**Supporting Information**

# Identification of 2-Anilino-9-methoxy-5,7-dihydro-6*H*-pyrimido[5,4-*d*][1]benzazepin-6-ones as Dual PLK1/VEGF-R2 Kinase Inhibitor Chemotypes by Structure-Based Lead Generation

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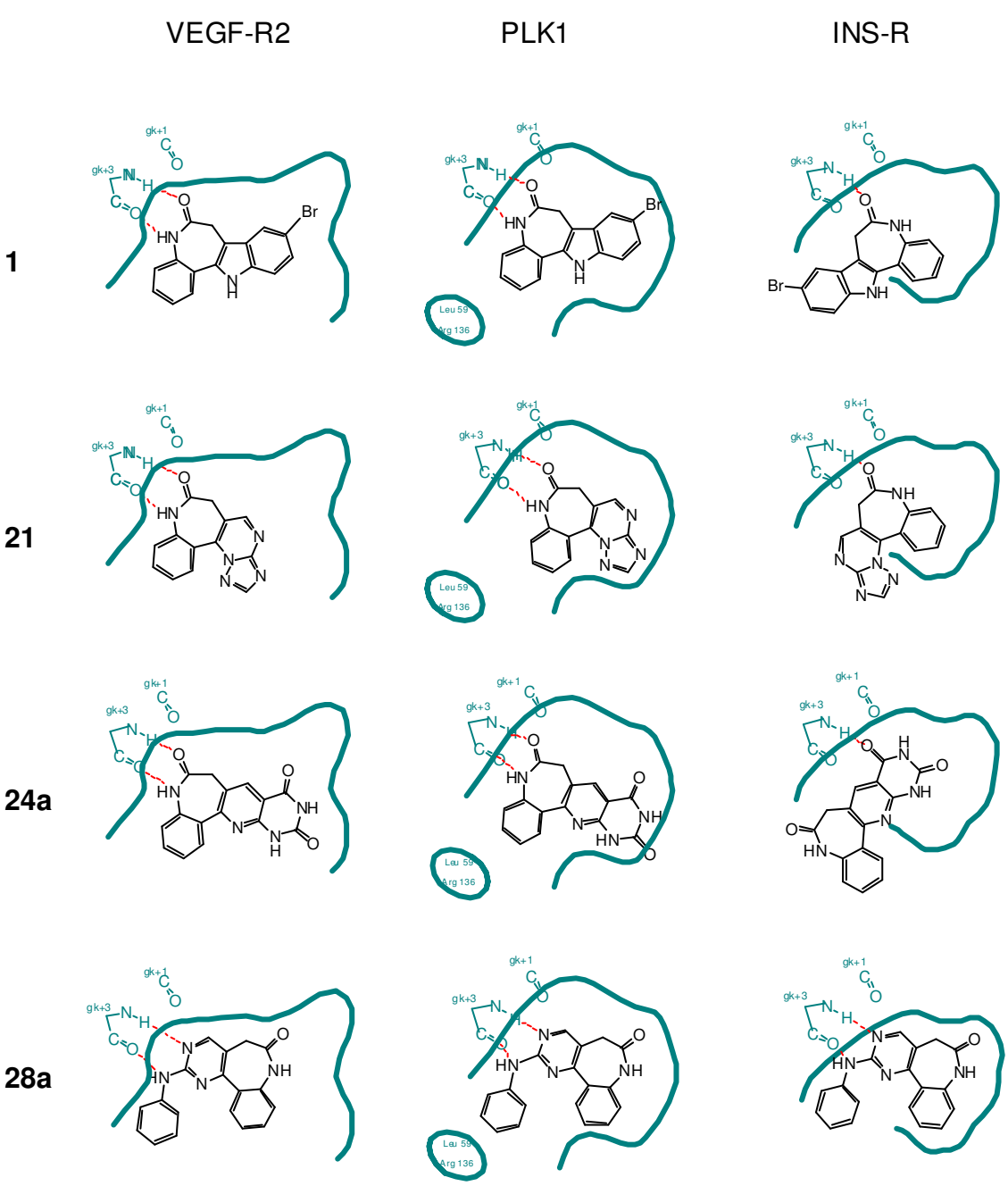


Figure: Simplified 2-D representations of docking poses generated for **1** (kenpaullone, first row), **21** (prototype B, second row), **24a** (prototype C, third row) and **28a** (prototype D, bottom row). Columns correspond to VEGF-R2 (left), PLK1 (middle), and INS-R (right). The following structures were used as basis for the docking: 1YWN (VEGF-R2); 2OWB (PLK1); 3BU6 (INS-R). The sketches were drawn on the basis of the Ligand Interactions module of MOE [1] and slab-mode illustrations

by VIDA [2]. Schrödinger's Glide [3-5] was applied to dock into the binding pockets. The docking generated a list of poses which were evaluated by the Glide XP scoring function. The Figure on page 2 displays sketches of the highest-ranking binding modes for representatives of prototypes B, C and D in the ATP binding sites of VEGF-R2, PLK1, and INS-R, respectively, showing that dependent on the global architecture of the binding pocket rather different poses are favored. Kenpaullone (**1**) was orientated in VEGF-R2 and PLK1 in a mode similar to its proposed position in GSK-3 and the cyclin-dependent kinases. In particular, in this binding fashion the lactam group builds a pair of hydrogen bonds to the amino acid that is located 3 positions carboxyterminal to the gatekeeper residue (the "gk+3" residue). The kenpaullone indole ring points to the inner part of the pocket and the benzene ring annulated to the azepine is directed out of the pocket towards the solvent. In INS-R, the molecule is reoriented with the indol ring pointing out of the ATP binding cleft towards the solvent. Both VEGF-R2 and PLK1 accommodate the majority of the ligands in a "paullone-like" binding fashion, e.g. compounds **21** (representative of prototype B) and **24a** (representative of prototype C). The docking pose of **21** in INS-R is similar to that of kenpaullone **1** in INS-R. In contrast, the docking of **24a** into INS-R places the benzolactam substructure near the pocket entrance, while the carbonyl group in position 9 of the ring system acts as a hydrogen bond acceptor for gk+3. For **28a** (prototype D) a position supported by a pair of hydrogen bonds connecting the anilinopyrimidine partial structure and the gk+3 residue was predicted for the binding to the hinge region of the three investigated protein kinases. The mentioned anilinopyrimidine partial structure is a well known ATP site binding motif known from a number of other kinase inhibitors. [6]

**$^{13}$C-NMR data of 10, 29i, and 29o**

4-[(Dimethylamino)methylidene]-8-methoxy-3,4-dihydro-1*H*-1-benzazepine-2,5-dione (**10**)

$^{13}$C NMR ($CHCl_3$-$d_1$, 100.6 MHz): $\delta$ (ppm) = 44.0 (2C, -$N(CH_3)_2$), 55.5 (-$OCH_3$); 31.7 ($CH_2$); 105.6, 110.9, 133.3, 150.9 (tert. C); 99.7, 125.9, 137.9, 162.3, 173.9, 189.0 (quat. C).

2-(4-Ethoxyanilino)-9-methoxy-5,7-dihydro-6*H*-pyrimido[5,4-*d*][1]benzazepin-6-one (**29i**)

$^{13}$C NMR (DMSO-$d_6$, 150.9 MHz): $\delta$ (ppm) = 14.1 (-$OCH_2CH_3$), 55.7 (-$OCH_3$); 35.7 ($CH_2$), 62.3 (-$OCH_2CH_3$); 105.6, 110.0, 113.6 (2C), 119.7 (2C), 130.7, 156.5 (tert. C); 115.2, 120.9, 133.0, 138.8, 152.6, 158.9, 160.7, 170.7 (quat. C; one signal missing due to peak overlap).

2-(3-Chloro-4-hydroxyanilino)-9-methoxy-5,7-dihydro-6*H*-pyrimido[5,4-*d*][1]benz-azepin-6-one (**29o**)

$^{13}$C NMR (DMSO-$d_6$, 100.6 MHz): $\delta$ (ppm) = 55.4 (-$OCH_3$); 36.4 ($CH_2$); 106.4, 110.6, 116.2, 119.0, 120.2, 131.3, 157.2 (tert. C); 116.4, 121.5, 133.3, 139.5, 147.5, 159.3, 160.5, 161.4, 171.3 (quat. C, one signal missing due to peak overlap).

**General Procedure A for the preparation of enaminones 10, 11, 12**

A slurry of the respective azepinedione **6**, **7** or **8** (1.00 mmol) in DMF-DMA (3.50 mL, 26.0 mmol) was stirred at 115-120 °C for 2.5 h. After cooling to room temperature the resulting precipitate was collected, washed with petrolether and crystallized from ethanol.

4-[(Dimethylamino)methylidene]-3,4-dihydro-1*H*-pyrido[4,3-*b*]azepine-2,5-dione (**11**)

Preparation according to General Procedure A yielded light-red crystals (52%); m.p. 250 °C (dec.); IR (KBr): 3429 $cm^{-1}$ (NH), 1695 $cm^{-1}$ and 1646 $cm^{-1}$ (C=O); $^1$H NMR (DMSO-$d_6$, 400 MHz): $\delta$ (ppm) = 3.24 (s, 6H, -N($CH_3$)$_2$), 3.32 (s, 2H, $CH_2$, superimposed by $H_2O$ peak), 6.98 (d, 1H, *J* = 5.5 Hz, ar. H), 7.64 (s, 1H, C=H), 8.44 (d, 1H, *J* = 5.4 Hz, ar. H), 8.77 (s, 1H, pyridine-H), 10.36 (s, 1H, NH); $^{13}$C NMR (DMSO-$d_6$, 150.9 MHz): $\delta$ (ppm) = 39.6 (2C, -N($CH_3$)$_2$, detectable only in the $^{13}$C-DEPT spektrum); 31.2 ($CH_2$); 114.6, 150.7, 150.9, 152.0 (tert. C); 98.4, 127.1, 143.7, 172.8, 186.2 (quat. C); ($C_{12}H_{13}N_3O_2$) HRMS (EI) (m/z) [$M^+$] calcd 231.10077, found 231.10038; HPLC(MeOH:$H_2O$+$(Et_3NH)_2SO_4$ 10:90): purity: 98.6% at 254 nm, 99.6% at 280 nm; $t_s$: 2.21 min, $t_m$(DMSO): 1.03 min.

8-[(Dimethylamino)methylidene]-7,8-dihydro-5*H*-pyrido[3,2-*b*]azepine-6,9-dione (**12**)

Preparation according to General Procedure A yielded red crystals (42%), m.p. 265 °C (dec.); IR (KBr): 3217 $cm^{-1}$ (NH), 2957 $cm^{-1}$ (CH aliph), 1686 $cm^{-1}$ and 1636 $cm^{-1}$ (C=O); $^1$H NMR (DMSO-$d_6$, 400 MHz): $\delta$ (ppm) = 3.24 (s, 6H, -N($CH_3$)$_2$), 3.33 [$CH_2$, superimposed by $H_2O$ peak, in $CDCl_3$ 3.42 (s, 2H, $CH_2$)], 7.42 (dd, 1H, *J* = 8.3/4.3 Hz, ar. H), 7.45 (dd, 1H, *J* = 8.3/1.8 Hz, ar. H), 7.65 (s, 1H, C=H), 8.42 (dd, 1H, *J* = 8.4/1.8 Hz, ar. H), 9.98 (s, 1H, NH); $^{13}$C NMR (DMSO-$d_6$, 100.6 MHz): $\delta$ (ppm) = 39.3 (2C, -N($CH_3$)$_2$, detectable only in the $^{13}$C-DEPT spectrum); 30.8 ($CH_2$); 125.0, 129.0, 145.1, 150.7 (tert. C); 99.7, 134.3, 148.6, 172.9, 186.2 (quat. C); $C_{12}H_{13}N_3O_2$ HRMS (EI) (m/z) [$M^+$] calcd 231.10077, found 231.10073; HPLC (MeOH:$H_2O$+$(Et_3NH)_2SO_4$ 20:80): purity: 99.6% at 254 nm, 99.8% at 280 nm; $t_N$: 2.76 min; $t_m$(DMSO): 1.03 min.

**General Procedure C for the preparation of the *d*- annulated benzazepinones 17a-b, 18 a-b, 21, 22 and the aza-analogues 19, 20a-b and 23**

A slurry of the enaminone **9**, **10**, **11** or **12** (1.00 mmol) and the respective heterocyclic amine **13a**-**b** or **14** (1.02 mmol) in acetic acid (4 mL) is stirred at 120-140 °C in a sealed microwave reaction vessel in a microwave device. Every 10 min the reaction is monitored by tlc. After completion of the reaction (requires 10-30 min) the reaction mixture is cooled to room temperature and is then poured into 5% aqueous sodium acetate solution (30 mL). The mixture is adjusted to pH 6-7 by addition of 10% sodium hydroxide solution. After further cooling the resulting precipitate is collected, washed with water and petroleum ether and crystallized from the given solvent. If no precipitate is formed, the aqueous phase is extracted with ethyl acetate (4 x 50 mL). The organic layer is dried over $Na_2SO_4$ and evaporated. The residue is purified by crystallization from the given solvent.

6,8-Dihydro-7*H*-pyrazolo[5´,1´:2,3]pyrimido[5,4-*d*][1]benzazepin-7-one (**17a**)

Preparation according to General Procedure C (reaction temperature 120 °C). Crystallization from ethyl acetate yielded 70% yellow crystals; mp.: 285 - 286 °C; IR (KBr): 3206 $cm^{-1}$ (NH Lactam), 1670 $cm^{-1}$ (C=O); $^1$H-NMR (DMSO-$d_6$, 400 MHz): $\delta$ (ppm) = 3.28 (d, 1 H, *J* = 13.6 Hz, $CH_2$,superimposed by HOD signal), 3.68 (dd, 1 H, *J* = 1.8/13.6 Hz, $CH_2$), 6.86 (d, 1 H, *J* = 2.3 Hz, ar. H), 7.34 - 7.38 (m, 2 H, ar. H), 7.63 (ddd, 1 H, *J* = 1.5/7.6/8.1 Hz, ar. H), 8.24 (d, 1 H, *J* = 2.3 Hz, ar. H), 8.49 (dd, 1 H, *J* = 1.5/8.1 Hz, ar. H), 8.65 (s, 1 H, ar. H), 10.41 (s, 1 H, NH lactam); $^{13}$C-NMR (DMSO-d6, 100.6 MHz): $\delta$ (ppm) = 35.8 (sec. C), 97.0, 122.4, 122.8, 130.9, 131.8, 144.2, 149.5 (tert. C), 115.5, 120.6, 138.5, 139.3, 148.5, 172.2 (C lactam) (quat. C); Anal. ($C_{14}H_{10}N_4O$) C, H, N. HPLC (ACN:$H_2O$ 20:80): purity 99.3% at 254 nm, 99.7% at 280 nm; $t_N$: 4.39 min; $t_m$(DMSO): 1.03 min.

2-Phenyl-6,8-dihydro-7*H*-pyrazolo[5´,1´:2,3]pyrimido[5,4-*d*][1]benzazepin-7-one (**17b**)

Preparation according to General Procedure C (reaction temperature 120 °C). Crystallization from ethyl acetate yielded 57% yellow crystals; mp.: 316 - 317 °C; IR (KBr): 3201 $cm^{-1}$ (NH lactam), 1689 $cm^{-1}$ (C=O); $^1$H-NMR (DMSO-$d_6$, 400 MHz): $\delta$

(ppm) = 3.29 (d, 1 H, *J* = 13.6 Hz, $CH_2$), 3.68 (dd, 1 H, *J* = 1.1/13.6 Hz, $CH_2$), 7.35 - 7.52 (m, 6 H, ar. H), 7.66 (ddd, 1 H, *J* = 1.5/8.3/8.7 Hz, ar. H), 8.00 - 8.03 (m, 2 H, ar. H), 8.61 - 8.64 (m, 2 H, ar. H), 10.44 (s, 1 H, NH lactam); $^{13}$C-NMR (DMSO-$d_6$, 100.6 MHz): $\delta$ (ppm) = 35.9 (sec. C), 93.8, 122.5, 122.9, 126.1 (2 C), 128.8 (2 C), 129.0, 130.9, 131.9, 149.6 (tert. C), 115.7, 120.7, 132.4, 138.6, 139.1, 149.8, 154.4, 172.2 (C lactam) (quat. C); Anal ($C_{20}H_{14}N_4O$) C, H, N; HPLC (ACN:$H_2O$ 45:55): purity: 99.9% at 254 nm, 100.0% at 280 nm; $t_N$: 4.69 min; $t_m$(DMSO): 1.04 min.

10-Methoxy-6,8-dihydro-7*H*-pyrazolo[5',1':2,3]pyrimido[5,4-*d*][1]benzazepin-7-one (**18a**)

Preparation according to General Procedure C (reaction time 10 min at 120 °C). Crystallization from EtOH yielded 69% yellow crystals; m.p. 343 °C; IR (KBr): 3200 $cm^{-1}$ (NH), 1681 $cm^{-1}$ (C=O); $^1$H NMR (DMSO-$d_6$, 600 MHz): $\delta$ (ppm) = 3.29 (d, 1H, *J* = 13.7 Hz, $CH_2$), 3.67 (dd, 1H, *J* = 13.8/2.0 Hz, $CH_2$), 3.88 (s, 3H, -$OCH_3$), 6.84 (d, 1H, *J* = 2.4 Hz, ar. H), 6.87 (d, 1H, *J* = 2.7 Hz, ar. H), 7.00 (dd, 1H, *J* = 9.0/2.7 Hz, ar. H), 8.24 (d, 1H, *J* = 2.4 Hz, ar. H), 8.46 (d, 1H, *J* = 9.0 Hz, ar. H), 8.62 (s, 1H, pyrimidine H), 10.38 (s, 1H, NH); $^{13}$C NMR (DMSO-$d_6$, 150.9 MHz): $\delta$ (ppm) = 55.4 ($OCH_3$); 35.8 ($CH_2$); 96.7, 106.5, 109.7, 132.5, 144.0, 149.4 (tert. C); 113.1, 114.2, 139.5, 140.2, 148.5, 161.4, 171.8 (quat. C); ($C_{15}H_{12}N_4O_2$) HRMS (EI) (*m/z*) [$M^+$] calcd 280.09604, found 280.09580; HPLC (ACN:$H_2O$ 25:75): purity: 99.9% at 254 nm, 99.7% at 280 nm; $t_N$: 3.21 min, $t_m$(DMSO): 1.03 min.

10-Methoxy-2-phenyl-6,8-dihydro-7*H*-pyrazolo[5',1':2,3]pyrimido[5,4-*d*][1]benzazepin-7-one (**18b**)

Preparation according to General Procedure C (reaction time 10 min at 120 °C). Crystallization from EtOH yielded 79% yellow crystals; m.p. 324 °C; IR (KBr): 3198 $cm^{-1}$ (NH), 1683 $cm^{-1}$ (C=O); $^1$H NMR (DMSO-$d_6$, 600 MHz): $\delta$ (ppm) = 3.30 (d, 1H, *J* = 14.0 Hz, $CH_2$), 3.67 (dd, 1H, *J* = 14.0/1.9 Hz, $CH_2$), 3.90 (s, 3H, -$OCH_3$), 6.89 (d, 1H, *J* = 2.6 Hz, ar. H), 7.08 (dd, 1H, *J* = 9.0/2.7 Hz, ar. H), 7.34 (s, 1H, ar. H), 7.43 (tt, 1H, *J* = 7.3/1.3 Hz, ar. H), 7.48-7.51 (m, 2H, ar. H), 8.02-8.04 (m, 2H, ar. H), 8.60-8.61 (m, 2H, ar. H), 10.40 (s, 1H, NH); $^{13}$C NMR (DMSO-$d_6$, 150.9 MHz): $\delta$ (ppm) = 55.5 ($OCH_3$); 35.9 ($CH_2$); 93.5, 106.7, 109.6, 126.0 (2C), 128.7 (2C), 128.9, 132.5,

149.5 (tert. C); 113.1, 114.5, 132.4, 139.3, 140.3, 149.7, 154.1, 161.4, 171.8 (quat. C); Anal. ($C_{21}H_{16}N_4O_2$) C, H, N; HPLC (ACN:$H_2O$ 50:50): purity: 99.9% at 254 nm, 100.0% at 280 nm; $t_N$: 3.72 min, $t_m$(DMSO): 1.03 min.

2-Phenyl-6,8-dihydro-7*H*-pyrazolo[5',1':2,3]pyrimido[4,5-*d*]pyrido[4,3-*b*]azepin-7-one (**19**)

Preparation according to General Procedure C (reaction time 10 min at 120 °C). Crystallization from EtOH yielded 62% yellow crystals; m.p. 340 °C; IR (KBr): 3208 $cm^{-1}$ (NH), 1703 $cm^{-1}$ (C=O); $^1$H NMR (DMSO-$d_6$, 600 MHz): $\delta$ (ppm) = 3.45 (d, 1H, *J* = 14.0 Hz, $CH_2$), 3.77 (d, 1H, *J* = 14.0 Hz, $CH_2$), 7.33 (d, 1H, *J* = 5.7 Hz, ar. H), 7.40 (s, 1H, ar. H), 7.44 (tt, 1H, *J* = 7.3/1.4 Hz, ar. H), 7.49-7.51 (m, 2H, ar. H), 8.01-8.03 (m, 2H, ar. H), 8.66 (s, 1H, ar. H), 8.67 (d, 1H, *J* = 5.7 Hz, ar. H), 9.76 (s, 1H, ar. H), 10.92 (s, 1H, NH); $^{13}$C NMR (DMSO-$d_6$, 150.9 MHz): $\delta$ (ppm) = 35.8 ($CH_2$); 94.0, 116.2, 126.1 (2C), 128.8 (2C), 129.1, 149.8, 151.1 152.4 (tert. C); 115.7, 116.1, 132.2, 137.5, 144.8, 149.6, 154.4, 171.6 (quat. C); ($C_{19}H_{13}N_5O$) HRMS (EI) (*m/z*): [M-H]$^+$ calcd 326.10419, found 326.10307; HPLC (ACN:$H_2O$ 35:65): purity: 99.6% at 254 nm, 98.2% at 280 nm; $t_N$: 3.54 min, $t_m$(DMSO): 1.03 min.

6,8-Dihydro-7*H*-pyrazolo[5',1':2,3]pyrimido[4,5-*d*]pyrido[3,2-*b*]azepin-7-one (**20a**)

Preparation according to General Procedure C (reaction time 10 min at 120 °C). Crystallization from EtOH yielded 43% yellow crystals; m.p. 322 °C; IR (KBr): 3196 $cm^{-1}$ (NH), 1685 $cm^{-1}$ (C=O); $^1$H NMR (DMSO-$d_6$, 600 MHz): $\delta$ (ppm) = 3.44 (d, 1H, *J* = 14.3 Hz, $CH_2$), 3.71 (d, 1H, *J* = 14.3 Hz, $CH_2$), 6.88 (d, 1H, *J* = 2.3 Hz, ar. H), 7.67 (dd, 1H, *J* = 8.3/4.5 Hz, ar. H), 7.76 (dd, 1H, *J* = 8.3/1.7 Hz, ar. H), 8.22 (d, 1H, *J* = 2.4 Hz, ar. H), 8.66 (dd, 1H, *J* = 4.5/1.7 Hz, ar. H), 8.69 (s, 1H, pyrimidine H), 10.56 (s, 1H, NH); $^{13}$C NMR (DMSO-$d_6$, 150.9 MHz): $\delta$ (ppm) = 35.5 ($CH_2$); 96.8, 125.8, 130.4, 144.3, 144.6, 149.2 (tert. C); 116.7, 136.0, 138.0, 139.4, 148.6, 172.0 (quat. C); ($C_{13}H_9N_5O$) HRMS (EI) (*m/z*) [$M^{+\bullet}$] calcd 251.08070, found 251.08002; HPLC (ACN:$H_2O$ 10:90): purity: 97.4% at 254 nm, 99.8% at 280 nm; $t_N$: 2.20 min; $t_m$(DMSO): 1.03 min.

2-Phenyl-6,8-dihydro-7*H*-pyrazolo[5',1':2,3]pyrimido[4,5-*d*]pyrido[3,2-*b*]azepin-7-one (**20b**)

Preparation according to General Procedure C (reaction time 10 min at 120 °C). Crystallization from EtOH yielded 72% yellow crystals; m.p. 290 °C; IR (KBr): 3210 $cm^{-1}$ (NH), 1691 $cm^{-1}$ (C=O); $^1$H NMR (DMSO-$d_6$, 600 MHz): $\delta$ (ppm) = 3.46 (d, 1H, *J* = 13.9 Hz, $CH_2$), 3.71 (d, 1H, *J* = 14.1 Hz, $CH_2$), 7.39 (s, 1H, ar. H), 7.42 (tt, 1H, *J* = 7.4/1.4 Hz, ar. H), 7.46-7.49 (m, 2H, ar. H), 7.70 (dd, 1H, *J* = 8.0/4.2 Hz, ar. H), 7.78 (dd, 1H, *J* = 8.2/1.6 Hz, ar. H), 7.97-7.99 (m, 2H, ar. H), 8.68 (s, 1H, ar. H), 8.73 (dd, 1H, *J* = 4.4/1.7 Hz, ar. H), 10.57 (s, 1H, NH); $^{13}$C NMR (DMSO-$d_6$, 150.9 MHz): $\delta$ (ppm) = 35.2 ($CH_2$); 93.3, 125.5, 125.7 (2C), 128.3 (2C), 128.5, 130.1, 144.3, 148.9 (tert. C); 116.5, 131.9, 135.7, 137.5, 139.0, 149.5, 154.1, 171.6 (quat. C); ($C_{19}H_{13}N_5O$) HRMS (EI) (*m/z*) [$M^{+\bullet}$] calcd 327.11200, found 327.11094; HPLC (ACN:$H_2O$ 30:70): purity: 100.0% at 254 nm, 100.0% at 280 nm; $t_N$: 3.44 min, $t_m$(DMSO): 1.03 min.

6,8-Dihydro-7*H*-[1,2,4]triazolo[5´,1´:2,3]pyrimido[5,4-*d*][1]benzazepin-7-one (**21**)

Preparation according to General Procedure C (reaction temperature 140 °C). Crystallization from EtOH yielded 54% yellow crystals; mp.: 285 - 286 °C (starting decomposition), IR (KBr): 3186 $cm^{-1}$ (NH lactam), 1680 $cm^{-1}$ (C=O); $^1$H-NMR (DMSO-$d_6$, 400 MHz): $\delta$ (ppm) = 3.37 (d, 1 H, *J* = 13.9 Hz, $CH_2$, superimposed by HOD-signal), 3.80 (d, 1 H, *J* = 12.6 Hz, $CH_2$), 7.35 - 7.42 (m, 2 H, ar. H), 7.67 (ddd, 1 H, *J* = 1.5/7.3/8.3 Hz, ar. H), 8.45 (dd, 1 H, *J* = 1.5/8.1 Hz, ar. H), 8.70 (s, 1 H, ar. H), 9.00 (s, 1 H, ar. H), 10.50 (s, 1 H, NH Lactam); $^{13}$C-NMR (DMSO-$d_6$, 100.6 MHz): $\delta$ (ppm) = 35.8 (sec. C), 122.5, 123.0, 131.1, 132.5, 154.8, 155.4 (tert. C), 117.6, 119.9, 138.7, 141.4, 154.9, 171.7 (C lactam) (quat. C); ($C_{13}H_9N_5O$) MS (EI): m/z (%) = 251 (100) $[M]^{+\cdot}$; HRMS (EI): (m/z) $[M]^{+\bullet}$ calcd. 251.0807; found 251.0802; HPLC (ACN:$H_2O$ 15:85): purity 98.8% at 254 nm, 99.9% at 280 nm; $t_N$: 3.41 min; $t_m$(DMSO): 1.06 min.

10-Methoxy-6,8-dihydro-7*H*-[1,2,4]triazolo[5',1':2,3]pyrimido[5,4-*d*][1]benzazepin-7-one (**22**)

Preparation according to General Procedure C (reaction time 20 min at 140 °C). Crystallization from EtOH yielded 72% light yellow crystals; m.p. 296 °C; IR (KBr): 3206 $cm^{-1}$ (NH), 1682 $cm^{-1}$ (C=O); $^1$H NMR (DMSO-$d_6$, 400 MHz): $\delta$ (ppm) = 3.37 (d, 1H, *J* = 14.1 Hz, $CH_2$), 3.79 (d, 1H, *J* = 14.1 Hz, $CH_2$), 3.88 (s, 3H, -$OCH_3$), 6.89 (d, 1H, *J* = 2.5 Hz, ar. H), 7.03 (dd, 1H, *J* = 9.3/2.6 Hz, ar. H), 8.42 (d, 1H, *J* = 9.1 Hz, ar. H), 8.67 (s, 1H, ar. H), 8.94 (s, 1H, ar. H), 10.42 (s, 1H, NH); $^{13}$C NMR (DMSO-$d_6$, 100.6 MHz): $\delta$ (ppm) = 55.6 (-$OCH_3$); 35.9 ($CH_2$); 106.6, 110.0, 132.7, 154.6, 155.2 (tert. C); 112.4, 116.3, 140.6, 141.6, 155.0, 162.0, 171.3 (quat. C); ($C_{14}H_{11}N_5O_2$) HRMS (EI) (*m/z*) [$M^{+\bullet}$] calcd 281.09128, found 281.09092; HPLC (ACN:$H_2O$ 15:85): purity: 97.0% at 254 nm, 97.8% at 280 nm; $t_N$: 2.64 min; $t_m$(DMSO): 1.03 min.

6,8-Dihydro-7*H*-pyrido[3,2-*b*][1,2,4]triazolo[5',1':2,3]pyrimido[4,5-*d*]azepin-7-one (**23**)

Preparation according to General Procedure C (reaction time 10 min at 140 °C). Extraction with ethylacetate and crystallization from EtOH yielded 19% red-brown crystals; m.p. 325 °C; IR (KBr): 3117 $cm^{-1}$ (NH), 3070 $cm^{-1}$ and 3029 $cm^{-1}$ (CH arom), 2894 $cm^{-1}$ (CH aliph), 1696 $cm^{-1}$ (C=O); $^1$H NMR (DMSO-$d_6$, 600 MHz): $\delta$ (ppm) = 3.55 (d, 1H, *J* = 14.3 Hz, $CH_2$), 3.84 (d, 1H, *J* = 14.3 Hz, $CH_2$), 7.72 (dd, 1H, *J* = 8.4/4.5 Hz, ar. H), 7.78 (dd, 1H, *J* = 8.3/1.5 Hz, ar. H), 8.68 (s, 1H, ar. H), 8.70 (dd, 1H, *J* = 4.3/1.6 Hz, ar. H), 9.06 (s, 1H, ar. H), 10.67 (s, 1H, NH); $^{13}$C NMR (DMSO-$d_6$, 150.9 MHz): $\delta$ (ppm) = 34.7 ($CH_2$); 125.5, 129.7, 144.1, 154.1, 154.7 (tert. C); 118.0, 135.6, 137.5, 139.2, 154.2, 170.6 (quat. C); ($C_{12}H_8N_6O$) HRMS (EI) (*m/z*) [$M^{+\bullet}$] calcd 252.07597, found 252.07544; HPLC (MeOH:$H_2O$+$(Et_3NH)_2SO_4$ 10:90): purity: 98.6% at 254 nm, 99.2% at 280 nm; $t_N$: 3.23 min; $t_m$(DMSO): 1.03 min.

**General Procedure D for the preparation of 7,12-dihydro-5*H*-pyrimido[5',4':5,6]-pyrido[3,2-*d*][1]benzazepine-6,9,11(10*H*)-triones 24 and 25 and the aza-analogues 26 and 27**

The enaminone **9**, **10**, **11** or **12** (1.00 mmol) was refluxed with the respective 6-aminouracil (1.00 mmol) in acetic acid (8 mL) for 4-12 h. After cooling to room

temperature, the mixture was poured into 5% aqueous sodium acetate solution (30 mL). The resulting precipitate was collected, washed with water and petroleum ether and crystallized from the given solvent.

7,12-Dihydro-5*H*-pyrimido[5',4':5,6]pyrido[3,2-*d*][1]benzazepine-6,9,11(10*H*)-trione (**24a**)

Preparation according to General Procedure D (reaction time 4 h). Crystallization from DMF yielded 54% light yellow powder; m.p. > 395 °C; IR (KBr): 3442 $cm^{-1}$ and 3180 $cm^{-1}$ (NH), 1734 $cm^{-1}$ and 1672 $cm^{-1}$ (C=O); $^1$H NMR (DMSO-$d_6$, 600 MHz): $\delta$ (ppm) = 3.54 (s, 2H, $CH_2$), 7.23 (dd, 1H, *J* = 8.0/1.0 Hz, ar. H), 7.30-7.35 (m, 1H, ar. H), 7.55 (dt, 1H, *J* = 7.9/1.6 Hz, ar. H), 7.98 (dd, 1H, *J* = 8.0/1.6 Hz, ar. H), 8.31 (s, 1H, pyridine H), 10.27 (s, 1H, NH, signal disappears on addition of $D_2O$), 11.47 (s, 1H, NH, signal disappears on addition of $D_2O$), 11.73 (s, 1H, NH, signal disappeares on $D_2O$ addition); $^{13}$C NMR (DMSO-$d_6$, 150.9 MHz): $\delta$ (ppm) = 38.3 ($CH_2$); 121.3, 123.1, 130.2, 130.3, 135.8 (tert. C); 108.7, 124.0, 128.6, 137.2, 149.8, 150.6, 157.1, 161.5, 170.5 (quat. C); ($C_{15}H_{10}N_4O_3$) HRMS (EI) (*m/z*) [$M^{+\bullet}$] calcd 294.07529, found 294.07483; HPLC (ACN:$H_2O$ 15:85): purity: 100.0% at 254 nm, 99.9% at 280 nm; $t_N$: 1.99 min, $t_m$(DMSO): 1.03 min.

10,12-Dimethyl-7,12-dihydro-5*H*-pyrimido[5',4':5,6]pyrido[3,2-*d*][1]benzazepine-6,9,11-(10*H*)-trione (**24b**)

Preparation according to General Procedure D (reaction time 4 h). Crystallization from EtOH yielded 50% light yellow powder; m.p. > 385 °C (dec.); IR (KBr): 3188 $cm^{-1}$ (NH), 1717 $cm^{-1}$, 1702 $cm^{-1}$ and 1662 $cm^{-1}$ (C=O); $^1$H NMR (DMSO-$d_6$, 600 MHz): $\delta$ (ppm) = 3.33 (s, 3H, -$NCH_3$), 3.65 (s, 3H, -$NCH_3$), 3.60 (s, 2H, $CH_2$), 7.24 (d, 1H, *J* = 8.1 Hz, ar. H), 7.36 (dt, 1H, *J* = 8.4/1.1 Hz, ar. H), 7.57 (ddd, 1H, *J* = 8.0/7.3/1.6 Hz, ar. H), 8.11 (dd, 1H, *J* = 7.9/1.4 Hz, ar. H), 8.44 (s, 1H, pyridine H), 10.34 (s, 1H, NH); $^{13}$C NMR (DMSO-$d_6$, 150.9 MHz): $\delta$ (ppm) = 28.5 (-$NCH_3$), 29.6 (-$NCH_3$); 39.1 ($CH_2$); 122.3, 124.4, 131.2, 131.4, 137.4 (tert. C); 110.1, 125.0, 129.6, 138.3, 149.8, 151.4, 157.4, 161.1, 171.5 (quat. C); ($C_{17}H_{14}N_4O_3$) HRMS (EI) (*m/z*): calcd 322.10657, found 322.10643; HPLC (ACN:$H_2O$ 25:75): purity: 99.7% at 254 nm, 99.6% at 280 nm; $t_N$: 3.96 min, $t_m$(DMSO): 1.03 min.

3-Methoxy-7,12-dihydro-5*H*-pyrimido[5',4':5,6]pyrido[3,2-*d*][1]benzazepine-6,9,11-(10*H*)-trione (**25a**)

Preparation according to General Procedure D (reaction time 6 h). Crystallization from EtOH yielded 38% yellow powder; m.p. > 380 °C (dec.); IR (KBr): 3434 $cm^{-1}$ and 3200 $cm^{-1}$ (NH), 1729 $cm^{-1}$, 1701 $cm^{-1}$ and 1684 $cm^{-1}$ (C=O); $^1$H NMR (DMSO-$d_6$, 600 MHz): $\delta$ (ppm) = 3.83 (s, 3H, -$OCH_3$), 3.53 (s, 2H, $CH_2$), 6.76 (d, 1H, *J* = 2.5 Hz, ar. H), 6.95 (dd, 1H, *J* = 8.8/2.5 Hz, ar. H), 7.93 (d, 1H, *J* = 8.8 Hz, ar. H), 8.26 (s, 1H, pyridine H), 10.22 (s, 1H, NH), 11.45 (s, 1H, NH), 11.70 (s, 1H, NH); $^{13}$C NMR (DMSO-$d_6$, 150.9 MHz): $\delta$ (ppm) = 56.3 (-$OCH_3$); 40.0 ($CH_2$); 107.0, 111.6, 133.2, 137.3, (tert. C); 109.6, 123.0, 124.6, 140.2, 151.4, 152.2, 158.7, 162.1, 163.1, 171.8 (quat. C); ($C_{16}H_{12}N_4O_4$) HRMS (EI) (*m/z*) [$M^{+\bullet}$] calcd 324.08588, found 324.08525; HPLC (ACN:$H_2O$ 15:85): purity: 98.9% at 254 nm, 95.1% at 280 nm; $t_N$: 2.60 min; $t_m$(DMSO): 1.03 min.

3-Methoxy-10,12-dimethyl-7,12-dihydro-5*H*-pyrimido[5',4':5,6]pyrido[3,2-*d*][1]benz-azepine-6,9,11(10*H*)-trione (**25b**)

Preparation according to General Procedure D (reaction time 5 h). Crystallization from EtOH yielded 59% beige powder; m.p. > 390; IR (KBr): 3196 $cm^{-1}$ (NH), 3097 $cm^{-1}$ and 3066 $cm^{-1}$ (CH arom), 2953 $cm^{-1}$ and 2926 $cm^{-1}$ (CH aliph), 1718 $cm^{-1}$, 1703 $cm^{-1}$ and 1668 $cm^{-1}$ (C=O); $^1$H NMR (DMSO-$d_6$, 600 MHz): $\delta$ (ppm) = 3.33 (s, 3H, -$NCH_3$), 3.64 (s, 3H, -$NCH_3$), 3.84 (s, 3H, -$OCH_3$), 3.40 (azepine $CH_2$ superimposed by $H_2O$ peak), 6.77 (d, 1H, *J* = 2.7 Hz, ar. H), 6.97 (dd, 1H, *J* =8.8/2.8 Hz, ar. H), 8.07 (d, 1H, *J* = 8.8 Hz, ar. H), 8.39 (s, 1H, pyridine H), 10.27 (s, 1H, NH); ($C_{18}H_{16}N_4O_4$) HRMS (EI) (*m/z*) [$M^{+\bullet}$] calcd 352.11713, found 352.11625; HPLC: (ACN:$H_2O$ 30:70) purity: 99.2% at 254 nm, 98.4% at 280 nm; $t_s$: 6.10 min; $t_m$(DMSO): 1.03 min.

7,12-Dihydro-5*H*-pyrido[4,3-*b*]pyrimido[5',4':5,6]pyrido[2,3-*d*]azepine-6,9,11(10*H*)-trione (**26a**)

Preparation according to General Procedure D (reaction time 12 h). Crystallization from EtOH yielded 41% light yellow powder; m.p. > 395 °C (dec.); IR (KBr): 3512 $cm^{-1}$, 3414 $cm^{-1}$ and 3181 $cm^{-1}$ (NH), 1696 $cm^{-1}$ (C=O); $^1$H NMR (DMSO-$d_6$, 400 MHz): $\delta$

(ppm) = 3.66 (s, 2H, $CH_2$), 7.17 (d, 1H, *J* = 5.5 Hz, ar. H), 8.36 (s, 1H, pyridine H), 8.57 (d, 1H, *J* = 5.3 Hz, ar. H), 9.08 (s, 1H, pyridine H), 10.69 (s, 1H, NH), 11.49 (s, 1H, NH), 11.78 (s, 1H, NH); $^{13}$C NMR (DMSO-$d_6$, 150.9 MHz): δ (ppm) = 38.8 ($CH_2$); 115.2, 136.9, 150.6, 151.7 (tert. C); 109.8, 123.9, 124.4, 144.2, 150.4, 151.3, 155.6, 162.0, 171.0 (quat. C); ($C_{14}H_9N_5O_3$) HRMS (EI) (*m/z*) [$M^{+\bullet}$] calcd 295.07053; found 295.07033; HPLC (MeOH:$H_2O$ 20:80): purity: 96.9% at 254 nm, 95.0% at 280 nm; $t_N$: 5.74 min; $t_m$(DMSO): 1.03 min.

10,12-Dimethyl-7,12-dihydro-5*H*-pyrido[4,3-*b*]pyrimido[5',4':5,6]pyrido[2,3-*d*]azepine-6,9,11(10*H*)-trione (**26b**)

Preparation according to General Procedure D (reaction time 7 h). Crystallization from EtOH yielded 42% beige powder; m.p. > 390 °C (degradation); IR (KBr): 3187 $cm^{-1}$ (NH), 3043 $cm^{-1}$ (CH arom.), 2940 $cm^{-1}$ (CH aliph), 1716 $cm^{-1}$ and 1681 $cm^{-1}$ (C=O); $^1$H NMR (DMSO-$d_6$, 400 MHz): δ (ppm) = 3.34 (s, 3H, -$NCH_3$, partly superimposed by $H_2O$ peak), 3.66 (s, 3H, -$NCH_3$), 3.72 (s, 2H, $CH_2$), 7.19 (d, 1H, *J* = 5.5 Hz, ar. H), 8.49 (s, 1H, pyridine H), 8.60 (d, 1H, *J* = 5.4 Hz, ar. H), 9.22 (s, 1H, pyridine H), 10.73 (s, 1H, NH); $^{13}$C NMR (DMSO-$d_6$, 150.9 MHz): δ (ppm) = 28.1 (-$NCH_3$), 29.2 (-$NCH_3$); 38.6 ($CH_2$); 115.3, 137.5, 150.7, 151.8 (tert. C); 110.1, 124.1, 124.4, 144.2, 149.5, 151.0, 154.9, 160.6, 170.9 (quat. C); ($C_{16}H_{13}N_5O_3$) HRMS (EI) (*m/z*) [$M^{+\bullet}$] calcd 323.10184, found 323.10152; HPLC(ACN:$H_2O$ 20:80): purity: 99.7% at 254 nm, 99.3% at 280 nm; $t_s$: 3.20 min, $t_m$(DMSO): 1.03 min.

7,12-Dihydro-5*H*-pyrido[3,2-*b*]pyrimido[5',4':5,6]pyrido[2,3-*d*]azepine-6,9,11(10*H*)-trione (**27a**)

Preparation according to General Procedure D (reaction time 8 h). Crystallization from EtOH yielded 50% brown powder; m.p. > 380 °C (dec.); IR (KBr): 3440 $cm^{-1}$, 3164 $cm^{-1}$ and 3123 $cm^{-1}$ (NH), 1691 $cm^{-1}$ (C=O); $^1$H NMR (DMSO-$d_6$, 600 MHz): δ (ppm) = 3.62 (s, 2H, $CH_2$), 7.59 (dd, 1H, *J* = 8.2/4.3 Hz, ar. H), 7.64 (dd, 1H, *J* = 8.3/1.7 Hz, ar. H), 8.37 (s, 1H, pyridine H), 8.60 (dd, 1H, *J* = 4.4/1.7 Hz, ar. H), 10.38 (s, 1H, NH), 11.53 (s, 1H, NH), 11.90 (s, 1H, NH); $^{13}$C NMR (DMSO-$d_6$, 150.9 MHz): δ (ppm) = 38.5 ($CH_2$); 125.0, 129.9, 136.5, 145.3 (tert. C); 110.1, 125.6, 135.2, 145.3, 150.4, 151.5, 156.8, 162.1, 171.3 (quat. C); ($C_{14}H_9N_5O_3$) HRMS (EI) (*m/z*) [$M^{+\bullet}$] calcd

295.07053, found 295.07046; HPLC (MeOH:$H_2O$ 20:80): purity: 99.7% at 254 nm, 98.9% at 280 nm; $t_N$: 2.69 min, $t_m$(DMSO): 1.03 min.

10,12-Dimethyl-7,12-dihydro-5*H*-pyrido[3,2-*b*]pyrimido[5',4':5,6]pyrido[2,3-*d*]azepine-6,9,11(10*H*)-trione (**27b**)

Preparation according to General Procedure D (reaction time 7 h). Crystallization from EtOH yielded 39% light brown powder; m.p. > 390 °C (dec.); IR (KBr): 3429 $cm^{-1}$ (NH), 1715 $cm^{-1}$, 1698 $cm^{-1}$ and 1663 $cm^{-1}$ (C=O); $^1$H NMR (DMSO-$d_6$, 400 MHz): $\delta$ (ppm) = 3.63 (s, 3H, -$NCH_3$), (second $NCH_3$ superimposed by $H_2O$ peak), 3.66 (s, 2H, $CH_2$), 7.60 (dd, 1H, *J* = 8.3/4.4 Hz, ar. H), 7.65 (dd, 1H, *J* = 8.2/1.6 Hz, ar. H), 8.47 (s, 1H, pyridine H), 8.65 (dd, 1H, *J* = 4.4/1.5 Hz, ar. H), 10.34 (s, 1H, NH); $^{13}$C NMR (DMSO-$d_6$, 150.9 MHz): $\delta$ (ppm) = 28.1 (-$NCH_3$), 29.2 (-$NCH_3$); 38.3 ($CH_2$); 125.0, 129.9, 137.1, 145.6 (tert. C); 110.5, 125.7, 135.4, 145.4, 149.6, 151.0, 156.0, 160.7, 171.3 (quat. C); ($C_{16}H_{13}N_5O_3$) HRMS (EI) (*m/z*) [$M^{+\bullet}$] calcd. 323.10184, found 323.10089; HPLC (ACN:$H_2O$ 15:85): purity: 99.9% at 254 nm, 98.0% at 280 nm; $t_N$: 2.64 min, $t_m$(DMSO): 1.03 min.

**General Procedure B for the synthesis of 2-anilino-5,7-dihydro-6*H*-pyrimido[5,4-*d*][1]-benzazepin-6-ones 28 and 29 and the analogues 30 and 31**

Method 1

The enaminone **9**, **10**, **11** or **12** (1.00 mmol) was refluxed with the respective arylguanidinium nitrate **16** (1.2 mmol) and NaOH (48 mg, 1.2 mmol) in propan-2-ol (5 mL) for the indicated reaction time. After cooling to room temperature, the resulting precipitate was collected and successively washed with water and petrolether.

Method 2

The enaminone **9** (1.00 mmol) was reacted with the respective arylguanidinium nitrate **16** (1.2 mmol) and NaOH (48 mg, 1.2 mmol) in propan-2-ol (5 mL). The reaction was conducted in a microwave device using a sealed microwave reaction vessel for 30-40 min at 150 °C. After cooling to room temperature, the resulting precipitate was collected and successively washed with water and petrolether.

2-Anilino-5,7-dihydro-6*H*-pyrimido[5,4-*d*][1]benzazepin-6-one (**28a**)

Preparation according to General Procedure B, method 1 (reaction time 6 h). Crystallization from EtOH yielded 60% colorless crystals; mp. 286-287 °C; IR (KBr): 3255 $cm^{-1}$, 3194 $cm^{-1}$ (NH), 3066 $cm^{-1}$, 1673 $cm^{-1}$ (C=O); $^1$H-NMR (DMSO-$d_6$, 400 MHz): $\delta$ (ppm) = 3.38 (s, 2H, $CH_2$), 6.95 (ddd, 1H, *J* = 7.3/7.3/1.0 Hz, ar. H), 7.03 (dd, 1H, *J* = 8.2/1.0 Hz, ar. H), 7.28-7.37 (m, 3H, ar. H), 7.56 (ddd, 1H, *J* = 8.1/8.3/1.5 Hz, ar. H), 7.82-7.84 (m, 2H, ar. H), 8.08 (dd, 1H, *J* = 7.8/1.5 Hz, ar. H), 8.51 (s, 1H, ar. H), 9.73 (s, 1H, NH), 10.25 (s, 1H, NH); $^{13}$C-NMR (DMSO-$d_6$, 100.6 MHz): $\delta$ (ppm) = 36.2 ($CH_2$); 118.7 (2C), 121.3, 122.1, 123.9, 128.5 (2C), 129.8, 131.2, 157.4 (tert. C); 117.4, 128.7, 138.1, 140.6, 159.4, 160.6, 171.6 (quat. C); Anal. ($C_{18}H_{14}N_4O$) H, N; C calcd. 71.51, C found 71.19; HPLC (ACN:$H_2O$ 40:60): purity 99.9% at 254 nm, 99.9% at 280 nm; $t_N$: 3.18 min; $t_m$(DMSO): 1.03 min.

2-(4-Iodoanilino)-5,7-dihydro-6*H*-pyrimido[5,4-*d*][1]benzazepin-6-one (**28b**)

Preparation according to General Procedure B, method 2 (reaction time 45 min). Crystallization from EtOH yielded 47% yellow-green crystals; mp.: 295 °C (dec.); IR (KBr): 3266 $cm^{-1}$ and 3186 $cm^{-1}$ (NH), 1673 $cm^{-1}$ (C=O); $^1$H-NMR (DMSO-$d_6$, 400 MHz): $\delta$ (ppm) = 3.38 (s, 2H, $CH_2$), 7.23 (dd, 1H, *J* = 8.0/0.9 Hz, ar. H), 7.35 (ddd, 1H, *J* = 8.0/7.2/0.9 Hz, ar. H), 7.56 (ddd, 1H, *J* = 8.2/7.2/1.6 Hz, ar. H), 7.60-7.62 (m, 2H, ar. H), 7.67-7.70 (m, 2H, ar. H), 8.06 (dd, 1H, *J* = 8.2/1.4 Hz, ar. H), 8.53 (s, 1H, ar. H), 9.87 (s, 1H, NH), 10.24 (s, 1H, NH); Anal. ($C_{18}H_{13}IN_4O$) C, H, N; HPLC (ACN:$H_2O$ 50:50): purity: 97.0% at 254 nm, 97.5% at 280 nm; $t_N$: 3.70 min; $t_m$(DMSO): 1.02 min.

2-(4-Methoxyanilino)-5,7-dihydro-6*H*-pyrimido[5,4-*d*][1]benzazepin-6-one (**28c**)

Preparation according to General Procedure B, method 1 (reaction time 9 h). Crystallization from EtOH yielded 64%light green crystals; mp. 262-263 °C; IR (KBr): 3271 $cm^{-1}$, 3195 $cm^{-1}$ (NH), 1681 $cm^{-1}$ (C=O); $^1$H-NMR (DMSO-$d_6$, 400 MHz): $\delta$ (ppm) = 3.35 (s, 2H, $CH_2$), 3.73 (s, 3H, $OCH_3$), 6.87-6.91 (m, 2H, ar. H), 7.23 (dd, 1H, *J* = 8.1/0.8 Hz, ar. H), 7.33 (ddd, 1H, *J* = 8.3/7.9/1.1 Hz, ar. H), 7.55 (ddd, 1H, *J* = 8.1/7.7/1.6 Hz, ar. H), 7.68-7.72 (m, 2H, ar. H), 8.05 (dd, 1H, *J* = 7.9/1.5 Hz, ar. H),

8.45 (s, 1H, ar. H), 9.53 (s, 1H, NH), 10.22 (s, 1H, NH); $^{13}$C-NMR (DMSO-$d_6$, 100.6 MHz): δ (ppm) = 36.2 ($CH_2$); 55.1 ($OCH_3$); 113.7 (2C), 120.5 (2C), 122.0, 123.9, 129.8, 131.1, 157.4 (tert. C); 116.9, 128.9, 133.7, 134.1, 138.0, 154.1, 159.6, 171.7 (quat. C); Anal. ($C_{19}H_{16}N_4O_2$) C, H, N; HPLC (ACN:$H_2O$ 35:65): purity 99.4% at 254 nm, 99.6% at 280 nm; $t_N$: 3.05 min; $t_m$(DMSO): 1.04 min.

2-(4-Chloroanilino)-5,7-dihydro-6*H*-pyrimido[5,4-*d*][1]benzazepin-6-one (**28d**)

Preparation according to General Procedure B, method 2 (reaction time 40 min). Crystallization from EtOH yielded 61% colorless crystals; mp.: 297-299 °C; IR (KBr): 3268 cm$^{-1}$, 3192 cm$^{-1}$ (NH), 1679 cm$^{-1}$ (C=O); $^1$H-NMR (DMSO-$d_6$, 400 MHz): δ (ppm) = 3.38 (s, 2H, $CH_2$), 7.23 (dd, 1H, *J* = 8.1/0.7 Hz, ar. H), 7.33-7.37 (m, 3H, ar. H), 7.56 (ddd, 1H, *J* = 8.1/7.3/1.6 Hz, ar. H), 7.84-7.88 (m, 2H, ar. H), 8.06 (dd, 1H, *J* = 7.9/1.5 Hz, ar. H), 8.31 (s, 1H, ar. H), 9.90 (s, 1H, NH), 10.25 (s, 1H, NH); Anal. ($C_{18}H_{13}ClN_4O$) C, H, N; HPLC (ACN:$H_2O$ 40:60): purity 99.8% at 254 nm, 100.0 % at 280 nm, $t_N$: 5.81 min; $t_m$(DMSO): 1.03 min.

2-(4-Nitroanilino)-5,7-dihydro-6*H*-pyrimido[5,4-*d*][1]benzazepin-6-one (**28e**)

Preparation according to General Procedure B, method 2 (reaction time 60 min). Washing with hot EtOH yielded 65% of a light brown powder; mp.: 325-326 °C (dec.); IR (KBr): 3272 cm$^{-1}$ and 3197 cm$^{-1}$ (NH), 1670 cm$^{-1}$ (C=O); $^1$H-NMR (DMSO-$d_6$, 400 MHz): δ (ppm) = 3.44 (s, 2H, $CH_2$), 7.26 (dd, 1H, *J* = 8.1/0.8 Hz, ar. H), 7.38 (ddd, 1H, *J* = 7.8/7.3/1.0 Hz, ar. H), 7.59 (ddd, 1H, *J* = 8.1/7.3/1.5 Hz, ar. H), 8.06-8.11 (m, 2H, ar. H and dd, 1H, *J* = 7.8/1.5 Hz, ar. H; superimposed), 8.20-8.24 (m, 2H, ar. H ), 8.65 (s, 1H, ar. H), 10.29 (s, 1H, NH), 10.57 (s, 1H, NH); Anal. ($C_{18}H_{13}N_5O_3$) C, H, N; HPLC (ACN:$H_2O$ 30:70): purity: 99.5% at 254 nm, 98.6% at 280 nm; $t_N$: 3.00 min.; $t_m$(DMSO): 1.03 min.

2-(4-Methylanilino)-5,7-dihydro-6*H*-pyrimido[5,4-*d*][1]benzazepin-6-one (**28f**)

Preparation according to General Procedure B, method 2 (reaction time 45 min). Crystallization from EtOH yielded 48% yellow crystals, mp.: 287-289 °C; IR (KBr): 3279 cm$^{-1}$, 3189 cm$^{-1}$ (NH), 1683 cm$^{-1}$ (C=O); $^1$H-NMR (DMSO-$d_6$, 400 MHz): δ (ppm)

= 2.25 (s, 3H, $CH_3$), 3.35 (s, 2H, $CH_2$), 7.09-7.11 (m, 2H, ar. H), 7.23 (dd, 1H, *J* = 8.1/0.8 Hz, ar. H), 7.34 (ddd, 1H, *J* = 7.8/7.3/1.0 Hz, ar. H), 7.55 (ddd, 1H, *J* = 8.1/7.3/1.5 Hz, ar. H), 7.68-7.70 (m, 2H, ar. H), 8.06 (dd, 1H, *J* = 7.8/1.5 Hz, ar. H), 8.48 (s, 1H, ar. H), 9.60 (s, 1H, NH), 10.21 (s, 1H, NH); Anal. ($C_{19}H_{16}N_4O$) C, H, N; HPLC (ACN:$H_2O$ 45:55): purity: 99.6% at 254 nm, 99.8% at 280 nm; $t_N$: 1.95 min; $t_m$(DMSO): 1.02 min.

2-(4-Hydroxyanilino)-5,7-dihydro-6*H*-pyrimido[5,4-*d*][1]benzazepin-6-one (**28g**)

Preparation according to General Procedure B, method 2 (reaction time 30 min). Crystallization from EtOH yielded 71% yellow-green crystals; mp.: 356-357 °C; IR (KBr): 3260 $cm^{-1}$ and 3198 $cm^{-1}$ (NH; OH broad, overlapping), 1659 $cm^{-1}$ (C=O); $^1$H-NMR (DMSO-$d_6$, 400 MHz): $\delta$ (ppm) = 3.32 (s, 2H, $CH_2$ partially superimposed by HOD signal), 6.69-6.72 (m, 2H, ar. H), 7.23 (dd, 1H, *J* = 8.1/1.0 Hz, ar. H), 7.32 (ddd, 1H, *J* = 8.1/7.1/1.0 Hz, ar. H), 7.51-7.55 (m, 3H, ar. H), 8.03 (dd, 1H, *J* = 7.8/1.5 Hz, ar. H), 8.41 (s, 1H, ar. H), 9.01 (s, 1H, OH), 9.35 (s, 1H, NH), 10.18 (s, 1H, NH); Anal. ($C_{18}H_{14}N_4O_2$) [318.33]: C, H; N; HPLC (ACN:$H_2O$/TFA mixture pH 1.5 25:75): purity 98.4% at 254 nm, 99.8% at 280 nm; $t_N$: 2.21 min; $t_m$(DMSO): 1.04 min.

2-(4-Bromoanilino)-5,7-dihydro-6*H*-pyrimido[5,4-*d*][1]benzazepin-6-one (**28h**)

Preparation according to General Procedure B, method 2 (reaction time 30 min). Crystallization from ethyl acetate yielded 28% of a light brown powder; mp.: 303 °C; IR (KBr): 3263 $cm^{-1}$ and 3192 $cm^{-1}$ (NH), 1673 $cm^{-1}$ (C=O); $^1$H-NMR (DMSO-$d_6$, 400 MHz): $\delta$ (ppm) = 3.38 (s, 2H, $CH_2$), 7.24 (dd, 1H, *J* = 8.1/0.8 Hz, ar. H), 7.35 (ddd, 1H, *J* = 7.8/7.3/1.0 Hz, ar. H), 7.45-7.49 (m, 2H, ar. H), 7.56 (ddd, 1H, *J* = 8.1/7.1/1.5 Hz, ar. H), 7.79-7.83 (m, 2H, ar. H), 8.07 (dd, 1H, *J* = 7.8/1.5 Hz, ar. H), 8.53 (s, 1H, ar. H), 9.90 (s, 1H, NH), 10.25 (s, 1H, NH); Anal. ($C_{18}H_{13}BrN_4O$) C, H. N; HPLC (ACN:$H_2O$ 50:50): purity 100.0% at 254, 100.0% at 280 nm; $t_N$: 4.49 min; $t_m$(DMSO): 1.02 min.

2-(4-Ethoxyanilino)-5,7-dihydro-6*H*-pyrimido[5,4-*d*][1]benzazepin-6-one (**28i**)

Preparation according to General Procedure B, method 2 (reaction time 30 min). Crystallization from EtOH yielded 56% light green crystals; mp.: 249 °C; IR (KBr): 3292 $cm^{-1}$ and 3192 $cm^{-1}$ (NH), 1691 $cm^{-1}$ (C=O); $^1$H-NMR (DMSO-$d_6$, 400 MHz): $\delta$ (ppm) = 1.31 (t, 3H, *J* = 6.8 Hz, -$CH_3$ (ethoxy)), ~ 3.33 ($CH_2$ superimposed by water signal), 3.99 (q, 2H, *J* = 6.8 Hz, $CH_2$ (ethoxy)), 6.85-6.89 (m, 2H, ar. H), 7.22 (dd, 1H, *J* = 8.1/0.8 Hz, ar. H), 7.33 (ddd, 1H, *J* = 8.3/7.8/1.0 Hz, ar. H), 7.56 (ddd, 1H, *J* = 8.1/7.1/1.5 Hz, ar. H), 7.66-7.70 (m, 2H, ar. H), 8.05 (dd, 1H, *J* = 7.8/1.5 Hz, ar. H), 8.44 (s, 1H, ar. H), 9.51 (s, 1H, NH), 10.21 (s, 1H, NH); Anal. ($C_{20}H_{18}N_4O_2$) C, H, N; HPLC (ACN:$H_2O$ 50:50): purity 99.9% at 254 nm, 99.9% at 280 nm; $t_N$: 2.75 min; $t_m$(DMSO): 1.02 min.

2-(3-Hydroxyanilino)-5,7-dihydro-6*H*-pyrimido[5,4-*d*][1]benzazepin-6-one (**28j**)

Preparation according to General Procedure B, method 2 (reaction time 30 min). Crystallization from EtOH yielded 46% beige crystals; mp.: 288-289 °C; IR (KBr): 3432 $cm^{-1}$ (NH), 3210 $cm^{-1}$ (NH; OH (broad, superimposed), 1656 $cm^{-1}$ (C=O); $^1$H-NMR (DMSO-$d_6$, 400 MHz): $\delta$ (ppm) = 3.37 (s, 2H, $CH_2$), 6.38 (dd, 1H, *J* = 8.1/1.5 Hz, ar. H), 7.22 (t, 1H, *J* = 8.1/7.8 Hz, ar. H), 7.22 and 7.23 (dd, 1H, *J* = 8.1/1.3 Hz, ar. H and dd 1H, *J* = 8.1/0.8 Hz, ar. H, superimposed), 7.33-7.37 (m, 2H, ar. H), 7.56 (ddd, 1H, *J* = 8.1/7.3/1.5 Hz, ar. H), 8.09 (dd, 1H, *J* = 7.8/1.5 Hz, ar. H), 8.50 (s, 1H, ar. H), 9.25 (s, 1H, OH), 9.60 (s, 1H, NH), 10.23 (s, 1H, NH); $^{13}$C-NMR (DMSO-$d_6$, 100.6 MHz): $\delta$ (ppm) = 36.2 ($CH_2$); 105.9, 108.6, 109.7, 122.1, 123.9, 129.0, 130.0, 131.1, 157.4 (tert. C); 117.3, 128.8, 138.1, 141.6, 157.3, 159.5, 160.6, 171.6 (quat. C); Anal ($C_{18}H_{14}N_4O_2$) C, H, N; HPLC (ACN:$H_2O$ 30:70): purity 99.8% at 254 nm, 100.0% at 280 nm; $t_N$: 3.73 min; $t_m$(DMSO): 1.03 min.

2-(2-Chloroanilino)-5,7-dihydro-6*H*-pyrimido[5,4-*d*][1]benzazepin-6-one (**28k**)

Preparation according to General Procedure B, method 2 (reaction time 60 min). Crystallization from ethyl acetate yielded 65% colorless crystals; mp.: 279-280 °C; IR (KBr): 3411 $cm^{-1}$ and 3185 $cm^{-1}$ (NH), 1692 $cm^{-1}$ (C=O); $^1$H-NMR (DMSO-$d_6$, 400 MHz): $\delta$ (ppm) = 3.36 (s, 2H, $CH_2$), 7.16 (ddd, 1H, *J* = 7.8/7.6/1.5 Hz, ar. H), 7.21 (dd,

1H, *J* = 8.1/1.0 Hz, ar. H), 7.29 (ddd, 1H, *J* = 7.8/7.3/1.0 Hz, ar. H), 7.35 (ddd, 1H, *J* = 8.1/7.6/1.3 Hz, ar. H), 7.51 and 7.53 (dd, 1H, *J* = 7.8/1.5 Hz, ar. H and ddd" 1H, *J* = 8.1/7.3/1.5 Hz, ar. H, signals superimposed), 7.89 (dd, 1H, *J* = 8.1/1.5 Hz, ar. H), 7.98 (dd, 1H, *J* = 8.1/1.5 Hz, ar. H), 8.47 (s, 1H, ar. H), 8.88 (s, 1H, NH), 10.22 (s, 1H, NH); $^{13}$C-NMR (DMSO-$d_6$, 100.6 MHz): δ (ppm) = 36.2 ($CH_2$); 121.0, 123.8, 125.1, 125.4, 127.4, 129.4, 129.9, 131.2, 157.5 (tert. C); 117.9, 127.0, 128.5, 136.5, 138.1, 159.7, 160.7, 171.5 (quat. C); Anal ($C_{18}H_{13}ClN_4O$) C, H, N; HPLC (ACN:$H_2O$ 50:50): purity 99.6% at 254 nm, 99.7% at 280 nm; $t_N$: 3.96 min; $t_m$(DMSO): 1.02 min.

2-(2-Bromoanilino)-5,7-dihydro-6*H*-pyrimido[5,4-*d*][1]benzazepin-6-one (**28l**)

Preparation according to General Procedure B, method 2 (reaction time 45 min). Crystallization from ethyl acetate yielded 53% colorless crystals; mp.: 285-286 °C; IR (KBr): 3394 cm$^{-1}$, 3185 cm$^{-1}$ (NH), 1692 cm$^{-1}$ (C=O); $^1$H-NMR (DMSO-$d_6$, 400 MHz): δ (ppm) = 3.36 (s, 2H, $CH_2$), 7.09 (ddd, 1H, *J* = 7.8/7.6/1.5 Hz, ar. H), 7.21 (dd, 1H, *J* = 8.1/0.5 Hz, ar. H), 7.29 (ddd, 1H, *J* = 8.3/7.8/1.0 Hz, ar. H), 7.40 (ddd, 1H, *J* = 8.1/7.3/1.5 Hz, ar. H), 7.53 (ddd 1H, *J* = 8.1/7.3/1.5 Hz, ar. H), 7.68 (dd, 1H, *J* = 8.1/1.3 Hz, ar. H), 7.86 (dd, 1H, *J* = 8.1/1.5 Hz, ar. H), 7.97 (dd, 1H, *J* = 7.8/1.5 Hz, ar. H), 8.46 (s, 1H, ar. H), 8.81 (s, 1H, NH), 10.22 (s, 1H, NH); Anal ($C_{18}H_{13}BrN_4O$) C, H; N calcd. 14.70 N found 14.22; HPLC (ACN:$H_2O$ 50:50): purity 99.2% at 254, 99.5% at 280 nm; $t_N$: 4.40 min; $t_m$(DMSO): 1.02 min.

2-(2-Hydroxyanilino)-5,7-dihydro-6*H*-pyrimido[5,4-*d*][1]benzazepin-6-one (**28m**)

Preparation according to General Procedure B, method 2 (reaction time 30 min). Crystallization from EtOH yielded 35% yellow-green crystals; mp.: 262-263 °C; IR (KBr): 3364 cm$^{-1}$ and 3192 cm$^{-1}$ (NH), 3075 cm$^{-1}$ (CH ar. and OH (broad, overlapping), 1684 cm$^{-1}$ (C=O); $^1$H-NMR (DMSO-$d_6$, 400 MHz): δ (ppm) = 3.37 (s, 2H, $CH_2$), 6.80-6.90 (m, 3H, ar. H), 7.23 (d, 1H, *J* = 8.1 Hz, ar. H), 7.34 (t, 1H, *J* = 7.3/7.3 Hz, ar. H), 7.56 (ddd, 1H, *J* = 8.3/7.1/1.3 Hz, ar. H), 8.04 (dd, 1H, *J* = 7.8/1.0 Hz, ar. H), 8.09 (d, 1H, *J* = 7.6 Hz, ar. H), 8.23 (s, 1H, ar. H), 8.50 (s, 1H, OH), 9.94 (s, 1H, NH), 10.25 (s, 1H, NH); $^{13}$C-NMR (DMSO-$d_6$, 100.6 MHz): δ (ppm) = 36.2 ($CH_2$); 115.1, 119.1, 120.4, 122.1, 122.8, 124.0, 129.8, 131.3, 157.6 (tert. C); 117.4, 127.8, 128.6, 138.1, 147.1, 159.4, 160.7, 171.6 (quat. C); Anal. ($C_{18}H_{14}N_4O_2$) H, N, C calcd.

67.91, C found 67.50; HPLC (ACN:$H_2O$ 30:70): purity 96.6% at 254, 97.9% at 280 nm; $t_N$: 5.59 min; $t_m$(DMSO): 1.03 min.

2-(3-Hydroxy-4-methoxyanilino)-5,7-dihydro-6*H*-pyrimido[5,4-*d*]-[1]benzazepin-6-one (**28n**)

Preparation according to General Procedure B, method 2 (reaction time 30 min). Crystallization from EtOH yielded 56% light green crystals; mp.: 272 °C; IR (KBr): 3372 $cm^{-1}$ and 3318 $cm^{-1}$ (NH), 1685 $cm^{-1}$ (C=O); $^1$H-NMR (DMSO-$d_6$, 400 MHz): $\delta$ (ppm) = 3.34 (s, 2H, $CH_2$), 3.73 (s, 3H, $OCH_3$), 6.84 (d, 1H, *J* = 8.9 Hz, ar. H), 7.18 (dd, 1H, *J* = 8.6/2.5 Hz, ar. H), 7.22 (dd, 1H, *J* = 8.1/1.0 Hz, ar. H), 7.31 (d, 1H, *J* = 2.5 Hz, ar. H), 7.34 (dd, 1H, *J* = 8.3/1.3 Hz, ar. H), 7.54 (ddd, 1H, *J* = 8.1/7.3/1.5 Hz, ar. H), 8.07 (dd, 1H, *J* = 8.1/1.5 Hz, ar. H), 8.44 (s, 1H, ar. H), 8.87 (s, 1H, OH), 9.42 (s, 1H, NH), 10.20 (s, 1H, NH); $^{13}$C-NMR (DMSO-$d_6$, 100.6 MHz): $\delta$ (ppm) = 56.1 ($OCH_3$); 36.2 ($CH_2$); 107.8, 109.8, 112.7, 122.0, 123.9, 129.9, 131.1, 157.3 (tert. C); 116.8, 128.9, 134.3, 138.0, 142.7, 146.3, 159.6, 160.5, 171.7 (quat. C); Anal. ($C_{19}H_{16}N_4O_3$) C, H; N calcd. 16.08, N found 15.66; HPLC (ACN:$H_2O$ 30:70): purity 95.9% at 254 nm, 97.4% at 280 nm; $t_N$: 3.98 min; $t_m$(DMSO): 1.03 min.

2-(3-Chloro-4-hydroxyanilino)-5,7-dihydro-6*H*-pyrimido[5,4-*d*][1]benz-azepin-6-one (**28o**)

Preparation according to General Procedure B, method 1 (reaction time 10 h). Crystallization from EtOH yielded 44% yellow crystals; mp.: 293 °C (decomposition starting); IR (KBr): 3256 $cm^{-1}$ and 3194 $cm^{-1}$ (NH; OH (broad, overlapping), 1662 $cm^{-1}$ (C=O); $^1$H-NMR (DMSO-$d_6$, 400 MHz): $\delta$ (ppm) = 3.35 (s, 2H, $CH_2$), 6.91 (d, 1H, *J* = 8.8 Hz, ar. H), 7.23 (dd, 1H, *J* = 8.3/0.8 Hz, ar. H), 7.33 (ddd, 1H, *J* = 8.3/7.8/1.0 Hz, ar. H), 7.49 (dd, 1H, *J* = 8.8/2.5 Hz, ar. H), 7.55 (ddd, 1H, *J* = 8.1/7.3/1.5 Hz, ar. H), 7.91 (d, 1H, *J* = 2.5 Hz, ar. H), 8.05 (dd, 1H, *J* = 7.8/1.5 Hz, ar. H), 8.48 (s, 1H, ar. H), 9.59 (s, 1H, OH), 9.68 (s, 1H, NH), 10.23 (s, 1H, NH); $^{13}$C-NMR (DMSO-$d_6$, 100.6 MHz): $\delta$ (ppm) = 36.0 ($CH_2$); 116.4, 119.01, 120.3, 122.1, 123.9, 129.8, 131.2, 157.4 (tert. C); 117.1, 118.98, 128.7, 133.1, 138.1, 147.6, 159.4, 160.5, 171.6 (quat. C); Anal ($C_{18}H_{13}ClN_4O_2$) C, H, N; HPLC (ACN:$H_2O$ 30:70): purity 95.4% at 280 nm; $t_N$: 4.47 min; $t_m$(DMSO): 1.03 min.

2-(4-Hydroxy-2-methylanilino)-5,7-dihydro-6*H*-pyrimido[5,4-*d*]-[1]benzazepin-6-one (**28p**)

Preparation according to General Procedure B, method 2 (reaction time 30 min). Crystallization from EtOH yielded 56% yellow-green crystals; mp. 293 °C (starting dec.); IR (KBr): 3272 $cm^{-1}$, 3217 $cm^{-1}$ and 3130 $cm^{-1}$ (NH; OH (broad, overlapping), 1666 $cm^{-1}$ (C=O); $^1$H-NMR (DMSO-$d_6$, 400 MHz): $\delta$ (ppm) = 2.12 (s, 3H, $CH_3$), 3.28 (s, 2H, $CH_2$), 6.58 (dd, 1H, *J* = 8.6/2.5 Hz, ar. H), 6.64 (d, 1H, *J* = 2.5 Hz, ar. H), 7.13 (d, 1H, *J* = 8.6 Hz, ar. H), 7.18 (dd, 1H, *J* = 8.1/0.5 Hz, ar. H), 7.26 (ddd, 1H, *J* = 8.3/7.8/1.0 Hz, ar. H), 7.50 (ddd, 1H, *J* = 8.1/7.3/1.5 Hz, ar. H), 7.89 (dd, 1H, *J* = 7.3/0.5 Hz, ar. H), 8.31 (s, 1H, ar. H), 8.64 (s,1H, OH), 9.14 (s, 1H, NH), 10.16 (s, 1H, NH); $^{13}$C-NMR (DMSO-$d_6$, 100.6 MHz): $\delta$ (ppm) = 17.9 ($CH_3$); 35.9 ($CH_2$); 112.6, 116.5, 121.9, 123.7, 127.4, 129.8, 130.9, 157.4 (tert. C); 116.1, 128.9, 129.3, 134.8, 137.9, 154.6, 160.6, 161.3, 171.7 (quat. C); Anal. ($C_{19}H_{16}N_4O_2$) C, H, N; HPLC (ACN:$H_2O$ 30:70): purity 99.9% at 254 nm, 100.0% at 280 nm; $t_N$: 2.63 min; $t_m$(DMSO): 1.03 min.

2-(4-Methoxyanilino)-9-methoxy-5,7-dihydro-6*H*-pyrimido[5,4-*d*][1]benzazepin-6-one (**29c**)

Preparation according to General Procedure B, Method 1 (reaction time 18 h). Crystallization from EtOH yielded 56% light-green crystals; m.p. 288 °C; IR (KBr): 3268 $cm^{-1}$ and 3200 $cm^{-1}$ (NH), 1685 $cm^{-1}$ (C=O); $^1$H NMR (DMSO-$d_6$, 600 MHz): $\delta$ (ppm) = 3.33 (s, 2H, $CH_2$), 3.72 (s, 3H, -$OCH_3$), 3.82 (s, 3H, -$OCH_3$), 6.76 (d, 1H, *J* = 2.6 Hz, ar. H), 6.88-6.89 (m, 2H, ar. H), 6.96 (dd, 1H, *J* = 8.8/2.6 Hz, ar. H), 7.68-7.70 (m, 2H, ar. H), 8.00 (d, 1H, *J* = 8.7 Hz, ar. H), 8.40 (s, 1H, pyrimidine H), 9.50 (s, 1H, NH), 10.18 (s, 1H, NH); $^{13}$C-NMR (DMSO-$d_6$, 150.9 MHz): $\delta$ (ppm) = 55.0 (-$OCH_3$), 55.4 (-$OCH_3$); 36.3 ($CH_2$); 106.3, 110.6, 113.6 (2C), 120.3 (2C), 131.3, 157.2 (tert. C); 115.8, 121.6, 133.7, 139.4, 154.0, 159.5, 160.4, 161.3, 171.3 (quat. C); ($C_{20}H_{18}N_4O_3$) HRMS (EI) (*m/z*) [$M^{+\bullet}$] calcd 362.13788, found 362.13660; HPLC (ACN:$H_2O$+$(Et_3NH)_2SO_4$ 40:60): purity: 99.9% at 254 nm, 99.9% at 280 nm; $t_N$: 4.46 min; $t_m$(DMSO): 1.03 min.

2-(4-Hydroxyanilino)-9-methoxy-5,7-dihydro-6*H*-pyrimido[5,4-*d*][1]benzazepin-6-one (**29g**)

Preparation according to General Procedure B, Method 1 (reaction time 15 h). Crystallization from EtOH yielded 69% colorless crystals; m.p. 349 °C; IR (KBr): 3260 $cm^{-1}$ and 3197 $cm^{-1}$ (NH; OH), 1660 $cm^{-1}$ (C=O); $^1$H NMR (DMSO-$d_6$, 400 MHz): $\delta$ (ppm) = 3.32 (s, 2H, $CH_2$), 3.83 (s, 3H, -$OCH_3$), 6.69-6.71 (m, 2H, ar. H), 6.76 (d, 1H, *J* = 3.0 Hz, ar. H), 6.95 (dd, 1H, *J* = 8.6/3.0 Hz, ar. H), 7.52-7.54 (m, 2H, ar. H), 7.98 (d, 1H, *J* = 9.1 Hz, ar. H), 8.36 (s, 1H, pyrimidine H), 9.02 (s, 1H, OH), 9.31 (s, 1H, NH), 10.13 (s, 1H, NH); $^{13}$C NMR (DMSO-$d_6$, 150.9 MHz): $\delta$ (ppm) = 55.0 (-$OCH_3$); 36.0 ($CH_2$); 105.9, 110.3, 114.5 (2C), 120.5 (2C), 131.0, 156.8 (tert. C); 115.2, 121.3, 131.8, 139.1, 151.8, 159.3, 160.0, 160.9, 171.0 (quat. C); Anal. ($C_{19}H_{16}N_4O_3$) C, H, N; HPLC (ACN:$H_2O$+$(Et_3NH)_2SO_4$ 30:70): purity: 98.8% at 254 nm, 99.1% at 280 nm; $t_N$: 3.27 min, $t_m$(DMSO): 1.03 min.

2-(3-Hydroxyanilino)-9-methoxy-5,7-dihydro-6*H*-pyrimido[5,4-*d*][1]benzazepin-6-one (**29j**)

Preparation according to General Procedure B, Method 1 (reaction time 16 h). Crystallization from EtOH yielded 43% beige crystals; m.p. 280 °C; IR (KBr): 3270 $cm^{-1}$ and 3192 $cm^{-1}$ (NH), 2800-3300 $cm^{-1}$ (OH), 1660 $cm^{-1}$ (C=O); $^1$H NMR (DMSO-$d_6$, 600 MHz): $\delta$ (ppm) = 3.36 ($CH_2$ superimposed by $H_2O$ peak), 3.84 (s, 3H, -$OCH_3$), 6.37 (ddd, 1H, *J* = 8.0/2.3/0.9 Hz, ar. H), 6.78 (d, 1H, *J* = 2.6 Hz, ar. H), 6.97 (dd, 1H, *J* = 8.9/2.6 Hz, ar. H), 7.05 (t, 1H, *J* = 8.1 Hz, ar. H), 7.20-7.23 (m, 1H, ar. H), 7.36 (t, 1H, *J* = 2.0 Hz, ar. H), 8.04 (d, 1H, *J* = 8.7 Hz, ar. H), 8.44 (s, 1H, pyrimidine H), 9.25 (s, 1H, OH), 9.54 (s, 1H, NH), 10.16 (s, 1H, NH); $^{13}$C NMR (DMSO-$d_6$, 100.6 MHz): $\delta$ (ppm) = 55.4 (-$OCH_3$); 36.4 ($CH_2$); 105.8, 106.4, 108.5, 109.7, 110.7, 129.0, 131.5, 157.1 (tert. C); 116.4, 121.6, 139.5, 141.7, 157.5, 159.4, 160.5, 161.4, 171.3 (quat. C); ($C_{19}H_{16}N_4O_3$) HRMS (EI) (*m/z*): $[M-H]^+$ calcd 347.11441, found 347.11385; HPLC (ACN:$H_2O$+$(Et_3NH)_2SO_4$ 30:70): purity: 99.7% at 254 nm, 99.9% at 280 nm; $t_N$: 4.60 min; $t_m$(DMSO): 1.03 min.

2-(3-Hydroxy-4-methoxyanilino)-9-methoxy-5,7-dihydro-6*H*-pyrimido[5,4-*d*][1]benz-azepin-6-one (**29n**)

Preparation according to General Procedure B, Method 1 (reaction time 30 h). Crystallization from EtOH yielded 17% colorless crystals; m.p. 278 °C; IR (KBr): 3259 $cm^{-1}$ and 3207 $cm^{-1}$ (NH), 2800-3300 (OH), 1673 $cm^{-1}$ (C=O); $^1$H NMR (DMSO-$d_6$, 600 MHz): $\delta$ (ppm) = 3.32 (s, 2H, $CH_2$), 3.72 (s, 3H, -$OCH_3$), 3.83 (s, 3H, $OCH_3$), 6.76 (d, 1H, *J* = 2.6 Hz, ar. H), 6.83 (d, 1H, *J* = 9.0, ar. H), 6.95 (dd, 1H, *J* = 8.9/2.6 Hz, ar. H), 7.17 (dd, 1H, *J* = 8.7/2.6 Hz, ar. H), 7.30 (d, 1H, *J* = 2.6 Hz, ar. H), 8.02 (d, 1H, *J* = 8.7 Hz, ar. H), 8.39 (s, 1H, pyrimidine H), 8.91 (s, 1H, OH), 9.40 (s, 1H, NH), 10.17 (s, 1H, NH); $^{13}$C NMR (DMSO-$d_6$, 150.9 MHz): $\delta$ (ppm) = 55.4 (-$OCH_3$), 55.9 ($OCH_3$); 36.3 ($CH_2$); 106.3, 107.5, 109.5, 110.5, 112.5, 131.4, 157.1 (tert. C); 115.8, 121.6, 134.3, 139.4, 142.5, 146.2, 159.4, 160.3, 161.3, 171.3 (quat. C); ($C_{20}H_{18}N_4O_4$) HRMS (EI) (*m/z*) [$M^{+\bullet}$]: calcd 378.13281, found 378.13268; HPLC (ACN:$H_2O$ 30:70): purity: 95.7% at 254 nm, 98.1% at 280 nm; $t_N$: 4.11 min; $t_m$(DMSO): 1.03 min.

2-(4-Methoxyanilino)-5,7-dihydro-6*H*-pyrido[4,3-*b*]pyrimido[4,5-*d*]azepin-6-one (**30c**)

Preparation according to General Procedure B, Method 1 (reaction time 16 h). Crystallization from EtOH yielded 49% green crystals; m.p. 275 °C; IR (KBr): 3427 $cm^{-1}$ and 3262 $cm^{-1}$ (NH), 1686 $cm^{-1}$ (C=O); $^1$H NMR (DMSO-$d_6$, 600 MHz): $\delta$ (ppm) = 3.47 (s, 2H, $CH_2$), 3.73 (s, 3H, -$OCH_3$), 6.90-6.92 (m, 2H, ar. H), 7.17 (d, 1H, *J* = 5.6 Hz, ar. H), 7.67-7.69 (m, 2H, ar. H), 8.50 (s, 1H, pyrimidine H), 8.59 (d, 1H, *J* = 5.6 Hz, ar. H), 9.15 (s, 1H, ar. H), 9.64 (s, 1H, NH), 10.69 (s, 1H, NH); $^{13}$C NMR (DMSO-$d_6$, 150.9 MHz): $\delta$ (ppm) = 55.1 ($OCH_3$); 36.2 ($CH_2$); 113.7 (2C), 115.4, 120.6 (2C), 150.9, 151.0, 157.9 (tert. C); 116.5, 123.5, 133.4, 144.5, 154.2, 158.6, 159.5, 171.5 (quat. C); Anal. ($C_{18}H_{15}N_5O_2$) C, H, N; HPLC (ACN:$H_2O$+$(Et_3NH)_2SO_4$ 15:85): purity: 99.9% at 254 nm, 99.9% at 280 nm; $t_N$: 5.53 min; $t_m$(DMSO): 1.03 min.

2-(4-Hydroxyanilino)-5,7-dihydro-6*H*-pyrido[4,3-*b*]pyrimido[4,5-*d*]azepin-6-one (**30g**)

Preparation according to General Procedure B, Method 1 (reaction time 24 h). Crystallization from EtOH yielded 60% yellow crystals; m.p. 317 °C; IR (KBr): 3399 $cm^{-1}$ (NH), 1684 $cm^{-1}$ (C=O); $^1$H NMR (DMSO-$d_6$, 600 MHz): $\delta$ (ppm) = 3.45 (s, 2H,

$CH_2$), 6.71-6.73 (m, 2H, ar. H), 7.17 (d, 1H, *J* = 5.5 Hz, ar. H), 7.51-7.54 (m, 2H, ar. H), 8.47 (s, 1H, pyrimidine H), 8.58 (d, 1H, *J* = 5.5 Hz, ar. H), 9.10 (s, 1H, OH), 9.13 (s, 1H, ar. H), 9.49 (s, 1H, NH), 10.68 (s, 1H, NH); $^{13}$C NMR (DMSO-$d_6$, 150.9 MHz): $\delta$ (ppm) = 35.0 ($CH_2$); 113.7 (2C), 114.2, 119.9 (2C), 149.7, 149.8, 156.7 (tert. C); 115.0, 122.3, 130.6, 143.2, 151.2, 157.4, 158.4, 170.3 (quat. C); Anal. ($C_{17}H_{13}N_5O_2$) C, H, N; HPLC (MeOH:$H_2O$+$(Et_3NH)_2SO_4$ 25:75): purity 100.0% at 254 nm, 99.9% at 280 nm; $t_N$: 5.60 min; $t_m$(DMSO): 1.03 min.

2-(4-Ethoxyanilino)-5,7-dihydro-6*H*-pyrido[4,3-*b*]pyrimido[4,5-*d*]azepin-6-one (**30i**)

Preparation according to General Procedure B, Method 1 (reaction time 12 h). Crystallization from EtOH yielded 29% yellow crystals; m.p. 276 °C; IR (KBr): 3264 cm$^{-1}$ and 3183 cm$^{-1}$ (NH), 1696 cm$^{-1}$ (C=O); $^1$H NMR (DMSO-$d_6$, 600 MHz): $\delta$ (ppm) = 1.32 (t, 3H, *J* = 7.0 Hz, -$OCH_2CH_3$), 3.46 (s, 2H, $CH_2$), 3.99 (q, 2H, *J* = 6.9, -$OCH_2CH_3$), 6.87-6.91 (m, 2H, ar. H), 7.17 (d, 1H, *J* = 5.6 Hz, ar. H), 7.64-7.68 (m, 2H, ar. H), 8.50 (s, 1H, pyrimidine H), 8.59 (d, 1H, *J* = 5.8 Hz, ar. H), 9.15 (s, 1H, ar. H), 9.62 (s, 1H, NH, signal disappears on $D_2O$ addition), 10.68 (s, 1H, NH, signal disappears on $D_2O$ addition); $^{13}$C NMR (DMSO-$d_6$, 150.9 MHz): $\delta$ (ppm) = 14.3 ($OCH_2CH_3$); 35.8 ($CH_2$), 62.6 (-$OCH_2CH_3$); 113.8 (2C), 115.0, 120.2 (2C), 150.5, 150.6, 157.5 (tert. C); 116.1, 123.1, 132.9, 144.1, 153.1, 158.2, 159.1, 171.1 (quat. C); ($C_{19}H_{17}N_5O_2$) HRMS (EI) (*m/z*) [$M^{+\bullet}$]: calcd 347.13824, found 347.13874; HPLC (ACN:$H_2O$ 30:70): purity: 99.0% at 254 nm, 99.1% at 280 nm; $t_N$: 5.35 min; $t_m$(DMSO): 1.03 min.

2-(3-Hydroxyanilino)-5,7-dihydro-6*H*-pyrido[4,3-*b*]pyrimido[4,5-*d*]azepin-6-one (**30j**)

Preparation according to General Procedure B, Method 1 (reaction time 30 h). Crystallization from EtOH yielded 34% colourless crystals; m.p. 340 °C; IR (KBr): 3420 cm$^{-1}$ and 3262 cm$^{-1}$ (NH), 1707 cm$^{-1}$ (C=O); $^1$H NMR (DMSO-$d_6$, 600 MHz): $\delta$ (ppm) = 3.49 (s, 2H, $CH_2$), 6.39 (ddd, 1H, *J* = 8.0/2.4/0.8 Hz, ar. H), 7.07 (t, 1H, *J* = 8.2 Hz, ar. H), 7.18 (d, 1H, *J* = 5.6 Hz, ar. H), 7.19-7.20 (m, 1H, ar. H), 7.36 (t, 1H, *J* = 2.2 Hz, ar. H), 8.55 (s, 1H, pyrimidine H), 8.60 (d, 1H, *J* = 5.8 Hz, ar. H), 9.19 (s, 1H, ar. H), 9.35 (s, 1H, OH), 9.72 (s, 1H, NH), 10.71 (s, 1H, NH); $^{13}$C NMR (DMSO-$d_6$, 150.9 MHz): $\delta$ (ppm) = 36.2 ($CH_2$); 105.9, 108.7, 109.8, 115.4, 129.0, 151.0,

151.3, 157.9 (tert. C); 117.0, 123.4, 141.3, 144.5, 157.5, 158.6, 159.3, 171.4 (quat. C); ($C_{17}H_{13}N_5O_2$) HRMS (EI) (*m/z*) $[M-H]^+$ calcd 318.09912, found 318.09827; HPLC (MeOH:$H_2O$+$(Et_3NH)_2SO_4$ 30:70): purity: 99.9% at 254 nm, 99.9% at 280 nm; $t_N$: 5.11 min; $t_m$(DMSO): 1.03 min.

2-(3-Chloro-4-hydroxyanilino)-5,7-dihydro-6*H*-pyrido[4,3-*b*]pyrimido[4,5-*d*]azepin-6-one (**30o**)

Preparation according to General Procedure B, Method 1 (reaction time 15 h). Crystallization from EtOH yielded 35% light green crystals; m.p. 294 °C (degradation); IR (KBr): 3265 $cm^{-1}$ and 3198 $cm^{-1}$ (NH), 1689 $cm^{-1}$ (C=O); $^1H$ NMR (DMSO-$d_6$, 400 MHz): $\delta$ (ppm) = 3.48 (s, 2H, $CH_2$), 6.93 (d, 1H, *J* = 8.3 Hz, ar. H), 7.19 (d, 1H, *J* = 5.6 Hz, ar. H), 7.49 (dd, 1H, *J* = 8.9/2.5 Hz, ar. H), 7.89 (d, 1H, *J* = 2.5 Hz, ar. H), 8.53 (s, 1H, pyrimidine H), 8.60 (d, 1H, *J* = 5.5 Hz, ar. H), 9.16 (s, 1H, ar. H), 9.66 (s, 1H, NH), 9.73 (s, 1H, OH), 10.67 (s, 1H, NH); $^{13}C$ NMR (DMSO-$d_6$, 100.6 MHz): $\delta$ (ppm) = 36.3 ($CH_2$); 115.4, 116.4, 119.3, 120.5, 151.0, 157.9 (tert. C, one signal is missing due to peak overlap); 116.8, 119.0, 123.4, 132.9, 144.5, 147.7, 158.7, 159.3, 171.4 (quat. C); ($C_{17}H_{12}ClN_5O_2$) HRMS (EI) (*m/z*) $[M-H]^+$ calcd. 352.06015, found 352.05897; HPLC (ACN:$H_2O$+$(Et_3NH)_2SO_4$ 20:80): purity: 99.7% at 254 nm, 99.6% at 280 nm; $t_N$: 3.11 min, $t_m$(DMSO): 1.03 min.

2-(4-Methoxyanilino)-5,7-dihydro-6*H*-pyrido[3,2-*b*]pyrimido[4,5-*d*]azepin-6-one (**31c**)

Preparation according to General Procedure B, Method 1 (reaction time 16 h). Crystallization from EtOH yielded 50% green crystals; m.p. 256 °C; IR (KBr): 3265 $cm^{-1}$ and 3202 $cm^{-1}$ (NH), 1679 $cm^{-1}$ (C=O); $^1H$ NMR (DMSO-$d_6$, 400 MHz): $\delta$ (ppm) = 3.42 (s, 2H, $CH_2$), 3.72 (s, 3H, -$OCH_3$), 6.85-6.89 (m, 2H, ar. H), 7.58 (dd, 1H, *J* = 8.2/4.3 Hz, ar. H), 7.64 (dd, 1H, *J* = 8.0/1.6 Hz, ar. H), 7.73-7.75 (m, 2H, ar. H), 8.51 (s, 1H, pyrimidine H), 8.61 (dd, 1H, *J* = 4.2/1.6 Hz, ar. H), 9.68 (s, 1H, NH), 10.28 (s, 1H, NH); $^{13}C$ NMR (DMSO-$d_6$, 100.6 MHz): $\delta$ (ppm) = 55.1 (-$OCH_3$); 36.0 ($CH_2$); 113.7 (2C), 120.3 (2C), 125.2, 130.0, 145.4, 157.5 (tert. C); 117.9, 133.8, 135.5, 145.2, 154.1, 159.8, 160.1, 171.8 (quat. C); ($C_{18}H_{15}N_5O_2$) HRMS (EI) (*m/z*) $[M^{+\bullet}]$ calcd. 333.12259, found 333.12286; HPLC (ACN:$H_2O$+$(Et_3NH)_2SO_4$ 25:75): purity: 100.0% at 254 nm, 100.0% at 280 nm; $t_N$: 3.17 min, $t_m$(DMSO): 1.03 min.

2-(4-Hydroxyanilino)-5,7-dihydro-6*H*-pyrido[3,2-*b*]pyrimido[4,5-*d*]azepin-6-one (**31g**)

Preparation according to General Procedure B, Method 1 (reaction time 14 h). Crystallization from EtOH yielded 41% yellow crystals; m.p. 310 °C (dec.); IR (KBr): 3430 $cm^{-1}$ and 3367 $cm^{-1}$ (NH), 1687 $cm^{-1}$ (C=O); $^1$H NMR (DMSO-$d_6$, 600 MHz): $\delta$ (ppm) = 3.39 (s, 2H, $CH_2$), 6.67-6.70 (m, 2H, ar. H), 7.57-7.59 (m, 3H, ar. H), 7.63 (dd, 1H, *J* = 7.9/1.5 Hz, ar. H), 8.48 (s, 1H, pyrimidine H), 8.61 (dd, 1H, *J* = 4.1/1.5 Hz, ar. H), 9.04 (s, 1H, OH), 9.58 (s, 1H, NH), 10.30 (s, 1H, NH); $^{13}$C NMR (DMSO-$d_6$, 150.9 MHz): $\delta$ (ppm) = 35.2 ($CH_2$); 114.2 (2C), 120.0 (2C), 124.5, 129.3, 144.7, 156.8 (tert. C); 116.9, 131.5, 134.8, 144.6, 151.4, 159.3, 159.4, 171.2 (quat. C); ($C_{17}H_{13}N_5O_2$) HRMS (EI) (*m/z*) $[M-H]^+$ calcd. 318.09912, found 318.09896; HPLC (ACN:$H_2O$+$(Et_3NH)_2SO_4$ 15:85): purity: 100.0% at 254 nm, 100.0% at 280 nm; $t_N$: 2.60 min; $t_m$(DMSO): 1.03 min.

2-(4-Ethoxyanilino)-5,7-dihydro-6*H*-pyrido[3,2-*b*]pyrimido[4,5-*d*]azepin-6-one (**31i**)

Preparation according to General Procedure B, Method 1 (reaction time 15 h). Crystallization from EtOH yielded 48% light green crystals; m.p. 248 °C; IR (KBr): 3308 $cm^{-1}$ and 3205 $cm^{-1}$ (NH), 1681 $cm^{-1}$ (C=O); $^1$H NMR (DMSO-$d_6$, 400 MHz): $\delta$ (ppm) = 1.31 (t, 3H, *J* = 7.1 Hz, -$OCH_2CH_3$), 3.41 (s, 2H, $CH_2$), 3.98 (q, 2H, *J* = 6.9, -$OCH_2CH_3$), 6.83-6.87 (m, 2H, ar. H), 7.58 (dd, 1H, *J* = 8.2/4.0 Hz, ar. H), 7.64 (dd, 1H, *J* = 8.2/1.8 Hz, ar. H), 7.71-7.75 (m, 2H, ar. H), 8.51 (s, 1H, pyrimidine H), 8.61 (dd, 1H, *J* = 4.5/1.3 Hz, ar. H), 9.68 (s, 1H, NH), 10.28 (s, 1H, NH); $^{13}$C NMR (DMSO-$d_6$, 100.6 MHz): $\delta$ (ppm) = 14.7 (-$OCH_2CH_3$); 36.0 ($CH_2$), 63.1 (-$OCH_2CH_3$); 114.3 (2C), 120.3 (2C), 125.2, 130.0, 145.2, 157.5 (tert. C); 117.9, 133.7, 135.5, 145.4, 153.3, 159.8, 160.1, 171.8 (quat. C); ($C_{19}H_{17}N_5O_2$) HRMS (EI) (*m/z*) $[M^{+\bullet}]$ calcd. 347.13824, found 347.13793; HPLC (ACN:$H_2O$+$(Et_3NH)_2SO_4$ 30:70): purity: 100.0% at 254 nm, 99.9% at 280 nm; $t_N$: 3.38 min; $t_m$(DMSO): 1.03 min.

2-(3-Hydroxyanilino)-5,7-dihydro-6*H*-pyrido[3,2-*b*]pyrimido[4,5-*d*]azepin-6-one (**31j**)

Preparation according to General Procedure B, Method 1 (reaction time 14 h). Crystallization from EtOH yielded 58% light green crystals; m.p. 350 °C (dec); IR (KBr): 3308 $cm^{-1}$ and 3205 $cm^{-1}$ (NH), 1681 $cm^{-1}$ (C=O); $^1$H NMR (DMSO-$d_6$, 400

MHz): δ (ppm) = 3.43 (s, 2H, $CH_2$), 6.37 (ddd, 1H, *J* = 7.9/2.4/0.9 Hz, ar. H), 7.03 (t, 1H, *J* = 7.9 Hz, ar. H), 7.28-7.30 (m, 1H, ar. H), 7.36 (t, 1H, *J* = 2.2 Hz, ar. H), 7.59 (dd, 1H, *J* = 8.3/4.2 Hz, ar. H), 7.64 (dd, 1H, *J* = 8.3/1.7 Hz, ar. H), 8.56 (s, 1H, pyrimidine H), 8.61 (dd, 1H, *J* = 4.2/1.6 Hz, ar. H), 9.22 (s, 1H, OH), 9.76 (s, 1H, NH), 10.30 (s, 1H, NH); $^{13}$C NMR (DMSO-$d_6$, 100.6 MHz): δ (ppm) = 36.0 ($CH_2$); 105.9, 108.5, 109.8, 125.3, 129.0, 130.0, 145.1, 157.5 (tert. C); 118.4, 135.6, 141.7, 145.4, 159.7, 160.1, 171.8 (quat. C, one signal is missing due to peak overlap); ($C_{17}H_{13}N_5O_2$) HRMS (EI) (*m/z*) $[M-H]^+$ calcd. 318.09912, found 318.09915; HPLC (ACN:$H_2O$+$(Et_3NH)_2SO_4$ 15:85): purity: 99.5% at 254 nm, 99.8% at 280 nm; $t_N$: 4.96 min; $t_m$(DMSO): 1.03 min.

2-(3-Chloro-4-hydroxyanilino)-5,7-dihydro-6*H*-pyrido[3,2-*b*]pyrimido[4,5-*d*]azepin-6-one (**31o**)

Preparation according to General Procedure B, Method 1 (reaction time 15 h). Crystallization from EtOH yielded 25% green crystals; m.p. 300 °C (dec.); IR (KBr): 3386 $cm^{-1}$ and 3287 $cm^{-1}$ (NH), 1673 $cm^{-1}$ (C=O); $^1$H NMR (DMSO-$d_6$, 600 MHz): δ (ppm) = 3.42 (s, 2H, $CH_2$), 6.89 (d, 1H, *J* = 8.8 Hz, ar. H), 7.53 (dd, 1H, *J* = 8.8/2.3 Hz, ar. H), 7.59 (dd, 1H, *J* = 8.3/4.4 Hz, ar. H), 7.64 (dd, 1H, *J* = 8.5/1.4 Hz, ar. H), 7.99 (s (broad), 1H, ar. H), 8.55 (s, 1H, pyrimidine H), 8.61 (dd, 1H, *J* = 4.2/1.4 Hz, ar. H), 9.71 (s, 1H, OH), 9.80 (s, 1H, NH), 10.33 (s, 1H, NH); $^{13}$C NMR (DMSO-$d_6$, 150.9 MHz): δ (ppm) = 35.9 ($CH_2$); 116.3, 118.7, 119.9, 125.3, 129.9, 145.4, 157.6 (tert. C); 118.0, 118.9, 133.2, 135.5, 144.9, 147.4, 159.5, 160.0, 171.7 (quat. C); ($C_{17}H_{12}ClN_5O_2$) HRMS (EI) (*m/z*) $[M^{+\bullet}]$: calcd. 353.06796, found 353.06714; HPLC (ACN:$H_2O$+$(Et_3NH)_2SO_4$ 20:80): purity: 99.9% at 254 nm, 99.9% at 280 nm; $t_N$: 3.28 min; $t_m$(DMSO): 1.03 min.

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