This is an Accepted Manuscript, which has been through the Royal Society of Chemistry peer review process and has been accepted for publication.

Accepted Manuscripts are published online shortly after acceptance, before technical editing, formatting and proof reading. Using this free service, authors can make their results available to the community, in citable form, before we publish the edited article. We will replace this Accepted Manuscript with the edited and formatted Advance Article as soon as it is available.

You can find more information about Accepted Manuscripts in the Information for Authors.

Please note that technical editing may introduce minor changes to the text and/or graphics, which may alter content. The journal's standard Terms & Conditions and the Ethical guidelines still apply. In no event shall the Royal Society of Chemistry be held responsible for any errors or omissions in this Accepted Manuscript or any consequences arising from the use of any information it contains.
OBC aims to provide authors with a quick decision on their manuscript. We would appreciate you assisting us in providing this service by submitting your review by the deadline in the invitation message.

When assessing this manuscript please take the following into account:

- **OBC** articles should report **new work** which makes a **highly-significant impact** in the field. For synthetic methodology articles please identify in your report the specific advance in the reaction or substrate scope.

- Articles should be scientifically sound with the conclusions supported by the experimental data.

- Please comment on the **novelty and likely impact** of the work. **Routine and incremental work** should generally **not** be recommended for publication in **OBC**; even if competently researched and reported. If you rate the article as ‘routine’ yet recommend acceptance, please give specific reasons for this in your report.

- **OBC** has recently updated its **characterisation guidelines**.

Best wishes,

Richard Kelly
Editor, *Organic & Biomolecular Chemistry*

* ISI Citation information 2014*
Organic & Biomolecular Chemistry

Synthesis of (E)-Oxindolylidene Acetate using One-pot Tandem Palladium-Catalyzed Heck and Alkoxy carbonylation Reactions

Dear Editor,                                          September 7th, 2015

We are pleased to submit our manuscript entitled “Synthesis of (E)-Oxindolylidene Acetate using One-pot Tandem Palladium-Catalyzed Heck and Alkoxy carbonylation Reactions” as an original article for publication. The content of this manuscript has not been published and is not currently submitted for publication elsewhere. This manuscript described the development of one-pot tandem Pd-catalyzed Heck and alkoxy carbonylation reactions for the production of the new anticancer agents based on (E)-oxindolylidene acetates. The optimal reaction conditions and scope of the reactions were also established. These (E)-oxindolylidene acetates exhibit potent anticancer activities against human cancer cells. We believe this work will provide the valuable synthetic methods, structure-activity relationships, and bioactivity results to discover potential anticancer agents. Your kind consideration for publication would be greatly appreciated.

Sincerely,

Wen-Tai Li, Ph.D.
National Research Institute of Chinese Medicine
Ministry of Health and Welfare
155-1, Sec. 2, Linong St., Beitou District,
Taipei 11221, Taiwan, ROC
Phone: +886 2 2820 1999 ext. 8261
Fax: +886 2 2825 0743
E-mail: wtli@nricm.edu.tw
Synthesis of (E)-Oxindolylidene Acetate using Tandem Palladium-Catalyzed Heck and Alkoxycarbonylation Reactions

Dear Editor: October 28th, 2015

Thank you very much for giving us the opportunity to revise our paper, entitled “Synthesis of (E)-Oxindolylidene Acetate using Tandem Palladium-Catalyzed Heck and Alkoxycarbonylation Reactions”, which was initially submitted for publication in the journal Organic & Biomolecular Chemistry on September 7th, 2015.

We have completed the required revisions, closely following the suggestions of the editor and reviewers. The attached files describe these revisions in detail. We believe that we have fulfilled all of the requirements for re-submission of our manuscript; however, if you find that any details have been overlooked, or if you need any further information, please do not hesitate to contact us.

We look forward to your positive response.

Yours sincerely,

Sincerely,

Wen-Tai Li, Ph.D.
National Research Institute of Chinese Medicine
Ministry of Health and Welfare
155-1, Sec. 2, Linong St., Beitou Distrcet,
Taipei 11221, Taiwan, ROC
Phone: +886 2 2820 1999 ext. 8261
Fax: +886 2 2825 0743
E-mail: wtli@nricm.edu.tw
Synthesis of (\(E\))-Oxindolylidene Acetate using Tandem Palladium-Catalyzed Heck and Alkoxy carbonylation Reactions

Thank you for your useful comments regarding our manuscript. We have revised the manuscript according to your suggestions, and detailed corrections are listed below point by point:

Referee: #1:
(1) The authors used “one-pot” reaction in the manuscript, but this reviewer does not think it is appropriate here.
   ✓ In accordance with your suggestion, we have deleted the term “one-pot” in the revised manuscript.

(2) Can this reaction be scale up to gram scale?
   ✓ We did not scale the reaction up to grams, but we believe that it would be possible to do so.

(3) It better to put the H NMR and C13 NMR of each compound together.
   ✓ In accordance with this suggestion, we have reported the \(^1\)H NMR and \(^{13}\)C NMR of each compound together in the Supporting Information.

(4) The following references about palladium-catalyzed Heck-type alkoxy carbonylation reaction should be cited.
   2) JACS, 1985, 107, 8289.
   3) JACS, 1996, 118, 5919.

   ✓ We have added the above references to the revised manuscript in accordance with the reviewer’s suggestion.

Referee: #2:
(1) The yield of the optimized reaction is 71% yield (table 1), which still leaves room for improvement. Have you tried using CsF as the base? CsF was identified as the optimal base for a similar process in the report by Takemoto and coworkers (J. Org. Chem. 2005, 70, 6972).
We did try using CsF as the base when carrying out the reactions. The resulting yield was 64%, similar to KF. This result has been added to Table 1.

(2) Also, have you tried other monodendate phosphine ligands? PCy3, P(p-FC6H4) etc.

✓ We did try reacting other monodendate phosphine ligands of PCy3; however, the reaction yield was poor.

(3) How many equivalent of PPh3 was employed in the optimization table? This information seems to be lost in the paper.

✓ The reaction was performed using the equivalent of 0.2 PPh3. We have added this information to the revised manuscript.

(4) There are limited examples of various R3 substituents in the substrate table. Please explore the effect of the substitution R3 in the aryl ring, which would affect the oxidative addition of Pd(0) to the aryl-iodide; both electronic and steric effects should be considered.

✓ For the revised manuscript, we investigated an additional electron withdrawing substituent of CF3 in the aryl ring, which resulted in a yield of 45%.

(5) Does this reaction tolerate di-substituted alkynes besides terminal alkynes? It would give rise to tetrastubstituted oxindolylidene products, which will provide more varieties in the product library.

✓ We attempted to use a phenyl substituent as the terminal alkynyl, but the reaction provided better results when an H substituent was used as the terminal alkynyl. We found a lot of starting materials recovered under the same reaction condition of ynamide with phenyl substituent at terminal alkynyl.

Other comments:
(6) Table 2, missing PPh3 in the reaction conditions. Please also indicate the equivalent of PPh3.

✓ The reaction was performed using the equivalent of 0.2 PPh3. This information has been added to Table 2 in the revised manuscript.

(7) Also, there is no description of PPh3 in the general procedures of preparing 3a in the SI.
This information is now included in the revised manuscript.

(8) Misspelling: “...as the core structure of a biologically active compound include sunitinib and hesperidin...” "hesperidin" should be "hesperadin". Hesperidin and hesperadin are two different compounds and only hesperadin has the ylideneoxindole moiety (see J Cell Biol 2003;161:281.).

✓ We have corrected the spelling of hesperadin in the revised manuscript.

(9) In the SI, please report all the characterization date of N-substituted propiolamides starting materials those are not reported in the literature.

✓ We have reported the N-substituted propiolamides starting materials in the SI.

(10) Also, compound 1a is missing HRMS.

✓ We have added HRMS information for compound 1a in the spectra data.

Referee: #3:
(1) All reactions presented were performed with substrates having terminal alkynyl moieties. Would not the method work with substituted alkynyl groups?

✓ We attempted to use a phenyl substituent as the terminal alkynyl, but the reaction provided better results when an H substituent was used as the terminal alkynyl. We found a lot of starting materials recovered under the same reaction condition of ynamide with phenyl substituent at terminal alkynyl.

(2) The solvent volume and concentration of methanol should be added to the Table 1.

✓ In accordance with the reviewer’s suggestion, we have described reaction conditions such as solvent volume and methanol concentration in Table 1 of the revised manuscript.

(3) The article needs a careful edition for typos and grammatical errors.

✓ We have carefully revised the entire manuscript, ensuring that there are no grammar or syntax errors. We believe that the language is now acceptable for publication in an English language journal.
Synthesis of (E)-Oxindolylidene Acetate using Tandem Palladium-Catalyzed Heck and Alkoxy carbonylation Reactions

Wei-Jen Lin, a Kak-Shan Shia, b Jen-Shin Song, b Ming-Hsien Wu b and Wen-Tai Li a

a National Research Institute of Chinese Medicine, Ministry of Health and Welfare
Taipei 11221, Taiwan

b Institute of Biotechnology and Pharmaceutical Research, National Health Research Institutes
Miaoli 35053, Taiwan

* Correspondence to:
Wen-Tai Li, Ph.D.
National Research Institute of Chinese Medicine, Ministry of Health and Welfare
155-1, Sec. 2, Linong St., Beitou District,
Taipei 11221, Taiwan, ROC
Tel: +886 2 2820 1999 ext. 8261;
Fax: +886 2 2825 0743;
E-mail: wtli@nricm.edu.tw
Abstract

Tandem reactions use consecutive reaction steps to efficiently synthesize compounds of high molecular complexity. This paper presents a tandem Pd-catalyzed Heck and alkoxycarbonylation reaction for the stereoselective synthesis of (E)-oxindolylidene acetates. The mechanism underlying the Pd-catalyzed tandem reaction involves the syn-carbopalladation of ynamides followed by alkoxycarbonylation with CO and alcohol. This method makes it possible to obtain the desired (E)-configuration of oxindolylidene acetates exclusively. We evaluated the scope of the reaction by applying optimal reaction conditions to the facile synthesis of a library of (E)-oxindolylidene acetates. The resulting (E)-oxindolylidene acetates exhibited potent anticancer activities against a variety of human cancer cell lines. The anticancer activities of some (E)-oxindolylidene acetates were even superior to those of known CDK inhibitors indirubin-3’-oxime and roscovitine.

Keywords: (E)-oxindolylidene acetate, Heck and alkoxycarbonylation reactions, anticancer activity.
Introduction

The 3-ylideneoxindole moiety presents a skeleton of pharmacologically important compounds, which appear as the core structure in a variety of bioactive molecules exhibiting potent antifungal,\textsuperscript{1} anticancer,\textsuperscript{2} and antiviral activities.\textsuperscript{3} For example, 3-ylideneoxindole is the core structure in biologically active compounds such as sunitinib and hesperadin, which possess the capacity to bind receptor tyrosine kinase (RTK) and Aurora B with high affinity.\textsuperscript{4-6} 3-Ylideneoxindole also exists in a number of natural indole alkaloids (including neolaugeric,\textsuperscript{7} costinone A, and costinine B\textsuperscript{8}) which possess a variety of biological properties.

Tandem reactions are a series of consecutive reactions that provide a highly efficient means of assembling compounds.\textsuperscript{9} The molecular complexity and diversity that can be created using this facile approach is suitable for combinatorial library synthesis as it is able to produce a large number of compounds using a minimum number of steps.\textsuperscript{10}

The synthesis of 3-ylideneoxindole moiety has attracted considerable interest among researchers, and impressive advances have already been made in which 3-alkylideneoxindole was used as an important intermediate such as TMC-95A.\textsuperscript{11} The stereoselective synthesis of various substituted 3-alkylideneoxindoles from a series of ynamides and boronic acids by way of palladium-catalyzed Heck-Suzuki-Miyaura domino reactions has also been reported.\textsuperscript{12} The domino reaction, which further expands the utility of ynamides, has been applied in the preparation of natural, biologically active products.

Oxindolylidene acetate is commonly used as a synthetic target due to its interesting biological activity.\textsuperscript{13} Previous successes involving the use of metal-catalyzed tandem reactions led us to consider whether Pd-catalyzed tandem Heck and alkoxy carbonylation reactions of ynamides with carbon monoxide (CO) and alcohols in a single pot could be used to produce oxindolylidene acetate. In the following, we report a concise method for the stereoselective synthesis of (E)-oxindolylidene acetates using the tandem Pd-catalyzed Heck and alkoxy carbonylation reactions of \textit{N}-substituted
propiolamides. The resulting (E)-oxindolylidene acetates exhibited potent anticancer activities against a variety of human cancer cell lines.

Results and Discussion

Tandem Pd-catalyzed Heck and alkoxycarbonylation reactions were combined to develop an efficient stereocontrolled method for the synthesis of (E)-oxindolylidene acetates using CO and alcohols in one pot (Chart 1). Tandem Pd-catalyzed Heck-Suzuki-Miyaura domino reactions have previously been used to synthesize 3-alkylideneoxindoles;\textsuperscript{12} however, this is the first study to report on the use of tandem metal-catalyzed reactions in the synthesis of oxindolylidene acetates from ynamides. At the outset of our investigation, N-(2-iodophenyl)-N-(4-nitrobenzyl)propiolamide (1a) was selected as the model compound for the evaluation of tandem reactions. We initially evaluated the reaction of N-(2-iodophenyl)-N-(4-nitrobenzyl)propiolamide (1a) and methanol (3 equiv.) under CO at atmospheric pressure at elevated temperatures. The reaction was conducted in the presence of triphenylphosphine (0.5 equiv.) in THF, and Pd(OAc)$_2$ was used as a catalyst.\textsuperscript{14} The desired (E)-oxindolylidene acetate (3a) was obtained at a yield of 23% wherein only the (E)-configuration was found (Table 1, entry 1).

Notably, additives and phosphine ligands were shown to play important roles in the Pd-catalyzed tandem reaction. In fact, the addition of KF increased the yield from 23% to 66% (Table 1, entry 4); therefore, we subsequently turned our attention to the evaluation of various additives with the aim of further improving reaction yields (Table 1, entries 2-6). A number of carbonates, such as potassium carbonate and cesium carbonate, were used as additives; however, the resulting yields were lower than the yield achieved using KF (Table 1, entries 2-4). Conversely, using potassium fluoride, cesium fluoride, or potassium iodide as additives resulted in better yields of (E)-oxindolylidene acetate (Table 1, entries 4-6). Phosphine ligands were also shown to exert a strong effect on the yield of the Pd-catalyzed tandem reaction, as the reaction without the phosphine ligand resulted in poor yield (Table 1, entry 7), and reactions with bulky bidentate ligands (dppp and
dppe) or monodentate phosphine ligands (PPh$_2$Me and PCy$_3$), provided only slightly better yields than reactions without the addition of ligands (Table 1, entries 8-12). As shown in Table 1, PPh$_3$ proved to be a more effective ligand for this reaction and others. A variety of palladium catalysts were subsequently used to evaluate the stereoselective synthesis of (E)-oxindolylidene acetate under CO at atmospheric pressure at elevated temperatures. The palladium catalysts Pd(OAc)$_2$ and Pd(dppf)Cl$_2$ proved efficient for this tandem reaction; however, other palladium catalysts produced lower yields (Table 1, entries 4, 13-16).

We further evaluated how a variety of solvents affected this Pd-catalyzed tandem reaction. Among these, methanol and THF provided the best results. In addition, trace quantities of N-substituted dimethyl 2-(2-oxoindolin-3-ylidene)malonate was also observed in this reactions, perhaps due to the presence of trace quantities of oxygen, which may have caused the oxidative alkoxy carbonylation of the terminal alkyne in the first step.$^{15}$

After establishing the optimal reaction conditions, we investigated a series of N-substituted propiolamides 1 with various primary, secondary, and aryl alcohols in order to determine the scope of the reaction (Table 2). Alkoxy carbonylation is sensitive to the steric features of alcohols, and we observed that when N-substituted propiolamides 1 and various primary aliphatic alcohols, such as methanol, ethanol, and n-butanol underwent Pd-catalyzed tandem Heck and alkoxy carbonylation reactions the yield was good. Conversely, isopropanol, phenol, and benzyl alcohols were unreactive (Table 2, entries 34-36). In addition, The Pd-catalyzed tandem Heck-alkoxy carbonylation reactions revealed excellent functional group tolerance with benzyl substituents at R$^1$ bearing electron withdrawing groups at the phenyl ring, such as nitro, methyl ester, trifluoromethyl and cyano resulting in a smooth reaction, resulting in corresponding oxindolylidene acetates 3a, 3f, 3g, 3h in good yields. Benzyl and p-methoxybenzyl in R$^1$ position were also well tolerated in the reaction, thereby producing corresponding oxindolylidene acetates 3m and 3b in yields of 64% and 67%, respectively. In addition, substitution at R$^1$ position with isoxazolylmethyl ring, methyl and H, the
products 3n, 3t and 3u were obtained exclusively in fair yield. Finally, the reaction conditions were found to be favorable when functional groups 5-methyl, 5-methoxyl, and 5-chloride were substituted at R³ (Table 2, entries 17, 18, 27, and 28), such that the resulting reactions respectively produced corresponding oxindolylidene acetates 3q, 3r, 4e and 4f in good yields.

One plausible mechanism for the formation of compounds 3-5 is presented in Scheme 1. The formation of the products may initially have followed the Heck reaction mechanism, which involves the syn-carbopalladation of ynamide with a palladium catalyst to form the intermediate A. The resulting products 3-5 were obtained following alkoxy carbonylation of intermediate A treated with CO and alcohols. This mechanism involves a syn migratory insertion of the alkyne into the Ar–Pd bond, followed by the alkoxy carbonylation of CO and alcohols, leading to the only (E)-configuration of oxindolylidene acetate.

All of the synthesized (E)-oxindolylidene acetates 3-5 obtained via tandem Pd-catalyzed reactions were evaluated for anticancer activities using human NCI-H460 lung cancer cells. We then studied the structure-activity relationships (SARs) in compounds containing various substitutions in the (E)-oxindolylidene acetate scaffold. Specifically, we examined the antiproliferative effects of various R¹ and R² groups on oxindolylidene acetates. Compounds 3d, 3h, and 5b, containing para-substituents on the phenyl ring of the R¹ group, presented slightly better anticancer activity than did compounds 3i, 3j, 3l, and 5a, which contained meta- and ortho-substituents on the phenyl ring of oxindolylidene acetates. Interestingly, compound 3n, containing an isoxazolyl ring, was found to decrease anticancer activity to below that of compounds with a phenyl ring at R¹. In our evaluation of the anticancer activities of methyl, ethyl, and n-butyl groups at R², the activity of the methyl group was found to be superior to that of ethyl and n-butyl groups, and the order of activity of R² groups against NCI-H460 cancer cells can be described as methyl > ethyl > n-butyl in most examples. However, substitutions at R³ did not have significant effects on anticancer activity.
Further evaluation of anticancer activities was conducted on selected active \((E)\)-oxindolylidene acetates using six different cancer cell lines: human lung adenocarcinoma cell CL 1-5, human epidermoid carcinoma KB, human gastric cancer MKN-45, human breast adenocarcinoma MCF-7, human pancreatic carcinoma MIA Paca-2, and human central nervous system cancer SF-268 (Table 4). Most of the 3-ylideneoxindole acetamides exhibited a broad spectrum of anticancer activity against human cancer cells, with effects even more pronounced than those associated with well-known anticancer drug candidates indirubin-3’-oxime and roscovitine.

In summary, this study developed tandem Pd-catalyzed Heck and alkoxy carbonylation reactions for the production of the new anticancer agents based on \((E)\)-oxindolylidene acetates. This stereoselective reaction proceeds through the key steps of \textit{syn}-carbopalladation and alkoxy carbonylation in the presence of CO and alcohols, resulting in only the \((E)\)-configuration of oxindolylidene acetates. We also established the optimal conditions and scope of the reactions. The resulting \((E)\)-oxindolylidene acetates exhibit potent anticancer activity against a variety of human cancer cells.

**Experimental section**

**General procedure for synthesis of \textit{N}-(2-iodophenyl)-\textit{N}-(4-nitrobenzyl) propiolamide (1a).**

\textit{N}-(2-Iodophenyl)propiolamide was synthesized with slightly modifications according to the reported method.\(^{16}\) To a solution of \textit{N}-(2-iodophenyl)propiolamide (400 mg, 1.48 mmol) in DMF (20 mL) was added NaHCO\(_3\) (248 mg, 2.95 mmol) portionwise. The mixture was stirred at 0 °C for 30 min and 4-nitrobenzyl chloride (329 mg, 1.92 mmol) was added dropwise. The reaction mixture was heated to reflux for 6 h until complete by TLC. The reaction was quenched by addition of water and extracted with ethyl acetate. The combined organic layers were washed with brine solution, dried
over MgSO₄ and concentrated in vacuo. The residue was purified by flash column chromatography furnished the desired N-(2-iodophenyl)-N-(4-nitrobenzyl)propiolamide 1a (463 mg, 77 %) as a yellow solid (two rotamers at a ratio of 7:1). Mp = 145-147 °C. IR (KBr) νmax: 3210, 2106, 1646, 1520, 1345, 1310 cm⁻¹. ¹H NMR (600 MHz, CDCl₃) major/minor δ: 8.13/8.16 (d, J = 8.4 Hz, 2H), 7.93/7.89 (dd, J = 7.9, 1.2 Hz, 1H), 7.40/7.42 (d, J = 8.4 Hz, 2H), 7.25/7.21 (dt, J = 7.8, 1.2 Hz, 1H), 7.08/7.01 (dt, J = 7.8, 1.2 Hz, 1H), 6.81/6.71 (dd, J = 7.8, 1.2 Hz, 1H), 5.56/5.58 (d, J = 15.0, 1H), 4.24/4.70 (d, J = 15.0 Hz, 1H), 2.78/3.35 (s, 1H). ¹³C NMR (150 MHz, CDCl₃) major/minor δ: 153.3/152.6, 147.6/147.8, 143.0/142.7, 142.5/141.0, 140.3/140.3, 130.9/129.8, 130.7/129.6, 130.3/130.2, 129.2/129.3, 123.8/123.9, 100.0/98.1, 80.1/80.7, 75.6/75.8, 50.8/54.4. HRMS calcd for C₁₆H₁₂IN₂O₃ (M+1)+ 406.9893, found 406.9894.

**General procedure for synthesis of (E)-methyl 2-(1-(4-nitrobenzyl)-2-oxoindolin-3-ylidene)acetate (3a).**

N-(2-Iodophenyl)-N-(4-nitrobenzyl)propiolamide 1a (200 mg, 0.49 mmol) in CH₃OH (10 mL) was added Pd(OAc)₂ (11 mg, 0.05 mmol), PPh₃ (26 mg, 0.10 mmol) and potassium fluoride (85 mg, 1.47 mmol) in a 25-mL round flask. The flask was evacuated under vacuum and back-filled with carbon monoxide from a balloon. The cycle was repeated three times and vessel left open to a dynamic atmosphere of CO. The mixture was then heated to 60 °C under vigorous stirring until complete by TLC. Then the mixture was filtered and concentrated in vacuo. The residue dissolved in EtOAc and then washed with water. The water phase was extracted with EtOAc (10 mL) twice. The organic layers were combined, dried over MgSO₄ and concentrated. The crude mixture was purified
by flash column chromatography to afford the title compound 3a (118 mg, 71%) as a yellowish solid. 

Mp = 172-174 °C. IR (KBr) v max: 3415, 1700, 1602, 1468, 1342, 1214 cm\(^{-1}\). \(^1\)H NMR (600 MHz, CDCl\(_3\)) \(\delta\): 8.58 (d, \(J = 7.8\) Hz, 1H), 8.17 (d, \(J = 8.4\) Hz, 2H), 7.43 (d, \(J = 8.4\) Hz, 2H), 7.26 (t, \(J = 7.2\) Hz, 1H), 7.07 (t, \(J = 7.8\) Hz, 1H), 6.98 (s, 1H), 6.59 (d, \(J = 8.4\) Hz, 1H), 5.02 (s, 2H), 3.88 (s, 3H). \(^{13}\)C NMR (150 MHz, CDCl\(_3\)) \(\delta\): 167.7, 165.9, 147.6, 144.4, 142.8, 137.4, 132.6, 129.2, 128.0, 124.2, 123.4, 122.9, 120.0, 108.7, 52.3, 43.3. HRMS calcd for C\(_{18}\)H\(_{14}\)N\(_2\)O\(_5\) (M)\(^+\) 338.0882, found 338.0892.

\((E)\)-Methyl 2-(1-(4-methoxybenzyl)-2-oxoindolin-3-ylidene)acetate (3b). Yield: 67%. Orange solid. Mp = 94-96 °C. IR (KBr) v max: 2949, 2921, 1711, 1602, 1511, 1464, 1337, 1199 cm\(^{-1}\). \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\): 8.53 (d, \(J = 8.0\) Hz, 1H), 7.26-7.21 (m, 3H), 7.00 (dt, \(J = 8.0, 1.0\) Hz, 1H), 6.95 (s, 1H), 6.83-6.80 (m, 2H), 6.69 (d, \(J = 8.0\) Hz, 1H), 4.85 (s, 2H), 3.86 (s, 3H), 3.75 (s, 3H). \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\): 167.6, 166.1, 159.1, 145.2, 138.0, 132.4, 128.8, 128.6, 127.4, 122.8, 122.1, 119.9, 114.2, 109.1, 55.2, 52.1, 43.3. HRMS calcd for C\(_{19}\)H\(_{17}\)NO\(_4\) (M)\(^+\) 323.1151, found 323.1154.

\((E)\)-Methyl 2-(1-(4-fluorobenzyl)-2-oxoindolin-3-ylidene)acetate (3c). Yield: 60%. Yellow solid. Mp = 113-115 °C. IR (KBr) v max: 3411, 1704, 1606, 1504, 1464, 1344, 1214 cm\(^{-1}\). \(^1\)H NMR (600 MHz, CDCl\(_3\)) \(\delta\): 8.54 (d, \(J = 7.8\) Hz, 1H), 7.26-7.23 (m, 3H), 7.01 (t, \(J = 7.8\) Hz, 1H), 6.98-6.94 (m, 3H), 6.65 (d, \(J = 7.8\) Hz, 1H), 4.86 (s, 2H), 3.85 (s, 3H). \(^{13}\)C NMR (150 MHz, CDCl\(_3\)) \(\delta\): 167.5, 165.9, 162.2 (d, \(\text{J}_{C,F} = 245.0\) Hz), 144.8, 137.7, 132.4, 131.1 (d, \(\text{J}_{C,F} = 2.9\) Hz), 128.9 (d, \(\text{J}_{C,F} = 8.1\) Hz), 108.5.
Hz), 128.8, 122.9, 122.2, 120.0, 115.7 (d, \(^2J_{CF} = 21.3\) Hz), 108.9, 52.1, 43.1. HRMS calcd for C\(_{18}H_{14}FNO_3\) (M\(^+\)) 311.0946, found 311.0952.

\textit{(E)}-Methyl 2-(1-(4-chlorobenzyl)-2-oxoindolin-3-ylidene)acetate (3d). Yield: 68%. Yellow solid. Mp = 135-137 °C. IR (KBr) \(\nu_{\text{max}}\): 3415, 2957, 1700, 1606, 1464, 1344, 1217 cm\(^{-1}\). \(^1\)H NMR (600 MHz, CDCl\(_3\)) \(\delta\): 8.56 (d, \(J = 7.8\) Hz, 1H), 7.28-7.23 (m, 3H), 7.21 (d, \(J = 8.4\) Hz, 2H), 7.03 (dt, \(J = 7.8, 1.2\) Hz, 1H), 6.96 (s, 1H), 6.64 (d, \(J = 7.8\) Hz, 1H), 4.88 (s, 2H), 3.87 (s, 3H). \(^{13}\)C NMR (150 MHz, CDCl\(_3\)) \(\delta\): 167.6, 166.0, 144.8, 137.8, 133.9, 133.7, 132.5, 129.0, 129.0, 128.6, 123.1, 122.4, 119.9, 108.9, 52.2, 43.2. HRMS calcd for C\(_{18}H_{14}ClNO_3\) (M\(^+\)) 327.0658, found 327.0660.

\textit{(E)}-Methyl 2-(1-(4-bromobenzyl)-2-oxoindolin-3-ylidene)acetate (3e). Yield: 64%. Brown solid. Mp = 133-135 °C. IR (KBr) \(\nu_{\text{max}}\): 2924, 2844, 1708, 1646, 1606, 1464, 1352, 1203 cm\(^{-1}\). \(^1\)H NMR (600 MHz, CDCl\(_3\)) \(\delta\): 8.57 (d, \(J = 6.0\) Hz, 1H), 7.60 (d, \(J = 6.5\) Hz, 2H), 7.05 (dt, \(J = 6.5, 1.0\) Hz, 1H), 7.03 (dt, \(J = 6.5, 1.0\) Hz, 1H), 6.97 (s, 1H), 6.58 (d, \(J = 6.5\) Hz, 1H), 4.97 (s, 2H), 3.87 (s, 3H). \(^{13}\)C NMR (CDCl\(_3\)) \(\delta\): 167.7, 165.9, 144.4, 140.8, 137.4, 132.7, 132.5, 129.1, 127.8, 123.4, 122.8, 120.0, 118.4, 111.8, 108.7, 52.3, 43.5. HRMS calcd for C\(_{18}H_{14}BrNO_3\) (M\(^+\)) 371.0135, found 371.0146.

\textit{(E)}-Methyl 4-((3-(2-methoxy-2-oxoethylidene)-2-oxoindolin-1-yl)methyl) benzoate (3f). Yield: 74%. Yellow solid. Mp = 127-129 °C. IR (KBr) \(\nu_{\text{max}}\): 2861, 2224, 1712, 1607, 1469, 1367, 1340, 1214 cm\(^{-1}\). \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\): 8.56 (d, \(J = 6.5\) Hz, 1H), 7.96 (d, \(J = 6.5\) Hz, 1H), 7.33 (d, \(J = 6.5\) Hz, 2H), 7.24 (m, 1H), 7.03 (dt, \(J = 6.0, 0.5\) Hz, 1H), 6.97 (s, 1H), 6.61 (d, \(J = 6.0\) Hz,
1H), 4.97 (s, 2H), 3.87 (s, 6H). $^{13}$C NMR (125 MHz, CDCl$_3$) δ: 167.7, 166.6, 160.0, 144.7, 140.5, 137.7, 132.5, 130.2, 129.7, 128.9, 127.1, 123.1, 122.5, 119.9, 114.0, 109.0, 52.2, 43.6. HRMS calcd for C$_{20}$H$_{17}$NO$_3$ (M)$^+$ 351.1093, found 351.1100.

(E)-Methyl 2-(2-oxo-1-(4-(trifluoromethyl)benzyl)indolin-3-ylidene)acetate (3g). Yield: 70%. Orange solid. Mp = 134-136 °C. IR (KBr) vmax: 3415, 2917, 1715, 1606, 1352, 1326, 1203, 1119 cm$^{-1}$. $^1$H NMR (500 MHz, CDCl$_3$) δ: 8.57 (d, $J$ = 6.5 Hz, 1H), 7.56 (d, $J$ = 6.5 Hz, 2H), 7.38 (d, $J$ = 7.0 Hz, 2H), 7.26 (dt, $J$ = 6.5, 1.0 Hz, 1H), 7.04 (dt, $J$ = 6.5, 1.0 Hz, 1H), 6.97 (s, 1H), 6.62 (d, $J$ = 6.5 Hz, 1H), 4.97 (s, 2H), 3.87 (s, 3H). $^{13}$C NMR (125 MHz, CDCl$_3$) δ: 167.7, 165.8, 144.6, 139.5, 137.6, 132.5, 130.1 (q, $^2$J$_{C,F}$ = 26.9 Hz), 129.0, 127.5, 125.8 (q, $^3$J$_{C,F}$ = 2.9 Hz), 123.9 (q, $^1$J$_{C,F}$ = 225.6 Hz), 123.2, 122.6, 119.9, 108.9, 52.2, 43.4. HRMS calcd for C$_{19}$H$_{14}$F$_3$NO$_3$ (M)$^+$ 361.0939, found 361.0932.

(E)-Methyl 2-(1-(4-cyanobenzyl)-2-oxoindolin-3-ylidene)acetate (3h). Yield: 66%. Orange solid. Mp = 192-194 °C. IR (KBr) vmax: 3400, 2950, 2223, 1697, 1602, 1468, 1344, 1217 cm$^{-1}$. $^1$H NMR (500 MHz, CDCl$_3$) δ: 8.57 (d, $J$ = 6.0 Hz, 1H), 7.60 (d, $J$ = 6.5 Hz, 2H), 7.38 (d, $J$ = 6.5 Hz, 2H), 7.26 (dt, $J$ = 7.0, 1.0 Hz, 1H), 7.05 (dt, $J$ = 6.5, 1.0 Hz, 1H), 6.97 (s, 1H), 6.58 (d, $J$ = 6.5 Hz, 1H), 4.97 (s, 2H), 3.87 (s, 3H). $^{13}$C NMR (125 MHz, CDCl$_3$) δ: 167.7, 165.9, 144.4, 140.8, 137.4, 132.7, 132.5, 129.1, 127.8, 123.4, 122.8, 120.0, 118.4, 111.8, 108.7, 52.3, 43.5. HRMS calcd for C$_{19}$H$_{14}$N$_2$O$_3$ (M)$^+$ 318.1024, found 318.1014.

(E)-Methyl 2-(1-(3-cyanobenzyl)-2-oxoindolin-3-ylidene)acetate (3i). Yield: 51%. Yellow
solid. Mp = 95-97 °C. IR (KBr) v_max: 2861, 2224, 1712, 1607, 1469, 1367, 1340, 1214 cm<sup>-1</sup>. <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>) δ: 8.55 (d, J = 7.8 Hz, 1H), 7.42 (d, J = 8.4 Hz, 2H), 7.25 (dt, J = 7.8, 1.2 Hz, 1H), 7.24 (s, 1H), 7.15 (d, J = 9.0 Hz, 2H), 7.03 (dt, J = 7.8, 1.2 Hz, 1H), 6.96 (s, 1H), 6.63 (d, J = 7.8 Hz, 1H), 4.86 (s, 2H), 3.87m (s, 3H). <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>) δ: 167.6, 166.0, 144.8, 137.7, 134.4, 132.5, 132.0, 128.9, 123.1, 122.4, 121.7, 120.0, 109.0, 52.2, 43.3. HRMS calcd for C<sub>19</sub>H<sub>14</sub>N<sub>2</sub>O<sub>3</sub> (M)± 318.1018, found 318.1011.

*(E)*-Methyl 2-((3-chlorobenzyl)-2-oxoindolin-3-ylidene)acetate (3j). Yield: 58%. Yellow solid. Mp = 84-86 °C. IR (KBr) v_max: 2943, 1711, 1602, 1468, 1337, 1214 cm<sup>-1</sup>. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ: 8.56 (d, J = 6.5 Hz, 1H), 7.27-7.24 (m, 3H), 7.15 (t, J = 3.5 Hz, 1H), 7.03 (dt, J = 6.5, 0.5 Hz, 1H), 6.96 (s, 1H), 6.64 (d, J = 6.5 Hz, 1H), 4.87 (s, 2H), 3.86 (s, 3H).<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ: 167.5, 165.9, 144.7, 137.6, 137.4, 134.7, 132.5, 130.1, 128.9, 128.0, 127.2, 125.3, 123.0, 122.4, 119.8, 108.9, 52.2, 43.2. HRMS calcd for C<sub>18</sub>H<sub>14</sub>ClNO<sub>3</sub> (M)± 327.0675, found 327.0669.

*(E)*-Methyl 2-((naphthalen-2-ylmethyl)-2-oxoindolin-3-ylidene)acetate (3k). Yield: 59%. Orange solid. IR (KBr) v_max: 2943, 1711, 1602, 1468, 1337, 1214 cm<sup>-1</sup>. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ: 8.55 (d, J = 6.5 Hz, 1H), 7.79-7.75 (m, 3H), 7.71 (s, 1H), 7.47-7.42 (m, 3H), 7.38 (dd, J = 6.5, 1.5 Hz), 7.20 (dt, J = 6.5, 1.0 Hz, 1H), 7.02-6.99 (m, 2H), 6.70 (d, J = 6.5 Hz, 1H), 5.08 (s, 2H), 3.88 (s, 3H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ: 167.3, 166.1, 145.1, 138.0, 133.3, 132.8, 132.8, 132.5, 128.8, 128.8, 127.7, 127.7, 126.4, 126.1, 126.0, 125.1, 122.9, 122.3, 119.9, 113.9, 109.3, 52.2, 44.1.
HRMS calcd for C$_{22}$H$_{17}$NO$_3$ (M)$^+$ 343.1208, found 343.1214

*(E)-Methyl 2-(1-(2-chlorobenzyl)-2-oxoindolin-3-ylidene)acetate (3l).* Yield: 57%. Yellow solid. Mp = 106-109 °C. IR (KBr) vmax: 2371, 1715, 1599, 1472, 1348, 1196 cm$^{-1}$. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$: 8.57 (d, $J = 7.0$ Hz, 1H), 7.38 (dd, $J = 8.1$, 1.0 Hz, 1H), 7.25 (dt, $J = 8.0$, 1.0 Hz, 1H), 7.20 (dt, $J = 7.5$, 1.0 Hz, 1H), 7.14 (dt, $J = 8.0$, 1.5 Hz, 1H), 7.08-7.03 (m, 2H), 6.98 (s, 1H), 6.63 (d, $J = 7.5$Hz, 1H), 5.04 (s, 2H), 3.87 (3H). $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$: 167.8, 166.0, 144.8, 137.8, 132.8, 132.6, 129.7, 128.9, 128.8, 127.8, 127.2, 123.1, 122.4, 119.9, 109.1, 52.2, 41.3. HRMS calcd for C$_{18}$H$_{14}$NO$_3$Cl (M)$^+$ 327.0664, found 327.0663.

*(E)-Methyl 2-(1-benzyl-2-oxoindolin-3-ylidene)acetate (3m).* Yield: 64%. Yellow solid. Mp = 118-120 °C. IR (KBr) vmax: 2917, 1711, 1602, 1468, 1344, 1195 cm$^{-1}$. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$: 8.54 (dt, $J = 7.5$, 0.5 Hz, 1H), 7.32-7.22 (m, 6H), 7.01 (dt, $J = 8.0$, 1.0 Hz, 1H), 6.96 (s, 1H), 6.67 (d, $J = 8.0$ Hz, 1H). $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$: 167.6, 166.1, 145.1, 137.9, 135.4, 132.4, 128.8, 128.8, 127.7, 127.2, 122.9, 122.2, 119.9, 109.2, 52.2, 43.9. HRMS calcd for C$_{18}$H$_{15}$NO$_3$ (M)$^+$ 293.1048, found 293.1050.

*(E)-Methyl 2-(1-((3-methylisoxazol-5-yl)methyl)-2-oxoindolin-3-ylidene)acetate (3n).* Yield: 55%. Yellow solid. Mp = 131-134 °C. IR (KBr) vmax: 2957, 1720, 1613, 1470, 1356, 1208 cm$^{-1}$. $^1$H NMR (600 MHz, CDCl$_3$) $\delta$: 8.55 (d, $J = 7.8$ Hz, 1H), 7.33 (t, $J = 7.8$ Hz, 1H), 7.07 (t, $J = 7.8$ Hz, 1H), 6.92 (s, 1H), 6.85 (d, $J = 7.8$ Hz, 1H), 6.00 (s, 1H), 4.96 (s, 2H), 3.86 (s, 3H), 2.22 (s, 3H). $^{13}$C NMR (150 MHz, CDCl$_3$) $\delta$: 167.2, 166.0, 165.8, 160.1, 144.1, 137.3, 132.7, 129.0, 123.4, 122.6, 119.8, ...
108.7, 103.6, 52.2, 35.6, 11.3. HRMS calcd for C_{16}H_{14}N_2O_4 (M)^+ 298.0959, found 298.0956.

*(E)-Methyl 2-(1-(2,6-dichlorobenzyl)-2-oxoindolin-3-ylidene)acetate (3o). Yield: 59%.

Orange solid. Mp = 143-145 °C. IR (KBr) v max: 3077, 2943, 1711, 1472, 1348, 1199 cm	extsuperscript{-1}. \(^1\)H NMR (500 MHz, CDCl	extsubscript{3}) \(\delta\): 8.52 (d, \(J = 6.5\) Hz, 1H), 7.30 (d, \(J = 7.0\) Hz, 2H), 7.27 (d, \(J = 7.0\) Hz, 1H), 7.19-7.13 (m, 3H), 6.97 (dt, \(J = 6.0, 1.0\) Hz, 1H), 6.91 (s, 1H), 6.61 (d, \(J = 6.5\) Hz, 1H), 5.19 (s, 2H), 3.84 (s, 3H). \(^{13}\)C NMR (125 MHz, CDCl	extsubscript{3}) \(\delta\): 167.2, 166.0, 144.7, 137.6, 136.2, 132.4, 130.0, 129.8, 128.9, 128.7, 122.6, 122.1, 120.0, 109.1, 52.1, 40.1. HRMS calcd for C_{18}H_{13}Cl_2NO_3 (M)^+ 361.0254, found 361.0263.

*(E)-Methyl 2-(2-oxo-1-(3,4,5-trimethoxybenzyl)indolin-3-ylidene)acetate (3p). Yield: 68%.

Yellow solid. Mp = 145-148 °C. IR (KBr) v max: 2943, 2839, 1700, 1595, 1469, 1355, 1204 cm	extsuperscript{-1}. \(^1\)H NMR (600 MHz, CDCl	extsubscript{3}) \(\delta\): 8.55 (d, \(J = 7.8\) Hz, 1H), 7.27 (t, \(J = 7.8\) Hz, 1H), 7.03 (t, \(J = 7.8\) Hz, 2H), 6.60 (s, 1H), 6.71 (d, \(J = 7.8\) Hz, 1H), 6.49 (s, 2H), 4.84 (s, 2H), 3.87 (s, 3H), 3.78 (s, 6H). \(^{13}\)C NMR (150 MHz, CDCl	extsubscript{3}) \(\delta\): 167.7, 166.0, 153.5, 145.2, 137.9, 137.5, 132.5, 131.1, 128.8, 123.0, 122.3, 119.9, 109.2, 104.3, 60.8, 56.2, 52.2, 44.2. HRMS calcd for C_{21}H_{21}NO_6 (M)^+ 383.1369, found 383.1375.

*(E)-Methyl 2-(1-(4-chlorobenzyl)-5-methyl-2-oxoindolin-3-ylidene)acetate (3q). Yield: 67%.

Yellow solid. Mp = 109-111 °C. IR (KBr) v max: 2917, 2845, 1712, 1487, 1352, 1205 cm	extsuperscript{-1}. \(^1\)H NMR (600 MHz, CDCl	extsubscript{3}) \(\delta\): 8.342 (s, 1H), 7.25 (d, \(J = 8.4\) Hz, 2H), 7.20 (d, \(J = 8.4\) Hz, 2H), 7.05 (d, \(J = 7.8\) Hz, 1H), 6.93 (s, 1H), 6.51 (d, \(J = 7.8\) Hz, 1H), 4.85 (s, 2H), 3.87 (s, 3H), 2.30 (s, 3H). \(^{13}\)C NMR
(150 MHz, CDCl$_3$) $\delta$: 167.6, 166.1, 142.6, 138.1, 134.1, 133.6, 132.9, 132.6, 129.5, 129.0, 128.6, 122.0, 119.9, 108.7, 52.2, 43.2, 21.1. HRMS calcd for C$_{19}$H$_{16}$ClNO$_3$ (M)$^+$ 341.0798, found 341.0808.

(E)-Methyl 2-(1-(4-chlorobenzyl)-5-methoxy-2-oxoindolin-3-ylidene)acetate (3r). Yield: 64%. Yellow solid. Mp = 169-171 °C. IR (KBr) v max: 2987, 2947, 1700, 1642, 1591, 1486, 1337, 1239, 1199 cm$^{-1}$. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$: 8.27 (d, $J = 2.5$ Hz, 1H), 7.25 (d, $J = 8.5$ Hz, 2H), 7.19 (d, $J = 8.5$ Hz, 2H), 6.95 (s, 1H), 6.80 (dd, $J = 8.5, 3.0$ Hz, 1H), 6.51 (d, $J = 8.5$ Hz, 1H), 4.84 (s, 2H), 3.86 (s, 3H), 3.78 (s, 3H). $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$: 167.5, 165.9, 155.9, 138.6, 138.3, 134.0, 134.0, 129.0, 128.6, 122.5, 120.6, 118.4, 114.7, 109.4, 55.8, 52.2, 43.3. HRMS calcd for C$_{19}$H$_{16}$ClNO$_4$ (M)$^+$ 357.0774, found 357.0771.

(E)-Methyl 2-(1-((6-bromobenzo[d][1,3]dioxol-5-yl)methyl)-2-oxoindolin-3- ylidene)acetate (3s). Yield: 54%. Orange solid. Mp = 203-205 °C. IR (KBr) v max: 3427, 2824, 1701, 1603, 1473, 1353, 1201 cm$^{-1}$. $^1$H NMR (600 MHz, CDCl$_3$) $\delta$: 8.56 (dd, $J = 7.8, 0.6$ Hz, 1H), 7.27 (dt, $J = 7.8, 0.6$ Hz, 1H), 7.05 (dt, $J = 7.8, 0.6$ Hz, 1H), 7.01 (s, 1H), 6.97 (s, 1H), 6.66 (d, $J = 7.8$ Hz, 1H), 6.55 (s, 1H), 5.90 (s, 2H), 4.93 (s, 2H), 3.88 (s, 3H). $^{13}$C NMR (150 MHz, CDCl$_3$) $\delta$: 167.8, 166.0, 148.0, 144.7, 137.8, 132.7, 128.9, 127.3, 123.2, 122.5, 119.9, 113.1, 112.8, 109.3, 107.8, 101.9, 52.2, 43.7. EIMS: 415.26 (M)$^+$. 

(E)-Methyl 2-(1-methyl-2-oxoindolin-3-ylidene)acetate (3t). Yield: 61%. Yellow solid. Mp = 129-131 °C. IR (KBr) v max: 2947, 1711, 1602, 1464, 1435, 1344, 1206 cm$^{-1}$. $^1$H NMR (600 MHz, CDCl$_3$) $\delta$: 8.58 (d, $J = 1.8$ Hz, 1H), 7.34 (dt, $J = 7.8, 0.6$ Hz, 1H), 7.04 (t, $J = 1.2$ Hz, 1H), 7.02 (d, $J =
0.6 Hz, 1H), 6.82 (dd, $J = 7.8, 1.2$ Hz, 1H), 3.84 (s, 3H), 3.20 (s, 3H). $^{13}$C NMR (150 MHz, CDCl$_3$) $\delta$: 167.4, 166.1, 146.0, 138.1, 132.5, 128.7, 122.8, 121.8, 119.7, 108.1, 52.1, 26.2. HRMS calcd for C$_{12}$H$_{11}$NO$_3$ (M)$^+$ 217.0722, found 217.0730.

$(E)$-Methyl 2-(2-oxoindolin-3-ylidene)acetate (3u). Yield: 51%. Yellow solid. Mp = 171-173 °C. IR (KBr) v$_{\text{max}}$: 3190, 2917, 1719, 1610, 1464, 1344, 1210 cm$^{-1}$. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$: 8.51 (d, $J = 7.5$ Hz, 2H), 7.29 (dt, $J = 8.1, 1.0$ Hz, 1H), 7.02 (dt, $J = 8.1, 1.0$ Hz, 1H), 6.85 (s, 1H), 6.84 (d, $J = 9.0$ Hz, 1H), 3.86 (s, 3H). $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$: 169.1, 166.0, 143.4, 138.4, 132.6, 129.0, 122.9, 122.0, 120.3, 110.1, 52.2. HRMS calcd for C$_{11}$H$_9$NO$_3$ (M)$^+$ 203.0601, found 203.0592.

$(E)$-Methyl 2-(1-(4-nitrobenzyl)-2-oxo-5-(trifluoromethyl)indolin-3-ylidene) acetate (3v). Yield: 45%. Orange solid. Mp = 178-180 °C. IR (KBr) v$_{\text{max}}$: 3486, 1720, 1618, 1526, 1383, 1210, 1108 cm$^{-1}$. $^1$H NMR (600 MHz, CDCl$_3$) $\delta$: 8.94 (s, 1H), 8.18 (dd, $J = 9.0, 1.8$ Hz, 2H), 7.55 (d, $J = 7.8$ Hz, 1H), 7.43 (d, $J = 9.0$ Hz, 2H), 7.07 (s, 1H), 6.70 (d, $J = 8.4$ Hz, 1H), 5.06 (s, 2H), 3.91 (s, 3H). $^{13}$C NMR (150 MHz, CDCl$_3$) $\delta$: 167.5, 165.5, 147.8, 146.7, 142.1, 136.1, 129.7 (q, $^3J_{C,F} = 3.5$ Hz), 128.0, 126.4 (q, $^3J_{C,F} = 3.9$ Hz), 125.9 (q, $^2J_{C,F} = 32.9$ Hz), 125.0, 124.3, 123.9 (q, $^1J_{C,F} = 270.2$ Hz), 120.2, 108.6, 52.6, 43.4. HRMS calcd for C$_{19}$H$_{13}$F$_3$N$_2$O$_5$ (M)$^+$ 406.0777, found 406.0773.

$(E)$-Ethyl 2-(1-(4-nitrobenzyl)-2-oxoindolin-3-ylidene)acetate (4a). Yield: 62%. Orange solid. Mp = 149-152 °C. IR (KBr) v$_{\text{max}}$: 3440, 2924, 2854, 1706, 1608, 1467, 1342, 1202 cm$^{-1}$. $^1$H NMR (600 MHz, CDCl$_3$) $\delta$: 8.58 (d, $J = 7.8$ Hz, 1H), 8.16 (d, $J = 8.4$ Hz, 2H), 7.43 (d, $J = 8.4$ Hz, 2H),
7.26 (dt, J = 7.8, 1.2 Hz, 1H), 7.05 (dt, J = 7.8, 1.2 Hz, 1H), 6.97 (s, 1H), 6.59 (d, J = 7.8 Hz, 1H), 5.01 (s, 2H), 4.33 (q, J = 7.2 Hz, 2H), 1.36 (t, J = 7.2 Hz, 3H). $^{13}$C NMR (150 MHz, CDCl$_3$) δ: 167.7, 165.4, 147.6, 144.3, 142.8, 137.1, 132.4, 129.1, 127.9, 124.1, 123.4, 123.6, 120.0, 108.6, 61.3, 43.2, 14.2. HRMS calcd for C$_{19}$H$_{16}$N$_2$O$_5$ (M)$^+$ 352.1060, found 352.1059.

(E)-Ethyl 2-(1-(4-chlorobenzyl)-2-oxoindolin-3-ylidene)acetate (4b). Yield: 59%. Yellow solid. Mp = 75-77 °C. IR (KBr) v$_{max}$: 2923, 1709, 1604, 1346, 1199 cm$^{-1}$. $^1$H NMR (600 MHz, CDCl$_3$) δ: 8.55 (d, J = 7.8 Hz, 1H), 7.27 (d, J = 7.8 Hz, 2H), 7.27-7.23 (m, 1H), 7.21 (d, J = 7.8 Hz, 2H), 7.02 (t, J = 7.8 Hz, 1H), 6.95 (s, 1H), 6.63 (d, J = 7.8 Hz, 1H), 4.88 (s, 2H), 4.32 (q, J = 7.2 Hz, 2H), 1.36 (t, J = 7.2 Hz, 3H). $^{13}$C NMR (150 MHz, CDCl$_3$) δ: 167.7, 165.6, 144.7, 137.4, 134.0, 133.6, 132.4, 129.0, 128.9, 128.6, 123.0, 120.0, 108.9, 61.3, 43.2, 14.2. HRMS calcd for C$_{19}$H$_{16}$ClNO$_3$ (M)$^+$ 341.0803, found 341.0811.

(E)-Ethyl 2-(1-(4-bromobenzyl)-2-oxoindolin-3-ylidene)acetate (4c). Yield: 57%. Brown solid. Mp = 107-110 °C. IR (KBr) v$_{max}$: 2988, 1712, 1605, 1359, 1203 cm$^{-1}$. $^1$H NMR (600 MHz, CDCl$_3$) δ: 8.55 (d, J = 7.8 Hz, 1H), 7.41 (d, J = 8.4 Hz, 2H), 7.25 (t, J = 7.8 Hz, 1H), 7.14 (d, J = 7.8 Hz, 1H), 7.03 (t, J = 7.8 Hz, 1H), 6.95 (s, H), 6.62 (d, J = 7.8 Hz, 1H), 4.86 (s, 2H), 4.32 (q, J = 7.2 Hz, 2H), 1.36 (t, J = 7.2 Hz, 3H). $^{13}$C NMR (150 MHz, CDCl$_3$) δ: 167.7, 165.6, 144.7, 137.4, 134.5, 132.4, 132.0, 128.9, 128.9, 123.1, 121.7, 120.0, 108.9, 61.3, 43.3, 14.2. HRMS calcd for C$_{19}$H$_{16}$BrNO$_3$ (M)$^+$ 385.0314, found 385.0319.

(E)-Ethyl 2-(2-oxo-1-(3,4,5-trimethoxybenzyl)indolin-3-ylidene)acetate (4d). Yield: 64%.
Yellow solid. Mp = 168-173 °C. IR (KBr) vmax: 2996, 1700, 1593, 1356, 1195 cm⁻¹. ¹H NMR (600 MHz, CDCl₃) δ: 8.55 (d, J = 7.8 Hz, 1H), 7.27 (t, J = 7.8 Hz, 1H), 7.03 (t, J = 7.8 Hz, 1H), 6.96 (s, 1H), 6.72 (d, J = 7.8 Hz, 1H), 6.47 (s, 2H), 4.84 (s, 2H), 4.32 (q, J = 7.2 Hz, 2H), 3.79 (s, 3H), 1.36 (t, J = 7.2 Hz, 3H). ¹³C NMR (150 MHz, CDCl₃) δ: 167.7, 165.6, 153.5, 145.1, 137.6, 137.5, 132.4, 131.2, 128.8, 123.0, 122.9, 120.0, 109.2, 104.3, 61.3, 60.8, 56.2, 44.2, 14.2. HRMS calcd for C₂₂H₂₃NO₆ (M)⁺ 397.1526, found 397.1533.

(E)-Ethyl 2-(5-chloro-1-(4-chlorobenzyl)-2-oxoindolin-3-ylidene)acetate (4e). Yield: 55%.

Yellow solid. Mp = 136-139 °C. IR (KBr) vmax: 2990, 1717, 1606, 1348, 1212 cm⁻¹. ¹H NMR (600 MHz, CDCl₃) δ: 8.59 (d, J = 1.8 Hz, 1H), 7.26 (d, J = 8.4 Hz, 2H), 7.22 (dd, J = 8.4, 1.8 Hz, 1H), 7.17 (d, J = 8.4 Hz, 1H), 6.99 (s, 1H), 6.55 (d, J = 8.4 Hz, 1H), 4.87 (s, 2H), 4.33 (q, J = 7.2 Hz, 2H), 1.37 (t, J = 7.2 Hz, 3H). ¹³C NMR (150 MHz, CDCl₃) δ: 167.2, 165.6, 143.1, 136.6, 133.8, 133.5, 132.0, 129.1, 129.0, 128.6, 124.5, 121.2, 109.8, 61.5, 43.3, 14.2. HRMS calcd for C₁₉H₁₅Cl₂NO₃ (M)⁺ 376.0507, found 376.0480.

(E)-Ethyl 2-(1-(4-chlorobenzyl)-5-methoxy-2-oxoindolin-3-ylidene)acetate (4f). Yield: 61%.

Yellow solid. Mp = 144-149 °C. IR (KBr) vmax: 2982, 1704, 1652, 1488, 1196 cm⁻¹. ¹H NMR (600 MHz, CDCl₃) δ: 8.26 (d, J = 2.4 Hz, 1H), 7.25 (d, J = 8.4 Hz, 2H), 7.19 (d, J = 8.4 Hz, 2H), 6.95 (s, 1H), 6.79 (dd, J = 8.4, 2.4 Hz, 1H), 6.51 (d, J = 8.4 Hz, 1H), 4.85 (s, 2H), 4.32 (q, J = 7.2 Hz, 2H), 3.78 (s, 3H), 1.35 (t, J = 7.2 Hz, 3H). ¹³C NMR (150 MHz, CDCl₃) δ: 167.6, 165.5, 155.9, 138.5, 138.0, 134.0, 133.6, 129.0, 128.6, 123.2, 120.7, 118.2, 114.7, 109.4, 61.3, 55.9, 43.3, 14.2. HRMS
calcd for C\textsubscript{20}H\textsubscript{18}ClNO\textsubscript{4} (M)+ 371.0925, found 371.0932.

\textit{(E)}-Ethyl 2-(1-methyl-2-oxoindolin-3-ylidene)acetate (4g). Yield: 58%. Yellow solid. Mp = 78-81 °C. IR (KBr) \nu\textsubscript{max}: 2985, 1712, 1608, 1196 cm\textsuperscript{-1}. \textsuperscript{1}H NMR (600 MHz, CDCl\textsubscript{3}) \delta: 8.53 (d, \textit{J} = 7.8 Hz, 1H), 7.35 (t, \textit{J} = 7.8 Hz, 1H), 7.04 (dt, \textit{J} = 7.8, 0.6 Hz, 1H), 6.89 (s, 1H), 6.77 (d, \textit{J} = 7.8 Hz, 1H), 4.30 (q, \textit{J} = 7.2 Hz, 2H), 3.21 (s, 3H), 1.35 (t, \textit{J} = 7.2 Hz, 3H). \textsuperscript{13}C NMR (150 MHz, CDCl\textsubscript{3}) \delta: 167.6, 165.7, 145.9, 137.9, 132.4, 128.7, 122.8, 122.5, 119.8, 108.1, 61.2, 26.2, 14.2. HRMS calcd for C\textsubscript{14}H\textsubscript{11}NO\textsubscript{3} (M)+ 231.0896, found 231.0896.

\textit{(E)}-Butyl 2-(1-(3-cyanobenzyl)-2-oxoindolin-3-ylidene)acetate (5a). Yield: 57%. Orange solid. Mp = 134-138 °C. IR (KBr) \nu\textsubscript{max}: 2957, 1717, 1606, 1468, 1344, 1207 cm\textsuperscript{-1}. \textsuperscript{1}H NMR (600 MHz, CDCl\textsubscript{3}) \delta: 8.58 (d, \textit{J} = 7.8 Hz, 1H), 7.57-7.55 (m, 1H), 7.53-7.51 (m, 1H), 7.43 (t, \textit{J} = 7.8 Hz, 1H), 7.27 (t, \textit{J} = 7.8 Hz, 1H), 7.06 (t, \textit{J} = 7.8 Hz, 1H), 7.00 (s, 1H), 6.62 (d, \textit{J} = 7.8 Hz, 1H), 4.94 (s, 2H), 4.27 (t, \textit{J} = 7.2 Hz, 2H), 1.73-1.69 (m, 2H), 1.45-1.41 (m, 2H), 0.95 (t, \textit{J} = 7.2 Hz, 3H). \textsuperscript{13}C NMR (150 MHz, CDCl\textsubscript{3}) \delta: 167.8, 165.6, 144.3, 137.2, 137.1, 132.4, 131.6, 131.6, 130.7, 129.8, 129.2, 123.5, 123.4, 120.0, 118.4, 113.1, 108.6, 65.2, 43.1, 30.6, 19.1, 13.7. HRMS calcd for C\textsubscript{22}H\textsubscript{20}N\textsubscript{2}O\textsubscript{3} (M)+ 360.1474, found 360.1472.

\textit{(E)}-Butyl 2-(1-(4-cyanobenzyl)-2-oxoindolin-3-ylidene)acetate (5b). Yield: 53%. Orange solid. Mp = 129-134 °C. IR (KBr) \nu\textsubscript{max}: 2959, 1703, 1607, 1345, 1199 cm\textsuperscript{-1}. \textsuperscript{1}H NMR (600 MHz, CDCl\textsubscript{3}) \delta: 8.58 (d, \textit{J} = 7.8 Hz, 1H), 7.59 (d, \textit{J} = 8.4 Hz, 2H), 7.38 (d, \textit{J} = 8.4 Hz, 2H), 7.26 (t, \textit{J} = 7.8 Hz, 1H), 7.06 (t, \textit{J} = 7.8 Hz, 1H), 6.97 (s, 1H), 6.58 (d, \textit{J} = 7.8 Hz, 1H), 4.97 (s, 2H), 4.27 (t, \textit{J} = 6.6 Hz, 2H), 1.69-1.65 (m, 2H), 1.45-1.41 (m, 2H), 0.95 (t, \textit{J} = 7.2 Hz, 3H). \textsuperscript{13}C NMR (150 MHz, CDCl\textsubscript{3}) \delta: 167.8, 165.6, 144.3, 137.2, 137.1, 132.4, 131.6, 131.6, 130.7, 129.8, 129.2, 123.5, 123.4, 120.0, 118.4, 113.1, 108.6, 65.2, 43.1, 30.6, 19.1, 13.7. HRMS calcd for C\textsubscript{22}H\textsubscript{20}N\textsubscript{2}O\textsubscript{3} (M)+ 360.1474, found 360.1472.
Hz, 2H), 1.73-1.68 (m, 2H), 1.45-1.41 (m, 2H), 0.95 (t, J = 6.6 Hz, 3H). $^{13}$C NMR (150 MHz, CDCl$_3$) δ: 167.8, 165.6, 144.3, 140.9, 137.1, 132.7, 132.4, 129.1, 127.8, 123.4, 123.3, 120.0, 118.4, 111.8, 108.7, 65.2, 43.4, 30.6, 19.1, 13.7. HRMS calcd for C$_{22}$H$_{20}$N$_2$O$_3$ (M)$^+$ 360.1474, found 360.1478.

**(E)-Butyl 2-(1-(4-nitrobenzyl)-2-oxoindolin-3-ylidene)acetate (5c).** Yield: 55%. Orange solid. Mp = 110-115 °C. IR (KBr) v max: 2954, 1709, 1608, 1342, 1204 cm$^{-1}$. $^1$H NMR (600 MHz, CDCl$_3$) δ: 8.56 (d, J = 8.4 Hz, 1H), 7.37 (dt, J = 7.8, 7.2 Hz, 1H), 7.09 (t, J = 7.8 Hz, 1H), 7.00 (d, J = 7.8 Hz, 1H), 6.90 (s, 1H), 4.51 (d, J = 1.8 Hz, 2H), 3.85 (s, 3H), 2.26 (s, J = 1.8 Hz, 1H). $^{13}$C NMR (150 MHz, CDCl$_3$) δ: 166.6, 165.9, 144.0, 137.6, 132.5, 128.9, 123.2, 122.4, 120.0, 109.1, 76.5, 72.5, 52.2, 29.3. HRMS calcd for C$_{21}$H$_{20}$N$_2$O$_5$ (M)$^+$ 380.1372, found 380.1347.

**(E)-Ethyl 2-(2-oxoindolin-3-ylidene)acetate (4h).** Yield: 58%. Yellow solid. Mp = 260-264 °C. IR (KBr) v max: 3188, 1718, 1612, 1463, 1323, 1200 cm$^{-1}$. $^1$H NMR (600 MHz, CDCl$_3$) δ: 8.52 (d, J = 7.2 Hz, 1H), 8.36 (br, 1H), 7.30 (dt, J = 7.8, 1.2 Hz, 1H), 7.03 (dt, J = 7.8, 1.2 Hz, 1H), 6.86 (s, 1H), 6.83 (d, J = 7.8 Hz, 1H), 4.32 (q, J = 7.2 Hz, 2H), 1.35 (t, J = 7.2 Hz, 3H). $^{13}$C NMR (150 MHz, CDCl$_3$) δ: 169.1, 165.6, 143.2, 138.0, 132.5, 129.1, 122.9, 122.7, 120.4, 110.1, 61.2, 14.2. EIMS: 217.0 (M)$^+$. HRMS calcd for C$_{12}$H$_{11}$NO$_3$ (M)$^+$ 217.0739, found 217.0749.

**Cancer cell growth inhibition assay**

Human cancer cell lines, included human lung adenocarcinoma cell CL 1-5, human epidermoid carcinoma KB, human gastric cancer MKN-45, human breast adenocarcinoma MCF-7, Human
pancreatic carcinoma MIA Paca-2 and human central nervous system cancer SF-268, were seeded in 96-well plates and incubated for 24 h at 37 °C in a 5% CO₂ incubator. Test compounds were dissolved in dimethylsulfoxide (DMSO) and diluted for cell treatment in culture medium containing DMSO at the final concentration of 0.5%. Cells were treated with test compounds of various concentrations in triplicates per concentration in the culture medium and incubated at 37 °C for 72 h. Actinomycin D of 10 nM and 0.3% DMSO were used as the positive and vehicle controls, respectively. A colorimetric assay using the MTS/PMS system was used to determine the cytotoxic activity of the test compounds. The optical density (OD) values at 490 nm were measured with a 1420-multilabel counter VICTOR from Wallac (Turku, Finland). The IC₅₀, the concentration that inhibited 50% of the cancer cell growth activity, was then determined. All experiments were repeated three times.¹⁷

Acknowledgements. We gratefully acknowledge the financial support of the National Science Council (Grant NSC 102-2113-M-077-002-MY2).

Supporting Information Available: Compound characterization and spectral (¹H and ¹³C NMR) data. This material is available free of charge via the Internet at

Notes and references


10. (a) I. Akritopoulou-Zanze, *Curr. Opin. Chem. Biol.*, 2008, 12, 324. (b) P. Janvier, X. Sun, H.


15. There is a byproduct, N-(2-iodophenyl)-3-methoxy-N-(4-nitrobenzyl)acrylamide, generated in the other palladium catalysts. The byproduct was contributed from the addition of methanol to
terminal alkyne.


Table 1. Optimization of reaction conditions$^a$

<table>
<thead>
<tr>
<th>Entry</th>
<th>[Pd]</th>
<th>ligand</th>
<th>additive</th>
<th>solvent</th>
<th>yield (%)$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pd(OAc)$_2$</td>
<td>PPh$_3$</td>
<td>-</td>
<td>THF</td>
<td>23</td>
</tr>
<tr>
<td>2</td>
<td>Pd(OAc)$_2$</td>
<td>PPh$_3$</td>
<td>K$_2$CO$_3$</td>
<td>THF</td>
<td>12</td>
</tr>
<tr>
<td>3</td>
<td>Pd(OAc)$_2$</td>
<td>PPh$_3$</td>
<td>Cs$_2$CO$_3$</td>
<td>THF</td>
<td>34</td>
</tr>
<tr>
<td>4</td>
<td>Pd(OAc)$_2$</td>
<td>PPh$_3$</td>
<td>KF</td>
<td>THF</td>
<td>66</td>
</tr>
<tr>
<td>5</td>
<td>Pd(OAc)$_2$</td>
<td>PPh$_3$</td>
<td>CsF</td>
<td>THF</td>
<td>64</td>
</tr>
<tr>
<td>6</td>
<td>Pd(OAc)$_2$</td>
<td>PPh$_3$</td>
<td>KI</td>
<td>THF</td>
<td>51</td>
</tr>
<tr>
<td>7</td>
<td>Pd(OAc)$_2$</td>
<td>-</td>
<td>KF</td>
<td>THF</td>
<td>14</td>
</tr>
<tr>
<td>8</td>
<td>Pd(OAc)$_2$</td>
<td>dppe</td>
<td>KF</td>
<td>THF</td>
<td>15</td>
</tr>
<tr>
<td>9</td>
<td>Pd(OAc)$_2$</td>
<td>dppe</td>
<td>KI</td>
<td>THF</td>
<td>24</td>
</tr>
<tr>
<td>10</td>
<td>Pd(OAc)$_2$</td>
<td>dppe</td>
<td>-</td>
<td>THF</td>
<td>18</td>
</tr>
<tr>
<td>11</td>
<td>Pd(OAc)$_2$</td>
<td>PPh$_2$Me</td>
<td>KF</td>
<td>THF</td>
<td>41</td>
</tr>
<tr>
<td>12</td>
<td>Pd(OAc)$_2$</td>
<td>PCy$_3$</td>
<td>KF</td>
<td>THF</td>
<td>21</td>
</tr>
<tr>
<td>13</td>
<td>Pd(PPh$_3$)$_4$</td>
<td>-</td>
<td>KF</td>
<td>THF</td>
<td>38</td>
</tr>
<tr>
<td>14</td>
<td>Pd(PPh$_3$)$_2$Cl$_2$</td>
<td>-</td>
<td>KF</td>
<td>THF</td>
<td>43</td>
</tr>
<tr>
<td>15</td>
<td>Pd$_2$(dba)$_3$</td>
<td>PPh$_3$</td>
<td>KF</td>
<td>THF</td>
<td>36</td>
</tr>
<tr>
<td>16</td>
<td>Pd(dpff)Cl$_2$</td>
<td>-</td>
<td>KF</td>
<td>THF</td>
<td>65</td>
</tr>
<tr>
<td>17</td>
<td>Pd(OAc)$_2$</td>
<td>PPh$_3$</td>
<td>KF</td>
<td>m-xylene</td>
<td>19</td>
</tr>
<tr>
<td>18</td>
<td>Pd(OAc)$_2$</td>
<td>PPh$_3$</td>
<td>KF</td>
<td>CH$_3$CN</td>
<td>8</td>
</tr>
<tr>
<td>19</td>
<td>Pd(OAc)$_2$</td>
<td>PPh$_3$</td>
<td>KF</td>
<td>DME</td>
<td>47</td>
</tr>
<tr>
<td>20</td>
<td>Pd(OAc)$_2$</td>
<td>PPh$_3$</td>
<td>KF</td>
<td>1,4-dioxane</td>
<td>22</td>
</tr>
<tr>
<td>21</td>
<td>Pd(OAc)$_2$</td>
<td>PPh$_3$</td>
<td>KF</td>
<td>DMSO</td>
<td>5</td>
</tr>
<tr>
<td>22</td>
<td>Pd(OAc)$_2$</td>
<td>PPh$_3$</td>
<td>KF</td>
<td>CH$_3$OH</td>
<td>71</td>
</tr>
</tbody>
</table>

$^a$Reaction conditions: 1.0 equiv of ynamide 1a (0.05 M in solvent), 3.0 equiv of CH$_3$OH (except entry 22), 0.1 equiv of Pd catalyst, 0.2 equiv of ligand, and 3.0 equiv of additive for 6 h; temperature was 60 °C and CO pressure was 1 atmosphere. $^b$Yields refer to isolated and purified compounds.
Table 2. Reaction scope

<table>
<thead>
<tr>
<th>Entry</th>
<th>R¹</th>
<th>R²</th>
<th>R³</th>
<th>product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>p-NO₂-PhCH₂</td>
<td>Me</td>
<td>H</td>
<td>3a</td>
<td>71</td>
</tr>
<tr>
<td>2</td>
<td>p-MeO-PhCH₂</td>
<td>Me</td>
<td>H</td>
<td>3b</td>
<td>67</td>
</tr>
<tr>
<td>3</td>
<td>p-F-PhCH₂</td>
<td>Me</td>
<td>H</td>
<td>3c</td>
<td>60</td>
</tr>
<tr>
<td>4</td>
<td>p-Cl-PhCH₂</td>
<td>Me</td>
<td>H</td>
<td>3d</td>
<td>68</td>
</tr>
<tr>
<td>5</td>
<td>p-Br-PhCH₂</td>
<td>Me</td>
<td>H</td>
<td>3e</td>
<td>64</td>
</tr>
<tr>
<td>6</td>
<td>p-CO₂Me-PhCH₂</td>
<td>Me</td>
<td>H</td>
<td>3f</td>
<td>74</td>
</tr>
<tr>
<td>7</td>
<td>p-CF₃-PhCH₂</td>
<td>Me</td>
<td>H</td>
<td>3g</td>
<td>70</td>
</tr>
<tr>
<td>8</td>
<td>p-CN-PhCH₂</td>
<td>Me</td>
<td>H</td>
<td>3h</td>
<td>66</td>
</tr>
<tr>
<td>9</td>
<td>m-CN-PhCH₂</td>
<td>Me</td>
<td>H</td>
<td>3i</td>
<td>51</td>
</tr>
<tr>
<td>10</td>
<td>m-Cl-PhCH₂</td>
<td>Me</td>
<td>H</td>
<td>3j</td>
<td>58</td>
</tr>
<tr>
<td>11</td>
<td>2-Np-CH₂</td>
<td>Me</td>
<td>H</td>
<td>3k</td>
<td>59</td>
</tr>
<tr>
<td>12</td>
<td>o-Cl-PhCH₂</td>
<td>Me</td>
<td>H</td>
<td>3l</td>
<td>57</td>
</tr>
<tr>
<td>13</td>
<td>Bn</td>
<td>Me</td>
<td>H</td>
<td>3m</td>
<td>64</td>
</tr>
<tr>
<td>14</td>
<td>3-methyl-5-isoxazolymethyl</td>
<td>Me</td>
<td>H</td>
<td>3n</td>
<td>55</td>
</tr>
<tr>
<td>15</td>
<td>2,6-CI₂-PhCH₂</td>
<td>Me</td>
<td>H</td>
<td>3o</td>
<td>59</td>
</tr>
<tr>
<td>16</td>
<td>3,4,5-(MeO)₃-PhCH₂</td>
<td>Me</td>
<td>H</td>
<td>3p</td>
<td>68</td>
</tr>
<tr>
<td>17</td>
<td>p-Cl-PhCH₂</td>
<td>Me</td>
<td>5-Me</td>
<td>3q</td>
<td>67</td>
</tr>
<tr>
<td>18</td>
<td>p-Cl-PhCH₂</td>
<td>Me</td>
<td>5-OMe</td>
<td>3r</td>
<td>64</td>
</tr>
<tr>
<td>19</td>
<td>(6-Bromobenzo[d][1,3]dioxol-5-yl)CH₂</td>
<td>Me</td>
<td>H</td>
<td>3s</td>
<td>54</td>
</tr>
<tr>
<td>20</td>
<td>Me</td>
<td>Me</td>
<td>H</td>
<td>3t</td>
<td>61</td>
</tr>
<tr>
<td>21</td>
<td>H</td>
<td>Me</td>
<td>H</td>
<td>3u</td>
<td>51</td>
</tr>
<tr>
<td>22</td>
<td>p-NO₂-PhCH₂</td>
<td>Me</td>
<td>5-CF₃</td>
<td>3v</td>
<td>45</td>
</tr>
<tr>
<td>23</td>
<td>p-NO₂-PhCH₂</td>
<td>Et</td>
<td>H</td>
<td>4a</td>
<td>62</td>
</tr>
<tr>
<td>24</td>
<td>p-Cl-PhCH₂</td>
<td>Et</td>
<td>H</td>
<td>4b</td>
<td>59</td>
</tr>
<tr>
<td>25</td>
<td>p-Br-PhCH₂</td>
<td>Et</td>
<td>H</td>
<td>4c</td>
<td>57</td>
</tr>
<tr>
<td>26</td>
<td>3,4,5-(MeO)₃-PhCH₂</td>
<td>Et</td>
<td>H</td>
<td>4d</td>
<td>64</td>
</tr>
<tr>
<td>27</td>
<td>p-Cl-PhCH₂</td>
<td>Et</td>
<td>5-Cl</td>
<td>4e</td>
<td>55</td>
</tr>
<tr>
<td>28</td>
<td>p-Cl-PhCH₂</td>
<td>Et</td>
<td>5-OMe</td>
<td>4f</td>
<td>61</td>
</tr>
<tr>
<td>29</td>
<td>Me</td>
<td>Et</td>
<td>H</td>
<td>4g</td>
<td>58</td>
</tr>
<tr>
<td></td>
<td>Substituent 1</td>
<td>Substituent 2</td>
<td>Substituent 3</td>
<td>Product</td>
<td>Yield</td>
</tr>
<tr>
<td>---</td>
<td>-------------</td>
<td>-------------</td>
<td>-------------</td>
<td>---------</td>
<td>-------</td>
</tr>
<tr>
<td>30</td>
<td>m-CN-PhCH₂</td>
<td>&quot;Bu</td>
<td>H</td>
<td>5a</td>
<td>57</td>
</tr>
<tr>
<td>31</td>
<td>p-CN-PhCH₂</td>
<td>&quot;Bu</td>
<td>H</td>
<td>5b</td>
<td>53</td>
</tr>
<tr>
<td>32</td>
<td>p-NO₂-PhCH₂</td>
<td>&quot;Bu</td>
<td>H</td>
<td>5c</td>
<td>55</td>
</tr>
<tr>
<td>33</td>
<td>H</td>
<td>Et</td>
<td>H</td>
<td>4h</td>
<td>58</td>
</tr>
<tr>
<td>34</td>
<td>p-NO₂-PhCH₂</td>
<td>&quot;Pr</td>
<td>H</td>
<td></td>
<td>-c</td>
</tr>
<tr>
<td>35</td>
<td>p-NO₂-PhCH₂</td>
<td>Ph</td>
<td>H</td>
<td></td>
<td>-c</td>
</tr>
<tr>
<td>36</td>
<td>p-NO₂-PhCH₂</td>
<td>Bn</td>
<td>H</td>
<td></td>
<td>-c</td>
</tr>
</tbody>
</table>

*a* Reaction conditions: 1.0 equiv of ynamides 1 (0.05 M in CH₃OH), 0.1 equiv of Pd catalyst, 0.2 equiv of PPh₃ and 3.0 equiv of KF for 6 h; temperature was 60 °C and CO pressure was 1 atmosphere. *b* Yields refer to isolated and purified compounds, and only the (E)-configuration of oxindolylidene acetate was found. *c* The yield was negligible.
Table 3. *In vitro* anticancer activities of (E)-oxindolylidene acetate in NCI-H460 cells\textsuperscript{a}.

<table>
<thead>
<tr>
<th>Compound</th>
<th>IC\textsubscript{50} (µM)</th>
<th>Compound</th>
<th>IC\textsubscript{50} (µM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3a</td>
<td>5.2 ± 0.7</td>
<td>3r</td>
<td>3.7 ± 0.1</td>
</tr>
<tr>
<td>3b</td>
<td>5.1 ± 0.4</td>
<td>3s</td>
<td>18.8 ± 1.9</td>
</tr>
<tr>
<td>3c</td>
<td>6.3 ± 0.3</td>
<td>3t</td>
<td>7.8 ± 1.6</td>
</tr>
<tr>
<td>3d</td>
<td>6.8 ± 0.8</td>
<td>3u</td>
<td>5.5 ± 0.4</td>
</tr>
<tr>
<td>3e</td>
<td>7.4 ± 0.6</td>
<td>4a</td>
<td>8.7 ± 0.5</td>
</tr>
<tr>
<td>3f</td>
<td>4.3 ± 0.3</td>
<td>4b</td>
<td>6.8 ± 0.7</td>
</tr>
<tr>
<td>3g</td>
<td>2.0 ± 0.1</td>
<td>4c</td>
<td>8.3 ± 0.5</td>
</tr>
<tr>
<td>3h</td>
<td>5.3 ± 0.6</td>
<td>4d</td>
<td>6.2 ± 0.3</td>
</tr>
<tr>
<td>3i</td>
<td>8.9 ± 0.7</td>
<td>4e</td>
<td>9.3 ± 0.7</td>
</tr>
<tr>
<td>3j</td>
<td>9.6 ± 0.5</td>
<td>4f</td>
<td>7.7 ± 0.8</td>
</tr>
<tr>
<td>3k</td>
<td>4.2 ± 0.8</td>
<td>4g</td>
<td>11.8 ± 1.3</td>
</tr>
<tr>
<td>3l</td>
<td>6.2 ± 0.6</td>
<td>5a</td>
<td>17.3 ± 1.6</td>
</tr>
<tr>
<td>3m</td>
<td>5.1 ± 0.7</td>
<td>5b</td>
<td>14.9 ± 1.9</td>
</tr>
<tr>
<td>3n</td>
<td>52.0 ± 3.4</td>
<td>5c</td>
<td>19.2 ± 1.7</td>
</tr>
<tr>
<td>3o</td>
<td>4.4 ± 1.5</td>
<td>4h</td>
<td>38.6 ± 3.7</td>
</tr>
<tr>
<td>3p</td>
<td>1.2 ± 0.1</td>
<td>Indirubin-3’-oxime</td>
<td>32.6±5.1</td>
</tr>
<tr>
<td>3q</td>
<td>3.9 ± 0.4</td>
<td>Roscovitine</td>
<td>11.6±1.9\textsuperscript{b}</td>
</tr>
</tbody>
</table>

\textsuperscript{a}IC\textsubscript{50} values represent the mean ± SD of three determinations.

\textsuperscript{b}Reported IC\textsubscript{50} = 13.1 µM.
Table 4. *In vitro* anticancer activities of (E)-oxindolylidene acetate against various cancer cell lines\(^a\).

<table>
<thead>
<tr>
<th>Compd</th>
<th>CL 1-5</th>
<th>KB</th>
<th>MKN-45</th>
<th>MCF-7</th>
<th>MIA Paca-2</th>
<th>SF-268</th>
</tr>
</thead>
<tbody>
<tr>
<td>3b</td>
<td>4.6±0.5</td>
<td>5.5±1.7</td>
<td>3.4±0.6</td>
<td>27.1±0.5</td>
<td>39.4±2.8</td>
<td>3.7±0.4</td>
</tr>
<tr>
<td>3f</td>
<td>5.7±0.6</td>
<td>5.6±0.6</td>
<td>5.0±0.6</td>
<td>8.5±5.1</td>
<td>38.3±2.2</td>
<td>3.9±0.5</td>
</tr>
<tr>
<td>3g</td>
<td>5.3±0.2</td>
<td>4.3±0.3</td>
<td>5.1±0.2</td>
<td>8.3±4.5</td>
<td>37.6±2.8</td>
<td>4.4±0.6</td>
</tr>
<tr>
<td>3h</td>
<td>7.3±0.3</td>
<td>4.9±0.1</td>
<td>6.4±0.1</td>
<td>21.4±1.3</td>
<td>35.0±2.5</td>
<td>15.9±1.4</td>
</tr>
<tr>
<td>3k</td>
<td>5.2±0.2</td>
<td>11.0±3.4</td>
<td>4.5±0.4</td>
<td>23.9±0.3</td>
<td>39.1±3.3</td>
<td>5.8±0.4</td>
</tr>
<tr>
<td>3o</td>
<td>6.1±0.5</td>
<td>5.3±0.3</td>
<td>6.6±0.3</td>
<td>17.5±1.5</td>
<td>37.1±2.1</td>
<td>5.6±0.5</td>
</tr>
<tr>
<td>3p</td>
<td>3.7±0.2</td>
<td>4.5±0.2</td>
<td>3.2±0.2</td>
<td>5.6±1.4</td>
<td>30.2±1.7</td>
<td>3.4±0.3</td>
</tr>
<tr>
<td>3q</td>
<td>7.0±0.6</td>
<td>11.9±3.2</td>
<td>12.2±4.1</td>
<td>25.2±3.5</td>
<td>37.3±10.7</td>
<td>12.4±2.6</td>
</tr>
<tr>
<td>3r</td>
<td>3.1±0.2</td>
<td>3.5±0.4</td>
<td>3.6±0.6</td>
<td>4.6±0.9</td>
<td>38.6±2.4</td>
<td>5.4±0.3</td>
</tr>
<tr>
<td>Indirubin-3'-oxime</td>
<td>21.2±1.3</td>
<td>19.2±0.6</td>
<td>36.7±2.0</td>
<td>25.5±3.2</td>
<td>29.5±3.7</td>
<td>37.5±3.8</td>
</tr>
<tr>
<td>Roscovitine</td>
<td>8.9±0.1</td>
<td>24.6±1.9(^b)</td>
<td>7.6±2.2</td>
<td>19.6±2.2(^c)</td>
<td>17.9±0.8</td>
<td>11.6±1.5</td>
</tr>
</tbody>
</table>

\(^a\)IC\(_{50}\) values represent the mean ± SD of three determinations. \(^b\)Reported IC\(_{50}\) = 30.1 µM. 
\(^c\)Reported IC\(_{50}\) = 14.7 µM.
Chart 1. Tandem Pd-catalyzed Heck and alkoxy carbonylation reactions

\[
\begin{align*}
\text{R}^3 \text{I} & \quad \text{N} \quad \text{R}^1 \\
\text{R}^3 & \quad \text{N} \quad \text{R}^1 \\
\text{R}^2 = \text{Me, Et, } n\text{-Bu}
\end{align*}
\]

10 mol% Pd(OAc)$_2$, PPh$_3$, KF

CO (balloon), R$_2$OH

60 °C, 6 h
Scheme 1.
One-pot tandem Pd-catalyzed Heck and alkoxy carbonylation reactions for the production of the new anticancer agents were established based on (E)-oxindolyldene acetates.
Supporting Information

Synthesis of (E)-Oxindolylidene Acetate using Tandem Palladium-Catalyzed Heck and Alkoxy carbonylation Reactions

Wei-Jen Lin, a Kak-Shan Shia, b Jen-Shin Song, b Ming-Hsien Wu b and Wen-Tai Li*a

a National Research Institute of Chinese Medicine, Ministry of Health and Welfare
Taipei 11221, Taiwan

b Institute of Biotechnology and Pharmaceutical Research, National Health Research Institutes, Miaoli 35053, Taiwan

Table of Contents
1. General .................................................................................................................................. S1
2. Characterization data ........................................................................................................... S3
3. NMR Spectra ....................................................................................................................... S18

1. General
Starting materials were used as received from commercial suppliers unless otherwise stated. Dichloromethane (DCM) and N, N’-dimethylformamide (DMF) were dried over calcium hydride for 48 h prior to distillation. Tetrahydrofuran (THF) was distilled from sodium/benzophenone ketyl under nitrogen. The proton and carbon NMR
spectra were obtained on Bruker Avance 400 (400 MHz), Varian Unity Inova 500 (500 MHz) and Varian VNMRS600 (600 MHz) spectrometers. Deuterated chloroform of spectrograde was used as solvent. All NMR chemical shifts were reported as δ values in parts per million (ppm), and coupling constants (J) were given in hertz (Hz). The splitting pattern abbreviations are as follows: s, singlet; d, doublet; t, triplet; q, quartet; br, broad; m, unresolved multiplet due to the field strength of the instrument; dd, doublet of doublet and dt, doublet of triplet. Melting points were measured on a Yanaco MP-S3 micro melting point apparatus and are uncorrected. Mass spectra were carried out on ThermoQuest Finnigan and Microsaic 4000MiD mass spectrometers. Purification was performed by using preparative separations in flash column chromatography (Merck silica gel 60, particle size of 230-400 mesh). Analytical TLC was carried out on precoated plates (Merck silica gel 60, F254). Compounds analyzed on the TLC plates were visualized by using UV light, I₂ vapor, or basic aqueous potassium permanganate (KMnO₄) with heating. RPMI 1640 medium, fetal bovine serum (FBS), penicillin, streptomycin, and all other tissue culture regents were obtained from GIBCO/BRL Life Technologies (Grand Island, NY). MTS and PMS were purchased from Promega Corp. (Madison, WI).
2. Characterization data

\[
\text{N-}(2\text{-Iodophenyl})-\text{N-}(4\text{-methoxybenzyl})\text{propiolamide} \ (1b). \quad \text{Yield: 78\% (two rotamers at a ratio of 7:1). Yellow oil. IR (KBr) \nu_{\text{max}}: 3278, 2106, 1643, 1512, 1248, 1176 \text{ cm}^{-1}.} \\
\text{\textsuperscript{1}H NMR (600 MHz, CDCl}_3\text{) major/minor } \delta: 7.90/7.86 (d, J = 7.8 \text{ Hz, 1H}), 7.19/7.16 (dt, J = 7.8, 1.2 \text{ Hz, 1H}), 7.08/7.10 (d, J = 8.4 \text{ Hz, 2H}), 7.03/6.98 (dt, J = 7.8, 1.8 \text{ Hz, 1H}), 6.77/6.82 (d, J = 8.4 \text{ Hz, 2H}), 6.72/6.60 (dd, J = 7.8, 1.8 \text{ Hz, 1H}), 5.51/5.52 (d, J = 14.4 \text{ Hz, 1H}), 4.00/4.43 (d, J = 14.4 \text{ Hz, 1H}), 3.77/3.76 (s, 3H), 2.71/3.30 (s, 1H).} \\
\text{\textsuperscript{13}C NMR (150 MHz, CDCl}_3\text{) major/minor } \delta: 159.2/159.5, 153.0/152.7, 142.7/141.3, 139.8/139.9, 131.5/130.6, 130.9/130.3, 130.2/130.1, 128.8/128.6, 127.8/127.6, 113.7/113.9, 100.2/98.2, 79.2/80.0, 76.2/71.4, 55.2/54.8, 50.5/55.3. HRMS calcd for C_{17}H_{15}INO_2 (M+1)\textsuperscript{+} 392.0147, found 392.0147.}
\]

\[
\text{N-}(4\text{-Fluorobenzyl})-\text{N-}(2\text{-iodophenyl})\text{propiolamide} \ (1c). \quad \text{Yield: 83\% (two rotamers at a ratio of 9:1). Yellow solid. Mp = 54-55 \text{ \degree C. IR (KBr) \nu_{\text{max}}: 3202, 2103,}
\]
1636, 1508, 1391, 1230 cm$^{-1}$. $^1$H NMR (600 MHz, CDCl$_3$) major/minor $\delta$: 7.89/7.86 (d, $J = 7.8$ Hz, 1H), 7.20/7.21 (t, $J = 7.8$ Hz, 1H), 7.16-7.13 (m, 2H), 7.04/7.03 (t, $J = 7.8$ Hz, 1H), 6.92/6.96 (t, $J = 8.4$ Hz, 2H), 6.73/6.61 (dd, $J = 7.8$, 0.6 Hz, 1H), 5.47/5.48 (d, $J = 14.4$ Hz, 1H), 4.06/4.51 (d, $J = 14.4$ Hz, 1H), 2.73/3.34 (s, 1H).

$^{13}$C NMR (150 MHz, CDCl$_3$) major/minor $\delta$: 162.3/162.5 (d, $^1$J$_{C-F}$ = 245.4 Hz), 153.0/152.5, 142.0/141.0, 139.9/140.0, 131.5/131.2 (d, $^4$J$_{C-F}$ = 3.0 Hz), 131.3/130.1, 131.2/130.6 (d, $^3$J$_{C-F}$ = 8.1 Hz), 130.3/129.9, 128.8/128.9, 115.3/115.5 (d, $^2$J$_{C-F}$ = 21.2 Hz), 100.1/98.2, 79.5/80.3, 75.9/76.0, 50.4/54.5. HRMS calcd for C$_{16}$H$_{12}$IFNO (M+1)$^+$ 379.9948, found 379.9947.

\begin{center}
\begin{tikzpicture}
\node[draw,thick] (n1) at (0,0) {N-\text{aryl(4-Chlorobenzyl)-N-aryl(2-iodophenyl)propiolamide (1d)}};
\end{tikzpicture}
\end{center}

$N$-(4-Chlorobenzyl)$-N$-(2-iodophenyl)propiolamide (1d). Yield: 85% (two rotamers at a ratio of 9:1). Yellow solid. Mp = 78-80 °C. IR (KBr) v max: 3213, 2107, 1637, 1389, 1293 cm$^{-1}$. $^1$H NMR (600 MHz, CDCl$_3$) major/minor $\delta$: 7.90/7.87 (dd, $J = 7.8$, 1.2 Hz, 1H), 7.26-7.21 (m, 3H), 7.12-7.11 (m, 2H), 7.05/6.99 (dt, $J = 7.8$, 1.2 Hz, 1H), 6.75/6.65 (dd, $J = 7.8$, 1.8 Hz, 1H), 5.49/5.50 (d, $J = 14.4$ Hz, 1H), 4.04/4.50 (d, $J = 14.4$ Hz, 1H), 2.74/3.32 (s, 1H). $^{13}$C NMR (150 MHz, CDCl$_3$) major/minor $\delta$: 153.1/152.6, 142.5/141.1, 140.0/140.1, 134.2/134.1, 133.8/134.0, 131.2/130.1, 130.9/130.1, 130.4/129.9, 128.9/129.0, 128.7/128.8, 100.1/98.1, 79.6/80.3, 75.9/76.0,
50.5/54.6. HRMS calcd for C\textsubscript{16}H\textsubscript{12}ClINO (M+1\textsuperscript{+}) 395.9652, found 395.9658.

![Chemical Structure](image)

\textit{N-(4-Bromobenzyl)-N-(2-iodophenyl)propiolamide (1e).} Yield: 79\% (two rotamers at a ratio of 9:1). Yellow solid. Mp = 94-96 °C. IR (KBr) v\textsubscript{max}: 3209, 2105, 1534, 1291 cm\textsuperscript{-1}. \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) major/minor δ: 7.91/7.88 (dd, J = 8.0, 1.5 Hz, 1H), 7.38/7.41 (d, J = 8.0 Hz, 2H), 7.22/7.19 (dt, J = 7.5, 1.5 Hz, 1H), 7.07-7.04 (m, 3H), 6.75/6.65 (dd, J = 8.0, 1.5 Hz, 1H), 5.48 (d, J = 14.5 Hz, 1H), 4.03/4.47 (d, J = 14.5 Hz, 1H), 2.74/3.31 (s, 1H). \textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}) major/minor δ: 153.1/152.7, 142.6/141.1, 140.0/140.1, 134.7/134.5, 131.7/131.8, 131.2/130.1, 131.2/130.0, 130.5/130.0, 129.0/129.1, 122.0/122.3, 100.0/98.1, 79.6/80.3, 75.9/76.1, 50.6/54.7. HRMS calcd for C\textsubscript{16}H\textsubscript{11}BrINO (M\textsuperscript{+}) 438.9067, found 438.9070.

![Chemical Structure](image)

\textit{Methyl 4-((N-(2-iodophenyl)propiolamido)methyl)benzoate (1f).} Yield: 74\% (two rotamers at a ratio of 8:1). Light yellow oil. IR (KBr) v\textsubscript{max}: 3231, 2106, 1718,
1647, 1468, 1386, 1280, 1106 cm$^{-1}$. $^1$H NMR (600 MHz, CDCl$_3$) major/minor $\delta$: 7.91/7.94 (d, $J = 8.4$ Hz, 2H), 7.90/7.84 (dd, $J = 7.8$, 1.2 Hz, 1H), 7.25/7.28 (d, $J = 8.4$ Hz, 2H), 7.19/7.18 (dt, $J = 7.8$, 1.2 Hz, 1H), 7.03/6.92 (dt, $J = 7.8$, 1.8 Hz, 1H), 6.74/6.64 (dd, $J = 8.4$, 1.8 Hz, 1H), 5.57/5.58 (d, $J = 14.4$ Hz, 1H), 4.11/4.46 (d, $J = 14.4$ Hz, 1H), 2.76/3.34 (s, 3H). $^{13}$C NMR (150 MHz, CDCl$_3$) major/minor $\delta$: 166.6/166.5, 153.2/152.7, 142.5/141.1, 140.7/140.5, 139.9/140.1, 131.1/130.4, 130.4/129.9, 129.8/129.6, 129.3/129.0, 129.0/128.7, 100.0/98.1, 79.8/80.5, 75.8/75.9, 52.1/55.0, 50.9/52.0. HRMS calcd for C$_{18}$H$_{15}$INO$_3$ (M+1)$^+$ 420.0097, found 420.0095.

\[
\text{N-(2-Iodophenyl)-N-(4-(trifluoromethyl)benzyl)propiolamide (1g). Yield: 78%}
\] (two rotamers at a ratio of 8:1). Brown solid. Mp =106-107 °C. IR (KBr) $\nu$max: 3227, 2108, 1637, 1392, 1158, 1114 cm$^{-1}$. $^1$H NMR (600 MHz, CDCl$_3$) major/minor $\delta$: 7.93/7.90 (dd, $J = 7.8$, 1.2 Hz, 1H), 7.53/7.57 (d, $J = 8.4$ Hz, 2H), 7.33/7.36 (d, $J = 7.8$ Hz, 2H), 7.24/7.21 (dt, $J = 7.8$, 1.2 Hz, 1H), 7.07/7.02 (dt, $J = 7.8$, 1.8 Hz, 1H), 6.78/6.69 (dd, $J = 7.8$, 1.2 Hz, 1H), 5.58/5.59 (d, $J = 14.4$ Hz, 1H), 4.13/4.59 (d, $J = 14.4$ Hz, 1H), 2.76/3.31 (s, 1H). $^{13}$C NMR (150 MHz, CDCl$_3$) major/minor $\delta$: 153.3/153.2, 142.7/142.7, 140.2/140.3, 139.7/139.6, 131.1/130.0, 130.5/130.3, 130.0/129.9 (q, $^2$J$_{C,F}$=
15.4 Hz), 129.8/129.2, 129.1/129.0, 125.5/125.6 (q, $^3J_{C,F} = 4.1$ Hz), 123.9/123.1 (q, $^3J_{C,F} = 270.7$ Hz), 100.1/100.0, 79.8/80.4, 75.8/75.9, 50.9/54.9. HRMS calcd for $C_{17}H_{12}F_3INO (M+1)^+ 429.9916$, found 429.9922.

![Chemical structure](image)

**N-(4-Cyanobenzyl)-N-(2-iodophenyl)propiolamide (1h).** Yield: 83% (two rotamers at a ratio of 8:1). Yellow solid. Mp = 101-102 °C. IR (KBr) $\nu$max: 3260, 2222, 2100, 1647, 1467, 1380, 1304 cm$^{-1}$. $^1$H NMR (500 MHz, CDCl$_3$) major/minor $\delta$: 7.91/7.87 (d, $J = 8.0$ Hz, 1H), 7.56/7.59 (d, $J = 8.0$ Hz, 2H), 7.32/7.33 (d, $J = 8.0$ Hz, 2H), 7.24/7.20 (t, $J = 7.0$ Hz, 1H), 7.07/6.99 (t, $J = 7.0$ Hz, 1H), 6.78/6.68 (d, $J = 8.0$ Hz, 1H), 5.50/5.52 (d, $J = 14.5$ Hz, 1H), 4.17/4.61 (d, $J = 14.5$ Hz, 1H), 2.77/3.37 (s, 1H).

$^{13}$C NMR (125 MHz, CDCl$_3$) major/minor $\delta$: 153.3, 142.5, 141.0, 140.2/140.2, 132.3/132.5, 130.9, 130.6, 130.0/129.7, 129.1/129.4, 118.5/118.3, 111.9/112.4, 100.0, 80.1/80.6, 75.6/75.7, 51.0/54.9. HRMS calcd for $C_{17}H_{12}IN_2O (M+1)^+ 386.9994$, found 386.9996.
N-(3-Cyanobenzyl)-N-(2-iodophenyl)propiolamide (1i). Yield: 74% (two rotamers at a ratio of 8:1). Yellow solid. Mp = 95-96 °C. IR (KBr) v max: 3223, 2225, 2102, 1637, 1470, 1392, 1301 cm⁻¹. ¹H NMR (500 MHz, CDCl₃) major/minor δ: 7.91/7.86 (dd, J = 8.0, 1.5 Hz, 1H), 7.56-7.53 (m, 1H), 7.50-7.46 (m, 2H), 7.39/7.42 (t, J = 8.0 Hz, 1H), 7.25/7.21 (dt, J = 7.5, 1.5 Hz, 1H), 7.07/6.98 (dt, J = 8.0, 1.5 Hz, 1H), 6.78/6.70 (dd, J = 7.5, 1.5 Hz, 1H), 5.45 (d, J = 14.5 Hz, 1H), 4.17 (d, J = 14.5 Hz, 1H), 2.77/3.37 (s, 1H). ¹³C NMR (125 MHz, CDCl₃) major/minor δ: 153.2/152.5, 142.4/140.8, 140.1/140.2, 137.2/136.3, 133.8/133.6, 132.7/133.2, 131.6/132.2, 130.8/132.1, 130.6/130.1, 129.4/129.7, 129.2/129.6, 118.3/118.2, 112.7/113.0, 99.9/98.1, 80.0/80.7, 75.6/75.8, 50.7/54.6. HRMS calcd for C₁₇H₁₂IN₂O (M+1)⁺ 386.9994, found 386.9995.

N-(3-Chlorobenzyl)-N-(2-iodophenyl)propiolamide (1j). Yield: 80% (two
rotamers at a ratio of 8:1). Yellow solid. Mp = 79-80 °C. IR (KBr) v max: 3192, 2103, 1627, 1471, 1387, 1297, 1211 cm⁻¹. ¹H NMR (500 MHz, CDCl₃) major/minor δ: 7.92/7.89 (d, J = 8.0 Hz, 1H), 7.29-7.18 (m, 5H), 7.12-7.05 (m, 2H), 6.80/6.69 (d, J = 8.0 Hz, 1H), 5.52/5.53 (d, J = 14.5 Hz, 1H), 4.05/4.51 (d, J = 14.5 Hz, 1H), 2.75/3.33 (s, 1H). ¹³C NMR (125 MHz, CDCl₃) major δ: 153.2, 142.6, 140.1, 137.7, 134.4, 131.2, 130.5, 129.8, 129.5, 129.0, 128.2, 127.6, 100.1, 79.7, 75.9, 50.8. HRMS calcd for C₁₆H₁₂ClINO (M+1)⁺ 395.9652, found 395.9659.

![Chemical Structure](image)

**N-(2-Iodophenyl)-N-(naphthalen-2-ylmethyl)propiolamide (1k).** Yield: 84% (two rotamers at a ratio of 6:1). Orange oil. IR (KBr) v max: 3447, 2107, 1646, 1467, 1287 cm⁻¹. ¹H NMR (500 MHz, CDCl₃) major/minor δ: 7.92/7.89 (d, J = 7.8, 1.2 Hz, 1H), 7.81-7.76 (m, 2H), 7.73-7.71 (m, 1H), 7.58 (s, 1H), 7.46-7.43 (m, 2H), 7.38 (dd, J = 8.5, 1.5 Hz, 1H), 7.11/7.09 (dt, J = 8.0, 1.5 Hz, 1H), 7.02/6.95 (dt, J = 7.5, 1.5 Hz, 1H), 6.71/6.62 (dd, J = 8.0, 1.5 Hz, 1H), 5.78/5.77 (d, J = 14.5 Hz, 1H), 4.19/4.62 (d, J = 14.5 Hz, 1H), 2.75/3.33 (s, 1H). ¹³C NMR (125 MHz, CDCl₃) major/minor δ: 153.3/152.9, 142.7/141.3, 139.9/140.0, 133.2/133.1, 133.1/133.0, 132.9/132.9, 131.3/130.1,
130.3/129.9, 128.9/129.0, 128.5/128.9, 128.4/128.9, 127.8/127.6, 127.6/127.5,
127.2/126.4, 126.1/126.4, 126.0/126.3, 100.1/98.2, 79.5/80.3, 76.1/76.2, 51.3/55.5.

HRMS calcd for C_{20}H_{15}INO (M+1)^+ 412.0198, found 412.0198.

![Chemical Structure](image)

**N-(2-Chlorobenzyl)-N-(2-iodophenyl)propiolamide (II).** Yield: 78% (two
rotamers at a ratio of 8:1). Brown solid. Mp = 90-93 °C. IR (KBr) v max: 3202, 2103,
1636, 1470, 1387 cm^{-1}. \(^1\)H NMR (500 MHz, CDCl\(_3\)) major/minor \(\delta\): 7.88/7.86 (d, \(J =
8.0\) Hz, 1H), 7.40-7.37 (m, 1H), 7.32-7.25 (m, 1H), 7.19-7.15 (m, 3H), 7.02/6.96 (dt, \(J =
8.0, 1.5\) Hz, 1H), 6.82/6.71 (dd, \(J = 8.0, 1.5\) Hz, 1H), 5.56/5.57 (d, \(J = 14.5\) Hz, 1H),
4.52/4.91 (d, \(J = 14.5\) Hz, 1H), 2.75/3.27 (s, 1H). \(^{13}\)C NMR (125 MHz,
CDCl\(_3\)) major/minor \(\delta\): 153.2/153.1, 142.4/141.0, 139.9/140.0, 134.5/134.4, 133.2/133.0,
131.8/130.0, 131.4/130.9, 130.3/129.9, 129.5/129.8, 129.4/129.7, 128.9/129.0,
127.1/127.0, 100.2/98.2, 79.6/80.1, 76.0/76.1, 47.8/52.3. HRMS calcd for C_{16}H_{12}ClINO
(M+1)^+ 395.9652, found 395.9658.
**N-Benzyl-N-(2-iodophenyl)propiolamide (1m).** Yield: 81% (two rotamers at a ratio of 7:1). Dark brown oil. IR (KBr) \( \nu \) max: 3421, 2958, 2104, 1646, 1469, 1395, 1302 cm\(^{-1}\). \(^1\)H NMR (600 MHz, CDCl\(_3\)) major/minor \( \delta \): 7.89/7.88 (d, \( J = 7.8 \) Hz, 1H), 7.28-7.23 (m, 3H), 7.19-7.16 (m, 3H), 7.03/6.96 (t, \( J = 7.8 \) Hz, 1H), 6.73/6.64 (d, \( J = 7.8 \) Hz, 1H), 5.57/5.58 (d, \( J = 14.4 \) Hz, 1H), 4.04/4.48 (d, \( J = 14.4 \) Hz, 1H), 2.72/3.31 (s, 1H). \(^{13}\)C NMR (150 MHz, CDCl\(_3\)) major/minor \( \delta \): 153.1/152.8, 142.7/141.3, 139.9/140.0, 135.7/135.5, 131.3/130.2, 130.3/129.8, 129.5/128.9, 128.8/128.7, 128.5/128.6, 127.9/128.2, 100.1/98.2, 79.4/80.1, 51.1/55.3. HRMS calcd for C\(_{16}\)H\(_{13}\)INO (M+1)\(^+\) 362.0042, found 362.0051.

**N-(2-Iodophenyl)-N-((3-methylisoxazol-5-yl)methyl)propiolamide (1n).** Yield: 68% (two rotamers at a ratio of 9:1). Light yellow oil. IR (KBr) \( \nu \) max: 2454, 3253, 2106, 1650, 1469, 1386, 1298, 1193 cm\(^{-1}\). \(^1\)H NMR (600 MHz, CDCl\(_3\)) major/minor \( \delta \): 7.92/7.89 (dd, \( J = 7.8, 1.2 \) Hz, 1H), 7.34/7.31 (dt, \( J = 7.8, 1.8 \) Hz, 1H), 7.16/6.98 (dd, \( J =
7.8, 1.2 Hz, 1H), 7.10/7.04 (dt, J = 7.8, 1.8 Hz, 1H), 6.10 (s, 1H), 5.43 (d, J = 15.6 Hz, 1H), 4.27 (d, J = 15.6 Hz, 1H), 2.77/3.10 (s, 1H), 2.25/2.10 (s, 3H). $^{13}$C NMR (150 MHz, CDCl$_3$) major/minor δ: 153.2/152.9, 148.2/148.4, 147.6/147.6, 142.2/140.7, 139.8/140.0, 131.2/130.1, 130.4/130.0, 129.0/129.1, 128.0/127.6, 115.6/115.5, 112.4/112.7, 111.1/110.3, 101.9/102.0, 100.3/98.3, 79.7/80.4, 75.9/76.0, 49.9/54.4. HRMS calcd for C$_{14}$H$_{12}$IN$_2$O$_2$ (M+1)$^+$ 366.9943, found 366.9948.

N-(2,6-Dichlorobenzyl)-N-(2-iodophenyl)propiolamide (1o). Yield: 77% (two rotamers at a ratio of 8:1). Yellow solid. Mp = 170-171 °C. IR (KBr) νmax: 3238, 2360, 2102, 1647, 1377, 1288 cm$^{-1}$. $^1$H NMR (500 MHz, CDCl$_3$) major/minor δ: 7.84/7.65 (d, J = 8.0 Hz, 1H), 7.21-7.18 (m, 2H), 7.13-7.09 (m, 1H), 7.06/6.91 (t, J = 7.5 Hz, 1H), 6.98 (t, J = 8.0 Hz, 1H), 6.58/6.42 (d, J = 7.5 Hz, 1H), 5.76/5.65 (d, J = 14.5 Hz, 1H), 4.83/5.26 (d, J = 14.5 Hz, 1H), 2.72/3.32 (s, 1H). $^{13}$C NMR (125 MHz, CDCl$_3$) major/minor δ: 152.6/153.3, 140.9/140.3, 139.6/139.7, 137.4/137.4, 131.1/130.4, 130.8/131.1, 130.4/131.7, 129.9/130.0, 128.5/128.6, 128.2/128.4, 101.6/99.4, 79.4/80.1, 75.9/76.3, 44.1/49.2. HRMS calcd for C$_{16}$H$_{11}$Cl$_2$INO (M+1)$^+$ 429.9262, found 429.9268.
N-(2-Iodophenyl)-N-(3,4,5-trimethoxybenzyl)propiolamide (1p). Yield: 81% (two rotamers at a ratio of 8:1). Yellow solid. Mp = 118-120 °C. IR (KBr) vmax: 3195, 2107, 1633, 1394, 1123 1288 cm⁻¹. ¹H NMR (600 MHz, CDCl₃) major/minor δ: 7.89/7.86 (dd, J = 7.8, 1.2 Hz, 2H), 7.22/7.20 (dt, J = 7.8, 1.8 Hz, 1H), 7.04/6.98 (dt, J = 7.8, 1.8 Hz, 1H), 6.78/6.70 (dd, J = 7.8, 1.8 Hz, 1H), 6.36/6.38 (s, 2H), 5.44/5.46 (d, J = 13.8 Hz, 1H), 3.97/4.40 (d, J = 13.8 Hz, 1H), 3.77/3.79 (s, 3H), 3.71/3.72 (s, 6H), 2.74/3.33 (s, 1H). ¹³C NMR (150 MHz, CDCl₃) major/minor δ: 153.0/153.2, 153.0/152.6, 142.6/141.3, 139.8/139.9, 137.6/137.8, 131.4/131.0, 131.2/130.1, 130.3/129.9, 128.8/129.0, 106.6/105.7, 100.2/98.2, 79.5/80.1, 76.0/76.2, 60.8/60.8, 56.0/55.6, 51.4/51.4. HRMS calcd for C₁₉H₁₈NaINO₄ (M+Na)⁺ 474.0178, found 474.0178.

N-(4-Chlorobenzyl)-N-(2-iodo-4-methylphenyl)propiolamide (1q). Yield: 79% (two rotamers at a ratio of 9:1). Yellow oil. IR (KBr) vmax: 3287, 2108, 1646, 1484,
N-((6-Bromobenzo[d][1,3]dioxol-5-yl)methyl)-N-(2-iodophenyl)propiolamide

(1s). Yield: 72% (two rotamers at a ratio of 8:1). Dark red solid. Mp = 142-143 °C. IR (KBr) νmax: 3220, 2110, 1626, 1481, 1394, 1237, 1033 cm⁻¹. ¹H NMR (600 MHz, CDCl₃) major/minor δ: 7.88/7.86 (dd, J = 7.8, 1.2 Hz, 1H), 7.21/7.18 (dt, J = 7.8, 1.2 Hz, 1H), 7.04/6.99 (dt, J = 7.8, 1.8 Hz, 1H), 6.96/6.89 (s, 1H), 6.86/6.86 (s, 1H), 6.82/6.70 (dd, J = 7.8, 1.2 Hz), 5.94/5.97 (dd, J = 12.0, 1.2 Hz, 2H), 5.45/5.46 (d, J = 14.4 Hz, 2H), 4.46/4.82 (d, J = 14.4 Hz, 1H), 2.76/3.30 (s, 1H). ¹³C NMR (150 MHz, CDCl₃) major/minor δ: 153.2/152.9, 148.2/148.4, 147.6/147.6, 142.2/140.7, 139.8/140.0,
131.2/130.1, 130.4/130.0, 129.0/129.1, 128.1/127.6, 115.6/115.5, 112.4/112.7,
111.2/110.3, 101.9/102.0, 100.3/98.3, 79.7/80.6, 75.9/76.1, 50.0/54.4. HRMS calcd for
C_{17}H_{12}BrINO_3 (M+1)^+ 483.9045, found 483.9050.

\[
\text{N-(2-Iodophenyl)-N-methylpropiolamide (1t). Yield: 79\% (two rotamers at a}
\]
\[
\text{ratio of 8:1). Dark brown solid. Mp = 101-102 °C. IR (KBr) vmax: 3214, 2104, 1635,
\]
\[
1466, 1376, 1298, 1133 \text{ cm}^{-1}. {^1} \text{H NMR (600 MHz, CDCl}_3\text{) major/minor } \delta: 7.90/7.89 (dd,
\]
\[
J = 7.8, 1.2 \text{ Hz, 1H}), 7.41/7.39 (dt, J = 7.8, 1.2 \text{ Hz, 1H}), 7.30/7.19 (dd, J = 7.8, 1.2 \text{ Hz,}
\]
\[
1H), 7.09/7.04 (dt, J = 7.8, 1.2 \text{ Hz, 1H}), 3.21/3.47 (s, 3H), 2.71/3.21 (s, 1H). {^{13}} \text{C NMR}
\]
\[
(150 \text{ MHz, CDCl}_3\text{) major/minor } \delta: 153.1/152.9, 144.9/143.7, 139.9/140.0, 130.3/129.9,
\]
\[
129.5/129.8, 128.4/128.4, 99.3/97.8, 79.0/79.9, 76.0/76.0, 35.3/39.0. HRMS calcd for
\]
\[
C_{10}H_9INO_4 (M+1)^+ 285.9729, found 285.9732.
\]

\[
\text{N-(2-Iodo-4-(trifluoromethyl)phenyl)-N-(4-nitrobenzyl)propiolamide (1v).}
\]
\[
\text{Yield: 77\% (two rotamers at a ratio of 8:1). Colorless oil. IR (KBr) vmax: 3286, 2111,}
\]
1651, 1600, 1522, 1347, 1320, 1133 cm$^{-1}$. $^1$H NMR (600 MHz, CDCl$_3$) major/minor $\delta$: 8.16/8.15 (d, $J = 1.2$ Hz, 1H), 8.15/8.19 (dd, $J = 8.4$, 2.4 Hz, 2H), 7.53/7.47 (dd, $J = 7.8$, 1.2 Hz, 1H), 7.43/7.44 (d, $J = 8.4$ Hz, 2H), 6.93/6.83 (dd, $J = 8.4$, 1.2 Hz, 1H), 5.57/5.61 (dd, $J = 14.4$, 2.4 Hz, 1H), 4.24/4.71 (d, $J = 14.4$ Hz, 1H), 2.83/3.39 (s, 1H). $^{13}$C NMR (150 MHz, CDCl$_3$) major/minor $\delta$: 152.8/152.5, 147.8/148.0, 145.9/144.5, 142.5/142.2, 137.3 (q, $^3J_{C-F} = 2.4$ Hz), 132.5 (q, $^2J_{C-F} = 31.1$ Hz), 131.2/130.0, 130.2/129.5, 126.3 (q, $^3J_{C-F} = 3.45$ Hz), 124.0/124.1, 122.3 (q, $^1J_{C-H} = 271.2$ Hz), 100.3/98.5, 80.8/81.2, 75.4/75.3, 50.6/54.4. HRMS calcd for C$_{17}$H$_{11}$F$_3$IN$_2$O$_3$ (M+1)$^+$ 474.9766, found 474.9758.

\[ \text{N-(4-Chloro-2-iodophenyl)-N-(4-chlorobenzyl)propiolamide (1w). Yield: 75\% (two rotamers at a ratio of 8:1). White solid. Mp } = 82-85 \degree \text{C. IR (KBr) } \nu \text{max: 3253, 2105, 1634, 1465, 1396, 1292, 1090 cm}^{-1}. \]

$^1$H NMR (600 MHz, CDCl$_3$) major/minor $\delta$: 7.90/7.86 (d, $J = 1.8$ Hz, 1H), 7.24/7.27 (d, $J = 8.4$ Hz, 2H), 7.20/7.17 (dd, $J = 8.4$, 1.8 Hz, 1H), 7.12/7.13 (d, $J = 8.4$ Hz, 2H), 6.65/6.53 (d, $J = 8.4$, 1H), 5.48/5.50 (d, $J = 14.4$ Hz, 1H), 4.00/4.46 (d, $J = 14.4$ Hz, 1H), 2.79/3.33 (s, 1H). $^{13}$C NMR (150 MHz, CDCl$_3$) major/minor $\delta$: 153.0/152.8, 141.3/139.8, 139.4/139.5, 135.5/135.0, 134.1/134.4,
134.0/133.7, 131.6/130.6, 130.9/130.1, 129.2/129.3, 128.8/129.0, 100.5/98.6, 80.0/80.6, 75.8/75.8, 50.5/54.6. HRMS calcd for C\textsubscript{16}H\textsubscript{11}Cl\textsubscript{2}INO (M+1)\textsuperscript{+} 429.9262, found 429.9267.
3. NMR Spectra

(E)-Methyl 2-(1-(4-nitrobenzyl)-2-oxoindolin-3-ylidene)acetate (3a).

$^1$H NMR

$^{13}$C NMR
(E)-Methyl 2-(1-(4-methoxybenzyl)-2-oxoindolin-3-ylidene)acetate (3b).

$^1$H NMR

$^{13}$C NMR
(E)-Methyl 2-(1-(4-fluorobenzyl)-2-oxoindolin-3-ylidene)acetate (3c).

$^1$H NMR

$^{13}$C NMR
(E)-Methyl 2-[(1-(4-chlorobenzyl)-2-oxoindolin-3-ylidene)acetate (3d).

$^1$H NMR

$^{13}$C NMR
(E)-Methyl 2-(1-(4-bromobenzyl)-2-oxoindolin-3-ylidene)acetate (3e).

$^1$H NMR

$^{13}$C NMR
(E)-Methyl 4-((3-(2-methoxy-2-oxoethylidene)-2-oxoindolin-1-yl)methyl)benzoate (3f).

$^1$H NMR

$^{13}$C NMR
(E)-Methyl 2-(2-oxo-1-(4-(trifluoromethyl)benzyl)indolin-3-ylidene)acetate (3g).

$^1$H NMR

$^{13}$C NMR
(E)-Methyl 2-(1-(4-cyanobenzyl)-2-oxoindolin-3-ylidene)acetate (3h).

$^1$H NMR

$^{13}$C NMR
(E)-Methyl 2-(1-(3-cyanobenzyl)-2-oxindolin-3-ylidene)acetate (3i).

$^1$H NMR

$^{13}$C NMR
(E)-Methyl 2-(1-(3-chlorobenzyl)-2-oxoindolin-3-ylidene)acetate (3j).

$^1$H NMR

$^{13}$C NMR
(E)-Methyl 2-((1-(naphthalen-2-ylmethyl)-2-oxoindolin-3-ylidene)acetate (3k).

$^1$H NMR

$^{13}$C NMR
(E)-Methyl 2-(1-(2-chlorobenzyl)-2-oxoindolin-3-ylidene)acetate (3l). 

$^1$H NMR

$^{13}$C NMR
(E)-Methyl 2-(1-benzyl-2-oxoindolin-3-ylidene)acetate (3m).

\[ \text{H NMR} \]

\[ \text{C NMR} \]
(E)-Methyl 2-(1-((3-methylisoxazol-5-yl)methyl)-2-oxoindolin-3-ylidene)acetate (3n).

$^1$H NMR

$^{13}$C NMR
(E)-Methyl 2-(1-(2,6-dichlorobenzyl)-2-oxoindolin-3-ylidene)acetate (3o).

$^1$H NMR

$^{13}$C NMR
(E)-Methyl 2-(2-oxo-1-(3,4,5-trimethoxybenzyl)indolin-3-ylidene)acetate (3p)

$^1$H NMR

$^{13}$C NMR
(E)-Methyl 2-(1-(4-chlorobenzyl)-5-methyl-2-oxoindolin-3-ylidene)acetate (3q).

$^1$H NMR

$^{13}$C NMR
(E)-Methyl 2-[(1-(4-chlorobenzyl)-5-methoxy-2-oxoindolin-3-ylidene)acetate (3r).

$^1$H NMR

$^{13}$C NMR
(E)-Methyl 2-((6-bromobenzo[d][1,3]dioxol-5-yl)methyl)-2-oxoindolin-3-ylidene) acetate (3s).

$^1$H NMR

$^{13}$C NMR
(E)-Methyl 2-(1-methyl-2-oxoindolin-3-ylidene)acetate (3t).

\(^1\)H NMR

\(^{13}\)C NMR
(E)-Methyl 2-(2-oxoindolin-3-ylidene)acetate (3u).

$^1$H NMR

$^{13}$C NMR
(E)-Methyl 2-(1-(4-nitrobenzyl)-2-oxo-5-(trifluoromethyl)indolin-3-ylidene) acetate (3v).

$^1$H NMR

$^{13}$C NMR
(E)-Ethyl 2-(1-(4-nitrobenzyl)-2-oxoindolin-3-ylidene)acetate (4a).

$^1$H NMR

$^{13}$C NMR
(E)-Ethyl 2-(1-(4-chlorobenzyl)-2-oxoindolin-3-ylidene)acetate (4b).

$^1$H NMR

$^{13}$C NMR
(E)-Ethyl 2-(1-(4-bromobenzyl)-2-oxoindolin-3-ylidene)acetate (4c).

$^1$H NMR

$^{13}$C NMR
(E)-Ethyl 2-(2-oxo-1-(3,4,5-trimethoxybenzyl)indolin-3-ylidene)acetate (4d).

$^1$H NMR

$^{13}$C NMR
(E)-Ethyl 2-(5-chloro-1-(4-chlorobenzyl)-2-oxoindolin-3-ylidene)acetate (4e).

$^1$H NMR

$^{13}$C NMR
(E)-Ethyl 2-(1-(4-chlorobenzyl)-5-methoxy-2-oxoindolin-3-ylidene)acetate (4f).

$^1$H NMR

$^{13}$C NMR
(E)-Ethyl 2-(1-methyl-2-oxoindolin-3-ylidene)acetate (4g).

$^1$H NMR

$^{13}$C NMR
(E)-Butyl 2-((1-(3-cyanobenzyl)-2-oxoindolin-3-ylidene)acetate (5a).

$^1$H NMR

$^{13}$C NMR
(E)-Butyl 2-(1-(4-cyanobenzyl)-2-oxoindolin-3-ylidene)acetate (Sb).

$^{1}H$ NMR

$^{13}C$ NMR
(E)-Butyl 2-(1-(4-nitrobenzyl)-2-oxoindolin-3-ylidene)acetate (5c).

$^1$H NMR

$^{13}$C NMR
(E)-Ethyl 2-(2-oxoindolin-3-ylidene)acetate (4h).

$^1$H NMR

$^{13}$C NMR