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Synthesis of a Tetracyclic G∧C Scaffold for the Assembly of Rosette Nanotubes with 1.7 nm Inner Diameter

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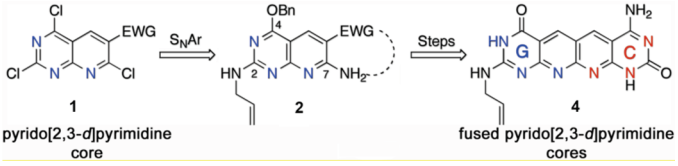

The synthesis of a tetracyclic self-complementary molecule **4** for self-assembly into rosette nanotubes is presented. This new heterocycle has a core structure containing two pyrido[2,3-*d*]pyrimidine molecules fused together and features the Watson−Crick hydrogen bond donor−acceptor arrays of both guanine (G) and cytosine (C). Current methods to synthesize pyrido[2,3-*d*]pyrimidines require harsh conditions and long reaction times and result usually in low product yields. This is particularly problematic for the direct incorporation of functional groups that cannot withstand these conditions. Here, we present an efficient approach to access the multifunctional pyrido[2,3-*d*]pyrimidine intermediate **2** under relatively mild conditions using three regioselective S_NAr reactions at C2, C4, and C7 on the trichloro compound **1**. The electron-withdrawing group and amino functionalities on **2** are then used as a handle to install the third and fourth rings of **4** using a Friedländer-type condensation followed by mixed urea synthesis and cyclization.

Introduction

During the course of our studies of the synthesis and self-assembly of rosette nanotubes (RNTs),[1] we became interested in tetracyclic ××G∧C (Figure 1), which has a highly conjugated core structure of two pyrido[2,3-*d*]pyrimidine molecules fused together. This self-complementary heterotetracycle, which has not been reported thus far, features the Watson−Crick H-bond donor/acceptor arrays of both guanine and cytosine (G∧C motif).[1,2] It is an extended version of the bicyclic G∧C[1] and tricyclic ×G∧C[3] motifs, which should self-assemble into RNTs via the $\pi-\pi$ stacking of intermediate H-bonded hexameric rosettes (Figure 1). The RNTs assembled from bicyclic G∧C have an internal diameter of ca. 1 nm,[1] whereas with tricyclic ×G∧C, the diameter is extended to ca. 1.4 nm.[3] Tetracyclic ××G∧C, with its larger core structure, has the potential to self-assemble into RNTs with an even larger internal diameter (ca. 1.7 nm), which will be crucial for the internal functionalization of these architectures and for applications in biomaterials engineering and drug delivery.[4]

From the synthetic approach perspective, target compound **4** (Scheme 1) may be viewed as the juxtaposition of two pyrido[2,3-*d*]pyrimidine cores and can therefore be approached from the G face or the C face. A standard procedure for the preparation of pyrido[2,3-*d*]pyrimidines and their derivatives

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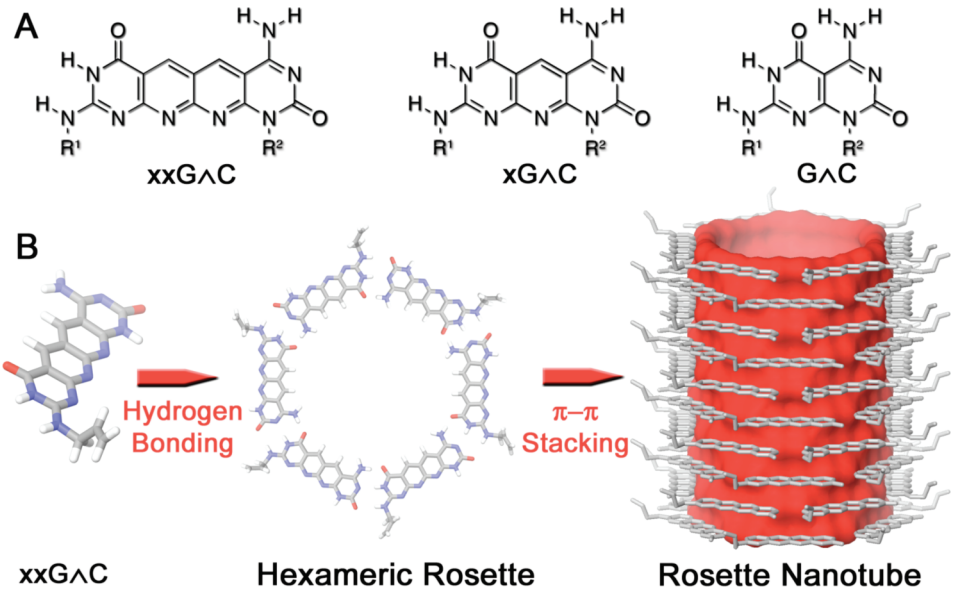
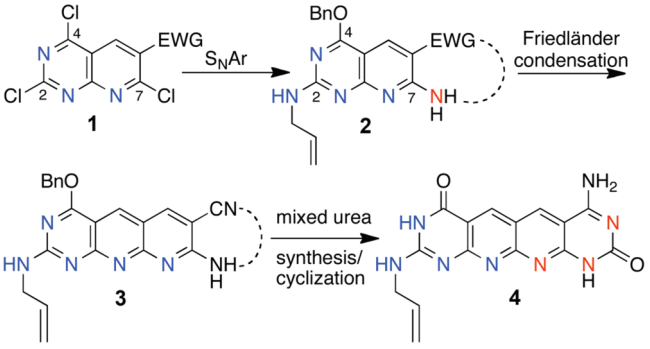


FIGURE 1. (A) Self-complementary G∧C motifs: tetracycle (××G∧C), tricycle (×G∧C), and bicycle (G∧C). (B) Self-assembly of ××G∧C into hexameric rosettes, which $\pi-\pi$ stack to form RNTs (R^1 = allyl, R^2 = H).

SCHEME 1



involves the condensation of 4-aminouracil with conjugated alkenes.[5] Despite the extensive range of biological activities[6–10] associated with this class of heterocycles, current synthetic approaches suffer from long reaction times and relatively harsh conditions, result in low product yield, and do not allow for the direct incorporation of sensitive functional groups. Other methods based on the annulation of a pyridine ring on a pyrimidine (and *vice versa*) were also reported,[11] but they usually suffer from similar challenges. Thus, alternative and efficient synthetic strategies that can provide a rapid entry into fused and nonfused pyrido[2,3-*d*]pyrimidines functionalized with a broader range of substituents for further elaboration are of considerable value.

Regardless of whether we approach the synthesis form the G or the C side, our strategy for the synthesis of **4** required the multifunctional pyrido[2,3-*d*]pyrimidine intermediate **2** (Scheme 1). This molecule contains a protected alcohol at C4, which becomes the carbonyl group in **4**. The NH_2 group at C7 is used as a handle along with the electron-withdrawing group (EWG) to install the third ring using Friedländer-type condensation, followed by mixed urea synthesis/cyclization for the final cytosine ring. In order to confer unique chemical and physical properties upon these RNT architectures, it was also necessary to have the flexibility to append a variety of functional groups at the C2 position. Given the challenges associated with the classical methods for the preparation of pyrido[2,3-*d*]pyrimidines,[5–11] we chose to explore the formation of **2** using three regioselective S_NAr reactions at C2, C4, and C7 on the trichloro substituted molecule **1**. An earlier report by Broom and co-workers[12] suggests that regioselective S_NAr on pyrido[2,3-*d*]pyrimidine is a viable

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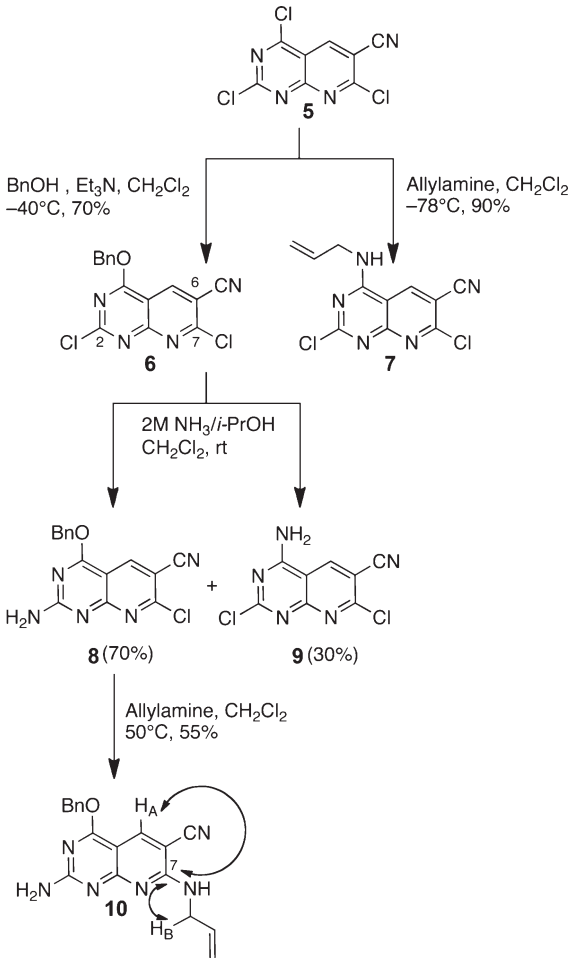
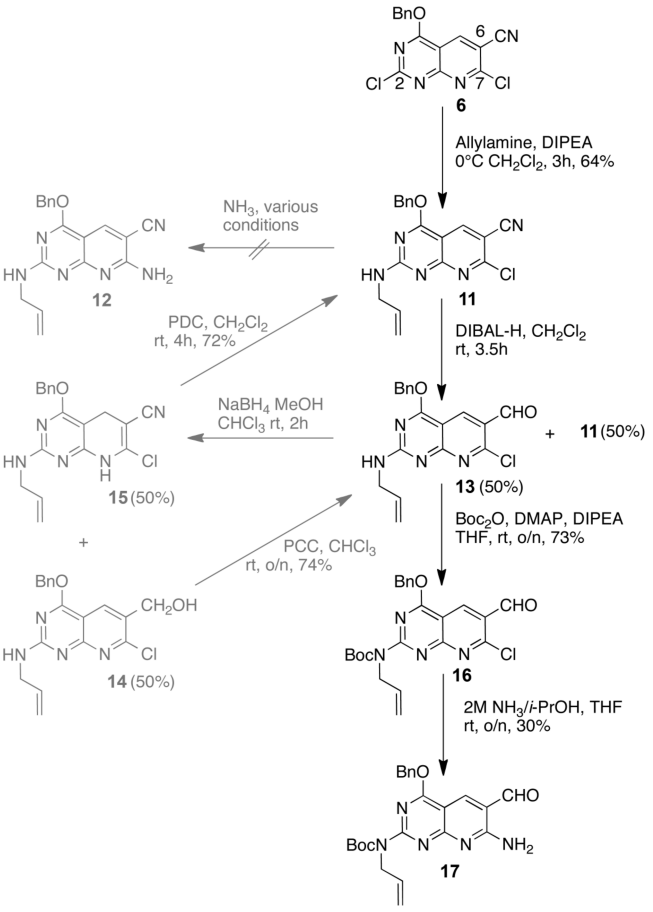
SCHEME 2



SCHEME 3



strategy, although to the best of our knowledge, C6-substituted pyrido[2,3-*d*]pyrimidine have never been reported.

Results and Discussion

The synthesis of tetracycle **4** commenced with the preparation of 2,4,7-trichloro[2,3-*d*]pyrimidine-6-carbonitrile **5** according to a modified procedure reported by Beck.[13] With this compound in hand, we explored the relative reactivity of positions C2, C4, and C7 toward S_NAr (Scheme 2). On the basis of earlier work on simple chloro-substituted pyrido[2,3-*d*]pyrimidines,[12,14] we anticipated that position C4 would be the most reactive. Thus, reaction with allylamine at −78 °C in CH_2Cl_2 yielded compound **7** in 90% yield, whereas reaction with benzyl alcohol at −40 °C in CH_2Cl_2 gave the desired compound **6** in 70% yield.

The next step in our strategy called for a Friedländer-type condensation to build the third ring. It was therefore necessary to introduce an amino group at C7 and convert the -CN group at C6 to an aldehyde. Earlier work by Broom and co-workers[12] suggests that C7 should be more reactive than C2 toward S_NAr when the molecule is functionalized at C4 with an electron-donating group (EDG). Since compound **6** has an EDG (OBn) at C4 in addition to an EWG at C6 that could further enhance its reactivity, we anticipated the S_NAr to occur at C7. Unexpectedly, when **6** was treated with ammonia in CH_2Cl_2 at room temperature, compounds **8** and **9** (Scheme 2) were isolated in ca. 70% and ca. 30% yield, respectively. Whereas **9** was the result of BnO- displacement by ammonia, in the case of **8** we had to carry out an additional transformation to establish the site of S_NAr displacement. Thus, **8** was treated with allylamine in CH_2Cl_2 at 50 °C, and the resulting product (isolated in 55% yield) **10** was characterized by 1D and 2D NMR (HMBC) techniques. The coupling of H_A and H_B to C7 confirmed that ammonia had indeed displaced the chloride at C2. This interesting reversal in reactivity suggests the importance of electronic/inductive effects on the substitution pattern of this class of compounds. One may hypothesize in this case that preferential reaction at C2 is due to the electron-withdrawing ability of (a) the adjoining deactivated pyridyl ring and (b) the adjacent pyrimidine ring nitrogens.

To achieve the correct substitution pattern, the order of nucleophilic addition was therefore reversed. Compound **6** was first treated with allylamine to provide target compound **11** in 64% yield (Scheme 3). Interestingly, however, all attempts at the S_NAr reaction of **11** with ammonia to generate **12** were unsuccessful, and only starting material was isolated. This result could be attributed to (a) decreased nucleophilicity of ammonia relative to allylamine and in particular (b) ring system deactivation toward S_NAr at C7 as a result of the two strong EDG (-OBn, -NHallyl).

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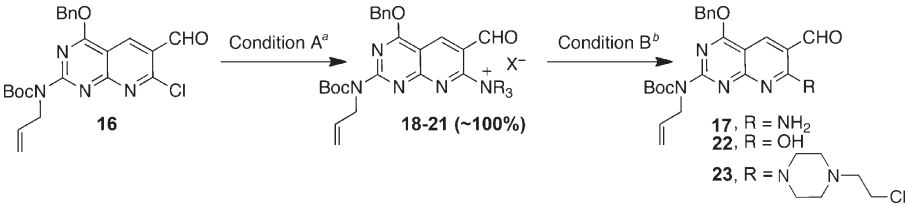
SCHEME 4



[a]Compounds **18**−**21** correspond to the DMAP (X = Cl^-), 4-methoxypyridine (X = Cl^-), DABCO (X = NO_3^-), and 4-(pyrrolidin-1-yl)pyridine (X = Cl^-) adduct, respectively. Condition A: all reactions were performed overnight at room temperature in acetonitrile with DMAP for **18**, 4-methoxypyridine for **19**, DABCO and $AgNO_3$ for **20** and 4-(pyrrolidin-1-yl)pyridine for **21**. [b]Condition B: all reactions were performed overnight at room temperature in THF for **18** and acetonitrile for **19**−**21** using ammonia 2 M in *i*-PrOH (10 equiv).

At this stage we had the option of (a) reducing the electron density in the ring system by protecting the allylamino group with an EWG (e.g., Boc) and then carrying out the reduction of the nitrile with DIBAL-H to the corresponding aldehyde for the subsequent Friedländer condensation, or (b) the opposite sequence. Unfortunately, all attempts at protecting the allylamino moiety of **11** with a Boc group failed. This lack of reactivity was attributed to the strong electron-withdrawing ability of the neighboring pyridyl ring (bearing -Cl and -CN groups). These results prompted us to proceed with the DIBAL-H reduction (Scheme 3), which gave the desired product **13** in 50% yield along with recovered starting material **11** (ca. 50%). We also reasoned that if the Boc protection did not proceed with compound **13**, we could further reduce it to the corresponding alcohol. Incidentally, the separation of compounds **11** and **13** proved to be very challenging because of their similar polarities. Therefore to facilitate the isolation of **13** and to test the reduction of aldehyde **13** to the corresponding alcohol **14**, the mixture was treated with $NaBH_4$ in $MeOH/CHCl_3$. While the resulting products (**14** and **15**) were readily separated by silica gel flash chromatography, we did not expect the pyridyl ring of **11** to undergo reduction to the corresponding dihydropyridine **15** (in 50% yield). This compound could indeed be reoxidized back to **11** in 72% yield using PDC, whereas **14** could be converted back to **13** in 74% yield using PCC. It should be noted at this stage that, as expected, compound **13** did not undergo S_NAr at C7 when treated with ammonia under a variety of conditions (data not shown). Reaction of **13** with Boc_2O in the presence of DMAP and DIPEA furnished **16** in 73% yield (Scheme 3). After numerous attempts, we determined that treatment of activated compound **16** with 10 equiv of ammonia (2 M in *i*-PrOH) in THF overnight provided the desired trisubstituted product **17**, but with only a maximum yield of ca. 30%.

While optimizing the conditions for the Boc protection of **13**, we observed that the yield of **16** decreased substantially as the number of equivalents of DMAP increased. Investigation of the reaction kinetics and product distribution by ^1H NMR in CD_3CN, suggested that the addition of 1 equiv of DMAP at room temperature led to quantitative conversion of the starting material to adduct **18** (Scheme 4), which was apparent by the upfield shift of the aldehyde proton and downfield shift of the DMAP protons. The formation of **18** was also confirmed by mass spectrometry.

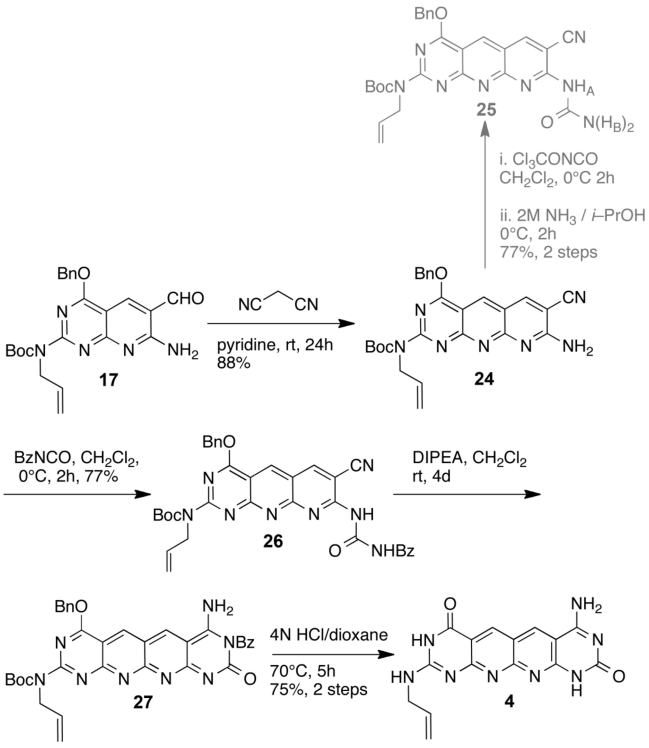
The similarity of this reaction with the first step of the Baylis−Hillman process led us to postulate that DMAP and other tertiary amines could act as catalysts for our third S_NAr. That is, addition of DMAP to **16** would generate a stable yet more reactive intermediate species that may be more amenable to S_NAr with ammonia. We therefore examined DMAP, 4-methoxypyridine, 4-pyrrolidinopyridine, and DABCO as possible catalysts for this reaction (Scheme 4).

While the addition of tertiary amines to compound **16** were nearly quantitative, subsequent displacement with ammonia proceeded in poor yields (20−30%) (Scheme 4). For instance, with 10 equiv of ammonia (2 M in *i*-PrOH) at room temperature in THF (optimal conditions) the DMAP adduct **18** gave target compound **17** in only 20% yield. Adduct **20** with DABCO was formed within 10 min but decomposed over time. Only when this reaction was conducted in the presence of $AgNO_3$ (to remove the nucleophilic chloride counterion from solution) was adduct **20** found to be stable when monitored by ^1H NMR over a period of 12 h. Unfortunately, subsequent treatment with ammonia provided the desired product **17**, but only in 20% yield. Adduct **19** with 4-methoxypyridine gave a moderately better yield of **17** (30%) upon treatment with ammonia. Finally, subjecting **21** to the same conditions did not provide the aminated product, but rather the unexpected hydrolysis product **22** in 46% yield. With these rather low yields, we further explored a one-pot reaction of **16** with DABCO, DIPEA, and various ammonia solutions. Interestingly, using 0.5 M ammonia in dioxane provided **17** in only 25% yield along with the ring-opened adduct **23** in 50% yield. The most favorable results were obtained, however, when 0.5 M ammonia in THF was used to furnish **17** in 52% yield along with the hydrolysis product **22** in 40% yield. We expect the outcome of this reaction to improve dramatically under anhydrous conditions.

Our subsequent task was to perform the Friedländer-type condensation on compound **17** in order to generate the third (pyridine) ring on compound **24** (Scheme 5). The reaction of **17** with malononitrile was found to occur in good yield (88%) when conducted in pyridine overnight at room temperature (Scheme 5).

The fourth ring to be synthesized, which was a pyrimidine ring, was initially attempted by treating **24** with trichlorocarbonyl isocyanate at 0 °C in dichloromethane for 2 h, followed by the addition of ammonia (2 M in *i*-PrOH). Although these conditions typically result in *in situ* cyclization of the urea onto the nitrile,[1] an IR vibration at 2200 cm^{-1} confirmed that the nitrile was still present and thus the cyclization had not occurred. Ring closure of **25** was subsequently attempted using other bases such as 7 M NH_3 in MeOH, NaH, or *t*-BuONa in THF at various temperatures,

SCHEME 5



but without success (data not shown). In order to increase the acidity of H_B relative to H_A and therefore promote ring closure, **24** was converted to **26** in the presence of benzoyl isocyanate in dichloromethane at 0 °C. Subsequent treatment of **26** with DIPEA in dichloromethane at room temperature for 4 days provided the cyclized adduct **27** (Scheme 5). Finally, deprotection of the crude product **27** with 4 M HCl in dioxane at 70 °C afforded our target tetracyclic adduct **4** in 75% yield (two steps). This product, which is presented in only one of the many tautomeric forms, was found to be soluble in DMSO, hot DMF, and protic acids such as TFA.

Conclusion

The synthesis of the tetracyclic self-complementary molecule **4** was achieved. Our approach to preparing the key trisubstituted pyrido[2,3-*d*]pyrimidine intermediate **17** involves three regioselective S_NAr reactions on the trichloro precursor **5**. Interestingly, we have determined that the order of chloride displacement at C4, C2, and C7 of **5** differs from that reported for a very similar compound.[11] Furthermore, a key step to the success of this strategy is a base-catalyzed S_NAr process that allowed us to effectively install the third substituent on the pyrido[2,3-*d*]pyrimidine core. In general, this strategy should enable the synthesis of a variety of pyrido[2,3-*d*]pyrimidine derivatives and in particular provide rapid access to those which contain one or more fused rings involving the substitutents at C6 and C7.

Future efforts will be focused on the synthesis and self-assembly of **4** and its derivatives. For instance, the synthesis of a bis-allyl version of **4** ($R_5 = R_6 =$ Allyl), wherein the allyl groups could serve as a handle for further functionalization[1] is currently underway. This will improve the solubility of the tetracyclic motif and allow for functionalization of the outer periphery of the corresponding RNTs.

Experimental Section

2-Amino-4-(benzyloxy)-7-chloropyrido[2,3-*d*]pyrimidine-6-carbonitrile (8). Compound **6** (50 mg, 0.15 mmol) was dissolved in anhydrous CH_2Cl_2 (6 mL) and treated with a 2 M solution of NH_3 in *i*-PrOH (0.32 mL, 0.64 mmol). The solution was stirred overnight at room temperature and then concentrated under reduced pressure. Purification by flash chromatography on silica gel (0−2% MeOH/CH_2Cl_2) provided **8** ($C_{15}H_{10}ClN_5O$, 33 mg) in 70% yield as a white solid. R_f = 0.5 (1% MeOH/CH_2Cl_2). Mp = 227.5−229.1 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm) 8.78 (C_6H, sharp s, 1H), 7.99 (NH, brs, 1H), 7.89 (NH, brs, 1H), 7.58−7.37 (C_{9-11}H, m, 5H), 5.55 (C_{15}H, m, 2H). ^{13}C NMR (150 MHz, DMSO-d_6) δ (ppm) 166.9 164.2 162.4 155.1 (C_1) (C_2) (C_3) (C_4), 141.5 135.3 (C_5) (C_6), 128.4 128.2 128.1 (C_9) (C_{10}) (C_{11}), 115.4 104.3 100.5 (C_8) (C_{13}) (C_{14}), 68.6 (C_{15}). ESI-MS: calcd for $(M + H^+)$/z, 312.1, found 312.4 [$(M + H^+)$/z]. HRMS (ESI): calcd for $C_{15}H_{11}ClN_5O$, 312.0647, found 312.0640. **4-Amino-2,7-dichloropyrido[2,3-*d*]pyrimidine-6-carbonitrile** (**9**, $C_8H_3Cl_2N_5$, 11 mg) was also isolated in 30% yield from the reaction mixture. R_f = 0.3 (2% MeOH/CH_2Cl_2). Mp = 218.1−218.7 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm) 9.31 (C_6H, sharp s, 1H), 9.17 (NH, broad s, 1H), 8.97 (NH, broad s, 1H). ^{13}C NMR (150 MHz, DMSO-d_6) δ (ppm) 163.9 163.7 160.1 154.8 (C_1) (C_2) (C_3) (C_4), 143.5 (C_6), 114.9 106.9 105.9 (C_8) (C_{13}) (C_{14}). ESI-MS: calcd for $(M + H^+)$/z, 240.0, found 240.3 [$(M + H^+)$/z]. HRMS (ESI): calcd for $C_8H_4Cl_2N_5$, 239.9838, found 239.9841.

7-(Allylamino)-2-amino-4-(benzyloxy)pyrido[2,3-*d*]pyrimidine-6-carbonitrile (10). Allylamine (0.044 mL, 0.59 mmol) was added to a solution of compound **8** (73 mg, 0.23 mmol) in anhydrous CH_2Cl_2 (6 mL) in a sealed tube. After stirring overnight at 50 °C, the solvent was removed *in vacuo*. Purification by flash chromatography on silica gel (0−2% MeOH/CH_2Cl_2) provided compound **10** ($C_{18}H_{16}N_6O$, 43 mg) in 55% yield as a solid. R_f = 0.5 (7.5% MeOH/CH_2Cl_2). Mp = 213.4−215.1 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm) 8.31 (C_6H, sharp s, 1H), 7.64−7.62 (NH, brs, 1H), 7.52−7.33 (C_{9-11}H, m, 5H), 7.22 (NH, brs, 2H), 5.98−5.82 (C_7H, m, 1H), 5.46 (C_{15}H, s, 2H), 5.14−5.03 (C_{12}H, m, 2H), 4.02 (C_{16}H, s, 2H). ^{13}C NMR (150 MHz, DMSO-d_6) δ (ppm) 166.6 163.8 163.4 159.1 (C_1) (C_2) (C_3) (C_4), 140.3 (C_6), 136.1 (C_5), 135.2 (C_7), 128.4 128.0 127.9 (C_9) (C_{10}) (C_{11}), 116.5 (C_{14}), 115.3 (C_{12}), 97.1 87.8 (C_{13}) (C_8), 67.6 (C_{15}), 42.9 (C_{16}). ESI-MS: calcd for $(M + H^+)$/z, 333.1, found 333.4 [$(M + H^+)$/z]. HRMS (ESI): calcd for $C_{18}H_{17}N_6O$, 333.1458, found 333.1454.

2-(Allylamino)4-(benzyloxy)-7-chloropyrido[2,3-*d*]pyrimidine-6-carbonitrile (11). 4-(Benzyloxy)-2,7-dichloropyrido[2,3-*d*]pyrimidine-6-carbonitrile (**6**) (1.0 g, 3.0 mmol) was dissolved in CH_2Cl_2 (125 mL), cooled to 0 °C, and then treated with DIPEA (1.1 mL, 6.0 mmol) and allylamine (246 μL, 3.3 mmol). After 3 h of stirring, the precipitate was collected, washed with CH_2Cl_2, and dried under high vacuum to yield compound **11** ($C_{18}H_{14}ClN_5O$, 688 mg) in 64% yield as a solid. R_f = 0.2 (30% EtOAc/hexane). Mp = 234.7−235.7 °C. ^{1}H NMR (600 MHz, DMSO-d_6, 90 °C) δ (ppm) 8.70 (C_6H, sharp s, 1H), 8.35 (NH, broad s, 1H), 7.54−7.35 (C_{9-11}H, m, 5H), 5.98−5.83 (C_7H, m, 1H), 5.59 (C_{15}H, s, 2H), 5.24−5.09 (C_{12}H, m, 2H), 4.08−4.07 (C_{16}H, m, 2H). ^{13}C NMR (150 MHz, DMSO-d_6, 90 °C) δ (ppm) 166.2 162.1 161.9 154.9 (C_1) (C_2) (C_3) (C_4), 141.3 135.2 134.4 (C_5) (C_6) (C_7), 128.2 128.1 128.0 (C_9) (C_{10}) (C_{11}), 115.6 115.2 104.9 100.7 (C_8) (C_{12}) (C_{13}) (C_{14}), 68.5 (C_{15}), 43.1 (C_{16}). Positive ESI-MS: calcd for $(M + H^+)$/z, 352.1, found 352.5 [$(M + H^+)$/z]. HRMS (ESI): calcd for $C_{18}H_{15}ClN_5O$, 352.0960, found 352.0966.

(2-(Allylamino)-4-(benzyloxy)-7-chloropyrido[2,3-*d*]pyrimidin-6-yl)methanol (14). DIBAL-H (21.3 mL, 1 M in CH_2Cl_2, 21.3 mmol) was added dropwise to a solution of **11** (3 g, 8.5 mmol) in

CH_2Cl_2 (450 mL). After stirring for 3.5 h at rt, the reaction was quenched with MeOH (10 mL), followed by 1 M $HCl_{(aq)}$ (30 mL), and the resulting suspension was stirred for 15 min. The organic phase was separated, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude mixture was then dissolved in a 1:1 mixture of $CHCl_3$\MeOH (170 mL) and treated with $NaBH_4$ (643 mg, 17.0 mmol). After 2 h of stirring, dH_2O (100 mL) was added, and the organic phase was extracted and concentrated. Purification by silica gel flash chromatography (0−1% MeOH/CH_2Cl_2) provided compound **14** ($C_{18}H_{17}ClN_4O_2$, 1.5 g) in ca. 50% yield as a solid. R_f = 0.8 (3% MeOH/CH_2Cl_2). Mp = 166.3−167.9 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm) 8.26 (C_6H, sharp s, 1H), 7.51−7.33 (C $_{9-11}$H, m, 5H), 6.04−5.97 (C $_7$H, m, 1H), 5.57 (C_{15}H, m, 2H), 5.21 (C_{12}H, dd, J = 1.2 Hz, J = 16.8 Hz, 1H), 5.07 (C_{12}H, dd, J = 1.2 Hz, J = 10.2 Hz, 1H), 4.55 (C_{14}H, s, 2H), 4.04−4.02 (C $_{16}$H, m, 2H). ^{13}C NMR (150 MHz, DMSO-d_6) δ (ppm) 167.2 161.5 161.0 154.9 (C_1) (C_2) (C_3) (C_4), 136.5 135.9 133.5 (C_5) (C_6) (C_7), 129.8 128.9 128.7 128.6 (C_8) (C_9) (C_{10}) (C_{11}), 115.7 105.5 68.7 (C_{12}) (C_{13}) (C_{14}), 60.2 (C_{15}), 43.8 (C_{16}). Positive ESI-MS: calcd for (M + H^+)/z, 357.5, found 357.4 [(M + H^+)/z]. HRMS (ESI): calcd for $C_{18}H_{18}ClN_4O_2$, 357.1113, found 357.1110. **2-(Allylamino)-4-(benzyloxy)-7-chloro-5,8-dihydropyrido[2,3-*d*]pyrimidine-6-carbonitrile** (**15**, $C_{18}H_{16}ClN_5O$, 1.5 g) was also isolated from the reaction mixture in ca. 50% yield as an oil. ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm) 10.43 (NH, sharp s, 1H), 7.39−7.28 (C_{9-11}H, m, 5H), 7.15 (NH, broad s, 1H), 5.85−5.82 (C_7H, m, 1H), 5.31 (C_{15}H, s, 2H), 5.12−5.00 (C_{12}H, m, 2H), 3.84−3.82 (C_{16}H, m, 2H), 3.40 (C_6H, s, 2H). ^{13}C NMR (150 MHz, DMSO-d_6) δ (ppm) 166.9 160.8 156.6 140.2 (C_1) (C_2) (C_3) (C_4), 137.3 136.5 (C_5) (C_7), 128.9 128.18 128.15 (C_9) (C_{10}) (C_{11}), 118.8 115.3 (C_{12}) (C_{14}), 83.3 79.6 (C_8) (C_{13}), 67.3 (C_{15}), 43.5 (C_{16}), 23.4 (C_6). Positive ESI-MS: calcd for (M + H^+)/z, 354.5, found 354.3 [(M + H^+)/z]. HRMS (ESI): calcd for $C_{18}H_{17}ClN_5O$, 354.1116, found 354.1115.

2-(Allylamino)-4-(benzyloxy)-7-chloropyrido[2,3-*d*]pyrimidine-6-carbaldehyde (**13**)**.** PCC (1.2 g, 5.4 mmol) was added to a solution of **14** (950 mg, 2.7 mmol) in $CHCl_3$ (70 mL). After stirring overnight, the reaction mixture was filtered through a pad of Celite, treated with 1 M $HCl_{(aq)}$ (30 mL), and stirred for 15 min. The organic phase was then separated, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by silica gel flash chromatography (0−1% MeOH/CH_2Cl_2) provided compound **13** as a solid ($C_{18}H_{15}ClN_4O_2$, 700 mg) in 74% yield. R_f = 0.8 (3% MeOH/CH_2Cl_2). Decomposes > 280 °C. ^{1}H NMR (600 MHz, $CDCl_3$, 50 °C) δ (ppm) 10.37 (C_{14}H, s, 1H), 8.75 (C_6H, sharp s, 1H), 7.47−7.37 (C_{9-11}H, m, 5H), 6.25 (NH, brs, 1H), 6.00−5.97 (C_7H, m, 1H), 5.53 (C_{15}H, s, 2H), 5.32−5.21 (C_{12}H, m, 2H), 4.31 (C_{16}H, m, 2H). ^{13}C NMR (150 MHz, $CDCl_3$, 50 °C) δ (ppm) 188.2 (C_{14}), 168.4 163.9 162.8 158.7 (C_1) (C_2) (C_3) (C_4), 136.8 135.3 134.0 (C_5) (C_6) (C_7), 129.04 129.01 128.6 123.7 (C_8) (C_9) (C_{10}) (C_{11}), 117.3 106.7 (C_{12}) (C_{13}), 69.8 (C_{15}), 44.5 (C_{16}). Positive ESI-MS: calcd for (M + H^+)/z, 355.5, found 355.4 [(M + H^+)/z]. HRMS (ESI): calcd for $C_{18}H_{16}ClN_4O_2$, 355.0956, found 355.0956.

***tert*-Butyl Allyl(4-(benzyloxy)-7-chloro-6-formylpyrido[2,3-*d*]pyrimidin-2-yl)carbamate** (**16**)**.** Compound **13** (693 mg, 1.95 mmol) was suspended in THF (100 mL) and then treated with DIPEA (0.68 mL, 3.9 mmol), DMAP (24 mg, 0.2 mmol), and Boc_2O (468 mg, 2.15 mmol). After the mixture stirred overnight, dH_2O (10 mL) was added, and the THF was removed under reduced pressure (rotavap). The residue was then extracted with CH_2Cl_2, and the combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated. Purification by silica gel flash chromatography (0−15% EtOAc/hexane) provided compound **16** as a solid ($C_{23}H_{23}ClN_4O_4$, 650 mg) in 73% yield. R_f = 0.9 (3% MeOH/CH_2Cl_2). Mp = 130.3−131.1 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 10.43 (C_{14}H, s, 1H), 8.88 (C_6H, sharp s, 1H), 7.50−7.38 (C $_{9-11}$H, m, 5H), 6.02−5.98 (C $_7$H, m, 1H), 5.62 (C_{15}H, s, 2H), 5.25 (C_{12}H, dd, J = 17.4 Hz, 1.8 Hz, 1H), 5.12 (C_{12}H, dd, J = 10.8 Hz, 1.8 Hz, 1H), 4.74−4.72 (C $_{16}$H, m, 2H), 1.57 (C_{19}H, s, 9H). ^{1}H NMR (600 MHz, CD_3CN) δ (ppm) 10.33 (C_{14}H, s 1H), 8.75 (C_6H, sharp s, 1H), 7.57−7.39 (C $_{9-11}$H, m, 5H), 6.02−6.01 (C $_7$H, m, 1H), 5.65 (C_{15}H, s, 2H), 5.25 (C_{12}H, dd, J = 17.4 Hz, J = 1.8 Hz, 1H), 5.14 (C_{12}H, dd, J = 10.8 Hz, J = 1.8 Hz, 1H), 4.64−4.63 (C $_{16}$H, m, 2H), 1.55 (C_{19}H, s, 9H). ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) 187.9 (C_{14}) 168.3 162.2 161.8 158.3 (C_1) (C_2) (C_3) (C_4) 152.6 (C_{17}), 136.9 134.8 133.5 (C_5) (C_6) (C_7), 128.9 128.8 128.7 125.6 (C_8) (C_9) (C_{10}) (C_{11}), 116.7 107.2 (C_{12}) (C_{13}), 82.7 (C_{18}), 70.3 (C_{15}), 49.9 (C_{16}) 28.1 (C_{19}). Positive ESI-MS: calcd for (M + H^+)/z, 455.5, found 455.4 [(M + H^+)/z]. HRMS (ESI): calcd for $C_{23}H_{24}ClN_4O_4$, 455.1481, found 455.1475.

***tert*-Butyl Allyl(7-amino-4-(benzyloxy)-6-formylpyrido[2,3-*d*]pyrimidin-2-yl)carbamate** (**17**)**.** Compound **16** (100 mg, 0.22 mmol) was dissolved in 0.5 M NH_3 in THF (4.4 mL, 2.2 mmol). DIPEA (0.038 mL, 0.22 mmol) and DABCO (27 mg, 0.24 mmol) were then added, and the solution was stirred for 13 h. The solvent was removed *in vacuo*, and the crude product was purified by silica gel flash chromatography (0−100% EtOAc/hexane) to provide compound **17** as a solid ($C_{23}H_{25}N_5O_4$, 50 mg) in 52% yield. R_f = 0.5 (5% MeOH/CH_2Cl_2). Mp = 196.7−198.6 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 9.86 (C_{14}H), 8.49 (C_6H, sharp s, 1H), 7.49−7.36 (C $_{9-11}$H, m, 5H), 6.05−5.96 (C $_7$H, m, 1H), 5.56 (C_{15}H, s, 2H), 5.22 (C_{12}H, dd, J = 17.4 Hz, 1.8 Hz, 1H), 5.09 (C_{12}H, dd, J = 10.2 Hz, 1.2 Hz, 1H), 4.68−4.67 (C $_{16}$H, m, 2H), 1.53 (C_{19}H, s, 9H). ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) 191.2 (C_{14}), 167.6 163.4 162.3 160.7 (C_1) (C_2) (C_3) (C_4), 153.1 (C_{17}), 144.2 135.7 134.1 (C_5) (C_6) (C_7), 128.8 128.7 128.7 (C_9) (C_{10}) (C_{11}), 116.2 115.2 101.2 (C_8) (C_{12}) (C_{13}), 82.1 (C_{18}), 69.4 (C_{15}), 49.9 (C_{16}), 28.2 (C_{19}). Positive ESI-MS: calcd for (M + H^+)/z, 436.5, found 436.6 [(M + H^+)/z]. HRMS (ESI): calcd for $C_{23}H_{26}N_5O_4$, 436.1979, found 436.1976.

***tert*-Butyl Allyl(4-(benzyloxy)-6-formyl-7-hydroxypyrido[2,3-*d*]pyrimidin-2-yl)carbamate** (**22**, $C_{23}H_{24}N_4O_5$, 38 mg) was also isolated in 40% yield from the reaction mixture. R_f = 0.3 (5% MeOH/CH_2Cl_2). Mp = 158.1−159.7 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 10.26 (C_{14}H), 8.54 (C_6H, sharp s, 1H), 7.43−7.36 (C $_{9-11}$H, m, 5H), 5.93−5.88 (C $_7$H, m, 1H), 5.50 (C_{15}H, s, 2H), 5.21−5.17 (C $_{12}$H, m, 2H), 4.54 (C_{16}H, m, 2H), 1.53 (C_{19}H, s, 9H). ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) 188.3 (C_{14}), 167.6 162.8 162.3 157.6 (C_1) (C_2) (C_3) (C_4), 152.4 (C_{17}), 137.4 135.0 133.4 (C_5) (C_6) (C_7), 128.8 128.7 128.5 (C_9) (C_{10}) (C_{11}), 123.6 116.8 (C_8) (C_{12}), 96.0 (C_{13}) 83.1 (C_{18}), 69.8 (C_{15}) 48.8 (C_{16}), 28.1 (C_{19}). Positive ESI-MS: calcd for (M + H^+)/z, 437.5, found 437.4 [(M + H^+)/z]. HRMS (ESI): calcd for $C_{23}H_{25}N_4O_5$, 437.1819, found 437.1830.

***N*-(1-(2-(Allyl(*tert*-butoxycarbonyl)amino)-4-(benzyloxy)-6-formylpyrido[2,3-*d*]pyrimidin-7-yl)pyridin-4(1*H*)-ylidene)-*N*-methylmethanaminium Chloride** (**18**)**.** ^{1}H NMR (600 MHz, CD_3CN) δ (ppm) 10.00 (C_{14}H, s 1H), 9.17 (C_6H, sharp s, 1H), 8.37 ((C_{22})-(C_{23})H, dd, J = 6.0 Hz, J = 1.8 Hz, 1H), 8.11 ((C_{22})(C_{23})H, dd, J = 5.4 Hz, J = 1.8 Hz, 1H), 7.61−7.45 (C_{9-11}H, m, 5H), 7.04 ((C_{20})-(C_{21})H, dd, J = 5.4 Hz, J = 1.2 Hz, 1H), 6.55 ((C_{20})(C_{21})H, dd, J = 5.4 Hz, J = 1.8 Hz, 1H), 6.02−6.00 (C_7H, m, 1H), 5.72 (C_{15}H, s, 2H), 5.24 (C_{12}H, dd, J = 18.0 Hz, J = 1.8 Hz, 1H), 5.16 (C_{12}H, dd, J=10.8 Hz, J=1.2 Hz, 1H), 4.67 (C_{16}H, m, 2H), 3.32, 2.96 ($C_{25, 26}$H, s, 6H), 1.55 (C_{19}H, s, 9H). HRMS (EI): calcd for $C_{30}H_3N_6O_4^+$ 541.2558, found 541.2556.

1-(2-(Allyl(*tert*-butoxycarbonyl)amino)-4-(benzyloxy)-6-formylpyrido[2,3-*d*]pyrimidin-7-yl)-4-methoxypyridinium Chloride (**19**)**.** ^{1}H NMR (600 MHz, CD_3CN) δ (ppm) 9.99 (C_{14}H, s 1H), 9.00 (C_6H, sharp s, 1H), 8.37 ((C_{20})(C_{21})H, dd, J = 4.8 Hz, J=1.8 Hz, 1H), 7.91−7.89 ((C_{20})(C_{21})H, m, 1H), 7.61−7.39 (C_{9-11}H, m, 5H), 6.88 ((C_{22})(C_{23})H, dd, J = 4.8 Hz, J = 1.2 Hz, 1H), 6.29 ((C_{22})(C_{23})H, m, 1H), 6.02−6.00 (C_7H, m, 1H), 5.69 (C_{15}H, s, 2H), 5.24 (C_{12}H, dd, J=18.0 Hz, J=1.8 Hz, 1H), 5.16 (C_{12}H, dd, J = 10.8 Hz, J = 1.2 Hz, 1H), 4.65 (C_{16}H, m, 2H),

4.23 ($C_{25}H$, s, 3H), 1.55 ($C_{19}H$, s, 9H). Positive ESI-MS: calcd for $(M + H^+)/z$, 528.2, found 528.4 $[(M + H^+)/z]$

1-(2-(Allyl(*tert*-butoxycarbonyl)amino)-4-(benzyloxy)-6-formylpyrido[2,3-*d*]pyrimidin-7-yl)-4-aza-1-azoniabicyclo[2.2.2]octane (20). ^{1}H NMR (600 MHz, CD_3CN) δ (ppm) 10.07 ($C_{14}H$, s 1H), 9.32 (C_6H, sharp s, 1H), 7.61−7.41 ($C_{9-11}H$, m, 5H), 6.05−6.01 (C_7H, m, 1H), 5.73 ($C_{15}H$, s, 2H), 5.25 ($C_{12}H$, dd, J = 17.4 Hz, J = 1.8 Hz, 1H), 5.16 ($C_{12}H$, dd, J = 10.8 Hz, J = 1.8 Hz, 1H), 4.69 ($C_{16}H$, m, 2H), 4.01 ($C_{20}H$, t, J = 7.8 Hz, 6H), 3.34 ($C_{21}H$, t, J = 7.8 Hz, 6H), 1.57 ($C_{19}H$, s, 9H). Positive ESI-MS: calcd for M^+/z, 532.3, found 531.5 $[M^+/z]$.

1-(1-(2-(Allyl(*tert*-butoxycarbonyl)amino)-4-(benzyloxy)-6-formylpyrido[2,3-*d*]pyrimidin-7-yl)pyridin-4(1*H*)-ylidene)pyrrolidinium Chloride (21). ^{1}H NMR (600 MHz, CD_3CN) δ (ppm) 10.00 ($C_{14}H$, s 1H), 9.17 (C_6H, sharp s, 1H), 8.35−8.34 ((C_{22})(C_{23})H, m, 1H), 8.07−8.06 ((C_{22})(C_{23})H, m, 1H), 7.61−7.45 ($C_{9-11}H$, m, 5H), 6.90 ((C_{20})(C_{21})H, m, 1H), 6.50−6.49 ((C_{20})(C_{21})H, m, 1H), 6.09−6.00 (C_7H, m, 1H), 5.72 ($C_{15}H$, s, 2H), 5.24 ($C_{12}H$, dd, J = 18.0 Hz, J = 1.8 Hz, 1H), 5.16 ($C_{12}H$, dd, J = 10.8 Hz, J = 1.2 Hz, 1H), 4.67 ($C_{16}H$, m, 2H), 3.27, 1.98 ($C_{25-26}H$, s, 8H), 1.55 ($C_{19}H$, s, 9H). HRMS (ESI): calcd for $C_{32}H_{35}N_6O_4^+$, 567.2714, found 567.2714.

***tert*-Butyl Allyl(4-(benzyloxy)-7-(4-(2-chloroethyl)piperazin-1-yl)-6-formylpyrido[2,3-*d*]pyrimidin-2-yl)carbamate (23).** A solution of compound **16** (100 mg, 0.22 mmol) in 0.5 M NH_3 in dioxane (4.4 mL, 2.2 mmol) was treated with DABCO (27 mg, 0.24 mmol) and DIPEA (0.038 mL, 0.22 mmol). After stirring for 24 h, the solution was concentrated *in vacuo*. Purification by silica gel flash chromatography (0−100% EtOAc/hexane) offered compound **23** ($C_{29}H_{35}ClN_6O_4$, 62 mg) in 50% yield as a white solid. R_f = 0.2 (30% EtOAc/hexane). Decomposes > 200 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 9.89 ($C_{14}H$), 8.59 (C_6H, sharp s, 1H), 7.47−7.35 ($C_{9-11}H$, m, 5H), 5.99−5.88 (C_7H, m, 1H), 5.55 ($C_{15}H$, s, 2H), 5.21 ($C_{12}H$, dd, J = 16.8 Hz, 1.2 Hz, 1H), 5.17 ($C_{12}H$, dd, J = 10.2 Hz, 1.2 Hz, 1H), 4.62 ($C_{16}H$, m, 2H), 3.70 ($C_{20}H$, t, J = 4.8 Hz, 4H), 3.60 ($C_{23}H$, t, J = 6.6 Hz, 2H), 2.77 ($C_{22}H$, t, J = 6.6 Hz, 2H), 2.67 ($C_{21}H$, t, J = 4.8 Hz, 4H), 1.52 ($C_{19}H$, s, 9H). ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) 188.1(C_{14}), 167.9 162.4 161.9 153.2, 153.1 (C_1) (C_2) (C_3) (C_4) (C_{17}), 141.9 135.6, 134.3 (C_5) (C_6) (C_7), 128.7 128.6 128.5 (C_9) (C_{10}) (C_{11}), 119.4 116.2 102.1 (C_8) (C_{12}) (C_{13}), 81.9 (C_{18}), 69.3 (C_{15}), 59.7 53.0 50.0 49.7 39.9 (C_{16}) (C_{20}) (C_{21}) (C_{22}) (C_{23}) 28.2 (C_{19}). ESI-MS: calcd for $(M + H^+)/z$, 567.2, found 567.5 $[(M + H^+)/z]$. HRMS (ESI): calcd for $C_{29}H_{36}ClN_6O_4$, 567.2481, found 567.2469.

***tert*-Butyl Allyl(8-amino-4-(benzyloxy)-7-cyanopyrimido[4,5-*b*][1,8]naphthyridine)carbamate (24).** A solution of **17** (150 mg, 0.34 mmol) and malononitrile (25 mg, 0.38 mmol) in pyridine (15 mL) was stirred for 24 h at rt. The solution was then concentrated under reduced pressure (rotavap), and the crude material was purified by silica gel flash chromatography (0−5% MeOH/CH_2Cl_2) to provide compound of **24** ($C_{26}H_{25}N_7O_3$, 146 mg) as a clear oil in 88% yield. R_f = 0.3 (5% MeOH/CH_2Cl_2). ^{1}H NMR (600 MHz, CD_2Cl_2) δ (ppm) 8.81 (C_6H, sharp s, 1H), 8.42 ($C_{14}H$, sharp s, 1H), 7.56−7.39 ($C_{9-11}H$, m, 5H), 6.15 (NH, brs, 2H), 6.08−6.03 (C_7H, m, 1H), 5.66 ($C_{15}H$, s, 2H), 5.31 ($C_{12}H$, dd, J = 17.4 Hz, 1.2 Hz, 1H), 5.15 ($C_{12}H$, dd, J = 10.2, 1.2 Hz, 1H), 4.73−4.72 ($C_{16}H$, m, 2H), 1.55 ($C_{19}H$, s, 9H). ^{13}C NMR (150 MHz, CD_2Cl_2) δ (ppm) 168.7 163.0 161.8 160.5 (C_1) (C_2) (C_3) (C_4), 159.5 (C_{22}), 153.7 (C_{17}), 147.0 (C_{14}), 137.8 136.1 134.8 (C_5) (C_6) (C_7), 129.3 129.24 129.23 (C_9) (C_{10}) (C_{11}), 116.6 115.8, 115.4, 107.5, 97.8 (C_8) (C_{12}) (C_{13}) (C_{20}) (C_{21}), 82.8 (C_{18}), 70.4 (C_{15}), 50.5 (C_{16}), 28.5 (C_{19}). Positive ESI-MS: calcd for $(M + H^+)/z$, 484.1, found 484.4 $[(M + H^+)/z]$. HRMS (ESI): calcd for $C_{26}H_{26}N_7O_3$, 484.2092, found 484.2095.

***tert*-Butyl Allyl(4-(benzyloxy)-7-cyano-8-ureidopyrimido[4,5-*b*][1,8]naphthyridine)carbamate (25).** Trichlorocarbonyl isocyanate (0.030 mL, 0.25 mmol) was added to a solution of **24** (60 mg, 0.12 mmol) in CH_2Cl_2 (9 mL) at 0 °C. After the mixture stirred for 2 h, NH_3 (2 M in *i*-PrOH, 1 mL, 2 mmol) was added, and the solution was stirred for an additional 2 h. Upon warming to rt, the solvent was removed under reduced pressure, and the resulting crude material was purified by silica gel flash chromatography (0−3% MeOH/CH_2Cl_2) to provide compound **25** ($C_{27}H_{26}N_8O_4$, 50 mg) in 77% yield as a white solid. R_f = 0.3 (5% MeOH/CH_2Cl_2). Mp = 209.1−211.0 °C. ^{1}H NMR (600 MHz, CD_2Cl_2) δ (ppm) 9.65 (NH, brs, 1H), 8.95 (C_6H, sharp s, 1H), 8.60 ($C_{14}H$, sharp s, 1H), 7.65 (NH, broad s, 1H), 7.58−7.40 ($C_{9-11}H$, m, 5H), 6.06−6.03 (C_7H, m, 1H), 5.69 ($C_{15}H$, s, 2H), 5.65 (NH, bs, 1H), 5.28 ($C_{12}H$, dd, J = 17.4 Hz, 1.2 Hz, 1H), 5.18 ($C_{12}H$, dd, J = 10.2 Hz, 1.8 Hz, 1H), 4.75−4.72 ($C_{16}H$, m, 2H), 1.58 ($C_{19}H$, s, 9H). ^{13}C NMR (150 MHz, CD_2Cl_2) δ (ppm) 168.7 163.2 162.3 158.0 154.3 153.9 153.3 (C_1) (C_2) (C_3) (C_4) (C_{17}) (C_{22}) (C_{23}), 147.8 138.3 135.8 134.4 (C_5) (C_6) (C_7) (C_{14}), 129.4 129.3 129.3 (C_9) (C_{10}) (C_{11}), 116.7 115.9 114.7 109.1 98.4 (C_8) (C_{12}) (C_{13}) (C_{20}) (C_{21}), 83.1 (C_{18}), 70.8 (C_{15}), 50.5 (C_{16}), 28.5 (C_{19}). ESI-MS: calcd for $(M + H^+)/z$, 527.2, found 527.2 $[(M + H^+)/z]$.

***tert*-Butyl Allyl(4-(benzyloxy)-7-cyano-8-(3-phenylcarbonylureido)pyrimido[4,5-*b*][1,8]naphthyridine)carbamate (26).** Benzoyl isocyanate (25 mg, 0.17 mmol) was added to a solution of **24** (40 mg, 0.083 mmol) in CH_2Cl_2 (6 mL) at 0 °C. After 2 h, the reaction mixture was warmed to rt and quenched with dH_2O (3 mL). The organic phase was then extracted with CH_2Cl_2, dried over anhydrous Na_2SO_4, filtered, and concentrated. Purification by silica gel flash chromatography (0−3% MeOH/CH_2Cl_2) provided compound **26** ($C_{34}H_{30}N_8O_5$, 40 mg) as a yellow foam in 77% yield. R_f = 0.4 (5% MeOH/CH_2Cl_2). ^{1}H NMR (600 MHz, CD_2Cl_2) δ (ppm) 8.99 (C_6H, sharp s, 1H), 8.66 ($C_{14}H$, sharp s, 1H), 8.44 (NH, broad s, 2H), 7.71−7.41 ($C_{9-11}H$, $C_{26-28}H$, m, 10H), 6.19−6.05 (C_7H, m, 1H), 5.71 ($C_{15}H$, s, 2H), 5.37−5.22 ($C_{12}H$, m, 2H), 4.81−4.80 ($C_{16}H$, m, 2H), 1.61 ($C_{19}H$, s, 9H). ^{13}C NMR (150 MHz, CD_2Cl_2) δ (ppm) 168.7 163.2 162.5 157.6 153.8 153.4 149.2 148.2 (C_1) (C_2) (C_3) (C_4) (C_{17}) (C_{22}) (C_{23}) (C_{24}), 138.5 135.8 134.5 134.0 132.9 132.4 129.7 129.5 129.4 129.3 129.0 (C_5) (C_6) (C_7) (C_9) (C_{10}) (C_{11}) (C_{14}) (C_{25}) (C_{26}) (C_{27}) (C_{28}), 127.9 117.0 116.3 114.6 109.7 (C_8) (C_{12}) (C_{13}) (C_{20}) (C_{21}), 83.2 (C_{18}), 70.8 (C_{15}), 50.8 (C_{16}), 28.4 (C_{19}). Positive ESI-MS: calcd for $(M + H^+)/z$, 631.2, found 631.4 $[(M + H^+)/z]$. HRMS (ESI): calcd for $C_{34}H_{31}N_8O_5$, 631.2412, found 631.2414.

××G∧C Motif (4). A solution of **26** (30 mg, 0.05 mmol) and DIPEA (0.07 mL, 0.4 mmol) in CH_2Cl_2 (3 mL) was stirred at rt for 4 days and then concentrated. The crude product was then dissolved in 4 M HCl/dioxane (90 mL) and heated at 70 °C for 5 h in a sealed tube. The resulting residue was collected and washed with CH_2Cl_2 to give target compound **4** ($C_{15}H_{12}N_8O_2$, 12 mg) as a yellow solid in 75% yield (2 steps). Decomposition > 400 °C. ^{1}H NMR (600 MHz, CF_3CO_2D) δ (ppm) 9.47 9.37 (C_6H, $C_{14}H$, two sharp s, 2H), 5.91−5.89 (C_7H, m, 1H), 5.38−5.32 ($C_{12}H$, m, 2H), 4.33−4.32 ($C_{16}H$, m, 2H). ^{13}C NMR (150 MHz, CF_3CO_2D) δ (ppm) 164.3 163.0 160.5 157.6 157.2 154.9 154.0 (C_1) (C_2) (C_3) (C_4) (C_{20}) (C_{22}) (C_{23}), 150.5 146.9 (C_6) (C_{14}), 131.6 (C_7), 121.6 (C_{12}), 117.7 116.2 113.3 (C_8) (C_{13}) (C_{21}), 46.8 (C_{16}). HRMS (ESI): calcd for $C_{15}H_{12}DN_8O_2$, 338.1146, found 338.1218.

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Supporting Information Available: Experimental procedures not described in the Experimental Section and ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.