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Development of Synthetic Strategies for the Construction of Pyrido[4,3-*d*]-pyrimidine Libraries – the Discovery of a New Class of PDE-4 Inhibitors

Mi-Yeon Jang,[a] Steven De Jonghe,[b] Ling-Jie Gao,[b] Jef Rozenski,[a] and Piet Herdewijn*[a]

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The synthesis of a pyrido[4,3-*d*]pyrimidine library from 4,6-diamino-2-bromonicotinamide and 4,6-diaminonicotinamide is described. A systematic variation of the substituents at positions 2, 4, 5 and 7 of the pyrido[4,3-*d*]pyrimidine scaffold was carried out, leading to a wide variety of structural analogues. This strategy led to the discovery of a new structural class of PDE-4 inhibitors.

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Introduction

Bicyclic heterocycles (such as purines,[1] quinazolines[2] and pyrido[2,3-*d*]pyrimidines[3]) are well-known pharmacophores in drug discovery. Examples of marketed drugs (Figure 1) with a bicyclic core structure include gefitinib (a quinazoline analogue used for the treatment of non-small-cell lung cancer), prazosine (an α_1-antagonist based on a quinazoline scaffold, used as a antihypertensive and for the treatment of benign prostate hypertrophy), theophylline (a purine analogue used for the treatment of asthma), and triamterene (a pteridine derivative, used for the treatment of hypertension).

As part of an ongoing medicinal chemistry research program to discover anti-inflammatory agents based on TNF-α inhibition, we became very interested in the synthesis of pyrido[4,3-*d*]pyrimidine analogues (Figure 2). These types of compounds possess five possible substitution sites (R^2, R^4, R^5, R^7, and R^8), which means that the number and combination of substituents that ultimately can lead to a drug is very high. Therefore, there is a clear need for synthetic schemes that can be used for rapidly exploring the structure–activity relationship (SAR) of the pyrido[4,3-*d*]-pyrimidine scaffold with respect to a well-defined biological target.

Combinatorial and parallel chemistry are powerful tools for medicinal chemists in drug discovery programs. It has encouraged chemists to work out synthetic strategies and approaches that can be used for the construction of libraries. Combinatorial chemistry can be carried out on a solid support or in solution. Although solid-phase chemistry definitively has some advantages (mainly related to purification), we opted for the construction of libraries with the solution-phase approach. The synthetic schemes described in the literature for the preparation of pyrido[4,3-*d*]pyrimidine analogues allow structural variety to be introduced in only one or two particular positions of the scaffold.[4] To the best of our knowledge, no systematic studies have been done on how to elaborate, in a systematic way, the chemistry of this compound class. Therefore, the main goal of this paper is to develop synthetic schemes that can be easily adapted for use in parallel chemistry, and hence, are suitable to establish SAR studies. In that respect, we have attempted to introduce a broad structural variety into the pyrido[4,3-*d*]pyrimidine scaffold in which three or more substitution sites can be varied in one synthetic cycle.

[a] REGA Institute, Laboratory for Medicinal Chemistry, Minderbroedersstraat 10, 3000 Leuven, Belgium
Fax: +32-16-33-73-40
E-mail: piet.herdewijn@rega.kuleuven.be
[b] 4AZA Bioscience, Department of Medicinal Chemistry, Kapucijnenvoer 33, 3000 Leuven, Belgium

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Results and Discussion

Chemistry

It was envisioned that 4,6-diamino-2-bromo-3-cyanopyridine (**2**) could act as a versatile starting material for the synthesis of pyrido[4,3-*d*]pyrimidine libraries. The bromine atom on the pyridine ring offers the possibility of performing nucleophilic aromatic substitutions as well as Pd-catalyzed cross coupling reactions to construct C–O, C–N, C–S and C–C bonds.[5] Moreover, the bromine atom can be reduced off by catalytic hydrogenation to gain access to 5-unsubstituted compounds. In this respect, compound **2** was prepared from malonitrile according to a published patent procedure.[6]

Nicotinamide **3** was synthesized from 4,6-diamino-2-bromo-3-cyanopyridine (**2**) by direct hydrolysis of the nitrile

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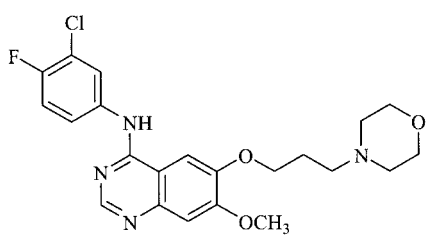
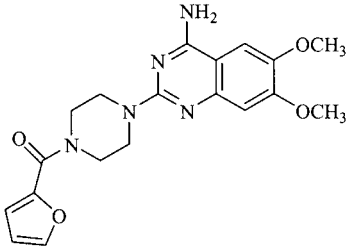
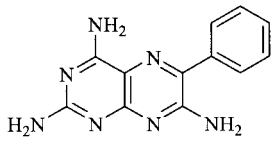


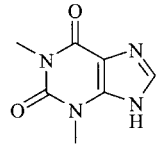
Gefitinib



Prazosine



Triamterene



Theophylline

Figure 1. Structures of marketed bicyclic drugs.

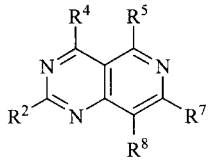
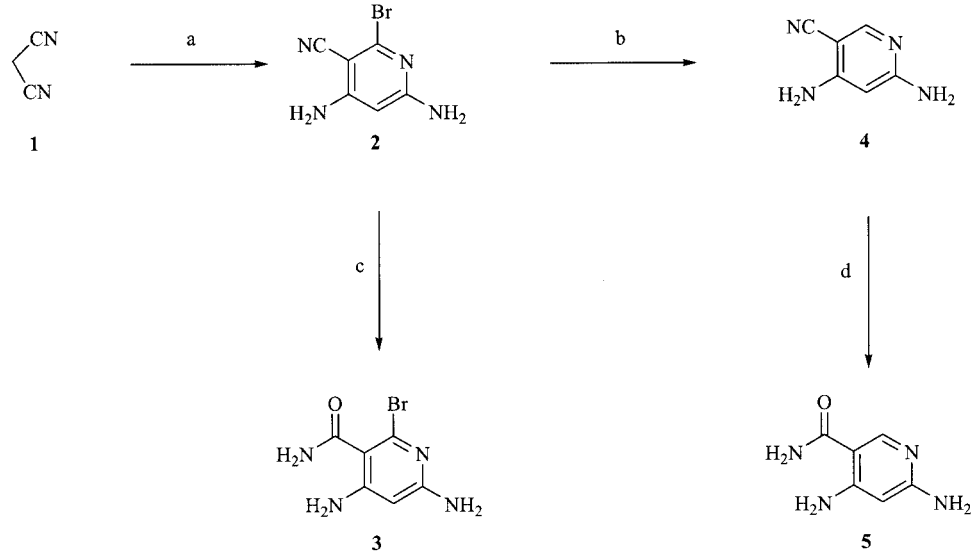


Figure 2. Pyrido[4,3-*d*]pyrimidine scaffold.

group to form the corresponding carboxamide by treatment with hydrogen peroxide under aqueous alkaline conditions.[7] Alternatively, 5-unsubstituted compounds could be obtained by hydrogenolysis of compound **2** with 10% Pd/C in a mixture of THF and MeOH, yielding compound **4**, which was converted into the corresponding amide **5** with concentrated sulfuric acid (Scheme 1).[6]

Nicotinamides **3** and **5** are both valuable starting materials for the construction of the pyrido[4,3-*d*]pyrimidin-4(3*H*)-one scaffold (Scheme 2). Within this context, both nicotinamides were treated with a set of orthoesters to form the pyrimidine ring (Entries 1–2 and 4–5 of Table 1). In this way, hydrogen atoms and methyl groups could be introduced at position 2 of the scaffold. Unfortunately, the number of commercially available orthoesters is limited. Alternative strategies to introduce structural variety at position 2 of the pyrido[4,3-*d*]pyrimidine were considered. An obvious choice was to effect the ring closure reaction with acid chlorides, as a wide range of these building blocks is commercially available. As a representative example, we tried a condensation of pyridine analogue **3** with meth-



Scheme 1. Synthesis of nicotinamides **3** and **5**. a) HBr (g), 0 °C, 2 h, toluene, then 100 °C, 2 h; b) 10% Pd/C, H_2, KOAc, THF/MeOH (2:1), room temp., 4 h; c) H_2O_2, NaOH, DMSO, 50 °C, 1 d; d) 90% H_2SO_4, 80 °C, 3 h.

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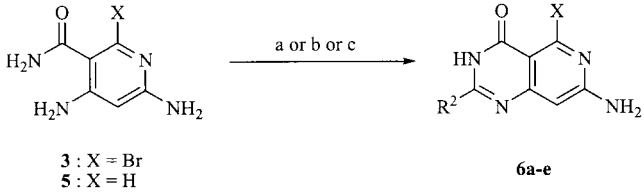
Table 1. Synthesis of the pyrido[4,3-*d*]pyrimidin-4(3*H*)-one scaffold.

entry	compound	X	Reagent	R^2	Yield (%)
1	**6a**	H	$HC(OEt)_3$	H	60
2	**6b**	H	$MeC(OEt)_3$	Me	72
3	**6c**	H	$MeOCH_2COCl$	$MeOCH_2$	50
4	**6d**	Br	$HC(OEt)_3$	H	88
5	**6e**	Br	$MeC(OEt)_3$	Me	60

oxyacetyl chloride (Table 1, Entry 3), and the transformation consisted of a two-step, one-pot procedure.[8] In the first step, the exocyclic amino group was coupled with the acid chloride in a mixture of DMF and pyridine. Once the amide was formed (which was indicated by a new TLC spot with a higher R_f value), the formation of the pyrimidine ring was effected under aqueous alkaline conditions. This procedure can be easily adopted to a wide range of acid chlorides, and should make it possible to fully explore SARs at position 2.



Scheme 2. Synthesis of the pyrido[4,3-*d*]pyrimidin-4(3*H*)-one scaffold. a) Triethyl orthoformate, 140 °C, 24 h; b) triethyl orthoacetate, 140 °C, 24 h; c) methoxyacetyl chloride, pyridine, DMF, room temp., 3 h, then 5 N NaOH, room temp., 24 h.

The bromine atom at position 5 can act as a versatile starting material functionality for a wide variety of Pd-catalyzed cross coupling reactions to form new C–C bonds (e.g. Suzuki, Heck and Sonogashira reactions). Standard reaction conditions were used for the Suzuki coupling of compound **6d** with a number of (heteroaryl)boronic acids. The use of tetrakis(triphenylphosphane)palladium(0) as catalyst, aqueous potassium carbonate as base and 1,4-dioxane as solvent yielded the desired biaryl compounds **7a**–**e** in good yields (Scheme 3, reaction a).[9] Table 2 gives an overview of the compounds synthesized by this procedure.

In order to introduce a number of alkenyl substituents, a Heck reaction was performed with methyl acrylate under standard reaction conditions.[10] However, none of the desired alkenyl compounds could be isolated. Alternatively, alkenyl substituents can be introduced with commercially available alkenylboronic acids {e.g. [(*E*)-2-phenylvinyl]-boronic acid and [(*E*)-1-propenyl]boronic acid}, yielding the desired compounds **8a**–**b** in good yields. Methods to prepare alkenylboronic acids from the corresponding acetylenes are well known in the literature,[11] and therefore, this methodology provides a powerful tool to construct double-bond-containing analogues.

Sonogashira coupling[12] of **6d** with commercially available phenylacetylene did not lead to the formation of the expected alkyne derivative. Careful analysis of the ^{13}C NMR spectrum did not reveal any ^{13}C signals between δ = 70 and 90 ppm, indicating the absence of a triple bond. Moreover, in the ^1H NMR spectrum, three singlets were observed. If the desired compound had been formed, only two singlets should be present (from the protons at positions 2 and 8). The third signal indicated the presence of an alkene moiety. Therefore, we concluded that a tricyclic by-product **9a** was isolated in 48% yield. These types of side reactions have been previously observed in the Pd-catalyzed coupling of terminal alkynes with 5-iodopyrimidine nucleosides, yielding nucleoside analogues with a fluorescent furano-pyrimidine base and potent antiviral activity.[13] Likewise, in our case, the isolated side product had fluorescent properties according to TLC, which suggested the formation of compound **9a**. As this compound showed interesting biological activity, we prepared a number of new tricyclic analogues **9b**–**9f** with commercially available acetylene derivatives. When trimethylsilylacetylene was used as the coupling partner, in situ deprotection of the silyl group was observed (Table 3). For the synthesis of compound **9a** (Entry 1), a copper-free version of the Sonogashira reaction was performed.[14] This might be important for industrial applications, as copper is very tedious to recycle.

As the bromine atom is part of a vinylogous acid bromide, it was anticipated that it would undergo substitution reactions easily. To that end, the bromine atom at position 5 of the pyrido[4,3-*d*]pyrimidine scaffold was subjected to a number of nucleophilic aromatic substitutions in order to exchange the bromine atom for a nucleophile [e.g. morpholine, aniline, *n*-butylamine and (2-thienylmethyl)amine]. However, it seemed very difficult to displace the bromine atom, as only starting material could be recovered. The

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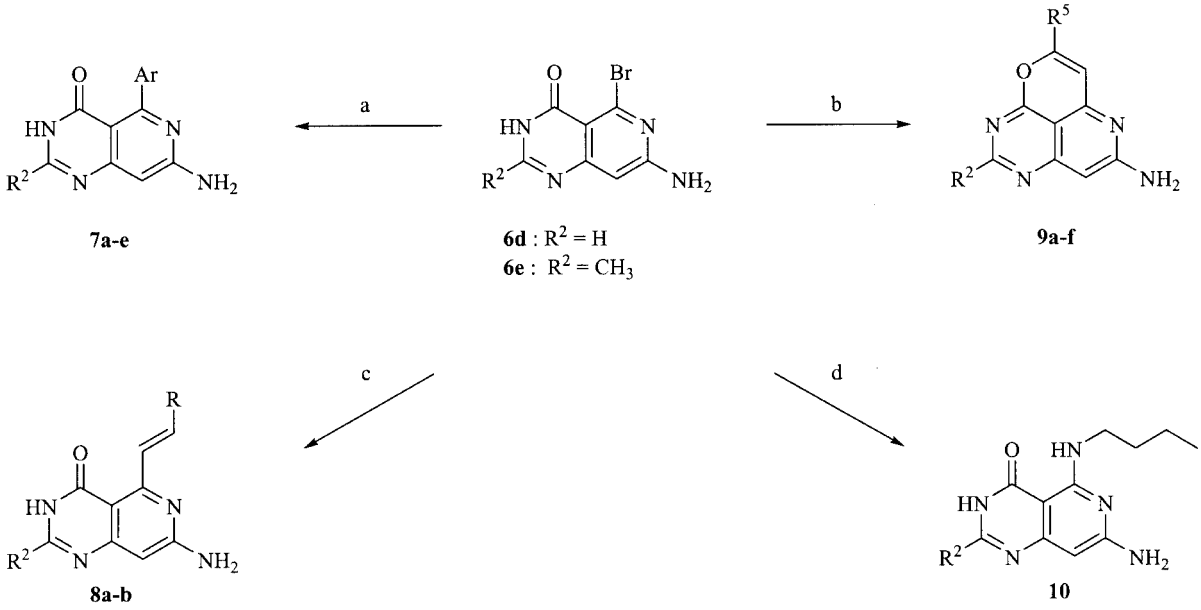


Scheme 3. a) Boronic acid, K_2CO_3, $Pd(PPh_3)_4$, dioxane/H_2O (3:1), reflux, 2 h; b) alkyne, $(PPh_3)_2Pd(OAc)_2$, CuI, triethylamine, DMF, 60–70 °C, 3 h–1 d; c) boronic acid, K_2CO_3, $Pd(PPh_3)_4$, dioxane/H_2O (3:1), reflux, 2 h; d) *n*-butylamine, KO*t*Bu, $Pd(PPh)_4$, dioxane, reflux, 1 d.

Table 2. Suzuki reactions of compounds **6d** and **6e**.

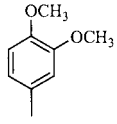
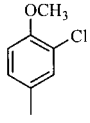
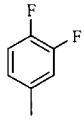
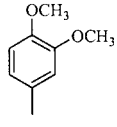
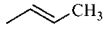
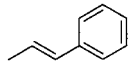
entry	compound	R^2	Ar	Yield (%)
1	**7a**	H		94
2	**7b**	H		64
3	**7c**	H		58
4	**7d**	H		73
5	**7e**	CH_3		79
6	**8a**	CH_3		55
7	**8b**	CH_3		83

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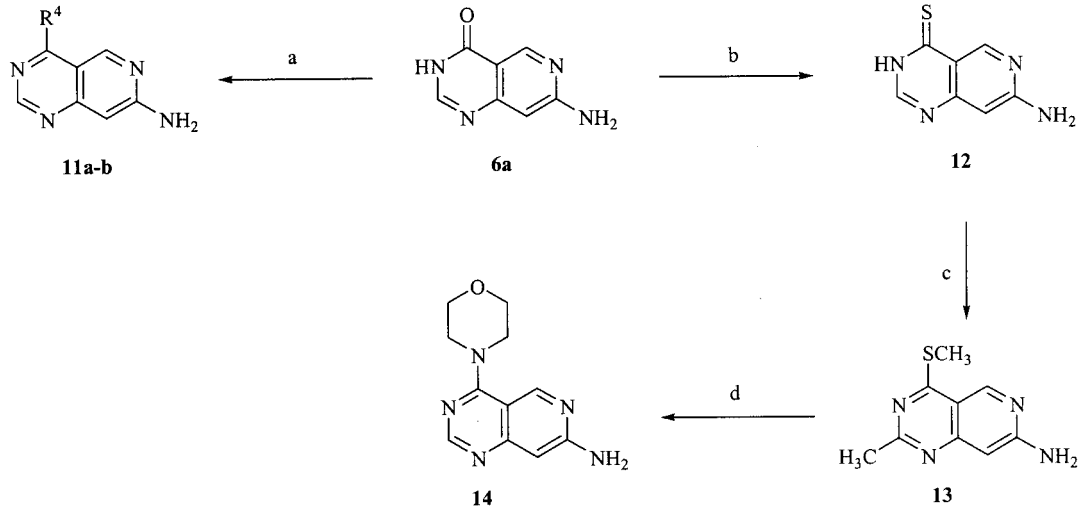
Table 3. Sonogashira reactions of compounds **6d** and **6e**.

entry	compound	R^2	alkyne	R^5	Yield (%)
1	**9a**	H	phenylacetylene		48
2	**9b**	CH_3	1-ethynylcyclohexene		17
3	**9c**	CH_3	5-ethynyl-1-methyl-1*H*-imidazole		65
4	**9d**	CH_3	propargyl alcohol		88
5	**9e**	CH_3	1-dimethylamino-2-propyne		50
6	**9f**	CH_3	trimethylsilylacetylene	H	17

weak leaving-group capacity of the bromine atom might be attributed to the electron-donating effect of the amino group at position 7. Since S_NAr was cumbersome, we switched our attention to Pd-catalyzed chemistry, as in recent years plenty of research had been done to construct C–N bonds.[15] *n*-Butylamine could be introduced at position 5 by subjecting compound **6d** to Buchwald–Hartwig reaction conditions with *n*-butylamine, potassium *tert*-butoxide as a strong base and tetrakis(triphenylphosphane)palladium(0) as a catalyst, yielding compound **10** (Scheme 3, reaction d).

In order to introduce structural variety at position 4, several possibilities were considered (Scheme 4). The easiest and fastest approach to introduce nucleophiles at position 4 would be a one-step procedure. This was possible through silylation/amination of the lactam moiety. This method is well known in the nucleoside field,[16] but, to the best of our knowledge, has never been applied in pyrido[4,3-*d*]pyrimidine chemistry. Therefore, compound **6a** was heated in 5 equiv. of 1,1,1,3,3,3-hexamethyldisilazane (HMDS) and an appropriate amine with ammonium sulfate as catalyst.[17] The reaction turned out to be successful only for primary amines, such as benzylamine and (2-thienylmethyl)amine, yielding the final compounds **11a**–**b**.

As the silylation/amination approach seemed to be restricted to primary amines, we have been investigating two-step procedures in which a good leaving group was first introduced at position 4 and then be exchanged for nucleophiles in a second step. The carbonyl group at position 4 of compound **6a** was activated as its 4-thio counterpart (see compound **12**) by heating with phosphorus pentasulfide in



Scheme 4. a) 1,1,1,3,3,3-Hexamethyldisilazane, amine, ammonium sulfate, 120 °C, 1–3 d; b) phosphorus pentasulfide, pyridine, reflux, 5 h; c) MeI, triethylamine, DMSO, room temp., 12 h; d) morpholine, ethanol, reflux, 24 h.

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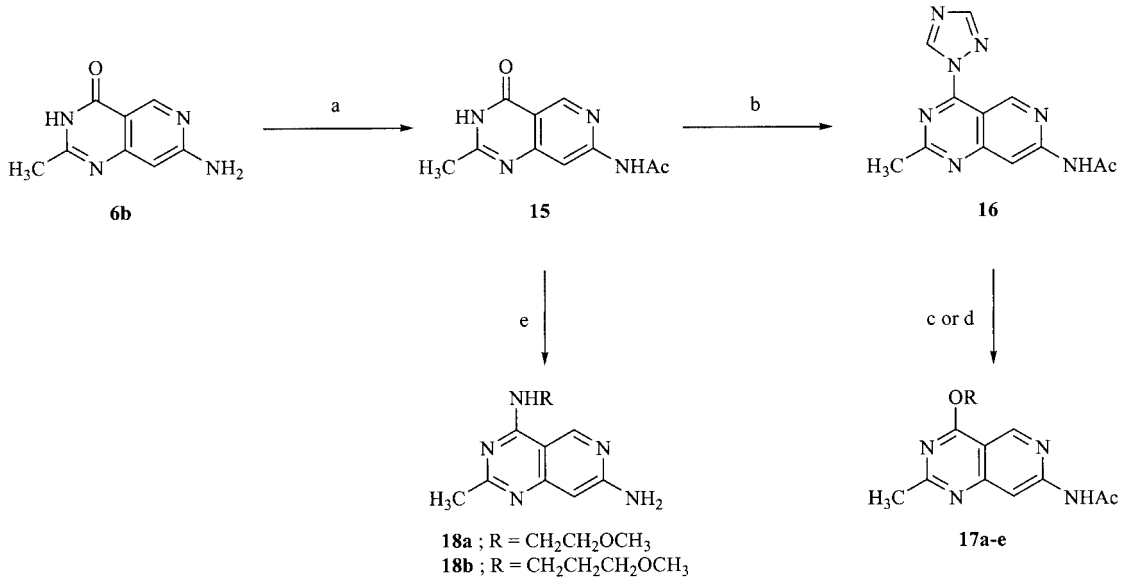
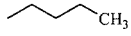
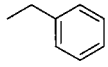
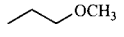
pyridine, followed by methylation with iodomethane under alkaline conditions.[6] The thiomethyl group of compound **13** can be exchanged for morpholine (as a representative for a wide range of nucleophiles), affording the final compound **14**. In case of less reactive nucleophiles (e.g. aniline), it might be anticipated that it would be necessary to oxidize the thiomethyl group to the corresponding sulfoxide or sulfone prior to a nucleophilic displacement reaction.

Alternatively, activation of the 4-oxo group for nucleophilic displacement reactions as a 1,2,4-triazole is a well-known procedure to convert uridine into cytidine.[18] It has also been applied to activate position 4 of pyrido[2,3-*d*]pyrimidines for nucleophilic displacement reactions.[19] However, this methodology has never been applied to pyrido[4,3-*d*]pyrimidines. Prior to introduction of the 1,2,4-triazole at position 4, the exocyclic amino group of compound **6b** was protected as an acetyl group by reaction with acetic anhydride in pyridine (Scheme 5). Introduction of the 1,2,4-triazole group was achieved by reaction of compound **15** with $POCl_3$, triethylamine and 1,2,4-triazole in a mixture of acetonitrile and dichloromethane. The triazole group seemed to be sufficiently reactive to be displaced by a number of neutral alcohols (even without preparing first the sodium alkoxides from the corresponding alcohols by treatment with sodium or sodium hydride). Therefore, treatment of compound **16** with a number of neutral alcohols (either in the alcohol itself or in DMF as solvent) yielded compounds **17a**–**e**, which could easily be purified by silica gel column chromatography (Table 4). Compound **15** was also used as a starting material for the one-step silylation/amination approach (as described in Scheme 4) with (2-methoxyethyl)amine and (3-methoxypropyl)amine as nu-



Scheme 5. a) Acetic anhydride, pyridine, reflux, 30 min; b) phosphorus oxychloride, triethylamine, 1,2,4-triazole, CH_3CN/CH_2Cl_2 (2:1), room temp., 24 h; c) alcohol, reflux, 12 h; d) alcohol, K_2CO_3, DMF, 120 °C, 6–12 h; e) 1,1,1,3,3,3-hexamethyldisilazane, amine, ammonium sulfate, 120 °C, 2 d.

Table 4. Synthesis of 4-alkoxypyrido[4,3-*d*]pyrimidine analogues.

entry	compound	alcohol	condition	R	Yield (%)
1	**17a**	methanol	c	CH_3	57
2	**17b**	*n*-butanol	c		90
3	**17c**	benzyl alcohol	d		26
4	**17d**	cyclohexanol	d		78
5	**17e**	2-methoxyethanol	c		92

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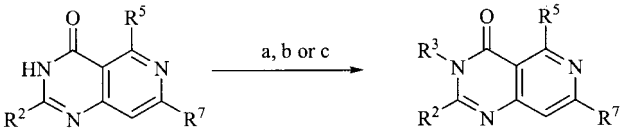
cleophiles. The vigorous reaction conditions led to cleavage of the acetyl group, affording compounds **18a**–**b** (Scheme 5).

Regioselective *N*-alkylation of the lactam moiety of the pyrimidine ring could easily be achieved by stirring the reaction mixtures under alkaline conditions in DMF (Scheme 6).[20] Potassium carbonate as a base seemed to work better than sodium hydride (Table 5, Entries 1 and 2). Therefore, for the synthesis of compounds **20**–**24**, potassium carbonate was used as a base and the desired compounds could be isolated in good yields (see Table 5). In order to prove that selective *N*-alkylation was obtained, compound **24** was prepared. The corresponding 4-methoxy derivative **17a** had been prepared before through the 1,2,4-triazole approach. Comparison of the ^{1}H NMR spectroscopic data of derivatives **17a** and **24** showed that the methoxy signals appeared at δ = 4.18 ppm, whereas the methylamino signals of compound **24** appeared at δ = 3.61 ppm. The downfield shift of the signal of the methyl protons of **17a** to a lower field is in complete accordance with the presence of a methoxy group.

An alternative approach for alkylation is a Mitsunobu reaction.[21] Mitsunobu reactions have the disadvantage of leading to mixtures of *O*- and *N*-alkylated products, and the outcome is sometimes difficult to predict. Treatment of compound **15** with triphenylphosphane, diisopropyl azodicarboxylate (DIAD) and methanol in dioxane furnished a compound in 68% yield, the ^{1}H NMR spectrum of which was identical with that of compound **24**, indicating that a Mitsunobu reaction on this class of heterocycle leads preferentially to *N*-alkylation.

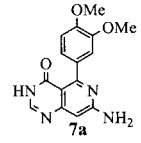
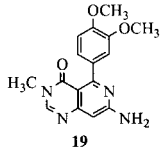
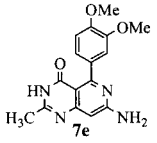
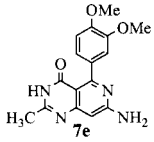
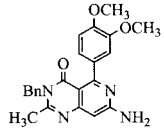
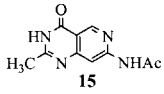
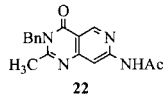
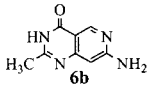
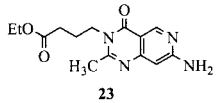
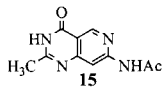
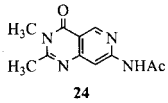


Scheme 6. a) Alkyl halide, NaH, DMF, 60–80 °C, 3 h; b) alkyl halide, K_2CO_3, DMF, room temp., 24 h; c) alkyl halide, K_2CO_3, DMF, 80 °C, 24 h.

The aniline group at position 7 can be converted into halogens by a diazotization procedure. A chlorine or bromine atom would be a useful starting material functionality for further Pd-catalyzed cross coupling reactions. On the other hand, a fluorine atom on an aromatic ring can easily be displaced by a wide variety of nucleophiles.

As a representative example, compound **7e** was treated with sodium nitrite and tetrafluoroboric acid to give the diazonium fluoroborate salt, which was converted into the 7-fluoro compound **25** in situ (Schiemann reaction).[6] In diethyl ether as solvent, no reaction took place, probably because of the poor solubility of compound **7e**. Therefore, we switched to a mixture of diethyl ether, DMF and water. In this case, the fluoro compound could be isolated by flash

Table 5. N-Alkylation of pyrido[4,3-*d*]pyrimidin-4(3*H*)-one analogues.

entry	substrate	alkyl halide	condition	product	Yield (%)
1	 **7a**	MeI	a	 **19**	35
2	 **7e**	MeI	b	 **20**	50
3	 **7e**	BnBr	b	 **21**	67
4	 **15**	BnBr	c	 **22**	79
5	 **6b**	ethyl 4-bromobutyrate	c	 **23**	61
6	 **15**	MeI	c	 **24**	53

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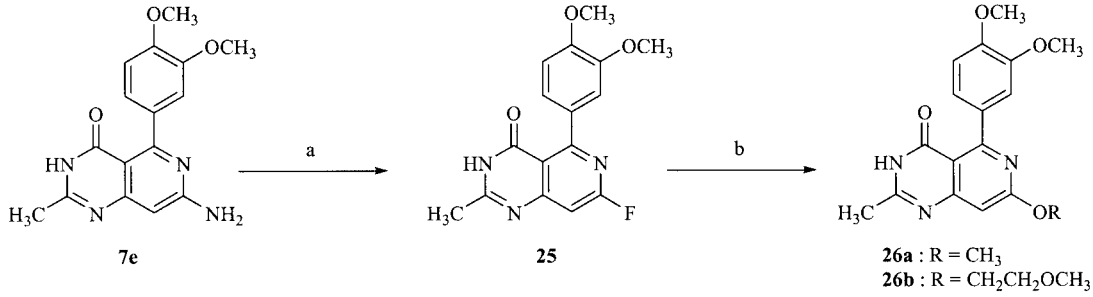
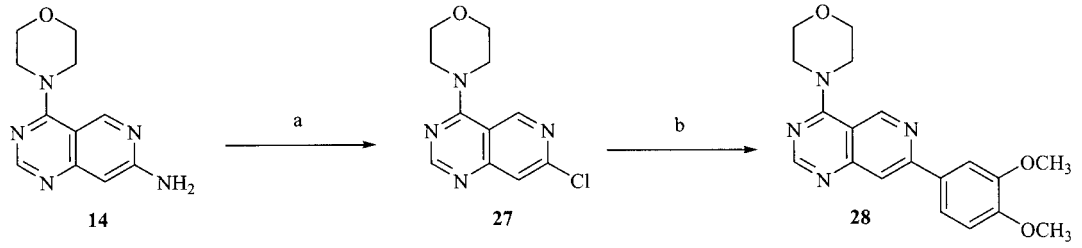


Scheme 7. a) 60% HBF_4, $NaNO_2$, DMF, 0 °C to room temp., 3 h; b) NaH, ROH, reflux, 4 h.



Scheme 8. a) 6 N HCl, CuCl, $NaNO_2$, –15 °C to room temp., 1 h then 60 °C, 1 h; b) (3,4-dimethoxyphenyl)boronic acid, K_2CO_3, Pd-$(PPh_3)_4$, dioxane/H_2O (3:1), reflux, 2 h.

chromatography on silica in fairly good yields. Nucleophilic substitution of the fluorine atom by sodium alkoxides furnished the final compounds **26a**–**b** (Scheme 7).

In order to introduce a chlorine atom at position 7, compound **14** was chosen as a representative example. Diazotization of **14** in 6 N HCl with sodium nitrite, followed by decomposition of the diazonium salt with cuprous chloride (Sandmeyer reaction) gave access to the 7-chloro derivative **27** in a low yield (34%).[6,19] Sufficient material could be isolated to conduct a Suzuki-type reaction with (3,4-dimethoxphenyl)boronic acid, leading to the formation of compound **28** (Scheme 8). However, the low yield of the Sandmeyer reaction prevents us from using this approach for parallel chemistry purposes, and studies are currently conducted in order to obtain easier access to 7-chloro-substituted pyrido[4,3-*d*]pyrimidine compounds and will be reported in due course.

All isolated compounds submitted for biological testing were more than 95% pure, based on LC/MS or HPLC-UV analysis (Table S1 in the Supporting Information).

Biological Evaluation

Tumor necrosis factor alpha (TNF-α) overexpression is associated with a number of diseases, such as rheumatoid arthritis and Crohn's disease. Inhibition of TNF-α production has been shown to be beneficial in preclinical models of rheumatoid arthritis, which makes inhibition of TNF-α production an attractive target for the treatment of various inflammatory and autoimmune diseases.[22] As part of an ongoing drug discovery program dedicated to finding new small-molecule TNF-α inhibitors, the compounds disclosed above were evaluated for their ability to block the production of TNF-α in human peripheral blood monocytes, stimulated by a bacterial lipopolysacharide (LPS).[23] None of the compounds was able to block the production of TNF-α, as they all displayed an $IC_{50} > 10$ μM. Interestingly, the side products (compounds **9a**–**9f**) isolated from the Sonogashira coupling showed biological activity (Table 6). The most active compounds contained either a phenyl (compound **9a**) or a cyclohexene (compound **9b**) ring. Introduction of a heteroaromatic ring (such as the imidazole-containing compound **9c**) led to a 10-fold loss in activity. The unsubstituted compound **9f** completely lost biological activity, and compounds containing more polar substituents [such as (dimethylamino)methyl in **9e** and hydroxymethyl in **9d**] were devoid of biological activity, indicating that a neutral and rather large substituent was necessary in order to obtain biologically active compounds.

Table 6. TNF-α inhibition by compounds **9a**–**9f**.

Compound	TNF-α IC_{50} [μM]
9a	0.9
9b	0.6
9c	8.6
9d	>10
9e	3.2
9f	>10

The molecular target of compounds **9a** and **9b** could not be determined with a cell-based assay. By employing a broad target-based screening, it was discovered that cyclic AMP-specific phosphodiesterase type 4 (PDE-4) turned out to be the molecular target. Compound **9a** gave 90% PDE-4 inhibition at 10 μM. It is well known from the literature that there is a correlation between PDE-4 inhibition and inhibition of TNF-α release from monocytes.[24]

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Different structural classes of compounds are known as PDE-4 inhibitors.[25] However, PDE-4 inhibitors based on a pyrido[4,3-*d*]pyrimidine scaffold are not known, and therefore, compounds **9a** and **9b** represent new lead structures in the design of new PDE-4 inhibitors useful for the treatment of a wide range of inflammatory and autoimmune disorders.

Conclusions

Considering the synthetic approaches described above, it is possible to vary, in one synthetic cycle, up to 5 substitution sites of the pyrido[4,3-*d*]pyrimidine template. Position 2 can be diversified by reaction with different orthoesters or acid chlorides. Position 3 can be *N*-alkylated with different alkyl halides, and at position 4, different N-, O- or S-nucleophiles can be incorporated. The bromine atom at position 5 can be hydrogenated or can be used for Pd-catalyzed chemistry. An amino group is present at position 7, which can be easily converted into different halogens by diazotization procedures, and the resulting halides are useful starting materials for further derivatisations.

We have demonstrated that a new series of pyrido[4,5-*d*]-pyrimidine analogues can be prepared, and that this type of chemistry is useful for parallel synthesis. The full exploitation of the discussed strategy would allow for the preparation of highly diverse libraries based on the pyrido[4,3-*d*]-pyrimidine scaffold. In addition, the application of this strategy led to the discovery of a new structural class of PDE-4 inhibitors.

Experimental Section

General: For all reactions, analytical-grade solvents were used. All moisture-sensitive reactions were carried out in oven-dried (135 °C) glassware. ^{1}H and ^{13}C NMR spectra were recorded with a Varian Gemini 200 (^{1}H NMR: 200 MHz, ^{13}C NMR: 50 MHz) or a Bruker Avance 300 (^{1}H NMR: 300 MHz, ^{13}C NMR: 75 MHz) spectrometer, with tetramethylsilane as an internal standard for ^{1}H NMR spectra and [D$_6$]DMSO (δ = 39.5 ppm) or $CDCl_3$ (δ = 77.2 ppm) for ^{13}C NMR spectra. Abbreviations used are: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br. s = broad signal. Coupling constants are expressed in Hz. Mass spectra were obtained with a Finnigan LCQ advantage Max (ion trap) mass spectrophotometer from Thermo Finnigan, San Jose, CA, USA. Exact mass measurements were performed with a quadrupole time-of-flight mass spectrometer (Q-tof-2, Micromass, Manchester, UK) equipped with a standard electrospray-ionization (ESI) interface. Samples were infused in *i*PrOH/H_2O (1:1) at 3 μL/min. Melting points were determined with a Büchi SMP-20 apparatus and are uncorrected. Infrared spectra were recorded with a Perkin–Elmer Spectrum RX I FT-IR System in KBr. Vibration frequencies in IR spectra are expressed in cm^{-1}. Precoated aluminum sheets (Fluka Silica gel/TLC cards, 254 nm) were used for TLC. Column chromatography was performed on ICN silica gel (63–200 mesh, 60 Å). Compounds **2**, **4** and **5** were synthesized according to literature protocols.[6] Compound **6a** is also a known compound.[4b]

7-Amino-2-methylpyrido[4,3-*d*]pyrimidin-4(3*H*)-one (6b): A solution of 4,6-diaminonicotinamide (**4**, 3 g, 13 mmol) in triethyl orthoacetate (60 mL) was refluxed under N_2 for 24 h. After removing the solvent, the residue was dissolved in hot 2 M NaOH (20 mL) for 30 min and neutralized with 6 N HCl (6–7 mL). On cooling, 7-amino-2-methylpyrido[4,3-*d*]pyrimidin-4(3*H*)-one precipitated. The yellow solid was filtered off and dried in a vacuum oven, affording the pure title compound **6b** (2.4 g, 72%). M.p. > 290 °C. ^{1}H NMR (200 MHz, [D$_6$]DMSO, 25 °C): δ = 11.79 (br. s, 1 H, NH), 8.68 (s, 1 H, 5-H), 6.68 (br. s, 2 H, NH_2), 6.28 (s, 1 H, 8-H), 2.25 (s, 3 H, 2-CH_3) ppm. ^{13}C NMR (50 MHz, [D$_6$]DMSO, 25 °C): δ = 163.8, 161.3, 158.4, 155.1, 150.0, 107.4, 98.3, 21.6 ppm. MS: *m*/*z* (%) = 177.30 (100) $[M+H]^+$.

7-Amino-2-(methoxymethyl)pyrido[4,3-*d*]pyrimidin-4(3*H*)-one (6c): To a solution of 4,6-diaminonicotinamide (**4**, 0.395 g, 2.6 mmol) in DMF (12 mL) were added methoxyacetyl chloride (0.498 mL, 5.45 mmol) and pyridine (0.525 mL, 6.46 mmol). The reaction mixture was stirred at room temperature under N_2. After 3 h, 5 N NaOH (8 mL) was added, and the reaction mixture was stirred for an additional 18 h. The reaction mixture was concentrated in vacuo and acidified with a concentrated HCl solution. On cooling, 7-amino-2-(methoxymethyl)pyrido[4,3-*d*]pyrimidin-4(3*H*)-one (**6c**) precipitated. The pale yellow solid was collected by filtration and dried in a vacuum oven, furnishing the pure title compound (0.27 g, 50%). M.p. 272–273 °C. ^{1}H NMR (200 MHz, [D$_6$]DMSO, 25 °C): δ = 11.70 (br. s, 1 H, NH), 8.71 (s, 1 H, 5-H), 6.74 (s, 2 H, NH_2), 6.35 (s, 1 H, 8-H), 4.24 (s, 2 H, 2-CH_2), 3.33 (s, 3 H, OCH_3) ppm. ^{13}C NMR (50 MHz, [D$_6$]DMSO, 25 °C): δ = 164.0, 161.2, 157.9, 154.7, 150.4, 108.0, 99.0, 71.6, 58.7 ppm. IR (KBr): $\tilde{\nu}$ = 3407, 3328, 3201, 2826, 1697, 1655, 1598, 1486, 1261, 1115 cm^{-1}. MS: *m*/*z* (%) = 207.21 (100) $[M+H]^+$.

7-Amino-5-bromopyrido[4,3-*d*]pyrimidin-4(3*H*)-one (6d): A mixture of 4,6-diamino-2-bromonicotinamide (**3**, 2.1 g, 9.09 mmol) in triethyl orthoformate (45 mL) was refluxed under N_2 for 24 h. The solvent was removed under reduced pressure, and the residue was redissolved in hot 2 M NaOH (20 mL) for 30 min and neutralized with 6 N HCl (6–7 mL). On cooling, 7-amino-5-bromopyrido[4,3-*d*]pyrimidin-4(3*H*)-one (**6d**) precipitated. The precipitate was filtered off and dried in a vacuum oven, yielding the title compound as a yellow solid (1.95 g, 88%). M.p. > 290 °C. ^{1}H NMR (200 MHz, [D$_6$]DMSO, 25 °C): δ = 11.86 (br. s, 1 H, NH), 7.94 (s, 1 H, 2-H), 7.06 (br. s, 2 H, NH_2), 6.33 (s, 1 H, 8-H) ppm. ^{13}C NMR (50 MHz, [D$_6$]DMSO, 25 °C): δ = 161.6, 158.2, 157.3, 149.2, 140.8, 107.4, 99.4 ppm. IR (KBr): $\tilde{\nu}$ = 3436, 3317, 3171, 3067, 2925, 2854, 1683, 1623, 1585, 1522, 1466, 1382, 1299, 1240, 1214, 1133, 1091 cm^{-1}. MS: *m*/*z* (%) = 240.9 (80) $[M+H]^+$, 242.9 (100) $[M+H]^+$.

7-Amino-5-(3,4-dimethoxyphenyl)pyrido[4,3-*d*]pyrimidin-4(3*H*)-one (7a): To a solution of 7-amino-5-bromopyrido[4,3-*d*]pyrimidin-4(3*H*)-one (**6d**, 0.33 g, 1.37 mmol) in dioxane/H_2O (3:1, 14 mL), were added (3,4-dimethoxyphenyl)boronic acid (0.299 g, 1.64 mmol), K_2CO_3 (0.757 g, 5.48 mmol) and $Pd(PPh_3)_4$ (0.158 g, 0.14 mmol). The reaction mixture was refluxed under N_2 for 2 h. After cooling to room temperature, 1 N HCl was added slowly to neutralize the mixture to pH = 7–8. The solvents were removed under reduced pressure. The residue was diluted with H_2O (10 mL) and filtered. The crude solid was redissolved in MeOH, pre-adsorbed on silica gel and purified by chromatography on silica gel (CH_2Cl_2/MeOH, 30:1), yielding 7-amino-5-(3,4-dimethoxyphenyl)-pyrido[4,3-*d*]pyrimidin-4(3*H*)-one (**7a**) as a pale yellow solid (0.383 g, 94%). M.p. > 290 °C. ^{1}H NMR (200 MHz, [D$_6$]DMSO, 25 °C): δ = 11.55 (br. s, 1 H, NH), 7.92 (s, 1 H, 2-H), 7.00–6.88 (m, 3 H, ArH), 6.70 (br. s, 2 H, NH_2), 6.36 (s, 1 H, 8-H), 3.79 (s, 3 H, OCH_3), 3.72 (s, 3 H, OCH_3) ppm. ^{13}C NMR (50 MHz, [D$_6$]-

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DMSO, 25 °C): δ = 161.9, 161.1, 159.3, 157.0, 148.8, 148.6, 147.3, 134.0, 122.0, 113.6, 110.3, 106.4, 98.6, 55.5 ppm. IR (KBr): ṽ = 3438, 3327, 3210, 3068, 2842, 1678, 1651, 1582, 1519, 1387, 1257, 1225, 1160, 1140 cm^{-1}. HRMS: calcd. for $C_{15}H_{15}N_4O_3$ 299.1144; found 299.1148.

7-Amino-2-methyl-5-[(*E*)-prop-1-enyl]pyrido[4,3-*d*]pyrimidin-4(3*H*)-one (8a): To a solution of 7-amino-5-bromo-2-methylpyrido[4,3-*d*]-pyrimidin-4(3*H*)-one (**6e**, 0.1 g, 0.39 mmol) in dioxane/H_2O (3:1, 4 mL) were added (*E*)-propenylboronic acid (40 mg, 0.47 mmol), K_2CO_3 (0.217 g, 1.57 mmol) and $Pd(PPh_3)_4$ (45 mg, 0.04 mmol). The reaction mixture was refluxed under N_2 for 1 h. After cooling to room temperature, 1 N HCl was added slowly to neutralize the mixture to pH = 7–8. The solvents were removed under reduced pressure. The residue was diluted with H_2O (5 mL) and filtered. The crude solid was redissolved in MeOH, pre-adsorbed on silica gel and purified by chromatography on silica gel (CH_2Cl_2/MeOH, 30:1) affording 7-amino-2-methyl-5-[(*E*)-prop-1-enyl]pyrido[4,3-*d*]-pyrimidin-4(3*H*)-one (**8a**) as a pale yellow solid (67 mg, 55%). M.p. 263 °C. ^{1}H NMR (200 MHz, [D$_6$]DMSO, 25 °C): δ = 11.59 (br. s, 1 H, NH), 7.94 (d, ^3J = 15.4 Hz, 1 H, vinyl-H), 6.96–6.81 (m, 1 H, vinyl-H), 6.47 (br. s, 2 H, NH_2), 6.19 (s, 1 H, 8-H), 2.19 (s, 3 H, 2-CH_3), 1.88 (d, ^3J = 7 Hz, 3 H, 3′-CH_3) ppm. ^{13}C NMR (50 MHz, [D$_6$]DMSO, 25 °C): δ = 161.6, 161.4, 157.2, 157.0, 157.0, 133.1, 129.6, 103.8, 98.6, 21.1, 18.2 ppm. IR (KBr): ṽ = 3420, 3294, 3167, 3056, 2922, 1675, 1618, 1575, 1457, 1437, 1288, 1199, 1139 cm^{-1}. HRMS: calcd. for $C_{11}H_{13}N_4O$ 217.1089; found 217.1083.

(5-Phenyl-4-oxa-1,3,7-triazaphenalen-8-yl)amine (9a): To a mixture of bis(triphenylphosphane)palladium(II) acetate (6 mg, 0.01 mmol), 7-amino-5-bromopyrido[4,3-*d*]pyrimidin-4(3*H*)-one (**6d**, 0.1 g, 0.41 mmol) and triethylamine (0.415 mL) in DMF (8 mL) was added a solution of phenylacetylene (0.091 mL, 0.83 mmol) in DMF (0.3 mL) over a period of 30 min. The reaction mixture was refluxed under N_2 for 1 h and cooled to room temperature. The volatiles were removed under reduced pressure. The crude residue was diluted with CH_2Cl_2 and washed with H_2O. The combined organic layers were dried with $MgSO_4$ and concentrated in vacuo. The crude residue was purified by chromatography on silica gel (CH_2Cl_2/MeOH, 30:1), yielding the pure title compound **9a** as a yellowish green solid (52 mg, 48%). M.p. 276 °C. ^{1}H NMR (200 MHz, [D$_6$]DMSO, 25 °C): δ = 8.50 (s, 1 H, 2-H), 8.03–7.99 (m, 2 H, ArH), 7.59–7.54 (m, 3 H, ArH), 7.31 (s, 1 H, 6-H), 6.98 (br. s, 2 H, NH_2), 6.27 (s, 1 H, 9-H) ppm. ^{13}C NMR (50 MHz, [D$_6$]DMSO, 25 °C): δ = 165.7, 164.3, 160.0, 157.6, 155.9, 153.4, 131.2, 131.8, 129.2, 128.7, 125.7, 106.2, 93.4 ppm. IR (KBr): ṽ = 3318, 3167, 1645, 1590, 1565, 1464, 1451, 1428, 1375, 1335, 1270, 1191, 1211, 1077, 1003 cm^{-1}. HRMS: calcd. for $C_{15}H_{11}N_4O$ 263.0932; found 263.0930.

7-Amino-5-(butylamino)-2-methylpyrido[4,3-*d*]pyrimidin-4(3*H*)-one (10): To a solution of 7-amino-5-bromo-2-methylpyrido[4,3-*d*]pyrimidin-4(3*H*)-one (**6e**, 50 mg, 0.20 mmol) in dioxane (1.5 mL) were added *n*-butylamine (0.039 g, 0.39 mmol), potassium *tert*-butoxide (31 mg, 0.27 mmol) and $Pd(PPh_3)_4$ (9 mg, 0.01 mmol). The reaction mixture was refluxed under N_2 for 24 h and cooled to room temperature. The solvents were removed under reduced pressure. The crude residue was diluted with MeOH and pre-adsorbed onto silica gel. After removing the solvent, the residue was purified by chromatography on silica gel (CH_2Cl_2/MeOH, 30:1), yielding 7-amino-5-(butylamino)-2-methylpyrido[4,3-*d*]pyrimidin-4(3*H*)-one (**10**) as a light brown solid (20 mg, 41%). M.p. 270–272 °C. ^{1}H NMR (200 MHz, [D$_6$]DMSO, 25 °C): δ = 11.44 (s, 1 H, NH), 8.66 (t, ^3J = 5.8 Hz, 1 H, 5-NH), 6.24 (s, 2 H, NH_2), 5.52 (s, 1 H, 8-H), 3.35 (q, ^3J = 5.8 Hz, 2 H, 1′-CH_2), 1.55–1.44 (m, 2 H, 2′-CH_2), 1.39–1.28 (m, 2 H, 3′-CH_2), 0.89 (t, ^3J = 7.4 Hz, 3 H, 4′-CH_3) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO, 25 °C): δ = 162.5, 162.3, 159.7, 156.6, 90.7, 88.1, 31.2, 21.2, 19.7, 13.7 ppm. IR (KBr): ṽ = 3470, 3323, 3165, 2951, 2923, 2870, 1656, 1612, 1567, 1476, 1374, 1339, 1283, 1210, 1147, 1130, 1091, 1057 cm^{-1}. HRMS: calcd. for $C_{12}H_{18}N_5O$ 248.1511; found 248.1516.

***N*^{4}-Benzylpyrido[4,3-*d*]pyrimidine-4,7-diamine (11a):** A reaction mixture consisting of 7-aminopyrido[4,3-*d*]pyrimidin-4(3*H*)-one (**6a**, 0.1 g, 0.62 mmol), 1,1,1,3,3,3-hexamethyldisilazane (0.386 mL, 1.85 mmol), benzylamine (0.202 mL, 1.85 mmol) and ammonium sulfate (8 mg, 0.006 mmol) was heated at 120 °C for 3 d. After cooling to room temperature, ethanol (10 mL) was added, and the reaction mixture was concentrated in vacuo. The residue was purified by column chromatography on silica gel (CH_2Cl_2/MeOH, 40:1), yielding *N*^{4}-benzylpyrido[4,3-*d*]pyrimidine-4,7-diamine (**11a**, 30 mg, 20%) as a light brown solid. M.p. 236 °C. ^{1}H NMR (200 MHz, [D$_6$]DMSO, 25 °C): δ = 9.10 (s, 1 H, 5-H), 8.85 (t, ^3J = 5.4 Hz, 1 H, NH), 8.24 (s, 1 H, 2-H), 7.34–7.24 (m, 5 H, ArH), 6.45 (br. s, 2 H, NH_2), 6.35 (s, 1 H, 8-H), 4.73 (d, ^3J = 5.4 Hz, 2 H, NCH_2) ppm. ^{13}C NMR (50 MHz, [D$_6$]DMSO, 25 °C): δ = 161.7, 159.3, 158.4, 154.3, 147.8, 139.3, 128.2, 127.1, 126.7, 103.8, 96.9, 43.1 ppm. IR (KBr): ṽ = 3455, 3262, 3123, 2923, 1651, 1593, 1543, 1497, 1466, 1420, 1370, 1337, 1260, 1209, 1159, 1136, 1077, 1010 cm^{-1}. HRMS: calcd. for $C_{14}H_{14}N_5$ 252.1249; found 252.1238.

7-Aminopyrido[4,3-*d*]pyrimidine-4(3*H*)-thione (12): Phosphorus pentasulfide (0.754 g, 3.39 mmol) was added to a solution of 7-aminopyrido[4,3-*d*]pyrimidine-4(3*H*)-one (**6a**, 0.5 g, 3.08 mmol) in pyridine (16 mL). The mixture was refluxed for 5 h. On cooling, a precipitate formed, and the supernatant was decanted. The solid was suspended in H_2O and filtered to yield 7-aminopyrido[4,3-*d*]-pyrimidine-4(3*H*)-thione (**12**, 0.465 g, 85%) as a brown solid. M.p. 245 °C. ^{1}H NMR (200 MHz, [D$_6$]DMSO, 25 °C): δ = 13.14 (br. s, 1 H, NH), 9.17 (s, 1 H, 5-H), 7.97 (s, 1 H, 2-H), 7.10 (br. s, 2 H, NH_2), 6.34 (s, 1 H, 8-H) ppm. ^{13}C NMR (50 MHz, [D$_6$]DMSO, 25 °C): δ = 184.1, 164.0, 154.0, 150.6, 146.9, 116.7, 98.2 ppm. IR (KBr): ṽ = 3446, 3306, 3123, 2924, 2853, 1653, 1594, 1479, 1393, 1356, 1323, 1252, 1162 cm^{-1}. MS: *m*/*z* (%) = 179.1 (100) $[M+H]^+$.

4-(Methylthio)pyrido[4,3-*d*]pyrimidin-7-amine (13): To a solution of 7-aminopyrido[4,3-*d*]pyrimidine-4(3*H*)-thione (**12**, 0.437 g, 2.45 mmol) in DMSO (12 mL) were added triethylamine (0.854 mL, 6.13 mmol) and iodomethane (0.305 mL, 4.90 mmol). The reaction mixture was stirred at room temperature under N_2 for 12 h. The mixture was poured into H_2O and extracted with EtOAc. The combined organic layers were dried with $MgSO_4$ and concentrated in vacuo to yield 4-(methylthio)pyrido[4,3-*d*]pyrimidin-7-amine (**13**, 0.345 g, 73%) as a brown solid. M.p. 186 °C. ^{1}H NMR (200 MHz, [D$_6$]DMSO, 25 °C): δ = 8.98 (s, 1 H, 5-H), 8.71 (s, 1 H, 2-H), 6.93 (s, 2 H, NH_2), 6.49 (s, 1 H, 8-H), 2.63 (s, 3 H, SCH_3) ppm. ^{13}C NMR (50 MHz, [D$_6$]DMSO, 25 °C): δ = 171.1, 162.6, 156.6, 152.5, 149.3, 112.5, 96.5, 11.4 ppm. MS: *m*/*z* (%) = 193.1 (100) $[M+H]^+$.

4-Morpholinopyrido[4,3-*d*]pyrimidin-7-amine (14): A mixture of 4-(methylthio)pyrido[4,3-*d*]pyrimidin-7-amine (**13**, 260 mg, 1.35 mmol) and morpholine (0.237 mL, 2.27 mmol) in ethanol (6 mL) was refluxed for 24 h. The volatiles were removed by evaporation in vacuo. The crude residue was purified by chromatography on silica gel (CH_2Cl_2/MeOH, 30:1), yielding 4-morpholinopyrido[4,3-*d*]pyrimidin-7-amine (**14**) as a light brown solid (225 mg, 72%). M.p. 154–156 °C. ^{1}H NMR (200 MHz, [D$_6$]DMSO, 25 °C): δ = 8.85 (s, 1 H, 5-H), 8.34 (s, 1 H, 2-H), 6.58 (br. s, 2 H, NH_2), 6.41 (s, 1 H, 8-H), 3.78 (br. s, 4 H, morpholinyl 3-H), 3.75 (br. s, 4 H, morpholinyl 2-H) ppm. ^{13}C NMR (50 MHz, [D$_6$]DMSO,

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25 °C): δ = 162.7, 161.2, 157.0, 156.5, 150.2, 104.4, 96.7, 66.1, 49.3 ppm. IR (KBr): $\tilde{\nu}$ = 3430, 3338, 3227, 2925, 1640, 1605, 1565, 1528, 1498, 1464, 1384, 1358, 1331, 1269, 1224, 1109, 1066, 1031 cm^{-1}. HRMS: calcd. for $C_{11}H_{14}N_5O$ 232.1198; found 232.1192.

***N*-(2-Methyl-4-oxo-3,4-dihydropyrido[4,3-*d*]pyrimidin-7-yl)acetamide (15):** A mixture of 7-amino-2-methylpyrido[4,3-*d*]pyrimidin-4(3*H*)-one (**6b**, 700 mg, 3.97 mmol) in acetic anhydride/pyridine (1:1, 20 mL) was refluxed for 30 min. The solvents were removed in vacuo, and the residue was purified by chromatography on silica gel (CH_2Cl_2/MeOH, 30:1), yielding *N*-(2-methyl-4-oxo-3,4-dihydropyrido[4,3-*d*]pyrimidin-7-yl)acetamide (**15**, 0.75 g, 86%) as a pale yellow solid. M.p. > 290 °C. ^{1}H NMR (200 MHz, [D$_6$]DMSO, 25 °C): δ = 12.33 (br. s, 1 H, 3-NH), 10.84 (s, 1 H, 7-NH), 8.98 (s, 1 H, 5-H), 8.10 (s, 1 H, 8-H), 2.35 (s, 3 H, 2-CH_3), 2.13 (s, 3 H, $COCH_3$) ppm. ^{13}C NMR (50 MHz, [D$_6$]DMSO, 25 °C): δ = 170.0, 160.8, 159.7, 155.6, 148.8, 112.8, 106.7, 24.0, 21.8 ppm. IR (KBr): $\tilde{\nu}$ = 3335, 3127, 3074, 2926, 2789, 1702, 1606, 1564, 1524, 1431, 1374, 1256, 1173, 1133, 1040 cm^{-1}. MS: *m*/*z* (%) = 177.1 (100) $[M+H]^+$.

***N*-{2-Methyl-4-(1*H*-1,2,4-triazol-1-yl)pyrido[4,3-*d*]pyrimidin-7-yl}acetamide (16):** To a solution of *N*-(2-methyl-4-oxo-3,4-dihydropyrido[4,3-*d*]pyrimidin-7-yl)acetamide (**15**, 0.595 g, 2.73 mmol) in acetonitrile/CH_2Cl_2 (2:1, 27 mL) were added phosphorus oxychloride (0.762 mL, 8.18 mmol) and triethylamine (1.14 mL, 8.18 mmol). The reaction mixture was stirred at room temperature for 24 h. The solvents were removed in vacuo, and the residue was redissolved in CH_2Cl_2 and washed with iced H_2O until pH = 6–7. The residue was dried with $MgSO_4$ and concentrated to yield *N*-{2-methyl-4-(1*H*-1,2,4-triazol-1-yl)pyrido[4,3-*d*]pyrimidin-7-yl}acetamide (**16**) as a crude product (0.464 g, 77%). M.p. > 290 °C. ^{1}H NMR (200 MHz, [D$_6$]DMSO, 25 °C): δ = 11.23 (s, 1 H, NH), 10.16 (s, 1 H, 5′-H), 9.65 (s, 1 H, 5-H), 8.59 (s, 1 H, 3′-H), 8.40 (s, 1 H, 8-H), 2.77 (s, 3 H, 2-CH_3), 2.19 (s, 3 H, $COCH_3$) ppm. ^{13}C NMR (50 MHz, [D$_6$]DMSO, 25 °C): δ = 170.3, 167.3, 157.8, 154.7, 153.6, 153.3, 152.7, 145.7, 106.8, 105.2, 26.1, 24.1 ppm. MS: *m*/*z* (%) = 270.16 (100) $[M+H]^+$.

***N*-(4-Methoxy-2-methylpyrido[4,3-*d*]pyrimidin-7-yl)acetamide (17a):** A mixture of *N*-{2-methyl-4-(1*H*-1,2,4-triazol-1-yl)pyrido[4,3-*d*]pyrimidin-7-yl}acetamide (**16**, 45 mg, 0.17 mmol) in MeOH (1.6 mL) was refluxed for 12 h. The solvents were evaporated in vacuo. The residue was redissolved in CH_2Cl_2 and washed with H_2O. The combined organic layers were dried with $MgSO_4$ and concentrated in vacuo. The crude residue was purified by chromatography on silica gel (CH_2Cl_2/MeOH, 20:1), yielding *N*-(4-methoxy-2-methylpyrido[4,3-*d*]pyrimidin-7-yl)acetamide (**17a**) as a pale yellow solid (22 mg, 57%). M.p. 210 °C. ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 9.16 (s, 1 H, 5-H), 8.52 (s, 1 H, 8-H), 8.18 (br. s, 1 H, NH), 4.18 (s, 3 H, 4-OCH_3), 2.72 (s, 3 H, 2-CH_3), 2.27 (s, 3 H, $COCH_3$) ppm. ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C): δ = 168.6, 167.9, 166.5, 156.3, 152.1, 147.2, 107.3, 106.2, 53.6, 26.1, 24.1 ppm. IR (KBr): $\tilde{\nu}$ = 3447, 3266, 2926, 1686, 1624, 1570, 1475, 1400, 1361, 1243, 1186, 1127, 1019 cm^{-1}. HRMS: calcd. for $C_{11}H_{13}N_4O_2$ 233.1038; found 233.1030.

***N*^{4}-(2-Methoxyethyl)-2-methylpyrido[4,3-*d*]pyrimidine-4,7-diamine (18a):** A reaction mixture consisting of 7-amino-2-methylpyrido[4,3-*d*]pyrimidin-4(3*H*)-one (**15**, 0.10 g, 0.46 mmol), 1,1,1,3,3,3-hexamethyldisilazane (0.382 mL, 1.83 mmol), (2-methoxyethyl)-amine (0.159 mL, 1.83 mmol) and ammonium sulfate (6 mg, 0.005 mmol) was heated at 120 °C for 2 d. After cooling to room temperature, ethanol (10 mL) was added, and the reaction mixture was concentrated in vacuo. The residue was purified by column chromatography on silica gel (acetone/MeOH, 50:1), yielding *N*^{4}-(2-methoxyethyl)-2-methylpyrido[4,3-*d*]pyrimidine-4,7-diamine (**18a**) as a pale yellow solid (74 mg, 69%). M.p. 268 °C. ^{1}H NMR (300 MHz, [D$_6$]DMSO, 25 °C): δ = 9.00 (s, 1 H, 5-H), 8.23 (br. s, 1 H, 4-NH), 6.33 (s, 2 H, 7-NH_2), 6.27 (s, 1 H, 8-H), 3.64 (t, ^3J = 5.3 Hz, 2 H, 2′-CH_2), 3.54 (t, ^3J = 5.3 Hz, 2 H, 1′-CH_2), 3.29 (s, 3 H, OCH_3), 2.33 (s, 3 H, 2-CH_3) ppm. ^{13}C NMR (75 MHz, [D$_6$]-DMSO, 25 °C): δ = 167.0, 161.6, 159.4, 155.1, 147.5, 102.4, 96.6, 70.2, 57.9, 39.7, 26.7 ppm. IR (KBr): $\tilde{\nu}$ = 3416, 3262, 3142, 2974, 2932, 1655, 1601, 1561, 1501, 1459, 1397, 1343, 1267, 1204, 1120 cm^{-1}. HRMS: calcd. for $C_{11}H_{16}N_5O$ 234.1355; found 234.1370.

7-Amino-5-(3,4-dimethoxyphenyl)-3-methylpyrido[4,3-*d*]pyrimidin-4(3*H*)-one (19): To a solution of 7-amino-5-(3,4-dimethoxyphenyl)-pyrido[4,3-*d*]pyrimidin-4(3*H*)-one (**7a**, 0.11 g, 0.37 mmol) in DMF (4 mL) was added NaH (60% in mineral oil, 10 mg, 0.41 mmol). The resulting slurry was heated at 65 °C for 30 min, at which time a solution was obtained. It was cooled to 50 °C, and a solution of iodomethane (0.028 mL, 0.44 mmol) in DMF (0.3 mL) was added dropwise to the mixture. The mixture was maintained at 60–80 °C for 3 h and cooled to room temperature. The reaction mixture was concentrated in vacuo, and the residue was purified by chromatography on silica gel (CH_2Cl_2/MeOH, 50:1), yielding 7-amino-5-(3,4-dimethoxyphenyl)-3-methylpyrido[4,3-*d*]pyrimidin-4(3*H*)-one (**19**) as a pale yellow solid (40 mg, 35%). M.p. 231–233 °C. ^{1}H NMR (200 MHz, [D$_6$]DMSO, 25 °C): δ = 8.23 (s, 1 H, 2-H), 6.96 (s, 1 H, ArH), 6.90 (s, 2 H, ArH), 6.70 (br. s, 2 H, NH_2), 6.35 (s, 1 H, 8-H), 3.79 (s, 3 H, OCH_3), 3.72 (s, 3 H, OCH_3), 3.26 (s, 3 H, 3-CH_3) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO, 25 °C): δ = 161.8, 161.0, 159.1, 156.4, 151.4, 148.6, 147.3, 134.1, 121.7, 113.3, 110.3, 105.5, 98.3, 55.52, 55.48, 33.2 ppm. IR (KBr): $\tilde{\nu}$ = 3424, 3181, 2924, 2853, 1687, 1634, 1589, 1513, 1465, 1419, 1327, 1256, 1187, 1137, 1025 cm^{-1}. MS: *m*/*z* (%) = 313.1 (100) $[M+H]^+$.

7-Amino-5-(3,4-dimethoxyphenyl)-2,3-dimethylpyrido[4,3-*d*]pyrimidin-4(3*H*)-one (20): To a solution of 7-amino-5-(3,4-dimethoxyphenyl)-2-methylpyrido[4,3-*d*]pyrimidin-4(3*H*)-one (**7e**, 50 mg, 0.16 mmol) in DMF (1 mL) were added K_2CO_3 (27 mg, 0.19 mmol) and iodomethane (0.012 mL, 0.19 mmol). The resulting slurry was stirred at room temperature for 24 h. After removing the volatiles, the residue was diluted with H_2O and extracted with EtOAc. The combined organic phases were dried with $MgSO_4$ and concentrated in vacuo. The crude residue was purified by chromatography on silica gel (CH_2Cl_2/MeOH, 50:1), yielding 7-amino-5-(3,4-dimethoxyphenyl)-2,3-dimethylpyrido[4,3-*d*]pyrimidin-4(3*H*)-one (**20**) as a pale yellow solid (26 mg, 50%). M.p. 290 °C. ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 7.05–6.91 (m, 3 H, ArH), 6.45 (s, 1 H, 8-H), 4.89 (br. s, 2 H, NH_2), 3.92 (s, 3 H, OCH_3), 3.90 (s, 3 H, OCH_3), 3.45 (s, 3 H, 3-CH_3), 2.56 (s, 3 H, 2-CH_3) ppm. ^{13}C NMR (50 MHz, [D$_6$]DMSO, 25 °C): δ = 161.1, 159.1, 158.9, 158.1, 154.4, 147.7, 146.5, 133.4, 120.9, 112.4, 109.6, 103.4, 96.6, 54.6, 29.1, 22.4 ppm. IR (KBr): $\tilde{\nu}$ = 3424, 3310, 3192, 2924, 2853, 1681, 1635, 1577, 1513, 1466, 1420, 1373, 1338, 1259, 1155, 1136, 1025 cm^{-1}. HRMS: calcd. for $C_{17}H_{19}N_4O_3$ 327.1457; found 327.1458.

***N*-(2,3-Dimethyl-4-oxo-3,4-dihydropyrido[4,3-*d*]pyrimidin-7-yl)acetamide (24). Method A:** To a solution of *N*-(2-methyl-4-oxo-3,4-dihydropyrido[4,3-*d*]pyrimidin-7-yl)acetamide (**15**, 34 mg, 0.16 mmol) in DMF (2 mL) were added K_2CO_3 (26 mg, 0.19 mmol) and benzyl bromide (0.012 mL, 0.19 mmol). The resulting slurry was stirred at room temperature for 24 h. The solvents were removed under reduced pressure. The residue was diluted with CH_2Cl_2 and washed with H_2O. The combined organic layers were dried with $MgSO_4$

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and concentrated in vacuo. The crude residue was purified by chromatography on silica gel (CH_2Cl_2/MeOH, 30:1) to give *N*-(2,3-dimethyl-4-oxo-3,4-dihydropyrido[4,3-*d*]pyrimidin-7-yl)acetamide (**24**) as a pale yellow solid (19 mg, 53%). **Method B:** To a mixture of *N*-(2-methyl-4-oxo-3,4-dihydropyrido[4,3-*d*]pyrimidin-7-yl)acetamide (**15**, 0.10 g, 0.46 mmol), triphenylphosphane (0.18 g, 0.69 mmol) and MeOH (0.028 mL, 0.69 mmol) in dioxane (4.5 mL) was added DIAD (0.135 mL, 0.69 mmol). The reaction mixture was stirred at room temperature for 1 d, after which the same amounts of triphenylphosphane, MeOH and dioxane were added. The resulting reaction mixture was stirred for an additional 1 d. After removing the volatiles, the residue was purified by column chromatography on silica gel (CH_2Cl_2/MeOH, 50:1) to give *N*-(2,3-dimethyl-4-oxo-3,4-dihydropyrido[4,3-*d*]pyrimidin-7-yl)acetamide (**24**, 73 mg, 68%) as a pale yellow solid. M.p. 237–239 °C. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 9.16 (s, 1 H, 5-H), 8.32 (s, 1 H, 8-H), 8.11 (br. s, 1 H, NH), 3.61 (s, 3 H, 3-CH_3), 2.64 (s, 3 H, 2-CH_3), 2.25 (s, 3 H, $COCH_3$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 168.8, 161.3, 159.8, 154.7, 154.6, 150.2, 113.0, 107.7, 31.0, 25.0, 24.2 ppm. IR (KBr): $\tilde{\nu}$ = 3350, 3178, 2924, 2364, 1676, 1614, 1594, 1522, 1417, 1385, 1260, 1172, 1145, 1032 cm^{-1}. HRMS: calcd. for $C_{11}H_{13}N_4O_2$ 233.1039; found 233.1030.

5-(3,4-Dimethoxyphenyl)-7-fluoro-2-methylpyrido[4,3-*d*]pyrimidin-4(3*H*)-one (25): To a solution of 7-amino-5-(3,4-dimethoxyphenyl)-2-methylpyrido[4,3-*d*]pyrimidin-4(3*H*)-one (**7e**, 0.218 g, 0.70 mmol) in 60% HBF_4 (in diethyl ether/DMF, 1:1, 4.5 mL) at 0 °C was added dropwise a solution of $NaNO_2$ (96 mg, 1.40 mmol) in H_2O (0.5 mL). The reaction mixture was stirred at 0 °C for another 1 h and at room temperature for 3 h. The resulting mixture was ice-cooled, neutralized with a saturated aqueous sodium carbonate solution and extracted with EtOAc. The combined organic layers were dried with $MgSO_4$ and concentrated in vacuo. The crude residue was purified by chromatography on silica gel (CH_2Cl_2/MeOH, 60:1), yielding 5-(3,4-dimethoxyphenyl)-7-fluoro-2-methylpyrido[4,3-*d*]pyrimidin-4(3*H*)-one (**25**) as a solid (176 mg, 79%). M.p. 240–244 °C. ^{1}H NMR (200 MHz, [D$_6$]DMSO, 25 °C): δ = 12.37 (br. s, 1 H, NH), 7.15–7.09 (m, 3 H, ArH), 7.01 (s, 1 H, 8-H), 3.82 (s, 3 H, OCH_3), 3.74 (s, 3 H, OCH_3), 2.37 (s, 3 H, 2-CH_3) ppm. ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C): δ = 165.0 (d, $^1J_{C,F}$ = 265 Hz), 162.4 (d, $^3J_{C,F}$ = 9 Hz), 162.4, 161.2 (d, $^3J_{C,F}$ = 13 Hz), 158.8, 150.5, 148.5, 131.8, 123.1, 113.2, 110.3, 103.3 (d, $^2J_{C,F}$ = 36 Hz), 97.1, 56.2, 21.7 ppm. IR (KBr): $\tilde{\nu}$ = 3168, 3051, 2944, 1665, 1633, 1593, 1519, 1420, 1410, 1356, 1326, 1261, 1225, 1168, 1128, 1022 cm^{-1}. HRMS: calcd. for $C_{16}H_{15}FN_3O_3$ 316.1097; found 316.1100.

5-(3,4-Dimethoxyphenyl)-7-methoxy-2-methylpyrido[4,3-*d*]pyrimidin-4(3*H*)-one (26a): A solution of 5-(3,4-dimethoxyphenyl)-7-fluoro-2-methylpyrido[4,3-*d*]pyrimidin-4(3*H*)-one (**25**, 70 mg, 0.21 mmol) in sodium methoxide (30 wt.-% solution in MeOH, 3 mL) was stirred at reflux for 4 h. The resulting mixture was concentrated under reduced pressure, diluted with H_2O, neutralized with 2 N HCl and extracted with CH_2Cl_2. The combined organic layers were dried with $MgSO_4$ and concentrated in vacuo. The crude residue was purified by chromatography on silica gel (CH_2Cl_2/MeOH, 30:1), yielding 5-(3,4-dimethoxyphenyl)-7-methoxy-2-methylpyrido[4,3-*d*]pyrimidin-4(3*H*)-one (**26a**, 58 mg, 83%) as a solid. M.p. 245–248 °C. ^{1}H NMR (200 MHz, [D$_6$]DMSO, 25 °C): δ = 12.00 (br. s, 1 H, NH), 7.14 (s, 1 H, ArH), 7.11 (d, ^3J = 8.2 Hz, 1 H, ArH), 6.96 (d, ^3J = 8.2 Hz, 1 H, ArH), 6.71 (s, 1 H, 8-H), 3.93 (s, 3 H, 7-OCH_3), 3.81 (s, 3 H, OCH_3), 3.73 (s, 3 H, OCH_3), 2.31 (s, 3 H, 2-CH_3) ppm. ^{13}C NMR (50 MHz, [D$_6$]DMSO, 25 °C): δ = 164.9, 160.6, 160.4, 158.8, 149.4, 147.4, 133.0, 122.6, 114.2, 110.5, 109.2, 101.4, 97.8, 55.5, 53.8, 21.3 ppm. IR (KBr): $\tilde{\nu}$ = 3056, 2926, 1684, 1618, 1587, 1520, 1457, 1420, 1391, 1363, 1252, 1232, 1178, 1137, 1021 cm^{-1}. HRMS: calcd. for $C_{17}H_{18}N_3O_4$ 328.1297; found 328.1303.

4-(7-Chloropyrido[4,3-*d*]pyrimidin-4-yl)morpholine (27): A solution of $NaNO_2$ (54 mg, 0.78 mmol) in H_2O (0.2 mL) was added dropwise to a solution of 4-morpholinopyrido[4,3-*d*]pyrimidin-7-amine (**14**, 90 mg, 0.39 mmol) in 6 N HCl (2 mL) at –15 °C over 20 min. This reaction mixture was stirred for another 10 min, after which a cold suspension of CuCl (116 mg, 1.17 mmol) in 6 N HCl (0.2 mL) was added. The temperature of the reaction was gradually raised to room temperature over 1 h, and the mixture was stirred at 60 °C for another 1 h. The pH of the mixture was adjusted to 5–6 with a 10 N NaOH solution. The mixture was extracted with CH_2Cl_2. The combined organic layers were dried with $MgSO_4$ and concentrated in vacuo. The crude residue was purified by chromatography on silica gel (CH_2Cl_2/MeOH, 40:1), yielding pure 4-(7-chloropyrido[4,3-*d*]pyrimidin-4-yl)morpholine (**27**) as a solid (33 mg, 34%). M.p. 132 °C. ^{1}H NMR (200 MHz, [D$_6$]DMSO, 25 °C): δ = 9.21 (s, 1 H, 5-H), 8.45 (s, 1 H, 2-H), 7.73 (s, 1 H, 8-H), 3.99 (br. s, 4 H, morpholinyl 3-H), 3.77 (br. s, 4 H, morpholinyl 2-H) ppm. ^{13}C NMR (50 MHz, [D$_6$]DMSO, 25 °C): δ = 161.8, 158.1, 157.2, 150.8, 119.4, 110.8, 66.0, 48.9 ppm. HRMS: calcd. for $C_{11}H_{12}N_4OCl$ 251.0699; found 251.0699.

4-{7-(3,4-Dimethoxyphenyl)pyrido[4,3-*d*]pyrimidin-4-yl}morpholine (28): To a solution of 4-(7-chloropyrido[4,3-*d*]pyrimidin-4-yl)-morpholine (**27**, 34 mg, 0.14 mmol) in dioxane/H_2O (3:1, 2 mL), was added (3,4-dimethoxyphenyl)boronic acid (30 mg, 0.16 mmol), K_2CO_3 (75 mg, 0.54 mmol) and $Pd(PPh_3)_4$ (16 g, 0.01 mmol). The reaction mixture was refluxed under N_2 for 2 h. After cooling to room temperature, 1 N HCl was added slowly to neutralize the mixture to pH = 7–8. After removing the solvents under reduced pressure, the residue was extracted with CH_2Cl_2. The combined organic layers were dried with $MgSO_4$ and concentrated in vacuo. The crude residue was purified by chromatography on silica gel (CH_2Cl_2/MeOH, 40:1), yielding 4-{7-(3,4-dimethoxyphenyl)pyrido[4,3-*d*]pyrimidin-4-yl}morpholine (**28**, 40 mg, 83%) as a white solid. M.p. 148 °C. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 9.32 (s, 1 H, 5-H), 8.75 (s, 1 H, 2-H), 1.05 (s, 1 H, 8-H), 8.00–7.64 (m, 2 H, ArH), 7.01 (d, ^3J = 8.5 Hz,1 H, ArH), 4.04–3.99 (m, 7 H, morpholinyl 3-H, OCH_3), 3.97 (s, 3 H, OCH_3), 3.92–3.88 (m, 4 H, morpholinyl 2-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 163.1, 158.0, 157.6, 150.9, 149.5, 149.1, 132.3, 132.2, 132.1, 132.1, 131.0, 128.8, 128.6, 120.2, 115.7, 111.5, 110.1, 66.9, 56.2, 50.0 ppm. IR (KBr): $\tilde{\nu}$ = 2995, 2924, 2850, 1608, 1560, 1534, 1434, 1405, 1340, 1207, 1149, 1119, 1026 cm^{-1}. HRMS: calcd. for $C_{19}H_{21}N_4O_3$ 353.1614; found 353.1605.

Supporting Information (see footnote on the first page of this article): Synthetic procedures and analytical data for **6e**, **7b**, **7c**, **7d**, **7e**, **8b**, **9b**, **9c**, **9d**, **9e**, **9f**, **11b**, **17b**, **17c**, **17d**, **17e**, **18b**, **21**, **22**, **23**, **26b**; Table S1 with the purity of the final compounds as measured by LC/MS or LC/UV.

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