# Preparation of Novel 2,3,8-Trisubstituted Pyrido[3,4-*b*]pyrazines and Pyrido[2,3-*b*]pyrazines

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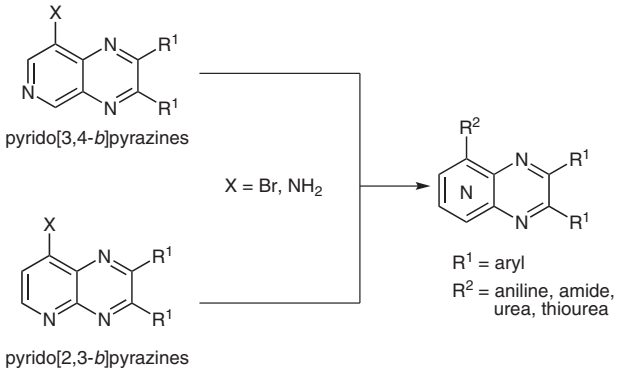
**Abstract:** A four-step synthesis of 8-bromo-2,3-disubstituted pyrido[3,4-*b*]pyrazines and a six-step synthesis of 8-amino-2,3-disubstituted pyrido[3,4-*b*]pyrazines have been developed. A particularly valuable feature of this synthetic route is the possibility to build 2,3-disubstituted pyrido[3,4-*b*]pyrazines with a large variety of substituents in position 8 (aniline, amide, urea, thiourea). Our protocol was extended to the synthesis of 2,3,8-trisubstituted pyrido[2,3-*b*]pyrazines.

**Key words:** pyrido[3,4-*b*]pyrazine, pyrido[2,3-*b*]pyrazine, diaminopyridine, urea, thiourea, amide

Recently, an increasing interest in the synthesis of functionalized pyridopyrazines with promising biological properties has been observed. Pyridinylpyridopyrazines were synthesized as novel p38α MAP kinase inhibitors for the treatment of cytokine-driven disorders like inflammatory bowel disease or rheumatoid arthritis.[1] Novel pyrido[2,3-*b*]pyrazine derivatives have been described as kinase inhibitors for the treatment of malignant and other diseases based on pathological cell proliferations.[2] Pyrido[2,3-*b*]pyrazines and pyrido[3,4-*b*]pyrazines were also reported as useful vasculostatic agents for treating a variety of disorders including, for example, myocardial infarction, ischemia reperfusion injury, and autoimmune diseases such as rheumatoid arthritis.[3] The antimicrobial activity of pyridopyrazines was demonstrated by inhibition of FtsZ polymerization.[4] In addition, pyrido[2,3-*b*]pyrazines exhibited fungicidal activity.[5]

Despite medical interest in 2,3-disubstituted pyrido[2,3-*b*]pyrazines and pyrido[3,4-*b*]pyrazines due to their biological activity, very little work has been reported on the general synthesis of such derivatives substituted in position 8 by amines.[6] Therefore, the development of synthetic routes addressed to this kind of compound constitutes an interesting challenge to organic chemists. In this paper, we first describe the synthesis of 8-bromo-2,3-disubstituted pyrido[3,4-*b*]pyrazines and 8-amino-2,3-disubstituted pyrido[3,4-*b*]pyrazines, key intermediates leading to the corresponding amides, anilines, ureas, and thioureas (Scheme 1).




**Scheme 1** Precursors of 2,3,8-trisubstituted pyrido[3,4-*b*]pyrazines and pyrido[2,3-*b*]pyrazines

In a second part, we have extended our protocol to the synthesis of 8-bromo-2,3-disubstituted pyrido[2,3-*b*]pyrazines and 8-amino-2,3-disubstituted pyrido[2,3-*b*]pyrazines, precursors of 2,3,8-trisubstituted pyrido[2,3-*b*]pyrazines with a large variety of substituents in position 8.

With 3,4-diaminopyridine (**1**) in hand, we proceeded to the construction of the pyrido[3,4-*b*]pyrazine ring via condensation with benzil (**2a**) or 4,4′-dimethoxybenzil (**2b**) (Scheme 2).

This reaction was carried out in refluxing dioxane with complete starting material conversion, providing the expected 2,3-disubstituted pyrido[3,4-*b*]pyrazines **3a**,**b** in good yields (75–82%). Subsequent bromination of 2,3-diphenylpyrido[3,4-*b*]pyrazine (**3a**) upon treatment with hydrobromic acid in hydrogen peroxide at 80 °C gave 8-bromo-2,3-diphenylpyrido[3,4-*b*]pyrazine (**4a**) in good yield (method 1). However, when the same reaction was applied to 2,3-bis(4-methoxyphenyl)pyrido[3,4-*b*]pyrazine (**3b**) we were unable to obtain 8-bromo-2,3-bis(4-methoxyphenyl)pyrido[3,4-*b*]pyrazine (**4b**). Indeed, it would be expected that the methoxy donating group would induce the formation of byproducts, in particular by bromination on the phenyl ring as detected by LC-MS analysis.

Based on these results, we had to develop another access route to 8-bromo-2,3-disubstituted pyrido[3,4-*b*]pyrazines that allowed the introduction of various aryl groups in positions 2 and 3. This new strategy involved the introduction of the bromine atom on the *ortho*-diaminopyri-

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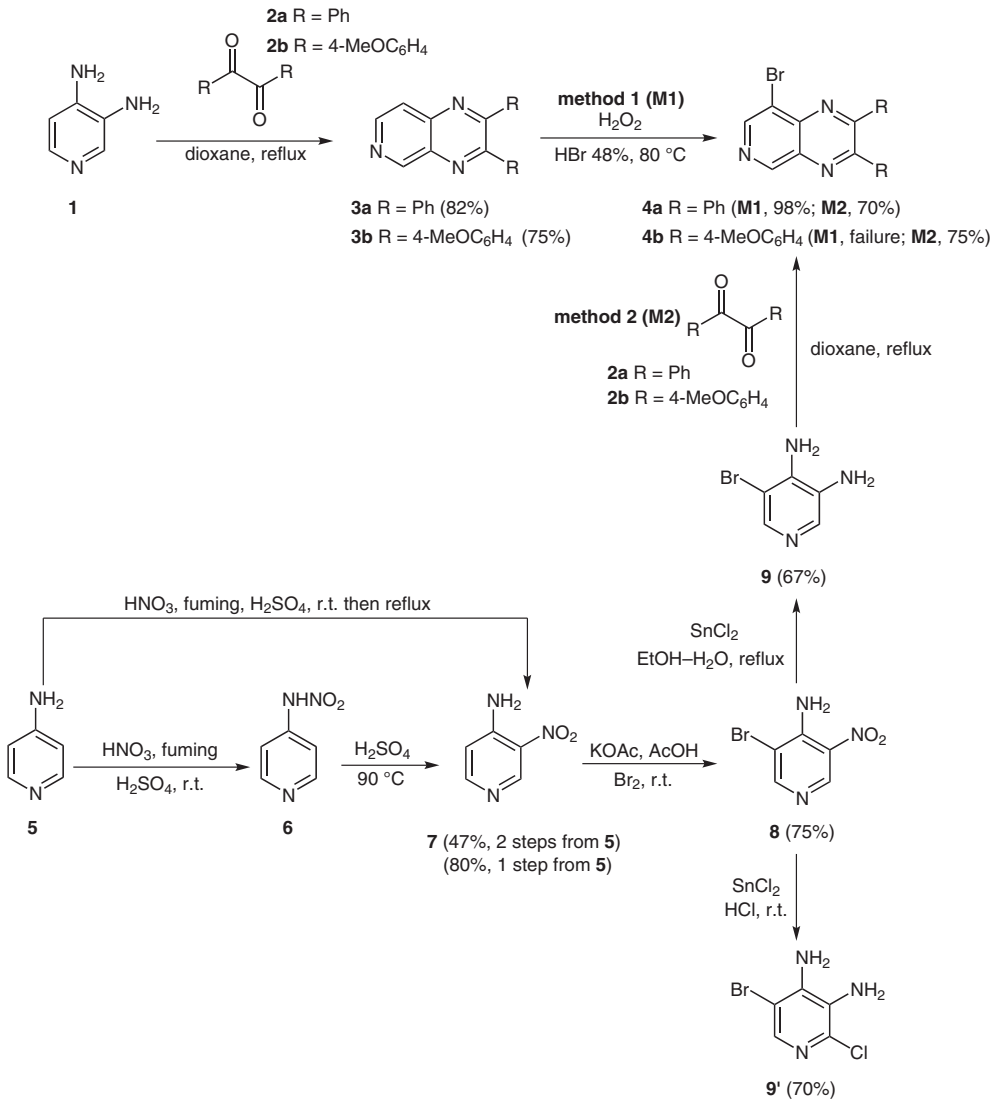



**Scheme 2** Preparation of 8-bromo-2,3-disubstituted pyrido[3,4-*b*]pyrazines **4a**,**b** from 3,4-diaminopyridine (**1**) (method 1, M1) or 3,4-diamino-5-bromopyridine (**9**) (method 2, M2).

dine in the correct position before condensation with the benzil. 3,4-Diamino-5-bromopyridine (**9**)[7] was easily prepared in three steps from 4-aminopyridine (**5**) (Scheme 2). 4-Aminopyridine (**5**) was transformed into 4-amino-3-nitropyridine (**7**) via a modified Koenig procedure[8] in two steps in 47% yield as described previously. Treatment of commercially available 4-aminopyridine (**5**) with fuming nitric acid in concentrated sulfuric acid at room temperature gave 4-(nitramino)pyridine (**6**). The rearrangement of 4-(nitramino)pyridine (**6**) to 4-amino-3-nitropyridine (**7**) was accomplished by heating in concentrated sulfuric acid. Finally, we found that 4-amino-3-nitropyridine (**7**) could be obtained in one step from 4-aminopyridine (**5**) in 80% yield without isolating the intermediate 4-(nitramino)pyridine (**6**). Subsequent bromination of 4-amino-3-nitropyridine (**7**) with bromine in glacial acetic acid, followed by reduction of the nitro group with tin(II) chloride in a mixture of ethanol and water afforded 3,4-diamino-5-bromopyridine (**9**). 4-Amino-3-bromo-5-nitropyridine (**8**) could also be obtained by aromatic nitramine rearrangement from 4-amino-3-bromopyridine.[7d]

As previously suggested, reduction of 4-amino-3-bromo-5-nitropyridine (**8**) with tin(II) chloride in concentrated hydrochloric acid at room temperature afforded 3,4-diamino-5-bromo-2-chloropyridine (**9′**) in 70% yield.[7d] This side reaction is very interesting because this compound could be a key intermediate to access of new 2,3,5,8-tetrasubstituted pyrido[3,4-*b*]pyrazines by the same procedure as previously described.

Condensation of 3,4-diamino-5-bromopyridine (**9**) with benzils **2a**,**b** in refluxing dioxane provided 8-bromo-2,3-disubstituted pyrido[3,4-*b*]pyrazines **4a**,**b** with good yields (Scheme 2, method 2).

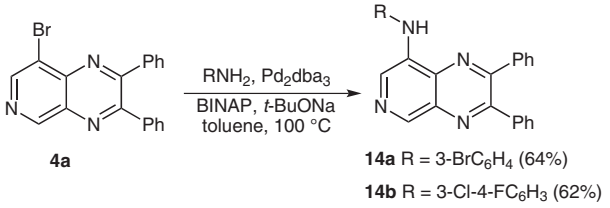
We first checked the possibility of obtaining the corresponding 8-amino-2,3-disubstituted pyrido[3,4-*b*]pyrazines **11a**,**b** or a precursor thereof by direct nucleophilic substitution but, as expected, amination with ammonium hydroxide, formation of the nitro derivative by reaction

with sodium nitrite, and formation of the azido intermediate by reaction with sodium azide failed. Finally, 8-amino-2,3-disubstituted pyrido[3,4-*b*]pyrazines **11a**,**b** were obtained by a two-step procedure (Scheme 3).

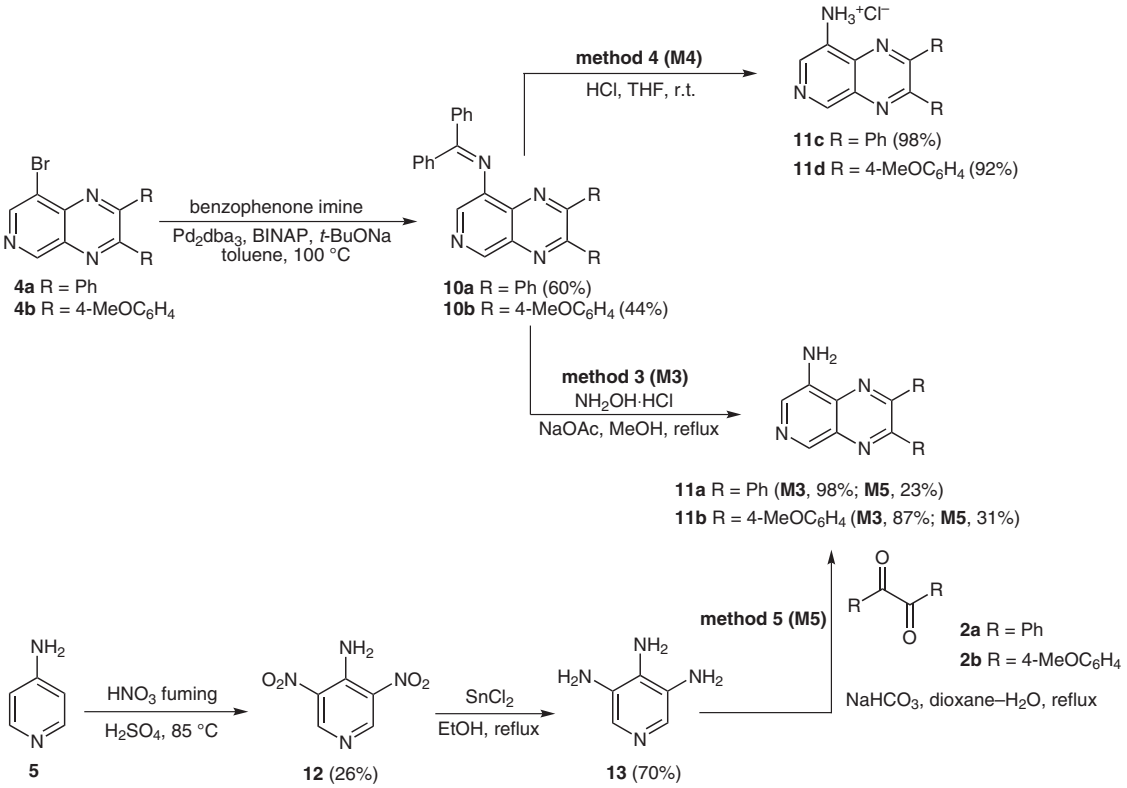
8-Bromo-2,3-disubstituted pyrido[3,4-*b*]pyrazines **4a**,**b** were converted using the Buchwald reaction [$Pd_2(dba)_3$, BINAP, *t*-BuONa, toluene, 100 °C] into the corresponding benzophenone imines **10a**,**b** in moderate yields.[9] Transamination by reaction with hydroxylamine hydrochloride in the presence of sodium acetate in methanol[10] (method 3) provided **11a**,**b** in very good yields (87–98%). Hydrolysis of **10a**,**b** with hydrochloric acid in tetrahydrofuran[10] (method 4) gave 8-amino-2,3-disubstituted pyrido[3,4-*b*]pyrazines hydrochlorides **11c**,**d** in good yields (92–98%).

From these results, we next explored the preparation of 8-amino-2,3-disubstituted pyrido[3,4-*b*]pyrazines **11a**,**b** by the reaction sequence illustrated in Scheme 3, via condensation of 3,4,5-triaminopyridine (**13**) with benzils.[6a] Conversion of 4-aminopyridine (**5**) into 3,4,5-triaminopyridine (**13**) was accomplished in two steps.[11] Treatment of 4-aminopyridine (**5**) with fuming nitric acid in concentrated sulfuric acid at 85 °C led to 4-amino-3,5-dinitropyridine (**12**) with poor yield (but the reaction could be performed on a large scale). Subsequent reduction of 4-amino-3,5-dinitropyridine (**12**) with tin(II) chloride in refluxing ethanol afforded 3,4,5-triaminopyridine (**13**) in good yield. Benzils **2a**,**b** were allowed to react with 3,4,5-triaminopyridine (**13**) in the presence of sodium bicarbonate in refluxing dioxane and water in order to obtain 8-amino-2,3-disubstituted pyrido[3,4-*b*]pyrazines **11a**,**b** (method 5). Thus 8-amino-2,3-disubstituted pyrido[3,4-*b*]pyrazines **11a**,**b** were obtained in only 4–6% yield from 4-aminopyridine (**5**) in three steps, due particularly to the poor solubility of 3,4,5-triaminopyridine (**13**) in the condensation reaction with benzils. These compounds have already been obtained in 13–17% yield from 4-aminopyridine (**5**) in six steps via the corresponding 8-bromo-2,3-disubstituted pyrido[3,4-*b*]pyrazines **4a**,**b**.

With the aim of preparing a large series of 8-substituted pyrido[3,4-*b*]pyrazines, we envisioned an examination of the functionalization of 8-bromo-2,3-disubstituted pyrido[3,4-*b*]pyrazines **4a**,**b** and 8-amino-2,3-disubstituted pyrido[3,4-*b*]pyrazines **11a**,**b**. Reaction of 8-bromo-2,3-diphenylpyrido[3,4-*b*]pyrazine (**4a**) with anilines via the Buchwald procedure [$Pd_2(dba)_3$, BINAP, *t*-BuONa] led to the formation of 8-anilinopyrido[3,4-*b*]pyrazines **14a**,**b** in 62–64% yield (Scheme 4).




**Scheme 4** Synthesis of anilines **14a**,**b** from 8-bromo-2,3-diphenylpyrido[3,4-*b*]pyrazine (**4a**)




**Scheme 3** Synthesis of 8-amino-2,3-disubstituted pyrido[3,4-*b*]pyrazines **11a–d** from 8-bromo-2,3-disubstituted pyrido[3,4-*b*]pyrazines **4a**,**b** (methods 3 and 4, M3 and M4) and by condensation of 3,4,5-triaminopyridine (**13**) with benzils (method 5, M5)

As outlined in Tables 1, 8-amino-2,3-disubstituted pyrido[3,4-*b*]pyrazines **11a**,**b** reacted with isocyanates or isothiocyanates to afford, respectively, ureas and thioureas **15a**–**h** in average to good yields. Method 6 (NaH, DMF, r.t.) was employed with aryl isocyanates, whereas method 7 (pyridine, reflux) was used with alkyl isocyanates and alkyl isothiocyanates. Indeed, when 8-amino-2,3-diphenylpyrido[3,4-*b*]pyrazine (**11a**) was allowed to react with ethyl isocyanate using Method 6, the major product was a byproduct, *N*-(2,3-diphenylpyrido[3,4-*b*]pyrazin-8-yl)-*N*,*N*′-diethyldicarbonimidic diamide (**15i**) in a mixture with starting material.

Amides **16a**–**c** were also prepared by reaction of 8-amino-2,3-disubstituted pyrido[3,4-*b*]pyrazines **11a**,**b** with acid chlorides in the presence of cesium carbonate in refluxing acetonitrile in good yields (Table 1, entries 9–11).

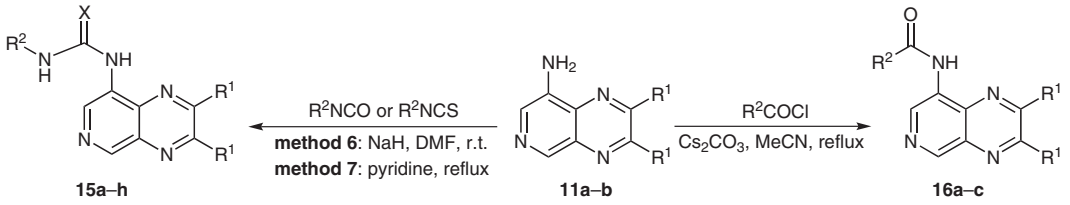
As our protocol allowed the preparation of numerous 2,3,8-trisubstituted pyrido[3,4-*b*]pyrazines from 4-aminopyridine, we decided to extend it to the synthesis of 2,3,8-trisubstituted pyrido[2,3-*b*]pyrazines. To our knowledge there are only a few papers describing the preparation of pyrido[2,3-*b*]pyrazines bearing a substituent in position 8.[6b–6e] Therefore, we decided to synthesize 8-bromo-2,3-disubstituted and 8-amino-2,3-disubstituted pyrido[2,3-*b*]pyrazines, precursors of a large series of 8-substituted pyrido[2,3-*b*]pyrazines.

8-Bromo-2,3-disubstituted pyrido[2,3-*b*]pyrazines **20a**,**b** were obtained by condensation of 2,3-diamino-4-bromopyridine (**19**) with benzil (**2a**) or 4,4′-dimethoxybenzil (**2b**) as described for previous series. 2,3-Diamino-4-bromopyridine (**19**) was synthesized in two steps from 3-amino-2-nitropyridine (**17**) (Scheme 5). In the first step, bromination of 3-amino-2-nitropyridine (**17**) using bromine in the presence of potassium acetate in acetic acid provided 3-amino-4-bromo-2-nitropyridine (**18**). Reduction of the nitro group with tin(II) chloride in refluxing ethanol and water gave 2,3-diamino-3-bromopyridine (**19**).[12]

Subsequently, condensation of 2,3-diamino-4-bromopyridine (**19**) with benzils **2a**,**b** in refluxing dioxane (method 8) proceeded efficiently to give 8-bromo-2,3-disubstituted pyrido[2,3-*b*]pyrazines **20a**,**b** in good yield (75%). This reaction was also performed using microwave irradiation; optimal reaction conditions (45 W, 75 °C) were applied for the preparation of 8-bromo-2,3-disubstituted pyrido[2,3-*b*]pyrazines **20a**,**b** in methanol and acetic acid[13] (method 9) in 40 minutes (instead of 5 d for the classical method) in good yields (66–70%).

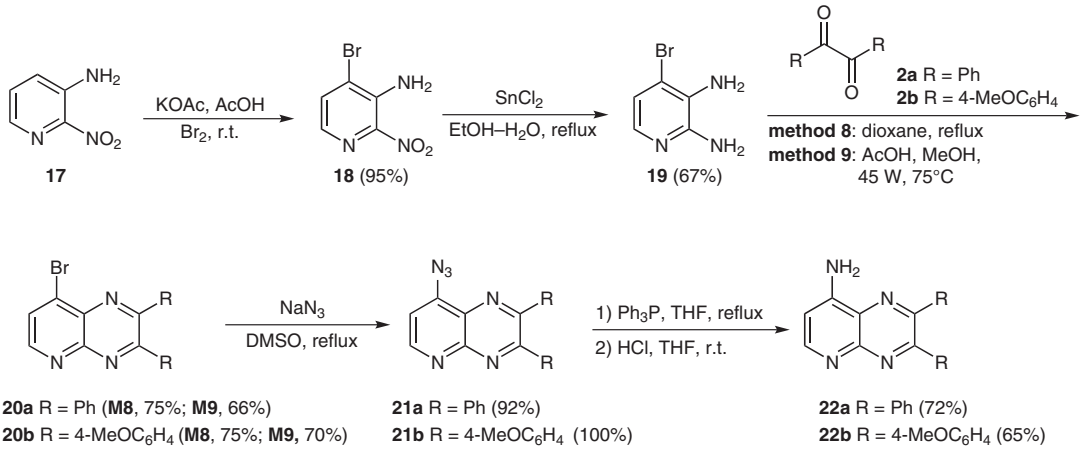
Transformation of 8-bromo-2,3-disubstituted pyrido[2,3-*b*]pyrazines **20a**,**b** into 8-amino-2,3-disubstituted pyrido[2,3-*b*]pyrazines via the corresponding benzophenone imines as previously described for pyrido[3,4-*b*]pyrazines was unsuccessful. Other attempt using direct amination with aqueous ammonium hydroxide also failed. Finally, 8-amino-2,3-disubstituted pyrido[2,3-*b*]pyrazines **22a**,**b** were synthesized in two steps by the route illustrated in Scheme 5. 8-Bromo-2,3-disubstituted pyrido[2,3-*b*]pyrazines **20a**,**b** were converted into azido derivatives **21a**,**b**

**Table 1** Synthesis of Ureas and Thioureas **15a**–**h** and Amides **16a**–**c** from 8-Amino-2,3-disubstituted Pyrido[3,4-*b*]pyrazines **11a**,**b**




| Entry | Substrate | $R^1$ | Product | $R^2$ | X | Method | Time (h) | Yield[a] (%) |
|---|---|---|---|---|---|---|---|---|
| 1 | **11a** | Ph | **15a** | Et | O | M7 | 24 | 54 |
| 2 | **11a** | Ph | **15b** | Ph | O | M6 | 7 | 57 |
| 3 | **11a** | Ph | **15c** | 3-$MeOC_6H_4$ | O | M6 | 8 | 52 |
| 4 | **11a** | Ph | **15d** | 3-$ClC_6H_4$ | O | M6 | 8 | 58 |
| 5 | **11a** | Ph | **15e** | 4-Cl-3-$(F_3C)C_6H_3$ | O | M6 | 5 | 52 |
| 6 | **11b** | 4-$MeOC_6H_4$ | **15f** | Ph | O | M6 | 6 | 53 |
| 7 | **11a** | Ph | **15g** | Et | S | M7 | 24 | 63 |
| 8 | **11b** | 4-$MeOC_6H_4$ | **15h** | Et | S | M7 | 24 | 75 |
| 9 | **11a** | Ph | **16a** | Me | – | – | 19 | 75 |
| 10 | **11b** | 4-$MeOC_6H_4$ | **16b** | Me | – | – | 24 | 87 |
| 11 | **11a** | Ph | **16c** | 4-$MeOC_6H_4$ | – | – | 24 | 78 |

[a] Isolated yield.




**Scheme 5** Synthesis of 8-bromo-2,3-disubstituted pyrido[2,3-*b*]pyrazines **20a**,**b** and 8-amino-2,3-disubstituted pyrido[2,3-*b*]pyrazines **22a**,**b**

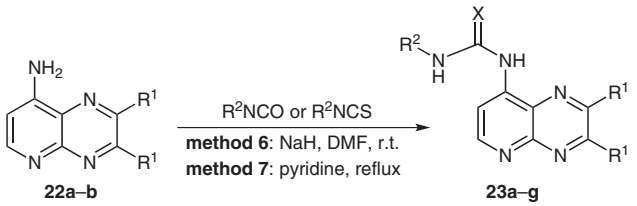
by reaction with sodium azide in refluxing dimethyl sulfoxide in good yields. Staudinger reaction using triphenylphosphine in refluxing tetrahydrofuran[14] followed by a treatment with hydrochloric acid provided 8-amino-2,3-disubstituted pyrido[2,3-*b*]pyrazines **22a**,**b**.

In this series, seven examples of ureas and thioureas **23a**–**g** have been prepared by the reaction between 8-amino-2,3-disubstituted pyrido[2,3-*b*]pyrazines **22a**,**b** and suitable isocyanates or isothiocyanates in moderate to good yields (Table 2).

In summary, we have developed an efficient synthetic approach for the preparation of 2,3,8-trisubstituted pyrido[3,4-*b*]pyrazines, compounds of potential biological interest. Methods used to decorate the scaffold allowed the introduction of various substituents late in the synthetic scheme from 8-bromo-2,3-disubstituted pyrido[3,4-*b*]pyrazines **4a**,**b** and 8-amino-2,3-disubstituted pyrido[3,4-*b*]pyrazines **11a**,**b**. Therefore, this approach greatly facilitates the preparation of 2,3-disubstituted pyrido[3,4-*b*]pyrazines with possible diversity at the C8 position. The method has been applied to synthesis of novel 2,3,8-trisubstituted pyrido[2,3-*b*]pyrazines from the corresponding 8-amino precursors **22a**,**b**. Our continued efforts to synthesize novel pyrido[3,4-*b*]pyrazines with substituents in position 8 will be described in future publications, in particular 2,8- and 3,8-disubstituted pyrido[3,4-*b*]pyrazines of biological interest.

$^1$H and $^{13}$C NMR spectra were recorded in DMSO-$d_6$ at r.t. using TMS as internal standard with Bruker Avance 400 MHz high-resolution NMR spectrometers. IR spectra were recorded on a Paragon 1000 PC Perkin Elmer spectrophotometer. Mass spectra were recorded using an Electrospray Ionization Method with ESQUIRE-LC ion trap system. Melting points were determined in capillary tubes on an Electrothermal IA 9000 and are uncorrected. Reactions were monitored by TLC analysis using Merck silica gel 60F-254 thin layer plates. Column chromatography was carried out on silica

**Table 2** Synthesis of Ureas and Thioureas **23a**–**g** from 8-Amino-2,3-disubstituted Pyrido[2,3-*b*]pyrazines **22a**,**b**




| Entry | Substrate | $R^1$ | Product | $R^2$ | X | Method | Time (h) | Yield[a] (%) |
|---|---|---|---|---|---|---|---|---|
| 1 | **22a** | Ph | **23a** | Et | O | M7 | 24 | 82 |
| 2 | **22a** | Ph | **23b** | Ph | O | M6 | 6 | 55 |
| 3 | **22a** | Ph | **23c** | 3-Cl$C_6H_4$ | O | M6 | 7 | 53 |
| 4 | **22b** | 4-Me$OC_6H_4$ | **23d** | Et | O | M7 | 24 | 50 |
| 5 | **22b** | 4-Me$OC_6H_4$ | **23e** | Ph | O | M6 | 7 | 51 |
| 6 | **22a** | Ph | **23f** | Et | S | M7 | 24 | 55 |
| 7 | **22a** | Ph | **23g** | Ph | S | M6 | 8 | 48 |

[a] Isolated yield.

gel Merck 60 (70–230 mesh ASTM). Elemental analyses were found within ±0.4% of the theoretical values. Reactions using microwave irradiation were performed in a CEM Discover microwave.

**2,3-Diphenylpyrido[3,4-*b*]pyrazine (3a); Typical Procedure**
A mixture of 3,4-diaminopyridine (**1**, 3.0 g, 27.5 mmol) and benzil (**2a**, 5.8 g, 27.5 mmol) in dioxane (80 mL) was heated at reflux for 5 d. After cooling to r.t., the solvent was removed under reduced pressure and the crude product was purified by column chromatography (silica gel, $CH_2Cl_2$) to give **3a** (6.4 g, 82%) as a yellow solid; mp 173–174 °C; $R_f$ = 0.75 ($CH_2Cl_2$–EtOH, 9:1).

IR (KBr): 1579, 1543 $cm^{-1}$.

$^1H$ NMR (400 MHz, DMSO-$d_6$): δ = 9.60 (s, 1 H), 8.91 (d, *J* = 5.8 Hz, 1 H), 8.13 (d, *J* = 5.8 Hz, 1 H), 7.57–7.39 (m, 10 H).

$^{13}C$ NMR (100 MHz, DMSO-$d_6$): δ = 157.7 (C), 155.1 (C), 153.7 (CH), 147.4 (CH), 142.8 (C), 138.1 (C), 138.1 (C), 135.6 (C), 129.7 (CH), 129.7 (CH), 129.4 (CH), 129.2 (CH), 128.1 (CH), 121.1 (CH).

MS (ESI): *m*/*z* (%) = 284 [(M + H), 100].

Anal. Calcd for $C_{19}H_{13}N_3$: C, 80.54; H, 4.62; N, 14.83. Found: C, 80.82; H, 4.64; N, 14.54.

**2,3-Bis(4-methoxyphenyl)pyrido[3,4-*b*]pyrazine (3b)**
Yellow powder; yield: 7.1 g (75%); mp 147–148 °C; $R_f$ = 0.77 ($CH_2Cl_2$–EtOH, 9:1).

IR (KBr): 1600, 1507, 1241 $cm^{-1}$.

$^1H$ NMR (400 MHz, DMSO-$d_6$): δ = 9.51 (s, 1 H), 8.83 (d, *J* = 5.8 Hz, 1 H), 8.03 (d, *J* = 5.8 Hz, 1 H), 7.55–7.50 (m, 4 H), 6.99 (d, *J* = 8.5 Hz, 4 H), 3.83 (s, 6 H).

$^{13}C$ NMR (100 MHz, DMSO-$d_6$): δ = 160.8 (C), 160.6 (C), 157.6 (C), 155.1 (C), 153.9 (CH), 147.5 (CH), 143.2 (C), 136.0 (C), 131.9 (CH), 131.7 (CH), 131.1 (C), 131.0 (C), 121.4 (CH), 114.2 (CH), 55.7 ($CH_3$), 55.7 ($CH_3$).

MS (ESI): *m*/*z* (%) = 344 [(M + H), 100].

Anal. Calcd for $C_{21}H_{17}N_3O_2$: C, 73.45; H, 4.99; N, 12.24. Found: C, 73.24; H, 4.98; N, 12.32.

**8-Bromo-2,3-diphenylpyrido[3,4-*b*]pyrazine (4a); Typical Procedure**
*Method 1*: A soln of **3a** (150 mg, 0.5 mmol) in HBr (0.35 mL) was heated at 80 °C. 35% $H_2O_2$ (1 mL) was added slowly, keeping the temperature below 83 °C. The mixture was stirred at 80 °C for 1 h then quenched with brine. The aqueous layer was extracted with $CH_2Cl_2$ and the combined organic extracts were washed with brine, separated, and dried ($Na_2SO_4$). The solvent was removed under reduced pressure to give **4a** (177 mg, 98%) as a beige powder.

*Method 2*: A mixture of **9** (150 mg, 0.5 mmol) and benzil (**2a**, 105 mg, 0.5 mmol) in dioxane (6 mL) was refluxed for 4 h. The mixture was quenched with $H_2O$, the aqueous layer was extracted with $CH_2Cl_2$, the combined organic extracts were dried ($Na_2SO_4$), and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (silica gel, $CH_2Cl_2$–EtOH, 10:0 to 9:1) to give **4a** (127 mg, 70%) as a beige powder; mp 200–201 °C; $R_f$ = 0.89 ($CH_2Cl_2$–EtOH, 9:1).

IR (KBr): 1569, 1538 $cm^{-1}$.

$^1H$ NMR (400 MHz, DMSO-$d_6$): δ = 9.56 (s, 1 H), 9.17 (s, 1 H), 7.62–7.54 (m, 4 H), 7.52–7.40 (m, 6 H).

$^{13}C$ NMR (100 MHz, DMSO-$d_6$): δ = 158.1 (C), 156.0 (C), 153.1 (CH), 148.3 (CH), 140.8 (C), 137.7 (C), 136.6 (C), 130.0 (CH), 129.8 (CH), 129.7 (CH), 129.5 (CH), 128.2 (CH), 119.3 (C).

MS (ESI): *m*/*z* (%) = 362 [(M + H), 100], 364 [(M + H) + 2, 100].

Anal. Calcd for $C_{19}H_{12}BrN_3$: C, 63.00; H, 3.34; N, 11.60. Found: C, 63.31; H, 3.33; N, 11.52.

**8-Bromo-2,3-bis(4-methoxyphenyl)pyrido[3,4-*b*]pyrazine (4b)**
Yellow powder; yield: 158 mg (75%, method 2); mp 119–120 °C; $R_f$ = 0.86 ($CH_2Cl_2$–EtOH, 9:1).

IR (KBr): 1622, 1227 $cm^{-1}$.

$^1H$ NMR (400 MHz, DMSO-$d_6$): δ = 9.46 (s, 1 H), 9.09 (s, 1 H), 7.90 (m, 4 H), 7.06–7.00 (m, 4 H), 3.84 (s, 6 H).

$^{13}C$ NMR (100 MHz, DMSO-$d_6$): δ = 160.7 (C), 160.3 (C), 157.4 (C), 155.3 (C), 152.7 (CH), 147.9 (CH), 140.6 (C), 136.4 (C), 131.6 (CH), 131.2 (CH), 130.1 (C), 130.0 (C), 119.1 (C), 113.8 (CH), 113.7 (CH), 55.3 ($CH_3$), 55.2 ($CH_3$).

MS (ESI): *m*/*z* (%) = 422 [(M + H), 100], 424 [(M + H) + 2, 100].

Anal. Calcd for $C_{21}H_{16}BrN_3O_2$: C, 59.73; H, 3.82; N, 9.95. Found: C, 59.51; H, 3.85; N, 9.99.

**4-(Nitramino)pyridine (6)**
To a soln of 4-aminopyridine (**5**, 5.0 g, 53.2 mmol) in concd $H_2SO_4$ (20 mL) cooled in an ice bath was added fuming $HNO_3$ (2.5 mL, 55.3 mmol) over 30 min, keeping the temperature below 10 °C. The mixture was stirred at r.t. for 5 h and then was poured into a mixture of ice and $H_2O$ yielding a precipitate. After filtration, the soln was made basic by addition of aq $NH_3$ soln, leading to a precipitate that was collected by filtration and air-dried to yield crude **6** as a yellow powder; mp 194–195 °C; $R_f$ = 0.45 ($CH_2Cl_2$–EtOH, 9:1).

$^1H$ NMR (400 MHz, DMSO-$d_6$): δ = 8.27 (d, *J* = 7.0 Hz, 2 H), 7.51 (d, *J* = 7.0 Hz, 2 H).

The data are in conformity with the literature.[8]

MS (ESI): *m*/*z* (%) = 140 [(M + H), 100].

**4-Amino-3-nitropyridine (7) from 4-(Nitramino)pyridine (6)**
A soln of **6** in concd $H_2SO_4$ (10 mL) was heated at 90 °C for 3 h, and then stirred at r.t. overnight. The mixture was then quenched with a mixture of ice and $H_2O$ and aq $NH_3$ soln was added until a yellow precipitate formed that was collected by filtration to yield **7** (3.5 g, 47% in two steps from **5**).

**4-Amino-3-nitropyridine (7) from 4-Aminopyridine (5)**
To a soln of 4-aminopyridine (**5**, 5.0 g, 53.2 mmol) in concd $H_2SO_4$ (20 mL) cooled in an ice bath was added fuming $HNO_3$ (2.5 mL, 55.3 mmol) over 30 min, keeping the temperature below 10 °C. The resulting mixture was stirred at r.t. for 5 h, and then heated at 90 °C for 3 h. The soln was stirred at r.t. overnight and then poured into a mixture of ice and $H_2O$. Aq $NH_3$ soln was added until a yellow precipitate formed that was collected by filtration and air-dried to yield **7** (5.9 g, 80% in one step); mp 225–226 °C; $R_f$ = 0.47 ($CH_2Cl_2$–EtOH, 9:1).

IR (KBr): 3210, 1635, 1548, 1464, 1353 $cm^{-1}$.

$^1H$ NMR (400 MHz, DMSO-$d_6$): δ = 9.00 (s, 1 H), 8.16 (d, *J* = 6.0 Hz, 1 H), 7.97 (br s, 2 H), 6.92 (d, *J* = 6.0 Hz, 1 H).

The data are in conformity with the literature.[8]

$^{13}C$ NMR (100 MHz, DMSO-$d_6$): δ = 151.7 (CH), 149.4 (C), 148.0 (CH), 128.7 (C), 112.7 (CH).

MS (ESI): *m*/*z* (%) = 140 [(M + H), 100].

Anal. Calcd for $C_5H_5N_3O_2$: C, 43.17; H, 3.62; N, 30.21. Found: C, 43.11; H, 3.65; N, 30.17.

**4-Amino-3-bromo-5-nitropyridine (8)**
A mixture of **7** (500 mg, 3.6 mmol) and KOAc (353 mg, 3.6 mmol) in glacial AcOH (5 mL) was stirred at r.t. for 1 h and then $Br_2$ (180 μL, 3.6 mmol) was added dropwise. The resulting mixture was

stirred at r.t. overnight. The reaction was quenched with $H_2O$, the aqueous layer was extracted with $CH_2Cl_2$, the combined organic extracts were dried ($Na_2SO_4$), and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (silica gel, $CH_2Cl_2$–EtOH, 10:0 to 9:1) to give **8** (586 mg, 75%) as an orange powder; mp 174–175 °C; $R_f$ = 0.79 ($CH_2Cl_2$–EtOH, 9:1).

IR (KBr): 3320, 1630, 1584, 1456, 1348 $cm^{-1}$.

$^1H$ NMR (400 MHz, DMSO-$d_6$): δ = 9.01 (s, 1 H), 8.59 (s, 1 H), 7.85 (br s, 2 H).

$^{13}C$ NMR (100 MHz, DMSO-$d_6$): δ = 153.5 (CH), 146.9 (CH), 146.5 (C), 129.8 (C), 108.7 (C).

MS (ESI): *m*/*z* (%) = 218 [(M + H), 100], 220 [(M + H) + 2, 100].

Anal. Calcd for $C_5H_4BrN_3O_2$: C, 27.55; H, 1.85; N, 19.27. Found: C, 27.81; H, 1.83; N, 19.17.

**3,4-Diamino-5-bromopyridine (9)**

A mixture of **8** (200 mg, 0.9 mmol) and $SnCl_2$ (872 mg, 4.6 mmol) in a mixture of EtOH (5 mL) and $H_2O$ (1 mL) was heated at reflux for 2 h. The mixture was cooled and quenched with aq NaOH soln. The aqueous layer was extracted with $CH_2Cl_2$ and the combined organic extracts were dried ($Na_2SO_4$) and the solvents were removed under reduced pressure to give **9** (111 mg, 67%) as a beige powder; mp 121–123 °C; $R_f$ = 0.17 ($CH_2Cl_2$–EtOH, 9:1).

IR (KBr): 3250, 1624 $cm^{-1}$.

$^1H$ NMR (400 MHz, DMSO-$d_6$): δ = 7.69 (s, 1 H), 7.62 (s, 1 H), 5.57 (br s, 2 H), 4.94 (br s, 2 H).

The data are in conformity with the literature.[7]

$^{13}C$ NMR (100 MHz, DMSO-$d_6$): δ = 139.6 (CH), 138.3 (C), 133.1 (CH), 131.8 (C), 105.0 (C).

MS (ESI): *m*/*z* (%) = 188 [(M + H), 100], 190 [(M + H) + 2, 100].

Anal. Calcd for $C_5H_6BrN_3$: C, 31.94; H, 3.22; N, 22.35. Found: C, 32.02; H, 3.18; N, 22.41.

**3,4-Diamino-5-bromo-2-chloropyridine (9′)**

A soln containing **8** (2.0 g, 9.2 mmol) and $SnCl_2$ (5.2 g, 27.5 mmol) in concd HCl was stirred at r.t. for 5 h. The resulting mixture was made basic by addition of NaOH soln. The aqueous layer was extracted with $CH_2Cl_2$, the organic layer was dried ($Na_2SO_4$), and the solvent was removed under reduced pressure to give **9′** (1.4 g, 70%) as a beige powder; mp 233–234 °C; $R_f$ = 0.23 ($CH_2Cl_2$–EtOH, 9:1).

IR (KBr): 3334, 1637 $cm^{-1}$.

$^1H$ NMR (400 MHz, DMSO-$d_6$): δ = 7.56 (s, 1 H), 6.03 (br s, 2 H), 5.15 (br s, 2 H).

MS (ESI): *m*/*z* (%) = 222 [(M + H), 75], 224 [(M + H) + 2, 100], 226 [(M + H) + 4, 25].

Anal. Calcd for $C_5H_5BrClN_3$: C, 26.99; H, 2.27; N, 18.89. Found: C, 26.54; H, 2.30; N, 19.01.

***N*-(2,3-Diphenylpyrido[3,4-*b*]pyrazin-8-yl)benzophenone Imine (10a); Typical Procedure**

To a soln of **4a** (1.2 g, 3.3 mmol) in toluene (40 mL) under argon was added successively benzophenone imine (667 μL, 4.0 mmol), $Pd_2(dba)_3$ (10 mg, 2.5.10–5 mol), BINAP (4 mg, 8.3.10–6 mol), and *t*-BuONa (446 mg, 4.6 mmol). The mixture was heated at 100 °C for 12 h and then cooled to r.t. EtOAc (60 mL) was added, the mixture was washed with $H_2O$, and extracted with EtOAc. The organic layer was dried ($Na_2SO_4$) and the solvents were removed under reduced pressure. The crude product was purified by column chromatography (silica gel, $CH_2Cl_2$–EtOH, 10:0 to 9:1) to give **10a** (916 mg, 60%) as a yellow powder; mp 88–89 °C; $R_f$ = 0.86 ($CH_2Cl_2$–EtOH, 9:1).

IR (KBr): 1619 $cm^{-1}$.

$^1H$ NMR (400 MHz, DMSO-$d_6$): δ = 9.15 (s, 1 H), 8.28 (s, 1 H), 7.82–7.21 (m, 20 H).

$^{13}C$ NMR (100 MHz, DMSO-$d_6$): δ = 171.2 (C), 156.4 (C), 154.9 (C), 148.0 (CH), 143.1 (C), 138.5 (C), 138.3 (C), 136.9 (CH), 135.5 (C), 135.3 (C), 129.9 (CH), 129.8 (CH), 129.6 (CH), 129.5 (CH), 129.2 (CH), 128.8 (CH), 128.5 (CH), 128.4 (CH), 128.3 (CH), 128.2 (CH).

MS (ESI): *m*/*z* (%) = 463 [(M + H), 100].

Anal. Calcd for $C_{32}H_{22}N_4$: C, 83.09; H, 4.79; N, 12.11. Found: C, 82.97; H, 4.77; N, 12.26.

***N*-[2,3-Bis(4-methoxyphenyl)pyrido[3,4-*b*]pyrazin-8-yl]benzophenone Imine (10b)**

Yellow powder; yield: 759 mg (44%); mp 94–95 °C; $R_f$ = 0.85 ($CH_2Cl_2$–EtOH, 9:1).

IR (KBr): 1606, 1252 $cm^{-1}$.

$^1H$ NMR (400 MHz, DMSO-$d_6$): δ = 9.06 (s, 1 H), 8.22 (s, 1 H), 7.49–7.42 (m, 9 H), 6.99–6.95 (m, 9 H), 3.82 (s, 3 H), 3.79 (s, 3 H).

$^{13}C$ NMR (100 MHz, DMSO-$d_6$): δ = 170.7 (C), 160.2 (C), 160.0 (C), 155.4 (C), 154.0 (C), 147.4 (CH), 142.7 (C), 136.3 (CH), 135.1 (C), 134.7 (C), 131.5 (CH), 131.3 (CH), 131.1 (CH), 131.0 (C), 130.5 (C), 130.4 (C), 129.2 (CH), 128.9 (CH), 128.5 (CH), 128.2 (CH), 127.8 (CH), 113.7 (CH), 113.6 (CH), 55.2 ($CH_3$), 55.1 ($CH_3$).

MS (ESI): *m*/*z* (%) = 523 [(M + H), 100].

Anal. Calcd for $C_{34}H_{26}N_4O_2$: C, 78.14; H, 5.01; N, 10.72. Found: C, 78.36; H, 4.98; N, 10.64.

**8-Amino-2,3-diphenylpyrido[3,4-*b*]pyrazine (11a); Typical Procedure**

*Method 3*: To a soln of **10a** (200 mg, 0.4 mmol) in MeOH (5 mL) was added NaOAc (85 mg, 1.04 mmol) and $NH_2OH$·HCl (54 mg, 0.8 mmol). The mixture was stirred at 75 °C for 48 h and then cooled to r.t. The soln was poured into NaOH soln and extracted with $CH_2Cl_2$. The organic layer was dried ($Na_2SO_4$) and the solvent removed under reduced pressure to give **11a** (128 mg, 98%) as an orange powder.

*Method 5*: To a soln of 3,4,5-triaminopyridine (**13**, 398 mg, 3.2 mmol) in $H_2O$ (6 mL) was added $NaHCO_3$ (338 mg, 3.2 mmol) and a soln of benzil (**2a**, 673 mg, 3.2 mmol) in dioxane (3 mL). The resulting mixture was heated at reflux for 6 h and was then allowed to cool to r.t. The mixture was quenched with $H_2O$, the aqueous layer was extracted with $CH_2Cl_2$, the combined organic extracts were dried ($Na_2SO_4$), and the solvents were removed under reduced pressure to give **11a** (220 mg, 23%) as an orange powder; mp 192–193 °C; $R_f$ = 0.76 ($CH_2Cl_2$–EtOH, 9:1).

IR (KBr): 3220, 1614 $cm^{-1}$.

$^1H$ NMR (400 MHz, DMSO-$d_6$): δ = 8.69 (s, 1 H), 8.23 (s, 1 H), 7.61–7.29 (m, 10 H), 6.30 (br s, 2 H).

$^{13}C$ NMR (100 MHz, DMSO-$d_6$): δ = 154.8 (C), 153.7 (C), 140.5 (C), 138.8 (C), 138.5 (C), 138.4 (CH), 135.7 (C), 132.0 (C), 130.1 (CH), 129.8 (CH), 129.5 (CH), 129.3 (CH), 129.2 (CH), 128.3 (CH), 128.2 (CH).

MS (ESI): *m*/*z* (%) = 299 [(M + H), 100].

Anal. Calcd for $C_{19}H_{14}N_4$: C, 76.49; H, 4.73; N, 18.78. Found: C, 76.45; H, 4.74; N, 18.81.

**8-Amino-2,3-bis(4-methoxyphenyl)pyrido[3,4-*b*]pyrazine (11b)**

Orange powder; yield: 125 mg (87%, method 3); yield: 355 mg (31%, method 5); mp 146–147 °C; $R_f$ = 0.78 ($CH_2Cl_2$–EtOH, 9:1).

IR (KBr): 3250, 1662, 1242 $cm^{-1}$.

$^1$H NMR (400 MHz, DMSO-$d_6$): δ = 8.63 (s, 1 H), 8.17 (s, 1 H), 7.58 (d, *J* = 8.9 Hz, 2 H), 7.50 (d, *J* = 8.9 Hz, 2 H), 6.98 (dd, *J* = 8.9, 3.4 Hz, 4 H), 6.22 (br s, 2 H), 3.83 (s, 6 H).

$^{13}$C NMR (100 MHz, DMSO-$d_6$): δ = 160.3 (C), 160.1 (C), 154.2 (C), 153.2 (C), 140.3 (C), 138.4 (CH), 135.5 (C), 131.8 (C), 131.6 (CH), 131.2 (CH), 131.0 (C), 129.2 (CH), 113.8 (CH), 113.7 (CH), 55.2 ($CH_3$), 55.1 ($CH_3$).

MS (ESI): *m*/*z* (%) = 359 [(M + H), 100].

Anal. Calcd for $C_{21}H_{18}N_4O_2$: C, 70.38; H, 5.06; N, 15.63. Found: C, 70.49; H, 5.03; N, 15.58.

**8-Amino-2,3-diphenylpyrido[3,4-*b*]pyrazine Hydrochloride (11c); Typical Procedure**

*Method 4*: A mixture of **10a** (200 mg, 0.4 mmol) and 2 M HCl (0.4 mL) in THF (3 mL) was stirred at r.t. for 5 h. The precipitate was filtered off and air-dried to yield **11c** (131 mg, 98%) as an orange powder; mp 208–209 °C.

IR (KBr): 1641 cm$^{-1}$.

$^1$H NMR (400 MHz, DMSO-$d_6$): δ = 9.02 (s, 1 H), 8.14 (s, 1 H), 7.70–7.43 (m, 10 H).

$^{13}$C NMR (100 MHz, DMSO-$d_6$): δ = 157.5 (C), 156.7 (C), 144.9 (C), 137.9 (C), 137.5 (C), 136.4 (C), 134.3 (C), 132.9 (CH), 131.3 (CH), 130.4 (CH), 130.3 (CH), 130.0 (CH), 129.8 (CH), 129.8 (CH), 128.8 (CH), 128.5 (CH), 128.4 (CH), 119.6 (CH).

**8-Amino-2,3-bis(4-methoxyphenyl)pyrido[3,4-*b*]pyrazine Hydrochloride (11d)**

Orange powder; yield: 145 mg (92%); mp 162–163 °C.

IR (KBr): 1628, 1233 cm$^{-1}$.

$^1$H NMR (400 MHz, DMSO-$d_6$): δ = 8.96 (s, 1 H), 8.06 (s, 1 H), 7.72 (d, *J* = 8.8 Hz, 2 H), 7.57 (d, *J* = 8.9 Hz, 2 H), 7.04 (d, *J* = 8.9 Hz, 2 H), 7.01 (d, *J* = 8.9 Hz, 2 H), 3.84 (s, 6 H).

$^{13}$C NMR (100 MHz, DMSO-$d_6$): δ = 160.2 (C), 160.1 (C), 157.2 (C), 156.4 (C), 144.3 (C), 137.2 (C), 137.1 (C), 136.2 (C), 133.9 (C), 132.8 (CH), 131.1 (CH), 130.2 (CH), 130.1 (CH), 129.9 (CH), 129.6 (CH), 129.5 (CH), 114.4 (CH), 114.5 (CH), 55.8 ($CH_3$), 55.7 ($CH_3$).

**4-Amino-3,5-dinitropyridine (12)**

To a soln of 4-aminopyridine (**5**, 23.5 g, 0.25 mol) in concd $H_2SO_4$ (100 mL) cooled in an ice bath was added dropwise fuming $HNO_3$ (13.5 mL) keeping the temperature below 10 °C. The mixture was warmed slowly to r.t. and then heated at 85 °C. When the temperature reached 85 °C, the soln was rapidly cooled in an ice bath. Fuming $HNO_3$ (13.5 mL) was added to the resulting soln and the mixture was heated at 85 °C. After 1 h, the mixture was cooled to r.t., then poured into a mixture of ice and $H_2O$. Aq NaOH soln was added and the precipitate was collected by filtration. Then aq $NH_3$ soln was added and more product was collected by filtration and added to the first precipitate. The residue was dissolved in $CH_2Cl_2$ and then filtered; the residue was washed further with $CH_2Cl_2$. The solvent was removed under reduced pressure to give **12** (12.0 g, 26%) as yellow flocks; mp 167–168 °C; $R_f$ = 0.68 ($CH_2Cl_2$–EtOH, 9:1).

IR (KBr): 3326, 1627, 1573, 1374 cm$^{-1}$.

$^1$H NMR (400 MHz, DMSO-$d_6$): δ = 9.26 (s, 2 H), 8.77 (br s, 2 H).

$^{13}$C NMR (100 MHz, DMSO-$d_6$): δ = 151.9 (CH), 143.6 (C), 132.2 (C).

MS (ESI): *m*/*z* (%) = 185 [(M + H), 100].

Anal. Calcd for $C_5H_4N_4O_4$: C, 32.62; H, 2.19; N, 30.43. Found: C, 32.58; H, 2.21; N, 30.38.

**3,4,5-Triaminopyridine (13)**

A mixture of **12** (4.0 g, 22 mmol) and $SnCl_2$ (20.0 g, 10.8 mmol) in EtOH (200 mL) was heated at reflux for 6 h. The mixture was then cooled to r.t. and acidified by addition of HCl. The precipitate was collected by filtration. The hydrochloride was dissolved in aq NaOH soln and the free base was extracted by EtOAc. The organic layer was dried ($Na_2SO_4$), filtered, and evaporated in vacuo to give **13** (1.9 g, 70%) as a brown paste; $R_f$ = 0.12 ($CH_2Cl_2$–EtOH, 9:1).

IR (KBr): 3357, 1618 cm$^{-1}$.

$^1$H NMR (400 MHz, DMSO-$d_6$): δ = 7.51 (s, 2 H).

$^{13}$C NMR (100 MHz, DMSO-$d_6$): δ = 132.1, 131.2, 124.9.

The data are in conformity with the literature.[11]

MS (ESI): *m*/*z* (%) = 125 [(M + H), 100].

**Anilines 14a,b from 4a; General Procedure**

To a soln of **4a** (0.8 mmol) in toluene (30 mL) under argon, was added successively an aniline (1.0 mmol), $Pd_2(dba)_3$ (6.2.10–5 mmol), BINAP (2.1.10–5 mmol), and *t*-BuONa (1.2 mmol). The resulting mixture was stirred at 100 °C until the reaction was complete (monitored by TLC) and then allowed to cool to r.t. EtOAc was added, the organic phase was washed with $H_2O$ (3 ×), collected, dried ($Na_2SO_4$), and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (silica gel, $CH_2Cl_2$–EtOH, from 10:0 to 9:1) to give the desired compounds.

***N*-(3-Bromophenyl)-2,3-diphenylpyrido[3,4-*b*]pyrazin-8-amine (14a)**

Orange powder; yield: 232 mg (64%); mp 77–79 °C; $R_f$ = 0.85 ($CH_2Cl_2$–EtOH, 9:1).

IR (KBr): 3212, 1634 cm$^{-1}$.

$^1$H NMR (400 MHz, DMSO-$d_6$): δ = 9.05 (s, 1 H), 8.86 (br s, 1 H), 8.74 (s, 1 H), 7.66–7.20 (m, 14 H).

$^{13}$C NMR (100 MHz, DMSO-$d_6$): δ = 155.9 (C), 154.4 (C), 154.1 (C), 151.9 (C), 147.8 (CH), 142.5 (CH), 139.0 (C), 138.6 (CH), 138.1 (CH), 136.9 (CH), 135.2 (C), 134.1 (CH), 133.5 (C), 130.1 (CH), 124.9 (CH), 124.1 (CH), 123.8 (CH), 122.4 (CH), 120.8 (CH), 120.7 (CH), 120.1 (C), 119.9 (C), 117.5 (CH).

MS (ESI): *m*/*z* (%) = 453 [(M + H), 100], 455 [(M + H) + 2, 100].

Anal. Calcd for $C_{25}H_{17}BrN_4$: C, 66.24; H, 3.78; N, 12.36. Found: C, 66.12; H, 3.79; N, 12.41.

***N*-(3-Chloro-4-fluorophenyl)-2,3-diphenylpyrido[3,4-*b*]pyrazin-8-amine (14b)**

Orange powder; yield: 212 mg (62%); mp 85–87 °C; $R_f$ = 0.82 ($CH_2Cl_2$–EtOH, 9:1).

IR (KBr): 3206, 1622 cm$^{-1}$.

$^1$H NMR (400 MHz, DMSO-$d_6$): δ = 9.02 (s, 1 H), 8.81 (br s, 1 H), 8.64 (s, 1 H), 7.66–7.38 (m, 13 H).

$^{13}$C NMR (100 MHz, DMSO-$d_6$): δ = 156.6 (C), 154.5 (C), 154.4 (C), 153.8 (C), 152.1 (C), 148.5 (CH), 142.9 (CH), 139.1 (C), 138.7 (CH), 138.5 (CH), 137.4 (CH), 135.7 (C), 133.8 (C), 130.4 (CH), 125.0 (CH), 124.2 (CH), 124.00 (CH), 122.6 (CH), 120.9 (CH), 120.9 (CH), 120.2 (C), 120.05 (C), 117.7 (CH).

MS (ESI): *m*/*z* (%) = 427 [(M + H), 100], 429 [(M + H) + 2, 40].

Anal. Calcd for $C_{25}H_{16}ClFN_4$: C, 70.34; H, 3.78; N, 13.12. Found: C, 70.16; H, 3.81; N, 13.19.

**Ureas and Thioureas 15a–h from 11a,b; General Procedure**

*Method 6*: To a soln of **11a** or **11b** (0.5 mmol) in DMF (15 mL) was added portionwise 60% NaH in mineral oil (0.6 mmol). The mixture was stirred at r.t. for 30 min and then an isocyanate or an isothiocy-

anate (0.5 mmol) was added. The reaction was stirred at r.t. until the reaction was complete (monitored by TLC). The crude product was purified by column chromatography (silica gel, $CH_2Cl_2$–EtOH, from 10:0 to 9:1) to give the desired compounds.

*Method 7*: To a soln of **11a** or **11b** (0.8 mmol) in pyridine (20 mL) was added an isocyanate or an isothiocyanate (0.8 mmol) and the mixture was heated at reflux until the reaction was complete (monitored by TLC). Pyridine was removed under reduced pressure and the crude product was purified by column chromatography (silica gel, $CH_2Cl_2$–EtOH, from 10:0 to 4:1) to yield the desired compounds.

**_N_-(2,3-Diphenylpyrido[3,4-*b*]pyrazin-8-yl)-_N′_-ethylurea (15a)**
Beige powder; yield: 160 mg (54%, method 7); mp 246–247 °C; $R_f$ = 0.60 ($CH_2Cl_2$–EtOH, 9:1).

IR (KBr): 3268, 1682, 1545 $cm^{-1}$.

$^1$H NMR (400 MHz, DMSO-$d_6$): δ = 9.66 (br s, 1 H), 9.11 (s, 1 H), 9.00 (s, 1 H), 7.64–7.41 (m, 11 H), 3.29–3.21 (m, 2 H), 1.18–1.08 (m, 3 H).

$^{13}$C NMR (100 MHz, DMSO-$d_6$): δ = 158.3 (C), 155.5 (C), 155.4 (C), 154.8 (C), 144.3 (CH), 138.5 (C), 138.2 (C), 135.2 (C), 133.6 (C), 133.1 (C), 132.1 (C), 130.4 (CH), 130.0 (CH), 129.8 (CH), 129.5 (CH), 128.4 (CH), 34.3 ($CH_2$), 15.5 ($CH_3$).

MS (ESI): *m*/*z* (%) = 370 [(M + H), 100].

Anal. Calcd for $C_{22}H_{19}N_5O$: C, 71.53; H, 5.18; N, 18.96. Found: C, 71.52; H, 5.22; N, 18.93.

**_N_-(2,3-Diphenylpyrido[3,4-*b*]pyrazin-8-yl)-_N′_-phenylurea (15b)**
Yellow powder; yield: 119 mg (57%, method 6); mp 284–285 °C; $R_f$ = 0.81 ($CH_2Cl_2$–EtOH, 9:1).

IR (KBr): 3254, 1703, 1603 $cm^{-1}$.

$^1$H NMR (400 MHz, DMSO-$d_6$): δ = 10.38 (br s, 1 H), 9.73 (br s, 1 H), 9.68 (s, 1 H), 9.41 (s, 1 H), 7.76–7.08 (m, 15 H).

$^{13}$C NMR (100 MHz, DMSO-$d_6$): δ = 161.3 (C), 159.8 (C), 151.5 (C), 144.3 (CH), 139.6 (C), 137.5 (CH), 137.1 (CH), 134.5 (C), 133.1 (CH), 132.5 (C), 131.5 (CH), 131.2 (CH), 131.1 (C), 130.8 (C), 130.6 (C), 129.1 (CH), 122.8 (CH), 117.6 (CH), 115.2 (CH), 115.1 (CH).

MS (ESI): *m*/*z* (%) = 418 [(M + H), 100].

Anal. Calcd for $C_{26}H_{19}N_5O$: C, 74.80; H, 4.59; N, 16.78. Found: C, 74.83; H, 4.58; N, 16.76.

**_N_-(2,3-Diphenylpyrido[3,4-*b*]pyrazin-8-yl)-_N′_-(3-methoxyphenyl)urea (15c)**
Yellow powder; yield: 116 mg (52%, method 6); mp 219–220 °C; $R_f$ = 0.75 ($CH_2Cl_2$–EtOH, 9:1).

IR (KBr): 3282, 1706, 1605 $cm^{-1}$.

$^1$H NMR (400 MHz, DMSO-$d_6$): δ = 10.15 (br s, 1 H), 9.71 (br s, 1 H), 9.45 (s, 1 H), 9.23 (s, 1 H), 7.69–7.08 (m, 14 H), 3.80 (s, 3 H).

$^{13}$C NMR (100 MHz, DMSO-$d_6$): δ = 160.9 (C), 159.6 (C), 151.1 (C), 144.6 (CH), 139.2 (C), 138.7 (CH), 138.1 (CH), 137.4 (CH), 136.9 (CH), 135.6 (C), 133.3 (CH), 132.1 (C), 131.4 (CH), 131.2 (CH), 131.0 (C), 130.6 (C), 130.4 (C), 129.2 (CH), 123.1 (CH), 118.1 (CH), 115.4 (CH), 115.3 (CH), 55.2 ($CH_3$).

MS (ESI): *m*/*z* (%) = 448 [(M + H), 100].

Anal. Calcd for $C_{27}H_{21}N_5O_2$: C, 72.47; H, 4.73; N, 15.65. Found: C, 72.43; H, 4.74; N, 15.68.

**_N_-(3-Chlorophenyl)-_N′_-(2,3-diphenylpyrido[3,4-*b*]pyrazin-8-yl)urea (15d)**
Yellow powder; yield: 131 mg (58%, method 6); mp 238–239 °C; $R_f$ = 0.79 ($CH_2Cl_2$–EtOH, 9:1).

IR (KBr): 3228, 1687, 1595, 1539 $cm^{-1}$.

$^1$H NMR (400 MHz, DMSO-$d_6$): δ = 10.22 (br s, 1 H), 9.45 (br s, 1 H), 9.70 (s, 1 H), 9.22 (s, 1 H), 7.86 (s, 1 H), 7.66–7.62 (m, 2 H), 7.56–7.36 (m, 10 H), 7.14–7.10 (m, 1 H).

$^{13}$C NMR (100 MHz, DMSO-$d_6$): δ = 160.8 (C), 159.5 (C), 151.2 (C), 144.9 (CH), 139.1 (C), 138.6 (CH), 137.9 (CH), 137.2 (CH), 136.8 (CH), 135.4 (C), 133.1 (CH), 132.3 (C), 131.3 (CH), 131.1 (CH), 131.0 (C), 130.5 (C), 130.2 (C), 129.4 (CH), 123.9 (CH), 118.6 (CH), 117.3 (CH), 117.1 (CH).

MS (ESI): *m*/*z* (%) = 452 [(M + H), 100], 454 [(M + H) + 2, 40]

Anal. Calcd for $C_{26}H_{18}ClN_5O$: C, 69.10; H, 4.01; N, 15.50. Found: C, 69.14; H, 4.02; N, 15.45.

**_N_-[4-Chloro-3-(trifluoromethyl)phenyl]-_N′_-(2,3-diphenylpyrido[3,4-*b*]pyrazin-8-yl)urea (15e)**
Yellow powder; yield: 135 mg (52%, method 6); mp > 250 °C; $R_f$ = 0.71 ($CH_2Cl_2$–EtOH, 9:1).

IR (KBr): 3237, 1676, 1535 $cm^{-1}$.

$^1$H NMR (400 MHz, DMSO-$d_6$): δ = 10.45 (br s, 1 H), 9.69 (s, 1 H), 9.42 (br s, 1 H), 9.23 (s, 1 H), 8.17 (d, *J* = 1.9 Hz, 1 H), 7.79–7.42 (m, 12 H).

$^{13}$C NMR (100 MHz, DMSO-$d_6$): δ = 161.4 (C), 154.9 (C), 154.6 (C), 151.0 (C), 144.6 (CH), 138.0 (C), 137.2 (C), 137.1 (C), 134.2 (C), 133.0 (C), 132.3 (CH), 131.3 (CH), 129.9 (C), 129.2 (CH), 128.9 (CH), 128.7 (CH), 128.4 (CH), 127.3 (CH), 127.2 (CH), 122.1 (CH), 118.4 (C).

MS (ESI): *m*/*z* (%) = 520 [(M + H), 100], 522 [(M + H) + 2, 40].

Anal. Calcd for $C_{27}H_{17}ClF_3N_5O$: C, 62.37; H, 3.30; N, 13.47. Found: C, 62.32; H, 3.32; N, 13.55.

**_N_-[2,3-Bis(4-methoxyphenyl)pyrido[3,4-*b*]pyrazin-8-yl]-_N′_-phenylurea (15f)**
Yellow powder; yield: 127 mg (53%, method 6); mp 225–226 °C; $R_f$ = 0.76 ($CH_2Cl_2$–EtOH, 9:1).

IR (KBr): 3225, 1663, 1544, 1213 $cm^{-1}$.

$^1$H NMR (400 MHz, DMSO-$d_6$): δ = 9.99 (br s, 1 H), 9.65 (s, 1 H), 9.31 (br s, 1 H), 9.12 (s, 1 H), 7.65–7. 50 (m, 6 H), 7.37 (t, *J* = 7.9 Hz, 2 H), 7.09–6.98 (m, 5 H), 3.86 (s, 3 H), 3.84 (s, 3 H).

$^{13}$C NMR (100 MHz, DMSO-$d_6$): δ = 160.3 (C), 160.0 (C), 154.9 (C), 154.7 (C), 151.9 (C), 144.7 (CH), 139.2 (C), 134.8 (C), 133.4 (CH), 132.9 (C), 131.6 (CH), 131.1 (CH), 131.0 (C), 130.5 (C), 130.3 (C), 128.8 (CH), 122.2 (CH), 118.3 (CH), 113.6 (CH), 113.6 (CH), 55.2 ($CH_3$), 55.1 ($CH_3$).

MS (ESI): *m*/*z* (%) = 478 [(M + H), 100].

Anal. Calcd for $C_{28}H_{23}N_5O_3$: C, 70.43; H, 4.85; N, 14.67. Found: C, 70.57; H, 4.83; N, 14.61.

**_N_-(2,3-Diphenylpyrido[3,4-*b*]pyrazin-8-yl)-_N′_-ethylthiourea (15g)**
Yellow powder; yield: 194 mg (63%, method 7); mp 176–177 °C; $R_f$ = 0.70 ($CH_2Cl_2$–EtOH, 9:1).

IR (KBr): 3267, 1544, 1236 $cm^{-1}$.

$^1$H NMR (400 MHz, DMSO-$d_6$): δ = 9.90 (br s, 1 H), 9.87 (s, 1 H), 9.30 (s, 1 H), 8.95 (br s, 1 H), 7.63–7.42 (m, 10 H), 3.54–3.59 (m, 2 H), 1.21 (t, *J* = 7.0 Hz, 3 H).

$^{13}$C NMR (100 MHz, DMSO-$d_6$): δ = 180.2 (C), 156.1 (C), 155.5 (C), 147.0 (CH), 138.6 (CH), 138.3 (C), 138.1 (C), 135.7 (C), 135.4 (C), 131.4 (C), 130.3 (CH), 130.0 (CH), 129.9 (CH), 129.8 (CH), 129.5 (CH), 128.4 (CH), 128.3 (CH), 55.1 ($CH_2$), 14.0 ($CH_3$).

MS (ESI): *m*/*z* (%) = 386 [(M + H), 100].

Anal. Calcd for $C_{22}H_{19}N_5S$: C, 68.55; H, 4.97; N, 18.17. Found: C, 68.52; H, 4.95; N, 18.19.

**_N_-[2,3-Bis(4-methoxyphenyl)pyrido[3,4-*b*]pyrazin-8-yl]-_N′_-ethylthiourea (15h)**

Yellow powder; yield: 167 mg (75%, method 7); mp 124–125 °C; $R_f$ = 0.67 ($CH_2Cl_2$–EtOH, 9:1).

IR (KBr): 3215, 1623, 1531, 1219 cm$^{-1}$.

$^1$H NMR (400 MHz, DMSO-$d_6$): δ = 9.81 (br s, 2 H), 9.21 (s, 1 H), 8.91 (br s, 1 H), 7.61 (d, *J* = 8.9 Hz, 2 H), 7.52 (d, *J* = 8.9 Hz, 2 H), 6.98–7.04 (m, 4 H), 3.84 (s, 3 H), 3.83 (s, 3 H), 3.61–3.56 (m, 2 H), 1.21 (t, *J* = 7.3 Hz, 3 H).

$^{13}$C NMR (100 MHz, DMSO-$d_6$): δ = 180.2 (C), 160.7 (C), 160.3 (C), 155.4 (C), 154.8 (C), 147.0 (CH), 138.6 (CH), 135.4 (C), 135.2 (C), 131.9 (CH), 131.4 (CH), 131.0 (C), 130.7 (C), 130.5 (C), 113.9 (CH), 55.5 ($CH_3$), 55.4 ($CH_3$), 39.1 ($CH_2$), 14.1 ($CH_3$).

MS (ESI): *m*/*z* (%) = 446 [(M + H), 100].

Anal. Calcd for $C_{24}H_{23}N_5O_2S$: C, 64.70; H, 5.20; N, 15.72. Found: C, 64.81; H, 5.17; N, 15.68.

**_N_-(2,3-Diphenylpyrido[3,4-*b*]pyrazin-8-yl)-_N_,_N′_-diethyldicarbonimidic Diamide (15i)**

Yellow powder; yield: 75 mg (34%, method 6); mp 214–215 °C; $R_f$ = 0.77 ($CH_2Cl_2$–EtOH, 9:1).

IR (KBr): 3240, 1697 cm$^{-1}$.

$^1$H NMR (400 MHz, DMSO-$d_6$): δ = 13.31 (s, 1 H, NH), 9.69 (s, 1 H), 9.23 (s, 1 H), 7.98–7.75 (m, 10 H and NH), 3.92–3.88 (m, 2 H), 3.34–3.27 (m, 2 H), 1.26–1.18 (m, 6 H).

$^{13}$C NMR (100 MHz, DMSO-$d_6$): δ = 156.1 (C), 155.1 (C), 154.9 (C), 152.2 (C), 145.8 (CH), 138.3 (C), 137.4 (C), 134.8 (C), 134.2 (CH), 133.7 (C), 130.9 (C), 130.2 (CH), 129.9 (CH), 129.6 (CH), 129.3 (CH), 128.3 (CH), 128.0 (CH), 35.3 ($CH_2$), 29.0 ($CH_2$), 14.7 ($CH_3$), 13.9 ($CH_3$).

MS (ESI): *m*/*z* (%) = 441 [(M + H), 100].

Anal. Calcd for $C_{25}H_{24}N_6O_2$: C, 68.17; H, 5.49; N, 19.08. Found: C, 68.02; H, 5.50; N, 19.12.

**Amides 16a–c from 11a,b; General Procedure**

To a soln of **11a** or **11b** (0.8 mmol) in MeCN (20 mL) was added $Cs_2CO_3$ (0.9 mmol) and an acid chloride (0.9 mmol) and the mixture was heated at reflux until the reaction was complete (monitored by TLC). The resulting soln was filtered and the solvent was removed under reduced pressure. The crude product was purified by column chromatography ($CH_2Cl_2$–EtOH, from 10:0 to 9:1) to give the desired compounds.

**_N_-(2,3-Diphenylpyrido[3,4-*b*]pyrazin-8-yl)acetamide (16a)**

Beige powder; yield: 204 mg (75%); mp 230–231 °C; $R_f$ = 0.69 ($CH_2Cl_2$–EtOH, 9:1).

IR (KBr): 3313, 1687, 1518 cm$^{-1}$.

$^1$H NMR (400 MHz, DMSO-$d_6$): δ = 10.14 (br s, 1 H), 9.62 (s, 1 H), 9.30 (s, 1 H), 7.70–7.66 (m, 2 H), 7.57–7.53 (m, 2 H), 7.50–7.40 (m, 6 H), 2.35 (s, 3 H).

$^{13}$C NMR (100 MHz, DMSO-$d_6$): δ = 169.3 (CO), 155.8 (C), 155.1 (C), 147.3 (CH), 138.1 (C), 137.8 (C), 136.9 (CH), 135.0 (C), 134.2 (C), 130.2 (CH), 130.0 (C), 129.7 (CH), 129.6 (CH), 129.2 (CH), 128.1 (CH), 128.0 (CH), 24.0 ($CH_3$).

MS (ESI): *m*/*z* (%) = 341 [(M + H), 100].

Anal. Calcd for $C_{21}H_{16}N_4O$: C, 74.10; H, 4.74; N, 16.46. Found: C, 73.92; H, 4.75; N, 16.57.

**_N_-[2,3-Bis(4-methoxyphenyl)pyrido[3,4-*b*]pyrazin-8-yl]acetamide (16b)**

Yellow powder; yield: 279 mg (87%); mp 161–162 °C; $R_f$ = 0.63 ($CH_2Cl_2$–EtOH, 9:1).

IR (KBr): 3329, 1692, 1246 cm$^{-1}$.

$^1$H NMR (400 MHz, DMSO-$d_6$): δ = 10.06 (br s, 1 H), 9.56 (s, 1 H), 9.22 (s, 1 H), 7.69 (d, *J* = 8.6 Hz, 2 H), 7.53 (d, *J* = 8.6 Hz, 2 H), 7.02 (d, *J* = 8.9 Hz, 4 H), 3.85 (s, 6 H), 2.34 (s, 3 H).

$^{13}$C NMR (100 MHz, DMSO-$d_6$): δ = 169.5 (C), 155.5 (C), 155.1 (C), 147.5 (CH), 139.5 (C), 139.4 (C), 137.9 (C), 137.5 (C), 136.2 (CH), 135.2 (C), 134.6 (C), 130.3 (CH), 130.1 (CH), 129.1 (CH), 113.1 (CH), 113.0 (CH), 55.4 ($CH_3$), 55.3 ($CH_3$), 24.1 ($CH_3$).

MS (ESI): *m*/*z* (%) = 401 [(M + H), 100].

Anal. Calcd for $C_{23}H_{20}N_4O_3$: C, 68.99; H, 5.03; N, 13.99. Found: C, 68.95; H, 5.04; N, 14.01.

**_N_-(2,3-Diphenylpyrido[3,4-*b*]pyrazin-8-yl)-4-methoxybenzamide (16c)**

Brown powder; yield: 270 mg (78%); mp 199–200 °C; $R_f$ = 0.77 ($CH_2Cl_2$–EtOH, 9:1).

IR (KBr): 3296, 1675, 1532, 1236 cm$^{-1}$.

$^1$H NMR (400 MHz, DMSO-$d_6$): δ = 10.36 (br s, 1 H), 9.60 (s, 1 H), 9.40 (s, 1 H), 8.09 (d, *J* = 8.9 Hz, 2 H), 7.70–7.44 (m, 10 H), 7.18 (d, *J* = 8.9 Hz, 2 H), 3.91 (s, 3 H).

$^{13}$C NMR (100 MHz, DMSO-$d_6$): δ = 168.7 (C), 156.1 (C), 155.3 (C), 152.3 (C), 151.5 (C), 147.5 (CH), 138.6 (C), 137.3 (C), 137.0 (CH), 135.3 (C), 134.1 (C), 131.5 (CH), 131.3 (CH), 130.4 (CH), 130.3 (C), 129.6 (CH), 129.4 (CH), 129.1 (CH), 128.3 (CH), 128.1 (CH), 114.1 (CH), 113.9 (CH), 55.3 ($CH_3$).

MS (ESI): *m*/*z* (%) = 433 [(M + H), 100].

Anal. Calcd for $C_{27}H_{20}N_4O_2$: C, 74.98; H, 4.66; N, 12.95. Found: C, 75.07; H, 4.67; N, 12.88.

**3-Amino-4-bromo-2-nitropyridine (18)**

To a soln of 3-amino-2-nitropyridine (**17**, 500 mg, 3.6 mmol) in glacial AcOH (5 mL) was added KOAc (353 mg, 3.6 mmol) and the mixture was stirred at r.t. for 1 h. $Br_2$ (180 μL, 3.6 mmol) was then added dropwise. The mixture was stirred at r.t. overnight and the precipitate was filtered off to give **18** (744 mg, 95%) as a yellow powder; mp 217–218 °C; $R_f$ = 0.70 ($CH_2Cl_2$–EtOH, 9:1).

IR (KBr): 3311, 1637, 1572, 1464, 1332 cm$^{-1}$.

$^1$H NMR (400 MHz, DMSO-$d_6$): δ = 7.69 (d, *J* = 8.8 Hz, 1 H), 7.62 (br s, 2 H), 7.52 (d, *J* = 8.8 Hz, 1 H).

$^{13}$C NMR (100 MHz, DMSO-$d_6$): δ = 149.6 (CH), 146.7 (CH), 146.3 (C), 128.6 (C), 110.2 (C).

MS (ESI): *m*/*z* (%) = 218 [(M + H), 100], 220 [(M + H) + 2, 100].

Anal. Calcd for $C_5H_4BrN_3O_2$: C, 27.55; H, 1.85; N, 19.27. Found: C, 27.41; H, 1.84; N, 19.32.

**2,3-Diamino-4-bromopyridine (19)**

A soln of **18** (200 mg, 0.9 mmol) and $SnCl_2$ (872 mg, 4.6 mmol) in a mixture of EtOH (5 mL) and $H_2O$ (1 mL) was refluxed for 2 h. After cooling to r.t., NaOH soln was added until the mixture was basic. The aqueous layer was extracted with $CH_2Cl_2$ and dried ($Na_2SO_4$), and the solvent was removed under reduced pressure to provide **19** (113 mg, 67%) as a brown powder; mp 154–155 °C; $R_f$ = 0.48 ($CH_2Cl_2$–EtOH, 9:1).

IR (KBr): 3241, 1637 $cm^{-1}$.

$^1H$ NMR (400 MHz, DMSO-$d_6$): δ = 6.65 (d, *J* = 7.6 Hz, 1 H), 6.51 (d, *J* = 7.6 Hz, 1 H), 5.84 (br s, 2 H).

$^{13}C$ NMR (100 MHz, DMSO-$d_6$): δ = 148.8 (C), 129.3 (C), 123.8 (C), 120.7 (CH), 114.8 (CH).

MS (ESI): *m*/*z* (%): 188 [(M + H), 100], 190 [(M + H) + 2, 100].

Anal. Calcd for $C_5H_6BrN_3$: C, 31.94; H, 3.22; N, 22.35. Found: C, 31.90; H, 3.20; N, 22.39.

**8-Bromo-2,3-diphenylpyrido[2,3-*b*]pyrazine (20a); Typical Procedure**

*Method 8*: A soln of **19** (500 mg, 2.7 mmol) in dioxane (5 mL) was added benzil (**2a**, 559 mg, 2.7 mmol). The resulting mixture was heated at reflux for 5 d. The mixture was quenched with $H_2O$, the aqueous layer was extracted with $CH_2Cl_2$, the combined organic extracts were dried ($Na_2SO_4$), and the solvents were removed under reduced pressure to give **20a** (733 mg, 75%) as a beige powder.

*Method 9*: A mixture of **19** (500 mg, 2.7 mmol) and benzil (**2a**, 559 mg, 2.7 mmol) in MeOH (27 mL) and AcOH (3 mL) was heated under microwave irradiation (45 W) at 75 °C for 40 min. The solvents were evaporated under reduced pressure and the residue was taken into $CH_2Cl_2$. The organic layer was washed with $H_2O$, separated, and dried ($Na_2SO_4$) and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (silica gel, $CH_2Cl_2$) to give **20a** (645 mg, 66%) as a beige powder; mp 164–165 °C; $R_f$ = 0.83 ($CH_2Cl_2$–EtOH, 9:1).

IR (KBr): 1592, 815 $cm^{-1}$.

$^1H$ NMR (400 MHz, DMSO-$d_6$): δ = 8.58 (d, *J* = 8.9 Hz, 1 H), 8.12 (d, *J* = 8.9 Hz, 1 H), 7.55–7.38 (m, 10 H).

$^{13}C$ NMR (100 MHz, DMSO-$d_6$): δ = 156.6 (C), 154.7 (C), 149.1 (C), 144.8 (C), 140.9 (CH), 138.2 (C), 138.0 (C), 135.4 (C), 130.8 (CH), 130.0 (CH), 129.9 (CH), 129.8 (CH), 129.7 (CH), 129.5 (CH), 128.3 (CH).

MS (ESI): *m*/*z* (%) = 362 [(M + H), 100], 364 [(M + H) + 2, 100].

Anal. Calcd for $C_{19}H_{12}BrN_3$: C, 63.00; H, 3.34; N, 11.60. Found: C, 63.15; H, 3.37; N, 11.51.

**8-Bromo-2,3-bis(4-methoxyphenyl)pyrido[2,3-*b*]pyrazine (20b)**

Beige powder; yield: 855 mg (75%, method 8); yield: 798 mg (70%, method 9); mp 221–222 °C; $R_f$ = 0.85 ($CH_2Cl_2$–EtOH, 9:1).

IR (KBr): 1600, 830 $cm^{-1}$.

$^1H$ NMR (400 MHz, DMSO-$d_6$): δ = 8.50 (d, *J* = 8.6 Hz, 1 H), 8.05 (d, *J* = 8.6 Hz, 1 H), 7.53 (t, *J* = 8.8 Hz, 4 H), 7.00 (dd, *J* = 8.8, 1.8 Hz, 4 H), 3.84 (s, 3 H), 3.83 (s, 3 H).

$^{13}C$ NMR (100 MHz, DMSO-$d_6$): δ = 160.6 (C), 160.4 (C), 156.1 (C), 154.2 (C), 144.2 (C), 140.6 (CH), 131.6 (CH), 131.4 (CH), 130.6 (C), 130.4 (C), 130.3 (CH), 113.9 (CH), 55.5 ($CH_3$).

MS (ESI): *m*/*z* (%) = 422 [(M + H), 100], 424 [(M + H) + 2, 100].

Calcd for $C_{21}H_{16}BrN_3O_2$: C, 59.73; H, 3.82; N, 9.95. Found: C, 59.68; H, 3.81; N, 10.02.

**8-Azido-2,3-diphenylpyrido[2,3-*b*]pyrazine (21a); Typical Procedure**

A mixture of **20a** (1.8 g, 5.0 mmol) and $NaN_3$ (840 mg, 12.9 mmol) in DMSO (50 mL) was refluxed for 1 h. The mixture was then allowed to warm to r.t. and it was taken up with EtOAc. The organic layer was washed with $H_2O$, separated, and dried ($Na_2SO_4$) and the solvents were removed under reduced pressure to yield **21a** (1.5 g, 92%) as a yellow powder; mp 188–189 °C; $R_f$ = 0.73 ($CH_2Cl_2$–EtOH, 9:1).

IR (KBr): 1594, 1354 $cm^{-1}$.

$^1H$ NMR (400 MHz, DMSO-$d_6$): δ = 8.52 (d, *J* = 9.4 Hz, 1 H), 8.47 (d, *J* = 9.4 Hz, 1 H), 7.65–7.46 (m, 10 H).

$^{13}C$ NMR (100 MHz, DMSO-$d_6$): δ = 154.7 (C), 153.3 (C), 149.8 (C), 138.4 (C), 137.8 (C), 137.1 (C), 135.2 (C), 134.8 (CH), 130.8 (CH), 130.6 (CH), 130.5 (CH), 130.2 (CH), 129.3 (CH), 129.2 (CH), 118.2 (CH).

MS (ESI): *m*/*z* (%) = 325 [(M + H), 100].

Anal. Calcd for $C_{19}H_{12}N_6$: C, 70.36; H, 3.73; N, 25.91. Found: C, 70.51; H, 3.71; N, 25.78.

**8-Azido-2,3-bis(4-methoxyphenyl)pyrido[2,3-*b*]pyrazine (21b)**

Yellow powder; yield: 1.9 g (100%); mp 191–192 °C; $R_f$ = 0.69 ($CH_2Cl_2$–EtOH, 9:1).

IR (KBr): 1246, 1174 $cm^{-1}$.

$^1H$ NMR (400 MHz, DMSO-$d_6$): δ = 8.44 (d, *J* = 9.4 Hz, 1 H), 8.40 (d, *J* = 9.4 Hz, 1 H), 7.62 (d, *J* = 8.8 Hz, 2 H), 7.55 (d, *J* = 8.8 Hz, 2 H), 7.08–7.02 (m, 4 H), 3.86 (s, 3 H), 3.84 (s, 3 H).

$^{13}C$ NMR (100 MHz, DMSO-$d_6$): δ = 160.6 (C), 160.1 (C), 153.3 (C), 152.0 (C), 148.8 (C), 135.9 (C), 133.6 (C), 131.5 (CH), 131.1 (CH), 130.0 (C), 129.4 (C), 116.6 (CH), 114.0 (CH), 113.9 (CH), 55.3 ($CH_3$), 55.2 ($CH_3$).

MS (ESI): *m*/*z* (%) = 385 [(M + H), 100].

Anal. Calcd for $C_{21}H_{16}N_6O_2$: C, 65.62; H, 4.20; N, 21.86. Found: C, 65.48; H, 4.23; N, 22.01.

**8-Amino-2,3-diphenylpyrido[2,3-*b*]pyrazine (22a); Typical Procedure**

A mixture of **21a** (1.3 g, 4.4 mmol) and $Ph_3P$ (1.2 g, 4.8 mmol) in THF (50 mL) was heated at reflux for 24 h. The mixture was cooled to r.t. and poured into $H_2O$. The aqueous layer was extracted with $CH_2Cl_2$, the organic layer was dried ($Na_2SO_4$), and the solvent was evaporated under reduced pressure to give an orange oil. The crude product was dissolved in THF (30 mL) and concd HCl (8 mL) was added. The mixture was stirred at r.t. overnight. $CH_2Cl_2$ (50 mL) was added, the organic layer was washed with $H_2O$ and dried ($Na_2SO_4$) and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (silica gel, $CH_2Cl_2$–EtOH, 100:0 to 95:5) to give **22a** (945 mg, 72%) as a yellow powder; mp 265–266 °C; $R_f$ = 0.50 ($CH_2Cl_2$–EtOH, 9:1).

IR (KBr): 3287, 1630 $cm^{-1}$.

$^1H$ NMR (400 MHz, DMSO-$d_6$): δ = 8.10 (d, *J* = 9.2 Hz, 1 H), 7.48–7.32 (m, 10 H), 7.26 (br s, 2 H), 7.14 (d, *J* = 9.2 Hz, 1 H).

$^{13}C$ NMR (100 MHz, DMSO-$d_6$): δ = 161.2 (C), 157.7 (C), 150.5 (C), 147.5 (C), 139.3 (C), 138.2 (CH), 132.5 (C), 129.9 (CH), 129.8 (CH), 128.8 (CH), 128.3 (CH), 128.2 (CH).

MS (ESI): *m*/*z* (%) = 299 [(M + H), 100].

Anal. Calcd for $C_{19}H_{14}N_4$: C, 76.49; H, 4.73; N, 18.78. Found: C, 76.43; H, 4.74; N, 18.83.

**8-Amino-2,3-bis(4-methoxyphenyl)pyrido[2,3-*b*]pyrazine (22b)**

Yellow powder; yield: 1.0 g (65%); mp 260–261 °C; $R_f$ = 0.50 ($CH_2Cl_2$–EtOH, 9:1).

IR (KBr): 1625, 1246 $cm^{-1}$.

$^1H$ NMR (400 MHz, DMSO-$d_6$): δ = 8.04 (d, *J* = 9.0 Hz, 1 H), 7.43 (d, *J* = 8.8 Hz, 2 H), 7.38 (d, *J* = 8.8 Hz, 2 H), 7.15 (br s, 2 H), 7.07–7.49 (d, *J* = 9.0 Hz, 1 H), 6.93 (dd, *J* = 8.8, 2.2 Hz, 4 H), 3.81 (s, 3 H), 3.80 (s, 3 H).

$^{13}C$ NMR (100 MHz, DMSO-$d_6$): δ = 159.1 (C), 157.8 (C), 157.3 (C), 151.2 (C), 148.5 (C), 145.1 (C), 136.0 (CH), 130.1 (C), 129.8 (C), 129.7 (C), 129.3 (CH), 129.0 (CH), 115.4 (CH), 111.7 (CH), 53.4 ($CH_3$), 53.3 ($CH_3$).

MS (ESI): *m*/*z* (%) = 359 [(M + H), 100].

Anal. Calcd for $C_{21}H_{18}N_4O_2$: C, 70.38; H, 5.06; N, 15.63. Found: C, 70.24; H, 5.05; N, 15.69.

**Ureas and Thioureas 23a–f from 22a,b; General Procedure**

*Method 6*: To a soln of **22a**,**b** (0.5 mmol) in DMF (15 mL) was added portionwise 60% NaH in mineral oil (0.6 mmol). The mixture was stirred at r.t. for 30 min and then an isocyanate or an isothiocyanate (0.5 mmol) was added. The reaction was stirred at r.t. until the reaction was complete (monitored by TLC). The crude product was purified by column chromatography (silica gel, $CH_2Cl_2$–EtOH, from 10:0 to 9:1) to give the desired compounds.

*Method 7*: To a soln of **22a**,**b** (0.8 mmol) in pyridine (20 mL) was added an isocyanate or an isothiocyanate (0.8 mmol) and the mixture was heated at reflux until the reaction was complete (monitored by TLC). Pyridine was removed under reduced pressure and the crude product was purified by column chromatography (silica gel, $CH_2Cl_2$–EtOH, from 10:0 to 4:1) to yield the desired compounds.

***N*-(2,3-Diphenylpyrido[2,3-*b*]pyrazin-8-yl)-*N*′-ethylurea (23a)**

Yellow powder; yield: 151 mg (82%, method 7).

IR (KBr): 3219, 2954, 1674, 1543 $cm^{-1}$; mp 257–258 °C; $R_f$ = 0.61 ($CH_2Cl_2$–EtOH, 9:1).

$^1$H NMR (400 MHz, DMSO-$d_6$): δ = 10.19 (br s, 1 H), 9.14 (br s, 1 H), 8.46 (d, *J* = 9.1 Hz, 1 H), 7.75 (d, *J* = 9.1 Hz, 1 H), 7.53–7.38 (m, 10 H), 3.40 (m, 2 H), 1.21 (t, *J* = 7.3 Hz, 3 H).

$^{13}$C NMR (100 MHz, DMSO-$d_6$): δ = 155.7 (CO), 155.2 (C), 154.3 (C), 148.0 (C), 139.6 (CH), 138.7 (C), 138.6 (C), 133.2 (C), 129.9 (CH), 129.8 (CH), 129.1 (CH), 128.8 (CH), 128.3 (CH), 128.2 (CH), 118.6 (CH), 34.2 ($CH_2$), 15.5 ($CH_3$).

MS (ESI): *m*/*z* (%) = 370 [(M + H), 100].

Anal. Calcd for $C_{22}H_{19}N_5O$: C, 71.53; H, 5.18; N, 18.96. Found: C, 71.42; H, 5.17; N, 19.02.

***N*-(2,3-Diphenylpyrido[2,3-*b*]pyrazin-8-yl)-*N*′-phenylurea (23b)**

Beige powder; yield: 115 mg (55%, method 6); mp 255–256 °C; $R_f$ = 0.61 ($CH_2Cl_2$–EtOH, 9:1).

IR (KBr): 3234, 3040, 1682, 1600, 1558 $cm^{-1}$.

$^1$H NMR (400 MHz, DMSO-$d_6$): δ = 11.54 (br s, 1 H), 10.48 (br s, 1 H), 8.55 (d, *J* = 9.2 Hz, 1 H), 7.89 (d, *J* = 9.2 Hz, 1 H), 7.72–7.39 (m, 14 H), 7.13 (t, *J* = 7.4 Hz, 1 H).

$^{13}$C NMR (100 MHz, DMSO-$d_6$): δ = 161.2 (C), 160.0 (C), 151.4 (C), 144.1 (CH), 140.1 (C), 137.2 (CH), 136.9 (CH), 134.6 (C), 132.9 (CH), 132.2 (C), 131.4 (CH), 131.1 (CH), 130.9 (C), 130.7 (C), 130.5 (C), 129.3 (CH), 122.5 (CH), 118.1 (CH), 117.3 (CH), 117.2 (CH).

MS (ESI): *m*/*z* (%) = 418 [(M + H), 100].

Anal. Calcd for $C_{26}H_{19}N_5O$: C, 74.80; H, 4.59; N, 16.78. Found: C, 74.82; H, 4.58; N, 16.79.

***N*-(3-Chlorophenyl)-*N*′-(2,3-diphenylpyrido[2,3-*b*]pyrazin-8-yl)urea (23c)**

Beige powder; yield: 120 mg (53%, method 6); mp 243–244 °C; $R_f$ = 0.64 ($CH_2Cl_2$–EtOH, 9:1).

IR (KBr): 3222, 1692, 1595, 1549 $cm^{-1}$.

$^1$H NMR (400 MHz, DMSO-$d_6$): δ = 11.63 (br s, 1 H), 10.55 (br s, 1 H), 8.56 (d, *J* = 9.2 Hz, 1 H), 7.99–7.89 (m, 3 H), 7.57–7.17 (m, 12 H).

$^{13}$C NMR (100 MHz, DMSO-$d_6$): δ = 155.5 (C), 155.1 (C), 152.0 (C), 151.7 (C), 147.7 (C), 140.2 (CH), 140.2 (C), 138.6 (C), 138.5 (C), 133.6 (C), 133.4 (C), 130.9 (CH), 130.0 (CH), 129.9 (CH), 129.3 (CH), 128.9 (CH), 128.4 (CH), 128.3 (CH), 123.1 (CH), 118.9 (CH), 118.5 (CH), 117.8 (CH).

MS (ESI): *m*/*z* (%) = 404 [(M + H), 100], 406 [(M + H) + 2, 40].

Anal. Calcd for $C_{22}H_{18}ClN_5O$: C, 69.10; H, 4.01; N, 15.50. Found: C, 69.06; H, 4.02; N, 15.47.

***N*-[2,3-Bis(4-methoxyphenyl)pyrido[2,3-*b*]pyrazin-8-yl]-*N*′-ethylurea (23d)**

Yellow powder; yield: 107 mg (50%, method 7); mp 242–243 °C; $R_f$ = 0.64 ($CH_2Cl_2$–EtOH, 9:1).

IR (KBr): 3215, 1689, 1609, 1561 $cm^{-1}$.

$^1$H NMR (400 MHz, DMSO-$d_6$): δ = 10.12 (br s, 1 H), 9.16 (br s, 1 H), 8.40 (d, *J* = 9.0 Hz, 1 H), 7.68 (d, *J* = 9.0 Hz, 1 H), 7.51–7.47 (m, 4 H), 7.00–6.94 (m, 4 H), 3.83 (s, 3 H), 3.82 (s, 3 H) 3.50 (q, *J* = 7.3 Hz, 2 H), 1.20 (t, *J* = 7.3 Hz, 3 H).

$^{13}$C NMR (100 MHz, DMSO-$d_6$): δ = 160.1 (C), 159.8 (C), 155.4 (C), 154.7 (C), 154.4 (C), 150.6 (C), 147.8 (C), 139.5 (CH), 132.8 (C), 131.4 (CH), 131.2 (CH), 131.1 (C), 131.0 (C), 118.0 (CH), 113.9 (CH), 113.8 (CH), 55.4 ($CH_3$), 55.3 ($CH_3$), 34.2 ($CH_2$), 15.5 ($CH_3$).

MS (ESI): *m*/*z* (%) = 430 [(M + H), 100].

Anal. Calcd for $C_{24}H_{23}N_5O_3$: C, 67.12; H, 5.40; N, 16.31. Found: C, 67.02; H, 5.38; N, 16.33.

***N*-[2,3-Bis(4-methoxyphenyl)pyrido[2,3-*b*]pyrazin-8-yl]-*N*′-phenylurea (23e)**

Yellow powder; yield: 122 mg (51%, method 6); mp 244–245 °C; $R_f$ = 0.61 ($CH_2Cl_2$–EtOH, 9:1).

IR (KBr): 3210, 3045, 1687, 1600, 1559 $cm^{-1}$.

$^1$H NMR (400 MHz, DMSO-$d_6$): δ = 11.59 (br s, 1 H), 10.42 (br s, 1 H), 8.49 (d, *J* = 9.2 Hz, 1 H), 7.83 (d, *J* = 9.2 Hz, 1 H), 7.65–7.39 (m, 8 H), 7.14 (t, *J* = 7.3 Hz, 1 H), 7.01 (d, *J* = 8.9 Hz, 2 H), 6.98 (d, *J* = 8.9 Hz, 2 H), 3.84 (s, 3 H), 3.82 (s, 3 H).

$^{13}$C NMR (100 MHz, DMSO-$d_6$): δ = 160.2 (CO), 159.8 (C), 155.0 (C), 152.0 (C), 151.1 (C), 147.6 (C), 140.0 (CH), 138.7 (C), 133.0 (C), 131.5 (CH), 131.2 (CH), 131.0 (CH), 129.3 (CH), 123.4 (CH), 119.5 (CH), 118.0 (CH), 114.0 (CH), 113.8 (CH), 55.4 ($CH_3$), 55.30 ($CH_3$).

MS (ESI): *m*/*z* (%) = 478 [(M + H), 100].

Anal. Calcd for $C_{28}H_{23}N_5O_3$: C, 70.43; H, 4.85; N, 14.67. Found: C, 70.19; H, 4.88; N, 14.73.

***N*-(2,3-Diphenylpyrido[2,3-*b*]pyrazin-8-yl)-*N*′-ethylthiourea (23f)**

Yellow powder; yield: 169 mg (55%, method 7); mp 233–234 °C; $R_f$ = 0.77 ($CH_2Cl_2$–EtOH, 9:1).

IR (KBr): 3412, 3194, 1566, 1524, 1232 $cm^{-1}$.

$^1$H NMR (400 MHz, DMSO-$d_6$): δ = 12.23 (br s, 1 H), 11.31 (br s, 1 H), 8.54 (d, *J* = 8.9 Hz, 1 H), 7.72 (d, *J* = 8.9 Hz, 1 H), 7.74–7.30 (m, 10 H), 3.77 (m, 2 H), 1.32 (t, *J* = 7.3 Hz, 3 H).

$^{13}$C NMR (100 MHz, DMSO-$d_6$): δ = 179.7 (C), 155.6 (C), 155.3 (C), 151.8 (C), 147.2 (C), 140.3 (CH), 138.6 (C), 133.4 (C), 130.0 (CH), 129.9 (CH), 129.3 (CH), 129.0 (CH), 128.4 (CH), 128.3 (CH), 119.2 (CH), 55.2 ($CH_2$), 14.1 ($CH_3$).

MS (ESI): *m*/*z* (%) = 386 [(M + H), 100].

Anal. Calcd for $C_{22}H_{19}N_5S$: C, 68.55; H, 4.97; N, 18.17. Found: C, 68.54; H, 4.96; N, 18.19.

***N*-(2,3-Diphenylpyrido[2,3-*b*]pyrazin-8-yl)-*N*′-phenylthiourea (23g)**

Beige powder; yield: 104 mg (48%, method 6); mp 217–218 °C; $R_f$ = 0.73 ($CH_2Cl_2$–EtOH, 9:1).

IR (KBr): 3227, 1569, 1158 $cm^{-1}$.

$^1H$ NMR (400 MHz, DMSO-$d_6$): δ = 14.36 (br s, 1 H), 11.66 (br s, 1 H), 8.62 (d, *J* = 9.2 Hz, 1 H), 7.84–7.75 (m, 3 H), 7.54–7.32 (m, 13 H).

$^{13}C$ NMR (100 MHz, DMSO-$d_6$): δ = 178.7 (CS), 155.7 (C), 155.1 (C), 152.2 (C), 146.0 (C), 140.7 (CH), 138.6 (C), 138.5 (C), 138.4 (C), 133.5 (C), 129.9 (CH), 129.8 (CH), 129.3 (CH), 129.0 (CH), 128.4 (CH), 128.3 (CH), 126.3 (CH), 124.6 (CH).

MS (ESI): *m*/*z* (%) = 434 [(M + H), 100].

Anal. Calcd for $C_{26}H_{19}N_5S$: C, 72.03; H, 4.42; N, 16.15. Found: C, 72.31; H, 4.43; N, 16.08.

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