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# Synthesis and Functionalization of C6/C7 Substituted Pyrido[3,2-*d*]pyrimidines

Philipp E. Hofmann[+],[a] Jannick Meinecke[+],[a] Klaus Harms,[a] and Ulrich Koert*[a]

*Dedicated to the memory of Prof. Dr. Klaus Hafner.*

An efficient synthesis of functionalized pyrido[3,2-*d*]pyrimidines is reported. Starting from 4-aminopyrimidine-3-carbaldehydes, a Horner-Wadsworth-Emmons olefination followed by a photoisomerization/cyclization installed the fused pyridine ring. Using substituted HWE-reagents various substituents could be introduced in the 7-position of the pyrido[3,2-*d*]pyrimidines. Functionalization of the pyridone substructure allowed late variation in the 6-position. In order to obtain amine-linked bis-pyridopyrimidines, 7-bromo-pyridopyrimidines were converted with their 7-amino-counterpart by Hartwig–Buchwald amination.

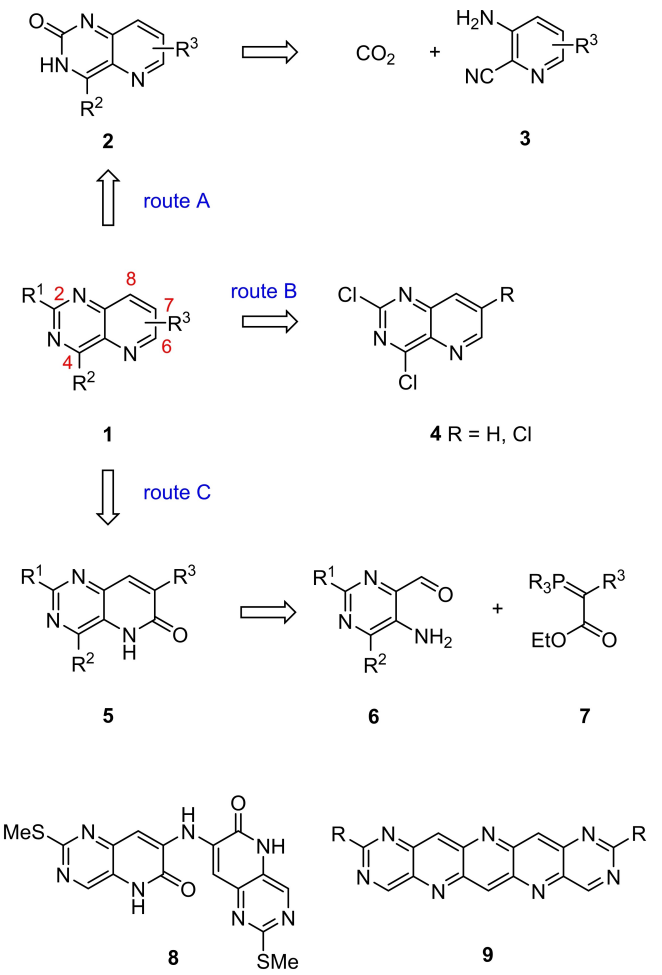
## Introduction

Pyridopyrimidines are heteroaromatic scaffolds of interest for life-science applications in particular medicinal chemistry.[1] Among them pyrido[3,2-*d*]pyrimidines play a prominent role. Selected recent examples for their use in the development of drug type compounds include: toll-like receptor 8 agonist selgantolimod,[2] dual PI3 K/mTor inhibitor cmG002,[3] kinase ERK5 probe BAY-885,[4] PI3Kd-inhibitor seletalisib,[5] and p38a MAP-kinase inhibitor R1487.[6] Furthermore, pyrido[3,2-*d*] pyrimidines are promising building blocks for functional materials e. g. organic nanotubes.[7]

The chemistry of pyridopyrimidines and synthetic access to various substitution patterns for this heteroaromatic system are an active field of organic synthesis.[8]

Synthetic routes to substituted pyrido[3,2-*d*]pyrimidines **1** can be divided into three approaches (Scheme 1).[8] The first route A uses intermediates of type **2** which can be prepared starting from a substituted pyridine for example by condensation of carbon dioxide with an 3-amino-2-cyano-pyridine **3**.[9] The second route B uses sequential chemoselective substitution reactions of commercially available di- and trichloropyridopyrimidines **4**. This approach was mainly developed by the Orleans group of Guillaumet and Routier.[10]

The third approach C utilizes intermediates of type **5** which could be prepared from a substituted pyrimidine for example by an olefination reaction of an 4-aminopyrimidine-3-carboxaldehyde **6** with a Wittig-type reagent **7** followed by pyridone ring closure. This route is less developed.[11] We intended to apply bis-pyrido[3,2-*d*]pyrimidines **8** for the synthesis of polyazapentacene **9** with interesting semiconductor properties.[12] Here we report the use of the third synthetic route C as an




**Scheme 1.** Three synthetic routes to substituted pyrido[3,2-*d*]pyrimidines **1** and structures of bis-pyrido[3,2-*d*]pyrimidines **8** and polyazapentacene **9**.

[a] *Dr. P. E. Hofmann,[+] J. Meinecke,[+] Dr. K. Harms, Prof. Dr. U. Koert*
*Fachbereich Chemie, Philipps-Universität Marburg*
*Hans-Meerwein Straße 4, 35032 Marburg*
*E-mail: koert@chemie.uni-marburg.de*
https://www.uni-marburg.de/fb15/ag-koert

[+] *Autors contributed equally.*

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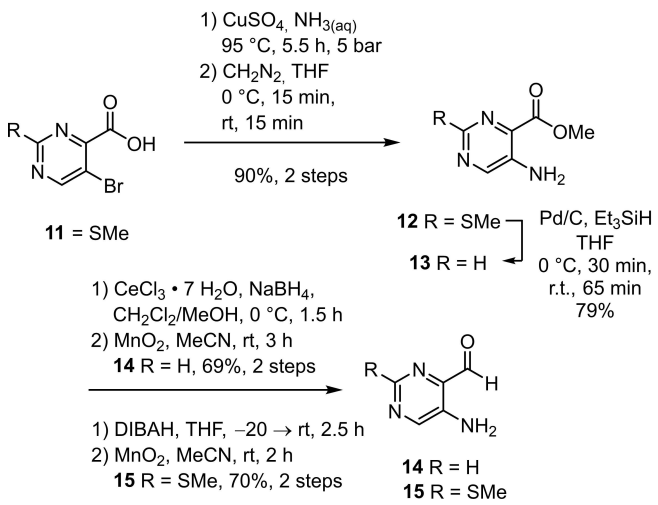
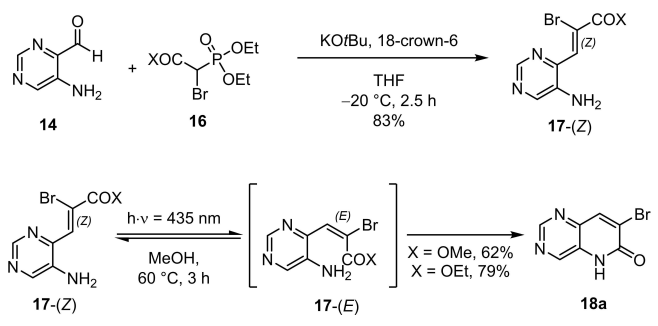
efficient access to substituted pyrido[3,2-*d*]pyrimidines such as **5** and to dimers of type **8**.

## Results and Discussion

Starting point for the synthesis of the aminopyrimidine carbaldehyde moiety **6** was the bromo-pyrimidine carboxylic acid **11** (Scheme 2). With catalytic amounts of copper(II) sulfate in ammonia at 95 °C amination was achieved.[13] Subsequent esterification to methyl ester **12** succeeded with diazomethane. In comparison to esterification with HBTU, DMAP in methanol (2 d, 65 °C, 74%) and an existing protocol [14] shorter reaction times and higher yield were obtained with diazomethane. Optional desulfurization of thioether **12** was adapted from a procedure of Graham[15] and gave pyrimidine **13**. Which was then reduced under Luche conditions to the corresponding alcohol in 85%, whereas reduction of ester **12** to the corresponding alcohol proceeded best with DIBAH. Finally both alcohols underwent oxidation in a convenient manner with manganese dioxide[14] to furnish respective aldehydes **14** in five steps (49%) and **15** in four steps (63%).




**Scheme 2.** Synthesis of aminopyrimidine carbaldehydes **14** and **15**.



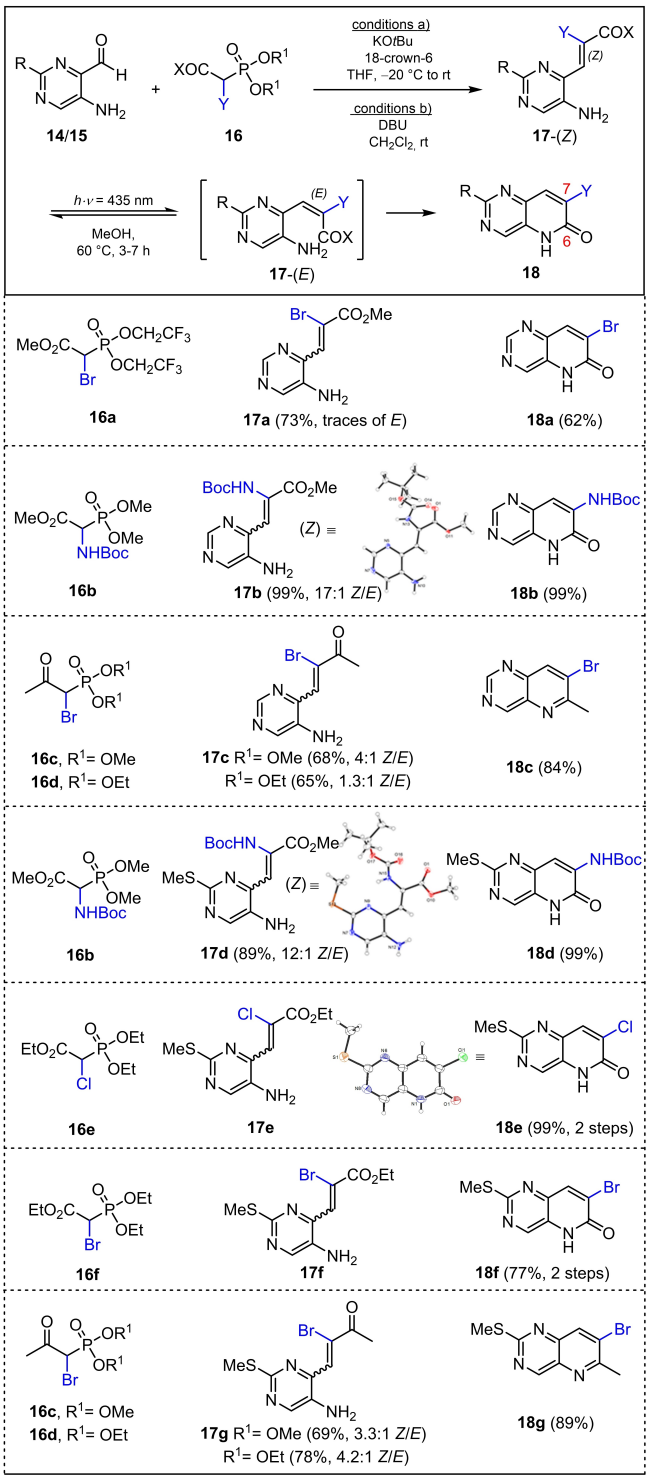

**Scheme 3.** HWE-reaction of aldehyde **14** resulted in *Z*-olefin **17**-(*Z*) which underwent isomerization and condensation to pyridopyrimidine **18a**.

Having the 5-aminopyrimidine carbaldehyde **14** in hand, we investigated its olefination reaction. While ethyl nitroacetate failed to deliver the desired Knoevenagel product, Horner-Wadsworth-Emmons (HWE) reaction with phosphonate **16**[16] resulted in 83% of the *Z*-olefin **17**-(*Z*) (Scheme 3). With an isomerization of the obtained *Z*-olefin to the corresponding *E*-olefin the condensation reaction should be enabled. Earlier work from Horaguchi demonstrated that *E-ortho*-aminocinnamoyl derivatives underwent a light-induced isomerization (400 W high-pressure mercury lamp with Pyrex filter) in advance to intramolecular amidation to 2-quinolones.[17] Guided by this we found optimal conditions for the isomerization in the pyrimidine case (LED 435 nm, MeOH, 60 °C) of the *Z*-isomer **17**-(*Z*) to *E*-isomer **17**-(*E*) and its subsequent spontaneous intramolecular condensation to the pyrido[3,2-*d*]pyrimidine-core **18**.

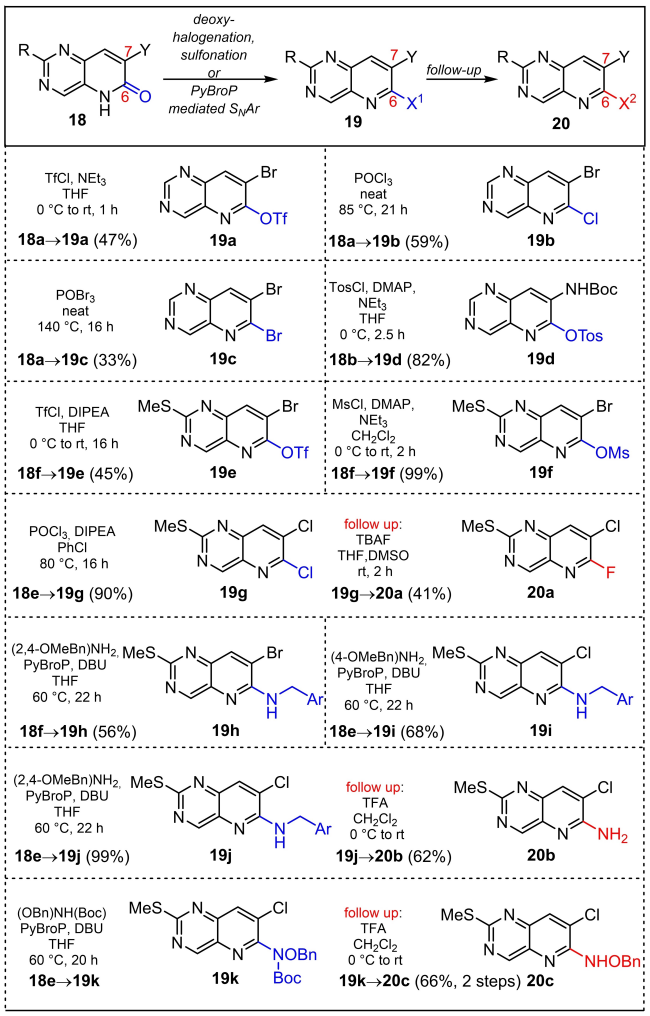
The scope of the HWE reaction of aldehydes **14**/**15** with different phosphonates **16** to alkenes **17** and their subsequent photoisomerization/cyclization to pyrido[3,2-*d*]pyrimidines **18** is summarized in Scheme 4. By modifying the HWE-reaction pendants we were able to aim for various substitution patterns in 6,7-position of the resulting pyridopyrimidines.

The utilization of a Still–Gennari phosphonate **16a**[18] provided **17a**-(*Z*) with traces of **17a**-(*E*) while no direct cyclization to the pyridinone was observed, product **18a** was obtained in the subsequent step. Introduction of an amine moiety succeeded with commercially available phosphonate **16b** in excellent yield. Herein, the condensation product **18b** was already obtained during olefination to **17b**, which led us to the conclusion of receiving a 1:17 *E*/*Z* ratio. In an attempt to obtain a 2-picolin motif (**14**+**16c**/**d**→**18c**) with β-keto-phosphonates[19] we were able to isolate a mixture of the non-cyclized *E*-olefin **17c** and its analogue *Z*-olefin. A significant improvement of solubility and yield was obtained with a thioether incorporated in 2-position of the pyrimidine (**15**+**16b**→**18d**). Commercially available chloro-functionalized phosphonate **16e** expanded the scope of applicable HWE-pendants and gave pyridopyrimidine **18e** in 99% over two steps. Using the bromo-substituted HWE-reagent **16f** the pyridone **18f** was accessible. The β-ketophosphonates **16c**/**d** led to the picolino-pyrimidine **18g**.

With different substituents implemented in the 7-position by usage of the respective phosphonate, we addressed the conversion of pyridone-motifs in 6-position next. Three types of reactions were chosen for examination: deoxyhalogenation, sulfonate formation, and PyBroP mediated $S_NAr$ reaction (Scheme 5). Triflation of the amide proceeded in moderate yield unaffected of the thioether presence (**19a**, **19e**). Neat deoxy-halogenation towards chloride **19b** as well as bromide **19c** was achieved with neat $POCl_3$ and $POBr_3$, respectively. Subsequent fluorination of chloride **19g** with TBAF resulted in fluoride **20a** (41%) and pyridone **18e** (57%) as major side product through hydrolysis. Deoxychlorination of pyridopyrimidine **18f** (Y = Br) exhibited excellent NMR-yield but resulted in an inseparable mixture of the product and a side product which originated from nucleophilic aromatic substitution of the halide in 7-position (not shown). Tosylation of carbamate-containing pyridopyrimidine (**18b**→**19d**) proceeded with selective *O*-




**Scheme 4.** Scope of the HWE-reaction/photoisomerization/cyclization sequence to produce various pyrido[3,2-*d*]pyrimidines **18**. All phosphonates except for carbamate-functionalized phosphonate **16b** (conditions b)), were treated with conditions a).




**Scheme 5.** Functionalization in C6-position of pyridopyrimidones **18** via deoxyhalogenation, sulfonation, or PyBrop mediated $S_NAr$.

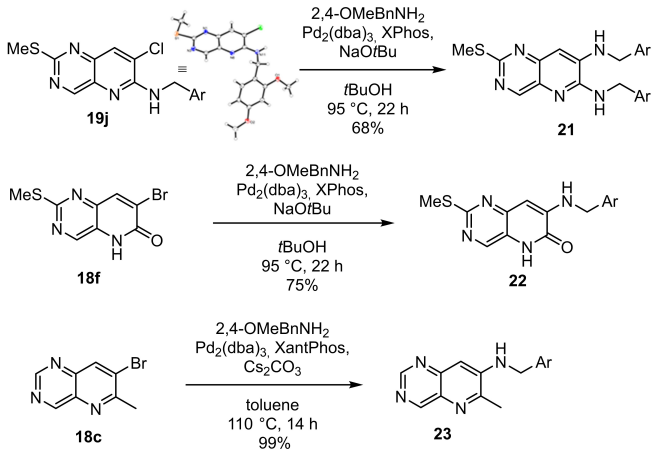
sulfonation in 82% proved by x-ray (see SI). The best result for this type of conversion was obtained by mesylation to sulfonate **19f** in excellent yield.

A direct approach for the introduction of *N*-nucleophiles was realised with the *in situ* generation of a phosphonium leaving group induced by PyBroP.[20] Nucleophilic substitution of **18f** and **18e** provided the 6-amino-pyridopyrimidines **19h**, **19i**, and **19j**. The latter could be debenzylated to **20b**. With (BnO)NH(Boc) the pyridopyrimidine **19k** was produced which could be Boc-deprotected to the hydroxylamine derivative **20c**.

A feasible connection to amino-bridged bis-pyridopyrimidines was primed with the free amine **20b**, which was synthesized by $S_NAr$ with strong nucleophilic, easily soluble and acid labile benzylamine derivative (**18e**→**19j**→**20b**).

Scheme 6 displays viability of the 7-position for palladium-catalyzed Hartwig–Buchwald coupling reactions.

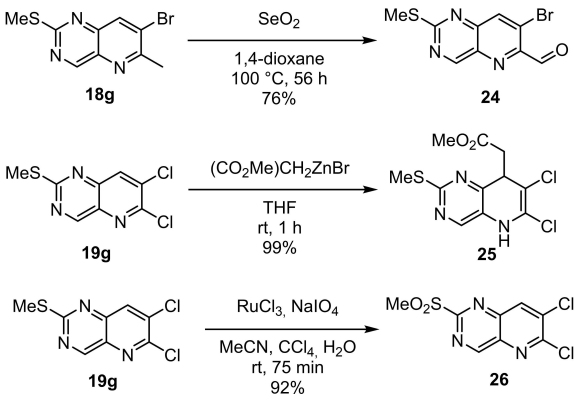
Mono aminated pyridopyrimidine **19j** gave under strongly basic conditions diamino compound **21** in reasonable yield. Conversion of the aryl-bromide **18f** to amine **22** could be achieved, too. Apparently, no further conversion from secondary amine **22** to an amine bridged bis-pyridopyrimidine occurred. The pyridopyrimidine **18c**, which was synthesized




**Scheme 6.** Hartwig–Buchwald coupling enabled amination in 7-position.

from β-keto-phosphonate **16c**/**16d**, also underwent Hartwig–Buchwald coupling to yield amine **23** in very good yield.

On the way to bis-pyridopyrimidines we came across a sample of miscellaneous reactions to pyridopyrimidines **24**–**26** (Scheme 7). Benzylic oxidation of **18g** with selenium dioxide gave the corresponding aldehyde **24** in reasonable yield.




**Scheme 7.** Miscellaneous reactions to valuable building blocks **24**–**26**.

Attempted $S_NAr$ for **19g** with a Reformatski reagent gave surprisingly full conversion to compound **25**. One could anticipate Lewis-acid activation on the pyridine nitrogen through the reagent itself with subsequent vinylogous attack in C8-position. Attempts to introduce this moiety with palladium catalysis led to the same observation.

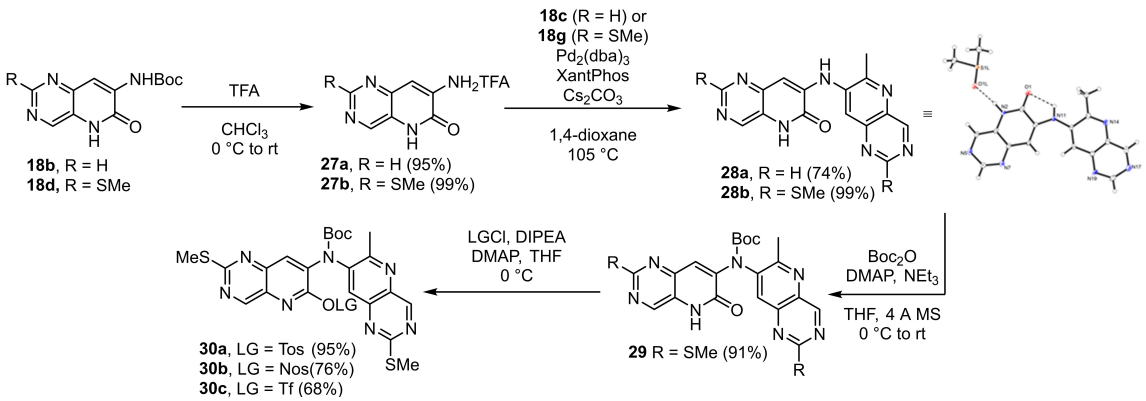
In order to decrease electron density in dichloride **19g** the thioether was oxidized to sulfone **26**.

A primary amino group in the 7 position should be less sterically hindered and therefore exhibits a promising building block for the synthesis of amino-bridged bis-pyridopyrimidines. Towards this end the *N*-Boc group in pyridopyrimidines **18b**/**d** were cleaved to deliver the primary amines as TFA salts **27a**/**b** (Scheme 8). Palladium catalyzed coupling with the respective aryl bromides **18c**/**18g** gave bis-pyridopyrimidines **28a** and **28b**. An X-ray structure of compound **28a** proved unequivocally the structural assignment. The thiomethyl ether group in **28b** increased the solubility and allowed follow up chemistry. *N*-Boc protection of **28b** gave carbamate **29**, which could be converted into various sulfonates **30**.

Due to the modular, mild and chemoselective conversion, the synthetic progress in the pyrido[3,2-*d*]pyrimidine area reported here, displays a valuable addition to the harsh condensation mediated pyrimidine ring synthesis (according to route A, Scheme 1) as default method in medicinal chemistry.[2–5] In contrast to present aldol condensations of 5-aminopyrimidine carbaldehydes to symmetrical ketones, the synthesis of the pyridine herein was enclosed in a regioselective manner and should therefore allow tailored design of novel pharmacophores or functional materials. The demonstrated follow-up conversions can help medicinal and material chemists to get a better understanding of reactivity and selectivity of 6,7-substituted pyrido[3,2-*d*]pyrimidines. Therefore the utilization of pyrido[3,2-*d*]pyrimidines in these fields can be expanded.

## Conclusion

Substituted pyrido[3,2-*d*]pyrimidines are accessible by a reaction sequence consisting of HWE-reaction, a *Z*/*E*-photoisomerization, and ring closure of the pyridine ring. Substituents in the




**Scheme 8.** Access to bis-pyridopyrimidines was enabled by Hartwig-Buchwald coupling of amines **27** with the respective aryl bromide.

7-position can be brought in by substituted HWE-reagents, while substituents in the 6-position are accessible by late stage functionalization of the pyridine substructure. Bis-pyridopyrimidines can be obtained from 7-amino-pyrido[3,2-*d*]pyrimidines.

## Experimental Section

**Crystallographic data**. CCDC 2081819–2081824 contain supplementary crystallographic data for **17b**, **17d**, **19d**, **19j**, **18e** & **28a**.

**General Information**. All anhydrous reactions were carried out using flame-dried glassware under argon atmosphere. All solvents were distilled by rotary evaporation. THF for anhydrous reactions was dried with KOH and subsequently distilled from sodium/benzophenone and from Solvona® respectively. All other solvents employed under anhydrous and/or anaerobic conditions were bought in anhydrous form. All commercially available reagents and reactants were used without further purification unless otherwise noted. Reactions were monitored by thin layer chromatography (TLC) using MERCK Silica Gel 60 F254 and visualized by fluorescence quenching under UV-light. In addition, TLC-plates were stained using a cerium sulfate/phosphomolybdic acid stain or a potassium permanganate stain. Chromatographic purification of products was performed on MACHEREY-NAGEL Silica Gel 60 (230–400 mesh) using a forced flow of eluents. All crude products were adsorbed onto silica by dissolving in an appropriate solvent and removing the solvent under reduced pressure. Concentration under reduced pressure was performed by rotary evaporation at 40 °C and appropriate pressure and by exposing to high vacuum at room temperature if necessary.

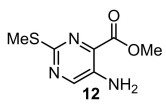
**NMR-Spectroscopy**. NMR-spectra were recorded on a BRUKER AVIII HD250, AVII 300, AVIII HD300, AVIII 500 or AVIII HD500 spectrometer at room temperature unless otherwise mentioned. Chemical shifts are reported in ppm with the solvent resonance as internal standard. All reported $^{19}$F-NMR spectra are proton decoupled $^{19}$F{$^{1}$H}-measurements and referenced to external $CFCl_3$. Data are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, m = multiplet and combination thereof. All correlations of atoms from NMR spectra of new compounds could be achieved via additional 2D-NMR data (HSQC- and HMBC-spectra) which is not shown within these SI. All $^{13}$C{$^{19}$F} spectra were recorded on AVIII 500 equipped with a 5 mm BBO (broadband observation) Cryo probe Prodigy.

**High Resolution Mass Spectrometry**. HR-ESI and APCI mass spectra were acquired with a Finnigan LTQ-FT Ultra mass spectrometer (THERMO FISCHER SCIENTIFIC). EI mass spectra were acquired with an AccuTOF GCv (JEOL) mass spectrometer.

**Infrared Spectroscopy**. FT-IR spectra were recorded on a BRUKER IFS 200 spectrometer. Intensities are reported as follows: s = strong, m = medium, w = weak.

**Melting Points**. Melting points were determined on a MP70 (METTLER TOLEDO) using one end closed capillary tubes.

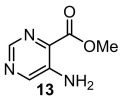
### Methyl 5-amino-2-(methylthio)pyrimidine-4-carboxylate (12)



**12**

Following a modified patent procedure[13] in a pressure vessel carboxylic acid **11** (5.00 g, 20.1 mmol, 1.00 eq) and $CuSO_4$ (150 mg, 602 µmol, 0.03 eq) were dissolved in concentrated ammonia solution (32.0 mL) and heated to 95 °C for 5.5 h during which the pressure increased to 5 bar. The warm reaction mixture was filtered over a pad of celite and activated carbon and rinsed with water (10 mL). The filtrate was cooled to 0 °C and the pH was adjusted to 3 with aqueous HCl (2 M, approx. 250 mL). At a pH value of 7 a yellow solid started to precipitate which reached a greater extent until pH value of 3. The precipitate was filtered and washed with aqueous HCl (0.001 M, 10 mL) and *n*-pentane (10 mL). After evaporation of the residual solvents in fine vacuum the amine was obtained as yellow solid (3.36 g, 18.1 mmol, 90 %). $R_f$ = 0.70 (EtOAc/MeOH 1:1; 1 % AcOH was added). $^{1}$H-NMR (500 MHz, DMSO-d6): $\delta$ = 8.68 (s(br), 2H, N$H_2$), 8.44 (s, 1H, C$H_{arom}$), 2.47 (s, 3H, SC$H_3$) ppm. $^{13}$C-NMR (126 MHz, DMSO-d6): $\delta$ = 167.7 (1 C, *C*OOH), 154.8 (1 C, $C_{arom}$SCH$_3$), 150.3 (1 C, *C*H$_{arom}$), 140.7 (1 C, $C_{arom}$), 131.5 (1 C, $C_{arom}$), 13.6 (1 C, SCH$_3$) ppm. FT-IR: neat; $\tilde{\nu}$ = 3450 (w), 3288 (w), 3156 (w), 2933 (w), 2737 (w), 2622 (w), 2199 (w), 2179 (w), 2139 (w), 2034 (w), 2005 (w), 1965 (w), 1932 (w), 1905 (w), 1674 (s), 1614 (m), 1570 (m), 1537 (w), 1447 (w), 1414 (s), 1338 (w), 1321 (w), 1298 (w), 1230 (s), 1134 (m), 1048 (w), 961 (w), 933 (w), 891 (m), 792 (w), 739 (m), 723 (w), 702 (s) cm$^{-1}$. m.p.: 193 °C (MeOH). HRMS (ESI$^+$): *m/z* calc. for $C_6H_7N_3O_2S_1Na_1$ [M + Na]$^+$: 208.0151, found: 208.0151. The obtained compound (926 mg, 5.00 mmol, 1.00 eq) was then dissolved in THF (12.0 mL) and cooled to 0 °C. An ethereal solution of freshly distilled $CH_2N_2$ (approx. 20 mL, 5.00 mmol, 1.00 eq), which was prepared following literature procedure, was added dropwise.[21] After stirring for 15 min the reaction mixture was allowed to warm to rt and stirred for additional 15 min before glacial acetic acid (3.0 mL) was added slowly. The reaction mixture was poured into saturated aqueous $NaHCO_3$ solution (50 mL) and extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with brine (50 mL), dried over $Na_2SO_4$ and the solvent was evaporated under reduced pressure to obtain compound **12** (997 mg, 5.00 mol, 99 %) as yellow solid. $R_f$ = 0.24 (*n*-pentane/EtOAc 2:1). $^{1}$H-NMR (300 MHz, DMSO-d6): $\delta$ = 8.47 (s, 1H, C$H_{arom}$), 6.54 (s, 2H, N$H_2$), 3.85 (s, 3H, OC$H_3$), 2.46 (s, 3H, SC$H_3$) ppm. $^{13}$C-NMR (75.5 MHz, DMSO-d6): $\delta$ = 166.2 (1 C, *C*OOCH$_3$), 154.9 (1 C, $C_{arom}$), 150.5 (1 C, *C*H$_{arom}$), 140.5 (1 C, $C_{arom}$), 130.6 (1 C, $C_{arom}$), 52.1 (1 C, OCH$_3$), 13.5 (1 C, SCH$_3$) ppm. FT-IR: neat; $\tilde{\nu}$ = 3439 (m), 3283 (m), 3200 (m), 3157 (m), 2992 (w), 2947 (m), 2928 (w), 3851 (w), 2198 (w), 2085 (w), 1998 (w), 1927 (w), 1693 (s), 1609 (s), 1568 (m), 1533 (m), 1442 (s), 1413 (s), 1389 (m), 1346 (m), 1323 (m), 1291 (m), 1222 (s), 1152 (m), 1121 (s), 1048 (m), 971 (m), 931 (m), 885 (m), 814 (m), 738 (s), 709 (s), 662 (s), 562 (w), 465 (m), 432 (m) cm$^{-1}$. m.p.: 124 °C (EtOAc). HRMS (ESI$^+$): *m/z* calc. for $C_7H_9N_3O_2S_1Na_1$ [M + Na]$^+$: 222.0308, found: 222.0308.

### Methyl 5-aminopyrimidine-4-carboxylate (13)

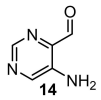


**13**

Methylthiopyrimidine **12** (600 mg, 3.01 mmol, 1.00 eq) and Pd/C (10 wt %, 96.1 mg, 90.0 µmol, 0.03 eq) were suspended in THF (4.70 mL) cooled to 0 °C and $Et_3SiH$ (1.44 mL, 9.04 mmol, 3.00 eq) was added. After 30 min the reaction mixture was allowed to warm to room temperature and stirred for additional 65 min. The reaction was stopped by filtration through a plug of celite and rinsed with EtOAc (100 mL). The solvent was evaporated under reduced pressure and the crude product was purified by column chromatography on silica (EtOAc) to give compound **13** (365 mg, 2.38 mmol, 79 %) as pale yellow solid. The yield is only reproducible in this scale and under exact compliance with these reaction times. $R_f$ = 0.38 (EtOAc). $^{1}$H-NMR (300 MHz, $CDCl_3$): $\delta$ = 8.66 (s, 1H, C$H_{arom}$), 8.42 (s, 1H, C$H_{arom}$), 5.68 (s, 2H, N$H_2$), 4.01 (s, 3H, OC$H_3$) ppm. $^{13}$C-

NMR (75.5 MHz, DMSO-d6): $\delta$ = 166.6 (1 C, *C*OOCH$_3$), 148.8 (1 C, *C*H$_{arom}$), 145.2 (1 C, *C*H$_{arom}$), 143.5 (1 C, *C*$_{arom}$), 129.6 (1 C, *C*$_{arom}$), 52.0 (1 C, OCH$_3$) ppm. FT-IR: neat; $\tilde{\nu}$ = 3552 (w), 3462 (m), 3264 (m), 3197 (m), 3137 (m), 3021 (w), 2952 (m), 2840 (w), 2124 (w), 1936 (w), 1840 (w), 1688 (m), 1608 (s), 1572 (m), 1461 (w), 1425 (s), 1442 (s), 1358 (w), 1327 (s), 1275 (m), 1205 (s), 1116 (s), 1047 (m), 970 (m), 901 (m), 870 (m), 814 (m), 713 (s), 668 (s), 599 (w), 541 (w), 462 (s), 420 (m) cm$^{-1}$. m.p.: 187 °C (EtOAc). HRMS (ESI$^+$): *m/z* calc. for $C_6H_7N_3O_2Na_1$ [M + Na]$^+$: 176.0430, found: 176.0431.

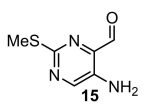
### 5-Aminopyrimidine-4-carbaldehyde (14)



**14**

Pyrimidine ester **13** (590 mg, 3.85 mmol, 1.00 eq) was dissolved in $CH_2Cl_2$ (19.0 mL) and cooled to 0 °C before a solution of $CeCl_3 \bullet 7 H_2O$ (1.46 g, 3.93 mmol, 1.02 eq) in MeOH (19.0 mL) was added slowly. After 15 min $NaBH_4$ (583 mg, 15.4 mmol, 4.00 eq) was added portionwise (gas evolution). The reaction mixture was stirred for 1 h. Aqueous HCl (2 M, approx. 3 mL) was added until gas evolution stopped. All solvents were evaporated under reduced pressure and the crude product was purified by column chromatography on silica ($CHCl_3$/MeOH 9:1 to 8:1) to give the corresponding alcohol (410 mg, 3.28 mmol, 85%) as brown semisolid. $R_f$ = 0.20 ($CHCl_3$/MeOH 10:1). $^1$H-NMR (300 MHz, DMSO-d6): $\delta$ = 8.33 (s, 1H, C*H*$_{arom}$), 8.08 (s, 1H, C*H*$_{arom}$), 5.39 (s, 2H, N*H*$_2$), 5.29 (t, J = 4.2 Hz, 1H, O*H*), 4.49 (d, J = 4.0 Hz, 2H, C*H*$_2$) ppm. $^{13}$C-NMR (75.5 MHz, DMSO-d6): $\delta$ = 150.4 (1 C, *C*$_{arom}$), 146.3 (1 C, *C*H$_{arom}$), 141.9 (1 C, *C*H$_{arom}$), 140.4 (1 C, *C*$_{arom}$), 62.4 (1 C, *C*H$_2$) ppm. FT-IR: neat; $\tilde{\nu}$ = 3332 (s), 3222 (s), 2842 (m), 2409 (w), 2195 (w), 2153 (w), 1738 (w), 1641 (m), 1574 (m), 1444 (m), 1411 (s), 1337 (m), 1261 (m), 1199 (m), 1141 (m), 1054 (s), 894 (m), 796 (w), 729 (m), 633 (m), 544 (m), 504 (m) cm$^{-1}$. m.p.: 159 °C decomposition (MeOH). HRMS (ESI$^+$): *m/z* calc. for $C_5H_7N_3O_1Na_1$ [M + Na]$^+$: 148.0492, found: 148.0481. The obtained pyrimidine alcohol (50.0 mg, 400 µmol, 1.00 eq) was then dissolved in MeCN (8.00 mL) and $MnO_2$ (347 mg, 4.00 mmol, 10.0 eq) was added. The reaction mixture was stirred for 3 h at rt. before it was filtered over a pad of celite and rinsed with EtOAc (approx. 10 mL) until the filtrate turned colorless. The solvent was evaporated under reduced pressure. Due to decomposition during column chromatography the crude product was used without further purification. Compound **14** (40.0 mg, 324 µmol, 81%) was isolated as pale yellow solid. $R_f$ = 0.62 (EtOAc). $^1$H-NMR (500 MHz, $CDCl_3$): $\delta$ = 10.06 (s, 1H, C*H*O), 8.72 (s, 1H, C*H*$_{arom}$), 8.45 (s, 1H, C*H*$_{arom}$), 5.91 (s, 2H, N*H*$_2$) ppm. $^{13}$C-NMR (75 MHz, DMSO-d6): $\delta$ = 195.9 (1 C, *C*HO), 149.3 (1 C, *C*H$_{arom}$), 145.8 (1 C, *C*H$_{arom}$), 142.0 (1 C, *C*$_{arom}$), 134.5 (1 C, *C*$_{arom}$) ppm. FT-IR: neat; $\tilde{\nu}$ = 3407 (m), 3285 (w), 3149 (m), 2878 (w), 2670 (w), 2083 (w), 1833 (w), 1689 (m), 1624 (s), 1572 (w), 1463 (w), 1424 (s), 1351 (w), 1299 (w), 1266 (w), 1181 (s), 1057 (m), 891 (s), 797 (w), 772 (m), 746 (w), 665 (s), 600 (w), 554 (w), 475 (s) cm$^{-1}$. m.p.: 174 °C (EtOAc). HRMS (ESI$^+$): *m/z* calc. for $C_6H_9N_3O_2H_1$ [M + H]$^+$: 156.0768, found: 156.0766.

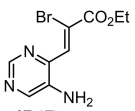
### 5-Amino-2-(methylthio)pyrimidine-4-carbaldehyde (15)



**15**

Pyrimidine ester **12** (100 mg, 500 µmol, 1.00 eq) was dissolved in THF (1.40 mL) and cooled to –20 °C before DIBAH (1 M in THF, 1.05 mL, 1.05 mmol, 2.10 eq) was added dropwise. The deep red reaction mixture was stirred for 2.5 h during which it warmed up to 10 °C. It was then cooled back to 0 °C before additional DIBAH (1 M in THF, 0.25 mL, 0.25 mmol, 0.50 eq) was added. After 1 h aqueous HCl (2 M, approx. 5 mL) was added and extracted with EtOAc (20 mL). The organic phase was discarded, while the aqueous phase was added saturated aqueous $NaHCO_3$ solution (15 mL) and extracted with EtOAc (3×20 mL). The combined organic layers were washed with brine (20 mL), dried over $Na_2SO_4$ and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography on silica (*n*-pentane/EtOAc 1:1 to EtOAc) to give the alcohol (76.0 mg, 440 µmol, 88%) as yellow solid. $R_f$ = 0.41 ($CHCl_3$/MeOH 8:1); $R_f$ = 0.25 (*n*-pentane/EtOAc 1:1). $^1$H-NMR (500 MHz, DMSO-d6): $\delta$ = 8.03 (s, 1H, C*H*$_{arom}$), 5.31 (t, J = 5.8 Hz, 1H, O*H*), 5.16 (s, 2H, N*H*$_2$), 4.45 (d, J = 5.9 Hz, 2H, C*H*$_2$), 2.43 (s, 3H, SC*H*$_3$) ppm. $^{13}$C-NMR (126 MHz, DMSO-d6): $\delta$ = 155.9 (1 C, *C*$_{arom}$SCH$_3$), 152.5 (1 C, *C*$_{arom}$), 143.5 (1 C, *C*H$_{arom}$), 137.1 (1 C, *C*$_{arom}$), 62.4 (1 C, *C*H$_2$), 13.6 (1 C, SCH$_3$) ppm. FT-IR: neat; $\tilde{\nu}$ = 3447 (w), 3410 (w), 3310 (w), 3204 (m), 2921 (w), 2835 (w), 2717 (w), 2607 (w), 2116 (w), 1865 (w), 1644 (m), 1578 (w), 1552 (m), 1458 (w), 1418 (m), 1368 (s), 1314 (w), 1280 (w), 1233 (w), 1207 (w), 1167 (w), 1090 (w), 1058 (w), 1036 (m), 993 (w), 970 (w), 918 (m), 786 (w), 752 (w), 724 (w), 661 (m), 577 (m), 475 (m) cm$^{-1}$. m.p.: 108 °C (MeOH). HRMS (ESI$^+$): *m/z* calc. for $C_6H_9N_3O_1S_1Na_1$ [M + Na]$^+$: 194.0359, found: 194.0359. The obtained pyrimidine alcohol (802 mg, 4.68 mmol, 1.00 eq) was dissolved in MeCN (80.0 mL) and $MnO_2$ (4.07 g, 46.8 mmol, 10.0 eq) was added. The reaction mixture was stirred for 2 h at rt before it was filtered over a pad of celite and rinsed with EtOAc (approx. 50 mL) until the filtrate turned colorless. The solvent was evaporated under reduced pressure. Due to decomposition during column chromatography the crude product was used without further purification. Compound **15** (626 mg, 3.70 mmol, 80%) was isolated as highly yellow solid. $R_f$ = 0.79 (EtOAc). $^1$H-NMR (500 MHz, $CDCl_3$): $\delta$ = 10.02 (d, J = 0.7 Hz, 1H, C*H*O), 8.35 (d, J = 0.7 Hz, 1H, C*H*$_{arom}$), 5.68 (s, 2H, N*H*$_2$), 2.59 (s, 3H, SC*H*$_3$) ppm. $^{13}$C-NMR (75 MHz, DMSO-d6): $\delta$ = 195.2 (1 C, *C*HO), 155.4 (1 C, *C*$_{arom}$SCH$_3$), 151.1 (1 C, *C*H$_{arom}$), 139.2 (1 C, *C*$_{arom}$), 135.4 (1 C, *C*$_{arom}$), 13.6 (1 C, SCH$_3$) ppm. FT-IR: neat; $\tilde{\nu}$ = 3416 (m), 3273 (m), 3198 (w), 3159 (w), 2928 (w), 2838 (w), 2711 (w), 2083 (w), 1853 (w), 1668 (m), 1615 (s), 1566 (m), 1477 (w), 1415 (s), 1401 (w), 1313 (w), 1283 (w), 1186 (m), 1147 (s), 1055 (w), 969 (w), 930 (w), 902 (m), 775 (m), 760 (w), 735 (w), 719 (m), 644 (m), 460 (m), 438 (w), 413 (w) cm$^{-1}$. m.p.: 137 °C (EtOAc). HRMS (ESI$^+$): *m/z* calc. for $C_6H_7N_3O_1S_1Na_1$ [M + Na]$^+$: 192.0202, found: 192.0202.

### Ethyl (*Z*)-3-(5-aminopyrimidin-4-yl)-2-bromoacrylate (17-(*Z*))

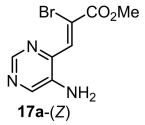


**17**-(*Z*)

Phosphonate **16** (X = OEt, 515 mg, 1.70 mmol, 1.10 eq) and 18-crown-6 (494 mg, 1.85 mmol, 1.20 eq) were dissolved in THF (15.0 mL) and cooled to –20 °C. KO*t*Bu (186 mg, 1.62 mmol, 1.05 eq) was added portionwise. After 30 min aldehyde **14** (190 mg, 1.54 mmol, 1.00 eq) was added as solid and the resulting deep brown reaction mixture was stirred for 2.5 h while reaching 0 °C. The reaction mixture was poured into saturated aqueous $NH_4Cl$ solution (15 mL) and extracted with EtOAc (3×20 mL). The combined organic layers were washed with brine (30 mL), dried over $Na_2SO_4$ and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography on silica ($CHCl_3$/MeOH 10:1) to give exclusively **17**-(*Z*) (348 mg, 1.28 mmol, 83%) as yellow solid. $R_f$ = 0.20 (*n*-pentane/

EtOAc 1:2). $^1$H-NMR (500 MHz, $CDCl_3$): $\delta = 8.73$ (s, 1H, $CH_{arom}$), 8.30 (s, 1H, $CH_{arom}$), 8.14 (s, 1H, $CH_{olef}$), 4.37 (q, $J = 7.1$ Hz, 2H, $CH_2CH_3$), 3.89 (s, 2H, $NH_2$), 1.39 (t, $J = 7.1$ Hz, 3H, $CH_2CH_3$) ppm. $^{13}$C-NMR (126 MHz, $CDCl_3$): $\delta = 162.2$ (1 C, *C*OOEt), 149.2 (1 C, $CH_{arom}$), 145.4 (1 C, $CH_{arom}$), 144.5 (1 C, $C_{arom}$), 138.2 (1 C, $C_{arom}$), 135.0 (1 C, $CH_{olef}$), 121.0 (1 C, $CBr_{olef}$), 63.5 (1 C, $CH_2CH_3$), 14.3 (1 C, $CH_2CH_3$) ppm. FT-IR: neat; $\tilde{\nu} = 3434$ (w), 3321 (w), 3196 (m), 2972 (w), 2853 (w), 2719 (w), 2107 (w), 1899 (w), 1714 (s), 1647 (w), 1569 (w), 1537 (m), 1449 (w), 1411 (s), 1365 (w), 1343 (w), 1300 (w), 1280 (w), 1248 (s), 1209 (w), 1183 (w), 1166 (w), 1120 (w), 1092 (w), 1023 (s), 968 (w), 904 (m), 860 (w), 831 (w), 798 (w), 769 (w), 744 (w), 726 (w) cm$^{-1}$. m.p.: 80 °C (EtOAc). HRMS (ESI$^+$): *m/z* calc. for $C_9H_{10}Br_1N_3O_2H_1$ $[M+H]^+$: 272.0029 & 274.0009, found: 272.0030 & 274.0010.

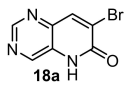
### Methyl (*Z*)-3-(5-aminopyrimidin-4-yl)-2-bromoacrylate (17 a-(*Z*))



**17a**-(*Z*)

Phosphonate **16 a** (99.2 mg, 250 μmol, 1.10 eq) and 18-crown-6 (72.7 mg, 272 μmol, 1.20 eq) were dissolved in THF (2.00 mL) and cooled to −20 °C. KO*t*Bu (27.3 mg, 238 μmol, 1.05 eq) was added portionwise. After 30 min aldehyde **14** (30.0 mg, 227 μmol, 1.00 eq) was added as solid and the resulting deep brown reaction mixture was stirred for 25 min. The reaction mixture was poured into saturated aqueous $NH_4Cl$ solution (5 mL) and extracted with EtOAc (3×10 mL). The combined organic layers were washed with brine (10 mL), dried over $Na_2SO_4$ and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography on silica (*n*-pentane/EtOAc 1:2) to give a mixture of **17 a**-(*Z*) (43.0 mg, 167 μmol, 73 %) and traces of **17 a**-(*E*) as yellow solid. Data for pure **17 a**-(*Z*): $R_f = 0.16$ (*n*-pentane/EtOAc 1:2). $^1$H-NMR (500 MHz, $CDCl_3$): $\delta = 8.75$ (s, 1H, $CH_{arom}$), 8.31 (s, 1H, $CH_{arom}$), 8.15 (s, 1H, $CH_{olef}$), 3.93 (s, 3H, $CH_3$), 3.89 (s, 2H, $NH_2$) ppm. $^{13}$C-NMR (126 MHz, $CDCl_3$): $\delta = 162.8$ (1 C, *C*OOMe), 149.2 (1 C, $CH_{arom}$), 145.4 (1 C, $CH_{arom}$), 144.4 (1 C, $C_{arom}$), 138.2 (1 C, $C_{arom}$), 135.2 (1 C, $CH_{olef}$), 120.3 (1 C, $CBr_{olef}$), 54.1 (1 C, $CH_3$) ppm. FT-IR: neat; $\tilde{\nu} = 3584$ (w), 3410 (m), 3326 (w), 3181 (w), 3018 (w), 2955 (w), 2923 (w), 2853 (w), 2718 (w), 2120 (w), 1894 (w), 1716 (m), 1655 (s), 1593 (w), 1568 (w), 1535 (m), 1449 (w), 1413 (s), 1347 (w), 1295 (w), 1254 (s), 1213 (w), 1184 (w), 1127 (w), 1076 (w), 1029 (m), 1004 (w), 952 (w), 935 (w), 898 (m), 828 (w), 766 (w), 736 (m) cm$^{-1}$. m.p.: 159 °C decomposition (EtOAc). HRMS (ESI$^+$): *m/z* calc. for $C_8H_8Br_1N_3O_2H_1$ $[M+H]^+$: 257.9873 & 259.9853, found: 257.9875 & 259.9855.

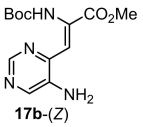
### 7-Bromopyrido[3,2-*d*]pyrimidin-6(5*H*)-one (18 a)



**18a**

Pyrimidine **17**-(*Z*) (210 mg, 814 μmol, 1.00 eq) or pyrimidine **17 a**-(*Z*) (52.0 mg, 201 μmol, 1.00 eq) was dissolved in MeOH (5 mM respectively) and heated to 60 °C for 3 h under irradiation of light ($\lambda = 435$ nm). All solvents were evaporated under reduced pressure and the crude product was purified by column chromatography on silica (EtOAc) to give compound **18 a** (28.0 mg, 124 μmol, 62 % for **17 a**-(*Z*) or 145 mg, 642 μmol, 79 % for **17**-(*Z*)) as pale brownish solid. $R_f = 0.33$ (EtOAc). $^1$H-NMR (500 MHz, DMSO-d6): $\delta = 12.68$ (s, 1H, N*H*), 9.03 (s, 1H, $CH_{arom}$), 8.85 (s, 1H, $CH_{arom}$), 8.53 (s, 1H, $CH_{arom}$) ppm. $^{13}$C-NMR (126 MHz, $CDCl_3$): $\delta = 156.8$ (1 C, NCO), 152.3 (1 C, $CH_{arom}$), 145.6 (1 C, $CH_{arom}$), 141.1 (1 C, $CH_{arom}$), 140.4 (1 C, $C_{arom}$), 131.7 (1 C, $C_{arom}$), 128.3 (1 C, $CBr_{arom}$) ppm. FT-IR: neat; $\tilde{\nu} = 3312$ (w), 3151 (w), 3000 (w), 2901 (w), 2830 (w), 2749 (m), 1931 (w), 1894 (w), 1758 (w), 1653 (s), 1588 (w), 1478 (w), 1443 (w), 1399 (m), 1354 (w), 1308 (w), 1216 (w), 1181 (m), 1155 (w), 1110 (w), 998 (m), 951 (w), 915 (w), 891 (s), 824 (w), 742 (m), 638 (m), 580 (s), 460 (m) cm$^{-1}$. m.p.: 231 °C decomposition (EtOAc). HRMS (APCI$^+$): *m/z* calc. for $C_7H_4Br_1N_3O_1H_1$ $[M+H]^+$: 225.9611 & 227.9590, found: 225.9612 & 227.9592.

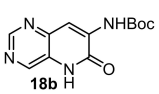
### Methyl (*Z*)-3-(5-aminopyrimidin-4-yl)-2-((tert-butoxycarbonyl) amino)-acrylate (17 b-(*Z*))



**17b**-(*Z*)

Phosphonate **16 b** (244 mg, 804 μmol, 1.10 eq) was dissolved in $CH_2Cl_2$ (1.75 mL) and DBU (116 μL, 768 μmol, 1.05 eq) was added. After stirring for 5 min the solution was given to a solution of pyrimidine carbaldehyde **14** (90.0 mg, 731 μmol, 1.00 eq) in $CH_2Cl_2$ (3.00 mL). The highly fluorescent yellow reaction mixture was stirred for 7 h at rt before it was poured into saturated aqueous $NH_4Cl$ solution (5 mL) and extracted with EtOAc (3×10 mL). The combined organic layers were washed with brine (10 mL), dried over $Na_2SO_4$ and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography on silica (*n*-pentane/EtOAc 1:2) to give a mixture of **17 b**-(*Z*) and the cyclized compound **18 b** which comes from *in situ* cyclisation of **17 b**-(*E*) (overall 223 mg, 99 %) as highly yellow solid. The ratio of **17 b**-(*Z*) to pyridopyrimidine **18 b** is 16.8:1 which should reflect the *Z*/*E* ratio during the reaction. Data for pure **17 b**-(*Z*): $R_f = 0.30$ (*n*-pentane/EtOAc 1:2). $^1$H-NMR (600 MHz, $CDCl_3$): $\delta =$ 10.74 (s, 1H, N*H*Boc) 8.65 (s, 1H, $CH_{arom}$), 8.18 (s, 1H, $CH_{arom}$), 6.05 (s, 1H, $CH_{olef}$), 3.88 (s, 3H, $CH_3$), 3.83 (s, 2H, $NH_2$), 1.49 (s, 9H, $C(CH_3)_3$) ppm. $^{13}$C-NMR (75.5 MHz, $CDCl_3$): $\delta = 165.8$ (1 C, *C*OOMe), 152.3 (*C*NHBoc), 148.6 (1 C, $CH_{arom}$), 146.5 (1 C, $C_{arom}$), 144.4 (1 C, $CH_{arom}$), 137.6 (1 C, $C_{arom}$), 137.5 (1 C, N(*C*O)O), 103.5 (1 C, $CH_{olef}$), 81.5 (1 C, $C(CH_3)_3$), 52.9 ($CH_3$), 28.3 (3 C, $C(CH_3)_3$) ppm. FT-IR: neat; $\tilde{\nu} = 3460$ (m), 3373 (m), 3258 (w), 3070 (w), 3003 (w), 2979 (w), 2951 (w), 1727 (w), 1706 (s), 1648 (w), 1629 (m), 1562 (w), 1545 (m), 1437 (s), 1411 (w), 1369 (w), 1335 (w), 1300 (m), 1277 (w), 1243 (m), 1210 (w), 1151 (s), 1061 (m), 1033 (w), 987 (w), 905 (w), 879 (w), 850 (w), 810 (m), 777 (w), 753 (m), 718 (w), 669 (w) cm$^{-1}$. m.p.: 205 °C decomposition ($CHCl_3$). HRMS (ESI$^+$): *m/z* calc. for $C_{13}H_{18}N_4O_4H_1$ $[M+H]^+$: 295.1401, found: 295.1402.

### *tert*-Butyl (6-oxo-5,6-dihydropyrido[3,2-*d*]pyrimidin-7-yl) carbamate (18 b)

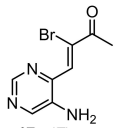


**18b**

Pyrimidine **17 b**-(*Z*) (665 mg, 2.26 mmol, 1.00 eq) was dissolved in MeOH (90.0 mL) and heated to 65 °C for 5.5 h under irradiation of light ($\lambda = 435$ nm). All solvents were evaporated under reduced pressure and the crude product was purified by column chromatography on silica (EtOAc/MeOH 10:1) to give compound **18 b** (590 mg, 2.25 μmol, 99 %) as pale yellow solid. $R_f = 0.22$ (*n*-pentane/EtOAc 1:3). $^1$H-NMR (500 MHz, DMSO-d6): $\delta = 12.64$ (s, 1H, N*H*), 8.94 (s, 1H, $CH_{arom}$), 8.71 (s, 1H, $CH_{arom}$), 8.41 (s, 1H, N*H*$CO_2t$Bu), 8.13 (s, 1H, $CH_{arom}$), 1.50 (s, 9H, $C(CH_3)_3$) ppm. $^{13}$C-NMR (126 MHz, DMSO-d6): $\delta =$

156.1 (1 C, NCO), 152.7 (1 C, $CH_{arom}$), 151.8 (1 C, $C_{arom}$), 143.7 (1 C, $CH_{arom}$), 142.8 (1 C, $CO_2NH$), 136.6 (1 C, $C_{arom}$), 127.3 (1 C, $C_{arom}$), 115.2 (1 C, $CH_{arom}$), 81.4 (1 C, $C(CH_3)_3$), 27.8 (3 C, $C(CH_3)_3$) ppm. FT-IR: neat; $\tilde{\nu}$ = 3390 (w), 3310 (w), 2972 (w), 2940 (w), 2851 (w), 1734 (m), 1649 (s), 1611 (w), 1590 (w), 1559 (w), 1506 (s), 1451 (w), 1369 (m), 1303 (w), 1253 (m), 1192 (w), 1145 (s), 1032 (s), 948 (w), 926 (w), 898 (m), 850 (m), 787 (w), 762 (w), 705 (m), 635 (w), 610 (m), 591 (w), 521 (w), 463 (w), 439 (w) $cm^{-1}$. m.p.: 331 °C decomposition ($CHCl_3$). HRMS ($ESI^+$): *m/z* calc. for $C_{12}H_{14}N_4O_3H_1$ $[M+H]^+$: 263.1139, found: 263.1140.

### (*Z*)-4-(5-Aminopyrimidin-4-yl)-3-bromobut-3-en-2-one (17 c-(*Z*))



**17c**-(*Z*)

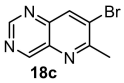
Compound **17 c**-(*Z*) was synthesized starting from phosphonate **16 c** or phosphonate **16 d**.

Phosphonate **16 c** (442 mg, 1.80 mmol, 1.15 eq) and 18-crown-6 (502 mg, 1.88 mmol, 1.20 eq) were dissolved in THF (15.0 mL) and cooled to −20 °C. KO*t*Bu (189 mg, 1.65 mmol, 1.05 eq) was added portionwise. After 15 min aldehyde **14** (193 mg, 1.57 mmol, 1.00 eq) in THF (15.0 mL) was added dropwise. The resulting deep orange to brown reaction mixture was stirred for 16 h while reaching rt. The reaction mixture was poured into saturated aqueous $NH_4Cl$ solution (20 mL) and extracted with EtOAc (3×40 mL). The combined organic layers were washed with brine (40 mL), dried over $Na_2SO_4$ and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography on silica (*n*-pentane/EtOAc 1:2) to give a 4:1 mixture of **17 c**-(*Z*) to **17 c**-(*E*) (overall: 258 mg, 1.07 mmol, 68 %) as orange solid.

Or:

Phosphonate **16 d** (476 mg, 1.74 mmol, 1.43 eq) and 18-crown-6 (390 mg, 1.46 mmol, 1.20 eq) were dissolved in THF (10.0 mL) and cooled to −20 °C. KO*t*Bu (147 mg, 1.28 mmol, 1.05 eq) was added portionwise. After 15 min aldehyde **14** (150 mg, 1.22 mmol, 1.00 eq) in THF (10.0 mL) was added dropwise. The resulting deep orange to brown reaction mixture was stirred for 16 h while reaching rt. The reaction mixture was poured into saturated aqueous $NH_4Cl$ solution (20 mL) and extracted with EtOAc (3×40 mL). The combined organic layers were washed with brine (40 mL), dried over $Na_2SO_4$ and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography on silica (*n*-pentane/EtOAc 1:2) to give a 1.3:1 mixture of **17 c**-(*Z*) to **17 c**-(*E*) (overall: 192 mg, 793 µmol, 65 %) as orange solid. Data for **17 c**-(*Z*): $R_f$ = 0.38 (*E*) & 0.29 (*Z*) (EtOAc). $^1$H-NMR (500 MHz, $CDCl_3$): $\delta$ = 8.74 (s, 1H, $CH_{arom}$), 8.32 (s, 1H, $CH_{arom}$), 7.96 (s, 1H, $CH_{olef}$), 3.93 (s, 2H, $NH_2$), 2.63 (s, 3H, $CH_3$) ppm. $^{13}$C-NMR (126 MHz, $CDCl_3$): $\delta$ = 192.8 (1 C, CO), 149.0 (1 C, $CH_{arom}$), 145.4 (1 C, $CH_{arom}$), 144.6 (1 C, $C_{arom}$), 138.3 (1 C, $C_{arom}$), 133.2 (1 C, $CH_{olef}$), 129.4 (1 C, $CBr_{arom}$), 27.3 (1 C, $CH_3$) ppm. FT-IR: neat; $\tilde{\nu}$ = 3001 (m), 3326 (w), 3200 (m), 3008 (w), 2920 (w), 1837 (w), 1683 (m), 1647 (m), 1610 (m), 1564 (m), 1541 (m), 1487 (m), 1461 (m), 1415 (w), 1358 (w), 1335 (s), 1304 (m), 1275 (w), 1247 (w), 1216 (s), 1191 (m), 1125 (m), 1062 (w), 1012 (m), 979 (m), 943 (m), 910 (w), 848 (m), 826 (m), 804 (m), 777 (w), 757 (w), 715 (w), 674 (w), 642 (w), 619 (m), 565 (m), 463 (w), 439 (w) $cm^{-1}$. m.p.: 125 °C decomposition (EtOAc). HRMS ($ESI^+$): *m/z* calc. for $C_8H_8Br_1N_3O_1H_1$ $[M+H]^+$: 241.9924, found: 241.9924.

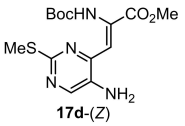
### 7-Bromo-6-methylpyrido[3,2-*d*]pyrimidine (18 c)



**18c**

Pyrimidine **17 c**-(*Z*) (254 mg, 863 µmol, 1.00 eq) was dissolved in MeOH (180 mL) and heated to 60 °C for 3.5 h under irradiation of light (λ = 435 nm). All solvents were evaporated under reduced pressure and the crude product was purified by column chromatography on silica (*n*-pentane/EtOAc 1:1 to 1:2) to give compound **18 c** (162 mg, 723 µmol, 84 %) as pale brownish solid. $R_f$ = 0.66 (EtOAc). $^1$H-NMR (500 MHz, $CDCl_3$): $\delta$ = 9.54 (s, 1H, $CH_{arom}$), 9.34 (s, 1H, $CH_{arom}$), 8.54 (s, 1H, $CH_{arom}$), 2.92 (s, 3H, $CH_3$) ppm. $^{13}$C-NMR (126 MHz, $CDCl_3$): $\delta$ = 161.1 (1 C, $NCCH_3$), 161.0 (1 C, $CH_{arom}$), 155.9 (1 C, $CH_{arom}$), 145.9 (1 C, $C_{arom}$), 139.0 (1 C, $CH_{arom}$), 138.6 (1 C, $C_{arom}$), 127.3 (1 C, $CBr_{arom}$), 26.2 (1 C, $CH_3$) ppm. FT-IR: neat; $\tilde{\nu}$ = 3204 (w), 3051 (w), 2924 (w), 2532 (w), 2396 (w), 2336 (w), 2151 (w), 1985 (w), 1913 (w), 1858 (w), 1688 (w), 1588 (w), 1565 (m), 1547 (w), 1493 (w), 1452 (w), 1435 (w), 1401 (s), 1376 (w), 1351 (w), 1318 (w), 1281 (w), 1251 (w), 1220 (w), 1169 (w), 1082 (m), 1028 (w), 977 (s), 939 (m), 916 (w), 794 (w), 722 (w), 676 (s) $cm^{-1}$. m.p.: 134 °C (EtOAc). HRMS ($ESI^+$): *m/z* calc. for $C_8H_6Br_1N_3H_1$ $[M+H]^+$: 223.9818 & 225.9797, found: 223.9818 & 225.9798.

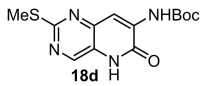
### Methyl (*Z*)-3-(5-amino-2-(methylthio) pyrimidin-4-yl)-2-((tert-butoxy-carbonyl)amino)acrylate (17 d-(*Z*))



**17d**-(*Z*)

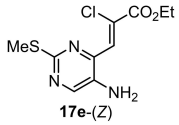
Phosphonate **16 b** (592 mg, 1.95 mmol, 1.10 eq) was dissolved in $CH_2Cl_2$ (20.0 mL) and DBU (283 µL, 1.86 mmol, 1.05 eq) was added. After stirring for 5 min the solution was given to a solution of pyrimidine carbaldehyde **15** (300 mg, 1.77 mmol, 1.00 eq) in $CH_2Cl_2$ (15.0 mL). The highly fluorescent yellow reaction mixture was stirred for 1 h at rt before it was poured into saturated aqueous $NH_4Cl$ solution (30 mL) and extracted with $CHCl_3$ (3×30 mL). The combined organic layers were washed with brine (30 mL), dried over $Na_2SO_4$ and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography on silica (*n*-pentane/EtOAc 2:1 to 1:1) to give a mixture of **17 d**-(*Z*) (494 mg, 1.45 mmol, 82 %) and the cyclized compound **18 d** (38.0 mg, 123 mmol, 7 %) which comes from *in situ* cyclisation of **17 d**-(*E*) (overall 89 %) both as highly yellow solid. The ratio of **17 d**-(*Z*) to pyridopyrimidine **18 d** is 11.7:1 which should reflect the *Z*/*E* ratio during the reaction. Data for pure **17 d**-(*Z*): $R_f$ = 0.53 (*n*-pentane/EtOAc 1:2). $^1$H-NMR (500 MHz, $CDCl_3$): $\delta$ = 10.88 (s, 1H, $NHCO_2tBu$), 8.12 (s, 1H, $CH_{arom}$), 6.03 (s, 1H, $CH_{olef}$), 3.89 (s, 3H, $CO_2CH_3$), 2.80 (s, 2H, $NH_2$), 2.59 (s, 3H, $SCH_3$), 1.49 (s, 9H, $C(CH_3)_3$) ppm. $^{13}$C-NMR (126 MHz, $CDCl_3$): $\delta$ = 165.5 (1 C, $CO_2CH_3$), 160.2 (1 C, $C_{arom}SCH_3$), 151.9 (1 C, $CO_2NH$), 148.2 (1 C, $C_{arom}$), 145.6 (1 C, $CH_{arom}$), 137.8 (1 C, $C_{arom}$), 134.1 (1 C, $C_{arom}$), 103.0 (1 C, $CH_{olef}$), 82.0 (1 C, $C(CH_3)_3$), 53.0 (1 C, $CO_2CH_3$), 28.2 (3 C, $C(CH_3)_3$), 14.7 (1 C, $SCH_3$) ppm. FT-IR: neat; $\tilde{\nu}$ = 3451 (w), 3367 (m), 3251 (w), 2983 (w), 2927 (w), 1729 (w), 1706 (s), 1644 (w), 1623 (w), 1557 (w), 1539 (w), 1457 (w), 1432 (w), 1396 (s), 1369 (w), 1291 (m), 1248 (w), 1225 (m), 1133 (s), 1083 (w), 1062 (w), 1032 (w), 982 (w), 962 (w), 938 (w), 872 (w), 848 (w), 810 (m), 774 (m), 753 (w), 714 (w), 667 (w), 636 (w), 605 (w), 557 (w), 492 (w) $cm^{-1}$. m.p.: 175 °C (EtOAc). HRMS ($ESI^+$): *m/z* calc. for $C_{14}H_{20}N_4O_4S_1Na_1$ $[M+Na]^+$: 363.1097, found: 363.1098.

### *tert*-Butyl (2-(methylthio)-6-oxo-5,6-dihydropyrido[3,2-*d*] pyrimidin-7-yl)carbamate (18 d)



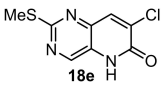

Pyrimidine **17 d**-(*Z*) (48.0 mg, 140 μmol, 1.00 eq) was dissolved in MeOH (7.00 mL) and heated to 60 °C for 2 h under irradiation of light (λ = 435 nm). All solvents were evaporated under reduced pressure and the crude product was purified by column chromatography on silica (*n*-pentane/EtOAc 1:1 to 1:2) to give compound **18 d** (42.0 mg, 140 μmol, 99 %) as yellow solid. $R_f$ = 0.70 (*n*-pentane/EtOAc 1:2). $^1$H-NMR (500 MHz, $CDCl_3$): $\delta$ = 11.75 (s, 1H, N*H*), 8.72 (s, 1H, C$H_{arom}$), 8.45 (s, 1H, C$H_{arom}$), 7.97 (s, 1H, N*H*$CO_2t$Bu), 2.62 (s, 3H, S$CH_3$), 1.57 (s, 9H, C($CH_3$)$_3$) ppm. $^{13}$C-NMR (126 MHz, $CDCl_3$): $\delta$ = 166.5 (1 C, $C_{arom}SCH_3$), 157.4 (1 C, *C*ONH), 151.9 (1 C, $CO_2$NH), 145.4 (1 C, $C_{arom}$), 144.0 (1 C, *C*H$_{arom}$), 136.9 (1 C, $C_{arom}$), 123.2 (1 C, $C_{arom}$), 116.8 (1 C, *C*H$_{arom}$), 82.7 (1 C, *C*($CH_3$)$_3$), 28.3 (3 C, C($CH_3$)$_3$), 14.6 (1 C, S$CH_3$) ppm. FT-IR: neat; $\tilde{\nu}$ = 3390 (w), 2971 (w), 2874 (w), 2819 (w), 2761 (w), 1734 (w), 1653 (m), 1605 (w), 1583 (w), 1563 (w), 1507 (m), 1434 (w), 1369 (s), 1312 (m), 1277 (w), 1252 (m), 1234 (w), 1207 (w), 1146 (s), 1049 (w), 1019 (w), 935 (w), 901 (m), 865 (w), 805 (w), 765 (w), 725 (m), 634 (m), 597 (m), 539 (m), 428 (w), 415 (w) cm$^{-1}$. m.p.: 342 °C decomposition (EtOAc). HRMS (ESI$^+$): *m/z* calc. for $C_{13}H_{16}N_4O_3S_1Na_1$ [M + Na]$^+$: 331.0835, found: 331.0834.

### Ethyl (*Z*)-3-(5-amino-2-(methylthio) pyrimidin-4-yl)-2-chloroacrylate (17 e-(*Z*))



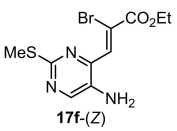

Phosphonate **16 e** (714 μL, 3.24 mmol, 1.05 eq) and 18-crown-6 (906 mg, 3.39 mmol, 1.10 eq) were dissolved in THF (15.0 mL) and cooled to −20 °C. KO*t*Bu (371 mg, 3.24 mmol, 1.05 eq) was added portionwise. After 15 min aldehyde **15** (522 mg, 3.09 mmol, 1.00 eq) in THF (5.00 mL) was added dropwise. The resulting deep orange to brown reaction mixture was stirred for 30 min. The reaction mixture was poured into saturated aqueous $NH_4Cl$ solution (20 mL) and extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with brine (30 mL), dried over $Na_2SO_4$ and the solvent was evaporated under reduced pressure. The solid orange crude product which is a mixture of **17 e**-(*Z*), cyclized compound **18 e** - which comes from *in situ* cyclisation of **17 e**-(*E*) - and phosphonate **16 e** was used for the next reaction without further purification. The yield is given over two steps. Data for pure **17 e**-(*Z*): $R_f$ = 0.35 (*n*-pentane/EtOAc 1:1). $^1$H-NMR (500 MHz, $CDCl_3$): $\delta$ = 8.18 (s, 1H, C$H_{arom}$), 7.81 (s, 1H, C$H_{olef}$), 4.37 (q, *J* = 7.2 Hz, 2H, $CH_2$), 3.73 (s, 2H, N$H_2$), 2.55 (s, 3H, S$CH_3$), 1.38 (t, *J* = 7.2 Hz, 3H, $CH_3$) ppm. $^{13}$C-NMR (126 MHz, $CDCl_3$): $\delta$ = 162.4 (1 C, $CO_2$Et), 161.0 (1 C, $C_{arom}SCH_3$), 147.3 (1 C, *C*H$_{arom}$), 144.6 (1 C, $C_{arom}$), 135.1 (1 C, $C_{arom}$), 130.5 (1 C, *C*H$_{olef}$), 129.3 (1 C, $C_{arom}$Cl), 63.2 (1 C, $CH_2$), 14.6 (1 C, S$CH_3$), 14.3 (1 C, $CH_3$) ppm. FT-IR: neat; $\tilde{\nu}$ = 3419 (m), 3319 (w), 3216 (w), 3046 (w), 2990 (w), 2945 (w), 2919 (w), 2722 (w), 2294 (w), 2241 (w), 2107 (w), 1983 (w), 1693 (w), 1643 (w), 1601 (w), 1576 (w), 1521 (w), 1470 (w), 1402 (w), 1361 (w), 1322 (w), 1277 (w), 1233 (w), 1195 (w), 1142 (w), 1082 (w), 1040 (w), 1016 (w), 938 (w), 907 (w), 870 (w), 833 (w), 771 (w), 750 (w), 723 (w), 700 (w), 635 (w), 589 (w), 498 (w), 471 (w), 445 (w), 427 (w) cm$^{-1}$. m.p.: 132 °C ($CHCl_3$). HRMS (ESI$^+$): *m/z* calc. for $C_{10}H_{12}Cl_1N_3O_2S_1H_1$ [M + H]$^+$: 274.0412, found: 274.0408.

### 7-Chloro-2-(methylthio)pyrido[3,2-*d*]pyrimidin-6(5*H*)-one (18 e)




The crude pyrimidine **17 e**-(*Z*) (850 mg) was dissolved in MeOH (300 mL) and was divided into two different flasks which were irradiated simultaneously. The two reaction mixtures were heated to 60 °C for 7 h under irradiation of light (λ = 435 nm). The combined reaction mixtures were concentrated until a yellow precipitate formed. It was cooled to 0 °C, filtered and washed with cold *n*-pentane/EtOAc (10:1, 50 mL). The filter cake consisted of pure compound **18 e** (575 mg, 2.53 mmol, 82 % over two steps), while there was still product in the filtrate left. All solvents were evaporated under reduced pressure and the crude product which consisted of trace amounts of OEt compound (no pyridone, but NCOEt), compound **18 e** and phosphonate **16 e** (212 mg) was subjected to a saponification reaction. Therefore NaOH (425 mg, 10.6 mmol, 3.27 eq related to phosphonate **16 e**) was added to a mixture of crude product in THF (5.00 mL) and $H_2O$ (0.50 mL) and stirred for 2 h. The reaction mixture was poured into saturated aqueous $NaHCO_3$ solution (5 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over $Na_2SO_4$ and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography on silica (*n*-pentane/EtOAc 1:1 to EtOAc) to give additional compound **18 e** (120 mg, 527 μmol, 17 %, 99 % combined yield over two steps). $R_f$ = 0.27 (*n*-pentane/EtOAc 1:1). $^1$H-NMR (500 MHz, DMSO-d6): $\delta$ = 12.60 (s, 1H, OCN*H*), 8.70 (s, 1H, C$H_{arom}$), 8.22 (s, 1H, C$H_{arom}$), 2.55 (s, 3H, S$CH_3$) ppm. $^{13}$C-NMR (126 MHz, DMSO-d6): $\delta$ = 164.2 (1 C, $C_{arom}SCH_3$), 156.2 (1 C, $C_{arom}$Cl), 146.3 (1 C, *C*H$_{arom}$), 141.2 (1 C, $C_{arom}$), 136.4 (1 C, *C*ON), 136.3 (1 C, *C*H$_{arom}$), 128.2 (1 C, $C_{arom}$), 13.7 (1 C, $SCH_3$) ppm. FT-IR: neat; $\tilde{\nu}$ = 3132 (w), 3042 (w), 2827 (m), 2762 (w), 1656 (s), 1597 (w), 1575 (m), 1463 (w), 1414 (m), 1377 (s), 1317 (w), 1225 (w), 1196 (m), 1143 (s), 1029 (m), 967 (w), 928 (m), 891 (w), 861 (w), 770 (w), 750 (w), 724 (w), 639 (s), 589 (m), 541 (m), 417 (m) cm$^{-1}$. m.p.: 253 °C (EtOAc). HRMS (ESI$^+$): *m/z* calc. for $C_8H_6Cl_1N_3O_1S_1Na_1$ [M + Na]$^+$: 249.9812, found: 249.9809.

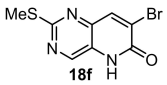
### Ethyl (Z)-3-(5-amino-2-(methylthio) pyrimidin-4-yl)-2-bromoacrylate (17 f-(*Z*))




Phosphonate **16 f** (1.18 g, 3.90 mmol, 1.10 eq) and 18-crown-6 (1.14 g, 4.26 mmol, 1.20 eq) were dissolved in THF (16.0 mL) and cooled to −20 °C. KO*t*Bu (426 mg, 3.72 mmol, 1.05 eq) was added portionwise. After 15 min aldehyde 176 (600 mg, 3.55 mmol, 1.00 eq) in THF (8.00 mL) was added dropwise. The resulting deep orange to brown reaction mixture was stirred for 2.5 h. The reaction mixture was poured into saturated aqueous $NH_4Cl$ solution (20 mL) and extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with brine (30 mL), dried over $Na_2SO_4$ and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography on silica (*n*-pentane/EtOAc 1:1) to give a mixture of **17 f**-(*Z*) and the cyclized compound **18 f** which comes from *in situ* cyclisation of **17 f**-(*E*) both as orange solid. This mixture was used for the next reaction and the yield is given over two steps. Data for pure **17 f**-(*Z*): $R_f$ = 0.30 (*n*-pentane/EtOAc 1:1). $^1$H-NMR (500 MHz, $CDCl_3$): $\delta$ = 8.17 (s, 1H, C$H_{arom}$), 8.09 (s, 1H,

$CH_{arom}$), 4.34 (q, $J$=7.1 Hz, 2H, $CH_2$), 3.79 (s, 2H, $NH_2$), 2.55 (s, 3H, $SCH_3$), 1.36 (t, $J$=7.2 Hz, 3H, $CH_3$) ppm. $^{13}$C-NMR (126 MHz, $CDCl_3$): $\delta$=162.4 (1 C, $COOCH_2$), 160.7 (1 C, $C_{arom}SCH_3$), 147.2 (1 C, $CH_{arom}$), 145.3 (1 C, $C_{arom}$), 135.0 (1 C, $C_{arom}$), 134.1 (1 C, $CH_{arom}$), 120.5 (1 C, CBr), 63.4 (1 C, $CH_2$), 14.6 (1 C, $SCH_3$), 14.2 (1 C, $CH_3$) ppm. FT-IR: neat; $\tilde{\nu}$=3419 (m), 3317 (w), 3212 (w), 3035 (w), 2989 (w), 2921 (w), 2721 (w), 2144 (w), 1691 (s), 1642 (w), 1595 (m), 1522 (m), 1470 (w), 1405 (s), 1363 (w), 1317 (w), 1275 (s), 1234 (w), 1197 (m), 1138 (w), 1083 (m), 1033 (m), 1008 (w), 939 (w), 908 (w), 870 (w), 830 (w), 772 (w), 748 (m), 685 (w), 626 (m), 588 (m), 504 (w) cm$^{-1}$. m.p.: 131 °C ($CHCl_3$). HRMS (ESI$^+$): *m/z* calc. for $C_{10}H_{12}Br_1N_3O_2S_1Na_1$ $[M+Na]^+$: 339.9726 & 341.9705, found: 339.9722 & 341.9702.

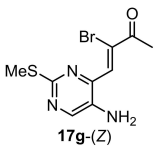
### 7-Bromo-2-(methylthio)pyrido[3,2-*d*]pyrimidin-6(5*H*)-one (18 f)



**18f**

Crude pyrimidine **17 f**-(*Z*) (933 mg) was dissolved in MeOH (200 mL) and heated to 60 °C for 4 h under irradiation of light ($\lambda$=435 nm). All solvents were evaporated under reduced pressure and the crude product was purified by column chromatography on silica (*n*-pentane/EtOAc 1:1 to EtOAc) to give OEt compound (no pyrimidone, but NCOEt, 113 mg, 377 µmol, 11% over two steps) and compound **18 f** (735 mg, 2.70 µmol, 77% over two steps) both as pale yellow solid. $R_f$=0.58 (EtOAc). $^1$H-NMR (500 MHz, DMSO-d6): $\delta$=12.58 (s, 1H, O*H*), 8.71 (s, 1H, $CH_{arom}$), 8.44 (d, J=0.6 Hz, 1H, $CH_{arom}$), 2.55 (s, 3H, $SCH_3$) ppm. $^{13}$C-NMR (126 MHz, DMSO-d6): $\delta$=164.2 (1 C, $C_{arom}SCH_3$), 156.5 (1 C, $NC_{arom}O$), 146.6 (1 C, $CH_{arom}$), 141.3 (1 C, $C_{arom}$), 140.4 (1 C, $CH_{arom}$), 128.9 (1 C, $C_{arom}$), 128.7 (1 C, $C_{arom}$), 13.8 (1 C, $SCH_3$) ppm. FT-IR: neat; $\tilde{\nu}$=3128 (w), 3037 (w), 2988 (w), 2927 (w), 2859 (w), 2823 (w), 2757 (w), 2197 (w), 2059 (w), 2035 (w), 1979 (w), 1865 (w), 1651 (s), 1597 (w), 1572 (m), 1462 (w), 1414 (m), 1379 (s), 1319 (w), 1258 (w), 1225 (w), 1195 (m), 1144 (s), 1041 (w), 1003 (m), 963 (w), 931 (m), 895 (w), 857 (w), 766 (w), 748 (w), 732 (w), 658 (w), 641 (w), 609 (m), 587 (m), 544 (m), 482 (w), 418 (m) cm$^{-1}$. m.p.: 197 °C (EtOAc). HRMS (ESI$^-$): *m/z* calc. for $C_8H_5Br_1N_3O_1S_1$ $[M-H]^-$: 269.9342 & 271.9321, found: 269.9335 & 271.9316.

### (*Z*)-4-(5-Aminopyrimidin-4-yl)-3-bromobut-3-en-2-one (17 g-(*Z*))



**17g**-(*Z*)

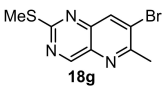
Compound **17 g**-(*Z*) was synthesized starting from phosphonate **16 c** or phosphonate **16 d**.

Phosphonate **16 c** (192 mg, 768 µmol, 1.30 eq) and 18-crown-6 (189 mg, 709 mmol, 1.20 eq) were dissolved in THF (6.00 mL) and cooled to 0 °C. KO*t*Bu (71.1 mg, 621 µmol, 1.05 eq) was added portionwise. After 15 min aldehyde **15** (100 mg, 591 µmol, 1.00 eq) in THF (5.00 mL) was added dropwise. The resulting deep orange to brown reaction mixture was stirred for 16 h while reaching rt. The reaction mixture was poured into saturated aqueous $NH_4Cl$ solution (10 mL) and extracted with EtOAc (3×20 mL). The combined organic layers were washed with brine (20 mL), dried over $Na_2SO_4$ and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography on silica (*n*-pentane/EtOAc 2:1 to 1:1) to give **17 g**-(*Z*) (89.0 mg, 309 mmol, 53%) and the cyclized compound **18 g** (26.0 mg, 96 µmol, 16%) which comes from *in situ* cyclisation of **17 g**-(*E*) (overall 69%) both as orange solid. The ratio of **17 g**-(*Z*) to pyridopyrimidine **18 g** is 3.3:1 which should reflect the *Z*/*E* ratio during the reaction.

Or:

Phosphonate **16 d** (189 mg, 768 µmol, 1.30 eq) and 18-crown-6 (189 mg, 709 mmol, 1.20 eq) were dissolved in THF (6.00 mL) and cooled to 0 °C. KO*t*Bu (71.1 mg, 621 µmol, 1.05 eq) was added portionwise. After 15 min aldehyde **15** (100 mg, 591 µmol, 1.00 eq) in THF (5.00 mL) was added dropwise. The resulting deep orange to brown reaction mixture was stirred for 19 h during it reached rt. The reaction mixture was poured into saturated aqueous $NH_4Cl$-solution (10 mL) and extracted with EtOAc (3×20 mL). The combined organic layers were washed with brine (20 mL), dried over $Na_2SO_4$ and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography on silica (*n*-pentane/EtOAc 2:1 to 1:1) to give **17 g**-(*Z*) (107 mg, 371 mmol, 63%) and the cyclized compound **18 g** (24.0 mg, 89 µmol, 15%) which comes from *in situ* cyclisation of **17 g**-(*E*) (overall 78%) both as orange solid. The ratio of **17 g**-(*Z*) to pyridopyrimidine **18 g** is 4.2:1 which should reflect the *Z*/*E*-ratio during the reaction. Data for pure **17 g**-(*Z*): $R_f$=0.10 (*n*-pentane/EtOAc 2:1). $^1$H-NMR (500 MHz, $CDCl_3$): $\delta$=8.20 (s, 1H, $CH_{arom}$), 7.93 (s, 1H, $CH_{arom}$), 3.57 (s, 2H, $NH_2$), 2.62 (s, 3H, $CH_3$), 2.57 (s, 3H, $SCH_3$) ppm. $^{13}$C-NMR (126 MHz, $CDCl_3$): $\delta$=193.0 (1 C, *C*O), 161.0 (1 C, $C_{arom}SCH_3$), 147.2 (1 C, $CH_{arom}$), 145.6 (1 C, $C_{arom}$), 135.0 (1 C, $C_{arom}$), 132.4 (1 C, $CH_{arom}$), 128.9 (1 C, $CBr_{arom}$), 27.4 (1 C, $CH_3$), 14.6 (1 C, $SCH_3$) ppm. FT-IR: neat; $\tilde{\nu}$=3398 (w), 3321 (w), 3200 (m), 2997 (w), 2923 (w), 2108 (w), 2001 (w), 1927 (w), 1666 (s), 1594 (w), 1560 (w), 1523 (m), 1405 (s), 1298 (w), 1268 (w), 1226 (w), 1197 (s), 1131 (w), 1078 (w), 1011 (w), 971 (w), 935 (w), 921 (w), 892 (w), 862 (w), 810 (w), 767 (w), 676 (w), 650 (w), 620 (w), 597 (w), 556 (m), 507 (w), 442 (w) cm$^{-1}$. m.p.: 101 °C decomposition (EtOAc). HRMS (ESI$^+$): *m/z* calc. for $C_9H_8Br_1N_3S_1H_1$ $[M+H]^+$: 287.9801 & 289.9780, found: 287.9800 & 289.9780.

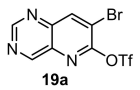
### 7-Bromo-6-methyl-2-(methylthio)pyrido[3,2-*d*]pyrimidine (18 g)



**18g**

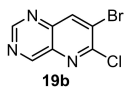
Pyrimidine **17 g**-(*Z*) (85.0 mg, 295 µmol, 1.00 eq) was dissolved in MeOH (15.0 mL) and heated to 60 °C for 3.5 h under irradiation of light ($\lambda$=435 nm). All solvents were evaporated under reduced pressure and the crude product was purified by column chromatography on silica (*n*-pentane/EtOAc 2:1) to give compound **18 g** (70.4 mg, 261 µmol, 89%) as pale brownish solid. $R_f$=0.73 (*n*-pentane/EtOAc 2:1). $^1$H-NMR (500 MHz, $CDCl_3$): $\delta$=9.30 (s, 1H, $CH_{arom}$), 8.37 (s, 1H, $CH_{arom}$), 2.87 (s, 3H, $CH_3$), 2.67 (s, 3H, $SCH_3$) ppm. $^{13}$C-NMR (126 MHz, $CDCl_3$): $\delta$=170.3 (1 C, $C_{arom}SCH_3$), 160.4 (1 C, $CH_{arom}$), 158.6 (1 C, $C_{arom}$), 146.5 (1 C, $C_{arom}$), 137.7 (1 C, $CH_{arom}$), 136.3 (1 C, $C_{arom}$), 127.5 (1 C, $CBr_{arom}$), 25.7 (1 C, $CH_3$), 14.8 (1 C, $SCH_3$) ppm. FT-IR: neat; $\tilde{\nu}$=3044 (w), 2996 (w), 2956 (w), 2924 (m), 2853 (w), 2272 (w), 2054 (w), 1846 (w), 1726 (m), 1589 (m), 1553 (w), 1534 (s), 1431 (s), 1395 (m), 1362 (w), 1330 (w), 1284 (m), 1242 (w), 1181 (m), 1122 (s), 1071 (w), 1030 (w), 1006 (w), 972 (s), 955 (w), 925 (w), 822 (w), 797 (w), 754 (w), 698 (m), 651 (m), 594 (m), 548 (m), 510 (w), 481 (w), 425 (w) cm$^{-1}$. m.p.: 147 °C decomposition (EtOAc). HRMS (ESI$^+$): *m/z* calc. for $C_9H_8Br_1N_3S_1H_1$ $[M+H]^+$: 269.9695 & 271.9674, found: 269.9694 & 271.9673.

### 7-Bromopyrido[3,2-*d*]pyrimidin-6-yl trifluoromethanesulfonate (19a)


19a

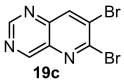
Pyridopyrimidine **18a** (35.0 mg, 155 μmol, 1.00 eq) was suspended in THF (1.00 mL) and $Et_3N$ (30.0 μL, 217 μmol, 1.40 eq) was added. The suspension was cooled to 0 °C before TfCl (19.0 μL, 170 μmol, 1.10 eq) was added. The reaction mixture was stirred for 1 h while it was allowed to warm to rt. The brown reaction mixture was poured into saturated aqueous $NH_4Cl$ solution (5 mL) and extracted with EtOAc (3×10 mL). The combined organic layers were washed with brine (10 mL), dried over $Na_2SO_4$ and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography on silica (*n*- pentane/EtOAc 3:1) to give compound **19a** (30.0 mg, 72.0 μmol, 47%) as pale yellow solid. $R_f$ = 0.31 (*n*-pentane/EtOAc 3:1). $^1$H-NMR (300 MHz, $CDCl_3$): $\delta$ = 9.59 (d, $J$ = 0.7 Hz, 1H, $CH_{arom}$), 9.48 (s, 1H, $CH_{arom}$), 8.79 (d, $J$ = 0.7 Hz, 1H, $CH_{arom}$) ppm. $^{13}$C-NMR (76 MHz, $CDCl_3$): $\delta$ = 160.8 (1 C, $CH_{arom}$), 157.5 (1 C, $CH_{arom}$), 151.3 (1 C, $COTf_{arom}$), 146.3 (1 C, $C_{arom}$), 144.9 (1 C, $CH_{arom}$), 136.7 (1 C, $C_{arom}$), 118.6 (q, $J$ = 321.0 Hz, 1 C, $CF_3$), 116.9 (1 C, $CBr_{arom}$) ppm. $^{19}$F-NMR (283 MHz, $CDCl_3$): $\delta$ = 72.7 (s, 3F, $CF_3$) ppm. FT-IR: neat; $\tilde{\nu}$ = 3029 (w), 2926 (w), 1935 (w), 1697 (w), 1590 (w), 1572 (w), 1422 (s), 1402 (w), 1337 (w), 1310 (w), 1214 (s), 1188 (w), 1128 (m), 1084 (w), 999 (m), 955 (w), 924 (m), 905 (w), 853 (s), 801 (m), 769 (w), 746 (w), 688 (m), 634 (s), 604 (w), 585 (w), 568 (m), 541 (w), 500 (w), 478 (m), 423 (w) cm$^{-1}$. m.p.: 57 °C (EtOAc). HRMS (ESI$^+$): *m/z* calc. for $C_8H_4Br_1F_3N_3O_3S_1$ $[M+H]^+$: 357.9103 & 359.9083, found: 357.9112 & 359.9092.

### 7-Bromo-6-chloropyrido[3,2-*d*]pyrimidine (19b)


19b

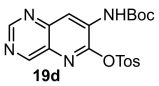
Pyridopyrimidine **18a** (23.5 mg, 104 μmol, 1.00 eq) was dissolved in $POCl_3$ (190 μL, 2.08 mmol, 20.0 eq) and heated to 85 °C for 20.5 h. The brown reaction mixture was poured into saturated aqueous $NaHCO_3$-solution (5 mL) and extracted with EtOAc (3×10 mL). The combined organic layers were washed with brine (10 mL), dried over $Na_2SO_4$ and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography on silica (*n*-pentane/EtOAc 5:1) to give compound **19b** (15.0 mg, 61.4 μmol, 59%) as pale yellow solid. $R_f$ = 0.28 (*n*-pentane/EtOAc 5:1). $^1$H-NMR (500 MHz, $CDCl_3$): $\delta$ = 9.56 (d, $J$ = 0.8 Hz, 1H, $CH_{arom}$), 9.41 (s, 1H, $CH_{arom}$), 8.47 (dd, $J$ = 0.9, 0.5 Hz, 1H, $CH_{arom}$) ppm. $^{13}$C-NMR (126 MHz, $CDCl_3$): $\delta$ = 160.4 (1 C, $CH_{arom}$), 156.9 (1 C, $CH_{arom}$), 151.2 (1 C, $CCl_{arom}$), 145.8 (1 C, $C_{arom}$), 138.1 (1 C, $C_{arom}$), 137.9 (1 C, $CH_{arom}$), 136.0 (1 C, $CBr_{arom}$) ppm. FT-IR: neat; $\tilde{\nu}$ = 3419 (w), 3318 (w), 3216 (w), 3060 (w), 3025 (w), 2990 (w), 2959 (w), 2921 (m), 2852 (w), 1693 (w), 1644 (w), 1582 (m), 1561 (w), 1538 (w), 1442 (m), 1412 (s), 1384 (w), 1346 (w), 1323 (w), 1301 (w), 1277 (w), 1261 (m), 1216 (w), 1169 (w), 1137 (w), 1112 (w), 1079 (s), 1034 (w), 1017 (w), 981 (m), 941 (m), 907 (m), 798 (m), 751 (w), 693 (s), 658 (w), 635 (m), 600 (m), 557 (s), 519 (w), 483 (w), 455 (w) cm$^{-1}$. m.p.: 133 °C (EtOAc). HRMS (APCI$^+$): *m/z* calc. for $C_7H_3Br_1Cl_1N_3H_1$ $[M+H]^+$: 245.9249 & 243.9272, found: 245.9249 & 243.9269.

### 6,7-Dibromopyrido[3,2-*d*]pyrimidine (19c)


19c

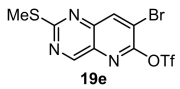
Pyridopyrimidine **18a** (41.0 mg, 181 μmol, 1.00 eq) and $POBr_3$ (82.1 mg, 272 μmol, 1.50 eq) were mixed and heated to 140 °C for 16 h. The brown reaction mixture was allowed to cool to rt before it was diluted with saturated aqueous $NaHCO_3$ solution (5 mL) and extracted with EtOAc (3×10 mL). The combined organic layers were washed with brine (10 mL), dried over $Na_2SO_4$ and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography on silica (*n*-pentane/EtOAc 1:2) to give compound **19c** (17.0 mg, 58.8 μmol, 33%) as brownish solid. $R_f$ = 0.67 (*n*-pentane/EtOAc 1:2). $^1$H-NMR (500 MHz, $CDCl_3$): $\delta$ = 9.58 (s, 1H, $CH_{arom}$), 9.43 (s, 1H, $CH_{arom}$), 8.66 (s, 1H, $CH_{arom}$) ppm. $^{13}$C-NMR (126 MHz, $CDCl_3$): $\delta$ = 160.7 (1 C, $CH_{arom}$), 156.9 (1 C, $CH_{arom}$), 146.0 (1 C, $C_{arom}$), 145.7 (1 C, $C_{arom}$), 141.1 (1 C, $CH_{arom}$), 139.0 (1 C, $CBr_{arom}$), 129.3 (1 C, $CBr_{arom}$) ppm. FT-IR: neat; $\tilde{\nu}$ = 3368 (w), 3021 (w), 2922 (s), 2852 (w), 2341 (w), 2100 (w), 1962 (w), 1928 (w), 1902 (w), 1860 (w), 1727 (w), 1670 (m), 1577 (m), 1553 (w), 1533 (w), 1466 (w), 1439 (m), 1410 (s), 1378 (w), 1340 (w), 1319 (w), 1300 (m), 1276 (w), 1211 (w), 1170 (w), 1119 (s), 1076 (m), 941 (s), 890 (w), 790 (w), 723 (w), 681 (m), 628 (s) cm$^{-1}$. m.p.: 183 °C ($CHCl_3$). HRMS (APCI$^+$): *m/z* calc. for $C_7H_3Br_2N_3H_1$ $[M+H]^+$: 287.8766 & 289.8746 & 291.8726, found: 287.8769 & 289.8748 & 291.8728.

### 7-((*tert*-Butoxycarbonyl)amino)pyrido[3,2-*d*] pyrimidin-6-yl4-methylbenzene-sulfonate (19d)


19d

Pyridopyrimidine **18b** (289 mg, 1.10 mmol, 1.00 eq) was dissolved in THF (11.0 mL) and $Et_3N$ (214 μL, 1.56 mmol, 1.40 eq) was added. The solution was cooled to 0 °C before TosCl (233 mg, 1.21 mmol, 1.10 eq) and DMAP (13.6 mg, 110 μmol, 0.10 eq) was added. The reaction mixture was stirred for 2.5 h while it was allowed to warm to rt. The yellow reaction mixture was poured into saturated aqueous $NH_4Cl$-solution (10 mL) and extracted with EtOAc (3×20 mL). The combined organic layers were washed with brine (20 mL), dried over $Na_2SO_4$ and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography on silica (*n*-pentane/EtOAc 2:1) to give compound **19d** (375 mg, 901 μmol, 82%) as pale yellow solid. The position of the protecting group of compound **19d** was proved by a crystal structure. $R_f$ = 0.26 (*n*-pentane/EtOAc 2:1). $^1$H-NMR (500 MHz, $CDCl_3$): $\delta$ = 9.26 (s, 1H, $CH_{arom}$), 9.16 (s, 1H, $CH_{arom}$), 8.99 (s, 1H, $CH_{arom}$), 8.14 (d, $J$ = 8.4 Hz, 2H, 2×$CH_{arom}$), 7.42 (d, $J$ = 8.1 Hz, 2H, 2×$CH_{arom}$), 7.28 (s, 1H, N*H*Boc), 2.48 (s, 3H, $CH_3$), 1.58 (s, 9H, $C(CH_3)_3$) ppm. $^{13}$C-NMR (126 MHz, $CDCl_3$): $\delta$ = 158.4 (1 C, $CH_{arom}$), 156.2 (1 C, $CH_{arom}$), 151.5 (1 C, N(*C*O)O), 147.3 (1 C, $C_{arom}$), 147.1 (1 C, $C_{arom}$), 146.7 (1 C, $C_{arom}$), 133.2 (1 C, $C_{arom}$), 132.5 (1 C, $C_{arom}$), 131.2 (1 C, $C_{arom}$), 129.9 (2 C, 2×$CH_{arom}$), 129.8 (2 C, 2×$CH_{arom}$), 122.9 (1 C, $CH_{arom}$), 83.2 (1 C, $C(CH_3)_3$), 28.3 (3 C, $C(CH_3)_3$), 22.0 (1 C, $CH_3$) ppm. FT-IR: neat; $\tilde{\nu}$ = 3358 (w), 3100 (w), 2979 (w), 2923 (w), 1731 (m), 1601 (w), 1568 (w), 1515 (s), 1457 (w), 1422 (m), 1375 (m), 1346 (w), 1307 (w), 1248 (m), 1228 (w), 1195 (w), 1178 (w), 1157 (w), 1136 (s), 1090 (m), 1047 (w), 1018 (w), 946 (w), 921 (m), 856 (w), 808 (m), 785 (w), 730 (s), 701 (w), 659 (m), 616 (w), 587 (s), 546 (s) cm$^{-1}$. m.p.: 149 °C (EtOAc). HRMS (ESI$^+$): *m/z* calc. for $C_{19}H_{20}N_4O_5S_1Na_1$ $[M+Na]^+$: 439.1047, found: 439.1050.

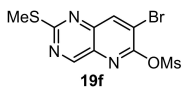
### 7-Bromo-2-(methylthio)pyrido[3,2-*d*]pyrimidin-6-yl trifluoromethanesulfonate (19e)



19e

Compound **18b** (40.0 mg, 147 μmol, 1.00 eq) was dissolved in THF (1.50 mL) and cooled to 0 °C. DIPEA (50 μL, 294 μmol, 2.00 eq) was added. After 5 min TfCl (17 μL, 162 μmol, 1.10 eq) was added dropwise. The brown solution was stirred for 16 h during it warmed up to rt. It was poured into saturated aqueous $NH_4Cl$-solution (5 mL) and extracted with EtOAc (3×10 mL). The combined organic layers were washed with brine (10 mL), dried over $Na_2SO_4$ and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography on silica (*n*-pentane/EtOAc 10:1 to EtOAc) to give compound **19e** (27.0 mg, 67 μmol, 45%, 79% brsm) as yellow solid. $R_f$ = 0.78 (*n*-pentane/EtOAc 5:1). $^1$H-NMR (500 MHz, $CDCl_3$): $\delta$ = 9.26 (d, $J$ = 0.7 Hz, 1H, C$H_{arom}$), 8.87 (d, $J$ = 0.7 Hz, 1H, C$H_{arom}$), 2.67 (s, 3H, SC$H_3$) ppm. $^{13}$C-NMR (126 MHz, $CDCl_3$): $\delta$ = 172.9 (1 C, $C_{arom}SCH_3$), 160.1 (1 C, $CH_{arom}$), 149.8 (1 C, $C_{arom}SO_3CF_3$), 146.9 (1 C, $C_{arom}$), 143.0 (1 C, $CH_{arom}$), 134.3 (1 C, $C_{arom}$), 118.6 (q, $J$ = 320.9 Hz, 1 C, $CF_3$), 117.1 (1 C, $C_{arom}Br$), 14.9 (1 C, $SCH_3$) ppm. $^{19}$F-NMR (283 MHz, $CDCl_3$): $\delta$ = −72.7 (3F, $CF_3$) ppm. FT-IR: neat; $\tilde{\nu}$ = 3030 (w), 2931 (w), 1591 (w), 1569 (w), 1535 (m), 1414 (s), 1377 (w), 1331 (m), 1309 (w), 1205 (s), 1123 (m), 1003 (s), 962 (w), 927 (w), 875 (m), 804 (s), 751 (m), 712 (m), 661 (w), 638 (m), 599 (m), 578 (w), 547 (w), 529 (w), 508 (w), 478 (w), 459 (w), 429 (w) cm$^{-1}$. m.p.: 90 °C ($CHCl_3$). HRMS (ESI$^+$): *m/z* calc. for $C_9H_6Br_1F_3N_3O_3S_2$ $[M+H]^+$: 405.8959 & 403.8981, found: 405.8958 & 403.8978.

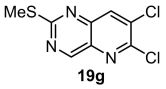
### 7-Bromo-2-(methylthio)pyrido[3,2-*d*]pyrimidin-6-yl methanesulfonate (19f)



19f

Compound **18f** (100 mg, 367 μmol, 1.00 eq) was dissolved in $CH_2Cl_2$ (2.00 mL) and cooled to 0 °C. DMAP (9.0 mg, 73 μmol, 0.20 eq) and $Et_3N$ (102 μL, 735 μmol, 2.00 eq) were added. After 5 min MsCl (34 μL, 441 μmol, 1.20 eq) was added dropwise. The solution was stirred for 1.5 h before it was poured into saturated aqueous $NH_4Cl$-solution (5 mL) and extracted with EtOAc (3×10 mL). The combined organic layers were washed with brine (10 mL), dried over $Na_2SO_4$ and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography on silica (*n*-pentane/EtOAc 2:1 to 1:1) to give compound **19f** (129 mg, 368 μmol, 99%) as yellow solid. $R_f$ = 0.63 (*n*-pentane/EtOAc 1:1). $^1$H-NMR (500 MHz, $CDCl_3$): $\delta$ = 9.22 (d, $J$ = 0.8 Hz, 1H, C$H_{arom}$), 8.53 (d, $J$ = 0.8 Hz, 1H, C$H_{arom}$), 3.65 (s, 3H, OC$H_3$), 2.66 (s, 3H, SC$H_3$) ppm. $^{13}$C-NMR (126 MHz, $CDCl_3$): $\delta$ = 171.8 (1 C, $C_{arom}SCH_3$), 159.7 (1 C, $CH_{arom}$), 151.9 (1 C, $C_{arom}$), 146.6 (1 C, $C_{arom}$), 142.3 (1 C, $CH_{arom}$), 134.3 (1 C, $C_{arom}$), 118.4 (1 C, $C_{arom}Br$), 41.6 (1 C, $SO_2CH_3$), 14.8 (1 C, $SCH_3$) ppm. FT-IR: neat; $\tilde{\nu}$ = 2929 (w), 2853 (w), 1734 (w), 1680 (w), 1638 (w), 1590 (w), 1565 (m), 1540 (w), 1419 (m), 1371 (s), 1313 (m), 1246 (w), 1214 (w), 1168 (s), 1127 (m), 1008 (m), 964 (m), 927 (w), 870 (s), 797 (s), 770 (w), 735 (m), 714 (w), 616 (m), 586 (w), 540 (s), 517 (w), 490 (w), 448 (w), 423 (w) cm$^{-1}$. m.p.: 136 °C ($CH_2Cl_2$). HRMS (ESI$^+$): *m/z* calc. for $C_9H_9Br_1N_3O_3S_2$ $[M+H]^+$: 349.9263 & 351.9242, found: 349.9264 & 351.9243

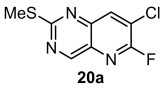
### 6,7-Dichloro-2-(methylthio)pyrido[3,2-*d*]pyrimidine (19g)



19g

Pyridone **18f** (100 mg, 439 μmol, 1.00 eq) was suspended in PhCl (0.89 mL) and cooled to 10 °C before DIPEA (90 μL, 527 μmol, 1.20 eq) was added. After 5 min $POCl_3$ (52 μL, 571 μmol, 1.30 eq) was added dropwise and the reaction mixture was stirred for 30 min at 10 °C before it was allowed to warm up to rt. After 1 h the reaction mixture was heated to 80 °C and stirred for 16 h. The reaction mixture was carefully poured into saturated aqueous $NaHCO_3$-solution (5 mL) and extracted with EtOAc (3×10 mL). The combined organic layers were washed with brine (10 mL), dried over $Na_2SO_4$ and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography on silica (*n*-pentane/EtOAc 10:1) to give compound **19g** (97.3 mg, 395 μmol, 90%) as pale yellow solid. $R_f$ = 0.45 (*n*-pentane/EtOAc 10:1). $^1$H-NMR (500 MHz, $CDCl_3$): $\delta$ = 9.26 (s, 1H, C$H_{arom}$), 8.26 (s, 1H, C$H_{arom}$), 2.66 (s, 3H, SC$H_3$) ppm. $^{13}$C-NMR (126 MHz, $CDCl_3$): $\delta$ = 171.8 (1 C, $C_{arom}SCH_3$), 159.9 (1 C, $CH_{arom}$), 148.7 (1 C, $C_{arom}Cl$), 146.4 (1 C, $C_{arom}$), 136.4 (1 C, $CH_{arom}$), 136.0 (1 C, $C_{arom}Cl$), 135.9 (1 C, $C_{arom}$), 14.9 (1 C, $SCH_3$) ppm. FT-IR: neat; $\tilde{\nu}$ = 3041 (m), 2929 (w), 2336 (w), 2047 (w), 1849 (w), 1585 (m), 1553 (w), 1529 (s), 1416 (s), 1370 (w), 1342 (w), 1302 (s), 1239 (w), 1191 (w), 1153 (m), 1120 (s), 983 (m), 965 (w), 918 (w), 803 (w), 733 (w), 705 (m), 651 (m), 620 (s), 527 (m), 475 (m) cm$^{-1}$. m.p.: 162 °C ($CHCl_3$). HRMS (APCI$^+$): *m/z* calc. for $C_8H_5Cl_2N_3S_1H_1$ $[M+H]^+$: 245.9654, found: 245.9650.

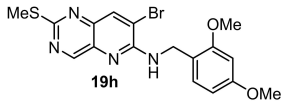
### 7-Chloro-6-fluoro-2-(methylthio)pyrido[3,2-*d*]pyrimidine (20a)



20a

Compound **19g** (20.8 mg, 85 μmol, 1.00 eq) was dissolved in DMSO (0.21 mL) before TBAF (1 M in THF, 211 μL, 211 μmol, 2.50 eq) was added dropwise. The yellow to greenish reaction mixture was stirred for 2 h at rt. It was poured into saturated aqueous $NH_4Cl$-solution (5 mL) and extracted with EtOAc (3×10 mL). The combined organic layers were washed with brine (10 mL), dried over $Na_2SO_4$ and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography on silica (*n*-pentane/EtOAc 10:1 to EtOAc) to give compound **20a** (8.0 mg, 35 μmol, 41%) as colorless solid and the hydrolysis product pyridone **18e** (11.0 mg, 48 μmol, 57%). $R_f$ = 0.55 (*n*-pentane/EtOAc 10:1). $^1$H-NMR (500 MHz, $CDCl_3$): $\delta$ = 9.20 (s, 1H, C$H_{arom}$), 8.31 (dd, $J$ = 8.1, 0.8 Hz, 1H, C$H_{arom}$), 2.66 (s, 3H, SC$H_3$) ppm. $^{13}$C-NMR (126 MHz, $CDCl_3$): $\delta$ = 171.2 (d, $J$ = 3.0 Hz, 1 C, $C_{arom}SCH_3$), 159.5 (d, $J$ = 2.0 Hz, 1 C, $CH_{arom}$), 155.7 (d, $J$ = 246.6 Hz, 1 C, $CF_{arom}$), 146.7 (d, $J$ = 2.0 Hz 1 C, $C_{arom}$), 139.1 (d, $J$ = 4.0 Hz, 1 C, $CH_{arom}$), 133.5 (d, $J$ = 14.0 Hz, 1 C, $C_{arom}$), 125.8 (d, $J$ = 39.2 Hz, 1 C, $CCl_{arom}$) 14.8 (1 C, $SCH_3$) ppm. $^{19}$F-NMR (283 MHz, $CDCl_3$): $\delta$ = −64.5 (s, 1F, $CF_{arom}$) ppm. FT-IR: neat; $\tilde{\nu}$ = 3054 (w), 3011 (w), 2929 (w), 2848 (w), 2687 (w), 228.2 (w), 2096 (w), 1859 (w), 1577 (m), 1540 (s), 1425 (s), 1377 (m), 1329 (m), 1305 (w), 1242 (m), 1184 (w), 1126 (m), 1035 (s), 962 (w), 928 (w), 850 (w), 758 (w), 718 (m), 666 (m), 631 (m), 573 (m), 538 (m) cm$^{-1}$. m.p.: 122 °C ($CHCl_3$). HRMS (APCI$^+$): *m/z* calc. for $C_8H_5Cl_1F_1N_3S_1H_1$ $[M+H]^+$: 229.9950, found: 229.9946.

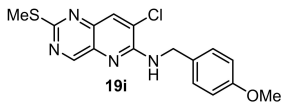
### 7-Bromo-*N*-(2,4-dimethoxybenzyl)-2-(methylthio)pyrido[3,2-*d*] pyrimi-din-6-amine (19h)



19h

Pyridone **18f** (400 mg, 1.47 mmol, 1.00 eq) and PyBroP (891 mg, 1.91 mmol, 1.30 eq) were suspended in THF (14.0 mL) and DBU (331 µL, 2.21 mmol, 1.50 eq) was added dropwise at rt. The resulting solution was stirred for 10 min before 2,4-dimethoxybenzylamine (663 µL, 4.41 mmol, 3.00 eq) was added. The reaction mixture was heated to 60 °C for 22 h before it was poured into saturated aqueous $NH_4Cl$-solution (20 mL) and extracted with EtOAc (3×30 mL). The combined organic layers were washed with brine (30 mL), dried over $Na_2SO_4$ and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography on silica (*n*-pentane/EtOAc 7:1 to 1:1) to give compound **19h** (349 mg, 828 µmol, 56%) as orange solid. $R_f$ = 0.32 (*n*-pentane/EtOAc 5:1). $^1$H-NMR (500 MHz, $CDCl_3$): $\delta$ = 9.02 (d, $J$ = 0.7 Hz 1H, $CH_{hetarom}$), 8.12 (d, $J$ = 0.8 Hz, 1H, $CH_{hetarom}$), 7.32 (d, $J$ = 8.3 Hz, 1H, $CH_{arom}$), 6.51 (d, $J$ = 2.7 Hz, 1H, $CH_{arom}$), 6.45 (dd, $J$ = 8.3 Hz, 2.5 Hz, 1H, $CH_{arom}$), 6.11 (t, $J$ = 5.4 Hz, 1H, N*H*), 4.71 (d, $J$ = 5.6 Hz, 2H, $CH_2$), 3.88 (s, 3H, $OCH_3$), 3.80 (s, 3H, $OCH_3$), 2.63 (s, 3H, $SCH_3$) ppm. $^{13}$C-NMR (126 MHz, $CDCl_3$): $\delta$ = 164.9 (1 C, $C_{hetarom}SCH_3$), 160.8 (1 C, $C_{arom}$), 159.0 (1 C, $C_{arom}$), 157.8 (1 C, $CH_{hetarom}$), 152.6 (1 C, $C_{hetarom}$), 144.1 (1 C, $C_{hetarom}$), 137.8 (1 C, $CH_{hetarom}$), 136.9 (1 C, $C_{hetarom}$), 130.9 (1 C, $CH_{arom}$), 118.9 (1 C, $C_{arom}$), 117.2 (1 C, $C_{hetarom}$), 104.1 (1 C, $CH_{arom}$), 99.0 (1 C, $CH_{arom}$), 55.6 (1 C, $CH_3$), 55.6 (1 C, $CH_3$), 41.7 (1 C, $CH_2$), 14.6 (1 C, $SCH_3$) ppm. FT-IR: neat; $\tilde{\nu}$ = 3263 (w), 3000 (w), 2952 (w), 2924 (m), 2830 (w), 2103 (w), 1671 (w), 1589 (w), 1560 (m), 1503 (s), 1451 (w), 1420 (w), 1391 (m), 1353 (w), 1333 (m), 1311 (w), 1285 (w), 1258 (m), 1208 (m), 1180 (w), 1154 (w), 1125 (s), 1044 (w), 1028 (m), 1011 (w), 955 (m), 922 (w), 894 (w), 830 (m), 812 (w), 763 (w), 730 (w), 643 (m), 595 (m), 536 (m), 468 (w), 425 (w) cm$^{-1}$. m.p.: 142 °C (EtOAc). HRMS (ESI$^+$): *m/z* calc. for $C_{17}H_{18}Br_1N_4O_2S_1$ $[M+H]^+$: 421.0328 & 423.0309, found: 421.0340 & 423.0320.

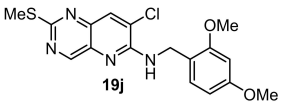
### 7-Chloro-*N*-(4-methoxybenzyl)-2-(methylthio)pyrido[3,2-*d*] pyrimidin-6-amine (19i)



19i

Pyridone **18e** (100 mg, 439 µmol, 1.00 eq) and PyBroP (266 mg, 571 µmol, 1.30 eq) were suspended in THF (3.50 mL) and DBU (165 µL, 1.10 mmol, 2.50 eq) was added dropwise at rt. The resulting solution was stirred for 10 min before 4-methoxybenzylamine (172 µL, 1.32 mmol, 3.00 eq) was added. The reaction mixture was heated to 65 °C for 20 h before it was poured into saturated aqueous $NH_4Cl$-solution (15 mL) and extracted with EtOAc (3×20 mL). The combined organic layers were washed with brine (20 mL), dried over $Na_2SO_4$ and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography on silica (*n*-pentane/EtOAc 5:1 to 3:1) to give compound **19i** (103 mg, 297 µmol, 68%) as yellow solid. $R_f$ = 0.45 (*n*-pentane/EtOAc 5:1). $^1$H-NMR (500 MHz, $CDCl_3$): $\delta$ = 9.02 (d, $J$ = 0.6 Hz, 1H, $CH_{hetarom}$), 7.96 (d, $J$ = 0.7 Hz, 1H, $CH_{hetarom}$), 7.36–7.33 (m, 2H, 2× $CH_{arom}$), 6.92–6.89 (m, 2H, 2×$CH_{arom}$), 5.75 (t, $J$ = 5.1 Hz, 1H, N*H*), 4.72 (d, $J$ = 5.5 Hz, 2H, $CH_2$), 3.81 (s, 3H, $OCH_3$), 2.63 (s, 3H, $SCH_3$) ppm. $^{13}$C-NMR (126 MHz, $CDCl_3$): $\delta$ = 165.2 (1 C, $C_{hetarom}SCH_3$), 159.3 (1 C, $C_{arom}$), 157.6 (1 C, $CH_{hetarom}$), 151.9 (1 C, $C_{hetarom}$), 144.1 (1 C, $C_{hetarom}$), 136.4 (1 C, $C_{hetarom}$), 133.9 (1 C, $CH_{hetarom}$), 130.3 (1 C, $C_{arom}$), 129.5 (2 C, 2×$CH_{arom}$), 125.9 (1 C, $C_{hetarom}$), 114.3 (2 C, 2×$CH_{arom}$), 55.5 (1 C, $OCH_3$), 45.5 (1 C, $CH_2$), 14.7 (1 C, $SCH_3$) ppm. FT-IR: neat; $\tilde{\nu}$ = 3431 (w), 3029 (w), 2947 (w), 2926 (w), 2900 (w), 2828 (w), 2166 (w), 2056 (w), 1879 (w), 1684 (w), 1602 (m), 1563 (m), 1543 (w), 1502 (s), 1465 (w), 1391 (m), 1339 (w), 1287 (m), 1243 (s), 1224 (w), 1185 (w), 1135 (w), 1086 (m), 1030 (s), 987 (w), 950 (w), 926 (m), 900 (w), 879 (w), 840 (w), 814 (s), 791 (w), 761 (w), 730 (m), 711 (w), 667 (w), 643 (w), 624 (w), 579 (m), 516 (w), 478 (w) cm$^{-1}$. m.p.: 114 °C (EtOAc). HRMS (ESI$^+$): *m/z* calc. for $C_{16}H_{16}Cl_1N_4O_1S_1$ $[M+H]^+$: 347.0728, found: 347.0737.

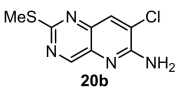
### 7-Chloro-*N*-(2,4-dimethoxybenzyl)-2-(methylthio)pyrido[3,2-*d*] pyrimidin-6-amine (19j)



19j

Pyridone **18e** (200 mg, 878 µmol, 1.00 eq) and PyBroP (532 mg, 1.14 mmol, 1.30 eq) were suspended in THF (7.00 mL) and DBU (198 µL, 1.32 mmol, 1.50 eq) was added dropwise at rt. The resulting solution was stirred for 10 min before 2,4-dimethoxybenzylamine (396 µL, 2.64 mmol, 3.00 eq) was added. The reaction mixture was heated to 60 °C for 22 h before it was poured into saturated aqueous $NH_4Cl$-solution (10 mL) and extracted with EtOAc (3×20 mL). The combined organic layers were washed with brine (20 mL), dried over $Na_2SO_4$ and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography on silica (*n*-pentane/EtOAc 5:1 to 1:1) to give compound **19j** (330 mg, 876 µmol, 99%) as orange solid. $R_f$ = 0.30 (*n*-pentane/EtOAc 5:1). $^1$H-NMR (500 MHz, $CDCl_3$): $\delta$ = 9.05 (s, 1H, $CH_{hetarom}$), 7.92 (d, $J$ = 0.6 Hz, 1H, $CH_{hetarom}$), 7.34 (d, $J$ = 8.2 Hz, 1H, $CH_{arom}$), 6.50 (d, $J$ = 2.4 Hz, 1H, $CH_{arom}$), 6.45 (dd, $J$ = 8.2 Hz, 2.4 Hz, 1H, $CH_{arom}$), 6.07 (t, $J$ = 5.6 Hz, 1H, N*H*), 4.73 (d, $J$ = 5.6 Hz, 2H, $CH_2$), 3.88 (s, 3H, $OCH_3$), 3.80 (s, 3H, $OCH_3$), 2.63 (s, 3H, $SCH_3$) ppm. $^{13}$C-NMR (126 MHz, $CDCl_3$): $\delta$ = 164.9 (1 C, $C_{hetarom}SCH_3$), 160.8 (1 C, $C_{arom}$), 159.0 (1 C, $C_{arom}$), 157.4 (1 C, $CH_{hetarom}$), 152.1 (1 C, $C_{hetarom}$), 144.0 (1 C, $C_{hetarom}$), 136.3 (1 C, $C_{hetarom}$), 133.8 (1 C, $CH_{hetarom}$), 131.0 (1 C, $CH_{arom}$), 126.3 (1 C, $C_{hetarom}$), 118.7 (1 C, $C_{arom}$), 104.0 (1 C, $CH_{arom}$), 98.9 (1 C, $CH_{arom}$), 55.6 (1 C, $CH_3$), 55.6 (1 C, $CH_3$), 41.4 (1 C, $CH_2$), 14.7 (1 C, $SCH_3$) ppm. FT-IR: neat; $\tilde{\nu}$ = 3248 (w), 3073 (w), 3001 (w), 2954 (w), 2926 (w), 2830 (w), 1604 (m), 1562 (s), 1521 (w), 1504 (m), 1452 (w), 1423 (w), 1394 (s), 1354 (w), 1336 (m), 1314 (w), 1286 (w), 1260 (m), 1210 (m), 1181 (w), 1156 (w), 1139 (w), 1126 (s), 1046 (w), 1024 (m), 968 (m), 942 (w), 922 (w), 890 (m), 853 (w), 832 (m), 811 (w), 764 (w), 734 (w), 647 (w), 627 (w), 608 (m), 584 (w), 540 (m), 471 (w), 432 (w) cm$^{-1}$. m.p.: 149 °C (EtOAc). HRMS (ESI$^+$): *m/z* calc. for $C_{17}H_{18}Cl_1N_4O_2S_1$ $[M+H]^+$: 377.0834, found: 377.0841.

### 7-Chloro-2-(methylthio)pyrido[3,2-*d*]pyrimidin-6-amine (20b)

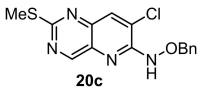


20b

Pyridine **19j** (43.0 mg, 114 µmol, 1.00 eq) was suspended in $CH_2Cl_2$ (0.25 mL) and cooled to 0 °C. TFA (0.75 mL, 9.74 mmol, 85.0 eq) was added dropwise and the resulting solution was stirred for 2.5 h. The intense red reaction mixture was poured into saturated aqueous $NaHCO_3$-solution (10 mL) and extracted with EtOAc (3×10 mL). The combined organic layers were washed with brine (10 mL), dried over $Na_2SO_4$ and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography on silica (*n*-pentane/EtOAc 2:1 to 1:1) to give compound

**20b** (16.0 mg, 71 μmol, 62%) as beige solid. $R_f$ = 0.33 (*n*-pentane/EtOAc 2:1). $^1$H-NMR (500 MHz, $CDCl_3$): $\delta$ = 8.97 (s, 1H, $CH_{arom}$), 8.03 (s, 1H, $CH_{arom}$), 5.47 (s, 2H, $NH_2$), 2.63 (s, 3H, $SCH_3$) ppm. $^{13}$C-NMR (126 MHz, $CDCl_3$): $\delta$ = 166.2 (1 C, $C_{arom}SCH_3$), 157.4 (1 C, $CH_{arom}$), 153.4 (1 C, $C_{arom}NH_2$), 144.3 (1 C, $C_{arom}$), 135.9 (1 C, $C_{arom}$), 134.9 (1 C, $CH_{arom}$), 125.3 (1 C, $C_{arom}Cl$), 14.7 (1 C, $SCH_3$) ppm. FT-IR: neat; $\tilde{\nu}$ = 3427 (w), 3305 (w), 3249 (w), 3146 (m), 2925 (w), 1732 (w), 1645 (m), 1554 (m), 1473 (m), 1425 (w), 1395 (m), 1340 (w), 1308 (w), 1237 (w), 1184 (w), 1138 (s), 1014 (m), 935 (w), 892 (w), 856 (w), 765 (w), 734 (w), 670 (w), 637 (w), 618 (m), 576 (w), 475 (w), 430 (w) cm$^{-1}$. m.p.: 196 °C (EtOAc). HRMS (ESI$^+$): *m/z* calc. for $C_8H_7Cl_1N_4S_1H_1$ $[M+H]^+$: 227.0153, found: 227.0159.

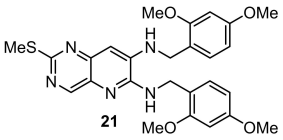
### *O*-Benzyl-*N*-(7-chloro-2-(methylthio)pyrido[3,2-*d*]pyrimidin-6-yl)hydroxylamine (20c)



**20c**

Pyridone **18e** (100 mg, 439 μmol, 1.00 eq) and PyBroP (266 mg, 571 μmol, 1.30 eq) were suspended in THF (4.00 mL) and DBU (198 μL, 1.32 mmol, 3.00 eq) was added dropwise at rt. The resulting solution was stirred for 10 min before *tert*-butyl (benzyloxy) carbamate (294 mg, 1.32 mmol, 3.00 eq) was added. The reaction mixture was stirred for 30 min and heated to 60 °C for 20 h before it was poured into saturated aqueous $NH_4Cl$-solution (15 mL) and extracted with EtOAc (3×20 mL). The combined organic layers were washed with brine (20 mL), dried over $Na_2SO_4$ and the solvent was evaporated under reduced pressure. The crude product was dissolved in $CH_2Cl_2$ (7.00 mL), cooled to 0 °C and TFA (4.42 mL, 57.7 mmol, 132 eq) was added dropwise. After 30 min the reaction mixture was allowed to warm to r.t. and was stirred for additional 1 h before it was poured into saturated aqueous $NaHCO_3$-solution (20 mL) and extracted with EtOAc (3×20 mL). The combined organic layers were washed with brine (20 mL), dried over $Na_2SO_4$ and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography on silica (*n*-pentane/EtOAc 10:1 to 5:1) to give compound **20c** (96.0 mg, 289 μmol, 66%) as yellow solid over two steps. It was isolated as a 5:1 mixture with amidine-like pyridone tautomer. The equilibrium between both could be changed by the addition of different acids. NMR analytics are given for the main tautomer **20c**. $R_f$ = 0.38 (*n*-pentane/EtOAc 5:1). $^1$H-NMR (300 MHz, $CDCl_3$): δ = 8.24 (s, 1H, $CH_{hetarom}$), 8.01 (s, 1H, N*H*), 7.48–7.35 (m, 5H, 5×$CH_{arom}$), 7.28 (d, *J* = 0.6 Hz, 1H, $CH_{hetarom}$), 5.20 (s, 2H, $CH_2$), 2.55 (s, 3H, $SCH_3$) ppm. $^{13}$C-NMR (75 MHz, $CDCl_3$): $\delta$ = 164.9 (1 C, $C_{hetarom}SCH_3$), 144.4 (1 C, $C_{hetarom}$), 143.3 (1 C, $C_{hetarom}$), 142.3 (1 C, $CH_{hetarom}$), 133.1 (1 C, $C_{hetarom}$), 130.0 (1 C, $CH_{hetarom}$), 129.4 (2 C, 2×$CH_{arom}$), 129.2 (1 C, $C_{arom}$), 128.7 (2 C, 2×$CH_{arom}$), 128.6 (1 C, $C_{arom}$), 127.9 (1 C, $C_{hetarom}$), 77.2 (1 C, $CH_2$), 14.5 (1 C, $SCH_3$) ppm. FT-IR: neat; $\tilde{\nu}$ = 3240 (w), 3147 (w), 3032 (w), 2925 (w), 2872 (w), 1617 (w), 1590 (m), 1567 (w), 1537 (w), 1446 (m), 1388 (s), 1317 (w), 1221 (w), 1186 (s), 1155 (w), 1082 (w), 1043 (s), 1020 (w), 945 (m), 884 (w), 836 (w), 778 (w), 745 (m), 693 (s), 670 (w), 643 (m), 587 (w), 551 (w), 491 (w), 443 (w) cm$^{-1}$. m.p.: 159 °C (EtOAc). HRMS (ESI$^+$): *m/z* calc. for $C_{15}H_{14}Cl_1N_4O_1S_1$ $[M+H]^+$: 333.0577, found: 333.0571.

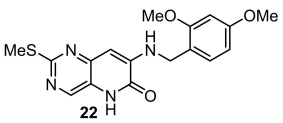
### *N*6,*N*7-Bis(2,4-dimethoxybenzyl)-2-(methylthio)pyrido[3,2-*d*]pyrimidine-6,7-diamine (21)



**21**

Pyridine **19j** (25.0 mg, 66.3 μmol, 1.00 eq), $Pd_2(dba)_3$ (2.2 mg, 7 μmol, 0.04 eq), XPhos (3.8 mg, 8 μmol, 0.12 eq) and NaO$^t$Bu (7.5 mg, 80 μmol, 1.20 eq) were suspended in $^t$BuOH (0.30 mL). 2,4-dimethoxybenzylamine (11 μL, 69.7 mmol, 1.05 eq) was added and the resulting suspension was heated to 95 °C for 22 h. The intense red reaction mixture was poured into saturated aqueous $NH_4Cl$-solution (5 mL) and extracted with EtOAc (3×10 mL). The combined organic layers were washed with brine (10 mL), dried over $Na_2SO_4$ and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography on silica (*n*-pentane/EtOAc 2:1 to 1:1) to give compound **21** (22.6 mg, 45 μmol, 68%) as orange oil. $R_f$ = 0.55 (*n*-pentane/EtOAc 1:1). $^1$H-NMR (500 MHz, $CDCl_3$): $\delta$ = 8.83 (s, 1H, $CH_{hetarom}$), 7.32 (d, *J* = 8.1 Hz, 1H, $CH_{arom}$), 7.14 (d, *J* = 8.4 Hz, 1H, $CH_{arom}$), 6.89 (s, 1H, $CH_{hetarom}$), 6.45–6.39 (m, 4H, 4×$CH_{arom}$), 5.11 (s, 1H, N*H*), 4.65 (d, *J* = 4.9 Hz, 2H, $CH_2$), 4.54 (s, 1H, N*H*), 4.30 (d, *J* = 5.0 Hz, 2H, $CH_2$), 3.78–3.77 (m, 12H, 4×$OCH_3$),2.63 (s, 3H, $SCH_3$) ppm. $^{13}$C-NMR (75 MHz, $CDCl_3$): $\delta$ = 164.3 (1 C, $C_{hetarom}SCH_3$), 160.9 (1 C, $C_{arom}$), 160.7 (1 C, $C_{arom}$), 158.9 (1 C, $C_{arom}$), 158.7 (1 C, $C_{arom}$), 154.9 (1 C, $CH_{hetarom}$), 149.7 (1 C, $C_{hetarom}$), 147.8 (1 C, $C_{hetarom}$), 139.9 (1 C, $C_{hetarom}$), 131.4 (1 C, $CH_{arom}$), 131.2 (1 C, $C_{hetarom}$), 130.6 (1 C, $CH_{arom}$), 119.3 (1 C, $C_{arom}$), 117.5 (1 C, $C_{arom}$), 107.3 (1 C, $CH_{hetarom}$), 104.3 (1 C, $CH_{arom}$), 104.1 (1 C, $CH_{arom}$), 98.9 (1 C, $CH_{arom}$), 98.8 (1 C, $CH_{arom}$), 55.5 (1 C, $OCH_3$), 55.5 (1 C, $OCH_3$), 55.5 (2 C, 2×$OCH_3$), 43.3 (1 C, $CH_2$), 41.7 (1 C, $CH_2$), 14.6 (1 C, $SCH_3$) ppm. FT-IR: neat; $\tilde{\nu}$ = 3345 (w), 2931 (w), 2838 (w), 2251 (w), 1613 (w), 1588 (w), 1559 (w), 1507 (m), 1489 (w), 1463 (w), 1438 (w), 1400 (w), 1375 (w), 1288 (w), 1254 (w), 1207 (m), 1156 (m), 1129 (w), 1036 (m), 904 (s), 836 (w), 791 (w), 724 (s), 647 (w), 588 (w), 509 (w), 464 (w). HRMS (ESI$^+$): *m/z* calc. for $C_{26}H_{30}N_5O_4S_1$ $[M+H]^+$: 508.2013, found: 508.2019.

### 7-((2,4-Dimethoxybenzyl)amino)-2-(methylthio)pyrido[3,2-*d*]pyrimidin-6(5*H*)-one (22)

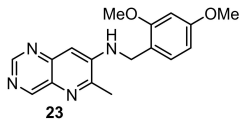


**22**

Pyridone **18f** (74.4 mg, 272 μmol, 1.00 eq), benzylamine (44 μL, 286 μmol, 1.05 eq), $Pd_2dba_3$ (10.0 mg, 11 μmol, 0.04 eq), XPhos (15.6 mg, 33 μmol, 0.12 eq) and NaO$^t$Bu (57.5 mg, 598 μmol, 2.20 eq) were suspended in $^t$BuOH (1.00 mL) and heated to 95 °C for 22 h. The greenish reaction mixture was filtered over a pad of celite which was rinsed with EtOAc/MeOH (10:1, 10.0 mL) and all solvents were evaporated from the filtrate under reduced pressure. The crude product was purified by column chromatography on silica (*n*-pentane/EtOAc 1:1 to EtOAc) to give compound **22** (73.0 mg, 204 μmol, 75%) as yellow solid. $R_f$ = 0.51 (EtOAc). $^1$H-NMR (500 MHz, DMSO-d6): $\delta$ = 12.10 (s, 1H, $NCOH_{hetarom}$), 8.31 (s, 1H, $CH_{hetarom}$), 7.28 (t, *J* = 6.3 Hz, 1H, N*H*), 7.09 (d, *J* = 8.5 Hz, 1H, $CH_{arom}$), 6.60 (d, *J* = 2.5 Hz, 1H, $CH_{arom}$), 6.47 (dd, *J* = 8.2, 2.3 Hz, 1H, $CH_{arom}$), 6.24 (s, 1H, $CH_{hetarom}$), 4.35 (d, *J* = 6.2 Hz, 2H, $CH_2$), 3.86 (s, 3H, $OCH_3$), 3.73 (s, 3H, $OCH_3$), 2.46 (s, 3H, $SCH_3$) ppm. $^{13}$C-NMR (126 MHz, DMSO-d6): $\delta$ = 163.4 (1 C, $C_{hetarom}SCH_3$), 159.9 (1 C, $C_{arom}$), 157.8 (1 C, $C_{arom}$), 156.3 (1 C, $C_{hetarom}$), 145.9 (1 C, $C_{hetarom}$), 144.7 (1 C, $NC_{hetarom}O$),

142.0 (1 C, $CH_{hetarom}$), 128.5 (1 C, $CH_{arom}$), 121.8 (1 C, $C_{hetarom}$), 116.9 (1 C, $C_{arom}$), 104.6 (1 C, $CH_{arom}$), 99.5 (1 C, $CH_{hetarom}$), 98.4 (1 C, $CH_{arom}$), 55.5 (1 C, $OCH_3$), 55.1 (1 C, $OCH_3$), 39.9 (1 C, $CH_2$), 13.6 (1 C, $SCH_3$) ppm. FT-IR: neat; $\tilde{\nu}$ = 3371 (w), 3126 (w), 2993 (w), 2923 (w), 2832 (m), 2749 (w), 1659 (s), 1587 (s), 1562 (w), 1503 (m), 1456 (m), 1417 (w), 1373 (s), 1288 (m), 1262 (w), 1204 (m), 1158 (m), 1133 (w), 1065 (w), 1034 (m), 973 (w), 926 (w), 890 (w), 857 (w), 828 (m), 770 (w), 752 (w), 720 (w), 669 (w), 634 (w), 608 (w), 589 (w), 537 (m), 451 (m), 414 (w) $cm^{-1}$. m.p.: 232 °C (EtOAc). HRMS ($ESI^+$): *m/z* calc. for $C_{17}H_{19}N_4O_3S_1$ $[M+H]^+$: 359.1172, found: 359.1168.

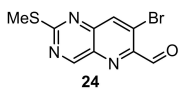
### *N*-(2,4-Dimethoxybenzyl)-6-methylpyrido[3,2-*d*]pyrimidin-7-amine (23)



**23**

Pyridopyrimidine **18c** (20.0 mg, 89 μmol, 1.00 eq), $Pd_2dba_3$ (3.3 mg, 4 μmol, 0.04 eq), XantPhos (6.2 mg, 11 μmol, 0.12 eq) and $Cs_2CO_3$ (40.7 mg, 125 μmol, 1.40 eq) were suspended in toluene (0.50 mL) and benzylamine (16.4 μL, 107 μmol, 1.20 eq) was added before the reaction mixture was heated to 110 °C for 14 h. The greenish reaction mixture was poured into saturated aqueous $NaHCO_3$-solution (5 mL) and extracted with EtOAc (3×10 mL). The combined organic layers were washed with brine (10 mL), dried over $Na_2SO_4$ and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography on silica (EtOAc to EtOAc/MeOH 10:1) to give compound **23** (27.6 mg, 89 μmol, 99%) as pale yellow solid. $R_f$ = 0.26 (EtOAc). $^1$H-NMR (500 MHz, $CDCl_3$): $\delta$ = 9.21 (s, 1H, $CH_{hetarom}$), 9.09 (s, 1H, $CH_{hetarom}$), 7.23 (d, $J$ = 8.2 Hz, 1H, $CH_{arom}$), 7.13 (s, 1H, $CH_{hetarom}$), 6.51 (d, $J$ = 2.2 Hz, 1H, $CH_{arom}$), 6.46 (dd, $J$ = 8.3, 2.2 Hz, 1H, $CH_{arom}$), 4.94 (t, $J$ = 5.6 Hz, 1H, N*H*), 4.43 (d, $J$ = 5.5 Hz, 2H, $CH_2$), 3.87 (s, 3H, $OCH_3$), 3.81 (s, 3H, $OCH_3$), 2.61 (s, 3H, $CH_3$) ppm. $^{13}$C-NMR (126 MHz, $CDCl_3$): $\delta$ = 161.1 (1 C, $C_{arom}$), 158.8 (1 C, $C_{arom}$), 158.0 (1 C, $CH_{hetarom}$), 155.3 (1 C, $CH_{hetarom}$), 152.3 (1 C, $C_{hetarom}$), 148.9 (1 C, $C_{hetarom}$), 146.7 (1 C, $C_{hetarom}$), 132.9 (1 C, $C_{hetarom}$), 130.4 (1 C, $CH_{arom}$), 117.1 (1 C, $C_{arom}$), 106.6 (1 C, $CH_{hetarom}$), 104.2 (1 C, $CH_{arom}$), 99.1 (1 C, $CH_{arom}$), 55.6 (2 C, 2×$OCH_3$), 43.3 (1 C, $CH_2$), 21.6 (1 C, $CH_3$) ppm. FT-IR: neat; $\tilde{\nu}$ = 3272 (m), 3050 (w), 3001 (w), 2942 (w), 2840 (w), 2366 (w), 2202 (w), 2176 (w), 2136 (w), 2058 (w), 2009 (w), 1945 (w), 1719 (w), 1611 (w), 1579 (m), 1530 (s), 1503 (w), 1454 (w), 1431 (m), 1414 (w), 1375 (w), 1354 (m), 1301 (m), 1258 (w), 1230 (w), 1208 (s), 1152 (m), 1124 (m), 1091 (w), 1061 (w), 1034 (m), 995 (w), 920 (m), 844 (m), 827 (w), 795 (w), 760 (w), 743 (w), 712 (m), 688 (w), 636 (w), 615 (m), 580 (s), 544 (w) $cm^{-1}$. m.p.: 148 °C (EtOAc). HRMS ($ESI^+$): *m/z* calc. for $C_{17}H_{18}N_4O_2H_1$ $[M+H]^+$: 311.1503, found: 311.1503.

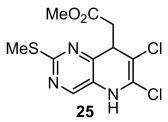
### 7-Amino-2-(methylthio)pyrido[3,2-*d*]pyrimidine-6-carbaldehyde (24)



**24**

Pyridopyrimidine **18g** (20.0 mg, 74 μmol, 1.00 eq) was suspended in 1,4-dioxane (0.50 mL) and $SeO_2$ (9.9 mg, 89 μmol, 1.20 eq) was added. The suspension was stirred for 56 h at 100 °C before it was poured into saturated aqueous $NH_4Cl$-solution (5 mL) and extracted with EtOAc (3×10 mL). The combined organic layers were washed with brine (10 mL), dried over $Na_2SO_4$ and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography on silica (*n*-pentane/EtOAc 10:1 to 5:1) to give compound **24** (16.0 mg, 56 mmol, 76%) as yellow solid. $R_f$ = 0.09 (*n*-pentane/EtOAc 10:1). $^1$H-NMR (500 MHz, $CDCl_3$): $\delta$ = 10.30 (s, 1H, *CH*O), 9.46 (d, $J$ = 0.8 Hz, 1H, $CH_{arom}$), 8.51 (t, $J$ = 0.8 Hz, 1H, $CH_{arom}$), 2.70 (s, 3H, $SCH_3$) ppm. $^{13}$C-NMR (126 MHz, $CDCl_3$): $\delta$ = 189.6 (1 C, CHO), 174.4 (1 C, $C_{arom}SCH_3$), 162.1 (1 C, $CH_{arom}$), 147.8 (1 C, $NC_{arom}CHO$), 147.3 (1 C, $C_{arom}$), 140.5 (1 C, $CH_{arom}$), 136.7 (1 C, $C_{arom}$), 123.6 (1 C, $CBr_{arom}$), 15.0 (1 C, $SCH_3$) ppm. FT-IR: neat; $\tilde{\nu}$ = 3037 (m), 2925 (w), 2828 (w), 2554 (w), 2372 (w), 2220 (w), 2149 (w), 2050 (w), 1717 (s), 1581 (s), 1550 (w), 1527 (w), 1420 (w), 1397 (m), 1358 (m), 1338 (w), 1298 (w), 1240 (m), 1179 (w), 1127 (s), 985 (s), 926 (w), 809 (w), 779 (s), 734 (w), 711 (w), 694 (w), 631 (m), 597 (w), 481 (w), 448 (m), 428 (w) $cm^{-1}$. m.p.: 153 °C (EtOAc). HRMS ($APCI^+$): *m/z* calc. for $C_9H_6Br_1N_3O_1S_1H_1$ $[M+H]^+$: 285.9467 & 283.9488, found: 285.9469 & 283.9489.

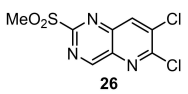
### Methyl 2-(6,7-dichloro-2-(methylthio)-5,8-dihydropyrido[3,2-*d*]pyrimi-din-8-yl)acetate (25)



**25**

Pyridine **19g** (25.0 mg, 102 μmol, 1.00 eq) was dissolved in THF (0.55 mL) and Reformatsky-reagent (1 m in THF, 152 μL, 152 μmol, 1.50 eq) was added at rt. After 1 h the reaction mixture was poured into saturated aqueous $NH_4Cl$-solution (5 mL) and extracted with EtOAc (3×10 mL). The combined organic layers were washed with brine (5 mL), dried over $Na_2SO_4$ and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography on silica (*n*-pentane/EtOAc 5:1 to 2:1) to give compound **25** (33.0 mg, 102 μmol, 99%) as colorless solid $R_f$ = 0.07 (*n*-pentane/EtOAc 5:1). $^1$H-NMR (500 MHz, $CDCl_3$): $\delta$ = 7.41 (s, 1H, $CH_{arom}$), 6.10 (s, 1H, N*H*), 5.04 (dd, $J$ = 10.8, 2.4 Hz, 1H, *CH*), 3.74 (s, 3H, $CO_2CH_3$), 3.00 (dd, $J$ = 17.5, 2.5 Hz, 1H, $CH_aH_bCO_2CH_3$), 2.80 (dd, $J$ = 17.5, 10.8 Hz, 1H, $CH_aH_bCO_2CH_3$), 2.49 (s, 3H, $SCH_3$) ppm. $^{13}$C-NMR (126 MHz, $CDCl_3$): $\delta$ = 172.2 (1 C, $CO_2CH_3$), 160.1 (1 C, $C_{arom}SCH_3$), 142.3 (1 C, $C_{olef}Cl$), 141.5 (1 C, $C_{arom}$), 138.9 (1 C, $C_{olef}Cl$), 132.9 (1 C, $CH_{arom}$), 130.0 (1 C, $C_{arom}$), 52.4 (1 C, $CO_2CH_3$), 52.2 (1 C, $CHCH_2$), 40.8 (1 C, $CH_2CO_2CH_3$), 13.8 (1 C, $SCH_3$) ppm. FT-IR: neat; $\tilde{\nu}$ = 3325 (w), 2954 (w), 2927 (w), 2851 (w), 1723 (w), 1591 (w), 1542 (w), 1498 (w), 1435 (w), 1405 (w), 1380 (w), 1316 (w), 1287 (w), 1244 (w), 1225 (w), 1194 (w), 1172 (w), 1148 (w), 1034 (w), 980 (w), 952 (w), 892 (w), 802 (w), 748 (w), 712 (w), 666 (w), 633 (w), 575 (w), 540 (w), 460 (w), 424 (w) $cm^{-1}$. m.p.: 144 °C (EtOAc). HRMS ($ESI^+$): *m/z* calc. for $C_{11}H_{11}Cl_2N_3O_2S_1H_1$ $[M+H]^+$: 320.0022 & 321.9993, found: 320.0024 & 321.9993.

### 6,7-Dichloro-2-(methylsulfonyl)pyrido[3,2-*d*]pyrimidine (26)

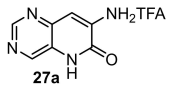


**26**

Pyridine **19g** (144 mg, 585 μmol, 1.00 eq) was suspended in MeCN (0.91 mL), $CCl_4$ (0.91 mL) and $H_2O$ (1.82 mL) before $RuCl_3$ • x $H_2O$ (12.1 mg, 59 μmol, 0.10 eq) and $NaIO_4$ (563 mg, 2.63 mmol, 4.50 eq) was added. The resulting deep brown biphasic reaction mixture was stirred for 75 min at rt. It was then poured into brine (10 mL) and extracted with EtOAc (3×10 mL). The combined organic layers were dried over $Na_2SO_4$ and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography on silica (*n*-pentane/EtOAc 3:2 to 1:1) to give

compound **26** (150 mg, 539 μmol, 92%) as colorless solid. $R_f$ = 0.29 (*n*-pentane/EtOAc 2:1). $^1$H-NMR (500 MHz, $CDCl_3$): $\delta$ = 9.70 (d, *J* = 0.9 Hz, 1H, C*H*$_{arom}$), 8.62 (d, *J* = 0.9 Hz, 1H, C*H*$_{arom}$), 3.47 (s, 3H, $SO_2CH_3$) ppm. $^{13}$C-NMR (126 MHz, $CDCl_3$): $\delta$ = 163.5 (1 C, $C_{arom}SO_2CH_3$), 162.5 (1 C, *C*H$_{arom}$), 154.2 (1 C, *C*Cl$_{arom}$), 145.9 (1 C, *C*$_{arom}$), 138.3 (1 C, *C*$_{arom}$), 138.1 (1 C, *C*Cl$_{arom}$), 137.9 (1 C, *C*H$_{arom}$), 39.6 (1 C, $SO_2CH_3$) ppm. FT-IR: neat; $\tilde{\nu}$ = 3070 (w), 3038 (w), 2929 (w), 2323 (w), 2124 (w), 1729 (w), 1582 (w), 1560 (w), 1543 (w), 1431 (m), 1410 (w), 1371 (w), 1303 (s), 1195 (w), 1150 (w), 1123 (s), 984 (w), 961 (m), 920 (m), 806 (w), 765 (s), 710 (w), 650 (w), 616 (m), 548 (m), 526 (m), 491 (s), 440 (w), 420 (w) cm$^{-1}$. m.p.: 185 °C ($CH_2Cl_2$). HRMS (ESI$^+$): *m/z* calc. for $C_8H_5Cl_2N_3O_2S_1Na_1$ $[M+Na]^+$: 299.9372 & 301.9342, found: 299.9367 & 301.3993.

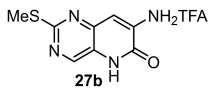
### 7-Aminopyrido[3,2-*d*]pyrimidin-6(5*H*)-one 2,2,2-trifluoroacetate (27 a)



**27a**

Pyridopyrimidine **18 b** (41.0 mg, 156 μmol, 1.00 eq) was suspended in $CHCl_3$ (3.00 mL) and cooled to 0 °C before TFA (608 μL, 7.82 mmol, 50.0 eq) was added dropwise. The solution was stirred for 15 min before it was allowed to warm to rt and stirred for additional 8 h. All solvents were evaporated under reduced pressure and the crude product was purified by column chromatography on silica ($CHCl_3$/MeOH 8:1 to 7:1) to give TFA salt of compound **27 a** (41.0 mg, 149 μmol, 95%) as brown solid. $R_f$ = 0.27 ($CHCl_3$/MeOH 7:1). $^1$H-NMR (500 MHz, DMSO-d6): $\delta$ = 12.12 (s, 1H, N*H*), 8.67 (s, 1H, C*H*$_{arom}$), 8.44 (s, 1H, C*H*$_{arom}$), 6.66 (s, 2H, N*H*$_2$), 6.65 (s, 1H, C*H*$_{arom}$) ppm. $^{13}$C-NMR (126 MHz, $CDCl_3$): $\delta$ = 157.7 (q, *J* = 30.9 Hz, 1 C, *C*OCF$_3$), 156.8 (1 C, *C*$_{arom}$), 152.2 (1 C, *C*H$_{arom}$), 146.0 (1 C, NH*C*O), 145.1 (1 C, *C*$_{arom}$), 141.1 (1 C, *C*H$_{arom}$), 125.2 (1 C, *C*$_{arom}$), 117.3 (q, *J* = 291.5 Hz, 1 C, *C*F$_3$), 102.6 (1 C, *C*H$_{arom}$) ppm. $^{19}$F-NMR (283 MHz, $CDCl_3$): $\delta$ = –75.8 (s, 3F, *C*F$_3$), –164.9 (s, 6F, internal standard $C_6F_6$) ppm. FT-IR: neat; $\tilde{\nu}$ = 3398 (m), 3276 (w), 3138 (w), 3006 (w), 2939 (w), 2833 (w), 2765 (w), 2702 (w), 2164 (w), 2018 (w), 1940 (w), 1897 (w), 1674 (m), 1626 (w), 1577 (s), 1503 (w), 1467 (m), 1406 (w), 1366 (m), 1316 (w), 1286 (w), 1193 (m), 1143 (s), 953 (m), 925 (w), 898 (w), 846 (m), 800 (m), 772 (w), 720 (m), 631 (w), 606 (w), 588 (w) cm$^{-1}$. m.p.: 269 °C decomposition (MeOH). HRMS (ESI$^+$): *m/z* calc. for $C_7H_6N_4O_1H_1$ $[M+H]^+$: 163.0614, found: 163.0615.

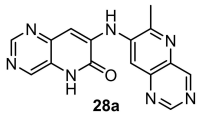
### 7-Amino-2-(methylthio)pyrido[3,2-*d*]pyrimidin-6(5*H*)-one 2,2,2-tri-fluoroacetate (27 b)



**27b**

Pyridopyrimidine **18 d** (38.0 mg, 120 μmol, 1.00 eq) was suspended in $CHCl_3$ (2.50 mL) and cooled to 0 °C before TFA (480 μL, 6.16 mmol, 50.0 eq) was added dropwise. The solution was stirred for 15 min before it was allowed to warm to rt and stirred for additional 18 h. All solvents were evaporated under reduced pressure and the crude product was purified by column chromatography on silica (EtOAc/MeOH 20:1 to 10:1) to give TFA salt of compound **27 b** (41.0 mg, 120 μmol, 99%) as brownish solid. If the reaction was scaled up to 1.88 mmol the yield dropped to 70%. $R_f$ = 0.41 (EtOAc). $^1$H-NMR (500 MHz, DMSO-d6): $\delta$ = 12.04 (s, 1H, N*H*CO), 8.29 (s, 1H, C*H*$_{arom}$), 6.76 (s, 2H, N*H*$_2$), 6.54 (s, 1H, C*H*$_{arom}$), 2.48 (s, 3H, S*CH*$_3$) ppm. $^{13}$C-NMR (126 MHz, $CDCl_3$): $\delta$ = 163.2 (1 C, $C_{arom}SCH_3$), 157.7 (q, *J* = 30.9 Hz, 1 C, $CF_3CO_2H$), 156.4 (1 C, *C*ONH), 146.6 (1 C, *C*$_{arom}$), 146.1 (1 C, *C*$_{arom}$), 141.8 (1 C, *C*H$_{arom}$), 122.3 (1 C, *C*$_{arom}$), 117.4 (q, *J* = 304.1 Hz, 1 C, *C*F$_3$), 102.0 (1 C, *C*H$_{arom}$), 13.7 (1 C, *SCH*$_3$) ppm. $^{19}$F-NMR (283 MHz, $CDCl_3$): $\delta$ = –75.8 (s, 3F, *C*F$_3$), –164.9 (s, 6F, internal standard $C_6F_6$) ppm. FT-IR: neat; $\tilde{\nu}$ = 3437 (w), 3328 (m), 3150 (w), 2926 (w), 2882 (w), 2437 (w), 1665 (m), 1605 (w), 1564 (s), 1445 (m), 1359 (s), 1314 (w), 1272 (w), 1244 (w), 1198 (w), 1173 (w), 1134 (s), 942 (w), 870 (w), 844 (m), 801 (m), 769 (w), 724 (m), 654 (w), 600 (w), 563 (w), 534 (m), 461 (w), 428 (w) cm$^{-1}$. m.p.: 251 °C decomposition (MeOH). HRMS (ESI$^+$): *m/z* calc. for $C_8H_8N_4O_1S_1H_1$ $[M+H]^+$: 209.0492, found: 209.0491.

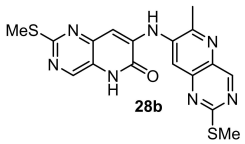
### 7-((6-Methylpyrido[3,2-*d*]pyrimidin-7-yl)amino)pyrido[3,2-*d*] pyrimi-din-6(5*H*)-one (28 a)



**28a**

Pyridopyrimidine TFA salt **27 a** (24.7 mg, 89 μmol, 1.00 eq), pyridopyrimidine **18 c** (20.0 mg, 89 μmol, 1.00 eq), $Pd_2dba_3$ (3.3 mg, 4 μmol, 0.04 eq), XantPhos (6.2 mg, 11 μmol, 0.12 eq) and $Cs_2CO_3$ (61.1 mg, 187 μmol, 2.10 eq) were suspended in 1,4-dioxane (0.90 mL) and heated to 105 °C for 2.5 h. The greenish reaction mixture was filtered over a pad of celite which was rinsed with MeOH (5.00 mL) and all solvents were evaporated from the filtrate under reduced pressure. The crude product was purified by column chromatography on silica ($CHCl_3$/MeOH 12:1) to give compound **28 a** (20.0 mg, 66 μmol, 74%) as highly yellow solid. $R_f$ = 0.36 ($CHCl_3$/MeOH 8:1). $^1$H-NMR (500 MHz, DMSO-d6): $\delta$ = 12.72 (s, 1H, N*H*CO), 9.51 (s, 1H, C*H*$_{arom}$), 9.31 (s, 1H, C*H*$_{arom}$), 8.88 (s, 1H, C*H*$_{arom}$), 8.73 (s, 1H, N*H*), 8.68 (s, 1H, C*H*$_{arom}$), 8.31 (s, 1H, C*H*$_{arom}$), 7.26 (s, 1H, C*H*$_{arom}$), 2.76 (s, 3H, *CH*$_3$) ppm. $^{13}$C-NMR (126 MHz, DMSO-d6): $\delta$ = 159.2 (1 C, *C*H$_{arom}$), 157.9 (1 C, *C*$_{arom}$), 156.9 (1 C, *C*$_{arom}$), 155.4 (1 C, *C*H$_{arom}$), 152.7 (1 C, *C*H$_{arom}$), 146.3 (1 C, *C*$_{arom}$), 143.6 (1 C, *C*$_{arom}$), 142.9 (1 C, *C*H$_{arom}$), 140.1 (1 C, *C*$_{arom}$), 139.4 (1 C, *C*$_{arom}$), 135.9 (1 C, *C*$_{arom}$), 126.6 (1 C, *C*$_{arom}$), 123.3 (1 C, *C*H$_{arom}$), 107.6 (1 C, *C*H$_{arom}$), 21.9 (1 C, *C*H$_3$) ppm. FT-IR: neat; $\tilde{\nu}$ = 3308 (w), 2993 (w), 2901 (w), 2837 (w), 2742 (w), 2128 (w), 1674 (m), 1619 (w), 1587 (w), 1525 (s), 1460 (w), 1416 (w), 1360 (m), 1245 (w), 1217 (w), 1196 (w), 1174 (w), 1122 (w), 1090 (w), 1023 (w), 1002 (w), 933 (w), 872 (m), 758 (w), 691 (w), 639 (m), 575 (m), 509 (w), 472 (w), 450 (w) cm$^{-1}$. m.p.: 253 °C decomposition (MeOH). HRMS (ESI$^+$): *m/z* calc. for $C_{15}H_{11}N_7O_1H_1$ $[M+H]^+$: 306.1098, found: 306.1099.

### 7-((6-Methyl-2-(methylthio)pyrido[3,2-*d*]pyrimidin-7-yl) amino)-2-(methylthio)-pyrido[3,2-*d*]pyrimidin-6(5*H*)-one (28 b)

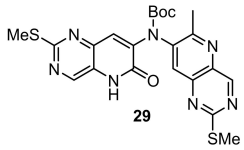


**28b**

Pyridopyrimidine TFA salt **27 b** (83.5 mg, 259 μmol, 1.00 eq), pyridopyrimidine **18 g** (70.0 mg, 259 μmol, 1.00 eq), $Pd_2dba_3$ (9.5 mg, 10 μmol, 0.04 eq), XantPhos (18.0 mg, 31 μmol, 0.12 eq) and $Cs_2CO_3$ (177 mg, 544 μmol, 2.10 eq) were suspended in 1,4-dioxane (2.50 mL) and heated to 105 °C for 8.5 h. The greenish reaction mixture was filtered over a pad of celite which was rinsed with EtOAc/MeOH (10:1, 10.0 mL) and all solvents were evaporated from the filtrate under reduced pressure. The crude product was purified by column chromatography on silica ($CHCl_3$/MeOH 20:1) to give compound **28 b** (103 mg, 259 μmol, 99%) as highly yellow

solid. $R_f = 0.29$ (EtOAc). $^1$H-NMR (500 MHz, DMSO-d6): $\delta = 12.59$ (s, 1H, NHCO), 9.27 (s, 1H, $CH_{arom}$), 8.68 (s, 1H, NH), 8.51 (s, 1H, $CH_{arom}$), 8.11 (s, 1H, $CH_{arom}$), 7.13 (s, 1H, $CH_{arom}$), 2.71 (s, 3H, $CH_3$), 2.64 (s, 3H, $SCH_3$), 2.50 (s, 3H, $SCH_3$) ppm. $^{13}$C-NMR (126 MHz, DMSO-d6): $\delta =$ 168.2 (1 C, $C_{arom}SCH_3$), 164.1 (1 C, $C_{arom}SCH_3$), 159.3 (1 C, $CH_{arom}$), 156.4 (1 C, NHCO), 155.6 (1 C, $C_{arom}$), 147.0 (1 C, $C_{arom}$), 144.6 (1 C, $C_{arom}$), 143.6 (1 C, $CH_{arom}$), 140.3 (1 C, $C_{arom}$), 139.5 (1 C, $C_{arom}$), 133.8 (1 C, $C_{arom}$), 123.5 (1 C, $C_{arom}$), 121.9 (1 C, $CH_{arom}$), 106.8 (1 C, $CH_{arom}$), 21.5 (1 C, $CH_3$), 14.0 (1 C, $SCH_3$), 13.7 (1 C, $SCH_3$) ppm. FT-IR: neat; $\tilde{\nu} = 3264$ (w), 3144 (w), 2840 (w), 2740 (w), 2192 (w), 1679 (m), 1617 (w), 1599 (w), 1576 (w), 1536 (s), 1444 (w), 1421 (w), 1398 (w), 1371 (m), 1334 (w), 1312 (w), 1223 (w), 1179 (w), 1132 (m), 963 (w), 940 (w), 851 (w), 760 (w), 708 (w), 690 (w), 656 (w), 636 (w), 604 (w), 582 (m), 533 (w), 514 (w), 448 (w), 417 (w) cm$^{-1}$. m.p.: 285 °C decomposition (MeOH). HRMS (ESI$^+$): *m/z* calc. for $C_{17}H_{15}N_7O_1S_2H_1$ $[M+H]^+$: 398.0852, found: 398.0850.

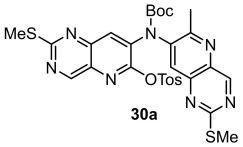
### *tert*-Butyl (6-methyl-2-(methylthio)pyrido[3,2-*d*] pyrimidin-7-yl)(2-(methylthio)-6-*oxo*-5,6-dihydropyrido[3,2-*d*] pyrimidin-7-yl)carbamate (29)



**29**

Compound **28 b** (100 mg, 252 μmol, 1.00 eq) and DMAP (3.1 mg, 25 μmol, 0.10 eq) were suspended in THF (4.50 mL) cooled to 0 °C and DIPEA (90 μL, 528 μmol, 2.10 eq) was added. The solution was stirred for 5 min before $Boc_2O$ (1 m in THF, 516 μL, 516 μmol, 2.05 eq) was added. The reaction mixture was stirred for 5.5 h while it was allowed to warm to rt. The dark orange reaction mixture was poured into saturated aqueous $NH_4Cl$-solution (10 mL) and extracted with EtOAc (3×20 mL). The combined organic layers were washed with brine (20 mL), dried over $Na_2SO_4$ and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography on silica (*n*-pentane/EtOAc 2:1 to EtOAc) to give as single regioisomer $Boc_2$-compound (71.0 mg, 119 μmol, 47 %, 51 % brsm) as white foam and $Boc_1$-compound **29** (55.0 mg, 111 μmol, 44 %, 48 % brsm) as pale yellow solid. By doing 2D-TLC it was found that $Boc_2$-compound decomposes during column chromatography on silica to $Boc_1$-compound **29** with the free amide-functionality. That's why $Boc_2$-compound was later on converted into $Boc_1$-compound **29** by doing another column. The overall yield is 91 % and 99 % brsm respectively. $R_f = 0.81$ (EtOAc). $^1$H-NMR (500 MHz, DMSO-d6): $\delta = 12.44$ (s, 1H, NHCO), 9.35 (s, 1H, $CH_{arom}$), 8.70 (s, 1H, $CH_{arom}$), 8.05 (s, 1H, $CH_{arom}$), 8.04 (s, 1H, $CH_{arom}$), 2.71 (s, 3H, $CH_3$), 2.57 (s, 3H, $SCH_3$), 2.53 (s, 3H, $SCH_3$), 1.42 (s, 9H, $C(CH_3)_3$) ppm. $^{13}$C-NMR (126 MHz, DMSO-d6): $\delta = 168.3$ (1 C, $C_{arom}SCH_3$), 164.2 (1 C, $C_{arom}SCH_3$), 160.1 (1 C, $CH_{arom}$), 159.7 (1 C, $C_{arom}$), 157.6 (1 C, $C_{arom}$), 151.6 (1 C, $NCO_2{}^tBu$), 146.3 (1 C, $C_{arom}$), 146.0 (1 C, $CH_{arom}$), 142.0 (1 C, $C_{arom}$), 141.8 (1 C, $C_{arom}$), 141.2 (1 C, NHCO), 135.6 (1 C, $C_{arom}$), 134.1 (1 C, $CH_{arom}$), 130.4 (1 C, $CH_{arom}$), 128.1 (1 C, $C_{arom}$), 82.7 (1 C, $C(CH_3)_3$), 27.6 (3 C, $C(CH_3)_3$), 21.8 (1 C, $CH_3$), 14.0 (1 C, $SCH_3$), 13.8 (1 C, $SCH_3$) ppm. FT-IR: neat; $\tilde{\nu} = 2975$ (w), 2925 (w), 2849 (w), 2544 (w), 2219 (w), 2188 (w), 2167 (w), 2102 (w), 2036 (w), 2003 (w), 1967 (w), 1709 (s), 1659 (s), 1606 (w), 1569 (m), 1548 (w), 1474 (w), 1446 (w), 1386 (s), 1310 (m), 1261 (w), 1241 (w), 1190 (w), 1144 (w), 1125 (s), 1043 (w), 1021 (w), 958 (w), 935 (w), 911 (w), 866 (w), 823 (w), 804 (w), 766 (w), 731 (w), 708 (w), 672 (w), 648 (w), 605 (m), 579 (w), 561 (w), 542 (w), 474 (w), 447 (w) cm$^{-1}$. m.p.: 305 °C decomposition (EtOAc). HRMS (ESI$^+$): *m/z* calc. for $C_{22}H_{23}N_7O_3S_2Na_1$ $[M+Na]^+$: 520.1196, found: 520.1205.

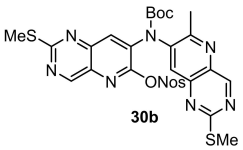
### 7-((*tert*-Butoxycarbonyl)(6-methyl-2-(methylthio)pyrido[3,2-*d*] pyrimidin-7-yl)amino)-2-(methylthio)pyrido[3,2-*d*] pyrimidin-6-yl 4-methylbenzenesulfonate (30 a)



**30a**

Compound **29** (100 mg, 201 μmol, 1.00 eq), TosCl (46.0 mg, 241 μmol, 1.20 eq) and DMAP (2.5 mg, 20 μmol, 0.10 eq) were suspended in THF (3.50 mL) cooled to 0 °C and DIPEA (41.0 μL, 241 μmol, 1.20 eq) was added. The solution was stirred for 6 h before it was poured into saturated aqueous $NH_4Cl$-solution (10 mL) and extracted with EtOAc (3×20 mL). The combined organic layers were washed with brine (20 mL), dried over $Na_2SO_4$ and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography on silica (*n*-pentane/EtOAc 2:1) to give as single regioisomer compound **30 a** (124 mg, 190 μmol, 95 %, 99 % brsm) as pale yellow foam. $R_f = 0.39$ (*n*-pentane/EtOAc 2:1). $^1$H-NMR (500 MHz, $CDCl_3$): $\delta = 9.38$ (s, 1H, $CH_{arom}$), 9.08 (s, 1H, $CH_{arom}$), 7.95 (s, 1H, $CH_{arom}$), 7.93 (d, $J = 8.3$ Hz, 2H, $2\times CH_{Tos}$), 7.85 (s, 1H, $CH_{arom}$), 7.31 (d, $J = 8.3$ Hz, 2H, $2\times CH_{Tos}$), 2.78 (s, 3H, $CH_3$), 2.63 (s, 3H, $SCH_3$), 2.61 (s, 3H, $SCH_3$), 2.45 (s, 3H, Tos-$CH_3$) ppm. $^{13}$C-NMR (126 MHz, $CDCl_3$): $\delta = 171.1$ (1 C, $C_{arom}SCH_3$), 170.3 (1 C, $C_{arom}SCH_3$), 159.9 (1 C, $CH_{arom}$), 159.1 (1 C, $CH_{arom}$), 159.0 (1 C, $C_{arom}$), 151.6 (1 C, $NCO_2{}^tBu$), 151.0 (1 C, $C_{arom}$), 146.6 (1 C, $C_{arom}$), 146.4 (1 C, $C_{arom}$) 146.4 (1 C, $C_{Tos}$), 141.7 (1 C, $C_{arom}$), 136.0 (1 C, $C_{arom}$), 135.1 (1 C, $CH_{arom}$), 134.2 (1 C, $C_{arom}$), 133.5 (1 C, $C_{arom}$), 133.5 (1 C, $C_{Tos}$), 132.7 (1 C, $CH_{arom}$), 129.8 (2 C, $2\times CH_{Tos}$), 129.4 (2 C, $2\times CH_{Tos}$), 84.9 (1 C, $C(CH_3)_3$), 28.1 (3 C, $C(CH_3)_3$), 21.9 (1 C, Tos-$CH_3$), 21.9 (1 C, $CH_3$), 14.8 (1 C, $SCH_3$), 14.7 (1 C, $SCH_3$) ppm. FT-IR: neat; $\tilde{\nu} = 2978$ (w), 2927 (w), 1723 (m), 1601 (w), 1567 (m), 1546 (w), 1433 (w), 1387 (m), 1294 (m), 1255 (w), 1152 (w), 1125 (s), 1087 (w), 1040 (w), 1016 (w), 948 (w), 904 (w), 868 (w), 811 (w), 788 (w), 745 (m), 711 (w), 684 (w), 663 (m), 611 (w), 575 (w), 546 (m), 527 (w), 450 (w) cm$^{-1}$. m.p.: 126 °C (EtOAc). HRMS (ESI$^+$): *m/z* calc. for $C_{29}H_{29}N_7O_5S_3Na_1$ $[M+Na]^+$: 674.1285, found: 674.1279.

### 7-((*tert*-Butoxycarbonyl)(6-methyl-2-(methylthio)pyrido[3,2-*d*] pyrimidin-7-yl)amino)-2-(methylthio)pyrido[3,2-*d*] pyrimidin-6-yl 2-nitrobenzenesulfonate (30 b)

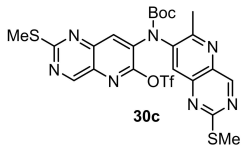


**30b**

Compound **29** (13.5 mg, 27 μmol, 1.00 eq), 2-NosCl (6.8 mg, 27 μmol, 1.10 eq) and DMAP (0.3 mg, 3 μmol, 0.10 eq) were suspended in THF (0.50 mL) cooled to 0 °C and DIPEA (5.0 μL, 30 μmol, 1.10 eq) was added. The solution was stirred for 2.5 h before it was poured into saturated aqueous $NH_4Cl$-solution (5 mL) and extracted with EtOAc (3×10 mL). The combined organic layers were washed with brine (10 mL), dried over $Na_2SO_4$ and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography on silica (*n*-pentane/EtOAc 2:1 to 1:1) to give as single regioisomer compound **30 b** (14.0 mg, 21 μmol, 76 %) as pale yellow foam. $R_f = 0.47$ (*n*-pentane/EtOAc 1:1). $^1$H-NMR (500 MHz, $CDCl_3$): $\delta = 9.34$ (s, 1H, $CH_{arom}$), 8.91 (s, 1H, $CH_{arom}$), 8.43 (d, $J = 7.52$ Hz, 1H, $CH_{Nos}$), 8.05 (s, 1H, $CH_{arom}$), 7.94 (s, 1H, $CH_{arom}$), 7.89–7.83 (m, 3H, $3\times CH_{Nos}$), 2.82 (s, 3H, $CH_3$), 2.62 (s, 3H, $SCH_3$), 2.61 (s, 3H, $SCH_3$), 1.52 (s, 9H, $C(CH_3)_3$) ppm. $^{13}$C-NMR (126

MHz, $CDCl_3$): $\delta = 171.5$ (1 C, $C_{arom}SCH_3$), 170.0 (1 C, $C_{arom}SCH_3$), 160.2 (1 C, $CH_{arom}$), 159.2 (1 C, $C_{arom}$), 158.8 (1 C, $CH_{arom}$), 151.6 (1 C, $NCO_2{}^tBu$), 150.8 (1 C, $C_{arom}$), 148.8 (1 C, $C_{Nos}$), 146.6 (1 C, $C_{arom}$), 146.6 (1 C, $C_{arom}$), 141.4 (1 C, $C_{arom}$), 136.5 (1 C, $C_{arom}$), 135.8 (1 C, $CH_{Nos}$), 135.6 (1 C, $CH_{arom}$), 133.3 (1 C, $CH_{Nos}$), 133.2 (1 C, $C_{arom}$), 132.7 (1 C, $CH_{arom}$), 132.2 (1 C, $CH_{Nos}$), 130.9 (1 C, $C_{arom}$), 130.0 (1 C, $C_{Nos}$), 125.1 (1 C, $CH_{Nos}$), 85.2 (1 C, $C(CH_3)_3$), 28.1 (3 C, $C(CH_3)_3$), 22.0 (1 C, $CH_3$), 14.8 (1 C, $SCH_3$), 14.7 (1 C, $SCH_3$) ppm. FT-IR: neat; $\tilde{\nu} = 2977$ (w), 2927 (w), 1724 (m), 1604 (w), 1568 (w), 1543 (s), 1435 (w), 1394 (m), 1367 (w), 1330 (w), 1296 (m), 1255 (w), 1191 (w), 1151 (w), 1123 (s), 1041 (w), 1017 (w), 948 (w), 905 (w), 869 (w), 796 (m), 760 (w), 733 (m), 652 (w), 609 (w), 582 (m), 528 (w), 448 (w) $cm^{-1}$. m.p.: 110 °C (EtOAc). HRMS (ESI$^+$): *m/z* calc. for $C_{28}H_{26}N_8O_7S_3Na_1$ $[M+Na]^+$: 705.0979, found: 705.0973.

**7-((*tert*-Butoxycarbonyl)(6-methyl-2-(methylthio)pyrido[3,2-*d*]pyrimidin-7-yl)amino)-2-(methylthio)pyrido[3,2-*d*]pyrimidin-6-yl trifluoromethanesulfonate (30c)**



**30c**

Compound **29** (33.0 mg, 66 µmol, 1.00 eq) and DMAP (0.8 mg, 7 µmol, 0.10 eq) were suspended in THF (1.00 mL) cooled to 0 °C and DIPEA (16.0 µL, 93 µmol, 1.40 eq) was added. After 5 min TfCl (8.0 µL, 80 µmol, 1.20 eq) was added dropwise. The solution was stirred for 16 h during which it was allowed to warm up to rt before it was poured into saturated aqueous $NaHCO_3$-solution (5 mL) and extracted with EtOAc (3×10 mL). The combined organic layers were washed with brine (10 mL), dried over $Na_2SO_4$ and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography on silica (*n*-pentane/EtOAc 2:1) to give compound **30c** (28.0 mg, 45 µmol, 68%, 89% brsm) as pale yellow foam. $R_f = 0.77$ (*n*-pentane/EtOAc 1:1). $^1$H-NMR (500 MHz, $CDCl_3$): $\delta = 9.34$ (d, $J = 0.8$ Hz, 1H, $CH_{arom}$), 9.24 (d, $J = 0.8$ Hz, 1H, $CH_{arom}$), 7.94 (s, 1H, $CH_{arom}$), 7.88 (d, $J = 0.7$ Hz, 1H, $CH_{arom}$), 2.76 (s, 3H, $CH_3$), 2.64 (s, 3H, $SCH_3$), 2.61 (s, 3H, $SCH_3$), 1.50 (s, 9H, $C(CH_3)_3$) ppm. $^{13}$C-NMR (126 MHz, $CDCl_3$): $\delta = 172.6$ (1 C, $C_{arom}SCH_3$), 170.6 (1 C, $C_{arom}SCH_3$), 160.3 (1 C, $CH_{arom}$), 159.6 (1 C, $CH_{arom}$), 158.2 (1 C, $C_{arom}$), 151.4 (1 C, $NCO_2{}^tBu$), 149.1 (1 C, $C_{arom}$), 147.1 (1 C, $C_{arom}$), 146.5 (1 C, $C_{arom}$), 141.0 (1 C, $C_{arom}$), 136.7 (1 C, $C_{arom}$), 135.3 (1 C, $CH_{arom}$), 134.4 (1 C, $C_{arom}$), 133.3 (1 C, $CH_{arom}$), 133.3 (1 C, $C_{arom}$), 118.7 (q, $J =$ 321.2 Hz, 1 C, $CF_3$), 85.5 (1 C, $C(CH_3)_3$), 28.0 (3 C, $C(CH_3)_3$), 22.0 (1 C, $CH_3$), 14.8 (1 C, $SCH_3$), 14.8 (1 C, $SCH_3$) ppm. $^{19}$F-NMR (283 MHz, $CDCl_3$): $\delta = -72.6$ (s, 3F, $CF_3$) ppm. FT-IR: neat; $\tilde{\nu} = 2979$ (w), 2928 (w), 1727 (m), 1603 (w), 1567 (w), 1545 (w), 1427 (m), 1405 (w), 1371 (w), 1294 (w), 1212 (m), 1124 (s), 1040 (w), 1015 (w), 946 (w), 901 (w), 874 (m), 808 (m), 757 (w), 713 (w), 640 (w), 598 (m), 504 (w), 451 (w) $cm^{-1}$. m.p.: 107 °C (EtOAc). HRMS (ESI$^+$): *m/z* calc. for $C_{23}H_{22}F_3N_7O_5S_3H_1$ $[M+H]^+$: 630.0869, found: 630.0869.

Deposition Numbers 2081819 (for **18e**), 2081820 (for **17b**), 2081821 (for **19d**), 2081822 (for **28a**), 2081823 (for **19j**), and 2081824 (for **17d**) contain the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service www.ccdc.cam.ac.uk/structures.

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## Conflict of Interest

The authors declare no conflict of interest.

**Keywords:** HWE-reaction · Nitrogen heterocycles · Photoisomerization · Pyridopyrimidine · Synthetic methods

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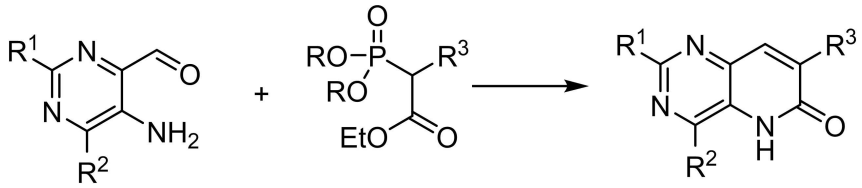


*Dr. P. E. Hofmann, J. Meinecke, Dr. K. Harms, Prof. Dr. U. Koert**



Substituted pyrido[3,2-*d*]pyrimidines are accessible by a reaction sequence consisting of HWE-reaction, a *Z*/*E*-photoisomerization, and ring closure of the pyridine ring. Bis-pyridopyrimidines can be obtained from 7-amino-pyrido[3,2-*d*]pyrimidines.