Reaction of Ethyl 5-Acetyl-3,4-dihydropyridine-1(2*H*)-carboxylate with 1,3-*N*,*N*-Bis-nucleophiles: A Facile Access to Novel Pyrimidine Derivatives

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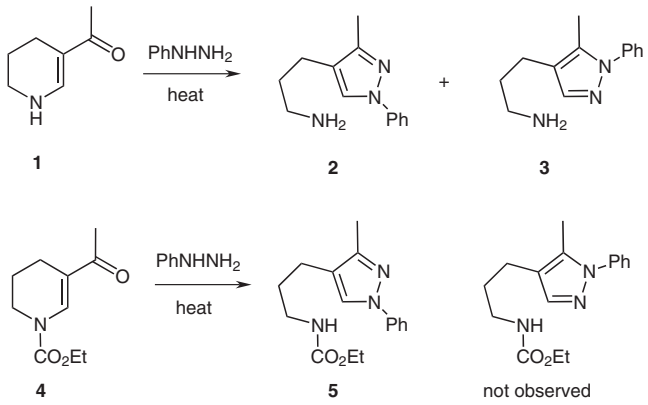
Abstract: Reaction of ethyl 5-acetyl-3,4-dihydropyridine-1(2*H*)-carboxylate with diverse 1,3-*N*,*N*-bis-nucleophiles results in the regioselective formation of the correspondingly substituted pyrimidines in good yields.

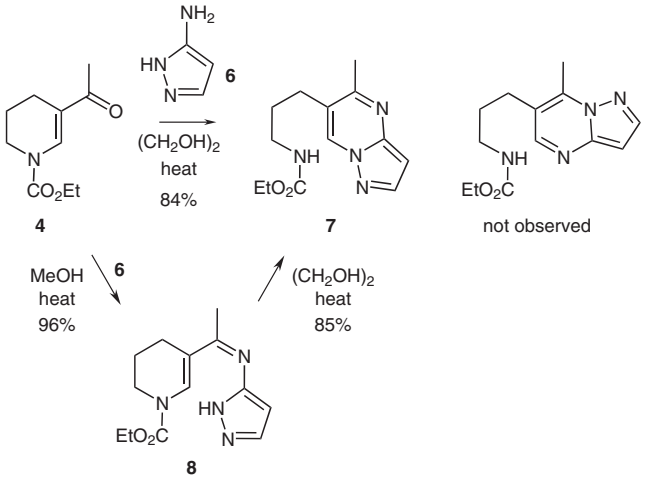
Key words: pyrimidines, amidines, amino heterocycles, tetrahydropyridine

In 1970, Quin and Pinion showed that β-enamino ketone **1** reacts with phenylhydrazine to form a mixture of two isomeric pyrazoles **2/3** (Scheme 1).[1] Recently, we found that the *N*-ethoxycarbonyl-substituted compound **4**, in contrast to **1**, regioselectively reacts with various hydrazines to form only one isomer of the corresponding pyrazoles, e.g. **5** (Scheme 1).[2] Herein, we report our studies on the reaction of compound **4** with 1,3-*N*,*N*-bis-nucleophiles to regioselectively form novel pyrimidine derivatives.[3]



Scheme 1 Synthesis of the mixture of pyrazoles **2/3** according to the literature method[1] and regioselective synthesis of pyrazole **5**, also according to the literature[2]

3-Aminopyrazole (**6**) was used as a simple model of a heterocyclic 1,3-*N*,*N*-bis-nucleophile. Heating a mixture of *N*-ethoxycarbonyl-protected compound **4**[4] and 3-aminopyrazole (**6**) in anhydrous ethylene glycol at 150 °C for six hours resulted in the formation of pyrimidine **7** as a single isomer in a good yield of 84% (Scheme 2). Moreover, performing the reaction at 60 °C in methanol allowed isolation of the corresponding intermediate **8** from the reaction mixture. As expected, heating imine **8** at 150 °C in anhydrous ethylene glycol afforded pyrimidine **7**, again as the sole isomer (Scheme 2).



Scheme 2 Synthesis of pyrimidine **7**

Having at hand a successful result, we next tested a set of various 1,3-*N*,*N*-bis-nucleophiles **9**–**20** (Figure 1).

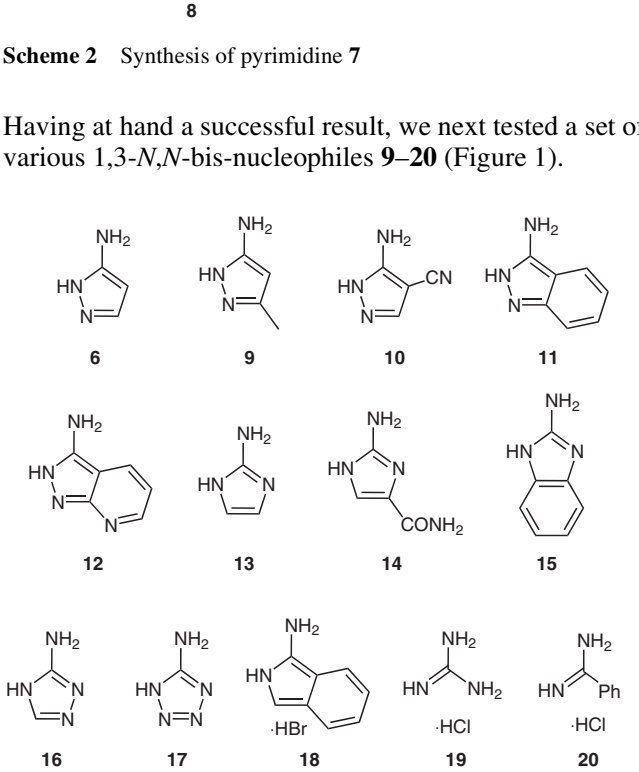


Figure 1 1,3-*N*,*N*-Bis-nucleophiles **6**, **9**–**20**

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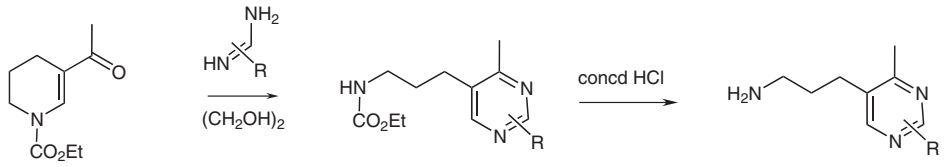
Indeed, all products were obtained as single regioisomers **21**–**32** in 25–82% yield (Table 1). It is worth noting that aminotetrazole **17** gave the corresponding product **29** in only 25% yield, probably due to the highly electron-withdrawing nature of the tetrazole moiety.

Table 1 Structures of Pyrimidines **7**, **21**–**32** Arising from the Reaction of β-Enamino Ketone **4** with 1,3-*N*,*N*-Bis-nucleophiles **6**, **9**–**20**, and the Corresponding Amines **33**–**45**



4 **7**, **21**–**32** **33**–**45**

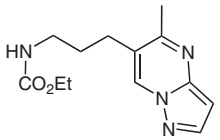
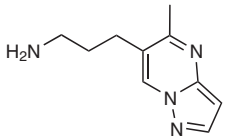
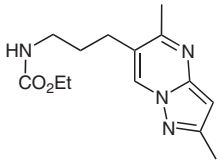
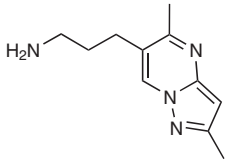
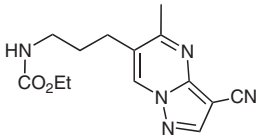
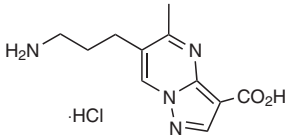
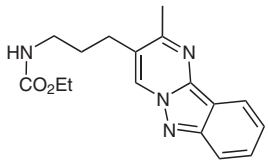
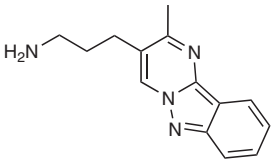
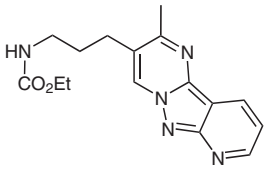
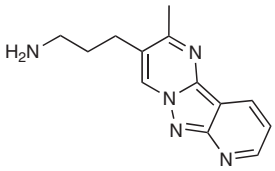
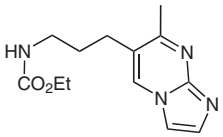
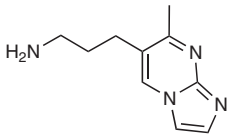
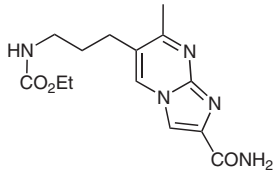
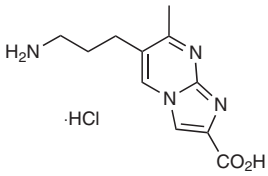
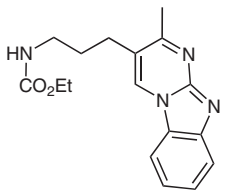
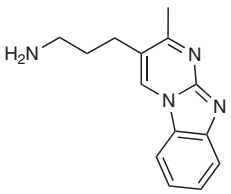
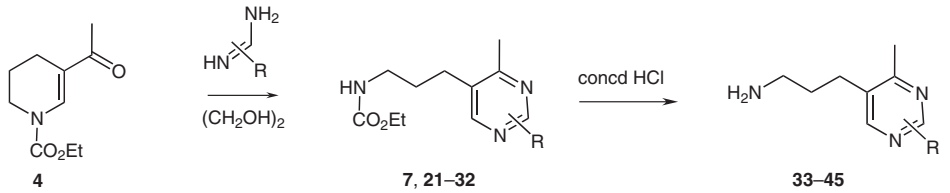
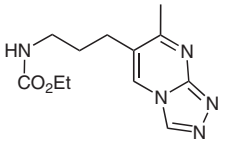
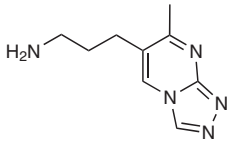
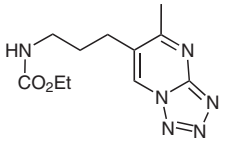
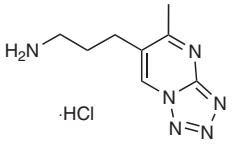
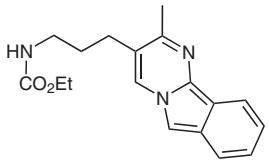
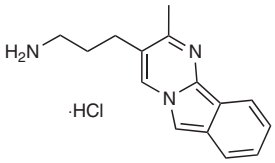
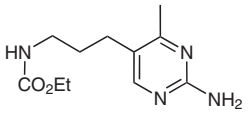
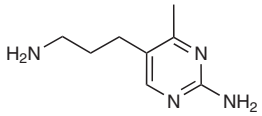
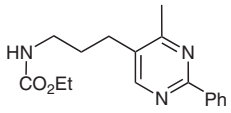
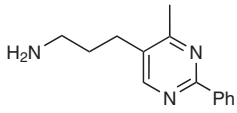
1,3-*N*,*N*-Bis-nucleophile	Protected pyrimidine	Yield (%)	Amine[a]	Yield (%)
6	**7** 	84	**33** 	95
9	**21** 	72	**34** 	91
10	**22** 	71	**35** 	99
11	**23** 	60	**36** 	96
12	**24** 	82	**37** 	92
13	**25** 	66	**38** 	89
14	**26** 	63	**39** 	99
15	**27** 	54	**40** 	83

Table 1 Structures of Pyrimidines **7**, **21**–**32** Arising from the Reaction of β-Enamino Ketone **4** with 1,3-*N*,*N*-Bis-nucleophiles **6**, **9**–**20**, and the Corresponding Amines **33**–**45** (continued)



1,3-*N*,*N*-Bis-nucleophile	Protected pyrimidine		Yield (%)	Amine[a]		Yield (%)
16	**28**		56	**41**		94
17	**29**		25	**42**		99
18	**30**		46	**43**		95
19	**31**		66	**44**		84
20	**32**		52	**45**		96

[a] Compounds **35**, **39**, **42** and **43** were isolated as the hydrochloride salts.

Non-heterocyclic 1,3-*N*,*N*-bis-nucleophiles **19** and **20** were used as the hydrochlorides. Notably, the cyclization was successfully performed without the addition of any base. Moreover, when the reaction was performed in the presence of triethylamine, the corresponding products **31**, **32** were isolated in only 5–10% yield, probably due to the instability of the free amidines **19** and **20** at high temperature.

The structures of compounds **25** and **28** were additionally confirmed by NOESY experiments (Figure 2).

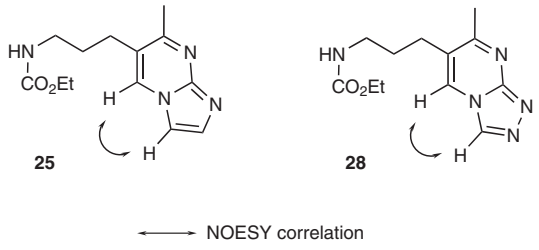


Figure 2 The key correlations in the NOESY spectra of compounds **25** and **28**

Finally, the protected pyrimidines **7**, **21**–**32** were easily converted into the corresponding amines **33**–**45** by heating in concentrated hydrochloric acid (Table 1). Indeed, under these reaction conditions, hydrolysis of the nitrile group in compound **22** and the amide group in compound **26** also occurred, so that amino acids **35** and **39**, respectively, were isolated.

In summary, we have shown that the reaction of ethyl 5-acetyl-3,4-dihydropyridine-1(2*H*)-carboxylate (**4**) with 1,3-*N*,*N*-bis-nucleophiles occurs in a regioselective manner to provide novel pyrimidine derivatives in good yields.

Solvents were purified according to standard procedures. Compound **4** was prepared according to the literature method.[3] All other materials were purchased from Enamine Ltd. Melting points were measured using a Thiele tube. Analytical TLC was perfomed using Polychrom SI F_{254} plates. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance 500 spectrometer (at 499.9 MHz and 124.9 MHz, respectively). Chemical shifts are reported in ppm downfield from TMS as an internal standard. Mass spectra were recorded on an Agilent 1100 LC/MSD SL instrument using chemical ionization (CI).

Pyrimidines 7, 21–32; General Procedure

A 25-mL reaction vessel equipped with a condenser was charged with a soln of the 1,3-*N*,*N*-bis-nucleophile (10.0 mmol) and compound **4** (2.07 g, 10.5 mmol) in anhyd ethylene glycol (10–15 mL). The solution was stirred under inert atmosphere at 80 °C for 3 h and at 150–160 °C for 6 h. Then, the volatiles were evaporated under reduced pressure. The gummy residue was dissolved in $CHCl_3$ (50 mL), then washed with 5% aq HCl (2 × 20 mL) and sat. aq $NaHCO_3$ (2 × 30 mL), and dried ($MgSO_4$). The solvent was removed under reduced pressure to give the corresponding pure pyrimidine derivative **7**, **21**–**32**.

Ethyl 3-(5-Methylpyrazolo[1,5-*a*]pyrimidin-6-yl)propylcarbamate (7)

Yield: 2.31 g (84% from **4**), 2.23 g (85% from **8**); yellow solid; mp 56–58 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.35 (s, 1 H, CH), 7.83 (s, 1 H, NC*H*CH), 6.34 (s, 1 H, NCHC*H*), 5.75 (br s, 1 H, NH), 3.95 (q, ^3J = 6.5 Hz, 2 H, OCH_2), 3.11 (m, ^3J = 6 Hz, 2 H, CH_2NH), 2.45 (t, ^3J = 6.5 Hz, 2 H, CCH_2), 2.38 (s, 3 H, CH_3), 1.68 (m, ^3J = 7 Hz, 2 H, CH_2), 1.01 (t, ^3J = 6.5 Hz, 3 H, CH_3CH$_2$).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.12 (s, *tert*-C, Me*C*), 157.07 (s, CO), 146.73 (s, *tert*-C, NCN), 144.00 (s, N*C*HCH), 132.28 (s, CH), 120.67 (s, *tert*-C, *C*CH$_2$), 95.08 (s, NCH*C*H), 60.68 (s, OCH_2), 40.05 (s, CH_2NH), 29.15 (s, C*C*H$_2$), 26.84 (s, CH_2), 22.45 (s, CH_3), 14.52 (s, *C*H$_3$CH$_2$).

MS: *m*/*z* = 263.3 [M + 1]$^+$.

Ethyl 3-(2,5-Dimethylpyrazolo[1,5-*a*]pyrimidin-6-yl)propylcarbamate (21)

Yield: 2.01 g (72%); pale brown oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.24 (s, 1 H, CH), 6.18 (s, 1 H, NCMeCH), 5.48 (br s, 1 H, NH), 4.02 (q, ^3J = 6 Hz, 2 H, OCH_2), 3.16 (m, 2 H, CH_2NH), 2.51 (t, ^3J = 7.5 Hz, 2 H, CCH_2), 2.41 (s, 3 H, CH_3), 2.35 (s, 3 H, CH_3), 1.72 (m, ^3J = 7.5 Hz, 2 H, CH_2), 1.13 (t, ^3J = 6 Hz, 3 H, CH_3CH$_2$).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 158.57 (s, *tert*-C, MeC), 156.96 (s, CO), 154.28 (s, N*C*MeCH), 147.66 (s, *tert*-C, NCN), 131.78 (s, CH), 119.53 (s, *tert*-C, *C*CH$_2$), 94.38 (s, NCMe*C*H), 60.72 (s, OCH_2), 40.12 (s, CH_2NH), 29.42 (s, C*C*H$_2$), 26.91 (s, CH_2), 22.49 (s, CH_3), 14.57 (s, *C*H$_3$CH$_2$), 14.38 (s, CH_3).

MS: *m*/*z* = 277.3 [M + 1]$^+$.

Ethyl 3-(3-Cyano-5-methylpyrazolo[1,5-*a*]pyrimidin-6-yl)propylcarbamate (22)

Yield: 2.10 g (71%); pale brown solid; mp 84–86 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.46 (s, 1 H, CH), 7.50 (s, 1 H, NCHCCN), 5.92 (br s, 1 H, NH), 3.97 (q, ^3J = 6.5 Hz, 2 H, OCH_2), 3.09 (m, ^3J = 6 Hz, 2 H, CH_2NH), 2.66 (t, ^3J = 6.5 Hz, 2 H, CCH_2), 2.55 (s, 3 H, CH_3), 1.72 (m, ^3J = 7 Hz, 2 H, CH_2), 1.12 (t, ^3J = 6.5 Hz, 3 H, CH_3CH$_2$).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 163.94 (s, *tert*-C, MeC), 156.77 (s, *C*O), 150.53 (s, *tert*-C, NCN), 140.54 (s, N*C*HCCN), 134.13 (s, CH), 122.64 (s, *tert*-C, *C*CH$_2$), 116.19 (s, CN), 95.08 (s, NCH*C*CN), 59.83 (s, OCH_2), 41.85 (s, CH_2NH), 27.31 (s, C*C*H$_2$), 25.08 (s, CH_2), 21.74 (s, CH_3), 15.06 (s, *C*H$_3$CH$_2$).

MS: *m*/*z* = 288.4 [M + 1]$^+$.

Ethyl 3-(2-Methylpyrimido[1,2-*b*]indazol-3-yl)propylcarbamate (23)

Yield: 1.96 g (60%); pale brown oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.46 (s, 1 H, CH), 8.11 (d, ^3J = 6.5 Hz, 1 H, C_6H_4), 7.62 (t, ^3J = 6.5 Hz, 1 H, C_6H_4), 7.44 (t, ^3J = 6.5 Hz, 1 H, C_6H_4), 7.11 (t, ^3J = 6.5 Hz, 1 H, C_6H_4), 5.54 (br s, 1 H, NH), 4.04 (q, ^3J = 6.5 Hz, 2 H, OCH_2), 3.14 (m, ^3J = 6 Hz, 2 H, CH_2NH), 2.44 (s, 3 H, CH_3), 2.38 (t, ^3J = 7 Hz, 2 H, CCH_2), 1.66 (m, ^3J = 7 Hz, 2 H, CH_2), 1.15 (t, ^3J = 6.5 Hz, 3 H, CH_3CH$_2$).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 156.95 (s, *tert*-C, MeC), 155.66 (s, CO), 150.75 (s, *tert*-C, NCN), 141.57 (s, *tert*-C, C_6H_4), 131.05 (s, CH), 129.27 (s, CH, C_6H_4), 124.67 (s, *tert*-C, C_6H_4), 120.51 (s, *tert*-C, *C*CH$_2$), 120.15 (s, CH, C_6H_4), 115.59 (s, CH, C_6H_4), 112.62 (s, CH, C_6H_4), 60.74 (s, OCH_2), 40.16 (s, CH_2NH), 29.00 (s, C*C*H$_2$), 27.28 (s, CH_2), 22.28 (s, CH_3), 14.68 (s, *C*H$_3$CH$_2$).

MS: *m*/*z* = 313.2 [M + 1]$^+$.

Ethyl 3-(2-Methylpyrido[2′,3′:3,4]pyrazolo[1,5-*a*]pyrimidin-3-yl)propylcarbamate (24)

Yield: 2.70 g (82%); yellow caramel.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.75 (s, 1 H, CH), 8.11 (d, ^3J = 4.5 Hz, 1 H, py), 8.31 (d, ^3J = 8 Hz, 1 H, py), 6.98 (dd, ^3J = 7.7, 3.4 Hz, 1 H, py), 5.59 (br s, 1 H, NH), 4.00 (q, ^3J = 6.5 Hz, 2 H, OCH_2), 3.15 (m, ^3J = 6 Hz, 2 H, CH_2NH), 2.57 (s, 3 H, CH_3), 2.44 (t, ^3J = 7 Hz, 2 H, CCH_2), 1.54 (m, ^3J = 7 Hz, 2 H, CH_2), 1.02 (t, ^3J = 6.5 Hz, 3 H, CH_3CH$_2$).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.62 (s, *tert*-C, MeC), 157.15 (s, CO), 153.32 (s, *tert*-C, NCN), 140.61 (s, *tert*-C, py), 132.26 (s, CH, py), 130.29 (s, CH), 120.51 (s, *tert*-C, *C*CH$_2$), 117.77 (s, CH, py), 116.85 (s, CH, py), 105.45 (s, *tert*-C, py), 60.39 (s, OCH_2), 40.38 (s, CH_2NH), 30.56 (s, C*C*H$_2$), 27.34 (s, CH_2), 22.27 (s, CH_3), 14.57 (s, *C*H$_3$CH$_2$).

MS: *m*/*z* = 314.4 [M + 1]$^+$.

Ethyl 3-(7-Methylimidazo[1,2-*a*]pyrimidin-6-yl)propylcarbamate (25)

Yield: 1.81 g (66%); brown caramel.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.24 (s, 1 H, CH), 7.51 (s, 1 H, NCHC*H*NC), 7.36 (s, 1 H, NC*H*CHNC), 5.74 (br s, 1 H, NH), 4.03 (q, ^3J = 6 Hz, 2 H, OCH_2), 3.19 (m, ^3J = 6 Hz, 2 H, CH_2NH), 2.57 (t, ^3J = 6 Hz, 2 H, CCH_2), 2.46 (s, 3 H, CH_3), 1.75 (m, ^3J = 6 Hz, 2 H, CH_2), 1.15 (t, ^3J = 6 Hz, 3 H, CH_3CH$_2$).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 160.10 (s, *tert*-C, MeC), 157.07 (s, CO), 147.75 (s, *tert*-C, NCN), 136.90 (s, NCH*C*HNC), 133.71 (s, CH), 121.37 (s, *tert*-C, *C*CH$_2$), 110.10 (s, N*C*HCHNC), 60.66 (s, OCH_2), 39.94 (s, CH_2NH), 29.28 (s, C*C*H$_2$), 26.74 (s, CH_2), 22.68 (s, CH_3), 14.61 (s, *C*H$_3$CH$_2$).

MS: *m*/*z* = 263.0 [M + 1]$^+$.

Ethyl 3-[2-(Aminocarbonyl)-7-methylimidazo[1,2-*a*]pyrimidin-6-yl]propylcarbamate (26)

Yield: 2.02 g (63%); red crystalline; mp 96–98 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.95 (d, 2 H, $CONH_2$), 8.22 (s, 1 H, CH), 8.10 (s, 1 H, NCHCN), 5.42 (br s, 1 H, NH), 4.03 (q, ^3J = 6 Hz, 2 H, OCH_2), 3.21 (m, ^3J = 6 Hz, 2 H, CH_2NH), 2.55 (t, ^3J = 6 Hz, 2 H, CCH_2), 2.44 (s, 3 H, CH_3), 1.74 (m, ^3J = 6 Hz, 2 H, CH_2), 1.09 (t, ^3J = 6 Hz, 3 H, CH_3CH$_2$).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 164.15 (s, $CONH_2$), 161.51 (s, *tert*-C, MeC), 157.63 (s, CO), 145.74 (s, *tert*-C, NCN), 136.43 (s, CH), 133.62 (s, N*C*HCN), 122.40 (s, *tert*-C, *C*CONH$_2$), 121.28 (s, *tert*-C, *C*CH$_2$), 60.43 (s, OCH_2), 39.54 (s, CH_2NH), 29.21 (s, C*C*H$_2$), 26.35 (s, CH_2), 22.42 (s, CH_3), 14.62 (s, *C*H$_3$CH$_2$).

MS: *m*/*z* = 306.4 [M + 1]$^+$.

Ethyl 3-(2-Methylpyrimido[1,2-*a*]benzimidazol-3-yl)propylcarbamate (27)

Yield: 1.71 g (54%); pale brown caramel.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.32 (s, 1 H, CH), 7.98 (d, ^3J = 6.5 Hz, 1 H, C_6H_4), 7.79 (t, ^3J = 6.5 Hz, 1 H, C_6H_4), 7.45 (t, ^3J = 6.5 Hz, 1 H, C_6H_4), 7.35 (t, ^3J = 6.5 Hz, 1 H, C_6H_4), 5.65 (br s, 1 H, NH), 4.01 (q, ^3J = 6.5 Hz, 2 H, OCH_2), 3.16 (m, ^3J = 6 Hz, 2 H, CH_2NH), 2.45 (s, 3 H, CH_3), 2.40 (t, ^3J = 7 Hz, 2 H, CCH_2), 1.69 (m, ^3J = 7 Hz, 2 H, CH_2), 1.22 (t, ^3J = 6.5 Hz, 3 H, CH_3CH_2).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 157.52 (s, *tert*-C, MeC), 156.61 (s, CO), 152.45 (s, *tert*-C, NCN), 142.78 (s, *tert*-C, C_6H_4), 132.01 (s, CH), 127.65 (s, CH, C_6H_4), 125.61 (s, *tert*-C, C_6H_4), 122.22 (s, *tert*-C, CCH_2), 121.46 (s, CH, C_6H_4), 119.19 (s, CH, C_6H_4), 112.59 (s, CH, C_6H_4), 60.78 (s, OCH_2), 40.03 (s, CH_2NH), 29.04 (s, CCH_2), 26.26 (s, CH_2), 22.14 (s, CH_3), 14.77 (s, CH_3CH_2).

MS: *m*/*z* = 313.4 $[M + 1]^+$.

Ethyl 3-(7-Methyl[1,2,4]triazolo[4,3-*a*]pyrimidin-6-yl)propylcarbamate (28)

Yield: 1.55 g (56%); brown caramel.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.65 (s, 1 H, NCHN), 8.13 (s, 1 H, CH), 5.15 (br s, 1 H, NH), 3.95 (q, ^3J = 6 Hz, 2 H, OCH_2), 3.21 (m, ^3J = 6 Hz, 2 H, CH_2NH), 2.56 (t, ^3J = 6 Hz, 2 H, CCH_2), 2.42 (s, 3 H, CH_3), 1.74 (m, ^3J = 6 Hz, 2 H, CH_2), 1.26 (t, ^3J = 6 Hz, 3 H, CH_3CH_2).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 161.29 (s, *tert*-C, MeC), 157.34 (s, CO), 149.86 (s, *tert*-C, NCN), 138.59 (s, NCHN), 135.31 (s, CH), 122.08 (s, *tert*-C, CCH_2), 60.62 (s, OCH_2), 39.66 (s, CH_2NH), 29.23 (s, CCH_2), 26.54 (s, CH_2), 21.88 (s, CH_3), 14.37 (s, CH_3CH_2).

MS: *m*/*z* = 264.4 $[M + 1]^+$.

Ethyl 3-(5-Methyltetrazolo[1,5-*a*]pyrimidin-6-yl)propylcarbamate (29)

Yield: 0.69 g (25%); brown caramel.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.83 (s, 1 H, CH), 5.69 (br s, 1 H, NH), 4.05 (q, ^3J = 6.5 Hz, 2 H, OCH_2), 3.07 (m, ^3J = 6 Hz, 2 H, CH_2NH), 2.35 (t, ^3J = 7 Hz, 2 H, CCH_2), 2.20 (s, 3 H, CH_3), 1.48 (m, ^3J = 7 Hz, 2 H, CH_2), 1.19 (t, ^3J = 6.5 Hz, 3 H, CH_3CH_2).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 167.27 (s, *tert*-C, MeC), 166.14 (s, CO), 162.05 (s, NCN), 157.58 (s, CH), 121.22 (s, *tert*-C, CCH_2), 59.35 (s, OCH_2), 41.74 (s, CH_2NH), 30.15 (s, CCH_2), 25.92 (s, CH_2), 21.20 (s, CH_3), 14.87 (s, CH_3CH_2).

MS: *m*/*z* = 265.2 $[M + 1]^+$.

Ethyl 3-(2-Methylpyrimido[2,1-*a*]isoindol-3-yl)propylcarbamate (30)

Yield: 1.50 g (46%); pale brown oil.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.56 (s, 1 H, CH), 7.63 (s, 1 H, NCH), 7.34 (m, 2 H, C_6H_4), 7.24 (m, 2 H, C_6H_4), 5.44 (br s, 1 H, NH), 3.93 (q, ^3J = 6.5 Hz, 2 H, OCH_2), 3.00 (m, ^3J = 6 Hz, 2 H, CH_2NH), 2.40 (s, 3 H, CH_3), 2.23 (t, ^3J = 7 Hz, 2 H, CCH_2), 1.67 (m, ^3J = 7 Hz, 2 H, CH_2), 1.12 (t, ^3J = 6.5 Hz, 3 H, CH_3CH_2).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 166.45 (s, *tert*-C, MeC), 161.20 (s, *tert*-C, NCN), 157.34 (s, CO), 144.51 (s, NCH), 133.01 (s, CH), 131.73 (s, CH, C_6H_4), 128.09 (s, CH, C_6H_4), 124.17 [s, 2 C (CH + *tert*-C), C_6H_4], 123.15 [s, 2 C (CH + *tert*-C), C_6H_4], 121.53 (s, *tert*-C, CCH_2), 59.35 (s, OCH_2), 45.46 (s, CH_2NH), 31.21 (s, CCH_2), 25.80 (s, CH_2), 20.40 (s, CH_3), 15.19 (s, CH_3CH_2).

MS: *m*/*z* = 312.4 $[M + 1]^+$.

Ethyl 3-(2-Amino-4-methylpyrimidin-5-yl)propylcarbamate (31)

Yield: 1.65 g (66%); yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.67 (s, 1 H, CH), 5.51 (br s, 2 H, NH_2), 5.15 (br s, 1 H, NH), 4.05 (q, ^3J = 6 Hz, 2 H, OCH_2), 3.28 (m, 2 H, CH_2NH), 2.35 (t, ^3J = 6 Hz, 2 H, CCH_2), 2.14 (s, 3 H, CH_3), 1.77 (m, ^3J = 6 Hz, 2 H, CH_2), 1.14 (t, ^3J = 6 Hz, 3 H, CH_3CH_2).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 174.40 (s, *tert*-C, CNH_2), 158.31 (s, *tert*-C, MeC), 156.75 (s, CO), 145.58 (s, CH), 108.79 (s, *tert*-C, CCH_2), 60.65 (s, OCH_2), 40.97 (s, CH_2NH), 29.68 (s, CCH_2), 26.56 (s, CH_2), 22.41 (s, CH_3), 14.80 (s, CH_3CH_2).

MS: *m*/*z* = 239.3 $[M + 1]^+$.

Ethyl 3-(4-Methyl-2-phenylpyrimidin-5-yl)propylcarbamate (32)

Yield: 1.63 g (52%); red oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.60 (s, 1 H, CH), 7.67 (d, ^3J = 7.5 Hz, 2 H, Ph), 7.40 (t, ^3J = 7.5 Hz, 2 H, Ph), 7.21 (t, ^3J = 7.5 Hz, 1 H, Ph), 5.45 (br s, 1 H, NH), 4.02 (q, ^3J = 6 Hz, 2 H, OCH_2), 3.33 (m, 2 H, CH_2NH), 2.31 (t, ^3J = 6 Hz, 2 H, CCH_2), 2.12 (s, 3 H, CH_3), 1.72 (m, ^3J = 6 Hz, 2 H, CH_2), 1.24 (t, ^3J = 6 Hz, 3 H, CH_3CH_2).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 161.12 (s, *tert*-C, CPh), 157.05 (s, *tert*-C, MeC), 156.75 (s, CO), 140.16 (s, *tert*-C, Ph), 130.54 (s, CH), 129.32 (s, 2 C, Ph), 125.32 (s, Ph), 121.54 (s, *tert*-C, CCH_2), 118.37 (s, 2 C, Ph), 60.55 (s, OCH_2), 40.84 (s, CH_2NH), 29.23 (s, CCH_2), 25.59 (s, CH_2), 21.48 (s, CH_3), 14.85 (s, CH_3CH_2).

MS: *m*/*z* = 300.4 $[M + 1]^+$.

Ethyl 5-[(1*Z*)-1-(1*H*-Pyrazol-5-ylimino)ethyl]-3,4-dihydropyridine-1(2*H*)-carboxylate (8)

A 50-mL reaction vessel equipped with a condenser was charged with a soln of 3-aminopyrazole (**6**; 0.83 g, 10 mmol) and compound **4** (1.97 g, 10 mmol) in MeOH (30 mL). The solution was heated at reflux for 4 h. Thereafter, the solvent was evaporated under reduced pressure. The residue was washed with H_2O (30 mL) and hexane (25 mL), and dried under reduced pressure to give pure imine **8**; yield: 2.52 g (96%); mp 81–83 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.85 (s, 1 H, CH), 7.62 (d, ^3J = 2 Hz, 1 H, NC*H*CH), 5.75 (br s, 1 H, NH), 5.70 (d, ^3J = 2 Hz, 1 H, NCHC*H*), 4.08 (q, ^3J = 7 Hz, 2 H, OCH_2), 3.40 (t, ^3J = 6 Hz, 2 H, NCH_2), 2.08 (m, 5 H, $CH_2C + CH_3$), 1.60 (m, ^3J = 6 Hz, 2 H, CH_2), 1.14 (t, ^3J = 7 Hz, 3 H, CH_3CH_2).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.39 (s, CO), 151.11 (s, *tert*-C, CN), 137.46 (s, *tert*-C, NCN), 131.37 (s, CH*C*HN), 123.33 (s, CH), 119.00 (s, *tert*-C), 91.92 (s, *C*HCHN), 62.97 (s, OCH_2), 42.37 (s, CH_2N), 24.33 (s, CCH_2), 20.19 (s, CH_2), 19.54 (s, CH_3), 14.19 (s, CH_3CH_2).

MS: *m*/*z* = 263.4 $[M + 1]^+$.

Amines 33–45; General Procedure

A one-necked 50-mL round-bottomed flask equipped with a reflux condenser was charged with an ethyl carbamate **7**, **21**–**32** (10 mmol) and concd HCl (25 mL). The solution was heated at reflux for 16 h. Thereafter, the volatiles were evaporated under reduced pressure. The residue was suspended in 10% NaOH soln (20 mL) and extracted with $CHCl_3$ (3 × 25 mL). The organic layer was washed with H_2O (40 mL) and dried ($MgSO_4$). The solvent was removed under reduced pressure to give the corresponding (aminopropyl)pyrimidine derivative **33**–**45** (except for **35**, **39**, **42**, **43**).

For compounds **35**, **39**, **42**, **43**, the soln of the amine hydrochloride in concd HCl was washed with CH_2Cl_2 (3 × 5 mL). The aqueous phase was concentrated under reduced pressure to provide the pure product **35**, **39**, **42**, **43** as the hydrochloride salt.

3-(5-Methylpyrazolo[1,5-*a*]pyrimidin-6-yl)propan-1-amine (33)

Yield: 1.80 g (95%); yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.41 (s, 1 H, CH), 7.73 (s, 1 H, NC*H*CH), 6.39 (s, 1 H, NCHC*H*), 3.42 (m, ^3J = 6 Hz, 2 H, CH_2NH$_2$), 2.41 (t, ^3J = 6.5 Hz, 2 H, CCH$_2$), 2.34 (br s, 2 H, NH$_2$), 2.25 (s, 3 H, CH$_3$), 1.70 (m, ^3J = 7 Hz, 2 H, CH$_2$).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.20 (s, *tert*-C, MeC), 145.82 (s, N*C*HCH), 145.37 (s, *tert*-C, NCN), 135.11 (s, CH), 120.52 (s, *tert*-C, *C*CH$_2$), 95.14 (s, NCHCH), 39.43 (s, CH$_2$NH$_2$), 27.65 (s, C*C*H$_2$), 25.66 (s, CH$_2$), 21.41 (s, CH$_3$).

MS: *m*/*z* = 191.2 [M + 1]$^+$.

3-(2,5-Dimethylpyrazolo[1,5-*a*]pyrimidin-6-yl)propan-1-amine (34)
Yield: 1.86 g (91%); pale brown oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.35 (s, 1 H, CH), 6.22 (s, 1 H, NCMeCH), 3.36 (m, 2 H, CH_2NH$_2$), 2.41 (t, ^3J = 7.5 Hz, 2 H, CCH$_2$), 2.33 (s, 3 H, CH$_3$), 2.24 (s, 3 H, CH$_3$), 2.11 (br s, 2 H, NH$_2$), 1.75 (m, ^3J = 7.5 Hz, 2 H, CH$_2$).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 157.61 (s, *tert*-C, MeC), 152.32 (s, N*C*MeCH), 145.64 (s, *tert*-C, NCN), 130.88 (s, CH), 119.46 (s, *tert*-C, *C*CH$_2$), 95.21 (s, NCMe*C*H), 39.67 (s, CH$_2$NH$_2$), 28.44 (s, C*C*H$_2$), 25.89 (s, CH$_2$), 22.42 (s, CH$_3$), 14.45 (s, CH$_3$).

MS: *m*/*z* = 205.3 [M + 1]$^+$.

6-(3-Aminopropyl)-5-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylic Acid Hydrochloride (35)
Yield: 2.67 g (99%); white crystalline; mp 187–189 °C (dec).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 11.20 (br s, 1 H, COOH), 8.49 (s, 1 H, CH), 8.32 (br s, 3 H, NH$_3^+$), 7.59 (s, 1 H, NCHCCN), 3.35 (m, ^3J = 6 Hz, 2 H, CH_2NH$_3^+$), 2.56 (t, ^3J = 6.5 Hz, 2 H, CCH$_2$), 2.46 (s, 3 H, CH$_3$), 1.88 (m, ^3J = 7 Hz, 2 H, CH$_2$).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 171.11 (s, COOH), 164.12 (s, *tert*-C, MeC), 149.32 (s, *tert*-C, NCN), 141.61 (s, N*C*HCCN), 132.02 (s, CH), 122.68 (s, *tert*-C, *C*CH$_2$), 95.44 (s, NCH*C*CN), 44.89 (s, CH$_2$NH$_3^+$), 27.39 (s, C*C*H$_2$), 25.13 (s, CH$_2$), 21.72 (s, CH$_3$).

MS: *m*/*z* = 271.7 [M + 1]$^+$.

3-(2-Methylpyrimido[1,2-*b*]indazol-3-yl)propan-1-amine (36)
Yield: 2.31 g (96%); pale brown oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.41 (s, 1 H, CH), 8.13 (d, ^3J = 6.5 Hz, 1 H, C$_6$H$_4$), 7.66 (t, ^3J = 6.5 Hz, 1 H, C$_6$H$_4$), 7.45 (t, ^3J = 6.5 Hz, 1 H, C$_6$H$_4$), 7.16 (t, ^3J = 6.5 Hz, 1 H, C$_6$H$_4$), 3.34 (m, ^3J = 6 Hz, 2 H, CH_2NH$_2$), 2.49 (s, 3 H, CH$_3$), 2.41 (t, ^3J = 7 Hz, 2 H, CCH$_2$), 2.24 (br s, 2 H, NH$_2$), 1.77 (m, ^3J = 7 Hz, 2 H, CH$_2$).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 156.01 (s, *tert*-C, MeC), 151.21 (s, *tert*-C, NCN), 141.45 (s, *tert*-C, C$_6$H$_4$), 132.03 (s, CH), 128.68 (s, CH, C$_6$H$_4$), 124.54 (s, *tert*-C, C$_6$H$_4$), 120.56 (s, *tert*-C, *C*CH$_2$), 120.32 (s, CH, C$_6$H$_4$), 115.68 (s, CH, C$_6$H$_4$), 112.31 (s, CH, C$_6$H$_4$), 39.52 (s, CH$_2$NH$_2$), 27.85 (s, C*C*H$_2$), 26.84 (s, CH$_2$), 22.21 (s, CH$_3$).

MS: *m*/*z* = 241.4 [M + 1]$^+$.

3-(2-Methylpyrido[2′,3′:3,4]pyrazolo[1,5-*a*]pyrimidin-3-yl)propan-1-amine (37)
Yield: 2.22 g (92%); pale yellow, gummy substance.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.71 (s, 1 H, CH), 8.32 (d, ^3J = 4.5 Hz, 1 H, py), 8.20 (d, ^3J = 8 Hz, 1 H, py), 6.88 (dd, ^3J = 7.7, 3.4 Hz, 1 H, py), 3.31 (m, ^3J = 6 Hz, 2 H, CH_2NH$_2$), 2.49 (s, 3 H, CH$_3$), 2.39 (t, ^3J = 7 Hz, 2 H, CCH$_2$), 2.10 (br s, 2 H, NH$_2$), 1.59 (m, ^3J = 7 Hz, 2 H, CH$_2$).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 158.54 (s, *tert*-C, MeC), 152.39 (s, *tert*-C, NCN), 141.16 (s, *tert*-C, py), 131.92 (s, CH), 131.78 (s, CH, py), 121.54 (s, *tert*-C, *C*CH$_2$), 117.70 (s, CH, py), 116.82 (s, CH, py), 106.53 (s, *tert*-C, py), 39.99 (s, CH$_2$NH$_2$), 28.35 (s, C*C*H$_2$), 26.56 (s, CH$_2$), 22.22 (s, CH$_3$).

MS: *m*/*z* = 242.3 [M + 1]$^+$.

3-(7-Methylimidazo[1,2-*a*]pyrimidin-6-yl)propan-1-amine (38)
Yield: 1.69 g (89%); brown oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.36 (s, 1 H, CH), 7.59 (s, 1 H, NCHC*H*NC), 7.44 (s, 1 H, NC*H*CHNC), 3.39 (m, ^3J = 6 Hz, 2 H, CH_2NH$_2$), 2.48 (t, ^3J = 6 Hz, 2 H, CCH$_2$), 2.36 (s, 3 H, CH$_3$), 2.14 (br s, 2 H, NH$_2$), 1.78 (m, ^3J = 6 Hz, 2 H, CH$_2$).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.02 (s, *tert*-C, MeC), 147.65 (s, *tert*-C, NCN), 136.95 (s, NCH*C*HNC), 133.56 (s, CH), 120.42 (s, *tert*-C, *C*CH$_2$), 111.23 (s, N*C*HCHNC), 39.67 (s, CH$_2$NH$_2$), 27.89 (s, C*C*H$_2$), 26.71 (s, CH$_2$), 22.39 (s, CH$_3$).

MS: *m*/*z* = 191.3 [M + 1]$^+$.

6-(3-Aminopropyl)-7-methylimidazo[1,2-*a*]pyrimidine-2-carboxylic Acid Hydrochloride (39)
Yield: 2.68 g (99%); red crystalline; mp 178–180 °C (dec).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 11.28 (br s, 1 H, COOH), 8.42 (s, 1 H, CH), 8.28 (s, 1 H, NCHCN), 8.02 (br s, 3 H, NH$_3^+$), 3.44 (m, ^3J = 6 Hz, 2 H, CH_2NH$_3^+$), 2.61 (t, ^3J = 6 Hz, 2 H, CCH$_2$), 2.42 (s, 3 H, CH$_3$), 1.80 (m, ^3J = 6 Hz, 2 H, CH$_2$).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 173.07 (s, COOH), 161.54 (s, *tert*-C, MeC), 145.62 (s, *tert*-C, NCN), 135.83 (s, CH), 132.97 (s, N*C*HCN), 122.87 (s, *tert*-C, *C*COOH), 121.21 (s, *tert*-C, *C*CH$_2$), 44.46 (s, CH$_2$NH$_3^+$), 28.42 (s, C*C*H$_2$), 26.33 (s, CH$_2$), 22.12 (s, CH$_3$).

MS: *m*/*z* = 271.7 [M + 1]$^+$.

3-(2-Methylpyrimido[1,2-*a*]benzimidazol-3-yl)propan-1-amine (40)
Yield: 1.99 g (83%); pale brown, gummy substance.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.42 (s, 1 H, CH), 7.96 (d, ^3J = 6.5 Hz, 1 H, C$_6$H$_4$), 7.73 (t, ^3J = 6.5 Hz, 1 H, C$_6$H$_4$), 7.40 (t, ^3J = 6.5 Hz, 1 H, C$_6$H$_4$), 7.29 (t, ^3J = 6.5 Hz, 1 H, C$_6$H$_4$), 3.35 (m, ^3J = 6 Hz, 2 H, CH_2NH$_2$), 2.43 (s, 3 H, CH$_3$), 2.33 (t, ^3J = 7 Hz, 2 H, CCH$_2$), 2.25 (br s, 2 H, NH$_2$), 1.71 (m, ^3J = 7 Hz, 2 H, CH$_2$).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 157.12 (s, *tert*-C, MeC), 151.66 (s, *tert*-C, NCN), 141.29 (s, *tert*-C, C$_6$H$_4$), 131.68 (s, CH), 127.68 (s, CH, C$_6$H$_4$), 125.66 (s, *tert*-C, C$_6$H$_4$), 122.34 (s, *tert*-C, *C*CH$_2$), 121.33 (s, CH, C$_6$H$_4$), 119.25 (s, CH, C$_6$H$_4$), 112.51 (s, CH, C$_6$H$_4$), 39.83 (s, CH$_2$NH$_2$), 28.24 (s, C*C*H$_2$), 26.39 (s, CH$_2$), 22.17 (s, CH$_3$).

MS: *m*/*z* = 241.2 [M + 1]$^+$.

3-(7-Methyl[1,2,4]triazolo[4,3-*a*]pyrimidin-6-yl)propan-1-amine (41)
Yield: 1.79 g (94%); pale brown oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.67 (s, 1 H, NCHN), 8.17 (s, 1 H, CH), 3.36 (m, ^3J = 6 Hz, 2 H, CH_2NH$_2$), 2.52 (t, ^3J = 6 Hz, 2 H, CCH$_2$), 2.43 (s, 3 H, CH$_3$), 2.15 (br s, 2 H, NH$_2$), 1.78 (m, ^3J = 6 Hz, 2 H, CH$_2$).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 161.33 (s, *tert*-C, MeC), 149.80 (s, *tert*-C, NCN), 138.62 (s, NCHN), 134.85 (s, CH), 122.12 (s, *tert*-C, *C*CH$_2$), 41.06 (s, CH$_2$NH$_2$), 28.41 (s, C*C*H$_2$), 25.22 (s, CH$_2$), 21.64 (s, CH$_3$).

MS: *m*/*z* = 192.3 [M + 1]$^+$.

3-(5-Methyltetrazolo[1,5-*a*]pyrimidin-6-yl)propan-1-amine Hydrochloride (42)
Yield: 2.26 g (99%); brown crystalline; mp 204–206 °C (dec).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.44 (s, 1 H, CH), 4.22 (br s, 3 H, NH_3^+), 3.41 (m, ^3J = 6 Hz, 2 H, $CH_2NH_3^+$), 2.34 (t, ^3J = 7 Hz, 2 H, CCH_2), 2.21 (s, 3 H, CH_3), 1.51 (m, ^3J = 7 Hz, 2 H, CH_2).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 167.85 (s, *tert*-C, MeC), 161.82 (s, NCN), 156.22 (s, CH), 121.29 (s, *tert*-C, CCH_2), 40.76 (s, $CH_2NH_3^+$), 28.11 (s, CCH_2), 25.99 (s, CH_2), 21.26 (s, CH_3).

MS: *m*/*z* = 229.7 $[M + 1]^+$.

3-(2-Methylpyrimido[2,1-*a*]isoindol-3-yl)propan-1-amine Hydrochloride (43)
Yield: 2.61 g (95%); red crystalline; mp 202–203 °C (dec).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.51 (s, 1 H, CH), 8.09 (br s, 3 H, NH_3^+), 7.68 (s, 1 H, NCH), 7.33 (m, 2 H, C_6H_4), 7.22 (m, 2 H, C_6H_4), 3.11 (m, ^3J = 6 Hz, 2 H, $CH_2NH_3^+$), 2.42 (s, 3 H, CH_3), 2.28 (t, ^3J = 7 Hz, 2 H, CCH_2), 1.69 (m, ^3J = 7 Hz, 2 H, CH_2).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 166.24 (s, *tert*-C, MeC), 161.15 (s, *tert*-C, NCN), 144.56 (s, NCH), 133.11 (s, CH), 131.69 (s, CH, C_6H_4), 128.14 (s, CH, C_6H_4), 124.15 [s, 2 C (CH + *tert*-C), C_6H_4], 123.13 [s, 2 C (CH + *tert*-C), C_6H_4], 121.57 (s, *tert*-C, CCH_2), 46.32 (s, $CH_2NH_3^+$), 31.22 (s, CCH_2), 25.83 (s, CH_2), 21.64 (s, CH_3).

MS: *m*/*z* = 240.4 $[M – HCl + 1]^+$.

5-(3-Aminopropyl)-4-methylpyrimidin-2-amine (44)
Yield: 1.39 g (84%); pale brown oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.45 (s, 1 H, CH), 5.25 (br s, 2 H, NH_2), 3.22 (m, 2 H, CH_2NH_2), 3.01 (br s, 2 H, NH_2), 2.34 (t, ^3J = 6 Hz, 2 H, CCH_2), 2.12 (s, 3 H, CH_3), 1.79 (m, ^3J = 6 Hz, 2 H, CH_2).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 174.40 (s, *tert*-C, CNH_2), 158.31 (s, *tert*-C, MeC), 145.58 (s, CH), 108.79 (s, *tert*-C, CCH_2), 40.97 (s, CH_2NH_2), 28.19 (s, CCH_2), 23.66 (s, CH_2), 20.66 (s, CH_3).

MS: *m*/*z* = 167.2 $[M + 1]^+$.

3-(4-Methyl-2-phenylpyrimidin-5-yl)propan-1-amine (45)
Yield: 2.18 g (96%); pale brown oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.62 (s, 1 H, CH), 7.65 (d, ^3J = 7.5 Hz, 2 H, Ph), 7.40 (t, ^3J = 7.5 Hz, 2 H, Ph), 7.25 (t, ^3J = 7.5 Hz, 1 H, Ph), 3.39 (m, 2 H, CH_2NH_2), 2.30 (t, ^3J = 6 Hz, 2 H, CCH_2), 2.24 (s, 3 H, CH_3), 2.03 (br s, 2 H, NH_2), 1.72 (m, ^3J = 6 Hz, 2 H, CH_2).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 161.16 (s, *tert*-C, CPh), 157.12 (s, *tert*-C, MeC), 140.11 (s, *tert*-C, Ph), 133.14 (s, CH), 129.38 (s, 2 C, Ph), 125.30 (s, Ph), 121.59 (s, *tert*-C, CCH_2), 118.30 (s, 2 C, Ph), 39.54 (s, CH_2NH_2), 29.11 (s, CCH_2), 25.59 (s, CH_2), 20.68 (s, CH_3).

MS: *m*/*z* = 228.3 $[M + 1]^+$.

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