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Highly selective substitutions in 2,3-dichloropyrazine. A novel general approach to aloisines

Dmitriy S. Chekmarev,[a,b] Sergey V. Shorshnev,[a] Alexander E. Stepanov[b] and Alexander N. Kasatkin[a,*]

[a]*ChemBridge Corporation, Malaya Pirogovskaya 1, Build. 5, 119435 Moscow, Russia*
[b]*M.V. Lomonosov Moscow State Academy of Fine Chemical Technology, Prospekt Vernadskogo 86, 119571 Moscow, Russia*

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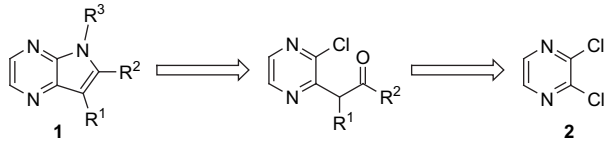
Abstract—A highly efficient synthesis of the potent CDKs (cyclin-dependent kinases) inhibitors, aloisines (substituted 5*H*-pyrrolo[2,3-*b*]pyrazines) is presented. The method is based on highly selective monosubstitution of a single chlorine atom in 2,3-dichloropyrazine with lithiated ketones, esters, and nitriles followed by co-cyclization of the resulting intermediates with primary amines or hydrazines.

1. Introduction

The family of compounds **1** bearing 5*H*-pyrrolo[2,3-*b*]pyrazine fragment has recently attracted a great interest since they have been shown to inhibit cyclin-dependent kinases (CDKs).[1,2] Due to potential applications of CDK inhibitors as novel agents for a variety of neurodegenerative disorders such as Alzheimer's disease, the authors named this family of compounds as 'aloisines', following the first name (Aloiz) of Dr. Alzheimer.[1] Up to now, the two general approaches to aloisines have been developed, one using the reaction of methylpyrazines with aromatic nitriles[1,3] and the other based on a cyclization of 2-chloro-3-(methanesulfonamido)pyrazine with substituted alkynes under thermal[4] or microwave assisted conditions.[5] However, both these methods have limitations concerning yields, variety of R^1–R^3 substituents, and utilizing a microwave technology that is rather effective but still not widely available method. Thus, a more general and practical approach to the compounds of general formula **1** seemed to be needed.

In this paper we describe a new general method for the synthesis of aloisines **1** where the substituents R^1, R^2, and R^3 can be varied independently. Our strategy is based on highly selective substitution of a single chlorine atom in commercially available 2,3-dichloropyrazine (**2**) with α-lithiated ketones, esters, and nitriles followed by cyclization with primary amines or hydrazines (Scheme 1).



Scheme 1.

2. Results and discussion

As it can be seen from our results represented by Table 1, the reactions of 2,3-dichloropyrazine (**2**) with 1.1 equiv of various ketones, esters, and nitriles and 2.2 equiv of LiHMDS[6] led to highly selective formation of the monosubstitution products **3**, **4**, and **5**, respectively (Scheme 2).

The reactions of **2** with *n*-alkyl phenyl and *n*-alkyl hetaryl ketones provided the corresponding monoketones **3a–g** in moderate to high yields (entries 1–10) although increasing the temperature from 20 to 60 °C was required in most cases. Only traces of the disubstitution product were detected by LC/MS in the reaction with 2.2 equiv of *n*-PrC(O)Ph and 4.4 equiv of LiHMDS (entry 4). It is noteworthy that the use of 1.1 equiv of the base decreased conversion of the starting materials, thus, indicating that the Li-enolates of **3** were the reaction products before hydrolysis. Compared to the *n*-alkyl ketones, Li-enolate of *i*-PrC(O)Ph proved to be much less reactive presumably owing to steric reasons (entries 11 and 12). Although Pd-complexes are known to be effective catalysts for arylations of ketone or ester enolates,[6–9] the presence of the catalyst (Pd_2dba_3+Xantphos)[9] did not improve the yield of the desired monoketone **3h** (entry 13). The reaction of **2** with acetone was accompanied by the formation of aldol type condensation products (entry 14),

Keywords: 2,3-Dichloropyrazine; Aloisines; Substituted 5*H*-pyrrolo[2,3-*b*]pyrazines; α-Arylation; Cross-coupling reactions; Cyclization.
* Corresponding author. Tel.: +7 495 775 0654; fax: +7 495 956 4948; e-mail: kasatkin@chembridge.ru

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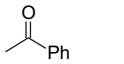
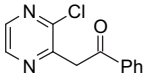
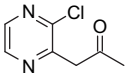
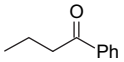
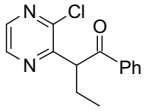
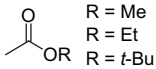
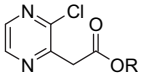
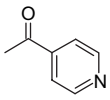
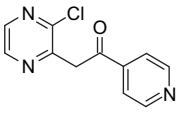
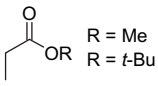
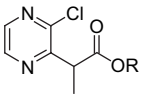
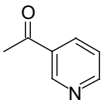
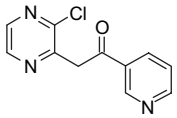
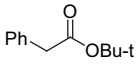
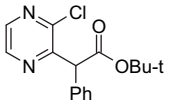
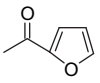
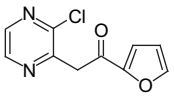
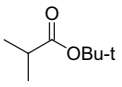
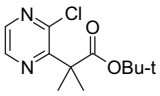
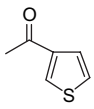
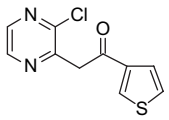
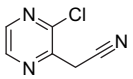
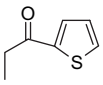
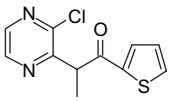
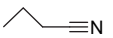
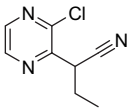
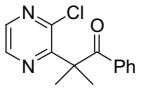
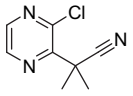
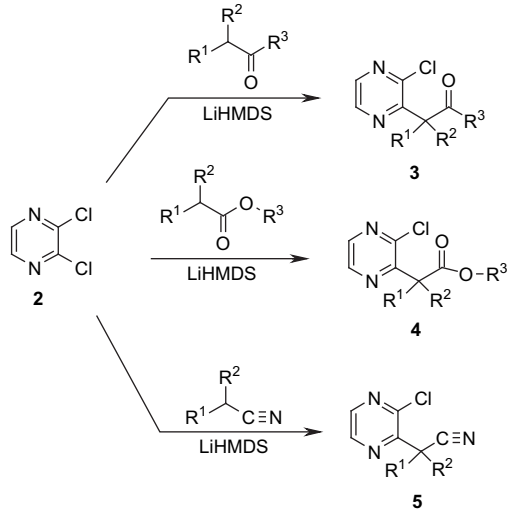
Table 1. Reactions of 2,3-dichloropyrazine (**2**) with lithiated ketones, esters, and nitriles[a]

Entry	Substrate	Product	Temp (°C)	Yield[b] (%)	Entry	Substrate	Product	Temp (°C)	Yield[b] (%)
1		 **3a**	20	62[c]	14		 **3i**	20	21[g]
2			20	54	15			20	42
3		 **3b**	60	96	16	 R = Me, R = Et, R = *t*-Bu	 **4a**, **4b**, **4c**	20	50
4			60	81[d]	17			20	92
5		 **3c**	20	34[c]	18	 R = Me, R = *t*-Bu	 **4d**, **4e**	20	26
6			60	51[c]	19			20	82
7		 **3d**	60	53[c]	20		 **4f**	20	86
8		 **3e**	20	50[c]	21		 **4g**	20	26[e]
22								60	17[e]
9		 **3f**	60	61[c]	23		 **5a**	20	95
10		 **3g**	60	85	24		 **5b**	20	98
11			20	<5[e]					
12		 **3h**	60	8[e]	25		 **5c**	20	98
13			60	<5[e,f]					

[a] Reaction conditions: 1 equiv of **2**, 1.1 equiv of ketone, ester or nitrile, 2.2 equiv of LiHMDS, toluene, 24 h, under Ar.
[b] Isolated yields (average of two runs).
[c] The products were isolated as ketone and enol mixtures according to ^{1}H NMR data.
[d] The ketone (2.2 equiv) and LiHMDS (4.4 equiv) were used.
[e] More than 70% of the starting material **2** was recovered.
[f] $Pd(dba)_2$ (2.5 mol %) and Xantphos (3 mol %) were added.
[g] The aldol type condensation product of **3i** with acetone was isolated in 25% yield.



Scheme 2.

which limits generality of the method; the use of dialkyl ketones (excluding ones having a trisubstituted α-carbon) seems to be more problematic.

The reactions of **2** with α-unbranched *tert*-butyl esters and nitriles smoothly afforded the monoesters **4c**,**e**,**f** (entries 17, 19, and 20) and mononitriles **5a**,**b** (entries 23 and 24) at room temperature. Although the maximal yield of 26% was obtained for the α,α-disubstituted ester **4g** (entry 21), the corresponding nitrile (*i*-PrCN) gave the desired monosubstitution product **5c** in high yield (entry 25). Regarding variation of the ester group, the yields of the monosubstitution products decreased in the following order: **4c** (R=*t*-Bu)>**4b** (R=Et)>**4a** (R=Me) (entries 15–17) as well as **4e** (R=*t*-Bu)>**4d** (R=Me) (entries 18 and 19). Thus, *tert*-butyl esters represented most appropriate substrates (probably due to their low tendency to Claisen type condensations).[10]

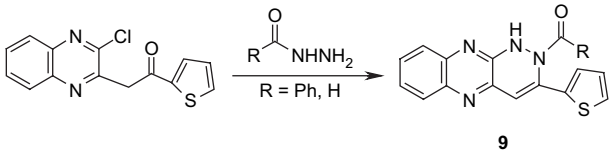
It should be pointed out that nucleophilic (S_NAr) substitutions of a single chlorine atom in **2** were reported for a variety

of *N*-, *O*-, and *S*-nucleophiles (including ammonia,[5,11] amines[12] and aminoalcohols,[13] sulfamides,[4,5] thiols,[14,15] and alcohols[15,16]). However, the selective monosubstitution with C-nucleophiles has been studied to a much lesser extent. To our knowledge, the only known examples included the use of anions generated from methyl *tert*-butyl ketone[17] and α-stabilized nitriles.[18]

Being succeeded in the synthesis of the monosubstitution products **3**–**5** (Table 1), we turned our attention to the second (co-cyclization) step to afford the target aloisines **1**. The chloroketone **3b** was chosen as a model representative compound. We found that the reactions of **3b** with primary amines and hydrazines in xylene at 145–170 °C in the presence of PTSA provided the co-cyclization products **1** and **6** in high yields (Scheme 3; Table 2).

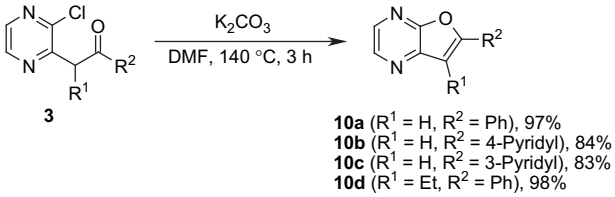
As it can be seen from Table 2, the treatment of **3b** with ammonia (entry 1), alkylamines (entries 2–4), benzylamine (entries 5–7), ethanolamine (entry 8), and 4-methoxyaniline (entries 9 and 10) provided the expected trisubstituted 5*H*-pyrrolo[2,3-*b*]pyrazines **1a**–**f**. The use of microwave irradiation in the reaction with 4-$MeOC_6H_4NH_2$ gave moderate advantage, shorting the reaction time (entry 10). By the treatment of **3b** with hydrazine hydrate, realization of both the cyclization pathways of the intermediate **7** (R=H) took place, thus, affording the mixture of 5*H*-pyrrolo[2,3-*b*]pyrazine **1g** and 1,4-dihydropyrazino[2,3-*c*]pyridazine **6a** (entry 11). However, when phenyl- and methylhydrazines were introduced into the reaction, only the corresponding 1,4-dihydropyrazino[2,3-*c*]pyridazines **6b**,**c** were isolated (entries 12–14). The role of PTSA is crucial for the reactions to be completed: the yields of both **1g** and **6a** decreased dramatically (entry 11) and the hydrazone **7** (R=Ph) was obtained as a main product instead of **6b** (entry 13) in the absence of PTSA. It should be noted that although the imine intermediates **8** were postulated in the reactions of **3b** with primary amines, we could not isolate or detect them at lower temperatures (entries 2, 5, and 6) or in the absence of PTSA. Therefore for 5*H*-pyrrolo[2,3-*b*]pyrazines **1**, the alternative mechanism including Cl-substitution with the amines[12,13] followed by cyclization could be suggested.

It should be pointed out that the similar co-cyclizations of 2-chloro-3-(2-thienoylmethyl)-quinoxaline with carboxylic acid hydrazides exhibited different regiochemistry,[19] giving (in contrast to **6b**,**c**) 2-substituted 1,2-dihydropyridazine derivatives **9** (Scheme 4). The structures of **6a**–**c** were confirmed by the presence of characteristic peaks (doublets of the doublets) of CH-4 protons at 4.42–4.56 ppm in their ^1H spectra.



Scheme 4.

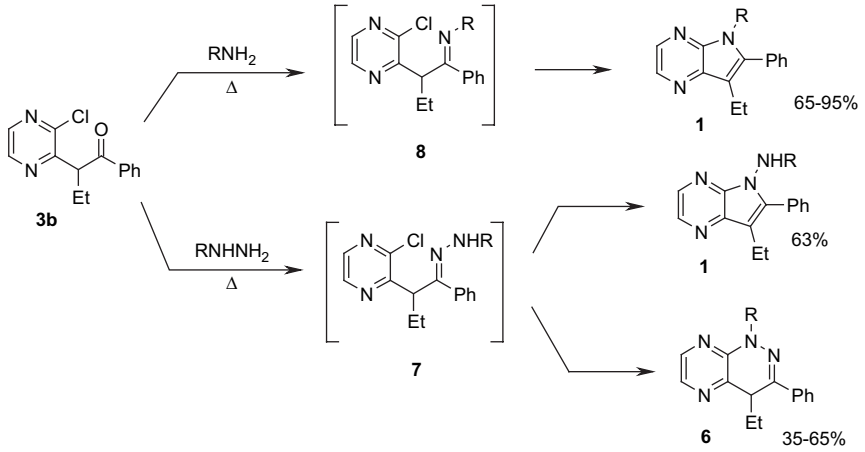
Cyclization of the chloroketones **3** into the furo[2,3-*b*]pyrazines **10** (the oxo-analogs of aloisines) was found to be effective by treatment of **3** with K_2CO_3 in DMF at 140 °C (Scheme 5).[20]



Scheme 5.

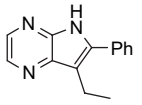
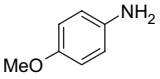
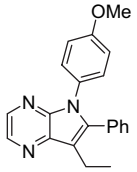
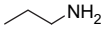
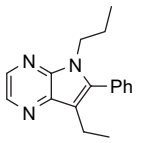
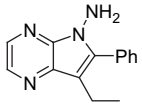
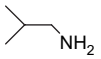
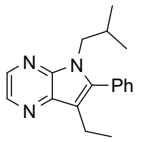
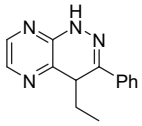
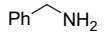
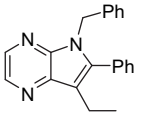
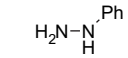
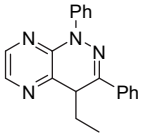
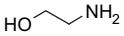
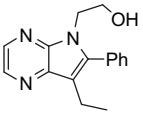
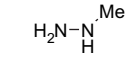
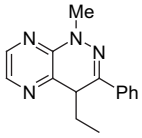
With the goal to synthesize aloisines **1** having *N*- and *O*-substituents, the possibility of using the chloronitriles **5** and the chloroesters **4** as appropriate co-cyclizations partners was briefly investigated.

The reaction of the chloronitrile **5b** with isobutylamine (3 equiv) in xylene at 170 °C (72 h) followed by treatment of the crude mixture with aq HCl led to the 2-aminosubstituted 2*H*-pyrrolo[2,3-*b*]pyrazine **1h** (as HCl-salt) in 49% isolated yield. The proposed mechanism represented by Scheme 6 includes the Cl-substitution with the amine at the first step. This has been confirmed by the fact that the intermediate **11** was isolated as a main product from the reaction at 140 °C. Interestingly that our attempts to transform the hydrochloride into the free base (by addition of aq



Scheme 3.

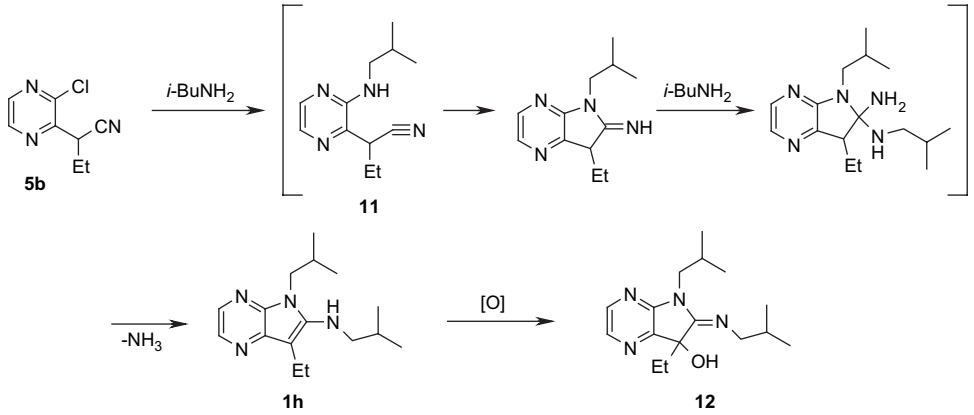
Table 2. Reactions of monosubstitution products **3–5** with amines and hydrazines[a]

Entry	Amine or hydrazine	Product		Temp (°C)	Time (h)	Yield[b] (%)	Entry	Amine or hydrazine	Product		Temp (°C)	Time (h)	Yield[b] (%)
1	NH_3		**1a**	170	72	75[c]	9			**1f**	145	72	98
							10				145	24	86[f]
2			**1b**	145	72	68				**1g**			63
3				160	48	86							32[g]
							11	$H_2N–NH_2$			160	72	
4			**1c**	145	72	93				**6a**			35
													14[g]
5			**1d**	80	100	12[d]	12			**6b**	150	72	63
6				110	48	51[e]	13				150	72	<5[g,h]
7				145	48	95							
8			**1e**	145	72	65	14			**6c**	170	72	65

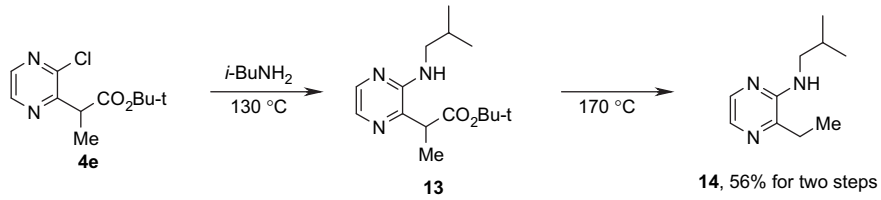
[a] All the reactions were carried out in sealed vials in xylene in the presence of 0.1 equiv of PTSA.
[b] Isolated yields (average of two runs).
[c] A solution of NH_3 (1.6 M) in MeOH was used.
[d] Benzene was used as a solvent.
[e] Toluene was used as a solvent.
[f] Microwave heating (150 W) was used.
[g] In the absence of PTSA.
[h] The hydrazone intermediate **7** (R=Ph) was isolated in 65% yield.

K_2CO_3) failed due to the fast spontaneous air oxidation of **1h** into the hydroxy derivative **12**.[21,22]

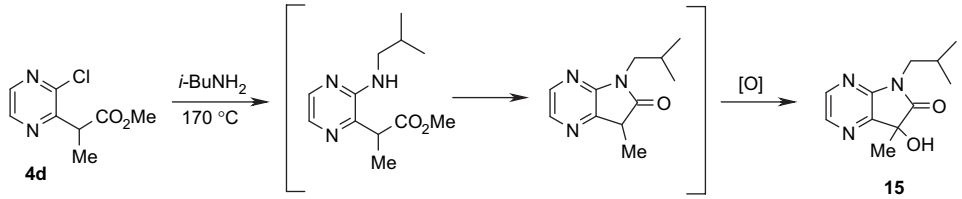
The *tert*-butyl chloroester **4e** when treated with isobutylamine at 130 °C gave mainly the Cl-substitution product **13**. Subsequent heating of the reaction mixture at 170 °C led to the dealkoxycarbonylation product **14** (Scheme 7). The use of the methyl chloroester **4d** instead of **4e** (to prevent dealkoxycarbonylation) was accompanied by tarring and afforded a complex mixture of products. However, the α-hydroxylactam **15** (as HCl-salt) was detected as a main product by LC/MS and NMR analyses of the crude mixture



Scheme 6.



Scheme 7.



Scheme 8.

after treatment with aq HCl, thus, indicating that the acidic conditions did not prevent from the oxidation in this case (Scheme 8).[21] The product **15**[22] was then isolated in pure form (but only in 30% yield) by column chromatography of the free base.

3. Conclusion

The results presented here suggest a novel and highly efficient synthesis of the potent CDKs (cyclin-dependent kinases) inhibitors, aloisines (substituted [5*H*]pyrrolo[2,3-*b*]pyrazines). The suggested approach is based on highly selective monosubstitution of a single chlorine atom in commercially available 2,3-dichloropyrazine with Li-derivatives of ketones, esters, and nitriles followed by co-cyclization of the resulting intermediates with primary amines or hydrazines. Compared with other reports, this methodology delivers the desired products in higher yield and allows to synthesize a wide range of aloisines where R^1–R^3 substituents can be varied independently.

4. Experimental

4.1. General

All manipulations were carried out in a nitrogen-filled glovebox, unless otherwise stated. Toluene and xylene were distilled under nitrogen from molten sodium. 2,3-Dichloropyrazine (**2**) was purchased from Aldrich Chemical Co. and Pyrazine Specialties, Inc. Lithium hexamethyldisilazide (LiHMDS) was purchased from Aldrich; the bulk of this material was stored in a nitrogen-filled glovebox. All other reagents were available from commercial sources and were used without further purification. Melting points (mp) were determined on a Kofler hot stage apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively, on a Bruker DRX 400 Avance spectrometer. Low-resolution mass analyses (MS) were performed on an Agilent 1100 LC/MS SL series instrument using atmospheric pressure chemical ionization (APCI) interface. Elemental analyses were carried out with Carlo-Ebra 1106 and 1500 instruments. Infrared (IR) spectra reported in this paper were measured as thin films (from dichloromethane solution) on KBr disks or as KBr pellets, using a Bruker Equinox 55 FT-IR instrument, wave numbers are given in cm^{-1}. In vacuo refers to evaporation at reduced pressure using a rotary evaporator and diaphragm pump, followed by the removal of trace volatiles using a vacuum (oil) pump.

4.2. General procedure for the reactions of 2,3-dichloropyrazine (2) with ketones, esters, and nitriles in the presence of LiHMDS (Table 1)

LiHMDS (770 mg, 4.60 mmol) and **2** (298 mg, 2.00 mmol) were suspended in 4 mL of toluene in a screw-capped vial containing a stirbar. A ketone, an ester, or a nitrile (2.20 mmol) in 2 mL of toluene was added dropwise to this suspension. The vial was sealed with a cap containing a PTFE septum and removed from the drybox. The reaction mixture was stirred at room temperature or at 60 °C for the time specified. After cooling, if necessary, the reaction mixture was diluted with Et_2O (20 mL) and was quenched with saturated aq NH_4Cl (10 mL). The organic phase was washed with a saturated NaCl solution (10 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel using 15% ethyl acetate in hexanes, unless otherwise stated.

4.2.1. 2-(3-Chloropyrazin-2-yl)-1-phenylethanone, 3a (Table 1, entry 1). The general procedure was followed. 1-Phenylethanone (265 mg, 2.20 mmol) was used. The reaction was carried out at room temperature for 24 h. The product was isolated as ketone and enol mixture. The yield was 288 mg (62%), yellow viscous oil. ^{1}H NMR (DMSO-d_6) for the keto form, δ 4.82 (s, 2H), 7.55–7.61 (m, 2H), 7.68–7.73 (m, 1H), 8.06–8.10 (m, 2H), 8.47 (d, J=2.6 Hz, 1H), 8.64 (d, J=2.6 Hz, 1H); for the enol form, δ 6.54 (s, 1H), 7.49–7.53 (m, 3H), 7.88–7.92 (m, 2H), 8.25 (d, J=2.8 Hz, 1H), 8.50 (d, J=2.8 Hz, 1H), 14.29 (s, 1H). ^{13}C NMR (DMSO-d_6) for the keto form, δ 45.53, 128.31, 128.92, 133.84, 135.98, 142.90, 149.01, 151.08, 195.36; for the enol form, δ 89.59, 125.65, 128.80, 130.74, 134.54, 138.55, 138.66, 144.12, 151.26, 165.94. IR, ν_{max}: 3432,

2923, 1627, 1576, 1492, 1452, 1432, 1247, 1148, 1072, 899, 774, 743, 688, 466 cm^{-1}. LC/MS: expected, 232.67; observed, *m/z*: 233.0 $[M+H]^+$. Anal. Calcd for $C_{12}H_9ClN_2O$ (232.67): C, 61.95; H, 3.90; Cl, 15.24; N, 12.04. Found: C, 61.87; H, 3.77; Cl, 14.98; N, 12.03.

4.2.2. 2-(3-Chloropyrazin-2-yl)-1-phenylbutan-1-one, 3b (Table 1, entries 2–4). The general procedure was followed. 1-Phenylbutan-1-one (326 mg, 2.20 mmol) was used. The reaction was carried out at 60 °C for 24 h. The yield was 500 mg (96%), yellow viscous oil. ^1H NMR (DMSO-d_6) δ 0.94 (t, J=7.3 Hz, 3H), 1.96–2.16 (m, 2H), 5.21 (dd, J=7.7, 5.8 Hz, 1H), 7.48–7.54 (m, 2H), 7.58–7.63 (m, 1H), 7.91–7.95 (m, 2H), 8.41 (d, J=2.4 Hz, 1H), 8.61 (d, J=2.4 Hz, 1H). ^{13}C NMR (DMSO-d_6) δ 11.90, 23.46, 52.48, 128.07, 128.95, 133.36, 136.11, 142.78, 143.03, 148.35, 153.45, 197.45. IR, ν_{max}: 3057, 2967, 2933, 2875, 1689, 1596, 1447, 1383, 1341, 1281, 1213, 1145, 1101, 1054, 988, 842, 744, 723, 692, 664, 470 cm^{-1}. LC/MS: expected, 260.73; observed, *m/z*: 261.1 $[M+H]^+$. Anal. Calcd for $C_{14}H_{13}ClN_2O$ (260.73): C, 64.50; H, 5.03; Cl, 13.60; N, 10.74. Found: C, 64.69; H, 4.94; Cl, 13.49; N, 10.72.

4.2.3. 2-(3-Chloropyrazin-2-yl)-1-pyridin-4-ylethanone, 3c (Table 1, entries 5 and 6). The general procedure was followed. 1-Pyridin-4-ylethanone (267 mg, 2.20 mmol) was used. The reaction was carried out at 60 °C for 24 h. The product was isolated by column chromatography on silica gel using 30% hexanes in ethyl acetate as ketone and enol mixture. The yield was 238 mg (51%), yellow solid, mp 123–125 °C. ^1H NMR (DMSO-d_6) for the keto form, δ 4.87 (s, 2H), 7.91–7.94 (m, 2H), 8.49 (d, J=2.6 Hz, 1H), 8.64 (d, J=2.6 Hz, 1H), 8.85–8.87 (m, 2H); for the enol form, δ 6.71 (s, 1H), 7.81–7.84 (m, 2H), 8.35 (d, J=2.7 Hz, 1H), 8.56 (d, J=2.7 Hz, 1H), 8.70–8.73 (m, 2H), 14.20 (s, 1H). ^{13}C NMR (DMSO-d_6) for the keto form, δ 45.69, 121.34, 141.84, 142.97, 143.13, 148.89, 150.40, 151.01, 195.81; for the enol form, δ 92.06, 119.47, 138.97, 139.87, 141.66, 144.65, 150.38, 150.58, 162.64. IR, ν_{max}: 3428, 3028, 2922, 1623, 1593, 1554, 1491, 1435, 1410, 1254, 1149, 1074, 843, 814, 790, 751, 659, 448 cm^{-1}. LC/MS: expected, 233.66; observed, *m/z*: 234.0 $[M+H]^+$. Anal. Calcd for $C_{11}H_8ClN_3O$ (233.66): C, 56.55; H, 3.45; Cl, 15.17; N, 17.98. Found: C, 56.44; H, 3.39; Cl, 14.88; N, 17.93.

4.2.4. 2-(3-Chloropyrazin-2-yl)-1-pyridin-3-ylethanone, 3d (Table 1, entry 7). The general procedure was followed. 1-Pyridin-3-ylethanone (267 mg, 2.20 mmol) was used. The reaction was carried out at 60 °C for 24 h. The product was isolated by column chromatography on silica gel using 30% hexanes in ethyl acetate as ketone and enol mixture. The yield was 245 mg (53%), yellow solid, mp 126–128 °C. ^1H NMR (DMSO-d_6) for the keto form, δ 4.88 (s, 2H), 7.58–7.64 (m, 1H), 8.37–8.42 (m, 1H), 8.48 (d, J=2.7 Hz, 1H), 8.64 (d, J=2.7 Hz, 1H), 8.83–8.86 (m, 1H), 9.24–9.26 (m, 1H); for the enol form, δ 6.59 (s, 1H), 7.49–7.54 (m, 1H), 8.24–8.27 (m, 1H), 8.28 (d, J=2.7 Hz, 1H), 8.51 (d, J=2.7 Hz, 1H), 8.66–8.69 (m, 1H), 9.06–9.08 (m, 1H), 14.31 (s, 1H). ^{13}C NMR (DMSO-d_6) for the keto form, δ 45.69, 124.04, 131.35, 135.84, 142.95, 143.04, 148.98, 149.59, 150.62, 153.98, 195.03; for the enol form, δ 90.74, 123.79, 130.36, 133.26, 138.62, 139.08, 144.30, 146.80, 150.88, 151.18, 163.73. IR, ν_{max}: 3431, 3071, 2924, 2853, 1626, 1490, 1439, 1378, 1256, 1152, 1077, 1019, 845, 793, 751, 696, 473 cm^{-1}. LC/MS: expected, 233.66; observed, *m/z*: 234.0 $[M+H]^+$. Anal. Calcd for $C_{11}H_8ClN_3O$ (233.66): C, 56.55; H, 3.45; Cl, 15.17; N, 17.98. Found: C, 56.51; H, 3.37; Cl, 15.01; N, 17.94.

4.2.5. 2-(3-Chloropyrazin-2-yl)-1-(2-furyl)ethanone, 3e (Table 1, entry 8). The general procedure was followed. 1-(2-Furyl)ethanone (242 mg, 2.20 mmol) was used. The reaction was carried out at room temperature for 24 h. The product was isolated by column chromatography on silica gel using 30% ethyl acetate in hexanes as ketone and enol mixture. The yield was 225 mg (50%), yellow viscous oil. ^1H NMR (DMSO-d_6) for the keto form, δ 4.60 (s, 2H), 6.78 (dd, J=3.7, 1.7 Hz, 1H), 7.63 (dd, J=3.7, 0.7 Hz, 1H), 8.06 (dd, J=1.7, 0.7 Hz, 1H), 8.47 (d, J=2.5 Hz, 1H), 8.64 (d, J=2.5 Hz, 1H); for the enol form, δ 6.36 (s, 1H), 6.68–6.71 (m, 1H), 7.04–7.06 (m, 1H), 7.90–7.91 (m, 1H), 8.20 (d, J=2.7 Hz, 1H), 8.44 (d, J=2.7 Hz, 1H), 13.84 (s, 1H). ^{13}C NMR (DMSO-d_6) for the keto form, δ 44.89, 112.83, 119.67, 142.94, 143.04, 148.44, 148.84, 150.33, 151.30, 183.27. IR, ν_{max}: 3341, 3132, 2926, 2854, 1677, 1636, 1570, 1466, 1385, 1331, 1276, 1215, 1150, 1085, 1010, 883, 856, 762, 594, 464 cm^{-1}. LC/MS: expected, 222.63; observed, *m/z*: 223.1 $[M+H]^+$. Anal. Calcd for $C_{10}H_7ClN_2O_2$ (222.63): C, 53.95; H, 3.17; Cl, 15.92; N, 12.58. Found: C, 54.15; H, 3.24; Cl, 15.74; N, 12.40.

4.2.6. 2-(3-Chloropyrazin-2-yl)-1-(3-thienyl)ethanone, 3f (Table 1, entry 9). The general procedure was followed. 1-(3-Thienyl)ethanone (277 mg, 2.20 mmol) was used. The reaction was carried out at 60 °C for 24 h. The product was isolated by column chromatography on silica gel using 30% ethyl acetate in hexanes as ketone and enol mixture. The yield was 290 mg (61%), yellow viscous oil. ^1H NMR (DMSO-d_6) for the keto form, δ 4.72 (s, 2H), 7.56–7.58 (m, 1H), 7.67–7.70 (m, 1H), 8.47 (d, J=2.6 Hz, 1H), 8.64 (d, J=2.6 Hz, 1H), 8.63–8.65 (m, 1H); for the enol form, δ 6.42 (s, 1H), 7.57–7.59 (m, 1H), 7.65–7.68 (m, 1H), 8.11–8.13 (m, 1H), 8.21 (d, J=2.8 Hz, 1H), 8.47 (d, J=2.8 Hz, 1H), 14.06 (s, 1H); for the keto form, δ 46.40, 126.55, 127.85, 134.85, 141.11, 142.92, 148.99, 150.76, 189.46; for the enol form, δ 89.75, 125.23, 127.62, 131.61, 137.49, 138.18, 138.72, 148.11, 151.59, 162.34. IR, ν_{max}: 3336, 3104, 2922, 1675, 1618, 1509, 1491, 1413, 1383, 1317, 1260, 1229, 1175, 1148, 1085, 1061, 1010, 878, 790, 636, 464 cm^{-1}. LC/MS: expected, 238.70; observed, *m/z*: 239.2 $[M+H]^+$. Anal. Calcd for $C_{10}H_7ClN_2OS$ (238.70): C, 50.32; H, 2.96; Cl, 14.85; N, 11.74; S, 13.43. Found: C, 50.58; H, 2.91; Cl, 14.45; N, 11.49; S, 13.68.

4.2.7. 2-(3-Chloropyrazin-2-yl)-1-(2-thienyl)propan-1-one, 3g (Table 1, entry 10). The general procedure was followed. 1-(2-Thienyl)propan-1-one (308 mg, 2.20 mmol) was used. The reaction was carried out at 60 °C for 24 h. The residue was purified by column chromatography on silica gel using 30% ethyl acetate in hexanes. The yield was 429 mg (85%), yellow solid, mp 70–71 °C. ^1H NMR (DMSO-d_6) δ 1.55 (d, J=6.9 Hz, 3H), 5.24 (q, J=6.9 Hz, 1H), 7.22–7.26 (m, 1H), 7.91–7.94 (m, 1H), 7.99–8.03 (m, 1H), 8.45 (d, J=2.5 Hz, 1H), 8.65 (d, J=2.5 Hz, 1H). ^{13}C NMR (DMSO-d_6) δ 15.84, 47.21, 128.92, 133.42, 135.30,

142.47, 142.92, 142.97, 147.89, 154.07, 191.30. IR, ν_{max}: 3314, 3083, 3008, 2938, 1666, 1512, 1411, 1384, 1273, 1229, 1140, 1090, 1051, 858, 733, 467 cm^{-1}. LC/MS: expected, 252.72; observed, *m/z*: 253.0 $[M+H]^+$. Anal. Calcd for $C_{11}H_9ClN_2OS$ (252.72): C, 52.28; H, 3.59; Cl, 14.03; N, 11.08; S, 12.69. Found: C, 52.22; H, 3.60; Cl, 13.86; N, 11.19; S, 12.59.

4.2.8. 2-(3-Chloropyrazin-2-yl)-2-methyl-1-phenylpropan-1-one, 3h (Table 1, entries 11–13). The general procedure was followed. 2-Methyl-1-phenylpropan-1-one (326 mg, 2.20 mmol) was used. The reaction was carried out at 60 °C for 24 h. The yield was 43 mg (8%), yellow viscous oil. ^1H NMR (DMSO-d_6) δ 1.71 (s, 6H), 7.29–7.35 (m, 2H), 7.43–7.55 (m, 3H), 8.47 (d, J=2.5 Hz, 1H), 8.81 (d, J=2.5 Hz, 1H). ^{13}C NMR (DMSO-d_6) δ 25.32, 53.13, 128.41, 128.49, 132.69, 135.03, 142.96, 142.99, 147.06, 157.18, 199.72. IR, ν_{max}: 3058, 2982, 2930, 1681, 1465, 1363, 1245, 1152, 1119, 1061, 973, 864, 718, 481 cm^{-1}. LC/MS: expected, 260.73; observed, *m/z*: 261.1 $[M+H]^+$. Anal. Calcd for $C_{14}H_{13}ClN_2O$ (260.73): C, 64.50; H, 5.03; Cl, 13.60; N, 10.74. Found: C, 64.65; H, 4.90; Cl, 13.51; N, 10.70.

4.2.9. 1-(3-Chloropyrazin-2-yl)acetone, 3i (Table 1, entry 14). The general procedure was followed. Acetone (128 mg, 2.20 mmol) was used. The reaction was carried out at room temperature for 24 h. The yield was 71 mg (21%), yellow viscous oil. ^1H NMR (DMSO-d_6) δ 2.27 (s, 3H), 4.21 (s, 2H), 8.43 (d, J=2.5 Hz, 1H), 8.61 (d, J=2.5 Hz, 1H). ^{13}C NMR (DMSO-d_6) δ 30.07, 49.62, 142.86, 142.90, 148.78, 150.54, 203.53. IR, ν_{max}: 3054, 2925, 2853, 1725, 1666, 1449, 1383, 1194, 1145, 1087, 1061, 864, 463 cm^{-1}. LC/MS: expected, 170.60; observed, *m/z*: 171.0 $[M+H]^+$. Anal. Calcd for $C_7H_7ClN_2O$ (170.60): C, 49.28; H, 4.14; Cl, 20.78; N, 16.42. Found: C, 49.22; H, 4.06; Cl, 20.61; N, 16.53.

4.2.10. Methyl (3-chloropyrazin-2-yl)acetate, 4a (Table 1, entry 15). The general procedure was followed. Methyl acetate (163 mg, 2.20 mmol) was used. The reaction was carried out at room temperature for 24 h. The yield was 157 mg (42%), pale yellow viscous oil. ^1H NMR (DMSO-d_6) δ 3.66 (s, 3H), 4.07 (s, 2H), 8.47 (d, J=2.5 Hz, 1H), 8.63 (d, J=2.5 Hz, 1H). ^{13}C NMR (DMSO-d_6) δ 40.86, 52.18, 142.94, 143.30, 148.49, 149.43, 169.13. IR, ν_{max}: 3465, 3001, 2954, 1743, 1521, 1437, 1386, 1339, 1266, 1199, 1175, 1087, 1012, 864, 691, 577, 466 cm^{-1}. LC/MS: expected, 186.60; observed, *m/z*: 187.1 $[M+H]^+$. Anal. Calcd for $C_7H_7ClN_2O_2$ (186.60): C, 45.06; H, 3.78; Cl, 19.00; N, 15.01. Found: C, 45.23; H, 3.69; Cl, 18.93; N, 14.95.

4.2.11. Ethyl (3-chloropyrazin-2-yl)acetate, 4b (Table 1, entry 16). The general procedure was followed. Ethyl acetate (194 mg, 2.20 mmol) was used. The reaction was carried out at room temperature for 24 h. The yield was 200 mg (50%), pale yellow viscous oil. ^1H NMR (DMSO-d_6) δ 1.19 (t, J=7.1 Hz, 3H), 4.05 (s, 2H), 4.13 (q, J=7.1 Hz, 3H), 8.47 (d, J=2.4 Hz, 1H), 8.63 (d, J=2.4 Hz, 1H). ^{13}C NMR (DMSO-d_6) δ 13.99, 41.09, 60.89, 142.90, 143.24, 148.53, 149.52, 168.62. IR, ν_{max}: 2982, 2935, 1739, 1448, 1386, 1333, 1264, 1186, 1086, 1062, 1028, 849, 466 cm^{-1}. LC/MS: expected, 200.63; observed, *m/z*: 201.1 $[M+H]^+$. Anal. Calcd for $C_8H_9ClN_2O_2$ (200.63): C, 47.89; H, 4.52; Cl, 17.67; N, 13.96. Found: C, 48.19; H, 4.66; Cl, 17.44; N, 13.74.

4.2.12. *tert*-Butyl (3-chloropyrazin-2-yl)acetate, 4c (Table 1, entry 17). The general procedure was followed. *tert*-Butyl acetate (256 mg, 2.20 mmol) was used. The reaction was carried out at room temperature for 24 h. The yield was 420 mg (92%), pale yellow viscous oil. ^1H NMR (DMSO-d_6) δ 1.40 (s, 9H), 3.95 (s, 2H), 8.46 (d, J=2.4 Hz, 1H), 8.61 (d, J=2.4 Hz, 1H). ^{13}C NMR (DMSO-d_6) δ 27.62, 42.30, 81.27, 142.82, 143.06, 148.62, 149.84, 167.78. IR, ν_{max}: 3435, 2986, 2927, 1727, 1407, 1386, 1369, 1339, 1269, 1208, 1155, 1087, 1064, 893, 838, 758, 457 cm^{-1}. LC/MS: expected, 228.68; observed, *m/z*: 172.0 $[M-C_4H_9+H]^+$. Anal. Calcd for $C_{10}H_{13}ClN_2O_2$ (228.68): C, 52.52; H, 5.73; Cl, 15.50; N, 12.25. Found: C, 52.82; H, 5.95; Cl, 15.39; N, 12.07.

4.2.13. Methyl 2-(3-chloropyrazin-2-yl)propanoate, 4d (Table 1, entry 18). The general procedure was followed. Methyl propionate (194 mg, 2.2 mmol) was used. The reaction was carried out at room temperature for 24 h. The yield was 105 mg (26%), pale yellow viscous oil. ^1H NMR (DMSO-d_6) δ 1.48 (d, J=7.1 Hz, 3H), 3.62 (s, 3H), 4.35 (q, J=7.1 Hz, 1H), 8.46 (d, J=2.5 Hz, 1H), 8.65 (d, J=2.5 Hz, 1H). ^{13}C NMR (DMSO-d_6) δ 15.14, 43.75, 52.20, 142.97, 143.08, 147.76, 153.45, 171.94. IR, ν_{max}: 3471, 2991, 2952, 1744, 1522, 1455, 1386, 1322, 1289, 1204, 1150, 1103, 1056, 966, 865, 705, 461 cm^{-1}. LC/MS: expected, 200.63; observed, *m/z*: 201.1 $[M+H]^+$. Anal. Calcd for $C_8H_9ClN_2O_2$ (200.63): C, 47.89; H, 4.52; Cl, 17.67; N, 13.96. Found: C, 48.05; H, 4.54; Cl, 17.47; N, 13.84.

4.2.14. *tert*-Butyl 2-(3-chloropyrazin-2-yl)propanoate, 4e (Table 1, entry 19). The general procedure was followed. *tert*-Butyl propionate (286 mg, 2.20 mmol) was used. The reaction was carried out at room temperature for 24 h. The yield was 400 mg (82%), pale yellow viscous oil. ^1H NMR (DMSO-d_6) δ 1.34 (s, 9H), 1.46 (d, J=7.1 Hz, 3H), 4.19 (q, J=7.1 Hz, 1H), 8.44 (d, J=2.4 Hz, 1H), 8.64 (d, J=2.4 Hz, 1H). ^{13}C NMR (DMSO-d_6) δ 14.86, 27.51, 44.77, 80.81, 142.74, 148.04, 153.66, 170.69. IR, ν_{max}: 3451, 2979, 2938, 1734, 1457, 1384, 1369, 1322, 1288, 1252, 1149, 1102, 1052, 850, 752 cm^{-1}. LC/MS: expected, 242.71; observed, *m/z*: 187.0 $[M-C_4H_9+H]^+$. Anal. Calcd for $C_{11}H_{15}ClN_2O_2$ (242.71): C, 54.44; H, 6.23; Cl, 14.61; N, 11.54. Found: C, 54.46; H, 6.34; Cl, 14.82; N, 11.41.

4.2.15. *tert*-Butyl (3-chloropyrazin-2-yl)(phenyl)acetate, 4f (Table 1, entry 20). The general procedure was followed. *tert*-Butyl phenylacetate (422 mg, 2.20 mmol) was used. The reaction was carried out at room temperature for 24 h. The yield was 523 mg (86%), pale yellow viscous oil. ^1H NMR (DMSO-d_6) δ 1.37 (s, 9H), 5.51 (s, 1H), 7.27–7.39 (m, 5H), 8.46 (d, J=2.5 Hz, 1H), 8.63 (d, J=2.5 Hz, 1H). ^{13}C NMR (DMSO-d_6) δ 27.55, 56.03, 81.47, 127.49, 128.25, 129.72, 135.18, 142.67, 143.02, 148.06, 152.61, 168.71. IR, ν_{max}: 3443, 3062, 2978, 2932, 1742, 1497, 1454, 1375, 1300, 1258, 1211, 1142, 1079, 1058, 965, 858, 747, 720, 698, 577, 470 cm^{-1}. LC/MS: expected, 304.78; observed, *m/z*: 249.0 $[M-C_4H_9+H]^+$. Anal. Calcd for $C_{16}H_{17}ClN_2O_2$ (304.78): C, 63.05; H, 5.62; Cl, 11.63; N, 9.19. Found: C, 63.10; H, 5.61; Cl, 11.52; N, 9.14.

4.2.16. *tert*-Butyl 2-(3-chloropyrazin-2-yl)-2-methylpropanoate, 4g (Table 1, entries 21 and 22). The general procedure was followed. *tert*-Butyl 2-methylpropanoate (317 mg, 2.20 mmol) was used. The reaction was carried out at room temperature for 24 h. The yield was 135 mg (26%), pale yellow viscous oil. ^{1}H NMR (DMSO-d_6) δ 1.34 (s, 9H), 1.53 (s, 6H), 8.44 (d, J=2.4 Hz, 1H), 8.64 (d, J=2.4 Hz, 1H). ^{13}C NMR (DMSO-d_6) δ 24.27, 27.30, 49.08, 80.73, 141.91, 142.41, 149.06, 152.65, 171.22. IR, ν_{max}: 3368, 2978, 2933, 1736, 1469, 1366, 1287, 1256, 1142, 1059, 847, 472 cm^{-1}. LC/MS: expected, 256.73; observed, *m/z*: 257.1 [M+H]$^+$ (minor); 201.0 [M$-$C$_4$H$_9$+H]$^+$. Anal. Calcd for $C_{12}H_{17}ClN_2O_2$ (256.73): C, 56.14; H, 6.67; Cl, 13.81; N, 10.91. Found: C, 56.24; H, 6.56; Cl, 13.71; N, 10.84.

4.2.17. (3-Chloropyrazin-2-yl)acetonitrile, 5a (Table 1, entry 23). The general procedure was followed. Acetonitrile (90 mg, 2.20 mmol) was used. The reaction was carried out at room temperature for 24 h. The yield was 292 mg (95%), yellow viscous oil. ^{1}H NMR (DMSO-d_6) δ 4.46 (s, 2H), 8.53 (d, J=2.4 Hz, 1H), 8.69 (d, J=2.4 Hz, 1H). ^{13}C NMR (DMSO-d_6) δ 24.55, 116.28, 142.88, 143.73, 146.54, 147.17. IR, ν_{max}: 3494, 3061, 2915, 2263, 1530, 1447, 1393, 1303, 1192, 1149, 1083, 1062, 946, 854, 728, 483, 448 cm^{-1}. LC/MS: expected, 153.57; observed, *m/z*: 154.0 [M+H]$^+$. Anal. Calcd for $C_6H_4ClN_3$ (153.57): C, 46.93; H, 2.63; Cl, 23.09; N, 27.36. Found: C, 47.10; H, 2.70; Cl, 23.02; N, 27.16.

4.2.18. 2-(3-Chloropyrazin-2-yl)butanenitrile, 5b (Table 1, entry 24). The general procedure was followed. Butyronitrile (152 mg, 2.20 mmol) was used. The reaction was carried out at room temperature for 24 h. The yield was 356 mg (98%), yellow viscous oil. ^{1}H NMR (DMSO-d_6) δ 1.04 (t, J=7.3 Hz, 3H), 1.91–2.10 (m, 2H), 4.66 (dd, J=8.2, 6.0 Hz, 1H), 8.56 (d, J=2.5 Hz, 1H), 8.73 (d, J=2.5 Hz, 1H). ^{13}C NMR (DMSO-d_6) δ 11.15, 25.06, 37.42, 118.75, 143.17, 144.20, 146.93, 149.20. IR, ν_{max}: 3058, 2975, 2938, 2879, 2247, 1522, 1459, 1391, 1314, 1194, 1151, 1076, 1055, 865, 484 cm^{-1}. LC/MS: expected, 181.63; observed, *m/z*: 182.1 [M+H]$^+$. Anal. Calcd for $C_8H_8ClN_3$ (181.63): C, 52.90; H, 4.44; Cl, 19.52; N, 23.14. Found: C, 52.73; H, 4.50; Cl, 19.33; N, 23.15.

4.2.19. 2-(3-Chloropyrazin-2-yl)-2-methylpropanenitrile, 5c (Table 1, entry 25). The general procedure was followed. 2-Methylpropanenitrile (152 mg, 2.20 mmol) was used. The reaction was carried out at room temperature for 24 h. The yield was 358 mg (98%), yellow viscous oil. ^{1}H NMR (DMSO-d_6) δ 1.82 (s, 6H), 8.58 (d, J=2.4 Hz, 1H), 8.72 (d, J=2.4 Hz, 1H). ^{13}C NMR (DMSO-d_6) δ 25.44, 37.52, 122.01, 142.45, 144.11, 146.60, 150.83. IR, ν_{max}: 3053, 2993, 2943, 2239, 1723, 1524, 1466, 1362, 1268, 1210, 1149, 1121, 1058, 864, 774, 481, 449 cm^{-1}. LC/MS: expected, 181.63; observed, *m/z*: 182.1 [M+H]$^+$. Anal. Calcd for $C_8H_8ClN_3$ (181.63): C, 52.90; H, 4.44; Cl, 19.52; N, 23.14. Found: C, 52.72; H, 4.55; Cl, 19.62; N, 23.15.

4.3. General procedure for the co-cyclization of the chloroketone 3b with amines and hydrazines (Table 2)

To a solution of **3b** (313 mg, 1.20 mmol) and an amine (3.60 mmol) in 6 mL of xylene in a screw-cap glass pressure vessel was added PTSA (23 mg, 0.12 mmol). The pressure vessel was sealed with a cap containing a PTFE septum and removed from the drybox. The reaction mixture was stirred and heated at the temperatures and for the times specified. After cooling, the reaction mixture was filtered through a plug of Celite that was then washed with chloroform. The combined organic phase was concentrated in vacuo. The residue was purified by column chromatography on silica gel using 20% ethyl acetate in hexanes, unless otherwise stated.

4.3.1. 7-Ethyl-6-phenyl-5*H*-pyrrolo[2,3-*b*]pyrazine, 1a (Table 2, entry 1). The general procedure was followed. A solution of NH_3 (1.6 M) in MeOH (2.25 mL, 3.60 mmol) was used. The reaction was carried out at 170 °C for 72 h. The residue was purified by column chromatography on silica gel using 50% ethyl acetate in hexanes. The yield was 201 mg (75%), yellow solid, mp 200–202 °C. ^{1}H NMR (DMSO-d_6) δ 1.29 (t, J=7.5 Hz, 3H), 2.92 (q, J=7.5 Hz, 2H), 7.43–7.49 (m, 1H), 7.53–7.59 (m, 2H), 7.68–7.73 (m, 2H), 8.22 (d, J=2.6 Hz, 1H), 8.36 (d, J=2.6 Hz, 1H), 12.07 (s, 1H). ^{13}C NMR (DMSO-d_6) δ 14.99, 16.46, 112.83, 128.22, 128.50, 128.86, 131.73, 136.92, 137.59, 138.61, 139.45, 141.96. IR, ν_{max}: 3432, 3152, 3058, 2961, 2928, 2868, 1471, 1398, 1342, 1221, 1177, 1145, 1113, 1043, 926, 842, 769, 696, 588, 446 cm^{-1}. LC/MS: expected, 223.28; observed, *m/z*: 224.1 [M+H]$^+$. Anal. Calcd for $C_{14}H_{13}N_3$ (223.28): C, 75.31; H, 5.87; N, 18.82. Found: C, 74.93; H, 5.77; N, 18.56.

4.3.2. 7-Ethyl-6-phenyl-5-propyl-5*H*-pyrrolo[2,3-*b*]pyrazine, 1b (Table 2, entries 2 and 3). The general procedure was followed. Propylamine (213 mg, 3.60 mmol) was used. The reaction was carried out at 160 °C for 48 h. The yield was 273 mg (86%), yellow viscous oil. ^{1}H NMR (DMSO-d_6) δ 0.60 (t, J=7.4 Hz, 3H), 1.17 (t, J=7.5 Hz, 3H), 1.42–1.54 (m, 2H), 2.66 (q, J=7.5 Hz, 2H), 4.10 (t, J=7.4 Hz, 2H), 7.48–7.53 (m, 2H), 7.54–7.62 (m, 3H), 8.27 (d, J=2.6 Hz, 1H), 8.41 (d, J=2.6 Hz, 1H). ^{13}C NMR (DMSO-d_6) δ 10.93, 15.17, 16.44, 22.60, 43.36, 113.58, 128.79, 129.03, 129.92, 130.45, 136.54, 137.75, 138.43, 140.98, 141.38. IR, ν_{max}: 3048, 2965, 2932, 2873, 1695, 1555, 1360, 1254, 1196, 1178, 1150, 1056, 949, 841, 764, 703, 567, 466 cm^{-1}. LC/MS: expected, 265.36; observed, *m/z*: 266.0 [M+H]$^+$. Anal. Calcd for $C_{17}H_{19}N_3$ (265.36): C, 76.95; H, 7.22; N, 15.84. Found: C, 76.69; H, 7.18; N, 15.55.

4.3.3. 7-Ethyl-5-isobutyl-6-phenyl-5*H*-pyrrolo[2,3-*b*]pyrazine, 1c (Table 2, entry 4). The general procedure was followed. Isobutylamine (263 mg, 3.60 mmol) was used. The reaction was carried out at 145 °C for 72 h. The yield was 312 mg (93%), yellow solid, mp 97–99 °C. ^{1}H NMR (DMSO-d_6) δ 0.56 (d, J=6.7 Hz, 6H), 1.16 (t, J=7.5 Hz, 3H), 1.71–1.83 (m, 1H), 2.66 (q, J=7.5 Hz, 2H), 4.02 (d, J=7.6 Hz, 2H), 7.48–7.63 (m, 5H), 8.27 (d, J=2.6 Hz, 1H), 8.41 (d, J=2.6 Hz, 1H). ^{13}C NMR (DMSO-d_6) δ 15.19, 16.43, 19.66, 28.25, 48.90, 113.67, 128.76, 128.98, 129.99, 130.60, 136.56, 137.75, 138.29, 141.25, 141.48. IR, ν_{max}: 3380, 3044, 2960, 2926, 2868, 1693, 1467, 1390, 1353, 1330, 1260, 1197, 1153, 1058, 949, 840, 769, 711, 583, 467, 439 cm^{-1}. LC/MS: expected, 279.39; observed, *m/z*: 280.2 [M+H]$^+$. Anal. Calcd for

$C_{18}H_{21}N_3$ (279.39): C, 77.38; H, 7.58; N, 15.04. Found: C, 77.14; H, 7.34; N, 14.89.

4.3.4. 5-Benzyl-7-ethyl-6-phenyl-5*H*-pyrrolo[2,3-*b*]pyrazine, 1d (Table 2, entries 5–7). The general procedure was followed. Benzylamine (386 mg, 3.60 mmol) was used. The reaction was carried out at 145 °C for 48 h. The yield was 357 mg (95%), yellow solid, mp 107–109 °C. ^{1}H NMR (DMSO-d_6) δ 1.19 (t, J=7.6 Hz, 3H), 2.69 (q, J=7.6 Hz, 2H), 5.38 (s, 2H), 6.75–6.79 (m, 2H), 7.12–7.18 (m, 3H), 7.37–7.42 (m, 2H), 7.48–7.52 (m, 3H), 8.29 (d, J=2.5 Hz, 1H), 8.45 (d, J=2.5 Hz, 1H). ^{13}C NMR (DMSO-d_6) δ 15.11, 16.51, 45.02, 114.19, 126.36, 127.11, 128.38, 128.69, 129.09, 130.02, 136.94, 137.76, 138.17, 138.61, 141.10, 141.46. IR, ν_{max}: 3429, 3050, 2964, 2930, 2871, 1457, 1397, 1357, 1195, 1160, 1067, 940, 839, 766, 731, 701, 462 cm^{-1}. LC/MS: expected, 313.41; observed, m/z: 314.1 [M+H]$^+$. Anal. Calcd for $C_{21}H_{19}N_3$ (313.41): C, 80.48; H, 6.11; N, 13.41. Found: C, 80.19; H, 5.99; N, 13.29.

4.3.5. 2-(7-Ethyl-6-phenyl-5*H*-pyrrolo[2,3-*b*]pyrazin-5-yl)ethanol, 1e (Table 2, entry 8). The general procedure was followed. 2-Aminoethanol (220 mg, 3.60 mmol) was used. The reaction was carried out at 145 °C for 72 h. The residue was purified by column chromatography on silica gel using 30% hexanes in ethyl acetate. The yield was 208 mg (65%), yellow solid, mp 155–157 °C. ^{1}H NMR (DMSO-d_6) δ 1.17 (t, J=7.5 Hz, 3H), 2.65 (q, J=7.5 Hz, 2H), 3.52–3.58 (m, 2H), 4.18 (t, J=6.5 Hz, 2H), 4.78 (t, J=5.6 Hz, 1H), 7.51–7.61 (m, 5H), 8.27 (d, J=2.6 Hz, 1H), 8.42 (d, J=2.6 Hz, 1H). ^{13}C NMR (DMSO-d_6) δ 15.15, 16.51, 44.50, 59.06, 113.47, 128.67, 128.97, 130.24, 130.35, 136.44, 137.74, 138.60, 141.14, 141.81. IR, ν_{max}: 3278, 3052, 2929, 2879, 1465, 1434, 1399, 1366, 1341, 1193, 1164, 1063, 940, 844, 761, 708, 656, 508, 457 cm^{-1}. LC/MS: expected, 267.33; observed, m/z: 268.1 [M+H]$^+$. Anal. Calcd for $C_{16}H_{17}N_3O$ (267.33): C, 71.89; H, 6.41; N, 15.72. Found: C, 71.98; H, 6.55; N, 15.52.

4.3.6. 7-Ethyl-5-(4-methoxyphenyl)-6-phenyl-5*H*-pyrrolo[2,3-*b*]pyrazine, 1f (Table 2, entries 9 and 10). The general procedure was followed. 4-Methoxyaniline (443 mg, 3.60 mmol) was used. The reaction was carried out at 145 °C for 72 h. The yield was 387 mg (98%), dark brown solid, mp 132–134 °C. ^{1}H NMR (DMSO-d_6) δ 1.27 (t, J=7.5 Hz, 3H), 2.80 (q, J=7.5 Hz, 2H), 3.75 (s, 3H), 6.89–6.94 (m, 2H), 7.14–7.20 (m, 2H), 7.30–7.35 (m, 2H), 7.35–7.42 (m, 3H), 8.23 (d, J=2.6 Hz, 1H), 8.48 (d, J=2.6 Hz, 1H). ^{13}C NMR (DMSO-d_6) δ 15.03, 16.59, 55.31, 114.01, 114.60, 128.34, 128.38, 128.50, 129.50, 130.25, 130.32, 137.30, 138.59, 138.77, 141.31, 142.19, 158.29. IR, ν_{max}: 3429, 3059, 2964, 2934, 2872, 1608, 1515, 1442, 1348, 1291, 1250, 1208, 1170, 1105, 1023, 831, 766, 699, 577, 452 cm^{-1}. LC/MS: expected, 329.41; observed, m/z: 330.1 [M+H]$^+$. Anal. Calcd for $C_{21}H_{19}N_3O$ (329.41): C, 76.57; H, 5.81; N, 12.76. Found: C, 76.57; H, 5.85; N, 12.65.

4.3.7. 7-Ethyl-6-phenyl-5*H*-pyrrolo[2,3-*b*]pyrazin-5-amine, 1g (Table 2, entry 11). The general procedure was followed. Hydrazine hydrate (180 mg, 3.60 mmol) was used. The reaction was carried out at 160 °C for 72 h. The residue was purified by column chromatography on silica gel using 50% ethyl acetate in hexanes. The yield was 179 mg (63%), brown solid, mp 92–94 °C. ^{1}H NMR (DMSO-d_6) δ 1.23 (t, J=7.5 Hz, 3H), 2.76 (q, J=7.5 Hz, 2H), 5.74 (s, 2H), 7.44–4.50 (m, 1H), 7.51–7.57 (m, 2H), 7.58–7.62 (m, 2H), 8.28 (d, J=2.6 Hz, 1H), 8.40 (d, J=2.6 Hz, 1H). ^{13}C NMR (DMSO-d_6) δ 15.30, 16.55, 110.58, 128.00, 128.34, 129.95, 130.66, 136.64, 136.66, 137.83, 140.64, 141.85. IR, ν_{max}: 3347, 3267, 3053, 2962, 2925, 2863, 1580, 1444, 1350, 1198, 1170, 1126, 1069, 1024, 944, 833, 761, 699, 670, 558, 463 cm^{-1}. LC/MS: expected, 238.29; observed, m/z: 239.1 [M+H]$^+$. Anal. Calcd for $C_{14}H_{14}N_4$ (238.29): C, 70.57; H, 5.92; N, 23.51. Found: C, 70.86; H, 6.12; N, 23.31.

4.3.8. 4-Ethyl-3-phenyl-1,4-dihydropyrazino[2,3-*c*]pyridazine, 6a (Table 2, entry 11). The general procedure was followed. Hydrazine hydrate (180 mg, 3.60 mmol) was used. The reaction was carried out at 160 °C for 72 h. The residue was purified by column chromatography on silica gel using 50% ethyl acetate in hexanes. The yield was 101 mg (35%), brown solid, mp 193–195 °C. ^{1}H NMR (DMSO-d_6) δ 0.73 (t, J=7.4 Hz, 3H), 1.56–1.69 (m, 2H), 4.42 (dd, J=7.0, 5.0 Hz, 1H), 7.34–7.46 (m, 3H), 7.85–7.90 (m, 2H), 8.12 (d, J=2.5 Hz, 1H), 8.15 (d, J=2.5 Hz, 1H), 10.85 (s, 1H). ^{13}C NMR (DMSO-d_6) δ 9.87, 26.06, 40.35, 125.44, 128.62, 128.77, 135.64, 136.22, 138.28, 141.28, 144.32, 146.43. IR, ν_{max}: 3430, 3223, 3133, 3011, 2962, 2923, 1542, 1427, 1364, 1190, 1123, 1075, 955, 835, 760, 688, 600 cm^{-1}. LC/MS: expected, 238.29; observed, m/z: 239.1 [M+H]$^+$. Anal. Calcd for $C_{14}H_{14}N_4$ (238.29): C, 70.57; H, 5.92; N, 23.51. Found: C, 70.28; H, 6.12; N, 23.24.

4.3.9. 4-Ethyl-1,3-diphenyl-1,4-dihydropyrazino[2,3-*c*]pyridazine, 6b (Table 2, entries 12 and 13). The general procedure was followed. Phenylhydrazine (390 mg, 3.60 mmol) was used. The reaction was carried out at 150 °C for 72 h. The residue was purified by column chromatography on silica gel using 20% hexanes in ethyl acetate. The yield was 238 mg (63%), brown solid, mp 141–143 °C. ^{1}H NMR (DMSO-d_6) δ 0.83 (t, J=7.5 Hz, 3H), 1.70–1.80 (m, 2H), 4.56 (dd, J=7.0, 5.3 Hz, 1H), 7.25–7.31 (m, 1H), 7.43–7.50 (m, 5H), 7.62–7.66 (m, 2H), 7.96–8.01 (m, 2H), 8.15 (d, J=2.7 Hz, 1H), 8.32 (d, J=2.7 Hz, 1H). ^{13}C NMR (DMSO-d_6) δ 10.06, 26.10, 41.18, 124.50, 125.61, 126.04, 128.56, 128.78, 129.49, 134.79, 137.84, 139.56, 140.60, 142.02, 145.36, 146.31. IR, ν_{max}: 3428, 3059, 2958, 2920, 2852, 1592, 1492, 1416, 1374, 1290, 1184, 1154, 1121, 1058, 957, 843, 768, 734, 691, 575, 479 cm^{-1}. LC/MS: expected, 314.39; observed, m/z: 315.1 [M+H]$^+$. Anal. Calcd for $C_{20}H_{18}N_4$ (314.39): C, 76.41; H, 5.77; N, 17.82. Found: C, 76.27; H, 5.65; N, 17.65.

4.3.10. 4-Ethyl-1-methyl-3-phenyl-1,4-dihydropyrazino[2,3-*c*]pyridazine, 6c (Table 2, entry 14). The general procedure was followed. Methylhydrazine (166 mg, 3.60 mmol) was used. The reaction was carried out at 170 °C for 72 h. The residue was purified by column chromatography on silica gel using 20% hexanes in ethyl acetate. The yield was 197 mg (65%), brown viscous oil. ^{1}H NMR (DMSO-d_6) δ 0.72 (t, J=7.5 Hz, 3H), 1.52–1.71 (m, 2H), 3.56 (s, 3H), 4.43 (dd, J=7.6, 4.9 Hz, 1H),

7.38–7.47 (m, 3H), 7.87–7.92 (m, 2H), 8.18 (d, J=2.7 Hz, 1H), 8.21 (d, J=2.7 Hz, 1H). ^{13}C NMR (DMSO-d_6) δ 9.97, 25.88, 38.12, 40.91, 125.59, 128.65, 129.03, 135.03, 137.66, 137.72, 140.89, 144.50, 146.21. IR, ν_{max}: 3054, 2965, 2929, 2873, 1700, 1562, 1534, 1435, 1399, 1365, 1308, 1186, 1118, 1079, 1025, 954, 839, 767, 693, 658, 566, 509 cm^{-1}. LC/MS: expected, 252.32; observed, m/z: 253.1 [M+H]$^+$. Anal. Calcd for $C_{15}H_{16}N_4$ (252.32): C, 71.40; H, 6.39; N, 22.20. Found: C, 71.11; H, 6.19; N, 22.01.

4.3.11. (1*Z*)-2-(3-Chloropyrazin-2-yl)-1-phenylbutan-1-one phenylhydrazone, 7. The general procedure was followed. Phenylhydrazine (390 mg, 3.60 mmol) was used. The reaction was carried out at 150 °C for 72 h in the absence of PTSA. The residue was purified by column chromatography on silica gel using 20% hexanes in ethyl acetate. The product was isolated as a mixture of *syn* and *anti* isomers. The yield was 287 mg (65%), dark brown viscous oil. ^{1}H NMR (DMSO-d_6) δ 0.86 (t, J=7.3 Hz, 3H-*syn*), 1.07 (t, J=7.3 Hz, 3H-*anti*), 1.95–2.20 (m, 2H-*syn*+2H-*anti*), 4.42 (dd, J=9.0, 4.9 Hz, 1H-*syn*), 4.94–5.00 (m, 1H-*anti*), 6.63–6.69 (m, 1H-*syn*), 6.78–6.85 (m, 2H-*syn*+1H-*anti*), 7.03–7.10 (m, 2H-*syn*), 7.14–7.21 (m, 3H-*anti*), 7.22–7.29 (m, 3H-*syn*+1H-*anti*), 7.37–7.42 (m, 3H-*anti*), 7.42–7.50 (m, 2H-*syn*+2H-*anti*), 8.36 (d, J=2.5 Hz, 1H-*anti*), 8.38 (d, J=2.4 Hz, 1H-*syn*), 8.56 (br s, 1H-*syn*), 8.68 (d, J=2.4 Hz, 1H-*syn*), 8.73 (d, J=2.5 Hz, 1H-*anti*), 9.98 (s, 1H-*anti*). ^{13}C NMR (DMSO-d_6) for *syn* isomer, δ 12.23, 23.54, 52.32, 112.49, 118.72, 127.74, 128.65, 128.76, 129.10, 134.12, 141.95, 142.74, 145.12, 145.75, 149.16, 155.05. IR, ν_{max}: 3334, 3256, 3054, 2967, 2931, 2874, 1691, 1601, 1503, 1445, 1383, 1252, 1151, 1093, 1060, 999, 850, 750, 694, 508, 475 cm^{-1}. LC/MS: expected, 350.85; observed, m/z: 351.1 [M+H]$^+$. Anal. Calcd for $C_{20}H_{19}ClN_4$ (350.85): C, 68.47; H, 5.46; Cl, 10.10; N, 15.97. Found: C, 68.84; H, 5.28; Cl, 9.72; N, 15.70.

4.4. General procedure for the cyclization of the chloroketones 3 into the furo[2,3-*b*]pyrazines 10

To a solution of **3** (1.00 mmol) in 7 mL of DMF was added K_2CO_3 (552 mg, 4.00 mmol), the resulting suspension was stirred under reflux for 3 h. After cooling, the reaction mixture was filtered through a plug of Celite that was then washed with chloroform. The combined organic phase was concentrated in vacuo. The residue was purified by column chromatography on silica gel using 20% ethyl acetate in hexanes, unless otherwise stated.

4.4.1. 6-Phenylfuro[2,3-*b*]pyrazine, 10a.[20] The general procedure was followed. Intermediate **3a** (232 mg, 1.00 mmol) was used. The yield was 190 mg (97%), yellow solid, mp 112–113 °C. ^{1}H NMR (DMSO-d_6) δ 7.50–7.61 (m, 3H), 7.80 (s, 1H), 8.02–8.08 (m, 2H), 8.33 (d, J=2.8 Hz, 1H), 8.61 (d, J=2.8 Hz, 1H). ^{13}C NMR (DMSO-d_6) δ 102.06, 125.49, 128.41, 129.24, 130.58, 137.61, 141.88, 142.00, 155.02, 159.34. IR, ν_{max}: 3426, 3107, 3043, 1545, 1447, 1367, 1264, 1182, 1014, 841, 756, 682, 656, 437 cm^{-1}. LC/MS: expected, 196.21; observed, m/z: 197.1 [M+H]$^+$. Anal. Calcd for $C_{12}H_8N_2O$ (196.21): C, 73.46; H, 4.11; N, 14.28. Found: C, 73.59; H, 4.14; N, 14.15.

4.4.2. 6-Pyridin-4-ylfuro[2,3-*b*]pyrazine, 10b. The general procedure was followed. Intermediate **3c** (234 mg, 1.00 mmol) was used. The residue was purified by column chromatography on silica gel using pure ethyl acetate. The yield was 165 mg (84%), brown solid, mp 224–225 °C. ^{1}H NMR (DMSO-d_6) δ 7.96–8.00 (m, 2H), 8.12 (s, 1H), 8.43 (d, J=2.7 Hz, 1H), 8.70 (d, J=2.7 Hz, 1H), 8.76–8.79 (m, 2H). ^{13}C NMR (DMSO-d_6) δ 105.72, 119.08, 135.37, 139.05, 141.04, 142.67, 150.68, 155.28, 156.47. IR, ν_{max}: 3431, 3071, 3032, 2924, 1606, 1554, 1490, 1416, 1367, 1272, 1197, 1028, 849, 821, 784, 670, 441 cm^{-1}. LC/MS: expected, 197.20; observed, m/z: 198.1 [M+H]$^+$. Anal. Calcd for $C_{11}H_7N_3O$ (197.20): C, 67.00; H, 3.58; N, 21.31. Found: C, 67.13; H, 3.61; N, 21.20.

4.4.3. 6-Pyridin-3-ylfuro[2,3-*b*]pyrazine, 10c. The general procedure was followed. Intermediate **3d** (234 mg, 1.00 mmol) was used. The residue was purified by column chromatography on silica gel using pure ethyl acetate. The yield was 162 mg (83%), brown solid, mp 206–207 °C. ^{1}H NMR (DMSO-d_6) δ 7.58–7.63 (m, 1H), 7.95 (s, 1H), 8.37 (d, J=2.7 Hz, 1H), 8.38–8.43 (m, 1H), 8.65 (d, J=2.7 Hz, 1H), 8.68–8.71 (m, 1H), 9.24–9.27 (m, 1H). ^{13}C NMR (DMSO-d_6) δ 103.52, 124.14, 124.67, 132.69, 138.14, 141.40, 142.28, 146.58, 150.98, 155.13, 156.84. IR, ν_{max}: 3431, 3098, 2959, 2925, 1604, 1546, 1483, 1415, 1369, 1268, 1190, 1054, 1010, 923, 897, 850, 810, 785, 700, 646, 435 cm^{-1}. LC/MS: expected, 197.20; observed, m/z: 198.1 [M+H]$^+$. Anal. Calcd for $C_{11}H_7N_3O$ (197.20): C, 67.00; H, 3.58; N, 21.31. Found: C, 67.06; H, 3.46; N, 21.11.

4.4.4. 7-Ethyl-6-phenylfuro[2,3-*b*]pyrazine, 10d. The general procedure was followed. Intermediate **3b** (260 mg, 1.00 mmol) was used. The yield was 220 mg (98%), yellow solid, mp 49–50 °C. ^{1}H NMR (DMSO-d_6) δ 1.34 (t, J=7.6 Hz, 3H), 2.99 (q, J=7.6 Hz, 2H), 7.50–7.56 (m, 1H), 7.57–7.63 (m, 2H), 7.83–7.88 (m, 2H), 8.34 (d, J=2.7 Hz, 1H), 8.62 (d, J=2.7 Hz, 1H). ^{13}C NMR (DMSO-d_6) δ 13.37, 16.07, 117.68, 127.02, 129.14, 129.21, 129.88, 137.90, 141.39, 141.71, 153.86, 154.25. IR, ν_{max}: 3430, 3061, 2961, 2928, 2872, 1540, 1464, 1410, 1360, 1195, 1054, 949, 852, 768, 690, 441 cm^{-1}. LC/MS: expected, 224.26; observed, m/z: 225.0 [M+H]$^+$. Anal. Calcd for $C_{14}H_{12}N_2O$ (224.26): C, 74.98; H, 5.39; N, 12.49. Found: C, 74.76; H, 5.50; N, 12.31.

4.4.5. 2-[3-(Isobutylamino)pyrazin-2-yl]butanenitrile, 11. To a solution of **5b** (218 mg, 1.20 mmol) in 6 mL of xylene in a screw-cap glass pressure vessel was added isobutylamine (263 mg, 3.60 mmol). The pressure vessel was sealed with a cap containing a PTFE septum and removed from the drybox. The reaction mixture was stirred and heated at 140 °C for 72 h. After cooling, the reaction mixture was filtered through a plug of Celite that was then washed with chloroform. The combined organic phase was concentrated in vacuo. The residue was purified by column chromatography on silica gel using 15% ethyl acetate in hexanes. The yield was 138 mg (53%), yellow viscous oil. ^{1}H NMR (DMSO-d_6) δ 0.88 (d, J=6.6 Hz, 3H), 0.89 (d, J=6.6 Hz, 3H), 1.01 (t, J=7.3 Hz, 3H), 1.80–2.10 (m, 3H), 3.08–3.22 (m, 2H), 4.44 (dd, J=8.2, 6.0 Hz, 1H), 6.82 (m, 1H), 7.71 (d, J=2.7 Hz, 1H), 7.97 (d, J=2.7 Hz, 1H). ^{13}C NMR (DMSO-d_6) δ 11.22, 20.27, 24.42, 27.13, 34.85, 48.09,

119.75, 130.08, 136.15, 141.35, 151.78. IR, ν_{max}: 3412, 3050, 2961, 2872, 2246, 1658, 1580, 1511, 1460, 1385, 1256, 1185, 1156, 1105, 1078, 1055, 944, 842, 613, 485 cm^{-1}. LC/MS: expected, 218.30; observed, *m/z*: 219.2 $[M+H]^+$. Anal. Calcd for $C_{12}H_{18}N_4$ (218.30): C, 66.02; H, 8.31; N, 25.66. Found: C, 66.07; H, 8.35; N, 25.60.

4.4.6. 7-Ethyl-*N*,5-diisobutyl-5*H*-pyrrolo[2,3-*b*]pyrazin-6-amine hydrochloride, 1h. To a solution of **5b** (218 mg, 1.20 mmol) in 6 mL of xylene in a screw-cap glass pressure vessel was added isobutylamine (263 mg, 3.60 mmol). The pressure vessel was sealed with a cap containing a PTFE septum and removed from the drybox. The reaction mixture was stirred and heated at 170 °C for 72 h. After cooling, the reaction mixture was transferred to the oxygen-free drybox and quenched with 0.7 mL of 12 M aq HCl. After removing from the drybox, the solvent was evaporated in vacuo; the residue was suspended in 60 mL of hot 40:60 mixture of chloroform and ethyl acetate. The suspension was filtered, the organic phase was concentrated under reduced pressure, the residue was dissolved in 60 mL of THF under reflux, the resulting solution was cooled to −18 °C, and the precipitated *i*-$BuNH_2 \cdot HCl$ was filtered out. After concentration of the organic phase under reduced pressure, the residue was crystallized from 40 mL of THF to give 183 mg (49% yield) of the desired product as a hydrochloride salt, yellow solid, mp 174–178 °C (decomp.). ^1H NMR (DMSO-d_6) δ 0.83 (d, J=6.6 Hz, 6H), 0.96 (d, J=6.6 Hz, 6H), 1.15 (t, J=7.3 Hz, 3H), 1.88–2.01 (m, 1H), 2.09–2.22 (m, 1H), 2.81 (q, J=7.3 Hz, 2H), 3.36 (m, 2H), 4.10 (d, J=7.8 Hz, 2H), 7.76 (s, 2H), 8.38 (m, 1H), 14.85 (br s, 1H). ^{13}C NMR (DMSO-d_6) δ 15.27, 15.86, 19.38, 19.68, 27.40, 29.29, 46.96, 50.13, 90.24, 121.44, 126.81, 131.36, 146.40, 154.89. IR, ν_{max}: 3181, 3148, 3070, 3024, 2960, 2872, 2766, 2566, 1859, 1589, 1523, 1462, 1382, 1292, 1217, 1159, 1102, 1046, 955, 801, 664, 494 cm^{-1}. LC/MS: expected, 274.41; observed, *m/z*: 275.3 $[M+H]^+$. Anal. Calcd for $C_{16}H_{26}N_4$+HCl (274.41+36.46): C, 61.82; H, 8.75; Cl, 11.40; N, 18.02. Found: C, 61.71; H, 8.87; Cl, 11.54; N, 18.00.

4.4.7. (6*E*)-7-Ethyl-5-isobutyl-6-(isobutylimino)-6,7-dihydro-5*H*-pyrrolo[2,3-*b*]pyrazin-7-ol, 12. To a solution of **1h**·HCl (90 mg, 0.29 mmol) in 10 mL of chloroform was added 6 mL (1.45 mmol) of 0.242 M aq K_2CO_3. The reaction mixture was stirred at room temperature for 18 h on air, then filtered through a plug of Celite that was then washed with chloroform. The organic phase was concentrated in vacuo. The residue was purified by column chromatography on silica gel using 30% ethyl acetate in hexanes. The yield was 75 mg (89%), yellow solid, mp 82–84 °C. ^1H NMR (DMSO-d_6) δ 0.58 (t, J=7.5 Hz, 3H), 0.86 (d, J=6.8 Hz, 3H), 0.89 (d, J=6.8 Hz, 3H), 0.93 (d, J=6.7 Hz, 3H), 0.94 (d, J=6.7 Hz, 3H), 1.71–1.82 (m, 1H), 2.05–2.24 (m, 3H), 3.41–3.61 and 3.68–3.75 (m, 4H), 6.24 (s, 1H), 7.89 (d, J=3.2 Hz, 1H), 7.95 (d, J=3.2 Hz, 1H). ^{13}C NMR (DMSO-d_6) δ 7.81, 20.22, 20.23, 20.46, 20.47, 26.31, 29.75, 30.20, 45.98, 54.08, 76.07, 134.39, 141.32, 148.37, 153.62, 157.34. IR, ν_{max}: 3178, 2956, 2869, 1696, 1569, 1482, 1419, 1361, 1311, 1244, 1137, 1106, 1019, 940, 883, 838, 695, 554, 475 cm^{-1}. LC/MS: expected, 290.41; observed, *m/z*: 291.2 $[M+H]^+$. Anal. Calcd for $C_{16}H_{26}N_4O$ (290.41): C, 66.17; H, 9.02; N, 19.29. Found: C, 66.21; H, 9.09; N, 19.24.

4.4.8. *tert*-Butyl 2-[3-(isobutylamino)pyrazin-2-yl]propanoate, 13. To a solution of **4e** (291 mg, 1.20 mmol) in 6 mL of xylene in a screw-cap glass pressure vessel was added isobutylamine (263 mg, 3.60 mmol). The pressure vessel was sealed with a cap containing a PTFE septum and removed from the drybox. The reaction mixture was stirred and heated at 130 °C for 72 h. After cooling, the reaction mixture was filtered through a plug of Celite that was then washed with chloroform. The organic phase was concentrated in vacuo. The residue was purified by column chromatography on silica gel using 10% ethyl acetate in hexanes to give the unreacted starting material (48%) and the desired product. The yield was 75 mg (23%), yellow solid, mp 72–73 °C. ^1H NMR (DMSO-d_6) δ 0.88 (d, J=6.8 Hz, 6H), 1.29 (d, J=6.8 Hz, 3H), 1.33 (s, 9H), 1.86–1.97 (m, 1H), 3.07–3.21 (m, 2H), 4.44 (q, J=6.8 Hz, 1H), 6.50 (m, 1H), 7.60 (d, J=2.7 Hz, 1H), 7.84 (d, J=2.7 Hz, 1H). ^{13}C NMR (DMSO-d_6) δ 14.94, 20.29, 27.27, 27.72, 41.63, 48.11, 79.96, 129.84, 139.79, 142.00, 152.38, 171.67. IR, ν_{max}: 3423, 2970, 2927, 2870, 1722, 1580, 1512, 1459, 1368, 1322, 1234, 1149, 1085, 848, 758, 481 cm^{-1}. LC/MS: expected, 279.39; observed, *m/z*: 280.1 $[M+H]^+$. Anal. Calcd for $C_{15}H_{25}N_3O_2$ (279.39): C, 64.49; H, 9.02; N, 15.04. Found: C, 64.41; H, 9.01; N, 15.09.

4.4.9. 3-Ethyl-*N*-isobutylpyrazin-2-amine, 14. The procedure described above for **13** was followed. The reaction mixture was carried out at 170 °C for 72 h. The residue was purified by column chromatography on silica gel using 30% ethyl acetate in hexanes. The yield was 121 mg (56%), yellow viscous oil. ^1H NMR (DMSO-d_6) δ 0.87 (d, J=6.8 Hz, 6H), 1.18 (t, J=7.4 Hz, 3H), 1.87–1.99 (m, 1H), 2.62 (q, J=7.4 Hz, 2H), 3.13 (dd, J=7.1, 5.9 Hz, 2H), 6.42–6.47 (m, 1H), 7.57 (d, J=2.7 Hz, 1H), 7.78 (d, J=2.7 Hz, 1H). ^{13}C NMR (DMSO-d_6) δ 10.66, 20.29, 25.38, 27.13, 48.00, 129.62, 138.79, 143.93, 152.57. IR, ν_{max}: 3364, 3043, 2959, 2871, 1580, 1542, 1509, 1465, 1382, 1352, 1260, 1184, 1069, 1031, 829, 611 cm^{-1}. LC/MS: expected, 179.27; observed, *m/z*: 180.1 $[M+H]^+$. Anal. Calcd for $C_{10}H_{17}N_3$ (179.27): C, 67.00; H, 9.56; N, 23.44. Found: C, 67.21; H, 9.55; N, 23.16.

4.4.10. 7-Hydroxy-5-isobutyl-7-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*b*]pyrazin-6-one, 15. To a solution of **4d** (241 mg, 1.20 mmol) in 6 mL of xylene in a screw-cap glass pressure vessel was added isobutylamine (263 mg, 3.60 mmol). The pressure vessel was sealed with a cap containing a PTFE septum and removed from the drybox. The reaction mixture was stirred and heated at 170 °C for 72 h. After cooling, the reaction mixture was transferred to the oxygen-free drybox and quenched with 0.7 mL of 12 M aq HCl. After removing from the drybox, the solvent was evaporated, the residue was suspended in 50 mL of THF under reflux, the resulting solution was cooled to −18 °C, and the precipitated *i*-$BuNH_2 \cdot HCl$ was filtered out. The organic phase was concentrated in vacuo and the probe was taken for the NMR. Then the residue was dissolved in 20 mL of chloroform and quenched with 10 mL of saturated aq K_2CO_3. The organic layer was separated and the aqueous layer was extracted twice with additional chloroform. The organics were combined, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel using 50% ethyl acetate in hexanes.

The yield was 80 mg (30%), yellow viscous oil. ^{1}H NMR (DMSO-d_6) δ 0.87 (d, J=6.5 Hz, 3H), 0.89 (d, J=6.5 Hz, 3H), 1.45 (s, 3H), 2.07–2.19 (m, 1H), 3.50 (d, J=7.3 Hz, 2H), 6.30 (s, 1H), 8.16 (s, 2H). ^{13}C NMR (DMSO-d_6) δ 19.94, 21.89, 26.46, 45.50, 71.33, 137.54, 141.69, 148.72, 151.74, 176.58. IR, ν_{max}: 3384, 3065, 2961, 2930, 2873, 1743, 1574, 1460, 1370, 1319, 1250, 1194, 1137, 1045, 922, 846, 756, 627, 569, 508 cm^{-1}. LC/MS: expected, 221.26; observed, *m/z*: 222.1 [M+H]$^+$. Anal. Calcd for $C_{11}H_{15}N_3O_2$ (221.26): C, 59.71; H, 6.83; N, 18.99. Found: C, 59.37; H, 6.57; N, 18.95.

References and notes

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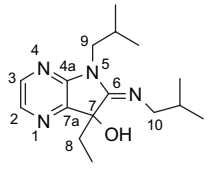

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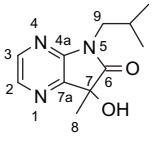

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