Synthesis of Tricyclic 4-Chloro-pyrimido[4,5-*b*][1,4]benzodiazepines

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Commercial reagents were used as received without additional purification. Melting point was uncorrected. Mass spectra and HPLC (ELSD) data was recorded on an 1100 LC/MS system (Agilent Technology Corporation) with Alltech ELSD 2000 using a YMC ODS-A, 5- μ m, 120-Å, 4.6 $\times$ 50 mm (Waters, Inc.), and the retention time (R_t) for the expected product was recorded. ^1H NMR data was obtained using a 300-MHz Varian VXR-300S NMR spectrometer with TMS as the internal standard and CDCl_3 as solvent. Multiplicities are indicated as the following: s, singlet; d, doublet; t, triplet; m, multiplet; dd, doubled doublet; br, broad. Coupling constants (J values) where noted are quoted in hertz. Compounds **3.0** were prepared according to the literature method¹².

General procedure for the Preparation of **6-chloro-5-nitropyrimidin-4-amine (2)**.

To a solution of 4,6-dichloro-5-nitro-pyrimidine (**1**) (8.00 g, 41.5 mmol) and triethylamine (6.9 mL, 49.2 mmol) in anhydrous THF (40 mL) was added a solution of the appropriate amine (41.5 mmol) in THF (40 mL) slowly. The reaction mixture was stirred at room temperature over night. The reaction mixture was concentrated in vacuo, diluted with water, and extracted with EtOAc. The organic phase was washed with 1N HCl, brine, dried over anhydrous MgSO_4 , and concentrated in vacuo to yield the crude product as a solid. Purification by recrystallization from methanol provided the desired

pure product **2.1** and **2.2** (Product **2.3** was used directly in the next step without further purification).

(6-Chloro-5-nitro-pyrimidine-4-yl)-methylphenylamine (2.1). Yellow solid, 81%, mp: 133.8-135.5 °C. ES-MS: 265 ((M+1)⁺). ¹H NMR δ 8.52 (s, 1H), 7.37-7.39 (m, 3H), 7.15-7.18 (m, 2H), 3.58 (s, 3H).

(6-Chloro-5-nitropyrimidin-4-yl)-methyl-*p*-tolylamine (2.2). Yellow solid, 84 %, mp: 133.3-134.3 °C. ES-MS: 279 ((M+1)⁺). ¹H NMR δ 8.49 (s, 1H), 7.16-7.19 (d, *J* = 9.0 Hz, 2H), 7.03-7.06 (d, *J* = 9.0 Hz, 2H), 3.55 (s, 3H), 2.38 (s, 3H).

(6-Chloro-5-nitropyrimidine-4-yl)-(4-fluorophenyl)-methylamine (2.3). Brown solid, ES-MS: 283 ((M+1)⁺).

General procedure for the Preparation of **6-Chloro-*N*⁴-pyrimidine-4,5-diamines (3)**

Compound **2** (33.0 mmol) was dissolved in a mixture of ethanol (118.0 mL) and water (33.0 mL). Iron powder (5.54 g, 98.9 mmol) and NH₄Cl (1.06 g, 19.8 mmol) was added to it. The mixture was then stirred in reflux for 5 h, cooled to room temperature, and filtered through a pad of celite. The filtrate was concentrated in vacuo. The residue was extracted with EtOAc, and the organic extract was washed with saturated NaHCO₃, water, and brine and dried over anhydrous MgSO₄. It was then filtered and concentrated in vacuo to the crude product which was purified by flash chromatography (elution with 9% EtOAc in petroleum ether followed by 20% EtOAc in petroleum ether) to give **3.1**, **3.2**, **3.3**.

6-chloro-*N*⁴-methyl-*N*⁴-phenylpyrimidine-4,5-diamine (3.1). White solid, 80 %, mp: 81.0-82.6 °C. ES-MS: 235 ((M+1)⁺). ¹H NMR δ 8.22 (s, 1H), 7.35-7.40 (t, *J* = 7.5 Hz, 2H), 7.17-7.22 (t, *J* = 7.5 Hz, 1H), 7.05-7.08 (d, *J* = 9.0 Hz, 2H), 3.51 (s, 3H).

6-chloro-*N*⁴-methyl- *N*⁴-*p*-tolylpyrimidine-4,5-diamine (3.2). White solid, 80%, mp: 114.9-116.1 °C. ES-MS: 249 ((M+1)⁺). ¹H NMR δ 8.19 (s, 1H), 7.16-7.19 (d, *J* = 9.0 Hz, 2H), 6.97-7.00 (d, *J* = 9.0 Hz, 2H), 4.82 (br, 2H), 3.47 (s, 3H), 2.35(s, 3H).

6-chloro-*N*⁴-(4-fluorophenyl) -*N*⁴-methylpyrimidine-4,5-diamine (3.3). Yellow solid, 77 % (two steps), mp: 106-108 °C. ES-MS: 253 ((M+1)⁺). ¹H NMR δ 8.21 (s, 1H), 7.05-7.08 (m, 4H), 3.47 (s, 3H).

General procedure for the Preparation of 4-chloropyrimido[4,5-*b*][1,4] benzodiazepine (4)

6-Chloro-*N*⁴-pyrimidinyl-4,5-diamines(3) (1.3 mmol), the appropriate acid or its derivatives (1.9 mmol) and PPA (0.63 g, 1.9 mmol) were dissolved in POCl₃ (6.0 mL), and stirred under reflux for 0.5-12 h. The reaction mixture was concentrated in vacuo, diluted with water (15 mL), and extracted with EtOAc (3 x 10 mL). The water layer was treated with 5N NaOH to pH 10 and extracted with EtOAc (2 x 10 mL). The combined EtOAc layer was washed with saturated NaHCO₃, brine, dried over anhydrous MgSO₄, concentrated in vacuo and purified by flash chromatography (elution with 20 % EtOAc in petroleum ether for the compound **4.6**, **4.12**, **4.18**, elution with 2.5 % EtOAc in petroleum ether followed by 9 % EtOAc in petroleum ether for the others).

4-chloro-11-methyl-6-propylpyrimido[4,5-*b*][1,4]benzodiazepine (4.1). Yellow solid, 60%, mp: 125.3-126.9 °C. ES-MS: 287 ((M+1)⁺), HPLC (ELSD): 100% (R_t = 3.66 min). ¹H NMR (300 Hz, CDCl₃) δ 8.35 (s, 1H), 7.38-7.44 (t, *J* = 9.0 Hz, 1H), 7.32-7.35 (d, *J* = 9.0 Hz, 1H), 7.08-7.14 (t, *J* = 9.0 Hz, 1H), 6.98-7.01 (d, *J* = 9.0 Hz, 1H), 3.28 (s, 3H), 2.84-2.89 (t, *J* = 7.5 Hz, 2H), 1.70-1.83 (m, 2H), 1.02-1.07 (t, *J* = 7.5 Hz, 3H). ¹³C

NMR (300 Hz, CDCl₃) δ 177.5, 162.9, 156.0, 153.3, 153.0, 132.1, 131.0, 130.4, 128.3, 124.2, 119.3, 42.2, 35.9, 20.4, 13.7.

4-chloro-6,11-dimethylpyrimido[4,5-*b*][1,4]benzodiazepine (4.2). Yellow solid, 52%, mp: 121.1-122.6 °C. ES-MS: 259 ((M+1)⁺), HPLC (ELSD): 100% (R_t = 3.10min). ¹H NMR (300 Hz, CDCl₃) δ 8.36 (s, 1H), 7.40-7.45 (t, *J* = 7.8 Hz, 1H), 7.34-7.36 (d, *J* = 6.9 Hz, 1H), 7.10-7.15 (t, *J* = 7.5 Hz, 1H), 6.98-7.00 (d, *J* = 8.1 Hz, 1H), 3.30 (s, 3H), 2.64 (s, 3H).

4-chloro-11-methyl-6-phenylpyrimido[4,5-*b*][1,4]benzodiazepine (4.3) Yellow solid, 74%, mp: 127.1-128.9 °C. ES-MS: 321 ((M+1)⁺), HPLC (ELSD): 100% (R_t = 3.89 min). ¹H NMR (300 Hz, CDCl₃) δ 8.39 (s, 1H), 7.80-7.83 (d, *J* = 9.0 Hz, 2H), 7.42-7.55 (m, 4H), 7.09-7.14 (t, *J* = 7.5 Hz, 3H), 3.35 (s, 3H). ¹³C NMR (300 Hz, CDCl₃) δ 173.0, 162.8, 156.7, 154.0, 153.9, 139.6, 133.0, 132.0, 131.6, 130.2, 129.1, 128.5, 124.1, 120.1, 36.2.

4-chloro-11-methyl-6-(4'-fluorophenyl)-pyrimido[4,5-*b*][1,4]benzodiazepine (4.4). Orange solid, 79%, mp: 196.1-197.1 °C. ES-MS: 339 ((M+1)⁺), HPLC (ELSD): 100% (R_t = 3.76 min). ¹H NMR (300 Hz, CDCl₃) δ 8.40 (s, 1H), 7.81-7.86 (m, 2H), 7.48-7.52 (m, 1H), 7.10-7.19 (m, 5H), 3.35 (s, 3H).

4-chloro-11-methyl-6-(4'-methyl-phenyl)-pyrimido[4,5-*b*][1,4]benzodiazepine (4.5) Orange solid, 90%, mp: 200.9-201.8 °C. ES-MS: 335 ((M+1)⁺), HPLC (ELSD): 100% (R_t = 3.93 min). ¹H NMR (300 Hz, CDCl₃) δ 8.38 (s, 1H), 7.70-7.73 (d, *J* = 8.1 Hz, 2H), 7.46-7.52 (m, 1H), 7.23-7.26 (d, *J* = 8.4 Hz, 2H), 7.06-7.15 (m, 3H), 3.34 (s, 3H), 2.43 (s, 3H). ¹³C NMR (300 Hz, CDCl₃) δ 173.0, 162.9, 156.4, 153.6, 142.2, 136.7, 133.0, 132.1, 131.4, 130.4, 130.2, 129.4, 129.2, 129.1, 124.0, 120.0, 36.2, 21.8.

4-chloro-11-methyl-6-(4'-nitro-phenyl)-pyrimido[4,5-*b*][1,4]benzodiazepine (4f).

Orange solid, 38%, mp: 213.4-214.6 °C. ES-MS: 366 ((M+1)⁺), HPLC (ELSD): 100% (R_t = 3.83 min). ¹H NMR (300 Hz, CDCl₃) δ 8.44(s, 1H), 8.29-8.31 (d, *J* = 8.4 Hz, 2H), 7.99-8.02 (d, *J*=8.4 Hz, 2H), 7.52-7.57 (t, *J* = 7.5 Hz, 1H), 7.12-7.14 (m, 2H), 7.01-7.04 (m, 1H), 3.37(s, 3H).

4-chloro-8,11-dimethyl-6-propylpyrimido[4,5-*b*][1,4]benzodiazepine (4.7).

Yellow solid, 65%, mp: 114.8-116.4 °C. ES-MS: 301 ((M+1)⁺), HPLC (ELSD): 100% (R_t = 3.88 min). ¹H NMR (300 Hz, CDCl₃) δ 8.33 (s, 1H), 7.19-7.23 (d, *J* = 6.0 Hz, 1H), 7.12 (s, 1H), 6.87-6.90 (d, *J* = 9.0 Hz, 1H), 3.26 (s, 3H), 2.83-2.88 (t, *J* = 7.5 Hz, 2H), 2.31 (s, 3H), 1.70-1.83 (m, 2H), 1.02-1.07 (t, *J* = 7.5 Hz, 3H). ¹³C NMR (300 Hz, CDCl₃) δ 177.5, 163.1, 155.8, 153.2, 150.4, 134.0, 132.7, 130.9, 130.2, 128.6, 119.1, 42.1, 35.8, 20.6, 20.4, 13.7

4-chloro-6,8,11-trimethylpyrimido[4,5-*b*][1,4]benzodiazepine (4.8).

Yellow solid, 57%, mp: 117.9-119.6 °C. ES-MS: 273 ((M+1)⁺), HPLC (ELSD): 100% (R_t = 3.35 min). ¹H NMR (300 Hz, CDCl₃) δ 8.34 (s, 1H), 7.20-7.23 (m, 1H), 7.14 (s, 1H), 6.86-6.89 (d, *J* = 8.1 Hz, 1H), 3.27 (s, 3H), 2.63 (s, 3H), 2.31 (s, 3H).

4-chloro-8,11-dimethyl-6-phenylpyrimido[4,5-*b*][1,4]benzodiazepine (4.9).

Orange solid, 85%, mp: 170.4-171.5 °C. ES-MS: 335 ((M+1)⁺), HPLC (ELSD): 100% (R_t = 4.08 min). ¹H NMR (300 Hz, CDCl₃) δ 8.37 (s, 1H), 7.82-7.85 (m, 2H), 7.43-7.53 (m, 3H), 7.28 (s, 1H), 6.98-7.00 (d, *J*=8.4Hz, 1H), 6.92 (s, 1H), 3.32 (s, 3H), 2.25 (s, 3H).

4-chloro-8,11-dimethyl-6-(4'-fluorophenyl)-pyrimido[4,5-*b*][1,4]benzodiazepine

(4.10). Yellow solid, 88%, mp: 166.0-167.6 °C. ES-MS: 353 ((M+1)⁺), HPLC (ELSD):

100% (R_t = 3.92 min). ^1H NMR (300 Hz, CDCl_3) δ 8.38 (s, 1H), 7.82-7.87 (m, 2H), 7.27-7.32 (m, 1H), 7.12-7.18 (m, 2H), 6.98-7.00 (d, J =8.4 Hz, 1H), 6.90 (s, 1H), 3.31 (s, 3H), 2.25 (s, 3H).

4-chloro-8,11-dimethyl-6-(4'-methyl-phenyl)-pyrimido[4,5-*b*][1,4]benzodiazepine

(4.11). Yellow solid, 97%, mp: 231.0-232.1 °C. ES-MS: 349 ($(\text{M}+1)^+$), HPLC (ELSD): 100% (R_t = 4.08 min). ^1H NMR (300 Hz, CDCl_3) δ 8.36 (s, 1H), 7.71-7.74 (d, J = 8.1 Hz, 2H), 7.24-7.30 (m, 3H), 6.97-7.00 (d, J = 8.4 Hz, 1H), 6.93 (s, 1H), 3.32 (s, 3H), 2.44 (s, 3H), 2.24 (s, 3H). ^{13}C NMR (300 Hz, CDCl_3) δ 172.9, 163.0, 156.3, 153.5, 151.3, 142.0, 136.7, 133.7, 133.5, 132.2, 130.4, 130.2, 129.3, 129.2, 128.9, 119.8, 36.1, 21.7, 20.7.

4-chloro-8,11-dimethyl-6-(4'-nitro-phenyl)-pyrimido[4,5-*b*][1,4]benzodiazepine

(4.12). Orange solid, 49%, mp: 229.6-230.8 °C. ES-MS: 380 ($(\text{M}+1)^+$), HPLC (ELSD): 100% (R_t = 4.00 min). ^1H NMR (300 Hz, CDCl_3) δ 8.42 (s, 1H), 8.29-8.32 (d, J = 8.7 Hz, 2H), 7.99-8.02 (d, J = 8.7 Hz, 2H), 7.33-7.35 (d, J = 7.2 Hz, 1H), 7.00-7.03 (d, J = 8.4 Hz, 1H), 6.80 (s, 1H), 3.34 (s, 3H), 2.26 (s, 3H).

4-chloro-8-fluoro-11-methyl-6-propylpyrimido[4,5-*b*][1,4]benzodiazepine (4.13).

Yellow solid, 50%, mp: 119.4-120.5 °C. ES-MS: 305 ($(\text{M}+1)^+$), HPLC (ELSD): 100% (R_t = 3.49 min). ^1H NMR (300 Hz, CDCl_3) δ 8.37 (s, 1H), 7.11-7.15 (m, 1H), 7.02-7.06 (m, 1H), 6.94-6.98 (m, 1H), 3.26 (s, 3H), 2.82-2.86 (t, J = 7.2 Hz, 2H), 1.72-1.84 (m, 2H), 1.03-1.08 (t, J = 7.2 Hz, 3H).

4-chloro-8-fluoro-6,11-dimethylpyrimido[4,5-*b*][1,4]benzodiazepine (4.14).

Yellow solid, 45%, mp: 140.5-141.5 °C. ES-MS: 277 ($(\text{M}+1)^+$), HPLC (ELSD): 100% (R_t = 3.18 min). ^1H NMR (300 Hz, CDCl_3) δ 8.37 (s, 1H), 7.10-7.15 (m, 1H), 7.03-7.07 (m, 1H), 6.93-6.98 (m, 1H), 3.27 (s, 3H), 2.63 (s, 3H).

4-chloro-8-fluoro-11-methyl-6-phenylpyrimido[4,5-*b*][1,4]benzodiazepine (4.15).

Orange solid, 88%, mp: 207.7-208.7 °C. ES-MS: 339 ((M+1)⁺), HPLC (ELSD): 100% (R_t = 3.90 min). ¹H NMR (300 Hz, CDCl₃) δ 8.40 (s, 1H), 7.82-7.84 (d, J = 8.1 Hz, 2H), 7.44-7.57 (m, 3H), 7.18-7.26 (m, 1H), 7.04-7.09 (m, 1H), 6.83-6.86 (m, 1H), 3.20 (s, 3H).

4-chloro-8-fluoro -11-methyl-6-(4'-fluorophenyl)-pyrimido[4,5-*b*][1,4]benzodiazepine (4.16). Yellow solid, 81%, mp: 204.9-205.7 °C. ES-MS: 357 ((M+1)⁺), HPLC (ELSD): 100% (R_t = 3.91 min). ¹H NMR (300 Hz, CDCl₃) δ 8.40 (s, 1H), 7.83-7.88 (m, 2H), 7.05-7.22 (m, 4H), 6.82-6.85 (m, 1H), 3.32 (s, 3H).

4-chloro-8-fluoro -11-methyl-6-(4'-methylphenyl)-pyrimido[4,5-*b*][1,4]benzodiazepine (4.17). Yellow solid, 90%, mp: 190.8-191.9 °C. ES-MS: 353 ((M+1)⁺), HPLC (ELSD): 100% (R_t = 4.12 min). ¹H NMR (300 Hz, CDCl₃) δ 8.40 (s, 1H), 7.71-7.74 (d, J = 8.1 Hz, 2H), 7.17-7.28 (m, 3H), 7.03-7.08 (m, 1H), 6.84-6.87 (m, 1H), 3.31 (s, 3H), 2.44 (s, 3H).

4-chloro-8-fluoro -11-methyl-6-(4'-nitrophenyl)-pyrimido[4,5-*b*][1,4]benzodiazepine (4.18). Orange solid, 37%, mp: 226.7-229.0 °C. ES-MS: 384 ((M+1)⁺), HPLC (ELSD): 100% (R_t = 3.82 min). ¹H NMR (300 Hz, CDCl₃) δ 8.45 (s, 1H), 8.31-8.34 (d, J = 8.7 Hz, 2H), 8.00-8.03 (d, J = 8.4 Hz, 2H), 7.24 (s, 1H), 7.08-7.12 (m, 1H), 6.73-6.76 (m, 1H), 3.34 (s, 3H).

4-hydroxy -11-methyl-6-phenylpyrimido[4,5-*b*][1,4]benzodiazepine (4.19). Orange oil, 61%. ES-MS: 303 ((M+1)⁺). ¹H NMR (300 Hz, CDCl₃) δ 7.92 (s, 1H), 7.82-7.84 (d, J = 6.6 Hz, 2H), 7.37-7.46 (m, 5H), 7.04-7.07 (m, 2H), 3.29 (s, 3H).

General procedure for the Preparation of 4-aminopyrimido[4,5-*b*][1,4] benzodiazepine
(5)

4-chloro-8- fluoro -11-methyl-6-(4'-methyl-phenyl)-pyrimido[4,5-*b*][1,4]benzodiazepine(**4.17**) (0.14 mmol), the appropriate amine (0.28 mmol) and Et₃N(0.04mL, 0.28 mmol) were dissolved in n-BuOH (2.0 mL), and stirred under reflux for 5 h. The reaction mixture was concentrated in vacuo, dissolved with EtOAc (15 mL), and washed with water (2 x 15 mL), brine, dried over anhydrous MgSO₄, concentrated in vacuo and purified by flash chromatography (CH₂Cl₂/ EtOAc,10:1 for compound **5.1** and CH₂Cl₂/ EtOAc,5:1 for compound **5.2**).

4-(butylamino)-8- fluoro -11-methyl-6-(4'-methyl-phenyl)-pyrimido[4,5-*b*][1,4] benzodiazepine(5.1**)**. Orange oil, 84%. ES-MS: 390 ((M+1)⁺), HPLC (ELSD): 100% (R_t = 3.80 min).

4-(pyrrolidin-1-yl)-8- fluoro -11-methyl-6-(4'-methylphenyl)-pyrimido[4,5-*b*][1,4] benzodiazepine(5.2**)**. Orange oil, 89%. ES-MS: 388 ((M+1)⁺), HPLC (ELSD): 100% (R_t = 2.58 min).