

Supplementary Information

Efficient synthesis of novel disubstituted pyrido[3,4-*b*]pyrazines for the design of protein kinase inhibitors†

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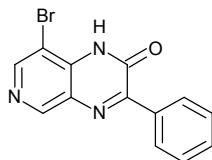
Chemistry

General methods: Melting points were determined with an Electrothermal IA9300 digital melting point apparatus and are uncorrected. ¹H and ¹³C NMR spectra were recorded on a Bruker Avance 400 spectrometer (400 MHz). Chemical shifts (δ) are expressed in ppm relative to tetramethylsilane as internal standard. NMR signals are described as follows: s=singlet, d=doublet, t=triplet, q=quadruplet, sext=sextuplet, m=multiplet and br=broad. Coupling constants (J) are given in hertz. Infrared spectra (IR) were recorded on a Shimadzu IRAffinity-1 IR-FT spectrophotometer equipped with a MIRacle 10 accessory ATR. Only the most significant absorption bands are reported. Electrospray mass spectrometric analysis was performed on a Waters Acquity UPLC System ZQ 2000 single quadrupole. All tested compounds displayed purity of >97%. All reactions were monitored by thin-layer chromatography (TLC) using 0.2-mm-thick silica gel plates 60 F254 (5735 Merck). Column chromatography was carried out with silica gel 60 (70–230 mesh, ASTM, Merck). Chemicals and solvents used were commercially available. Elemental analyses were performed on a Thermo Scientific Elemental Analyzer Flash EA 1112 and were found to be within ±0.4% of theoretical values.

Synthesis of halogenated pyrido[3,4-*b*]pyrazine precursors 6a, 6b, 12a, 12b, 16 and 17

Synthesis of 8-bromo-3-phenylpyrido[3,4-*b*]pyrazine (6a)

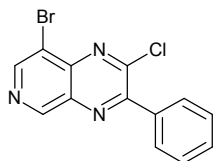
8-Bromo-3-phenylpyrido[3,4-*b*]pyrazin-2(1*H*)-one (3)



To a solution of 3,4-diamino-5-bromopyridine **2** (3.76 g, 20.0 mmol) in methanol (150 mL) was added methyl oxo(phenyl)acetate (3.90 g, 20.0 mmol) and the reaction mixture was stirred at room temperature for 24 h. The resulting mixture was filtered, and then stirred for more 24 h. The solution was filtered again, the two batches of powder were mixed together and were purified by silica gel column chromatography using dichloromethane/ethanol (19/1) as eluent to give compound **3** as a beige powder (5.74 g, 95%). *R*_f 0.60 (CH₂Cl₂/EtOH 19:1); Mp 253–254 °C; ¹H NMR (400 MHz, DMSO-*d*₆): δ 8.99 (s, 1H), 8.76 (s, 1H), 8.32–8.27 (m, 2H), 7.59–7.56 (m, 3H); ¹³C NMR (100 MHz, DMSO-*d*₆): δ 157.7 (C), 157.0 (C), 150.7 (CH), 150.2 (CH), 138.1 (C), 135.8 (C), 131.7 (CH), 130.5 (C), 130.4 (2CH), 128.9 (2CH), 106.7 (C); IR (ATR): 3170, 3070, 3028, 1680, 1597, 1533, 1265, 1169, 1009, 937, 732 cm⁻¹; MS (ESI) *m/z* (%) = 303.1

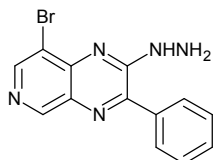
(100) $[M+H]^+$, 305.1 (95) $[M+H+2]^+$. Anal. calcd for $C_{13}H_8BrN_3O$: C 51.68, H 2.67, N 13.91. Found: C 51.59, H 2.69, N 14.00.

8-Bromo-2-chloro-3-phenylpyrido[3,4-*b*]pyrazine (**4**)



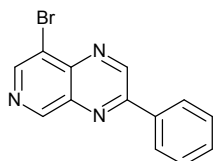
8-Bromo-3-phenylpyrido[3,4-*b*]pyrazin-2(1*H*)-one **3** (5.00 g, 16.5 mmol) was refluxed in phosphorus oxychloride (40 mL) overnight. Then phosphorus oxychloride was removed under reduce pressure, the residue was taken up with dichloromethane (200 mL). An aqueous saturated solution of sodium hydrogenocarbonate (200 mL) was added carefully after cooling with ice bath. The aqueous layer was extracted with dichloromethane, the organic layer was dried over Na_2SO_4 , filtered and then the solvent was removed under reduce pressure. The crude product was purified by silica gel column chromatography using dichloromethane as eluent to give compound **4** as an orange powder (4.81 g, 90%). R_f 0.51 (CH_2Cl_2); Mp 158-160 °C; 1H NMR (400 MHz, $DMSO-d_6$): δ 9.03 (s, 1H), 8.79 (s, 1H), 8.30-8.28 (m, 2H), 7.61-7.54 (m, 3H); ^{13}C NMR (100 MHz, $DMSO-d_6$): δ 158.2 (C), 156.4 (C), 150.1 (CH), 149.4 (CH), 138.0 (C), 135.5 (C), 132.0 (CH), 130.4 (2CH), 130.3 (C), 129.0 (2CH), 106.3 (C); IR (ATR): 3042, 3012, 1690, 1589, 1543, 1485, 1194, 1126, 984 cm^{-1} ; MS (ESI) m/z (%) = 319.9(74) $[M+H]^+$, 321.9(100) $[M+H+2]^+$, 323.9(22) $[M+H+4]^+$. Anal. calcd for $C_{13}H_7BrClN_3$: C 48.40, H 2.81, N 13.03. Found: C 48.46, H 2.80, N 12.98.

8-Bromo-2-hydrazino-3-phenylpyrido[3,4-*b*]pyrazine (**5**)



To a solution of 8-bromo-2-chloro-3-phenylpyrido[3,4-*b*]pyrazine **4** (3.00 g, 9.4 mmol) in ethanol (60 mL) was added dropwise hydrazine hydrate (1.14 mL, 37.6 mmol). The mixture was refluxed for 2 h, then cooled and filtered. The crude product was purified by silica gel column chromatography using dichloromethane/ethanol (19/1) as eluent to give the desired compound **5** as a beige powder (2.52g, 85%). R_f 0.62 (CH_2Cl_2 /EtOH 19:1); Mp 213-214 °C; 1H NMR (400 MHz, $DMSO-d_6$): δ 8.87 (s, 1H), 8.70 (s, 1H), 7.81-7.77 (m, 2H), 7.60-7.57 (m, 3H); ^{13}C NMR (100 MHz, $DMSO-d_6$): δ 154.7 (CH), 150.6 (CH), 149.9 (C), 142.1 (C), 139.6 (C), 136.1 (C), 132.8 (CH), 131.4 (2CH), 129.1 (C), 128.6 (2CH), 120.7 (C); IR (ATR): 3280, 3257, 3042, 3021, 1545, 1516, 1429, 1408, 1120, 1012, 930 cm^{-1} ; MS (ESI) m/z (%) = 317.1 (100) $[M+H]^+$, 319.1 (96) $[M+H+2]^+$. Anal. calcd for $C_{13}H_{10}BrN_5$: C 49.07, H 3.80, N 22.01. Found: C 49.22, H 3.77, N 21.89.

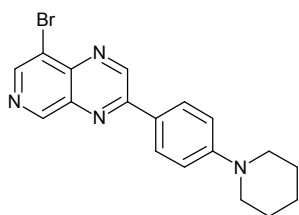
8-Bromo-3-phenylpyrido[3,4-*b*]pyrazine (**6a**)



A mixture of 8-bromo-2-hydrazino-3-phenylpyrido[3,4-*b*]pyrazine **5** (1.27 g, 4.0 mmol), manganese dioxide (1.40 g, 16 mmol) and charcoal (1.40 g, 10 mmol) in chloroform (100 mL) was stirred at room

temperature for 24h. The resulting solution was filtered on Celite, and the pad was washed with dichloromethane. The solvent was removed under reduce pressure and the resulting crude product was purified by silica gel column chromatography using dichloromethane as eluent to give compound **6a** as a beige powder (0.74g, 65%). R_f 0.40 (CH_2Cl_2); Mp 151-152 °C; ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 9.96 (s, 1H), 9.55 (s, 1H), 8.46-8.42 (m, 2H), 7.70-7.66 (m, 3H); ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$): δ 154.5 (CH), 150.3 (CH), 148.8 (CH), 142.4 (C), 138.7 (C), 135.8 (C), 132.3 (CH), 130.2 (2CH), 129.3 (C), 128.9 (2CH), 120.5 (C); IR (ATR): 3062, 3028, 1672, 1562, 1450, 1310, 1207, 1180, 1045, 964 cm^{-1} ; MS (ESI) m/z (%) = 287.1 (100) $[\text{M}+\text{H}]^+$, 289.1 (100) $[\text{M}+\text{H}+2]^+$. Anal. calcd for $\text{C}_{13}\text{H}_8\text{BrN}_3$: C 54.57, H 2.82, N 14.69. Found: C 54.64, H 2.83, N 14.60.

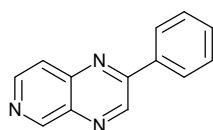
Synthesis of 8-bromo-3-(4-piperidin-1-ylphenyl)pyrido[3,4-b]pyrazine (6b), see reference 14



Synthesis of 5-chloro-2-phenylpyrido[3,4-b]pyrazine (12a)

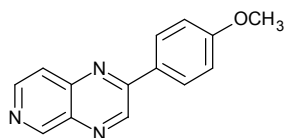
and 5-chloro-2-(4-methoxyphenyl)pyrido[3,4-b]pyrazine (12b)

2-Phenylpyrido[3,4-b]pyrazine (**11a**)



A mixture of 3,4-diaminopyridine **10** (3.00 g, 45.8 mmol) and phenylglyoxal monohydrate (6.11 g, 45.8 mmol) in dioxane (150 mL) was refluxed for 6 h. The solution was then cooled to room temperature and dichloromethane was added. The organic layer was washed with water, dried over sodium sulfate, filtered and the solvents were removed under reduced pressure. The crude product was recrystallized from isopropyl ether to give compound **11a** as a white powder (7.90 g, 83%). R_f 0.62 ($\text{CH}_2\text{Cl}_2/\text{EtOH}$ 19:1); Mp 123-124 °C (lit. [30]: 125-126 °C); ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 9.78 (s, 1H), 9.54 (d, 1H, $^4J=0.6$ Hz), 8.89 (d, 1H, $^3J=5.8$ Hz), 8.46-8.41 (m, 2H), 8.08 (dd, 1H, $^3J=5.8$ Hz, $^4J=0.7$ Hz), 7.69-7.66 (m, 3H); ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$): δ 156.0 (C), 154.6 (CH), 148.6 (CH), 146.8 (CH), 144.9 (C), 137.1 (C), 136.2 (C), 132.4 (CH), 130.1 (2CH), 129.2 (2CH), 122.5 (CH); IR (ATR): 3057, 3032, 1593, 1545, 1440, 1400, 1315, 1232, 959 cm^{-1} ; MS (ESI) m/z (%) = 208.2 (100) $[\text{M}+\text{H}]^+$. Anal. calcd for $\text{C}_{13}\text{H}_9\text{N}_3$: C 75.35, H 4.38, N 20.28. Found: C 75.41, H 4.39, N 20.21.

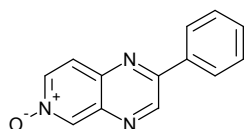
2-(4-Methoxyphenyl)pyrido[3,4-b]pyrazine (**11b**)



Compound **11b** was obtained following the procedure used for 2-phenylpyrido[3,4-b]pyrazine **11a**. The crude product was purified by silica gel column chromatography using dichloromethane/ethanol (19/1) as eluent to give compound **11b** as a white powder (9.61 g, 89%). R_f 0.61 ($\text{CH}_2\text{Cl}_2/\text{EtOH}$ 19:1); Mp 143-144 °C (lit. [30]:

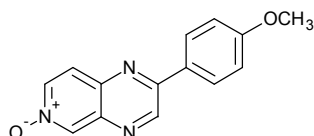
140-142 °C); $^1\text{H NMR}$ (400 MHz, $\text{DMSO-}d_6$): δ 9.72 (s, 1H), 9.46 (d, 1H, $^4J=0.6$ Hz), 8.83 (dd, 1H, $^3J=5.5$ Hz, $^4J=0.7$ Hz), 8.41 (d, 2H, $^3J=8.9$ Hz), 8.00 (dd, 1H, $^3J=5.5$ Hz, $^4J=0.7$ Hz), 7.18 (d, 2H, $^3J=8.9$ Hz), 3.91 (s, 3H); $^{13}\text{C NMR}$ (100 MHz, $\text{DMSO-}d_6$): δ 163.0 (C), 155.6 (C), 154.4 (CH), 148.6 (CH), 146.5 (CH), 145.1 (C), 136.8 (C), 130.8 (2CH), 128.5 (C), 122.3 (CH), 115.7 (2CH), 56.4 (CH_3); IR (ATR): 3044, 3021, 1593, 1537, 1514, 1448, 1277, 1254, 1229, 1177, 1020, 959 cm^{-1} ; MS (ESI) m/z (%) = 238.1 (100) $[\text{M}+\text{H}]^+$. Anal. calcd for $\text{C}_{14}\text{H}_{11}\text{N}_3\text{O}$: C 70.87, H 4.67, N 17.71. Found: C 70.82, H 4.65, N 17.78.

2-Phenylpyrido[3,4-*b*]pyrazine-6-oxide (crude)



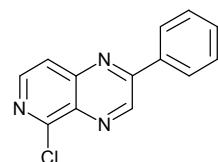
A solution of 2-phenylpyrido[3,4-*b*]pyrazine **11a** (500 mg, 2.4 mmol) and *m*CPBA (416 mg, 2.4 mmol) in CH_2Cl_2 (20 mL) was refluxed for 6h. Dichloromethane was added and the organic layer was washed with a saturated aqueous solution of sodium carbonate and brine, then dried over sodium sulfate and filtered. The solvent was removed under reduced pressure to give the crude 2-phenylpyrido[3,4-*b*]pyrazine-6-oxide as a yellow powder (420 mg, 78%). R_f 0.51 ($\text{CH}_2\text{Cl}_2/\text{EtOH}$ 19:1); Mp 173-175 °C; $^1\text{H NMR}$ (400 MHz, $\text{DMSO-}d_6$): δ 9.70 (s, 1H), 9.09 (d, 1H, $^4J=1.8$ Hz), 8.51 (dd, 1H, $^3J=7.5$ Hz, $^4J=1.8$ Hz), 8.40-8.36 (m, 2H), 8.13 (d, 1H, $^3J=7.4$ Hz), 7.67-7.64 (m, 3H); MS (ESI) m/z (%) = 224.1 (100) $[\text{M}+\text{H}]^+$.

2-(4-Methoxyphenyl)pyrido[3,4-*b*]pyrazine-6-oxide (crude)



The *N*-oxide was obtained following the procedure used for 2-phenylpyrido[3,4-*b*]pyrazine-6-oxide to give the crude 2-(4-methoxyphenyl)pyrido[3,4-*b*]pyrazine-6-oxide as a yellow powder (395 mg, 65%). R_f 0.48 ($\text{CH}_2\text{Cl}_2/\text{EtOH}$ 19:1); Mp 186-177 °C; $^1\text{H NMR}$ (400 MHz, $\text{DMSO-}d_6$): δ 9.67 (s, 1H), 9.04 (d, 1H, $^4J=0.8$ Hz), 8.47 (d, 1H, $^3J=5.2$ Hz), 8.37 (d, 2H, $^3J=8.8$ Hz), 8.13 (d, 1H, $^3J=5.8$ Hz), 7.20 (d, 2H, $^3J=8.8$ Hz), 3.92 (s, 3H); MS (ESI) m/z (%) = 254.2 (100) $[\text{M}+\text{H}]^+$.

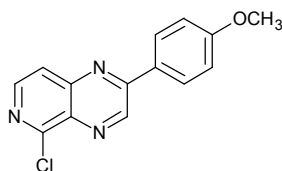
5-Chloro-2-phenylpyrido[3,4-*b*]pyrazine (**12a**)



A solution of crude 2-phenylpyrido[3,4-*b*]pyrazine-6-oxide (270 mg, 1.2 mmol) and phosphorus oxychloride (114 μL , 1.2 mmol) in dichloromethane (10 mL) was refluxed for 8 h. Dichloromethane was added and an aqueous saturated solution of sodium hydrogenocarbonate (30 mL) was added carefully after cooling with ice bath. The aqueous layer was extracted with dichloromethane, the organic layer was dried over Na_2SO_4 , filtered and then the solvent was removed under reduce pressure. The crude product was purified by silica gel column chromatography using dichloromethane as eluent to give compound **12a** as a beige powder (160 mg, 55%). R_f 0.48 ($\text{CH}_2\text{Cl}_2/\text{EtOH}$ 19:1); Mp 187-189 °C (lit. [22]: 189-190 °C); $^1\text{HNMR}$ (400 MHz, $\text{DMSO-}d_6$): δ 9.85 (s, 1H), 8.68 (d, 1H, $^3J=5.8$ Hz), 8.47-8.43 (m, 2H), 8.11 (d, 1H, $^3J=5.8$

Hz), 7.72-7.69 (m, 3H), 6.30 (br s, 2H); ^{13}C NMR (100 MHz, DMSO- d_6): δ 156.1 (C), 154.3 (CH), 149.2 (C), 147.3 (CH), 146.1 (C), 136.1 (C), 135.4 (C), 133.1 (CH), 130.6 (2CH), 129.3 (2CH), 122.5 (2CH); IR (ATR): 3030, 1697, 1620, 1537, 1400, 1313, 1244, 1211, 1120, 939 cm^{-1} ; MS (ESI) m/z (%) = 242.1 (100) $[\text{M}+\text{H}]^+$, 244.1 (40) $[\text{M}+\text{H}+2]^+$. Anal. calcd for $\text{C}_{13}\text{H}_8\text{ClN}_3$: C 64.61, H 3.34, N 17.39. Found: C 64.64, H 3.33, N 17.37.

5-Chloro-2-(4-methoxyphenyl)pyrido[3,4-*b*]pyrazine (**12b**)



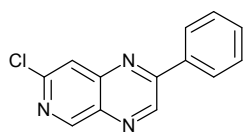
Compound **12b** was obtained following the procedure used for 5-chloro-2-phenylpyrido[3,4-*b*]pyrazine **12a**. The crude product was purified by silica gel column chromatography using dichloromethane as eluent to give compound **12b** as a white powder (180 mg, 55%). R_f 0.68 ($\text{CH}_2\text{Cl}_2/\text{EtOH}$ 19:1); Mp 193-195 $^\circ\text{C}$; ^1H NMR (400 MHz, DMSO- d_6): δ 9.80 (s, 1H), 8.63 (d, 1H, $^3J=5.8$ Hz), 8.44 (d, 2H, $^3J=8.5$ Hz), 8.03 (d, 1H, $^3J=6.0$ Hz), 7.23 (d, 2H, $^3J=8.8$ Hz), 3.92 (s, 3H); ^{13}C NMR (100 MHz, DMSO- d_6): δ 162.7 (C), 152.6 (C), 147.4 (CH), 142.7 (CH), 139.2 (C), 138.9 (C), 137.2 (C), 130.2 (2CH), 128.5 (C), 125.9 (CH), 115.7 (2CH), 56.4 (CH_3); IR (ATR): 3010, 2922, 1595, 1564, 1516, 1294, 1278, 1252, 1186, 1029, 960 cm^{-1} ; MS (ESI) m/z (%) = 272.1 (100) $[\text{M}+\text{H}]^+$, 274.1 (40) $[\text{M}+\text{H}+2]^+$. Anal. calcd for $\text{C}_{14}\text{H}_{10}\text{ClN}_3\text{O}$: C 61.89, H 3.71, N, 15.47. Found: C 61.93, H 3.73, N 17.41.

Synthesis of 7-chloro-2-phenylpyrido[3,4-*b*]pyrazine (**16**)

and 7-chloro-3-phenylpyrido[3,4-*b*]pyrazine (**17**)

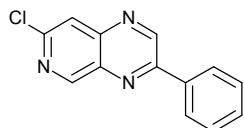
Compounds **16** and **17** were synthesized by reaction of 2,3-diamino-6-chloropyridine **15** and phenylglyoxal monohydrate following the procedure used for **11a-b**. The crude mixture of products was purified by silica gel column chromatography using dichloromethane as eluent to give compound **16** as a white powder (4.92 g, 44%) and compound **17** as a white powder (1.51 g, 14%).

7-chloro-2-phenylpyrido[3,4-*b*]pyrazine (**16**)



R_f 0.32 (CH_2Cl_2); Mp 146-148 $^\circ\text{C}$; ^1H NMR (400 MHz, DMSO- d_6): δ 9.81 (s, 1H), 9.43 (s, 1H), 8.46-8.42 (m, 2H), 8.27 (s, 1H), 7.71-7.68 (m, 3H); ^{13}C NMR (100 MHz, DMSO- d_6): δ 156.7 (C), 154.8 (CH), 149.5 (C), 147.4 (CH), 146.7 (C), 136.4 (C), 135.8 (C), 132.8 (CH), 130.2 (2CH), 129.2 (2CH), 122.0 (2CH); IR (ATR): 3061, 3035, 1579, 1562, 1541, 1444, 1423, 1387, 1309, 1263, 1072, 1022, 956 cm^{-1} ; MS (ESI) m/z (%) = 242.1 (100) $[\text{M}+\text{H}]^+$, 244.1(39) $[\text{M}+\text{H}+2]^+$. Anal. calcd for $\text{C}_{13}\text{H}_8\text{ClN}_3$: C 64.61, H 3.34, N 17.39. Found: C 64.64, H 3.36, N 17.34.

7-Chloro-3-phenylpyrido[3,4-*b*]pyrazine (**17**)

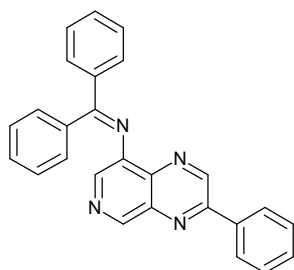


R_f 0.57 (CH_2Cl_2); Mp 157-159 °C; ^1H NMR (400 MHz, $\text{DMSO-}d_6$): δ 9.90 (s, 1H), 9.47 (s, 1H), 8.45-8.40 (m, 2H), 8.29 (s, 1H), 7.69-7.66 (m, 3H); ^{13}C NMR (100 MHz, $\text{DMSO-}d_6$): δ 155.2 (CH), 154.0 (C), 150.5 (CH), 148.6 (C), 145.9 (C), 136.8 (C), 136.0 (C), 132.2 (CH), 130.2 (2CH), 128.7 (2CH), 121.9 (CH); IR (ATR): 3060, 3041, 1580, 1537, 1462, 1425, 1367, 1303, 1278, 1058, 1024, 952 cm^{-1} ; MS (ESI) m/z (%) = 242.1 (100) $[\text{M}+\text{H}]^+$, 244.1 (37) $[\text{M}+\text{H}+2]^+$. Anal. calcd for $\text{C}_{13}\text{H}_8\text{ClN}_3$: C 64.61, H 3.34, N 17.39. Found: C 64.62, H 3.36, N 17.36.

Synthesis of aminopyrido[3,4-*b*]pyrazine intermediates 8 and 13

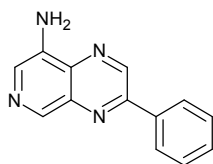
Synthesis of 8-amino-3-phenylpyrido[3,4-*b*]pyrazine (8)

N-[3-Phenylpyrido[3,4-*b*]pyrazin-8-yl]benzophenone imine (7)



To a solution of 8-bromo-3-phenylpyrido[3,4-*b*]pyrazine **6** (1.90 g, 6.6 mmol) in toluene (80 mL) under argon was added successively benzophenone imine (1.33 mL, 8.0 mmol), tris(dibenzylideneacetone) palladium (20 mg, 5.10^{-5} mol), 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (8 mg, $1.7.10^{-5}$ mol) and sodium *tert*-butoxide (892 mg, 9.2 mmol). The reaction mixture was heated at 110 °C for 12 h and was cooled to room temperature. Ethyl acetate (120 mL) was added. The reaction mixture was washed with brine and water. The organic layer was dried over sodium sulfate, filtrated and the solvents were removed under reduced pressure. The crude product was purified by silica gel column chromatography using dichloromethane/ethanol mixtures (from 10:0 to 19:1) as eluent to give compound **7** as a beige powder (1.83 g, 72%). R_f 0.64 ($\text{CH}_2\text{Cl}_2/\text{EtOH}$ 19:1); Mp 181-182 °C; ^1H NMR (400 MHz, $\text{DMSO-}d_6$): δ 9.77 (s, 1H), 9.13 (s, 1H), 8.40-8.36 (m, 2H), 8.20 (s, 1H), 7.81-7.58 (m, 8H), 7.25-7.20 (m, 5H); ^{13}C NMR (100 MHz, $\text{DMSO-}d_6$): δ 171.8 (C), 153.4 (C), 149.0 (CH), 148.2 (CH), 144.0 (C), 138.8 (C), 137.9 (C), 137.2 (C), 136.9 (C), 136.7 (CH), 136.2 (C), 133.6 (CH), 132.6 (CH), 132.0 (CH), 130.5 (CH), 130.2 (2CH), 130.1 (CH), 129.9 (CH), 129.5 (2CH), 129.0 (CH), 128.6 (CH); IR (ATR): 3061, 3028, 1624, 1537, 1446, 1313, 1276, 1259, 1180, 875 cm^{-1} ; MS (ESI) m/z (%) = 387.2 (100) $[\text{M}+\text{H}]^+$. Anal. calcd for $\text{C}_{26}\text{H}_{18}\text{N}_4$: C 80.81, H 4.69, N 14.50. Found: C 80.89, H 4.66, N 14.45.

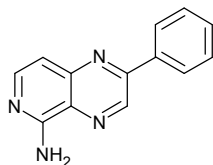
8-Amino-3-phenylpyrido[3,4-*b*]pyrazine (8)



To a solution of *N*-[3-phenylpyrido[3,4-*b*]pyrazin-8-yl]benzophenone imine **7** (900 mg, 2.4 mmol) in methanol (30 mL) was added sodium acetate (510 mg, 3.24 mmol) and hydroxylamine hydrochloride (324 mg, 4.8 mmol). The reaction mixture was stirred at 75 °C for 48 h and cooled to room temperature. The solution was poured into a 1M aqueous solution of sodium hydroxide and extracted with dichloromethane. The organic layer was dried over sodium sulfate, filtrated and the solvent was removed

under reduced pressure. The crude product was purified by silica gel column chromatography using dichloromethane/ethanol mixtures (from 10:0 to 19:1) as eluent to give compound **8** as a brown powder (279 mg, 69%). R_f 0.51 (CH₂Cl₂/EtOH 19:1); Mp 201-202 °C; ¹H NMR (400 MHz, DMSO-*d*₆): δ 9.62 (s, 1H), 8.69 (s, 1H), 8.41-8.36 (m, 2H), 8.20 (s, 1H), 7.67-7.64 (m, 3H), 6.30 (br s, 2H); ¹³C NMR (100 MHz, DMSO-*d*₆): δ 153.4 (C), 145.3 (CH), 141.3 (C), 139.5 (CH), 137.5 (C), 136.6 (C), 133.3 (C), 131.6 (CH), 130.1 (2CH), 128.5 (2CH); IR (ATR): 3442, 3248, 3101, 1610, 1556, 1508, 1448, 1369, 1269, 1184, 937 cm⁻¹; MS (ESI) m/z (%) = 223.1 (100) [M+H]⁺. Anal. calcd for C₁₃H₁₀N₄: C 70.26, H 4.54, N 25.21. Found: C 70.13, H 4.52, N 25.36.

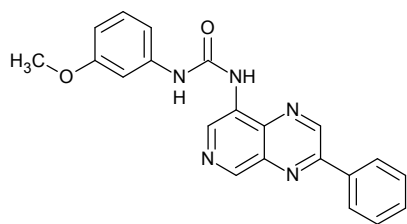
Synthesis of 5-amino-2-phenylpyrido[3,4-*b*]pyrazine (**13**)



In a sealed tube, a solution of 5-chloro-2-phenylpyrido[3,4-*b*]pyrazine **12a** (500 mg, 2.2 mmol) in a mixture of ammonium hydroxide and 1,4-dioxane (10 mL/10 mL) was heated at 120 °C for 24 h. The dioxane was then removed under reduced pressure, and the resulting mixture was poured in water. The precipitate was filtered and recrystallized from methanol to give compound **13** as a yellow powder (420 mg, 91%). R_f 0.57 (CH₂Cl₂/EtOH 19:1); Mp 191-193 °C; ¹H NMR (400 MHz, DMSO-*d*₆): δ 9.44 (s, 1H), 8.37-8.34 (m, 2H), 8.13 (d, 1H, ³J=5.8 Hz), 7.66-7.63 (m, 3H), 7.29 (br s, 2H), 7.08 (d, 1H, ³J=6.0 Hz); ¹³C NMR (100 MHz, DMSO-*d*₆): δ 159.1 (C), 155.8 (C), 147.1 (C), 146.8 (CH), 142.3 (CH), 136.5 (C), 131.9 (CH), 130.1 (2CH), 128.7 (2CH), 127.6 (C), 110.4 (CH); IR (ATR): 3311, 3196, 3059, 3039, 1641, 1543, 1485, 1440, 1303, 1274, 1186, 153, 939 cm⁻¹; MS (ESI) m/z (%) = 223.2 (100) [M+H]⁺. Anal. calcd for C₁₃H₁₀N₄: C 70.26, H 4.54, N 25.21. Found: C 70.23, H 4.55, N 25.23.

General procedure for the synthesis of *N*-aryl-*N'*-(phenylpyrido[3,4-*b*]pyrazinyl)ureas **9a**, **9b** and **14a**

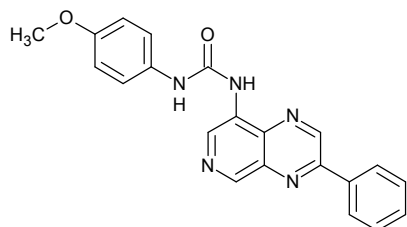
N-(3-Methoxyphenyl)-*N'*-(3-phenylpyrido[3,4-*b*]pyrazin-8-yl)urea (**9a**)



To a solution of 8-amino-3-phenylpyrido[3,4-*b*]pyrazine **8** (200 mg, 0.9 mmol) in *N,N*-dimethylformamide (10 mL) was added portionwise sodium hydride at 60% in mineral oil (43 mg, 1.1 mmol). The reaction mixture was stirred at room temperature for 30 minutes and 3-methoxyphenylisocyanate (118 μL, 0.9 mmol) was added. The reaction mixture was stirred for 3 h at room temperature and then quenched with water. The aqueous layer was extracted with dichloromethane, the combined organic extracts were dried over sodium sulfate, filtrated and the solvent was removed under reduced pressure. The crude product was purified by silica gel column chromatography using dichloromethane/ethanol mixtures (from 10:0 to 19:1) as eluent to give compound **9a** as a beige powder (200 mg, 60%); R_f 0.54 (CH₂Cl₂/EtOH 19:1); Mp 260-261 °C; ¹H NMR (400 MHz, DMSO-*d*₆): δ 9.94 (br s, 1H), 9.81 (s, 1H), 9.68 (s, 1H), 9.60 (br s, 1H), 9.19 (s, 1H), 8.45-8.43 (m, 2H), 7.69-7.68 (m, 3H), 7.29-6.64 (m, 4H), 3.80 (s, 3H); ¹³C NMR (100 MHz, DMSO-

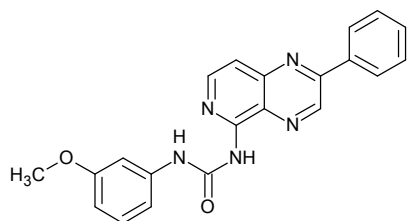
d_6): δ 160.7 (C), 156.9 (C), 152.1 (C), 151.6 (C), 146.3 (C), 145.3 (CH), 144.5 (CH), 140.5 (C), 136.0 (C), 132.5 (CH), 130.7 (CH), 130.2 (2CH), 129.0 (2CH), 127.3 (C), 116.3 (CH), 112.7 (CH), 109.6 (CH), 106.2 (CH), 56.1 (CH₃); IR (ATR): 3240, 3153, 3078, 2935, 1697, 1597, 1564, 1485, 1300, 1250, 1163, 1047 cm⁻¹; MS (ESI) m/z (%) = 372.3 (100) [M+H]⁺. Anal. calcd for C₂₁H₁₇N₅O₂: C 67.91, H 4.61, N 8.62. Found: C 67.84, H 4.63, N 8.67.

***N*-(4-Methoxyphenyl)-*N'*-(3-phenylpyrido[3,4-*b*]pyrazin-8-yl)urea (9b)**



Compound **9b** was obtained following the representative procedure, using 8-amino-3-phenylpyrido[3,4-*b*]pyrazine **8** (200 mg, 0.9 mmol) and 4-methoxyphenylisocyanate (117 μ L, 0.9 mmol), as a yellow powder (257 mg, 77%); R_f 0.52 (CH₂Cl₂/EtOH 19:1); Mp 270-271 °C. ¹H NMR (400 MHz, DMSO-*d*₆): δ 9.78 (br s, 1H), 9.67 (s, 1H), 9.53-9.52 (m, 2H), 9.15 (s, 1H), 8.48-8.45 (m, 2H), 7.68-7.67 (m, 3H), 7.52-6.91 (m, 4H), 3.77 (s, 3H); ¹³C NMR (100 MHz, DMSO-*d*₆): δ 154.9 (C), 153.2 (C), 152.3 (C), 146.2 (CH), 145.2 (CH), 136.2 (C), 135.6 (C), 133.8 (C), 133.5 (CH), 132.6 (C), 131.8 (C), 131.2 (CH), 129.4 (2CH), 128.0 (2CH), 120.2 (2CH), 114.3 (2CH), 55.4 (CH₃); IR (ATR): 3315, 3240, 1703, 1522, 1508, 1415, 1296, 1238, 1197, 1174, 1021, 825 cm⁻¹; MS (ESI) m/z (%) = 372.1 (100) [M+H]⁺. Anal. calcd for C₂₁H₁₇N₅O₂: C 67.91, H 4.61, N 8.62. Found: C 67.93, H 4.62, N 8.59.

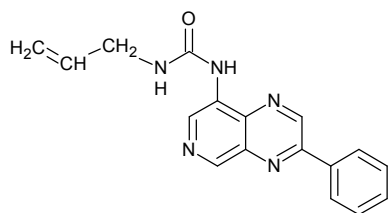
***N*-(3-Methoxyphenyl)-*N'*-(2-phenylpyrido[3,4-*b*]pyrazin-5-yl)urea (14a)**



Compound **14a** was obtained following the representative procedure, using 5-amino-2-phenylpyrido[3,4-*b*]pyrazine **13** (200 mg, 0.9 mmol) and 3-methoxyphenylisocyanate (118 μ L, 0.9 mmol), as a yellow powder (180 mg, 54%); R_f 0.66 (CH₂Cl₂/EtOH 19:1); Mp 205-207 °C. ¹H NMR (400 MHz, DMSO-*d*₆): δ 11.93 (br s, 1H), 9.71 (s, 1H), 9.34 (br s, 1H), 8.57 (d, 1H, ³J=6.0 Hz), 8.45-8.43 (m, 2H), 7.70-7.67 (m, 4H), 7.42 (t, 1H, ⁴J=2.0 Hz), 7.32 (t, 1H, ³J=8.1 Hz), 7.21 (d, 1H, ³J=8.1 Hz), 6.73 (dd, 1H, ³J=8.1 Hz, ⁴J=2.1 Hz), 3.82 (s, 3H); ¹³C NMR (100 MHz, DMSO-*d*₆): δ 160.7 (C), 156.9 (C), 152.1 (C), 151.6 (C), 146.4 (C), 145.3 (CH), 144.5 (CH), 140.5 (C), 136.0 (C), 132.5 (CH), 130.7 (CH), 130.2 (2CH), 129.0 (2CH), 127.4 (C), 116.3 (CH), 112.7 (CH), 109.6 (CH), 106.3 (CH), 56.0 (CH₃); IR (ATR): 3581, 3431, 3055, 2924, 1703, 1598, 1517, 1495, 1381, 1313, 1255, 1226, 1114, 1078, 931 cm⁻¹; MS (ESI) m/z (%) = 372.2 (100) [M+H]⁺. Anal. calcd for C₂₁H₁₇N₅O₂: C 67.91, H 4.61, N 8.62. Found: C 67.88, H 4.60, N 8.90.

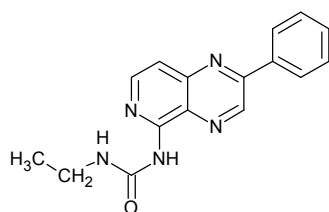
General procedure for the synthesis of *N*-alkyl-*N'*-(phenylpyrido[3,4-*b*]pyrazinyl)ureas **9c and **14b****

***N*-Allyl-*N'*-(3-phenylpyrido[3,4-*b*]pyrazin-8-yl)urea (9c)**



To a solution of 8-amino-3-phenylpyrido[3,4-*b*]pyrazine **8** (200 mg, 0.9 mmol) in pyridine (8 mL) was added allylisocyanate (79 μ L, 0.9 mmol) and the reaction mixture was heated at reflux overnight. Pyridine was removed under reduced pressure and the crude product was purified by silica gel column chromatography using dichloromethane/ethanol mixtures (from 10:0 to 19:1) as eluent to give compound **9c** as a yellow powder (143 mg, 52%); R_f 0.53 ($\text{CH}_2\text{Cl}_2/\text{EtOH}$ 19:1); Mp 232-233 $^\circ\text{C}$; ^1H NMR (400 MHz, $\text{DMSO-}d_6$): δ 9.74 (br s, 1H), 9.60 (s, 1H), 9.40 (s, 1H), 9.11 (br s, 1H), 8.41-8.38 (m, 2H), 7.67-7.65 (m, 4H), 5.93-5.87 (m, 1H), 5.28-5.15 (m, 2H), 3.84-3.82 (m, 2H); ^{13}C NMR (100 MHz, $\text{DMSO-}d_6$): δ 154.7 (C), 153.1 (C), 146.1 (CH), 144.7 (CH), 136.2 (C), 136.0 (CH), 135.6 (C), 133.7 (C), 133.2 (CH), 132.3 (C), 131.2 (CH), 129.4 (2CH), 128.0 (2CH), 115.2 (CH_2), 41.7 (CH_2); IR (ATR): 3312, 3286, 1655, 1555, 1517, 1259, 12461020, 921 cm^{-1} ; MS (ESI) m/z (%) = 306.1 (100) $[\text{M}+\text{H}]^+$. Anal. calcd for $\text{C}_{17}\text{H}_{15}\text{N}_5\text{O}$: C 66.87, H 4.95, N 5.24. Found: C 66.84, H 4.96, N 5.26.

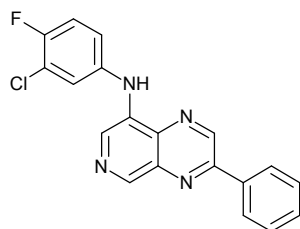
***N*-Ethyl-*N'*-(2-phenylpyrido[3,4-*b*]pyrazin-5-yl)urea (**14b**)**



Compound **14b** was obtained following the representative procedure, using 5-amino-2-phenylpyrido[3,4-*b*]pyrazine **13** (200 mg, 0.9 mmol) and ethylisocyanate (71 μ L, 0.9 mmol), as a beige powder (161 mg, 61%); R_f 0.61 ($\text{CH}_2\text{Cl}_2/\text{EtOH}$ 19:1); Mp 165-166 $^\circ\text{C}$; ^1H NMR (400 MHz, $\text{DMSO-}d_6$): δ 9.67 (s, 1H), 9.48 (t, 1H, $^3J=4.5$ Hz), 8.91 (br s, 1H), 8.44-8.41 (m, 3H), 7.69-7.66 (m, 3H), 7.59 (d, 1H, $^3J=6.4$ Hz), 3.37 (m, 2H), 1.23 (t, 3H, $^3J=7.0$ Hz); ^{13}C NMR (100 MHz, $\text{DMSO-}d_6$): δ 156.7 (C), 154.0 (C), 152.3 (C), 146.2 (C), 145.4 (CH), 144.4 (CH), 136.0 (C), 132.4 (CH), 130.2 (2CH), 128.9 (2CH), 127.0 (C), 115.6 (CH), 35.2 (CH_2), 16.2 (CH_3); IR (ATR): 3398, 3233, 3059, 2968, 1710, 1552, 1487, 1450, 1298, 1248, 1174, 1072, 937 cm^{-1} ; MS (ESI) m/z (%) = 294.2 (100) $[\text{M}+\text{H}]^+$. Anal. calcd for $\text{C}_{16}\text{H}_{15}\text{N}_5\text{O}$: C 65.52, H 5.15, N 23.88. Found: C 65.50, H 5.16, N 23.90.

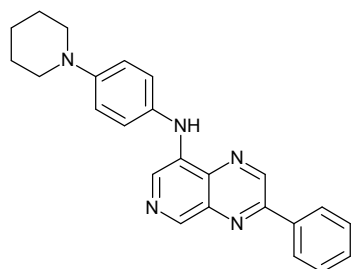
General procedure for the synthesis of *N*-aryl-phenylpyrido[3,4-*b*]pyrazinamines **9d-g, **14c-j**, **18a-c** and **19****

***N*-(3-Chloro-4-fluorophenyl)-3-phenylpyrido[3,4-*b*]pyrazin-8-amine (**9d**)**



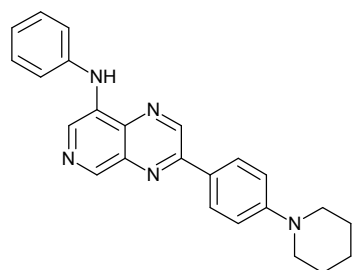
To a solution of 8-bromo-3-phenylpyrido[3,4-*b*]pyrazine **6a** (150mg, 0.5 mmol) in toluene (8 mL) under argon was added successively 3-chloro-4-fluoroaniline (87 mg, 0.6 mmol), Pd₂(dba)₃ (2 mg, 3.9·10⁻⁶ mol), BINAP (1 mg, 1.3·10⁻⁶ mol) and *t*-BuONa (71 mg, 0.7 mmol). The resulting mixture was stirred at 100 °C for 4 h and then allowed to cool to room temperature. Ethyl acetate (15 mL) was added, the combined organic layers were washed with water (3 × 15 mL), dried over sodium sulfate, filtrated and the solvent was removed under reduced pressure. The crude product was purified by silica gel column chromatography using dichloromethane/ethanol mixtures (from 10:0 to 19:1) as eluent to give compound **9d** as an orange powder (86 mg, 49%); *R*_f 0.66 (CH₂Cl₂/EtOH 19:1); Mp 232-234 °C; ¹H NMR (400 MHz, DMSO-*d*₆): δ 9.78 (s, 1H), 9.08 (br s, 1H), 9.04 (s, 1H), 8.63 (s, 1H), 8.46-8.42 (m, 2H), 7.70-7.66 (m, 4H), 7.47-7.42 (m, 2H); ¹³C NMR (100 MHz, DMSO-*d*₆): δ 153.9 (C), 146.5 (CH), 143.9 (C), 142.2 (CH), 139.9 (CH), 137.7 (C), 136.5 (C), 136.3 (C), 135.4 (C), 132.0 (CH), 130.2 (2CH), 128.7 (2CH), 122.7 (CH), 121.2 (C), 120.7 (C), 118.3 (CH), 118.1 (CH); IR (ATR): 3186, 3070, 3047, 1591, 1566, 1525, 1493, 1373, 1313, 1261, 1221, 1053, 947cm⁻¹; MS (ESI) *m/z* (%) = 351.1 (100) [M+H]⁺, 353.1 (38) [M+H+2]⁺. Anal. calcd for C₁₉H₁₂ClFN₄: C 65.06, H 3.45, N 15.97. Found: C 64.99, H 3.44, N 16.05.

3-Phenyl-N-(4-piperidin-1-ylphenyl)pyrido[3,4-*b*]pyrazin-8-amine (**9e**)



Compound **9e** was obtained following the representative procedure, using 8-bromo-3-phenylpyrido[3,4-*b*]pyrazine **6a** (150 mg, 0.5 mmol) and 4-(piperidin-1-yl)aniline (106 mg, 0.6 mmol), as a beige powder (114 mg, 60%); *R*_f 0.58 (CH₂Cl₂/EtOH 19:1); Mp 242-244 °C; ¹H NMR (400 MHz, DMSO-*d*₆): δ 9.62 (s, 1H), 8.74 (s, 1H), 8.64 (s, 1H), 8.51 (s, 1H), 8.19 (d, 2H, ³J=8.7 Hz), 7.30-7.28 (m, 1H), 7.22-7.09 (m, 4H), 6.95 (d, 2H, ³J=8.7 Hz), 3.13-3.12 (m, 4H), 1.69-1.67 (m, 4H), 1.54-1.52 (m, 2H); ¹³C NMR (100 MHz, DMSO-*d*₆): δ 160.9 (C), 153.2 (C), 143.9 (C), 142.6 (2CH), 133.2 (C), 131.7 (C), 130.1 (2CH), 128.9 (2CH), 128.5 (C), 124.1 (C), 116.2 (CH), 115.0 (2CH), 112.3 (CH), 107.9 (CH), 105.1 (CH), 49.2 (2CH₂), 25.4 (2CH₂), 24.1 (CH₂); IR (ATR): 3254, 3032, 2927, 2867, 1608, 1564, 1505, 1335, 1221, 1202, 1012, 956 cm⁻¹; MS (ESI) *m/z* (%) = 382.3 (100) [M+H]⁺. Anal. calcd for C₂₄H₂₃N₅: C 75.56, H 6.08, N 18.36. Found: C 75.60, H 6.11, N 18.44.

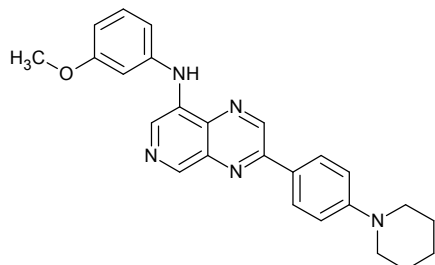
N-Phenyl-3-(4-piperidin-1-ylphenyl)pyrido[3,4-*b*]pyrazin-8-amine (**9f**)



Compound **9f** was obtained following the representative procedure, using 8-bromo-3-(4-piperidin-1-ylphenyl)pyrido[3,4-*b*]pyrazine **6b** (185 mg, 0.5 mmol) and aniline (55 μL, 0.6 mmol), as a yellow powder (101 mg, 53%); *R*_f 0.55 (CH₂Cl₂/EtOH 19:1); Mp 250-252 °C; ¹H NMR (400 MHz, DMSO-*d*₆): δ 9.61 (s, 1H), 8.72 (s, 1H), 8.62 (s, 1H), 8.56 (br s, 1H), 8.25 (d, 2H, ³J=9.1 Hz), 7.29 (m, 1H), 7.24-7.02 (m, 5H), 6.70-6.68

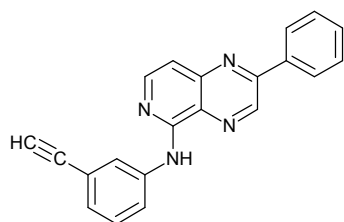
(m, 1H), 3.40-3.43 and 1.65-1.63 (m, 10H); ^{13}C NMR (100 MHz, DMSO- d_6): δ 161.3 (C), 153.1 (C), 144.2 (C), 143.8 (2CH), 134.1 (C), 132.7 (C), 130.5 (2CH), 129.9 (2CH), 129.7 (C), 123.9 (C), 115.1 (2CH), 115.9 (CH), 112.1 (CH), 108.4 (CH), 106.7 (CH), 49.4 (2CH $_2$), 25.9 (2CH $_2$), 24.7 (CH $_2$); IR (ATR): 3261, 3039, 2922, 2848, 1604, 1587, 1564, 1516, 1357, 1238, 1209, 1024, 916 cm^{-1} ; MS (ESI) m/z (%) = 382.1 (100) $[\text{M}+\text{H}]^+$. Anal. calcd for $\text{C}_{24}\text{H}_{23}\text{N}_5$: C 75.56, H 6.08, N 18.36. Found: C 75.53, H 6.10, N 18.42.

***N*-(3-Methoxyphenyl)-3-(4-piperidin-1-ylphenyl)pyrido[3,4-*b*]pyrazin-8-amine (9g)**



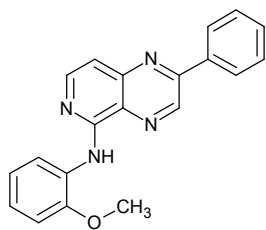
Compound **9g** was obtained following the representative procedure, using 8-bromo-3-(4-piperidin-1-ylphenyl)pyrido[3,4-*b*]pyrazine **6b** (185 mg, 0.5 mmol) and 3-methoxyaniline (74 mg, 0.6 mmol), as a yellow powder (128 mg, 62%); R_f 0.60 ($\text{CH}_2\text{Cl}_2/\text{EtOH}$ 19:1); Mp 223-225 $^\circ\text{C}$; ^1H NMR (400 MHz, DMSO- d_6): δ 9.65 (s, 1H), 8.87 (s, 1H), 8.70 (s, 1H), 8.63 (br s, 1H), 8.30 (d, 2H, $^3J=9.1$ Hz), 7.28 (m, 1H), 7.17-7.08 (m, 4H), 6.68-6.66 (m, 1H), 3.80 (s, 3H), 3.44-3.42 and 1.67-1.65 (m, 10H); ^{13}C NMR (100 MHz, DMSO- d_6): δ 161.1 (C), 153.7 (C), 145.7 (CH), 143.7 (C), 143.1 (CH), 134.5 (C), 132.5 (C), 130.9 (CH), 129.7 (2CH), 129.2 (C), 124.7 (C), 115.4 (2CH), 112.6 (CH), 108.7 (CH), 106.4 (CH), 55.9 (CH $_3$), 49.1 (2CH $_2$), 25.8 (2CH $_2$), 24.9 (CH $_2$); IR (ATR): 3256, 3023, 2932, 2846, 1609, 1554, 1544, 1505, 1323, 1247, 1213, 1012, 951 cm^{-1} ; MS (ESI) m/z (%) = 412.4 (100) $[\text{M}+\text{H}]^+$. Anal. calcd for $\text{C}_{25}\text{H}_{25}\text{N}_5\text{O}$: C 72.97, H 6.12, N 17.02. Found: C 72.88, H 6.15, N 17.08.

***N*-(3-Ethynylphenyl)-2-phenylpyrido[3,4-*b*]pyrazin-5-amine (14c)**



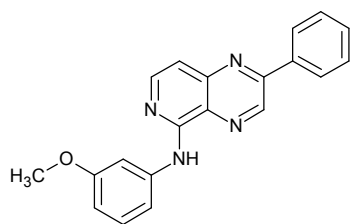
Compound **14c** was obtained following the representative procedure, using 5-chloro-2-phenylpyrido[3,4-*b*]pyrazine **12a** (121 mg, 0.5 mmol) and 3-ethynylaniline (71 mg, 0.6 mmol), as a yellow powder (79 mg, 49%); R_f 0.68 ($\text{CH}_2\text{Cl}_2/\text{EtOH}$ 19:1); Mp 152-153 $^\circ\text{C}$; ^1H NMR (400 MHz, DMSO- d_6): δ 9.97 (br s, 1H), 9.58 (s, 1H), 8.41-8.38 (m, 4H), 8.14 (dd, 1H, $^3J=8.1$ Hz, $^4J=1.0$ Hz), 7.69-7.65 (m, 3H), 7.44-7.38 (m, 2H), 7.18 (d, 1H, $^3J=8.1$ Hz), 4.22 (s, 1H); ^{13}C NMR (100 MHz, DMSO- d_6): δ 155.9 (C), 154.2 (C), 147.2 (CH), 146.4 (C), 142.7 (CH), 141.3 (C), 136.4 (C), 132.1 (CH), 130.1 (2CH), 129.8 (2CH), 128.8 (2CH), 128.2 (C), 126.3 (CH), 123.6 (CH), 122.7 (C), 121.7 (CH), 113.2 (CH), 84.8 (C), 81.2 (CH); IR (ATR): 3364, 3281, 2249, 1597, 1571, 1533, 1435, 1392, 1276, 1070 cm^{-1} ; MS (ESI) m/z (%) = 323.4 (100) $[\text{M}+\text{H}]^+$. Anal. calcd for $\text{C}_{21}\text{H}_{14}\text{N}_4$: C 78.24, H 4.38, N 17.38. Found: C 78.27, H 4.37, N 17.36.

***N*-(2-Methoxyphenyl)-2-phenylpyrido[3,4-*b*]pyrazin-5-amine (14d)**



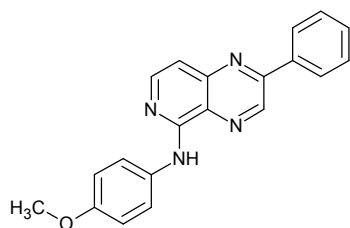
Compound **14d** was obtained following the representative procedure, using 5-chloro-2-phenylpyrido[3,4-*b*]pyrazine **12a** (121 mg, 0.5 mmol) and 2-methoxyaniline (68 μ L, 0.6 mmol), as a yellow powder (85 mg, 52%); R_f 0.63 ($\text{CH}_2\text{Cl}_2/\text{EtOH}$ 19:1); Mp 151-152 $^\circ\text{C}$; ^1H NMR (400 MHz, $\text{DMSO-}d_6$): δ 9.65 (s, 1H), 9.61 (br s, 1H), 8.97-8.93 (m, 1H), 8.42-8.39 (m, 3H), 7.69-7.66 (m, 3H), 7.38 (d, 1H, $^3J=6.1$ Hz), 7.20-7.16 (m, 1H), 7.10-7.06 (m, 2H), 4.03 (s, 3H); ^{13}C NMR (100 MHz, $\text{DMSO-}d_6$): δ 156.1 (C), 153.5 (C), 148.9 (C), 147.3 (CH), 146.2 (C), 143.3 (CH), 136.4 (C), 132.1 (CH), 130.2 (2CH), 129.7 (C), 128.8 (2CH), 128.2 (C), 123.1 (CH), 121.6 (CH), 119.0 (CH), 112.9 (CH), 111.5 (CH), 57.0 (CH_3); IR (ATR): 3366, 3047, 3016, 2954, 1602, 1568, 1535, 1483, 1390, 1230, 1122, 1022, 906 cm^{-1} ; MS (ESI) m/z (%) = 329.3 (100) $[\text{M}+\text{H}]^+$. Anal. calcd for $\text{C}_{20}\text{H}_{16}\text{N}_4\text{O}$: C 73.15, H 4.91, N 17.06. Found: C 73.17, H 4.92, N 17.03.

***N*-(3-Methoxyphenyl)-2-phenylpyrido[3,4-*b*]pyrazin-5-amine (14e)**



Compound **14e** was obtained following the representative procedure, using 5-chloro-2-phenylpyrido[3,4-*b*]pyrazine **12a** (121 mg, 0.5 mmol) and 3-methoxyaniline (74 mg, 0.6 mmol), as a yellow powder (82 mg, 50%); R_f 0.52 ($\text{CH}_2\text{Cl}_2/\text{EtOH}$ 19:1); Mp 164-166 $^\circ\text{C}$; ^1H NMR (400 MHz, $\text{DMSO-}d_6$): δ 9.77 (br s, 1H), 9.56 (s, 1H), 8.41-8.38 (m, 2H), 8.37 (d, 1H, $^3J=5.9$ Hz), 7.88 (t, 1H, $^4J=2.1$ Hz), 7.76 (dd, 1H, $^3J=8.0$ Hz, $^4J=1.5$ Hz), 7.69-7.66 (m, 3H), 7.35 (d, 1H, $^3J=5.9$ Hz), 7.29 (t, 1H, $^3J=8.0$ Hz), 6.66 (dd, 1H, $^3J=8.1$ Hz, $^4J=2.3$ Hz), 3.82 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $\text{DMSO-}d_6$): δ 160.4 (C), 155.8 (C), 154.2 (C), 147.3 (CH), 146.4 (C), 142.6 (CH), 142.2 (C), 136.4 (C), 132.1 (CH), 130.1 (2CH), 128.8 (2CH), 128.2 (C), 113.2 (CH), 112.8 (CH), 108.5 (CH), 106.8 (CH), 55.9 (CH_3); IR (ATR): 3356, 3043, 2962, 1600, 1566, 1531, 1489, 1436, 1388, 1334, 1257, 1176, 1045, 953 cm^{-1} ; MS (ESI) m/z (%) = 329.2 (100) $[\text{M}+\text{H}]^+$. Anal. calcd for $\text{C}_{20}\text{H}_{16}\text{N}_4\text{O}$: C 73.15, H 4.91, N 17.06. Found: C 73.12, H 4.90, N 17.10.

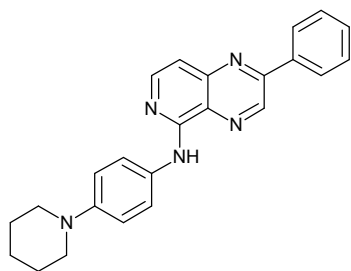
***N*-(4-Methoxyphenyl)-2-phenylpyrido[3,4-*b*]pyrazin-5-amine (14f)**



Compound **14f** was obtained following the representative procedure, using 5-chloro-2-phenylpyrido[3,4-*b*]pyrazine **12a** (121 mg, 0.5 mmol) and 4-methoxyaniline (69 μ L, 0.6 mmol), as a yellow powder (82 mg, 50%); R_f 0.67 ($\text{CH}_2\text{Cl}_2/\text{EtOH}$ 19:1); Mp 156-158 $^\circ\text{C}$; ^1H NMR (400 MHz, $\text{DMSO-}d_6$): δ 9.71 (br s, 1H), 9.53 (s,

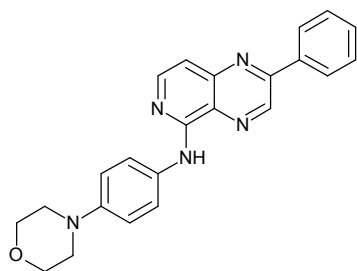
1H), 8.40-8.38 (m, 2H), 8.29 (d, 1H, $^3J=5.8$ Hz), 7.99 (d, 2H, $^3J=9.1$ Hz), 7.68-7.66 (m, 3H), 7.27 (d, 1H, $^3J=6.1$ Hz), 6.98 (d, 2H, $^3J=8.9$ Hz), 4.03 (s, 3H). ^{13}C NMR (100 MHz, DMSO- d_6): δ 155.8 (C), 154.5 (C), 147.6 (CH), 146.7 (C), 142.5 (CH), 136.7 (C), 134.3 (C), 131.9 (CH), 130.0 (2CH), 128.7 (2CH), 128.1 (C), 122.8 (2CH), 122.2 (C), 114.6 (2CH), 111.8 (CH), 55.9 (CH $_3$); IR (ATR): 3373, 3064, 3024, 2995, 2935, 1600, 1575, 1531, 1504, 1438, 1396, 1300, 1238, 1172, 1105, 1035, 829 cm^{-1} ; MS (ESI) m/z (%) = 329.2 (100) [M+H] $^+$. Anal. calcd for C $_{20}$ H $_{16}$ N $_4$ O: C 73.15, H 4.91, N 17.06. Found: C 73.18, H 4.90, N 17.04.

2-Phenyl-N-(4-piperidin-1-ylphenyl)pyrido[3,4-b]pyrazin-5-amine (14g)



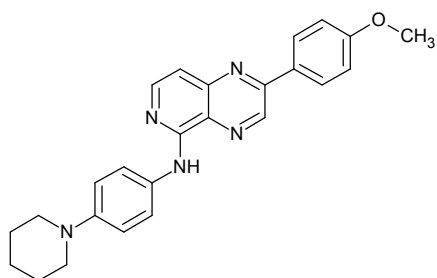
Compound **14g** was obtained following the representative procedure, using 5-chloro-2-phenylpyrido[3,4-*b*]pyrazine **12a** (121 mg, 0.5 mmol) and 4-(piperidin-1-yl)aniline (106 mg, 0.6 mmol), as a red powder (107 mg, 56%); R_f 0.55 (CH $_2$ Cl $_2$ /EtOH 19:1); Mp 172-174 $^{\circ}\text{C}$; ^1H NMR (400 MHz, DMSO- d_6): δ 9.61 (br s, 1H), 9.51 (s, 1H), 8.39-8.37 (m, 2H), 8.28 (d, 1H, $^3J=8.9$ Hz), 7.91 (d, 2H, $^3J=8.9$ Hz), 7.68-7.65 (m, 3H), 7.24 (d, 1H, $^3J=5.8$ Hz), 6.98 (d, 2H, $^3J=8.7$ Hz), 3.13-3.12 (m, 4H), 1.68-1.67 (m, 4H), 1.58-1.56 (m, 2H); ^{13}C NMR (100 MHz, DMSO- d_6): δ 155.7 (C), 154.5 (C), 147.8 (C), 147.7 (CH), 146.6 (C), 142.2 (CH), 136.5 (C), 132.8 (C), 132.0 (CH), 130.1 (2CH), 128.7 (2CH), 128.3 (C), 122.3 (2CH), 117.1 (2CH), 111.6 (CH), 51.2 (2CH $_2$), 26.3 (2CH $_2$), 24.8 (CH $_2$); IR (ATR): 2934, 2851, 1736, 1600, 1582, 1530, 1512, 1460, 1384, 1234, 1215, 1105, 1024, 914 cm^{-1} ; MS (ESI) m/z (%) = 382.4 (100) [M+H] $^+$. Anal. calcd for C $_{24}$ H $_{23}$ N $_5$: C 75.56, H 6.08, N 18.26. Found: C 75.58, H 6.09, N 18.23.

N-(4-Morpholin-4-ylphenyl)-2-phenylpyrido[3,4-b]pyrazin-5-amine (14h)



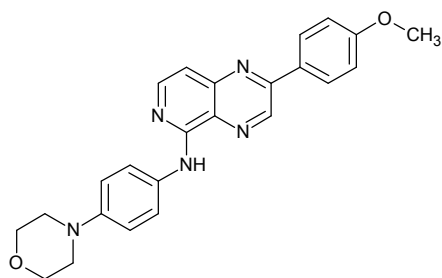
Compound **14h** was obtained following the representative procedure, using 5-chloro-2-phenylpyrido[3,4-*b*]pyrazine **12a** (121 mg, 0.5 mmol) and 4-(morpholin-4-yl)aniline (107 mg, 0.6 mmol), as a red powder (111 mg, 58%); R_f 0.36 (CH $_2$ Cl $_2$ /EtOH 19:1); Mp 210-212 $^{\circ}\text{C}$; ^1H NMR (400 MHz, DMSO- d_6): δ 9.65 (br s, 1H), 9.52 (s, 1H), 8.30-8.38 (m, 2H), 8.28 (d, 1H, $^3J=6.2$ Hz), 7.95 (d, 2H, $^3J=9.1$ Hz), 7.68-7.65 (m, 3H), 7.25 (d, 1H, $^3J=6.4$ Hz), 6.99 (d, 2H, $^3J=9.0$ Hz), 3.79-3.77 (m, 4H), 3.14-3.10 (m, 4H); ^{13}C NMR (100 MHz, DMSO- d_6): δ 155.7 (C), 154.5 (C), 147.8 (C), 147.7 (CH), 146.6 (C), 142.3 (CH), 136.5 (C), 133.4 (C), 132.0 (CH), 130.1 (2CH), 128.7 (2CH), 128.3 (C), 122.3 (2CH), 116.3 (2CH), 111.7 (CH), 67.1 (2CH $_2$), 50.1 (2CH $_2$); IR (ATR): 3354, 3059, 3024, 2945, 2821, 1597, 1583, 1529, 1510, 1483, 1396, 1263, 1224, 1114, 1068, 920 cm^{-1} ; MS (ESI) m/z (%) = 384.3 (100) [M+H] $^+$. Anal. calcd for C $_{23}$ H $_{21}$ N $_5$ O: C 72.04, H 5.52, N 18.36. Found: C 72.08, H 5.50, N 18.34.

2-(4-Methoxyphenyl)-N-(4-piperidin-1-ylphenyl)pyrido[3,4-b]pyrazin-5-amine (14i)



Compound **14i** was obtained following the representative procedure, using 5-chloro-2-(4-methoxyphenyl)pyrido[3,4-*b*]pyrazine **12b** (136 mg, 0.5 mmol) and 4-(piperidin-1-yl)aniline (106 mg, 0.6 mmol), as a red powder (128 mg, 62%); R_f 0.57 (CH₂Cl₂/EtOH 19:1); Mp 170-172 °C; ¹H NMR (400 MHz, DMSO-*d*₆): δ 9.53 (br s, 1H), 9.47 (s, 1H), 8.38 (d, 2H, ³J=8.9 Hz), 8.24 (d, 1H, ³J=5.8 Hz), 7.90 (d, 2H, ³J=9.1 Hz), 7.21 (d, 2H, ³J=8.9 Hz), 7.19 (d, 1H, ³J=6.1 Hz), 6.97 (d, 2H, ³J=9.1 Hz), 3.92 (s, 3H), 3.13-3.10 (m, 4H), 1.68-1.66 (m, 4H), 1.58-1.55 (m, 2H); ¹³C NMR (100 MHz, DMSO-*d*₆): δ 162.7 (C), 155.2 (C), 154.4 (C), 148.5 (C), 147.5 (CH), 146.6 (C), 141.8 (CH), 132.8 (C), 130.3 (2CH), 128.8 (C), 127.7 (C), 122.2 (2CH), 117.1 (2CH), 115.6 (2CH), 111.6 (CH), 56.4 (CH₃), 51.2 (2CH₂), 26.3 (2CH₂), 24.8 (CH₂); IR (ATR): 3371, 3024, 2924, 2846, 1593, 1581, 1512, 1523, 1448, 1384, 1251, 1217, 1174, 1022, 914 cm⁻¹; MS (ESI) m/z (%) = 412.4 (100) [M+H]⁺. Anal. calcd for C₂₅H₂₅N₅O: C 72.97, H 6.12, N 17.02. Found: C 72.98, H 6.11, N 17.02.

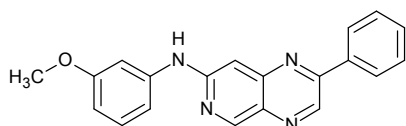
2-(4-Methoxyphenyl)-N-(4-morpholin-4-ylphenyl)pyrido[3,4-b]pyrazin-5-amine (14j)



Compound **14j** was obtained following the representative procedure, using 5-chloro-2-(4-methoxyphenyl)pyrido[3,4-*b*]pyrazine **12b** (136 mg, 0.5 mmol) and 4-(morpholin-4-yl)aniline (107 mg, 0.6 mmol), as an orange powder (114 mg, 55%); R_f 0.49 (CH₂Cl₂/EtOH 19:1); Mp 204-206 °C; ¹H NMR (400 MHz, DMSO-*d*₆): δ 9.57 (br s, 1H), 9.48 (s, 1H), 8.38 (d, 2H, ³J=9.2 Hz), 8.25 (d, 1H, ³J=6.1 Hz), 7.95 (d, 2H, ³J=9.2 Hz), 7.23-7.17 (m, 3H), 6.99 (d, 1H, ³J=9.0 Hz), 3.92 (s, 3H), 3.81-3.77 and 3.13-3.08 (m, 8H); ¹³C NMR (100 MHz, DMSO-*d*₆): δ 162.1 (C), 155.4 (C), 154.2 (C), 148.7 (C), 147.6 (CH), 146.4 (C), 141.1 (CH), 133.1 (C), 130.1 (2CH), 128.2 (C), 127.5 (C), 122.4 (2CH), 117.3 (2CH), 116.1 (2CH), 111.4 (CH), 65.9 (2CH₂), 55.2 (CH₃), 48.9 (2CH₂); IR (ATR): 3352, 3005, 2954, 2927, 1598, 1538, 1531, 1510, 1327, 1286, 1253, 1168, 1114, 1039, 9290 cm⁻¹; MS (ESI) m/z (%) = 414.3 (100) [M+H]⁺. Anal. calcd for C₂₄H₂₃N₅O₂: C 69.72, H 5.61, N 16.94. Found: C 69.68, H 5.62, N 16.97.

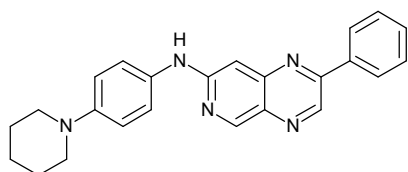
Synthesis of 2,7- and 3,7-disubstituted pyrido[3,4-*b*]pyrazines 18a-c and 19

N-(3-Methoxyphenyl)-2-phenylpyrido[3,4-*b*]pyrazin-7-amine (18a)



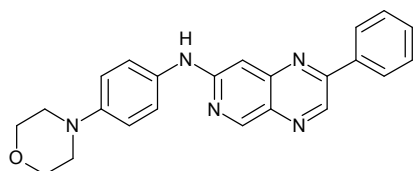
Compound **18a** was obtained following the representative procedure, using 7-chloro-2-phenylpyrido[3,4-*b*]pyrazine **16** (121 mg, 0.5 mmol) and 3-methoxyaniline (74 mg, 0.6 mmol), as a yellow powder (83 mg, 52%); R_f 0.51 (CH₂Cl₂/EtOH 19:1); Mp 180-182 °C; ¹H NMR (400 MHz, DMSO-*d*₆): δ 9.54 (br s, 1H), 9.36 (s, 1H), 9.22 (s, 1H), 8.39-8.36 (m, 2H), 7.66-7.64 (m, 3H), 7.33-7.20 (m, 4H), 6.63 (d, 1H, ³J=7.8 Hz), 3.82 (s, 3H); ¹³C NMR (100 MHz, DMSO-*d*₆): δ 160.8 (C), 156.6 (C), 156.0 (C), 153.6 (CH), 147.2 (C), 143.0 (C), 142.4 (CH), 136.6 (C), 132.8 (C), 132.1 (CH), 130.6 (CH), 130.1 (2CH), 128.8 (2CH), 112.5 (CH), 107.9 (CH), 106.0 (CH), 101.3 (CH), 55.9 (CH₃); IR (ATR): 3235, 3064, 3032, 2964, 1616, 1593, 1552, 1490, 1456, 1425, 1319, 1186, 1157, 1037, 960 cm⁻¹; MS (ESI) m/z (%) = 329.3(100) [M+H]⁺. Anal. calcd for C₂₀H₁₆N₄O: C 73.15, H 4.91, N 17.06. Found: C 73.12, H 4.90, N 17.10.

2-Phenyl-N-(4-piperidin-1-ylphenyl)pyrido[3,4-*b*]pyrazin-7-amine (18b)



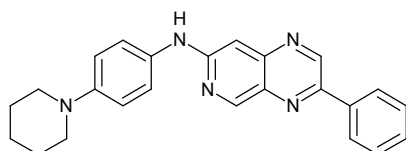
Compound **18b** was obtained following the representative procedure, using 7-chloro-2-phenylpyrido[3,4-*b*]pyrazine **16** (121 mg, 0.5 mmol) and 4-(piperidin-1-yl)aniline (106 mg, 0.6 mmol), as an orange powder (107 mg, 56%); R_f 0.42 (CH₂Cl₂/EtOH 19:1); Mp 237-239 °C; ¹H NMR (400 MHz, DMSO-*d*₆): δ 9.28 (s, 1H), 9.21 (br s, 1H), 9.14 (s, 1H), 8.36-8.32 (m, 2H), 7.69-7.62 (m, 3H), 7.40 (d, 2H, ³J=8.6 Hz), 7.03-6.99 (m, 3H), 3.24-3.20 and 1.62-1.60 (m, 10H); ¹³C NMR (100 MHz, DMSO-*d*₆): δ 157.8 (C), 155.9 (C), 153.9 (CH), 148.8 (C), 147.5 (C), 141.5 (CH), 136.7 (C), 133.0 (C), 132.5 (C), 132.0 (CH), 130.0 (2CH), 128.7 (2CH), 122.9 (2CH), 117.7 (2CH), 98.5 (CH), 51.2 (CH₂), 26.3 (CH₂), 24.8 (CH₂); IR (ATR): 3205, 3019, 2928, 2853, 1607, 1537, 1512, 1450, 1236, 1209, 1166, 1126, 1024, 916 cm⁻¹; MS (ESI) m/z (%) = 382.4 (100) [M+H]⁺. Anal. calcd for C₂₄H₂₃N₅: C 75.56, H 6.08, N 18.36. Found: C 75.62, H 6.07, N 17.31.

N-(4-Morpholin-4-ylphenyl)-2-phenylpyrido[3,4-*b*]pyrazin-7-amine (18c)



Compound **18c** was obtained following the representative procedure, using 7-chloro-2-phenylpyrido[3,4-*b*]pyrazine **16** (121 mg, 0.5 mmol) and 4-(morpholin-4-yl)aniline (107 mg, 0.6 mmol), as a red powder (105 mg, 55%); R_f 0.47 (CH₂Cl₂/EtOH 19:1); Mp 283-285 °C; ¹H NMR (400 MHz, DMSO-*d*₆): δ 9.28 (s, 1H), 9.25 (br s, 1H), 9.14 (s, 1H), 8.35-8.33 (m, 2H), 7.65-7.63 (m, 3H), 7.44 (d, 2H, ³J=9.1 Hz), 7.05-7.00 (m, 2H), 3.74-3.71 (m, 4H), 2.91-2.89 (m, 4H). ¹³C NMR (100 MHz, DMSO-*d*₆): δ 157.8 (C), 156.0 (C), 154.0 (CH), 148.0 (C), 147.5 (C), 141.6 (CH), 136.7 (C), 133.7 (C), 132.6 (C), 132.0 (CH), 130.1 (2CH), 128.8 (2CH), 122.8 (2CH), 117.0 (2CH), 98.7 (CH), 67.1 (CH₂), 50.0 (CH₂); IR (ATR): 3217, 3030, 2951, 2852, 1608, 1541, 1512, 1444, 1255, 1228, 1166, 1112, 1060, 923 cm⁻¹; MS (ESI) m/z (%) = 384.4 (100) [M+H]⁺. Anal. calcd for C₂₃H₂₁N₅O: C 72.04, H 5.52, N 18.26. Found: C 72.00, H 5.53, N 18.29.

3-Phenyl-N-(4-piperidin-1-ylphenyl)pyrido[3,4-*b*]pyrazin-7-amine (19)



Compound **18b** was obtained following the representative procedure, using 7-chloro-3-phenylpyrido[3,4-*b*]pyrazine **16** (121 mg, 0.5 mmol) and 4-(piperidin-1-yl)aniline (109 mg, 0.6 mmol), as a red powder (110 mg, 58%); R_f 0.53 ($\text{CH}_2\text{Cl}_2/\text{EtOH}$ 19:1); Mp 247-249 °C; ^1H NMR (400 MHz, $\text{DMSO-}d_6$): δ 9.54 (s, 1H), 9.25 (br s, 1H), 9.19 (s, 1H), 8.29 (d, 2H, $^3J=7.4$ Hz), 7.64-7.56 (m, 3H), 7.40 (d, 2H, $^3J=8.8$ Hz), 7.06 (s, 1H), 7.00 (d, 2H, $^3J=8.8$ Hz), 3.14-3.11 (m, 4H), 1.71-1.65 (m, 4H), 1.59-1.56 (m, 2H); ^{13}C NMR (100 MHz, $\text{DMSO-}d_6$): δ 157.1 (C), 154.3 (CH), 149.5 (CH), 148.8 (C), 148.7 (C), 146.8 (C), 136.9 (C), 133.0 (C), 132.6 (C), 130.8 (CH), 130.0 (2CH), 127.7 (2CH), 122.6 (2CH), 117.7 (2CH), 98.7 (CH), 51.2 (CH_2), 26.3 (CH_2), 24.8 (CH_2); IR (ATR): 3215, 3028, 2934, 2850, 1587, 1512, 1433, 1348, 1217, 1024, 950 cm^{-1} ; MS (ESI) m/z (%) = 382.3 (100) $[\text{M}+\text{H}]^+$. Anal. calcd for $\text{C}_{24}\text{H}_{23}\text{N}_5$: C 75.56, H 6.08, N 18.36. Found: C 75.58, H 6.07, N 18.35.

References

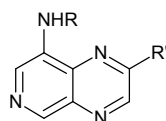
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Biological evaluation

In vitro kinase inhibition assay

Recombinant kinases were purchased from Millipore or ProQinase. An AlphaScreen Protein-A Detection Kit (PerkinElmer) was used to quantify kinase activity. For the assessment of IC₅₀ values, compounds were tested at ten final concentrations between 3.16 nM and 100 μM. Each kinase, 10 μM ATP, kinase substrate, and the test compound were incubated for 1 h on a 384-well Optiplate in a final volume of 15 μL. The kinase reaction was stopped by adding 10 μL Alpha Beadmix. The readout was performed the following morning using an Envision reader (PerkinElmer). IC₅₀ values were calculated with GraphPad Prism software. Kinase testing was performed by the Target Lab (Dr. Seipelt, Preclinical Development) at Æterna Zentaris GmbH, Frankfurt/Main (Germany).

Table 4 Inhibitory activity against a panel of seven protein kinases of 2,8-disubstituted pyrido[3,4-*b*]pyrazines **20a-p**



Compounds	R	R'	IC ₅₀ (μM) ^a						
			ERK2	HIPK1	Pim1	KDR	TrkA	c-Abl	Yes
20a	3-MeOC ₆ H ₄ NHCO	C ₆ H ₅	>100	21.53	12.42	>100	>100	15.06	19.21
20b	4-MeOC ₆ H ₄ NHCO	C ₆ H ₅	>31.6	>100	>100	>100	>31.6	>100	>100
20c	CH ₃ CH ₂ NHCO	C ₆ H ₅	>100	>100	>100	>100	>100	>100	>100
20d	CH ₂ =CHCH ₂ NHCO	C ₆ H ₅	>100	>100	>100	>100	>100	>100	>100
20e	3-Cl-4-FC ₆ H ₃	C ₆ H ₅	>100	>100	>100	>100	>100	>100	>100
20f	3-ethynylC ₆ H ₄	C ₆ H ₅	>100	>100	>100	>100	>100	>100	>100
20g	2-MeOC ₆ H ₄	C ₆ H ₅	>100	2.01	>100	2.24	1.97	2.94	3.96
20h	3-MeOC ₆ H ₄	C ₆ H ₅	9.15	9.83	>100	18.9	20.8	15.8	19.8
20i	4-MeOC ₆ H ₄	C ₆ H ₅	9.01	7.70	14.5	21.4	13.7	10.7	8.12
20j	4-(piperidin-1-yl)C ₆ H ₄	C ₆ H ₅	2.02	2.59	2.61	1.56	3.23	2.16	5.56
20k	4-(morpholin-4-yl)C ₆ H ₄	C ₆ H ₅	8.43	8.15	8.30	6.12	5.32	5.27	5.11
20l	2,5-(MeO) ₂ C ₆ H ₃	4-MeOC ₆ H ₄	3.79	13.1	8.57	1.60	1.45	1.37	2.01
20m	4-(piperidin-1-yl)C ₆ H ₄	4-MeOC ₆ H ₄	3.13	3.21	2.83	2.05	3.72	2.27	5.34
20n	4-(morpholin-4-yl)C ₆ H ₄	4-MeOC ₆ H ₄	4.26	4.02	4.40	3.31	2.48	2.49	2.41
20o	C ₆ H ₅	4-(piperidin-1-yl)C ₆ H ₄	12.21	11.85	31.20	11.05	7.79	6.84	8.82
20p	3-MeOC ₆ H ₄	4-(piperidin-1-yl)C ₆ H ₄	16.63	12.65	11.34	8.84	9.36	7.71	11.10

^a Values are the mean of at least three independent determinations and are within ± 15% SD.