A Convenient Synthesis of Novel 2,8-Disubstituted Pyrido[3,4-*b*]pyrazines Possessing Biological Activity

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Abstract: A regioselective synthetic route to 2,8-disubstituted pyrido[3,4-*b*]pyrazines, by initial condensation reaction between suitable diaminopyridines and α-keto aldehydes equivalents, has been developed. Focusing on the functionalization on C-8, 2-aryl-8-bromo- and 8-amino-2-arylpyrido[3,4-*b*]pyrazines have been synthesized. Anilines, amides, and ureas have been introduced at the 8-position from key intermediates. 2,8-Disubstituted pyrido[3,4-*b*]pyrazines thus prepared were found to be of biological interest.

Key words: pyrido[3,4-*b*]pyrazines, pyridines, thioacetals, phenylglyoxals, regioselectivity, condensation

In recent years, some pyrido[2,3-*b*]pyrazines and pyrido[3,4-*b*]pyrazines have been described in the literature as compounds with promising biological properties. In particular, 2,3,8-trisubstituted pyrido[2,3-*b*]pyrazines have been used for the treatment of malignant tumors and other diseases associated to pathological cell proliferations.[1] Other compounds bearing a pyridopyrazine scaffold have been described as vasculostatic agents (by inhibition of Src-family kinases: c-Src and Yes) and as inhibitors of FtsZ polymerization.[2] In addition, pyrido[3,4-*b*]pyrazine derivatives exhibited tubulin polymerization inhibition in the micromolar range.[3]

As part of our continuing efforts to identify new chemical classes of kinase inhibitors, we previously developed an efficient synthetic approach for the preparation of 2,3,8-trisubstituted pyrido[3,4-*b*]pyrazines,[4] but unfortunately they did not exhibit any kinase inhibitory activity (data not shown).

A literature survey revealed that no example of 2,8-disubstituted pyrido[3,4-*b*]pyrazines targeting kinase pathway was described. To our knowledge, only a few papers have reported on the preparation of 2- or 2,8-disubstituted pyrido[3,4-*b*]pyrazines.[5–9] Thus, it was decided to synthesize new compounds with a pyrido[3,4-*b*]pyrazine scaffold bearing only one aryl group, in position 2, and an urea, an amide or an aniline in position 8, expecting to better interact with the target protein.

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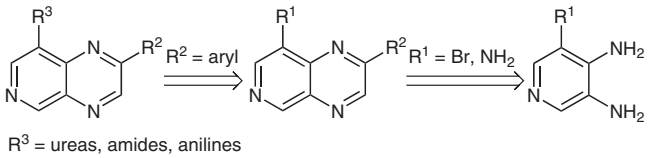
In this paper, we present a regioselective synthetic route to 2,8-disubstituted pyrido[3,4-*b*]pyrazines obtained by initial condensation reaction between suitable diaminopyridines and α-keto aldehyde equivalents (Scheme 1).



Scheme 1 Structures of synthesized 2,8-disubstituted pyrido[3,4-*b*]pyrazines

Our synthetic strategy was to functionalize directly 2- and 8-positions of the pyrido[3,4-*b*]pyrazine scaffold by ring-closing reaction. We envisioned to prepare our key intermediates, 2-aryl-8-bromo- and then 8-amino-2-arylpyrido[3,4-*b*]pyrazines by an initial condensation reaction between 3,4-diamino-5-bromopyridine and an α-dioxo partner.

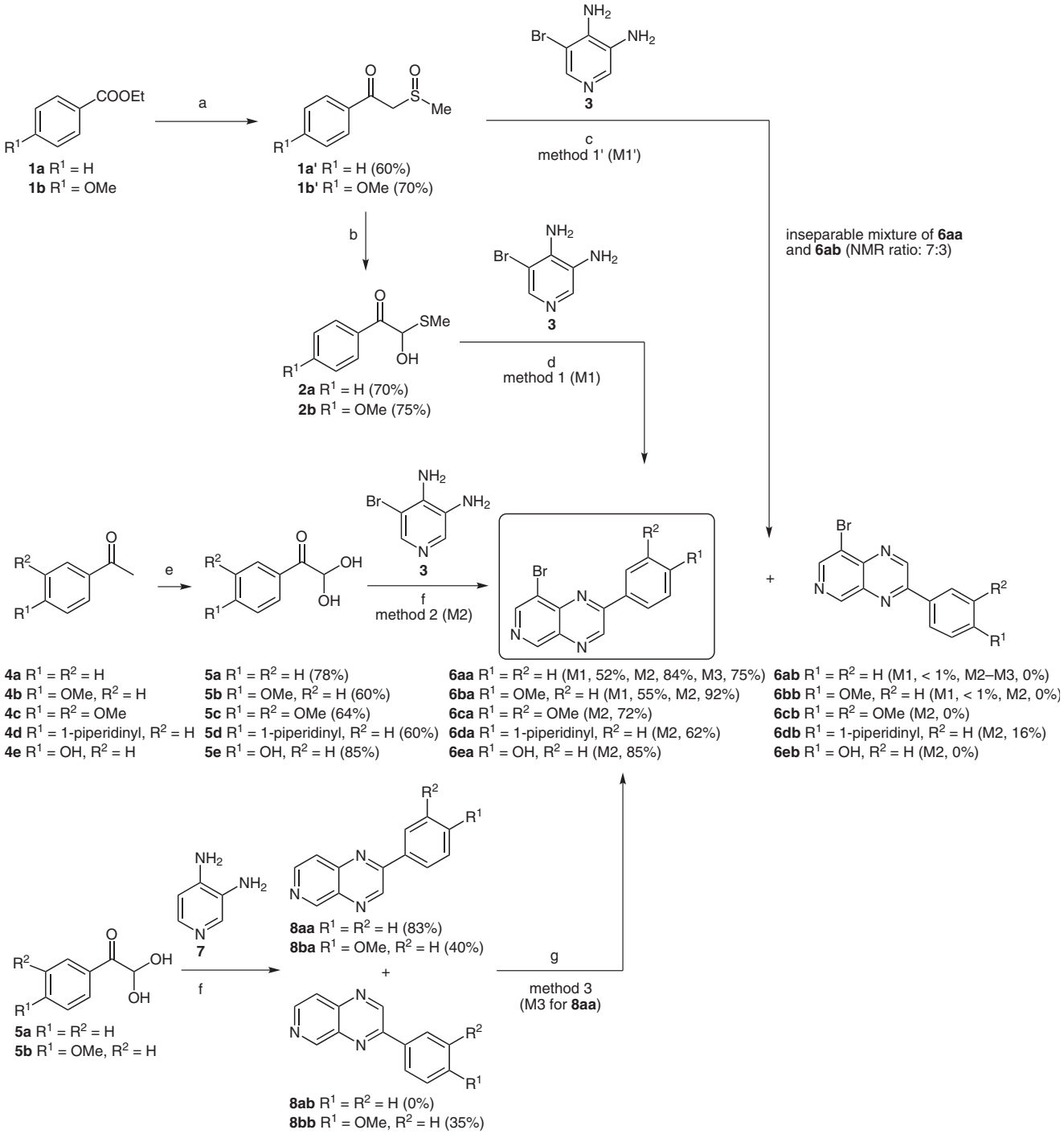
β-Oxosulfoxides or corresponding hemithioacetals were first used as 1,2-diketone equivalents.[6,10] The reaction was carried out in the past with 3,4-diaminopyridine and 2-aryl-2-oxoethyl methyl sulfoxides in a mixture of benzene and acetic acid to give selectively 2-arylpyrido[3,4-*b*]pyrazines.[6] This synthetic approach was applied to prepare 2-aryl-8-bromopyrido[3,4-*b*]pyrazines by reaction with 3,4-diamino-5-bromopyridine (**3**), which was obtained in three steps from commercially available 4-aminopyridine as previously described.[4]

β-Oxosulfoxides were synthesized by a modified Corey and Chaykovsky method,[11–13] using sodium hydride in dimethyl sulfoxide in the presence of a suitable ethyl benzoate **1a**,**b**, as depicted in Scheme 2. The corresponding hemithioacetals **2a**,**b** were prepared by acidic hydrolysis of β-oxosulfoxides **1a′**,**b′** via a Pummerer rearrangement.[12,13] Reaction of 2-phenyl-2-oxoethyl methyl sulfoxide (**1a′**) with 3,4-diamino-5-bromopyridine (**3**) in benzene containing few drops of acetic acid (method M1′) produced a mixture of two regioisomers, 8-bromo-2-phenylpyrido[3,4-*b*]pyrazine (**6aa**) and 8-bromo-3-phenylpyrido[3,4-*b*]pyrazine (**6ab**) in 55% yield (NMR ratio: 7:3).

The mixture was unfortunately inseparable by column chromatography.

In order to try to develop a regioselective access route to 2-aryl-8-bromopyrido[3,4-*b*]pyrazines, the reaction of 3,4-diamino-5-bromopyridine (**3**) with hemithioacetals **2a**,**b** that behave as 1,2-diketones was next explored. This reaction was carried out in refluxing acetic acid, in the presence of sodium acetate (method 1, Scheme 2), to afford regioselectively 2-aryl-8-bromopyrido[3,4-*b*]pyrazines **6aa**–**6ba** in moderate yields (52–55%).

The synthesis of our target compounds by the reaction between 3,4-diamino-5-bromopyridine (**3**) and various substituted phenylglyoxals was next examined. Interestingly, phenylglyoxals could be obtained easily in one step by oxidation of the corresponding acetophenones; and many acetophenones with a large variety of substituents are commercially available. Phenylglyoxal monohydrates **5a**–**e** were prepared by oxidation of corresponding acetophenones **4a**–**e** using selenium dioxide in 1,4-dioxane–water mixture in good yields as depicted in Scheme 2.[14–16]



Scheme 2 Preparation of 2-aryl-8-bromopyrido[3,4-*b*]pyrazines **6aa**–**ea**. *Reagents and conditions*: (a) NaH, DMSO, 0 °C to r.t.; (b) DMSO, H_2O, HCl, r.t.; (c) benzene, AcOH, reflux; (d) NaOAc, AcOH, reflux; (e) SeO_2, 1,4-dioxane, reflux, then H_2O, reflux; (f) 1,4-dioxane, reflux; (g) Br_2, AcOH, r.t.

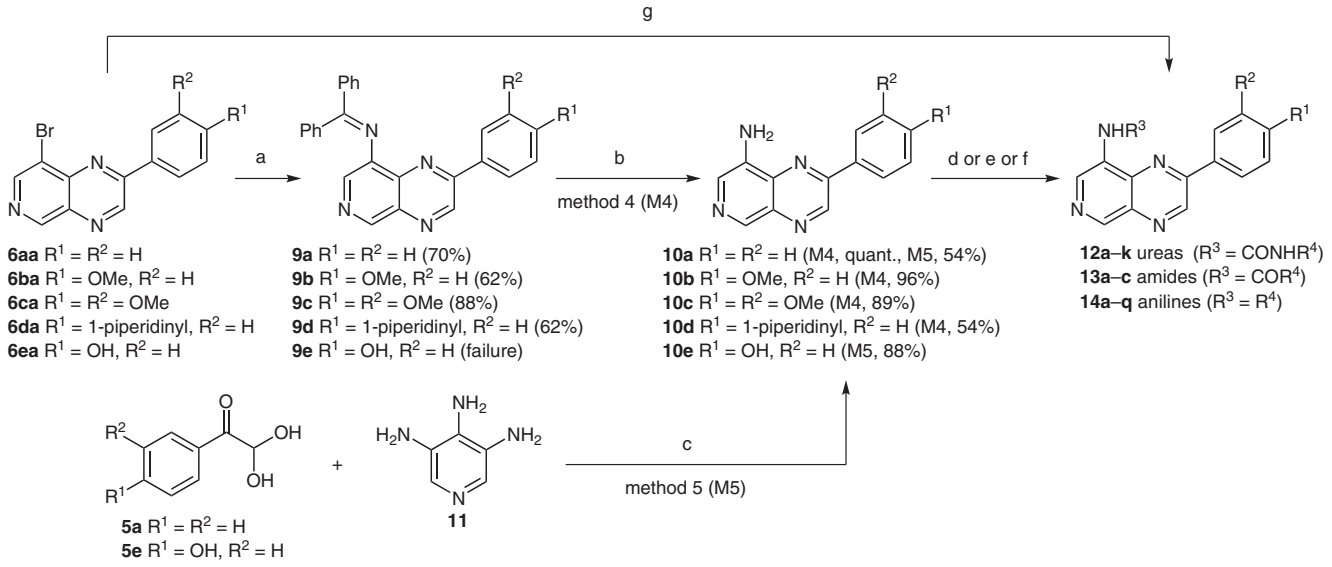
Reaction of 3,4-diamino-5-bromopyridine (**3**) with phenylglyoxals **5a–e** in refluxing 1,4-dioxane led to the desired regioisomers, 2-aryl-8-bromopyrido[3,4-*b*]pyrazines **6aa–ea** in very good yields (method 2, Scheme 2), except with 4-(piperidin-1-yl)phenylglyoxal (**5d**), which afforded a mixture of two regioisomers, 8-bromo-2-[4-(piperidin-1-yl)phenyl]pyrido[3,4-*b*]pyrazine (**6da**) and 8-bromo-3-[4-(piperidin-1-yl)phenyl]pyrido[3,4-*b*]pyrazine (**6db**) in 62% and 16% yield, respectively. In this last case, the two compounds were easily separated by column chromatography unlike the phenyl analogues **6aa** and **6ab**.

The regioselective formation of 2-substituted pyrido[3,4-*b*]pyrazines is obvious since the more nucleophilic 3-amino group of compound **3** attacks the more electrophilic formyl function of phenylglyoxals **5a–e** before the cyclization step.

In addition, reaction of phenylglyoxal (**5a**) with commercially available 3,4-diaminopyridine (**7**) under the same conditions yielded exclusively the previously described[6] 2-phenylpyrido[3,4-*b*]pyrazine (**8aa**), which could be brominated using bromine in acetic acid to give 8-bromo-2-phenylpyrido[3,4-*b*]pyrazine (**6aa**) in 75% yield (method 3, Scheme 2). Nevertheless, this synthetic route applied to substituted 4-methoxyphenylglyoxal (**5b**) gave unfortunately a mixture of two inseparable regioisomers **8ba** and **8bb**. In addition, it would be expected that electron-donating methoxy group would induce the formation of by-products, in particular by bromination on phenyl ring in the second step.

Preparation of 2-aryl-8-aminopyrido[3,4-*b*]pyrazines was accomplished using the same method as previously described for the synthesis of 2,3,8-trisubstituted pyrido[3,4-*b*]pyrazines.[4] 8-Bromo-2-arylpyrido[3,4-*b*]pyrazines **6aa–da** were converted to the corresponding benzophenone imine derivatives via a Buchwald reaction using tris(dibenzylideneacetone)dipalladium [$Pd_2(dba)_3$], 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (BINAP), and *t*-BuONa in toluene to give benzophenone imines **9a–d** in good yields as outlined in Scheme 3. The reaction failed for the hydroxy derivative **9e**, probably because of its poor solubility (starting material was recovered). Subsequent reaction with hydroxylamine hydrochloride in methanol in the presence of sodium acetate led to the desired 8-amino-2-arylpyrido[3,4-*b*]pyrazines **10a–d** in good yields (method 4, Scheme 3). In a second strategy, 8-amino-2-arylpyrido[3,4-*b*]pyrazines **10a** and **10e** were synthesized by the reaction of 3,4,5-triaminopyridine (**11**), prepared in two steps from 4-aminopyridine,[4] with the corresponding phenylglyoxal monohydrates in methanol in the presence of sodium carbonate in moderate to good yields (method 5, Scheme 3).

From our key intermediates, 2-aryl-8-bromopyrido[3,4-*b*]pyrazines **6aa–ea** and 8-amino-2-arylpyrido[3,4-*b*]pyrazines **10a–e**, various chains (ureas, amides, anilines, Table 1) were introduced in position 8 in order to obtain broad functionality for an evaluation of kinase activity for example. Ureas **12a–k** were prepared from 2-aryl-8-aminopyrido[3,4-*b*]pyrazines **10a**,**b** using suitable isocyanates, by reaction with sodium hydride in dimethylformamide for aryl isocyanates, or in pyridine for alkyl isocyanates as depicted in Scheme 3. Unfortunately, ureas were not obtained using these conditions from 8-amino-2-(4-hydroxyphenyl)pyrido[3,4-*b*]pyrazine (**10e**); in these cases no reaction was observed and the starting material was recovered. Amides **13a–c** were synthesized by reaction between 2-aryl-8-aminopyrido[3,4-*b*]pyrazines **10a**,**b** and various acid chlorides in refluxing acetonitrile with acceptable yields. Anilines **14a–q** were prepared by a Buchwald palladium-catalyzed reaction between 2-aryl-8-bromopyrido[3,4-*b*]pyrazines **6aa–ea** and various anilines. Nevertheless, the desired product was not obtained from 8-bromo-2-(4-hydroxyphenyl)pyrido[3,4-



Scheme 3 Functionalization of 2-aryl-8-bromopyrido[3,4-*b*]pyrazines **6aa–ea**. *Reagents and conditions*: (a) benzophenone imine, $Pd_2(dba)_3$, BINAP, *t*-BuONa, toluene, 110 °C; (b) $NH_2OH{\cdot}HCl$, NaOAc, MeOH, 75 °C; (c) Na_2CO_3, MeOH, H_2O, reflux; (d) 1) NaH, DMF, r.t., 2) R^4NCO, r.t.; (e) R^4NCO, pyridine, reflux; (f) R^4COCl, MeCN, reflux; (g) RNH_2, $Pd_2(dba)_3$, BINAP, *t*-BuONa, toluene, 110 °C.

b]pyrazine (**6ea**) as previously observed for the preparation of ureas.

In an initial screening, **12a–k**, **13a–c** and **14a–q** were tested for inhibition of a panel of 8 cancer-related protein kinases.[17] Compounds were examined for their ability to inhibit activation of mitogen-activated protein (MAP) kinase pathway (cRaf-Erk, Erk). An assessment of other kinases, which include receptor tyrosine kinases (KDR,

Table 1 2,8-Disubstituted Pyrido[3,4-*b*]pyrazines **12a–k**, **13a–c** and **14a–q**

Product	R^1	R^2	R^3	R^4	Yield (%)[a,b]
12a	H	H	$CONHR^4$	Et	53
12b	H	H	$CONHR^4$	allyl	51
12c	H	H	$CONHR^4$	Ph	57
12d	H	H	$CONHR^4$	2-ClC_6H_4	58
12e	H	H	$CONHR^4$	2-$MeOC_6H_4$	62
12f	H	H	$CONHR^4$	3-$MeOC_6H_4$	67
12g	H	H	$CONHR^4$	4-$MeOC_6H_4$	66
12h	H	H	$CONHR^4$	3,5-$(MeO)_2C_6H_3$	62
12i	OMe	H	$CONHR^4$	Ph	55
12j	OMe	H	$CONHR^4$	3-$MeOC_6H_4$	64
12k	OMe	H	$CONHR^4$	4-$MeOC_6H_4$	67
13a	H	H	COR^4	Me	66
13b	H	H	COR^4	Ph	71
13c	H	H	COR^4	4-$MeOC_6H_4$	62
14a	H	H	R^4	3-BrC_6H_4	63
14b	H	H	R^4	2-$MeOC_6H_4$	52
14c	H	H	R^4	3-$MeOC_6H_4$	70
14d	H	H	R^4	4-$MeOC_6H_4$	67
14e	H	H	R^4	3-(ethynyl)C_6H_4	56
14f	H	H	R^4	4-(piperidin-1-yl)C_6H_4	55
14g	H	H	R^4	4-(morpholin-4-yl)C_6H_4	56
14h	H	H	R^4	4-HOC_6H_4	21
14i	OMe	H	R^4	3-BrC_6H_4	58
14j	OMe	H	R^4	4-(piperidin-1-yl)C_6H_4	68
14k	OMe	H	R^4	4-(morpholin-4-yl)C_6H_4	67
14l	OMe	H	R^4	2,5-$(MeO)_2C_6H_3$	72
14m	OMe	OMe	R^4	3-$MeOC_6H_4$	77
14n	OMe	OMe	R^4	4-(piperidin-1-yl)C_6H_4	65
14o	OMe	OMe	R^4	4-(morpholin-4-yl)C_6H_4	65
14p	piperidin-1-yl	H	R^4	Ph	59
14q	piperidin-1-yl	H	R^4	3-$MeOC_6H_4$	54

[a] Reaction conditions: R^4NCO, pyridine, reflux (for **12a–b**); NaH, DMF, r.t., 30 min, then R^4NCO, r.t. (for **12c–k**); R^4COCl, MeCN, reflux (for **13a–c**); R^4NH_2, $Pd_2(dba)_3$, BINAP, *t*-BuONa, toluene, 110 °C (for **14a–q**).
[b] Isolated yields.

TrkA), nonreceptor tyrosine kinases (c-Abl, Yes), and serine/threonine kinases (HIPK1, Pim1) was also performed.

While ureas **12a**–**k** and amides **13a**–**c** failed to exhibit significant kinase inhibition, results revealed that some derivatives from 8-arylamino series **14a**–**q** inhibit kinases in micromolar concentration range. Most active compounds were **14b**, **14f**, **14k**, and **14l** (IC_{50} values from 1.4 to 5.3 μM) bearing phenyl or 4-methoxyphenyl in position 2 of pyrido[3,4-*b*]pyrazine ring and 2-methoxyaniline, 4-(piperidin-1-yl)aniline, 4-(morpholin-4-yl)aniline, and 2,5-dimethoxyaniline in position 8, respectively. These compounds did not exhibit any selectivity towards the panel of kinases. Compared to **14f** (IC_{50} values from 2.0 to 2.6 μM), introduction of an oxygen atom in the piperidine ring (morpholine analogue **14g**) was deleterious for the activity. Shifting the position of methoxy group on 8-anilino substituent from ortho (**14b**) to meta (**14c**) or para (**14d**) led to loss of activity. Demethylated analogues **10f** of **14h** remained inactive.

Compound **14f** was the only derivative that showed a beginning of activity on MAP kinase pathway (IC_{50} = 2 μM for cRaf-Erk and Erk) and surprisingly, 4-methoxy analogue **14j** was inactive. In contrast, 4-(morpholin-4-yl)aniline derivative **14k** (IC_{50} values from 2.5 to 5.3 μM) was more active than its unsubstituted counterpart **14g**. We attempted to invert the substituents in positions 2 and 8 of *N*-(4-piperidin-1-ylphenyl)-2-phenylpyrido[3,4-*b*]pyrazin-8-amine (**14f**), but this chemical modification produced only inactive compound **14p**.

In summary, many 2,8-disubstituted pyrido[3,4-*b*]pyrazines, with promising biological activity have been prepared easily from our key intermediates, 2-aryl-8-bromopyrido[3,4-*b*]pyrazines and 8-amino-2-arylpyrido[3,4-*b*]pyrazines. This synthetic approach enabled selective introduction of a large variety of aryl groups in position 2 of the scaffold and also introduction of various chains in position 8 at the end of synthesis due to the presence of bromine atom and amine function.

Our continued efforts to synthesize novel pyrido[3,4-*b*]pyrazines with substituents in position 8 will be described in future publications, in particular 3,8-disubstituted pyrido[3,4-*b*]pyrazine analogues of biological interest.

All reactions were carried out under argon. All reactions were monitored by TLC analysis using Merck silica gel 60F-254 thin-layer plates. Column chromatography was carried out on silica gel Merck 60 (70–230 mesh ASTM). Melting points were determined on a Electrothermal IA 9000 melting point apparatus and are uncorrected. IR spectra were recorded on a Paragon 1000 PC PerkinElmer spectrometer. ^{1}H and ^{13}C NMR spectra were performed in DMSO-d_6 using a Bruker Avance 400 MHz spectrometer. Chemical shifts are reported as δ values relative to TMS as internal standard and coupling constants (*J*) are given in hertz (Hz). Standard abbreviations are used to describe peak patterns. Mass spectra were recorded using an electrospray ionization method with Waters ZQ 2000 spectrometer. Elemental analyses were performed on a Thermo Scientific Elemental Analyzer Flash EA 1112 and were found within ± 0.4% of the theoretical values.

2-Phenyl-2-oxoethyl Methyl Sulfoxide (1a′); Typical Procedure

A solution of NaH at 60% in mineral oil (2.00 g, 50.0 mmol) in DMSO (30 mL) was heated at 70 °C for 1 h. The resulting solution was cooled in an ice bath and ethyl benzoate (**1a**; 3.6 mL, 25.0 mmol) was added dropwise noting that the temperature did not increase after each addition. The reaction mixture was stirred at r.t. overnight and then quenched with H_2O (40 mL). Concd HCl was added to reach pH 1 and the aqueous layer was extracted with CH_2Cl_2 (2 × 30 mL). The combined organic phases were dried (Na_2SO_4) and the solvent was removed under reduced pressure to give **1a′** (2.73 g, 60%) as a yellow powder; mp 84–85 °C (Lit.[11] mp 86–86.5 °C, Lit.[12] mp 85–86 °C).

IR (KBr): 3399, 1695, 1680, 1108, 960 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.09–7.96 (m, 1 H), 7.78–7.51 (m, 3 H), 4.72 (d, *J* = 14.9 Hz, 1 H), 4.63 (d, *J* = 14.9 Hz, 1 H), 2.74 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 193.7 (C), 136.3 (C), 134.2 (CH), 129.0 (CH), 128.9 (CH), 62.0 (CH_2), 38.8 (CH_3).

MS (ESI): *m*/*z* (%) = 183 [(M + H), 100].

Anal. Calcd for $C_9H_{10}O_2S$: C, 59.32; H, 5.53. Found: C, 59.41; H, 5.51.

2-(4-Methoxyphenyl)-2-oxoethyl Methyl Sulfoxide (1b′)

Compound **1b′** was obtained as a white powder; yield: 3.71 g (70%); mp 98–99 °C (Lit.[11] mp 96 °C and 104–105 °C, Lit.[12] mp 101–102 °C).

IR (KBr): 3429, 1684, 1599, 1265, 1168, 1102 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.04 (d, *J* = 8.8 Hz, 2 H), 7.12 (d, *J* = 8.8 Hz, 2 H), 4.63 (d, *J* = 14.6 Hz, 1 H), 4.56 (d, *J* = 14.6 Hz, 1 H), 3.90 (s, 3 H), 2.72 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 191.7 (C), 164.0 (C), 131.4 (CH), 129.3 (CH), 114.2 (CH), 61.7 (CH_2), 55.8 (CH_3), 38.8 (CH_3).

MS (ESI): *m*/*z* (%) = 213 [(M + H), 100].

Anal. Calcd for $C_{10}H_{12}O_3S$: C, 56.58; H, 5.70. Found: C, 56.64; H, 5.67.

2-Hydroxy-2-(methylsulfanyl)-1-phenylethanone (2a); Typical Procedure

A solution of **1a′** (1.00 g, 5.5 mmol) and concd HCl (2.1 mL) in a mixture of H_2O (16 mL) and DMSO (2.1 mL) was stirred at r.t. for 24 h. The reaction mixture was quenched with aq $NaHCO_3$ (30 mL) and extracted with CH_2Cl_2 (2 × 20 mL). The combined organic extracts were dried (Na_2SO_4) and the solvent was removed under reduced pressure to give the desired compound **2a** (700 mg, 70%) as a beige powder; mp 104–105 °C (Lit.[12] mp 106–107 °C).

IR (KBr): 3387, 1674, 1259, 1093, 1071 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.06 (d, *J* = 7.3 Hz, 2 H), 7.67 (t, *J* = 7.3 Hz, 1 H), 7.58–7.51 (m, 2 H), 6.51 (d, *J* = 8.1 Hz, 1 H), 6.40 (d, *J* = 8.1 Hz, 1 H), 1.98 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 192.8 (C), 167.3 (C), 133.3 (CH), 128.5 (CH), 128.4 (CH), 75.0 (CH), 10.2 (CH_3).

MS (ESI): *m*/*z* (%) = 183 [(M + H), 100].

Anal. Calcd for $C_9H_{10}O_2S$: C, 59.32; H, 5.53. Found: C, 59.28; H, 5.54.

2-Hydroxy-1-(4-methoxyphenyl)-2-(methylsulfanyl)ethanone (2b)

Compound **2b** was obtained as a beige powder; yield: 875 mg (75%); mp 91–93 °C (Lit.[12] mp 92–94 °C).

IR (KBr): 3387, 1668, 1599, 1262, 1168, 1068, 969 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 8.05 (d, *J* = 8.9 Hz, 2 H), 7.07 (d, *J* = 8.9 Hz, 2 H), 6.36 (d, *J* = 8.5 Hz, 1 H), 6.33 (d, *J* = 8.5 Hz, 1 H), 3.88 (s, 3 H), 1.98 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 193.3 (C), 164.9 (C), 132.5 (CH), 127.9 (C), 115.4 (CH), 76.5 (CH), 57.1 (CH_3), 12.0 (CH_3).

MS (ESI): *m*/*z* (%) = 213 [(M + H), 100].

Anal. Calcd for $C_{10}H_{12}O_3S$: C, 56.58; H, 5.70. Found: C, 56.61; H, 5.68.

2,2-Dihydroxy-1-phenylethanone (5a); Typical Procedure

To a solution of SeO_2 (9.23 g, 83.2 mmol) in a mixture of 1,4-dioxane (42 mL) and H_2O (2 mL) was added acetophenone (**4a**; 10.00 g, 83.2 mmol). The reaction mixture was heated at reflux for 2 h and after cooling to r.t., filtered on Celite. The solvent was removed under reduced pressure, the residue was dissolved in H_2O (200 mL), and heated at reflux for 5 h. The resulting solution was cooled in an ice bath to give a white precipitate, which was collected by filtration and air-dried to give **5a** (9.87 g, 78%) as a beige powder; mp 74–76 °C (Lit.[15] mp 70–74 °C); R_f = 0.69 (CH_2Cl_2–EtOH, 9:1).

^1H NMR (400 MHz, DMSO-d_6): δ = 8.10 (dd, *J* = 8.2, 1.2 Hz, 2 H), 7.69–7.65 (m, 1 H), 7.56 (d, *J* = 8.2 Hz, 2 H), 6.80 (d, *J* = 7.2 Hz, 2 H), 5.73 (t, *J* = 7.2 Hz, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 196.1 (C), 133.6 (C), 133.2 (CH), 129.3 (CH), 128.4 (CH), 89.1 (CH).

MS (ESI): *m*/*z* (%) = 153 [(M + H), 100].

Anal. Calcd for $C_8H_8O_3$: C, 63.15; H, 5.30. Found: C, 63.03; H, 5.33.

2,2-Dihydroxy-1-(4-methoxyphenyl)ethanone (5b)

White powder; yield: 4.37 g (60%); mp 112–114 °C (Lit.[15] mp 110–114 °C); R_f = 0.66 (CH_2Cl_2–EtOH, 9:1).

^1H NMR (400 MHz, DMSO-d_6): δ = 8.09 (d, *J* = 7.5 Hz, 2 H), 7.08 (d, *J* = 7.5 Hz, 2 H), 6.67 (d, *J* = 7.3 Hz, 2 H), 5.68 (t, *J* = 7.3 Hz, 1 H), 3.88 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 192.0 (C), 163.4 (C), 131.8 (CH), 126.1 (C), 114.1 (CH), 90.6 (CH), 55.5 (CH_3).

MS (ESI): *m*/*z* (%) = 183 [(M + H), 100].

Anal. Calcd for $C_9H_{10}O_4$: C, 59.34; H, 5.53. Found: C, 59.48; H, 5.48.

2,2-Dihydroxy-1-(3,4-dimethoxyphenyl)ethanone (5c)

Red oil; yield: 5.43 g (64%); R_f = 0.67 (CH_2Cl_2–EtOH, 9:1).

^1H NMR (400 MHz, DMSO-d_6): δ = 7.81 (dd, *J* = 8.6, 2.0 Hz, 1 H), 7.58 (d, *J* = 1.9 Hz, 1 H), 7.10 (d, *J* = 8.6 Hz, 1 H), 5.72 (br s, 1 H), 3.88 (s, 3 H), 3.84 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 192.5 (C), 154.2 (C), 149.7 (C), 130.1 (C), 122.1 (CH), 115.2 (CH), 114.0 (CH), 90.8 (CH), 56.5 (CH_3), 56.3 (CH_3).

MS (ESI): *m*/*z* (%) = 213 [(M + H), 100].

Anal. Calcd for $C_{10}H_{12}O_5$: C, 56.60; H, 5.70. Found: C, 56.67; H, 5.69.

2,2-Dihydroxy-1-[4-(piperidin-1-yl)phenyl]ethanone (5d)

Red oil; yield: 5.64 g (60%); R_f = 0.66 (CH_2Cl_2–EtOH, 9:1).

^1H NMR (400 MHz, DMSO-d_6): δ = 7.98–7.91 (m, 2 H), 7.04–6.92 (m, 2 H), 5.96 (br s, 2 H), 5.66 (br s, 1 H), 3.45–3.41, 1.63–1.60 (m, 10 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 192.2 (C), 154.4 (C), 129.7 (CH), 126.3 (C), 114.2 (CH), 90.7 (CH), 52.4 (CH_2), 25.9 (CH_2), 25.5 (CH_2).

MS (ESI): *m*/*z* (%) = 236 [(M + H), 100].

Anal. Calcd for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28; N, 5.95. Found: C, 66.45; H, 7.19; N, 5.93.

2,2-Dihydroxy-1-(4-hydroxyphenyl)ethanone (5e)

Yellow powder; yield: 5.71 g (85%); mp 64–65 °C; R_f = 0.52 (CH_2Cl_2–EtOH, 9:1).

^1H NMR (400 MHz, DMSO-d_6): δ = 10.44 (br s, 1 H), 7.98 (d, *J* = 8.9 Hz, 2 H), 6.88 (d, *J* = 8.9 Hz, 2 H), 6.58 (d, *J* = 7.5 Hz, 2 H), 5.66 (t, *J* = 7.1 Hz, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 192.5 (C), 162.9 (C), 130.2 (CH), 129.4 (C), 115.8 (CH), 90.4 (CH).

MS (ESI): *m*/*z* (%) = 169 [(M + H), 100].

Anal. Calcd for $C_8H_8O_4$: C, 57.14; H, 4.80. Found: C, 56.99; H, 4.84.

8-Bromo-2-phenylpyrido[3,4-*b*]pyrazine (6aa); Typical Procedures

Method 1′ (β-Oxosulfoxide, AcOH, Benzene): A mixture of 3,4-diamino-5-bromopyridine (**3**; 111 mg, 0.6 mmol) and 2-phenyl-2-oxoethyl methyl sulfoxide (**1a′**; 108 mg, 0.6 mmol) in benzene (5 mL) containing few drops of AcOH was refluxed for 8 h. After removal of the solvent, the residue was made basic by addition of ammonia and the aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layers were dried (Na_2SO_4), filtered, and the solvent was removed under reduced pressure to give **6aa** admixed with 8-bromo-3-phenylpyrido[3,4-*b*]pyrazine (**6ab**) (7:3 NMR ratio in 55% yield).

Method 1 (Hemithioacetal, NaOAc, AcOH): To a solution of 3,4-diamino-5-bromopyridine (**3**; 200 mg, 1.1 mmol) in glacial AcOH (6 mL) was added successively NaOAc (194 mg, 1.1 mmol) and 2-hydroxy-2-(methylsulfanyl)-1-phenylethanone (**2a**; 194 mg, 1.1 mmol). The reaction mixture was stirred at r.t. for 30 minutes, then heated at reflux for 4 h (methylmercaptan formed was trapped in a solution of NaOH). The solution was cooled in an ice bath, the precipitate was collected by filtration and washed with *i*-Pr_2O (5 mL) to afford **6aa** (164 mg, 52%) as a beige powder.

Method 2 (Phenylglyoxal Monohydrate, 1,4-Dioxane): A mixture of 3,4-diamino-5-bromopyridine (**3**; 200 mg, 1.1 mmol) and 2,2-dihydroxy-1-phenylethanone (**5a**; 167 mg, 1.1 mmol) in 1,4-dioxane (10 mL) was heated at reflux for 6 h. The reaction mixture was cooled to r.t., and poured into H_2O (10 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL), the combined organic layers were dried (Na_2SO_4) and the solvent was removed under reduced pressure. The residue was triturated with *i*-Pr_2O (5 mL) and then filtered to give **6aa** (264 mg, 84%) as a beige powder.

Method 3 (Br_2, KOAc, AcOH): A mixture of 2-phenylpyrido[3,4-*b*]pyrazine (**8aa**; 400 mg, 1.9 mmol) and KOAc (190 mg, 1.9 mmol) in glacial AcOH (10 mL) was stirred at r.t. for 1 h and then Br_2 (100 μL, 1.9 mmol) was added dropwise. The resulting mixture was stirred at r.t. for 5 h. The reaction was quenched with H_2O (10 mL) and the aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layers were dried (Na_2SO_4) and the solvent was removed under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with CH_2Cl_2 to give **6aa** (408 mg, 75%) as a beige powder; mp 142–143 °C; R_f = 0.66 (CH_2Cl_2–EtOH, 9:1).

IR (KBr): 3411, 1557, 1307, 1183, 972, 770, 686 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 9.87 (s, 1 H), 9.51 (s, 1 H), 9.16 (s, 1 H), 8.52–8.50 (m, 2 H), 7.73–7.70 (m, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 154.5 (C), 152.2 (CH), 147.9 (CH), 145.8 (CH), 141.1 (C), 136.4 (C), 134.0 (C), 131.0 (CH), 128.5 (CH), 127.4 (CH), 118.9 (C).

MS (ESI): *m*/*z* (%) = 286 [(M + H), 100], 288 [(M + H) + 2, 100].

Anal. Calcd for $C_{13}H_8BrN_3$: C, 54.57; H, 2.82; N, 14.69. Found: C, 54.59; H, 2.85; N, 14.67.

8-Bromo-2-(4-methoxyphenyl)pyrido[3,4-*b*]pyrazine (6ba)
Beige powder; yield: 191 mg (55%, method 1); yield: 320 mg (92%, method 2); mp 168–169 °C; R_f = 0.68 (CH_2Cl_2–EtOH, 9:1).

IR (KBr): 3044, 1551, 1312, 975 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.81 (s, 1 H), 9.44 (s, 1 H), 9.11 (s, 1 H), 8.52 (d, *J* = 9.2 Hz, 2 H), 7.25 (d, *J* = 9.2 Hz, 2 H), 3.93 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 162.1 (C), 154.5 (C), 152.4 (CH), 148.2 (CH), 145.9 (CH), 141.7 (C), 136.5 (C), 129.7 (CH), 126.7 (C), 119.1 (C), 114.5 (CH), 55.1 (CH_3).

MS (ESI): *m*/*z* (%) = 316 [(M + H), 100], 318 [(M + H) + 2, 100].

Anal. Calcd for $C_{14}H_{10}BrN_3O$: C, 53.19; H, 3.19; N, 13.29. Found: C, 53.16; H, 3.17; N, 13.31.

8-Bromo-2-(3,4-dimethoxyphenyl)pyrido[3,4-*b*]pyrazine (6ca)
Yellow powder; yield: 274 mg (72%, method 2); mp 172–173 °C; R_f = 0.59 (CH_2Cl_2–EtOH, 9:1).

IR (KBr): 3047, 1554, 1309, 982 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.86 (s, 1 H), 9.44 (s, 1 H), 9.11 (s, 1 H), 8.18 (dd, *J* = 8.5, 1.8 Hz, 1 H), 8.09 (d, *J* = 1.8 Hz, 1 H), 7.27 (d, *J* = 8.5 Hz, 1 H), 3.97 (s, 3 H), 3.93 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 155.0 (C), 152.8 (CH), 152.4 (C), 149.3 (C), 148.6 (CH), 146.4 (CH), 142.0 (C), 137.0 (C), 127.2 (C), 122.2 (CH), 119.5 (C), 112.0 (CH), 110.8 (CH), 55.8 (CH_3), 55.7 (CH_3).

MS (ESI): *m*/*z* (%) = 346 [(M + H), 100], 348 [(M + H) + 2, 100].

Anal. Calcd for $C_{15}H_{12}BrN_3O_2$: C, 52.04; H, 3.49; N, 12.14. Found: C, 51.91; H, 3.51; N, 12.15.

8-Bromo-2-[4-(piperidin-1-yl)phenyl]pyrido[3,4-*b*]pyrazine (6da)
Red powder; yield: 252 mg (62%, method 2); mp 176–178 °C; R_f = 0.48 (CH_2Cl_2–EtOH, 9:1).

IR (KBr): 2929, 1608, 1551, 1521, 1349, 1244, 1199, 1180, 1120, 972, 818 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.73 (s, 1 H), 9.35 (s, 1 H), 9.04 (s, 1 H), 8.40 (d, *J* = 8.9 Hz, 2 H), 7.17 (d, *J* = 8.9 Hz, 2 H), 3.45–3.43, 1.66–1.64 (m, 10 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 155.0 (C), 153.3 (C), 152.4 (CH), 148.5 (CH), 146.2 (CH), 142.4 (C), 136.6 (C), 129.8 (CH), 122.6 (C), 119.2 (C), 114.1 (CH), 47.8 (CH_2), 24.9 (CH_2), 24.0 (CH_2).

MS (ESI): *m*/*z* (%) = 369 [(M + H), 100], 371 [(M + H) + 2, 100].

Anal. Calcd for $C_{18}H_{17}BrN_4$: C, 58.55; H, 4.64; N, 15.17. Found: C, 58.61; H, 4.67; N, 15.11.

8-Bromo-3-[4-(piperidin-1-yl)phenyl]pyrido[3,4-*b*]pyrazine (6db)
Red powder; yield: 65 mg (16%, method 2); mp 201–203 °C; R_f = 0.66 (CH_2Cl_2–EtOH, 9:1).

IR (KBr): 2926, 1550, 1523, 1342, 1237, 1100, 952 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.85 (s, 1 H), 9.40 (s, 1 H), 9.00 (s, 1 H), 8.31 (d, *J* = 8.9 Hz, 2 H), 7.15 (d, *J* = 8.9 Hz, 2 H), 3.45–3.43, 1.66–1.64 (m, 10 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 152.9 (C), 149.6 (C), 148.9 (CH), 148.1 (CH), 144.7 (CH), 141.8 (C), 139.3 (C), 128.4 (CH), 122.7 (C), 121.0 (C), 114.8 (CH), 52.4 (CH_2), 25.9 (CH_2), 25.5 (CH_2).

MS (ESI): *m*/*z* (%) = 369 [(M + H), 100], 371 [(M + H) + 2, 100].

Anal. Calcd for $C_{18}H_{17}BrN_4$: C, 58.55; H, 4.64; N, 15.17. Found: C, 58.64; H, 4.66; N, 15.12.

8-Bromo-2-(4-hydroxyphenyl)pyrido[3,4-*b*]pyrazine (6ea)
Brown powder; yield: 282 mg (85%, method 2); mp 221–223 °C; R_f = 0.69 (CH_2Cl_2–EtOH, 9:1).

IR (KBr): 3363, 1557, 1533, 1307, 1280, 1246, 1168, 1114 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.77 (s, 1 H), 9.43 (s, 1 H), 9.10 (s, 1 H), 8.43 (d, *J* = 8.9 Hz, 2 H), 7.07 (d, *J* = 8.9 Hz, 2 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 161.5 (C), 155.2 (C), 152.6 (CH), 148.6 (CH), 146.2 (CH), 142.1 (C), 136.8 (C), 130.3 (CH), 125.5 (C), 119.4 (C), 116.2 (CH).

MS (ESI): *m*/*z* (%) = 302 [(M + H), 100], 304 [(M + H) + 2, 100].

Anal. Calcd for $C_{13}H_8BrN_3O$: C, 51.68; H, 2.67; N, 13.91. Found: C, 51.75; H, 2.69; N, 13.88.

2-Phenylpyrido[3,4-*b*]pyrazine (8aa)
Compound **8aa** was obtained by the reaction of 3,4-diaminopyridine (**7**) with 2,2-dihydroxy-1-phenylethanone (**5a**) following the procedure described for **6aa**; white powder; yield: 189 mg (83%, method 2); mp 123–124 °C (Lit.[6] mp 125–126 °C); R_f = 0.52 (CH_2Cl_2–EtOH, 9:1).

IR (KBr): 3417, 1557, 1542, 1439, 1394, 1313, 1232, 957, 680 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.78 (s, 1 H), 9.54 (d, *J* = 0.6 Hz, 1 H), 8.89 (d, *J* = 5.8 Hz, 1 H), 8.46–8.41 (m, 2 H), 8.08 (dd, *J* = 5.8, 0.6 Hz, 1 H), 7.69–7.66 (m, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 155.3 (C), 153.3 (CH), 147.0 (CH), 146.1 (CH), 144.3 (C), 135.2 (C), 131.5 (CH), 129.2 (CH), 128.2 (CH), 121.9 (CH).

MS (ESI): *m*/*z* (%) = 208 [(M + H), 100].

Anal. Calcd for $C_{13}H_9N_3$: C, 75.35; H, 4.38; N, 20.28. Found: C, 75.11; H, 4.41; N, 20.48.

***N*-(2-Phenylpyrido[3,4-*b*]pyrazin-8-yl)benzophenone Imine (9a); Typical Procedure**
To a solution of 8-bromo-2-phenylpyrido[3,4-*b*]pyrazine (**6aa**; 944 mg, 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, $2.5\cdot10^{-5}$ mol), BINAP (4 mg, $8.3\cdot10^{-6}$ mol), and *t*-BuONa (446 mg, 4.6 mmol). The reaction mixture was heated at 100 °C for 12 h, cooled to r.t., and then EtOAc (60 mL) was added. The mixture was washed with H_2O (40 mL) and extracted with EtOAc (2 × 30 mL). The combined organic layers were dried (Na_2SO_4) and the solvents were removed under reduced pressure. The crude product was purified by column chromatography on silica gel eluting with CH_2Cl_2–EtOH mixtures (from 10:0 to 9:1) to give the title compound **9a** (893 mg, 70%) as a yellow powder; mp 179–180 °C; R_f = 0.63 (CH_2Cl_2–EtOH, 9:1).

IR (KBr): 3026, 1563, 1512, 1425, 1293, 1255, 1134, 1010, 954 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.69 (s, 1 H), 9.10 (s, 1 H), 8.33 (s, 1 H), 7.90–7.20 (m, 15 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 171.3 (C), 153.7 (C), 147.9 (CH), 145.7 (CH), 143.5 (C), 137.4 (CH), 136.2 (C), 136.1 (C), 135.5 (C), 132.2 (CH), 131.8 (CH), 131.5 (CH), 129.5 (CH), 129.2 (CH), 128.9 (CH), 128.3 (CH), 128.2 (CH), 128.1 (CH), 128.0 (CH).

MS (ESI): *m*/*z* (%) = 387 [(M + H), 100].

Anal. Calcd for $C_{26}H_{18}N_4$: C, 80.81; H, 4.69; N, 14.50. Found: C, 80.89; H, 4.68; N, 14.43.

_N_-[2-(4-Methoxyphenyl)pyrido[3,4-*b*]pyrazin-8-yl]benzophenone Imine (9b)

Yellow powder; yield: 851 mg (62%); mp 77–78 °C; R_f = 0.62 (CH_2Cl_2–EtOH, 9:1).

IR (KBr): 3021, 1553, 1532, 1434, 1285, 1245, 1152, 1023, 972 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.65 (s, 1 H), 9.04 (s, 1 H), 8.33 (d, *J* = 8.9 Hz, 2 H), 8.31 (s, 1 H), 7.84–7.17 (m, 12 H), 3.88 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 171.0 (C), 161.9 (C), 152.9 (C), 147.4 (CH), 145.0 (CH), 143.0 (C), 138.0 (C), 137.1 (CH), 135.8 (C), 135.5 (C), 131.5 (CH), 129.4 (CH), 129.1 (CH), 128.8 (C), 128.5 (CH), 128.0 (CH), 127.8 (CH), 127.5 (C), 114.7 (CH), 55.4 (CH_3).

MS (ESI): *m*/*z* (%) = 417 [(M + H), 100].

Anal. Calcd for $C_{27}H_{20}N_4O$: C, 77.87; H, 4.84; N, 13.45. Found: C, 77.78; H, 4.87; N, 13.49.

_N_-[2-(3,4-Dimethoxyphenyl)pyrido[3,4-*b*]pyrazin-8-yl]benzophenone Imine (9c)

Yellow powder; yield: 1.30 g (88%); mp 81–83 °C; R_f = 0.64 (CH_2Cl_2–EtOH, 9:1).

IR (KBr): 3411, 1557, 1518, 1454, 1283, 1265, 1238, 1144, 1018, 978 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.67 (s, 1 H), 9.04 (s, 1 H), 8.45 (s, 1 H), 8.02 (dd, *J* = 8.6, 2.1 Hz, 1 H), 7.94 (d, *J* = 2.1 Hz, 1 H), 7.87–7.17 (m, 11 H), 3.88 (s, 3 H), 3.67 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 152.6 (C), 151.8 (C), 149.1 (C), 147.2 (CH), 144.9 (CH), 143.1 (C), 138.2 (C), 137.5 (CH), 136.3 (C), 135.6 (C), 135.1 (C), 132.7 (CH), 131.5 (CH), 129.6 (CH), 129.2 (CH), 128.9 (CH), 128.5 (CH), 128.2 (CH), 127.8 (CH), 127.5 (C), 121.3 (C), 111.9 (CH), 110.0 (CH), 55.7 (CH_3), 55.0 (CH_3).

MS (ESI): *m*/*z* (%) = 447 [(M + H), 100].

Anal. Calcd for $C_{28}H_{22}N_4O_2$: C, 75.32; H, 4.97; N, 12.55. Found: C, 75.41; H, 4.96; N, 12.52.

_N_-{2-[4-(Piperidin-1-yl)phenyl]pyrido[3,4-*b*]pyrazin-8-yl}benzophenone Imine (9d)

Yellow powder; yield: 960 mg (62%); mp 87–88 °C; R_f = 0.67 (CH_2Cl_2–EtOH, 9:1).

IR (KBr): 3417, 2922, 1602, 1560, 1527, 1436, 1234, 1183, 1123, 698 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.56 (s, 1 H), 8.95 (s, 1 H), 8.25 (s, 1 H), 8.20 (d, *J* = 8.9 Hz, 2 H), 7.83–7.18 (m, 10 H), 7.08 (d, *J* = 8.9 Hz, 2 H), 3.45–3.43, 1.66–1.64 (m, 10 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 170.8 (C), 153.1 (C), 152.8 (C), 147.2 (CH), 144.9 (CH), 142.9 (C), 138.2 (C), 137.0 (CH), 136.2 (C), 136.1 (C), 135.3 (C), 131.5 (CH), 129.1 (CH), 129.0 (CH), 128.8 (CH), 128.6 (CH), 128.0 (CH), 127.8 (CH), 123.2 (C), 114.3 (CH), 47.8 (CH_2), 24.8 (CH_2), 24.0 (CH_2).

MS (ESI): *m*/*z* (%) = 470 [(M + H), 100].

Anal. Calcd for $C_{31}H_{27}N_5$: C, 79.29; H, 5.80; N, 14.91. Found: C, 79.34; H, 5.81; N, 14.85.

8-Amino-2-phenylpyrido[3,4-*b*]pyrazine (10a); Typical Procedure

Method 4: To a solution of *N*-(2-phenylpyrido[3,4-*b*]pyrazin-8-yl)benzophenone imine (**9a**; 155 mg, 0.4 mmol) in MeOH (5 mL) was added NaOAc (85 mg, 1.04 mmol) and hydroxylamine hydrochloride (54 mg, 0.8 mmol). The reaction mixture was stirred at 75 °C for 48 h and then cooled to r.t. The solution was poured into aq NaOH (5%, 5 mL) and extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layers were dried (Na_2SO_4) and the solvent removed under reduced pressure to give **10a** (88.9 mg, ~100%) as a brown powder.

Method 5: To a solution of 3,4,5-triaminopyridine (**11**; 500 mg, 3.2 mmol) in H_2O (6 mL) was added $NaHCO_3$ (338 mg, 3.2 mmol) and a solution of 2,2-dihydroxy-1-phenylethanone (**5a**; 485 mg, 3.2 mmol) in 1,4-dioxane (3 mL). The reaction mixture was refluxed for 6 h. After cooling to r.t., CH_2Cl_2 (10 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (2 × 15 mL) and the combined organic extracts were dried (Na_2SO_4). The solvent was removed under reduced pressure to yield the title compound **10a** (384 mg, 54%) as a brown powder; mp 172–173 °C; R_f = 0.39 (CH_2Cl_2–EtOH, 9:1).

IR (KBr): 3415, 1608, 1518, 1447, 1312, 1265, 1122, 1017 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.70 (s, 1 H), 8.64 (s, 1 H), 8.58–8.53 (m, 2 H), 8.21 (s, 1 H), 7.66–7.63 (m, 3 H), 6.41 (br s, 2 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 151.0 (C), 145.0 (CH), 140.6 (C), 138.0 (CH), 136.1 (C), 135.4 (C), 133.1 (CH), 132.7 (C), 130.8 (CH), 129.4 (CH), 129.0 (CH), 128.6 (CH), 127.8 (CH), 127.7 (CH).

MS (ESI): *m*/*z* (%) = 223 [(M + H), 100].

Anal. Calcd for $C_{13}H_{10}N_4$: C, 70.26; H, 4.54; N, 25.21. Found: C, 70.12; H, 4.59; N, 25.29.

8-Amino-2-(4-methoxyphenyl)pyrido[3,4-*b*]pyrazine (10b)

Orange powder; yield: 96.8 mg (96%, method 4); mp 178–179 °C; R_f = 0.36 (CH_2Cl_2–EtOH, 9:1).

IR (KBr): 3425, 1619, 1528, 1443, 1322, 1275, 1131, 1019 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.64 (s, 1 H), 8.60 (s, 1 H), 8.53 (d, *J* = 8.9 Hz, 2 H), 8.18 (s, 1 H), 7.17 (d, *J* = 8.9 Hz, 2 H), 6.34 (br s, 2 H), 3.92 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 161.6 (C), 150.8 (C), 144.7 (CH), 140.4 (C), 138.1 (CH), 135.7 (C), 132.8 (C), 129.4 (CH), 129.3 (CH), 127.9 (C), 114.4 (CH), 55.4 (CH_3).

MS (ESI): *m*/*z* (%) = 253 [(M + H), 100].

Anal. Calcd for $C_{14}H_{12}N_4O$: C, 66.65; H, 4.79; N, 22.21. Found: C, 66.72; H, 4.76; N, 22.23.

8-Amino-2-(3,4-dimethoxyphenyl)pyrido[3,4-*b*]pyrazine (10c)

Yellow powder; yield: 100 mg (89%, method 4); mp 182–184 °C; R_f = 0.44 (CH_2Cl_2–EtOH, 9:1).

IR (KBr): 3435, 1611, 1539, 1518, 1454, 1334, 1286, 1265, 1132, 1015 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.68 (s, 1 H), 8.60 (s, 1 H), 8.18 (s, 1 H), 8.14–8.11 (m, 2 H), 7.17 (d, *J* = 8.9 Hz, 1 H), 6.39 (br s, 2 H), 3.99 (s, 3 H), 3.91 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 151.5 (C), 151.0 (C), 149.3 (C), 145.0 (CH), 140.5 (C), 138.1 (CH), 135.8 (C), 132.8 (C), 129.4 (CH), 128.1 (C), 121.2 (CH), 111.7 (CH), 110.7 (CH), 55.9 (CH_3), 55.7 (CH_3).

MS (ESI): *m*/*z* (%) = 283 [(M + H), 100].

Anal. Calcd for $C_{15}H_{14}N_4O_2$: C, 63.82; H, 5.00; N, 19.85. Found: C, 63.89; H, 4.98; N, 19.82.

8-Amino-2-[4-(piperidin-1-yl)phenyl]pyrido[3,4-*b*]pyrazine (10d)

Orange powder; yield: 65.9 mg (54%, method 4); mp 187–189 °C; R_f = 0.38 (CH_2Cl_2–EtOH, 9:1).

IR (KBr): 3423, 1602, 1533, 1241, 1189, 1120 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 9.58 (s, 1 H), 8.56 (s, 1 H), 8.39 (d, *J* = 9.0 Hz, 2 H), 8.14 (s, 1 H), 7.10 (d, *J* = 9.0 Hz, 2 H), 6.23 (br s, 2 H), 3.38–3.36, 1.64–1.63 (m, 10 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 152.8 (C), 151.2 (C), 144.7 (CH), 140.2 (C), 138.2 (CH), 135.5 (C), 133.1 (C), 129.3 (CH), 129.0 (CH), 124.0 (C), 114.4 (CH), 48.1 (CH_2), 24.9 (CH_2), 24.0 (CH_2).

MS (ESI): *m*/*z* (%) = 306 [(M + H), 100].

Anal. Calcd for $C_{18}H_{19}N_5$: C, 70.80; H, 6.27; N, 22.93. Found: C, 70.87; H, 6.26; N, 22.87.

8-Amino-2-(4-hydroxyphenyl)pyrido[3,4-*b*]pyrazine (10e)

Orange powder; yield: 670 mg (88%, method 5); mp >250 °C; R_f = 0.31 (CH_2Cl_2–EtOH, 9:1).

IR (KBr): 3405, 3299, 1525, 1452, 1312, 1264, 1121, 1022 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 9.87 (s, 1 H), 8.89 (s, 1 H), 8.58 (d, *J* = 8.9 Hz, 2 H), 8.05 (s, 1 H), 7.05 (d, *J* = 8.9 Hz, 2 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 158.5 (C), 152.9 (C), 145.3 (C), 145.1 (C), 144.2 (CH), 139.0 (CH), 137.6 (CH), 136.0 (C), 128.9 (CH), 125.7 (C), 116.4 (CH).

MS (ESI): *m*/*z* (%) = 239 [(M + H), 100].

Anal. Calcd for $C_{13}H_{10}N_4O$: C, 65.54; H, 4.23; N, 23.52. Found: C, 65.43; H, 4.27; N, 23.56.

***N*-Ethyl-*N*′-(2-phenylpyrido[3,4-*b*]pyrazin-8-yl)urea (12a); Typical Procedure**

To a solution of 8-amino-2-phenylpyrido[3,4-*b*]pyrazine (**10a**; 200 mg, 0.9 mmol) in pyridine (8 mL) was added ethyl isocyanate (71 μL, 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 column chromatography on silica gel eluting with CH_2Cl_2–EtOH mixtures (from 10:0 to 9:1) to yield **12a** (140 mg, 53%) as a yellow powder; mp 176–177 °C; R_f = 0.62 (CH_2Cl_2–EtOH, 9:1).

IR (KBr): 3211, 2983, 1663, 1564, 1244 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 9.92–9.84 (m, 3 H), 9.24 (s, 1 H), 8.97 (m, 1 H), 8.60–8.58 (m, 2 H), 7.72–7.69 (m, 3 H), 3.63–3.57 (m, 2 H), 1.23 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 153.1 (C), 146.9 (CH), 145.7 (CH), 138.9 (CH), 136.4 (C), 135.7 (C), 135.0 (C), 131.6 (CH), 131.1 (C), 129.2 (CH), 128.3 (CH), 115.7 (CH), 30.6 (CH_2), 13.9 (CH_3).

MS (ESI): *m*/*z* (%) = 294 [(M + H), 100].

Anal. Calcd for $C_{16}H_{15}N_5O$: C, 65.52; H, 5.15; N, 23.88. Found: C, 65.41; H, 5.11; N, 23.93.

***N*-Allyl-*N*′-(2-phenylpyrido[3,4-*b*]pyrazin-8-yl)urea (12b)**

Yellow powder; yield: 140 mg (51%); mp 215–217 °C; R_f = 0.62 (CH_2Cl_2–EtOH, 9:1).

IR (KBr): 3308, 1638, 1560, 1548, 1403, 1234 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 9.83 (s, 1 H), 9.66 (s, 1 H), 9.16 (s, 1 H), 9.08 (br s, 1 H), 8.66–8.62 (m, 2 H), 7.83 (t, *J* = 5.8 Hz, 1 H), 7.73–7.69 (m, 3 H), 6.04–5.93 (m, 1 H), 5.35–5.16 (m, 2 H), 3.92–3.87 (m, 2 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 154.6 (C), 152.7 (C), 145.8 (CH), 144.3 (CH), 136.0 (CH), 135.7 (C), 135.2 (C), 134.0 (C), 133.9 (CH), 132.1 (C), 131.7 (CH), 129.3 (CH), 128.5 (CH), 115.5 (CH_2), 41.7 (CH_2).

MS (ESI): *m*/*z* (%) = 306 [(M + H), 100].

Anal. Calcd for $C_{17}H_{15}N_5O$: C, 66.87; H, 4.95; N, 22.94. Found: C, 66.94; H, 4.99; N, 22.87.

***N*-Phenyl-*N*′-(2-phenylpyrido[3,4-*b*]pyrazin-8-yl)urea (12c); Typical Procedure**

To a solution of 8-amino-2-phenylpyrido[3,4-*b*]pyrazine (**10a**; 200 mg, 0.9 mmol) in DMF (10 mL) was added portionwise NaH (60% in mineral oil, 43 mg, 1.1 mmol). The reaction mixture was stirred at r.t. for 30 min and phenyl isocyanate (98 μL, 0.9 mmol) was added. The reaction mixture was stirred for 3 h at r.t. and then quenched with H_2O (10 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL), the combined organic extracts were dried (Na_2SO_4), and the solvent was removed under reduced pressure to give **12c** (175 mg, 57%) as an orange powder; mp 214–215 °C; R_f = 0.62 (CH_2Cl_2–EtOH, 9:1).

IR (KBr): 3263, 1669, 1542, 1513, 1409, 1312, 1211 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 10.01 (br s, 1 H), 9.85 (s, 1 H), 9.71 (s, 1 H), 9.41 (br s, 1 H), 9.15 (s, 1 H), 8.66–8.62 (m, 2 H), 7.76–7.71 (m, 3 H), 7.62 (dd, *J* = 8.6, 1.2 Hz, 2 H), 7.39 (m, 2 H), 7.10 (t, *J* = 7.5 Hz, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 152.8 (C), 151.9 (C), 145.8 (CH), 144.8 (CH), 139.2 (C), 135.4 (C), 135.0 (C), 134.1 (C), 134.0 (CH), 131.5 (CH), 131.3 (C), 129.2 (CH), 128.9 (CH), 128.3 (CH), 122.3 (CH), 118.4 (CH).

MS (ESI): *m*/*z* (%) = 342 [(M + H), 100].

Anal. Calcd for $C_{20}H_{15}N_5O$: C, 70.37; H, 4.43; N, 20.52. Found: C, 70.45; H, 4.42; N, 20.47.

***N*-(3-Chlorophenyl)-*N*′-(2-phenylpyrido[3,4-*b*]pyrazin-8-yl)urea (12d)**

Yellow powder; yield: 198 mg (58%); mp 245–246 °C; R_f = 0.65 (CH_2Cl_2–EtOH, 9:1).

IR (KBr): 3275, 1667, 1542, 1534, 1412, 1314, 1211 cm^{-1}.

^1H NMR (250 MHz, DMSO-d_6): δ = 10.21 (br s, 1 H), 9.85 (s, 1 H), 9.69 (s, 1 H), 9.44 (br s, 1 H), 9.17 (s, 1 H), 8.64–8.62 (m, 2 H), 7.88 (s, 1 H), 7.74–7.71 (m, 3 H), 7.40–7.39 (m, 2 H), 7.13–7.12 (m, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 152.8 (C), 151.8 (C), 145.9 (CH), 145.1 (CH), 140.7 (C), 135.4 (C), 134.9 (C), 134.2 (CH), 133.3 (C), 131.5 (CH), 131.0 (C), 130.5 (CH), 129.2 (CH), 128.3 (CH), 122.0 (CH), 117.7 (CH), 116.7 (CH).

MS (ESI): *m*/*z* (%) = 377 [(M + H), 100], 379 [(M + H) + 2, 40].

Anal. Calcd for $C_{20}H_{14}ClN_5O$: C, 63.92; H, 3.75; N, 18.64. Found: C, 64.02; H, 3.73; N, 18.62.

***N*-(2-Methoxyphenyl)-*N*′-(2-phenylpyrido[3,4-*b*]pyrazin-8-yl)urea (12e)**

Orange powder; yield: 207 mg (62%); mp 87–89 °C; R_f = 0.60 (CH_2Cl_2–EtOH, 9:1).

IR (KBr): 3285, 1672, 1545, 1521, 1403, 1322, 1204 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 9.94 (br s, 1 H), 9.85 (s, 1 H), 9.69 (s, 1 H), 9.48 (br s, 1 H), 9.15 (s, 1 H), 8.68–8.63 (m, 2 H), 8.12 (d, *J* = 8.2 Hz, 1 H), 7.74–7.71 (m, 3 H), 3.95 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 153.0 (C), 152.3 (C), 148.9 (C), 145.8 (CH), 144.6 (CH), 135.6 (C), 135.0 (C), 134.7 (C), 134.5 (CH), 131.8 (C), 131.5 (CH), 129.1 (CH), 128.5 (CH), 127.8 (C), 123.0 (CH), 120.5 (CH), 120.4 (CH), 111.0 (CH), 55.7 (CH_3).

MS (ESI): *m*/*z* (%) = 372 [(M + H), 100].

Anal. Calcd for $C_{21}H_{17}N_5O_2$: C, 67.91; H, 4.61; N, 18.86. Found: C, 68.02; H, 4.59; N, 18.84.

_N_-(3-Methoxyphenyl)-_N′_-(2-phenylpyrido[3,4-*b*]pyrazin-8-yl)urea (12f)

Orange powder; yield: 224 mg (67%); mp 195–196 °C; R_f = 0.60 (CH_2Cl_2–EtOH, 9:1).

IR (KBr): 3282, 1669, 1537, 1520, 1409, 1325, 1213 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.02 (br s, 1 H), 9.85 (s, 1 H), 9.70 (s, 1 H), 9.40 (br s, 1 H), 9.15 (s, 1 H), 8.66–8.62 (m, 2 H), 7.76–7.71 (m, 3 H), 7.32–7.25 (m, 2 H), 7.11 (dd, *J* = 8.1, 1.1 Hz, 1 H), 6.66 (dd, *J* = 7.8, 1.6 Hz, 1 H), 3.81 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 159.7 (C), 152.8 (C), 151.9 (C), 145.9 (CH), 144.9 (CH), 140.4 (C), 135.5 (C), 135.0 (C), 134.2 (C), 134.1 (CH), 131.5 (CH), 131.3 (C), 129.7 (CH), 129.2 (CH), 128.4 (CH), 110.7 (CH), 107.9 (CH), 104.2 (CH), 55.0 (CH_3).

MS (ESI): *m*/*z* (%) = 372 [(M + H), 100].

Anal. Calcd for $C_{21}H_{17}N_5O_2$: C, 67.91; H, 4.61; N, 18.86. Found: C, 68.00; H, 4.62; N, 18.82.

_N_-(4-Methoxyphenyl)-_N′_-(2-phenylpyrido[3,4-*b*]pyrazin-8-yl)urea (12g)

Orange powder; yield: 220 mg (66%); mp 207–208 °C; R_f = 0.62 (CH_2Cl_2–EtOH, 9:1).

IR (KBr): 3398, 1702, 1545, 1505, 1241, 991 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.09 (br s, 1 H), 9.94 (s, 1 H), 9.68 (s, 1 H), 9.56 (br s, 1 H), 9.29 (s, 1 H), 8.71–8.69 (m, 2 H), 7.75–7.72 (m, 3 H), 7.53 (d, *J* = 8.9 Hz, 2 H), 6.98 (d, *J* = 8.9 Hz, 2 H), 3.79 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 154.8 (C), 152.7 (C), 152.2 (C), 145.8 (CH), 144.6 (CH), 135.5 (C), 135.0 (C), 134.2 (C), 134.0 (CH), 132.3 (C), 131.6 (C), 131.5 (CH), 129.2 (CH), 128.4 (CH), 120.4 (CH), 114.1 (CH), 55.2 (CH_3).

MS (ESI): *m*/*z* (%) = 372 [(M + H), 100].

Anal. Calcd for $C_{21}H_{17}N_5O_2$: C, 67.91; H, 4.61; N, 18.86. Found: C, 67.87; H, 4.64; N, 18.84.

_N_-(3,5-Dimethoxyphenyl)-_N′_-(2-phenylpyrido[3,4-*b*]pyrazin-8-yl)urea (12h)

Orange powder; yield: 224 mg (62%); mp 134–136 °C; R_f = 0.63 (CH_2Cl_2–EtOH, 9:1).

IR (KBr): 3314, 1629, 1548, 1527, 1409, 1219, 1201, 1147 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.00 (br s, 1 H), 9.86 (s, 1 H), 9.70 (s, 1 H), 9.39 (br s, 1 H), 9.16 (s, 1 H), 8.65–8.61 (m, 2 H), 7.75–7.71 (m, 3 H), 6.82 (d, *J* = 2.2 Hz, 2 H), 6.25 (t, *J* = 2.2 Hz, 1 H), 3.80 (s, 6 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 160.7 (C), 152.9 (C), 151.8 (C), 145.9 (CH), 145.0 (CH), 141.0 (C), 135.5 (C), 135.0 (C), 134.2 (C), 134.1 (CH), 131.5 (CH), 131.3 (C), 129.2 (CH), 129.1 (CH), 128.3 (CH), 127.8 (CH), 55.1 (CH_3).

MS (ESI): *m*/*z* (%) = 402 [(M + H), 100].

Anal. Calcd for $C_{22}H_{19}N_5O_3$: C, 65.83; H, 4.77; N, 17.45. Found: C, 65.78; H, 4.76; N, 17.44.

_N_-[2-(4-Methoxyphenyl)pyrido[3,4-*b*]pyrazin-8-yl]-_N′_-phenylurea (12i)

Yellow powder; yield: 184 mg (55%); mp 236–237 °C; R_f = 0.60 (CH_2Cl_2–EtOH, 9:1).

IR (KBr): 3375, 1671, 1608, 1527, 1506, 1297, 1250, 1171, 1017, 833 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.00 (br s, 1 H), 9.83 (s, 1 H), 967 (s, 1 H), 9.39 (br s, 1 H), 9.11 (s, 1 H), 8.68–8.64 (m, 2 H), 7.62 (d, *J* = 7.5 Hz, 2 H), 7.43–7.36 (m, 2 H), 7.28 (d, *J* = 7.5 Hz, 2 H), 7.15–7.09 (m, 1 H), 3.96 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 162.4 (C), 152.7 (C), 152.2 (C), 145.8 (CH), 145.0 (CH), 139.5 (C), 135.4 (C), 134.5 (C), 134.3 (CH), 131.4 (C), 130.4 (CH), 129.1 (CH), 127.6 (C), 122.6 (CH), 118.6 (CH), 114.9 (CH), 55.7 (CH_3).

MS (ESI): *m*/*z* (%) = 372 [(M + H), 100].

Anal. Calcd for $C_{21}H_{17}N_5O_2$: C, 67.91; H, 4.61; N, 18.86. Found: C, 68.01; H, 4.58; N, 18.84.

_N_-(3-Methoxyphenyl)-_N′_-[2-(4-methoxyphenyl)pyrido[3,4-*b*]pyrazin-8-yl]urea (12j)

Yellow powder; yield: 231 mg (64%); mp 195–196 °C; R_f = 0.62 (CH_2Cl_2–EtOH, 9:1).

IR (KBr): 3272, 1666, 1541, 1519, 1411, 1332, 1213 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.01 (br s, 1 H), 9.83 (s, 1 H), 9.67 (s, 1 H), 9.38 (br s, 1 H), 9.11 (s, 1 H), 8.65 (d, *J* = 9.1 Hz, 2 H), 7.34–7.25 (m, 4 H), 7.12 (dd, *J* = 9.1, 1.8 Hz, 1 H), 6.66 (dd, *J* = 8.2, 1.8 Hz, 1 H), 3.96 (s, 3 H), 3.82 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 162.4 (C), 160.0 (C), 152.7 (C), 152.2 (C), 145.8 (CH), 145.1 (CH), 140.7 (C), 135.4 (C), 134.5 (C), 134.4 (CH), 131.4 (C), 130.4 (CH), 130.0 (CH), 127.6 (C), 115.0 (CH), 111.0 (CH), 108.2 (CH), 104.4 (CH), 55.8 (CH_3), 55.2 (CH_3).

MS (ESI): *m*/*z* (%) = 402 [(M + H), 100].

Anal. Calcd for $C_{22}H_{19}N_5O_3$: C, 65.83; H, 4.77; N, 17.45. Found: C, 65.78; H, 4.78; N, 17.47.

_N_-(4-Methoxyphenyl)-_N′_-[2-(4-methoxyphenyl)pyrido[3,4-*b*]pyrazin-8-yl]urea (12k)

Yellow powder; yield: 242 mg (67%); mp 231–323 °C; R_f = 0.62 (CH_2Cl_2–EtOH, 9:1).

IR (KBr): 3274, 1660, 1536, 1524, 1405, 1326, 1204 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.81 (br s, 2 H), 9.66 (s, 1 H), 9.29 (br s, 1 H), 9.09 (s, 1 H), 8.64 (d, *J* = 9.1 Hz, 2 H), 7.52 (d, *J* = 8.9 Hz, 2 H), 7.28 (d, *J* = 8.9 Hz, 2 H), 6.98 (d, *J* = 9.1 Hz, 2 H), 3.95 (s, 3 H), 3.79 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 162.4 (C), 155.1 (C), 152.6 (C), 152.4 (C), 145.8 (CH), 144.8 (CH), 135.4 (C), 134.4 (C), 134.2 (CH), 132.4 (C), 131.6 (C), 130.4 (CH), 127.6 (C), 120.7 (CH), 114.9 (CH), 114.4 (CH), 55.8 (CH_3), 55.4 (CH_3).

MS (ESI): *m*/*z* (%) = 402 [(M + H), 100].

Anal. Calcd for $C_{22}H_{19}N_5O_3$: C, 65.83; H, 4.77; N, 17.45. Found: C, 65.91; H, 4.79; N, 17.39.

_N_-(2-Phenylpyrido[3,4-*b*]pyrazin-8-yl)acetamide (13a); Typical Procedure

To a solution of 8-amino-2-phenylpyrido[3,4-*b*]pyrazine (**10a**; 200 mg, 0.9 mmol) in MeCN (10 mL) was added acetyl chloride (78 μL, 1.1 mmol) and the reaction mixture was heated at reflux for 6 h. The resulting solution was filtered off and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel eluting with CH_2Cl_2–EtOH mixtures (from

10:0 to 9:1) to give **13a** (157 mg, 66%) as a beige powder; mp 210–211 °C; R_f = 0.58 (CH_2Cl_2–EtOH, 9:1).

IR (KBr): 3346, 2995, 1656, 1519, 1415, 1335, 1222 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 10.21 (br s, 1 H), 9.85 (s, 1 H), 9.65 (s, 1 H), 9.25 (s, 1 H), 8.69–8.64 (m, 2 H), 7.72–7.68 (m, 3 H), 2.39 (s, 3 H).

^{13}C NMR spectrum could not be obtained due to poor solubility.

MS (ESI): *m*/*z* (%) = 265 [(M + H), 100].

Anal. Calcd for $C_{15}H_{12}N_4O$: C, 68.17; H, 4.58; N, 21.20. Found: C, 68.34; H, 4.56; N, 21.16.

_N_-(2-Phenylpyrido[3,4-*b*]pyrazin-8-yl)benzamide (13b)
Yellow powder; yield: 208 mg (71%); mp 243–244 °C; R_f = 0.56 (CH_2Cl_2–EtOH, 9:1).

IR (KBr): 3387, 1662, 1521, 1406, 1328, 1300, 1247, 708 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 10.69 (br s, 1 H), 9.92 (s, 1 H), 9.64 (s, 1 H), 9.47 (s, 1 H), 8.61–8.56 (m, 2 H), 8.19–8.15 (m, 2 H), 7.73–7.68 (m, 6 H).

^{13}C NMR spectrum could not be obtained due to poor solubility.

MS (ESI): *m*/*z* (%) = 327 [(M + H), 100].

Anal. Calcd for $C_{20}H_{14}N_4O$: C, 73.61; H, 4.32; N, 17.17. Found: C, 73.68; H, 4.33; N, 17.14.

4-Methoxy-_N_-(2-phenylpyrido[3,4-*b*]pyrazin-8-yl)benzamide (13c)
Yellow powder; yield: 199 mg (62%); mp 214–215 °C; R_f = 0.56 (CH_2Cl_2–EtOH, 9:1).

IR (KBr): 3369, 1524, 1506, 1436, 1406, 1247, 1177, 1020 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 10.43 (br s, 1 H), 9.86 (s, 1 H), 9.62 (s, 1 H), 9.34 (s, 1 H), 8.57–8.53 (m, 2 H), 8.15 (d, *J* = 8.8 Hz, 2 H), 7.72–7.69 (m, 3 H), 7.20 (d, *J* = 8.8 Hz, 2 H), 3.93 (s, 3 H).

^{13}C NMR spectrum could not be obtained due to poor solubility.

MS (ESI): *m*/*z* (%) = 357 [(M + H), 100].

Anal. Calcd for $C_{21}H_{16}N_4O_2$: C, 70.77; H, 4.53; N, 15.72. Found: C, 70.79; H, 4.54; N, 15.68.

_N_-(3-Bromophenyl)-2-phenylpyrido[3,4-*b*]pyrazin-8-amine (14a); Typical Procedure
To a solution of 8-bromo-2-phenylpyrido[3,4-*b*]pyrazine (**6aa**; 150 mg, 0.5 mmol) in toluene (8 mL) under argon was added successively 3-bromoaniline (68 μL, 0.6 mmol), $Pd_2(dba)_3$ (2 mg, $3.9 \cdot 10^{-6}$ mol), BINAP (1 mg, $1.3 \cdot 10^{-6}$ 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 r.t. EtOAc (15 mL) was added, the combined organic layers were washed with H_2O (3 × 15 mL), collected, dried (Na_2SO_4) and the solvent was removed under reduced pressure. The crude product was purified by column chromatography on silica gel eluting with CH_2Cl_2–EtOH mixtures (from 10:0 to 9:1) to afford **14a** (119 mg, 63%) as an orange powder; mp 194–196 °C; R_f = 0.61 (CH_2Cl_2–EtOH, 9:1).

IR (KBr): 3329, 1592, 1544, 1518, 1486, 1413, 1224, 1017 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 9.82 (s, 1 H), 8.99 (s, 1 H), 8.94 (br s, 1 H), 8.73 (s, 1 H), 8.62–8.60 (m, 2 H), 7.69–7.65 (m, 4 H), 7.53–7.51 (m, 1 H), 7.36 (t, *J* = 8.1 Hz, 1 H), 7.26–7.23 (m, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 152.5 (C), 145.9 (CH), 143.7 (C), 143.2 (CH), 136.4 (C), 135.4 (C), 135.3 (C), 135.2 (C), 131.5 (CH), 131.3 (CH), 130.9 (CH), 129.3 (CH), 128.5 (CH), 124.8 (CH), 122.6 (CH), 122.3 (C), 118.4 (CH).

MS (ESI): *m*/*z* (%) = 377 [(M + H), 100], 379 [(M + H) + 2, 100].

Anal. Calcd for $C_{19}H_{13}BrN_4$: C, 60.49; H, 3.47; N, 14.85. Found: C, 60.54; H, 3.44; N, 14.94.

_N_-(2-Methoxyphenyl)-2-phenylpyrido[3,4-*b*]pyrazin-8-amine (14b)
Red powder; yield: 85.3 mg (52%); mp 156–158 °C; R_f = 0.53 (CH_2Cl_2–EtOH, 9:1).

IR (KBr): 3332, 1599, 1548, 1539, 1493, 1457, 1406, 1238, 1027, 731, 686 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 9.81 (s, 1 H), 8.89 (s, 1 H), 8.58–8.53 (m, 3 H), 8.43 (s, 1 H), 7.72–7.61 (m, 4 H), 7.20–7.08 (m, 3 H), 3.94 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 160.3 (C), 152.5 (C), 145.4 (CH), 142.6 (C), 141.8 (CH), 136.7 (C), 135.5 (C), 135.2 (C), 134.4 (C), 131.2 (CH), 130.5 (CH), 129.2 (CH), 129.0 (CH), 128.5 (CH), 112.1 (CH), 108.4 (CH), 106.2 (CH), 55.2 (CH_3).

MS (ESI): *m*/*z* (%) = 329 [(M + H), 100].

Anal. Calcd for $C_{20}H_{16}N_4O$: C, 73.15; H, 4.91; N, 17.06. Found: C, 73.11; H, 4.90; N, 17.09.

_N_-(3-Methoxyphenyl)-2-phenylpyrido[3,4-*b*]pyrazin-8-amine (14c)
Orange powder; yield: 114 mg (70%); mp 111–113 °C; R_f = 0.35 (CH_2Cl_2–EtOH, 9:1).

IR (KBr): 3362, 1596, 1548, 1529, 1491, 1280, 1162, 765, 686 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 9.81 (br s, 1 H), 8.92 (s, 1 H), 8.77 (s, 1 H), 8.69 (s, 1 H), 8.69–8.63 (m, 2 H), 7.68–7.65 (m, 3 H), 7.34 (t, *J* = 8.1 Hz, 1 H), 7.14–7.09 (m, 2 H), 6.70 (d, *J* = 8.1 Hz, 2 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 160.2 (C), 152.0 (C), 145.6 (CH), 142.4 (C), 141.8 (CH), 136.2 (C), 135.8 (C), 135.2 (C), 134.6 (C), 131.2 (CH), 130.0 (CH), 129.5 (CH), 129.1 (CH), 128.2 (CH), 112.5 (CH), 108.3 (CH), 106.3 (CH), 55.1 (CH_3).

MS(ESI): *m*/*z* (%) = 329 [(M + H), 100].

Anal. Calcd for $C_{20}H_{16}N_4O$: C, 73.15; H, 4.91; N, 17.06. Found: C, 73.32; H, 4.89; N, 17.02.

_N_-(4-Methoxyphenyl)-2-phenylpyrido[3,4-*b*]pyrazin-8-amine (14d)
Red powder; yield: 110 mg (67%); mp 128–130 °C; R_f = 0.52 (CH_2Cl_2–EtOH, 9:1).

IR (KBr): 3356, 1591, 1551, 1519, 1482, 1273, 1164, 769, 693 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 9.79 (s, 1 H), 8.80 (s, 1 H), 8.66–8.63 (m, 3 H), 8.34 (s, 1 H), 7.66–7.64 (m, 3 H), 7.45 (d, *J* = 8.5 Hz, 2 H), 7.05 (d, *J* = 8.5 Hz, 2 H), 3.83 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 155.8 (C), 151.6 (C), 145.4 (CH), 140.1 (CH), 137.6 (C), 136.1 (C), 135.3 (C), 133.8 (C), 133.4 (C), 131.1 (CH), 129.0 (CH), 128.2 (CH), 127.2 (CH), 124.4 (CH), 114.6 (CH), 55.2 (CH_3).

MS (ESI): *m*/*z* (%) = 329 [(M + H), 100].

Anal. Calcd for $C_{20}H_{16}N_4O$: C, 73.15; H, 4.91; N, 17.06. Found: C, 73.19; H, 4.89; N, 17.04.

_N_-(3-Ethynylphenyl)-2-phenylpyrido[3,4-*b*]pyrazin-8-amine (14e)
Orange powder; yield: 90.1 mg (56%); mp 190–191 °C; R_f = 0.61 (CH_2Cl_2–EtOH, 9:1).

IR (KBr): 3351, 2216, 1592, 1539, 1524, 1461, 1272, 1152 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.82 (s, 1 H), 8.96 (s, 1 H), 8.87 (br s, 1 H), 8.69–8.61 (m, 3 H), 7.68–7.65 (m, 3 H), 7.61–7.58 (m, 2 H), 7.46–7.39 (m, 1 H), 7.19 (d, *J* = 7.6 Hz, 1 H), 4.25 (s, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 152.4 (C), 145.8 (CH), 142.7 (CH), 142.0 (C), 136.4 (C), 135.6 (C), 135.4 (C), 135.1 (C), 131.5 (CH), 130.2 (CH), 129.9 (CH), 129.3 (CH), 128.5 (CH), 125.8 (CH), 123.4 (CH), 122.8 (C), 120.7 (CH), 83.6 (C), 80.9 (CH).

MS (ESI): *m*/*z* (%) = 323 [(M + H), 100].

Anal. Calcd for $C_{21}H_{14}N_4$: C, 78.24; H, 4.38; N, 17.38. Found: C, 78.29; H, 4.37; N, 17.34.

2-Phenyl-*N*-[4-(piperidin-1-yl)phenyl]pyrido[3,4-*b*]pyrazin-8-amine (14f)

Red powder; yield: 105 mg (55%); mp 189–191 °C; R_f = 0.47 (CH_2Cl_2–EtOH, 9:1).

IR (KBr): 3393, 1542, 1515, 1442, 1328, 1238, 1183, 1093, 918, 777, 686 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.78 (s, 1 H), 8.77 (s, 1 H), 8.68–8.65 (m, 2 H), 8.58 (br s, 1 H), 8.34 (s, 1 H), 7.67–7.64 (m, 3 H), 7.36 (d, *J* = 9.0 Hz, 2 H), 7.05 (d, *J* = 9.0 Hz, 2 H), 3.17–3.15, 1.69–1.50 (m, 10 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 151.5 (C), 148.5 (C), 145.3 (CH), 139.7 (CH), 137.7 (C), 136.1 (C), 135.3 (C), 133.7 (C), 131.7 (C), 131.1 (CH), 129.0 (CH), 128.2 (CH), 127.2 (CH), 123.8 (CH), 118.1 (CH), 116.8 (CH), 114.7 (CH), 52.0 (CH_2), 50.0 (CH_2), 25.8 (CH_2), 25.4 (CH_2), 23.9 (CH_2).

MS (ESI): *m*/*z* (%) = 382 [(M + H), 100].

Anal. Calcd for $C_{24}H_{23}N_5$: C, 75.56; H, 6.08; N, 18.36. Found: C, 75.61; H, 6.07; N, 18.32.

***N*-[4-(Morpholin-4-yl)phenyl]-2-phenylpyrido[3,4-*b*]pyrazin-8-amine (14g)**

Red powder; yield: 107 mg (56%); mp 187–189 °C; R_f = 0.48 (CH_2Cl_2–EtOH, 9:1).

IR (KBr): 3417, 1539, 1515, 1442, 1325, 1231, 1126, 922 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.78 (s, 1 H), 8.78 (s, 1 H), 8.68–8.64 (m, 2 H), 8.61 (br s, 1 H), 8.36 (s, 1 H), 7.67–7.64 (m, 3 H), 7.40 (d, *J* = 8.8 Hz, 2 H), 7.06 (d, *J* = 8.8 Hz, 2 H), 3.82–3.78 (m, 4 H), 3.17–3.13 (m, 4 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 151.5 (C), 147.7 (C), 145.4 (CH), 139.9 (CH), 137.5 (C), 136.1 (C), 135.3 (C), 133.7 (C), 132.4 (C), 131.1 (CH), 129.0 (CH), 128.2 (CH), 127.2 (CH), 123.7 (CH), 116.0 (CH), 66.1 (CH_2), 48.8 (CH_2).

MS (ESI): *m*/*z* (%) = 384 [(M + H), 100].

Anal. Calcd for $C_{23}H_{21}N_5O$: C, 72.04; H, 5.52; N, 18.26. Found: C, 71.98; H, 5.55; N, 18.31.

***N*-(4-Hydroxyphenyl)-2-phenylpyrido[3,4-*b*]pyrazin-8-amine (14h)**

Red powder; yield: 33.0 mg (21%); mp 252–254 °C; R_f = 0.53 (CH_2Cl_2–EtOH, 9:1).

IR (KBr): 3387, 1518, 1279, 1243, 1093, 1023, 828, 767 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.79 (s, 1 H), 9.42 (br s, 1 H), 8.76 (s, 1 H), 8.68–8.66 (m, 2 H), 8.56 (br s, 1 H), 8.26 (s, 1 H), 7.67–7.64 (m, 3 H), 7.32 (d, *J* = 8.8 Hz, 2 H), 6.88 (d, *J* = 8.8 Hz, 2 H).

^{13}C NMR spectrum could not be obtained due to poor solubility.

MS (ESI): *m*/*z* (%) = 315 [(M + H), 100].

Anal. Calcd for $C_{19}H_{14}N_4O$: C, 72.60; H, 4.49; N, 17.82. Found: C, 72.69; H, 4.49; N, 17.71.

***N*-(3-Bromophenyl)-2-(4-methoxyphenyl)pyrido[3,4-*b*]pyrazin-8-amine (14i)**

Orange powder; yield: 118 mg (58%); mp 159–161 °C; R_f = 0.61 (CH_2Cl_2–EtOH, 9:1).

IR (KBr): 3319, 1583, 1534, 1525, 1472, 1422, 1213, 1019 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.77 (s, 1 H), 8.95 (s, 1 H), 8.88 (br s, 1 H), 8.71–8.60 (m, 3 H), 7.67 (s, 1 H), 7.54–7.50 (m, 1 H), 7.39–7.32 (m, 1 H), 7.25–7.18 (m, 3 H), 3.92 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 162.2 (C), 152.2 (C), 145.6 (CH), 143.8 (C), 143.2 (CH), 136.0 (C), 135.4 (C), 134.9 (C), 131.2 (CH), 130.9 (CH), 130.3 (CH), 127.8 (C), 124.6 (CH), 122.4 (CH), 122.3 (C), 118.1 (CH), 114.7 (CH), 55.7 (CH_3).

MS (ESI): *m*/*z* (%) = 407 [(M + H), 100], 409 [(M + H) + 2, 100].

Anal. Calcd for $C_{20}H_{15}BrN_4O$: C, 58.98; H, 3.71; N, 13.76. Found: C, 58.98; H, 3.73; N, 13.73.

2-(4-Methoxyphenyl)-*N*-[4-(piperidin-1-yl)phenyl]pyrido[3,4-*b*]pyrazin-8-amine (14j)

Red powder; yield: 140 mg (68%); mp 185–187 °C; R_f = 0.45 (CH_2Cl_2–EtOH, 9:1).

IR (KBr): 3368, 1578, 1521, 1279, 1247, 1177, 1023, 831 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.73 (s, 1 H), 8.72 (s, 1 H), 8.64 (d, *J* = 8.6 Hz, 2 H), 8.51 (br s, 1 H), 8.31 (s, 1 H), 7.34 (d, *J* = 8.7 Hz, 2 H), 7.18 (d, *J* = 7.9 Hz, 2 H), 7.04 (d, *J* = 8.1 Hz, 2 H), 3.92 (s, 3 H), 3.16–3.14, 1.68–1.57 (m, 10 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 161.8 (C), 151.3 (C), 148.4 (C), 145.1 (CH), 139.7 (CH), 137.4 (C), 135.7 (C), 133.8 (C), 131.8 (C), 129.9 (CH), 127.7 (C), 127.1 (CH), 123.7 (CH), 116.8 (CH), 114.5 (CH), 55.4 (CH_3), 50.0 (CH_2), 30.7 (CH_2), 25.3 (CH_2), 23.8 (CH_2).

MS (ESI): *m*/*z* (%) = 412 [(M + H), 100].

Anal. Calcd for $C_{25}H_{25}N_5O$: C, 72.97; H, 6.12; N, 17.02. Found: C, 72.92; H, 6.13; N, 17.03.

2-(4-Methoxyphenyl)-*N*-[4-(morpholin-4-yl)phenyl]pyrido[3,4-*b*]pyrazin-8-amine (14k)

Red powder; yield: 138 mg (67%); mp 204–206 °C; R_f = 0.56 (CH_2Cl_2–EtOH, 9:1).

IR (KBr): 3368, 1603, 1542, 1518, 1436, 1252, 1117, 1024, 925 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.73 (s, 1 H), 8.74 (s, 1 H), 8.64 (d, *J* = 8.9 Hz, 2 H), 8.54 (br s, 1 H), 8.33 (s, 1 H), 7.39 (d, *J* = 8.5 Hz, 2 H), 7.18 (d, *J* = 9.0 Hz, 2 H), 7.06 (d, *J* = 8.5 Hz, 2 H), 3.92 (s, 3 H), 3.82–3.78, 3.17–3.13 (m, 8 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 161.8 (C), 151.3 (C), 147.6 (C), 145.0 (CH), 139.9 (CH), 137.3 (C), 135.7 (C), 133.8 (C), 132.5 (C), 129.9 (CH), 127.7 (C), 127.2 (CH), 123.6 (CH), 116.0 (CH), 114.4 (CH), 66.1 (CH_2), 55.4 (CH_3), 48.9 (CH_2).

MS(ESI): *m*/*z* (%) = 414 [(M + H), 100].

Anal. Calcd for $C_{24}H_{23}N_5O_2$: C, 69.72; H, 5.61; N, 16.94. Found: C, 69.75; H, 5.60; N, 16.92.

***N*-(2,5-Dimethoxyphenyl)-2-(4-methoxyphenyl)pyrido[3,4-*b*]pyrazin-8-amine (14l)**

Red powder; yield: 140 mg (72%); mp 158–159 °C; R_f = 0.52 (CH_2Cl_2–EtOH, 9:1).

IR (KBr): 3411, 1608, 1557, 1529, 1210, 1177, 1020, 794 cm^{-1}.

^{1}H NMR (250 MHz, DMSO-d_6): δ = 9.77 (s, 1 H), 8.88 (s, 1 H), 8.55–8.47 (m, 4 H), 7.23 (d, *J* = 8.2 Hz, 2 H), 7.17 (d, *J* = 2.8 Hz, 1 H), 7.11 (d, *J* = 9.2 Hz, 1 H), 6.70 (dd, *J* = 9.0, 2.8 Hz, 1 H), 3.93 (s, 3 H), 3.90 (s, 3 H), 3.80 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 162.0 (C), 153.5 (C), 151.6 (C), 145.3 (CH), 144.8 (C), 141.5 (CH), 135.6 (C), 134.6 (C), 134.1 (C), 130.3 (C), 129.6 (CH), 128.5 (CH), 127.5 (C), 114.7 (CH), 112.4 (CH), 107.1 (CH), 106.2 (CH), 56.3 (CH_3), 55.5 (CH_3), 55.4 (CH_3).

MS (ESI): *m*/*z* (%) = 389 [(M + H), 100].

Anal. Calcd for $C_{22}H_{20}N_4O_3$: C, 68.03; H, 5.19; N, 14.42. Found: C, 67.99; H, 5.21; N, 14.45.

2-(3,4-Dimethoxyphenyl)-*N*-(3-methoxyphenyl)pyrido[3,4-*b*]pyrazin-8-amine (14m)

Red powder; yield: 149 mg (77%); mp 156–158 °C; R_f = 0.59 (CH_2Cl_2–EtOH, 9:1).

IR (KBr): 3350, 1602, 1529, 1515, 1457, 1403, 1286, 1253, 1211, 1168, 1153, 1014 cm^{-1}.

^{1}H NMR (250 MHz, DMSO-d_6): δ = 9.78 (s, 1 H), 8.89 (s, 1 H), 8.72 (br s, 1 H), 8.65 (s, 1 H), 8.21 (dd, *J* = 8.5, 1.5 Hz, 1 H), 8.13 (d, *J* = 1.5 Hz, 1 H), 7.32 (t, *J* = 8.1 Hz, 1 H), 7.20 (d, *J* = 8.5 Hz, 1 H), 7.10–7.04 (m, 2 H), 6.67 (dd, *J* = 8.1, 2.1 Hz, 1 H), 3.96 (s, 3 H), 3.92 (s, 3 H), 3.80 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 160.2 (C), 152.0 (C), 145.6 (CH), 142.4 (C), 141.8 (CH), 136.2 (C), 135.8 (C), 135.2 (C), 134.6 (C), 131.2 (CH), 130.0 (CH), 129.5 (CH), 129.1 (CH), 128.2 (CH), 112.5 (CH), 108.3 (CH), 106.3 (CH), 55.1 (CH_3).

MS (ESI): *m*/*z* (%) = 389 [(M + H), 100].

Anal. Calcd for $C_{22}H_{20}N_4O_3$: C, 68.03; H, 5.19; N, 14.42. Found: C, 68.04; H, 5.20; N, 14.43.

2-(3,4-Dimethoxyphenyl)-*N*-[4-(piperidin-1-yl)phenyl]pyrido[3,4-*b*]pyrazin-8-amine (14n)

Red powder; yield: 143 mg (65%); mp 202–204 °C; R_f = 0.54 (CH_2Cl_2–EtOH, 9:1).

IR (KBr): 3393, 1542, 1517, 1457, 1282, 1262, 1225, 1156, 1117, 1020, 925 cm^{-1}.

^{1}H NMR (250 MHz, DMSO-d_6): δ = 9.76 (s, 1 H), 8.74 (s, 1 H), 8.50 (br s, 1 H), 8.29 (s, 1 H), 8.29–8.17 (m, 2 H), 7.35 (d, *J* = 8.6 Hz, 2 H), 7.19 (d, *J* = 8.2 Hz, 1 H), 7.05 (d, *J* = 8.6 Hz, 2 H), 3.98 (s, 3 H), 3.92 (s, 3 H), 3.18–3.16, 1.70–1.68 (m, 10 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 152.9 (C), 150.3 (C), 149.8 (C), 146.9 (C), 144.7 (CH), 143.6 (C), 139.6 (C), 139.0 (CH), 137.6 (CH), 136.0 (C), 132.6 (C), 126.4 (C), 120.8 (CH), 117.9 (CH), 117.5 (CH), 115.8 (CH), 115.4 (CH), 115.1 (CH), 112.3 (CH), 56.1 (CH_3), 55.8 (CH_3), 52.4 (CH_2), 26.0 (CH_2), 25.5 (CH_2).

MS (ESI): *m*/*z* (%) = 442 [(M + H), 100].

Anal. Calcd for $C_{26}H_{27}N_5O_2$: C, 70.73; H, 6.16; N, 15.86. Found: C, 70.69; H, 6.14; N, 15.89.

2-(3,4-Dimethoxyphenyl)-*N*-[4-(morpholin-1-yl)phenyl]pyrido[3,4-*b*]pyrazin-8-amine (14o)

Red powder; yield: 144 mg (65%); mp 205–207 °C; R_f = 0.52 (CH_2Cl_2–EtOH, 9:1).

IR (KBr): 3382, 1539, 1522, 1463, 1272, 1234, 1163, 1112, 1022, 921 cm^{-1}.

^{1}H NMR (250 MHz, DMSO-d_6): δ = 9.77 (s, 1 H), 8.75 (s, 1 H), 8.53 (br s, 1 H), 8.31 (s, 1 H), 8.24–8.17 (m, 2 H), 7.39 (d, *J* = 9.1 Hz, 2 H), 7.20 (d, *J* = 8.2 Hz, 1 H), 7.06 (d, *J* = 8.9 Hz, 2 H), 3.98 (s, 3 H), 3.92 (s, 3 H), 3.80–3.78, 3.16–3.14 (m, 8 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 151.7 (C), 151.4 (C), 149.3 (C), 147.7 (C), 145.3 (CH), 140.0 (CH), 137.4 (C), 135.8 (C), 133.8 (C), 132.6 (C), 127.9 (C), 127.5 (CH), 123.8 (CH), 121.8 (CH), 116.0 (CH), 111.7 (CH), 111.2 (CH), 66.1 (CH_2), 56.0 (CH_3), 55.7 (CH_3), 48.9 (CH_2).

MS (ESI): *m*/*z* (%) = 444 [(M + H), 100].

Anal. Calcd for $C_{25}H_{25}N_5O_3$: C, 67.70; H, 5.68; N, 15.79. Found: C, 67.63; H, 5.69; N, 15.82.

***N*-Phenyl-2-[4-(piperidin-1-yl)phenyl]pyrido[3,4-*b*]pyrazin-8-amine (14p)**

Red powder; yield: 112 mg (59%); mp 132–134 °C; R_f = 0.48 (CH_2Cl_2–EtOH, 9:1).

IR (KBr): 3441, 1605, 1517, 1497, 1238, 1198, 1126 cm^{-1}.

^{1}H NMR (250 MHz, DMSO-d_6): δ = 9.66 (s, 1 H), 8.80 (br s, 1 H), 8.61 (s, 1 H), 8.58 (s, 1 H), 8.48 (d, *J* = 8.9 Hz, 2 H), 7.52–7.39 (m, 5 H), 7.10 (d, *J* = 8.9 Hz, 2 H), 3.37–3.36, 1.66–1.65 (m, 10 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 152.9 (C), 152.3 (C), 145.2 (CH), 140.9 (C), 140.9 (CH), 135.8 (C), 135.3 (C), 135.0 (C), 129.5 (CH), 129.4 (CH), 128.9 (CH), 128.0 (CH), 123.1 (C), 122.8 (CH), 120.5 (CH), 114.7 (CH), 114.2 (CH), 47.9 (CH_2), 24.7 (CH_2), 23.8 (CH_2).

MS(ESI): *m*/*z* (%) = 382 [(M + H), 100].

Anal. Calcd for $C_{24}H_{23}N_5$: C, 75.56; H, 6.08; N, 18.36. Found: C, 75.54; H, 6.09; N, 18.37.

***N*-(3-Methoxyphenyl)-2-[4-(piperidin-1-yl)phenyl]pyrido[3,4-*b*]pyrazin-8-amine (14q)**

Red powder; yield: 111 mg (54%); mp 129–131 °C; R_f = 0.56 (CH_2Cl_2–EtOH, 9:1).

IR (KBr): 3411, 1605, 1545, 1524, 1494, 1352, 1241, 1192, 1165, 1123, 818 cm^{-1}.

^{1}H NMR (250 MHz, DMSO-d_6): δ = 9.68 (s, 1 H), 8.82 (s, 1 H), 8.64 (s, 1 H), 8.61 (br s, 1 H), 8.49 (d, *J* = 8.9 Hz, 2 H), 7.32 (t, *J* = 7.9 Hz, 1 H), 7.14–7.08 (m, 4 H), 6.68–6.66 (m, 1 H), 3.82 (s, 3 H), 3.44–3.42, 1.66–1.64 (m, 10 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 160.2 (C), 152.9 (C), 152.0 (C), 145.1 (CH), 142.7 (C), 141.8 (CH), 135.5 (C), 135.2 (C), 135.0 (C), 129.9 (CH), 129.6 (CH), 129.6 (CH), 123.5 (C), 114.2 (CH), 112.0 (CH), 108.0 (CH), 105.8 (CH), 55.0 (CH_3), 48.0 (CH_2), 24.9 (CH_2), 23.9 (CH_2).

MS (ESI): *m*/*z* (%) = 412 [(M + H), 100].

Anal. Calcd for $C_{25}H_{25}N_5O$: C, 72.97; H, 6.12; N, 17.02. Found: C, 73.02; H, 6.11; N, 16.99.

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(17) *Kinase Inhibition Assay*: Recombinant kinases were purchased from Millipore or ProQinase. AlphaScreen Bead Kits from Perkin-Elmer were used to quantify the kinase activity. For the assessment of IC_{50} values, compounds were tested at 10 final concentrations between 3.16 nM and 100 μM. 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 read out was done on the next morning using an Envision reader (PerkinElmer). IC_{50} values were calculated using Graph Pad Prism software.

