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ORIGINAL ARTICLE

One-pot synthesis of novel 1-(1*H*-tetrazol-5-yl)-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine derivatives via an Ugi-azide 4CR process

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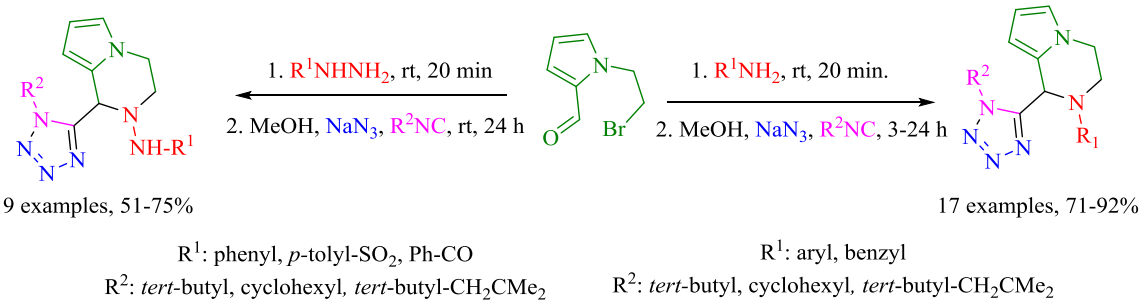
Abstract
A facile one-pot method has been developed for the synthesis of novel pyrrolo[2,1-*a*]pyrazine scaffolds. A variety of 1-(1*H*-tetrazol-5-yl)-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine derivatives were obtained in moderate to high yields in methanol using a one-pot four-component condensation of 1-(2-bromoethyl)-1*H*-pyrrole-2-carbaldehyde, amine, isocyanide and sodium azide at room temperature. These reactions presumably proceed *via* a domino imine formation, intramolecular annulation and Ugi-azide reaction. Unambiguous assignment of the molecular structures was carried out by single-crystal X-ray diffraction.

Graphical Abstract



Keywords Ugi-azide · Tetrahydropyrrolo[1, 2-*a*]pyrazine · Tetrazole · MCRs

Introduction

In recent years, multicomponent reactions (MCRs) have extensively been developed as efficient synthetic strategies for the construction of biologically interesting compounds [1–3]. The need of modern methods in organic synthesis as well as medicinal chemistry has led chemists to design processes in which reactions occur not through a single-step procedure, but rather via several sequential steps involving cascades or domino reactions [4]. The advantages of MCRs include one-pot reaction, time saving, greater efficiency, and atom economy with the generation of simultaneous several bond formations leading to complex structures [5,6].

Isocyanide-based multicomponent reactions (IMCRs), which are a subclass of MCRs, are defined as processes in which an isocyanide is used as one of the starting materials to prepare new compounds [7–12]. In this context, the work of Ugi is perhaps the first report of IMCR [13–17]. Thereafter, there have been many reports on the synthesis of more complex structures through tandem Ugi/post-Ugi reactions [18–24].

In the Ugi-azide reaction, which is another aspect of the Ugi multicomponent process, carboxylic acid is replaced by hydrazoic acid, trimethylsilyl azide ($TMSN_3$) or sodium azide in order to achieve the novel biologically important 1,5-disubstituted-1*H*-tetrazole (1,5-DS-1*H*-T) [25–36]. Par-

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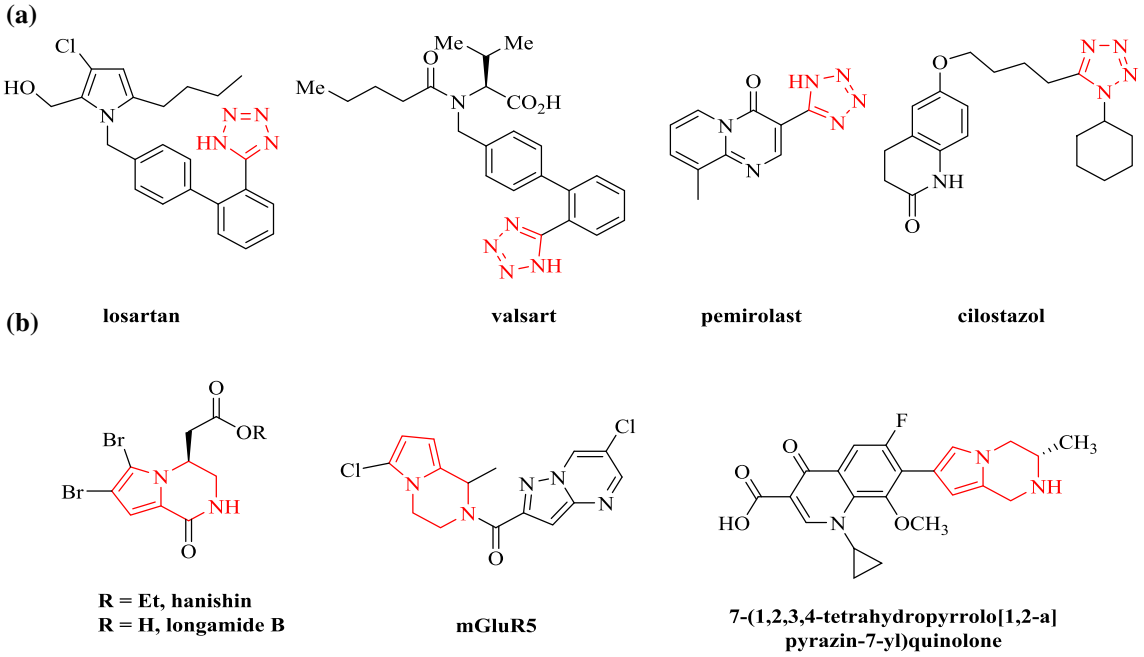


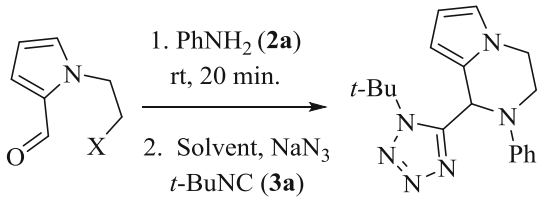
Fig. 1 **a** Drugs containing a tetrazole ring, **b** example of natural products and bioactive molecules containing a pyrrolo[1,2-*a*]pyrazine scaffold

ticularly significant in this regard is the first use of an internally generated secondary amine in order to obtain fused ketopiperazine-tetrazoles [37]. Other approaches to obtaining tetrazoles through post-condensation modifications on the initially prepared Ugi-azide product often by an internal nucleophilic substitution may not also be overlooked [38,39].

1,5-DS-1*H*-Ts are bioisosteres of *cis*-amide bond [40–43]. Due to their metabolic stability [44], 1,5-DS-1*H*-T heterocycles are important in medicinal chemistry. Certain derivatives of 1,5-DS-1*H*-Ts are active on the central nervous system (CNS) [45]. Pharmaceutically important tetrazoles including losartan, valsartan, pemirolast and cilostazol have been used for the treatment of cardiovascular diseases [46], antihypertension [47], allergies [48] and reducing the symptoms of intermittent claudication [49], respectively (Fig. 1a). Non-biological properties such as primary explosives [50] and ligands [51] have also been reported for some tetrazole derivatives.

1,2,3,4-Tetrahydropyrrolo[1,2-*a*]pyrazines are important heterocyclic skeletons exhibiting antiarrhythmic [52], psychotropic [53], antiamnesic and antihypersensitive [54], antiamnesic [55], and antihypoxic (Fig. 1b) [56].

We became interested in the synthesis of tetrahydropyrrolo[1,2-*a*]pyrazine and 1,5-DS-1*H*-T heterocycles due to their biological activities and uses. Based on our contribution to Ugi-azide reactions [57,58] as well as synthesis of 2-chloropyridinium adducts [59–61], herein, we report a new methodology for the synthesis of novel 1-(1*H*-tetrazol-5-yl)-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine derivatives *via* a facile Ugi-azide four-component process using 1-(2-



Scheme 1 Synthesis of **4a** *via* a two-step Ugi-azide reaction

Table 1 Optimization of reaction conditions

Entry	Solvent	Time (h)	X	Temperature (°C)	Yield (%)[a]
1	DCM	24	Br	rt	28
2	THF	24	Br	rt	37
3	EtOH	6	Br	rt	63
4	MeOH	3	Br	rt	92
5	MeOH	3	Br	40	83
6	MeOH	6	Cl	rt	53
7	MeOH	6	Cl	40	55
8[b]	MeOH	3	Br	rt	55
9[c]	MeOH	3	Br	rt	46

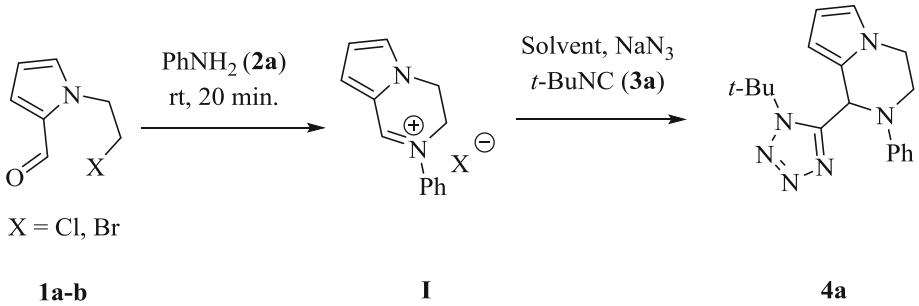
Reaction conditions: All reactions were carried out using a two-step procedure as depicted in Scheme 1 using 1-(2-haloethyl)-1*H*-pyrrole-2-carbaldehyde **1a–b** (1 mmol), aniline **2a** (1mmol), *t*BuNC **4a** (1 mmol), NaN_3 (1 mmol) and solvent (4 mL)

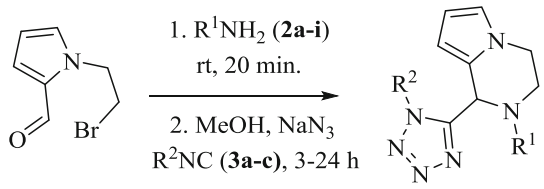
[a]Isolated yields

[b]Using $TMSN_3$ instead of NaN_3

[c]One-step 4CR in MeOH

Scheme 2 Role of iminium **I** intermediate in the synthesis of tetrazole **4a**





Scheme 3 Synthesis of **4a–r** *via* a two-step Ugi-azide reaction

bromoethyl)-1-*H*-pyrrole-2-carbaldehyde, aromatic or benzyl amines, phenylhydrazine, phenylhydrazide, *p*-toluenesulfonyl hydrazide and isocyanide or sodium azide.

Results and discussion

Initially, 1-(2-haloethyl)-1*H*-pyrrole-2-carbaldehydes **1a–b** were synthesized according to the literature [62]. In order to optimize reaction conditions, 1-(2-bromoethyl)-1*H*-pyrrole-2-carbaldehyde **1a** and aniline **2a** were initially condensed within 20 min, followed by addition of solvent, *t*-butylisocyanide **3a** and sodium azide in room temperature (rt) (Scheme 1, Table 1). Although DCM and THF furnished tetrazole **4a** in low yields (entries 1 and 2, Table 1), this product was obtained in 63 and 92% yields within 6 and 3 h in EtOH and MeOH, respectively (entries 3 and 4, Table 1). Increasing the temperature to 40 °C lowers the yield of **4a** (entry 5, Table 1). Compound **4a** was obtained in lower yield either using 1-(2-chloroethyl)-1*H*-pyrrole-2-carbaldehyde **1b** at rt or 40 °C, or replacing NaN_3 by $TMSN_3$

Table 2 Synthesis of **4a–r** *via* a two-step Ugi-azide reaction

Entry	Amine	Isocyanide	Product	Yield (%)[a]
1	Ph-NH_2 (**2a**)	*t*-BuNC (**3a**)	**4a**	92
2	Bn- NH_2 (**2b**)	*t*-BuNC (**3a**)	**4b**	81
3	2-Me-Ph-NH_2 (**2c**)	*t*-BuNC (**3a**)	**4c**	67
4	3-Me-Ph-NH_2 (**2d**)	*t*-BuNC (**3a**)	**4d**	89
5	4-Me-Ph-NH_2 (**2e**)	*t*-BuNC (**3a**)	**4e**	93
6	3, 4-diMe-Ph-NH_2 (**2f**)	*t*-BuNC (**3a**)	**4f**	88
7	4-Cl-Ph-NH_2 (**2g**)	*t*-BuNC (**3a**)	**4g**	71
8	4-MeO-Ph-NH_2 (**2h**)	*t*-BuNC (**3a**)	**4h**	90
9	Bn-NH_2 (**2b**)	CyNC (3**b**)	**4i**	73
10	3-Me-Ph-NH_2 (**2d**)	CyNC (3**b**)	**4j**	76
11	4-Me-Ph-NH_2 (**2e**)	CyNC (**3b**)	**4k**	90
12	3, 4-diMe-Ph-NH_2 (**2f**)	CyNC (**3b**)	**4l**	72
13[b]	4-Cl-Ph-NH_2 (**2g**)	CyNC (**4b**)	**4m**[c]	68
14	4-MeO-Ph-NH_2 (**2h**)	Cy-NC (**3b**)	**4n**	93
15	Pyridine-3-NH_2 (**2i**)	CyNC (**3b**)	**4o**	47
16	Ph-NH_2 (**2b**)	*t*-BuCH_2CMe_2NC (**3c**)	**4p**	84
17	4-Me-Ph-NH_2 (**2e**)	*t*-BuCH_2CMe_2NC (**3c**)	**4q**	87

Reaction conditions: All reactions were carried out using a two-step procedure as depicted in Scheme 1 with 1-(2-bromoethyl)-1*H*-pyrrole-2-carbaldehyde **1a** (1 mmol), amines **2a–i** (1 mmol), isocyanides **3a–c** (1 mmol), NaN_3 (1 mmol) and MeOH (4 mL) at rt for 3 h

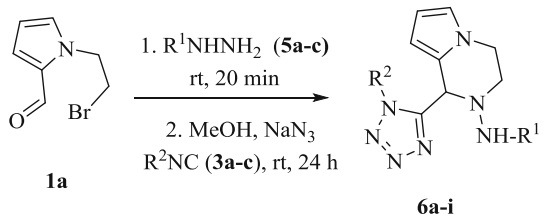
[a]Isolated yields

[b]Structure of **4m** was confirmed by single-crystal X-ray diffraction analysis

(entries 6–8, Table 1). Finally, carrying out the reaction in one step in MeOH afforded **4a** in 46% (entry 9, Table 1).

The iminium **I** was suggested to be generated as an intermediate in order to rationalize the results shown in Table 1. Since Br is a better leaving group than Cl (entries 4 and 6, Table 1), the iminium ion **I** is generated more efficiently from **1a** in comparison with that of Cl analogue **1b** (Scheme 2). Therefore, the Ugi-azide reaction of 1-(2-bromoethyl)-1*H*-pyrrole-2-carbaldehyde **1a** to tetrazole **4a** proceeds faster accordingly. The utilization of NaN_3 as a stronger nucleophile in comparison with that of $TMSN_3$ also affords tetrazole **4a** in higher yield (entries 4 and 8, Table 1). Moreover, generation of **I** apparently occurs faster under solvent-free condition since a decrease in yield is observed when using a solvent (entries 4 and 9, Table 1). On the other hand, obtaining lower yield of **4a** at 40 °C can be rationalized by partial instability of **1a** since the reaction color turned black under this condition.

With the optimized reaction conditions in hand, the generality of this reaction was studied. The reaction of 1-(2-bromoethyl)-1*H*-pyrrole-2-carbaldehyde **1a**, amines **2a–j** and isocyanides **4a–c** afforded products **5a–r** in moderate to high yields (Scheme 3, Table 2). Whether strong or weak amines such as *n*-butylamine, cyclohexylamine and 2- or 4-



R^1: phenyl, *p*-tolyl-SO_2, Ph-CO
R^2: *tert*-Butyl, cyclohexyl, *tert*-butyl-CH_2CMe_2

Scheme 4 Preparation of **6a–i** *via* a two-step Ugi-azide reaction

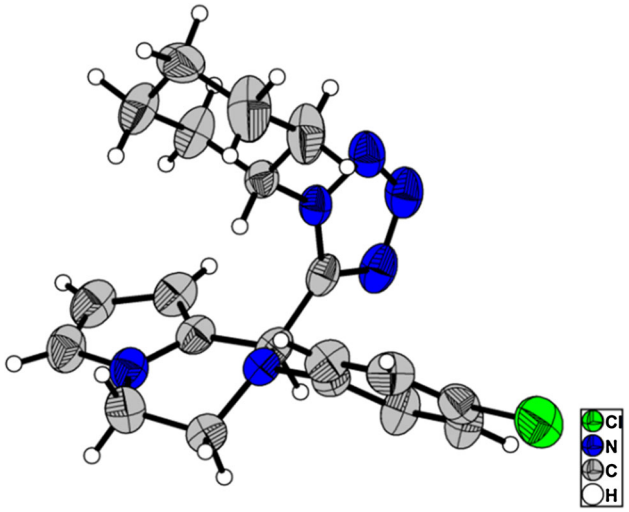


Fig. 2 ORTEP diagram of compound **4m**

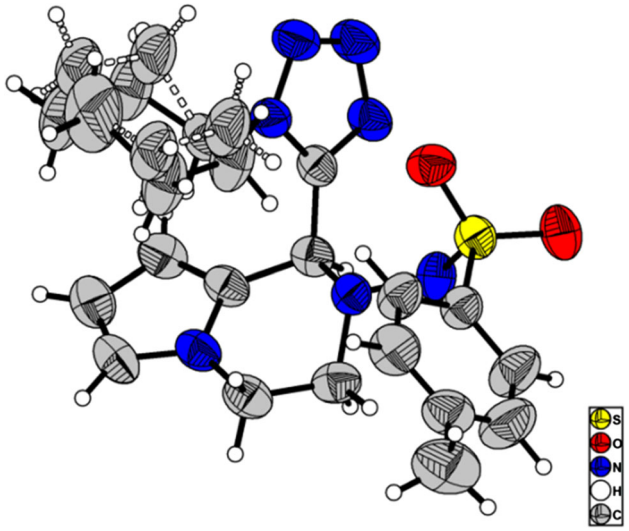


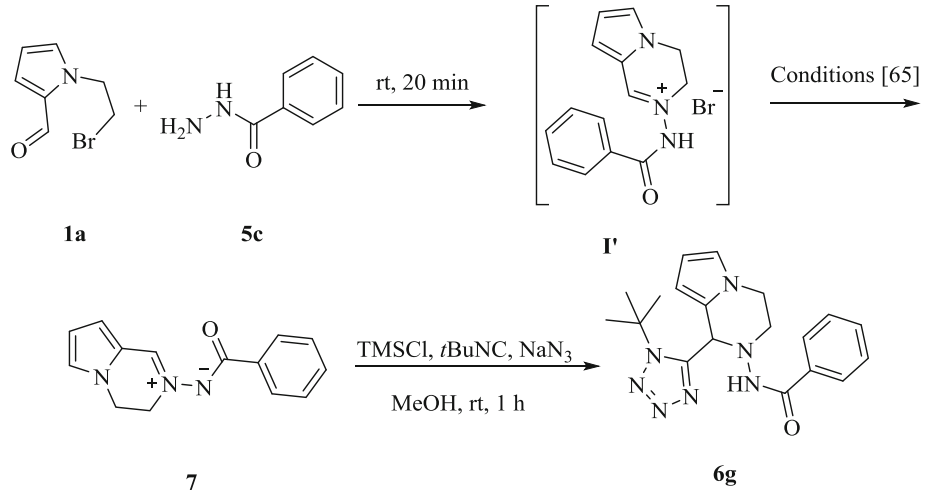
Fig. 3 ORTEP diagram of compound **6e**

Table 3 Synthesis of **6a–i** *via* a two-step Ugi-azide reaction

Entry	Amine source	Isocyanide	Product	Yield (%)[a]
1	PhNH-NH_2 (**5a**)	*t*-BuNC (**3a**)	**6a**	57
2	PhNH-NH_2 (**5a**)	CyNC (**3b**)	**6b**	51
3	PhNH-NH_2 (**5a**)	*t*-BuCH_2CMe_2NC (**3c**)	**6c**	60
4	4-Me-PhSO_2NH-NH_2 (**5b**)	t-BuNC (**3a**)	**6d**	74
5[b]	4-Me-PhSO_2NH-NH_2 (**5b**)	CyNC (**3b**)	**6e**[b]	68
6	4-Me-PhSO_2NH-NH_2 (**5b**)	t-BuCH_2CMe_2NC (**3c**)	**6f**	75
7	PhCONH-NH_2 (**5c**)	t-BuNC (**3a**)	**6g**	73
8	PhCONH-NH_2 (**5c**)	CyNC (**3b**)	**6h**	70
9	PhCONH-NH_2 (**5c**)	t-BuCH_2CMe_2NC (**3c**)	**6i**	65

Reaction conditions: All reactions were carried out with 1-(2-bromoethyl)-1*H*-pyrrole-2-carbaldehyde **1a** (1 mmol), NaN_3 (1 mmol), isocyanides **3a–c** (1 mmol), amines **5a–c** (1 mmol) and MeOH (4 mL) at rt for 24 h
[a]Isolated yields
[b]Structure of **6e** was confirmed by single-crystal X-ray diffraction analysis

Scheme 5 Alternate synthetic route to **6g**



aminopyridine were used, they were found to be inefficient perhaps due to the formation of highly stable iminium intermediates or the inefficiency of weak heteroaromatic amines in forming the corresponding imines, respectively.

To explore the versatility of the reaction, substituted hydrazines **5a–c** were used as amine source. Interestingly, the corresponding products **6a–i** were obtained in good yields (Scheme 4, Table 3).

Compounds **4a–r** and **6a–i** were characterized and confirmed by elemental analysis, MS, IR, and ^{1}H and ^{13}C NMR spectroscopy. An unambiguous evidence for the proposed structures of **4m** and **6e** was obtained by single-crystal X-ray diffractometry, and ORTEP diagrams are shown in Figs. 2 and 3. The CCDC deposition number for compound **4m** is 1530979. Formula: C_{20} H_{23} Cl N_6. Unit cell parameters: $a = 16.079(5)$ Å, $b = 8.3270(17)$ Å, $c = 29.813(6)$ Å, $\alpha = 90°$, $\beta = 93.41(4)°$, $\gamma = 90°$, space group $C2/c$. The CCDC deposition number for compound **6e** is 1530978. Formula: C_{21} H_{27} N_7 O_2 S. Unit cell parameters: $a = 9.4374(19)$ Å, $b = 11.577(2)$ Å, $c = 12.175(2)$ Å, $\alpha = 108.87(3)°$, $\beta = 112.26(3)°$, $\gamma = 93.59(3)°$, space group $P-1$.

Synthesis of **6g** was also carried out in 93% yield using a previously reported procedure (Scheme 5) [63,64]. The initially generated iminium intermediate **I′** from condensation of **1a** with benzohydrazide (**5c**) was converted to azomethine imine **7** [65]. This imine then reacted with chlorotrimethylsilane, *t*-BuNC and NaN_3, to afford **6g** in 82% yield [66] (Scheme 5).

Conclusion

In summary, we have developed a simple and convenient strategy for the synthesis of several bifunctional novel 1-(1*H*-tetrazol-5-yl)-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine derivatives **4a–r** and **6a–i** as biologically interesting derivatives with good to excellent yields. These new structures broaden the scaffolds that are accessible through Ugi-azide reaction, and many of them may represent interesting pharmacophores.

Experimental

General information

The chemicals and reagents used in this work were purchased from Merck Chemical Company and used without further purification. Melting points were obtained with an electrothermal model 9100 apparatus and are uncorrected. IR spectra were recorded using a Shimadzu 4300 spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DRX-300-ADVANCE spectrometer at 300 (^{1}H) and 75 MHz (^{13}C) using $CDCl_3$ or DMSO as solvent. Chemical shifts (δ in ppm) are referenced to the solvent $CDCl_3$ ($\delta = 7.26$ ppm for ^{1}H and 77.0 ppm for ^{13}C NMR). Multiplicity abbreviations used for the chemical shifts are as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. Mass spectra were recorded on an HP (Agilent technologies) 5937 Mass Selective Detector. Elemental analyses were performed using a CHN-Rapid Heraeus elemental analyzer (Wellesley, MA).

General procedure for the synthesis of compounds 5a–r

1-(2-Bromoethyl)-1*H*-pyrrole-2-carbaldehyde **1a** (202 mg, 1 mmol) and primary amines **2a–i** (1 mmol) were taken in a 5-mL round-bottom flask and then stirred for 20 min to form solid iminium intermediates **3a–i**. Methanol (4 mL) was then added to dissolve the solid. Sodium azide (65 mg, 1 mmol) and isocyanides **4a–c** (1 mmol) were added, and the reaction mixture was stirred at room temperature for 3 h. After completion of the reaction as indicated by TLC, the

solvent was removed under reduced pressure and the reaction mixture was extracted with ethyl acetate (2 × 30 mL). The organic phase was washed with brine (30 mL) and dried over anhydrous Na_2SO_4. The crude products were purified by column chromatography through a silica gel column using ethyl acetate and hexane (30%) as eluents to afford desired solid products **5a–r**.

1-(1-(tert-Butyl)-1H-tetrazol-5-yl)-2-phenyl-1,2,3,4 tetrahydropyrrolo[1,2-a]pyrazine (5a)

White solid (296 mg, 92%); mp 169–171 °C; IR (KBr) ν_{max}: 2978, 1595, 1494, 1360, 1237, 1208, 1171, 1112, 817, 769, 704 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.66 (s, 9H), 3.57–3.65 (m, 1H), 3.87–4.07 (m, 3H), 5.93 (d, J = 2.5 Hz, 1H), 6.20 (t, J = 3.3 Hz, 1H), 6.35 (s, 1H), 6.65 (t, J = 2.2 Hz, 1H), 6.97–7.04 (m, 3H), 7.27 (t, J = 7.8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 29.9, 41.7, 46.3, 51.1, 62.1, 105.2, 108.5, 120.1, 120.6, 122.8, 123.5, 129.6, 148.7, 154.9 ppm; m/z (EI, 70 eV) 322 (19, M^+) 266 (13), 197 (100), 119 (55), 104 (32), 77 (58), 57 (44%); Anal. Calcd for $C_{18}H_{22}N_6$: C, 67.06; H, 6.88; N, 26.07. Found: C, 67.09; H, 6.90; N, 26.05%.

2-Benzyl-1-(1-(tert-butyl)-1H-tetrazol-5-yl)-1,2,3,4 -tetrahydropyrrolo[1,2-a]pyrazine (5b)

White solid (272 mg, 81%); mp 124–126 °C; IR (KBr) ν_{max}: 2986, 2941, 2807, 1485, 1451, 1406, 1305, 1238, 760, 731 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.63 (s, 9H), 2.73 (m, 1H), 3.39 (m, 1H), 3.45 (d, J = 13 Hz, 1H), 3.75 (d, J = 13 Hz, 1H), 3.98–4.11 (m, 2H), 5.52 (t, J = 1.7 Hz, 1H), 5.64 (s, 1H), 6.11 (t, J = 3.3 Hz, 1H), 6.61 (d, J = 1.7 Hz, 1H), 7.24–7.36 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 30.2, 43.2, 47.1, 56.7, 58.7, 63.1, 105.0, 108.8, 119.2, 125.2, 127.7, 128.6, 128.9, 136.6, 154.3 ppm; m/z (EI, 70 eV) 336 (11, M^+) 280 (9), 210 (53), 119 (47), 91 (100), 57 (31%); Anal. Calcd for $C_{19}H_{24}N_6$: C, 67.83; H, 7.19; N, 24.98. Found: C, 67.87; H, 7.21; N, 25.01%.

1-(1-(tert-Butyl)-1H-tetrazol-5-yl)-2-(o-tolyl)-1,2,3,4 -tetrahydropyrrolo[1,2-a]pyrazine (5c)

White solid (225 mg, 67%); mp 192–194 °C; IR (KBr) ν_{max}: 2951, 1595, 1489, 1433, 1239, 1078, 818, 757, 707 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.55 (s, 9H), 2.31 (s, 3H), 3.17 (d, J = 13.3 Hz, 1H), 3.97–4.04 (m, 2H), 4.35 (s, 1H), 5.79 (s, 1H), 6.15 (s, 1H), 6.20 (s, 1H), 6.70 (s, 1H), 6.89 (s, 1H), 7.04 (t, J = 3.7 Hz, 2H), 7.19 (t, J = 3.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.8, 30.1, 42.3, 44.9, 52.3, 61.5, 104.2, 108.5, 119.9, 122.9, 124.5, 125.2, 127.1, 131.3, 133.5, 147.7, 154.9 ppm; m/z (EI, 70 eV) 336 (61, M^+) 280 (42), 251 (27), 211 (100), 173 (18), 133 (56), 118 (61), 106 (21), 91 (43), 57 (26%); Anal. Calcd for $C_{19}H_{24}N_6$: C, 67.83; H, 7.19; N, 24.98. Found: C, 67.80; H, 7.23; N, 25.01%.

1-(1-(tert-Butyl)-1H-tetrazol-5-yl)-2-(m-tolyl)-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine (5d)

White solid (300 mg, 89%); mp 155–157 °C; IR (KBr) ν_{max}: 2971, 1604, 1580, 1492, 1294, 1236, 1115, 933, 773, 708 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.67 (s, 9H), 2.29 (s, 3H), 3.57–3.64 (m, 1H), 3.87–4.05 (m, 3H), 5.91 (d, J = 2.3 Hz, 1H), 6.20 (t, J = 3.3 Hz, 1H), 6.34 (s, 1H), 6.65 (t, J = 2.3 Hz, 1H), 6.80–6.83 (m, 3H), 7.14 (t, J = 7.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.6, 29.9, 41.8, 46.3, 51.1, 62.1, 105.2, 108.4, 117.4, 120.1, 121.3, 123.5, 123.6, 129.3, 139.3, 148.7, 154.9 ppm; m/z (EI, 70 eV) 336 (18, M^+) 280 (9), 251 (10), 211 (100), 167 (14), 149 (38), 133 (52), 91 (48), 69 (83), 57 (78%); Anal. Calcd for $C_{19}H_{24}N_6$: C, 67.83; H, 7.19; N, 24.98. Found: C, 67.80; H, 7.21; N, 24.97%.

1-(1-(tert-Butyl)-1H-tetrazol-5-yl)-2-(p-tolyl)-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine (5e)

White solid (313 mg, 93%); mp 153–155 °C; IR (KBr) ν_{max}: 2988, 2947, 1510, 1450, 1237, 1204, 1113, 820, 774, 704 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.65 (s, 9H), 2.27 (s, 3H), 3.51–3.54 (m, 1H), 3.94–3.96 (m, 3H), 5.89 (s, 1H), 6.20 (s, 1H), 6.27 (s, 1H), 6.64 (s, 1H), 6.92 (d, J = 7.6 Hz, 2H), 7.06 (d, J = 7.6 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.6, 29.9, 41.6, 46.7, 51.5, 62.1, 105.1, 108.4, 120.0, 121.0, 123.7, 130.1, 132.6, 146.3, 154.9 ppm; m/z (EI, 70 eV) 336 (22, M^+) 280 (11), 251 (8), 211 (100), 197 (11), 133 (59), 118 (18), 104 (16), 91 (40), 57 (24%); Anal. Calcd for $C_{19}H_{24}N_6$: C, 67.83; H, 7.19; N, 24.98. Found: C, 67.80; H, 7.18; N, 24.95%.

1-(1-(tert-Butyl)-1H-tetrazol-5-yl)-2-(3,4-dimethylphenyl)-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine (5f)

White solid (308 mg, 88%); mp 178–180 °C; IR (KBr) ν_{max}: 2982, 2943, 1609, 1571, 1498, 1450, 1237, 1209, 1156, 819, 705 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.66 (s, 9H), 2.18 (s, 3H), 2.20 (s, 3H), 3.51–3.58 (m, 1H), 3.90–3.99 (m, 3H), 5.88–5.90 (m, 1H), 6.19 (t, J = 3.5 Hz, 1H), 6.29 (s, 1H), 6.63–6.65 (m, 1H), 6.75 (dd, J = 8.1, 2.4 Hz, 1H), 6.82 (s, 1H), 6.99 (d, J = 8.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.0, 20.1, 29.9, 41.6, 46.7, 51.4, 62.1, 105.1, 108.4, 118.1, 120.0, 122.4, 123.7, 130.5, 131.2, 137.7, 146.6, 155.0 ppm; m/z (EI, 70 eV) 350 (18, M^+) 294 (6), 265 (7), 225 (100), 211 (21), 147 (41), 105 (31), 57 (51%); Anal. Calcd for $C_{20}H_{26}N_6$: C, 68.54; H, 7.48; N, 23.98. Found: C, 68.50; H, 7.51; N, 24.00%.

1-(1-(tert-Butyl)-1H-tetrazol-5-yl)-2 -(4-chlorophenyl)-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine (5g)

White solid (254 mg, 71%); mp 182–184 °C; IR (KBr) ν_{max}: 3118, 2978, 1593, 1491, 1360, 1297, 1234, 1208, 821, 725 cm $^{-1}$; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.66 (s, 9H), 3.53–3.59 (m, 1H), 3.86–4.05 (m, 3H), 5.91 (s, 1H), 6.19 (s, 1H), 6.28 (s, 1H), 6.65 (s, 1H), 6.95(d, J = 8.5 Hz, 2H), 7.21 (d, J = 8.5 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 29.9, 41.6, 46.4, 51.2, 62.2, 77.3, 105.4, 108.6, 120.3, 121.8, 123.0, 127.9, 129.6, 147.3, 154.6 ppm; m/z (EI, 70 eV) 356 (27, M^+) 300 (24), 271 (11), 231 (100), 153 (31), 111 (18), 57 (17%); Anal. Calcd for $C_{18}H_{21}ClN_6$: C, 60.58; H, 5.93; Cl, 9.93; N, 23.55. Found: C, 60.55; H, 5.94; N, 23.56%.

1-(1-(tert-Butyl)-1H-tetrazol-5-yl)-2-(4-methoxyphenyl)-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine (5h)

White solid (317 mg, 90%); mp 145–147 °C; IR (KBr) ν_{max}: 3129, 2975, 1582, 1503, 1447, 1297, 1240, 1176, 1028, 829, 726 cm $^{-1}$; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.62 (s, 9H), 3.39–3.44 (m, 1H), 3.74 (s, 3H), 3.91–4.02 (m, 3H), 5.83 (d, J = 2.3 Hz, 1H), 6.17–6.19 (m, 2H), 6.65 (s, 1H), 6.78(d, J = 8.8 Hz, 2H), 6.97 (d, J = 8.8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 29.9, 41.8, 47.5, 52.4, 55.4, 55.5, 62.1, 104.9, 108.5, 114.6, 119.9, 123.3, 123.9, 142.3, 154.8, 155.9 ppm; m/z (EI, 70 eV) 352 (16, M^+) 296 (6), 227 (100), 149 (39), 104 (17), 69 (18), 57 (41%); Anal. Calcd for $C_{19}H_{24}N_6O$: C, 64.75; H, 6.86; N, 23.85; O, 4.54. Found: C, 64.76; H, 6.86; N, 23.88%.

2-Benzyl-1-(1-cyclohexyl-1H-tetrazol-5-yl)-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine (5i)

White solid (266 mg, 73%); mp 157–159 °C; IR (KBr) ν_{max}: 2930, 2859, 1494, 1446, 1300, 1059, 898, 749, 723, 698 cm $^{-1}$; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.90–1.04 (m, 1H), 1.16–1.37 (m, 3H), 1.58–1.79 (m, 3H), 1.87–2.09 (m, 3H), 2.68–2.77 (m, 1H), 3.24 (dt, J = 11.8, 3.0 Hz, 1H), 3.41 (d, J = 13.9 Hz, 1H), 3.75 (d, J = 13.9 Hz, 1H), 4.02–4.16 (m, 2H), 4.28–4.39 (m, 1H), 5.47 (s, 1H), 5.51–5.52 (m, 1H), 6.10 (t, J = 3.0, Hz, 1H), 6.63 (s, 1H), 7.21–7.35 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.9, 25.5, 25.6, 31.8, 32.8, 44.8, 48.1, 55.7, 58.6, 58.9, 105.6, 109.2, 119.3, 124.0, 127.6, 128.5, 128.6, 136.4, 153.7 ppm; m/z (EI, 70 eV) 362 (22, M^+) 230 (5), 210 (46), 197 (7), 119 (41), 106 (13), 91 (100), 55 (26%); Anal. Calcd for $C_{21}H_{26}N_6$: C, 69.58; H, 7.23; N, 23.19. Found: C, 69.60; H, 7.20; N, 23.20%.

1-(1-Cyclohexyl-1H-tetrazol-5-yl)-2-(m-tolyl)-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine (5j)

White solid (275 mg, 76%); mp 123–125 °C; IR (KBr) ν_{max}: 2943, 2860, 1602, 1492, 1444, 1384, 1307, 1239, 767, 695 cm $^{-1}$; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.00–1.39 (m, 4H), 1.63–1.82 (m, 4H), 1.85–1.93 (m, 2H), 2.27 (s, 3H), 3.53–3.61 (m, 1H), 3.85 (dt, J = 13.2, 4.7 Hz, 1H), 4.16 (dt, J = 12.1, 4.1 Hz, 1H), 4.26–4.36 (m, 2H), 5.71 (t, J = 1.7, Hz, 1H), 6.16 (t, J = 3.2, Hz, 1H), 6.27 (s, 1H), 6.68 (s, 1H), 6.79–6.87 (m, 3H), 7.12 (t, J = 7.8, Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.5, 24.8, 25.5, 25.6, 32.2, 32.7, 44.8, 49.6, 51.9, 58.4, 105.7, 109.1, 117.6, 119.7, 121.2, 123.7, 124.2, 129.2, 139.3, 148.6, 153.6 ppm; m/z (EI, 70 eV) 362 (33, M^+) 230 (10), 211 (100), 197 (16), 133 (41), 91 (42), 55 (31%); Anal. Calcd for $C_{21}H_{26}N_6$: C, 69.58; H, 7.23; N, 23.19. Found: C, 69.61; H, 7.22; N, 23.21%.

1-(1-Cyclohexyl-1H-tetrazol-5-yl)-2-(p-tolyl)-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine (5k)

White solid (326 mg, 90%); mp 165–167 °C; IR (KBr) ν_{max}: 2939, 2852, 1512, 1439, 1308, 1210, 1142, 827, 768, 709 cm $^{-1}$; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.98–1.34 (m, 4H), 1.58–1.79 (m, 4H), 1.83–1.91 (m, 2H), 2.24 (s, 3H), 3.47–3.56 (m, 1H), 3.78 (dt, J = 13.0, 4.4 Hz, 1H), 4.15 (dt, J = 12.0, 4.2 Hz, 1H), 4.25–4.38 (m, 2H), 5.66 (m, 1H), 6.14 (t, J = 3.4, Hz, 1H), 6.23 (s, 1H), 6.67 (d, J = 1.7, Hz, 1H), 6.96 (d, J = 8.5, Hz, 2H), 7.03 (d,J = 8.5, Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.6, 24.9, 25.5, 25.6, 32.1, 32.6, 44.9, 50.6, 52.3, 58.4, 105.7, 109.1, 119.7, 121.2, 123.8, 130.0, 133.4, 146.3, 153.5 ppm; m/z (EI, 70 eV) 362 (24, M^+), 211 (100), 197 (20), 149 (31), 133 (41), 119 (29), 91 (78), 55 (81%); Anal. Calcd for $C_{21}H_{26}N_6$: C, 69.58; H, 7.23; N, 23.19. Found: C, 69.60; H, 7.24; N, 23.21%.

1-(1-Cyclohexyl-1H-tetrazol-5-yl)-2-(3,4-dimethylphenyl)-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine (5l)

White solid (271 mg, 72%); mp 138–140 °C; IR (KBr) ν_{max}t: 2945, 2854, 1608, 1502, 1441, 1339, 1284, 1209, 1137, 1033, 820, 766, 707 cm $^{-1}$; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.98–1.33 (m, 4H), 1.59–1.81 (m, 4H), 1.84–1.92 (m, 2H), 2.15 (s, 3H), 2.18 (s, 3H), 3.47–3.56 (m, 1H), 3.78 (dt, J = 13.0, 4.4 Hz, 1H), 4.15 (dt, J = 12.1, 4.1 Hz, 1H), 4.26–4.39 (m, 2H), 5.66 (m, 1H), 6.15 (t,J = 3.5, Hz, 1H), 6.23 (s, 1H), 6.68 (t, J = 1.8, 1H), 6.79 (dd,J = 8.1, 2.4 Hz, 1H), 6.86 (d,J = 2.2, Hz, 1H), 6.98 (d,J = 8.1, Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.0, 20.0, 24.9, 25.5, 25.6, 32.2, 32.7, 45.0, 50.5, 52.4, 58.4, 105.6, 109.1, 118.6, 119.6, 122.6, 123.9, 130.4, 132.2, 137.7, 146.6, 153.6 ppm; m/z (EI, 70 eV) 376 (56, M^+), 225 (100), 211 (23), 147 (38), 121 (21), 105 (24),

55 (16%); Anal. Calcd for $C_{22}H_{28}N_6$: C, 70.18; H, 7.50; N, 22.32. Found: C, 70.21; H, 7.51; N, 22.30%.

2-(4-Chlorophenyl)-1-(1-cyclohexyl-1H-tetrazol-5-yl)-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine (5m)

White solid (261 mg, 68%); mp 145–147 °C; IR (KBr) ν_{max}: 2943, 2852, 1488, 1442, 1340, 1308, 1212, 1129, 1010, 949, 836, 771, 714 cm $^{-1}$; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.01–1.42 (m, 4H), 1.64–1.79 (m, 4H), 1.85–1.88 (m, 2H), 3.52–3.60 (m, 1H), 3.80 (dt, J = 13.0, 4.5 Hz, 1H), 4.15 (dt, J = 12.4, 4.4 Hz, 1H), 4.20–4.33 (m, 2H), 5.70 (d,J = 2.2, Hz, 1H), 6.14 (t,J = 3.0, Hz, 1H), 6.24 (s, 1H), 6.68 (s, 1H), 6.98 (d,J = 8.7, Hz, 2H), 7.18 (d,J = 8.7, Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.8, 25.4, 25.6, 32.3, 32.7, 44.6, 49.8, 51.8, 58.5, 105.8, 109.2, 119.9, 121.6, 123.1, 128.3, 129.4, 147.1, 153.4 ppm; m/z (EI, 70 eV) 382 (56, M^+), 271 (7), 231 (100), 127 (10), 111 (17), 55 (16%); Anal. Calcd for $C_{20}H_{23}ClN_6$: C, 62.74; H, 6.05; Cl, 9.26; N, 21.95. Found: C, 62.76; H, 6.04; N, 21.92%.

1-(1-Cyclohexyl-1H-tetrazol-5-yl)-2-(4-methoxyphenyl)-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine (5n)

White solid (352 mg, 93%); mp 168–170 °C; IR (KBr) ν_{max}: 2938, 2848, 1510, 1444, 1284, 1242, 1210, 1034, 846, 772, 750, 713 cm $^{-1}$; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.95–1.32 (m, 4H), 1.55–1.81 (m, 4H), 1.85–1.88 (m, 2H), 3.42–3.50 (m, 1H), 3.64–3.70 (m, 4H), 4.14 (dt, J = 11.9, 3.6 Hz, 1H), 4.25–4.37 (m, 2H), 5.61 (s, 1H), 6.13 (t,J = 2.9, Hz, 1H), 6.15 (s, 1H), 6.67 (s, 1H), 6.75 (d,J = 8.8, Hz, 2H), 7.01 (d,J = 8.8, Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.9, 25.5, 25.6, 32.0, 32.6, 45.1, 51.6, 53.1, 55.4, 58.4, 105.6, 119.1, 114.6, 119.6, 123.4, 123.9, 142.0, 153.4, 156.4 ppm; m/z (EI, 70 eV) 378 (11, M^+), 362 (6), 227 (48), 211 (26), 149 (25), 81 (55), 69 (100), 57 (58%); Anal. Calcd for $C_{21}H_{26}N_6O$: C, 66.64; H, 6.92; N, 22.21; O, 4.23. Found: C, 66.66; H, 6.90; N, 22.25%.

1-(1-Cyclohexyl-1H-tetrazol-5-yl)-2-(pyridin-3-yl)-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine (5o)

White solid (164 mg, 47%); mp 183–185 °C; IR (KBr) ν_{max}: 2928, 2861, 1579, 1489, 1443, 1349, 1229, 1136, 1078, 948, 768, 713 cm $^{-1}$; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.02–1.35 (m, 3H), 1.47–1.50 (m, 1H), 1.65–1.93 (m, 6H), 3.61–3.70 (m, 1H), 3.88 (dt, J = 12.8, 4.8 Hz, 1H), 4.14–4.25 (m, 2H), 4.30–4.38 (m, 1H), 5.75 (d,J = 2.7, Hz, 1H), 6.15 (t,J = 2.9, Hz, 1H), 6.29 (s, 1H), 6.68 (d,J = 1.3, Hz, 1H), 7.14 (dd,J = 8.3, 4.6 Hz, 1H), 7.35 (d,J = 8.3, Hz, 1H), 8.19 (d,J = 4.6, Hz, 1H), 8.35 (d,J = 2.7, Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.7, 25.4, 25.5, 32.4, 32.7, 44.4, 49.1, 51.1, 58.6, 105.9, 109.2, 120.1, 122.7, 123.7, 125.8, 142.6, 143.8, 144.5, 153.2 ppm; m/z (EI, 70 eV) 349 (27, M^+), 227 (100), 198 (95), 149 (28), 119 (38), 105 (34), 78 (44), 55 (46%); Anal. Calcd for $C_{19}H_{23}N_7$: C, 65.31; H, 6.63; N, 28.06. Found: C, 65.30; H, 6.64; N, 27.99%.

2-Phenyl-1-(1-(2,4,4-trimethylpentan-2-yl)-1H-tetrazol-5-yl)-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine (5p)

White solid (318 mg, 84%); mp 166–168 °C; IR (KBr) ν_{max}: 2956, 1597, 1491, 1361, 1295, 1211, 1175, 1088, 926, 839, 767, 703 cm $^{-1}$; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.75 (s, 9H), 1.74 (s, 3H), 1.79 (s, 3H), 1.95 (s, 2H), 3.62 (d, J = 13.9 Hz, 1H), 3.82–3.98 (m, 2H), 4.10–4.19 (m, 1H), 5.93 (m, 1H), 6.20 (t,J = 3.4 Hz, 1H), 6.41 (s, 1H), 6.64 (t,J = 2.5 Hz, 1H), 6.96–7.04 (m, 3H), 7.25–7.30 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 30.2, 30.3, 30.7, 31.6, 41.0, 45.8, 50.4, 53.8, 65.6, 105.0, 108.4, 120.2, 120.4, 122.6, 123.2, 129.6, 148.7, 155.0 ppm; m/z (EI, 70 eV) 378 (30, M^+), 266 (47), 237 (13), 197 (100), 173 (14), 148 (11), 119 (44), 77 (23%), 57 (31); Anal. Calcd for $C_{22}H_{30}N_6$: C, 69.81; H, 7.99; N, 22.20. Found: C, 69.82; H, 8.03; N, 22.23%.

2-(p-Tolyl)-1-(1-(2,4,4-trimethylpentan-2-yl)-1H-tetrazol-5-yl)-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine (5q)

White solid (341 mg, 87%); mp 170–172 °C; IR (KBr) ν_{max}: 2946, 1611, 1509, 1477, 1448, 1355, 1202, 1082, 1021, 827, 770, 719 cm $^{-1}$; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.76 (s, 9H), 1.73 (s, 3H), 1.78 (s, 3H), 1.95 (s, 2H), 2.27 (s, 3 H), 3.54 (d, J = 13.9 Hz, 1H), 3.81–3.95 (m, 2H), 4.05–4.14 (m, 1H), 5.92 (d,J = 2.5 Hz, 1H), 6.20 (t,J = 3.2 Hz, 1H), 6.34 (s, 1H), 6.64 (s, 1H), 6.93 (d, J = 8.4 Hz, 2H), 7.07 (d, J = 8.2 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.6, 30.1, 30.4, 30.7, 31.6, 40.9, 46.0, 50.7, 53.8, 65.6, 104.9, 108.3, 120.1, 120.7, 123.4, 130.1, 132.2, 146.3, 155.0 ppm; m/z (EI, 70 eV) 392 (21, M^+), 280 (39), 251 (10), 251 (100), 197 (9), 133 (41), 118 (12), 91 (18), 57 (27%); Anal. Calcd for $C_{23}H_{32}N_6$: C, 70.37; H, 8.22; N, 21.41. Found: C, 70.40; H, 8.18; N, 21.43%.

2-(4-Methoxyphenyl)-1-(1-(2,4,4-trimethylpentan-2-yl)-1H-tetrazol-5-yl)-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine (5r)

White solid (375 mg, 92%); mp 114–116 °C; IR (KBr) ν_{max}: 2984, 1507, 1447, 1247, 1205, 1109, 1039, 976, 936, 832, 800, 718 cm $^{-1}$; ^{1}H NMR (300 MHz, DMSO): δ 0.67 (s, 9H), 1.69 (s, 3H), 1.70 (s, 3H), 1.91 (s, 2H), 3.57–3.77 (m, 6H), 3.94 (d,J = 8.6 Hz, 1H), 5.85 (s, 1H), 6.03 (s, 1H), 6.42 (s, 1H), 6.71 (s, 1H), 6.84 (d, J = 7.2 Hz, 2H), 7.01(d, J = 7.2 Hz, 2H); ^{13}C NMR (75 MHz, DMSO) δ 28.9, 29.8, 30.2, 31.2, 45.0, 50.1, 53.0, 55.1, 65.5, 104.9, 107.6, 114.5, 119.8, 121.3, 123.6, 141.5, 154.5, 155.0 ppm; m/z (EI, 70 eV) 408 (13, M^+), 296 (16), 227 (100), 184 (4), 149 (21), 104 (12),

57 (29%); Anal. Calcd for $C_{23}H_{32}N_6O$: C, 67.62; H, 7.90; N, 20.57; O, 3.92. Found: C, 67.60; H, 7.89; N, 20.55%.

General procedure for the synthesis of compounds 7a–i

1-(2-Bromoethyl)-1*H*-pyrrole-2-carbaldehyde **1a** (202 mg, 1 mmol) and amines **6a–c** (1 mmol) were taken in a 5-mL round-bottom flask and then stirred for 20 min to form the corresponding iminium intermediates. Methanol (4 mL) was then added to dissolve the solid. Sodium azide (65 mg, 1 mmol) and isocyanides **4a–c** (1 mmol) were added, and the reaction mixture was stirred at room temperature for 24 h. After completion of the reaction as indicated by TLC, the solvent was removed under reduced pressure and the reaction mixture was extracted with ethyl acetate (2 × 30 mL). The organic phase was washed with brine (30 mL) and dried over anhydrous Na_2SO_4. The crude products were purified by column chromatography through a silica gel column using ethyl acetate and hexane (30%) as eluents to afford the desired products **7a–i**.

1-(1-(tert-Butyl)-1H-tetrazol-5-yl)-N-phenyl-3,4-dihydropyrrolo[1,2-a]pyrazin-2(1H)-amine (7a)

White solid (192 mg, 57%); mp 237–239 °C (Decompose); IR (KBr) ν_{max}: 3245, 2990, 1601, 1492, 1448, 1253, 1067, 857, 754, 713 cm $^{-1}$; ^{1}H NMR (300 MHz, DMSO): δ 1.68 (s, 9H), 3.10–3.30 (m, 1H), 3.40–3.60 (m, 1H), 4.10–4.30 (m, 2H), 5.38 (s, 1H), 5.84 (s, 1H), 6.00 (t, J = 2.9 Hz, 1H), 6.65 (t, J = 7.1 Hz, 1H), 6.75 (s, 1H), 6.84–6.89 (m, 3H), 7.08 (t, J = 7.8 Hz, 2H); ^{13}C NMR (75 MHz, DMSO) δ 29.9, 44.2, 50.3, 57.7, 61.8, 104.6, 108.4, 113.4, 118.6, 119.4, 126.0, 128.7, 147.6, 155.0 ppm; m/z (EI, 70 eV) 337 (76, M^+) 281 (16), 211 (100), 188 (16), 161 (32), 133 (40), 119 (65), 105 (62), 92 (42), 77 (57), 57 (37%); Anal. Calcd for $C_{18}H_{23}N_7$: C, 64.07; H, 6.87; N, 29.06. Found: C, 64.11; H, 6.85; N, 29.10%.

1-(1-Cyclohexyl-1H-tetrazol-5-yl)-N-phenyl-3,4-dihydropyrrolo[1,2-a]pyrazin-2(1H)-amine (7b)

White solid (185 mg, 51%); mp 235–237 °C (Decompose); IR (KBr) ν_{max}: 3212, 2934, 2856, 1602, 1492, 1448, 1312, 1080, 894, 749, 718, 683 cm $^{-1}$; ^{1}H NMR (300 MHz, DMSO): δ 0.90–1.25 (m, 2H), 1.30–1.50 (m, 3H), 1.55–1.90 (m, 5H), 3.10 (dt, J = 11.1, 3.9 Hz, 1H), 3.43 (d, J = 11.1 Hz, 1H), 4.10–4.40 (m, 2H), 4.63 (t, J = 11.1 Hz, 1H), 5.29 (s, 1H), 5.69 (s, 1H), 6.01 (t, J = 3.0 Hz, 1H), 6.66 (t, J = 7.2 Hz, 1H), 6.70–6.90 (m, 3H), 7.10 (t, J = 9.2 Hz, 3H); ^{13}C NMR (75 MHz, DMSO) δ 24.5, 24.6, 24.8, 31.8, 32.3, 44.6, 50.9, 57.2, 57.3, 104.6, 108.5, 112.8, 118.6, 120.0, 124.5, 128.9, 146.9, 153.4 ppm; m/z (EI, 70 eV) 363 (40, M^+) 316 (7), 256 (13), 231 (13), 211 (100), 133 (25), 119 (77), 106 (50), 92 (44), 77 (58), 55 (44%); Anal. Calcd for $C_{20}H_{25}N_7$: C, 66.09; H, 6.93; N, 26.98. Found: C, 66.12; H, 6.90; N, 26.99%.

N-Phenyl-1-(1-(2,4,4-trimethylpentan-2-yl)-1H-tetrazol-5-yl)-3,4-dihydropyrrolo[1,2-a]pyrazin-2(1H)-amine (7c)

White solid (236 mg, 60%); mp 178–180 °C; IR (KBr) ν_{max}: 3330, 2955, 1602, 1492, 1401, 1255, 1113, 1071, 805, 750, 711, 655 cm $^{-1}$; ^{1}H NMR (300 MHz, DMSO): δ 0.70 (s, 9H), 1.76 (s, 6H), 1.96 (d, J = 14.9 Hz, 1H), 2.15 (brds, 1H), 3.19 (brds, 1H), 3.48 (d, J = 11.3 Hz, 1H), 4.16 (brds, 2H), 5.38 (s, 1H), 5.86 (s, 1H), 5.99 (s, 1H), 6.64 (t, J = 7.1 Hz, 1H), 6.75 (s, 1H), 6.80–7.00 (m, 3H), 7.07 (t, J = 7.4 Hz, 2H); ^{13}C NMR (75 MHz, DMSO) δ 29.5, 30.3, 31.3, 43.8, 49.8, 53.1, 57.0, 65.6, 104.7, 108.2, 113.5, 118.6, 119.4, 125.9, 128.6, 147.4, 155.3 ppm; m/z (EI, 70 eV) 393 (24, M^+) 287 (54), 211 (76), 161 (39), 133 (52), 119 (79), 105 (85), 92 (51), 77 (81), 57 (100%); Anal. Calcd for $C_{22}H_{31}N_7$: C, 67.15; H, 7.94; N, 24.91. Found: C, 67.17; H, 7.93; N, 24.95%.

N-(1-(1-(tert-Butyl)-1H-tetrazol-5-yl)-3,4-dihydropyrrolo[1,2-a]pyrazin-2(1H)-yl)-4-methylbenzenesulfonamide (7d)

White solid (307 mg, 74%); mp 201–203 °C (Decompose); IR (KBr) ν_{max}: 3189, 2936, 1598, 1485, 1453, 1418, 1355, 1241, 1162, 1094, 895, 782, 744, 666 cm $^{-1}$; ^{1}H NMR (300 MHz, DMSO): δ 1.76 (s, 9H), 2.39 (s, 3H), 3.73 (brds, 2H), 3.91 (brds, 2H), 5.59 (s, 1H), 5.98 (t, J = 3.2 Hz, 1H), 6.06 (s, 1H), 6.66 (t, J = 1.8 Hz, 1H), 7.41 (d, J = 8.1 Hz, 2H), 7.70 (d, J = 8.0 Hz, 2H), 9.13 (s, 1H); ^{13}C NMR (75 MHz, DMSO) δ 21.1, 30.1, 43.9, 49.4, 52.3, 62.3, 104.8, 108.4, 119.6, 124.4, 127.6, 129.6, 135.8, 143.6, 153.8 ppm; m/z (EI, 70 eV) 415 (6, M^+) 287 (78), 176 (76), 148 (18), 106 (100), 91 (33), 57 (28%); Anal. Calcd for $C_{19}H_{25}N_7O_2S$: C, 54.92; H, 6.06; N, 23.60; O, 7.70; S, 7.72. Found: C, 54.95; H, 6.10; N, 23.58; S, 7.76%.

N-(1-(1-Cyclohexyl-1H-tetrazol-5-yl)-3,4-dihydropyrrolo[1,2-a]pyrazin-2(1H)-yl)-4-methylbenzenesulfonamide (7e)

White solid (300 mg, 68%); mp 205–207 °C (Decompose); IR (KBr) ν_{max}: 3040, 2927, 2850, 1598, 1445, 1335, 1303, 1160, 1092, 1027, 925, 810, 743, 660 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.22–1.40 (m, 3H), 1.70–1.96 (m, 7H), 2.44 (s, 3H), 2.93 (brds, 1H), 3.50 (brds, 1H), 3.99 (brds, 2H), 4.10–4.30 (m, 1H), 5.67 (s, 1H), 5.74 (s, 1H), 6.12 (s, 1H), 6.60 (s, 1H), 7.07 (s, 1H), 7.28 (d, J = 7.6 Hz, 2H), 7.71 (d, J = 7.5 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.6, 24.9, 25.4, 25.6, 32.5, 43.9, 50.6, 56.6, 58.5, 106.5, 109.5, 119.9, 122.4, 127.9, 129.7, 135.3, 144.4, 152.4 ppm; m/z (EI, 70

eV) 441 (7, M^+) 365 (29), 258 (37), 213 (17), 176 (81), 148 (24), 135 (30), 119 (24), 106 (100), 91 (47), 55 (44%); Anal. Calcd for $C_{21}H_{27}N_7O_2S$: C, 57.12; H, 6.16; N, 22.21; O, 7.25; S, 7.26. Found: C, 57.11; H, 6.18; N, 22.19; S, 7.28%.

4-Methyl-N-(1-(1-(2,4,4-trimethylpentan-2-yl)-1H-tetrazol-5-yl)-3,4-dihydropyrrolo[1,2-a]pyrazin-2(1H)-yl)benzenesulfonamide (7f)

White solid (353 mg, 75%); mp 117–119 °C; IR (KBr) ν_{max}: 3073, 2954, 1597, 1452, 1399, 1336, 1298, 1163, 1093, 1029, 814, 776, 719, 659 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.90 (s, 9H), 1.87 (s, 3H), 1.89 (s, 3H), 2.08 (m, 2H), 2.41 (s, 3H), 2.52 (brd, 1H), 3.80–3.88 (m, 1H), 4.01–4.09 (m, 2H), 5.74 (d, J = 2.2 Hz, 1H), 6.08 (t, J = 3.1 Hz, 1H), 6.17 (s, 1H), 6.56 (s, 1H), 6.91 (s, 1H), 7.26 (d, J = 7.9 Hz, 2H), 7.72 (d, J = 8.0 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.6, 30.4, 30.6, 30.9, 31.8, 43.4, 48.5, 50.5, 56.0, 106.1, 108.9, 120.1, 123.6, 128.2, 129.6, 135.2, 144.2 153.7 ppm; m/z (EI, 70 eV) 471 (4, M^+) 287 (16), 204 (17), 176 (53), 106 (100), 57 (50%); Anal. Calcd for $C_{23}H_{33}N_7O_2S$: C, 58.57; H, 7.05; N, 20.79; O, 6.78; S, 6.80. Found: C, 58.60; H, 7.07; N, 20.80; S, 6.77%.

N-(1-(1-(tert-Butyl)-1H-tetrazol-5-yl)-3,4-dihydropyrrolo[1,2-a]pyrazin-2(1H)-yl)benzamide (7g)

White solid (266 mg, 73%); mp 228–230 °C (Decompose); IR (KBr) ν_{max}: 3231, 2986, 2940, 2876, 1661, 1512, 1478, 1311, 1232, 1077, 951, 901, 811, 707 cm^{-1}; ^1H NMR (300 MHz, DMSO): δ 1.56 (s, 9H), 2.54 (s, 1H), 3.63 (s, 1H), 4.19 (brds, 2H), 5.36 (s, 1H), 6.19 (s, 1H), 6.79 (s, 1H), 7.41 (t, J = 7.2 Hz, 2H), 7.49 (t, J = 6.5 Hz, 1H), 7.58 (d, J = 7.1 Hz, 2H), 9.91 (s, 1H); ^{13}C NMR (75 MHz, DMSO) δ 29.5, 43.9, 51.6, 57.3, 63.2, 104.2, 108.6, 119.6, 125.3, 127.2, 128.3, 131.5, 133.3, 153.4, 165.4 ppm; m/z (EI, 70 eV) 365 (2, M^+) 308 (4), 262 (6), 244 (87), 215 (13), 188 (30), 161 (48), 146 (16), 119 (34), 105 (100), 77 (55), 57 (20%); Anal. Calcd for $C_{19}H_{23}N_7O$: C, 62.45; H, 6.34; N, 26.83; O, 4.38. Found: C, 62.44; H, 6.31; N, 26.80; %.

N-(1-(1-Cyclohexyl-1H-tetrazol-5-yl)-3,4-dihydropyrrolo[1,2-a]pyrazin-2(1H)-yl)benzamide (7h)

White solid (274 mg, 70%); mp 203–205 °C (Decompose); IR (KBr) ν_{max}: 3218, 2932, 2857, 1678, 1515, 1486, 1448, 1270, 1077, 1004, 909, 787, 697, 670 cm^{-1}; ^1H NMR (300 MHz, DMSO): δ 0.88–1.84 (m, 9H), 2.33 (d, J = 8.9 Hz, 1H), 3.44–3.57 (m, 2H), 4.26 (s, 2H), 4.49 (s, 1H), 5.40 (s, 1H), 5.99 (s, 1H), 6.04 (s, 1H), 6.84 (s, 1H), 7.41 (t, J = 7.1 Hz, 2H), 7.51 (t, J = 6.8 Hz, 1H), 7.60 (d, J = 7.0 Hz, 2H), 9.92 (s, 1H); ^{13}C NMR (75 MHz, DMSO) δ 24.6, 25.0, 25.2, 31.5, 31.7, 44.7, 52.1, 56.1, 57.9, 104.8, 108.8, 120.0, 123.5, 127.2, 128.3, 131.6, 133.3, 152.9, 164.9 ppm; m/z (EI, 70 eV) 391 (2, M^+) 368 (3), 321 (5), 287 (93), 270 (86), 241 (15), 213 (18), 189 (22), 161 (100), 146 (64), 119 (36), 105 (92%); Anal. Calcd for $C_{21}H_{25}N_7O$: C, 64.43; H, 6.44; N, 25.05; O, 4.09. Found: C, 64.40; H, 6.47; N, 25.03; %.

N-(1-(1-(2,4,4-Trimethylpentan-2-yl)-1H-tetrazol-5-yl)-3,4-dihydropyrrolo[1,2-a]pyrazin-2(1H)-yl)benzamide (7i)

White solid (274 mg, 65%); mp 179–181 °C; IR (KBr) ν_{max}: 3194, 2952, 1659, 1524, 1482, 1370, 1313, 1239, 1116, 1077, 951, 809, 770, 709 cm^{-1}; ^1H NMR (300 MHz, DMSO): δ 0.68 (s, 9H), 1.66 (s, 6H), 1.90 (d, J = 14.8 Hz, 1H), 2.02 (d, J = 14.8 Hz, 1H), 3.33 (brds, 2H), 4.18 (brds, 2H), 5.41 (s, 1H), 6.03 (t, J = 2.9 Hz, 1H), 6.28 (s, 1H), 6.79 (s, 1H), 7.40 (t, J = 7.6 Hz, 2H), 7.49 (t, J = 7.2 Hz, 1H), 7.61 (d, J = 7.2 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.1, 29.9, 30.5, 31.2, 43.2, 51.1, 54.0, 56.7, 66.7, 104.5, 108.2, 119.7, 124.7, 127.3, 128.2, 131.4, 133.3, 153.7 165.3 ppm; m/z (EI, 70 eV) 421 (3, M^+) 300 (7), 280 (9), 262 (12), 240 (24), 188 (82), 161 (61), 146 (12), 119 (38), 97 (55), 77 (48), 57 (100%); Anal. Calcd for $C_{23}H_{31}N_7O$: CC, 65.53; H, 7.41; N, 23.26; O, 3.80. Found: C, 65.55; H, 7.40; N, 23.22; %.

Benzoyl(3,4-dihydropyrrolo[1,2-a]pyrazin-2-ium-2-yl)amide (8)

Yellow solid (220 mg, 92%); mp 172–174 °C (Decompose); IR (KBr) ν_{max}: 3074, 3019, 2945, 1727, 1661, 1584, 1546, 1474, 1409, 1317, 1287, 1059, 1018, 884, 698 cm^{-1}; ^1H NMR (300 MHz, DMSO): δ 4.27 (t, J = 6.7 Hz, 2H), 4.41 (t, J = 6.7 Hz, 2H), 6.37 (dd,J = 3.8, 2.4 Hz, 1H), 6.87 (dd,J = 3.9, 1.1 Hz, 1H), 7.32–7.38 (m, 4H), 7.96–7.99 (m, 2H),9.48 (s, 1H); ^{13}C NMR (75 MHz, DMSO) δ 42.6, 53.4, 112.1, 117.8, 122.4, 127.4, 127.5, 128.9, 129.4, 138.5, 141.2, 168.4 ppm; m/z (EI, 70 eV) 239 (93, M^+) 162 (10), 119 (100), 105 (61), 77 (75), 51 (29%); Anal. Calcd for $C_{14}H_{13}N_3O$: C, 70.28; H, 5.48; N, 17.56; O, 6.69. Found: C, 70.30; H, 5.47; N, 17.55; %.

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