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Reactions of Uracils, 24. Multiple Anellation to Uracils and their Analogs - An Approach to Nevirapine-Type Tricycles

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Reactions of Uracils, 24[1]. Multiple Anellation to Uracils and their Analogs - An Approach to Nevirapine-Type Tricycles

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ABSTRACT: Starting with 6-amino-1,3-dimethyluracil **1** a structural analog of the NNRTI Nevirapine **16** is synthesized in a sequence of two ring anellations and a Beckmann rearrangement. The anellation behavior of **3** is studied in general leading to the anellated systems **5**, **7a-c**, **12 a-c**.

Uracils are versatile starting materials in the synthesis of anellated heterocycles [2]. The 6-amino-1,3-dimethyluracil **1** could easily be converted into a 7-amino-1,3-dimethylpyrido[2,3-*d*]pyrimidine-2,4,5(1H,3H,8H)trione **3** [3]. **3** represents a versatile starting material for the synthesis of several new heterocyclic systems.

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The synthetic sequence of adding cyanoacetic acid and pyridine as a catalyst to **1** forming the 6-amino-5-cyanoacetyl-1,3-dimethyluracil **2** in a yield of 70.1% which in turn is cyclized by sodium ethoxide in ethanol to **3**, could be repeated also successfully with **3** itself to afford 7-amino-6-cyanoacetyl-1,3-dimethylpyrido[2,3-*d*]pyrimidine-2,4,5(1H,3H,8H)trione **4** in a yield of 22.5% and 8-amino-1,3-dimethylpyrimido[4,5-b][1,8]naphthyridine-2,4,5,6(1H,3H,9H,10H)= tetraone **5** in 98% yield, respectively. A third anellation sequence could not be realized as **5** is highly insoluble and the reagents employed, especially cyanoacetic acid, polymerize at temperatures higher than 75°C.

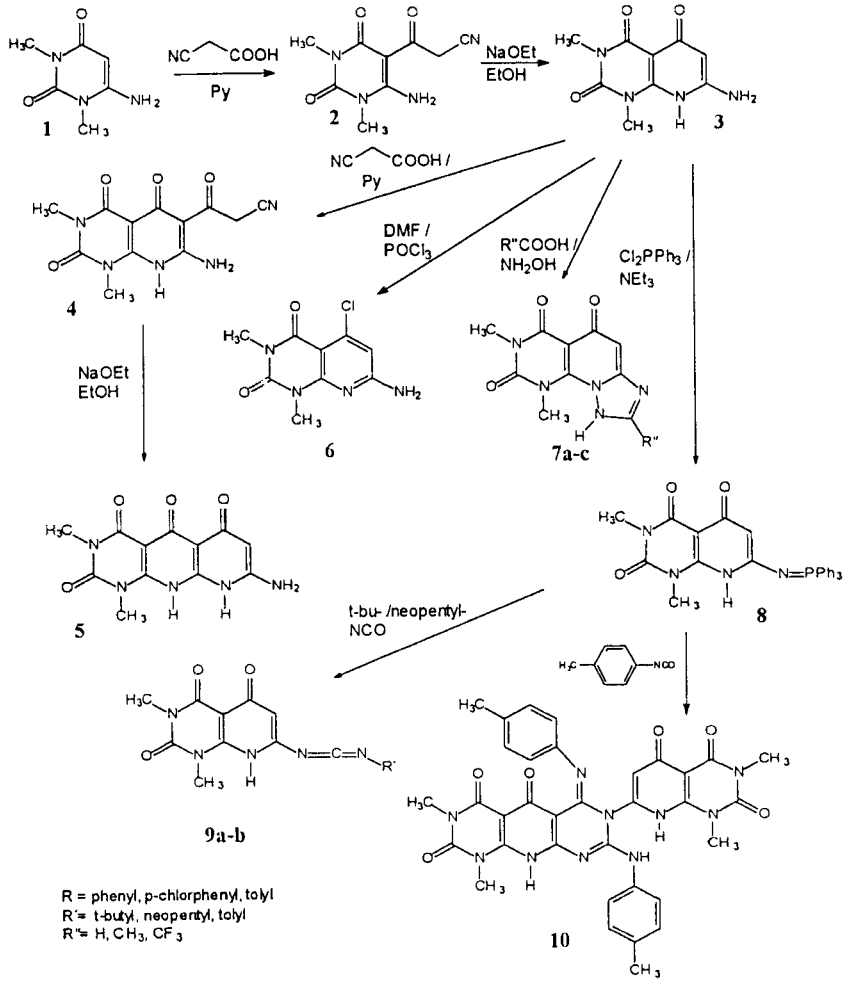
By Vilsmeier-Haack reaction, **3** is converted into 7-amino-5-chloro-1,3-dimethylpyrimido[2,3-*d*]pyrimidine-2,4(1H,3H)dione **6** a hitherto unknown highly substituted pyrido[2,3-*d*]pyrimidine [4].

The reaction of **3** with hydroxylamine in formic, acetic, or trifluoracetic acid affords the 1,2,4-triazolo[3′,2′: 2,1]pyrido[2,3-*d*]pyrimidines **7a-c** in moderate yields.

Conversion of the amino group of **3** with dichlorotriphenylphosphorane gives the iminophosphorane **8** starting point for a broad choice of interesting synthetic alternatives [5]: thus, employing isocyanates the carbodiimides **9a-c** are formed [6]. The alkyl substituted carbodiimides **9a,b** are considerably stable and can be purified by recrystallization. However, under these reaction conditions the tolyl substituted **9c** forms its dimer **10**.

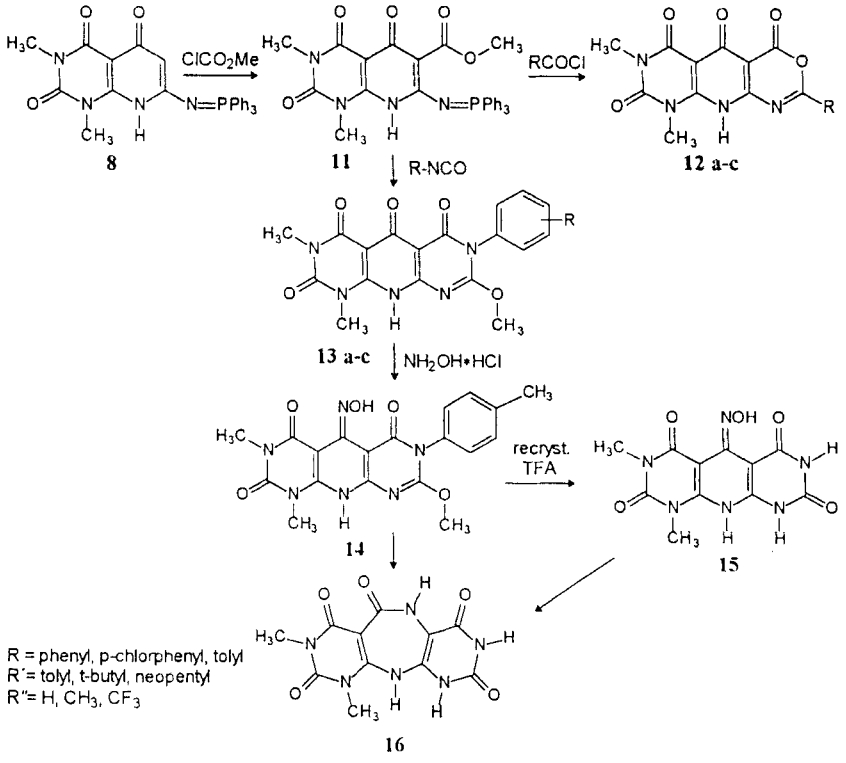
By treatment with methyl chloroformate/triethylamine in toluene another ester group was easily introduced to C-6 of **8** to give **11**. Employing acid chlorides

Scheme 1



the oxazinones **12a-c** are obtained in highly yields[7], and in turn with isocyanates the pyrimidines **13a-c** are formed. These pyrimido[5′,6′:5,6]pyrido=[2,3-*d*]pyrimidine-2,4,5,6(1H,3H,7H,10H)tetrones **13a-c** possess only one reactive 5-oxo group which (**13c** 1 mmol) affords with hydroxylamine (4 mmol) selectively

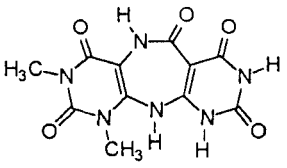
Scheme 2



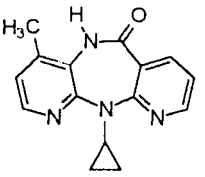
the corresponding 5-oxime **14** (86%) which was in turn converted by Beckmann rearrangement [8] leading to the desired central 1,4-diazepinone moiety **16**.

14 could not be purified because of its poor solubility being only soluble in trifluoracetic acid. The addition of water gives a new tricyclic oxime **15** (98%) where both the 7-tolyl and 8-ethoxy group surprisingly have been splitted off. The same phenomenon was observed upon purification attempts of diazepinone **16** (99%). A diazepinone carrying any substituents in positions 8 and 9 could not be isolated.

Scheme 3



16



17

Diazepinone **16** represents a structural analog of the non nucleoside reverse transcriptase inhibitor (NNRTI) Nevirapine **17** [9] which recently found use as a drug against HIV (Viramune®). The potential activity of **16** against HIV is currently investigated.

In order to circumvent these insolubilities and to effect a better handling of the condensed systems, at present derivatives of the diazepine are studied alkylated at N-11. Furthermore, the synthesis of additional Nevirapine analogs is presently carried out for obtaining a broader choice of these anellated diazepinones; the results will be the subject of forthcoming publications.

Experimental

6-Amino-5-cyanacetyl-1,3-dimethyluracil (2). In acetic acid anhydride (200 ml) 6-amino-1,3-dimethyl-uracil **1** (35.3g, 250 mmol) was suspended. Pyridine (5 ml) was added and heated to 65°C. Cyanoacetic acid (25.5 g, 300 mmol) solved in acetic acid anhydride (100 ml) was dropped to the suspension. After 3h the suspension was cooled to room temperature and hydrolyzed with water (200 ml).

The product recrystallized from DMF. **Yield** 36.4 g (70.1 %). **mp**.: 257°C. **HRMS:** Found (Required) 222.0749 (222.0761). **^{1}H NMR:** (200MHz, DMSO-d_6) δ [ppm]= 3.12 (s, 3H, 10-H), 3.31 (s, 3H, 11-H), 4.34 (s, 2H, 8-H), 8.51 (s, 1H, NH_2), 10.62 (s, 1H, NH_2). **^{13}C NMR:** (62.90MHz, DMSO-d_6) δ [ppm] = 27.6 (C-10), 29.7 (C-8), 33.3 (C-11), 89.4 (C-5), 116.5 (C-9), 149.4 (C-7), 158.1 (C-6), 161.2 (C-4), 186.6 (C-2). **IR:** ν[cm^{-1}] = 3450 (NH), 2975, 2940 (CH), 2243 (Nitrile), 1710, 1650 (C=O), 1520 (NH). **CHN** ($C_9H_{10}N_4O_3$): Found (Required) C 48.63 (48.83), H 4.54 (4.53), N 25.22 (25.72).

7-Amino-1,3-dimethyl-pyrido[2,3-*d*]pyrimidine-2,4,5(1H,3H,8H)-trione (3). Sodium (7.8 g, 340 mmol) was dissolved in ethanol (340 ml) and **2** (37.8 g, 170 mmol) were added. After 1h the reaction was quenched with acetic acid (3%). The product was washed with ethanol and recrystallized from DMF. **Yield** 34.5 g (91.2 %). **mp**.: >260°C subl. **MS:** (MS 50 / DE 180°C / 70 eV / 300 mA): m/z (rel. Int.): 223 (M^++1, 6), 222 (M^+, 100), 194 (19), 193 (23), 110 (32). **HRMS:** Found (Required) 222.0750 (222.0761). **^{1}H NMR:** (400 MHz, DMSO-d_6) δ [ppm]= 3.20 (s, 3H, 10-H), 3.40 (s, 3H, 9-H), 5.62 (s, 1H, 6-H), 7.05 (s, 2H, 11-H), 11.98 (s, 1H, 8-H). **IR:** ν[cm^{-1}] = 3450 (m) (NH), 3350 (m) (NH), 1695 (s) (C=O), 1680 (s) (C=O), 1520 (s) (NH).

7-Amino-6-cyanoacetyl-1,3-dimethylpyrido[2,3-*d*]pyrimidine-2,4,5(1H,3H,8H)= trione (4). Reaction like **2** starting from **3** (4.4 g, 20 mmol). **Yield:** 1.3 g (22.5 %). **mp**.: >280°C. **MS:** m/z (rel. Int.): 290 (M^++1, 20), 289 (M^+, 100), 288 (M^+-1, 10),

249 (32), 223 (13), 222 (90), 194 (14), 193 (15), 110 (16). **^{1}H NMR:** (200 MHz, CDCl3) δ [ppm]= 1.68 (s, 2H, 12-H), 2.69 (s, 3H, 9-H), 2.96 (s, 3H, 10-H), 8.01 (s, 2H, 14-H), 11.94 (s, 1H, 8-H). **^{13}C NMR:** (62.90 MHz, DMSO-d_6) δ [ppm]= 27.3 (C-10), 29.3 (C-12), 30.8 (C-9), 93.6 (C-4a), 94.4 (C-6), 115.4 (C-13), 150.3 (C-8a), 154.6 (C-2), 162.3 (C-4), 163.2 (C-7), 164.5 (C-5), 168.7 (C-11).

IR: ν[cm^{-1}] = 3315 (w) (N-H), 2960 (w) (C-H), 2920 (w) (C-H), 2255 (w) (CN), 1708 (s) (C=O), 1680 (s) (C=O). **CHN:** Found (Required) C 49.92 (49.83), H 4.48 (3.83), N 23.63 (24.21).

8-Amino-1,3-dimethylpyrimido[4,5-*b*][1,8]naphthyridine-2,4,5,6-(1H,3H,= 9H,10H)tetraone (5). **4** (2.89 g, 10 mmol) was treated like **3**. **Yield:** 2.85 g (98 %). **mp.**:>270°C. **MS:** m/z (rel. Int.): 289 (M$^+$, 4), 223 (16), 222 (100), 195 (4), 194 (38), 193 (40), 110 (49). **HRMS:** Found (Required) 289.0817 (289.0811). **^{1}H NMR:** (250 MHz, DMSO-d_6) δ [ppm]= 3.22 (s, 3H, 12-H), 3.43 (s, 3H, 11-H), 5.62 (s, 1H, 7-H), 7.03 (s, 2H, 13-H), 11.95 (s, 1H, 9-H). **^{13}C NMR:** (62.90 MHz, DMSO-d_6) δ [ppm]= 27.0 (C-12), 29.0 (C-11), 87.0 (C-7), 93.4 (C-4a), 115.4 (C-5a), 150.5 (C-10a), 152.2 (C-9a), 154.6 (C-2), 163.2 (C-8), 164.4 (C-4), 166.5 (C-6), 168.6 (C-5). **IR:** ν [cm^{-1}] = 3440 (s), 3340 (s), 3230 (m) (N-H), 2960 (w), 2920 (w) (C-H), 1650 (s) (C=O), 1630 (s) (C=O), 1590 (s) (C=O).

7-Amino-5-chloro-1,3-dimethylpyrido[2,3-*d*]pyrimidine-2,4(1H,3H)dione (6). At 0°C DMF (2.4 g, 30 mmol) was dropped to $POCl_3$ (15.4 g, 100 mmol) for 30 min.. The solution was heated for 2 h at 60°C. To the cooled solution **3** (2.22 g, 10

mmol) in DMF (2.4 g, 30 mmol) was added. The reaction was heated to 130°C for 12 h, $POCl_3$ was removed in vacuo and the residue was quenched with ice/water (200 ml). The light brown product was recrystallized from DMF. **Yield:** 1.96 g (81.4 %). **mp.**: 208 - 210°C. **MS:** m/z (rel. Int.): 257 (M^++1, 10), 256 (M^+, 16), 203 (41), 154 (20), 153 (38), 139 (100), 110 (42).

^{1}H NMR: (400 MHz, DMSO-d_6/TFA-d) δ [ppm]= 3.28 (s, 3H, 10-H), 3.52 (s, 3H, 9-H), 6.51 (s, 1H, 6-H), 12.21 (s, 2H, 11-H).

^{13}C NMR: (100.62 MHz, DMSO-d_6/TFA-d) δ [ppm]= 27.1 (C-10), 29.1 (C-9), 96.7 (C-4a), 105.4 (C-6), 144.2 (C-5), 150.6 (C-2), 153.1 (C-7), 160.4 (C-4), 162.6 (C-8a). **IR:** ν[cm^{-1}] = 3424 (s) (N-H), 3320 (s) (N-H), 3230 (m) (N-H), 3022 (w) (C-H), 2965 (w) (C-H), 1691 (s) (C=O), 1630 (s) (C=O), 1580 (s) (C=O), 1428 (s) (C=N), 780 (m) (C-Cl), 750 (m) (C-Cl). **CHN:** Found (Required) C 44.55 (44.99), H 4.06 (3.78), N 23.17 (23.33).

1,3-Dimethyltriazolo[3′,2′:2,1]pyrido[2,3-*d*]pyrimidine-2,4,5-(1H,3H,10H)-trione (7a). **3** (2.22 g, 10 mmol) was dissolved in formic acid (98 %, 15 ml) and treated with hydroxylamine hydrochloride (1.2 g, 15 mmol). The solution was refluxed for 4 h and quenched with ice. After neutralization with NaOH **7a** was filtered off and was recrystallized from ethanol. **Yield:** 650 mg (26.32%). **mp.**: >270 °C. **MS:** (MS50 / DE 180°C / 70eV / 300mA): m/z = 250 (M^+ +3, 18), 248 (M^+ +1, 3), 247 (M^+, 3), 222 (45), 194 (12), 193 (14), 110 (18), 73 (100).

^{1}H NMR: (400 MHz, DMSO-d_6) δ [ppm]= 3.17 (s, 3H, 11-H), 3.40 (s, 3H, 10-H),

5.42 (s, 1H, 6-H), 9.23 (d, ^{3}J=10.3 Hz, 1H, 8-H), 10.04 (d, ^{3}J=10.3 Hz, 1H, 9-H).

^{13}C NMR: (62.90 MHz, DMSO-d_6) δ [ppm]= 29.2 (C-11), 35.8 (C-10), 97.3 (C-4a), 98.3 (C-6), 151.3 (C-9b), 152.1 (C-6a), 153.5 (C-2), 162.0 (C-4), 162.6 (C-8), 177.7 (C-5). **IR:** ν[cm^{-1}] = 3340 (w) (N-H), 3130 (m) (N-H), 2950 (w) (C-H), 1700 (s) (C=O), 1640 (s) (C=O), 1600 (s) (C=O), 1250 (s) (C=N).

CHN: Found (Required) C 47.91 (48.59), H 3.82 (3.67), N 28.14 (28.33).

1,3,8-Trimethyltriazolo[3′,2′:2,1]pyrido[2,3-*d*]pyrimidine-2,4,5(1H,3H,10H)=trione (7b). Like **7a** using acetic acid (15ml). **Yield:** 1.23g (47.1 %). **mp.**:>300°C. **MS:** (MS50 / DE 180°C / 70eV / 300mA): m/z = 262 (M$^+$+1, 5), 222 (100), 194 (23), 193 (24), 110 (28). **HRMS:** Found (Required) 261.0865 (261.0862).

^{1}H NMR: (400 MHz, DMSO-d_6) δ [ppm]= 1.62 (s, 3H, 13-H), 3.18 (s, 3H, 12-H), 3.42 (s, 3H, 11-H), 5.66 (s, 1H, 6-H), 9.50 (s, 1H, 9-H).

^{13}C NMR: (62.90 MHz, DMSO-d_6) δ [ppm]= 29.2 (C-12), 35.8 (C-11), 97.3 (C-4a), 98.3 (C-6), 151.3 (C-10a), 152.1 (C-6a), 153.5 (C-2), 162.0 (C-4), 162.6 (C-8), 177.7 (C-5). **IR:** ν[cm^{-1}] = 3340 (w) (N-H), 3130 (m) (N-H), 2950 (w) (C-H), 1700 (s) (C=O), 1640 (s) (C=O), 1600 (s) (C=O), 1250 (s) (C=N).

1,3-Dimethyl-8-trifluoromethyltriazolo[3′,2′:2,1]pyrido[2,3-*d*]pyrimidine-2,4,5(1H,3H,10H)trione (7c). Like **7a** using trifluoroacetic acid (15 ml). The product was recrystallized from DMF. **Yield:** 150 mg (4.7%). **mp.**: > 280°C.

MS: (MS50 / DE 180°C / 70eV / 300mA): m/z = 316 (M$^+$+1, 4), 222 (100), 194

(27), 193 (29), 110 (20), 69 (44). **HRMS:** Found (Required) 315.0584 (315.0579). **^{1}H NMR:** (400 MHz, DMSO-d_6) δ [ppm]= 3.18 (s, 3H, 12-H), 3.42 (s, 3H, 11-H), 5.66 (s, 1H, 6-H), 9.50 (s, 1H, 9-H). **^{13}C NMR:** (62.90 MHz, DMSO-d_6) δ [ppm]= 29.2 (C-12), 35.8 (C-11), 97.3 (C-4a), 98.3 (C-6), 151.3 (C-9b), 152.1 (C-6a), 153.5 (C-2), 162.0 (C-4), 162.6 (C-8), 177.7 (C-5). **IR:** ν[cm^{-1}] = 3340 (w) (N-H), 3130 (w) (N-H), 2950 (w) (C-H), 1700 (s) (C=O), 1640 (s) (C=O), 1600 (s) (C=O), 1250 (s) (C=N).

1,3-Dimethyl-7(triphenylphosphoranylidenamino)pyrido[2,3-*d*]pyrimidine-2,4,5(1H,3H,8H)trione (8). To absol. acetonitrile (800 ml) **3** (33.3 g, 300 mmol), triphenylphosphan (43.3 g, 160 mmol), triethylamine (30.0 g), and hexachloroethane (32.5 g, 150 mmol) were added. After stirring for 5 h the reaction was refluxed for a few min. and the solvent evaporated under reduced pressure. The residue was dissolved in hot toluene heated and filtered. The precipitated product was recrystallized from ethanol. **Yield:** 18.95g (26%). **mp**.: 200 - 201°C.

MS: (MS50 / DE 180°C / 70eV / 300mA): m/z (rel. Int.): 482 (M^++1, 90) 481 (M^+, 100), 183 (30). **^{1}H NMR:** (200 MHz, $CDCl_3$) δ [ppm] = 2.85 (s, 3H, 9-H), 3.30 (s, 3H, 10-H), 6.21 (s, 1H, 6-H), 7.40-7.80 (m, 15H, 12 - 14-H), 11.72 (s, 1H, 8-H).

^{13}C NMR: (62.90 MHz, $CDCl_3$) δ [ppm] = 27.0 (C-9), 28.9 (C-10), 89.7 (C-7), 97.5 (C-6), 128.0-132.6 (C-18, C-11 - C-14), 150.5 (C-4a), 15115 (C-8a), 164.9

(C-5), 167.1 (C-4), 167.9 (C-2). **IR:** ν[cm^{-1}] = 1701 (s) (C=O), 1657 (s) (C=O), 1592 (s) (C=O), 1408 (P=N), 718, 694 (mono subst. Ar.).

CHN: Found (Required) C 66.87 (67.21), H 4.66 (4.80), N 11.60 (11.61).

N-[1,3-Dimethyl-2,4,5(1H,3H,8H)trioxopyrido[2,3-*d*]pyrimidine-7′-yl]-N′-tert. butylcarbodiimide (9a). To absol. toluene (10 ml) **8** (2.4 g, 5 mmol) and tert.-butylisocyanate (2.47 ml, 25 mmol) were added and heated for 10 min.. The solution was cooled to room temperature and then filtered, and the product was recrystallized from chloroform. **Yield:** 0.2g (13%). **mp.**: 143°C. **MS:** m/z (rel. Int.): 304 (M^++1, 1), 303 (M^+, 10), 247 (100). **^{1}H NMR:** (200 MHz, $CDCl_3$) δ [ppm] = 1.30-1.62 (m, 9H, 11 - 13-H), 3.43 (s, 3H, 9-H), 3.57 (s, 3H, 10-H), 6.14 (s, 1H, 6-H), 11.82 (s, N-H). **^{13}C NMR:** (62,90 MHz, $CDCl_3$) δ [ppm] = 27.6 (C-9), 30.0 (3C, C-13), 30.1 (C-10), 31.6 (C-12), 91.9 (C-4a), 98.9 (C-6), 128.5 (C-7), 132.6 (C-12), 151.0 (C-8a), 157.6 (C-5), 165.2 (C4), 167.6 (C-2). **IR:** ν[cm^{-1}] = 2970 (w) (C-H), 2135 (s) (N=C=N), 1700 (s) (C=O), 1653 (s) (C=O), 1617 (s) (C=O).

N-[1,3-Dimethyl-2,4,5(1H,3H,8H)trioxopyrido[2,3-*d*]pyrimidine-7′-yl]-N′-neopentylcarbodiimide (9b). Like **9a** with neopentylisocyanate (2.94 ml, 25 mmol). **Yield:** 0.5 g (32%). **mp.:** 151°C. **MS:** m/z (rel. Int.): 318 (M^++1, 19), 317 (M^+, 73), 247 (100). **HRMS**: Found (Required) 277.0795 (277.0795). **^{1}H NMR:** (200 MHz, $CDCl_3$) δ [ppm]= 1.00 (s, 9H, 16-H), 3.29 (s, 2H, 12-H), 3.42 (s, 3H,

9-H), 3.57 (s, 3H, 10-H), 6.08 (s, 6-H), 12.11 (s, 8-H). **^{13}C NMR:** (62.90 MHz, $CDCl_3$) δ [ppm]= 26.9 (3C, C-14,15,16), 27.6 (C-9), 29.7 (C-10), 32.8 (C-13), 58.1 (C-12), 93.7 (C-4a), 98.8 (C-6), 129.0 (C-7), 132.1 (C-11), 150.2 (C-5), 165.4 (C4), 169.6 (C-2). **IR:** ν[cm^{-1}] = 2957 (w) (C-H), 2213 (s) (N=C=N), 1700 (s) (C=O), 1669 (s) (C=O), 1609 (s) (C=O).

2-Phenylamino-4(3H)-phenylimino-7,9-dimethyl-3-[1′,3′-dimethyl-2′,4′,5′ (1′H,3′H,8′H)trioxopyrido[2,3-*d*]pyrimidine-7′-yl]-pyrimido[5′,6′:5,6]= pyrido[2,3d]pyrimidine-5,6,8(7H,9H,10H)trione (10). **8** (2.7 g, 5 mmol) was heated with tolueneisocyanate (1 g, 10 mmol) in toluene. The light yellow product was recrystallized from DMF. **Yield:** 2.4 g (74%). **mp.**: >300°C. **MS:** (MS50 / DE 180°C / 70eV / 300mA): m/z (rel. Int.): 647 (M^+, 5); 527 (8), 453 (12), 452 (63, 451 (37), 323 (25), 248 (61), 222 (53), 136 (35), 119 (70), 93 (100 C_6H_7N). **^{1}H NMR:** (200 MHz, DMSO-d_6): δ [ppm] = 3.35 (s, 3H, 12-H), 3.45 (s, 3H, 11-H), 3.60 (s, 3H, 26-H), 4.08 (s, 3H, 27-H), 7,10 - 7,50 (m, 10H, 14 - 17-H, 29 - 32-H), 11.10 (s, 1H, 28-H). **IR:** ν[cm^{-1}] = 3360 (s) (N-H), 3330 (m) (N-H), 3320 (s) (N-H), 2950 (m) (C-H), 1640 (s) (C=O), 785 (Ar.). **CHN:** Found (Required) C 59.10 (59.44), H 4.09 (4.05), N 21.65 (21.66).

Methyl 1,3-dimethyl-2,4,5(1H,3H,8H)trioxo-7-(triphenylphosphoranylidene-amino)pyrido[2,3-*d*]pyrimidine-6-carboxylate (11). **8** (4.82 g, 10 mmol) was suspended in toluene (20 ml), methyl chloroformiate (1.5 g, 15 mmol) was added and the solution refluxed for 1 h. The solution was cooled to room temperature

and the triethylamine hydrochloride precipitated was separated. The solution was quenched with ice and the product was recrystallized from methanol/DMF (1:1). **Yield:** 4.14 g (83 %). **mp.**: 197 - 198°C. **MS:** m/z (rel. Int.): 541 (M^++1, 3), 540 (M^+, 10), 539 (M^+-H, 4), 484 (4), 483 (37), 482 (100), 481 (98), 480 (4), 405 (6), 262 (10), 261 (8), 260 (16), 202 (6), 105 (12), 104 (4), 103 (30). **^{1}H NMR:** (200MHz, DMSO-d_6) δ [ppm] = 2.25 (s, 3H, 10-H), 2.70 (s, 3H, 1-CH_3), 3.15 (s, 3H, 3-CH_3), 7.5 - 7.7 (m, 15H, 11-H), 11.80 (s, 1H, 8-H). **^{13}C NMR:** (62.90 MHz, DMSO-d_6) δ [ppm] = 21.0 (C-10), 27.0 (1-CH_3), 28.5 (3-CH_3), 89.0 (C-6), 96.5 (C-4a), 125.0-132,5 (C-11), 137.5 (C-9), 150.3 (C-8a), 150.5 (C-7), 164.5 (C-5), 166.4 (C-4), 167.4 (C-2). **IR:** ν[cm^{-1}] = 3400 (w) (N-H), 3050 (w) (C-H ar.), 2975 (w) (C-H), 2940 (w) (C-H), 1770 (s) (C=O), 1695 (s) (C=O), 1650 (s) (C=O), 1595 (s) (C=O). **CHN:** Found (Required) C 64.30 (64.44), H 4.59 (4.66), N 10.31 (10.37).

6,8-Dimethyl-3-phenylpyrimido[5′,6′:5,6]pyrido[2,3-*d*][3,1]oxazine-1,7,9,10=(5H,6H,8H)tetrone (12a). **11** (2.34 g, 4.44 mmol) was solved in acetonitril (20 ml). Benzoyl chloride (0.74 g, 5.3 mmol) and triethylamine (2.1 ml, 8.88 mmol) were added. The solution was refluxed for 4 h and cooled to room temperature. The product was washed with acetonitrile, refluxed in toluene, and hot filtered. **12a** crystallizes from the solution. **Yield:** 1.40 g (90.1%). **mp.**: >270°C. **MS:** m/z (rel. Int.): 353 (M^++1, 2), 352 (M^+, 4), 277 (9), 262 (20), 185 (14), 183 (31), 115 (100), 92 (19), 91 (24), 44 (47). **^{1}H NMR:** (250 MHz, $CDCl_3$) δ[ppm] = 2.79 (s, 3H, 12-H), 3.21 (s, 3H, 11-H), 7.60 - 7.80 (m, 5H, 14 - 16-H), 8.20 (s, 1H, 10-H).

^{13}C NMR: (62.90 MHz, DMSO-d_6) δ [ppm] = 27.8 (C-12), 30.0 (C-11), 89.3 (C-4a), 103.6 (C-5a), 128.6 (C-15), 129.1 (C-14), 130.8 (C-16), 137.3 (C-13), 152.2 (C-10a), 155.2 (C-2), 160.0 (C-4), 160.8 (C-9a), 169.1 (C-8), 178.5 (C-5). **IR:** ν[cm^{-1}] = 3060 (w) (C-H ar.), 2940 (w) (C-H al.), 1745 (s) (C=O), 1695 (s) (C=O), 1650 (s) (C=O), 1600 (s) (C=O).

6,8-Dimethyl-3(4′-chlorphenyl)pyrimido[5′,6′:5,6]pyrido[2,3-*d*][3,1]= oxazine-1,7,9,10(5H,6H,8H)tetrone (12b). Like **12a** with 4-chlorobenzoyl chloride). **Yield:** 1.43 g (83%). **mp.**: > 280°C. **MS:** m/z (rel Int.): 387 (M^++1, 3), 352 (M^+, 6), 278 (3), 277 (10), 262 (27), 185 (14), 183 (28), 139 (31)108 (8).

^{1}H NMR: (250 MHz, $CDCl_3$) δ [ppm] = 2.81 (s, 3H, 12-H), 3.23 (s, 3H, 11-H), 7.60 - 7.80 (m, 4H, 14 - 15-H), 8.14 (s, 1H, 10-H). **^{13}C NMR:** (62.90 MHz, DMSO-d_6) δ [ppm] = 27.8 (C-12), 30.0 (C-11), 89.4 (C-4a), 104.6 (C-5a), 129.0 (C-15), 130.4 (C-14), 135.4 (C-13), 136.1 (C-16), 152.3 (C-10a), 155.2 (C-2), 160.4 (C-4), 162 7 (C-9a), 170.8 (C-8), 182.1 (C-5).

IR: ν [cm^{-1}] = 3060 (w) (C-H ar.), 2940 (w) (C-H al.), 1771 (s) (C=O), 1700 (s) (C=O), 1653 (s) (C=O), 1607 (s) (C=O).

3,6,8-Trimethylpyrimido[5′,6′:5,6]pyrido[2,3-d][3,1]oxazine-1,7,9,10(5H,= 6H, 8H)tetrone (12c). Like **12a** using acetyl chloride (0.5 g, 6 mmol). The product was recrystallized from acetonitrile. **Yield:** 1.4 g (4.8 mmol) 96%. **mp.**: >300°C. **MS:** m/z (rel Int.): 291 (M^++1, 5), 290 (M^+, 8), 262 (13), 185 (5), 183

(14), 118 (8). **^{1}H NMR:** (250 MHz; $CDCl_3$) δ [ppm] = 1.65 (s, 3H, 13-H) 2.79 (s, 3H, 12-H), 3.30 (s, 3H, 11-H), 11.7 (s, 1H, 10-H). **^{13}C NMR:** (62.90 MHz, DMSO-d_6) δ [ppm] = 19.0 (C-13), 26.5 (C-12), 28.2 (C-11), 88.7 (C-4a), 103.2 (C-5a), 151.3 (C-10a), 155.7 (C-2), 164.7 (C-9a), 166.3 (C-4), 169.2 (C-8), 179.0 (C-5). **IR:** ν [cm^{-1}] = 2940 (w) (C-H), 1754 (s) (C=O), 1690 (s) (C=O), 1645 (s) (C=O), 1595 (s) (C=O).

1,3-Dimethyl-7(4′-methylphenyl)-8-methoxypyrimido[5′,6′:5,6]pyrido[2,3-d] pyrimidine-2,4,5,6(1H,3H,7H,10H)tetrone (13a). **11** (5.4 g, 10 mmol) was dissolved in dry toluene (20 ml) and treated with p-tolylisocyanate (1.5 g, 12 mmol). The solution was refluxed for 16 h. The product was washed with hot ethanol. **Yield:** 3.2 g (59.3%). **mp.**: >280°C (dec.). **MS:** m/z (rel. Int.): 396 (M^++1, 12), 395 (M^+, 65), 338 (20), 337 (100), 336 (25), 307 (15), 308 (25), 223 (14), 222 (80), 91 (50). **^{1}H NMR:** (250 MHz, DMSO-d_6) δ [ppm] = 2.20 (s, 3H, 17-H), 2.75 (s, 3H, 11-H), 2.90 (s, 3H, 18-H), 3.20 (s, 3H, 12-H), 7.05 (d ^{3}J=8.5 Hz, 1H, 15-H), 7.25 (d ^{3}J=7.5Hz, 1H, 14-H), 12.00 (s, 1H, 10-H).

^{13}C NMR: (62.90 MHz, DMSO-d_6) δ [ppm] = 21.7 (C-17), 28.8 (C-12), 31.6 (C-11), 56.9 (C-18), 89.3 (C-4a), 105.3 (C-5a), 126.0 (C-14), 128.8 (C-15), 129.6 (C-16), 131.0 (C-13), 151.1 (C-10a), 152.9 (C-2), 158.9 (C-9a), 160.0 (C-4), 163.8 (C-6), 168.8 (C-8), 187.0 (C-5). **IR:** ν [cm^{-1}] = 2950 (w) (C-H), 1740 (s) (C=O), 1715 (s) (C=O), 1660 (s) (C=O), 1640 (s) (C=O).

CHN: Found (Required) C 57.59 (57.72), H 4.71 (4.33), N 17.61 (17.71).

1,3-Dimethyl-7-phenyl-8-methoxypyrimido[5′,6′:5,6]pyrido[2,3-*d*]pyrimidine-2,4,5,6(1H,3H,7H,10H)tetrone (13b). Like **13a** with phenylisocyanate (0.21 g, 1.8 mmol). **Yield:** 60 mg (7%). **mp.**: >290°C. **MS:** m/z (rel. Int.): 382 (M^++1, 9), 381 (M^+, 58), 338 (31), 337 (100), 336 (28), 308 (14), 223 (18), 222 (91), 91 (42). **^{1}H NMR:** (250 MHz, DMSO-d_6) δ [ppm] = 3.21 (s, 3H, 11-H), 3.39 (s, 3H, 12-H), 3.52 (s, 3H, 17-H), 7.00 - 7.50 (m, 5-H, 14 - 16-H), 11.01 (s, 1H, 10-H). **^{13}C NMR:** (62 90 MHz, DMSO-d_6) δ [ppm] = 29.1 (C-12), 30.7 (C-11), 45.6 (C-17), 89.0 (C-4a), 105.8 (C-5a), 120.4 (C-14), 124.1 (C-16), 128.7 (C-15), 140.9 (C-13), 152.2 (C-10a), 155.2 (C-2), 158.9 (C-9a), 162.1 (C-4), 164.2 (C-6), 167.9 (C-8), 185.2 (C-5). **IR:** ν[cm^{-1}] = 3060 (w) (C-H), 2990 (w) (C-H), 1769 (s) (C=O), 1705 (s) (C=O), 1635 (s) (C=O), 1572 (s) (C=O). **CHN:** Found (Required) C 56.82 (56.68), H 3.85 (3.97), N 18.05 (18.37).

1,3-Dimethyl-7(4′-chlorphenyl)-8-methoxypyrimido[5′,6′:5,6]pyrido[2,3-*d*]=pyrimidine-2,4,5,6(1H,3H,7H,10H)tetrone (13c). Like **13a** using p-chlorphenylisocyanate (0.25 g, 1.8 mmol). **Yield:** 70 mg (8.1%). **mp.**: >280°C. **MS:** m/z (rel. Int.): 416 (M^++1, 8), 415 (M^+, 47), 338 (31), 337 (100), 336 (10), 308 (35), 223 (25), 222 (95), 91 (37). **HRMS**: Found (Required) 415.0678 (415.0683). **^{1}H NMR:** (250 MHz, DMSO-d_6) δ [ppm] = 3.10 (s, 3H, 12-H), 3.29 (s, 3H, 11-H), 3.43 (s, 3H, 17-H), 7.00 - 7.50 (m, 4H, 14 - 15-H), 11.22 (s, 1H, 10-H). **^{13}C NMR:** (62.90 MHz, DMSO-d_6) δ [ppm] = 27.5 (C-12), 29.9 (C-11), 48.7 (C-17), 90.5 (C-4a), 107.3 (C-5a), 123.2 (C-14), 130.5 (C-15), 129.6 (C-16), 138.9 (C-13), 153.0 (C-10a), 155.0 (C-2), 158.6 (C-9a), 160.4 (C-4), 166.3 (C-6),

170.8 (C-8), 185.1 (C-5). **IR:** ν [cm^{-1}] = 3080 (w) (C-H), 2960 (w) (C-H), 1700 (s) (C=O), 1630 (s) (C=O), 1590 (s) (C=O), 1570 (s) (C=O).

1,3-Dimethyl-7(4′-methylphenyl)-8-methoxy-5-oximino-10H-pyrimido=[5′,6′:5,6] pyrido[2,3-*d*]pyrimidine-2,4,6(1H,3H,7H)trione (14). 13a (0.4 g, 1 mmol) was treated with hydroxylamine hydrochloride (0.3 g, 4 mmol) in methanol (10 ml, 50%) and refluxed for 4 h. The light yellow product was washed with hot DMF. **Yield:** 0.33 g (86 %). **mp**.: > 380°C. **MS:** m/z (rel. Int.): 412 (M^++2, 10), 410 (M^+, 23), 396 (30), 337 (21), 280 (25), 248 (57), 222 (56), 165 (22), 133 (100), 106 (C_7H_9N, 63), 91 (35), 77 (30). **^{1}H NMR:** (250 MHz, TFA-d) and **^{13}C NMR:** (62.90 MHz, TFA-d): like **15** loosing the O-methyl and tolyl groups. **IR:** ν [cm^{-1}] = 3270 (w) (NH), 2940 (w) (C-H), 2920 (w) (C-H), 1700 (s) (C=O), 1650 (s) (C=O), 1630 (s) (C=O), 1600 (s) (C=O). **CHN** (crude product): Found (Required) C 53.77 (55.49), H 4.72 (4.42), N 21.18 (20.49).

1,3-Dimethyl-5-oximino-10H-pyrimido[5′,6′:5,6]pyrido[2,3-*d*]pyrimidine-2,4,6,8-(1H,3H,7H,9H)tetrone (15). Recrystallization of **14** (0.41 g, 1 mmol) in TFA (5ml) and H_2O (1 ml) gave **15**. **Yield:** 0.26 g (98 %). **mp**.: > 380°C. **MS:** m/z (rel. Int.): 306 (M+, 11), 277 (M - (N=OH), 10), 248 (78), 222 (69), 136 (47), 105 (97), 106 (100), 77 (30). **^{1}H NMR:** (250 MHz, TFA-d) δ [ppm] = 3.36 (s, 3H, 13-H), 3.79 (s, 3H, 12-H). (N-H and O-H protons exchangeable). **^{13}C NMR:** (62.90 MHz, TFA-d) δ [ppm] = 31.8 (C-13), 34.9 (C-12), 100.0 (C-5a), 101.4 (C-4a), 154.5 (C-10a), 154.6 (C-9a), 156.2 (C-8), 157.5 (C-2), 165.3 (C-5), 168.9

(C-4), 174.9 (C-6). **IR:** ν [cm^{-1}] = 3270 (w) (NH), 2940 (w) (C-H), 2920 (w) (C-H), 1700 (s) (C=O), 1650 (s) (C=O), 1630 (s) (C=O), 1600 (s) (C=O).

1,3-Dimethylpyrimido[4,5-*b*]pyrimido[5,4-*f*][1,4]diazepine-2,4,5,7,9(1H,=3H,6H,8H,10H)pentaone (16). 14 (0.21 g, 0.5 mmol) was suspended in acetone (4 ml) and water (1 ml) and treated with toluenesulfonic acid chloride (0.09 g, 0.05 mmol). The reaction was refluxed for 24 h. The light yellow product was recrystallized from TFA/water like **15** giving the trifluoro acetate from **16**. **Yield:** 0.2 g (99%). **mp.**: >300°C. **^{1}H NMR:** (400 MHz, TFA-d) δ [ppm] = 3.72 (s, 3H, 13-H), 4.15 (s, 3H, 12-H). **^{13}C NMR:** (62.90 MHz, TFA-d) δ [ppm] = 31.2 (C-13), 34.2 (C-12), 99.6 (C-4a), 100.9 (C-5a), 125.1 (C-10a), 154.0 (C-11a), 154.9 (C-9), 155.3 (C-2), 157.0 (C-7), 168.6(C-4), 174.5 (C-5). **IR:** ν[cm^{-1}] = 1930 (w) (C-H), 1700 (s) (C=O), 1650 (s) (C=O).

CH: Found (Required) C 38.75 (38.80), H 2.62 (2.50).

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