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Synthesis of 1-(1*H*-Tetrazol-5-yl)-2*H*-isoindole Derivatives through Ugi Four-Component and Silver-Catalyzed Reactions

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A facile and efficient one-pot, two-step synthesis of 1,2-disubstituted 3-(1*H*-tetrazol-5-yl)-2*H*-isoindoles through Ugi four-component reaction/$AgNO_3$-catalyzed reaction of 2-alkynylbenzaldehydes, amines, isonitriles, and Me_3SiN_3 is described. This transformation proceeds through 5-*exo*-*dig* cyclization, [1,3]-H shift, and [1,5]-H shift to generate the products in moderate to excellent yields.

Introduction

Rapid advances in medicinal chemistry continue to highlight the need for practical and efficient routes to generate drug-like compounds.[1] Due to their high degree of atom economy, convergence and productivity, isocyanide-based multicomponent reactions (IMCRs) have been shown to be a promising approach through which to efficiently generate drug-like nitrogen heterocycles in medicinal chemistry.[2] For many years, there has been growing interest in combinations of IMCRs such as Ugi reaction,[2a] Passerini reaction,[3] and Van Leusen reaction[4] with subsequent secondary transformations to increase scaffold and molecular complexity.[5] Recently, silver-catalyzed reactions have gained considerable attention owing to their ability to activate various π-systems such as alkenes, alkynes, and allenes under mild conditions with low-catalyst loading.[1b,1d,6] Especially, the silver-catalyzed intramolecular addition of nitrogen nucleophiles to alkynes giving rise to a variety of N-heterocycles, has recently emerged as an important synthetic method for many organic transformations.[5f,7]

Among heterocycles, isoindoles are interesting skeletons because of their fluorescent properties and potential medicinal value.[8] Therefore, continuous efforts have focused on the synthesis of various isoindole moieties.[9] For example, Suginome and co-workers used a Pd-catalyzed reaction of isoindolines to prepare 1-borylisoindoles.[10] Stevens et al. have synthesized 1-cyanoisoindoles[9d] and phosphorylated isoindoles.[11] Wu et al.[12] reported the synthesis of 2*H*-isoindol-1-ylphosphonates, some of which displayed promising activity as HCT-116 (human colon cancer cells) inhibitors. Li and co-workers[13] reported the synthesis of 1-carboxamidoisoindoles from *ortho*-phthalaldehydes. Tetrazoles have been developed as important nitrogen-rich heterocycles that exhibit interesting biological properties[14] such as anti-inflammatory,[15] antihypertensive,[16] antibacterial, and antiallergy activities.[17] The attractive properties of this latter group has prompted its rapid development, and has led to the construction of a class of antihypertension drugs of angiotensin II receptor blockers – sartans.

Recently, 2-alkynylbenzaldehydes have been used as important building blocks to synthesize various cyclic compounds, such as 1*H*-isochromenes, benzofurans, naphthalenes, isoquinolines, quinolones, indoles, and isoindoles.[18] To the best of our knowledge, there have been no reports on the synthesis of 1-(1*H*-tetrazol-5-yl)-2*H*-isoindole derivatives. Herein, we consider the possibility of exploiting a MCR/silver-catalyzed strategy to synthesize 1-(1*H*-tetrazol-5-yl)-2*H*-isoindole derivatives from 2-alkynylbenzaldehydes. We hypothesized that in the presence of a suitable silver catalyst, compound **5**, formed by Ugi four-component reaction (Ugi-4CR) (for example **5a**, see Exp. Sect.), might serve as a nucleophile when a triple bond is available in the molecule to give 1-(1*H*-tetrazol-5-yl)-2*H*-isoindole **6** through 5-*exo*-*dig* cyclization and/or 1,2-dihydroisoquinoline **7** through 6-*endo*-*dig* cyclization. The proposed synthetic route is presented in Scheme 1.

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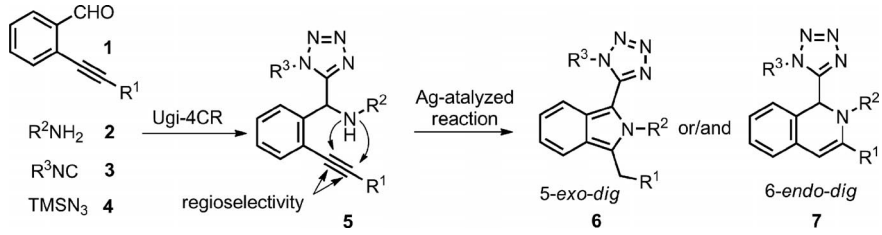


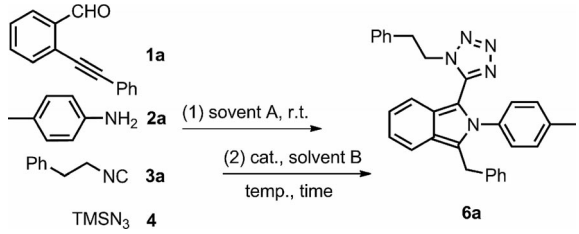
Scheme 1. The proposed Ugi-4CR/silver-catalyzed reaction.

Results and Discussion

To examine the hypothesis, 2-alkynylbenzaldehyde **1a**, *p*-toluidine (**2a**), (2-isocyanoethyl)benzene (**3a**), and trimethylsilyl azide ($TMSN_3$; **4**) were chosen as substrates (Table 1). We investigated the effects of various parameters in the second step to optimize the reaction conditions. At the outset, catalysts such as AgOTf (Tf = triflate), $PdCl_2$, AgOAc, and $AgNO_3$ were employed in the reaction (Table 1, entries 1–6). To our delight, only the 5-*exo*-*dig* cyclization product 1-(1*H*-tetrazol-5-yl)-2*H*-isoindole **6a** was obtained. When 10 mol-% $AgNO_3$ was employed, compound **6a** was obtained in 77% yield (Table 1, entry 6). We further explored the reaction in various solvents, such as MeCN (Table 1, entries 7, 8, and 15), H_2O (entry 9), MeOH (entries 10 and 11), EtOH (entries 12 and 13), and *i*PrOH (entry 14). Among them, acetonitrile was demonstrated as the best choice (Table 1, entry 7). When the amount of catalyst was decreased, the yield of **6a** was reduced (Table 1, entry 8). Thus, the optimized conditions were identified (Table 1, entry 7).

With this promising result in hand, we started to investigate the scope of this reaction under the optimized conditions [MeOH, room temp., $AgNO_3$ (10 mol-%), MeCN, 80 °C]. The results are summarized in Table 2. We found that these conditions were effective for the four-component reactions. For most cases, 2-alkynylbenzaldehyde **1** reacted

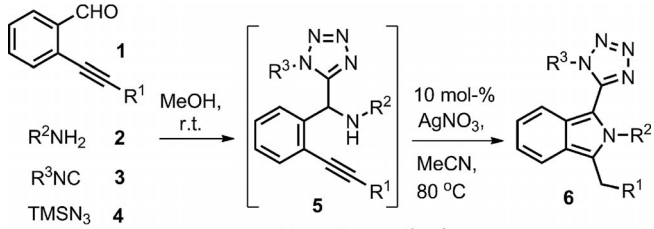
Table 1. Optimization of reaction conditions.[a]



Entry	Cat. [mol-%]	Solvent A	Solvent B	*T* [°C]	*t* [h][b]	Yield [%][c]
1	AgOTf (10)	MeOH	MeCN	80	12	25
2	AgOTf (10)	MeOH	toluene	110	12	25
3	AgOTf (20)	MeOH	toluene	110	12	30
4	$PdCl_2$ (10)	MeOH	MeCN	80	36	20
5	AgOAc(10)	MeOH	MeCN	80	36	9
6	$AgNO_3$ (10)	MeOH	toluene	80	2	77
7	$AgNO_3$ (10)	MeOH	MeCN	80	2	89
8	$AgNO_3$ (5)	MeOH	MeCN	80	2	56
9	$AgNO_3$ (10)	MeOH	H_2O	85	2	trace
10	$AgNO_3$ (5)	MeOH	MeOH	60	5.5	73
11	$AgNO_3$ (10)	MeOH	MeOH	60	2	46
12	$AgNO_3$ (5)	EtOH	EtOH	60	4	68
13	$AgNO_3$ (10)	EtOH	EtOH	60	6	60
14	$AgNO_3$ (10)	*i*PrOH	*i*PrOH	80	12	37
15	$AgNO_3$ (10)	MeCN	MeCN	80	3	34

[a] Reaction conditions: **1a** (0.5 mmol, 1.0 equiv.), **2a** (1.0 equiv.), **3a** (1.2 equiv.), **4** (1.2 equiv.), solvent A (2 mL), room temperature. After completion of the reaction as indicated by TLC, catalyst was added and the mixture was heated in solvent B. [b] Reaction time for the second step. [c] Isolated yield based on **1a**.

Table 2. Synthesis of 1,2-disubstituted 3-(1*H*-tetrazol-5-yl)-2*H*-isoindoles **6** through Ugi-4CR/$AgNO_3$-catalyzed reaction of 2-alkynylbenzaldehyde **1**, amine **2**, isonitrile **3**, and $TMSN_3$ **4**.



Entry	R^1	R^2	R^3	Yield [%][a]
1	Ph	4-MeC_6H_4	$C_6H_5(CH_2)_2$	89 (**6a**)
2	Ph	4-MeC_6H_4	1-cyclohexyl	93 (**6b**)
3	Ph	4-MeC_6H_4	*t*Bu	61 (**6c**)
4	Ph	4-$EtOC_6H_4$	$C_6H_5(CH_2)_2$	47 (**6d**)
5	Ph	Ph	$C_6H_5(CH_2)_2$	56 (**6e**)
6	Ph	Bn	$C_6H_5(CH_2)_2$	54 (**6f**)
7	Ph	4-BrC_6H_4	$C_6H_5(CH_2)_2$	80 (**6g**)
8	Ph	4-$MeOC_6H_4$	$C_6H_5(CH_2)_2$	50 (**6h**)
9	4-MeC_6H_4	4-$MeOC_6H_4$	$C_6H_5(CH_2)_2$	82 (**6i**)
10	4-MeC_6H_4	4-MeC_6H_4	$C_6H_5(CH_2)_2$	77 (**6j**)
11	4-MeC_6H_4	4-$EtOC_6H_4$	$C_6H_5(CH_2)_2$	50 (**6k**)
12	4-MeC_6H_4	1-cyclohexyl	$C_6H_5(CH_2)_2$	70 (**6l**)
13	4-MeC_6H_4	4-BrC_6H_4	$C_6H_5(CH_2)_2$	52 (**6m**)
14	4-MeC_6H_4	4-$MeOC_6H_4$	1-cyclohexyl	52 (**6n**)
15	4-MeC_6H_4	4-ClC_6H_4	$C_6H_5(CH_2)_2$	69 (**6o**)
16	1-cyclopropyl	4-MeC_6H_4	$C_6H_5(CH_2)_2$	40 (**6p**)
17	1-cyclopropyl	1-cyclohexyl	$C_6H_5(CH_2)_2$	60 (**6q**)
18	1-cyclopropyl	Ph	$C_6H_5(CH_2)_2$	50 (**6r**)
19	1-cyclopropyl	4-$MeOC_6H_4$	$C_6H_5(CH_2)_2$	53 (**6s**)
20	1-cyclopropyl	4-FC_6H_4	$C_6H_5(CH_2)_2$	44 (**6t**)
21	*n*-Pr	Ph	$C_6H_5(CH_2)_2$	69 (**6u**)
22	*n*-Pr	4-$MeOC_6H_4$	$C_6H_5(CH_2)_2$	52 (**6v**)
23	*n*-Pr	4-$MeOC_6H_4$	Bn	47 (**6w**)
24	*n*-Pr	1-cyclohexyl	$C_6H_5(CH_2)_2$	56 (**6x**)
25	*n*-Pr	4-BrC_6H_4	$C_6H_5(CH_2)_2$	67 (**6y**)
26	Me_3Si	4-ClC_6H_4	$C_6H_5(CH_2)_2$	70 (**6z**) (R^1 = **H**)

[a] Isolated yield based on 2-alkynylbenzaldehyde **1**.

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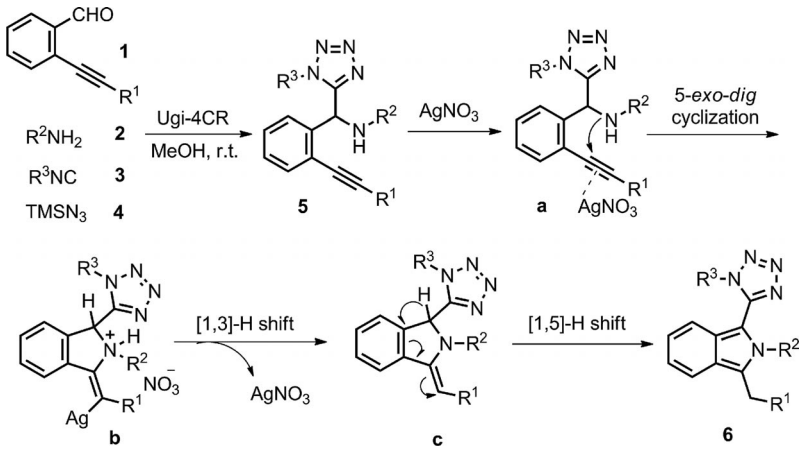

Scheme 2. Plausible reaction mechanism.

with amines **2**, isoindoles **3** and $TMSN_3$ **4** to generate target compounds **6** in 40–93% yields.

It was found that when R^1 was an aryl group (Table 2, entries 1–15) the reactions showed better reactivity and gave higher yields than aliphatic groups (Table 2, entries 16–25). We reasoned that the aryl group attached to the triple bond might facilitate its [1,5]-H shift after 5-*exo*-*dig* cyclization in the reaction process.[12b] Moreover, the reaction conditions were proved to be useful for anilines (Table 2, entries 1–5, 7–11, 13–16, 18–23, 25, and 26) and aliphatic amines (Table 2, entries 6, 12, 17, and 24). Both electron-rich (Table 2, entries 1–6, 8–11, 14, 16, 18, 19, and 21–23) and electron-poor anilines (Table 2, entries 7, 13, 15, 20, 25, and 26) were suitable partners in the process. Different functional groups such as methyl, methoxyl, ethoxyl, and halogen groups such as Br (Table 2, entries 7, 13, 25), Cl (Table 2, entries 15, 26), and F (Table 2, entry 20), were well-tolerated under the reaction conditions. Some of these halogen groups (Br, Cl) provide the possibility for further functionalization through cross-coupling reactions.

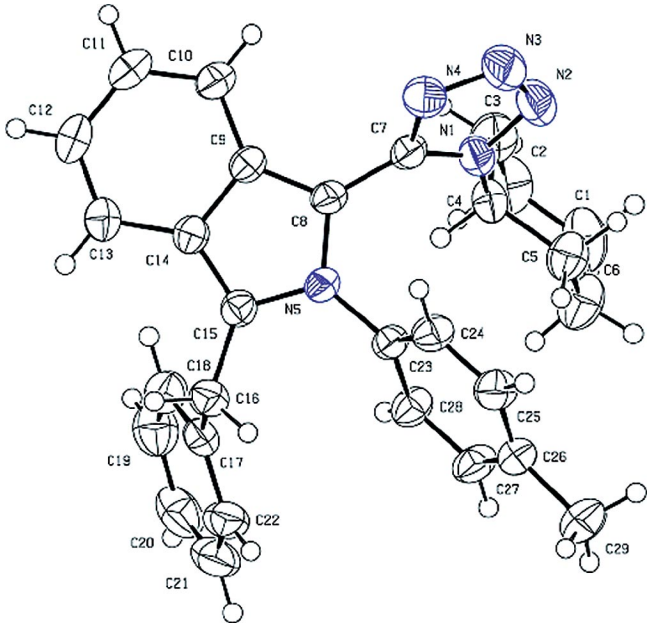

Figure 1. X-ray crystallographic analysis of compound **6b**.

As shown in Table 2, the desired isoindole compounds were obtained in moderate to excellent yields by using commercially available isonitriles, such as *tert*-butyl isocyanide, cyclohexyl isocyanide, benzyl isocyanide, and (2-isocyanoethyl)benzene. Even with the hindered *tert*-butyl isocyanide, the reaction proceeded smoothly to give the corresponding product **6c** in 61% yield (Table 2, entry 3). 2-[(Trimethylsilyl)ethynyl]benzaldehyde reacted smoothly under the standard experimental conditions and an unexpected product **6z** was generated in 70% yield, because trimethylsilyl is an easy leaving group (Table 2, entry 26). The structure of isoindole **6b** was further determined by X-ray crystallographic analysis (see Figure 1).

Based on the results described above, a plausible reaction mechanism is depicted in Scheme 2. At first, 2-alkynylbenzaldehydes, amines, isonitriles, and TMS-azides react to produce compound **5** through Ugi-4CR, then the triple bond of compound **5** coordinates to the silver nitrate, and the nitrogen atom attacks the triple bond through 5-*exo*-*dig* cyclization to afford ammonium **b**. Finally aromatization occurs by a [1,3]-H shift and a [1,5]-H shift to afford the more stable compound **6** (Scheme 2).

Conclusions

We have developed a facile and efficient route for the synthesis of diverse 1,2-disubstituted 3-(1*H*-tetrazol-5-yl)-2*H*-isoindoles through Ugi-4CR/$AgNO_3$-catalyzed reaction of 2-alkynylbenzaldehydes with amines, isonitriles, and $TMSN_3$. The reaction proceeds with high efficiency through Ugi-4CR, 5-*exo*-*dig* cyclization, [1,3]-H shift and [1,5]-H shift. The products could be isolated in moderate to excellent yields. Work is ongoing to investigate the further synthetic applications and biological properties of the new compounds.

Experimental Section

General Information: All reagents were obtained from commercial sources (purity > 99%) and used without further purification, un-

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less otherwise indicated. Reactions were stirred with Teflon-coated magnetic stir bars. Elevated temperatures were maintained by using thermostat-controlled silicone oil baths. Organic solutions were concentrated using a rotary evaporator with a desktop vacuum pump. Thin-layer chromatography (TLC) was performed on silica gel G plates and visualized by UV light (254 nm). The products were isolated by column chromatography on silica gel (200–300 mesh) using petroleum ether (60–90 °C) and ethyl acetate as eluent. All yields described are isolated yields after column chromatography.

Melting points are reported uncorrected. NMR spectra were recorded in $CDCl_3$, unless otherwise indicated, at ambient temperature, operating at 400 MHz for ^1H and 100 MHz for ^{13}C. Data for ^1H NMR spectra are reported as follows: chemical shift (ppm, referenced to TMS; s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, dt = doublet of triplets, m = multiplet), coupling constant [Hz], and integration. Data for ^{13}C NMR spectra are reported as chemical shift (ppm) relative to residual solvent peak ($CDCl_3$: 77.2 ppm). IR absorption spectra were recorded as a film on KBr. Mass spectra were measured with a Finnigan Trace DSQ instrument or GCT Premier mass spectrometer. High-resolution mass spectra (HRMS) were recorded with a Bruker Apex III mass spectrometer (ESI) with an FT-ICR analyzer.

4-Methyl-*N*-{(1-phenethyl-1*H*-tetrazol-5-yl)[2-(phenylethynyl)-phenyl]methyl}aniline (5a). Typical Procedure: To a round-bottomed single-necked flask (10 mL) equipped with a magnetic stirring bar, was added 2-(phenylethynyl)benzaldehyde (**1a**; 0.5 mmol, 103 mg), *p*-toluidine (**2a**; 0.5 mmol, 54 mg, 1.0 equiv.), and MeOH (2 mL). The reaction was stirred for 30 min at room temperature, then (2-isocyanoethyl)benzene (0.6 mmol, 79 mg, 1.2 equiv.) and azidotrimethylsilane (0.6 mmol, 69 mg, 1.2 equiv.) were added. After completion of the reaction as indicated by TLC, the solvent was removed under reduced pressure and the residue was purified by column chromatograph on silica gel (ethyl acetate/petroleum ether, 1:4 v/v) to give the desired product **5a** (202 mg, 86%) as a light-yellow liquid. R_f 0.45 (petroleum ether/ethyl acetate, 80:20 v/v). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.58–7.54 (m, 1 H), 7.35–7.20 (m, 8 H), 7.14–7.07 (m, 3 H), 6.93–6.90 (m, 4 H), 6.56 (d, J = 8 Hz, 2 H), 6.25 (s, 1 H, C-H), 4.85 (s, 1 H, N-H), 4.55–4.43 (m, 2 H), 3.11–3.03 (m, 1 H), 2.89–2.82 (m, 1 H), 2.19 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.4, 143.4, 139.2, 136.0, 132.6, 131.4 (2×C), 129.7 (2×C), 129.4, 128.8, 128.6 (2×C), 128.4 (5×C), 128.1, 127.5, 126.9, 122.3, 122.1, 114.1 (2×C), 95.8, 86.7, 51.6, 48.8, 35.8, 20.5 ppm. IR (KBr): $\tilde{\nu}$ = 3389 (N–H), 3028, 2930, 2832, 2213, 1604 (C=N), 1511, 1455, 1235, 1180, 1105, 1035 cm^{-1}. MS (ESI): m/z (%) = 492.2 (100) $[M + Na]^+$. HRMS (ESI): m/z calcd. for $C_{31}H_{27}N_5Na$ $[M + Na]^+$ 492.2164; found 492.2158.

Synthesis of 6. General Procedure: To a round-bottomed single-necked flask (10 mL) equipped with a magnetic stirring bar, was added 2-alkynylbenzaldehyde **1** (0.5 mmol), amine **2** (0.5 mmol, 1.0 equiv.), and MeOH (2 mL). After 30 min, isocyanide **3** (0.6 mol, 1.2 equiv.) and azidotrimethylsilane **4** (0.6 mmol, 69 mg, 1.2 equiv.) were added and the mixture was stirred for 3–10 h. After completion of the reaction as indicated by TLC, the solvent was removed under reduced pressure, then $AgNO_3$ (0.05 mmol, 8.5 mg, 10 mol-%) and MeCN (2 mL) were added. The mixture was stirred for 1–8 h at 80 °C under a nitrogen atmosphere. After completion of the reaction as indicated by TLC, the solvent was removed under reduced pressure and the residue was purified by column chromatograph on silica gel (ethyl acetate/petroleum ether) to give the desired product **6**.

1-Benzyl-3-(1-phenethyl-1*H*-tetrazol-5-yl)-2-(*p*-tolyl)-2*H*-isoindole (6a): The product was obtained as a white solid (209 mg, 89%); m.p. 168.5–170.5 °C; R_f 0.65 (petroleum ether/ethyl acetate, 75:25 v/v). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.57 (dd, J = 8, 4 Hz, 1 H), 7.20–7.10 (m, 11 H), 6.89–6.86 (m, 4 H), 6.65 (d, J = 8 Hz, 2 H), 4.33 (t, J = 8 Hz, 2 H), 4.23 (s, 2 H), 3.06 (t, J = 8 Hz, 2 H), 2.33 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.2, 138.8, 138.7, 136.2, 134.0, 129.5 (2×C), 128.5 (2×C), 128.4 (2×C), 128.3 (2×C), 128.1 (2×C), 127.9, 127.2 (2×C), 126.8, 126.1, 126.0, 124.5, 123.2, 121.6, 120.0, 117.7, 103.4, 49.1, 35.4, 31.2, 21.3 ppm. IR (KBr): $\tilde{\nu}$ = 1628, 1572, 1515, 1454, 1385, 1372, 1088 cm^{-1}. MS (ESI): m/z (%) = 470.2 (100) $[M + H]^+$. HRMS (ESI): m/z calcd. for $C_{31}H_{28}N_5$ $[M + H]^+$ 470.2339; found 470.2336.

1-Benzyl-3-(1-cyclohexyl-1*H*-tetrazol-5-yl)-2-(*p*-tolyl)-2*H*-isoindole (6b): The product was obtained as a white solid (208 mg, 93%); m.p. 127.4–127.8 °C; R_f 0.57 (petroleum ether/ethyl acetate, 80:20 v/v). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.57 (dt, J = 8.4, 1 Hz, 1 H), 7.33 (dt, J = 8.4, 1 Hz, 1 H), 7.18–7.02 (m, 7 H), 6.92 (m, 4 H), 4.27 (s, 2 H), 2.34 (s, 3 H), 1.90–1.76 (m, 4 H), 1.62 (d, J = 12.4 Hz, 1 H), 1.48 (d, J = 12.4 Hz, 2 H), 1.26–1.11 (m, 4 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.3, 139.2, 138.9, 134.5, 129.7 (2×C), 128.5 (2×C), 128.2 (2×C), 127.7, 127.5 (2×C), 126.7, 126.4, 124.5, 123.4, 121.8, 120.0, 117.9, 104.1, 58.2, 33.2 (2×C), 31.5, 25.5 (2×C), 25.0, 21.4 ppm. IR (KBr): $\tilde{\nu}$ = 2934, 2858, 1632, 1566, 1494, 1453, 1383, 1367, 1339, 1155, 1050 cm^{-1}. MS (ESI): m/z (%) = 470.1 (100) $[M + Na]^+$. HRMS (ESI): m/z calcd. for $C_{29}H_{29}N_5Na$ $[M + Na]^+$ 470.2315; found 470.2308.

1-Benzyl-3-[1-(*tert*-butyl)-1*H*-tetrazol-5-yl]-2-(*p*-tolyl)-2*H*-isoindole (6c): The product was obtained as a white solid (128 mg, 61%); m.p. 154.5–154.7 °C; R_f 0.50 (petroleum ether/ethyl acetate, 80:20 v/v). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.53 (dt, J = 8, 1 Hz, 1 H), 7.18–7.10 (m, 4 H), 7.07–6.96 (m, 6 H), 6.91 (dd, J = 7.2, 1.6 Hz, 2 H), 4.34 (d, J = 16.8 Hz, 1 H), 4.17 (d, J = 16.8 Hz, 1 H), 2.30 (s, 3 H), 1.34 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 146.4, 139.4, 139.0, 134.2, 129.5 (3×C), 128.4 (3×C), 128.1 (2×C), 126.8, 126.3, 126.1, 123.9, 123.2, 121.5, 119.9, 118.3, 104.7, 62.2, 31.4, 30.2 (3×C), 21.3 ppm. IR (KBr): $\tilde{\nu}$ = 2986, 2931, 1627, 1602, 1585, 1558, 1514, 1495, 1454, 1395, 1371, 1354, 1336, 1279, 1240, 1176, 1118, 1087, 1031 cm^{-1}. MS (ESI): m/z (%) = 444.1 (100) $[M + Na]^+$. HRMS (ESI): m/z calcd. for $C_{27}H_{28}N_5$ $[M + H]^+$ 422.2339; found 422.2340.

1-Benzyl-2-(4-ethoxyphenyl)-3-(1-phenethyl-1*H*-tetrazol-5-yl)-2*H*-isoindole (6d): The product was obtained as a white solid (117 mg, 47%); m.p. 131.0–133.0 °C; R_f 0.67 (petroleum ether/ethyl acetate, 75:25 v/v). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.57 (dt, J = 8.4, 1 Hz, 1 H), 7.21–7.09 (m, 8 H), 7.06–7.02 (m, 1 H), 6.88–6.85 (m, 8 H), 6.69–6.63 (m, 4 H), 4.34 (t, J = 7.2 Hz, 2 H), 4.22 (s, 3 H), 3.97 (q, J = 6.8 Hz, 2 H), 3.07 (t, J = 7.2 Hz, 2 H), 1.41 (t, J = 6.8 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.1, 148.5, 139.0, 136.5, 129.3, 128.8 (5×C), 128.6 (2×C), 128.5 (2×C), 128.2 (2×C), 127.0, 126.4, 126.2, 124.6, 123.3, 121.8, 120.2, 117.9, 114.7 (2×C), 103.8, 64.0, 49.3, 35.6, 31.5, 15.0 ppm. IR (KBr): $\tilde{\nu}$ = 2977, 1625, 1604, 1569, 1512, 1475, 1454, 1393, 1384, 1369, 1345, 1292, 1246, 1170, 1150, 1112, 1087, 1043, 1009 cm^{-1}. MS (ESI): m/z (%) = 500.2 (100) $[M + H]^+$. HRMS (ESI): m/z calcd. for $C_{32}H_{30}N_5O$ $[M + H]^+$ 500.2445; found 500.2448.

1-Benzyl-3-(1-phenethyl-1*H*-tetrazol-5-yl)-2-phenyl-2*H*-isoindole (6e): The product was obtained as a white solid (128 mg, 56%); m.p. 162.0–164.0 °C; R_f 0.55 (petroleum ether/ethyl acetate, 75:25 v/v). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.59 (d, J = 8.4 Hz, 1 H), 7.31 (tt, J = 7.4, 1 Hz, 1 H), 7.22–7.18 (m, 3 H), 7.15–7.11 (m, 6 H), 7.08–7.01 (m, 2 H), 6.88–6.83 (m, 4 H), 6.75 (d, J = 7.2 Hz, 2 H), 4.34 (t, J = 7.2 Hz, 2 H), 4.23 (s, 2 H), 3.08 (t, J = 7.2 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.4, 138.8, 136.9,

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136.4, 129.1 (3×C), 128.8 (2×C), 128.6 (2×C), 128.5 (2×C), 128.3, 128.1 (2×C), 127.8 (2×C), 127.1, 126.4, 126.3, 124.8, 123.5, 121.9, 120.2, 118.0, 103.8, 49.3, 35.6, 31.5 ppm. IR (KBr): $\tilde{\nu}$ = 3053, 3027, 1628, 1597, 1568, 1494, 1453, 1423, 1367, 1350, 1291, 1231, 1153, 1115, 1087, 1075, 1028 cm^{-1}. MS (ESI): *m*/*z* (%) = 478.1 (100) [M + Na]$^+$. HRMS (ESI): *m*/*z* calcd. for $C_{30}H_{26}N_5$ [M + H]$^+$ 456.2183; found 456.2176.

1,2-Dibenzyl-3-(1-phenethyl-1*H*-tetrazol-5-yl)-2*H*-isoindole (6f): The product was obtained as a white solid (126 mg, 54%); m.p. 46.0–48.0 °C; R_f 0.44 (petroleum ether/ethyl acetate, 80:20 v/v). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.63 (d, *J* = 8.4 Hz, 1 H), 7.29–7.20 (m, 4 H), 7.13–7.00 (m, 11 H), 6.81 (dd, *J* = 6.8, 1.6 Hz, 2 H), 6.67 (m, 2 H), 5.21 (s, 2 H), 4.36 (s, 2 H), 4.26 (t, *J* = 7.6 Hz, 2 H), 2.81 (t, *J* = 7.6 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.5, 138.2, 136.7, 136.4, 128.9 (3×C), 128.7 (5×C), 128.6 (2×C), 128.2 (2×C), 127.7, 127.0, 126.9, 126.4, 125.5, 124.6, 123.7, 121.4, 120.2, 117.2, 102.4, 49.4, 49.3, 35.7, 31.1 ppm. IR (KBr): $\tilde{\nu}$ = 3060, 3027, 2925, 1629, 1602, 1567, 1537, 1494, 1453, 1384, 1353, 1220, 1157, 1108, 1077, 1029, 1001 cm^{-1}. MS (ESI): *m*/*z* (%) = 492.2 (100) [M + Na]$^+$. HRMS (ESI): *m*/*z* calcd. for $C_{31}H_{28}N_5$ [M + H]$^+$ 470.2339; found 470.2320.

1-Benzyl-2-(4-bromophenyl)-3-(1-phenethyl-1*H*-tetrazol-5-yl)-2*H*-isoindole (6g): The product was obtained as a white solid (214 mg, 80%); m.p. 164.7–166.7 °C; R_f 0.66 (petroleum ether/ethyl acetate, 75:25 v/v). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.61 (d, *J* = 8.4 Hz, 1 H), 7.28 (d, *J* = 8.4 Hz, 2 H), 7.18–7.06 (m, 9 H), 6.87–6.82 (m, 4 H), 6.45 (d, *J* = 7.6 Hz, 2 H), 4.49 (t, *J* = 7 Hz, 2 H), 4.19 (s, 2 H), 3.17 (t, *J* = 7 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.3, 138.5, 136.4, 135.8, 132.1 (2×C), 129.4 (2×C), 128.8 (2×C), 128.7 (2×C), 128.6, 128.5, 128.1, 127.6, 127.1, 126.6, 125.9, 125.1, 123.5, 123.2, 122.1, 120.3, 117.7, 116.8, 103.7, 49.5, 35.7, 31.4 ppm. IR (KBr): $\tilde{\nu}$ = 1628, 1569, 1493, 1454, 1386, 1370, 1068, 1013 cm^{-1}. IR (KBr): $\tilde{\nu}$ = 1627, 1568, 1493, 1453, 1385, 1370, 1067, 1013 cm^{-1}. MS (ESI): *m*/*z* (%) = 556.0 (100) [M + Na]$^+$. HRMS (ESI): *m*/*z* calcd. for $C_{30}H_{24}BrN_5Na$ [M + Na]$^+$ 556.1107; found 556.1113.

1-Benzyl-2-(4-methoxyphenyl)-3-(1-phenethyl-1*H*-tetrazol-5-yl)-2*H*-isoindole (6h): The product was obtained as a white solid (121 mg, 50%); m.p. 141.9–143.0 °C; R_f 0.77 (petroleum ether/ethyl acetate, 67:33 v/v). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.58 (t, *J* = 8.4, 1 Hz, 1 H), 7.19–7.10 (m, 8 H), 7.07–7.03 (m, 1 H), 6.88–6.86 (m, 4 H), 6.70–6.65 (m, 4 H), 4.36 (t, *J* = 7.2 Hz, 2 H), 4.22 (s, 2 H), 3.77 (s, 3 H), 3.08 (t, *J* = 7.2 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.7, 148.5, 138.9, 136.5, 129.5, 128.8 (2×C), 128.7 (3×C), 128.6 (2×C), 128.5 (2×C), 128.2 (2×C), 127.1, 126.4, 126.1, 124.7, 123.3, 121.8, 120.2, 117.9, 114.2 (2×C), 103.8, 55.7, 49.3, 35.6, 31.5 ppm. IR (KBr): $\tilde{\nu}$ = 3053, 3028, 3002, 2934, 2836, 1625, 1606, 1590, 1566, 1512, 1494, 1453, 1442, 1388, 1367, 1351, 1302, 1251, 1178, 1153, 1111, 1086, 1031 cm^{-1}. MS (ESI): *m*/*z* (%) = 508.2 (100) [M + Na]$^+$. HRMS (ESI): *m*/*z* calcd. for $C_{31}H_{27}N_5NaO$ [M + Na]$^+$ 508.2113; found 508.2110.

2-(4-Methoxyphenyl)-1-(4-methylbenzyl)-3-(1-phenethyl-1*H*-tetrazol-5-yl)-2*H*-isoindole (6i): The product was obtained as a white solid (205 mg, 82%); m.p. 150.6–152.1 °C; R_f 0.51 (petroleum ether/ethyl acetate, 75:25 v/v). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.57 (d, *J* = 8.4 Hz, 1 H), 7.19–7.10 (m, 5 H), 7.04 (t, *J* = 7.2 Hz, 1 H), 6.97 (d, *J* = 8 Hz, 2 H), 6.88–6.86 (m, 2 H), 6.77 (d, *J* = 8 Hz, 2 H), 6.69 (t, *J* = 9.6 Hz, 4 H), 4.35 (t, *J* = 7.2 Hz, 2 H), 4.17 (s, 2 H), 3.80 (s, 3 H), 3.08 (t, *J* = 7.2 Hz, 2 H), 2.28 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.6, 148.5, 136.4, 135.8, 129.4, 129.1 (2×C), 128.8, 128.7 (5×C), 128.6 (2×C), 128.0 (2×C), 127.0, 126.0, 124.6, 123.2, 121.6, 120.2, 117.8, 114.1 (2×C), 103.5, 55.6, 49.3, 35.6, 31.0, 21.3 ppm. IR (KBr): $\tilde{\nu}$ = 2925, 1699, 1683, 1635, 1568, 1514, 1456, 1385, 1370, 1252, 1300, 1252, 1110, 1025 cm^{-1}. MS (ESI): *m*/*z* (%) = 522.1 (100) [M + Na]$^+$. HRMS (ESI): *m*/*z* calcd. for $C_{32}H_{29}N_5NaO$ [M + Na]$^+$ 522.2264; found 522.2257.

1-(4-Methylbenzyl)-3-(1-phenethyl-1*H*-tetrazol-5-yl)-2-(*p*-tolyl)-2*H*-isoindole (6j): The product was obtained as a white solid (186 mg, 77%); m.p. 160.7–162.2 °C; R_f 0.67 (petroleum ether/ethyl acetate, 75:25 v/v). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.55 (dd, *J* = 8, 4 Hz, 1 H), 7.20–7.09 (m, 5 H), 7.05–6.96 (m, 5 H), 6.86 (t, *J* = 4 Hz, 2 H), 6.78 (d, *J* = 4 Hz, 2 H), 6.67 (d, *J* = 4 Hz, 2 H), 4.32 (t, *J* = 6 Hz, 2 H), 4.18 (s, 2 H), 3.05 (t, *J* = 6 Hz, 2 H), 2.33 (s, 3 H), 2.28 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.5, 139.0, 136.4, 135.9, 135.8, 134.2, 129.7 (2×C), 129.1 (2×C), 128.7 (3×C), 128.6 (2×C), 128.0 (2×C), 127.4 (2×C), 127.0, 126.2, 124.6, 123.3, 121.7, 120.2, 117.9, 103.4, 49.3, 35.6, 31.0, 21.4, 21.3 ppm. IR (KBr): $\tilde{\nu}$ = 2921, 1627, 1569, 1514, 1455, 1385, 1371, 1111, 1088, 1046, 1021 cm^{-1}. MS (ESI): *m*/*z* (%) = 506.1 (100) [M + Na]$^+$. HRMS (ESI): *m*/*z* calcd. for $C_{32}H_{30}N_5$ [M + H]$^+$ 484.2496; found 484.2495.

2-(4-Ethoxyphenyl)-1-(4-methylbenzyl)-3-(1-phenethyl-1*H*-tetrazol-5-yl)-2*H*-isoindole (6k): The product was obtained as a light-yellow solid (128 mg, 50%); m.p. 44.5–47.9 °C; R_f 0.63 (petroleum ether/ethyl acetate, 75:25 v/v). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.56 (d, *J* = 8.4 Hz, 1 H), 7.20–7.11 (m, 5 H), 7.06–7.01 (m, 1 H), 6.96 (d, *J* = 7.6 Hz, 2 H), 6.86 (m, 2 H), 6.77 (d, *J* = 8 Hz, 2 H), 6.68 (s, 4 H), 4.33 (t, *J* = 7.2 Hz, 2 H), 4.17 (s, 2 H), 3.98 (q, *J* = 6.8 Hz, 2 H), 3.07 (t, *J* = 7.2 Hz, 2 H), 2.28 (s, 3 H), 1.41 (t, *J* = 6.8 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.0, 148.5, 136.4, 135.9, 135.8, 130.2, 129.1 (2×C), 128.8 (5×C), 128.6 (2×C), 128.0, 127.0, 126.1, 124.6, 123.2, 121.6, 120.2, 117.8, 114.6 (2×C), 107.7, 103.5, 63.9, 49.3, 35.6, 31.0, 21.3, 15.0 ppm. IR (KBr): $\tilde{\nu}$ = 2978, 1625, 1604, 1565, 1514, 1495, 1454, 1384, 1345, 1292, 1118, 1043, 1009 cm^{-1}. MS (ESI): *m*/*z* (%) = 514.1 (100) [M + H]$^+$. HRMS (ESI): *m*/*z* calcd. for $C_{33}H_{32}N_5O$ [M + H]$^+$ 514.2602; found 514.2579.

2-Cyclohexyl-1-(4-methylbenzyl)-3-(1-phenethyl-1*H*-tetrazol-5-yl)-2*H*-isoindole (6l): The product was obtained as a white solid (166 mg, 70%); m.p. 112.0–113.1 °C; R_f 0.70 (petroleum ether/ethyl acetate, 80:20 v/v). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.53 (d, *J* = 8.4 Hz, 1 H), 7.29–7.13 (m, 3 H), 7.04–6.86 (m, 9 H), 4.42 (s, 4 H), 3.21 (t, *J* = 7.4 Hz, 2 H), 2.29 (s, 3 H), 1.61–0.95 (m, 11 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.8, 136.5, 136.1, 135.8, 129.4, 129.3 (2×C), 128.8 (2×C), 128.7 (2×C), 127.9 (2×C), 127.1, 126.8, 126.3, 124.0, 123.4, 121.0, 120.0, 117.0, 59.5 (2×C), 49.6, 35.7, 31.3 (2×C), 26.6 (2×C), 25.1, 21.3 ppm. IR (KBr): $\tilde{\nu}$ = 3025, 2931, 2852, 1626, 1563, 1510, 1453, 1429, 1401, 1369, 1348, 1223, 1114, 1018 cm^{-1}. MS (ESI): *m*/*z* (%) = 476.2 (100) [M + H]$^+$. HRMS (ESI): *m*/*z* calcd. for $C_{31}H_{33}N_5Na$ [M + Na]$^+$ 498.2634; found 498.2630.

2-(4-Bromophenyl)-1-(4-methylbenzyl)-3-(1-phenethyl-1*H*-tetrazol-5-yl)-2*H*-isoindole (6m): The product was obtained as a white solid (142 mg, 52%); m.p. 155.0–156.0 °C; R_f 0.70 (petroleum ether/ethyl acetate, 75:25 v/v). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.59 (dt, *J* = 8.4, 1 Hz, 1 H), 7.30–7.27 (m, 2 H), 7.18–7.04 (m, 6 H), 6.97 (d, *J* = 8 Hz, 2 H), 6.86 (dd, *J* = 7.6, 1 Hz, 2 H), 6.72 (d, *J* = 8 Hz, 2 H), 6.47 (d, *J* = 8 Hz, 2 H), 4.48 (t, *J* = 7 Hz, 2 H), 4.15 (s, 2 H), 3.17 (t, *J* = 7 Hz, 2 H), 2.29 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.3, 136.0, 132.1 (2×C), 129.4 (3×C), 129.2 (2×C), 128.8 (3×C), 128.7 (2×C), 127.9 (2×C), 127.1, 125.9, 125.1, 124.2, 123.4, 123.2, 122.4, 121.9, 120.4, 117.6, 103.5, 49.5, 35.7, 30.9, 21.3 ppm. IR (KBr): $\tilde{\nu}$ = 2917, 1634, 1568, 1494, 1455, 1385, 1370, 1068, 1013 cm^{-1}. MS (ESI): *m*/*z* (%) = 570.1 (100) [M + Na]$^+$.

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HRMS (ESI): *m/z* calcd. for $C_{31}H_{26}BrN_5Na$ $[M + Na]^+$ 570.1264; found 570.1260.

1-(1-Cyclohexyl-1*H*-tetrazol-5-yl)-2-(4-methoxyphenyl)-3-(4-methylbenzyl)-2*H*-isoindole (6n): The product was obtained as a white solid (124 mg, 52%); m.p. 171.6–173.6 °C; R_f 0.63 (petroleum ether/ethyl acetate, 75:25 v/v). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.58 (d, J = 8.4 Hz, 1 H), 7.31 (d, J = 8.8 Hz, 1 H), 7.14–7.10 (m, 1 H), 7.06–7.02 (m, 1 H), 7.00–6.95 (m, 4 H), 6.81–6.78 (m, 4 H), 4.22 (s, 2 H), 3.78 (s, 3 H), 2.28 (s, 3 H), 1.92–1.77 (m, 4 H), 1.63 (d, J = 11.2 Hz, 2 H), 1.54 (d, J = 12 Hz, 2 H), 1.25–1.12 (m, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.8, 147.3, 135.8, 129.8, 129.1 (3×C), 128.9 (2×C), 128.2, 128.0 (2×C), 126.6, 124.4, 123.3, 121.7, 120.1, 117.8, 114.3 (2×C), 104.1, 58.2, 55.7, 33.2 (2×C), 31.1, 25.5 (2×C), 25.0, 21.2 ppm. IR (KBr): $\tilde{\nu}$ = 2935, 2857, 1627, 1565, 1513, 1451, 1398, 1384, 1365, 1301, 1253, 1174, 1107, 1024 cm^{-1}. MS (ESI): *m/z* (%) = 478.2 (100) $[M + H]^+$. HRMS (ESI): *m/z* calcd. for $C_{30}H_{32}N_5O$ $[M + H]^+$ 478.2601; found 478.2598.

2-(4-Chlorophenyl)-1-(4-methylbenzyl)-3-(1-phenethyl-1*H*-tetrazol-5-yl)-2*H*-isoindole (6o): The product was obtained as a white solid (174 mg, 69%); m.p. 166.0–168.0 °C; R_f 0.58 (petroleum ether/ethyl acetate, 75:25 v/v). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.59 (d, J = 8.4 Hz, 1 H), 7.16–7.05 (m, 8 H), 6.96 (d, J = 7.6 Hz, 2 H), 6.87 (d, J = 6.4 Hz, 2 H), 6.72 (d, J = 8 Hz, 2 H), 6.53 (d, J = 7.6 Hz, 2 H), 4.48 (t, J = 6.8 Hz, 2 H), 4.15 (s, 2 H), 3.17 (t, J = 6.8 Hz, 2 H), 2.28 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.3, 136.5, 136.1, 135.5, 135.4, 135.1, 129.2 (7×C), 128.9, 128.8 (2×C), 128.7, 128.0 (2×C), 127.1, 126.1, 125.1, 123.5, 122.0, 120.4, 117.7, 103.8, 49.5, 35.7, 31.0, 21.3 ppm. IR (KBr): $\tilde{\nu}$ = 2974, 1634, 1569, 1496, 1455, 1385, 1090, 1049 cm^{-1}. MS (ESI): *m/z* (%) = 504.1 (100) $[M + H]^+$. HRMS (ESI): *m/z* calcd. for $C_{31}H_{26}ClN_5Na$ $[M + Na]^+$ 526.1774; found 526.1754.

1-(Cyclopropylmethyl)-3-(1-phenethyl-1*H*-tetrazol-5-yl)-2-(*p*-tolyl)-2*H*-isoindole (6p): The product was obtained as a white solid (87 mg, 40%); m.p. 118.0–120.0 °C; R_f 0.64 (petroleum ether/ethyl acetate, 75:25 v/v). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.68 (dt, J = 8.4, 1 Hz, 1 H), 7.19–7.09 (m, 7 H), 7.06–7.02 (m, 1 H), 6.91 (dd, J = 7.6, 1.6 Hz, 2 H), 6.85 (d, J = 7.6 Hz, 2 H), 4.35 (t, J = 7.2 Hz, 2 H), 3.11 (t, J = 7.2 Hz, 2 H), 2.81 (d, J = 7.2 Hz, 2 H), 2.37 (s, 3 H), 0.83 (m, 1 H), 0.41–0.37 (m, 2 H), 0.04–0.01 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.5, 139.1, 136.5, 134.6, 130.4 (2×C), 129.7, 128.7 (2×C), 128.6, 127.7 (2×C), 127.0, 126.2, 124.5, 122.7, 121.2, 120.4, 120.4, 117.7, 103.2, 49.2, 35.6, 30.1, 21.4, 11.5, 5.5 (2×C) ppm. IR (KBr): $\tilde{\nu}$ = 3032, 2997, 2923, 1625, 1565, 1514, 1494, 1454, 1389, 1365, 1350, 1108, 1018 cm^{-1}. MS (ESI): *m/z* (%) = 434.3 (100) $[M + H]^+$. HRMS (ESI): *m/z* calcd. for $C_{28}H_{28}N_5$ $[M + H]^+$ 434.2339; found 434.2329.

2-Cyclohexyl-1-(cyclopropylmethyl)-3-(1-phenethyl-1*H*-tetrazol-5-yl)-2*H*-isoindole (6q): The product was obtained as a colorless semi-solid (128 mg, 60%); R_f 0.70 (petroleum ether/ethyl acetate, 80:20 v/v). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.56 (d, J = 8.4 Hz, 1 H), 7.34–7.31 (m, 1 H), 7.19–7.14 (m, 3 H), 7.02–6.93 (m, 3 H), 6.83 (d, J = 8.4 Hz, 1 H), 4.31 (t, J = 7.2 Hz, 2 H), 3.24 (t, J = 7.2 Hz, 2 H), 3.05 (d, J = 6 Hz, 2 H), 1.79–0.88 (m, 12 H), 0.59–0.53 (m, 2 H), 0.32–0.26 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.0, 136.6, 128.9 (2×C), 128.7 (2×C), 128.4, 127.1, 126.6, 123.9, 122.8, 120.5, 120.3, 116.9, 59.4, 49.6, 35.7, 30.1 (2×C), 26.8 (3×C), 25.2, 11.8, 5.7 (2×C) ppm. IR (KBr): $\tilde{\nu}$ = 2930, 2854, 1708, 1681, 1626, 1559, 1496, 1453, 1374, 1349, 1269, 1216, 1111, 1078, 1049, 1018 cm^{-1}. MS (ESI): *m/z* (%) = 426.1 (100) $[M + H]^+$. HRMS (ESI): *m/z* calcd. for $C_{27}H_{31}N_5Na$ $[M + Na]^+$ 448.2472; found 448.2453.

1-(Cyclopropylmethyl)-3-(1-phenethyl-1*H*-tetrazol-5-yl)-2-phenyl-2*H*-isoindole (6r): The product was obtained as a white solid (105 mg, 50%); m.p. 136.0–137.0 °C; R_f 0.59 (petroleum ether/ethyl acetate, 75:25 v/v). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.69 (dt, J = 8.4, 1 Hz, 1 H), 7.41–7.26 (m, 4 H), 7.18–7.09 (m, 4 H), 7.07–7.03 (m, 1 H), 6.97 (d, J = 7.6 Hz, 2 H), 6.92–6.90 (m, 2 H), 4.37 (t, J = 7.2 Hz, 2 H), 3.12 (t, J = 7.2 Hz, 2 H), 2.82 (d, J = 6.4 Hz, 2 H), 0.85–0.78 (m, 1 H), 0.41–0.36 (m, 2 H), 0.04–0.01 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.5, 137.3, 136.6, 130.5, 129.1 (4×C), 128.8 (2×C), 128.7, 128.1 (2×C), 127.1, 126.3, 124.7, 122.8, 121.4, 120.5, 117.8, 103.3, 49.3, 35.6, 30.2, 11.5, 5.6 (2×C) ppm. IR (KBr): $\tilde{\nu}$ = 3053, 2940, 2924, 1627, 1597, 1566, 1507, 1496, 1455, 1437, 1388, 1363, 1348, 1293, 1226, 1212, 1165, 1112, 1076, 1044, 1015 cm^{-1}. MS (ESI): *m/z* (%) = 442.2 (100) $[M + Na]^+$. HRMS (ESI): *m/z* calcd. for $C_{27}H_{25}N_5Na$ $[M + Na]^+$ 442.2002; found 442.1999.

1-(Cyclopropylmethyl)-2-(4-methoxyphenyl)-3-(1-phenethyl-1*H*-tetrazol-5-yl)-2*H*-isoindole (6s): The product was obtained as a white solid (119 mg, 53%); m.p. 128.5–131.5 °C; R_f 0.53 (petroleum ether/ethyl acetate, 75:25 v/v). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.68 (dt, J = 8.4, 1 Hz, 1 H), 7.26–6.87 (m, 10 H), 6.80 (dt, J = 7.6, 1.2 Hz, 2 H), 4.39 (t, J = 7.4 Hz, 2 H), 3.81 (s, 3 H), 3.13 (t, J = 7.2 Hz, 2 H), 2.80 (d, J = 6.8 Hz, 2 H), 0.88–0.79 (m, 1 H), 0.42–0.37 (m, 2 H), 0.08–0.01 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.7, 148.6, 136.6, 130.7, 129.9, 129.0 (2×C), 128.7 (4×C), 127.0, 126.1, 124.6, 122.7, 121.2, 120.5, 117.7, 114.2 (2×C), 103.3, 55.7, 49.3, 35.6, 30.2, 11.5, 5.6 (2×C) ppm. IR (KBr): $\tilde{\nu}$ = 1626, 1561, 1514, 1386, 1349, 1301, 1250, 1183, 1108, 1029 cm^{-1}. MS (ESI): *m/z* (%) = 472.2 (100) $[M + Na]^+$. HRMS (ESI): *m/z* calcd. for $C_{28}H_{28}N_5O$ $[M + H]^+$ 450.2288; found 450.2292.

1-(Cyclopropylmethyl)-2-(4-fluorophenyl)-3-(1-phenethyl-1*H*-tetrazol-5-yl)-2*H*-isoindole (6t): The product was obtained as a white solid (96 mg, 44%); m.p. 126.0–128.0 °C; R_f 0.71 (petroleum ether/ethyl acetate, 80:20 v/v). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.69 (d, J = 8.4 Hz, 1 H), 7.21–7.11 (m, 5 H), 7.08–7.04 (m, 1 H), 6.97 (t, J = 8.4 Hz, 2 H), 6.92–6.90 (m, 2 H), 6.85–6.82 (m, 2 H), 4.50 (t, J = 7 Hz, 2 H), 3.20 (t, J = 7 Hz, 2 H), 2.78 (d, J = 6.8 Hz, 2 H), 0.83–0.76 (m, 1 H), 0.43–0.38 (m, 2 H), 0.04–0.01 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.7, 161.2, 148.4, 136.6, 133.1, 130.9, 129.9, 128.8 (4×C), 127.1, 125.9, 124.9, 122.7, 121.4, 120.6, 117.5, 116.2, 115.9, 103.5, 49.4, 35.7, 30.1, 11.5, 5.6 (2×C) ppm. IR (KBr): $\tilde{\nu}$ = 3076, 3004, 2945, 2908, 1720, 1626, 1562, 1508, 1455, 1392, 1351, 1219, 1149, 1103, 1091 cm^{-1}. MS (ESI): *m/z* (%) = 438.1 (100) $[M + H]^+$. HRMS (ESI): *m/z* calcd. for $C_{27}H_{24}FN_5Na$ $[M + Na]^+$ 460.1908; found 460.1895.

1-Butyl-3-(1-phenethyl-1*H*-tetrazol-5-yl)-2-phenyl-2*H*-isoindole (6u): The product was obtained as a white solid (145 mg, 69%); m.p. 117.4–117.9 °C; R_f 0.63 (petroleum ether/ethyl acetate, 75:25 v/v). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.64 (d, J = 8.4 Hz, 1 H), 7.37–7.26 (m, 4 H), 7.18–7.12 (m, 4 H), 7.06–7.02 (m, 1 H), 6.91 (t, J = 7 Hz, 4 H), 4.37 (t, J = 7.2 Hz, 2 H), 3.11 (t, J = 7.2 Hz, 2 H), 1.49–1.41 (m, 2 H), 1.22–1.15 (m, 2 H), 0.78 (t, J = 7.4 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.5, 137.2, 136.6, 131.0, 129.1 (2×C), 129.0, 128.8 (2×C), 128.7 (2×C), 127.8 (2×C), 127.1, 126.2, 124.7, 122.6, 121.1, 120.3, 117.8, 102.9, 49.3, 35.6, 32.4, 25.1, 22.7, 14.0 ppm. IR (KBr): $\tilde{\nu}$ = 3049, 2949, 2921, 2855, 1628, 1597, 1566, 1535, 1507, 1496, 1455, 1433, 1388, 1367, 1325, 1293, 1230, 1166, 1103, 1076, 1024 cm^{-1}. MS (ESI): *m/z* (%) = 444.2 (100) $[M + Na]^+$. HRMS (ESI): *m/z* calcd. for $C_{27}H_{27}N_5Na$ $[M + Na]^+$ 444.2159; found 444.2186.

1-Butyl-2-(4-methoxyphenyl)-3-(1-phenethyl-1*H*-tetrazol-5-yl)-2*H*-isoindole (6v): The product was obtained as a white solid (117 mg,

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52%); m.p. 123.9–124.9 °C; R_f 0.70 (petroleum ether/ethyl acetate, 75:25 v/v). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.63 (d, J = 8 Hz, 1 H), 7.17–7.08 (m, 5 H), 7.03 (t, J = 8 Hz, 1 H), 6.91 (q, J = 4 Hz, 2 H), 6.82 (q, J = 8 Hz, 4 H), 4.38 (t, J = 8 Hz, 2 H), 3.81 (s, 3 H), 3.12 (t, J = 8 Hz, 2 H), 2.86 (t, J = 8 Hz, 2 H), 1.49–1.42 (m, 2 H), 1.25–1.16 (m, 2 H), 0.80 (t, J = 8 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.7, 148.6, 136.6, 131.2, 129.8, 128.8 (5×C), 128.7, 127.1, 126.1, 124.6, 122.5, 121.0, 120.4, 117.7, 114.3 (2×C), 103.1, 55.7, 49.3, 35.7, 32.5, 25.2, 22.7, 14.0 ppm. IR (KBr): $\tilde{\nu}$ = 2960, 2933, 2871, 1625, 1607, 1566, 1512, 1450, 1439, 1367, 1299, 1248, 1173, 1101, 1024 cm^{-1}. MS (ESI): *m*/*z* (%) = 452.1 (100) $[M + H]^+$. HRMS (ESI): *m*/*z* calcd. for $C_{28}H_{30}N_5O$ $[M + H]^+$ 452.2445; found 452.2453.

1-(1-Benzyl-1*H*-tetrazol-5-yl)-3-butyl-2-(4-methoxyphenyl)-2*H*-isoindole (6w): The product was obtained as a white solid (103 mg, 47%); m.p. 136.7–137.7 °C; R_f 0.47 (petroleum ether/ethyl acetate, 75:25 v/v). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.66 (dt, J = 8.8, 1 Hz, 1 H), 7.26–7.21 (m, 2 H), 7.18–7.13 (m, 3 H), 7.07–7.03 (m, 1 H), 6.74–6.68 (m, 4 H), 6.59 (d, J = 8 Hz, 2 H), 5.47 (s, 2 H), 3.78 (s, 3 H), 2.81 (t, J = 7.6 Hz, 2 H), 1.45–1.38 (m, 2 H), 1.24–1.15 (m, 2 H), 0.80 (t, J = 7.4 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.7, 148.5, 134.0, 131.1, 129.6, 128.9 (2×C), 128.7 (2×C), 128.5, 128.1 (2×C), 125.6, 124.6, 122.5, 120.9, 120.6, 117.5, 113.9 (2×C), 55.6, 55.6, 51.7, 32.5, 25.1, 22.6, 14.0 ppm. IR (KBr): $\tilde{\nu}$ = 3052, 2957, 2929, 2857, 1627, 1605, 1573, 1513, 1441, 1368, 1297, 1246, 1177, 1101, 1020 cm^{-1}. MS (ESI): *m*/*z* (%) = 438.1 (100) $[M + H]^+$. HRMS (ESI): *m*/*z* calcd. for $C_{27}H_{28}N_5O$ $[M + H]^+$ 438.2294; found 438.2289.

1-Butyl-2-cyclohexyl-3-(1-phenethyl-1*H*-tetrazol-5-yl)-2*H*-isoindole (6x): The product was obtained as a colorless semisolid (120 mg, 56%); R_f 0.78 (petroleum ether/ethyl acetate, 80:20 v/v). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.55 (d, J = 8.4 Hz, 1 H), 7.18–7.11 (m, 3 H), 7.02–6.93 (m, 4 H), 6.85 (d, J = 8.4 Hz, 1 H), 4.40 (s, 2 H), 3.23 (t, J = 7.2 Hz, 2 H), 3.07 (t, J = 7.8 Hz, 2 H), 1.76–1.62 (m, 8 H), 1.49–1.39 (m, 3 H), 1.31–1.26 (m, 3 H), 1.14–1.08 (m, 1 H), 0.98 (t, J = 7.4 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.9, 136.6, 129.3, 128.8 (2×C), 128.6 (2×C), 127.0, 126.4, 123.9, 122.6, 120.2, 120.1, 116.9, 99.3, 59.1, 49.5, 35.6, 33.0 (3×C), 26.7 (2×C), 25.7, 25.2, 22.9, 14.1 ppm. IR (KBr): $\tilde{\nu}$ = 3028, 2930, 2856, 1709, 1681, 1633, 1560, 1453, 1415, 1397, 1370, 1266, 1209, 1163, 1127, 1030, 1016 cm^{-1}. MS (ESI): *m*/*z* (%) = 428.2 (100) $[M + H]^+$. HRMS (ESI): *m*/*z* calcd. for $C_{27}H_{33}N_5Na$ $[M + Na]^+$ 450.2634; found 450.2626.

2-(4-Bromophenyl)-1-butyl-3-(1-phenethyl-1*H*-tetrazol-5-yl)-2*H*-isoindole (6y): The product was obtained as a white solid (168 mg, 67%); m.p. 151.0–151.7 °C; R_f 0.50 (petroleum ether/ethyl acetate, 80:20 v/v). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.64 (d, J = 8.4 Hz, 1 H), 7.40 (d, J = 8.8 Hz, 2 H), 7.20–7.13 (m, 5 H), 7.07–7.03 (m, 1 H), 6.90 (dd, J = 7.4, 1.4 Hz, 2 H), 6.64 (d, J = 7.6 Hz, 2 H), 4.50 (t, J = 6.8 Hz, 2 H), 3.20 (t, J = 6.8 Hz, 2 H), 2.84 (t, J = 7.6 Hz, 2 H), 1.47–1.40 (m, 2 H), 1.25–1.15 (m, 2 H), 0.80 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.4, 136.6, 136.1, 132.3 (2×C), 131.2, 129.4 (2×C), 128.8 (4×C), 127.1, 126.0, 125.0, 123.2, 122.7, 121.3, 120.5, 117.5, 103.0, 49.5, 35.7, 32.5, 25.1, 22.7, 14.0 ppm. IR (KBr): $\tilde{\nu}$ = 2949, 2927, 2867, 1626, 1562, 1508, 1490, 1454, 1397, 1371, 1350, 1098, 1067, 1010 cm^{-1}. MS (ESI): *m*/*z* (%) = 522.0 (100) $[M + Na]^+$. HRMS (ESI): *m*/*z* calcd. for $C_{27}H_{26}BrN_5Na$ $[M + Na]^+$ 522.1264; found 522.1248.

2-(4-Chlorophenyl)-1-methyl-3-(1-phenethyl-1*H*-tetrazol-5-yl)-2*H*-isoindole (6z): The product was obtained as a white solid (145 mg, 70%); m.p. 168.0–169.0 °C; R_f 0.64 (petroleum ether/ethyl acetate, 75:25 v/v). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.6 (d, J = 8.4 Hz, 1 H), 7.26 (d, J = 8.4 Hz, 2 H), 7.21–7.11 (m, 5 H), 7.08–7.04 (m, 1 H), 6.90 (m, 2 H), 6.73 (d, J = 8.4 Hz, 2 H), 4.48 (t, J = 7 Hz, 2 H), 3.20 (t, J = 7 Hz, 2 H), 2.43 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.4, 136.5, 135.6, 135.0, 129.4 (2×C), 128.9 (2×C), 128.8 (4×C), 127.1, 126.3, 126.1, 125.1, 122.9, 121.4, 120.3, 117.6, 103.0, 49.5, 35.7, 11.3 ppm. IR (KBr): $\tilde{\nu}$ = 3061, 2927, 2933, 1628, 1564, 1508, 1493, 1454, 1402, 1365, 1346, 1282, 1231, 1163, 1091, 1013 cm^{-1}. MS (ESI): *m*/*z* (%) = 414.1 (100) $[M + H]^+$. HRMS (ESI): *m*/*z* calcd. for $C_{24}H_{21}ClN_5$ $[M + H]^+$ 414.1480; found 414.1461.

X-ray Crystal Data of 6b: CCDC-986608 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam. ac. uk/data_request/cif.

Supporting Information (see footnote on the first page of this article): ^{1}H and ^{13}C NMR spectra of all compounds, crystal data and details of X-ray experiments for **6b**.

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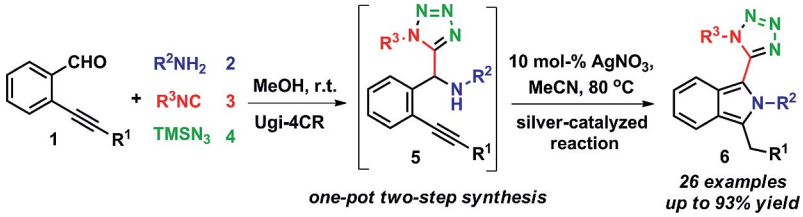

A one-pot, two-step synthesis of 1-(1*H*-tetrazol-5-yl)-2*H*-isoindole derivatives through Ugi four-component reaction/$AgNO_3$-catalyzed reaction of 2-alkynylbenzaldehydes, amines, isonitriles, and Me_3SiN_3 has been developed. The transformation proceeds through 5-*exo*-*dig* cyclization, [1,3]-H shift, and [1,5]-H shift to generate the products in moderate to excellent yields.

Keywords: Multicomponent reactions / Cyclization / Nitrogen heterocycles / Alkynes / Silver

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