Enantioconservative Synthesis of Polysubstituted Pyrimido[4,5-*b*]azepines

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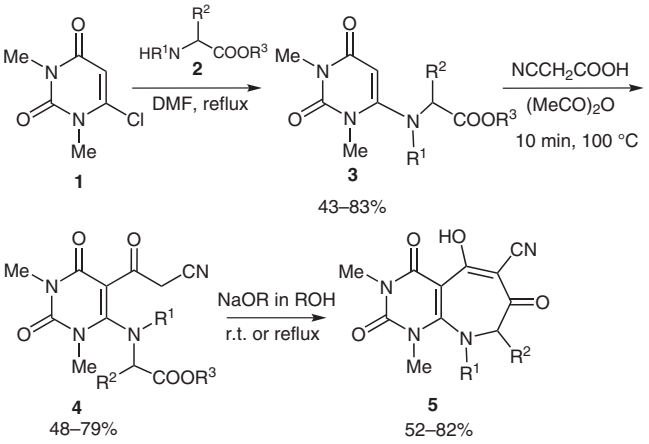
Abstract: A three-step enantioconservative protocol was developed for the synthesis of polysubstituted pyrimido[4,5-*b*]azepines. First, 1,3-dimethyl-6-[*N*-(2-alkoxycarbonylalkyl)amino]uracils were synthesized by nucleophilic substitution of 6-chloro-1,3-dimethyluracil with amino acids. Subsequent acylation of the uracils by a mixture of acetic anhydride and cyanoacetic acid gave the corresponding 5-cyanoacetylated pyrimidines. In the final step, the pyrimidines were subjected to Dieckmann cyclization with a sodium alcoholate in the corresponding alcohol to afford the corresponding pyrimido[4,5-*b*]azepines. By using uracils of *N*-monosubstituted amino acids, cyclization was combined with ring opening of the pyrimidine ring system to afford polysubstituted azepines.

Key words: ring closure, heterocycles, stereoselective synthesis, pyrimidoazepines, nucleophilic substitutions

Adenosine receptors (ARs) have emerged as important targets for the synthesis of mono- and bicyclic annulated pyrimidines.[1] Important physiological processes are modulated by adenosine, especially when it acts at AR subtypes A_1 and A_{2A}, which are 'high-affinity subtypes' that are activated at low-nanomolar concentrations.[2] Selective antagonists of the AR subtype A_1 have been proposed for use as kidney-protective diuretics, in the treatment of congestive heart failure,[3] and in treatment of brain diseases such as dementia.[4] Antagonists that are selective towards AR subtype A_{2A} are very effective in the symptomatic treatment of Parkinson's disease, and they may exhibit neuroprotective effects.[5,6] Currently, the nonselective AR antagonists theophylline and caffeine are the only AR antagonists that are used as drugs.

We found that the successful replacement of the xanthine scaffold by substituted 1,3-dimethylpyrido[2,3-*d*]pyrimidine-(1*H*,3*H*)-2,4-dione moieties could provide potent and selective ligands for adenosine receptors.[7] This success in the development of novel AR antagonists prompted us to investigate seven-membered-ring annulated pyrimidines, such as pyrimido[4,5-*e*]diazepines and pyrimido[4,5-*b*]azepines.[8]

In applying a procedure for the preparation of pyrimido[4,5-*e*]diazepines that is analogous to that used to prepare benzodiazepines,[9,10] we recently discovered an unexpected sodium methoxide-catalyzed rearrangement of 6-amino-5-aroyl-1,3-dimethyluracils to form novel cinnamamides.[11] Here we report the application of our approach to the synthesis of pyrimido[4,5-*b*]azepines **5a–f** (Scheme 1).



Scheme 1 General three-step procedure for preparing pyrimido[4,5-*b*]azepines **5**

Table 1 Conversion of Amino Acid Esters **2** into Azepines **5** and Related Compounds

Amino acid	R^1	R^2	R^3	Yields (%)				
				3	**4**	**5**	**6**	**7**
2a	H	H	Et	45	65	82	–	–
rac-**2b**	H	Me	Me	83	52	52	–	–
rac-**2c**	H	*i*-Pr	Et	55	27	82	–	–
(*S*)-**2d**	H	Bn	Me	41	51	80	–	–
rac-**2e**	H	$(CH_2)_2Ph$	Et	52	75	82	–	–
rac-**2f**	H	1-naphthylmethyl	Et	43	79	75	–	–
rac-**2g**	$(CH_2)_4$		Et	78	50	–	50	–
rac-**2h**	$(CH_2)_3$		Me	47	48	–	10	–
2i	Me	H	Me	58	63	–	–	25

6-Chloro-1,3-dimethyluracil (**1**) was obtained from *N*,*N*′-dimethylbarbituric acid and phosphoryl chloride by using the procedure described by Pfleiderer.[12] Treatment of chlorouracil **1** with two equivalents of an amino acid ester **2** in *N*,*N*-dimethylformamide gave moderate yields of the corresponding *N*-(6-pyrimidinyl)amino acid ester **3**. Note, however, that the nucleophilic substitution causes hydrolysis as well as aminolysis of the ester through formation

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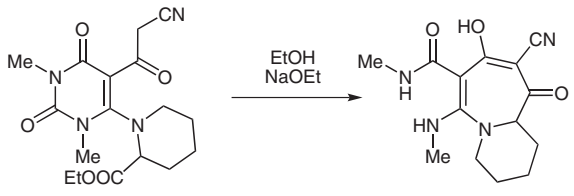
of dimethylamine as a decomposition product of *N*,*N*-dimethylformamide. The use of very pure and dry solvents or ionic liquids[13] minimized these side reactions. For example, in the case of the nucleophilic substitution reaction with amino acid **2b**, we obtained higher yields by using butylmethylimidazolium bromide as the solvent. Cyanoacetylation of the pyrimidines **3** by treatment with a mixture of cyanoacetic acid and acetic anhydride gave good yields of corresponding cyanoacetate esters **4**. The mechanism of this reaction involves formation of cyanoketene and electrophilic attack at the 5-position of the pyrimidine ring.[14,15] The cyano esters **4** readily underwent Dieckmann cyclization in sodium alcoholate in a few minutes at room temperature. The reaction products were analyzed by means of one- and two-dimensional NMR spectroscopy. This cyclization procedure (Scheme 1) could only be used in the case of derivatives of primary amino acids.

To examine whether racemization occurred under the basic conditions of the reaction, the sequence was carried out with commercially available methyl L-phenylalaninate [(*S*)-**2d**], as well as with the corresponding D-enantiomer. Careful chromatography of the commercial available amino acid esters (*S*)-**2d** on a chiral phase [(*R*,*R*)-Whelk 01 column] and of the resulting enantiomeric annulated azepines **5d** (Chiralcel OD-R column) confirmed that only 3% of racemization occurred. The azepine **5d** was obtained in 94% ee.

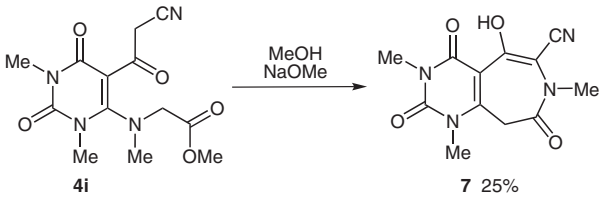
Initial attempts to perform the Dieckmann cyclization on substrates **4g–i** under the same experimental conditions were disappointing. We therefore attempted the reaction on the cyclic amino acid ester **4g** by refluxing it for six hours. It is well known in the literature[16,17] that the pyrimidine scaffold in xanthines can be cleaved by heating in alkaline solution. In an analogous manner, the Dieckmann cyclization products were formed after cleavage of the pyrimidine moiety. It is likely that steric hindrance (Scheme 2) prevents the formation of tricyclic pyrido[1,2-*a*]pyrimido[5,4-*f*]azepines when the reaction is performed at room temperature for a few minutes.



Scheme 2 Dieckmann cyclization of the cyclic amino acid derivative **4g**

The use of sarcosine (**2i**) in the reaction sequence resulted in an unexpected rearrangement when cyanoacetate was refluxed for 90 minutes, and the pyrimido[4,5-*d*]azepine **7** was obtained in 25% yield. The structure of this product was deduced from a complete analysis of its one- and two-dimensional NMR spectra, especially its ^{1}H,^{13}C-heteronuclear multiple bond coherence spectrum.

We assume that the rearrangement to form **7** occurs by a ring-opening/ring-closure sequence (Scheme 3).



Scheme 3 Formation of the pyrimido[4,5-*d*]azepine **7**

In conclusion, we have developed a synthetic strategy for the preparation of the new substituted pyrimido[4,5-*b*]azepines **5**, which have potential medicinal applications. The conceptually novel procedure involves only three chemical operations: nucleophilic substitution of the uracil **1** by an amino acid ester, cyanoacetylation, and Dieckmann cyclisation.

^{1}H (300 MHz) and ^{13}C (75 MHz) NMR spectra of samples in $CDCl_3$ or DMSO-d_6 were recorded on a Bruker Avance III 300 MHz spectrometer. Signals are quoted in ppm as δ shifts downfield from TMS (δ = 0.00 ppm), and coupling constants (*J*) are given in Hz. IR spectra were recorded on a Perkin-Elmer 1600 PC FT-IR spectrophotometer by using KBr pellets. ESI mass spectra were recorded on a Bruker Esquire LC with electrospray ionization. EI mass spectra were recorded on a Hewlett Packard 5989 A mass spectrometer at an ionization energy of 70 eV. HRMS (70 eV) were recorded on a Finnigan MAT 8230 spectrometer at the Department of Organic Chemistry of the Christian Albrechts University of Kiel. Elemental analyses were performed at the Department of Inorganic Chemistry of the Christian Albrechts University of Kiel using a CHNS analyzer (HEKAtech GmbH). Column chromatography and TLC were performed on Merck silica gel 60 and GF 254, respectively. HPLC analyses were carried out on a Merck-Hitachi System with an L-5000 LC Controller, a 655AA-11 LC chromatograph, an AS-2000 autosampler, an L-4200 UV-vis detector, and a D-2500 Chromato-Integrator, using a chiral stationary-phase column (CHIRALCEL OD-R; 250 × 4.6 mm). Melting points were recorded on a Stuart Scientific SMP03 melting point apparatus and are uncorrected. Unless otherwise stated, all chemicals were obtained from commercial sources and were used as received.

Uracils 3; General Procedure

A mixture of 6-chloro-1,3-dimethyluracil (10 mmol, 1.74 g), amino acid ester **2** (20 mmol), and Et_3N (40 mmol, 4.04 g) in DMF (20 mL) was stirred at 156 °C, while the reaction was monitored by TLC. When the reaction was complete, the solvent was evaporated, crushed ice was added, and the mixture was extracted with CH_2Cl_2 (3 × 50 mL). The combined extracts were dried (Na_2SO_4), filtered, and concentrated in vacuo to give a crude product that was purified by column chromatography [silica gel, MeOH–CH_2Cl_2 (1:19)]. The resulting product was used without further characterization.

Chloroacetyl Uracils 4; General Procedure

A mixture of uracil **3** (10 mmol), $NCCH_2CO_2H$ (20 mmol), and Ac_2O (0.2 mol) was heated to 100 °C and maintained at this temperature for 10 min.

Method A: The mixture was cooled to r.t. and the resulting white crystals were filtered off, washed, and recrystallized from the specified solvent.

Method B: Ac_2O was removed under reduced pressure and the residue was treated with crushed ice with vigorous stirring. The crystalline crude product that formed was filtered off and recrystallized from the specified solvent.

Method C: Ac_2O was removed under reduced pressure and the residue was treated with crushed ice. The mixture was extracted with CH_2Cl_2 (3 × 50 mL), and the combined extracts were dried (Na_2SO_4) and concentrated to give a crude product that was crystallized from the specified solvent.

Ethyl *N*-[5-(Cyanoacetyl)-1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl]glycinate (4a)

Method A: White solid; yield: 4.0 g (65%); mp 160.8 °C (EtOH).

IR (KBr): 2986 (m, ν, CH_2), 2258 (w, ν, CN) 1740 (s, ν, $COOCH_2CH_3$), 1652 (s, ν, RNCONR), 1596 (m, δ, NH), 1456 cm^{-1} (m, δ, CH_2).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.31 (t, ^3J = 7.1 Hz, 3 H, OCH_2CH_3), 3.32 (s, 3 H, N^3-CH_3), 3.49 (s, 3 H, N^1-CH_3), 4.26 (m_c, 6 H, $NHCH_2COOCH_2CH_3$, $COCH_2CN$, OCH_2CH_3), 11.64, (1 H, $NHCH_2COOCH_2CH_3$).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0 (OCH_2CH_3), 28.3 (N^3-CH_3), 33.8 ($COCH_2CN$), 35.3 (N^1-CH_3), 47.9 ($NHCH_2COOCH_2CH_3$), 62.7 (OCH_2CH_3), 94.0 (C-5), 115.2 (CN), 150.7 (C-2), 161.5 (C-4), 162.5 (C-6), 167.6 ($COOCH_2CH_3$), 187.5 (CO).

MS (EI, 70 eV): *m/z* = 308 M^+ (9), 268 (100), 235 (14), 208 (22), 194 (69), 82 (34), 69 (52), 42 (18).

ESI-MS: *m/z* = 309 $[M + H]^+$, 331 $[M + Na]^+$.

Anal. Calcd for $C_{13}H_{16}N_4O_5$ (308.30): C, 50.65; H, 5.23; N, 18.17. Found: C, 50.59; H, 5.34; N, 18.07.

Methyl *N*-[5-(Cyanoacetyl)-1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl]alaninate (4b)

Method A: White solid; yield: 3.2 g (52%); mp 124.3 °C (MeOH).

IR (KBr): 2956 (w, ν, CH_2), 2260 (m, ν, CN), 1716 (s, ν, CO), 1652 (s, ν, RNCONR), 1522 (m, δ, NH), 1464 cm^{-1} (m, δ, CH_2).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.63 (d, ^3J = 7.0 Hz, 3 H, CH_3), 3.10 (s, 3 H, N^3-CH_3), 3.43 (s, 3 H, N^3-CH_3), 3.77 (s, 3 H, OCH_3), 4.32 (AB-system, J_{AB} = 19.5 Hz, 2 H, $COCH_2CN$), 4.49 (dq, $^3J_{CH/NH}$ = 8.1 Hz, $^3J_{CH/CH3}{}'$ = 7.1, 1 H, CH), 11.43 (d, ^3J = 8.1 Hz, 1 H, NH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.1 (CH_3), 29.0 (N^3-CH_3), 34.5 (CH_2), 36.4 (N^1-CH_3), 53.9 (OCH_3), 55.5 (CH), 95.0 (C-5), 115.8 (CN), 151.23 (C-2), 162.2 (C-4), 162.8 (C-6), 171.9 ($COOCH_3$), 188.4 (CO).

MS (EI, 70 eV): *m/z* = 308 M^+ (5), 268 (68), 249 (27), 208 (100), 110 (44), 82 (61), 68 (32), 42 (36) cm^{-1}.

ESI-MS: *m/z* = 309 $[M + H]^+$, 331 $[M + Na]^+$.

Anal. Calcd for $C_{13}H_{16}N_4O_5$ (308.30): C, 50.65; H, 5.23; N, 18.17. Found: C, 50.44; H, 5.27; N, 18.04.

Ethyl *N*-[5-(Cyanoacetyl)-1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl]valinate (4c)

Method A: White solid; yield: 3.4 g; 52%; mp 124.3 °C (EtOH).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.04 [d, ^3J = 6.8 Hz, 3 H, $CH(CH_3)_2$], 1.08 [d, ^3J = 6.9 Hz, 3 H, $CH(CH_3)_2$], 1.28 (t, ^3J = 7.1 Hz, 3 H, OCH_2CH_3), 2.37 [m_c, 1 H, $CH(CH_3)_2$], 3.30 (s, 3 H, N^3-CH_3), 3.42 (s, 3 H, N^1-CH_3), 4.26 (m_c, 5 H, $NHCHRCO_2CH_3$, $COCH_2CN$, OCH_2CH_3), 11.47 (d, ^3J = 8.2 Hz, 1 H, NH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.8 (OCH_2CH_3), 18.4 [$CH(CH_3)_2$], 19.7 [$CH(CH_3)_2$], 29.0 (N^3-CH_3), 33.3 [$CH(CH_3)_2$], 34.5 ($COCH_2CN$), 37.1 (N^1-CH_3), 62.8 (OCH_2CH_3), 66.2 ($NHCHRCO_2C_2H_5$), 99.7 (C-5), 115.9 (CN), 151.4 (C-2), 162.2 (C-4), 163.6 (C-6), 170.3 ($CO_2C_2H_5$), 188.2 ($COCH_2CN$).

MS (EI, 70 eV): *m/z* = 350 M^+ (2), 310 (20), 277 (31), 236 (50), 208 (13), 156 (25), 129 (42), 110 (34), 82 (100), 55 (85), 41 (44).

ESI-MS: *m/z* = 351 $[M + H]^+$, 373 $[M + Na]^+$.

Anal. Calcd for $C_{16}H_{22}N_4O_5$ (350.58): C, 54.85; H, 6.33; N, 15.99. Found: C, 54.53; H, 6.40; N, 15.60.

Methyl *N*-[5-(Cyanoacetyl)-1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl]-l-phenylalaninate [(*S*)-4d]

Method A: White solid; yield: 3.91 g (51%); mp 152.3 °C (MeOH).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.21 (AB part of ABX-system, ^3J = 10.0 Hz, ^3J = 4.3 Hz, ^2J = 14.0 Hz, 2 H, CH_2Ar), 3.23 (s, 3 H, N^3-CH_3), 3.26 (s, 3 H, N^1-CH_3), 3.82 (s, 3 H, OCH_3), 4.21 (AB-system, ^2J = 19.6 Hz, 2 H, $COCH_2CN$), 4.62 (X part of ABX-system, ^3J = 9.5 Hz, ^3J = 4.3 Hz, 1 H, CH), 7.25 (m_c, 5 H, Ar-H), 11.32 (d, ^3J = 9.4 Hz, 1 H, NH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.2 (N^3-CH_3), 33.8 ($COCH_2CN$), 36.2 (N^1-CH_3), 40.4 (CH_2-Ar), 53.3 (OCH_3), 61.2 (CH), 87.2 (C-5), 115.1 (CN), 127.0 (C-4′), 128.7 (C-2′, C-6′), 129.4 (C-3′, C-5′), 135.8 (C-1′), 153.0 (C-2), 161.1 (C-6), 163.7 (C-4), 171.9 (CO_2CH_3), 187.7 ($COCH_2CN$).

MS (EI, 70 eV): *m/z* = 384 M^+ (4), 344 (11), 293 (10), 284 (12), 233 (33), 208 (11), 162 (100), 131 (23), 91 (47), 82 (37), 42 (11).

ESI-MS: *m/z* = 385 $[M + H]^+$.

Anal. Calcd for $C_{19}H_{20}N_4O_5$ (384.40): C, 59.37; H, 5.24; N, 14.58. Found: C, 59.68; H, 5.33; N, 14.53.

Ethyl 2-{[5-(Cyanoacetyl)-1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl]amino}-4-phenylbutanoate (4e)

Method A: White solid; yield: 6.0 g (75%); mp 116.9 °C (EtOH).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.28 (t, ^3J = 7.13 Hz, 3 H, OCH_2CH_3), 2.31 (m_c, 2 H, CH_2CH_2-Ar), 2.81 (m_c, 2 H, CH_2CH_2-Ar), 3.21 (s, 3 H, N^3-CH_3), 3.31 (s, 3 H, N^1-CH_3), 4.24 (m_c, 3 H, CH, OCH_2CH_3), 4.31 (AB-system, J_{AB} = 19.7 Hz, 2 H, $COCH_2CN$), 7.21 (m_c, 5 H, H-2″, H-3″, H-4″, H-5″, H-6″), 11.59 (d, ^3J = 8.52 Hz, 1 H, NH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.8 (OCH_2CH_3), 29.0 (N^3-CH_3), 32.2 ($COCH_2CN$), 34.6 (CH_2CH_2-Ar), 35.6 (CH_2CH_2-Ar), 36.4 (N^1-CH_3), 59.1 (OCH_2CH_3), 63.1 (CH), 94.7 (C-5), 115.9 (CN), 127.5 (C-4′), 129.1 (C-2′, C-6′), 129.5 (C-3′, C-5′), 139.6 (C-1′), 151.2 (C-2), 162.2 (C-6), 163.1 (C-4), 170.9 ($COOCH_2CH_3$), 188.5 ($COCH_2CN$).

MS (EI, 70 eV): *m/z* = 308 (6), 268 (6), 208 (27), 117 (13), 91 (100), 68 (11), 41 (16).

ESI-MS: *m/z* = 413 $[M + H]^+$.

Anal. Calcd for $C_{21}H_{24}N_4O_5$ (412.45): C, 61.16; H, 5.87; N, 13.58. Found: C, 61.35; H, 6.09; N, 13.94.

Ethyl *N*-[5-(Cyanoacetyl)-1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl]-3-(1-naphthyl)alaninate (4f)

Method C: White solid; yield: 3.5 g (43%); mp 114.2 °C (EtOH).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.34 (t, ^3J = 7.20 Hz, 3 H, OCH_2CH_3), 2.95 (s, 3 H, N^3-CH_3), 3.10 (s, 3 H, N^1-CH_3), 3.67 (AB-part of the ABMX-system, J_{AX} = 4.1 Hz, J_{BX} = 10.1 Hz, J_{AB} = 14.3 Hz, 2 H, CH_2), 4.16 (AB-system, J_{AB} = 19.75 Hz, 2 H, $COCH_2CN$), 4.26 (q, ^3J = 7.1 Hz, 2 H, OCH_2CH_3,), 4.88 (dt, X-part of the ABMX-system, $^3J_{AX}$ = 4.1 Hz, $^3J_{BX}$ = $^3J_{XNH}$ = 10.1 Hz, 1 H, CH), 7.29 (m_c, 2 H, H-2′, H-3′), 7.53 (m_c, 2 H, H-6′, H-7′), 7.68 (m_c, 1 H,

H-4′), 7.84 (m_c, 1 H, H-5′), 7.98 (m_c, 1 H, H-8′), 11.41 (d, M-part of the ABMX-system, 1 H, ^3J = 9.9 Hz, NH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1 (O*C*H$_2$CH$_3$), 27.9 (*N*^{3}-CH$_3$), 33.7 (CO*C*H$_2$CN), 35.9 (*N*^{1}-CH$_3$), 38.1 (CH$_2$), 60.0 (CH), 62.7 (O*C*H$_2$CH$_3$), 94.6 (C-5), 115.2 (CN), 122.3 (C-8′), 125.3 (C-3′), 126.2 (C-6′), 127.0 (C-7′), 128.7 (2C, C-4′, C-2′), 129.2 (C-5′), 131.0 (C-8a′), 131.2 (C-1′), 133.8 (C-4a′), 149.9 (C-2), 162.3 (C-6), 162.3 (C-4), 169.5 (*C*OOCH$_2$CH$_3$), 187.1 (CO).

MS (EI, 70 eV): *m/z* = 448 M$^+$ (1), 307 (2), 226 (23), 153 (24), 141 (45), 82 (26), 55 (95), 41 (100).

Anal. Calcd for $C_{24}H_{24}N_4O_5$ (448.48): C, 64.28; H, 5.39; N, 12.49. Found: C, 64.30; H, 5.51; N, 12.88.

Ethyl 1-[5-(Cyanoacetyl)-1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl]piperidine-2-carboxylate (4g)

Method A: White solid; yield: 3.6 g (50%); mp 102.4 °C (EtOH).

IR (KBr): 2936 (m, ν, CH$_2$, CH$_3$), 2200 (s, ν, CN), 1736 (s, ν, COOCH$_2$CH$_3$), 1646 (s, ν, RNCONR), 1474 (m, δ, NH), 1430 cm^{-1} (m, δ, CH$_2$, CH$_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.20 (t, ^3J = 7.1 Hz, 3 H, OCH$_2$C*H*$_3$), 1.67 (m_c, 4 H, piperidine-H$_a$-3, H$_a$-4, H$_{a,e}$-5), 1.92 (m_c, 1 H, piperidine-H$_e$-4), 2.09 (m_c, 1 H, piperidine-H$_e$-3), 3.15 (m_c, 2 H, piperidine-N-H$_a$-6, H$_e$-6), 3.33 (s, 3 H, *N*^{3}-CH$_3$), 3.58 (s, 3 H, *N*^{1}-CH$_3$), 3.78 (dd, ^3J = 3.3 Hz, ^3J = 9.4 Hz, 1 H, piperidine-N-H-2), 4.11 (AB-system, J_{AB} = 19.6 Hz, 2 H, COCH$_2$CN], 4.12 (m_c, 2 H, OC*H*$_2$CH$_3$).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0 (OCH$_2$*C*H$_3$), 22.5 (piperidine-C-4), 24.3 (piperidine-C-5), 28.4 (*N*^{3}-CH$_3$), 29.5 (piperidine-C-3), 33.4 (*N*^{1}-CH$_3$), 34.1 (CO*C*H$_2$CN), 50.8 (piperidine-C-6), 60.9 (piperidine-C-2), 61.6 (O*C*H$_2$CH$_3$), 104.6 (C-5), 114.7 (CN), 151.5 (C-2), 161.8 (C-6), 162.8 (C-4), 171.4 (*C*OOCH$_2$CH$_3$), 186.9 (*C*OCH$_2$CN).

MS (EI, 70 eV): *m/z* = 362 M$^+$ (1), 322 (47), 289 (52), 248 (21), 191 (36), 156 (22), 149 (16), 110 (17), 82 (100), 55 (40), 41 (27).

ESI-MS: *m/z* = 363 [M + H]$^+$, 747 [2M + Na]$^+$.

Anal. Calcd for $C_{17}H_{22}N_4O_5$ (362.39): C, 56.35; H, 6.12; N, 15.48. Found: C, 56.28; H, 6.17; N, 15.42.

Methyl 1-[5-(Cyanoacetyl)-1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl]prolinate (4h)

Method C: Pale yellow oil; yield: 3.21 g (48%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.06 (m_c, 3 H, pyrrolidine-H$_a$-3, H$_{a,e}$-4), 2.60 (m_c, 1 H, pyrrolidine-H$_e$-3), 3.22 (m_c, 1 H, pyrrolidine-H$_a$-5), 3.33 (s, 3 H, *N*^{3}-CH$_3$), 3.58 (s, 3 H, *N*^{1}-CH$_3$), 3.58 (m_c, 1 H, pyrrolidine-H$_e$-5), 3.70 (s, 3 H, OCH$_3$), 4.14 (AB-system, J_{AB} = 19.4 Hz, 2 H, COCH$_2$CN], 4.27 (dd, ^3J = 6.1, ^3J = 8.3, 1 H, pyrrolidine-H-2).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.5 (pyrrolidine-C-4), 28.5 (*N*^{3}-CH$_3$), 30.4 (pyrrolidine-C-3), 34.4 (CO*C*H$_2$CN), 35.1 (*N*^{1}-CH$_3$), 52.5 (OCH$_3$), 52.8 (pyrrolidine-C-5), 63.0 (pyrrolidine-C-2), 100.7 (C-5), 115.1 (CN), 151.6 (C-2), 160.1 (C-4), 162.5 (C-6), 172.8 (*C*OOCH$_3$), 185.4 (*C*OCH$_2$CN).

MS (EI, 70 eV): *m/z* = 334 M$^+$ (1), 294 (42), 275 (24), 234 (23), 207 (11), 177 (24), 149 (24), 82 (100), 68 (86), 41 (90).

ESI-MS: *m/z* = 335 [M + H]$^+$.

HRMS (EI): *m/z* = M$^+$ calcd for $C_{15}H_{18}N_4O_5$: 334.12772; found: 334.12780.

Methyl *N*-[5-(Cyanoacetyl)-1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl]-*N*-methylglycinate (4i)

Method B: White solid; yield: 3.9 g (63%); mp 102.4 °C (MeOH).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.91 (s, 3 H, *N*-CH$_3$), 3.27 (s, 3 H, *N*^{3}-CH$_3$), 3.57 (s, 3 H, *N*^{1}-CH$_3$), 3.72 (s, 2 H, CH$_2$), 3.76 (s, 3 H, OCH$_3$), 4.17 (s, 2 H, COCH$_2$CN).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.5 (*N*^{3}-CH$_3$), 34.5 (CO*C*H$_2$CN), 34.8 (*N*^{1}-CH$_3$), 41.0 (N-CH$_3$), 52.5 (OCH$_3$), 54.4 (CH$_2$), 100.8 (C-5), 115.0 (CN), 151.6 (C-2), 162.3 (C-4), 163.3 (C-6), 169.5 (*C*OOCH$_3$), 185.3 (*C*OCH$_2$CN).

ESI-MS: *m/z* = 309 [M + H]$^+$, 639 [2M + Na]$^+$.

Anal. Calcd for $C_{13}H_{16}N_4O_5$ (308.30): C, 50.65; H, 5.23; N, 18.17. Found: C, 50.41; H, 5.19; N, 18.46.

Cyclization of 4; General Procedure

Method A: A mixture of cyanoacetate **4** (1 mmol) and Na (1 mmol) in EtOH (or MeOH for methyl esters) was stirred at r.t. while the reaction was monitored by TLC. When the reaction was complete, the solvent was removed under reduced pressure and crushed ice was added to the residue. The resulting solution was acidified with glacial AcOH until a crude product formed. This was filtered off and crystallized from the specified solvent.

Method B: A soln of **4** (3.6 mmol) and NaOMe (45 mmol) in MeOH (50 mL) was refluxed until the reaction was complete. The solvent was evaporated, crushed ice was added to the residue, and the mixture was acidified with glacial AcOH. The crude product was recovered by filtration and crystallization from the specified solvent.

5-Hydroxy-1,3-dimethyl-2,4,7-trioxo-2,3,4,7,8,9-hexahydro-1*H*-pyrimido[4,5-*b*]azepine-6-carbonitrile (5a)

Method A: White solid; yield: 0.35 g (82%); mp 281–282 °C (EtOH–H$_2$O).

IR (KBr): 3225 (m, ν, OH), 2226 (s, ν, CN) 1716 (s, ν, CO), 1652 (s, ν, RNCONR), 1596 (m, δ, NH), 1480 cm^{-1} (m, δ, CH$_2$).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.29 (s, 3 H, *N*^{3}-CH$_3$), 3.44 (s, 3 H, *N*^{1}-CH$_3$), 3.81 (s, 2 H, CH$_2$), 9.57 (s, 1 H, NH), 15.42 (s, 1 H, OH).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 28.4 (*N*^{3}-CH$_3$), 31.0 (*N*^{1}-CH$_3$), 51.9 (CH$_2$), 87.1 (C-4a), 89.3 (C-6), 116.5 (CN), 148.2 (C-2), 156.9 (C-9a), 167.3 (C-4), 176.6 (C-5), 183.7 (C-7).

MS (EI, 70 eV): *m/z* = 262 M$^+$ (3), 218 (5), 164 (5), 82 (22), 57 (27), 44 (100).

ESI-MS: *m/z* = 263 [M + H]$^+$, 524 [2M + H]$^+$.

Anal. Calcd for $C_{11}H_{10}N_4O_4$ (262.23): C, 50.38; H, 3.84; N, 21.37. Found: C, 50.45; H, 3.94; N, 21.31.

5-Hydroxy-1,3,8-trimethyl-2,4,7-trioxo-2,3,4,7,8,9-hexahydro-1*H*-pyrimido[4,5-*b*]azepine-6-carbonitrile (5b)

Method A: White solid; yield: 144 mg (52%); mp 237.5 °C (EtOH).

IR (KBr): 2956 (w, ν, CH$_2$), 2260 (m, ν, CN), 1716 (s, ν, CO), 1652 (s, ν, RNCONR), 1522 (m, δ, NH), 1464 cm^{-1} (m, δ, CH$_2$).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.36 (d, ^3J = 7.0 Hz, 3 H, CH$_3$), 3.26 (s, 3 H, *N*^{3}-CH$_3$), 3.43 (s, 3 H, *N*^{1}-CH$_3$), 3.82 (q, ^3J = 7.0 Hz, 1 H, CH), 8.63 (br s, 1 H, NH), 15.54 (br s, 1 H, OH).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 18.1 (CH$_3$), 28.3 (*N*^{3}-CH$_3$), 31.2 (*N*^{1}-CH$_3$), 56.1 (C-8), 87.8 (C-4a), 88.7 (C-6), 116.7 (CN), 148.4 (C-2), 155.5 (C-9a), 167.2 (C-4), 175.8 (C-5), 188.4 (C-7).

MS (EI, 70 eV): *m/z* = 276 M$^+$ (1), 82 (17), 44 (100).

ESI-MS: *m/z* = 277 [M + H]$^+$, 299 [M + Na]$^+$.

HRMS (EI): *m/z* = M$^+$ calcd for $C_{12}H_{12}N_4O_4$: 276.08585; found: 276.08568.

Anal. Calcd for $C_{12}H_{12}N_4O_4$ (276.25): C, 52.17; H, 4.38; N, 20.28. Found: C, 51.88; H, 4.46; N, 19.92.

5-Hydroxy-8-isopropyl-1,3-dimethyl-2,4,7-trioxo-2,3,4,7,8,9-hexahydro-1*H*-pyrimido[4,5-*b*]azepine-6-carbonitrile (5c)

Method A: White solid; yield: 250 mg (82%); mp 268.2 °C (EtOH).

IR (KBr): 3236 (m, ν, OH), 2222 (w, ν, CN), 1712 (s, ν, CO), 1636 (s, ν, RNCONR), 1574 (m, δ, NH), 1360 cm^{-1} (m, δ, OH).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 0.84 [d, ^3J = 6.1 Hz, 3 H, CH(CH_3)$_2$], 0.86 [d, ^3J = 6.1 Hz, 3 H, CH(CH_3)$_2$], 1.99 [m$_c$, 1 H, CH(CH$_3$)$_2$], 3.25 (s, 3 H, N^3-CH$_3$), 3.45 (m$_c$, 4 H, N^1-CH$_3$, CH), 8.88 (br s, 1 H, NH), 15.85 (br s, 1 H, OH).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 18.6 [(CH(*C*H$_3$)$_2$], 19.4 [CH(*C*H$_3$)$_2$], 25.7 [*C*H(CH$_3$)$_2$], 28.4 (N^3-CH$_3$), 31.2 (N^1-CH$_3$), 67.8 (C-8), 87.5 (C-4a), 88.2 (C-6), 116.6 (CN), 148.4 (C-2), 154.1 (C-9a), 167.0 (C-4), 175.2 (C-5), 185.0 (C-7).

MS (EI, 70 eV): *m/z* = 259 (10), 246 (7), 221 (5), 138 (5), 82 (20), 55 (25), 44 (100).

ESI-MS: *m/z* = 305 [M + H]$^+$, 609 [2M + H]$^+$.

Anal. Calcd for $C_{14}H_{16}N_4O_4$ (304.31): C, 55.26; H, 5.30; N, 18.41. Found: C, 55.31; H, 5.43; N, 18.36.

(8*S*)-5-Hydroxy-1,3-dimethyl-8-(2-methylphenyl)-2,4,7-trioxo-2,3,4,7,8,9-hexahydro-1*H*-pyrimido[4,5-*b*]azepine-6-carbonitrile [(*S*)-5d]

Method A: White solid; yield: 282 mg (80%); mp 252.8 °C (dioxane); $[\alpha]_D^{20}$ +113.9 (*c* 1.00, DMF).

HPLC: CHIRALCEL OD-R column, aq K_2HPO_4 buffer (pH 2)–MeCN (3:2); injection volume: 10.0 μL of **5d** and its *R*-enantiomer; flow rate: 0.6 mL/min; UV detection: 254 nm; *S*-enantiomer t_R = 13.54 min; *R*-enantiomer t_R = 14.88 min.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.09 (AB part of ABX-system, ^3J = 10.4 Hz, ^3J = 5.1 Hz, ^2J = 14.2 Hz, 2 H, CH_2Ar), 3.09 (s, 3 H, N^3-CH$_3$), 3.24 (s, 3 H, N^1-CH$_3$), 4.02 (X part of ABX-system, ^3J = 10.2 Hz, ^3J = 5.1 Hz, 1 H, CH), 7.24 (m$_c$, 5 H, Ar-H), 8.56 (br s, 1 H, NH), 15.74 (br s, 1 H, OH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.8 (N^3-CH$_3$), 31.1 (N^1-CH$_3$), 33.4 (CH$_2$-Ar), 62.3 (CH), 88.5 (C-4a), 89.1 (C-6), 117.0 (CN), 127.0 (C-4′), 128.7 (C-2′, C-6′), 129.4 (C-3′, C-5′), 136.9 (C-1′), 148.6 (C-2), 155.2 (C-9a), 167.2 (C-4), 175.8 (C-5), 185.4 (C-7).

MS (EI, 70 eV): *m/z* = 259 (2), 111 (11), 91 (20), 83 (32), 55 (100), 43 (80).

ESI-MS: *m/z* = 353 [M + H]$^+$.

Anal. Calcd for $C_{18}H_{16}N_4O_4$ (352.35): C, 61.36; H, 4.58; N, 15.90. Found: C, 61.27; H, 4.61; N, 15.98.

5-Hydroxy-1,3-dimethyl-2,4,7-trioxo-8-(2-phenylethyl)-2,3,4,7,8,9-hexahydro-1*H*-pyrimido[4,5-*b*]azepine-6-carbonitrile (5e)

Method A: White solid; yield: 300 mg (82%); mp 230.5 °C (dioxane).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.07 (m$_c$, 2 H, CH_2CH$_2$-Ar), 2.61 (m$_c$, 2 H, CH$_2$CH_2-Ar), 3.25 (s, 3 H, N^3-CH$_3$), 3.38 (s, 3 H, N^1-CH$_3$), 3.78 (t, ^3J = 7.3 Hz, 1 H, CH), 7.22 (m$_c$, 5 H, Ar-H), 8.74 (br s, 1 H, NH), 15.76 (br s, 1 H, OH).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 28.4 (N^3-CH$_3$), 28.9 (CH$_2$*C*H$_2$-Ar), 31.2 (N^1-CH$_3$), 31.3 (*C*H$_2$CH$_2$-Ar), 60.5 (CH), 87.8 (C-4a), 88.5 (C-6), 116.7 (CN), 125.9 (C-4′), 128.2 (C-2′, C-6′), 128.2 (C-3′, C-5′), 140.7 (C-1′), 148.3 (C-2), 155.1 (C-9a), 167.1 (C-4), 175.7 (C-5), 185.1 (C-7).

MS (EI, 70 eV): *m/z* = 366 M$^+$(1), 104 (12), 91 (53), 65 (16), 44 (100).

HRMS (EI): *m/z* = M$^+$ calcd for $C_{19}H_{18}N_4O_4$: 366.13281; found: 366.13264.

Anal. Calcd for $C_{19}H_{18}N_4O_4$ (366.38): C, 62.29; H, 4.95; N, 15.29. Found: C, 62.01; H, 5.01; N, 15.21.

5-Hydroxy-1,3-dimethyl-8-(1-naphthylmethyl)-2,4,7-trioxo-2,3,4,7,8,9-hexahydro-1*H*-pyrimido[4,5-*b*]azepine-6-carbonitrile (5f)

Method A: White solid; yield: 302 mg (75%); mp 291.2 °C (dioxane).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.04 (s, 3 H, N^1-CH$_3$), 3.24 (s, 3 H, N^3-CH$_3$), 3.52 [z_{AB} (1056 Hz), AB-part of the ABX-system, J_{AX} = 4.6 Hz, J_{BX} = 9.9 Hz, J_{AB} = 14.7 Hz, C = 36.42 Hz, $\nu_0\delta$ = 0.24 ppm (71 Hz), ν_a = 3.64 ppm (1092 Hz), ν_b = 3.40 ppm (1020 Hz), 2 H, CH$_2$], 4.19 (X-part of ABX-system, dd, ^3J = 4.6 Hz, ^3J = 9.9 Hz, 1 H, CH), 7.43 (m$_c$, 2 H, H-2′, H-3′), 7.55 (m$_c$, 2 H, H-6′, H-7′), 7.84 (d, ^3J = 7.3 Hz, 1 H, H-4′), 7.94 (d, ^3J = 7.2 Hz, 1 H, H-5′), 8.06 (d, ^3J = 7.9 Hz, 1 H, H-8′), 8.54 (br s, 1 H, NH), 15.91 (br s, 1 H, OH).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 28.5 (N^3-CH$_3$), 30.7 (CH$_2$), 30.9 (N^1-CH$_3$), 61.6 (CH), 88.2 (C-4a), 89.0 (C-6), 116.7 (CN), 123.2 (C-8′), 125.3 (C-3′), 125.7 (C-6′), 126.3 (C-7′), 127.5 (C-4′), 127.6 (C-2′), 128.7 (C-5′), 131.2 (C-8a′), 132.5 (C-1′), 133.5 (C-4a′), 148.2 (C-2), 154.7 (C-9a), 167.1 (C-4), 175.6 (C-5), 185.2 (C-7).

MS (EI, 70 eV): *m/z* = 402 M$^+$ (1), 141 (8), 57 (26), 44 (100).

ESI-MS: *m/z* = 403 [M + H]$^+$, 805 [2M + H]$^+$.

Anal. Calcd for $C_{22}H_{18}N_4O_4$ (402.41): C, 65.67; H, 4.51; N, 13.92. Found: C, 65.88; H, 4.59; N, 14.05.

9-Cyano-8-hydroxy-*N*-methyl-6-(methylamino)-10-oxo-1,2,3,4,10,10a-hexahydropyrido[1,2-*a*]azepine-7-carboxamide (6a)

Method A: White solid; yield: 146 mg (50%); mp 291.2 °C (dioxane).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.63 (m$_c$, 4 H, H$_a$-1, H$_a$-2, H$_{a,e}$-3), 2.11 (m$_c$, 1 H, H$_e$-2), 2.73 (m$_c$, 5 H, H$_e$-1, H$_a$-4, HNCH_3), 2.89 (m$_c$, 1 H, H$_e$-4), 3.31 (s, 3 H, H_3CNHCO), 3.86 (m$_c$, 1 H, H-10a), 7.78 (br s, 1 H, NH), 8.02 (br s, 1 H, NH), 15.86 (br s, 1 H, OH).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 19.1 (C-2), 21.9 (C-3), 23.2 (C-1), 25.8 (HNCH_3), 32.3 (H$_3$*C*NHCO), 44.5 (C-4), 58.9 (C-10a), 79.3 (C-9), 84.8 (C-7), 119.0 (CN), 162.6 (H$_3$CNH*C*O), 170.8 (C-6), 177.2 (C-8), 187.0 (C-10).

MS (EI, 70 eV): *m/z* = 223 (70), 193 (61), 137 (28), 84 (100), 58 (63), 41 (45).

ESI-MS: *m/z* = 291 [M + H]$^+$, 581 [M + M]$^+$.

HRMS (EI): *m/z* = M$^+$ calcd for $C_{14}H_{18}N_4O_3$: 290.13788; found: 290.13793.

8-Cyano-7-hydroxy-*N*-methyl-5-(methylamino)-9-oxo-2,3,9,9a-tetrahydro-1*H*-pyrrolo[1,2-*a*]azepine-6-carboxamide (6b)

Method A: White solid; yield: 28 mg (10%); mp 240.1 °C (dioxane).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.77 (m$_c$, 2 H, pyrrolidine-H$_a$-1, -H$_a$-2), 2.01 (m$_c$, 1 H, pyrrolidine-H$_e$-2), 2.58 (m$_c$, 1 H, H$_e$-1), 2.73 (m$_c$, 3 H, HNCH_3,), 3.32 (s, 3 H, CONHCH_3), 3.34 (m, 1 H, H$_a$-3), 3.48 (m$_c$, 1 H, H$_e$-3), 3.99 (d, 1 H, H-9a), 7.42 (br s, 1 H, NH), 7.92 (br s, 1 H, NH), 15.55 (br s, 1 H, OH).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 23.3 (C-2), 24.6 (C-1), 25.7 (CONHCH_3), 32.3 (NHCH_3), 48.0 (C-3), 64.3 (C-9a), 81.0 (C-8), 84.3 (C-6), 119.4 (CN), 158.1 (C-5), 170.1 (*C*ONHCH$_3$), 175.6 (C-7), 184.7 (C-9).

MS (EI, 70 eV): *m/z* = 241 (38), 168 (33), 155 (4), 140 (35), 111 (44), 82 (100), 55 (98).

ESI-MS: *m/z* = 277 [M + H]$^+$, 553 [2M + H]$^+$.

HRMS (EI): *m/z* = M^+ calcd for $C_{13}H_{16}N_4O_3$: 276.12225; found: 276.12224.

5-Hydroxy-1,3,7-trimethyl-2,4,8-trioxo-2,3,4,7,8,9-hexahydro-1*H*-pyrimido[4,5-*d*]azepine-6-carbonitrile (7)

Method B: Pale yellow solid; yield: 69 mg (25%); mp 251.9 °C (dioxane).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.54 (s, 3 H, *N*-CH_3), 3.23 (s, 3 H, N^3-CH_3), 3.68 (s, 3 H, N^1-CH_3), 5.00 (br s, 2 H, CH_2), 13.44 (s, 1 H, OH).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 27.5 (N^3-CH_3), 34.9 (N^1-CH_3), 36.3 (*N*-CH_3), 66.3 (C-9), 84.0 (C-4a), 93.0 (C-6), 114.2 (CN), 140.2 (C-9a), 151.1 (C-2), 162.6 (C-5), 164.8 (C-8), 165.4 (C-4).

ESI-MS: *m/z* = 277 $[M + H]^+$, 553 $[2M + H]^+$.

HRMS (EI): *m/z* = M^+ calcd for $C_{12}H_{12}N_4O_4$: 276.08585; found: 276.08584.

Anal. Calcd for $C_{12}H_{12}N_4O_4$ (276.25): C, 52.17; H, 4.38; N, 20.28. Found: C, 50.42; H, 4.49; N, 20.15.

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