A Comprehensive Study of the Heterocyclizations of *N*-Arylmaleimides and 6-Aminouracils

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Abstract: Heterocyclization reactions between *N*-arylmaleimides and 6-aminouracils were studied in detail. It was established that several directions are possible depending on the nature of reaction medium and the substituent character in the uracil component. The synthetic procedure leading to *N*-phenyl-2,4,7-trioxopyrido[2,3-*d*]pyrimidine-5-carboxamides in good-to-high yields was developed and key stages of the corresponding reaction were established.

Key words: heterocycles, nucleophilic addition, ring opening, pyridines, pyrroles, annulation, regioselectivity

Fused heterocyclic systems containing partially hydrogenated pyridine and pyrimidine moieties possess different types of biological activity[1] and, therefore, are of interest as potential objects for investigations in medicinal chemistry. Important systems of this kind are derivatives of pyridopyrimidines based on 6-aminouracils, which can be synthesized by their condensation with different unsaturated carbonyl compounds or with CH acids and aldehydes.[2]

N-Substituted maleimides are well-known polyelectrophilic compounds, which can react either as dienophiles/dipolarophiles with dienes/1,3-dipoles or as 1,2- and 1,3-dinucleophiles with different mono- and dinucleophiles. From the viewpoint of synthetic organic chemistry, the reactions of maleimides as 1,2- or 1,3-dinucleophiles leading to several classes of heterocyclic compounds are of special interest. However, only a relatively small number of such transformations were described. Among them the heterocyclization of maleimides with thiourea and its derivatives are most frequently encountered[3] while there are only a few examples of reactions with another dinucleophiles. For example, the reactions involving *o*-aminothiophenols,[4] 2,4-diamino-5-hydroxypyrimidines,[5] aliphatic 1,4-diamines,[6] 2-mercapto-1,2,4-triazole,[7] 3-aminocrotonates[8] have been described. It is also known that the reaction of 6-aminouracils and maleimides leads either to Michael adducts **I**[9] (Scheme 1) or to compounds **II** formed with participation of an exocyclic amino group.[10] In turn, similar reaction with maleic anhydride, being a synthetic analogue of maleimides, yields pyrrolo[4,3-*c*]pyridines **III** or **IV**.[9]

In our previous research it was shown that in the reaction of maleimides with 3-amino-1,2,4-triazole depending on the solvent applied the formation of either triazolo[4,3-*c*]pyridine **V** or triazolo[1,5-*a*]pyridine **VI**[11] (Scheme 1) was observed, while the reactions involving substituted 3-aminopyrazoles led to pyrazolo[4,3-*b*]pyridines **VII** or pyrazolo[1,5-*a*]pyrimidines **VIII**.[12]

Thus, synthetic approaches based on reactions of dinucleophiles and maleimides seem to be quite convenient for the preparation of new pyridine and pyrimidine derivatives. On the other hand, such methods are not sufficiently developed which makes study in this area promising.

In the present article we disclose our recent results regarding the behavior of *N*-arylmaleimides in their reactions with substituted 6-aminouracils.

It was found that the reaction of 6-aminouracil (**1a**; $R^1 = R^2 = H$) with maleimide **2b** (Scheme 2) carried out under conditions described by Velchinskaya et al.,[10] by refluxing in ethanol or propan-2-ol for 10 hours, yielded quantitatively only the starting 6-aminouracil. No compound like **II** (Scheme 1) was found in the reaction medium. In our opinion, it can be explained both by the low temperature of the medium being insufficient for the reaction to proceed and by the poor solubility of 6-aminouracil (**1a**) in these alcohols.

The same reactions of aminouracil (**1a**) carried out in boiling acetonitrile, under conditions described by Cobo et al.,[9] also allowed to isolate only the starting materials. On the other hand, in the case of **1b** after 12 hours of heating, the formation of a mixture of several products was observed. Three of them were identified as compounds **3**, **4**, and **5** (Scheme 2) in ca. 1:1:1 ratio.

In order to improve yields and selectivity, we studied the reaction specified in solvents with different nature, specifically acetic acid and *N*,*N*-dimethylformamide.

The outcome of the reaction between 6-aminouracils and maleimides in acetic acid depended on the nature of R^1 and R^2 substituents in the azine component. Thus, refluxing of equimolar mixture of aminouracil (**1a**) and *N*-phenylmaleimide (**2a**) in acetic acids for eight hours led to the isolation of a mixture of fused pyridine derivative **3a** and

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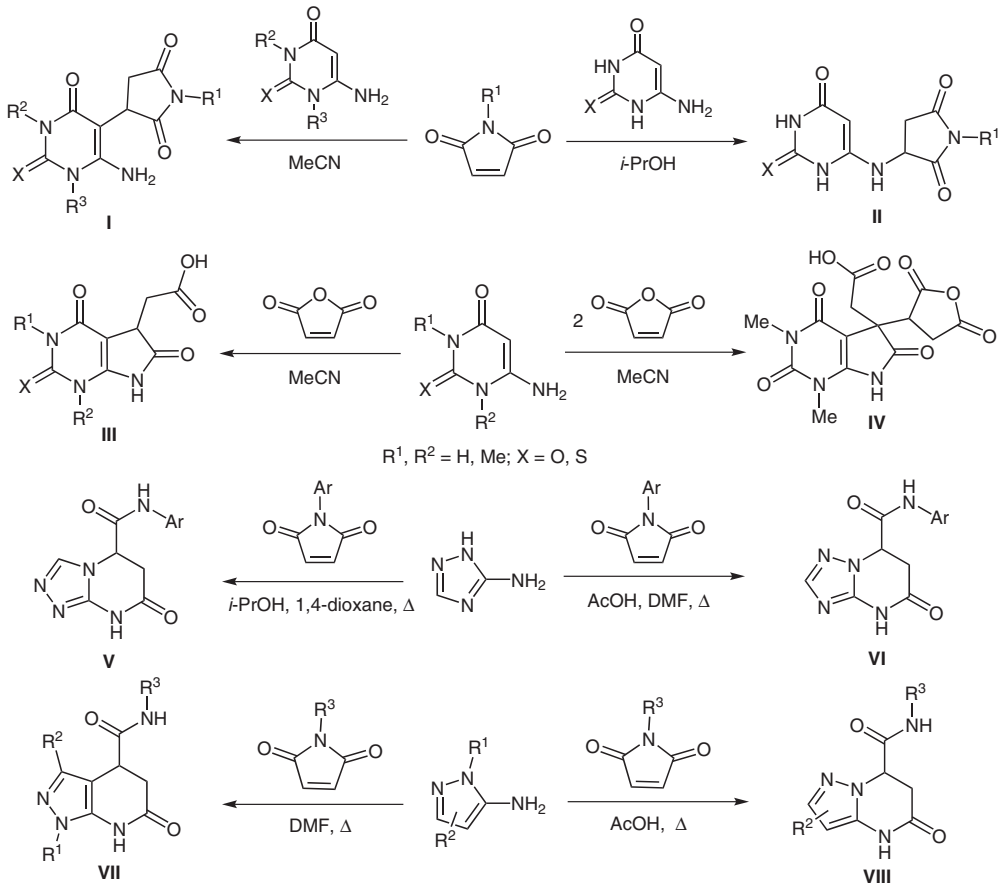


Scheme 1 Some examples of the reactions of maleimides (maleic anhydride) with 6-aminouracils and aminoazoles

the adduct **5a** in a 1:2 ratio in a general yield of 20% (Scheme 2). In the mother liquor sufficient amounts of the starting materials were found as well.

Reaction of 1,3-dimethyl-6-aminouracil (**1b**) and *N*-arylmaleimides **2a**,**c**,**f**,**g** under the same conditions allowed to obtain a mixture of pyrimidopyridones **3f–i** and pyrimidopyrrolones **4f–i** in a 4:1 ratio while treatment involving aminouracils **1c**,**d** (R^1 = H, R^2 = Bn or $PhCH_2CH_2$) yielded fused pyrimidines **3k–q** as sole reaction products.

The best results from the viewpoint of yields, selectivity, and universality of the procedure were obtained when the reaction studied was carried out in *N*,*N*-dimethylformamide. Heterocyclization of 6-aminouracils **1a**,**b** with maleimides **2a–h** in boiling *N*,*N*-dimethylformamide for three hours led to the formation of pyrimidopyridones **3a–j** in 54–68% yields (Scheme 2, Table 1).

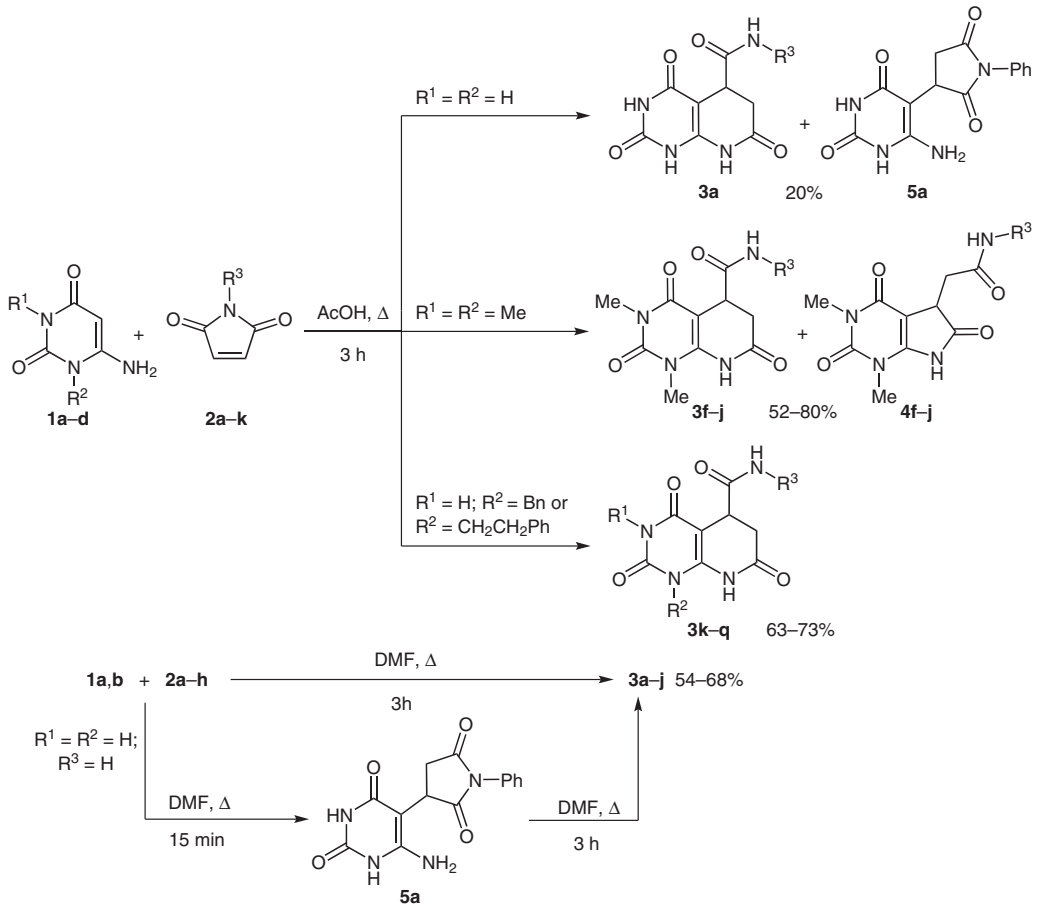
It was also found that decreasing the duration of the reaction of 6-aminouracil (**1a**) with *N*-phenylmaleimide (**2a**) in *N*,*N*-dimethylformamide led to the formation of mixtures of pyrimidopyridone **3a** and compound **5a**. The same treatment carried out for 15 minutes yielded mainly Michael adduct **5a** followed with impurities of starting materials and compound **3a** (up to 10%). Additionally, adduct **5a** underwent recyclization into heterocycle **3a** by heating in *N*,*N*-dimethylformamide for three hours.

These experimental facts allow us to propose that the reaction takes place by an attack of the C=C bond of maleimide at the CH reaction center of 6-aminouracil with formation of adduct **5** and its further recyclization into the target compound **3** as key steps of the reaction studied.

The structures of compounds **3**, **4**, and **5** were established with help of elemental analyses, MS, and NMR (^{1}H and ^{13}C) spectra. For instance, the mass spectra of **3a–q** and **5a** contain peaks of molecular ions, while their elemental analyses confirms the quantitative content of the compounds synthesized.

^{1}H NMR spectra of compounds **3** exhibit signals being typical for the ABX system with AB part at 2.60–2.90 ppm, while the chemical shift of X-proton is within 3.80–4.06 ppm, broad singlets at 9.0–11.5 ppm corresponding to NH protons, signals of aromatic protons, and their terminal substituents. The spectra of heterocycles **4**, which were not isolated in individual state, are very similar to the spectra described above for compounds **3**; however, AB part of ABX spin system shifted downfield to 2.60–2.80 ppm while the doublet of doublet of X proton shifted upfield to 3.60–3.70 ppm.

However, these spectral data are insufficient to make a final decision about the structure of the compounds obtained. In addition several NOE experiments were carried out, which showed differences in the spatial location of



Scheme 2

methine CH and amide NH for heterocycles **3** and **4** (Figure 1).

The ^{1}H NMR spectra of **5a** contain, in addition to signals of an ABX system, aromatic protons and other substituents, a broad singlet of NH_2 group at 6.36 ppm, which confirms that the reaction proceeds with participation of uracil CH but not with the NH_2 reaction center.

The structure of heterocycles **3** was also proven with the help of X-ray diffraction data obtained for compound **3j** (Figure 2).

The X-ray diffraction study reveals that the tetrahydropyridone ring of bicyclic fragment adopts an intermediate conformation between chair and twist-boat, which is typical for this ring[13] conformation. Deviations of the C1 and C2 atoms from the mean plane of remaining atoms of the ring are 0.26 Å and 0.63 Å, respectively. Tetrahydropydropyrimidindione ring adopts a flattened chair conformation with deviation of the N3 atom from mean plane of remaining atoms of ring by 0.08 Å. Such a nonplanar geometry of the uracil fragment is caused by its high conformational flexibility.[14]

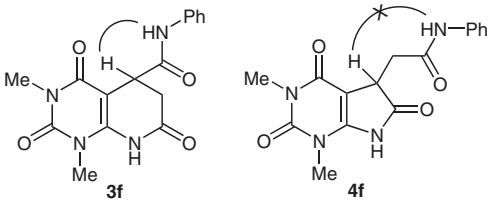


Figure 1 Some data of NOE experiments for compounds **3f** and **4f**

The substituent at the C3 atom has axial orientation and is turned to a relatively bicyclic fragment [the C10–C3–C4–C5 and C4–C3–C10–O4 torsion angles are –96.3(3)° and 106.8(3)°, respectively]. Such orientation of this substituent is stabilized additionally by formation of intramolecular hydrogen bond N4-H···O3 (H···O 2.14 Å N-H···O 143°). Difluoro-substituted phenyl ring has an *ap*-conformation relative to the C3–C10 bond [the C11–N4–C10–

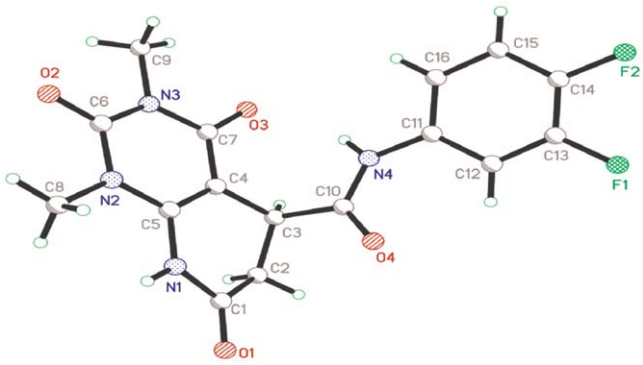


Figure 2 Molecular structure of compound **3j** (X-ray diffraction data)

Table 1 Synthesis of Compounds **3a–q**

6-Aminouracil **1**	R^1	R^2	*N*-Arylmaleimide **2** R^3		Product	Yield (%)
1a	H	H	**2a**	Ph	**3a**	54[a]
1a	H	H	**2b**	4-ClC_6H_4	**3b**	58[a]
1a	H	H	**2c**	2,4-$Me_2C_6H_3$	**3c**	62[a]
1a	H	H	**2d**	4-MeO-3-ClC_6H_3	**3d**	60[a]
1a	H	H	**2e**	4-$CF_3C_6H_4$	**3e**	65[a]
1b	Me	Me	**2a**	Ph	**3f**	57[a]
1b	Me	Me	**2f**	2-$MeOC_6H_4$	**3g**	68[a]
1b	Me	Me	**2c**	2,4-$Me_2C_6H_3$	**3h**	59[a]
1b	Me	Me	**2g**	4-$MeOC_6H_4$	**3i**	58[a]
1b	Me	Me	**2h**	3,4-$F_2C_6H_3$	**3j**	64[a]
1c	H	Bn	**2a**	Ph	**3k**	70[b]
1c	H	Bn	**2f**	2-$MeOC_6H_4$	**3l**	63[b]
1c	H	Bn	**2i**	2-ClC_6H_4	**3m**	71[b]
1c	H	Bn	**2j**	2,4-$Cl_2C_6H_3$	**3n**	73[b]
1d	H	$PhCH_2CH_2$	**2a**	Ph	**3o**	63[b]
1d	H	$PhCH_2CH_2$	**2f**	2-$MeOC_6H_4$	**3p**	65[b]
1d	H	$PhCH_2CH_2$	**2k**	2-FC_6H_4	**3q**	66[b]

[a] Reaction in DMF.
[b] Reaction in AcOH.

C3 torsion angle is 178.4(2)°] and is noncoplanar to carbamide fragment [the C10–N4–C11–C12 torsion angle is 27.2(4)°] in spite of the presence of the weak hydrogen bond C12–H···O2 (H···O 2.42 Å C–H···O 115°).

In summary, the heterocyclizations between *N*-arylmaleimides and 6-aminouracils were studied in detail. An influence of the reaction parameters and the structure of the azine component on their directions were established. It was found that the treatment carried out in low-boiling solvents like ethanol, propan-2-ol, or acetonitrile delivered either no product or complicated mixtures. The reaction in boiling acetic acid can yield several different compounds and their mixtures depending on the substituents character in aminouracil. Application of *N*,*N*-dimethylformamide as a medium to carry out the heterocyclization permitted obtaining individual *N*-aryl-2,4,7-trioxopyrido[2,3-*d*]pyrimidine-5-carboxamides in good-to-high yields. 6-Amino-5-(2,5-dioxo-1-arylpyrrolidin-3-yl)pyrimidine-2,4-diones were found to be the intermediates of the reaction studied that allowed to propose the key stages.

Melting points were obtained on a standard melting point apparatus in open capillary tubes. The ^1H and ^{13}C NMR spectra were recorded in DMSO-d_6 at 200 MHz (50 MHz for ^{13}C) on Varian Mercury VX-200 spectrometers. Mass spectra were measured on a GC-MS Varian 1200L (ionizing voltage 70 eV). Elemental analysis was made on a EuroVector EA-3000. TLC analyses were performed on precoated (silica gel 60 HF254) plates. All solvents and chemicals were obtained from standard commercial vendors and were used without any additional purification.

N-Aryl-2,4,7-trioxo-1,2,3,4,5,6,7,8-octahydropyrido[2,3-*d*]pyrimidine-5-carboxamides 3a–q; General Procedure

A mixture of the 6-aminouracil **1** (0.003 mol) and the corresponding *N*-arylmaleimide **2** (0.003 mol) in the noted solvent (3 mL, Table 1) was heated at reflux for 3 h. After cooling, the precipitate formed was filtered and if needed recrystallized from acetone, and air dried (Table 1).

N-Phenyl-2,4,7-trioxo-1,2,3,4,5,6,7,8-octahydropyrido[2,3-*d*]pyrimidine-5-carboxamide (3a)

Colorless solid; mp >300 °C.

^1H NMR (200 MHz, DMSO-d_6): δ = 2.59 (dd, $^2J_{AB}$ = 16.7 Hz, $^3J_{AX}$ = 0.9 Hz, 1 H, 6-H_a), 2.92 (dd, $^3J_{BX}$ = 7.7 Hz, 1 H, 6-H_b), 3.82 (dd, 1 H, 5-H_x), 7.03–7.53 (m, 5 H_{arom}), 9.89 (br s, 1 H, NH), 9.5–10.5 (br s, 2 H, NH), 11.03 (br s, 1 H, NH_{pyr}).

^{13}C NMR (50 MHz, DMSO-d_6): δ = 170.4, 168.4, 162.9, 149.7, 147.3, 137.3, 128.2, 126.8, 120.7, 84.9, 35.7, 32.8.

MS (EI, 70 eV): *m*/*z* (%) = 300 (2, [M^+]), 180 (100), 179 (76), 151 (53).

Anal. Calcd for $C_{14}H_{12}N_4O_4$: C, 56.00; H, 4.03; N, 18.66. Found: C, 55.9; H, 4.1; N, 18.7.

_N_-(4-Chlorophenyl)-2,4,7-trioxo-1,2,3,4,5,6,7,8-octahydropyrido[2,3-*d*]pyrimidine-5-carboxamide (3b)
Yellow solid; mp >300 °C.

^{1}H NMR (200 MHz, DMSO-d_6): δ = 2.59 (dd, $^2J_{AB}$ = 15.7 Hz, $^3J_{AX}$ = 1.3 Hz, 1 H, 6-H$_a$), 2.93 (dd, $^3J_{BX}$ = 7.5 Hz, 1 H, 6-H$_b$), 3.80 (dd, 1 H, 5-H$_x$), 7.32–7.60 (m, 4 H$_{arom}$), 10.04 (br s, 1 H, NH), 9.6–10.4 (br s, 2 H, NH), 11.03 (br s, 1 H, NH$_{pyr}$).

^{13}C NMR (50 MHz, DMSO-d_6): δ = 170.2, 168.5, 163.0, 149.6, 147.1, 138.4, 128.3, 123.1, 119.1, 85.1, 35.6, 32.9.

MS (EI, 70 eV): *m*/*z* (%) = 335 (2, [M$^+$ – 1]), 333 (2, [M$^+$ – 1]), 179 (29), 178 (67), 150 (59), 149 (32).

Anal. Calcd for $C_{14}H_{11}ClN_4O_4$: C, 50.24; H, 3.31; N, 16.74. Found: C, 50.1; H, 3.3; N, 16.8.

_N_-(2,4-Dimethylphenyl)-2,4,7-trioxo-1,2,3,4,5,6,7,8-octahydropyrido[2,3-*d*]pyrimidine-5-carboxamide (3c)
Colorless solid; mp 275–276 °C.

^{1}H NMR (200 MHz, DMSO-d_6): δ = 2.11 (s, 3 H, CH$_3$), 2.22 (s, 3 H, CH$_3$), 2.65 (dd, $^2J_{AB}$ = 16.4 Hz, $^3J_{AX}$ = 1.3 Hz, 1 H, 6-H$_a$), 2.83 (dd, $^3J_{BX}$ = 7.6 Hz, 1 H, 6-H$_b$), 3.87 (dd, 1 H, 5-H$_x$), 6.9–7.44 (m, 3 H$_{arom}$), 9.04 (br s, 1 H, NH), 9.7–10.3 (br s, 2 H, NH), 11.09 (br s, 1 H, NH$_{pyr}$).

^{13}C NMR (50 MHz, DMSO-d_6): δ = 169.9, 168.7, 163.4, 149.8, 147.2, 133.5, 133.4, 130.4, 129.6, 126.1, 122.9, 85.1, 35.0, 32.5, 20.0, 17.0.

MS (EI, 70 eV): *m*/*z* (%) = 327 (2, [M$^+$ – 1]), 326 (3, [M$^+$ – 2]), 179 (33), 178 (100), 177 (74), 150 (73), 149 (60).

Anal. Calcd for $C_{16}H_{16}N_4O_4$: C, 58.53; H, 4.91; N, 17.06. Found: C, 58.6; H, 5.1; N, 17.0.

_N_-(3-Chloro-4-methoxyphenyl)-2,4,7-trioxo-1,2,3,4,5,6,7,8-octahydropyrido[2,3-*d*]pyrimidine-5-carboxamide (3d)
Yellow solid; mp >300 °C.

^{1}H NMR (200 MHz, DMSO-d_6): δ = 2.58 (dd, $^2J_{AB}$ = 17.2 Hz, $^3J_{AX}$ = 1.3 Hz, 1 H, 6-H$_a$), 2.92 (dd, $^3J_{BX}$ = 8.0 Hz, 1 H, 6-H$_b$), 3.76 (dd, 1 H, 5-H$_x$), 3.80 (s, 3 H, CH$_3$O), 7.06–7.72 (m, 3 H$_{arom}$), 9.91 (br s, 1 H, NH), 9.7–10.4 (br s, 2 H, NH), 11.0 (br s, 1 H, NH$_{pyr}$).

^{13}C NMR (50 MHz, DMSO-d_6): δ = 170.1, 168.8, 163.5, 149.8, 148.6, 145.5, 136.1, 121.0, 120.6, 119.3, 113.0, 85.3, 55.1, 35.3, 32.6.

MS (EI, 70 eV): *m*/*z* (%) = 364 (2, [M$^+$]), 180 (27), 142 (100), 114 (50).

Anal. Calcd for $C_{15}H_{13}ClN_4O_5$: C, 49.39; H, 3.59; N, 15.36. Found: C, 49.4; H, 3.6; N, 15.2.

2,4,7-Trioxo-_N_-[4-(trifluoromethyl)phenyl]-1,2,3,4,5,6,7,8-octahydropyrido[2,3-*d*]pyrimidine-5-carboxamide (3e)
Colorless solid; mp >300 °C.

^{1}H NMR (200 MHz, DMSO-d_6): δ = 2.63 (dd, $^2J_{AB}$ = 17.0 Hz, $^3J_{AX}$ = 1.3 Hz, 1 H, 6-H$_a$), 2.95 (dd, $^3J_{BX}$ = 8.2 Hz, 1 H, 6-H$_b$), 3.84 (dd, 1 H, 5-H$_x$), 7.63–7.78 (m, 4 H$_{arom}$), 10.29 (br s, 1 H, NH), 9.8–10.5 (br s, 2 H, NH), 11.04 (br s, 1 H, NH$_{pyr}$).

^{13}C NMR (50 MHz, DMSO-d_6): δ = 171.0, 168.4, 163.0, 149.7, 147.4, 142.0, 126.6, 125.0 (1 C, q, $^1J_{CF}$ = 271.2 Hz, CF$_3$), 124.4 (1 C, q, $^2J_{CF}$ = 32.2 Hz, *C*CF$_3$), 120.1, 85.8, 36.8, 33.8.

MS (EI, 70 eV): *m*/*z* (%) = 368 (2, [M$^+$]), 367 (3), 180 (25), 179 (100), 150 (38).

Anal. Calcd for $C_{15}H_{11}F_3N_4O_4$: C, 48.92; H, 3.01; N, 15.21. Found: C, 49.1; H, 3.0; N, 15.3.

1,3-Dimethyl-2,4,7-trioxo-_N_-phenyl-1,2,3,4,5,6,7,8-octahydropyrido[2,3-*d*]pyrimidine-5-carboxamide (3f)
Colorless solid; mp 275–276 °C.

^{1}H NMR (200 MHz, DMSO-d_6): δ = 2.62 (dd, $^2J_{AB}$ = 16.3 Hz, $^3J_{AX}$ = 1.3 Hz, 1 H, 6-H$_a$), 2.90 (dd, $^3J_{BX}$ = 7.7 Hz, 1 H, 6-H$_b$), 3.19 (s, 3 H, CH$_3$), 3.38 (s, 3 H, CH$_3$), 3.93 (dd, 1 H, 5-H$_x$), 7.00–7.55 (m, 5 H$_{arom}$), 9.86 (br s, 1 H, NH), 10.53 (br s, 1 H, NH$_{pyr}$).

^{13}C NMR (50 MHz, DMSO-d_6): δ = 170.1, 169.7, 161.1, 150.5, 147.3, 138.4, 128.3, 123.2, 119.3, 86.8, 36.5, 33.0, 30.0, 27.5.

MS (EI, 70 eV): *m*/*z* (%) = 327 (2), 328 (3, [M$^+$ – 1]), 208 (6).

Anal. Calcd for $C_{16}H_{16}N_4O_4$: C, 58.53; H, 4.91; N, 17.06. Found: C, 58.5; H, 5.1; N, 17.0.

_N_-(2-Methoxyphenyl)-1,3-dimethyl-2,4,7-trioxo-1,2,3,4,5,6,7,8-octahydropyrido[2,3-*d*]pyrimidine-5-carboxamide (3g)
Colorless solid; mp 265–266 °C.

^{1}H NMR (200 MHz, DMSO-d_6): δ = 2.67 (dd, $^2J_{AB}$ = 16.4 Hz, $^3J_{AX}$ = 3.3 Hz, 1 H, 6-H$_a$), 2.75 (dd, $^3J_{BX}$ = 5.6 Hz, 1 H, 6-H$_b$), 3.24 (s, 3 H, CH$_3$), 3.37 (s, 3 H, CH$_3$), 3.83 (s, 3 H, CH$_3$O), 4.06 (dd, 1 H, 5-H$_x$), 6.85–8.05 (m, 4 H$_{arom}$), 9.16 (br s, 1 H, NH), 10.54 (br s, 1 H, NH$_{pyr}$).

^{13}C NMR (50 MHz, DMSO-d_6): δ = 169.7, 169.6, 161.4, 150.3, 148.4, 146.8, 127.5, 123.5, 120.2, 119.7, 111.2, 86.5, 55.8, 35.9, 31.9, 30.0, 27.5.

MS (EI, 70 eV): *m*/*z* (%) = 358 (3), 357 (18, [M$^+$ – 1]), 208 (7), 207 (45), 206 (100), 149 (16), 148 (19).

Anal. Calcd for $C_{17}H_{18}N_4O_5$: C, 56.98; H, 5.06; N, 15.63. Found: C, 57.1; H, 4.9; N, 15.7.

_N_-(2,4-Dimethylphenyl)-1,3-dimethyl-2,4,7-trioxo-1,2,3,4,5,6,7,8-octahydropyrido[2,3-*d*]pyrimidine-5-carboxamide (3h)
Colorless solid; mp 269–270 °C.

^{1}H NMR (200 MHz, DMSO-d_6): δ = 2.11 (s, 3 H, CH$_3$), 2.23 (s, 3 H, CH$_3$), 2.70 (dd, $^2J_{AB}$ = 16.0 Hz, $^3J_{AX}$ = 1.3 Hz, 1 H, 6-H$_a$), 2.84 (dd, $^3J_{BX}$ = 7.2 Hz, 1 H, 6-H$_b$), 3.22 (s, 3 H, CH$_3$), 3.37 (s, 3 H, CH$_3$), 3.95 (dd, 1 H, 5-H$_x$), 6.9–7.4 (m, 3 H$_{arom}$), 9.0 (br s, 1 H, NH), 10.5 (br s, 1 H, NH$_{pyr}$).

^{13}C NMR (50 MHz, DMSO-d_6): δ = 169.7, 169.6, 161.28, 161.27, 150.4, 147.1, 133.4, 130.4, 129.7, 126.1, 123.0, 86.8, 35.8, 32.6, 30.0, 27.4, 20.0, 17.0.

MS (EI, 70 eV): *m*/*z* (%) = 356 (2), 355 (3, [M$^+$ – 1]), 207 (61), 206 (100), 149 (14), 148 (13).

Anal. Calcd for $C_{18}H_{20}N_4O_4$ (%): C, 60.66; H, 5.66; N, 15.72. Found: C, 60.7; H, 5.6; N, 15.8.

_N_-(4-Methoxyphenyl)-1,3-dimethyl-2,4,7-trioxo-1,2,3,4,5,6,7,8-octahydropyrido[2,3-*d*]pyrimidine-5-carboxamide (3i)
Colorless solid; mp 279–280 °C.

^{1}H NMR (200 MHz DMSO-d_6): δ = 2.61 (dd, $^2J_{AB}$ = 16.3 Hz, $^3J_{AX}$ = 1.4 Hz, 1 H, 6-H$_a$), 2.89 (dd, $^3J_{BX}$ = 7.6 Hz, 1 H, 6-H$_b$), 3.19 (s, 3 H, CH$_3$), 3.37 (s, 3 H, CH$_3$), 3.70 (s, 3 H, CH$_3$O), 3.88 (dd, 1 H, 5-H$_x$), 6.83–7.47 (m, 4 H$_{arom}$), 9.71 (br s, 1 H, NH), 10.54 (br s, 1 H, NH$_{pyr}$).

^{13}C NMR (50 MHz, DMSO-d_6): δ = 169.65, 169.6, 161.0, 155.3, 150.5, 147.2, 131.6, 120.9, 113.7, 86.9, 55.0, 36.3, 33.1, 30.0, 27.4.

MS (EI, 70 eV): *m*/*z* (%) = 358 (7), 357 (30, [M$^+$ – 1]), 356 (28), 208 (5), 207 (56), 206 (100), 149 (51), 148 (64).

Anal. Calcd for $C_{17}H_{18}N_4O_5$: C, 56.98; H, 5.06; N, 15.63. Found: C, 57.1; H, 5.1; N, 15.6.

N-(3,4-Difluorophenyl)-1,3-dimethyl-2,4,7-trioxo-1,2,3,4,5,6,7,8-octahydropyrido[2,3-*d*]pyrimidine-5-carboxamide (3j)
Colorless solid; mp 282–283 °C.

^{1}H NMR (200 MHz, DMSO-d_6): δ = 2.63 (dd, $^2J_{AB}$ = 16.3 Hz, $^3J_{AX}$ = 1.4 Hz, 1 H, 6-H$_a$), 2.91 (dd, $^3J_{BX}$ = 7.8 Hz, 1 H, 6-H$_b$), 3.18 (s, 3 H, CH$_3$), 3.38 (s, 3 H, CH$_3$), 3.89 (dd, 1 H, 5-H$_x$), 7.22–7.80 (m, 3 H$_{arom}$), 10.14 (br s, 1 H, NH), 10.55 (br s, 1 H, NH$_{pyr}$).

^{13}C NMR (50 MHz, DMSO-d_6): δ = 170.3, 169.3, 160.8, 150.3, 148.6 (1 C, dd, $^1J_{CF}$ = 244 Hz, $^2J_{CF}$ = 13.3 Hz, C$_{Ar}$), 147.2, 145.2 (1 C, dd, $^1J_{CF}$ = 242 Hz, $^2J_{CF}$ = 12.3 Hz, C$_{Ar}$), 135.3 (1 C, dd, $^3J_{CF}$ = 9.4 Hz, $^4J_{CF}$ = 3.1 Hz, C$_{Ar}$), 116.8 (1 C, dd, $^2J_{CF}$ = 17.7 Hz, $^3J_{CF}$ = 1.0 Hz, C$_{Ar}$), 115.6 (1 C, dd, $^3J_{CF}$ = 5.1 Hz, $^4J_{CF}$ = 3.1 Hz, C$_{Ar}$), 108.3 (1 C, d, $^2J_{CF}$ = 21.9 Hz, C$_{Ar}$), 86.5, 36.4, 32.8, 29.9, 27.3.

MS (EI, 70 eV): *m*/*z* (%) = 364 (3, [M$^+$]), 208 (56), 207 (100), 150 (51), 148 (64).

Anal. Calcd for $C_{16}H_{14}F_2N_4O_4$: C, 52.75; H, 3.87; N, 15.38. Found: C, 52.7; H, 3.8; N, 15.5.

X-ray Structural Analysis of 3j[15]
The colorless crystals of **3j** ($C_{16}H_{14}F_2N_4O_4$) are triclinic. At 293 K, *a* = 8.205(3), *b* = 8.977(3), *c* = 12.096(4) Å, *α* = 90.30(2)°, *β* = 109.68(3)°, *γ* = 110.04(3)°, V = 780.7(4) Å^3, Mr = 364.31, *Z* = 2, space group P1, d_{calc} = 1.550 g/cm^3, μ(MoK$_\alpha$) = 0.129 mm^{-1}, F(000) = 376. Intensities of 5770 reflections (2671 independent, *R*int = 0.057) were measured on the 'Xcalibur-3' diffractometer (graphite monochromated MoK$_\alpha$ radiation, CCD detector, w-scanning, 2θmax = 50°). The structure was solved by direct method using SHELXTL package.[16] Positions of the hydrogen atoms were located from electron density difference maps and refined by 'riding' model with U_{iso} = nU_{eq} of the carrier atom (n = 1.5 for methyl groups and n = 1.2 for other hydrogen atoms). Full-matrix least-squares refinement against F2 in anisotropic approximation for non-hydrogen atoms using 2635 reflections was converged to *wR*2 = 0.099 (*R*1 = 0.045 for 1397 reflections with *F* >4σ(*F*), S = 0.861).

1-Benzyl-2,4,7-trioxo-*N*-phenyl-1,2,3,4,5,6,7,8-octahydropyrido[2,3-*d*]pyrimidine-5-carboxamide (3k)
Colorless solid; mp 295–296 °C.

^{1}H NMR (200 MHz, DMSO-d_6): δ = 2.56 (dd, $^2J_{AB}$ = 16.5 Hz, $^3J_{AX}$ = 0.9 Hz, 1 H, 6-H$_a$), 2.92 (dd, $^3J_{BX}$ = 7.7 Hz, 1 H, 6-H$_b$), 3.91 (dd, 1 H, 5-H$_x$), 5.16 (d, $^2J_{AB}$ = 17.2 Hz, 1 H, CH$_{2a}$), 5.36 (d, $^2J_{AB}$ = 17.2 Hz, 1 H, CH$_{2b}$), 7.01–7.57 (m, 10 H$_{arom}$), 9.93 (br s, 1 H, NH), 10.52 (br s, 1 H, NH), 11.51 (br s, 1 H, NH).

^{13}C NMR (50 MHz, DMSO-d_6): δ = 170.0, 169.7, 161.6, 150.1, 147.9, 138.4, 135.9, 128.3, 128.2, 127.0, 126.0, 123.2, 119.2, 88.0, 43.7, 35.9, 32.8.

MS (EI, 70 eV): *m*/*z* (%) = 389 (2, [M$^+$ – 1]), 270 (4), 269 (14), 268 (100), 178 (16).

Anal. Calcd for $C_{21}H_{18}N_4O_4$ (%): C, 64.61; H, 4.65; N, 14.35. Found: C, 64.3; H, 4.6; N, 14.3

1-Benzyl-2,4,7-trioxo-*N*-(2-methoxyphenyl)-1,2,3,4,5,6,7,8-octahydropyrido[2,3-*d*]pyrimidine-5-carboxamide (3l)
Colorless solid, mp 288–289 °C.

^{1}H NMR (200 MHz, DMSO-d_6): δ = 2.67 (dd, $^2J_{AB}$ = 16.4 Hz, $^3J_{AX}$ = 2.0 Hz, 1 H, 6-H$_a$), 2.75 (dd, $^3J_{BX}$ = 6.6 Hz, 1 H, 6-H$_b$), 3.83 (s, 3 H, CH$_3$O), 4.03 (dd, 1 H, 5-H$_x$), 5.13 (d, $^2J_{AB}$ = 17.1 Hz, 1 H, CH$_{2a}$), 5.32 (d, $^2J_{AB}$ = 17.1 Hz, 1 H, CH$_{2b}$), 6.85–8.08 (m, 9 H$_{arom}$), 9.12 (br s, 1 H, NH), 10.41 (br s, 1 H, NH), 11.56 (br s, 1 H, NH).

^{13}C NMR (50 MHz, DMSO-d_6): δ = 169.9, 169.6, 162.1, 150.0, 148.4, 147.5, 135.9, 128.3, 127.5, 127.0, 126.0, 123.7, 120.2, 119.7, 111.1, 87.7, 55.9, 43.8, 35.4, 31.8.

MS (EI, 70 eV): *m*/*z* (%) = 420 (2, [M$^+$]), 270 (4), 269 (9), 178 (7), 91 (100).

Anal. Calcd for $C_{22}H_{20}N_4O_5$: C, 62.85; H, 4.79; N, 13.33. Found: C, 62.9; H, 4.7; N, 13.4.

1-Benzyl-*N*-(2-chlorophenyl)-2,4,7-trioxo-1,2,3,4,5,6,7,8-octahydropyrido[2,3-*d*]pyrimidine-5-carboxamide (3m)
Colorless solid; mp 291–292 °C.

^{1}H NMR (200 MHz, DMSO-d_6): δ = 2.68 (dd, $^2J_{AB}$ = 16.5 Hz, $^3J_{AX}$ = 2.0 Hz, 1 H, 6-H$_a$), 2.83 (dd, $^3J_{BX}$ = 7.1 Hz, 1 H, 6-H$_b$), 4.06 (dd, 1 H, 5-H$_x$), 5.13 (d, $^2J_{AB}$ = 17.0 Hz, 1 H, CH-2a), 5.33 (d, $^2J_{AB}$ = 17.0 Hz, 1 H, CH-2b), 7.1–8.0 (m, 9 H$_{arom}$), 9.37 (br s, 1 H, NH), 10.53 (br s, 1 H, NH), 11.65 (br s, 1 H, NH).

^{13}C NMR (50 MHz, DMSO-d_6): δ = 170.1, 169.8, 162.2, 150.1, 147.7, 135.9, 134.7, 129.1, 128.3, 127.3, 127.0, 126.0, 125.3, 124.1, 123.3, 87.4, 43.8, 35.4, 31.9.

MS (EI, 70 eV): *m*/*z* (%) = 424 (2, [M$^+$]), 272 (11), 271 (17), 270 (32), 180 (17), 127 (100), 126 (56), 101 (18), 77 (44).

Anal. Calcd for $C_{21}H_{17}ClN_4O_4$: C, 59.37; H, 4.03; N, 13.19. Found: C, 59.3; H, 4.1; N, 13.0

1-Benzyl-*N*-(2,4-dichlorophenyl)-2,4,7-trioxo-1,2,3,4,5,6,7,8-octahydropyrido[2,3-*d*]pyrimidine-5-carboxamide (3n)
Colorless solid; mp 300–301 °C.

^{1}H NMR (200 MHz, DMSO-d_6): δ = 2.70 (dd, $^2J_{AB}$ = 16.4 Hz, $^3J_{AX}$ = 1.3 Hz, 1 H, 6-H$_a$), 2.81 (dd, $^3J_{BX}$ = 7.2 Hz, 1 H, 6-H$_b$), 4.06 (dd, 1 H, 5-H$_x$), 5.14 (d, $^2J_{AB}$ = 17.2 Hz, 1 H, CH-2a), 5.32 (d, $^2J_{AB}$ = 17.2 Hz, 1 H, CH-2b), 7.18–8.01 (m, 8 H$_{arom}$), 9.4 (br s, 1 H, NH), 10.47 (br s, 1 H, NH), 11.58 (br s, 1 H, NH).

^{13}C NMR (50 MHz, DMSO-d_6): δ = 169.9, 169.5, 162.0, 149.9, 147.6, 135.8, 134.6, 128.9, 128.1, 127.1, 126.9, 125.9, 125.1, 123.9, 123.1, 87.3, 43.7, 35.3, 31.8.

MS (EI, 70 eV): *m*/*z* (%) = 458 (5, [M$^+$]), 460 (2), 272 (13), 271 (12), 270 (100), 180 (47), 154 (18), 153 (28), 91 (98).

Anal. Calcd for $C_{21}H_{16}Cl_2N_4O_4$: C, 54.92; H, 3.51; N, 12.2. Found: C, 54.8; H, 3.45; N, 12.3.

***N*-Phenyl-2,4,7-trioxo-1-(2-phenylethyl)-1,2,3,4,5,6,7,8-octahydropyrido[2,3-*d*]pyrimidine-5-carboxamide (3o)**
Colorless solid; mp 278–279 °C.

^{1}H NMR (200 MHz, DMSO-d_6): δ = 2.54 (dd, $^2J_{AB}$ = 16.2 Hz, $^3J_{AX}$ = 1.2 Hz, 1 H, 6-H$_a$), 2.78 (dd, $^3J_{BX}$ = 7.1 Hz, 1 H, 6-H$_b$), 2.83 (t, ^3J = 7.1 Hz, 2 H, CH$_2$), 3.87 (dd, 1 H, 5-H$_x$), 4.21 (m, 2 H, CH$_2$), 6.98–7.52 (m, 10 H$_{arom}$), 9.77 (br s, 1 H, NH), 10.48 (br s, 1 H, NH), 11.30 (br s, 1 H, NH).

^{13}C NMR (50 MHz, DMSO-d_6): δ = 169.9, 169.6, 161.6, 149.8, 147.8, 138.4, 137.5, 128.6, 128.3, 127.9, 126.0, 123.1, 119.2, 87.6, 42.1, 35.7, 33.3, 32.6.

MS (EI, 70 eV): *m*/*z* (%) = 404 (2, [M$^+$]), 284 (7), 283 (15), 282 (23), 180 (2), 179 (10), 178 (27), 177 (21), 100 (100).

Anal. Calcd for $C_{22}H_{20}N_4O_4$: C, 65.34; H, 4.98; N, 13.85. Found: C, 65.3; H, 5.1; N, 13.7.

***N*-(2-Methoxyphenyl)-2,4,7-trioxo-1-(2-phenylethyl)-1,2,3,4,5,6,7,8-octahydropyrido[2,3-*d*]pyrimidine-5-carboxamide (3p)**
Colorless solid; mp 282–283 °C.

^{1}H NMR (200 MHz, DMSO-d_6): δ = 2.66 (m, 2 H, 6-H$_a$ + H$_b$), 2.81 (t, ^3J = 7.3 Hz, 2 H, CH$_2$), 3.82 (s, 3 H, CH$_3$O), 3.98 (dd,

^3J = 6.6, 2.2 Hz, 1 H, 5-H_x), 4.16 (m, 2 H, CH_2), 6.87–8.07 (m, 9 H_{arom}), 9.12 (br s, 1 H, NH), 10.50 (br s, 1 H, NH), 11.48 (br s, 1 H, NH).

^{13}C NMR (50 MHz, DMSO-d_6): δ = 169.7, 169.5, 161.9, 149.6, 148.3, 147.3, 137.4, 128.5, 127.8, 127.5, 126.0, 123.4, 120.1, 119.6, 111.2, 87.2, 55.8, 42.0, 35.2, 33.3, 31.6.

MS (EI, 70 eV): *m*/*z* (%) = 434 (2, [M$^+$]), 284 (12), 283 (17), 282 (10), 180 (2), 179 (5), 103 (93), 102 (96), 101 (100).

Anal. Calcd for $C_{23}H_{22}N_4O_5$: C, 63.59; H, 5.10; N, 12.90. Found: C, 63.5; H, 5.2; N, 13.0

_N_-(2-Fluorophenyl)-2,4,7-trioxo-1-(2-phenylethyl)-1,2,3,4,5,6,7,8-octahydropyrido[2,3-*d*]pyrimidine-5-carboxamide (3q)

Colorless solid; mp 281–282 °C.

^{1}H NMR (200 MHz, DMSO-d_6): δ = 2.67 (m, 2 H, 6-H_a + H_b), 2.83 (t, ^3J = 7.2 Hz, 2 H, CH_2), 4.00 (t, ^3J = 4.6 Hz, 1 H, 5-H_x), 4.18 (m, 2 H, CH_2), 7.06–8.0 (m, 9 H_{arom}), 9.43 (br s, 1 H, NH), 10.47 (br s, 1 H, NH), 11.40 (br s, 1 H, NH).

^{13}C NMR (50 MHz, DMSO-d_6): δ = 170.1, 169.6, 162.1, 152.5 (1 C, d, $^1J_{CF}$ = 244 Hz, C_{Ar}), 149.7, 147.7, 137.5, 128.6, 127.9, 126.1, 126.0 (1 C, d, $^2J_{CF}$ = 19.2 Hz, C_{Ar}), 124.4 (1 C, d, $^3J_{CF}$ = 7.4 Hz, C_{Ar}), 124.0 (1 C, d, $^3J_{CF}$ = 2.7 Hz, C_{Ar}), 122.3, 114.8 (1 C, d, $^2J_{CF}$ = 19.3 Hz, C_{Ar}), 87.0, 42.1, 35.2, 33.3, 31.8.

MS (EI, 70 eV): *m*/*z* (%) = 422 (3, [M$^+$]), 284 (37), 283 (100), 282 (13), 178 (2), 177 (6), 103 (40), 102 (26), 100 (2).

Anal. Calcd for $C_{22}H_{19}FN_4O_4$: C, 62.55; H, 4.53; N, 13.26. Found: C, 62.3; H, 4.6; N, 13.1

6-Amino-5-(2,5-dioxo-1-phenylpyrrolidin-3-yl)pyrimidine-2,4(1*H*,3*H*)-dione (5a)

A mixture of 6-aminouracil (**1a**; 0.003 mol) and *N*-phenylmaleimide (**2a**; 0.003 mol) in DMF (2 mL) was refluxed for 15 min. After cooling, EtOH (10 mL) was added. The reaction mixture was allowed to stand at r.t. for ~4 h and then the precipitate formed was filtered. The solid product was washed with EtOH (10 mL) and dried on air at r.t.

^{1}H NMR (200 MHz, DMSO-d_6): δ = 2.56 (dd, $^2J_{AB}$ = 18.1 Hz, $^3J_{AX}$ = 4.8 Hz, 1 H, H_a), 3.05 (dd, $^3J_{BX}$ = 9.8 Hz, 1 H, H_b), 3.98 (dd, 1 H, 4-H_x), 6.36 (br s, 2 H, NH_2), 7.20–7.50 (m, 5 H_{arom}), 10.18 (br s, 1 H, NH_{pyr}), 10.46 (br s, 1 H, NH_{pyr}).

^{13}C NMR (50 MHz, DMSO-d_6): δ = 178.2, 176.0, 163.8, 152.6, 150.2, 133.2, 128.8, 127.3, 125.5, 83.7, 34.4, 32.5.

MS (EI, 70 eV): *m*/*z* (%) = 300 (3, [M$^+$]), 180 (100), 179 (56), 151 (43).

Transformation of 5a into 3a

The pyrimidine dione **5a** (0.003 mol) and DMF (2 mL) were placed in a flask and the mixture refluxed for 5 h. The mixture was poured into H_2O (20 mL) and the precipitated compound **3a** was filtered and dried at r.t. under air.

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