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PAPER

Divergent synthesis of novel 9-deazaxanthine derivatives *via* late-stage cross-coupling reactions†

Francesca Bartoccini,[a] Giovanni Piersanti,*[a] Marco Mor,[b] Giorgio Tarzia,[a] Patrizia Minetti*[c] and Walter Cabri[c]

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A small library of 8-substituted 9-deazaxanthines has been prepared by late-stage diversification of an 8-bromo-9-deazaxanthine. By utilizing palladium-catalyzed cross-coupling reactions a single key precursor can be transformed into a variety of 8-substituted-9-deazaxanthine compounds. Three key 8-bromo-9-deazaxanthine intermediates were efficiently prepared from commercially available 6-chlorouracil in six steps.

Introduction

In light of their occurrence in a wide range of biologically active molecules, pharmaceuticals, and natural products, xanthines have triggered increasing attention in both the synthetic and medicinal chemistry communities.[1] The xanthine subunit is not only essential for its bioactivity but is also a privileged pharmacophore in drug discovery.[2] Particularly, pyrrolo[3,2-*d*]pyrimidine derivatives (9-deazaxanthine or pyrimidinedione derivatives) have been shown to have good antagonistic potencies and selectivity profiles for human adenosine receptors,[3] whereas some others have antiviral activity or are enzyme inhibitors.[4] Consequently, efficient and selective methods to access this class of compounds are highly valuable.

As part of an ongoing project aimed at the synthesis and biological evaluation of adenosine receptor antagonists,[5] we desired a procedure that would provide 8-substituted-9-deazaxanthines (1,3-dialkyl-6-substituted-1*H*-pyrrolo[3,2-*d*]pyrimidine-2,4(3*H*,5*H*)-diones) directly from the parent functionalized 9-deazaxanthines, thereby avoiding commonly employed fragment-based approaches to 9-deazaxanthines[6,7] that typically rely on the stepwise construction of the 5-nitro-1,3-dialkyl-6-styryluracil intermediate followed by reductive ring closure to give N7–H 9-deazaxanthine with neat triethyl phosphite at high temperature,[7a] formic acid and sodium dithionite,[7b,c] or $SnCl_2$ in the presence of DMF.[7d] However, all these methods are limited by their low cyclization reaction yields (11–65%), harsh reaction conditions, and limited selectivities and functional group tolerance. Moreover, they have disadvantages in terms of flexibility and generality. In fact, they are limited to 8-aryl- or 8-styryl-9-deazaxanthine derivatives, which limit the synthetic diversity required in modern drug discovery. Because of the limited substrate scope of the methods outlined above, a novel procedure for the late-stage functionalization of deazaxanthines that would constitute a new approach to 8-substituted-9-deazaxanthines was sought.

Palladium-catalyzed C–C bond-forming methods are widely recognized as convenient and efficient means of introducing aryl, alkenyl, alkynyl, and, more recently, alkyl groups.[8] Compared to conventional noncatalytic organic synthesis, these versatile coupling reactions allow the use of easily available substrates for synthesizing structurally diverse molecules. These state of the art methods have been implemented in the industrial manufacturing of pharmaceuticals, advanced materials, and fine chemicals in the last decade.[9] The use of a palladium-catalyzed cross-coupling reaction is also an effective approach for the rapid introduction of chemical diversity into a system, since the number of steps requiring independent optimization is greatly reduced.

With the aim of creating new synthetic strategies to efficiently gain access to 8-substituted-9-deazaxanthines, we envisioned the use of a short route to prepare reactive precursors to which a diverse range of palladium-catalyzed cross-coupling reactions could be applied.

Our retrosynthetic analysis (Scheme 1) focused on the 9-deazaxanthine substructure rather than on a single synthetic target, with the ultimate goal of establishing a systematically varied library of derivatives. Step economy arises in this strategy

[a]*Department of Biomolecular Sciences, University of Urbino, Piazza Rinascimento 6, 61029 Urbino (PU), Italy. E-mail: giovanni.piersanti@uniurb.it; Fax: +390722303313; Tel: +390722303320*
[b]*Dipartimento Farmaceutico, Università degli Studi di Parma, Viale G.P. Usberti 27 A, I-43124 Parma, Italy. Fax: +390521905006, +390521905007*
[c]*Chemistry & Analytical Development Department, Sigma-Tau, Via Pontina Km 30, 400, 00040 Pomezia, Roma, Italy. E-mail: patrizia.minetti@sigma-tau.it; Fax: +390691393638; Tel: +390691393906*

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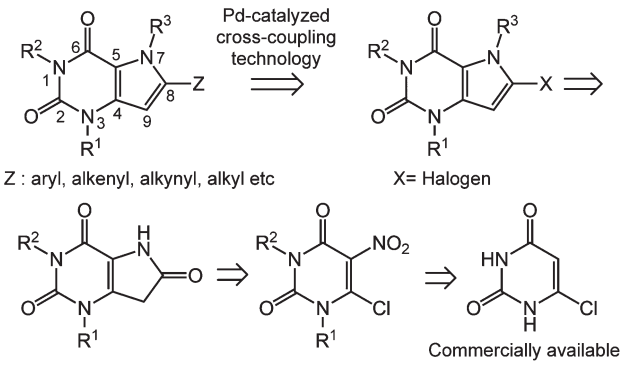


Scheme 1 Retrosynthetic analysis.

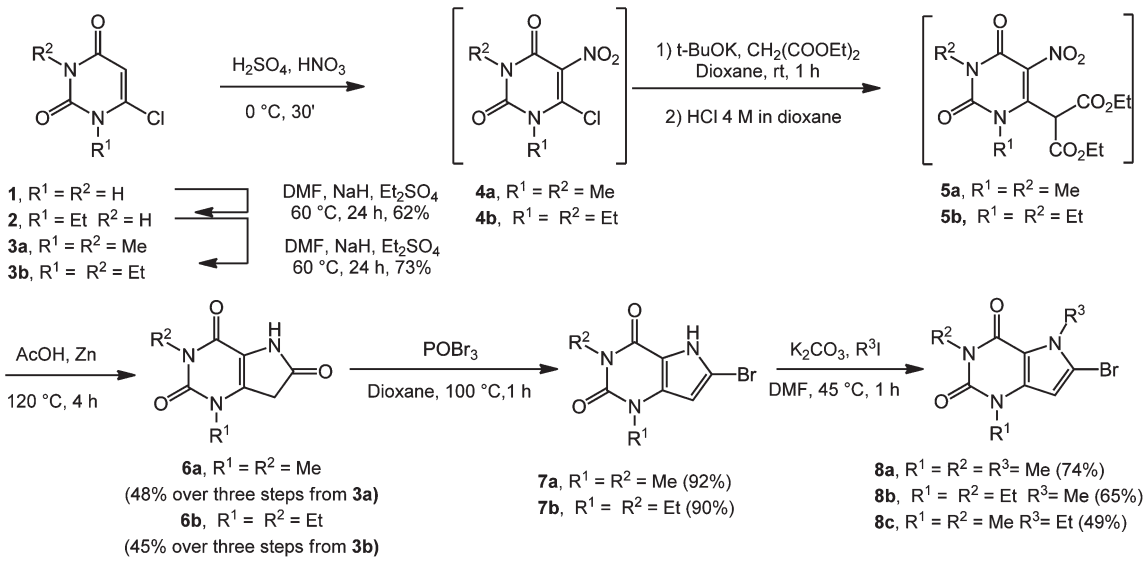
through the development of a single synthetic route to an advanced intermediate that, on late-stage differential diversification, would provide access to the greatest number of targets in short parallel sequences. The late-stage intermediates **8a–c** serve this function, and they allow for the differential modification of key nitrogen atoms (N1, N3, and N7) that would enable access to the majority of known 9-deazaxanthines and unexplored analogues. We anticipated that the densely substituted pyrrolo[3,2-*d*]-pyrimidines **8a–c** could be assembled by using sequential dehydroxy-bromination and nitrogen alkylation and that the key fused-lactam intermediates **6a,b** could be obtained by a one-pot nitro reduction, amidation, and subsequent decarboxylation of **5a,b** (decarboxylative cyclization). The key feature of this new approach is the regio- and chemoselective C–C bond formation with a relevant two-carbon nucleophile to provide a suitable and easily accessible functionalized electrophilic uracil derivative (**4a,b**).

Although some arylations of uracil derivatives have been reported in recent years,[10] the development of a practical method for the proposed strategies, which are initiated by a Michael substitution, remains a challenge. Moreover, no further transformation of these compounds to pyrimidine-fused ring systems has been described so far.

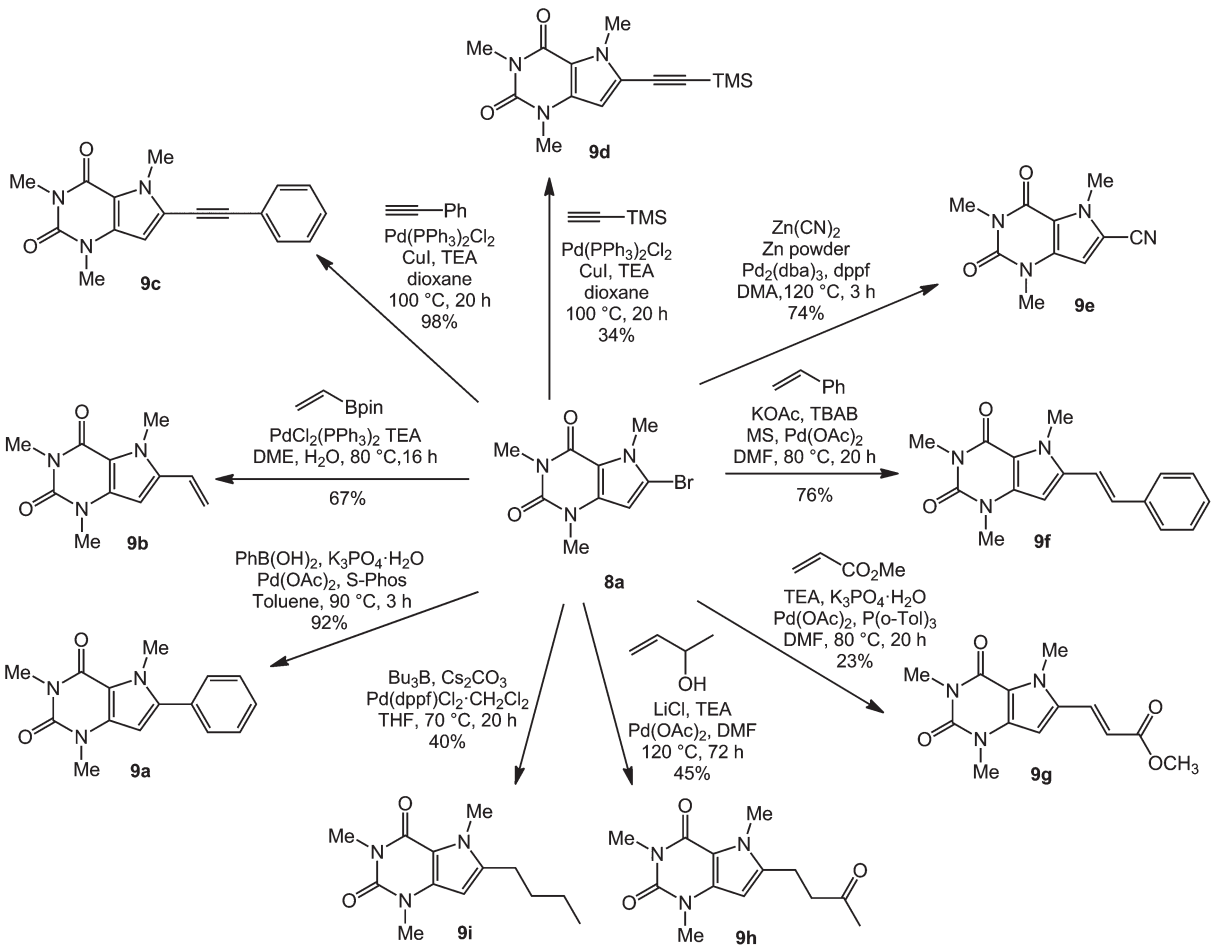
Results and discussion

We decided to test our hypothesis and study the incorporation of the acetic acid side chain *via* malonate chemistry on 6-chloro-1,3-dimethyl-5-nitrouracil,[11] which can be accessed by nitration of inexpensive and commercially available 6-chloro-1,3-dimethyluracil (**3a**). The N1,N3-substituted 6-chlorouracil compounds (**2**, **3b**) are easily accessible from **1**, thus opening up pathways to the synthesis of a wide range of substituted heterocyclic lactams (Scheme 2).[12]

In an attempt to minimize reaction optimization and chromatographic purification steps, we first developed the one-pot synthesis of the key advanced lactams **6a,b** by a conjugate substitution reaction with malonate, reduction of the nitro group followed by intramolecular cyclization and facile decarboxylation of the redundant carboxyl group. Significantly, all the steps proceeded in good yield, and reaction co-products could be removed without column chromatography. Multigram amounts of **6a,b**[13] were generated rapidly in a sequence carried out in a single reaction vessel. Additionally, by an appropriate choice of the alkylating agent, aldehyde, or ketone in the reductive alkylation of **7a,b**, this route is a versatile process for the synthesis of deazaxanthines with a diverse range of N7-substituents. Direct conversion of lactams **6a,b** to 8-bromodeazaxanthines **7a,b** was carried out by treatment with $POBr_3$ (3 equiv.) for a short reaction time (1 h) to avoid additional C9 bromination and competitive N-dealkylation. Finally, treatment of **7a,b** with alkyl iodide in DMF in the presence of K_2CO_3 gave the *N*7-alkylated derivatives **8a–c** in good yield. Notably, direct bromination of unsubstituted deazaxanthine[14] took place exclusively in the beta position of the pyrrole ring (behavior similar to indole), providing C9 bromination as reported elsewhere.[15] Overall, the process was safe, reproducible, reliable, robust, and high yielding.



Scheme 2 Synthesis of late-stage intermediates **8a–c**.



Scheme 3 Palladium-catalyzed cross-coupling reactions of late-stage intermediate **8a**.

Isolation of final products was very convenient, and the purity and impurity profiles were strictly controlled and reproducible.

With this practical synthesis of **8a–c** in hand, we then tested the reactivity of **8a** in order to assess the range of 8-substituted-9-deazaxanthines that could be produced (Scheme 3). In particular, 8-phenyl- and 8-vinyl-9-deazaxanthines (**9a,b**) were prepared in good to excellent yields by palladium-catalyzed reactions of **8a** with commercially available boronic acid or boronic ester (Suzuki coupling).[16] Similarly, 8-alkynyl derivative **9c** was synthesized in good yield starting from **8a** and phenylacetylene following Sonogashira's protocol. A coupling reaction between trimethylsilylacetylene and **8a** was also performed. The resulting 8-(trimethylsilyl)ethynyl-9-deazaxanthine (**9d**) was obtained in moderate yield. The TMS group could be deprotected under basic conditions to give a terminal arylalkyne that can be used for a second palladium-catalyzed Sonogashira reaction with an aryl halide for the synthesis of unsymmetrical diarylalkynes.[17] In addition, we explored palladium-catalyzed cyanation because the nitrile group serves as an intermediate for multiple transformations into other important functional groups and a series of catalytic methods to convert C–CN bonds into C–Si, C–H, and C–B bonds in the presence of a rhodium catalyst has been developed recently.[18] The reaction performed with zinc cyanide and catalytic amounts of $Pd_2(dba)_3$, dppf, and Zn in dimethylacetamide at 120 °C for 3 h afforded the aromatic nitrile (**9e**) in good yield. Among the 8-substituted-9-deazaxanthines, those containing the styryl moiety are the most interesting and are used in pharmaceutical chemistry. Next, we tried to accomplish the synthesis of these compounds *via* the Heck–Mizoroki cross-coupling reaction, one of the most powerful and versatile cross-coupling reactions used to date. The coupling of aryl halides with alkenes has been used in the synthesis of several industrially applicable compounds along with a number of natural products. After reaction condition optimization, we found that Jeffery conditions gave rise to the desired disubstituted alkene (**9f**) in good yield and stereoselectivity. However, whereas the reaction between **8a** and styrene gave the corresponding product in good yield, the electron-deficient olefin methyl acrylate reacted with **8a** to give the regioselectively coupled product (**9g**) in only 23% yield. Longer reaction times or different conditions afforded a side product resulting from a dehalogenation process. This result is probably related to the low nucleophilicity of this alkene with respect to styrene and the difficulty of insertion of the substrate carbon–carbon double bond into the metal–carbon bond.[19] Furthermore, we examined other olefin arylation conditions using a secondary allylic alcohol as the alkylating agent. A regioselective Heck coupling reaction between aryl bromide **8a** and but-3-en-2-ol led to the generation of an arylated allylic alcohol that isomerized *in situ* to give β-aryl ketone **9h**.[20] Ketone **9h** was obtained regioselectively

in moderate yield by the treatment of **8a** with but-3-en-2-ol in the presence of $Pd(OAc)_2$, LiCl and triethylamine in DMF at 120 °C for 72 h. This reaction is quite remarkable because highly functionalized carbonyl compounds can be readily transformed to numerous valuable synthons. In addition, it represents the first "formal" example of introducing a functionalized alkyl group. The favorable results obtained so far prompted us to explore the more challenging cross-coupling of $C(sp^3)$ organometallic compounds. Based on our previous palladium-catalyzed direct alkylation of 2-halopurines[21] with triethyl- or tri-*n*-butylborane, we applied a B-alkyl Suzuki–Miyaura cross-coupling reaction in the presence of Cs_2CO_3 and catalytic amounts of $Pd(dppf)Cl_2{\cdot}CH_2Cl_2$ in THF with **8a** to afford 8-*n*-butyl-9-deazaxanthine (**9i**) in acceptable yield. A small comparative study with other organometallics revealed that, with the exception of tetra-*n*-butyltin, no other organometallics, including *n*-butylzinc chloride, were able to produce the alkylated product.

Conclusions

In conclusion, we were able to access compounds **8a–c** (Scheme 2) as key late-stage intermediates that could be rapidly diversified en route to 8-substituted-9-deazaxanthines, an interesting scaffold that exhibits a remarkable range of potent biological activities, in a practical step-economical sequence. The key steps in the synthesis are a selective C–C bond formation by conjugate substitution of malonate on reactive 6-chloro-1,3-dimethyl-5-nitrouracil and a zinc-mediated reductive cyclization to form the adjacent fused, five-membered ring. The practical benefits include readily available and inexpensive starting materials, substrate versatility, experimentally straightforward procedures, and good product yields. The utility of **8a** was demonstrated by the rapid preparation of six categorically distinct analogues of 9-deazaxanthine. The synthesis of these compounds (**9a–i**) was enabled by a late-stage diversification strategy relying on palladium-catalyzed methodology. But, in some cases, the yields for the palladium-catalyzed cross-coupling reaction were attenuated due to the reason discussed above. Nonetheless, this strategy allowed the rapid diversification of **8a** to evaluate the effects of sterically and electronically differentiated groups in this position of the pyrrole ring to investigate structure–activity relationships. Facile access to these structures is desirable in a medicinal chemistry[22] program because it enables the rapid generation of diversity around a basic structure.

Experimental section

All reactions were run in air unless otherwise noted. Column chromatography purifications were performed in flash conditions using Merck 230–400 mesh silica gel. Analytical thin layer chromatography (TLC) was carried out on Merck silica gel plates (silica gel 60 F_{254}), that were visualized by exposure to ultraviolet light. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance 200 spectrometer, using $CDCl_3$ or DMSO-d_6 as a solvent. Chemical shifts (δ scale) are reported in parts per million (ppm) relative to the central peak of the solvent. Coupling constants (J values) are given in Hertz (Hz). ESI-MS spectra were taken on a Waters Micromass ZQ instrument, only molecular ions (M + 1 or M − 1) are given. IR spectra were obtained on a Nicolet Avatar 360 FT-IR spectrometer, absorbance values are reported in cm^{-1}. Melting points were determined on a Buchi SMP-510 capillary melting point apparatus and are uncorrected. Elemental analyses were performed on a Carlo Erba analyzer and the results are within ±0.3 of the theoretical values (C,H,N).

6-Chlorouracil (**1**) and 6-chloro-1,3-dimethyluracil (**3a**) are commercially available.

General procedure for alkylation of 6-chlorouracil derivatives

To a solution of the appropriate 6-chlorouracil derivatives (**1** or **2**) (1 equiv.) in dry DMF (2.5 ml × mmol) was added NaH (60% dispersion in mineral oil) (2.2 equiv.). The mixture was stirred for 50 min, then was added diethyl sulfate. The mixture was stirred at 60 °C for 24 h, cooled at room temperature, diluted with water (5 ml × mmol) and extracted with CH_2Cl_2 (3 × (7 ml × mmol)). The combined organic phases were dried over anhydrous Na_2SO_4, the solvent was evaporated under reduced pressure and the residue obtained was purified by flash chromatography.

6-Chloro-1-ethylpyrimidine-2,4(1*H*,3*H*)-dione (2).[23] The general procedure was followed using 6-chloro-uracil (**1**) (1 g, 6.8 mmol) and diethyl sulfate (5.3 ml, 41 mmol). The residue was purified by flash chromatography (gradient from cyclohexane–ethyl acetate 8 : 2 to cyclohexane–ethyl acetate 1 : 1) to give **2** (735 mg, 62%). White solid, mp: 193–195 °C (methanol); ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.85 (bs, 1H), 5.90 (s, 1H), 4.18 (q, J = 7.0 Hz, 2H), 1.32 (t, J = 7.0 Hz, 3H); IR (nujol, cm^{-1}): 1682, 1647; MS (ESI) (m/z): 175 $[M + H]^+$; Anal. Calcd for $C_6H_7ClN_2O_2$ (174.02): C, 41.28; H, 4.04; N, 16.05. Found: C, 41.36; H, 3.98; N, 16.11.

6-Chloro-1,3-diethylpyrimidine-2,4(1*H*,3*H*)-dione (3b).[24] The general procedure was followed using 6-chloro-1-ethyluracil (**2**) (950 mg, 5.5 mmol) and diethyl sulfate (1.6 ml, 12 mmol). The residue was purified by flash chromatography (cyclohexane–ethyl acetate 1 : 1) to give **3b** (810 mg, 73%). White solid, mp: 121–123 °C (methanol); ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.89 (s, 1H), 4.13 (q, J = 7.0 Hz, 2H), 3.97 (q, J = 7.0 Hz, 2H), 1.31 (t, J = 7.0 Hz, 3H), 1.22 (t, J = 7.0 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 12.7, 13.9, 36.9, 42.4, 102.1, 145.4, 150.4, 160.6; IR (nujol, cm^{-1}): 1682, 1647; MS (ESI) (m/z): 203 $[M + H]^+$; Anal. Calcd for $C_8H_{11}ClN_2O_2$ (202.05): C, 47.42; H, 5.47; N, 13.82. Found: C, 47.38; H, 5.51; N, 13.88.

General procedure for nitration, substitution with diethyl malonate, reduction, amidation and subsequent decarboxylation of 6-chloro-1,3-dialkyluracil

(a) To concentrated sulphuric acid (0.5 ml × mmol), at 0 °C, the appropriate 6-chloro-1,3-dialkyluracil (**3a** or **3b**) (1 equiv.) was added portionwise. The mixture was stirred at 0 °C for 2 min, then was slowly added fuming nitric acid (0.16 ml × mmol). The solution was stirred at this temperature for 30 min, then poured onto ice, diluted with water (4 ml × mmol) and extracted with CH_2Cl_2 (3 × (6 ml × mmol)). The combined organic phases

were dried over anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure to give 6-chloro-5-nitro-1,3-dialkyluracil (**4a**[24] or **4b**). (Note: The aqueous solution must be extracted immediately otherwise you have degradation of product.)

(b) To a solution of diethyl malonate (1.2 equiv.) in anhydrous dioxane (2.4 ml × mmol), under N_2, was added potassium *t*-butoxide (2 equiv.). The mixture was stirred for 10 min, then was added a solution of the appropriate 6-chloro-5-nitro-1,3-dialkyluracil (**4a** or **4b**) (1 equiv.) in dioxane (1.2 ml × mmol). The mixture was stirred at room temperature for 1 h, then was added anhydrous HCl 4 M in dioxane (2 equiv.) (the colour of the solution changed from orange to yellowish). The solvent was evaporated under reduced pressure to give diethyl 2-(1,3-dialkyl-5-nitro-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)malonate (**5a** or **5b**).

(c) To a solution of the appropriate malonate derivatives **5a** or **5b** (1 equiv.) in acetic acid (3.5 ml × mmol), at 60 °C, zinc powder (15 equiv.) was added portionwise. The mixture was stirred at 120 °C for 4 h, then filtered through a pad of Celite keeping the solution hot and washed with hot acetic acid (2 × (3 ml × mmol)) and hot methanol (2 × (3 ml × mmol)). The solvents were evaporated under reduced pressure and the residue obtained was purified by flash chromatography.

6-Hydroxy-1,3-dimethyl-1*H*-pyrrolo[3,2-*d*]pyrimidine-2,4(3*H*,5*H*)-dione (6a). The general procedure was followed using 6-chloro-1,3-dimethyluracil (**3a**) (3 g, 17.2 mmol). The residue was purified by flash chromatography (gradient from CH_2Cl_2–MeOH 99 : 1 to CH_2Cl_2–MeOH 94 : 6) to give **6a** (1.62 g). Overall yield from **3a**: 48%. Yellowish solid, mp: >260 °C (methanol); ^{1}H NMR (200 MHz, DMSO-d_6): δ 11.41 (bs, 1H), 5.18 (d, J = 2.0 Hz, 1H), 3.38 (bs, 1H), 3.29 (s, 3H), 3.18 (s, 3H); ^{13}C NMR (50 MHz, DMSO-d_6): δ 27.7, 32.1, 76. 3, 100.7, 115.6, 137.1, 151.7, 153.6; IR (nujol, cm^{-1}): 3350, 3120, 1701, 1647; MS (ESI) (*m*/*z*): 196 $[M + H]^+$ and 194 $[M - H]^-$; Anal. Calcd for $C_8H_9N_3O_3$ (195.06): C, 49.23; H, 4.65; N, 21.53. Found: C, 49.12; H, 4.59; N, 21.58.

1,3-Diethyl-6-hydroxy-1*H*-pyrrolo[3,2-*d*]pyrimidine-2,4(3*H*,5*H*)-dione (6b). The general procedure was followed using 6-chloro-1,3-diethyluracil (**3b**) (1 g, 4.9 mmol). The residue was purified by flash chromatography (gradient from CH_2Cl_2–MeOH 99 : 1 to CH_2Cl_2–MeOH 94 : 6) to give **6b** (495 mg). Overall yield from **3b**: 45%. Yellowish solid, mp: >260 °C; ^{1}H NMR (200 MHz, DMSO-d_6): δ 11.34 (bs, 1H), 11.23 (bs, 1H), 5.18 (d, J = 2.0 Hz, 1H), 3.92–3.75 (m, 4H), 1.15 (t, J = 7.0 Hz, 3H), 1.08 (t, J = 7.0 Hz, 3H); ^{13}C NMR (50 MHz, DMSO-d_6): δ 13.1, 13.7, 35.2, 39.5, 75.9, 101.1, 136.1, 150.4, 152.9, 153.5; IR (nujol, cm^{-1}): 3352, 3118, 1703, 1653; MS (ESI) (*m*/*z*): 224 $[M + H]^+$ and 222 $[M - H]^-$; Anal. Calcd for $C_{10}H_{13}N_3O_3$ (223.10): C, 53.80; H, 5.87; N, 18.82. Found: C, 53.75; H, 5.83; N, 18.96.

General procedure for the dehydroxy-bromination

To a solution of the appropriate lactam derivatives **6a** or **6b** (1 equiv.) in dioxane (10 ml × mmol) was added $POBr_3$ (3 equiv.). The mixture was stirred at 100 °C for 1 h, cooled and then poured on a saturated solution of $NaHCO_3$ (12 ml × mmol) and ethyl acetate (12 ml × mmol). The phases were separated and the aqueous phase was extracted with further ethyl acetate (8 × (7 ml × mmol)). The combined organic phases were dried over anhydrous Na_2SO_4, the solvent was evaporated under reduced pressure and the residue obtained was used for the following reaction without further purification.

6-Bromo-1,3-dimethyl-1*H*-pyrrolo[3,2-*d*]pyrimidine-2,4(3*H*,5*H*)-dione (7a). The general procedure was followed using 6-hydroxy-1,3-dimethyl-1*H*-pyrrolo[3,2-*d*]pyrimidine-2,4(3*H*,5*H*)-dione (**6a**) (1.6 g, 8.2 mmol) to give **7a** (1.93 g, 92%). An analytical sample was purified by flash chromatography (CH_2Cl_2–MeOH 94 : 6) for the characterization. Off-white solid, mp: >220 °C (methanol); ^{1}H NMR (200 MHz, DMSO-d_6): δ 12.95 (bs, 1H), 6.39 (d, J = 2.0 Hz, 1H), 3.34 (s, 3H), 3.22 (s, 3H); ^{13}C NMR (50 MHz, DMSO-d_6): δ 28.0, 32.4, 98.35, 110.8, 111.5, 136.1, 151.3, 154.2; IR (nujol, cm^{-1}): 3125, 1701, 1647; MS (ESI) (*m*/*z*): 258–260 $[M + H]^+$ and 256–258 $[M - H]^-$; Anal. Calcd for $C_8H_8BrN_3O_2$ (256.98): C, 37.23; H, 3.12; N, 16.28. Found: C, 37.31; H, 3.16; N, 16.21.

6-Bromo-1,3-diethyl-1*H*-pyrrolo[3,2-*d*]pyrimidine-2,4(3*H*,5*H*)-dione (7b). The general procedure was followed using 6-hydroxy-1,3-dimethyl-1*H*-pyrrolo[3,2-*d*]pyrimidine-2,4(3*H*,5*H*)-dione (**6b**) (495 mg, 2.2 mmol) to give **7b** (565 mg, 90%). An analytical sample was purified by flash chromatography (CH_2Cl_2–MeOH 94 : 6) for the characterization. Off-white solid, mp: >220 °C (methanol); ^{1}H NMR (200 MHz, DMSO-d_6): δ 12.89 (bs, 1H), 6.40 (d, J = 2.0 Hz, 1H), 3.90 (q, J = 7.0 Hz, 2H), 3.87 (q, J = 7.0 Hz, 2H), 1.16 (t, J = 7.0 Hz, 3H), 1.11 (t, J = 7.0 Hz, 3H); ^{13}C NMR (50 MHz, DMSO-d_6): δ 13.2, 13.7, 35.9, 39.8, 98.1, 111.0, 111.8, 135.1, 150.3, 153.8; IR (nujol, cm^{-1}): 3120, 1696, 1660; MS (ESI) (*m*/*z*): 286–288 $[M + H]^+$ and 284–282 $[M - H]^-$; Anal. Calcd for $C_{10}H_{12}BrN_3O_2$ (285.01): C, 41.98; H, 4.23; N, 14.69. Found: C, 42.06; H, 4.18; N, 14.78.

General procedure for N7 alkylation

To a solution of the appropriate brominated derivatives **7a** or **7b** (1 equiv.) in dry DMF (7.5 ml × mmol) were added K_2CO_3 (1.1 equiv.) and alkyl iodide (10 equiv.). The mixture was stirred at 45 °C for 1 h, cooled at room temperature, diluted with water (4 ml × mmol) and extracted with CH_2Cl_2 (3 × (4 ml × mmol)). The combined organic phases were dried over anhydrous Na_2SO_4, the solvent was evaporated under reduced pressure and the residue obtained was purified by flash chromatography.

6-Bromo-1,3,5-trimethyl-1*H*-pyrrolo[3,2-*d*]pyrimidine-2,4(3*H*,5*H*)-dione (8a). The general procedure was followed using **7a** (1.9 g, 7.4 mmol) and methyl iodide (4.6 ml, 74 mmol). The residue obtained was purified by flash chromatography (CH_2Cl_2–MeOH 96 : 4) to obtain **8a** (1.5 g, 74%). White solid, mp: 207–209 °C (ethanol); ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.04 (s, 1H), 4.00 (s, 3H), 3.44 (s, 3H), 3.41 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 27.8, 31.7, 33.9, 96.8, 111.2, 115.7, 135.6, 151.3, 155.1; IR (nujol, cm^{-1}): 1701, 1647; MS (ESI) (*m*/*z*): 274–272 $[M + H]^+$; Anal. Calcd for $C_9H_{10}BrN_3O_2$ (271.00): C, 39.73; H, 3.70; N, 15.44. Found: C, 39.84; H, 3.65; N, 15.51.

6-Bromo-1,3-diethyl-5-methyl-1*H*-pyrrolo[3,2-*d*]pyrimidine-2,4-(3*H*,5*H*)-dione (8b). The general procedure was followed using **7b** (565 mg, 2.0 mmol) and methyl iodide (1.2 ml, 20 mmol). The residue obtained was purified by flash chromatography (CH_2Cl_2–MeOH 96 : 4) to obtain **8b** (390 mg, 65%). White solid, mp: 196–198 °C (ethanol); ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.03 (s, 1H), 4.09 (q, J = 7.0 Hz, 2H), 4.01 (s, 3H), 3.93 (q, J = 7.0 Hz, 2H), 1.31 (t, J = 7.0 Hz, 3H), 1.26 (t, J = 7.0 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 12.8, 13.3, 33.9, 36.3, 40.3, 96.5, 111.6, 115.5, 134.7, 150.4, 154.8; IR (nujol, cm^{-1}): 1705, 1652; MS (ESI) (*m*/*z*): 300–302 [M + H]$^+$; Anal. Calcd for $C_{11}H_{14}BrN_3O_2$ (299.03): C, 44.02; H, 4.70; N, 14.00. Found: C, 44.14; H, 4.73; N, 13.96.

6-Bromo-5-ethyl-1,3-dimethyl-1*H*-pyrrolo[3,2-*d*]pyrimidine-2,4-(3*H*,5*H*)-dione (8c). The general procedure was followed using **7a** (200 mg, 0.78 mmol) and ethyl iodide (0.6 ml, 7.8 mmol). The residue obtained was purified by flash chromatography (CH_2Cl_2–MeOH 96 : 4) to obtain **8c** (110 mg, 49%). White solid, mp: 212–214 °C (ethanol); ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.02 (s, 1H), 4.47 (q, J = 7.0 Hz, 2H), 3.42 (s, 3H), 3.40 (s, 3H), 1.35 (t, J = 7.0 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 16.1, 27.9, 31.7, 42.2, 96.9, 110.3, 114.3, 135.8, 151.4, 154.6; IR (nujol, cm^{-1}): 1705, 1652; MS (ESI) (*m*/*z*): 286–288 [M + H]$^+$; Anal. Calcd for $C_{10}H_{12}BrN_3O_2$ (285.01): C, 41.98; H, 4.23; N, 14.69. Found: C, 42.05; H, 4.19; N, 14.76.

1,3,5-Trimethyl-6-phenyl-1*H*-pyrrolo[3,2-*d*]pyrimidine-2,4(3*H*,5*H*)-dione (9a). A flame-dried Schlenk tube was charged with 6-bromo-1,3,5-trimethyl-1*H*-pyrrolo[3,2-*d*]pyrimidine-2,4(3*H*,5*H*)-dione (**8a**) (108 mg, 0.4 mmol), phenylboronic acid (73.15 mg, 0.6 mmol), powdered $K_3PO_4{\cdot}H_2O$ (460.6 mg, 2 mmol), $Pd(OAc)_2$ (9 mg, 0.04 mmol), 2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl (S-Phos) (33 mg, 0.08 mmol) and toluene (2 ml), under nitrogen. The mixture was heated at 90 °C for 3 h. The solvent was evaporated under reduced pressure and the residue obtained was purified by flash chromatography (CH_2Cl_2–MeOH 98 : 2) to give **9a** (100 mg, 92%). White solid, mp: 184–186 °C (ethanol); ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.46 (s, 5H), 5.97 (s, 1H), 3.97 (s, 3H), 3.48 (s, 3H), 3.43 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 27.85, 31.70, 33.63, 94.20, 111.29, 128.76, 128.93, 129.20, 130.66, 135.61, 143.12, 151.65, 156.12; IR (nujol, cm^{-1}): 1691, 1641; MS (ESI) (*m*/*z*): 270 [M + H]$^+$; Anal. Calcd for $C_{15}H_{15}N_3O_2$ (269.12): C, 66.90; H, 5.61; N, 15.60. Found: C, 66.98; H, 5.59; N, 15.53.

1,3,5-Trimethyl-6-vinyl-1*H*-pyrrolo[3,2-*d*]pyrimidine-2,4(3*H*,5*H*)-dione (9b). A flame-dried Schlenk tube was charged with 6-bromo-1,3,5-trimethyl-1*H*-pyrrolo[3,2-*d*]pyrimidine-2,4(3*H*,5*H*)-dione (**8a**) (100 mg, 0.37 mmol), 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (91 mg, 0.59 mmol), $PdCl_2(PPh_3)_2$ (26 mg, 0.037 mmol), DME (0.84 ml), H_2O (0.16 ml) and TEA (155 µl, 0.59 mmol). The mixture was stirred at 80 °C for 16 h. The solvent was evaporated under reduced pressure and the residue obtained was purified by flash chromatography (cyclohexane–ethyl acetate 7 : 3) to give **9b** (54 mg, 67%). Off-white solid, mp: 216–218 °C (ethanol); ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.68 (dd, J_1 = 17.5 and J_2 = 11.0 Hz, 1H), 6.09 (s, 1H), 5.82 (d, J = 17.5 Hz, 1H), 5.48 (d, J = 11.0 Hz, 1H), 4.03 (s, 3H), 3.47 (s, 3H), 3.42 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 27.8, 31.6, 31.7, 90.7, 110.8, 118.6, 123.8, 135.4, 140.0, 151.5, 156.0; IR (nujol, cm^{-1}): 2924, 1684, 1646; MS (ESI) (*m*/*z*): 220 [M + H]$^+$; Anal. Calcd for $C_{11}H_{13}N_3O_2$ (219.10): C, 60.26; H, 5.98; N, 19.17. Found: C, 60.36; H, 5.91; N, 19.26.

1,3,5-Trimethyl-6-(phenylethynyl)-1*H*-pyrrolo[3,2-*d*]pyrimidine-2,4(3*H*,5*H*)-dione (9c). A flame-dried Schlenk tube was charged with 6-bromo-1,3,5-trimethyl-1*H*-pyrrolo[3,2-*d*]pyrimidine-2,4(3*H*,5*H*)-dione (**8a**) (108 mg, 0.4 mmol), $Pd(PPh_3)_2Cl_2$ (14 mg, 0.02 mmol), CuI (8 mg, 0.04 mmol), dioxane (1.6 ml) and TEA (84 µL, 0.6 mmol), under N_2. Phenylacetylene (48 µl, 0.44 mmol) was then added and the resulting black reaction mixture was stirred at 100 °C for 20 h. The mixture was diluted with CH_2Cl_2 (3 ml), filtered through a pad of Celite and washed with CH_2Cl_2 (3 × 10 ml). The solvent was evaporated under reduced pressure and the residue obtained was purified by flash chromatography (CH_2Cl_2–MeOH 98 : 2) to give **9c** (115 mg, 98%). White solid, mp: 186–188 °C (ethanol); ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.56–7.53 (m, 2H), 7.41–7.38 (m, 3H), 6.18 (s, 1H), 4.10 (s, 3H), 3.46 (s, 3H), 3.42 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 27.9, 31.7, 33.5, 78.8, 97.1, 98.1, 111.3, 121.7, 123.9, 128.6, 129.3, 131.5, 134.6, 151.5, 155.5; IR (nujol, cm^{-1}): 2201, 1690, 1653; MS (ESI) (*m*/*z*): 294 [M + H]$^+$; Anal. Calcd for $C_{17}H_{15}N_3O_2$ (293.12): C, 69.61; H, 5.15; N, 14.33. Found: C, 69.72; H, 5.22; N, 14.26.

1,3,5-Trimethyl-6-((trimethylsilyl)ethynyl)-1*H*-pyrrolo[3,2-*d*]-pyrimidine-2,4(3*H*,5*H*)-dione (9d). A flame-dried Schlenk tube was charged with 6-bromo-1,3,5-trimethyl-1*H*-pyrrolo[3,2-*d*]-pyrimidine-2,4(3*H*,5*H*)-dione (**8a**) (108 mg, 0.4 mmol), $Pd(PPh_3)_2Cl_2$ (14 mg, 0.02 mmol), CuI (8 mg, 0.04 mmol), dioxane (1.6 ml) and TEA (84 µL, 0.6 mmol), under N_2. Trimethylsilylacetylene (62 µl, 0.44 mmol) was then added and the resulting black reaction mixture was stirred at 100 °C for 20 h. The mixture was diluted with CH_2Cl_2 (3 ml), filtered through a pad of Celite and washed with CH_2Cl_2 (3 × 10 ml). The solvent was evaporated under reduced pressure and the residue obtained was purified by flash chromatography (cyclohexane–ethyl acetate 7 : 3) to give **9d** (40 mg, 34%). White solid, mp: 132–134 °C (acetone–hexane); ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.11 (s, 1H), 4.01 (s, 3H), 3.42 (s, 3H), 3.40 (s, 3H), −0.28 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$): δ −0.3, 27.9, 31.7, 33.4, 93.7, 98.4, 103.9, 111.1, 123.7, 134.3, 151.5, 155.5; IR (nujol, cm^{-1}): 2157, 1697, 1654; MS (ESI) (*m*/*z*): 290 [M + H]$^+$; Anal. Calcd for $C_{14}H_{19}N_3O_2Si$ (289.12): C, 58.10; H, 6.62; N, 14.52. Found: C, 58.16; H, 6.69; N, 14.63.

1,3,5-Trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1*H*-pyrrolo[3,2-*d*]-pyrimidine-6-carbonitrile (9e). To a suspension of 6-bromo-1,3,5-trimethyl-1*H*-pyrrolo[3,2-*d*]pyrimidine-2,4(3*H*,5*H*)-dione (**8a**) (136 mg, 0.5 mmol) in dimethylacetamide (0.4 ml) were added zinc powder (3 mg, 0.048 mmol), diphenylphosphinoferrocene (10 mg, 0.018 mmol), zinc cyanide (35 mg, 0.3 mmol), and tris-(dibenzylideneacetone)dipalladium(0) (8 mg, 0.009 mmol) under nitrogen. The mixture was heated at 120 °C for 3 h and then was cooled at room temperature. The reaction mixture was directly transferred onto a column and purified by flash chromatography (CH_2Cl_2–MeOH 98 : 2) to give **9e** (81 mg, 74%). White solid, mp: 256–258 °C (acetone–hexane); ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.48 (s, 1H), 4.15 (s, 3H), 3.46 (s, 3H),

3.41 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 28.1, 31.8, 34.6, 101.8, 111.5, 111.6, 113.9, 133.7, 151.1, 155.5; IR (nujol, cm^{-1}): 2229, 1688, 1657; MS (ESI) (*m*/*z*): 219 $[M + H]^+$; Anal. Calcd for $C_{10}H_{10}N_4O_2$ (218.08): C, 55.04; H, 4.62; N, 25.68. Found: C, 55.13; H, 4.68; N, 25.79.

(*E*)-1,3,5-Trimethyl-6-styryl-1*H*-pyrrolo[3,2-*d*]pyrimidine-2,4-(3*H*,5*H*)-dione (9f). A flame-dried Schlenk tube was charged with potassium acetate (73 mg, 0.74 mmol), tetrabutylammonium bromide (119 mg, 0.37 mmol), powder 3 Å molecular sieves (74 mg) and dry DMF (0.4 ml), the mixture was stirred for 15 min. 6-Bromo-1,3,5-trimethyl-1*H*-pyrrolo[3,2-*d*]pyrimidine-2,4(3*H*,5*H*)-dione (**8a**) (100 mg, 0.37 mmol) and styrene (85 µl, 0.74 mmol) were then successively added and the suspension was stirred for another 15 min before addition of $Pd(OAc)_2$ (4 mg, 0.019 mmol). The mixture was then stirred at 80 °C for 20 h. The mixture was cooled at room temperature, diluted with CH_2Cl_2 (3 ml), filtered through a pad of Celite and washed with CH_2Cl_2 (3 × 10 ml). The solvent was evaporated under reduced pressure and the residue obtained was purified by flash chromatography (CH_2Cl_2–MeOH 98 : 2) to give **9f** (83 mg, 76%). Off-white solid, mp: 142–144 °C (ethanol); ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.55–7.50 (m, 2H), 7.45–7.36 (m, 3H), 7.16 (d, J = 16.0 Hz, 1H), 7.00 (d, J = 16.0 Hz, 1H), 6.20 (s, 1H), 4.11 (s, 3H), 3.50 (s, 3H), 3.43 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 27.9, 31.7, 31.8, 90.6, 111.1, 114.7, 126.7, 128.7, 128.9, 133.1, 135.7, 136.2, 140.2, 151.6, 155.8; IR (nujol, cm^{-1}): 1687, 1651; MS (ESI) (*m*/*z*): 296 $[M + H]^+$; Anal. Calcd for $C_{17}H_{17}N_3O_2$ (295.13): C, 69.14; H, 5.80; N, 14.23. Found: C, 69.31; H, 5.84; N, 14.30. The chemical–physical data are according to the literature.[3f]

(*E*)-Methyl 3-(1,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1*H*-pyrrolo[3,2-*d*]pyrimidin-6-yl)acrylate (9g). A flame-dried Schlenk tube was charged with 6-bromo-1,3,5-trimethyl-1*H*-pyrrolo[3,2-*d*]pyrimidine-2,4(3*H*,5*H*)-dione (**8a**) (120 mg, 0.44 mmol), methyl acrylate (80 µl, 0.88 mmol), triethylamine (61 µl, 0.88 mmol), powdered $K_3PO_4{\cdot}H_2O$ (202 mg, 0.88 mmol), $Pd(OAc)_2$ (4 mg, 0.02 mmol), tri(*o*-tolyl)phosphine (11 mg, 0.036 mmol) and dry DMF (0.4 ml), under nitrogen. The mixture was heated at 80 °C for 20 h. The solvent was evaporated under reduced pressure and the residue obtained was purified by flash chromatography (cyclohexane–ethyl acetate 6 : 4) to give **9g** (28 mg, 23%). White solid, mp: 135–137 °C (ethanol); ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.65 (d, J = 16.0 Hz, 1H), 6.43 (d, J = 16.0 Hz, 1H), 6.29 (s, 1H), 4.13 (s, 3H), 3.84 (s, 3H), 3.48 (s, 3H), 3.43 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 28.1, 29.7, 32.1, 52.2, 93.5, 120.1, 128.5, 130.3, 134.9, 135.9, 154.7, 156.0, 166.6; IR (nujol, cm^{-1}): 1701, 1687, 1643; MS (ESI) (*m*/*z*): 278 $[M + H]^+$; Anal. Calcd for $C_{13}H_{15}N_3O_4$ (277.1): C, 56.31; H, 5.45; N, 15.15. Found: C, 56.24; H, 5.51; N, 15.09.

1,3,5-Trimethyl-6-(3-oxobutyl)-1*H*-pyrrolo[3,2-*d*]pyrimidine-2,4-(3*H*,5*H*)-dione (9h). A flame-dried Schlenk tube was charged with 6-bromo-1,3,5-trimethyl-1*H*-pyrrolo[3,2-*d*]pyrimidine-2,4-(3*H*,5*H*)-dione (**8a**) (108 mg, 0.4 mmol), 1-buten-3-ol (104 µl, 1.2 mmol), $Pd(OAc)_2$ (9 mg, 0.04 mmol), LiCl (34 mg, 0.8 mmol), triethylamine (67 µl, 0.48 mmol) and dry DMF (4 ml). The mixture was stirred at 120 °C for 72 h. The solvent was evaporated under reduced pressure and the residue obtained was purified by flash chromatography (CH_2Cl_2–MeOH 98 : 2) to give **9h** (47 mg, 45%). White solid, mp: 161–163 °C (acetone–hexane); ^{1}H NMR (200 MHz, $CDCl_3$): δ 5.68 (s, 1H), 3.96 (s, 3H), 3.43 (s, 3H), 3.40 (s, 3H), 2.90–2.87 (m, 4H), 2.23 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 19.9, 27.7, 30.0, 31.6, 31.7, 41.6, 92.1, 110.1, 135.5, 142.0, 151.6, 155.8, 206.2; IR (nujol, cm^{-1}): 1713, 1687, 1643; MS (ESI) (*m*/*z*): 264 $[M + H]^+$; Anal. Calcd for $C_{13}H_{17}N_3O_3$ (263.13): C, 59.30; H, 6.51; N, 15.96. Found: C, 59.25; H, 6.46; N, 16.03.

6-Butyl-1,3,5-trimethyl-1*H*-pyrrolo[3,2-*d*]pyrimidine-2,4(3*H*,5*H*)-dione (9i). A flame-dried Schlenk tube was charged with 6-bromo-1,3,5-trimethyl-1*H*-pyrrolo[3,2-*d*]pyrimidine-2,4(3*H*,5*H*)-dione (**8a**) (108 mg, 0.4 mmol), Cs_2CO_3 (390 mg, 1.2 mmol), $Pd(dppf)Cl_2{\cdot}CH_2Cl_2$ (20 mg, 0.024 mmol) and freshly distilled THF (1.0 ml), under an Ar atmosphere. To the stirred suspension was added tributylborane 1 M solution in THF (1.2 ml, 1.2 mmol) and the mixture was stirred at 70 °C for 20 h. To the cooled reaction mixture was added 50% aqueous HOAc (0.5 ml) and the whole was refluxed for 1 h. The cooled solution was basified with a saturated solution of $NaHCO_3$ and then extracted with dichloromethane (3 × 10 ml). The combined organic layer was washed successively with water and brine, dried over Na_2SO_4, filtered, and the solvent evaporated under reduced pressure. The residue was purified by flash chromatography (cyclohexane–ethyl acetate 8 : 2) to give **9i** (40 mg, 40%). Yellowish solid, mp: 124–126 °C (acetone–hexane); ^{1}H NMR (200 MHz, $CDCl_3$): δ 5.71 (s, 1H), 3.93 (s, 3H), 3.44 (s, 3H), 3.41 (s, 3H), 2.61 (t, J = 7.0 Hz, 2H), 1.73–1.64 (m, 2H), 1.61–1.35 (m, 2H), 0.98 (t, J = 7.0 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 13.8, 22.4, 26.0, 27.7, 30.3, 31.5, 31.6, 92.2, 109.9, 135.6, 143.9, 151.7, 155.8; IR (nujol, cm^{-1}): 1686, 1644; Anal. MS (ESI) (*m*/*z*): 250 $[M + H]^+$; Calcd for $C_{13}H_{19}N_3O_2$ (249.15): C, 62.63; H, 7.68; N, 16.85. Found: C, 62.56; H, 7.76; N, 16.79.

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Notes and references

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