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# 香兰素衍生物的合成与生物活性的前沿探索

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## 摘　要

**香兰素是食品添加剂中广泛使用的天然香料，因其自身在多种领域展现出色的生物活性，其独特的结构框架有助于与各种有效的基团直接、高效、低成本地结合，所以对其药用活性衍生物的研究引起广泛关注。在此背景下，这篇综述阐述对香兰素进行结构修饰和改造，合成出具有各种独特生物活性的香兰素衍生物。通过深入研究这些香兰素衍生化合物的设计、合成、生物活性，有助于深入理解结构与性能的关系。还概述了探索这种物质的更多可能方向。**

## 关键词

**香兰素，衍生物，生物活性**

# Frontier Exploration of Synthesis and Biological Activity of Vanillin Derivatives

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## Abstract

**Vanillin is a widely used natural flavoring in food additives. Due to its excellent bioactivity in various fields and its unique structural framework that facilitates direct, efficient, and cost-effective combination with a variety of active groups, research on its medicinal active derivatives has attracted widespread attention. Against this backdrop, this review discusses the structural modification and transformation of vanillin to synthesize vanillin derivatives with various unique bioactivities. In-depth studies on the design, synthesis, and bioactivity of these vanillin derivative compounds contribute to a deeper understanding of the relationship between structure and performance. It also outlines more potential directions for exploring this substance.**

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**Keywords**

**Vanillin, Derivatives, Bioactivity**



## 1. 研究香兰素衍生物的目的

香兰素源自香草植物(*Vanilla planifolia*)的豆荚，这种香草植物是一种热带攀缘兰花，最初原产于墨西哥，但目前在多个国家种植，包括马达加斯加、塔希提岛、印度尼西亚和汤加[1]，化学名称为 4-羟基-3-甲氧基苯甲醛，因其独特的化学结构，使它具有浓郁的香气，所以常被用作香料，为食品增添独特的风味，并广泛应用于香水和面霜等产品的调配[2]。在医药方面，香兰素可作为屏蔽气味的药剂，用于制造一些对气味有特定要求的药品，具有抗氧化抗自由基作用[3] [4]。此外，香兰素还可作为饲料添加剂，用于改善动物的食欲和生长状况[5]。香兰素作为一种重要的有机化合物，在众多领域展现出了巨大的应用价值[6]。为了增强其生物活性，对香兰素进行结构修饰和改造，合成出具有各种独特生物活性的香兰素衍生物，可以拓展其应用范围。在药物研发领域，通过对香兰素结构的修饰，有望开发出具有更高疗效、更低副作用的新型药物[7] [8]。研究香兰素衍生物不仅在学术上有助于深入理解结构与性能的关系，在实际应用中也能推动相关产业的发展，具有重要的价值。

## 2. 香兰素衍生物的合成及活性的研究

香兰素的结构不复杂，但是对其结构改造的报道较少，其结构包含两个具有高反应性和可修饰性的官能团[9] [10]。羟基(–OH)通常可以在碱性条件下进行去质子化，从而产生表现为亲核试剂的羟基阴离子。随后与亲电试剂的反应。这种策略将有效基团与香兰素骨架相连，包括噻吩嘧啶[11]、香豆素[12]，甚至是近年来被研究颇多的中离子结构[13]。根据文献调研，以香兰素为原料，生成的香兰素衍生物并研究其生物活性的报导主要有：

2023 年 Poliana A.等设计合成了一系列 1,2,3-三唑香兰素衍生物[14]，通过将有效的基团与香豆素相结合，提高了香豆素的抗真菌活性，通过不同基团取代的香豆素与芳香环中具有不同基团的苄基叠氮化物发生 CuAAC 点击反应，对香豆素的酚羟基进行修饰，合成香豆素衍生物。如图 1。

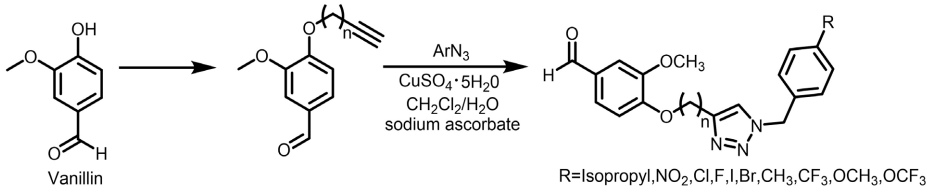


**Figure 1.** The modification 1 of phenolic hydroxyl groups
**图 1.** 对酚羟基的修饰一

通过对香兰素衍生物的抗真菌活性评价，表明香兰素衍生物能够在较低浓度下均表现出广谱抗真菌活性且抑制隐球菌的生长。天然芳基糖苷类药物具有的低毒性水溶性好等特点，香草醛苷对乙酰胆碱酯酶的可逆抑制活性[15] [16]，可以作为治疗阿尔茨海默病的有前途的候选药物[17]。2022 年首次实现了香

兰素糖苷化[18] [19]，形成的醚键在药物设计中起着至关重要的作用[20]，这种键可以在药物分子的各个区域引入或取代，以改变其物理化学性质，例如其亲脂性、溶解度和代谢稳定性[21]。此外，醚可以参与与靶蛋白、酶或受体的氢键相互作用。这些相互作用有助于药物－靶标结合亲和力、特异性和分子识别。通过对其酚羟基进行改造，为糖苷类药物扩充选择。酰胺作为有机合成中的关键活性基序之一，有多种多样的生物活性，杀菌、除草[22] [23]、抗病毒、杀虫[24] [25]等。烟草花叶病毒作为一个是烟草生产上分布最广、发生最为普遍的一类病害，含香兰素骨架的新型 $\alpha$-酮酰胺衍生物可以抗此病毒，如图 2。筛选出抗烟草花叶病毒(TMV)活性的化合物，酰胺基团加强了香豆素对 TMV 外壳蛋白的结合亲和力，使得 TMV 颗粒的自组装能力下降，从而抗烟草花叶病毒[26]。

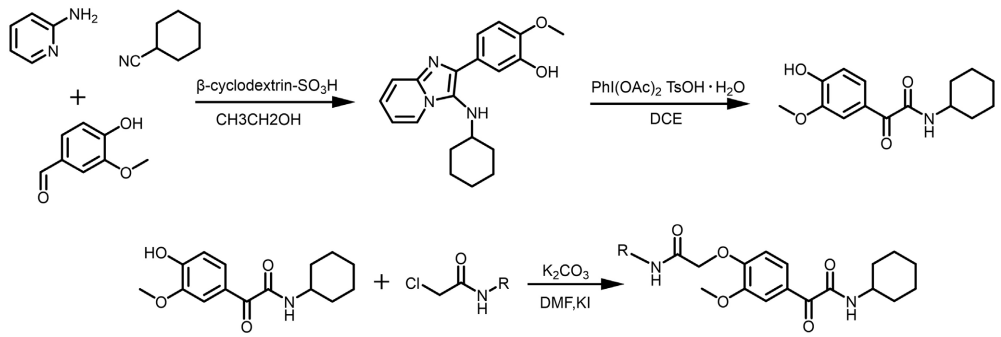


**Figure 2.** Vanillyl $\alpha$-ketamide derivatives
**图 2.** 香兰素 $\alpha$-酮酰胺衍生物

DNA 或细胞保护的机制可以通过直接抗氧化活性或通过上调抗氧化防御来实现，而香兰素和一系列胺之间发生还原胺化反应合成的所有化合物在 DPPH、FRAP 和 ORAC 测定中表现出很强的抗氧化特性[27]如表 1 大多数化合物表现出从良好到非常好的抗氧化的改良。在 DNA 保护测定的情况下，很可能充当自由基清除剂，并且可以预防紫外线[28]。香兰素具有抗氧化和抗增殖活性[29]，将具有两个哈马林片段和香兰素缩合为二聚体化合物，对癌细胞有抑制作用，这比哈马林和香兰素单独使用更有效[30]。

**Table 1.** Antioxidant properties of selected vanillin derivatives
**表 1.** 所选香兰素衍生物的抗氧化性能

| Compound<br>化合物 | ORAC (TE)<br>氧化自由基吸收能力 | DNA Protection ($IC_{50}$μM)<br>DNA 保护($IC_{50}$μM) |
|---|---|---|
| 1 b | 6.02 ± 0.56 | 3.60 ± 0.87 |
| 1 g | 5.34 ± 1.54 | 3.80 ± 1.40 |
| 1 h | 4.08 ± 0.82 | 61.50 ± 5.20 |
| 2 a | INSOLUBLE | 13.60 ± 1.20 |
| 2 c | 20.40 ± 1.30 | 0.60 ± 0.10 |
| 2e | 7.54 ± 1.25 | 13.90 ± 4.20 |
| 3 | 1.85 ± 0.90 | 3.80 ± 1.20 |
| 4 | 3.16 ± 1.15 | 4.10 ± 1.90 |
| Vanillin | 2.19 ± 0.28 | 5.60 ± 0.60 |
| Syringaldehyde | 1.45 ± 0.12 | 9.50 ± 0.30 |

注：Results from each assay are expressed as a mean ± SD of three independent experiments 每次测定的结果表示为三个独立实验的平均 ± SD。

2022 年 Hanuman Narode [31]设计合成含 9H-芴砜支架的香兰素衍生物，如图 3。

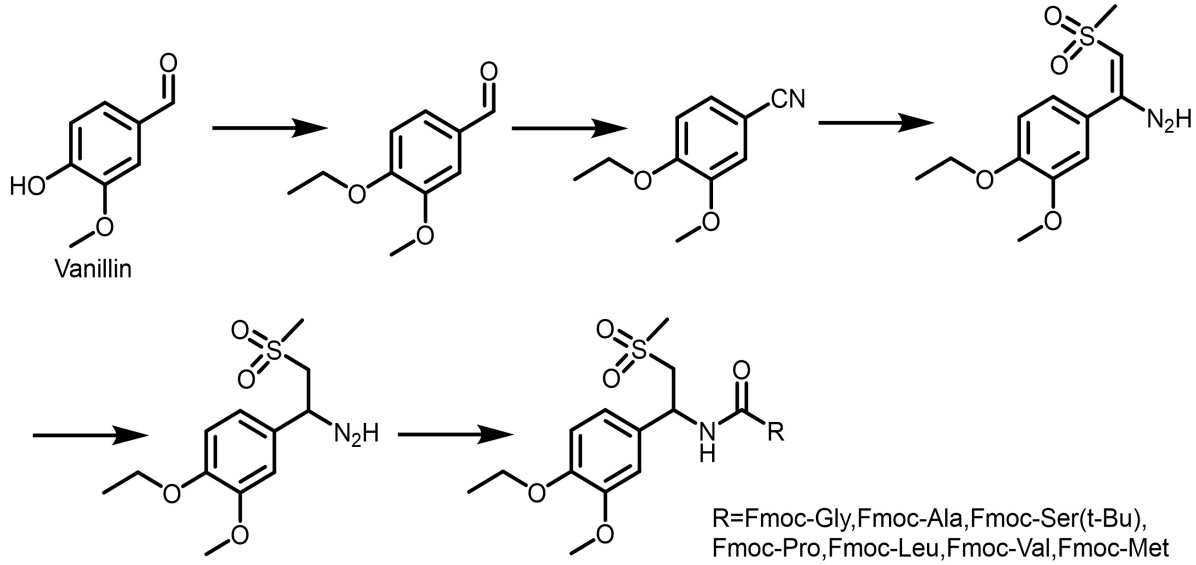


**Figure 3.** Vanillin derivatives containing 9H-fluorene sulfone scaffolds
**图 3.** 含 9H-芴砜支架的香兰素衍生物

在肽偶联试剂六氟磷酸苯并三唑四甲基脲(HBTU)下，将砜胺与氨基酸的羧酸基团偶联来制备含有 9H-芴砜的香草醛化合物。抗菌评估显示，化合物对金黄色葡萄球菌，白色念珠菌罐头、黑曲霉和克拉瓦图斯曲霉表现出相当大的抗真菌活性和抗疟活性[32] [33]研究的结果证实了砜类香兰素衍生化在治疗寄生虫感染和微生物感染中的重要性[34]。新型香兰素磺烷衍生物在大鼠模型中的代谢情况[35]。身体清除率和排泄表现出性别差异，如图 4，利用 LC-QTOF-MS 检测到一种偶联物和两种氧化代谢物。结果表明，香草硫烷暴露 7 天会导致两性肝损伤和男性性腺损伤[36]。但要揭示出人体药物代谢性别差异的原因，显然要比动物困难得多，涉及诸多因素，还有待研究。

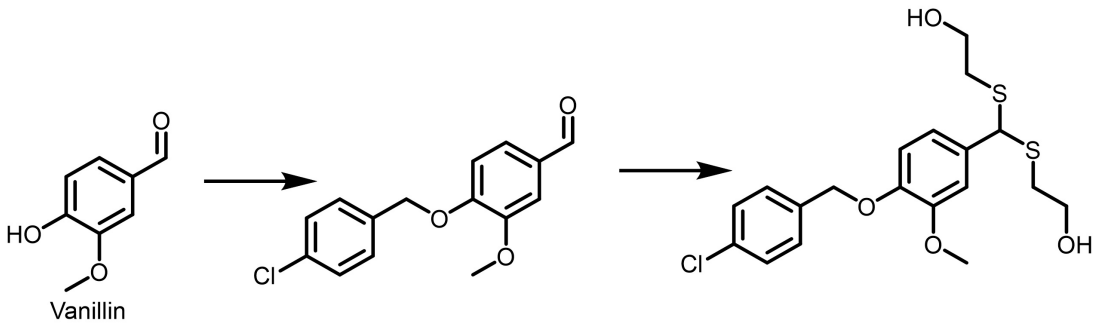


**Figure 4.** Vanillyl sulfide derivatives
**图 4.** 香兰素磺烷衍生物

香兰素衍生物在农业方面也有应用，香兰素中离子结构衍生物[37]，如图 5。具有提高水稻叶绿素含量和防御酶活性的能力。提高这些酶的活性可以增强水稻对细菌感染的抵抗力。蛋白质组学方法对抗菌机制的研究表明化合物通过调节光合途径，增强水稻相关防御酶的活性，增加叶绿素含量，加强水稻对细菌侵染的抗性，设计合成中离子结构，提高了香兰素的杀菌活性。

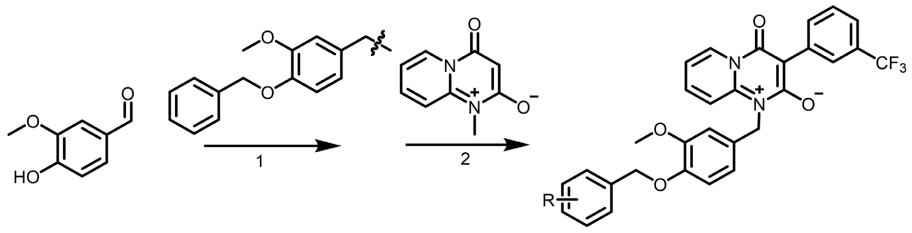

**Figure 5.** Vanillin ion structure derivatives
**图 5.** 香兰素中离子结构衍生物

查尔酮的活性非常广范，基于香兰素母体结构合成的查尔酮[38]，如图 6，对 A549、MCF7 和 MIA PaCa-2 细胞表现出良好的抗癌活性。

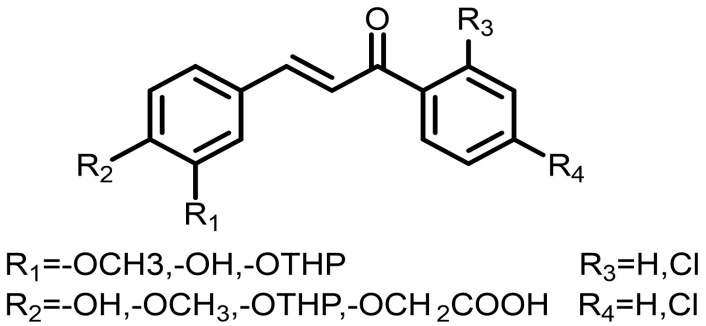


**Figure 6.** Vanillin chalcone
**图 6.** 香兰素查尔酮

抗癌机制分析，香兰素查尔酮使得 MIA PaCa-2 细胞的细胞形态发生变化、细胞迁移受到抑制、细胞周期进程停滞[39] [40]化合物 5f 活性高于姜黄素[41]如图 7。

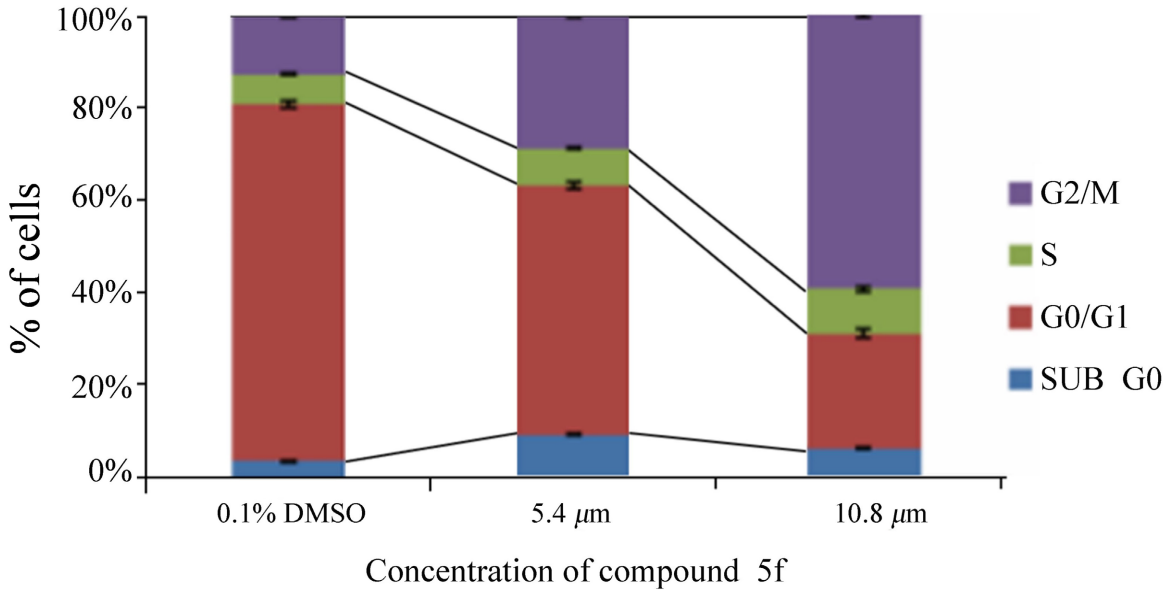


**Figure 7.** Distribution of MIA PaCa-2 cells in various stages of the cell cycle on treatment with compound 5f at IC50 concentration and 29IC50 concentration
**图 7.** IC50 和 29IC50 浓度化合物 5f 处理后 MIA PaCa-2 细胞在细胞周期各个阶段的分布

SARs 分析，引入了供电子基团能加强该查尔酮对癌细胞的作用。引入吸电子基团增加了 MCF7 的活性，从而降低了 A549 和 MIAPaCa-2 的活性。为药物的设计提供了新的思路[42]。香豆素衍生物抗癌作用多元，它能诱导肿瘤细胞凋亡[7] [43]，通过调节凋亡蛋白和作用线粒体来实现；抑制肿瘤细胞增殖，干扰细胞周期与 DNA 合成[44]；阻碍肿瘤血管生成，影响相关信号通路与酶活性[45]；增强免疫功能，激活免疫细胞和调节细胞因子[46] [47]；还能逆转肿瘤细胞多药耐药，抑制耐药蛋白外排，在抗癌领域潜力巨大[48] [49]。

## 3. 结论与展望

香兰素衍生物在合成及生物活性方面，香兰素衍生物展现出了抗菌、抗肿瘤、抗氧化、抗炎等多种生物活性，其作用机制也得到了一定程度的研究。未来的研究可以重点探索新型的香兰素衍生物，通过结构修饰和创新合成方法，开发具有更优异性能的衍生物；深入研究构效关系，为分子设计提供更坚实的理论基础；拓展应用领域，将香兰素衍生物应用于更多的实际场景，推动相关产业的发展。

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