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题　目：基于α-吡啶活泼亚甲基的螺环化/芳构化反应构建吲哚嗪

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基于α-吡啶活泼亚甲基的螺环化/芳构化反应构建吲哚嗪

摘要

吲哚嗪又称中氮茚，是一类重要的含氮杂环化合物，因其独特的结构赋予了吲哚嗪特殊的化学性质和广泛的生物活性，在许多天然产物和药物分子中都能看见吲哚嗪及其衍生物的身影。因此，构建吲哚嗪及研究其性能在有机合成领域备受关注。目前，已有文献报道了构建吲哚嗪骨架的方法，尽管有些方法能比较高效的构建吲哚嗪，但仍存在不同程度的局限性。例如，起始原料的来源困难；部分反应条件苛刻，需要在高温下进行；使用大量的促进剂或价格昂贵的催化剂；反应机理较为单一，大部分都是通过环加成反应得到吲哚嗪衍生物。鉴于以上这些原因，我们开发出了基于α-吡啶活泼亚甲基的螺环化/芳构化反应构建吲哚嗪的新方法。具体内容如下：

(1) 研究了亚烷基氧化吲哚与 2-(吡啶-2-基)乙酸酯衍生物的反应。首先，建立亚烷基氧化吲哚与 2-吡啶乙酸乙酯的模型反应，对反应的条件如卤代试剂、温度、溶剂等进行探索确定了最优反应条件。具体方案如下：亚烷基氧化吲哚、1.0 当量 2-(吡啶-2-基)乙酸酯衍生物和 1.0 当量 NIS 在 DMSO 中于 80 °C 反应 8 小时。随后，在这个最优反应条件下，我们以 50-91%的收率合成了 42 个吲哚嗪类化合物，同时通过 X-射线单晶衍射进一步确定产物的结构，并通过控制性实验提出了可能的反应机理。该反应能够有效和直接地构建各种吲哚嗪，且合成的吲哚嗪衍生物富含多个官能团，并能进一步修饰。该方法具有高效性、广泛的官能团耐受性等特点，而且该方法反应条件温和、成本低、起始原料简单易得，为构建吲哚嗪类化合物提

供了一种新途径。

(2) 研究了机械化学条件下铜催化的环外α,β-不饱和异噁唑酮与2-(吡啶-2-基)乙酸酯衍生物的反应。首先，我们建立了反应模型，并通过核磁共振（NMR）确定了产物结构。随后，我们对反应的条件如催化剂、氧化剂、助溶剂等进行探索确定了最优合成条件并利用该方法高效合成出了30个吲哚嗪类衍生物，收率在39-85%之间。并通过控制性实验提出了可能的反应机理。该方法具有原料易得、高效环保、底物适用性广等特点，为构建吲哚嗪衍生物提供了新途径。

上述反应所得到的所有产物的结构均通过核磁共振氢谱（^{1}H NMR）、碳谱（^{13}C NMR）及高分辨质谱（HRMS）进行了表征，其中亚烷基氧化吲哚与2-(吡啶-2-基)乙酸酯衍生物的反应我们通过代表性产物的单晶X-射线衍射进一步证实了其结构。最为重要的是，相比较其他方法，本文提出了一种新颖而有趣的螺环化/开环芳构化构建吲哚嗪的反应机理，为高效构建吲哚嗪提供了一种新的选择。

关键词：吲哚嗪；2-取代吡啶衍生物；亚烷基氧化吲哚；α,β-不饱和异噁唑酮；螺环化/芳构化反应

Synthesis of Indolizines via Spiroannulation/Aromatization of 2-(Pyridin-2-yl)acetate Derivatives

ABSTRACT

Indolizine, also known as pyrindole, represents an important class of nitrogen-containing heterocyclic compounds. Its unique structure endows indolizine with distinctive chemical properties and broad biological activities, making it prevalent in numerous natural products and pharmaceutical molecules. Consequently, the construction and investigation of indolizine derivatives have attracted significant attention in organic synthesis. Although existing literature reports various methods for constructing indolizine skeletons, current approaches still present limitations such as limited availability of starting materials, harsh reaction conditions requiring elevated temperatures, excessive use of promoters or expensive catalysts, and mechanistic constraints predominantly relying on cycloaddition reactions. Addressing these challenges, we developed novel strategies for indolizine construction through spirocyclization/aromatization reactions based on α-pyridyl active methylene compounds. The main findings are outlined below:

(1) We investigated the reaction between alkylidene oxindoles and 2-(pyridin-2-yl)acetate derivatives. After establishing a model reaction between alkylidene oxindoles and ethyl 2-pyridylacetate, we

systematically optimized reaction parameters including halogenating reagents, temperature, and solvents. The optimal conditions were determined as: alkylidene oxindole, 1.0 equivalent of 2-(pyridin-2-yl)acetate derivative, and 1.0 equivalent of N-iodosuccinimide (NIS) in DMSO at 80 ^{o}C for 8 hours. Under these conditions, 42 indolizine derivatives were synthesized with yields ranging from 50% to 91%. Structural elucidation was achieved through single-crystal X-ray diffraction analysis, and control experiments revealed a plausible reaction mechanism. This method features efficient functional group tolerance, mild conditions, cost-effectiveness, and readily available starting materials, providing a novel pathway for indolizine synthesis while generating multi-functional derivatives amenable to further modifications.

(2) We explored copper-catalyzed reactions between exocyclic α,β-unsaturated isoxazolones and 2-(pyridin-2-yl)acetate derivatives under mechanochemical conditions. After establishing the reaction model and verifying product structures by nuclear magnetic resonance (NMR), we optimized catalytic systems, oxidants, and co-solvents. This approach efficiently synthesized 30 indolizine derivatives with yields of 39-85%, demonstrating advantages of environmental friendliness, broad substrate compatibility, and operational simplicity. Mechanistic insights were proposed based on control experiments.

All synthesized compounds were fully characterized by ^{1}H NMR,

^{13}C NMR, and high-resolution mass spectrometry (HRMS). Notably, single-crystal X-ray diffraction analysis of representative products from the first reaction series confirmed structural assignments. Most importantly, compared with existing methods, this work proposes a novel spirocyclization/ring-opening aromatization mechanism for indolizine construction, offering a distinctive alternative for efficient synthesis of these heterocyclic compounds.

KEY WORDS: Indolizine, 2-Substituted pyridine derivatives, Alkylidene oxindoles, α,β-unsaturated isoxazolones, Spirocyclization/aromatization reaction

目录

第 1 章 绪论

1.1 引言

含氮杂环化合物在药物化学、材料化学、农药等领域具有广泛的应用，构建含氮杂环化合物一直是合成界的热门研究课题[1-5]。吲哚嗪又称中氮茚，是一类重要的含氮杂环化合物，其核心结构可以看做是吡咯环和吡啶环的融合体，因其独特的结构赋予了吲哚嗪特殊的化学性质和广泛的生物活性[6-13]。许多天然产物和药物分子中含有吲哚嗪骨架，如抗肿瘤药物(**a**)、抗菌剂(**b**)、消炎剂(**c**)等[14-17]。此外，吲哚嗪及其衍生物因具有良好的荧光特性和高量子产率，使其在材料化学领域也占据一席之地，例如，吲哚嗪衍生物可用作染料(**d**)和电致发光材料(**e**)等[18-20]。在农业化学领域可见含有吲哚嗪骨架的除草剂(**f**)等[21,22]。

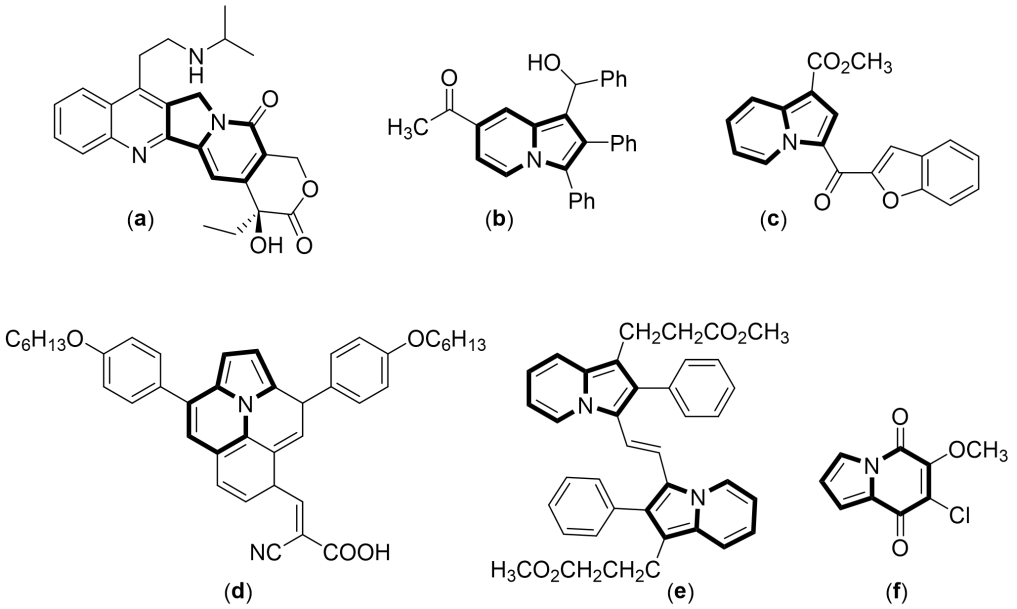

图 1-1 含吲哚嗪骨架的分子

(Figure 1-1 Molecules with Indolezine Skeleton)

1.2 吲哚嗪骨架在医药领域的应用

1.2.1 抗肿瘤性

肿瘤是由体内细胞异常增殖形成的组织团块，其中恶性肿瘤（癌症）会破坏正常组织的结构及功能，且其具有侵略性和转移性，会通过血液或者淋巴系统转移到身体其他部位，是导致死亡的重要原因。癌症具有发病率高，治疗难度大、易复发等特点，给患者及其亲属带来巨大的精神压力和经济负担，因此

研究抗癌药物具有极其重要的必要性[23-28]。

喜树碱 **1**（Camptothecin，CPT）是一种具有细胞毒性的天然生物碱，在植物来源的抗癌药物中占有一席之地[29]，其结构如图 1-2 所示。喜树碱近年来在临床研究领域备受关注，这类药物主要作为 DNA 拓扑异构酶IB 的抑制剂发挥抗癌作用[30-36]。

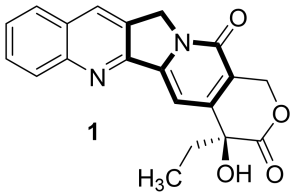

图 1-2 喜树碱

(Figure 1-2 Camptothecin)

片螺素 **2**（Lamellarin）是一类具有生物活性的吡咯生物碱类化合物，其中之一的结构如图 1-3 所示。自其被发现以来，已鉴定出 70 多种衍生物。其中，片螺素 D 是最引人瞩目的一员，它是一种强效的拓扑异构酶 1 抑制剂，对多种癌细胞表现生物毒性[37-42]。

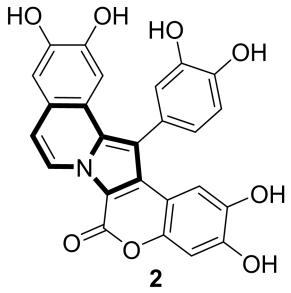

图 1-3 片螺素

(Figure 1-3 Lamellarin)

2010 年，Shen 等人[43] 通过环加成反应的一锅法策略合成了一系列吲哚嗪衍生物，并运用 MTT 比色法评估了这些化合物对人肝癌细胞株 Hep-G2 的抗增殖效果。其中，化合物 **3** 的抗增殖活性最好，结构如图 1-4 所示。作者认为吲哚嗪核上的氰基比相同位置的酯官能团表现出更好的活性，卤素原子和甲基的存在可能提高抗癌活性。

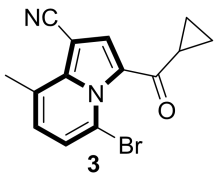

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图 1-4 对肝癌细胞株具有抗增殖活性的吲哚嗪衍生物

(Figure 1-4 Indolezine derivatives with anti proliferative activity against liver cancer cell lines)

1.2.2 抗菌活性

细菌和真菌无处不在，致病菌和病原真菌会引发疾病，威胁人类健康。例如，结核杆菌、霍乱弧菌等会引发感染性疾病、白色念珠菌致鹅口疮、黄曲霉会产生致癌毒素等，因此研究所合成药物的抗菌性也是当下热门之一[44-46]。

长时间来未有新型抗结核药物问世，表明对新型抗结核药物的需求十分迫切[47]。2003 年，Gundersen 等人合成了吲哚嗪衍生物并测试其对结核分枝杆菌 H37Rv 的抑菌活性[17]。其中，化合物 **4** 表现出抗真菌活性，其 MIC 值为 6.25 μg/mL，结构如图 1-5 所示。

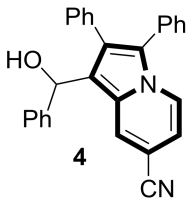

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图 1-5 具有抗结核分枝杆菌活性的吲哚嗪衍生物

(Figure 1-5 Indolezine derivatives with anti tuberculosis activity against Mycobacterium tuberculosis)

Zhou 等人[48]开展了一项关于吲哚嗪类化合物抗菌性能的研究。他们选取了金黄色葡萄球菌、大肠杆菌和枯草芽孢杆菌等多种代表性菌株作为实验对象，通过标准的涂布平板法系统评估了系列吲哚嗪化合物的抗菌效果。结果表明，吲哚嗪衍生物 **5** 和 **6** 对某些革兰氏阴性和阳性菌表现出一定的抗菌活性，其结构如图 1-6 所示。

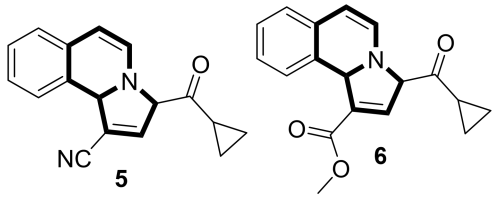

图 1-6 具有抗革兰氏菌活性的吲哚嗪衍生物

(Figure 1-6 Indolizine Derivatives with Anti-Gram-Staining Bacterial Activity)

1.2.3 抗炎活性

炎症是机体的一种自然防御反应，出现红肿、发热、疼痛和功能障碍等都是机体有炎症的表现[49-51]。过度的或持续长时间的炎症可能会给身体带来不可挽回的损伤，因此研究抗炎活性有其重要意义。抗炎活性指某些物质能够有效抑制或减轻生物体内炎症反应的能力[52-54],而有机合成的发展为开发新型抗炎药物提供丰富多样的分子库。在文献查阅中发现，吲哚嗪骨架也具有抗炎活性。

1996 年，Hagishita 等人[55]合成了多种吲哚嗪衍生物，并发现 1-氨基甲酰甲基吲哚嗪 **7** 和 1-氧代甲酰基吲哚嗪 **8** 具有显著的磷脂酶 A2（PLA2）抑制活性，其结构如图 1-7 所示。

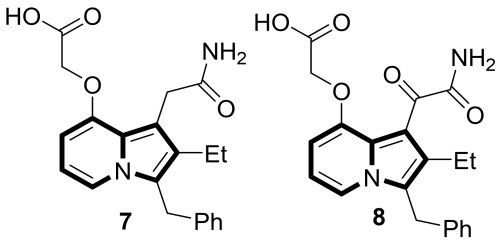

图 1-7 具有抗炎活性的吲哚嗪衍生物

(Figure 1-7 Indolezine derivatives with anti-inflammatory activity)

1999 年，Yokota 等人[56]研究发现，吲哚嗪衍生物 **9** 通过阻断磷脂酶 A2-IB（PLA2-IB）与小鼠磷脂酶 A2 受体（PLA2R）的结合，表现出对小鼠内毒素休克的有效活性，其结构如图 1-8 所示。作者认为，羧基基团与磷脂酶 A2（PLA2）活性中心 Ca^{2+}离子之间的配位作用很可能是影响其抗炎功效的决定性因素。

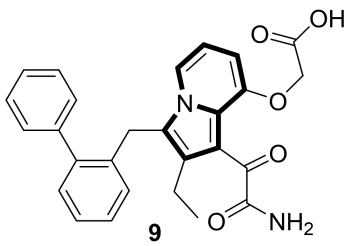

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图 1-8 具有抗炎活性的吲哚嗪衍生物

(Figure 1-8 Indolezine derivatives with anti-inflammatory activity)

1.2.4 调节神经系统活性

神经系统是调控人体生理功能和行为的中枢，其活性异常引起多种疾病如神经退行性疾病、精神障碍、癫痫等[57-59]。通过调节神经系统活性，可以改善神经功能、缓解疾病症状并提高生活质量。许多合成的小分子具有特定神经活性，可以进一步被修饰用于受体激动剂、拮抗剂等，从而精准调控神经信号传导[60-64]。研究表明，许多具有吲哚嗪骨架的分子具有调节神经系统活性。

1990 年，Cingolani 等人[65]合成了吲哚嗪衍生物 **10**，并对其进行了进一步研究，其结构如图 1-9 所示。实验数据表明，该化合物对组胺受体、乙酰胆碱受体和 5-羟色胺受体具有非选择性拮抗作用，是一种多靶点受体拮抗剂。

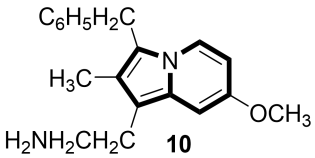

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图 1-9 具有吲哚嗪结构的非选择性拮抗剂

(Figure 1-9 Non selective Antagonists with Indolezine Structure)

2003 年，Chai 等人[66]合成了 13 种含二丙基氧基苯基侧链的吲哚嗪类化合物，以寻找新型非咪唑类 H3 受体拮抗剂。其中，化合物 **11** 是这些化合物中最有效的 H3 受体拮抗剂，有望用于治疗神经系统疾病，其结构如图 1-10 所示。

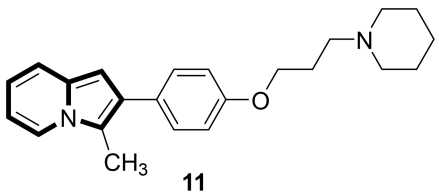

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图 1-10 具有吲哚嗪结构的 H_3 拮抗剂

(Figure 1-10 H_3 Antagonist with Indolezine Structure)

1.3 吲哚嗪骨架在材料领域的应用

吲哚嗪在功能性染料和光电材料领域具有广泛的应用，如吲哚嗪衍生物可在染料敏化太阳能电池（DSSC）中作为光敏剂，通过供体-受体结构（如 D-π-A 结构）将光能高效转化为电能[67,68]。

2016 年，Delcamp 等人[69]研发出了一种用于敏化太阳能电池（DSCs）的新型敏化剂 **12**，其结构如图 1-11 所示。这类敏化剂以高度烷基化的表面阻断吲哚嗪供体（AH3）为核心结构，具有光吸收率高、重组率低等特性。同年，该团队进一步开发了两种新型 D-A 结构染料[70]。2019 年，该课题组[71]在前期工作基础上取得新突破，创新性地将吲哚嗪结构单元引入 D-π-A 型染料分子骨架，设计合成了一类新型的吲哚嗪-卟啉推拉电子体系。这类新型染料在近红外区域展现出优异的光吸收特性，被成功应用于太阳能电池器件。

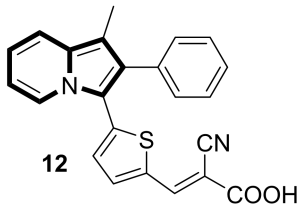


图 1-11 太阳能电池敏化剂 AH3

(Figure 1-11 Sensitizer AH3 for Solar Cells)

此外，吲哚嗪衍生物因其高荧光量子产率和良好的光稳定性，被广泛用于生物标记和荧光探针[72]。荧光探针是一种利用荧光特性进行检测和分析的工具，其核心原理是荧光团吸收特定波长的光后发射更长波长的光，通过识别基团与目标物结合引发荧光信号的变化[73-75]。

2017 年，Zheng 等人[76]开发了一种基于 FRET 的 Cu^{2+}比率荧光探针 TY-2（**13**），其结构如图 1-11 所示，合成的荧光团为新型吲哚嗪衍生物。该荧光探针展现出显著的光学特性：斯托克斯位移大、灵敏度高、选择性优异，在宽 pH 范围（5~12）内可实现 Cu^{2+}的快速响应。此外，该探针还可用于活神经胶质瘤细胞中的 Cu^{2+}成像，这表明其良好的生物应用潜力。

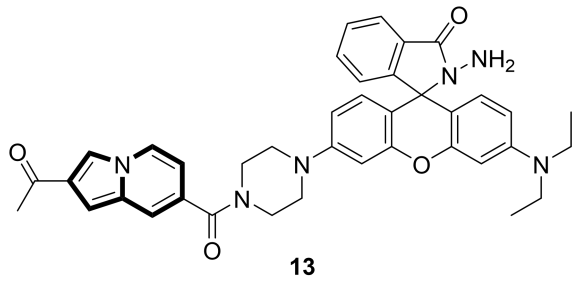


图 1-12 Cu^{2+} 比率荧光探针 TY-2

(Figure 1-12 Cu^{2+} ratio fluorescent probe TY-2)

1.4 吲哚嗪骨架在农业领域的应用

2005 年，Smith 等人[22]研究了一系列吲哚嗪衍生物的除草活性，结果表明化合物 **14** 是除草性能最佳的衍生物（SERP = -0.25 V，除草活性为 6.2）。

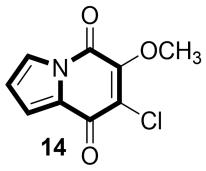


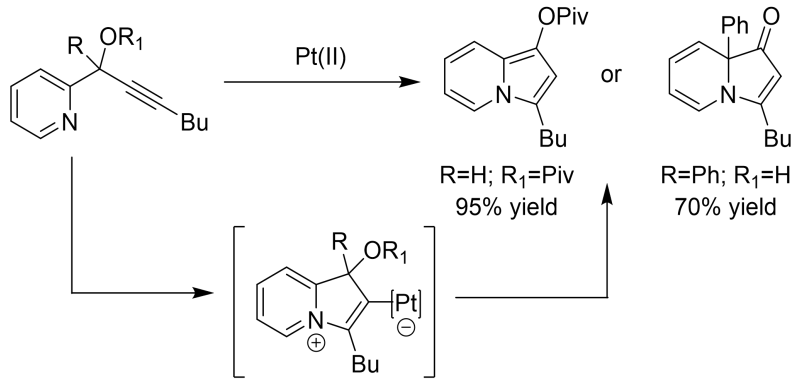
图 1-13 具有除草活性的吲哚嗪衍生物

(Figure 1-13 Indolezine derivatives with herbicidal activity)

1.5 吲哚嗪化合物的合成研究进展

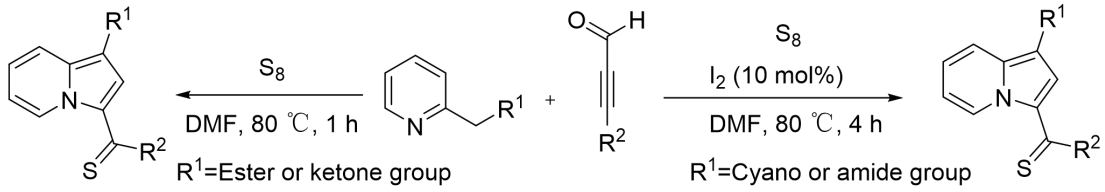
1.5.1 从吡啶及其衍生物构建吲哚嗪

2007 年，Smith 等人[77]通过 Pt(II)催化的环异构化反应或吡啶炔丙醇及其衍生物的串联环化/1,2-迁移反应合成了吲哚嗪、吡咯酮和吲哚嗪酮类杂环化合物。该方法原料易得、收率高且产物具有多官能团。



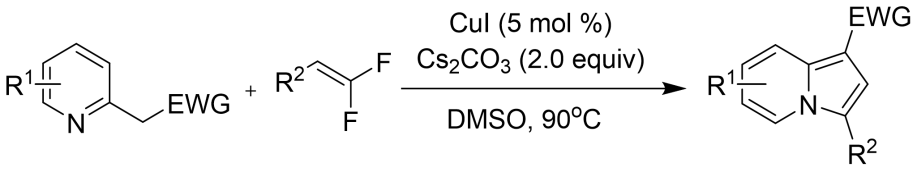
Scheme 1-1

2019 年，Chen 等人[78]报道了炔的无金属氨基化反应：从 2-烷基吡啶和单质硫合成吲哚并硫酮。该工作中，作者通过 C−C、C−N 和 C−S 键的串联，实现了无金属催化的三组分环化反应，合成了吲哚并硫酮。



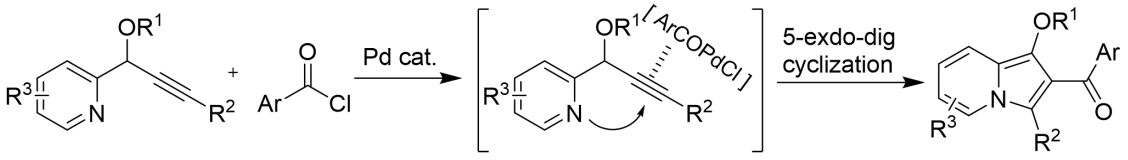
Scheme 1-2

2020 年，Lu 等人[79] 通过铜催化的 2-(吡啶-2-基)乙酸酯与偕二氟烯烃的偶联环化反应，高效构建了双取代的吲哚嗪类化合物。该方法以中等至良好的收率合成了一系列双取代吲哚嗪衍生物，并表现出优异的官能团兼容性。



Scheme 1-3

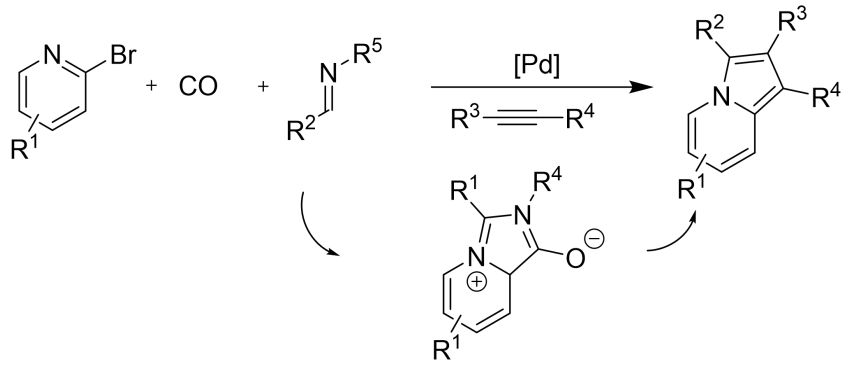
2020 年，Xu 等人[80]开发了一种钯催化的吲哚嗪衍生物合成方法。该方法通过芳酰氯与 Pd(0)络合物的氧化加成触发反应，经过 Pd(II)中间体介导的环化和还原消除，生成目标产物。该方法具有条件温和、底物适用范围广、收率高等优点，且机理研究验证了所提出的催化循环。



Scheme 1-4

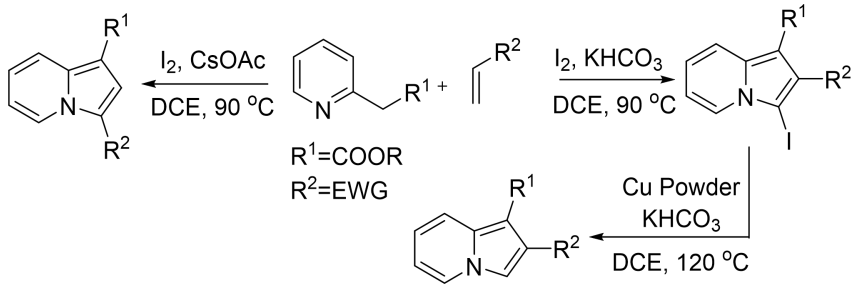
2020 年，Roy 等人[81]利用 2-溴吡啶、亚胺和炔烃成功构建了吲哚嗪。该反应通过羰基化形成高能量的介离子吡啶基 1,3-偶极子进行，该偶极子能够与炔

烃发生自发环加成反应。



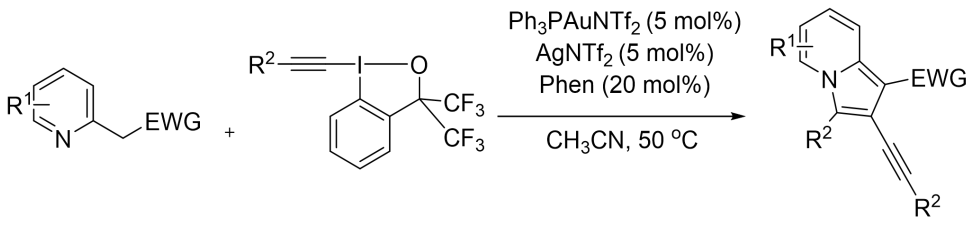
Scheme 1-5

2020 年，Fang 等人[82]通过碘介导的 2-取代吡啶衍生物与丙烯酸酯的碱调控反应，选择性合成 1,3-二取代和 1,2-二取代吲哚嗪。当以 CsOAc 作为碱时，2-取代吡啶衍生物与丙烯酸酯通过一锅法反应生成 1,3-二取代吲哚嗪；而当以 $KHCO_3$ 作为碱时，则促进 C3-碘代吲哚的生成。在铜粉存在下，C3-碘代吲哚进一步发生脱碘反应，最终生成 1,2-二取代吲哚嗪。



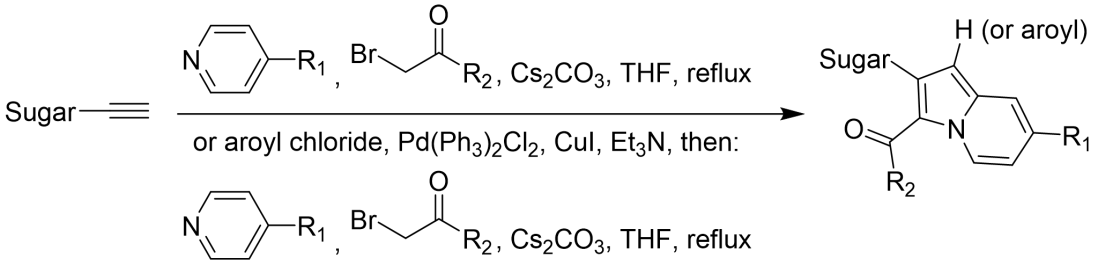
Scheme 1-6

2021 年，Han 等人[83]用高价碘(III)试剂催化 2-取代吡啶的 C(sp3)−H 烷基化/氨基化双金/银催化级联反应合成吲哚嗪。该反应以优异的收率制备了多种功能化的吲哚嗪衍生物。



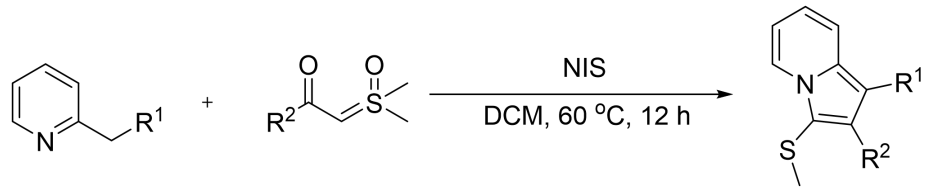
Scheme 1-7

2021 年，Kong 等人[84]通过糖炔、吡啶和α-溴代羰基化合物的一锅三组分偶联反应，成功合成了新型吲哚嗪 C-核苷类似物。该合成方法简便、实用且高效，适用于多种底物。



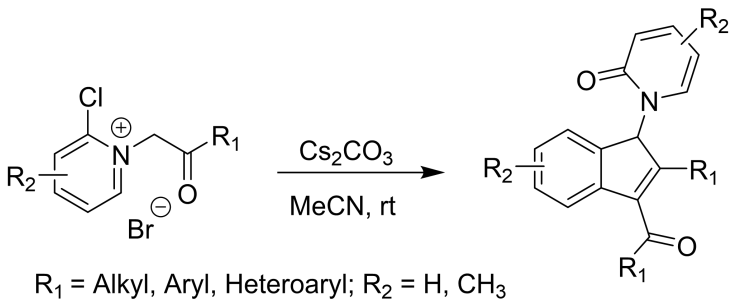
Scheme 1-8

2021 年，Su 等人[85]通过 2-(吡啶-2-基)乙酸酯衍生物和亚砜鎓化物的自由基交叉偶联/环化成功合成了功能化的 1,2,3-三取代吲哚嗪衍生物。该反应经历了 C−H 活化、互变异构、自由基转移、歧化和脱甲基化等过程最终得到了一个从未被合成过的新化合物。



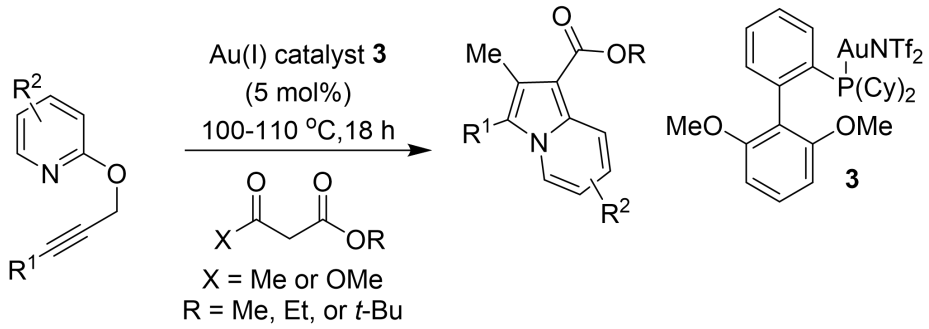
Scheme 1-9

2022 年，Cao 等人[86]通过吡啶鎓盐的自[3+2]环化反应合成了合成 *N*-吲哚嗪取代的吡啶-2(1*H*)-酮类化合物。该方法在温和的反应条件下进行，无需任何贵金属催化剂，以中等至良好的收率获得产物。



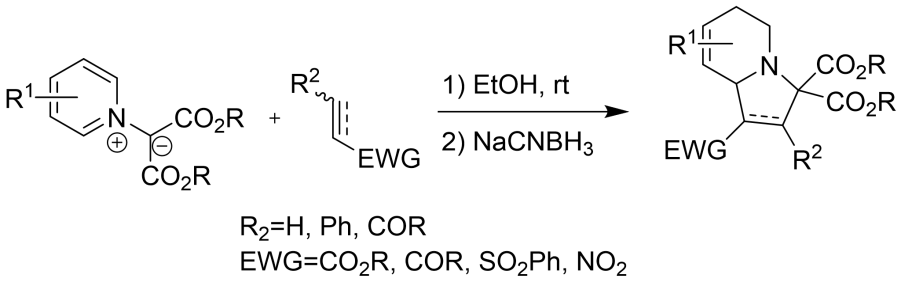
Scheme 1-10

2022 年，Anderson 等人[87]通过金(I)催化的方法，以 2-炔丙氧基吡啶与乙酰乙酸酯或丙二酸二甲酯为原料，成功合成了酯基取代的吲哚嗪类化合物。这些反应对多种官能团具有耐受性，能够在产物的三个不同位置（R、R^1、R^2）实现多样化修饰。



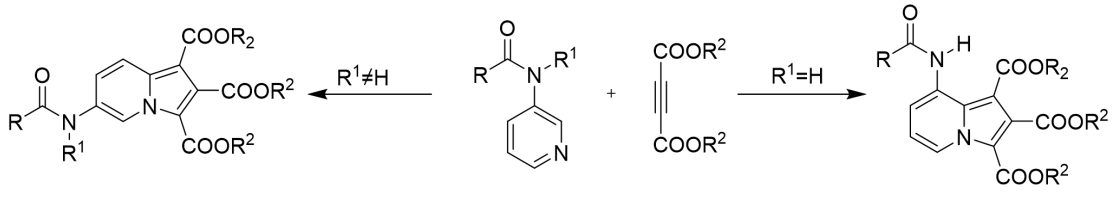
Scheme 1-11

2023 年，Zhou 等人[88]使用 $NaBH_3CN$ 作为还原剂，实现了异喹啉鎓/吡啶鎓叶立德与缺电子烯烃的[3+2]环加成反应构建吲哚嗪。该方法具有广泛的底物适用性和优异的非对映选择性。



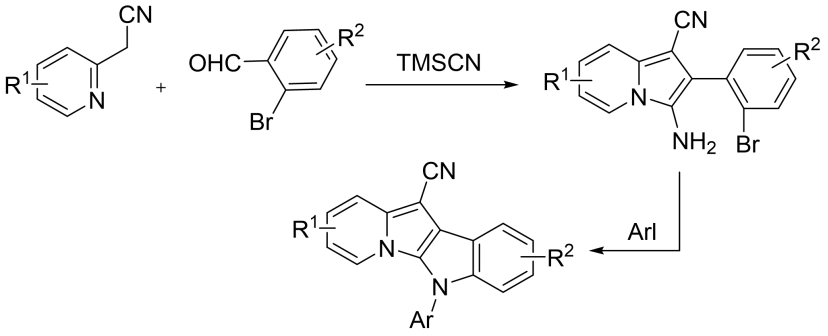
Scheme 1-12

2023 年，Tiwari 等人[89]通过[2+2+1]环加成反应，以间位酰胺取代的吡啶和炔烃为原料，实现了吲哚嗪的区域选择性合成。该反应通过碳碳三键的断裂进行，合成的产物含有重要的酰胺基团，可进一步功能化以制备具有生物活性的化合物。



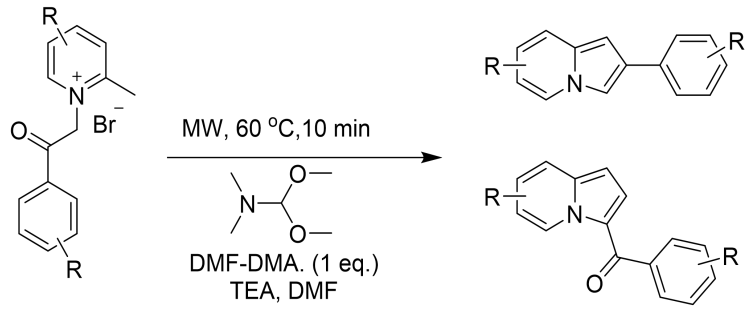
Scheme 1-13

2023 年，Nam 等人[90]发表了有关铜催化的 Ullmann 型双 C−N 偶联反应合成吲哚嗪的方法。作者以 2-吡啶乙腈、2-溴苯甲醛和 TMSCN 为原料，通过一锅三组分组装和铜催化的 Ullmann 型双 C−N 偶联反应的策略组合合成了吲哚嗪衍生物，该方法通过两个步骤形成五个新键。



Scheme 1-14

2023 年，Sumanth 等人[91]通过微波辐射下的双组分反应合成了 3-苯甲酰基吲哚嗪。该方法具有广泛的普适性且在微波辐射下以良好的收率获得目标产物 3-苯甲酰基吲哚嗪。

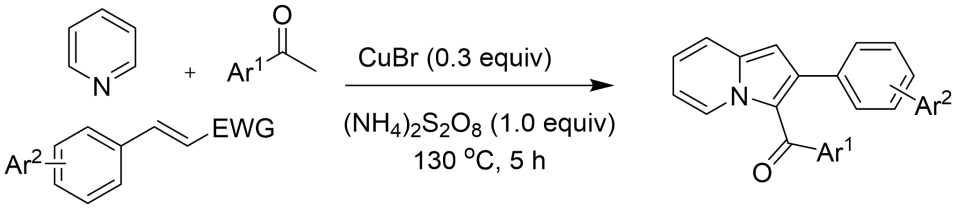


Scheme 1-15

2024 年，Liu 等人[92]开发了一种新颖且灵活的 I_2/BF_3 促进的苯并呋喃酮与吡啶-2-基活性亚甲基化合物的多米诺反应。该方法具有优异的产物选择性、高原子经济性、良好的官能团耐受性等特点，且适用于大规模合成。

Scheme 1-16

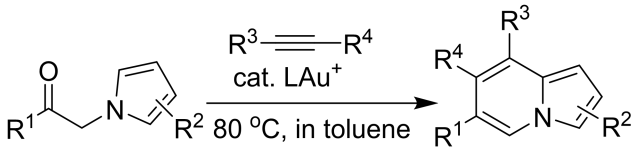
2024 年，Zhang 等人[92]通过铜催化吡啶、苯乙酮和硝基烯烃的反应合成了具有高立体选择性和优异官能团耐受性的新型吲哚嗪化合物。



Scheme 1-17

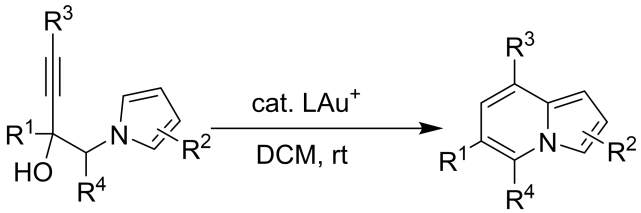
1.5.2 从吡咯衍生物构建吲哚嗪

2016 年，Li 等人[94]通过金催化的级联氢芳基化/环芳构化反应，利用α-(*N*-吡咯基)酮与炔烃合成多取代吲哚嗪。该反应能够在吡啶单元上区域选择性地引入多种官能团。



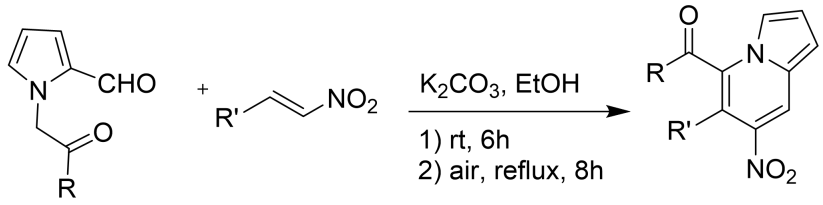
Scheme 1-18

在先前的基础上，他们对反应进行了进一步探索。2017 年，开发了一种金催化的吡咯-炔烃分子内氢芳基化/芳构化反应[95]，简洁直接地合成了功能化吲哚嗪。



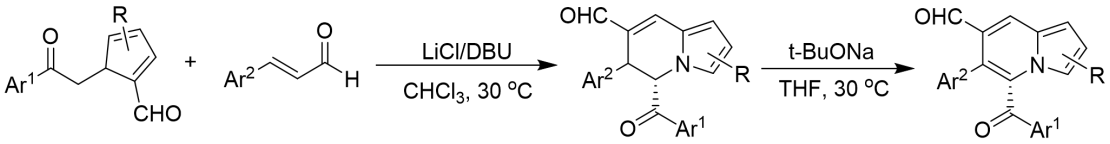
Scheme 1-19

2017 年，Zhong 等人[96]通过吡咯-2-甲醛与硝基乙烯的反应构建吲哚嗪。



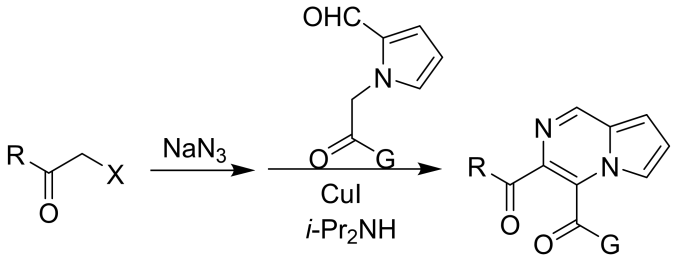
Scheme 1-20

2019 年，Gong 等人[97]通过 1-乙酰芳基 2-甲酰基吡咯与烯醛的 [4+2]环化反应，成功合成了多取代吲哚嗪。该反应无需过渡金属催化，具有条件温和、底物适用性广及官能团兼容性好等特点。



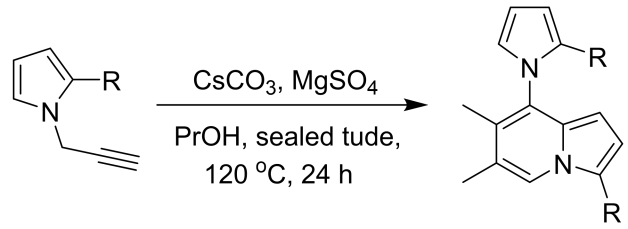
Scheme 1-21

2020 年，Dagar 等人[98]开发了一种温和条件下合成 3,4-二酰基吡咯并[1,2-a]吡嗪的新方法。该方法以α-卤代酮、叠氮化物和 N-取代吡咯-2-甲醛为原料，通过α-亚胺酮原位生成、分子间曼尼希反应、分子内亚胺形成及芳构化等多步串联过程，高效构建了目标分子骨架。



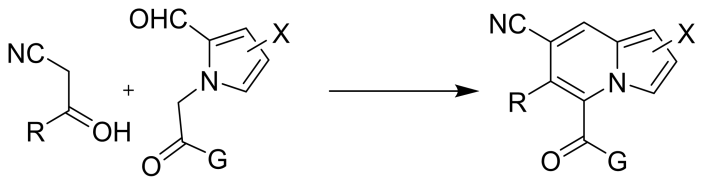
Scheme 1-22

2021 年，Kuzu 等人[99]合成了十种在 C-2 位具有不同取代基的 *N*-炔丙基吡咯衍生物。通过在碱性介质中加热 PrOH，使这些衍生物通过 [2+2]环加成反应转化为吲哚嗪衍生物。



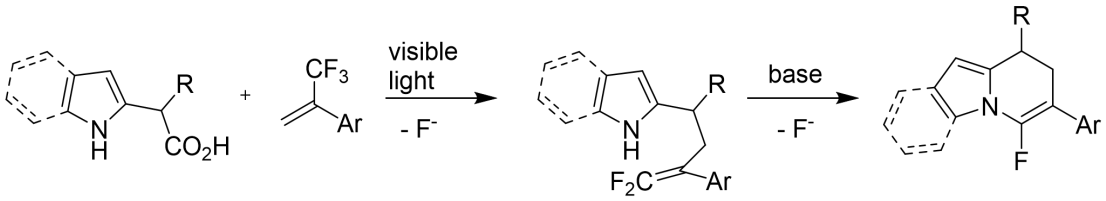
Scheme 1-23

2021 年，Kim 等人[100]通过区域选择性的[4 + 2]环化反应，成功合成了 5-酰基吲哚嗪-7-甲腈类化合物。该方法合成了多种具有多官能化吡啶结构的新型吲哚嗪衍生物，拓展了吲哚嗪的化学空间，为其进一步应用提供了可能。



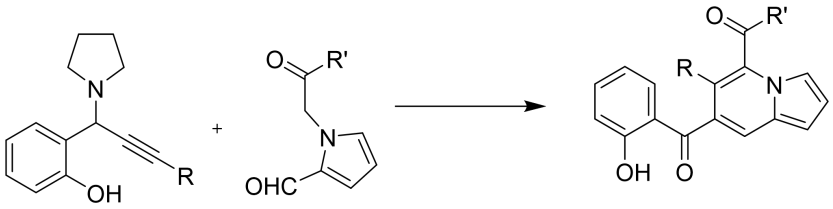
Scheme 1-24

2022 年，Sun 等人[101]报道了一种通过三氟甲基中的双 C–F 键断裂合成 5-氟-二氢吲哚嗪的方法。该反应通过吡咯-2-乙酸与α-三氟甲基烯烃的光催化脱氟偶联反应断裂了第一个 C–F 键，生成了带有未保护吡咯基团的偕二氟烯烃。随后，通过分子内 SNV 反应形成 C–N 键的同时断裂第二个 C–F 键，完成环化反应。



Scheme 1-25

2024 年，Wang 等人[102]通过碱促进吡咯-2-甲醛衍生物与邻羟基苯基炔丙胺氧化[4+2]环化反应，合成了高度取代的吲哚嗪衍生物。



Scheme 1-26

1.6 本课题的研究目的、内容及意义

综上所述，吲哚嗪类化合物在医学、生物学、材料科学、农学等领域有着广泛的应用。因此，吲哚嗪的构建及其性能的研究在有机合成领域备受关注。目前，已有文献报道了吲哚嗪骨架的构建，尽管有些方法能高效构建吲哚嗪，但仍存在不同程度的局限性。例如，起始原料来源困难；部分反应条件苛刻，需要在高温下进行；使用大量促进剂或价格昂贵的催化剂；反应机理单一，大部分都是通过环加成反应得到吲哚嗪衍生物。此外，直接合成具有多种官能团（如酯基、三氟甲基、氰基和酮羰基）的吲哚嗪核心结构仍然极为罕见。基于上述局限性，开发一种使用常规原料和廉价催化剂、操作简单高效且环境友好的新型合成方法，用于构建多种功能化的吲哚嗪，已成为当前研究的迫切需求。另一方面，亚烷基氧化吲哚和不饱和异噁唑已被证明是有机合成中的多功能合成子，而以吡啶衍生物为原料是构建吲哚嗪的常用思路，且本课题组已经发表了多篇螺环化/芳构化构建含氮杂环的文章。因此，我们便对以亚烷基氧化吲哚、不饱和异噁唑和 2-取代吡啶衍生物为原料的螺环化/芳构化反应进行了深入研究，旨在开发一种新型的、高效的吲哚嗪合成方法。该方法将利用廉价易得的原料和催化剂，在温和条件下实现吲哚嗪骨架的构建。同时也探索了其反应机理和应用潜力，为吲哚嗪类化合物的合成提供新的思路。

基于以上思路，本论文主要研究了 1）亚烷基氧化吲哚与 2-(吡啶-2-基)乙酸酯衍生物的反应；2）不饱和异噁唑酮与 2-(吡啶-2-基)乙酸酯衍生物在球磨条件下的反应。上述两种方法具有操作简便、反应条件温和、收率高以及环境友好等显著优势，为构建结构多样化的吲哚嗪骨架提供了新的合成策略。

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第 2 章 烷叉氧化吲哚与 2-烷基吡啶的螺环化/芳构化反应研究

2.1 实验部分

2.1.1 仪器与试剂

Table 2-1. Main experimental instrument

仪器名称	型号	生产厂家
核磁共振（NMR）波谱仪	AVANCE ONE（500 MHz）	德国布鲁克科技有限公司
高分辨质谱仪	ORBITRAP EXPLORIS 120	赛默飞世尔科技（中国）有限公司
集热式恒温加热磁力搅拌器	DF-101D	巩义市予华仪器有限责任公司
低温冷却液循环泵	DLSB-5L/20	巩义市予华仪器有限责任公司
循环水式真空泵	SHZ-D	巩义市予华仪器有限责任公司
旋片式真空泵	2XZ-2	上海雅潭真空设备有限公司
旋转蒸发仪	41K30RA-C	巩义市予华仪器有限责任公司
电子天平	PX224ZH/E	奥豪斯仪器（常州）有限公司
电热鼓风干燥箱	CZX-9146 MBE	上海博讯实业有限公司医疗设备厂
真空干燥箱	DZF-6020	上海一恒科学仪器有限公司
手提式紫外分析仪	ZF-7A	骥辉分析仪器（上海）有限公司
X-射线单晶衍射仪	SMART APEX CCD	美国 Bruker 公司
熔点仪	WRS-3	上海仪电物理光学仪器有限公司

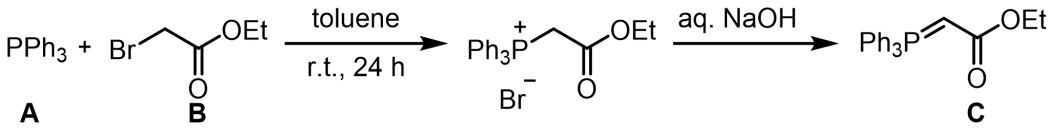
Table 2-2. Main experimental chemicals

试剂名称	规格	生产厂家

靛红	分析纯	国药集团化学试剂有限公司
溴乙酸乙酯	分析纯	萨恩化学技术（上海）有限公司
氢氧化钠	分析纯	国药集团化学试剂有限公司
乙酸酐	分析纯	国药集团化学试剂有限公司
2-吡啶乙酸乙酯	分析纯	安徽泽升科技有限公司
吡啶-2-乙腈	分析纯	安徽泽升科技有限公司
1-吡啶-2-基-2-丙酮	分析纯	安徽泽升科技有限公司
3-溴-2-吡啶乙酸乙酯	分析纯	安徽泽升科技有限公司
5-溴-2-吡啶乙酸乙酯	分析纯	安徽泽升科技有限公司
三苯基膦	分析纯	国药集团化学试剂有限公司
常规溶剂	分析纯	国药集团化学试剂有限公司
活性炭	化学纯	国药集团化学试剂有限公司
薄层层析硅胶（400 目）	化学纯	青岛海洋化工有限公司
柱层层析硅胶（200-300 目）	化学纯	青岛海洋化工有限公司

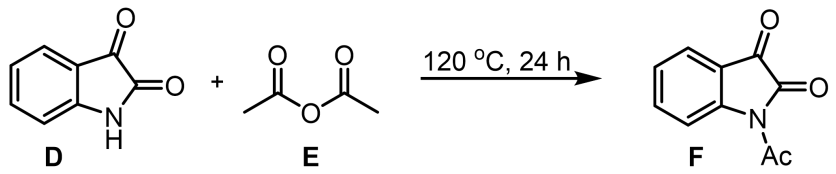
2.1.2 原料的合成

（1）磷叶立德的制备



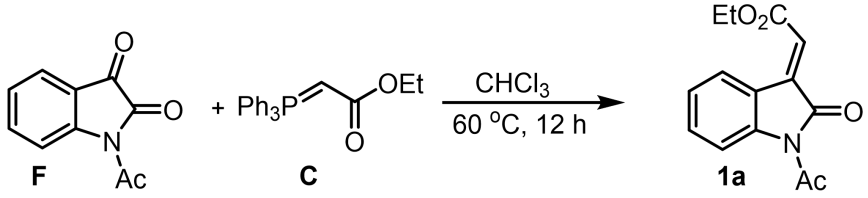
Scheme 2-1

（2）*N*-乙酰基靛红的制备



Scheme 2-2

（3）亚烷基氧化吲哚的制备

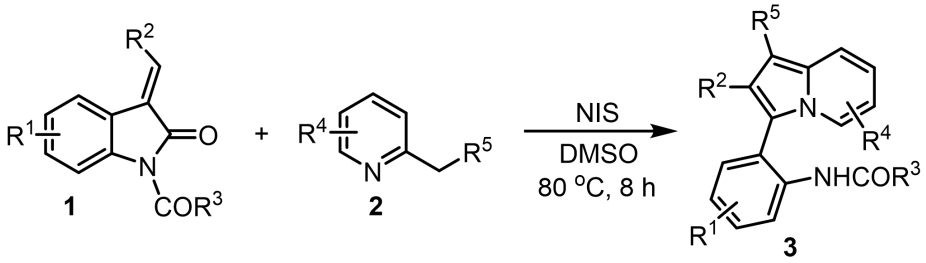


Scheme 2-3

以合成 **1a** 为例，（1）将三苯基膦 **A**（5.24 g，20 mmol）、溴乙酸乙酯 **B**（20 mmol）和甲苯（40 mL）加入 100 mL 反应瓶中，常温反应 24 小时。反应后抽滤，用乙酸乙酯（50 mL）洗涤滤饼。将白色固体溶于二氯甲烷（100 mL），加入 4N 氢氧化钠水溶液（200 mL），搅拌后分离有机层。水相用二氯甲烷（2 × 50 mL）萃取，合并有机相并用无水硫酸钠干燥，浓缩后得膦叶立德试剂 **C**。（2）将靛红 **D**（20 mmol）与乙酸酐 **E**（50 mL）在 120 °C 反应 12 小时。冷却后倒入水（200 mL）中，搅拌析出固体，抽滤并水洗，真空干燥得 N-乙酰基靛红粗产物 **F**。（3）将 N-乙酰基靛红 **F**（10 mmol）与膦叶立德试剂 **C**（3.83 g，11 mmol）在氯仿（50 mL）中 60 °C 反应 12 小时。反应后加入硅胶旋干，柱色谱分离（石油醚/乙酸乙酯=8:1），粗产物经乙醇重结晶得纯净亚烷基氧化吲哚 **1a**。

其他亚烷基氧化吲哚的合成步骤参考 **1a**。

2.1.3 产物的合成



Scheme 2-4 Synthesis of Compound **3**

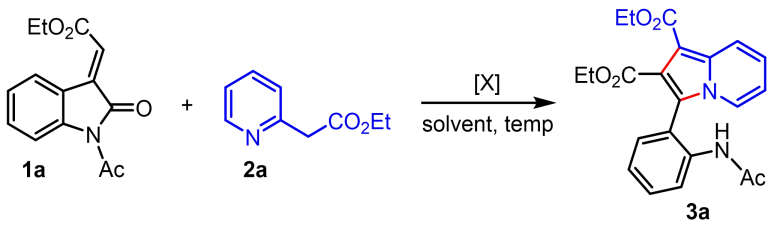
以合成 **3a** 为例，在 25 mL 试管中，将亚烷基氧化吲哚 **1a**（0.3 mmol）、2-吡啶乙酸乙酯 **2a**（0.3 mmol，1.0 当量）、NIS（0.3 mmol、1.0 当量）和 DMSO（3 mL）混合，并在空气中油浴锅加热到 80 °C 搅拌 8 小时。冷却后，用饱和 NaCl 水溶液（20 mL）洗涤反应混合物，用乙酸乙酯（3×10 mL）萃取。然后，将合并的有机相用无水 Na_2SO_4 干燥并真空浓缩。残余物通过硅胶柱色谱法分离，用乙酸乙酯/石油醚作为洗脱剂（PE:EA = 2:1），得到产物 **3a**,产率为 83%。

2.2 实验结果与讨论

2.2.1 条件优化

选择亚烷基氧化吲哚 **1a** 和 2-吡啶乙酸乙酯 **2a** 作为模型底物，探索反应条件。首先，在 50 ºC 下，**1a** 和 **2a** 以 NIS（1.0 当量）作为卤化剂，以 1,2-二氯乙烷（DCE）作为溶剂试验反应（Table 2-3, entry 1）。我们成功获得了所需的吲哚嗪衍生物 **3a**，产率为 49%。有了这一结果我们随后尝试了其他卤化剂，包括 N-溴琥珀酰亚胺（NBS）、N-氯琥珀酰胺（NCS）、I_2 和 $PhI(OAc)_2$（Table 2-3, entries 2–5）。但是使用这些卤代剂的结果不尽如人意，目标产物的收率很低。为了进一步优化反应条件，我们将 NIS 增加到 1.2 当量，但产物收率与 1.0 当量相差无几（Table 2-3, entry 6 vs. entry 1），这个结果表明 1.0 当量的 NIS 足以用于该反应。同样地，增加 **2a** 的量并没有提高目标产物 **3a** 的收率（Table 2-3, entry 7）。接下来，在保持 **1a**、**2a** 和 NIS 的摩尔比为 1:1:1 的条件下，我们研究了该反应的溶剂效应（Table 2-3, entries 8–13）。我们发现当以 DMSO 作为溶剂时，**3a** 的收率提高到 63%（Table 2-3, entry 13），而其他溶剂如乙醇、四氢呋喃（THF）、乙腈、甲苯和 *N*，*N*-二甲基甲酰胺（DMF）的收率较低（Table 2-3, entries 8–12）。随后，我们优化了反应温度。降低温度导致产品收率显著降低（Table 2-3, entry 14），这促使我们对更高温度进行探索。令人高兴的是，当反应在 60 ºC 下进行时，**3a** 的收率略微提高到 68%（Table 2-3, entry 15）。进一步将反应温度提高到 80 ºC，在更短的反应时间内得到了更高收率的 **3a**，收率为 83%（Table 2-3, entry 16）。然而，在 100 ºC 下进行反应并没有进一步提高收率（Table 2-3, entry 17）。接下来，我们在优化条件下使用化学计量或催化量的 I_2 进行反应，但这两种情况下的收率均显著降低（Table 2-3, entries 18 and 19）。基于这些结果，我们确定了以下最佳反应条件：**1a**、**2a**（1.0 当量）和 NIS（1.0 当量）在 DMSO 中于 80 ºC 下反应 8 小时（Table 2-3, entry 16）。

Table 2-3. Optimization of the reaction conditions[a]



entry	[X] (equiv)	solvent	temp (℃)	time (h)	yield[b] (%)
1	NIS (1.0)	DCE	50	20	49
2	NBS (1.0)	DCE	50	20	trace
3	NCS (1.0)	DCE	50	20	trace
4	I_2 (1.0)	DCE	50	20	13
5	$PhI(OAc)_2$(1.0)	DCE	50	20	trace
6	NIS (1.2)	DCE	50	20	46
7[c]	NIS (1.0)	DCE	50	20	47
8	NIS (1.0)	EtOH	50	20	20
9	NIS (1.0)	THF	50	20	36
10	NIS (1.0)	MeCN	50	20	32
11	NIS (1.0)	toluene	50	20	30
12	NIS (1.0)	DMF	50	20	43
13	NIS (1.0)	DMSO	50	20	63
14	NIS (1.0)	DMSO	30	24	42
15	NIS (1.0)	DMSO	60	15	68
16	NIS (1.0)	DMSO	80	8	83
17	NIS (1.0)	DMSO	100	8	83
18	I_2 (1.0)	DMSO	80	8	57
19	I_2 (0.2)	DMSO	80	8	8

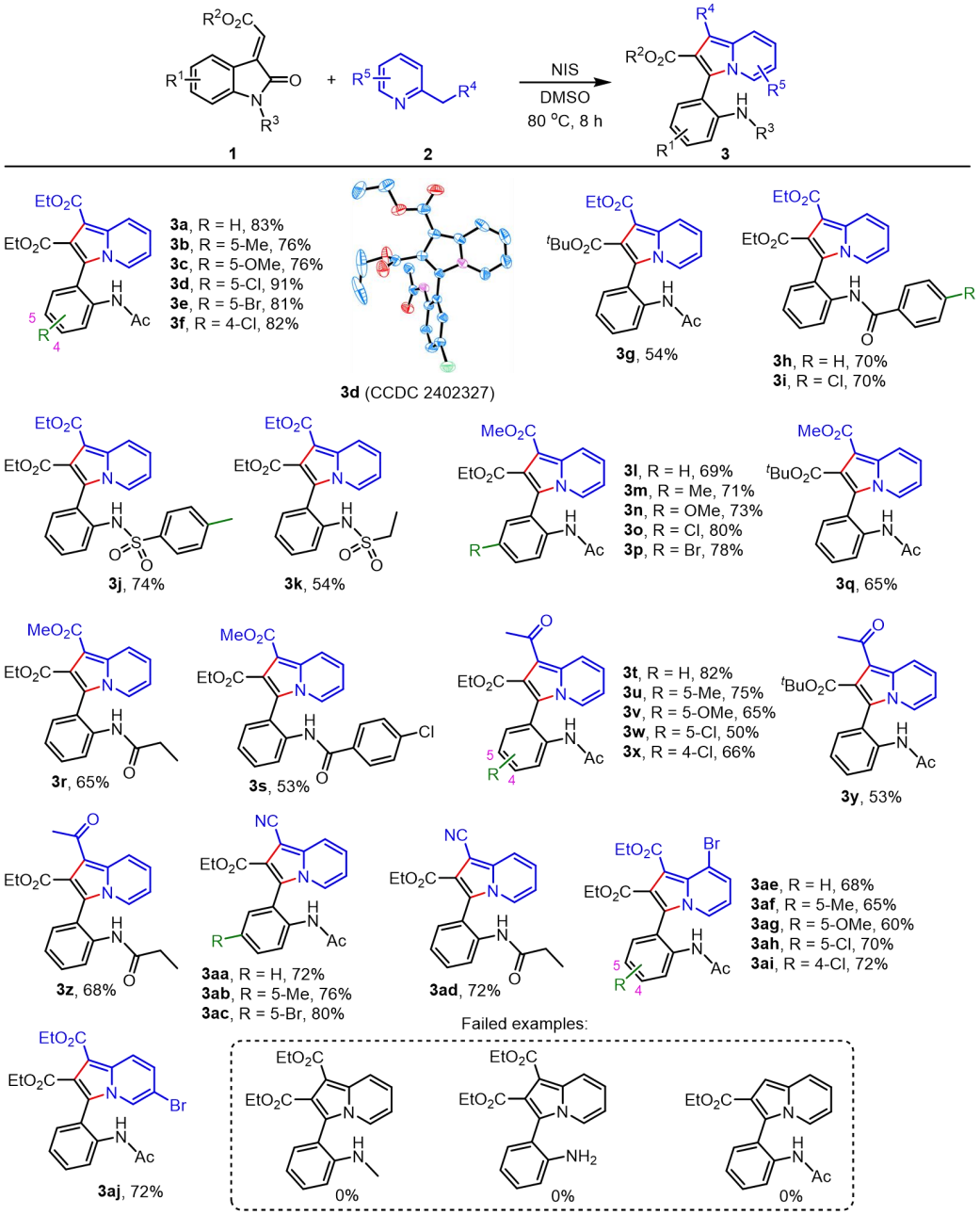
[a] Unless otherwise noted, the reaction conditions were as follows: **1a** (0.30 mmol), **2a** (0.30 mmol), and halogenating agent in solvent (3 mL) were stirred at the designated temperature. [b]Isolated yields based on **1a**. [c]Using 1.2 equiv of **2a**.

2.2.2 底物拓展

在确定最佳反应条件后，我们进一步探索了螺环化/开环芳构化反应的普适性，结果总结于表 2-4 中。首先，对一系列亚烷基氧化吲哚 **1** 进行了研究。在最佳反应条件下，苯环上带有不同取代基（包括 Me、OMe、Cl 和 Br）的亚烷基氧化吲哚与 **2a** 顺利反应，得到相应的芳构化产物 **3b–f**，收率为 76–91%。将亚烷基氧化吲哚中的乙酯基团替换为叔丁酯基团不会阻碍反应，以 54%的收率得到目标产物 **3g**。此外，苯甲酰基和对氯苯甲酰基取代的亚烷基氧化吲哚在该转化中表现出良好的耐受性，分别以良好收率生成产物 **3h** 和 **3i**。氮原子上带有磺酰基的亚烷基氧化吲哚在该转化中也表现出良好的反应性。接下来，我们研究了反应物 **2** 的范围。在标准条件下，2-吡啶乙酸甲酯与亚烷基氧化吲哚 **1** 反应，高效制备了多种吲哚嗪 **3l–s**。值得注意的是，2-吡啶丙酮和 2-吡啶乙腈也

表现出良好的反应性，以 50–82%的收率得到吲哚嗪 **3t**–**ad**。此外，吡啶环上含有取代基的底物也能有效反应，以 60–72%的产率得到产物 **3ae**–**aj**。在底物的探索中我们发现 *N*-甲基和 *N*-无保护的亚烷基氧化吲哚与 2-甲基吡啶在标准条件下未能反应生成相应产物，且起始原料未被消耗。

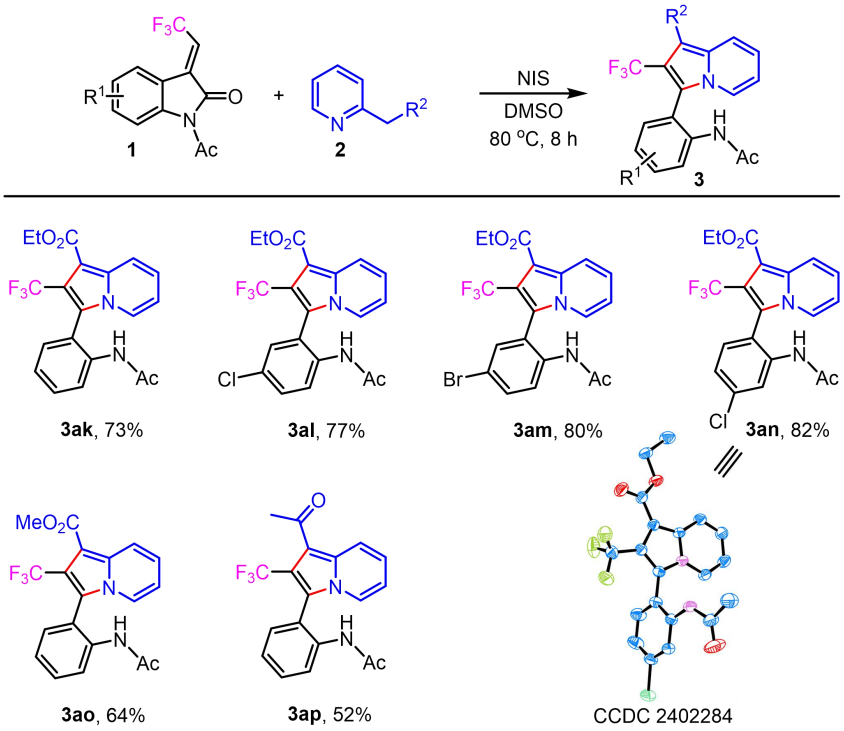
Table 2-4. NIS-Promoted Reactions of Ester Group-Substituted Alkylidene Oxindoles with 2-(Pyridin-2-yl)acetate Derivatives[a,b]



[a] Reaction conditions: A mixture of **1** (0.3 mmol), **2** (0.3 mmol), NIS (0.3 mmol), and DMSO (3 mL) was stirred at 80 °C in air for 8 h. [b] Isolated yields based on **1**.

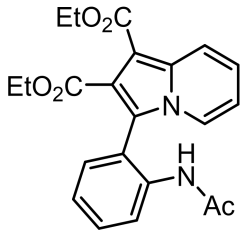
含三氟甲基的分子在药物开发中具有重要价值，2023 年最畅销的 200 种小分子药物中，21 种含有三氟甲基[103-105]。基于此，我们探索了利用三氟甲基取代的氧化吲哚合成含三氟甲基的吲哚嗪（Table 2-5）。值得注意的是，三氟甲基取代的氧化吲哚在该多米诺反应中表现出优异的相容性和高反应性，能够以中等至良好的产率高效合成一系列含三氟甲基的吲哚嗪 **3ak**–**ap**。这些结果表明该方案具有广泛的适用性，展现了其对不同底物和官能团的良好适应性。

Table 2-5. NIS-Promoted Reactions of Trifluoromethyl-Substituted Alkylidene Oxindoles with 2-(Pyridin-2-yl)acetate Derivatives[a,b]



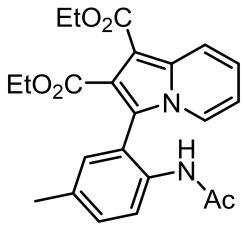
[a] Reaction conditions: A mixture of **1** (0.3 mmol), **2** (0.3 mmol), NIS (0.3 mmol), and DMSO (3 mL) was stirred at 80 °C in air for 8 h. [b] Isolated yields based on **1**.

2.3 化合物表征

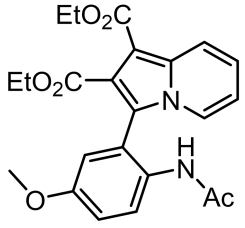


Diethyl 3-(2-Acetamidophenyl)indolizine-1,2-dicarboxylate (3a). Ethyl acetate/petroleum ether = 1:2 as the eluent; Yellow solid, 83% yield (98.6 mg), mp

127–129 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.24 (d, J = 9.2 Hz, 1H), 8.15 (d, J = 8.2 Hz, 1H), 8.03 (s, 1H), 7.62 (d, J = 7.0 Hz, 1H), 7.52 (td, J = 7.8, 1.3 Hz, 1H), 7.31 (d, J = 6.5 Hz, 1H), 7.26 (t, J = 7.4 Hz, 1H), 7.17 (dd, J = 8.5, 6.9 Hz, 1H), 6.73 (td, J = 6.8, 0.9 Hz, 1H), 4.45–4.34 (m, 2H), 4.27 (q, J = 7.1 Hz, 2H), 1.98 (s, 3H), 1.41 (t, J = 7.1 Hz, 3H), 1.22 (t, J = 7.2 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.0, 167.0, 163.8, 137.7, 135.8, 131.9, 130.9, 125.1, 124.4, 124.19, 124.17, 123.2, 120.5, 120.3, 120.2, 113.8, 102.2, 61.9, 60.2, 24.5, 14.6, 14.0; HRMS (ESI-TOF) calcd for $C_{22}H_{22}N_2O_5Na$ $[M + Na]^+$ 417.1426, found 417.1428.

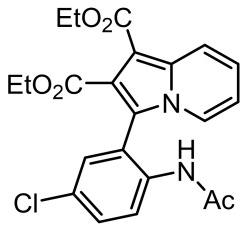


Diethyl 3-(2-Acetamido-5-methylphenyl)indolizine-1,2-dicarboxylate (3b). Ethyl acetate/petroleum ether = 1:2 as the eluent; Yellow solid, 76% yield (93.1 mg), mp 142–144 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.24 (d, J = 9.2 Hz, 1H), 7.98 (d, J = 8.3 Hz, 1H), 7.92 (s, 1H), 7.64 (d, J = 7.1 Hz, 1H), 7.32 (dd, J = 8.4, 1.7 Hz, 1H), 7.16 (ddd, J = 9.0, 6.6, 0.6 Hz, 1H), 7.12 (s, 1H), 6.72 (td, J = 6.8, 1.1 Hz, 1H), 4.45–4.34 (m, 2H), 4.28 (q, J = 7.1 Hz, 2H), 2.35 (s, 3H), 1.96 (s, 3H), 1.41 (t, J = 7.1 Hz, 3H), 1.24 (t, J = 7.2 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.0, 167.1, 163.8, 135.8, 135.2, 135.0, 132.1, 131.6, 124.6, 124.4, 124.1, 123.1, 120.9, 120.4, 120.3, 113.8, 102.2, 61.9, 60.2, 24.4, 20.9, 14.6, 14.0; HRMS (ESI-TOF) calcd for $C_{23}H_{24}N_2O_5Na$ $[M + Na]^+$ 431.1583, found 431.1588.

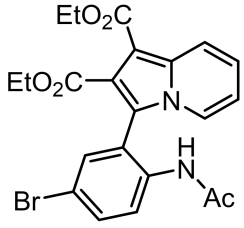


Diethyl 3-(2-Acetamido-5-methoxyphenyl)indolizine-1,2-dicarboxylate (3c). Ethyl acetate/petroleum ether = 1:1 as the eluent; Orange solid, 76% yield (97.0 mg), mp

130–132 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.23 (d, J = 9.1 Hz, 1H), 7.96 (s, 1H), 7.91 (d, J = 9.0 Hz, 1H), 7.69 (d, J = 6.9 Hz, 1H), 7.17 (t, J = 8.3 Hz, 1H), 7.07 (dd, J = 8.9, 2.2 Hz, 1H), 6.86 (s, 1H), 6.74 (t, J = 6.7 Hz, 1H), 4.45–4.33 (m, 2H), 4.29 (q, J = 7.1 Hz, 2H), 3.80 (s, 3H), 1.93 (s, 3H), 1.41 (t, J = 7.1 Hz, 3H), 1.25 (t, J = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.1, 167.1, 163.7, 156.8, 135.7, 130.6, 126.8, 124.3, 124.1, 122.9, 122.3, 120.7, 120.2, 116.5, 116.3, 113.8, 102.1, 61.9, 60.1, 55.6, 24.1, 14.5, 14.0; HRMS (ESI-TOF) calcd for $C_{23}H_{25}N_2O_6$ $[M + H]^+$ 425.1713, found 425.1710.

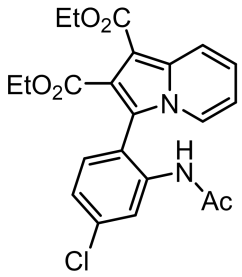


Diethyl 3-(2-Acetamido-5-chlorophenyl)indolizine-1,2-dicarboxylate (3d). Ethyl acetate/petroleum ether = 1:1 as the eluent; Yellow solid, 91% yield (117.1 mg), mp 153–155 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.25 (d, J = 9.2 Hz, 1H), 8.14 (d, J = 8.9 Hz, 1H), 8.01 (s, 1H), 7.64 (d, J = 7.1 Hz, 1H), 7.48 (dd, J = 8.9, 2.4 Hz, 1H), 7.31 (d, J = 2.4 Hz, 1H), 7.20 (dd, J = 8.7, 7.0 Hz, 1H), 6.78 (t, J = 6.5 Hz, 1H), 4.45–4.34 (m, 2H), 4.29 (q, J = 7.1 Hz, 2H), 1.99 (s, 3H), 1.41 (t, J = 7.1 Hz, 3H), 1.26 (t, J = 7.2 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.0, 166.9, 163.6, 136.5, 135.9, 131.5, 130.9, 130.0, 125.6, 124.4, 124.0, 123.6, 121.7, 120.4, 118.9, 114.2, 102.6, 62.1, 60.3, 24.5, 14.6, 14.0; HRMS (ESI-TOF) calcd for $C_{22}H_{21}{}^{35}ClN_2O_5Na$ $[M + H]^+$ 451.1037, found 451.1039.

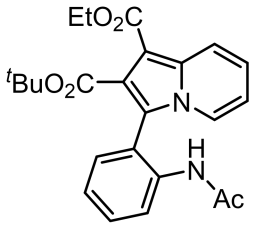


Diethyl 3-(2-Acetamido-5-bromophenyl)indolizine-1,2-dicarboxylate (3e). Ethyl acetate/petroleum ether = 1:2 as the eluent; White solid, 81% yield (114.8 mg), mp

162–164 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.25 (d, J = 9.2 Hz, 1H), 8.09 (d, J = 8.9 Hz, 1H), 8.01 (s, 1H), 7.65–7.60 (m, 2H), 7.46 (d, J = 2.4 Hz, 1H), 7.20 (ddd, J = 9.1, 6.7, 0.9 Hz, 1H), 6.78 (td, J = 6.9, 1.2 Hz, 1H), 4.44–4.34 (m, 2H), 4.33–4.26 (m, 2H), 1.98 (s, 3H), 1.41 (t, J = 7.2 Hz, 3H), 1.26 (t, J = 7.2 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.0, 166.9, 163.6, 137.0, 136.0, 134.4, 133.8, 125.8, 124.4, 124.0, 123.6, 122.0, 120.4, 118.8, 117.5, 114.2, 102.6, 62.2, 60.3, 24.5, 14.6, 14.0; HRMS (ESI-TOF) calcd for $C_{22}H_{21}{}^{79}BrN_2O_5Na$ $[M + H]^+$ 495.0532, found 495.0526.

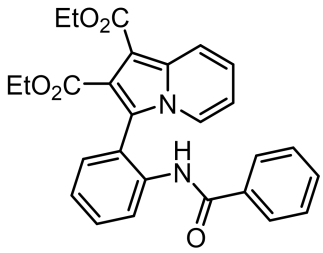


Diethyl 3-(2-Aacetamido-4-chlorophenyl)indolizine-1,2-dicarboxylate (3f). Ethyl acetate/petroleum ether = 1:2 as the eluent; White solid, 82% yield (105.2 mg), mp 173–175 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.30 (s, 1H), 8.25 (d, J = 8.9 Hz, 1H), 8.03 (s, 1H), 7.60 (d, J = 6.9 Hz, 1H), 7.24 (s, 2H), 7.19 (t, J = 7.7 Hz, 1H), 6.76 (t, J = 6.7 Hz, 1H), 4.45–4.33 (m, 2H), 4.28 (q, J = 7.1 Hz, 2H), 2.00 (s, 3H), 1.41 (t, J = 7.1 Hz, 3H), 1.25 (t, J = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.9, 166.9, 163.6, 138.9, 136.7, 136.0, 132.8, 125.1, 124.3, 123.95, 123.88, 123.5, 120.4, 119.1, 117.9, 114.1, 102.5, 62.1, 60.2, 24.6, 14.6, 14.0; HRMS (ESI-TOF) calcd for $C_{22}H_{21}{}^{35}ClN_2O_5Na$ $[M + Na]^+$ 451.1037, found 451.1036.

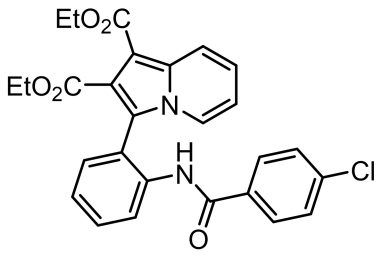


2-(***tert*-Butyl) 1-Ethyl 3-(2-Acetamidophenyl)indolizine-1,2-dicarboxylate (3g).** Ethyl acetate/petroleum ether = 1:2 as the eluent; Pea-green solid, 54% yield (68.5 mg), mp 143–145 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.25 (d, J = 9.2 Hz, 1H), 8.22 (d,

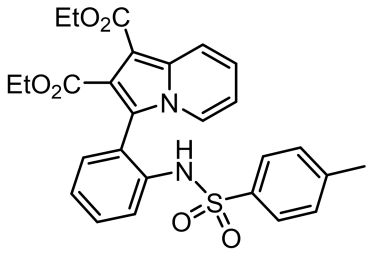
J = 8.5 Hz, 1H), 7.68 (s, 1H), 7.59 (d, *J* = 7.0 Hz, 1H), 7.53 (td, *J* = 7.8, 1.4 Hz, 1H), 7.32 (d, *J* = 7.6 Hz, 1H), 7.26 (t, *J* = 7.5 Hz, 1H), 7.15 (dd, *J* = 9.1, 6.7 Hz, 1H), 6.71 (t, *J* = 6.8 Hz, 1H), 4.41 (q, *J* = 7.1 Hz, 2H), 1.96 (s, 3H), 1.42 (t, *J* = 7.1 Hz, 3H), 1.38 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.9, 165.5, 163.9, 137.9, 135.8, 131.9, 130.9, 124.90, 124.87, 124.1, 124.0, 123.6, 120.4, 120.14, 120.07, 113.8, 102.0, 82.6, 60.2, 27.9 (3C), 24.6, 14.7; HRMS (ESI-TOF) calcd for $C_{24}H_{27}N_2O_5$ $[M + H]^+$ 423.1920, found 423.1915.



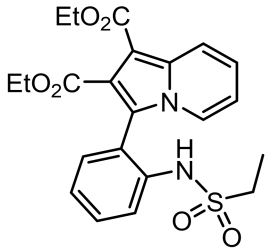
Diethyl 3-(2-Benzamidophenyl)indolizine-1,2-dicarboxylate (3h). Ethyl acetate/petroleum ether = 1:2 as the eluent; Yellow solid, 70% yield (96.2 mg), mp 139–141 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.96 (s, 1H), 8.29 (d, *J* = 8.3 Hz, 1H), 8.21 (d, *J* = 9.2 Hz, 1H), 7.72 (dd, *J* = 7.8, 0.9 Hz, 2H), 7.64 (d, *J* = 7.1 Hz, 1H), 7.58 (td, *J* = 7.6, 1.3 Hz, 1H), 7.43 (t, *J* = 7.4 Hz, 1H), 7.39–7.27 (m, 4H), 7.10 (td, *J* = 7.9, 1.4 Hz, 1H), 6.66 (t, *J* = 6.9 Hz, 1H), 4.40 (q, *J* = 7.1 Hz, 2H), 4.30 (q, *J* = 7.1 Hz, 2H), 1.41 (t, *J* = 7.1 Hz, 3H), 1.22 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.1, 165.6, 163.6, 137.9, 135.7, 134.1, 131.9, 131.8, 130.8, 128.6 (2C), 127.1 (2C), 125.3, 124.9, 124.11, 124.07, 123.0, 120.9, 120.7, 120.1, 113.8, 102.1, 61.9, 60.0, 14.5, 13.9; HRMS (ESI-TOF) calcd for $C_{27}H_{24}N_2O_5Na$ $[M + Na]^+$ 479.1583, found 479.1582.



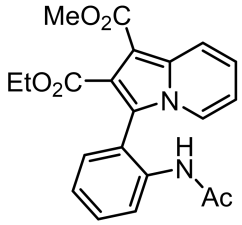
Diethyl 3-(2-(4-Chlorobenzamido)phenyl)indolizine-1,2-dicarboxylate (3i). Ethyl acetate/petroleum ether = 1:3 as the eluent; White solid, 70% yield (89.4 mg), mp 101–103 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.10 (s, 1H), 8.24 (d, J = 8.3 Hz, 1H), 8.21 (d, J = 9.2 Hz, 1H), 7.71 (d, J = 8.4 Hz, 2H), 7.65 (d, J = 7.1 Hz, 1H), 7.59 (t, J = 7.7 Hz, 1H), 7.40–7.29 (m, 4H), 7.13 (dd, J = 8.5, 7.2 Hz, 1H), 6.69 (t, J = 6.9 Hz, 1H), 4.41 (q, J = 7.1 Hz, 2H), 4.32 (q, J = 7.1 Hz, 2H), 1.42 (t, J = 7.1 Hz, 3H), 1.24 (t, J = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.6, 164.7, 163.7, 138.2, 137.8, 135.8, 132.7, 132.0, 131.0, 129.0 (2C), 128.8 (2C), 125.6, 125.2, 124.2 (2C), 123.0, 121.1, 120.6, 120.3, 113.9, 102.2, 62.2, 60.2, 14.6, 14.0; HRMS (ESI-TOF) calcd for $C_{27}H_{23}{}^{35}ClN_2O_5Na$ $[M + Na]^+$ 513.1193, found 513.1187.



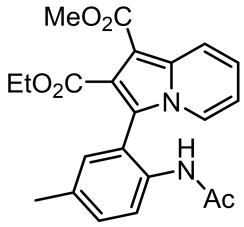
Diethyl 3-(2-((4-Methylphenyl)sulfonamido)phenyl)indolizine-1,2-dicarboxylate (3j). Ethyl acetate/petroleum ether = 1:2 as the eluent; Light yellow solid, 74% yield (112.7 mg), mp 175–177 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.49 (s, 1H), 8.17 (d, J =9.1 Hz, 1H), 7.81 (d, J = 8.2 Hz, 1H), 7.52 (t, J = 7.8 Hz, 1H), 7.30 (t, J = 7.5 Hz, 1H), 7.21 (d, J = 8.2 Hz, 2H), 7.17 (d, J = 7.6 Hz, 1H), 7.06 (dd, J = 9.0, 6.7 Hz, 1H), 6.97 (d, J = 7.1 Hz, 1H), 6.74 (d, J = 8.1 Hz, 2H), 6.42 (t, J = 6.8 Hz, 1H), 4.43 (q, J = 7.1 Hz, 2H), 4.34–4.24 (m, 2H), 2.16 (s, 3H), 1.44 (t, J = 7.1 Hz, 3H), 1.25 (t, J = 7.2 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.4, 163.6, 142.8, 136.8, 136.3, 135.6, 131.8, 131.1, 129.0 (2C), 128.2, 126.7, 126.1 (2C), 123.64, 123.58, 123.55, 122.0, 120.3, 120.0, 113.4, 102.3, 62.2, 60.2, 21.5, 14.6, 13.8; HRMS (ESI-TOF) calcd for $C_{27}H_{27}N_2O_6S$ $[M + H]^+$ 507.1590, found 507.1592.



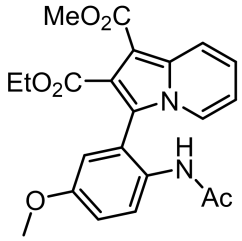
Diethyl 3-(2-(Ethylsulfonamido)phenyl)indolizine-1,2-dicarboxylate (3k). Ethyl acetate/petroleum ether = 1:3 as the eluent; Light yellow solid, 68% yield (90.5 mg), mp 131–133 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.26 (d, J = 9.2 Hz, 1H), 7.76 (d, J = 8.2 Hz, 1H), 7.59 (d, J = 7.1 Hz, 1H), 7.54 (ddd, J = 8.8, 6.7, 2.5 Hz, 1H), 7.36–7.30 (m, 2H), 7.26 (s, 1H), 7.18 (ddd, J = 8.9, 6.7, 0.7 Hz, 1H), 6.76 (td, J = 7.0, 1.0 Hz, 1H), 4.44–4.35 (m, 2H), 4.31–4.21 (m, 2H), 2.97 (dq, J = 14.7, 7.4 Hz, 1H), 2.79 (dq, J = 14.7, 7.4 Hz, 1H), 1.41 (t, J = 7.1 Hz, 3H), 1.23 (t, J = 7.2 Hz, 3H), 0.99 (t, J = 7.4 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.5, 163.6, 137.4, 135.8, 132.6, 131.5, 125.8, 124.1, 123.6, 123.5, 123.2, 121.6, 120.5, 120.2, 114.2, 102.6, 61.9, 60.2, 46.7, 14.5, 13.9, 7.7; HRMS (ESI-TOF) calcd for $C_{22}H_{25}N_2O_6S$ $[M + H]^+$ 445.1433, found 445.1439.



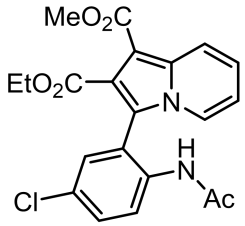
2-Ethyl 1-Methyl 3-(2-Acetamidophenyl)indolizine-1,2-dicarboxylate (3l). Ethyl acetate/petroleum ether = 1:2 as the eluent; Yellow solid, 69% yield (78.8 mg), mp 135–137 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.23 (d, J = 9.1 Hz, 1H), 8.14 (d, J = 8.2 Hz, 1H), 8.11 (s, 1H), 7.63 (d, J = 6.7 Hz, 1H), 7.52 (t, J = 7.4 Hz, 1H), 7.30 (s, 1H), 7.26 (t, J = 7.0 Hz, 1H), 7.17 (t, J = 7.6 Hz, 1H), 6.73 (t, J = 6.4 Hz, 1H), 4.35–4.19 (m, 2H), 3.91 (s, 3H), 1.98 (s, 3H), 1.22 (t, J = 7.0 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.0, 166.9, 164.1, 137.6, 135.8, 131.8, 130.8, 125.0, 124.4, 124.22, 124.19, 122.9, 120.8, 120.1 (2C), 113.8, 101.9, 61.9, 51.3, 24.3, 14.0; HRMS (ESI-TOF) calcd for $C_{21}H_{20}N_2O_5Na$ $[M + Na]^+$ 403.1270, found 403.1271.



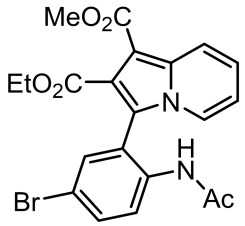
2-Ethyl 1-Methyl 3-(2-Acetamido-5-methylphenyl)indolizine-1,2-dicarboxylate (3m). Ethyl acetate/petroleum ether = 1:2 as the eluent; White solid, 71% yield (84.4 mg), mp 201–203 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.23 (d, J = 9.1 Hz, 1H), 7.98 (d, J = 8.2 Hz, 1H), 7.97 (s, 1H), 7.65 (d, J = 7.0 Hz, 1H), 7.33 (d, J = 8.3 Hz, 1H), 7.17 (dd, J = 9.0, 6.8 Hz, 1H), 7.11 (s, 1H), 6.73 (t, J = 6.8 Hz, 1H), 4.37–4.22 (m, 2H), 3.92 (s, 3H), 2.36 (s, 3H), 1.96 (s, 3H), 1.24 (t, J = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.9, 167.0, 164.2, 135.8, 135.1, 134.9, 132.0, 131.5, 124.6, 124.3, 124.2, 122.8, 121.1, 120.4, 120.1, 113.8, 101.8, 61.9, 51.3, 24.3, 20.8, 14.0; HRMS (ESI-TOF) calcd for $C_{22}H_{23}N_2O_5$ $[M + H]^+$ 395.1607, found 395.1609.



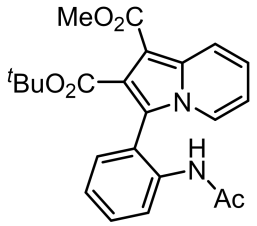
2-Ethyl 1-Methyl 3-(2-Acetamido-5-methoxyphenyl)indolizine-1,2-dicarboxylate (3n). Ethyl acetate/petroleum ether = 1:2 as the eluent; Yellow solid, 73% yield (89.9 mg), mp 131–133 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.23 (d, J = 9.1 Hz, 1H), 7.99 (s, 1H), 7.91 (d, J = 9.0 Hz, 1H), 7.69 (d, J = 7.0 Hz, 1H), 7.17 (t, J = 7.8 Hz, 1H), 7.07 (dd, J = 9.0, 2.4 Hz, 1H), 6.85 (d, J = 2.2 Hz, 1H), 6.74 (t, J = 6.8 Hz, 1H), 4.28–4.22 (m, 2H), 3.92 (s, 3H), 3.80 (s, 3H), 1.94 (s, 3H), 1.26 (t, J = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.1, 167.1, 164.2, 156.8, 135.8, 130.7, 126.9, 124.4, 124.3, 122.8, 122.4, 120.9, 120.2, 116.5, 116.3, 113.9, 101.8, 62.0, 55.6, 51.4, 24.1, 14.0; HRMS (ESI-TOF) calcd for $C_{22}H_{23}N_2O_6$ $[M + H]^+$ 411.1556, found 411.1552.



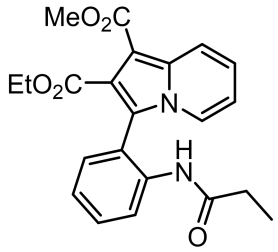
2-Ethyl 1-Methyl 3-(2-Acetamido-5-chlorophenyl)indolizine-1,2-dicarboxylate (3o). Ethyl acetate/petroleum ether = 1:2 as the eluent; Yellow solid, 80% yield (99.3 mg), mp 163–165 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.24 (d, J = 9.1 Hz, 1H), 8.15 (s, 1H), 8.12 (d, J = 8.9 Hz, 1H), 7.64 (d, J = 7.0 Hz, 1H), 7.48 (dd, J = 8.9, 2.3 Hz, 1H), 7.33 (d, J = 2.2 Hz, 1H), 7.20 (dd, J = 8.6, 7.1 Hz, 1H), 6.80 (t, J = 6.8 Hz, 1H), 4.36–4.24 (m, 2H), 3.90 (s, 3H), 1.97 (s, 3H), 1.26 (t, J = 7.2 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.2, 166.7, 164.0, 136.4, 136.0, 131.5, 130.7, 129.9, 125.7, 124.5, 124.1, 123.2, 121.7, 120.2, 119.3, 114.2, 102.2, 62.1, 51.4, 24.3, 14.0; HRMS (ESI-TOF) calcd for $C_{21}H_{19}{}^{35}ClN_2O_5Na$ $[M + Na]^+$ 437.0880, found 437.0885.



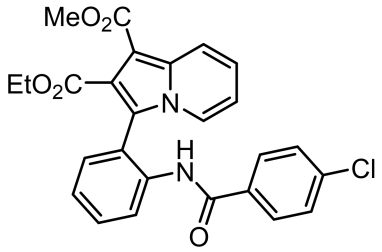
2-Ethyl 1-Methyl 3-(2-Acetamido-5-bromophenyl)indolizine-1,2-dicarboxylate (3p). Ethyl acetate/petroleum ether = 1:2 as the eluent; Yellow solid, 78% yield (107.6 mg), mp 166–168 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.25 (d, J = 9.2 Hz, 1H), 8.10 (d, J = 8.9 Hz, 1H), 8.01 (s, 1H), 7.66–7.60 (m, 2H), 7.45 (d, J = 2.2 Hz, 1H), 7.20 (dd, J = 8.8, 7.0 Hz, 1H), 6.79 (t, J = 6.9 Hz, 1H), 4.38–4.23 (m, 2H), 3.92 (s, 3H), 1.99 (s, 3H), 1.27 (t, J = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.9, 166.8, 164.1, 137.1, 136.1, 134.4, 133.9, 125.8, 124.5, 124.1, 123.5, 122.0, 120.4, 119.0, 117.5, 114.3, 102.4, 62.2, 51.5, 24.6, 14.1; HRMS (ESI-TOF) calcd for $C_{21}H_{19}{}^{79}BrN_2O_5Na$ $[M + Na]^+$ 481.0375, found 481.0367.



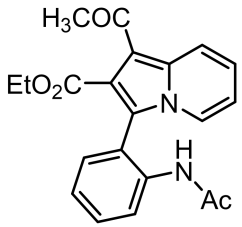
2-(***tert*-Butyl) 1-Methyl 3-(2-acetamidophenyl)indolizine-1,2-dicarboxylate (3q).** Ethyl acetate/petroleum ether = 1:1 as the eluent; Yellow solid, 65% yield (79.8 mg), mp 180–182 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.25 (d, J = 9.2 Hz, 1H), 8.21 (d, J = 8.2 Hz, 1H), 7.77 (s, 1H), 7.61 (d, J = 6.9 Hz, 1H), 7.53 (t, J = 7.8 Hz, 1H), 7.32 (d, J = 7.4 Hz, 1H), 7.26 (t, J = 7.4 Hz, 1H), 7.16 (t, J = 7.8 Hz, 1H), 6.72 (t, J = 6.7 Hz, 1H), 3.93 (s, 3H), 1.97 (s, 3H), 1.40 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.9, 165.7, 164.3, 137.8, 135.9, 131.9, 130.9, 125.0, 124.8, 124.2, 124.1, 123.8, 120.3, 120.11, 120.07, 113.8, 101.6, 82.7, 51.3, 27.9 (3C), 24.6; HRMS (ESI-TOF) calcd for $C_{23}H_{24}N_2O_5Na$ $[M + Na]^+$ 431.1583, found 431.15787.



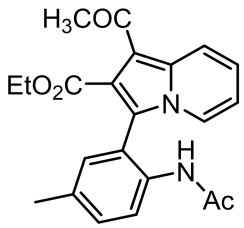
Ethyl 3-Oxo-2'-phenyl-2'*H*,3*H*-spiro[benzofuran-2,3'-indolizine]-1'-carboxylate (3r). Ethyl acetate/petroleum ether = 1:2 as the eluent; White solid, 65% yield (76.8 mg), mp 107–109 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.23 (d, J = 9.2 Hz, 1H), 8.18 (d, J = 8.2 Hz, 1H), 7.91 (s, 1H), 7.61 (d, J = 7.1 Hz, 1H), 7.52 (td, J = 7.8, 1.2 Hz, 1H), 7.32 (d, J = 6.6 Hz, 1H), 7.25 (d, J = 7.4 Hz, 1H), 7.17 (dd, J = 8.7, 7.0 Hz, 1H), 6.73 (t, J = 6.5 Hz, 1H), 4.34–4.20 (m, 2H), 3.91 (s, 3H), 2.27–2.10 (m, 2H), 1.21 (t, J = 7.1 Hz, 3H), 1.02 (t, J = 7.6 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.5, 166.6, 164.1, 137.7, 135.8, 131.8, 130.8, 124.9, 124.2 (3C), 123.0, 120.8, 120.1, 120.0, 113.8, 101.8, 61.8, 51.3, 30.4, 13.9, 9.4; HRMS (ESI-TOF) calcd for $C_{22}H_{23}N_2O_5$ $[M + H]^+$ 395.1607, found 395.1606.



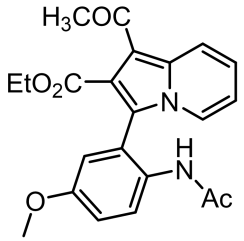
2-**Ethyl 1-Methyl 3-(2-(4-Chlorobenzoyl)phenyl)indolizine-1,2-dicarboxylate (3s).** Ethyl acetate/petroleum ether = 1:2 as the eluent; Orange solid, 53% yield (78.6 mg), mp 127–129 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.16 (s, 1H), 8.22 (d, J = 8.3 Hz, 1H), 8.19 (d, J = 9.3 Hz, 1H), 7.71 (d, J = 8.4 Hz, 2H), 7.65 (d, J = 7.0 Hz, 1H), 7.59 (t, J = 7.7 Hz, 1H), 7.39–7.30 (m, 4H), 7.12 (t, J = 7.9 Hz, 1H), 6.68 (t, J = 6.8 Hz, 1H), 4.42–4.23 (m, 2H), 3.93 (s, 3H), 1.25 (t, J = 7.2 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.5, 164.6, 164.0, 138.0, 137.7, 135.8, 132.6, 131.9, 130.9, 128.8 (2C), 128.7 (2C), 125.5, 125.2, 124.25, 124.15, 122.8, 121.1, 120.7, 120.1, 113.9, 101.8, 62.1, 51.3, 14.0; HRMS (ESI-TOF) calcd for $C_{26}H_{21}{}^{35}ClN_2O_5Na$ $[M + Na]^+$ 499.1037, found 499.1045.



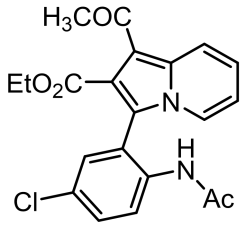
Ethyl 3-(2-Acetamidophenyl)-1-acetylindolizine-2-carboxylate (3t). Ethyl acetate/petroleum ether = 1:1 as the eluent; Yellow solid, 82% yield (89.5 mg), mp 103–105 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.33 (d, J = 9.2 Hz, 1H), 8.17 (d, J = 8.3 Hz, 1H), 7.93 (s, 1H), 7.63 (d, J = 7.0 Hz, 1H), 7.54 (t, J = 7.6 Hz, 1H), 7.33–7.25 (m, 2H), 7.23 (dd, J = 8.6, 7.2 Hz, 1H), 6.78 (t, J = 6.8 Hz, 1H), 4.29–4.19 (m, 2H), 2.54 (s, 3H), 1.99 (s, 3H), 1.15 (t, J = 7.2 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 193.1, 169.1, 166.9, 137.7, 135.7, 131.9, 130.8, 125.5, 125.0, 124.19, 124.15, 122.3, 121.9, 120.8, 120.2, 114.5, 112.4, 62.0, 30.1, 24.4, 13.8; HRMS (ESI-TOF) calcd for $C_{21}H_{20}N_2O_4Na$ $[M + Na]^+$ 387.1321, found 387.1321.



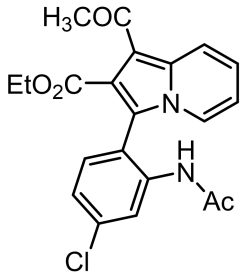
Ethyl 3-(2-Acetamido-5-methylphenyl)-1-acetylindolizine-2-carboxylate (3u). Ethyl acetate/petroleum ether = 1:1 as the eluent; White solid, 75% yield (84.9 mg), mp 198–201 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.34 (d, J = 9.2 Hz, 1H), 8.01 (d, J = 8.3 Hz, 1H), 7.72 (s, 1H), 7.64 (d, J = 6.8 Hz, 1H), 7.34 (d, J = 8.3 Hz, 1H), 7.22 (t, J = 7.8 Hz, 1H), 7.10 (s, 1H), 6.77 (t, J = 6.7 Hz, 1H), 4.31–4.20 (m, 2H), 2.56 (s, 3H), 2.36 (s, 3H), 1.96 (s, 3H), 1.17 (t, J = 7.0 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 193.0, 168.9, 167.0, 135.6, 135.2, 135.0, 132.1, 131.6, 125.4, 124.3 (2C), 122.2, 122.1, 120.8, 120.4, 114.4, 112.4, 62.0, 30.1, 24.4, 20.9, 13.9; HRMS (ESI-TOF) calcd for $C_{22}H_{23}N_2O_4$ $[M + H]^+$ 379.1658, found 379.1661.



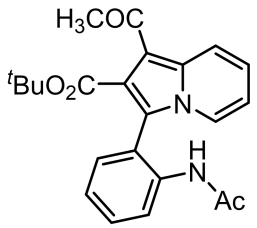
Ethyl 3-(2-Acetamido-5-methoxyphenyl)-1-acetylindolizine-2-carboxylate (3v). Ethyl acetate/petroleum ether = 1:1 as the eluent; White solid, 65% yield (77.1 mg), mp 167–169 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.33 (d, J = 9.2 Hz, 1H), 7.95 (d, J = 9.1 Hz, 1H), 7.72 (s, 1H), 7.67 (d, J = 7.0 Hz, 1H), 7.22 (t, J = 7.8 Hz, 1H), 7.08 (dd, J = 9.0, 2.9 Hz, 1H), 6.83 (d, J = 2.8 Hz, 1H), 6.78 (t, J = 6.8 Hz, 1H), 4.32–4.21 (m, 2H), 3.81 (s, 3H), 2.56 (s, 3H), 1.94 (s, 3H), 1.20 (t, J = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 192.9, 169.0, 167.0, 156.9, 135.6, 130.8, 126.6, 125.5, 124.4, 122.4, 122.2, 121.9, 120.7, 116.6, 116.4, 114.5, 112.4, 62.1, 55.7, 30.1, 24.2, 13.9; HRMS (ESI-TOF) calcd for $C_{22}H_{23}N_2O_5$ $[M + H]^+$ 395.1607, found 395.1559.



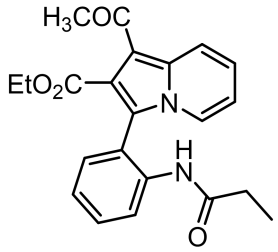
Ethyl 3-(2-Acetamido-5-chlorophenyl)-1-acetylindolizine-2-carboxylate (3w). Ethyl acetate/petroleum ether = 2:1 as the eluent; Yellow solid, 50% yield (59.8 mg), mp 190–192 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.32 (d, J = 9.2 Hz, 1H), 8.18 (d, J = 8.9 Hz, 1H), 7.85 (s, 1H), 7.63 (d, J = 7.0 Hz, 1H), 7.50 (dd, J = 8.9, 2.0 Hz, 1H), 7.30 (d, J = 1.9 Hz, 1H), 7.25 (t, J = 7.9 Hz, 1H), 6.83 (t, J = 6.8 Hz, 1H), 4.32–4.22 (m, 2H), 2.54 (s, 3H), 1.99 (s, 3H), 1.20 (t, J = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 193.1, 169.1, 166.7, 136.5, 135.8, 131.6, 130.9, 130.0, 125.6, 125.3, 124.0, 122.7, 121.7, 121.0, 120.2, 114.8, 112.7, 62.2, 30.2, 24.5, 13.9; HRMS (ESI-TOF) calcd for $C_{21}H_{19}{}^{35}ClN_2O_4Na$ $[M + Na]^+$ 421.0931, found 421.0932.



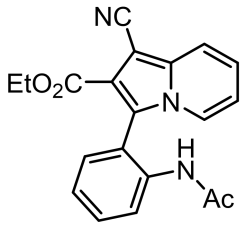
Ethyl 3-(2-Acetamido-4-chlorophenyl)-1-acetylindolizine-2-carboxylate (3x). Ethyl acetate/petroleum ether = 1:2 as the eluent; Orange solid, 66% yield (79.0 mg), mp 143–145 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.32 (s, 1H), 8.28 (d, J = 9.2 Hz, 1H), 8.07 (s, 1H), 7.61 (d, J = 7.0 Hz, 1H), 7.26–7.19 (m, 3H), 6.82 (t, J = 6.8 Hz, 1H), 4.25 (q, J = 7.1 Hz, 2H), 2.49 (s, 3H), 2.01 (s, 3H), 1.18 (t, J = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 193.0, 169.2, 166.6, 138.9, 136.6, 135.8, 132.8, 125.5, 125.0, 123.9, 123.7, 122.6, 120.9, 120.6, 118.1, 114.7, 112.5, 62.0, 30.0, 24.4, 13.8; HRMS (ESI-TOF) calcd for $C_{21}H_{19}{}^{35}ClN_2O_4Na$ $[M + Na]^+$ 421.0931, found 421.0936.



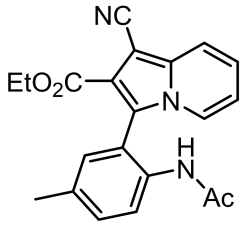
***tert*-Butyl 3-(2-Acetamidophenyl)-1-acetylindolizine-2-carboxylate (3y).** Ethyl acetate/petroleum ether = 1:2 as the eluent; Yellow solid, 53% yield (62.2 mg), mp 141–143 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.40 (d, J = 9.2 Hz, 1H), 8.29 (d, J = 8.3 Hz, 1H), 7.59 (d, J = 7.0 Hz, 1H), 7.56 (s, 1H), 7.54 (d, J = 8.1 Hz, 1H), 7.32–7.24 (m, 2H), 7.22 (dd, J = 8.4, 7.4 Hz, 1H), 6.78 (t, J = 6.8 Hz, 1H), 2.58 (s, 3H), 1.98 (s, 3H), 1.34 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 193.2, 168.9, 165.8, 137.9, 135.7, 131.9, 131.0, 125.4, 124.8, 124.3, 124.0, 123.2, 121.1, 121.0, 119.9, 114.6, 111.8, 83.0, 30.2, 27.8 (3C), 24.7; HRMS (ESI-TOF) calcd for $C_{23}H_{24}N_2O_4Na$ $[M + Na]^+$ 415.1634, found 415.1634.



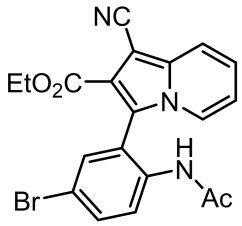
Ethyl 1-Acetyl-3-(2-propionamidophenyl)indolizine-2-carboxylate (3z). Ethyl acetate/petroleum ether = 1:2 as the eluent; Yellow solid, 68% yield (77.1 mg), mp 123–125 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.35 (d, J = 9.2 Hz, 1H), 8.22 (d, J = 8.2 Hz, 1H), 7.68 (s, 1H), 7.60 (d, J = 7.0 Hz, 1H), 7.54 (t, J = 7.7 Hz, 1H), 7.32–7.24 (m, 2H), 7.22 (dd, J = 8.9, 7.0 Hz, 1H), 6.77 (t, J = 6.8 Hz, 1H), 4.29–4.18 (m, 2H), 2.56 (s, 3H), 2.27–2.11 (m, 2H),1.14 (t, J = 7.1 Hz, 3H), 1.02 (t, J = 7.6 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 193.1, 172.5, 166.7, 137.8, 135.6, 131.8, 130.9, 125.4, 124.9, 124.2, 123.9, 122.3, 121.9, 120.8, 120.1, 114.5, 112.4, 61.9, 30.5, 30.1, 13.8, 9.5; HRMS (ESI-TOF) calcd for $C_{22}H_{23}N_2O_4$ $[M + H]^+$ 379.1658, found 379.1656.



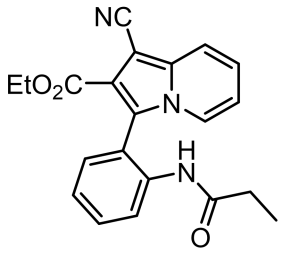
Ethyl 3-(2-Acetamidophenyl)-1-cyanoindolizine-2-carboxylate (3aa). Ethyl acetate/petroleum ether = 1:1 as the eluent; White solid, 72% yield (75.1 mg), mp 167–169 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 (d, J = 8.2 Hz, 1H), 7.80 (s, 1H), 7.72–7.66 (m, 2H), 7.55 (t, J = 7.5 Hz, 1H), 7.34–7.25 (m, 2H), 7.24–7.18 (m, 1H), 6.80 (t, J = 6.9 Hz, 1H), 4.31–4.20 (m, 2H), 1.94 (s, 3H), 1.25 (t, J = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.5, 163.1, 138.6, 137.5, 131.9, 130.9, 125.6, 125.5, 125.2, 125.0, 124.7, 121.3, 119.7, 118.4, 115.2, 114.7, 83.2, 61.6, 24.0, 13.8; HRMS (ESI-TOF) calcd for $C_{20}H_{17}N_3O_3Na$ $[M + Na]^+$ 370.1168, found 370.1171.



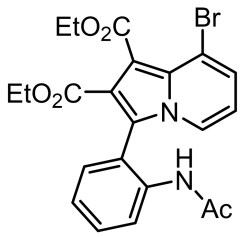
Ethyl 3-(2-Acetamido-5-methylphenyl)-1-cyanoindolizine-2-carboxylate (3ab). Ethyl acetate/petroleum ether = 1:1 as the eluent; Yellow solid, 76% yield (82.3 mg), mp 184–186 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86 (d, J = 8.3 Hz, 1H), 7.75 (s, 1H), 7.68 (d, J = 7.1 Hz, 1H), 7.64 (d, J = 9.0 Hz, 1H), 7.36 (d, J = 8.0 Hz, 1H), 7.20 (dd, J = 8.3, 7.2 Hz, 1H), 7.07 (s, 1H), 6.79 (t, J = 6.7 Hz, 1H), 4.29–4.16 (m, 2H), 2.37 (s, 3H), 1.91 (s, 3H), 1.23 (t, J = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.3, 163.0, 138.5, 135.1, 135.0, 132.1, 131.6, 125.9, 125.3, 125.1, 124.5, 121.3, 119.6, 118.3, 115.1, 114.6, 83.1, 61.4, 23.9, 20.9, 13.8; HRMS (ESI-TOF) calcd for $C_{21}H_{19}N_3O_3Na$ $[M + Na]^+$ 384.1324, found 384.1333.



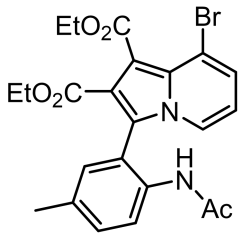
Ethyl 3-(2-Acetamido-5-bromophenyl)-1-cyanoindolizine-2-carboxylate (3ac). Ethyl acetate/petroleum ether = 1:1 as the eluent; Yellow solid, 80% yield (102.0 mg), mp 184–186 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.21 (s, 1H), 7.81 (d, J = 8.5 Hz, 1H), 7.76 (d, J = 9.0 Hz, 1H), 7.73–7.67 (m, 2H), 7.65 (s, 1H), 7.34 (t, J = 7.6 Hz, 1H), 6.97 (t, J = 6.5 Hz, 1H), 4.20–4.00 (m, 2H), 1.75 (s, 3H), 1.06 (t, J = 6.9 Hz, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 168.7, 161.9, 138.2, 137.5, 134.5, 132.7, 126.3, 125.3, 125.2, 124.4, 123.5, 119.0, 117.6, 116.2, 115.4, 114.9, 82.2, 60.6, 23.2, 13.6; HRMS (ESI-TOF) calcd for $C_{20}H_{16}{}^{79}BrN_3O_3Na$ $[M + Na]^+$ 448.0273, found 448.0268.



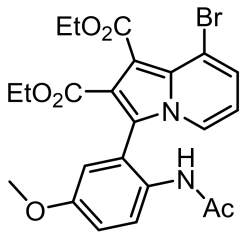
Ethyl 1-Cyano-3-(2-propionamidophenyl)indolizine-2-carboxylate (3ad). Ethyl acetate/petroleum ether = 1:2 as the eluent; Orange solid, 72% yield (77.9 mg), mp 183–185 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 (d, J = 7.8 Hz, 1H), 7.70 (d, J = 9.0 Hz, 1H), 7.66 (d, J = 7.0 Hz, 1H), 7.56 (t, J = 7.4 Hz, 1H), 7.51 (s, 1H), 7.33–7.24 (m, 2H), 7.20 (t, J = 7.8 Hz, 1H), 6.79 (t, J = 6.7 Hz, 1H), 4.34–4.20 (m, 2H), 2.24–2.06 (m, 2H), 1.26 (t, J = 7.0 Hz, 3H), 0.99 (t, J = 7.5 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.7, 163.0, 138.6, 137.7, 131.7, 131.0, 125.4, 125.3, 125.0, 124.9, 124.6, 121.0, 119.9, 118.5, 115.1, 114.7, 83.3, 61.6, 30.4, 13.9, 9.6; HRMS (ESI-TOF) calcd for $C_{21}H_{19}N_3O_3Na$ $[M + Na]^+$ 384.1324, found 384.1319.



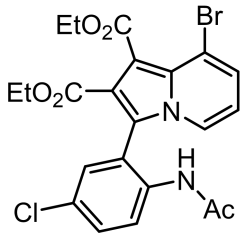
Diethyl 3-(2-Acetamidophenyl)-8-bromoindolizine-1,2-dicarboxylate (3ae). Ethyl acetate/petroleum ether = 1:2 as the eluent; Yellow solid, 68% yield (96.8 mg), mp 139–141 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.15 (d, J = 8.1 Hz, 1H), 7.53 (t, J = 7.8 Hz, 1H), 7.50 (d, J = 7.2 Hz, 1H), 7.39 (s, 1H), 7.26 (t, J = 7.4 Hz, 1H), 7.22 (d, J = 7.4 Hz, 1H), 7.17 (d, J = 7.1 Hz, 1H), 6.45 (t, J = 7.1 Hz, 1H), 4.55–4.41 (m, 2H), 4.26–4.13 (m, 2H), 1.97 (s, 3H), 1.47 (t, J = 7.2 Hz, 3H), 1.15 (t, J = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.9, 166.3, 163.8, 137.6, 131.8, 130.8, 128.4, 125.2, 125.1, 124.2, 123.9, 123.1, 121.2, 118.5, 113.0, 112.8, 110.4, 62.1, 61.3, 24.6, 14.2, 13.9; HRMS (ESI-TOF) calcd for $C_{22}H_{21}{}^{79}BrN_2O_5Na$ $[M + Na]^+$ 495.0532, found 495.0537.



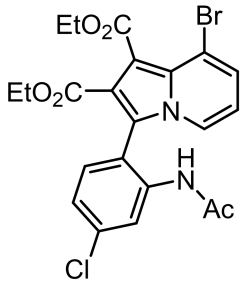
Diethyl 3-(2-Acetamido-5-methylphenyl)-8-bromoindolizine-1,2-dicarboxylate (3af). Ethyl acetate/petroleum ether = 1:2 as the eluent; Yellow solid, 65% yield (94.7 mg), mp 166–168 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94 (d, J = 8.3 Hz, 1H), 7.52 (d, J = 7.0 Hz, 1H), 7.41 (s, 1H), 7.32 (d, J = 8.3 Hz, 1H), 7.16 (d, J = 7.0 Hz, 1H), 7.02 (s, 1H), 6.44 (t, J = 7.0 Hz, 1H), 4.55–4.39 (m, 2H), 4.27–4.13 (m, 2H), 2.34 (s, 3H), 1.93 (s, 3H), 1.46 (t, J = 7.1 Hz, 3H), 1.17 (t, J = 7.0 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.9, 166.3, 163.8, 134.92, 134.89, 131.9, 131.4, 128.1, 124.9, 124.4, 124.1, 123.1, 121.4, 118.1, 112.8, 112.5, 110.2, 61.9, 61.1, 24.3, 20.9, 14.1, 13.8; HRMS (ESI-TOF) calcd for $C_{23}H_{23}{}^{79}BrN_2O_5Na$ $[M + Na]^+$ 509.0688, found 509.0688.



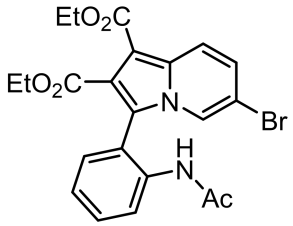
Diethyl 3-(2-Acetamido-5-methoxyphenyl)-8-bromoindolizine-1,2-dicarboxylate (3ag). Ethyl acetate/petroleum ether = 1:1 as the eluent; Yellow solid, 60% yield (90.5 mg), mp 142–144 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89 (d, J = 9.0 Hz, 1H), 7.56 (d, J = 7.2 Hz, 1H), 7.38 (s, 1H), 7.17 (d, J = 7.1 Hz, 1H), 7.07 (dd, J = 9.0, 2.8 Hz, 1H), 6.75 (d, J = 2.8 Hz, 1H), 6.45 (t, J = 7.1 Hz, 1H), 4.54–4.41 (m, 2H), 4.28–4.14 (m, 2H), 3.78 (s, 3H), 1.92 (s, 3H), 1.46 (t, J = 7.2 Hz, 3H), 1.19 (t, J = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.0, 166.3, 163.8, 156.8, 130.5, 128.1, 126.6, 125.0, 124.0, 123.4, 123.2, 118.1, 116.5, 116.2, 112.9, 112.5, 110.1, 62.0, 61.2, 55.6, 24.2, 14.2, 13.9; HRMS (ESI-TOF) calcd for $C_{23}H_{24}{}^{79}BrN_2O_6$ $[M + H]^+$ 503.0818, found 503.0809.



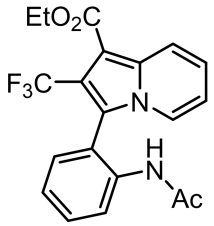
Diethyl 3-(2-Acetamido-5-chlorophenyl)-8-bromoindolizine-1,2-dicarboxylate (3ah). Ethyl acetate/petroleum ether = 1:2 as the eluent; White solid, 70% yield (107.0 mg), mp 176–178 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.11 (d, J = 8.9 Hz, 1H), 7.52–7.46 (m, 2H), 7.42 (s, 1H), 7.22 (d, J = 2.3 Hz, 1H), 7.20 (d, J = 7.1 Hz, 1H), 6.51 (t, J = 7.1 Hz, 1H), 4.53–4.41 (m, 2H), 4.27–4.13 (m, 2H), 1.95 (s, 3H), 1.46 (t, J = 7.2 Hz, 3H), 1.18 (t, J = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.9, 166.1, 163.5, 136.2, 131.5, 130.7, 129.9, 128.4, 125.24, 125.17, 122.8, 122.6, 122.0, 118.5, 113.3, 112.8, 110.6, 62.0, 61.3, 24.4, 14.1, 13.8; HRMS (ESI-TOF) calcd for $C_{22}H_{20}{}^{79}Br^{35}ClN_2O_5Na$ $[M + Na]^+$ 529.0142, found 529.0139.



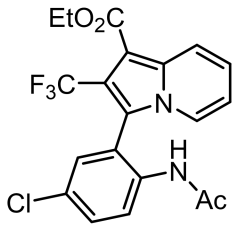
Diethyl 3-(2-Acetamido-4-chlorophenyl)-8-bromoindolizine-1,2-dicarboxylate (3ai). Ethyl acetate/petroleum ether = 1:2 as the eluent; Pea-green solid, 72% yield (109.5 mg), mp 120–122 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.25 (s, 1H), 7.50 (s, 1H), 7.48 (d, J = 7.2 Hz, 1H), 7.23 (d, J = 8.2 Hz, 1H), 7.19 (d, J = 7.1 Hz, 1H), 7.15 (d, J = 8.2 Hz, 1H), 6.49 (t, J = 7.1 Hz, 1H), 4.53–4.40 (m, 2H), 4.25–4.13 (m, 2H), 1.95 (s, 3H), 1.46 (t, J = 7.2 Hz, 3H), 1.18 (t, J = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.9, 166.1, 163.5, 138.5, 136.5, 132.7, 128.4, 125.13, 125.09, 123.6, 122.7, 122.4, 119.0, 118.4, 113.2, 112.7, 110.5, 62.0, 61.3, 24.5, 14.1, 13.8; HRMS (ESI-TOF) calcd for $C_{22}H_{20}{}^{79}Br^{35}ClN_2O_5Na$ $[M + Na]^+$ 529.0142, found 529.0149.



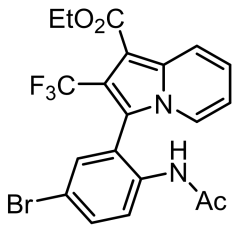
2-Ethyl 1-Methyl 3-(2-Propionamidophenyl)indolizine-1,2-dicarboxylate (3aj). Ethyl acetate/petroleum ether = 1:2 as the eluent; Orange solid, 72% yield (102.3 mg), mp 84–86 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.19–8.12 (m, 2H), 8.11 (s, 1H), 7.76 (s, 1H), 7.59–7.52 (m, 1H), 7.32–7.26 (m, 2H), 7.21 (d, J = 9.6 Hz, 1H), 4.45–4.33 (m, 2H), 4.27 (q, J = 7.1 Hz, 2H), 2.02 (s, 3H), 1.41 (t, J = 7.1 Hz, 3H), 1.22 (t, J = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.0, 166.7, 163.4, 137.8, 133.9, 131.7, 131.3, 127.4, 125.3, 124.7, 124.1, 123.4, 121.0, 120.9, 119.6, 109.0, 103.4, 62.1, 60.5, 24.5, 14.6, 14.0; HRMS (ESI-TOF) calcd for $C_{22}H_{21}{}^{79}BrN_2O_5Na$ $[M + Na]^+$ 495.0532, found 495.0533.



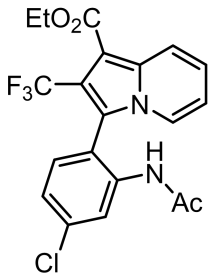
Ethyl 3-(2-Acetamidophenyl)-2-(trifluoromethyl)indolizine-1-carboxylate (3ak). Ethyl acetate/petroleum ether = 1:2 as the eluent; Orange solid, 73% yield (85.8 mg), mp 169–171 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.28 (d, J = 9.1 Hz, 1H), 8.19 (d, J = 7.5 Hz, 1H), 7.59–7.50 (m, 2H), 7.32–7.25 (m, 2H), 7.18 (t, J = 7.6 Hz, 1H), 7.13 (s, 1H), 6.75 (t, J = 6.1 Hz, 1H), 4.42–4.31 (m, 2H), 1.91 (s, 3H), 1.41 (t, J = 6.9 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.9, 163.4, 137.4, 137.1, 131.9, 131.0, 125.2, 124.8, 124.1, 123.3, 122.9 (q, J = 270.2 Hz), 121.4 (q, J = 4.0 Hz), 120.6, 120.3, 118.0 (q, J = 35.5 Hz), 114.2, 101.9, 60.4, 24.3, 14.3; ^{19}F NMR (471 MHz, $CDCl_3$) δ -54.65 (s, 3F); HRMS (ESI-TOF) calcd for $C_{20}H_{17}F_3N_2O_3Na$ $[M + Na]^+$ 413.1089, found 413.1087.



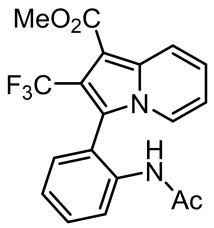
Ethyl 3-(2-Acetamido-5-chlorophenyl)-2-(trifluoromethyl)indolizine-1-carboxylate (3al). Ethyl acetate/petroleum ether = 1:2 as the eluent; White solid, 77% yield (98.2 mg), mp 175–177 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.27 (d, J = 9.2 Hz, 1H), 8.18 (d, J = 8.7 Hz, 1H), 7.56 (d, J = 7.0 Hz, 1H), 7.50 (dd, J = 8.9, 2.2 Hz, 1H), 7.28 (s, 1H), 7.24–7.16 (m, 2H), 6.80 (t, J = 6.5 Hz, 1H), 4.40–4.29 (m, 2H), 1.91 (s, 3H), 1.41 (t, J = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.9, 163.2, 137.3, 136.3, 131.6, 131.1, 130.1, 124.9, 124.5, 123.9, 122.7 (q, J = 270.4 Hz), 121.8, 120.7, 119.8 (q, J = 3.8 Hz), 118.3 (q, J = 35.5 Hz), 114.6, 102.2, 60.5, 24.2, 14.2; ^{19}F NMR (471 MHz, $CDCl_3$) δ -54.65 (s, 3F); HRMS (ESI-TOF) calcd for $C_{20}H_{16}F_3{}^{35}ClN_2O_3Na$ $[M + Na]^+$ 447.0699, found 447.0703.



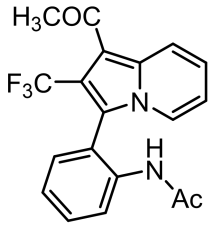
Ethyl 3-(2-Acetamido-5-bromophenyl)-2-(trifluoromethyl)indolizine-1-carboxylate (3am). Ethyl acetate/petroleum ether = 1:3 as the eluent; White solid, 80% yield (113.0 mg), mp 170–172 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.23 (d, J = 9.2 Hz, 1H), 8.10 (d, J = 8.7 Hz, 1H), 7.64 (dd, J = 8.9, 2.0 Hz, 1H), 7.56 (d, J = 7.1 Hz, 1H), 7.42 (d, J = 2.0 Hz, 1H), 7.40 (s, 1H), 7.19 (dd, J = 8.6, 7.1 Hz, 1H), 6.80 (t, J = 6.8 Hz, 1H), 4.37–4.25 (m, 2H), 1.90 (s, 3H), 1.40 (t, J = 7.2 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.0, 163.2, 137.2, 136.8, 134.4, 133.9, 124.9, 124.7, 123.9, 122.7 (q, J = 270.4 Hz), 122.1, 120.6, 119.8 (q, J = 3.7 Hz), 118.3 (q, J = 35.6 Hz), 117.5, 114.5, 102.1, 60.5, 24.1, 14.2; ^{19}F NMR (471 MHz, $CDCl_3$) δ -54.60 (s, 3F); HRMS (ESI-TOF) calcd for $C_{20}H_{16}F_3{}^{79}BrN_2O_3Na$ $[M + Na]^+$ 491.0194, found 491.0196.



Ethyl 3-(2-Acetamido-4-chlorophenyl)-2-(trifluoromethyl)indolizine-1-carboxylate (3an). Ethyl acetate/petroleum ether = 1:2 as the eluent; White solid, 82% yield (104.3 mg), mp 209–211 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.39 (s, 1H), 8.25 (d, J = 9.1 Hz, 1H), 7.99 (s, 1H), 7.69 (d, J = 6.9 Hz, 1H), 7.44–7.32 (m, 3H), 6.93 (t, J = 6.7 Hz, 1H), 4.39–4.28 (m, 2H), 1.82 (s, 3H), 1.34 (t, J = 7.1 Hz, 3H);^{13}C NMR (126 MHz, DMSO-d6) δ 168.8, 162.5, 139.6, 136.5, 134.5, 133.6, 125.4, 124.8, 124.5, 123.9, 122.9 (q, J = 269.5 Hz), 121.7 (q, J = 3.6 Hz), 119.9, 119.6, 116.1 (q, J =34.7 Hz), 114.2, 100.8, 59.7, 23.3, 14.2; ^{19}F NMR (471 MHz, DMSO-d_6) δ -53.96 (s, 3F); HRMS (ESI-TOF) calcd for $C_{20}H_{16}F_3{}^{35}ClN_2O_3Na$ $[M + Na]^+$ 447.0699, found 447.0692.



Methyl 3-(2-Acetamidophenyl)-2-(trifluoromethyl)indolizine-1-carboxylate (3ao). Ethyl acetate/petroleum ether = 1:1 as the eluent; White solid, 64% yield (72.5 mg), mp 151–153 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.26 (d, J = 9.2 Hz, 1H), 8.16 (d, J = 8.0 Hz, 1H), 7.59–7.51 (m, 2H), 7.32–7.26 (m, 2H), 7.22–7.15 (m, 2H), 6.76 (t, J = 6.8 Hz, 1H), 3.90 (s, 3H), 1.90 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.0, 163.8, 137.5, 137.1, 131.9, 131.0, 125.2, 124.8, 124.2, 123.5, 122.8 (q, J = 270.1 Hz), 121.7, 120.5, 120.4, 117.9 (q, J = 35.4 Hz), 114.2, 101.5, 51.4, 24.1; ^{19}F NMR (471 MHz, $CDCl_3$) δ -54.90 (s, 3F); HRMS (ESI-TOF) calcd for $C_{19}H_{15}F_3N_2O_3Na$ $[M + Na]^+$ 399.0932, found 399.0927.



***N*-(2-(1-Acetyl-2-(trifluoromethyl)indolizin-3-yl)phenyl)acetamide (3ap).** Ethyl acetate/petroleum ether = 1:1 as the eluent; Green solid, 52% yield (55.9 mg), mp 139–141 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.25 (d, J = 9.2 Hz, 1H), 8.20 (d, J = 8.0 Hz, 1H), 7.60–7.52 (m, 2H), 7.44 (bs, 1H), 7.33–7.26 (m, 2H), 7.20 (dd, J = 8.7, 7.1 Hz, 1H), 6.79 (t, J = 6.8 Hz, 1H), 2.58 (s, 3H), 1.93 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 193.6, 169.1, 137.5, 136.7, 132.1, 131.1, 125.8, 125.2, 124.1, 123.7, 123.3 (q, J = 270.2 Hz), 121.9 (q, J = 4.0 Hz), 121.1, 120.3, 116.9 (q, J = 34.7 Hz), 114.7, 111.8, 30.6 (q, J = 3.9 Hz), 24.2; ^{19}F NMR (471 MHz, $CDCl_3$) δ -51.75 (s, 3F); HRMS (ESI-TOF) calcd for $C_{19}H_{15}F_3N_2O_2Na$ $[M + Na]^+$383.0983, found 383.0988.

2.4 化合物 3d 的单晶衍射数据

化合物 **3d** 的单晶通过将其溶于丙酮/正己烷混合溶剂中，低温缓慢蒸发获得。单晶 X 射线衍射数据在配备 CCD 面探测器的 Bruker APEX-II 衍射仪上收集，使用石墨单色 MoKα辐射（λ=0.71073 Å），扫描范围为 4.154° < 2θ < 54.946°。结构通过 SHELXT 程序采用直接法求解，并通过最小二乘精修法进行精修。晶体数据已存入剑桥晶体学数据中心，编号为 CCDC 2402327。

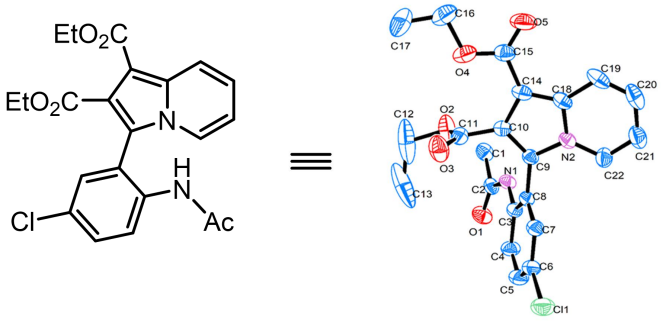


Figure 2-1. ORTEP Diagram of **3d** with 30% thermal ellipsoids

Table 2-6. Crystal Data and Structure Refinement for 3d

CCDC number	2402327
Empirical formula	$C_{22}H_{21}ClN_2O_5$
Formula weight	428.86
Temperature [K]	273.15
Crystal system	trigonal
Space group	$P3_2$ (145)
a [Å]	11.3207(3)
b [Å]	11.3207(3)
c [Å]	14.4325(5)
α [°]	90
β [°]	90
γ [°]	120
Volume [Å^3]	1601.84(10)
Z	3
ρ_{calc} [gcm^{-3}]	1.334
μ [mm^{-1}]	0.215

F(000)	672.0
Crystal size [mm^3]	0.4×0.2×0.2
Radiation	MoK$_\alpha$ (λ=0.71073 Å)
2θ range [°]	4.154 to 54.946
Index ranges	−14 ≤ h ≤ 14, −14 ≤ k ≤ 14, −18 ≤ l ≤ 18
Reflections collected	53502
Independent reflections	4851[R$_{int}$ = 0.0882, R$_{sigma}$ = 0.0334]
Data / Restraints / Parameters	4851/1/274
Goodness-of-fit on F^2	1.039
Final *R* indexes [I≥2σ(I)]	R_1 = 0.0513, wR_2 = 0.1349
Final *R* indexes [all data]	R_1 = 0.0733, wR_2 = 0.1540
Largest peak/hole [eÅ^{-3}]	0.37/-0.24

2.5 化合物 **3an** 的单晶衍射数据

3an 的单晶通过将其溶于丙酮/正己烷混合溶剂，在 5 ºC 下缓慢蒸发获得。单晶 X 射线衍射数据在配备 CCD 面探测器的 Bruker APEX-II 衍射仪上收集，使用石墨单色 MoKα辐射（λ=0.71073 Å），扫描范围为 4.716° < 2θ < 55.002°。结构通过 SHELXT 程序采用直接法求解，并通过最小二乘精修法进行精修。晶体学数据已存入剑桥晶体学数据中心，编号为 CCDC 2402284。

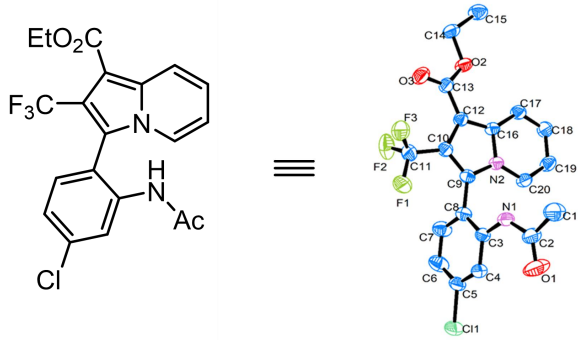


Figure 2-2. ORTEP Diagram of **3an** with 40% thermal ellipsoids

Table 2-7. Crystal Data and Structure Refinement for 3an

CCDC number	2402284
Empirical formula	$C_{20}H_{16}N_2O_3ClF_3$
Formula weight	424.80

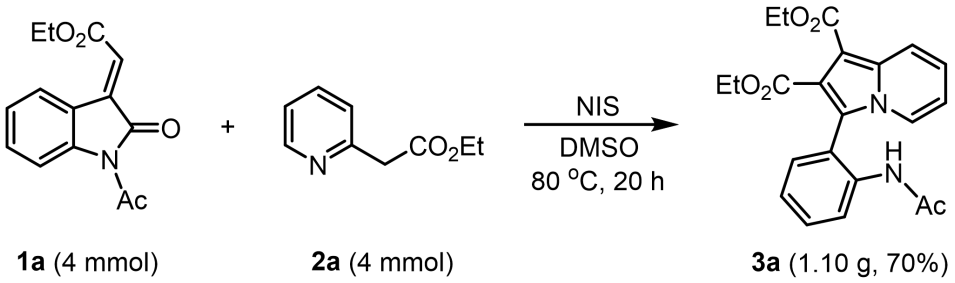
Temperature [K]	273.15
Crystal system	monoclinic
Space group	*C*2/*c* (15)
a [Å]	24.034(14)
b [Å]	9.142(9)
c [Å]	17.924(11)
α [°]	90
β [°]	105.465(9)
γ [°]	90
Volume [Å^3]	3796(5)
Z	8
ρ_{calc} [gcm^{-3}]	1.487
μ [mm^{-1}]	0.255
F(000)	1744.0
Crystal size [mm^3]	0.4×0.2×0.2
Radiation	MoK$_\alpha$ (λ=0.71073 Å)
2θ range [°]	4.716 to 55.002
Index ranges	-29 ≤ h ≤ 31, -11 ≤ k ≤ 11, -23 ≤ l ≤ 23
Reflections collected	48631
Independent reflections	4352[R_{int} = 0.0943, R_{sigma} = 0.0292]
Data / Restraints / Parameters	4352/0/264
Goodness-of-fit on F^2	1.070
Final *R* indexes [I≥2σ(I)]	R_1 = 0.0623, wR_2 = 0.1309
Final *R* indexes [all data]	R_1 = 0.0805, wR_2 = 0.1406
Largest peak/hole [eÅ^{-3}]	0.26/-0.22

2.6 放大（克级）反应与衍生化实验

2.6.1 放大（克级）反应

将 **1a**（1.04 g，4 mmol）、**2a**（0.66 g，4 mmol，1.0 当量）和 NIS（0.90 g，4 mmol，1.0 当量）溶于 DMSO（40 mL，0.1 M）中，在 50 mL 圆底烧瓶中于 80 °C 油浴中搅拌反应 20 小时。冷却后，用饱和 NaCl 水溶液（200 mL）洗涤反应混合物，并用乙酸乙酯萃取三次（3 × 50 mL）。合并有机相，用无水 Na_2SO_4

干燥后减压浓缩。残余物通过硅胶柱色谱法分离，以乙酸乙酯/石油醚（1:2，v/v）为洗脱剂，得到吲哚嗪 **3a**（1.10 g，产率 70%，Scheme 2-5）。

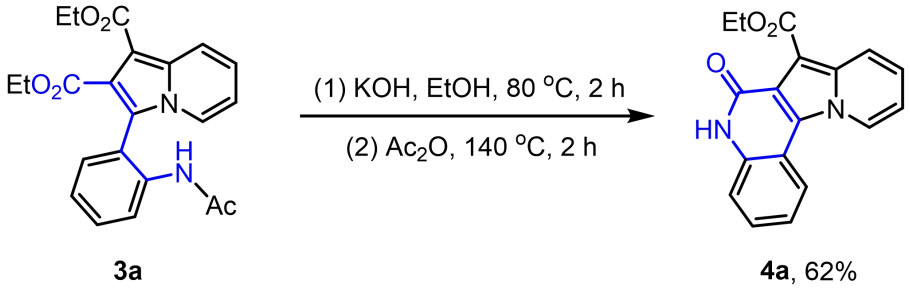


1a (4 mmol) **2a** (4 mmol) **3a** (1.10 g, 70%)

Scheme 2-5 Gram-Scale Synthesis of **3a**

2.6.2 衍生化实验

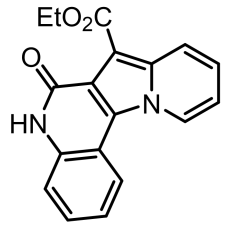
吲哚嗪 **3** 的官能团可进一步衍生化。以 **3a** 为例，具体操作如下：在 25 mL 试管中，将 **2a**（78.9 mg，0.2 mmol）和 KOH（44.9 mg，0.8 mmol，4.0 当量）在乙醇（2 mL，0.1 M）中混合搅拌并在油浴中加热至 80 °C 反应 2 小时。随后将混合物冷却至 0 °C，收集析出的钾盐并溶解于水（5 mL）中。用盐酸（5 M）将溶液酸化至 pH 2.0，得到棕色固体，将其溶解于乙酸酐（2 mL）中，并在油浴中加热至 140 °C 反应 2 小时。冷却后，将所得混合物用水洗涤并用乙酸乙酯（3 × 10 mL）萃取。合并有机相，用无水 Na_2SO_4 干燥并在真空下浓缩。残留物通过硅胶柱色谱分离，以乙酸乙酯为洗脱剂，最终以 62% 的收率（38.1 mg）获得内酰胺 **4a**（Scheme 2-6）。这一结果表明该方法具有实际应用潜力。



3a **4a**, 62%

Scheme 2-6 Derivatization experiment

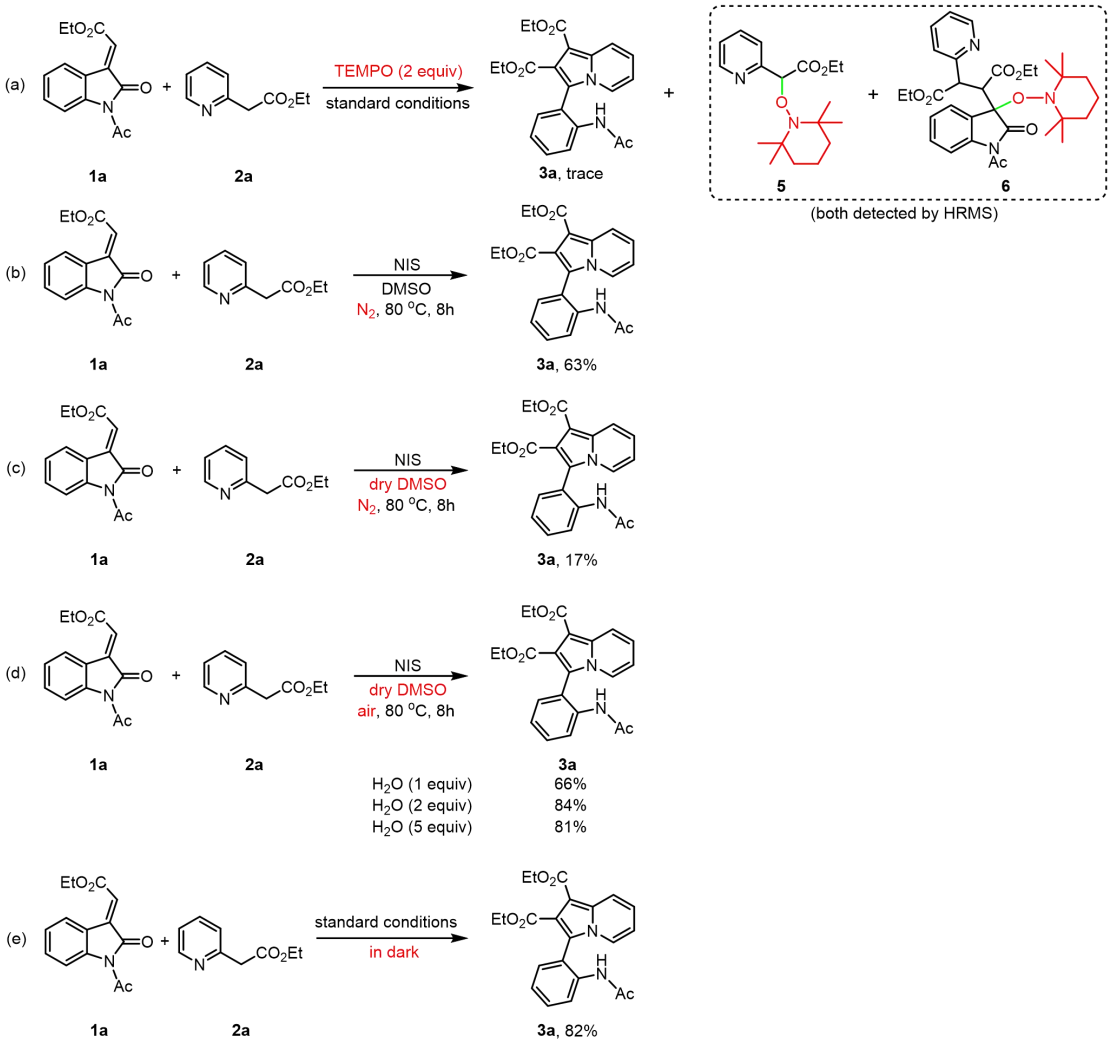
2.6.3 化合物 4a 的表征



Ethyl 6-Oxo-5,6-dihydroindolizino[2,3-c]quinoline-7-carboxylate (4a). Ethyl acetate as the eluent; Yellow solid, 62% yield (38.1 mg), mp 262–264 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.66 (s, 1H), 9.33 (d, J = 7.2 Hz, 1H), 8.52 (d, J = 8.2 Hz, 1H), 8.10 (d, J = 9.2 Hz, 1H), 7.52 (d, J = 7.9 Hz, 1H), 7.47 (t, J = 7.6 Hz, 1H), 7.35 (dd, J = 9.0, 6.9 Hz, 1H), 7.32 (t, J = 7.7 Hz, 1H), 7.11 (t, J = 6.8 Hz, 1H), 4.35 (q, J = 7.1 Hz, 2H), 1.37 (t, J = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (126 MHz, DMSO- d_6) δ 163.5, 157.8, 136.9, 136.2, 127.3, 127.2, 125.6, 124.3, 122.0, 121.0, 119.5, 117.0, 116.1, 114.3, 112.3, 102.3, 60.0, 14.3; HRMS (ESI-TOF) calcd for $C_{18}H_{14}N_2O_3Na$ [M + Na]$^+$ 329.0902, found 329.0909.

2.7 反应机理探究

为确定反应是否通过自由基途径进行，我们进行了自由基捕获实验（Scheme 2-7a）。加入 2 当量 2,2,6,6-四甲基哌啶氮氧自由基（TEMPO）后，**1a** 与 **2a** 的反应几乎被完全抑制。HRMS 检测到 2-(吡啶-2-基)乙酸乙酯自由基捕获产物 **5** 和自由基加合物 **6**（Figure 2-3、Figure 2-4），这表明该反应可能涉及自由基机制，2-吡啶乙酸乙酯自由基和自由基加合物是该转化的关键中间体。反应在氮气条件下顺利进行，但产率降低至 63%（Scheme 2-7b）。当反应在无水 DMSO 中于惰性气氛下进行时，**3a** 的产率显著降低至 17%（Scheme 2-7c）。结果表明，溶剂中的水对吲哚嗪的形成至关重要。为了进一步研究水在该反应中的作用，我们使用无水 DMSO 作为溶剂，并添加不同当量的水进行了实验（Scheme 2-7d）。结果表明，2 当量的水足以高效促进该转化。此外，反应在完全黑暗的条件下进行，获得了与之前收率相当的 **3a**（Scheme 2-7e），有效排除了光诱导反应的可能性。



Scheme 2-7 Control Experiments

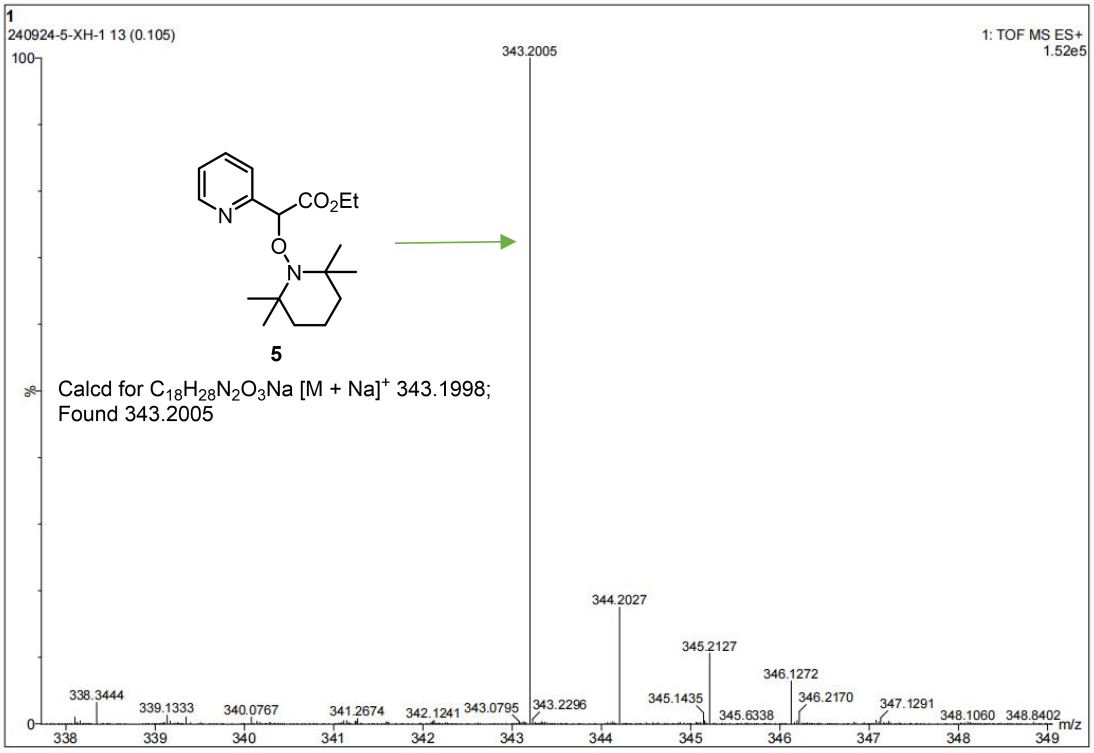


Figure 2-3. HRMS of free radical trapping adduct **5**

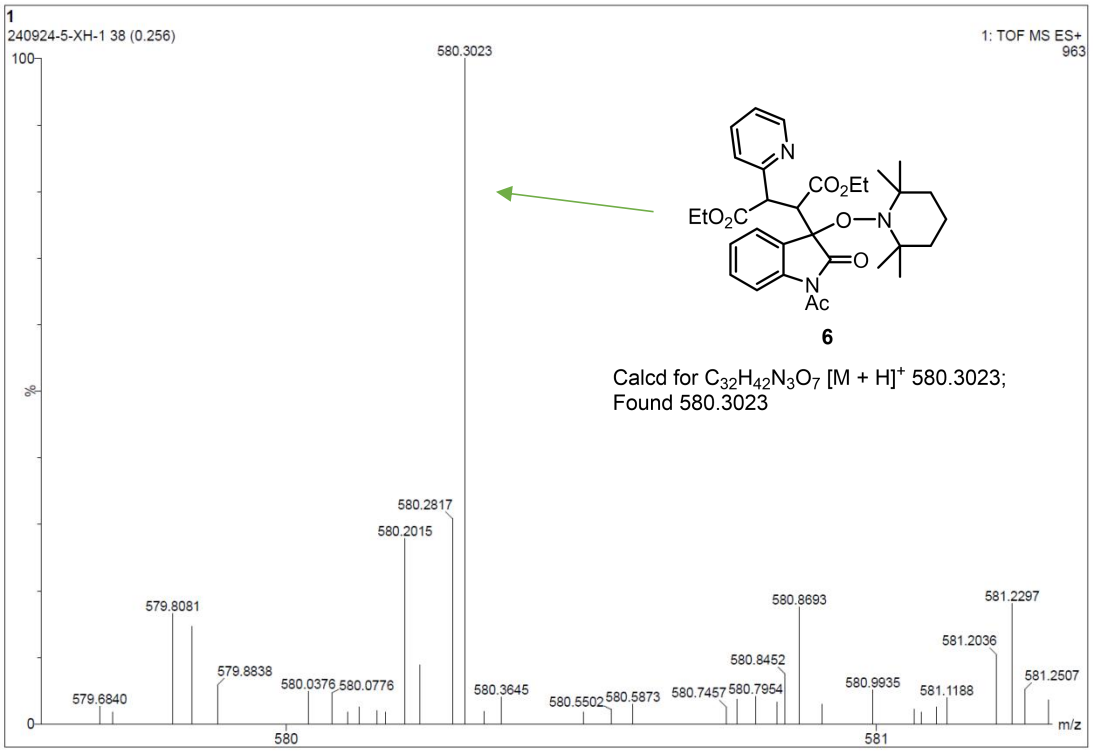
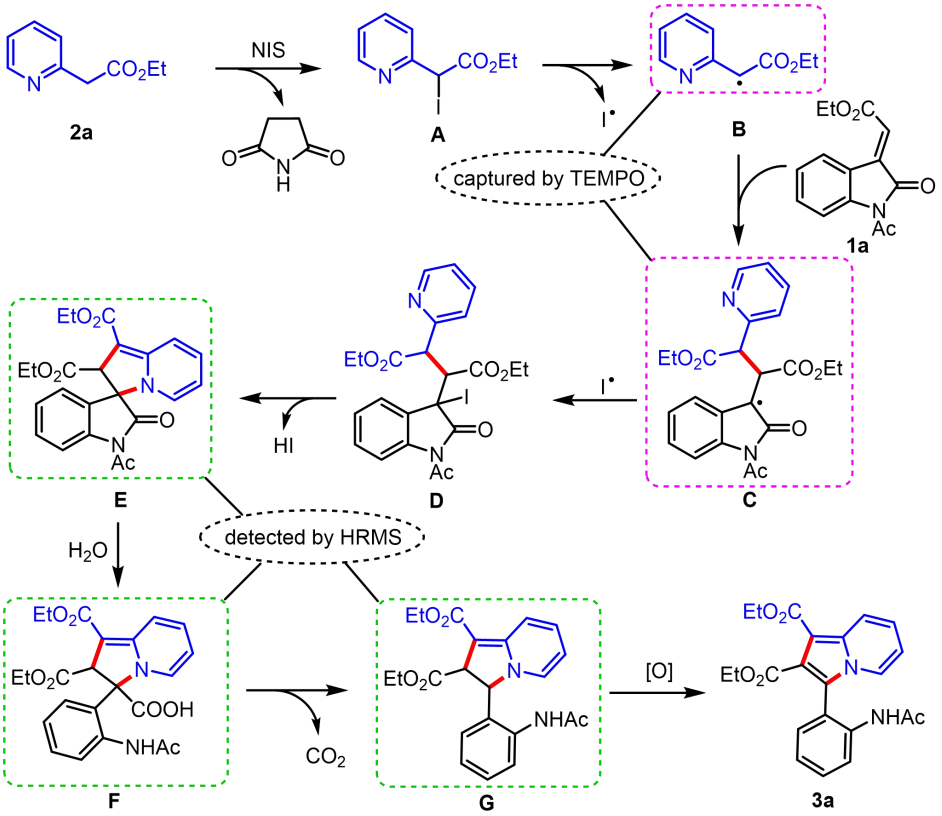


Figure 2-4. HRMS of free radical trapping adduct **6**

基于上述实验结果和相关文献报道，我们提出了一种可能的机制，以 **1a** 和 **2a** 形成 **3a** 为例，如 Scheme 2-8 所示。首先，**2a** 与 NIS 反应形成碘化中间体 **A**。中间体 **A** 经历 C-I 键的均裂，产生自由基中间体 **B** 和碘自由基。然后，中间体 **B** 与 **1a** 发生自由基加成反应，产生自由基物种 **C**，其立即与碘自由基结合产生碘化物 **D**。随后，发生分子内亲核取代反应，形成螺环中间体 **E**。中间体 **E** 在体系中水的存在下进行水解，形成开环中间体 **F**，然后通过脱羧反应转化为二氢中氮茚 **G**。最后，**G** 在空气中被 DMSO[106-108]或氧气氧化，得到产物 **3a**。值得一提的是，中间体 **E**、**F** 和 **G** 都被 HRMS 检测到（Figure 2-5- 2-7）。该反应的成功可能取决于自由基中间体的稳定性。当吸电子基团连接到烷基吡啶上时，它们分散了自由基中间体 **B** 的电子密度，从而促进其形成相对稳定的中间体。类似地，吸电子基团连接到亚烷基氧化吲哚的氮原子上也有助于自由基中间体 **C** 的生成。这也解释了 Table 2-2 出现失败案例的原因。



Scheme 2-8. Proposed Reaction Mechanism

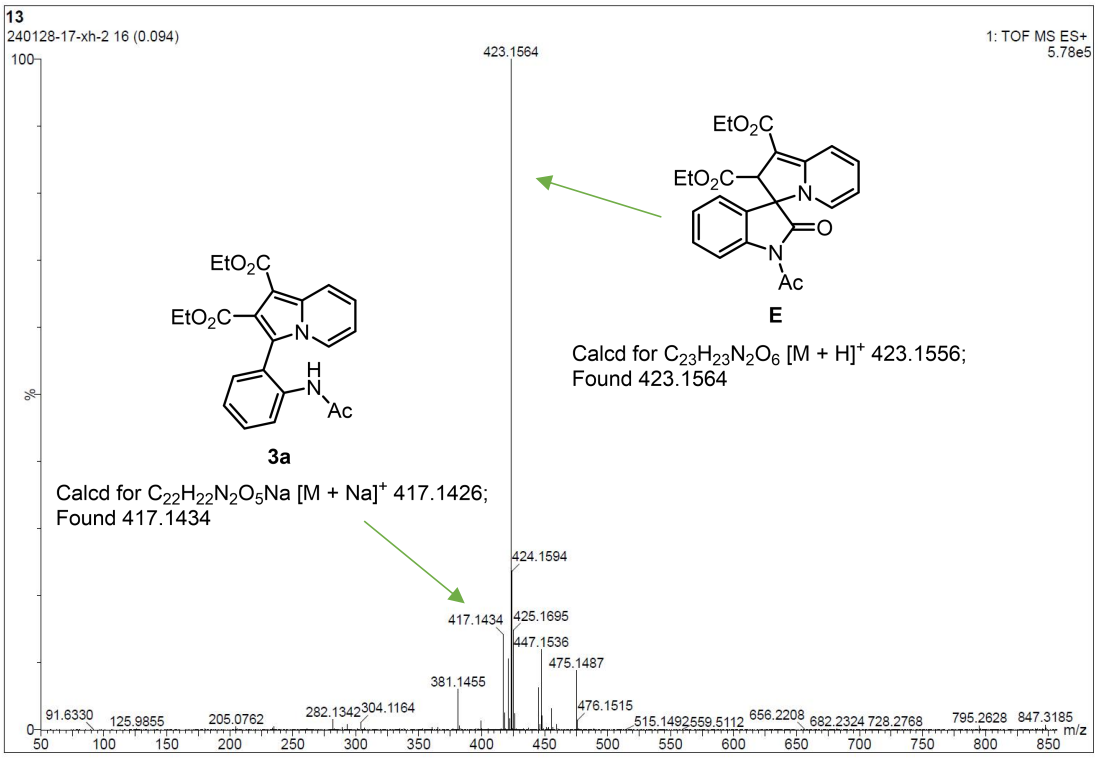


Figure 2-5**.** HRMS of intermediate **E** and product **3a**

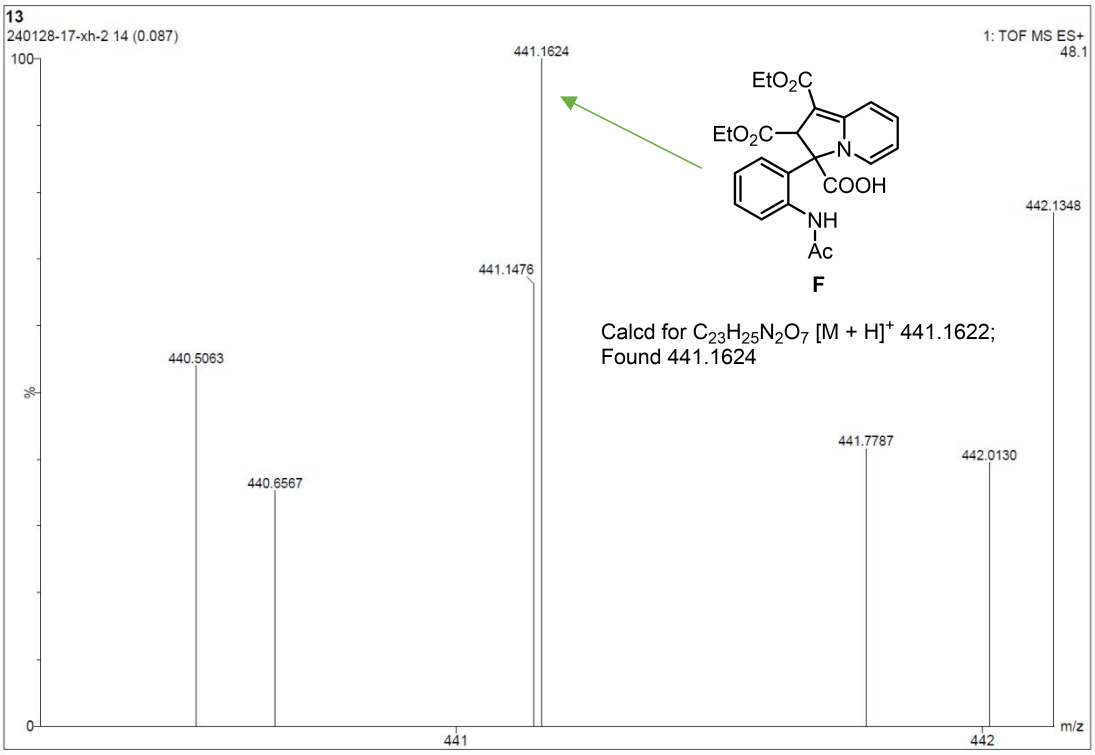


Figure 2-6. HRMS of intermediate **F**

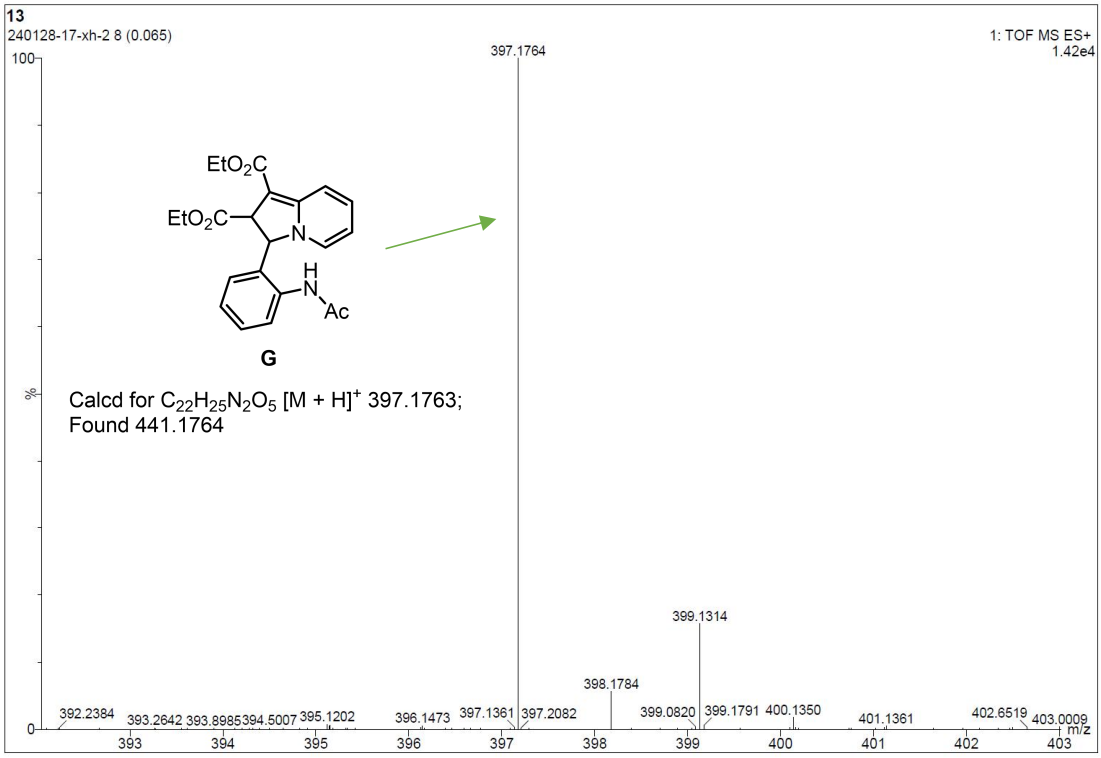


Figure 2-7. HRMS of intermediate **G**

2.8 本章小结

综上所述，我们开发了一种亚烷基氧化吲哚与 2-(吡啶-2-基)乙酸酯衍生物的螺环化/开环芳构化反应，用于构建吲哚嗪。首先，我们建立了模型反应并通过条件筛选确定了最优反应条件：亚烷基氧化吲哚 **1**、1.0 当量 2-(吡啶-2-基)乙酸酯衍生物 **2** 和 1.0 当量 NIS 在 DMSO 中于 80 ºC 反应 8 小时。在最优条件下，我们以 50–91%的收率合成了 42 个吲哚嗪类化合物，并通过 X-射线单晶衍射进一步确定了产物结构，同时提出了可能的反应机理。该反应能够高效、直接地构建多种吲哚嗪衍生物，产物富含多个官能团，便于进一步修饰。该方法具有高效性、广泛的官能团耐受性、条件温和、成本低、原料易得等优点，为吲哚嗪类化合物的合成提供了一种新途径。

第 3 章 不饱和异恶唑酮与 2-烷基吡啶的螺环化/芳构化反应研究

3.1 实验部分

3.1.1 仪器与试剂

新增仪器如下，其他仪器同上一章节。

Table 3-1. Main experimental instrument

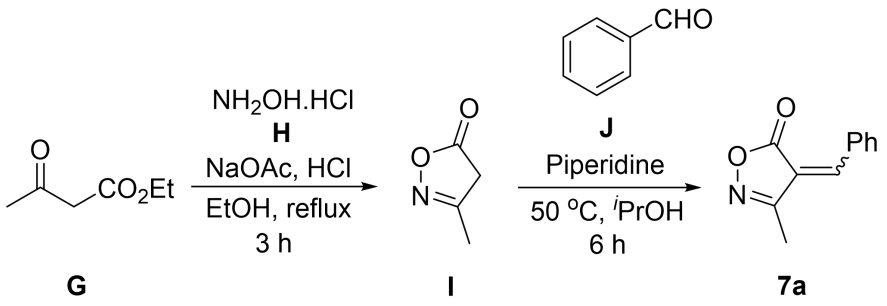
仪器名称	型号	生产厂家
球磨机	MM 400	德国 Retsch 公司

新增试剂如下。

Table 3-2. Main experimental chemicals

试剂名称	纯度	生产厂家
盐酸	分析纯	国药集团化学试剂有限公司
盐酸羟胺	分析纯	上海泰坦科技有限公司
乙酰乙酸乙酯	分析纯	上海泰坦科技有限公司
乙酸钠	分析纯	萨恩化学技术（上海）有限公司
六氢哌啶	分析纯	上海泰坦科技有限公司

3.1.2 原料的合成

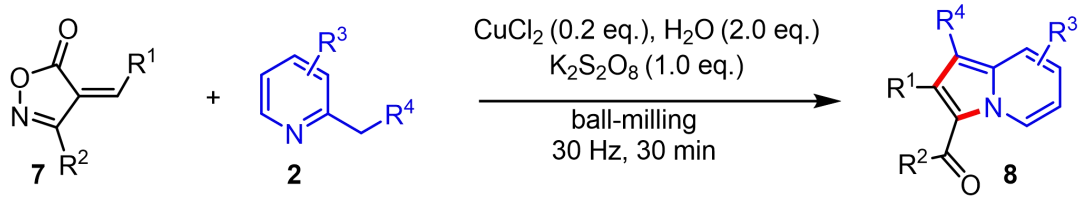


Scheme 3-1 Synthesis of unsaturated-isoxazolone

以合成 **7a** 为例，先将 NaOAc（15 mmol, 1.23 g）与盐酸羟胺 **H**（15 mmol, 1.04 g）加入 50 mL 圆底烧瓶中，然后加入 20 mL 乙醇，将圆底烧瓶放入 78 °C 的油浴锅中搅拌 5 min，随后缓慢加入乙酰乙酸乙酯 **G**（10 mmol, 1.30 g），使用 TLC 对反应进行监控（乙酸乙酯:石油醚=1:2），当乙酰乙酸乙酯完全消耗后产物中会残留未反应完全的中间体，此时加入 50 μL 盐酸继续反应 3 h 直至中间

体完全消失后过滤。收集滤液，旋干后加入适量乙酸乙酯萃取，重复操作三次合并有机相后进行柱层析（乙酸乙酯:石油醚=1:2）分离后得到黄色油状中间产物 **I**（89%, 0.88 g）。随后将 **I**（8 mmol, 0.79 g）和苯甲醛 **J**（9.6 mmol, 1.02 g）加入到盛有 20 mL 异丙醇的 50 mL 圆底烧瓶中，再加入 40 μL 哌啶,于 50 °C 下反应 6 h，逐渐有黄色固体产生。待到反应结束后过滤得到黄色异噁唑酮固体 **7a**（83%, 1.24 g）。

3.1.3 产物的合成



Scheme 3-2 Synthesis of Compound **8**

以合成 **8aa** 为例，将 **7a**（0.2 mmol）、**2a**（0.2 mmol）、$CuCl_2$（0.04 mmol）、$K_2S_2O_8$（0.2 mmol）和 H_2O（0.4 mmol）加入装有 4 颗研磨球（直径 6 mm）的 5 mL 不锈钢研磨罐中。将密封的研磨罐固定在 Retsch MM400 研磨仪上，于室温下以 1800 rpm（30 Hz）研磨 30 分钟。反应完成后，用乙酸乙酯溶解混合物，转移至茄形瓶，加入少量硅胶，减压浓缩至粉末状，经柱色谱法分离得到产物 **8aa**。

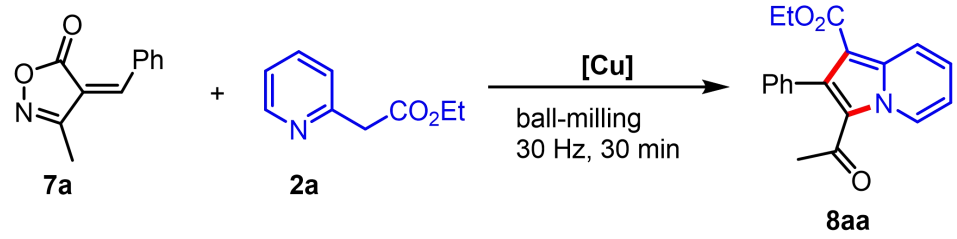
3.2 实验结果与讨论

3.2.1 条件优化

以异噁唑酮 **7a** 和 2-吡啶乙酸乙酯 **2a** 作为模型底物，在球磨机中系统优化反应条件。首先，我们将 **7a**（0.2 mmol）、**2a**（0.2 mmol，1.0 当量）、$CuCl_2$（0.04 mmol，0.2 当量）、$K_2S_2O_8$（0.2 mmol，1.0 当量）与 H_2O（0.2 mmol，1.0 当量）混合，在球磨条件下反应 30 分钟。使用 TLC 对反应进行监控，分离疑似目标产物。通过核磁共振（NMR）分析，确认为吲哚嗪类衍生物 **8aa**（Table 3-3, entry 1）。随后，我们对添加 H_2O 的量进行探索。我们发现在无添加 H_2O 时，几乎没有目标产物生成（Table 3-3, entry 2），这说明在该反应中

H_2O 是必要的。当添加 2.0 当量水时（Table 3-3, entry 3），反应效果最佳，收率为 85%。然而，继续增加水的量，收率并没有进一步提高（Table 3-3, entries 4-5）。接下来，我们尝试了其它的铜盐作为催化剂，如 CuI、$CuSO_4 \cdot 5H_2O$、$CuBr_2$、CuCN 等（Table 3-3, entries 6–13），发现还是当 $CuCl_2$ 作为催化剂时反应效果最佳（Table 3-3, entry 3）。然后，我们又对氧化剂进行筛选（Table 3-3, entries 14-18），发现当氧化剂为过硫酸盐时其反应效果较佳，其中过硫酸钾的反应效果最好（Table 3-3, entry 3）。最后，我们对氧化剂过硫酸钾的量进行筛选（Table 3-3, entries 19-21），发现其在 1.0 当量的时候就能较好的得到目标产物，进一步增加过硫酸钾的量收率没有显著提升。因此,最终确定的最优反应条件为：**7a**、**2a**（1.0 当量）、$CuCl_2$（0.2 当量）、$K_2S_2O_8$（1.0 当量）与 H_2O（2.0 当量）混合,在球磨条件下反应 30 分钟。

Table 3-3. Optimization of the Reaction Conditions[a]



Entry	[Cu] (mol%)	H_2O (equiv.)	Additive (equiv.)	Yield[b] (%)
1	$CuCl_2$ (20)	1.0	$K_2S_2O_8$ (1.0)	63
2	$CuCl_2$ (20)		$K_2S_2O_8$ (1.0)	trace
3	$CuCl_2$ (20)	2.0	$K_2S_2O_8$ (1.0)	85
4	$CuCl_2$ (20)	3.0	$K_2S_2O_8$ (1.0)	78
5	$CuCl_2$ (20)	4.0	$K_2S_2O_8$ (1.0)	67
6	CuI (20)	2.0	$K_2S_2O_8$ (1.0)	58
7	$CuSO_4 \cdot 5H_2O$ (20)	2.0	$K_2S_2O_8$ (1.0)	n.d.
8	$CuBr_2$ (20)	2.0	$K_2S_2O_8$ (1.0)	65
9	$Cu(acac)_2$ (20)	2.0	$K_2S_2O_8$ (1.0)	n.d.
10	$Cu(OAc)_2 \cdot H_2O$ (20)	2.0	$K_2S_2O_8$ (1.0)	trace
11	CuCN (20)	2.0	$K_2S_2O_8$ (1.0)	trace
12	CuCl (20)	2.0	$K_2S_2O_8$ (1.0)	53
13	CuO (20)	2.0	$K_2S_2O_8$ (1.0)	trace

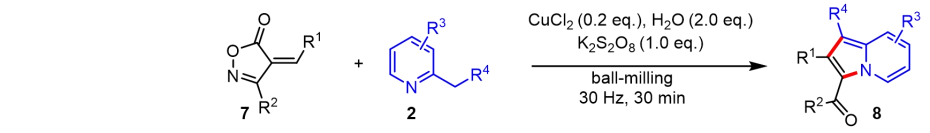
14	$CuCl_2$ (20)	2.0	$(NH_4)_2S_2O_8$ (1.0)	70
15	$CuCl_2$ (20)	2.0	$NaIO_4$ (1.0)	20
16	$CuCl_2$ (20)	2.0	$KMnO_4$ (1.0)	n.d.
17	$CuCl_2$ (20)	2.0	$Na_2S_2O_8$ (1.0)	75
18	$CuCl_2$ (20)	2.0	$K_2Cr_2O_7$ (1.0)	trace
19	$CuCl_2$ (20)	2.0	$K_2S_2O_8$ (0.5)	68
20	$CuCl_2$ (20)	2.0	$K_2S_2O_8$ (0.8)	72
21	$CuCl_2$ (20)	2.0	$K_2S_2O_8$ (1.2)	83

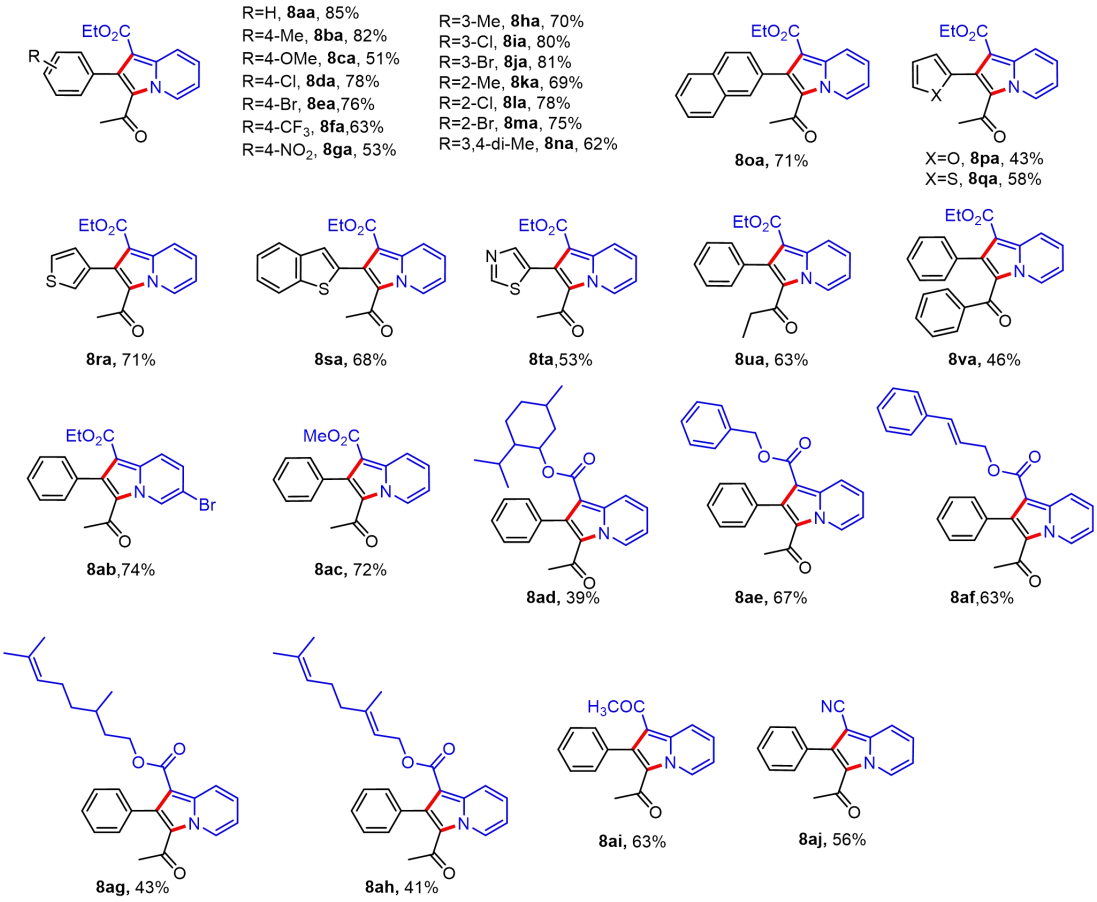
[a]Unless otherwise noted, the reaction conditions were as follows: **7a** (0.2 mmol), **2a** (0.2 mmol), a copper salt, an oxidant, and H_2O together with four stainless balls (6 mm in diameter) were milled in a Retsch MM400 mixer mill at 30 Hz for 30 min. [b]Isolated yields based on **7a**.

3.2.2 底物扩展

在确定了最优反应条件后，我们对该方法的普适性进行了探索，结果总结在表 3-2 中。首先，考察了一系列异噁唑 **1** 的反应性。在优化条件下，苯环上带有不同取代基（如 Me、OMe、Cl、Br、NO_2 和 CF_3）的异噁唑与 **2a** 顺利反应，得到相应的芳构化产物 **8ba–ma**，收率为 51–82%。接下来，我们将异噁唑中的苯环替换为其他杂环以测试普适性。结果表明，当苯基被替换为萘、呋喃、噻吩、苯并噻吩或噻唑时，皆能得到相应的目标产物 **8oa**–**ta**，收率为 43–71%。此外，我们将异噁唑上的甲基替换为乙基或苯基，反应也能顺利进行，分别以 63%和 46%的收率得到目标产物 **8ua** 和 **8va**。随后，我们对 2-(吡啶-2-基)乙酸酯衍生物的反应性进行探索。当在吡啶环上引入溴时，反应仍能较好进行，目标产物 **8ab** 的收率为 74%。当我们将 2-吡啶衍生物上的乙酯替换为其他酯类（如甲酯等）也能得到目标产物 **8ac–ah**，收率为 39–72%。为进一步扩展底物范围，我们将乙酸乙酯基替换为其他吸电子基团（如酰基和氰基），也能得到相应的目标产物 **8ai** 和 **8aj** 的收率分别为 63%和 56%。

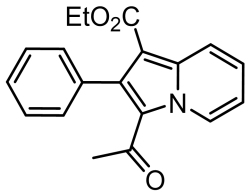
Table 3-4. Reaction of Unsaturated Isoxazolones with 2-(Pyridin-2-yl)acetate Derivatives under Mechanochemical Conditions[a,b]





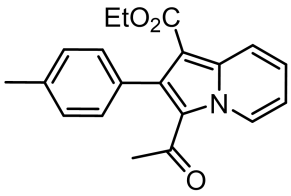
[a]Unless otherwise noted, the reaction conditions were as follows: **7** (0.2 mmol), **2** (0.2 mmol), $CuCl_2$ (0.04 mmol), $K_2S_2O_8$ (0.2 mmol), and H_2O (0.4 mmol) together with four stainless balls (6 mm in diameter) were milled in a Retsch MM400 mixer mill at 30 Hz for 30 min. [b]Isolated yields based on **7**.

3.3 化合物表征

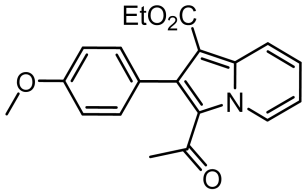


Ethyl 3-acetyl-2-phenylindolizine-1-carboxylate (8aa). Ethyl acetate/petroleum ether = 1:8 as the eluent; Yellow oil, 85% yield (78.3 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.07 (d, J = 7.1 Hz, 1H), 8.46 (d, J = 9.0 Hz, 1H), 7.47–7.40 (m, 4H),

7.36–7.31 (m, 2H), 7.05 (t, J = 6.6 Hz, 1H), 4.09 (q, J = 7.1 Hz, 2H), 1.90 (s, 3H), 0.99 (t, J = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 190.1, 164.4, 141.1, 138.8, 136.4, 129.4 (2C), 129.2, 128.0 (2C), 127.9, 127.6, 122.5, 119.5, 115.4, 105.9, 59.6, 30.8, 13.9; HRMS (ESI-TOF) calcd for $C_{19}H_{18}NO_3$ $[M + H]^+$ 308.1287, found 308.1290.

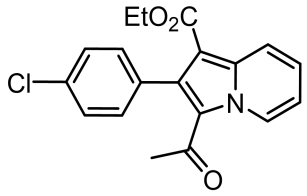


Ethyl 3-acetyl-2-(*p*-tolyl)indolizine-1-carboxylate (8ba). Ethyl acetate/petroleum ether = 1:8 as the eluent; Yellow solid, 82% yield (79.4 mg), mp 132–134 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.05 (d, J = 7.1 Hz, 1H), 8.42 (d, J = 8.9 Hz, 1H), 7.41 (t, J = 7.8 Hz, 1H), 7.25 (d, J = 7.5 Hz, 2H), 7.21 (d, J = 7.5 Hz, 2H), 7.02 (t, J = 6.9 Hz, 1H), 4.12 (q, J = 7.0 Hz, 2H), 2.43 (s, 3H), 1.93 (s, 3H), 1.05 (t, J = 7.0 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 190.1, 164.3, 141.4, 138.6, 137.5, 133.1, 129.2 (2C), 129.1, 128.7 (2C), 127.4, 122.6, 119.4, 115.2, 105.9, 59.6, 30.8, 21.4, 13.9; HRMS (ESI-TOF) calcd for $C_{20}H_{20}NO_3$ $[M + H]^+$ 322.1443, found 322.1442.

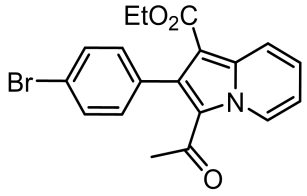


Ethyl 3-acetyl-2-(4-methoxyphenyl)indolizine-1-carboxylate (8ca). Ethyl acetate/petroleum ether = 1:6 as the eluent; Yellow solid, 51% yield (51.6 mg), mp 132–134 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.05 (d, J = 7.2 Hz, 1H), 8.43 (d, J = 8.9 Hz, 1H), 7.42 (ddd, J = 8.9, 6.9, 1.1 Hz, 1H), 7.25 (dt, J = 8.7, 2.4 Hz, 2H), 7.04 (td, J = 7.0, 1.4 Hz, 1H), 6.99 (dt, J = 8.7, 2.4 Hz, 2H), 4.13 (q, J = 7.1 Hz, 2H), 3.88 (s, 3H), 1.94 (s, 3H), 1.08 (t, J = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 190.2, 164.5, 159.5, 141.1, 138.7, 130.6 (2C), 129.2, 128.2, 127.5, 122.8, 119.5, 115.3, 113.5 (2C), 106.0, 59.7, 55.4, 30.8, 14.1; HRMS (ESI-TOF) calcd for $C_{20}H_{20}NO_4$ $[M + H]^+$

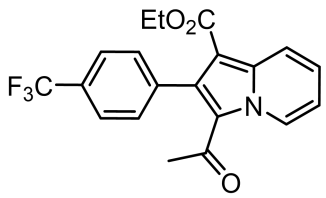
338.1392, found 338.1397.



Ethyl 3-acetyl-2-(4-chlorophenyl)indolizine-1-carboxylate (8da). Ethyl acetate/petroleum ether = 1:8 as the eluent; Yellow solid, 78% yield (79.6 mg), mp 171–173 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.04 (d, J = 7.1 Hz, 1H), 8.44 (d, J = 8.8 Hz, 1H), 7.47–7.38 (m, 3H), 7.29 (d, J = 7.3 Hz, 2H), 7.05 (t, J = 7.0 Hz, 1H), 4.12 (q, J = 7.1 Hz, 2H), 1.93 (s, 3H), 1.06 (t, J = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 189.6, 164.1, 139.5, 138.7, 134.9, 134.0, 130.8 (2C), 129.1, 128.3 (2C), 127.7, 122.5, 119.5, 115.5, 105.8, 59.8, 30.9, 13.9; HRMS (ESI-TOF) calcd for $C_{19}H_{17}{}^{35}ClNO_3$ $[M + H]^+$ 342.0897, found 342.0899.

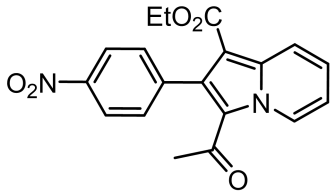


Ethyl 3-acetyl-2-(4-bromophenyl)indolizine-1-carboxylate (8ea). Ethyl acetate/petroleum ether = 1:8 as the eluent; Yellow solid, 76% yield (87.8 mg), mp 176–178 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.03 (d, J = 7.0 Hz, 1H), 8.43 (d, J = 8.9 Hz, 1H), 7.59 (d, J = 7.4 Hz, 2H), 7.42 (t, J = 7.8 Hz, 1H), 7.23 (d, J = 7.5 Hz, 2H), 7.04 (t, J = 6.8 Hz, 1H), 4.12 (q, J = 7.0 Hz, 2H), 1.93 (s, 3H), 1.06 (t, J = 7.0 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 189.4, 164.0, 139.3, 138.6, 135.3, 131.1 (2C), 131.0 (2C), 129.0, 127.6, 122.3, 122.0, 119.4, 115.4, 105.6, 59.7, 30.9, 13.9; HRMS (ESI-TOF) calcd for $C_{19}H_{17}{}^{79}BrNO_3$ $[M + H]^+$ 386.0392, found 386.0398.

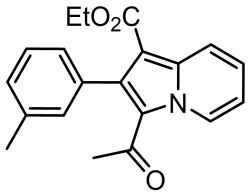


Ethyl 3-acetyl-2-(4-(trifluoromethyl)phenyl)indolizine-1-carboxylate (8fa). Ethyl

acetate/petroleum ether = 1:6 as the eluent; Yellow solid, 63% yield (71.3 mg), mp 192–194 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.07 (d, J = 7.2 Hz, 1H), 8.47 (d, J = 8.9 Hz, 1H), 7.73 (d, J = 8.0 Hz, 2H), 7.50 (d, J = 8.0 Hz, 2H), 7.47 (ddd, J = 8.9, 6.9, 1.1 Hz, 1H), 7.08 (td, J = 7.0, 1.4 Hz, 1H), 4.08 (q, J = 7.1 Hz, 2H), 1.90 (s, 3H), 0.97 (t, J = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 189.5, 164.1, 140.6, 139.1, 138.8, 130.3 (q, J = 32.6 Hz), 129.9 (2C), 129.3, 128.0, 125.0 (q, J = 3.6 Hz, 2C), 124.3 (q, J = 272.6 Hz), 122.4, 119.6, 115.7, 105.8, 59.8, 31.0, 13.7; ^{19}F NMR (471 MHz, $CDCl_3$) δ -62.45 (s, 1F); HRMS (ESI-TOF) calcd for $C_{20}H_{17}F_3NO_3$ $[M + H]^+$ 376.1161, found 376.1160.

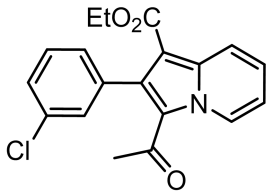


Ethyl 3-acetyl-2-(4-nitrophenyl)indolizine-1-carboxylate (8ga). Ethyl acetate/petroleum ether = 1:4 as the eluent; Yellow solid, 53% yield (55.8 mg), mp 217–219 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.07 (d, J = 7.2 Hz, 1H), 8.47 (d, J = 9.0 Hz, 1H), 8.35 (d, J = 8.7 Hz, 2H), 7.57 (d, J = 8.7 Hz, 2H), 7.50 (ddd, J = 8.9, 7.0, 1.1 Hz, 1H), 7.12 (td, J = 7.0, 1.4 Hz, 1H), 4.12 (q, J = 7.1 Hz, 2H), 1.90 (s, 3H), 1.05 (t, J = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 189.1, 163.8, 147.7, 143.9, 138.7, 138.1, 130.6 (2C), 129.3, 128.2, 123.3 (2C), 122.2, 119.7, 115.9, 105.7, 60.0, 31.1, 14.0; HRMS (ESI-TOF) calcd for $C_{19}H_{17}N_2O_5$ $[M + H]^+$ 353.1137, found 353.1141.

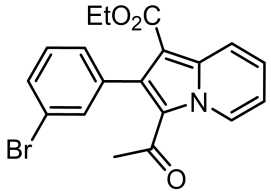


Ethyl 3-acetyl-2-(*m*-tolyl)indolizine-1-carboxylate (8ha). Ethyl acetate/petroleum ether = 1:8 as the eluent; Yellow oil, 70% yield (67.4 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.05 (dt, J = 7.2, 1.0 Hz, 1H), 8.44 (dt, J = 8.9, 1.2 Hz, 1H), 7.41 (ddd, J = 8.9, 6.9, 1.2 Hz, 1H), 7.32 (t, J = 7.6 Hz, 1H), 7.23 (d, J = 7.7 Hz, 1H), 7.15 (s, 1H),

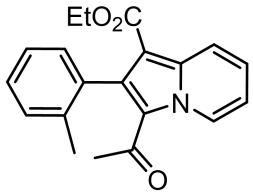
7.13 (d, J = 7.6 Hz, 1H), 7.03 (td, J = 7.0, 1.4 Hz, 1H), 4.14–4.05 (m, 2H), 2.41 (s, 3H), 1.92 (s, 3H), 1.00 (t, J = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 190.1, 164.3, 141.2, 138.7, 137.4, 136.2, 130.0, 129.1, 128.5, 127.8, 127.5, 126.5, 122.5, 119.4, 115.2, 105.8, 59.5, 30.7, 21.5, 13.8; HRMS (ESI-TOF) calcd for $C_{20}H_{20}NO_3$ [M + H]$^+$ 322.1443, found 322.1443.



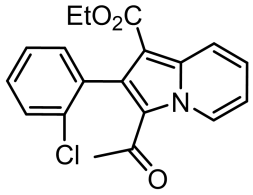
Ethyl 3-acetyl-2-(3-chlorophenyl)indolizine-1-carboxylate (8ia). Ethyl acetate/petroleum ether = 1:8 as the eluent; Yellow solid, 80% yield (81.7 mg), mp 106–108 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.04 (d, J = 7.1 Hz, 1H), 8.46 (d, J = 9.0 Hz, 1H), 7.46–7.36 (m, 4H), 7.24 (d, J = 7.3 Hz, 1H), 7.05 (td, J = 6.9, 1.1 Hz, 1H), 4.17–4.03 (m, 2H), 1.94 (s, 3H), 1.02 (t, J = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 189.5, 164.0, 138.9, 138.7, 138.2, 133.8, 129.6, 129.2, 129.1, 128.0, 127.8, 127.7, 122.3, 119.5, 115.5, 105.8, 59.7, 30.9, 13.8; HRMS (ESI-TOF) calcd for $C_{19}H_{17}{}^{35}ClNO_3$ [M + H]$^+$ 342.0897, found 342.0892.



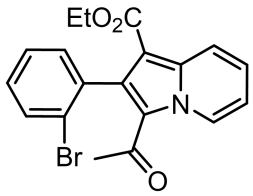
Ethyl 3-acetyl-2-(3-bromophenyl)indolizine-1-carboxylate (8ja). Ethyl acetate/petroleum ether = 1:8 as the eluent; Yellow solid, 81% yield (93.9 mg), mp 173–175 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.04 (d, J = 7.1 Hz, 1H), 8.44 (d, J = 9.0 Hz, 1H), 7.59 (d, J = 8.2 Hz, 2H), 7.44 (t, J = 7.9 Hz, 1H), 7.23 (d, J = 8.3 Hz, 2H), 7.05 (t, J = 6.9 Hz, 1H), 4.12 (q, J = 7.1 Hz, 2H), 1.93 (s, 3H), 1.06 (t, J = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 189.6, 164.1, 139.4, 138.7, 135.4, 131.2 (2C), 131.1 (2C), 129.2, 127.8, 122.4, 122.2, 119.5, 115.5, 105.8, 59.8, 31.0, 13.9; HRMS (ESI-TOF) calcd for $C_{19}H_{17}{}^{79}BrNO_3$ [M + H]$^+$ 386.0392, found 386.0391.



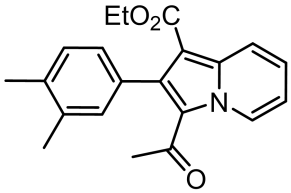
Ethyl 3-acetyl-2-(*o*-tolyl)indolizine-1-carboxylate (8ka). Ethyl acetate/petroleum ether = 1:8 as the eluent; Yellow solid, 69% yield (66.5 mg), mp 98–100 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.11 (d, J = 7.2 Hz, 1H), 8.48 (d, J = 9.0 Hz, 1H), 7.44 (ddd, J = 8.9, 6.9, 1.1 Hz, 1H), 7.35–7.28 (m, 2H), 7.26 (t, J = 7.3 Hz, 1H), 7.16 (d, J = 7.4 Hz, 1H), 7.06 (td, J = 7.0, 1.4 Hz, 1H), 4.14–4.02 (m, 2H), 2.12 (s, 3H), 1.87 (s, 3H), 0.97 (t, J = 7.2 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 189.8, 164.3, 140.5, 139.2, 136.13, 136.11, 129.7, 129.4, 129.0, 128.1, 127.6, 125.6, 121.8, 119.4, 115.3, 105.4, 59.6, 30.0, 20.2, 13.8; HRMS (ESI-TOF) calcd for $C_{20}H_{20}NO_3$ $[M + H]^+$ 322.1443, found 322.1437.



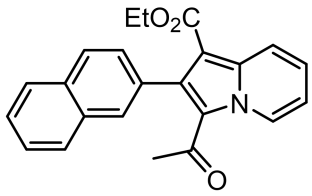
Ethyl 3-acetyl-2-(2-chlorophenyl)indolizine-1-carboxylate (8la). Ethyl acetate/petroleum ether = 1:8 as the eluent; Yellow solid, 78% yield (80.2 mg), mp 78–80 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.08 (d, J = 7.1 Hz, 1H), 8.49 (d, J = 9.0 Hz, 1H), 7.51 (d, J = 7.8 Hz, 1H), 7.45 (t, J = 7.9 Hz, 1H), 7.40 (t, J = 6.6 Hz, 1H), 7.36 (t, J = 7.3 Hz, 1H), 7.31 (d, J = 7.3 Hz, 1H), 7.07 (t, J = 7.0 Hz, 1H), 4.17–4.03 (m, 2H), 1.95 (s, 3H), 0.99 (t, J = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 189.5, 164.0, 139.0, 137.4, 135.8, 133.7, 130.9, 129.5, 129.35, 129.31, 127.7, 126.6, 122.0, 119.6, 115.5, 105.6, 59.7, 29.9, 13.8; HRMS (ESI-TOF) calcd for $C_{19}H_{17}{}^{35}ClNO_3$ $[M + H]^+$ 342.0897, found 342.0897.



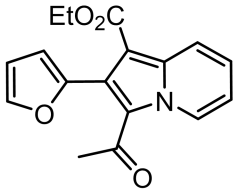
Ethyl 3-acetyl-2-(2-bromophenyl)indolizine-1-carboxylate (8ma). Ethyl acetate/petroleum ether = 1:8 as the eluent; Yellow solid, 75% yield (83.2 mg), mp 61–63 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.08 (d, J = 7.2 Hz, 1H), 8.49 (d, J = 9.0 Hz, 1H), 7.69 (d, J = 7.8 Hz, 1H), 7.43 (t, J = 8.0 Hz, 1H), 7.40 (t, J = 6.9 Hz, 1H), 7.34–7.27 (m, 2H), 7.05 (td, J = 7.0, 1.0 Hz, 1H), 4.18–4.01 (m, 2H), 1.95 (s, 3H), 0.99 (t, J = 7.2 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 189.3, 163.9, 138.9, 138.8, 137.8, 132.4, 130.8, 129.5, 129.2, 127.5, 127.1, 124.0, 121.7, 119.5, 115.4, 105.4, 59.6, 30.0, 13.8; HRMS (ESI-TOF) calcd for $C_{19}H_{17}{}^{79}BrNO_3$ $[M + H]^+$ 386.0392, found 386.0381.



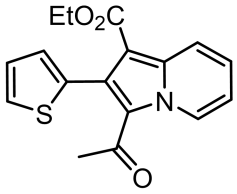
Ethyl 3-acetyl-2-(3,4-dimethylphenyl)indolizine-1-carboxylate (8na). Ethyl acetate/petroleum ether = 1:8 as the eluent; Yellow oil, 62% yield (62.3 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.05 (d, J = 6.9 Hz, 1H), 8.41 (d, J = 8.9 Hz, 1H), 7.39 (t, J = 7.8 Hz, 1H), 7.19 (d, J = 7.5 Hz, 1H), 7.10 (s, 1H), 7.05 (d, J = 7.6 Hz, 1H), 7.01 (t, J = 6.9 Hz, 1H), 4.19–4.06 (m, 2H), 2.34 (s, 3H), 2.31 (s, 3H), 1.94 (s, 3H), 1.05 (t, J = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 190.2, 164.3, 141.5, 138.6, 136.0, 135.9, 133.4, 130.5, 129.2, 129.1, 127.3, 126.8, 122.6, 119.4, 115.1, 105.8, 59.5, 30.7, 19.8, 19.7, 13.9; HRMS (ESI-TOF) calcd for $C_{21}H_{22}NO_3$ $[M + H]^+$ 336.1600, found 336.1607.



Ethyl 3-acetyl-2-(naphthalen-2-yl)indolizine-1-carboxylate (8oa). Ethyl acetate/petroleum ether = 1:6 as the eluent; Yellow solid, 71% yield (75.9 mg), mp 96–98 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.09 (d, J = 7.1 Hz, 1H), 8.48 (d, J = 8.9 Hz, 1H), 7.98–7.88 (m, 2H), 7.87–7.82 (m, 1H), 7.80 (s, 1H), 7.55–7.50 (m, 2H), 7.49 (d, J = 8.4 Hz, 1H), 7.45 (t, J = 7.9 Hz, 1H), 7.06 (t, J = 6.7 Hz, 1H), 4.03 (q, J = 7.1 Hz, 2H), 1.87 (s, 3H), 0.82 (t, J = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, CDCl3) δ 190.1, 164.4, 140.9, 138.8, 133.8, 133.1, 132.9, 129.2, 128.4, 128.1, 127.9, 127.7 (2C), 127.5, 126.4, 126.3, 122.8, 119.5, 115.4, 106.1, 59.7, 30.9, 13.8; HRMS (ESI-TOF) calcd for $C_{23}H_{20}NO_3$ $[M + H]^+$ 358.1443, found 358.1444.

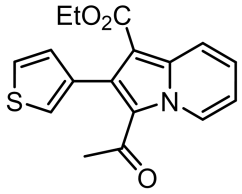


Ethyl 3-acetyl-2-(furan-2-yl)indolizine-1-carboxylate (8pa). Ethyl acetate/petroleum ether = 1:8 as the eluent; Yellow oil, 43% yield (38.3 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.98 (d, J = 7.2 Hz, 1H), 8.42 (d, J = 9.0 Hz, 1H), 7.63 (d, J = 1.6 Hz, 1H), 7.41 (ddd, J = 8.9, 7.0, 1.0 Hz, 1H), 7.04 (td, J = 7.0, 1.3 Hz, 1H), 6.58 (dd, J = 3.2, 1.9 Hz, 1H), 6.51 (d, J = 3.3 Hz, 1H), 4.22 (q, J = 7.1 Hz, 2H), 2.07 (s, 3H), 1.21 (t, J = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 189.8, 163.8, 145.8, 142.4, 138.3, 128.8, 128.6, 127.4, 123.3, 119.7, 115.7, 111.5, 111.3, 106.8, 59.9, 28.8, 14.2; HRMS (ESI-TOF) calcd for $C_{17}H_{16}NO_4$ $[M + H]^+$ 298.1079, found 298.1076.

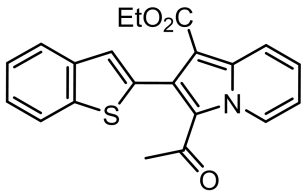


Ethyl 3-acetyl-2-(thiophen-2-yl)indolizine-1-carboxylate (8qa). Ethyl

acetate/petroleum ether = 1:8 as the eluent; Yellow oil, 58% yield (54.4 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.03 (d, J = 7.2 Hz, 1H), 8.44 (d, J = 9.0 Hz, 1H), 7.48 (dd, J = 5.1, 1.1 Hz, 1H), 7.43 (ddd, J = 8.9, 6.9, 1.1 Hz, 1H), 7.13 (dd, J = 5.1, 3.5 Hz, 1H), 7.08–7.02 (m, 2H), 4.17 (q, J = 7.1 Hz, 2H), 2.11 (s, 3H), 1.11 (t, J = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 190.2, 164.1, 138.6, 135.7, 132.5, 129.0, 128.5, 127.6, 126.9, 126.8, 123.5, 119.6, 115.6, 107.2, 59.8, 29.8, 14.0; HRMS (ESI-TOF) calcd for $C_{17}H_{16}NO_3S$ $[M + H]^+$ 314.0851, found 314.0850.

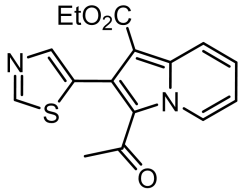


Ethyl 3-acetyl-2-(thiophen-3-yl)indolizine-1-carboxylate (8ra). Ethyl acetate/petroleum ether = 1:8 as the eluent; Yellow solid, 71% yield (66.7 mg), mp 76–78 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.02 (d, J = 7.2 Hz, 1H), 8.44 (d, J = 9.0 Hz, 1H), 7.44–7.39 (m, 2H), 7.20 (dd, J = 3.0, 1.2 Hz, 1H), 7.11 (dd, J = 4.9, 1.2 Hz, 1H), 7.03 (td, J = 7.0, 1.4 Hz, 1H), 4.14 (q, J = 7.1 Hz, 2H), 2.00 (s, 3H), 1.09 (t, J = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 190.0, 164.3, 138.8, 135.7, 135.3, 129.3, 129.0, 127.5, 125.1, 123.9, 122.8, 119.4, 115.3, 106.2, 59.7, 30.0, 14.0; HRMS (ESI-TOF) calcd for $C_{17}H_{16}NO_3S$ $[M + H]^+$ 314.0851, found 314.0859.

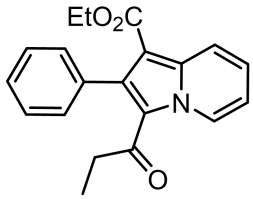


Ethyl 3-acetyl-2-(benzo[*b*]thiophen-2-yl)indolizine-1-carboxylate (8sa). Ethyl acetate/petroleum ether = 1:6 as the eluent; Yellow solid, 68% yield (73.9 mg), mp 177–179 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.05 (d, J = 7.2 Hz, 1H), 8.47 (d, J = 9.0 Hz, 1H), 7.87 (d, J = 7.8 Hz, 1H), 7.82 (d, J = 7.2 Hz, 1H), 7.44 (ddd, J = 8.8, 7.0, 1.0 Hz, 1H), 7.42–7.35 (m, 2H), 7.28 (s, 1H), 7.07 (td, J = 7.0, 1.3 Hz, 1H), 4.12 (q, J = 7.1 Hz, 2H), 2.20 (s, 3H), 0.94 (t, J = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ

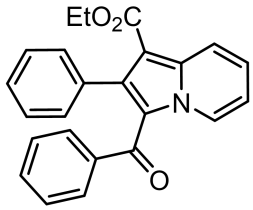
190.1, 163.9, 141.0, 139.7, 138.7, 136.6, 132.1, 129.1, 127.7, 125.4, 124.6 (2C), 123.8, 123.3, 122.2, 119.7, 115.8, 107.1, 59.9, 30.0, 13.8; HRMS (ESI-TOF) calcd for $C_{21}H_{18}NO_3S$ $[M + H]^+$ 364.1007, found 364.1005.



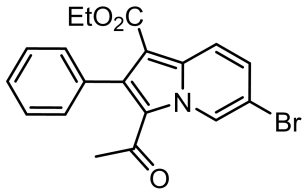
Ethyl 3-acetyl-2-(thiazol-5-yl)indolizine-1-carboxylate (8ta). Ethyl acetate/petroleum ether = 1:2 as the eluent; Yellow solid, 53% yield (49.9 mg), mp 100–102 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.02 (d, J = 6.8 Hz, 1H), 9.01 (s, 1H), 8.47 (d, J = 8.8 Hz, 1H), 7.83 (s, 1H), 7.45 (t, J = 7.6 Hz, 1H), 7.08 (t, J = 6.2 Hz, 1H), 4.16 (q, J = 6.9 Hz, 2H), 2.09 (s, 3H), 1.11 (t, J = 6.9 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 189.3, 163.6, 154.2, 143.5, 138.7, 130.7, 128.9, 127.8, 127.4, 123.4, 119.5, 115.9, 107.2, 59.9, 30.3, 14.0; HRMS (ESI-TOF) calcd for $C_{16}H_{15}N_2O_3S$ $[M + H]^+$ 315.0803, found 315.0806.



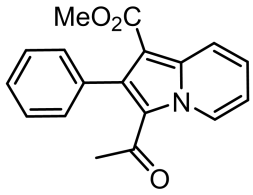
Ethyl 2-phenyl-3-propionylindolizine-1-carboxylate (8ua). Ethyl acetate/petroleum ether = 1:8 as the eluent; Yellow oil, 63% yield (61.2 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.06 (d, J = 7.2 Hz, 1H), 8.45 (d, J = 8.9 Hz, 1H), 7.47–7.39 (m, 4H), 7.35–7.31 (m, 2H), 7.03 (td, J = 7.0, 1.2 Hz, 1H), 4.08 (q, J = 7.1 Hz, 2H), 2.15 (q, J = 7.3 Hz, 2H), 0.99 (t, J = 7.1 Hz, 3H), 0.92 (t, J = 7.3 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 193.8, 164.5, 140.3, 138.8, 136.5, 129.4 (2C), 129.2, 128.0 (2C), 127.9, 127.4, 122.4, 119.5, 115.3, 105.8, 59.6, 35.0, 13.9, 8.9; HRMS (ESI-TOF) calcd for $C_{20}H_{20}NO_3$ $[M + H]^+$ 322.1443, found 322.1139.



Ethyl 3-benzoyl-2-phenylindolizine-1-carboxylate (8va). Ethyl acetate/petroleum ether = 1:8 as the eluent; Yellow solid, 46% yield (51.0 mg), mp 112–114 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.61 (d, J = 7.1 Hz, 1H), 8.46 (d, J = 9.0 Hz, 1H), 7.42 (t, J = 7.7 Hz, 1H), 7.35 (d, J = 7.3 Hz, 2H), 7.15 (t, J = 7.4 Hz, 1H), 7.11–7.06 (m, 2H), 7.06–6.93 (m, 6H), 4.16 (q, J = 7.1 Hz, 2H), 1.07 (t, J = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 188.5, 164.5, 140.4, 139.5, 139.3, 134.0, 131.3 (2C), 131.1, 129.3 (2C), 128.2, 127.5 (2C), 127.3, 127.2, 126.8 (2C), 122.4, 119.9, 115.0, 104.9, 59.8, 14.0; HRMS (ESI-TOF) calcd for $C_{24}H_{19}NO_3Na$ $[M + Na]^+$ 392.1263, found 392.1268.

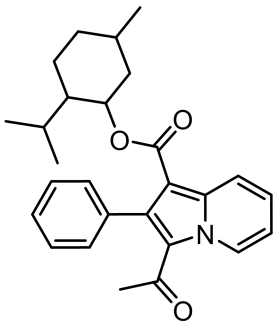


Ethyl 3-acetyl-6-bromo-2-phenylindolizine-1-carboxylate (8ab). Ethyl acetate/petroleum ether = 1:8 as the eluent; Yellow solid, 74% yield (85.5 mg), mp 111–113 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.25 (s, 1H), 8.35 (d, J = 9.5 Hz, 1H), 7.48 (dd, J = 9.5, 1.5 Hz, 1H), 7.46–7.42 (m, 3H), 7.34–7.30 (m, 2H), 4.08 (q, J = 7.1 Hz, 2H), 1.90 (s, 3H), 0.97 (t, J = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 190.2, 164.0, 140.8, 136.8, 135.8, 130.6, 129.3 (2C), 129.1, 128.1, 128.0 (2C), 122.5, 120.0, 110.3, 106.6, 59.8, 30.7, 13.8; HRMS (ESI-TOF) calcd for $C_{19}H_{17}{}^{79}BrNO_3$ $[M + H]^+$ 386.0392, found 386.0395.

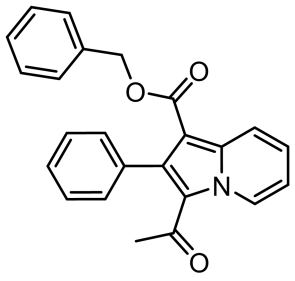


Methyl 3-acetyl-2-phenylindolizine-1-carboxylate (8ac). Ethyl acetate/petroleum

ether = 1:8 as the eluent; Yellow solid, 72% yield (63.4 mg), mp 135–137 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.06 (dt, J = 7.2, 1.0 Hz, 1H), 8.42 (dt, J = 9.0, 1.2 Hz, 1H), 7.48–7.41 (m, 4H), 7.36–7.32 (m, 2H), 7.05 (td, J = 7.0, 1.4 Hz, 1H), 3.65 (s, 3H), 1.89 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 190.2, 164.7, 141.3, 138.6, 136.1, 129.4 (2C), 129.3, 128.1 (2C), 128.0, 127.7, 122.7, 119.6, 115.4, 105.6, 51.0, 30.7; HRMS (ESI-TOF) calcd for $C_{18}H_{16}NO_3$ $[M + H]^+$ 294.1130, found 294.1131.

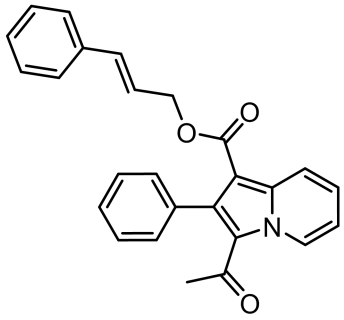


2-Isopropyl-5-methylcyclohexyl 3-acetyl-2-phenylindolizine-1-carboxylate (8ad). Ethyl acetate/petroleum ether = 1:8 as the eluent; Yellow oil, 39% yield (49.3 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.06 (d, J = 7.1 Hz, 1H), 8.52 (dt, J = 9.0, 1.1 Hz, 1H), 7.47–7.39 (m, 4H), 7.36–7.29 (m, 2H), 7.04 (td, J = 7.0, 1.4 Hz, 1H), 4.70 (td, J = 10.8, 4.4 Hz, 1H), 1.97–1.92 (m, 1H), 1.89 (s, 3H), 1.64–1.58 (m, 1H), 1.56–1.49 (m, 2H), 1.44–1.38 (m, 1H), 0.99–0.90 (m, 1H), 0.85 (d, J = 8.3 Hz, 3H), 0.81–0.65 (m, 3H), 0.74 (d, J = 7.0 Hz, 3H), 0.64 (d, J = 7.0 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 190.1, 164.1, 140.7, 139.1, 136.7, 129.6 (2C), 129.2, 127.9 (2C), 127.8, 127.6, 122.6, 119.6, 115.4, 106.3, 73.3, 46.8, 41.0, 34.4, 31.5, 30.8, 25.7, 23.0, 22.1, 21.1, 16.0; HRMS (ESI-TOF) calcd for $C_{27}H_{32}NO_3$ $[M + H]^+$ 418.2382, found 418.2380.

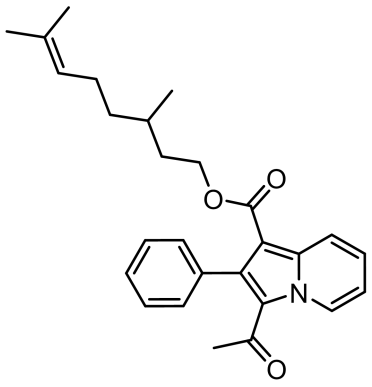


Benzyl 3-acetyl-2-phenylindolizine-1-carboxylate (8ae). Ethyl acetate/petroleum ether = 1:8 as the eluent; Yellow solid, 67% yield (74.5 mg), mp 71–73 °C; ^{1}H NMR

(500 MHz, $CDCl_3$) δ 10.05 (dt, J = 7.2, 1.0 Hz, 1H), 8.46 (dt, J = 9.0, 2.4 Hz, 1H), 7.43–7.37 (m, 4H), 7.35–7.31 (m, 2H), 7.27–7.23 (m, 3H), 7.06–6.99 (m, 3H), 5.11 (s, 2H), 1.86 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 190.1, 164.2, 140.9, 139.0, 136.15, 136.08, 129.5 (2C), 129.2, 128.4 (2C), 128.1 (2C), 128.0 (3C), 127.85, 127.78, 122.8, 119.6, 115.4, 105.4, 65.7, 30.7; HRMS (ESI-TOF) calcd for $C_{24}H_{20}NO_3$ $[M + H]^+$ 370.1443, found 370.1443.

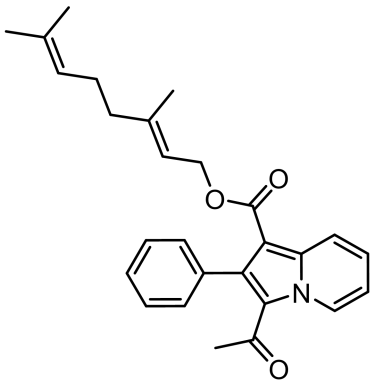


Cinnamyl 3-acetyl-2-phenylindolizine-1-carboxylate (8af). Ethyl acetate/petroleum ether = 1:8 as the eluent; Yellow solid, 63% yield (74.5 mg), mp 71–73 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 10.06 (dt, J = 7.2, 0.9 Hz, 1H), 8.47 (dt, J = 9.0, 1.1 Hz, 1H), 7.45–7.39 (m, 4H), 7.37–7.35 (m, 2H), 7.33–7.31 (m, 4H), 7.28–7.23 (m, 1H), 7.05 (td, J = 7.0, 1.4 Hz, 1H), 6.40 (dt, J = 16.0, 1.3 Hz, 1H), 5.99 (dt, J = 15.9, 6.3 Hz, 1H), 4.72 (dd, J = 6.3, 1.4 Hz, 2H), 1.90 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 190.1, 164.1, 141.1, 138.9, 136.6, 136.3, 133.3, 129.5 (2C), 129.3, 128.7 (2C), 128.1 (2C), 128.03, 127.97, 127.8, 126.6 (2C), 123.6, 122.7, 119.6, 115.4, 105.6, 64.4, 30.8; HRMS (ESI-TOF) calcd for $C_{26}H_{22}NO_3$ $[M + H]^+$ 396.1600, found 396.1607.

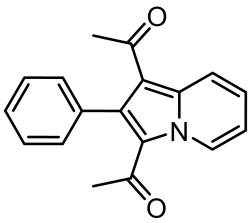


3,7-Dimethyloct-6-en-1-yl 3-acetyl-2-phenylindolizine-1-carboxylate (8ag). Ethyl

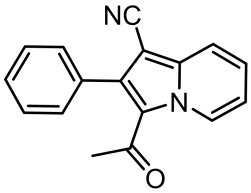
acetate/petroleum ether = 1:8 as the eluent; Yellow oil, 43% yield (53.7 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.06 (dt, J = 7.2, 1.0 Hz, 1H), 7.04 (dt, J = 9.0, 1.1 Hz, 1H), 7.46–7.40 (m, 4H), 7.36–7.32 (m, 2H), 7.04 (td, J = 7.0, 1.4 Hz, 1H), 5.09–5.04 (m, 1H), 4.15–4.09 (m, 1H), 4.07–4.01 (m, 1H), 2.01–1.83 (m, 2H), 1.88 (s, 3H), 1.67 (s, 3H), 1.60 (s, 3H), 1.43–1.34 (m, 1H), 1.28–1.20 (m, 2H), 1.19–1.12 (m, 1H), 1.11–1.03 (m, 1H), 0.79 (d, J = 6.5 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 190.1, 164.6, 140.9, 138.9, 136.4, 131.3, 129.5 (2C), 129.2, 128.1 (2C), 127.9, 127.6, 124.8, 122.7, 119.6, 115.4, 105.9, 62.2, 37.0, 35.4, 30.7, 29.2, 25.8, 25.5, 19.3, 17.8; HRMS (ESI-TOF) calcd for $C_{27}H_{32}NO_3$ $[M + H]^+$ 418.2382, found 418.2379.



(E)-3,7-Dimethylocta-2,6-dien-1-yl 3-acetyl-2-phenylindolizine-1-carboxylate (8ah). Ethyl acetate/petroleum ether = 1:8 as the eluent; Yellow oil, 41% yield (51.3 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.06 (d, J = 7.1 Hz, 1H), 8.45 (d, J = 8.9 Hz, 1H), 7.46–7.40 (m, 4H), 7.35–7.31 (m, 2H), 7.04 (td, J = 7.0, 1.4 Hz, 1H), 5.11–5.07 (m, 1H), 5.06–5.02 (m, 1H), 4.57 (d, J = 6.9 Hz, 2H), 2.09–2.03 (m, 2H), 2.00–1.95 (m, 2H), 1.89 (s, 3H), 1.69 (s, 3H), 1.62 (s, 3H), 1.59 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 190.1, 164.4, 141.4, 141.1, 138.8, 136.3, 131.9, 129.5 (2C), 129.2, 128.0 (2C), 127.9, 127.6, 124.0, 122.6, 119.6, 118.5, 115.4, 105.9, 60.8, 39.5, 30.8, 26.4, 25.8, 17.8, 16.6; HRMS (ESI-TOF) calcd for $C_{27}H_{30}NO_3$ $[M + H]^+$ 416.2226, found 416.2221.



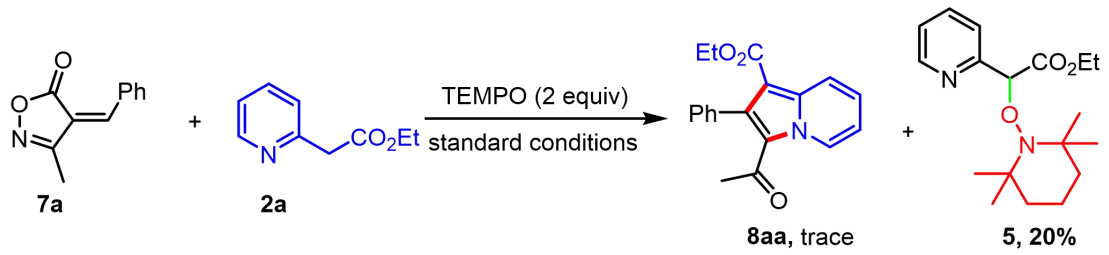
1,1'-(2-Phenylindolizine-1,3-diyl)bis(ethan-1-one) (8ai). Ethyl acetate/petroleum ether = 1:6 as the eluent; Yellow solid, 63% yield (52.4 mg), mp 163–165 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.08 (d, J = 7.1 Hz, 1H), 8.72 (d, J = 9.0 Hz, 1H), 7.55–7.47 (m, 4H), 7.45–7.40 (m, 2H), 7.10 (td, J = 7.0, 1.2 Hz, 1H), 1.87 (s, 3H), 1.83 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 195.2, 190.0, 139.9, 138.8, 136.4, 129.9 (2C), 129.1, 128.9 (4C), 122.4, 120.5, 116.2, 115.6, 30.9, 30.7; HRMS (ESI-TOF) calcd for $C_{18}H_{16}NO_2$ $[M + H]^+$ 278.1181, found 278.1182.



3-Acetyl-2-phenylindolizine-1-carbonitrile (8aj). Ethyl acetate/petroleum ether = 1:6 as the eluent; Yellow solid, 56% yield (44.0 mg), mp 132–134 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.00 (dt, J = 7.2, 1.0 Hz, 1H), 7.79 (dt, J = 8.8, 1.2 Hz, 1H), 7.55–7.50 (m, 3H), 7.49–7.45 (m, 3H), 7.10 (td, J = 7.0, 1.4 Hz, 1H), 2.05 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 189.5, 142.1, 139.6, 133.0, 129.7 (3C), 129.4, 128.9 (2C), 127.9, 121.7, 117.2, 116.0, 115.1, 87.4, 30.5; HRMS (ESI-TOF) calcd for $C_{17}H_{12}N_2ONa$ $[M + Na]^+$ 283.0847, found 283.0852.

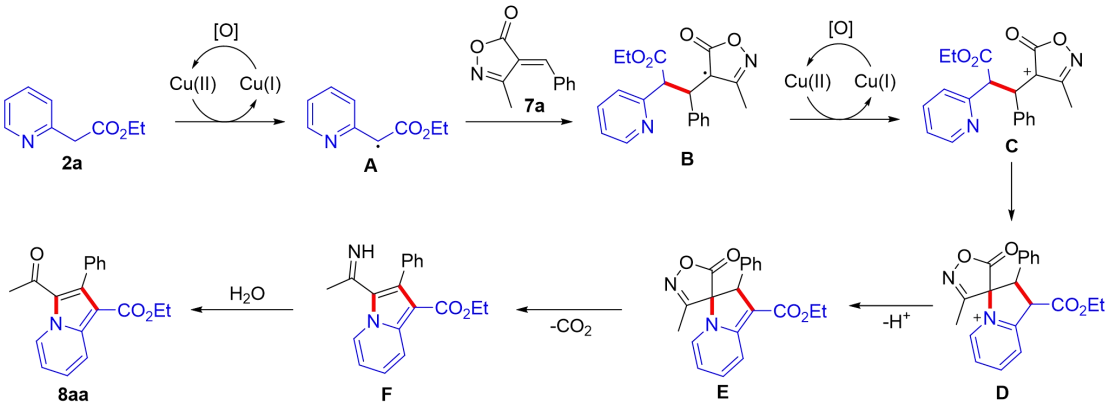
3.4 反应机理探究

为确定反应是否涉及自由基途径，我们进行了自由基捕获实验（Scheme 3-4）。加入 2 当量 2,2,6,6-四甲基哌啶氮氧自由基（TEMPO，一种常见自由基捕获剂）后，**7a** 与 **2a** 的反应几乎被完全抑制。随后我们对反应液进行处理，分离出了 2-(吡啶-2-基)乙酸乙酯的自由基捕获产物 **5**，这一结果表明该反应可能通过自由基途径进行。



Scheme 3-4 Controlled experiment

基于上述实验结果和相关文献报道，我们提出了 **7a** 和 **2a** 形成 **8aa** 的可能机制（Scheme 3-5）。首先，**2a** 与铜配位生成自由基中间体 **A**。随后，中间体 **A** 与 **7a** 发生自由基加成反应，生成自由基物种 **B**，其再与铜配位形成碳正离子中间体 **C**。接着，**C** 经历分子内亲核取代反应，生成螺环中间体 **E**。中间体 **E** 通过脱羧过程转化为亚胺中间体 **F**。最后，**F** 在水的作用下发生水解，得到产物 **8aa**。这也解释了添加微量水能促进反应顺利进行。



Scheme 3-5 Plausible mechanism for the reaction

3.5 本章小结

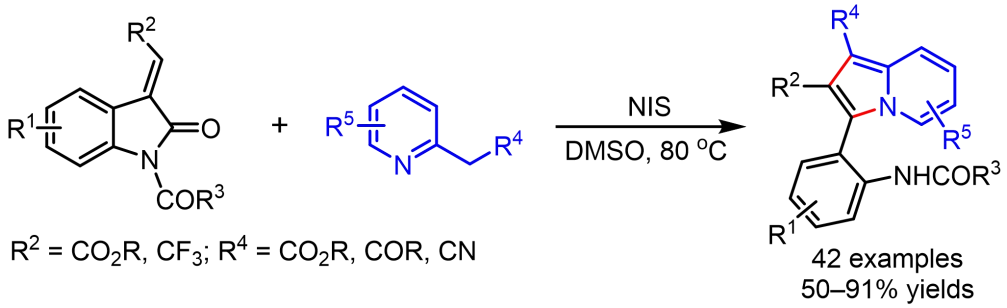
本章研究了不饱和异噁唑酮与 2-(吡啶-2-基)乙酸酯衍生物在球磨条件下的反应。首先，我们建立了反应模型并通过核磁共振（NMR）确定了产物结构，随后通过条件筛选确定了最优反应条件。在最优条件下，通过改变不饱和异噁唑酮或 2-(吡啶-2-基)乙酸酯衍生物，研究了底物范围，并成功合成了 30 个化合物，收率为 39–85%。该方法具有原料易得、反应高效、环境友好、底物适用范围广等优点，为吲哚嗪衍生物的合成提供了一种新途径。

第 4 章 结论与展望

4.1 结论

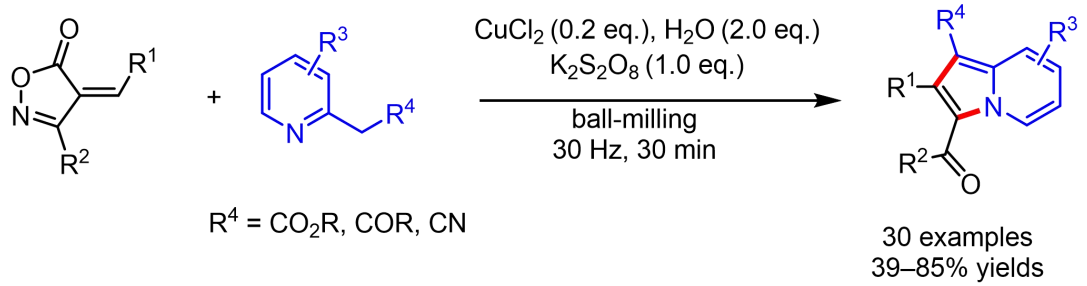
吲哚嗪又称中氮茚，是一类重要的含氮杂环化合物，因其独特的结构赋予了吲哚嗪特殊的化学性质和广泛的生物活性，天然产物和药物分子中都能看见吲哚嗪及其衍生物的身影。因此，构建吲哚嗪及研究其性能在有机合成领域备受关注。目前，已有文献报道了构建吲哚嗪骨架的方法，尽管有些方法能比较高效的构建吲哚嗪，但仍存在不同程度的局限性，例如，起始原料的来源困难；部分反应条件苛刻，需要在高温下进行；使用大量的促进剂或价格昂贵的催化剂；反应机理较为单一，大部分都是通过环加成反应得到吲哚嗪衍生物。鉴于以上这些原因，我们开发出了基于α-吡啶活泼亚甲基的螺环化/芳构化反应构建吲哚嗪的新方法。具体内容如下：

(1) 研究了亚烷基氧化吲哚与 2-(吡啶-2-基)乙酸酯衍生物的反应。首先，建立亚烷基氧化吲哚与 2-吡啶乙酸乙酯的模型反应，对反应的条件如卤代试剂、温度、溶剂等进行探索确定了最优反应条件，具体方案如下：亚烷基氧化吲哚、1.0 当量 2-(吡啶-2-基)乙酸酯衍生物和 1.0 当量 NIS 在 DMSO 中于 80 °C 反应 8 小时。随后，在这个最优反应条件下，我们以 50-91%的产率合成 42 个吲哚嗪类化合物，同时通过 X-射线单晶衍射进一步确定产物的结构，并提出了可能的反应机理。该反应能够有效和直接地构建各种吲哚嗪，且合成的吲哚嗪衍生物富含多个官能团，并能进一步修饰。该方法具有高效性、广泛的官能团耐受性等特点，而且该方法反应条件温和、成本低、起始原料简单易得，为构建吲哚嗪类化合物提供了一种新途径。



(2) 研究了机械化学条件下铜催化的环外α,β-不饱和异噁唑酮与 2-(吡啶-2-基)乙酸酯衍生物的反应。首先，我们建立了反应模型，并通过核磁共振

（NMR）确定了产物结构。随后，我们对反应的条件如催化剂、助溶剂、氧化剂等进行探索确定了最优合成条件，并利用该方法高效合成出了 30 个吲哚嗪类衍生物，收率在 39-85%之间。同时，我们也通过控制性实验提出了可能的反应机理。上述方法具有原料易得，反应高效，清洁环保、底物范围广等优点，这为构建吲哚嗪衍生物提供了一种新途径。



本工作与其他吲哚嗪类化合物的合成方法相比，主要创新点在于螺环化/芳构化的构建方式，以往大多数构建吲哚嗪的反应多是通过环加成反应得到吲哚嗪衍生物，而本工作则从机理上为构建吲哚嗪类化合物提出新的可能。且本工作所用到的原料简单易得、所用到的卤化剂/催化剂廉价安全、反应高效简洁。不饱和异恶唑酮和 2-(吡啶-2-基)乙酸酯衍生物的反应则是采用机械化学方法合成，且使用微量的水，大大减少了溶剂的使用和消耗，使反应更加绿色环保。

4.2 展望

本文主要研究了基于α-吡啶活泼亚甲基的螺环化/芳构化反应构建吲哚嗪，包括亚烷基氧化吲哚与 2-(吡啶-2-基)乙酸酯衍生物的反应以及不饱和异噁唑酮与 2-(吡啶-2-基)乙酸酯衍生物的反应。这两种方法具有操作简便、高产率、环境友好等特点。值得注意的是，通过亚烷基氧化吲哚与 2-(吡啶-2-基)乙酸酯衍生物的螺环化/芳构化反应构建的吲哚嗪衍生物已成功进行衍生化实验，表明该方法合成的吲哚嗪类化合物有望通过进一步修饰应用于医药、农药和功能材料等领域。此外，通过不饱和异噁唑酮与 2-(吡啶-2-基)乙酸酯衍生物的反应构建的吲哚嗪衍生物也富含官能团，可进一步修饰用于相关领域研究。此外，可借鉴本方法，以 2-(吡啶-2-基)乙酸酯衍生物与其他底物为原料，通过多米诺反应构建不同类型的吲哚嗪类化合物。同时，我们计划进一步探索利用实验室其他常用原料构建更多螺环化/开环芳构化产物。从机理上看，这些方案均具有可行性，因此我们将继续深入研究这一领域。

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附录 代表性化合物的 NMR 谱图

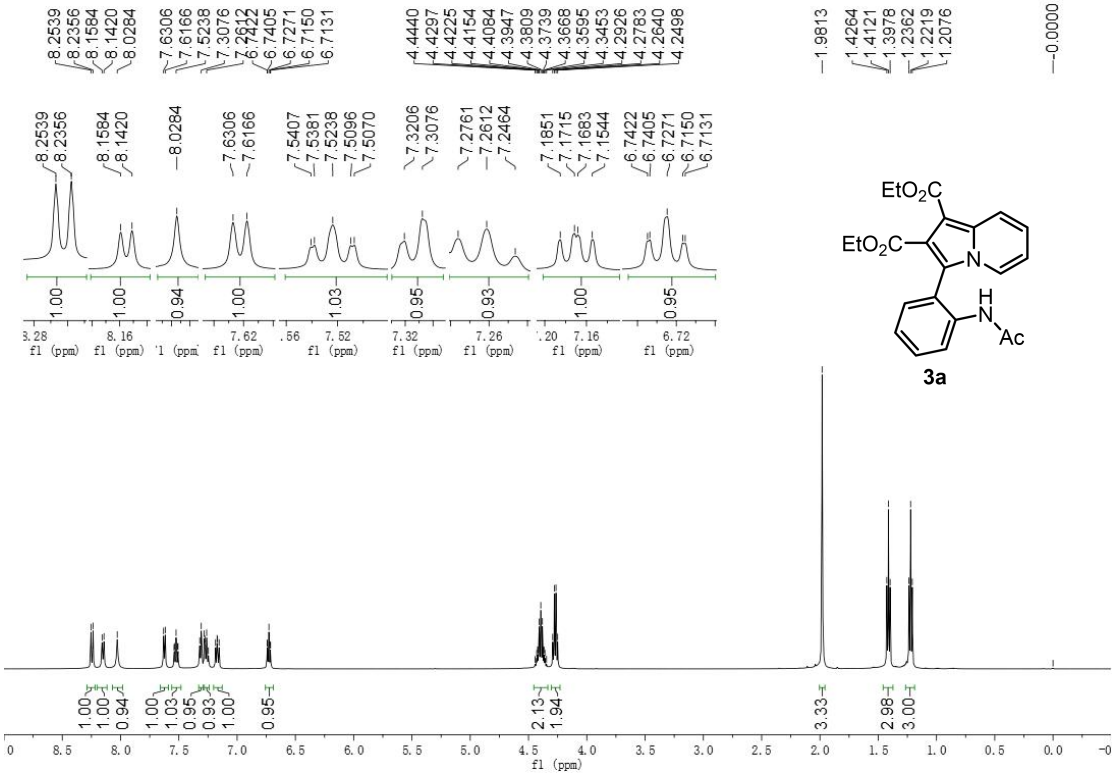

Figure S1. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **3a**

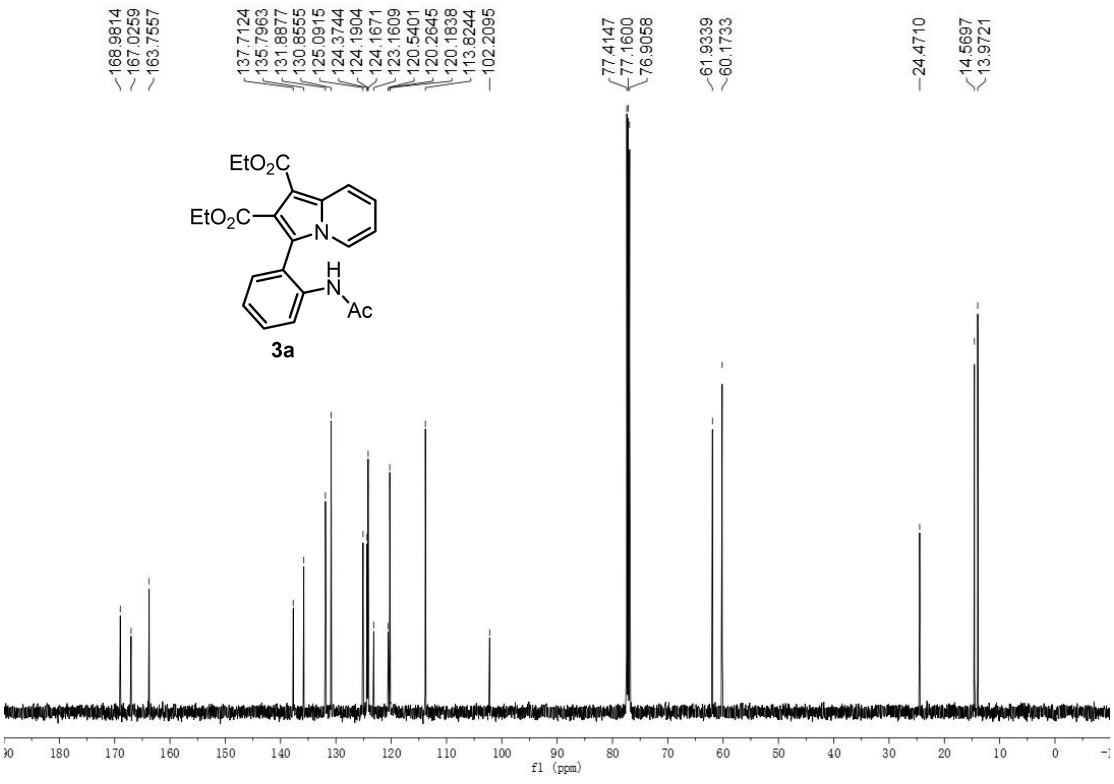

Figure S2. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **3a**

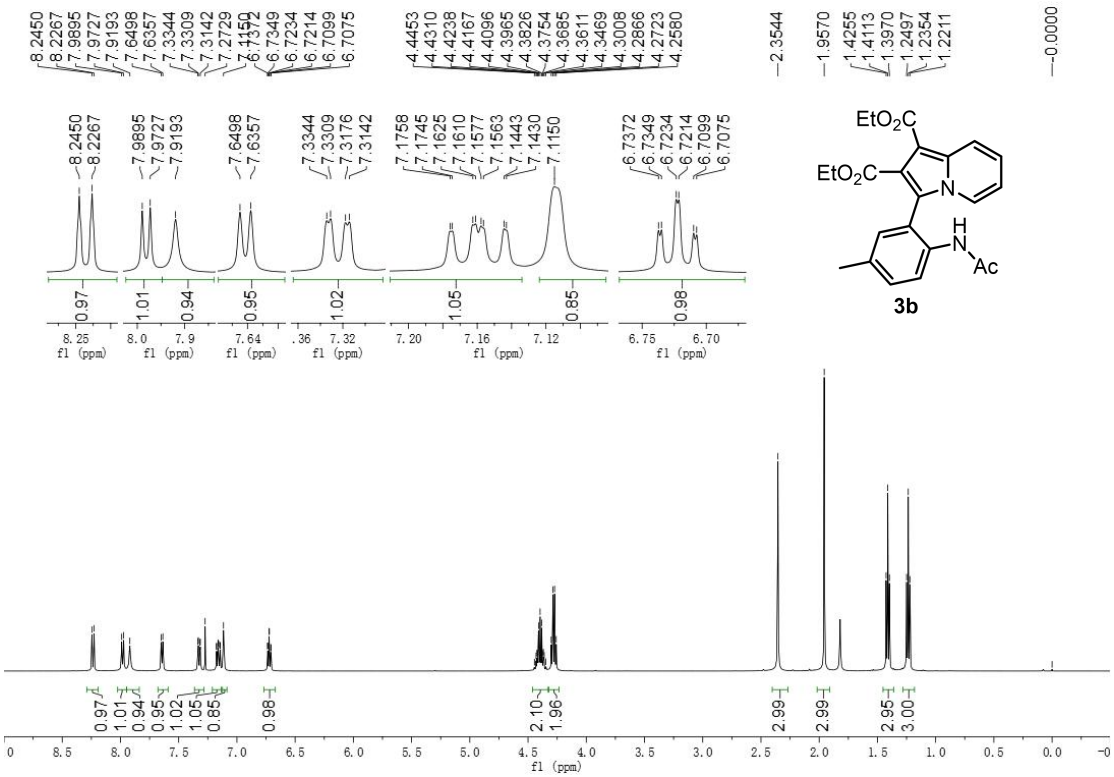

Figure S3. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **3b**

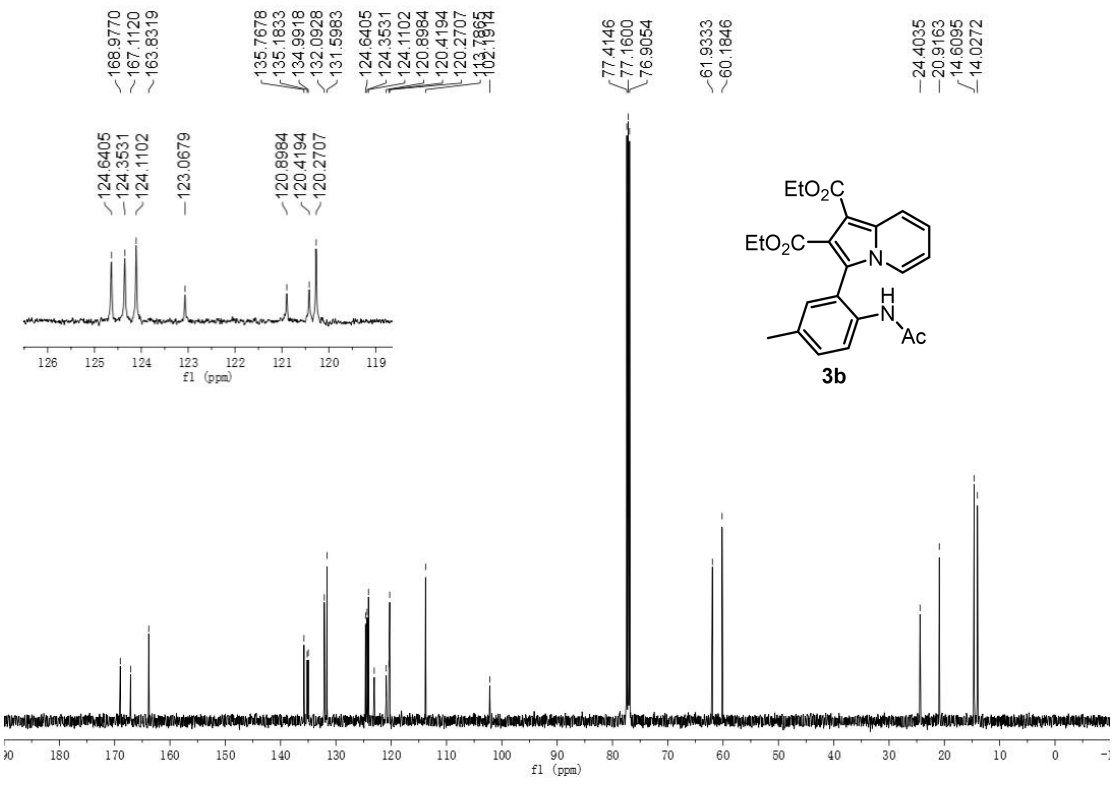

Figure S4. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **3b**

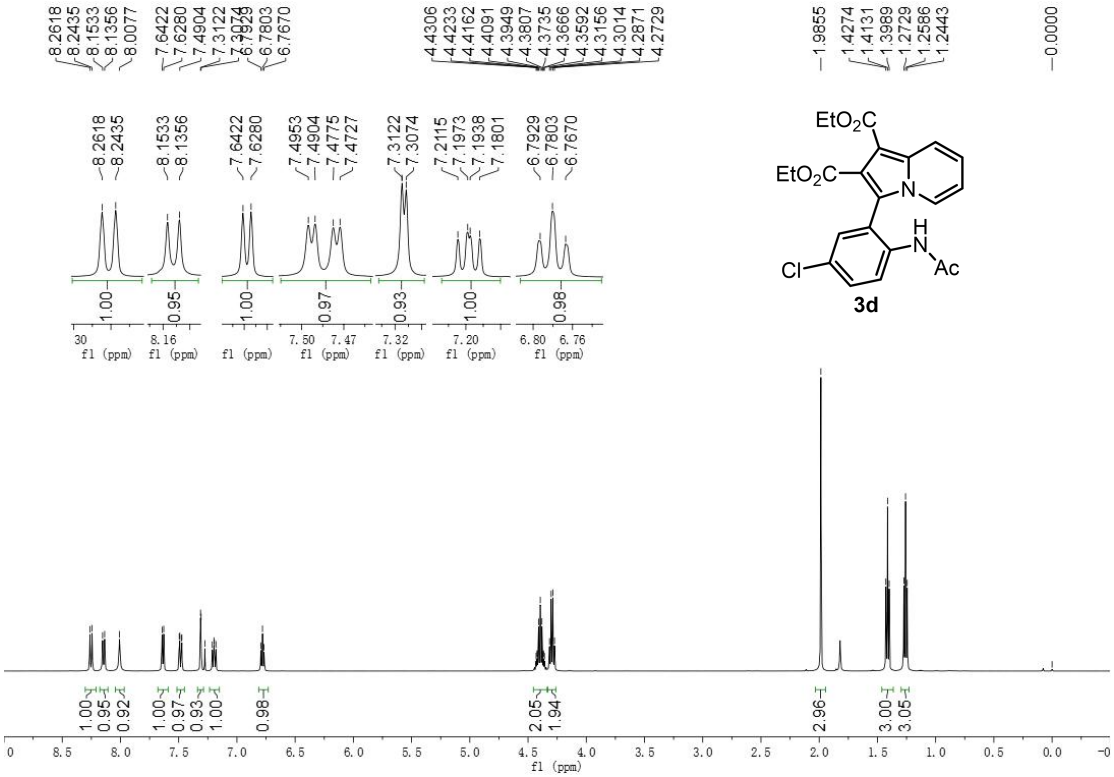

Figure S5. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **3d**

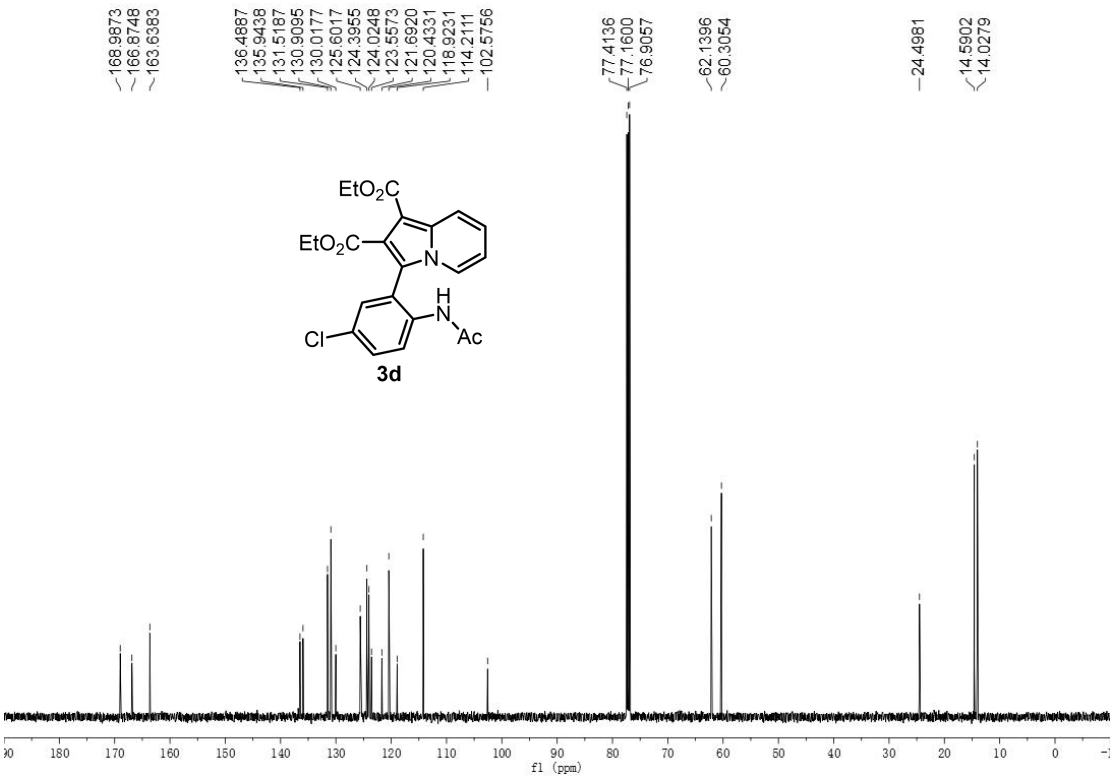

Figure S6. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **3d**

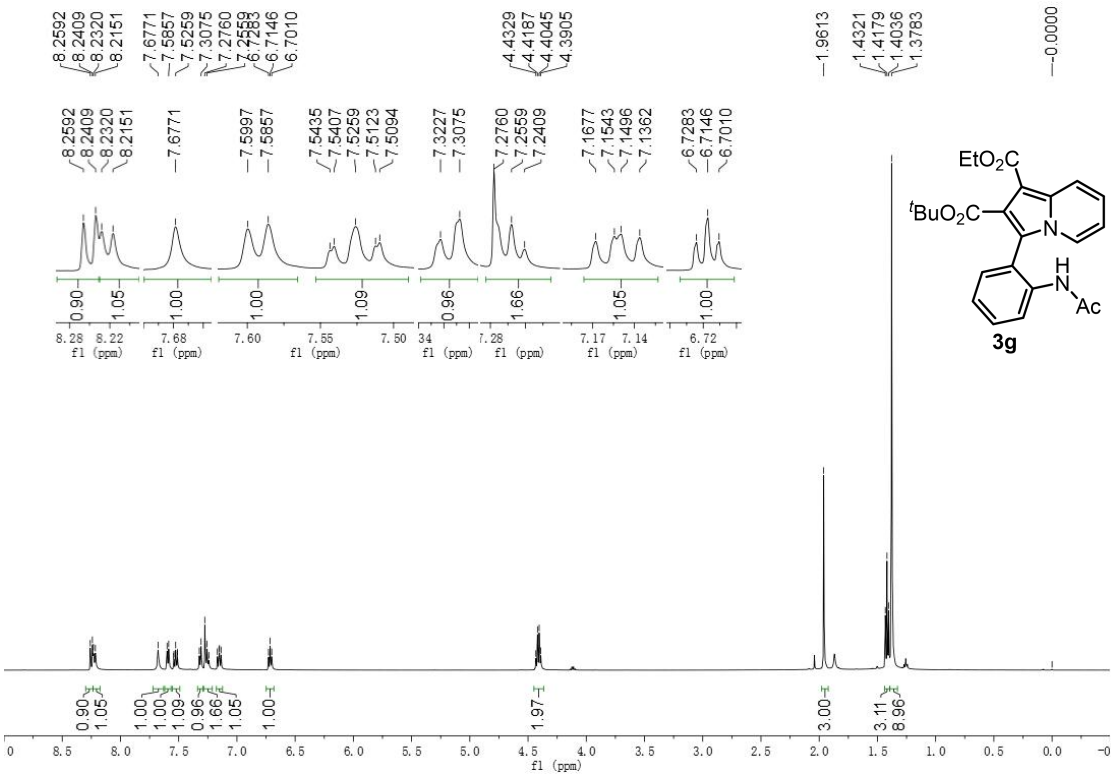

Figure S7. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **3g**

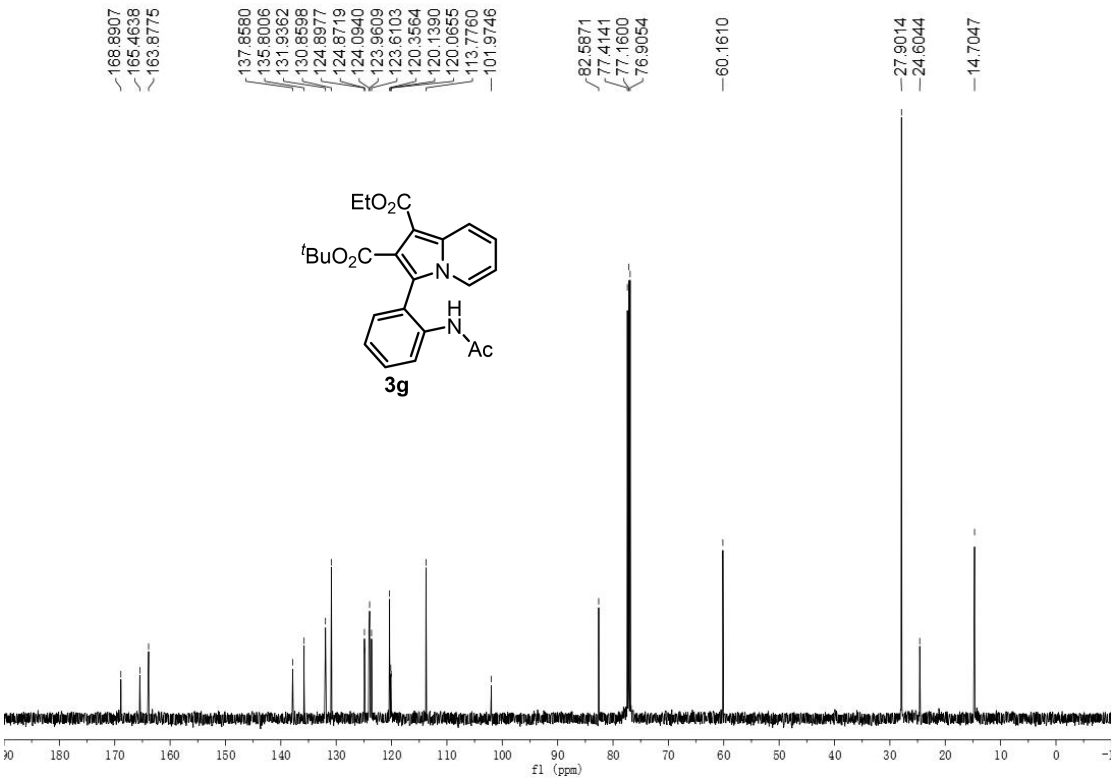

Figure S8. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **3g**

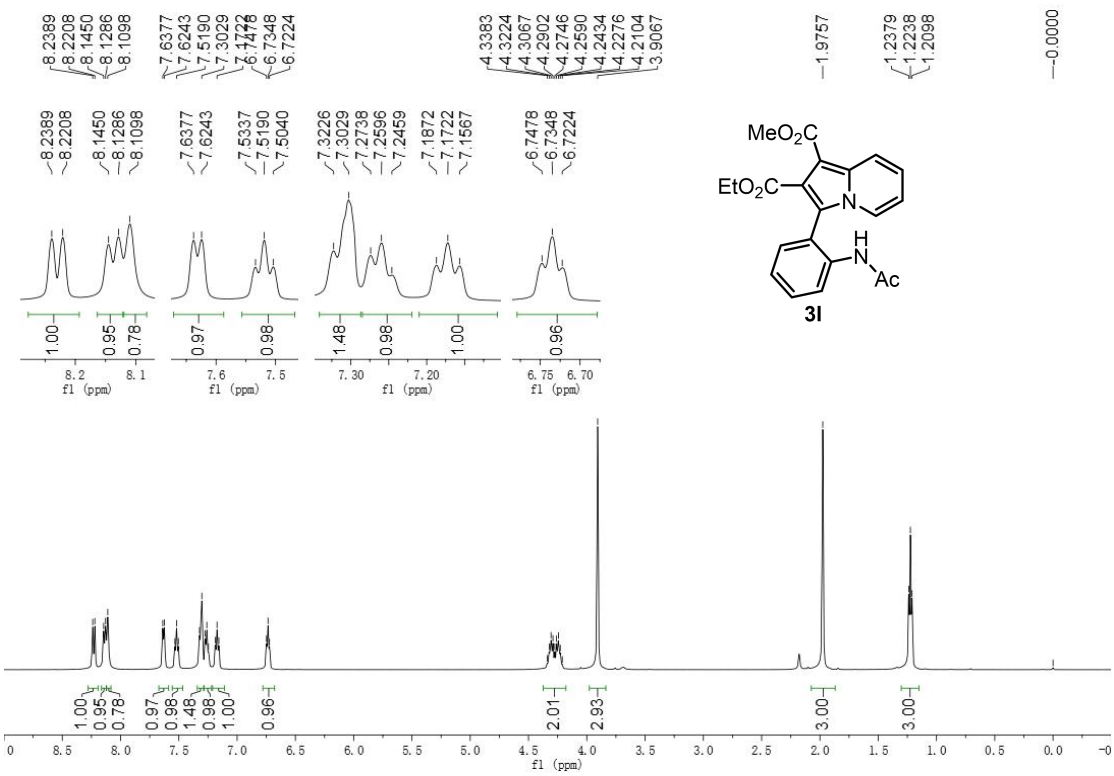

Figure S9. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **3l**

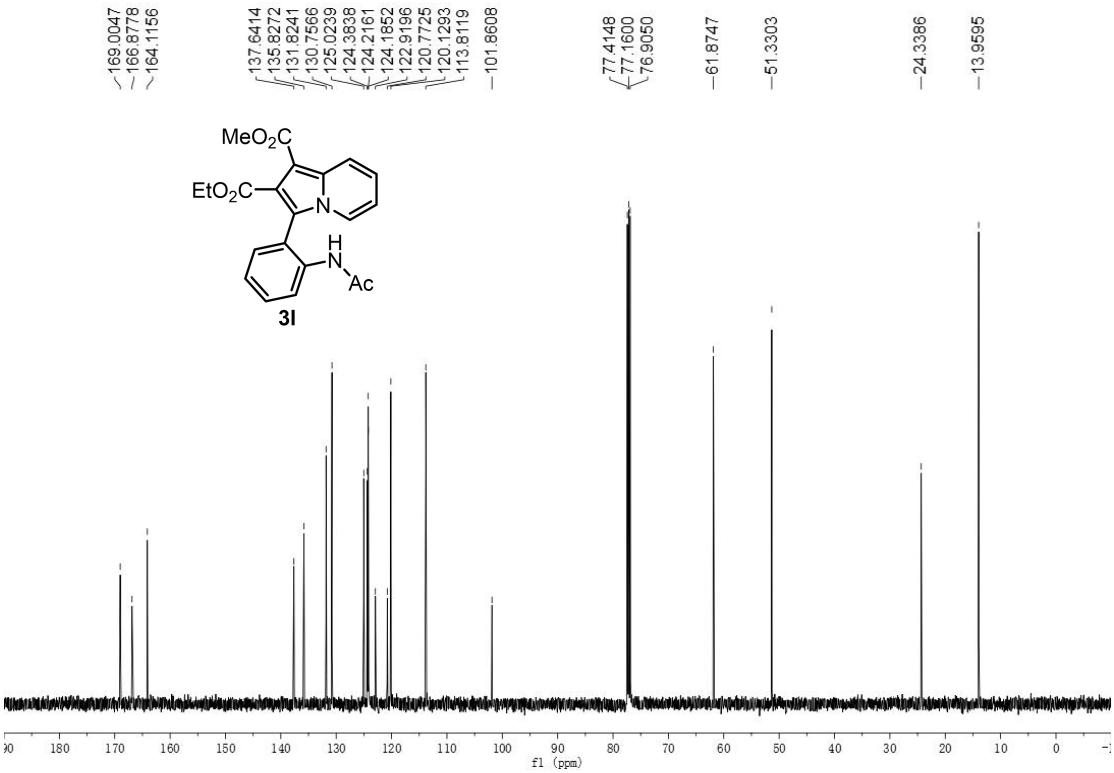

Figure S10. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **3l**

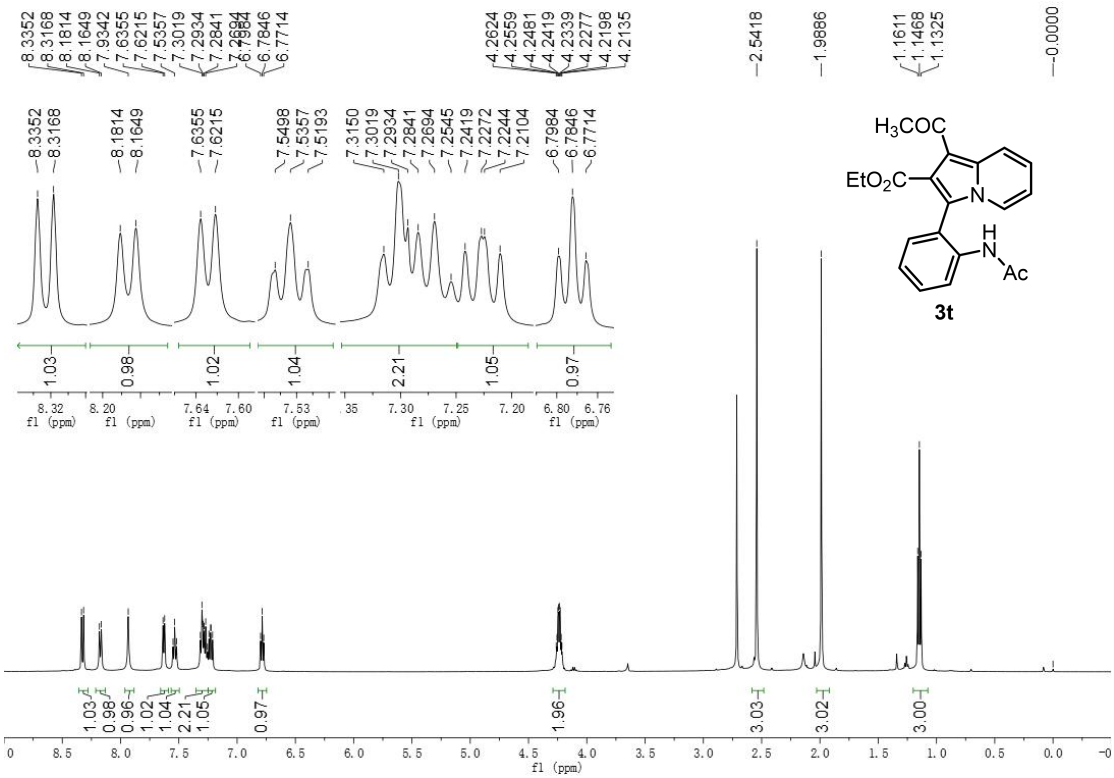

Figure S11. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **3t**

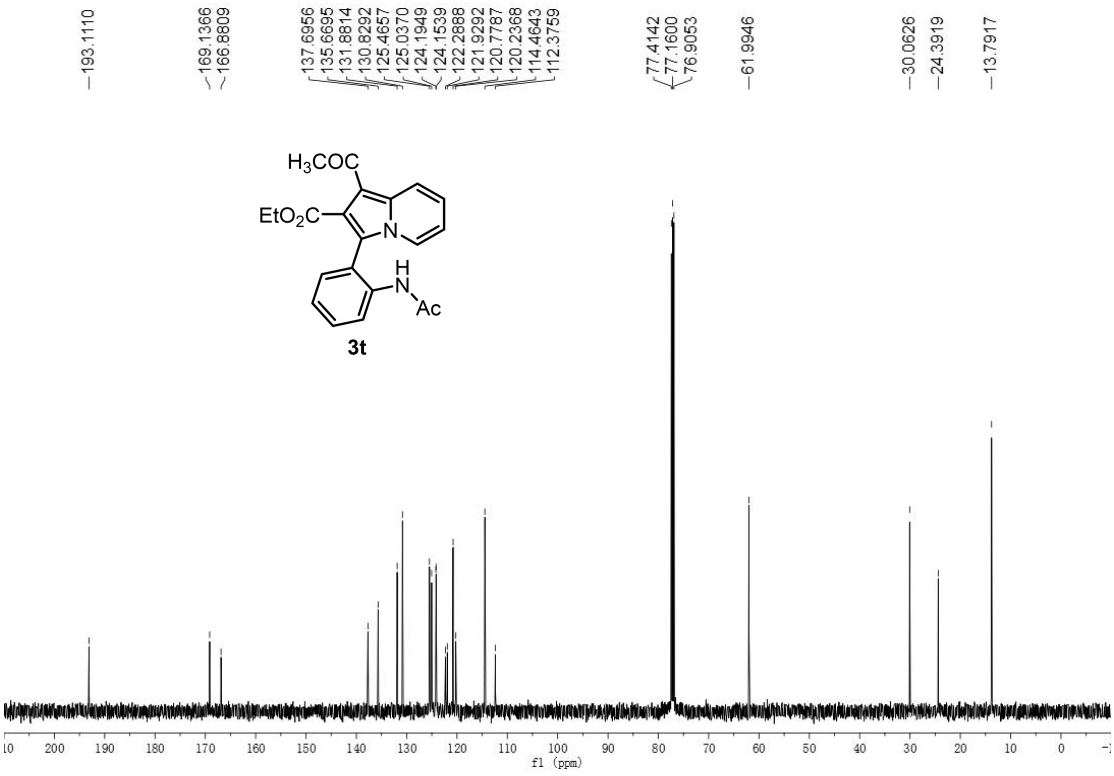

Figure S12. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **3t**

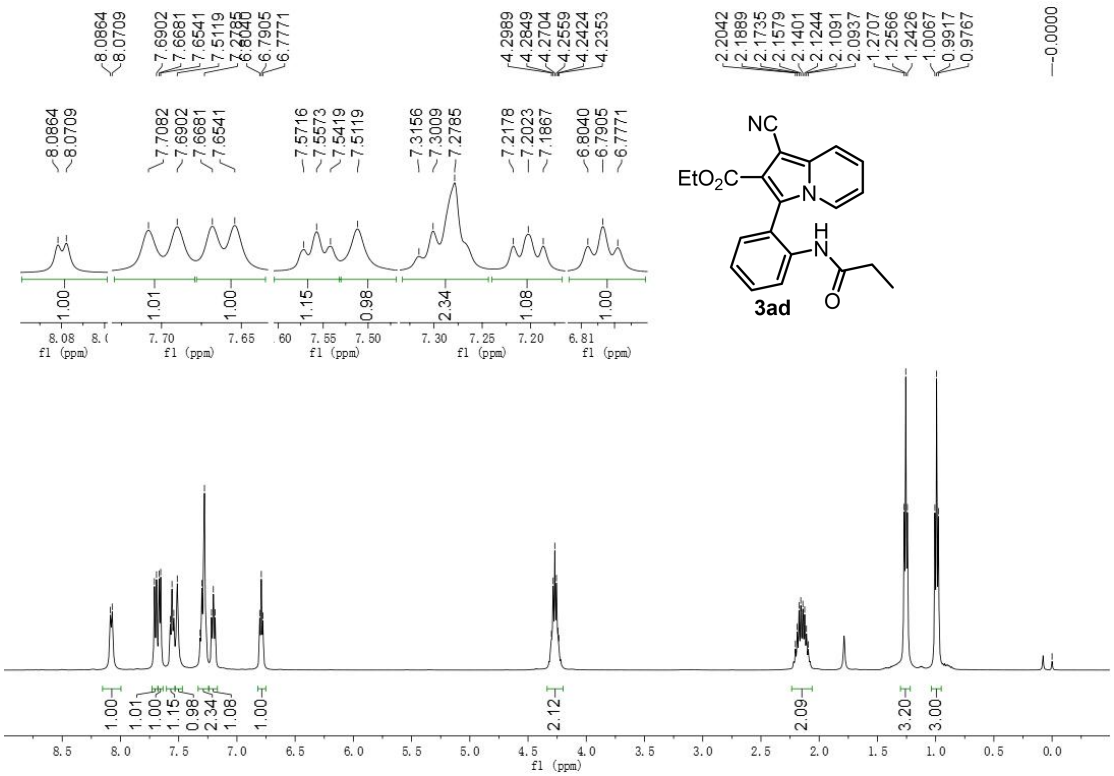

Figure S13. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **3ad**

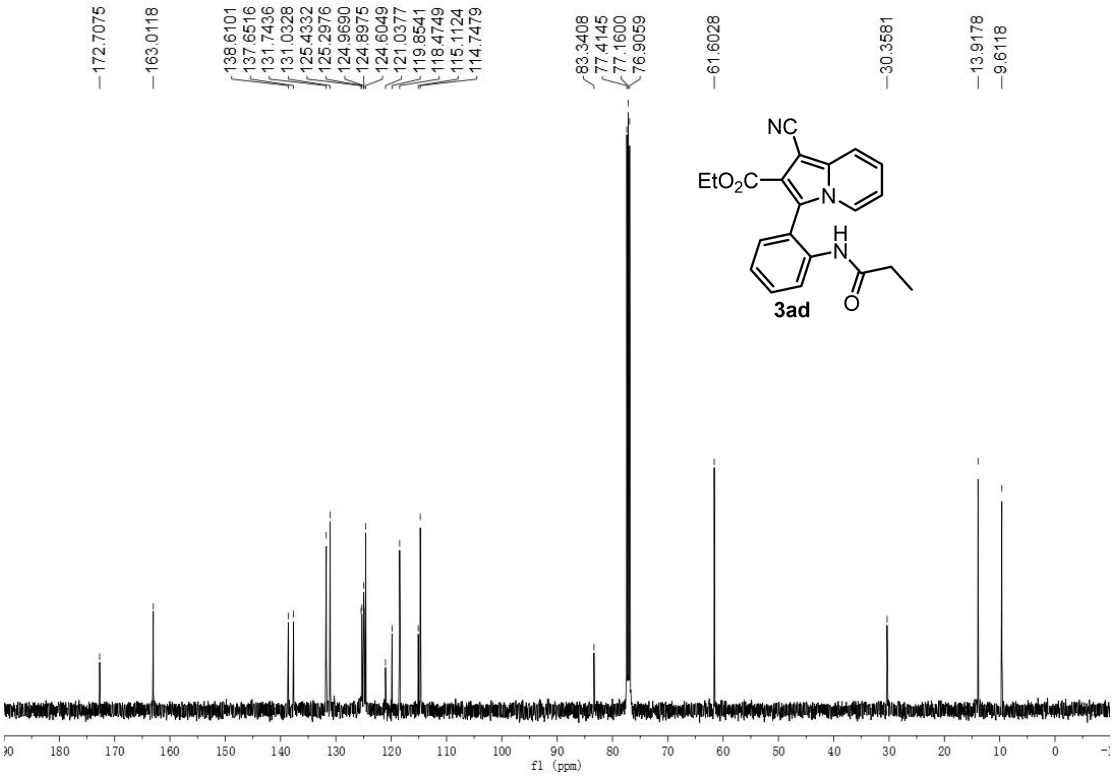

Figure S14. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **3ad**

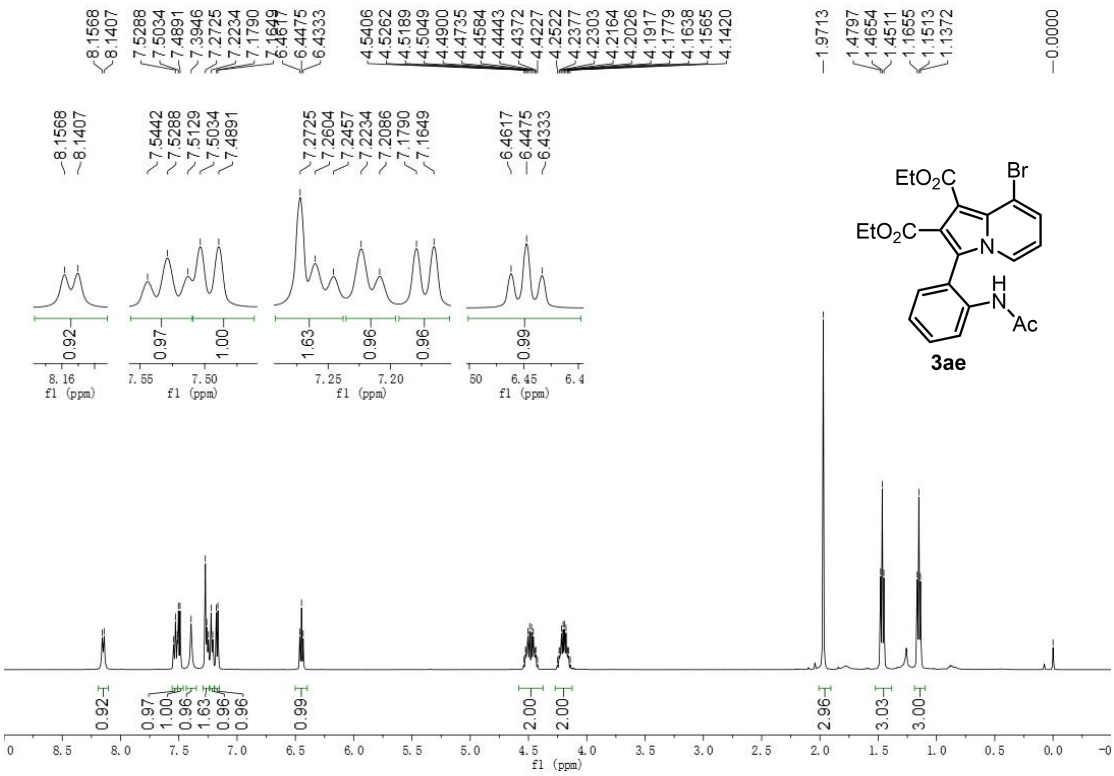

Figure S15. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **3ae**

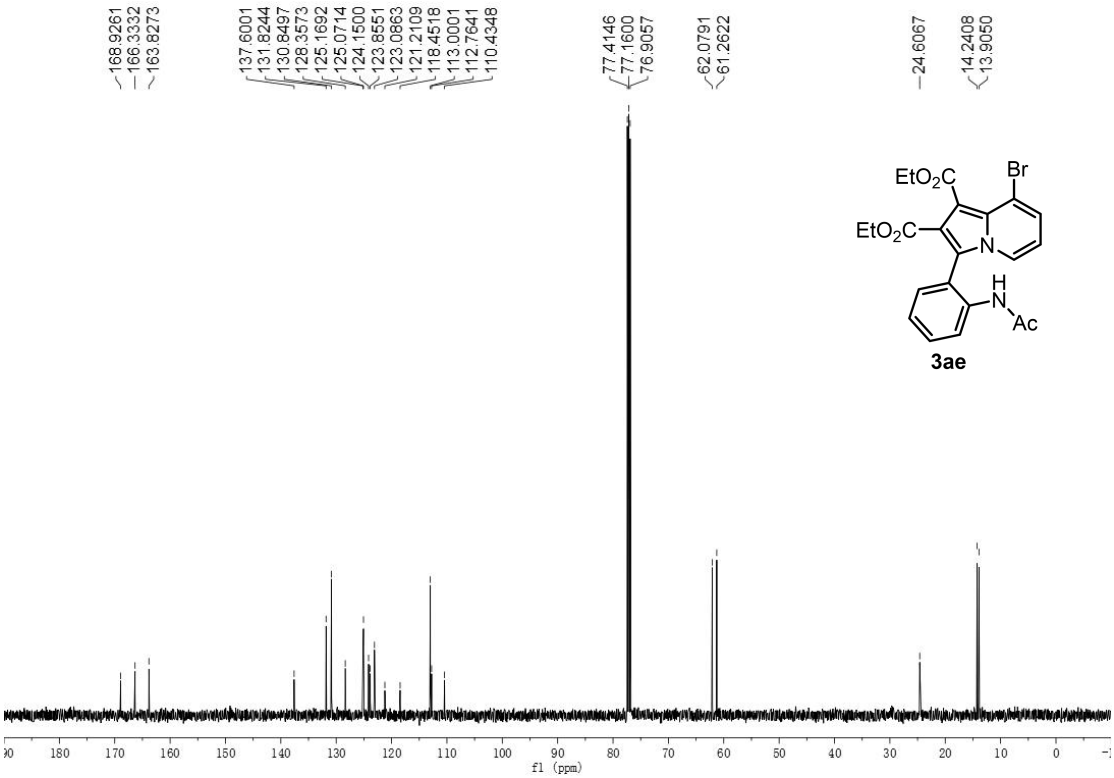

Figure S16. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **3ae**

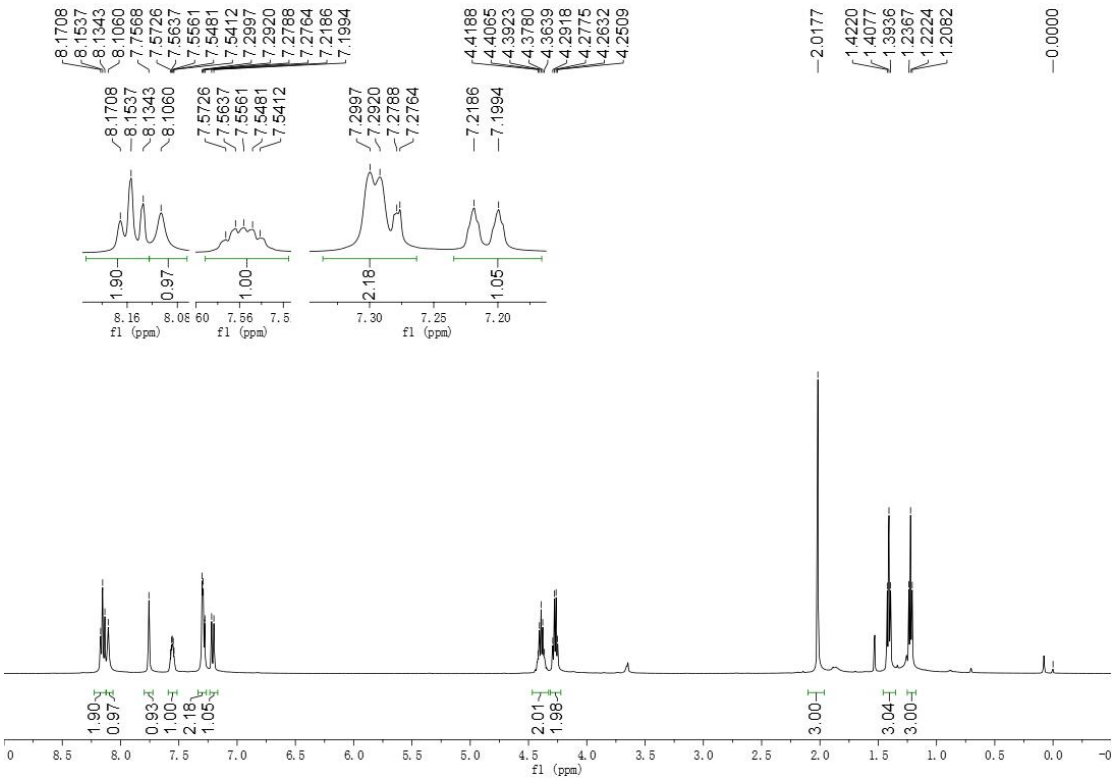

Figure S17. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **3aj**

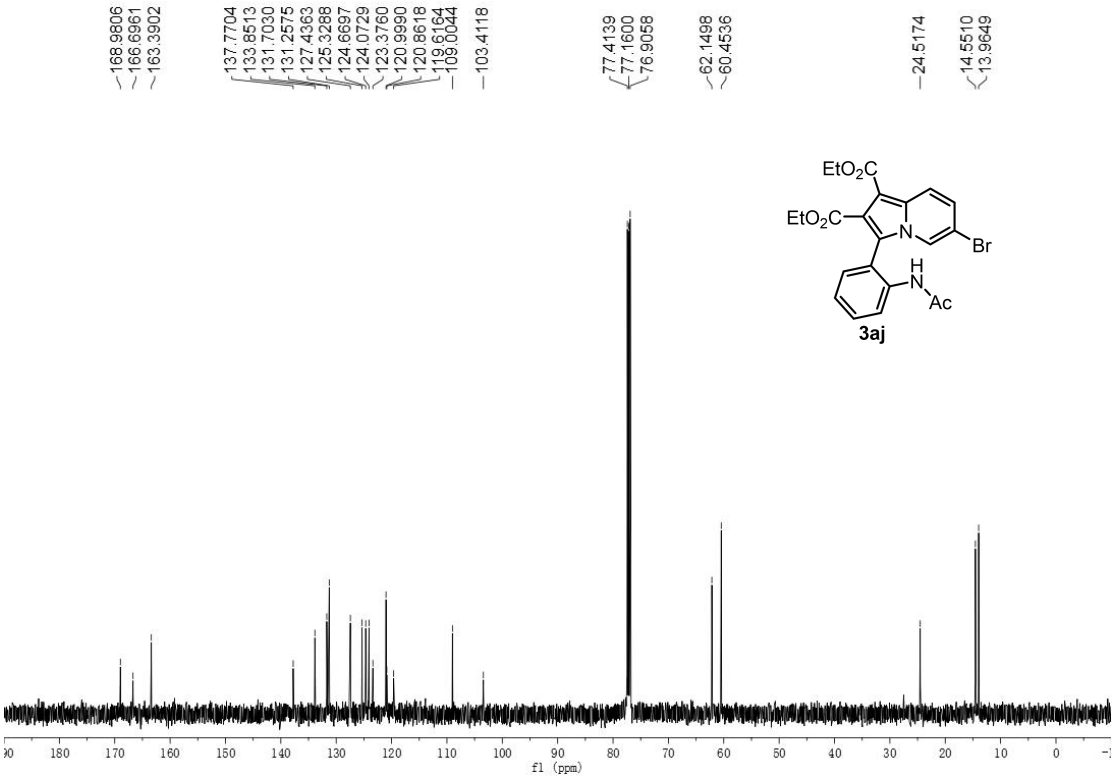

Figure S18. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **3aj**

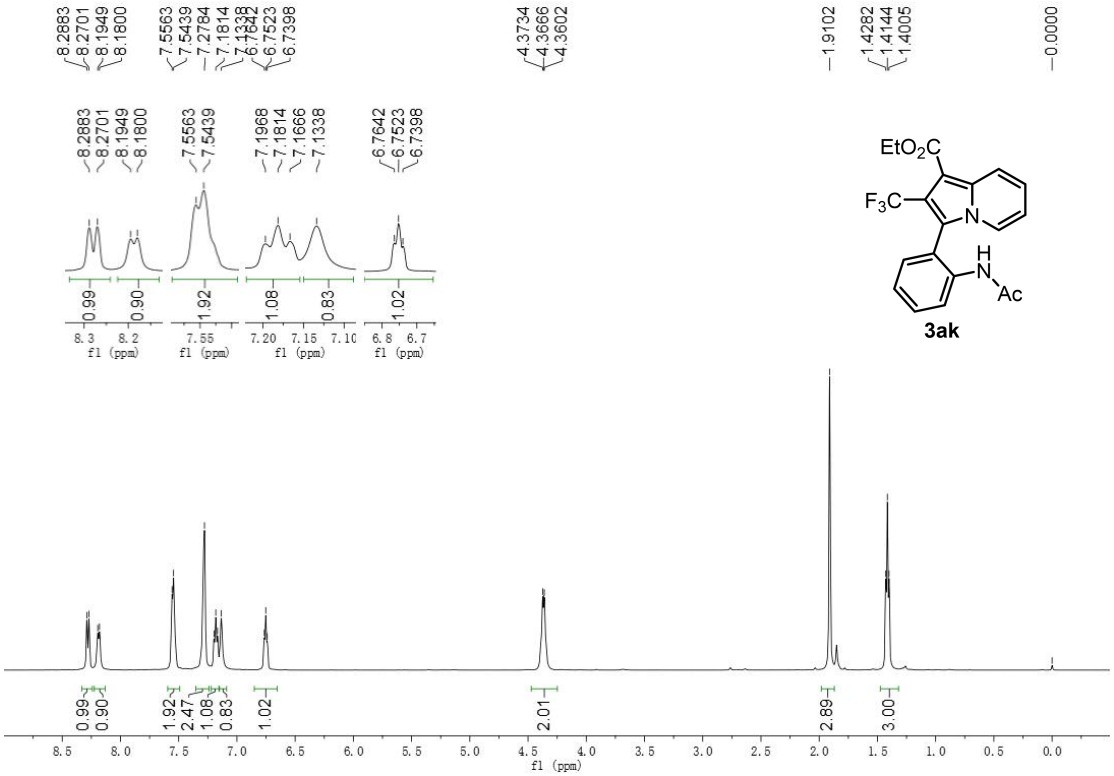

Figure S19. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **3ak**

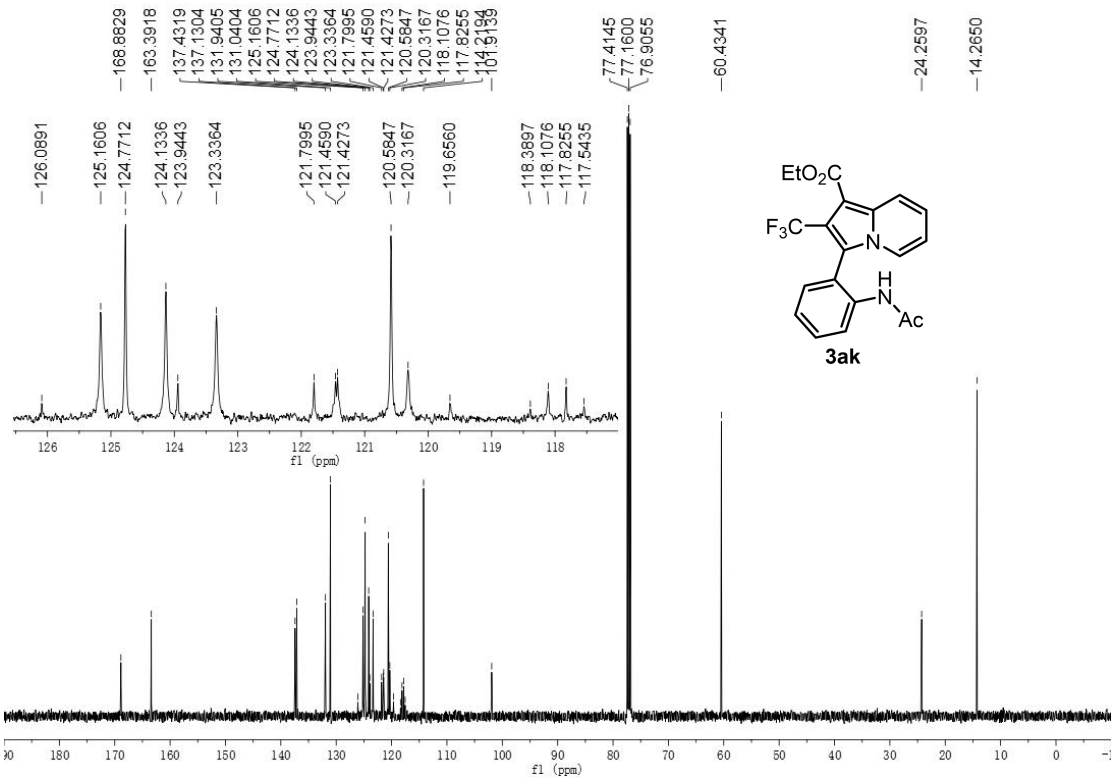

Figure S20. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **3ak**

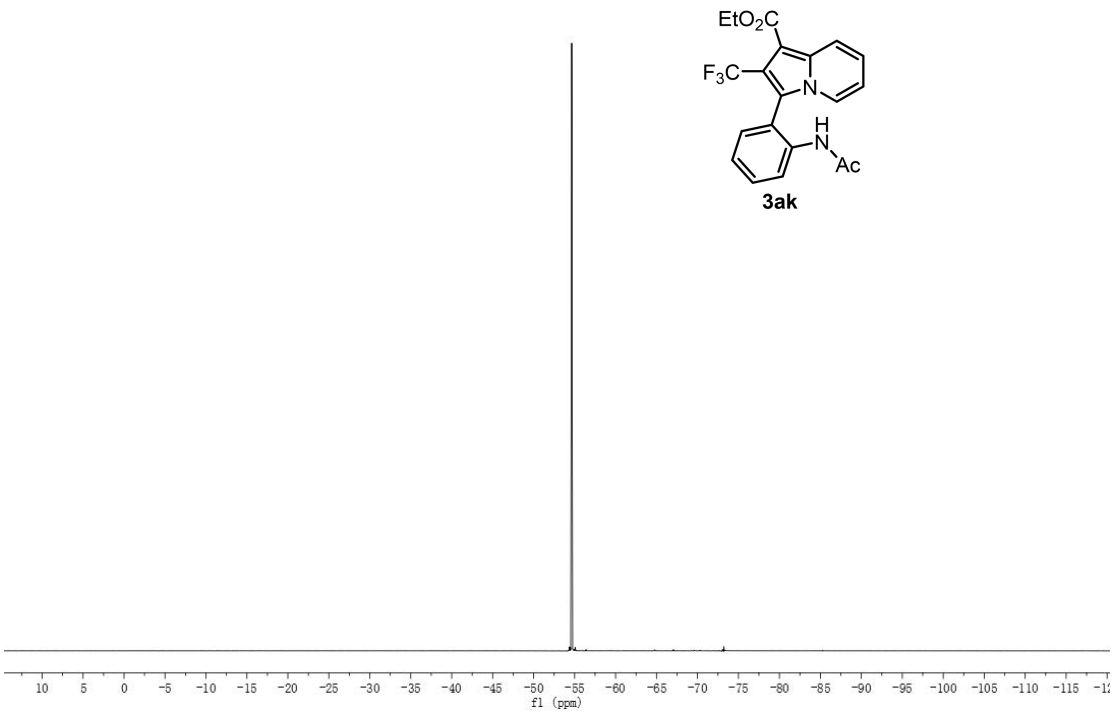

Figure S21. ^{19}F NMR (471 MHz, $CDCl_3$) of compound **3ak**

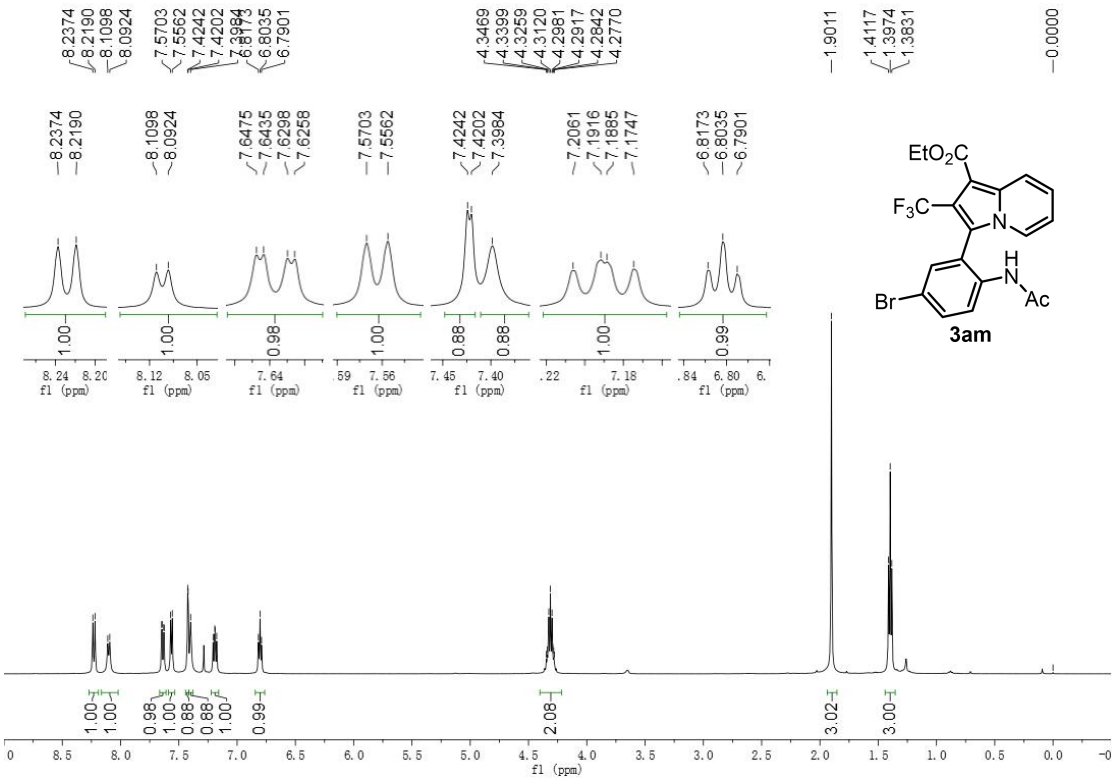

Figure S22. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **3am**

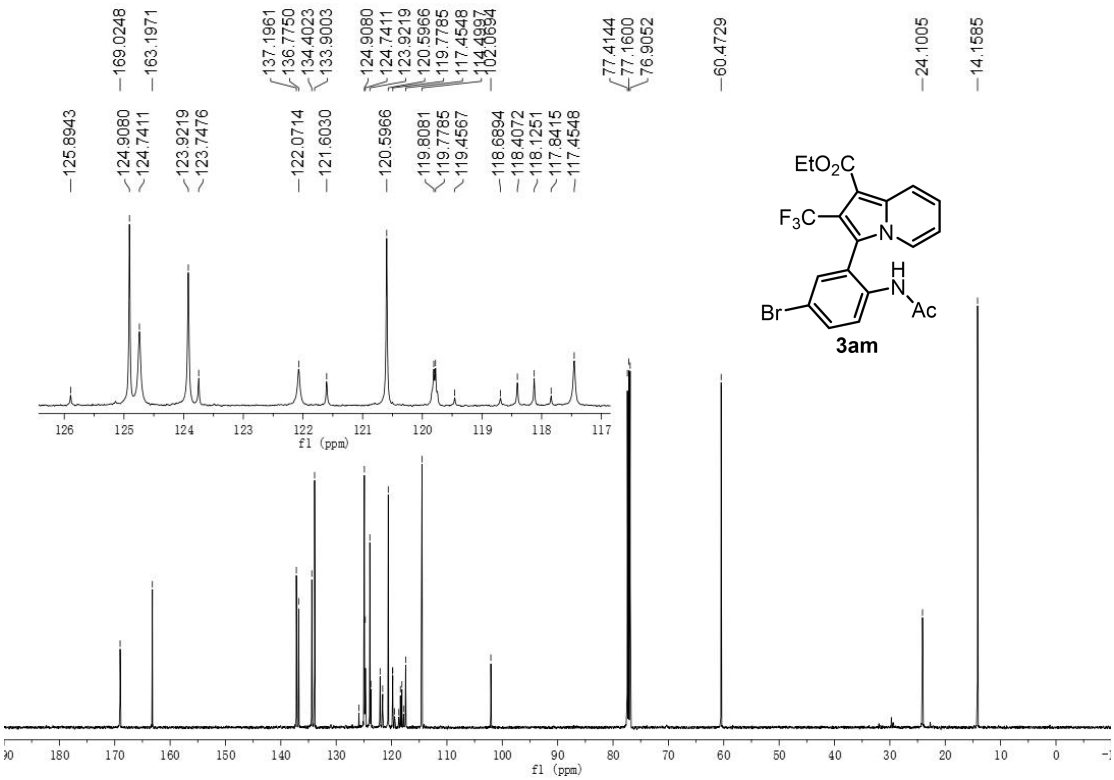

Figure S23. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **3am**

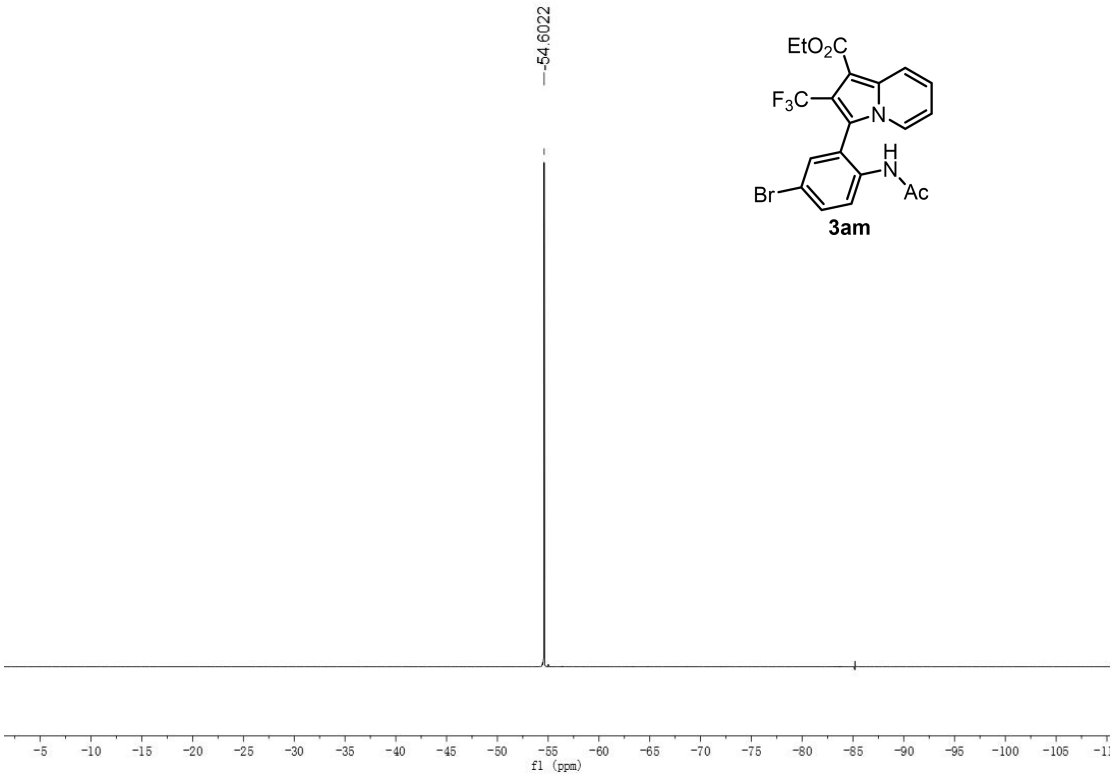

Figure S24. ^{19}F NMR (471 MHz, $CDCl_3$) of compound **3am**

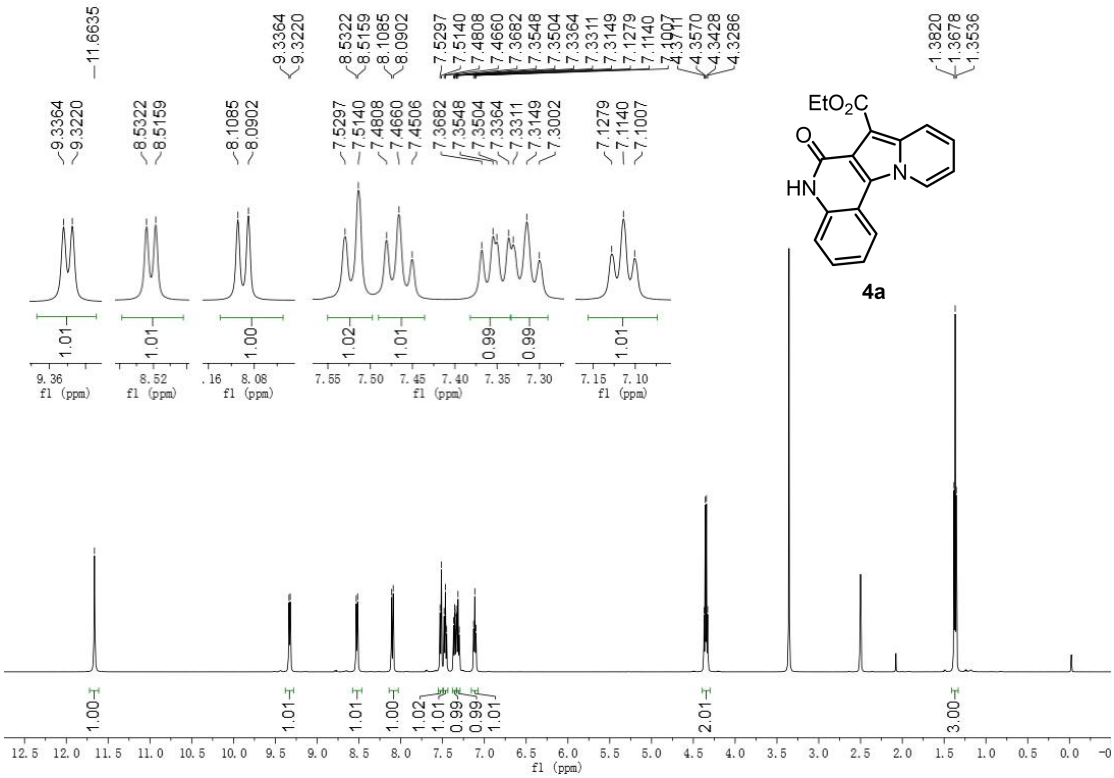

Figure S25. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **4a**

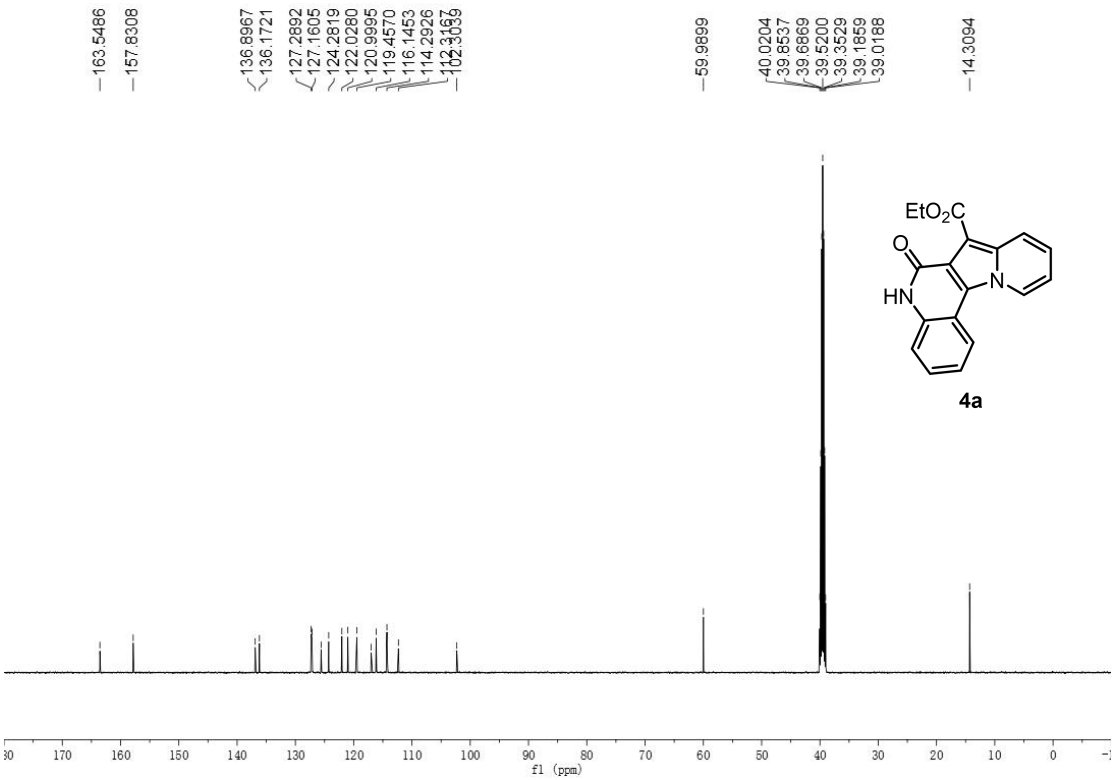

Figure S26. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **4a**

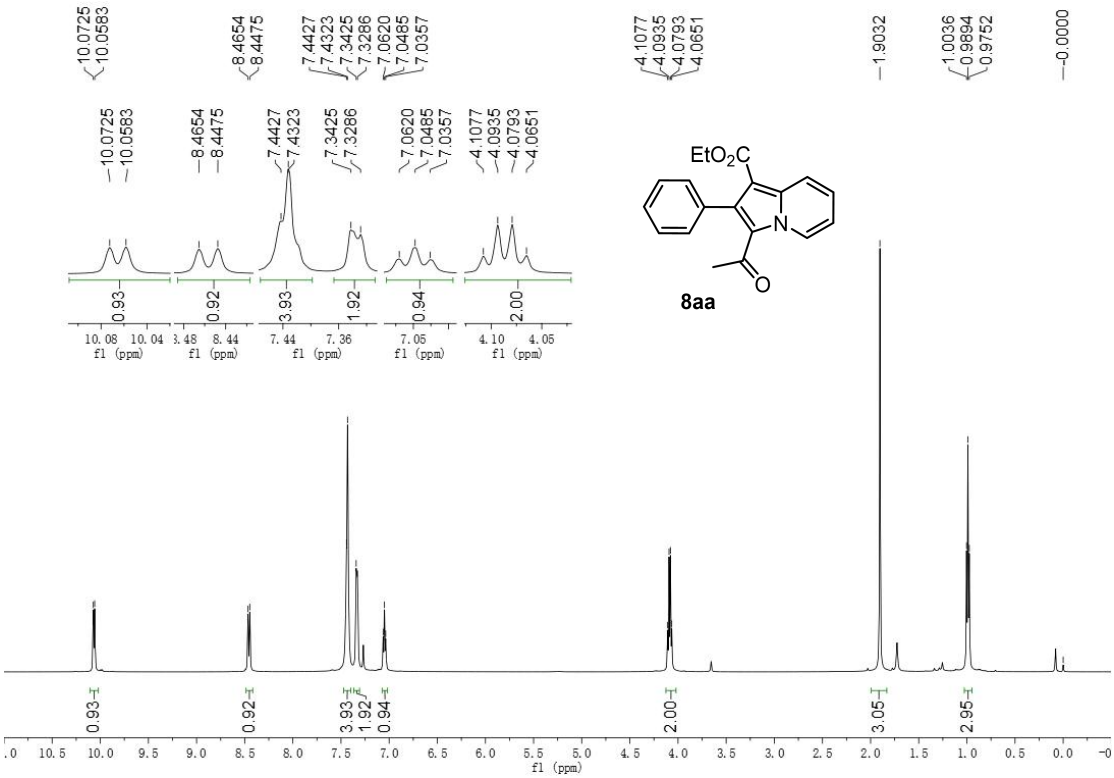

Figure S27. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **8aa**

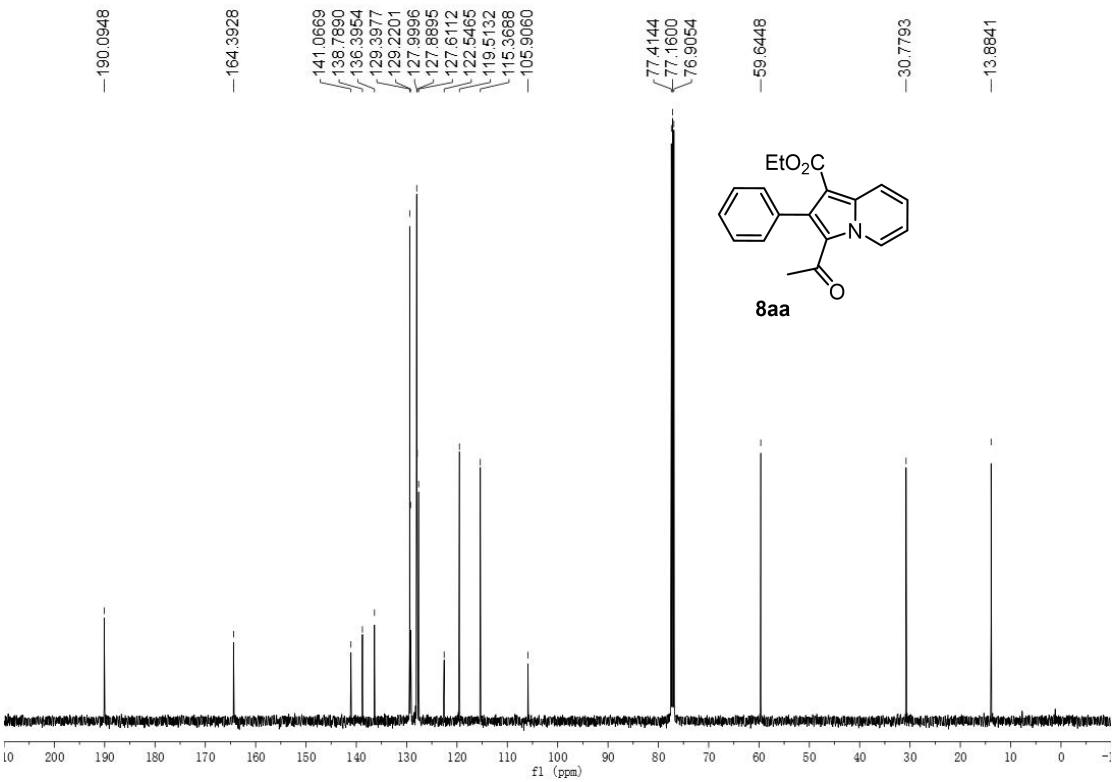

Figure S28. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **8aa**

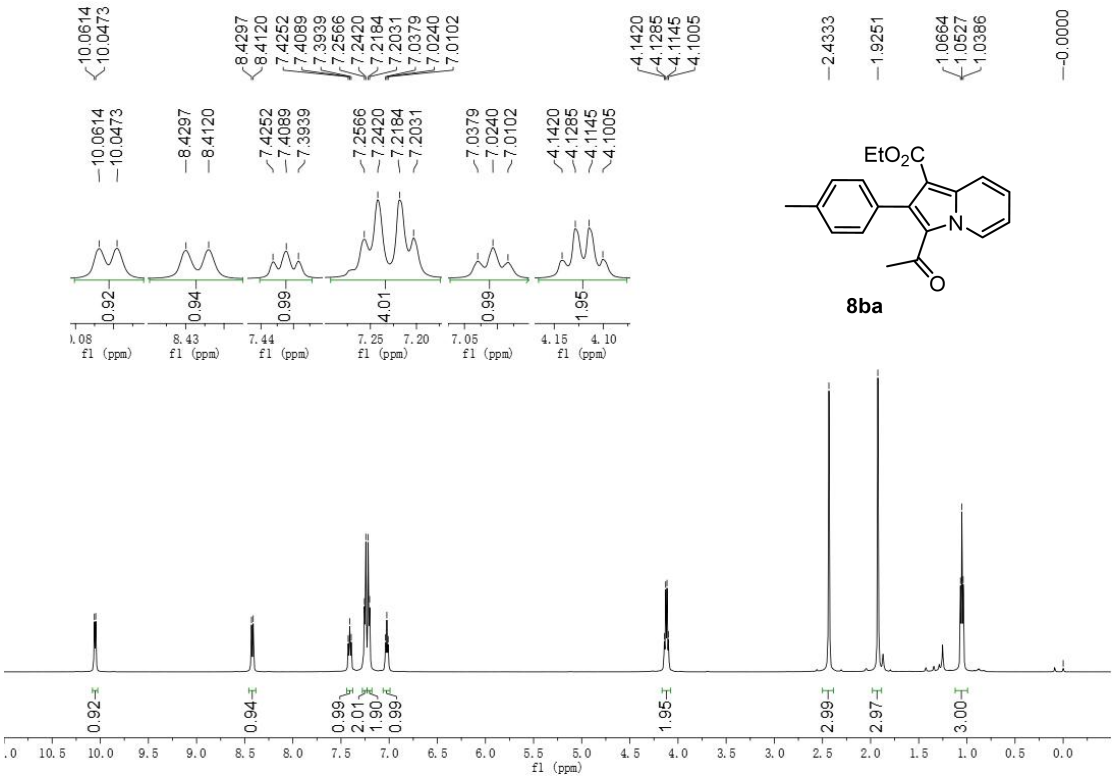

Figure S29. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **8ba**

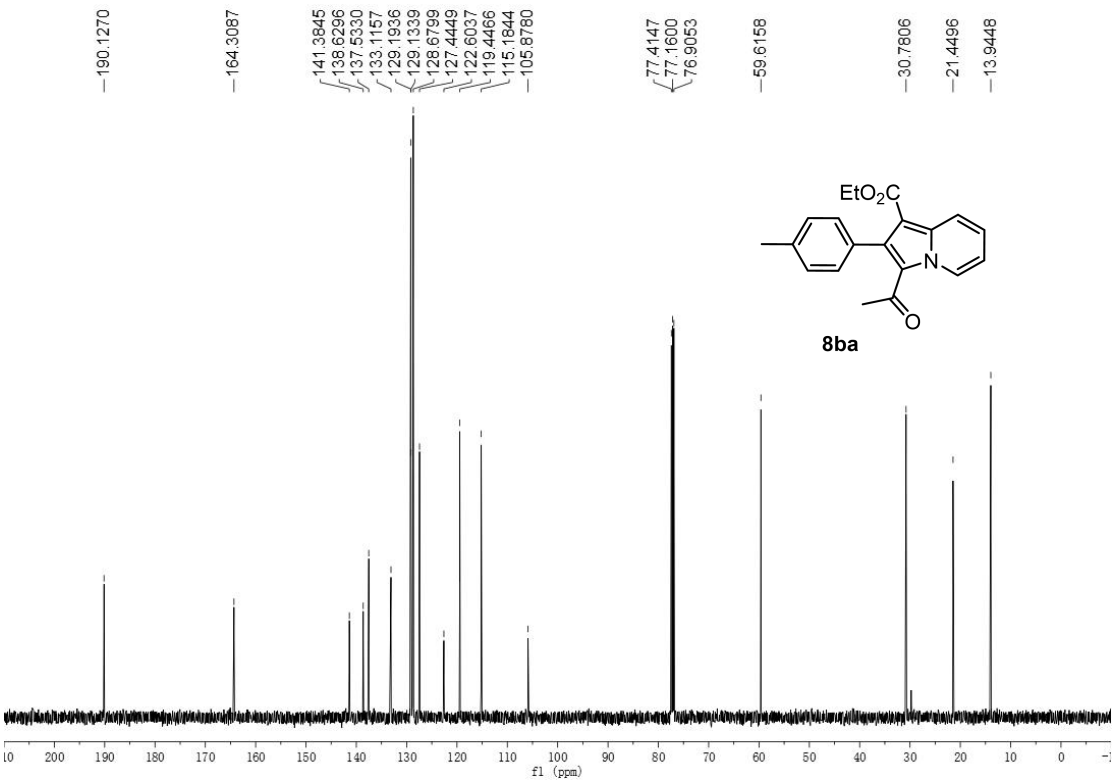

Figure S30. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **8ba**

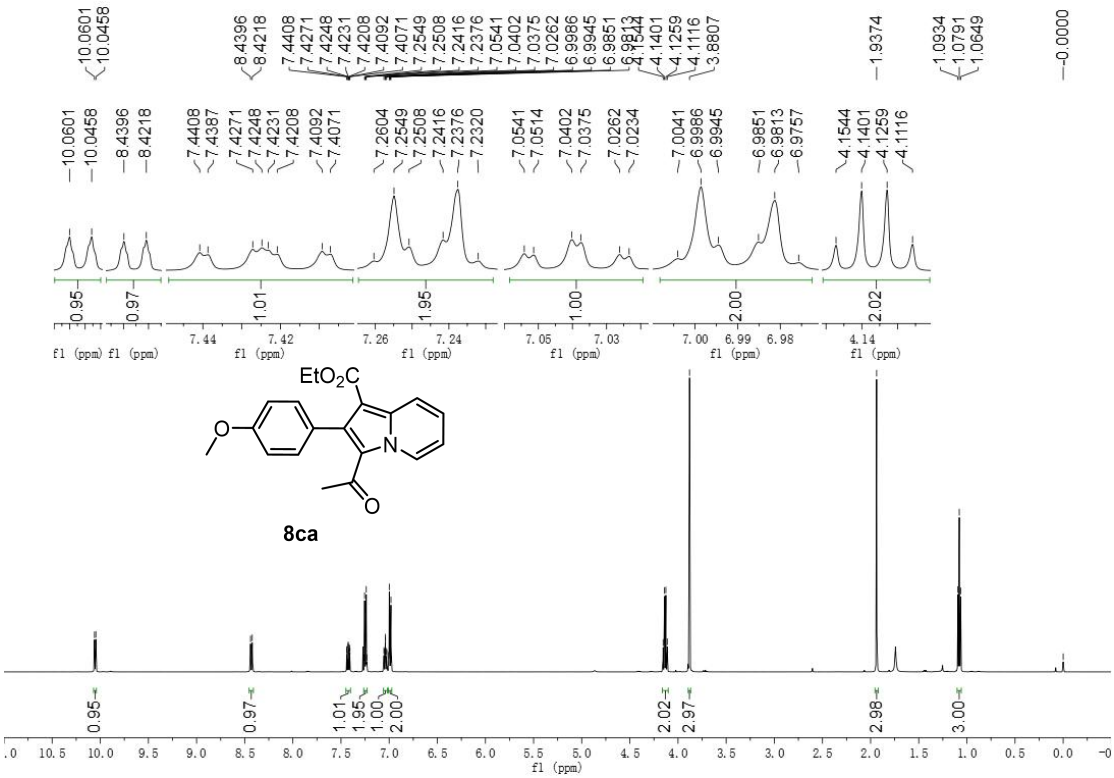

Figure S31. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **8ca**

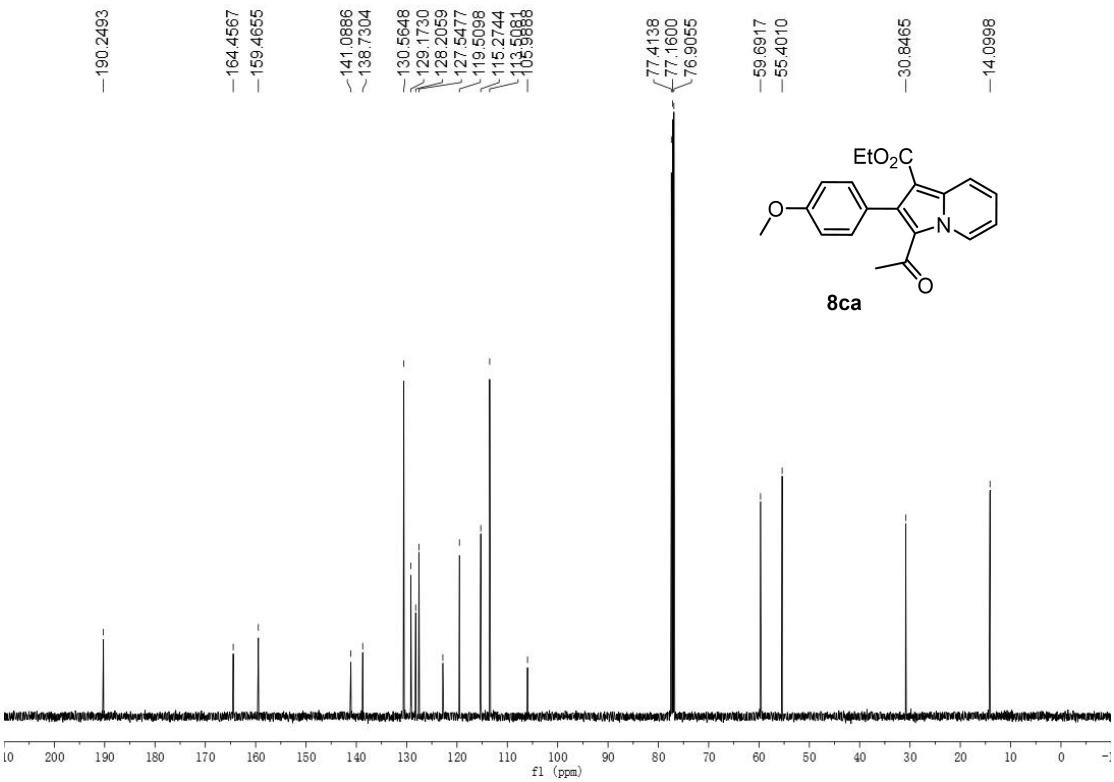

Figure S32. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **8ca**

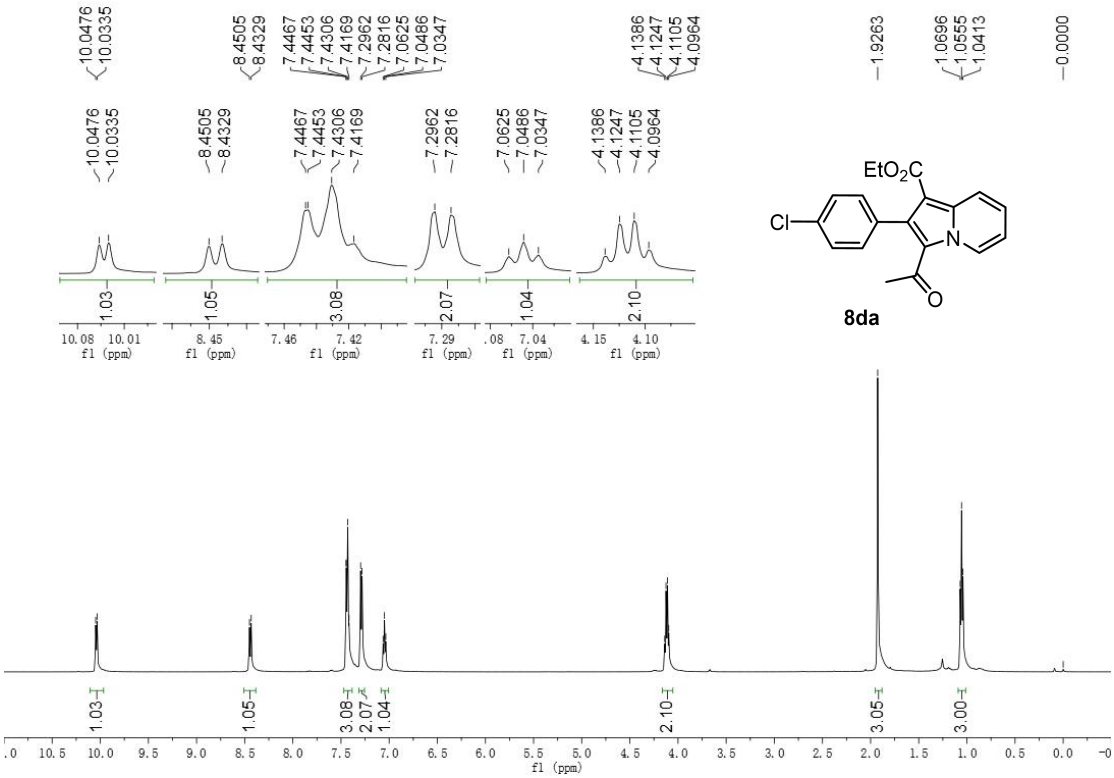

Figure S33. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **8da**

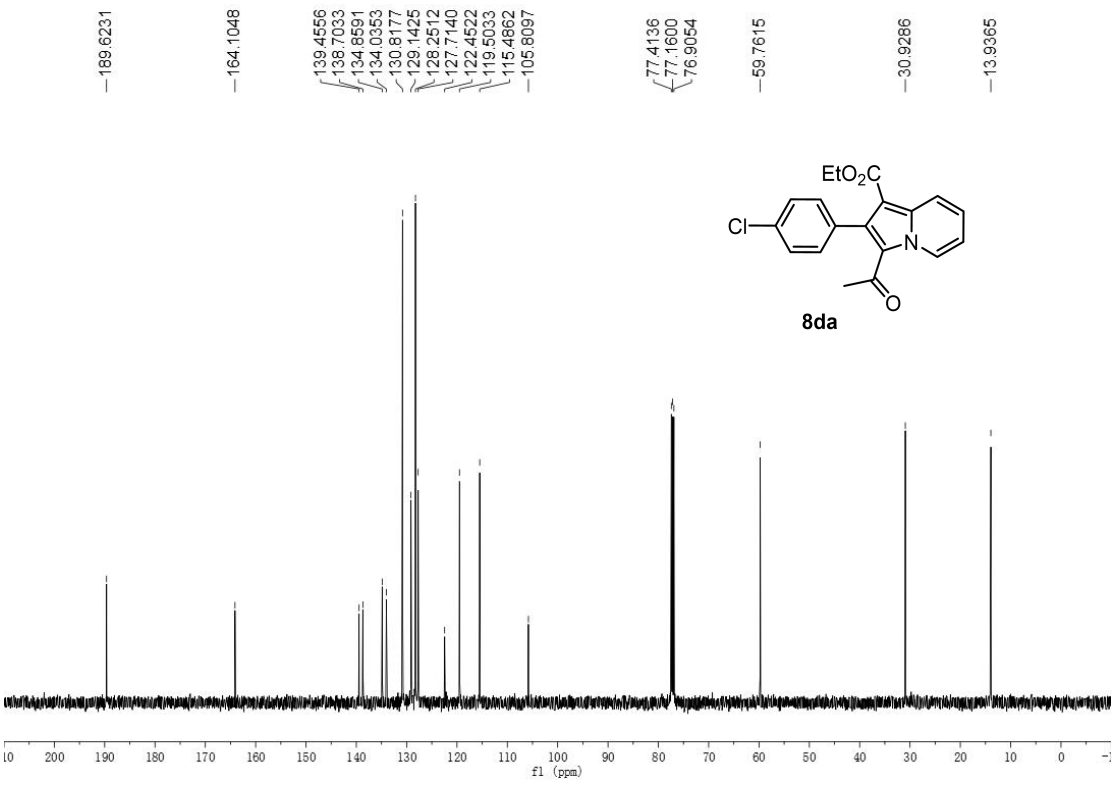

Figure S34. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **8da**

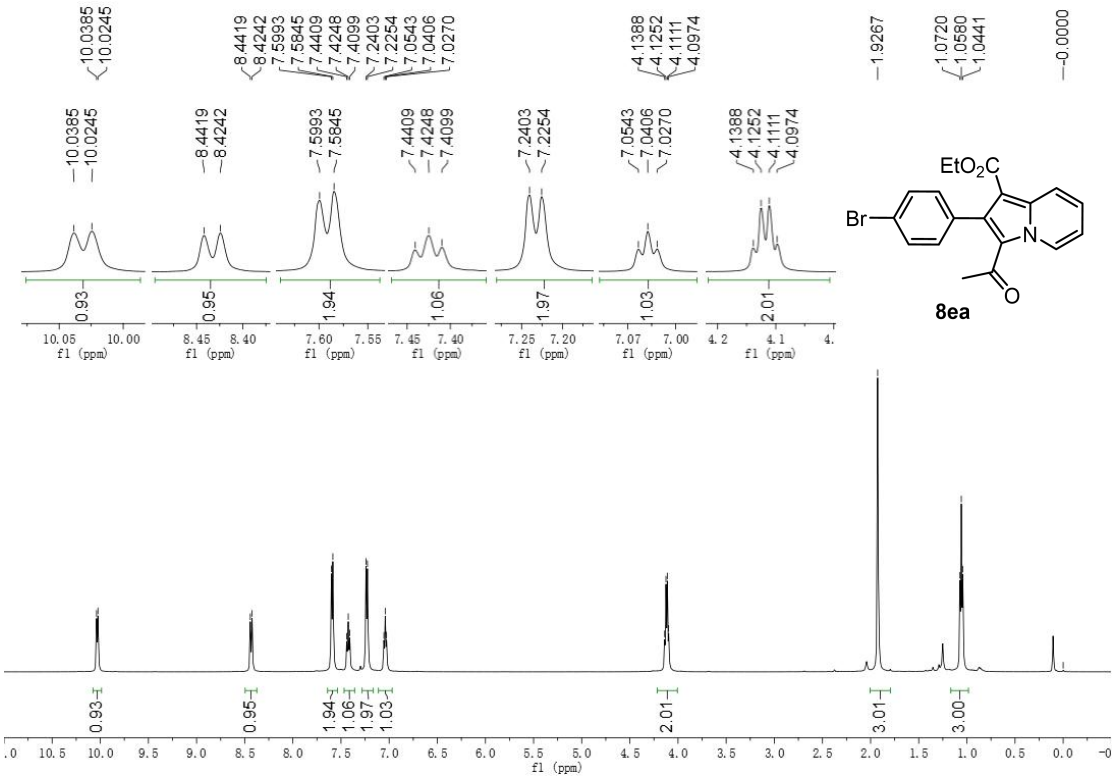

Figure S35. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **8ea**

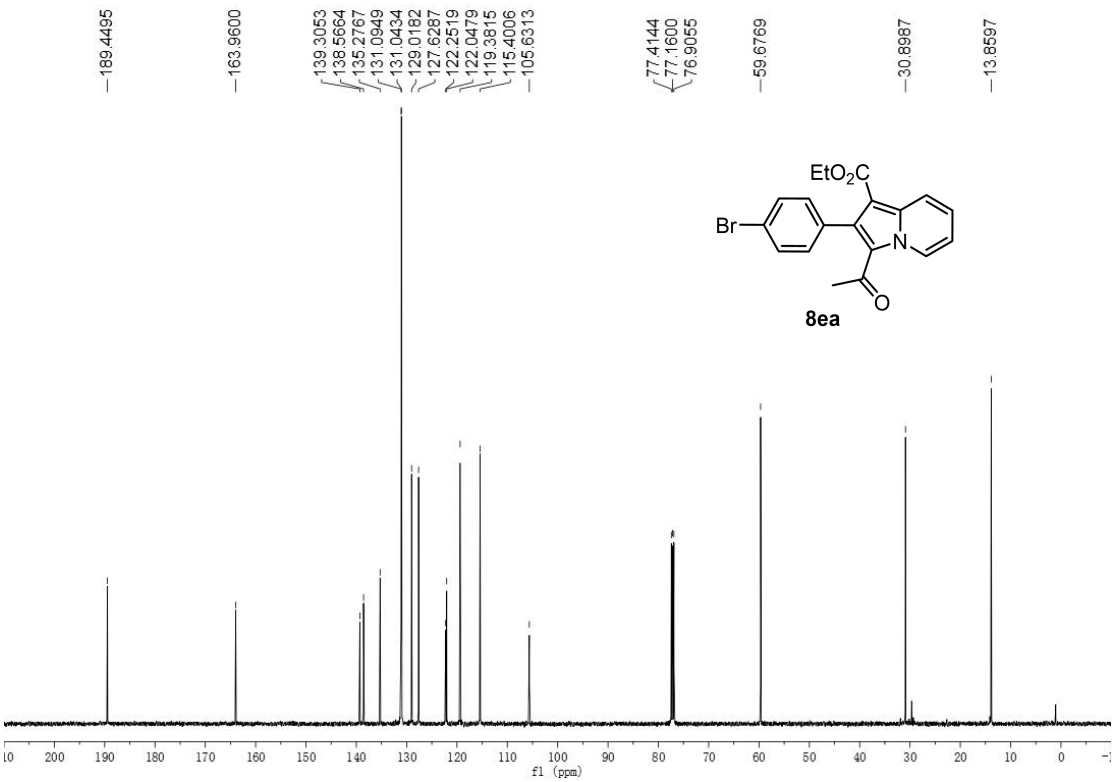

Figure S36. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **8ea**

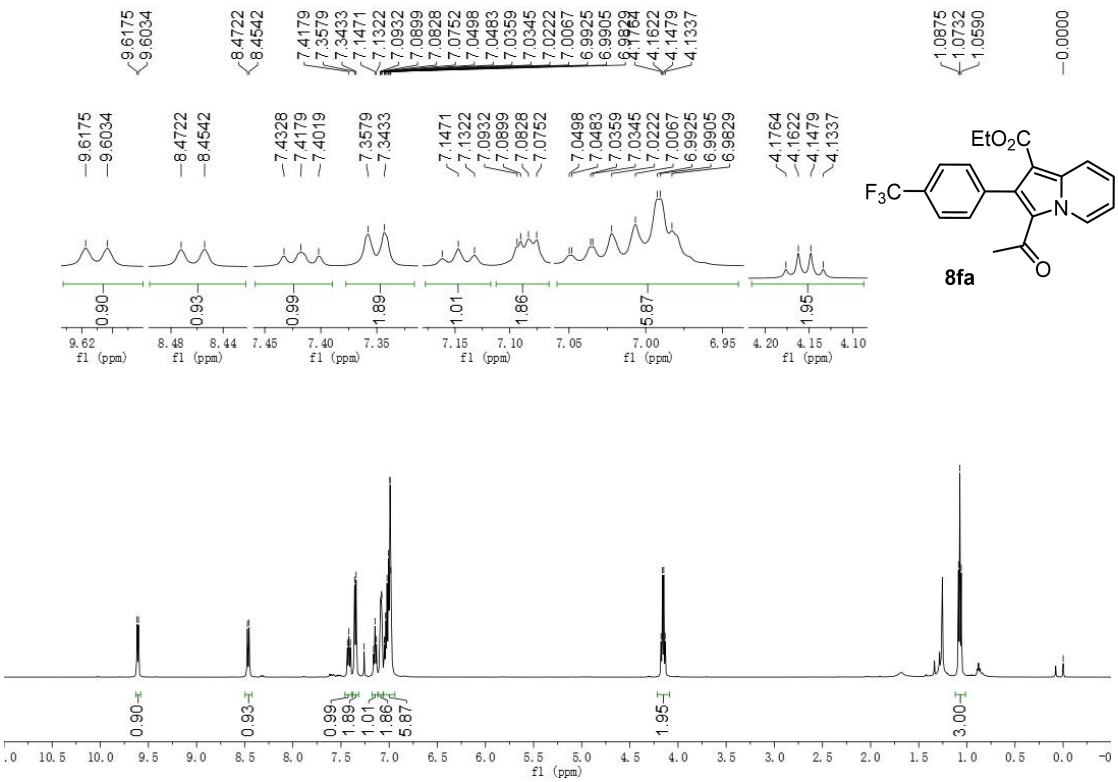

Figure S37. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **8fa**

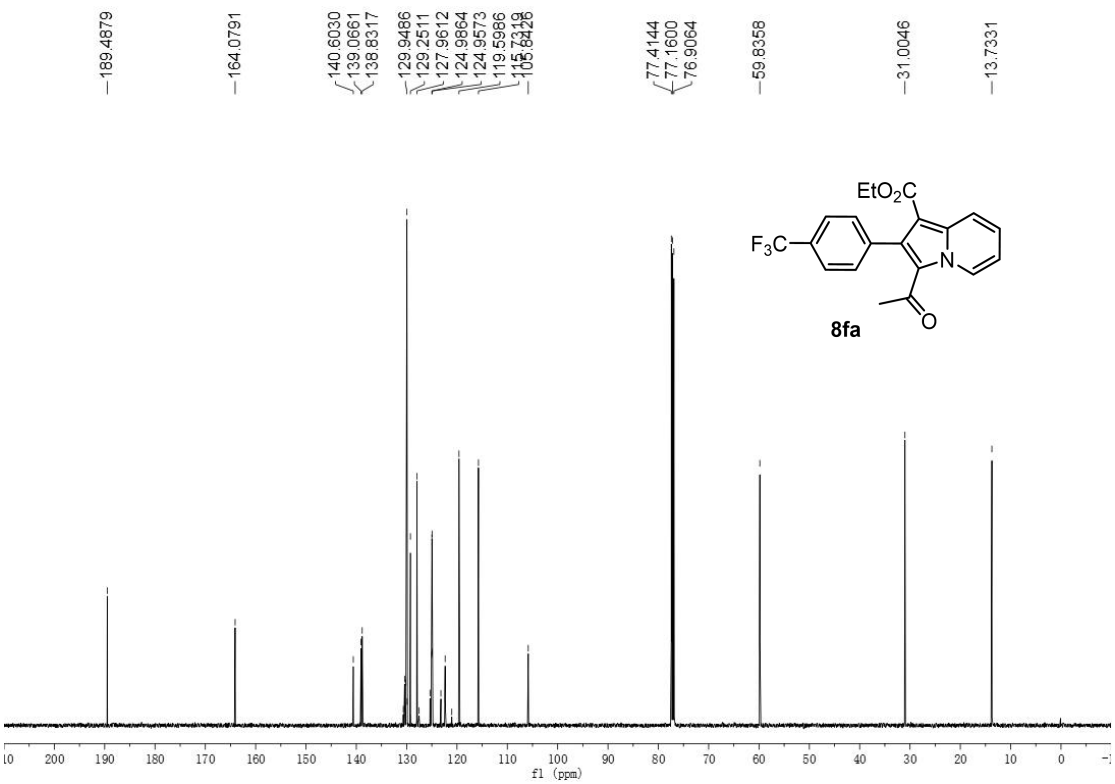

Figure S38. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **8fa**

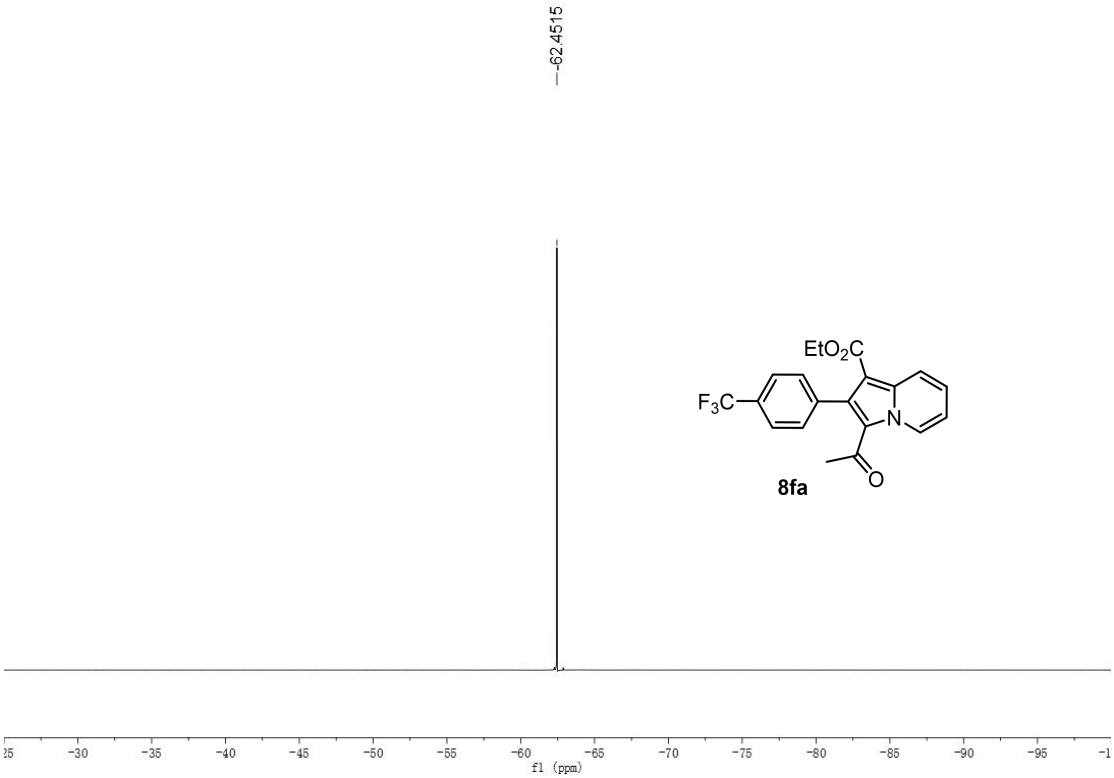

Figure S39. ^{19}F NMR (471 MHz, CDCl3) of compound **8fa**

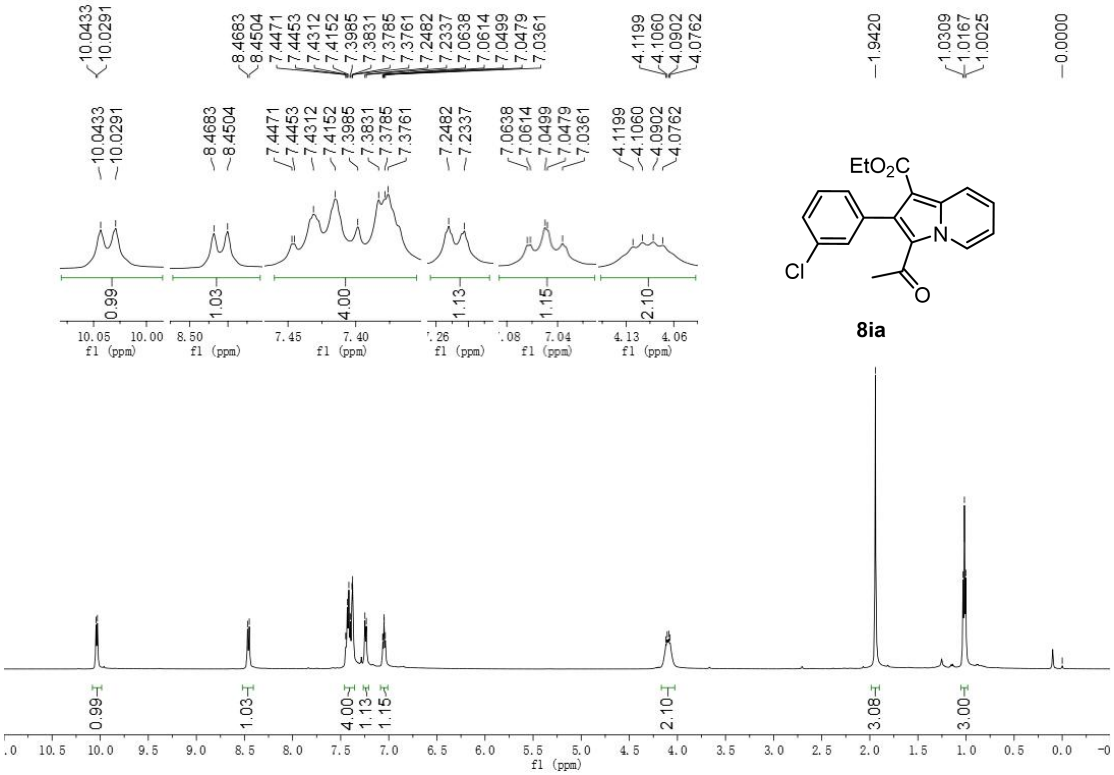

Figure S40. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **8ia**

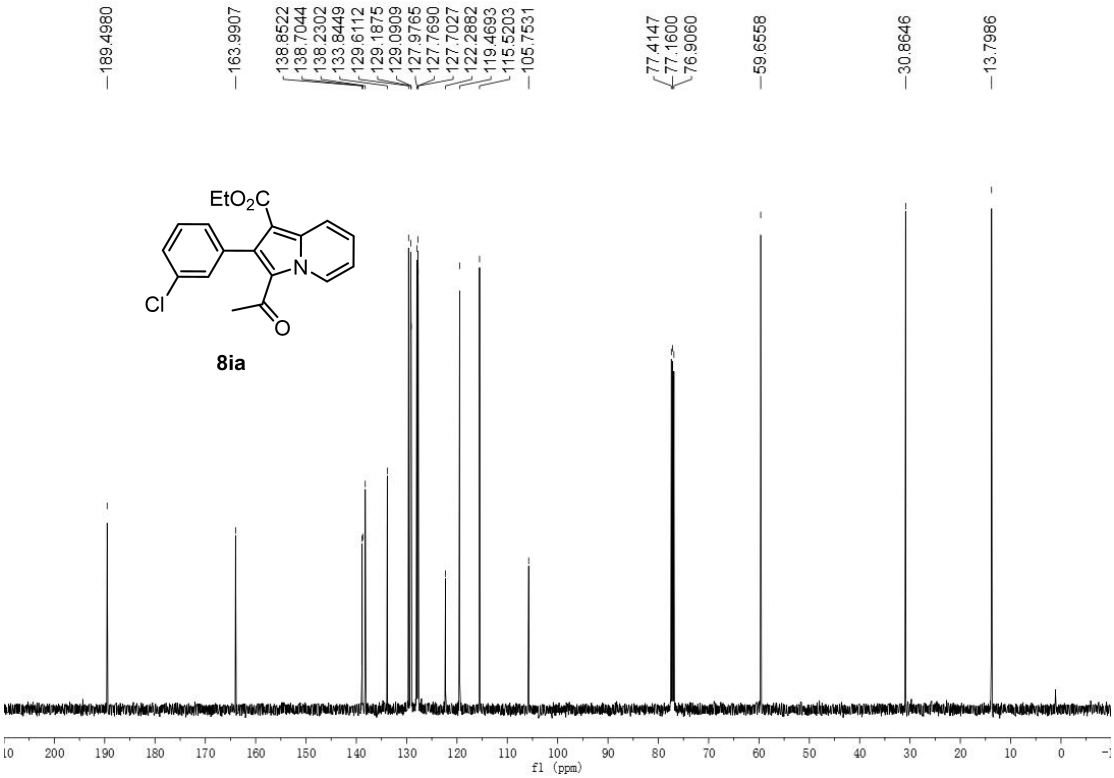

Figure S41. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **8ia**

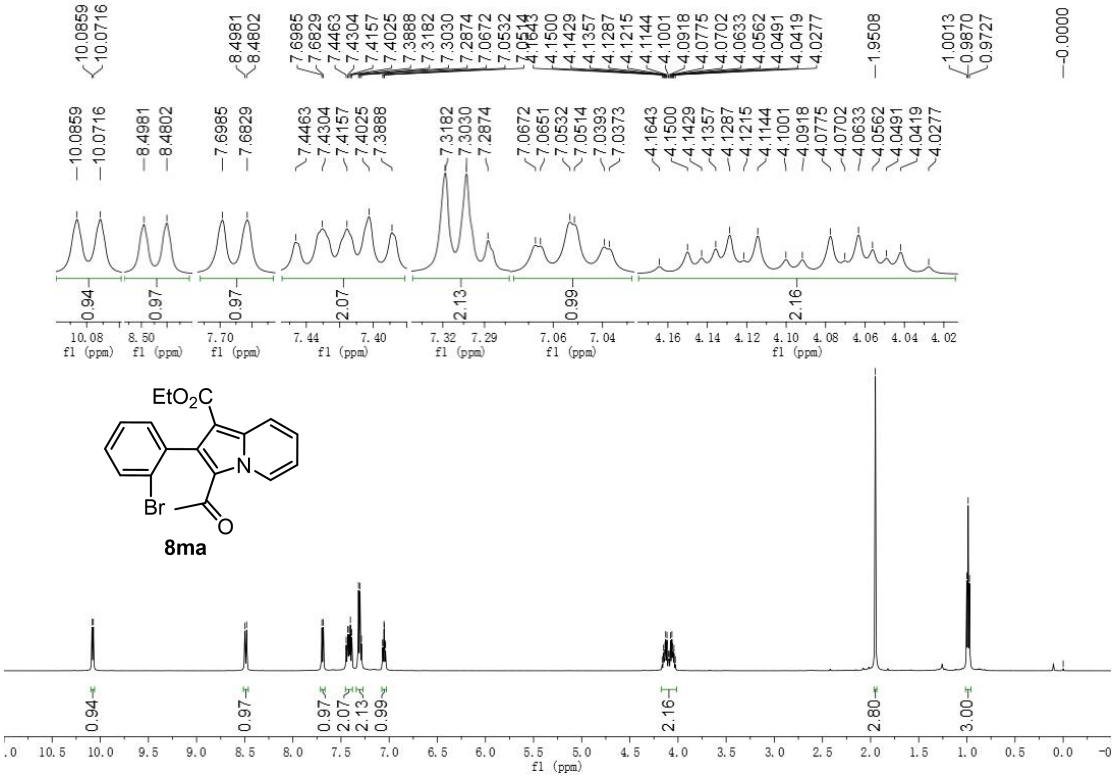

Figure S42. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **8ma**

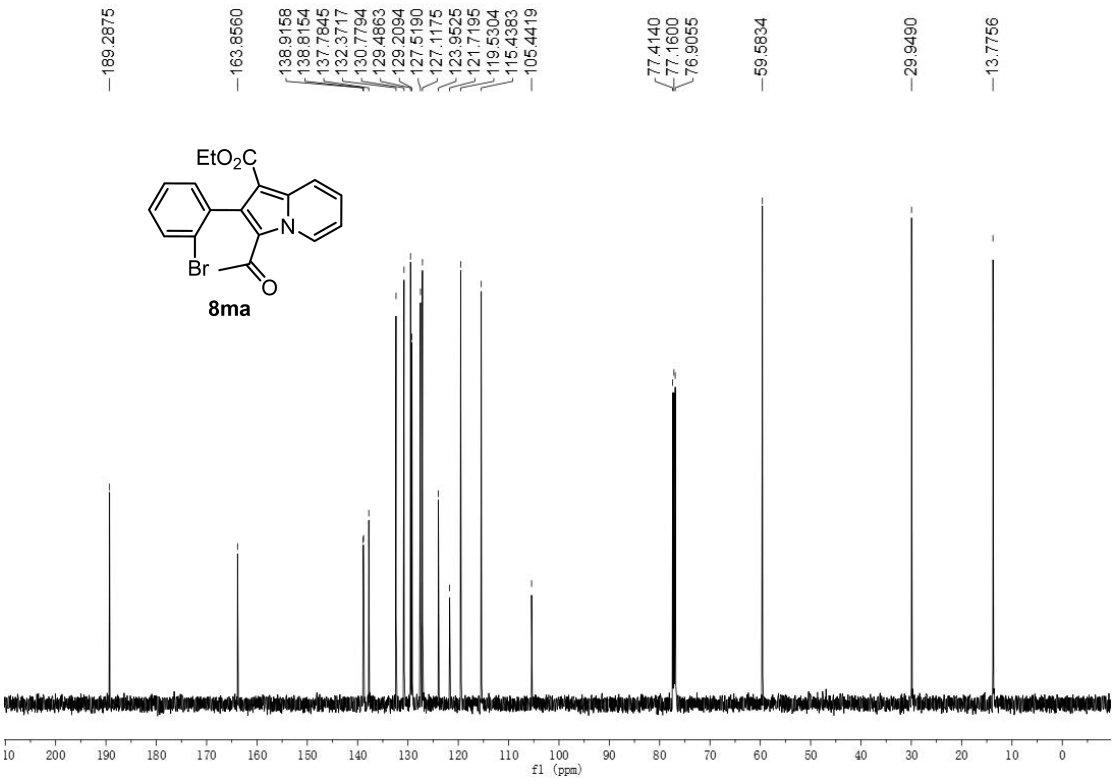

Figure S43. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **8ma**

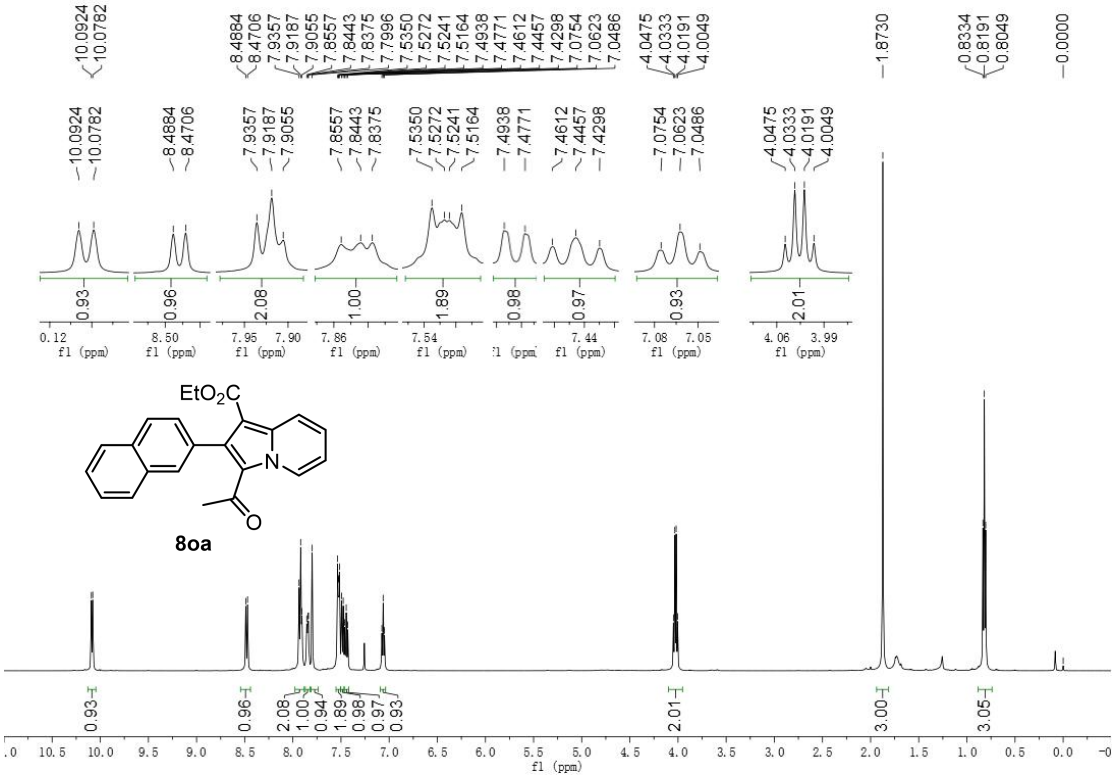

Figure S44. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **8oa**

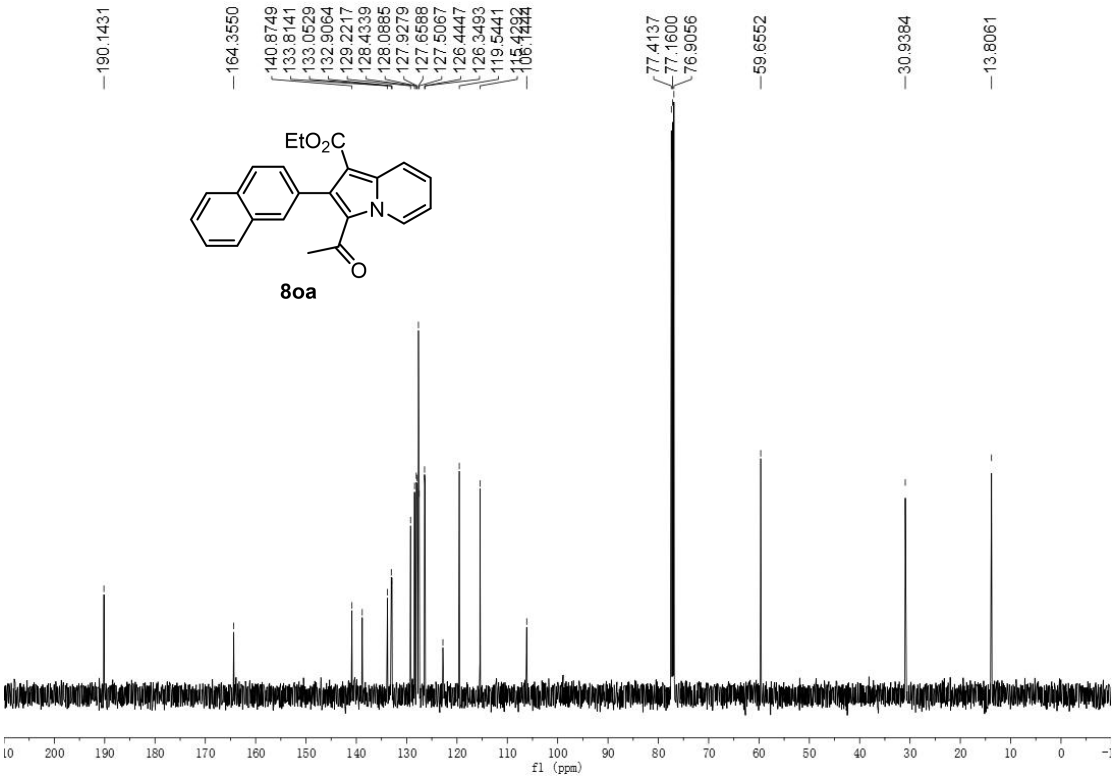

Figure S45. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **8oa**

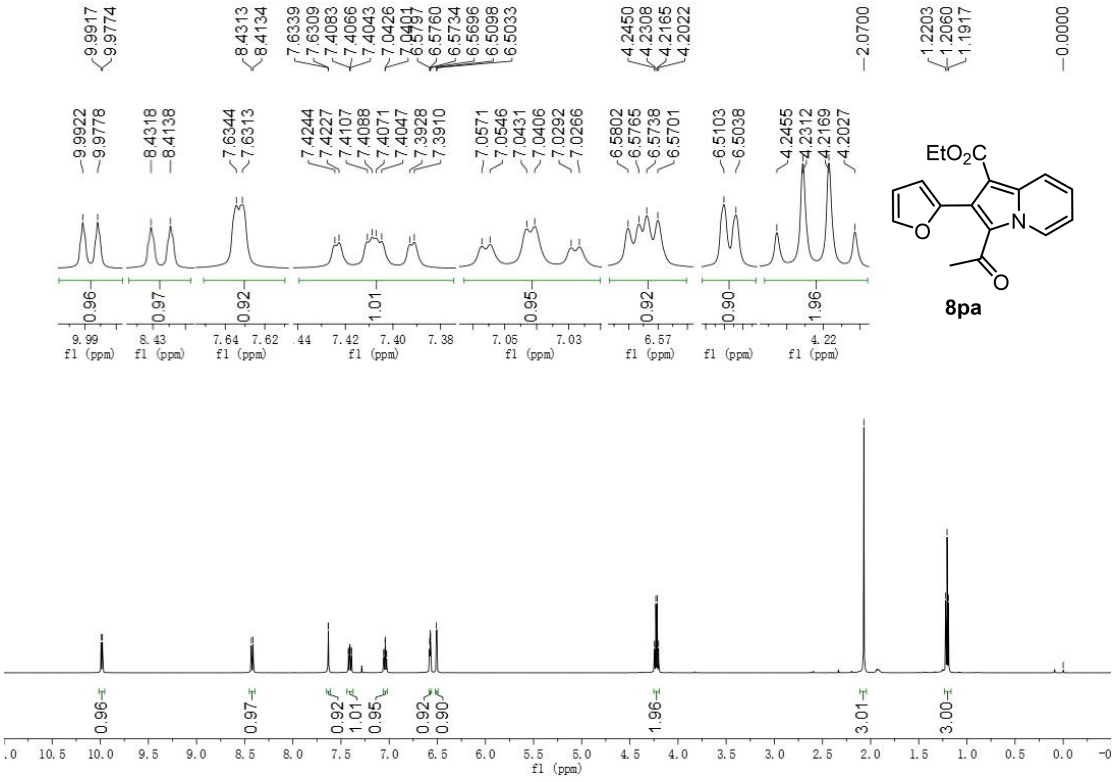

Figure S46. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **8pa**

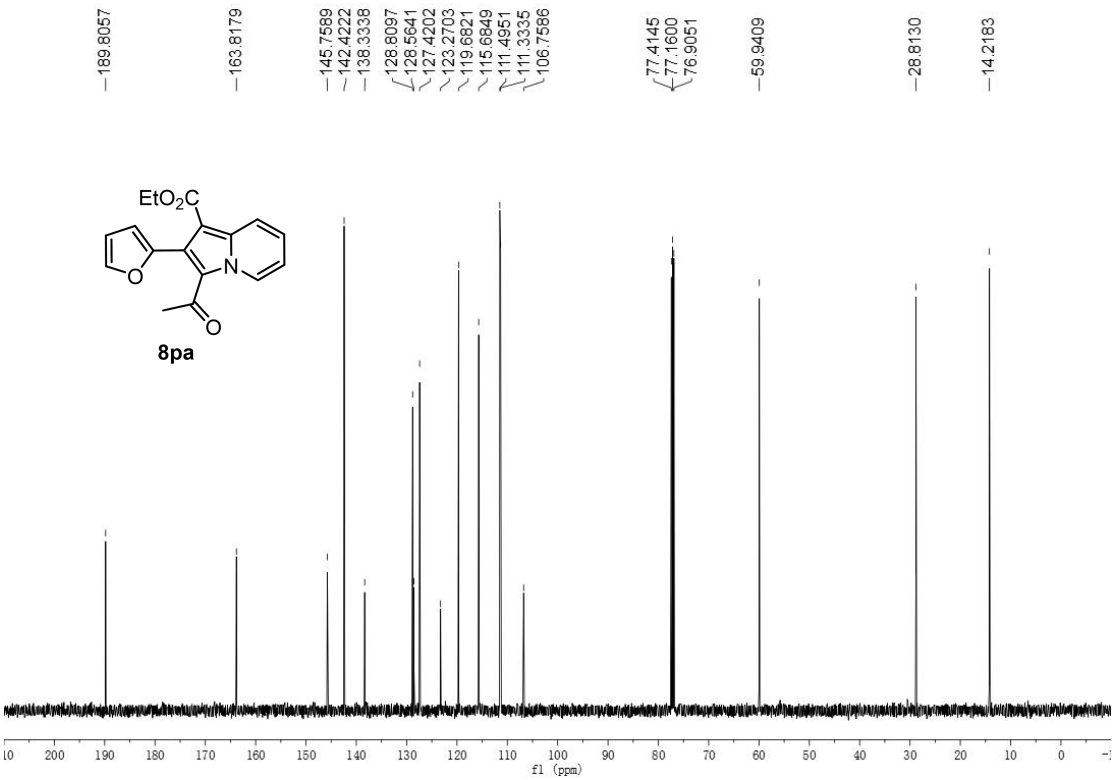

Figure S47. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **8pa**

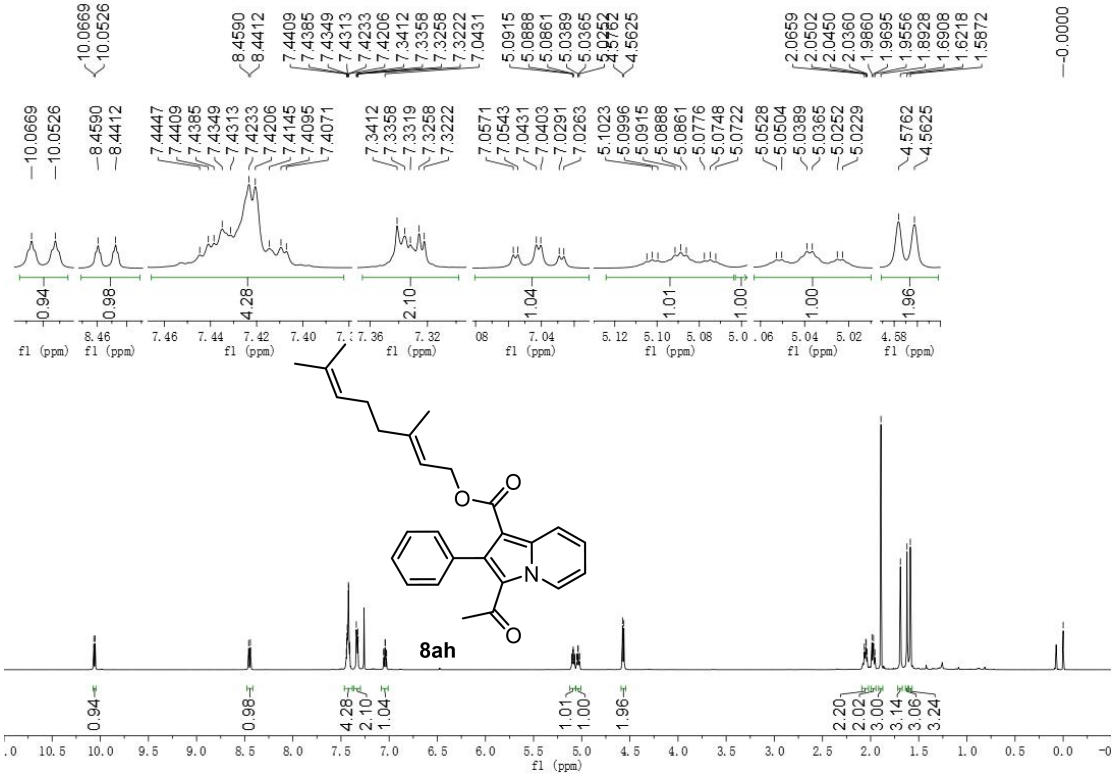

Figure S48. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **8ah**

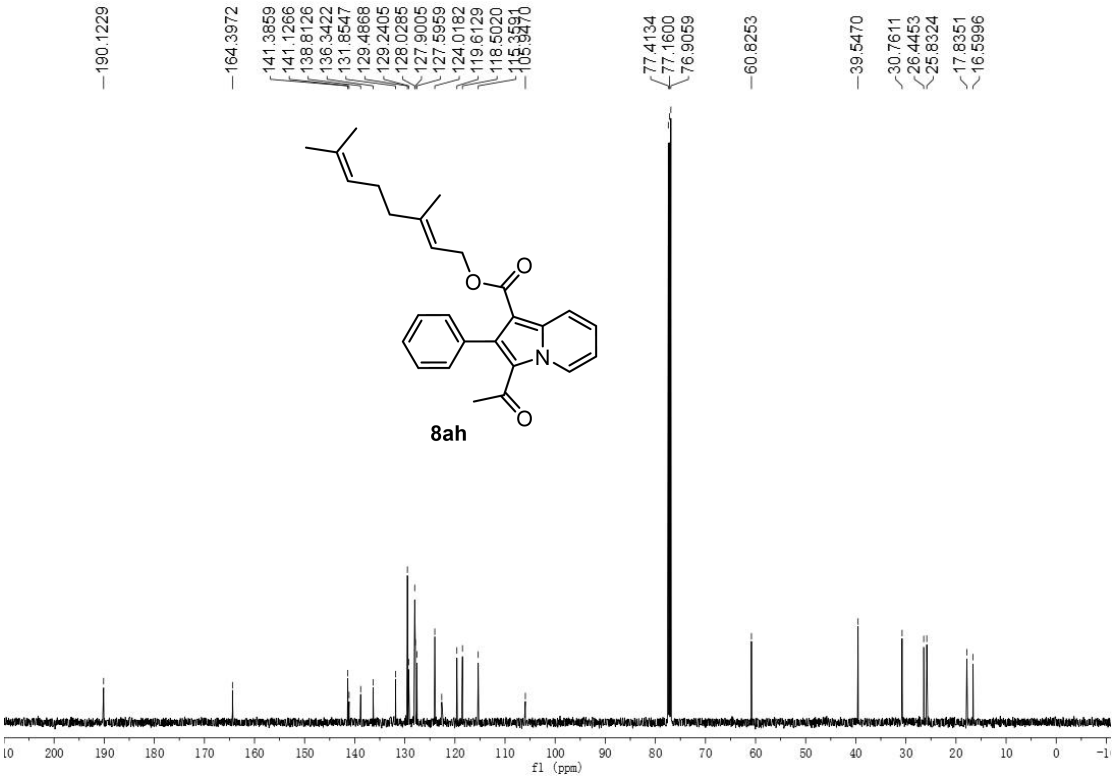

Figure S49. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **8ah**

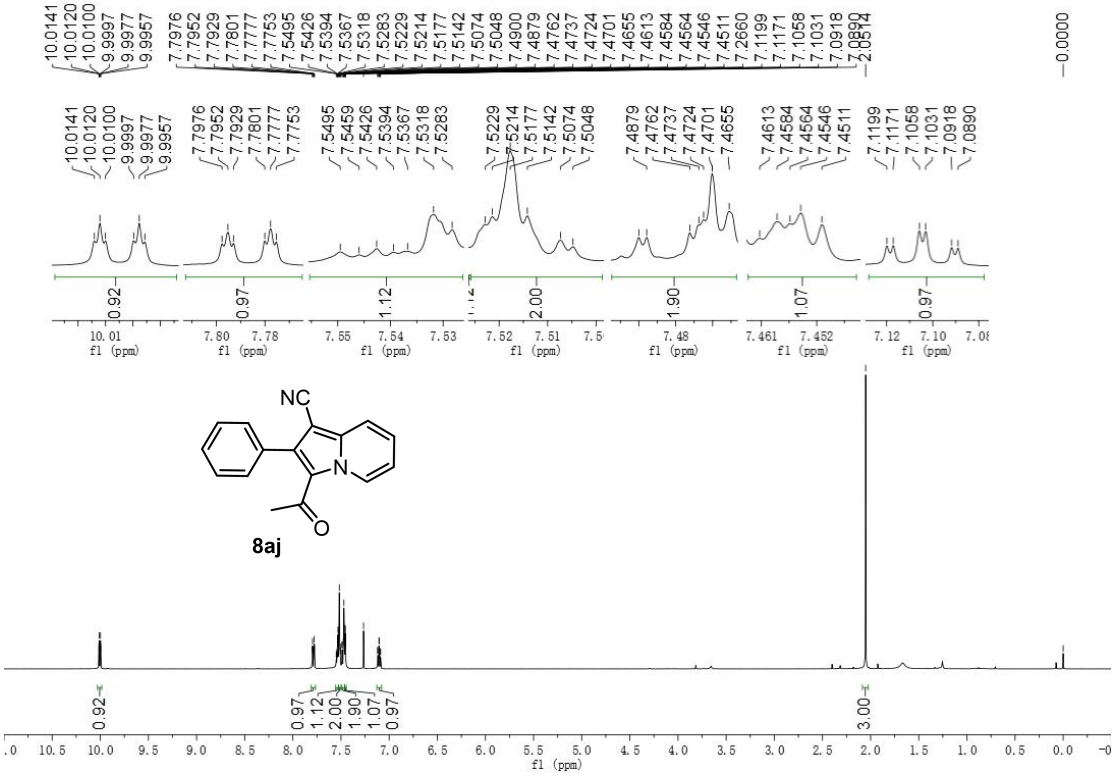

Figure S50. ^{1}H NMR (500 MHz, $CDCl_3$) of compound **8aj**

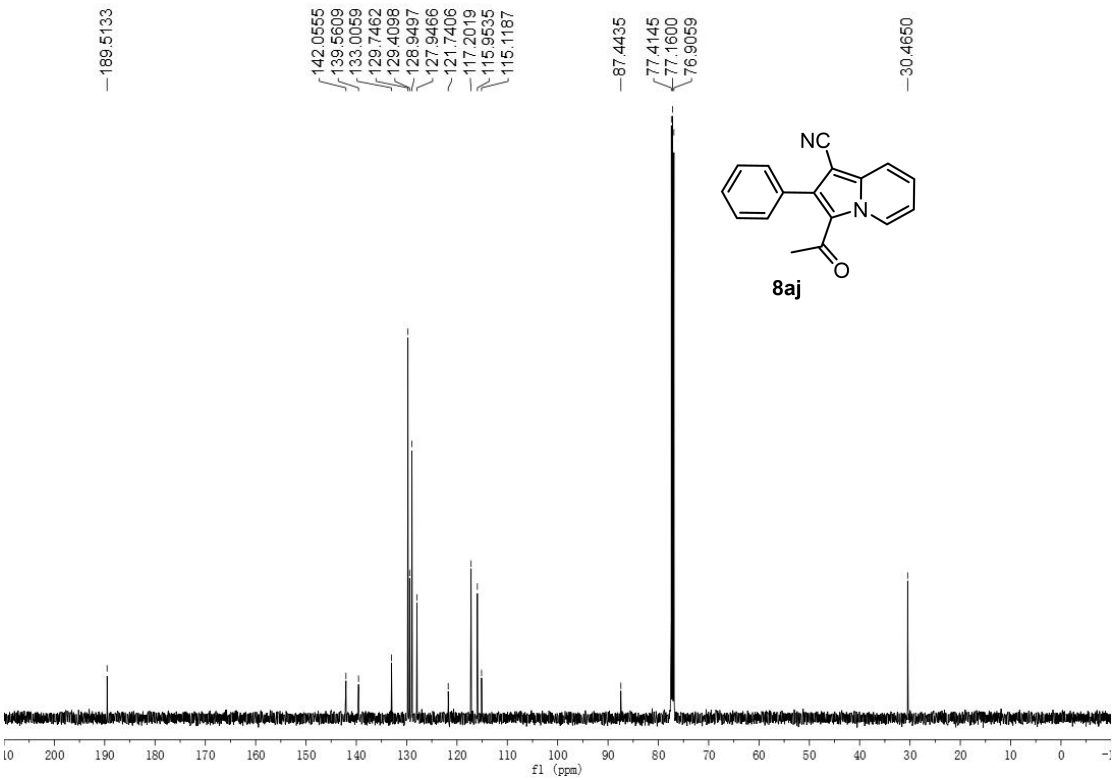

Figure S50. ^{13}C NMR (126 MHz, $CDCl_3$) of compound **8aj**

攻读硕士期间发表论文情况

[1] **Wu, L.-T.;** Diao, H.-L.; Wu, Y.; Shu, J.-S.; He, Z.-Y.; Xu, P.; Chen S.-Q.; Li, P.; Zhang, Z.; Xu, H. Synthesis of Highly Functionalized Indolizines via NIS-Promoted Spiroannulation/Ring-Opening Aromatization of Alkylidene Oxindoles with 2-(Pyridin-2-yl)acetate Derivatives. *J. Org. Chem.* **2025**, *90*, 4046–4053.

[2] Li, M.-J.; Xiao, H.-J.; Xu, P.; **Wu, L.-T.;** Chen, S.-Q.; Zhang, Z.*; Xu, H.* Mechanosynthesis of Pyrrole-2-carboxylic Acids via Copper-Catalyzed Spiroannulation/Ring-Opening Aromatization of 4-Arylidene Isoxazol-5-ones with Enamino Esters. *Org. Lett.* **2024**, *26*, 4189–4193.

[3] Li, M.-J.; Lu, M.-M.; Xu, P.; Chen, S.-Q.; **Wu, L.-T.;** Zhang, Z.*; Xu, H.* Chemodivergent mechanosynthesis of cyclopentenyl and pyrrolinyl spirobarbiturates from unsaturated barbiturates and enamino esters. *Chem. Commun.* **2024**, *60*, 3958–3961.

致谢

时光如一首未完成的诗，字里行间藏着无数未曾言说的情愫。三年光阴，似一缕轻烟，研究生生涯如同一场漫长的跋涉，沿途有风雨，也有晴空；有迷茫的雾霭，也有清澈的星光。而在这段旅程中，最珍贵的，是那些悄然无声的陪伴与指引，是那些如细雨般润泽心灵的教诲与关怀。

在这段旅程中，我最感激的是我的导师徐绘老师。您如一位隐于书卷中的诗人，以智慧为笔，以耐心为墨，悄然书写着我的成长。论文中的每一处批注，实验中的每一次指点，都如诗行般细腻而深刻。每当我迷茫时，您从不急于给出答案，而是以温和的语言，引导我拨开云雾，看见远方的星光。您让我明白，学术的路上，重要的不仅是结果，更是那份执着与热爱。您对每一个细节的严谨，对每一组数据的推敲，都让我深深感受到何为“精益求精”。还要感谢张泽老师的指点。虽然交集不多，但您的严谨与专注，为我树立了榜样，让我明白何为真正的学者风范。

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