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A New Approach for Fused Isoindolines via hexadehydro-Diels-Alder Reaction (HDDA) by Fe (0) Catalysis

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Jaya Kishore Vandavasi,[a] Wan-Ping Hu,[b] Cheng-Tien Hsiao,[a] Gopal Chandru Senadi,[a] Jeh-Jeng Wang*,[a]

A simple method has been developed for the synthesis of fused isoindolines via a cascade HDDA approach catalyzed by $Fe_2(CO)_9$. In this work, 1, 3-diyne was involved in a [4+2] cycloisomerization with a diynophile to give aryne intermediate, which was subsequently trapped with –OH nucleophile to beget the fused isoindolines in high yields.

Introduction

Fused heterocycles are important class of compounds mostly in pharmaceutical and natural products. Among them, nitrogen and oxygen containing molecules have more potent role in medicinal chemistry. In particular, isoindolines belonging to nitrogen heterocycles exhibit a number of biological functions such as diuretic, antitumor, selective serotonin uptake inhibitors, herbicidal activities,[1,2] antipsychotic agents I (Fig. 1)[3] and Alzheimer's disease II.[4] On other hand, the dihydrobenzofuran structural motif from oxygen heterocycles also play a pivotal role in many bio-active natural products III & IV (Fig. 1), as well as synthetic drugs used in the treatment of hypertension, central nervous system trauma, pulmonary, and atherosclerotic peripheral arterial disease.[5,6] Hence, the study on isoindolines and 2,3-dihydrobenzofurans continue to be an interesting research field.

In general, synthesis of isoindolines and 2,3-dihydrobenzofurans have been described by several approaches.[7,8] The most common methods include the utilization of transition metal catalysts[9] and bases.[10] By knowing the biological importance of these two cores, we hereby designed a new synthetic protocol to convert both the cores in one molecule as shown in Scheme 1E.

The synthesis of complex heterocyclic compounds via a cascade process has been a captivating area in organic chemistry. In this view, many researchers have focused on triynes A (Scheme 1) as potential precursor for building fused ring systems. For representative examples, the combined use of enyne metathesis and metallotropic [1,3]-shift of alkynyl ruthenium carbenes is used to construct enediynes and oligoenynes (scheme 1, B).[11] In a similar way, the construction of fused yne-substituted aryl halides were developed with Pd and Ag (Scheme 1, C & D).[12,13] Very recently, Hoye and Lee

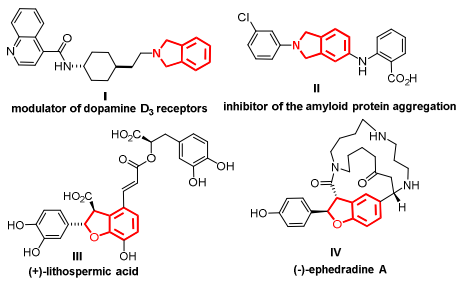
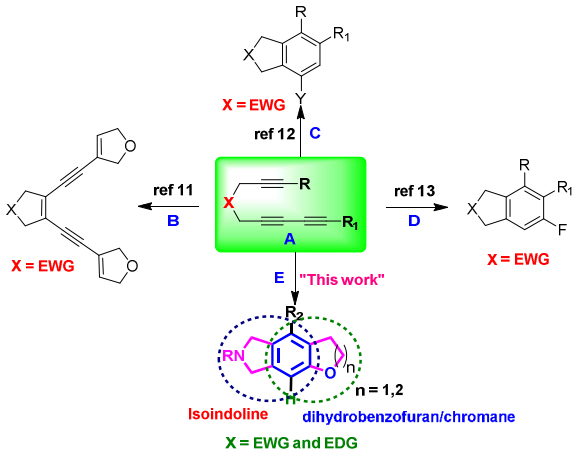


Fig. 1 Pharmaceutical and natural compounds.



Scheme 1 Synthetic approaches with triyne molecule.

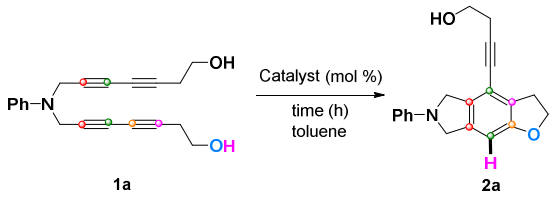
individually developed HDDA for constructing fused ring systems by using triynes.[14-16] In this context, and following our ongoing interest in the synthesis of bicyclic[1,2,3]-triazole

from alkynols, we envisioned the possibility of exploring new reagents and development of a catalytic cascade reactions with alkynols to undergo the HDDA reaction. Herein, we have developed a new synthetic pathway to afford fused isoindolines through generation of *o*-arynes via Fe(0) catalysis for the first time with broad substrate scope in high yields (Scheme 1E).

Results and discussion

To optimize the reaction condition, compound 1a was synthesized and used as a model substrate. The initial investigation of **1a** with AgOTf failed to produce the desired compound **2a** (Table 1, entry 1). We next evaluated the feasibility of the reaction with various metal salts (entries 2-12). Among them Fe salts shown good results compared with other metal salts (entries 10-12). In particular, $Fe_2(CO)_9$ underwent smooth reaction to give compound **2a** in best yield 92% (entry 11). Further, the reaction was carried out with lower catalyst loading and there was no any substantial change in the reaction yield (entry 13). According to the observations from the optimizing studies, the best condition was found to be with 5 mol% of $Fe_2(CO)_9$ in toluene at 80°C for 2h to afford the compound **2a** in 92% yield (entry 13).

Table 1 Optimizing conditions to construct fused heterocycles.



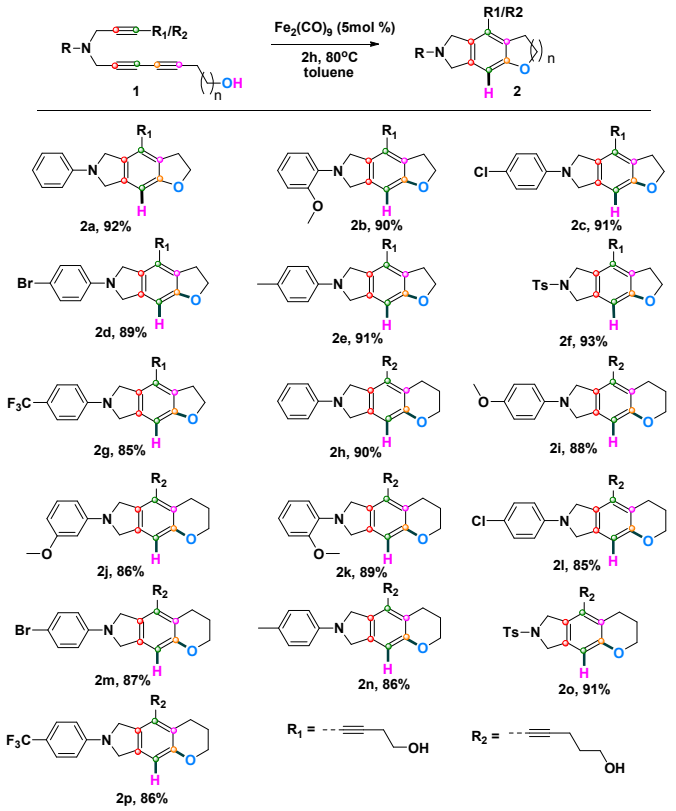
1a 2a

S.No	catalyst	time	Yield (%)[d]
1	AgOTf	6h	-----[a]
2	$ZnCl_2$	4h	82
3	$Pd(OAc)_2$	2h	-----[a]
4[b]	$Pd(OAc)_2$	24h	80
5[b]	PPh_3AuCl	6h	72
6	$Cu(OTf)_2$	6h	79
7	$Fe(OTf)_3$	6h	83
8	$Sc(OTf)_3$	6h	75
9	$Zn(OTf)_2$	6h	73
10	$FeCl_3$	2h	88
11	$Fe_2(CO)_9$	2h	92
12	$FeBr_3$	2h	85
13[c]	**$Fe_2(CO)_9$**	**2h**	**92**

Reaction conditions: Compound **1** (0.5 mmol), catalyst (10 mol%), toluene (3 mL), temp at 80°C and time (h). [a] Complex mixture. [b] 28°C. [c] 5 mol%. [d] Isolated yields.

With the optimal reaction conditions (Table 1, entry 13) in hand, we have conducted HDDA reaction with various substrates in Table 2, which follows a [4+2] cycloisomerization of 1,3-diyne with a 'diynophile' to give a reactive aryne intermediate which was subsequently trapped with –OH nucleophiles was studied (entry 1, 92%). We conducted reactions with EDG as –OMe/Me on phenyl ring and the reactions produced with high yields (entries 2b and 2e). Reaction were also tested with electron withdrawing groups like Cl/Br/Ts/CF3 and all of them are progressed well to produce high yields (entries **2c-d** and **2f-g**). The synthetic strategy was extended to construct fused chromane scaffolds (entries **2h-p**). The electronic effects were also studied for this reaction with various functionalities such as -OMe/Me (entries **2i-k** and **2n**) at o/m/p positions. In similar way, electron withdrawing groups such as Cl/Br/Ts/CF_3 obeyed the reaction condition to produce the desired compounds in good yields (entries **2l-m** and **2o-p**). It is noteworthy to mention that this method is the first example for HDDA reaction with EDG on phenyl ring attached to nitrogen.

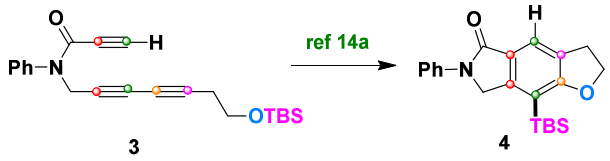
Table 2 Investigation of reaction with $Fe_2(CO)_9$ to synthesize fused Isoindolines.[a]



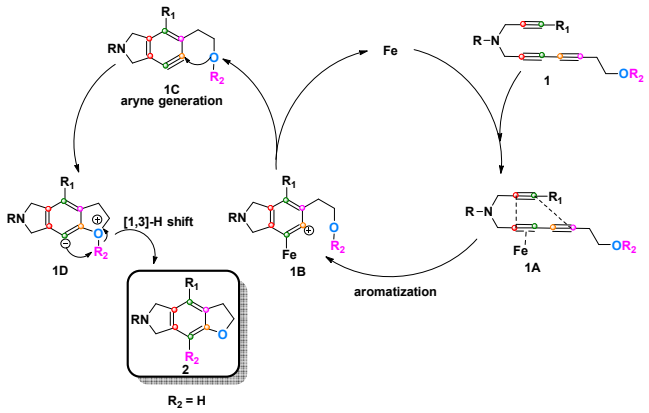
[a] Reaction Condition: Comp **1** (0.5 mmol), $Fe_2(CO)_9$ (5 mol%), toluene (3 mL), temp 80°C and time 2h.

Based on the previous literature reports[18] and our observed results, a plausible mechanism was outlined in Scheme 3. The initial co-ordination of Fe to compound **1** resulted in the formation of intermediate **1A**. Further, the intermediate **1A** underwent [4+2] cycloaddition to afford the key aryne

intermediate **1C** via iron-complex compound **1B** and Fe was regenerated for the next catalytic cycle. Finally, the compound **1C** was trapped by intramolecular –OH nucleophile followed by [1, 3]-H shift to achieve the desired fused isoindolines **2**. The 1, 3-shift was explored previously by using –OTBS (scheme 2), deuterium labelling and DFT experiments.[14a, 16a] By this results, we also predict that our reaction was followed a 1,3-shift to beget the desired compound.



Scheme 2. HDDA reaction 1,3-shift.



Scheme 3. A Plausible mechanism

Conclusions

In conclusion, we have developed a simple method for the synthesis of fused isoindolines via a cascade HDDA approach catalyzed by $Fe_2(CO)_9$. The key features of this reaction are easy handling, atom efficiency, time economic and good reaction yields with broad substrate scope irrespective of electronic factors. It is noteworthy to mention that this method is the first example for HDDA reaction with EDG on phenyl ring attached to nitrogen. Further, extension of this method for trapping with other carbo or hetero nucleophiles are under progress.

Experimental Section

General Information:

Melting points are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively, using $CDCl_3$ as a solvent. ^{1}H NMR chemical shifts are referenced to TMS or $CDCl_3$ (7.26 ppm). ^{13}C NMR was referenced to $CDCl_3$ (77.0 ppm). Multiplicities were determined by the DEPT sequence as s, d, t, q. Mass spectra and high-resolution mass spectra (HRMS) were measured using the ESI-Ion trap technique by Taichung Regional Instrument Center of NSC at NCHU. Flash chromatography was carried out on silica gel 60 (E. Merck, 230-400 mesh).

General Procedure to Synthesis Compound 2:

A 50 mL round-bottomed flask was charged with the comp **1** (0.5 mmol) and toluene (4 mL). To this, $Fe_2(CO)_9$ (5 mol%) was added. After stirring at 90°C for 2 h under air the completion of reaction was monitored by TLC. Removal of the solvent in vacuo and purification of the residue by silica gel column chromatography afforded the desired product **2.**

4-(6-phenyl-3,5,6,7-tetrahydro-2H-furo[2,3-f]isoindol-4-yl)but-3-yn-1-ol (2a): According to general procedure, title compound was synthesized **(2a)**. The product was purified by silica gel flash column chromatography (hexane→hexane/AcOEt = 5/1) to afford **2a** as off-white solid (140.3 mg, 92% yield). **Melting Point**: 105-107°C. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.29 (t, *J* = 7.8 Hz, 2H), 6.75-6.65 (m, 4H), 4.61 (t, *J* = 8.8 Hz, 2H), 4.56 (s, 4H), 3.86 (t, 6.4 Hz, 2H), 3.23 (t, 8.8 Hz, 2H), 2.77 (t, 6.4 Hz, 2H), 1.83 (brs, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 159.5, 147.0, 137.6, 131.8, 129.3, 128.7, 116.0, 114.7, 111.4, 103.7, 92.9, 78.0, 71.6, 61.2, 54.2, 53.1, 29.4, 24.0. **HRMS** (ESI): calculated for $[C_{20}H_{20}NO_2]^+$ requires 306.14886, found 306.14884.

4-(6-(3-methoxyphenyl)-3,5,6,7-tetrahydro-2H-furo[2,3-f]isoindol-4-yl)but-3-yn-1-ol (2b): According to general procedure, title compound was synthesized **(2b)**. The product was purified by silica gel flash column chromatography (hexane→hexane/AcOEt = 5/1) to afford **2b** as a light yellow sticky mass (142.3 mg, 85% yield). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.18 (t, *J* = 8.4 Hz, 1H), 6.64 (s, 1H), 6.284 (dddd, *J* = 2.4 Hz, 2H), 6.17 (t, *J* = 2.4 Hz, 1H), 4.57 (t, *J* = 8.4 Hz, 2H), 4.50 (s, 4H), 3.84 (t, *J* = 6.4 Hz, 2H), 3.82 (s, 3H), 3.18 (t, *J* = 8.4 Hz, 2H), 2.76 (t, *J* = 6.4 Hz, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 160.8, 159.5, 148.4, 137.5, 131.6, 130.0, 128.6, 114.7, 104.6, 103.5, 101.0, 97.8, 93.0, 77.9, 71.6, 61.2, 55.1, 54.2, 53.1, 29.3, 23.9. **HRMS** (ESI): calculated for $[C_{21}H_{22}NO_3]^+$ requires 336.15942, found 336.15941.

4-(6-(4-chlorophenyl)-3,5,6,7-tetrahydro-2H-furo[2,3-f]isoindol-4-yl)but-3-yn-1-ol (2c): According to general procedure, title compound was synthesized **(2c)**. The product was purified by silica gel flash column chromatography (hexane→hexane/AcOEt = 5/1) to afford **2c** as white solid (149.1 mg, 88% yield). **Melting Point**: 116-118°C. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.21 (d, *J* = 8.8 Hz, 2H), 6.65 (s, 1H), 6.53 (d, *J* = 9.2 Hz, 2H), 4.60 (t, *J* = 8.8 Hz, 2H), 4.49 (s, 4H), 3.85 (t, *J* = 6.4 Hz, 2H), 3.21 (t, *J* = 8.8 Hz, 2H), 2.77 (t, *J* = 6.4 Hz, 2H), 1.90 (brs, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 159.6, 145.6, 137.3, 131.4, 129.0, 128.8, 120.9, 114.7, 112.3, 103.6, 93.0, 77.9, 71.6, 61.2, 54.3, 53.2, 29.3, 23.9. **HRMS** (ESI): calculated for $[C_{20}H_{18}NO_2Cl]^+$ requires 339.1026, found 339.1025.

4-(6-(4-bromophenyl)-3,5,6,7-tetrahydro-2H-furo[2,3-f]isoindol-4-yl)but-3-yn-1-ol (2d): According to general procedure, title compound was synthesized **(2d)**. The product was purified by silica gel flash column chromatography (hexane→hexane/AcOEt = 5/1) to afford **2d** as off-white solid (160.8 mg, 84% yield). **Melting Point**: 85-87°C. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.33 (d, *J* = 9.2 Hz, 2H),

6.64 (s, 1H), 6.48 (d, *J* = 9.2 Hz, 2H), 4.59 (t, *J* = 8.8 Hz, 2H), 4.47 (s, 4H), 3.85 (t, *J* = 6.4 Hz, 2H), 3.20 (t, *J* = 8.8 Hz, 2H), 2.76 (t, *J* = 6.4 Hz, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 159.6, 145.9, 137.2, 131.8, 131.3, 128.8, 114.7, 112.9, 107.9, 103.5, 93.1, 77.8, 71.6, 61.2, 54.2, 53.1, 29.3, 23.9. **HRMS** (ESI): calculated for $[C_{20}H_{18}BrNO_2+Na]^+$ requires 406.0413, found 406.0411.

4-(6-(p-tolyl)-3,5,6,7-tetrahydro-2H-furo[2,3-f]isoindol-4-yl)but-3-yn-1-ol (2e): According to general procedure, title compound was synthesized **(2e)**. The product was purified by silica gel flash column chromatography (hexane→hexane/AcOEt = 5/1) to afford **2e** as a light yellow sticky mass (135 mg, 85% yield). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.10 (d, *J* = 8.4 Hz, 2H), 6.67 (s, 1H), 6.57 (d, *J* = 8.8 Hz, 2H), 4.60 (t, *J* = 8.8 Hz, 2H), 4.53 (s, 4H), 3.85 (t, *J* = 6.4 Hz, 2H), 3.22 (t, *J* = 8.8 Hz, 2H), 2.77 (t, *J* = 6.4 Hz, 2H), 2.28 (s, 3H), 1.81 (brs, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 159.4, 145.0, 137.8, 132.0, 129.8, 128.5, 125.1, 114.6, 111.4, 103.7, 92.8, 78.1, 71.6, 61.2, 54.4, 53.2, 29.4, 24.0, 20.2. **HRMS** (ESI): calculated for $[C_{21}H_{22}NO_2]^+$ requires 320.1645, found 320.1644.

4-(6-tosyl-3,5,6,7-tetrahydro-2H-furo[2,3-f]isoindol-4-yl)but-3-yn-1-ol (2f): According to general procedure, title compound was synthesized **(2f)**. The product was purified by silica gel flash column chromatography (hexane→hexane/AcOEt = 5/1) to afford **2f** as a light yellow sticky mass (178 **mg, 93% yield**). Spectral data are in agreement with the literature. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.76 (d, *J* = 8.4 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 6.47 (s, 1H), 4.58-4.52 (m, 6H), 3.82 (t, *J* = 6.4 Hz, 2H), 3.16 (t, *J* = 8.4 Hz, 2H), 2.72 (t, *J* = 6.4 Hz, 2H), 2.40 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 159.9, 143.6, 135.7, 133.7, 129.8, 129.4, 127.5, 115.0, 103.4, 93.8, 71.7, 61.1, 54.1, 53.2, 29.6, 29.2, 23.8, 21.4. **HRMS** (ESI): calculated for $[C_{21}H_{21}NO_4S+Na]^+$ requires 406.10835, found 406.10837.

4-(6-(4-(trifluoromethyl)phenyl)-3,5,6,7-tetrahydro-2H-furo[2,3-f]isoindol-4-yl)but-3-yn-1-ol (2g): According to general procedure, title compound was synthesized **(2g)**. The product was purified by silica gel flash column chromatography (hexane→hexane/AcOEt = 5/1) to afford **2g** off-white solid (152.9 mg, 82% yield). **Melting Point**: 156-158°C. **^{1}H NMR** (400 MHz, $CDCl_3$): 7.50 (d, *J* = 8.8 Hz, 2H), 6.68 (s, 1H), 6.64 (D, *J* = 8.8 Hz, 2H), 4.64-4.59 (m, 6H), 3.87 (t, *J* = 6.4 Hz, 2H), 3.23 (t, *J* = 8.4 Hz, 2H), 2.78 (*J* = 6.4 Hz, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$): 159.8, 149.0, 136.9, 130.9, 129.1, 126.5 (q, *J* = 3.8 Hz), 117.7, 117.4, 114.8, 110.7, 103.6, 93.3, 77.8, 71.7, 61.2, 54.2, 53.1, 29.4, 24.0. **HRMS** (ESI): calculated for $[C_{21}H_{19}NO_2F_3]^+$ requires 374.1290, found 374.1292.

5-(7-phenyl-2,3,4,6,7,8-hexahydropyrano[2,3-f]isoindol-5-yl)pent-4-yn-1-ol (2h): According to general procedure, title compound was synthesized **(2h)**. The product was purified by silica gel flash column chromatography (hexane→hexane/AcOEt = 5/1) to afford **2h** as off-white solid (148 mg, 89% yield). **Melting Point**: 124-126°C. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.29 (t, *J* = 8.0 Hz, 2H), 6.75-6.72 (m, 2H), 6.66 (d, *J* = 8.0 Hz, 2H), 4.56 (s,4H), 4.15 (t, *J* = 5.2 Hz, 2H), 3.87 (t, *J* = 6.0 Hz, 2H), 2.85 (t, *J* = 6.8 Hz, 2H), 2.65 (t, *J* = 7.2 Hz, 2H), 2.05-1.99 (m, 2H), 1.92 (quint, *J* = 6.8 Hz, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 154.4, 147.1, 136.3, 132.4, 129.3, 122.8, 118.4, 115.9, 111.4, 110.5, 97.8, 76.8, 66.2, 61.7, 54.0, 53.4, 31.6, 23.8, 22.1, 16.2. **HRMS** (ESI): calculated for $[C_{22}H_{23}NO_2]^+$ requires 333.1729, found 333.1727.

5-(7-(4-methoxyphenyl)-2,3,4,6,7,8-hexahydropyrano[2,3-f]isoindol-5-yl)pent-4-yn-1-ol (2i): According to general procedure, title compound was synthesized **(2i).** The product was purified by silica gel flash column chromatography (hexane→hexane/AcOEt = 5/1) to afford **2i** as a light yellow sticky mass (157.9 mg, 87% yield). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 6.91 (d, *J* = 9.2 Hz, 2H), 6.71(s, 1H), 6.61 (d, *J* = 9.2 Hz, 2H), 4.52 (s, 4H), 4.15 (t, *J* = 5.2 Hz, 2H), 3.87 (t, *J* = 6.4 Hz, 2H), 3.78 (s, 3H), 2.85 (t, *J* = 6.8 Hz, 2H), 2.64 (t, *J* = 6.8 Hz, 2H), 2.04-1.98 (m, 2H), 1.91 (quint, *J* = 6.4 Hz, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 154.3, 151.0, 142.1, 136.6, 132.7, 122.7, 118.3, 115.1, 112.2, 110.5, 97.7, 66.1, 61.7, 55.9, 54.5, 53.9, 31.6, 23.7, 22.1, 16.2. **HRMS** (ESI): calculated for $[C_{23}H_{26}NO_3]^+$ requires 364.1834, found 364.1831.

5-(7-(3-methoxyphenyl)-2,3,4,6,7,8-hexahydropyrano[2,3-f]isoindol-5-yl)pent-4-yn-1-ol (2j): According to general procedure, title compound was synthesized **(2j)**. The product was purified by silica gel flash column chromatography (hexane→hexane/AcOEt = 5/1) to afford **2j** as off-white solid (1**56 mg, 86% yield**). **Melting Point**: 123-125°C. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.19 (t, *J* = 8.4 Hz, 1H), 6.70 (s, 1H), 6.32-6.27 (m, 2H), 6.19 (t, *J* = 2.4 Hz, 1H), 4.53 (s, 4H), 4.14 (t, *J* = 5.2 Hz, 2H), 3.86 (t, *J* = 6.4 Hz, 2H), 3.83 (s, 3H), 2.83 (t, *J* = 6.4 Hz, 2H), 2.64 (t, *J* = 6.8 Hz, 2H), 2.03-1.98 (m, 2H), 1.91 (quint, *J* = 6.4 Hz, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 160.8, 154.3, 148.4, 136.1, 132.3, 130.0, 122.8, 118.4, 110.4, 104.6, 100.9, 97.8, 66.1, 61.6, 55.1, 54.0, 53.4, 31.6, 23.7, 22.1, 16.2. **HRMS** (ESI): calculated for $[C_{23}H_{25}NO_3]^+$ requires 363.1834, found 363.1831.

5-(7-(2-methoxyphenyl)-2,3,4,6,7,8-hexahydropyrano[2,3-f]isoindol-5-yl)pent-4-yn-1-ol (2k): According to general procedure, title compound was synthesized **(2k)**. The product was purified by silica gel flash column chromatography (hexane→hexane/AcOEt = 5/1) to afford **2k** as a light yellow sticky mass (161.5 mg, 89% yield). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 6.96-6.80 (m, 4H), 6.68 (s, 1H), 4.71 (s, 2H), 4.67 (s, 2H), 4.14 (t, *J* = 5.2 Hz, 2H), 3.86-3.84 (m, 5H), 2.84 (t, *J* = 6.8 Hz, 2H), 2.62 (t, *J* = 6.8 Hz, 2H), 2.04-1.98 (m, 2H), 1.89 (quint, *J* = 6.4 Hz, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 154.0, 149.8, 138.6, 137.2, 133.1, 122.3, 121.6, 119.0, 117.9, 115.3, 112.7, 110.1, 97.3, 77.0, 66.1, 61.6, 56.5, 56.0, 55.6, 31.5, 23.7, 22.1, 16.2. **HRMS** (ESI): calculated for $[C_{23}H_{25}NO_3]^+$ requires 363.1834, found 363.1833.

5-(7-(4-chlorophenyl)-2,3,4,6,7,8-hexahydropyrano[2,3-f]isoindol-5-yl)pent-4-yn-1-ol (2l): According to general procedure, title compound was synthesized **(2l)**. The product was purified by silica gel flash column chromatography (hexane→hexane/AcOEt = 5/1) to afford **2l** as a light yellow solid (157.8 mg, 86% yield). **Melting Point**: 144-146°C. **^{1}H NMR** (400 MHz, $CDCl_3$): 7.22 (d, *J* = 8.8 Hz, 2H), 6.71 (s, 1H), 6.56 (d, *J* = 9.6 Hz, 2H), 4.53 (s, 4H), 4.15 (t, *J* = 5.2 Hz, 2H), 3.86 (t, *J* = 6.4 Hz, 2H), 2.85 (t, *J* = 6.8 Hz, 2H), 2.65 (t, *J* = 6.8 Hz, 2H), 2.053-1.99 (m, 2H), 1.92 (quint, *J* = 6.4 Hz, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$): 154.4, 145.6, 136.0,

132.0, 129.0, 123.0, 120.8, 118.4, 112.4, 110.5, 97.9, 76.7, 66.2, 61.7, 54.1, 53.5, 31.6, 29.6, 23.7, 22.0, 16.2. **HRMS** (ESI): calculated for $[C_{22}H_{23}ClNO_2]^+$ requires 368.14118, found 363.14119.

5-(7-(4-bromophenyl)-2,3,4,6,7,8-hexahydropyrano[2,3-f]isoindol-5-yl)pent-4-yn-1-ol (2m): According to general procedure, title compound was synthesized **(2m)**. The product was purified by silica gel flash column chromatography (hexane→hexane/AcOEt = 5/1) to afford **2m** as off-white solid (172.6 mg, 84% yield). **Melting Point**: 142-144°C. **^{1}H NMR** (400 MHz, $CDCl_3$): 7.35 (d, *J* = 8.8 Hz, 2H), 6.17 (s, 1H), 6.52 (d, *J* = 8.8 Hz, 2H), 4.52 (s, 4H), 4.15 (t, *J* = 5.2 Hz, 2H), 3.86 (t, *J* = 6.4 Hz, 2H), 2.85 (t, *J* = 6.4 Hz, 2H), 2.65 (t, *J* = 7.2 Hz, 2H), 2.05-1.99 (m, 2H), 1.92 (quint, *J* = 6.4 Hz, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$): 154.5, 146.0, 135.9, 132.0, 131.9, 123.0, 118.5, 113.0, 110.5, 107.9, 97.9, 76.7, 66.2, 61.7, 54.1, 53.5, 31.6, 23.8, 22.0, 16.2. **HRMS** (ESI): calculated for $[C_{22}H_{22}NO_2Br]^+$ requires 411.0834 found 411.0837.

5-(7-(p-tolyl)-2,3,4,6,7,8-hexahydropyrano[2,3-f]isoindol-5-yl)pent-4-yn-1-ol (2n): According to general procedure, title compound was synthesized **(2n)**. The product was purified by silica gel flash column chromatography (hexane→hexane/AcOEt = 5/1) to afford **2n** as off-white solid (150.9 mg, 87% yield). **Melting Point**: 128-130°C. **^{1}H NMR** (400 MHz, $CDCl_3$): 7.09 (d, *J* = 8.4 Hz, 2H), 6.70 (s, 1H), 6.57 (d, *J* = 8.4 Hz, 2H), 4.52 (s, 4H), 4.14 (t, *J* = 5.2 Hz, 2H), 3.85 (t, *J* = 6.4 Hz, 2H), 2.83 (t, *J* = 6.8 Hz, 2H), 2.63 (t, *J* = 6.8 Hz, 2H), 2.27 (s, 3H), 2.03-1.98 (m, 2H), 1.90 (quint, *J* = 6.4 Hz, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$): 154.3, 145.0, 136.4, 132.6, 129.8, 124.9, 122.7, 118.3, 111.4, 110.5, 97.7, 76.8, 66.1, 61.6, 54.1, 53.5, 31.6, 29.6, 23.7, 22.1, 20.2, 16.2. **HRMS** (ESI): calculated for $[C_{23}H_{25}NO_2]^+$ requires 347.1885, found 347.1885.

5-(7-tosyl-2,3,4,6,7,8-hexahydropyrano[2,3-f]isoindol-5-yl)pent-4-yn-1-ol (2o): According to general procedure, title compound was synthesized **(2o)**. The product was purified by silica gel flash column chromatography (hexane→hexane/AcOEt = 5/1) to afford **2o** as a light yellow sticky mass (184.9 mg, 90% yield). 1**H NMR** (400 MHz, CDCl3): 7.76 (d, *J* = 8.4 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 6.52 (s, 1H), 4.54 (d, *J* = 8.0 Hz, 4H), 4.10-4.07 (m, 2H), 3.82 (t, *J* = 6.4 Hz, 2H), 2.77 (t, *J* = 6.4 Hz, 2H), 2.59 (t, *J* = 6.8 Hz, 2H), 2.40 (s, 3H), 1.98-1.93 (m, 2H), 1.87 (quint, 2H). **13C NMR** (100 MHz, CDCl3): 154.8, 143.5, 134.4, 133.7, 130.4, 129.8, 127.5, 123.5, 118.7, 110.3, 98.6, 76.1, 66.2, 61.6, 54.0, 53.6, 31.5, 29.6, 23.7, 21.9, 21.4, 16.1. **HRMS** (ESI): calculated for [C23H25NO4S+Na]+ requires 434.1396, found 434.1397.

5-(7-(4-(trifluoromethyl)phenyl)-2,3,4,6,7,8-hexahydropyrano[2,3-f]isoindol-5-yl)pent-4-yn-1-ol (2p): According to general procedure, title compound was synthesized **(2p)**. The product was purified by silica gel flash column chromatography (hexane→hexane/AcOEt = 5/1) to afford **2p** as off-white solid (174.4 mg, 87% yield). **Melting Point**: 150-152°C. **^{1}H NMR** (400 MHz, $CDCl_3$): 7.50 (d, *J* = 8.4 Hz, 2H), 6.72 (s, 1H), 6.65 (d, *J* = 8.8 Hz, 2H), 4.60 (s, 4H), 4.17-4.14 (m, 2H), 3.87 (t, *J* = 6.4 Hz, 2H), 2.85 (t, *J* = 6.8 Hz, 2H), 2.66 (t, *J* = 7.2 Hz, 2H), 2.05-1.99 (m, 2H), 1.92 (quint, *J* = 6.8 Hz, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$): 154.6, 149.1, 135.5, 131.6, 126.5 (d, *J* = 3.8 Hz), 123.2, 118.6, 110.8, 110.5, 98.2, 66.2, 61.7, 54.0, 53.4, 31.6, 23.8, 22.0, 16.3. **HRMS** (ESI): calculated for $[C_{23}H_{23}NO_2F_3]^+$ requires 402.1603, found 401.1605.

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Notes and references

[a] Department of Medicinal and Applied chemistry, Kaohsiung Medical University, Kaohsiung, Taiwan.
[b] Department of Biotechnology, Kaohsiung Medical University, Kaohsiung, Taiwan.

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