An Efficient Ugi-Azide Four-Component Approach for the Preparation of Novel 1-(1*H*-tetrazol-5-yl)-10-chloro-1,2,3,4-tetrahydropyrazino[1,2-*a*] Indoles

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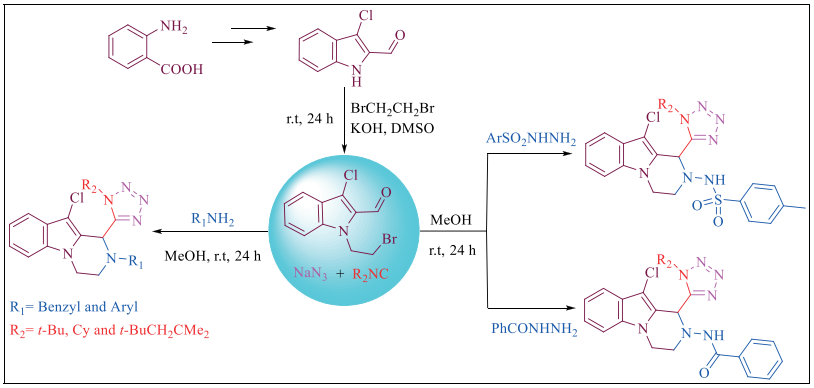

The synthesis of novel 1-(1*H*-tetrazol-5-yl)-10-chloro-1,2,3,4-tetrahydropyrazino[1,2-*a*] indole derivatives starting from the initially prepared 1-(2-bromoethyl)-3-chloro-1*H*-indole-2-carbaldehyde is described. A variety of likely biologically relevant pyrazino[1,2-*a*] indole-based 1,5-disubstituted tetrazoles was obtained in moderate to high yields *via* an Ugi-azide reaction. These reactions presumably proceed by the imine formation, intramolecular cyclization to iminium ion, and nucleophilic addition tandem reactions, respectively.

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INTRODUCTION

Expansion and diversification of drug candidate libraries increasingly need new one-pot multicomponent reactions (MCRs) in order to fuse the privileged structures with bioactive scaffolds. Results obtained in this regard provide an opportunity to the synthesis of "drug-like" complex compounds, and also, the simplicity, high efficiency, and atom economy are some advantages of MCRs in general and their isocyanide-based subclass (IMCRs) in particular. Combining three or more starting materials in a vessel in order to obtain the desired molecules *via* an expedient method is the unique feature of this category of reactions [1–4].

The classical Ugi reaction is perhaps the most known IMCR, which is widely used in the synthesis of peptides. On the other hand, the Ugi-azide reaction as the most popular subclass of Ugi reaction is traditionally the easiest approach to the synthesis of 1,5-disubstituted-1*H*-tetrazole (1,5-DS-1*H*-T) [5,6]. A variety of pharmacological properties including anti-inflammatory [7], antimalarial activity [8], and anticancer activity [9], agonist of the GHS receptor [10], anandamide transport blocker LY218324010 [11], and cannabinoid CB_1 receptor antagonists [12] has been reported for 1,5-DS-1*H*-T rings (Fig. 1) [13]. Recall that replacement of cis-amide in somatostatin peptide with 1,5-DS-1*H*-Ts can be used for the synthesis of more biologically active cyclic hexapeptide analogues [14].

In 1988, Evans published an article, in which the term "privileged structures" was mentioned [15]. The so-called privileged structure is a molecular scaffold, which provides potent and selective ligands to a variety of biological targets *via* modification of functional groups.

These prominent molecules usually exhibit drug-like properties [16,17]. This in turn leads to more compound libraries and leads. Among which, indole is the central active scaffold due to its wide range of known pharmacological and biochemical properties. Furthermore, the presence of indole ring in the structure of a large number of natural and synthetic bioactive molecules makes this scaffold an interesting candidate for the design of new drugs (Fig. 2) [18–20].

On the other hand, the piperazine nucleus is one of the most important building blocks in today's drug discovery. Interestingly, the broad range of bioactivities found for piperazines in the regulation of a wide variety of biological processes has led to them being included in

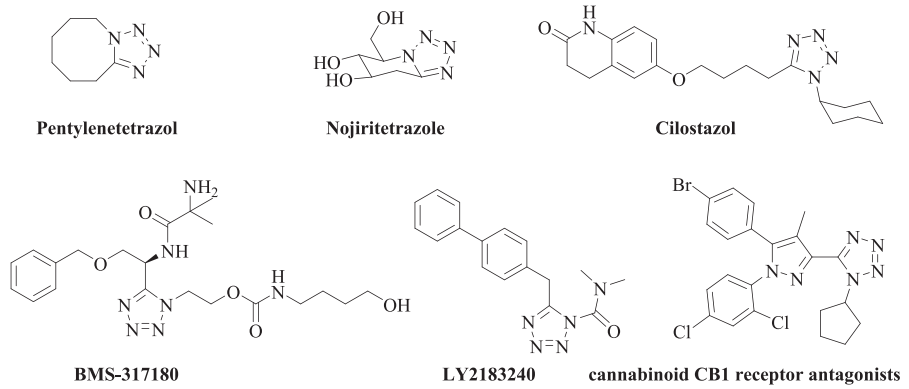


Figure 1. Examples of drugs and bioactive molecules containing a 1,5-disubstituted-1*H*-tetrazole scaffold.

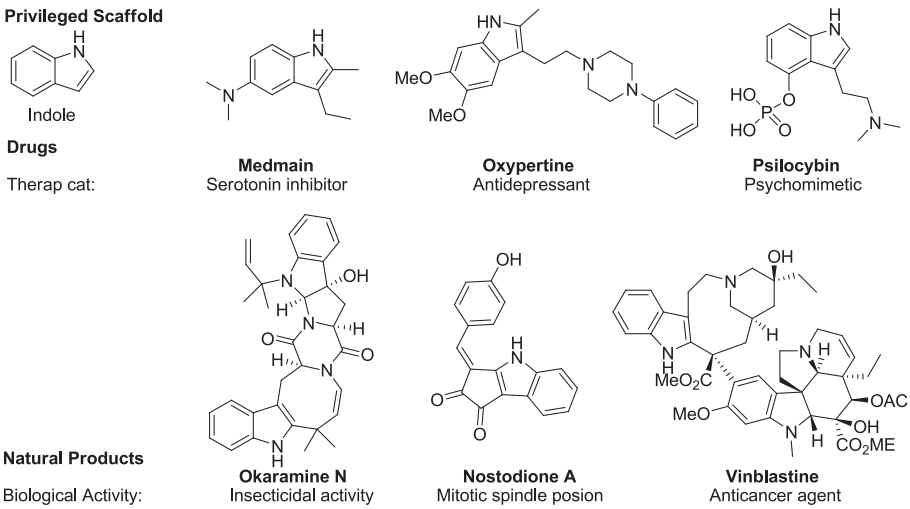


Figure 2. Examples of drugs and natural products containing an indole privileged scaffold [20].

the privileged structure category. Some piperazine derivatives have pharmacological and therapeutic properties including ligands for melanocortin-4 receptors [21], farnesyltransferase and geranylgeranyl transferase-I inhibitory activity [22], and D_2/D_4 receptor antagonists [23].

On the basis of the documented biological properties such as an inhibition of protein kinase C [24], 5-HT_{2A}, 5-HT_{2C} agonist [25,26], and antibacterial and antifungal activities [27] of heterocyclic compounds containing the 1,2,3,4-tetrahydropyrazino[1,2-*a*] indole scaffolds, we became interested in the synthesis of novel fused heterocycles encompassing fused bioactive indole as well as piperazine moieties.

In continuation of our previous approaches to the synthesis of pyrazino[1,2-*a*] benzimidazoles [28], indoloketopiperazines [29], 2,6-diketopiperazines [30], *N*, *N*′-disubstituted piperazines [31], 1-(1*H*-tetrazol-5-yl)-1,2,3,4-tetrahydropyrrolo[1,2-*a*] pyrazine derivatives [32], tetazoles [33], and bis-tetrazolopiperazines [34], herein, we disclose our new synthetic method to novel 1-(1*H*-tetrazol-5-yl)-10-chloro-1,2,3,4-tetrahydropyrazino[1,2-*a*] indoles derivatives (Fig. 3).

RESULTS AND DISCUSSION

Initially, 3-chloro-1*H*-indole-2-carbaldehyde **2** was prepared using the previously reported procedures (Scheme 1) [35]. In the next step, *N*-alkylation of **2** with 1,2-dibromoethane or 1,2 dichloroethane as indicated in Scheme 1 afforded 1-(2-bromoethyl)-3-chloro-1*H*-indole-2-carbaldehyde **3a** and 3-chloro-1-(2-chloroethyl)-1*H*-indole-2-carbaldehyde **3b** in 77% and 93% yields, respectively [36].

To optimize reaction conditions, condensation of bifunctional starting material **3a** with benzylamine, *tert*-butyl isocyanide, and trimethylsilyl azide ($TMSN_3$) was selected as a model to investigate the one-pot four-component Ugi-azide reaction in methanol at room

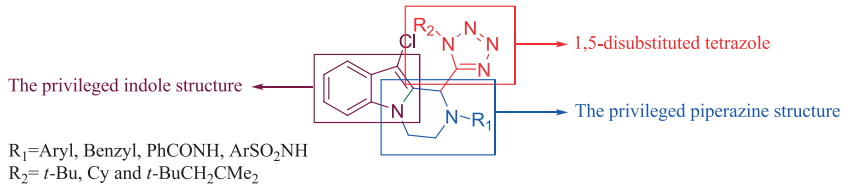
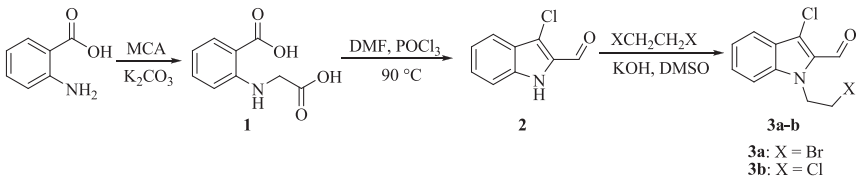


Figure 3. 1-(1*H*-Tetrazol-5-yl)-10-chloro-1,2,3,4-tetrahydropyrazino[1,2-*a*] indole containing indole and piperazine privileged structures. [Color figure can be viewed at wileyonlinelibrary.com]

Scheme 1. Synthesis of compounds **3a** and **3b**.



Scheme 2. Synthesis of **5a** *via* four-component Ugi-azide reaction.

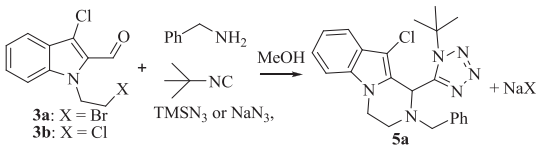


Table 1

Optimization of reaction conditions.[a]

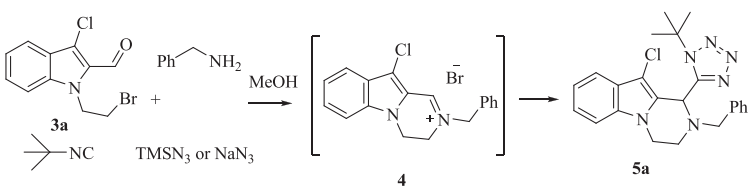
Entry	Aldehyde	Time (h)	Temperature (°C)	Yield (%)[b]
1	**3a**	12	RT	31
2	**3a**	24	RT	33
3	**3a**	12	40	30
4[c]	**3a**	12	RT	44
5[d]	**3a**	12	RT	70
6	**3b**	12	RT	28

RT, room temperature.
[a]Reaction conditions: All reactions were carried out using 1-(2-bromoethyl) 3-chloro-1*H*-indole-2-carbaldehyde **3a** (0.50 mmol), benzylamine (0.50 mmol), *tert*-butyl isocyanide (0.55 mmol), $TMSN_3$ (0.55 mmol), and MeOH (3 mL).
[b]Isolated yields.
[c]NaN_3 was used instead of $TMSN_3$.
[d]Using a two-step procedure: initial stirring a mixing of **3a** with benzylamine in MeOH for 1 h, followed by addition of isocyanide and $TMSN_3$ or NaN_3.

temperature (RT) (Scheme 2). Product **5a** was obtained in 31% yield within 12 h (entry 1, Table 1). Whereas increasing the reaction time or temperature partially improved the yields (entries 2–3, Table 1), utilization of sodium azide instead of $TMSN_3$ significantly enhanced the yield of **5a** to 44% (entry 4, Table 1). The higher nucleophilicity of NaN_3 in comparison with that of $TMSN_3$ seems to be responsible for the formation of **5a** in higher yield. Surprisingly, **5a** was obtained in 70% yield when **3a** initially was stirred with benzylamine in methanol for 1 h at RT, followed by addition of isocyanide and sodium azide (entry 5, Table 1). Such Ugi-azide method has been reported by others and us previously [32,37,38] since reaction presumably proceeds *via* the formation of iminium ion **4** (Scheme 3). On the other hand, **5a** was obtained in 28% yield when 1-(2-chloroethyl)-3-chloro-1*H*-indole-2-carbaldehyde **3b** was used in the Ugi-azide reaction (entry 6, Table 1). Compared with 1-(2-bromoroethyl)-3-chloro-1*H*-indole-2-carbaldehyde **3a**, which affords **5a** and NaBr in higher yields, utilization of 1-(2-chlorooethyl)-3-chloro-1*H*-indole-2-carbaldehyde **3a** furnishes **5a** and NaCl more slowly because Cl^- is a rather weaker leaving group than that of Br^-.

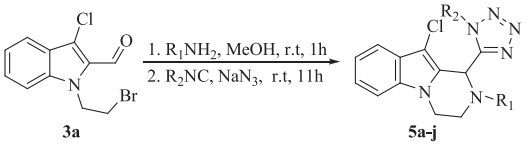
This new method was then applied to a reaction of **3a** with a variety of commercially available primary amines, isocyanides, and sodium azide. The novel 1-(1*H*-tetrazol-

Scheme 3. Transformation of **3a** to **5a** through intermediate **4**.



5-yl)-10-chloro-1,2,3,4-tetrahydropyrazino [1,2-*a*] indole derivatives **5a–j** were obtained in moderate to high yields (Scheme 4 and Table 2). As indicated in Table 2, whereas the Ugi-azide reactions with stronger benzylic amines afforded the corresponding products in significant yields (**5a–e**, Table 2), those with weaker aromatic amines resulted in the desired products in rather lower yields (**5f–j**, Table 2).

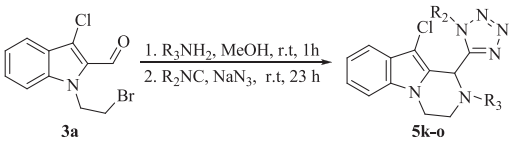
Scheme 4. Synthesis of novel 1-(1*H*-tetrazol-5-yl)-10-chloro-1,2,3,4-tetrahy-dropyrazino[1,2-*a*] indole derivatives **5a–j**.



3a **5a-j**

R_1= Benzyl, Aryl
R_2= *t*-Bu, Cy and *t*-BuCH_2CMe_2

Scheme 5. Synthesis of novel 1-(1*H*-tetrazol-5-yl)-10-chloro-1,2,3,4-tetrahy-dropyrazino[1,2-*a*] indole derivatives **5k–o**.

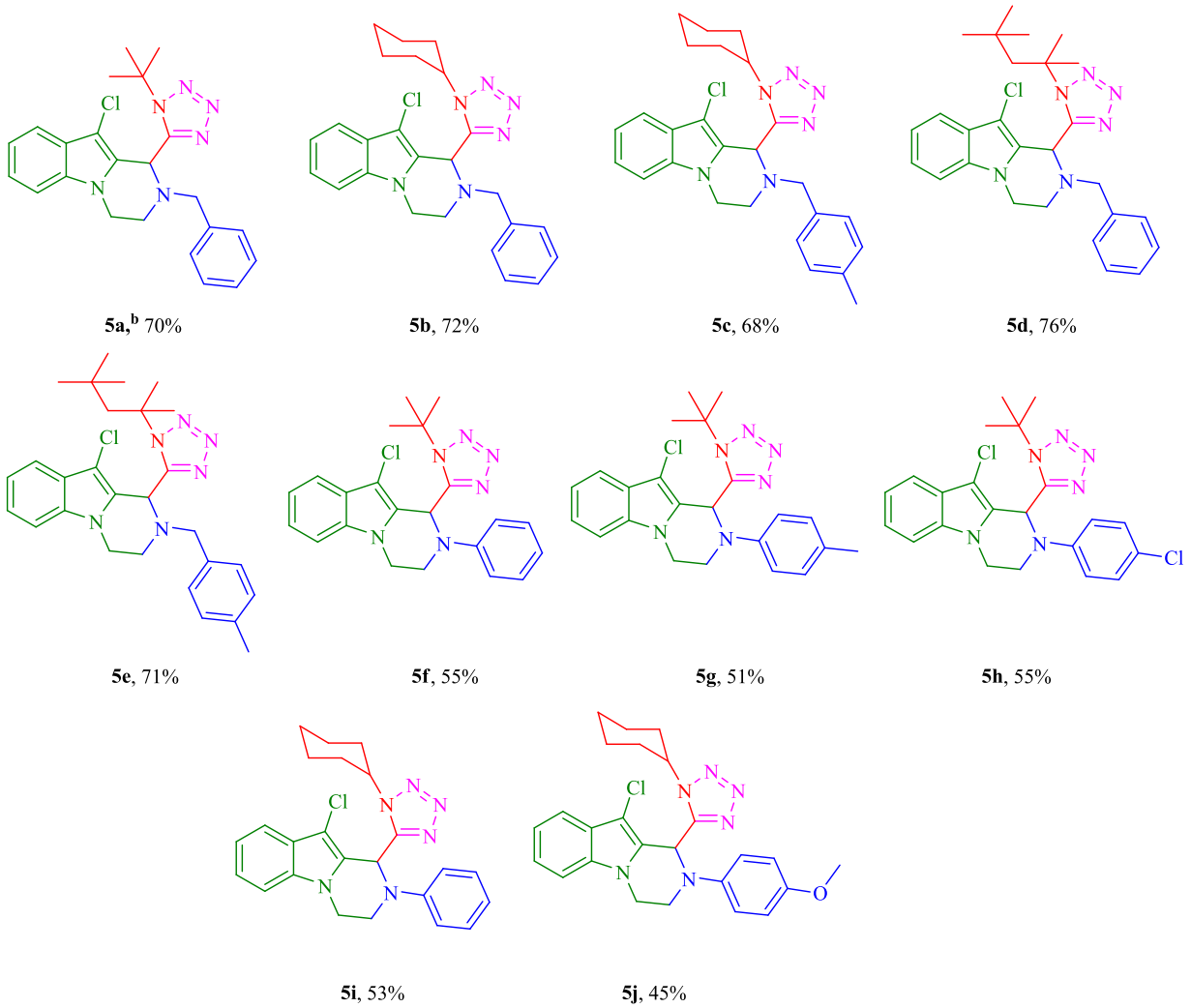


3a **5k-o**

R_3= NHCOPh and $NHSO_2$Aryl
R_2= *t*-Bu, Cy and *t*-BuCH_2CMe_2

Table 2

Synthesis of 1-(1*H*-tetrazol-5-yl)-10-chloro-1,2,3,4-tetrahydropyrazino[1,2-*a*] indoles **5a–j**.[a]



5a,[b] 70% **5b**, 72% **5c**, 68% **5d**, 76%

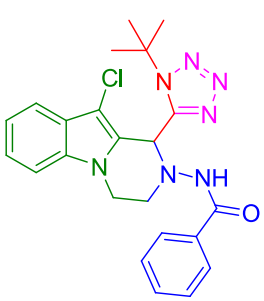
5e, 71% **5f**, 55% **5g**, 51% **5h**, 55%

5i, 53% **5j**, 45%

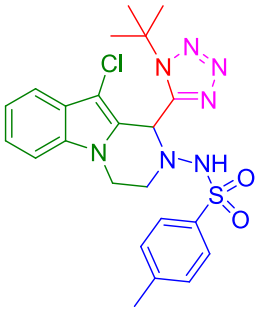
[a]Reaction conditions: All reactions were carried out using a two-step procedure as depicted in Scheme 3 with 1-(2-bromoethyl)-3-chloro-1*H*-indole-2-carbaldehyde **3a** (0.5 mmol), amine or amine source (0.5 mmol), isocyanide (0.55 mmol), NaN_3 (0.55 mmol), and MeOH (3 mL) at RT for 12 h.
[b]Structure of **5a** was confirmed by single-crystal X-ray diffraction analysis.

Table 3

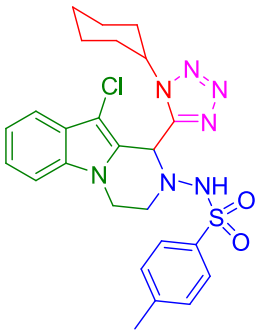
Synthesis of 1-(1*H*-tetrazol-5-yl)-10-chloro-1,2,3,4-tetrahydropyrazino[1,2-*a*] indoles **5k–o**.[a]



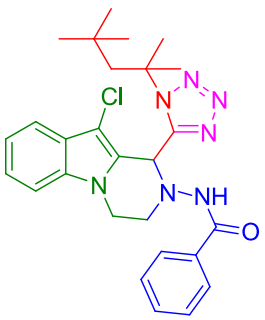
5k, 81%



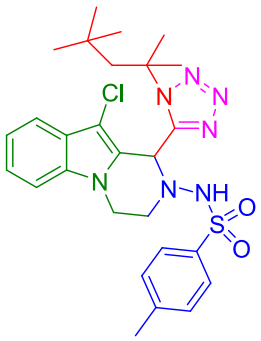
5l, 73%



5m,[b] 75%



5n, 83%



5o, 71%

[a]Reaction conditions: All reactions were carried out using a two-step procedure as depicted in Scheme 3 with 1-(2-bromoethyl)-3-chloro-1*H*-indole-2-carbaldehyde **3a** (0.5 mmol), amine source (0.5 mmol), isocyanide (0.55 mmol), NaN_3 (0.55 mmol), and MeOH (3 mL) at RT for 24 h.
[b]Structure of **5m** was confirmed by single-crystal X-ray diffraction analysis.

Products **5k–o** were then obtained in high yields when this new method was applied to a reaction of **3a**, benzhydrazide and *p*-toluenesulfonyl hydrazide, isocyanides, and sodium azide. It was found that these reactions proceed to completion within 24 h at RT (Scheme 5 and Table 3).

All compounds were characterized by elemental analysis, MS, IR, and ^{1}H and ^{13}C NMR spectroscopy. Unambiguous evidence for the proposed structures of **5a** [39] and **5m** [40] was finally obtained by single-crystal X-ray diffraction analysis, and the ORTEP diagrams are shown in Figure 4.

The proposed mechanism for the Ugi-azide reaction is illustrated in Scheme 6. The *in situ* generated iminium ion **4** as the key intermediate from the condensation of **3a** and amine undergoes nucleophilic reaction with isocyanide to furnish nitrilium ion **I** (Scheme 6). Subsequent addition of sodium azide to the nitrilium ion **I** gives the azidoazomethine intermediate **II**. Finally, it is transformed to the desired products **5a–j** perhaps through intramolecular 1,3-dipolar cycloaddition reactions (Scheme 6).

CONCLUSION

In summary, we have developed a practical and convenient method for the synthesis of novel 1-(1*H*-tetrazol-5-yl)-10-chloro-1,2,3,4-tetrahydropyrazino[1,2-*a*] indoles *via* an Ugi-azide four-component approach in moderate to high yields. These reactions presumably proceed *via* the *in situ* generated iminium ion followed by reaction with isocyanide and sodium azide. Simplicity, greater efficiency, readily available chemicals, and prompt isolation of the products with a generation of molecular complexity are some advantages of this protocol. The obtained novel privileged compounds broaden the scaffolds that are prepared through the Ugi-azide reactions, and many of them may represent interesting pharmacophores. Study of the biological properties of the

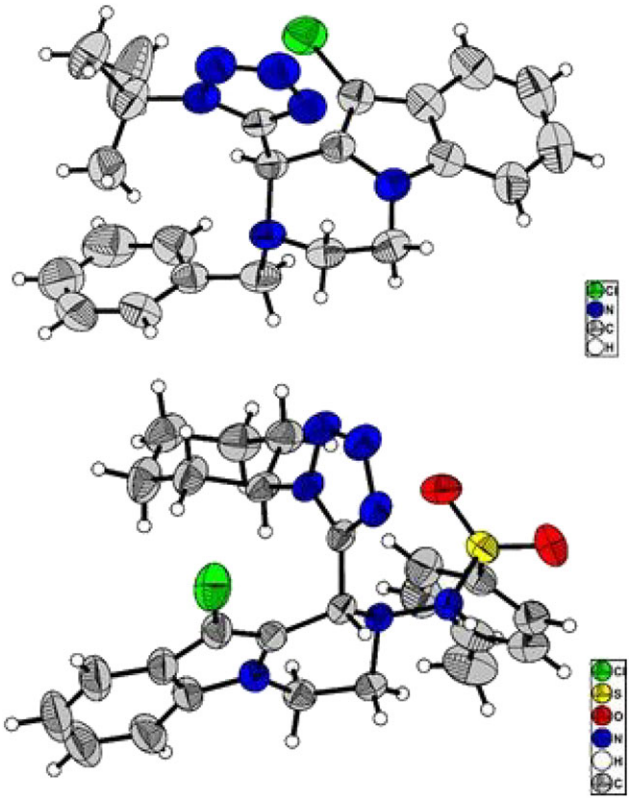
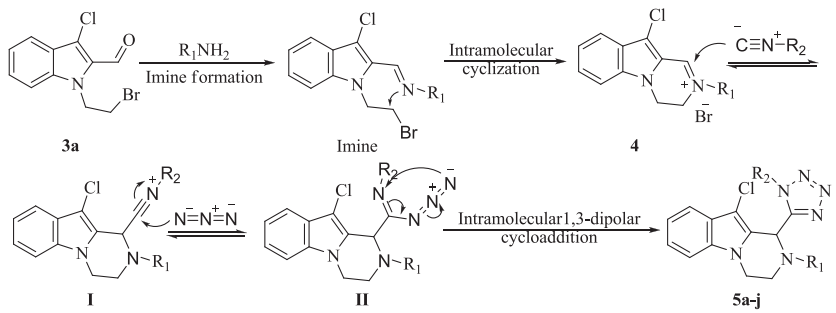


Figure 4. ORTEP diagrams of compounds **5a** and **5m** [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.].

Scheme 6. Suggested mechanism for the formation of **5a–j**.



prepared pyrazino[1,2-*a*] indole-based 1,5-disubstituted tetrazoles is currently under investigation in our laboratory.

EXPERIMENTAL

General information. The chemicals and reagents used in this work were purchased from Merck Chemical Company (Merck, Kenilworth, NJ) and used without further purification. Melting points were obtained with an electrothermal model 9100 apparatus and are uncorrected. IR spectra were recorded using a Bruker Alpha spectrometer (Bruker Corp., Billerica, MA), with diamond ATR–FTIR detection. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DRX-300-ADVANCE spectrometer (Bruker Corp.) at 300 MHz or Varian Unity INOVA 500 MHz using $CDCl_3$ or DMSO-d_6 as the solvent. Chemical shifts (δ in ppm) are referenced to the solvent $CDCl_3$ (δ = 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, and m = multiplet. Mass spectra were recorded on an HP (Agilent Technologies, Santa Clara, CA, USA) 5937 Mass Selective Detector. Elemental analyses were performed using a CHN-Rapid Heraeus elemental analyzer (Heraeus Deutschland GmbH & Co. KG, Hanau, Germany).

Preparation method for the synthesis of compound 3a. KOH (5.9 g, 100 mmol) was added in one portion to a stirred solution of 3-chloro-1*H*-indole-2-carbaldehyde (**2**) (1.8 g, 10 mmol) in dimethyl sulfoxide (DMSO) (10 mL) at RT. After 1 h, Br $(CH_2)_2$Br (20 mL) was slowly added at 0°C and the resulting solution stirred overnight at RT. The reaction was quenched by addition of H_2O (10 mL), and the organic product was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine (20 mL) and dried with Na_2SO_4. After evaporation of the solvent under reduced pressure, the crude product was purified by flash column chromatography [SiO_2, cyclohexane–EtOAc (9:1)] to give a yellow solid [36].

1-(2-Bromoethyl)-3-chloro-1H-indole-2-carbaldehyde (3a). Yellow solid (2.2 g, 77%); mp 62–64°C; IR (KBr) ν_{max}: 3300, 2845, 2738, 1660, 1611, 1511, 1456, 1356, 890, 856, 742 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.64 (t, *J* = 6.7 Hz, 2H), 4.81 (t, *J* = 6.7 Hz, 2H), 7.21–7.27 (m, 1H), 7.41–7.50 (m, 2H), 7.71 (d, *J* = 8.2 Hz, 1H), 10.12 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 30.2, 46.2, 110.8, 120.6, 120.7, 122.0, 124.3, 128.4, 128.6, 138.4, 180.8 ppm; *m/z* (EI, 70 eV) 287 (33, M^+), 285 (26, M^+), 206 (100), 192 (52), 178 (15), 164 (15), 150 (22), 123 (44), 114 (22), 89 (15%); *Anal*. Calcd for $C_{11}H_9BrClNO$: C, 46.11; H, 3.17; Br, 27.88; Cl, 12.37; N, 4.89; O, 5.58. Found: C, 46.13; H, 3.16; Br, 27.84; Cl, 12.39; N, 4.91; O, 5.60%.

Preparation method for the synthesis of compound 3b. 1,2-Dichloroethane (10 mL), Bu_4NI (1.02 g, 2.8 mmol), and 50% aq NaOH (5 mL) were added to a solution of 3-chloro-1*H*-indole-2-carbaldehyde (**2**) (0.500 g, 2.8 mmol) in CH_2Cl_2 (2 mL), and the mixture was vigorously stirred overnight. H_2O (2 mL) was added, and the organic product was extracted with CH_2Cl_2 (3 × 20 mL) and washed with 1 M HCl (2 × 20 mL), saturated aqueous $NaHCO_3$ (2 × 20 mL), and brine (2 × 20 mL) and dried with Na_2SO_4. After evaporation of the solvent under reduced pressure, the crude product was purified by column chromatography [SiO_2, cyclohexane–EtOAc (9:1)] to give a white solid [36].

3-Chloro-1-(2-chloroethyl)-1H-indole-2-carbaldehyde (3b). White solid (0.53 g, 93%); mp 76–78°C; IR (KBr) ν_{max}: 3060, 3025, 2960, 2726, 1660, 1612, 1510, 1345, 858, 745, 660 cm^{-1}; ^1H NMR (300 MHz, DMSO): δ 3.92 (t, *J* = 6.0 Hz, 2H), 4.86 (t, *J* = 6.0 Hz, 2H), 7.27 (t, *J* = 7.7 Hz, 1H), 7.50 (t, *J* = 7.8 Hz, 1H), 7.69 (d, *J* = 8.1 Hz, 1H), 7.75 (d, *J* = 8.6 Hz, 1H), 10.06 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 43.8, 45.6, 112.0, 118.0, 119.6, 122.0, 123.4, 128.2, 128.4, 138.1, 180.8 ppm; *m/z* (EI, 70 eV) 243 (37, M^+), 241 (59, M^+), 221 (44), 206 (88), 192 (100), 177 (30), 164 (30), 123 (88), 114 (22), 77 (37%); *Anal*. Calcd for $C_{11}H_9Cl_2NO$: C, 54.57; H, 3.75; Cl, 29.29; N, 5.79; O, 6.61. Found: C, 54.60; H, 3.71; Cl, 29.32; N, 5.82; O, 6.60%.

General procedure for the synthesis of compounds 5a–o. 1-(2-Bromoethyl)-3-chloro-1*H*-indole-2-carbaldehyde **3a** (143 mg, 0.5 mmol) and primary amine (0.5 mmol) in methanol (3 mL) were stirred for 1 h at RT. Consequently, sodium azide (36 mg, 0.55 mmol) and isocyanide (0.55 mmol) were added, and the reaction mixture stirred for 23 h. After completion of the reaction as indicated by thin-layer chromatography, the crude product was collected by filtration and recrystallized from acetonitrile to afford the desired solid products **5a–o**.

2-Benzyl-1-(1-(tert-Butyl)-1H-tetrazol-5-yl)-10-chloro-1,2,3,4-tetrahydropyrazino[1,2-a] indole (5a). White solid (149 mg, 71%); mp 121–123°C; IR (KBr) ν_{max}: 3043, 2992, 2885, 2827, 1492, 1220, 1174, 1016, 813, 737, 698 cm^{-1}; ^1H NMR (300 MHz, DMSO): δ 1.78 (s, 9H), 2.86 (dd, J_1 = 14.0, J_2 = 3.0 Hz, 1H), 3.25 (dt, J_1 = 15.0, J_2 = 5.0 Hz, 1H), 3.83 (d, *J* = 13.0 Hz, 1H), 4.06 (d, *J* = 13.0 Hz, 2H), 4.25 (dt, J_1 = 12.1, J_2 = 4.7 Hz, 1H), 5.97 (s, 1H), 7.21 (t, *J* = 7.4 Hz, 1H), 7.30 (t, *J* = 7.9 Hz, 2H), 7.33–7.40 (m, 4H), 7.50 (d, *J* = 7.7 Hz, 1H), 7.58 (d, *J* = 8.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 29.3, 37.4, 43.7, 51.1, 55.3, 62.2, 100.4, 110.3, 116.9, 120.7, 122.3, 124.2, 127.0, 127.6, 128.5, 129.0, 134.7, 137.1, 152.8 ppm; *m/z* (EI, 70 eV) 422 (15, M^+), 420 (37, M^+), 364 (15), 295 (74), 203 (44), 91 (100), 57 (22%); *Anal*. Calcd for $C_{23}H_{25}ClN_6$: C, 65.63; H, 5.99; Cl, 8.42; N, 19.97. Found: C, 65.64; H, 5.96; Cl, 8.45; N, 19.99%.

2-Benzyl-10-chloro-1-(1-cyclohexyl-1H-tetrazol-5-yl)-1,2,3,4-tetrahydropyrazino[1,2-a] indole (5b). White solid (165 mg, 74%); mp 116–118°C; IR (KBr) ν_{max}: 3064, 3031, 2936, 2855, 1668, 1449, 1362, 1232, 1009, 739, 696 cm^{-1}; ^1H NMR (300 MHz, DMSO): δ 0.90–1.40 (m, 3H), 1.50–2.10 (m, 6H), 2.90–3.02 (m, 1H), 3.20–3.35 (m, 1H), 3.78 (q, *J* = 13 Hz, 2H), 4.10–4.32 (m, 3H), 5.84 (s, 1H), 7.20 (t, *J* = 7.7 Hz, 1H), 7.26–7.41 (m, 6H), 7.48 (d, *J* = 7.7 Hz, 1H), 7.57 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.3, 24.5, 24.6, 32.0, 32.8, 43.1, 49.9, 55.8, 57.1, 100.5, 110.2, 117.0, 120.8, 122.5, 124.3, 126.1, 127.6, 128.6, 128.9, 134.6, 137.2, 152.1 ppm; *m/z* (EI, 70 eV) 448 (7, M^+), 446 (22, M^+), 315 (7), 295 (52), 203 (37), 91 (100), 55 (15%); *Anal*. Calcd for $C_{25}H_{27}ClN_6$: C, 67.18; H, 6.09; Cl, 7.93; N, 18.80. Found: C, 67.16; H, 6.10; Cl, 7.96; N, 18.84%.

10-Chloro-1-(1-cyclohexyl-1H-tetrazol-5-yl)-2-(4-methylbenzyl)-1,2,3,4-tetrahydropyrazino[1,2-a] indole (5c). White solid (161 mg, 70%); mp 131–133°C; IR (KBr) ν_{max}: 3056, 2935, 2854, 1612, 1475, 1363, 1312, 1179, 1099, 806, 747 cm^{-1}; ^1H NMR (300 MHz, DMSO): δ 0.90–1.40 (m, 3H), 1.50–2.10 (m, 7H), 2.29 (s, 3H), 2.90–3.02 (m, 1H), 3.10–3.21 (m, 1H), 3.73 (q, *J* = 13 Hz, 2H), 4.12–4.30 (m, 3H), 5.78 (s, 1H), 7.00–

7.27 (m 5H), 7.29 (t, J = 7.2 Hz, 1H), 7.48 (d, J = 7.8 Hz, 1H), 7.57 (d, J = 8.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.7, 24.3, 24.4, 24.5, 31.9, 32.8, 38.3, 43.1, 49.6, 55.5, 57.0, 100.5, 110.2, 116.9, 120.8, 122.5, 124.3, 126.1, 129.0, 129.2, 134.1, 134.6, 136.9, 152.2 ppm; *m/z* (EI, 70 eV) 462 (7, M^+), 460 (22, M^+), 308 (52), 205 (22), 203 (44), 146 (15), 105 (100%); *Anal*. Calcd for $C_{26}H_{29}ClN_6$: C, 67.74; H, 6.34; Cl, 7.69; N, 18.23. Found: C, 67.70; H, 6.36; Cl, 7.72; N, 18.20%.

2-Benzyl-10-chloro-1-(1-(2,4,4-trimethylpentan-2-yl)-1H-tetrazol-5-yl)-1,2,3,4-tetrahydropyrazino[1,2-a] indole (5d). White solid (184 mg, 77%); mp 110–112°C; IR (KBr) ν_{max}: 2952, 1666, 1608, 1359, 1223, 1113, 920, 740, 701 cm^{-1}; ^{1}H NMR (500 MHz, DMSO): δ 0.80 (s, 9H), 1.77 (s, 3H), 1.88 (s, 3H), 1.98 (d, J = 15.1 Hz, 1H), 2.19 (d, J = 15.1 Hz, 1H), 2.96 (dd, J_1 = 14.2, J_2 = 4.0 Hz, 1H), 3.17–3.26 (m, 1H), 3.88 (d, J = 13.1 Hz, 1H), 4.00 (d, J = 13.1 Hz, 1H), 4.11 (dd, J_1 = 12.2, J_2 = 4.7 Hz, 1H), 4.25 (Sextet, J = 4.9 Hz, 1H), 5.93 (s, 1H), 7.23 (t, J = 7.5 Hz, 1H), 7.29–7.34 (m, 2H), 7.35–7.43 (m, 4H), 7.52 (d, J = 7.8 Hz, 1H), 7.59 (d, J = 8.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 29.8, 29.9, 30.8, 31.7, 35.7, 51.2, 53.2, 55.7, 66.4, 101.0, 110.8, 117.4, 121.2, 122.8, 124.7, 127.5, 128.2, 129.0, 129.9, 135.4, 137.2, 153.4 ppm; *m/z* (EI, 70 eV) 478 (2, M^+), 476 (7, M^+), 364 (15), 295 (52), 203 (37), 168 (15), 91 (100%); *Anal*. Calcd for $C_{27}H_{33}ClN_6$: C, 67.98; H, 6.97; Cl, 7.43; N, 17.62. Found: C, 68.01; H, 6.98; Cl, 7.45; N, 17.66%.

10-Chloro-2-(4-methylbenzyl)-1-(1-(2,4,4-trimethylpentan-2-yl)-1H-tetrazol-5-yl)-1,2,3,4-tetrahydropyrazino [1,2-a] indole (5e). White solid (179 mg, 73%); mp 115–117°C; IR (KBr) ν_{max}: 2952, 1511, 1457, 1361, 1271, 1221, 1172, 1116, 978, 831, 745 cm^{-1}; ^{1}H NMR (500 MHz, DMSO): δ 0.81 (s, 9H), 1.77 (s, 3H), 1.87 (s, 3H), 1.97 (d, J = 15.1 Hz, 1H), 2.19 (d, J = 15.1 Hz, 1H), 2.31 (s, 3H), 2.98 (d, J = 10.9 Hz, 1H), 3.20–3.26 (m, 1H), 3.83 (d, J = 12.9 Hz, 1H), 3.91 (d, J = 12.9 Hz, 1H), 4.09 (dd, J_1 = 12.2, J_2 = 5.1 Hz, 1H), 4.24 (Sextet, J = 5.0 Hz, 1H), 5.89 (s, 1H), 7.18–7.26 (m, 5H), 7.31 (t, J = 7.3 Hz, 1H), 7.52 (d, J = 7.8 Hz, 1H), 7.58 (d, J = 8.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.2, 29.7, 29.9, 30.8, 31.7, 35.7, 51.1, 53.1, 55.5, 66.4, 101.0, 110.8, 117.4, 121.2, 122.7, 124.7, 127.5, 129.5, 129.9, 134.1, 135.4, 137.5, 153.4 ppm; *m/z* (EI, 70 eV) 492 (3, M^+), 490 (7, M^+), 378 (15), 308 (52), 245 (7), 203 (44), 105 (100%); *Anal*. Calcd for $C_{28}H_{35}ClN_6$: C, 68.48; H, 7.18; Cl, 7.22; N, 17.11. Found: C, 68.45; H, 7.20; Cl, 7.25; N, 17.14%.

1-(1-(tert-Butyl)-1H-tetrazol-5-yl)-10-chloro-2-phenyl-1,2,3,4-tetrahydropyrazino[1,2-a] indole (5f). White solid (116 mg, 57%); mp 181°C decompose; IR (KBr) ν_{max}: 3055, 2992, 2885, 2952, 2879, 1596, 1452, 1356, 1116, 737, 702 cm^{-1}; ^{1}H NMR (300 MHz, DMSO): δ 1.68 (s, 9H), 3.70 (quint, J = 12.0 Hz, 2H), 4.06 (d, J = 12.0 Hz, 1H), 4.21 (d, J = 9.0 Hz, 1H), 6.57 (s, 1H), 6.97 (t, J = 7.2 Hz, 1H), 7.12 (d, J = 8.0 Hz, 2H), 7.17–7.32 (m, 4H), 7.51 (dd, J_1 = 11.9, J_2 = 7.5 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 29.0, 37.6, 43.4, 48.0, 62.5, 100.5, 110.3, 117.1, 119.1, 120.9, 122.3, 122.5, 124.0, 126.6, 129.8, 134.8, 147.0, 152.3 ppm; *m/z* (EI, 70 eV) 408 (7, M^+), 406 (15, M^+), 350 (15), 281 (100), 245 (15), 205 (15), 192 (15), 123 (7), 104 (15), 77 (30%); *Anal*. Calcd for $C_{22}H_{23}ClN_6$: C, 64.94; H, 5.70; Cl, 8.71; N, 20.65. Found: C, 64.93; H, 5.70; Cl, 8.73; N, 20.66%.

1-(1-(tert-Butyl)-1H-tetrazol-5-yl)-10-chloro-2-(p-tolyl)-1,2,3,4-tetrahydropyrazino[1,2-a] indole (5g). White solid (111 mg, 53%); mp 174°C decompose; IR (KBr) ν_{max}: 3060, 2981, 2884, 1725, 1666, 1513, 1454, 1414, 1172, 808, 740 cm^{-1}; ^{1}H NMR (300 MHz, DMSO): δ 1.68 (s, 9H), 2.18 (s, 3H), 3.36–3.67 (m, 2H), 3.89–4.05 (m, 1H), 4.10–4.23 (m, 1H), 6.48 (s, 1H), 6.98 (d, J = 8.3 Hz, 2H), 7.09 (d, J = 8.3 Hz, 2H), 7.17–7.27 (m, 2H), 7.46–7.53 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.1, 29.0, 38.7, 43.7, 48.2, 62.5, 100.5, 110.3, 117.1, 119.3, 120.9, 122.5, 124.1, 126.7, 130.2, 131.4, 134.8, 144.7, 152.4 ppm; *m/z* (EI, 70 eV) 422 (7, M^+), 420 (15, M^+), 364 (15), 297 (37), 295 (100), 259 (15), 188 (22), 154 (15), 118 (15), 91 (37%); *Anal*. Calcd for $C_{23}H_{25}ClN6$: C, 65.63; H, 5.99; Cl, 8.42; N, 19.97. Found: C, 65.62; H, 6.01; Cl, 8.45; N, 19.96%.

1-(1-(tert-Butyl)-1H-tetrazol-5-yl)-10-chloro-2-(4-chlorophenyl)-1,2,3,4-tetrahydropyrazino[1,2-a] indole (5h). White solid (123 mg, 56%); mp 175°C decompose; IR (KBr) ν_{max}: 3057, 2963, 2930, 1721, 1593, 1493, 1358, 1211, 1106, 823, 741 cm^{-1}; ^{1}H NMR (300 MHz, DMSO): δ 1.69 (s, 9H), 3.34–3.73 (m, 2H), 4.06 (d, J = 12.5 Hz, 1H), 4.19–4.23 (m, 1H), 6.54 (s, 1H), 7.08–7.28 (m, 4H), 7.33 (d, J = 8.7 Hz, 2H), 7.50 (t, J = 8.0 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 29.0, 37.6, 43.5, 48.0, 62.5, 100.7, 110.3, 117.1, 120.1, 122.5, 124.0, 126.1, 126.2, 129.5, 134.8, 146.0, 152.2 ppm; *m/z* (EI, 70 eV) 442 (7, M^+), 440 (10, M^+), 317 (59), 315 (100), 279 (7), 188 (22), 154 (15), 140 (15), 111 (22), 57 (44%); *Anal*. Calcd for $C_{22}H_{22}Cl_2N_6$: C, 59.87; H, 5.02; Cl, 16.06; N, 19.04. Found: C, 59.90; H, 5.00; Cl, 16.07; N, 19.03%.

10-Chloro-1-(1-cyclohexyl-1H-tetrazol-5-yl)-2-phenyl-1,2,3,4-tetrahydropyrazino[1,2-a] indole (5i). White solid (119 mg, 55%); mp 183°C decompose; IR (KBr) ν_{max}: 3053, 2934, 2860, 1594, 1489, 1446, 1226, 1088, 961, 741, 700 cm^{-1}; ^{1}H NMR (500 MHz, DMSO): δ 0.80–2.15 (m, 10H), 3.75–3.90 (m, 2H), 4.8 (Sextet, J = 5.0 Hz, 1H), 4.42–4.55 (m, 2H), 6.92–7.02 (m, 2H), 7.21 (t, J = 7.5 Hz, 1H), 7.25–7.35 (m, 5H), 7.50 (d, J = 7.9 Hz, 1H), 7.60 (d, J = 8.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.9, 25.2, 33.0, 33.2, 41.2, 42.5, 49.2, 57.7, 100.1, 110.8, 117.5, 120.5, 121.3, 122.9, 123.0, 124.8, 127.9, 129.8, 134.8, 148.4, 152.1 ppm; *m/z*

(EI, 70 eV) 434 (7, M^+), 432 (30, M^+), 281 (100), 245 (15), 188 (15), 154 (7), 104 (15), 77 (30%); *Anal*. Calcd for $C_{24}H_{25}ClN_6$: C, 66.58; H, 5.82; Cl, 8.19; N, 19.41. Found: C, 66.60; H, 5.82; Cl, 8.17; N, 19.44%.

10-Chloro-1-(1-cyclohexyl-1H-tetrazol-5-yl)-2-(4-methoxyphenyl)-1,2,3,4-tetrahydropyrazino[1,2-a] indole (5j). White solid (111 mg, 48%); mp 177°C decompose; IR (KBr) ν_{max}: 2923, 2853, 1609, 1507, 1447, 1222, 1029, 836, 740, 634 cm^{-1}; ^1H NMR (500 MHz, DMSO): δ 0.79 (d, *J* = 11.0 Hz, 1H), 1.08 (q, *J* = 12.7 Hz, 1H), 1.17 (q, *J* = 12.7 Hz, 1H), 1.43 (q, *J* = 12.6 Hz, 1H), 1.53 (q, *J* = 12.8 Hz, 1H), 1.62 (d, *J* = 11.1 Hz, 2H), 1.760 (t, *J* = 11.8 Hz, 1H), 1.82 (d, *J* = 15.1 Hz, 1H), 2.07 (t, *J* = 8.7 Hz, 1H), 3.60 (d, *J* = 11.9 Hz, 1H), 3.69 (s, 3H), 3.85 (t, *J* = 9.8 Hz, 1H), 4.11 (Sextet, *J* = 3.7 Hz, 1H), 4.35 (t, *J* = 11.1 Hz, 1H), 4.49 (d, *J* = 11.3 Hz, 1H), 6.76 (s, 1H), 6.87 (d, *J* = 8.5 Hz, 2H), 7.15 (d, *J* = 8.5 Hz, 2H), 7.21 (t, *J* = 7.4 Hz, 1H) 7.30 (t, *J* = 7.4 Hz, 1H), 7.49 (d, *J* = 7.8 Hz, 1H), 7.60 (d, *J* = 8.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.9, 25.1 25.2, 32.7, 33.3, 41.7, 43.8, 50.3, 55.8, 57.6, 99.8, 110.7, 114.9, 117.4, 121.3, 122.9, 123.2, 124.8, 128.3, 134.7, 142.0, 151.8, 156.1 ppm; *m/z* (EI, 70 eV) 464 (7, M^+), 462 (22, M^+), 313 (37), 311 (100), 275 (7), 190 (15), 154 (15), 123 (22), 83 (7%); *Anal*. Calcd for $C_{25}H_{27}ClN_6O$: C, 64.86; H, 5.88; Cl, 7.66; N, 18.15; O, 3.46. Found: C, 64.87; H, 5.91; Cl, 7.65; N, 18.18; O, 3.49%.

N-(1-(1-(tert-Butyl)-1H-tetrazol-5-yl)-10-chloro-3,4-dihydropyrazino[1,2-a]indol-2(1H)-yl) benzamide (5k). White solid (182 mg, 81%); mp 140–142°C; IR (KBr) ν_{max}: 3375, 3188, 2980, 1662, 1537, 1455, 1279, 1024, 917, 748, 702 cm^{-1}; ^1H NMR (300 MHz, DMSO): δ 1.71 (s, 9H), 3.60 (bs, 2H), 4.31 (bs, 2H), 6.29 (s, 1H), 7.20 (t, *J* = 7.4 Hz, 1H), 7.30 (t, *J* = 7.1 Hz, 1H), 7.40–7.54 (m, 4H), 7.59 (d, *J* = 8.1 Hz, 1H), 7.69 (bs, 2H), 10.21 (bs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 29.5, 38.7, 43.6, 48.6, 62.5, 100.5, 110.4, 117.1, 119.3, 120.8, 124.5, 127.2, 127.5, 128.2, 131.5, 133.3, 144.7, 152.4, 164.8 ppm; *m/z* (EI, 70 eV) 449 (3, M^+), 346 (4), 330 (15), 328 (44), 272 (15), 244 (22), 218 (52), 203 (22), 190 (22), 105 (100), 77 (52), 57 (22%); *Anal*. Calcd for $C_{23}H_{24}ClN_7O$: C, 61.40; H, 5.38; Cl, 7.88; N, 21.79; O, 3.56. Found: C, 61.41; H, 5.41; Cl, 7.85; N, 21.77; O, 3.57%.

N-(1-(1-(tert-Butyl)-1H-tetrazol-5-yl)-10-chloro-3,4-dihydropyrazino[1,2-a]indol-2(1H)-yl)-4-methylbenzenesulfonamide (5l). White solid (182 mg, 73%); mp 148–150°C; IR (KBr) ν_{max}: 3056, 2992, 2884, 2786, 1598, 1452, 1370, 1344, 1232, 1163, 752 cm^{-1}; ^1H NMR (300 MHz, DMSO): δ 1.91 (s, 9H), 2.40 (s, 4H), 3.59 (s, 1H), 3.85 (s, 1H), 4.26 (s, 1H), 6.33 (s, 1H), 7.17 (t, *J* = 7.5 Hz, 1H), 7.27 (t, *J* = 7.1 Hz, 1H), 7.42–7.50 (m, 4H), 7.35 (d, *J* = 8.0 Hz, 2H), 9.33 (s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.1, 30.2, 37.4, 43.6, 53.9, 63.8, 99.5, 110.4, 117.0, 120.9, 122.6, 124.3, 127.7, 128.0, 129.9, 134.1, 135.6, 143.9, 150.9 ppm; *m/z* (EI, 70 eV) 501 (1, M^+), 499 (3, M^+), 315 (7), 260 (30), 192 (37), 190 (100), 154 (22), 139 (30), 91 (44), 57 (44%); *Anal*. Calcd for $C_{23}H_{26}ClN_7O_2S$: C, 55.25; H, 5.24; Cl, 7.09; N, 19.61; O, 6.40; S, 6.41. Found: C, 55.22; H, 5.25; Cl, 7.11; N, 19.59; O, 6.43; S, 6.40%.

N-(10-Chloro-1-(1-cyclohexyl-1H-tetrazol-5-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1H)-yl)-4-methylbenzenesulfonamide (5m). White solid (197 mg, 75%); mp 151–153°C; IR (KBr) ν_{max}: 3315, 3100, 2943, 2859, 1450, 1339, 1165, 1092, 1020, 831, 750 cm^{-1}; ^1H NMR (300 MHz, DMSO): δ 0.90–1.40 (m, 3H), 1.50–2.20 (m, 7H), 2.40 (s, 3H), 3.00–3.40 (m, 2H), 3.95 (s, 1H), 4.19 (s, 1H), 4.80 (s, 1H), 5.98 (s, 1H), 7.18 (t, *J* = 7.7 Hz, 1H), 7.27 (t, *J* = 7.1 Hz, 1H), 7.40–7.55 (m, 4H), 7.74 (d, *J* = 8.0 Hz, 2H), 9.42 (s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.1, 24.5, 24.8, 24.9, 32.4, 33.0, 46.7, 48.6, 57.5, 100.1, 110.3, 117.0, 120.9, 122.7, 124.3, 126.6, 127.5, 129.8, 134.2, 135.5, 143.9, 150.5 ppm; *m/z* (EI, 70 eV) 527 (1, M^+), 525 (3, M^+), 341 (15), 260 (22), 192 (37), 190 (100), 154 (37), 91 (37), 55 (44%); *Anal*. Calcd for $C_{25}H_{28}ClN_7O_2S$: C, 57.08; H, 5.37; Cl, 6.74; N, 18.64; O, 6.08; S, 6.09. Found: C, 57.10; H, 5.38; Cl, 6.72; N, 18.66; O, 6.05; S, 6.11%.

N-(10-Chloro-1-(1-(2,4,4-trimethylpentan-2-yl)-1H-tetrazol-5-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1H)-yl) benzamide (5n). White solid (209 mg, 83%); mp 125–127°C; IR (KBr) ν_{max}: 3377, 3186, 2943, 2957, 1661, 1538, 1411, 1358, 1278, 1097, 1023, 916, 746, 706 cm^{-1}; ^1H NMR (300 MHz, DMSO): δ 0.82 (s, 9H), 1.88 (s, 6H), 2.06 (bs, 1H), 2.24 (bs, 1H), 3.54 (bs, 2H), 4.30 (bs, 2H), 6.26 (s, 1H), 7.21 (t, *J* = 7.6 Hz, 1H), 7.30 (t, *J* = 7.1 Hz, 1H), 7.40–7.58 (m, 5H), 7.75 (d, *J* = 6.0 Hz, 2H), 10.25 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 29.0, 29.1, 30.5, 31.3, 35.6, 48.6, 53.4, 66.7, 100.0, 110.3, 116.8, 120.8, 122.3, 124.4, 126.9, 127.7, 128.1, 131.4, 133.4, 151.9, 165.1 ppm; *m/z* (EI, 70 eV) 505 (2, M^+), 449 (2), 384 (9), 324 (5), 301 (9), 272 (18), 244 (27), 209 (9), 188 (18), 121 (54), 105 (100), 57 (100%); *Anal*. Calcd for $C_{27}H_{32}ClN_7O$: C, 64.08; H, 6.37; Cl, 7.01; N, 19.38; O, 3.16. Found: C, 64.12; H, 6.40; Cl, 6.59; N, 19.37; O, 3.13%.

N-(10-Chloro-1-(1-(2,4,4-trimethylpentan-2-yl)-1H-tetrazol-5-yl)-3,4-dihydropyrazino[1,2-a]indol-2(1H)-yl)-4-methylbenzenesulfonamide (5o). White solid (197 mg, 71%); mp 157–159°C; IR (KBr) ν_{max}: 3117, 2952, 2871, 1596, 1452, 1370, 1239, 1164, 1094, 812, 743, 671 cm^{-1}; ^1H NMR (300 MHz, DMSO): δ 0.88 (s, 9H), 2.00 (s, 3H), 2.07 (s, 3H), 2.20–2.34 (m, 2H), 2.35–2.55 (m, 4H), 3.55 (bs, 1H), 3.85 (bs, 1H), 4.25 (d, *J* = 8.9 Hz, 1H), 6.29 (s, 1H), 7.19 (t, *J* = 7.5 Hz, 1H), 7.28 (t, *J* = 7.8 Hz, 1H), 7.35–7.60 (m, 4H), 7.75 (d, *J* = 8.1 Hz, 2H), 9.31 (s, 1H); ^{13}C NMR (75 MHz,

$CDCl_3$) δ 21.1, 28.8, 29.1, 30.6, 31.4, 35.7, 44.4, 54.4, 67.5, 99.7, 110.4, 117.0, 120.9, 122.7, 124.2, 127.6, 129.8, 134.5, 135.7, 143.9, 150.0 ppm; *m/z* (EI, 70 eV) 555 (1, M^+), 371 (9), 259 (18), 190 (45), 156 (18), 139 (14), 113 (27), 97 (41), 57 (100%); *Anal*. Calcd for $C_{27}H_{34}ClN_7O_2S$: C, 58.31; H, 6.16; Cl, 6.37; N, 17.63; O, 5.75; S, 5.76. Found: C, 58.30; H, 6.18; Cl, 6.36; N, 17.61; O, 5.72; S, 5.77%.

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[40] Copies of these, data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html (or, from the Cambridge Crystallographic Data Centre, 12Union Road, Cambridge, CB2 1EZ, UK; fax: þ44 1223 336 033; or e-mail: deposit@ccdc.cam.ac.uk). The CCDC deposition number for compound 5m is 1851773. Formula: $C_{25}H_{28}ClN_7O_2S$. Unit cell parameters: a 16.551(3) b 9.1966(18) c 20.251(8) P21/c.

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