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# Reactions of 6-Aminopyrimidin-4(3*H*)-ones with Electron-Deficient Alkenyl Derivatives. Easy Preparation of Heterocyclic Analogues of Sangivamicine.

**Justo Cobo, Adolfo Sánchez*, Manuel Nogueras**
Dept. Química Inorgánica y Orgánica, Universidad de Jaén, E-23071 Jaén (Spain)

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***Abstract***: The electron-deficient maleic derivatives, maleic anhydride and maleimide, act against 6-aminopyrimidines almost exclusively as activated alkenyl derivatives, affording Michael adducts which in the case of less reactive maleimide are stable and can be isolated, and in the case of maleic anhydride those adducts evolve to pyrrolo[2,3-*d*]pyrimidines. Dienophilic character of maleimide towards 6-aminopyrimidin-4(3*H*)-one could also be observed in one case, where a pyrrolo[3,4-*c*]pyridine derivative was isolated.


## INTRODUCTION

Both nucleosidic and heterocyclic purine structural analogues such as pyrrolo[2,3-*d*]pyrimidines have shown a wide range of biological applications. The use of Sangivamicine or Toyocamicine as antibiotics is well known, and the antiviral application of their analogues has been reported.[1] Besides, other pyrrolo[2,3-*d*]pyrimidines present different biological applications like: anticonvulsive,[2] bactericides,[3] and antitumoral,[4] activities and can even be used in the treatment of neuronal diseases.[5]

In this work, we present the synthesis of several pyrrolo[2,3-*d*]pyrimidine derivatives from 6-aminopyrimidines and maleic acid derivatives. These reactions have two points of interest: first, to obtain new derivatives with potential biological applications, and second to explore into the reactivity of 6-aminopyrimidin-4(*3H*)-one with electron-deficient alkenyl compounds; these reactions, as we previously reported in the case of electron-deficient acetylenic dienophiles, could evolve through two different ways: via a Diels-Alder reaction between the C(2)-C(5) atoms, or via a Michael addition at the C(5) atom of the pyrimidine ring.[6]

The synthesis of pyrrolo[2,3-*d*]pyrimidine derivatives from 6-aminopyrimidines and DMAD,[7] ethylenediketones[8] and chloroformylacetates[9] has been reported. In our case we have used maleic anhydride and maleimide as electron-deficient reactants with 6-aminopyridimidin-4(*3H*)-ones **1**.

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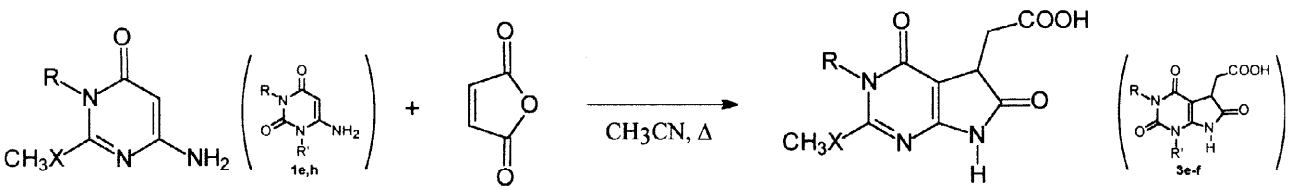
## RESULTS AND DISCUSSION

For this work, 6-amino-2-methoxy (and 2-methylthio)pyrimidin-4(*3H*)-ones **1a,b** and their N-methyl derivatives **1c,d** as well as N(1) and/or N(3)-methyl uracils **1e-h** were used. The reactions of the above compounds against maleic derivatives revealed a different behaviour for the reactions with maleic anhydride **2a** and with maleimide **2b**.

Concerning reactions between maleic anhydride **2a** and 6-aminopyrimidin-4(3*H*)-ones **1**, different reaction media were probed (only for **1c**), such as ethanol, methanol, toluene, and acetonitrile, which were carried out under reflux. In all cases, pyrrolo[2,3-*d*]pyrimidine derivatives **3** were obtained (See Scheme 1), acetonitrile affording higher yields and pure products. The reaction with 4-aminouracil **1e** was carried out in DMF at 90 °C, because its insolubility in acetonitrile necessitated too long a reaction time.




**1a-d** **2a** **3a-d**

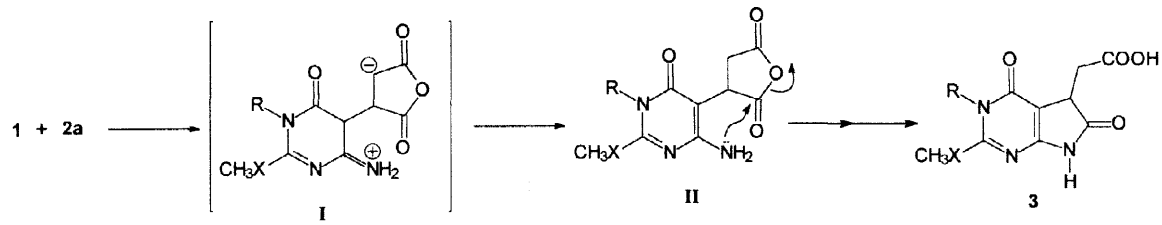
**Scheme 1**: Reaction of 6-aminopyrimidin-4(3*H*)-ones derivatives **1a-h** with maleic anhydride.

**Table 1**: Analytical and UV spectroscopic data of pyrrolo[2,3-*d*]pyrimidine derivatives **3**.

| Comp. | R | X | R' | react. time (hours) | Yield % | Mp[a] °C | M.F.[b] | UV $\lambda_{max}$ (log ε) $H_2O$ |
|---|---|---|---|---|---|---|---|---|
| **3a** | H | O | | 33 | 70 | 252 | $C_9H_9N_3O_5$ | 212 (4.59); 285 (4.01) |
| **3b** | H | S | | 58 | 71 | 250 | $C_9H_9N_3O_4S$ | 200 (3.71);215 (4.05); 239 (4.08); 298 (3.60) |
| **3c** | $CH_3$ | O | | 22 | 82 | 217 | $C_{10}H_{11}N_3O_5$ | 215 (4.44); 285 (3.81) |
| **3d** | $CH_3$ | S | | 7 | 67 | 218 | $C_{10}H_{11}N_3O_4S$ | 197 (4.31); 220 (4.32);238 (4.41); 301 (3.92) |
| **3e**[d] | H | | H | 3 | 69 | 301 | $C_8H_7N_3O_5$ | 199 (4.36); 230 (3.67)[c]; 286 (3.93) |
| **3f**[e] | $CH_3$ | | H | 210 | 93 | 283 | $C_9H_9N_3O_5$ | 198 (4.44); 233 (3.70)[c]; 285 (4.04) |
| **3g** | H | | $CH_3$ | 105 | 95 | 272 | $C_9H_9N_3O_5$ | 204 (4.55); 230 (3.94)[c]; 290 (4.17) |
| **3h**[e] | $CH_3$ | | $CH_3$ | 52 | 67 | 250 | $C_{10}H_{11}N_3O_5$ | 204 (4.31); 233 (3.63)[c]; 290 (3.92) |
| **4h** | $CH_3$ | | $CH_3$ | 91 | 71 | 281 | $C_{14}H_{13}N_3O_8$ | 207 (4.22); 236 (3.66)[c]; 289 (3.84) |

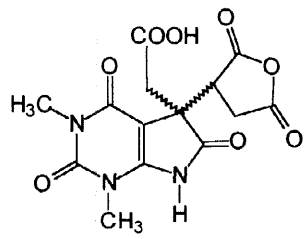
a.- Decomposition point;
b.- Molecular formula determined by elemental analysis and MS spectrum.
c.- Shoulder
d.- The medium reaction was DMF at 90 °C
e.- Results obtained using 1.2 eq. of maleic anhydride

The most probable mechanism to afford pyrrolopyrimidines **3**, which is shown in Scheme 2, involves two steps, first a Michael addition reaction of the pyrimidine ring through C-5 carbon atom to **2a** to give, via zwitterionic structure **I**, the intermediate **II**, which then undergoes a ring closure resulting in product **3**.




**Scheme 2**: Mechanism postulated for the reaction of 6-aminopyrimidines and maleic anhydride.

This mechanism is supported by the detection by nmr of structure type **II** in some reactions, these compounds appear as a mixture together with the desired compounds **3** after insufficient reaction times. On the other hand, the reactions with N(3)-methyl uracils **1f** and **1h** were accomplished with only 1.2 equivalents of **2a** (in contrast with all the rest which were carried out with 2 equivalents) to avoid formation of product **4** (Figure 1), which could arise from a further Michael addition of pyrrolo[2,3-*d*]pyrimidine derivatives **3** with another maleic anhydride molecule. This new product **4** was only isolated from **1h** for characterization.




**4h**

**Figure 1**

Compounds **3a-h** and **4h** were fully characterized by spectroscopic methods (see Table 1 and Table 2). In the $^1$H-nmr spectra the signal for -$CH_2$-5 can be observed not as a doublet but as a pseudotriplet or multiplet, because the two hydrogen are diastereotopic, and have similar chemical shifts. On the other hand, in the case of **3c**, **3d** and **3h**, H-5 in the $^1$H-nmr spectra was exchangeable with deuterium, and in that case the corresponding signal for -$CH_2$-5 was simplified. This shows its enolic character, and it agrees with the further Michael addition reaction through this position towards another maleic anhydride molecule to afford **4h**. Two-dimensional nmr spectra (COSY-DQF, TOCSY, $^1$H-$^{13}$C HSQC, $^1$H-$^{13}$C HMBC) were used for a complete characterization of structure of **4h**.

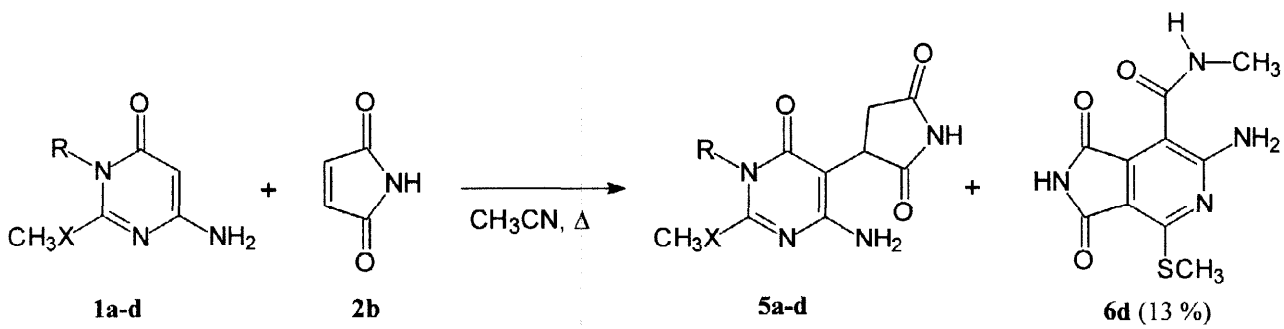
**Table 2**: Selected $^{1}$H- and $^{13}$C-NMR data for pyrrolo[2,3-*d*]pyrimidine **3a-h** in DMSO-$d_6$ [δ (ppm), multiplicity]

| Comp | HN-7[a] | COOH[a] | $CH_2$-5 ($J_{CH2-5}$) | H-5 | $H_3C$- | 5-$CH_2$[c] | C-5[d] | C-4a[e] | C-2; C-7a; C-4[e] | COOH[e] | C-6[e] |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **3a** | 12.20 b s[f] | 10,92 s | 2.83 d (4.4 Hz) | 3.55 t | 3.89 s | 31.89 | 40.15 | 94.58 | 158.30; 159.70; 163.14 | 171.60 | 178.95 |
| **3b** | 12.4 b s[f] | 10.96 s | 2.85 pt (4.5 Hz) | 3.59 t | 2.50 s | 31.75 | 40.10 | 97.07 | 158.24; 162.67; 164.66 | 171.57 | 178.51 |
| **3c** | 12.25 b s | 10,92 s | 2.84 d (4.7 Hz) | 3.57 t | 3.25 s 3.98 s | 31.91 | 40.68 | 93.75 | 157.10;158.77; 161.23 | 171.75 | 178.98 |
| **3d** | 12.25 b s | 10.95 s | 2.85 pt (4.6 Hz) | 3.60 t | 2.55 s 3.37 s | 31.72 | 40.72 | 96.02 | 156.70; 160.62; 165.33 | 171.75 | 178.65 |
| **3e**[g] | 12.8-11.3 b s[f] | 10.97 s | 2.8 pt (4.8 Hz) | 3.49 pt | -- | 32.38 | 39.84 | 87.29 | 151.16;153.06;159.59 | 171.77 | 179.01 |
| **3f** | 12.24 s[f] | 11.02 s | 2.83 pt (4.5 Hz) | 3.53 t | 3.09 s | 32.24 | 40.10 | 86.78 | 151.13; 151.42; 158.65 | 171.69 | 187.76 |
| **3g**[g] | 12.33 s | 10.92 s | 2.83 d (4.6 Hz) | 3.60 t | 3.25 s | 32.37 | 40.57 | 87.87 | 150.82; 154.20; 158.58 | 171.67 | 179.02 |
| **3h** | 11.93 b s[f] | -[b] | 2.84 d (4.8 Hz) | 3.63 t | 3.26 s 3.04 s | 32.37 | 40.80 | 87.30 | 151.11; 152.86; 157.76 | 171.70 | 178.87 |

a.- Deuterium exchangeable.
b.- This signal appears together with the proton of HN-7 group.
c.- Signal inverted in the DEPT (135°) spectra.
d.- Signal maintained in the DEPT (135°) spectra.
e.- Signal disappeared in the DEPT (135°) spectra.
f.- The observed integral for this signal corresponds to 2H
g.- Another **H**-N signal appears at 10.97 and 11.49 ppm for **3e** and **3g** respectively, as a deuterium exchangeable singlet.

Products arising from a possible cycloaddition reaction as it was observed with DMAD[6] were not isolated or detected in the case of maleic anhydride.

When maleimide **2b** was used, pyrrolopyrimidines similar to those obtained from maleic anhydride were not isolated but the major products were the 5-succinimidin-3-yl-pyrimidines **5**, which are structural analogues of the intermediates **II** in the synthesis of pyrrolopyrimidines **3**. These reactions were carried out on the 2-azadienic pyrimidines **1a-d** and the 6-amino-1,3-dimethyluracil **1h**, under the same conditions as the reactions with maleic anhydride (See Scheme 3 and Table 3).




**1a-d** **2b** **5a-d** **6d** (13 %)

**Scheme 3**: Reaction of 6-aminopyrimidin-4(3*H*)-ones derivatives **1a-d** with maleimide.

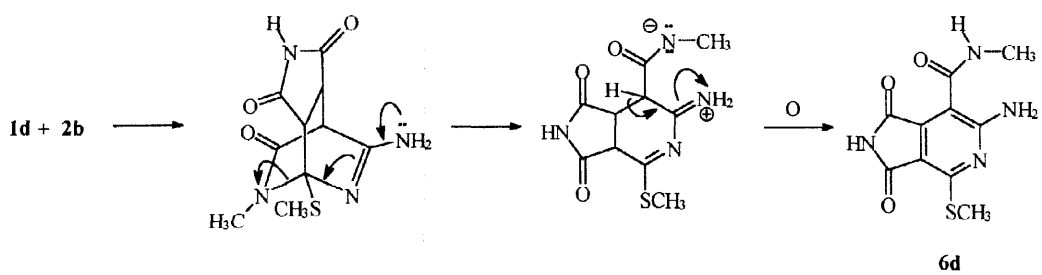
**Table 3**: Analytical and UV spectroscopic data of the 5-succinimidin-3-yl-pyrimidines derivatives **5**.

| Comp. | R | X | R' | react. time (days) | Yield % | Mp[a] °C | M.F.[b] | UV $\lambda_{max}$ (log ε) $H_2O$ |
|---|---|---|---|---|---|---|---|---|
| **5a** | H | O | | 6 | 80 | 269 | $C_9H_{10}N_4O_4$ | 194 (4.25); 206[c] (4.13); 264 (3.88) |
| **5b** | H | S | | 7 | 87 | 258 | $C_9H_{10}N_4O_3S$ | 196 (4.44); 211 (4.29); 230 (4.19); 280 (3.97) |
| **5c** | $CH_3$ | O | | 3.3 | 74 | 220 | $C_{10}H_{12}N_4O_4$ | 195 (4.6); 207[c] (4.35); 264 (4.06) |
| **5d** | $CH_3$ | S | | 5 | 62 | 243 | $C_{10}H_{12}N_4O_3S$ | 194 (4.47); 213 (4.34); 230 (4.28); 278 (4.03) |
| **5h** | $CH_3$ | | $CH_3$ | 4 | 86 | 261 | $C_{10}H_{12}N_4O_4$ | 196 (4.47); 220[c] (3.75); 270 (4.21) |
| **6d** | $CH_3$ | S | | 5 | 13 | 253 | $C_{10}H_{10}N_4O_3S$ | 203 (4.21); 247 (3.35); 308 (4.22); 404 (3.75) |

a.- Decomposition point
b.- Molecular formula determined by elemental analysis and MS spectrum.
c.- Shoulder

These results show the higher reactivity of the anhydride vs. imide, not only by prevention of Michael adducts **5**, but also due to the longer reaction times achieved in the case of maleimide. In the reaction of **1d** with maleimide the pyrrolo[3,4-*c*]pyridine derivative **6d**, arising from a cycloaddition reaction, could be isolated (see Scheme 3).

Compound **6d** is formed by he mechanism shown in Scheme 4, in which the first step is a Diels-Alder reaction between maleimide and the pyrimidine ring, to afford a bicyclic structure, which evolves towards pyrrolo[3,4-*c*]pyridine by a ring opening and hydrogen migration, affording after oxidative aromatization the isolated compound.




**Scheme 4**: Mechanism postulated for obtaining 5-amino-4-(N-methylcarboxamide)-7-methylthiopyrrolo [3, 4-*c*]pyridin-1,3(2*H*)-dione **6d**.

All these compounds, that is, 5-succinimidin-3-yl-pyrimidines **5a-d,h** and the pyrrolo[3,4-*c*]pyridine **6d** were fully characterized by spectroscopic methods (Table 3 and 4). Where the main characteristic feature is the coupling system observed, which is typical of cyclic structures.

**Table 4:** Selected $^{1}$H- and $^{13}$C-NMR data for 5-succinimidin-3-yl-pyrimidines **5a-d,h** in DMSO-$d_6$ [δ (ppm), multiplicity]

| Comp. | H-N(1')[a] | 6-N$H_2$[a] | H-3' | $H_3$C | $H_2$-4' | $CH_3$[d] | C-4'[c] | C-3'[d] | C-5[e] | C-2/C-4/C-6[e] | C=O[e] |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **5a**[h] | 11.0 s | 6.51 s | 3.86[g] dd (5.6, 9.3 Hz) | 3.82 s | 2.48 dd (5.7,17.6 Hz) 2.78 dd (9.4, 17.6 Hz) | 54.09 | 35.5 | 37.5 | 88.2 | 155.9; 160.9; 162.3 | 178.1 180.1 |
| **5b**[h] | 11.0 s | 6.53 s | 3.85 dd (5.5, 9.2 Hz) | 2.45 s | 2.47[g] dd (5.6, 17.5 Hz) 2.85 dd (9.3, 17.5 Hz) | 12.5 | 35.4 | 37.6 | 90.6 | 159.1; 160.4; 161.8 | 178.2 179.9 |
| **5c** | 11.0 s | 6.50 s | 3.86[g] dd (5.6, 9.4 Hz) | 3.90 s 3.14 s | 2.44 dd (5.5,17.6 Hz) 2.77 dd (9.4, 17.6 Hz) | 26.7 55.2 | 35.5 | 38.0 | 88.1 | 155.1; 159.2; 161.2 | 178.2 180.2 |
| **5d** | 11.0 s | 6.55s | 3.86 dd (5.5, 9.3 Hz) | 2.50 s | 2.44[g] dd (5.5, 17.6 Hz) 2.86 dd (9.3, 17.5 Hz) | 14.2 29.1 | 35.4 | 38.1 | 90.1 | 158.8; 160.0; 160.6 | 178.2 180.0 |
| **5h** | 11.0 s | 6.82 s | 3.92 dd (5.6, 9.2 Hz) | 3.32 s 3.08 s | 2.44 dd (5.5, 17.6 Hz) 2.78 dd (9.4, 17.6 Hz) | 27.2 30.0 | 35.9 | 38.0 | 83.5 | 150.8; 152.6; 160.8 | 178.1 180.1 |

g.- This signal appears together with the protons of $H_3$CX-6 groups, the coupling system being determined by COSY-DQF.
h.- H-N(3) for the pyrimidine ring was observed for **5a** and **5b** as a deuterium exchangeable singlet at 11.48 and 11.88 ppm respectively.
For the other captions see Table 2

In summary, it is possible to obtain Sangivamicine analogues in good to excellent yields by the simple reaction of 6-aminopyrimidine derivatives **1** with maleic anhydride. The different reactivity of these two maleic derivatives is also shown; maleic anhydride, which has a more reactive double bond reacts more quickly with the most nucleophilic atom of the pyrimidine ring through a Michael addition reaction, and leads to pyrrolopyrimidine derivatives due to the high acylating character of the anhydride moiety. In contrast, maleimide is not as reactive as maleic anhydride towards Michael addition and the reaction times are longer, allowing it to act as a dienophile with the pyrimidine ring, which displays 2-azadienic behaviour in Diels-Alder reactions. The lower reactivity of the imide moiety permits isolation of the Michael addition adducts.

## EXPERIMENTAL SECTION.

Melting Points were determined in a Electrothermal IA9000 series, Digital Melting Points Apparatus and are uncorrected. Nuclear Magnetic Resonance spectra were recorded in Bruker DPX-300 from "Servicios Técnicos de la Universidad de Jaén (STUJA)", the following abbreviations are used to described signal coupling: s= singlet; bs=broad singlet; d=doublet; t=triplet; dd=double doublet, pt=pseudotriplet. Ultraviolet and Visible (UV) spectra were recorded in a GBC UV/VIS 911 spectrophotometer. Infrared spectra were recorded in a Perkin-Elmer 1760X FT-IR spectrophotometer from STUJA (potassium bromide pellets). The following abbreviations are used to describe signal strength: b=broad; s=strong; w=weak. Mass spectra were recorded in a Hewlett-Packard HP-5989-B from STUJA. The analysis C, H and N were performed in a Perkin-Elmer 240 C from "Servicios Técnicos de la Universidad de Granada". Reaction progress and purity of the products were monitored by thin layer chromatography (tlc) on Merck Silica Gel $60GF_{254}$ (0.2 mm) aluminium precoated sheets with fluorescent indicator, the spots were visualized by ultraviolet irradiation. Maleic anhydride and maleimide (99 %) were purchased from Aldrich, and used directly without further purification.

**General procedure to obtain (pyrrolo[2,3-d]pyrimidin-4(3*H*)-one-5-yl)acetic acid, 3.** To a suspension of 1 g of the corresponding *6-aminopyrimidin-4(3H)-one* **1** in dry acetonitrile (4 ml/mmol **1**) was added maleic anhydride **2a** (molar ratio 1:2), and the mixture was stirred under reflux until the starting compound **1** was not detected by tlc (methylene chloride/methanol/acetic acid 9:1:0.1). Then the solid precipitated was filtered off and washed with fresh acetonitrile yielding **3**, which in most cases recrystallises from water.

***(2-methoxypyrrolo[2,3-d]pyrimidin-4,6(3H,5H,7H)-dione-5-yl)acetic acid* 3a**. Starting from *2-methoxy-6-aminopyrimidin-4(3H)-one*, **1a**. After 33 hours under reflux, 1.18 g (70 %) of **3a** were obtained. tlc: Rf= 0.15 (methylene chloride/methanol/acetic acid 9:1:0.1). Anal. calcd. for $C_9H_9N_3O_5$: C, 45.20; H, 3.79; N, 17.57. Found: C, 44.80; H, 3.60; N, 17.21; $IR_{max}$ ($cm^{-1}$):, 3170-2500, b s; 2953, s; 1730, s; 1650, s; 1589, s; 1524, s; 1433, s; 1377, s; 1226, s; Ms m/z (abundance %); 207($[M-HOCH_3]^+$, 10), 193 (75), 180 (11); 151 (8); 137 (19), 73 (19), 45 (45), 44 (100).

***(2-methylthiopyrrolo[2,3-d]pyrimidin-4,6(3H,5H,7H)-dione-5-yl)acetic acid* 3b**. Starting from *2-methylthio-6-aminopyrimidin-4(3H)-one*, **1b**. After 58 hours under reflux, 1.16 g (71 %) of **3b** were obtained tlc: Rf = 0.19 (methylene chloride/methanol/acetic acid 9:1:0.1). Anal. calcd. for $C_9H_9N_3O_4S \cdot H_2O$: C, 39.56; H, 4.06; N, 15.38.; S:11.73. Found: C, 38.13; H, 4.25; N, 15.46; S:11.74; $IR_{max}$ ($cm^{-1}$):, 3424, s; 3269, s; 3207, s; 2936, w; 2862, s; 1738, s; 1702, s; 1642, s; 1591, s; 1537, s; 1410, s; 1359, s; 1227, s; Ms m/z (abundance %); 211 ($[M-CO_2]^+$, 7), 157 (6), 73 (6), 45 (26), 44 (100).

***(2-methoxy-3-methylpyrrolo[2,3-d]pyrimidin-4,6(3H,5H,7H)-dione-5-yl)acetic acid* 3c**. Starting from *2-methoxy-3-methyl-6-aminopyrimidin-4(3H)-one*, **1c**. After 22 hours under reflux, 1.34 g (82 %) of **3c** were obtained. tlc: Rf = 0.24 (methylene chloride/methanol/acetic acid 9:1:0.1). Anal. calcd. for $C_{10}H_{11}O_5N_3$: C, 47.43; H, 4.37; N, 16.59. Found: C, 47.41; H, 4.40; N, 16.78; $IR_{max}$ ($cm^{-1}$):, 3480, w; 3290-2500, b; 2960, w; 1725, s; 1705, s; 1650, s; 1618, s; 1559, s; 1510, w; 1450, s; 1383, s; 1230, w; Ms m/z (abundance %); 253 ($M^+$, 10), 221 (2), 207 (100), 194 (9), 176 (3); 137 (15), 72 (9), 45 (15), 44 (2).

***(3-methyl-2-methylthiopyrrolo[2,3-d]pyrimidin-4,6(3H,5H,7H)-dione-5-yl)acetic acid* 3d**. Starting from *2-methylthio-3-methyl-6-aminopyrimidin-4(3H)-one*, **1d**. After 7 hours under reflux, 1.07 g (67 %) of **3d** were obtained. tlc: Rf = 0.36 (methylene chloride/methanol/acetic acid 9:1:0.1). Anal. calcd. for $C_{10}H_{11}N_3O_5S$: C,

44.60; H, 4.12; N, 15.61; S, 11.91. Found: C, 44.47; H, 4.07; N, 15.31; S, 11.62. $IR_{max}$ ($cm^{-1}$):, 3419, w; 3210-2300, b; 2940, w; 1734, s; 1700, s; 1647, s; 1597, s; 1554, w; 1521, s; 1446, s; 1302, s; 1253, s; Ms m/z (abundance %); 269 ($M^+$, 10), 223 (100), 221 (1), 210 (11), 176 (35); 153 (2), 72 (5), 45 (22), 44 (53).

***(pyrrolo[2,3-d]pyrimidin-4,6(3H,5H,7H)-dione-5-yl)acetic acid* 3e.** Starting from *6-aminouracil*, **1e**. After 3 hours under DMF at 90 °C, solvent removing and treatment of the syrup residue with boiling methanol, a solid remained in suspension which was filtered off, yielding 0.57g (32%) of **3e**, from the methanolic suspension crystallised a further fraction and another 0.66 (37%) of **3e** were obtained. tlc: Rf = 0.01 (methylene chloride/methanol/acetic acid 9:1:0.1). Anal. calcd. for $C_8H_7N_3O_5 \cdot ½\ H_2O$: C, 41.03; H, 3.44; N, 17.94. Found: C, 40.87; H, 3.27; N, 17.74. $IR_{max}$ ($cm^{-1}$):, 3468, b s; 3200-2500, b; 2835, w; 1755, s; 1708, s; 1662, s; 1639, s; 1573, s; 1421, s; 1397, s; 1244, s; Ms m/z (abundance %); 179 ([M- $CH_2COOH$]$^+$, 15), 136 (15), 67 (20), 45 (69), 44 (100).

***(3-methylpyrrolo[2,3-d]pyrimidin-4,6(3H,5H,7H)-dione-5-yl)acetic acid* 3f.** Starting from *6-amino-3-methyluracil*, **1f** and 1.2 equivalent of **2a**. After 210 hours under reflux, 1.59 g (94 %) of **3f** were obtained. tlc: Rf = 0.1 (methylene chloride/methanol/acetic acid 9:1:0.1). Anal. calcd. for $C_9H_9N_3O_5$: C, 45.19; H, 3.79; N, 17.57. Found: C, 45.04; H, 3.83; N, 17.57. $IR_{max}$ ($cm^{-1}$):, s; 3417, w; 3246, s; 3150-2500 b; 3065, s; 2961, s; 2920, s; 2841, s; 1762, s; 1752, s; 1700, s; 1642, s; 1573, s; 1427, s; 1397, s; 1015, s; Ms m/z (abundance %); 195 ([M-$CO_2$]$^+$, 10), 136 (21), 123 (13), 95 (10), 66 (28), 45 (100), 44 (50).

***(1-methylpyrrolo[2,3-d]pyrimidin-4,6(3H,5H,7H)-dione-5-yl)acetic acid* 3g.** Starting from *6-amino-1-methyluracil*, **1g**. After 105 hours under reflux, 1.61 g (95 %) of **3g** were obtained. tlc: Rf = 0.05 (methylene chloride/methanol/acetic acid 9:1:0.1). Anal. calcd. for $C_9H_9N_3O_5$: C, 45.19; H, 3.79; N, 17.57. Found: C, 44.91; H, 3.70; N, 17.29. $IR_{max}$ ($cm^{-1}$):, s; 3451, b s; 3207-2500 b; 2815, s; 1747, s; 1727, s; 1696, s; 1647, s; 1541, s; 1453, s; 1367, s; 1084, s; Ms m/z (abundance %); 239 ($M^+$, 7), 209 (4), 195 (82), 180 (69), 166 (26), 151 (46), 137 (54), 122 (15), 95 (25), 66 (56), 45 (32), 44 (54).

***(1,3-dimethylpyrrolo[2,3-d]pyrimidin-4,6(3H,5H,7H)-dione-5-yl)acetic acid* 3h.** Starting from *6-amino-1,3-dimethyluracil*, **1h** and 1.2 equivalent of **2a**. After 52 hours under reflux, 1.1 g (67 %) of **3h** were obtained tlc: Rf = 0.01 (methylene chloride/methanol/acetic acid 9:1:0.1). Anal. calcd. for $C_{10}H_{11}N_3O_5S$: C, 44.60; H, 4.12; N, 15.61; S, 11.91. Found: C, 44.47; H, 4.07; N, 15.31; S, 11.62. $IR_{max}$ ($cm^{-1}$):, s; 3462, b s; 3189,-2500 b; 2896, s; 1741, s; 1695, s; 1657, s; 1638, s; 1536, s; 1421, s; 1370, s; 1025, s; Ms m/z (abundance %); 254 ($M^+$, 7), 207 (100), 194 (11), 180 (8), 166 (1), 150 (40), 137 (32), 122 (14), 95 (9), 83 (13); 66 (21), 45 (29), 44 (6).

***[1,3-dimethyl-5-furan-2,4(3H,5H)dione-3-ylpyrrolo[2,3-d]pyrimidin-4,6(3H,5H,7H)dione-5-yl]acetic acid* 4h.** Starting from *6-amino-1,3-dimethyluracil*, **1h** and 2 equivalent of **2a**. After 90 hours under reflux, 1.6 g (71 %) of **4h** were obtained tlc: Rf = 0.01 (methylene chloride/methanol/acetic acid 9:1:0.1). Anal. calcd. for $C_{14}H_{13}N_3O_8$: C, 47.87; H, 3.73; N, 11.96; Found: C, 47.51; H, 3.72; N, 11.97. $^1$H-NMR (dimethyl sulfoxide-$d_6$) (ppm)[10]: 2.8-3.05 (two d, 2H, -C**H**$_2$-COOH, 15.7 and 15.7 Hz); 3.13 (s, 3H, N(3)-C**H**$_3$); 3.16[g] (dd, 1H, **H**-4'a, 10.3 and 19.1 Hz); 3.32 (s, 3H, N(1)-C**H**$_3$); 3.51 (dd, 1H, **H**-4'b, 6.0 and 19.0 Hz); 3.76 (dd, 1H, **H**-3', 6.0 and 10.2 Hz); 11.8-12.6 (bs[a], 2H, N(7)-**H** and COO**H**); $^{13}$C-NMR (dimethyl sulfoxide-$d_6$)[10]: 27.5[d] (N(3)-**C**H$_3$), 31.6[11] (N(1)-**C**H$_3$ and **C**(4')H$_2$), 37.6[c] (5-**C**H$_2$-COOH); 47.4[d] (**C-3'**H); 50.56[e] (**C-5**); 87.0[e] (**C-4a**); 150.8[e] (**C-2**); 155.0[e] (**C-4**); 158.1[e] (**C-7a**); 170.4[e] (**C-6**); 170.7[e] (**C-2'**) , 171.5[e] (**C-5'**); 179.0[e] (**C**OOH); $IR_{max}$ ($cm^{-1}$):, s; 3418, b s;3235, s; 3015, s; 2932, s; 1868, w; 1856, w; 1791, s; 1770, s; 1731, s; 1709, s; 1619, b s; 1551, s; 1414, s;

1384, s; 1261, s; 1047, s; Ms m/z (abundance %); 254 ($M^+$, 7), 207 (100), 194 (11), 180 (8), 166 (1), 150 (40), 137 (32), 122 (14), 95 (9), 83 (13); 66 (21), 45 (29), 44 (6).

**General procedure to obtain 6-amino-5-succinimidin-3-yl-pyrimidin-4(3*H*)-ones 5a-d,h.** To a suspension of 1 g of the corresponding 6-aminopyrimidin-4(3*H*)-one **1** in dry acetonitrile (5 ml/mmol **1**) was added maleimide **2b** (molar ratio 1:2), and the mixture was stirred under reflux until the starting compound **1** was not detected in by (methylene chloride/methanol 9:1). Then the solid precipitated was filtered off and washed with fresh acetonitrile yielding **5**, which in most cases recrystallises from water.

***6-amino-2-methoxy-5-succinimidin-3-yl-pyrimidin-4(3H)-one*** **5a**. Starting from *6-amino-2-methoxy pyrimidin-4(3H)-one*, **1a**. After 6 days under reflux, 1.35 g (80 %) of **5a** were obtained. tlc: Rf= 0.15 (methylene chloride/methanol/acetic acid 9:1:0.1). Anal. calcd. for $C_9H_{10}N_4O_4$: C, 45.38; H, 4.23; N, 23.52. Found: C, 44.98; H, 4.13; N, 23.07; $IR_{max}$ ($cm^{-1}$):, 3450-2800, b s; 2768, s; 1770, w; 1718, b s; 1638, b s; 1570, w; 1402, w; 1351, s; 1288, s; Ms m/z (abundance %); 238 ($M^+$, 69), 194 (39), 166 (100), 141 (10); 97 (6); 71 (4), 44 (49), 42 (22).

***6-amino-2-methylthio-5-succinimidin-3-yl-pyrimidin-4(3H)-one*** **5b**. Starting from *6-amino-2-methylthio-pyrimidin-4(3H)-one*, **1b**. After 7 days under reflux, 1.40 g (87 %) of **3b** were obtained. tlc: Rf= 0.1 (methylene chloride/methanol/acetic acid 9:1:0.1). Anal. calcd. for $C_9H_{10}N_4O_3S$: C, 42.51; H, 3.96; N, 22.03; S, 12.61. Found: C, 42.70; H, 3.99; N, 22.17; S, 12.52; $IR_{max}$ ($cm^{-1}$):, 3462, s; 3322, s; 3266, b s; 2929, w; 1812, w; 1755 b s; 1699, b s; 1610, s; 1581, s; 1528, s; 1421, s; 1382, s; 1241, s; Ms m/z (abundance %); 254 ($M^+$, 100), 210 (33), 183 (47), 157 (4); 97 (1); 74 (20), 44 (24), 42 (16).

***6-amino-2-methoxy-3-methyl-5-succinimidin-3-yl-pyrimidin-4(3H)-one*** **5c**. Starting from *6-amino-2-methoxy-3-methyl-pyrimidin-4(3H)-one*, **1c**. After 3 days and 8 hours under reflux, 1.2 g (74 %) of **3c** were obtained. tlc: Rf= 0.24 (methylene chloride/methanol 9:1). Anal. calcd. for $C_{10}H_{12}N_4O_4$: C, 47.61; H, 4.79; N, 22.21. Found: C, 47.33; H, 4.65; N, 22.03; $IR_{max}$ ($cm^{-1}$):, 3409, s; 3346, s; 3246, s; 3168, s; 2963, w; 1786, w; 1723 b s; 1653, s; 1627, s; 1543, s; 1453, s; 1352, s; 1223, w; Ms m/z (abundance %); 252 ($M^+$, 100), 208 (22), 180 (81), 155 (6); 97 (2); 72 (18), 44 (11), 42 (16).

***6-amino-3-methyl-2-methylthio-5-succinimidin-3-yl-pyrimidin-4(3H)-one*** **5d**. Starting from 6-amino-*3-methyl-2-methylthiopyrimidin-4(3H)-one*, **1d**. After 5 days under reflux, 1.01 g (64 %) of **5d** were obtained. tlc: Rf= 0.3 (methylene chloride/methanol 9:1). Anal. calcd. for $C_{10}H_{12}N_4O_3S$: C, 44.77; H, 4.51; N, 20.88; S, 11.95.. Found: C, 45.00; H, 4.50; N, 20.54; S, 11.99; $IR_{max}$ ($cm^{-1}$):, 3408, s; 3338, s; 3206, b s; 2973, w; 1781, w; 1723 b s; 1651, s; 1597, s; 1574, s; 1521, s; 1453, s; 1347, s; 1226, w; Ms m/z (abundance %); 268 ($M^+$, 63), 225 (9), 196 (45), 171 (6); 72 (6), 44 (100), 42 (19). From the remaining solution crystallized yellow needles which were filtered off, washed with fresh acetonitrile yielding 0.2 g (13%) of 5-amino-4-(N-methylcarboxamide)-7-methylthiopyrrolo[3,4-*d*]pyridin-1,3(2*H*)-dione **6d**. tlc: Rf= 0.46 (methylene chloride/methanol 9:1). Anal. calcd. for $C_{10}H_{10}N_4O_3S$: C, 45.11; H, 3.79; N, 21.04; S, 12.04. Found: C, 44.91; H, 4.02; N, 20.64; S, 11.98; $^1$H-NMR (dimethyl sulfoxide-$d_6$) (ppm):[10] 2.78 (d, 3H, NH-C**H**$_3$, 4.7 Hz, collapsed after deuterium oxide addition); 7.67 ($s^a$, 2H, 5-N**H**$_2$); 8.80 ($q^a$, 1H, N**H**-$CH_3$, 4.7 Hz); 11.15 (s, 1H, N(2)-**H**); $^{13}$C-NMR (dimethyl sulfoxide-$d_6$): 11.1$^d$ (7-S**C**$H_3$), 25.9$^d$ (NH-**C**$H_3$), 105.0$^e$ (**C-7**), 109.1$^e$ (**C-3a**), 139.6$^e$ (**C-7a**), 157.7$^e$, 160.2$^e$ (**C-5**; **C-7**) , 164.0$^e$ (4-**C**ONHCH$_3$); 166.9$^e$, 167.6$^e$ (**C-1**, **C-3**); $IR_{max}$ ($cm^{-1}$):, 3450, b s; 3433,

s; 3278, s; 2927, w; 1752, s; 1710 s; 1693, s;1628, s; 1598, s; 1580, s; 1556, s; 1404, w; 1322, w; Ms m/z (abundance %); 266 ($M^+$, 100), 236 (41), 219 (4), 207 (78); 188 (24), 92 (42), 44 (80).

***6-amino-1,3-methyl-5-succinimidin-3-yl-uracile* 5h**. Starting from *6-amino-1,3-dimethyl-uracile*, **1h**. After 3 days and 4 days under reflux, 1.5 g (92 %) of **3c** were obtained. tlc: Rf= 0.1 (methylene chloride/methanol 9:1). Anal. calcd. for $C_{10}H_{12}N_4O_4$: C, 47.61; H, 4.79; N, 22.21. Found: C, 47.28; H, 4.95; N, 21.88; $IR_{max}$ ($cm^{-1}$):, 3444, s; 3374, s; 3242, s; 3198, s; 2952, w; 1793, w; 1763, w; 1713 b s; 1664, b s; 1621, s; 1546, w; 1500, s; 1464, s; 1365, s; 1216, w; Ms m/z (abundance %); 252 ($M^+$, 18), 208 (100), 180 (26), 151 (66); 97 (11); 44 (72), 42 (25).

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10. All the captions are referred to the previous Tables 2 and 4
11. This signal was split into two signals in the DEPT-135 spectrum, one maintained and the other one inverted, both with the same chemical shift. In addition, the $^1H$-$^{13}C$ HSQC spectrum shows three different correlations for this signal, one with N(1)-C**H**$_3$, and the other two with the signals assigned to the two diastereotopic protons **H**-4'a and **H**-4'b.