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A61P 35/02(2006.01)

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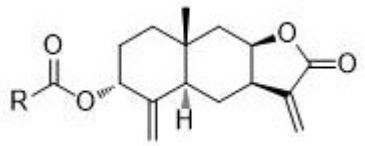
(54)发明名称

异土木香内酯衍生物,其药物组合物及其用途

(57)摘要

本发明涉及一种异土木香内酯衍生物,其药物组合物及其用途,特别是式(I)所示的异土木香内酯衍生物或其盐药物化合物,在制备治疗癌症的药物和在制备治疗癌症的辅助药物中的用途,含有治疗有效量的异土木香内酯衍生物(I)或其盐及药学上可接受的载体的药物组合物或与其他抗癌药物的组合物。


(I)。

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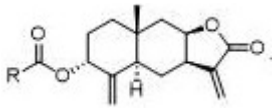
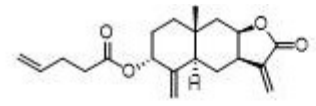
1.一种如下式(I)的化合物，



(I)

其中,R为烷基、环烷基、烯基、芳基、烷基芳基、芳基烷基、芳基烯基、杂环基、吡啶环基、芳氧烷基。

2.根据权利要求1所述的化合物,化合物为3-42，



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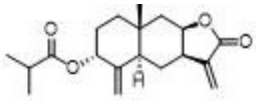

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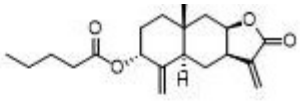

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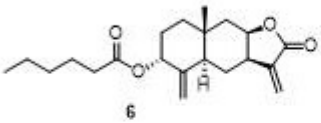

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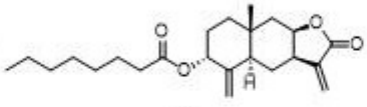

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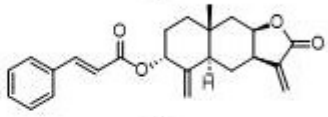

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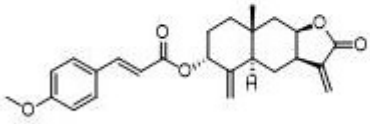

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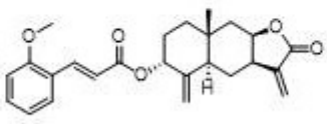

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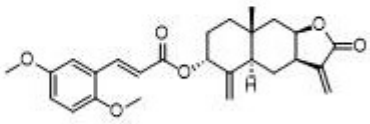

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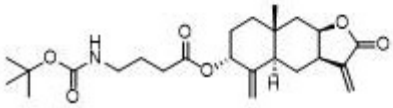

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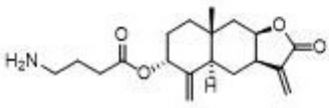

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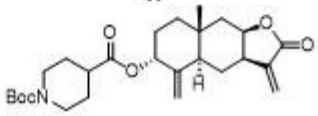

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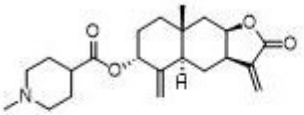

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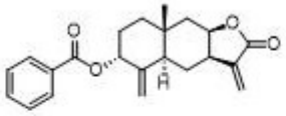

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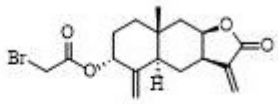

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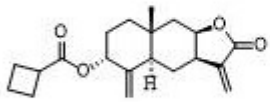

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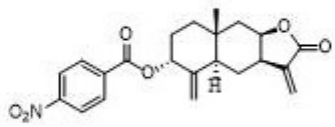

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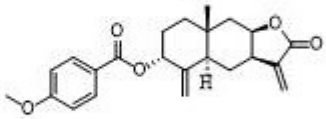

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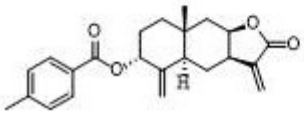

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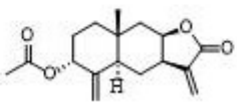

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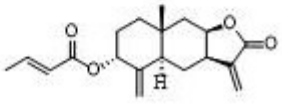

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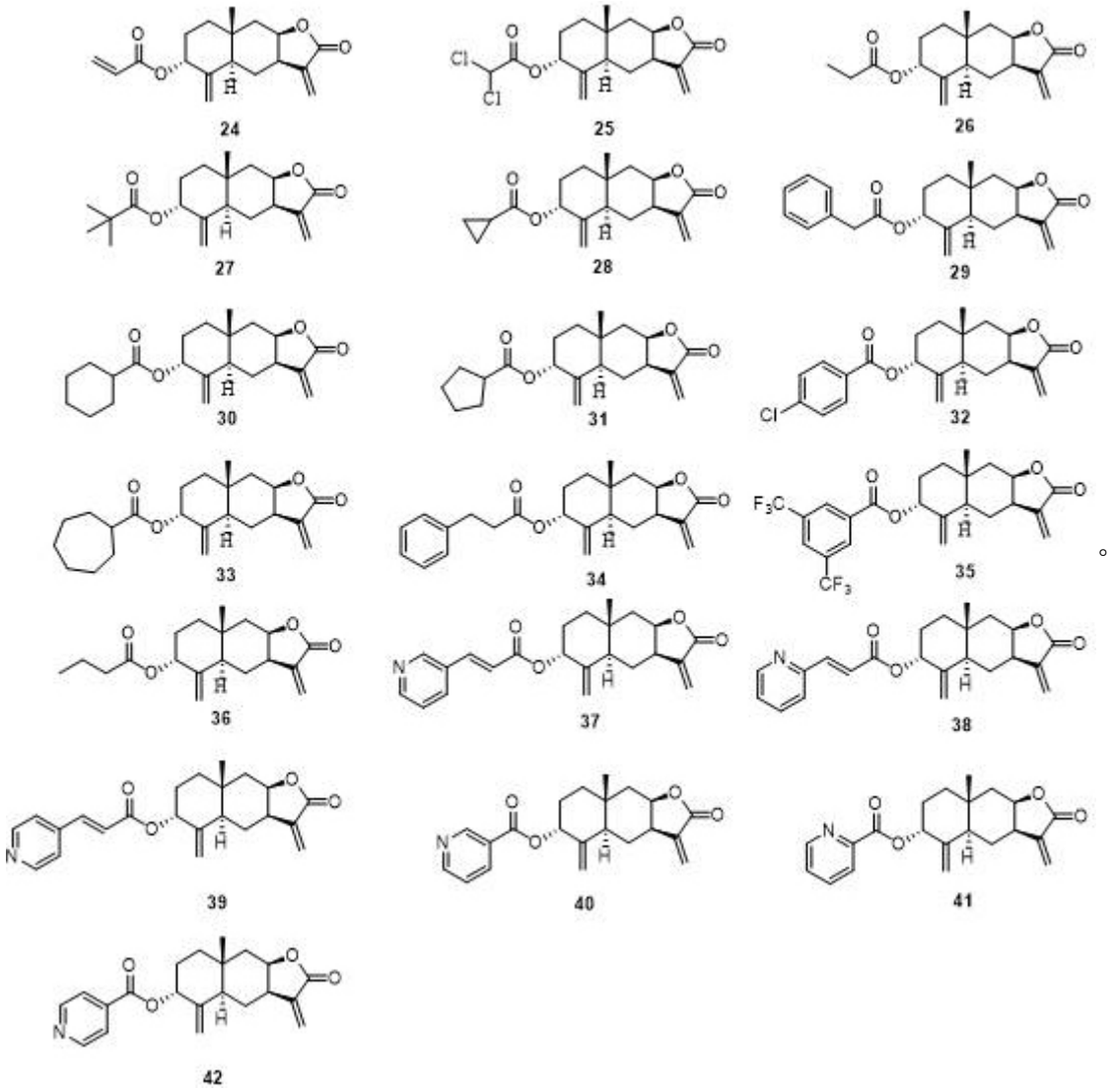

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3.本发明还提供了一种式(I)的异土木香内酯衍生物或其盐在制备治疗癌症的药物中的用途,其中癌症为白血病。

4.本发明还提供了一种式(I)的异土木香内酯衍生物或其盐在制备治疗癌症的辅助药物中的用途,其中癌症为白血病。

5.本发明还提供了一种用于治疗癌症的药物组合物,其中含有有效量的式(I)的异土木香内酯衍生物和药学上可接受的载体或与其他抗癌药物的组合物。

6.本发明还提供了式3-42化合物在制备治疗癌症的药物中的用途,其中癌症为白血病。

7.本发明还提供了式3-42化合物在制备治疗癌症的辅助药物中的用途,其中癌症为白血病。

8.本发明还提供了一种用于治疗癌症的药物组合物,其中含有有效量的式3-42化合物和药学上可接受的载体或与其他抗癌药物的组合物。

异土木香内酯衍生物,其药物组合物及其用途

技术领域

[0001] 本发明属于药物技术领域,具体地说,涉及异土木香内酯衍生物或其盐,以其为有效成分的治疗癌症或辅助治疗癌症的药物组合物,以及该药物化合物和组合物在制备抗癌或辅助抗癌药物中的应用。

背景技术

[0002] 倍半萜内酯是一种大而多样的天然产物。近年来,各种倍半萜内酯的抗癌性质引起了科学家们极大的兴趣,异土木香内酯能够抑制炎症反应,防止增殖和诱导凋亡的多生物活性的倍半萜内酯类化合物之一,药理学的研究领域已经证实了倍半萜内酯对各种人癌细胞系的抗癌活性。

[0003] 土木香是一种富含倍半萜内酯类化合物的植物,生长在我国大部分地区,其根茎具有一定的抗炎、抗菌、抗肿瘤活性,异土木香内酯可以从土木香中分离得到。

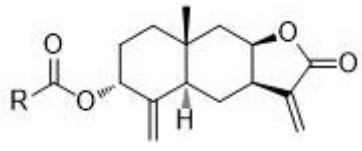
[0004] 从土木香中分离得到的异土木香内酯属于[6+6+5]型的桉叶烷型倍半萜内酯类结构,其活性基团就是C环上的α,β不饱和内酯,它能够选择性的杀死白血病细胞。但是其水溶性、血浆稳定性较差,而且活性也较低,有望通过对其进行结构修饰来进一步提高其活性、水溶性以及血浆稳定性。本发明合成了异土木香内酯的衍生物或其盐,以其为有效成分的治疗癌症或辅助治疗癌症的药物组合物,以及该药物化合物和组合物在制备抗癌或辅助抗癌药物中的应用。

发明内容

[0005] 本发明提供了一种异土木香内酯的衍生物或其盐,含有效量的式(I)异土木香内酯衍生物或其盐及可药用载体的治疗癌症的药物组合物或与其他抗癌药物的组合物,其制备方法,以及式(I)异土木香内酯衍生物或其盐及其药物组合物在制备治疗癌症药物中的应用。

[0006] 为了实现本发明的上述目的,本发明提供如下的技术方案:

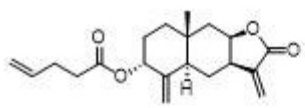
一种如下式(I)的化合物,



(I)

其中,R为烷基、环烷基、烯基、芳基、烷基芳基、芳基烷基、芳基烯基、杂环基、吡啶环基、芳氧烷基.。

[0007] 根据上述的化合物,化合物为3-42,



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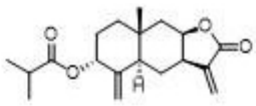

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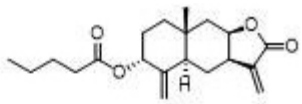

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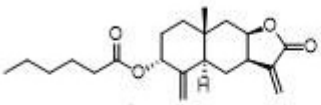

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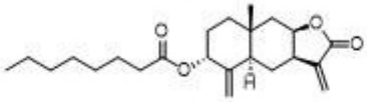

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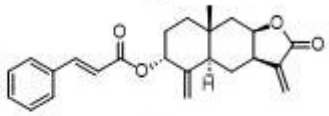

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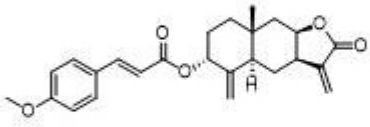

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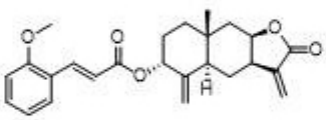

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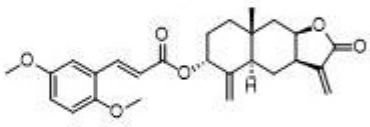

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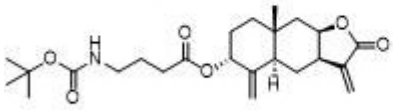

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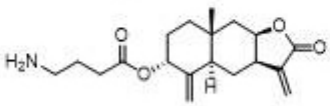

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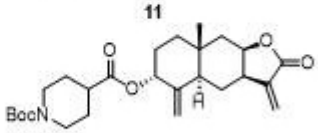

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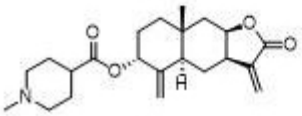

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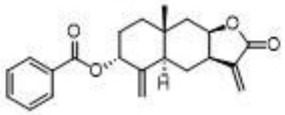

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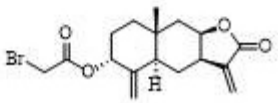

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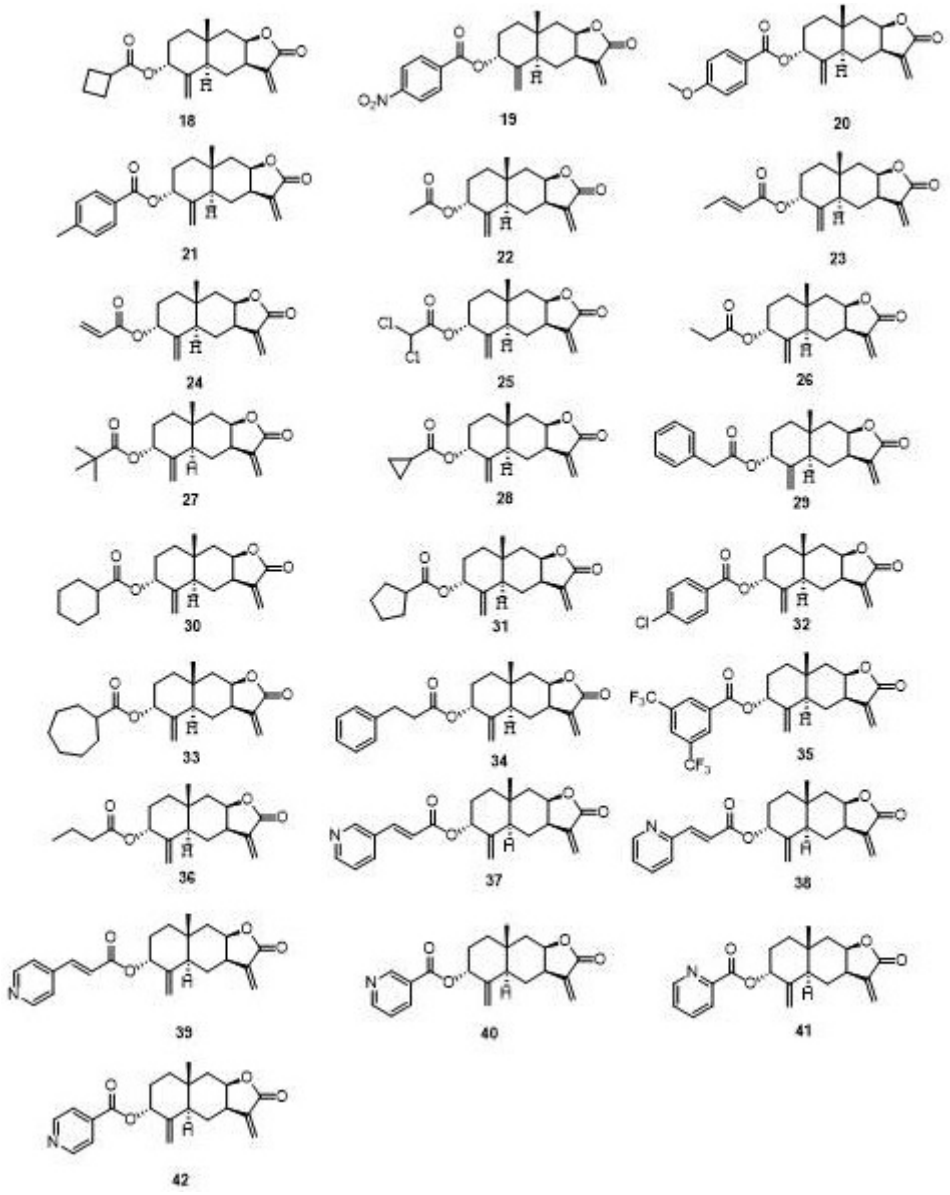


本发明还提供了一种式(I)的异土木香内酯衍生物或其盐在制备治疗癌症的药物中的用途,其中癌症为白血病。

[0008] 本发明还提供了一种式(I)的异土木香内酯衍生物或其盐在制备治疗癌症的辅助药物中的用途,其中癌症为白血病。

[0009] 本发明还提供了一种用于治疗癌症的药物组合物,其中含有有效量的式(I)的异土木香内酯衍生物和药学上可接受的载体或与其他抗癌药物的组合物。

[0010] 本发明还提供了式3-42化合物在制备治疗癌症的药物中的用途,其中癌症为白血病。

[0011] 本发明还提供了式3-42化合物在制备治疗癌症的辅助药物中的用途,其中癌症为白血病。

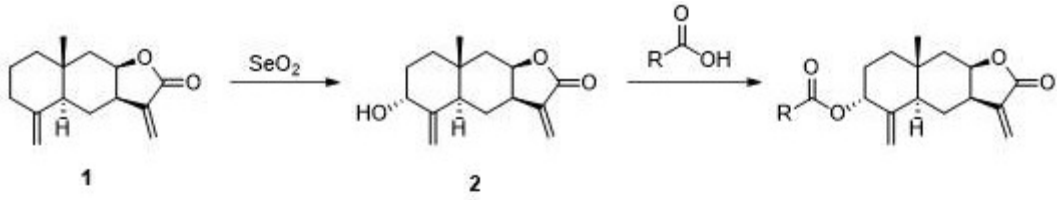
[0012] 本发明还提供了一种用于治疗癌症的药物组合物,其中含有有效量的式3-42化合物和药学上可接受的载体或与其他抗癌药物的组合物。

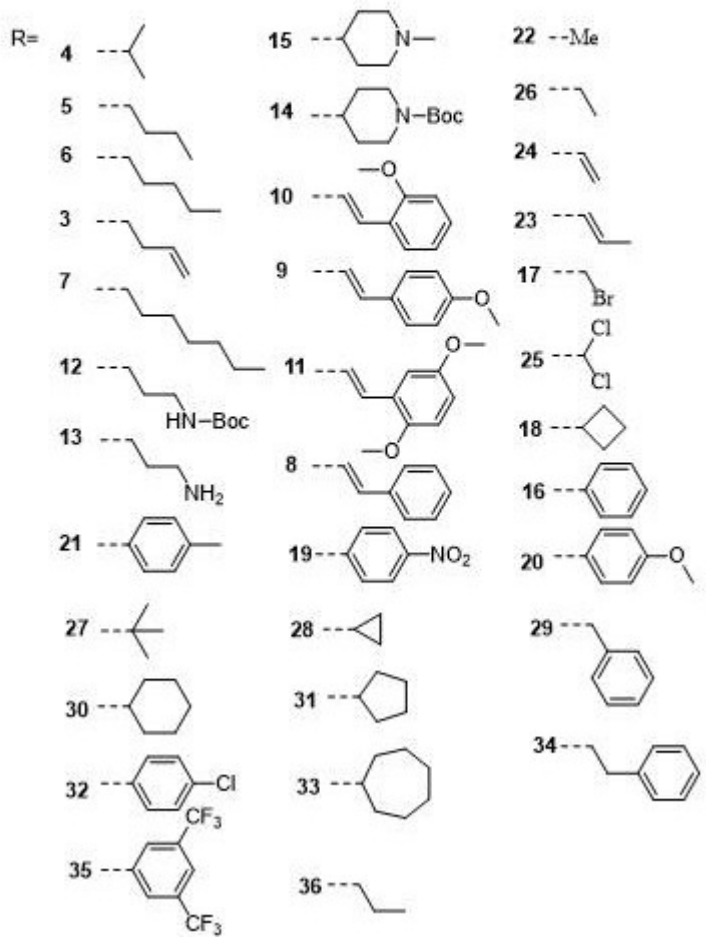
具体实施方式

[0013] 为了理解本发明，下面以实施例进一步说明本发明，但不意于限制本发明的保护范围。

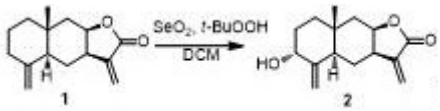
[0014] 实施例1：

结构式如下式的制备路线：





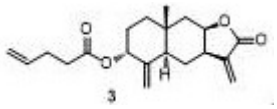
化合物2的合成



在0℃下，将SeO_2(1990.0 mg, 17.93 mmol)溶解在重蒸的二氯甲烷(DCM)(199.0 mL)中，加入干燥的t-BuOOH(6.4 mL)，30分钟后，将化合物1异土木香内酯(11940.0 mg, 51.39 mmol)溶解在重蒸的二氯甲烷(199.0 mL)中缓慢的加入到上述体系中，反应体系在室温下搅拌24小时，TLC检测反应完之后，加入饱和的硫代硫酸钠溶液(200.0 mL)，用二氯甲烷萃取三次，有机相用无水硫酸镁($MgSO_4$)干燥，减压浓缩，过硅胶色谱柱(石油醚/乙酸乙酯=5:1至2:1)得化合物2(白色无定型固体，2585.5 mg，产率44.9 %)，回收原料6554.6 mg。^{1}H NMR (400 MHz, $CDCl_3$) δ 6.10 (s, 1H), 5.57 (s, 1H), 4.97 (s, 1H), 4.52 (d, J =

27.1 Hz, 2H), 4.30 (s, 1H), 2.98 (dt, J = 11.9, 5.8 Hz, 1H), 2.40 (d, J = 12.8 Hz, 1H), 2.17 (d, J = 15.5 Hz, 1H), 1.77 (s, 1H), 1.73 (s, 2H), 1.68 (d, J = 11.7 Hz, 2H), 1.55 (d, J = 15.4 Hz, 1H), 1.33 (q, J = 12.2, 11.5 Hz, 2H), 0.78 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 150.3, 142.2, 120.3, 109.9, 76.9, 73.3, 41.1, 40.5, 40.3, 35.8, 34.2, 29.1, 27.1, 17.0. HRMS (ESI) calcd for $C_{15}H_{20}O_3$ $[M+H]^+$ 249.1485, found 249.1483.

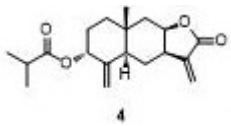
化合物3的合成



3

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.13 (s, 1H), 5.87 - 5.76 (m, 1H), 5.59 (s, 1H), 5.36 (s, 1H), 5.12 (s, 1H), 5.09 - 4.96 (m, 2H), 4.69 (s, 1H), 4.51 (s, 1H), 3.01 (dt, J = 12.0, 6.3 Hz, 2H), 2.45 - 2.31 (m, 4H), 2.22 (d, J = 15.1 Hz, 3H), 1.80 (s, 1H), 1.71 (dd, J = 11.6, 7.2 Hz, 1H), 1.56 (d, J = 11.0 Hz, 2H), 1.43 - 1.31 (m, 2H), 0.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.5, 141.9, 171.9, 170.4, 136.7, 120.3, 115.4, 112.5, 75.2, 41.4, 40.9, 40.4, 40.4, 36.4, 33.8, 33.8, 28.9, 27.0, 26.9, 17.0. HRMS (ESI) calcd for $C_{20}H_{26}O_4$ $[M+H]^+$ 331.1904, found 331.1907.

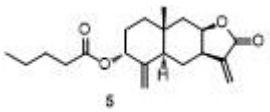
化合物4的合成



4

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.10 (s, 1H), 5.57 (s, 1H), 5.30 (s, 1H), 5.09 (s, 1H), 4.67 (s, 1H), 4.49 (t, J = 4.1 Hz, 1H), 3.07 - 2.94 (m, 1H), 2.50 (d, J = 7.0 Hz, 1H), 2.19 (d, J = 13.8 Hz, 2H), 1.77 (d, J = 7.2 Hz, 2H), 1.72-1.66 (m, 1H), 1.54 (dd, J = 15.7, 4.6 Hz, 2H), 1.41 - 1.32 (m, 2H), 1.13 (t, J = 7.0 Hz, 6H), 0.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.0, 170.5, 145.6, 142.0, 120.4, 112.5, 76.7, 75.0, 41.6, 41.1, 40.4, 36.5, 34.3, 33.9, 27.1, 27.0, 19.2, 18.9, 17.1. HRMS (ESI) calcd for $C_{19}H_{26}O_4$ $[M+H]^+$ 319.1904, found 319.1902.

化合物5的合成

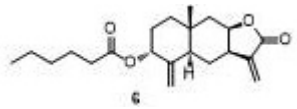


5

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.12 (s, 1H), 5.58 (s, 1H), 5.34 (t, J = 2.4 Hz, 1H), 5.11 (s, 1H), 4.68 (s, 1H), 4.51 (t, J = 4.2 Hz, 1H), 3.00 (dt, J = 11.9, 6.3 Hz, 1H), 2.28 (t, J = 7.5 Hz, 2H), 2.20 (d, J = 15.3 Hz, 2H), 1.78 (dd, J = 7.3, 3.7 Hz, 2H), 1.70 (dd, J = 16.4, 7.0 Hz, 1H), 1.62-1.55 (m, 3H), 1.53 (d, J = 5.9 Hz, 1H), 1.39 (s, 1H), 1.37-1.30 (m, 3H), 0.89 (t, J = 7.3 Hz, 3H), 0.81 (s, 3H); ^{13}C NMR (100MHz, $CDCl_3$) δ 172.9, 170.5, 145.7,

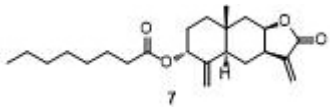
142.0, 120.4, 112.5, 76.7, 75.1, 41.6, 41.1, 40.5, 36.5, 34.5, 33.9, 27.2, 27.1, 27.0, 22.3, 17.1, 13.8. HRMS (ESI) calcd for $C_{20}H_{28}O_4$ $[M+H]^+$ 333.2060, found 333.2054.

化合物6的合成



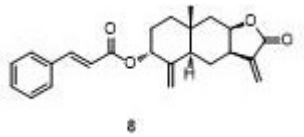
^1H NMR (400 MHz, $CDCl_3$) δ 6.11 (s, 1H), 5.57 (s, 1H), 5.33 (s, 1H), 5.10 (s, 1H), 4.67 (s, 1H), 4.53-4.46 (m, 1H), 2.99 (dt, *J* = 11.9, 6.3 Hz, 1H), 2.26 (t, *J* = 7.5 Hz, 2H), 2.21 (s, 1H), 2.17 (s, 1H), 1.77 (dd, *J* = 6.5, 2.9 Hz, 2H), 1.69 (ddd, *J* = 14.0, 7.0, 2.5 Hz, 1H), 1.62 - 1.54 (m, 3H), 1.54 - 1.49 (m, 1H), 1.37 (d, *J* = 6.8 Hz, 1H), 1.34 (d, *J* = 6.0 Hz, 1H), 1.27 (dd, *J* = 6.8, 3.1 Hz, 3H), 1.23 (s, 1H), 0.86 (t, *J* = 6.9 Hz, 3H), 0.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.8, 170.5, 145.6, 142.0, 120.4, 112.5, 76.7, 75.0, 41.5, 41.0, 40.4, 36.5, 34.7, 33.9, 31.3, 27.1, 27.0, 24.8, 22.4, 17.1, 14.0. HRMS (ESI) calcd for $C_{21}H_{30}O_4$ $[M+H]^+$ 347.2217, found 347.2212.

化合物7的合成



^1H NMR (400 MHz, $CDCl_3$) δ 6.11 (s, 1H), 5.57 (s, 1H), 5.33 (s, 1H), 5.10 (s, 1H), 4.67 (s, 1H), 4.52 - 4.47 (m, 1H), 2.99 (dt, *J* = 11.9, 6.4 Hz, 1H), 2.28 (s, 2H), 2.19 (d, *J* = 15.3 Hz, 2H), 1.81 - 1.74 (m, 2H), 1.69 (dd, *J* = 13.9, 7.0 Hz, 1H), 1.61 - 1.54 (m, 3H), 1.52 (d, *J* = 4.6 Hz, 1H), 1.40 - 1.35 (m, 1H), 1.26 (s, 3H), 1.25 (s, 3H), 1.24 (s, 2H), 0.84 (t, *J* = 6.8 Hz, 4H), 0.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.9, 170.5, 145.6, 142.0, 120.4, 112.5, 76.7, 75.0, 41.5, 41.0, 40.4, 36.5, 34.8, 33.9, 31.8, 29.1, 29.0, 27.1, 27.0, 25.1, 22.7, 17.1, 14.1. HRMS (ESI) calcd for $C_{23}H_{34}O_4$ $[M+H]^+$ 375.2530, found 375.2524.

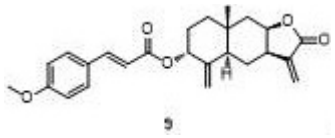
化合物8的合成



^1H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, *J* = 16.0 Hz, 1H), 7.53 (d, *J* = 5.8 Hz, 2H), 7.45-7.34 (m, 3H), 6.45 (d, *J* = 16.0 Hz, 1H), 6.15 (s, 1H), 5.60 (s, 1H), 5.49 (s, 1H), 5.20 (s, 1H), 4.75 (s, 1H), 4.54 (t, *J* = 4.2 Hz, 1H), 3.03 (dt, *J* = 11.8, 6.2 Hz, 1H), 2.28 (dd, *J* = 21.1, 14.4 Hz, 2H), 1.96 - 1.80 (m, 2H), 1.75 (dd, *J* = 13.9, 7.0 Hz, 1H), 1.63 (td, *J* = 15.6, 14.3, 4.8 Hz, 2H), 1.41 (dd, *J* = 26.9, 14.0 Hz, 2H), 0.87 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 166.2, 145.6, 144.9, 142.0, 134.5, 130.4, 129.0, 128.2, 120.6, 118.6,

112.9, 76.8, 75.5, 41.7, 41.1, 40.5, 36.6, 34.0, 27.2, 27.1, 17.2. HRMS (ESI) calcd for $C_{24}H_{26}O_4$ $[M+H]^+$ 379.1904, found 379.1903 .

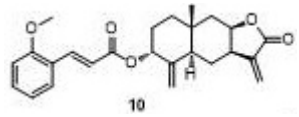
化合物9的合成



9

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, *J* = 17.9 Hz, 1H), 7.49 (d, *J* = 6.5 Hz, 2H), 6.96 - 6.86 (m, 2H), 6.32 (d, *J* = 18.6 Hz, 1H), 6.15 (s, 1H), 5.60 (s, 1H), 5.48 (s, 1H), 5.20 (s, 1H), 4.74 (s, 1H), 4.54 (s, 1H), 3.85 (s, 3H), 3.08 - 2.98 (m, 1H), 2.28 (dd, *J* = 22.7, 14.2 Hz, 2H), 1.89 (t, *J* = 17.2 Hz, 2H), 1.64 (d, *J* = 12.4 Hz, 2H), 1.41 (dd, *J* = 25.7, 12.2 Hz, 3H), 0.87 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 166.5, 161.5, 145.8, 144.5, 142.1, 129.8, 127.3, 120.5, 116.1, 114.4, 112.8, 76.8, 75.3, 55.5, 41.7, 41.2, 40.6, 36.7, 34.1, 27.3, 27.2, 17.2. HRMS (ESI) calcd for $C_{25}H_{28}O_5$ $[M+H]^+$ 409.2004, found 409.2008.

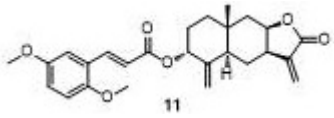
化合物10的合成



10

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, *J* = 16.1 Hz, 1H), 7.51 (d, *J* = 9.2 Hz, 1H), 7.44 - 7.31 (m, 1H), 6.96 (t, *J* = 7.6 Hz, 1H), 6.92 (d, *J* = 8.3 Hz, 1H), 6.52 (d, *J* = 16.1 Hz, 1H), 6.14 (s, 1H), 5.59 (s, 1H), 5.48 (t, *J* = 2.6 Hz, 1H), 5.20 (s, 1H), 4.74 (s, 1H), 4.53 (t, *J* = 5.4 Hz, 1H), 3.89 (s, 3H), 3.02 (dt, *J* = 11.9, 6.6 Hz, 1H), 2.31 (d, *J* = 12.4 Hz, 1H), 2.25 (d, *J* = 14.3 Hz, 1H), 1.96 - 1.89 (m, 1H), 1.74 (dt, *J* = 15.0, 7.9, 3.9 Hz, 1H), 1.69 - 1.63 (m, 1H), 1.62 - 1.56 (m, 1H), 1.43 (d, *J* = 11.5 Hz, 1H), 1.40 - 1.31 (m, 1H), 1.25 (s, 1H), 0.87 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 166.7, 158.4, 145.8, 142.1, 140.4, 131.6, 129.0, 123.5, 120.8, 120.5, 119.1, 112.7, 111.3, 75.3, 55.7, 41.7, 41.2, 40.6, 36.7, 34.1, 29.8, 27.3, 27.1, 17.2. HRMS (ESI) calcd for $C_{25}H_{28}O_5$ $[M+H]^+$ 409.2010, found 409.2007.

化合物11的合成

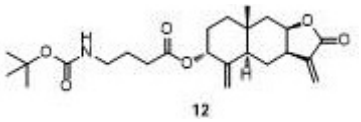


11

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, *J* = 16.1 Hz, 1H), 7.04 (s, 1H), 6.95 - 6.80 (m, 2H), 6.48 (d, *J* = 16.1 Hz, 1H), 6.15 (s, 1H), 5.60 (s, 1H), 5.48 (s, 1H), 5.20 (s, 1H), 4.74 (s, 1H), 4.53 (s, 1H), 3.82 (d, *J* = 21.3 Hz, 6H), 3.10- 2.97 (m, 1H), 2.28 (dd, *J* = 25.6, 13.9 Hz, 2H), 1.88 (d, *J* = 23.2 Hz, 2H), 1.60 (d, *J* = 10.3 Hz, 3H), 1.41 (dd, *J* = 25.2, 12.7 Hz, 3H), 0.87 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 166.6, 153.6, 152.9, 145.8, 142.1,

140.1, 124.1, 120.5, 119.3, 117.1, 113.6, 112.8, 112.6, 76.8, 75.4, 56.3, 55.9, 41.7, 41.2, 40.6, 36.7, 34.1, 27.27, 27.1, 17.3. HRMS (ESI) calcd for $C_{26}H_{30}O_6$ $[M+H]^+$ 439.2115, found 439.2114.

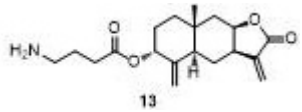
化合物12的合成



12

^1H NMR (400 MHz, $CDCl_3$) δ 6.10 (s, 1H), 5.56 (s, 1H), 5.32 (s, 1H), 5.09 (s, 1H), 4.67 (s, 2H), 4.49 (t, *J* = 4.0 Hz, 1H), 3.12 (d, *J* = 6.3 Hz, 2H), 3.01 (dt, *J* = 11.6, 5.9 Hz, 1H), 2.31 (t, *J* = 7.3 Hz, 2H), 2.19 (t, *J* = 13.8 Hz, 2H), 1.83 - 1.73 (m, 4H), 1.69 (dd, *J* = 13.8, 5.0 Hz, 1H), 1.60 - 1.49 (m, 2H), 1.39 (s, 9H), 1.32 (s, 1H), 1.30 - 1.20 (m, 1H), 0.79 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.2, 170.5, 156.0, 145.5, 142.0, 120.4, 112.7, 79.2, 76.7, 75.4, 41.5, 41.0, 40.4, 40.0, 36.4, 33.9, 32.1, 28.5, 27.1, 27.0, 25.5, 17.1. HRMS (ESI) calcd for $C_{24}H_{35}NO_6$ $[M+H]^+$434.2537, found 434.2536.

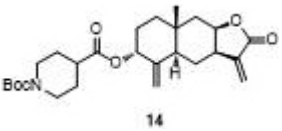
化合物13的合成



13

^1H NMR (400 MHz, $CDCl_3$) δ 6.11 (s, 1H), 5.59 (d, *J* = 3.1 Hz, 1H), 5.33 (s, 1H), 5.10 (s, 4H), 4.69 (s, 1H), 4.50 (s, 1H), 3.19 - 2.70 (m, 4H), 2.46 - 2.30 (m, 2H), 2.17 (t, *J* = 14.8 Hz, 2H), 1.92 (s, 2H), 1.77 (s, 2H), 1.56 (d, *J* = 10.4 Hz, 3H), 1.37 (d, *J* = 11.8 Hz, 1H), 0.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.2, 170.6, 142.0, 120.6, 112.9, 76.8, 76.0, 41.5, 40.9, 40.4, 36.4, 34.4, 33.9, 31.7, 29.8, 27.1, 17.3, 17.1. HRMS (ESI) calcd for $C_{19}H_{27}NO_4$ $[M+H]^+$ 334.2013, found 334.2013.

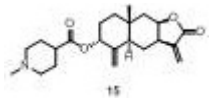
化合物14的合成



14

^1H NMR (400 MHz,$CDCl_3$) δ 6.03 (s, 1H), 5.52 (s, 1H), 5.26 (s, 1H), 5.03 (s, 1H), 4.61 (s, 1H), 4.43 (t, *J* = 3.9 Hz, 1H), 3.92 (s, 2H), 2.96 (dt, *J* = 11.6, 6.1 Hz, 1H), 2.74 (s, 2H), 2.35 (t, *J* = 11.0 Hz, 1H), 2.15 - 2.08 (m, 2H), 1.78 (s, 2H), 1.73 - 1.67 (m, 2H), 1.63 (dd, *J* = 12.8, 5.9 Hz, 1H), 1.49 (dd, *J* = 15.3, 5.1 Hz, 4H), 1.35 (s, 9H), 1.24 (d, *J* = 13.2 Hz, 1H), 0.73 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.2, 170.3, 154.5, 145.2, 141.8, 120.3, 112.6, 79.4, 76.4, 75.1, 41.4, 41.2, 40.8, 40.1, 36.3, 33.7, 28.3, 28.0, 27.8, 27.0, 26.9, 26.8, 16.9. HRMS (ESI) calcd for $C_{26}H_{37}NO_6$ $[M+Na]^+$ 482.2513, found 482.2508.

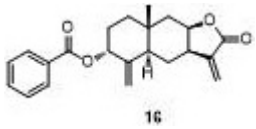
化合物15的合成



15

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.13 (s, 1H), 5.59 (s, 1H), 5.34 (s, 1H), 5.11 (s, 1H), 4.68 (s, 1H), 4.51 (s, 1H), 3.00 (dt, *J* = 11.6, 5.8 Hz, 1H), 2.81 (d, *J* = 10.7 Hz, 2H), 2.26 (s, 3H), 2.25 - 2.16 (m, 3H), 1.97 (t, *J* = 11.5 Hz, 2H), 1.88 (s, 2H), 1.79 (s, 1H), 1.77 (s, 2H), 1.70 (dd, *J* = 14.1, 7.5 Hz, 2H), 1.54 (d, *J* = 12.5 Hz, 2H), 1.38 (d, *J* = 18.7 Hz, 2H), 1.33 - 1.21 (m, 1H), 0.82 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.0, 170.5, 145.5, 142.0, 120.5, 112.7, 76.7, 75.2, 55.1, 55.1, 46.5, 41.7, 41.2, 41.1, 40.5, 36.6, 34.0, 28.6, 28.4, 27.2, 27.1, 17.1; HRMS (ESI) calcd for $C_{22}H_{31}NO_4$ $[M+H]^+$ 374.2326, found 374.2318.

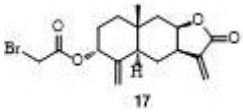
化合物16的合成



16

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 - 8.00 (m, 2H), 7.57 (t, *J* = 7.4 Hz, 1H), 7.45 (t, *J* = 7.6 Hz, 2H), 6.14 (s, 1H), 5.60 (d, *J* = 2.5 Hz, 1H), 5.59 (s, 1H), 5.25 (s, 1H), 4.77 (s, 1H), 4.54 (dd, *J* = 4.7, 3.7 Hz, 1H), 3.09 - 2.93 (m, 1H), 2.33 (d, *J* = 11.3 Hz, 1H), 2.30 - 2.24 (m, 1H), 2.02 - 1.85 (m, 2H), 1.79 - 1.67 (m, 2H), 1.62 (dd, *J* = 15.6, 4.7 Hz, 1H), 1.49 (dd, *J* = 10.2, 3.1 Hz, 1H), 1.38 (dd, *J* = 26.1, 12.5 Hz, 1H), 0.89 (s, 3H);^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 164.4, 144.4, 140.9, 131.9, 129.8, 128.5, 127.4, 119.4, 111.9, 75.6, 74.8, 40.7, 40.0, 39.3, 35.7, 32.9, 26.2, 25.9, 16.1; HRMS (ESI) calcd for $C_{22}H_{24}O_4$ $[M+H]^+$ 353.1753, found 353.1753.

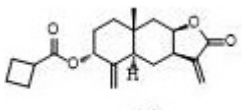
化合物17的合成



17

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.12 (s, 1H), 5.59 (s, 1H), 5.38 (s, 1H), 5.15 (s, 1H), 4.74 (s, 1H), 4.51 (t, J = 3.9 Hz, 1H), 3.81 (s, 2H), 3.07 - 2.95 (m, 1H), 2.32 - 2.15 (m, 2H), 1.83 (dt, J = 13.1, 6.7 Hz, 2H), 1.75 - 1.70 (m, 1H), 1.59 (ddd, J = 19.6, 14.5, 5.0 Hz, 2H), 1.44 - 1.29 (m, 2H), 0.82 (s, 3H); ^{13}C NMR(100MHz,$CDCl_3$) δ 170.6, 166.2, 144.8, 142.0, 120.6, 113.6, 77.6, 76.7, 41.5, 41.0, 40.4,36.3,33.9,27.0,26.9,26.5,17.1; HRMS (ESI) calcd for $C_{17}H_{22}BrO_4$ $[M+H]^+$ 369.0696, found 369.0695.

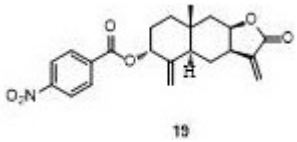
化合物18的合成



18

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.14 (d, *J* = 0.7 Hz, 1H), 5.59 (s, 1H), 5.34 (t, *J* = 2.6 Hz, 1H), 5.13 (s, 1H), 4.70 (s, 1H), 4.52 (dd, *J* = 4.8, 3.5 Hz, 1H), 3.11 (m, 1H), 3.06 - 2.95 (m, 1H), 2.32 - 2.11 (m, 6H), 1.94 (m, 2H), 1.80 (m, 2H), 1.72 (m, 1H), 1.61 - 1.50 (m, 2H), 1.43 - 1.29 (m, 2H), 0.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.5, 170.5, 145.7, 142.1, 120.4, 112.5, 76.7, 75.0, 41.6, 41.1, 40.5, 38.5, 36.5, 33.9, 27.1, 27.0, 25.4, 25.2, 18.5, 17.1; HRMS (ESI) calcd for $C_{23}H_{26}O_4$ $[M+H]^+$ 331.1909, found 331.1906.

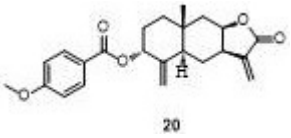
化合物19的合成



19

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (d, *J* = 8.2 Hz, 2H), 8.18 (d, *J* = 7.7 Hz, 2H), 6.14 (s, 1H), 5.64 (s, 1H), 5.59 (s, 1H), 5.27 (s, 1H), 4.81 (s, 1H), 4.54 (t, *J* = 4.7 Hz, 1H), 3.05 (dt, *J* = 11.8, 6.0 Hz, 1H), 2.29 (m, 2H), 1.98 (m, 2H), 1.82 - 1.69 (m, 2H), 1.63 (dd, *J* = 15.7, 4.5 Hz, 1H), 1.52 (d, *J* = 13.4 Hz, 1H), 1.39 (q, *J* = 13.0 Hz, 1H), 0.89 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 163.7, 150.6, 144.9, 141.9, 136.3, 130.7, 123.7, 120.6, 113.8, 77.2, 76.6, 42.0, 41.1, 40.4, 36.8, 34.1, 27.2, 27.0, 17.1; HRMS (ESI) calcd for $C_{22}H_{23}NO_6$ $[M+H]^+$ 398.1604, found 398.1601.

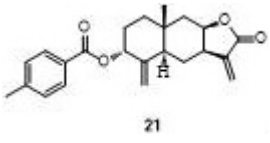
化合物20的合成



20

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, *J* = 8.3 Hz, 2H), 6.92 (d, *J* = 8.3 Hz, 2H), 6.13 (s, 1H), 5.58 (s, 2H), 5.23 (s, 1H), 4.75 (s, 1H), 4.53 (s, 1H), 3.86 (s, 3H), 3.03 (dt, *J* = 11.7, 5.9 Hz, 1H), 2.32 (d, *J* = 12.5 Hz, 1H), 2.26 (d, *J* = 15.6 Hz, 1H), 1.91 (m, 2H), 1.77 - 1.68 (m, 2H), 1.61 (dd, *J* = 15.6, 4.4 Hz, 1H), 1.47 (d, *J* = 13.1 Hz, 1H), 1.38 (q, *J* = 12.8 Hz, 1H), 0.88 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 165.3, 163.4, 145.7, 142.0, 131.7, 123.3, 120.5, 113.7, 112.9, 76.7, 75.6, 55.6, 41.9, 41.2, 40.5, 36.9, 34.1, 27.4, 27.1, 17.2; HRMS (ESI) calcd for $C_{23}H_{26}O_5$ $[M+H]^+$ 383.1858, found 383.1856.

化合物21的合成

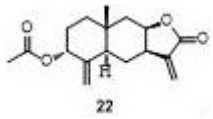


21

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, *J* = 8.0 Hz, 2H), 7.13 (d, *J* = 7.9 Hz, 2H), 6.02 (s, 1H), 5.47 (s, 2H), 5.12 (s, 1H), 4.65 (s, 1H), 4.42 (t, *J* = 4.2 Hz, 1H), 2.92 (dt, *J* = 11.8, 6.1 Hz, 1H), 2.30 (s, 3H), 2.22 (d, *J* = 12.5 Hz, 1H), 2.15 (d, *J* = 15.5 Hz, 1H), 1.81 (m, 2H), 1.68 - 1.56 (m, 2H), 1.51 (dd,

J = 15.6, 4.6 Hz, 1H), 1.37 (d, *J* = 13.1 Hz, 1H), 1.27 (q, *J* = 12.7 Hz, 1H), 0.77 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 165.6, 145.6, 143.6, 142.0, 129.6, 129.2, 128.1, 120.5, 112.9, 76.7, 75.7, 41.8, 41.1, 40.4, 36.8, 34.0, 27.3, 27.0, 21.7, 17.2; HRMS (ESI) calcd for $C_{23}H_{26}O_4$ $[M+H]^+$ 367.1909, found 367.1910.

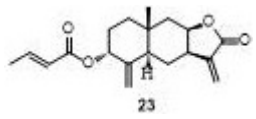
化合物22的合成



22

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.12 (s, 1H), 5.58 (s, 1H), 5.33 (s, 1H), 5.11 (s, 1H), 4.69 (s, 1H), 4.50 (s, 1H), 3.01 (dt, *J* = 11.6, 5.9 Hz, 1H), 2.21 (m, 2H), 2.03 (s, 3H), 1.82 - 1.67 (m, 3H), 1.65 - 1.49 (m, 2H), 1.36 (m, 2H), 0.82 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 170.1, 145.7, 142.1, 120.4, 112.6, 76.7, 75.4, 41.5, 41.1, 40.5, 36.4, 33.9, 27.1, 27.0, 21.6, 17.1; HRMS (ESI) calcd for$C_{23}H_{26}O_4$ $[M+H]^+$ 291.1596, found 291.1596.

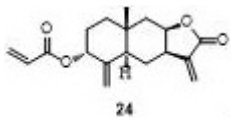
化合物23的合成



23

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.95 (dq, *J* = 15.5, 6.9 Hz, 1H), 6.13 (s, 1H), 5.84 (d, *J* = 15.5, 1H), 5.58 (s, 1H), 5.39 (s, 1H), 5.14 (s, 1H), 4.70 (s, 1H), 4.51 (t, *J* = 4.2 Hz, 1H), 3.01 (dt, *J* = 11.9, 6.0 Hz, 1H), 2.23 (m, 2H), 1.87 (d, *J* = 6.9, 3H), 1.85 - 1.78 (m, 2H), 1.75 - 1.69 (m, 1H), 1.64 - 1.53 (m, 2H), 1.42 - 1.30 (m, 2H), 0.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 165.5, 145.6, 144.6, 141.9, 123.1, 120.4, 112.6, 76.6, 75.0, 41.5, 41.0, 40.4, 36.5, 33.9, 27.1, 27.0, 18.0, 17.1; HRMS (ESI) calcd for $C_{19}H_{24}O_4$ $[M+H]^+$ 317.1753, found 317.1756.

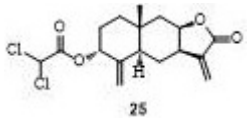
化合物24的合成



24

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.40 (d, *J* = 17.3 Hz, 1H), 6.15 (s, 1H), 6.12 (dd, *J* = 17.3, 10.4 Hz, 1H), 5.83 (d, *J* = 10.4 Hz, 1H), 5.60 (s, 1H), 5.44 (s, 1H), 5.18 (s, 1H), 4.73 (s, 1H), 4.52 (t, *J* = 4.6 Hz, 1H), 3.02 (dt, *J* = 11.9, 6.1 Hz, 1H), 2.31 - 2.19 (m, 2H), 1.85 (m, 2H), 1.76 - 1.66 (m, 2H), 1.64 (m, 1H), 1.56 (m, 1H), 1.47 - 1.30 (m, 2H), 0.85 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 165.3, 145.5, 142.0, 130.7, 129.0, 120.6, 113.0, 76.7, 75.6, 41.7, 41.1, 40.5, 36.6, 34.0, 27.2, 27.1, 17.2; HRMS (ESI) calcd for $C_{18}H_{22}O_4$ $[M+H]^+$ 303.1596, found 303.1598.

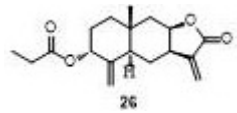
化合物25的合成



25

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.14 (s, 1H), 5.93 (s, 1H), 5.61 (s, 1H), 5.43 (s, 1H), 5.20 (s, 1H), 4.80 (s, 1H), 4.52 (t, *J* = 4.2 Hz, 1H), 3.03 (dt, *J* = 11.9, 6.1 Hz, 1H), 2.23 (d, *J* = 15.3 Hz, 2H), 1.97 - 1.82 (m, 2H), 1.74 (ddd, *J* = 13.9, 7.0, 2.3 Hz, 1H), 1.64 - 1.52 (m, 2H), 1.49 - 1.41 (m, 1H), 1.35 (q, *J* = 12.6 Hz, 1H), 0.85 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 163.4, 144.1, 141.9, 120.7, 114.3, 79.3, 76.6, 64.8, 41.5, 41.0, 40.4, 36.3, 33.9, 27.0, 26.8, 17.1; HRMS (ESI) calcd for $C_{17}H_{20}Cl_2O_4$ $[M+H]^+$ 359.0817, found 359.0808.

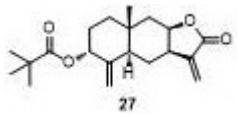
化合物26的合成



26

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.14 (s, 1H), 5.59 (s, 1H), 5.36 (s, 1H), 5.13 (s, 1H), 4.70 (s, 1H), 4.52 (t, *J* = 4.4 Hz, 1H), 3.02 (dt, *J* = 11.8, 6.0 Hz, 1H), 2.32 (q, *J* = 7.5 Hz, 2H), 2.22 (d, *J* = 14.8 Hz, 2H), 1.79 (m, 2H), 1.72 (dd, *J* = 12.9, 6.0 Hz, 1H), 1.56 (m, 2H), 1.38 (m, 2H), 1.13 (t, *J* = 7.6 Hz, 3H), 0.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.6, 170.6, 145.7, 142.1, 120.5, 112.6, 76.7, 75.2, 41.6, 41.1, 40.5, 36.5, 34.0, 28.1, 27.2, 27.1, 17.2, 9.3; HRMS (ESI) calcd for $C_{18}H_{24}O_4$ $[M+H]^+$ 305.1753, found 305.1755.

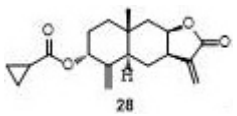
化合物27的合成



27

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.15 (d, J = 0.8 Hz, 1H), 5.60 (s, 1H), 5.32 (t, J = 2.7 Hz, 1H), 5.13 (s, 1H), 4.70 (s, 1H), 4.52 (dd, J = 4.8, 3.5 Hz, 1H), 3.08 - 2.95 (m, 1H), 2.23 (m, 2H), 1.83 - 1.78 (m, 2H), 1.74 (ddd, J = 13.9, 7.0, 2.6 Hz, 1H), 1.61 - 1.56 (m, 1H), 1.53 (m, 1H), 1.45 - 1.31 (m, 2H), 1.20 (s, 9H), 0.85 (s, 3H) .^{13}C NMR (101 MHz, $CDCl_3$) δ 177.5, 170.6, 145.7, 142.1, 120.5, 112.5, 76.7, 75.1, 41.8, 41.3, 40.6, 39.1, 36.8, 34.0, 27.3, 27.2, 27.1, 17.1.

化合物28的合成

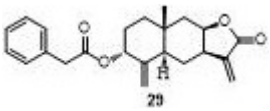


28

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.14 (d, J = 0.8 Hz, 1H), 5.59 (s, 1H), 5.35 (t, J = 2.7 Hz, 1H), 5.13 (s, 1H), 4.70 (s, 1H), 4.52 (td, J = 4.8, 1.4 Hz, 1H), 3.08 - 2.97 (m, 1H), 2.26 (d, J = 7.7, 1H), 2.23 (d, J = 10.8, 1H), 1.87 - 1.70 (m, 3H), 1.64 - 1.56 (m, 3H), 1.44 - 1.30 (m, 2H), 0.98 (m, 2H), 0.86

(m, 1H), 0.84 (s, 3H), 0.84 - 0.81 (m, 1H) ;^{13}C NMR (101 MHz, $CDCl_3$) δ 174.0, 170.6, 145.7, 142.1, 120.5, 112.6, 76.8, 75.4, 41.7, 41.2, 40.6, 36.6, 34.0, 27.2, 27.1, 17.2, 13.4, 8.7, 8.6.

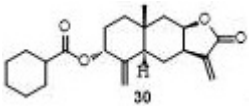
化合物29的合成



29

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (d, J = 8.6 Hz, 5H), 6.13 (s, 1H), 5.59 (s, 1H), 5.33 (s, 1H), 5.11 (s, 1H), 4.67 (s, 1H), 4.47 (s, 1H), 3.61 (s, 2H), 2.90 (s, 1H), 2.16 (d, J = 15.1 Hz, 1H), 1.96 (d, J = 11.7 Hz, 1H), 1.69 (d, J = 64.9 Hz, 4H), 1.49 - 1.14 (m, 6H), 0.79 (s, 3H) ;^{13}C NMR (101 MHz, $CDCl_3$) δ 170.5, 170.4, 145.4, 142.0, 134.6, 129.4, 128.6, 127.0, 120.4, 112.6, 76.6, 75.8, 42.0, 41.2, 41.0, 40.4, 36.3, 33.8, 27.0, 26.9, 17.1.

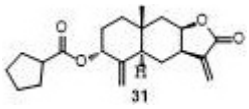
化合物30的合成



30

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.13 (s, 1H), 5.59 (s, 1H), 5.33 (s, 1H), 5.12 (s, 1H), 4.69 (s, 1H), 4.52 (t, J = 4.2 Hz, 1H), 3.08 - 2.96 (m, 1H), 2.28 (m, 1H), 2.22 (d, J = 14.2 Hz, 2H), 1.88 (m, 2H), 1.83 - 1.67 (m, 5H), 1.67 - 1.53 (m, 3H), 1.48 - 1.32 (m, 4H), 1.30 - 1.21 (m, 3H), 0.83 (s, 3H) ;^{13}C NMR (101 MHz, $CDCl_3$) δ 174.9, 170.4, 145.7, 142.0, 120.3, 112.4, 76.6, 74.8, 43.4, 41.6, 41.1, 40.4, 36.5, 33.9, 29.2, 28.9, 27.1, 27.0, 25.8, 25.5, 25.4, 17.0.

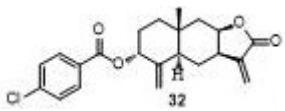
化合物31的合成



31

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.14 (s, 1H), 5.60 (s, 1H), 5.34 (s, 1H), 5.13 (s, 1H), 4.70 (s, 1H), 4.52 (t, J = 4.6 Hz, 1H), 3.02 (dt, J = 11.9, 6.2 Hz, 1H), 2.81 - 2.66 (m, 1H), 2.23 (d, J = 15.0 Hz, 2H), 1.97 - 1.64 (m, 9H), 1.57 (m, 4H), 1.43 - 1.30 (m, 2H), 0.84 (s, 3H) ;^{13}C NMR (101 MHz, $CDCl_3$) δ 175.8, 170.6, 145.8, 142.1, 120.5, 112.5, 76.7, 75.0, 44.3, 41.7, 41.2, 40.5, 36.6, 34.0, 30.2, 29.9, 27.2, 27.1, 25.9, 25.9, 17.1.

化合物32的合成

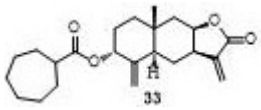


32

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 - 7.87 (m, 2H), 7.41 (d, J = 7.5 Hz, 2H), 6.13 (s, 1H), 5.58 (s, 2H), 5.24 (s, 1H), 4.77 (s, 1H), 4.53 (s, 1H), 3.03 (dt, J = 11.6, 5.9 Hz, 1H), 2.28 (t, J = 13.1 Hz, 2H), 1.92 (d, J = 14.9 Hz,

2H), 1.73 (dd, J = 21.9, 7.7 Hz, 2H), 1.61 (dd, J = 15.8, 4.4 Hz, 1H), 1.49 - 1.40 (m, 1H), 1.38 - 1.29 (m, 1H), 0.88 (s, 3H);^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 164.7, 145.3, 142.0, 139.4, 131.0, 129.3, 128.8, 120.6, 113.3, 76.6, 76.3, 41.9, 41.2, 40.4, 36.8, 34.1, 27.3, 27.0, 17.2.

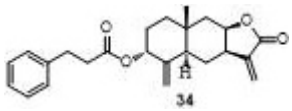
化合物33的合成



33

^{1}H NMR (400 MHz, $CDCl_3$)δ 6.11 (s, 1H), 5.58 (s, 1H), 5.30 (s, 1H), 5.09 (s, 1H), 4.67 (s, 1H), 4.50 (t, J = 4.0 Hz, 1H), 3.01 (dt, J = 11.8, 6.2 Hz, 1H), 2.43 - 2.30 (m, J = 8.9, 4.3 Hz, 1H), 2.20 (d, J = 14.4 Hz, 2H), 1.95 - 1.83 (m, 2H), 1.76 (dt, J = 7.1, 3.8 Hz, 2H), 1.69 (d, J = 11.6, 4.7, 3.5 Hz, 3H), 1.64 (s, 1H), 1.62 (d, J = 4.3 Hz, 1H), 1.58 - 1.45 (m, 8H), 1.41 - 1.27 (m, 2H), 0.81 (s, 3H);^{13}C NMR (100 MHz, $CDCl_3$) δ 176.0, 170.5, 145.7, 142.0, 120.4, 112.4, 76.7, 74.8, 45.3, 41.6, 41.1, 40.4, 36.5, 33.9, 31.0, 30.7, 28.4, 28.3, 27.1, 27.0, 26.4, 26.3, 17.1.

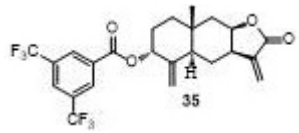
化合物34的合成



34

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 - 7.25 (m, 2H), 7.20 (m, 3H), 6.14 (s, 1H), 5.60 (s, 1H), 5.35 (s, 1H), 5.12 (s, 1H), 4.68 (s, 1H), 4.50 (t, J = 4.2 Hz, 1H), 2.97 (m, 3H), 2.65 (t, J = 7.7 Hz, 2H), 2.18 (d, J = 15.5 Hz, 1H), 2.08 (d, J = 12.5 Hz, 1H), 1.76 (m, 2H), 1.71 - 1.61 (m, 1H), 1.47 (m, 2H), 1.38 - 1.24 (m, 2H), 0.81 (s, 3H) ;^{13}C NMR (101 MHz, $CDCl_3$) δ 171.9, 170.5, 145.5, 142.0, 140.5, 128.5, 128.3, 126.3, 120.4, 112.6, 76.6, 75.4, 41.4, 40.9, 40.4, 36.3, 36.1, 33.8, 31.0, 27.0, 26.9, 17.1.

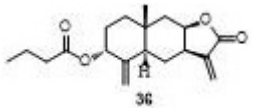
化合物35的合成



35

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (s, 2H), 8.06 (s, 1H), 6.14 (s, 1H), 5.66 (s, 1H), 5.59 (s, 1H), 5.29 (s, 1H), 4.84 (s, 1H), 4.55 (d, J = 4.5 Hz, 1H), 3.06 (dt, J = 11.4, 5.9 Hz, 1H), 2.27 (m, 2H), 2.06 - 1.90 (m, 2H), 1.77 (dd, J = 13.6, 6.9 Hz, 1H), 1.66 (m, 2H), 1.53 (d, J = 13.4 Hz, 1H), 1.42 - 1.34 (m, 1H), 0.90 (s, 3H) ;^{13}C NMR (101 MHz, $CDCl_3$) δ 170.5, 163.1, 144.7, 141.9, 133.1, 132.3 (q, J = 34.0 Hz), 129.7, 126.4 (m), δ 123.0 (q, J = 273.0 Hz), 120.7, 114.2, 77.6, 76.6, 42.0, 41.1, 40.4, 36.8, 34.0, 27.1, 27.0, 17.1.

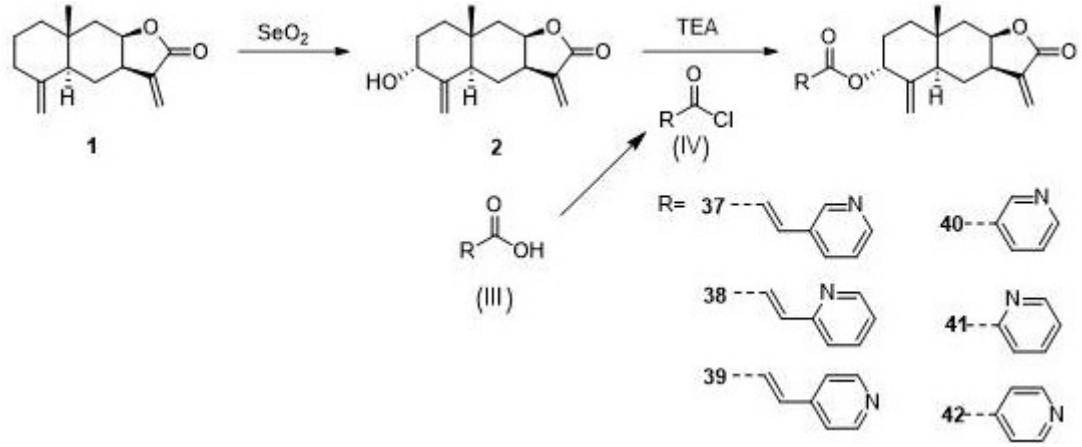
化合物36的合成



36

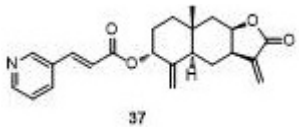
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.14 (s, 1H), 5.59 (s, 1H), 5.36 (t, *J* = 2.6 Hz, 1H), 5.13 (s, 1H), 4.69 (s, 1H), 4.52 (dd, *J* = 4.7, 3.6 Hz, 1H), 3.10 - 2.95 (m, 1H), 2.27 (t, *J* = 7.4 Hz, 2H), 2.22 (d, *J* = 15.2 Hz, 2H), 1.84 - 1.51 (m, 8H), 1.37 (m, 2H), 0.94 (t, *J* = 7.4 Hz, 3H), 0.83 (s, 3H) ;^{13}C NMR (100 MHz, $CDCl_3$) δ 172.8, 170.6, 145.7, 142.1, 120.5, 112.6, 76.7, 75.1, 41.6, 41.1, 40.5, 36.8, 36.5, 34.0, 27.2, 27.1, 18.7, 17.2, 13.8.

化合物37-42的合成路线：



将烘干的10 mL圆底烧瓶中加入酸(Ⅲ)，加入溶剂二氯甲烷，开始搅拌，然后加入1.1 eq的草酰氯加入0.1 eq的N,N-二甲基甲酰胺，2 h后将反应处理，真空浓缩即得化合物酰氯(Ⅳ)。将化合物2溶于DCM中，加入1.5 eq的三乙胺(TEA)，搅拌1-2 min后加入1.2 eq的酰氯，室温下搅拌1 h，用TLC检测反应完全，用蒸馏水淬灭反应，用DCM萃取三次，合并有机相，用无水Na2SO4干燥，过滤，滤液减压浓缩，过硅胶色谱柱(石油醚/乙酸乙酯)得目标化合物37-42(白色无定型固体)。

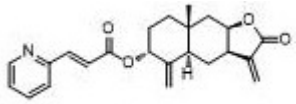
[0015] 化合物37的合成



37

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.77 (s, 1H), 8.62 (s, 1H), 7.85 (d, *J* = 7.6 Hz, 1H), 7.66 (d, *J* = 16.1 Hz, 1H), 7.35 (s, 1H), 6.53 (d, *J* = 18.1 Hz, 1H), 6.15 (s, 1H), 5.60 (s, 1H), 5.52 (s, 1H), 5.22 (s, 1H), 4.77 (s, 1H), 4.55 (s, 1H), 3.14 - 2.98 (m, 1H), 2.35 - 2.23 (m, 2H), 1.90 (d, *J* = 15.4 Hz, 2H), 1.63 (d, *J* = 13.6 Hz, 2H), 1.46 (d, *J* = 17.8 Hz, 2H), 1.29 (s, 1H), 0.88 (s, 3H);^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 165.4, 151.0, 149.6, 145.4, 142.0, 141.0, 134.5, 130.4, 123.9, 120.9, 120.5, 113.1, 76.7, 75.9, 41.7, 41.1, 40.5, 36.6, 34.0, 29.8, 27.2, 17.7. HRMS (ESI) calcd for $C_{23}H_{25}NO_4$ $[M+H]^+$ 380.1856, found 380.1863.

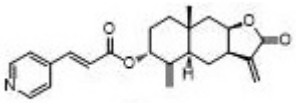
化合物38的合成



38

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.65 (s, 1H), 7.78 - 7.62 (m, 2H), 7.44 (d, *J* = 8.1 Hz, 1H), 7.30 (s, 1H), 6.94 (d, *J* = 15.7 Hz, 1H), 6.15 (s, 1H), 5.60 (s, 1H), 5.50 (s, 1H), 5.20 (s, 1H), 4.74 (s, 1H), 4.54 (s, 1H), 3.07 - 2.97 (m, 1H), 2.28 (dd, *J* = 28.7, 13.5 Hz, 2H), 1.87 (d, *J* = 12.0, 10.7 Hz, 2H), 1.62 (d, *J* = 20.0 Hz, 3H), 1.43 (d, *J* = 10.7 Hz, 2H), 0.86 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 165.8, 153.0, 150.3, 143.3, 142.1, 137.1, 124.5, 124.4, 123.0, 120.6, 112.8, 76.8, 75.7, 41.6, 41.1, 40.5, 36.5, 34.1, 27.3, 27.1, 17.2. HRMS (ESI) calcd for $C_{23}H_{25}NO_4$ $[M+H]^+$ 380.1856, found 380.1858.

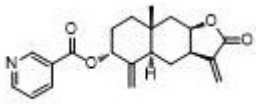
化合物39的合成



39

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.65 (d, *J* = 6.0 Hz, 2H), 7.58 (d, *J* = 16.0 Hz, 1H), 7.37 (d, *J* = 6.0 Hz, 2H), 6.60 (d, *J* = 16.0 Hz, 1H), 6.15 (s, 1H), 5.59 (s, 1H), 5.50 (s, 1H), 5.21 (s, 1H), 4.76 (s, 1H), 4.53 (t, *J* = 4.2 Hz, 1H), 3.03 (dt, *J* = 11.9, 6.3 Hz, 1H), 2.32 - 2.21 (m, 2H), 1.89 (dt, *J* = 14.3, 3.3 Hz, 2H), 1.75 (dd, *J* = 14.0, 7.0 Hz, 1H), 1.69 - 1.56 (m, 2H), 1.45 (d, *J* = 18.3 Hz, 1H), 1.41 - 1.31 (m, 1H), 0.87 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 165.2, 150.7, 145.3, 142.0, 141.9, 141.7, 123.3, 121.9, 120.6, 113.3, 76.7, 76.1, 41.7, 41.1, 40.5, 36.6, 34.1, 27.2, 27.1, 17.2. HRMS (ESI) calcd for $C_{23}H_{25}NO_4$ $[M+H]^+$ 380.1856, found 380.1848.

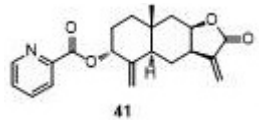
化合物40的合成



40

^{1}H NMR (400 MHz,$CDCl_3$) δ 9.21 (s, 1H), 8.77 (d, *J* = 4.1 Hz, 1H), 8.28 (d, *J* = 7.9 Hz, 1H), 7.46 - 7.37 (m, 1H), 6.13 (s, 1H), 5.63 (s, 1H), 5.58 (s, 1H), 5.25 (s, 1H), 4.78 (s, 1H), 4.53 (t, *J* = 4.2 Hz, 1H), 3.02 (dt, *J* = 11.8, 6.1 Hz, 1H), 2.35 - 2.22 (m, 2H), 1.94 (d, *J* = 14.9, 13.6 Hz, 3H), 1.73 (s, 2H), 1.61 (d, *J* = 15.6 Hz, 1H), 1.50 (d, *J* = 13.3 Hz, 1H), 1.38 (d, *J* = 12.7 Hz, 1H), 0.88 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 164.2, 153.5, 150.9, 145.1, 142.0, 137.3, 126.8, 123.5, 120.6, 113.5, 76.6, 76.6, 41.9, 41.2, 40.5, 36.8, 34.1, 27.3, 27.1, 17.2. HRMS (ESI) calcd for $C_{21}H_{23}NO_4$ $[M+H]^+$ 354.1694, found 354.1706.

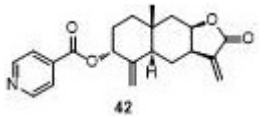
化合物41的合成



41

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.89-8.67 (m, 1H), 8.07 (d, *J* = 7.8 Hz, 1H), 7.83 (t, *J* = 7.5 Hz, 1H), 7.47 (s, 1H), 6.13 (s, 1H), 5.66 (s, 1H), 5.57 (s, 1H), 5.26 (s, 1H), 4.78 (s, 1H), 4.52 (s, 1H), 3.03 (dt, *J* = 10.8, 5.8 Hz, 1H), 2.37 (d, *J* = 12.5 Hz, 1H), 2.24 (d, *J* = 15.5 Hz, 1H), 1.92 (t, *J* = 14.6 Hz, 1H), 1.80 - 1.69 (m, 2H), 1.68 - 1.59 (m, 1H), 1.51-1.35 (m, 2H), 0.88 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 164.3, 150.1, 148.7, 145.2, 142.1, 137.0, 126.8, 125.1, 120.5, 113.6, 77.0, 76.8, 41.8, 41.1, 40.5, 36.7, 34.0, 27.2, 27.1, 17.2. HRMS (ESI) calcd for $C_{21}H_{23}NO_4$ $[M+H]^+$ 354.1700, found 354.1707.

化合物42的合成



42

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.79 (s, 2H), 7.84 (s, 2H), 6.15 (s, 1H), 5.61 (d, *J* = 13.0 Hz, 2H), 5.27 (s, 1H), 4.81 (s, 1H), 4.55 (s, 1H), 3.05 (s, 1H), 2.29 (d, *J* = 14.3 Hz, 2H), 1.95 (d, *J* = 13.5 Hz, 2H), 1.80 - 1.58 (m, 4H), 1.52 (d, *J* = 13.4 Hz, 1H), 1.39 (d, *J* = 13.7 Hz, 1H), 0.89 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 164.1, 150.7, 144.9, 141.9, 138.1, 123.0, 120.7, 113.9, 77.1, 76.6, 42.0, 41.1, 40.5, 36.8, 34.1, 27.2, 27.0, 17.2. HRMS (ESI) calcd for $C_{21}H_{23}NO_4$ $[M+H]^+$ 354.1700, found 354.1703.

实施例18:异土木香内酯及其衍生物的药理作用

将各种癌细胞配成2×10^5/mL细胞悬液,加入24孔板圆底细胞培养板内,分别加入待测化合物,每一测试浓度5孔,置37 ℃、5%CO_2饱和湿度条件下培养72小时,用MTT法在酶联检测仪570 nm波长测得吸光度(A)值,计算出本发明化合物对测试癌细胞的抑制作用。

[0016] 表1 异土木香内酯及其衍生物对各种癌细胞的抑制活性(IC_{50},μM)

化合物	HL60	HL60/A	KG1a
阿霉素（对照）	0.024±0.006	4.84±1.485	0.72±0.12
1	10.3±0.8	12.28±4.09	9.38±1.85
2	25.64±3.69	33.14±6.6	22.39±1.82
3	12±1.17	41.57±4.6	7.31±0.50
4	7.49±0.63	8.29±2.12	14.01±6.48
5	7.26±1.65	8.11±0.94	6.17±1.02
6	6.67±1.66	9.65±1.36	5.84±1.71
7	4.93±0.52	5.76±1.24	4.72±0.16
8	5.4±0.42	6.85±2.47	4.01±0.09
9	3.57±0.95	5.34±0.55	4.29±1.21
10	2.44±0.31	3.79±0.48	1.92±0.78
11	31.3±4.23	43.6±3.67	30.7±5.78
12	42.5±2.44	56.34±6.32	40.5±6.77
13	52.6.±6.85	68.9±4.89	59.45±7.32
14	65.3±5.98	76.5±6.12	60.6±2.92
15	5.42±0.64	6.52±1.34	3.68±0.59
16	2.71±0.47	2.01±0.25	0.39±0.18
17	0.28±0.11	0.25±0.01	3.92±1.79
18	8.4±1.27	10.25±0.21	4.2±0.14
19	3.86±0.95	2.78±1.37	4.38±0.4
20	6.06±0.8	5.02±0.12	3.7±0.47

化合物	HL60	HL60/A	KG1a
21	4.5±0.5	8.69±3.22	4.55±1.51
22	31.93±0.23	26.60±3.23	33.51±6.94
23	11.55±1.34	7.6±0.28	7.77±0.13
24	10.69±3.47	7.45±0.07	8.17±2.05
25	16.03±1.88	11.07±0.54	17.36±1.72
26	12.35±3.25	12.4±1.98	8.65±0.71
27	10.38±0.81	23±0.21	5.64±0.57
28	9.08±2.21	7.23±0.88	2.71±0.9
29	4.9±0.39	5.88±1.98	1.73±0.19
30	1.85±0.51	2.21±0.41	0.7±0.12
31	3.81±1.05	4.97±0.42	1.32±0.28
32	3.37±0.38	3.71±1.14	3.03±0.7
33	4.15±0.07	2.9±1.13	1.37±0.18
34	9.25±0.21	8.25±0.92	6.1±0.73
35	3.35±1.06	3.5±2.12	3.76±0.5
36	7.95±1.34	8.6±1.7	8.71±0.86
37	7.69±2.28	2.29±0.34	6.15±0.22
38	13.82±2.74	16.78±2.79	14.65±2.63
39	16.43±3.55	17.99±3.89	21.84±4.31
40	4.76±2.45	9.63±2.30	5.54±1.60
41	15.87±0.74	48.83±2.11	27.07±0.90
42	21.67±4.85	19.52±1.61	21.63±2.63

其中HL-60、HL-60/A、KG1a分别表示急性白血病细胞株、耐阿霉素急性白血病细胞株、人白血病细胞株。

[0017] 活性测试结果表明，筛选的化合物对受试细胞显示出抑制活性。因此测试化合物具有用于治疗癌症的用途。

[0018] 本发明的化合物、用途和方法已经通过具体的实施例进行了描述。本领域技术人员可以借鉴本发明的内容适当改变原料、工艺条件等环节来实现相应的其它目的，其相关改变都没有脱离本发明的内容，所有类似的替换和改动对于本领域技术人员来说是显而易见的，都被视为包括在本发明的范围之内。