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Functionalized N-containing heterocyclic scaffolds derived from N-substituted pyrroles via inter- and intramolecular annulations

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ABSTRACT

Two series of N-containing heterocycles were synthesized by one-step intramolecular or intermolecular annulations of N-substituted pyrrole-2-carbaldehydes and pyrrole-2-carbonitriles. These facile and atom-economic synthetic routes involved the inherent three potential electrophilic and nucleophilic reactive sites of the synthons and the reaction solvent plays a crucial role leading to these different types of products. Additionally, plausible mechanisms are proposed.

1. Introduction

N-containing heterocycles are extensively prevalent in bioactive natural products, as well as in pharmaceuticals, organic dyes and many other compounds of industrial use [1]. During the past decades, constructions of these heterocycles from substituted pyrroles have been gradually recognized [2]. N-substituted pyrroles **1** (Fig. 1), containing at least two potential electrophilic α and γ (X = CHO, CN, etc.) and one nucleophilic (β) sites, are highly versatile synthons which provide potential two-, four- or five-atom units to generate molecular diversity. Among these biologically interesting scaffolds (Fig. 1) [3], the most frequently occurring 5,6,7-trisubstituted indolizines (Fig. 1) were synthesized by Knoevenagel condensation of **1** with various 1,3-dicarbonyl compounds or malononitrile [4]. Alkynes, another two-atom unit, could also afford indolizine derivatives by Michael addition of **1**, while the same strategy with alkenes provided the dihydroindolizines [5]. When chloro-substituted cyclopropyl derivatives were applied, pyrrolo[1,2-*a*]azepin derivatives were obtained with a newly built seven-membered ring through a [4 + 3] annulation reaction, and the four-atom unit (β, γ) of substrates **1** served as donor-acceptor sites [6]. Derivatives of another fused five- and seven-membered pyrrolotriazepine were formed by hydrazinium and the five-atom unit (α, γ) of substrates **1** [7]. Monoamination of the dicarbonyl (α, γ) of **1** provided dehydrated cyclization products of pyrrolo[1,2-*a*]pyrazines by reacting with ammonium chloride [8].

These intermolecular reactions usually took place between the β/γ or α/γ sites of **1** and other different kinds of reagents. However, there is also an underrated two-atom unit between α and β positions in substrates **1**, which gives good opportunity to build six-membered blocks with four-atom unit of other reactants, or even themselves. Intrigued by this, we report herein the intramolecular or intermolecular reactions of **1** (Fig. 1). Aldol cyclization of two molecules of N-substituted pyrrole-2-carbaldehydes (**1a**) at corresponding β/γ and α/β sites afforded indolizine derivatives while intramolecular cyclization of N-substituted pyrrole-2-carbonitriles (**1b**) at α and γ sites gave the products of pyrrolo[1,2-*a*]pyrazin-1(2*H*)-ones. Furthermore, We also present an interesting example showing the synthetic capacity of the indolizine product originating from **1a**. Novel highly fused pyrrolo[1′,2′:1,6]pyrazino[2,3-g]indolizines were synthesized by one-step reaction from **2a**.

2. Results and discussion

Initially, we chose 1-(2-oxo-2-phenylethyl)-1*H*-pyrrole-2-carbaldehyde **1a-1** as the substrate to optimize the reaction

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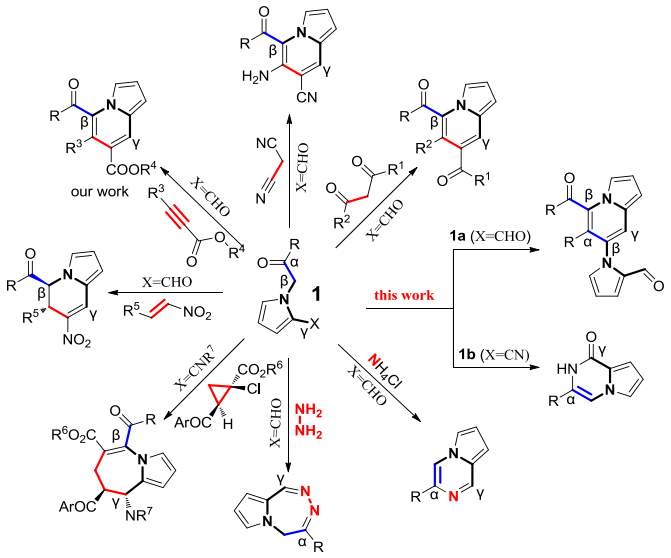
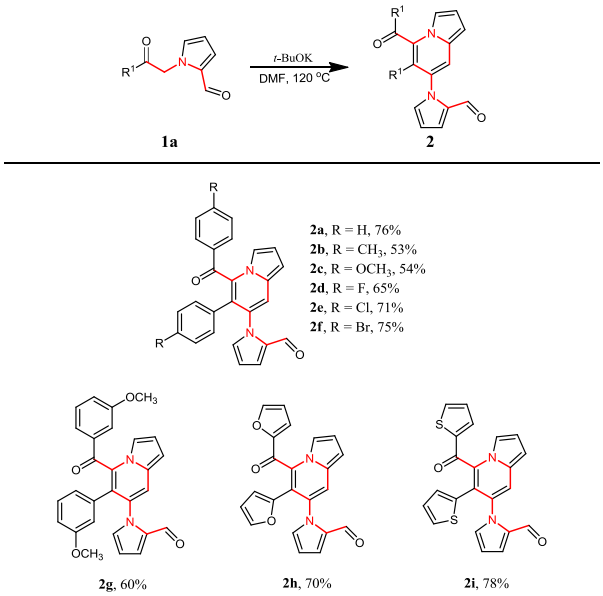


Fig. 1. Substrates **1** for N-containing heterocycles.

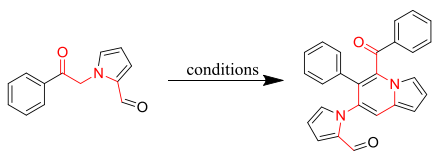


Scheme 1. Scope of intermolecular aldol cyclization of N-substituted pyrrole-2-carbaldehydes. Reaction Conditions: **1a** (0.2 mmol, 1.0 equiv.), *t*-BuOK (0.24 mmol, 1.2 equiv.), 2.0 ml of DMF, 120 °C, 12 h.

conditions. We tested several kinds of solvents at 80 °C in the presence of K_2CO_3, and the results indicated that DMF was the most favorable solvent to give product **2a** (Table 1, entries 1–6). Next, both organic and inorganic base were tested, revealing that the yield increased with the enhancement of alkalinity, and *t*-BuOK was identified as the most favorable base (Table 1, entries 6–10). A notable increase of the reaction yield of **2a** was observed when the temperature was increased from 40 to 120 °C (Table 1, 44–76%, entries 8, 11 and 12).

With the optimized conditions in hand, various substrates of **1a** were employed for the preparation of **2** under the optimized conditions (Scheme 1). The result demonstrated that substrates with electron-donating groups on the phenyl ring had lower yields (**2b**, **2c** and **2g**, 53–60%) than electron-withdrawing groups (**2d**–**2f**, 65–75%). But the electron-rich five-membered substrates with furanyl and thiophenyl gave the most impressive transformation (70% and 78% for **2h** and **2i**). Complex mixture were observed when methyl-, *t*-butyl-, cyclo-propyl- and *o*-mehthoxyl-phenyl were used as the substituents.

Table 1
Optimization of intermolecular aldol cyclization conditions.[a]



1a-1 **2a**

entry	base	solvent	temp (°C)	yield[b] (%)
1	K_2CO_3	toluene	80	0
2	K_2CO_3	CH_3CN	80	0
3	K_2CO_3	EtOH	80	59
4	K_2CO_3	CH_2Cl_2	80	0
5	K_2CO_3	THF	80	0
6	K_2CO_3	DMF	80	62
7	$NaHCO_3$	DMF	80	15
8	*t*-BuOK	DMF	80	64
9	Et_3N	DMF	80	0
10	DBU	DMF	80	26
11	*t*-BuOK	DMF	40	44
12	***t*-BuOK**	**DMF**	**120**	**76**

It's the most optimized reaction condition which is also used in the reaction for compounds preparation.

[a] Reaction Conditions: 1-(2-oxo-2-phenylethyl)-1*H*-pyrrole-2-carbaldehyde (0.2 mmol, 1.0 equiv.), base (0.24 mmol, 1.2 equiv.), 2.0 ml of solvent, 12 h.

[b] Isolated yield.

After the reactive activities of **1a** were fully studied, we tested 1-(2-oxo-2-phenylethyl)-1*H*-pyrrole-2-carbonitriles (**1b-1**) at the same condition. Interestingly, **3a** was found as the product which was completely different from **2**. To find the optimal condition for the intramolecular preparation of **3a**, different reaction conditions were examined based on **1b-1**. Initially, *t*-BuOK was chosen as the base to optimize the reaction solvents, and the results showed that toluene was the best solvent to afford an impressive 98% yield of **4a** (Table 2, entries 1–6). Various bases were tested next, and *t*-BuOK was still found to be the most favorable one (Table 2, entries 1 and 7–10). Significant improvement in the reaction yield was observed when the temperature was increased from 20 to 80 °C (Table 2, 45–98%, entries 1, 11 and 12). However, further increase of temperature resulted in a slight decrease in the yield (Table 2, entry 13). As in the transformation of **1a** to **2** (Scheme 1), solvent selection is also crucial in a successful conversion of **1b** to **3**. Non-polar solvents are preferable in this reaction, while polar solvents, such as DMF, barely gave any of the desired product **3**, in contrast to the conversion of **1a** to **2**. It was shown that the best isolated yield of **3a** (98%) from **1b-1** was obtained in toluene at 80 °C in the presence of *t*-BuOK.

Under the above optimized conditions, different substitutions of **1b** were tested for the scope of this cyclization. In general, a wide variety of groups was tolerated with impressive isolated yields (Scheme 3, 82–98%). Electron-withdrawing groups (such as –F, –Cl and –Br) on a phenyl ring delivered the annulated products (**3d**–**3f**, 92–95%) in better yields than electron-donating groups (**3b**–**3c**, 89–91%). The cyclization also accepted substrates that contained methoxyl at *ortho*-, *meta*- and *para*-positions on the phenyl ring with similar yields (**3c** and **3g**–**3h**, 87–90%). Electron-rich alkyl, furanyl and thiophenyl groups gave relatively lower yields (**3i**–**3m**,

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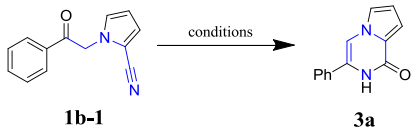
Table 2
Optimization of intramolecular cyclization conditions.[a]



entry	base	solvent	temp (°C)	yield[b] (%)
1	***t*-BuOK**	**toluene**	**80**	**98**
2	*t*-BuOK	CH_3CN	80	32
3	*t*-BuOK	EtOH	80	44
4	*t*-BuOK	CH_2Cl_2	80	83
5	*t*-BuOK	THF	80	24
6	*t*-BuOK	DMF	80	0
7	$NaHCO_3$	toluene	80	0
8	K_2CO_3	toluene	80	0
9	Et_3N	toluene	80	0
10	DBU	toluene	80	0
11	*t*-BuOK	toluene	20	45
12	*t*-BuOK	toluene	40	67
13	*t*-BuOK	toluene	120	86

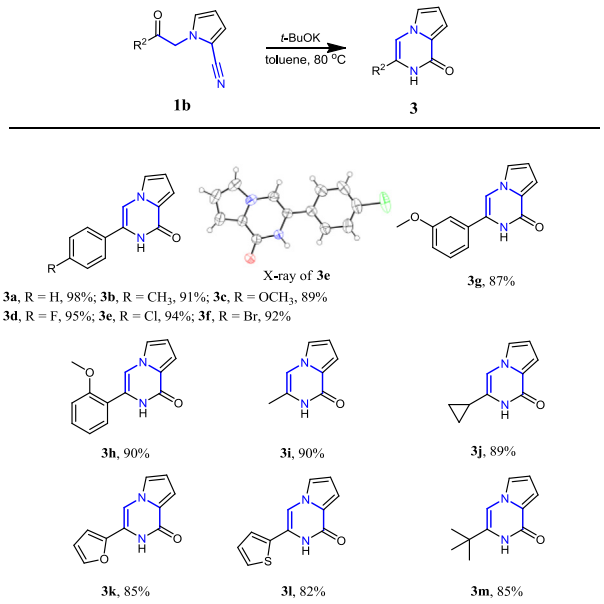
It's the most optimized reaction condition which is also used in the reaction for compounds preparation.

[a] Reaction Conditions: 1-(2-oxo-2-phenylethyl)-1*H*-pyrrole-2-carbonitrile (0.2 mmol, 1.0 equiv.), base (0.24 mmol, 1.2 equiv.), 2.0 ml of solvent, 12 h.

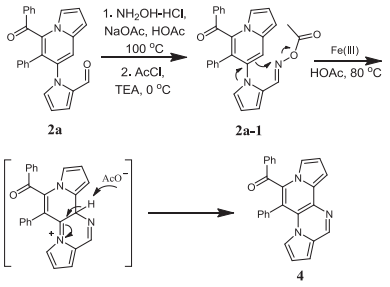
[b] Isolated yield.

82–90%). The structure of compound **3** was confirmed by single crystal X-ray diffraction using **3e** (Scheme 2) as an example. In comparison with previously reported methods [9], we have developed a one-step, facile and efficient approach to provide 3-substituted pyrrolo[1,2-*a*]pyrazin-1(2*H*)-ones **3** with extraordinarily high yields.

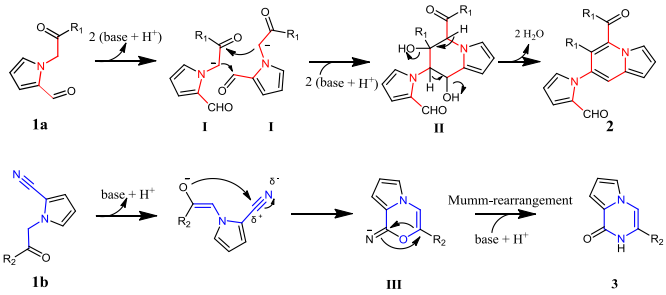
Meanwhile, product **2** from **1a**, possessing a free reactive aldehyde group and an interesting indolizine structure [10], can be readily harnessed for further synthetic manipulation to **4** (Scheme 3). The *O*-acetyl oxime from aldehyde group was used as a directing group and the following acidic cleavage of N–O bond and formation of C–N bond spontaneously afforded the conjugate product **4**. The isolated yield increased from 52% to 74% when Fe(III) participated in this transformation by enhancing deacetylation.



Scheme 2. Scope of intramolecular cyclization by N-substituted pyrrole-2-carbonitriles. Reaction Conditions: **1b** (0.2 mmol, 1.0 equiv.), *t*-BuOK (0.24 mmol, 1.2 equiv.), 2.0 ml of toluene, 80 °C, 12 h.



Scheme 3. Further functionalization of **2a**.



Scheme 4. Possible mechanism for the reactions.

As shown in Scheme 4, possible mechanisms of these reactions were proposed. Formation of **II** can be visualized as an intermolecular aldol condensation of two molecules of intermediate **I** in the presence of base. One molecule of **I** provides a two-carbon unit of methylene and carbonyl groups and the other provides methylene and aldehyde groups as a four-atom unit. Subsequent dehydration of the intermediate **II** affords product **2**. The oxygen anion from enol intermediates of **1b** attacked cyano to give O-alkyl imidate **III** which could rearrange in a type of Mumm-rearrangement to compounds **3**.

3. Conclusions

In summary, we have developed facile and atom-efficient routes to prepare two types of N-containing heterocycles by intramolecular or intermolecular annulations of N-substituted pyrrole-2-carbaldehydes and pyrrole-2-carbonitriles. These two substrates, having very similar potential electrophilic and nucleophilic sites, provided two-atom or four-atom units as structural elements for these syntheses. Aldol cyclization plays the key role in the intermolecular reaction of pyrrole-2-carbaldehydes to indolizines, while intramolecular reaction to pyrrolo[1,2-*a*]pyrazin-1(2*H*)-one derivatives was facilitated by Mumm-rearrangement. Due to the remaining reactive aldehyde group originating from pyrrole-2-carbaldehydes, we also had a chance to further functionalize the indolizine product. The results described herein give further insights to the property of the highly versatile synthons N-substituted pyrroles **1** providing an excellent opportunity to construct diversified heterocycles.

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4. Experimental section

4.1. General

Unless otherwise noted, materials were purchased from commercial suppliers and used without further purification. All the solvents were treated according to general methods. Analytical thin layer chromatography (TLC) was performed on Merck precoated silica gel 60 F_{254}. Visualization on TLC was achieved by the use of UV light (254 nm). Solvents mixtures were understood as volume/volume. Purifications of reaction products were carried out by chromatography using silica gel (200–300 mesh). Melting points were determined with a SGW X-4 digital melting point apparatus, and the thermometer was uncorrected. NMR spectra were mostly recorded for ^{1}H NMR at 500 MHz and for ^{13}C NMR at 125 MHz. For ^{1}H NMR, tetramethylsilane (TMS) served as internal standard (δ). The spectra data presented here are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), and coupling constant (s) in Hertz. For ^{13}C NMR TMS ($\delta = 0$), $CDCl_3$ ($\delta = 77.05$) or DMSO-d_6 ($\delta = 39.99$) was used as internal standard and spectra were obtained with complete proton decoupling. HRMS were obtained using ESI ionization.

4.2. General procedure for systhesis of **2**

A mixture of *N*-substituted pyrrole-2-carbaldehyde **1a** (0.2 mmol, 1.0 equiv.), t-BuOK (0.24 mmol, 1.2 equiv.) was stirred in 2.0 mL DMF at 120 °C under N_2. After being stirred for 12 h, the reaction was quenched by 2.0 mL water. The mixture was extracted with EtOAc (3 × 4.0 mL) and the organic layer was dried over anhydrous Na_2SO_4. The concentrated residue was purified by column chromatography on silica gel to provide the desired product **2**.

4.2.1. 1-(5-Benzoyl-6-phenylindolizin-7-yl)-1H-pyrrole-2-carbaldehyde (**2a**)

Following the general procedure, 1-(2-oxo-2-phenylethyl)-1*H*-pyrrole-2-carbaldehyde **1a-1** (42.6 mg, 0.2 mmol) was used. Purification via column chromatography on silica gel (hexane:EtOAc = 15:1, $R_f = 0.5$) afforded **2a** as yellow solid (31.1 mg, 76% yield). Mp: 112–114 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.38 (1H, s), 7.74 (2H, dd, $J = 8.0$, 1.0 Hz), 7.56 (1H, s), 7.47 (1H, tt, $J = 7.0$, 1.0 Hz), 7.31 (2H, t, $J = 8.0$ Hz), 7.20 (1H, d, $J = 2.5$ Hz), 7.00 (1H, tt, $J = 7.0$, 1.5 Hz), 6.93 (2H, t, $J = 7.5$ Hz), 6.89 (2H, dd, $J = 8.0$, 1.0 Hz), 6.87 (1H, dd, $J = 4.0$, 1.5 Hz), 6.86 (1H, dd, $J = 4.0$, 3.0 Hz), 6.81 (1H, dd, $J = 4.0$, 1.5 Hz), 6.67 (1H, dd, $J = 4.0$, 1.0 Hz), 6.18 (1H, dd, $J = 4.0$, 2.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 191.8, 178.8, 135.8, 134.3, 133.5, 132.8, 132.0, 131.6, 130.0, 129.5, 128.8, 127.8, 127.7, 122.9, 118.3, 115.8, 113.5, 110.5, 102.2; HRMS Calcd. for $C_{26}H_{18}N_2O_2 + H^+$: 391.1447, found: 391.1448.

4.2.2. 1-(5-(4-Methylbenzoyl)-6-(p-tolyl)indolizin-7-yl)-1H-pyrrole-2-carbaldehyde (**2b**)

Following the general procedure, 1-(2-oxo-2-(*p*-tolyl)ethyl)-1*H*-pyrrole-2-carbaldehyde **1a-2** (45.4 mg, 0.2 mmol) was used. Purification via column chromatography on silica gel (hexane:EtOAc = 15:1, $R_f = 0.5$) afforded **2b** as yellow solid (23.1 mg, 53% yield). Mp: 108–110 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.39 (1H, s), 7.67 (2H, d, $J = 8.5$ Hz), 7.53 (1H, s), 7.14 (2H, d, $J = 8.0$ Hz), 7.10 (1H, m), 6.88 (1H, m), 6.83 (1H, dd, $J = 4.5$, 2.0 Hz), 6.82 (1H, d, $J = 4.0$, 3.0 Hz), 6.78 (2H, d, $J = 8.5$ Hz), 6.74 (2H, d, $J = 8.0$ Hz), 6.64 (1H, dd, $J = 4.0$, 1.5 Hz), 6.19 (1H, dd, $J = 4.0$, 2.5 Hz), 2.35 (3H, s), 2.12 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 191.1, 178.7, 145.5, 137.4, 133.4, 133.2, 131.9, 131.8, 131.5, 129.7, 129.6, 129.6, 129.0, 128.4, 122.3, 117.9, 115.6, 113.3, 110.3, 101.9, 21.8, 21.1; HRMS Calcd. for $C_{28}H_{22}N_2O_2 + H^+$: 419.1760, found: 419.1753.

4.2.3. 1-(5-(4-Methoxybenzoyl)-6-(4-methoxyphenyl)indolizin-7-yl)-1H-pyrrole-2-carbaldehyde (**2c**)

Following the general procedure, 1-(2-(4-methoxyphenyl)-2-oxoethyl)-1*H*-pyrrole-2-carbaldehyde **1a-3** (48.6 mg, 0.2 mmol) was used. Purification via column chromatography on silica gel (hexane:EtOAc = 15:1, $R_f = 0.5$) afforded **2c** as yellow solid (23.1 mg, 54% yield). Mp: 118–120 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.39 (1H, s), 7.76 (2H, d, $J = 9.0$ Hz), 7.51 (1H, s), 7.13 (1H, d, $J = 2.0$ Hz), 6.88 (1H, m), 6.83 (5H, m), 6.80 (1H, s), 6.64 (1H, d, $J = 4.0$ Hz), 6.49 (2H, d, $J = 8.5$ Hz), 6.20 (1H, dd, $J = 3.5$, 2.5 Hz), 3.81 (3H, s), 3.63 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 190.0, 178.7, 164.6, 159.0, 133.5, 132.1, 132.0, 131.9, 131.5, 131.0, 129.2, 128.7, 125.1, 121.8, 117.8, 115.6, 114.2, 113.3, 110.4, 101.9, 55.5, 54.9; HRMS Calcd. for $C_{28}H_{22}N_2O_4 + H^+$: 451.1658, found: 451.1653.

4.2.4. 1-(5-(4-Fluorobenzoyl)-6-(4-fluorophenyl)indolizin-7-yl)-1H-pyrrole-2-carbaldehyde (**2d**)

Following the general procedure, 1-(2-(4-fluorophenyl)-2-oxoethyl)-1*H*-pyrrole-2-carbaldehyde **1a-4** (46.2 mg, 0.2 mmol) was used. Purification via column chromatography on silica gel (hexane:EtOAc = 15:1, $R_f = 0.5$) afforded **2d** as yellow solid (28.9 mg, 65% yield). Mp: 120–122 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.37 (1H, s), 7.78 (2H, ddd, $J = 9.0$, 5.5, 1.5 Hz), 7.54 (1H, s), 7.18 (1H, m), 7.00 (2H, td, $J = 9.0$, 2.0 Hz), 6.86 (4H, m), 6.83 (1H, dd, $J = 4.0$, 1.5 Hz), 6.68 (1H, dd, $J = 4.0$, 0.5 Hz), 6.66 (2H, t, $J = 9.0$ Hz), 6.21 (1H, dd, $J = 4.0$, 2.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 190.0, 178.7, 164.4 (d, $J = 256.6$ Hz), 162.2 (d, $J = 256.6$ Hz), 133.5, 132.3 (d, $J = 9.6$ Hz), 132.2 (d, $J = 2.9$ Hz), 132.0, 131.6, 131.4, 128.9, 128.7(d, $J = 3.3$ Hz), 121.9, 118.3, 116.3, 116.1, 116.0, 115.0, 114.8, 113.5, 110.6, 102.5; HRMS Calcd. for $C_{26}H_{16}F_2N_2O_2 + H^+$: 427.1258, found: 427.1254.

4.2.5. 1-(5-(4-Chlorobenzoyl)-6-(4-chlorophenyl)indolizin-7-yl)-1H-pyrrole-2-carbaldehyde (**2e**)

Following the general procedure, 1-(2-(4-chlorophenyl)-2-oxoethyl)-1*H*-pyrrole-2-carbaldehyde **1a-5** (55.4 mg, 0.2 mmol) was used. Purification via column chromatography on silica gel (hexane:EtOAc = 15:1, $R_f = 0.5$) afforded **2e** as yellow solid (38.0 mg, 71% yield). Mp: 132–134 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.36 (1H, s), 7.69 (2H, dd, $J = 7.0$, 2.0 Hz), 7.53 (1H, s), 7.32 (2H, t, $J = 8.5$ Hz), 7.14 (1H, m), 6.94 (2H, d, $J = 8.5$ Hz), 6.89 (1H, m), 6.86 (1H, d, $J = 4.0$, 2.5 Hz), 6.83 (1H, dd, $J = 3.5$, 2.0 Hz), 6.82 (2H, d, $J = 7.0$ Hz), 6.68 (1H, dd, $J = 4.0$, 1.0 Hz), 6.22 (1H, dd, $J = 4.0$, 2.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 190.2, 178.6, 141.1, 134.2, 134.1, 133.5, 132.0, 131.6, 131.3, 131.2, 130.8, 129.4, 128.8, 128.0, 123.1, 121.9, 118.4, 116.1, 113.5, 110.7, 102.6; HRMS Calcd. for $C_{26}H_{16}Cl_2N_2O_2 + H^+$: 459.0667, found: 459.0665.

4.2.6. 1-(5-(4-Bromobenzoyl)-6-(4-bromophenyl)indolizin-7-yl)-1H-pyrrole-2-carbaldehyde (**2f**)

Following the general procedure, 1-(2-(4-bromophenyl)-2-oxoethyl)-1*H*-pyrrole-2-carbaldehyde **1a-6** (58.0 mg, 0.2 mmol) was used. Purification via column chromatography on silica gel (hexane:EtOAc = 15:1, $R_f = 0.5$) afforded **2f** as yellow solid (42.2 mg, 75% yield). Mp: 138–140 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.36 (1H, s), 7.61 (2H, d, $J = 8.5$ Hz), 7.53 (1H, s), 7.50 (2H, d, $J = 8.5$ Hz), 7.12 (1H, d, $J = 2.5$ Hz), 7.10 (2H, d, $J = 8.5$ Hz), 6.89 (1H, m), 6.87 (1H, dd, $J = 4.0$, 3.0 Hz), 6.83 (1H, dd, $J = 4.5$, 1.5 Hz), 6.75 (2H, d, $J = 8.5$ Hz), 6.68 (1H, d, $J = 3.5$ Hz), 6.23 (1H, dd, $J = 4.0$, 2.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 190.4, 178.7, 134.4, 133.4, 132.4, 132.0, 131.7, 131.6, 131.5, 131.1, 131.0, 130.9, 130.2, 130.0, 128.8, 122.5, 122.0, 118.4, 116.1, 113.5, 110.7, 102.6; HRMS Calcd. for $C_{26}H_{16}Br_2N_2O_2 + H^+$: 546.9657, found: 546.9653.

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*4.2.7. 1-(5-(3-Methoxybenzoyl)-6-(3-methoxyphenyl)indolizin-7-yl)-1H-pyrrole-2-carbaldehyde (**2g**)*

Following the general procedure, 1-(2-(3-methoxyphenyl)-2-oxoethyl)-1*H*-pyrrole-2-carbaldehyde **1a-7** (48.6 mg, 0.2 mmol) was used. Purification via column chromatography on silica gel (hexate:EtOAc = 15:1, R_f = 0.5) afforded **2g** as yellow solid (28.1 mg, 60% yield). Mp: 115–117 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.40 (1H, s), 7.54 (1H, s), 7.33 (2H, dt, *J* = 8.5, 0.5 Hz), 7.22 (2H, m), 7.03 (1H, ddd, *J* = 8.5, 3.0, 1.0 Hz), 6.86 (4H, m), 6.67 (1H, dd, *J* = 4.0, 1.0 Hz), 6.56 (1H, ddd, *J* = 8.5, 2.5, 0.5 Hz), 6.52 (1H, dt, *J* = 7.5, 1.0 Hz), 6.42 (1H, t, *J* = 0.5 Hz), 6.21 (1H, dd, *J* = 4.0, 3.0 Hz), 3.78 (3H, s), 3.50 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 191.0, 178.2, 170.7, 159.3, 158.2, 136.7, 133.6, 133.1, 131.6, 131.1, 131.1, 129.4, 128.3, 128.3, 122.2, 122.2, 122.1, 120.8, 117.8, 115.4, 114.1, 113.0, 112.3, 110.1, 101.7, 55.0, 54.5; HRMS Calcd. for $C_{28}H_{22}N_2O_4 + H^+$: 451.1658, found: 451.1655.

*4.2.8. 1-(5-(Furan-2-carbonyl)-6-(furan-2-yl)indolizin-7-yl)-1H-pyrrole-2-carbaldehyde (**2h**)*

Following the general procedure, 1-(2-(furan-2-yl)-2-oxoethyl)-1*H*-pyrrole-2-carbaldehyde **1a-8** (40.6 mg, 0.2 mmol) was used. Purification via column chromatography on silica gel (hexane:EtOAc = 15:1, R_f = 0.5) afforded **2h** as yellow solid (27.2 mg, 70% yield). Mp: 114–116 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.50 (1H, s), 7.57 (1H, d, *J* = 1.0 Hz), 7.51 (1H, s), 7.50 (1H, dd, *J* = 2.5, 1.0 Hz), 7.07 (2H, dd, *J* = 3.0, 0.5 Hz), 7.03 (1H, dd, *J* = 4.0, 1.5 Hz), 6.94 (1H, m), 6.89 (1H, d, *J* = 4.0, 2.0 Hz), 6.66 (1H, dd, *J* = 4.0, 1.0 Hz), 6.39 (1H, dd, *J* = 3.5, 1.5 Hz), 6.33 (1H, dd, *J* = 4.0, 2.5 Hz), 6.06 (1H, dd, *J* = 4.0, 1.5 Hz), 5.72 (1H, d, *J* = 3.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 178.6, 177.8, 151.7, 148.6, 145.8, 143.3, 133.8, 131.6, 131.3, 130.3, 127.1, 121.9, 121.5, 119.5, 116.2, 114.2, 114.1, 112.6, 111.5, 111.2, 110.7, 103.1; HRMS Calcd. for $C_{22}H_{14}N_2O_4 + H^+$: 371.1032, found: 371.1048.

*4.2.9. 1-(6-(Thiophen-2-yl)-5-(thiophene-2-carbonyl)indolizin-7-yl)-1H-pyrrole-2-carbaldehyde (**2i**)*

Following the general procedure, 1-(2-oxo-2-(thiophen-2-yl) ethyl)-1*H*-pyrrole-2-carbaldehyde **1a-9** (43.8 mg, 0.2 mmol) was used. Purification via column chromatography on silica gel (hexane:EtOAc = 15:1, R_f = 0.5) afforded **2i** as yellow solid (32.8 mg, 78% yield). Mp: 118–120 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.48 (1H, s), 7.65 (1H, dd, *J* = 5.0, 1.0 Hz), 7.55 (1H, d, *J* = 2.0 Hz), 7.52 (1H, s), 7.34 (1H, m), 7.07 (1H, dd, *J* = 5.5, 1.5 Hz), 6.97 (1H, dd, *J* = 5.0, 4.0 Hz), 6.95 (1H, d, *J* = 4.0, 1.5 Hz), 6.89 (2H, dd, *J* = 4.0, 3.0 Hz), 6.78 (1H, dd, *J* = 3.5, 1.0 Hz), 6.68 (1H, dd, *J* = 5.0, 3.5 Hz), 6.67 (1H, dd, *J* = 4.0, 1.5 Hz), 6.27 (1H, d, *J* = 4.0, 3.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 183.4, 178.7, 142.7, 136.5, 136.0, 134.1, 133.6, 132.1, 132.0, 131.5, 130.4, 128.4, 128.3, 126.4, 118.6, 116.1, 115.9, 113.8, 110.7, 102.7; HRMS Calcd. for $C_{22}H_{14}N_2O_2S_2 + H^+$: 403.0575, found: 403.0572.

4.3. General procedure for systhesis of 3

A mixture of N-substituted pyrrole-2-carbonitrile **1b** (0.2 mmol, 1.0 equiv.), t-BuOK (0.24 mmol, 1.2 equiv.) was stirred in 2.0 mL toluene at 80 °C. After being stirred for 12 h, $CHCl_3$ (4.0 mL) was added to the mixture and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel ($CHCl_3$:CH_3OH = 20:1) to provide the desired product **3**.

*4.3.1. 3-Phenylpyrrolo[1,2-a]pyrazin-1(2H)-one (**3a**)*

Following the general procedure, 1-(2-oxo-2-(*p*-tolyl)ethyl)-1*H*-pyrrole-2-carbonitrile **1b-1** (42.0 mg, 0.2 mmol) was used. Purification via column chromatography on silica gel ($CHCl_3$:CH_3OH = 20:1, R_f = 0.7) afforded **3a** as white solid (41.2 mg, 98% yield). Mp: 151–153 °C. ^{1}H NMR (500 MHz, DMSO): δ 9.05 (1H, s), 7.57 (2H, dt, *J* = 8.5, 1.5 Hz), 7.48 (2H, tt, *J* = 8.5, 1.0 Hz), 7.42 (1H, tt, *J* = 8.5, 1.5 Hz), 7.21 (1H, dd, *J* = 2.5, 1.0 Hz), 7.16 (1H, ddd, *J* = 4.0, 1.5, 1.0 Hz), 6.61 (1H, dd, *J* = 4.0, 2.5 Hz); ^{13}C NMR (125 MHz, DMSO): δ 156.8, 138.6, 129.8, 127.0, 126.3, 123.3, 120.0, 112.6, 109.4, 105.6; HRMS Calcd. for $C_{13}H_{10}N_2O$ + H+: 211.0871, found: 211.0873.

*4.3.2. 3-(p-Tolyl)pyrrolo[1,2-a]pyrazin-1(2H)-one (**3b**)*

Following the general procedure, 1-(2-oxo-2-(*p*-tolyl)ethyl)-1*H*-pyrrole-2-carbonitrile **1b-2** (44.8 mg, 0.2 mmol) was used. Purification via column chromatography on silica gel ($CHCl_3$:CH_3OH = 20:1, R_f = 0.7) afforded **3b** as white solid (40.8 mg, 91% yield). Mp: 189–191 °C. ^{1}H NMR (500 MHz, DMSO): δ 10.74 (1H, s), 7.70 (1H, s), 7.56 (2H, d, *J* = 8.0 Hz), 7.50 (1H, dd, *J* = 2.5, 1.5 Hz), 7.26 (2H, d, *J* = 8.0 Hz), 6.90 (1H, dd, *J* = 4.0, 2.0 Hz), 6.56 (1H, dd, *J* = 3.5, 2.5 Hz), 2.34 (3H, s); ^{13}C NMR (125 MHz, DMSO): δ 156.8, 138.6, 129.8, 127.0, 126.3, 123.3, 120.0, 112.6, 109.4, 105.6, 21.2; HRMS Calcd. for $C_{14}H_{12}N_2O + H^+$: 225.1028, found: 225.1036.

*4.3.3. 3-(4-Methoxyphenyl)pyrrolo[1,2-a]pyrazin-1(2H)-one (**3c**)*

Following the general procedure, 1-(2-(4-methoxyphenyl)-2-oxoethyl)-1*H*-pyrrole-2-carbonitrile **1b-3** (48.0 mg, 0.2 mmol) was used. Purification via column chromatography on silica gel ($CHCl_3$:CH_3OH = 20:1, R_f = 0.7) afforded **3c** as white solid (42.7 mg, 89% yield). Mp: 200–202 °C. ^{1}H NMR (500 MHz, DMSO): δ 10.72 (1H, s), 7.64 (1H, s), 7.60 (2H, dd, *J* = 6.5, 2.0 Hz), 7.43 (1H, dd, *J* = 2.5, 1.5 Hz), 7.02 (2H, dd, *J* = 7.0, 2.0 Hz), 6.89 (1H, dd, *J* = 4.0, 1.0 Hz), 6.56 (1H, dd, *J* = 4.0, 2.5 Hz), 3.34 (3H, s); ^{13}C NMR (125 MHz, DMSO): δ 160.1, 156.8, 127.8, 126.9, 124.9, 123.2, 119.9, 114.6, 112.5, 109.3, 105.1, 55.7; HRMS Calcd. for $C_{14}H_{12}N_2O_2 + H^+$: 241.0977, found: 241.0971.

*4.3.4. 3-(4-Fluorophenyl)pyrrolo[1,2-a]pyrazin-1(2H)-one (**3d**)*

Following the general procedure, 1-(2-(4-fluorophenyl)-2-oxoethyl)-1*H*-pyrrole-2-carbonitrile **1b-4** (45.6 mg, 0.2 mmol) was used. Purification via column chromatography on silica gel ($CHCl_3$:CH_3OH = 20:1, R_f = 0.7) afforded **3d** as white solid (43.3 mg, 95% yield). Mp: 205–207 °C. ^{1}H NMR (500 MHz, DMSO): δ 10.82(1H, s), 7.71 (3H, m), 7.45 (1H, dd, *J* = 2.5, 1.5 Hz), 7.30 (2H, t, *J* = 9.0 Hz), 6.91 (1H, dd, *J* = 3.0, 1.0 Hz), 6.57 (1H, dd, *J* = 4.0, 2.5 Hz); ^{13}C NMR (125 MHz, DMSO): δ 162.7 (d, *J* = 244.5 Hz), 156.8, 129.1 (d, *J* = 3.3 Hz), 128.7 (d, *J* = 8.3 Hz), 126.2, 123.3, 120.2, 116.1 (d, *J* = 21.8 Hz), 112.7, 109.5, 106.2; HRMS Calcd. for $C_{13}H_9FN_2O + H^+$: 229.0777, found: 229.0771.

*4.3.5. 3-(4-Chlorophenyl)pyrrolo[1,2-a]pyrazin-1(2H)-one (**3e**)*

Following the general procedure, 1-(2-(4-chlorophenyl)-2-oxoethyl)-1*H*-pyrrole-2-carbonitrile **1b-5** (48.8 mg, 0.2 mmol) was used. Purification via column chromatography on silica gel ($CHCl_3$:CH_3OH = 20:1, R_f = 0.7) afforded **3e** as white solid (45.9 mg, 94% yield). Mp: 226–227 °C. ^{1}H NMR (500 MHz, DMSO): δ 10.72 (1H, s), 7.78 (1H, s), 7.69 (2H, m), 7.52 (2H, d, *J* = 9.0 Hz), 7.46 (1H, dd, *J* = 2.5, 1.5 Hz), 6.92 (1H, dd, *J* = 3.5, 0.5 Hz), 6.58 (1H, dd, *J* = 4.0, 2.5 Hz); ^{13}C NMR (125 MHz, DMSO): δ 156.7, 133.7, 131.5, 129.2, 128.2, 126.0, 123.3, 120.3, 112.8, 109.6, 106.6; HRMS Calcd. for $C_{13}H_9ClN_2O + H^+$: 245.0482, found: 245.0473.

*4.3.6. 3-(4-Bromophenyl)pyrrolo[1,2-a]pyrazin-1(2H)-one (**3f**)*

Following the general procedure, 1-(2-(4-bromophenyl)-2-oxoethyl)-1*H*-pyrrole-2-carbonitrile **1b-6** (57.6 mg, 0.2 mmol) was used. Purification via column chromatography on silica gel ($CHCl_3$:CH_3OH = 20:1, R_f = 0.7) afforded **3f** as white solid (53.0 mg, 92% yield). Mp: 235–236 °C. ^{1}H NMR (500 MHz, DMSO): δ 10.84 (1H, s), 7.79 (1H, s), 7.64 (4H, m), 7.46 (1H, dd, *J* = 2.5, 1.5 Hz), 6.92 (1H, dd, *J* = 4.0, 1.0 Hz), 6.59 (1H, dd, *J* = 4.0, 2.5 Hz); ^{13}C NMR (125 MHz, DMSO): δ 156.7, 132.1, 131.9, 128.5, 126.0, 123.3, 122.2,

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120.3, 112.9, 109.7, 106.5; HRMS Calcd. for $C_{13}H_9BrN_2O + H^+$: 288.9977, found: 288.9974.

*4.3.7. 3-(3-Methoxyphenyl)pyrrolo[1,2-a]pyrazin-1(2H)-one (**3g**)*

Following the general procedure, 1-(2-(3-methoxyphenyl)-2-oxoethyl)-1*H*-pyrrole-2-carbonitrile **1b-7** (48.0 mg, 0.2 mmol) was used. Purification via column chromatography on silica gel ($CHCl_3$:CH_3OH = 20:1, R_f = 0.7) afforded **3g** as white solid (41.8 mg, 87% yield). Mp: 207–209 °C. ^{1}H NMR (500 MHz, DMSO): δ 10.78 (1H, s), 7.79 (1H, s), 7.46 (1H, dd, *J* = 2.5, 1.5 Hz), 7.36 (1H, t, *J* = 8.0 Hz), 7.25 (2H, m), 6.95 (1H, ddd, *J* = 8.5, 3.0, 0.5 Hz), 6.92 (1H, m), 6.58 (1H, dd, *J* = 4.0, 2.5 Hz), 3.83 (3H, s); ^{13}C NMR (125 MHz, DMSO): δ 160.0, 156.8, 133.9, 130.3, 126.8, 123.4, 120.2, 118.5, 115.1, 112.8, 111.5109.5, 106.3, 55.7; HRMS Calcd. for $C_{14}H_{12}N_2O_2 + H^+$: 241.0977, found: 241.0973.

*4.3.8. 3-(2-Methoxyphenyl)pyrrolo[1,2-a]pyrazin-1(2H)-one (**3h**)*

Following the general procedure, 1-(2-(2-methoxyphenyl)-2-oxoethyl)-1*H*-pyrrole-2-carbonitrile **1b-8** (48.0 mg, 0.2 mmol) was used. Purification via column chromatography on silica gel ($CHCl_3$:CH_3OH = 20:1, R_f = 0.7) afforded **3h** as white solid (43.2 mg, 90% yield). Mp: 204–206 °C. ^{1}H NMR (500 MHz, DMSO): δ 10.49 (1H, s), 7.45 (1H, dd, *J* = 2.0, 1.5 Hz), 7.43 (1H, s), 7.41 (2H, m), 7.12 (1H, d, *J* = 8.0), 7.03 (1H, td, *J* = 7.5, 0.5 Hz), 6.90 (1H, m), 6.56 (1H, dd, *J* = 3.5, 2.5 Hz), 3.82 (3H, s); ^{13}C NMR (125 MHz, DMSO): δ 157.6, 156.3, 130.9, 130.5, 124.8, 123.5, 121.7, 120.8, 119.8, 112.4, 112.0, 109.1, 107.4, 56.0; HRMS Calcd. for $C_{14}H_{12}N_2O_2 + H^+$: 241.0977, found: 241.0975.

*4.3.9. 3-Methylpyrrolo[1,2-a]pyrazin-1(2H)-one (**3i**)*

Following the general procedure, 1-(2-oxopropyl)-1*H*-pyrrole-2-carbonitrile **1b-9** (29.6, mg, 0.2 mmol) was used. Purification via column chromatography on silica gel ($CHCl_3$:CH_3OH = 20:1, R_f = 0.7) afforded **3i** as white solid (42.7 mg, 90% yield). Mp: 201–203 °C. ^{1}H NMR (500 MHz, DMSO): δ 10.44 (1H, s), 7.32 (1H, dd, *J* = 2.5, 1.5 Hz), 7.09 (1H, s), 6.80 (1H, m), 6.46 (1H, dd, *J* = 4.0, 2.5 Hz), 2.01 (3H, d, *J* = 1.0 Hz); ^{13}C NMR (125 MHz, DMSO): δ 156.6, 123.7, 123.3, 119.1, 111.7, 108.8, 104.9, 16.0; HRMS Calcd. for $C_8H_8N_2O + H^+$: 149.0715, found: 149.0710.

*4.3.10. 3-Cyclopropylpyrrolo[1,2-a]pyrazin-1(2H)-one (**3j**)*

Following the general procedure, 1-(2-cyclopropyl-2-oxoethyl)-1*H*-pyrrole-2-carbonitrile **1b-10** (34.8 mg, 0.2 mmol) was used. Purification via column chromatography on silica gel ($CHCl_3$:CH_3OH = 20:1, R_f = 0.7) afforded **3j** as white solid (31.0 mg, 89% yield). Mp: 212–214 °C. ^{1}H NMR (500 MHz, DMSO): δ 10.52 (1H, s), 7.29 (1H, t, *J* = 2.0 Hz), 7.11 (1H, s), 6.80 (1H, m), 6.47 (1H, dd, *J* = 3.5, 2.5 Hz), 1.68 (1H, m), 0.80 (2H, ddd, *J* = 10.5, 4.0, 2.0 Hz), 0.68 (2H, ddd, *J* = 10.5, 3.5, 1.5 Hz); ^{13}C NMR (125 MHz, DMSO): δ 156.6, 129.6, 123.4, 119.2, 111.7, 108.8, 103.7, 11.0, 6.2; HRMS Calcd. for $C_{10}H_{10}N_2O + H^+$: 175.0871, found: 175.0865.

*4.3.11. 3-(Furan-2-yl)pyrrolo[1,2-a]pyrazin-1(2H)-one (**3k**)*

Following the general procedure, 1-(2-(furan-2-yl)-2-oxoethyl)-1*H*-pyrrole-2-carbonitrile **1b-11** (40.0 mg, 0.2 mmol) was used. Purification via column chromatography on silica gel ($CHCl_3$:CH_3OH = 20:1, R_f = 0.7) afforded **3k** as white solid (34.0 mg, 85% yield). Mp: 230–232 °C. ^{1}H NMR (500 MHz, DMSO): δ 10.86 (1H, s), 7.81 (1H, s), 7.77 (1H, d, *J* = 1.0 Hz), 7.54 (1H, dd, *J* = 2.5, 1.5 Hz), 7.14 (1H, d, *J* = 3.0 Hz), 6.92 (1H, m), 6.62 (1H, dd, *J* = 3.5, 2.0 Hz), 6.58 (1H, dd, *J* = 4.0, 2.5 Hz); ^{13}C NMR (125 MHz, DMSO): δ 156.4, 146.2, 143.8, 123.3, 120.8, 119.0, 112.8, 112.3, 110.2, 108.1, 104.2; HRMS Calcd. for $C_{11}H_8N_2O_2 + H^+$: 201.0664, found: 201.0671.

*4.3.12. 3-(Thiophen-2-yl)pyrrolo[1,2-a]pyrazin-1(2H)-one (**3l**)*

Following the general procedure, 1-(2-oxo-2-(thiophen-2-yl) ethyl)-1*H*-pyrrole-2-carbonitrile **1b-12** (33.2 mg, 0.2 mmol) was used. Purification via column chromatography on silica gel ($CHCl_3$:CH_3OH = 20:1, R_f = 0.7) afforded **3l** as white solid (27.2 mg, 82% yield). Mp: 240–242 °C. ^{1}H NMR (500 MHz, DMSO): δ 10.87 (1H, s), 7.77 (1H, d, *J* = 1.0 Hz), 7.62 (1H, dd, *J* = 3.5, 1.0 Hz), 7.56 (1H, dd, *J* = 5.0, 1.0 Hz), 7.50 (1H, dd, *J* = 2.5, 1.5 Hz), 7.13 (1H, dd, *J* = 5.0, 3.5), 6.91 (1H, m), 6.56 (1H, dd, *J* = 4.0, 2.5 Hz); ^{13}C NMR (125 MHz, DMSO): δ 156.4, 134.7, 128.5, 126.3, 126.1, 123.2, 121.9, 120.5, 112.8, 110.0, 105.3; HRMS Calcd. for $C_{11}H_8N_2OS + H^+$: 217.0436, found: 217.0433.

*4.3.13. 3-(tert-Butyl)pyrrolo[1,2-a]pyrazin-1(2H)-one (**3m**)*

Following the general procedure, 1-(3,3-dimethyl-2-oxobutyl)-1*H*-pyrrole-2-carbonitrile **1b-13** (38.0 mg, 0.2 mmol) was used. Purification via column chromatography on silica gel ($CHCl_3$:CH_3OH = 20:1, R_f = 0.7) afforded **3m** as white solid (32.3 mg, 85% yield). Mp: 211–213 °C. ^{1}H NMR (500 MHz, DMSO): δ 10.25 (1H, s), 7.39 (1H, t, *J* = 2.0 Hz), 7.14 (1H, s), 6.80 (1H, dd, *J* = 3.5, 2.5 Hz), 6.49 (1H, dd, *J* = 3.5, 2.5 Hz), 1.25 (9H, s); ^{13}C NMR (125 MHz, DMSO): δ 157.0, 135.5, 123.0, 119.7, 112.0, 108.6, 102.9, 33.3, 28.6; HRMS Calcd. for $C_{11}H_{14}N_2O + H^+$: 191.1184, found: 191.1182.

*4.4. General procedure for systhesis of **4***

To a round-bottom flask (50 mL) was added **2a** (780 mg, 2.0 mmol) in EtOH (15.0 mL), hydroxylamine hydrochloride (276 mg, 4.0 mmol) and NaOAc (328 mg, 4.0 mmol). The mixture was heated at 100 °C for 6 h. After cooling off, the reaction was quenched by water, the mixture was extracted with CH_2Cl_2 (3 × 4.0 mL), the organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure, and then CH_2Cl_2 (15.0 mL) and triethylamine (TEA, 404 mg, 4.0 mmol) were added at 0 °C. A solution of acetyl chloride (360 mg, 4.6 mmol) in CH_2Cl_2 (5.0 mL) was added dropwise to this stirred cooled solution. The reaction mixture was stirred at room temperature for 2 h. After the reaction was quenched by water, the mixture was extracted with CH_2Cl_2 (3 × 10.0 mL), and the combined extracts were washed with saturated $NaHCO_3$ solution (10.0 mL) and brine (10.0 mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane:EtOAc = 10:1, R_f = 0.4) to provide the desired product **2a-1** as red solid (650 mg, 73% yield). To a round-bottom flask (15 mL) was added **2a-1** (447 mg, 1.0 mmol) and $Fe(acac)_3$ (20 mol %) in acetic acid (3.0 mL). The mixture was heated at 80 °C for 4 h. After cooling off, the reaction was quenched by water and neutralized with NaHCO3 (saturated solution), the mixture was extracted with EtOAc (3 × 4.0 mL), the organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The concentrated residue was purified by column chromatography on silica gel (hexene:EtOAc = 10:1, R_f = 0.6) to provide the desired product **4** as yellow solid (286.5 mg, 74% yield). And without $Fe(acac)_3$, the isolated yield was 54%. Mp: 116–118 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.70 (2H, dd, *J* = 7.0, 1.0 Hz), 7.66 (1H, s), 7.46 (1H, t, *J* = 7.5 Hz), 7.30 (2H, t, *J* = 7.5 Hz), 7.24 (1H, m), 7.00 (5H, m), 6.90 (1H, dd, *J* = 4.0, 2.5 Hz), 6.75 (1H, d, *J* = 4.0 Hz), 6.73 (1H, dd, *J* = 4.0, 1.0 Hz), 6.61 (1H, dd, *J* = 2.5, 2.0 Hz), 6.02 (1H, dd, *J* = 4.0, 3.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 191.6, 135.6, 134.4, 132.3, 132.0, 131.3, 130.0, 129.4, 128.9, 128.8, 128.1, 128.0, 127.1, 122.1, 120.6, 119.0, 116.3, 113.9, 113.8, 109.0, 106.1, 103.1; HRMS Calcd. for $C_{26}H_{17}N_3O + H^+$: 388.1450, found: 388.1453.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found in the online version, at https://doi.org/10.1016/j.tet.2018.08.022. These data include MOL files and InChiKeys of the most important compounds described in this article.

References

[1] (a) E. Vitaku, D. Smith, J. Njardarson, J. Med. Chem. 57 (2014) 10257–10274;
b) D. Sucunza, A. Curadro, J. Alvarez-Builla, J. Vaquero, J. Org. Chem. 81 (2016) 10126–10135;
c) J. Homer, J. Sperry, J. Nat. Prod. 80 (2017) 2178–2187;
d) J. Delcamp, A. Yella, W. Holcombe, M. Nazeeruddin, M. Grätzel, Angew Chem. Int. Ed. Engl. 52 (2013) 376–380.

[2] a) J. Lee, I. Kim, J. Org. Chem. 78 (2013) 1283–1288;
b) G. Singh, E. Meatli, Eur. J. Med. Chem. 46 (2011) 5237–5257;
c) M. Kucukdisli, T. Opatz, J. Org. Chem. 78 (2013) 6670–6676;
d) D. Chai, M. Lautens, J. Org. Chem. 74 (2009) 3054–3061.

[3] a) Y. Lee, J. Lee, S. Kim, Y. Lee, Bioorg. Med. Chem. 24 (2016) 2843–2851;
b) M. Bolli, J. Marfurt, C. Grisostomi, C. Boss, C. Binkert, P. Hess, A. Treiber, E. Thorin, K. Morrison, S. Buchmann, D. Bur, H. Ramuz, M. Clozel, W. Fischli, T. Weller, J. Med. Chem. 47 (2004) 2776–2795;
c) I. McDonald, C. Austin, I. Buck, D. Dunstone, E. Griffin, E. Harper, R. Hull, S. Kalindjian, I. Linney, C. Low, M. Pether, J. Spencer, P. Wright, T. Adatia, A. Bashall, J. Med. Chem. 49 (2006) 2253–2261;
d) R. Oslund, N. Cermak, M. Gelb, J. Med. Chem. 51 (2008) 4708–4714;
e) P. Chen, A. Chaikuad, P. Bamborough, M. Bantscheff, C. Bountra, C. Chung, O. Fedorov, P. Grandi, D. Jung, R. Lesniak, M. Lindon, S. Müller, M. Philpott, R. Prinjha, C. Rogers, C. Selenski, C. Tallant, T. Werner, T. Willson, S. Knapp, D. Drenry, J. Med. Chem. 59 (2016) 1410–1424.

[4] a) M. Kim, Y. Jung, I. Kim, J. Org. Chem. 78 (2013) 10395–10404;
b) S. Moon, Y. Jung, S. Kim, I. Kim, Bioorg. Med. Chem. Lett. 26 (2016) 110–113.

[5] a) H. Zhu, J. Stöckigt, Y. Yu, H. Zou, Org. Lett. 13 (2011) 2792–2794;
b) X. Jiang, B. Tan, C. Barbas III, Angew. Chem. Int. Ed. 52 (2013) 9261–9265;
c) W. Zhong, H. Zhu, H. Zou, Tetrahedron 73 (2017) 3181–3187.

[6] J. Hu, Y. Liu, Y. Gong, Adv. Synth. Catal. 357 (2015) 2781–2787.

[7] a) N. Menges, O. Sari, Y. Abdullayev, S. Sag Erdem, M. Balc, J. Org. Chem. 78 (2013) 5184–5195;
b) G. Reddy, P. Kumar, R. Anand, K. Mukkanti, P. Reddy, Synlett 9 (2009) 1463–1465.

[8] S. Park, Y. Jung, I. Kim, Tetrahedron 70 (2014) 7534–7550.

[9] Dieter, D.; HansPeter, N.; Gérard, M.; Ansgar, G. PCT. WO2013143663, Bicyclic Pyrazinone Derivatives. 03, 10, 2013.

[10] Z. Zhang, J. Li, G. Zhang, N. Ma, Q. Liu, T. Liu, J. Org. Chem. 80 (2015) 6875–6884.

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