. HRMS (ES+): calcd for $C_{14}H_{10}ClN_2O$ (M + 1), 257.04762; found, 257.04848.

(2*E*,2′*E*)-3,3′-(2-Chloropyridine-3,4-diyl)bis(*N*-phenylacrylamide) (8c). ^{1}H NMR (400.25 MHz) d_6-DMSO: δ 10.41 (s, 1H), 10.38 (s, 1H), 8.45 (d, J = 5.1 Hz, 1H), 7.73−7.65 (m, 7H), 7.37−7.30 (m, 4H), 7.08 (m, 2H), 7.01 (d, J = 15.6 Hz, 1H), 6.50 (d, J 15.8 Hz, 1H). ^{13}C NMR (100.65 MHz) d_6-DMSO; δ 162.3, 162.1, 150.5, 149.0, 144.3, 138.82, 138.80, 135.3, 133.7, 132.1, 129.7, 129.1, 128.8 (4H), 123.8 (2C), 120.8, 119.41 (2H), 119.36 (2H). LCMS: $C_{23}H_{18}ClN_3O_2$; *m/e* 426.1 = M + Na.

5-Chloro-1-(4-fluorophenyl)-1,6-naphthyridin-2(1*H*)-one (7d). ^{1}H NMR (400.25 MHz) $CDCl_3$: δ 8.19 (dd, J = 10.0, 0.6 Hz, 1H), 8.14 (d, J = 5.9, 1H), 7.33−7.21 (m, 4H), 6.85 (d, J = 10.0 Hz, 1H), 6.50 (dd, J = 5.9, 0.6 Hz, 1H). ^{13}C NMR (100.65 MHz) $CDCl_3$: δ 163.0 (d, J = 250.4 Hz), 161.6, 151.1, 148.4, 148.1, 136.5, 132.2 (d, J = 3.2 Hz), 130.4 (d, J = 8.8 Hz, 2C), 124.4, 117.7 (d, J = 23.3 Hz, 2C), 114.4, 110.0. LCMS: $C_{14}H_8ClFN_2O$; *m/e* 275.0 = M + 1. HRMS (ES+): calcd for $C_{14}H_9ClFN_2O$ (M + 1), 275.03820; found, 275.03893.

(2*E*,2′*E*)-3,3′-(2-Chloropyridine-3,4-diyl)bis[*N*-(4-fluorophenyl)acrylamide] (8d). ^{1}H NMR (400.25 MHz) d_6-DMSO: δ 10.47 (s, 1H), 10.44 (s, 1H), 8.45 (d, J = 5.1 Hz, 1H), 7.75−7.66 (om, 7H), 7.20−7.14 (om, 4H), 6.98 (d, J = 15.6 Hz, 1H), 6.50 (d, J = 15.9 Hz, 1H). ^{13}C NMR (100.65 MHz) d_6-DMSO: δ 162.2, 162.0, 158.3 (d, J = 240.9 Hz, 2C), 150.5, 149.0, 144.3, 135.4, 135.2 (dd, J = 2.4 Hz, 2C), 133.8, 131.9, 129.6, 128.9, 121.19 (d, J = 8.0 Hz, 2C), 121.10 (d, J = 8.0 Hz, 2C), 120.8, 115.4 (d, J = 22.5 Hz, 4H). LCMS: $C_{23}H_{16}ClF_2N_3O_2$; *m/e* 462.1 = M + Na.

5-Chloro-1-(4-chlorophenyl)-1,6-naphthyridin-2(1*H*)-one (7e). ^{1}H NMR (400.25 MHz) $CDCl_3$: δ 8.20 (dd, J = 10.0, 0.7 Hz, 1H), 8.14 (d, J = 5.9 Hz, 1H), 7.61−7.55 (m, 2H), 7.22−7.17 (m, 2H), 6.86 (d, J = 10.0 Hz, 1H), 6.51 (dd, J = 5.9, 0.7 Hz, 1H). ^{13}C NMR (100.65 MHz) $CDCl_3$: δ 161.5, 151.1, 148.4, 147.8, 136.6, 136.0, 134.8, 130.9 (2C), 130.0 (2C), 124.4, 114.4, 110.0. LCMS: $C_{14}H_8Cl_2N_2O$; *m/e* 291.0 = M + 1. HRMS (ES+): calcd for $C_{14}H_9Cl_2N_2O$ (M + 1), 291.00864; found, 291.00936.

(2*E*,2′*E*)-3,3′-(2-Chloropyridine-3,4-diyl)bis[*N*-(4-chlorophenyl)acrylamide] (8e). ^{1}H NMR (400.25 MHz) d_6-DMSO: δ 10.54 (s, 1H), 10.50 (s, 1H), 8.44 (d, J = 5.1 Hz, 1H), 7.71−7.64 (m, 7H), 7.40−7.35 (m, 4H), 6.97 (d, J = 15.6 Hz, 1H), 6.49 (d, J = 15.8 Hz, 1H). ^{13}C NMR (100.65 MHz) d_6-DMSO: δ 162.4, 162.1, 150.5, 149.0, 144.2, 137.7 (2C), 135.7, 134.1, 131.8, 129.6, 128.8 (5C), 127.4 (2C), 121.0 (2C), 120.9 (2C), 120.8. LCMS: $C_{23}H_{16}Cl_3N_3O$; *m/e* 494.0 = M + Na.

5-Chloro-1-(2,6-difluorophenyl)-1,6-naphthyridin-2(1*H*)-one (7f). ^{1}H NMR (400.25 MHz) $CDCl_3$: δ 8.21 (om, 2H), 7.54 (m, 1H), 7.18−7.12 (m, 2H), 6.86 (d, J = 10.0 Hz, 1H), 6.55 (m, 1H). ^{13}C NMR (100.65 MHz) $CDCl_3$: δ 160.2, 158.8 (dd, J = 254.9, 3.9 Hz, 2C), 151.2, 149.0, 147.1, 137.1, 132.0 (t, J = 9.6 Hz), 124.0, 114.7, 113.0 (t, J = 16.9 Hz), 112.9 (dd, J = 19.3, 4.0 Hz, 2C), 109.1. LCMS: $C_{14}H_7ClF_2N_2O$; *m/e* 293.0 = M + 1. HRMS (ES+): calcd for $C_{14}H_8ClF_2N_2O$ (M + 1), 293.02877; found, 293.03006.

(2*E*,2′*E*)-3,3′-(2-Chloropyridine-3,4-diyl)bis[*N*-(2,6-difluorophenyl)acrylamide] (8f). ^{1}H NMR (400.25 MHz) d_6-DMSO: δ 10.2 (s, 2H), 8.48 (d, J = 5.2 Hz, 1H), 7.75 (d, J = 5.2 Hz, 1H), 7.73 (d, J = 15.9 Hz, 2H), 7.43−7.34 (m, 2H), 7.23−7.17 (m, 4H), 7.06 (d, J = 15.8 Hz, 1H), 6.57 (d, J = 15.9 Hz, 1H). ^{13}C NMR (100.65 MHz) d_6-DMSO: δ 162.7, 162.4, 157.6 (d, J = 251.2, 4C), 150.4, 149.2, 144.1 (2C), 136.1, 134.6, 130.4, 129.8, 128.3 (t, J = 9.6, 2C), 127.4, 120.9, 114.1 (t, J = 16.9), 112.0 (m, 4C) LCMS: $C_{23}H_{14}ClF_4N_3O_2$; *m/e* 498.1 = M + Na.

5-Chloro-1-(2,6-dichlorophenyl)-1,6-naphthyridin-2(1*H*)-one (7 g). ^{1}H NMR (400.25 MHz) $CDCl_3$: δ 8.23 (d, J = 10.0 Hz, 1H), 8.18 (d, J = 5.8 Hz, 1H), 7.55 (m, 2H), 7.45 (m, 1H), 6.88 (d, J = 10.0 Hz, 1H), 6.34 (d, J = 5.8 Hz, 1H). ^{13}C NMR (100.65 MHz) $CDCl_3$: δ 159.9, 151.1, 149.0, 146.3, 137.1, 134.8 (2C), 132.0, 131.6, 129.5 (2C), 124.3, 114.5, 108.7. HRMS (ES+): calcd for $C_{14}H_8Cl_3N_2O$ (M + 1), 324.96967; found, 324.97048.

(2*E*,2′*E*)-3,3′-(2-Chloropyridine-3,4-diyl)bis[*N*-(2,6-dichlorophenyl)acrylamide] (8 g). ^{1}H NMR (400.25 MHz) d_6-DMSO: δ 10.33 (s, 1H), 10.30 (s, 1H), 8.47 (d, J = 5.1 Hz, 1H), 7.77 (d, J = 5.1 Hz, 1H), 7.71 (d, J = 15.7 Hz, 1H), 7.69 (d, J = 15.9 Hz, 1H), 7.62−7.50 (m, 4H), 7.43−7. 30 (m, 2H), 7.10 (d, J = 15.7 Hz, 1H), 6.59 (d, J = 15.9 Hz, 1H). ^{13}C NMR (100.65 MHz) d_6-DMSO: δ 162.8, 162.4, 150.4, 149.1, 143.9, 135.8, 134.5, 133.6, 132.61, 132.59, 130.7, 130.0, 129.4, 128.62, 128.60, 127.6, 120.7, 114.1. LCMS: $C_{23}H_{14}Cl_5N_3O_2$; *m/e* 541.9 (M + 1, 45), 564.0 (M + Na, 20), 379.0 (100). HRMS (ES+): calcd for $C_{23}H_{14}Cl_5N_3O_2$ (M + 1), 539.9606; found, 539.9607.

Supporting Information Available: ^{1}H NMR and ^{13}C NMR spectra for compounds **3**, **4**, **6g**, **7a**−**g**, **8a**−**g**, **13**, and **15.** This material is available free of charge via the Internet at http://pubs.acs.org.

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