硕士学位论文

题　目： 环外 α,β-不饱和环酮与烯胺的选择性环化反应研究

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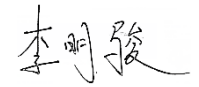
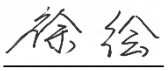
学位论文作者签名：  日期：2024 年 6 月 7 日

导 师 签 名：  日期：2024 年 6 月 7 日

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环外 α,β-不饱和环酮与烯胺的选择性环化反应研究

摘要

螺环结构作为一种重要的有机分子骨架，在药物化学、有机化学和材料科学等众多领域都具有广泛的应用。特别是由于其较强的刚性结构，螺环骨架能够满足药物设计中对构象刚性的特定需求，从而突显了螺环化合物高效合成方法研发的重要性。目前，螺环化合物已在抗菌、抗癌、抗糖尿病、抗炎及镇痛、抗氧化、防治人类免疫缺陷病毒（HIV）及抗细胞毒性等方面发挥显著作用，展现出其广阔的发展前景。本论文主要研究了环外 α,β-不饱和环酮与 β-烯胺酯的环化反应，通过控制反应条件（如温度、促进/催化剂、添加剂等）精准调控环化历程，高效且高选择性地合成出二氢吡咯、二氢呋喃、环戊烯螺环化合物和多取代吡咯。具体如下：

（1）研究了机械化学条件下卤代试剂促进的环外 α,β-不饱和巴比妥酸与 β-烯胺酯的环化反应，选择性构建了不同类型的巴比妥酸螺环化合物。利用该方法高效合成出了 24 个二氢吡咯螺环化合物及 24 个环戊烯螺环化合物，并提出了可能的选择性反应机制。

（2）研究了卤代试剂促进的硫代橙酮与 β-烯胺酯的环化反应，选择性构建了不同类型的硫代橙酮螺环化合物。利用该方法分别合成出了 21 个硫代橙酮螺二氢呋喃化合物及 25 个硫代橙酮螺二氢吡咯化合物，另提出反应机理并对反应的选择性进行了解释。

（3）研究了机械化学条件下环外 α,β-不饱和异噁唑酮与 β-烯胺酯的环化反应，选择性合成出 27 个环戊烯螺环化合物及 32 个多取代的吡咯类化合物，并提出了可能的反应机理。

上述所有反应，底物连有吸电子基团和给电子基团都能给出中等到优良的产率，表明这些反应都具有很好的普适性。所有产物都通过 ^{1}H NMR、^{13}C NMR 和 HRMS 进行了表征。对于每个反应体系，我们则是通过代表性产物的单晶 X-射线衍射进一步证实了其结构。本方法具有选择性高、反应条件温和、原料易得、操作简便及适用于克级反应等优点，为高效合成结构新颖的螺环化合物及多取代吡咯提供了一种新的选择。

关键词：

螺环化合物；化学选择性；二氢吡咯；二氢呋喃；环戊烯；吡咯

INVESTIGATION ON THE SELECTIVE CYCLIZATION OF EXOCYCLIC α,β-UNSATURATED CYCLOKETONES WITH ENAMINES

ABSTRACT

Spiro structures, an important organic molecular skeleton, have been widely applied in numerous fields including medicinal chemistry, organic chemistry, and materials science. Particularly, spiro skeleton can meet the specific needs for conformational rigidity in drug design due to their strong rigidity, thus highlighting the importance of developing efficient synthetic methods for these compounds. Currently, spiro compounds have played significant roles in antibacterial, anticancer, antidiabetic, anti-inflammatory and analgesic, antioxidant, prevention and treatment of human immunodeficiency virus (HIV), and anticytotoxicity areas, showing their broad prospects. The main work of this thesis is the cyclization reaction between exocyclic α,β-unsaturated cycloketones and β-enamino esters, achieving the efficient and highly selective synthesis of dihydropyrrolyl, dihydrofuryl and cyclopentenyl spiro compounds and polysubstituted pyrroles by regulating the reaction conditions (such as temperatures, promoters/catalysts, additives, etc.). The details are as follows:

(1) The halogenating agents promoted cyclization reaction of

exocyclic α,β-unsaturated barbiturates with β-enamino esters under mechanochemical conditions to selectively synthesize different types of spirobarbiturates was studied. Following this protocol, 24 dihydropyrrolyl spiro compounds and 24 cyclopentenyl spiro compounds were efficiently obtained. A possible mechanism was also proposed to explain the reaction selectivity.

(2) The halogenating agents promoted cyclization reaction of thioaurones with β-enamino esters to selectively synthesize different types of spirothioaurones was studied. Following this protocol, 21 dihydrofuryl spirothioaurnes and 25 dihydropyrrolyl spirothioaurnes were obtained. In addition, a plausible reaction mechanism was proposed.

(3) The cyclization reaction of exocyclic α,β-unsaturated isoxazolones with β-enamino esters under mechanochemical conditions was studied. Following this protocol, 27 cyclopentenyl spiro compounds and 32 polysubstituted pyrroles were selectively synthesized. In addition, a plausible reaction mechanism was proposed.

In the above reaction systems, substrates with electron-withdrawing and electron-donating groups could react well to give the corresponding products in moderate to excellent yields, thus highlighting the good applicability of these reactions. All products were characterized by ^{1}H NMR, ^{13}C NMR and HRMS analyses. Additionally, their structures were further unambiguously confirmed by single-crystal X-ray diffraction

using representative products in each system. The present method has several advantages including high selectivity, mild reaction conditions, readily available starting materials, simple operation and feasibility for gram-scale synthesis, providing a new alternative to efficiently synthesize structurally novel spiro compounds and polysubstituted pyrroles.

KEY WORDS:

Spiro compounds; Chemoselectivity; Dihydropyrroles; Dihydrofurans; Cyclopentenes; Pyrroles

目录

第一章 绪论

1.1 引言

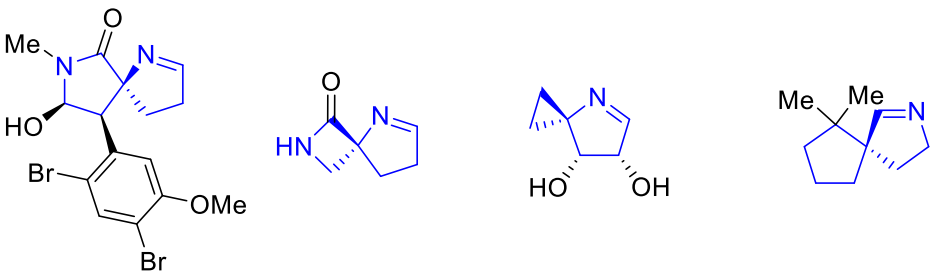
螺环化合物是一类至关重要的有机核心骨架，广泛分布于众多具有生物活性的分子中，并展示出多种生物活性，如降低胆固醇、具备抗肿瘤、抗菌、抗疟疾、抗微生物及抗结核活性。此外，螺环化合物还具有特殊的光、电性能，这些特性使得其在多个领域得到了广泛的应用[1-6]。因此，合成具有广泛生理和药理活性的螺环类化合物，成为了研究的一个热门方向[7-13]。在过去几十年里，螺环化合物在医药研发、材料科学、农业化学以及有机合成等多个领域都取得了显著进展。尽管如此，当前的研究进展仍无法完全满足人们对新药研发和新型合成方法探索的强烈需求，并且在合成螺环化合物时仍面临着许多挑战，包括有限的底物范围和化学选择性、苛刻的反应条件以及不可持续性等问题[14-23]。因此，探索和开发新型的螺环化合物合成策略，具有重大的科学意义和应用价值。

1.2 二氢吡咯螺环化合物的应用

含氮杂环化合物是一类极其重要的杂环化合物，由于它们独特的物理化学属性、生物活性和药理学价值，使之成为许多生物活性分子和药物的关键骨架，在有机化学和药物化学领域占据着举足轻重的地位。根据统计，2018 年在美国销量排名前 200 的处方药中，含氧和含氮杂环化合物共计 106 种，而在销量最高的 20 种品牌药物中，约有 80%含有氮原子，其中三分之二为含氮杂环化合物。因此，探索新的、高效的、原料易得的含氮杂环合成方法，是现代有机合成领域的重要研究方向[26-35]。

1.2.1 二氢吡咯螺环化合物在医药方面的应用

二氢吡咯螺环骨架普遍存在于天然产物和活性分子中，并表现出广谱的生物活性，如化合物 **1** 具有抗病毒活性、二氢吡咯螺环 **2** 有显著的抗菌活性、环丙基二氢吡咯螺环 **3** 表现出良好的镇痛效果[36]、环戊烷螺二氢吡咯化合物 **4** 具有优异的驱虫活性[37]（图 1-1）。

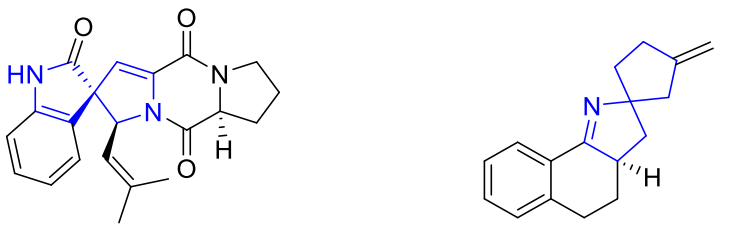


Antiviral drugs **1** | Antibiotics **2** | Neurologic drugs **3** | Anthelmintic **4**

图 1-1 含有二氢吡咯螺环骨架的药物分子

(Figure 1-1 Pharmaceutical molecules containing a spirodihydropyrrole framework)

此外，人工合成的天然活性产物，如人体前列腺素 **5** 和三尖杉碱中间体 **6** 目前也广泛应用在医药领域（图 1-2）[38,39]，因此二氢吡咯螺环化合物在生物医药领域具有很大的发展前景。



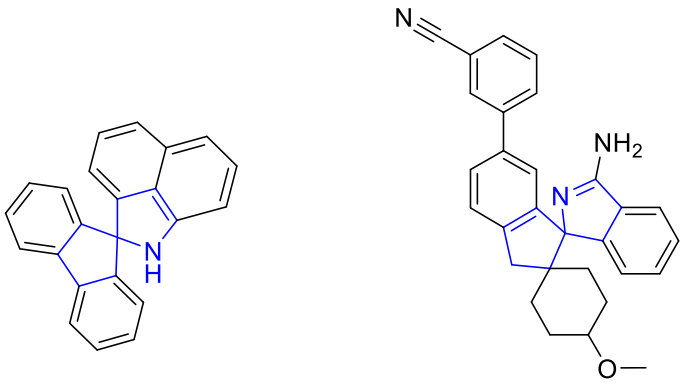
6-Methoxyspirotryprostatin B **5** | Intermediate of cephalotaxines **6**

图 1-2 人工合成的生物碱

(Figure 1-2 Artificially synthesized alkaloids)

1.2.2 二氢吡咯螺环化合物在材料方面的应用

在材料科学领域，二氢吡咯螺环化合物凭借其独特的电子性质，已成为制备高性能材料的最佳选择。这类化合物被广泛应用于有机电致发光材料（图 1-3）。这些先进材料在民用照明和多个高科技领域均展现出巨大潜力，包括数字图像处理、光通信、光集成技术，以及高清晰度数字电视、数字相机、摄像机、数字电影和信息高速公路等[40]。



7 **8**

图 1-3 螺二氢吡咯有机电致发光材料

(Figure 1-3 Spirodihydropyrrole organic electroluminescent materials)

1.3 环戊烯螺环化合物的应用

五元碳环在天然产物、药物和其它有机化合物中普遍存在。其中，环戊烯螺环化合物由于其生物活性和刚性构象，在药物开发中尤为重要，可用于开发新型的抗菌剂、抗炎药物和抗癌药物等[41-50]。此外，在材料科学领域，环戊烯螺环化合物的独特物理化学性质使它们成为高性能材料的潜在候选者，如在有机光电材料和液晶材料中的应用。

1.3.1 环戊烯螺环化合物在医药方面的应用

基于环戊烯骨架的螺环化合物在医药领域具有显著的应用潜力。迄今为止，已经有研究文献报道了环戊烯螺环化合物在生物医学领域的若干应用实例（图 1-4）。例如氧化吲哚螺环戊烯化合物 **9** 具有抗海洋白血病的细胞毒活性[10]，化合物 **10** 则具有很强的抗肿瘤活性[11]，螺环戊烯化合物 **11** 是灰色链霉菌的代谢产物，具有非常强大的抗肿瘤特性[59,60]。化合物 **12** 作为一种特异性抑制剂，能够增强人体的代谢功能并提高脑部血流量[61,62]。而化合物 **13**，一种抗阿尔茨海默症的药物，能有效减轻由胆碱缺乏引起的学习功能障碍，并预防神经系统疾病的发生。这些研究不仅展示了环戊烯螺环化合物的多样化医疗潜力，也为未来的药物开发和治疗策略提供了新的方向[63]。

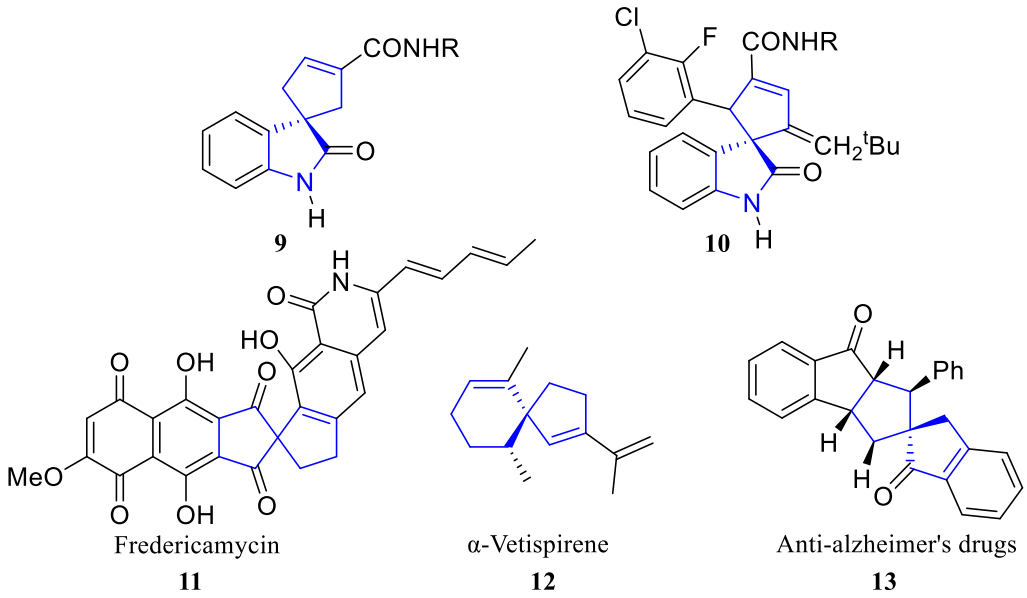


图 1-4 含有环戊烯螺环骨架的药物分子

(Figure 1-4 Pharmaceutical molecules containing a Spirocyclopentene framework)

1.3.2 环戊烯螺环化合物在材料方面的应用

有机电致发光器件因其在照明和平板显示等领域展现出的巨大商业潜力，近年来获得了广泛关注。通过巧妙设计并组合不同功能单元的连接结构，研究者能够构建出性能卓越的主体材料，以实现高效的有机电致发光器件。在开发高性能电致发光主体材料的研究中，已经投入了大量的努力[64]。特别是，基于环戊烯螺环骨架的材料 **14** 已被证明具备成为电致发光材料的基本要素（图 1-5）。这种结构利用环戊烯螺环化合物作为核心骨架，表现出高三重态能级、高玻璃化转变温度、高发光效率以及低驱动电压等优良特性，成为一种理想的电致发光器件材料[65]。

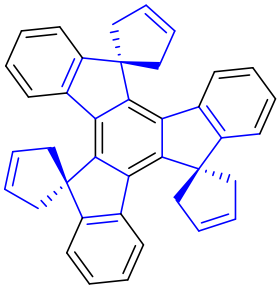


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图 1-5 螺环戊烯有机电致发光材料

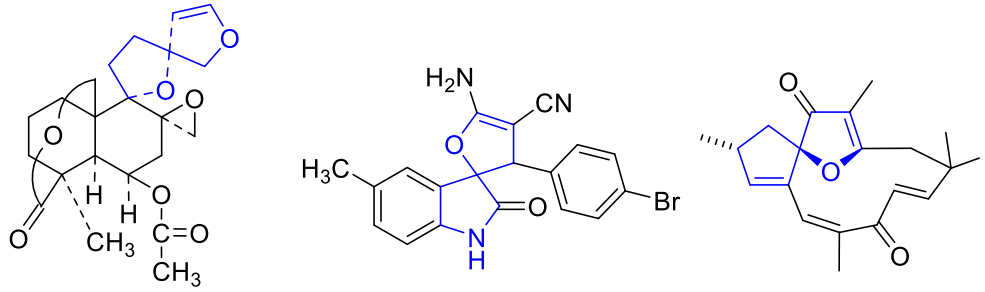
(Figure 1-5 Spirocyclopentene organic electroluminescent materials)

1.4 二氢呋喃螺环化合物的应用

氧杂环化合物是有机化合物中种类非常丰富和数量较多的一大类。特别是以呋喃为核心结构的化合物，这种结构在众多天然产物和药物分子中均有广泛存在[66-71]。以二氢呋喃作为核心骨架的化合物，因其在天然产物和生物医药中作为基础骨架而显示出的广泛生物活性，近年来吸引了各研究领域学者的浓厚兴趣。这类化合物在天然产物、合成药物和农业化学品等多个领域均展示出了重要的应用潜力，已被证明具有包括镇静、抗菌、杀虫、抗高血压、抗病毒和抗肿瘤在内的多种生物活性[72-81]。

1.4.1 二氢呋喃螺环化合物在医药方面的应用

根据一些文献报告，二氢呋喃螺环化合物在具备生物活性和药理活性的天然产物结构单元中扮演着至关重要的角色，表现出了显著的医疗价值（图 1-6）。例如，1974 年，美国科学家罗伯特通过 X-射线单晶衍射技术成功确定了化合物 **15** 的三维结构，揭示了其因含有二氢呋喃螺环结构而展现出强大的癌细胞抑制和抗肿瘤活性[82]。陈永平课题组的实验研究证实，带有卤素原子取代基的二氢呋喃螺环化合物 **16** 在抑制巨噬细胞活性方面表现出良好效果，有效抑制了巨噬细胞炎症因子的释放[83]。此外，天然活性分子 **17** 则展现出了抗过敏、抗菌和抗真菌的生物活性。这些研究不仅证实了二氢呋喃螺环化合物的多样化药理作用，也进一步突显了其在药物研发领域的重要价值[84]。



Nepetaefolin **15**　　Macrophage inhibitor **16**　　Jatrophone **17**

图 1-6 具有生物活性的二氢呋喃螺环化合物

(Figure 1-6 Biologically active spirodihydrofuran compounds)

1.4.2 二氢呋喃螺环化合物在材料方面的应用

有机电致发光器件（OLED）自诞生之初就因其卓越性能而受到广泛关注。OLED 中的关键材料包括发光材料、辅助材料与电极材料。其中，发光材料是器件发光功能的直接承载者，其发光效率、寿命及色度等特性对 OLED 的整体性能有着决定性影响。发光材料组成的发光层是 OLED 中至关重要的部分，对器件的电致发光效果起着核心作用[85]。二氢呋喃螺环化合物 **18** 为核心骨架的化合物已经被证明是一种有机电致发光材料（图 1-7）。该化合物的母核结构增加了分子的空间位阻，其不对称的特殊空间构形有助于降低分子间的凝聚力，进而提升了玻璃化转变温度。此外，其芳胺侧链基团作为电子给体，展现出优异的空穴传输性能，包括较高的空穴迁移率，这些特性使得该化合物在提高 OLED 性能方面展现出巨大潜力[86]。

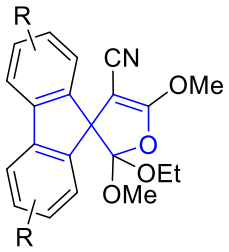


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图 1-7 螺二氢呋喃有机电致发光材料

(Figure 1-7 Spirodihydrofuran organic electroluminescent device materials)

1.5 多取代吡咯类化合物的应用

含氮杂环化合物在自然界中的广泛分布，使其成为众多天然产物和具有生物活性的分子的关键骨架。这类化合物在化学、生物学及工业领域中的应用极为广泛，对人类社会产生了重要的影响。吡咯是一种基本的杂环化合物，存在于众多具有活性的天然产物及合成分子中，并在药理学和材料科学领域扮演着关键角色。该类化合物展现出抗氧化、抗炎、抗菌、抗病毒、抗肿瘤等药物活性[87-91]。

1.5.1 多取代吡咯类化合物在医药方面的应用

多取代吡咯类化合物因其在众多天然产物和具有生物活性的分子中的广泛存在而被高度重视，这类化合物展现了多样化的药理特性（图 1-8）。例如，从粘细菌中分离得到的海洋天然产物 **19** 具有良好的抗肿瘤活性[92,93]。化合物 **20**，源自海洋无脊椎动物的生物碱，具备抗肿瘤和抗 HIV 活性。化合物 **21** 作为一种天然生物碱，展现出抗菌、免疫抑制和抗癌的效果，其通过诱导癌细胞自噬而导致细胞死亡，实现治疗肿瘤的目标，目前正在进行第 II 期临床试验。化合物 **22** 也称为吡咯喹啉醌（PQQ），是一种从细菌的脱氢酶和氧化酶中发现的新型辅酶，具有显著的抗氧化作用，能够有效清除超氧化物和过氧化物。同时，PQQ 作为神经保护剂，能够对抗因缺氧/缺血引起的神经毒性，并用于治疗血脂类疾病。舒尼替尼 **23** 是一种多靶点受体酪氨酸激酶（RTK）抑制剂，主要用于抑制恶性肿瘤细胞的生长和血管生成[94-96]。

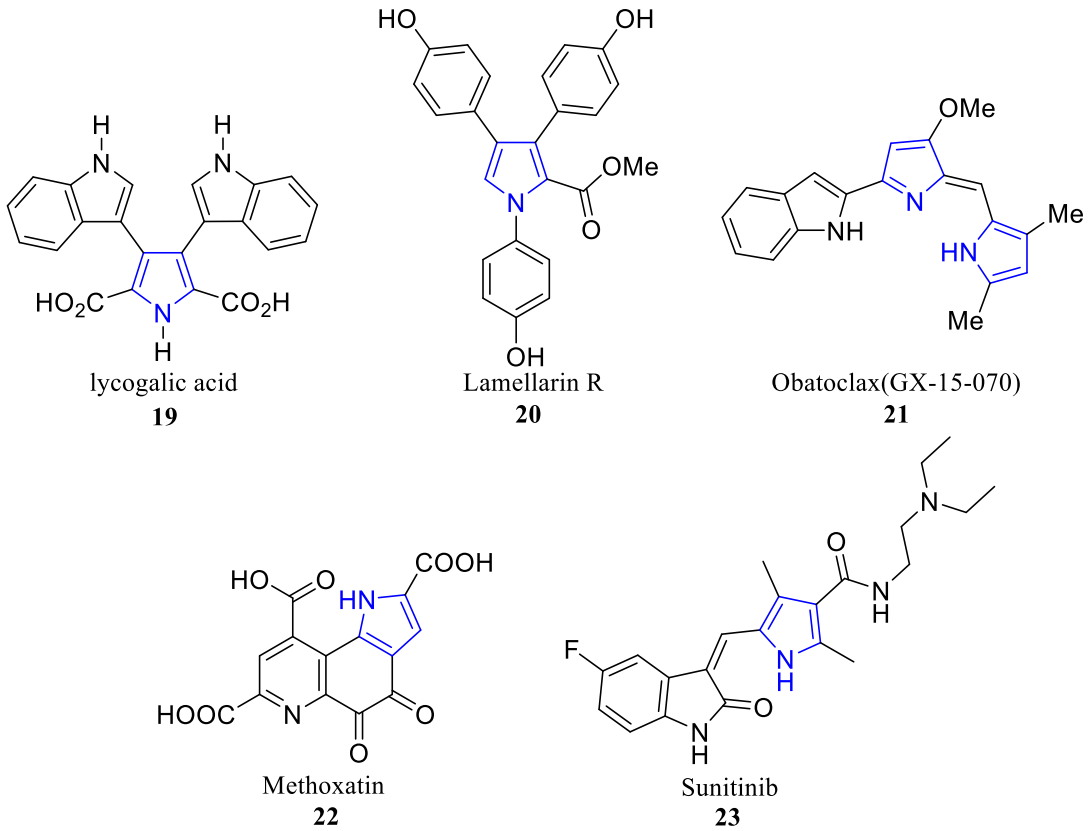


图 1-8 含有吡咯环骨架的药物分子

(Figure 1-8 Pharmaceutical molecules containing a pyrrole ring framework)

1.5.2 多取代吡咯类化合物在农药领域的应用

在 1987 年，美国氰胺公司从一种链霉菌菌株中分离出了一种名为二氧吡咯霉素 **24** 的化合物，该化合物初步显示了具有中等程度的杀虫和杀螨活性。随后，其他公司进一步研究这种化合物，并证明其具备作为抗生素的潜力（图 1-9），然而，在随后进行的小鼠实验中发现，该化合物具有较高的毒性。化合物 **25** 在对抗蛾类、螨类等昆虫方面展现出了杰出的杀灭效果，因此，它成为了一种高效的杀虫和杀螨剂，也是第一种商业化的基于吡咯化合物的杀虫、杀螨产品。此外化合物 **26**、**27** 和化合物 **28** 同样表现出强大的抑制效果，它们主要通过抑制成年草食性虫群的增长并减少虫群后代的繁殖能力来实现控制害虫数量的目的，有效地达到了减少害虫侵害的效果[104-106]。

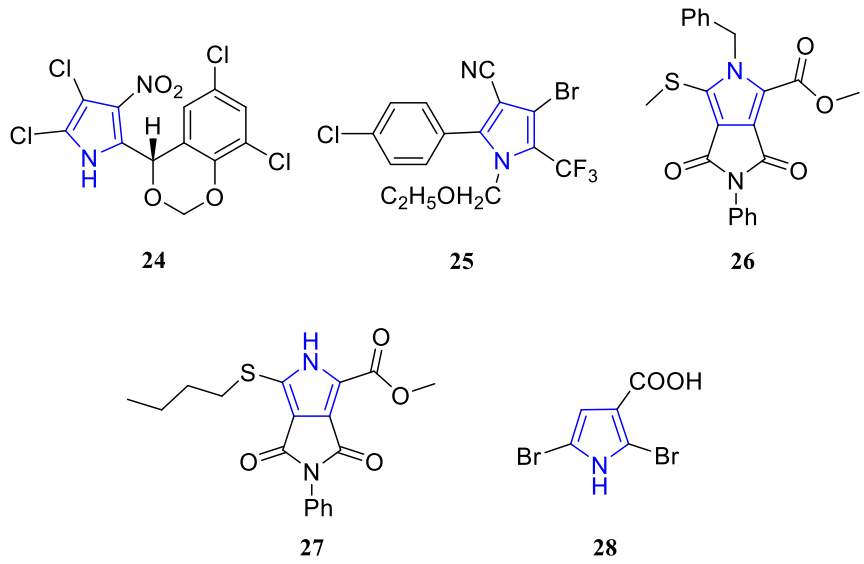


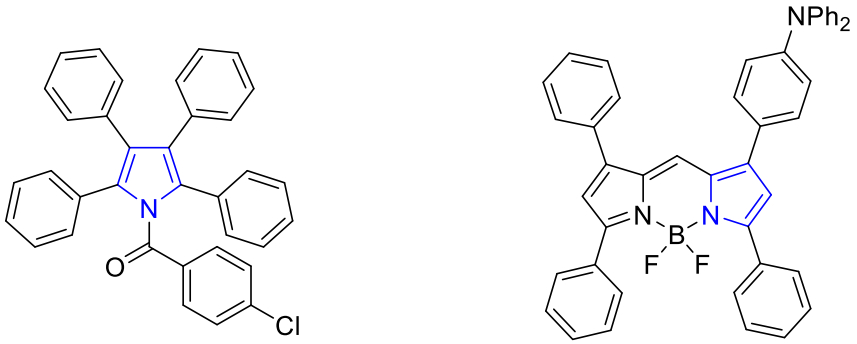
图 1-9 吡咯类化合物在农药中的应用

(Figure 1-9 Application of pyrrole compounds in pesticides)

1.5.3 多取代吡咯类化合物在材料方面的应用

多取代吡咯类化合物构成了一些有机半导体的基础框架。相较于无机半导体，作为薄膜电子器件中的活性材料的有机半导体展示了多项优势。首先，有机半导体材料可以通过各种不同方法进行加工，其中气相沉积法和基于溶液加工法，例如旋涂法和各类印刷技术尤为关键。其次，薄膜的沉积可在室温条件下进行，大幅降低了与无机光电器件相比的生产成本。最后，光电器件可在低成本的柔性基板上生产，为全塑料电子器件和透明器件的发展铺平了道路[97]。

然而，有机光电子器件在设备性能的可重复性和寿命（稳定性）方面面临着重大挑战，这主要归因于使用的有机材料的形态和热不稳定性，导致了有机电致发光器件的耐久性和热稳定性不足，这对材料科学家和器件工程师来说是一大挑战。以吡咯为核心骨架的电致发光材料 **29** 和 **30** 展现了出色的耐久性和热稳定性（图 1-10）[98]，满足了电致发光器件所需的基本条件。



29 **30**

图 1-10 吡咯类有机电致发光材料

(Figure 1-10 Pyrrole-based organic electroluminescent materials)

1.5.4 多取代吡咯类化合物在金属防腐蚀领域的应用

金属腐蚀问题不仅造成了巨大的损失，而且对自然环境产生了严重影响。鉴于此，研究人员一直致力于寻找更有效的防腐蚀策略，旨在高效抑制金属腐蚀并长期维持其防腐性能。聚吡咯（PPy）基于吡咯类化合物的骨架，是一种广泛研究的导电聚合物，其优点包括易于合成、高导电性、良好的稳定性、易于成膜以及对环境无污染等（图 1-11）。通过掺杂处理，聚吡咯可获得优异的导电性、抗静电性和耐腐蚀性。因此，聚吡咯成为一种理想的金属防腐蚀材料，展现了广泛的应用潜力[99-103]。

31

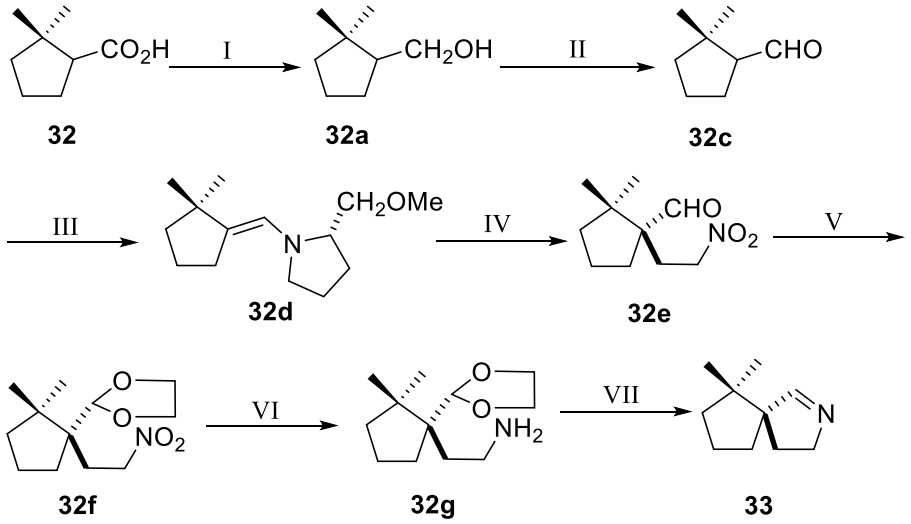
图 1-11 聚吡咯金属防腐蚀材料

(Figure 1-11 Polypyrrole metal anti-corrosion material)

1.6 二氢吡咯螺环化合物的合成研究进展

随着疾病谱的不断扩展和对新型药物的需求增加，寻找拥有新颖结构和未知生物活性的化合物已成为药物研发的关键任务。螺二氢吡咯化合物以其独特的螺环结构在药物设计中占据重要地位，成为新药开发的核心要素。研究这类化合物的合成不仅有助于加深我们对有机化学反应机理的理解，而且还能开拓其在材料科学、生物学及药物化学等多个领域的新应用。因此，广大学者对螺二氢吡咯化合物的合成投入了巨大的研究努力。

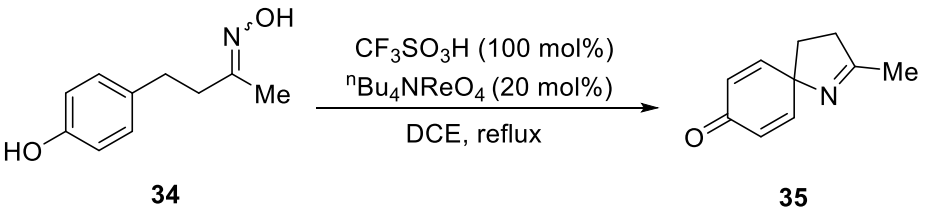
2000 年，Yasuyo 和 Kenji[107]以羧基环戊烷类化合物 **32** 为起始原料，通过一系列反应得到一种具有潜在的药用价值二氢吡咯螺环化合物 **33**（Scheme 1-1）。



Reagents: (I) $LiAlH_4$, Et_2O. (II) DMSO, $(COCl)_2$, DCM, Et_3N. (III) (S)-prolinol methyl ether, MS 4A, C_6H_6. (IV) i) $AcOCH_2CH_2NO_2$, N-ethylmorpholine, MeCN; ii) chromatog. (V) $HO(CH_2)_2OH$, TsOH, $HC(OEt)_3$. (VI) $LiAlH_4$, THF. (VII) 2 mol L^{-1} HCl, THF.

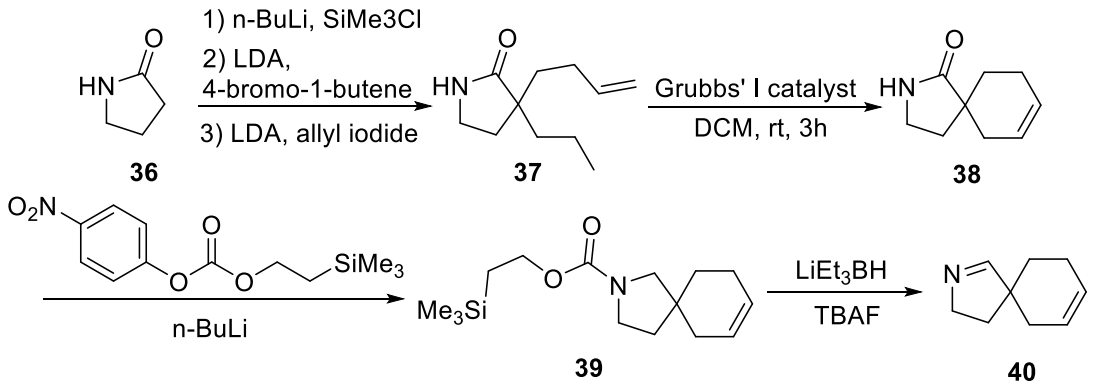
Scheme 1-1 Multistep synthesis of spiro dihydropyrrole spiro compounds

2005 年，Koichi 和 Mitsuru[108]以 4-羟基苯乙基肟 **34** 在四丁基高铼酸铵与三氟甲磺酸的协同催化下得到目标产物环己二烯酮螺二氢吡咯化合物 **35**，该方法操作简单且产率高（Scheme 1-2）。



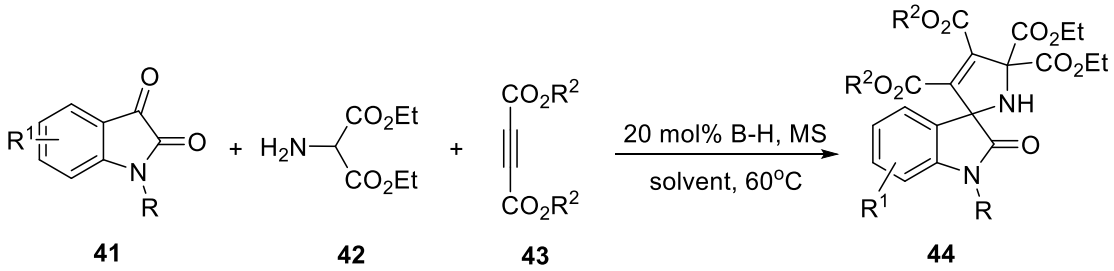
Scheme 1-2 Synthesis of cyclohexadienone spiro dihydropyrrole compounds

2011 年，Stéphanie 和 Margaret[109]首先将 γ-丁内酰胺转化成烃基吡咯酮 **37**，然后使用 Grubbs' I 型催化剂进行催化环化反应后得到 γ-丁内酰胺螺环己二烯化合物 **38**，随即加入正丁基锂与 *N*-TMS 将氨基保护后得到中间体 **39**，之后加入三乙基硼氢化锂与 TBAF 进行反应得到目标产物环己二烯螺二氢吡咯化合物 **40**（Scheme 1-3）。



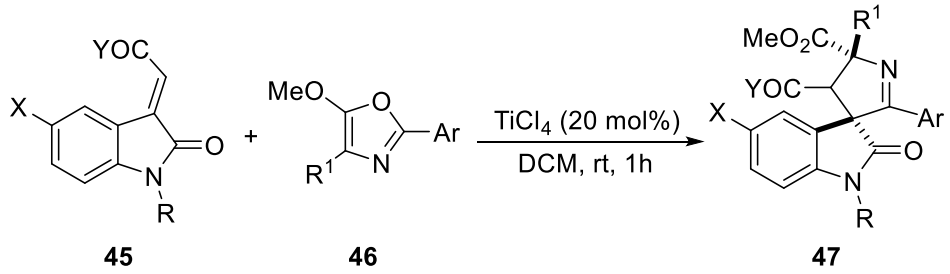
Scheme 1-3 Synthesis of cyclohexadiene spiro dihydropyrrole spiro compounds

2013 年，Tan 课题组[110]通过一种三组分反应成功合成了具有潜在生物活性的螺二氢吡咯骨架化合物。这一策略首次实现了电子缺乏的炔烃与亚甲基丙二酸酯进行 1,3-偶极环加成反应，提供了一个高效合成多取代螺二氢吡咯化合物 **44** 的方法。此外，这些结构独特的螺二氢吡咯化合物展示了对 MCF-7 细胞的潜在细胞毒性（Scheme 1-4）。



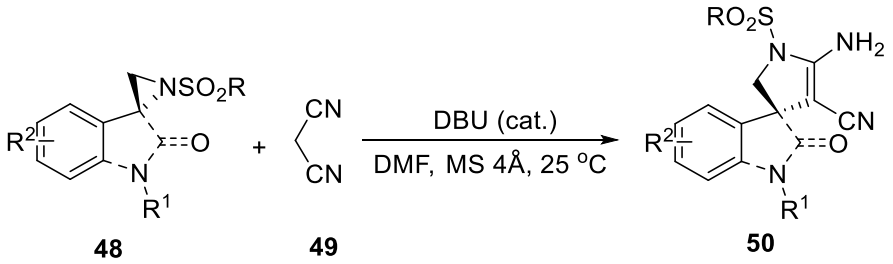
Scheme 1-4 Synthesis of oxidized indole spiro dihydropyrrole derivatives

2014 年，Joseph 等人[111]使用 5 mol%的 $TiCl_4$ 为催化剂，烷基氧化吲哚 **45** 和 5-甲氧基恶唑 **46** 为前驱体，以优异的收率和非对映选择性得到多取代的二氢吡咯螺环化合物 **47**（Scheme 1-5）。该方法普适性高、操作简单，且可以进一步应用于合成丙二酸烷基烯和香豆素衍生物的吡咯啉产物。



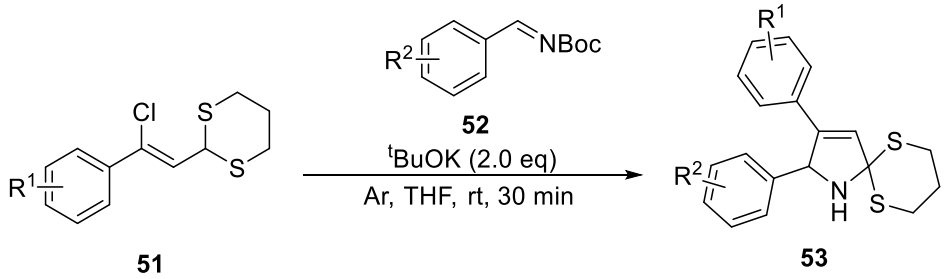
Scheme 1-5 Synthesis of oxidized indole spiro dihydropyrrole derivatives

2019 年，Saumen 课题组[112]在不需要任何金属和路易斯酸活化的情况下，首次实现了使用 DBU 合成多取代氧化吲哚螺二氢吡咯类化合物 **50**。该合成方法的特点是反应条件温和、产率高、普适性好且具有良好的区域选择性和立体选择性（Scheme 1-6）。



Scheme 1-6 Synthesis of oxidized indole spiro dihydropyrrole derivatives

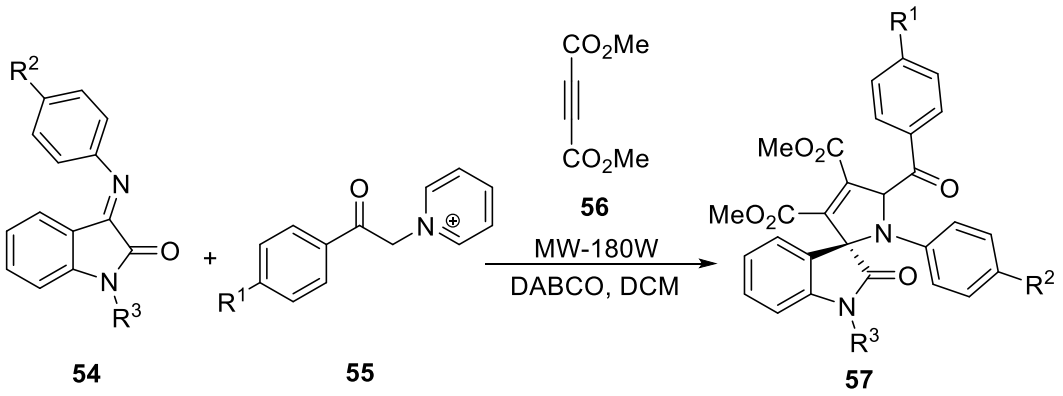
2020 年，Jia 等人[113]以二硫烷类化合物 **51** 与芳基亚胺 **52** 为前驱体、叔丁醇钾为碱、四氢呋喃为溶剂在氩气的条件下反应，以较高的区域选择性和立体选择性合成二硫烷螺芳基二氢吡咯类化合物 **53**（Scheme 1-7）。该反应具有条件温和、产率高和底物范围广等优点。



Scheme 1-7 Synthesis of disulfane spiro aryl dihydropyrrole compounds

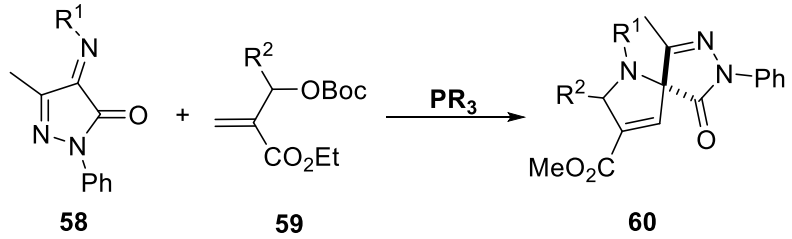
2022 年，Robabeh 等人[114]在低功率微波条件下，以氧化吲哚亚胺类化合物 **54**、吡啶盐 **55** 和炔烃 **56** 为原料，在 DABCO 的作用下通过三组分反应合成多

取代的氧化吲哚螺二氢吡咯类化合物 **57**（Scheme 1-8）。该方法具有反应条件温和、反应时间短、产率优良等优点。



Scheme 1-8 Synthesis of oxidized indole spiro dihydropyrrole derivatives

2023 年，Chen 等人[115]采用磷化氢催化的（3+2）环法反应制备了多种具有良好非对映选择性的吡唑啉酮螺二氢吡咯类化合物 **60**（Scheme 1-9）。利用该方法成功地进行了放大反应，具有产率高、选择性好、普适性强等优点。

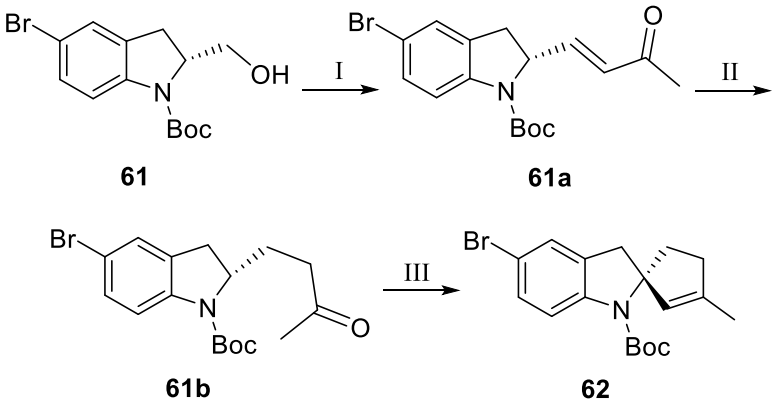


Scheme 1-9 Synthesis of pyrazolone spiro dihydropyrrole compounds

1.7 环戊烯螺环化合物的合成研究进展

环戊烯螺环核心骨架在天然产物及具有生物活性的分子中广泛存在，它们的结构多样性、药理活性及生物活性使得这类化合物成为新药开发过程中极具潜力的候选目标。螺环戊烯化合物能够通过引入多种官能团衍生出大量结构多样性的产物，从而为药物设计和合成提供了广阔的研究空间。此外，螺环戊烯结构在材料领域也展现出巨大的潜力，特别是在有机电子和光电材料领域[62,65]。因此，无论是在药物研发、材料科学还是基础化学研究领域，螺环戊烯化合物都因其独特的特性和潜在的应用价值，成为学者们研究的焦点。

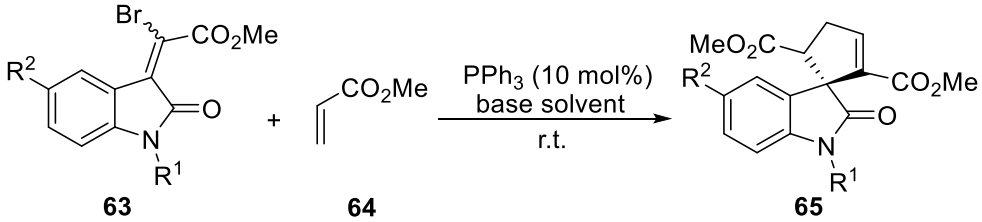
2008 年，Christopher 等人[116]以溴代吲哚化合物 **61** 为原料，首先将其醇羟基氧化为烯酮然后经过催化氢化反应，得到反应中间体 **61b**。最后进行环化反应得到溴代吲哚螺环戊烯化合物 **62**（Scheme 1-10），总体的反应收率可观。



Reagents and conditions: (I) (a) Dess–Martin periodinane, DCM, $NaHCO_3$; (b) acetylmethylene triphenylphosphorane; (II) H_2, Pd/C; (III) BuLi, $TMSCHN_2$, -78 ^oC to rt.

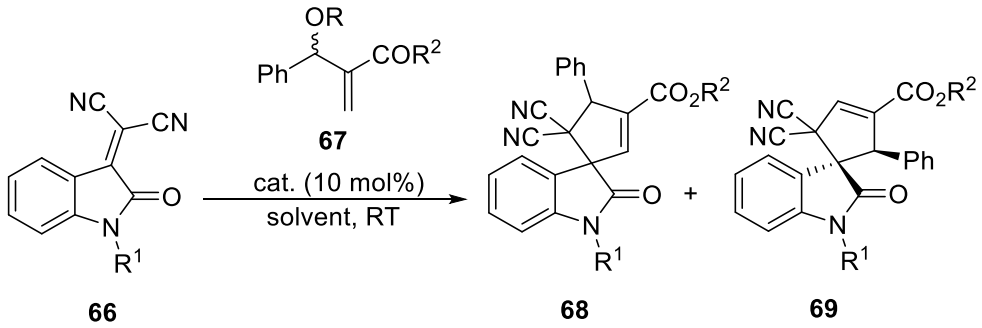
Scheme 1-10 Synthesis of bromoindole spiro cyclopentene compounds

2010 年，Kodirajan 等人[117]以氧化吲哚类化合物 **63** 与丙烯酸甲酯 **64** 为原料，三苯基膦为催化剂，在常温下以较高产率得到多取代的氧化吲哚螺环戊烯类化合物 **65**（Scheme 1-11），该方法具有操作简便、条件温和、普适性高等优点。



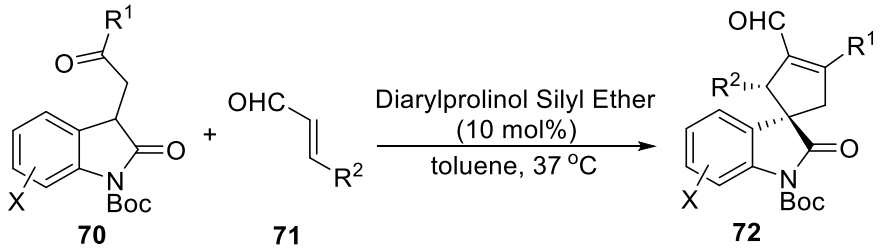
Scheme 1-11 Synthesis of oxyindole spirocyclopentene derivatives

2011 年，Fangrui 等人[118]报道了氨基酸衍生的磷化氢催化氧化吲哚类的衍生物 **66** 与 MBH 碳酸酯 **67** 的区域选择性[3+2]环化反应（Scheme 1-12）。该方法具有较高的区域选择性好、底物范围广、产率高等特点，为合成多取代的螺环戊烯化合物 **68**、**69** 提供了一种新方案。



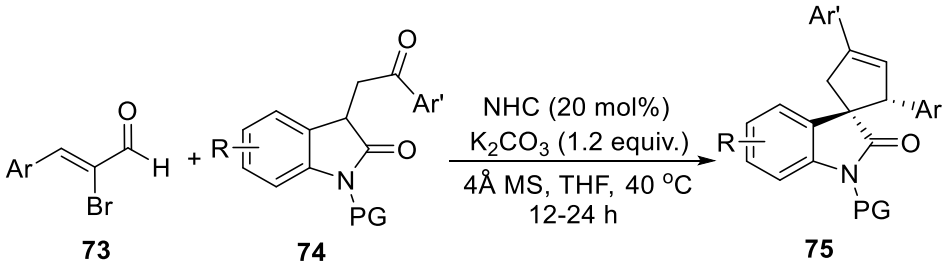
Scheme 1-12 Selective synthesis of oxyindole spirocyclopentene derivatives

2012 年，Klaus 等人[119]报道了一种新型的有机催化级联法合成多取代的氧化吲哚螺环戊烯化合物 **72** 的方法。在第二代脯氨酸醚的催化下，3-取代氧化吲哚 **70** 与 α,β-不饱和醛 **71** 在一步反应中获得了高收率和高对映选择性的产物，该方法普适性好、操作简单（Scheme 1-13）。



Scheme 1-13 Synthesis of oxyindole spirocyclopentene derivatives

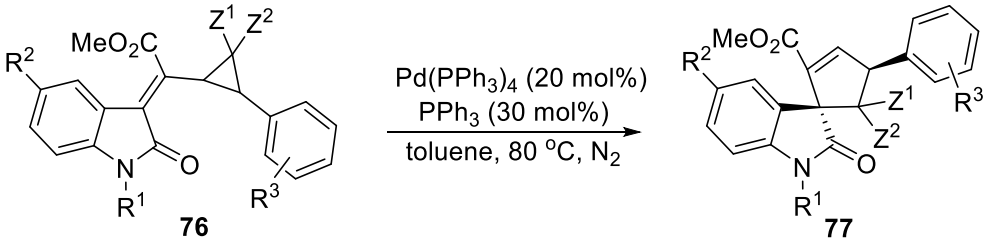
同年，Zhang 等人[120]采用 N-杂环卡宾类催化剂催化溴烯醛 **73** 与氧化吲哚类化合物 **74** 的串联反应，可以得到相应的手性氧化吲哚螺环戊烯化合物 **75**，为螺环戊烯化合物的合成提供了一条新的路线（Scheme 1-14）。该方法具有操作简单、条件温和、收率高、普适性良好、对映选择性好等优点。



Scheme 1-14 Synthesis of oxyindole spirocyclopentene derivatives

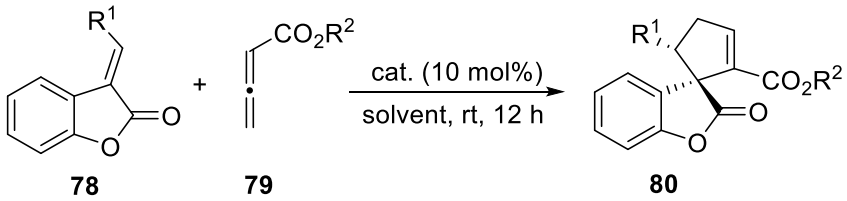
2013 年，Kandapalam 等人[121]报道了过渡金属钯催化合成新型的多取代氧化吲哚螺环戊烯化合物 **77**。该课题组以 3-乙烯基环丙烷-2-氧化吲哚 **76** 为原料，

经过乙烯基环丙烷重排后得到螺环戊烯（Scheme 1-15），该方法产率较高、普适性强，为合成氧化吲哚螺环戊烯化合物提供了一种新的参考。



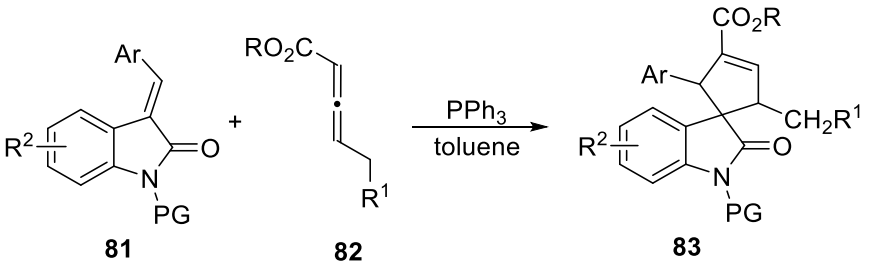
Scheme 1-15 Synthesis of oxyindole spirocyclopentene derivatives

2015 年，Wang 等人[122]以手性膦化氢为催化剂，苯并呋喃酮衍生烯烃 **78** 与丁二烯酸酯 **79** 为原料，通过区域选择性催化不对称[3+2]环加成反应，在温和条件下得到多取代苯并呋喃酮螺环戊烯化合物 **80**（Scheme 1-16），该方法收率高、底物范围广、对映选择性高。



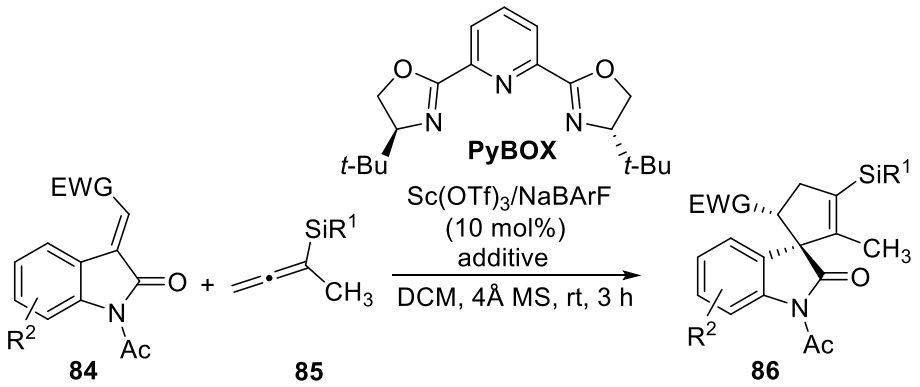
Scheme 1-16 Synthesis of benzofuranone spirocyclopentene derivatives

2018 年，Maxime 等人[123]报道了一种以氧化吲哚衍生物 **81** 与丁二烯酸酯衍生物 **82** 为原料，三苯基膦为催化剂，通过[3+2]环加成反应得到多取代的氧化吲哚螺环戊烯化合物 **83**（Scheme 1-17）。该报道对这些螺环戊烯衍生物展开了进一步的研究，建立了一种新型的生物活性支架。同时也为 MDM2-P53 抑制剂的开发提供了一个新的方向。



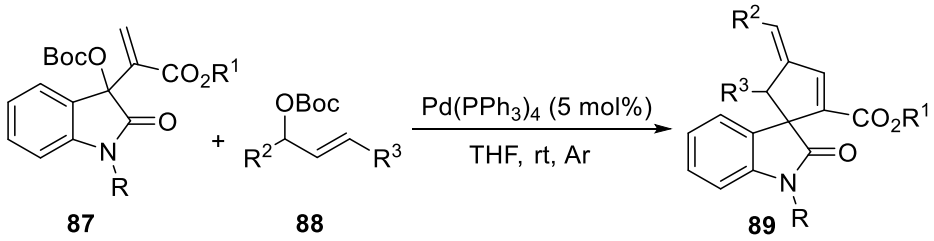
Scheme 1-17 Synthesis of oxyindole spirocyclopentene derivatives

2019 年，Angel 等人[124]报道了一种钪催化的[3+2]环加成反应，他们以氧化吲哚 **84** 与乙烯基硅烷 **85** 为原料，$Sc(OTf)_3$ 为催化剂，PyBOX 和 BArF 为配体，以较高的收率得到多取代的氧化吲哚螺环戊烯产物 **86**（Scheme 1-18）。该方法底物范围广、对映选择性高，为合成环戊烯螺环化合物提供了一种新的路径。



Scheme 1-18 Synthesis of oxyindole spirocyclopentene derivatives

同年，Chen 等人[125]以氧化吲哚衍生物 **87** 与苯甲酸烯丙酯衍生物 **88** 为原料，$Pd(PPh_3)_4$ 为催化剂，在常温氩气氛围得到多取代氧化吲哚螺环戊烯的目标产物 **89**（Scheme 1-19），该合成方法也是具有非常优异的普适性和反应产率。



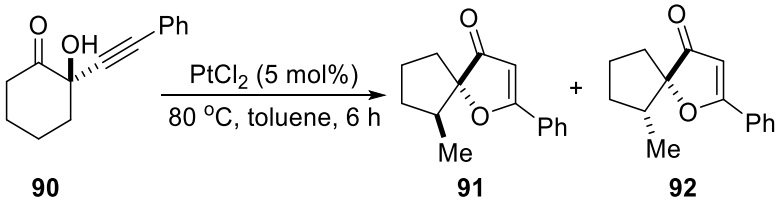
Scheme 1-19 Synthesis of oxyindole spirocyclopentene derivatives

1.8 二氢呋喃螺环化合物的合成研究进展

螺二氢呋喃化合物在一系列生物活性研究中展现出显著成效，涵盖了抗癌、抗炎以及抗微生物等多方面的活性[82-84]。这些显著的生物活性让螺二氢呋喃化合物成为新药研发和生物医药研究领域研究的焦点。不仅如此，螺二氢呋喃化合物在药物化学之外，亦在材料科学、农业化学及环境科学等多个领域表现出其潜在的应用前景[127-131]。因此目前已有许多的科研人员在该化合物的合成领域投入了研究精力。

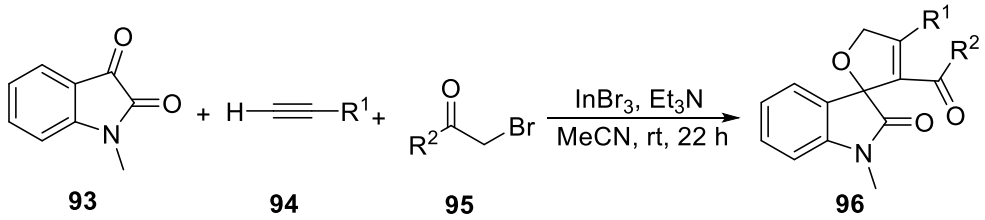
2006 年，Stefan 等人[126]报道了一种以多取代的苯乙炔基环己烯酮 **90** 为原

料，过渡金属催化剂 $PtCl_2$ 催化合成二氢呋喃螺环化合物的合成方法。并且可以通过取代基的调控选择性的合成一对多取代的二氢呋喃酮螺环戊烷的非对映异构体 **91** 和 **92**（Scheme 1-20），该方法具有选择性好，产率高等优点。



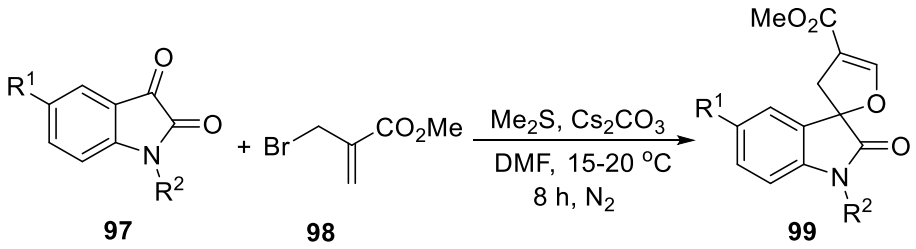
Scheme 1-20 Synthesis of cyclopentane spirodihydrofuranone derivatives

2013 年，Siddiqui 等人[127]报道了一种在室温条件下由 *N*-甲基靛红 **93**、炔烃 **94** 和苯酰基溴化物 **95** 选择性制备氧化吲哚螺二氢呋喃类化合物 **96**。该种方法（Scheme 1-21）显著的优点是无需使用昂贵的催化剂、产率高、底物范围广、操作简便等。



Scheme 1-21 Synthesis of oxyindole dihydrofuran derivatives

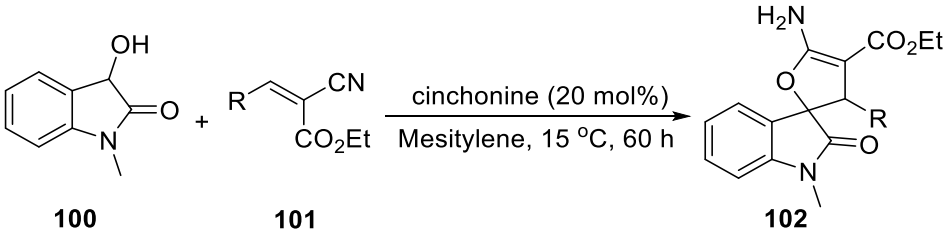
同年，Deevi 等人[128]报道了一种以 *N*-甲基靛红衍生物 **97** 和 2-溴甲基丙烯酸甲酯 **98** 为原料，二甲基硫为促进剂，碳酸铯为碱，在常温氮气氛围的溶剂相中以较高的收率得到氧化吲哚螺二氢呋喃类化合物 **99**（Scheme 1-22）。该种方法收率优良、底物范围广、对映选择性高，为二氢呋喃螺环化合物的合成提供了一条可以选择的合成路径。



Scheme 1-22 Synthesis of oxyindole dihydrofuran derivatives

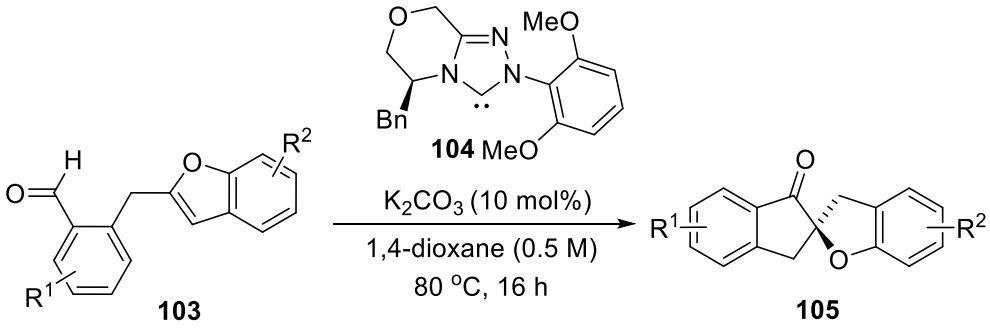
2014 年，Li 课题组[129]以 *N*-甲基-3-羟基-2-吲哚酮 **100** 和腈基苯乙烯衍生物

101 为原料，辛可宁(cinchonine)为手性催化剂在均三甲苯中反应后得到多取代的氧化吲哚螺二氢呋喃类化合物 **102**（Scheme 1-23）。



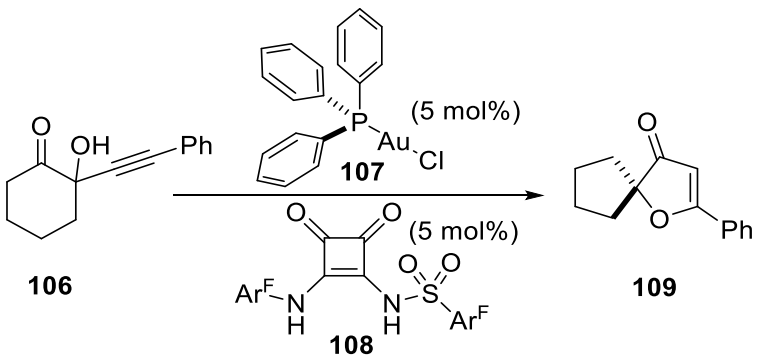
Scheme 1-23 Synthesis of oxyindole dihydrofuran derivatives

2016 年，Daniel 等人[130]报道了一种以苯并呋喃衍生物 **103** 为前体，氮杂环卡宾类化合物 **104** 为催化剂，通过 NHC 催化环化反应得到 1-茚酮螺苯并呋喃类化合物 **105**（Scheme 1-24），该合成方法同样可以应用于苯并噻吩螺环化合物的合成。



Scheme 1-24 Synthesis of 1-indenone spirobenzofuran derivatives

2023 年，Pilar 等人[131]以 2-羟基-2-苯乙炔基环己酮 **106** 为原料，过渡金属配合物 **107** 为催化剂，磺酰方酰胺类化合物 **108** 为助催化剂，在 70 °C 的 DCE 中以优异产率得到二氢呋喃酮螺环戊烷类化合物 **109**（Scheme 1-25），与 Stefan 等人[117]的合成方法相比，该方法利用了配体间的络合进行协同催化进而合成产物。

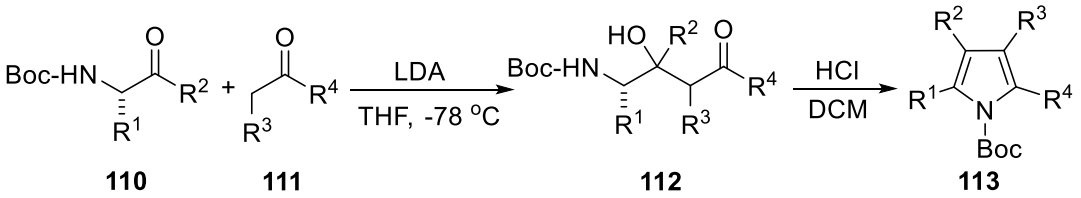


Scheme 1-25 Synthesis of spirocyclopentane derivatives of dihydrofuranone

1.9 多取代吡咯类化合物的合成研究进展

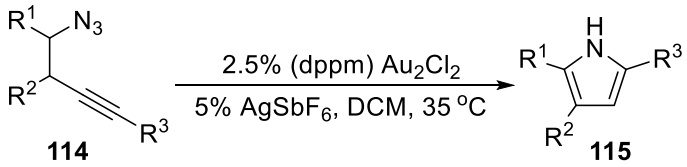
吡咯作为一种具备丰富生物活性的核心骨架，其化学结构的多样性为合成化学家开辟了广泛的研究领域，促使他们开发新颖的合成方法、策略及催化体系来构建复杂的吡咯衍生物。当前，吡咯类化合物不仅在医药领域得到了广泛应用，同时也在材料科学（例如有机电子材料）、农业（如植物生长调节剂）以及环境科学（比如污染物的生物降解）等多个领域展示了其潜在的应用前景[91-97]。鉴于吡咯类化合物在人类社会中的重要角色，众多研究者持续不断地探索这一领域，以发掘更多的可能性和应用。

1996 年，Pamela 和 Mark[132]以 Boc-α-氨基醛衍生物 **110** 与酮类化合物 **111** 为起始原料，二异丙基氨基锂为催化剂在低温的四氢呋喃中得到中间体 **112**，最后在酸性条件下生成多取代的吡咯化合物 **113**（Scheme 1-26）。



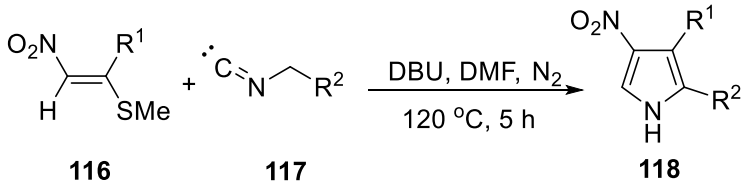
Scheme 1-26 Synthesis of polysubstituted pyrrole derivatives

2005 年，David 等人[133]报道了一种以叠氮炔类衍生物 **114** 为原料，并使用 Au_2Cl_2 与 $AgSbF_6$ 协同催化合成多取代吡咯类化合物 **115**（Scheme 1-27）。



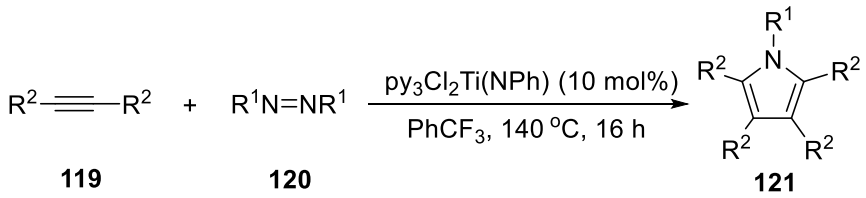
Scheme 1-27 Synthesis of polysubstituted pyrrole derivatives

2006 年，Misra 等人[134]以硝基芳烃类化合物 **116** 与亚甲基异氰化物 **117** 为原料，在碱性条件以较高的产率得到多取代的吡咯化合物 **118**（Scheme 1-28）。该方法普适性很好，可以合成多种类型的多取代吡咯化合物。



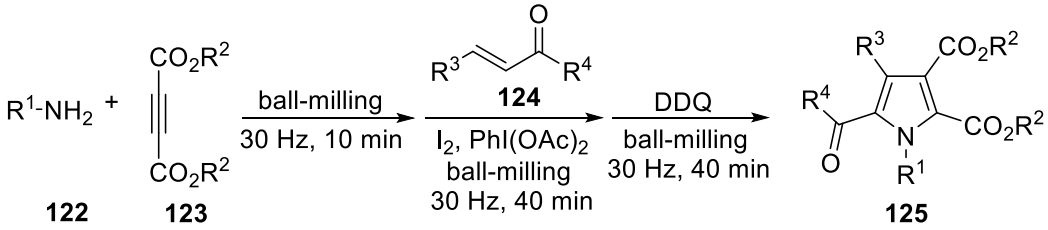
Scheme 1-28 Synthesis of polysubstituted nitropyrrole derivatives

2015 年，Zachary 等人[135]报道了一种多组分的[2+2+1]环化反应，以炔烃类化合物 **119** 和 0.5 当量的二氮烯衍生物 **120** 为原料，$py_3Cl_2Ti(NPh)$为催化剂。在催化剂的作用下首先发生偶联反应生成氮杂环丁烯中间体经过炔的二次插入，然后进行还原消除反应，最终形成多取代的吡咯类化合物 **121**（Scheme 1-29）。



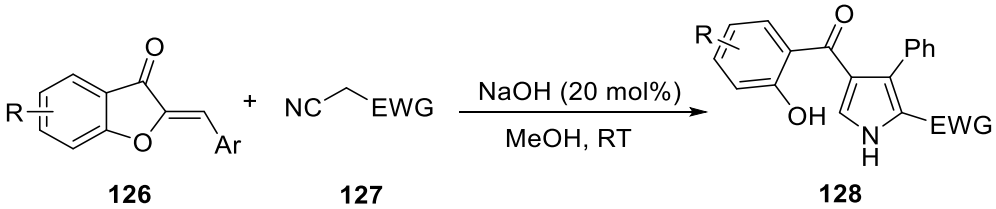
Scheme 1-29 Synthesis of polysubstituted pyrrole derivatives

2018 年，Xu 等人[136]报道了一种在无溶剂球磨条件下，以 I_2/$PhI(OAc)_2$ 为催化剂，使用一锅多步法构建了一种高效实用的胺 **122**、炔酯 **123** 与查尔酮 **124** 的反应，以较高收率制备多取代的吡咯化合物 **125**（Scheme 1-30）。该方法反应时间短，反应条件温和，底物范围广，具有大规模合成的可行性。



Scheme 1-30 Synthesis of polysubstituted acylpyrrole derivatives

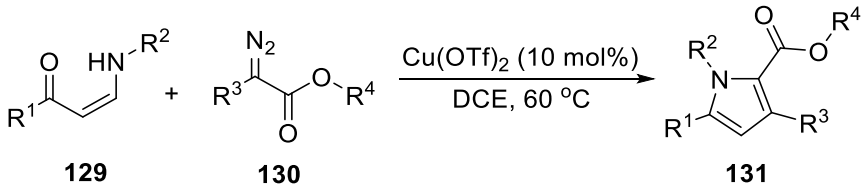
同年，Wang 等人[137]以橙酮衍生物 **126** 和吸电子基团的氰类化合物 **127** 为原料，氢氧化钠为催化剂，在常温的甲醇溶剂中以优异的收率得到多取代的吡咯类化合物 **128**（Scheme 1-31），该合成方案条件温和、操作简便、底物范围广、使用了廉价易得的催化剂进行催化，具备大规模生产的必要条件。



Scheme 1-31 Synthesis of polysubstituted pyrrole derivatives

2020 年，Li 等人[138]报道了一种过渡金属铜催化的酮胺化合物 **129** 和重氮

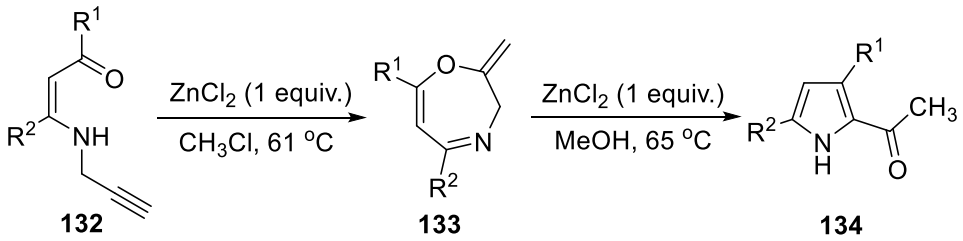
酯类化合物 **130** 合成多取代的吡咯类化合物 **131** 的合成方法（Scheme 1-32）。该方法可以在温和的条件下以较高收率有效地得到目标产物，具有普适性好、操作简便、原料易得等优点。



129　　130　　131

Scheme 1-32 Synthesis of polysubstituted pyrrole derivatives

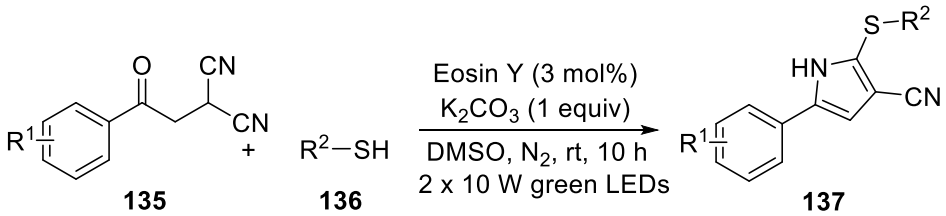
2021 年，Nilay 等人[139]以 *N*-丙炔基-β-酮胺类化合物 **132** 为原料，采用一锅两步法首先生成七元杂环中间体 **133**，最后改变溶剂合成多取代的乙酰基吡咯类化合物 **134**（Scheme 1-33）。该方案收率高、底物范围广、官能团耐受性好。



132　　133　　134

Scheme 1-33 Synthesis of polysubstituted pyrrole derivatives

2022 年，Ashish 等人[140]报道了一种以 2-苯乙酮基丙二腈类化合物 **135** 与硫醇衍生物 **136** 为原料，Eosin Y 为光敏剂的合成方法。在通入氮气的常温碱性条件下通过光催化的方式进行多取代吡咯类化合物 **137** 的合成（Scheme 1-34）。

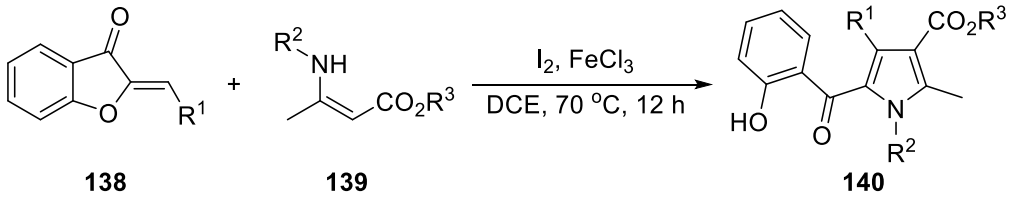


135　　136　　137

Scheme 1-34 Synthesis of polysubstituted pyrrole thioether derivatives

同年，Xu 等人[141]将橙酮 **138** 与 β-烯胺酯 **139** 作为起始原料，使用 I_2 与 $FeCl_3$ 协同催化发生迈克尔加成、碘化、分子内亲核取代和螺环开环等过程，开发了一种新颖高效的橙酮与烯胺酯的多米诺反应，以中等至优异的收率获得

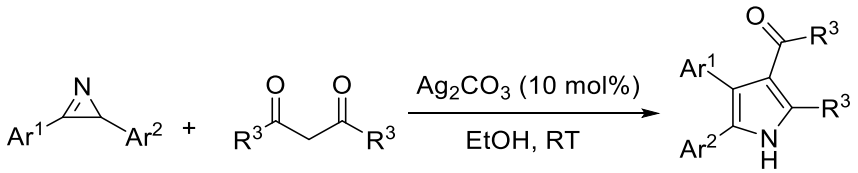
了种类繁多的多取代吡咯 **140**（Scheme 1-35）。该工艺具有反应条件温和、底物范围广、原子经济性和效率高、可大规模合成等特点。



138 **139** **140**

Scheme 1-35 Synthesis of polysubstituted pyrrole derivatives

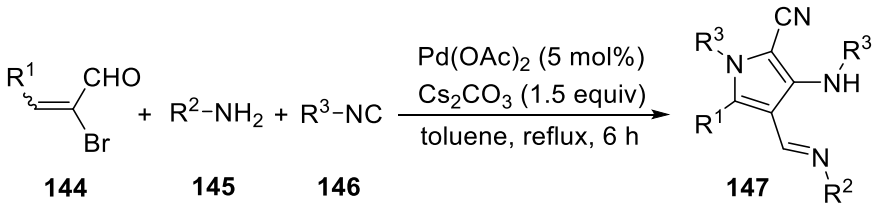
2023 年，Xu 课题组[142]以芳基叠氮啉 **141** 与 1,3-二羰基化合物 **142** 为原料，在 Ag_2CO_3 的催化下通过[3+2]环化反应以中等到优异的产率得到多取代的酰基吡咯化合物 **143**（Scheme 1-36），该类化合物都具有良好的区域选择性。



141 **142** **143**

Scheme 1-36 Synthesis of polysubstituted acylpyrrole derivatives

同年，Li 等人[143]报道了一种新型的一锅法合成多取代吡咯衍生物 **144**，通过 Pd 催化烯基溴化物 **145**，胺类化合物 **146** 和异氰类化合物 **147** 的三组分反应合成目标产物（Scheme 1-37）。该工艺底物范围广、反应收率较高、无需使用配体等特点。



144 **145** **146** **147**

Scheme 1-37 Synthesis of polysubstituted cyanopyrrole derivatives

1.10 本课题的研究目的、内容及意义

螺环化合物作为重要的有机化学原料和医药中间体在日常生活中有着广泛的应用，如在医药领域，它们可以作为抗肿瘤、镇痛以及抗菌药物；在农药领域，可应用于杀虫、除螨和抗真菌等；在半导体领域，可作为电致发光材料的核心骨架。此外，吡咯作为一种具备丰富生物活性的核心骨架在多个领域展示了其潜在的应用前景。考虑到传统合成螺环化合物和吡咯类化合物的方法往往需要使用苛刻的反应条件或是在其合成过程中，往往难以精确控制反应的选择性（包括立体选择性和官能团普适性），这可能导致目标产物的收率降低，并且产生大量难以分离的副产物。因此，为了克服这些问题，开发新型螺环化合物及吡咯的合成技术显得尤为重要。特别是能够通过化学选择性调控，利用相同起始原料合成不同螺、杂环的方法具有重大意义。本研究旨在通过调控环外α,β-不饱和环酮与烯胺的选择性环化反应，构建一系列具有应用潜力的螺环化合物及吡咯衍生物。

基于螺环化合物的重要应用和机械研磨法的优势，我们成功开发出以下三种选择性合成螺环化合物与吡咯衍生物的新方法：

（1）在机械化学条件下，以不饱和巴比妥酸和 β-烯胺酯为原料，在卤代试剂促进下，选择性地合成了巴比妥酸螺环戊烯与巴比妥酸螺二氢吡咯类化合物。

（2）以硫代橙酮与 β-烯胺酯为原料，在卤代试剂促进下，选择性地合成了硫代橙酮螺二氢呋喃和硫代橙酮螺二氢吡咯类化合物。

（3）在机械化学条件下，以不饱和异噁唑酮和 β-烯胺酯为原料，选择性地构建了异噁唑酮螺环戊烯化合物和吡咯衍生物。

与传统方法相比，这些使用机械化学的方法具有化学选择性高、反应时间短、反应条件温和、原料易得、操作简单、原子利用率高等优点。这为合成结构新颖、具有潜在应用价值的螺环化合物与吡咯类化合物的高效合成提供了一种简便、绿色的新方法。

第二章 机械化学条件下不饱和巴比妥酸与烯胺酯的选择性环化反应研究

2.1 实验部分

2.1.1 仪器与试剂

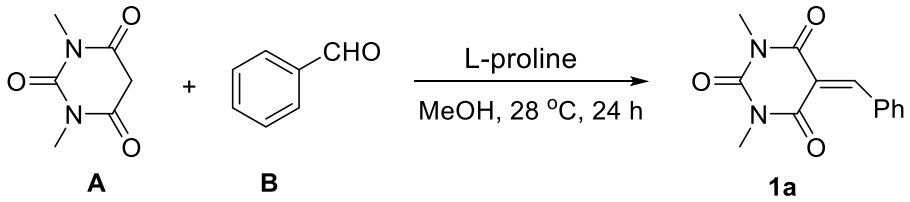
仪器名称	型号	生产厂家
核磁共振波谱仪	AVANCE ONE（500 MHz）	德国布鲁克科技有限公司
高分辨质谱仪	ORBITRAP EXPLORIS 120	赛默飞世尔科技（中国）有限公司
熔点仪	WRS-3	上海仪电物理光学仪器有限公司
恒温磁力搅拌器	DF-101D	巩义市予华仪器有限责任公司
低温冷却液循环泵	DLSB-5L/20	巩义市予华仪器有限责任公司
循环水式真空泵	SHZ-D	巩义市予华仪器有限责任公司
旋片式真空泵	2XZ-2	上海雅潭真空设备有限公司
旋转蒸发仪	41K30RA-C	巩义市予华仪器有限责任公司
电子天平	PX224ZH/E	奥豪斯仪器（常州）有限公司
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
球磨机	MM 400	德国 Retsch 公司
X-射线单晶衍射仪	SMART APEX CCD	美国 Bruker 公司

试剂名称	规格	生产厂家
乙酰乙酸乙酯	分析纯	上海泰坦科技有限公司
1,3-二甲基巴比妥酸	分析纯	萨恩化学技术（上海）有限公司
L-脯氨酸	分析纯	萨恩化学技术（上海）有限公司
邻/间/对甲基苯甲醛	分析纯	国药集团化学试剂有限公司
邻/间/对氯苯甲醛	分析纯	国药集团化学试剂有限公司
邻/间/对溴苯甲醛	分析纯	国药集团化学试剂有限公司
4-硝基苯甲醛	分析纯	国药集团化学试剂有限公司
4-三氟甲基苯甲醛	分析纯	上海泰坦科技有限公司
4-甲氧基苯甲醛	分析纯	国药集团化学试剂有限公司
4-奈基苯甲醛	分析纯	国药集团化学试剂有限公司
4-呋喃基苯甲醛	分析纯	国药集团化学试剂有限公司
苯甲醛	分析纯	国药集团化学试剂有限公司
异丁醛	分析纯	萨恩化学技术（上海）有限公司

3,4-二甲基苯甲醛	分析纯	国药集团化学试剂有限公司
3,4-二氯苯甲醛	分析纯	国药集团化学试剂有限公司
乙酰乙酸异丁酯	分析纯	萨恩化学技术（上海）有限公司
苯甲酰乙酸乙酯	分析纯	萨恩化学技术（上海）有限公司
乙酰乙酸叔丁酯	分析纯	萨恩化学技术（上海）有限公司
丙酰乙酸乙酯	分析纯	萨恩化学技术（上海）有限公司
乙酰乙酸异丙酯	分析纯	萨恩化学技术（上海）有限公司
乙酰乙酸甲酯	分析纯	国药集团化学试剂有限公司
苄胺	分析纯	国药集团化学试剂有限公司
间氟苄胺	分析纯	国药集团化学试剂有限公司
对氯苄胺	分析纯	国药集团化学试剂有限公司
邻氯苄胺	分析纯	国药集团化学试剂有限公司
对甲氧基苄胺	分析纯	国药集团化学试剂有限公司
苯胺	分析纯	萨恩化学技术（上海）有限公司
无水乙酸镍	分析纯	国药集团化学试剂有限公司
4-二甲氨基吡啶	分析纯	国药集团化学试剂有限公司
碳酸钠	分析纯	萨恩化学技术（上海）有限公司
无水硫酸钠	分析纯	萨恩化学技术（上海）有限公司
无水硫酸镁	分析纯	萨恩化学技术（上海）有限公司
碘	分析纯	萨恩化学技术（上海）有限公司
1,3-二溴-1,3,5-三嗪-2,4,6-三酮	分析纯	上海泰坦科技有限公司
三溴化吡啶鎓	分析纯	上海泰坦科技有限公司
碘代丁二酰亚胺	分析纯	上海泰坦科技有限公司
溴代丁二酰亚胺	分析纯	上海泰坦科技有限公司
溴化亚酞	分析纯	上海泰坦科技有限公司
1,3-二溴-5,5-二甲基海因	分析纯	上海泰坦科技有限公司
三苯基膦	分析纯	上海泰坦科技有限公司
常规溶剂	分析纯	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

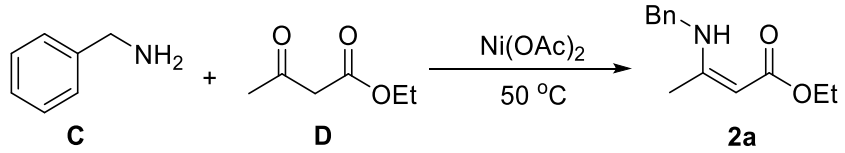
2.1.2.1 原料 **1** 的合成



Scheme 2-1 Synthesis of 2-benzalbarbituric acid

以合成 **1a** 为例，将 1,3-二甲基嘧啶-2,4,6（1*H*,3*H*,5*H*）-三酮 **A**（10 mmol, 1.56 g）、苯甲醛 **B**（11 mmol, 1.17 g）和 L-脯氨酸（3 mmol, 0.35 g）加入到 100 mL 圆底烧瓶中，在溶剂甲醇（50 mL）中室温搅拌 24 小时，通过 TLC 对反应进行监测。待反应结束以后冷却到室温，然后过滤、减压浓缩，再进行柱层析（乙酸乙酯:石油醚=1:4）分离得到白色固体 **1a**，产率为 89%。

2.1.2.2 原料 **2** 的合成

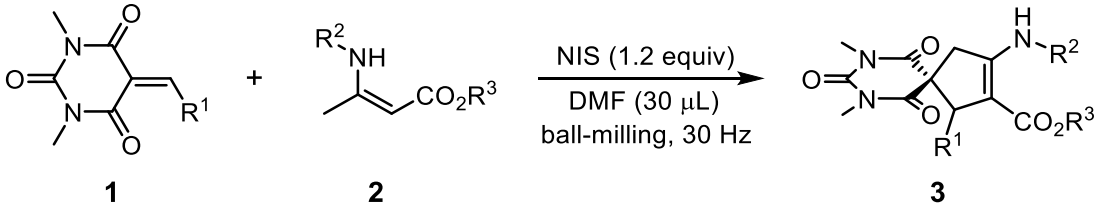


Scheme 2-2 Synthesis of enamine ester

以合成 **2a** 为例，将苄胺 **C**（50 mmol, 5.36 g）、乙酰乙酸乙酯 **D**（50 mmol, 6.51 g）和无水乙酸镍（5 mmol, 0.88 g）加入到 50 mL 圆底烧瓶中，于 50 ºC 下搅拌 12 h，待反应结束后冷却到室温，抽滤除去乙酸镍，再将滤液减压浓缩，最后进行柱层析（乙酸乙酯:石油醚=1:12）分离得到白色固体 **2a**，产率为 88%。

2.1.3 产物的合成

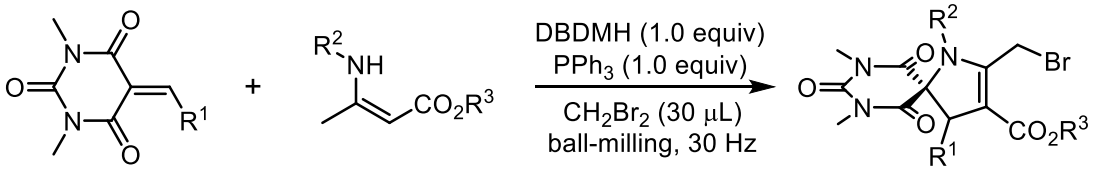
2.1.3.1 产物 **3** 的合成



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

将不饱和巴比妥酸 **1**（0.2 mmol）、β-烯胺酯 **2**（0.24 mmol）、NIS（0.24 mmol，54.0 mg）和 DMF（30 μL）加入到含有 4 个研磨球（直径 6 mm）的不锈钢罐（5 mL）中。将该研磨罐封闭并固定在 Retsch MM400 研磨仪的振动臂上，在室温下以 1800 转/分钟（30 Hz）的频率研磨 30 分钟。反应结束后，用乙酸乙酯溶解所得反应混合物并转移至茄形瓶中，加入少量硅胶后减压蒸馏至粉末状，然后进行柱层析分离得到产物 **3**。

2.1.3.2 **产物 4 的合成**



1 **2** **4**

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

将不饱和巴比妥酸 **1**（0.2 mmol）、β-烯胺酯 **2**（0.24 mmol）、1,3-二溴-5,5-二甲基海因（0.2 mmol，57.2 mg）和 CH_2Br_2（30 μL）加入到含有 4 个研磨球（直径 6 mm）的不锈钢罐（5 mL）中。将该研磨罐封闭并固定在 Retsch MM400 研磨仪的振动臂上，在室温下以 1800 转/分钟（30 Hz）的频率研磨 30 分钟。反应结束后，用乙酸乙酯溶解所得反应混合物并转移至茄形瓶中，加入少量硅胶后减压蒸馏至粉末状，然后进行柱层析分离得到产物 **4**。

2.2 实验结果与讨论

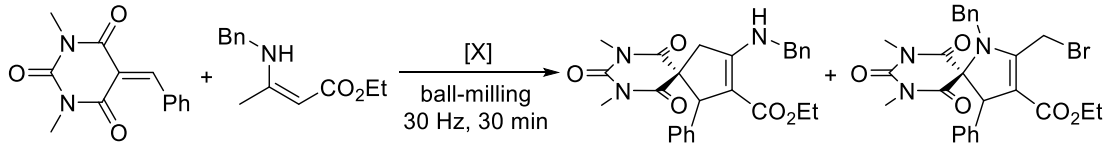
2.2.1 条件优化

我们首先选择不饱和巴比妥酸 **1a** 与 β-烯胺酯 **2a** 为模型底物筛选最佳反应条件。先将 **1a**（0.2 mmol）、**2a**（0.24 mmol）与 I_2（0.2 mmol）混合，在球磨条件下反应 30 分钟后发现有产物生成（entry 1），经过核磁共振波谱分析为巴比妥酸螺环戊烯化合物 **3aa**。之后我们又尝试了其它的卤代试剂，如 NBS、NIS 和 $PhI(OAc)_2$，发现使用了 NBS 催化的反应体系产生了一个新的产物（entry 3），经分析后发现该产物是巴比妥酸螺溴代二氢吡咯化合物 **4aa**，这个发现促使我们通过调控反应条件来选择性生成不同类型螺环化合物。我们首先对产物 **3aa** 进行条件优化，发现 NIS 对产物 **3aa** 的生成具有更好的促进作用，所以使用

NIS 作该反应体系的促进剂。在筛选 NIS 的用量时发现 1.2 当量为最佳选择（entry 6）。然后我们进行了助溶剂的筛选，发现以 DMF 为助溶剂时 **3aa** 的收率最高（entry 13）。

在完成 **3aa** 的条件优化后我们展开了对 **4aa** 的优化工作。考虑到 **4aa** 是在 NBS 作促进剂时产生，同时因为在 **4aa** 产物中引入了一个溴原子，所以我们使用 2 当量的 NBS 来尝试反应，结果发现 **4aa** 的收率只有轻微提高。接下来我们尝试了其它的溴代试剂，例如 N-溴代邻苯二甲基酰亚胺（NBP，2 当量）、三溴化吡啶鎓（PHBP，2 当量）、1,3-二溴-1,3,5-三嗪-2,4,6-三酮（DBI，1 当量）和 1,3-二溴-5,5-二甲基海因（DBDMH，1 当量）。这些溴代试剂中只有 DBDMH 对 **4aa** 的选择性有一定的促进效果（entry 16）。增加 DBDMH 的使用量对反应基本没有影响（entry 17）。随后我们也使用了上述助溶剂，发现二溴甲烷对 **4aa** 有不错的选择性，此时 **4aa** 的收率为 52%（entry 19）。我们还尝试了一些碱性添加剂，结果表明不论是无机碱还是有机碱对 **4aa** 的生成都是不利的（entries 24–27）。我们偶然发现当加入 1 当量三苯基膦到该体系能够显著地提高 **4aa** 的收率，并以 78%的分离收率得到产物（entry 28）。更进一步的实验表明 1 当量的三苯基膦是最佳的。根据上述实验结果，最终确定生成巴比妥酸螺环戊烯的最优条件是：1 当量不饱和巴比妥酸、1.2 当量烯胺酯和 1.2 当量的 NIS 以 DMF 为助溶剂在球磨条件下反应 30 分钟（entry 11）；而生成巴比妥酸螺二氢吡咯的最优条件是：1 当量不饱和巴比妥酸、1.2 当量烯胺酯、1 当量的 DBDMH 和 1 当量的 PPh_3 以 CH_2Br_2 为助溶剂在球磨条件下反应 30 分钟（entry 28）。

Table 2-1. Optimization of the reaction conditions[a]



1a **2a** **3aa** **4aa**

Entry	[X] (equiv.)	LAG solvent (30 μL)	Additive (equiv.)	Yield[b] (%)	
				3aa	**4aa**
1	I_2 (1.0)			46	N.D.[c]
2	NIS (1.0)			69	N.D.[c]
3	NBS (1.0)			28	11
4	NIS (1.2)			74	N.D.[c]
5	NIS (1.4)			74	N.D.[c]
6	NIS (1.2)	DCE		86	N.D.[c]
7	NIS (1.2)	CH_2Br_2		84	N.D.[c]
8	NIS (1.2)	MeCN		76	N.D.[c]
9	NIS (1.2)	toluene		86	N.D.[c]
10	NIS (1.2)	DMSO		83	N.D.[c]
11	**NIS (1.2)**	**DMF**		**91**	**N.D.[c]**
12	NBS (2.0)			34	13
13	NBP (2.0)			31	9
14	PHBP (2.0)			11	trace
15	DBI (1.0)			18	trace
16	DBDMH (1.0)			27	22
17	DBDMH (1.1)			28	22
18	DBDMH (1.0)	DCE		33	45
19	DBDMH (1.0)	CH_2Br_2		30	55
20	DBDMH (1.0)	MeCN		72	14
21	DBDMH (1.0)	toluene		43	41
22	DBDMH (1.0)	DMSO		39	36
23	DBDMH (1.0)	DMF		78	trace
24	DBDMH (1.0)	CH_2Br_2	Na_2CO_3 (1.0)	trace	N.D.[c]
25	DBDMH (1.0)	CH_2Br_2	K_2CO_3 (1.0)	15	N.D.[c]
26	DBDMH (1.0)	CH_2Br_2	TEA (1.0)	60	25
27	DBDMH (1.0)	CH_2Br_2	DMAP (1.0)	58	20
28	**DBDMH (1.0)**	**CH_2Br_2**	**PPh_3 (1.0)**	**12**	**78**
29	DBDMH (1.0)	CH_2Br_2	PPh_3 (0.5)	28	57
30	DBDMH (1.0)	CH_2Br_2	PPh_3 (1.5)	12	77

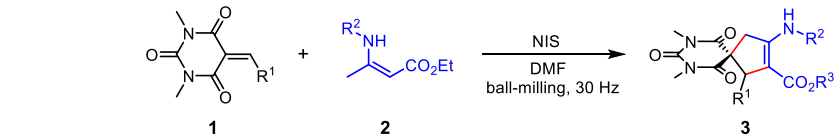
[a]A mixture of **1a** (0.2 mmol), **2a** (0.24 mmol), a halogenating reagent (0.24 mmol), an LAG solvent (30 μL) and four stainless balls (6 mm in diameter) was milled in a Retsch MM400 mixer mill at 30 Hz for 30 min. [b]Isolated yield based on **1a**. [c] N.D. = not detected.

2.2.2 底物拓展

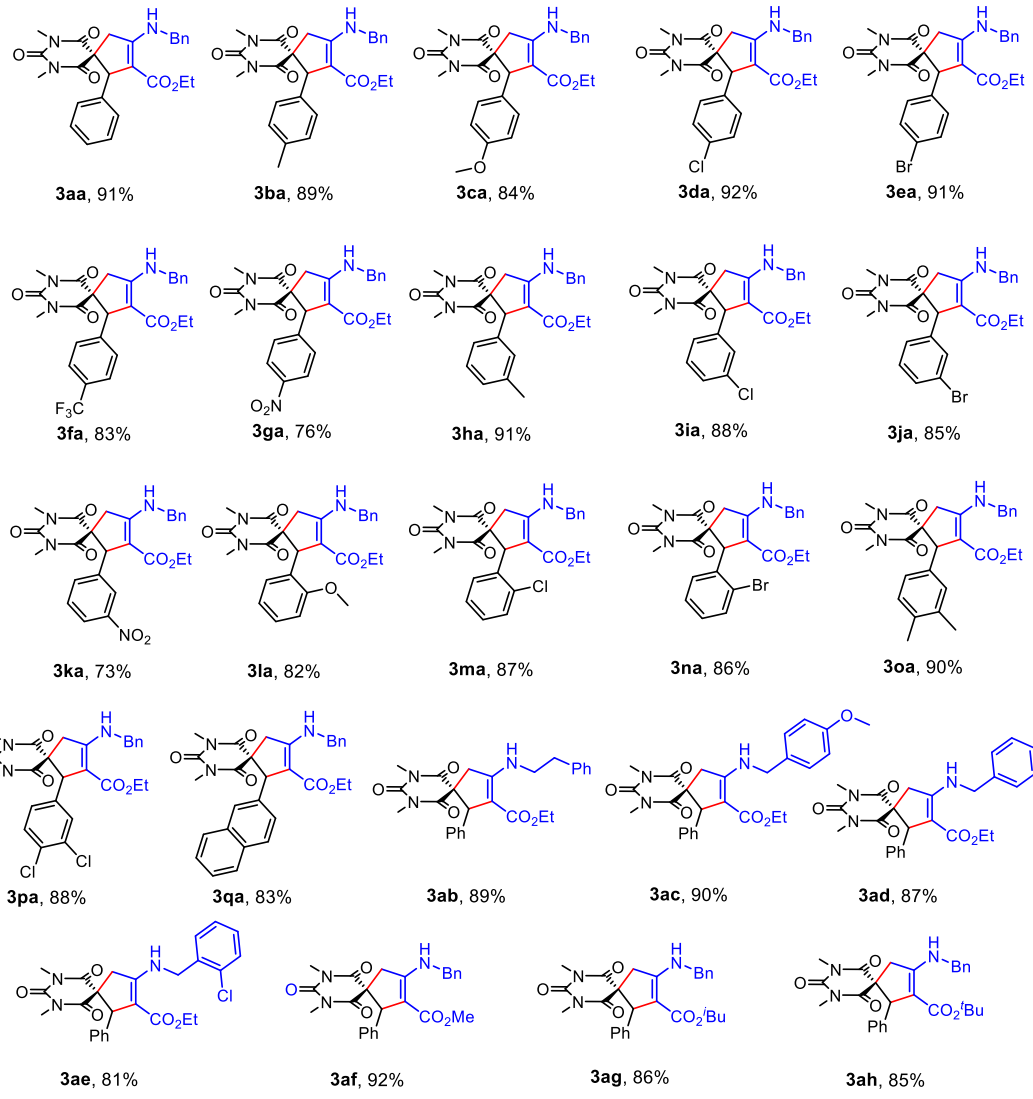
2.2.2.1 产物 3 的合成

在确定了合成巴比妥酸螺环戊烯化合物的最佳反应条件后，我们对该反应的底物适用性进行了探究（Table 2-2）。首先，我们使用了不同取代基的不饱和巴比妥酸（**1a-q**）和 β-烯胺酯 **2a** 进行反应。从表 2-2 中可以看出，当不饱和巴比妥酸的苯环上接有给电子基团（Me 和 OMe）以及吸电子基团（Cl, Br, CF_3 和 NO_2）时，巴比妥酸衍生物 **1** 均展现出较高的反应活性，顺利合成了一系列环戊烯基螺巴比妥酸衍生物 **3ba**–**pa**，产率为 73–92%。在优化的反应条件下，萘基取代的底物也反应良好，相应产物 **3qa** 以 83%的产率得到。接下来考察了不饱和巴比妥酸 **1a** 和 β-烯胺酯（**2a-h**）不同基团对反应的影响。将烯胺酯片段氮原子苄基上接有吸电子基团和供电子基团时，发现 β-烯胺酯依然具有很高的反应活性，例如 **3ac** 和 **3ad** 的收率分别为 90%和 87%。接下来我们考察位置对反应的影响，发现产率并未受到影响，并成功合成 **3ae** 产物。最后巴比妥酸螺环戊烯衍生物 **3ma** 的结构通过单晶 X-射线衍射分析得到了进一步确认。

Table 2-2. Selective synthesis of babiturate-spirocyclopentenes 3 from unsaturated barbiturates 1 and enamino esters 2[a,b]



1 + 2 → 3



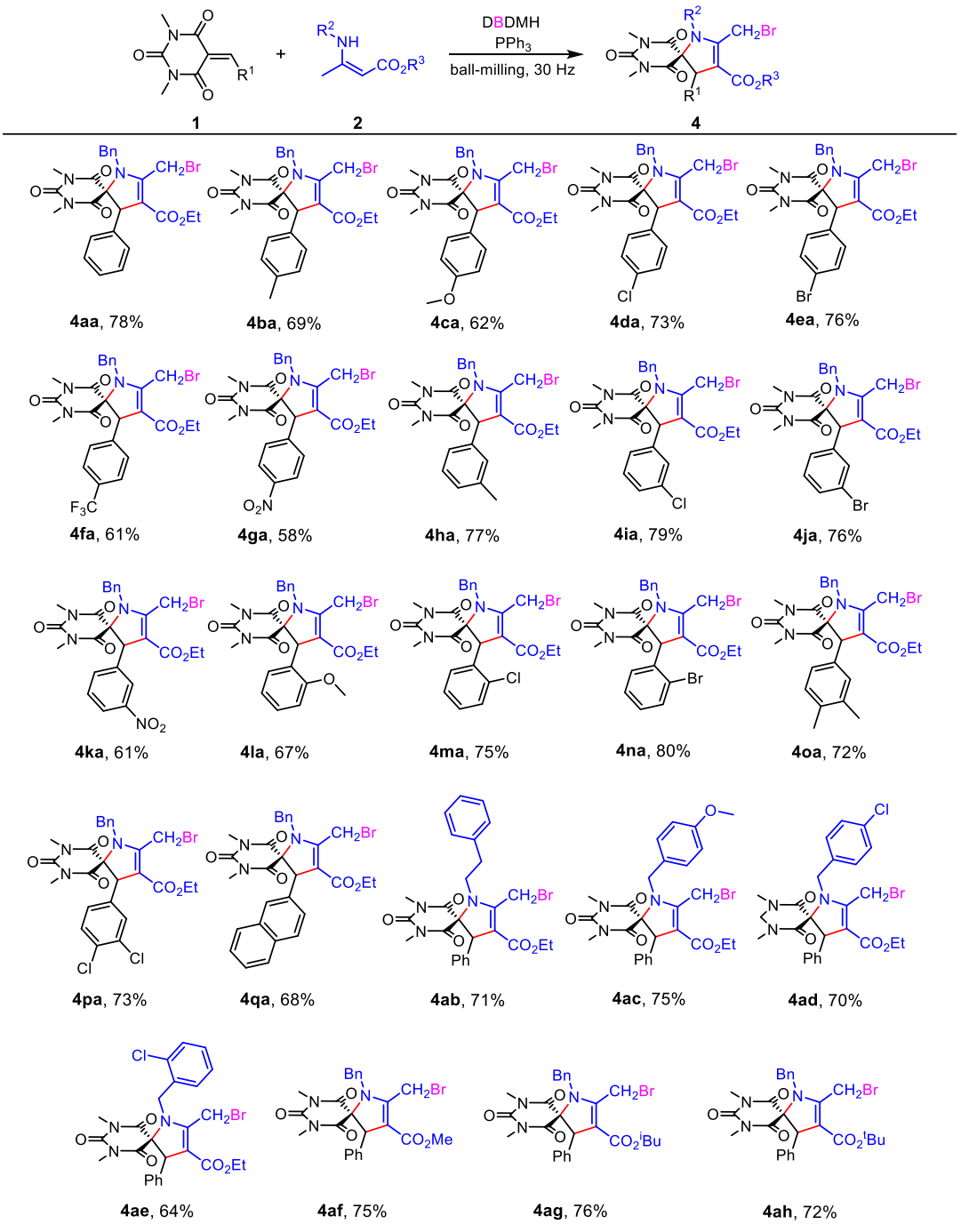
[a]Reaction conditions: a mixture of **1** (0.2 mmol), **2** (0.24 mmol), NIS (0.24 mmol), DMF (30 μL) and four stainless balls (6 mm in diameter) was milled in a Retsch MM400 mixer mill at 30 Hz for 30 min. [b]Isolated yields based on **1**.

2.2.2.2 产物 4 的合成

在确定了巴比妥酸螺二氢吡咯化合物最佳反应条件后我们对其普适性进行了探究（Table 2-3）。当不饱和巴比妥酸的苯环上接有给电子基团（Me 和 OMe）以及供电子基团（Cl, Br, CF_3 和 NO_2）时，巴比妥酸衍生物 **1** 同样展现出一定的

反应活性，合成了一系列二氢吡咯基螺巴比妥酸衍生物 **4ba–pa**，产率为 58–80%。在最佳条件下，我们同样发现萘基取代的不饱和巴比妥酸 **1q** 同样具有相对较好的反应活性，能以中等的产率得到产物 **4qa**。最后我们考察了烯胺酯片段的不同底物，同样以中等到良好的产率得到 **4ab–ah** 产物。

Table 2-3. Selective synthesis of barbiturate-spirodihydropyrroles 4 from unsaturated barbiturates 1 and enamino esters 2[a,b]

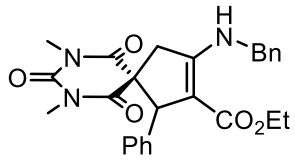


[a]Reaction conditions: a mixture of **1** (0.2 mmol), **2** (0.24 mmol), DBDMH (0.2 mmol), PPh_3 (0.2

mmol), CH_2Br_2 (30 μL) and four stainless balls (6 mm in diameter) was milled in a Retsch MM400 mixer mill at 30 Hz for 30 min. [b]Isolated yields based on **1**.

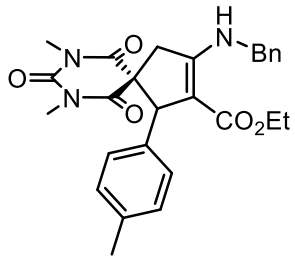
2.3 巴比妥酸螺环产物的表征

Ethyl 3-(benzylamino)-7,9-dimethyl-6,8,10-trioxo-1-phenyl-7,9-diazaspiro[4.5]dec-2-ene-2-carboxylate (3aa).



Ethyl acetate/petroleum ether = 1:4 as the eluent; White solid, 91% yield (84.3 mg), mp 157–159 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (bs, 1H), 7.44–7.37 (m, 4H), 7.34–7.29 (m, 1H), 7.26–7.19 (m, 3H), 7.01 (bs, 2H), 4.56 (d, J = 6.3 Hz, 2H), 4.47 (s, 1H), 3.93–3.86 (m, 1H), 3.82–3.74 (m, 1H), 3.49 (d, J = 16.8 Hz, 1H), 3.39 (d, J = 16.8 Hz, 1H), 3.37 (s, 3H), 2.56 (s, 3H), 0.79 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.2, 168.7, 167.1, 163.0, 151.2, 139.6, 138.3, 129.0 (2C), 128.1 (2C), 128.0 (2C), 127.9, 127.8, 127.1 (2C), 91.5, 63.1, 60.6, 58.7, 48.6, 35.4, 29.4, 28.4, 14.1; HRMS (ESI-TOF) calcd for $C_{26}H_{28}N_3O_5$ $[M + H]^+$ 462.2029, found 462.2036.

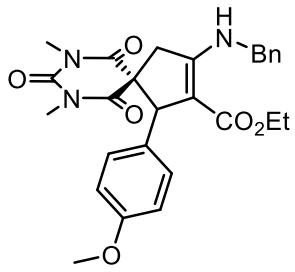
Ethyl 3-(benzylamino)-7,9-dimethyl-6,8,10-trioxo-1-(*p*-tolyl)-7,9-diazaspiro[4.5]dec-2-ene-2-carboxylate (3ba).



Ethyl acetate/petroleum ether = 1:4 as the eluent; White solid, 89% yield (84.8 mg), mp 139–141 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.00 (bs, 1H), 7.43–7.36 (m, 4H), 7.33–7.28 (m, 1H), 7.03 (d, J = 7.9 Hz, 2H), 6.88 (d, J = 6.5 Hz, 2H), 4.55 (d, J = 6.3 Hz, 2H), 4.43 (s, 1H), 3.93–3.77 (m, 2H), 3.48 (d, J = 16.8 Hz, 1H), 3.36(s, 3H), 3.35 (d, J = 16.8 Hz, 1H), 2.58 (s, 3H), 2.29 (s, 3H), 0.82 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.3, 168.8, 167.1, 162.9, 151.2, 138.4, 137.5, 136.4, 129.0 (2C), 128.7 (2C), 127.8 (2C), 127.7, 127.1 (2C), 91.6, 62.8, 60.6, 58.7, 48.6, 35.2, 29.3, 28.4, 21.2, 14.1; HRMS (ESI-TOF) calcd for $C_{27}H_{30}N_3O_5$ $[M + H]^+$ 476.2185, found 476.2182.

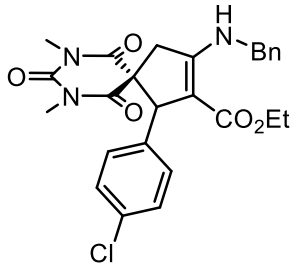
Ethyl 3-(benzylamino)-1-(4-methoxyphenyl)-7,9-dimethyl-6,8,10-trioxo-7,9-diazaspiro[4.5]dec-2-ene-2-carboxylate (3ca).

Ethyl acetate/petroleum ether = 1:3 as the eluent; White solid, 84% yield (82.2 mg), mp 141–143 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.00 (bs, 1H), 7.43–7.36 (m, 4H),



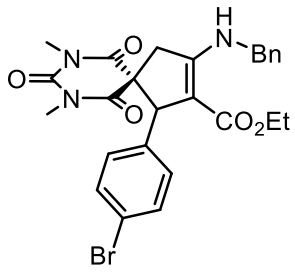
7.34–7.28 (m, 1H), 6.92 (d, *J* = 7.2 Hz, 2H), 6.77 (d, *J* = 8.7 Hz, 2H), 4.55 (d, *J* = 6.3 Hz, 2H), 4.42 (s, 1H), 3.94–3.86 (m, 1H), 3.85–3.78 (m, 1H), 3.78–3.75 (m, 3H), 3.49 (d, *J* = 16.8 Hz, 1H), 3.35 (d, *J* = 16.8 Hz, 1H), 3.37 (s, 3H), 2.63 (s, 3H), 0.84 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.3, 168.8, 167.1, 162.8, 159.3, 151.3, 138.4, 131.6, 129.1 (2C), 129.0 (2C), 127.8, 127.1 (2C), 113.5 (2C), 91.8, 62.6, 60.6, 58.7, 55.4, 48.6, 35.2, 29.3, 28.6, 14.2; HRMS (ESI-TOF) calcd for $C_{27}H_{30}N_3O_6$ $[M + H]^+$ 492.2135, found 492.2139.

Ethyl 3-(benzylamino)-1-(4-chlorophenyl)-7,9-dimethyl-6,8,10-trioxo-7,9-diazaspiro[4.5]dec-2-ene-2-carboxylate (3da).



Ethyl acetate/petroleum ether = 1:4 as the eluent; Whitesolid, 92% yield (91.1 mg), mp 156–158 ºC; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 (bs, 1H), 7.42–7.36 (m, 4H),7.34–7.29 (m, 1 H), 7.22 (d, *J* = 8.7 Hz, 2H), 6.96 (d, *J* = 7.4 Hz, 2H), 4.55 (d, *J* = 6.3 Hz, 2H), 4.43 (s, 1H), 3.93–3.86 (m, 1H), 3.84–3.77 (m, 1H), 3.49 (d, *J* = 16.8 Hz, 1H), 3.374 (d, *J* = 16.8 Hz, 1H), 3.372 (s, 3H), 2.64 (s, 3H), 0.83 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.1, 168.6, 166.9, 163.1, 151.1, 138.3, 138.2,133.7, 129.4 (2C), 129.1 (2C), 128.3 (2C), 127.9, 127.1 (2C), 91.3, 62.3, 60.3,58.8, 48.6, 35.5, 29.4, 28.6, 14.2; HRMS (ESI-TOF) calcd for $C_{26}H_{27}{}^{35}ClN_3O_5$ $[M + H]^+$ 496.1639, found 496.1643.

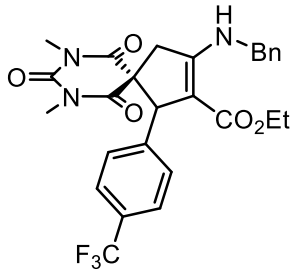
Ethyl 3-(benzylamino)-1-(4-bromophenyl)-7,9-dimethyl-6,8,10-trioxo-7,9-diazaspiro[4.5]dec-2-ene-2-carboxylate (3ea).



Ethyl acetate/petroleum ether = 1:4 as the eluent; White solid, 91% yield (97.9 mg), mp 151–153 ºC; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 (bs, 1H), 7.43–7.34 (m, 6H), 7.33–7.28 (m, 1H), 6.90 (d, *J* = 7.4 Hz, 2H), 4.55 (d, *J* = 6.3 Hz, 2H), 4.41 (s, 1H), 3.93–3.86 (m, 1H), 3.85–3.77 (m, 1H), 3.49 (d, *J* = 16.8 Hz, 1H), 3.370 (d, *J* = 16.8 Hz, 1H), 3.368 (s, 3H), 2.63 (s, 3H), 0.84 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.0, 168.5, 166.8, 163.2, 151.0, 138.8, 138.2, 131.2 (2C), 129.7 (2C), 129.0 (2C), 127.8, 127.1 (2C), 121.8, 91.2, 62.3, 60.2,

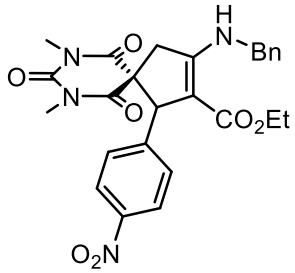
58.8, 48.6, 35.5, 29.4, 28.5, 14.2; HRMS (ESI-TOF) calcd for $C_{26}H_{27}{}^{79}BrN_3O_5$ [M + H]$^+$ 540.1134, found 540.1143.

Ethyl 3-(benzylamino)-7,9-dimethyl-6,8,10-trioxo-1-(4-(trifluoromethyl)phenyl)-7,9-diazaspiro[4.5]dec-2-ene-2-carboxylate (3fa).



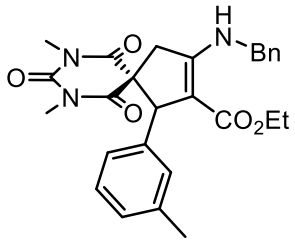
Ethyl acetate/petroleum ether = 1:3 as the eluent; White solid, 83% yield (88.0 mg), mp 149–151 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.05 (bs, 1H), 7.51 (d, *J* = 8.1 Hz, 2H), 7.44–7.36 (m, 4H), 7.34–7.29 (m, 1H), 7.15 (d, *J* = 7.1 Hz, 2H), 4.56 (d, *J* = 6.3 Hz, 2H), 4.51 (s, 1H), 3.93–3.85 (m, 1H), 3.82–3.75 (m, 1H), 3.51 (d, *J* = 16.8 Hz, 1H), 3.41 (d, *J* = 16.8 Hz, 1H), 3.38 (s, 3H), 2.55 (s, 3H), 0.79 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) *δ* 170.9, 168.4, 166.7, 163.3, 150.9, 144.0, 138.1, 130.2 (q, *J* = 32.5 Hz), 129.0 (2C), 128.5 (2C), 127.9, 127.1 (2C), 125.0 (q, *J* = 2.8 Hz, 2C), 124.1 (q, *J* = 272.1 Hz), 91.0, 62.4, 60.2, 58.8, 48.6, 35.7, 29.4, 28.4, 14.0; HRMS (ESI-TOF) calcd for $C_{27}H_{27}F_3N_3O_5$ [M + H]$^+$ 530.1903, found 530.1914.

Ethyl 3-(benzylamino)-7,9-dimethyl-1-(4-nitrophenyl)-6,8,10-trioxo-7,9-diazaspiro[4.5]dec-2-ene-2-carboxylate (3ga).



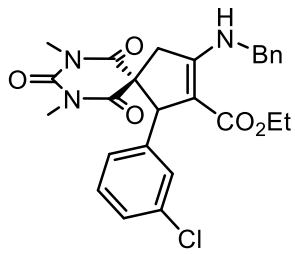
Ethyl acetate/petroleum ether = 1:2 as the eluent; White solid, 76% yield (77.4 mg), mp 159–161 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 8.12 (t, *J* = 8.7 Hz, 2H), 8.07 (bs, 1H), 7.46–7.36 (m, 4H), 7.35–7.30 (m, 1H), 7.22 (d, *J* = 7.5 Hz, 2H), 4.57 (d, *J* = 6.3 Hz, 2H), 4.54 (s, 1H), 3.92–3.77 (m, 2H), 3.53 (d, *J* = 16.9 Hz, 1H), 3.41 (d, *J* = 16.9 Hz, 1H), 3.39 (s, 3H), 2.62 (s, 3H), 0.81 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) *δ* 170.7, 168.2, 166.5, 163.5, 150.8, 147.5 (2C), 138.0, 129.08 (2C), 129.07 (2C), 127.9, 127.1 (2C), 123.3 (2C), 90.9, 61.9, 60.1, 58.9, 48.7, 35.8, 29.5, 28.5, 14.1; HRMS (ESI-TOF) calcd for $C_{26}H_{27}N_4O_7$ [M + H]$^+$ 507.1880, found 507.1871.

Ethyl 3-(benzylamino)-7,9-dimethyl-6,8,10-trioxo-1-(*m*-tolyl)-7,9-diazaspiro[4.5]dec-2-ene-2-carboxylate (3ha).



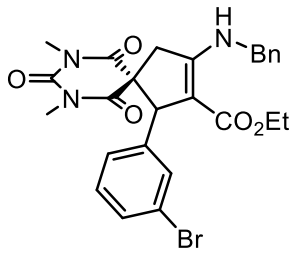
Ethyl acetate/petroleum ether = 1:4 as the eluent; White solid, 91% yield (86.5 mg), mp 141–143 ºC; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 (bs, 1H), 7.43–7.37 (m, 4H), 7.34–7.28 (m, 1H), 7.11 (t, J = 7.6 Hz, 1H), 7.02 (d, J = 7.5 Hz, 1H), 6.79 (bs, 2H), 4.56 (d, J = 6.3 Hz, 2H), 4.43 (s, 1H), 3.96–3.88 (m, 1H), 3.83–3.74 (m, 1H), 3.47 (d, J = 16.7 Hz, 1H), 3.38 (d, J = 16.7 Hz, 1H), 3.37 (s, 3H), 2.57 (s, 3H), 2.29 (s, 3H), 0.82 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.2, 168.7, 167.1, 163.0, 151.2, 139.4, 138.4, 137.7, 129.0 (2C), 128.6 (2C), 128.0, 127.8, 127.1 (2C), 125.1, 91.4, 63.1, 60.7, 58.6, 48.6, 35.3, 29.3, 28.4, 21.4, 14.2; HRMS (ESI-TOF) calcd for $C_{27}H_{30}N_3O_5$ $[M + H]^+$ 476.2186, found 476.2191.

Ethyl 3-(benzylamino)-1-(3-chlorophenyl)-7,9-dimethyl-6,8,10-trioxo-7,9-diazaspiro[4.5]dec-2-ene-2-carboxylate (3ia).



Ethyl acetate/petroleum ether = 1:4 as the eluent; White solid, 88% yield (87.7 mg), mp 146–148 ºC; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.05 (bs, 1H), 7.44–7.36 (m, 4H), 7.34–7.29 (m, 1H), 7.23–7.15 (m, 2H), 7.02 (s, 1H), 6.90 (bs, 1H), 4.55 (d, J = 6.3 Hz, 2H), 4.42 (s, 1H), 3.97–3.89 (m, 1H), 3.84–3.76 (m, 1H), 3.48 (d, J = 16.8 Hz, 1H), 3.37 (s, 3H), 3.36 (d, J = 16.8 Hz, 1H), 2.66 (s, 3H), 0.84 (t, J = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.9, 168.4, 166.8, 163.4, 151.0, 141.8, 138.1, 134.2, 129.3, 129.0 (2C), 128.1 (2C), 127.8, 127.1 (2C), 126.2, 90.9, 62.3, 60.4, 58.8, 48.6, 35.4, 29.4, 28.5, 14.2; HRMS (ESI-TOF) calcd for $C_{26}H_{27}{}^{35}ClN_3O_5$ $[M + H]^+$ 496.1639, found 496.1644.

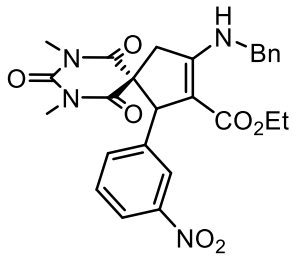
Ethyl 3-(benzylamino)-1-(3-bromophenyl)-7,9-dimethyl-6,8,10-trioxo-7,9-diazaspiro[4.5]dec-2-ene-2-carboxylate (3ja).



Ethyl acetate/petroleum ether = 1:4 as the eluent; White solid, 85% yield (91.8 mg), mp 136–138 ºC; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.05 (bs, 1H), 7.43–7.35 (m, 5H), 7.34–7.29 (m, 1H), 7.17 (s, 1H), 7.12 (t, J = 7.8 Hz, 1H), 6.95 (bs, 1H), 4.55 (d, J = 6.3 Hz, 2H), 4.41 (s, 1H), 3.98–3.90 (m, 1H), 3.84–3.76 (m, 1H), 3.47 (d, J = 16.8 Hz, 1H), 3.37 (s, 3H), 3.36 (d, J = 16.8 Hz, 1H),

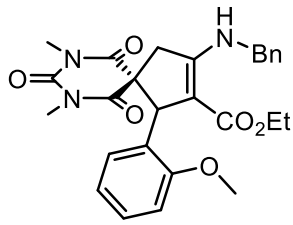
2.66 (s, 3H), 0.84 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.9, 168.4, 166.8, 163.4, 151.0, 142.1, 138.1, 131.0 (2C), 129.6, 129.0 (2C), 127.8, 127.1 (2C), 126.7, 122.3, 90.8, 62.3, 60.4, 58.8, 48.6, 35.4, 29.4, 28.6, 14.2; HRMS (ESI-TOF) calcd for $C_{26}H_{27}{}^{79}BrN_3O_5$ $[M + H]^+$ 540.1134, found 540.1138.

Ethyl 3-(benzylamino)-7,9-dimethyl-1-(3-nitrophenyl)-6,8,10-trioxo-7,9-diazaspiro[4.5]dec-2-ene-2-carboxylate (3ka).



Ethyl acetate/petroleum ether = 1:4 as the eluent; White solid, 73% yield (73.7 mg), mp 156–158 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.15–8.08 (m, 1H), 8.08 (bs, 1H), 7.91 (s, 1H), 7.48–7.35 (m, 6H), 7.35–7.30 (m, 1H), 4.58 (d, *J* = 6.3 Hz, 2H), 4.55 (s, 1H), 3.94–3.77 (m, 2H), 3.52 (d, *J* = 16.8 Hz, 1H), 3.39 (s, 3H), 3.38 (d, *J* = 16.8 Hz, 1H), 2.62 (s, 3H) , 0.82 (t, *J* = 6.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.7, 168.2, 166.5, 163.7, 150.8, 148.1, 142.2, 138.0, 134.1, 129.1 (2C), 129.0, 127.9, 127.0 (2C), 123.0 (2C), 90.6, 61.9, 60.1, 58.9, 48.7, 35.6, 29.5, 28.6, 14.2; HRMS (ESI-TOF) calcd for $C_{26}H_{27}N_4O_7$ $[M + H]^+$ 507.1880, found 507.1883.

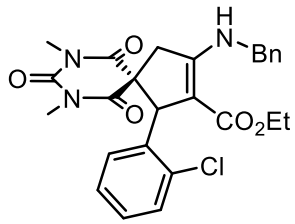
Ethyl 3-(benzylamino)-1-(2-methoxyphenyl)-7,9-dimethyl-6,8,10-trioxo-7,9-diazaspiro[4.5]dec-2-ene-2-carboxylate (3la).



Ethyl acetate/petroleum ether = 1:3 as the eluent; White solid, 82% yield (80.8 mg), mp 203–205 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97 (bs, 1H), 7.42–7.36 (m, 4H), 7.33–7.28 (m, 1H), 7.16 (td, *J* = 7.8, 1.6 Hz, 1H), 7.04 (dd, *J* = 7.6, 1.4 Hz, 1H), 6.85 (t, *J* = 7.5 Hz, 1H), 6.78 (d, *J* = 8.2 Hz, 1H), 5.14 (s, 1H), 4.54 (d, *J* = 6.3 Hz, 2H), 3.96–3.89 (m, 1H), 3.81–3.74 (m, 1H), 3.74–3.71 (m, 3H), 3.54 (d, *J* = 16.9 Hz, 1H), 3.36 (s, 3H), 3.33 (d, *J* = 16.9 Hz, 1H), 2.60 (s, 3H), 0.80 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.7, 169.1, 167.0, 162.7, 156.6, 151.5, 138.5, 129.5, 129.0 (2C), 128.6, 127.9, 127.7, 127.1 (2C), 120.5, 109.4, 91.5, 59.3, 58.6, 55.8, 53.8, 48.6, 36.2, 29.2, 28.3, 14.1; HRMS (ESI-TOF) calcd for $C_{27}H_{30}N_3O_6$ $[M + H]^+$ 492.2135, found 492.2133.

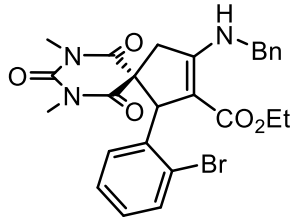
Ethyl 3-(benzylamino)-1-(2-chlorophenyl)-7,9-dimethyl-6,8,10-trioxo-7,9-diazasp

iro[4.5]dec-2-ene-2-carboxylate (3ma).



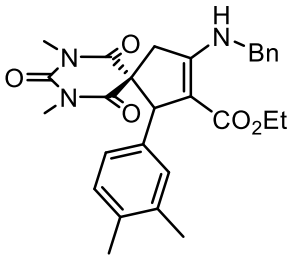
Ethyl acetate/petroleum ether = 1:4 as the eluent; White solid, 87% yield (86.0 mg), mp 173–175 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98 (bs, 1H), 7.43–7.37 (m, 4H), 7.34–7.28 (m, 2H), 7.19–7.11 (m, 3H), 5.18 (s, 1H), 4.55 (d, J = 6.3 Hz, 2H), 3.90–3.83 (m, 1H), 3.82–3.75 (m, 1H), 3.55 (d, J = 16.8 Hz, 1H), 3.36 (d, J = 16.8 Hz, 1H), 3.34 (s, 3H), 2.66 (s, 3H), 0.80 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.0, 168.8, 166.8, 163.0, 151.1, 138.3, 137.3, 133.7, 130.4, 129.02 (2C), 128.96, 128.8, 127.8, 127.1 (2C), 126.7, 92.0, 59.4, 58.7, 57.0, 48.6, 36.2, 29.4, 28.5, 14.0; HRMS (ESI-TOF) calcd for $C_{26}H_{27}{}^{35}ClN_3O_5$ $[M + H]^+$ 496.1639, found 496.1648.

Ethyl 3-(benzylamino)-1-(2-bromophenyl)-7,9-dimethyl-6,8,10-trioxo-7,9-diazasp iro[4.5]dec-2-ene-2-carboxylate (3na).



Ethyl acetate/petroleum ether = 1:4 as the eluent; White solid, 86% yield (92.9 mg), mp 167–169 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97 (bs, 1H), 7.48 (d, J = 7.9 Hz, 1H), 7.43–7.36 (m, 4H), 7.34–7.29 (m, 1H), 7.20 (t, J = 7.4 Hz, 1H), 7.11 (dd, J = 7.8, 1.5 Hz, 1H), 7.06 (td, J = 7.6, 1.6 Hz, 1H), 5.17 (s, 1H), 4.55 (dd, J = 6.3, 2.1 Hz, 2H), 3.89–3.76 (m, 2H), 3.57 (d, J = 16.8 Hz, 1H), 3.35 (s, 3H), 3.34 (d, J = 16.8 Hz, 1H), 2.66 (s, 3H), 0.81 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.9, 168.8, 166.7, 162.9, 151.1, 139.0, 138.3, 132.3, 130.6, 129.1, 129.0 (2C), 127.8, 127.2, 127.1 (2C), 124.6, 92.6, 59.8, 59.4, 58.7, 48.6, 36.2, 29.4, 28.5, 14.0; HRMS (ESI-TOF) calcd for $C_{26}H_{27}{}^{79}BrN_3O_5$ $[M + H]^+$ 540.1134, found 540.1131.

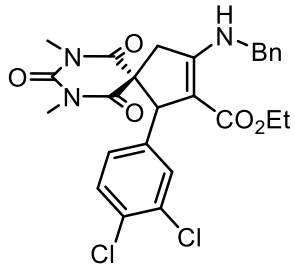
Ethyl 3-(benzylamino)-1-(3,4-dimethylphenyl)-7,9-dimethyl-6,8,10-trioxo-7,9-dia zaspiro[4.5]dec-2-ene-2-carboxylate (3oa).



Ethyl acetate/petroleum ether = 1:4 as the eluent; White solid, 90% yield (88.1 mg), mp 131–133 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.99 (bs, 1H), 7.43–7.37 (m, 4H), 7.34–7.28 (m, 1H), 6.98 (d, J = 7.7 Hz, 1H), 6.78–6.66 (m, 2H), 4.55 (d, J =

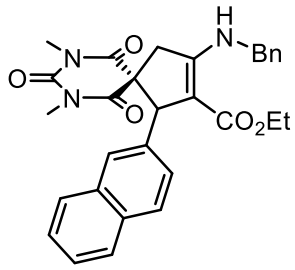
6.3 Hz, 2H), 4.41 (s, 1H), 3.95–3.87 (m, 1H), 3.86–3.79 (m, 1H), 3.47 (d, *J* = 16.8 Hz, 1H), 3.37 (s, 3H), 3.34 (d, *J* = 16.8 Hz, 1H), 2.58 (s, 3H), 2.20 (s, 3H), 2.19 (s, 3H), 0.85 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.3, 168.8, 167.2, 162.9, 151.3, 138.4, 136.7, 136.2, 136.1, 129.3, 129.0 (3C), 127.7, 127.1 (2C), 125.4, 91.6, 62.8, 60.8, 58.7, 48.6, 35.2, 29.3, 28.5, 19.8, 19.5, 14.2; HRMS (ESI-TOF) calcd for $C_{28}H_{32}N_3O_5$ $[M + H]^+$ 490.2342, found 490.2345.

Ethyl 3-(benzylamino)-1-(3,4-dichlorophenyl)-7,9-dimethyl-6,8,10-trioxo-7,9-diazaspiro[4.5]dec-2-ene-2-carboxylate (3pa).



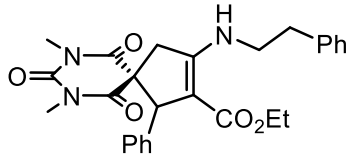
Ethyl acetate/petroleum ether = 1:4 as the eluent; White solid, 88% yield (93.7 mg), mp 167–169 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.05 (bs, 1H), 7.44–7.35 (m, 4H), 7.35–7.29 (m, 2H), 7.12 (s, 1H), 6.87 (d, *J* = 5.9 Hz, 1H), 4.55 (d, *J* = 6.3 Hz, 2H), 4.39 (s, 1H), 3.96–3.89 (m, 1H), 3.87–3.79 (m, 1H), 3.48 (d, *J* = 16.9 Hz, 1H), 3.37 (s, 3H), 3.34 (d, *J* = 16.9 Hz, 1H), 2.71 (s, 3H), 0.88 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.8, 168.3, 166.7, 163.4, 150.9, 140.2, 138.0, 132.4, 131.8, 130.0, 129.9, 129.0 (2C), 127.9, 127.4, 127.1 (2C), 90.7, 61.6, 60.2, 58.9, 48.6, 35.4, 29.4, 28.6, 14.2; HRMS (ESI-TOF) calcd for $C_{26}H_{26}{}^{35}Cl_2N_3O_5$ $[M + H]^+$ 530.1250, found 530.1258.

Ethyl 3-(benzylamino)-7,9-dimethyl-1-(naphthalen-2-yl)-6,8,10-trioxo-7,9-diazaspiro[4.5]dec-2-ene-2-carboxylate (3qa).



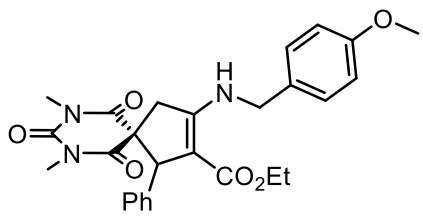
Ethyl acetate/petroleum ether = 1:4 as the eluent; White solid, 83% yield (85.2 mg), mp 170–172 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09 (bs, 1H), 7.80–7.74 (m, 2H), 7.72 (d, *J* = 8.5 Hz, 1H), 7.51–7.38 (m, 7H), 7.35–7.29 (m, 1H), 7.14 (bs, 1H), 4.64 (s, 1H), 4.59 (d, *J* = 6.3 Hz, 2H), 3.86–3.74 (m, 2H), 3.56 (d, *J* = 16.8 Hz, 1H), 3.41 (d, *J* = 16.8 Hz, 1H), 3.40 (s, 3H), 2.36 (s, 3H), 0.71 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.2, 168.6, 167.1, 163.2, 151.1, 138.3, 137.1, 133.1, 133.0, 129.0 (2C), 127.9, 127.8, 127.68, 127.65, 127.1 (2C), 127.0, 126.2, 126.0 (2C), 91.5, 63.0, 60.6, 58.7, 48.6, 35.4, 29.4, 28.4, 14.1; HRMS (ESI-TOF) calcd for $C_{30}H_{30}N_3O_5$ $[M + H]^+$ 512.2186, found 512.2181.

Ethyl 7,9-dimethyl-6,8,10-trioxo-3-(phenethylamino)-1-phenyl-7,9-diazaspiro[4.5] dec-2-ene-2-carboxylate (3ab).



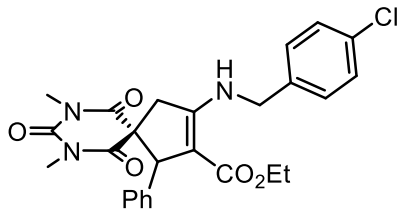
Ethyl acetate/petroleum ether = 1:4 as the eluent; White solid, 89% yield (84.4 mg), mp 97–99 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 (bs, 1H), 7.35 (t, J = 7.4 Hz, 2H), 7.29–7.18 (m, 6H), 7.00–6.93 (m, 2H), 4.42 (s, 1H), 3.92–3.85 (m, 1H), 3.81–3.73 (m, 1H), 3.61–3.55 (m, 2H), 3.40 (d, J = 16.7 Hz, 1H), 3.37 (s, 3H), 3.31 (d, J = 16.7 Hz, 1H), 3.02–2.92 (m, 2H), 2.57 (s, 3H), 0.78 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.2, 168.7, 166.9, 162.8, 151.2, 139.6, 138.4, 128.9 (2C), 128.8 (2C), 128.1 (2C), 128.0 (2C), 127.9, 126.8, 91.0, 63.0, 60.5, 58.6, 46.4, 37.6, 35.1, 29.3, 28.4, 14.1; HRMS (ESI-TOF) calcd for $C_{27}H_{30}N_3O_5$ $[M + H]^+$ 476.2186, found 476.2192.

Ethyl 3-((4-methoxybenzyl)amino)-7,9-dimethyl-6,8,10-trioxo-1-phenyl-7,9-diaza spiro[4.5]dec-2-ene-2-carboxylate (3ac).



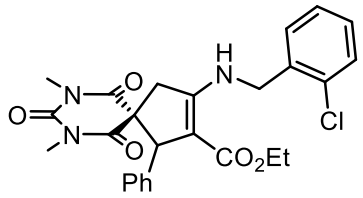
Ethyl acetate/petroleum ether = 1:4 as the eluent; White solid, 90% yield (88.2 mg), mp 128–130 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 (bs, 1H), 7.31 (d, J = 8.6 Hz, 2H), 7.25–7.19 (m, 3H), 7.01 (bs, 2H), 6.92 (d, J = 8.6 Hz, 2H), 4.48 (d, J = 6.2 Hz, 2H), 4.46 (s, 1H), 3.92–3.85 (m, 1H), 3.80 (d, J = 6.4 Hz, 3H), 3.80–3.73 (m, 1H), 3.49 (d, J = 16.8 Hz, 1H), 3.40 (d, J = 16.8 Hz, 1H), 3.37 (s, 3H), 2.56 (s, 3H), 0.78 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.2, 168.7, 167.0, 163.0, 159.2, 151.1, 139.6, 130.3, 128.4 (2C), 128.1 (2C), 127.94 (2C), 127.87, 114.3 (2C), 91.2, 63.0, 60.6, 58.6, 55.4, 48.0, 35.4, 29.3, 28.4, 14.0; HRMS (ESI-TOF) calcd for $C_{27}H_{30}N_3O_6$ $[M + H]^+$ 492.2135, found 492.2129.

Ethyl 3-((4-chlorobenzyl)amino)-7,9-dimethyl-6,8,10-trioxo-1-phenyl-7,9-diazasp iro[4.5]dec-2-ene-2-carboxylate (3ad).



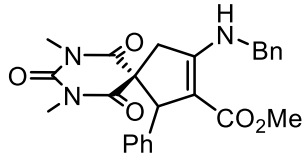
Ethyl acetate/petroleum ether = 1:4 as the eluent; White solid, 87% yield (86.5 mg), mp 130–132 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 (bs, 1H), 7.38 (d, J = 8.5 Hz, 2H), 7.33 (d, J = 8.5 Hz, 2H), 7.26–7.20 (m, 3H), 7.08–6.93 (m, 2H), 4.52 (d, J = 6.4 Hz, 2H), 4.46 (s, 1H), 3.94–3.86 (m, 1H), 3.82–3.74 (m, 1H), 3.46 (d, J = 16.7 Hz, 1H), 3.37 (s, 3H), 3.36 (d, J = 16.7 Hz, 1H), 2.56 (s, 3H), 0.79 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.2, 168.7, 167.1, 162.9, 151.1, 139.4, 137.0, 133.6, 129.2 (2C), 128.4 (2C), 128.2 (2C), 128.0 (3C), 91.9, 63.1, 60.6, 58.8, 47.9, 35.4, 29.4, 28.5, 14.1; HRMS (ESI-TOF) calcd for $C_{26}H_{27}{}^{35}ClN_3O_5$ $[M + H]^+$ 496.1639, found 496.1647.

Ethyl 3-((2-chlorobenzyl)amino)-7,9-dimethyl-6,8,10-trioxo-1-phenyl-7,9-diazaspiro[4.5]dec-2-ene-2-carboxylate (3ae).



Ethyl acetate/petroleum ether = 1:4 as the eluent; White solid, 81% yield (80.4 mg), mp 146–148 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 (bs, 1H), 7.51 (d, J = 7.5 Hz, 1H), 7.40 (d, J = 7.9 Hz, 1H), 7.36 (t, J = 7.5 Hz, 1H), 7.28 (d, J = 7.2 Hz, 1H), 7.26–7.19 (m, 3H), 7.01 (bs, 2H), 4.63 (d, J = 6.7 Hz, 2H), 4.47 (s, 1H), 3.95–3.87 (m, 1H), 3.83–3.76 (m, 1H), 3.49 (d, J = 16.8 Hz, 1H), 3.38 (d, J = 16.8 Hz, 1H), 3.37 (s, 3H), 2.55 (s, 3H), 0.80 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.2, 168.6, 167.1, 162.9, 151.1, 139.4, 136.0, 132.9, 129.7, 129.0, 128.6, 128.1 (2C), 127.9 (3C), 127.5, 91.9, 63.1, 60.5, 58.7, 46.3, 35.2, 29.3, 28.4, 14.1; HRMS (ESI-TOF) calcd for $C_{26}H_{27}{}^{35}ClN_3O_5$ $[M + H]^+$ 496.1639, found 496.1643.

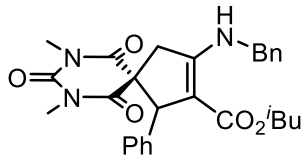
Methyl 3-(benzylamino)-7,9-dimethyl-6,8,10-trioxo-1-phenyl-7,9-diazaspiro[4.5]dec-2-ene-2-carboxylate (3af).



Ethyl acetate/petroleum ether = 1:4 as the eluent; White solid, 92% yield (82.3 mg), mp 190–192 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.07 (bs, 1H), 7.44–7.36 (m, 4H), 7.34–7.28 (m, 1H), 7.27–7.20 (m, 3H), 7.01 (bs, 2H), 4.56 (d, J = 6.3 Hz, 2H), 4.47 (s, 1H), 3.50 (d, J = 16.8 Hz, 1H), 3.38 (s, 3H), 3.37 (s, 3H), 3.34 (d, J = 16.8 Hz, 1H), 2.57 (s, 3H);

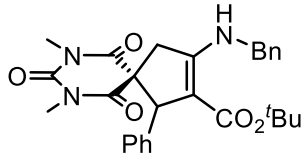
^{13}C NMR (125 MHz, $CDCl_3$) δ 171.2, 168.6, 167.5, 163.4, 151.1, 139.3, 138.3, 129.0 (2C), 128.2 (2C), 128.0, 127.9 (2C), 127.8, 127.1 (2C), 91.1, 62.8, 60.6, 50.3, 48.6, 35.3, 29.3, 28.5; HRMS (ESI-TOF) calcd for $C_{25}H_{26}N_3O_5$ $[M + H]^+$ 448.1873, found 448.1879.

Isobutyl 3-(benzylamino)-7,9-dimethyl-6,8,10-trioxo-1-phenyl-7,9-diazaspiro[4.5] dec-2-ene-2-carboxylate (3ag).



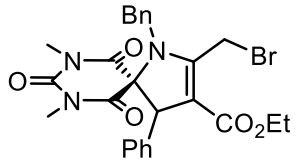
Ethyl acetate/petroleum ether = 1:4 as the eluent; White solid, 86% yield (84.1 mg), mp 160–162 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09 (bs, 1H), 7.45–7.35 (m, 4H), 7.33–7.28 (m, 1H), 7.27–7.17 (m, 3H), 7.02 (bs, 2H), 4.55 (d, J = 6.3 Hz, 2H), 4.47 (s, 1H), 3.72 (dd, J = 10.5, 6.4 Hz, 1H), 3.49 (d, J = 17.1 Hz, 1H), 3.50–3.44 (m, 1H), 3.39 (d, J = 17.1 Hz, 1H), 3.37 (s, 3H), 2.55 (s, 3H), 1.48–1.38 (m, 1H), 0.43 (d, J = 6.7 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.3, 168.7, 167.2, 163.2, 151.1, 139.5, 138.3, 129.0 (2C), 128.2 (2C), 128.0 (3C), 127.7, 127.1 (2C), 91.3, 69.0, 63.1, 60.5, 48.5, 35.4, 29.3, 28.4, 27.6, 18.68, 18.66; HRMS (ESI-TOF) calcd for $C_{28}H_{32}N_3O_5$ $[M + H]^+$ 490.2342, found 490.2338.

***tert*-Butyl 3-(benzylamino)-7,9-dimethyl-6,8,10-trioxo-1-phenyl-7,9-diazaspiro[4. 5]dec-2-ene-2-carboxylate (3ah).**



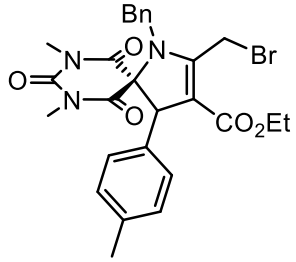
Ethyl acetate/petroleum ether = 1:4 as the eluent; White solid, 85% yield (83.0 mg), mp 143–145 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97 (bs, 1H), 7.43–7.36 (m, 4H), 7.33–7.28 (m, 1H), 7.26–7.19 (m, 3H), 7.01 (bs, 2H), 4.53 (d, J = 6.4 Hz, 2H), 4.42 (s, 1H), 3.45 (d, J = 17.7 Hz, 1H), 3.41 (d, J = 17.7 Hz, 1H), 3.37 (s, 3H), 2.53 (s, 3H), 1.03 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.3, 168.9, 166.9, 162.3, 151.1, 140.0, 138.5, 128.9 (2C), 128.0 (4C), 127.8, 127.7, 127.2 (2C), 92.7, 78.8, 63.6, 60.4, 48.5, 35.5, 29.3, 28.3, 28.1 (3C); HRMS (ESI-TOF) calcd for $C_{28}H_{32}N_3O_5$ $[M + H]^+$ 490.2342, found 490.2347.

Ethyl 1-benzyl-2-(bromomethyl)-7,9-dimethyl-6,8,10-trioxo-4-phenyl-1,7,9-triaza spiro[4.5]dec-2-ene-3-carboxylate (4aa).



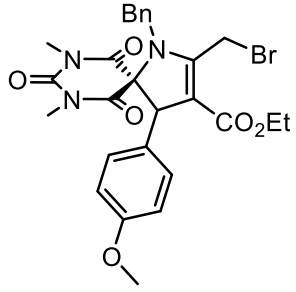
Ethyl acetate/petroleum ether = 1:4 as the eluent; White solid, 78% yield (84.5 mg), mp 133–135 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 (d, J = 7.2 Hz, 2H), 7.34–7.22 (m, 6H), 7.15 (bs, 1H), 6.91 (bs, 1H), 4.66 (d, J = 9.4 Hz, 1H), 4.61 (s, 1H), 4.58 (d, J = 14.5 Hz, 1H), 4.53 (d, J = 9.4 Hz, 1H), 4.48 (d, J = 14.5 Hz, 1H), 4.02–3.94 (m, 1H), 3.89–3.81 (m, 1H), 3.23 (s, 3H), 2.56 (s, 3H), 0.86 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.5, 165.2, 164.4, 159.5, 150.0, 136.7, 134.8, 129.7 (2C), 128.6 (3C), 128.53 (2C), 128.50 (2C), 128.4, 100.7, 79.7, 61.1, 59.4, 50.7, 29.3, 28.4, 19.9, 14.0; HRMS (ESI-TOF) calcd for $C_{26}H_{27}{}^{79}BrN_3O_5$ $[M + H]^+$ 540.1134, found 540.1130.

Ethyl 1-benzyl-2-(bromomethyl)-7,9-dimethyl-6,8,10-trioxo-4-(*p*-tolyl)-1,7,9-triazaspiro[4.5]dec-2-ene-3-carboxylate (4ba).



Ethyl acetate/petroleum ether = 1:4 as the eluent; White solid, 69% yield (76.9 mg), mp 66–68 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 (d, J = 6.9 Hz, 2H), 7.34–7.25 (m, 3H), 7.06 (bs, 3H), 6.80 (bs, 1H),4.67 (d, J = 9.0 Hz, 1H), 4.58–4.45 (m, 4H), 4.01–3.94 (m, 1H), 3.92–3.84 (m, 1H), 3.23 (s, 3H), 2.59 (s, 3H), 2.29 (s, 3H), 0.90 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.5, 165.3, 164.4, 159.2, 150.1, 138.1, 135.0, 133.6, 129.6 (2C), 129.0 (2C), 128.6 (2C), 128.5, 128.3 (2C), 101.0, 79.8, 60.8, 59.4, 50.7, 29.3, 28.4, 21.2, 20.0, 14.0; HRMS (ESI-TOF) calcd for $C_{27}H_{29}{}^{79}BrN_3O_5$ $[M + H]^+$ 554.1291, found 554.1285.

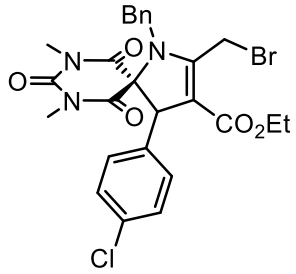
Ethyl 1-benzyl-2-(bromomethyl)-4-(4-methoxyphenyl)-7,9-dimethyl-6,8,10-trioxo-1,7,9-triazaspiro[4.5]dec-2-ene-3-carboxylate (4ca).



Ethyl acetate/petroleum ether = 1:3 as the eluent; White solid, 62% yield (70.6 mg), mp 66–68 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 (d, J = 7.2 Hz, 2H), 7.33–7.25 (m, 3H), 7.06 (bs, 1H), 6.80 (bs, 3H), 4.67 (d, J = 9.6 Hz, 1H), 4.58–4.46 (m, 2H), 4.02–3.94 (m, 1H), 3.91–3.84(m, 1H), 3.77 (s, 3H), 3.22 (s, 3H), 2.63 (s, 3H), 0.92 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.5, 165.4, 164.4, 159.6, 159.2, 150.1, 134.9, 129.7 (4C),

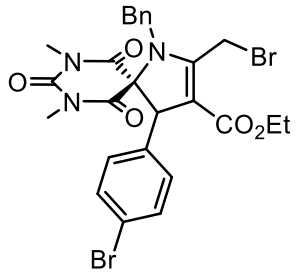
128.7, 128.6 (2C), 128.5, 113.7 (2C), 101.1, 79.7, 60.5, 59.4, 55.4, 50.7, 29.3, 28.5, 20.0, 14.1; HRMS (ESI-TOF) calcd for $C_{27}H_{29}{}^{79}BrN_3O_6$ $[M + H]^+$ 570.1240, found 570.1233.

Ethyl 1-benzyl-2-(bromomethyl)-4-(4-chlorophenyl)-7,9-dimethyl-6,8,10-trioxo-1, 7,9-triazaspiro[4.5]dec-2-ene-3-carboxylate (4da).



Ethyl acetate/petroleum ether = 1:4 as the eluent; White solid, 73% yield (84.5 mg), mp 132–134 ºC; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (d, J = 6.8 Hz, 2H), 7.33–7.20 (m, 5H), 7.12 (bs, 1H), 6.86 (bs, 1H), 4.69 (d, J = 9.5 Hz, 1H), 4.57–4.48 (m, 4H), 4.02–3.94 (m, 1H), 3.92–3.84 (m, 1H), 3.21 (s, 3H), 2.64 (s, 3H), 0.92 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.3, 165.1, 164.2, 159.7, 149.9, 135.4, 134.4, 134.3, 129.8 (4C), 128.6 (5C), 100.4, 79.1, 60.1, 59.6, 50.6, 29.3, 28.5, 19.7, 14.1; HRMS (ESI-TOF) calcd for $C_{26}H_{26}{}^{79}BrClN_3O_5$ $[M + H]^+$ 574.0744, found 574.0751.

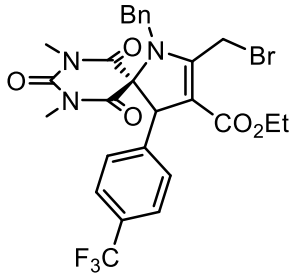
Ethyl 1-benzyl-2-(bromomethyl)-4-(4-bromophenyl)-7,9-dimethyl-6,8,10-trioxo-1, 7,9-triazaspiro[4.5]dec-2-ene-3-carboxylate (4ea).



Ethyl acetate/petroleum ether = 1:4 as the eluent; White solid, 76% yield (94.3 mg), mp 73–75 ºC; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47–7.34 (m, 4H), 7.33–7.25 (m, 3H), 7.03 (bs, 1H), 6.81 (bs, 1H), 4.69 (d, J = 10.1 Hz, 1H), 4.57–4.48 (m, 4H), 4.02–3.94 (m, 1H), 3.92–3.85 (m, 1H), 3.21 (s, 3H), 2.64 (s, 3H), 0.92 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.3, 165.0, 164.1, 159.7, 149.9, 135.9, 134.4, 131.5 (2C), 130.2 (2C), 129.8 (2C), 128.7, 128.6 (2C), 122.5, 100.3, 79.0, 60.2, 59.6, 50.6, 29.3, 28.5, 19.7, 14.1; HRMS (ESI-TOF) calcd for $C_{26}H_{26}{}^{79}Br_2N_3O_5$ $[M + H]^+$ 620.0219, found 620.0215.

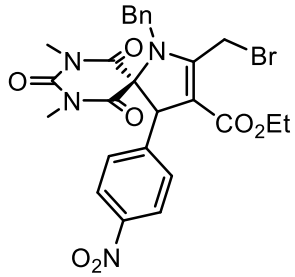
Ethyl 1-benzyl-2-(bromomethyl)-7,9-dimethyl-6,8,10-trioxo-4-(4-(trifluoromethyl) phenyl)-1,7,9-triazaspiro[4.5]dec-2-ene-3-carboxylate (4fa).

Ethyl acetate/petroleum ether = 1:3 as the eluent; White solid, 61% yield (74.1 mg), mp 66–68 ºC; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 (bs, 2H), 7.42 (d, J = 6.5 Hz, 2H), 7.34–7.24 (m, 4H), 7.07 (bs, 1H), 4.70 (s, 1H), 4.63 (s, 1H), 4.60–4.48 (m, 3H), 4.02–



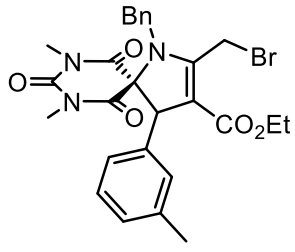
3.94 (m, 1H), 3.92–3.84 (m, 1H), 3.22 (s, 3H), 2.57 (s, 3H), 0.89 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) *δ* 168.2, 164.9, 164.1, 160.0, 149.8, 141.0, 134.2, 130.6 (q, *J* = 26.0 Hz), 130.0 (2C), 129.1 (2C), 128.8, 128.7 (2C), 125.3 (2C), 123.9 (q, *J* = 218.0 Hz), 100.1, 78.9, 60.3, 59.6, 50.6, 29.4, 28.4, 19.7, 14.0; HRMS (ESI-TOF) calcd for $C_{27}H_{26}{}^{79}BrF_3N_3O_5$ $[M + H]^+$ 608.1008, found 608.1018.

Ethyl 1-benzyl-2-(bromomethyl)-7,9-dimethyl-4-(4-nitrophenyl)-6,8,10-trioxo-1,7,9-triazaspiro[4.5]dec-2-ene-3-carboxylate (4ga).



Ethyl acetate/petroleum ether = 1:4 as the eluent; White solid, 58% yield (67.6 mg), mp 86–88 °C; ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 8.14 (bs, 2H), 7.50–7.28 (m, 6H), 7.14 (bs, 1H), 4.73 (d, *J* = 10.1 Hz, 1H), 4.65 (s, 1H), 4.60–4.50 (m, 3H), 4.01–3.94 (m, 1H), 3.93–3.85 (m, 1H), 3.22 (s, 3H), 2.62 (s, 3H), 0.92 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) *δ* 167.9, 164.7, 163.9, 160.2, 149.6, 147.7, 144.4, 133.9, 130.1 (2C), 129.6 (2C), 128.9, 128.7 (2C), 123.5 (2C), 99.9, 78.4, 59.8, 59.7, 50.5, 29.4, 28.5, 19.5, 14.1; HRMS (ESI-TOF) calcd for $C_{26}H_{26}{}^{79}BrN_4O_7$ $[M + H]^+$ 585.0985, found 585.0991.

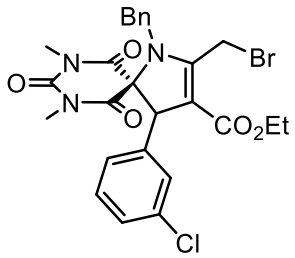
Ethyl 1-benzyl-2-(bromomethyl)-7,9-dimethyl-6,8,10-trioxo-4-(*m*-tolyl)-1,7,9-triazaspiro[4.5]dec-2-ene-3-carboxylate (4ha).



Ethyl acetate/petroleum ether = 1:4 as the eluent; White solid, 77% yield (85.7 mg), mp 61–64 °C; ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 7.46 (d, *J* = 7.0 Hz, 2H),7.33–7.25 (m, 3H), 7.15 (bs, 1H), 7.05 (d, *J* = 7.3 Hz, 1H), 6.94 (bs, 1H), 6.70 (bs, 1H), 4.65 (d, *J* = 9.8 Hz, 1H), 4.58 (d, *J* = 14.6 Hz, 1H), 4.57 (s, 1H), 4.52 (d, *J* = 9.8 Hz, 1H), 4.47 (d, *J* = 14.6 Hz, 1H), 4.04–3.96 (m, 1H), 3.91–3.83 (m, 1H), 3.22 (s, 3H), 2.57 (s, 3H), 2.29 (s, 3H), 0.89 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) *δ* 168.6, 165.2, 164.4, 159.4, 150.1, 138.0, 136.5, 134.9, 129.7 (2C), 129.1 (2C), 128.6 (2C), 128.5, 128.1, 125.6, 100.8, 79.9, 61.1, 59.4, 50.7, 29.2, 28.4, 21.4, 19.9, 14.0; HRMS (ESI-TOF) calcd for $C_{27}H_{29}{}^{79}BrN_3O_5$ $[M + H]^+$

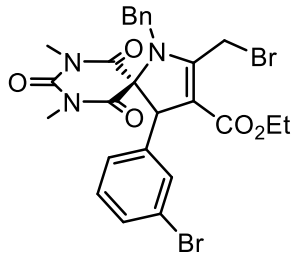
554.1291, found 554.1293.

Ethyl 1-benzyl-2-(bromomethyl)-4-(3-chlorophenyl)-7,9-dimethyl-6,8,10-trioxo-1, 7,9-triazaspiro[4.5]dec-2-ene-3-carboxylate (4ia).



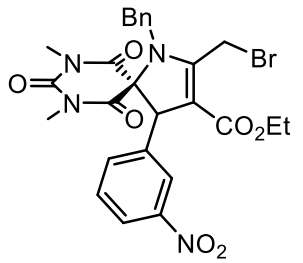
Ethyl acetate/petroleum ether = 1:4 as the eluent; White solid, 79% yield (90.8 mg), mp 64–66 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (d, J = 6.8 Hz, 2H), 7.34–7.04 (m, 6H), 6.98–6.70 (m, 1H), 4.72 (bs, 1H), 4.60–4.44 (m, 4H), 4.06–3.96 (m, 1H), 3.92–3.84 (m, 1H), 3.21 (s, 3H), 2.65 (s, 3H), 0.92 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.2, 164.9, 164.1, 159.9, 149.8, 138.8, 134.4 (2C), 129.8 (2C), 129.4, 128.6 (5C), 126.7, 100.1, 79.2, 60.2, 59.6, 50.6, 29.3, 28.5, 19.7, 14.1; HRMS (ESI-TOF) calcd for $C_{26}H_{26}{}^{79}Br^{35}ClN_3O_5$ $[M + H]^+$ 574.0744, found 574.0739.

Ethyl 1-benzyl-2-(bromomethyl)-4-(3-bromophenyl)-7,9-dimethyl-6,8,10-trioxo-1, 7,9-triazaspiro[4.5]dec-2-ene-3-carboxylate (4ja).



Ethyl acetate/petroleum ether = 1:4 as the eluent; White solid, 76% yield (93.6 mg), mp 65–67 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (d, J = 7.0 Hz, 2H), 7.40 (d, J = 7.8 Hz, 1H), 7.34–7.24 (m, 4H), 7.20–6.78 (m, 2H), 4.72 (bs, 1H), 4.62–4.42 (m, 4H), 4.06–3.96 (m, 1H), 3.91–3.83 (m, 1H), 3.21 (s, 3H), 2.65 (s, 3H), 0.92 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz,$CDCl_3$) δ 168.1, 164.9, 164.1, 159.9, 149.8, 139.1, 134.4, 131.4 (2C), 129.8 (3C), 128.6 (3C), 127.1, 123.0, 100.0, 79.1, 60.2, 59.5, 50.5, 29.3, 28.5, 19.6, 14.0; HRMS (ESI-TOF) calcd for $C_{26}H_{26}{}^{79}Br_2N_3O_5$ $[M + H]^+$ 620.0219, found 620.0223.

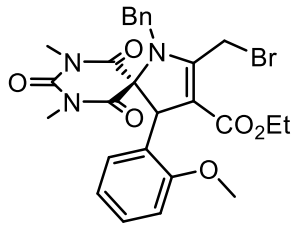
Ethyl 1-benzyl-2-(bromomethyl)-7,9-dimethyl-4-(3-nitrophenyl)-6,8,10-trioxo-1,7, 9-triazaspiro[4.5]dec-2-ene-3-carboxylate (4ka).



Ethyl acetate/petroleum ether = 1:2 as the eluent; White solid, 61% yield (71.1 mg), mp 140–142 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.14 (dd, J = 9.2, 2.2 Hz, 1H), 7.93 (bs, 1H), 7.48 (bs, 1H), 7.42 (d, J = 7.0 Hz, 2H), 7.35–7.25 (m, 4H), 5.00–

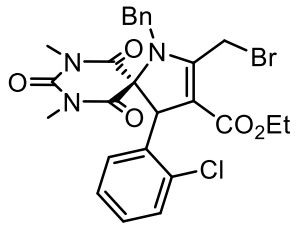
4.25 (m, 5H), 4.03–3.95 (m, 1H), 3.93–3.85 (m, 1H), 3.23 (s, 3H), 2.62 (s, 3H), 0.93 (t, J = 6.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.8, 164.8, 163.8, 160.3, 149.6, 148.2, 139.2, 134.5 (2C), 134.0, 129.9 (2C), 129.3, 128.8, 128.7 (2C), 123.4 (2C), 99.9, 78.5, 59.7, 50.4, 29.4, 28.5, 19.5, 14.1; HRMS (ESI-TOF) calcd for $C_{26}H_{26}{}^{79}BrN_4O_7$ $[M + H]^+$ 585.0985, found 585.0988.

Ethyl 1-benzyl-2-(bromomethyl)-4-(2-methoxyphenyl)-7,9-dimethyl-6,8,10-trioxo-1,7,9-triazaspiro[4.5]dec-2-ene-3-carboxylate (4la).



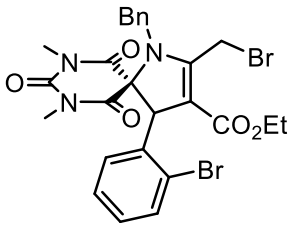
Ethyl acetate/petroleum ether = 1:3 as the eluent; White solid, 67% yield (76.6 mg), mp 64–66 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 (d, J = 6.7 Hz, 2H), 7.31–7.23 (m, 3H), 7.19 (td, J = 7.8, 1.4 Hz, 1H), 7.09 (d, J = 7.6 Hz, 1H), 6.90 (t, J = 7.5 Hz, 1H), 6.75 (d, J = 8.3 Hz, 1H), 5.16 (s, 1H), 4.78 (d, J = 9.7 Hz, 1H), 4.56 (d, J = 14.3 Hz, 1H), 4.53 (d, J = 9.7 Hz, 1H), 4.48 (d, J = 14.3 Hz, 1H), 4.05–3.98 (m, 1H), 3.90–3.83 (m, 1H), 3.65 (s, 3H), 3.16 (s, 3H), 2.57 (s, 3H), 0.90 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.7, 165.5, 164.5, 159.1, 156.4, 150.4, 134.4, 130.4, 130.0 (2C), 129.1, 128.49, 128.48 (2C), 125.3, 120.8, 109.4, 100.1, 77.9, 59.3, 55.7, 52.6, 50.4, 29.0, 28.1, 20.0, 14.0; HRMS (ESI-TOF) calcd for $C_{27}H_{29}{}^{79}BrN_3O_6$ $[M + H]^+$ 570.1240, found 570.1247.

Ethyl 1-benzyl-2-(bromomethyl)-4-(2-chlorophenyl)-7,9-dimethyl-6,8,10-trioxo-1,7,9-triazaspiro[4.5]dec-2-ene-3-carboxylate (4ma).



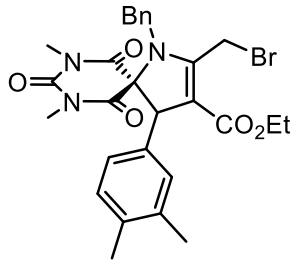
Ethyl acetate/petroleum ether = 1:4 as the eluent; White solid, 75% yield (86.3 mg), mp 63–65 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 (d, J = 6.5 Hz, 2H), 7.32–7.26 (m, 4H), 7.24–7.21 (m, 2H), 7.20–7.16 (m, 1H), 5.23 (s, 1H), 4.74 (d, J = 9.6 Hz, 1H), 4.58 (d, J = 9.6 Hz, 1H), 4.56 (d, J = 14.3 Hz, 1H), 4.51 (d, J = 14.3 Hz, 1H), 3.99–3.91 (m, 1H), 3.88–3.81 (m, 1H), 3.16 (s, 3H), 2.64 (s, 3H), 0.86 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.0, 165.2, 164.1, 159.6, 149.9, 134.8, 134.1, 133.5, 131.4, 130.1 (2C), 129.4, 128.8, 128.7, 128.6 (2C), 127.0, 100.6, 77.8, 59.4, 55.5, 50.4, 29.1, 28.3, 19.7, 13.9; HRMS (ESI-TOF) calcd for $C_{26}H_{26}{}^{79}Br^{35}ClN_3O_5$ $[M + H]^+$ 574.0744, found 574.0748.

Ethyl 1-benzyl-2-(bromomethyl)-4-(2-bromophenyl)-7,9-dimethyl-6,8,10-trioxo-1,7,9-triazaspiro[4.5]dec-2-ene-3-carboxylate (4na).



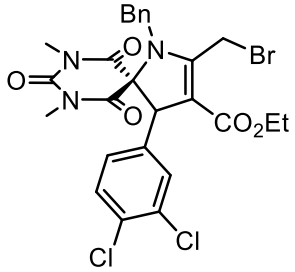
Ethyl acetate/petroleum ether = 1:4 as the eluent; White solid, 80% yield (98.6 mg), mp 118–120 ºC; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 (d, J = 7.9 Hz, 1H), 7.41 (d, J = 6.8 Hz, 2H), 7.32–7.26 (m, 4H), 7.23 (dd, J =7.7, 1.5 Hz, 1H), 7.10 (td, J = 7.6, 1.5 Hz, 1H), 5.22 (s, 1H), 4.75 (d, J = 9.9 Hz, 1H), 4.59–4.50 (m, 3H), 3.97–3.90 (m, 1H), 3.88–3.81 (m, 1H), 3.17 (s, 3H), 2.65 (s, 3H), 0.86 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.9, 165.2, 164.1, 159.5, 150.0, 136.6, 134.2, 132.2, 131.7, 130.1 (2C), 129.7, 128.7, 128.6 (2C), 127.6, 124.3, 101.2, 77.8, 59.5, 58.2, 50.4, 29.1, 28.4, 19.7, 13.9; HRMS (ESI-TOF) calcd for $C_{26}H_{26}{}^{79}Br_2N_3O_5$ $[M + H]^+$ 620.0219, found 620.0225.

Ethyl 1-benzyl-2-(bromomethyl)-4-(3,4-dimethylphenyl)-7,9-dimethyl-6,8,10-trioxo-1,7,9-triazaspiro[4.5]dec-2-ene-3-carboxylate (4oa).



Ethyl acetate/petroleum ether = 1:4 as the eluent; White solid, 72% yield (81.7 mg), mp 152–154 ºC; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 (d, J =7.1 Hz, 2H), 7.33–7.24 (m, 3H), 7.01 (bs, 1H), 6.86 (bs, 1H), 6.65 (bs, 1H), 4.67 (d, J = 7.9 Hz, 1H), 4.58–4.42 (m, 4H), 4.01–3.95 (m, 1H), 3.94–3.86 (m, 1H), 3.23 (s, 3H), 2.58 (s, 3H), 2.20 (s, 6H), 0.93 (t, J = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.6, 165.3, 164.5, 159.1, 150.1, 136.7, 135.1, 133.8, 129.5 (5C), 128.6 (2C), 128.4, 125.8, 101.0, 80.0, 60.8, 59.5, 50.7, 29.2, 28.4, 20.0, 19.8, 19.6, 14.1; HRMS (ESI-TOF) calcd for $C_{28}H_{31}{}^{79}BrN_3O_5$ $[M + H]^+$ 568.1447, found 568.1452.

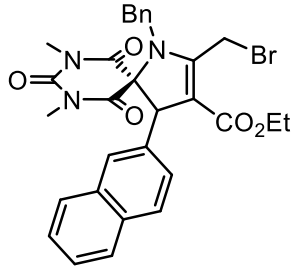
Ethyl 1-benzyl-2-(bromomethyl)-4-(3,4-dichlorophenyl)-7,9-dimethyl-6,8,10-trioxo-1,7,9-triazaspiro[4.5]dec-2-ene-3-carboxylate (4pa).



Ethyl acetate/petroleum ether = 1:4 as the eluent; White solid, 73% yield (89.1 mg), mp 130–132ºC; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 (d, J = 6.4 Hz, 2H), 7.39–7.27 (m, 4H), 7.24–

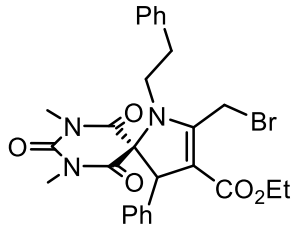
6.66 (m, 2H), 4.75 (bs, 1H), 4.56–4.44 (m, 4H), 4.05–3.97 (m, 1H), 3.95–3.88 (m, 1H), 3.21 (s, 3H), 2.70 (s, 3H), 0.97 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.0, 164.9, 164.0, 160.0, 149.8, 137.1, 134.2, 132.5, 130.6 (3C), 129.9 (2C), 128.8, 128.7 (2C), 127.9, 100.0, 78.7, 59.7, 59.5, 50.5, 29.4, 28.6, 19.6, 14.2; HRMS (ESI-TOF) calcd for $C_{26}H_{25}{}^{79}Br^{35}Cl_2N_3O_5$ $[M + H]^+$ 608.0355, found 608.0351.

Ethyl 1-benzyl-2-(bromomethyl)-7,9-dimethyl-4-(naphthalen-2-yl)-6,8,10-trioxo-1,7,9-triazaspiro[4.5]dec-2-ene-3-carboxylate (4qa).



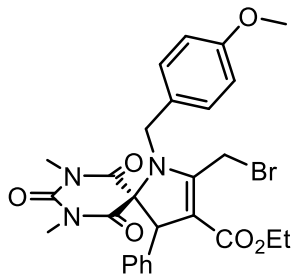
Ethyl acetate/petroleum ether = 1:4 as the eluent; White solid, 68% yield (79.9 mg), mp 85–87 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86–7.68 (m, 3H), 7.64–7.36 (s, 5H), 7.34–7.26 (m, 3H), 7.23–6.86 (m, 1H), 4.82–4.71 (m, 2H), 4.65–4.46 (m, 3H), 3.96–3.81 (m, 2H), 3.26 (s, 3H), 2.37 (s, 3H), 0.81 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.4, 165.2, 164.4, 159.6, 150.0, 134.8, 133.1, 133.0, 129.8 (2C), 128.63 (2C), 128.56, 128.1 (2C), 127.7 (2C), 126.5, 126.4, 126.3, 125.9, 100.8, 79.7, 61.1, 59.5, 50.7, 29.3, 28.4, 19.9, 14.0; HRMS (ESI-TOF) calcd for $C_{30}H_{29}{}^{79}BrN_3O_5$ $[M + H]^+$ 590.1291, found 590.1282.

Ethyl 2-(bromomethyl)-7,9-dimethyl-6,8,10-trioxo-1-phenethyl-4-phenyl-1,7,9-triazaspiro[4.5]dec-2-ene-3-carboxylate (4ab).



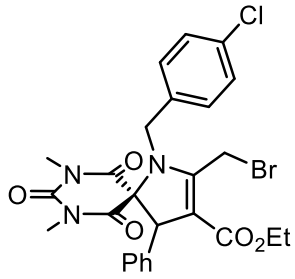
White solid, 71% yield (78.9 mg), mp 60–62 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31–7.24 (m, 5H), 7.23–7.18 (s, 3H), 7.11 (bs, 1H), 6.94 (bs, 1H), 4.57 (d, J = 10.3 Hz, 1H), 4.50 (s, 1H), 4.48 (d, J = 10.3 Hz, 1H), 4.00–3.92 (m, 1H), 3.88–3.81 (m, 1H), 3.64–3.51 (m, 2H), 3.37 (s, 3H), 3.05–2.93 (m, 2H), 2.58 (s, 3H), 0.86 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.4, 165.2, 164.3, 159.9, 150.2, 138.5, 136.9, 129.0 (2C), 128.7 (2C), 128.5, 128.4 (4C), 126.9, 99.4, 80.8, 61.3, 59.3, 48.0, 36.0, 29.6, 28.6, 19.3, 14.0; HRMS (ESI-TOF) calcd for $C_{27}H_{29}{}^{79}BrN_3O_5$ $[M + H]^+$ 554.1291, found 554.1298.

Ethyl 2-(bromomethyl)-1-(4-methoxybenzyl)-7,9-dimethyl-6,8,10-trioxo-4-phenyl-1,7,9-triazaspiro[4.5]dec-2-ene-3-carboxylate (4ac).



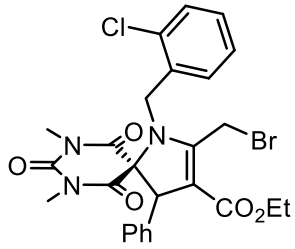
Ethyl acetate/petroleum ether = 1:3 as the eluent; White solid, 75% yield (85.8 mg), mp 63–65 ºC; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (d, J = 8.3Hz, 2H), 7.28–7.04 (m, 4H), 6.87 (bs, 1H), 6.81 (d, J = 8.3 Hz, 2H), 4.70 (d, J = 9.0 Hz, 1H), 4.63–4.57 (m, 2H), 4.55 (d, J = 14.0 Hz, 1H), 4.43 (d, J = 14.0 Hz, 1H), 4.01–3.93 (m, 1H), 3.89–3.81 (m, 1H), 3.77 (s, 3H), 3.21 (s, 3H), 2.55 (s, 3H), 0.86 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.7, 165.2, 164.4, 159.8, 159.5, 150.0, 136.8, 131.5 (2C), 128.6 (4C), 128.4, 126.1, 113.8 (2C), 100.4, 79.2, 61.0, 59.4, 55.4, 49.9, 29.2, 28.3, 20.0, 14.0; HRMS (ESI-TOF) calcd for $C_{27}H_{29}{}^{79}BrN_3O_6$ $[M + H]^+$ 570.1240, found 570.1243.

Ethyl 2-(bromomethyl)-1-(4-chlorobenzyl)-7,9-dimethyl-6,8,10-trioxo-4-phenyl-1, 7,9-triazaspiro[4.5]dec-2-ene-3-carboxylate (4ad).



Ethyl acetate/petroleum ether = 1:4 as the eluent; White solid, 70% yield (80.9 mg), mp 172–174 ºC; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49 (d, J = 8.3 Hz, 2H), 7.31 (d, J = 8.4 Hz, 2H), 7.30–7.24 (m, 3H), 7.12 (bs, 1H), 6.96 (bs, 1H), 4.62–4.54 (m, 2H), 4.52–4.41 (m, 3H), 4.01–3.93 (m, 1H), 3.89–3.81 (m, 1H), 3.30 (s, 3H), 2.59 (s, 3H), 0.87 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.3, 165.3, 164.2, 159.2, 150.0, 136.6, 134.3, 134.1, 130.4 (2C), 128.9 (2C), 128.5, 128.4 (4C), 101.3, 80.5, 60.9, 59.5, 50.3, 29.4, 28.5, 19.8, 14.0; HRMS (ESI-TOF) calcd for $C_{26}H_{26}{}^{79}Br^{35}ClN_3O_5$ $[M + H]^+$ 574.0744, found 574.0752.

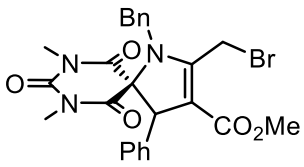
Ethyl 2-(bromomethyl)-1-(2-chlorobenzyl)-7,9-dimethyl-6,8,10-trioxo-4-phenyl-1, 7,9-triazaspiro[4.5]dec-2-ene-3-carboxylate (4ae).



Ethyl acetate/petroleum ether = 1:4 as the eluent; White solid, 64% yield (73.8 mg), mp 158–159 ºC; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61–7.56 (m, 1H), 7.36–7.33 (m, 1H), 7.30–6.85 (m, 7H), 4.74 (d, J = 10.3 Hz, 1H), 4.66 (d, J = 16.3 Hz, 1H), 4.64–4.57 (m, 3H), 4.03–3.95 (m, 1H), 3.90–3.83 (m, 1H), 3.22 (s, 3H), 2.57 (s, 3H), 0.88 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.9, 165.0, 164.2, 159.3, 150.1, 136.6, 134.3, 133.2, 130.5, 129.8, 129.6, 128.47 (2C), 128.45 (4C), 126.9,

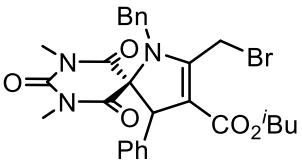
100.7, 61.3, 59.5, 48.1, 29.3, 28.4, 19.4, 14.0; HRMS (ESI-TOF) calcd for $C_{26}H_{26}{}^{79}Br^{35}ClN_3O_5$ $[M + H]^+$ 574.0744, found 574.0748.

Methyl 1-benzyl-2-(bromomethyl)-7,9-dimethyl-6,8,10-trioxo-4-phenyl-1,7,9-triazaspiro[4.5]dec-2-ene-3-carboxylate (4af).



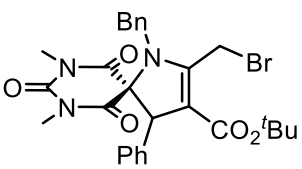
Ethyl acetate/petroleum ether = 1:4 as the eluent; White solid, 75% yield (78.8 mg), mp 77–79 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 (d, J = 6.9 Hz, 2H), 7.35–7.22 (m, 6H), 7.14 (bs, 1H), 6.91 (bs, 1H), 4.68 (d, J = 9.7 Hz, 1H), 4.60 (s, 1H), 4.56 (d, J = 14.6 Hz, 1H), 4.52 (d, J = 9.7 Hz, 1H), 4.50 (d, J = 14.6 Hz, 1H), 3.45 (s, 3H), 3.22 (s, 3H), 2.56 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.4, 165.2, 164.9, 159.8, 150.0, 136.6, 134.7, 129.7 (2C), 128.63 (2C), 128.57, 128.52, 128.47 (4C), 100.3, 79.7, 60.9, 50.9, 50.7, 29.3, 28.4, 19.9; HRMS (ESI-TOF) calcd for $C_{25}H_{25}{}^{79}BrN_3O_5$ $[M + H]^+$ 526.0978, found 526.0975.

Isobutyl 1-benzyl-2-(bromomethyl)-7,9-dimethyl-6,8,10-trioxo-4-phenyl-1,7,9-triazaspiro[4.5]dec-2-ene-3-carboxylate (4ag).



Ethyl acetate/petroleum ether = 1:4 as the eluent; White solid, 76% yield (86.3 mg), mp 105–107 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 (d, J =7.0 Hz, 2H), 7.35–7.12 (m, 7H), 6.90 (bs, 1H), 4.68 (d, J = 8.7 Hz, 1H), 4.63–4.53 (m, 3H), 4.48 (d, J = 14.5 Hz, 1H), 3.77 (dd, J = 10.7, 6.4 Hz, 1H), 3.56 (dd, J = 10.7, 6.0 Hz, 1H), 3.22 (s, 3H), 2.55 (s, 3H), 1.56–1.46 (m, 1H), 0.50 (dd, J = 6.8, 1.2 Hz , 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.6, 165.2, 164.5, 159.8, 150.0, 136.8, 134.7, 129.8 (2C), 128.6 (2C), 128.53 (5C), 128.48, 100.4, 79.6, 69.8, 61.1, 50.7, 29.3, 28.3, 27.6, 19.9, 18.8 (2C); HRMS (ESI-TOF) calcd for $C_{28}H_{31}{}^{79}BrN_3O_5$ $[M + H]^+$ 568.1447, found 568.1444.

***tert*-Butyl 1-benzyl-2-(bromomethyl)-7,9-dimethyl-6,8,10-trioxo-4-phenyl-1,7,9-triazaspiro[4.5]dec-2-ene-3-carboxylate (4ah).**



Ethyl acetate/petroleum ether = 1:4 as the eluent; White solid, 72% yield (81.5 mg), mp 104–106 °C; ^{1}H NMR (500

MHz, $CDCl_3$) δ 7.46 (d, J = 7.1 Hz, 2H), 7.34–7.14 (m, 7H), 6.88 (bs, 1H), 4.64–4.52 (m, 4H), 4.46 (d, J = 14.5 Hz, 1H), 3.23 (s, 3H), 2.55 (s, 3H), 1.11 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.8, 165.3, 163.7, 158.6, 150.1, 137.1, 135.0, 129.7 (2C), 128.6 (5C), 128.5, 128.3 (2C), 102.2, 79.9, 79.6, 61.6, 50.8, 29.3, 28.3, 28.0 (3C), 20.1; HRMS (ESI-TOF) calcd for $C_{28}H_{31}{}^{79}BrN_3O_5$ $[M + H]^+$ 568.1447, found 568.1453.

2.4 化合物 **3ma** 的单晶衍射数据

目前，所有已合成的巴比妥酸螺环戊烯化合物均通过核磁共振波谱进行了结构表征。为了进一步确认产物的结构，我们将化合物 **3ma** 溶解于丙酮和正己烷的混合溶剂中，在低温环境下让其缓慢挥发，得到晶型规整且透明的单晶。随后，在配备有 CCD 面阵探测器衍射仪（Bruker APEX-II）上使用石墨单色 MoKα 辐射（λ = 0.71073 Å），在 5.086 < 2θ < 49.996º 的扫描范围内获得了相关衍射参数如表 2-4 所示。经 SHELXT Structure Solution 程序使用本征相位法与 SHELXL 精化软件的最小二乘法解析出化合物 **3ma** 的结构，如图 2-1 所示。

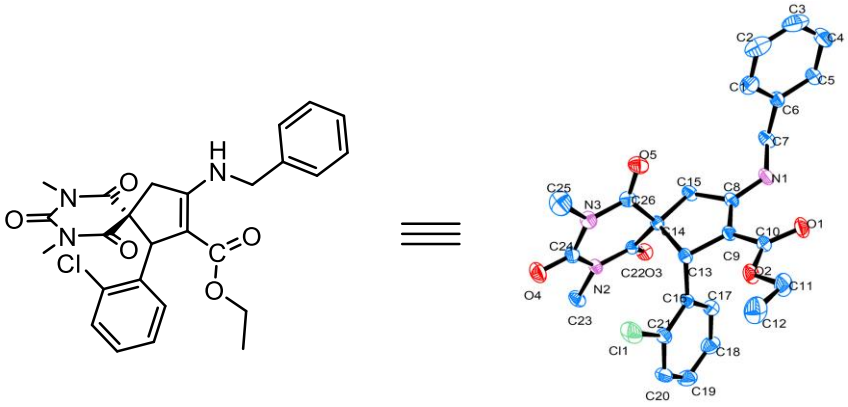


图 2-1 **3ma** 单晶衍射图

Table 2-4. Crystal data and structure refinement for 3ma

Identification code	CCDC 2305863
Empirical formula	$C_{26}H_{26}ClN_3O_5$
Formula weight	495.95
Temperature/K	293.15
Crystal system	triclinic
Space group	P-1
a/Å	8.2719 (11)
b/Å	10.9748 (14)

c/Å	14.3779 (18)
α/°	91.073 (2)
β/°	98.225 (2)
γ/°	110.945 (2)
Volume/Å^3	1203.0 (3)
Z	2
ρ_{calc}g/cm^3	1.369
μ/mm^{-1}	0.202
F(000)	520.0
Crystal size/mm^3	0.26 × 0.24 × 0.21
Radiation	MoKα (λ = 0.71073)
2θ range for data collection/°	5.086 to 49.996
Index ranges	-7 ≤ h ≤ 9, -13 ≤ k ≤ 12, -17 ≤ l ≤ 14
Reflections collected	6128
Independent reflections	4196 [R_{int} = 0.0147, R_{sigma} = 0.0323]
Data/restraints/parameters	4196/1/319
Goodness-of-fit on F^2	1.057
Final R indexes [I>=2σ (I)]	R_1 = 0.0474, wR_2 = 0.1220
Final R indexes [all data]	R_1 = 0.0686, wR_2 = 0.1297
Largest diff. peak/hole [e Å^{-3}]	0.53/-0.41

2.5 化合物 **4oa** 的单晶衍射数据

我们采用相同的方法得到化合物 **4oa** 的单晶，在配备有 CCD 面阵探测器衍射仪（Bruker APEX-II）上使用石墨单色 MoKα 辐射（λ = 0.71073 Å），在 4.48 < 2θ < 50.00º 的扫描范围内获得了相关衍射参数如表 2-5 所示。经 SHELXT Structure Solution 程序使用本征相位法与 SHELXL 精化软件的最小二乘法解析出化合物 **4oa** 的构型，晶体结构图 2-2 所示。

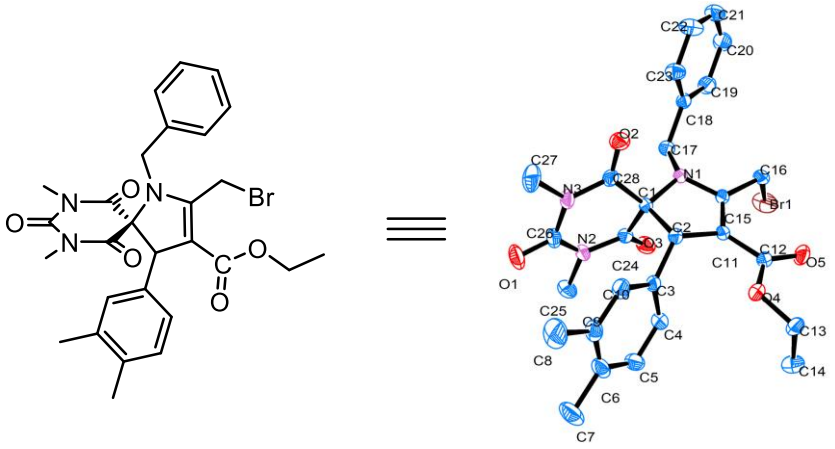


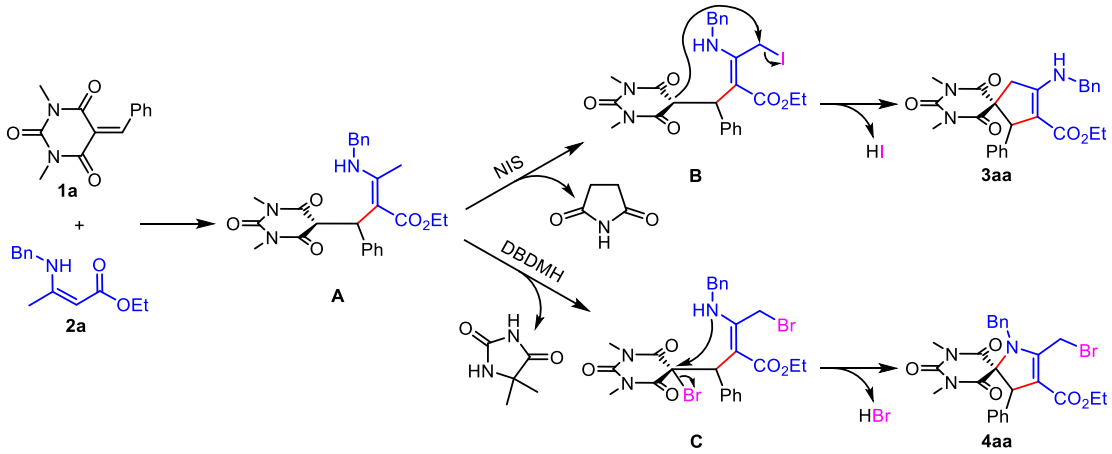
图 2-2 **4oa** 单晶衍射图

Tbale 2-5. Crystal data and structure refinement for 4oa	
Identification code	CCDC 2305868
Empirical formula	$C_{28}H_{30}BrN_3O_5$
Formula weight	568.65
Temperature/K	293.15
Crystal system	triclinic
Space group (number)	P-1 (2)
a/Å	11.0881 (8)
b/Å	11.9277 (9)
c/Å	12.1514 (9)
α/°	115.124 (2)
β/°	105.133 (3)
γ/°	100.196 (3)
Volume/Å^3	1326.22 (17)
Z	2
ρ_{calc}g/cm^3	1.424
μ/mm^{-1}	1.593
F(000)	588
Crystal size/mm^3	0.26×0.25×0.22
Crystal colour	colourless
Crystal shape	block
Radiation	MoK_α (λ=0.71073 Å)
2θ range for data collection/°	4.48 to 50.00 (0.84 Å)
Index ranges	$-13 \le h \le 13, -14 \le k \le 14, -14 \le l \le 14$
Reflections collected	37795
Independent reflections	4666 [R_{int} = 0.1052, R_{sigma} = 0.0570]
Data/Restraints/Parameters	4666/0/347
Goodness-of-fit on F^2	1.051
Final R indexes [I>=2σ (I)]	R_1 = 0.0415, wR_2 = 0.1067
Final R indexes [all data]	R_1 = 0.0609, wR_2 = 0.1144
Largest peak/hole [eÅ^{-3}]	0.29/-0.45

2.6 反应机理探究

基于上述实验结果及本课题组前期工作，我们以不饱和巴比妥酸 **1a** 与 β-烯胺酯 **2a** 的反应为例，给出了可能的反应机理（Scheme 2-5）。首先不饱和巴比妥酸 **1a** 与 β-烯胺酯 **2a** 之间发生迈克尔加成反应得到加成产物 **A**，其中巴比妥酸羰基位置的 α-H 和 β-烯胺酯甲基位置的烯丙基 H 在卤代试剂的作用下都有可能被卤代。当 NIS 作为卤代试剂时，由于碘原子体积较大且巴比妥酸羰基位置上的 α-H 具有很高的位阻，所以 β-烯胺酯甲基位置的烯丙基 H 会被优先碘代，得到中间体 **B**。随后巴比妥酸羰基位置的 α-C 对碘甲基进行亲核进攻后成环并脱去碘化氢，最终得到巴比妥酸螺环戊烯化合物 **3aa**。当 DMDMH 作为卤代试剂时，由于其具有相对较高的卤化活性且溴原子同时也具有相对较小的空间位

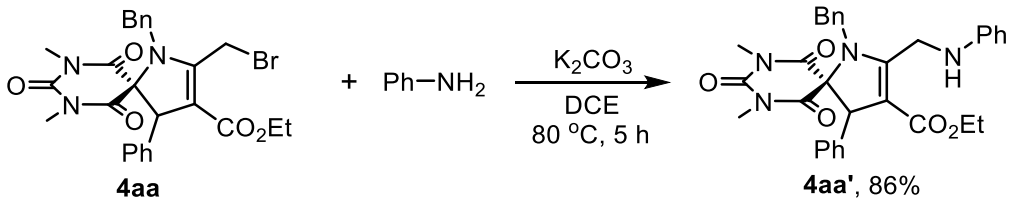
阻，因此巴比妥酸羰基位置的 α-H 和 β-烯胺酯甲基位置的烯丙基 H 都被溴代，进而得到中间体 **C**。然后烯胺片段的氮原子会对巴比妥酸羰基位置上的 α-C 发起亲核进攻并环化，同时脱去一分子溴化氢，最终得到巴比妥酸螺环戊烯化合物 **4aa**。



Scheme 2-5 Plausible mechanism for the reaction

2.7 巴比妥酸螺二氢吡咯的衍生化实验

为了进一步验证该方法的实用性，我们对产物 **4aa** 进行了衍生化反应。考虑到 **4aa** 中有溴原子，所以我们尝试其与一些亲核试剂发生取代反应。当 **4aa** 与苯胺在 K_2CO_3 存在下于 DCE 中加热反应 5 h，我们能以 86%的收率得到取代产物 **4aa′**。



Scheme 2-6 Derivatization experiment

2.8 本章小结

综上所述，本章的主要内容是研究了不饱和巴比妥酸与 β-烯胺酯在球磨条件下选择性螺环化反应。我们首先建立了模型反应，并通过筛选大量的反应条件最终确定了选择性合成巴比妥酸螺环戊烯化合物及巴比妥酸螺二氢吡咯化合物的反应条件，分别如下：1 当量不饱和巴比妥酸、1.2 当量烯胺酯、1.2 当量的 NIS 和 DMF（30 μL）在球磨下反应 30 min；1 当量不饱和巴比妥酸、1.2 当量烯胺酯、1 当量的 DBDMH、1 当量的 PPh_3 和 CH_2Br_2（30 μL）在球磨下反应 30 min。以 73–92%的产率合成 24 个巴比妥酸螺环戊烯化合物，并以 58–80%的产率合成 24 个巴比妥酸螺二氢吡咯化合物。同时两种螺环产物的结构通过 X-射线单晶衍射得到了进一步的确认，并从机理方面对该反应的选择性进行了阐释。该反应具有操作简单、原料易得、化学选择性好与原子利用率高等优点，符合绿色合成的理念。通过更换卤代试剂就能高效的选择性合成目标产物，为构建巴比妥酸螺环化合物提供了一种新途径。

第三章 硫代橙酮与烯胺酯的选择性环化反应研究

3.1 实验部分

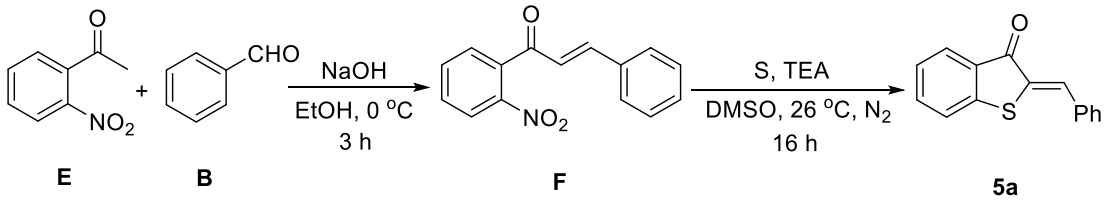
3.1.1 仪器与试剂

本章所使用的实验仪器和第二章部分相同，试剂种类有所不同。

试剂名称	规格	生产厂家
2-硝基苯乙酮	分析纯	上海泰坦科技有限公司
硫粉	分析纯	上海泰坦科技有限公司
氢氧化钠	分析纯	国药集团化学试剂有限公司
二甲基亚砜	分析纯	国药集团化学试剂有限公司
三乙胺	分析纯	国药集团化学试剂有限公司
氯化铁	分析纯	上海泰坦科技有限公司
六水和氯化铁	分析纯	萨恩化学技术（上海）有限公司

3.1.2 原料的合成

3.1.2.1 原料 5 的合成

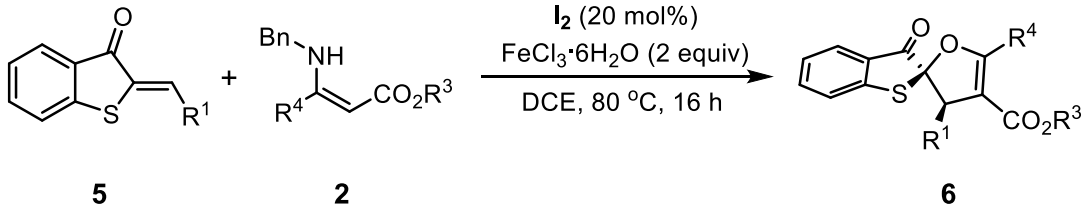


Scheme 3-1 Synthesis of thioaurones

以合成 **5a** 为例，先将 NaOH（12 mmol, 0.48 g）加入 100 mL 圆底烧瓶中，然后加入 40 mL 乙醇，在冰水浴中搅拌至 NaOH 完全溶解后缓慢加入 2-硝基苯乙酮 **E**（10 mmol, 1.65 g）与苯甲醛 **B**（10 mmol, 1.06 g），反应过程中会有白色固体逐渐析出，反应结束后抽滤得到硝基查尔酮 **F**（91%, 2.3 g）。然后将 **F**（9 mmol, 2.28 g）和硫粉（45 mmol, 1.45 g）加入到 50 mL 带活塞支管的圆底烧瓶中并用橡胶塞密封瓶口，随即利用活塞口充入氮气。待氮气充入完毕后用针管注射 DMSO（45 mmol, 3.51 g）与 TEA（45 mmol, 4.59 g）到圆底烧瓶中，并于室温下反应 16 小时。待反应结束加入适量乙酸乙酯萃取，重复操作三次合并有机相后加入适量的柱层析硅胶（200-300 目），减压浓缩成粉状，然后经柱层析（乙酸乙酯:石油醚 = 1:10）分离得到黄色固体，产率为 89%。

3.1.3 产物的合成

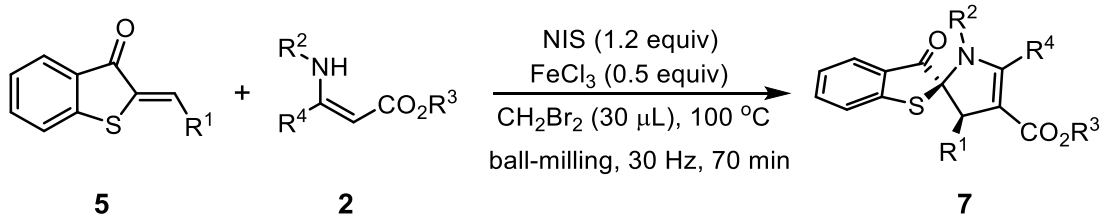
3.1.3.1 产物 **6** 的合成



Scheme 3-2 Synthesis of Compound **6**

向 25 mL 反应管中依次加入硫代橙酮 **5**（0.2 mmol）、β-烯胺酯 **2**（0.3 mmol）、I_2（0.02 mmol, 5.1 mg）、$FeCl_3·6H_2O$（0.4 mmol, 108 mg）和 DCE（2 mL），于 80 °C 油浴锅中反应 16 小时。反应结束后先冷却至室温，然后加入适量的乙酸乙酯与水，反复萃取三次合并有机相，再加入适量的柱层析硅胶（200-300 目），减压浓缩成粉状，随后依次通过柱层析分离得到产物 **6**。

3.1.3.2 产物 **7** 的合成



Scheme 3-3 Synthesis of Compound **7**

将硫代橙酮 **5**（0.2 mmol）、β-烯胺酯 **2**（0.24 mmol）、NIS（0.24 mmol, 54.0 mg）、$FeCl_3$（0.1 mmol，16.3 mg）和 CH_2Br_2（30 μL）加入到含有 4 个研磨球（直径 6 mm）的不锈钢罐（5 mL）中。将该研磨罐封闭并固定在 Retsch MM400 研磨仪的振动臂上，数显热风枪对其加热（显示为 100 °C），并以 1800 转/分钟（30 Hz）的频率研磨 70 分钟。反应结束后，用乙酸乙酯溶解所得的反应混合物并转移至茄形瓶中，加入硅胶后减压蒸馏至粉末状，然后进行柱层析分离得到产物 **7**。

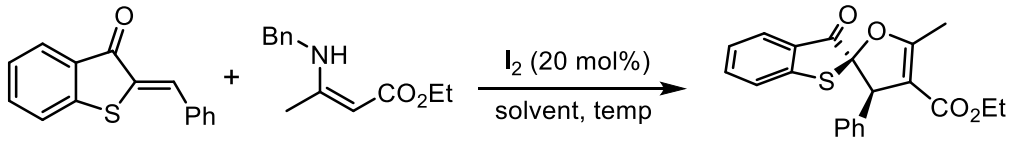
3.2 实验结果与讨论

3.2.1 条件优化

3.2.1.1 产物 6 的条件优化

首先，我们选择硫代橙酮 **5a** 与 β-烯胺酯 **2a** 为模型底物来筛选最佳反应条件（Table 3-1）。先将 **5a**（0.2 mmol）、**2a**（0.2 mmol）与 I_2（0.04 mmol）以 DCE 为溶剂，于 70 °C 下反应 10 小时（entry 1），结果分离得到目标产物硫代橙酮螺二氢呋喃 **6aa** 的收率为 22%。进一步的实验确定了 **1a** 与 **2a** 最佳的摩尔比为 1:2（entries 2–4）。接着，我们探讨了不同类型的添加剂对反应的影响，首先尝试了两种常用的碱（entries 5–6），但都不利于产物的生成。随后，又考察了路易斯酸的影响（entries 7–10），发现六水合三氯化铁对反应有显著的促进效果。在探究六水合氯化铁的添加量时，我们发现其最佳添加量为 2 当量（entry 13）。此外，通过温度和溶剂的筛选最终确定以 DCE 作溶剂、反应温度为 80 °C 时反应效果最佳，此时硫代橙酮螺二氢呋喃产物 **6aa** 的收率高达 91%（entry 22）。

Table 3-1. Optimization of the reaction conditions for the synthesis of 6aa[a]



5a **2a** **6aa**

Entry	Molar ratio (**5a**:**2a**)	Solvent	Additive (equiv.)	Temp (°C)	Time (h)	Yield[b] (%)
1	1:1	DCE		70	10	22
2	1:1.2	DCE		70	10	25
3	1:1.5	DCE		70	10	28
4	1:2	DCE		70	10	32
5	1:2	DCE	Na_2CO_3 (1.0)	70	10	trace
6	1:2	DCE	DMAP (1.0)	70	10	trace
7	1:2	DCE	$FeCl_3$ (1.0)	70	10	39
8	1:2	DCE	$FeCl_3·6H_2O$ (1.0)	70	10	69
9	1:2	DCE	$Fe_2(SO_4)_3$ (1.0)	70	10	35

10	1:2	DCE	$Fe_2(OAc)_3$ (1.0)	70	10	25
11	1:2	DCE	$FeCl_3·6H_2O$ (0.5)	70	10	59
12	1:2	DCE	$FeCl_3·6H_2O$ (1.5)	70	10	72
13	1:2	DCE	$FeCl_3·6H_2O$ (2.0)	70	10	80
14	1:2	DMF	$FeCl_3·6H_2O$ (2.0)	70	10	41
15	1:2	DMSO	$FeCl_3·6H_2O$ (2.0)	70	10	33
16	1:2	toluene	$FeCl_3·6H_2O$ (2.0)	70	10	71
17	1:2	MeCN	$FeCl_3·6H_2O$ (2.0)	70	10	58
18	1:2	DCE	$FeCl_3·6H_2O$ (2.0)	80	10	85
19	1:2	DCE	$FeCl_3·6H_2O$ (2.0)	90	10	79
20	1:2	DCE	$FeCl_3·6H_2O$ (2.0)	80	12	81
21	1:2	DCE	$FeCl_3·6H_2O$ (2.0)	80	14	85
22	**1:2**	**DCE**	**$FeCl_3·6H_2O$ (2.0)**	**80**	**16**	**91**
23	1:2	DCE	$FeCl_3·6H_2O$ (2.0)	80	18	91

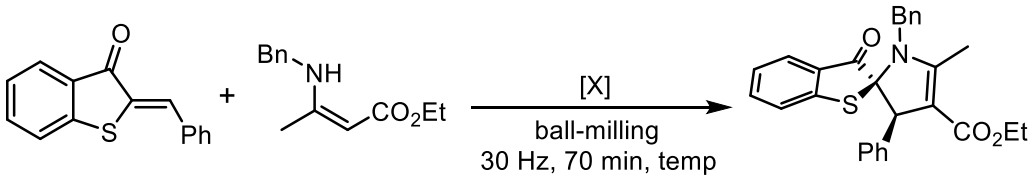
[a]Reaction conditions: a mixture of **5a** (0.2 mmol), **2a** (0.4 mmol), I_2 (20 mol%), $FeCl_3·6H_2O$ (0.4 mmol) and solvent (2 mL) was stirred at the given temperature. [b]Isolated yield based on **5a**.

3.2.1.2 产物 7 的条件优化

在成功完成硫代橙酮螺二氢呋喃化合物 **6aa** 的条件优化后，我们计划合成一种结构与 **6aa** 不同的硫代橙酮螺环化合物。考虑到硫代橙酮与 β-烯胺酯在溶剂中反应时，烯胺会发生水解反应。因此，我们计划使用无溶剂机械研磨或微量溶剂辅助研磨的方式探索是否能够合成目标产物 **7aa**，并最终在 NIS 促进下成功合成了硫代橙酮螺二氢吡咯化合物 **7aa**（entry 2），并通过单晶 X-射线衍射和核磁共振波谱确认。随后，我们着手进行反应条件的优化（Table 3-2）。将 **5a**（0.2 mmol）、**2a**（0.24 mmol）与不同的卤代试剂在球磨条件下反应 30 min，结果显示，除 NIS 外，其他卤代试剂未能生成任何产物，且当 NIS 的添加量为 1.2 当量时效果最为显著（entries 1–4）。我们进一步研究了不同助溶剂对反应的影响（entries 5–10），发现 CH_2Br_2 作助溶剂能得到最高的产率（entry 9）。在考察路易斯酸、碱及氧化剂对反应的影响时，我们发现在加入 DMAP 和 Na_2CO_3 后反应受到抑制（entries 11–12），而加入氧化剂后产物 **7aa** 完全消失（entry 13）。最终，在加入无水氯化铁作为路易斯酸后，反应得到促进，产率提高

（entry 14），并确定了无水氯化铁的最佳添加量为 0.5 当量，此条件下以 71%的收率得到产物 **7aa**（entry 15），但原料仍有部分剩余。为了进一步提高 **7aa** 的收率，我们尝试在研磨的同时使用数显热风枪对研磨罐进行加热。当热风枪的温度调整为 70 ℃时，**7aa** 的收率有所提高（entry 17）。随后我们尝试了不同温度下的反应，结果发现最佳温度为 100 ℃，此时产物 **7aa** 的收率为 91%（entry 20）。综上所述，合成硫代橙酮螺二氢吡咯化合物的最佳反应条件为：1 当量的硫代橙酮、1.2 当量的 β-烯胺酯、1.2 当量的 NIS 和 0.5 当量的无水 $FeCl_3$ 以 CH_2Br_2 为助溶剂，在显示 100 ºC 的数显热风枪加热下研磨 70 min（entry 20）。

Table 3-2. Optimization of the reaction conditions for the synthesis of 7aa[a]



5a **2a** **7aa**

Entry	[X] (equiv.)	LAG solvent (30 μL)	Additive (equiv.)	Temp (ºC)	Yield[b] (%)
1	I_2 (1.0)				0
2	NIS (1.0)				12
3	NBS (1.0)				trace
4	NIS (1.2)				18
5	NIS (1.2)	DCE			31
6	NIS (1.2)	DMSO			35
7	NIS (1.2)	toluene			29
8	NIS (1.2)	DCM			41
9	NIS (1.2)	CH_2Br_2			53
10	NIS (1.2)	MeCN			33
11	NIS (1.2)	CH_2Br_2	DMAP (1.0)		15
12	NIS (1.2)	CH_2Br_2	Na_2CO_3 (1.0)		33
13	NIS (1.2)	CH_2Br_2	$(NH_4)_2S_2O_8$ (1.0)		trace
14	NIS (1.2)	CH_2Br_2	$FeCl_3$ (1.0)		62
15	NIS (1.2)	CH_2Br_2	$FeCl_3$ (0.5)		71
16	NIS (1.2)	CH_2Br_2	$FeCl_3$ (1.5)		53

17	NIS (1.2)	CH_2Br_2	$FeCl_3$ (0.5)	70	76
18	NIS (1.2)	CH_2Br_2	$FeCl_3$ (0.5)	80	81
19	NIS (1.2)	CH_2Br_2	$FeCl_3$ (0.5)	90	86
20	**NIS (1.2)**	**CH_2Br_2**	**$FeCl_3$ (0.5)**	**100**	**91**
21	NIS (1.2)	CH_2Br_2	$FeCl_3$ (0.5)	110	87

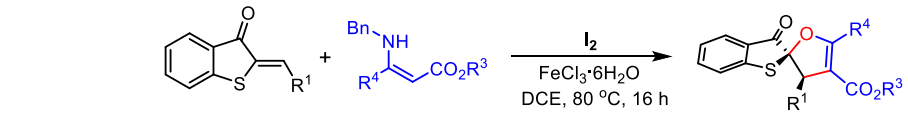
[a]For the reaction, a mixture of **5a** (0.2 mmol), **2a** (0.24 mmol), NIS (0.24 mmol), $FeCl_3$ (0.1 mmol) and four stainless balls (6 mm in diameter) was milled in a Retsch MM400 mixer mill at 30 Hz for 70 min. [b]Isolated yield based on **5a**.

3.2.2 底物扩展

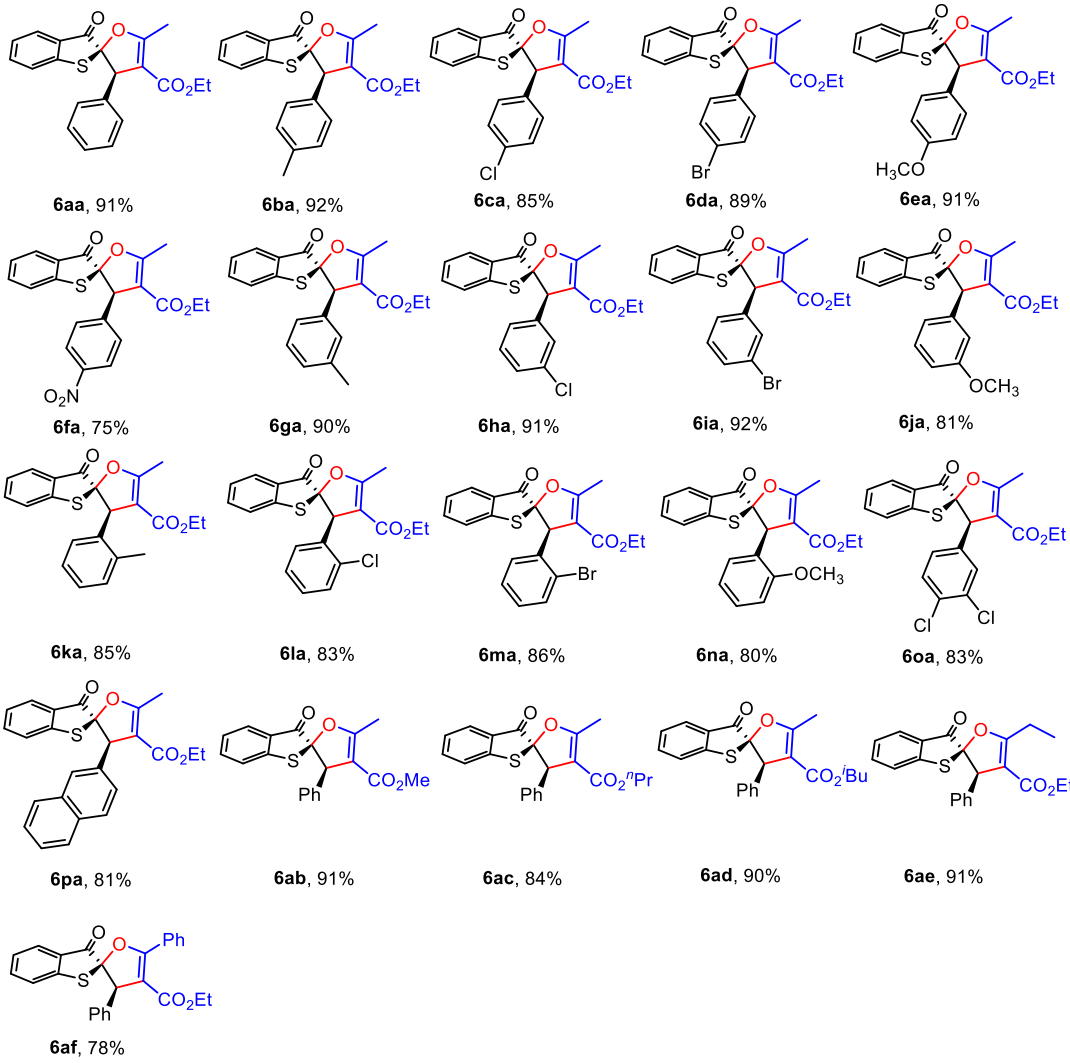
3.2.2.1 产物 6 的合成

在确定了合成硫代橙酮螺二氢呋喃化合物的最优反应条件之后，我们对该反应进行了一系列的底物普适性研究（Table 3-3）。通过使用不同取代基的硫代橙酮 **5** 和 β-烯胺酯 **2a** 进行反应，我们发现当硫代橙酮的 R^1 芳环上引入强吸电子基团时（NO_2），反应能够顺利进行，并以 75%的收率得到产物 **6fa**。当芳环对位上有强供电子基团（OCH_3）时，产物的收率不受影响，能以 91%的收率得到产物 **6ea**。对于 R^1 芳环对位连有卤素或其他常见基团时，反应仍能够顺利进行。随后，我们开始探究 R^1 芳环邻位和间位连有不同的取代基对反应的影响，发现硫代橙酮 **5** 仍然保持着良好的反应活性。总的来说，R^1 芳环的基团耐受性良好，能以 75–92%的收率合成产物 **6aa**–**pa**。接着，我们研究了硫代橙酮 **5a** 和不同基团取代的 β-烯胺酯 **2** 的反应效果。需要指出的是，除了异丙酯和叔丁酯取代的烯胺酯不能给出相应的产物外，其他基团取代的烯胺酯仍然可以得到相应产物。此外，当 R^2 基团为芳基和烷基时，该反应仍能高效进行。

Table 3-3. Selective synthesis of thioaurone-spirodihydrofurans 6 from thioaurones 5 and enamino esters 2[a,b]



5 2 6



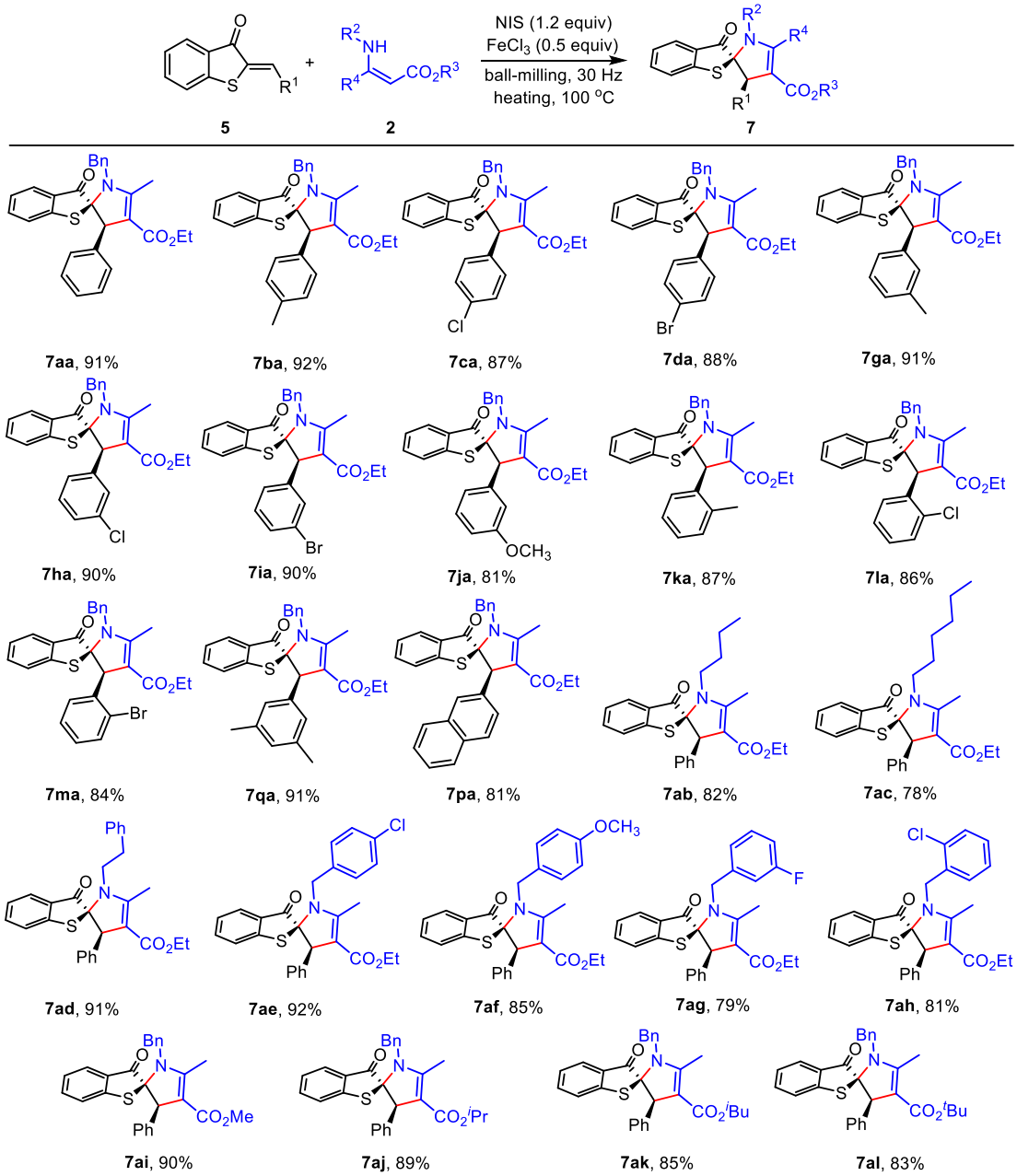
[a]Reaction conditions: a mixture of **5** (0.2 mmol), **2** (0.4 mmol), I_2 (0.04 mmol), $FeCl_3·6H_2O$ (0.4 mmol) and DCE (2 mL) was stirred at 80 ℃ in air for 16 h. [b]Isolated yields based on **5**.

3.2.2.2 产物 7 的合成

在确定了硫代橙酮螺二氢吡咯化合物的最佳反应条件后，我们展开了底物普适性研究（Table 3-4）。首先，我们通过改变硫代橙酮 **5** 芳环上的不同位置和电性的取代基来探究它们对反应结果的影响。当 R^1 中苯环上连有对位、间位或邻位取代基时，该反应都能顺利进行，并以优异的收率得到目标产物 **7ba–qa**。

这些实验结果表明位阻效应对该反应体系的影响不大。随后，我们探究了 β-烯胺酯 **2** 的底物范围。当烯胺酯 R^2 位置为烷基时，该反应仍能以优异的收率产生 **7ab** 和 **7ac**。此外，R^2 中的苯环上连有强供电子或强吸电子基团时，该反应依然能够顺利进行。最后，我们还考察了 R^3 上不同取代基的影响，发现无论是 ^{i}Pr、^{i}Bu 还是 ^{t}Bu 取代的底物，反应效果大致相同，从而得出结论，该位置的位阻效应对反应影响不大。

Table 3-4. Selective synthesis of thioaurone-spirodihydropyrroles 7 from thioaurones 5 and enamino esters 2[a,b]

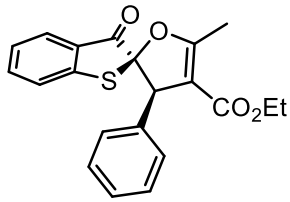


[a]Reaction conditions: a mixture of **5** (0.2 mmol), **2** (0.24 mmol), NIS (0.24 mmol), $FeCl_3$ (0.1

mmol), CH_2Br_2 (30 μL) and four stainless balls (6 mm in diameter) was milled in a Retsch MM400 mixer mill at 30 Hz for 70 min. [b]Isolated yields based on **5**.

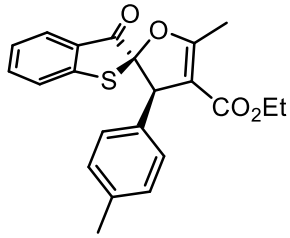
3.3 硫代橙酮螺环化合物的表征

Ethyl *cis*-5'-methyl-3-oxo-3'-phenyl-3*H*,3'*H*-spiro[benzo[b]thiophene-2,2'-furan]-4'-carboxylate (6aa).



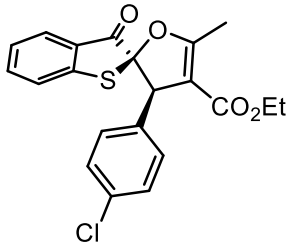
Ethyl acetate/petroleum ether = 1:8 as the eluent;Yellow solid, 91% yield (66.7 mg), dr = 91:9, mp 116–118 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (d, *J* = 7.6 Hz, 1H), 7.49 (t, *J* = 7.6 Hz, 1H), 7.31 (d, *J* = 7.1 Hz, 3H), 7.24–7.07 (m, 5H), 4.81 (s, 1H), 4.08–4.01 (m, 1H), 4.00–3.91 (m, 1H), 2.38 (s, 3H), 1.01 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.7, 166.7, 164.4, 149.7, 140.7, 137.1, 128.6 (2C), 128.3, 128.2, 127.9 (2C), 127.1, 125.9, 124.1, 108.8, 103.7, 59.8, 54.1, 14.2, 14.1; HRMS (ESI-TOF) calcd for $C_{21}H_{19}O_4S$ $[M + H]^+$ 367.1004, found 367.1011.

Ethyl *cis*-5'-methyl-3-oxo-3'-(*p*-tolyl)-3*H*,3'*H*-spiro[benzo[*b*]thiophene-2,2'-furan]-4'-carboxylate (6ba).



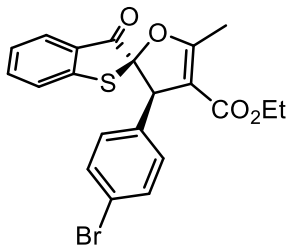
Ethyl acetate/petroleum ether = 1:8 as the eluent; Yellow solid, 92% yield (70.0 mg), dr = 97:3, mp 136–138 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (d, *J* = 7.4 Hz, 1H), 7.49 (t, *J* = 7.6 Hz, 1H), 7.20 (t, *J* = 7.5 Hz, 1H), 7.17–7.09 (m, 3H), 7.05 (d, *J* = 7.5 Hz, 2H), 4.76 (s, 1H), 4.08–4.02 (m, 1H), 4.01–3.95 (m, 1H), 2.37 (s, 3H), 2.34 (s, 3H), 1.04 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.8, 166.5, 164.5, 149.7, 137.7, 137.6, 137.0, 129.3 (2C), 127.9 (3C), 127.2, 125.8, 124.1, 108.9, 103.8, 59.8, 53.7, 21.4, 14.2, 14.1; HRMS (ESI-TOF) calcd for $C_{22}H_{21}O_4S$ $[M + H]^+$ 381.1161, found 381.1156.

Ethyl *cis*-3'-(4-chlorophenyl)-5'-methyl-3-oxo-3*H*,3'*H*-spiro[benzo[*b*]thiophene-2,2'-furan]-4'-carboxylate (6ca).



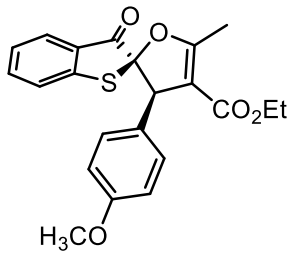
Ethyl acetate/petroleum ether = 1:8 as the eluent; Yellow solid, 85% yield (68.1 mg), dr > 99:1, mp 87–89 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (dd, J = 7.7, 0.7 Hz, 1H), 7.54–7.49 (m, 1H), 7.28 (d, J = 8.5 Hz, 2H), 7.25–7.20 (m, 1H), 7.15 (d, J = 7.9 Hz, 1H), 7.10 (d, J = 8.2 Hz, 2H), 4.79 (d, J = 1.6 Hz, 1H), 4.09–4.02 (m, 1H), 4.02–3.95 (m, 1H), 2.37 (d, J = 1.6 Hz, 3H), 1.05 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.5, 167.1, 164.2, 149.5, 139.1, 137.2, 133.7, 129.7, 128.8 (2C), 128.4, 128.0, 126.7, 126.0, 124.2, 108.4, 103.3, 60.0, 53.6, 14.2, 14.1; HRMS (ESI-TOF) calcd for $C_{21}H_{18}{}^{35}ClO_4S$ $[M + H]^+$ 401.0614, found 401.0619.

Ethyl *cis*-3'-(4-bromophenyl)-5'-methyl-3-oxo-3*H*,3'*H*-spiro[benzo[*b*]thiophene-2, 2'-furan]-4'-carboxylate (6da).



Ethyl acetate/petroleum ether = 1:8 as the eluent; Yellow solid, 89% yield (79.3 mg), dr > 99:1, mp 86–88 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (d, J = 8.2 Hz, 1H), 7.52 (td, J = 7.0, 1.3 Hz, 1H), 7.44 (d, J = 8.4 Hz, 2H), 7.22 (t, J = 7.2 Hz, 1H), 7.15 (d, J = 7.9 Hz, 1H), 7.04 (d, J = 8.1 Hz, 2H), 4.77 (s, 1H), 4.07–4.02 (m, 1H), 4.02–3.95 (m, 1H), 2.37 (s, 3H), 1.05 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.5, 167.1, 164.2, 149.4, 139.6, 137.2, 131.7 (2C), 131.3, 130.0, 128.0, 126.9, 126.0, 124.1, 121.8, 108.3, 103.1, 60.0, 53.7, 14.2, 14.1; HRMS (ESI-TOF) calcd for $C_{21}H_{18}{}^{79}BrO_4S$ $[M + H]^+$ 445.0109, found 445.0113.

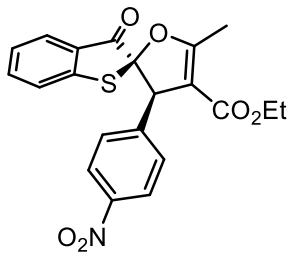
Ethyl *cis*-3'-(4-methoxyphenyl)-5'-methyl-3-oxo-3*H*,3'*H*-spiro[benzo[*b*]thiophene -2,2'-furan]-4'-carboxylate (6ea).



Ethyl acetate/petroleum ether = 1:6 as the eluent; Yellow solid, 91% yield (72.2 mg), dr > 99:1, mp 81–83 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 (d, J = 7.6 Hz, 1H), 7.49 (t, J = 7.6 Hz, 1H), 7.20 (t, J = 7.5 Hz, 1H), 7.14 (d, J = 7.9 Hz, 1H), 7.09 (d, J = 8.2 Hz, 2H), 6.84 (d, J = 8.4 Hz, 2H), 4.75 (s, 1H), 4.09–4.02 (m, 1H), 4.02–3.95 (m, 1H), 3.80 (s, 3H), 2.37 (s, 3H), 1.05 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.4, 189.2, 142.5, 141.0, 137.7, 135.6

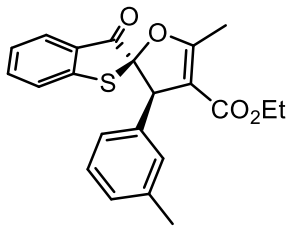
(2C), 135.4 (2C), 130.9, 129.2, 128.9, 128.0, 127.3, 123.4 (3C), 58.5, 52.4, 41.2, 21.5, 18.5; HRMS (ESI-TOF) calcd for $C_{22}H_{21}O_5S$ $[M + H]^+$ 397.1110, found 397.1105.

Ethyl *cis*-5'-methyl-3'-(4-nitrophenyl)-3-oxo-3*H*,3'*H*-spiro[benzo[*b*]thiophene-2,2'-furan]-4'-carboxylate (6fa).



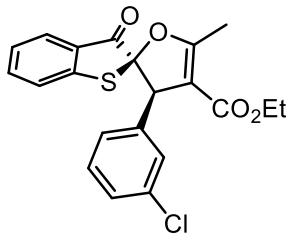
Ethyl acetate/petroleum ether = 1:4 as the eluent; Yellow solid, 75% yield (61.7 mg), dr > 99:1, mp 82–84 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.19 (d, J = 8.3 Hz, 2H), 7.80 (d, J = 7.7 Hz, 1H), 7.55 (t, J = 7.5 Hz, 1H), 7.35 (d, J = 8.2 Hz, 2H), 7.27 (d, J = 10.4 Hz, 1H), 7.16 (d, J = 7.8 Hz, 1H), 4.95 (s, 1H), 4.08–4.03 (m, 1H), 4.03–3.96 (m, 1H), 2.40 (s, 3H), 1.05 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.0, 167.9, 163.9, 149.0, 147.6, 147.5, 137.5, 129.3, 128.1, 126.6, 126.2, 124.1, 123.9 (2C), 123.4, 107.7, 102.3, 60.1, 54.1, 14.3, 14.1; HRMS (ESI-TOF) calcd for $C_{21}H_{18}NO_6S$ $[M + H]^+$ 412.0855, found 412.0859.

Ethyl *cis*-5'-methyl-3-oxo-3'-(*m*-tolyl)-3*H*,3'*H*-spiro[benzo[*b*]thiophene-2,2'-furan]-4'-carboxylate (6ga).



Ethyl acetate/petroleum ether = 1:8 as the eluent; Yellow solid, 90% yield (72.2 mg), dr = 96:4, mp 136–138 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (d, J = 7.1 Hz, 1H), 7.50 (td, J = 7.9, 1.3 Hz, 1H), 7.20 (td, J = 7.5, 2.4 Hz, 2H), 7.14 (d, J = 7.9 Hz, 1H), 7.10 (d, J = 7.5 Hz, 1H), 6.97 (s, 2H), 4.76 (d, J = 1.5 Hz, 1H), 4.06 (dq, J = 10.9, 7.1 Hz, 1H), 3.97 (dq, J = 10.8, 7.1 Hz, 1H), 2.38 (d, J = 1.5 Hz, 3H), 2.33 (s, 3H), 1.03 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.7, 166.6, 164.5, 149.8, 140.6, 138.2, 137.0, 128.7 (2C), 128.4, 127.9, 127.1, 125.8, 124.1 (2C), 108.9, 103.7, 59.8, 54.0, 21.6, 14.2, 14.1; HRMS (ESI-TOF) calcd for $C_{22}H_{21}O_4S$ $[M + H]^+$ 381.1161, found 381.1166.

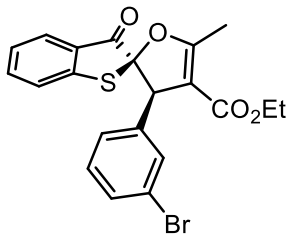
Ethyl *cis*-3'-(3-chlorophenyl)-5'-methyl-3-oxo-3*H*,3'*H*-spiro[benzo[*b*]thiophene-2,2'-furan]-4'-carboxylate (6ha).



Ethyl acetate/petroleum ether = 1:8 as the eluent; Yellow solid, 91% yield (73.0 mg), dr = 91:9, mp 128–130 °C; ^{1}H

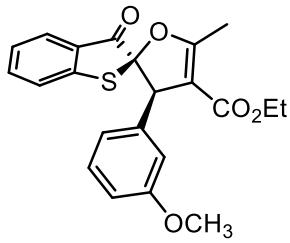
NMR (500 MHz, $CDCl_3$) δ 7.77 (d, J = 7.7 Hz, 1H), 7.52 (t, J = 7.6 Hz, 1H), 7.42 (d, J = 7.9 Hz, 1H), 7.31 (s, 1H), 7.22 (t, J = 7.5 Hz, 1H), 7.20–7.14 (m, 2H), 7.10 (d, J = 7.4 Hz, 1H), 4.76 (s, 1H), 4.08 (dq, J = 11.1, 7.3 Hz, 1H), 3.98 (dq, J = 10.8, 7.1 Hz, 1H), 2.38 (s, 3H), 1.05 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.4, 167.3, 164.1, 149.4, 142.9, 137.2, 131.0 (2C), 130.1, 128.0, 126.9, 126.0, 124.2 (2C), 122.7, 108.2, 103.1, 60.0, 53.8, 14.2, 14.1; HRMS (ESI-TOF) calcd for $C_{21}H_{18}{}^{35}ClO_4S$ $[M + H]^+$ 401.0614, found 401.0620.

Ethyl *cis*-3'-(3-bromophenyl)-5'-methyl-3-oxo-3*H*,3'*H*-spiro[benzo[*b*]thiophene-2,2'-furan]-4'-carboxylate (6ia).



Ethyl acetate/petroleum ether = 1:8 as the eluent; Yellow solid, 91% yield (81.0 mg), dr > 99:1, mp 99–101 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (d, J = 7.6 Hz, 1H), 7.52 (t, J = 7.5 Hz, 1H), 7.29–7.19 (m, 3H), 7.16 (d, J = 7.3 Hz, 2H), 7.06 (d, J = 6.4 Hz, 1H), 4.78 (s, 1H), 4.12–4.03 (m, 1H), 4.03–3.94 (m, 1H), 2.38 (s, 3H), 1.05 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.4, 167.3, 164.1, 149.4, 142.6, 137.2, 134.5, 129.9, 128.1 (2C), 128.0, 126.9, 126.0 (2C), 124.1, 108.2, 103.0, 59.9, 53.8, 14.2, 14.1; HRMS (ESI-TOF) calcd for $C_{21}H_{18}{}^{79}BrO_4S$ $[M + H]^+$ 445.0109, found 445.0113.

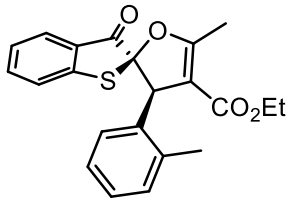
Ethyl *cis*-3'-(3-methoxyphenyl)-5'-methyl-3-oxo-3*H*,3'*H*-spiro[benzo[*b*]thiophene-2,2'-furan]-4'-carboxylate (6ja).



Ethyl acetate/petroleum ether = 1:6 as the eluent; Yellow solid, 81% yield (64.2 mg), dr > 99:1, mp 92–94 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (dd, J = 7.7, 0.7 Hz, 1H), 7.50 (td, J = 7.8, 1.3 Hz, 1H), 7.24 (d, J = 7.9 Hz, 1H), 7.22–7.18 (m, 1H), 7.14 (d, J = 7.9 Hz, 1H), 6.86–6.81 (m, 1H), 6.77 (d, J = 7.5 Hz, 1H), 6.70 (s, 1H), 4.77 (s, 1H), 4.06 (dq, J = 10.8, 7.1 Hz, 1H), 3.99 (dq, J = 10.8, 7.1 Hz, 1H), 3.78 (s, 3H), 2.37 (d, J = 1.6 Hz, 3H), 1.05 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.6, 166.7, 164.4, 159.8, 149.8, 142.3, 137.0, 129.6, 127.9, 127.1, 125.8, 124.1, 120.7, 113.9, 113.0, 108.6, 103.5, 59.8, 55.3, 54.0, 14.2, 14.1; HRMS (ESI-TOF) calcd for $C_{22}H_{21}O_5S$ $[M + H]^+$ 397.1110, found

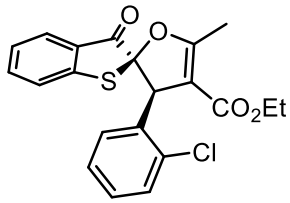
397.1105.

Ethyl *cis*-5'-methyl-3-oxo-3'-(*o*-tolyl)-3*H*,3'*H*-spiro[benzo[*b*]thiophene-2,2'-furan]-4'-carboxylate (6ka).



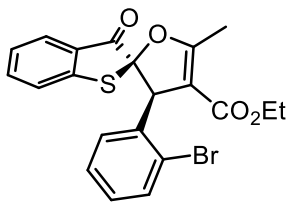
Ethyl acetate/petroleum ether = 1:8 as the eluent; Yellow soli d, 85% yield (64.7 mg), dr = 96:4, mp 101–103 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (ddd, J = 7.6, 1.2, 0.5 Hz, 1H), 7.5 1 (td, J = 8.3, 1.4 Hz, 1H), 7.24–7.16 (m, 4H),7.16–7.10 (m, 2H), 5.11 (q, J = 1.5 Hz, 1H), 4.07–4.01 (m, 1H), 4.01–3.94 (m, 1H), 2.39 (d, J = 1.6 Hz, 3H), 2.18 (s, 3H), 1.01 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.8, 166.6, 164.4, 150.0, 139.3, 137.1, 136.5, 130.2, 128.0, 127.6, 126.8 (2C), 126.3, 125.9, 124.2, 108.7, 103.6, 59.8, 49.0, 20.1, 14.1 (2C); HRMS (ESI-TOF) calcd for $C_{22}H_{21}O_4S$ $[M + H]^+$ 381.1161, found 381.1166.

Ethyl *cis*-3'-(2-chlorophenyl)-5'-methyl-3-oxo-3*H*,3'*H*-spiro[benzo[*b*]thiophene-2,2'-furan]-4'-carboxylate (6la).



Ethyl acetate/petroleum ether = 1:8 as the eluent; Yellow solid, 83% yield (66.5 mg), dr > 99:1, mp 111–113 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (dd, J = 7.7, 0.7 Hz, 1H), 7.54–7.49 (m, 2H), 7.30 (td, J = 8.0, 1.1 Hz, 1H), 7.26–7.19 (m, 2H), 7.17–7.13 (m, 2H), 5.42 (d, J = 1.6 Hz, 1H), 4.07 (dq, J = 10.7, 7.1 Hz, 1H), 3.98 (dq, J = 10.8, 7.1 Hz, 1H), 2.39 (s, 3H), 1.02 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.5, 167.6, 164.2, 150.0, 140.1, 137.0, 132.6, 129.2, 128.6, 128.0, 127.6, 126.6, 126.1, 125.9, 124.0, 107.0, 102.7, 59.9, 53.2, 14.2, 14.1; HRMS (ESI-TOF) calcd for $C_{21}H_{18}{}^{35}ClO_4S$ $[M + H]^+$ 401.0614, found 401.0613.

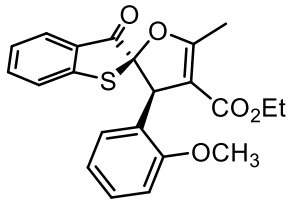
Ethyl *cis*-3'-(2-bromophenyl)-5'-methyl-3-oxo-3*H*,3'*H*-spiro[benzo[*b*]thiophene-2,2'-furan]-4'-carboxylate (6ma).



Ethyl acetate/petroleum ether = 1:8 as the eluent; Yellow solid, 86% yield (76.6 mg), dr = 96:4, mp 103–105 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (d, J = 7.7 Hz, 1H), 7.51 (t, J = 7.6 Hz, 1H), 7.33 (d, J = 7.1 Hz, 1H), 7.26–7.19 (m, 4H), 7.15 (d, J = 7.9 Hz, 1H), 5.44 (d, J = 1.5 Hz, 1H), 4.11–4.03 (m, 1H), 4.03–3.94 (m,

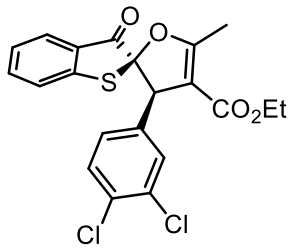
1H), 2.40 (d, *J* = 1.5 Hz, 3H), 1.04–0.99 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.5, 167.6, 164.2, 149.9, 138.3, 137.0, 135.1, 129.3, 128.9, 128.5, 128.0, 126.9, 126.5, 125.9, 124.0, 106.7, 102.8, 59.9, 50.6, 14.2, 14.1; HRMS (ESI-TOF) calcd for $C_{21}H_{18}{}^{79}BrO_4S$ $[M + H]^+$ 445.0109, found 445.0114.

Ethyl *cis*-3'-(2-methoxyphenyl)-5'-methyl-3-oxo-3*H*,3'*H*-spiro[benzo[*b*]thiophene-2,2'-furan]-4'-carboxylate (6na).



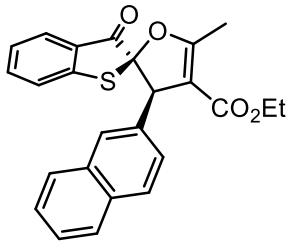
Ethyl acetate/petroleum ether = 1:6 as the eluent; Yellow solid, 80% yield (63.4 mg), dr > 99:1, mp 106–108 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (d, *J* = 7.5 Hz, 1H), 7.48 (t, *J* = 7.4 Hz, 1H), 7.25–7.15 (m, 2H), 7.11 (dd, *J* = 5.7, 2.0 Hz, 1H), 7.07 (d, *J* = 7.0 Hz, 1H), 6.92 (td, *J* = 8.3, 1.9 Hz, 1H), 6.73 (dd, *J* = 8.0, 1.7 Hz, 1H), 5.31 (s, 1H), 4.18–4.09 (m, 1H), 4.08–3.99 (m, 1H), 3.35 (d, *J* = 2.7 Hz, 3H), 2.37 (s, 3H), 1.07 (td, *J* = 8.4, 2.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.3, 167.1, 164.8, 157.5, 150.4, 136.6, 128.7, 128.5, 127.6, 127.4, 126.9, 125.4, 123.8, 120.2, 109.8, 105.7, 103.9, 59.8, 54.6, 48.8, 14.3, 14.2; HRMS (ESI-TOF) calcd for $C_{22}H_{21}O_5S$ $[M + H]^+$ 397.1110, found 397.1105.

Ethyl *cis*-3'-(3,4-dichlorophenyl)-5'-methyl-3-oxo-3*H*,3'*H*-spiro[benzo[*b*]thiophene-2,2'-furan]-4'-carboxylate (6oa).



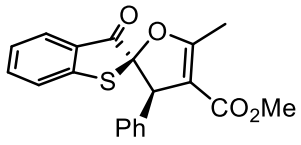
Ethyl acetate/petroleum ether = 1:8 as the eluent; Yellow solid, 83% yield (72.3 mg), dr = 96:4, mp 107–109 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (d, *J* = 7.7 Hz, 1H), 7.51 (t, *J* = 7.6 Hz, 1H), 7.39 (d, *J* = 8.2 Hz, 1H), 7.26–7.20 (m, 2H), 7.17 (d, *J* = 7.9 Hz, 1H), 7.01 (d, *J* = 7.9 Hz, 1H), 4.76 (s, 1H), 4.12–4.04 (m, 1H), 4.04–3.95 (m, 1H), 2.38 (s, 3H), 1.08 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.2, 167.6, 164.0, 149.2, 140.8, 137.3, 132.8, 131.9, 130.6, 130.1, 128.0, 127.4, 126.8, 126.1, 124.2, 107.9, 102.8, 60.1, 53.5, 14.3, 14.2; HRMS (ESI-TOF) calcd for $C_{21}H_{17}{}^{35}Cl_2O_4S$ $[M + H]^+$ 435.0225, found 435.0221.

Ethyl *cis*-5'-methyl-3'-(naphthalen-2-yl)-3-oxo-3*H*,3'*H*-spiro[benzo[*b*]thiophene-2,2'-furan]-4'-carboxylate (6pa).



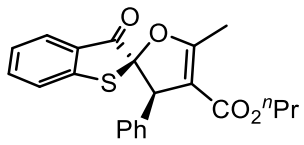
Ethyl acetate/petroleum ether = 1:8 as the eluent; Yellow solid, 81% yield (67.5 mg), dr = 97:3, mp 101–103 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86–7.73 (m, 4H), 7.62 (s, 1H), 7.52–7.39 (m, 3H), 7.30 (d, *J* = 8.0 Hz, 1H), 7.19 (td, *J* = 7.8, 0.7 Hz, 1H), 7.06 (d, *J* = 7.9 Hz, 1H), 4.99 (s, 1H), 4.02–3.97 (m, 1H), 3.97–3.91 (m, 1H), 2.43 (d, *J* = 1.4 Hz, 3H), 0.96 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.8, 166.9, 164.5, 149.8, 138.1, 137.1, 133.4, 133.1, 128.4, 128.1, 127.9(2C), 127.3, 127.0, 126.4, 126.1, 125.9(2C), 124.1, 108.7, 103.6, 59.9, 54.3, 14.3, 14.1; HRMS (ESI-TOF) calcd for $C_{25}H_{21}O_4S$ $[M + H]^+$ 417.1161, found 417.1158.

Methyl *cis*-5'-methyl-3-oxo-3'-phenyl-3*H*,3'*H*-spiro[benzo[*b*]thiophene-2,2'-furan]-4'-carboxylate (6ab).



Ethyl acetate/petroleum ether = 1:8 as the eluent; Yellow solid, 91% yield (64.1 mg), dr > 99:1, mp 138–140 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (dd, *J* = 7.7, 0.7 Hz, 1H), 7.50 (td, *J* = 8.3, 1.4 Hz, 1H), 7.34–7.28 (m, 3H), 7.21 (td, *J* = 7.9, 0.9 Hz, 1H), 7.18–7.15 (m, 2H), 7.13 (d, *J* = 7.9 Hz, 1H), 4.79 (d, *J* = 1.5 Hz, 1H), 3.56 (s, 3H), 2.38 (d, *J* = 1.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.6, 167.1, 164.8, 149.6, 140.5, 137.1, 128.7 (2C), 128.3, 128.2, 128.0, 127.9, 127.0, 125.9, 124.1, 108.5, 103.8, 53.9, 51.2, 14.2; HRMS (ESI-TOF) calcd for $C_{20}H_{17}O_4S$ $[M + H]^+$ 353.0848, found 353.0844.

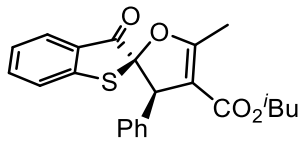
Propyl *cis*-5'-methyl-3-oxo-3'-phenyl-3*H*,3'*H*-spiro[benzo[*b*]thiophene-2,2'-furan]-4'-carboxylate (6ac).



Ethyl acetate/petroleum ether = 1:8 as the eluent; Yellow solid, 84% yield (63.9 mg), dr = 95:5, mp 94–96 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (dd, *J* = 7.7, 0.7 Hz, 1H), 7.50 (td, *J* = 7.9, 1.3 Hz, 1H), 7.35–7.28 (m, 3H), 7.21 (td, *J* = 7.9, 0.8 Hz, 1H), 7.17 (d, *J* = 6.2 Hz, 2H), 7.13 (d, *J* = 7.9 Hz, 1H), 4.81 (s, 1H), 3.98 (dt, *J* = 10.8, 6.6 Hz, 1H), 3.85 (dt, *J* = 10.8, 6.3 Hz, 1H), 2.39 (s, 3H), 1.44–1.34 (m, 2H), 0.64 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.7, 166.9, 164.6, 149.7, 140.7, 137.1,

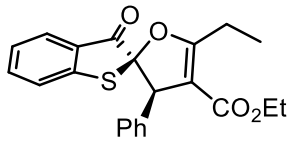
128.7 (2C), 128.3, 127.9 (3C), 127.1, 125.9, 124.2, 108.6, 103.8, 65.6, 54.1, 21.9, 14.2, 10.4; HRMS (ESI-TOF) calcd for $C_{22}H_{21}O_4S$ $[M + H]^+$ 381.1161, found 381.1166.

Isobutyl *cis*-5'-methyl-3-oxo-3'-phenyl-3*H*,3'*H*-spiro[benzo[*b*]thiophene-2,2'-furan]-4'-carboxylate (6ad).



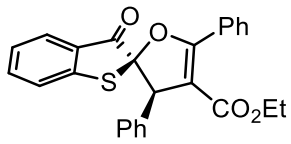
Ethyl acetate/petroleum ether = 1:8 as the eluent; Yellow solid, 90% yield (71.0 mg), dr > 99:1, mp 106–108 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (d, J = 7.6 Hz, 1H), 7.50 (td, J = 8.2, 1.2 Hz, 1H), 7.35–7.27 (m, 3H), 7.20 (t, J = 7.6 Hz, 1H), 7.17 (d, J = 6.9 Hz, 2H), 7.13 (d, J = 7.9 Hz, 1H), 4.82 (d, J = 1.4 Hz, 1H), 3.84 (dd, J = 10.6, 6.5 Hz, 1H), 3.66 (dd, J = 10.6, 6.1 Hz, 1H), 2.40 (d, J = 1.5 Hz, 3H), 1.70–1.60 (m, 1H), 0.64 (d, J = 2.3 Hz, 3H), 0.63 (d, J = 2.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.7, 167.1, 164.6, 149.7, 140.7, 137.1, 128.7 (2C), 128.3, 128.2, 127.9 (3C), 127.1, 125.9, 124.1, 108.5, 103.8, 54.0, 27.7, 19.0, 18.9, 14.2; HRMS (ESI-TOF) calcd for $C_{23}H_{23}O_4S$ $[M + H]^+$ 395.1317, found 395.1320.

Ethyl *cis*-5'-ethyl-3-oxo-3'-phenyl-3*H*,3'*H*-spiro[benzo[*b*]thiophene-2,2'-furan]-4'-carboxylate (6ae).



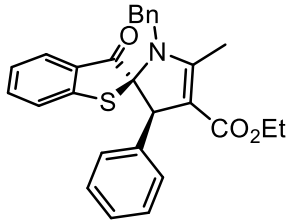
Ethyl acetate/petroleum ether = 1:8 as the eluent; Yellow solid, 91% yield (69.2 mg), dr > 99:1, mp 105–107 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (ddd, J = 7.7, 1.3, 0.5 Hz, 1H), 7.53–7.46 (m, 1H), 7.34–7.27 (m, 3H), 7.21 (td, J = 7.7, 0.9 Hz, 1H), 7.19–7.15 (m, 2H), 7.13 (d, J = 7.9 Hz, 1H), 4.77 (s, 1H), 4.04 (dq, J = 10.8, 7.1 Hz, 1H), 3.96 (dq, J = 10.8, 7.1 Hz, 1H), 2.88–2.77 (m, 2H), 1.22 (t, J = 7.6 Hz, 3H), 1.01 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.7, 171.6, 164.2, 149.8, 140.8, 137.0, 128.6 (2C), 128.3, 128.2, 127.9 (2C), 127.1, 125.8, 124.1, 107.9, 103.5, 59.7, 54.2, 21.3, 14.0, 11.3; HRMS (ESI-TOF) calcd for $C_{22}H_{21}O_4S$ $[M + H]^+$ 381.1161, found 381.1165.

Ethyl *cis*-3-oxo-3',5'-diphenyl-3*H*,3'*H*-spiro[benzo[*b*]thiophene-2,2'-furan]-4'-carboxylate (6af).



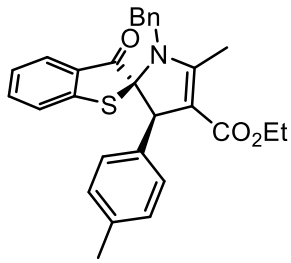
Ethyl acetate/petroleum ether = 1:8 as the eluent; Yellow solid, 78% yield (66.8 mg), dr > 99:1, mp 162–164 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87 (dd, J = 8.3, 1.4 Hz, 2H), 7.78 (dd, J = 7.7, 0.7 Hz, 1H), 7.48 (td, J = 7.8, 1.3 Hz, 1H), 7.43 (dt, J = 3.0, 2.3 Hz, 1H), 7.41–7.37 (m, 2H), 7.37–7.30 (m, 3H), 7.29–7.26 (m, 2H), 7.19 (td, J = 7.9, 0.8 Hz, 1H), 7.13 (d, J = 7.9 Hz, 1H), 5.03 (s, 1H), 4.03–3.97 (m, 1H), 3.97–3.91 (m, 1H), 0.94 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.6, 163.9, 163.6, 149.8, 140.6, 137.0, 131.0, 129.6 (2C), 128.7 (3C), 128.3 (2C), 128.0, 127.9, 127.8 (2C), 127.0, 125.8, 124.1, 108.9, 103.1, 60.1, 55.6, 13.8; HRMS (ESI-TOF) calcd for $C_{26}H_{21}O_4S$ $[M + H]^+$ 429.1161, found 429.1158.

Ethyl *cis*-1'-benzyl-5'-methyl-3-oxo-3'-phenyl-1',3'-dihydro-3*H*-spiro[benzo[*b*]thiophene-2,2'-pyrrole]-4'-carboxylate (7aa).



Ethyl acetate/petroleum ether = 1:4 as the eluent; Yellow solid, 91% yield (82.9 mg), dr > 99:1, mp 112–114 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 (d, J = 7.6 Hz, 1H), 7.41 (t, J = 7.6 Hz, 1H), 7.29–7.15 (m, 8H), 7.12–7.00 (m, 4H), 4.77 (d, J = 1.3 Hz, 1H), 4.37–4.26 (m, 2H), 3.98 (dq, J = 10.8, 7.1 Hz, 1H), 3.86 (dq, J = 10.8, 7.1 Hz, 1H), 2.32 (d, J = 1.3 Hz, 3H), 0.89 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.4, 166.0, 160.6, 151.3, 141.2, 137.6, 136.7 (2C), 128.6 (4C), 128.0 (2C), 127.5, 127.3, 127.1(3C), 125.1, 124.0, 102.8, 93.8, 58.8, 56.8, 48.6, 14.2, 13.4; HRMS (ESI-TOF) calcd for $C_{28}H_{26}NO_3S$ $[M + H]^+$ 456.1633, found 456.1639.

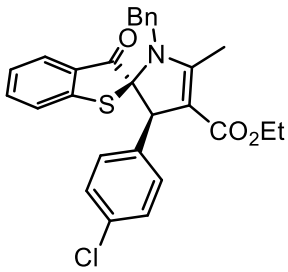
Ethyl *cis*-1'-benzyl-5'-methyl-3-oxo-3'-(*p*-tolyl)-1',3'-dihydro-3*H*-spiro[benzo[*b*]thiophene-2,2'-pyrrole]-4'-carboxylate (7ba).



Ethyl acetate/petroleum ether = 1:4 as the eluent; Yellow solid, 92% yield (86.4 mg), dr > 99:1, mp 101–103 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60–7.53 (m, 1H), 7.41 (td, J = 8.0, 1.2 Hz, 1H), 7.28–7.15 (m, 6H), 7.10–7.01 (m, 4H), 6.98 (bs, 2H), 4.72 (d, J = 1.2 Hz, 1H), 4.37–4.24 (m, 2H), 3.97 (dq, J = 10.8, 7.1 Hz, 1H), 3.88 (dq, J = 10.8, 7.1 Hz, 1H), 2.31 (d, J = 1.3 Hz, 3H), 2.30 (s, 3H), 0.93 (t, J = 7.1 Hz, 3H); ^{13}C NMR

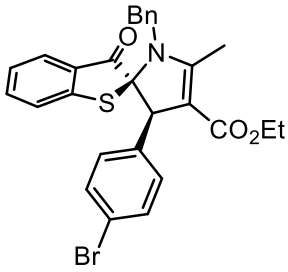
(125 MHz, $CDCl_3$) δ 200.5, 166.0, 160.3, 151.4, 138.3, 137.7, 136.6 (2C), 128.7 (2C), 128.6 (3C), 128.5 (2C), 127.5, 127.3, 127.1 (2C), 125.0, 124.0, 103.0, 93.9, 58.8, 56.3, 48.5, 21.3, 14.2, 13.4; HRMS (ESI-TOF) calcd for $C_{29}H_{28}NO_3S$ $[M + H]^+$ 470.1790, found 470.1783.

Ethyl *cis*-1'-benzyl-3'-(4-chlorophenyl)-5'-methyl-3-oxo-1',3'-dihydro-3*H*-spiro[benzo[*b*]thiophene-2,2'-pyrrole]-4'-carboxylate (7ca).



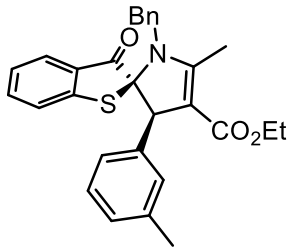
Ethyl acetate/petroleum ether = 1:4 as the eluent; Yellow solid, 87% yield (85.3 mg), dr > 99:1, mp 113–115 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 (d, J = 7.6 Hz, 1H), 7.44 (td, J = 7.6, 1.2 Hz, 1H), 7.32–7.14 (m, 8H), 7.10 (d, J = 7.5 Hz, 1H), 7.07 (d, J = 7.9 Hz, 1H), 7.02 (bs, 1H), 4.76 (d, J = 1.2 Hz, 1H), 4.31 (q, J = 16.6 Hz, 2H), 3.98 (dq, J = 10.8, 7.1 Hz, 1H), 3.89 (dq, J = 10.8, 7.1 Hz, 1H), 2.31 (d, J = 1.3 Hz, 3H), 0.93 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.2, 165.8, 160.9, 151.0, 139.4, 137.4, 136.9, 132.8, 130.1 (2C), 128.7 (2C), 128.6, 128.1 (2C), 127.6, 127.4, 127.1 (2C), 125.2, 124.1, 102.2, 93.5, 59.0, 56.3, 48.7, 14.2, 13.5; HRMS (ESI-TOF) calcd for $C_{28}H_{25}{}^{35}ClNO_3S$ $[M + H]^+$ 490.1244, found 490.1248.

Ethyl *cis*-1'-benzyl-3'-(4-bromophenyl)-5'-methyl-3-oxo-1',3'-dihydro-3*H*-spiro[benzo[*b*]thiophene-2,2'-pyrrole]-4'-carboxylate (7da).



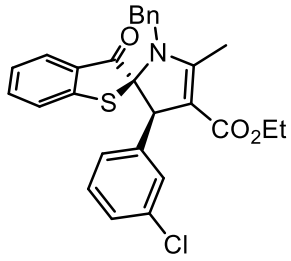
Ethyl acetate/petroleum ether = 1:4 as the eluent; Yellow solid, 88% yield (94.1 mg), dr > 99:1, mp 121–123 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 (d, J = 7.6 Hz, 1H), 7.43 (t, J = 7.5 Hz, 1H), 7.34 (d, J = 6.8 Hz, 2H), 7.29–7.20 (m, 3H), 7.17 (d, J = 7.2 Hz, 2H), 7.08 (dd, J = 14.7, 7.6 Hz, 2H), 6.96 (bs, 2H), 4.75 (s, 1H), 4.30 (q, J = 16.6 Hz, 2H), 4.03–3.94 (m, 1H), 3.93–3.83 (m, 1H), 2.31 (s, 3H), 0.93 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.1, 165.7, 160.9, 150.9, 139.9, 137.3, 136.9, 131.1 (2C), 130.4 (2C), 128.6 (2C), 128.5, 127.6, 127.3, 127.1 (2C), 125.2, 124.1, 120.9, 102.1, 93.4, 59.0, 56.4, 48.6, 14.2, 13.4; HRMS (ESI-TOF) calcd for $C_{28}H_{25}{}^{79}BrNO_3S$ $[M + H]^+$ 534.0739, found 534.0744.

Ethyl *cis*-1'-benzyl-5'-methyl-3-oxo-3'-(*m*-tolyl)-1',3'-dihydro-3*H*-spiro[benzo[*b*]thiophene-2,2'-pyrrole]-4'-carboxylate (7ga).



Ethyl acetate/petroleum ether = 1:4 as the eluent; Yellow solid, 91% yield (85.5 mg), dr > 99:1, mp 107–109 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 (d, J = 7.6 Hz, 1H), 7.41 (t, J = 7.1 Hz, 1H), 7.29–7.15 (m, 6H), 7.08 (d, J = 7.5 Hz, 1H), 7.06 (d, J = 7.9 Hz, 1H), 7.01 (d, J = 7.4 Hz, 1H), 6.90 (bs, 2H), 4.71 (s, 1H), 4.31 (s, 2H), 4.00 (dq, J = 10.8, 7.1 Hz, 1H), 3.87 (dq, J = 10.8, 7.1 Hz, 1H), 2.32 (s, 3H), 2.27 (s, 3H), 0.92 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.4, 166.0, 160.4, 151.4, 141.3, 137.8, 137.5, 136.6, 129.4, 125.7, 128.6 (3C), 127.9 (2C), 127.5, 127.3, 127.1 (2C), 125.0, 124.0, 103.0, 93.6, 58.8, 56.4, 48.4, 21.6, 14.2, 13.4; HRMS (ESI-TOF) calcd for $C_{29}H_{28}NO_3S$ $[M + H]^+$ 470.1790, found 470.1785.

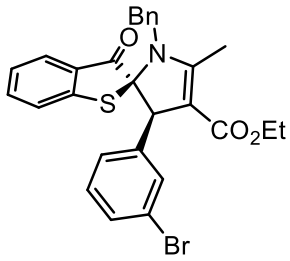
Ethyl *cis*-1'-benzyl-3'-(3-chlorophenyl)-5'-methyl-3-oxo-1',3'-dihydro-3*H*-spiro[benzo[*b*]thiophene-2,2'-pyrrole]-4'-carboxylate (7ha).



Ethyl acetate/petroleum ether = 1:4 as the eluent; Yellow solid, 90% yield (88.2 mg), dr > 99:1, mp 124–126 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 (d, J = 7.7 Hz, 1H), 7.43 (t, J = 7.6 Hz, 1H), 7.33–7.19 (m, 4H), 7.17 (d, J = 7.4 Hz, 3H), 7.08 (dd, J = 15.2, 7.7 Hz, 3H), 6.96 (bs, 1H), 4.74 (s, 1H), 4.31 (q, J = 16.6 Hz, 2H), 4.02 (dq, J = 10.8, 7.1 Hz, 1H), 3.87 (dq, J = 10.8, 7.1 Hz, 1H), 2.33 (d, J = 1.0 Hz, 3H), 0.93 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.0, 165.7, 161.0, 150.9, 143.1, 137.3, 136.8, 133.9, 129.2, 128.8, 128.6 (2C), 128.5, 127.6, 127.3 (2C), 127.1 (2C), 126.8, 125.2, 124.0, 102.0, 93.1, 58.9, 56.4, 48.5, 14.2, 13.4; HRMS (ESI-TOF) calcd for $C_{28}H_{25}{}^{35}ClNO_3S$ $[M + H]^+$ 490.1244, found 490.1241.

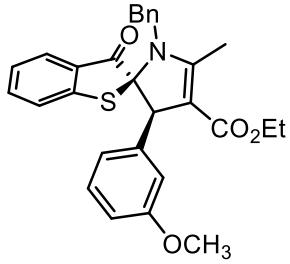
Ethyl *cis*-1'-benzyl-3'-(3-bromophenyl)-5'-methyl-3-oxo-1',3'-dihydro-3*H*-spiro[benzo[*b*]thiophene-2,2'-pyrrole]-4'-carboxylate (7ia).

Ethyl acetate/petroleum ether = 1:4 as the eluent; Yellow solid, 90% yield (96.2 mg), dr > 99:1, mp 134–136 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 (d, J = 7.7 Hz, 1H),



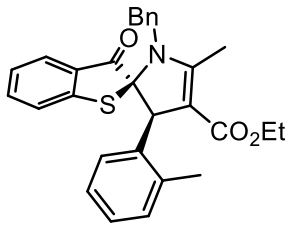
7.43 (t, *J* = 7.3 Hz, 1H), 7.32 (d, *J* = 7.7 Hz, 1H), 7.29–7.13 (m, 6H), 7.08 (dd, *J* = 15.1, 7.7 Hz, 3H), 7.00 (bs, 1H), 4.72 (s, 1H), 4.31 (q, *J* = 16.6 Hz, 2H), 4.02 (dq, *J* = 14.2, 7.1 Hz, 1H), 3.87 (dq, *J* = 10.9, 7.1 Hz, 1H), 2.32 (s, 3H), 0.93 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.0, 165.7, 161.0, 150.9, 143.4, 137.3, 136.8, 131.7, 130.2, 129.5, 128.6 (2C), 128.5, 127.6, 127.3 (2C), 127.1 (2C), 125.2, 124.1, 122.1, 102.0, 93.1, 58.9, 56.4, 48.5, 14.2, 13.4; HRMS (ESI-TOF) calcd for $C_{28}H_{25}{}^{79}BrNO_3S$ $[M + H]^+$ 534.0739, found 534.0744.

Ethyl *cis*-1'-benzyl-3'-(3-methoxyphenyl)-5'-methyl-3-oxo-1',3'-dihydro-3*H*-spiro [benzo[*b*]thiophene-2,2'-pyrrole]-4'-carboxylate (7ja).



Ethyl acetate/petroleum ether = 1:3 as the eluent; Yellow solid, 81% yield (78.7 mg), dr > 99:1, mp 103–105 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 (d, *J* = 7.6 Hz, 1H), 7.42 (t, *J* = 7.5 Hz, 1H), 7.32-7.12 (m, 6H),7.11–7.03 (m, 2H), 6.76 (dd, *J* = 8.0, 1.5 Hz, 1H), 6.68 (d, *J* = 38.7 Hz, 2H), 4.72 (s, 1H), 4.31 (s, 2H), 3.99 (dq, *J* = 10.8, 7.1 Hz, 1H) , 3.89 (td, *J* = 14.1, 7.1 Hz, 1H), 3.72 (s, 3H), 2.32 (s, 3H), 0.94 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.4, 165.9, 160.5, 159.4, 151.5, 143.0, 137.6, 136.7, 129.0, 128.6 (2C), 128.5, 127.5, 127.3, 127.1 (2C), 125.1, 124.0, 121.0, 114.1, 112.6, 102.6, 93.4, 58.9, 56.5, 55.2, 48.4, 14.2, 13.4; HRMS (ESI-TOF) calcd for $C_{29}H_{28}NO_4S$ $[M + H]^+$ 486.1739, found 486.1744.

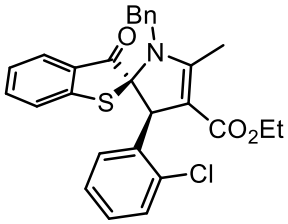
Ethyl *cis*-1'-benzyl-5'-methyl-3-oxo-3'-(*o*-tolyl)-1',3'-dihydro-3*H*-spiro[benzo[*b*]t hiophene-2,2'-pyrrole]-4'-carboxylate (7ka).



Ethyl acetate/petroleum ether = 1:4 as the eluent; Yellow solid, 87% yield (81.7 mg), dr > 99:1, mp 114–116 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 (d, *J* = 7.6 Hz, 1H), 7.43 (t, *J* = 7.6 Hz, 1H), 7.28–7.17 (m, 5H), 7.16–7.03 (m, 6H), 4.96 (s, 1H), 4.36 (d, *J* = 16.6 Hz, 1H), 4.26 (d, *J* = 16.7 Hz, 1H), 3.93 (dq, *J* = 10.7, 7.1 Hz, 1H), 3.85 (dq, *J* = 10.8, 7.1 Hz, 1H), 2.36 (s, 3H), 2.07 (s, 3H), 0.88 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.5, 165.8, 160.2, 151.5, 140.9, 137.8, 136.7, 136.5, 129.8, 128.6 (2C), 127.8, 127.5, 127.4 (2C), 126.9 (3C), 126.1, 125.2, 123.9,

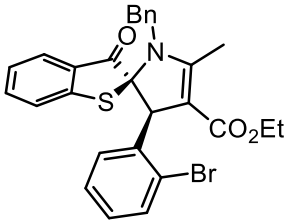
103.2, 92.5, 58.7, 50.5, 47.8, 20.1, 14.1, 13.4; HRMS (ESI-TOF) calcd for $C_{29}H_{28}NO_3S$ $[M + H]^+$ 470.1790, found 470.1797.

Ethyl *cis*-1'-benzyl-3'-(2-chlorophenyl)-5'-methyl-3-oxo-1',3'-dihydro-3*H*-spiro[benzo[*b*]thiophene-2,2'-pyrrole]-4'-carboxylate (7la).



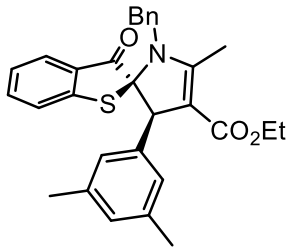
Ethyl acetate/petroleum ether = 1:4 as the eluent; Yellow solid, 86% yield (84.3 mg), dr > 99:1, mp 101–103 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59 (d, J = 7.7 Hz, 1H), 7.43 (t, J = 7.4 Hz, 1H), 7.30 (d, J = 7.6 Hz, 1H), 7.26-7.21 (m, 4H), 7.20–7.11 (m, 4H), 7.08 (t, J = 8.2 Hz, 2H), 5.31 (s, 1H), 4.36 (d, J = 16.8 Hz, 1H), 4.26 (d, J = 16.8 Hz, 1H), 3.96 (dq, J = 10.9, 7.1 Hz, 1H), 3.85 (dq, J = 10.8, 7.1 Hz, 1H), 2.35 (s, 3H), 0.88 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.2, 165.7, 161.1, 151.2, 139.8, 137.6, 136.6, 135.2, 129.5, 129.0, 128.6 (2C), 128.2, 128.0, 127.5, 127.4, 126.9 (2C), 126.7, 125.3, 123.8, 101.2, 91.8, 58.8, 52.0, 48.0, 14.1, 13.5; HRMS (ESI-TOF) calcd for $C_{28}H_{25}{}^{35}ClNO_3S$ $[M + H]^+$ 490.1244, found 490.1251.

Ethyl *cis*-1'-benzyl-3'-(2-bromophenyl)-5'-methyl-3-oxo-1',3'-dihydro-3*H*-spiro[benzo[*b*]thiophene-2,2'-pyrrole]-4'-carboxylate (7ma).



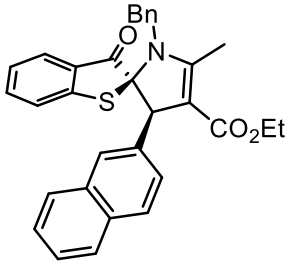
Ethyl acetate/petroleum ether = 1:4 as the eluent; Yellow solid, 84% yield (89.8 mg), dr > 99:1, mp 95–97 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 (d, J = 7.5 Hz, 1H), 7.46 (t, J = 7.7 Hz, 2H), 7.31–7.28 (m, 2H), 7.25–7.19 (m, 3H), 7.12 (t, J = 6.6 Hz, 3H), 7.09 (dd, J = 7.8, 3.2 Hz, 2H), 5.28 (d, J = 1.2 Hz, 1H), 4.37 (d, J = 16.8 Hz, 1H), 4.24 (d, J = 16.8 Hz, 1H), 3.95 (dq, J = 10.8, 7.1 Hz, 1H), 3.85 (dq, J = 10.8, 7.1 Hz, 1H), 2.35 (d, J = 1.1 Hz, 3H), 0.88 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.1, 165.6, 161.1, 151.3, 141.7, 137.7, 136.6, 132.3, 129.5, 128.6 (2C), 128.5, 128.1, 127.5, 127.4 (2C), 126.8 (2C), 126.3, 125.3, 123.8, 101.6, 91.6, 58.8, 54.5, 47.9, 14.1, 13.5; HRMS (ESI-TOF) calcd for $C_{28}H_{25}{}^{79}BrNO_3S$ $[M + H]^+$ 534.0739, found 534.0733.

Ethyl *cis*-1'-benzyl-3'-(3,5-dimethylphenyl)-5'-methyl-3-oxo-1',3'-dihydro-3*H*-spiro[benzo[*b*]thiophene-2,2'-pyrrole]-4'-carboxylate (7qa).



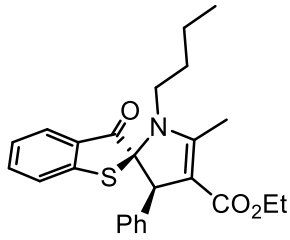
Ethyl acetate/petroleum ether = 1:4 as the eluent; Yellow solid, 91% yield (88.0 mg), dr > 99:1, mp 115–117 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 (d, J = 8.1 Hz, 1H), 7.41 (t, J = 7.6 Hz, 1H), 7.29–7.14 (m, 5H), 7.07 (t, J = 7.3 Hz, 2H), 6.84 (s, 1H), 6.71 (bs, 2H), 4.64 (s, 1H), 4.31 (s, 2H), 4.02 (dq, J = 10.9, 7.1 Hz, 1H), 3.87 (dq, J = 10.9, 7.1 Hz, 1H), 2.32 (s, 3H), 2.24 (s, 6H), 0.94 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.5, 166.1, 160.2, 151.5, 141.4, 137.8, 137.3 (2C), 136.6 (2C), 128.8, 128.6 (3C), 127.5, 127.3, 127.1 (4C), 125.0, 124.0, 103.1, 93.4, 58.8, 56.1, 48.2, 21.5, 14.2, 13.4; HRMS (ESI-TOF) calcd for $C_{30}H_{30}NO_3S$ $[M + H]^+$ 484.1946, found 484.1951.

Ethyl *cis*-1'-benzyl-5'-methyl-3'-(naphthalen-2-yl)-3-oxo-1',3'-dihydro-3*H*-spiro [benzo[*b*]thiophene-2,2'-pyrrole]-4'-carboxylate (7pa).



Ethyl acetate/petroleum ether = 1:4 as the eluent; Yellow solid, 81% yield (81.9 mg), dr > 99:1, mp 151–153 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81–7.77 (m, 1H), 7.72 (bs, 2H), 7.59 (d, J = 7.7 Hz, 1H), 7.50 (bs, 1H), 7.41 (dd, J = 5.6, 2.8 Hz, 2H), 7.36 (t, J = 7.5 Hz, 1H), 7.31–7.14 (m, 6H), 7.06 (t, J = 7.4 Hz, 1H), 6.96 (d, J = 7.9 Hz, 1H), 4.95 (s, 1H), 4.34 (q, J = 16.6 Hz, 2H), 3.98–3.88 (m, 1H), 3.88–3.79 (m, 1H), 2.37 (s, 3H), 0.82 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.4, 166.0, 160.8, 151.3, 138.7, 137.6, 136.7, 133.3, 132.8, 128.7 (2C), 128.5, 128.1, 127.7, 127.6 (2C), 127.3 (2C), 127.2 (3C), 125.9, 125.6, 125.1, 124.1, 102.7, 93.6, 58.9, 56.8, 48.5, 14.2, 13.5; HRMS (ESI-TOF) calcd for $C_{32}H_{28}NO_3S$ $[M + H]^+$ 506.1790, found 506.1796.

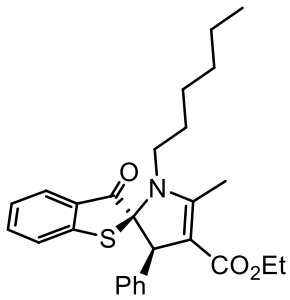
Ethyl *cis*-1'-butyl-5'-methyl-3-oxo-3'-phenyl-1',3'-dihydro-3*H*-spiro[benzo[*b*]thio phene-2,2'-pyrrole]-4'-carboxylate (7ab).



Ethyl acetate/petroleum ether = 1:8 as the eluent; Yellow solid, 82% yield (69.1 mg), dr > 99:1, mp 72–74 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (d, J = 7.7 Hz, 1H), 7.45 (t, J = 7.6 Hz, 1H), 7.22–7.12 (m, 4H), 7.08 (d, J = 7.9 Hz, 1H),

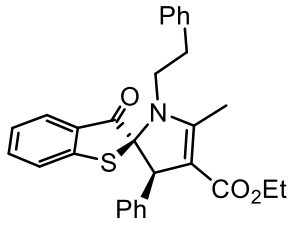
7.01 (bs, 2H), 4.67 (s, 1H), 4.01–3.92 (m, 1H), 3.89–3.79 (m, 1H), 3.17–3.08 (m, 1H), 3.08–2.99 (m, 1H), 2.46 (s, 3H), 1.59–1.50 (m, 1H), 1.45–1.36 (m, 1H), 1.23–1.12 (m, 2H), 0.87 (t, *J* = 7.1 Hz, 3H), 0.80 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.3, 166.1, 160.5, 151.7, 141.2, 136.8, 128.7 (2C), 127.8 (2C), 127.3, 127.0, 125.1, 124.1, 101.4, 93.7, 58.7, 57.2, 44.7, 32.9, 20.3, 14.2, 13.7, 12.9; HRMS (ESI-TOF) calcd for $C_{25}H_{28}NO_3S$ $[M + H]^+$ 422.1790, found 422.1796.

Ethyl *cis*-1'-hexyl-5'-methyl-3-oxo-3'-phenyl-1',3'-dihydro-3*H*-spiro[benzo[*b*]thiophene-2,2'-pyrrole]-4'-carboxylate (7ac).



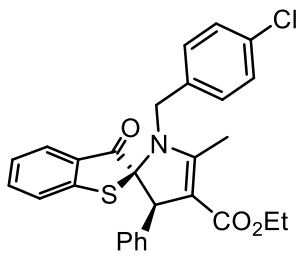
Ethyl acetate/petroleum ether = 1:8 as the eluent;Yellow solid, 78% yield (70.1 mg), dr > 99:1, mp 52–54 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 (dd, *J* = 7.7, 0.7 Hz, 1H), 7.45 (td, *J* = 6.9, 1.4 Hz, 1H), 7.22–7.12 (m, 4H), 7.07 (d, *J* = 7.9 Hz, 1H), 7.01 (bs, 2H), 4.67 (d, *J* = 1.4 Hz, 1H), 3.96 (dq, *J* = 10.8, 7.1 Hz, 1H), 3.84 (dq, *J* = 10.8, 7.1 Hz, 1H), 3.19-3.08 (m, 1H), 3.07–2.96 (m, 1H), 2.46 (d, *J* = 1.4 Hz, 3H), 1.59–1.49 (m, 1H), 1.48–1.36 (m, 1H), 1.23–1.10 (m, 6H), 0.87 (t, *J* = 7.1 Hz, 3H), 0.81 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.3, 166.1, 160.5, 151.7, 141.2, 136.8, 128.7 (3C), 127.8 (2C), 127.3, 127.0, 125.1, 124.1, 101.4, 93.6, 58.7, 57.1, 44.9, 31.3, 30.7, 26.7, 22.5, 14.2, 14.1, 12.9; HRMS (ESI-TOF) calcd for $C_{27}H_{32}NO_3S$ $[M + H]^+$ 450.2103, found 450.2109.

Ethyl *cis*-5'-methyl-3-oxo-1'-phenethyl-3'-phenyl-1',3'-dihydro-3*H*-spiro[benzo[*b*]thiophene-2,2'-pyrrole]-4'-carboxylate (7ad).



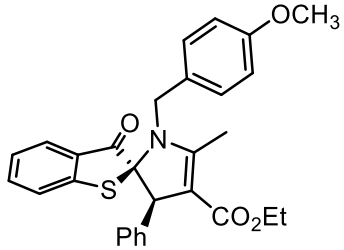
Ethyl acetate/petroleum ether = 1:4 as the eluent; Yellow solid, 92% yield (86.4 mg), dr > 99:1, mp 121–123 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (dd, *J* = 7.7, 0.6 Hz, 1H), 7.48 (t, *J* = 7.0, 1.3 Hz, 1H), 7.23 (t, *J* = 7.3 Hz, 2H), 7.21–7.14 (m, 5H), 7.10 (d, *J* = 7.9 Hz, 1H), 7.07–6.96 (m, 4H), 4.72 (d, *J* = 1.0 Hz, 1H), 3.97 (dq, *J* = 10.8, 7.1 Hz, 1H), 3.84 (dq, *J* = 10.8, 7.1 Hz, 1H), 3.44–3.34 (m, 1H), 3.31–3.22 (m, 1H), 2.84 (ddd, *J* = 13.4, 10.1, 6.3 Hz, 1H), 2.71 (ddd, *J* = 13.4, 10.1, 5.4 Hz, 1H), 2.35 (d, *J* = 1.4 Hz, 3H), 0.88 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.3,

166.0, 160.2, 151.7, 141.1, 138.5, 136.9, 128.8 (3C), 128.7 (4C), 127.9 (2C), 127.4, 127.1, 126.8, 125.3, 124.2, 101.7, 93.6, 58.8, 57.0, 46.6, 37.3, 14.2, 12.7; HRMS (ESI-TOF) calcd for $C_{29}H_{28}NO_3S$ $[M + H]^+$ 470.1790, found 470.1797. **Ethyl *cis*-1'-(4-chlorobenzyl)-5'-methyl-3-oxo-3'-phenyl-1',3'-dihydro-3*H*-spiro[benzo[*b*]thiophene-2,2'-pyrrole]-4'-carboxylate (7ae).**



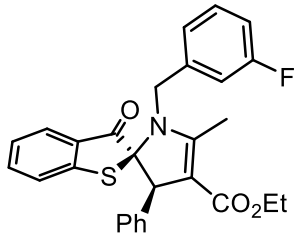
Ethyl acetate/petroleum ether = 1:4 as the eluent; Yellow solid, 92% yield (90.2 mg), dr > 99:1, mp 132–134 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 (d, J = 7.7 Hz, 1H), 7.14 (td, J = 7.1, 1.0 Hz, 1H), 7.21 (d, J = 8.4 Hz, 5H), 7.14–7.01 (m, 6H), 4.77 (d, J = 1.3 Hz, 1H), 4.28 (q, J = 16.7 Hz, 2H), 3.98 (dq, J = 10.8, 7.1 Hz, 1H), 3.86 (dq, J = 10.8, 7.1 Hz, 1H), 2.32 (d, J = 1.3 Hz, 3H), 0.89 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.4, 165.9, 160.1, 151.1, 140.9, 136.8, 136.0, 133.3, 128.7 (2C), 128.6, 128.6 (4C), 128.0 (2C), 127.3, 127.1, 125.1, 124.0, 103.0, 93.7, 58.9, 56.9, 48.0, 14.1, 13.3; HRMS (ESI-TOF) calcd for $C_{28}H_{25}{}^{35}ClNO_3S$ $[M + H]^+$ 490.1244, found 490.1238.

Ethyl *cis*-1'-(4-methoxybenzyl)-5'-methyl-3-oxo-3'-phenyl-1',3'-dihydro-3*H*-spiro[benzo[*b*]thiophene-2,2'-pyrrole]-4'-carboxylate (7af).



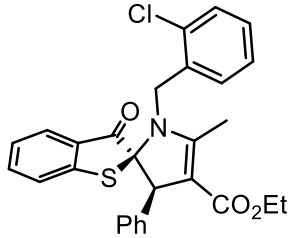
Ethyl acetate/petroleum ether = 1:3 as the eluent; Yellow solid, 85% yield (82.6 mg), dr > 99:1, mp 129–131 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 (d, J = 7.7 Hz, 1H), 7.40 (t, J = 7.5 Hz, 1H), 7.20 (s, 3H), 7.16–6.95 (m, 6H), 6.75 (d, J = 8.4 Hz, 2H), 4.75 (s, 1H), 4.31 (d, J = 16.2 Hz, 1H), 4.23 (d, J = 16.2 Hz, 1H), 4.03–3.92 (m, 1H), 3.90–3.82 (m, 1H), 3.77 (s, 3H), 2.34 (s, 3H), 0.88 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.5, 166.0, 160.6, 159.0, 151.2, 141.2, 136.6, 129.3, 128.7(2C), 128.6(3C), 127.9(2C), 127.2, 127.1, 124.9, 124.0, 113.9, 102.6, 93.7, 58.8, 56.9, 55.4, 48.0, 14.1, 13.4; HRMS (ESI-TOF) calcd for $C_{29}H_{28}NO_4S$ $[M + H]^+$ 486.1739, found 486.1745.

Ethyl *cis*-1'-(3-fluorobenzyl)-5'-methyl-3-oxo-3'-phenyl-1',3'-dihydro-3*H*-spiro[benzo[*b*]thiophene-2,2'-pyrrole]-4'-carboxylate (7ag).



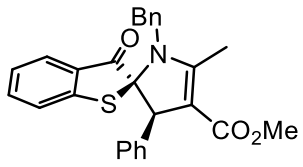
Ethyl acetate/petroleum ether = 1:3 as the eluent;Yellow solid, 79% yield (74.8 mg), dr > 99:1, mp 124–126 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 (d, J = 7.7 Hz, 1H), 7.42 (t, J = 7.6 Hz, 1H), 7.26-7.17 (m, 4H), 7.14–7.03 (m, 4H), 6.98 (d, J = 7.6 Hz, 1H), 6.91 (t, J = 8.3 Hz, 2H), 4.77 (s, 1H), 4.29 (s, 2H), 3.98 (dq, J = 10.8, 7.1 Hz, 1H), 3.86 (dq, J = 10.8, 7.1 Hz, 1H), 2.32 (s, 3H), 0.89 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.3, 165.9, 163.0 (d, J = 245.0 Hz), 160.1, 151.2, 141.0, 140.5, 140.4, 136.8, 130.2 (d, J = 8.2 Hz), 128.7, 128.5, 128.0 (2C), 127.3, 127.2, 125.2, 124.1, 122.6 (d, J = 2.7 Hz), 114.5 (d, J = 21.0 Hz), 114.1 (d, J = 22.0 Hz), 103.1, 93.7, 58.9, 56.7, 48.1, 14.1, 13.3; HRMS (ESI-TOF) calcd for $C_{28}H_{25}FNO_3S$ $[M + H]^+$ 474.1539, found 474.1544.

Ethyl *cis*-1'-(2-chlorobenzyl)-5'-methyl-3-oxo-3'-phenyl-1',3'-dihydro-3*H*-spiro[benzo[*b*]thiophene-2,2'-pyrrole]-4'-carboxylate (7ah).



Ethyl acetate/petroleum ether = 1:4 as the eluent; Yellow solid, 81% yield (79.4 mg), dr > 99:1, mp 107–109 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 (d, J = 7.7 Hz, 1H), 7.44–7.36 (m, 2H), 7.30–7.14 (m, 6H), 7.14–6.83 (m, 4H), 4.83 (s, 1H), 4.47 (d, J = 17.5 Hz, 1H), 4.36 (d, J = 17.5 Hz, 1H), 3.99 (dq, J = 10.8, 7.1 Hz, 1H), 3.87 (dq, J = 10.8, 7.1 Hz, 1H), 2.33 (d, J = 1.3 Hz, 3H), 0.89 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.2, 165.9, 160.2, 151.2, 140.7, 136.7, 134.8, 132.4, 129.4, 128.7 (4C), 128.5, 127.9 (2C), 127.2, 127.1, 127.0, 125.1, 124.1, 102.6, 93.6, 58.9, 57.0, 45.8, 14.1, 12.9; HRMS (ESI-TOF) calcd for $C_{28}H_{25}{}^{35}ClNO_3S$ $[M + H]^+$ 490.1244, found 490.1249.

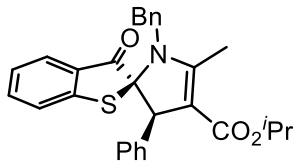
Methyl *cis*-1'-benzyl-5'-methyl-3-oxo-3'-phenyl-1',3'-dihydro-3*H*-spiro[benzo[*b*]thiophene-2,2'-pyrrole]-4'-carboxylate (7ai).



Ethyl acetate/petroleum ether = 1:4 as the eluent; Yellow solid, 90% yield (79.5 mg), dr > 99:1, mp 115–117 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 (d, J = 7.7 Hz, 1H), 7.40 (t, J = 7.6 Hz, 1H), 7.28–7.20 (m, 6H), 7.17 (d, J = 7.3 Hz, 2H), 7.08 (t, J = 7.5 Hz, 3H), 7.04 (d, J = 8.0 Hz, 1H), 4.75 (s, 1H), 4.31 (s, 2H), 3.45 (s, 3H), 2.32 (s, 3H); ^{13}C

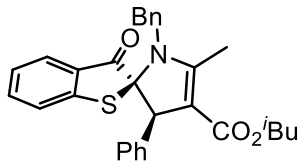
NMR (125 MHz, $CDCl_3$) δ 200.2, 166.4, 160.9, 151.2, 141.1, 137.6, 136.7 (2C), 128.6 (2C), 128.5 (2C), 128.1 (2C), 127.5, 127.3, 127.2, 127.0 (2C), 125.1, 124.0, 102.4, 93.8, 56.4, 50.4, 48.5, 13.5; HRMS (ESI-TOF) calcd for $C_{27}H_{24}NO_3S$ $[M + H]^+$ 442.1477, found 442.1481.

Isopropyl *cis*-1'-benzyl-5'-methyl-3-oxo-3'-phenyl-1',3'-dihydro-3*H*-spiro[benzo [*b*]thiophene-2,2'-pyrrole]-4'-carboxylate (7aj).



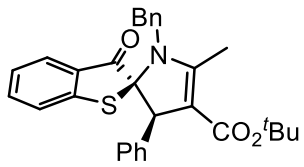
Ethyl acetate/petroleum ether = 1:4 as the eluent; Yellow solid, 89% yield (83.6 mg), dr > 99:1, mp 135–137 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 7.56 (d, J = 7.7 Hz, 1H), 7.40 (td, J = 7.0, 1.1 Hz, 1H), 7.29–7.15 (m, 8H), 7.06 (dd, J = 16.8, 7.8 Hz, 4H), 4.81 (dd, J = 12.4, 6.2 Hz, 1H), 4.78 (d, J = 1.4 Hz, 1H), 4.31 (q, J = 16.6 Hz, 2H), 2.31 (d, J = 1.4 Hz, 3H), 1.05 (d, J = 6.2 Hz, 3H), 0.69 (d, J = 6.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.6, 165.6, 160.3, 151.4, 141.3, 137.7, 136.7, 128.8 (2C), 128.7, 128.6 (2C), 127.9 (2C), 127.5, 127.3, 127.2 (2C), 127.0, 125.0, 124.1, 103.1, 93.8, 65.9, 57.0, 48.6, 22.2, 21.4, 13.3; HRMS (ESI-TOF) calcd for $C_{29}H_{28}NO_3S$ $[M + H]^+$ 470.1790, found 470.1797.

Isobutyl *cis*-1'-benzyl-5'-methyl-3-oxo-3'-phenyl-1',3'-dihydro-3*H*-spiro[benzo[*b*] thiophene-2,2'-pyrrole]-4'-carboxylate (7ak).



Ethyl acetate/petroleum ether = 1:4 as the eluent; Yellow solid, 85% yield (82.2 mg), dr > 99:1, mp 148–150 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 7.57 (d, J = 7.7 Hz, 1H), 7.41 (td, J = 7.1, 1.0 Hz, 1H), 7.31–7.16 (m, 8H), 7.16–6.92 (m, 4H), 4.77 (d, J = 1.2 Hz, 1H), 4.42–4.22 (m, 2H), 3.75 (dd, J = 10.6, 6.4 Hz, 1H), 3.58 (dd, J = 10.6, 6.1 Hz, 1H), 2.34 (d, J = 1.2 Hz, 3H), 1.61–1.65 (m, 1H), 0.56 (s, 3H), 0.55 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.5, 166.2, 160.9, 151.3, 141.2, 137.6, 136.7, 128.6 (5C), 128.1 (2C), 127.5, 127.3, 127.2, 127.1 (2C), 125.1, 124.0, 102.5, 93.9, 69.4, 56.7, 48.5, 27.7, 19.0 (2C), 13.4; HRMS (ESI-TOF) calcd for $C_{30}H_{30}NO_3S$ $[M + H]^+$ 484.1946, found 484.1950.

***tert*-Butyl *cis*-1'-benzyl-5'-methyl-3-oxo-3'-phenyl-1',3'-dihydro-3*H*-spiro[benzo [*b*]thiophene-2,2'-pyrrole]-4'-carboxylate (7al).**



Ethyl acetate/petroleum ether = 1:4 as the eluent; Yellow solid, 83% yield (80.3 mg), dr > 99:1, mp 167–169 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 (d, J = 7.3 Hz, 1H), 7.39 (td, J = 7.0, 1.2 Hz, 1H), 7.33–7.22 (m, 3H), 7.22–7.10 (m, 6H), 7.05 (dd, J = 16.2, 8.0 Hz, 3H), 4.77 (d, J = 1.5 Hz, 1H), 4.30 (dd, J = 41.6, 16.6 Hz, 2H), 2.28 (d, J = 1.5 Hz, 3H), 1.12 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.8, 165.6, 159.8, 151.4, 141.2, 137.7, 136.7, 129.0 (2C), 128.8, 128.6 (2C), 127.8 (2C), 127.5, 127.2 (3C), 126.9, 124.9, 124.1, 104.0, 94.0, 78.8, 57.6, 48.7, 28.1 (3C), 13.2; HRMS (ESI-TOF) calcd for $C_{30}H_{30}NO_3S$ $[M + H]^+$ 484.1946, found 484.1941.

3.4 化合物 6aa 的单晶衍射数据

目前，所有已合成的硫代橙酮螺二氢呋喃化合物均通过核磁共振波谱进行了结构的表征。为了进一步的确认产物的结构，所以我们将化合物 **6aa** 溶解于丙酮和正己烷的混合溶剂中，在低温环境下让其缓慢挥发，得到晶型规整且透明的单晶。随后，在配备有 CCD 面阵探测器衍射仪（Bruker APEX-II）上使用石墨单色 MoKα 辐射（λ = 0.71073 Å），在 4.586 < 2θ < 55.054° 的扫描范围内获得了相关单晶 X-射线衍射参数如表 3-5 所示。经 SHELXT Structure Solution 程序使用本征相位法与 SHELXL 精化软件的最小二乘法解析出化合物 **6aa** 的构型，晶体结构如下图 3-1 所示。

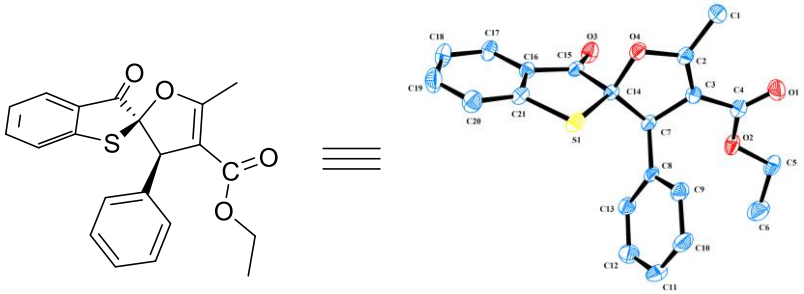


图 3-1 **6aa** 单晶衍射图

Table 3-5. Crystal data and structure refinement for 6aa

Identification code	**6aa**
Empirical formula	C21H18O4S
Formula weight	366.41
Temperature/K	293.15

Crystal system	triclinic
Space group	P-1
a/Å	8.3228 (8)
b/Å	9.5077 (12)
c/Å	12.1527 (12)
α/°	104.815 (2)
β/°	99.383 (4)
γ/°	101.722 (4)
Volume/Å3	886.51 (17)
Z	2
ρcalcg/cm3	1.373
μ/mm-1	0.206
F(000)	384.0
Crystal size/mm3	0.15 × 0.13 × 0.13
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	4.586 to 55.054
Index ranges	-10 ≤ h ≤ 10, -12 ≤ k ≤ 12, -15 ≤ l ≤ 13
Reflections collected	7916
Independent reflections	3973 [Rint = 0.0556, Rsigma = 0.0741]
Data/restraints/parameters	3973/0/237
Goodness-of-fit on F2	1.127
Final R indexes [I>=2σ (I)]	R_1 = 0.0710, wR_2 = 0.2009
Final R indexes [all data]	R_1 = 0.0815, wR_2 = 0.2077
Largest diff. peak/hole / e Å-3	0.72/-0.35

3.5 化合物 **7al** 的单晶衍射数据

我们将化合物 **7al** 溶解于二氯甲烷和正己烷的混合溶剂中，在低温环境下让其缓慢挥发，得到晶型规整且透明的 **7al** 单晶。在配备有 CCD 面阵探测器衍射仪（Bruker APEX-II）上使用石墨单色 MoKα 辐射（λ = 0.71073 Å），在 3.906 < 2θ < 55.136º 的扫描范围内获得了相关单晶 X-射线衍射参数如表 3-6 所示。经 SHELXT Structure Solution 程序使用本征相位法与 SHELXL 精化软件的最小二乘法解析出化合物 **7al** 的构型，晶体结构如下图 3-2 所示。

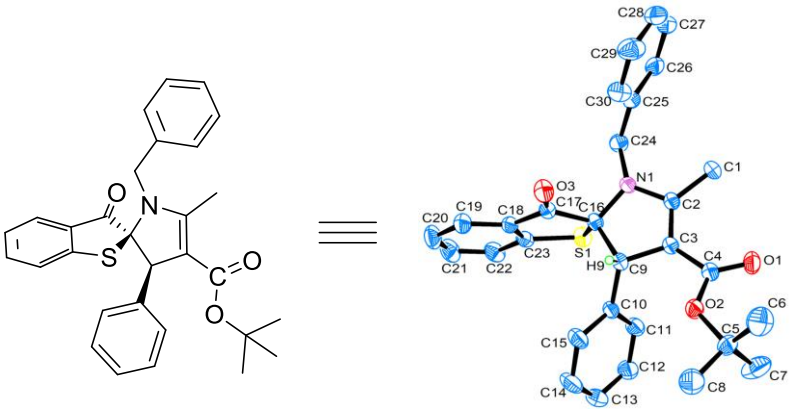


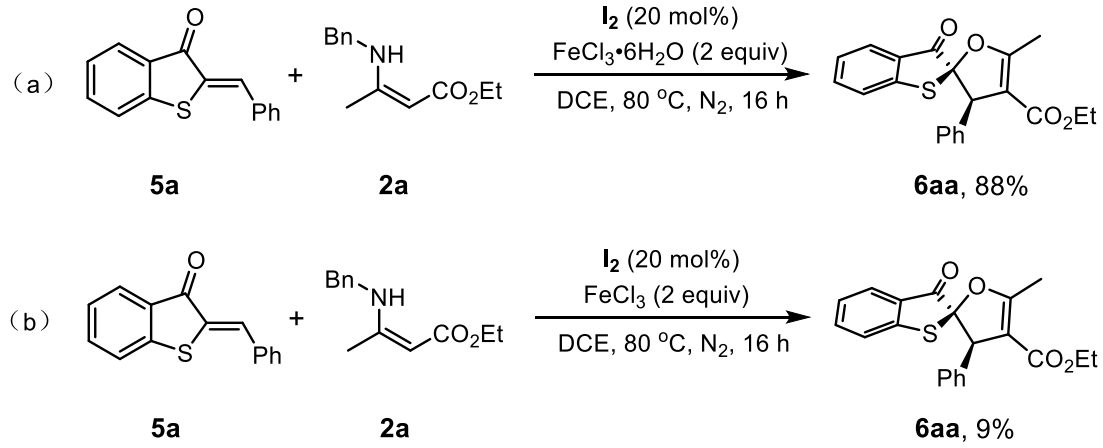
图 3-2 **7al** 单晶衍射图

Table 3-6. Crystal data and structure refinement for 7al

Identification code	**7al**
Empirical formula	$C_{30}H_{29}NO_3S$
Formula weight	483.60
Temperature/K	293.15
Crystal system	monoclinic
Space group	$P2_1/n$
a/Å	10.5127 (8)
b/Å	11.6650 (11)
c/Å	21.3853 (19)
α/°	90
β/°	102.807 (2)
γ/°	90
Volume/Å^3	2557.3 (4)
Z	4
ρ_{calc}g/cm^3	1.256
μ/mm^{-1}	0.158
F(000)	1024.0
Crystal size/mm^3	0.3 × 0.2 × 0.2
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	3.906 to 55.136
Index ranges	-13 ≤ h ≤ 13, -15 ≤ k ≤ 15, -27 ≤ l ≤ 27
Reflections collected	99060
Independent reflections	5912 [R_{int} = 0.1226, R_{sigma} = 0.0413]
Data/restraints/parameters	5912/0/320
Goodness-of-fit on F^2	1.027
Final R indexes [I>=2σ (I)]	R_1 = 0.0468, wR_2 = 0.1087
Final R indexes [all data]	R_1 = 0.0723, wR_2 = 0.1257
Largest diff. peak/hole / e Å^{-3}	0.18/-0.27

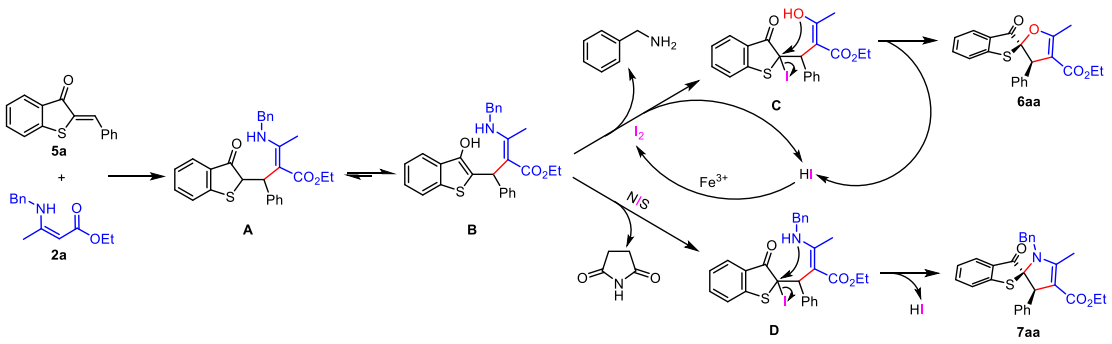
3.6 反应机理探究

针对该反应，我们还进行了控制性实验，以探究呋喃环上氧原子的来源。首先，在氮气保护下，将标准量的 **5a**、**2a**、I_2 及 $FeCl_3·6H_2O$ 置于无水无氧的 DCE 中在 80 ℃ 条件下反应 16 h（Scheme 3-4a），发现产率未受影响，反应顺利进行。同时我们将 $FeCl_3·6H_2O$ 替换为无水 $FeCl_3$，在氮气氛围下观察到反应受到明显抑制（Scheme 3-4b），由此推测呋喃环中的氧原子可能来源于 $FeCl_3·6H_2O$。



Scheme 3-4 Controlled experiment

综合以上实验结果及本课题组前期工作[141]，我们以硫代橙酮 **5a** 与 β-烯胺酯 **2a** 的反应为例，给出了可能的反应机理（Scheme 3-5）。首先硫代橙酮 **5a** 与 β-烯胺酯 **2a** 之间发生迈克尔加成反应得到加成产物 **A**，**A** 会互变为烯醇式异构体 **B**。接下来，β-烯胺片段在 $FeCl_3·6H_2O$ 作用下发生水解反应并脱去苄胺，同时硫代橙酮羰基位置的 α-H 被 I_2 卤代，然后被水解烯胺片段的氧原子对硫代橙酮的 α-C 位置发生亲核取代反应后环化，脱去 HI 在 Fe(III)的作用下被氧化为 I_2，完成 I_2 的催化循环，最终得到硫代橙酮螺二氢呋喃化合物 **6aa**。当硫代橙酮 **5a** 与 β-烯胺酯 **2a** 在球磨条件下发生反应时，烯胺将不再发生水解。首先 **5a** 与 **2a** 之间发生迈克尔加成反应得到加成产物 **A**，与此同时硫代橙酮羰基发生烯醇化得到互变异构体 **B**，接下来卤代试剂 NIS 将对羰基位置的 α-H 发生亲电取代，进而得到碘代中间体 **D**。随后烯胺片段的氮原子会对硫代橙酮羰基位置上的 α-C 发起亲核进攻并环化，同时脱去一分子碘化氢，最终得到硫代橙酮螺二氢吡咯化合物 **7aa**。



Scheme 3-5 Plausible mechanism for the reaction

3.7 本章小结

综上所述，本章的主要内容是研究了硫代橙酮与 β-烯胺酯的选择性螺环化反应。我们首先建立了模型反应，并通过筛选大量的反应条件最终确定了选择性合成硫代橙酮螺二氢呋喃化合物及硫代橙酮螺二氢吡咯化合物的反应条件，分别如下：1 当量硫代橙酮、2 当量烯胺酯、20 mol%的 I_2 和 2 当量的 $FeCl_3·6H_2O$ 在 DCE 中于 80 ºC 反应 16 h；1 当量硫代橙酮、1.2 当量烯胺酯、1.2 当量的 NIS、0.5 当量的 $FeCl_3$ 和 CH_2Br_2（30 μL）在球磨下加热反应 70 min。以 75–92%的产率合成出 21 个硫代橙酮螺二氢呋喃化合物，并以 89–92%的产率合成出 24 个硫代橙酮螺二氢吡咯化合物。两种螺环产物的相对构型通过 X-射线单晶衍射得到确定。此外，我们还提出了可能的机理对该反应的选择性进行了阐释。该反应具有原料易得、化学选择性高等优点，通过调控反应条件使得同样的原料经历不同历程生成不同产物，为构建结构新颖的且多元化的硫代橙酮螺环化合物发展了一种新方法。

第四章 不饱和异噁唑酮与烯胺酯的选择性环化反应研究

4.1 实验部分

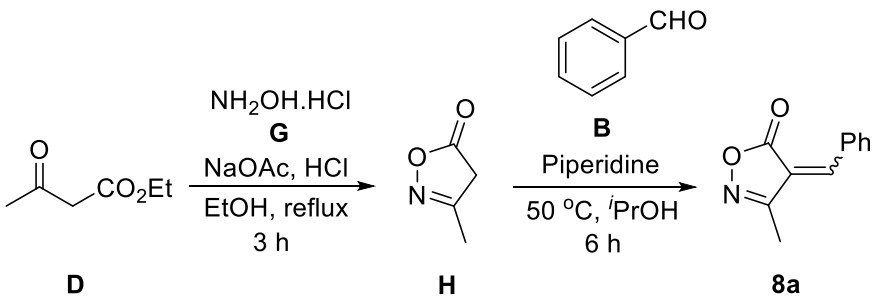
4.1.1 仪器与试剂

本章所使用的实验仪器和以上章节相同，试剂种类有所不同。

试剂名称	规格	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
乙酸钠	分析纯	萨恩化学技术（上海）有限公司
甲醇钠	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
乙酸铜	分析纯	上海泰坦科技有限公司
氯化铜	分析纯	上海泰坦科技有限公司
乙酰丙酮酸铜	分析纯	萨恩化学技术（上海）有限公司
溴化铜	分析纯	萨恩化学技术（上海）有限公司
氰化亚铜	分析纯	萨恩化学技术（上海）有限公司
碘化亚铜	分析纯	上海泰坦科技有限公司
氧化铜	分析纯	上海泰坦科技有限公司

4.1.2 原料的合成

4.1.2.1 原料 **8** 的合成



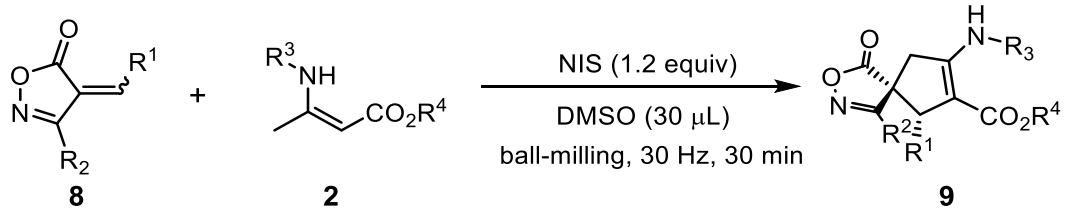
Scheme 4-1 Synthesis of unsaturated-isoxazolone

以合成 **8a** 为例，先将 NaOAc（15 mmol, 1.23 g）与盐酸羟胺（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 ºC 的油浴锅中搅拌 5 min，随后缓慢加入乙酰乙酸乙酯 **D**（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 **H**（89%, 0.88 g）。随后将 **H**（8 mmol, 0.79 g）和苯甲醛 **B**（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 哌啶后于 50 ºC 下反应 6 h，期间会逐渐有黄色固体产生。待到反应结束后过滤得到黄色 2-亚苄基-3-甲基异噁唑酮固体 **8a**（83%, 1.24 g）。

4.1.3 产物的合成

4.1.3.1 产物 9 的合成

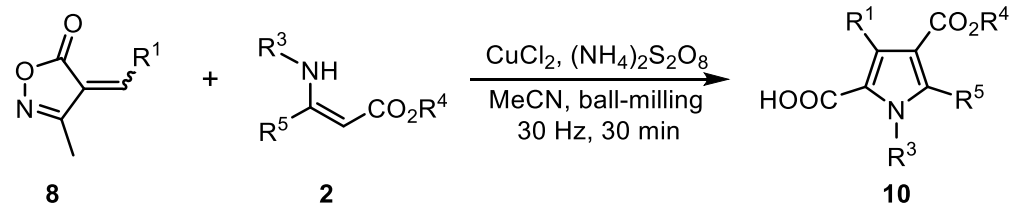


8 **2** **9**

Scheme 4-2 Synthesis of Compound **9**

将不饱和异噁唑酮 **8**（0.2 mmol）、β-烯胺酯 **2**（0.24 mmol）、NIS（0.24 mmol，54.0 mg）和 DMSO（30 μL）加入到含有 4 个研磨球（直径 6 mm）的不锈钢研磨罐（5 mL）中。将该研磨罐封闭并固定在 Retsch MM400 研磨仪的振动臂上，在室温下以 1800 转/分钟（30 Hz）的频率研磨 30 分钟。反应结束后，用乙酸乙酯溶解所得反应混合物并转移至茄形瓶中，加入少量硅胶后减压蒸馏至粉末状，然后进行柱层析分离得到产物 **9**。

4.1.3.2 产物 10 的合成



8 **2** **10**

Scheme 4-3 Synthesis of Compound **10**

将不饱和异噁唑酮 **8**（0.2 mmol）、β-烯胺酯 **2**（0.24 mmol）、$CuCl_2$（5.4 mg, 0.04 mmol）、$(NH_4)_2S_2O_8$（36.5 mg, 0.16 mmol）和 MeCN（30 μL）加入到

含有 4 个研磨球（直径 6 mm）的不锈钢罐（5 mL）中。将该研磨罐封闭并固定在 Retsch MM400 研磨仪的振动臂上，在室温下以 1800 转/分钟（30 Hz）的频率研磨 30 分钟。反应结束后，用乙酸乙酯溶解所得反应混合物并转移至茄形瓶中，加入适量硅胶后减压蒸馏至粉末状，然后进行柱层析分离得到产物 **10**。

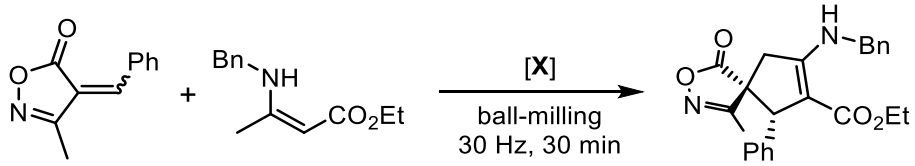
4.2 实验结果与讨论

4.2.1 条件优化

4.2.1.1 产物 9 的条件优化

最开始我们选择不饱和异噁唑酮 **8a** 与 β-烯胺酯 **2a** 为模型底物筛选最佳反应条件（Table 4-1）。先将 **8a**（0.2 mmol）、**2a**（0.24 mmol）与 I_2（0.2 mmol）混合，在球磨条件下反应 30 分钟后发现只有痕量产物生成（entry 1）。随后我们将 I_2 更换为 NBS 或 NIS 作促进剂来对反应进行尝试，发现两组反应均有产物 **9aa** 生成（entries 2 and 3）。然后我们计划对 **9aa** 产物的合成展开优化工作，首先我们调整最佳的卤代试剂比例，发现 1.2 当量 NIS 效果最佳，此时 **9aa** 的收率为 41%（entry 4）。接下来我们对助溶剂进行探究（entries 5–12），发现一些溶剂对反应有显著的促进作用，其中 DMSO 作助溶剂时 **9aa** 的收率高达 91%（entry 8）。综上所述，生成顺式异噁唑酮螺环戊烯化合物 **9aa** 的最优条件如下：1 当量不饱和异噁唑酮、1.2 当量烯胺酯、1.2 当量的 NIS 以 DMSO 为助溶剂在球磨条件下反应 30 分钟。

Table 4-1. Optimization of the conditions for the synthesis of 9aa[a]



8a **2a** **9aa**

Entry	[X] (equiv.)	LAG solvent (30 μL)	Yield[b] (%)
1	I_2 (1.0)		trace
2	NIS (1.0)		32
3	NBS (1.0)		21
4	NIS (1.2)		41
5	NIS (1.2)	MeCN	78

6	NIS (1.2)	pyridine	82
7	NIS (1.2)	CH_2Br_2	34
8	**NIS (1.2)**	**DMSO**	**91**
9	NIS (1.2)	toluene	75
10	NIS (1.2)	MeOH	25
11	NIS (1.2)	DMF	54
12	NIS (1.2)	DCE	35

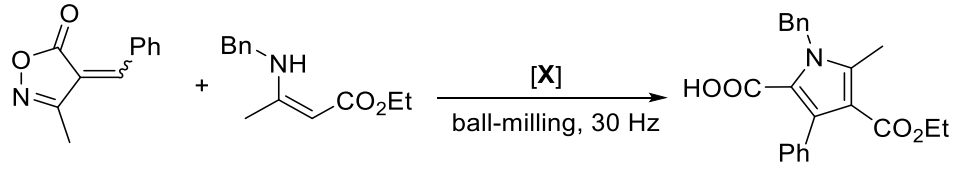
[a]Reaction conditions: a mixture of **8a** (0.2 mmol), **2a** (0.24 mmol), a halogenating reagent (0.24 mmol), an LAG solvent (30 μL) and four stainless balls (6 mm in diameter) was milled in a Retsch MM400 mixer mill at 30 Hz for 30 min. [b]Isolated yield based on **8a**.

4.2.1.2 产物 10 的条件优化

在确定了环戊烯螺环的最佳合成条件之后，我们想进一步通过调控反应条件来选择性构建二氢吡咯螺环。鉴于在卤代试剂作用下无二氢吡咯螺环生成，我们拟尝试铜催化的策略。首先，我们采用了 20 mol%不同的铜盐作为催化剂（Table 4-2），在球磨条件下使用 1 当量$(NH_4)_2S_2O_8$作氧化剂和 DCE（30 μL）作助溶剂对反应进行了尝试（entries 1–8）。结果发现在一些铜盐的催化下有新产物生成，但 NMR 波谱分析表明该新产物并非我们预期的二氢吡咯螺环，而是生成的二氢吡咯螺环再经开环反应得到的吡咯衍生物。在所有试验的铜盐中，$CuCl_2$表现出最佳的催化效果，并以 78%的收率得到吡咯衍生物 **10aa**（entry 2）。考虑到吡咯是一种极为重要的含氮杂环，因此我们想进一步筛选反应条件，以发展一种高效合成吡咯衍生物的新方法。当我们将 $CuCl_2$ 的用量减少到 10 mol%时，观察到产率显著下降（entry 9）。而不使用任何催化剂的进一步实验未能得到产物（entry 10）。在无溶剂条件下进行反应时，仅能获得微量的产物 **10aa**（entry 11）。这些对比的结果表明在此反应过程中助溶剂起到了促进作用，并促使我们对一系列常用溶剂进行了筛选（entries 12–17）。所有选用的溶剂均有利于产物 **10aa** 的生成，其中 MeCN 作为溶剂时反应效果最佳，以 92%的高收率得到产物 **10aa**（entry 13）。接下来通过对氧化剂的筛选实验，我们发现$(NH_4)_2S_2O_8$是最佳选择（entry 13 and entries 18–23）。此外，我们还对$(NH_4)_2S_2O_8$的用量进行了考察。当将$(NH_4)_2S_2O_8$的用量降低到 0.8 当量时，仍能以最类似的收率得到 **10aa**（entry 24）。但是，进一步减少$(NH_4)_2S_2O_8$至 0.6 当

量时，产物 **10aa** 的收率明显下降（entry 25）。为了与液相反应进行比较，我们以 MeCN 作溶剂于 25 ℃下尝试了该反应，结果发现反应 6 h 后产物 **10aa** 的收率为 86%（entry 26）。通过该对比实验，我们发现机械化学下的反应更具有优势，在更短的时间内即可完成反应，并且产物收率更高。

Table 4-2. Optimization of the conditions for the synthesis of 10aa[a]



8a **2a** **10aa**

Entry	[X] (mol%)	LAG solvent (30 μL)	Additive (equiv.)	Yield[b] (%)
1	$CuBr_2$ (20)	DCE	$(NH_4)_2S_2O_8$ (1.0)	58
2	$CuCl_2$ (20)	DCE	$(NH_4)_2S_2O_8$ (1.0)	78
3	$CuSO_4·5H_2O$ (20)	DCE	$(NH_4)_2S_2O_8$ (1.0)	42
4	$Cu(OAc)_2$ (20)	DCE	$(NH_4)_2S_2O_8$ (1.0)	18
5	$Cu(acac)_2$ (20)	DCE	$(NH_4)_2S_2O_8$ (1.0)	trace
6	CuO (20)	DCE	$(NH_4)_2S_2O_8$ (1.0)	trace
7	CuCN (20)	DCE	$(NH_4)_2S_2O_8$ (1.0)	trace
8	CuI (20)	DCE	$(NH_4)_2S_2O_8$ (1.0)	trace
9	$CuCl_2$ (10)	DCE	$(NH_4)_2S_2O_8$ (1.0)	45
10		DCE	$(NH_4)_2S_2O_8$ (1.0)	0
11	$CuCl_2$ (20)		$(NH_4)_2S_2O_8$ (1.0)	trace
12	$CuCl_2$ (20)	toluene	$(NH_4)_2S_2O_8$ (1.0)	45
13	$CuCl_2$ (20)	MeCN	$(NH_4)_2S_2O_8$ (1.0)	92
14	$CuCl_2$ (20)	EtOH	$(NH_4)_2S_2O_8$ (1.0)	83
15	$CuCl_2$ (20)	THF	$(NH_4)_2S_2O_8$ (0.5)	65
16	$CuCl_2$ (20)	DMF	$(NH_4)_2S_2O_8$ (1.0)	72
17	$CuCl_2$ (20)	DMSO	$(NH_4)_2S_2O_8$ (1.0)	78
18	$CuCl_2$ (20)	MeCN	$Na_2S_2O_8$ (1.0)	76
19	$CuCl_2$ (20)	MeCN	$K_2S_2O_8$ (1.0)	83
20	$CuCl_2$ (20)	MeCN	Oxone (1.0)	73
21	$CuCl_2$ (20)	MeCN	$NaIO_4$ (1.0)	trace
22	$CuCl_2$ (20)	MeCN	$KMnO_4$ (1.0)	0
23	$CuCl_2$ (20)	MeCN	$K_2Cr_2O_7$ (1.0)	0
24	**$CuCl_2$ (20)**	**MeCN**	**$(NH_4)_2S_2O_8$ (0.8)**	**93**
25	$CuCl_2$ (20)	MeCN	$(NH_4)_2S_2O_8$ (0.6)	77
26	$CuCl_2$ (20)		$(NH_4)_2S_2O_8$ (0.8)	86

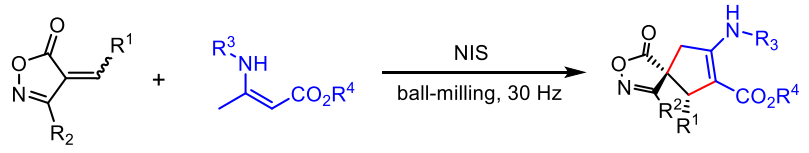
[a]Unless otherwise noted, the reaction conditions were as follows: **8a** (0.2 mmol), **2a** (0.24 mmol), a copper salt, an oxidant, and an LAG solvent (30 μL) together with four stainless balls (6 mm in diameter) were milled in a Retsch MM400 mixer mill at 30 Hz for 30 min. [b]Isolated yields based on **8a**. [c]The reaction was performed in MeCN (2 mL) at 25 °C for 6 h.

4.2.2 底物拓展

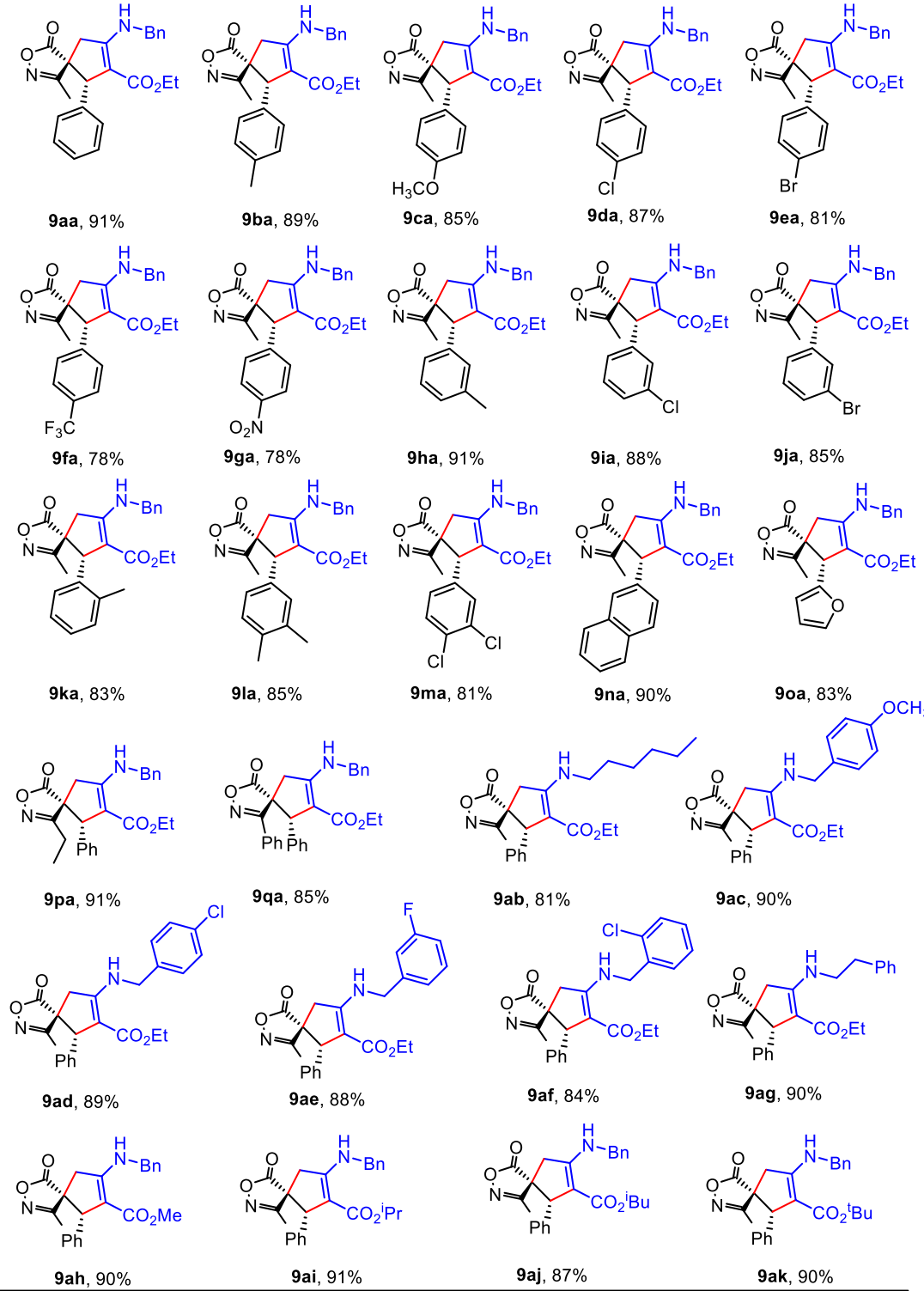
4.2.2.1 产物 9 的合成

在确定了选择性合成异噁唑酮螺环戊烯及吡咯衍生物的最佳反应条件后，我们对该选择性反应的普适性和底物范围进行了探究。我们首先考察了异噁唑酮螺环戊烯类化合物的底物范围（Table 4-3）。首先使用连有不同取代基的不饱和异噁唑酮 **8a**–**q** 和 β-烯胺酯 **2a** 进行反应，当 R^1 苯环上连有强吸电子基团时，反应可以顺利进行，并以中等到良好的收率得到产物 **9fa**、**9ga**。当该位置为强供电子和其他常规基团时，异噁唑酮衍生物 **8** 均展现出较高的反应活性，以 78–91%的收率合成了一系列异噁唑酮螺环戊烯衍生物 **9ba**–**9ea**、**9ba**–**9ea**。异噁唑酮片段的 R^2 位置我们探究了两种基团（Et, Ph），生成产物 **9pa** 和 **9qa 的**收率最高可达 91%。接下来我们研究了烯胺酯片段的各个位置不同的取代基对反应的影响，发现不同取代基的烯胺酯 **2** 均展现出优异的反应活性，以 81–91%的收率得到一系列异噁唑酮螺环戊烯化合物 **9ab**–**9ak**，充分证明该方法具有良好的底物普适性。最后异噁唑酮螺环戊烯衍生物 **9pa** 的相对构型我们已经通过 X-射线单晶衍射分析得到了确认。

Table 4-3. Selective synthesis of *cis*-Isoxazolone spirocyclopentenes 9 from unsaturated-isoxazolone 8 and enamino esters 2[a,b]



8 **2** **9**



9aa, 91% **9ba**, 89% **9ca**, 85% **9da**, 87% **9ea**, 81%

9fa, 78% **9ga**, 78% **9ha**, 91% **9ia**, 88% **9ja**, 85%

9ka, 83% **9la**, 85% **9ma**, 81% **9na**, 90% **9oa**, 83%

9pa, 91% **9qa**, 85% **9ab**, 81% **9ac**, 90%

9ad, 89% **9ae**, 88% **9af**, 84% **9ag**, 90%

9ah, 90% **9ai**, 91% **9aj**, 87% **9ak**, 90%

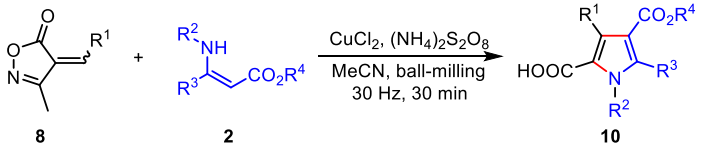
[a]Reaction conditions: a mixture of **8** (0.2 mmol), **2** (0.24 mmol), NIS (0.24 mmol), pyridine (30

μL) and four stainless balls (6 mm in diameter) was milled in a Retsch MM400 mixer mill at 30 Hz for 30 min. [b]Isolated yields based on **8**.

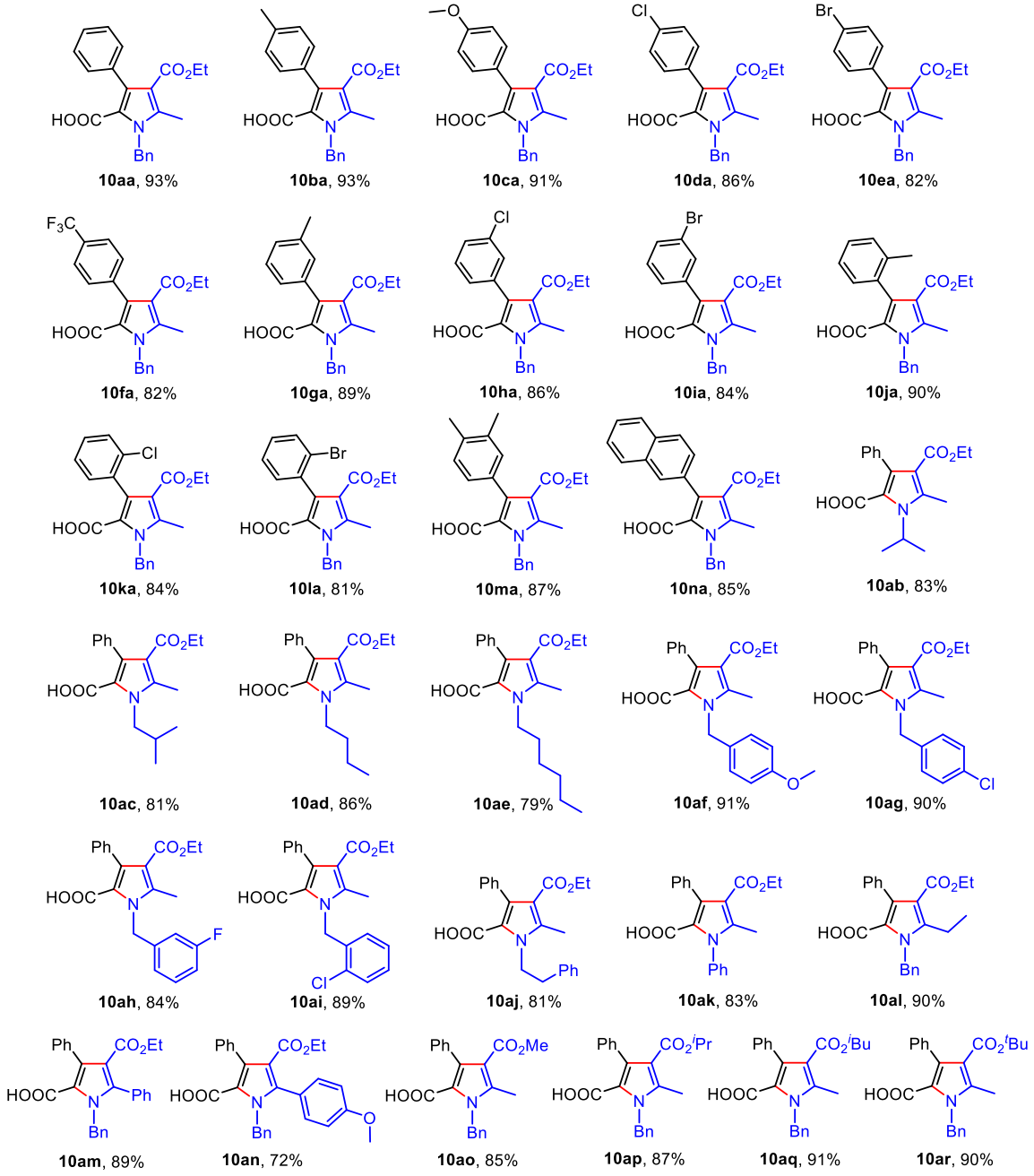
4.2.2.2 产物 10 的合成

接下来，我们进一步探索了选择性合成吡咯衍生物的普适性（Table 4-4）。首先，我们将一系列的 4-芳基亚甲基异噁唑-5-酮 **8** 在标准条件下与烯胺酯 **2a** 进行反应。不饱和异噁唑酮中苯环的对位不论是连有给电子基团还是吸电子基团都能顺利完成反应，并以 82–93%的收率合成出一系列吡咯衍生物 **10ba**–**fa**。值得一提的是，即便是那些苯环上带有间位、邻位或是双取代基的 4-芳基亚甲基异噁唑酮 **8** 也展现了高度的反应活性，成功地合成出多种吡咯化合物 **10ga**–**ma**，这一结果表明该反应具有优异的官能团兼容性。此外，含有 2-萘基取代基的底物 **8o** 在反应中同样适用，以 85%的良好收率得到相应产物 **10oa**。需要指出的是，烷叉基异噁唑酮的合成相对困难，因此没有应用到该反应中。产物 **10ga** 的结构通过单晶 X-射线衍射分析得以进一步确认。进而，我们又继续采用了一系列不同取代的烯胺酯，以深入探究该多米诺反应的底物适用范围。我们发现，在氮原子上带有不同烷基或苯基取代的烯胺酯 **2** 在机械研磨条件下与 **8a** 的反应依旧顺畅，成功以 79–91%的良好产率得到了相应的产物 **10ab**–**ak**。此外，当 R_2 中的甲基和 R^4 中的乙基被其他官能团所替换时，依旧能够高效地获得多种多取代的吡咯 **10al**–**ar**。

Table 4-4. Selective synthesis of carboxypyrrole compounds 10 from unsaturated-isoxazolone 8 and enamino ester 2[a,b]



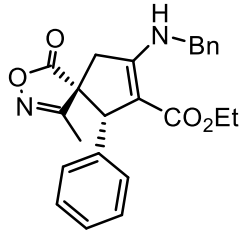
8 2 10



[a]Reaction conditions: a mixture of **8** (0.20 mmol), **2** (0.24 mmol), $CuCl_2$ (0.04 mmol), $(NH_4)_2S_2O_8$ (0.16 mmol), and MeCN (30 μL) together with four stainless balls (6 mm in diameter) was milled in a Retsch MM400 mixer mill at 30 Hz for 30 min. [b]Isolated yields based on **8**.

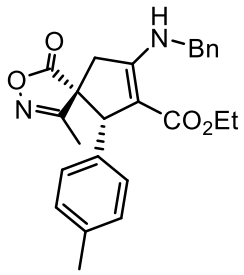
4.3 异噁唑酮螺环化合物与吡咯衍生物的表征

Ethyl *cis*-8-(benzylamino)-4-methyl-1-oxo-6-phenyl-2-oxa-3-azaspiro[4.4]nona-3, 7-diene-7-carboxylate (9aa).



Ethyl acetate/petroleum ether = 1:4 as the eluent; white solid, 91% yield (73.6 mg), dr > 99:1, mp 138–140 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.11 (s, 1H), 7.39 (t, J = 7.4 Hz, 2H), 7.34–7.20 (m, 6H), 7.06 (d, J = 7.1 Hz, 2H), 4.47 (qd, J = 15.9, 6.6 Hz, 2H), 4.26 (s, 1H), 4.08–3.98 (m, 1H), 3.97–3.87 (m, 1H), 3.13 (d, J = 17.3 Hz, 1H), 2.66 (d, J = 17.3 Hz, 1H), 2.00 (s, 3H), 0.93 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.2, 169.2, 167.1, 160.6, 138.3, 138.1, 129.2 (2C), 128.4 (2C), 128.0 (3C), 127.9, 126.7 (2C), 94.5, 59.2, 56.1, 55.6, 48.5, 36.9, 14.2, 12.0; HRMS (ESI-TOF) calcd for $C_{24}H_{25}N_2O_4$ $[M + H]^+$ 405.1814, found 405.1819.

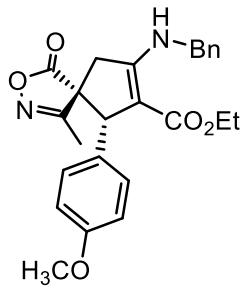
Ethyl *cis*-8-(benzylamino)-4-methyl-1-oxo-6-(*p*-tolyl)-2-oxa-3-azaspiro[4.4]nona-3, 7-diene-7-carboxylate (9ba).



Ethyl acetate/petroleum ether = 1:4 as the eluent; white solid, 89% yield (74.5 mg), dr > 99:1, mp 135–137 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 (s, 1H), 7.37 (t, J = 7.4 Hz, 2H), 7.33–7.25 (m, 3H), 7.07 (d, J = 7.9 Hz, 2H), 6.93 (d, J = 7.6 Hz, 2H), 4.44 (qd, J = 15.9, 6.6 Hz, 2H), 4.22 (s, 1H), 4.07–3.97 (m, 1H), 3.97–3.87 (m, 1H), 3.10 (d, J = 17.3 Hz, 1H), 2.64 (d, J = 17.3 Hz, 1H), 2.29 (s, 3H), 1.98 (s, 3H), 0.95 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.2, 169.2, 167.1, 160.4, 138.4, 137.3, 135.0, 129.1 (2C), 129.0 (2C), 127.9, 127.7 (2C), 126.7 (2C), 94.5, 59.1, 55.8, 55.6, 48.3, 36.7, 21.2, 14.2, 11.9; HRMS (ESI-TOF) calcd for $C_{25}H_{27}N_2O_4$ $[M + H]^+$ 419.1971, found 419.1977.

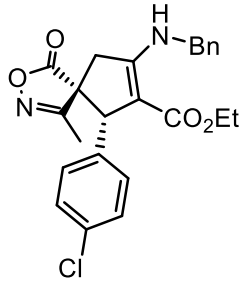
Ethyl *cis*-8-(benzylamino)-6-(4-methoxyphenyl)-4-methyl-1-oxo-2-oxa-3-azaspiro [4.4]nona-3,7-diene-7-carboxylate (9ca).

Ethyl acetate/petroleum ether = 1:3 as the eluent; white solid, 91% yield (79.1 mg), dr > 99:1, mp 118–120 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09 (s, 1H), 7.39 (t, J = 7.4 Hz, 2H), 7.35–7.26 (m, 3H), 6.97 (d, J = 8.2 Hz, 2H), 6.80 (d, J = 8.7 Hz, 2H), 4.46 (qd, J = 15.8, 6.6 Hz, 2H), 4.23 (s, 1H), 4.02 (dq, J = 10.9, 7.1 Hz, 1H), 3.94 (dq, J =



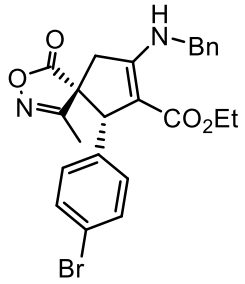
10.8, 7.1 Hz, 1H), 3.77 (s, 3H), 3.12 (d, *J* = 17.3 Hz, 1H), 2.65 (d, *J* = 17.3 Hz, 1H), 1.99 (s, 3H), 0.96 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) *δ* 177.3, 169.2, 167.2, 160.3, 159.2, 138.4, 130.2, 129.2 (2C), 129.0 (2C), 128.0, 126.7 (2C), 113.7 (3C), 94.8, 59.2, 55.7, 55.2, 48.4, 36.7, 14.3, 12.0; HRMS (ESI-TOF) calcd for $C_{25}H_{27}N_2O_5$ $[M + H]^+$ 435.1920, found 435.1927.

Ethyl *cis*-8-(benzylamino)-6-(4-chlorophenyl)-4-methyl-1-oxo-2-oxa-3-azaspiro[4.4]nona-3,7-diene-7-carboxylate (9da).



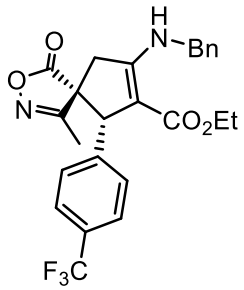
Ethyl acetate/petroleum ether = 1:4 as the eluent; white solid, 85% yield (74.6 mg), dr > 99:1, mp 131–133 °C; ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 8.07 (s, 1H), 7.36 (dd, *J* = 8.7, 2.1 Hz, 2H), 7.30–7.19 (m, 5H), 7.04 (d, *J* = 6.9 Hz, 2H), 4.42 (qd, *J* = 16.0, 6.6 Hz, 2H), 4.27 (s, 1H), 4.01 (dq, *J* = 10.8, 7.1 Hz, 1H), 3.91 (dq, *J* = 10.8, 7.1 Hz, 1H), 3.10 (d, *J* = 17.3 Hz, 1H), 2.65 (d, *J* = 17.3 Hz, 1H), 2.03 (s, 3H), 0.92 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) *δ* 177.2, 168.9, 167.1, 160.3, 138.0, 136.8, 133.8, 129.3 (2C), 128.3 (2C), 128.1 (2C), 127.9 (3C), 94.8, 59.2, 56.1, 55.6, 47.8, 36.8, 14.2, 12.0; HRMS (ESI-TOF) calcd for $C_{24}H_{24}{}^{35}ClN_2O_4$ $[M + H]^+$ 439.1425, found 439.1422.

Ethyl *cis*-8-(benzylamino)-6-(4-bromophenyl)-4-methyl-1-oxo-2-oxa-3-azaspiro[4.4]nona-3,7-diene-7-carboxylate (9ea).



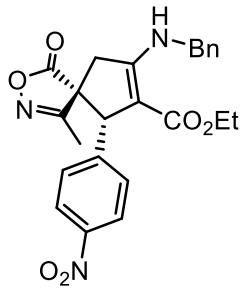
Ethyl acetate/petroleum ether = 1:4 as the eluent; white solid, 87% yield (84.1 mg), dr > 99:1, mp 145–147 °C; ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 8.10 (s, 1H), 7.37 (t, *J* = 8.0 Hz, 4H), 7.34–7.22 (m, 3H), 6.93 (d, *J* = 8.1 Hz, 2H), 4.44 (qd, *J* = 11.9, 6.9 Hz, 2H), 4.20 (s, 1H), 4.00 (dq, *J* = 10.8, 7.1 Hz, 1H), 3.93 (dq, *J* = 10.8, 7.1 Hz, 1H), 3.09 (d, *J* = 17.3 Hz, 1H), 2.67 (d, *J* = 17.4 Hz, 1H), 1.97 (s, 3H), 0.95 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) *δ* 177.1, 169.0, 166.8, 160.6, 138.2, 137.4, 131.4 (2C), 129.7 (2C), 129.1 (2C), 128.0, 126.7 (2C), 121.6, 93.9, 59.2, 55.4, 55.3, 48.4, 36.8, 14.2, 11.8; HRMS (ESI-TOF) calcd for $C_{24}H_{24}{}^{79}BrN_2O_4$ $[M + H]^+$ 483.0919, found 483.0923.

Ethyl *cis*-8-(benzylamino)-4-methyl-1-oxo-6-(4-(trifluoromethyl)phenyl)-2-oxa-3-azaspiro[4.4]nona-3,7-diene-7-carboxylate (9fa).



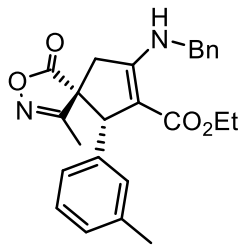
Ethyl acetate/petroleum ether = 1:3 as the eluent; white solid, 81% yield (76.5 mg), dr > 99:1, mp 95–97 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13 (s, 1H), 7.53 (d, J = 8.1 Hz, 2H), 7.38 (t, J = 7.4 Hz, 2H), 7.35–7.26 (m, 3H), 7.18 (d, J = 7.6 Hz, 2H), 4.46 (qd, J = 12.4, 6.9 Hz, 2H), 4.29 (s, 1H), 4.07–3.96 (m, 1H), 3.96–3.86 (m, 1H), 3.12 (d, J = 17.4 Hz, 1H), 2.70 (d, J = 17.4 Hz, 1H), 2.00 (s, 3H), 0.91 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.0, 168.9, 166.7, 160.8, 142.5, 138.1, 129.9 (q, J = 32.1 Hz), 129.2 (2C), 128.4 (2C), 128.0, 126.7 (2C), 125.3, 125.2, 124.2 (q, J = 270.5 Hz), 93.8, 59.3, 55.5, 55.3, 48.4, 36.9, 14.1, 11.8; HRMS (ESI-TOF) calcd for $C_{25}H_{24}F_3N_2O_4$ $[M + H]^+$ 473.1688, found 473.1691.

Ethyl *cis*-8-(benzylamino)-4-methyl-6-(4-nitrophenyl)-1-oxo-2-oxa-3-azaspiro[4.4]nona-3,7-diene-7-carboxylate (9ga).



Ethyl acetate/petroleum ether = 1:2 as the eluent; white solid, 78% yield (70.1 mg), dr > 99:1, mp 107–109 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.15 (d, J = 8.9 Hz, 3H), 7.41 (t, J = 7.4 Hz, 2H), 7.33 (t, J = 7.4 Hz, 1H), 7.29 (d, J = 7.1 Hz, 2H), 7.24 (d, J = 8.1 Hz, 2H), 4.49 (qd, J = 14.5, 6.9 Hz, 2H), 4.33 (s, 1H), 4.01 (dq, J = 10.9, 7.1 Hz, 1H), 3.93 (dq, J = 10.8, 7.1 Hz, 1H), 3.14 (d, J = 17.4 Hz, 1H), 2.74 (d, J = 17.5 Hz, 1H), 2.02 (s, 3H), 0.93 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.0, 168.8, 166.6, 161.0, 147.6, 146.1, 138.0, 129.3 (2C), 129.0 (2C), 128.2, 126.7 (2C), 123.6 (2C), 93.5, 59.4, 55.3 (2C), 48.5, 37.1, 14.2, 11.9; HRMS (ESI-TOF) calcd for $C_{24}H_{24}N_3O_6$ $[M + H]^+$ 450.1665, found 450.1668.

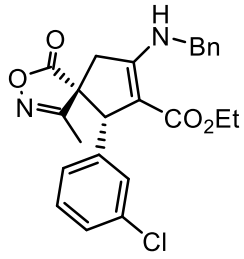
Ethyl *cis*-8-(benzylamino)-4-methyl-1-oxo-6-(*m*-tolyl)-2-oxa-3-azaspiro[4.4]nona-3,7-diene-7-carboxylate (9ha).



Ethyl acetate/petroleum ether = 1:4 as the eluent; white solid, 91% yield (76.2 mg), dr > 99:1, mp 125–127 °C; ^{1}H NMR (500 MHz,

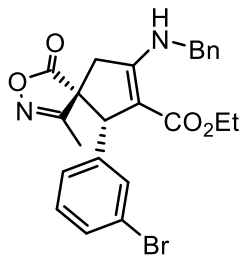
$CDCl_3$) δ 8.10 (s, 1H), 7.39 (t, J = 7.4 Hz, 2H), 7.35–7.27 (m, 3H), 7.16 (t, J = 7.6 Hz, 1H), 7.04 (d, J = 7.4 Hz, 1H), 6.85 (d, J = 9.8 Hz, 2H), 4.47 (qd, J = 12.3, 6.9 Hz, 2H), 4.21 (s, 1H), 4.03 (dq, J = 10.9, 7.1 Hz, 1H), 3.94 (dq, J = 10.8, 7.1 Hz, 1H), 3.13 (d, J = 17.3 Hz, 1H), 2.64 (d, J = 17.3 Hz, 1H), 2.30 (s, 3H), 1.99 (s, 3H), 0.95 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.2, 169.2, 167.2, 160.5, 138.4, 138.0, 137.8, 129.2 (2C), 128.7 (2C), 128.2, 128.0, 126.7 (2C), 125.1, 94.6, 59.2, 56.1, 55.6, 48.5, 36.9, 21.6, 14.3, 12.0; HRMS (ESI-TOF) calcd for $C_{25}H_{27}N_2O_4$ $[M + H]^+$ 419.1971, found 419.1968.

Ethyl *cis*-8-(benzylamino)-6-(3-chlorophenyl)-4-methyl-1-oxo-2-oxa-3-azaspiro[4.4]nona-3,7-diene-7-carboxylate (9ia).



Ethyl acetate/petroleum ether = 1:4 as the eluent; white solid, 88% yield (77.2 mg), dr > 99:1, mp 151–153 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.11 (s, 1H), 7.39 (dd, J = 10.2, 4.6 Hz, 2H), 7.33–7.26 (m, 3H), 7.22–7.16 (m, 2H), 7.05 (s, 1H), 6.95 (d, J = 2.9 Hz, 1H), 4.45 (qd, J = 14.3, 6.9 Hz, 2H), 4.20 (s, 1H), 4.04 (dq, J = 10.8, 7.1 Hz, 1H), 3.92 (dq, J = 10.8, 7.1 Hz, 1H), 3.12 (d, J = 17.4 Hz, 1H), 2.66 (d, J = 17.4 Hz, 1H), 1.98 (s, 3H), 0.95 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.0, 169.0, 166.8, 160.8, 140.5, 138.2, 134.2, 129.5, 129.2 (2C), 128.1, 128.0 (2C), 126.7 (2C), 126.3, 93.9, 59.2, 55.5, 55.3, 48.4, 36.9, 14.2, 11.8; HRMS (ESI-TOF) calcd for $C_{24}H_{24}{}^{35}ClN_2O_4$ $[M + H]^+$ 439.1425, found 439.1430.

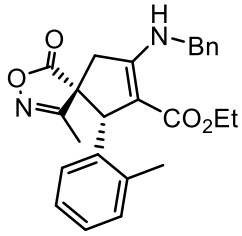
Ethyl *cis*-8-(benzylamino)-6-(3-bromophenyl)-4-methyl-1-oxo-2-oxa-3-azaspiro[4.4]nona-3,7-diene-7-carboxylate (9ja).



Ethyl acetate/petroleum ether = 1:4 as the eluent; white solid, 85% yield (82.2 mg), dr > 99:1, mp 160–161 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.11 (s, 1H), 7.38 (dd, J = 16.5, 8.6 Hz, 3H), 7.34–7.26 (m, 3H), 7.20 (s, 1H), 7.14 (t, J = 7.8 Hz, 1H), 6.99 (d, J = 7.4 Hz, 1H), 4.45 (qd, J = 14.7, 7.0 Hz, 2H), 4.19 (s, 1H), 4.04 (dq, J = 10.8, 7.1 Hz, 1H), 3.92 (dq, J = 10.8, 7.1 Hz, 1H), 3.12 (d, J = 17.4 Hz, 1H), 2.66 (d, J = 17.4 Hz, 1H), 1.97 (s, 3H), 0.96 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.9, 169.0, 166.8, 160.8, 140.7, 138.2, 130.9 (2C), 129.8, 129.2 (2C), 128.0,

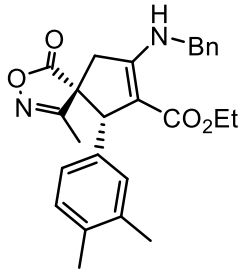
126.8, 126.7 (2C), 122.5, 93.9, 59.2, 55.5, 55.3, 48.4, 36.9, 14.2, 11.8; HRMS (ESI-TOF) calcd for $C_{24}H_{24}{}^{79}BrN_2O_4$ $[M + H]^+$ 483.0919, found 483.0923.

Ethyl *cis*-8-(benzylamino)-4-methyl-1-oxo-6-(*o*-tolyl)-2-oxa-3-azaspiro[4.4]nona-3,7-diene-7-carboxylate (9ka).



Ethyl acetate/petroleum ether = 1:4 as the eluent; white solid, 83% yield (69.5 mg), dr > 99:1, mp 161–163 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.07 (s, 1H), 7.42–7.35 (m, 2H), 7.34–7.26 (m, 3H), 7.18–7.08 (m, 3H), 7.08–7.04 (m, 1H), 4.52 (s, 1H), 4.45 (qd, J = 12.5, 7.0 Hz, 2H), 4.03–3.96 (m, 1H), 3.96–3.88 (m, 1H), 3.11 (d, J = 17.2 Hz, 1H), 2.62 (d, J = 17.3 Hz, 1H), 2.19 (s, 3H), 1.98 (s, 3H), 0.94 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.1, 169.7, 166.9, 160.3, 138.4, 136.0, 135.6, 130.4, 129.2 (2C), 128.0, 127.6, 127.4, 126.7 (2C), 125.9, 95.1, 59.1, 54.2, 51.0, 48.4, 37.3, 19.6, 14.2, 12.0; HRMS (ESI-TOF) calcd for $C_{25}H_{27}N_2O_4$ $[M + H]^+$ 419.1971, found 419.1976.

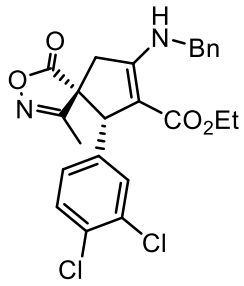
Ethyl *cis*-8-(benzylamino)-6-(3,4-dimethylphenyl)-4-methyl-1-oxo-2-oxa-3-azaspiro[4.4]nona-3,7-diene-7-carboxylate (9la).



Ethyl acetate/petroleum ether = 1:4 as the eluent; white solid, 85% yield (73.5 mg), dr > 99:1, mp 149–151 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 (s, 1H), 7.38 (t, J = 7.4 Hz, 2H), 7.33–7.25 (m, 3H), 7.01 (d, J = 8.0 Hz, 1H), 6.77 (d, J = 5.8 Hz, 2H), 4.46 (qd, J = 15.9, 6.7 Hz, 2H), 4.19 (s, 1H), 4.06–3.99 (m, 1H), 3.98–3.92 (m, 1H), 3.11 (d, J = 17.2 Hz, 1H), 2.63 (d, J = 17.3 Hz, 1H), 2.20 (s, 6H), 1.97 (s, 3H), 0.97 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.2, 169.3, 167.2, 160.4, 138.4, 136.3, 135.9, 135.3, 129.5, 129.1 (3C), 127.9, 126.7 (2C), 125.2, 94.7, 59.1, 55.9, 55.6, 48.4, 36.7, 20.0, 19.6, 14.3, 11.9; HRMS (ESI-TOF) calcd for $C_{26}H_{29}N_2O_4$ $[M + H]^+$ 433.2127, found 433.2130.

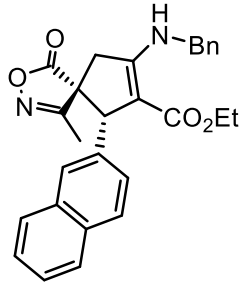
Ethyl *cis*-8-(benzylamino)-6-(3,4-dichlorophenyl)-4-methyl-1-oxo-2-oxa-3-azaspiro[4.4]nona-3,7-diene-7-carboxylate (9ma).

Ethyl acetate/petroleum ether = 1:4 as the eluent; white solid, 81% yield (76.7 mg), dr > 99:1, mp 101–103 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.11 (s, 1H), 7.38 (t, J = 7.5



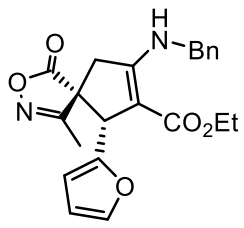
Hz, 2H), 7.35–7.24 (m, 4H), 7.15 (d, *J* = 1.4 Hz, 1H), 6.90 (d, *J* = 7.9 Hz, 1H), 4.45 (qd, *J* = 14.3, 6.9 Hz, 2H), 4.17 (s, 1H), 4.03 (dq, *J* = 10.9, 7.1 Hz, 1H), 3.95 (dq, *J* = 10.8, 7.1 Hz, 1H), 3.11 (d, *J* = 17.4 Hz, 1H), 2.67 (d, *J* = 17.4 Hz, 1H), 1.97 (s, 3H), 0.98 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.9, 168.9, 166.6, 160.8, 138.8, 138.1, 132.4, 131.7, 130.3, 129.9, 129.2 (2C), 128.1, 127.5, 126.7 (2C), 93.7, 59.3, 55.2, 54.9, 48.4, 36.9, 14.3, 11.8; HRMS (ESI-TOF) calcd for $C_{24}H_{23}{}^{35}Cl_2N_2O_4$ $[M + H]^+$ 473.1035, found 473.1041.

Ethyl *cis*-8-(benzylamino)-4-methyl-6-(naphthalen-2-yl)-1-oxo-2-oxa-3-azaspiro [4.4]nona-3,7-diene-7-carboxylate (9na).



Ethyl acetate/petroleum ether = 1:4 as the eluent; white solid, 90% yield (81.8 mg), dr > 99:1, mp 144–146 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.16 (s, 1H), 7.83–7.71 (m, 3H), 7.51 (s, 1H), 7.47–7.37 (m, 4H), 7.32 (dd, *J* = 10.7, 7.6 Hz, 3H), 7.18 (d, *J* = 7.6 Hz, 1H), 4.51 (qd, *J* = 14.4, 6.9 Hz, 2H), 4.42 (s, 1H), 4.02–3.85 (m, 2H), 3.18 (d, *J* = 17.4 Hz, 1H), 2.66 (d, *J* = 17.4 Hz, 1H), 2.03 (s, 3H), 0.86 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.2, 169.2, 167.2, 160.7, 138.3, 135.8, 133.3, 133.2, 129.2 (2C), 128.1, 128.0 (2C), 127.8, 126.9, 126.8, 126.7, 126.1 (2C), 125.9, 94.5, 59.2, 56.2, 55.6, 48.5, 37.0, 14.2, 12.0; HRMS (ESI-TOF) calcd for $C_{28}H_{27}N_2O_4$ $[M + H]^+$ 455.1971, found 455.1975.

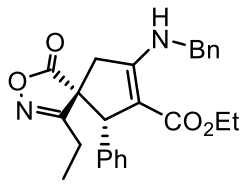
Ethyl *cis*-8-(benzylamino)-6-(furan-2-yl)-4-methyl-1-oxo-2-oxa-3-azaspiro[4.4]no na-3,7-diene-7-carboxylate (9oa).



Ethyl acetate/petroleum ether = 1:3 as the eluent; white solid, 83% yield (65.5 mg), dr > 99:1, mp 142–144 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10 (s, 1H), 7.38 (t, *J* = 7.4 Hz, 2H), 7.35–7.23 (m, 4H), 6.30 (dd, *J* = 3.1, 1.9 Hz, 1H), 6.10 (d, *J* = 3.2 Hz, 1H), 4.45 (qt, *J* = 16.5, 6.9 Hz, 2H), 4.30 (s, 1H), 4.12 (dq, *J* = 10.8, 7.1 Hz, 1H), 4.02 (dq, *J* = 10.8, 7.1 Hz, 1H), 3.21 (d, *J* = 17.1 Hz, 1H), 2.60 (d, *J* = 17.1 Hz, 1H), 1.92 (s, 3H), 1.09 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.0, 168.7, 166.9, 160.7, 151.4, 142.5, 138.2, 129.2 (2C), 128.0, 126.7 (2C), 110.4, 108.3, 92.2, 59.3, 54.3,

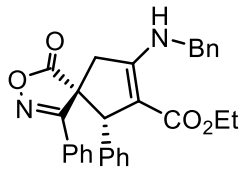
48.9, 48.4, 36.9, 14.4, 12.0; HRMS (ESI-TOF) calcd for $C_{22}H_{23}N_2O_5$ $[M + H]^+$ 395.1607, found 395.1611.

Ethyl *cis*-8-(benzylamino)-4-ethyl-1-oxo-6-phenyl-2-oxa-3-azaspiro[4.4]nona-3,7-diene-7-carboxylate (9pa).



Ethyl acetate/petroleum ether = 1:4 as the eluent; white solid, 91% yield (76.2 mg), dr > 99:1, mp 138–140 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.11 (s, 1H), 7.39 (t, J = 7.4 Hz, 2H), 7.34–7.19 (m, 6H), 7.05 (d, J = 7.0 Hz, 2H), 4.25 (s, 1H), 4.02 (dq, J = 10.8, 7.1 Hz, 1H), 3.92 (dq, J = 10.8, 7.1 Hz, 1H), 3.12 (d, J = 17.3 Hz, 1H), 2.68 (d, J = 17.3 Hz, 1H), 2.50 (dq, J = 17.6, 7.3 Hz, 1H), 2.16 (dq, J = 17.7, 7.3 Hz, 1H), 1.22 (t, J = 7.3 Hz, 3H), 0.93 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.5, 172.8, 167.2, 160.7, 138.3, 138.2, 129.2 (2C), 128.3 (2C), 128.0 (3C), 127.8, 126.8 (2C), 94.6, 59.2, 56.4, 55.7, 48.5, 37.1, 20.3, 14.2, 9.0; HRMS (ESI-TOF) calcd for $C_{25}H_{27}N_2O_4$ $[M + H]^+$ 419.1971, found 419.1977.

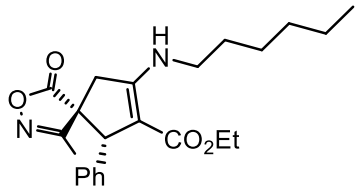
Ethyl *cis*-8-(benzylamino)-1-oxo-4,6-diphenyl-2-oxa-3-azaspiro[4.4]nona-3,7-diene-7-carboxylate (9qa).



Ethyl acetate/petroleum ether = 1:4 as the eluent; white solid, 85% yield (79.3 mg), dr > 99:1, mp 138–140 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.20 (s, 1H), 7.77 (d, J = 7.9 Hz, 2H), 7.55 (dd, J = 10.9, 3.9 Hz, 1H), 7.48 (t, J = 7.7 Hz, 2H), 7.39–7.31 (m, 2H), 7.31–7.22 (m, 6H), 7.11 (bs, 2H), 4.83 (s, 1H), 4.47 (qd, J = 14.0, 6.9 Hz, 2H), 4.06 (dq, J = 10.8, 7.1 Hz, 1H), 3.83 (dq, J = 10.8, 7.1 Hz, 1H), 3.31 (d, J = 17.8 Hz, 1H), 3.15 (d, J = 17.8 Hz, 1H), 0.82 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.6, 167.8, 167.3, 161.1, 138.6, 138.1, 132.1, 129.6 (2C), 129.1 (2C), 128.2 (2C), 128.0 (2C), 127.9 (2C), 126.9, 126.8 (2C), 126.7 (2C), 93.8, 59.1, 58.0, 55.4, 48.4, 39.3, 14.0; HRMS (ESI-TOF) calcd for $C_{29}H_{27}N_2O_4$ $[M + H]^+$ 467.1971, found 467.1975.

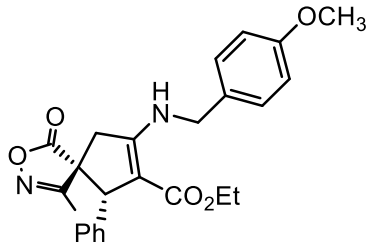
Ethyl *cis*-8-(hexylamino)-4-methyl-1-oxo-6-phenyl-2-oxa-3-azaspiro[4.4]nona-3,7-diene-7-carboxylate (9ab).

Ethyl acetate/petroleum ether = 1:8 as the eluent; white solid, 81% yield (64.6 mg),



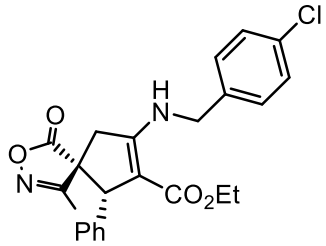
dr > 99:1, mp 101–103 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 (s, 1H), 7.37–7.16 (m, 3H), 7.05 (d, J = 7.1 Hz, 2H), 4.27 (s, 1H), 4.08–3.96 (m, 1H), 3.95–3.80 (m, 1H), 3.24 (dd, J = 13.5, 6.7 Hz, 2H), 3.14 (d, J = 17.2 Hz, 1H), 2.74 (d, J = 17.3 Hz, 1H), 2.14 (s, 3H), 1.68–1.54 (m, 2H), 1.47–1.25 (m, 6H), 0.91 (t, J = 6.6 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.4, 169.2, 167.2, 160.6, 138.4, 128.2 (2C), 127.9 (2C), 127.7, 92.6, 58.9, 56.0, 55.6, 45.0, 36.8, 31.5, 31.0, 26.5, 22.6, 14.2, 14.1, 12.0; HRMS (ESI-TOF) calcd for $C_{23}H_{31}N_2O_4$ $[M + H]^+$ 399.2284, found 399.2289.

Ethyl *cis*-8-((4-methoxybenzyl)amino)-4-methyl-1-oxo-6-phenyl-2-oxa-3-azaspiro [4.4]nona-3,7-diene-7-carboxylate (9ac).



Ethyl acetate/petroleum ether = 1:3 as the eluent; white solid, 89% yield (77.3 mg), dr > 99:1, mp 113–115 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04 (s, 1H), 7.34–7.16 (m, 5H), 7.05 (d, J = 7.0 Hz, 2H), 6.90 (d, J = 8.6 Hz, 2H), 4.38 (qd, J = 15.5, 6.5 Hz, 2H), 4.25 (s, 1H), 4.00 (dq, J = 10.8, 7.1 Hz, 1H), 3.91 (dq, J = 10.8, 7.1 Hz, 1H), 3.80 (s, 3H), 3.11 (d, J = 17.3 Hz, 1H), 2.68 (d, J = 17.4 Hz, 1H), 2.01 (s, 3H), 0.92 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.2, 169.2, 167.0, 160.5, 159.2, 138.2, 130.2, 128.2 (2C), 128.0 (2C), 127.9 (2C), 127.8, 114.4 (2C), 94.0, 59.0, 56.0, 55.5, 55.4, 47.9, 36.8, 14.2, 11.9; HRMS (ESI-TOF) calcd for $C_{25}H_{27}N_2O_5$ $[M + H]^+$ 435.1920, found 435.1923.

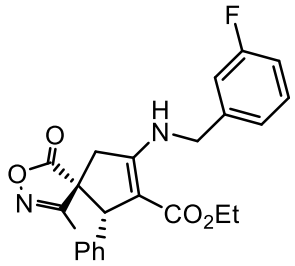
Ethyl *cis*-8-((4-chlorobenzyl)amino)-4-methyl-1-oxo-6-phenyl-2-oxa-3-azaspiro[4. 4]nona-3,7-diene-7-carboxylate (9ad).



Ethyl acetate/petroleum ether = 1:4 as the eluent; white solid, 90% yield (79.0 mg), dr > 99:1, mp 120–122 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.07 (s, 1H), 7.36 (dd, J = 8.7, 2.1 Hz, 2H), 7.30–7.19 (m, 6H), 7.04 (d, J = 6.9 Hz, 2H), 4.42 (qd, J = 16.0, 6.6 Hz, 2H), 4.27 (s, 1H), 4.01 (dq, J = 10.8, 7.1 Hz, 1H), 3.91 (dq, J = 10.8, 7.1 Hz, 1H), 3.10 (d, J = 17.3 Hz, 1H), 2.65 (d,

J = 17.3 Hz, 1H), 2.03 (s, 3H), 0.92 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) *δ* 177.2, 168.9, 167.1, 160.3, 138.0, 136.8, 133.8, 129.3 (2C), 128.3 (2C), 128.1 (2C), 127.9 (3C), 94.8, 59.2, 56.1, 55.6, 47.8, 36.8, 14.2, 12.0; HRMS (ESI-TOF) calcd for $C_{24}H_{24}{}^{35}ClN_2O_4$ $[M + H]^+$ 439.1425, found 439.1434.

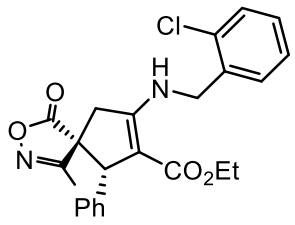
Ethyl *cis*-8-((3-fluorobenzyl)amino)-4-methyl-1-oxo-6-phenyl-2-oxa-3-azaspiro[4.4]nona-3,7-diene-7-carboxylate (9ae).



Ethyl acetate/petroleum ether = 1:3 as the eluent; white solid, 88% yield (74.4 mg), dr > 99:1, mp 130–132 °C; ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 8.11 (s, 1H), 7.41–7.33 (m, 1H), 7.32–7.20 (m, 3H), 7.15–6.92 (m, 5H), 4.47 (qd, *J* = 16.2, 6.7 Hz, 2H), 4.27 (s, 1H), 4.03 (dq, *J* = 10.8, 7.1 Hz, 1H), 3.93 (dq, *J* = 10.8, 7.1 Hz, 1H), 3.12 (d, *J* = 17.2 Hz, 1H), 2.64 (d, *J* = 17.3 Hz, 1H), 2.04 (s, 3H), 0.93 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) *δ* 177.2, 169.0, 167.2, 163.4 (d, *J* = 245.9 Hz),

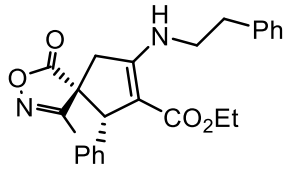
160.3, 141.1 (d, *J* = 6.5 Hz), 138.0, 130.9 (d, *J* = 8.2 Hz), 128.4 (2C), 128.0 (3C), 122.2 (d, *J* = 11.2 Hz), 115.0 (d, *J* = 21.0 Hz), 113.6 (d, *J* = 21.9 Hz), 95.0, 59.3, 56.2, 55.6, 47.9, 36.8, 14.2, 12.0; HRMS (ESI-TOF) calcd for $C_{24}H_{24}FN_2O_4$ $[M + H]^+$ 423.1720, found 423.1727.

Ethyl *cis*-8-((2-chlorobenzyl)amino)-4-methyl-1-oxo-6-phenyl-2-oxa-3-azaspiro[4.4]nona-3,7-diene-7-carboxylate (9af).



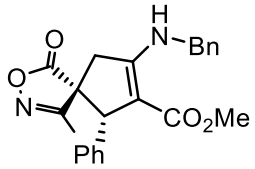
Ethyl acetate/petroleum ether = 1:4 as the eluent; white solid, 84% yield (73.7 mg), dr > 99:1, mp 174–176 °C; ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 8.09 (s, 1H), 7.41 (d, *J* = 7.6 Hz, 1H), 7.38 (d, *J* = 7.2 Hz, 1H), 7.35–7.19 (m, 5H), 7.06 (d, *J* = 7.1 Hz, 2H), 4.63–4.44 (m, 2H), 4.27 (s, 1H), 4.02 (dq, *J* = 10.8, 7.1 Hz, 1H), 3.92 (dq, *J* = 10.8, 7.1 Hz, 1H), 3.17 (d, *J* = 17.3 Hz, 1H), 2.73 (d, *J* = 17.3 Hz, 1H), 2.05 (s, 3H), 0.93 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) *δ* 177.2, 169.1, 167.1, 160.2, 138.1, 135.8, 133.1, 130.1, 129.4, 128.4 (3C), 128.0 (2C), 127.9, 127.5, 94.7, 59.2, 56.2, 55.6, 46.5, 36.7, 14.2, 12.0; HRMS (ESI-TOF) calcd for $C_{24}H_{24}{}^{35}ClN_2O_4$ $[M + H]^+$ 439.1425, found 439.1430.

Ethyl *cis*-4-methyl-1-oxo-8-(phenethylamino)-6-phenyl-2-oxa-3-azaspiro[4.4]non a-3,7-diene-7-carboxylate (9ag).



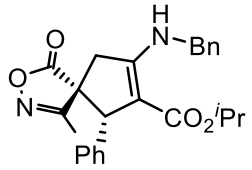
Ethyl acetate/petroleum ether = 1:4 as the eluent; white solid, 90% yield (75.3 mg), dr > 99:1, mp 153–155 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 (s, 1H), 7.33 (t, J = 7.4 Hz, 2H), 7.30–7.14 (m, 6H), 6.98 (d, J = 7.1 Hz, 2H), 4.18 (s, 1H), 3.98 (dq, J = 10.9, 7.1 Hz, 1H), 3.94–3.78 (m, 1H), 3.61–3.38 (m, 2H), 3.04–2.78 (m, 3H), 2.43 (d, J = 17.2 Hz, 1H), 1.94 (s, 3H), 0.89 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.3, 169.1, 167.0, 160.3, 138.3, 138.2, 129.0 (2C), 128.9 (2C), 128.2 (2C), 127.9 (2C), 127.7, 127.0, 92.9, 58.9, 56.0, 55.4, 46.6, 37.8, 36.7, 14.2, 11.8; HRMS (ESI-TOF) calcd for $C_{25}H_{27}N_2O_4$ $[M + H]^+$ 419.1971, found 419.1977.

Methyl *cis*-8-(benzylamino)-4-methyl-1-oxo-6-phenyl-2-oxa-3-azaspiro[4.4]nona-3,7-diene-7-carboxylate (9ah).



Ethyl acetate/petroleum ether = 1:4 as the eluent; white solid, 90% yield (70.3 mg), dr > 99:1, mp 166–168 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.14 (s, 1H), 7.37 (t, J = 7.4 Hz, 2H), 7.33–7.18 (m, 6H), 7.05 (d, J = 7.0 Hz, 2H), 4.43 (qd, J = 15.9, 6.6 Hz, 2H), 4.25 (s, 1H), 3.49 (s, 3H), 3.09 (d, J = 17.4 Hz, 1H), 2.63 (d, J = 17.4 Hz, 1H), 1.96 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.0, 169.2, 167.4, 160.9, 138.2, 138.0, 129.1 (2C), 128.4 (2C), 127.9 (2C), 127.8 (2C), 126.6 (2C), 93.7, 55.8, 55.6, 50.6, 48.3, 36.6, 11.8; HRMS (ESI-TOF) calcd for $C_{23}H_{23}N_2O_4$ $[M + H]^+$ 391.1658, found 391.1661.

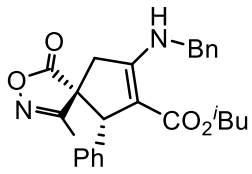
Isopropyl *cis*-8-(benzylamino)-4-methyl-1-oxo-6-phenyl-2-oxa-3-azaspiro[4.4]non a-3,7-diene-7-carboxylate (9ai).



Ethyl acetate/petroleum ether = 1:4 as the eluent; white solid, 91% yield (76.2 mg), dr > 99:1, mp 129–131 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 (s, 1H), 7.39 (t, J = 7.4 Hz, 2H), 7.34–7.18 (m, 6H), 7.05 (d, J = 7.1 Hz, 2H), 4.85 (dt, J = 12.4, 6.2 Hz, 1H), 4.46 (qd, J = 15.8, 6.6 Hz, 2H), 4.24 (s, 1H), 3.13 (d, J = 17.3 Hz, 1H), 2.67 (d, J = 17.3 Hz, 1H), 2.02 (s, 3H), 1.08 (d, J = 6.2 Hz, 3H), 0.73 (d, J = 6.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$)

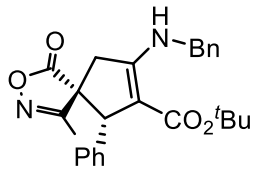
δ 177.3, 169.1, 166.8, 160.3, 138.4, 138.3, 129.2 (2C), 128.2 (2C), 128.0 (3C), 127.8, 126.8 (2C), 94.9, 66.4, 56.3, 55.5, 48.5, 36.9, 22.1, 21.5, 12.0; HRMS (ESI-TOF) calcd for $C_{25}H_{27}N_2O_4$ $[M + H]^+$ 419.1971, found 419.1968.

Isobutyl *cis*-8-(benzylamino)-4-methyl-1-oxo-6-phenyl-2-oxa-3-azaspiro[4.4]nona-3,7-diene-7-carboxylate (9aj).



Ethyl acetate/petroleum ether = 1:4 as the eluent; white solid, 87% yield (75.3 mg), dr > 99:1, mp 165–167 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.14 (s, 1H), 7.38 (t, J = 7.4 Hz, 2H), 7.34–7.17 (m, 6H), 7.06 (d, J = 6.8 Hz, 2H), 4.46 (qd, J = 15.8, 6.6 Hz, 2H), 4.25 (s, 1H), 3.85 (dd, J = 10.5, 6.5 Hz, 1H), 3.59 (dd, J = 10.5, 6.0 Hz, 1H), 3.13 (d, J = 17.3 Hz, 1H), 2.66 (d, J = 17.3 Hz, 1H), 1.99 (s, 3H), 1.62–1.49 (m, 1H), 0.53 (d, J = 2.8 Hz, 3H), 0.52 (d, J = 2.7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.2, 169.2, 167.2, 160.7, 138.3, 138.2, 129.2 (2C), 128.4 (2C), 128.0 (2C), 127.9 (2C), 126.7 (2C), 94.4, 69.3, 56.2, 55.5, 48.4, 36.8, 27.8, 18.7 (2C), 11.9; HRMS (ESI-TOF) calcd for $C_{26}H_{29}N_2O_4$ $[M + H]^+$ 433.2127, found 433.2132.

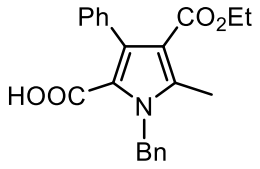
***tert*-Butyl *cis*-8-(benzylamino)-4-methyl-1-oxo-6-phenyl-2-oxa-3-azaspiro[4.4]nona-3,7-diene-7-carboxylate (9ak).**



Ethyl acetate/petroleum ether = 1:4 as the eluent; white solid, 90% yield (77.9 mg), dr > 99:1, mp 112–114 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (s, 1H), 7.39 (t, J = 7.5 Hz, 2H), 7.35–7.18 (m, 6H), 7.06 (d, J = 6.1 Hz, 2H), 4.44 (qd, J = 15.8, 6.5 Hz, 2H), 4.20 (s, 1H), 3.11 (d, J = 17.3 Hz, 1H), 2.66 (d, J = 17.3 Hz, 1H), 2.03 (s, 3H), 1.15 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.5, 169.1, 167.0, 159.7, 138.5 (2C), 129.1 (2C), 128.2 (2C), 128.1 (2C), 127.9, 127.7, 126.8 (2C), 95.8, 79.5, 56.6, 55.4, 48.4, 36.9, 28.2 (3C), 12.0; HRMS (ESI-TOF) calcd for $C_{26}H_{29}N_2O_4$ $[M + H]^+$ 433.2127, found 433.2125.

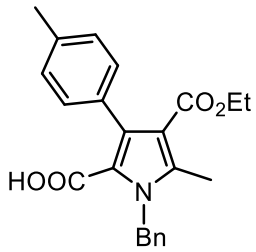
1-Benzyl-4-(ethoxycarbonyl)-5-methyl-3-phenyl-1*H*-pyrrole-2-carboxylic acid (10aa).

Ethyl acetate/petroleum ether = 1:4 as the eluent; White solid, 93% yield (67.6 mg), mp 139–141 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37–7.22 (m, 8H), 6.97 (d, J = 7.3



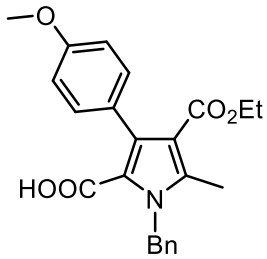
Hz, 2H), 5.66 (s, 2H), 3.96 (q, *J* = 7.1 Hz, 2H), 2.51 (s, 3H),0.86 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.0, 164.5, 142.4, 137.2, 136.0, 135.9, 129.8 (2C), 128.9 (2C), 127.42, 127.28 (2C), 127.0, 126.1 (2C), 118.8, 114.4, 59.7, 48.8, 13.7, 11.9; HRMS (ESI-TOF) calcd for $C_{22}H_{22}NO_4$ $[M + H]^+$ 364.1549, found 364.1556.

1-Benzyl-4-(ethoxycarbonyl)-5-methyl-3-(*p*-tolyl)-1*H*-pyrrole-2-carboxylic acid (10ba).



Ethyl acetate/petroleum ether = 1:4 as the eluent; White solid, 93% yield (70.2 mg), mp 148–150 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 (t, *J* = 7.3 Hz, 2H), 7.23 (t, *J* = 7.3 Hz, 1H), 7.14 (s, 4H), 6.96 (d, *J* = 7.4 Hz, 2H), 5.65 (s, 2H), 3.98 (q, *J* = 7.1 Hz, 2H), 2.49 (s, 3H), 2.38 (s, 3H), 0.92 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.0, 164.1, 142.2, 137.2, 136.8, 136.0, 132.5, 129.7 (2C), 128.9 (2C), 128.3 (2C), 127.4, 126.2 (2C), 118.8, 114.4, 59.8, 48.8, 21.5, 13.8, 11.9; HRMS (ESI-TOF) calcd for $C_{23}H_{24}NO_4$ $[M + H]^+$ 378.1705, found 378.1702.

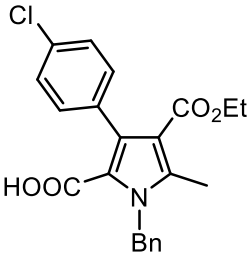
1-Benzyl-4-(ethoxycarbonyl)-3-(4-methoxyphenyl)-5-methyl-1*H*-pyrrole-2-carboxylic acid (10ca).



Ethyl acetate/petroleum ether = 1:3 as the eluent; Yellow solid, 91% yield (71.6 mg), mp 144–146 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 (t, *J* = 7.3 Hz, 2H), 7.23 (t, *J* = 7.2 Hz, 1H), 7.16 (d, *J* = 8.5 Hz, 2H), 6.95 (d, *J* = 7.4 Hz, 2H), 6.87 (d, *J* = 8.5 Hz, 2H), 5.64 (s, 2H), 3.99 (q, *J* = 7.1 Hz, 2H), 3.83 (s, 3H), 2.48 (s, 3H), 0.94 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.04, 164.97, 158.8, 142.3, 137.2, 135.8, 130.9 (2C), 128.8 (2C), 127.8, 127.4, 126.1 (2C), 118.9, 114.5, 112.9 (2C), 59.8, 55.3, 48.8, 13.9, 11.9; HRMS (ESI-TOF) calcd for $C_{23}H_{24}NO_5$ $[M + H]^+$ 394.1654, found 394.1652.

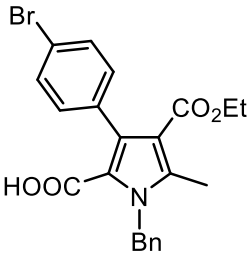
1-Benzyl-3-(4-chlorophenyl)-4-(ethoxycarbonyl)-5-methyl-1*H*-pyrrole-2-carboxylic acid (10da).

Ethyl acetate/petroleum ether = 1:4 as the eluent; Yellow solid, 86% yield (68.4 mg), mp 131–133 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29–7.20 (m, 5H), 7.12 (d, *J* = 8.3



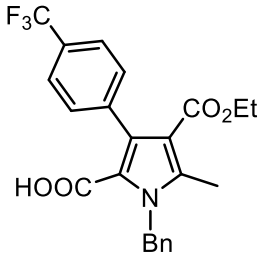
Hz, 2H), 6.91 (d, *J* = 7.1 Hz, 2H), 5.57 (s, 2H), 3.98 (q, *J* = 7.1 Hz, 2H), 2.48 (s, 3H), 0.93 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.4, 164.8, 142.4, 137.1, 134.7 (2C), 132.6, 131.2 (2C), 128.9 (2C), 127.4, 127.3 (2C), 126.0 (2C), 119.3, 114.2, 59.9, 48.7, 13.8, 11.9; HRMS (ESI-TOF) calcd for $C_{22}H_{21}{}^{35}ClNO_4$ $[M + H]^+$ 398.1159, found 398.1163.

1-Benzyl-3-(4-bromophenyl)-4-(ethoxycarbonyl)-5-methyl-1*H*-pyrrole-2-carboxy lic acid (10ea).



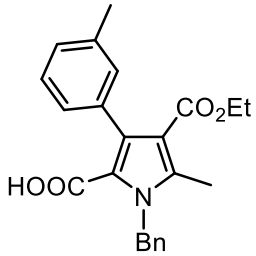
Ethyl acetate/petroleum ether = 1:4 as the eluent; Yellow solid, 82% yield (72.5 mg), mp 145–147 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 (d, *J* = 8.3 Hz, 2H), 7.29 (t, *J* = 7.3 Hz, 2H), 7.25 (t, *J* = 7.3 Hz, 1H), 7.10 (d, *J* = 8.3 Hz, 2H), 6.94 (d, *J* = 7.1 Hz, 2H), 5.63 (s, 2H), 3.98 (q, *J* = 7.1 Hz, 2H), 2.50 (s, 3H), 0.93 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.8, 164.7, 142.7, 137.0, 135.2, 135.1, 131.5 (2C), 130.4 (2C), 128.9 (2C), 127.5, 126.1 (2C), 121.0, 118.7, 114.3, 59.9, 48.8, 13.8, 11.9; HRMS (ESI-TOF) calcd for $C_{22}H_{21}{}^{79}BrNO_4$ $[M + H]^+$ 442.0654, found 442.0650.

1-Benzyl-4-(ethoxycarbonyl)-5-methyl-3-(4-(trifluoromethyl)phenyl)-1*H*-pyrrole-2-carboxylic acid (10fa).



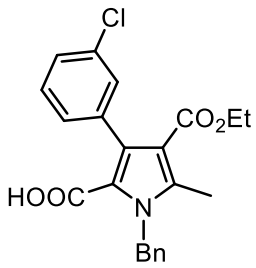
Ethyl acetate/petroleum ether = 1:2 as the eluent; White solid, 82% yield (70.8 mg), mp 109–111 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.81 (bs, 1H), 7.40 (d, *J* = 7.6 Hz, 2H), 7.21–7.09 (m, 5H), 6.79 (d, *J* = 5.5 Hz, 2H), 5.38 (s, 2H), 3.94 (q, *J* = 7.1 Hz, 2H), 2.44 (s, 3H), 0.84 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.8, 164.8, 141.5, 140.9, 137.3, 132.8, 130.2 (2C), 128.8 (2C), 128.6 (q, *J* = 32.0 Hz), 127.3, 125.8 (2C), 124.4 (q, *J* = 271.9 Hz), 123.8 (q, *J* = 3.2 Hz, 2C), 121.2, 113.5, 59.8, 48.4, 13.5, 11.7; ^{19}F NMR (471 MHz, $CDCl_3$) δ -62.16 (s, 3F); HRMS (ESI-TOF) calcd for $C_{23}H_{21}F_3NO_4$ $[M + H]^+$ 432.1423, found 432.1429.

1-Benzyl-4-(ethoxycarbonyl)-5-methyl-3-(*m*-tolyl)-1*H*-pyrrole-2-carboxylic acid (10ga).



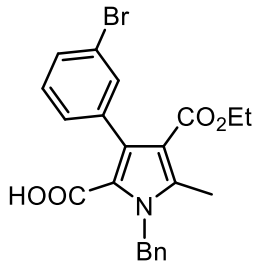
Ethyl acetate/petroleum ether = 1:4 as the eluent; White solid, 89% yield (67.2 mg), mp 144–146 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.87 (bs, 1H), 7.29–7.16 (m, 4H), 7.09 (d, J = 7.4 Hz, 1H), 7.04 (s, 1H), 7.02 (d, J = 8.0 Hz, 1H), 6.93 (d, J = 7.3 Hz, 2H), 5.60 (s, 2H), 3.95 (q, J = 7.1 Hz, 2H), 2.47 (s, 3H), 2.32 (s, 3H), 0.86 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.2, 165.1, 142.2, 137.2, 136.6, 136.1, 135.7, 130.4, 128.8 (2C), 127.7, 127.3, 127.2, 126.8, 126.1 (2C), 118.8, 114.4, 59.7, 48.7, 21.5, 13.6, 11.8; HRMS (ESI-TOF) calcd for $C_{23}H_{24}NO_4$ [M + H]$^+$ 378.1705, found 378.1704.

1-Benzyl-3-(3-chlorophenyl)-4-(ethoxycarbonyl)-5-methyl-1*H*-pyrrole-2-carboxyl ic acid (10ha).



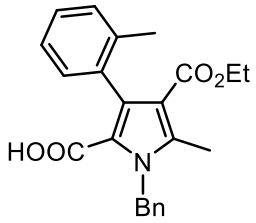
Ethyl acetate/petroleum ether = 1:4 as the eluent; Yellow solid, 86% yield (68.4 mg), mp 152–154 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31–7.26 (m, 3H), 7.26–7.20 (m, 3H), 7.10 (d, J = 7.5 Hz, 1H), 6.93 (d, J = 7.3 Hz, 2H), 5.62 (s, 2H), 3.97 (q, J = 7.1 Hz, 2H), 2.50 (s, 3H), 0.90 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.0, 164.7, 142.7, 138.1, 137.0, 134.7, 132.9, 129.9, 128.9 (2C), 128.4, 128.1, 127.5, 126.9, 126.1 (2C), 118.8, 114.3, 59.8, 48.8, 13.7, 11.9; HRMS (ESI-TOF) calcd for $C_{22}H_{21}{}^{35}ClNO_4$ [M + H]$^+$ 398.1159, found 398.1162.

1-Benzyl-3-(3-bromophenyl)-4-(ethoxycarbonyl)-5-methyl-1*H*-pyrrole-2-carboxy lic acid (10ia).



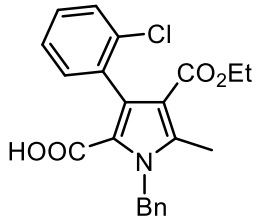
Ethyl acetate/petroleum ether = 1:4 as the eluent; Yellow solid, 84% yield (74.3 mg), mp 159–161 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (d, J = 7.3 Hz, 1H), 7.39 (s, 1H), 7.32–7.21 (m, 3H), 7.20–7.13 (m, 2H), 6.93 (d, J = 7.4 Hz, 2H), 5.62 (s, 2H), 3.97 (q, J = 7.1 Hz, 2H), 2.50 (s, 3H), 0.90 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.1, 164.7, 142.8, 138.3, 137.0, 134.6, 132.7, 129.8, 128.9 (2C), 128.7, 128.5, 127.5, 126.1 (2C), 121.1, 118.8, 114.3, 59.8, 48.8, 13.7, 11.9; HRMS (ESI-TOF) calcd for $C_{22}H_{21}{}^{79}BrNO_4$ [M + H]$^+$ 442.0654, found 442.0658.

1-Benzyl-4-(ethoxycarbonyl)-5-methyl-3-(*o*-tolyl)-1*H*-pyrrole-2-carboxylic acid (10ja).



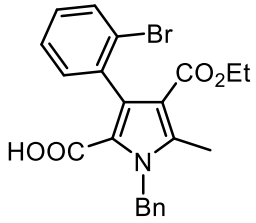
Ethyl acetate/petroleum ether = 1:4 as the eluent; White solid, 90% yield (67.9 mg), mp 143–145 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27 (t, J = 7.1 Hz, 2H), 7.25–7.16 (m, 3H), 7.13 (t, J = 7.1 Hz, 1H), 7.05 (d, J = 7.4 Hz, 1H), 6.92 (d, J = 7.5 Hz, 2H), 5.70 (d, J = 16.3 Hz, 1H), 5.61 (d, J = 16.3 Hz, 1H), 3.95–3.85 (m, 2H), 2.50 (s, 3H), 2.08 (s, 3H), 0.81 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.9, 164.7, 143.0, 137.3, 136.6, 136.0, 135.5, 129.3, 129.1, 128.8 (2C), 127.4, 127.2, 126.0 (2C), 124.9, 118.6, 114.0, 59.6, 48.7, 20.2, 13.6, 11.9 ; HRMS (ESI-TOF) calcd for $C_{23}H_{24}NO_4$ $[M + H]^+$ 378.1705, found 378.1705.

1-Benzyl-3-(2-chlorophenyl)-4-(ethoxycarbonyl)-5-methyl-1*H*-pyrrole-2-carboxylic acid (10ka).



Ethyl acetate/petroleum ether = 1:4 as the eluent; Yellow solid, 84% yield (66.8 mg), mp 145–147 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 (d, J = 7.6 Hz, 1H), 7.22–7.08 (m, 6H), 6.85 (d, J = 7.4 Hz, 2H), 5.56 (s, 2H), 3.94–3.81 (m, 2H), 2.43 (s, 3H), 0.77 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.0, 164.6, 142.8, 137.2, 135.9, 133.8, 133.0, 131.1, 128.9 (2C), 128.5, 128.2, 127.4, 126.0 (2C), 125.8, 119.2, 114.0, 59.7, 48.7, 13.6, 11.9; HRMS (ESI-TOF) calcd for $C_{22}H_{21}{}^{35}ClNO_4$ $[M + H]^+$ 398.1159, found 398.1163.

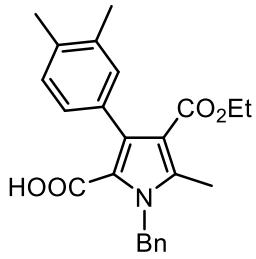
1-Benzyl-3-(2-bromophenyl)-4-(ethoxycarbonyl)-5-methyl-1*H*-pyrrole-2-carboxylic acid (10la).



Ethyl acetate/petroleum ether = 1:4 as the eluent; Yellow solid, 81% yield (71.7 mg), mp 151–153 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 (d, J = 7.9 Hz, 1H), 7.24–7.12 (m, 4H), 7.10 (d, J = 7.3 Hz, 1H), 7.07 (t, J = 7.4 Hz, 1H), 6.86 (d, J = 7.3 Hz, 2H), 5.62 (d, J = 16.3 Hz, 1H), 5.51 (d, J = 16.3 Hz, 1H), 3.94–3.79 (m, 2H), 2.43 (s, 3H), 0.76 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.0, 164.6, 142.8, 138.0, 137.1, 134.8, 131.6, 130.9, 128.9 (2C), 128.3, 127.4, 126.4, 126.0 (2C), 124.2, 119.0,

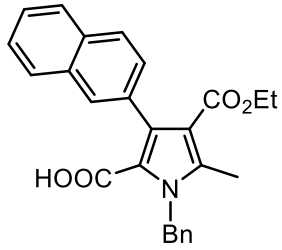
113.9, 59.7, 48.7, 13.6, 11.9; HRMS (ESI-TOF) calcd for $C_{22}H_{21}{}^{79}BrNO_4$ $[M + H]^+$ 442.0654, found 442.0648.

1-Benzyl-3-(3,4-dimethylphenyl)-4-(ethoxycarbonyl)-5-methyl-1*H*-pyrrole-2-carboxylic acid (10ma).



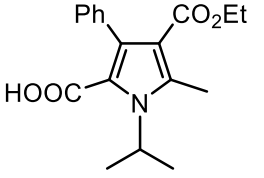
Ethyl acetate/petroleum ether = 1:3 as the eluent; Yellow solid, 87% yield (68.1 mg), mp 145–147 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 (t, J = 7.3 Hz, 2H), 7.23 (t, J = 7.3 Hz, 1H), 7.10 (d, J = 7.6 Hz, 1H), 7.03 (s, 1H), 6.99 (d, J = 7.7 Hz, 1H), 6.96 (d, J = 7.3 Hz, 2H), 5.65 (s, 2H), 3.98 (q, J = 7.1 Hz, 2H), 2.48 (s, 3H), 2.28 (s, 3H), 2.25 (s, 3H), 0.91 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.0, 164.2, 142.2, 137.2, 136.0, 135.57, 135.55, 132.6, 131.0, 128.9, 128.8 (2C), 127.4, 127.2, 126.2 (2C), 118.8, 114.4, 59.7, 48.8, 19.9, 19.7, 13.7, 11.9; HRMS (ESI-TOF) calcd for $C_{24}H_{26}NO_4$ $[M + H]^+$ 392.1862, found 392.1855.

1-Benzyl-4-(ethoxycarbonyl)-5-methyl-3-(naphthalen-2-yl)-1*H*-pyrrole-2-carboxylic acid (10na).



Ethyl acetate/petroleum ether = 1:4 as the eluent; White solid, 85% yield (70.3 mg), mp 159–161 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84 (d, J = 4.6 Hz, 1H), 7.77 (d, J = 6.6 Hz, 2H), 7.67(s, 1H), 7.49–7.42 (m, 2H), 7.36 (d, J = 7.6 Hz, 1H), 7.25–7.14 (m, 3H), 6.90 (d, J = 4.7 Hz, 2H), 5.59 (s, 2H), 3.86 (q, J = 6.9 Hz, 2H), 2.48 (s, 3H), 0.64 (t, J = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.0 (2C), 142.5, 137.1, 136.0, 133.6, 133.0, 132.6, 128.8 (2C), 128.6, 128.3, 128.1, 127.7, 127.4, 126.5, 126.1 (2C), 125.7, 125.6, 118.9, 114.6, 59.7, 48.7, 13.6, 11.9; HRMS (ESI-TOF) calcd for $C_{26}H_{24}NO_4$ $[M + H]^+$ 414.1705, found 414.1703.

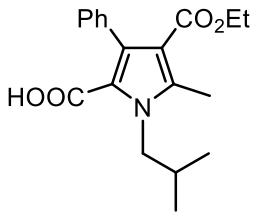
4-(Ethoxycarbonyl)-1-isopropyl-5-methyl-3-phenyl-1*H*-pyrrole-2-carboxylic acid (10ab).



Ethyl acetate/petroleum ether = 1:8 as the eluent; Yellow oil, 83% yield (52.4 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32–7.26 (m,

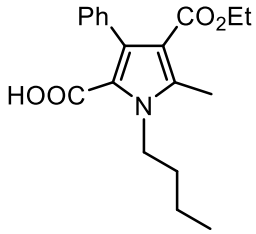
3H), 7.20 (d, *J* = 6.8 Hz, 2H), 5.32 (bs, 1H), 3.93 (q, *J* = 7.1 Hz, 2H), 2.67 (s, 3H), 1.55 (d, *J* = 6.9 Hz, 6H), 0.83 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) *δ* 165.3 (2C), 141.0, 136.4, 134.4, 129.8 (2C), 127.3 (2C), 126.8, 120.1, 114.3, 59.6, 49.3, 21.8 (2C), 13.7, 13.5; HRMS (ESI-TOF) calcd for $C_{18}H_{22}NO_4$ $[M + H]^+$ 316.1549, found 316.1551.

4-(Ethoxycarbonyl)-1-isobutyl-5-methyl-3-phenyl-1*H*-pyrrole-2-carboxylic acid (10ac).



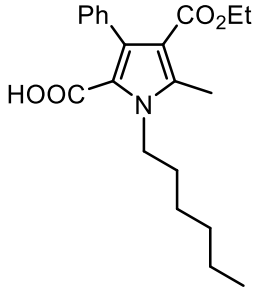
Ethyl acetate/petroleum ether = 1:8 as the eluent; Yellow oil, 81% yield (52.9 mg); ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 7.34–7.28 (m, 3H), 7.23–7.20 (m, 2H), 4.17 (bs, 2H), 3.94 (q, *J* = 7.1 Hz, 2H), 2.57 (s, 3H), 2.08–1.98 (m, 1H), 0.88 (d, *J* = 6.8 Hz, 6H), 0.85 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) *δ* 165.2, 164.6, 141.9, 136.2, 135.9, 129.7 (2C), 127.3 (2C), 126.9, 118.7, 113.8, 59.6, 52.1, 30.3, 19.9 (2C), 13.7, 12.3; HRMS (ESI-TOF) calcd for $C_{19}H_{24}NO_4$ $[M + H]^+$ 330.1705, found 330.1689.

1-Butyl-4-(ethoxycarbonyl)-5-methyl-3-phenyl-1*H*-pyrrole-2-carboxylic acid (10ad).



Ethyl acetate/petroleum ether = 1:8 as the eluent; Brown solid, 86% yield (56.7 mg), mp 71–73 °C; ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 7.74 (bs, 1H), 7.32–7.24 (m, 3H), 7.18 (d, *J* = 6.3 Hz, 2H), 4.27 (t, *J* = 7.2 Hz, 2H), 3.93 (q, *J* = 7.1 Hz, 2H), 2.57 (s, 3H), 1.69–1.59 (m, 2H), 1.37–1.28 (m, 2H), 0.91 (t, *J* = 7.3 Hz, 3H), 0.85 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) *δ* 165.2 (2C), 141.1, 136.3, 135.5, 129.7 (2C), 127.2 (2C), 126.7, 118.8, 113.7, 59.6, 45.5, 33.0, 20.0, 13.8, 13.7, 11.7; HRMS (ESI-TOF) calcd for $C_{19}H_{24}NO_4$ $[M + H]^+$ 330.1705, found 330.1706.

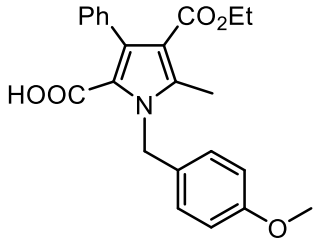
4-(Ethoxycarbonyl)-1-hexyl-5-methyl-3-phenyl-1*H*-pyrrole-2-carboxylic acid (10ae).



Ethyl acetate/petroleum ether = 1:8 as the eluent; Yellow oil, 79% yield (56.5 mg); ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 7.34–7.29 (m, 3H), 7.24–7.20 (m, 2H), 4.32–4.27 (m, 2H), 3.94 (q, *J* = 7.1 Hz,

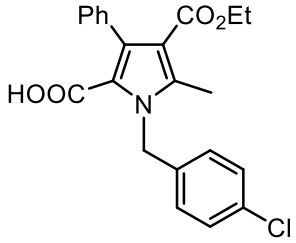
2H), 2.58 (s, 3H), 1.72–1.65 (m, 2H), 1.35–1.27 (m, 6H), 0.89 (t, *J* = 6.8 Hz, 3H), 0.85 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) *δ* 165.1, 164.1, 141.4, 136.1, 135.7, 129.8 (2C), 127.4 (2C), 127.0, 118.2, 113.8, 59.6, 45.8, 31.4, 30.9, 26.5, 22.6, 14.1, 13.7, 11.7; HRMS (ESI-TOF) calcd for $C_{21}H_{28}NO_4$ $[M + H]^+$ 358.2018, found 358.2019.

4-(Ethoxycarbonyl)-1-(4-methoxybenzyl)-5-methyl-3-phenyl-1*H*-pyrrole-2-carboxylic acid (10af).



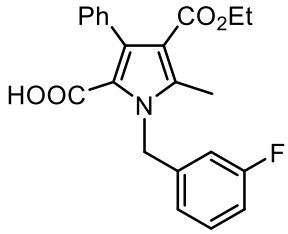
Ethyl acetate/petroleum ether = 1:2 as the eluent; White solid, 91% yield (71.6 mg), mp 135–137 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33–7.26 (m, 3H), 7.24–7.18 (m, 2H), 6.89 (d, *J* = 8.5 Hz, 2H), 6.80 (d, *J* = 8.5 Hz, 2H), 5.54 (s, 2H), 3.94 (q, *J* = 7.2 Hz, 2H), 3.76 (s, 3H), 2.50 (s, 3H), 0.85 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) *δ* 165.3, 165.0, 158.8, 142.2, 136.1, 136.0, 129.7 (2C), 129.2, 127.5 (2C), 127.2 (2C), 126.8, 118.7, 114.3, 114.2 (2C), 59.7, 55.4, 48.2, 13.6, 11.9; HRMS (ESI-TOF) calcd for $C_{23}H_{24}NO_5$ $[M + H]^+$ 394.1654, found 394.1651.

1-(4-Chlorobenzyl)-4-(ethoxycarbonyl)-5-methyl-3-phenyl-1*H*-pyrrole-2-carboxylic acid (10ag).



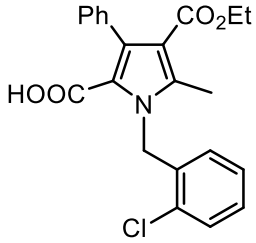
Ethyl acetate/petroleum ether = 1:4 as the eluent; Yellow solid, 90% yield (71.6 mg), mp 153–155 °C; ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 7.34–7.28 (m, 3H), 7.24 (d, *J* = 8.3 Hz, 2H), 7.22–7.17 (m, 2H), 6.86 (d, *J* = 8.2 Hz, 2H), 5.55 (s, 2H), 3.94 (q, *J* = 7.2 Hz, 2H), 2.48 (s, 3H), 0.85 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) *δ* 165.2, 164.9, 142.2, 136.3, 135.8, 135.7, 133.2, 129.7 (2C), 129.0 (2C), 127.5 (2C), 127.3 (2C), 126.9, 118.6, 114.6, 59.8, 48.2, 13.6, 11.8; HRMS (ESI-TOF) calcd for $C_{22}H_{21}{}^{35}ClNO_4$ $[M + H]^+$ 398.1159, found 398.1164.

4-(Ethoxycarbonyl)-1-(3-fluorobenzyl)-5-methyl-3-phenyl-1*H*-pyrrole-2-carboxylic acid (10ah).



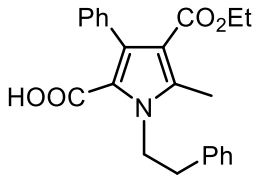
Ethyl acetate/petroleum ether = 1:3 as the eluent; White solid, 84% yield (64.1 mg), mp 138–140 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26–7.11 (m, 6H), 6.90 (t, J = 8.0 Hz, 1H), 6.69 (d, J = 7.1 Hz, 1H), 6.60 (d, J = 8.9 Hz, 1H), 5.52 (s, 2H), 3.95 (q, J = 7.1 Hz, 2H), 2.47 (s, 3H), 0.86 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.2, 165.0, 163.2 (d, J = 246.5 Hz), 141.6, 140.0 (d, J = 6.9 Hz), 136.1, 135.4, 130.4 (d, J = 8.2 Hz), 129.7 (2C), 127.2 (2C), 126.8, 121.7 (d, J = 2.3 Hz), 119.7, 114.32 (d, J = 21.1 Hz), 114.27, 113.1 (d, J = 22.2 Hz), 59.7, 48.2, 13.7, 11.8; ^{19}F NMR (471 MHz, $CDCl_3$) δ -112.34 (s, 1F); HRMS (ESI-TOF) calcd for $C_{22}H_{21}FNO_4$ $[M + H]^+$ 382.1455, found 382.1453.

1-(2-Chlorobenzyl)-4-(ethoxycarbonyl)-5-methyl-3-phenyl-1*H*-pyrrole-2-carboxylic acid (10ai).



Ethyl acetate/petroleum ether = 1:4 as the eluent; White solid, 89% yield (70.8 mg), mp 178–180 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 (d, J = 7.8 Hz, 1H), 7.34–7.28 (m, 3H), 7.25–7.21 (m, 2H), 7.18 (t, J = 7.3 Hz, 1H), 7.13 (t, J = 7.4 Hz, 1H), 6.41 (d, J = 7.5 Hz, 1H), 5.67 (s, 2H), 3.96 (q, J = 7.1 Hz, 2H), 2.43 (s, 3H), 0.87 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.9, 164.6, 142.4, 136.3, 135.7, 135.0, 131.9, 129.7 (2C), 129.5, 128.5, 127.4, 127.3 (2C), 127.1, 126.4, 118.9, 114.6, 59.8, 46.8, 13.7, 11.6; HRMS (ESI-TOF) calcd for $C_{22}H_{21}{}^{35}ClNO_4$ $[M + H]^+$ 398.1159, found 398.1169.

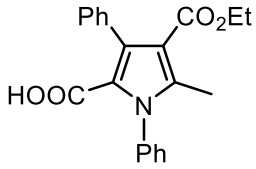
4-(Ethoxycarbonyl)-5-methyl-1-phenethyl-3-phenyl-1*H*-pyrrole-2-carboxylic acid (10aj).



Ethyl acetate/petroleum ether = 1:4 as the eluent; White solid, 81% yield (61.1 mg), mp 170–172 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38–7.31 (m, 3H), 7.29–7.21 (m, 5H), 7.12–7.07 (m, 2H), 4.47 (t, J = 7.7 Hz, 2H), 3.94 (q, J = 7.1 Hz, 2H), 2.98 (t, J = 7.7 Hz, 2H), 2.44 (s, 3H), 0.85 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.6, 165.0, 141.7, 138.0, 136.5, 136.2, 129.7 (2C), 129.0 (2C), 128.8 (2C), 127.2 (2C), 126.9, 126.8, 118.1, 114.0, 59.6, 47.5, 37.4, 13.6, 11.5; HRMS (ESI-TOF) calcd

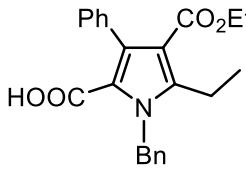
for $C_{23}H_{24}NO_4$ $[M + H]^+$ 378.1705, found 378.1701.

4-(Ethoxycarbonyl)-5-methyl-1,3-diphenyl-1*H*-pyrrole-2-carboxylic acid (10ak).



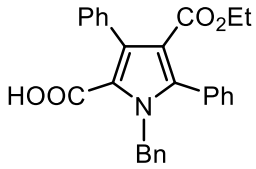
Ethyl acetate/petroleum ether = 1:4 as the eluent; White solid, 83% yield (58.0 mg), mp 142–144 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45–7.38 (m, 3H), 7.34–7.28 (m, 3H), 7.26 (d, J = 6.9 Hz, 2H), 7.20–7.12 (m, 2H), 3.98 (q, J = 7.1 Hz, 2H), 2.26 (s, 3H), 0.89 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.0, 163.7, 142.3, 138.5, 135.3, 135.2, 129.8 (2C), 129.1 (2C), 128.7, 127.7 (2C), 127.3 (2C), 127.0, 120.5, 114.2, 59.8, 13.7, 12.8; HRMS (ESI-TOF) calcd for $C_{21}H_{20}NO_4$ $[M + H]^+$ 350.1392, found 350.1399.

1-Benzyl-4-(ethoxycarbonyl)-5-ethyl-3-phenyl-1*H*-pyrrole-2-carboxylic acid (10al).



Ethyl acetate/petroleum ether = 1:4 as the eluent; White solid, 90% yield (67.9 mg), mp 144–146 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35–7.19 (m, 8H), 6.92 (d, J = 7.4 Hz, 2H), 5.63 (s, 2H), 3.96 (q, J = 7.1 Hz, 2H), 2.94 (q, J = 7.4 Hz, 2H), 1.12 (t, J = 7.4 Hz, 3H), 0.88 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.69, 164.66, 147.9, 137.7, 136.3, 135.9, 129.7 (2C), 128.8 (2C), 127.4, 127.3 (2C), 127.0, 125.9 (2C), 118.6, 113.6, 59.7, 48.5, 19.1, 13.9, 13.7; HRMS (ESI-TOF) calcd for $C_{23}H_{24}NO_4$ $[M + H]^+$ 378.1705, found 378.1712.

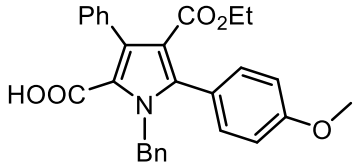
1-Benzyl-4-(ethoxycarbonyl)-3,5-diphenyl-1*H*-pyrrole-2-carboxylic acid (10am).



Ethyl acetate/petroleum ether = 1:4 as the eluent; White solid, 89% yield (75.7 mg), mp 163–165 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43–7.27 (m, 9H), 7.26–7.22 (m, 1H), 7.18–7.12 (m, 3H), 6.79–6.72 (m, 2H), 5.38 (s, 2H), 3.80 (q, J = 7.1 Hz, 2H), 0.68 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.8, 164.1, 144.0, 138.2, 135.4, 135.3, 131.1, 130.4 (2C), 130.0 (2C), 129.1, 128.5 (2C), 128.2 (2C), 127.4 (2C), 127.2 (2C), 126.1 (2C), 120.2, 115.4, 59.7, 49.8, 13.4; HRMS (ESI-TOF) calcd for $C_{27}H_{24}NO_4$ $[M + H]^+$ 426.1705, found 426.1705.

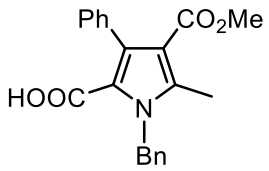
1-Benzyl-4-(ethoxycarbonyl)-5-(4-methoxyphenyl)-3-phenyl-1*H*-pyrrole-2-carbo

xylic acid (10an).



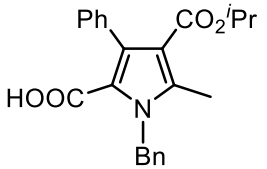
Ethyl acetate/petroleum ether = 1:2 as the eluent; White solid, 72% yield (65.6 mg), mp 143–145 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 (s, 5H), 7.20–7.04 (m, 5H), 6.88 (d, J = 8.1 Hz, 2H), 6.74 (s, 2H), 5.34 (s, 2H), 3.82(q, J = 6.9 Hz, 2H), 3.81 (s, 3H), 0.72 (t, J = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.2, 164.4, 160.1, 143.6, 138.5, 135.6, 134.8, 131.8 (2C), 130.0 (2C), 128.5 (2C), 127.3 (2C), 127.1, 127.0, 126.1 (2C), 123.1, 120.6, 115.3, 113.6 (2C), 59.7, 55.4, 49.6, 13.5; HRMS (ESI-TOF) calcd for $C_{28}H_{26}NO_5$ $[M + H]^+$ 456.1811, found 456.1814.

1-Benzyl-4-(methoxycarbonyl)-5-methyl-3-phenyl-1*H*-pyrrole-2-carboxylic acid (10ao).



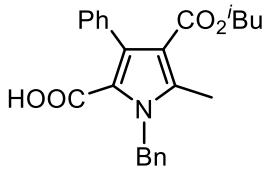
Ethyl acetate/petroleum ether = 1:4 as the eluent; White solid, 85% yield (59.4 mg), mp 145–147 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34–7.25 (m, 5H), 7.25–7.20 (m, 3H), 6.93 (d, J = 7.4 Hz, 2H), 5.62 (s, 2H), 3.48 (s, 3H), 2.47 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.3, 165.1, 142.3, 137.1, 136.3, 135.6, 129.7 (2C), 128.8 (2C), 127.4, 127.3 (2C), 127.0, 126.1 (2C), 118.9, 114.1, 50.9, 48.8, 12.0; HRMS (ESI-TOF) calcd for $C_{21}H_{20}NO_4$ $[M + H]^+$ 350.1392, found 350.1401.

1-Benzyl-4-(isopropoxycarbonyl)-5-methyl-3-phenyl-1*H*-pyrrole-2-carboxylic acid (10ap).



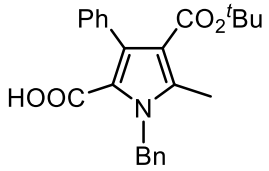
Ethyl acetate/petroleum ether = 1:4 as the eluent; White solid, 87% yield (65.7 mg), mp 155–157 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34–7.26 (m, 5H), 7.25–7.20 (m, 3H), 6.96 (d, J = 7.3 Hz, 2H), 5.63 (s, 2H), 4.90–4.82 (m, 1H), 2.49 (s, 3H), 0.89 (d, J = 6.3 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.0, 164.5, 142.3, 137.2, 136.14, 136.08, 129.8 (2C), 128.8 (2C), 127.4, 127.3 (2C), 126.9, 126.2 (2C), 118.7, 114.8, 67.1, 48.7, 21.5 (2C), 11.8; HRMS (ESI-TOF) calcd for $C_{23}H_{24}NO_4$ $[M + H]^+$ 378.1705, found 378.1711.

1-Benzyl-4-(isobutoxycarbonyl)-5-methyl-3-phenyl-1*H*-pyrrole-2-carboxylic acid (10aq).



Ethyl acetate/petroleum ether = 1:4 as the eluent; Yellow solid, 91% yield (71.2 mg), mp 149–151 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97 (bs, 1H), 7.31–7.15 (m, 8H), 6.92 (d, J = 6.6 Hz, 2H), 5.56 (s, 2H), 3.71 (d, J = 6.5 Hz, 2H), 2.49 (s, 3H), 1.54–1.43 (m, 1H), 0.62 (d, J = 6.7 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.3 (2C), 142.2, 137.2, 136.1, 135.6, 129.7 (2C), 128.8 (2C), 127.3 (3C), 126.9, 126.1 (2C), 119.5, 114.1, 70.5, 48.7, 27.5, 19.2 (2C), 12.0; HRMS (ESI-TOF) calcd for $C_{24}H_{26}NO_4$ $[M + H]^+$ 392.1862, found 392.1859.

1-Benzyl-4-(*tert*-butoxycarbonyl)-5-methyl-3-phenyl-1*H*-pyrrole-2-carboxylic acid (10ar).



Ethyl acetate/petroleum ether = 1:4 as the eluent; Yellow solid, 90% yield (70.5 mg), mp 169–171 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32–7.23 (m, 5H), 7.22 (d, J = 7.4 Hz, 1H), 7.19 (d, J = 6.8 Hz, 2H), 6.93 (d, J = 7.3 Hz, 2H), 5.57 (s, 2H), 2.46 (s, 3H), 1.13 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.2, 164.6, 141.8, 137.3, 136.5, 135.5, 129.8 (2C), 128.8 (2C), 127.35 (2C), 127.32, 126.7, 126.2 (2C), 118.8, 115.9, 80.2, 48.7, 27.8 (3C), 11.7; HRMS (ESI-TOF) calcd for $C_{24}H_{26}NO_4$ $[M + H]^+$ 392.1862, found 392.1866.

4.4 化合物 9pa 的单晶衍射数据

我们将化合物 **9pa** 溶解于二氯甲烷和正己烷的混合溶剂中，在低温环境下让其缓慢挥发，得到晶型规整且透明的 **9pa** 单晶。随后，在配备有 CCD 面阵探测器衍射仪（Bruker APEX-II）上使用石墨单色 CuKα 辐射（λ = 1.54178 Å），在 10.78 < 2θ < 136.204º 的扫描范围内获得了相关单晶 X-射线衍射参数如表 4-5 所示。经 SHELXT Structure Solution 程序使用本征相位法与 SHELXL 精化软件的最小二乘法解析出化合物 **9pa** 的构型，晶体结构如下图 4-1 所示。

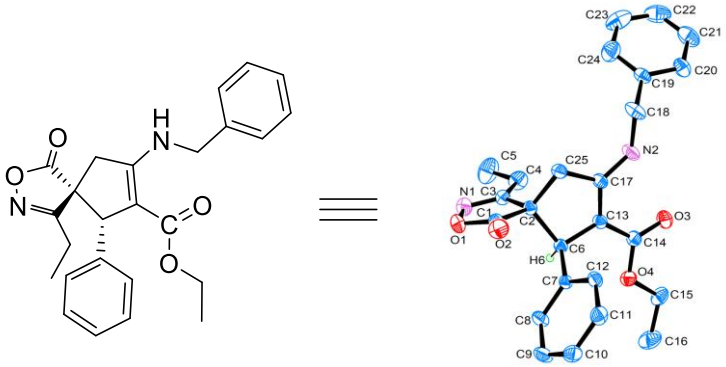


图 4-1 **9pa** 单晶衍射图

Table 4-5. Crystal data and structure refinement for 9pa

Identification code	**9pa**
Empirical formula	$C_{25}H_{26}N_2O_4$
Formula weight	418.48
Temperature/K	293.15
Crystal system	triclinic
Space group	P-1
a/Å	8.8339 (2)
b/Å	10.3135 (3)
c/Å	13.3200 (4)
α/°	80.3640 (10)
β/°	78.4260 (10)
γ/°	70.9200 (10)
Volume/Å^3	1116.76 (5)
Z	2
ρ_{calc}g/cm^3	1.244
μ/mm^{-1}	0.685
F(000)	444.0
Crystal size/mm^3	0.3 × 0.2 × 0.1
Radiation	CuKα (λ = 1.54178)
2Θ range for data collection/°	10.78 to 136.204

Index ranges	$-10 \le h \le 10, -12 \le k \le 12, -16 \le l \le 15$
Reflections collected	27170
Independent reflections	3938 [R_{int} = 0.0367, R_{sigma} = 0.0336]
Data/restraints/parameters	3938/35/282
Goodness-of-fit on F^2	1.087
Final R indexes [I>=2σ (I)]	R_1 = 0.0692, wR_2 = 0.1965
Final R indexes [all data]	R_1 = 0.0696, wR_2 = 0.1968
Largest diff. peak/hole / e $Å^{-3}$	0.76/-0.24

4.5 化合物 **10ga** 的单晶衍射数据

目前，所有合成的羧基吡咯类化合物均通过核磁共振波谱进行了结构表征。为了进一步的确认产物的结构，我们将化合物 **10ga** 溶解于二氯甲烷和正己烷的混合溶剂中，在低温环境下让其缓慢挥发，得到晶型规整且透明的 **10ga** 单晶。随后，在配备有 CCD 面阵探测器衍射仪 (Bruker APEX-II)上使用石墨单色 MoKα 辐射（λ = 0.71073 Å），在 $4.264 < 2\theta < 55.12^{o}$ 的扫描范围内获得了相关单晶 X 射线衍射参数如表 4-6 所示。经 SHELXT Structure Solution 程序使用本征相位法与 SHELXL 精化软件的最小二乘法解析出化合物 **10ga** 的构型，晶体结构如下图 4-2 所示。

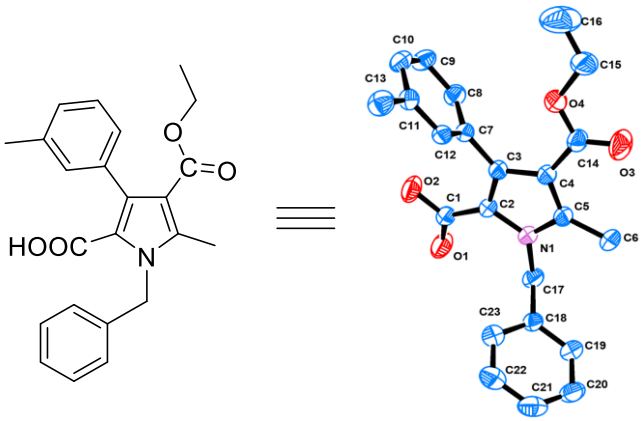


图 4-2 **10ga** 单晶衍射图

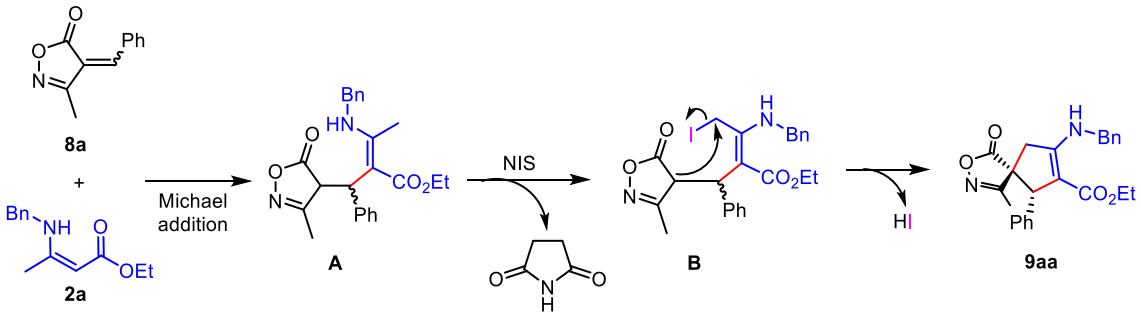
Tbale 4-6. Crystal data and structure refinement for 10ga	
Identification code	CCDC 2336966
Empirical formula	$C_{23}H_{22}NO_4$
Formula weight	376.41
Temperature [K]	293.15
Crystal system	triclinic
Space group	P-1
a [Å]	9.1097 (18)
b [Å]	10.3069 (19)

c [Å]	11.4146 (19)
α [°]	93.450 (6)
β [°]	93.450 (6)
γ [°]	93.450 (6)
Volume [Å^3]	984.5 (3)
Z	2
ρ_{calc} [gcm^{-3}]	1.270
μ [mm^{-1}]	0.087
F(000)	398.0
Crystal size [mm^3]	0.4×0.4×0.2
Radiation	MoK$_\alpha$ (λ=0.71073 Å)
2θ range [°]	4.264 to 55.12
Index ranges	−11 ≤ h ≤ 11, −13 ≤ k ≤ 13, −14 ≤ l ≤ 14
Reflections collected	41200
Independent reflections	4544 [R_{int} = 0.1353, R_{sigma} = 0.0655]
Data / Restraints / Parameters	4544/12/260
Goodness-of-fit on F^2	1.021
Final *R* indexes [$I \geq 2\sigma(I)$]	R_1 = 0.0813, wR_2 = 0.1897
Final *R* indexes [all data]	R_1 = 0.1436, wR_2 = 0.2293
Largest peak/hole [eÅ^{-3}]	0.37/-0.24

4.6 反应机理探究

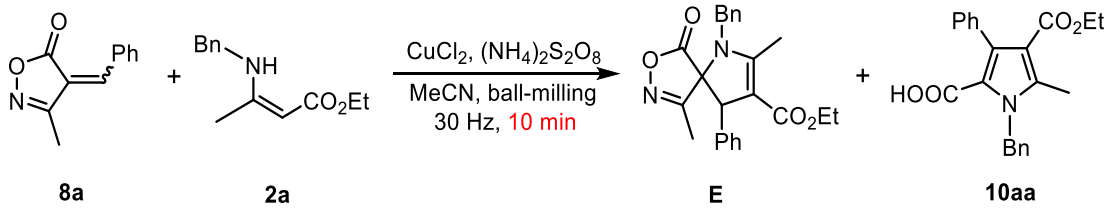
4.6.1 产物 9 反应机理的研究

基于本课题组前期工作，我们以不饱和异噁唑酮 **8a** 与 β-烯胺酯 **2a** 的反应为例，给出了可能的反应机理（Scheme 4-4）。首先不饱和异噁唑酮 **1a** 与 β-烯胺酯 **2a** 之间发生迈克尔加成反应得到加成产物 **A**，与此同时卤代试剂 NIS 会对 β-烯胺酯甲基位置的烯丙基 H 进行碘代，得到中间体 **B**，随后异噁唑酮羰基位置的 α-C 对碘甲基进行亲核进攻后环化，碘则以碘化氢的形式脱去，最终得到异噁唑酮螺环戊烯化合物 **9aa**。



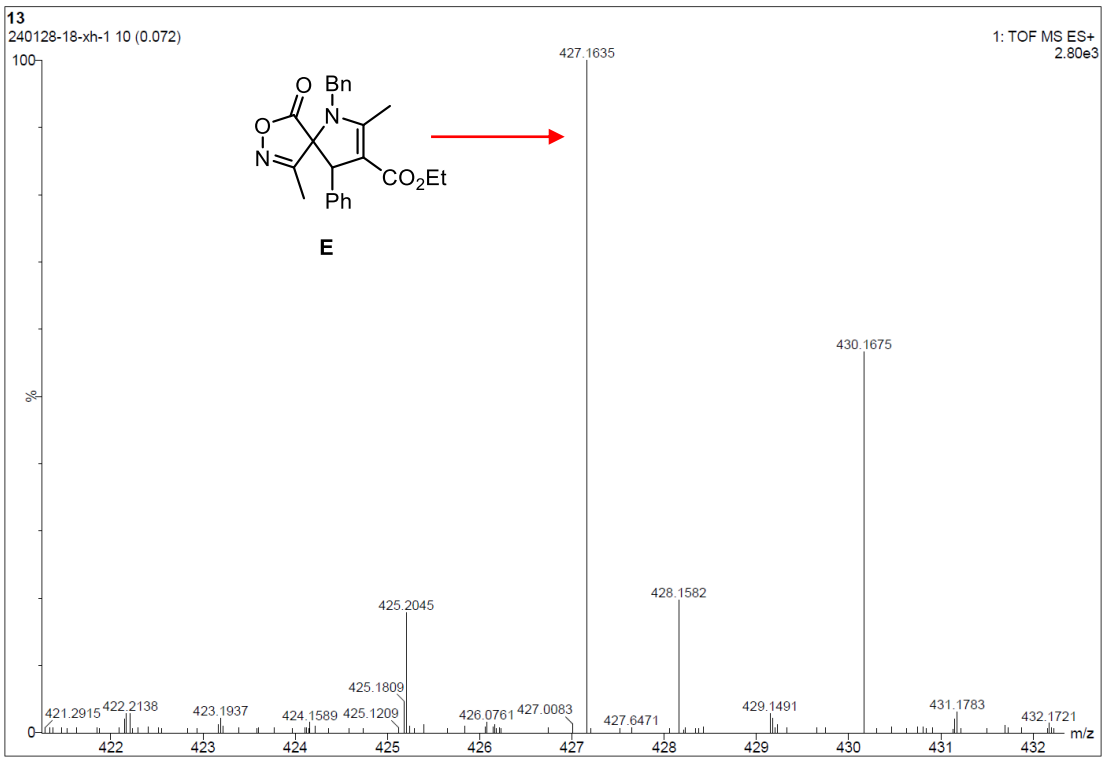
Scheme 4-4 Plausible mechanism for the reaction

4.6.2 产物 **10** 反应机理的研究



Scheme 4-5 Experimental investigation of HRMS

将 **1a**（0.2 mmol），**2a**（0.24 mmol），$CuCl_2$（20 mol%），$(NH_4)_2S_2O_8$（0.16 mmol），与 MeCN（30 μL）的混合物与四个不锈钢球（直径 6 mm）一起放入不锈钢瓶（5 mL）中。将反应容器与另一个相同的空容器一起固定在 Retsch MM400 搅拌磨的振动臂上，在室温下以 1800 转/分钟（30 Hz）的速率研磨 10 分钟（Scheme 4-5）。然后，直接通过 HRMS 分析所得的油状混合物（图 4-3）。



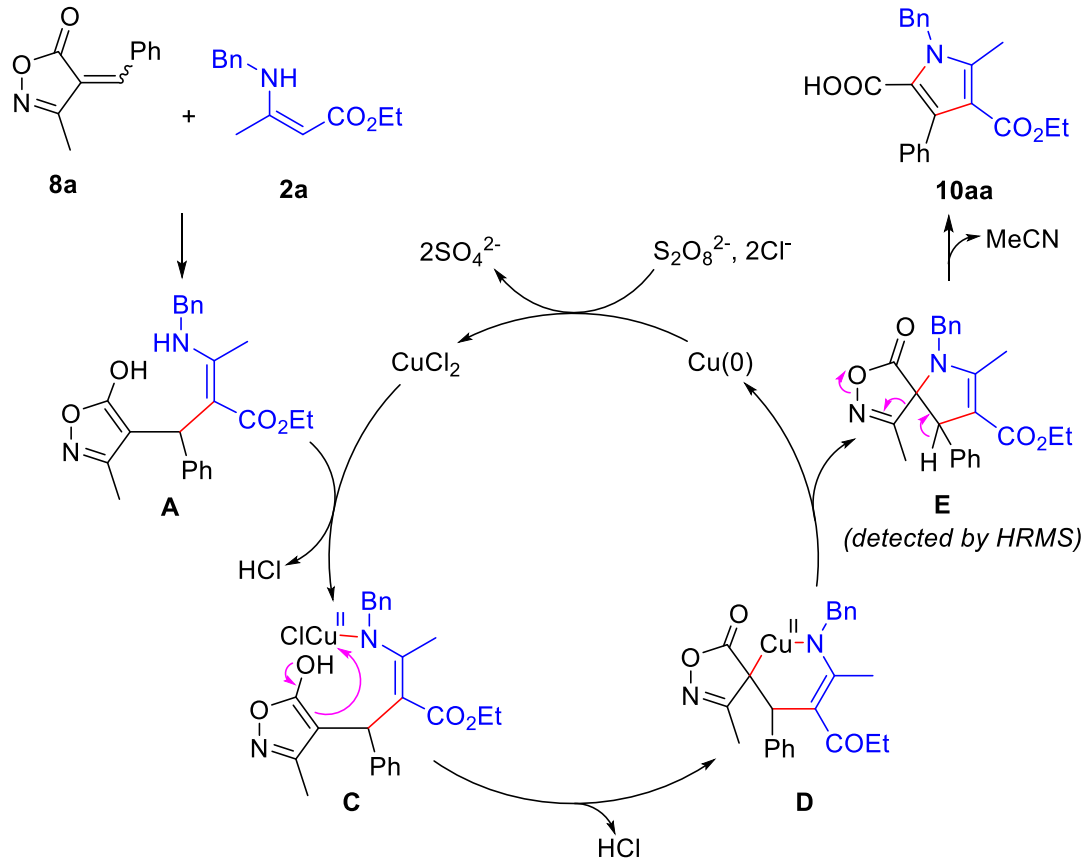
HRMS (ESI-TOF) calcd for $C_{24}H_{24}N_2O_4Na$ $[M + Na]^+$ 427.1634, found 427.1635.

图 4-3 中间体 **E** 的 HRMS 数据

在得到产物 **10** 之后，我们就着手对该体系反应机理进行了探究。我们以 **8a** 和 **2a** 的反应作为反应模型，对其进行自由基捕获实验。向反应中添加两个当量的自由基捕获剂四甲基哌啶氧化物（TEMPO），仍然以 85%的产率分离得

到化合物 **10aa**。除此之外，另一种自由基抑制剂 2,6-二叔丁基对甲酚（BHT）的添加使得产物 **10aa** 的产率略有下降。这个结果表明该反应不太可能涉及自由基反应进程。

我们以 **8a** 和 **2a** 合成 **10aa** 为例，根据高分辨质谱（HRMS）得到的结果（图 4-3）提出了合理的反应机理（Scheme 4-6）。最初，**8a** 和 **2a** 发生迈克尔加成反应，形成相应的加成物中间体 **A**。随后 β-烯胺酯片段中饱和氮原子与 Cu(II)配位后发生烯醇化，产生 Cu(II)络合物中间体 **C**，并释放出 1 当量的 HCl。然后，**C** 发生分子内的 S_N2 反应（烯醇的 π 电子对 Cu(II)的亲核进攻）形成环状 Cu(II)络合物中间体 **D**，并再释放出 1 当量的 HCl。最后，中间体 **D** 进行还原消除以完成催化偶联反应，得到异噁唑酮螺二氢吡咯中间体 **E** 并释放出 Cu(0)。Cu(0)在过硫酸铵和前述释放 HCl 的存在下被氧化回到 $CuCl_2$ 以完成催化循环。最后中间体 **E** 发生开环芳构化反应并脱去 1 当量 MeCN 后得到产物 **10aa**。



Scheme 4-6 Plausible mechanism for the reaction

4.7 本章小结

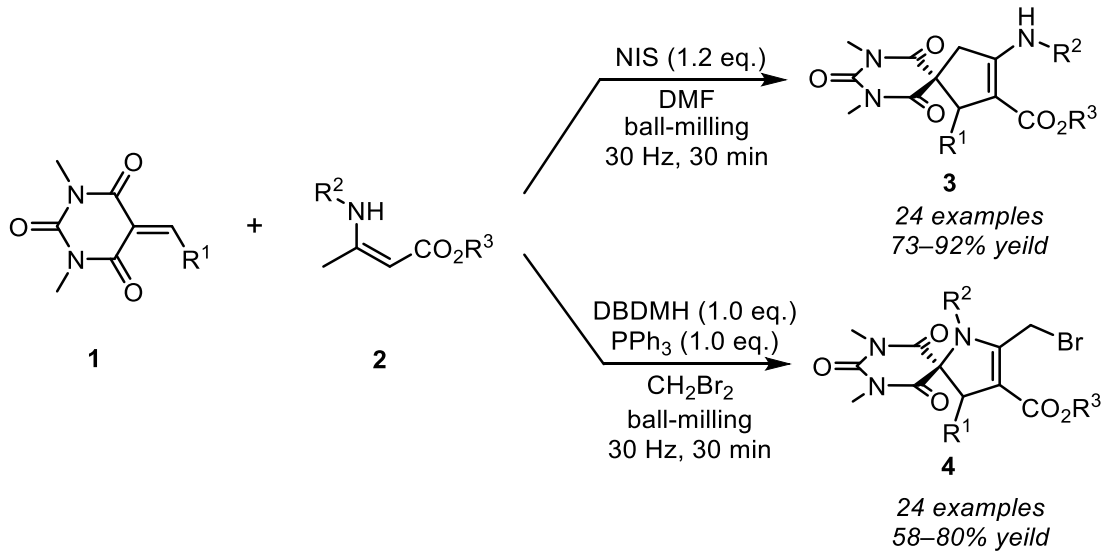
本章的工作主要是研究了不饱和异噁唑酮与 β-烯胺酯在球磨条件下选择性反应。我们首先建立了模型反应，并通过筛选大量的反应条件最终确定了选择性合成异噁唑酮螺环戊烯化合物及吡咯衍生物的反应条件，分别如下：1 当量不饱和异噁唑酮、1.2 当量烯胺酯、1.2 当量的 NIS 和 DMSO（30 μL）在球磨下反应 30 min；1 当量不饱和异噁唑酮、1.2 当量烯胺酯、20 mol%的 $CuCl_2$、0.8 当量的$(NH_4)_2S_2O_8$和 MeCN（30 μL）在球磨下反应 30 min。通过最佳条件，我们以 78–91%的产率合成 24 个异噁唑酮螺环戊烯化合物，以 73%–92%的产率合成 32 个吡咯类化合物。上述两种方法具有反应高效、条件温和、原料易得、最小的溶剂消耗、底物范围广、化学选择性高等优点，为构建异噁唑酮螺环戊烯与吡咯衍生物的提供了一种新途径。值得一提的是，我们实验室正在进一步利用合成吡咯的螺环化/开环芳构化反应策略，力争实现结构多样的共轭含氮杂环化合物的合成。

第五章 结论与展望

5.1 结论

本论文主要研究了环外 α,β-不饱和环酮与 β-烯胺酯的选择性环化反应，在廉价安全的催化试剂作用下，选择性合成二氢吡咯、二氢呋喃、环戊烯螺环化合物与吡咯衍生物，主要研究内容如下：

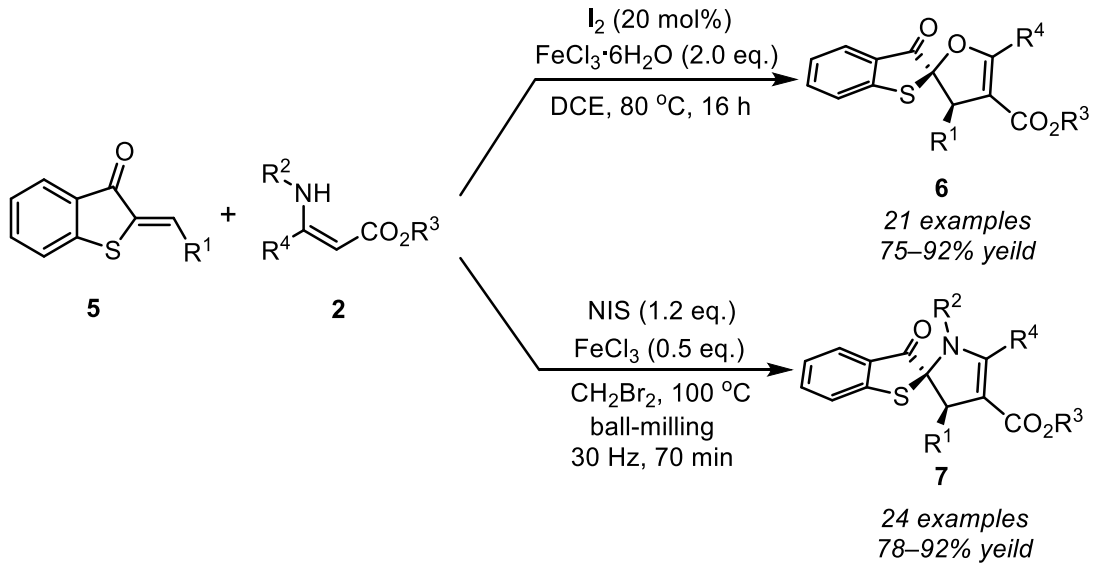
（1）研究了在机械研磨条件下不同卤代试剂选择性促进的环外不饱和巴比妥酸与 β-烯胺酯的串联反应，主要内容是关于不饱和巴比妥酸与 β-烯胺酯在球磨条件下的选择性螺环化反应（Scheme 5-1）。我们首先建立了模型反应，并通过筛选大量的反应条件最终确定了选择性合成巴比妥酸螺环戊烯化合物及巴比妥酸螺二氢吡咯化合物的反应条件，分别如下：1 当量不饱和巴比妥酸、1.2 当量烯胺酯、1.2 当量的 NIS 和 DMF（30 μL）在球磨条件下反应 30 min；1 当量不饱和巴比妥酸、1.2 当量烯胺酯、1 当量的 DBDMH、1 当量的 PPh_3 和 CH_2Br_2（30 μL）在球磨下研磨 30 min。以 73–92%的产率合成出 24 个巴比妥酸螺环戊烯化合物，并以 58–80%的产率合成出 24 个巴比妥酸螺二氢吡咯化合物。该方法为构建巴比妥酸螺环化合物提供了一种新途径。



Scheme 5-1 Synthesis of compound **3** and **4**

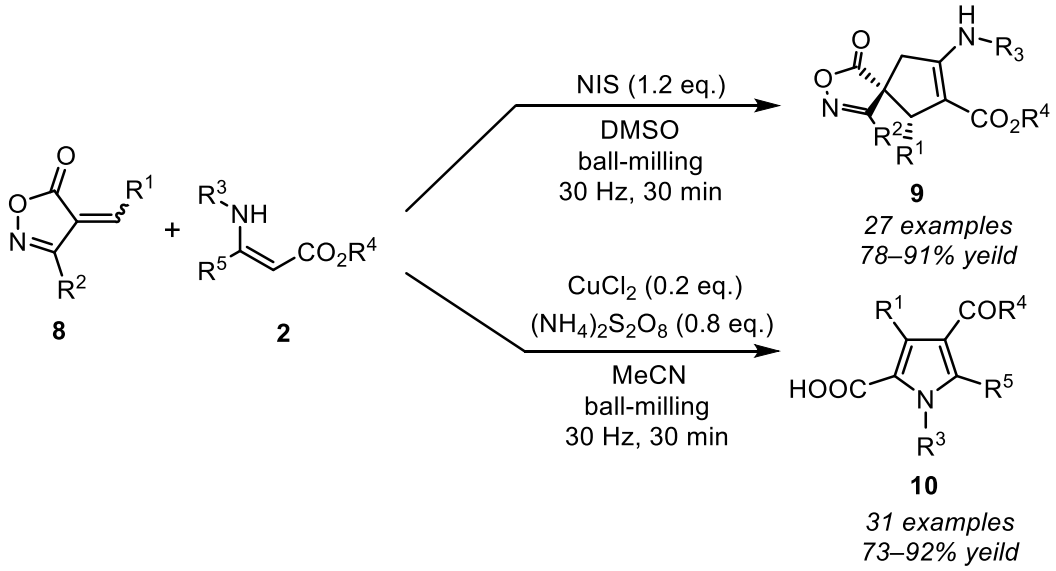
（2）研究了卤代试剂促进的硫代橙酮与 β-烯胺酯的串联反应，选择性构建了不同类型的硫代橙酮螺环化合物，并通过筛选大量的反应条件最终确定了选择性合成硫代橙酮螺二氢呋喃化合物及硫代橙酮螺二氢吡咯化合物的反应条件，分别如下：1 当量硫代橙酮、2 当量烯胺酯、20 mol%的 I_2 和 2 当量的

$FeCl_3·6H_2O$ 在 DCE 中于 80 ºC 反应 16 h；1 当量硫代橙酮、1.2 当量烯胺酯、1.2 当量的 NIS、0.5 当量的 $FeCl_3$ 和 CH_2Br_2（30 μL）在球磨下反应 70 min。以 75–92%的产率合成出 21 个顺式硫代橙酮螺二氢呋喃化合物，并以 89–92%的产率合成出 24 个顺式硫代橙酮螺二氢吡咯化合物（Scheme 5-2）。该合成策略为构建硫代橙酮螺环化合物提供了一种新方法。



Scheme 5-2 Synthesis of compound **6** and compound **7**

（3）主要研究了不饱和异噁唑酮与 β-烯胺酯在球磨条件下选择性反应。通过筛选大量的反应条件最终确定了选择性合成异噁唑酮螺环戊烯化合物与吡咯衍生物的反应条件，分别如下：1 当量不饱和异噁唑酮、1.2 当量 β-烯胺酯、1.2 当量的 NIS 和 DMSO（30 μL）在球磨下反应 30 min；1 当量不饱和异噁唑酮、1.2 当量 β-烯胺酯、20 mol%的 $CuCl_2$、0.8 当量的$(NH_4)_2S_2O_8$和 MeCN（30 μL）在球磨下反应 30 min。通过串联的螺环化反应，以 78–91%的产率合成 27 个顺式异噁唑酮螺环戊烯化合物。再通过螺环化/开环芳构化反应以 73%–92%的产率得到了 32 个吡咯类化合物（Scheme 5-3）。以上合成方案具有条件温和、原料易得、底物范围广、化学选择性高等优点，为构建异噁唑酮螺环戊烯与吡咯衍生物提供了一种简便、高效、绿色的选择。



Scheme 5-3 Synthesis of compound **9** and compound **10**

5.2 展望

文主要探讨了环外 α,β-不饱和环酮与 β-烯胺酯的选择性环化反应。并且成功地开发出几种螺环化合物的合成方法，包括螺二氢吡咯、螺二氢呋喃以及螺环戊烯化合物等。这些合成方法为螺环化合物的制备提供了一定价值的参考。在我们尝试合成异噁唑酮螺二氢吡咯化合物过程中，偶然发现了吡咯类化合物的形成，这一发现对我们接下来的研究有了一定的启发。我们发现当异噁唑酮在与烯胺酯发生反应时，会以螺环化/开环芳构化的反应进程形成吡咯类衍生物。因此，我们计划进一步探索利用 α,β-不饱和异噁唑酮构建更多螺环化/开环芳构化产物，例如通过让其与脒或 α-活泼亚甲基类化合物反应，来构建类似的开环芳构化产物。这些方案从机理上看都是可行的，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

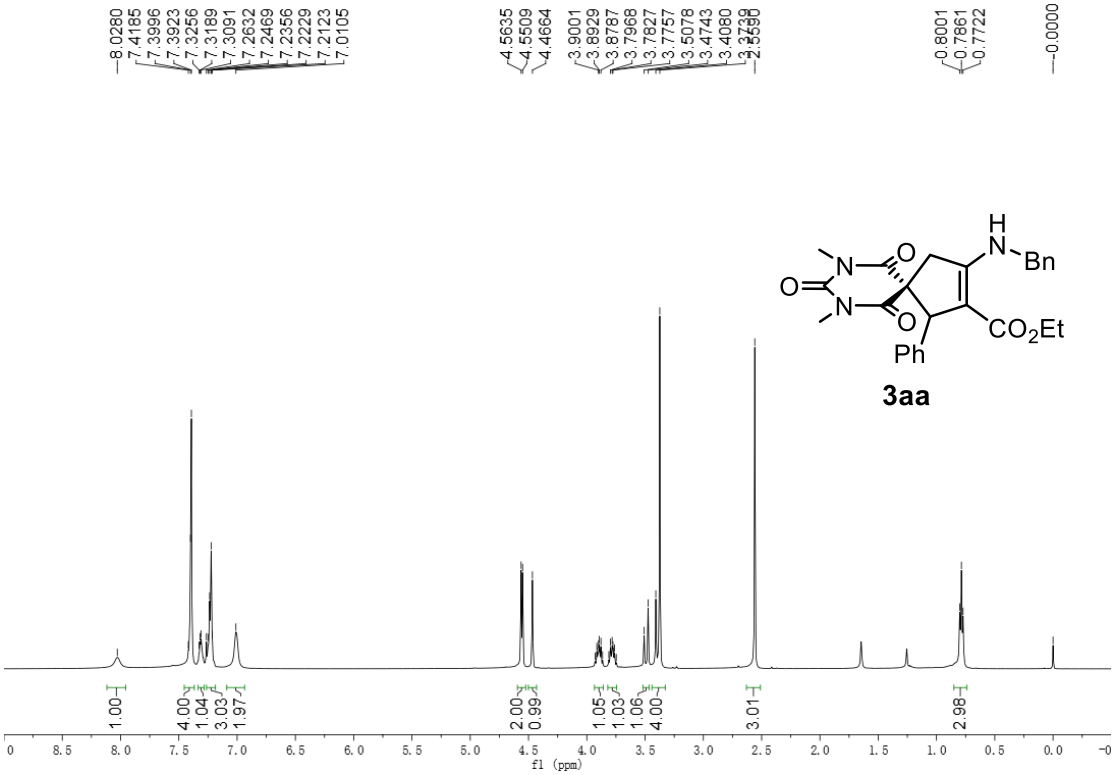


Figure S1. ^{1}H NMR (500 MHz, $CDCl_3$) of compound 3aa

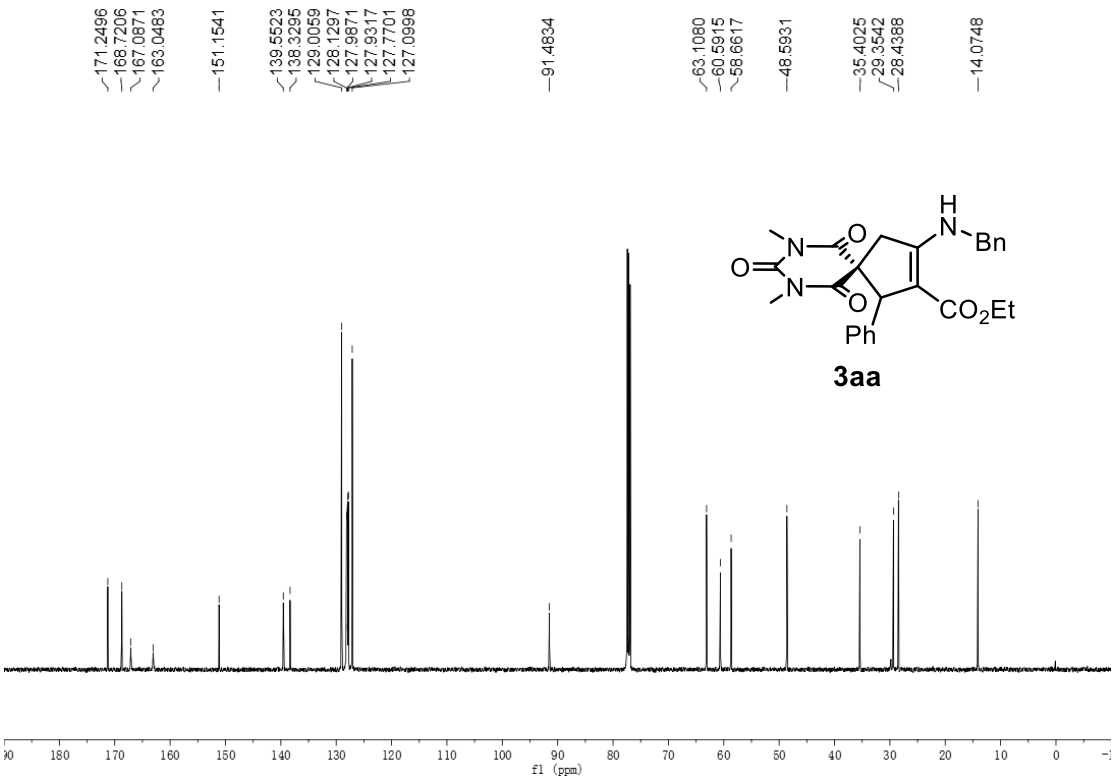


Figure S2. ^{13}C NMR (125 MHz, $CDCl_3$) of compound 3aa

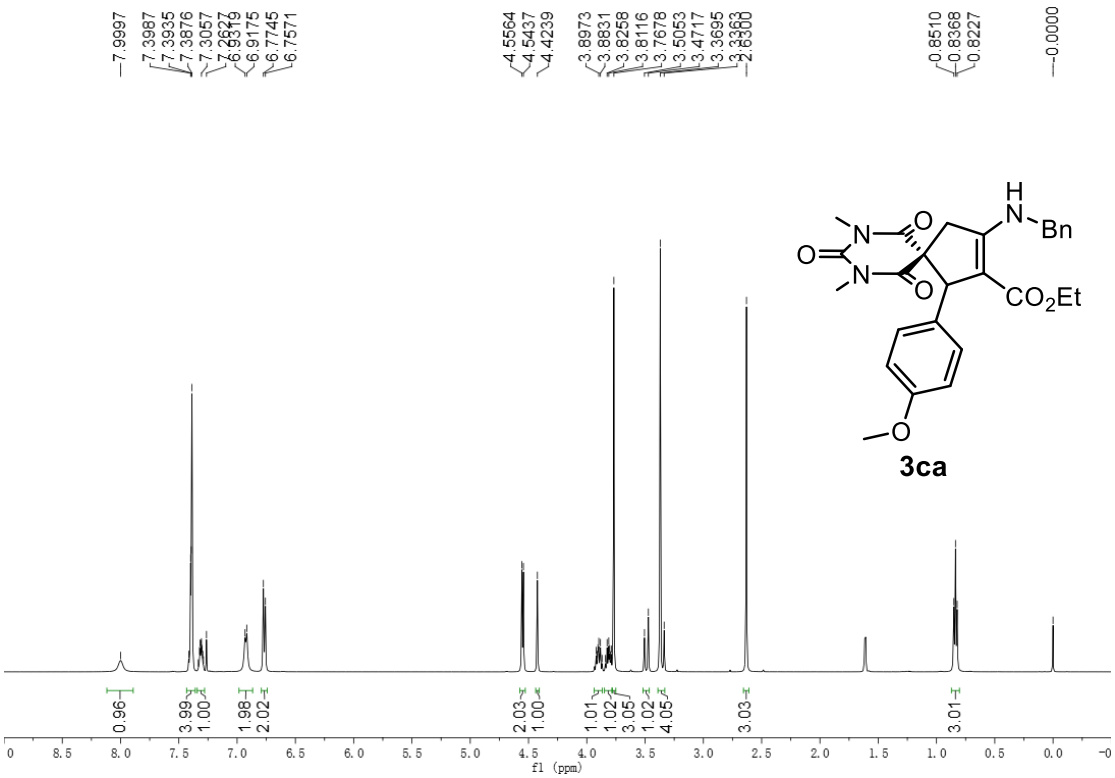


Figure S3. ^{1}H NMR (500 MHz, $CDCl_3$) of compound 3ca

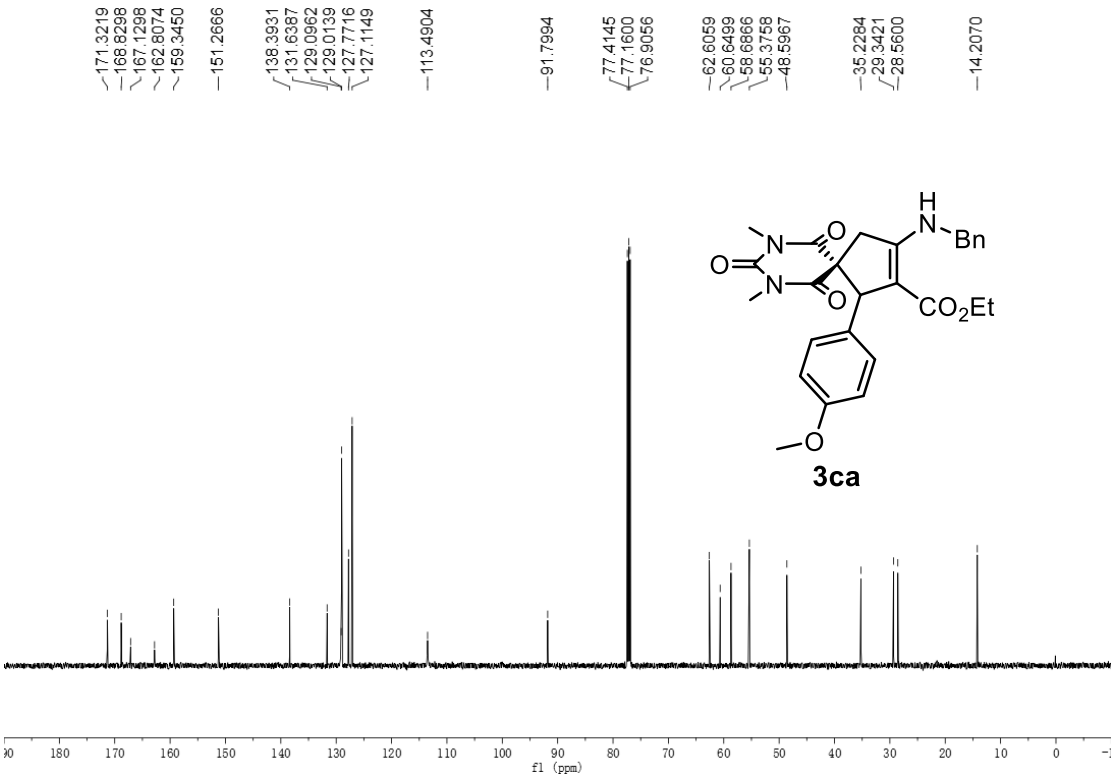


Figure S4. ^{13}C NMR (125 MHz, $CDCl_3$) of compound 3ca

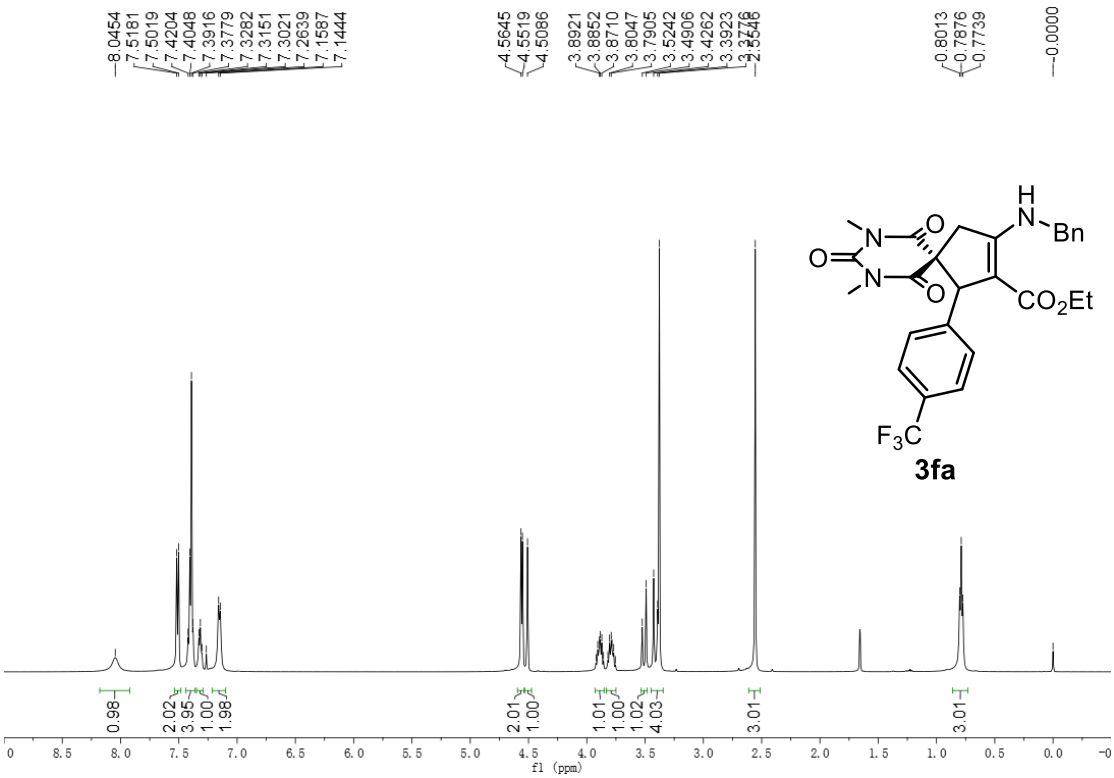


Figure S5. ^{1}H NMR (500 MHz, $CDCl_3$) of compound 3fa

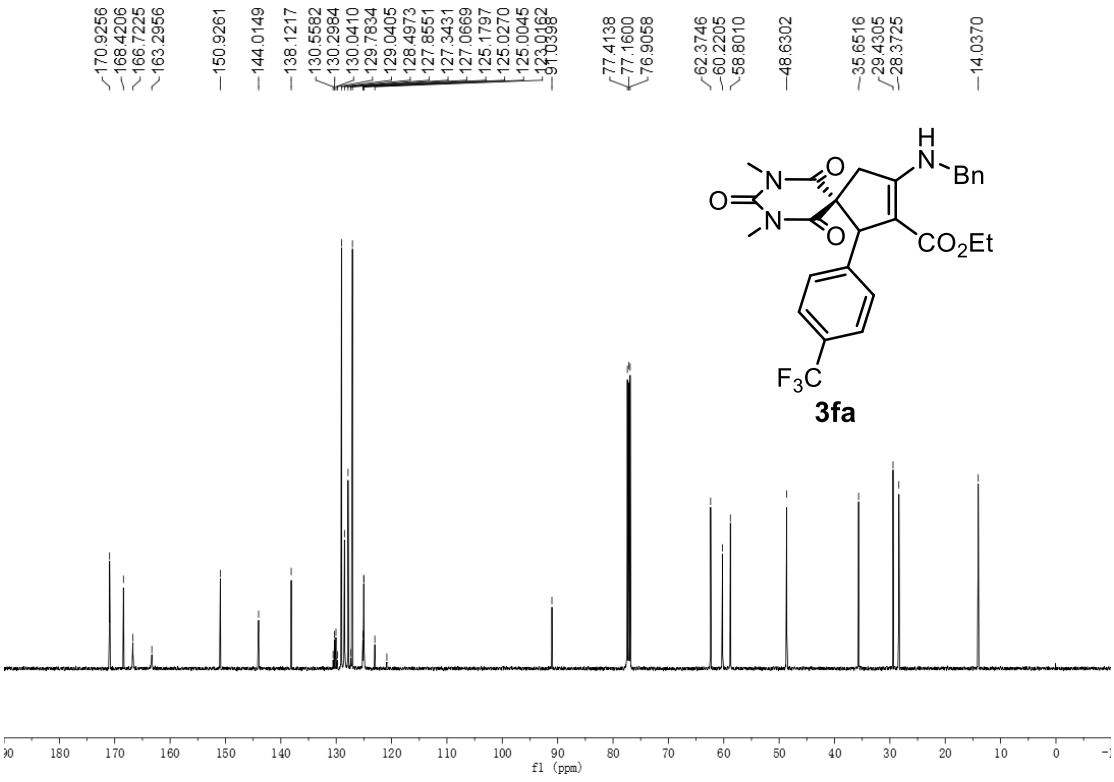


Figure S6. ^{13}C NMR (125 MHz, $CDCl_3$) of compound 3fa

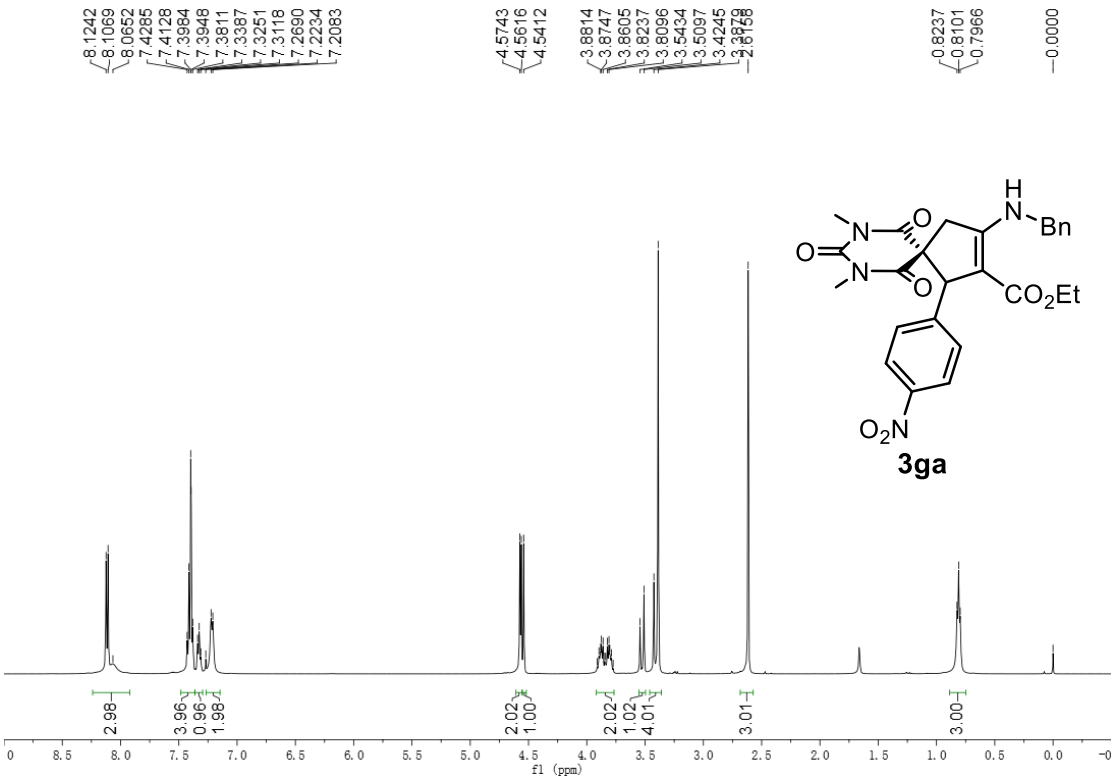


Figure S7. ^{1}H NMR (500 MHz, $CDCl_3$) of compound 3ga

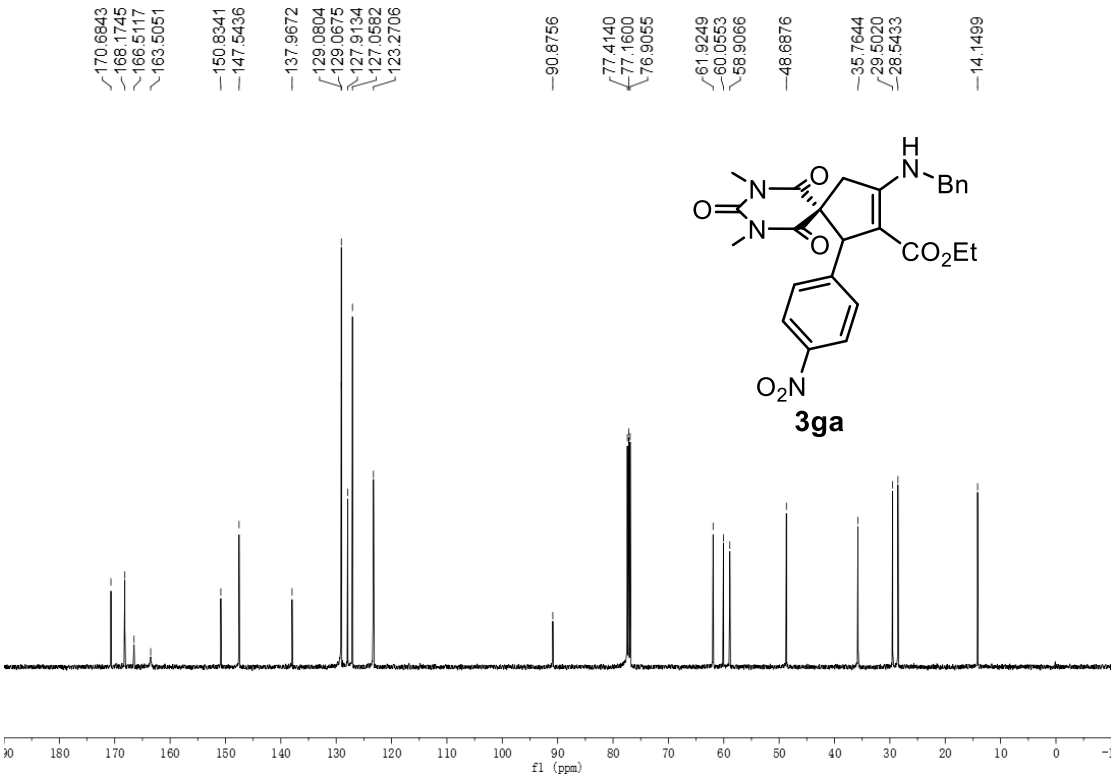
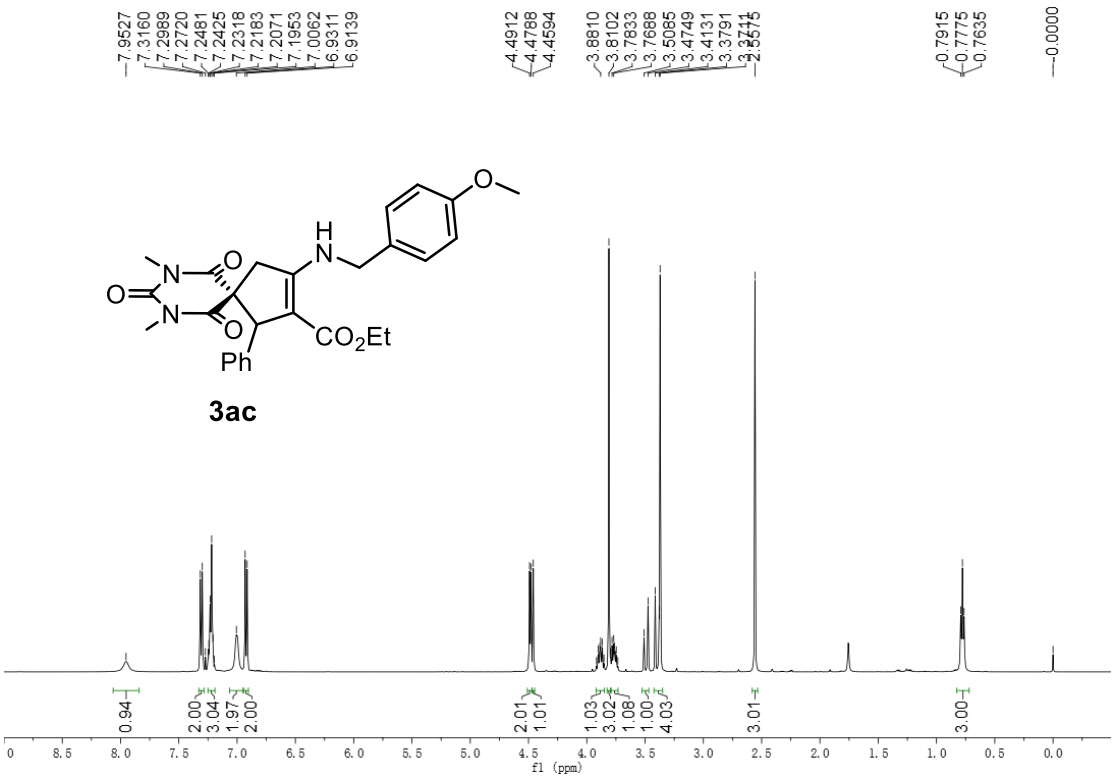
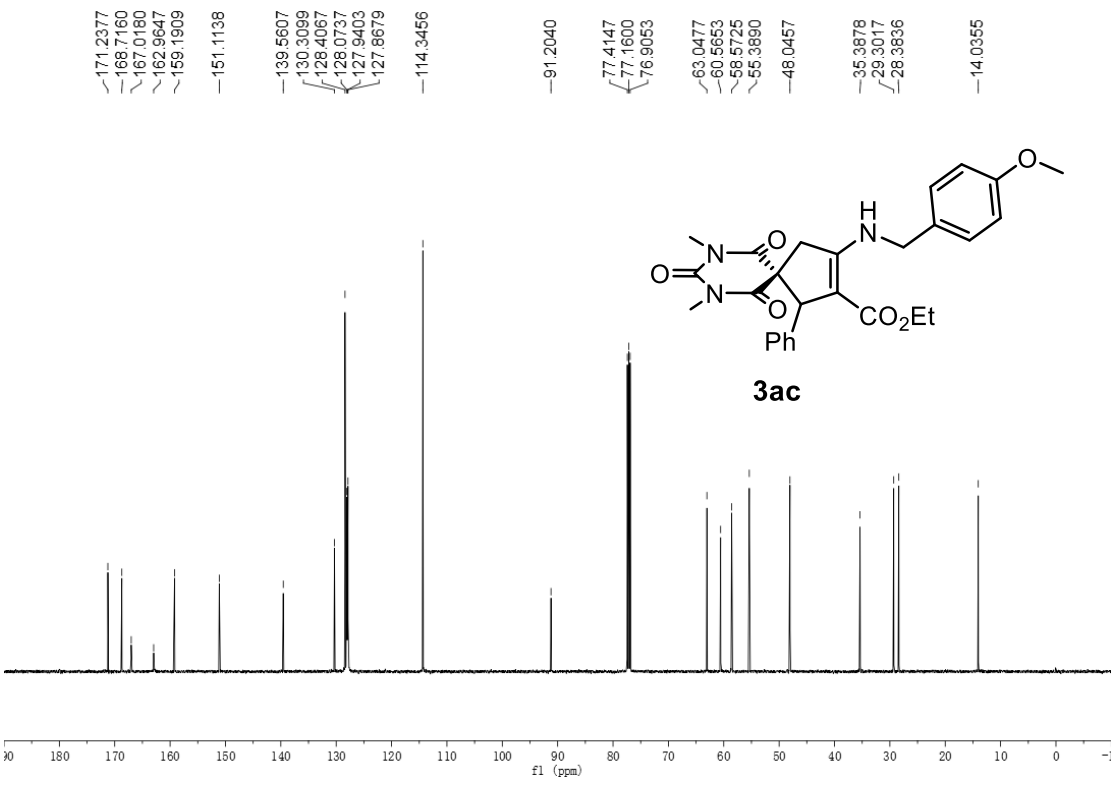


Figure S8. ^{13}C NMR (125 MHz, $CDCl_3$) of compound 3ga



3ac

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



3ac

Figure S10. ^{13}C NMR (125 MHz, $CDCl_3$) of compound 3ac

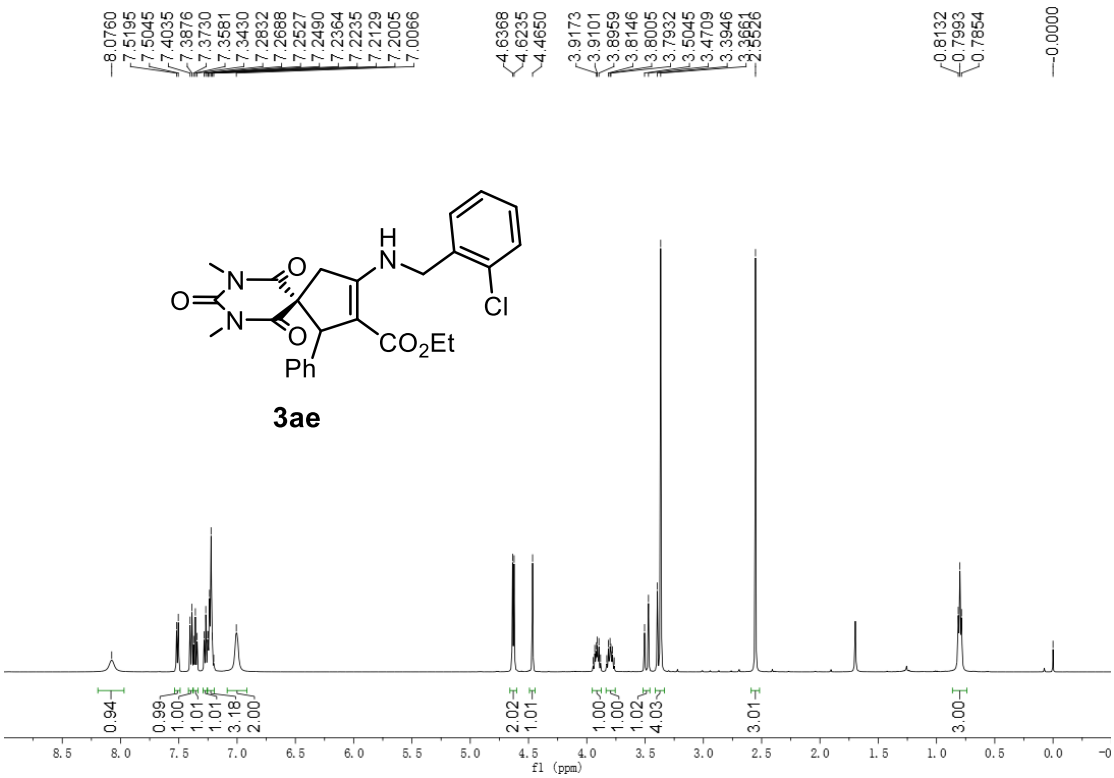


Figure S11. ^{1}H NMR (500 MHz, $CDCl_3$) of compound 3ae

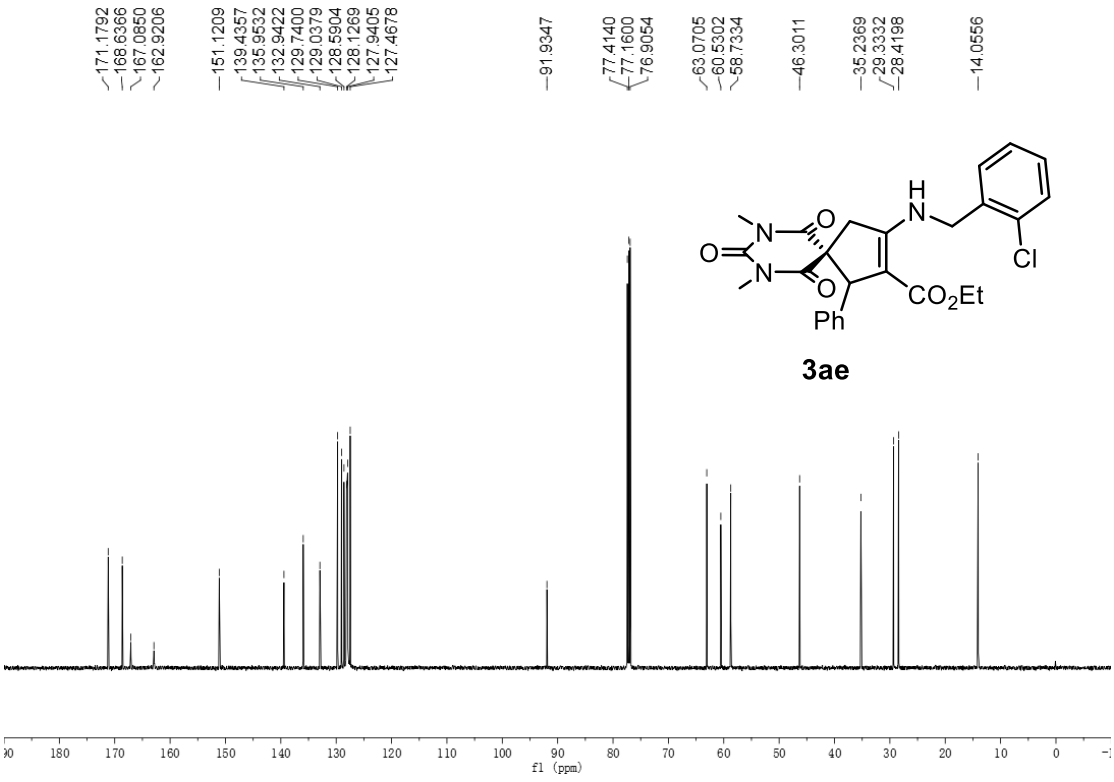


Figure S12. ^{13}C NMR (125 MHz, $CDCl_3$) of compound 3ae

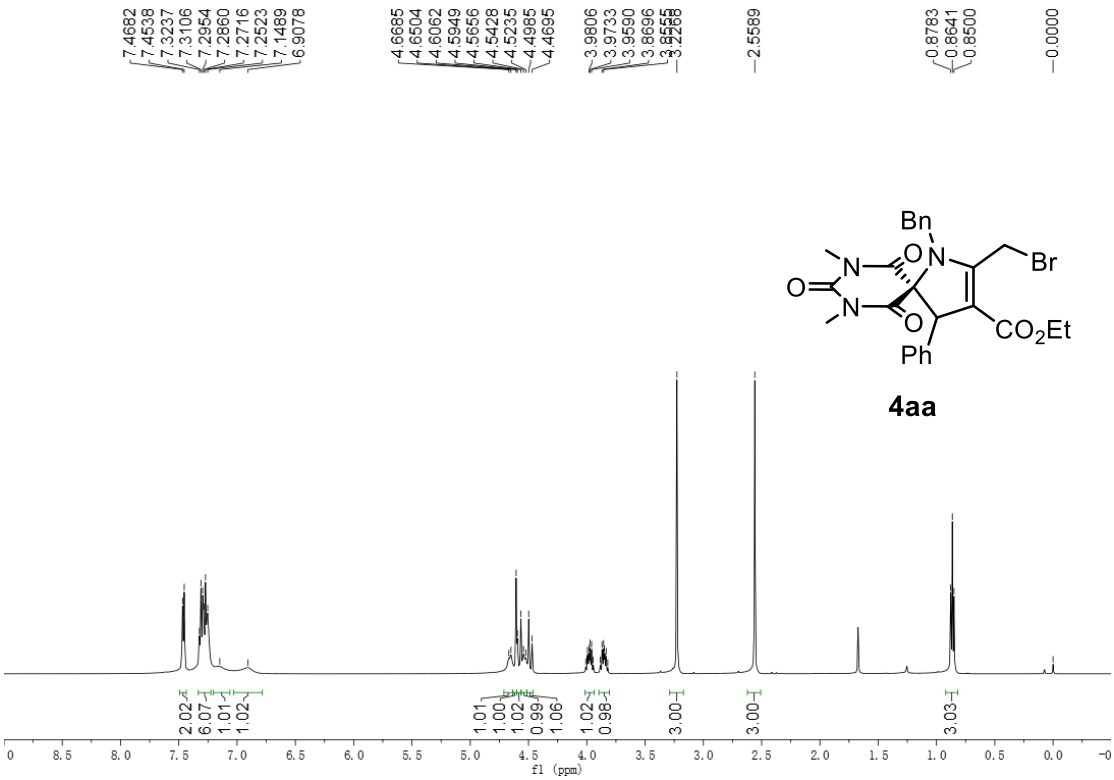


Figure S13. ^{1}H NMR (500 MHz, $CDCl_3$) of compound 4aa

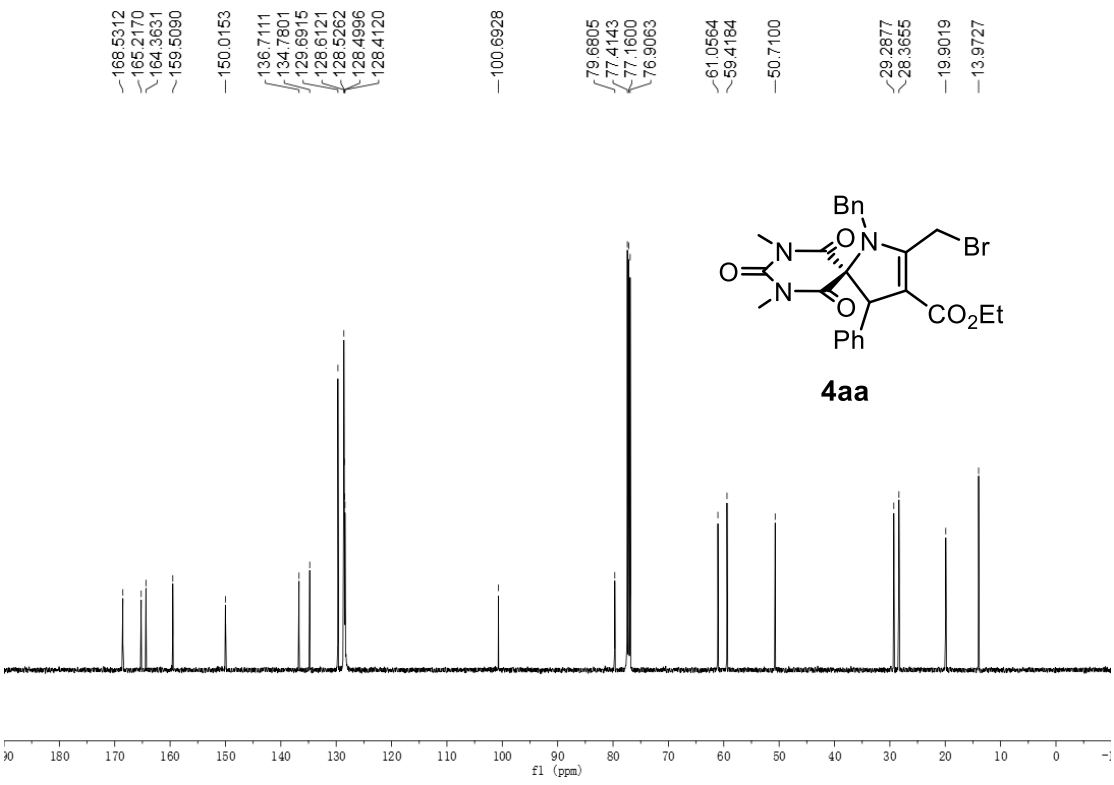


Figure S14. ^{13}C NMR (125 MHz, $CDCl_3$) of compound 4aa

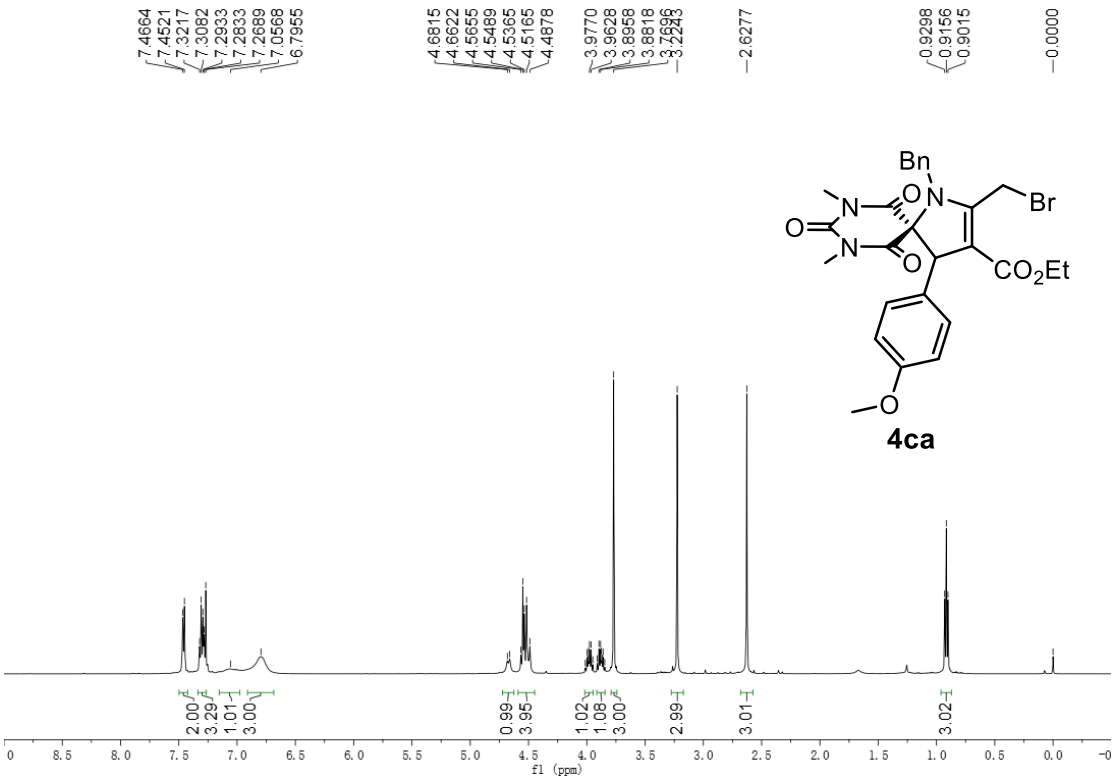


Figure S15. ^{1}H NMR (500 MHz, $CDCl_3$) of compound 4ca

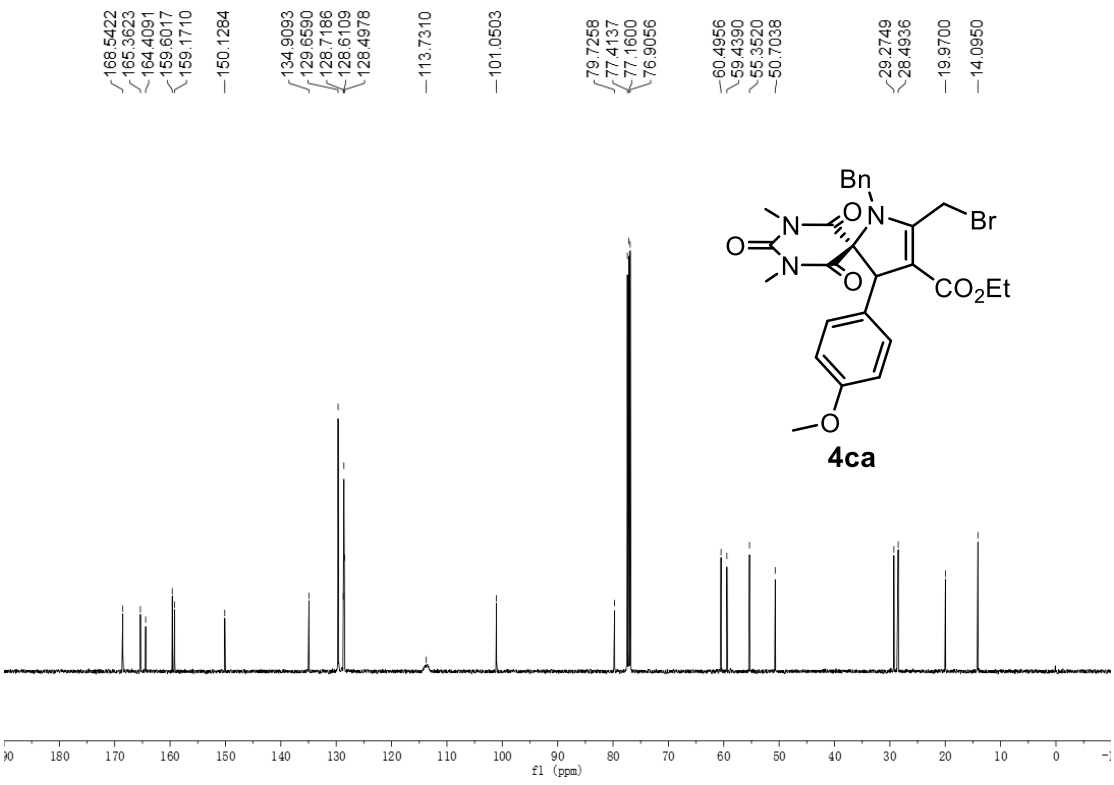


Figure S16. ^{13}C NMR (125 MHz, $CDCl_3$) of compound 4ca

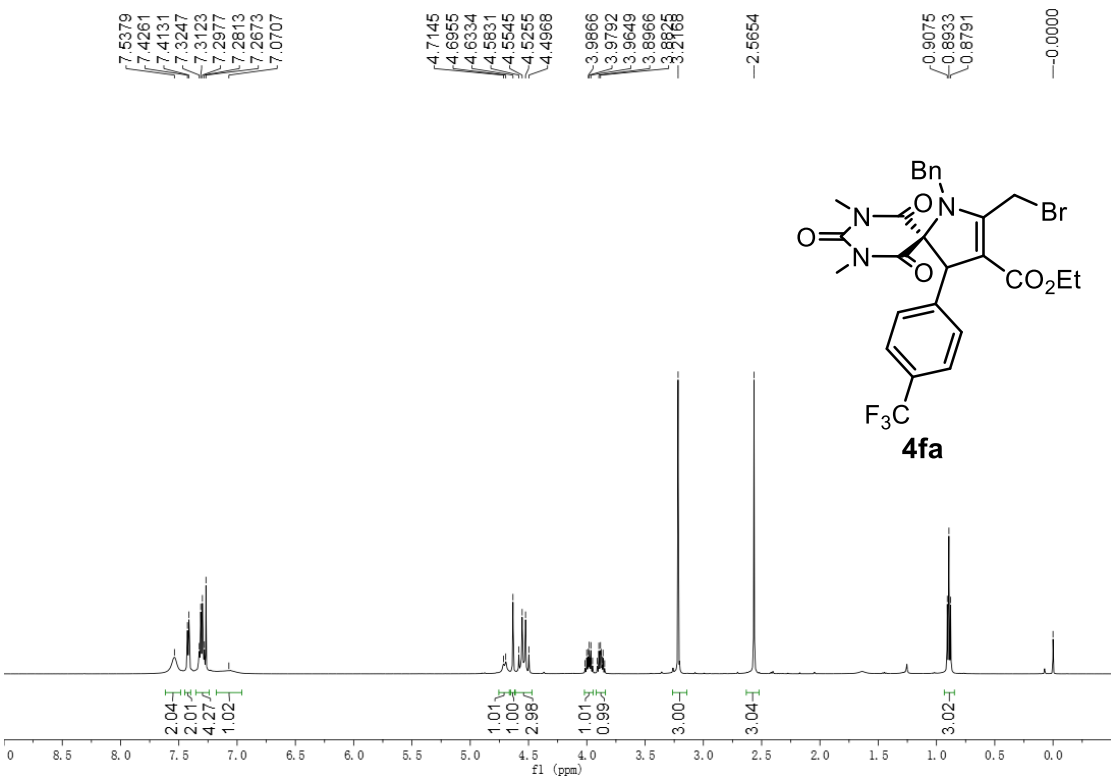


Figure S17. ^{1}H NMR (500 MHz, $CDCl_3$) of compound 4fa

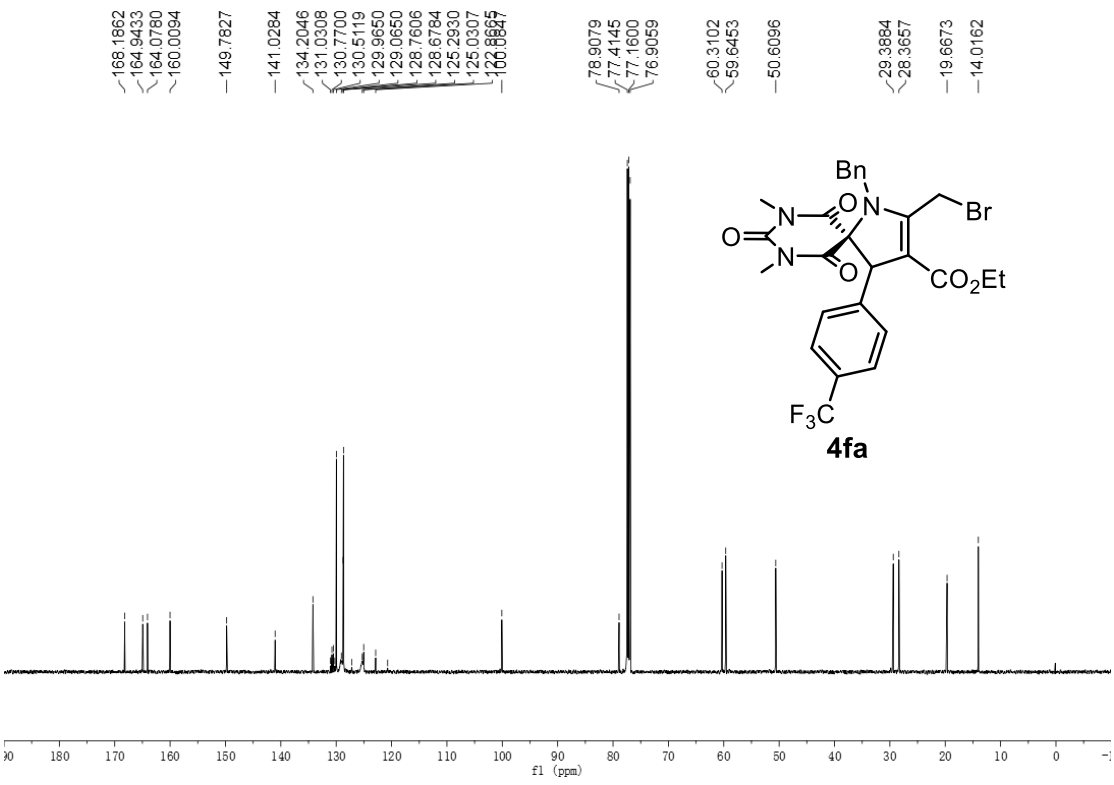


Figure S18. ^{13}C NMR (125 MHz, $CDCl_3$) of compound 4fa

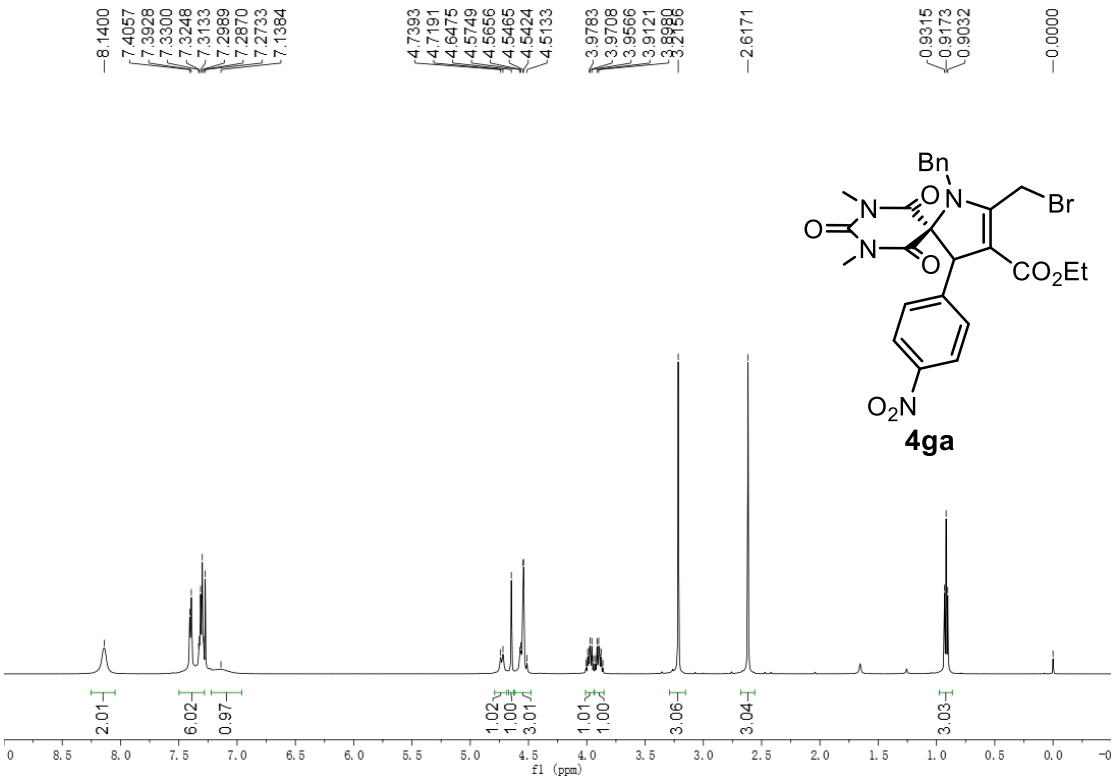


Figure S19. ^{1}H NMR (500 MHz, $CDCl_3$) of compound 4ga

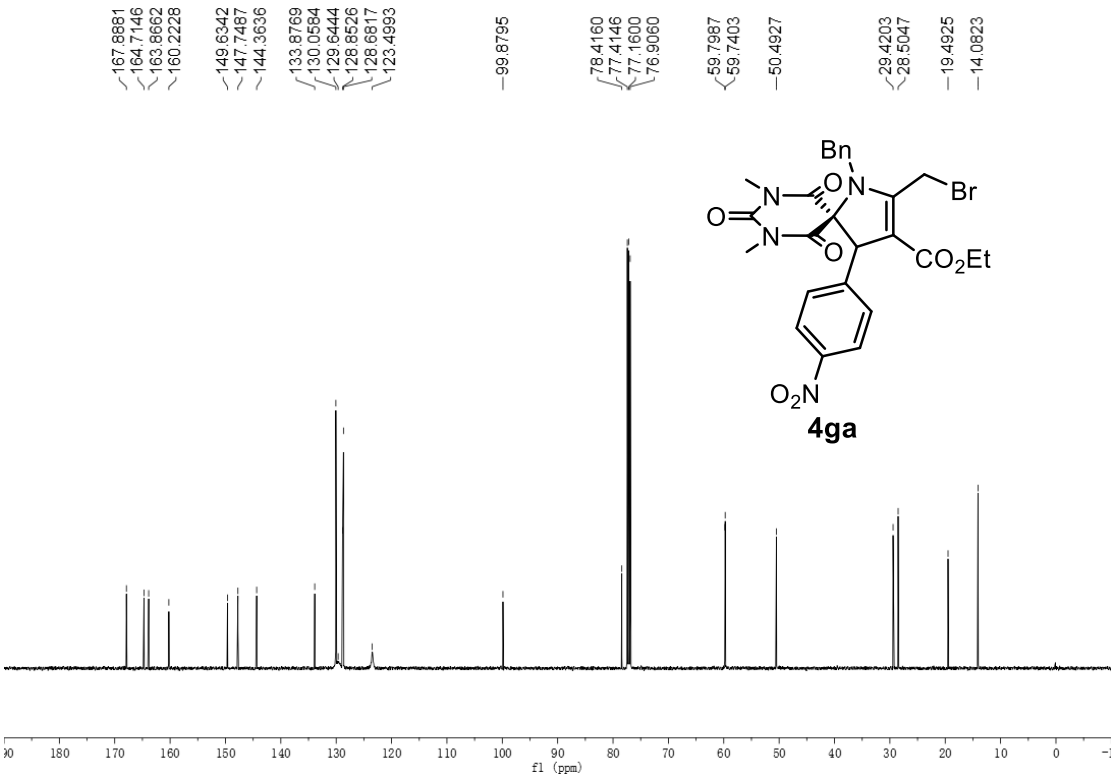


Figure S20. ^{13}C NMR (125 MHz, $CDCl_3$) of compound 4ga

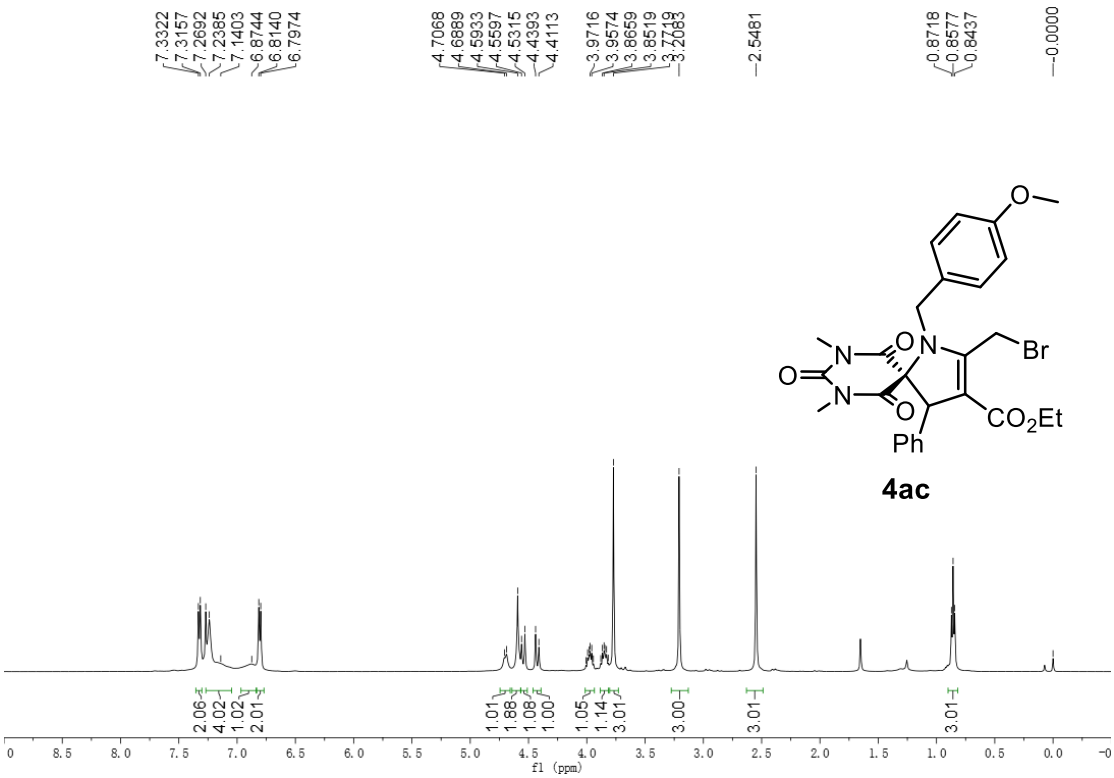


Figure S21. ^{1}H NMR (500 MHz, $CDCl_3$) of compound 4ac

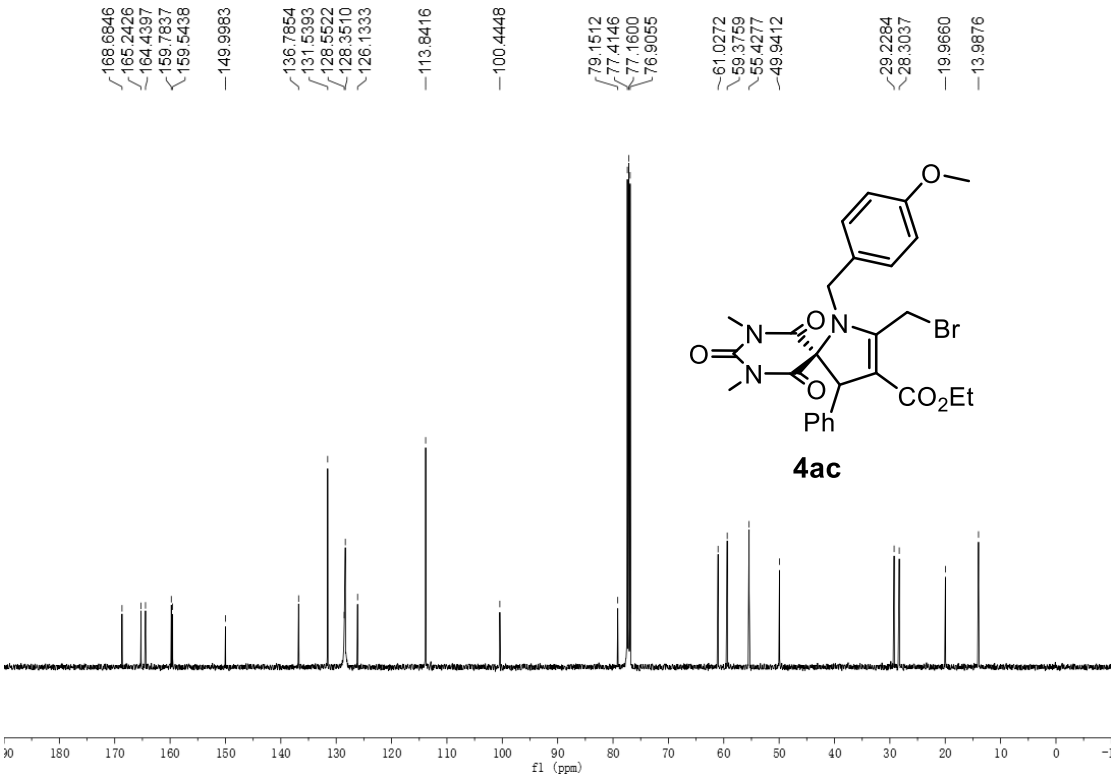


Figure S22. ^{13}C NMR (125 MHz, $CDCl_3$) of compound 4ac

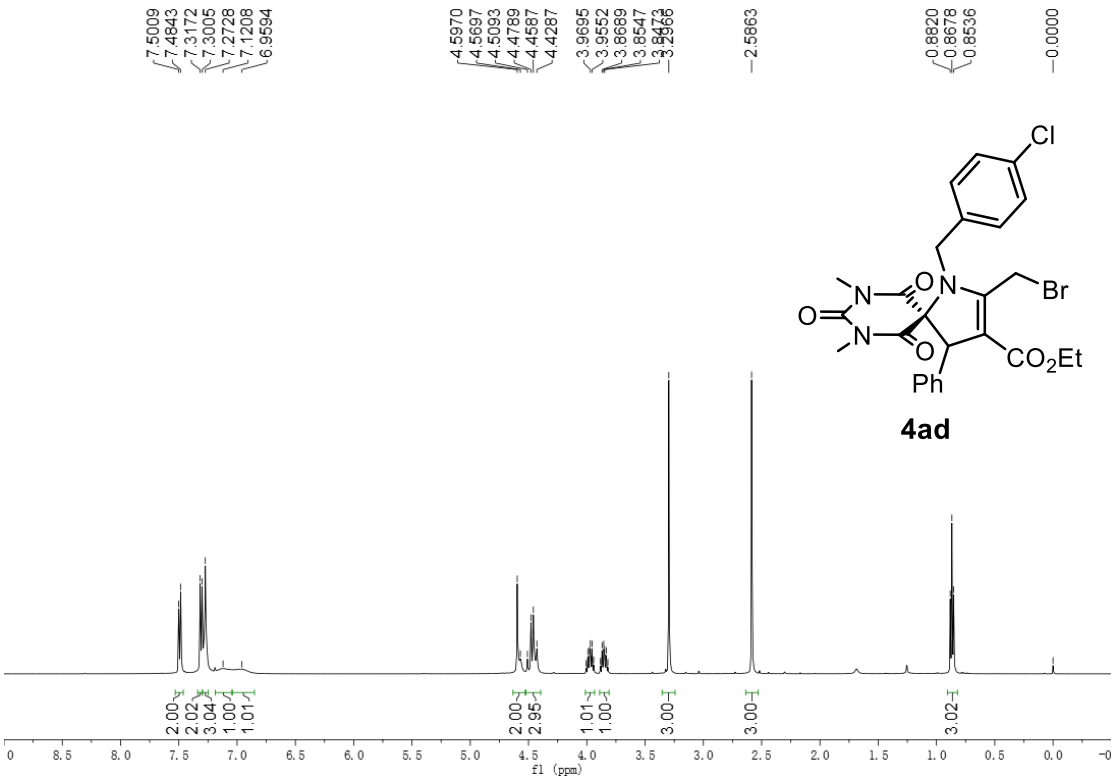


Figure S23. ^{1}H NMR (500 MHz, $CDCl_3$) of compound 4ad

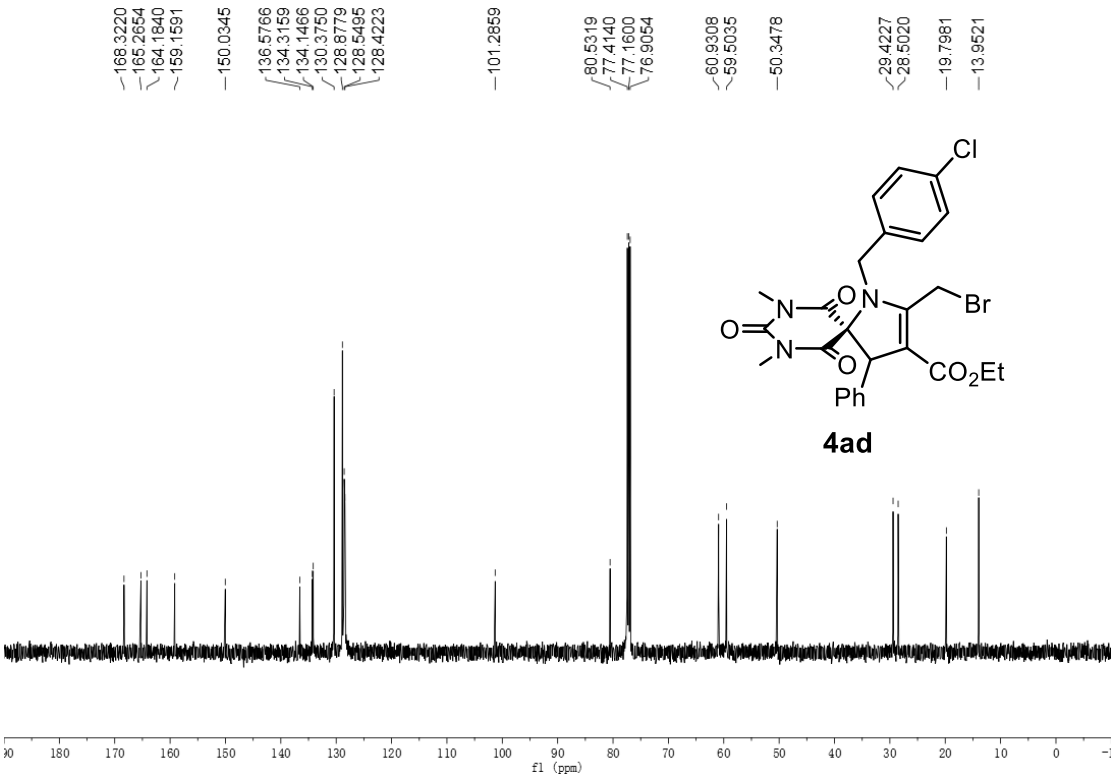


Figure S24. ^{13}C NMR (125 MHz, $CDCl_3$) of compound 4ad

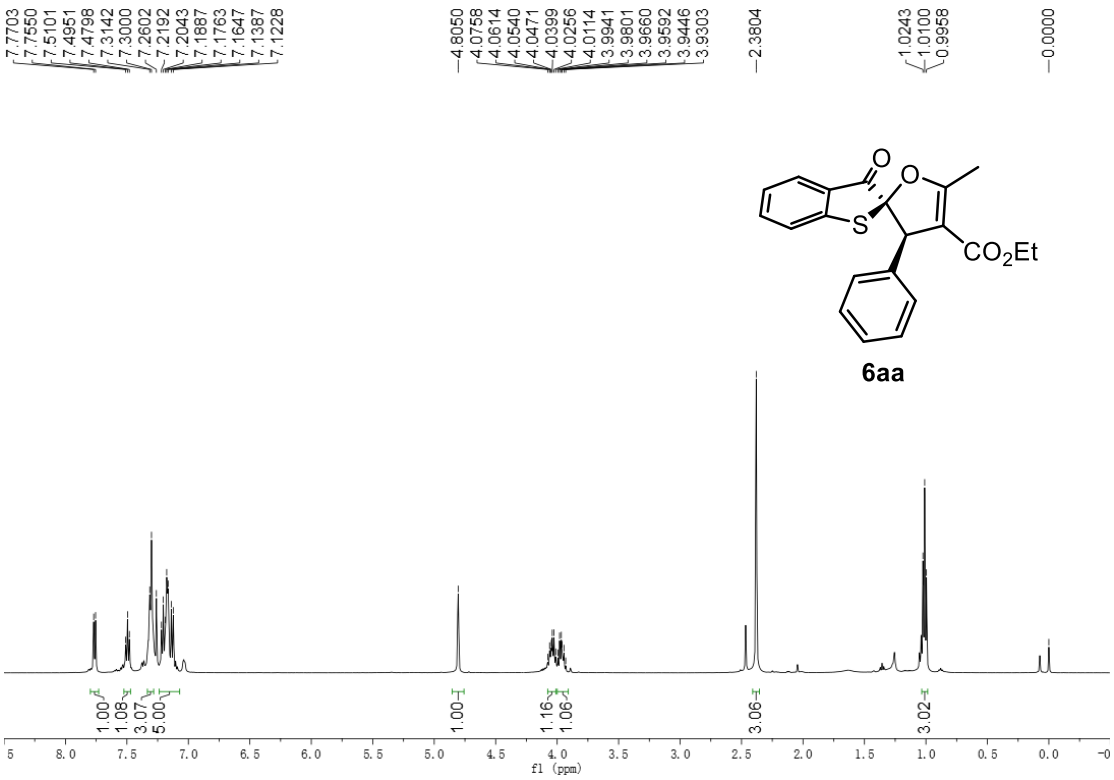


Figure S25. ^{1}H NMR (500 MHz, $CDCl_3$) of compound 6aa

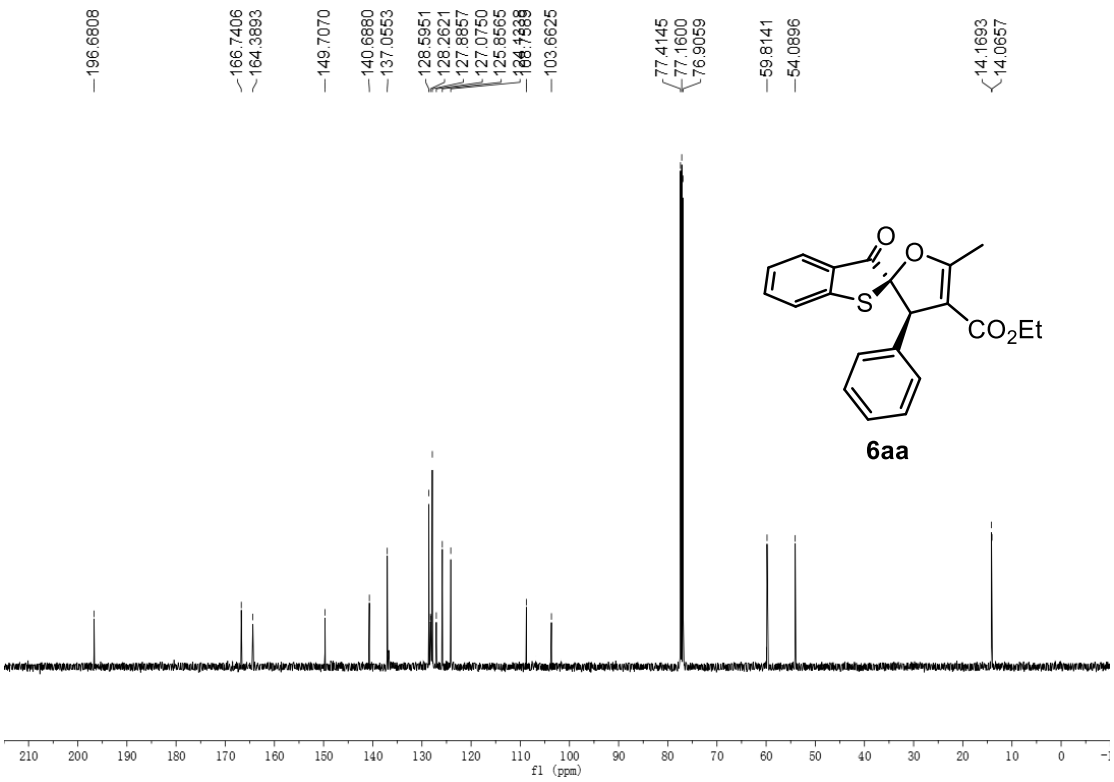


Figure S26. ^{13}C NMR (125 MHz, $CDCl_3$) of compound 6aa

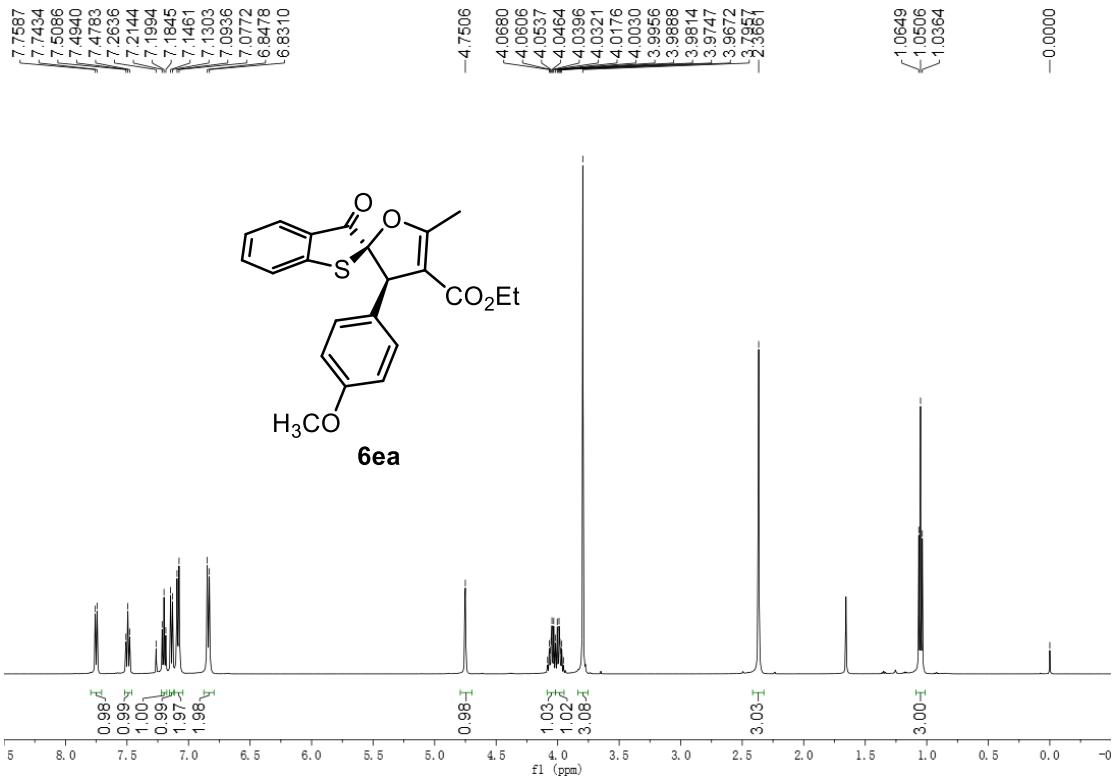


Figure S27. ^{1}H NMR (500 MHz, $CDCl_3$) of compound 6ea

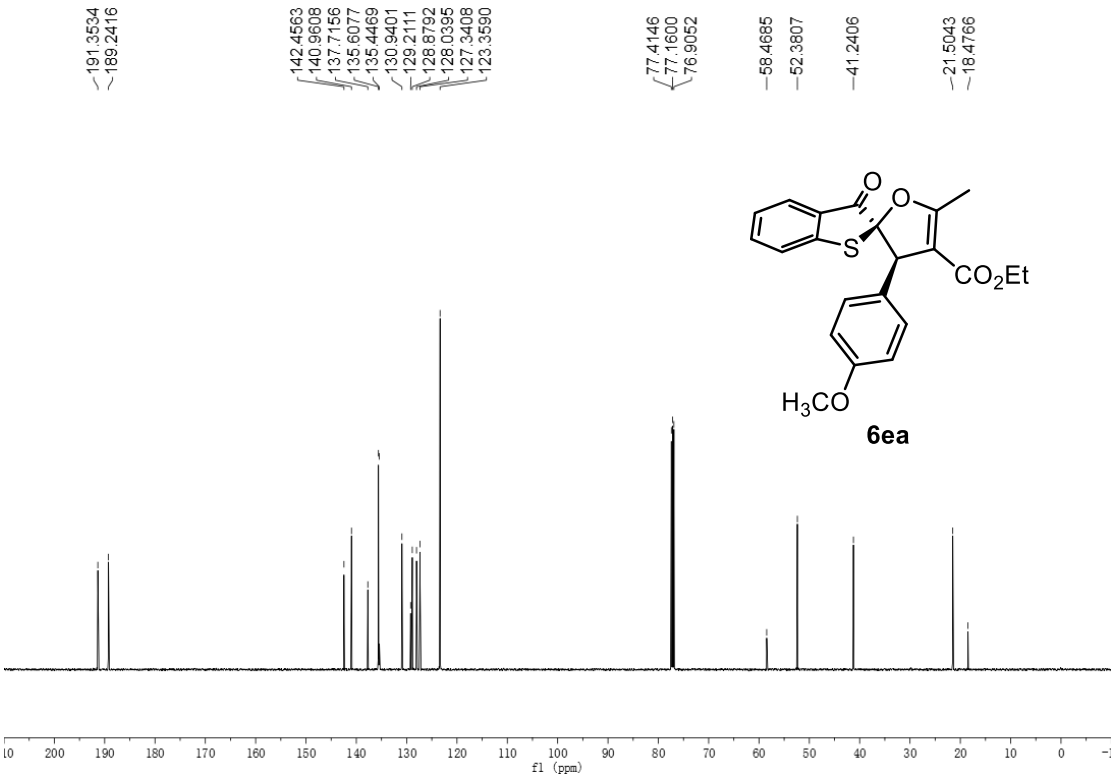


Figure S28. ^{13}C NMR (125 MHz, $CDCl_3$) of compound 6ea

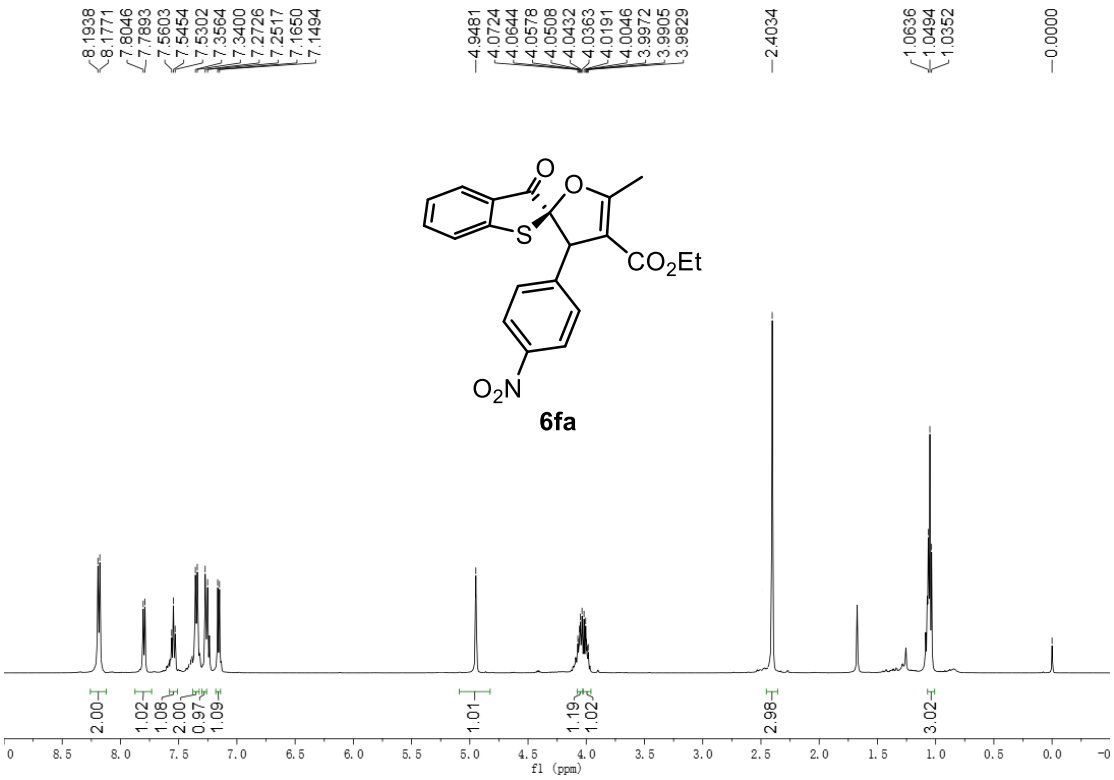


Figure S29. ^{1}H NMR (500 MHz, $CDCl_3$) of compound 6fa

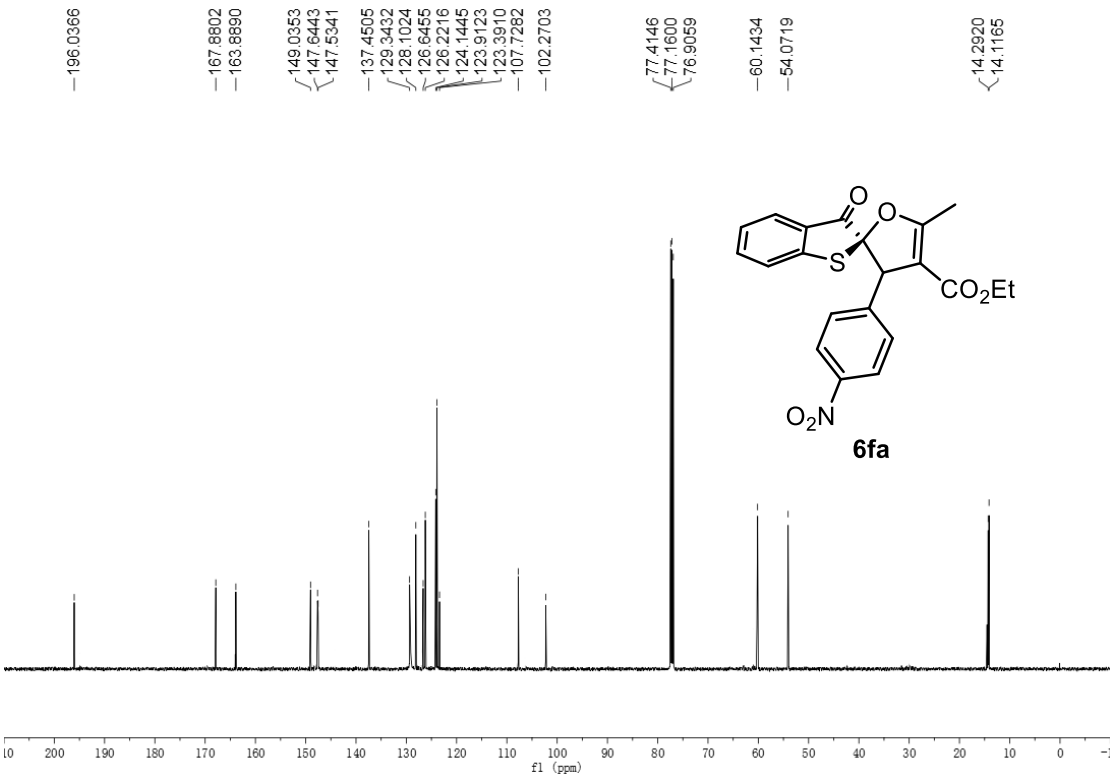


Figure S30. ^{13}C NMR (125 MHz, $CDCl_3$) of compound 6fa

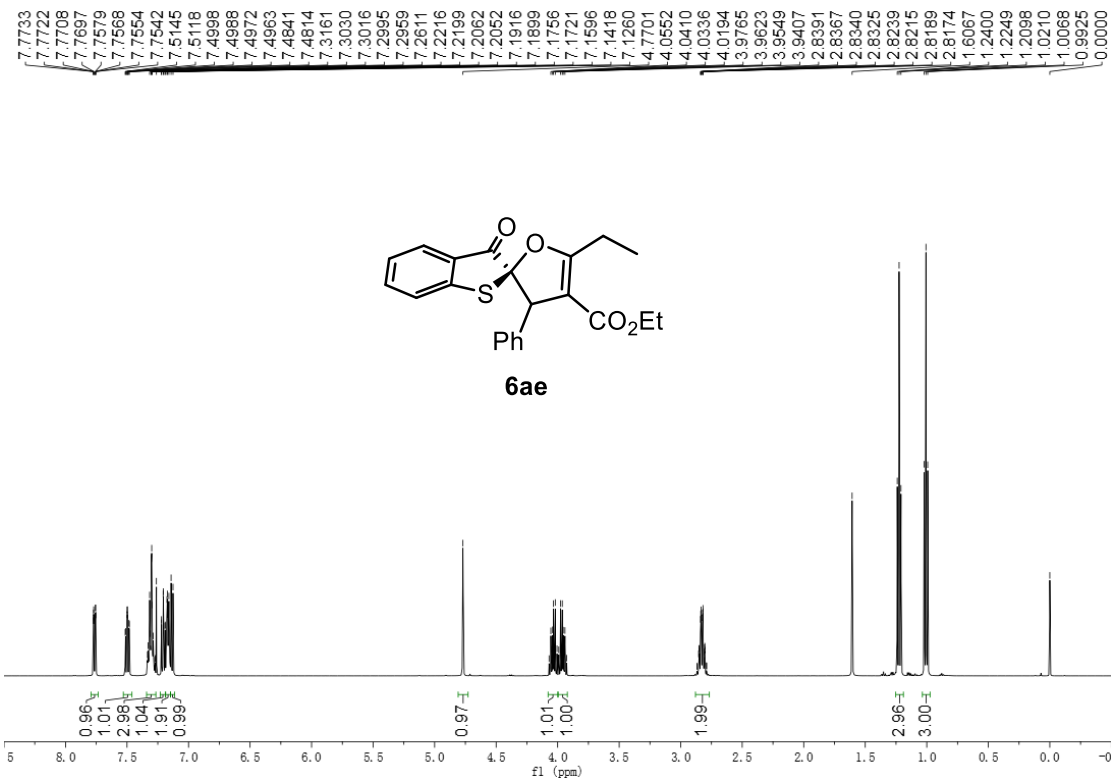


Figure S31. ^{1}H NMR (500 MHz, $CDCl_3$) of compound 6ae

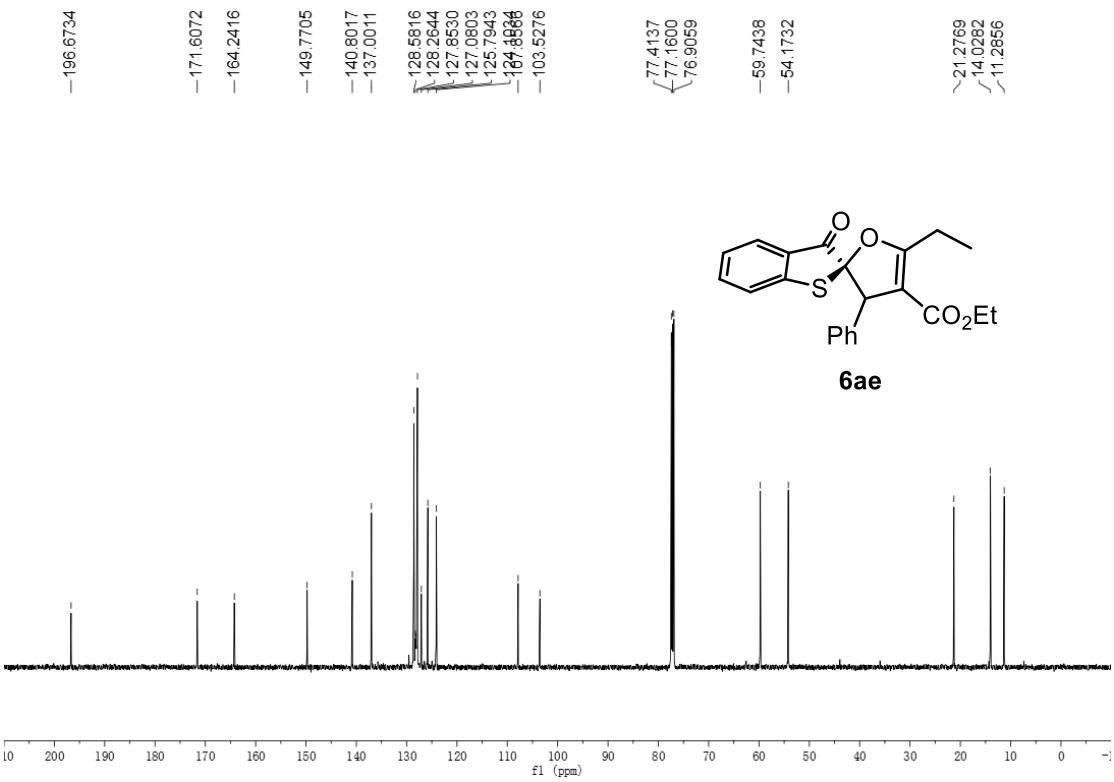


Figure S32. ^{13}C NMR (125 MHz, $CDCl_3$) of compound 6ae

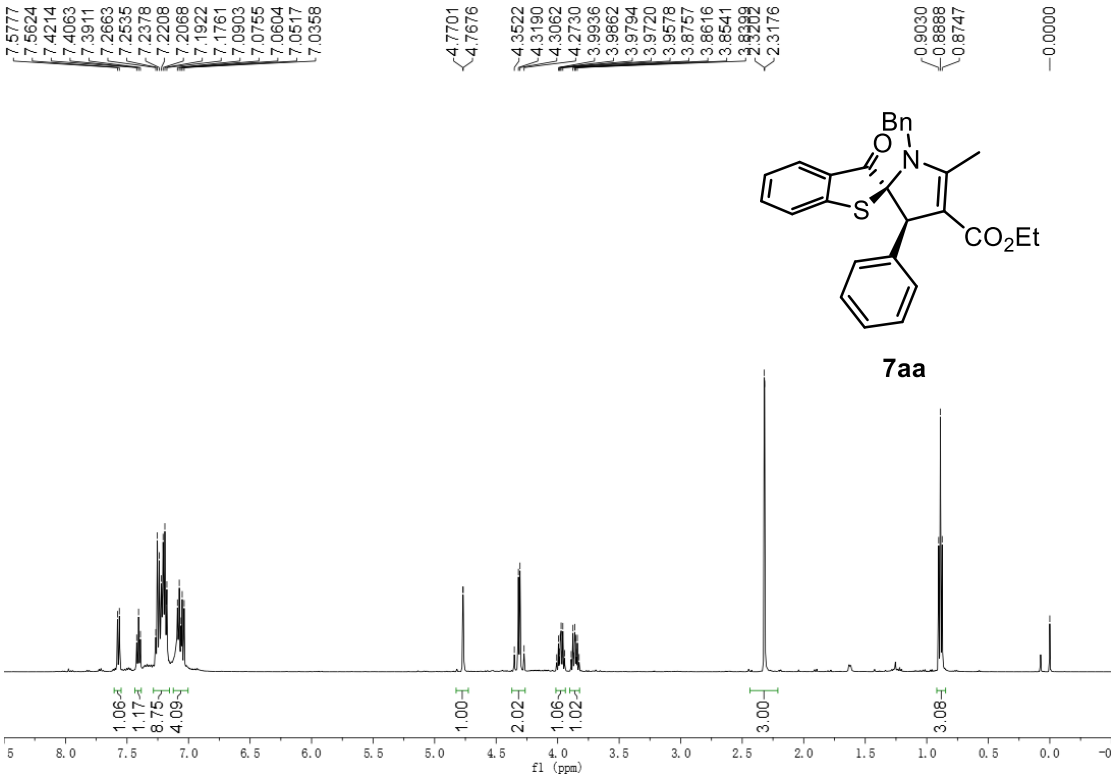


Figure S33. ^{1}H NMR (500 MHz, $CDCl_3$) of compound 7aa

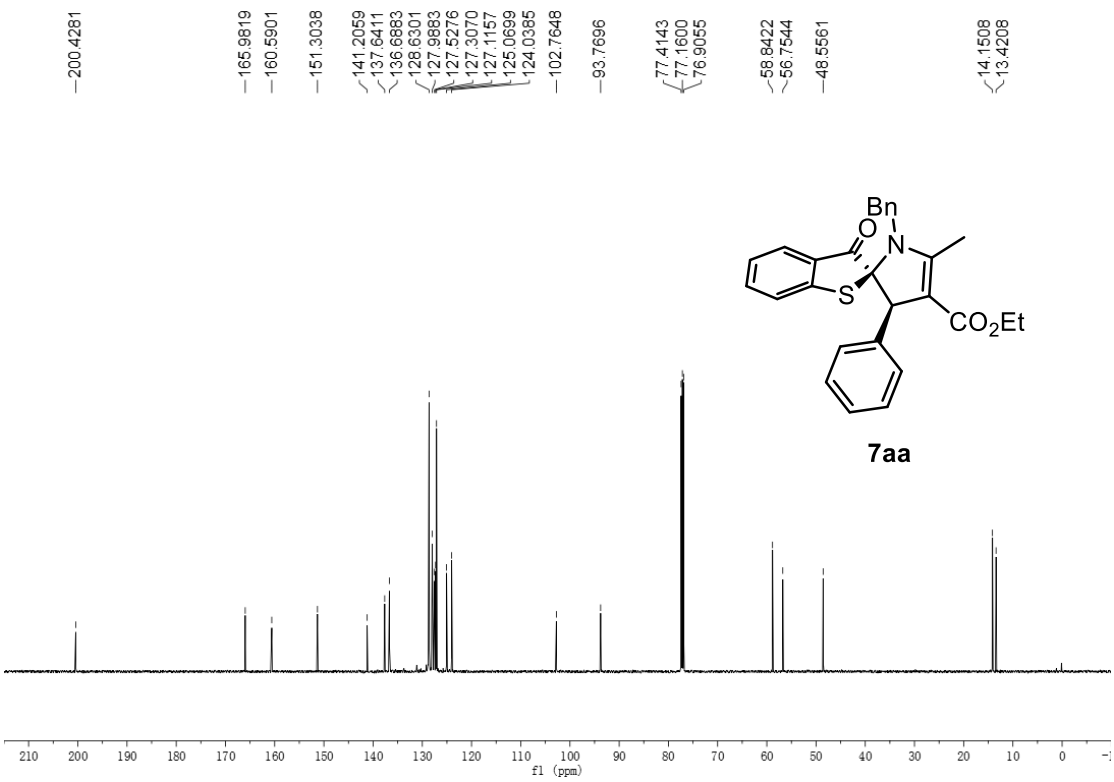


Figure S34. ^{13}C NMR (125 MHz, $CDCl_3$) of compound 7aa

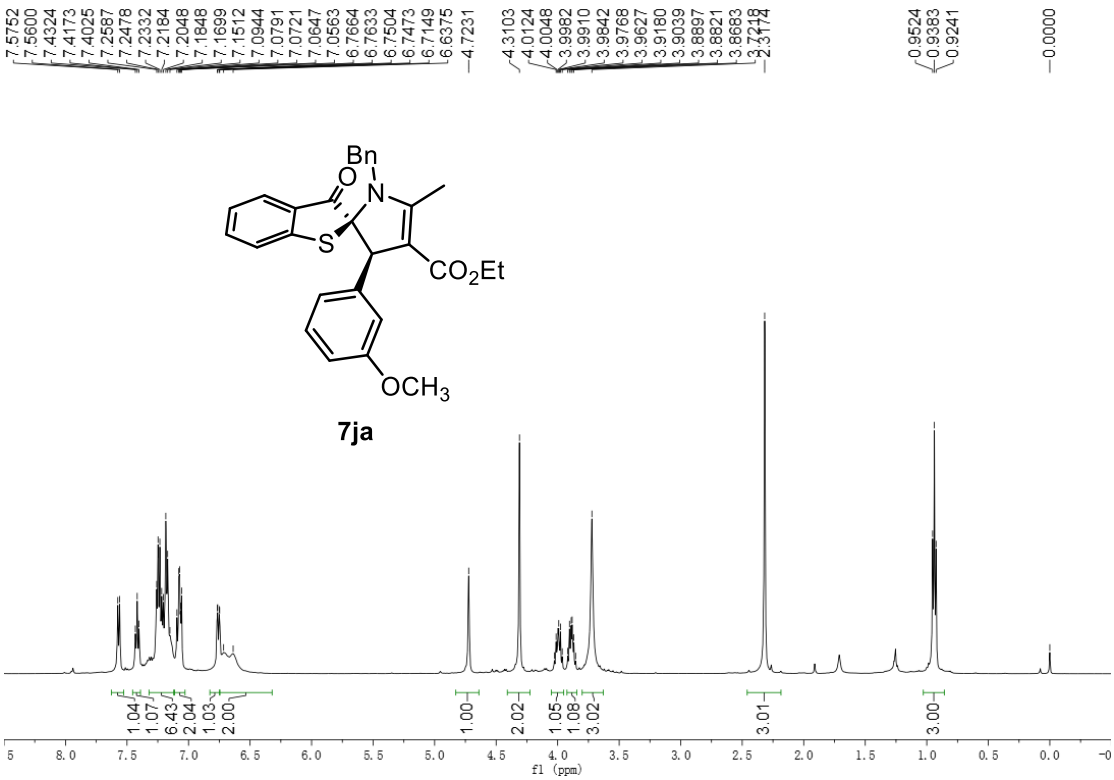


Figure S35. ^{1}H NMR (500 MHz, $CDCl_3$) of compound 7ja

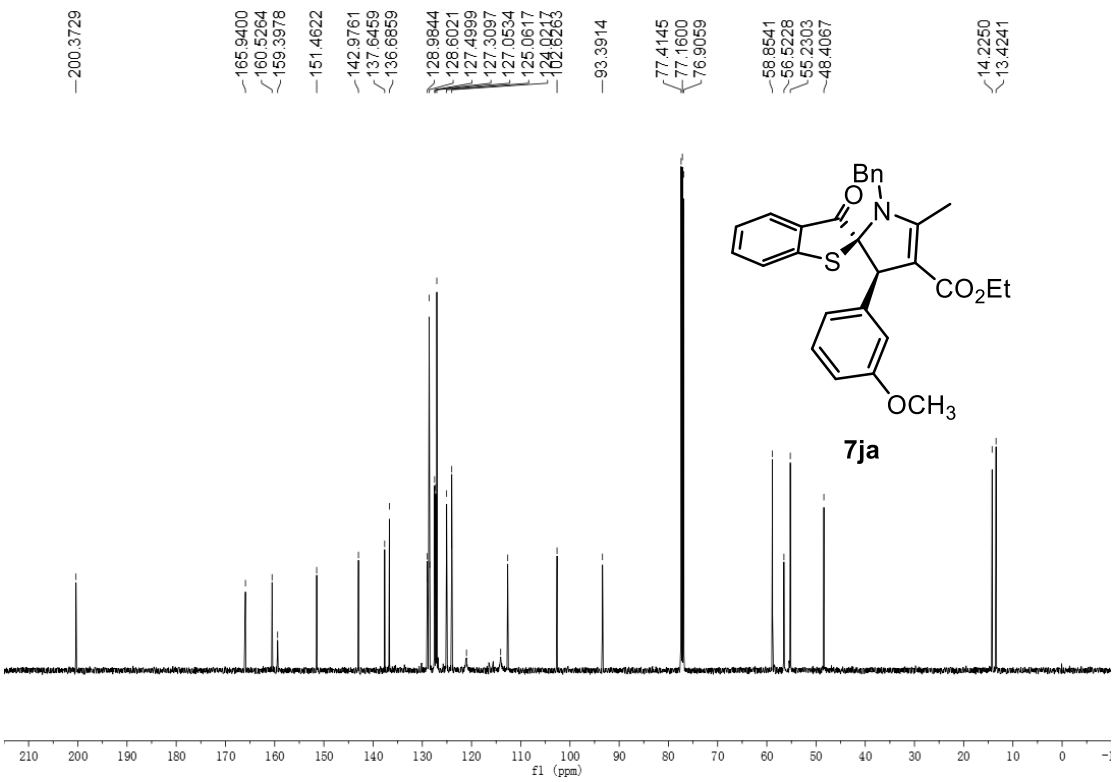


Figure S36. ^{13}C NMR (125 MHz, $CDCl_3$) of compound 7ja

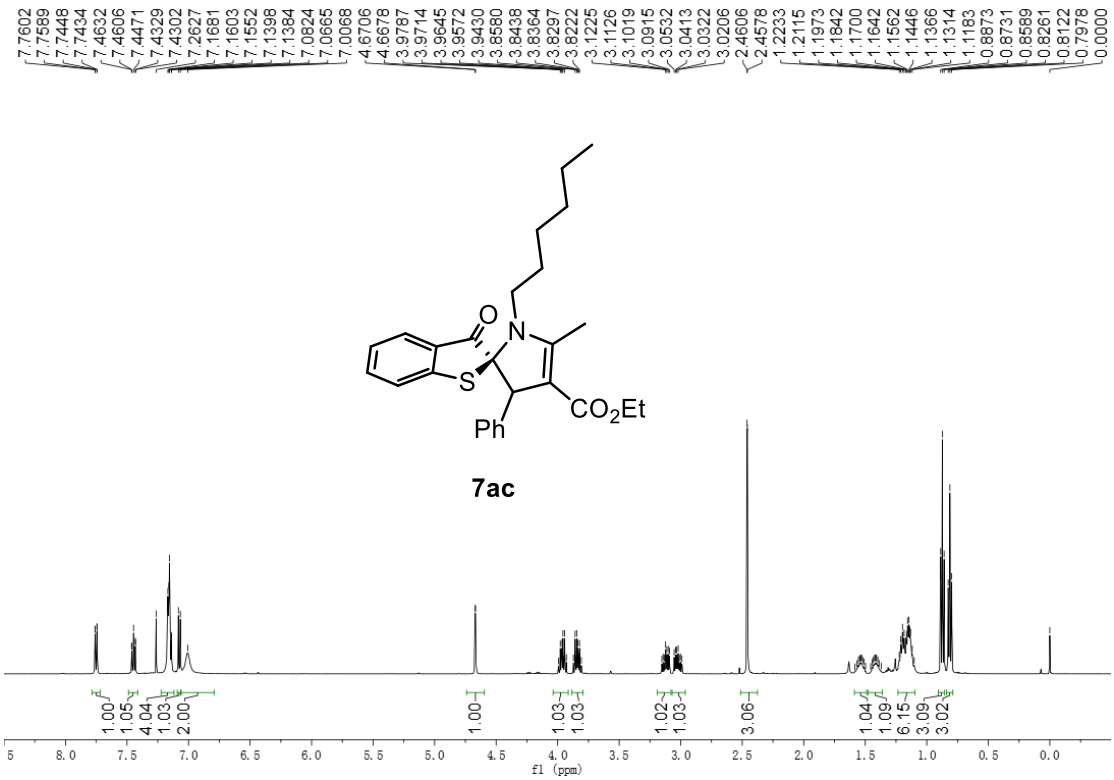


Figure S37. ^{1}H NMR (500 MHz, $CDCl_3$) of compound 7ac

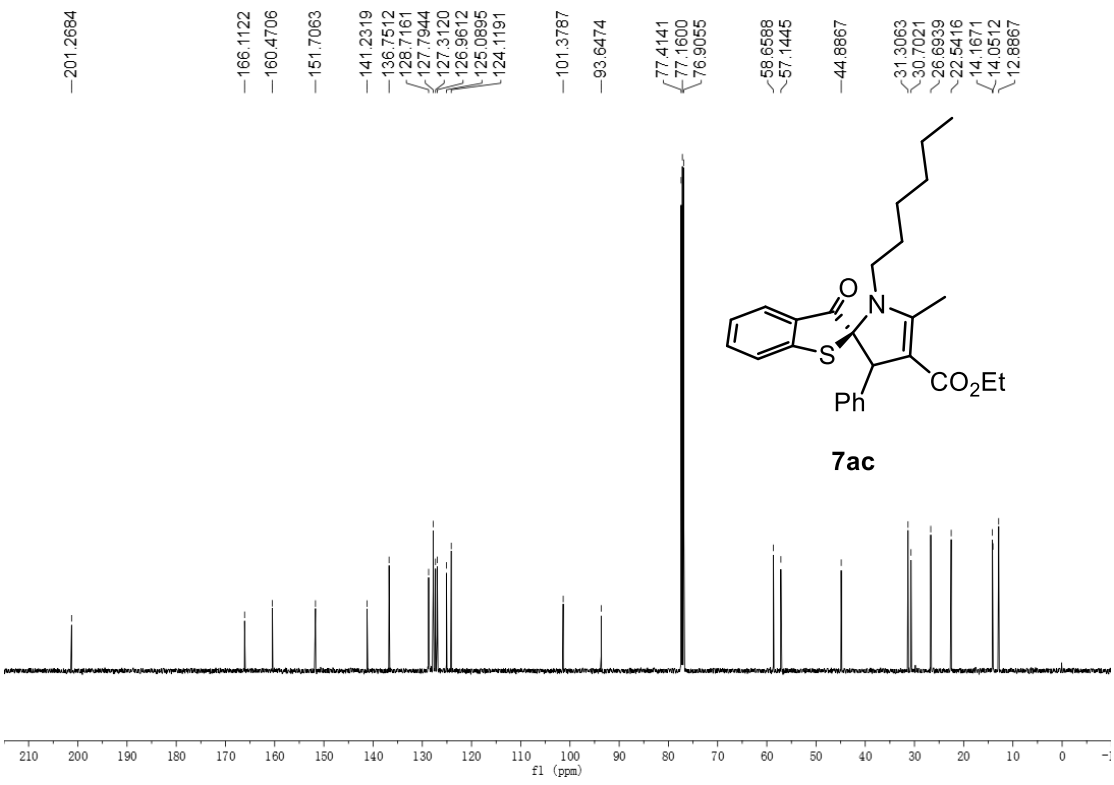


Figure S38. ^{13}C NMR (125 MHz, $CDCl_3$) of compound 7ac

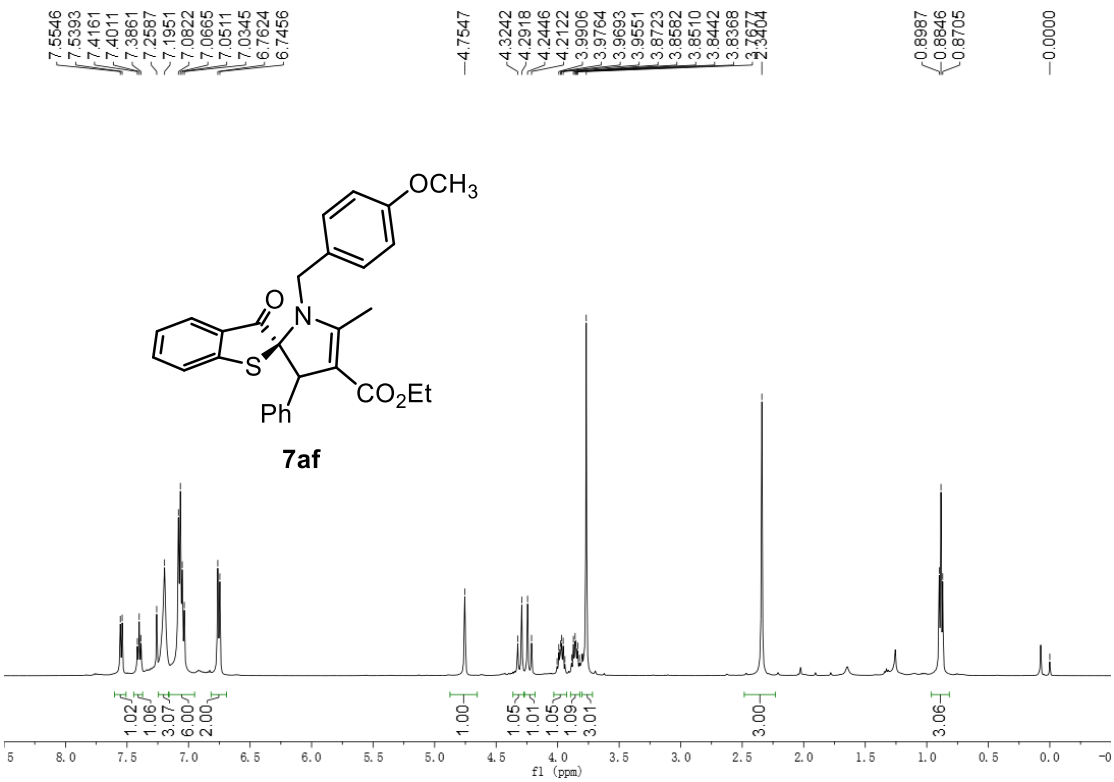


Figure S39. ^{1}H NMR (500 MHz, $CDCl_3$) of compound 7af

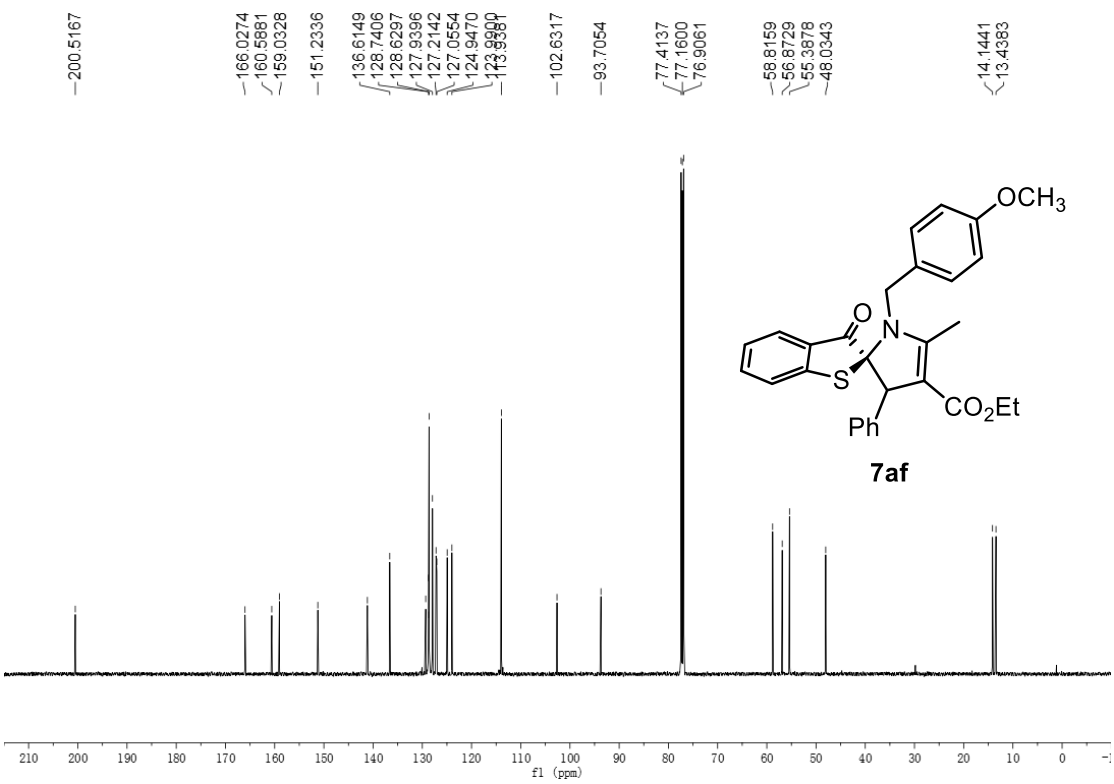


Figure S40. ^{13}C NMR (125 MHz, $CDCl_3$) of compound 7af

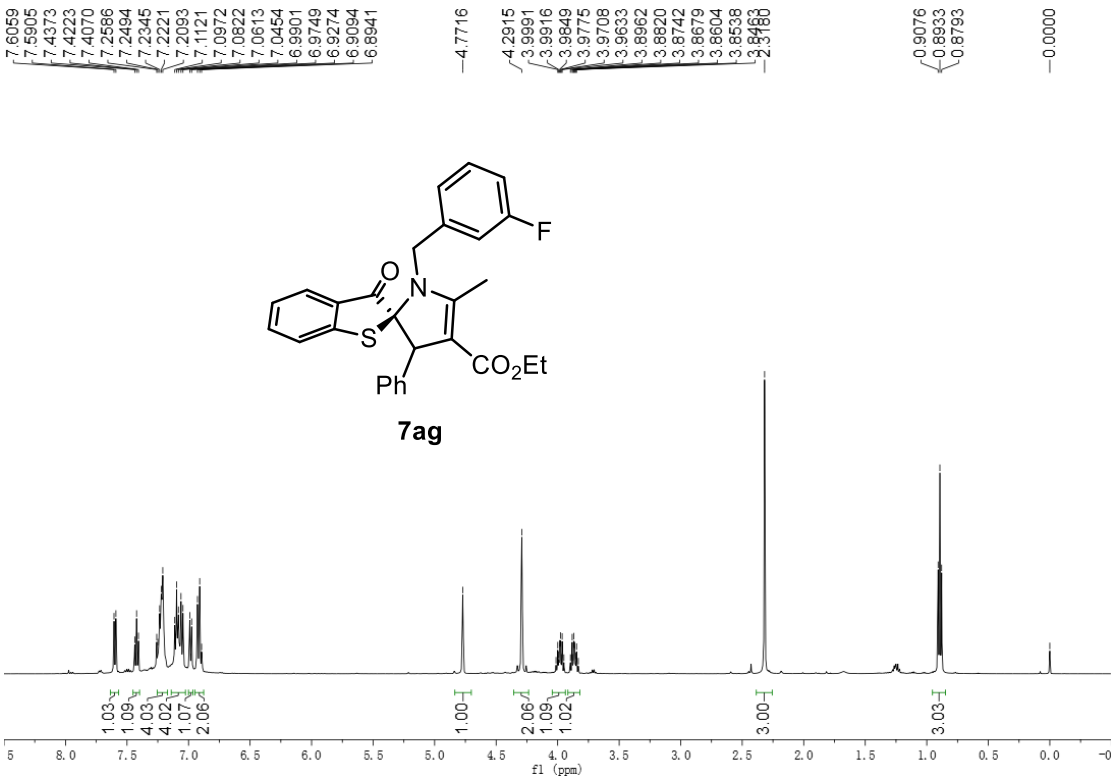


Figure S41. ^{1}H NMR (500 MHz, $CDCl_3$) of compound 7ag

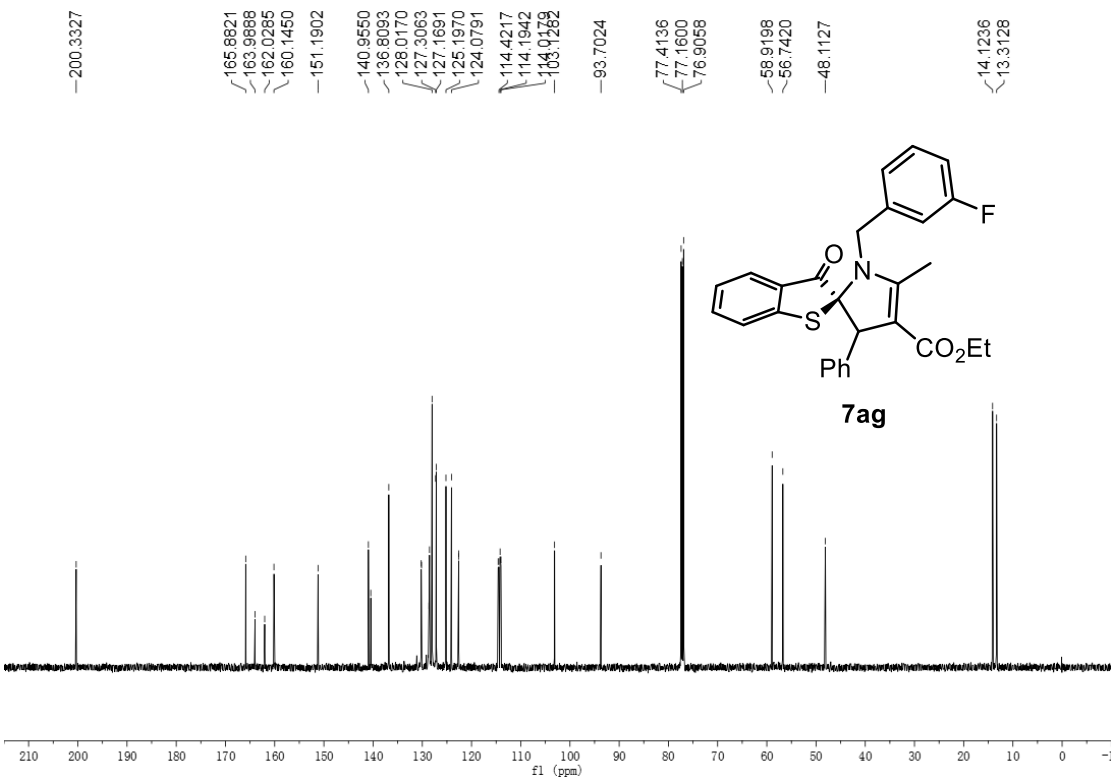


Figure S42. ^{13}C NMR (125 MHz, $CDCl_3$) of compound 7ag

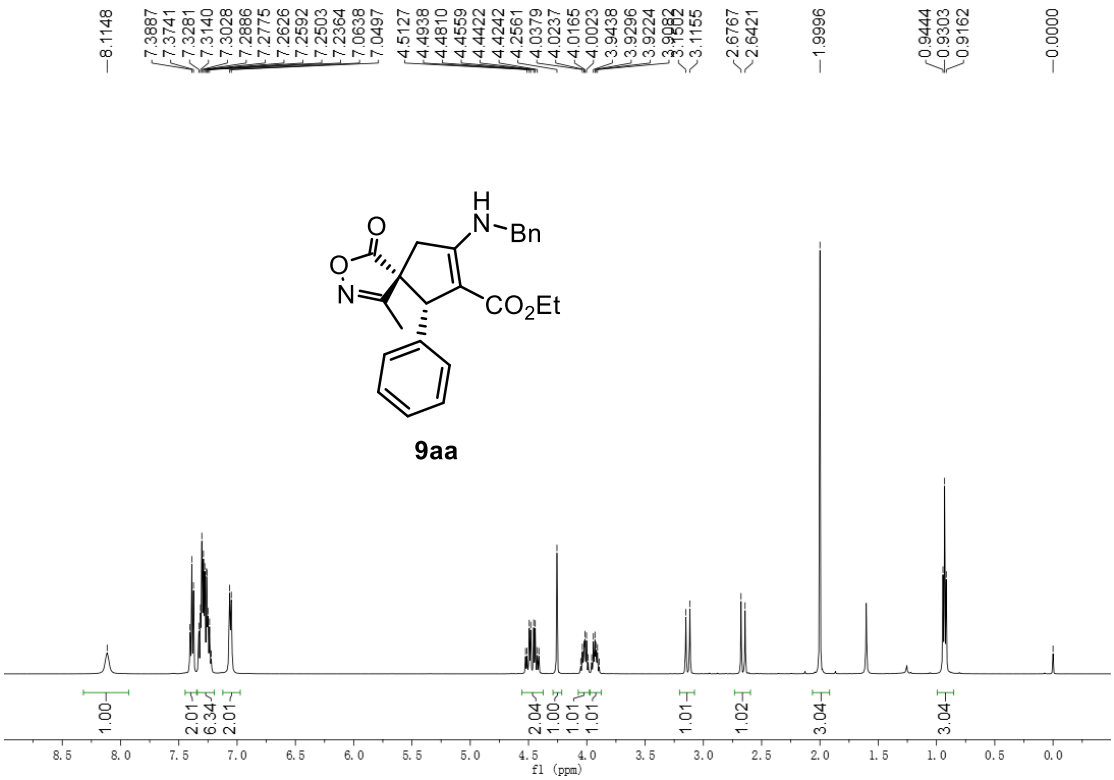


Figure S43. ^{1}H NMR (500 MHz, $CDCl_3$) of compound 9aa

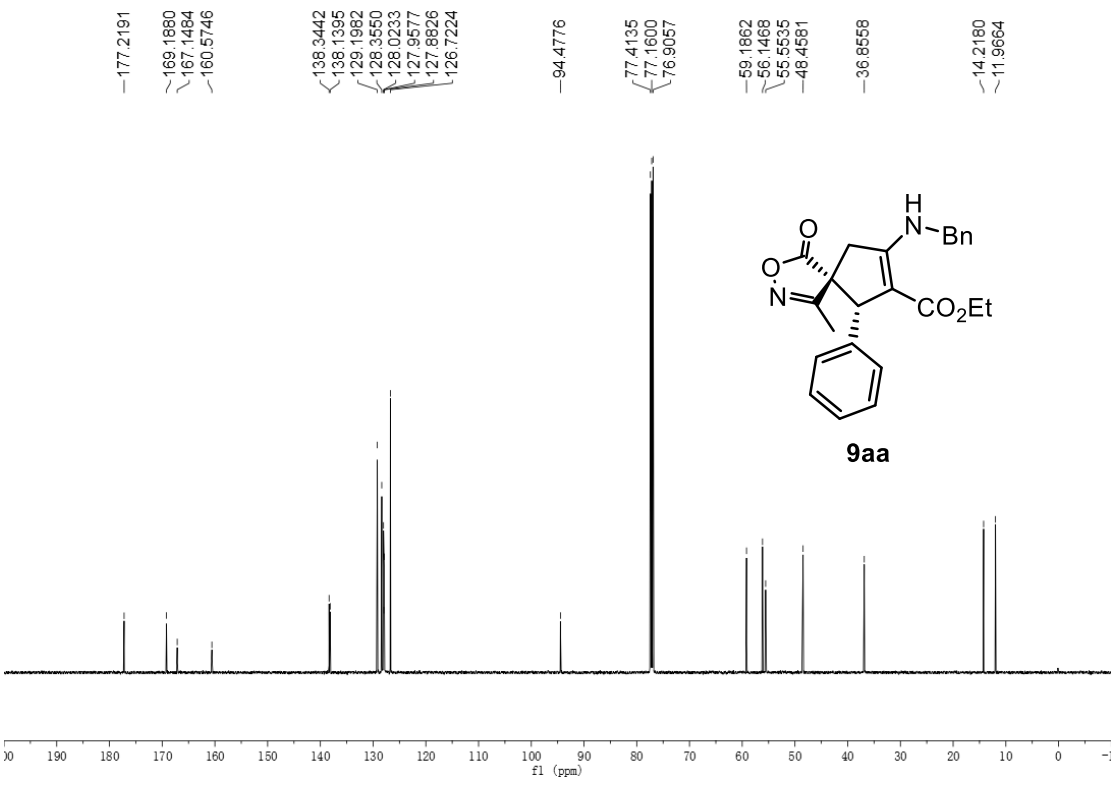


Figure S44. ^{13}C NMR (125 MHz, $CDCl_3$) of compound 9aa

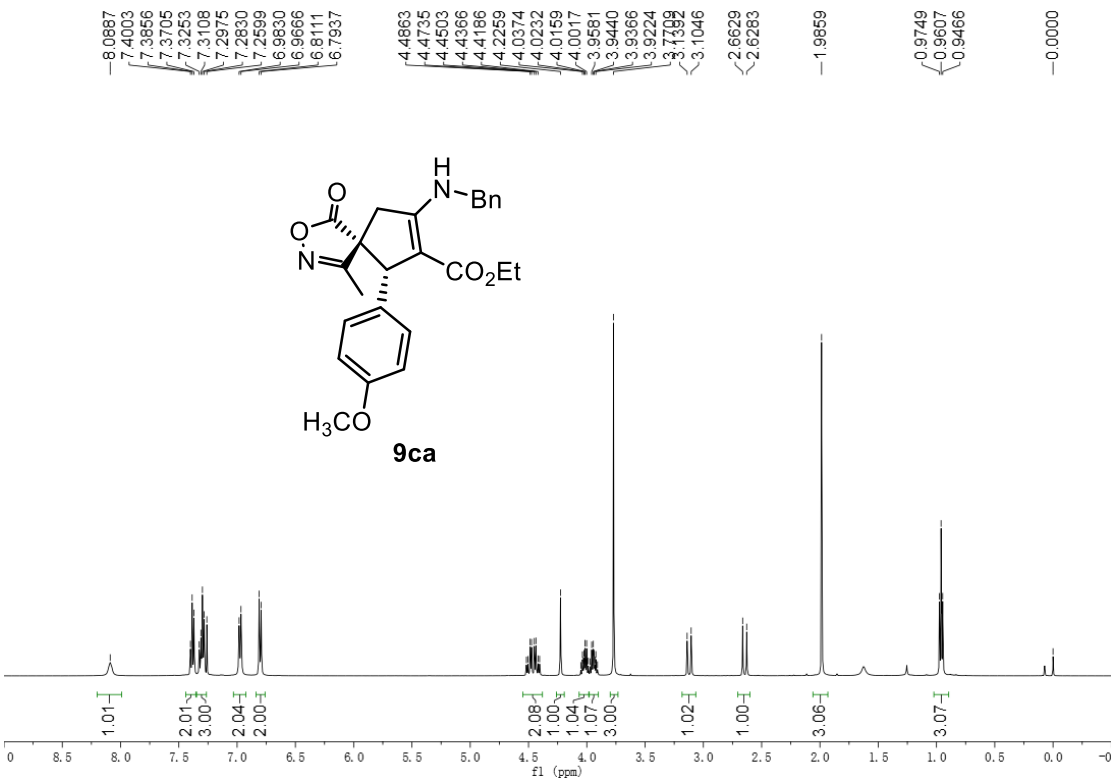


Figure S45. ^{1}H NMR (500 MHz, $CDCl_3$) of compound 9ca

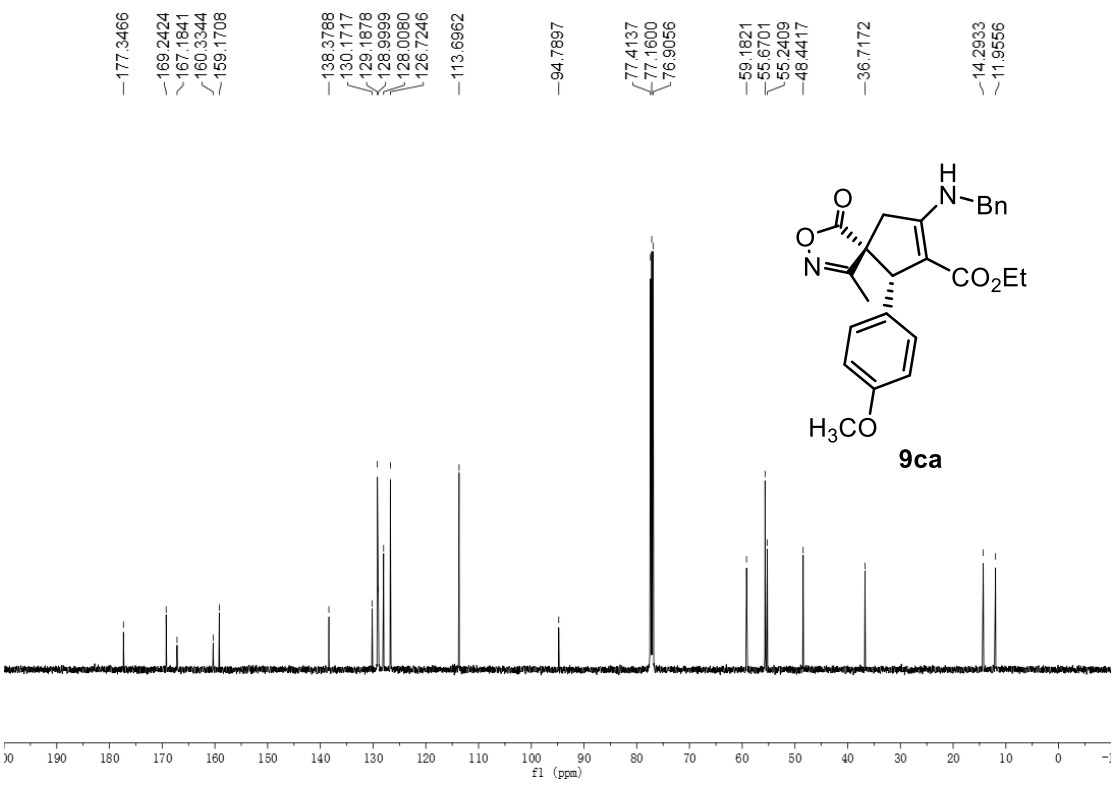


Figure S46. ^{13}C NMR (125 MHz, $CDCl_3$) of compound 9ca

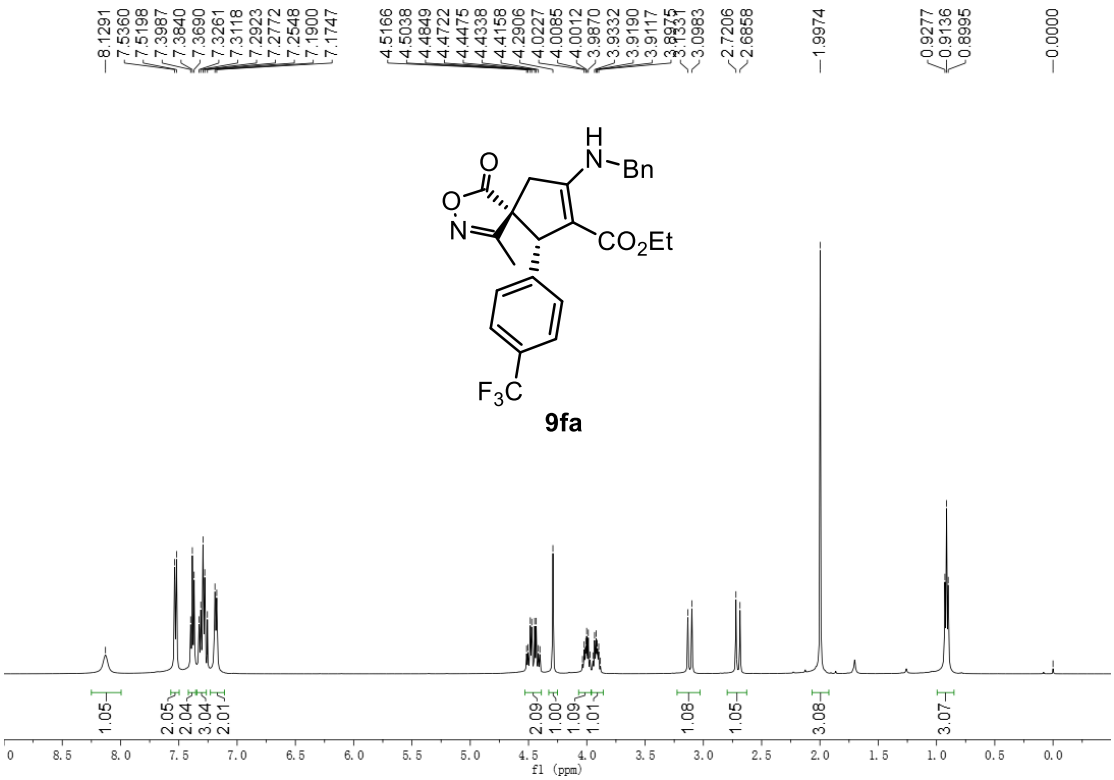


Figure S47. ^{1}H NMR (500 MHz, $CDCl_3$) of compound 9fa

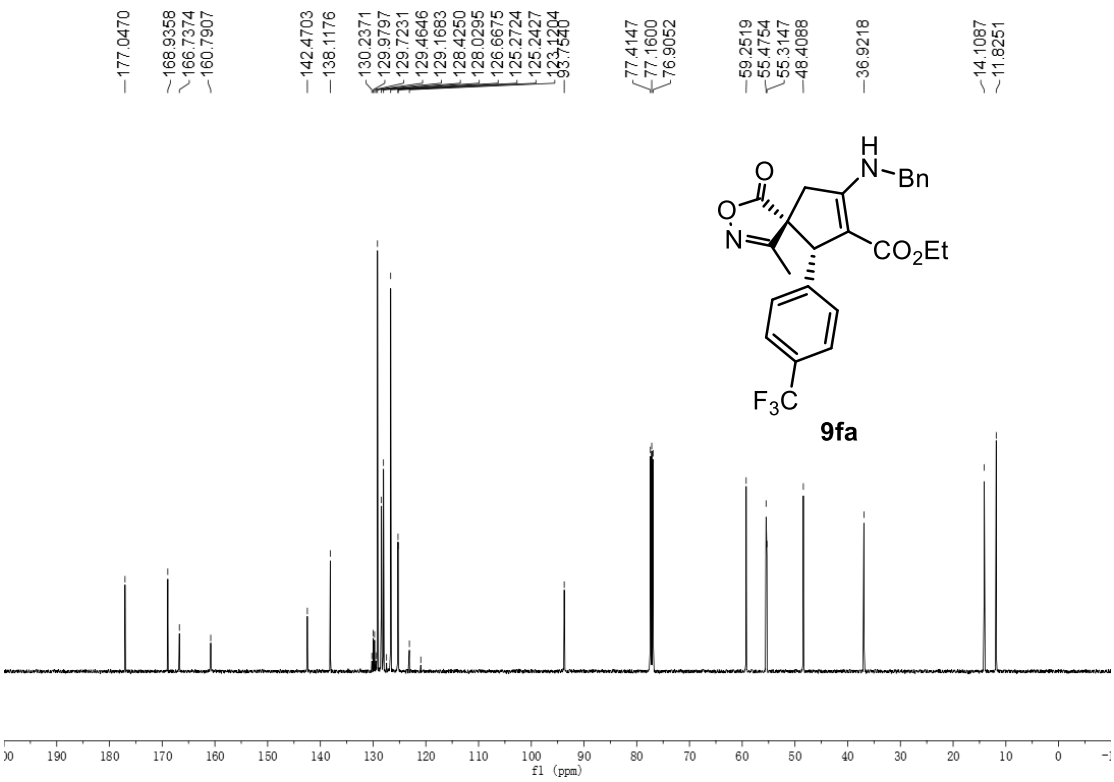


Figure S48. ^{13}C NMR (125 MHz, $CDCl_3$) of compound 9fa

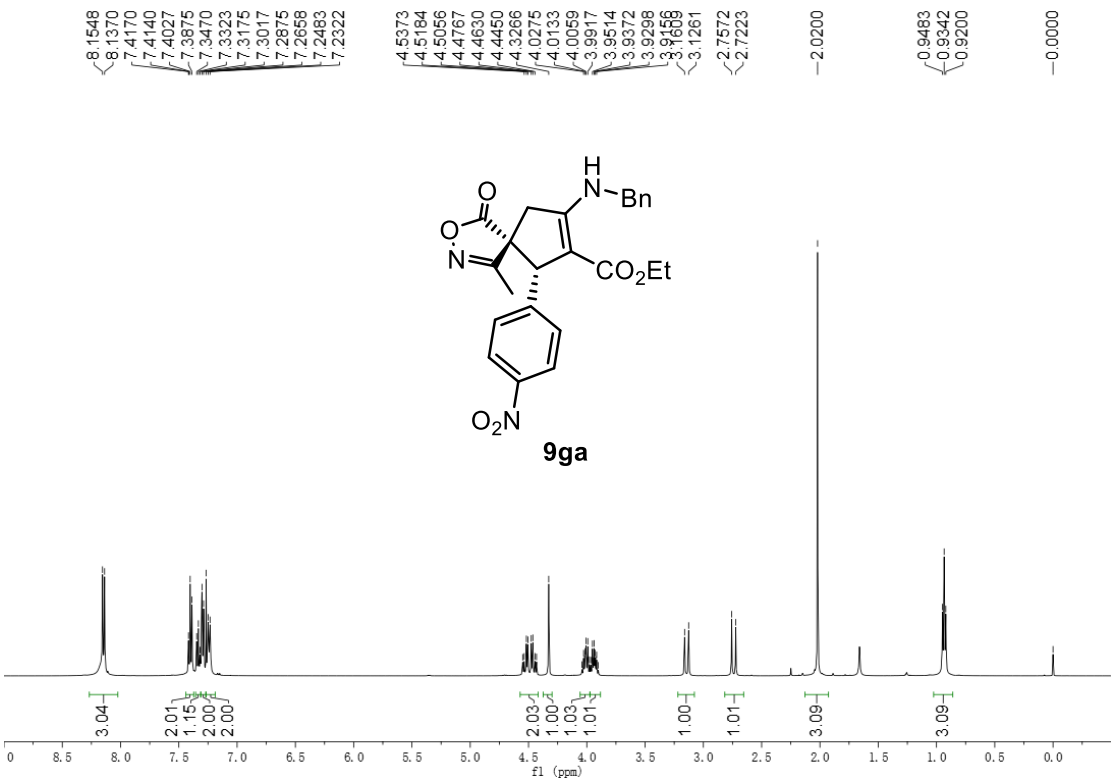


Figure S49. ^{1}H NMR (500 MHz, $CDCl_3$) of compound 9ga

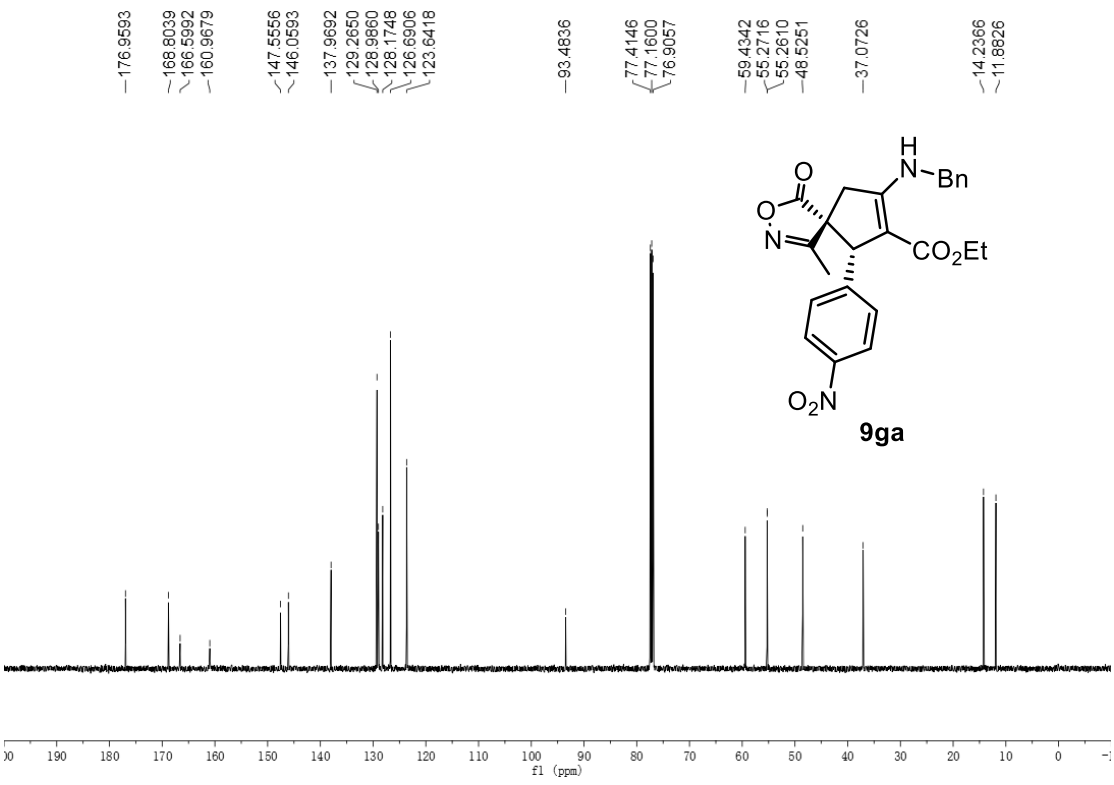


Figure S50. ^{13}C NMR (125 MHz, $CDCl_3$) of compound 9ga

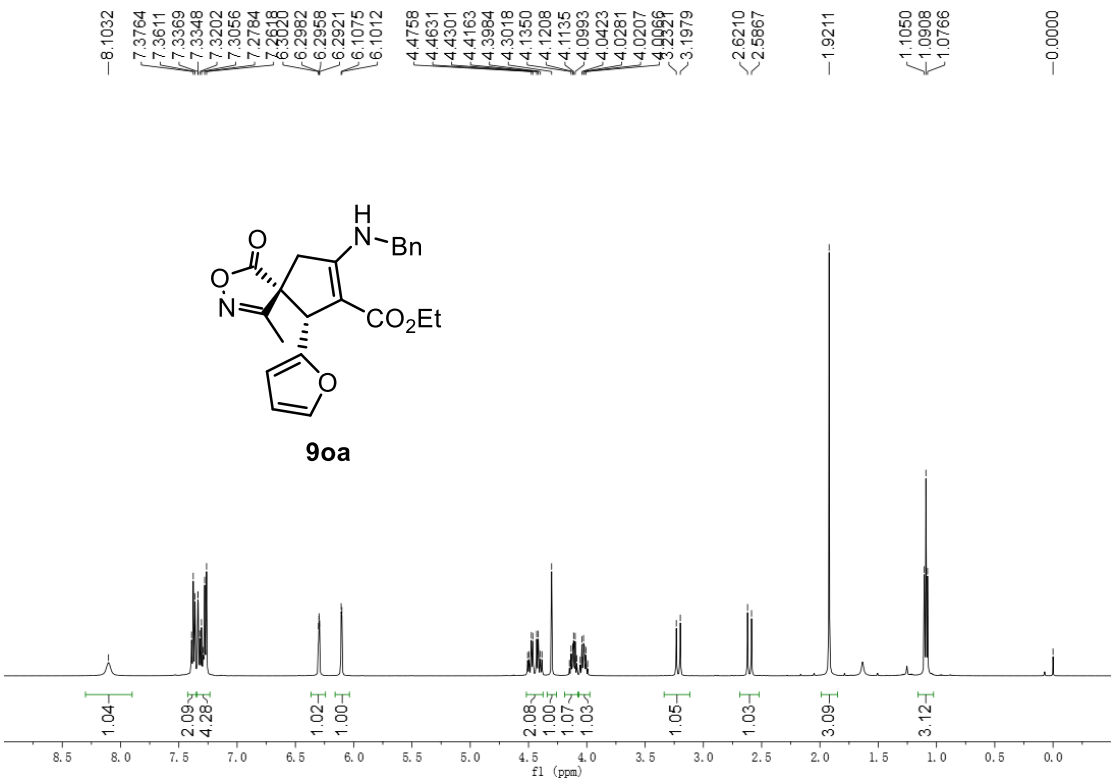


Figure S51. ^{1}H NMR (500 MHz, $CDCl_3$) of compound 9oa

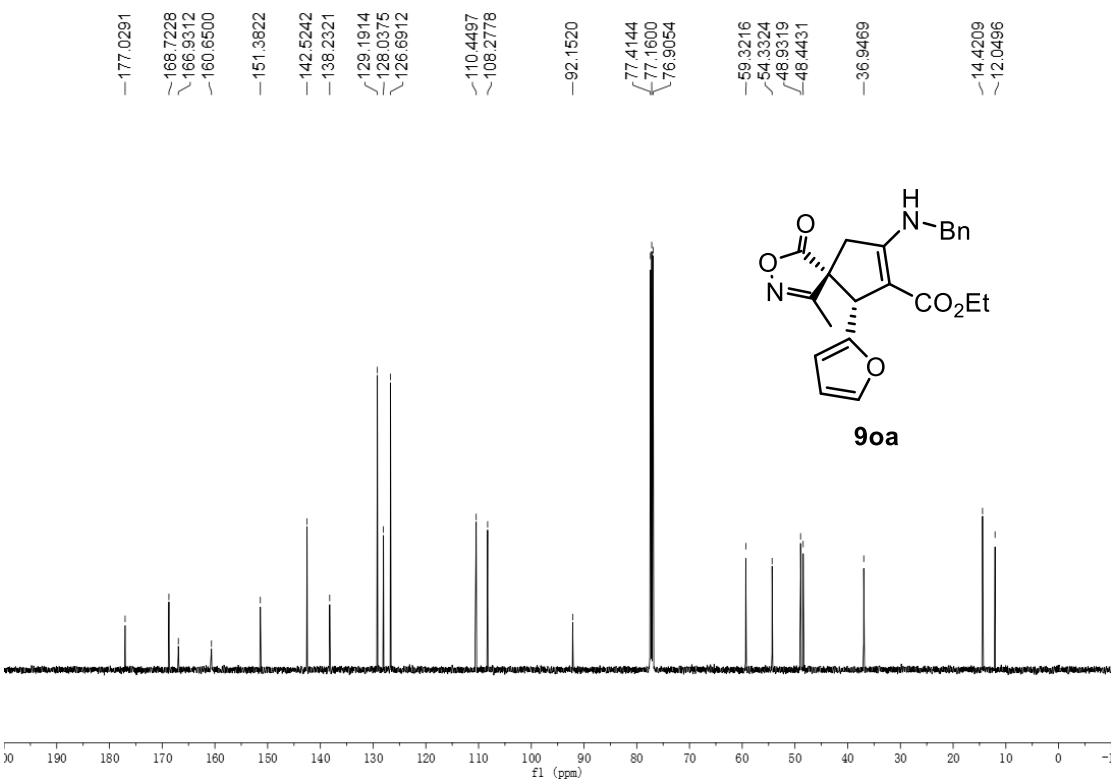


Figure S52. ^{13}C NMR (125 MHz, $CDCl_3$) of compound 9oa

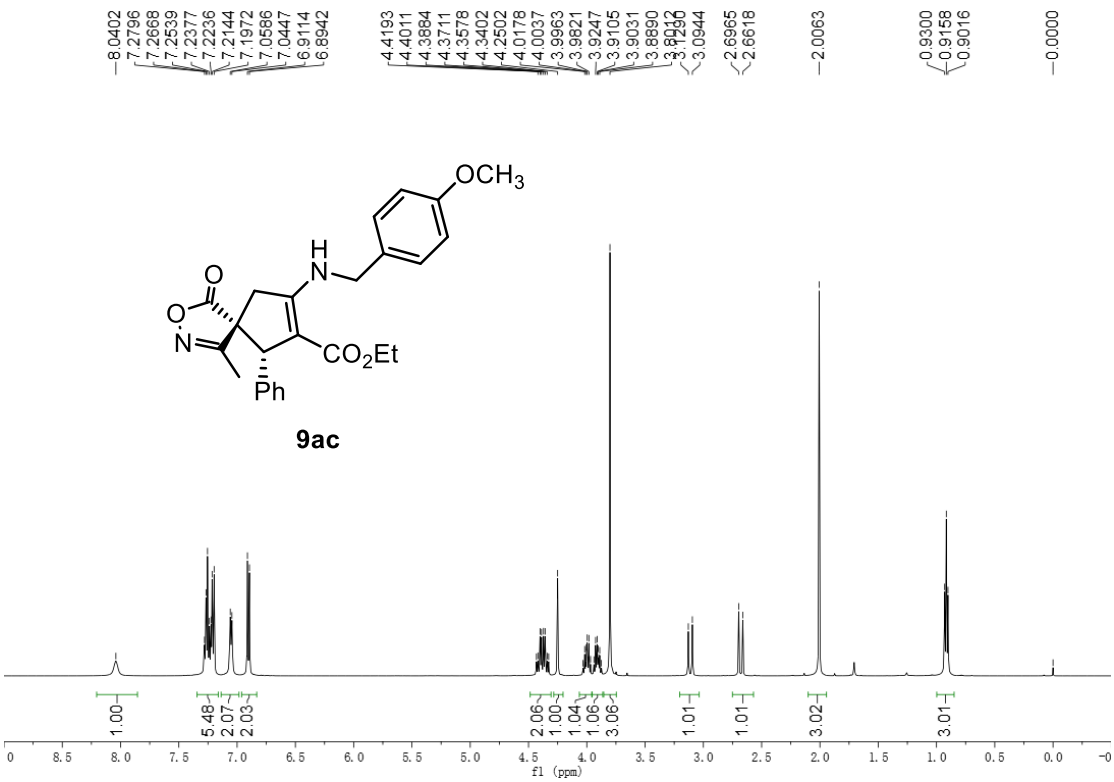


Figure S53. ^{1}H NMR (500 MHz, $CDCl_3$) of compound 9ac

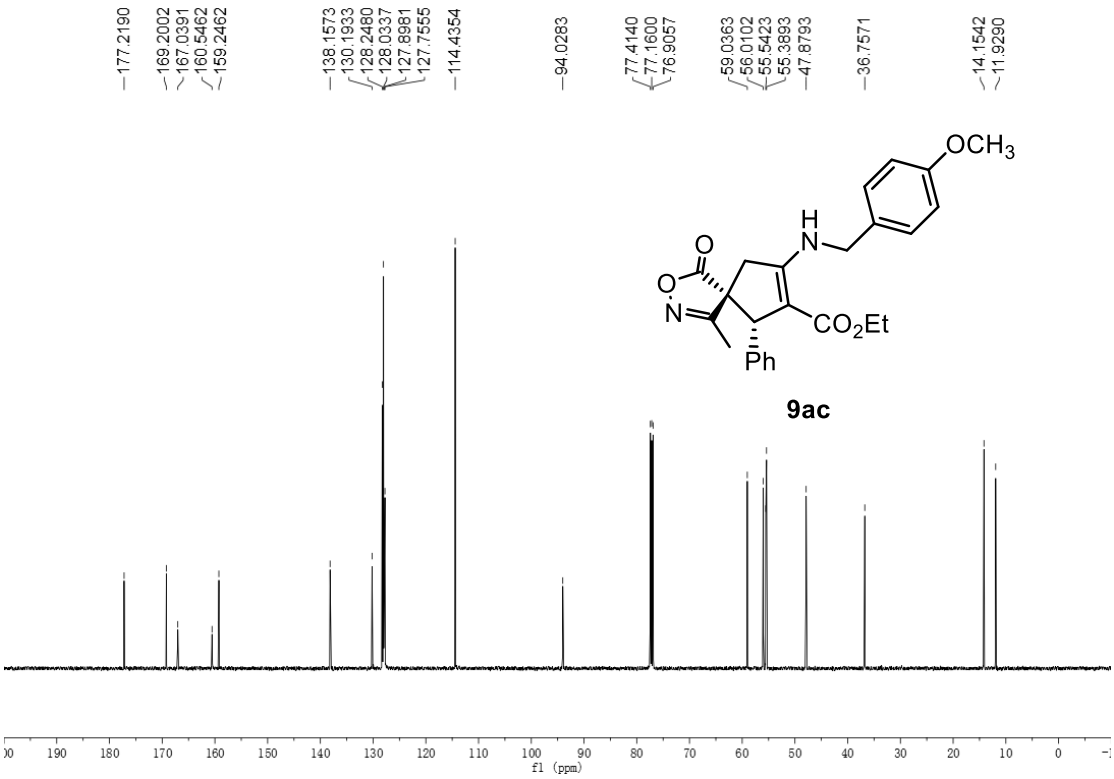


Figure S54. ^{13}C NMR (125 MHz, $CDCl_3$) of compound 9ac

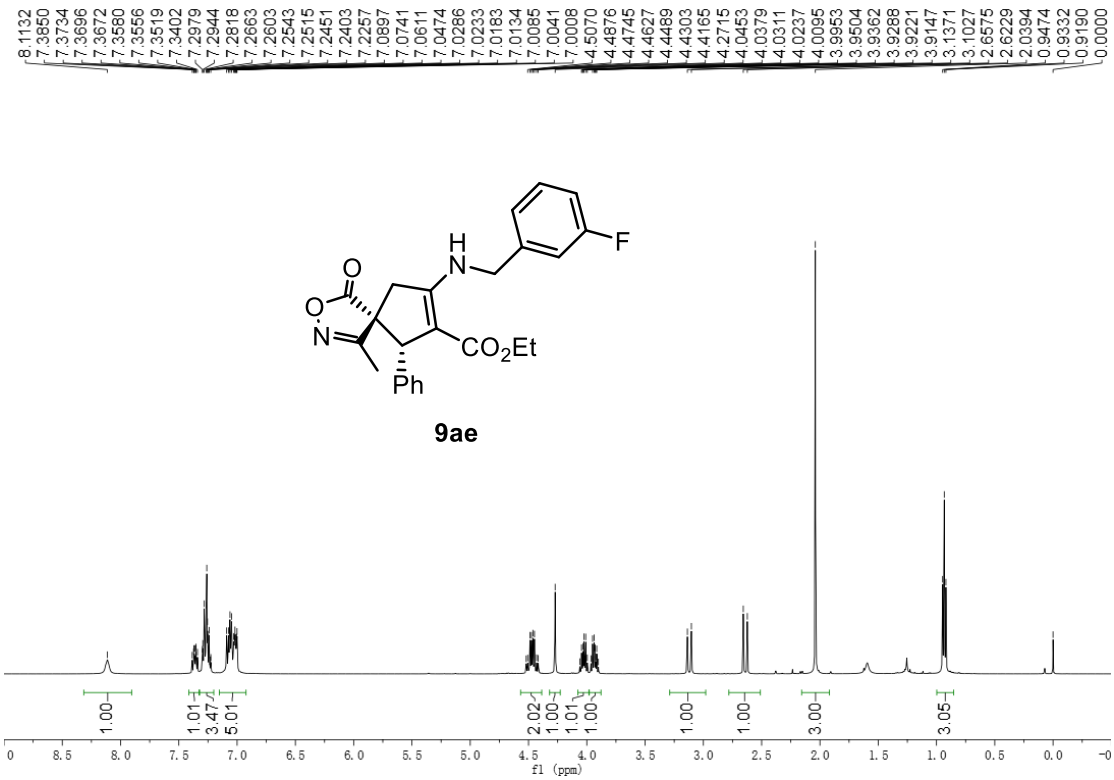


Figure S55. ^{1}H NMR (500 MHz, $CDCl_3$) of compound 9ae

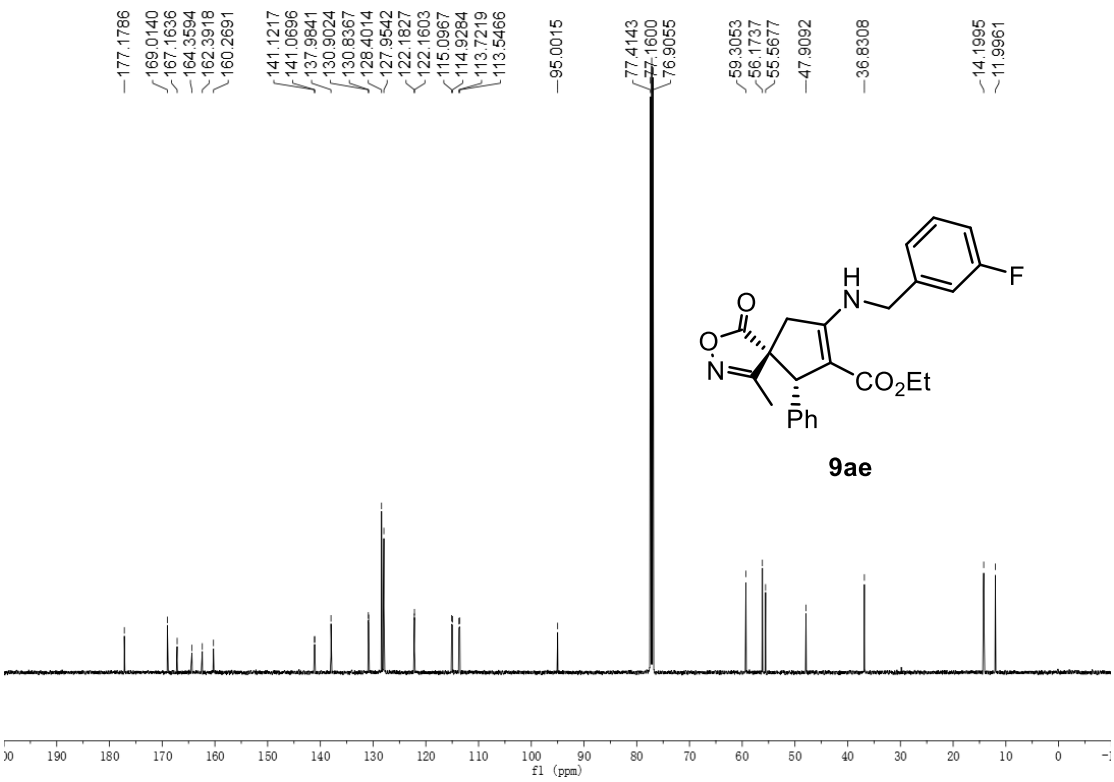


Figure S56. ^{13}C NMR (125 MHz, $CDCl_3$) of compound 9ae

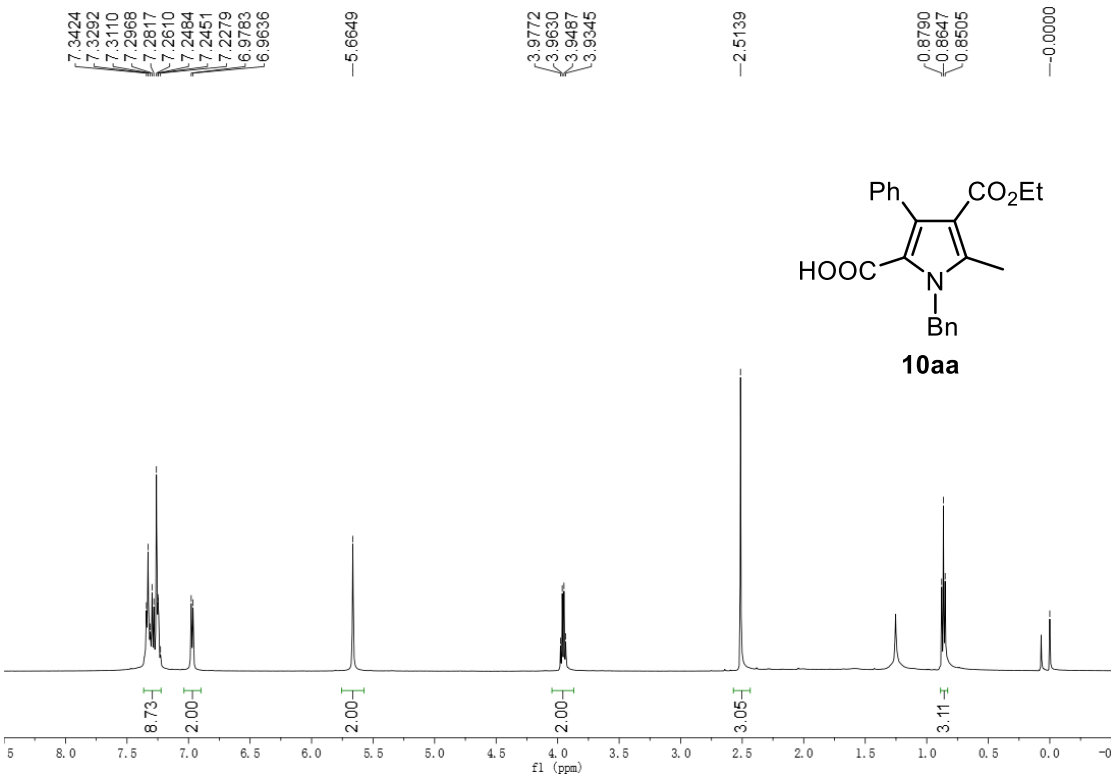


Figure S57. ^{1}H NMR (500 MHz, $CDCl_3$) of compound 10aa

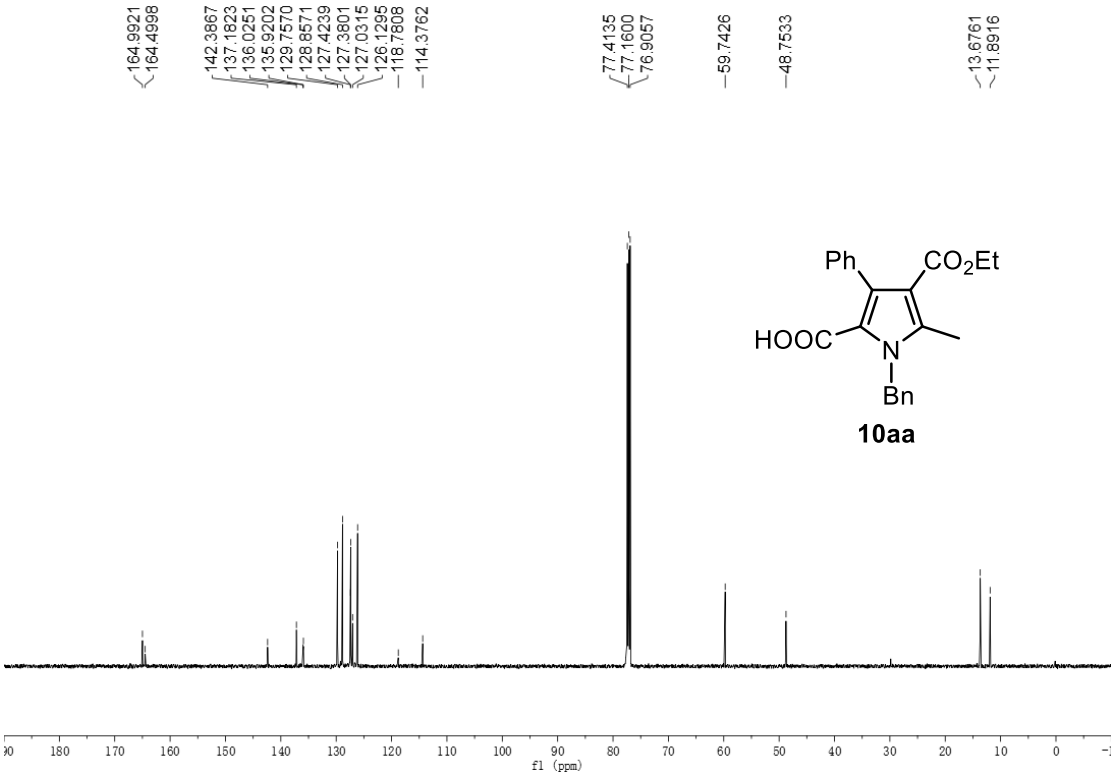


Figure S58. ^{13}C NMR (125 MHz, $CDCl_3$) of compound 10aa

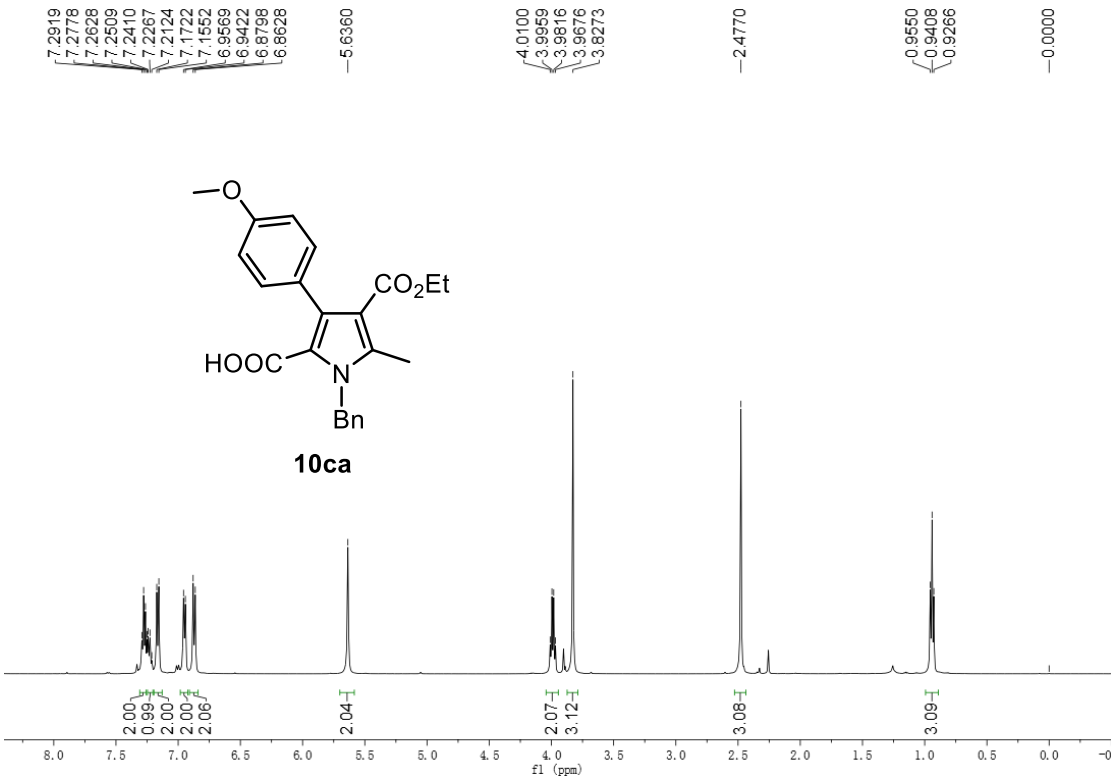


Figure S59. ^{1}H NMR (500 MHz, $CDCl_3$) of compound 10ca

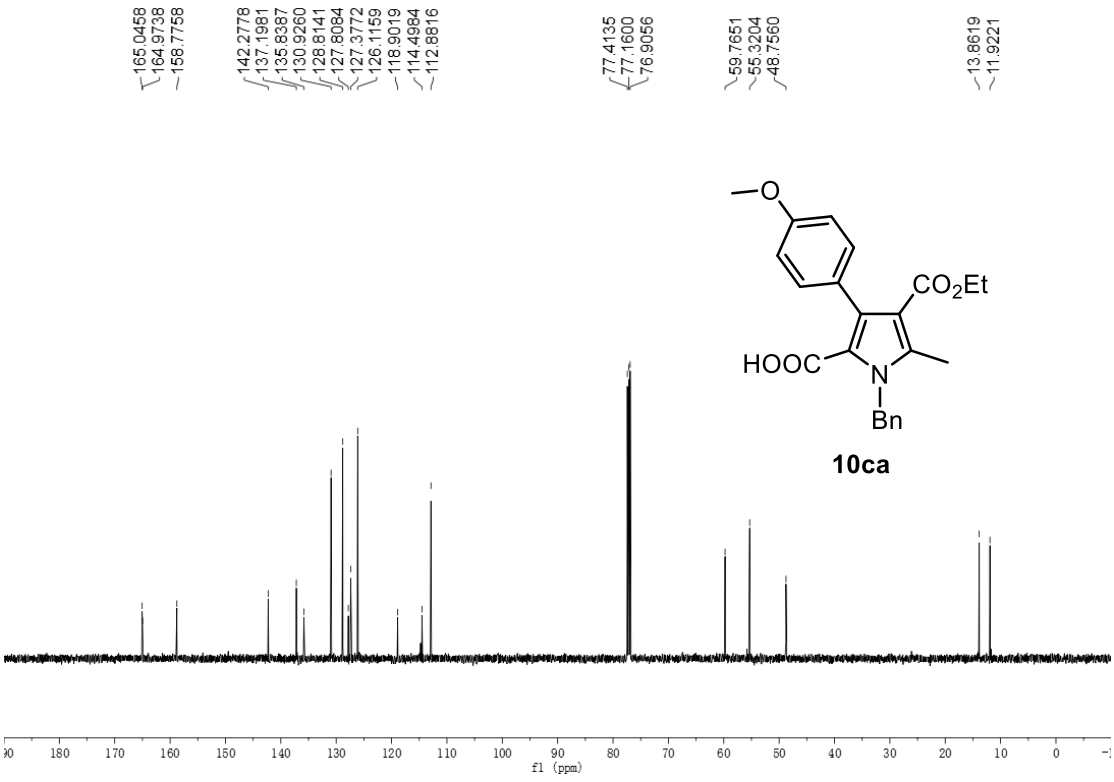


Figure S60. ^{13}C NMR (125 MHz, $CDCl_3$) of compound 10ca

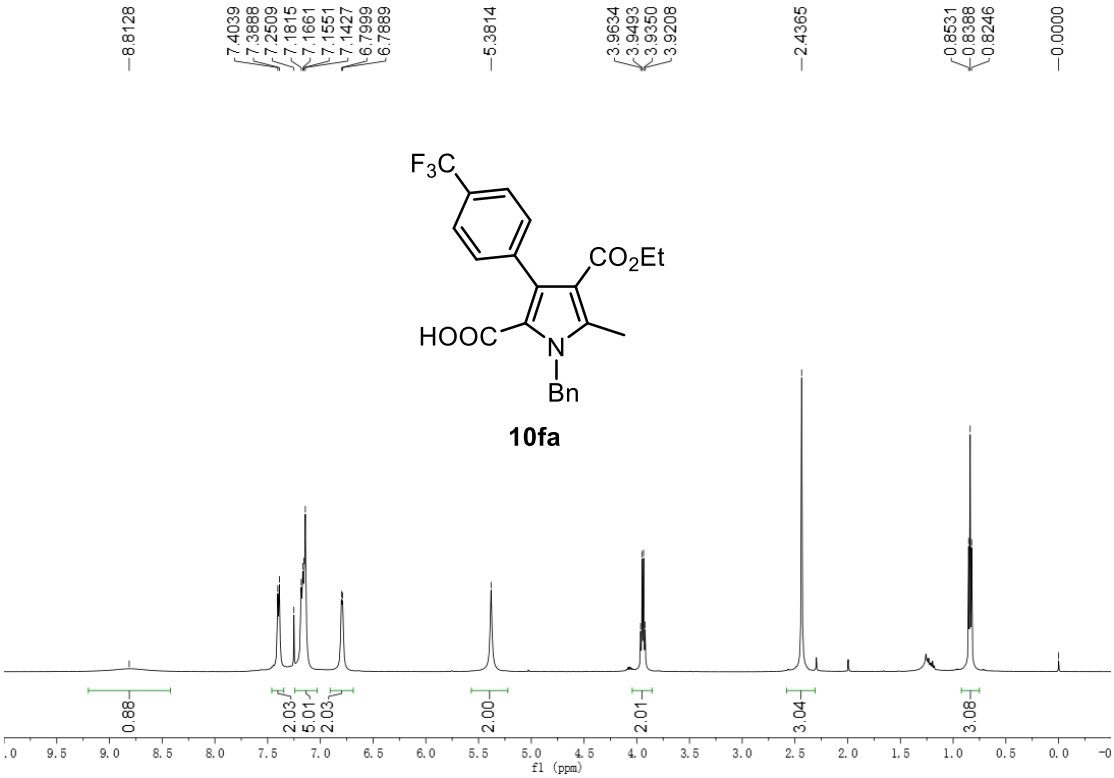


Figure S61. ^{1}H NMR (500 MHz, $CDCl_3$) of compound 10fa

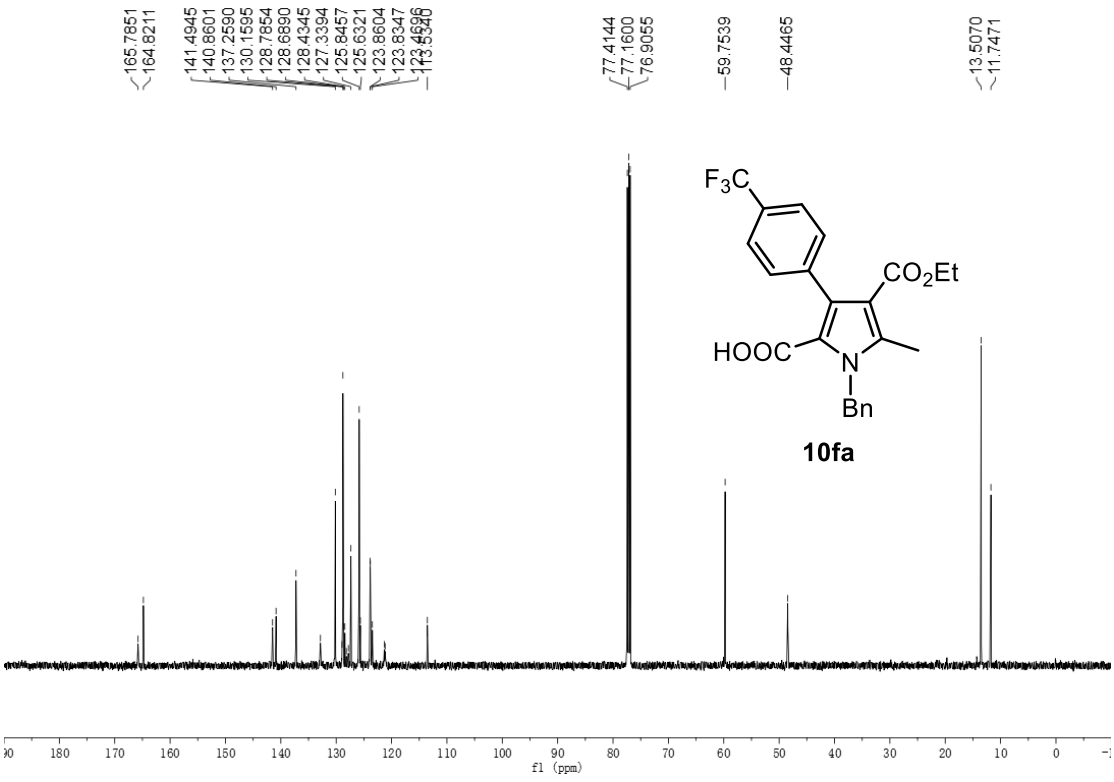


Figure S62. ^{13}C NMR (125 MHz, $CDCl_3$) of compound 10fa

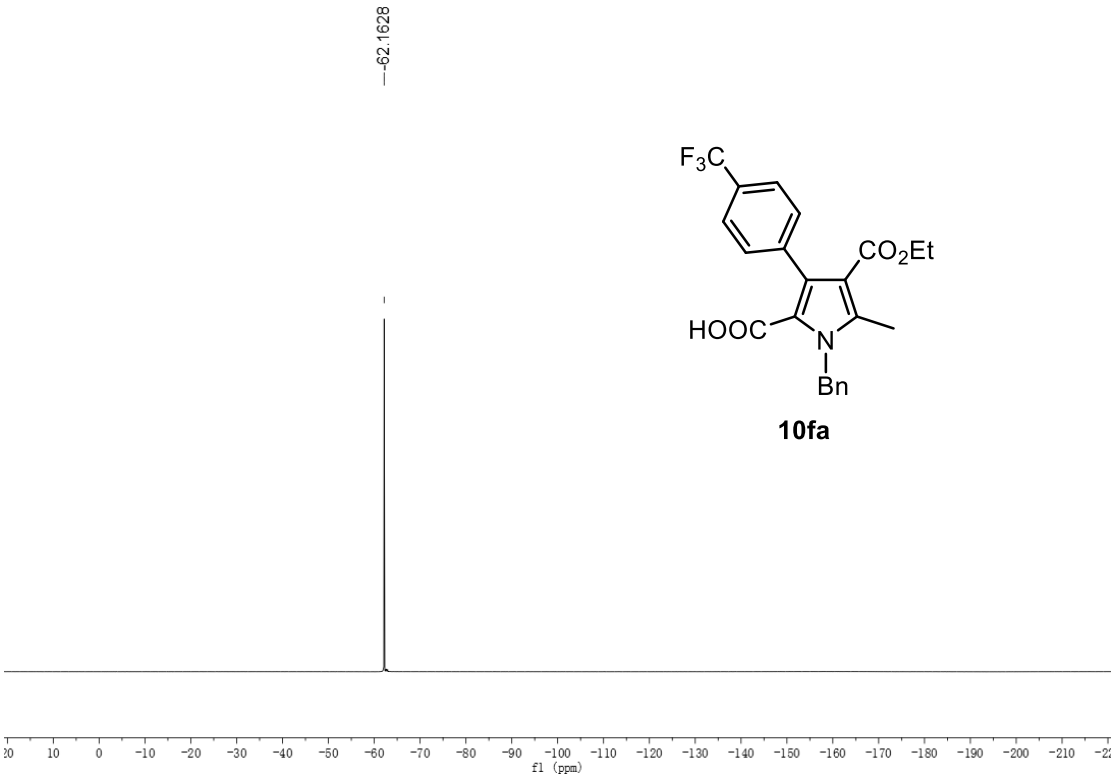


Figure S63. ^{19}F NMR (500 MHz, $CDCl_3$) of compound 10fa

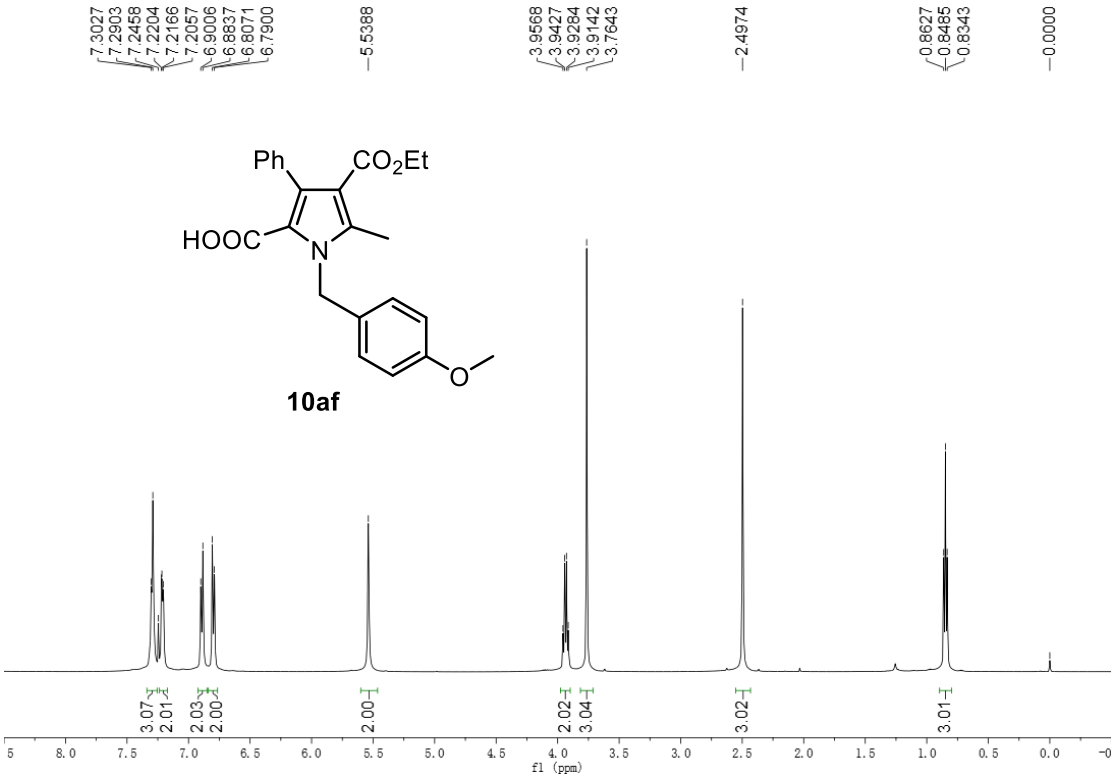


Figure S64. ^{1}H NMR (500 MHz, $CDCl_3$) of compound 10af

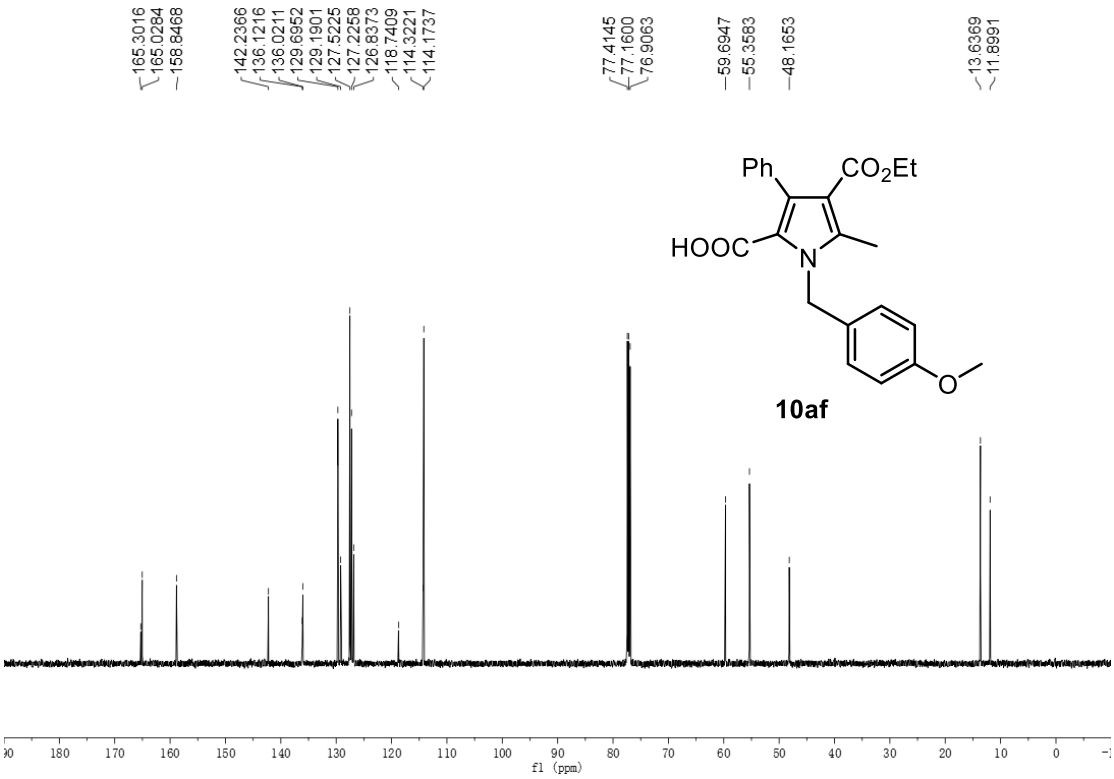


Figure S65. ^{13}C NMR (125 MHz, $CDCl_3$) of compound 10af

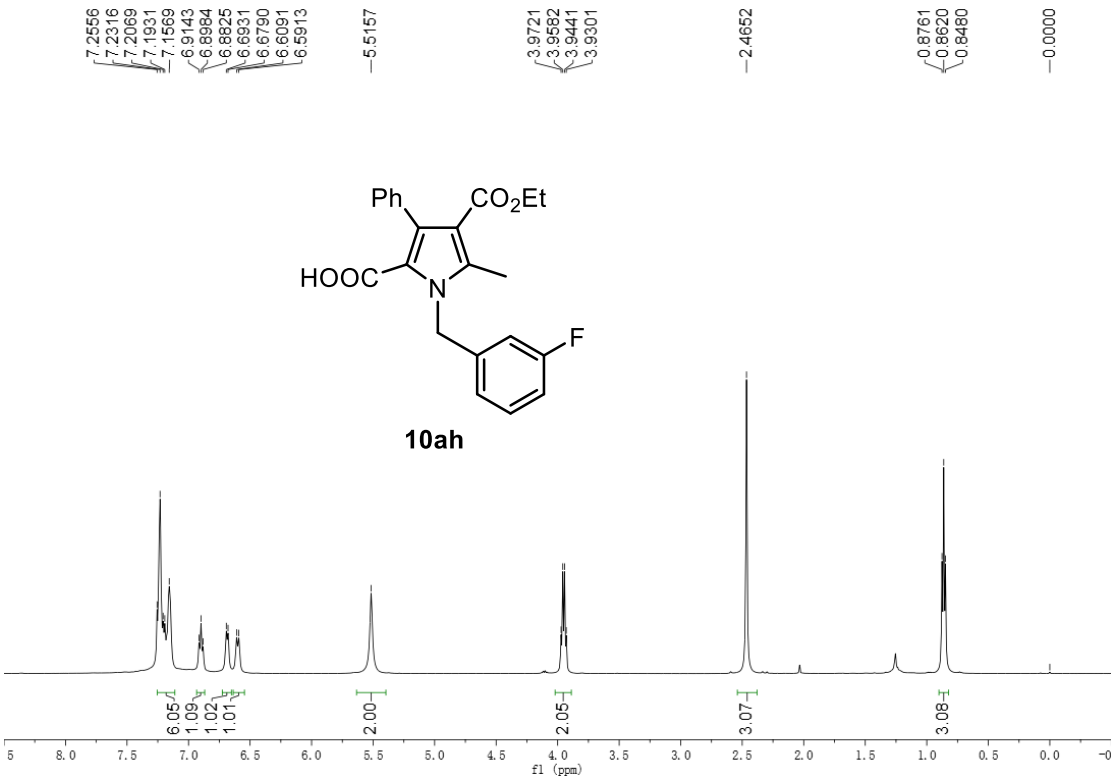


Figure S66. ^{1}H NMR (500 MHz, $CDCl_3$) of compound 10ah

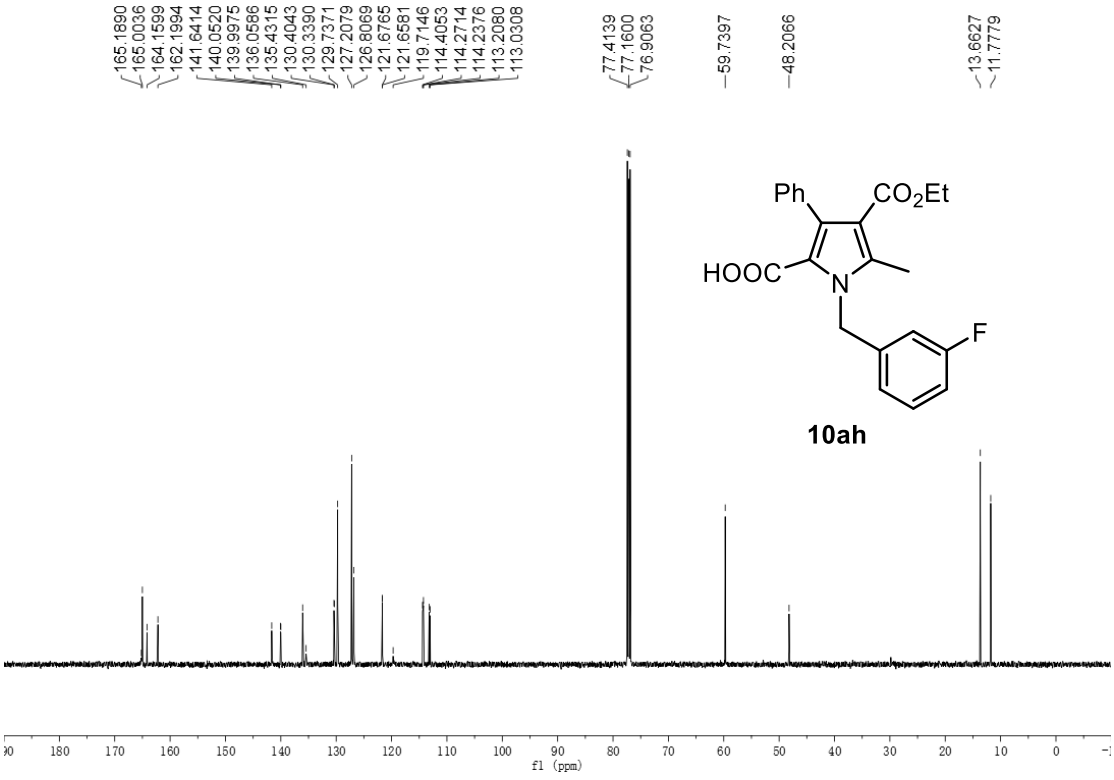


Figure S67. ^{13}C NMR (125 MHz, $CDCl_3$) of compound 10ah

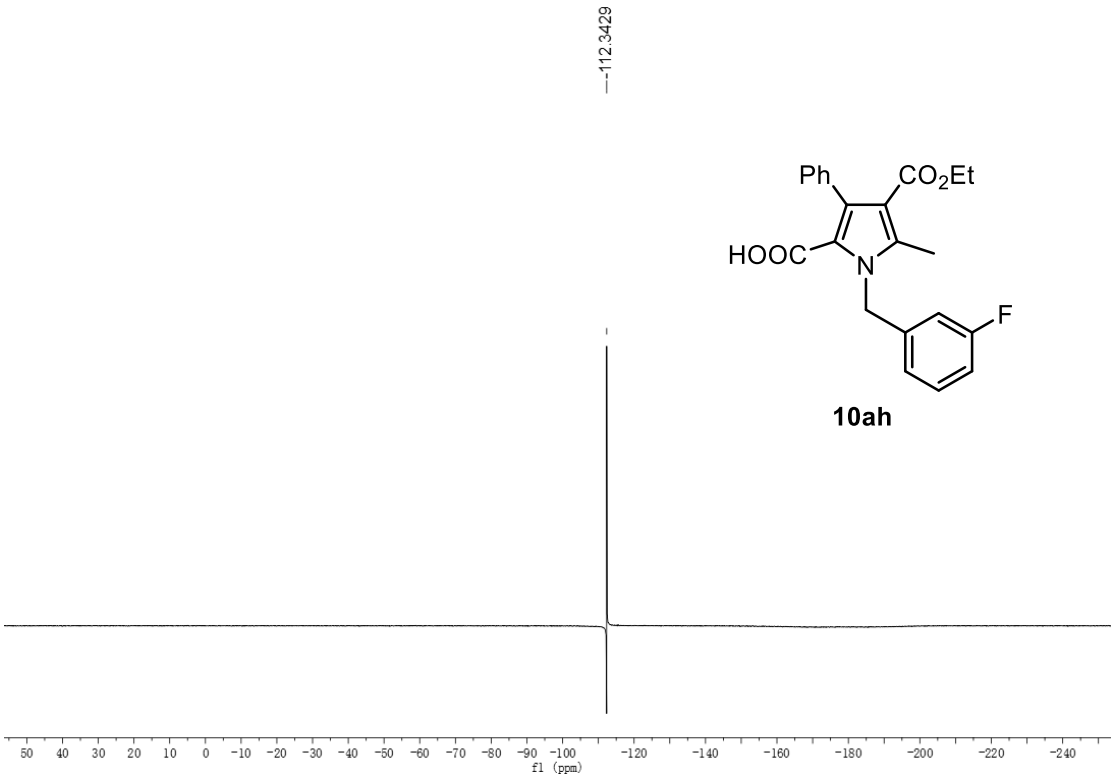


Figure S68. ^{19}F NMR (500 MHz, $CDCl_3$) of compound 10ah

攻读硕士期间发表论文情况

[1] **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.

[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] Xu, H.; **Li, M.-J.**; Chen, H.; Huang, F.-H.; Zhu, Q.-Y.; Wang, G.-W.*; Zhang, Z.* I_2/$FeCl_3$-Catalyzed Domino Reaction of Aurones with Enamino Esters for the Synthesis of Highly Functionalized Pyrroles. *Org. Lett*. **2022**, *24*, 8406–8411.

[4] Huang, F.-H.[#]; **Li, M.-J.**[#]; He, Z.-Y.; Zhu, Q.-Y.; Huang, Z.-M.; Li, Q.-H.; Xu, H.*; Zhang, Z.* Aerobic $CuBr_2$-Catalyzed Oxidative Coupling Reaction of Amidines with Exocyclic α,β-Unsaturated Cycloketones for the Synthesis of Spiroimidazolines. *J. Org. Chem.* **2023**, *88*, 6729–6735.

[5] **李明骏,** 陈红, 徐绘*, 张泽*. I_2/$FeCl_3$催化橙酮与 β-烯胺酯的多米诺反应构建多取代的吡咯[C]. 第 21 届全国金属有机化学学术讨论会. 芜湖, 2022 年 8 月.

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