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Article

# C3 Functionalization of Indolizines via HFIP-Promoted Friedel–Crafts Reactions with (Hetero)arylglyoxals

Euijin Jung,[†] Yerin Jeong,[†] Hyeyeon Kim, and Ikyon Kim*

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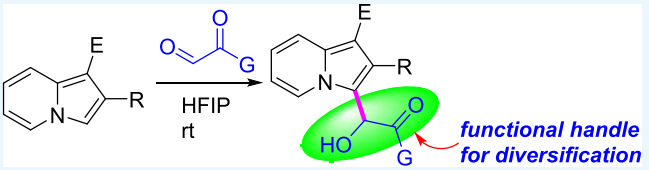
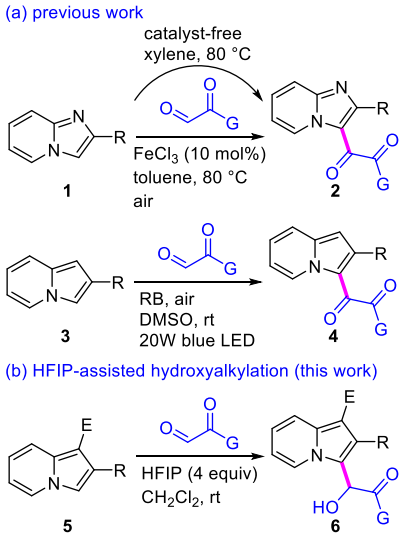
**ABSTRACT:** A highly efficient Friedel–Crafts type hydroxyalkylation at the C3 position of indolizines with (hetero)arylglyoxals has been achieved by the action of hexafluoroisopropanol (HFIP) under mild reaction conditions, leading to direct access to a variety of polyfunctionalized indolizines in excellent yields. Installation of more diverse functional groups at the C3 site of indolizine scaffold was realized via further elaboration of the resulting α-hydroxyketone moiety, allowing for expansion of indolizine chemical space.




## INTRODUCTION

Unique reactivity of reagents or catalysts employed in chemical reactions, sometimes, leads to unexpected and/or unprecedented results. In the course of our continuing efforts to expand N-fused heterocyclic chemical space,[1] we were able to find new outcomes from the reaction of **5** with (hetero)glyoxals in the presence of hexafluoroisopropanol (HFIP), which recently finds its use in a number of chemical transformations.[2,3] Previously, Friedel–Crafts reactions of N-fused heterocycle **1** with arylglyoxals under catalyst-free[4] and catalytic $FeCl_3$ conditions[5] have been reported to furnish the adduct **2** bearing a 1,2-dicarbonyl group, respectively (Scheme 1a). More recently, Cao and co-workers described visible-light-mediated conversion of indolizine **3**–**4**[6] via a radical mechanism.[7] Surprisingly, however, no direct access to **6** through Friedel–Crafts type monoaddition of indolizine **5**[8] to arylglyoxals has not been disclosed so far. In our study on C3 functionalization of indolizines,[9] we discovered that HFIP enabled us to decorate basic indolizine skeleton **5** with various (hetero)arylglyoxals via Friedel–Crafts type hydroxyalkylation, leading to a wide range of novel indolizines **6** with an α-hydroxyketone moiety at the C3 site in excellent yields (Scheme 1b). From the structural point of view, compound **6** can be viewed as a benzoin-type product, an α-hydroxyketone attached to two different (hetero)aromatic rings,[10] which is difficult to make by any other means. Here, we wish to describe our results on HFIP-mediated mild hydroxyalkylation of indolizines.

**Scheme 1. Functionalization of N-Fused Heterocycles with Glyoxals**




## RESULTS AND DISCUSSION

The reaction optimization was carried out with **5a** and phenylglyoxal under several catalysts (Table 1). When we reacted **5a** with phenylglyoxal (1 equiv) in the presence of HFIP (4 equiv) at room temperature (rt), a benzoin-type product **6a** was isolated in 98% yield (entry 1). Neither **6a′** nor **6a″** was observed in this case. Decreasing the amount of HFIP required more reaction times for complete conversion (entries 2 and 3). Seemingly, air oxidation of **6a** is very slow under these conditions as only a tiny amount of **6a′** is detected after 72 h. Notably, this is a highly atom-economical process as the two starting materials are fully incorporated in the product without any loss. Heating the reaction mixture without catalyst at 60 °C

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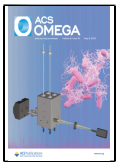





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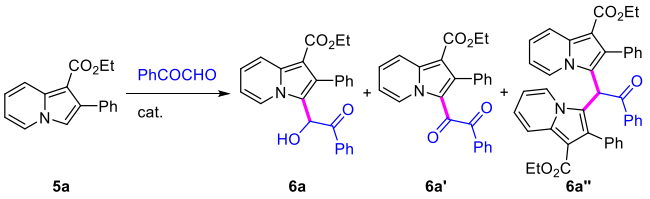
**Table 1. Reaction Optimization**[a]




| entry | catalyst (equiv) | temp (°C) | time (h) | yield (%)[b] 6a | 6a′ | 6a″ |
|---|---|---|---|---|---|---|
| 1 | HFIP (4) | 25 | 14 | 98 | | |
| 2 | HFIP (2) | 25 | 24 | 95 | trace | |
| 3 | HFIP (1) | 25 | 72 | 95 | trace | |
| 4[c] | | 60 | 18 | 26 | 51 | |
| 5[d,e] | | 60 | 120 | 70 | 10 | |
| 6 | $Sc(OTf)_3$ (0.1) | 25 | 2 | 14 | trace | 46 |
| 7 | $Bi(OTf)_3$ (0.1) | 25 | 2 | trace | 20 | 35 |
| 8 | $In(OTf)_3$ (0.1) | 25 | 2 | 17 | 19 | 38 |
| 9 | $Yb(OTf)_3$ (0.1) | 25 | 25 | 21 | 21 | 36 |
| 10 | PTSA (0.1) | 25 | 2 | 50 | trace | 18 |

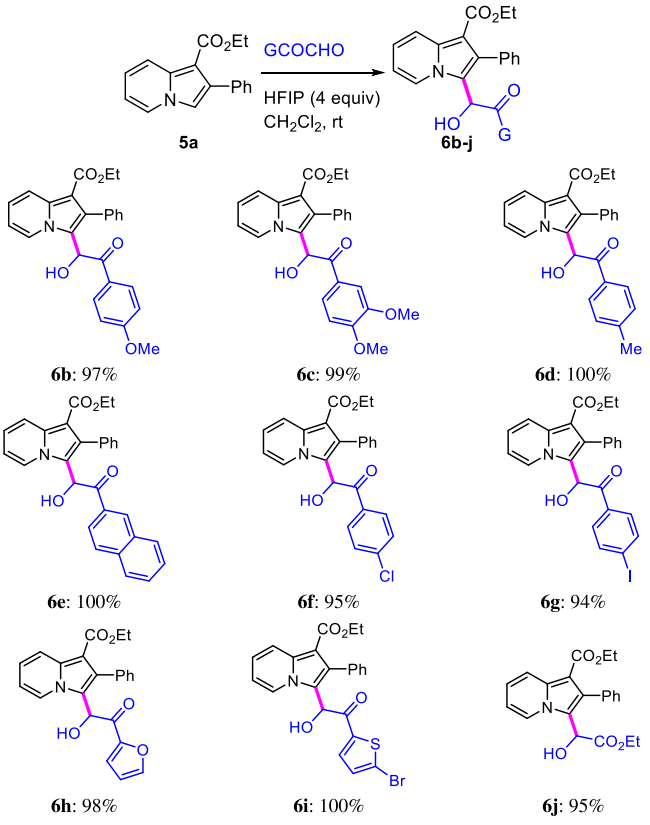
[a]A reaction mixture of **5a** (30 mg, 0.11 mmol), phenylglyoxal (1.0 equiv), and catalyst in $CH_2Cl_2$ (1 mL) was stirred at the indicated temperature. [b]Isolated yield (%). [c]The reaction in toluene. [d]The reaction in $CH_2Cl_2$. [e]80% conversion.

gave a mixture of **6a** and **6a′**: **6a′** was formed as a major product in toluene, whereas **6a** was obtained as a major product in $CH_2Cl_2$ although the reaction was not complete in the latter case even after 5 days (entries 4 and 5). It seemed air oxidation is more facile in toluene than in dichloromethane. Use of metal triflates as catalysts, surprisingly, afforded **6a″** in variable yields in addition to **6a** and **6a′** (entries 6−9).[11] Brønsted acid such as *p*-toluenesulfonic acid (PTSA) also furnished a mixture of **6a** and **6a″** (entry 10).

Scope of this reaction was first examined with several (hetero)arylglyoxals under the optimal conditions (use of HFIP (4 equiv) in $CH_2Cl_2$ at room temperature) (Table 2). Hydroxyalkylations of **5a** with arylglyoxals bearing methoxyl(s), methyl, or halogen proceeded smoothly to give the corresponding products **6b−g** in excellent yields. *α*-Hydroxyketones (**6h−i**) having a heterocycle such as furan or thiophene were readily obtained as well. Unfortunately, the reaction of **5a** with arylglyoxal with a 4-nitrophenyl moiety resulted in a complex mixture. The reaction with ethyl glyoxalate led to *α*-hydroxy ester **6j** in 95% yield.

More reaction scope was investigated with various indolizines **5b-p** (Figure 1).[12] Overall, the desired mono-addition of indolizine to a range of (hetero)arylglyoxals took place without any event to provide the corresponding products **6k-ad** in good to excellent yields, indicating good functional group tolerance under these conditions (Table 3). When **5o**[13] was used, the hydroxyalkylated products (**6ab** and **6ac**) were precipitated out from the reaction mixture; so, simple filtration was conducted to isolate the desired products. HFIP-promoted reactions of 2-phenylindolizine and 1-methyl-2-phenylindolizine with phenylglyoxal were carried out. While the former gave a complex mixture from which the product obtainable as a result of hydroxyalkylations both at the C1 and C3 sites was observed to some extent, the latter provided the desired product which, however, turned out to be relatively prone to facile oxidation,[14] indicating that the electron-withdrawing group at the C1 site of indolizines is important for success of this process.

**Table 2. Synthesis of 6b−j**[a,b]




[a]A mixture of **5a** (0.11 mmol), GCOCHO (1.0 equiv), and HFIP (4.0 equiv) in $CH_2Cl_2$ (1 mL) was stirred at rt. [b]Isolated yield (%).

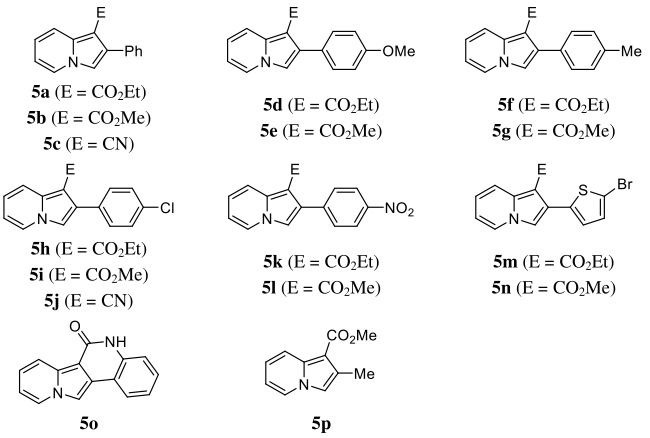



**Figure 1.** Indolizines **5**.

Scale-up reaction of **5a** (400 mg, 0.92 mmol) with 4-chlorophenylglyoxal was carried out (Scheme 2). The desired product **6f** was readily isolated as a green solid in a quantitative yield.[15] When benzofuran **7** was employed instead of indolizines in these HFIP-promoted reactions with arylglyoxals, the corresponding product **8** was obtained in 96% yield.[16] Interestingly, indole participated well as a nucleophile of this Friedel−Crafts type reaction with arylglyoxal under mild conditions to furnish **9**.[17]

Finally, the synthetic potential of this protocol was demonstrated by conducting several postfunctionalizations of the resulting products (**6**), thereby leading to further expansion of these indolizine-based chemical space (Scheme 3). Oxidation



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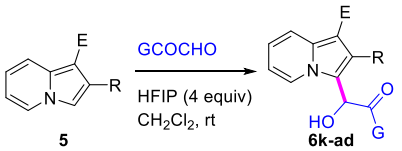
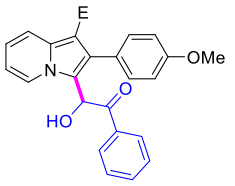
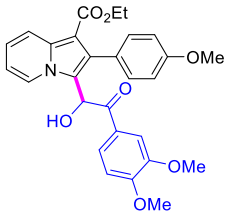
**Table 3. Synthesis of 6k-ad**[a,b]

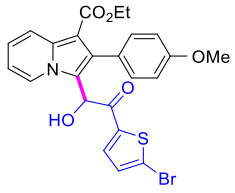


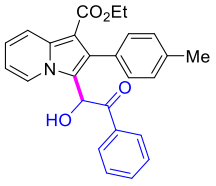

**6k** (E = $CO_2Et$): 97%
**6l** (E = $CO_2Me$): 83%



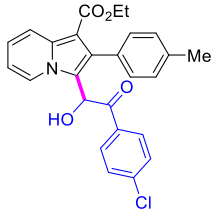

**6m**: 100%



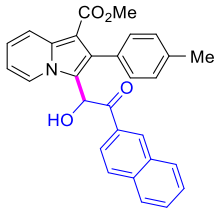

**6n**: 100%



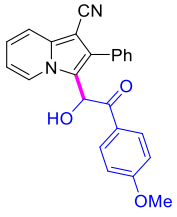

**6o**: 100%



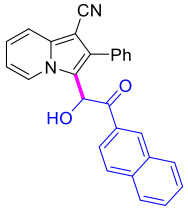

**6p**: 98%



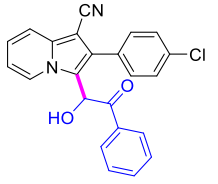

**6q**: 98%



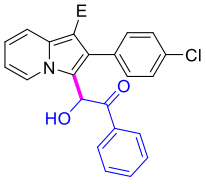

**6r**: 96%



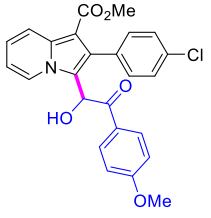

**6s**: 100%



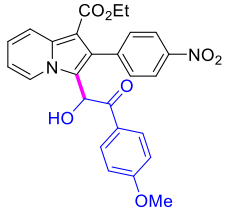

**6t**: 91%



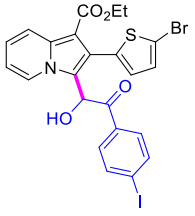

**6u** (E = $CO_2Et$): 95%
**6v** (E = $CO_2Me$): 92%



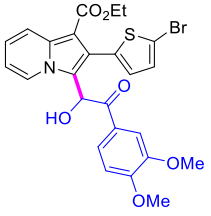

**6w**: 100%



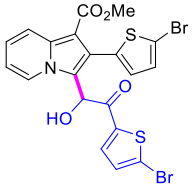

**6x**: 98%



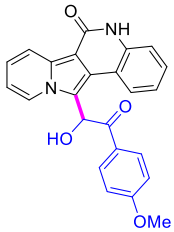

**6y**: 97%



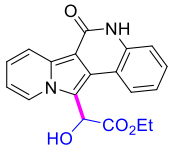

**6z**: 94%



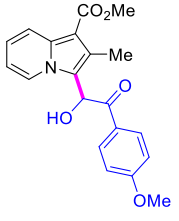

**6aa**: 90%




**6ab**: 83%




**6ac**: 84%




**6ad**: 73%

[a]A mixture of **5** (0.11 mmol), GCOCHO (1.0 equiv), and HFIP (4.0 equiv) in $CH_2Cl_2$ (1 mL) was stirred at rt. [b]Isolated yield (%).



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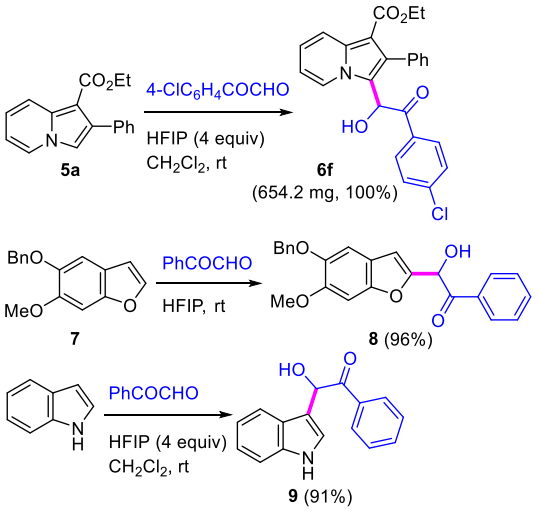
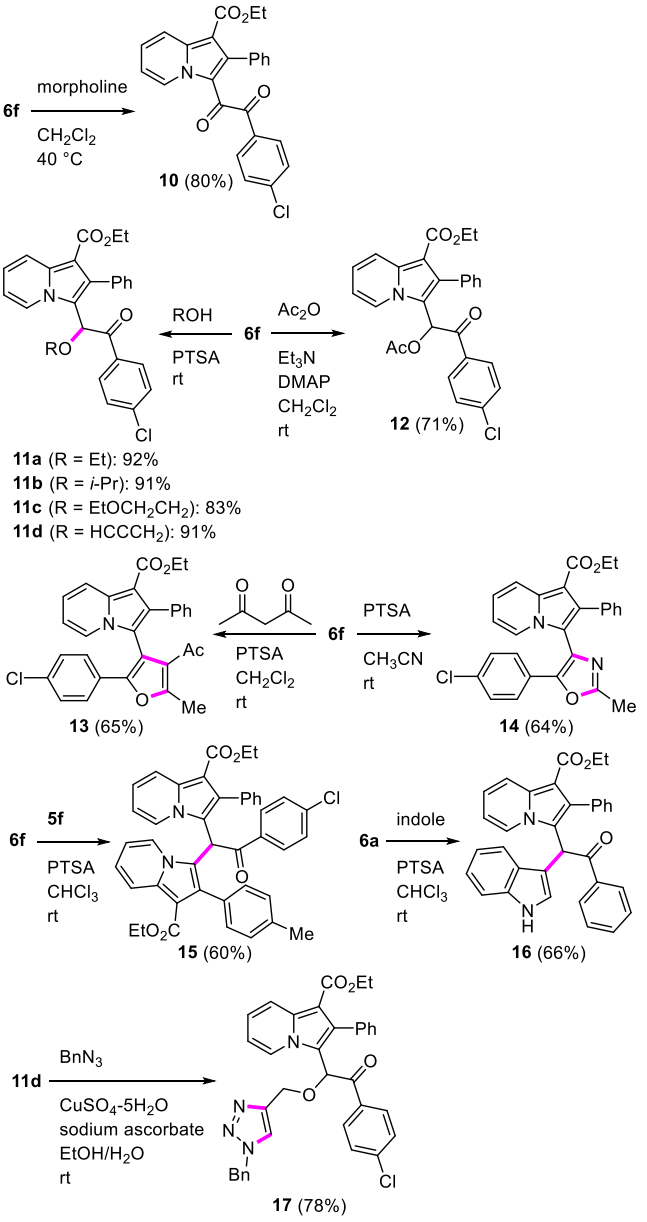
**Scheme 2. Scale-Up Reaction and Applications**




**Scheme 3. Derivatization**




of **6f** in the presence of morpholine proceeded well to furnish the 1,2-diketone **10**.[18] Replacing of the hydroxyl in **6f** by several alcohols was facilitated by the action of PTSA to give **11a−d**, respectively. Acetylation of **6f** afforded $\alpha$-acetyloxyketone **12**. Introduction of a furan or oxazole moiety at the C3 position of indolizine was also realized by manipulation of the $\alpha$-hydroxyketone motif in **6**: While the PTSA-mediated reaction of **6f** with pentane-2,4-dione led to **13** in 65% yield,[19] exposure of **6f** to PTSA in $CH_3CN$ induced Ritter reaction followed by intramolecular cyclization to give oxazole **14**.[20] In addition, the substitution of the hydroxyls in **6f** and **6a** with indolizine **5f** and indole in the presence of PTSA occurred to provide the ketones **15** and **16**, respectively, enabling installation of two different heteroaryl groups in (hetero)arylglyoxals. Cu-catalyzed [3+2] cycloaddition[21] of **11d** with benzyl azide produced the triazole **17** in 78% yield.

## CONCLUSIONS

In conclusion, HFIP-promoted Friedel−Crafts type hydroxyalkylation of indolizines with (hetero)arylglyoxals was established in a highly efficient and atom-economical manner, which enabled us to get facile access to a wide variety of benzoin-type products having two different (hetero)aryl moieties. To the best of our knowledge, this is the first example to reliably furnish $\alpha$-hydroxyketones at the C3 position of indolizines. This protocol was successfully applied to other heterocycles such as benzofuran and indole, leading to the corresponding products in excellent yields. Selective manipulation of the $\alpha$-hydroxyketone motifs of the resulting products allowed for further expansion of indolizine chemical space via installation of diverse functional groups at the C3 site. Application of HFIP-facilitated mono-addition of heteroarenes to arylglyoxals for construction of novel polyheterocycles is currently underway in our laboratory, and the results will be reported in due course.

## EXPERIMENTAL SECTION

**General Methods.** All reagents and starting materials were purchased from commercial sources and used as received without further purification, unless specified. "Concentration" refers to the removal of volatile solvents via distillation using a rotary evaporator. "Dried over $MgSO_4$" refers to pouring onto or passing through anhydrous magnesium sulfate followed by filtration. Column chromatography was performed using silica gel (230−400 mesh) with hexanes, ethyl acetate, and dichloromethane as the eluents. All reactions were monitored by thin-layer chromatography on 0.25 mm silica plates (F-254) visualized with UV light. A capillary melting point apparatus was used to measure melting points. A 400 MHz NMR spectrometer was used to record $^1H$ and $^{13}C$ NMR spectra, which were described as chemical shifts, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), coupling constant in hertz (Hz), and number of protons. An electrospray ionization (ESI) and QTOF mass analyzer was used to measure HRMS.

**General Procedure for the Synthesis of 6.** A reaction mixture of **5** (0.11 mmol, 1.0 equiv), glyoxal (1.0 equiv), and HFIP (4.0 equiv) in dichloromethane (1.0 mL) was stirred at room temperature for 14 h. The reaction mixture was concentrated *in vacuo* to give the crude residue, which was purified by silica gel column chromatography (hexane/ethyl acetate/dichloromethane = 20:1:2) to afford **6**.



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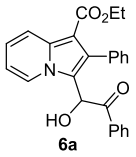
**Scale-Up Experiment.** Scale-up reaction of **5a** (400 mg, 1.51 mmol), 4-chlorophenylglyoxal (1.51 mmol), and HFIP (6.03 mmol) in dichloromethane (5.0 mL) was carried out. The reaction mixture was concentrated *in vacuo* to give the crude residue, which was triturated with ether to furnish **6f** as a green solid (654.2 mg, 100%).

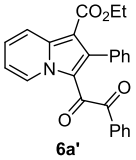
*Ethyl-3-(1-hydroxy-2-oxo-2-phenylethyl)-2-phenylindolizine-1-carboxylate (**6a**).*



**6a**

Brown solid, mp: 78.6−79.1 °C (43.1 mg, 98%); **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ 8.25 (d, $J$ = 9.2 Hz, 1H), 7.93 (d, $J$ = 7.2 Hz, 1H), 7.54−7.49 (m, 5H), 7.45 (t, $J$ = 8.2 Hz, 2H), 7.26−7.19 (m, 3H), 7.08 (t, $J$ = 8.2 Hz, 1H), 6.73 (t, $J$ = 6.8 Hz, 1H), 6.08 (s, 1H), 4.36 (s, 1H), 4.25−4.06 (m, 2H), 1.12 (t, $J$ = 7.2 Hz, 3H); **$^{13}$C{$^1$H} NMR** (100 MHz, $CDCl_3$) $\delta$ 199.2, 165.1, 137.3, 134.7, 134.5, 133.5, 133.2, 128.9, 128.8, 128.3, 128.1, 124.5, 123.6, 120.6, 119.7, 113.7, 102.9, 77.7, 77.4, 77.0, 69.7, 59.7, 14.4, 0.3; **HRMS** (ESI-QTOF) $m/z$ [M + Na]$^+$ calcd for $C_{25}H_{21}NNaO_4$ 422.1363, found, 422.1368.

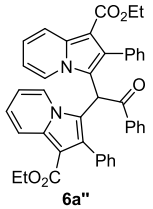
*Ethyl-3-(2-oxo-2-phenylacetyl)-2-phenylindolizine-1-carboxylate (**6a′**).*



**6a'**

Orange solid, mp: 147.4−148.2 °C; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ 10.10 (d, $J$ = 6.8 Hz, 1H), 8.52 (d, $J$ = 8.8 Hz, 1H), 7.63−7.46 (m, 4H), 7.29 (t, $J$ = 7.8 Hz, 2H), 7.21 (t, $J$ = 7.2 Hz, 1H), 7.09 (t, $J$ = 7.4 Hz, 1H), 6.99 (d, $J$ = 7.2 Hz, 2H), 6.92 (t, $J$ = 7.6 Hz, 2H), 4.10−4.01 (m, 2H), 0.93 (t, $J$ = 7.0 Hz, 3H); **$^{13}$C{$^1$H} NMR** (100 MHz, $CDCl_3$) $\delta$ 191.4, 185.4, 163.8, 143.8, 140.2, 133.8, 133.2, 132.1, 130.9, 129.4, 129.3, 129.2, 128.2, 127.9, 126.7, 120.2, 119.9, 116.3, 107.1, 77.3, 77.0, 76.7, 59.8, 13.7; **HRMS** (ESI-QTOF) $m/z$ [M + H]$^+$ calcd for $C_{25}H_{20}NO_4$ 398.1387, found, 398.1391.

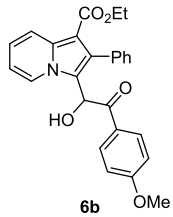
*Diethyl-3,3′-(2-oxo-2-phenylethane-1,1-diyl)bis(2-phenylindolizine-1-carboxylate) (**6a″**).*



**6a''**

Green solid, mp: 178.6−179.0 °C; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ 8.16 (d, $J$ = 9.2 Hz, 2H), 7.50 (d, $J$ = 8.0 Hz, 2H), 7.43 (d, $J$ = 7.2 Hz, 3H), 7.20 (t, $J$ = 7.6 Hz, 2H), 7.16−7.10 (m, 3H), 7.10−6.95 (m, 9H), 6.52 (t, $J$ = 6.8 Hz, 2H), 6.46 (s, 1H), 4.19−4.03 (m, 4H), 1.03 (t, $J$ = 7.0 Hz, 6H); **$^{13}$C{$^1$H} NMR** (100 MHz, $CDCl_3$) $\delta$ 190.1, 184.7, 163.7, 143.8, 140.3, 140.3, 132.2, 131.6, 130.9, 130.6, 129.4, 129.3, 128.6, 128.1, 126.8, 120.1, 119.9, 116.4, 107.2, 77.4, 77.0, 76.7, 59.8, 13.7; **HRMS** (ESI-QTOF) $m/z$ [M + H]$^+$ calcd for $C_{42}H_{35}N_2O_5$ 647.2540, found, 647.2540.

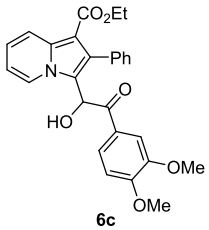
*Ethyl-3-(1-hydroxy-2-(4-methoxyphenyl)-2-oxoethyl)-2-phenylindolizine-1-carboxylate (**6b**).*



**6b**

Ivory solid, mp: 78.5−79.0 °C (45.8 mg, 97%); **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ 8.25 (d, $J$ = 9.2 Hz, 1H), 7.92 (d, $J$ = 6.8 Hz, 1H), 7.60−7.48 (m, 6H), 7.44 (t, $J$ = 7.8 Hz, 1H), 7.06 (t, $J$ = 7.8 Hz, 1H), 6.76−6.65 (m, 3H), 6.01 (s, 1H), 4.52 (s, 1H), 4.34−4.05 (m, 2H), 3.77 (s, 3H), 1.13 (t, $J$ = 7.0 Hz, 3H); **$^{13}$C{$^1$H} NMR** (100 MHz, $CDCl_3$) $\delta$ 196.8, 164.8, 164.4, 136.9, 134.3, 132.9, 131.1, 130.9, 128.0, 127.7, 125.6, 124.3, 123.2, 120.13, 120.07, 113.7, 113.2, 102.4, 77.4, 77.1, 76.8, 68.9, 59.3, 55.5, 14.1; **HRMS** (ESI-QTOF) $m/z$ [M + H]$^+$ calcd for $C_{26}H_{24}NO_5$ 430.1649, found, 430.1653.

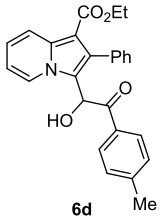
*Ethyl-3-(2-(3,4-dimethoxyphenyl)-1-hydroxy-2-oxoethyl)-2-phenylindolizine-1-carboxylate (**6c**).*



**6c**

Ivory solid, mp: 84.3−85.0 °C (50.0 mg, 99%); **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ 8.26 (d, $J$ = 8.8 Hz, 1H), 7.93 (d, $J$ = 6.8 Hz, 1H), 7.59−7.46 (m, 4H), 7.44 (d, $J$ = 7.2 Hz, 1H), 7.27 (s, 1H), 7.11−7.03 (m, 2H), 6.72 (t, $J$ = 7.2 Hz, 1H), 6.57 (d, $J$ = 8.4 Hz, 1H), 6.02 (s, 1H), 4.35−4.08 (m, 2H), 3.86 (s, 3H), 3.80 (s, 3H), 1.14 (t, $J$ = 7.2 Hz, 3H); **$^{13}$C{$^1$H} NMR** (100 MHz, $CDCl_3$) $\delta$ 196.9, 165.0, 154.4, 149.0, 137.0, 134.1, 132.9, 130.9, 127.9, 127.7, 125.7, 124.2, 123.9, 123.3, 120.4, 120.2, 113.4, 110.6, 109.7, 102.3, 77.4, 77.1, 76.7, 68.8, 59.5, 56.1, 56.0, 14.1; **HRMS** (ESI-QTOF) $m/z$ [M + H]$^+$ calcd for $C_{27}H_{26}NO_6$ 460.1755, found, 460.1759.

*Ethyl-3-(1-hydroxy-2-oxo-2-(p-tolyl)ethyl)-2-phenylindolizine-1-carboxylate (**6d**).*



**6d**

Ivory solid, mp: 75.8−76.4 °C (45.5 mg, 100%); **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ 8.25 (d, $J$ = 9.2 Hz, 1H), 7.90 (d, $J$ = 6.8 Hz, 1H), 7.58−7.48 (m, 4H), 7.49−7.42 (m, 3H), 7.07 (t, $J$ = 7.2 Hz, 1H), 7.02 (d, $J$ = 7.9 Hz, 2H), 6.70 (d, $J$ = 8.0 Hz, 1H), 6.04 (s, 1H), 4.42 (s, 1H), 4.28−4.05 (m, 2H), 2.29 (s, 3H), 1.13 (t, $J$ = 7.0 Hz, 3H); **$^{13}$C{$^1$H} NMR** (100 MHz, $CDCl_3$) $\delta$ 198.4, 164.7, 145.5, 136.9, 134.3, 133.1, 130.2, 129.2, 128.7, 128.0, 127.7, 124.2, 123.2, 120.2, 119.7, 113.3, 102.5, 77.3, 77.0, 76.7, 69.3, 59.3, 21.7, 14.1; **HRMS** (ESI-QTOF) $m/z$ [M + H]$^+$ calcd for $C_{26}H_{24}NO_4$ 414.1700, found, 414.1705.


https://doi.org/10.1021/acsomega.3c00236
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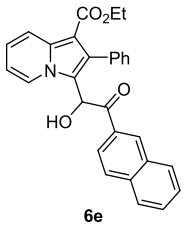
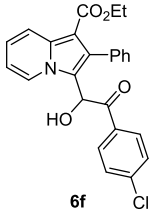
*Ethyl-3-(1-hydroxy-2-(naphthalen-2-yl)-2-oxoethyl)-2-phenylindolizine-1-carboxylate (**6e**).*




**6e**

Yellow solid, mp: 137.4−137.7 °C (49.4 mg, 100%); **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ 8.21 (d, $J$ = 8.8 Hz, 1H), 7.99 (d, $J$ = 7.2 Hz, 2H), 7.74 (t, $J$ = 8.2 Hz, 2H), 7.70 (s, 2H), 7.66−7.59 (m, 3H), 7.58−7.47 (m, 4H), 7.06 (t, $J$ = 8.0 Hz, 1H), 6.73 (t, $J$ = 6.8 Hz, 1H), 6.46 (s, 1H), 6.28 (s, 1H), 4.46 (s, 1H), 4.28−4.09 (m, 2H), 1.13 (t, $J$ = 7.7 Hz, 3H); **$^{13}$C{$^1$H} NMR** (100 MHz, $CDCl_3$) $\delta$ 198.8, 164.8, 137.1, 136.0, 134.2, 133.2, 132.0, 130.7, 130.1, 129.6, 129.2, 128.5, 128.2, 128.1, 127.9, 127.7, 127.0, 124.3, 123.7, 123.3, 120.2, 119.6, 113.4, 102.4, 77.3, 77.0, 76.7, 69.4, 59.4, 14.1; **HRMS** (ESI-QTOF) $m/z$ $[M + H]^+$ calcd for $C_{29}H_{24}NO_4$ 450.1700, found, 450.1702.

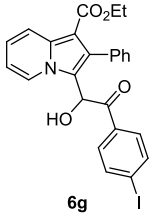
*Ethyl-3-(2-(4-chlorophenyl)-1-hydroxy-2-oxoethyl)-2-phenylindolizine-1-carboxylate (**6f**).*




**6f**

Green solid, mp: 87.3−88.4 °C (45.3 mg, 95%); **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ 8.26 (d, $J$ = 8.8 Hz, 1H), 7.91 (d, $J$ = 7.2 Hz, 1H), 7.52−7.48 (m, 4H), 7.48−7.43 (m, 3H), 7.20 (d, $J$ = 8.8 Hz, 2H), 7.10 (t, $J$ = 8.2 Hz, 1H), 6.74 (t, $J$ = 6.8 Hz, 1H), 6.05 (s, 1H), 4.30 (s, 1H), 4.25−4.08 (m, 2H), 1.13 (t, $J$ = 7.2 Hz, 3H); **$^{13}$C{$^1$H} NMR** (100 MHz, $CDCl_3$) $\delta$ 197.6, 164.8, 140.9, 137.1, 134.0, 133.2, 131.1, 129.9, 128.8, 128.1, 128.1, 127.9, 124.1, 123.4, 120.3, 119.0, 113.5, 102.5, 77.4, 77.0, 76.7, 69.4, 59.5, 14.1; **HRMS** (ESI-QTOF) $m/z$ $[M + H]^+$ calcd for $C_{25}H_{21}ClNO_4$ 434.1154, found, 434.1156.

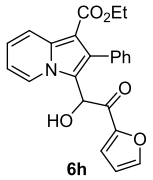
*Ethyl-3-(1-hydroxy-2-(4-iodophenyl)-2-oxoethyl)-2-phenylindolizine-1-carboxylate (**6g**).*




**6g**

Yellow solid, mp: 108.9−109.9 °C (54.3 mg, 94%); **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ 8.27 (d, $J$ = 8.8 Hz, 1H), 7.89 (d, $J$ = 6.8 Hz, 1H), 7.59 (d, $J$ = 8.4 Hz, 2H), 7.54−7.47 (m, 4H), 7.47−7.41 (m, 1H), 7.22 (d, $J$ = 8.4 Hz, 2H), 7.09 (t, $J$ = 8.0 Hz, 1H), 6.73 (t, $J$ = 6.8 Hz, 1H), 6.03 (s, 1H), 4.28 (s, 1H), 4.26−4.08 (m, 2H), 1.13 (t, $J$ = 7.0 Hz, 3H); **$^{13}$C{$^1$H} NMR** (100 MHz, $CDCl_3$) $\delta$ 198.2, 164.6, 156.0, 137.8, 137.0, 134.0, 133.2, 132.0, 129.7, 128.1, 127.9, 124.0, 123.3, 120.3, 118.9, 113.4, 102.8, 77.3, 77.0, 76.7, 69.4, 59.4, 29.7, 14.1; **HRMS** (ESI-QTOF) $m/z$ $[M + H]^+$ calcd for $C_{25}H_{21}INO_4$ 526.0510, found, 526.0515.

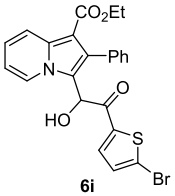
*Ethyl-3-(2-(furan-2-yl)-1-hydroxy-2-oxoethyl)-2-phenylindolizine-1-carboxylate (**6h**).*




**6h**

Brown solid, mp: 66.8−67.5 °C (42.0 mg, 98%); **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ 8.29 (d, $J$ = 9.2 Hz, 1H), 7.97 (d, $J$ = 6.8 Hz, 1H), 7.51 (d, $J$ = 7.2 Hz, 2H), 7.49−7.38 (m, 4H), 7.12 (t, $J$ = 7.8 Hz, 1H), 6.77−6.70 (m, 2H), 6.35 (s, 1H), 5.84 (s, 1H), 4.28−4.08 (m, 2H), 1.14 (t, $J$ = 7.0 Hz, 3H); **$^{13}$C{$^1$H} NMR** (100 MHz, $CDCl_3$) $\delta$ 186.1, 164.9, 149.0, 147.8, 137.0, 134.1, 133.6, 130.7, 127.8, 127.6, 124.4, 123.5, 120.5, 120.2, 119.1, 113.4, 112.5, 102.5, 77.4, 77.0, 76.7, 68.9, 59.5, 14.1; **HRMS** (ESI-QTOF) $m/z$ $[M + H]^+$ calcd for $C_{23}H_{20}NO_5$ 390.1336, found, 390.1337.

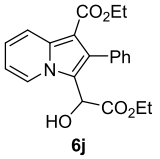
*Ethyl-3-(2-(5-bromothiophen-2-yl)-1-hydroxy-2-oxoethyl)-2-phenylindolizine-1-carboxylate (**6i**).*




**6i**

Yellow solid, mp: 79.6−80.4 °C (53.3 mg, 100%); **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ 8.32 (d, $J$ = 8.8 Hz, 1H), 7.88 (d, $J$ = 6.4 Hz, 1H), 7.54 (d, $J$ = 7.2 Hz, 2H), 7.51−7.37 (m, 3H), 7.13 (t, $J$ = 8.0 Hz, 1H), 7.01 (d, $J$ = 4.0 Hz, 1H), 6.89 (d, $J$ = 3.6 Hz, 1H), 6.74 (t, $J$ = 6.8 Hz, 1H), 5.77 (s, 1H), 4.31−4.11 (m, 2H), 1.15 (t, $J$ = 6.6 Hz, 3H); **$^{13}$C{$^1$H} NMR** (100 MHz, $CDCl_3$) $\delta$ 190.0, 164.8, 139.5, 137.3, 134.5, 133.9, 133.7, 131.5, 130.8, 128.0, 127.8, 125.1, 124.2, 123.7, 120.3, 118.9, 113.7, 102.6, 77.4, 77.0, 76.7, 69.5, 59.6, 14.1; **HRMS** (ESI-QTOF) $m/z$ $[M + H]^+$ calcd for $C_{23}H_{19}BrNO_4S$ 484.0213, found, 484.0208.

*Ethyl-3-(2-ethoxy-1-hydroxy-2-oxoethyl)-2-phenylindolizine-1-carboxylate (**6j**).*




**6j**

Ivory gum (38.4 mg, 95%); **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ 8.32 (d, $J$ = 8.8 Hz, 1H), 8.12 (d, $J$ = 6.8 Hz, 1H), 7.44−7.34 (m, 5H), 7.14 (t, $J$ = 8.0 Hz, 1H), 6.78 (t, $J$ = 6.8 Hz, 1H), 5.39 (s, 1H), 4.25−4.08 (m, 4H), 1.17 (t, $J$ = 6.8 Hz, 3H), 1.09 (t, $J$ = 6.8 Hz, 3H); **$^{13}$C{$^1$H} NMR** (100 MHz, $CDCl_3$) $\delta$ 172.8, 164.8, 136.7, 134.2, 133.3, 130.6, 127.4, 127.3, 124.5, 123.2, 120.2, 118.7, 113.0, 102.4, 77.4, 77.0, 76.7, 65.4, 62.8, 59.3, 14.1, 14.0; **HRMS** (ESI-QTOF) $m/z$ $[M + H]^+$ calcd for $C_{21}H_{22}NO_5$ 368.1492, found, 368.1496.



https://doi.org/10.1021/acsomega.3c00236
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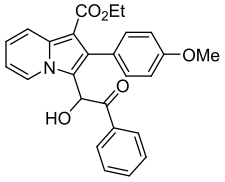
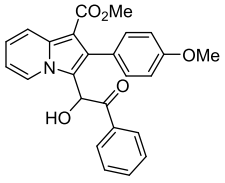
*Ethyl-3-(1-hydroxy-2-oxo-2-phenylethyl)-2-(4-methoxyphenyl)indolizine-1-carboxylate (**6k**).*




**6k**

Ivory solid, mp: 66.4−67.2 °C (45.8 mg, 97%); **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ 8.23 (d, $J$ = 8.8 Hz, 1H), 7.92 (d, $J$ = 6.8 Hz, 1H), 7.54 (d, $J$ = 6.8 Hz, 2H), 7.48−7.40 (m, 3H), 7.26−7.19 (m, 2H), 7.11−7.00 (m, 3H), 6.72 (t, $J$ = 6.8 Hz, 1H), 6.10 (s, 1H), 4.30−4.10 (m, 2H), 3.89 (s, 3H), 1.18 (t, $J$ = 7.0 Hz, 3H); **$^{13}$C{$^1$H} NMR** (100 MHz, $CDCl_3$) $\delta$ 198.9, 164.8, 159.3, 136.9, 134.3, 133.0, 132.8, 128.5, 128.4, 126.2, 124.1, 123.2, 120.2, 119.5, 113.5, 113.2, 102.5, 77.3, 77.0, 76.7, 69.5, 59.4, 55.3, 14.3; **HRMS** (ESI-QTOF) $m/z$ $[M + H]^+$ calcd for $C_{26}H_{24}NO_5$ 430.1649, found, 430.1651.

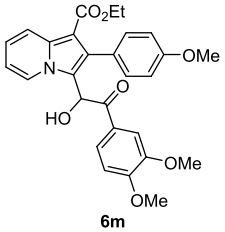
*Methyl-3-(1-hydroxy-2-oxo-2-phenylethyl)-2-(4-methoxyphenyl)indolizine-1-carboxylate (**6l**).*




**6l**

Green solid, mp: 149.0−149.8 °C (37.9 mg, 83%); **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ 8.22 (d, $J$ = 9.2 Hz, 1H), 7.92 (d, $J$ = 7.2 Hz, 1H), 7.53 (d, $J$ = 8.0 Hz, 2H), 7.48−7.42 (m, 3H), 7.23 (t, $J$ = 7.4 Hz, 2H), 7.11−7.01 (m, 3H), 6.72 (t, $J$ = 6.8 Hz, 1H), 6.10 (s, 1H), 4.37 (s, 1H), 3.90 (s, 3H), 3.72 (s, 3H); **$^{13}$C{$^1$H} NMR** (100 MHz, $CDCl_3$) $\delta$ 199.0, 165.3, 159.5, 137.0, 134.4, 133.2, 132.9, 128.7, 128.6, 126.2, 124.3, 123.4, 120.4, 119.7, 113.7, 113.4, 102.4, 77.5, 77.2, 76.8, 69.6, 55.5, 50.8; **HRMS** (ESI-QTOF) $m/z$ $[M + H]^+$ calcd for $C_{25}H_{22}NO_5$ 416.1492, found, 416.1497.

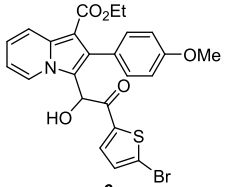
*Ethyl-3-(2-(3,4-dimethoxyphenyl)-1-hydroxy-2-oxoethyl)-2-(4-methoxyphenyl)indolizine-1-carboxylate (**6m**).*




**6m**

Brown solid, mp: 144.4−145.0 °C (53.8 mg, 100%); **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ 8.24 (d, $J$ = 9.2 Hz, 1H), 7.92 (d, $J$ = 7.2 Hz, 1H), 7.46 (d, $J$ = 8.4 Hz, 2H), 7.27 (s, 1H), 7.10−6.99 (m, 4H), 6.71 (t, $J$ = 6.4 Hz, 1H), 6.57 (d, $J$ = 8.4 Hz, 1H), 6.03 (s, 1H), 4.30−4.12 (m, 2H), 3.88 (s, 3H), 3.85 (s, 3H), 3.80 (s, 3H), 1.19 (t, $J$ = 7.0 Hz, 3H); **$^{13}$C{$^1$H} NMR** (100 MHz, $CDCl_3$) $\delta$ 197.0, 164.8, 159.3, 154.3, 149.0, 136.9, 132.6, 132.2, 126.1, 125.8, 124.1, 123.8, 123.1, 120.4, 120.2, 113.4, 113.2, 110.6, 109.7, 102.4, 77.4, 77.0, 76.7, 68.9, 59.4, 56.1, 56.0, 55.3, 14.3; **HRMS** (ESI-QTOF) $m/z$ $[M + H]^+$ calcd for $C_{28}H_{28}NO_7$ 490.1860, found, 490.1864.

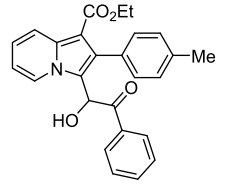
*Ethyl-3-(2-(5-bromothiophen-2-yl)-1-hydroxy-2-oxoethyl)-2-(4-methoxyphenyl)indolizine-1-carboxylate (**6n**).*




**6n**

Yellow solid, mp: 92.4−93.0 °C (56.6 mg, 100%); **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ 8.30 (d, $J$ = 9.2 Hz, 1H), 7.87 (d, $J$ = 7.2 Hz, 1H), 7.47 (d, $J$ = 8.0 Hz, 2H), 7.12 (t, $J$ = 7.8 Hz, 1H), 7.06−6.97 (m, 3H), 6.88 (d, $J$ = 4.0 Hz, 1H), 6.73 (t, $J$ = 6.8 Hz, 1H), 5.79 (s, 1H), 4.31−4.16 (m, 2H), 3.87 (s, 3H), 1.21 (t, $J$ = 7.2 Hz, 3H); **$^{13}$C{$^1$H} NMR** (100 MHz, $CDCl_3$) $\delta$ 190.0, 164.9, 159.4, 139.5, 137.2, 134.5, 133.8, 132.0, 131.5, 125.7, 125.0, 124.2, 123.6, 120.3, 119.0, 113.6, 113.5, 102.6, 77.4, 77.1, 76.7, 69.5, 59.6, 55.3, 14.2; **HRMS** (ESI-QTOF) $m/z$ $[M + H]^+$ calcd for $C_{24}H_{21}BrNO_5S$ 514.0318, found, 514.0318.

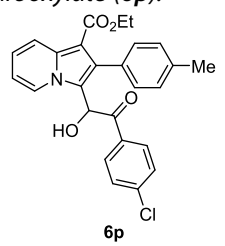
*Ethyl-3-(1-hydroxy-2-oxo-2-phenylethyl)-2-(p-tolyl)indolizine-1-carboxylate (**6o**).*




**6o**

Yellow solid, mp: 78.5−79.3 °C (45.5 mg, 100%); **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ 8.23 (d, $J$ = 8.8 Hz, 1H), 7.91 (d, $J$ = 7.2 Hz, 1H), 7.55 (d, $J$ = 7.6 Hz, 2H), 7.49−7.38 (m, 3H), 7.31 (d, $J$ = 7.6 Hz, 2H), 7.23 (t, $J$ = 7.6 Hz, 2H), 7.06 (t, $J$ = 7.8 Hz 1H), 6.72 (t, $J$ = 7.0 Hz, 1H), 6.09 (s, 1H), 4.37 (s, 1H), 4.31−4.08 (m, 2H), 2.45 (s, 3H), 1.17 (t, $J$ = 7.2 Hz, 3H); **$^{13}$C{$^1$H} NMR** (100 MHz, $CDCl_3$) $\delta$ 198.9, 164.7, 137.5, 136.9, 134.3, 133.4, 132.8, 131.0, 128.7, 128.6, 128.4, 124.1, 123.1, 120.2, 119.4, 113.2, 102.5, 77.3, 77.0, 76.7, 69.5, 59.4, 21.4, 14.2; **HRMS** (ESI-QTOF) $m/z$ $[M + H]^+$ calcd for $C_{26}H_{24}NO_4$ 414.1700, found, 414.1702.

*Ethyl-3-(2-(4-chlorophenyl)-1-hydroxy-2-oxoethyl)-2-(p-tolyl)indolizine-1-carboxylate (**6p**).*




**6p**

Yellow solid, mp: 89.6−90.1 °C (48.3 mg, 98%); **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ 8.23 (d, $J$ = 9.2 Hz, 1H), 7.88 (d, $J$ = 6.8 Hz, 1H), 7.48 (d, $J$ = 8.4 Hz, 2H), 7.40 (d, $J$ = 8.0 Hz, 2H), 7.31 (d, $J$ = 7.6 Hz, 2H), 7.20 (d, $J$ = 8.0 Hz, 2H), 7.08 (t, $J$ = 8.0 Hz, 1H), 6.72 (t, $J$ = 7.0 Hz, 1H), 6.06 (s, 1H), 4.30 (s, 1H), 4.26−4.10 (m, 2H), 2.45 (s, 3H), 1.18 (t, $J$ = 7.2 Hz, 3H); **$^{13}$C{$^1$H} NMR** (100 MHz, $CDCl_3$) $\delta$ 197.7, 164.8, 140.9, 137.7, 137.0, 133.4, 131.0, 130.8, 130.0, 128.9, 128.8, 124.1, 123.3, 120.3, 119.1, 113.4, 102.5, 77.3, 77.0, 76.7, 69.5, 59.5, 21.4, 14.2; **HRMS** (ESI-QTOF) $m/z$ $[M + H]^+$ calcd for $C_{26}H_{23}ClNO_4$ 448.1310, found, 448.1311.



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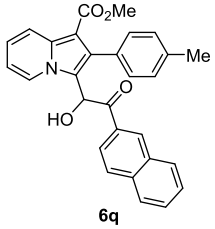
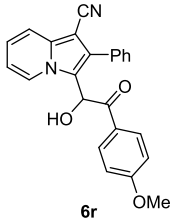
*Methyl-3-(1-hydroxy-2-(naphthalen-2-yl)-2-oxoethyl)-2-(p-tolyl)indolizine-1-carboxylate (**6q**).*




6q

Green solid, mp: 196.9−197.9 °C (48.5 mg, 98%); **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ 8.18 (d, $J$ = 8.8 Hz, 1H), 8.02−7.95 (m, 2H), 7.77−7.67 (m, 4H), 7.60−7.48 (m, 4H), 7.43 (s, 2H), 7.03 (t, $J$ = 7.5 Hz, 1H), 6.71 (t, $J$ = 5.9 Hz, 1H), 6.30 (s, 1H), 3.72 (s, 3H), 2.51 (s, 3H); **$^{13}$C{$^1$H} NMR** (100 MHz, $CDCl_3$) $\delta$ 198.8, 165.1, 137.7, 136.9, 136.0, 133.3, 131.9, 131.0, 130.7, 130.0, 129.6, 129.1, 129.00, 128.96, 128.4, 127.7, 126.9, 124.3, 123.7, 123.2, 120.3, 119.8, 113.3, 102.2, 77.4, 77.1, 76.8, 69.5, 50.6, 21.5; **HRMS** (ESI-QTOF) $m/z$ [M + H]$^+$ calcd for $C_{29}H_{24}NO_4$ 450.1700, found, 450.1704.

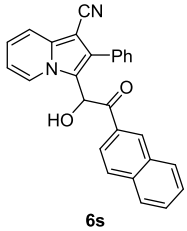
*3-(1-Hydroxy-2-(4-methoxyphenyl)-2-oxoethyl)-2-phenylindolizine-1-carbonitrile (**6r**).*




6r

Ivory solid, mp: 114.7−115.7 °C (40.4 mg, 96%); **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ 7.95 (d, $J$ = 7.2 Hz, 1H), 7.69 (d, $J$ = 7.2 Hz, 2H), 7.65−7.56 (m, 3H), 7.54−7.44 (m, 3H), 7.08 (t, $J$ = 7.8 Hz, 1H), 6.75 (t, $J$ = 6.8 Hz, 1H), 6.65 (d, $J$ = 8.8 Hz, 2H), 6.21 (s, 1H), 3.77 (s, 3H); **$^{13}$C{$^1$H} NMR** (100 MHz, $CDCl_3$) $\delta$ 195.8, 164.6, 138.6, 133.1, 131.7, 131.0, 129.8, 129.4, 128.8, 125.2, 125.0, 123.3, 119.0, 117.8, 116.3, 113.8, 113.8, 77.3, 77.0, 76.7, 68.8, 55.5; **HRMS** (ESI-QTOF) $m/z$ [M + H]$^+$ calcd for $C_{24}H_{19}N_2O_3$ 383.1390, found, 383.1388.

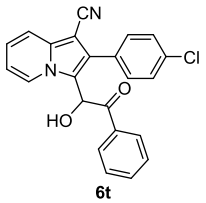
*3-(1-Hydroxy-2-(naphthalen-2-yl)-2-oxoethyl)-2-phenylindolizine-1-carbonitrile (**6s**).*




6s

Green solid, mp: 169.9−170.4 °C (44.3 mg, 100%); **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ 8.03 (d, $J$ = 5.6 Hz, 1H), 7.87 (s, 1H), 7.80−7.66 (m, 7H), 7.62−7.52 (m, 5H), 7.49 (d, $J$ = 6.0 Hz, 1H), 7.04 (t, $J$ = 7.4 Hz, 1H), 6.75 (t, $J$ = 6.8 Hz, 1H), 6.50 (s, 1H); **$^{13}$C{$^1$H} NMR** (100 MHz, $CDCl_3$) $\delta$ 197.5, 138.7, 136.0, 133.2, 131.8, 130.9, 130.0, 129.6, 129.4, 129.0, 128.6, 127.7, 127.1, 125.0, 123.5, 123.4, 118.6, 117.9, 116.3, 116.2, 115.1, 115.0, 113.8, 82.6, 77.4, 77.1, 76.7, 69.3; **HRMS** (ESI-QTOF) $m/z$ [M + H]$^+$ calcd for $C_{27}H_{19}N_2O_2$ 403.1441, found, 403.1437.

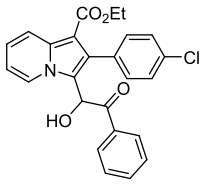
*2-(4-Chlorophenyl)-3-(1-hydroxy-2-oxo-2-phenylethyl)-indolizine-1-carbonitrile (**6t**).*




6t

Gray solid, mp: 168.5−169.3 °C (38.7 mg, 91%); **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ 7.98 (d, $J$ = 7.2 Hz, 1H), 7.62 (d, $J$ = 9.2 Hz, 1H), 7.59−7.52 (m, 4H), 7.45 (d, $J$ = 8.0 Hz, 3H), 7.22 (t, $J$ = 7.6 Hz, 2H), 7.12 (t, $J$ = 7.5 Hz, 1H), 7.12 (t, $J$ = 7.4 Hz, 1H), 6.80 (t, $J$ = 6.8 Hz, 1H), 6.21 (s, 1H), 4.44 (s, 1H); **$^{13}$C{$^1$H} NMR** (100 MHz, $CDCl_3$) $\delta$ 197.5, 138.6, 135.1, 134.6, 132.4, 132.0, 131.1, 130.1, 129.6, 128.6, 128.3, 124.8, 123.7, 118.5, 117.9, 115.9, 114.0, 82.6, 77.4, 77.0, 76.7, 69.1; **HRMS** (ESI-QTOF) $m/z$ [M + H]$^+$ calcd for $C_{23}H_{16}ClN_2O_2$ 387.0895, found, 387.0892.

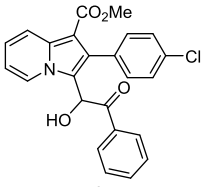
*Ethyl-2-(4-chlorophenyl)-3-(1-hydroxy-2-oxo-2-phenylethyl)indolizine-1-carboxylate (**6u**).*




6u

Yellow solid, mp: 72.1−72.8 °C (45.3 mg, 95%); **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ 8.25 (d, $J$ = 8.8 Hz, 1H), 7.95 (d, $J$ = 7.2 Hz, 1H), 7.51 (d, $J$ = 8.4 Hz, 2H), 7.48−7.38 (m, 5H), 7.26−7.21 (m, 2H), 7.10 (t, $J$ = 7.8 Hz, 1H), 6.75 (t, $J$ = 6.8 Hz, 1H), 6.04 (s, 1H), 4.36−4.01 (m, 2H), 1.17 (t, $J$ = 7.2 Hz, 3H); **$^{13}$C{$^1$H} NMR** (100 MHz, $CDCl_3$) $\delta$ 198.5, 164.6, 137.0, 134.4, 133.9, 132.8, 132.6, 131.8, 130.1, 128.5, 128.4, 128.2, 124.1, 123.5, 120.3, 119.5, 113.5, 102.4, 77.4, 77.0, 76.7, 69.2, 59.5, 14.2; **HRMS** (ESI-QTOF) $m/z$ [M + H]$^+$ calcd for $C_{25}H_{21}ClNO_4$ 434.1154, found, 434.1155.

*Methyl-2-(4-chlorophenyl)-3-(1-hydroxy-2-oxo-2-phenylethyl)indolizine-1-carboxylate (**6v**).*




6v

Ivory solid, mp: 162.9−163.5 °C (42.5 mg, 92%); **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ 8.23 (d, $J$ = 8.0 Hz, 1H), 7.94 (d, $J$ = 5.2 Hz, 1H), 7.52−7.39 (m, 7H), 7.26−7.20 (m, 3H), 7.10 (t, $J$ = 7.2 Hz, 1H), 6.76 (t, $J$ = 5.2 Hz, 1H), 6.03 (s, 1H), 4.39 (s, 1H), 3.71 (s, 3H); **$^{13}$C{$^1$H} NMR** (100 MHz, $CDCl_3$) $\delta$ 198.5, 164.9, 136.9, 134.4, 134.0, 132.8, 132.4, 131.8, 128.5, 128.4, 128.3, 128.2, 124.1, 123.5, 120.3, 119.6, 113.5, 102.2, 77.3, 77.0, 76.7, 69.2, 50.7; **HRMS** (ESI-QTOF) $m/z$ [M + H]$^+$ calcd for $C_{24}H_{19}ClNO_4$ 420.0997, found, 420.0993.



https://doi.org/10.1021/acsomega.3c00236
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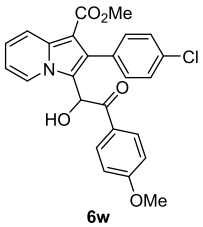
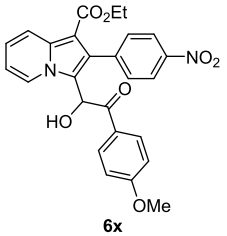
*Methyl-2-(4-chlorophenyl)-3-(1-hydroxy-2-(4-methoxyphenyl)-2-oxoethyl)indolizine-1-carboxylate (**6w**).*




**6w**

Yellow solid, mp: 135.7−136.6 °C (49.5 mg, 100%); **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ 8.22 (d, $J$ = 8.8 Hz, 1H), 7.93 (d, $J$ = 6.8 Hz, 1H), 7.54−7.46 (m, 6H), 7.08 (t, $J$ = 7.8 Hz, 1H), 6.75−6.65 (m, 3H), 5.95 (s, 1H), 3.77 (s, 3H), 3.72 (s, 3H); **$^{13}$C{$^1$H} NMR** (100 MHz, $CDCl_3$) $\delta$ 196.5, 165.0, 164.5, 136.9, 133.9, 132.5, 131.6, 131.0, 128.3, 125.5, 124.3, 123.5, 120.3, 120.2, 113.7, 113.5, 102.0, 101.7, 77.4, 77.0, 76.7, 68.8, 55.5, 50.7; **HRMS** (ESI-QTOF) $m/z$ [M + H]$^+$ calcd for $C_{25}H_{21}ClNO_5$ 450.1103, found, 450.1105.

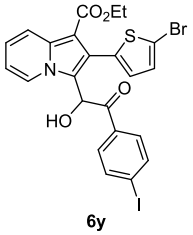
*Ethyl-3-(1-hydroxy-2-(4-methoxyphenyl)-2-oxoethyl)-2-(4-nitrophenyl)indolizine-1-carboxylate (**6x**).*




**6x**

Yellow solid, mp: 79.9−80.7 °C (51.1 mg, 98%); **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ 8.33 (d, $J$ = 8.0 Hz, 2H), 8.27 (d, $J$ = 9.2 Hz, 1H), 7.98 (d, $J$ = 6.8 Hz, 1H), 7.66 (d, $J$ = 6.4 Hz, 2H), 7.47 (d, $J$ = 9.2 Hz, 2H), 7.14 (t, $J$ = 7.8 Hz, 1H), 6.79 (t, $J$ = 7.0 Hz, 1H), 6.70 (d, $J$ = 8.8 Hz, 2H), 5.90 (s, 1H), 4.26−4.11 (m, 2H), 3.79 (s, 3H), 1.16 (t, $J$ = 7.2 Hz, 3H); **$^{13}$C{$^1$H} NMR** (100 MHz, $CDCl_3$) $\delta$ 195.9, 164.6, 164.3, 147.4, 141.5, 137.0, 130.9, 130.3, 125.4, 124.2, 123.9, 123.03, 122.97, 120.40, 120.37, 113.87, 113.85, 102.3, 77.3, 77.0, 76.7, 68.5, 59.7, 55.6, 14.2; **HRMS** (ESI-QTOF) $m/z$ [M + H]$^+$ calcd for $C_{26}H_{23}N_2O_7$ 475.1500, found, 475.1499.

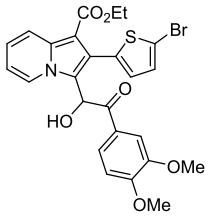
*Ethyl-2-(5-bromothiophen-2-yl)-3-(1-hydroxy-2-(4-iodophenyl)-2-oxoethyl)indolizine-1-carboxylate (**6y**).*




**6y**

Brown solid, mp: 87.0−88.0 °C (65.1 mg, 97%); **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ 8.24 (d, $J$ = 9.2 Hz, 1H), 7.86 (d, $J$ = 6.8 Hz, 1H), 7.67 (d, $J$ = 7.6 Hz, 2H), 7.35 (d, $J$ = 8.8 Hz, 2H), 7.15−7.07 (m, 2H), 6.96 (d, $J$ = 3.6 Hz, 1H), 6.75 (t, $J$ = 6.8 Hz, 1H), 6.15 (s, 1H), 4.31−4.17 (m, 2H), 1.26 (t, $J$ = 7.0 Hz, 3H); **$^{13}$C{$^1$H} NMR** (100 MHz, $CDCl_3$) $\delta$ 197.9, 164.1, 138.0, 136.9, 136.0, 131.9, 129.6, 124.2, 124.1, 123.8, 123.7, 120.7, 120.6, 120.49, 120.45, 113.9, 103.1, 77.3, 77.0, 76.7, 69.1, 59.8, 14.2; **HRMS** (ESI-QTOF) $m/z$ [M + H]$^+$ calcd for $C_{23}H_{18}BrINO_4S$ 609.9179, found, 609.9178.

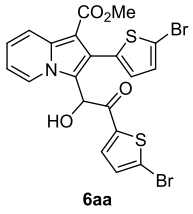
*Ethyl-2-(5-bromothiophen-2-yl)-3-(2-(3,4-dimethoxyphenyl)-1-hydroxy-2-oxoethyl)indolizine-1-carboxylate (**6z**).*




**6z**

Brown solid, mp: 77.4−78.2 °C (56.3 mg, 94%); **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ 8.23 (d, $J$ = 8.8 Hz, 1H), 7.90 (d, $J$ = 6.8 Hz, 1H), 7.32 (s, 1H), 7.19 (d, $J$ = 8.4 Hz, 1H), 7.14−7.04 (m, 2H), 6.99 (d, $J$ = 3.6 Hz, 1H), 6.73 (t, $J$ = 6.8 Hz, 1H), 6.65 (d, $J$ = 8.4 Hz, 1H), 6.13 (s, 1H), 4.55 (s, 1H), 4.32−4.20 (m, 2H), 3.88 (s, 3H), 3.83 (s, 3H), 1.26 (t, $J$ = 7.2 Hz, 3H); **$^{13}$C{$^1$H} NMR** (100 MHz, $CDCl_3$) $\delta$ 196.5, 164.3, 154.5, 149.1, 136.8, 136.1, 129.7, 129.6, 125.6, 124.0, 123.8, 123.6, 122.0, 120.3, 113.7, 113.7, 110.4, 109.9, 103.1, 68.6, 59.7, 56.2, 56.1, 14.3; **HRMS** (ESI-QTOF) $m/z$ [M + H]$^+$ calcd for $C_{25}H_{23}BrNO_6S$ 544.0424, found, 544.0419.

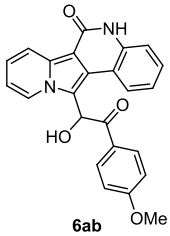
*Methyl-2-(5-bromothiophen-2-yl)-3-(2-(5-bromothiophen-2-yl)-1-hydroxy-2-oxoethyl)indolizine-1-carboxylate (**6aa**).*




**6aa**

Green solid, mp: 94.9−95.6 °C (55.0 mg, 90%); **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ 8.27 (d, $J$ = 8.8 Hz, 1H), 7.86 (d, $J$ = 6.8 Hz, 1H), 7.17−7.07 (m, 3H), 7.00 (d, $J$ = 3.2 Hz, 1H), 6.93 (d, $J$ = 4.0 Hz, 1H), 6.76 (t, $J$ = 6.6 Hz, 1H), 5.90 (s, 1H), 3.83 (s, 3H); **$^{13}$C{$^1$H} NMR** (100 MHz, $CDCl_3$) $\delta$ 189.5, 164.6, 139.3, 137.1, 135.5, 134.6, 131.7, 129.7, 129.6, 125.3, 125.2, 124.2, 124.1, 120.5, 120.4, 114.1, 113.9, 103.1, 77.4, 77.0, 76.7, 69.3, 51.0; **HRMS** (ESI-QTOF) $m/z$ [M + H]$^+$ calcd for $C_{20}H_{14}Br_2NO_4S_2$ 553.8726, found, 553.8717.

*12-(1-Hydroxy-2-(4-methoxyphenyl)-2-oxoethyl)indolizino[1,2-c]quinolin-6(5H)-one (**6ab**).*




**6ab**

Ivory solid, mp: 317.4−318.3 °C (36.4 mg, 83%); **$^1$H NMR** (400 MHz, DMSO-$d_6$) $\delta$ 11.09 (s, 1H), 8.62 (d, $J$ = 7.2 Hz, 1H), 8.47 (d, $J$ = 8.0 Hz, 1H), 8.38 (d, $J$ = 8.4 Hz, 1H), 7.78 (d, $J$ = 8.8 Hz, 2H), 7.48−7.37 (m, 2H), 7.29−7.21 (m, 2H), 7.10 (t, $J$ = 7.0 Hz, 1H), 6.79 (d, $J$ = 8.4 Hz, 2H), 6.40 (d, $J$ = 2.4 Hz, 1H), 5.76 (s, 1H), 3.69 (s, 3H); **$^{13}$C{$^1$H} NMR** (100 MHz, DMSO-$d_6$) $\delta$ 196.0, 163.6, 159.9, 138.4, 132.3, 130.7, 128.7, 128.0, 125.5, 125.4, 124.0, 122.4, 122.2, 119.3, 116.8, 116.5, 115.6, 114.8, 114.2, 103.2, 69.5, 55.9; **HRMS** (ESI-QTOF) $m/z$ [M + H]$^+$ calcd for $C_{24}H_{19}N_2O_4$ 399.1339, found, 399.1340.



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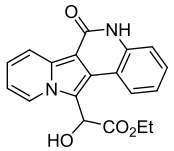
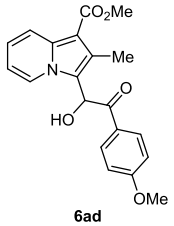
*Ethyl-2-hydroxy-2-(6-oxo-5,6-dihydroindolizino[1,2-c]-quinolin-12-yl)acetate (**6ac**).*




**6ac**

Green solid, mp: 377.5−378.3 °C (31.1 mg, 84%); **$^1$H NMR** (400 MHz, DMSO-$d_6$) $\delta$ 11.05 (s, 1H), 8.79 (d, $J$ = 7.2 Hz, 1H), 8.42 (d, $J$ = 8.8 Hz, 1H), 8.35 (d, $J$ = 8.0 Hz, 1H), 7.47−7.34 (m, 2H), 7.29 (t, $J$ = 7.8 Hz, 1H), 7.20 (t, $J$ = 7.8 Hz, 1H), 7.13 (t, $J$ = 6.8 Hz, 1H), 6.58 (d, $J$ = 4.0 Hz, 1H), 6.46 (d, $J$ = 3.6 Hz, 1H), 4.16−4.02 (m, 2H), 1.01 (t, $J$ = 7.2 Hz, 3H); **$^{13}$C{$^1$H} NMR** (100 MHz, DMSO-$d_6$) $\delta$ 171.4, 159.9, 138.3, 132.1, 128.5, 125.9, 125.6, 123.9, 122.3, 121.9, 119.3, 116.6, 116.0, 115.7, 114.6, 103.0, 65.6, 61.5, 14.4; **HRMS** (ESI-QTOF) $m/z$ [M + H]$^+$ calcd for $C_{19}H_{17}N_2O_4$ 337.1183, found, 337.1181.

*Methyl-3-(1-hydroxy-2-(4-methoxyphenyl)-2-oxoethyl)-2-methylindolizine-1-carboxylate (**6ad**).*

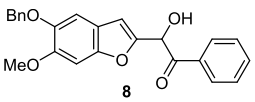



**6ad**

Green solid, mp: 130.1−131.2 °C (28.4 mg, 73%); **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ 8.14 (d, $J$ = 9.2 Hz, 1H), 7.87 (d, $J$ = 7.2 Hz, 1H), 7.81 (d, $J$ = 8.8 Hz, 2H), 7.01 (t, $J$ = 8.0 Hz, 1H), 6.79 (d, $J$ = 9.2 Hz, 2H), 6.65 (t, $J$ = 6.8 Hz, 1H), 6.25 (s, 1H), 4.58 (s, 1H), 3.89 (s, 3H), 3.78 (s, 3H), 2.72 (s, 3H); **$^{13}$C{$^1$H} NMR** (100 MHz, $CDCl_3$) $\delta$ 196.9, 165.8, 164.4, 136.9, 130.9, 127.9, 125.8, 123.9, 122.7, 119.6, 114.0, 112.6, 102.5, 77.3, 77.0, 76.7, 68.1, 55.4, 50.6, 11.9; **HRMS** (ESI-QTOF) $m/z$ [M + H]$^+$ calcd for $C_{20}H_{20}NO_5$ 354.1336, found, 354.1337.

*Synthesis of **8**.* A solution of 7 (30 mg, 1.0 equiv) and phenylglyoxal (1.0 equiv) in HFIP (1.0 mL) was stirred at room temperature for 12 h. The reaction mixture was concentrated *in vacuo* to give the crude residue, which was triturated with ether to afford **8** as an ivory solid (43.9 mg, 96%).

*2-(5-(Benzyloxy)-6-methoxybenzofuran-2-yl)-2-hydroxy-1-phenylethan-1-one (**8**).*

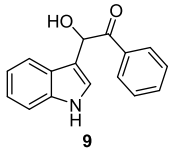



**8**

Ivory solid, mp: 149.8−150.6 °C (43.9 mg, 96%); **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ 8.00 (d, $J$ = 7.6 Hz, 2H), 7.56 (t, $J$ = 7.2 Hz, 1H), 7.46−7.38 (m, 4H), 7.36 (t, $J$ = 6.6 Hz, 2H), 7.30 (d, $J$ = 6.8 Hz, 1H), 6.98 (s, 1H), 6.95 (s, 1H), 6.58 (s, 1H), 6.10 (s, 1H), 5.12 (s, 2H), 4.49 (s, 1H), 3.88 (s, 3H); **$^{13}$C{$^1$H} NMR** (100 MHz, $CDCl_3$) $\delta$ 195.6, 153.0, 150.3, 149.2, 145.7, 137.1, 134.3, 133.1, 129.0, 128.8, 128.5, 127.8, 127.3, 119.6, 106.1, 105.8, 95.7, 77.3, 77.0, 76.7, 71.8, 69.7, 56.3; **HRMS** (ESI-QTOF) $m/z$ [M + Na]$^+$ calcd for $C_{24}H_{20}NaO_5$ 411.1203, found, 411.1205.

*Synthesis of **9**.* A solution of indole (30 mg, 1.0 equiv), phenylglyoxal (1.0 equiv), and HFIP (4.0 equiv) in dichloromethane (1.0 mL) was stirred at room temperature for 4 h. The reaction mixture was concentrated under reduced pressure to give the crude residue, which was triturated with mixed solvent (hexane/dichloromethane = 20:1). Filtration and drying afforded **9** as a pink solid (58.7 mg, 91%).

*2-Hydroxy-2-(1H-indol-3-yl)-1-phenylethan-1-one (**9**).*

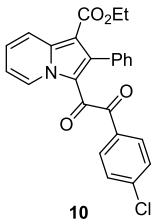



**9**

Pink solid, mp: 187.6−188.4 °C (58.7 mg, 91%); **$^1$H NMR** (400 MHz, DMSO-$d_6$) $\delta$ 11.04 (s, 1H), 8.00 (d, $J$ = 7.2 Hz, 2H), 7.62 (d, $J$ = 8.0 Hz, 1H), 7.50 (t, $J$ = 6.6 Hz, 1H), 7.40 (t, $J$ = 7.6 Hz, 2H), 7.35−7.28 (m, 2H), 7.05 (t, $J$ = 7.6 Hz, 1H), 6.97 (t, $J$ = 7.4 Hz, 1H), 6.35 (d, $J$ = 4.8 Hz, 1H), 5.51 (d, $J$ = 5.2 Hz, 1H); **$^{13}$C{$^1$H} NMR** (100 MHz, DMSO-$d_6$) $\delta$ 199.4, 136.7, 135.4, 133.4, 128.9, 128.9, 126.0, 125.4, 121.7, 119.7, 119.4, 113.7, 112.0, 69.8, 40.5, 40.3, 40.1, 39.9, 39.7, 39.5, 39.3; **HRMS** (ESI-QTOF) $m/z$ [M + Na]$^+$ calcd for $C_{16}H_{13}NNaO_2$ 274.0838, found, 274.0841.

*Synthesis of **10**.* To a solution of **6f** (20 mg, 0.05 mmol) in dichloromethane (1 mL) was added morpholine (8.0 $\mu$L, 0.09 mmol, 2.0 equiv) at room temperature. After being stirred at 40 °C for 6 h, the reaction mixture was concentrated under reduced pressure to give the crude residue, which was purified by silica gel column chromatography (hexane/ethyl acetate/dichloromethane = 10:1:2) to furnish **10** as a yellow solid (15.9 mg, 80%).

*Ethyl-3-(2-(4-chlorophenyl)-2-oxoacetyl)-2-phenylindolizine-1-carboxylate (**10**).*




**10**

Yellow solid, mp: 165.0−166.4 °C (23.9 mg, 80%); **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ 10.04 (d, $J$ = 7.2 Hz, 1H), 8.50 (d, $J$ = 8.8 Hz, 1H), 7.57 (t, $J$ = 8.0 Hz, 1H), 7.44 (d, $J$ = 8.0 Hz, 2H), 7.24 (d, $J$ = 4.4 Hz, 2H), 7.18 (d, $J$ = 7.2 Hz, 1H), 7.09 (t, $J$ = 6.8 Hz, 1H), 6.99−6.88 (m, 4H), 4.07−3.99 (m, 2H), 0.91 (t, $J$ = 7.0 Hz, 3H); **$^{13}$C{$^1$H} NMR** (100 MHz, $CDCl_3$) $\delta$ 190.1, 184.7, 163.7, 143.8, 140.33, 140.25, 132.2, 131.6, 130.9, 130.6, 129.4, 129.3, 128.6, 128.1, 126.8, 120.1, 119.9, 116.4, 107.2, 77.4, 77.0, 76.7, 59.8, 13.7; **HRMS** (ESI-QTOF) $m/z$ [M + H]$^+$ calcd for $C_{25}H_{19}ClNO_4$ 432.0997, found, 432.1002.

*Synthesis of **11**.* To a solution of **6f** (30 mg, 0.07 mmol) in alcohol (2 mL) was added PTSA (17.9 mg, 0.10 mmol, 1.5 equiv) at room temperature. The reaction was monitored by thin-layer chromatography (TLC). After being stirred at room temperature for 5−11 h, the reaction mixture was concentrated under reduced pressure, diluted with dichloromethane, and washed with water. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure to give the crude residue which was purified by silica gel column chromatography (dichloromethane) to afford the desired **11a−d** (83−92%).



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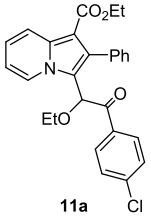
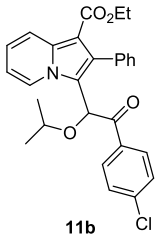
*Ethyl-3-(2-(4-chlorophenyl)-1-ethoxy-2-oxoethyl)-2-phenylindolizine-1-carboxylate (**11a**).*




11a

Yellow gum (29.2 mg, 92%); **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ 8.59 (d, $J$ = 7.2 Hz, 1H), 8.26 (d, $J$ = 8.8 Hz, 1H), 7.55−7.32 (m, 7H), 7.22−7.17 (m, 2H), 7.14 (t, $J$ = 8.0 Hz, 1H), 6.79 (t, $J$ = 7.0 Hz, 1H), 5.96 (s, 1H), 4.22−4.06 (m, 2H), 3.74−3.62 (m, 1H), 3.60−3.47 (m, 1H), 1.28 (t, $J$ = 7.0 Hz, 3H), 1.10 (t, $J$ = 7.2 Hz, 3H); **$^{13}$C{$^1$H} NMR** (100 MHz, $CDCl_3$) $\delta$ 192.8, 164.6, 139.9, 137.2, 134.5, 133.7, 133.0, 130.1, 128.6, 128.0, 127.8, 126.5, 123.7, 119.8, 116.4, 113.0, 102.6, 77.4, 77.0, 76.7, 75.4, 64.9, 59.3, 15.3, 14.1; **HRMS** (ESI-QTOF) $m/z$ $[M + H]^+$ calcd for $C_{27}H_{25}ClNO_4$ 462.1467, found, 462.1469.

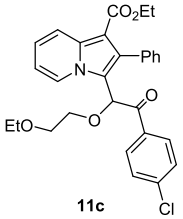
*Ethyl-3-(2-(4-chlorophenyl)-1-isopropoxy-2-oxoethyl)-2-phenylindolizine-1-carboxylate (**11b**).*




11b

Green gum (29.9 mg, 91%); **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ 8.63 (d, $J$ = 5.2 Hz, 1H), 8.25 (d, $J$ = 8.0 Hz, 1H), 7.55−7.36 (m, 7H), 7.24−7.19 (m, 2H), 7.13 (t, $J$ = 6.6 Hz, 1H), 6.78 (s, 1H), 6.06 (s, 1H), 4.14 (q, $J$ = 5.9 Hz, 2H), 3.75−3.65 (m, 1H), 1.26 (s, 3H), 1.16 (s, 3H), 1.09 (t, $J$ = 5.6 Hz, 3H); **$^{13}$C{$^1$H} NMR** (100 MHz, $CDCl_3$) $\delta$ 193.3, 164.6, 139.8, 137.3, 134.6, 133.4, 133.3, 130.1, 128.6, 127.90, 127.88, 127.7, 126.8, 123.6, 119.7, 116.9, 112.8, 102.5, 77.3, 77.0, 76.7, 73.0, 70.3, 59.2, 22.2, 22.0, 14.1; **HRMS** (ESI-QTOF) $m/z$ $[M + H]^+$ calcd for $C_{28}H_{27}ClNO_4$ 476.1623, found, 476.1627.

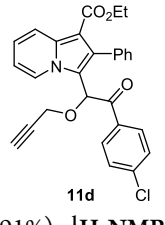
*Ethyl-3-(2-(4-chlorophenyl)-1-(2-ethoxyethoxy)-2-oxoethyl)-2-phenylindolizine-1-carboxylate (**11c**).*




11c

Green gum (29.1 mg, 83%); **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ 8.58 (d, $J$ = 7.2 Hz, 1H), 8.26 (d, $J$ = 9.2 Hz, 1H), 7.51−7.30 (m, 7H), 7.19 (d, $J$ = 8.8 Hz, 2H), 7.13 (t, $J$ = 7.4 Hz, 1H), 6.77 (t, $J$ = 6.2 Hz, 1H), 6.10 (s, 1H), 4.14 (q, $J$ = 5.2 Hz, 2H), 3.84−3.77 (m, 1H), 3.70−3.57 (m, 3H), 3.42 (q, $J$ = 5.1 Hz, 2H), 1.12−1.05 (m, 6H); **$^{13}$C{$^1$H} NMR** (100 MHz, $CDCl_3$) $\delta$ 192.7, 164.6, 139.8, 137.3, 134.4, 133.8, 133.1, 130.2, 128.6, 127.9, 127.7, 126.6, 123.7, 119.8, 116.4, 112.8, 102.6, 77.3, 77.0, 76.7, 76.1, 69.9, 68.7, 66.6, 59.3, 15.1, 14.1; **HRMS** (ESI-QTOF) $m/z$ $[M + H]^+$ calcd for $C_{29}H_{29}ClNO_5$ 506.1729, found, 506.1727.

*Ethyl-3-(2-(4-chlorophenyl)-2-oxo-1-(prop-2-yn-1-yloxy)-ethyl)-2-phenylindolizine-1-carboxylate (**11d**).*

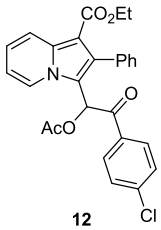



11d

Yellow gum (29.6 mg, 91%); **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ 8.51 (d, $J$ = 7.2 Hz, 1H), 8.27 (d, $J$ = 8.8 Hz, 1H), 7.61−7.30 (m, 7H), 7.20 (d, $J$ = 8.4 Hz, 2H), 7.15 (t, $J$ = 7.8 Hz, 1H), 6.79 (t, $J$ = 6.2 Hz, 1H), 6.31 (s, 1H), 4.32 (s, 2H), 4.14 (q, $J$ = 7.5 Hz, 2H), 2.43 (s, 1H), 1.10 (t, $J$ = 7.0 Hz, 3H); **$^{13}$C{$^1$H} NMR** (100 MHz, $CDCl_3$) $\delta$ 192.2, 164.5, 140.1, 137.4, 134.5, 134.1, 132.9, 130.2, 128.7, 127.83, 127.77, 126.4, 123.8, 119.9, 115.3, 113.0, 102.7, 102.0, 78.5, 77.4, 77.0, 76.7, 76.3, 73.7, 59.3, 56.1, 14.1; **HRMS** (ESI-QTOF) $m/z$ $[M + H]^+$ calcd for $C_{28}H_{23}ClNO_4$ 472.1310, found, 465.1308.

*Synthesis of **12**.* To a solution of **6f** (30 mg, 0.07 mmol), acetic anhydride (13.1 $\mu$L, 0.14 mmol, 2.0 equiv), and triethylamine (28.7 $\mu$L, 0.21 mmol, 3.0 equiv) in dichloromethane (1 mL) was added DMAP (0.86 mg, 0.01 mmol, 0.1 equiv) at 0 °C. After being stirred at room temperature for 3 h, the reaction mixture was concentrated under reduced pressure, diluted with dichloromethane, and washed with water. The combined organic layer was washed with saturated sodium bicarbonate solution, dried over $MgSO_4$, and concentrated under reduced pressure to give the crude residue, which was purified by silica gel column chromatography (hexane/ethyl acetate/dichloromethane = 20:1:2) to afford **12** as a yellow gum (23.3 mg, 71%).

*Ethyl-3-(1-acetoxy-2-(4-chlorophenyl)-2-oxoethyl)-2-phenylindolizine-1-carboxylate (**12**).*




12

Yellow gum (23.3 mg, 71%); **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ 8.52 (d, $J$ = 6.4 Hz, 1H), 8.26 (d, $J$ = 8.8 Hz, 1H), 7.54−7.36 (m, 7H), 7.19 (d, $J$ = 8.0 Hz, 2H), 7.14 (d, $J$ = 8.0 Hz, 1H), 6.78 (t, $J$ = 5.8 Hz, 1H), 5.85 (s, 1H), 4.13 (q, $J$ = 8.0 Hz, 2H), 3.47 (s, 3H), 1.10 (t, $J$ = 6.6 Hz, 3H); **$^{13}$C{$^1$H} NMR** (100 MHz, $CDCl_3$) $\delta$ 192.6, 164.5, 140.0, 137.3, 134.4, 134.1, 133.0, 130.6, 130.0, 128.6, 128.03, 127.98, 127.8, 126.4, 123.7, 119.8, 115.8, 113.1, 102.7, 59.3, 57.0, 14.1; **HRMS** (ESI-QTOF) $m/z$ $[M + H]^+$ calcd for $C_{27}H_{23}ClNO_5$ 476.1259, found, 476.1256.

*Synthesis of **13**.* To a solution of **6f** (30 mg, 0.07 mmol) in $CHCl_3$ (0.6 mL) was added PTSA (17.9 mg, 0.10 mmol, 1.5 equiv) at room temperature. After being stirred at rt for 10 h, the reaction mixture was concentrated under reduced pressure, diluted with dichloromethane, and washed with water. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure to give the crude residue which was purified by silica gel column chromatography (hexane/ethyl acetate/dichloromethane = 15:1:2) to afford **13** as a yellow gum (22.2 mg, 65%).



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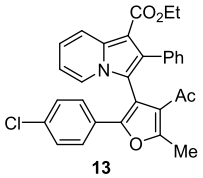
*3-(4-Acetyl-2-(4-chlorophenyl)-5-methylfuran-3-yl)-2-phenylindolizin-1-yl propionate (**13**).*

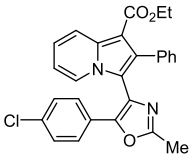



**13**

Yellow gum (22.2 mg, 65%); **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ 8.41 (d, $J$ = 9.2 Hz, 1H), 7.68 (d, $J$ = 6.8 Hz, 1H), 7.21−7.14 (m, 6H), 7.11−7.05 (m, 4H), 6.76 (t, $J$ = 6.0 Hz, 1H), 4.30−4.16 (m, 2H), 2.63 (s, 3H), 1.76 (s, 3H), 1.16 (t, $J$ = 7.0 Hz, 3H); **$^{13}$C{$^1$H} NMR** (100 MHz, $CDCl_3$) $\delta$ 194.2, 164.9, 159.2, 150.2, 136.8, 134.1, 134.0, 132.1, 129.8, 129.0, 127.7, 127.3, 127.0, 125.7, 124.0, 123.1, 120.4, 114.8, 113.6, 108.9, 103.1, 59.5, 28.7, 15.0, 14.1; **HRMS** (ESI-QTOF) $m/z$ $[M + H]^+$ calcd for $C_{30}H_{25}ClNO_4$ 498.1467, found, 498.1463.

*Synthesis of **14**.* To a solution of **6f** (20 mg, 0.05 mmol) in acetonitrile (1 mL) was added PTSA (11.9 mg, 0.07 mmol, 1.5 equiv) at room temperature. After being stirred at rt for 5 h, the reaction mixture was concentrated under reduced pressure, diluted with dichloromethane, and washed with water. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure to give the crude residue, which was purified by silica gel column chromatography (hexane/ethyl acetate/dichloromethane = 35:1:2) to afford **14** as a green solid (13.4 mg, 64%).

*Ethyl-3-(4-(4-chlorophenyl)-2-methyloxazol-5-yl)-2-phenylindolizine-1-carboxylate (**14**).*

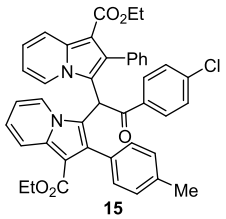



**14**

Green solid, mp: 154.1−155.5 °C (13.4 mg, 64%); **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ 8.36 (d, $J$ = 8.8 Hz, 1H), 7.98 (d, $J$ = 6.0 Hz, 1H), 7.19−7.09 (m, 8H), 7.03 (d, $J$ = 8.0 Hz, 2H), 6.75 (t, $J$ = 6.2 Hz, 1H), 4.21 (q, $J$ = 6.5 Hz, 2H), 2.55 (s, 3H), 1.15 (t, $J$ = 6.6 Hz, 3H); **$^{13}$C{$^1$H} NMR** (100 MHz, $CDCl_3$) $\delta$ 164.9, 160.9, 148.4, 137.1, 134.2, 134.0, 132.9, 130.4, 128.7, 126.9, 126.7, 126.3, 126.0, 124.8, 124.3, 123.3, 120.1, 115.0, 113.1, 102.7, 77.4, 77.0, 76.7, 59.4, 14.2, 14.1; **HRMS** (ESI-QTOF) $m/z$ $[M + H]^+$ calcd for $C_{27}H_{22}ClN_2O_3$ 457.1313, found, 457.1311.

*Synthesis of **15**.* To a solution of **6f** (20 mg, 0.05 mmol) and **5f** (15.5 mg, 0.06 mmol, 1.2 equiv) in $CHCl_3$ (1 mL) was added PTSA (1.6 mg, 0.01 mmol, 0.2 equiv) at room temperature. After being stirred at rt for 4 h, the reaction mixture was concentrated under reduced pressure to give the crude residue, which was purified by silica gel column chromatography (hexane/ethyl acetate/dichloromethane = 20:1:2) to furnish **15** as a green solid (19.2 mg, 60%).

*Ethyl-3-(2-(4-chlorophenyl)-1-(1-(ethoxycarbonyl)-2-(p-tolyl)indolizin-3-yl)-2-oxoethyl)-2-phenylindolizine-1-carboxylate (**15**).*

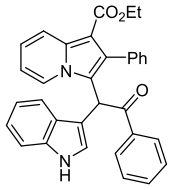



**15**

Green solid, mp: 138.0−138.8 °C (19.2 mg, 60%); **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ 8.19 (d, $J$ = 8.8 Hz, 1H), 8.13 (d, $J$ = 9.2 Hz, 1H), 7.45−7.37 (m, 4H), 7.16 (d, $J$ = 8.4 Hz, 2H), 7.13−6.98 (m, 9H), 6.86 (d, $J$ = 6.8 Hz, 2H), 6.53 (q, $J$ = 6.5 Hz, 2H), 6.41 (s, 1H), 4.19−4.08 (m, 4H), 2.23 (s, 3H), 1.12 (t, $J$ = 7.0 Hz, 3H), 1.06 (t, $J$ = 7.0 Hz, 3H); **$^{13}$C{$^1$H} NMR** (100 MHz, $CDCl_3$) $\delta$ 192.80, 192.79, 164.72, 164.68, 140.3, 136.7, 136.6, 136.5, 133.6, 133.3, 132.6, 132.4, 130.5, 129.8, 129.71, 129.67, 129.6, 128.8, 127.8, 127.0, 123.7, 122.5, 122.4, 119.83, 119.76, 116.4, 116.3, 113.0, 112.9, 103.3, 103.2, 77.3, 77.0, 76.7, 59.2, 44.6, 21.2, 14.2, 14.1; **HRMS** (ESI-QTOF) $m/z$ $[M + H]^+$ calcd for $C_{43}H_{36}ClN_2O_5$ 695.2307, found, 695.2316.

*Synthesis of **16**.* To a solution of **6a** (20 mg, 0.05 mmol) and indole (23.4 mg, 0.20 mmol, 4.0 equiv) in $CHCl_3$ (1 mL) was added PTSA (1.7 mg, 0.01 mmol, 0.2 equiv) at 0 °C. After being stirred at 40 °C for 24 h, the reaction mixture was concentrated under reduced pressure to give the crude residue, which was purified by silica gel column chromatography (hexane/ethyl acetate/dichloromethane = 20:1:2) to furnish **16** as an ivory solid (16.4 mg, 66%).

*Ethyl-3-(1-(1H-indol-3-yl)-2-oxo-2-phenylethyl)-2-phenylindolizine-1-carboxylate (**16**).*




**16**

Ivory solid, mp: 164.3−165.2 °C (16.4 mg, 66%); **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ 8.33 (d, $J$ = 6.7 Hz, 1H), 8.28 (d, $J$ = 8.8 Hz, 1H), 8.16 (s, 1H), 7.66 (d, $J$ = 7.2 Hz, 2H), 7.49 (t, $J$ = 7.0 Hz, 1H), 7.40−7.33 (m, 5H), 7.29 (d, $J$ = 8.0 Hz, 2H), 7.16 (t, $J$ = 7.0 Hz, 1H), 7.05−6.95 (m, 3H), 6.76 (s, 1H), 6.53 (s, 2H), 4.24−4.13 (m, 2H), 1.14 (t, $J$ = 6.0 Hz, 3H); **$^{13}$C{$^1$H} NMR** (100 MHz, $CDCl_3$) $\delta$ 196.4, 164.9, 136.9, 136.4, 135.8, 135.0, 133.4, 131.8, 128.8, 128.5, 127.8, 127.4, 126.3, 126.0, 123.5, 122.6, 122.5, 119.9, 119.7, 119.3, 119.0, 112.1, 111.3, 110.8, 102.1, 77.3, 77.0, 76.7, 59.2, 42.7, 14.1; **HRMS** (ESI-QTOF) $m/z$ $[M + H]^+$ calcd for $C_{33}H_{27}N_2O_3$ 499.2016, found, 499.2019.

*Synthesis of **17**.* To a solution of **11d** (20 mg, 0.04 mmol), benzyl azide (5.7 $\mu$L, 0.05 mmol, 1.1 equiv), copper sulfate pentahydrate (4.2 mg, 0.02 mmol, 0.4 equiv), and (+)-sodium-L-ascorbate (6.7 mg, 0.03 mmol, 0.8 equiv) in $EtOH/H_2O$ (1.2 mL, 5:1) at room temperature. After being stirred at rt for 9 h, the reaction mixture was concentrated under reduced pressure, diluted with dichloromethane, and washed with water. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure to give the crude residue, which was purified by silica gel column chromatography (dichloromethane) to afford **17** as a brown gum (19.8 mg, 78%).



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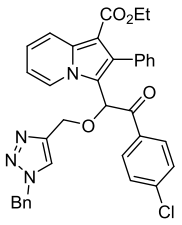
*Ethyl-3-(1-((1-benzyl-1H-1,2,3-triazol-4-yl)methoxy)-2-(4-chlorophenyl)-2-oxoethyl)-2-phenylindolizine-1-carboxylate (**17**).*




**17**

Brown gum (19.8 mg, 78%); **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ 8.51 (d, $J$ = 6.4 Hz, 1H), 8.25 (d, $J$ = 8.8 Hz, 1H), 7.45−7.32 (m, 9H), 7.29 (s, 1H), 7.25−7.19 (m, 3H), 7.18−7.09 (m, 3H), 6.74 (t, $J$ = 6.0 Hz, 1H), 6.08 (s, 1H), 5.50 (d, $J$ = 15.6 Hz, 1H), 5.46 (d, $J$ = 14.8 Hz, 1H), 4.76 (d, $J$ = 12.4 Hz, 1H), 4.68 (d, $J$ = 12.4 Hz, 1H), 4.13 (q, $J$ = 6.3 Hz, 2H), 1.09 (t, $J$ = 6.6 Hz, 3H); **$^{13}$C{$^1$H} NMR** (100 MHz, $CDCl_3$) $\delta$ 192.7, 164.5, 144.2, 140.0, 137.3, 134.4, 134.1, 134.0, 133.0, 130.1, 129.2, 128.9, 128.7, 128.1, 127.9, 127.7, 126.4, 123.7, 122.9, 119.9, 115.9, 113.0, 102.6, 77.3, 77.0, 76.7, 74.7, 62.3, 59.3, 54.2, 29.7, 14.1; **HRMS** (ESI-QTOF) $m/z$ $[M + Na]^+$ calcd for $C_{35}H_{29}ClN_4NaO_4$ 627.1770, found, 627.1768.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.3c00236.

$^1$H and $^{13}$C NMR spectra of synthesized compounds (PDF)

## ■ AUTHOR INFORMATION


### Corresponding Author

**Ikyon Kim** − *College of Pharmacy and Yonsei Institute of Pharmaceutical Sciences, Yonsei University, Incheon 21983, Republic of Korea;* orcid.org/0000-0002-0849-5517; Phone: +82 32 749 4515; Email: ikyonkim@yonsei.ac.kr; Fax: +82 32 749 4105

### Authors

**Euijin Jung** − *College of Pharmacy and Yonsei Institute of Pharmaceutical Sciences, Yonsei University, Incheon 21983, Republic of Korea*

**Yerin Jeong** − *College of Pharmacy and Yonsei Institute of Pharmaceutical Sciences, Yonsei University, Incheon 21983, Republic of Korea*

**Hyeyeon Kim** − *College of Pharmacy and Yonsei Institute of Pharmaceutical Sciences, Yonsei University, Incheon 21983, Republic of Korea*

Complete contact information is available at: https://pubs.acs.org/10.1021/acsomega.3c00236

### Author Contributions

†E.J. and Y.J. contributed equally to this work.


### Notes

The authors declare no competing financial interest.

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(15) See the Experimental Section for details.

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