

Suzuki reaction on pyridinium *N*-haloheteroarylaminides: regioselective synthesis of 3,5-disubstituted 2-aminopyrazines

Rafael Castillo, M. José Reyes, M. Luisa Izquierdo, Julio Alvarez-Builla*

Departamento de Química Orgánica, Universidad de Alcalá, 28871 Alcalá de Henares, Madrid, Spain

Received 1 October 2007; received in revised form 15 November 2007; accepted 16 November 2007
Available online 22 November 2007

Dedicated to Professor M. Yus on the occasion of his 60th birthday

Abstract

An extensive study of Suzuki–Miyaura cross-coupling processes on *N*-pyridinium bromoazinyll aminides has been performed. Mono- and disubstitution on 5- and 3,5-bromo derivatives produced the corresponding aryl derivatives. In the disubstituted compounds regioselective substitution at the 3-position occurred, vicinal to the aminide nitrogen, and this was more evident in pyrazine derivatives. The commonly used strategy involving *N*-alkylation and reduction of the N–N bond gave rise to a series of 2-alkylamino-3,5-disubstituted-pyrazines. © 2007 Elsevier Ltd. All rights reserved.

1. Introduction

Polysubstituted heterocycles belong to the most important class of organic compounds, they are widespread in nature and many of them show interesting biological activities.¹ Functionalization of halo- or metallated heteroaromatic compounds through metal-mediated cross-coupling reactions has become an important method for the preparation of different multiple carbon-substituted heterocycles² and, in recent years, selective Pd-mediated reactions have been developed to prepare highly functionalized heterocycles.³ The Suzuki–Miyaura cross-coupling reaction has proved to be a powerful and versatile method for the formation of Csp²–Csp² bonds.⁴ The process has important advantages over the other palladium-catalyzed cross-coupling processes and these include functional group compatibility, low toxicity of reagents and intermediates, ready availability of boron derivatives, high thermal stability and good tolerance against oxygen and aqueous solvents. Recently, efforts have been focused on the development of efficient and selective catalytic systems that either

allow the use of chlorinated substrates or avoid the use of organic solvents.⁵

Pyridinium heteroaryl-stabilized aminides **1** (Fig. 1), in which we have been interested for a number of years,⁶ are a subgroup of mesomeric betaines⁷ with interesting reactivity⁸ due to their particular structure.^{8b}

Regioselective halogenation^{8c} at the iminoazine moiety affords 3- or 3,5-halogenated aminides and these compounds have been used in radical cyclization processes⁹ and, more recently, preliminary results have been reported for the Suzuki cross-coupling reaction of compounds **2a**, **2b** and **2d** (Fig. 1) with boronic acids.¹⁰

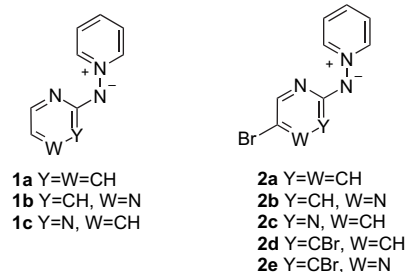


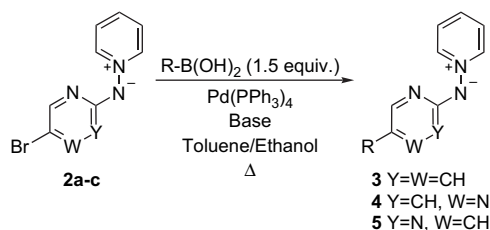
Figure 1.

* Corresponding author. Tel.: +34 91 885 46 06; fax: +34 91 885 46 86.
E-mail address: julio.alvarez@uah.es (J. Alvarez-Builla).

2. Results and discussion

2.1. Monosubstituted *N*-aminides

The reaction of pyridinium *N*-(5-bromoheteroaryl)aminides **2a**, **2b** and boronic acids worked effectively under standard conditions: i.e., aminide (1 mmol), boronic acid (1.5 mmol), Pd(PPh₃)₄ (5 mmol %) and Cs₂CO₃ (2 mmol) in refluxing toluene/ethanol (20:1, v/v)^{10a} (Table 1, method A) to afford the substituted products **3** and **4**. In all cases the process was continued until substrate **2** had been consumed. In addition, in the first attempt to prepare compound **3d** it was found that 4-(hydroxymethyl)phenylboronic acid had low solubility in toluene and, as a result, the ratio of toluene/ethanol had to be optimized, yielding 73% of **3d** with a 4:1 mixture of toluene/ethanol. Moreover, it is known that the base plays an important role in the Suzuki process,^{4a} with the amount and base strength being two important factors in the transmetalation step in terms of increasing the conversion yields. As in previous work, the use of hard bases^{10a} did not increase the yield of **3a** but a softer base, such as K₂CO₃, was tested in large excess¹¹ in the coupling of aminide **2a** with different boronic acids. In most cases, the method (Table 1, method B, with 10 mmol of base) produced high yields, often with shorter reaction times, particularly in the case of **3d**, which was obtained in excellent yield (92%) (Scheme 1).



Scheme 1.

Results for derivatives of pyridine, pyrazine and pyrimidine (compounds **3–5**, respectively) are given in Table 1.

2.2. Disubstituted *N*-aminides

Dibromoaminide **2d**^{8c} was tested in a double Suzuki process, using 3 equiv of boronic acid, 4 equiv of Cs₂CO₃ and a mixture of toluene/ethanol (20:1, v/v) under reflux^{10a} (Table 2, method A); alternatively, bearing in mind the previous results (Table 1, method B) a double coupling was also tested on pyridinium *N*-(3,5-dibromoazin-2-yl)aminides **2d** and **2e** and several boronic acids, using 20 equiv of K₂CO₃ in a toluene/ethanol (4:1) solvent mixture under reflux (Table 2). Yields were again higher on using method B and compounds **6** and **7** were obtained, as shown in Table 2.

Unexpectedly, **6h** was obtained in low yield (18%) together with the monosubstituted compound **8** as the main product (48%) and 28% of the starting material **2d**. This result indicates a possible preference in the coupling process that gives rise to compound **8** rather than its isomer **9**—the expected

compound if steric effects were predominant in the process (Scheme 2).^{10b}

Monocoupling of *N*-aminides appeared to be even more efficient in pyrazine derivatives **2a–2c**. As a consequence,^{10b} a method involving a modification of method B was developed in order to decrease the amount of boronic acids (1.1 mmol) required with the aim of minimizing double coupling (Table 3). A series of 3-aryl or heteroaryl *N*-(5-bromopyrazin-2-yl)pyridinium aminides **10** were obtained. Although compounds **10** were obtained in fairly good yield, traces of diaryl aminides **7** and 5'-aryl products were detected in the reaction mixture. A reduction in the amount of catalyst from 5 to 1 mol % minimized the insertion of Pd⁰ into the C–Br bond in the 5'-position and, although the reaction took place slowly, a considerable increase in selectivity and therefore in yield was observed (Table 3, compounds **10a** and **10c**).

A model for the intermediate, in which the unshared pair of the aminide nitrogen coordinates palladium to provide some extra stability to the complex, has been proposed to explain the observed selectivity (Scheme 3).^{10b}

A similar type of behaviour has been reported in the literature for Pd-mediated processes involving 3,5-dibromopyrazines that contain substituents with an unshared electron pair in the 2-position.^{3b,12} In addition, the recent regioselective reduction of 3,5-dibromopyrazin-2-ylamine produced only 5-bromo-pyrazin-2-ylamine on using various hydride donors, palladium sources, ligands, bases and solvents.^{12f} The authors suggest the participation of the neighbouring amino group as a ligand as an explanation for the observed regioselectivity.

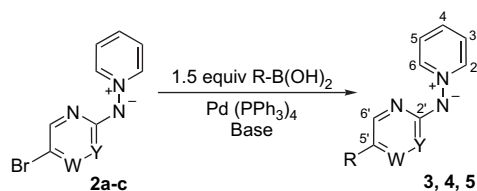
Once monocoupled aminides **10** had been prepared, a second coupling on the remaining bromine in the 5-position was achieved under previously described conditions (method B) to give almost quantitative yields of the unsymmetrical 3',5'-disubstituted pyrazin-2-ylaminides **11** (Scheme 4) reported in Table 4.

Two significant differences in chemical shifts can be observed in the ¹H NMR spectra of *N*-(3',5'-diarylpyrazin-2-yl)pyridinium aminides **7** and **10** in relation to the position of the aryl (or heteroaryl) substituent on the diazine ring: (a) substituents in the 5-position exert a deshielding effect on H6' (~0.5 ppm) and (b) the signals for the α-protons of the group in the 3'-position appear at lower field than those for the same substituent on the 5'-position. Representative chemical shifts for compounds **2d**, **4a**, **7a** and **10a** are given as examples in Figure 2.

3. Synthesis of 2-alkylaminoazines

The chemistry of pyridinium *N*-aminides has been well developed in our research group, and several publications refer to a regioselective *N*-alkylation and the subsequent reduction of the *N*–*N* bond in order to obtain 2-alkylaminoazines.^{8b,e,g,i} The preparation of 2-aminoazines is interesting not only because they are valuable intermediates in synthesis but also due to their interesting properties.¹² However, the preparation of highly functionalized 2-aminopyrazines is not an easy task.^{13,14} The present study could form the basis of a good

Table 1
Arylation of amidines **2a–c** with different arylboronic acids^a

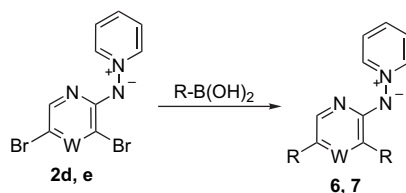


R ^a	Compound	W	Y	Method ^b	Time (h)	Yield (%)	R ^a	Compound	W	Y	Method ^b	Time (h)	Yield (%)
	3a	CH	CH	A B	8 8	90 95		31	CH	CH	A	2	95
	3b	CH	CH	A	8	88		4a	N	CH	A B	15 3	67 90
	3c	CH	CH	B	8	95		4b	N	CH	B	2	87
	3d	CH	CH	A B	12 12	25 92		4c	N	CH	A B	24 1	45 84
	3e	CH	CH	A	8	91		4d	N	CH	B	1	91
	3f	CH	CH	B	4	86		4e	N	CH	A B	2 1	71 89
	3g	CH	CH	A B	24 8	85 89		5a	CH	N	B	4	75
	3h	CH	CH	A B	72 4	64 95		5b	CH	N	B	4	70
	3i	CH	CH	A	8	75		5c	CH	N	B	5	81
	3j	CH	CH	A	8	70		5d	CH	N	B	4	73
	3k	CH	CH	B	8	89		5e	CH	N	B	2	95

^a Ring numbering employed in NMR analysis.

^b Method A: amidine (1 mmol), boronic acid (1.5 mmol), Cs₂CO₃ (2 mmol), Pd(PPh₃)₄ (5 mmol %), toluene/EtOH (20:1). Method B: amidine (1 mmol), boronic acid (1.5 mmol), K₂CO₃ (10 mmol), Pd(PPh₃)₄ (5 mmol %), toluene/EtOH (4:1).

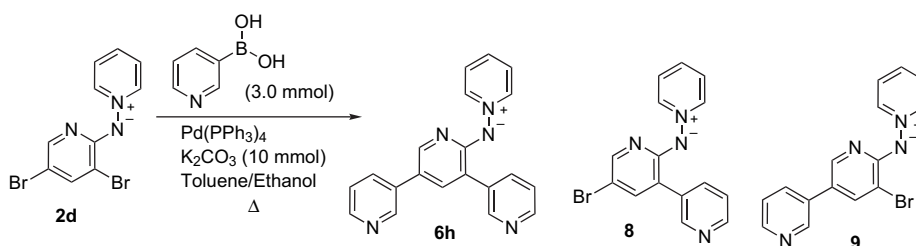
Table 2
Diarylation of aminides **2d,e** with different boronic acids



R	Compound	W	Method ^a	Time (h)	Yield (%)	R	Compound	W	Method ^a	Time (h)	Yield (%)
	6a	CH	A	8	63		7a	N	A B	15 8	67 90
	6b	CH	A	8	56		7b	N	B	2	86
	6c	CH	B	8	86		7c	N	A B	24 8	45 95
	6d	CH	A	3	90		7d	N	B	1	88
	6e	CH	B	8	70		7e	N	B	8	98
	6f	CH	A	8	78		7f	N	B	8	89
	6g	CH	A	3	85		7g	N	A B	2 8	71 89
	6h	CH	A	8	18 ^b						

^a Method A: boronic acid (3 mmol), Cs₂CO₃ (4 mmol), Pd(PPh₃)₄ (5 mol %), toluene/ethanol (20:1). Method B: boronic acid (3 mmol), K₂CO₃ (20 mmol), Pd(PPh₃)₄ (5 mol %), toluene/ethanol (4:1).

^b With 48% of aminide **8**.



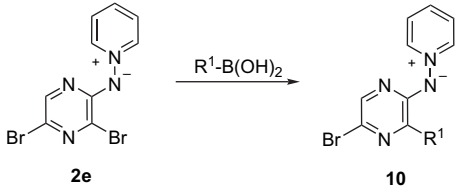
Scheme 2.


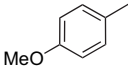
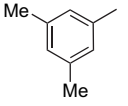
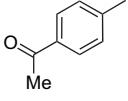
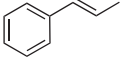

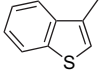



approach to produce 2-benzylamino-3,5-diarylpyrazines **13** with a high degree of variability, by reduction of salts **12** (Scheme 4).

Alkylation of aminides **11** was performed in anhydrous acetone and, once the solvent had been removed in vacuo, the pyridinium salts **12** were isolated by treatment with ethyl acetate, in which the excess alkylating agent and the unreacted aminide **11** remained in solution. The pyridinium salts **12** were used in the next step without further purification. The yields indicated in Table 5 are the result of the two steps: N-alkylation and N–N reduction.

In previous papers, we reported that the nuclear nitrogen on *N*-pyridin-2-yl pyridinium aminides is partially blocked by an intramolecular hydrogen bond, making the alkylation regioselective on the *exo*-nitrogen^{8b} (Fig. 3). Nevertheless, when this process was applied to unsubstituted diazine-stabilized aminides, where only one nitrogen can be blocked by the hydrogen bond, alkylation on the alternative nitrogen of the diazine ring was also detected.^{8e} In the case described here, the presence of two bulky aryl substituents at the 3'- and 5'-position makes N4' less accessible, and only the exocyclic nitrogen alkylation product is successfully obtained (Fig. 3).

Table 3
Monoarylation of 3',5'-dibromopyrazin-2'-yl pyridinium *N*-aminide **2e**



R ¹	Compound	Reaction time (h)	Yield (%)
	10a	3 (48) ^a	75 (87) ^a
	10b	5	71
	10c	8 (48) ^a	72 (85) ^a
	10d	8	65
	10e	4	50
	10f	12	84
	10g	12	81
	10h	2	65
	10i	4	77
	10j	16	60

^a Pd(PPh₃)₄ (1 mol %).

4. Conclusions

In conclusion, the peculiar reactivity of aminides **1**, which can be selectively mono- or dihalogenated,^{8c} allows an easy mono- or diarylation through the Suzuki reaction to produce compounds **3–7** with a diverse range of 3- and 3,5-aryl and heteroaryl substituents, all obtained with excellent yields. In most cases, the method employing an excess of K₂CO₃ (method B) gives rise to better results than the use of Cs₂CO₃.^{10a}

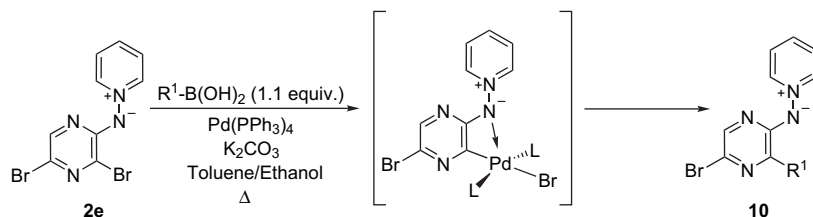
Moreover, the Suzuki process on dihalo derivatives of pyridine, such as **2e**, showed a regioselective arylation—predominantly at the 3'-position of the pyridine. The regioselectivity was higher with pyrazine derivatives and this yielded 3'-aryl derivatives, which were subsequently substituted with a different aryl group, thus yielding unsymmetrical pyridinium *N*-(3,5-diarylpyrazin-2-yl)aminides **11** in high yields. Finally, 2-alkylaminopyrazines **13** were prepared by alkylation of aminides **11** followed by N–N bond reduction of the corresponding aminopyridinium salts **12**.

In summary, the combination of the Suzuki arylation of pyridinium *N*-(3'-bromo or 3',5'-dibromoazinyl)aminides and conventional *N*-alkylation and *N*–*N* reduction allows the preparation of differently functionalized 2-alkylaminopyrazines, and eventually pyridines or pyrimidines, with high efficiency. Other Pd processes are currently being developed for these broadly useful substrates.

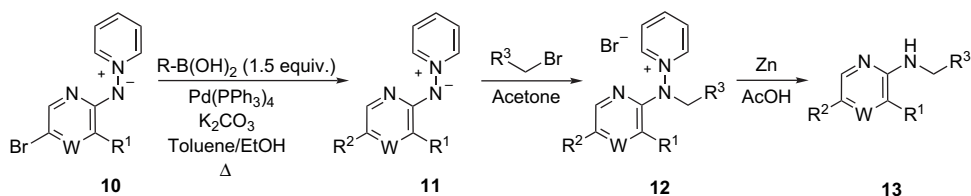
5. Experimental

5.1. General remarks

All melting points were determined in open capillary tubes on Gallenkamp MFB-595-010 M, Electrothermal LA6304 or Stuart Scientific SMP3 melting point apparatus and are uncorrected. IR spectra were obtained on a Perkin–Elmer FTIR 1725X spectrophotometer. ¹H and ¹³C NMR spectra were recorded on Varian Unity 300 or 500 MHz spectrometer or on



Scheme 3.



Scheme 4.

Table 4
Monoarylation of monocoupled aminides **10**

R ^{1a}	R ^{2b}	Compound	Reaction time (h)	Yield (%)
		11a	8	99
		11b	8	95
		11c	8	89
		11d	8	84
		11e	1	92 ^c
		11f	1	91 ^c
		11g	8	90
		11h	8	82
		11i	8	81
		11j	8	65
		11k	8	90
		11l	8	86
		11m	8	90

^a Positions labelled as (') for NMR analysis.

^b Positions labelled as (") for NMR analysis.

^c Yield has been improved in comparison to the first published results.^{10a}

a Varian Mercury VX-300 system at room temperature. Chemical shifts are given in parts per million (δ) downfield from TMS. Coupling constants (J) are in hertz (Hz) and signals are described as follows: s, singlet; d, doublet; t, triplet; m, multiplet; br, broad; ap, apparent. The tentative assignment of proton and carbon resonances has been made on the basis of double resonance, NOESY and TOCSY experiments, two-

dimensional H,H and H,C-correlation experiments, COSY, HSQC, HMBC or related spectra. In order to identify the signals in the description of each product, positions of the pyridinium ring are not labelled, positions of the azine ring are labelled ('), positions of the 3-aryl substituent are labelled ("), positions of the 5-aryl substituent (""') and positions of the aryl belonging to the aryl ring of the *N*-benzyl substituent, when present, are labelled ("""). Elemental analyses were carried out on a Heraeus Rapid CHN analyzer and were within 0.4% of the theoretical values for all the new compounds described. Low resolution mass spectra (MS) were taken on a Hewlett–Packard 5988A (70 eV) spectrometer using chemical ionization (CI) or electrospray (ESI) and high resolution analysis (FAB or TOF) was performed on a VG AutoSPEC (Micromass Instrument) or on an Agilent 6210 Time-of-flight LC/MS. All reagents and solvents were obtained from commercial sources, except 3-pyridineboronic acid,¹⁵ and were used without further purification. TLC analyses were performed on silica gel (Kieselgel 60 F₂₅₄, Macherey–Nagel) and spots were visualized under UV light. Column chromatography was carried out with silica gel 60 (40–63 μ m, Merck) and/or employing Biotage columns, using the mobile phase reported for each case.

5.2. General procedures for the preparation of 5-substituted *N*-(azin-2-yl)pyridinium aminides (**3**–**5**)

Method A. Aminides **2a**–**2c**^{8c} (1 mmol), the corresponding boronic acid (1.5 mmol) and Cs₂CO₃ (2 mmol) were dissolved in a toluene/ethanol mixture (20:1, 15 mL). Pd(PPh₃)₄ (5 mmol %) was added and the mixture was stirred under argon and heated under reflux for the reaction time indicated in Table 1.

Method B. Aminides **2a**–**2c**^{8c} (1 mmol), the corresponding boronic acid (1.5 mmol) and K₂CO₃ (10 mmol) were dissolved in a toluene/ethanol mixture (20:1, 15 mL). Pd(PPh₃)₄ (5 mmol %) was added and the mixture was stirred under argon and heated under reflux for the reaction time indicated in Table 1.

In both cases, the course of the reaction was followed by TLC, HPLC and/or ¹H NMR spectroscopy. Once the starting material had been consumed, the system was allowed to reach room temperature, the mixture was filtered through *Celite* or *silica gel* and washed with acetonitrile until colour was no longer observed in the filtrate. The combined filtrates were evaporated to dryness. The crude product was purified by flash chromatography on a silica gel column, with ethanol as the mobile phase, and recrystallized from a suitable solvent. Compound **3l** was isolated as a yellow oil, while compounds **3a**, **3c**, **3g**, **4c**, **4e** and **5a**–**5e** were transformed into the corresponding hydrobromides before purification.

5.2.1. *N*-(5-Phenylpyridin-2-yl)pyridinium aminide (**3a**)

See Ref. 10a.

5.2.2. *N*-[5-(4-Methylphenyl)pyridin-2-yl]pyridinium aminide (**3b**)

Orange solid (300 mg, 88%, ethyl acetate/hexane), mp 141–142 °C; IR (KBr) ν_{\max} (cm⁻¹): 1594, 1468, 1376, 1287, 1130, 809, 670; ¹H NMR (300 MHz, CD₃OD): δ 8.75 (2H, dd,

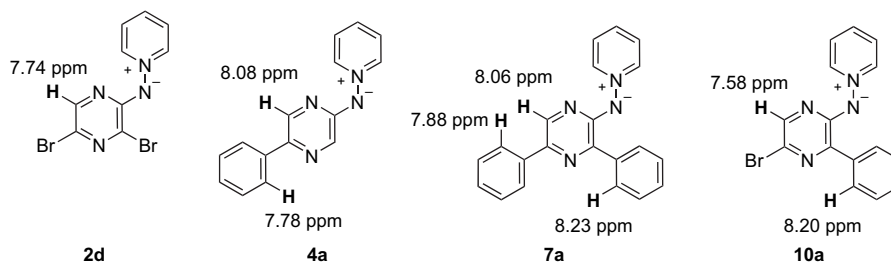
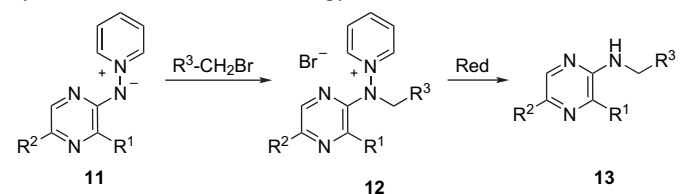


Figure 2.

$J=7.0$ and 1.3 Hz, $H2(6)$), 7.96 (1H, dd, $J=2.5$ and 0.7 Hz, $H6'$), 7.91 (1H, tt, $J=7.7$ and 1.3 Hz, $H4$), 7.71 (2H, dd, $J=7.7$ and 7.0 Hz, $H3(5)$), 7.65 (1H, dd, $J=8.9$ and 2.5 Hz, $H4'$), 7.37 (2H, d, $J=8.0$ Hz, $H2'''(6''')$), 7.17 (2H, d, $J=8.0$ Hz, $H3'''(5''')$), 6.61 (1H, dd, $J=8.9$ and 0.7 Hz, $H3'$),

2.34 (3H, s, CH_3); ^{13}C NMR (75 MHz, CD_3OD): δ 164.5 ($\text{C}2'$), 144.5 ($\text{C}6'$), 144.0 ($\text{C}2(6)$), 137.0 ($\text{C}4$), 137.0 ($\text{C}1'''$ or $\text{C}4'''$), 136.9 ($\text{C}1'''$ or $\text{C}4'''$), 136.8 ($\text{C}4'$), 130.5 ($\text{C}3'''(5''')$), 128.2 ($\text{C}3(5)$), 126.3 ($\text{C}2'''(6''')$), 125.5 ($\text{C}5'$), 112.4 ($\text{C}3'$), 21.1 (CH_3). MS (CI, m/z): 262 (100, $\text{M}+1$), 261 (40), 185 (11). Anal. Calcd for $\text{C}_{17}\text{H}_{15}\text{N}_3 \cdot 1/4\text{H}_2\text{O}$: C, 76.80; H, 5.88; N, 15.81. Found: C, 76.69; H, 6.15; N, 15.69.

Table 5

Synthesis of 3,5-disubstituted aminopyrazines **13**

R^{1a}	R^{2b}	R^{3c}	Compound	Yield
			12a	78
			12b	70
			12c	68
			12d	79
			12e	81 ^d
			12f	78
			13a	62
			13b	57
			13c	63

^a Positions labelled as ($''$) for NMR analysis.

^b Positions labelled as ($'''$) for NMR analysis.

^c Positions labelled as ($''''$) for NMR analysis.

^d Reaction time: 270 h.

5.2.3. *N*-[5'-(3-Hydroxymethylphenyl)pyridin-2-yl]-pyridinium aminide (**3c**)

Red oil (263 mg, 95%), mp hydrobromide 187–188 °C (yellowish solid, ethanol); IR (KBr) ν_{max} (cm^{-1}): 1597, 1469, 1377, 1299, 1150, 1000, 790; ^1H NMR (300 MHz, CD_3OD): δ 8.78 (2H, dd, $J=7.0$ and 1.2 Hz, $H2(6)$), 8.03 (1H, tt, $J=7.7$ and 1.2 Hz, $H4$), 7.98 (1H, br d, $J=2.6$ Hz, $H6'$), 7.82 (2H, dd, $J=7.7$ and 7.0 Hz, $H3(5)$), 7.72 (1H, dd, $J=8.9$ and 2.6 Hz, $H4'$), 7.52 (1H, m, $H2'''$), 7.42 (1H, dt, $J=7.6$ and 1.7 Hz, $H6'''$), 7.37 (1H, ap t, $J=7.3$ Hz, $H5'''$), 7.26 (1H, dt, $J=7.0$ and 1.7 Hz, $H4'''$), 6.62 (1H, d, $J=8.9$ Hz, $H3'$), 4.66 (2H, s, CH_2); ^{13}C NMR (75 MHz, CD_3OD): δ 165.0 ($\text{C}2'$), 144.9 ($\text{C}2(6)$), 144.5 ($\text{C}6'$), 143.3 ($\text{C}3'''$), 140.1 ($\text{C}1'''$), 137.7 ($\text{C}4$), 137.1 ($\text{C}4'$), 129.9 ($\text{C}5'''$), 128.5 ($\text{C}3(5)$), 125.9 ($\text{C}4'''$), 125.4 ($\text{C}5'$), 125.4 ($\text{C}6'''$), 125.0 ($\text{C}2'''$), 112.3 ($\text{C}3'$), 65.2 (CH_2). MS (CI, m/z): 278 (100, $\text{M}+1$), 277 (47), 260 (25), 201 (65). Anal. Calcd for $\text{C}_{17}\text{H}_{15}\text{N}_3\text{O} \cdot 2\text{HBr}$: C, 46.50; H, 3.90; N, 9.57. Found: C, 46.56; H, 3.69; N, 9.38.

5.2.4. *N*-[5-(4-Hydroxymethylphenyl)pyridin-2-yl]-pyridinium aminide (**3d**)

See Ref. 8i.

5.2.5. *N*-[5-(4-Methoxyphenyl)pyridin-2-yl]pyridinium aminide (**3e**)

Red solid (325 mg, 91%, dichloromethane/diethyl ether), mp 151–152 °C; IR (KBr) ν_{max} (cm^{-1}): 1598, 1466, 1376, 1279, 1248, 1133, 817, 669; ^1H NMR (300 MHz, CD_3OD):

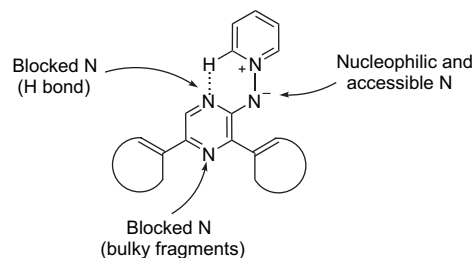


Figure 3.

δ 8.78 (2H, dd, $J=7.0$ and 1.3 Hz, $H2(6)$), 7.97 (1H, tt, $J=7.7$ and 1.3 Hz, $H4$), 7.92 (1H, dd, $J=2.5$ and 0.6 Hz, $H6'$), 7.75 (2H, dd, $J=7.7$ and 7.0 Hz, $H3(5)$), 7.64 (1H, dd, $J=8.8$ and 2.5 Hz, $H4'$), 7.41 (2H, d, $J=8.8$ Hz, $H2'''(6''')$), 6.95 (2H, d, $J=8.8$ Hz, $H3'''(5''')$), 6.60 (1H, dd, $J=8.8$ and 0.6 Hz, $H3'$), 3.81 (3H, s, CH_3); ^{13}C NMR (75 MHz, CD_3OD): δ 164.4 ($C2'$), 159.9 ($C4'''$), 144.2 ($C6'$), 144.2 ($C2(6)$), 137.2 ($C4$), 136.9 ($C4'$), 132.5 ($C1'''$), 128.4 ($C3(5)$), 127.6 ($C2'''(6''')$), 125.5 ($C5'$), 115.3 ($C3'''(5''')$), 112.4 ($C3'$), 55.7 (CH_3). MS (CI, m/z): 278 (100, $M+1$), 277 (71), 199 (9). Anal. Calcd for $C_{17}H_{15}N_3O \cdot 1/4H_2O$: C, 72.45; H, 5.54; N, 14.91. Found: C, 72.49; H, 5.51; N, 14.98.

5.2.6. *N*-[5-[4-(*N,N*-Dimethylamino)phenyl]pyridin-2-yl]-pyridinium aminide (**3f**)

Red solid (250 mg, 86%, ethyl acetate), mp 156–157 °C; IR (KBr) ν_{max} (cm^{-1}): 1612, 1598, 1471, 1381, 1302, 1138, 983, 815, 670; 1H NMR (300 MHz, CD_3OD): δ 8.79 (2H, dd, $J=7.0$ and 1.3 Hz, $H2(6)$), 7.96 (1H, tt, $J=7.7$ and 1.3 Hz, $H4$), 7.92 (1H, dd, $J=2.6$ and 0.7 Hz, $H6'$), 7.77 (2H, dd, $J=7.7$ and 7.0 Hz, $H3(5)$), 7.66 (1H, dd, $J=8.9$ and 2.6 Hz, $H4'$), 7.37 (2H, d, $J=9.0$ Hz, $H2'''(6''')$), 6.84 (2H, d, $J=9.0$ Hz, $H3'''(5''')$), 6.61 (1H, dd, $J=8.9$ and 0.7 Hz, $H3'$), 2.95 (6H, s, CH_3); ^{13}C NMR (75 MHz, CD_3OD): δ 164.1 ($C2'$), 151.0 ($C4'''$), 144.0 ($C2(6)$), 143.7 ($C6'$), 136.9 ($C4'$), 136.7 ($C4$), 128.6 ($C1'''$), 128.4 ($C3(5)$), 127.1 ($C2'''(6''')$), 126.2 ($C5'$), 114.6 ($C3'''(5''')$), 112.5 ($C3'$), 41.1 (CH_3). MS (CI, m/z): 291 (100, $M+1$), 290 (56), 214 (55), 108 (8), 80 (29). Anal. Calcd for $C_{18}H_{18}N_4 \cdot 1/4H_2O$: C, 73.31; H, 6.33; N, 19.01. Found: C, 73.60; H, 6.35; N, 18.89.

5.2.7. *N*-[5-(3-Chlorophenyl)pyridin-2-yl]pyridinium aminide (**3g**)

Orange oil (251 mg, 89%), mp hydrobromide 219–220 °C (yellowish solid, ethanol); IR (KBr) ν_{max} (cm^{-1}): 1590, 1464, 1385, 1121, 694; 1H NMR (500 MHz, CD_3OD): δ 8.77 (2H, dd, $J=6.9$ and 1.4 Hz, $H2(6)$), 7.99 (1H, tt, $J=7.7$ and 1.4 Hz, $H4$), 7.95 (1H, d, $J=2.6$ Hz, $H6'$), 7.78 (2H, dd, $J=7.7$ and 6.9 Hz, $H3(5)$), 7.63 (1H, dd, $J=8.9$ and 2.6 Hz, $H4'$), 7.48 (1H, t, $J=1.9$ Hz, $H2'''$), 7.39 (1H, ap dt, $J=7.8$ and 1.5 Hz, $H6'''$), 7.31 (1H, t, $J=7.8$ Hz, $H5'''$), 7.21 (1H, m, $H4'''$), 6.59 (1H, d, $J=8.9$ Hz, $H3'$); ^{13}C NMR (125 MHz, CD_3OD): δ 165.2 ($C2'$), 145.2 ($C6'$), 144.4 ($C2(6)$), 142.1 ($C1'''$), 137.6 ($C4$), 136.6 ($C4'$), 135.7 ($C3'''$), 131.3 ($C5'''$), 128.4 ($C3(5)$), 126.9 ($C4'''$), 126.1 ($C2'''$), 124.6 ($C6'''$), 123.6 ($C5'$), 112.3 ($C3'$). MS (CI, m/z): 284/282 (37/100, $M+1$), 283/281 (44/63), 246 (24), 205 (10). Anal. Calcd for $C_{16}H_{12}ClN_3 \cdot HBr \cdot 1/4H_2O$: C, 52.34; H, 3.71; N, 11.44. Found: C, 52.31; H, 3.79; N, 11.46.

5.2.8. *N*-[5-(4-Formylphenyl)pyridin-2-yl]pyridinium aminide (**3h**)

Orange solid (262 mg, 95%, ethanol/ethyl acetate), mp 163–164 °C; IR (KBr) ν_{max} (cm^{-1}): 1691, 1584, 1470, 1393, 1305, 1166, 769; 1H NMR (300 MHz, CD_3OD): δ 9.97 (1H, s, CHO), 8.80 (2H, dd, $J=6.8$ and 1.3 Hz, $H2(6)$), 8.12 (1H, m, $H4$), 8.10 (1H, m, $H6'$), 7.93 (2H, d, $J=8.4$ Hz, $H3'''(5''')$),

7.88 (2H, dd, $J=7.7$ and 6.8 Hz, $H3(5)$), 7.80 (1H, dd, $J=8.9$ and 2.6 Hz, $H4'$), 7.74 (2H, d, $J=8.4$ Hz, $H2'''(6''')$), 6.63 (1H, d, $J=8.9$ Hz, $H3'$); ^{13}C NMR (75 MHz, CD_3OD): δ 193.6 (CO), 165.7 ($C2'$), 146.4 ($C1'''$), 146.1 ($C6'$), 145.0 ($C2(6)$), 138.6 ($C4$), 136.7 ($C4'$), 135.6 ($C4'''$), 131.5 ($C3'''(5''')$), 128.7 ($C3(5)$), 126.3 ($C2'''(6''')$), 123.2 ($C5'$), 112.3 ($C3'$). MS (CI, m/z): 276 (100, $M+1$), 275 (29), 199 (17). Anal. Calcd for $C_{17}H_{13}N_3O \cdot 1/4H_2O$: C, 72.96; H, 4.87; N, 15.02. Found: C, 72.96; H, 5.17; N, 15.04.

5.2.9. *N*-[5-(4-Acetylphenyl)pyridin-2-yl]pyridinium aminide (**3i**)

Orange solid (217 mg, 75%, dichloromethane), mp 188–189 °C; IR (KBr) ν_{max} (cm^{-1}): 1671, 1582, 1458, 1374, 1267, 1144, 818; 1H NMR (300 MHz, CD_3OD): δ 8.80 (2H, dd, $J=7.0$ and 1.2 Hz, $H2(6)$), 8.11 (1H, tt, $J=7.7$ and 1.2 Hz, $H4$), 8.10 (1H, dd, $J=2.6$ and 0.8 Hz, $H6'$), 8.03 (2H, d, $J=8.6$ Hz, $H3'''(5''')$), 7.87 (2H, dd, $J=7.7$ and 7.0 Hz, $H3(5)$), 7.79 (1H, dd, $J=8.9$ and 2.6 Hz, $H4'$), 7.67 (2H, d, $J=8.6$ Hz, $H2'''(6''')$), 6.63 (1H, dd, $J=8.9$ and 0.8 Hz, $H3'$), 2.63 (3H, s, CH_3); ^{13}C NMR (75 MHz, CD_3OD): δ 200.2 (CO), 165.7 ($C2'$), 145.8 ($C6'$), 145.1 ($C1'''$), 145.0 ($C2(6)$), 138.5 ($C4$), 136.7 ($C4'$), 135.7 ($C4'''$), 130.3 ($C3'''(5''')$), 128.7 ($C3(5)$), 126.0 ($C2'''(6''')$), 123.5 ($C5'$), 112.3 ($C3'$), 26.5 (CH_3). Anal. Calcd for $C_{18}H_{15}N_3O$: C, 74.72; H, 5.23; N, 14.52. Found: C, 74.69; H, 5.42; N, 14.49.

5.2.10. *N*-[5-(*trans*-2-Phenylvinyl)pyridin-2-yl]pyridinium aminide (**3j**)

Red solid (191 mg, 70%, ethyl acetate/hexane), mp 159–160 °C; IR (KBr) ν_{max} (cm^{-1}): 1589, 1483, 1468, 1386, 1345, 1156, 958, 755; 1H NMR (300 MHz, CD_3OD): δ 8.75 (2H, dd, $J=7.0$ and 1.2 Hz, $H2(6)$), 8.03 (1H, tt, $J=7.8$ and 1.2 Hz, $H4$), 7.80 (2H, dd, $J=7.8$ and 7.0 Hz, $H3(5)$), 7.76 (1H, m, $H6'$), 7.74 (1H, m, $H4'$), 7.49 (2H, m, $H2'''(6''')$), 7.32 (2H, ap t, $J=7.6$ Hz, $H3'''(5''')$), 7.19 (1H, tt, $J=7.3$ and 1.3 Hz, $H4'''$), 7.01 (1H, ap d, $J=16.4$ Hz, H_{α}), 6.88 (1H, ap d, $J=16.4$ Hz, H_{β}), 6.57 (1H, dd, $J=8.4$ and 1.4 Hz, $H3'$); ^{13}C NMR (75 MHz, CD_3OD): δ 165.1 ($C2'$), 147.0 ($C6'$), 144.6 ($C2(6)$), 139.5 ($C1'''$), 137.9 ($C4$), 134.8 ($C4'$), 129.6 ($C3'''(5''')$), 128.5 ($C3(5)$), 127.7 ($C4'''$), 126.9 ($C2'''(6''')$), 126.8 (C_{α}), 124.9 (C_{β}), 122.6 ($C5'$), 112.8 ($C3'$). MS (CI, m/z): 274 (100, $M+1$), 273 (48), 197 (31). Anal. Calcd for $C_{18}H_{15}N_3 \cdot 1/4H_2O$: C, 78.24; H, 5.59; N, 15.21. Found: C, 78.31; H, 5.72; N, 15.21.

5.2.11. *N*-[5-(Benzo[*b*]furan-2-yl)pyridin-2-yl]pyridinium aminide (**3k**)

Orange solid (256 mg, 89%, ethyl acetate/hexane), mp 141–142 °C; IR (KBr) ν_{max} (cm^{-1}): 1619, 1487, 1451, 1395, 1137, 799, 744, 669; 1H NMR (300 MHz, CD_3OD): δ 8.75 (2H, dd, $J=6.9$ and 1.3 Hz, $H2(6)$), 8.22 (1H, br d, $J=2.1$ Hz, $H6'$), 8.08 (1H, tt, $J=7.7$ and 1.3 Hz, $H4$), 7.84 (2H, dd, $J=7.7$ and 6.9 Hz, $H3(5)$), 7.81 (1H, dd, $J=8.9$ and 2.4 Hz, $H4'$), 7.51 (1H, m, $H4'''$), 7.44 (1H, m, $H7'''$), 7.19 (2H, m, $H5'''$ and $H6'''$), 6.84 (1H, d, $J=0.9$ Hz, $H3'''$), 6.59 (1H, dd, $J=8.9$ and 0.6 Hz, $H3'$); ^{13}C NMR (75 MHz,

CD₃OD): δ 165.1 (C2'), 156.1 (C2'''), 155.3 (C7'''a), 144.6 (C2(6)), 143.8 (C6'), 138.2 (C4), 134.5 (C4'), 130.7 (C3'''a), 128.3 (C3(5)), 124.1 (C5''' or C6'''), 123.6 (C5''' or C6'''), 120.9 (C4'''), 115.1 (C5'), 111.9 (C3'), 111.2 (C7'''), 98.6 (C3'''). MS (CI, *m/z*): 288 (100, M+1), 211 (38), 108 (10), 80 (60). Anal. Calcd for C₁₈H₁₃N₃O·1/4H₂O: C, 74.01; H, 4.66; N, 14.41. Found: C, 74.24; H, 4.83; N, 14.43.

5.2.12. *N*-[5-(Pyridin-3-yl)pyridin-2-yl]pyridinium aminide (3l)

Yellow oil (236 mg, 95%); IR (KBr) ν_{\max} (cm⁻¹): 1598, 1462, 1417, 1376, 1300, 1147, 1019, 804; ¹H NMR (500 MHz, CD₃OD): δ 8.80 (2H, dd, *J*=7.0 and 1.2 Hz, H2(6)), 8.70 (1H, dd, *J*=2.4 and 0.7 Hz, H2'''), 8.41 (1H, dd, *J*=4.8 and 1.5 Hz, H6'''), 8.09 (1H, tt, *J*=7.7 and 1.2 Hz, H4), 8.00 (1H, dd, *J*=2.5 and 0.7 Hz, H6'), 7.98 (1H, ddd, *J*=8.0, 2.4 and 1.5 Hz, H4'''), 7.86 (2H, dd, *J*=7.7 and 7.0 Hz, H3(5)), 7.73 (1H, dd, *J*=8.9 and 2.5 Hz, H4'), 7.45 (1H, ddd, *J*=8.0, 4.8 and 0.7 Hz, H5'''), 6.64 (1H, dd, *J*=8.9 and 0.7 Hz, H3'); ¹³C NMR (125 MHz, CD₃OD): δ 165.7 (C2'), 147.4 (C6'''), 146.8 (C2'''), 145.5 (C6'), 144.9 (C2(6)), 138.3 (C4), 136.6 (C3'''), 136.6 (C4'), 134.6 (C4'''), 128.6 (C3(5)), 125.4 (C5'''), 121.1 (C5'), 112.4 (C3'). HRMS (FAB) calcd for C₁₅H₁₃N₄ [M+H]⁺ 249.1140, found 249.1149.

5.2.13. *N*-(5-Phenylpyrazin-2-yl)pyridinium aminide (4a)

Yellow solid (228 mg, 90%, dichloromethane/diethyl ether), mp 171–172 °C; IR (KBr) ν_{\max} (cm⁻¹): 1514, 1488, 1466, 1385, 1301, 1147, 992, 474; ¹H NMR (300 MHz, CD₃OD): δ 8.87 (2H, dd, *J*=7.0 and 1.3 Hz, H2(6)), 8.14 (1H, tt, *J*=7.7 and 1.3 Hz, H4), 8.08 (1H, d, *J*=1.5 Hz, H6'), 7.96 (1H, d, *J*=1.5 Hz, H3'), 7.89 (2H, dd, *J*=7.7 and 7.0 Hz, H3(5)), 7.78 (2H, ap dd, *J*=8.5 and 1.3 Hz, H2'''(6''')), 7.42 (2H, ap dd, *J*=8.5 and 7.4 Hz, H3'''(5''')), 7.30 (1H, tt, *J*=7.4 and 1.3 Hz, H4'''); ¹³C NMR (75 MHz, CD₃OD): δ 160.9 (C2'), 144.8 (C2(6)), 139.4 (C5'), 139.2 (C1'''), 139.0 (C4), 138.7 (C6'), 136.5 (C3'), 129.7 (C3'''(5''')), 128.6 (C3(5)), 128.2 (C4'''), 125.9 (C2'''(6''')). Anal. Calcd for C₁₅H₁₂N₄: C, 72.56; H, 4.87; N, 22.57. Found: C, 72.27; H, 5.03; N, 22.47.

5.2.14. *N*-[5-(4-Methoxyphenyl)pyrazin-2-yl]pyridinium aminide (4b)

Orange solid (242 mg, 87%, ethanol), mp 145–146 °C; IR (KBr) ν_{\max} (cm⁻¹): 1606, 1568, 1491, 1374, 1236, 1147, 992, 669; ¹H NMR (300 MHz, CD₃OD): δ 8.86 (2H, dd, *J*=7.0 and 1.3 Hz, H2(6)), 8.10 (1H, tt, *J*=7.6 and 1.3 Hz, H4), 8.01 (1H, d, *J*=1.6 Hz, H6'), 7.92 (1H, d, *J*=1.6 Hz, H3'), 7.86 (2H, dd, *J*=7.6 and 7.0 Hz, H3(5)), 7.69 (2H, d, *J*=8.8 Hz, H2'''(6''')), 6.97 (2H, d, *J*=8.8 Hz, H3'''(5''')), 3.84 (3H, s, CH₃); ¹³C NMR (75 MHz, CD₃OD): δ 160.2 (C4'''), 159.9 (C2'), 144.1 (C2(6)), 139.1 (C5'), 138.2 (C4), 137.6 (C6'), 135.9 (C3'), 131.2 (C1'''), 128.2 (C3(5)), 126.9 (C2'''(6''')), 114.9 (C3'''(5''')), 55.7 (CH₃). Anal. Calcd for C₁₆H₁₄N₄O: C, 69.05; H, 5.07; N, 20.13. Found: C, 68.69; H, 5.09; N, 20.00.

5.2.15. *N*-[5-(4-Acetylphenyl)pyrazin-2-yl]pyridinium aminide (4c)

Orange solid (244 mg, 84%), mp hydrobromide 210–211 °C (yellowish solid, ethanol/dichloromethane); IR (KBr) ν_{\max} (cm⁻¹): 1672, 1601, 1578, 1521, 1495, 1467, 1400, 1263, 1146, 994, 828, 666; ¹H NMR (300 MHz, CD₃OD): δ 8.86 (2H, dd, *J*=6.9 and 1.3 Hz, H2(6)), 8.20 (1H, d, *J*=1.5 Hz, H6'), 8.19 (1H, tt, *J*=8.0 and 1.3 Hz, H4), 8.05 (2H, d, *J*=8.5 Hz, H2'''(6''')), 7.99 (1H, d, *J*=1.5 Hz, H3'), 7.96 (2H, d, *J*=8.5 Hz, H3'''(5''')), 7.93 (2H, dd, *J*=8.0 and 6.9 Hz, H3(5)), 2.65 (3H, s, CH₃); ¹³C NMR (75 MHz, CD₃OD): δ 199.5 (CO), 160.8 (C2'), 144.6 (C2(6)), 143.5 (C1'''), 139.4 (C4), 139.2 (C6'), 136.9 (C5'), 136.6 (C3'), 136.1 (C4'''), 129.8 (C3'''(5''')), 128.4 (C3(5)), 125.1 (C2'''(6''')), 26.7 (CH₃). MS (CI, *m/z*): 291(100, M+1), 214(89), 108 (20), 80 (97). Anal. Calcd for C₁₇H₁₄N₄O·1/4H₂O: C, 69.24; H, 4.96; N, 19.01. Found: C, 69.44; H, 4.80; N, 19.17.

5.2.16. *N*-[5-(*trans*-2-Phenylvinyl)pyrazin-2-yl]pyridinium aminide (4d)

Red solid (250 mg, 91%, ethanol), mp 180–181 °C; IR (KBr) ν_{\max} (cm⁻¹): 1568, 1501, 1396, 1146, 1004, 748; ¹H NMR (300 MHz, CD₃OD): δ 8.84 (2H, dd, *J*=7.0 and 1.3 Hz, H2(6)), 8.13 (1H, tt, *J*=7.7 and 1.3 Hz, H4), 7.90 (1H, d, *J*=1.4 Hz, H6'), 7.88 (2H, dd, *J*=7.7 and 7.0 Hz, H3(5)), 7.72 (1H, d, *J*=1.4 Hz, H3'), 7.52 (2H, ap dd, *J*=8.6 and 1.3 Hz, H2'''(6''')), 7.34 (2H, ap dd, *J*=8.6 and 7.3 Hz, H3'''(5''')), 7.23 (1H, d, *J*=16.1 Hz, H_β), 7.22 (1H, tt, *J*=7.3 and 1.3 Hz, H4'''), 7.04 (1H, d, *J*=16.1 Hz, H_α); ¹³C NMR (75 MHz, CD₃OD): δ 160.3 (C2'), 144.3 (C2(6)), 140.6 (C3'), 139.1 (C5'), 138.7 (C4), 137.5 (C1'''), 137.0 (C6'), 129.3 (C3'''(5''')), 128.3 (C3(5)), 127.9 (C4'''), 127.0 (C2'''(6''')), 127.0 (C_β), 125.4 (C_α). Anal. Calcd for C₁₇H₁₄N₄: C, 74.43; H, 5.14; N, 20.42. Found: C, 74.16; H, 5.28; N, 20.21.

5.2.17. *N*-[5-(Pyridin-3-yl)pyrazin-2-yl]pyridinium aminide (4e)

Orange solid (217 mg, 89%, ethanol), mp 142–143 °C; IR (KBr) ν_{\max} (cm⁻¹): 1579, 1510, 1481, 1463, 1414, 1385, 1147, 996; ¹H NMR (300 MHz, CD₃OD): δ 8.98 (1H, dd, *J*=2.3 and 0.7 Hz, H2'''), 8.85 (2H, dd, *J*=7.0 and 1.3 Hz, H2(6)), 8.43 (1H, dd, *J*=4.8 and 1.6 Hz, H6'''), 8.23 (1H, ddd, *J*=8.1, 2.3 and 1.6 Hz, H4'''), 8.17 (1H, tt, *J*=7.8 and 1.3 Hz, H4), 8.13 (1H, d, *J*=1.6 Hz, H6'), 7.97 (1H, d, *J*=1.6 Hz, H3'), 7.91 (2H, dd, *J*=7.8 and 7.0 Hz, H3(5)), 7.46 (1H, ddd, *J*=8.1, 4.8 and 0.7 Hz, H5'''); ¹³C NMR (75 MHz, CD₃OD): δ 161.0 (C2'), 147.7 (C6'''), 146.1 (C2'''), 144.7 (C2(6)), 139.2 (C4), 138.9 (C6'), 137.0 (C3'), 135.3 (C3'''), 135.2 (C5'), 133.6 (C4'''), 128.5 (C3(5)), 125.1 (C5'''). MS (CI, *m/z*): 250 (100, M+1). Anal. Calcd for C₁₄H₁₁N₅·1.4H₂O: C, 66.26; H, 4.57; N, 27.60. Found: C, 66.58; H, 4.43; N, 27.31.

5.2.18. *N*-(5-Phenylpyrimidin-2-yl)pyridinium aminide (5a)

Yellow solid (186 mg, 75%), mp hydrobromide 222–223 °C (yellowish solid, ethanol/ethyl acetate); IR (KBr) ν_{\max} (cm⁻¹): 1600, 1438; ¹H NMR (300 MHz, CD₃OD): δ 8.75 (2H, dd, *J*=6.9 and 1.3 Hz, H2(6)), 8.40 (2H, s,

$H4'(6')$, 8.19 (1H, tt, $J=7.8$ and 1.3 Hz, $H4$), 7.91 (2H, dd, $J=7.8$ and 6.9 Hz, $H3(5)$), 7.49 (2H, dd, $J=8.4$ and 1.4 Hz, $H2''(6''')$), 7.41 (2H, dd, $J=8.4$ and 7.2 Hz, $H3'''(5''')$), 7.29 (1H, tt, $J=7.2$ and 1.4 Hz, $H4''$); ^{13}C NMR (75 MHz, CD_3OD): δ 168.8 ($C2'$), 157.2 ($C4'(6')$), 145.7 ($C2(6)$), 139.8 ($C4$), 137.0 ($C1'''$), 130.1 ($C3'''(5''')$), 128.7 ($C3(5)$), 127.8 ($C4''$), 126.1 ($C2''(6''')$), 122.4 ($C5'$). MS (CI, m/z): 249 (100, $M+1$), 200 (56), 172 (24). Anal. Calcd for $\text{C}_{15}\text{H}_{12}\text{N}_4 \cdot \text{HBr} \cdot \text{H}_2\text{O}$: C, 52.02; H, 4.37; N, 16.19. Found: C, 51.96; H, 3.98; N, 16.03.

5.2.19. *N*-[5-(4-Methylphenyl)pyrimidin-2-yl]pyridinium aminide (**5b**)

Yellow solid (184 mg, 70%), mp hydrobromide 242–244 °C (yellowish solid, ethanol/ethyl acetate); IR (KBr) ν_{max} (cm^{-1}): 1600, 1437; ν_{max} (KBr/hydrobromide) 2813, 1619, 1594, 1468, 1431, 818, 773, 669; ^1H NMR (300 MHz, CD_3OD): δ 8.74 (2H, dd, $J=6.9$ and 1.3 Hz, $H2(6)$), 8.36 (2H, s, $H4'(6')$), 8.17 (1H, tt, $J=7.8$ and 1.3 Hz, $H4$), 7.89 (2H, dd, $J=7.8$ and 6.9 Hz, $H3(5)$), 7.36 (2H, d, $J=8.2$ Hz, $H2''(6''')$), 7.22 (2H, d, $J=8.2$ Hz, $H3'''(5''')$), 2.36 (3H, s, CH_3); ^{13}C NMR (75 MHz, CD_3OD): δ 168.6 ($C2'$), 157.0 ($C4'(6')$), 145.6 ($C2(6)$), 139.6 ($C4$), 137.7 ($C4''$), 134.1 ($C1'''$), 130.7 ($C3'''(5''')$), 128.7 ($C3(5)$), 126.0 ($C2''(6''')$), 122.5 ($C5'$), 21.1 (CH_3). MS (CI, m/z): 263 (35, $M+1$), 186 (89), 80 (100). Anal. Calcd for $\text{C}_{16}\text{H}_{14}\text{N}_4 \cdot \text{HBr} \cdot 1/2\text{H}_2\text{O}$: C, 54.69; H, 4.31; N, 15.96. Found: C, 54.66; H, 4.41; N, 15.74.

5.2.20. *N*-[5-(4-Methoxyphenyl)pyrimidin-2-yl]pyridinium aminide (**5c**)

Yellow solid (225 mg, 81%), mp hydrobromide 235–236 °C (yellowish solid, ethanol); IR (KBr) ν_{max} (cm^{-1}): 1592, 1420, 1246, 820, 776; ^1H NMR (300 MHz, CD_3OD): δ 8.74 (2H, dd, $J=7.0$ and 1.3 Hz, $H2(6)$), 8.33 (1H, s, $H4'(6')$), 8.16 (1H, tt, $J=7.7$ and 1.3 Hz, $H4$), 7.89 (2H, dd, $J=7.7$ and 7.0 Hz, $H3(5)$), 7.39 (2H, d, $J=8.9$ Hz, $H2''(6''')$), 6.97 (2H, d, $J=8.9$ Hz, $H3'''(5''')$), 3.82 (3H, s, CH_3); ^{13}C NMR (75 MHz, CD_3OD): δ 168.2 ($C2'$), 160.0 ($C4''$), 156.6 ($C4'(6')$), 145.4 ($C2(6)$), 139.4 ($C4$), 129.3 ($C1'''$), 128.5 ($C3(5)$), 127.2 ($C2''(6''')$), 122.3 ($C5'$), 115.4 ($C3'''(5''')$), 55.7 (CH_3). MS (CI, m/z): 279 (100, $M+1$), 278 (32), 253 (33), 251 (34), 202 (57), 172 (20), 80 (34). Anal. Calcd for $\text{C}_{16}\text{H}_{14}\text{N}_4\text{O} \cdot \text{HBr} \cdot 1/4\text{H}_2\text{O}$: C, 52.83; H, 4.30; N, 15.40. Found: C, 52.65; H, 4.08; N, 15.21.

5.2.21. *N*-[5-(*trans*-2-Phenylvinyl)pyrimidin-2-yl]pyridinium aminide (**5d**)

Yellow solid (200 mg, 73%), mp hydrobromide 227–229 °C (yellowish solid, ethanol/ethyl acetate); IR (KBr) ν_{max} (cm^{-1}): 1591, 1438; ^1H NMR (300 MHz, CD_3OD): δ 8.71 (2H, dd, $J=6.8$ and 1.2 Hz, $H2(6)$), 8.32 (2H, s, $H4'(6')$), 8.16 (1H, tt, $J=7.8$ and 1.2 Hz, $H4$), 7.87 (2H, dd, $J=7.8$ and 6.8 Hz, $H3(5)$), 7.47 (2H, m, $H2''(6''')$), 7.31 (2H, ap t, $J=7.4$ Hz, $H3'''(5''')$), 7.20 (1H, tt, $J=7.4$ and 1.3 Hz, $H4''$), 6.92 (2H, m, H_α and H_β); ^{13}C NMR (75 MHz, CD_3OD): δ 168.1 ($C2'$), 156.8 ($C4'(6')$), 145.1 ($C2(6)$), 139.4 ($C4$), 138.6 ($C1'''$), 129.3 ($C3'''(5''')$), 128.3 ($C3(5)$), 127.8 ($C4''$), 126.8 ($C2''(6''')$), 125.5 (C_6),

123.3 (C_α), 119.4 ($C5'$). MS (CI, m/z): 275 (100, $M+1$), 274 (26), 198 (84), 80 (79). Anal. Calcd for $\text{C}_{17}\text{H}_{14}\text{N}_4 \cdot \text{HBr} \cdot 1/4\text{H}_2\text{O}$: C, 56.59; H, 4.63; N, 15.53. Found: C, 56.93; H, 4.36; N, 15.43.

5.2.22. *N*-[5-(Pyridin-3-yl)pyrimidin-2-yl]pyridinium aminide (**5e**)

Yellow oil (236 mg, 95%), mp hydrobromide >300 °C (yellowish solid, ethanol); IR (KBr) ν_{max} (cm^{-1}): 1602, 1446, 1307, 668; ^1H NMR (300 MHz, CD_3OD): δ 8.77 (2H, dd, $J=6.9$ and 1.3 Hz, $H2(6)$), 8.69 (1H, dd, $J=2.4$ and 0.9 Hz, $H2''$), 8.45 (1H, dd, $J=4.8$ and 1.6 Hz, $H6'''$), 8.44 (1H, s, $H4'(6')$), 8.23 (1H, tt, $J=7.7$ and 1.3 Hz, $H4$), 7.98 (1H, ddd, $J=8.1$, 2.4 and 1.6 Hz, $H4''$), 7.94 (2H, dd, $J=7.7$ and 6.9 Hz, $H3(5)$), 7.47 (1H, ddd, $J=8.1$, 4.8 and 0.9 Hz, $H5'''$); ^{13}C NMR (75 MHz, CD_3OD): δ 168.6 ($C2'$), 156.9 ($C4'(6')$), 147.6 ($C6'''$), 146.1 ($C2'''$), 145.3 ($C2(6)$), 139.8 ($C4$), 134.1 ($C4''$), 133.5 ($C3'''$), 128.4 ($C3(5)$), 125.2 ($C5'''$), 118.1 ($C5'$). MS (CI, m/z): 250 (100, $M+1$), 249 (19), 201 (70), 173 (34), 80 (34). Anal. Calcd for $\text{C}_{14}\text{H}_{11}\text{N}_5 \cdot 2\text{HBr} \cdot \text{H}_2\text{O}$: C, 39.19; H, 3.52; N, 16.32. Found: C, 39.74; H, 3.41; N, 15.99.

5.3. Synthesis of symmetrical 3,5-disubstituted aminides **6** and **7**: general procedure

Method A. Dibromoaminides **2d,e**^{8c} (1 mmol) and the corresponding boronic acid (3 mmol) were dissolved in a toluene/ethanol mixture (20:1, 15 mL). Cs_2CO_3 (4 mmol) was added, followed by $\text{Pd}(\text{PPh}_3)_4$ (5 mol %). After the addition, the mixture was kept under argon with vigorous stirring for 5 min, and then heated under reflux for the reaction time indicated in Table 2.

Method B. Dibromoaminides **2d,e**^{8c} (1 mmol) and the corresponding boronic acid (3 mmol) were dissolved in a toluene/ethanol mixture (4:1, 10 mL). K_2CO_3 (20 mmol) was added followed by $\text{Pd}(\text{PPh}_3)_4$ (5 mol %). After the addition, the mixture was kept under argon with vigorous stirring for 5 min, and then heated under reflux for the reaction time indicated in Table 2.

In both methods, as soon as the starting material has been consumed, the system was allowed to reach room temperature, the mixture was filtered through *Celite* or *silica gel* and the residue washed with acetonitrile until colour was no longer observed in the filtrate. The filtrates were combined, the solvent evaporated to dryness and the residue purified by flash chromatography through a silica gel column, using ethanol as the mobile phase. Finally, the compounds were, if possible, recrystallized from a suitable solvent. Compounds **6a** and **6h** were isolated as yellow oils. Compounds **6a**, **6e**, **6f**, **6g**, **7b**, **7d**, **7e** and **7f** were transformed into the corresponding hydrobromides by adding aqueous hydrogen bromide (48%, 3 equiv) and the salts were isolated after removal of excess acid. Ethyl acetate was then added and the aminide hydrobromide was treated in an ultrasonic bath. The remaining solid was filtered off and dried. Hydrobromides of compounds **6a**, **6g**, **7b** and **7d** were purified by recrystallization from ethanol. To recover the free aminides **6e**, **6f**, **7e** and **7f**, the

corresponding hydrobromide was poured into acetone and ion exchange resin Amberlite IRA-67 (3 equiv $C_E=1.6$ equiv/g) was added. When equilibration was complete, the resin was removed by filtration and the solvent evaporated to give the desired aminide, which was used without further purification.

5.3.1. *N*-[3,5-Diphenylpyridin-2-yl]pyridinium aminide (**6a**)

See Ref. 10a.

5.3.2. *N*-[3,5-Bis(4-methylphenyl)pyridin-2-yl]pyridinium aminide (**6b**)

Yellow oil (197 mg, 56%); IR (KBr) ν_{\max} (cm^{-1}): 1595, 1435, 1380, 1308, 1165, 815; ^1H NMR (300 MHz, CD_3OD): δ 8.62 (2H, dd, $J=7.0$ and 1.2 Hz, $H_2(6)$), 7.92 (1H, tt, $J=7.8$ and 1.2 Hz, H_4), 7.90 (1H, d, $J=2.5$ Hz, H_6'), 7.70 (2H, dd, $J=7.8$ and 7.0 Hz, $H_3(5)$), 7.60 (2H, d, $J=8.1$ Hz, $H_2''(6'')$), 7.54 (1H, d, $J=2.5$ Hz, H_4'), 7.39 (2H, d, $J=8.2$ Hz, $H_2'''(6''')$), 7.22 (2H, br d, $J=7.8$ Hz, $H_3''(5'')$), 7.18 (2H, br d, $J=7.9$ Hz, $H_3'''(5''')$), 2.37 (3H, s, CH_3), 2.33 (3H, s, CH_3); ^{13}C NMR (125 MHz, CD_3OD): δ 162.9 (C_2'), 144.8 ($C_2(6)$), 143.6 (C_6'), 138.1 (C_1''), 137.6 (C_4''), 137.3 (C_4'), 137.1 (C_1'''), 136.9 (C_4), 136.9 (C_4'''), 130.5 ($C_3'''(5''')$), 130.4 ($C_2''(6'')$), 129.8 ($C_3''(5'')$), 128.2 ($C_3(5)$), 126.3 ($C_2'''(6''')$), 125.6 (C_5'), 124.9 (C_3'), 21.3 (CH_3), 21.1 (CH_3). HRMS (FAB) calcd for $\text{C}_{24}\text{H}_{22}\text{N}_3$: $[\text{M}+\text{H}]^+$ 352.1814, found: 352.1829.

5.3.3. *N*-[3,5-Bis(4-hydroxymethylphenyl)pyridin-2-yl]pyridinium aminide (**6c**)

Red solid (329 mg, 86%, ethanol/toluene); mp 205–206 °C; IR (KBr) ν_{\max} (cm^{-1}): 3169, 3112, 1599, 1442, 1419, 1384, 1321, 1041, 824, 678, 594, 517; ^1H NMR (500 MHz, CD_3OD): δ 8.72 (2H, dd, $J=7.0$ and 1.2 Hz, $H_2(6)$), 8.06 (1H, tt, $J=7.8$ and 1.2 Hz, H_4), 7.96 (1H, d, $J=2.4$ Hz, H_6'), 7.82 (2H, dd, $J=7.8$ and 7.0 Hz, $H_3(5)$), 7.73 (2H, d, $J=8.3$ Hz, $H_2''(6'')$), 7.62 (1H, d, $J=2.4$ Hz, H_4'), 7.53 (2H, d, $J=8.5$ Hz, $H_2'''(6''')$), 7.44 (2H, d, $J=8.4$ Hz, $H_3''(5'')$), 7.40 (2H, d, $J=8.6$ Hz, $H_3'''(5''')$), 4.68 (2H, s, CH_2O), 4.64 (2H, s, CH_2O); ^{13}C NMR (125 MHz, CD_3OD): δ 161.3 (C_2'), 145.4 ($C_2(6)$), 144.1 (C_6'), 141.5 (C_4''), 140.8 (C_4'''), 139.8 (C_1''), 139.0 (C_1'''), 138.2 (C_4), 137.5 (C_4'), 130.4 ($C_2''(6'')$), 128.7 ($C_3'''(5''')$), 128.5 ($C_3(5)$), 127.9 ($C_3''(5'')$), 126.4 ($C_2'''(6''')$), 125.8 (C_5'), 124.8 (C_3'), 65.1 (CH_2O), 65.0 (CH_2O). MS (CI, m/z): 384 (4, $\text{M}+1$), 287 (27), 276 (25), 275 (100). Anal. Calcd for $\text{C}_{24}\text{H}_{21}\text{N}_3\text{O}_2 \cdot 1/2\text{H}_2\text{O}$: C, 73.45; H, 5.65; N, 10.71. Found: C, 73.34; H, 5.47; N, 10.60.

5.3.4. *N*-[3,5-Bis(4-methoxyphenyl)pyridin-2-yl]pyridinium aminide (**6d**)

Red solid (345 mg, 90%, ethanol), mp 94–96 °C; IR (KBr) ν_{\max} (cm^{-1}): 1594, 1510, 1436, 1418, 1403, 1241; ^1H NMR (300 MHz, CD_3OD): δ 8.68 (2H, dd, $J=7.0$ and 1.3 Hz, $H_2(6)$), 7.98 (1H, tt, $J=7.6$ and 1.3 Hz, H_4), 7.85 (1H, d, $J=2.3$ Hz, H_6'), 7.70 (2H, dd, $J=7.6$ and 7.0 Hz, $H_3(5)$), 7.66 (2H, d, $J=8.8$ Hz, $H_2''(6'')$), 7.53 (1H, d, $J=2.3$ Hz, H_4'), 7.44 (2H, d, $J=8.8$ Hz, $H_2'''(6''')$), 6.98 (2H, d, $J=8.8$ Hz, $H_3''(5'')$), 6.96 (2H, d, $J=8.8$ Hz, $H_3'''(5''')$), 3.85 (3H, s, OCH_3), 3.83 (3H, s, OCH_3); ^{13}C NMR (75 MHz, CD_3OD):

δ 162.3 (C_2'), 159.8 (C_4'''), 159.6 (C_4''), 144.5 ($C_2(6)$), 142.6 (C_6'), 136.8 (C_4'), 136.7 (C_4), 133.0 (C_1''), 132.3 (C_1'''), 131.2 ($C_2''(6'')$), 128.0 ($C_3(5)$), 127.2 ($C_2'''(6''')$), 125.4 (C_5'), 124.5 (C_3'), 115.1 ($C_3'''(5''')$), 114.3 ($C_3''(5'')$), 55.7 (OCH_3). MS (CI, m/z): 384 (100, $\text{M}+1$), 383 (65), 307 (54), 305 (46), 108 (17), 80 (63). Anal. Calcd for $\text{C}_{24}\text{H}_{21}\text{N}_3\text{O}_2 \cdot \text{H}_2\text{O}$: C, 71.80; H, 5.77; N, 10.47. Found: C, 72.13; H, 5.51; N, 10.31.

5.3.5. *N*-[3,5-Bis(3,5-dimethylphenyl)pyridin-2-yl]pyridinium aminide (**6e**)

Red solid (265 mg, 70%); mp 77–79 °C; IR (KBr) ν_{\max} (cm^{-1}): 2913, 1591, 1402, 1374, 1320, 1143, 1008, 845, 757, 698, 669; ^1H NMR (500 MHz, CD_3OD): δ 8.69 (2H, dd, $J=7.0$ and 1.2 Hz, $H_2(6)$), 8.04 (1H, tt, $J=7.7$ and 1.2 Hz, H_4), 7.92 (1H, d, $J=2.4$ Hz, H_6'), 7.81 (2H, dd, $J=7.7$ and 7.0 Hz, $H_3(5)$), 7.55 (1H, d, $J=2.4$ Hz, H_4'), 7.32 (2H, d, $J=1.6$ Hz, $H_2''(6'')$), 7.14 (2H, d, $J=1.6$ Hz, $H_2'''(6''')$), 6.99 (1H, t, $J=1.6$ Hz, H_4''), 6.92 (1H, t, $J=1.6$ Hz, H_4'''), 2.38 (6H, s, CH_3), 2.35 (6H, s, CH_3); ^{13}C NMR (125 MHz, CD_3OD): δ 162.8 (C_2'), 145.4 ($C_2(6)$), 144.0 (C_6'), 140.9 (C_1''), 140.0 (C_1'''), 139.6 (C_4), 138.9 (C_4'), 138.0 ($C_3'''(5''')$), 137.8 ($C_3''(5'')$), 129.7 (C_4''), 129.0 (C_4'''), 128.6 ($C_3(5)$), 128.4 ($C_2''(6'')$), 126.4 (C_5'), 125.5 (C_3'), 124.5 ($C_2'''(6''')$), 21.7 (CH_3), 21.6 (CH_3). MS (CI, m/z): 380 (7, $\text{M}+1$), 303 (40), 301 (100), 146 (23). Anal. Calcd for $\text{C}_{26}\text{H}_{25}\text{N}_3 \cdot 1/2\text{H}_2\text{O}$: C, 80.38; H, 6.75; N, 10.82. Found: C, 80.47; H, 6.51; N, 10.52.

5.3.6. *N*-[3,5-Bis(3-chlorophenyl)pyridin-2-yl]pyridinium aminide (**6f**)

Red solid (305 mg, 78%); mp 71–73 °C; IR (KBr) ν_{\max} (cm^{-1}): 1590, 1473, 1398, 1314, 1145, 1017, 785, 762, 695, 668; ^1H NMR (500 MHz, CD_3OD): δ 8.68 (2H, dd, $J=7.0$ and 1.3 Hz, $H_2(6)$), 8.05 (1H, tt, $J=7.7$ and 1.3 Hz, H_4), 7.93 (1H, d, $J=2.6$ Hz, H_6'), 7.81 (3H, m, $H_3(5)$ and H_2''), 7.62 (1H, ap dt, $J=7.7$ and 1.6 Hz, H_6''), 7.55 (1H, d, $J=2.6$ Hz, H_4'), 7.52 (1H, ap t, $J=1.9$ Hz, H_2'''), 7.43 (1H, ddd, $J=7.7$, 1.6 and 1.0 Hz, H_6'''), 7.40 (1H, ap t, $J=7.7$ Hz, H_5''), 7.34 (1H, ap t, $J=7.7$ Hz, H_5'''), 7.31 (1H, ddd, $J=7.9$, 1.9 and 1.0 Hz, H_4''), 7.23 (1H, ddd, $J=7.9$, 1.9 and 1.0 Hz, H_4'''); ^{13}C NMR (75 MHz, $(\text{CD}_3)_2\text{CO}$): δ 161.8 (C_2'), 145.3 ($C_2(6)$), 143.2 (C_6'), 143.2 (C_1''), 142.2 (C_1'''), 135.8 (C_4), 135.1 (C_3'''), 134.5 (C_4'), 133.6 (C_3''), 131.1 (C_5'''), 130.3 (C_5''), 129.9 (C_2''), 128.7 (C_6''), 127.0 ($C_3(5)$), 126.9 (C_4''), 126.2 (C_4'''), 125.5 (C_2'''), 124.2 (C_6'''), 122.4 (C_5'), 121.6 (C_3'). MS (CI, m/z): 396/394/392 (1/8/11, $\text{M}+1$), 317/315/313 (30/86/100), 278 (9), 146 (9). Anal. Calcd for $\text{C}_{22}\text{H}_{15}\text{Cl}_2\text{N}_3 \cdot 1/2\text{H}_2\text{O}$: C, 65.85; H, 4.02; N, 10.47. Found: C, 65.66; H, 3.87; N, 10.12.

5.3.7. *N*-[3,5-Bis(*trans*-2-phenylvinyl)pyridin-2-yl]pyridinium aminide (**6g**)

Yellow oil (319 mg, 85%), mp hydrobromide 187–189 °C (yellowish solid, ethanol); IR (KBr) ν_{\max} (cm^{-1}): 1619, 1584, 1451, 1388, 1148, 957, 741, 691; ^1H NMR (300 MHz, CD_3OD): δ 8.81 (2H, dd, $J=6.9$ and 1.3 Hz, $H_2(6)$), 8.27 (1H, tt, $J=7.7$ and 1.3 Hz, H_4), 8.10 (1H, d, $J=2.1$ Hz, H_6'),

7.96 (2H, dd, $J=7.7$ and 6.9 Hz, $H3(5)$), 7.75 (1H, d, $J=2.1$ Hz, $H4'$), 7.62 (2H, m, $H2''(6'')$), 7.50 (2H, m, $H2'''(6''')$), 7.49 (1H, d, $J=16.3$ Hz, $H_{\alpha'}$), 7.33 (1H, d, $J=16.3$ Hz, $H_{\beta'}$), 7.34 (4H, m, $H3''(5'')$ and $H3'''(5''')$), 7.25 (1H, tt, $J=7.3$ and 1.3 Hz, $H4''$), 7.20 (1H, tt, $J=7.3$ and 1.3 Hz, $H4'''$), 7.05 (2H, m, $H_{\beta''}$ and $H_{\alpha''}$); ^{13}C NMR (75 MHz, CD_3OD): δ 159.8 ($\text{C}2'$), 145.9 ($\text{C}2(6)$), 144.4 ($\text{C}4'$), 140.6 ($\text{C}4$), 131.5 ($\text{C}_{\beta''}$), 131.3 ($\text{C}1''$), 131.1 ($\text{C}6'$), 131.0 ($\text{C}1'''$), 129.4 ($\text{C}3'''(5''')$ or $\text{C}3''(5'')$), 129.3 ($\text{C}3'''(5''')$ or $\text{C}3''(5'')$), 128.8 ($\text{C}3(5)$), 128.4 ($\text{C}4''$), 127.8 ($\text{C}4'''$), 127.4 ($\text{C}2''(6'')$), 126.9 ($\text{C}2'''(6''')$), 126.5 ($\text{C}_{\alpha''}$ or $\text{C}_{\beta''}$), 125.8 ($\text{C}_{\beta''}$ or $\text{C}_{\alpha''}$), 124.2 ($\text{C}5'$), 124.0 ($\text{C}_{\alpha'}$), 121.4 ($\text{C}3'$). MS (CI, m/z): 376 (5, M+1), 375 (9), 374 (12), 299 (59), 279 (9), 101 (33), 80 (100). Anal. Calcd for $\text{C}_{26}\text{H}_{21}\text{N}_3 \cdot 2\text{HBr}$: C, 58.12; H, 4.31; N, 7.82. Found: C, 57.75; H, 4.32; N, 7.88.

5.3.8. *N*-[3,5-Bis(pyridin-3-yl)pyridin-2-yl]pyridinium aminide (**6h**) and *N*-[5-bromo-3-(pyridin-3-yl)-pyridin-2-yl]pyridinium aminide (**8**)^{10b}

Starting from dibromoaminide **2d** and following general procedure A, two main products were obtained and separated by flash chromatography:

N-[3,5-Bis(pyridin-3-yl)pyridin-2-yl]pyridinium aminide (**6h**): orange oil (59 mg, 18%); IR (KBr) ν_{max} (cm^{-1}): 1598, 1446, 1402, 1314, 1146, 806, 712; ^1H NMR (300 MHz, CD_3OD): δ 8.95 (1H, br d, $J=2.2$ Hz, $H2''$), 8.75 (3H, m, $H2'''$ and $H2(6)$), 8.49 (1H, dd, $J=5.0$ and 1.6 Hz, $H6''$), 8.42 (1H, dd, $J=4.9$ and 1.6 Hz, $H6'''$), 8.27 (1H, dd, $J=8.0$, 2.2 and 1.6 Hz, $H4''$), 8.13 (1H, tt, $J=7.6$ and 1.3 Hz, $H4$), 8.04 (1H, dd, $J=7.9$, 2.3 and 1.6 Hz, $H4'''$), 8.03 (1H, d, $J=2.5$ Hz, $H6'$), 7.86 (2H, dd, $J=7.6$ and 7.0 Hz, $H3(5)$), 7.72 (1H, d, $J=2.5$ Hz, $H4'$), 7.52 (1H, dd, $J=8.0$, 5.0 and 0.7 Hz, $H5''$), 7.47 (1H, dd, $J=7.9$, 4.9 and 0.7 Hz, $H5'''$); ^{13}C NMR (75 MHz, CD_3OD): δ 163.2 ($\text{C}2'$), 150.1 ($\text{C}2''$), 147.7 ($\text{C}6''$), 147.0 ($\text{C}6'''$), 146.4 ($\text{C}2''$), 145.5 ($\text{C}6'$), 145.3 ($\text{C}2(6)$), 138.8 ($\text{C}4''$), 138.5 ($\text{C}4$), 137.1 ($\text{C}3''$), 136.8 ($\text{C}4'$), 136.0 ($\text{C}3'''$), 134.4 ($\text{C}4'''$), 128.3 ($\text{C}3(5)$), 125.2 ($\text{C}5''$), 124.6 ($\text{C}5'''$), 120.8 ($\text{C}5'$), 120.2 ($\text{C}3'$). HRMS (FAB) calcd for $\text{C}_{20}\text{H}_{16}\text{N}_5$: $[\text{M}+\text{H}]^+$ 326.1406, found: 326.1402.

N-[5-bromo-3-(pyridin-3-yl)pyridin-2-yl]pyridinium aminide (**8**): orange oil (157 mg, 48%); IR (KBr) ν_{max} (cm^{-1}): 1705, 1570, 1524, 1472, 1385, 1331, 1259, 1191, 1146, 1008, 900, 805, 712; ^1H NMR (300 MHz, CD_3OD): δ 8.86 (1H, dd, $J=2.0$ and 0.7 Hz, $H2''$), 8.70 (2H, dd, $J=7.0$ and 1.3 Hz, $H2(6)$), 8.48 (1H, dd, $J=4.9$ and 1.6 Hz, $H6''$), 8.17 (1H, dd, $J=8.0$, 2.0 and 1.6 Hz, $H4''$), 8.12 (1H, tt, $J=7.8$ and 1.3 Hz, $H4$), 7.84 (2H, dd, $J=7.8$ and 7.0 Hz, $H3(5)$), 7.71 (1H, d, $J=2.4$ Hz, $H6'$), 7.49 (1H, dd, $J=8.0$, 4.9 and 0.7 Hz, $H5''$), 7.46 (1H, d, $J=2.4$ Hz, $H4'$); ^{13}C NMR (75 MHz, CD_3OD): δ 161.7 ($\text{C}2'$), 150.1 ($\text{C}2''$), 148.2 ($\text{C}6''$), 147.6 ($\text{C}6'$), 145.5 ($\text{C}2(6)$), 140.5 ($\text{C}4'$), 139.0 ($\text{C}4$), 138.7 ($\text{C}4''$), 136.1 ($\text{C}3'''$), 128.4 ($\text{C}3(5)$), 124.8 ($\text{C}5''$), 121.6 ($\text{C}3'$), 105.2 ($\text{C}5'$). HRMS (FAB) calcd for $\text{C}_{15}\text{H}_{12}\text{BrN}_4$: $[\text{M}+\text{H}]^+$ 327.0245, found: 327.0238.

5.3.9. *N*-(3,5-Diphenylpyrazin-2-yl)pyridinium aminide (**7a**)

Red solid (240 mg, 74%, ethanol), mp 186–188 °C; IR (KBr) ν_{max} (cm^{-1}): 1597, 1577, 1552, 1508, 1481, 1414,

1378, 1304, 1247, 748, 693, 663; ^1H NMR (300 MHz, CD_3OD): δ 8.76 (2H, dd, $J=6.9$ and 1.3 Hz, $H2(6)$), 8.23 (2H, dd, $J=8.4$ and 1.5 Hz, $H2''(6'')$), 8.14 (1H, tt, $J=7.7$ and 1.3 Hz, $H4$), 8.03 (1H, s, $H6'$), 7.88 (4H, m, $H3(5)$ and $H2'''(6''')$), 7.48 (2H, tt, $J=7.2$ and 1.6 Hz, $H3''(5'')$), 7.41 (3H, m, $H3'''(5''')$ and $H4''$), 7.28 (1H, tt, $J=7.3$ and 1.3 Hz, $H4'''$); ^{13}C NMR (75 MHz, CD_3OD): δ 158.8 ($\text{C}2'$), 145.3 ($\text{C}2(6)$), 141.9 ($\text{C}3'$), 139.8 ($\text{C}1''$), 139.0 ($\text{C}1'''$), 138.7 ($\text{C}4$), 138.4 ($\text{C}5'$), 136.7 ($\text{C}6'$), 130.0 ($\text{C}2''(6'')$), 129.3 ($\text{C}3'''(5''')$), 129.0 ($\text{C}4''$), 128.5 ($\text{C}3''(5'')$), 128.3 ($\text{C}3(5)$), 127.6 ($\text{C}4'''$), 125.5 ($\text{C}2'''(6''')$). MS (CI, m/z): 325 (100, M+1), 324 (40), 248 (51), 246 (30), 80 (63). Anal. Calcd for $\text{C}_{21}\text{H}_{16}\text{N}_4 \cdot 1/4\text{H}_2\text{O}$: C, 76.68; H, 5.06; N, 17.04. Found: C, 76.97; H, 4.84; N, 17.46.

5.3.10. *N*-[3,5-Bis(4-methoxyphenyl)pyrazin-2-yl]pyridinium aminide (**7b**)

Red solid (331 mg, 86%), mp hydrobromide 170–172 °C (yellowish solid, ethanol); IR (KBr) ν_{max} (cm^{-1}): 1606, 1509, 1489, 1435, 1397, 1371, 1244, 1176, 1144, 1031, 836; ^1H NMR (300 MHz, CD_3OD): δ 8.66 (2H, dd, $J=6.9$ and 1.2 Hz, $H2(6)$), 8.18 (2H, d, $J=8.9$ Hz, $H2''(6'')$), 8.01 (1H, tt, $J=7.8$ and 1.2 Hz, $H4$), 7.86 (1H, s, $H6'$), 7.77 (2H, d, $J=8.9$ Hz, $H2'''(6''')$), 7.76 (2H, dd, $J=7.8$ and 6.9 Hz, $H3(5)$), 6.97 (2H, d, $J=8.9$ Hz, $H3''(5'')$), 6.93 (2H, d, $J=8.9$ Hz, $H3'''(5''')$), 3.83 (3H, s, OCH_3), 3.79 (3H, s, OCH_3); ^{13}C NMR (75 MHz, CDCl_3): δ 160.8 ($\text{C}4''$), 160.0 ($\text{C}4'''$), 158.2 ($\text{C}2'$), 144.9 ($\text{C}2(6)$), 141.5 ($\text{C}3'$), 138.5 ($\text{C}5'$), 138.0 ($\text{C}4$), 135.2 ($\text{C}6'$), 132.2 ($\text{C}1''$), 131.8 ($\text{C}1'''$), 131.5 ($\text{C}2''(6'')$), 128.1 ($\text{C}3(5)$), 126.8 ($\text{C}2'''(6''')$), 114.7 ($\text{C}3'''(5''')$), 113.9 ($\text{C}3''(5'')$), 55.7 (OCH_3). MS (CI, m/z): 385 (43, M+1), 384 (24), 308 (100), 307 (26), 306 (24), 80 (64). Anal. Calcd for $\text{C}_{23}\text{H}_{20}\text{N}_4\text{O}_2 \cdot \text{HBr} \cdot \text{H}_2\text{O}$: C, 57.15; H, 4.80; N, 11.59. Found: C, 57.04; H, 4.80; N, 11.45.

5.3.11. *N*-[3,5-Bis(4-acetylphenyl)pyrazin-2-yl]pyridinium aminide (**7c**)

Red solid (274 mg, 95%, ethanol), mp 196–197 °C; IR (KBr) ν_{max} (cm^{-1}): 1666, 1598, 1489, 1398, 1269, 1147, 841; ^1H NMR (300 MHz, CD_3OD): δ 8.79 (2H, dd, $J=6.9$ and 1.3 Hz, $H2(6)$), 8.52 (2H, d, $J=8.6$ Hz, $H2''(6'')$), 8.23 (1H, s, $H6'$), 8.21 (1H, tt, $J=7.6$ and 1.3 Hz, $H4$), 8.12 (2H, d, $J=8.6$ Hz, $H3''(5'')$), 8.10 (2H, d, $J=8.8$ Hz, $H2'''(6''')$), 8.06 (2H, d, $J=8.8$ Hz, $H3'''(5''')$), 7.93 (2H, dd, $J=7.6$ and 6.9 Hz, $H3(5)$), 2.70 (3H, s, COCH_3), 2.65 (3H, s, COCH_3); ^{13}C NMR (75 MHz, CDCl_3): δ 198.0 (CO), 197.7 (CO), 157.3 ($\text{C}2'$), 143.6 ($\text{C}3'$), 142.9 ($\text{C}2(6)$), 142.7 ($\text{C}1''$), 139.3 ($\text{C}5'$), 137.9 ($\text{C}6'$), 136.5 ($\text{C}1'''$), 136.4 ($\text{C}4'''$), 135.3 ($\text{C}4''$), 135.0 ($\text{C}4$), 129.7 ($\text{C}2'''(6''')$), 129.1 ($\text{C}3'''(5''')$), 128.0 ($\text{C}3'''(5''')$ or $\text{C}3(5)$), 126.4 ($\text{C}3(5)$ or $\text{C}3'''(5''')$), 124.4 ($\text{C}2''(6'')$), 27.4 (CH_3), 27.2 (CH_3). MS (CI, m/z): 409 (7, M+1), 316 (17), 333 (39), 332 (100), 80 (86). Anal. Calcd for $\text{C}_{25}\text{H}_{20}\text{N}_4\text{O}_2 \cdot 1/4\text{H}_2\text{O}$: C, 72.70; H, 5.01; N, 13.57. Found: C, 72.61; H, 4.95; N, 13.67.

5.3.12. *N*-[3,5-Bis(trans-2-phenylvinyl)pyrazin-2-yl]pyridinium aminide (**7d**)

Red solid (331 mg, 88%), mp hydrobromide 207–209 °C (yellowish solid, ethanol); IR (KBr) ν_{max} (cm^{-1}): 1733,

1595, 1547, 1489, 1372, 1145, 965, 744, 691; ^1H NMR (500 MHz, CD_3OD): δ 8.80 (2H, dd, $J=6.9$ and 1.3 Hz, $H_2(6)$), 8.15 (1H, tt, $J=7.7$ and 1.3 Hz, H_4), 7.92 (1H, d, $J=16.1$ Hz, $H_{\beta'}$), 7.89 (2H, dd, $J=7.7$ and 6.9 Hz, $H_3(5)$), 7.71 (1H, d, $J=16.1$ Hz, $H_{\alpha'}$), 7.69 (2H, dd, $J=8.5$ and 1.3 Hz, $H_2''(6'')$), 7.64 (1H, s, H_6'), 7.56 (2H, dd, $J=8.6$ and 1.3 Hz, $H_2'''(6''')$), 7.41 (2H, dd, $J=8.5$ and 7.3 Hz, $H_3''(5'')$), 7.39 (1H, d, $J=16.1$ Hz, $H_{\beta'''}$), 7.35 (2H, dd, $J=8.6$ and 7.3 Hz, $H_3'''(5''')$), 7.31 (1H, tt, $J=7.3$ and 1.3 Hz, H_4''), 7.24 (1H, tt, $J=7.3$ and 1.3 Hz, H_4'''), 7.09 (1H, d, $J=16.1$ Hz, $H_{\alpha''}$); ^{13}C NMR (125 MHz, CD_3OD): δ 159.4 (C_2'), 145.7 ($C_2(6)$), 140.1 (C_3'), 140.0 (C_6'), 139.5 (C_1'''), 139.3 (C_4), 139.1 (C_1''), 137.9 (C_5'), 134.9 ($C_{\beta''}$), 129.9 ($C_3''(5'')$), 129.8 ($C_3'''(5''')$), 129.3 (C_4''), 128.8 ($C_3(5)$), 128.3 ($C_2''(6'')$), 128.2 (C_4'''), 127.5 ($C_2'''(6''')$ and $C_{\beta'''}$), 126.6 ($C_{\alpha''}$), 124.7 ($C_{\alpha''}$). MS (CI, m/z): 377 (50, $M+1$), 376 (21), 300 (100), 299 (29), 80 (20). Anal. Calcd for $\text{C}_{25}\text{H}_{20}\text{N}_4\cdot\text{HBr}$: C, 65.65; H, 4.63; N, 12.25. Found: C, 65.26; H, 4.79; N, 12.17.

5.3.13. *N*-[3,5-Bis(thiophen-3-yl)pyrazin-2-yl]pyridinium aminide (**7e**)

Red solid (328 mg, 98%), mp 82–84 °C, mp hydrobromide 134–137 °C (yellow solid); IR (KBr) ν_{max} (cm^{-1}): 3108, 1529, 1488, 1426, 1383, 1367, 1244, 1178, 1145, 768; ^1H NMR (500 MHz, $(\text{CD}_3)_2\text{CO}$): δ 8.94 (3H, m, $H_2(6)$ and H_2''), 8.25 (1H, dd, $J=5.1$ and 1.1 Hz, H_4''), 8.04 (1H, s, H_6'), 7.97 (1H, tt, $J=7.7$ and 1.2 Hz, H_4), 7.80 (2H, dd, $J=7.7$ and 7.0 Hz, $H_3(5)$), 7.76 (1H, dd, $J=3.0$ and 1.2 Hz, H_2'''), 7.66 (1H, dd, $J=5.0$ and 1.2 Hz, H_4'''), 7.46 (1H, dd, $J=5.0$ and 3.0 Hz, H_5'''), 7.41 (1H, dd, $J=5.1$ and 3.0 Hz, H_5''); ^{13}C NMR (75 MHz, $(\text{CD}_3)_2\text{CO}$): δ 157.1 (C_2'), 143.9 ($C_2(6)$), 142.3 (C_5'), 141.4 (C_3'), 136.0 (C_6'), 135.9 (C_4), 135.4 (C_3''), 134.6 (C_3'''), 129.8 (C_4''), 127.3 (C_2''), 127.2 ($C_3(5)$), 126.5 (C_5'''), 126.0 (C_4'''), 123.8 (C_5''), 118.5 (C_5'''). MS (EI, m/z): 336 (64, M^+), 257 (84), 121 (100), 79 (58). HRMS (ESI-TOF, CH_3OH) calcd for $\text{C}_{17}\text{H}_{13}\text{N}_4\text{S}_2$: $[\text{M}+\text{H}]^+$ 337.05761, found: 337.05976.

5.3.14. *N*-[3,5-Bis(benzo[*b*]thiophen-3-yl)pyrazin-2-yl]pyridinium aminide (**7f**)

Orange solid (387 mg, 89%), mp 104–106 °C; IR (KBr) ν_{max} (cm^{-1}): 1555, 1515, 1486, 1408, 1208, 1144, 862, 784, 758, 732, 700; ^1H NMR (500 MHz, $(\text{CD}_3)_2\text{CO}$): δ 9.28 (1H, s, H_2''), 9.08 (1H, ddd, $J=8.2$, 1.3 and 0.7 Hz, H_4''), 8.94 (2H, dd, $J=7.0$ and 1.3 Hz, $H_2(6)$), 8.56 (1H, ddd, $J=7.4$, 1.4 and 0.7 Hz, H_4'''), 8.10 (1H, s, H_6'), 8.06 (1H, tt, $J=7.7$ and 1.3 Hz, H_4), 7.97 (2H, m, H_7''' and H_7''), 7.87 (2H, dd, $J=7.7$ and 7.0 Hz, $H_3(5)$), 7.82 (1H, s, H_2'''), 7.34 (4H, m, H_5''' , H_5'' , H_6''' and H_6''); ^{13}C NMR (125 MHz, $(\text{CD}_3)_2\text{CO}$): δ 158.0 (C_2'), 144.4 ($C_2(6)$), 141.7 (C_7a''), 140.5 (C_7a''), 140.1 (C_3a''), 138.7 (C_3a'''), 138.2 (C_6'), 136.8 (C_4), 136.3 (C_3'), 134.6 (C_3'''), 133.8 (C_5'), 132.0 (C_3''), 130.5 (C_2''), 127.6 ($C_3(5)$), 127.3 (C_4''), 125.6 (C_4'''), 125.2 (C_6'''), 124.9 (C_5''' and C_5''), 124.8 (C_6''), 123.5 (C_7''), 123.1 (C_7'''), 122.0 (C_2'''). MS (ESI, m/z): 437 (100, $M+1$), 358 (80), 277

(41), 245 (56). HRMS (ESI-TOF, CH_3OH) calcd for $\text{C}_{25}\text{H}_{17}\text{N}_4\text{S}_2$: $[\text{M}+\text{H}]^+$ 437.08891, found: 437.09109.

5.3.15. *N*-[3,5-Bis(pyridin-3-yl)pyrazin-2-yl]pyridinium aminide (**7g**)

Orange solid (212 mg, 65%, ethanol/diethyl ether), mp 220–221 °C; IR (KBr) ν_{max} (cm^{-1}): 1555, 1496, 1445, 1407, 1365, 1309, 1270, 1147, 709; ^1H NMR (300 MHz, CD_3OD): δ 9.55 (1H, d, $J=2.1$ Hz, H_2''), 9.09 (1H, d, $J=2.3$ Hz, H_2'''), 8.85 (1H, ap dt, $J=8.1$ and 2.1 Hz, H_4''), 8.80 (2H, dd, $J=6.9$ and 1.3 Hz, $H_2(6)$), 8.55 (1H, dd, $J=4.9$ and 1.8 Hz, H_6''), 8.43 (1H, dd, $J=4.9$ and 1.8 Hz, H_6'''), 8.37 (1H, ap dt, $J=8.1$ and 2.3 Hz, H_4'''), 8.19 (1H, tt, $J=7.5$ and 1.3 Hz, H_4), 8.18 (1H, s, H_6'), 7.92 (2H, dd, $J=7.5$ and 6.9 Hz, $H_3(5)$), 7.55 (1H, dd, $J=8.1$ and 4.9 Hz, H_5''), 7.48 (1H, dd, $J=8.1$ and 4.9 Hz, H_5'''); ^{13}C NMR (75 MHz, CD_3OD): δ 159.4 (C_2'), 150.2 (C_2''), 148.5 (C_6'''), 147.4 (C_6''), 145.8 (C_2'''), 145.2 ($C_2(6)$), 139.2 (C_4), 138.5 (C_6'), 138.4 (C_4''), 137.7 (C_3'), 136.1 (C_3''), 135.3 (C_3'''), 134.6 (C_5'), 133.3 (C_4'''), 128.3 ($C_3(5)$), 125.0 (C_5'''), 124.2 (C_5''). MS (CI, m/z): 327 (7, $M+1$), 278 (10), 250 (60), 173 (10), 124 (10), 108 (17), 80 (100). Anal. Calcd for $\text{C}_{19}\text{H}_{14}\text{N}_6\cdot\frac{1}{2}\text{H}_2\text{O}$: C, 68.05; H, 4.51; N, 25.06. Found: C, 67.78; H, 4.42; N, 24.77.

5.4. Synthesis of aminides **10**: general procedure for the selective coupling over *N*-(3,5-dibromopyrazin-2-yl)-pyridinium aminide (**2e**)

Dibromoaminide **2e**^{8b,c,h} (330 mg, 1 mmol) and the corresponding boronic acid (1.1 mmol) were dissolved in a toluene/ethanol mixture (4:1, 15 mL). K_2CO_3 (10 mmol) was added followed by $\text{Pd}(\text{PPh}_3)_4$ (5 mol %). After the addition, the mixture was kept under argon with vigorous stirring for 5 min, and then heated under reflux for the reaction time indicated in Table 3 (i.e., until starting material was not detected by TLC). The system was allowed to reach room temperature and the mixture was filtered through *Celite* or *silica gel*. The residue was washed with acetonitrile until colour was no longer observed in the filtrates, which were combined and evaporated to dryness. The residue was purified by flash chromatography on a silica gel column, using ethanol as eluent. Finally, the bromo compounds **10** were, if possible, recrystallized from a suitable solvent.

5.4.1. *N*-(5-Bromo-3-phenylpyrazin-2-yl)pyridinium aminide (**10a**)

See Ref. 10b.

5.4.2. *N*-[5-Bromo-3-(4-methoxyphenyl)pyrazin-2-yl]pyridinium aminide (**10b**)

Orange solid (254 mg, 71%, ethyl acetate), mp 182–183 °C; IR (KBr) ν_{max} (cm^{-1}): 1483, 1417, 1375, 1270, 1214, 969, 744, 671; ^1H NMR (300 MHz, CD_3OD): δ 8.79 (2H, dd, $J=6.9$ and 1.3 Hz, $H_2(6)$), 8.28 (1H, tt, $J=7.8$ and 1.3 Hz, H_4), 8.12 (2H, d, $J=8.9$ Hz, $H_2''(6'')$), 7.96 (2H, dd, $J=7.8$ and 6.9 Hz, $H_3(5)$), 7.64 (1H, s, H_6'), 7.03 (2H,

d, $J=8.9$ Hz, $H3''(5'')$), 3.89 (3H, s, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 160.0 ($C4''$), 156.6 ($C2'$), 142.6 ($C2(6)$), 142.1 ($C3'$), 139.5 ($C6'$), 134.2 ($C4$), 131.0 ($C2''(6'')$), 130.2 ($C1''$), 126.3 ($C3(5)$), 122.0 ($C5'$), 113.4 ($C3''(5'')$), 55.7 (CH_3). Anal. Calcd for $C_{16}H_{13}BrN_4O$: C, 53.80; H, 3.67; N, 15.68. Found: C, 53.56; H, 3.84; N, 15.56.

5.4.3. *N*-[5-Bromo-3-(3,5-dimethylphenyl)pyrazin-2-yl]-pyridinium aminide (**10c**)

Brown solid (301 mg, 85%), mp 82–84 °C (mp hydrobromide 130–132 °C, yellowish solid, ethanol); IR (KBr) ν_{max} (cm^{-1}): 2913, 1600, 1521, 1487, 1398, 1212, 1142, 852, 765, 697, 671; 1H NMR (300 MHz, $(CD_3)_2CO$): δ 8.80 (2H, dd, $J=7.0$ and 1.3 Hz, $H2(6)$), 8.07 (1H, tt, $J=7.7$ and 1.3 Hz, $H4$), 8.02 (2H, br s, $H2''(6'')$), 7.86 (2H, dd, $J=7.7$ and 7.0 Hz, $H3(5)$), 7.51 (1H, s, $H6'$), 6.97 (1H, br s, $H4''$), 2.30 (6H, s, CH_3); ^{13}C NMR (75 MHz, $(CD_3)_2CO$): δ 158.6 ($C2'$), 144.4 ($C2(6)$), 141.0 ($C6'$), 138.6 ($C3'$), 137.2 ($C4$), 137.1 ($C1''$), 130.4 ($C3''(5'')$), 127.8 ($C3(5)$), 127.8 ($C2''(6'')$), 123.3 ($C4''$), 120.5 ($C5'$), 21.5 (CH_3). MS (CI, m/z): 357/355 (99/100, $M+1$), 278/276 (41/41). Anal. Calcd for $C_{17}H_{15}BrN_4$: C, 57.48; H, 4.26; N, 15.77. Found: C, 57.80; H, 4.46; N, 15.50.

5.4.4. *N*-[3-(4-Acetylphenyl)-5-bromopyrazin-2-yl]-pyridinium aminide (**10d**)

Orange solid (240 mg, 65%, ethyl acetate), mp 190–192 °C; IR (KBr) ν_{max} (cm^{-1}): 1664, 1602, 1473, 1428, 1399, 1359, 1274, 1162, 840, 759, 677; 1H NMR (300 MHz, CD_3OD): δ 8.73 (2H, dd, $J=6.9$ and 1.3 Hz, $H2(6)$), 8.38 (2H, d, $J=8.6$ Hz, $H2''(6'')$), 8.17 (1H, tt, $J=7.7$ and 1.3 Hz, $H4$), 8.06 (2H, d, $J=8.6$ Hz, $H3''(5'')$), 7.88 (2H, dd, $J=7.7$ and 6.9 Hz, $H3(5)$), 7.63 (1H, s, $H6'$), 2.67 (3H, s, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 198.1 (CO), 157.1 ($C2'$), 142.8 ($C2(6)$), 142.3 ($C1''$), 141.6 ($C6'$), 139.8 ($C3'$), 136.5 ($C4''$), 135.0 ($C4$), 129.5 ($C2''(6'')$), 128.0 ($C3''(5'')$), 126.5 ($C3(5)$), 121.8 ($C5'$), 27.2 (CH_3). Anal. Calcd for $C_{17}H_{13}BrN_4O$: C, 55.30; H, 3.55; N, 15.17. Found: C, 54.99; H, 3.71; N, 14.83.

5.4.5. *N*-[5-Bromo-3-(trans-2-phenylvinyl)pyrazin-2-yl]-pyridinium aminide (**10e**)

Orange solid (177 mg, 50%, ethyl acetate), mp 200–202 °C; IR (KBr) ν_{max} (cm^{-1}): 1602, 1507, 1471, 1398, 1365, 1243, 1172, 1015, 842, 814, 654; 1H NMR (300 MHz, CD_3OD): δ 8.77 (2H, dd, $J=6.9$ and 1.3 Hz, $H2(6)$), 8.18 (1H, tt, $J=7.7$ and 1.3 Hz, $H4$), 7.90 (2H, dd, $J=7.7$ and 6.9 Hz, $H3(5)$), 7.80 (1H, d, $J=16.0$ Hz, H_β), 7.65 (2H, m, $H2''(6'')$), 7.55 (1H, d, $J=16.0$ Hz, H_α), 7.53 (1H, s, $H6'$), 7.39 (2H, m, $H3''(5'')$), 7.30 (1H, tt, $J=7.2$ and 1.3 Hz, $H4''$); ^{13}C NMR (75 MHz, CD_3OD): δ 158.7 ($C2'$), 145.4 ($C2(6)$), 141.1 ($C6'$), 140.0 ($C3'$), 139.1 ($C4$), 138.3 ($C1''$), 135.0 (C_β), 129.5 ($C3''(5'')$), 129.0 ($C4''$), 128.3 ($C3(5)$), 127.9 ($C2''(6'')$), 123.0 (C_α), 121.7 ($C5'$). MS (CI, m/z): 355/353 (39/39, $M+1$), 278 (41), 276 (91), 274 (61), 196 (22), 108 (26), 80 (100). Anal. Calcd for $C_{17}H_{13}BrN_4 \cdot 1/4H_2O$: C, 57.08; H, 3.80; N, 15.66. Found: C, 57.09; H, 3.81; N, 15.46.

5.4.6. *N*-[5-Bromo-3-(thiophen-3-yl)pyrazin-2-yl]-pyridinium aminide (**10f**)

Red solid (279 mg, 84%, ethyl acetate/diethyl ether), mp 162–165 °C; IR (KBr) ν_{max} (cm^{-1}): 1526, 1484, 1409, 1369, 1349, 1242, 1190, 1146, 1106, 807, 768; 1H NMR (300 MHz, $(CD_3)_2CO$): δ 8.91 (1H, dd, $J=3.1$ and 1.3 Hz, $H2''$), 8.86 (2H, dd, $J=7.0$ and 1.3 Hz, $H2(6)$), 8.12 (1H, tt, $J=7.7$ and 1.3 Hz, $H4$), 7.98 (1H, dd, $J=5.1$ and 1.2 Hz, $H4''$), 7.90 (2H, dd, $J=7.7$ and 7.0 Hz, $H3(5)$), 7.53 (1H, s, $H6'$), 7.41 (1H, dd, $J=5.1$ and 3.1 Hz, $H5''$); ^{13}C NMR (75 MHz, $(CD_3)_2CO$): δ 157.7 ($C2'$), 144.4 ($C2(6)$), 140.3 ($C6'$), 139.9 ($C3'$), 137.4 ($C4$), 136.2 ($C3''$), 129.2 ($C4''$), 127.8 ($C2''$), 127.6 ($C3(5)$), 124.3 ($C5''$), 119.6 ($C5'$). MS (CI, m/z): 335/333 (35/35, $M+1$), 256/254 (67/64), 80 (100). Anal. Calcd for $C_{13}H_9BrN_4S$: C, 46.86; H, 2.72; N, 16.81, S, 9.62. Found: C, 46.90; H, 2.84; N, 16.49; S, 9.71.

5.4.7. *N*-[3-(Benzo[*b*]thiophen-3-yl)-5-bromopyrazin-2-yl]-pyridinium aminide (**10g**)

Orange solid (309 mg, 84%, ethyl acetate), mp 199–202 °C; IR (KBr) ν_{max} (cm^{-1}): 1513, 1481, 1405, 1215, 1145, 855, 811, 782, 754, 730, 660, 514, 472; 1H NMR (300 MHz, $(CD_3)_2CO$): δ 9.39 (1H, s, $H2''$), 9.07 (1H, m, $H4''$), 8.86 (2H, dd, $J=7.0$ and 1.3 Hz, $H2(6)$), 8.15 (1H, tt, $J=7.8$ and 1.3 Hz, $H4$), 7.97 (1H, m, $H7''$), 7.92 (2H, dd, $J=7.8$ and 7.0 Hz, $H3(5)$), 7.57 (1H, s, $H6'$), 7.46 (1H, ddd, $J=8.0$, 7.0 and 1.3 Hz, $H5''$ or $H6''$), 7.39 (1H, ddd, $J=7.7$, 7.4 and 1.5 Hz, $H6''$ or $H5''$); ^{13}C NMR (75 MHz, $(CD_3)_2CO$): δ 158.4 ($C2'$), 144.6 ($C2(6)$), 140.4 ($C7a''$), 140.1 ($C6'$), 139.4 ($C3a''$), 137.8 ($C4$), 136.6 ($C3'$), 132.0 ($C3''$), 131.4 ($C2''$), 127.7 ($C3(5)$), 126.8 ($C4''$), 125.0 ($C5''$ or $C6''$), 125.0 ($C6''$ or $C5''$), 123.1 ($C7''$), 118.8 ($C5'$). MS (CI, m/z): 385/383 (94/100, $M+1$), 306/304 (39/38), 113 (11). Anal. Calcd for $C_{17}H_{11}BrN_4S$: C, 53.28; H, 2.89; N, 14.62; S, 8.37. Found: C, 53.55; H, 2.91; N, 14.45; S, 8.17.

5.4.8. *N*-[5-Bromo-3-(pyridin-3-yl)pyrazin-2-yl]pyridinium aminide (**10h**)

Orange solid (204 mg, 65%, ethyl acetate/diethyl ether), mp 170–172 °C; IR (KBr) ν_{max} (cm^{-1}): 1524, 1489, 1475, 1430, 1401, 1369, 812, 670; 1H NMR (300 MHz, CD_3OD): δ 9.44 (1H, dd, $J=2.3$ and 0.8 Hz, $H2''$), 8.74 (2H, dd, $J=6.9$ and 1.3 Hz, $H2(6)$), 8.73 (1H, ddd, $J=8.1$, 2.3 and 1.7 Hz, $H4''$), 8.51 (1H, dd, $J=4.9$ and 1.7 Hz, $H6''$), 8.15 (1H, tt, $J=7.8$ and 1.3 Hz, $H4$), 7.87 (2H, dd, $J=7.8$ and 6.9 Hz, $H3(5)$), 7.63 (1H, s, $H6'$), 7.51 (1H, ddd, $J=8.1$, 4.9 and 0.8 Hz, $H5''$); ^{13}C NMR (75 MHz, CD_3OD): δ 159.1 ($C2'$), 150.0 ($C2''$), 148.6 ($C6''$), 145.1 ($C2(6)$), 142.8 ($C6'$), 139.0 ($C4$), 138.0 ($C4''$), 137.6 ($C3'$), 135.0 ($C3''$), 128.2 ($C3(5)$), 124.2 ($C5''$), 120.9 ($C5'$). HRMS (FAB) calcd for $C_{14}H_{11}BrN_5$: $[M+H]^+$ 328.0198, found: 328.0205.

5.4.9. *N*-[5-Bromo-3-(pyridin-4-yl)pyrazin-2-yl]pyridinium aminide (**10i**)

Green solid (252 mg, 77%, toluene), mp 229–231 °C; IR (KBr) ν_{max} (cm^{-1}): 1593, 1546, 1520, 1484, 1427, 1366, 1255, 1174, 1144, 823, 753, 658, 538; 1H NMR (300 MHz, $(CD_3)_2CO$): δ 8.82 (2H, dd, $J=7.0$ and 1.3 Hz, $H2(6)$), 8.59

(2H, m, $H2''(6'')$), 8.44 (2H, m, $H3''(5'')$), 8.18 (1H, tt, $J=7.7$ and 1.3 Hz, $H4$), 7.94 (2H, dd, $J=7.7$ and 7.0 Hz, $H3(5)$), 7.65 (1H, s, $H6'$); ^{13}C NMR (75 MHz, $(\text{CD}_3)_2\text{CO}$): δ 159.3 ($C2'$), 150.1 ($C2''(6'')$), 145.5 ($C4''$), 144.7 ($C2(6)$), 143.8 ($C6'$), 140.4 ($C3'$), 138.3 ($C4$), 128.0 ($C3(5)$), 123.5 ($C3''(5'')$), 120.1 ($C5'$). MS (CI, m/z): 330/328 (95/100, $M+1$), 249 (12), 248 (22). Anal. Calcd for $\text{C}_{14}\text{H}_{10}\text{BrN}_5 \cdot 1/2\text{H}_2\text{O}$: C, 49.87; H, 3.29; N, 20.77. Found: C, 49.50; H, 3.54; N, 20.70.

5.4.10. *N*-[5-Bromo-3-(pyrimidin-5-yl)pyrazin-2-yl]-pyridinium aminide (**10j**)

Orange solid (197 mg, 60%, toluene), mp 234–236 °C; IR (KBr) ν_{max} (cm^{-1}): 1614, 1527, 1476, 1463, 1414, 1204, 1042, 788, 749; ^1H NMR (300 MHz, $(\text{CD}_3)_2\text{CO}$): δ 9.74 (2H, s, $H4'''(6''')$), 9.07 (1H, s, $H2''$), 8.86 (2H, dd, $J=6.9$ and 1.3 Hz, $H2(6)$), 8.19 (1H, tt, $J=7.7$ and 1.3 Hz, $H4$), 7.95 (2H, dd, $J=7.7$ and 6.9 Hz, $H3(5)$), 7.65 (1H, s, $H6'$); ^{13}C NMR (75 MHz, $\text{DMSO}-d_6$): δ 157.5 ($C2'$), 156.6 ($C2''$), 155.5 ($C4''(6'')$), 143.4 ($C2(6)$), 142.4 ($C6'$), 137.9 ($C4$), 132.2 ($C5''$), 130.3 ($C3'$), 127.0 ($C3(5)$), 118.3 ($C5'$). MS (EI, m/z): 330/328 (6/6, $M+1$), 202 (31), 160 (100). Anal. Calcd for $\text{C}_{13}\text{H}_9\text{BrN}_6$: C, 47.44; H, 2.76; N, 25.53. Found: C, 47.20; H, 2.94; N, 25.80.

5.5. Synthesis of unsymmetrical disubstituted aminides **II**: general procedure

$\text{Pd}(\text{PPh}_3)_4$ (5 mol %), boronic acid (1.5 mmol), the corresponding aminide **10** (1 mmol) and K_2CO_3 (10 mmol) were stirred and heated under reflux under argon in a mixture of toluene/ethanol (4:1, 15 mL) until starting material was no longer detected by TLC (see Table 4). The system was then allowed to reach room temperature, the mixture was filtered through *Celite* or *silica gel* and the residue washed well with acetonitrile. The filtrates were combined and evaporated to dryness. Aminide **11** was purified by flash chromatography on a silica gel column, using ethanol as eluent, and recrystallized from the appropriate solvent where possible. Compound **11j** was obtained as an oil. Compounds **11a**, **11b**, **11f** and **11g** were treated with aqueous hydrobromic acid (48%) (3 equiv) and the corresponding salt was isolated after removal of excess acid. Ethyl acetate was then added and the aminide hydrobromide was triturated in an ultrasonic bath. The remaining solid was filtered off and dried. To recover the free aminides **11a**, **11b** and **11g**, hydrobromide was poured into acetone and ion exchange resin Amberlite IRA-67 (3 equiv $C_E=1.6$ equiv/g) was added. When deprotonation was complete, the resin was removed by filtration and the solvent evaporated to give the desired aminide, which was used without further purification for other synthetic steps. Compound **11f** was purified as the hydrobromide.

5.5.1. *N*-[5-(3,5-Dimethylphenyl)-3-phenylpyrazin-2-yl]-pyridinium aminide (**11a**)

Red solid (348 mg, 99%), mp 72–74 °C; IR (KBr) ν_{max} (cm^{-1}): 3051, 2915, 1599, 1500, 1404, 1240, 1143, 1028, 848, 758, 695, 666, 542; ^1H NMR (300 MHz, $(\text{CD}_3)_2\text{CO}$): δ 8.95

(2H, dd, $J=7.0$ and 1.3 Hz, $H2(6)$), 8.50 (2H, dd, $J=8.4$ and 1.4 Hz, $H2''(6'')$), 8.13 (1H, s, $H6'$), 8.04 (1H, tt, $J=7.7$ and 1.3 Hz, $H4$), 7.86 (2H, dd, $J=7.7$ and 7.0 Hz, $H3(5)$), 7.61 (2H, br s, $H2'''(6''')$), 7.38 (3H, m, $H3''$, $4''$ and $5''$), 6.89 (1H, br s, $H4'''$), 2.32 (6H, s, CH_3); ^{13}C NMR (75 MHz, $(\text{CD}_3)_2\text{CO}$): δ 158.1 ($C2'$), 144.0 ($C2(6)$), 140.4 ($C3'''(5''')$), 139.3 ($C1''$), 138.5 ($C3'$), 138.1 ($C1'''$), 136.8 ($C6'$), 136.3 ($C4$), 132.7 ($C5'$), 130.3 ($C2'''(6''')$), 128.9 ($C4''$), 128.4 ($C3''(5'')$), 128.0 ($C3(5)$), 127.5 ($C4'''$), 123.1 ($C2'''(6''')$), 21.5 (CH_3). MS (ESI, m/z): 353 (66, $M+1$), 274 (100), 245 (16). HRMS (ESI-TOF, CH_3OH) calcd for $\text{C}_{23}\text{H}_{21}\text{N}_4$: $[\text{M}+\text{H}]^+$ 353.17607, found: 353.17960.

5.5.2. *N*-[3-(3,5-Dimethylphenyl)-5-phenylpyrazin-2-yl]-pyridinium aminide (**11b**)

Dark red solid (334 mg, 95%), mp hydrobromide 173–175 °C; IR (KBr) ν_{max} (cm^{-1}): 3106, 1662, 1595, 1555, 1507, 1485, 1465, 1401, 1219, 855, 769, 760, 689, 667, 591; ^1H NMR (300 MHz, $(\text{CD}_3)_2\text{CO}$): δ 8.94 (2H, dd, $J=7.0$ and 1.3 Hz, $H2(6)$), 8.14 (1H, s, $H6'$), 8.07 (2H, br s, $H2''(6'')$), 8.05 (1H, tt, $J=7.7$ and 1.3 Hz, $H4$), 7.98 (2H, dd, $J=8.4$ and 1.3 Hz, $H2'''(6''')$), 7.86 (2H, dd, $J=7.7$ and 7.0 Hz, $H3(5)$), 7.38 (2H, ap t, $J=7.7$ Hz $H3'''(5''')$), 7.23 (1H, tt, $J=7.3$ and 1.3 Hz, $H4'''$), 6.98 (1H, br s, $H4''$), 2.35 (6H, s CH_3); ^{13}C NMR (75 MHz, $(\text{CD}_3)_2\text{CO}$): δ 157.8 ($C2'$), 144.1 ($C2(6)$), 140.4 ($C3''(5'')$), 140.1 ($C1''$ or $C1'''$), 139.5 ($C1'''$ or $C1''$), 137.7 ($C3'$), 137.1 ($C6'$), 136.6 ($C4$), 136.5 ($C5'$), 130.0 ($C4''$), 129.3 ($C3'''(5''')$), 128.2 ($C3(5)$), 127.5 ($C2'''(6''')$), 127.2 ($C4'''$), 125.1 ($C2'''(6''')$), 21.6 (CH_3). MS (ESI, m/z): 353(52, $M+1$), 302(10), 274(100), 245(8). HRMS (ESI-TOF, CH_3OH) calcd for $\text{C}_{23}\text{H}_{21}\text{N}_4$: $[\text{M}+\text{H}]^+$ 353.17607, found: 353.17911.

5.5.3. *N*-[5-(Benzo[*b*]thiophen-3-yl)-3-phenylpyrazin-2-yl]-pyridinium aminide (**11c**)

Red solid (346 mg, 89%, ethyl acetate), mp 82–84 °C; IR (KBr) ν_{max} (cm^{-1}): 3053, 1667, 1515, 1485, 1405, 1141, 760, 735, 696, 665, 535; ^1H NMR (300 MHz, $(\text{CD}_3)_2\text{CO}$): δ 9.05 (2H, dd, $J=7.0$ and 1.3 Hz, $H2(6)$), 8.68 (1H, m, $H4'''$), 8.50 (2H, m, $H2''(6'')$), 8.20 (1H, tt, $J=7.7$ and 1.3 Hz, $H4$), 8.19 (1H, s, $H6'$), 7.97 (3H, m, $H3(5)$ and $7'''$), 7.89 (1H, s, $H2''$), 7.43 (5H, m, $H3''(5'')$, $H4''$, $H5'''$ and $H6'''$); ^{13}C NMR (75 MHz, $(\text{CD}_3)_2\text{CO}$): δ 155.9 ($C2'$), 145.0 ($C2(6)$), 141.6 ($C7a'''$), 140.1 ($C3a'''$), 139.4 ($C1''$), 138.7 ($C4$), 138.6 ($C6'$), 137.8 ($C3'$), 137.8 ($C5'$), 135.4 ($C3'''$), 130.3 ($C2''(6'')$), 128.8 ($C4''$), 128.4 ($C3''(5'')$), 127.9 ($C3(5)$), 125.5 ($C4'''$), 125.2 ($C6'''$), 125.1 ($C5'''$), 123.5 ($C7'''$), 123.1 ($C2'''$). HRMS (ESI-TOF, CH_3OH) calcd for $\text{C}_{23}\text{H}_{17}\text{N}_4\text{S}$: $[\text{M}+\text{H}]^+$ 381.11684, found: 381.12026.

5.5.4. *N*-[3-(Benzo[*b*]thiophen-3-yl)-5-phenylpyrazin-2-yl]-pyridinium aminide (**11d**)

Red solid (338 mg, 89%, ethyl acetate), mp 90–92 °C; IR (KBr) ν_{max} (cm^{-1}): 3055, 1483, 1448, 1412, 1368, 1209, 1145, 1019, 763, 734, 694, 665; ^1H NMR (500 MHz, $(\text{CD}_3)_2\text{CO}$): δ 9.26 (1H, s, $H2''$), 9.20 (1H, ddd, $J=8.2$, 1.3 and 0.7 Hz, $H4''$), 8.99 (2H, dd, $J=7.0$ and 1.3 Hz, $H2(6)$),

8.23 (1H, s, $H6'$), 8.11 (1H, tt, $J=7.7$ and 1.3 Hz, $H4$), 8.07 (2H, m, $H2'''(6''')$), 8.03 (1H, ddd, $J=8.1$, 1.3 and 0.7 Hz, $H7''$), 7.92 (2H, dd, $J=7.7$ and 7.0 Hz, $H3(5)$), 7.51 (1H, ddd, $J=7.6$, 7.0 and 1.2 Hz, $H5''$ or $H6''$), 7.47 (2H, dd, $J=8.2$ and 7.4 Hz, $H3'''(5''')$), 7.46 (1H, m, $H6''$ or $H5''$), 7.31 (1H, tt, $J=7.4$ and 1.2 Hz, $H4''$); ^{13}C NMR (75 MHz, $(\text{CD}_3)_2\text{CO}$): δ 158.2 ($C2'$), 144.4 ($C2(6)$), 140.4 ($C7a''$), 140.1 ($C3a''$), 139.7 ($C1'''$), 136.8 ($C4$), 136.6 ($C3'$ or $C5'$), 136.5 ($C5'$ or $C3'$), 136.2 ($C6'$), 133.7 ($C3''$), 130.5 ($C2''$), 129.4 ($C3'''(5''')$), 127.5 ($C3(5)$), 127.1 ($C4''$ or $C4''$), 126.9 ($C4''$ or $C4''$), 125.1 ($C2'''(6''')$), 125.0 ($C5''$ or $C6''$), 124.9, ($C6''$ or $C5''$), 123.1 ($C7''$). MS (ESI, m/z): 381(59, $M+1$), 303 (30), 302 (100). Anal. Calcd for $\text{C}_{23}\text{H}_{16}\text{N}_4\text{S}$: C, 72.61; H, 4.24; N, 14.73; S, 8.43. Found: C, 72.29; H, 4.41; N, 14.36; S, 8.08.

5.5.5. *N*-[3-Phenyl-5-(pyridin-3-yl)pyrazin-2-yl]pyridinium amidine (**11e**)

See Ref. 10b.

5.5.6. *N*-[5-Phenyl-3-(pyridin-3-yl)pyrazin-2-yl]pyridinium amidine (**11f**)

Orange solid (221 mg, 68%), mp hydrobromide 207–209 °C (yellowish solid, ethanol); IR (KBr) ν_{max} (cm^{-1}): 1507, 1488, 1401, 1370, 1144, 757, 696, 665; ^1H NMR (300 MHz, CD_3OD): δ 9.52 (1H, d, $J=2.2$ Hz, $H2''$), 8.82 (1H, dt, $J=8.1$ and 1.9 Hz, $H6''$), 8.77 (2H, dd, $J=6.7$ and 1.3 Hz, $H2(6)$), 8.52 (1H, dd, $J=5.0$ and 1.6 Hz, $H4''$), 8.11 (1H, tt, $J=7.6$ and 1.3 Hz, $H4$), 8.09 (1H, s, $H6'$), 7.91 (2H, ap dd, $J=7.3$ and 1.4 Hz, $H2'''(6''')$), 7.85 (2H, dd, $J=7.6$ and 6.7 Hz, $H3(5)$), 7.52 (1H, dd, $J=8.1$ and 5.0 Hz, $H5''$), 7.40 (2H, ap t, $J=7.3$ Hz, $H3'''(5''')$), 7.28 (1H, tt, $J=7.3$ and 1.4 Hz, $H4''$); ^{13}C NMR (75 MHz, CD_3OD): δ 159.0 ($C2'$), 150.5 ($C2''$), 148.5 ($C4''$), 145.2 ($C2(6)$), 138.9 ($C1'''$), 138.7 ($C4$), 138.5 ($C6''$), 138.2 ($C5'$), 138.0 ($C6'$), 137.3 ($C3'$), 136.5 ($C3''$), 129.5 ($C3'''(5''')$), 128.3 ($C3(5)$), 127.8 ($C4''$), 125.5 ($C2'''(6''')$), 124.3 ($C5''$). MS (CI, m/z): 326 (100, $M+1$), 277 (18), 249 (83), 80 (39). Anal. Calcd for $\text{C}_{20}\text{H}_{17}\text{BrN}_5 \cdot 1/2\text{H}_2\text{O}$: C, 48.41; H, 3.66; N, 14.11. Found: C, 48.45; H, 3.76; N, 13.82.

5.5.7. *N*-[5-(Benzo[*b*]thiophen-3-yl)-3-(3,5-dimethylphenyl)pyrazin-2-yl]pyridinium amidine (**11g**)

Orange solid (367 mg, 90%), mp 69–71 °C; IR (KBr) ν_{max} (cm^{-1}): 2917, 1600, 1515, 1470, 1397, 1210, 1140, 761, 735, 669; ^1H NMR (300 MHz, $(\text{CD}_3)_2\text{CO}$): δ 8.95 (2H, dd, $J=6.8$ and 1.2 Hz, $H2(6)$), 8.68 (1H, m, $H4''$), 8.12 (2H, br s, $H2'''(6''')$), 8.09 (1H, s, $H6'$), 8.05 (1H, tt, $J=6.8$ and 1.2 Hz, $H4$), 7.96 (1H, m, $H7''$), 7.87 (2H, dd, $J=7.6$ and 6.8 Hz, $H3(5)$), 7.80 (1H, s, $H2'''$), 7.41 (2H, m, $H5'''$ and $6'''$), 7.00 (1H, br s, $H4''$), 2.35 (6H, s, CH_3); ^{13}C NMR (75 MHz, $(\text{CD}_3)_2\text{CO}$): δ 157.6($C2'$), 144.2 ($C2(6)$), 141.6 ($C7a''$), 140.1 ($C3''(5''')$), 140.0 ($C3a''$), 138.8 ($C1'''$), 138.6 ($C4$), 137.1 ($C6'$), 136.4 ($C3'$), 136.2 ($C5'$), 136.1 ($C3'''$), 130.0 ($C4''$), 128.1 ($C3(5)$), 127.5 ($C2''(6''')$), 125.6 ($C4''$), 125.1 ($C5'''$ or $C6'''$), 124.9 ($C6'''$ or $C5'''$), 123.4 ($C7'''$), 121.9 ($C2'''$), 21.6 (CH_3). HRMS (ESI-TOF, CH_3OH) calcd for $\text{C}_{25}\text{H}_{21}\text{N}_4\text{S}$: $[M+H]^+$ 409.14814, found: 409.15105.

5.5.8. *N*-[3-(Benzo[*b*]thiophen-3-yl)-5-(3,5-dimethylphenyl)pyrazin-2-yl]pyridinium amidine (**11h**)

Orange solid (335 mg, 82%, ethyl acetate), mp 77–79 °C; IR (KBr) ν_{max} (cm^{-1}): 2913, 1600, 1492, 1406, 1360, 1205, 1145, 760, 733, 697, 667; ^1H NMR (300 MHz, $(\text{CD}_3)_2\text{CO}$): δ 9.19 (1H, s, $H2''$), 9.16 (1H, m, $H4''$), 8.96 (2H, dd, $J=7.0$ and 1.3 Hz, $H2(6)$), 8.16 (1H, s, $H6'$), 8.06 (1H, tt, $J=7.7$ and 1.3 Hz, $H4$), 7.98 (1H, m, $H7''$), 7.88 (2H, dd, $J=7.7$ and 7.0 Hz, $H3(5)$), 7.64 (2H, br s, $H2'''(6''')$), 7.46 (1H, ddd, $J=7.6$, 7.0 and 1.4 Hz, $H5''$ or $H6''$), 7.39 (1H, ddd, $J=8.2$, 7.0 and 1.4 Hz, $H6''$ or $H5''$), 6.91 (1H, br s, $H4''$), 2.34 (6H, s, CH_3); ^{13}C NMR (75 MHz, $(\text{CD}_3)_2\text{CO}$): δ 157.7 ($C2'$), 144.3 ($C2(6)$), 140.5 ($C3'''(5''')$), 140.2 ($C7a''$), 139.6 ($C3a''$), 138.6 ($C4$), 137.3 ($C1'''$), 136.8 ($C3'$), 136.7 ($C5'$), 136.1 ($C6'$), 133.8 ($C3''$), 130.4 ($C2''$), 128.9 ($C4''$), 127.5 ($C3(5)$), 127.0 ($C4''$), 124.9 ($C5''$ or $C6''$), 124.8 ($C6''$ or $5''$), 123.3 ($C2'''(6''')$), 123.2 ($C7''$), 21.6 (CH_3). MS (ESI, m/z): 409 (73, $M+1$), 331 (25), 330 (100), 277 (9), 245 (13). HRMS (ESI-TOF, CH_3OH) calcd for $\text{C}_{25}\text{H}_{21}\text{N}_4\text{S}$: $[M+H]^+$ 409.14814, found: 409.15118.

5.5.9. *N*-[5-(4-Methoxyphenyl)-3-(thiophen-3-yl)pyrazin-2-yl]pyridinium amidine (**11i**)

Red solid (292 mg, 81%, ether), mp 149–150 °C; IR (KBr) ν_{max} (cm^{-1}): 3108, 2835, 1607, 1555, 1489, 1421, 1368, 1244, 1182, 1144, 1033, 834, 667; ^1H NMR (300 MHz, $(\text{CD}_3)_2\text{CO}$): δ 8.99 (2H, dd, $J=7.0$ and 1.2 Hz, $H2(6)$), 8.95 (1H, dd, $J=3.1$ and 1.2 Hz, $H2''$), 8.26 (1H, dd, $J=5.1$ and 1.2 Hz, $H4''$), 8.08 (1H, s, $H6'$), 8.00 (1H, tt, $J=7.6$ and 1.2 Hz, $H4$), 7.93 (2H, ap d, $J=8.9$ Hz, $H2'''(6''')$), 7.84 (2H, dd, $J=7.7$ and 7.0 Hz, $H3(5)$), 7.41 (1H, dd, $J=5.1$ and 3.1 Hz, $H5''$), 6.97 (2H, ap d, $J=8.9$ Hz, $H3'''(5''')$), 3.80 (3H, s, OCH_3); ^{13}C NMR (75 MHz, $(\text{CD}_3)_2\text{CO}$): δ 159.7 ($C4''$), 157.0 ($C2'$), 143.8 ($C2(6)$), 141.6 ($C3'$), 137.0 ($C5'$), 136.7 ($C3''$), 135.6 ($C6'$ or $C4$), 135.3 ($C4$ or $C6'$), 132.3 ($C1'''$), 129.8 ($C4''$), 127.3 ($C3(5)$), 127.2 ($C2''$), 126.4 ($C2'''(6''')$), 123.8 ($C5''$), 114.7, ($C3'''(5''')$), 55.5 (CH_3O). MS (CI, m/z): 361 (100, $M+1$), 360 (66), 284 (71), 282 (51), 80 (43). Anal. Calcd for $\text{C}_{20}\text{H}_{16}\text{N}_4\text{O}_S \cdot 1/2\text{H}_2\text{O}$: C, 65.02; H, 4.64; N, 15.26; S, 8.68. Found: C, 64.66; H, 4.40; N, 14.96; S, 8.79.

5.5.10. *N*-[3-(Benzo[*b*]thiophen-3-yl)-5-(*trans*-2-phenylvinyl)pyrazin-2-yl]pyridinium amidine (**11j**)

Red oil (264 mg, 65%); IR (KBr) ν_{max} (cm^{-1}): 3111, 3055, 2923, 1548, 1485, 1421, 1379, 1227, 1200, 1145, 751, 692, 668; ^1H NMR (300 MHz, $(\text{CD}_3)_2\text{CO}$): δ 9.19 (1H, s, $H2''$), 9.18 (1H, br d, $J=8.5$ Hz, $H4''$), 8.93 (2H, dd, $J=7.0$ and 1.3 Hz, $H2(6)$), 8.08 (1H, tt, $J=7.6$ and 1.3 Hz, $H4$), 7.98 (1H, br d, $J=7.9$ Hz, $H7''$), 7.88 (2H, dd, $J=7.6$ and 7.0 Hz, $H3(5)$), 7.70 (1H, s, $H6'$), 7.57 (2H, m, $H2'''(6''')$), 7.51 (1H, ddd, $J=8.2$, 7.0 and 1.3 Hz, $H5''$), 7.42 (1H, d, $J=16.0$ Hz, H_x), 7.40 (1H, m, $H6''$), 7.34 (2H, br t, $J=7.5$ Hz, $H3'''(5''')$), 7.23 (1H, d, $J=16.0$ Hz, H_β), 7.19 (1H, tt, $J=7.5$ and 1.3 Hz, $H4''$); ^{13}C NMR (75 MHz, $(\text{CD}_3)_2\text{CO}$): δ 158.3 ($C2'$), 144.3 ($C2(6)$), 140.4 ($C7a''$), 140.2 ($C3a''$), 139.5 ($C6'$), 139.2 ($C1'''$), 137.7 ($C3'$), 136.8 ($C4$), 135.8 ($C5'$), 133.7 ($C3''$), 130.7 ($C2''$), 129.4 ($C3'''(5''')$), 127.5 ($C3(5)$), 127.4

(C4'''), 127.1 (C4''), 127.0, (C_β), 126.9 (C2'''(6''')), 125.5, (C_α), 124.9 (C5'' and C6''), 123.1 (C7''). MS (ESI, *m/z*): 407 (81, M+1), 329 (27), 328 (100), 277 (9), 245 (13), 133 (16). HRMS (ESI-TOF, CH₃OH) calcd for C₂₅H₁₉N₄S: [M+H]⁺ 407.13249, found: 407.13536.

5.5.11. *N*-[3-(Benzo[*b*]thiophen-3-yl)-5-(pyrimidin-5-yl)-pyrazin-2-yl]pyridinium aminide (**11k**)

Orange solid (344 mg, 90%, ethanol), mp 215–217 °C; IR (KBr) ν_{\max} (cm⁻¹): 3111, 3046, 1548, 1489, 1405, 1221, 1146, 760, 734; ¹H NMR (300 MHz, (CD₃)₂CO): δ 9.30 (2H, s, H4'''(6''')), 9.24 (1H, s, H2''), 9.05 (1H, br d, *J*=7.7 Hz, H4''), 9.00 (1H, s, H2'''), 8.91 (2H, dd, *J*=7.0 and 1.3 Hz, H2(6)), 8.27 (1H, s, H6'), 8.20 (1H, tt, *J*=7.7 and 7.0 Hz, H4), 7.98 (3H, m, H3(5) and H7''), 7.50 (1H, ddd, *J*=8.2, 7.0 and 1.3 Hz, H5''), 7.42 (1H, ddd, *J*=8.1, 6.8 and 1.4 Hz, H6''); ¹³C NMR (75 MHz, (CD₃)₂CO): δ 159.2 (C2'), 156.9 (C2'''), 152.9 (C4'''(6''')), 144.8 (C2(6)), 140.5 (C7a''), 139.9 (C3a''), 138.1 (C4), 137.4 (C6'), 133.3 (C5'), 132.9 (C3'), 131.1 (C2''), 130.3 (C3''), 129.5 (C5'''), 127.8 (C3(5)), 126.6 (C4''), 125.1 (C5'' or C6''), 125.0 (C6'' or C5''), 123.3 (C7''). MS (EI, *m/z*): 382 (24, M⁺), 303 (100), 275 (26), 171 (24), 79(50). HRMS (ESI-TOF, CH₃OH) calcd for C₂₁H₁₅N₆S: [M+H]⁺ 383.10734, found: 383.11140. Anal. Calcd for C₂₁H₁₄N₆S: C, 65.95; H, 3.69; N, 21.97; S, 8.38. Found: C, 65.75; H, 3.68; N, 21.70; S, 8.34.

5.5.12. *N*-[5-(Benzo[*b*]thiophen-3-yl)-3-(pyrimidin-5-yl)-pyrazin-2-yl]pyridinium aminide (**11l**)

Orange solid (328 mg, 86%, ethanol/ethyl acetate), mp 217–220 °C; IR (KBr) ν_{\max} (cm⁻¹): 3051, 1548, 1516, 1491, 1405, 1145, 759; ¹H NMR (500 MHz, DMSO-*d*₆): δ 9.78 (2H, s, H4''(6'')), 9.13 (1H, s, H2''), 8.87 (2H, dd, *J*=7.0 and 1.2 Hz, H2(6)), 8.50 (1H, d, *J*=8.2 Hz, H4'''), 8.14 (1H, s, H6'), 8.13 (1H, tt, *J*=7.7 and 1.2 Hz, H4), 8.00 (1H, d, *J*=7.9 Hz, H7'''), 7.92 (1H, s, H2'''), 7.89 (2H, dd, *J*=7.7 and 7.0 Hz, H3(5)), 7.44 (1H, ddd, *J*=8.0, 7.1 and 1.2 Hz, H5'''), 7.40 (1H, ddd, *J*=8.2, 6.9 and 1.3 Hz, H6'''); ¹³C NMR (75 MHz, DMSO-*d*₆): δ 157.3 (C2'), 156.5 (C2''), 156.0 (C4''(6'')), 143.6 (C2(6)), 140.2(C6'), 139.8 (C7a'''), 137.6 (C4), 136.8 (C3a'''), 134.0 (C3'''), 133.5 (C5'), 131.9 (C3'), 130.8 (C5''), 127.0 (C3(5)), 124.2 (C5''' or C6'''), 124.1 (C6''' or C5'''), 123.7 (C4'''), 122.6 (C7'''), 121.8 (C2'''). MS (EI, *m/z*): 382 (100, M⁺), 303 (47), 275 (31), 172 (55), 79(50). Anal. Calcd for C₂₁H₁₄N₆S·1/2H₂O: C, 64.43; H, 3.86; N, 21.47; S, 8.19. Found: C, 64.10; H, 3.61; N, 21.07; S, 8.07.

5.5.13. *N*-[3-(Pyrimidin-5-yl)-5-(thiophen-3-yl)pyrazin-2-yl]-pyridinium aminide (**11m**)

Red solid (299 mg, 90%, ethyl acetate), mp 183–185 °C; IR (KBr) ν_{\max} (cm⁻¹): 3105, 2923, 1546, 1531, 1497, 1451, 1397, 1336, 1253, 1162, 1143, 1017, 758, 662; ¹H NMR (300 MHz, (CD₃)₂CO): δ 9.87 (2H, s, H4''(6'')), 9.07 (1H, s, H2''), 8.96 (2H, dd, *J*=7.0 and 1.3 Hz, H2(6)), 8.16 (1H, s, H6'), 8.10 (1H, tt, *J*=7.7 and 1.3 Hz, H4), 7.90 (2H, dd, *J*=7.7 and 7.0 Hz, H3(5)), 7.82 (1H, dd, *J*=2.9 and 1.3 Hz, H2'''), 7.68 (1H, dd, *J*=5.1 and 1.3 Hz, H4'''), 7.50 (1H, dd, *J*=5.1

and 2.9 Hz, H5'''); ¹³C NMR (75 MHz, (CD₃)₂CO): δ 158.3 (C2'), 157.7 (C2''), 157.6 (C4''(6'')), 144.2 (C2(6)), 141.7 (C3'), 138.9 (C6'), 137.0 (C4), 135.6 (C5'), 133.3 (C3'''), 127.9 (C5''), 127.6 (C3(5)), 126.7 (C4'''), 126.0 (C2'''), 119.0 (C5'''). MS (CI, *m/z*): 333 (100, M+1), 254 (51), 80 (9). HRMS (ESI-TOF, CH₃OH) calcd for C₁₇H₁₃N₆S: [M+H]⁺ 333.09169, found: 333.09588.

5.6. Reaction of 3,5-disubstituted *N*-(pyrazin-2'-yl)-pyridinium aminides (**11**) with benzyl bromides

General method. In a dried round-bottomed flask, a solution of the corresponding aminide (0.5 mmol) in anhydrous acetone (5 mL) was prepared. After addition of the corresponding alkyl bromide (4 mmol), the mixture was stirred at room temperature for the time indicated in Table 5, until starting aminide was no longer detected by TLC. Once the reaction was complete, the solvent was evaporated in vacuo and the remaining crude product was triturated with ethyl acetate in an ultrasonic bath. The resulting suspension was filtered and the solid washed well with ethyl acetate to remove the excess alkyl bromide. The isolated salts **12** were used without further purification in the next step.

5.6.1. 1-[*N*-Benzyl-*N*-[5-(3,5-dimethyl)phenyl-3-phenylpyrazin-2-yl]amino]pyridinium bromide (**12a**)

White solid (182 mg, 78%, ethanol), mp 182–184 °C; IR (KBr) ν_{\max} (cm⁻¹): 3103, 3033, 1616, 1467, 1416, 1371, 1335, 1240, 1158, 1017, 861, 720, 700, 682, 481; ¹H NMR (300 MHz, CD₃OD): δ 8.96 (1H, s, H6'), 8.92 (2H, dd, *J*=6.8 and 1.3 Hz, H2(6)), 8.51 (1H, tt, *J*=7.8 and 1.3 Hz, H4), 7.92 (2H, dd, *J*=7.8 and 6.8 Hz, H3(5)), 7.79 (4H, m, H2''(6'') and H2'''(6''')), 7.54 (3H, m, H3''(5'') and H4''), 7.30 (5H, ap s, *H*-Ph'''), 7.18 (1H, br s, H4'''), 5.12 (2H, s, CH₂), 2.42 (6H, s, CH₃); ¹³C NMR (75 MHz, CD₃OD): δ 152.1, 150.6, 148.3, 148.2, 147.9, 140.0, 138.7, 137.8, 136.6, 134.3, 132.8, 130.9, 130.7, 130.1, 130.1, 130.1, 130.0, 129.7, 125.8, 60.5, 21.4. MS (ESI, *m/z*): 443 (97, M⁺-Br), 364 (100). HRMS (ESI-TOF, CH₃OH) calcd for C₃₀H₂₇N₄: [M-Br]⁺ 443.2236, found: 443.2228.

5.6.2. 1-[*N*-Benzyl-*N*-[3-(3,5-dimethyl)phenyl-5-phenylpyrazin-2-yl]amino]pyridinium bromide (**12b**)

White solid (183 mg, 70%, ethanol), mp 181–183 °C; IR (KBr) ν_{\max} (cm⁻¹): 3000, 1615, 1529, 1467, 1399, 1374, 1226, 1184, 1158, 858, 766, 720, 692; ¹H NMR (300 MHz, CD₃OD): δ 8.96 (1H, s, H6'), 8.92 (2H, dd, *J*=6.7 and 1.3 Hz, H2(6)), 8.54 (1H, tt, *J*=7.8 and 1.3 Hz, H4), 8.16 (2H, dd, *J*=7.7 and 1.6 Hz, H2'''(6''')), 7.96 (2H, dd, *J*=7.8 and 6.7 Hz, H3(5)), 7.55 (3H, m, H3'''(5''') and H4'''), 7.37 (2H, br s, H2''(6'')), 7.30 (5H, m, H2''''(6''''), H3''''(5''') and H4''''), 7.18 (1H, br s, H4''), 5.13 (2H, s, CH₂), 2.42 (6H, s, CH₃); ¹³C NMR (75 MHz, CD₃OD): δ 151.5, 150.8, 148.3, 148.2, 148.0, 140.1, 138.4, 137.7, 136.7, 134.3, 132.3, 131.8, 131.2, 130.5, 130.2, 130.1, 129.7, 128.0, 127.4, 61.5, 21.3. MS (ESI, *m/z*): 443 (20, M⁺-Br), 364 (100). HRMS (ESI-TOF, CH₃OH) calcd for C₃₀H₂₇N₄: [M-Br]⁺ 443.2234, found: 443.2228.

5.6.3. 1-*N*-[5-(3,5-Dimethylphenyl)-3-phenylpyrazin-2-yl]-*N*-[(3-methyl)benzyl]amino}pyridinium bromide (**12c**)

White solid (182 mg, 68%, ethanol), mp 187–189 °C; IR (KBr) ν_{\max} (cm⁻¹): 3104, 3031, 2917, 1616, 1471, 1411, 1370, 1240, 1160, 1017, 859, 765, 745, 725, 700, 682, 656; ¹H NMR (300 MHz, CD₃OD): δ 8.96 (1H, s, H6'), 8.92 (2H, dd, *J*=6.8 and 1.3 Hz, H2(6)), 8.51 (1H, tt, *J*=7.8 and 1.3 Hz, H4), 7.93 (2H, dd, *J*=7.8 and 6.8 Hz, H3(5)), 7.81 (2H, m, H2''(6'')), 7.78 (2H, br s, H2'''(6''')), 7.55 (3H, m, H3''(5'') and H4''), 7.16 (3H, m, H4''''(5''''), H5'''' and H6''''), 7.06 (1H, br s, H4''''), 7.03 (1H, br s, H2''''), 5.06 (2H, s, CH₂), 2.42 (6H, s, CH₃), 2.27 (3H, s, CH₃); ¹³C NMR (75 MHz, CD₃OD): δ 152.3, 150.9, 148.6, 148.6, 148.2, 140.5, 140.2, 139.0, 138.1, 136.8, 134.4, 133.1, 131.6, 131.2, 131.1, 130.4, 130.3, 130.0, 130.0, 128.0, 126.1, 60.9, 21.7, 21.6. MS (ESI, *m/z*): 457 (100, M⁺-Br), 378 (66). HRMS (ESI-TOF, CH₃OH) calcd for C₃₁H₂₉N₄: [M-Br]⁺ 457.2392, found: 457.2384.

5.6.4. 1-*N*-[5-(Benzo[*b*]thiophen-3-yl)-3-phenylpyrazin-2-yl]-*N*-benzylamino}pyridinium bromide (**12d**)

White solid (201 mg, 79%, ethanol), mp 165–166 °C; IR (KBr) ν_{\max} (cm⁻¹): 3009, 2931, 1615, 1512, 1471, 1456, 1428, 1408, 1163, 1058, 760, 732, 702; ¹H NMR (500 MHz, CD₃OD): δ 8.94 (2H, *J*=6.9 and 1.3 Hz, H2(6)), 8.80 (1H, s, H6'), 8.59 (1H, dd, *J*=6.1 and 2.8 Hz, H4'''), 8.43 (1H, tt, *J*=7.8 and 1.3 Hz, H4), 8.30 (1H, s, H2'''), 7.87 (3H, m, H3(5) and 7'''), 7.77 (2H, dd, *J*=8.0 and 1.5 Hz, H2''(6'')), 7.51 (2H, tt, *J*=7.3 and 1.5 Hz, H3''(5'')), 7.46 (1H, tt, *J*=7.3 and 1.5 Hz, H4''), 7.33 (2H, m, H6'''' and 7''''), 7.25 (5H, m, H2''''(6''''), 3''''(5''') and 4'''), 4.99 (2H, s, CH₂); ¹³C NMR (75 MHz, CD₃OD): δ 157.2, 149.6, 149.1, 148.1, 148.0, 147.1, 141.9, 140.1, 140.1, 138.0, 137.5, 134.0, 132.7, 130.9, 130.6, 130.2, 130.0, 129.9, 129.6, 126.0, 125.9, 125.5, 123.7, 60.4. HRMS (ESI-TOF, CH₃OH) calcd for C₃₀H₂₃N₄S: [M-Br]⁺ 471.1643, found: 471.1634.

5.6.5. 1-*N*-[3-(Benzo[*b*]thiophen-3-yl)-5-phenylpyrazin-2-yl]-*N*-[(2-bromo)benzyl]amino}pyridinium bromide (**12e**)

Yellow solid (255 mg, 81%, ethanol), mp >130 °C (dec); IR (KBr) ν_{\max} (cm⁻¹): 3053, 1728, 1612, 1532, 1471, 1416, 1332, 1175, 1027, 766, 739, 694, 508, 472; ¹H NMR (300 MHz, CD₃OD): δ 9.24 (1H, s, H6'), 8.38 (2H, dd, *J*=6.7 and 1.5 Hz, H2(6)), 8.23(1H, tt, *J*=7.7 and 1.5 Hz, H4), 8.20(2H, dd, *J*=7.9 and 1.8 Hz, H2''(6'')), 7.94 (1H, m, H4''), 7.82 (1H, s, H2''), 7.65 (2H, dd, *J*=7.7 and 6.7 Hz, H3(5)), 7.62(1H, m, H7''), 7.55 (4H, m, H3''(5''), H4'' and H3'''), 7.44 (1H, ddd, *J*=8.5, 7.3 and 1.5 Hz, H5'' or H6''), 7.37 (1H, ddd, *J*=8.2, 7.3 and 1.5 Hz, H6'' or H5''), 7.28 (3H, m, H4''''(5''''), H5'''' and H6''''), 5.40 (2H, s, CH₂); ¹³C NMR (75 MHz, CD₃OD): δ 151.9, 151.8, 147.9, 147.5, 143.6, 141.1, 139.5, 138.2, 136.5, 134.7, 134.0, 133.7, 132.7, 132.2, 131.4, 130.2, 129.8, 129.7, 129.4, 128.1, 126.6, 126.3, 126.0, 124.0, 123.7, 60.2. MS (ESI, *m/z*): 551/549 (100/86, M⁺-Br), 472/470 (51/46). HRMS (ESI-TOF, CH₃OH) calcd for C₃₀H₂₂BrN₄S: [M-Br]⁺ 551.0728/549.0749, found: 551.0718/549.0734.

5.6.6. 1-*N*-[3-(Benzo[*b*]thiophen-3-yl)-5-(3,5-dimethylphenyl)pyrazin-2-yl]-*N*-benzylamino} pyridinium bromide (**12f**)

Yellow solid (226 mg, 78%, ethanol), mp >129 °C (dec); IR (KBr) ν_{\max} (cm⁻¹): 3004, 1613, 1532, 1471, 1430, 1371, 1334, 1237, 1179, 1042, 854, 763, 732, 700, 669; ¹H NMR (300 MHz, CD₃OD): δ 9.10 (1H, s, H6'), 8.55 (2H, dd, *J*=6.8 and 1.3 Hz, H2(6)), 8.28 (1H, tt, *J*=7.7 and 1.3 Hz, H4), 8.00 (1H, m, H4''), 7.98 (1H, s, H2''), 7.79 (2H, br s, H2''(6'')), 7.73 (2H, dd, *J*=7.7 and 6.8 Hz, H3(5)), 7.69 (1H, m, H7''), 7.47 (2H, m, H5'' and H6''), 7.23 (6H, m, H2''''(6''''), H3''''(5''''), H4'''' and H4'''), 5.20 (2H, s, CH₂), 2.42 (6H, s, CH₃); ¹³C NMR (75 MHz, CD₃OD): δ 152.0, 151.6, 147.8, 147.6, 143.2, 141.3, 140.0, 139.3, 139.2, 138.2, 136.5, 134.3, 133.0, 132.8, 130.9, 130.2, 130.1, 129.6, 126.6, 126.0, 125.8, 124.1, 123.9, 60.5, 21.4. MS (ESI, *m/z*): 499 (37, M⁺-Br), 420 (100).

5.7. Preparation of unsymmetrical benzyl(3,5-diarylpyrazin-2-yl)amines (**13**)

General method. Zinc dust (500 mg) was added to a solution of the corresponding pyridinium salt **12** (100 mg) in glacial acetic acid (25 mL) and the mixture was stirred at room temperature for 48 h. During this period a slight change in the colour of the solution was observed. Once the reaction had finished, the remaining solid was removed by filtration and the solvent evaporated. The residue was dissolved in a mixture of ethyl acetate (10 mL) and an aqueous solution of sodium hydroxide (20%) (5 mL). The organic layer was separated and the aqueous phase was re-extracted with ethyl acetate (2×5 mL). The combined organic layers were extracted with hydrochloric acid (20%) (2×5 mL) and the aqueous phase, containing the aminoazine hydrochloride, was then basified to pH=10 using solid sodium hydroxide. The free amine was extracted using ethyl acetate (3×10 mL). The combined organic phases were washed with brine, dried over MgSO₄, filtered and evaporated to dryness. The residue was purified by column chromatography on silica gel, using dichloromethane as eluent, and the corresponding benzyl(3,5-diarylpyrazin-2-yl)amine **13** was crystallized from a suitable solvent.

5.7.1. *N*-Benzyl-*N*-[5-(3,5-dimethyl)phenyl-3-phenylpyrazin-2-yl]amine (**13a**)

White solid (43 mg, 62%, ethyl acetate/hexane) mp 102–104 °C, IR (NaCl) ν_{\max} (cm⁻¹): 3435, 3028, 2917, 1668, 1604, 1580, 1506, 1359, 1218, 1163, 1027, 850, 742, 699; ¹H NMR (300 MHz, CDCl₃): δ 8.45 (1H, s, H6'), 7.74 (2H, dd, *J*=8.2 and 1.8 Hz, H2''(6'')), 7.53 (2H, br s, H2''''(6'''')), 7.46 (3H, m, H3''(5'') and H4''), 7.28 (5H, m, H-Ph'''), 6.97 (1H, br s, H4'''), 5.28 (1H, t, *J*=5.9 Hz, NH), 4.67 (2H, d, *J*=5.9 Hz, CH₂), 2.36 (6H, s, CH₃); ¹³C NMR (75 MHz, CDCl₃): δ 150.6 (C2'), 141.3 (C5'), 140.3 (C3'), 139.1 (C1''''), 138.2 (C6'), 137.7 (C3''(5'')), 137.3 (C1''' or C1''), 137.2 (C1'' or C1'''), 129.5 (C4'''), 129.2 (C3''(5'')), 129.0 (C4''), 128.6 (C3''''(5'''')), 128.5 (C2''(6'')), 127.5 (C2''''(6'''')), 127.3 (C4''''), 123.5 (C2'''(6''')), 45.4 (CH₂), 21.4 (CH₃). HRMS

(ESI-TOF, CH₃OH) calcd for C₂₅H₂₄N₃: [M+H]⁺ 366.1970, found: 366.1992.

5.7.2. N-Benzyl-N-[3-(3,5-dimethyl)phenyl]-5-phenylpyrazin-2-yl]amine (13b)

White solid (39 mg, 57%, ethyl acetate/hexane) mp 91–93 °C, IR (NaCl) ν_{\max} (cm⁻¹): 3432, 3030, 2920, 1602, 1513, 1488, 1195, 1163, 1028, 856, 764, 695; ¹H NMR (300 MHz, CDCl₃): δ 8.45 (1H, s, H6'), 7.93 (2H, dd, *J*=7.8 and 1.5 Hz, H2'''(6'''), 7.41 (3H, m, H3'''(5''') and H4'''), 7.32 (7H, m, H2''(6'') and H-Ph'''), 7.05 (1H, br s, H4''), 5.33 (1H, t, *J*=5.5 Hz, NH), 4.67 (2H, t, *J*=5.5 Hz, CH₂), 1.23 (6H, s, CH₃); ¹³C NMR (75 MHz, CDCl₃): δ 150.8 (C2'), 140.9 (C5' or C1'''), 140.8 (C1''' or C5'), 139.2 (C3'), 138.8 (C6'), 137.4 (C3''(5'') and C1'' or C1''), 137.0 (C1'' or C1'''), 130.7 (C4''), 128.7 (C3'''(5''') or C3'''(5''')), 128.6 (C3'''(5''') or C3'''(5''')), 127.7 (C4'''), 127.4 (C2'''(6''') or C2'''(6''')), 127.2 (C4'''), 126.1 (C2'''(6''') or C2'''(6''')), 125.6 (C2'''(6''') or C2'''(6''')), 45.4 (CH₂), 21.4 (CH₃). HRMS (ESI-TOF, CH₃OH) calcd for C₂₅H₂₄N₃: [M+H]⁺ 366.1970, found: 366.1987.

5.7.3. N-[5-(Benzo[b]thiophen-3-yl)-5-phenylpyrazin-2-yl]-N-benzylamine (13c)

Yellow oil (45 mg, 63%); IR (NaCl): ν_{\max} (cm⁻¹): 3434, 3059, 2921, 1577, 1524, 1494, 1452, 1425, 1349, 1218, 1161, 1027, 759, 734, 700; ¹H NMR (500 MHz, CDCl₃): δ 8.45 (1H, s, H6'), 8.42 (2H, m, H4'''), 7.88 (1H, m, H7'''), 7.78 (2H, m, H2''(6'')), 7.51 (2H, m, H3''(5'')), 7.44 (1H, m, H4''), 7.38 (2H, m, H5''' and H6'''), 7.35 (4H, m, H2'''(6''') and H3'''(5''')), 7.27 (1H, m, H4'''), 5.36 (1H, t, *J*=5.6 Hz, NH), 4.70 (2H, d, *J*=5.6 Hz, CH₂); ¹³C NMR (75 MHz, CDCl₃): δ 150.5 (C2'), 140.8 (C7a'''), 140.2 (C3'), 139.3 (C6'), 139.0 (C3'''), 138.7 (C3a'''), 137.4 (C1''), 137.0 (C1'''), 134.0 (C5'), 129.2 (C2''(6'') or 3''(5'')), 129.1 (C4''), 128.6 (C3''(5'') or C2''(6'')), 128.3 (C2'''(6''') or C3'''(5''')), 127.5 (C3'''(5''') or C2'''(6''')), 127.3 (C4'''), 124.4 (C4''' or C6'''), 124.4 (C6''' or C4'''), 124.0 (C2''' or C5'''), 123.8, (C5''' or C2'''), 122.7 (C7'''), 45.4 (CH₂). HRMS (APCI-TOF, CH₃OH) calcd for C₂₅H₂₀N₃S: [M+H]⁺ 394.1378, found: 394.1388.

Acknowledgements

The authors wish to thank the Comisión Interministerial de Ciencia y Tecnología (CICYT-BQU2001-1508 and CTQ2005-08902) and the Universidad de Alcalá (UAH GC2005/006) for financial support and the Ministerio de Educación y Ciencia (MEC) for two studentships (M.J.R. and R.C.). We also thank Professor Mijail Galajov for his assistance in the NMR study.

References and notes

- Pozharskii, A. F.; Soldatenkov, A. T.; Katrizky, A. R. *Heterocycles in Life and Society*; Wiley: New York, NY, 1997.
- (a) Collins, I. J. *Chem. Soc., Perkin Trans. 1* **2000**, 2845–2861; (b) Li, J. J.; Gribble, G. W. *Palladium in Heterocyclic Chemistry*; Pergamon: Amsterdam, 2000; (c) Agrofoglio, L. A.; Gillaizeau, I.; Saito, Y. *Chem. Rev.* **2003**, *103*, 1875–1916; (d) de Meijere, A.; Diederich, F.; *Metal-Catalysed Cross-Coupling Reactions*, 2nd ed.; Wiley-VCH: Weinheim, 2004; Vols. 1 and 2; (e) Kirch, G.; Hesse, S.; Comel, A. *Curr. Org. Synth.* **2004**, *1*, 47–63; (f) Corbet, J.-P.; Mignani, G. *Chem. Rev.* **2006**, *106*, 2651–2710.
- (a) Collins, I. J. *Chem. Soc., Perkin Trans. 1* **2002**, 1921–1940; (b) Schröter, S.; Christoph, S.; Bach, T. *Tetrahedron* **2005**, *61*, 2245–2267; (c) Large, J. M.; Clarke, M.; Williamson, D. M.; McDonald, E.; Collins, I. *Synlett* **2006**, 861–864.
- (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457–2495; (b) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147–168; (c) Kotha, S.; Lahiri, L.; Kashinath, D. *Tetrahedron* **2002**, *58*, 9633–9695.
- (a) Nájera, C.; Gil-Moltó, J.; Karlström, S. *Adv. Synth. Catal.* **2004**, *346*, 1798–1811; (b) Lu, G.; Fanzén, R.; Zahng, Q.; Xu, Y. *Tetrahedron Lett.* **2005**, *46*, 4255–4259; (c) Leadbeater, N. E. *Chem. Commun.* **2005**, 2881–2902; (d) Li, J.-H.; Zhu, Q.-M.; Xie, Y.-X. *Tetrahedron* **2006**, *62*, 10888–10895; (e) Kudo, N.; Perseghini, M.; Fu, G. C. *Angew. Chem., Int. Ed.* **2006**, *45*, 1282–1284; (f) Billingsley, K. L.; Anderson, K. W.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2006**, *45*, 3484–3488.
- Vaquero, J. J.; Alvarez-Builla, J. *Advances in Nitrogen Heterocycles*; JAI: Stamford, 2000; Vol. 4, pp 159–250.
- Ollis, D. W.; Stanforth, S. P. *Tetrahedron* **1985**, *41*, 2239–2329.
- (a) Carceller, R.; García-Navío, J. L.; Izquierdo, M. L.; Alvarez-Builla, J. *Tetrahedron Lett.* **1993**, *34*, 2019–2020; (b) Carceller, R.; García-Navío, J. L.; Izquierdo, M. L.; Alvarez-Builla, J.; Fajardo, M.; Gómez-Sal, P.; Gago, F. *Tetrahedron* **1994**, *50*, 4995–5012; (c) Burgos, C.; Delgado, F.; García-Navío, J. L.; Izquierdo, M. L.; Alvarez-Builla, J. *Tetrahedron* **1995**, *51*, 8649–8654; (d) García de Viedma, A.; Martínez-Barrasa, V.; Burgos, C.; Izquierdo, M. L.; Alvarez-Builla, J. *J. Org. Chem.* **1999**, *64*, 1007–1010; (e) Martínez-Barrasa, V.; Delgado, F.; Burgos, C.; García-Navío, J. L.; Izquierdo, M. L.; Alvarez-Builla, J. *Tetrahedron* **2000**, *56*, 2481–2490; (f) De la Rosa, R.; Martínez-Barrasa, V.; Burgos, C.; Alvarez-Builla, J. *Tetrahedron Lett.* **2000**, *41*, 5837–5840; (g) Reyes, M. J.; Delgado, F.; Izquierdo, M. L.; Alvarez-Builla, J. *Tetrahedron* **2002**, *58*, 8573–8579; (h) Reyes, M. J.; Burgos, C.; Izquierdo, M. L.; Alvarez-Builla, J. *Tetrahedron* **2004**, *60*, 1093–1097; (i) Castillo, R.; Izquierdo, M. L.; Alvarez-Builla, J. *Tetrahedron Lett.* **2007**, *48*, 5899–5903.
- (a) Martínez-Barrasa, V.; García de Viedma, A.; Burgos, C.; Alvarez-Builla, J. *Org. Lett.* **2000**, *2*, 3933–3935; (b) Nuñez, A.; García de Viedma, A.; Martínez-Barrasa, V.; Burgos, C.; Alvarez-Builla, J. *Synlett* **2002**, 1093–1096; (c) Nuñez, A.; Sánchez, A.; Burgos, C.; Alvarez-Builla, J. *Tetrahedron* **2004**, *60*, 6217–6224; (d) Sánchez, A.; Nuñez, A.; Alvarez-Builla, J.; Burgos, C. *Tetrahedron* **2004**, *60*, 11843–11850; (e) Sánchez, A.; Nuñez, A.; Burgos, C.; Alvarez-Builla, J. *Tetrahedron Lett.* **2006**, *47*, 8343–8346; (f) Nuñez, A.; Sánchez, A.; Burgos, C.; Alvarez-Builla, J. *Tetrahedron* **2007**, *63*, 6774–6783.
- (a) Reyes, M. J.; Izquierdo, M. L.; Alvarez-Builla, J. *Tetrahedron Lett.* **2004**, *45*, 8713–8715; (b) Reyes, M. J.; Castillo, R.; Izquierdo, M. L.; Alvarez-Builla, J. *Tetrahedron Lett.* **2006**, *47*, 6457–6460.
- (a) Sadighi, J. P.; Singer, R. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 4960–4976; (b) Garnier, E.; Audoux, J.; Pasquinet, E.; Suzenet, F.; Poullain, D.; Le Bret, B.; Guillaumet, G. *J. Org. Chem.* **2004**, *69*, 7809–7815.
- (a) Nakamura, H.; Aizawa, M.; Takeuchi, D.; Murai, A.; Shimoura, O. *Tetrahedron Lett.* **2000**, *41*, 2185–2188; (b) Wu, C.; Nakamura, H.; Murai, A.; Shimoura, O. *Tetrahedron Lett.* **2001**, *42*, 2997–3000; (c) Jiang, B.; Yang, C.-G.; Xiong, W.-N.; Wang, J. *Bioorg. Med. Chem.* **2001**, *9*, 1149–1154; (d) Adamczyk, M.; Akireddy, S. R.; Johnson, D. D.; Mattingly, P. G.; Pan, Y.; Reddy, R. E. *Tetrahedron* **2003**, *59*, 8129–8142; (e) Saito, R.; Inoue, C.; Katoh, A. *Heterocycles* **2004**, *63*, 759–764; (f) Itoh, T.; Kato, S.; Nonoyama, N.; Wada, T.; Maeda, K.; Mase, T.; Zhao, M. M.; Song, J. Z.; Tschäen, D. M.; McNamara, J. M. *Org. Process Res. Dev.* **2006**, *10*, 822–828.
- (a) Dubuisson, M. L. N.; Rees, J. F.; Marchand-Brynaert, J. *Mini-Rev. Med. Chem.* **2004**, *4*, 421–435; (b) Teranishi, K. *Bioorg. Chem.* **2007**,

- 35, 82–111; (c) Yang, C.-G.; Liu, G.; Jiang, B. *J. Org. Chem.* **2002**, *67*, 9392–9396; (d) Cavalier, J.-F.; Burton, M.; De Tollenaere, C.; Dussart, F.; Marchand, C.; Rees, J.-F.; Marchand-Brynaert, J. *Synthesis* **2001**, 768–772; (e) Jeanjot, P.; Bruyneel, F.; Arrault, A.; Gharbi, S.; Cavalier, J.-F.; Abels, A.; Marchand, C.; Touillaux, R.; Rees, J.-F.; Marchand-Brynaert, J. *Synthesis* **2003**, 513–522.
14. Birault, V.; Harris, J. C. WO 2005/003101, January 13, 2005.
 15. Cai, D.; Larsen, R. D.; Reider, P. J. *Tetrahedron Lett.* **2002**, *43*, 4285–4287.