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One-pot to fused pyrazoles by a double cyclization of *o*-alkynylaldehydes with ketones and hydrazine under metal-free condition

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ABSTRACT

An efficient one-pot synthesis of fused pyrazoles has been developed. The procedure involved three components reaction of *o*-alkynylaldehydes **1a**–**s** with ketones **2a**–**m** and hydrazine under mild, metal-free reaction conditions. The desired products were obtained in one-step up to 85% yield. The molecular structure was confirmed by the X-ray crystallographic analysis.

1. Introduction

The pyrazoles and their derivatives are found as essential subunits in a number of natural products and synthetic compounds that display important biological and pharmaceutical properties, including anti-cancer agent,[1] antipsychotic,[2] auxin transport inhibitor,[3–5] and insecticidal activities.[6–8] For example, the pyrazole based natural product withasomnine, isolated from the root of indian medicinal plant *Withania somnifera*, was particularly attractive due to its wide spectrum of pharmacological utility for treatment of enlarged spleen, migraines, many infections, and as an aphrodisiac as well (Fig. 1).[9–11] In view of its biological properties, extensive researches have been focused on the synthesis of fused pyrazoles and withasomnine analogues over the past decades. Traditional synthesis of these compounds usually adopt sydnone cycloaddition,[12–14] hydrazine 1,3-dicarbonyl cyclization,[15,16] multicomponent coupling,[17,18] and Claisen rearrangement[19] as the key steps. Among these, the Rh(III)-catalyzed oxidative coupling of 5-aryl-functionalized NH pyrazoles with acrylates using $Cu(OAc)_2$ as an oxidant represents a useful contribution to fused pyrazole synthesis.[20] Very recently, Namboothiri and co-workers reported the synthesis of withasomnine alkaloids in three steps from aldehydes and 4-nitro-1-butanol.[21] Although these methods have been shown to be highly efficient in the construction of substituted analogues of withsomnines, many of these processes still required the use of expensive transition metal complex as catalyst or extra synthetic steps to access the proper precursors. Also these reactions exhibited limited substrate scopes. Therefore, the development of new, more efficient route for rapid access to such functionalized pyrazole architectures from readily available starting materials under mild condition is highly desirable. As a part of our ongoing efforts to develop novel and efficient methodologies for the

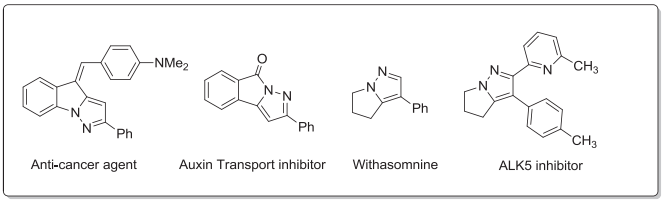

Fig. 1. Selected example of biologically active fused pyrazoles and withasomnine.

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synthesis of functionalized *N*-heterocycles,[22] we recently reported the new pathway for synthesis of phthalazine derivatives via cyclization of *ortho*-alkynylphenyl ketones.[23] On the base of our previous work, we hypothesized that it may be possible to realize the three components cyclization of ketone, hydrazine and *ortho*-alkynylaldehydes.

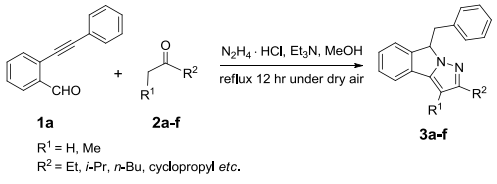
Herein, we present a metal-free, one-step formation of the skeleton of withasomnines by using commercially available ketones, hydrazine and *ortho*-alkynylaldehydes under very mild metal-free reaction condition. To the best of our knowledge, synthesis of nonnatural analogues of withasomnine from straightforward cyclization of *ortho*-alkynylaldehydes, ketone, and hydrazine has not been explored so far.

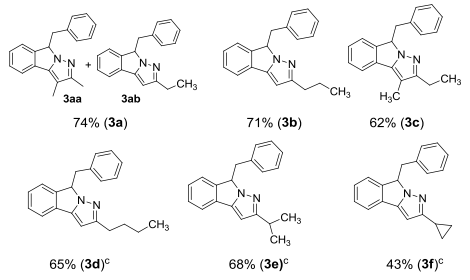
2. Results and discussion

Initially, we chose 2-phenylethynyl benzaldehyde (**1a**), 2-butanone, and hydrazine for our model study to optimize the reaction conditions. However, the use of $N_2H_4{\cdot}HCl$ (1 equiv), Et_3N (1 equiv), **2a** (2 equiv), and **1a** (1 equiv) failed to afford desired product **3a**. After a survey of reaction conditions, we found that the reaction was highly sensitive to the amount of triethyl amine and hydrazine as well as the oxygen (see Table S1 in the Supplementary data). It is notable that excess hydrazine and Et_3N were required to promote the reaction, indicating the pivotal role of Et_3N in the reaction. Solvents survey revealed that MeOH was found to be the optimum reaction medium. We also found that the oxygen played an important role in this cyclization reaction, usually the reaction needed to be conducted under the dry air or oxygen, inert atmosphere like argon led to a dramatic decrease of the product. Further optimization indicated that the optimal isolated yield (74%) of the corresponding pyrazoloisoindole **3a** was achieved by the use of 1 equiv benzaldehyde **1a**, 2 equiv of **2a**, and 5 equiv of hydrazine with 10 equiv triethyl amine in MeOH. Since the unsymmetrical ketone **2a** was used, a 1.7:1 mixture of two isomers of **3a** (**3aa** and **3ab**) were isolated due to the similarity between the methyl and the ethyl fragments.

Encouraged by the above results, the scope of the reaction was expanded to other dialkyl ketones **2a**–**f**. As seen from Table 1, this strategy is still effective for series of aliphatic ketones to give the desired products in good yields. The reactions of **1a** with 2-pentanone and 3-pentanone afforded the products **3b** and **3c** in 71% and 62% yields, respectively. When methyl cyclopropyl ketone **2f** was used, **3f** was isolated in 43% yield. In order to reveal the generality of the protocol, the reaction of **1a** with substituted aromatic ketones were also studied. Initially, we investigated the reaction of **1a** with acetophenone **2g** under various reaction conditions. A screening of reaction condition showed those 2 equiv of aromatic ketone, 5 equiv of hydrazine hydrogen chloride, and 10 equiv of NaOMe as the base in refluxing methanol led to **3g** in 75% yield. Furthermore, the reaction worked efficiently for both ketones bearing electron-withdrawing group or electron-donating group on the phenyl ring, and the products **3g**–**l** were obtained in good yields (Table 2). Heteroaromatic ketones, such as methyl 2-thienyl ketone **2l** also reacted with **1a** smoothly to give **3l** in 68% yield.

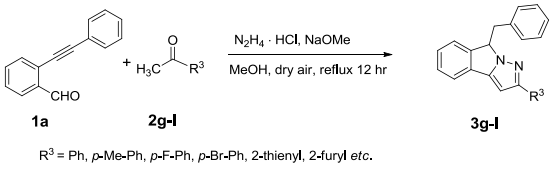
Table 1
Cyclization of **1a**, aliphatic ketones, and hydrazine[a,b]

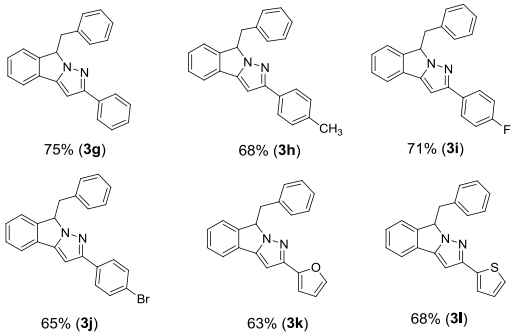




[a] Unless otherwise noted, the reaction conditions were as follows: 2-phenylethynyl benzaldehyde **1a** (0.4 mmol), aliphatic ketones (0.8 mmol), $N_2H_4{\cdot}HCl$ (2.0 mmol), Et_3N (4.0 mmol), in 5 mL MeOH, reflux for 12hr. [b] Isolated yield under dry air. [c] NaOMe (4.0 mmol) was used as the base.

Table 2
Cyclization of **1a**, aromatic acetone, and hydrazine[a,b]



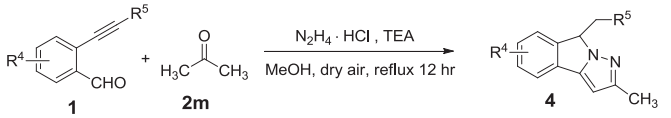


[a] Unless noted otherwise, the reaction conditions were as follows: 2-phenylethynyl benzaldehyde **1a** (0.4 mmol), aromatic ketones (0.8 mmol), $N_2H_4{\cdot}HCl$ (2.0 mmol), NaOMe (4.0mmol), in 5 mL MeOH, reflux for 12 hr under dry air. [b] Isolated yield.

In addition to the demonstrated the scope of this method, simple acetone was tested (Table 3). After optimizing the reaction condition (see Supplementary data Table S2), we examined the scope and generality of the reaction by employing a variety of *ortho*-alkynylaldehydes **1a**–**s** with acetone and hydrazine and moderate to good yields were provided. As shown in Table 3, the substituents R^4 and R^5 had almost no influence on the yield of the products. Irrespective of whether electron-rich or electron-deficient substituents on the benzene ring were used, the yields of the cyclized products **4a**–**r** were general good in a range of 70–85% (entries 1–16). For instance, the reaction of acetone and **1b** having *meta*-chlorophenyl group at R^5 proceeded well and gave the product **4b** in yield of 78% (entry 2). It seems that all substituents at R^4 are equally tolerated. When methyl group was used as R^4, and electron-rich aromatic or heteroaromatic substitutes were used as R^5, reactions proceeded well and **4m**–**r** were obtained in 66–72% yields (entries 13–18). In the case of *n*-hexyl substituent at R^5 position, the product **4s** was obtained in 47% (entry 19).

The regioselective formation of **4a**, **4d**, **4i**, **4m**, and **4q** was confirmed by X-ray crystallography (Fig. 2).[24]

Table 3
One-step synthesis of pyrazoloisoindoles[a]



Entry	R^4	R^5	Product	Yield[b] (%)
1	H	Ph	**4a**	85
2	H	*m*-Cl–C_6H_4	**4b**	78
3	4-F	3,5-Di-CF_3–C_6H_3	**4c**	82
4	H	*p*-Me–C_6H_4	**4d**	78
5	H	*p*-F–C_6H_4	**4e**	79
6	H	2-Thienyl	**4f**	78
7	4-F	2-Thienyl	**4g**	75
8	5-MeO	*p*-F–C_6H_4	**4h**	78
9	H	*p*-Et–C_6H_4	**4i**	74
10	H	*p*-MeO–C_6H_4	**4j**	70
11	H	*p*-Pr–C_6H_4	**4k**	72
12	H	*p*-Pentyl–C_6H_4	**4l**	70
13	4-Me	Ph	**4m**	72
14	4-Me	*p*-Me–C_6H_4	**4n**	72
15	4-Me	*p*-Et–C_6H_4	**40**	70
16	H	*o*-Br–C_6H_5	**4p**	72
17	4-Me	2-Thienyl	**4q**	66
18	4-Me	*p*-MeO–C_6H_4	**4r**	68
19	H	*n*-Hexyl	**4s**	47

[a] The reaction was performed in the using *ortho*-alkynylaldehydes **1** (0.4 mmol), acetone (2.8 mmol), hydrazine (4 mol), Et_3N (8 mol), in 5 mL of MeOH reflux for 12 hr under dry air.
[b] Isolated yield.

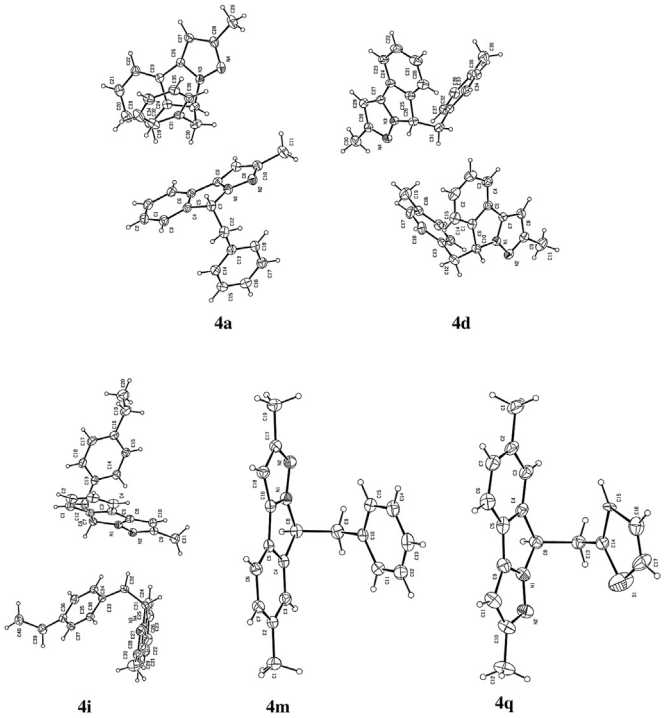
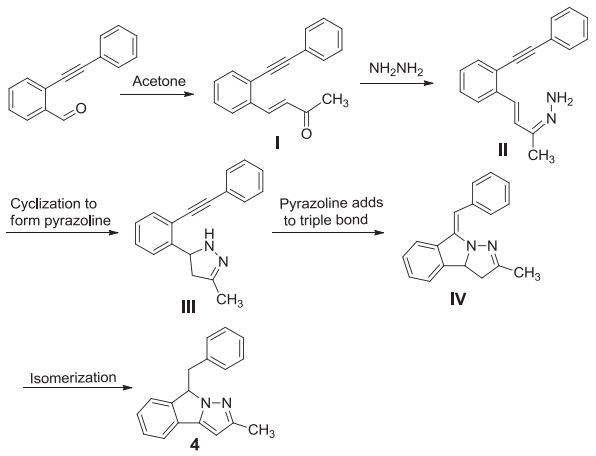


Fig. 2. X-ray crystallographic structures of **4a**, **4d**, **4i**, **4m**, and **4q.**

Based on the above results, a possible mechanism is proposed in Scheme 1. Presumably the acetone and 2-alkynyl aldehyde would generate the ketone intermediate I. Then the subsequent hydrazine addition to carbonyl carbon affords the key intermediate II. The intramolecular cyclization leads to the pyrazole III. Finally, the intramolecular attack of nitrogen on alkyne, followed by isomerization give the formation of the product **4**.[25] Same product was obtained under the similar reaction conditions from reaction using I as starting material, which demonstrated the proposed mechanism is plausible.



Scheme 1. Alternative mechanisms for formation of pyrazoloisoindoline.

3. Conclusions

In conclusion, for the first time, we have achieved the facile synthesis of nonnatural analogues of withasomnine alkaloids, by a simple three-component double cyclization of easily accessed *o*-alkynylaldehydes, ketones, and hydrazine under mild condition. This approach to withasomnine analogues represents a potential platform for practically construction of pyrazole based nitrogen-containing heterocyclic compounds with potential biological activities.

4. Experimental section

4.1. General

Analytical-grade solvents were purchased, and used as received. NMR spectra were measured at 400 MHz for ^1H spectra and 100 MHz for ^{13}C spectra and calibrated from residual solvent signal. Analytical thin-layer chromatography (TLC) was performed on silica gel aluminum sheets with F-254 indicator. Visualization was accomplished by UV light. Purification by chromatography was performed using 230–400 mesh SiO_2 with compressed air as a source of positive pressure. Mass spectra were recorded under electron impact conditions at 70 eV. The starting materials *o*-Phenylethynyl benzaldehyde was prepared according to the literature.[26]

4.2. Representative procedure for the synthesis of pyrazoles

To a solution of 2-phenylethynyl benzaldehyde **1a** (0.4 mmol), acetone (2.8 mmol), and hydrazine hydrochloride (4 mmol) in methanol (5 mL), TEA (8 mmol) was added under dry air. Then the mixture was refluxed for 12 h, after that, 5 mL of water was added, extracted with ethyl acetate (3×20 mL). Then the organic layer was dried with anhydrous sodium sulfate. Evaporation of ethyl acetate gave a yellow residue, which was further purified by gel column chromatography to afford the pure product.

*4.2.1. 8-Benzyl-2-ethyl-8H-pyrazole[5,1-α]isoindole (**3a**).* ^1H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, J=8.0 Hz, 1H), 7.26–7.31 (m, 3H), 7.01 (d, J=4.0 Hz, 2H), 7.01 (d, J=4.0 Hz, 2H), 6.90 (d, J=8.0 Hz, 1H), 6.11 (s,

1H), 5.34 (q, *J*=4.0 Hz, 1H), 3.73 (dd, *J*=8.0, 4.0 Hz, 1H), 3.10 (d, *J*=8.0 Hz, 1H), 2.78 (d, *J*=8.0 Hz, 2H), 1.34 (t, *J*=8.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.4, 145.6, 143.9, 135.5, 129.7, 128.1, 126.7, 126.5, 123.8, 120.1, 94.3, 63.2, 40.0, 22.3, 14.3. HRMS calcd for $C_{19}H_{18}N_2$ $(M)^+$: 274.1470, found: 274.1468.

*4.2.2. 8-Benzyl-2-propyl-8H-pyrazole[5,1-α]isoindole (**3b**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, *J*=8.0 Hz, 1H), 7.20 (t, *J*=8.0 Hz, 1H), 6.92–7.18 (m, 4H), 6.90 (d, *J*=4.0 Hz, 2H), 6.86 (d, *J*=8.0 Hz, 1H), 6.01 (s, 1H), 5.27 (q, *J*=4.0 Hz, 1H), 3.63 (dd, *J*=8.0, 4.0 Hz, 1H), 3.05 (d, *J*=8.0 Hz, 1H), 2.65 (t, *J*=8.0 Hz, 2H), 1.68 (m, 2H), 0.94 (t, *J*=8.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.9, 145.6, 143.9, 135.4, 130.8, 129.7, 128.1, 126.7, 126.5, 123.8, 120.1, 94.9, 63.2, 39.9, 31.2, 23.3, 13.9. HRMS calcd for $C_{20}H_{20}N_2$ $(M)^+$: 288.1626, found: 288.1620.

*4.2.3. 8-Benzyl-2-ethyl-3-methyl-8H-pyrazole[5,1-α]isoindole (**3c**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (d, *J*=8.0 Hz, 1H), 7.21 (t, *J*=8.0 Hz, 1H), 7.01–7.19 (m, 4H), 6.98 (d, *J*=8.0 Hz, 2H), 6.74 (d, *J*=8.0 Hz, 1H), 6.03 (s, 1H), 5.21 (q, *J*=4.0 Hz, 1H), 3.62 (dd, *J*=8.0, 4.0 Hz, 1H), 2.64 (dd, *J*=8.0, 4.0 Hz, 2H), 2.01 (s, 3H), 1.23 (t, *J*=8.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.3, 143.8, 142.9, 135.7, 128.1, 126.7, 123.8, 119.4, 104.9, 63.0, 40.2, 20.4, 14.1, 8.1. HRMS calcd for $C_{20}H_{20}N_2$ $(M)^+$: 288.1626, found: 288.1622.

*4.2.4. 8-Benzyl-2-butyl-8H-pyrazole[5,1-α]isoindole (**3d**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, *J*=8.0 Hz, 1H), 7.28 (t, *J*=8.0 Hz, 1H), 7.00–7.16 (m, 4H), 6.91–6.99 (m, 3H), 6.09 (s, 1H), 5.35 (q, *J*=4.0 Hz, 1H), 3.70 (dd, *J*=8.0, 4.0 Hz, 1H), 3.16 (d, *J*=8.0 Hz, 1H), 2.75 (d, *J*=8.0 Hz, 2H), 1.71 (m, 2H), 1.44 (m, 2H), 0.97 (t, *J*=8.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.1, 145.6, 143.9, 135.4, 130.8, 129.7, 128.0, 126.7, 126.5, 123.8, 120.1, 94.9, 63.2, 39.9, 32.2, 28.8, 22.4, 14.0. HRMS calcd for $C_{21}H_{22}N_2$ $(M)^+$: 302.1783, found: 302.1788.

*4.2.5. 8-Benzyl-2-isopropyl-8H-pyrazole[5,1-α]isoindole (**3e**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (d, *J*=8.0 Hz, 1H), 7.21 (d, *J*=8.0 Hz, 1H), 7.07–7.18 (m, 4H), 6.86–6.91 (m, 3H), 6.03 (s, 1H), 5.28 (q, *J*=4.0 Hz, 1H), 3.62 (dd, *J*=8.0, 4.0 Hz, 1H), 3.21–2.93 (m, 2H), 1.28 (d, *J*=8.0 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.1, 145.4, 143.9, 135.4, 130.9, 129.7, 128.0, 126.7, 126.4, 123.7, 120.1, 92.8, 63.2, 39.9, 28.7, 23.1. HRMS calcd for $C_{20}H_{20}N_2$ $(M)^+$: 288.1626, found: 288.1630.

*4.2.6. 8-Benzyl-2-cyclopropyl-8H-pyrazole[5,1-α]isoindole (**3f**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23–7.34 (m, 2H), 7.11–7.19 (m, 2H), 7.05–7.09 (m, 2H), 6.95 (br, 2H), 6.82 (d, *J*=8.0 Hz, 1H), 5.89 (s, 1H), 5.26 (q, *J*=4.0 Hz, 1H), 3.66 (dd, *J*=8.0, 4.0 Hz, 1H), 3.02 (dd, *J*=8.0, 4.0 Hz, 1H), 1.99 (m, 1H), 0.96 (m, 2H), 0.76 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.7, 143.9, 135.5, 131.7, 130.5, 129.7, 128.1, 126.7, 126.6, 123.8, 120.2, 92.5, 63.4, 40.0, 9.9, 8.2. HRMS calcd for $C_{20}H_{18}N_2$ $(M)^+$: 286.1470, found: 286.1476.

*4.2.7. 8-Benzyl-2-phenyl-8H-pyrazole[5,1-α]isoindole (**3g**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, *J*=8.0 Hz, 2H), 7.18–7.34 (m, 3H), 7.10–7.16 (m, 2H), 6.93–7.08 (m, 4H), 6.93 (br, 2H), 6.89 (d, *J*=8.0 Hz, 1H), 6.52 (s, 1H), 5.38 (q, *J*=4.0 Hz, 1H), 3.68 (dd, *J*=8.0, 4.0 Hz, 1H), 3.16 (dd, *J*=8.0, 4.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.9, 146.3, 143.8, 135.3, 134.2, 130.5, 129.8, 128.7, 128.3, 128.2, 127.6, 126.89, 126.82, 125.66, 123.88, 120.42, 93.49, 63.71, 40.03. HRMS calcd for $C_{23}H_{18}N_2$ $(M)^+$: 322.1470, found: 322.1471.

*4.2.8. 8-Benzyl-2-(p-tolyl)-8H-pyrazole[5,1-α]isoindole (**3h**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, *J*=8.0 Hz, 2H), 7.48 (d, *J*=8.0 Hz, 1H), 7.36–7.29 (m, 3H), 7.10–7.18 (m, 4H), 6.97–7.03 (m, 3H), 6.57 (s, 1H), 5.45 (q, *J*=4.0 Hz, 1H), 3.76 (d, *J*=8.0 Hz, 1H), 3.23 (d, *J*=8.0 Hz, 1H), 2.40 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.0, 146.3, 143.8, 137.4, 135.4, 131.6, 131.4, 130.5, 129.8, 129.3, 128.4, 128.2, 128.1, 126.9, 126.8, 125.5, 123.8, 120.3, 93.2, 63.6, 40.0, 21.3. HRMS calcd for $C_{24}H_{20}N_2$ $(M)^+$: 336.1626, found: 336.1623.

*4.2.9. 8-Benzyl-2-(4-fluorophenyl)-8H-pyrazole[5,1-α]isoindole (**3i**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (dd, *J*=8.0, 4.0 Hz, 2H), 7.48 (d, *J*=8.0 Hz, 1H), 6.96–7.26 (m, 10H), 6.54 (s, 1H), 5.44 (q, *J*=4.0 Hz, 1H), 3.75 (dd, *J*=8.0, 4.0 Hz, 1H), 3.21 (dd, *J*=8.0, 4.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.0, 146.5, 143.8, 135.3, 133.0, 131.5, 130.4, 129.7, 129.0, 128.9, 128.5, 128.3, 128.2, 127.3, 127.2, 126.9, 126.8, 123.8, 120.4, 115.6, 115.4, 93.2, 63.7, 40.0. HRMS calcd for $C_{23}H_{17}FN_2$ $(M)^+$: 340.1376, found: 340.1375.

*4.2.10. 8-Benzyl-2-(4-bromophenyl)-8H-pyrazole[5,1-α]isoindole (**3j**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, *J*=8.0 Hz, 2H), 7.53 (d, *J*=8.0 Hz, 2H), 7.46 (d, *J*=4.0 Hz, 1H), 7.32 (t, *J*=8.0 Hz, 1H), 7.25–7.12 (m, 4H), 7.08–6.90 (m, 3H), 6.55 (s, 1H), 5.43 (q, *J*=4.0 Hz, 1H), 3.74 (dd, *J*=8.0, 4.0 Hz, 1H), 3.20 (dd, *J*=8.0, 4.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.7, 146.5, 143.7, 135.2, 133.1, 131.7, 130.2, 129.7, 128.3, 128.2, 127.1, 127.0, 126.8, 123.9, 121.5, 120.4, 93.4, 63.7, 40.0. HRMS calcd for $C_{23}H_{17}BrN_2$ $(M)^+$: 400.0575, found: 400.0576.

*4.2.11. 8-Benzyl-2-(furan-2-yl)-8H-pyrazole[5,1-α]isoindole (**3k**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, *J*=8.0 Hz, 2H), 7.25 (t, *J*=8.0 Hz, 1H), 7.20–7.08 (m, 4H), 7.01–6.81 (m, 3H), 6.51–6.66 (m, 3H), 5.36 (q, *J*=4.0 Hz, 1H), 3.73 (q, *J*=4.0 Hz, 1H), 3.11 (dd, *J*=8.0, 4.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.3, 148.0, 146.1, 143.9, 141.7, 135.3, 130.1, 129.7, 128.3, 128.2, 127.0, 126.8, 123.9, 120.5, 111.3, 105.5, 93.2, 63.7, 39.9. HRMS calcd for $C_{21}H_{16}ON_2$ $(M)^+$: 312.1263, found: 312.1264.

*4.2.12. 8-Benzyl-2-(thiophen-2-yl)-8H-pyrazole[5,1-α]isoindole (**3l**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, *J*=8.0 Hz, 1H), 7.31 (d, *J*=4.0 Hz, 1H), 7.23 (t, *J*=8.0 Hz, 1H), 7.20–7.15 (m, 1H), 7.15–7.06 (m, 4H), 7.04–6.98 (m, 1H), 6.98–6.91 (m, 2H), 6.86 (d, *J*=8.0 Hz, 1H), 6.42 (s, 1H), 5.35 (q, *J*=4.0 Hz, 1H), 3.68 (dd, *J*=8.0, 4.0 Hz, 1H), 3.11 (dd, *J*=8.0, 4.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.9, 146.4, 143.8, 137.5, 135.3, 130.2, 129.8, 128.3, 128.2, 127.5, 127.0, 126.8, 124.3, 123.9, 123.4, 120.4, 93.5, 63.7, 39.9. HRMS calcd for $C_{21}H_{16}SN_2$ $(M)^+$: 328.1034, found: 328.1036.

*4.2.13. 8-Benzyl-2-methyl-8H-pyrazole[5,1-α]isoindole (**4a**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (d, *J*=8.0 Hz, 1H), 7.17 (d, *J*=8.0 Hz, 1H), 6.94–7.08 (m, 4H), 6.92 (d, *J*=8.0 Hz, 2H), 6.78 (d, *J*=8.0 Hz, 1H), 5.98 (s, 1H), 5.21 (dd, *J*=4.0 Hz, 1H), 3.63 (dd, *J*=4.0 Hz, 1H), 2.97 (dd, *J*=8.0 Hz, 1H), 2.32 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.9, 144.7, 142.8, 134.5, 129.6, 128.6, 127.1, 127.0, 125.7, 125.4, 122.7, 119.1, 94.8, 62.2, 38.9, 13.4. HRMS calcd for $C_{18}H_{16}N_2$ $(M)^+$: 260.1313, found: 260.1316.

*4.2.14. 8-(3-Chlorobenzyl)-2-methyl-8H-pyrazole[5,1-α]isoindole (**4b**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (d, *J*=4.0 Hz, 1H), 7.07 (d, *J*=8.0 Hz, 1H), 6.99 (d, *J*=8.0 Hz, 1H), 6.82–6.92 (m, 4H), 6.68 (d, *J*=8.0 Hz, 1H), 5.93 (s, 1H), 5.17 (dd, *J*=4.0 Hz, 1H), 3.45 (d, *J*=12.0 Hz, 1H), 3.07 (d, *J*=12.0 Hz, 1H), 2.29 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.2, 146.0, 143.5, 137.3, 133.8, 130.7, 129.8, 129.2, 128.3, 127.8, 126.9, 126.7, 123.5, 120.3, 96.0, 62.9, 39.4, 29.7, 14.3. HRMS calcd for $C_{18}H_{15}N_2Cl$ $(M+H)^+$: 295.1002, found: 295.0994.

*4.2.15. 8-(3,5-Bis(trifluoromethyl)benzyl)-2-methyl-8H-pyrazole[5,1-α]isoindole (**4c**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (s, 1H), 7.41–7.29 (m, 4H), 7.10 (s, 1H), 5.95 (s, 1H), 5.48 (t, *J*=4.0 Hz, 1H), 3.79 (d, *J*=8.0 Hz, 1H), 3.50 (d, *J*=4.0 Hz, 1H), 2.39 (s, 3H). ^{13}C NMR

(100 MHz, $CDCl_3$) δ 153.8, 146.3, 142.4, 136.7, 130.8, 130.4, 129.9, 128.6, 127.0, 124.4, 123.1, 121.7, 120.4, 96.1, 62.3, 38.9, 29.7, 15.3. HRMS calcd for $C_{20}H_{13}N_2F_7$ $(M)^+$: 414.0967, found: 414.0968.

*4.2.16. 8-(4-Methylbenzyl)-2-methyl-8H-pyrazole[5,1-α]isoindole (**4d**).* ^1H NMR (400 MHz, $CDCl_3$) δ 7.32 (d, *J*=8.0 Hz, 1H), 7.18 (dd, *J*=8.0, 4.0 Hz, 1H), 7.04 (d, *J*=4.0 Hz, 1H), 6.78–7.02 (m, 5H), 5.99 (s, 1H), 5.18 (d, *J*=4.0 Hz, 1H), 3.61 (dd, *J*=8.0, 4.0 Hz, 1H), 2.91 (dd, *J*=8.0, 4.0 Hz, 1H), 2.32 (s, 3H), 2.18 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.9, 145.7, 144.1, 136.2, 132.5, 130.7, 129.6, 128.9, 128.0, 126.5, 123.9, 120.1, 95.8, 63.4, 39.6, 31.6, 21.0, 14.4. HRMS calcd for $C_{19}H_{18}N_2$ $(M)^+$: 274.1470, found: 274.1472.

*4.2.17. 8-(4-Fluorobenzyl)-2-methyl-8H-pyrazole[5,1-α]isoindole (**4e**).* ^1H NMR (400 MHz, $CDCl_3$) δ 7.28 (d, *J*=8.0 Hz, 1H), 7.17 (br, 1H), 7.07 (br, 1H), 6.91 (d, *J*=4.0 Hz, 1H), 6.85–6.59 (m, 4H), 5.95 (s, 1H), 5.18 (d, *J*=4.0 Hz, 1H), 3.49 (d, *J*=8.0 Hz, 1H), 3.12 (d, *J*=8.0 Hz, 1H), 2.30 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.9, 160.5, 153.0, 145.9, 143.6, 131.2, 131.1, 128.2, 126.6, 123.5, 120.2, 114.9, 114.7, 95.9, 63.1, 38.8, 29.8, 14.4. HRMS calcd for $C_{18}H_{15}N_2F$ $(M)^+$: 278.1219, found: 278.1220.

*4.2.18. 2-Methyl-8-(thiophen-2ylmethyl)-8H-pyrazole[5,1-α]isoindole (**4f**).* ^1H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, *J*=8.0 Hz, 1H), 7.21 (t, *J*=8.0 Hz, 1H), 7.11 (t, *J*=8.0 Hz, 1H), 7.01 (d, *J*=8.0 Hz, 1H), 6.92 (d, *J*=8.0 Hz, 1H), 6.69 (d, *J*=4.0 Hz, 1H), 6.47 (s, 1H), 5.99 (s, 1H), 5.22 (br, 1H), 3.72 (dd, *J*=4.0 Hz, 1H), 3.43 (d, *J*=4.0 Hz, 1H), 2.31 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.1, 145.0, 142.5, 135.8, 129.9, 127.3, 125.7, 125.6, 125.5, 123.4, 122.5, 119.1, 95.0, 61.9, 32.8, 13.3. HRMS calcd for $C_{16}H_{14}N_2S$ $(M)^+$: 266.0978, found: 266.0976.

*4.2.19. 6-Fluoro-2-methyl-8-(thiophen-2ylmethyl)-8H-pyrazole [5,1-α]isoindole (**4g**).* ^1H NMR (400 MHz, $CDCl_3$) δ 7.37 (br, 1H), 7.00–7.08 (m, 2H), 6.81 (t, *J*=4.0 Hz, 2H), 6.59 (d, *J*=4.0 Hz, 1H), 6.06 (s, 1H), 5.31 (d, *J*=4.0 Hz, 1H), 3.80 (d, *J*=8.0 Hz, 1H), 3.51 (dd, *J*=8.0, 4.0 Hz, 1H), 2.40 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.8, 146.3, 142.4, 136.7, 130.8, 130.4, 129.9, 128.6, 127.0, 123.1, 121.7, 120.4, 96.1, 62.3, 38.9, 14.1. HRMS calcd for $C_{16}H_{14}N_2FS$ $(M)^+$: 285.0862, found: 285.0851.

*4.2.20. 8-(4-Fluorobenzyl)-5-methoxyl-2-methyl-8H-pyrazole[5,1-α]isoindole (**4h**).* ^1H NMR (400 MHz, $CDCl_3$) δ 6.90–6.71 (m, 6H), 6.64 (d, *J*=8.0 Hz, 1H), 5.97 (s, 1H), 5.18 (dd, *J*=4.0 Hz, 1H), 3.74 (s, 3H), 3.51 (dd, *J*=8.0, 4.0 Hz, 1H), 3.09 (dd, *J*=8.0, 4.0 Hz, 1H), 2.32 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.9, 158.8, 151.9, 144.8, 134.6, 131.0, 130.1, 130.0, 123.3, 113.9, 113.7, 111.4, 104.8, 94.8, 61.8, 54.4, 38.0, 13.3. HRMS calcd for $C_{19}H_{17}N_2FO$ $(M+H)^+$: 309.1403, found: 309.1400.

*4.2.21. 8-(4-Ethylbenzyl)-2-methyl-8H-pyrazole[5,1-α]isoindole (**4i**).* ^1H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, *J*=8.0 Hz, 1H), 7.18 (t, *J*=8.0 Hz, 1H), 7.03 (t, *J*=8.0 Hz, 1H), 6.95 (d, *J*=8.0 Hz, 2H), 6.89 (d, *J*=8.0 Hz, 2H), 6.76 (d, *J*=8.0 Hz, 1H), 5.99 (s, 1H), 5.17 (dd, *J*=4.0 Hz, 1H), 3.63 (dd, *J*=8.0, 4.0 Hz, 1H), 2.88 (br, 1H), 2.49 (q, *J*=8.0 Hz, 2H), 2.32 (s, 3H), 1.10 (t, *J*=8.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.0, 145.7, 144.2, 142.7, 132.9, 130.7, 129.7, 128.1, 127.7, 126.5, 123.9, 120.1, 95.8, 63.4, 39.7, 28.4, 15.5, 14.4. HRMS calcd for $C_{20}H_{20}N_2$ $(M)^+$: 288.1626, found: 288.1624.

*4.2.22. 8-(4-Methoxylbenzyl)-2-methyl-8H-pyrazole[5,1-α]isoindole (**4j**).* ^1H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, *J*=4.0 Hz, 1H), 7.19 (d, *J*=8.0 Hz, 1H), 7.07 (t, *J*=8.0 Hz, 1H), 6.83–6.88 (m, 3H), 6.62 (d, *J*=8.0 Hz, 2H), 5.99 (s, 1H), 5.20 (q, *J*=4.0 Hz, 1H), 3.65 (s, 3H), 3.57 (d, *J*=4.0 Hz, 1H), 2.96 (d, *J*=8.0 Hz, 1H), 2.33 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.3, 152.9, 145.8, 144.0, 133.0, 130.7, 128.0, 127.6, 126.5, 123.8, 120.2, 113.5, 95.8, 63.5, 55.1, 39.1, 14.4. HRMS calcd for $C_{19}H_{18}N_2O$ $(M)^+$: 290.1419, found: 290.1423.

*4.2.23. 8-(4-Propylbenzyl)-2-methyl-8H-pyrazole[5,1-α]isoindole (**4k**).* ^1H NMR (400 MHz, $CDCl_3$) δ 7.32 (d, *J*=8.0 Hz, 1H), 7.18 (t, *J*=4.0 Hz, 1H), 6.88–7.05 (m, 5H), 6.74 (d, *J*=8.0 Hz, 1H), 6.00 (s, 1H), 5.18 (dd, *J*=8.0, 4.0 Hz, 1H), 3.64 (dd, *J*=8.0, 4 Hz, 1H), 2.87 (dd, *J*=8.0, 4.0 Hz, 1H), 2.32 (s, 3H), 1.51 (d, *J*=8.0 Hz, 2H), 1.12 (m, 2H), 0.82 (t, *J*=8.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.0, 145.7, 144.2, 141.1, 132.9, 130.7, 129.7, 129.6, 128.3, 128.0, 127.7, 126.5, 123.9, 120.1, 95.8, 63.4, 39.8, 37.6, 24.4, 14.4, 13.7. HRMS calcd for $C_{21}H_{22}N_2$ $(M)^+$: 302.1783, found: 302.1776.

*4.2.24. 8-(4-Pentylbenzyl)-2-methyl-8H-pyrazole[5,1-α]isoindole (**4l**).* ^1H NMR (400 MHz, $CDCl_3$) δ 7.34 (d, *J*=8.0 Hz, 1H), 7.17 (d, *J*=4.0 Hz, 1H), 7.05 (d, *J*=8.0 Hz, 1H), 6.89–6.96 (m, 4H), 6.76 (d, *J*=8.0 Hz, 1H), 6.01 (s, 1H), 5.19 (dd, *J*=8.0, 4.0 Hz, 1H), 3.64 (dd, *J*=8.0, 4.0 Hz, 1H), 2.86 (d, *J*=8.0 Hz, 1H), 2.57–2.42 (m, 2H), 2.33 (s, 3H), 1.50 (m, 2H), 1.29–1.19 (m, 4H), 0.80 (t, *J*=8.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.0, 145.7, 144.2, 141.4, 132.9, 130.7, 129.6, 128.3, 128.0, 126.5, 123.9, 120.1, 95.8, 63.4, 39.8, 35.5, 31.4, 31.0, 22.5, 14.4, 14.0. HRMS calcd for $C_{23}H_{26}N_2$ $(M)^+$: 330.2096, found: 330.2098.

*4.2.25. 8-Benzyl-2,6-di-methyl-8H-pyrazole[5,1-α]isoindole (**4m**).* ^1H NMR (400 MHz, $CDCl_3$) δ 7.18 (d, *J*=8.0 Hz, 1H), 7.09 (br, 3H), 6.93–6.99 (m, 3H), 6.58 (s, 1H), 5.92 (s, 1H), 5.15 (q, *J*=4.0 Hz, 1H), 3.61 (d, *J*=8.0 Hz, 1H), 2.97 (d, *J*=8.0 Hz, 1H), 2.30 (s, 3H), 2.18 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.8, 145.9, 144.3, 136.5, 135.7, 129.8, 128.7, 128.1, 128.1, 126.7, 124.6, 119.9, 95.4, 63.2, 40.1, 21.6, 14.4. HRMS calcd for $C_{19}H_{18}N_2$ $(M)^+$: 274.1470, found: 274.1472.

*4.2.26. 8-(4-Methylbenzyl)-2,6-di-methyl-8H-pyrazole[5,1-α]isoindole (**4n**).* ^1H NMR (400 MHz, $CDCl_3$) δ 7.20 (d, *J*=8.0 Hz, 1H), 6.98 (d, *J*=8.0 Hz, 1H), 6.90 (d, *J*=8.0 Hz, 2H), 6.83 (t, *J*=4.0 Hz, 2H), 6.62 (s, 1H), 5.93 (s, 1H), 5.13 (q, *J*=4.0 Hz, 1H), 3.56 (dd, *J*=8.0, 4.0 Hz, 1H), 2.92 (d, *J*=8.0 Hz, 1H), 2.30 (s, 3H), 2.18 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.8, 145.9, 144.4, 136.4, 136.2, 132.7, 129.6, 128.8, 128.7, 128.1, 124.6, 119.9, 95.4, 63.3, 39.6, 21.6, 21.0, 14.4. HRMS calcd for $C_{20}H_{20}N_2$ $(M)^+$: 288.1626, found: 288.1630.

*4.2.27. 8-(4-Ethylbenzyl)-2,6-di-methyl-8H-pyrazole[5,1-α]isoindole (**4o**).* ^1H NMR (400 MHz, $CDCl_3$) δ 7.21–7.23 (m, 1H), 6.89–6.98 (m, 5H), 6.57 (s, 1H), 5.95 (s, 1H), 5.14 (q, *J*=4.0 Hz, 1H), 3.61 (dd, *J*=8.0, 4.0 Hz, 1H), 2.89 (d, *J*=8.0 Hz, 1H), 2.48 (m, 2H), 2.28 (s, 3H), 2.19 (s, 3H), 1.12 (t, *J*=8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.8, 145.8, 144.5, 142.7, 136.4, 133.0, 129.7, 128.7, 128.0, 127.7, 124.7, 119.9, 95.4, 63.3, 39.8, 28.4, 21.6, 15.5, 14.4. HRMS calcd for $C_{21}H_{22}N_2$ $(M)^+$: 302.1783, found: 302.1788.

*4.2.28. 8-(2-Bromobenzyl)-2-methyl-8H-pyrazole[5,1-α]isoindole (**4p**).* ^1H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, *J*=8.0 Hz, 1H), 7.33 (d, *J*=8.0 Hz, 1H), 7.17 (t, *J*=8.0 Hz, 1H), 7.01–7.11 (m, 1H), 6.94–7.03 (m, 2H), 6.92 (dd, *J*=4.0 Hz, 1H), 6.66 (d, *J*=8.0 Hz, 1H), 6.02 (s, 1H), 5.32 (q, *J*=4.0 Hz, 1H), 3.78 (d, *J*=8.0 Hz, 1H), 2.91 (dd, *J*=8.0 Hz, 1H), 2.30 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.1, 144.6, 142.6, 134.7, 131.9, 131.2, 129.5, 127.7, 127.1, 126.2, 125.4, 124.0, 123.0, 119.1, 94.9, 60.5, 39.4, 13.4. HRMS calcd for $C_{18}H_{15}N_2Br$ $(M)^+$: 338.0419, found: 338.0420.

*4.2.29. 2,6-Di-methyl-8-(thiophen-2ylmethyl)-8H-pyrazole [5,1-α] isoindole (**4q**).* ^1H NMR (400 MHz, $CDCl_3$) δ 7.23 (d, *J*=4.0 Hz, 1H), 7.05 (d, *J*=8.0 Hz, 1H), 6.98–6.93 (m, 1H), 6.85 (s, 1H), 6.71 (dd, *J*=4.0 Hz, 1H), 6.49 (d, *J*=4.0 Hz, 1H), 5.96 (s, 1H), 5.21 (br, 1H), 3.71 (dd, *J*=8.0, 4.0 Hz, 1H), 3.46 (dd, *J*=8.0 Hz, 1H), 2.31 (s, 3H), 2.27 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.1, 146.2, 143.9, 137.0, 136.8,

128.9, 128.3, 126.7, 126.5, 124.4, 124.3, 119.9, 95.6, 62.8, 33.8, 21.6, 14.4. HRMS calcd for $C_{17}H_{16}N_2S$ $(M)^+$: 280.1034, found: 280.1039.

*4.2.30. 8-(4-Methoxylbenzyl)-2,6-di-methyl-8H-pyrazole[5,1-α]isoindole (**4r**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.01–7.22 (m, 2H), 6.89–6.83 (m, 2H), 6.64–6.68 (m, 3H), 5.95 (s, 1H), 5.15 (q, J=4.0 Hz, 1H), 3.68 (s, 3H), 3.53 (d, J=4.0 Hz, 1H), 2.98 (d, J=4.0 Hz, 1H), 2.32 (s, 3H), 2.24 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.3, 152.8, 144.4, 136.5, 132.9, 130.7, 128.7, 128.1, 127.7, 124.5, 119.9, 113.5, 95.3, 63.4, 55.1, 39.1, 29.8, 21.6, 14.4. HRMS calcd for $C_{20}H_{20}N_2O$ $(M)^+$: 304.1576, found: 304.1580.

*4.2.31. 8-Hexyl-2-methyl-8H-pyrazole[5,1-α]isoindole (**4s**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, J=8.0 Hz, 1H), 7.19–7.32 (m, 3H), 6.05 (s, 1H), 5.03 (t, J=4.0 Hz, 1H), 2.31 (s, 3H), 2.21–2.09 (m, 1H), 2.06–1.98 (m, 1H), 1.15–1.27 (m, 6H), 0.73 (t, J=4.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.6, 140.7, 139.6, 125.6, 122.7, 121.6, 117.6, 114.9, 90.3, 57.6, 28.2, 26.3, 17.9, 17.1, 9.2, 8.7. HRMS calcd for $C_{17}H_{22}N_2$ $(M)^+$: 254.1783, found: 254.1780.

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Supplementary data

NMR spectra of products and X-ray data of compounds **4a**, **4d**, **4m**, **4i**, and **4q** are available. Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2014.04.032.

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