

Catalyst-free one-pot synthesis of isoindolin-1-imine derivatives via three-component reaction

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Abstract

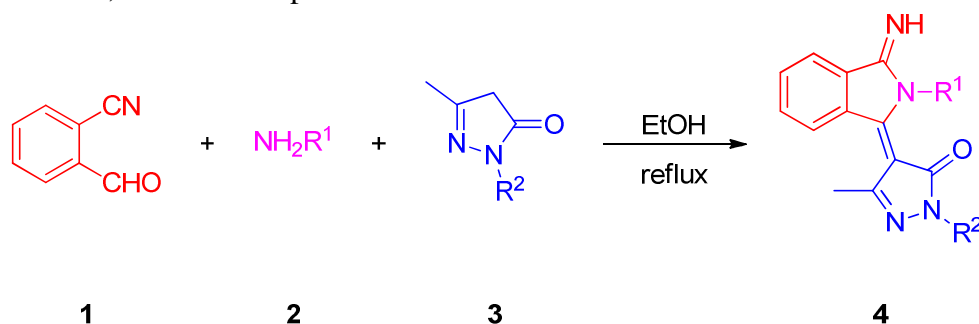
A novel, one-pot method has been developed for the synthesis of 4-(2-substituted-3-iminoisoindolin-1-ylidene)-1-substituted-3-methyl-1*H*-pyrazol-5(4*H*)-one derivatives via cascade three-component condensation of 2-cyanobenzaldehyde, amine, and 3-methyl-1*H*-pyrazol-5(4*H*)-one or 1,3-dimethyl-1*H*-pyrazol-5(4*H*)-one. The efficient and convenient reaction conditions provide the corresponding products from various substrates under reflux condition in ethanol with excellent yields (85-95%).

Keywords: 2-cyanobenzaldehyde, 3-methyl-1*H*-pyrazol-5(4*H*)-one, 1,3-dimethyl-1*H*-pyrazol-5(4*H*)-one, isoindolin-1-imine, multi-component reaction

Introduction

In the last few years, considerable attention has been attracted to the discovery and synthesis of isoindole analogues due to their large significant therapeutic and biological activities.¹⁻⁵ Among them, the class of isoindolin-1-imines has also received much effort due to their biological activities, such as NR2B-selective NMDA receptor antagonists,⁶ thrombin receptor (PAR-1) inhibitors,⁷⁻⁸ and antiproliferative effect.⁹ Many of the existing methods for the synthesis of isoindolin-1-imine analogs are based on nucleophilic addition reactions from substrates that have adjacent formyl or cyano groups on a benzene ring, but these suffer from certain limitations with respect to yields, multistep strategies, or reaction condition.⁶⁻¹³ Very recently, we found that a novel isoindolin-1-imine structure – a 2-substituted 3-alkoxy-isoindolin-1-imine – could be prepared by the three-component reaction of 2-cyanobenzaldehyde, an amine, and an alcohol catalyzed by acetic acid with good yields and wide scope.¹⁴ For further development we turned our attention towards other substrates.

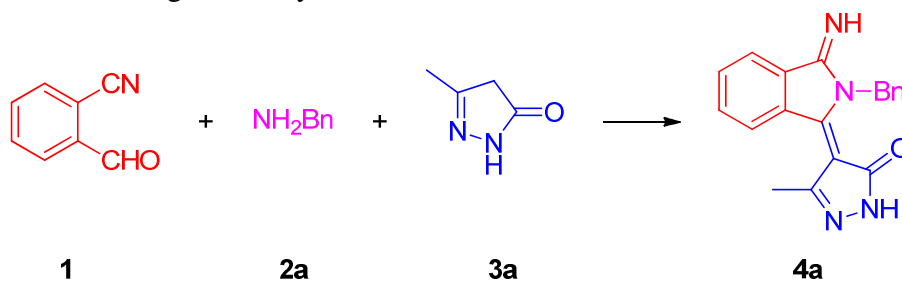
3-Methyl-1*H*-pyrazol-5(4*H*)-one has an active methylene group and can serve as starting scaffold for the synthesis of many different structures with various functional groups.¹⁵⁻¹⁹ In an effort to exploit the potential of 3-methyl-1*H*-pyrazol-5(4*H*)-one for the synthesis of isoindolin-1-imine analogues, we considered it worthwhile to investigate its multi-component condensations with 2-cyanobenzaldehyde and an amine. Herein, we describe a novel, catalyst-free, one-pot procedure for the synthesis of 4-(2-substituted 3-iminoisoindolin-1-ylidene)-1-substituted-3-methyl-1*H*-pyrazol-5(4*H*)-ones via a cascade three-component condensation of 2-cyanobenzaldehyde, an amine, and 3-methyl-1*H*-pyrazol-5(4*H*)-one or 1,3-dimethyl-1*H*-pyrazol-5(4*H*)-one with excellent yields, fast reaction times, and wide scope.



Scheme 1. Synthesis of 4-(2-substituted-3-iminoisoindolin-1-ylidene)-1 substituted-3-methyl-1*H*-pyrazol-5(4*H*)-ones **4**

Results and Discussion

Based on our previous results,¹⁴ we carried out a multi-component reaction of 2-cyanobenzaldehyde **1**, benzylamine **2a**, and 3-methyl-1*H*-pyrazol-5(4*H*)-one **3a** in ethanol. The reaction occurred smoothly under reflux conditions, and we obtained a red solid with the novel structure 4-(2-benzyl-3-iminoisoindolin-1-ylidene)-3-methyl-1*H*-pyrazol-5(4*H*)-one **4a** (Table 1, entry 1). To investigate the solvent effects, the condensation reaction was carried out in different solvents, however the results showed that the product **4a** was afforded with low to moderate yields in MeOH (entry 2), CH₃CN (entry 3), THF (entry 4), DCE (entry 5), and H₂O (entry 6). The reaction was also carried out at room temperature in ethanol, and found that the reaction occurred in 60% yield after 10 h (entry 7). Therefore, the reaction is best carried out in ethanol under reflux, and these conditions were used in further investigations.

Table 1. Solvent screening for the synthesis of **4a**^a

Entry	Solvent	Time (min)	Yield of 4a ^b (%)
1	EtOH	30	90
2	MeOH	30	65
3	CH ₃ CN	30	30
4	THF	30	42
5	DCE	30	22
6	H ₂ O	30	18
7 ^c	EtOH	600	50

^a Conditions: 2-cyanobenzaldehyde (3 mmol), benzylamine **2a** (3 mmol), 3-methyl-1H-pyrazol-5(4H)-one **3a** (3 mmol), solvent (5 mL), reflux.

^b Isolated yields.

^c Conditions: 2-cyanobenzaldehyde (3 mmol), benzylamine **2a** (3 mmol), 3-methyl-1H-pyrazol-5(4H)-one **3a** (3 mmol), ethanol (5 mL), room temperature.

To demonstrate the scope and limitations of the procedure, the condensation of 2-cyanobenzaldehyde **1**, amine **2**, and 3-methyl-1H-pyrazol-5(4H)-one **3a** or 1,3-dimethyl-1H-pyrazol-5(4H)-one **3b** was carried out in ethanol. A series of 4-(2-substituted-3-iminoisoindolin-1-ylidene)-3-methyl-1H-pyrazol-5(4H)-ones **4a-i** and 4-(2-substituted-3-iminoisoindolin-1-ylidene)-1,3-dimethyl-1H-pyrazol-5(4H)-ones **4j-p** were synthesized. The results are summarized in Table 2. The reaction scope of substituted aryl and alkyl amines was explored with 2-cyanobenzaldehyde and 3-methyl-1H-pyrazol-5(4H)-one or 1,3-dimethyl-1H-pyrazol-5(4H)-one. Aryl alkylamines carrying either electron-withdrawing or electron-donating groups (entries 1-5, 10-14) all reacted smoothly to afford the desired products with excellent yields. Heterocyclic alkyl amines (entry 6) also gave the desired isoindolin-1-imine derivatives. Alkyl amines such as *n*-propyl (entry 7), cyclopentyl (entry 8), *i*-butyl (entry 9), *n*-butyl (entry 15), and cyclopropyl (entry 16) appeared not to have a significant impact on the yields compared to others in Table 2. Whereas, only trace amount of desired products were observed when using aniline (entry 17) as substrates under the same reaction condition. Only a trace amount of **4q** (*m/z* 303.41, [M+H]⁺) was detected by LC-MS.

Table 2. Synthesis of isoindole-1-imine analogs product **4**^a

Entry	Product 4	R ¹	R ₂	Yield ^b (%)
1	4a	C ₆ H ₄ CH ₂	H	93
2	4b	4-ClC ₆ H ₄ CH ₂	H	94
3	4c	4-MeOC ₆ H ₄ CH ₂	H	92
4	4d	4-FC ₆ H ₄ (CH ₂) ₂	H	89
5	4e	3,4-(MeO) ₂ C ₆ H ₃ (CH ₂) ₂	H	87
6	4f	2-furylmethyl	H	85
7	4g	<i>n</i> -propyl	H	94
8	4h	cyclopentyl	H	91
9	4i	<i>i</i> -Butyl	H	90
10	4j	C ₆ H ₄ CH ₂	Me	94
11	4k	4-MeOC ₆ H ₄ CH ₂	Me	93
12	4l	4-FC ₆ H ₄ CH ₂	Me	90
13	4m	4-FC ₆ H ₄ (CH ₂) ₂	Me	92
14	4n	3,4-(MeO) ₂ C ₆ H ₃ (CH ₂) ₂	Me	88
15	4o	<i>n</i> -butyl	Me	92
16	4p	cyclopropyl	Me	85
17	4q	C ₆ H ₅	H	trace

^a Conditions: 2-cyanobenzaldehyde (3 mmol), benzylamine **2a** (3 mmol), 3-methyl-1*H*-pyrazol-5(4*H*)-one **3a** (3 mmol) or 1,3-dimethyl-1*H*-pyrazol-5(4*H*)-one **3b**, ethanol (5 mL), reflux for 30 min.

^b Isolated yields.

The novel structures of the isoindolin-1-imine derivatives **4a-p** were established from ¹H and ¹³C spectral data, as illustrated by the representative example **4a**. In its ¹H NMR spectrum, two hydrogen signals at 10.90 (brs) and 10.19 (brs) ppm are ascribed to amide and imine, respectively. The singlets at 4.91 and 2.46 ppm are assigned to H-8 and H-6', respectively. In its ¹³C NMR spectrum, the carbon of carbonyl group C-5' occurs at 169.2 ppm. The carbons of double bond C-3 and C-4 appear at 168.4 and 112.4, respectively. The carbons of imine of C-1 and C-3' occur at 164.2 and 149.5, respectively. The peaks at 46.3, and 18.9 ppm are assigned to C-8, and C-6', respectively.

To further investigate the mechanism of this condensation, several reactions were carried out under the conditions of Scheme 2. Firstly, the condensation of 2-cyanobenzaldehyde **1** and 1,3-dimethyl-1*H*-pyrazol-5(4*H*)-one **3b** was carried out in ethanol at room temperature for one hour, when compound **5b** (*m/z* 226.40, [M+H]⁺) and compound **6b** (*m/z* 338.53, [M+H]⁺) were detected by LC-MS in 5% and 80% conversion yields, respectively. The compound **5b** was perhaps unstable in this reaction system and reacted further with **3b** to give **6b** due to the reactivity of the cyano group. Subsequently, the major product **6b** was purified by

chromatography and was reacted with benzylamine **2a** to investigate whether the three-component condensation corresponding product **4j** could be afforded efficiently. Although the reaction of **6b** and **3b** was carried out in ethanol under reflux condition for five hours, product **4j** was obtained only in a trace amount. Therefore, that major product **6b** could not generate product **4j** smoothly, and perhaps the unstable compound **5b** is the primary intermediate of the condensation for the synthesis of **4j** from 2-cyanobenzaldehyde **1**, benzylamine **2a** and 1,3-dimethyl-1*H*-pyrazol-5(4*H*)-one **3b**.

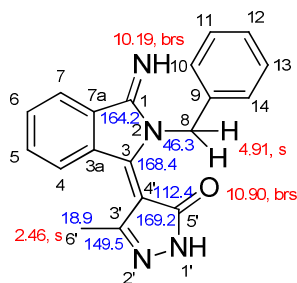
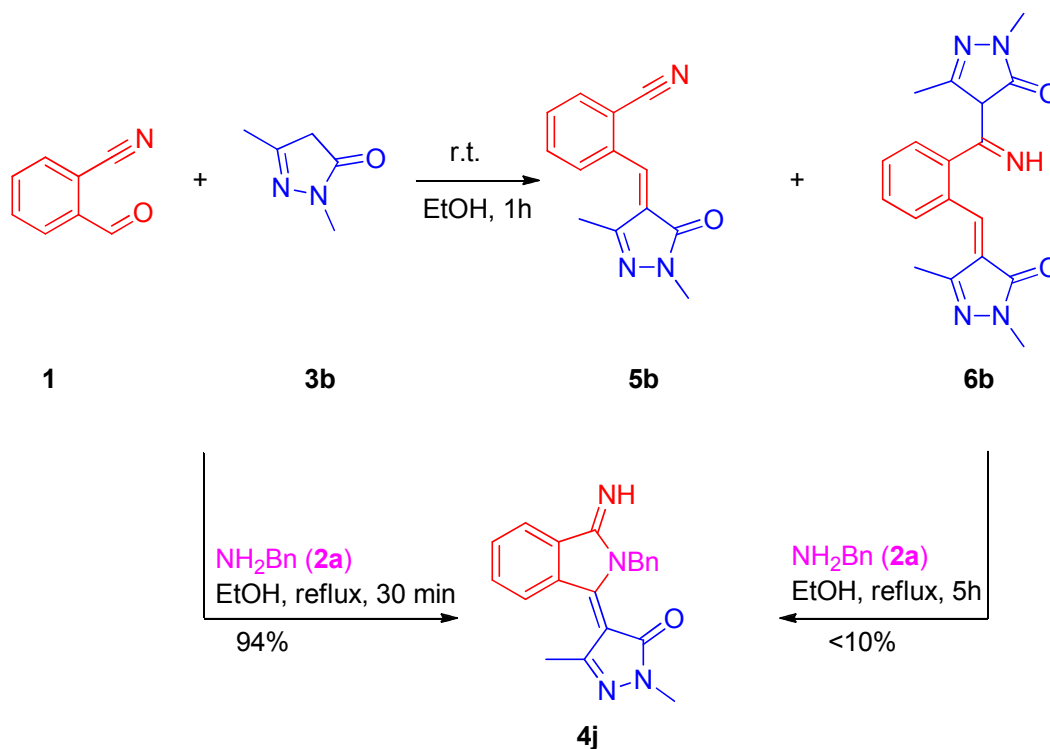
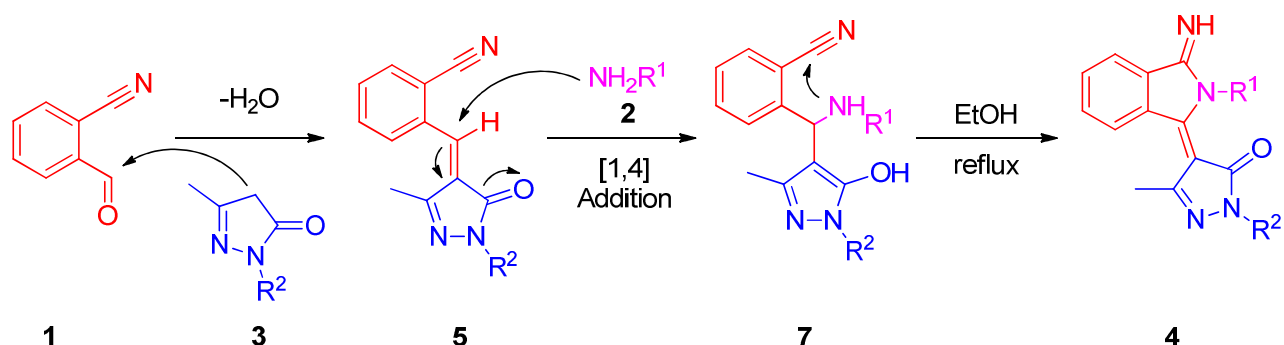


Figure 1. ^1H and ^{13}C NMR assignments for compound **4a**.



Scheme 2

Thus, on the basis of the results obtained, a plausible reaction mechanism can reasonably be proposed for the series of products **4** (Scheme 3). Initially, 2-cyanobenzaldehyde **1** reacts with **3a** or **3b** to produce the Knoevenagel condensation product **5**. Then, the adduct **5** proceeds to unstable intermediate **7** by 1,4-Michael addition with amine **2**. Finally, the intermediate **7** gives the title isoindolin-1-imine **4** via intramolecular cyclization and dehydrogenation reaction under the refluxing ethanol conditions.



Scheme 3. Possible mechanism for the formation of compounds **4**.

Conclusions

In conclusion, we have developed an efficient and convenient method for the preparation of the isoindolin-1-imines **4** via the three-component condensation reaction of 2-cyanobenzaldehyde **1**, amine **2**, and 3-methyl-1*H*-pyrazol-5(4*H*)-one **3a** or 1,3-dimethyl-1*H*-pyrazol-5(4*H*)-one **3b** in ethanol under catalyst-free condition with excellent yields. The straightforward procedure is a valid contribution to the methodology for the synthesis of isoindolin-1-imine derivatives.

Experimental Section

General. Reagents and all solvents were analytically pure grade and were used without further purification. TLC was performed on GF254 silica gel plates (Yantai Huiyou Inc., China). Melting points were determined with a WRS-1B apparatus. ¹H (400 MHz) and ¹³C (100, 125 MHz) NMR spectra were recorded on Bruker AMX 400 spectrometer or Bruker AMX 500 spectrometer using solvent peaks as a DMSO-*d*₆ solution. HRMS (ESI) were determined on a Micromass Q-ToF Global mass spectrometer and MS (ESI) were obtained on a Bruker Esquire 3000 Plus spectrometer.

General procedure for the synthesis of 4a-p. To a stirred ethanol solution of 2-cyanobenzaldehyde (**1**, 3 mmol) and 3-methyl-1*H*-pyrazol-5(4*H*)-one **3a** or 1,3-dimethyl-1*H*-pyrazol-5(4*H*)-one **3b** (3 mmol) was added amine (**2**, 3 mmol) at room temperature. Then the mixture was heated to reflux and stirred for 30 min. After completion of the reaction, the precipitate was filtered off, washed with ethanol, and recrystallized to afford a red solid **4a-p** (85-95%).

4-(2-Benzyl-3-iminoisoindolin-1-ylidene)-3-methyl-1*H*-pyrazol-5(4*H*)-one (4a). Red solid, yield 93%, mp 243.8–245.1 °C; ¹H NMR (400 MHz, DMSO-*d*₆): δ 10.90 (s, 1H), 10.19 (brs, 1H), 9.58 (dd, *J* = 6.2, 1.4 Hz, 1H), 8.01 (dd, *J* = 6.2, 1.8 Hz, 1H), 7.60 (qd, *J* = 7.4, 6.0 Hz, 2H), 7.44 (d, *J* = 7.1 Hz, 2H), 7.42–7.34 (m, 2H), 7.31 (d, *J* = 7.3 Hz, 1H), 4.91 (s, 2H), 2.41 (s, 3H); ¹³C NMR (100 MHz, DMSO-*d*₆): δ 69.2, 168.4, 164.2, 149.5, 139.8, 138.0, 133.8, 131.6, 130.7, 128.6(2C), 128.1, 127.9(2C), 127.5, 121.2, 112.4, 46.3, 19.0; MS (ESI): *m/z* 317.3 [M+H]⁺; HRMS (ESI) Calcd for C₁₉H₁₇N₄O [M+H]⁺: 317.1397; Found: 317.1407.

4-(2-(4-Chlorobenzyl)-3-iminoisoindolin-1-ylidene)-3-methyl-1*H*-pyrazol-5(4*H*)-one (4b). Red solid, yield 94%, mp 234.5–235.7 °C; ¹H NMR (400 MHz, DMSO-*d*₆): δ 10.91 (s, 1H), 10.17 (brs, 1H), 9.58 (d, *J* = 7.0 Hz, 1H), 8.00 (d, *J* = 6.6 Hz, 1H), 7.62 (dd, *J* = 13.0, 6.5 Hz, 2H), 7.53–7.36 (m, 4H), 4.89 (s, 2H), 2.40 (s, 3H); ¹³C NMR (125 MHz, DMSO-*d*₆): δ 169.6, 168.8, 164.5, 149.9, 140.2, 137.5, 134.2, 132.5, 132.1, 131.1, 130.2(2C), 129.0(2C), 128.6, 121.6, 113.0, 46.0, 19.4; MS (ESI): *m/z* 351.3 [M+H]⁺; HRMS (ESI) Calcd for C₁₉H₁₆ClN₄O [M+H]⁺: 351.1007; Found: 317.1017.

4-(3-Imino-2-(4-methoxybenzyl)isoindolin-1-ylidene)-3-methyl-1*H*-pyrazol-5(4*H*)-one(4c). Red solid, yield 92%, mp 216.5–217.8 °C; ¹H NMR (400 MHz, DMSO-*d*₆): δ 10.90 (s, 1H), 10.13 (brs, 1H), 9.59 (dd, *J* = 6.7, 1.6 Hz, 1H), 8.00 (dd, *J* = 6.4, 1.4 Hz, 1H), 7.66–7.53 (m, 2H), 7.38 (d, *J* = 8.7 Hz, 2H), 6.95 (d, *J* = 8.7 Hz, 2H), 4.84 (d, *J* = 6.3 Hz, 2H), 3.74 (s, 3H), 2.45 (s, 3H); ¹³C NMR (100 MHz, DMSO-*d*₆): δ 169.3, 168.7, 164.7, 159.1, 149.9, 140.2, 134.2, 131.9, 131.0, 130.2, 129.7 (2C), 128.5, 121.5, 114.3 (2C), 112.6, 55.4, 46.2, 19.4; MS (ESI): *m/z* 347.3 [M+H]⁺; HRMS (ESI) Calcd for C₂₀H₁₉N₄O₂ [M+H]⁺: 347.1503; Found: 347.1516.

4-(2-(4-Fluorophenethyl)-3-iminoisoindolin-1-ylidene)-3-methyl-1*H*-pyrazol-5(4*H*)-one (4d). Red solid, yield 89%, mp 258.3–259.5 °C; ¹H NMR (400 MHz, DMSO-*d*₆): δ 10.89 (s, 1H), 9.79 (brs, 1H), 9.57 (dd, *J* = 6.4, 1.8 Hz, 1H), 7.95 (dd, *J* = 5.7, 1.5 Hz, 1H), 7.64–7.54 (m, 2H), 7.37–7.26 (m, 2H), 7.18–7.07 (m, 2H), 3.89 (dd, *J* = 11.4, 6.4 Hz, 2H), 3.06 (t, *J* = 7.4 Hz, 2H), 2.46 (s, 3H); ¹³C NMR (100 MHz, DMSO-*d*₆): δ 169.5, 168.8, 164.74, 162.59, and 160.18 (¹*J*_{CF} = 241.0 Hz), 150.0, 140.1, 135.41, and 135.39 (⁴*J*_{CF} = 2.0 Hz), 134.2, 131.9, 131.1, 130.96, and 130.88 (³*J*_{CF} = 8.0 Hz)(2C), 128.5, 121.4, 115.69, and 115.48(²*J*_{CF} = 21.0 Hz)(2C), 112.6, 44.8, 34.3, 19.4; MS (ESI): *m/z* 349.3 [M+H]⁺; HRMS (ESI) Calcd for C₂₀H₁₈FN₄O [M+H]⁺: 349.1459; Found: 349.1468.

4-(2-(3,4-Dimethoxyphenethyl)-3-iminoisoindolin-1-ylidene)-3-methyl-1*H*-pyrazol-5(4*H*)-one (4e). Red solid, yield 87%, mp 229.1–230.6 °C; ¹H NMR (400 MHz, DMSO-*d*₆): δ 10.89 (s, 1H), 9.81 (brs, 1H), 9.56 (m, 1H), 7.97 (dd, *J* = 5.6, 1.5 Hz, 1H), 7.67–7.50 (m, 2H), 6.88 (d, *J* = 8.2 Hz, 2H), 6.78 (dd, *J* = 8.0, 2.0 Hz, 1H), 3.88 (t, *J* = 8.2 Hz, 2H), 3.71 (s, 3H), 3.70 (s, 3H),

2.99 (t, $J = 7.4$ Hz, 2H), 2.48 (s, 3H); ^{13}C NMR (125 MHz, DMSO- d_6): δ 169.5, 168.8, 164.8, 149.9, 149.0, 147.7, 140.1, 134.2, 131.8, 131.5, 131.0, 128.5, 121.4, 120.9, 112.7, 112.4, 112.3, 55.8, 55.6, 45.0, 34.7, 19.3; MS (ESI): m/z 391.3 $[\text{M}+\text{H}]^+$; HRMS (ESI) Calcd for $\text{C}_{22}\text{H}_{23}\text{N}_4\text{O}_3$ $[\text{M}+\text{H}]^+$: 391.1765; Found: 391.1779.

4-(2-(Furan-2-ylmethyl)-3-iminoisoindolin-1-ylidene)-3-methyl-1H-pyrazol-5(4H)-one (4f). Red solid, yield 85%, mp 219.3–220.6 °C; ^1H NMR (400 MHz, DMSO- d_6): δ 10.92 (s, 1H), 10.11 (brs, 1H), 9.57 (dd, $J = 6.6, 1.5$ Hz, 1H), 8.01 (dd, $J = 6.1, 1.3$ Hz, 1H), 7.68–7.66 (m, 1H), 7.64–7.56 (m, 2H), 6.48–6.44 (m, 2H), 4.92 (d, $J = 4.2$ Hz, 2H), 2.46 (s, 3H); ^{13}C NMR (125 MHz, DMSO- d_6): δ 169.3, 168.7, 164.2, 150.9, 149.9, 143.5, 140.1, 134.1, 132.0, 131.1, 128.5, 121.6, 113.1, 111.1, 108.8, 39.7, 19.3; MS (ESI): m/z 307.3 $[\text{M}+\text{H}]^+$; HRMS (ESI) Calcd for $\text{C}_{17}\text{H}_{15}\text{N}_4\text{O}_2$ $[\text{M}+\text{H}]^+$: 307.1190; Found: 307.1204.

4-(3-Imino-2-propylisoindolin-1-ylidene)-3-methyl-1H-pyrazol-5(4H)-one (4g). Red solid, yield 94%, mp 255.6–257.3 °C; ^1H NMR (400 MHz, DMSO- d_6): δ 10.86 (s, 1H), 9.72 (brs, 1H), 9.58 (dd, $J = 6.3, 2.4$ Hz, 1H), 7.99 (dd, $J = 6.0, 2.5$ Hz, 1H), 7.67–7.53 (m, 2H), 3.66 (t, $J = 7.0$ Hz, 2H), 2.43 (s, 3H), 1.75 (m, 2H), 0.97 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR (100 MHz, DMSO- d_6): δ 169.6, 168.8, 165.0, 150.0, 140.2, 134.2, 131.9, 131.0, 128.5, 121.5, 112.2, 45.0, 22.6, 19.3, 11.9; MS (ESI): m/z 269.3 $[\text{M}+\text{H}]^+$; HRMS (ESI) Calcd for $\text{C}_{15}\text{H}_{17}\text{N}_4\text{O}$ $[\text{M}+\text{H}]^+$: 269.1397; Found: 269.1409.

4-(2-Cyclopentyl-3-iminoisoindolin-1-ylidene)-3-methyl-1H-pyrazol-5(4H)-one (4h). Red solid, yield 91%, mp 269.5–270.4 °C; ^1H NMR (400 MHz, DMSO- d_6): δ 10.86 (s, 1H), 9.57 (dd, $J = 6.0, 2.6$ Hz, 1H), 9.53 (d, $J = 6.4$ Hz, 1H), 8.05 (dd, $J = 5.7, 2.6$ Hz, 1H), 7.65–7.53 (m, 2H), 4.58 (dd, $J = 13.6, 4.9$ Hz, 1H), 2.44 (s, 3H), 2.11 (m, 2H), 1.77–1.63 (m, 6H); ^{13}C NMR (125 MHz, DMSO- d_6): δ 168.8, 168.7, 164.8, 149.9, 140.1, 134.2, 131.7, 130.8, 128.4, 121.6, 112.3, 55.2, 32.6(2C), 24.3(2C), 19.3; MS (ESI): m/z 295.3 $[\text{M}+\text{H}]^+$; HRMS (ESI) Calcd for $\text{C}_{17}\text{H}_{19}\text{N}_4\text{O}$ $[\text{M}+\text{H}]^+$: 295.1553; Found: 295.1565.

4-(3-Imino-2-isobutylisoindolin-1-ylidene)-3-methyl-1H-pyrazol-5(4H)-one (4i). Red solid, yield 90%, mp 278.3–279.7 °C; ^1H NMR (400 MHz, DMSO- d_6): δ 10.87 (s, 1H), 9.74 (t, $J = 6.1$ Hz, 1H), 9.58 (dd, $J = 5.9, 2.2$ Hz, 1H), 8.02 (dd, $J = 5.7, 2.4$ Hz, 1H), 7.64–7.55 (m, 2H), 3.52 (t, $J = 6.5$ Hz, 2H), 2.43 (s, 3H), 2.09 (dt, $J = 13.4, 6.7$ Hz, 1H), 0.97 (d, $J = 6.7$ Hz, 6H); ^{13}C NMR (125 MHz, DMSO- d_6): δ 169.8, 168.7, 164.9, 149.9, 140.2, 134.2, 131.8, 130.9, 128.4, 121.4, 112.2, 50.7, 28.7, 20.6(2C), 19.2; MS (ESI): m/z 283.3 $[\text{M}+\text{H}]^+$; HRMS (ESI) Calcd for $\text{C}_{16}\text{H}_{19}\text{N}_4\text{O}$ $[\text{M}+\text{H}]^+$: 283.1553; Found: 283.1565.

4-(2-Benzyl-3-iminoisoindolin-1-ylidene)-1,3-dimethyl-1H-pyrazol-5(4H)-one (4j). Red solid, yield 94%, mp 118.3–120.1 °C; ^1H NMR (400 MHz, DMSO- d_6): δ 10.29 (s, 1H), 9.61 (dd, $J = 6.2, 2.3$ Hz, 1H), 8.03 (dd, $J = 5.7, 2.0$ Hz, 1H), 7.64–5.59 (m, 2H), 7.45 (d, $J = 7.2$ Hz, 2H), 7.39 (t, $J = 7.4$ Hz, 2H), 7.31 (t, $J = 7.2$ Hz, 1H), 4.92 (d, $J = 5.5$ Hz, 2H), 3.25 (s, 3H), 2.43 (s, 3H); ^{13}C NMR (125 MHz, DMSO- d_6): δ 169.8, 165.8, 165.2, 148.6, 140.2, 138.2, 134.2, 132.0, 131.2, 128.9(2C), 128.6, 128.3(2C), 127.8, 121.6, 112.3, 46.8, 31.2, 19.0; MS (ESI): m/z 331.3 $[\text{M}+\text{H}]^+$; HRMS (ESI) Calcd for $\text{C}_{20}\text{H}_{19}\text{N}_4\text{O}$ $[\text{M}+\text{H}]^+$: 331.1553; Found: 331.1565.

4-(3-Imino-2-(4-methoxybenzyl)isoindolin-1-ylidene)-1,3-dimethyl-1H-pyrazol-5(4H)-one (4k). Red solid, yield 93%, mp 93.4–94.2 °C; ¹H NMR (400 MHz, DMSO-*d*₆): δ 10.24 (s, 1H), 9.61 (dd, *J* = 6.2, 1.9 Hz, 1H), 8.01 (dd, *J* = 6.4, 2.3 Hz, 1H), 7.64–7.59 (m, 2H), 7.38 (d, *J* = 8.7 Hz, 2H), 6.94 (d, *J* = 8.7 Hz, 2H), 4.85 (d, *J* = 5.9 Hz, 2H), 3.74 (s, 3H), 3.25 (s, 3H), 2.47 (s, 3H); ¹³C NMR (125 MHz, DMSO-*d*₆): δ 169.6, 165.8, 165.3, 159.1, 148.6, 140.2, 134.2, 131.9, 131.1, 130.1, 129.8(2C), 128.6, 121.6, 114.3 (2C), 112.1, 55.4, 46.3, 31.1, 19.1; MS (ESI): *m/z* 361.3 [M+H]⁺; HRMS (ESI) Calcd for C₂₁H₂₁N₄O₂ [M+H]⁺: 361.1659; Found: 361.1667.

4-(2-(4-Fluorobenzyl)-3-iminoisoindolin-1-ylidene)-1,3-dimethyl-1H-pyrazol-5(4H)-one (4l). Red solid, yield 90%, mp 146.7–148.3 °C; ¹H NMR (400 MHz, DMSO-*d*₆): δ 10.27 (s, 1H), 9.61 (dd, *J* = 6.1, 2.1 Hz, 1H), 8.01 (dd, *J* = 6.1, 2.4 Hz, 1H), 7.63–7.59 (m, 2H), 7.49 (dd, *J* = 8.7, 5.6 Hz, 2H), 7.22 (t, *J* = 8.9 Hz, 2H), 4.90 (d, *J* = 5.8 Hz, 2H), 3.25 (s, 3H), 2.43 (s, 3H); ¹³C NMR (125 MHz, DMSO-*d*₆): δ 169.7, 165.8, 165.1, 162.86, and 160.93 (¹*J*_{CF} = 241.0 Hz), 148.6, 140.1, 134.50, and 134.47 (⁴*J*_{CF} = 3.8 Hz), 134.2, 132.0, 131.2, 130.42, and 130.36 (³*J*_{CF} = 7.5 Hz)(2C), 128.6, 121.6, 115.81, and 115.64 (²*J*_{CF} = 21.2 Hz)(2C), 112.4, 46.0, 31.1, 19.0; MS (ESI): *m/z* 349.3 [M+H]⁺; HRMS (ESI) Calcd for C₂₀H₁₈FN₄O [M+H]⁺: 349.1459; Found: 349.1467.

4-(2-(4-Fluorophenethyl)-3-iminoisoindolin-1-ylidene)-1,3-dimethyl-1H-pyrazol-5(4H)-one (4m). Red solid, yield 92%, mp 196.3–197.2 °C; ¹H NMR (400 MHz, DMSO-*d*₆): δ 9.90 (s, 1H), 9.60 (dd, *J* = 5.9, 2.3 Hz, 1H), 7.96 (dd, *J* = 5.2, 1.9 Hz, 1H), 7.63–7.59 (m, 2H), 7.31 (dd, *J* = 8.7, 5.6 Hz, 2H), 7.14 (t, *J* = 8.9 Hz, 2H), 3.89 (dd, *J* = 13.8, 6.8 Hz, 2H), 3.25 (s, 3H), 3.06 (t, *J* = 7.3 Hz, 2H), 2.47 (s, 3H); ¹³C NMR (125 MHz, DMSO-*d*₆): δ 169.7, 165.9, 165.3, 162.29, and 160.36 (¹*J*_{CF} = 241.3 Hz), 148.6, 140.0, 135.29, and 135.27 (⁴*J*_{CF} = 2.5 Hz), 134.2, 131.9, 131.1, 130.86, and 130.80 (³*J*_{CF} = 7.5 Hz)(2C), 128.5, 121.5, 115.60, and 115.43 (²*J*_{CF} = 21.2 Hz)(2C), 112.1, 44.8, 34.2, 31.1, 19.0; MS (ESI): *m/z* 363.3 [M+H]⁺; HRMS (ESI) Calcd for C₂₁H₂₀FN₄O [M+H]⁺: 363.1616; Found: 363.1623.

4-(2-(3,4-Dimethoxyphenethyl)-3-iminoisoindolin-1-ylidene)-1,3-dimethyl-1H-pyrazol-5(4H)-one (4n). Red solid, yield 88%, mp 98.3–99.6 °C; ¹H NMR (400 MHz, DMSO-*d*₆): δ 9.91 (s, 1H), 9.60 (dd, *J* = 5.6, 2.0 Hz, 1H), 7.98 (dd, *J* = 5.6, 2.6 Hz, 1H), 7.63–7.59 (m, 2H), 6.87 (d, *J* = 8.0 Hz, 2H), 6.78 (d, *J* = 8.1 Hz, 1H), 3.88 (dd, *J* = 13.4, 7.0 Hz, 2H), 3.70 (s, 3H), 3.70 (s, 2H), 3.25 (s, 3H), 2.99 (t, *J* = 7.4 Hz, 2H), 2.49 (s, 3H); ¹³C NMR (125 MHz, DMSO-*d*₆): δ 169.7, 165.9, 165.4, 149.0, 148.6, 147.8, 140.1, 134.2, 131.9, 131.5, 131.0, 128.5, 121.4, 120.9, 112.7, 112.3, 111.9, 55.8, 55.6, 45.0, 34.7, 31.1, 19.0; MS (ESI): *m/z* 405.3 [M+H]⁺; HRMS (ESI) Calcd for C₂₃H₂₅N₄O₃ [M+H]⁺: 405.1921; Found: 405.1932.

4-(2-Butyl-3-iminoisoindolin-1-ylidene)-1,3-dimethyl-1H-pyrazol-5(4H)-one (4o). Red solid, yield 92%, mp 91.6–92.8 °C; ¹H NMR (400 MHz, DMSO-*d*₆): δ 9.79 (s, 1H), 9.62–9.59 (m, 1H), 7.98 (dd, *J* = 5.4, 3.1 Hz, 1H), 7.62–7.56 (m, 2H), 3.69 (dd, *J* = 12.4, 6.4 Hz, 2H), 3.25 (s, 3H), 2.44 (s, 3H), 1.74–1.67 (m, 2H), 1.42–1.36 (m, 2H), 0.93 (t, *J* = 7.4 Hz, 3H); ¹³C NMR (125 MHz, DMSO-*d*₆): δ 169.8, 165.9, 165.6, 148.6, 140.1, 134.2, 131.9, 131.0, 128.5, 121.5, 111.7, 42.9, 31.1 (2C), 20.0, 18.9, 13.9; MS (ESI): *m/z* 297.3 [M+H]⁺; HRMS (ESI) Calcd for C₁₇H₂₁N₄O [M+H]⁺: 297.1710; Found: 297.1723.

4-(2-Cyclopropyl-3-iminoisindolin-1-ylidene)-1,3-dimethyl-1H-pyrazol-5(4H)-one (4p). Red solid, yield 85%, mp 171.3–172.5 °C; ¹H NMR (400 MHz, DMSO-*d*₆): δ 9.72 (s, 1H), 9.60 (dd, *J* = 6.1, 2.6 Hz, 1H), 7.93 (dd, *J* = 5.7, 2.8 Hz, 1H), 7.62–7.56 (m, 3H), 3.45–3.38 (m, 1H), 3.25 (s, 3H), 2.48 (s, 3H), 0.98–0.85 (m, 4H); ¹³C NMR (125 MHz, DMSO-*d*₆): δ 170.3, 165.9, 165.4, 148.7, 139.8, 134.1, 131.8, 131.0, 128.5, 121.4, 112.1, 31.1, 26.7, 18.9, 6.7(2C); MS (ESI): *m/z* 281.3 [M+H]⁺; HRMS (ESI) Calcd for C₁₆H₁₇N₄O [M+H]⁺: 281.1397; Found: 281.1409.

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