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权利要求书 7 页 说明书 124 页 附图 10 页

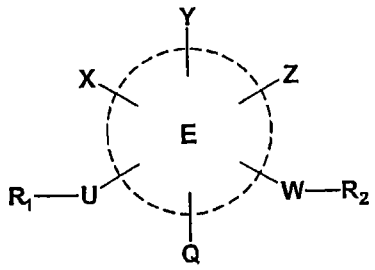
[54] 发明名称

抗 - 细胞凋亡 BCL - 2 家族成员的小分子抑制剂及其应用

[57] 摘要

本发明涉及起抗细胞凋亡 Bcl - 2 族成员蛋白质 (例如 Bcl - 2 和 Bcl - xL) 的抑制剂作用的小分子。本发明还涉及这些化合物在诱导细胞凋亡细胞死亡并且使细胞对诱导细胞凋亡细胞死亡致敏中的应用。

1. 具有式 I 的化合物:



I

或其药学上可接受的盐或前体药物，其中:

E 为苯基或杂芳族基团;

X、Y 和 Z 独立为 H、OH、羧酸、酰胺、磺酸、磺酰胺、亚磺酸、亚磺酰胺、醛、磷酸、膦酰胺、烷基、烷氧基或芳基，或 X 和 Y 或 Y 和 Z 之一形成杂环，并且 X、Y 和 Z 中至少一个为 OH、羧酸、酰胺、磺酸、磺酰胺、亚磺酸、亚磺酰胺、醛、磷酸或膦酰胺;

U 和 W 独立为 CO、SO、SO_2、$(CH_2)_n$、S、NH、NHCO、P、PO 或 PO_2;

n 为 0 或 1;

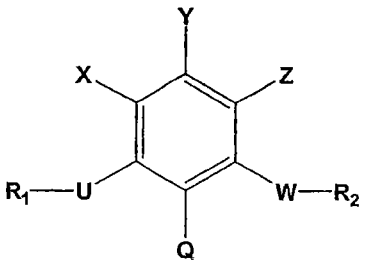
Q 为 H、烷基、链烯基、炔基或卤素; 或

Q 与 U 和/或 W 形成环;

R_1 和 R_2 独立为氢、烷基、链烯基、炔基、环烷基、芳基、杂芳基、部分饱和的杂环、杂环; NR_3R_4、OR_3、SR_3 或 $CR_3R_4R_5$，其中的任意一个可以任选被取代; 并且

R_3-R_5 独立为烷基、链烯基、炔基、环烷基、芳基、芳烷基、杂芳基、杂芳烷基、杂环或形成环，其中的任意一个可以任选被取代。

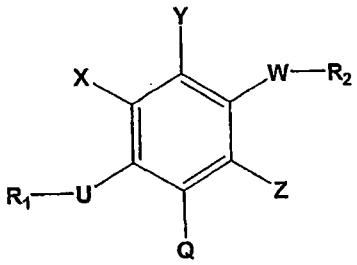
2. 权利要求 1 所述的具有式 II 的化合物，其中 X、Y 和 Z 中至少一个为 OH



II

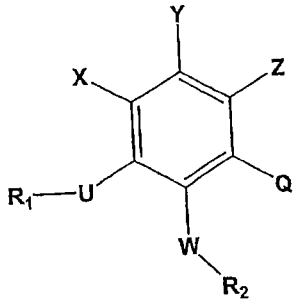
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3. 权利要求 1 所述的具有式 III 的化合物，其中 X、Y 和 Z 中至少一个为 OH



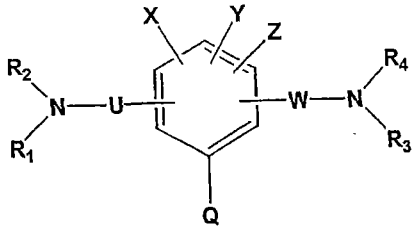
III 。

4. 权利要求 1 所述的具有式 IV 的化合物，其中 X、Y 和 Z 中至少一个为 OH



IV 。

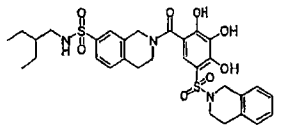
5. 权利要求 1 所述的具有式 V 的化合物，其中 X、Y 和 Z 中至少一个为 OH

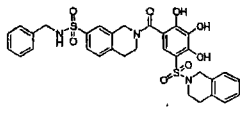


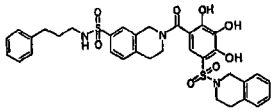
V 。

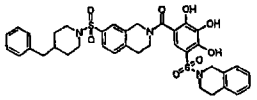
6. 权利要求 1 所述的化合物，其中 X、Y 和 Z 中至少一个为 OH。

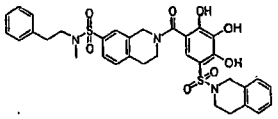
7. 权利要求 1 所述的化合物，其为：

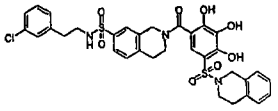

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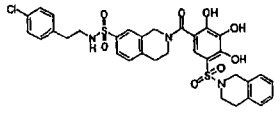

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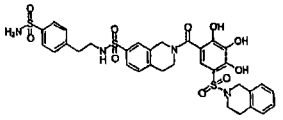

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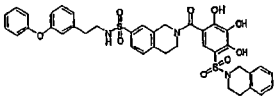

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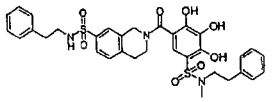

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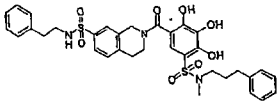

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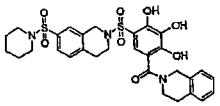

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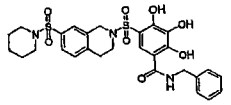

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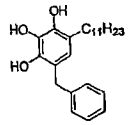

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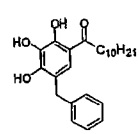

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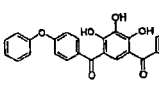

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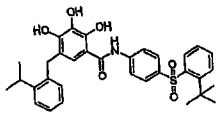

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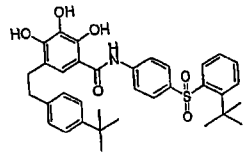
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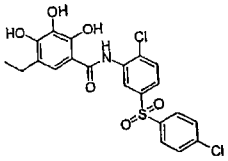

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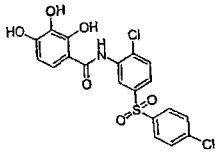
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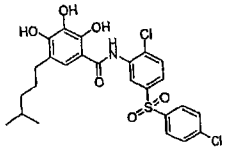
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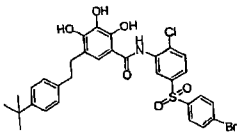

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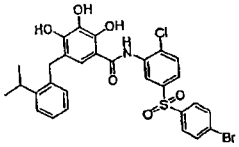

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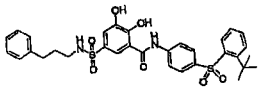

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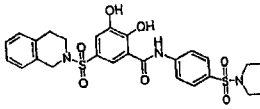

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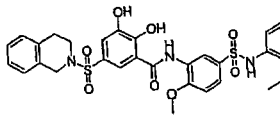

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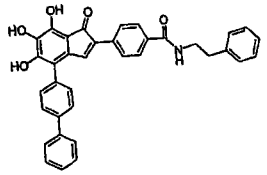

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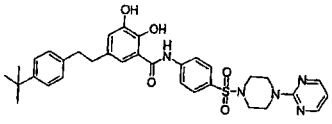

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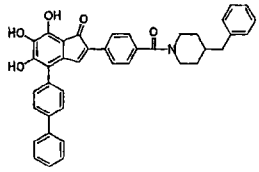

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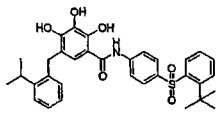


;或



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8. 权利要求 1 所述的化合物，其为：



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9. 药物组合物，包含权利要求 1 的化合物和药学上可接受的载体。

10. 诱导细胞中的细胞凋亡的方法，包含使该细胞接触权利要求 1 的化合物。

11. 使细胞对细胞凋亡诱导物敏感的方法，包含使该细胞接触权利要求 1 的化合物。

12. 权利要求 11 所述的方法，进一步包含使该细胞接触细胞凋亡诱导物。

13. 权利要求 12 所述的方法，其中所述的细胞凋亡诱导物为化疗剂。

14. 权利要求 12 所述的方法，其中所述的细胞凋亡诱导物为辐射。

15. 治疗、改善或预防动物对细胞凋亡诱导有应答的障碍的方法，包含对该动物给予治疗有效量的权利要求 1 的化合物。

16. 权利要求 15 所述的方法，进一步包含给予细胞凋亡诱导物。

17. 权利要求 16 所述的方法，其中所述的细胞凋亡诱导物为化疗剂。

18. 权利要求 16 所述的方法，其中所述的细胞凋亡诱导物为辐射。

19. 权利要求 15 所述的方法，其中所述的对细胞凋亡诱导有应答的病症为过度增殖性疾病。

20. 权利要求 19 所述的方法，其中所述的过度增殖性疾病为癌症。

21. 权利要求 16 所述的方法，其中在给予所述细胞凋亡诱导物前给予所述的权利要求 1 的化合物。

22. 权利要求 16 所述的方法，其中在给予所述细胞凋亡诱导物后给予所述的权利要求 1 的化合物。

23. 权利要求 16 所述的方法，其中同时给予所述的权利要求 1 的化合物和所述的细胞凋亡诱导物。

24. 试剂盒，包含权利要求 1 的化合物和给予动物所述化合物的说明书。

25. 权利要求 24 所述的试剂盒，进一步包含细胞凋亡诱导物。

26. 权利要求 25 所述的试剂盒，其中所述的细胞凋亡诱导物为化疗剂。

27. 权利要求 24 所述的试剂盒，其中所述的说明书用于给予患有过度增殖性疾病的动物所述的化合物。

28. 权利要求 27 所述的试剂盒，其中所述的过度增殖性疾病为癌症。

抗-细胞凋亡 BCL-2 家族成员的小分子抑制剂及其应用

发明背景

发明领域

本发明涉及药物化学领域。特别地，本发明涉及起抗细胞凋亡 Bcl-2 家族成员的蛋白质(例如 Bcl-2 和 Bcl-xL)的抑制剂作用的小分子。本发明还涉及这些化合物在诱导细胞凋亡性细胞死亡和使细胞对细胞凋亡性细胞死亡诱导敏感中的应用。

相关领域

侵害性的癌细胞表型为导致胞内信号传导途径失调的各种遗传性和后生改变的结果(Ponder, Nature 411:336 (2001))。然而，所有癌细胞的共性在于其无法执行细胞凋亡程序，并且因正常细胞凋亡机器缺陷而缺乏适当的细胞凋亡为癌症的标志(Lowe 等 Carcinogenesis 21:485 (2000))。大部分目前的癌症疗法，包括化疗剂、放射和免疫疗法通过间接诱导癌细胞中的细胞凋亡起作用。癌细胞因正常细胞凋亡机器缺陷而不能执行细胞凋亡程序由此通常与对化疗、放射或免疫疗法诱导的细胞凋亡的耐受性增加有关。不同来源的人癌因细胞凋亡缺陷而对目前治疗方案的原发性或获得性耐受性为目前癌症疗法中的主要问题(Lowe 等 Carcinogenesis 21:485 (2000); Nicholson, Nature [yen]07:810 (2000))。因此，对设计和研发新分子靶标-特异性抗癌疗法以改善癌症患者存活率和生活质量的目前和未来的尝试必须包括特异性靶向抗细胞凋亡的癌细胞的策略。在这方面，在直接抑制癌细胞中细胞凋亡中起中心作用的靶向决定性负调节物代表了对新的抗癌药设计而言具有高度富有前途的治疗策略。

已经鉴定了两类细胞凋亡的中心负调节物。第一类细胞凋亡的负调节物为细胞凋亡蛋白质的抑制剂(IAPs) (Deveraux 等 Genes Dev.

13:239 (1999); Salvesen 等 Nat. Rev. MoI. Cell. Biol 3:401 (2002))。IAP 蛋白质有效抑制癌细胞中各种细胞凋亡刺激物，包括化疗剂、放射和免疫疗法诱导的细胞凋亡。

作为两种有效抗细胞凋亡分子，第二类 Bcl-2 族蛋白质的中心负调节物为 Bcl-2 和 Bcl-xL 蛋白质(Adams 等 Science 281:1322 (1998); Reed, Adv. Pharmacol 41:501 (1997); Reed 等 J. Cell. Biochem. 60:23 (1996))。Bcl-2 族蛋白质目前包括:抗细胞凋亡分子,诸如 Bcl-2 和 Bcl-xL; 和前-细胞凋亡分子，诸如 Bax、Bak、Bid 和 Bad。已经广泛地综述了靶向癌症中抗细胞凋亡 Bcl-2 家族成员，诸如 Bcl-2 和 Bcl-xL 以恢复癌细胞敏感性和克服癌细胞对细胞凋亡的耐受性的治疗策略(Adams 等 Science 281:1322 (1998); Reed, Adv. Pharmacol. 41:501 (1997); Reed 等 J. Cell. Biochem. 60:23 (1996))。目前，Bcl-2 反义疗法处于用于治疗实体瘤和非实体瘤的几个 III 期临床试验中。几个实验室关注设计 Bcl-2 和 Bcl-xL 的小分子抑制剂。

发明概述

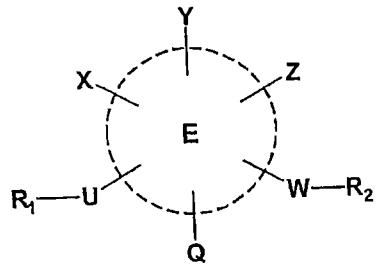
一般可接受的是，癌细胞或其支持细胞不能进行细胞凋亡作为对遗传性损害或接触细胞凋亡诱导物(诸如抗癌剂和放射)的应答为癌症发作和发展中的主要因素。认为在癌细胞或其支持细胞(例如肿瘤脉管系统中的新血管细胞)中诱导细胞凋亡为实际用于所有市售或目前实施中的有效癌症治疗药或放疗的通用作用机制。细胞不能进行细胞凋亡的一个原因在于 IAPs 的表达增加和蓄积。

本发明关注使患有癌症的动物接触治疗有效量的抑制抗细胞凋亡 Bcl-2 家族成员的功能的药物(例如小分子)将会杀伤癌细胞或支持细胞(持续存活依赖于抗细胞凋亡 Bcl-2 家族成员的过度活性的那些细胞)和/或赋予这类作为群体的细胞对诱导细胞死亡的癌症治疗药或放疗更为敏感。本发明关注，当作为单一疗法给予以便诱导依赖于抗细胞凋亡 Bcl-2 家族成员功能的癌细胞中细胞凋亡，或当以与其它诱导细胞死亡的癌症治疗药或放疗的临时相关性给予以赋予癌细胞或支持

细胞对执行细胞凋亡程序敏感的比例高于仅用癌症治疗药或单独放疗治疗的动物细胞的相应比例时，抗细胞凋亡 Bcl-2 家族成员的抑制剂满足了对治疗多种类型癌症而言未得到满足的需求。

在本发明的某些实施方案中，使用治疗有效量的本发明化合物与抗癌剂或放射联合治疗动物在这类动物中产生了比用单独的化合物或抗癌药/放射更大的肿瘤反应和临床有益性。而另一方面，因为这些化合物降低所有表达抗细胞凋亡 Bcl-2 家族成员的细胞的细胞凋亡阈值，所以成功执行细胞凋亡程序作为对诱导细胞凋亡活性的抗癌药/放射的应答的细胞比例得到增加。或者，本发明的化合物可以用以使给予低剂量的抗癌剂和/或放疗以便产生与单独常规剂量的抗癌剂/放疗相同的肿瘤应答/临床有益性成为可能，且由此毒性较低且更可耐受。由于已知所有批准的抗癌药和放疗的剂量，本发明关注其与本发明化合物的不同组合。此外，由于本发明化合物至少可以部分通过抑制抗细胞凋亡 Bcl-2 家族成员起作用，所以癌细胞和支持细胞接触治疗有效量的化合物应临时与同时尝试细胞执行细胞凋亡程序作为对抗癌剂或放疗的应答结合。因此，在某些实施方案中，涉及某些临时相关性的本发明的组合物的给药提供了尤其有效的治疗实践。

本发明涉及用于抑制抗细胞凋亡 Bcl-2 家族成员活性和增加细胞对细胞凋亡诱导物的敏感性的化合物。在一个具体的实施方案中，所述的化合物具有式 I:



I

或其药学上可接受的盐或前体药物，其中:

E 为苯基或杂芳族基团;

X、Y 和 Z 独立为 H、OH、羧酸、酰胺、磺酸、磺酰胺、亚磺酸、亚磺酰胺（sulfinamide）、醛、磷酸、膦酰胺、烷基、烷氧基或芳基，

或 X 和 Y 或 Y 和 Z 之一形成杂环，并且 X、Y 和 Z 中至少一个为 OH、羧酸、酰胺、磺酸、磺酰胺、亚磺酸、亚磺酰胺、醛、磷酸或膦酰胺；

U 和 W 独立为 CO、SO、SO_2、$(CH_2)_n$、S、NH、NHCO、P、PO 或 PO_2；

n 为 0 或 1；

Q 为 H、烷基、链烯基、炔基或卤素；或

Q 与 U 和/或 W 形成环；

R_1 和 R_2 独立为氢、烷基、链烯基、炔基、环烷基、芳基、杂芳基、部分饱和的杂环、杂环；NR_3R_4、OR_3、SR_3 或 $CR_3R_4R_5$，其中的任意一个可以任选被取代；并且

R_3-R_5 独立为烷基、链烯基、炔基、环烷基、芳基、芳烷基、杂芳基、杂芳烷基、杂环或形成环，其中的任意一个可以任选被取代。

在一个实施方案中，X、Y 和 Z 中至少一个为 OH。

本发明涉及由式 I 表示的化合物，其为抗细胞凋亡 Bc1-2 家族成员的抑制剂。本发明涉及本发明的化合物在诱导细胞中细胞凋亡中的应用。本发明还涉及本发明化合物在使细胞对细胞凋亡诱导物敏感中的应用。这些化合物用于治疗、改善或预防作为诱导细胞凋亡性细胞死亡应答的病症，例如特征在于细胞凋亡的病症，包括过度增殖性疾病，诸如癌症。在某些实施方案中，这些化合物可以用于治疗、改善或预防特征在于对癌症疗法产生抗性的癌症(例如那些为化学抗性、放射抗性、激素抗性等的癌症)。在其它实施方案中，这些化合物可以用于治疗过度增殖性疾病，其特征在于抗细胞凋亡 Bc1-2 家族成员的超表达。

本发明提供了包含式 I 化合物的药物组合物，所述化合物的用量为诱导细胞中细胞凋亡或使细胞对细胞凋亡诱导物敏感的治疗有效量。

本发明进一步提供了包含式 I 的化合物和将该化合物对动物给药的技术说明书的试剂盒。所述的试剂盒可以任选含有其它治疗剂，例如抗癌剂、细胞凋亡调节剂。

本发明还提供了制备式 I 化合物的方法。

图/附图简述

附图 1 表示通过 NMR 分析的 TW-37 与 Bc1-2 的结合。

附图 2 表示作为对 TW-37 的应答的癌细胞中细胞生长的抑制。

附图 3 表示作为对几种化合物的应答的癌细胞中细胞生长的抑制。

附图 4 表示作为对 TW-37 的应答的 PC-3 细胞中细胞凋亡的诱导。

附图 5 表示作为对 TW-37 的应答的 PC-3 和 PrEC 细胞中天冬氨酸特异性半胱氨酸蛋白酶-3 的活化。

附图 6 表示 TW-37 在 MDA-231 细胞中对顺铂细胞毒性的强化。

附图 7 表示作为对 TW-37 应答的小鼠肿瘤生长的抑制。

附图 8 表示 TW-37、泰索帝和顺铂对小鼠体重的作用。

附图 9 表示作为对单独的 TW-37 和泰索帝和联合用药的应答的小鼠肿瘤生长的抑制。

附图 10 表示单独的 TW-37 和泰索帝和联合用药对小鼠体重的作用。

发明详述

本发明涉及由式 I 代表的化合物，它们作为抗细胞凋亡 Bc1-2 家族成员的抑制剂起作用。通过抑制抗细胞凋亡 Bc1-2 家族成员，这些化合物使细胞对细胞凋亡诱导物敏感，并且在某些情况中，它们自身诱导细胞凋亡。因此，本发明涉及使细胞对细胞凋亡诱导物敏感的方法并且涉及诱导细胞中细胞凋亡的方法，包含使所述的细胞接触单独的式 I 的化合物或其与细胞凋亡诱导物的组合。本发明进一步涉及治疗、改善或预防作为对细胞凋亡诱导有应答的动物障碍的方法，包含对该动物给予式 I 的化合物和细胞凋亡诱导物。这类障碍包括那些特征在于细胞凋亡失调的病症和特征在于抗细胞凋亡 Bc1-2 家族成员超表达的病症。

本文所用的术语"抗细胞凋亡 Bc1-2 家族成员"意旨任何已知的具

有抗细胞凋亡活性的 Bcl-2 家族成员的蛋白质，包括但不限于 Bcl-2、Bcl-xL、Mcl-1、A1/BFL-1、BOO-DIVA、Bcl-w、Bcl-6、Bcl-8 和 Bcl-y。

本文所用的术语"抗细胞凋亡 Bcl-2 家族成员的超表达"意旨编码抗细胞凋亡 Bcl-2 家族成员蛋白质的 mRNAs 的升高水平(例如异常水平)，和/或与表达基础水平的编码抗细胞凋亡 Bcl-2 家族成员蛋白质的 mRNAs 或具有基础水平的抗细胞凋亡 Bcl-2 家族成员蛋白质的类似的相应非病理性细胞相比，细胞中抗细胞凋亡 Bcl-2 家族成员蛋白质水平升高。用于检测细胞中编码抗细胞凋亡 Bcl-2 家族成员蛋白质的 mRNAs 水平或细胞中抗细胞凋亡 Bcl-2 家族成员蛋白质水平的方法包括但不限于使用抗细胞凋亡 Bcl-2 家族成员蛋白质抗体的蛋白质印迹、免疫组织化学法和核酸扩增或直接 RNA 检测方法。与细胞中抗细胞凋亡 Bcl-2 家族成员蛋白质的绝对水平同样重要的在于确定它们超表达抗细胞凋亡 Bcl-2 家族成员蛋白质，由此还在于这类细胞中抗细胞凋亡 Bcl-2 家族成员蛋白质与其它前-细胞凋亡信号传导分子(例如前-细胞凋亡 Bcl-2 家族蛋白质)的相对水平。当两者的平衡使得它们并非指的是抗细胞凋亡 Bcl-2 家族成员蛋白质的水平时，前-细胞凋亡信号传导分子可以足以使细胞执行细胞凋亡程序并且死亡，所述的细胞可以依赖于用于其存活的抗细胞凋亡 Bcl-2 家族成员蛋白质。在这类细胞中，接触抑制有效量的抗-细胞凋亡 Bcl-2 家族成员蛋白质抑制剂足以使细胞执行细胞凋亡程序和死亡。因此，术语"抗细胞凋亡 Bcl-2 家族成员蛋白质的超表达"还指前-细胞凋亡信号和抗-细胞凋亡信号的相对水平，从而导致细胞经历细胞凋亡作为对抑制抗细胞凋亡 Bcl-2 家族成员蛋白质的功能的化合物的抑制有效量的应答。

本文所用的术语"抗癌剂"和"抗癌药"意旨用于治疗过度增殖性疾病，诸如癌症(例如哺乳动物中)的任意治疗剂(例如化疗化合物和/或分子治疗化合物)、放疗或外科手术。

本文所用的术语"前体药物"意旨需要在靶生理系统内生物转化(例如自发或酶促)以释放或将前体药物转化(例如通过酶促、机械、电磁)成活性药物的母体"药物"的药理学上无活性的衍生物。设计前体药

物以便克服与稳定性、毒性、缺乏特异性或生物利用度有限相关的问题。典型的前体药物包含活性药物分子自身和化学掩蔽基团(例如可逆地抑制药物活性的基团)。某些优选的前体药物为带有在代谢条件下可裂解的基团的化合物的变化形式或衍生物。典型的前体药物当在生理条件下进行溶剂解或经历酶促降解或其它生化转化(例如磷酸化、氢化、脱氢化、糖基化)时变成药学上具有活性的。前体药物通常提供在哺乳动物生物体内溶解度、组织相容性或延缓释放方面的优势(例如,参见 Bundgard, Design of Prodrugs, pp. 7-9, 21-24, Elsevier, Amsterdam (1985); 和 Silverman, The Organic Chemistry of Drug Design and Drug Action, pp. 352-401, Academic Press, San Diego, CA (1992))。常用的前体药物包括酸衍生物-诸如通过母体酸与合适的醇(例如低级链烷醇)反应制备的酯类，通过母体酸化合物与胺反应制备的酰胺类,或碱性基团反应而形成酰化的碱衍生物(例如低级烷基酰胺)。

本文所用的术语"药学上可接受的盐"意旨在靶动物(例如哺乳动物)体内为生理学可耐受的本发明化合物的任意盐(例如通过与酸或碱反应获得)。本发明化合物的盐可以来源于无机或有机酸和碱。酸的实例包括但不限于盐酸、氢溴酸、硫酸、硝酸、高氯酸、富马酸、马来酸、磷酸、乙醇酸、乳酸、水杨酸、琥珀酸、甲苯-对-磺酸、酒石酸、乙酸、柠檬酸、甲磺酸、乙磺酸、甲酸、苯甲酸、丙二酸、磺酸、萘-2-磺酸、苯磺酸等。其它酸，诸如草酸，其自身尽管不是药学上可接受的，但是仍然可以制备用作获得本发明化合物及其药学上可接受的盐的中间体。

碱的实例包括但不限于碱金属(例如钠)氢氧化物、碱土金属(例如镁)氢氧化物、氨和式 NW_4^+ 的化合物，其中 W 为 C_{1-4} 烷基等。

盐的实例包括但不限于：乙酸盐、己二酸盐、藻酸盐、天冬氨酸盐、苯甲酸盐、苯磺酸盐、硫酸氢盐、丁酸盐、柠檬酸盐、樟脑酸盐、樟脑磺酸盐、环戊烷丙酸盐、二葡糖酸盐、十二烷基硫酸盐、乙磺酸盐、富马酸盐、氟庚酸盐（flucoheptanoate）、甘油磷酸盐、半硫酸

盐、庚酸盐、己酸盐、氯化物、溴化物、碘化物、2-羟基乙磺酸盐、乳酸盐、马来酸盐、甲磺酸盐、2-萘磺酸盐、烟酸盐、草酸盐、扑酸盐、果胶酸盐（pectinate）、过硫酸盐、苯基丙酸盐、苦味酸盐、特戊酸盐、丙酸盐、琥珀酸盐、酒石酸盐、硫氰酸盐、甲苯磺酸盐、十一酸盐等。盐的其它实例包括本发明化合物与合适的阳离子，诸如 Na^+、NH_4^+和 NW_4^+化合的阴离子(其中 W 为 C_{1-4}烷基)等。就治疗应用而言，关注本发明化合物的盐为药学上可接受的。然而，例如，非药学上可接受的酸和碱的盐也可以应用于制备或纯化药学上可接受的化合物。

本文所用的术语"治疗有效量"意旨足以使病症的一种或多种症状得到改善或预防障碍发展或使障碍退化的用量。例如，就治疗癌症而言，治疗有效量优选意旨降低肿瘤生长率，减小肿瘤块，减少转移灶的数量，延长肿瘤发展的时间，或将存活时间增加至少 5%，优选至少 10%，至少 15%，至少 20%，至少 25%，至少 30%，至少 35%，至少 40%，至少 45%，至少 50%，至少 55%，至少 60%，至少 65%，至少 70%，至少 75%，至少 80%，至少 85%，至少 90%，至少 95%或至少 100%。

本文所用的术语"致敏（sensitize）"和"致敏（sensitizing）"意旨通过给予第一种活性剂(例如式 I 的化合物)使动物或动物体内的细胞对第二种活性剂的生物作用(例如促进或阻止细胞功能方面，包括但不限于细胞生长、增殖、侵害、血管发生或细胞凋亡)更敏感或更具反应性。可以将第一种活性剂对靶细胞的致敏作用测定为在给予第二种活性剂与和不与第一种活性剂给药时观察到的预期生物作用的差异(例如促进或阻止细胞功能方面，包括但不限于细胞生长、增殖、侵害、血管发生或细胞凋亡)。致敏细胞的应答可以比在没有第一种活性剂存在下的应答增加至少 10%，至少 20%，至少 30%，至少 40%，至少 50%，至少 60%，至少 70%，至少 80%，至少 90%，至少 100%，至少 150%，至少 200%，至少 350%，至少 300%，至少 350%，至少 400%，至少 450%或至少 500%。

本文所用的术语"细胞凋亡失调"意旨细胞通过细胞凋亡发生细胞死亡的能力中的任何异常(例如遗传缺陷)。细胞凋亡失调与各种疾病

相关或由它们诱导，包括：例如自身免疫性疾病(例如系统性红斑狼疮、系统性红斑狼疮、移植物抗宿主病、重症肌无力或斯耶格伦综合征)；慢性炎症疾病(例如牛皮癣、哮喘或克罗恩病)；过度增殖性病症(例如肿瘤、B 细胞淋巴瘤或 T 细胞淋巴瘤)；病毒感染(例如疱疹、乳头状瘤或 HIV)；和其它病症，诸如骨关节炎和动脉粥样硬化。应注意，当所述的失调由病毒感染诱导或与之相关时，病毒感染可以在失调发生时检测到，也可能在失调发生时无法检测到或观察到。即病毒诱导的失调甚至在病毒感染症状消失后也可能发生。

本文所用的术语"过度增殖性疾病"意旨动物的局限性增殖细胞群不受正常生长的常规限制控制的任意疾病。过度增殖性病症的实例包括肿瘤、赘生物、淋巴瘤等。如果赘生物不发生侵害或转移，那么认为赘生物为良性的，并且如果赘生物发生上述情况中的任一种，那么认为赘生物为恶性的。"转移性"细胞意旨细胞可以侵入和破坏相邻身体结构。超常增生为涉及组织或器官中的细胞数量增加、而不会显著改变结构或功能的细胞增殖形式。组织转化为一种类型的完全分化的细胞取代另一种类型的分化细胞的受控细胞生长形式。

活化的淋巴样细胞的病理性生长通常导致自身免疫性疾病或慢性炎症病症。本文所用的术语"自身免疫性疾病"意旨生物体产生识别生物体自身分子、细胞或组织的抗体或免疫细胞的任何疾病。自身免疫性疾病的非限制性实例包括自身免疫性溶血性贫血、自身免疫性肝炎、贝格尔病或 IgA 肾病、口炎性腹泻（celiac sprue）、慢性疲劳综合征、克罗恩病、克罗恩病、皮肌炎、纤维肌痛、移植物对抗宿主疾病、格雷夫斯病、桥本甲状腺炎、特发性血小板减少性紫癜、扁平苔癣、多发性硬化、重症肌无力、牛皮癣、风湿热、风湿性关节炎、硬皮病、斯耶格伦综合征、系统性红斑狼疮、1 型糖尿病、溃疡性结肠炎、白癜风等。

本文所用的术语"肿瘤性疾病"意旨为良性(非-癌性)或恶性(癌性)的细胞的任何异常生长。

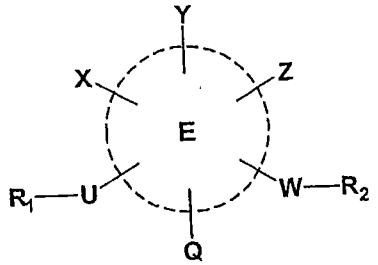
本文所用的术语"抗肿瘤药"意旨阻止靶向的(例如恶性)赘生物增

殖、生长或扩散的任意化合物。

本文所用的术语"预防（prevent）"、"预防（preventing）"和"预防（prevention）"意旨动物的病理性细胞(例如过度增殖或赘生性细胞)出现的降低。预防可以为完全的，例如使受试者的病理性细胞完全不存在。预防也可以为部分的，使得受试者的病理性细胞的出现率低于不使用本发明化合物时的出现率。

本文所用的术语"细胞凋亡调节剂"意旨涉及调节(例如抑制、减少、增加、促进)细胞凋亡的活性剂。细胞凋亡调节剂的实例包括包含死亡结构域的蛋白质，所述的死亡结构域诸如但不限于 Fas/CD95、TRAMP、TNF RI、DR1、DR2、DR3、DR4、DR5、DR6、FADD 和 RIP。细胞凋亡调节剂的其它实例包括但不限于 TNFα、Fas 配体、Fas/CD95 的抗体和其它 TNF 族受体、TRAIL、TRAILR1 或 TRAILR2 的抗体、Bcl-2、p53、BAX、BAD、Akt、CAD、PI3 激酶、PP1 和天冬氨酸特异性半胱氨酸蛋白酶蛋白质。调节剂广泛包括 TNF 族受体和 TNF 族配体的激动剂和拮抗剂。细胞凋亡调节剂可以为可溶性的或膜结合的(例如配体或受体)。优选的细胞凋亡调节剂为细胞凋亡诱导物，诸如 TNF 或 TNF-相关配体，特别是 TRAMP 配体、Fas/CD95 配体、TNFR-1 配体或 TRAIL。

本发明的抗细胞凋亡 Bcl-2 家族成员的抑制剂为通式 I 的化合物:



I

或其药学上可接受的盐或前体药物，其中:

E 为苯基或杂芳族基团;

X、Y 和 Z 独立为 H、OH、羧酸、酰胺、磺酸、磺酰胺、亚磺酸、亚磺酰胺、醛、磷酸、膦酰胺、烷基、烷氧基或芳基，或 X 和 Y 或 Y 和 Z 之一形成杂环，并且 X、Y 和 Z 中至少一个为 OH、羧酸、酰胺、磺酸、磺酰胺、亚磺酸、亚磺酰胺、醛、磷酸或膦酰胺;

U 和 W 独立为 CO、SO、SO_2、$(CH_2)_n$、S、NH、NHCO、P、PO 或 PO_2;

n为0或1；

Q为H、烷基、链烯基、炔基或卤素；或

Q与U和/或W形成环；

R_1和R_2独立为氢、烷基、链烯基、炔基、环烷基、芳基、杂芳基、部分饱和的杂环、杂环；NR_3R_4、OR_3、SR_3或$CR_3R_4R_5$，其中的任意一个可以任选被取代；并且

R_3-R_5独立为烷基、链烯基、炔基、环烷基、芳基、芳烷基、杂芳基、杂芳烷基、杂环或形成环，其中的任意一个可以任选被取代。

在一个实施方案中，X、Y和Z中的至少一个为OH。

有用的烷基包括直链或支链C_{1-18}烷基，尤其是甲基、乙基、丙基、异丙基、叔-丁基、仲-丁基、3-戊基、金刚烷基、降冰片基和3-己基。

有用的链烯基包括直链或支链C_{2-18}烷基，尤其是乙烯基、丙烯基、异丙烯基、丁烯基、异丁烯基和己烯基。

有用的炔基为C_{2-18}炔基，尤其是乙炔基、丙炔基、丁炔基和2-丁炔基。

有用的环烷基为C_{3-18}环烷基。典型的环烷基包括环丙基、环丁基、环戊基、环己基和环庚基。

有用的芳基包括C_{6-14}芳基，尤其是苯基、萘基、菲基、蒽基、茚基、䓛基、联苯、联苯烯基（biphenylenyl）和芴基。

有用的杂芳基包括噻吩基、苯并[b]噻吩基、萘并[2,3-b]噻吩基、噻蒽基、呋喃基、吡喃基、异苯并呋喃基、色烯基、呫吨基、吩呫吨基（phenoxantheneyl）、2H-吡咯基、吡咯基、咪唑基、吡唑基、吡啶基、吡嗪基、嘧啶基、哒嗪基、中氮茚基、异吲哚基、3H-吲哚基、吲哚基、吲唑基、嘌呤基、4H-喹嗪基、异喹啉基、喹啉基、酞嗪基（phthalzinyl）、萘啶基、喹唑啉基（quinozalinyl）、噌啉基、喋啶基、咔唑基、β-咔啉基、菲啶基、吖啶基、咱啶基、菲咯啉基、吩嗪基、异噻唑基、吩噻嗪基、异噁唑基、呋咱基、吩噁嗪基、1,4-二氢喹喔啉-2,3-二酮、7-氨基异香豆素、吡啶并[1,2-a]嘧啶-4-酮、1,2-苯并异噁唑-3-基、苯并咪唑基、2-羟吲哚基和2-氧代苯并咪唑基。如

果杂芳基在环上含有氮原子，那么这样的氮原子可以为N-氧化物形式，例如吡啶基N-氧化物、吡嗪基N-氧化物、嘧啶基N-氧化物等。

可选的取代基包括一个或多个烷基；卤素；卤代烷基；环烷基；任选被一个或多个低级烷基、低级烷氧基、亚甲二氧基、卤素、卤代烷基、氨基磺酰基、芳基或杂芳基取代的芳基；任选被一个或多个低级烷基、低级烷氧基、亚甲二氧基、卤素、卤代烷基、氨基磺酰基、芳基或杂芳基取代的芳氧基；任选被一个或多个低级烷基、低级烷氧基、亚甲二氧基、卤素、卤代烷基、氨基磺酰基、芳基或杂芳基取代的杂芳基；任选被一个或多个低级烷基、低级烷氧基、亚甲二氧基、卤素、卤代烷基、氨基磺酰基、芳基或杂芳基取代的杂芳氧基；烷氧基；烷硫基；芳硫基；酰氨基；氨基；氨基磺酰基；磺酰胺；任选被一个或多个低级烷基、低级烷氧基、亚甲二氧基、卤素、卤代烷基、氨基磺酰基、芳基或杂芳基取代的芳基磺酰基；酰氧基；任选被一个或多个低级烷基、低级烷氧基、亚甲二氧基、卤素、卤代烷基、氨基磺酰基、芳基或杂芳基取代的芳酰氧基；任选被一个或多个低级烷基、低级烷氧基、亚甲二氧基、卤素、卤代烷基、氨基磺酰基、芳基或杂芳基取代的二苯基膦氧基；任选被一个或多个低级烷基、低级烷氧基、亚甲二氧基、卤素、卤代烷基、氨基磺酰基、芳基、杂芳基、氨基酸取代的磺酰基或氨基酸衍生物取代的磺酰基及其低级烷基和芳烷基酯类取代的杂环；任选被一个或多个低级烷基、低级烷氧基、亚甲二氧基、卤素、卤代烷基、氨基磺酰基、芳基或杂芳基取代的杂环烷氧基；任选被一个或多个低级烷基、低级烷氧基、亚甲二氧基、卤素、卤代烷基、氨基磺酰基、芳基或杂芳基取代的部分不饱和的杂环烷基；或任选被一个或多个低级烷基、低级烷氧基、亚甲二氧基、卤素、卤代烷基、氨基磺酰基、芳基或杂芳基取代的部分不饱和的杂环烷氧基。

有用的氨基酸包括那些来源于D和L丙氨酸、缬氨酸、亮氨酸、异亮氨酸、脯氨酸、苯丙氨酸、色氨酸、甲硫氨酸、甘氨酸、丝氨酸、苏氨酸、半胱氨酸、酪氨酸、天冬酰胺、谷氨酰胺、天冬氨酸、谷氨酸、赖氨酸、精氨酸和组氨酸。氨基酸衍生物包括酰胺衍生物。

有用的饱和或部分饱和的碳环基为如上所述的环烷基以及环烯基，诸如环戊烯基、环庚烯基和环辛烯基。

有用的卤素（halo）或卤素（halogen）基团包括氟、氯、溴和碘。

有用的烷基芳基和烷基杂芳基包括被上述C_{6-14}芳基或杂芳基取代的任意上述的C_{1-18}烷基。有用的取值包括苄基、苯乙基和萘基甲基。

有用的卤代烷基包括被一个或多个氟、氯、溴或碘原子取代的C_{1-10}烷基，例如氟甲基、二氟甲基、三氟甲基、五氟乙基、1,1-二氟乙基、氯甲基、氯氟甲基和三氯甲基。

有用的烷氧基包括被上述C_{1-10}烷基之一取代的氧。

有用的烷硫基包括被上述C_{1-10}烷基之一取代的硫。还包括这类烷硫基的亚砜类和砜类。

有用的酰氨基包括羰基酰氨基(即与氨基结合的羰基)以及与氨基氮结合的任意可选取代的C_{1-6}酰基(烷酰基)，例如乙酰氨基，卤代乙酰氨基，诸如三氟乙酰氨基，丙酰氨基、丁酰氨基、戊酰氨基、己酰氨基以及芳基-取代的C_{2-6}取代的酰基。

有用的酰氧基为与氧(-O-)基结合的任意的C_{1-6}酰基(烷酰基)，例如甲酰氧基、乙酰氧基、丙酰氧基、丁酰氧基、戊酰氧基、己酰氧基等。

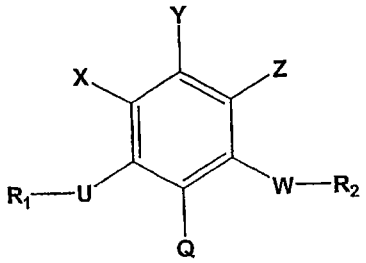
有用的芳酰氧基包括在任意上述酰氧基上取代的任意上述芳基，例如2,6-二氯苯甲酰氧基、2,6-二氟苯甲酰氧基和2,6-二-(三氟甲基)-苯甲酰氧基。

有用的氨基包括$-NH_2$、$-NHR_{11}$和$-NR_{11}R_{12}$，其中R_{11}和R_{12}为烷基、氨基烷基、任选取代的芳基、任选取代的芳基烷基或如上所述的环烷基，或其中R_{11}和R_{12}形成C_5-C_6杂环，诸如任选被氮上的杂芳基或酰基取代的哌啶基、吡咯烷基、吡嗪基或吗啉代。

有用的饱和或部分饱和的杂环基包括四氢呋喃基、吡喃基、哌啶基、吡咯烷基、咪唑烷基、咪唑啉基、二氢吲哚基、异二氢吲哚基、奎宁环基、吗啉基、异色满基、色满基、吡唑烷基、吡唑啉基、特窗酰基（tetronoyl）、tetramoyl或四氢异喹啉基。

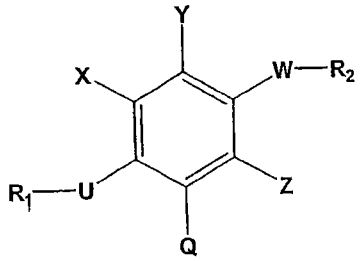
本发明化合物中的某些可以作为立体异构体存在，包括旋光异构体。本发明包括所有立体异构体和这类立体异构体的外消旋混合物以及可以按照本领域技术人员众所周知的方法分离的各个对映体。

在一个实施方案中，本发明的化合物具有式II，其中变量如上所述，并且X、Y和Z中的至少一个为OH。



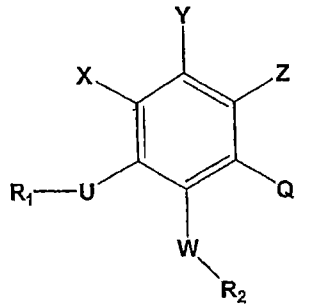
II

本发明的另一个实施方案为具有式III的化合物，其中变量如上所述，并且X、Y和Z中的至少一个为OH。



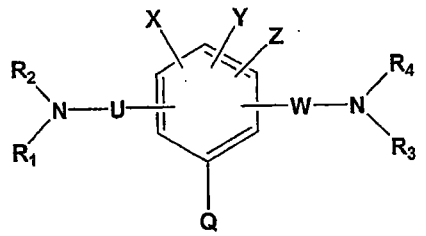
III

在一个实施方案中，本发明的化合物具有式IV，其中变量如上所述，并且X、Y和Z中的至少一个为OH。



IV

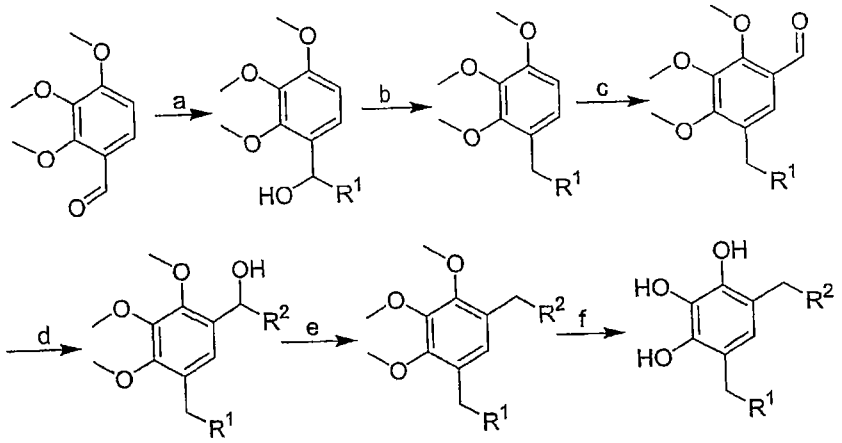
在一个实施方案中，本发明的化合物具有式V，其中变量如上所述，并且X、Y和Z中的至少一个为OH。



V

结合下列合成方案可以更好地理解本发明的化合物和方法，这些合成方案解释本发明的方法，通过这些方法可以制备本发明的化合物。原料可以获自商品来源或通过本领域技术人员公知的充分建立的文献中的方法制备。本领域技术人员显而易见的是可以通过在如下所示的合成中取代合适的试剂（reagent）和试剂（agents）合成上述定义的化合物。

方案1

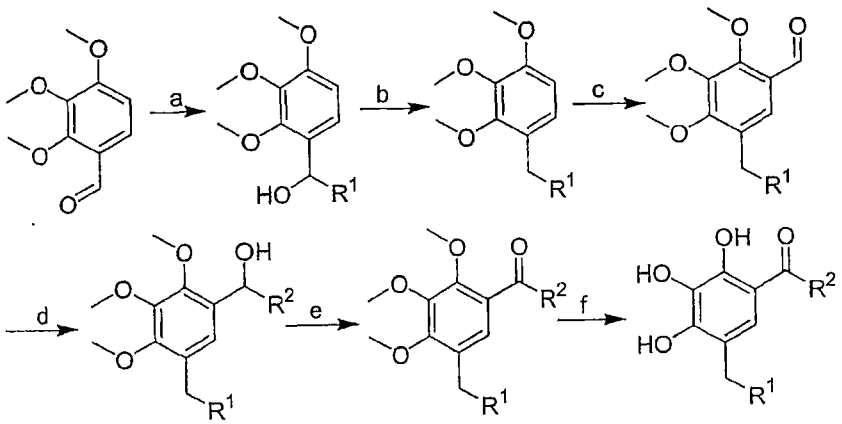


试剂和条件：a）锂，格利雅试剂，锌试剂等；b）Et_3SiH，TFA；c）ButLi，然后DMF；d）锂，格利雅试剂，锌试剂等；e）Et_3SiH，TFA；f）BBr_3，然后MeOH。

可以如方案1中所示合成多-取代的苯酚类似物。由商购的2,3,4-三甲氧基苯甲醛制备二取代的连苯三酚类似物。在醛与亲核格利雅试剂、锂或锌试剂之间的加成反应得到具有定量产率的仲醇。然后用在三氟乙酸溶剂中的三乙基硅烷除去羟基。在两步方案后，通过区域选

择性，经甲氧基的原位-诱导作用制备醛。通过重复相同的操作步骤引入仲烷基、芳基或杂芳基。通过(BBr_3)脱甲基化，用甲醇使反应停止获得终产物。基于用于中间体的保护基，氢化或酸性水解可有效除去苄基或甲氧基甲基。

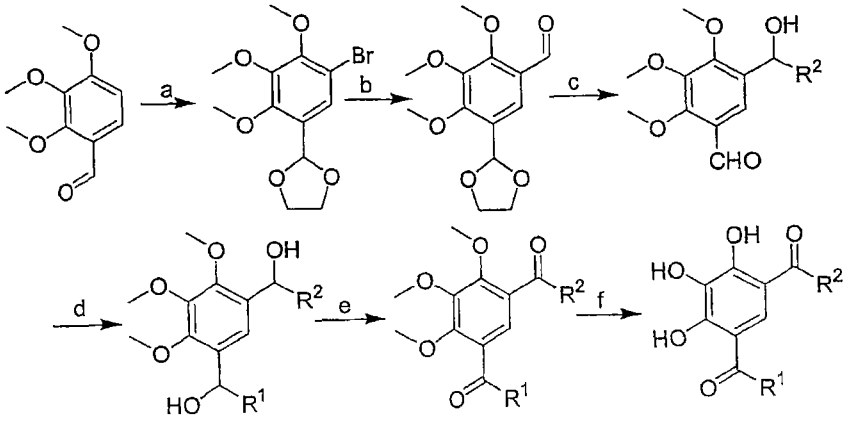
方案2



试剂和条件：a）锂，格利雅试剂，锌试剂等；b）Et_3SiH，TFA；c）ButLi，然后DMF；d）锂，格利雅试剂，锌试剂等；e）Dess-Martin Periodinane，DCM；f）BBr_3，然后MeOH。

方案2中所示的一-酮取代的苯酚类的合成主要与方案1的合成相同。然而，可以用一种经证实远比PCC有效的温和氧化剂Dess-Martin periodinane、用于这类化合物的活化的MnO_4将仲醇氧化成酮。将相同的保护基除去策略用于得到最终的酰化的苯酚类似物。

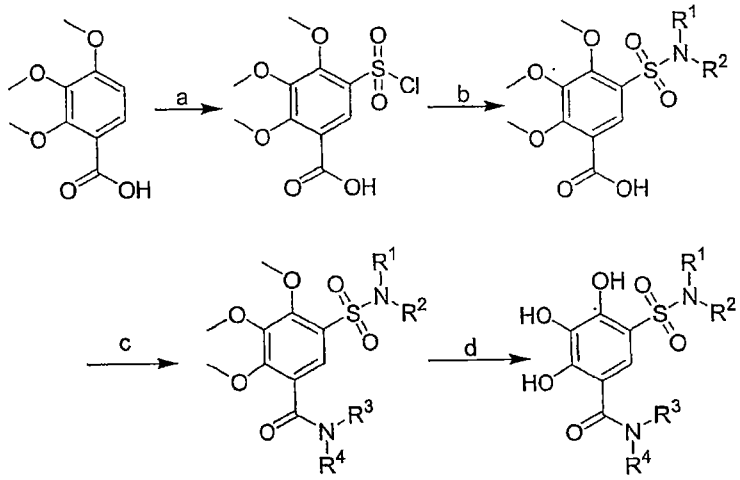
方案3



试剂和条件：a) 1. Br_2, AcOH; 2. TsOH, 乙二醇; b) ButLi, 然后DMF; c) 1. 锂, 格利雅试剂, 锌试剂等; 2. TsOH, 丙酮; d) 锂, 格利雅试剂, 锌试剂等; e) Dess-Martin Periodinane, DCM; f) BBr_3, 然后MeOH。

如方案3中所示，由简单的醛类制备二酰基取代的苯酚类。首先，用在乙酸中的溴经区域选择性溴化甲氧基苯甲醛。在将活性醛基转化成1,3-二氧戊环后，通过溴-金属交换反应引入仲醛基。通过与被保护的醛基之一的加成反应将第一种烷基或芳基引入分子。通过使用对-甲苯磺酸作为催化剂，极快地除去丙酮中的醛保护基(较长的反应时间将导致仲醇分解)。将两个醇基以中度产率氧化成二酮。通过使用BBr_3或HBr/HOAc，除去保护基而得到澄清的终产物。

方案4

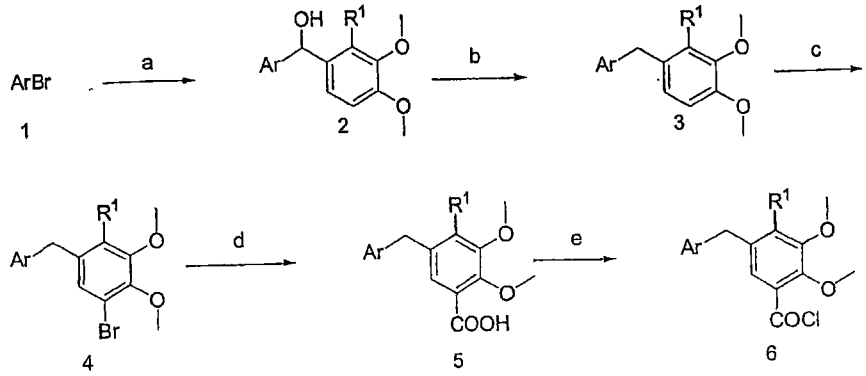


试剂和条件：a) 氯磺酸; b) NHR_1R_2, NEt_3; c) NHR_3R_4, EDCI, HOBt, NEt_3; d) BBr_3, 然后MeOH。

氨基磺酰基苯酚类的合成基于如方案4中所述的单纯酰胺偶联反应。使用商购的甲氧基苯甲酸，制备具有因来自甲氧基和羧基的位置效应而产生的极佳区域选择性的磺酰氯。通过将磺酰氯与胺在碱性条件下搅拌制备磺酰胺。通过进行传统的EDCI/HOBt偶联反应，获得酰胺。在两种酰胺碱形成反应中使用不同的胺类以便获得分子多样性。通过使用BBr_3或基于保护基特性的氢化获得最终的苯酚类。

可以使用下列方案合成本发明其它化合物。可以由酰氯和苯胺合成所述的化合物。方案V、VI和VII提供了合成各种酰氯的不同方法。

方案5



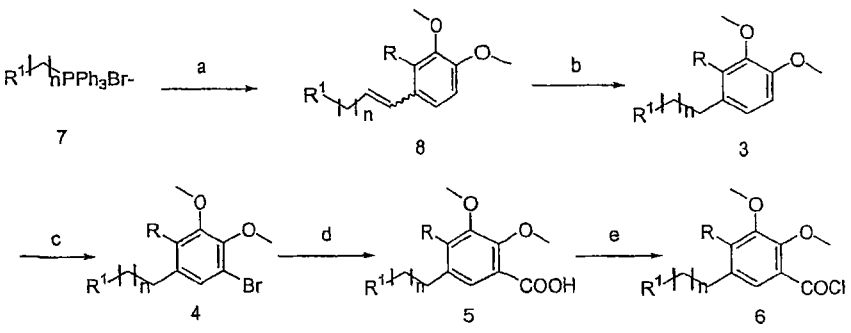
Ar: 芳基

R^1: 烷基

试剂和条件: a. n-buLi/-78℃/THF, 然后取代的苯醛; b. H_2/Pd-C/EtOAc; c. Br_2/-60℃/$CHCl_3$; d. n-buLi/-78℃/THF, 然后CO_2; e. $SOCl_2$/DMF (催化剂)/苯/70℃

方案5代表了使用一种或一种以上在5-位上的碳连接基合成酰氯的方法。可以在低温(-78℃)下用丁基锂将芳族溴转化成芳族锂。使锂试剂与商购的取代的苯醛反应而以高产率获得化合物2。在H_2气环境中和有Pd-C催化剂存在下除去2上的羟基得到3, 用Br_2将其溴化而得到4。该反应为区域选择性的。再使用丁基锂交换4上的溴而得到另一种锂试剂, 将其用干冰处理而得到酸5。使用DMF作为催化剂用在苯中的$SOCl_2$容易地将化合物5转化成酰氯。

方案6



R^1: 烷基、芳基,

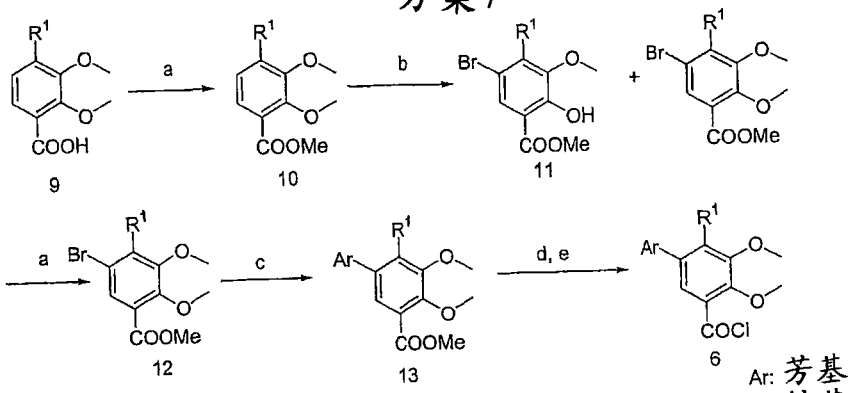
R: 甲氧基、H,

n = 0、1、2、3

试剂和条件：a. n-buLi/-78℃/THF，然后取代的苯醛；b. H_2/Pd-C/EtOAc；c. Br_2/-60℃/$CHCl_3$；d. n-buLi/-78℃/THF，然后CO_2；e. $SOCl_2$/DMF(催化剂)/苯/70℃

在方案6中，合成与方案5中相同，但原料为三苯基磷酸酯，使其通过维悌希反应与取代的苯醛反应而得到8。还原双键而得到3。

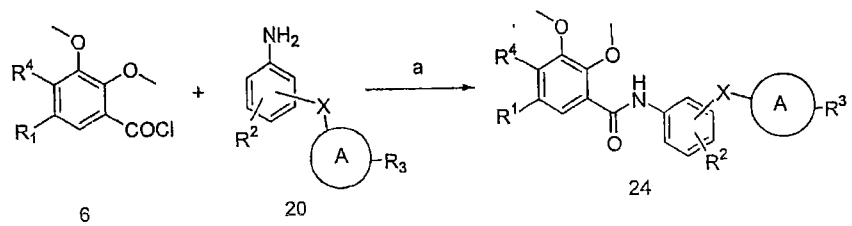
方案7

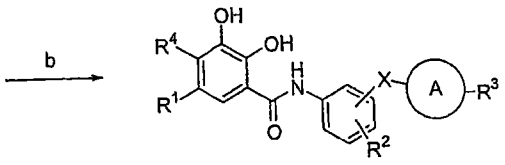


试剂和条件：a. H_2CO_3/CH_3I/DMF；b. Br_2/CH_2Cl_2/rt；c. $Pd(PPh_3)_4$ (10 mol %)/Na_2CO_3/DEG-H_2O/芳族硼酸/100℃；d. MeOH/KOH/H_2O/80℃；e. $SOCl_2$/DMF (催化剂)/苯/70℃

方案7披露了不使用在5-位上的碳连接基合成酰氯的方法。在两步骤中由商购的化合物9以高产率获得化合物12。可以通过甲基化将带有用溴化物除去的甲基而产生化合物11的任意化合物10转化成化合物12。可以将Suzuki偶联反应用于产生13。可以在MeOH/KOH系统中水解化合物13，且然后用$SOCl_2$酰化而以高产率得到酰氯。

方案8





25

R^1, R^2, R^3, R^4: 芳基、烷基;

A: 杂环、芳基;

X: 杂原子、砜、酰基

试剂和条件: a. 二异丙基乙胺(1.2. eq)/ CH_2Cl_2; b. $BBr_2/CH_2Cl_2/0℃$

在方案8中，在标准条件下使酰氯6与苯胺类20缩合，随后直接用BBr_3除去甲基保护基，得到最终的靶分子25。

本发明的重要方面在于式I的化合物诱导细胞凋亡并且还加强诱导细胞凋亡的能力作为对细胞凋亡诱导信号的应答。因此，关注这些化合物使细胞对细胞凋亡诱导物敏感，包括对这类诱导物产生抗性的细胞。本发明的抗细胞凋亡Bc1-2家族成员抑制剂可以用于诱导任何可通过诱导细胞凋亡治疗、改善或预防的病症中的细胞凋亡。因此，本发明提供了用于靶向特征为超表达抗细胞凋亡Bc1-2家族成员蛋白质的动物的组合物和方法。在这些实施方案中的某些中，细胞(例如癌细胞)表现出比非病理性样品(例如非-癌细胞)升高的抗细胞凋亡Bc1-2家族成员蛋白质表达水平。在其它实施方案中，细胞通过执行细胞凋亡程序和死亡作为对抑制剂有效量的式I化合物的应答而可操作地表现出升高的抗细胞凋亡Bc1-2家族成员蛋白质表达水平，所述的应答至少部分因这类细胞中对用于其存活的抗细胞凋亡Bc1-2家族成员蛋白质功能的依赖性而出现。

在另一个实施方案中，本发明涉及调节细胞凋亡相关状态，该状态与一种或多种细胞凋亡调节剂相关。细胞凋亡调节剂的实例包括但不限于Fas/CD95、TRAMP、TNF RI、DR1、DR2、DR3、DR4、DR5、DR6、FADD、RIP、TNFα、Fas配体、TRAIL、TRAILR1或TRAILR2的抗体、Bc1-2、p53、BAX、BAD、Akt、CAD、PI3激酶、PP1和天冬氨酸特异性半胱氨酸蛋白酶蛋白质。还包括涉及细胞凋亡的启动、决定和退化期的其它活

性剂。细胞凋亡调节剂的实例包括其活性、存在或浓度改变可以调节受试者细胞凋亡的药剂。优选的细胞凋亡调节剂为细胞凋亡诱导物，诸如TNF或TNF-相关配体，特别是TRAMP配体、Fas/CD95配体、TNFR-1配体或TRAIL。

在某些实施方案中，本发明的组合物和方法用于治疗动物(例如哺乳动物受试者，包括但不限于人和兽类动物)的患病细胞、组织、器官或病理情况和/或疾病状态。在这方面，对各种疾病和病理情况使用本发明的方法和组合物进行治疗或预防。这些疾病的非限制性典型清单中包括但不限于乳腺癌、前列腺癌、淋巴瘤、皮肤癌、胰腺癌、结肠癌、黑素瘤、恶性黑素瘤、卵巢癌、脑癌、原发性脑癌、头-颈癌、神经胶质瘤、成胶质细胞瘤、肝癌、膀胱癌、非-小细胞肺癌、头或颈癌、乳癌、卵巢癌、肺癌、小细胞肺癌、维尔姆斯肿瘤、宫颈癌、睾丸癌、膀胱癌、胰腺癌、胃癌、结肠癌、前列腺癌、泌尿生殖器癌、甲状腺癌、食道癌、骨髓瘤、多发性骨髓瘤、肾上腺癌、肾细胞癌、子宫内膜癌、肾上腺皮质癌、恶性胰脏胰岛素瘤、恶性类癌瘤癌、绒毛膜癌、蕈样霉菌病、恶性血钙过多、宫颈超常增生、白血病、急性淋巴细胞性白血病、慢性淋巴细胞性白血病、急性骨髓性白血病、慢性髓细胞性白血病、慢性粒细胞性白血病、急性粒细胞性白血病、毛细胞性白血病、神经母细胞瘤、横纹肌肉瘤、卡波西肉瘤、真性红细胞增多、原发性血小板增多、何杰金病、非何杰金淋巴瘤、软组织肉瘤、骨肉瘤、原发性巨球蛋白血症和视网膜成神经细胞瘤等、T和B细胞介导的自身免疫性疾病；炎性疾病；感染；过度增殖性疾病；AIDS；变性疾病、血管疾病等。在某些实施方案中，所治疗的癌细胞为转移性的。在其它实施方案中，所治疗的癌细胞对抗癌剂产生耐受性。

在某些实施方案中，适合于用本发明组合物和方法治疗的感染包括但不限于由病毒、细菌、真菌、支原体、阮病毒等导致的感染。

本发明的某些实施方案提供了给予有效量的式I化合物和至少一种额外的治疗剂(包括但不限于化疗抗肿瘤剂、细胞凋亡调节剂、抗微生物剂、抗病毒剂、抗真菌剂和抗炎剂)和/或治疗技术(例如外科手术

和/或放疗)的方法。

关注许多用于本发明方法的合适的抗癌剂。实际上，本发明关注但不限于给予大量的抗癌剂，诸如：诱导细胞凋亡的活性剂；多核苷酸(例如反义、核酶、siRNA)；多肽类(例如酶和抗体)；生物模拟物(例如棉酚或BH3模拟物)；与Bcl-2家族蛋白质，诸如Bax结合的活性剂(例如寡聚物或复合物)；生物碱类；烷化剂；抗肿瘤抗生素；抗代谢物；激素；铂化合物；单克隆或多克隆抗体(例如与抗癌药、毒素、防卫素缀合的抗体)、毒素；放射性核素；生物学反应修饰剂(例如干扰素(例如IFN-α)和白细胞介素(例如IL-2))；过继免疫治疗剂；造血生长因子；诱导肿瘤细胞分化的活性剂(例如全反式维甲酸)；基因疗法试剂(例如反义疗法试剂和核苷酸)；肿瘤疫苗；血管发生抑制剂；蛋白体抑制剂；NF-κB调节剂；抗-CDK化合物；HDAC抑制剂等。适合于与披露的化合物共同给予的化疗化合物和抗癌疗法为本领域技术人员公知的。

在优选的实施方案中，抗癌剂包括诱导或刺激细胞凋亡的活性剂。诱导细胞凋亡的活性剂包括但不限于：辐射(例如X-射线、γ射线、UV)；肿瘤坏死因子(TNF)-相关因子(例如TNF族受体蛋白、TNF族配体、TRAIL、TRAILR1或TRAILR2的抗体)；激酶抑制剂 (例如表皮生长因子受体(EGFR)激酶抑制剂、血管生长因子受体(VGFR)激酶抑制剂、成纤维细胞生长因子受体(FGFR)激酶抑制剂、血小板衍生的生长因子受体(PDGFR)激酶抑制剂，和Bcr-Abl激酶抑制剂(诸如GLEEVEC))；反义分子；抗体(例如HERCEPTIN、RITUXAN、ZEVALIN和AVASTIN)；抗雌激素药(例如雷洛昔芬和他莫昔芬)；抗雄激素药(例如氟他胺、比卡鲁胺，非那雄胺、氨鲁米特、酮康唑和皮质类固醇)；环加氧酶2(COX-2)抑制剂(例如塞来考昔、美洛昔康、NS-398和非类固醇抗炎药(NSAIDs))；抗炎药(例如保泰松、DECADRON、DELTASONE、地塞米松、dexamethasone intensol、DEXONE、HEXADROL、羟氯喹、METICORTEN、ORADEXON、ORASONE、羟基保泰松、PEDIAPRED、保泰松、PLAQUENIL、泼尼松龙、泼尼松、PRELONE和TANDEARIL)；和癌症化疗药(例如伊立替康

(CAMPTOSAR)、CPT-11、氟达拉滨(FLUDARA)、达卡巴嗪(DTIC)、地塞米松、米托蒽醌、MYLOTARG、VP-16、顺铂、卡铂、奥沙利铂、5-FU、多柔比星、吉西他滨、bortezomib、gefitinib、贝伐单抗、TAXOTERE或TAXOL)；细胞信号传导分子；神经酰胺类和细胞因子；星形孢菌素等。

在其它实施方案中，本发明的组合物和方法提供了式I的化合物和至少一种选自烷化剂、抗代谢物和天然产物(例如草药和其它植物和/或动物衍生的化合物)的抗增殖剂或抗肿瘤剂。

适用于本发明组合物和方法的烷化剂包括但不限于：1) 氮芥(例如氮芥、环磷酰胺、异环磷酰胺、美法仑(L-沙可来新)；和苯丁酸氮芥)；2) 氮丙啶类和甲基蜜胺类(例如六甲基蜜胺和塞替派)；3)磺酸烷基酯类(例如白消安)；4) 亚硝基脲类(例如卡莫司汀(BCNU)；洛莫司汀(CCNU)；司莫司汀(甲基-CCNU)；和链佐星(链脲霉素))；和5) 三氮烯类(例如达卡巴嗪(DTIC；二甲基三氮烯并咪唑甲酰胺)。

在某些实施方案中，适用于本发明组合物和方法的抗代谢物包括但不限于：1) 叶酸类似物(例如甲氨蝶呤（methotrexate）（甲氨蝶呤（amethopterin））)；2) 嘧啶类似物(例如氟尿嘧啶(5-氟尿嘧啶；5-FU)、氟尿嘧啶(氟脱氧尿苷；FudR)和阿糖胞苷（cytarabine）（阿糖胞苷（cytosine arabinoside））)；和3) 嘌呤类似物(例如巯嘌呤(6-巯嘌呤；6-MP)、硫鸟嘌呤(6-硫鸟嘌呤；TG)和喷司他丁（pentostatin）（2′-喷司他丁（deoxycoformycin））)。

在其它实施方案中，适用于本发明组合物和方法的化疗剂包括但不限于1) 长春花生物碱(例如长春碱(VLB)、长春新碱)；2)鬼臼毒素(例如依托泊苷和替尼泊苷)；3)抗生素(例如放线菌素D（dactinomycin）（放线菌素D（actinomycin D））、柔红霉素（daunorubicin）（柔红霉素（daunomycin）；柔红霉素（rubidomycin））、多柔比星、博来霉素、普卡霉素(plicamycin)（普卡霉素（mithramycin））和丝裂霉素(丝裂霉素C))；4) 酶(例如L-门冬酰胺酶)；5) 生物学反应修饰剂(例如干扰素-α)；6) 铂配位复合

物(例如顺铂(顺-DDP)和卡铂)；7)蒽醌类(例如米托蒽醌)；8) 取代的脲类(例如羟基脲)； 9) 甲基肼衍生物(例如丙卡巴肼(N-甲基肼；MIH))； 10) 肾上腺皮质抑制剂(例如米托坦(o,p′-DDD)和氨鲁米特)；11) 肾上腺皮质类固醇类(例如泼尼松)； 12) 黄体酮(例如己酸羟孕酮、醋酸甲羟孕酮和醋酸甲羟孕酮)； 13) 雌激素(例如己烯雌酚和乙炔雌二醇)； 14) 抗雌激素药(例如他莫昔芬)； 15) 雄激素(例如丙酸睾丸酮和氟甲睾酮)； 16) 抗雄激素药(例如抗雄激素)； 和17) 促性腺激素释放激素类似物(例如亮丙瑞林)。

常用于上下文中的癌症疗法的任意溶瘤剂（oncolytic agent）应用于本发明的组合物和方法。例如，美国食品与药品监督管理局维持了批准的溶瘤剂处方在美国的应用。U.S.F.D.A.的国际代理机构维持可相似的处方。表1中提供了批准在美国应用的典型抗肿瘤剂的清单。本领域技术人员可以理解所有美国批准的化疗剂上所需的"产品标签"描述了典型活性剂的批准的适应症、毒性数据等。

表1

阿地白介素 （去-丙氨酰基，丝氨酸-125人白细胞介素-2）		
阿仑单抗 （IgG1κ抗CD52抗体）		
阿利维A酸 （9-顺式-视黄酸）		
别嘌醇 （1,5-二氢-4H-吡唑并[3,4-d]嘧啶-4-酮一钠盐）		
六甲蜜胺 （N,N,N',N',N'',N''-六甲基-1,3,5-三嗪-2,4,6-三胺）	Hexalen	US Bioscience, West Conshohocken, PA
氨磷汀 （乙硫醇，2-[(3-氨基丙基)氨基]-，二氢磷酸盐(酯)）	Ethyol	US Bioscience
阿那曲唑 （1,3-苯二乙腈，a,a,a',a'-四甲基-5-(1H-1,2,4-三唑-1-基甲基)）	Arimidex	AstraZeneca Pharmaceuticals, LP, Wilmington, DE
三氧化二砷	Trisenox	Cell Therapeutic, Inc., Seattle, WA
门冬酰胺酶 （L-天冬酰胺酰氨基水解酶，EC-2型）	Elspar	Merck & Co., Inc., Whitehouse Station, NJ
活BCG （牛分支杆菌（Mycobacterium bovis）减毒菌株的冻干制品（卡介苗（Bacillus Calmette-Gukin）[BCG]，次代株Montreal））	TICE BCG	Organon Teknika, Corp., Durham, NC
贝沙罗汀胶囊 (4-[1-(5,6,7,8-四氢-3,5,5,8,8-五甲基-2-萘基)乙烯基]苯甲酸)	Targretin	Ligand Pharmaceuticals
贝沙罗汀凝胶	Targretin	Ligand Pharmaceuticals

博来霉素 （轮丝链霉菌（Streptomyces verticillus）产生的细胞毒性糖肽抗生素；博来霉素A_2和博来霉素B_2）	Blenoxane	Bristol-Myers Squibb Co., NY, NY
卡培他滨 (5’-脱氧-5-氟-N-[(戊氧基)羰基]-胞苷)	Xeloda	Roche
卡铂 (铂, 二胺[1, 1-环丁烷二羧酸(2-)0, 0’]-, (SP-4-2))	Paraplatin	Bristol-Myers Squibb
卡莫司汀 (1, 3-双(2-氯乙基)-1-亚硝基脲)	BCNU, BiCNU	Bristol-Myers Squibb
带有聚苯丙生20的卡莫司汀植入物	Gliadel Wafer	Guilford Pharmaceuticals, Inc., Baltimore, MD
塞来考昔 （作为4-[5-(4-甲基苯基)-3-(三氟甲基)-1H-吡唑-1-基]苯磺酰胺）	Celebrex	Searle Pharmaceuticals, England
苯丁酸氮芥 （4-[双(2氯乙基)氨基]苯丁酸）	Leukeran	GlaxoSmithKline
顺铂 （$PtCl_2H_6N_2$）	Platinol	Bristol-Myers Squibb
克拉屈滨 （2-氯-2’-脱氧-b-D-腺苷）	Leustatin, 2-CdA	R. W. Johnson Pharmaceutical Research Institute, Raritan, NJ
环磷酰胺 （2-[双(2-氯乙基)氨基]四氢-2H-13, 2-氧杂氮杂磷杂环己二烯（oxazaphosphorine）2-氧化物一水合物）	Cytoxan, Neosar	Bristol-Myers Squibb
阿糖胞苷 （1-b-D-阿糖呋喃糖基胞嘧啶，$C_9H_{13}N_3O_5$）	Cytosar-U	Pharmacia & Upjohn Company
阿糖胞苷脂质体	DepoCyt	Skye Pharmaceuticals, Inc., San Diego, CA

达卡巴嗪 (5-(3,3-二甲基-1-三氮烯基)-咪唑-4-甲酰胺(DTIC))	DTIC-Dome	Bayer AG,Leverkusen, Germany
放线菌素D (Dactinomycin), 放线菌素D (actinomycin D) (微小链霉菌(Streptomyces parvullus)产生的放线菌素D, $C_{62}H_{86}N_{12}O_{16}$)	Cosmegen	Merck
Darbepoetin α (重组肽)	Aranesp	Amgen,Inc.,Thousand Oaks,CA
柔红霉素脂质体 ((8S-顺式)-8-乙酰基-10-[(3-氨基-2,3,6-三脱氧-á-L-来苏-己吡喃糖基)氧基]-7,8,9,10-四氢-6,8,11-三羟基-甲氧基-5,12-萘二酮盐酸盐	DanuoXome	Nexstar Pharmaceuticals,Inc.,Boulder,CO
柔红霉素HCl, 柔红霉素((1S,3S)-3-乙酰基-1,2,3,4,6,11-六氢-3,5,12-三羟基-10-甲氧基-6,11-二氧代-1-萘基3-氨基-2,3,6-三脱氧-(α)-L-来苏-己吡喃糖苷盐酸盐)	Cerubidine	Wyeth Ayerst,Madison,NJ
地尼白介素-毒素连接物 (重组肽)	Ontak.	Seragen,Inc.,Hopkinton,MA
右雷佐生 ((S)-4,4' -(1-甲基-1,2-乙二基)双-2,6-哌嗪二酮)	Zinecard	Pharmacia & Upjohn Company
多西他赛 ((2R,3R)-N-羧基-3-苯基异丝氨酸,N-叔丁酯,13-酯与5b-20-环氧-12a,4,7b,10b,13a-六羟基紫杉(tax)-11-烯-9-酮4-乙酸酯2-苯甲酸酯,三水合物)	Taxotere	Aventis Pharmaceuticals,Inc., Bridgewater,NJ
多柔比星HCl (8S,10S)-10-[(3-氨基-2,3,6-三脱氧-a-L-来苏-己吡喃糖基)氧基]-8-乙醇酰基-7,8,9,10-四氢-6,8,11-三羟基-1-甲氧基-5,12-萘二酮盐酸盐)	Adriamycin, Rubex	Pharmacia & Upjohn Company

多柔比星	Adriamycin PFS Intravenous injection	Pharmacia & Upjohn Company
多柔比星脂质体	Doxil	Sequus Pharmaceuticals, Inc., Menlo Park, CA
丙酸屈他雄酮 (17b-羟基-2a-甲基-5a-雄甾烷-3-酮丙酸盐)	Dromostanol one	Eli Lilly & Company, Indianapolis, IN
	Masterone injection	Syntex, Corp., Palo Alto, CA
Elliott' s B 溶液	Elliott's B Solution	Orphan Medical, Inc
表柔比星 ((8S-顺式)-10-[(3-氨基-2, 3, 6-三脱氧-a-L-阿糖-己吡喃糖基)氧基]-8-乙醇酰基-7, 8, 9, 10-四氢-6, 8, 11-三羟基-8-(羟乙酰基)-1-甲氧基-5, 12-萘二酮盐酸盐)	Ellence	Pharmacia & Upjohn Company
红细胞生成素α (重组肽)	Epogen	Amgen, Inc
雌莫司汀 (雌-1, 3, 5(10)-三烯-3, 17-二醇(17(β))-, 3-[双(2-氯乙基)氨基甲酸酯]17-(二氢磷酸), 二钠盐, 一水合物, 或雌二醇3-[双(2-氯乙基)氨基甲酸酯]17-(二氢磷酸酯), 二钠盐, 一水合物)	Emcyt	Pharmacia & Upjohn Company
磷酸依托泊苷 (4' - 脱甲基表鬼臼毒素9-[4, 6-O-(R)-亚乙基-(β)-D-吡喃葡糖苷], 4' -(二氢磷酸酯))	Etopophos	Bristol-Myers Squibb
依托泊苷, VP-16 (4' - 脱甲基表鬼臼毒素9-[4, 6-O-(R)-亚乙基-(β)-D-吡喃葡糖苷]	Vepesid	Bristol-Myers Squibb

依西美坦 (6-亚甲基雄甾-1,4-二烯-3,17-二酮)	Aromasin	Pharmacia & Upjohn Company
非格司亭 (r-metHuG-CSF)	Neupogen	Amgen, Inc
氟尿嘧啶脱氧核苷(动脉内) (2'-脱氧-5-氟尿苷)	FUDR	Roche
氟达拉滨 (抗病毒剂阿糖腺苷的氟化核苷酸类似物,9-b-D-阿糖呋喃糖基腺嘌呤(ara-A))	Fludara	Berlex Laboratories, Inc., Cedar Knolls, NJ
氟尿嘧啶, 5-FU (5-氟-2,4-(1H,3H)-嘧啶二酮)	Adrucil	ICN Pharmaceuticals, Inc., Humacao, Puerto Rico
氟维司群 (7-α-[9-(4,4,5,5,5-五氟戊基亚磺酰基)壬基]雌甾-1,3,5-(10)-三烯-3,17-β-二醇)	Faslodex	IPR Pharmaceuticals, Guayama, Puerto Rico
吉西他滨 (2'-脱氧-2',2'-二氟胞苷一盐酸盐(b-异构体))	Gemzar	Eli Lilly
吉姆单抗 奥佐米星 (抗-CD33 hP67.6)	Mylotarg	Wyeth Ayerst
醋酸戈舍瑞林 ([D-Ser(But)^{6},Azgly^{10}]LHRH; pyro-Glu-His-Trp-Ser-Tyr-D-Ser(But)-Leu-Arg-Pro-Azgly-NH2乙酸盐 $[C_{59}H_{84}N_{18}O_{14} \cdot (C_2H_4O_2)_x$	Zoladex Implant	AstraZeneca Pharmaceuticals
羟基脲	Hydrea	Bristol-Myers Squibb

替伊莫单抗 (由单克隆抗体Ibrimomab和连接物-螯合物tixetan[N-[2-双(羧甲基)氨基]-3-(对-异硫氰酸根合苯基)-丙基]-[N-[2-双(羧甲基)氨基]-2-(甲基)-乙基]甘氨酸)之间的硫脲共价键导致的免疫缀合物	Zevalin	Biogen IDEC, Inc., Cambridge MA
伊达比星 (5,12-萘二酮,9-乙酰基-7-[(3-氨基-2,3,6-三脱氧-(α)-L-来苏-己吡喃糖基)氧基]-7,8,9,10-四氢-6,9,11-三羟基盐酸盐,(7S-顺式))	Idamycin	Pharmacia & Upjohn Company
异环磷酰胺 (3-(2-氯乙基)-2-[(2-氯乙基)氨基]四氢-2H-1,3,2-氧杂氮杂磷杂环己二烯2-氧化物)	IFEX	Bristol-Myers Squibb
甲磺酸伊马替尼 (4-[(4-甲基-1-哌嗪基)甲基]-N-[4-甲基-3-[[4-(3-吡啶基)-2-嘧啶基]氨基]-苯基]苯甲酰胺甲磺酸盐)	Gleevec	Novartis AG, Basel, Switzerland
干扰素α-2a (重组肽)	Roferon-A	Hoffmann-La Roche, Inc., Nutley, NJ
干扰素α-2b (重组肽)	Intron A (Lyophilized Betaseron)	Schering AG, Berlin, Germany
伊立替康 HCl ((4S)-4,11-二乙基-4-羟基-9-[(4-哌啶子基哌啶子基)羰基氧基]-1H-吡喃并[3',4':6,7]中氮茚并[1,2-b]喹啉-3,14(4H,12H)二酮盐酸盐三水合物)	Camptosar	Pharmacia & Upjohn Company
来曲唑 (4,4'-(1H-1,2,4-三唑-1-基亚甲基)二苄腈)	Femara	Novartis

亚叶酸钙 (L-谷氨酸,N[4[[(2氨基-5-甲酰基-1,4,5,6,7,8六氢4氧代6-蝶啶基)甲基]氨基]苯甲酰基),钙盐(1:1))	Wellcovorin, Leucovorin	Immunex,Corp.,Seattle, WA
左旋咪唑HCl ((-)-(S)-2,3,5,6-四氢-6-苯基咪唑并[2,1-b]噻唑一盐酸盐$C_{11}H_{12}N_2S \cdot HCl$)	Ergamisol	Janssen Research Foundation, Titusville,NJ
洛莫司汀 (1-(2-氯-N-(2-氯乙基)-3-环己基-1-亚硝基脲	CeeNU	Bristol-Myers Squibb
Meclorethamine, 氮芥 (2-氯-N-(2-氯乙基)-N-甲基乙胺盐酸盐)	Mustargen	Merck
醋酸甲地孕酮 17α(乙酰氧基)-6-甲基孕甾-4,6-二烯-3,20-二酮	Megace	Bristol-Myers Squibb
美法仑,L-PAM (4-[双(2-氯乙基)氨基]-L-苯丙氨酸)	Alkeran	GlaxoSmithKline
巯嘌呤,6-MP (1,7-二氢-6H-嘌呤-6-硫酮一水合物)	Purinethol	GlaxoSmithKline
美司钠 (2-巯基乙烷磺酸钠)	Mesnex	Asta Medica
甲氨蝶呤 (N-[4-[[(2,4-二氨基-6-蝶啶基]甲基]甲氨基]苯甲酰基)-L-谷氨酸)	Methotrexate	Lederle Laboratories
甲氧沙林 (9-甲氧基-7H-呋喃并[3,2-g]-苯并吡喃-7-酮)	Uvadex	Therakos,Inc., Way Exton,Pa
丝裂霉素C	Mutamycin	Bristol-Myers Squibb
丝裂霉素C	Mitozytrex	SuperGen, Inc.,Dublin,CA
米托坦 (1,1-二氯-2-(邻-氯苯基)-2-(对-氯苯基)乙烷)	Lysodren	Bristol-Myers Squibb

米托蒽醌 (1,4-二羟基-5,8-双[[2-[(2-羟乙基)氨基]乙基)氨基]-9,10-蒽二酮二盐酸盐)	Novantrone	Immunex Corporation
苯丙酸诺龙	Durabolin-50	Organon, Inc., West Orange, NJ
若莫单抗	Verluma	Boehringer Ingelheim Pharma KG, Germany
奥普瑞白介素 (IL-11)	Neumega	Genetics Institute, Inc., Alexandria, VA
奥沙利铂 (顺式-[(1R,2R)-1,2-环己烷二胺-N,N'][草酸(2-)-O,O']铂)	Eloxatin	Sanofi Synthelabo, Inc., NY, NY
紫杉醇 (5β,20-环氧-1,2a,4,7β,10β,13a-六羟基紫杉-11-烯-9-酮4,10-二乙酸酯2-苯甲酸酯13-酯与(2R,3R)-N-苯甲酰基-3-苯基异丝氨酸)	TAXOL	Bristol-Myers Squibb
氨羟二磷酸二钠 (磷酸(3-氨基-1-羟基亚丙基)双-,二钠盐五水合物,(APD))	Aredia	Novartis
培加酶 ((一甲氧基聚乙二醇琥珀酰亚胺基)11-17-腺苷脱氨酶)	Adagen (Pegademase Bovine	Enzon Pharmaceuticals, Inc., Bridgewater, NJ
培门冬酶 (一甲氧基聚乙二醇琥珀酰亚胺基L-门冬酰胺酶)	Oncaspar	Enzon
Pegfilgrastim (重组甲硫氨酰基人G-CSF(非格司亭)和一甲氧基聚乙二醇的共价缀合物)	Neulasta	Amgen, Inc
喷司他丁	Nipent	Parke-Davis Pharmaceutical Co., Rockville, MD
哌泊溴烷	Vercyte	Abbott Laboratories, Abbott Park, IL

普卡霉素(Plicamycin)，普卡霉素(mithramycin) (由褶链霉菌(Streptomyces plicatus)产生的抗生素)	Mithracin	Pfizer, Inc., NY, NY
卟吩姆钠	Photofrin	QLT Phototherapeutics, Inc., Vancouver, Canada
丙卡巴肼 (N-异丙基-μ-(2-甲基肼基)-对-甲苯酰胺一盐酸盐)	Matulane	Sigma Tau Pharmaceuticals, Inc., Gaithersburg, MD
米帕林 (6-氯-9-(1-甲基-4-二乙基-胺)丁氨基-2-甲氧基吖啶	Atabrine	Abbott Labs
拉布立酶 (重组肽)	Elitek	Sanofi-Synthelabo, Inc.,
美罗华 (重组抗-CD20抗体)	Rituxan	Genentech, Inc., South San Francisco, CA
沙格莫汀 (重组肽)	Prokine	Immunex Corp
链佐星 (链佐星2-脱氧-2-[[(甲基亚硝基氨基]羰基]氨基)-a(和 b)-D-吡喃葡糖和220mg无水柠檬酸	Zanosar	Pharmacia & Upjohn Company
滑石粉 ($Mg_3Si_4O_{10}(OH)_2$)	Sclerosol	Bryan, Corp., Woburn, MA
他莫昔芬 ((Z)2-[4-(1,2-二苯基-1-丁烯基)苯氧基]-N,N-二甲基乙胺 2-羟基-1,2,3-丙烷三羧酸酯(1:1))	Nolvadex	AstraZeneca Pharmaceuticals
替莫唑胺 (3,4-二氢-3-甲基-4-氧代咪唑并[5,1-d]-as-四嗪-8-甲酰 胺)	Temodar	Schering
替尼泊苷,VM-26 (4'-脱甲基表鬼臼毒素9-[4,6-O-(R)-2-噻吩亚甲基-(β)-D- 吡喃葡糖苷])	Vumon	Bristol-Myers Squibb

睾内酯 (13-羟基-3-氧代-13,17-裂雄甾-1,4-二烯-17-酸[dgr]-内酯	Teslac	Bristol-Myers Squibb
硫鸟嘌呤,6-TG (2-氨基-1,7-二氢-6H-嘌呤-6-硫酮)	Thioguanine	GlaxoSmithKline
塞替派 (氮丙啶,1,1',1''-膦基硫酰基次基三,或三(1-氮丙啶基)膦硫化物)	Thioplex	Immunex Corporation
托泊替康 HCl ((S)-10-[(二甲氨基)甲基]-4-乙基-4,9-二羟基-1H-吡喃并[3',4':6,7]中氮茚并[1,2-b]喹啉-3,14-(4H,12H)-二酮一盐酸盐)	Hycamtin	GlaxoSmithKline
托瑞米芬 (2-(对-[(Z)-4-氯-1,2-二苯基-1-丁烯基]-苯氧基)-N,N-二甲基乙胺柠檬酸盐(1:1))	Fareston	Roberts Pharmaceutical Corp.,Eatontown,NJ
托西莫单抗,I 131托西莫单抗 (重组鼠免疫治疗性单克隆$IgG_{2a}\lambda$抗-CD20抗体(I 131为放射性免疫治疗抗体))	Bexxar	Corixa Corp.,Seattle, WA
曲妥单抗 (重组单克隆$IgG_1\kappa$抗-HER2抗体)	Herceptin	Genentech,Inc
维A酸,ATRA (全反式维A酸)	Vesanoid	Roche
乌拉莫司汀	Uracil Mustard Capsules	Roberts Labs

戊柔比星,N-三氟乙酰基阿霉素-14-戊酸酯 ((2S-顺式)-2-[1,2,3,4,6,11]-六氢-2,5-12-三羟基-7甲氧基-6,11-二氧代-[[42,3,6-三脱氧-3-[(三氟乙酰基)-氨基-α-L-来苏-己吡喃糖基]氧基]-2-萘基]-2-氧代乙基戊酸酯	Valstar	Anthra→Medeva
长春碱，长春新碱 ($C_{46}H_{56}N_4O_{10} \cdot H_2SO_4$)	Velban	Eli Lilly
长春新碱 ($C_{46}H_{56}N_4O_{10} \cdot H_2SO_4$)	Oncovin	Eli Lilly
长春瑞滨 (3',4'-双脱氢-4'-脱氧-C'-去甲长春碱[R-(R*,R*)-2,3-二羟基丁二酸酯(1:2)(盐)])	Navelbine	GlaxoSmithKline
唑来膦酸盐，唑来膦酸 ((1-羟基-2-咪唑-1-基-膦酰基乙基)膦酸一水合物)	Zometa	Novartis

用于与本发明化合物一起给药的优选常用抗癌剂包括但不限于多柔比星、5-氟尿嘧啶、依托泊苷、喜树碱、放线菌素D、丝裂霉素C、顺铂、多西他赛、吉西他滨、卡铂、奥沙利铂、bortezomib、gefitinib和贝伐单抗。可以制备这些活性剂并且单独、在合并的治疗组合物中、在试剂盒中或与免疫治疗剂等联合使用。

为了更详细描述抗癌剂和其它治疗剂，本领域技术人员查阅了许多说明性的手册，包括但不限于Physician's Desk Reference和Goodman和Gilman的"Pharmaceutical Basis of Therapeutics" tenth edition, Eds. Hardman等，2002。

本发明提供了给予式I的化合物与放疗的方法。本发明并不限于用于给动物递送治疗放射剂量的类型、用量或递送和给药系统。例如，动物接受光子放疗、粒子束放疗、其它类型的放疗及其组合。在某些实施方案中，使用线性加速器将射线递送给动物。在其它实施方案中，使用γ刀递送射线

辐射源可以在动物的外部或内部。外部放射治疗最常用并且包括使用，例如线性加速器使高能辐射束定向于肿瘤部位。尽管射线束定位于肿瘤部位，但是几乎不可能避免接触正常的健康组织。然而，外部照射通常被患者充分耐受。内照射疗法包括将发射射线源，诸如珠、金属线、小丸、囊、颗粒等植入体内肿瘤部位或接近肿瘤部位，包括使用特异性靶向癌细胞的递送系统(例如使用与癌细胞结合配体结合的颗粒)。这类植入物可以在治疗后被除去或以无活性的方式保留在体内。内照射疗法的类型包括但不限于近距离辐射疗法、组织内照射、腔内照射、放射免疫疗法等。

动物可以任选接受放射致敏剂(例如甲硝唑、米索硝唑、动脉内溴苷、静脉内碘苷(IudR)、硝基咪唑、5-取代的-4-硝基咪唑类、2H-异吲哚二酮类、[[(2-溴乙基)-氨基]甲基]-硝基-1H-咪唑-1-乙醇、硝基苯胺衍生物、DNA-亲和性低氧选择性细胞毒素、卤化DNA配体、1,2,4 苯并三嗪氧化物、2-硝基咪唑衍生物、含氟的硝基吡咯衍生物、苯甲酰胺、烟酰胺、吖啶-嵌入剂、5-硫代四唑衍生物、3-硝基-1,2,4-三唑、

4,5-二硝基咪唑衍生物、羟化texaphrins、顺铂、丝裂霉素、tiripazamine、亚硝脲、巯嘌呤、甲氨蝶呤、氟尿嘧啶、博来霉素、长春新碱、卡铂、表柔比星、多柔比星、环磷酰胺、长春地辛、依托泊苷、紫杉醇、热(体温过高)等)、辐射防护剂(例如巯乙胺、氨基烷基二氢硫代磷酸酯、氨磷汀(WR 2721)、IL-I、IL-6等)。放射致敏剂促进杀伤肿瘤细胞。辐射防护剂保护健康组织受到辐射有害作用的侵害。

可以对患者给予任意类型的辐射,只要患者可以耐受该辐射剂量,而没有不可接受的不良副作用。放疗的合适类型包括:例如电离(电磁)放疗(例如X-射线或γ射线)或粒子束放疗(例如高线能量辐射)。将电离辐射定义为包含粒子或光子的辐射,所述的粒子或光子具有产生电离、即获得或失去电子的足够能量(例如,如美国专利US 5,770,581中所述,将该文献完整地引入本文作为参考)。辐射作用至少部分可以受到临床医师的控制。优选将辐射剂量分次,以便达到最大的靶细胞暴露并且降低毒性。

对动物给予的辐射总剂量优选约为.01戈瑞(Gy)-约100 Gy。更优选在治疗过程中给予约10 Gy-约65 Gy(例如约15 Gy,20 Gy,25 Gy,30 Gy,35 Gy,40 Gy,45 Gy,50 Gy,55 Gy或60 Gy)。尽管在某些实施方案中,可以在1天过程中给予完全的辐射剂量,但是理想的是将总剂量分次并且在几天内给予。理想的情况是,在至少约3天过程中给予放疗,例如至少5,7,10,14,17,21,25,28,32,35,38,42,46,52或56天(约1-8周)。因此,每日辐射剂量包含约1-5 Gy(例如约1 Gy,1.5 Gy,1.8 Gy,2 Gy,2.5 Gy,2.8 Gy,3 Gy,3.2 Gy,3.5 Gy,3.8 Gy,4 Gy,4.2 Gy或4.5 Gy),优选1-2 Gy(例如1.5-2 Gy)。每日辐射剂量应足以诱导对靶向的细胞破坏。如果在一段时间期限内拉长,那么不一定每天给予放疗,由此使动物休息并且使疗法的作用实现。例如,对每周治疗而言,理想的是在连续5天时给予辐射,但在2天内不给予,由此使每周有2天的休息。然而,可以根据动物反应性和任何潜在副作用的不同将辐射给予1 天/周,2天/周,3天/周,4天/

周，5天/周，6天/周或所有7天/周。可以在治疗期的任意时间时开始放疗。优选在第1周或第2周时开始放疗，并且给予治疗期的剩余期限。例如，在第1-6周或在第2-6周的治疗期中给予辐射，以便治疗例如实体瘤。或者，在包含5周的第1-5周或2-5周治疗期中给予辐射。不过，这些典型的放疗给予方案并不用来限度本发明。

抗微生物治疗剂也可以用作本发明中的治疗剂。可以使用可杀伤、抑制乃至减弱微生物生物体功能的任意活性剂，以及关注具有这类活性的任意活性剂。抗微生物剂包括但不限于天然和合成的抗生素、抗体、抑制性蛋白质(例如防卫素)、反义核酸、膜破坏剂等，可以将它们单独或联合使用。实际上，可以使用任意类型的抗生素，包括但不限于抗菌剂、抗病毒剂、抗真菌剂等。

在本发明的某些实施方案中，在下列条件中的一种或多种下对动物给予式I的化合物和一种或多种治疗剂或抗癌剂：以不同的周期性，以不同的期限，以不同的浓度，以不同的给药途径等。在某些实施方案中，在给予治疗或抗癌剂前，例如在给予治疗或抗癌剂前0.5，1，2，3，4，5，10，12或18小时；1，2，3，4，5或6天；1，2，3或4周给予所述的化合物。在某些实施方案中，在给予治疗或抗癌剂后，例如在给予抗癌剂后0.5，1，2，3，4，5，10，12或18小时；1，2，3，4，5或6天；1，2，3或4周给予所述的化合物。在某些实施方案中，同时、但使用不同的方案给予所述的化合物与治疗或抗癌剂，例如在每天给予所述的化合物，同时每周1次，每2周1次，每3周1次或每4周1次给予治疗或抗癌剂。在其它实施方案中，每周1次给予所述的化合物，同时每天，每周1次，每2周1次，每3周1次，或每4周1次给予治疗或抗癌剂。

本发明范围内的组合物包括所有的组合物，其中包含有效实现其预期目的用量的本发明组合物。尽管个体要求是可变的，但是确定每种成分的最佳有效量范围属于本领域技术人员的范围。一般而言，对哺乳动物，例如人给予的化合物的口服剂量为：对每天为治疗对诱导细胞凋亡有应答的病症的哺乳动物体重而言，为0.0025－50 mg/kg，或等效量的其药学上可接受的盐。优选口服给予约0.01－约10 mg/kg

以便治疗、改善或预防这类病症。就肌内注射而言，剂量一般约为口服剂量的一半。例如，合适的肌内剂量可以约为0.0025－约25 mg/kg，并且最优选约0.01－约5 mg/kg。

单位口服剂量可以包含约0.01－约1000 mg，优选约0.1－约100 mg的化合物。可以将该单位剂量作为各自含有约0.1－约10，便利的是约0.25－50 mg化合物或其溶剂合物的一片或多片或一粒或多粒胶囊每天给予一次或多次。

在局部制剂中，化合物可以以约0.01－100 mg/克载体的浓度存在。在一个优选的实施方案中，化合物以约0.07-1.0 mg/ml，更优选约0.1-0.5 mg/ml，最优选约0.4 mg/ml的浓度存在。

除作为原料给予本发明的化合物化合物外，还可以将其作为药物制剂的组成部分给予，所述的药物制剂含有合适的药学上可接受的载体，这些载体包含有利于将化合物加工成可以在药学上使用的制剂的赋形剂和助剂。优选制剂含有约0.01－99%，优选0.25－5%的活性化合物与赋形剂，所述的制剂特别是那些可以通过口服或局部给药并且可以用于优选给药类型的制剂，诸如片剂、锭剂、缓释锭剂和胶囊、口腔清洗剂和口腔洗剂、凝胶、液体混悬液、染发液、发胶、洗发剂，并且还有可以通过直肠给药的制剂，诸如栓剂，以及用于通过注射、局部或口服给药的合适的溶液。

可以将本发明的药物组合物对任意可能经历本发明有益作用的动物给药。在这类动物中位于最前列的是哺乳动物，例如人，不过，本发明并不限于此。其它动物包括兽类动物(牛、绵羊、猪、马、狗、猫等)。

可以通过实现其指定目的的任意方式给予所述的化合物及其药物组合物。例如，可以通过非肠道、皮下、静脉内、肌内、腹膜内、透皮、颊、鞘内、颅内、鼻内或局部途径进行给药。或者，或同时，可以通过口服途径给药。给药剂量取决于接受者的年龄、健康情况和体重、同时治疗的类型（如果有的话）、治疗的频率和所需作用的性质。

按照自身公知的方式，例如通过常规的混合、制粒、制锭、溶解

或冻干法制备本发明的药物制剂。因此，可以通过下列步骤获得口服应用的药物制剂：将活性化合物与固体赋形剂合并，任选研磨所得混合物，并且如果需要或必要，在添加合适的助剂后加工颗粒混合物而得到片芯或锭芯。

合适的赋形剂特别为：填充剂，诸如糖类，例如乳糖或蔗糖、甘露糖醇或山梨醇、纤维素制品和/或磷酸钙，例如磷酸三钙或磷酸氢钙；以及粘合剂，诸如使用可溶玉米淀粉、小麦淀粉、稻米淀粉、马铃薯淀粉的淀粉糊、明胶、西黄蓍胶。甲基纤维素、羟丙基甲基纤维素、羧甲基纤维素钠和/或聚乙烯吡咯烷酮。如果需要，可以加入崩解剂，诸如上述淀粉并且还有羧甲基-淀粉、交联聚乙烯吡咯烷酮、琼脂或藻酸或其盐，诸如藻酸钠。助剂尤其为流动调节剂和润滑剂，例如二氧化硅、滑石粉、硬脂酸或其盐，诸如硬脂酸镁或硬脂酸钙和/或聚乙二醇。如果需要，可以给锭芯包耐胃液的合适的包衣层。为了这一目的，可以使用可以任选含有阿拉伯树胶、滑石粉、聚乙烯吡咯烷酮、聚乙二醇和/或二氧化钛、漆溶液和合适的有机溶剂或溶剂混合物的浓糖溶液。为了产生耐胃液的包衣层，可以使用诸如邻苯二甲酸乙酰纤维素或邻苯二甲酸羟丙基甲基-纤维素这类合适的纤维素制品的溶液。可以将染料或色素加入到片剂或锭剂包衣层中，例如便于鉴别或为了表征活性化合物剂量的组合。

可以口服使用的其它药物制剂包括由明胶制成的推入嵌合式胶囊以及由明胶和增塑剂，诸如甘油或山梨醇制成的软密封胶囊。推入嵌合式胶囊可以含有颗粒形式的活性化合物，所述的颗粒中混合有：填充剂，诸如乳糖；粘合剂，诸如淀粉；和/或润滑剂，诸如滑石粉或硬脂酸镁，和任选的稳定剂。在软胶囊中，优选将活性化合物溶于或悬浮于合适的液体，诸如脂肪酸或液体石蜡。此外，可以加入稳定剂。

可以通过直肠使用的可能的药物制剂包括：例如由一种或多种活性化合物与栓剂基质的组合组成的栓剂。例如，合适的栓剂基质为天然或合成的甘油三酯类或链烷烃类。此外，还能够使用由活性化合物与基质的组合组成的直肠用明胶胶囊。可能的基质材料包括：例如液

体甘油三酯类、聚乙二醇类或链烷烃类

用于非肠道给药的合适的制剂包括水溶性形式的活性化合物的水溶液，例如水溶性盐和碱性溶液。此外，可以给予作为合适的油注射混悬液的活性化合物的混悬液。合适的亲脂性溶剂或媒介物包括脂肪酸，例如芝麻油，或合成脂肪酸酯类，例如油酸乙酯或甘油三酯类或聚乙二醇-400。含水的注射混悬液可以含有增加该混悬液粘度的物质，包括，例如羧甲基纤维素钠、山梨醇和/或葡聚糖。任选该混悬液中还可以含有稳定剂。

优选通过选择合适的载体将本发明的局部用组合物配制成油、霜剂、洗剂、软膏剂等。合适的载体包括植物油或矿物油、白凡士林(白软石蜡)、支链脂肪或油、动物脂肪和高分子量醇(大于C_{12})。优选的载体为那些活性组分可溶于其中的物质。如果需要，还可以包括乳化剂、稳定剂、保湿剂和抗氧化剂以及赋予颜色或香味的试剂。另外，在这些局部制剂中可以使用透皮促进剂。这类促进剂的实例可以在美国专利US3,989,816和US4,444,762中找到。

优选由矿物油、自乳化蜂蜡和水的混合物配制霜剂，在混合物中混合了溶于少量油、诸如杏仁油的活性组分。这类霜剂的典型实例为一种包括约40份水、约20份蜂蜡、约40份矿物油和约1份杏仁油的霜。

可以通过将活性组分在植物油、诸如杏仁油中的溶液与温热的石蜡混合并且使该混合物冷却配制软膏剂。这类软膏剂的典型实例为一种包括约30%重量的杏仁油和约70%重量的白凡士林的软膏剂。

可以通过将活性组分溶于合适的高分子量醇、诸如丙二醇或聚乙二醇便利地制备洗剂。

下列实施例是对本发明方法和组合物的解释，但不起限制作用。对一般在临床疗法中遇到的各种条件和参数的其它适当的变型和修改属于本发明的实质和范围，并且对本领域技术人员而言显而易见。

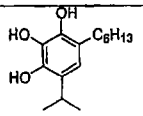
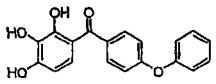
实施例1

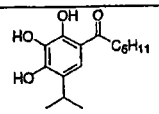
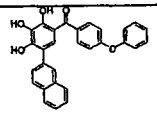
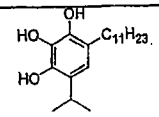
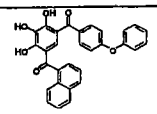
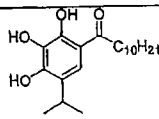
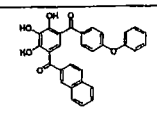
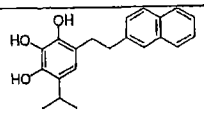
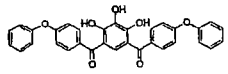
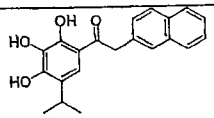
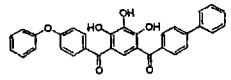
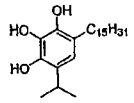
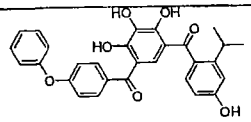
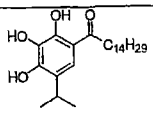
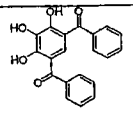
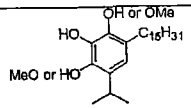
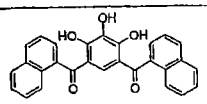
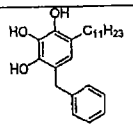
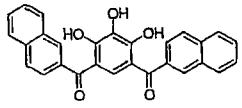
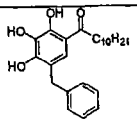
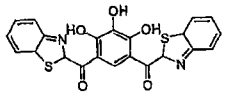
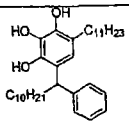
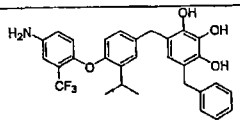
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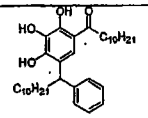
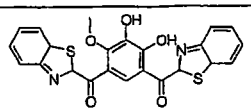
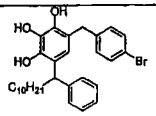
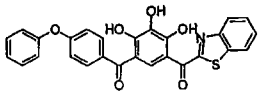
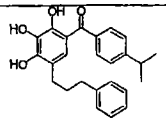
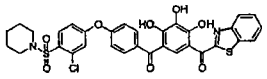
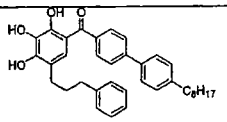
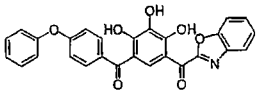
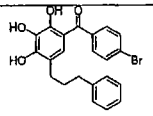
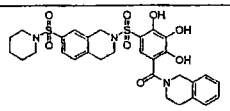
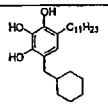
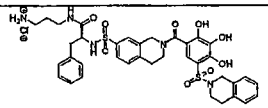
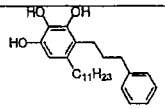
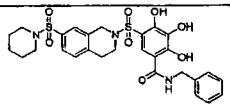
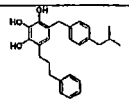
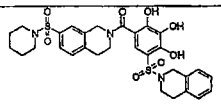
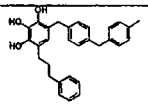
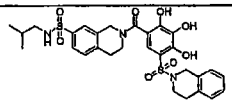
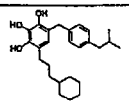
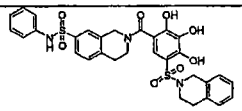
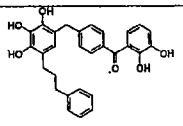
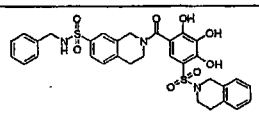
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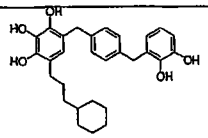
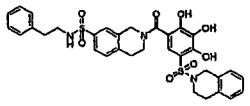
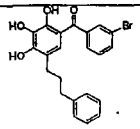
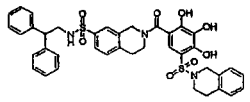
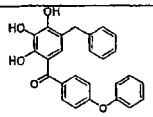
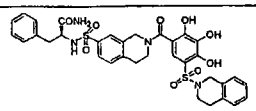
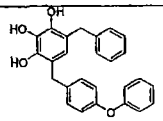
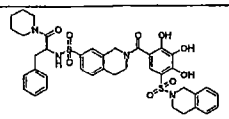
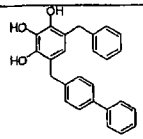
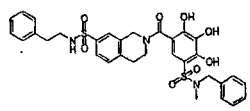
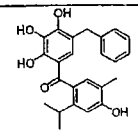
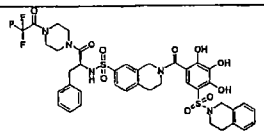
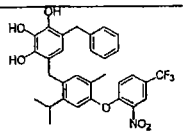
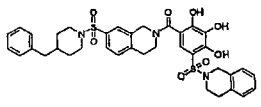
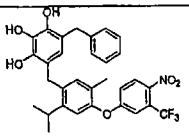
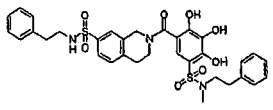
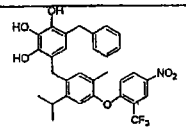
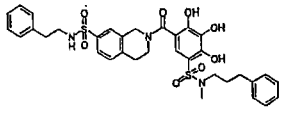
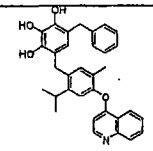
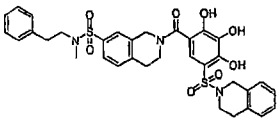
通过上述一般操作步骤合成下列化合物(表2-4)并且分析其结构。

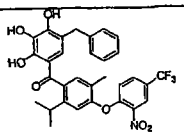
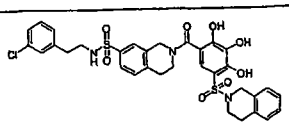
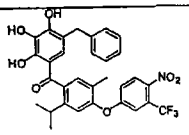
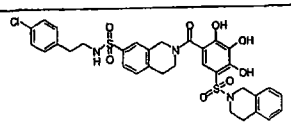
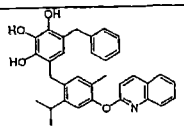
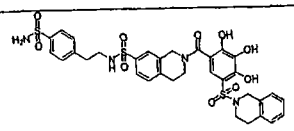
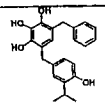
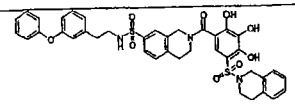
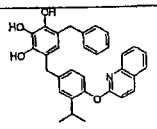
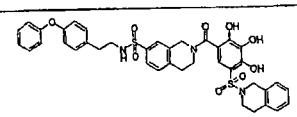
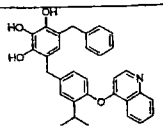
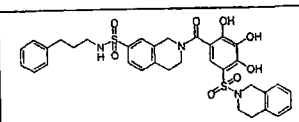
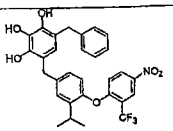
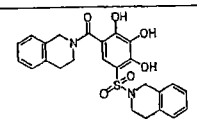
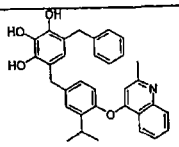
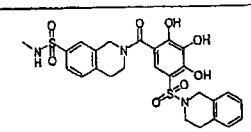
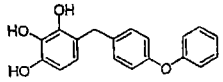
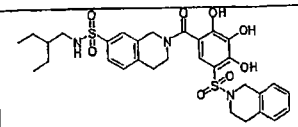
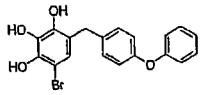
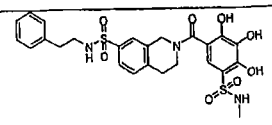
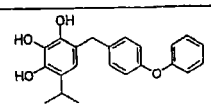
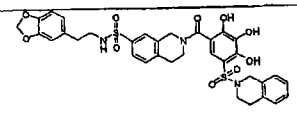
表 2

名称	化合物	名称	化合物
TM-103		TM-166	

TM-104		TM-167	
TM-105		TM-168	
TM-106		TM-169	
TM-107		TM-170	
TM-108		TM-171	
TM-109		TM-172	
TM-110		TM-173	
TM-111		TM-174	
TM-121		TM-175	
TM-122		TM-176	
TM-123		TM-177	

TM-124		TM-178	
TM-125		TM-179	
TM-126		TM-180	
TM-127		TM-183	
TM-128		TM-190	
TM-129		TM-191	
TM-130		TM-192	
TM-132		TM-193	
TM-133		TM-194	
TM-134		TM-195	
TM-135		TM-196	

TM-136		TM-197	
TM-137		TM-198	
TM-140		TM-199	
TM-141		TM-200 (1200)	
TM-142		TM-1201	
TM-143		TM-1202	
TM-144		TM-1203	
TM-145		TM-1205	
TM-146		TM-1206	
TM-147		TM-1207	

TM-148		TM-1208	
TM-149		TM-1209	
TM-150		TM-1210	
TM-152		TM-1211	
TM-153		TM-1212	
TM-154		TM-1213	
TM-155		TM-1214	
TM-156		TM-1215	
TM-157		TM-1216	
TM-158		TM-1217	
TM-159		TM-1218	

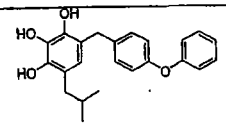
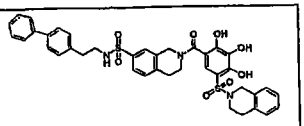
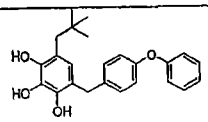
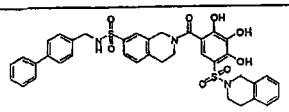
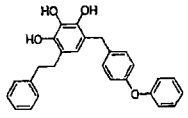
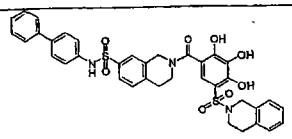
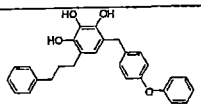
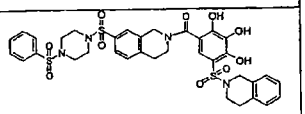
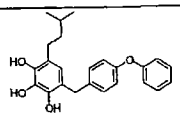
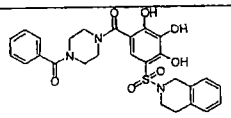
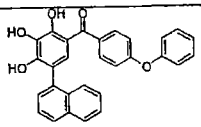
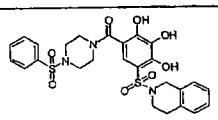
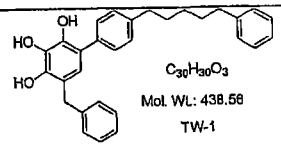
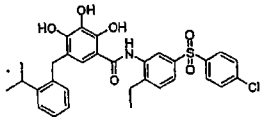
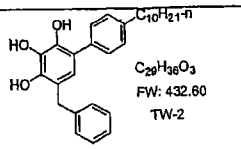
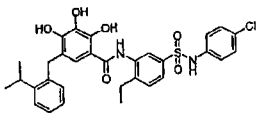
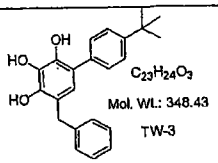
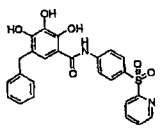
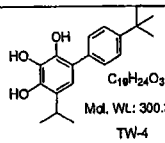
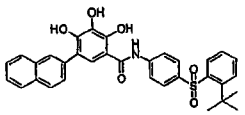
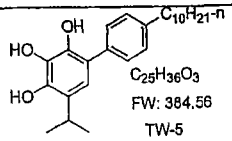
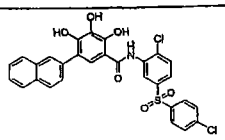
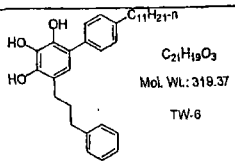
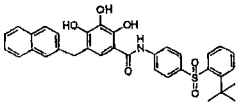
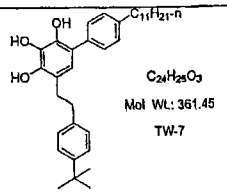
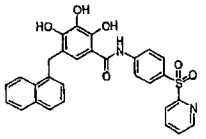
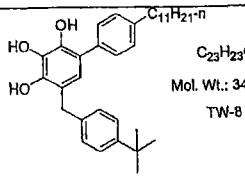
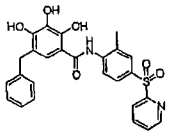
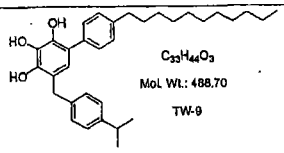
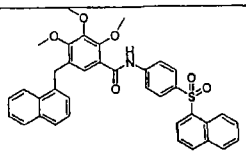
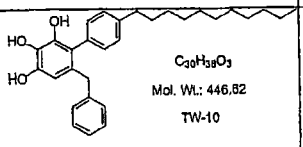
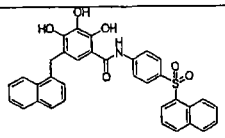
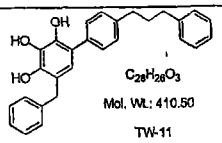
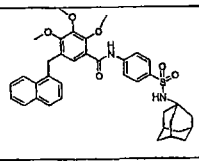
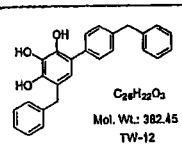
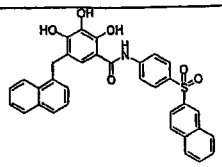
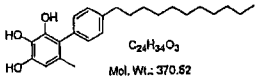
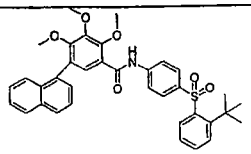
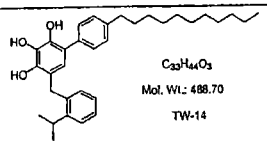
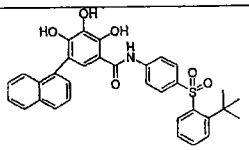
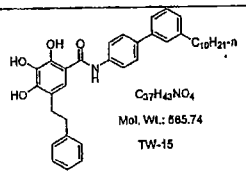
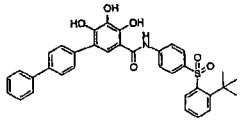
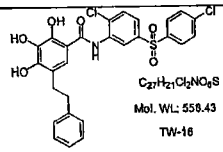
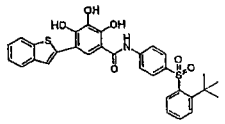
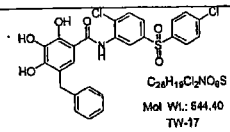
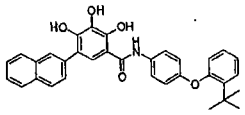
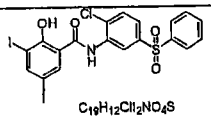
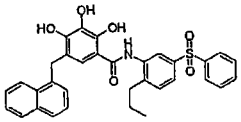
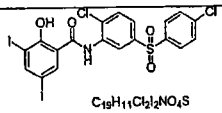
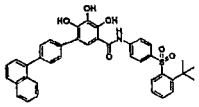
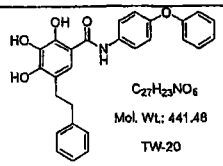
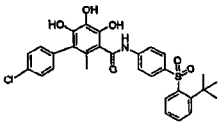
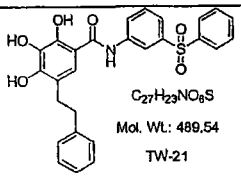
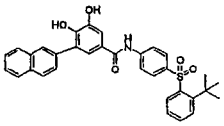
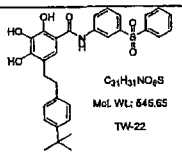
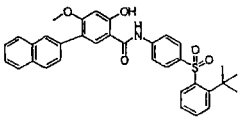
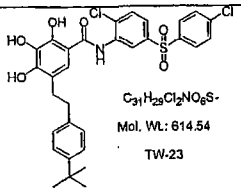
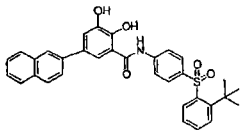
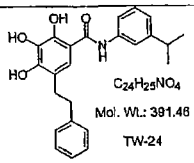
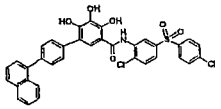
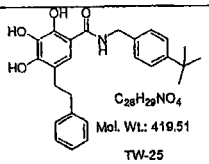
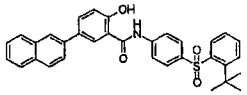
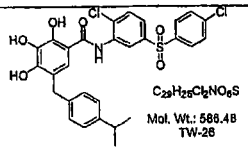
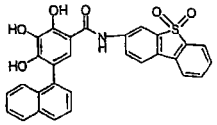
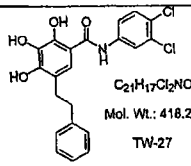
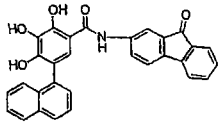
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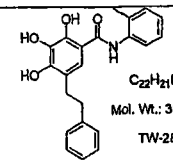
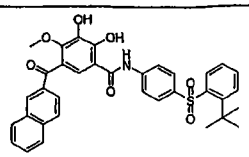
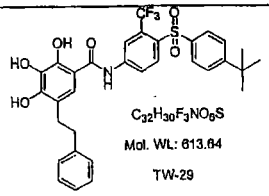
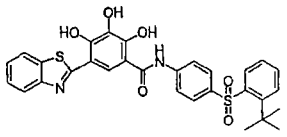
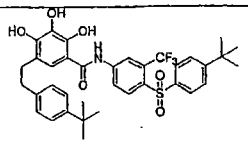
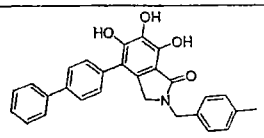
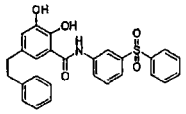
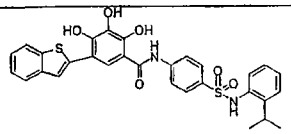
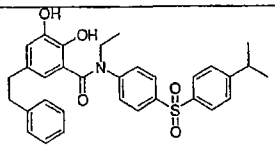
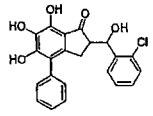
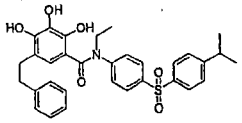
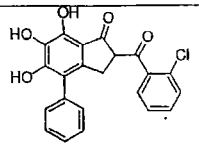
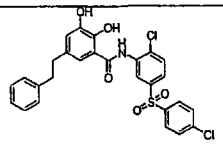
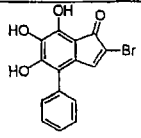
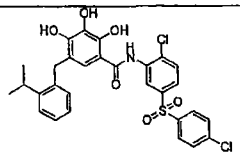
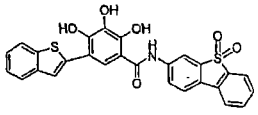
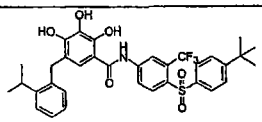
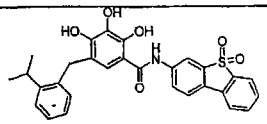
表 3

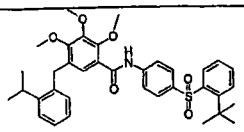
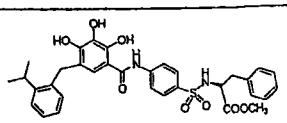
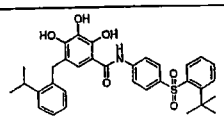
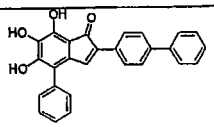
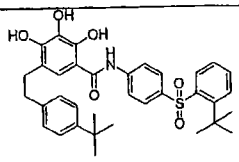
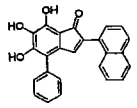
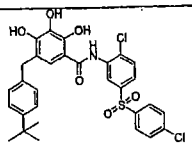
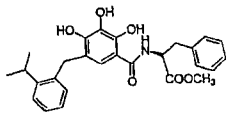
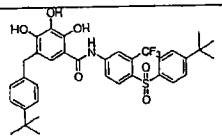
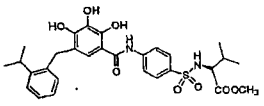
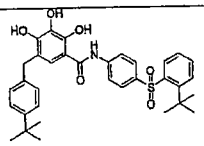
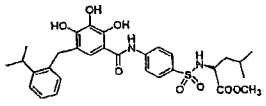
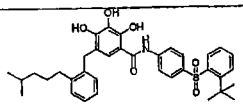
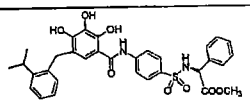
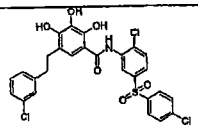
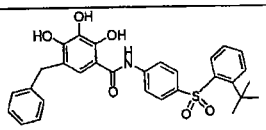
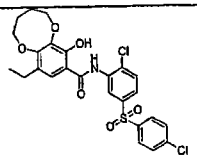
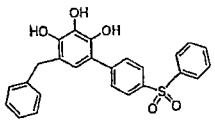
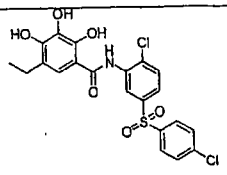
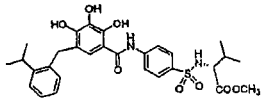
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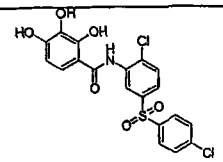
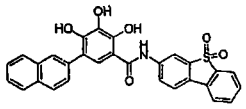
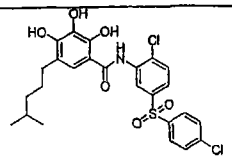
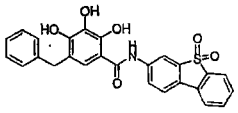
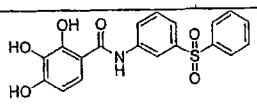
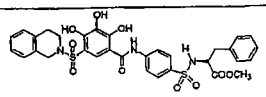
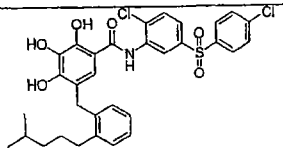
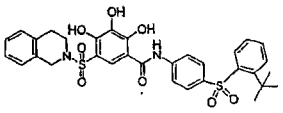
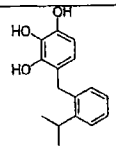
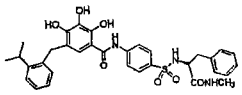
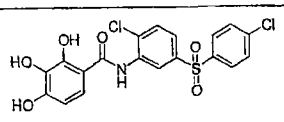
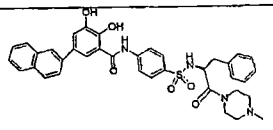
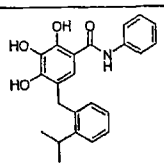
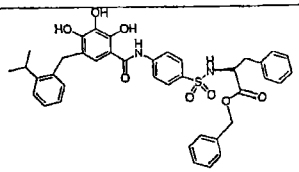
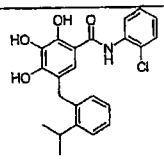
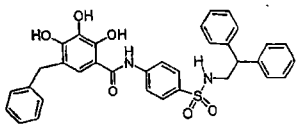
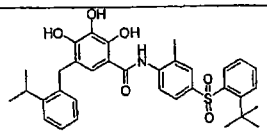
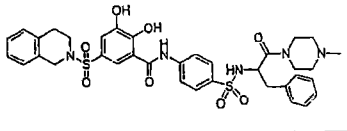
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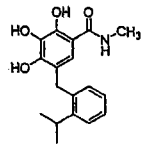
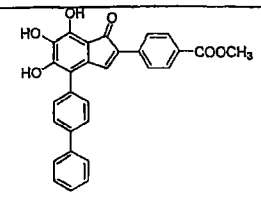
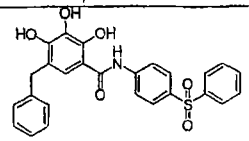
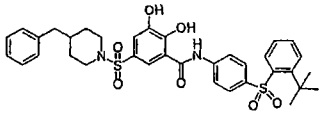
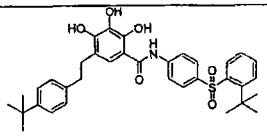
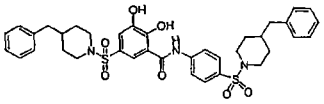
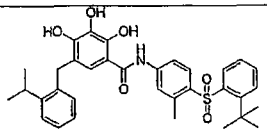
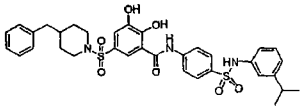
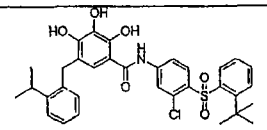
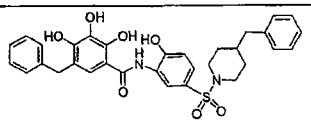
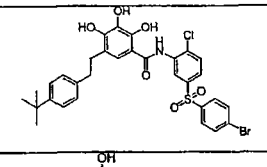
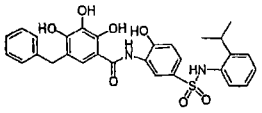
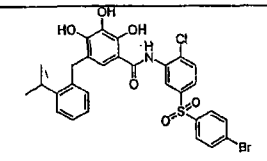
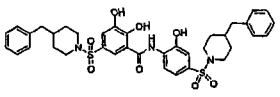
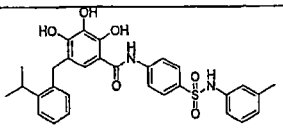
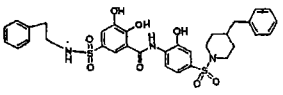
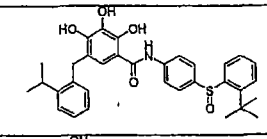
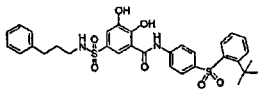
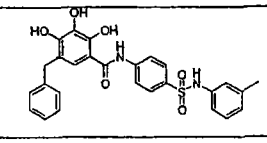
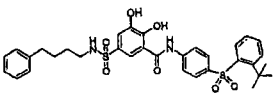
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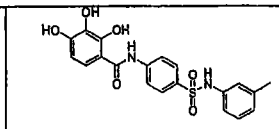
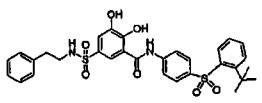
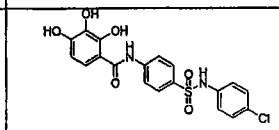
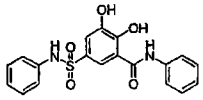
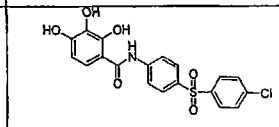
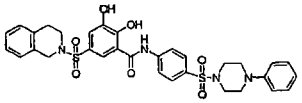
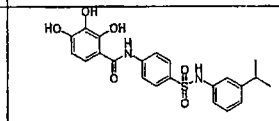
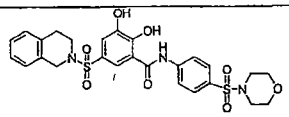
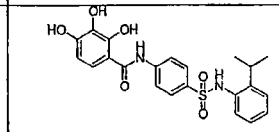
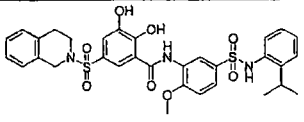
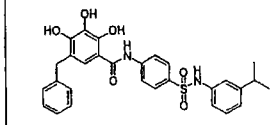
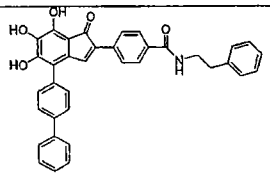
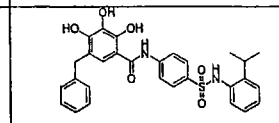
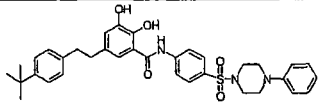
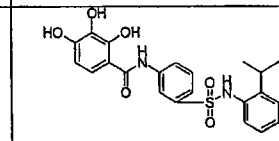
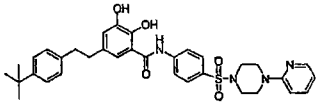
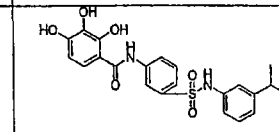
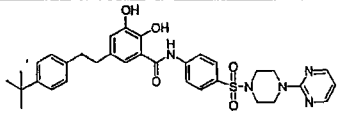
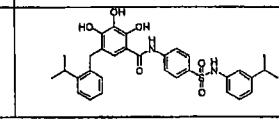
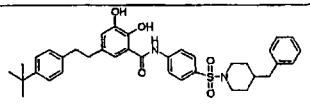
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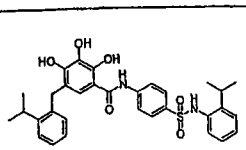
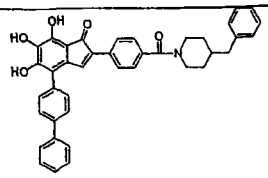
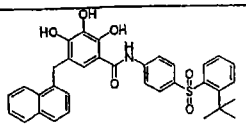
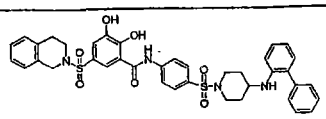
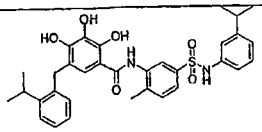
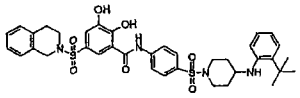
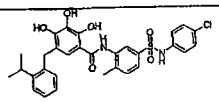
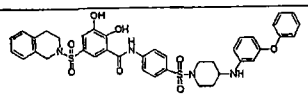
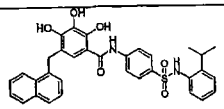
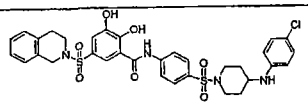
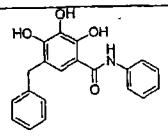
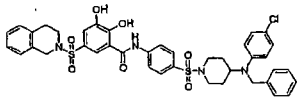
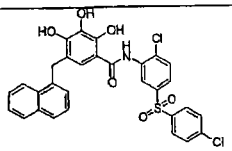
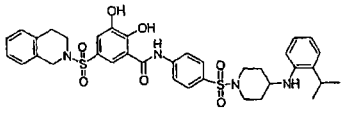
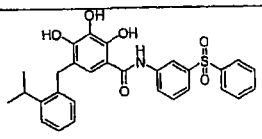
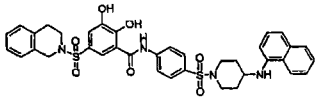
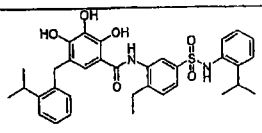
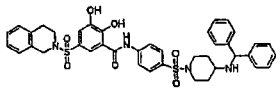
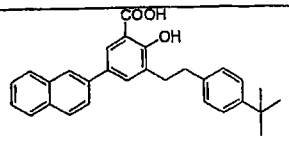
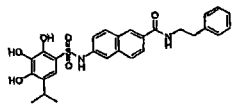
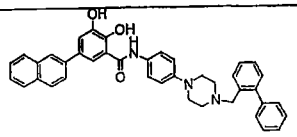
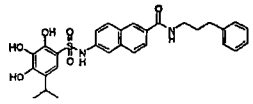
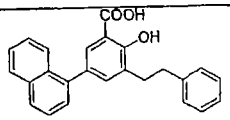
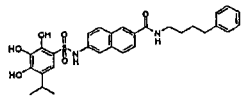
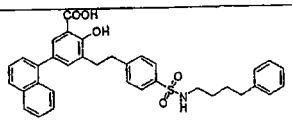
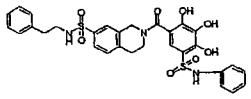
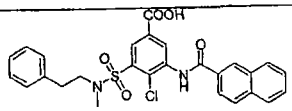
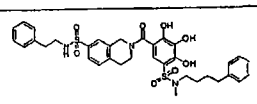
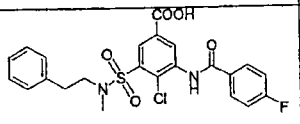
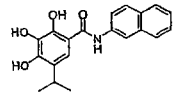
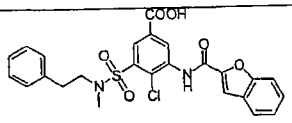
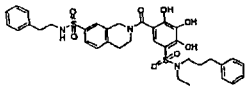
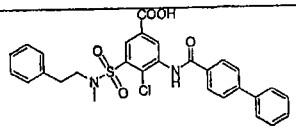
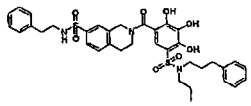
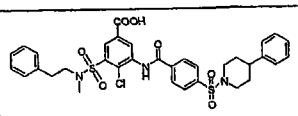
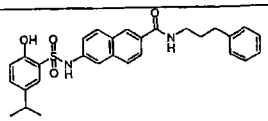
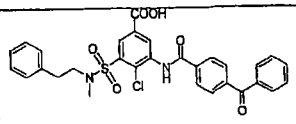
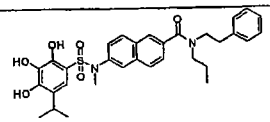
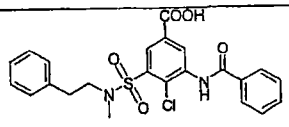
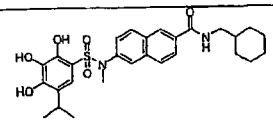
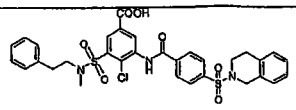
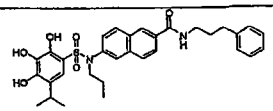
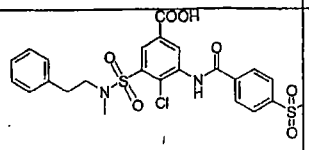
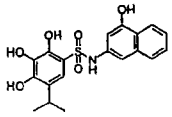
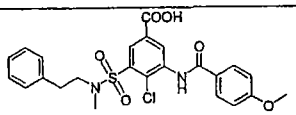
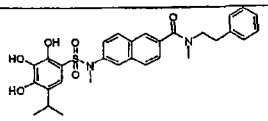
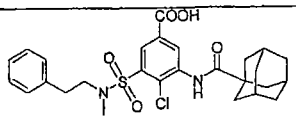
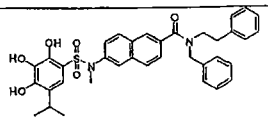
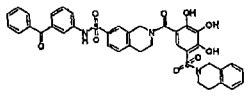
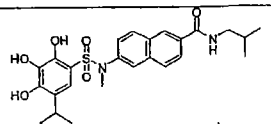
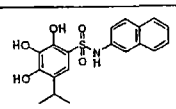
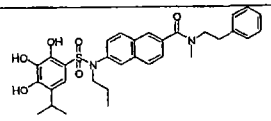
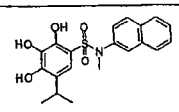
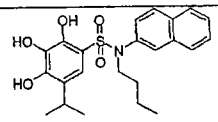
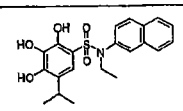
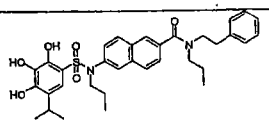
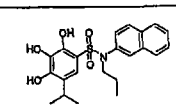
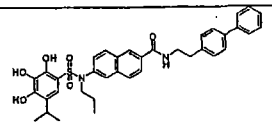
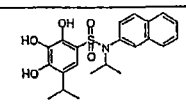
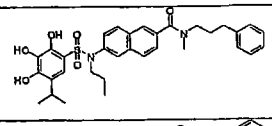
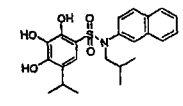
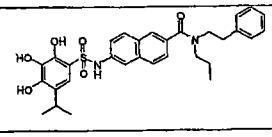
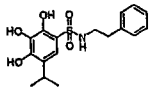
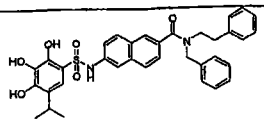
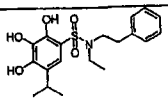
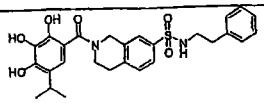
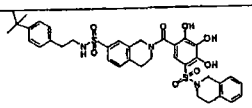
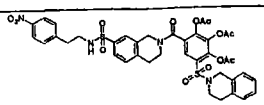
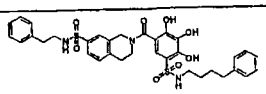
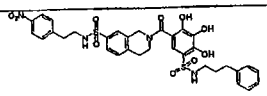
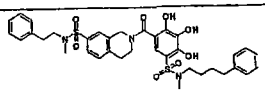
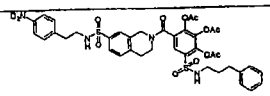
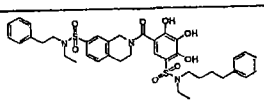
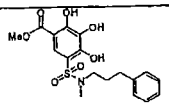
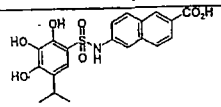
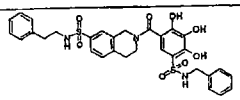
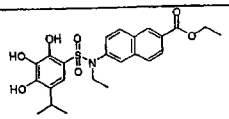
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TW-79		TW-174	
TW-80		TW-175	
TW-81		TW-176	
TW-82		TW-177	
TW-83		TW-178	
TW-85		TW-179	
TW-86		TW-180	

表 4

名称	化合物	名称	化合物

TW-183		TM-1245	
TW-184		TM-1246	
TW-189		TM-1247	
TW-190		TM-1248	
TW-194		TM-1249	
TW-195		TM-1250	
TW-196		TM-1251	
TW-198		TM-1252	
TW-199		TM-1253	
TW-200		TM-1254	
TW-201		TM-1255	

TW-202		TM-1256	
TW-203		TM-1257	
TW-204		TM-1258	
TW-205		TM-1259	
TM-1230		TM-1260	
TM-1231		TM-1261	
TM-1232		TM-1262	
TM-1233		TM-1263	
TM-1234		TM-1264	
TM-1235		TM-1265	
TM-1236		TM-1266	

TM-1237		TM-1267	
TM-1238		TM-1269	
TM-1239		TM-1271	
TM-1240		TM-1276	
TM-1241		TM-1277	
TM-1242		TM-1278	
TM-1243		TM-1282	
TM-1244			

TM-103

^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.49 (s, 1H), 6.02 (b, 1H), 5.50 (b, 1H), 5.41 (b, 1H), 3.07 (m, 1H), 2.48 (m, 2H), 1.53 (m, 2H), 1.27 (m, 6H), 1.18 (d, 6H), 0.87 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 139.79, 139.58, 131.67, 127.34, 121.45, 117.75, 31.76, 30.20, 29.75, 29.23, 26.85, 22.85, 22.67, 14.11.

TM-104

^{1}H NMR ($CDCl_3$, 300 MHz) δ 12.81 (s, OH), 7.17 (s, 1H), 6.07 (s, OH), 5.66 (s, OH), 3.22 (m, 1H), 2.92 (t, 2H), 1.74 (m, 2H), 1.38 (m, 4H),

1.25 (d, 6H), 0.92 (t, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 206.14, 148.70, 130.64, 126.64, 118.72, 112.86, 37.87, 31.52, 27.04, 24.56, 22.49, 13.95.

TM-108

^{1}H NMR ($CDCl_3$, 300 MHz) δ 12.59 (s, OH), 7.81-7.72 (m, 4H), 7.45-7.35 (m, 4H), 6.22 (s, OH), 5.86 (s, OH), 4.38 (s, 2H), 3.19 (m, 1H), 1.22 (d, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 203.27, 149.51, 148.66, 133.95, 132.85, 132.39, 131.13, 128.80, 128.64, 128.11, 128.04, 127.87, 127.37, 126.65, 126.28, 119.83, 112.92, 45.53, 27.33, 22.91.

TM-109

^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.49 (s, 1H), 5.50 (b, OH), 5.16 (b, OH), 5.04 (b, OH), 3.10 (m, 1H), 2.52 (t, 2H), 1.56 (m, 2H), 1.23 (m, 30H), 0.88 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 140.01, 139.84, 131.96, 127.13, 121.15, 117.75, 32.34, 32.01, 30.70, 30.11, 29.96, 29.78, 27.34, 23.25, 23.11, 23.07, 21.47.

TM-110

^{1}H NMR ($CDCl_3$, 300 MHz) δ 12.84 (s, OH), 7.17 (s, 1H), 6.13 (s, OH), 5.76 (s, OH), 3.20 (m, 1H), 2.92 (t, 2H), 1.72 (m, 2H), 1.35-1.24 (m, 28H), 0.86 (t, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 206.18, 148.72, 147.73, 130.62, 126.65, 118.74, 112.85, 37.92, 31.94, 29.68, 29.64, 29.50, 29.46, 29.38, 27.05, 24.92, 22.71, 22.49, 14.14.

TM-121

^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.30-7.19 (m, 5H), 6.47 (s, 1H), 5.31 (b, OH), 5.07 (b, OH), 4.79 (b, OH), 3.90 (s, 2H), 2.50 (t, 2H), 1.55 (m, 2H), 1.26 (m, 16H), 0.86 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 140.61, 140.16, 139.91,

132.09, 128.72, 128.46, 126.39, 121.90, 121.26, 119.01, 36.21, 31.94, 30.13, 29.69, 29.66, 29.56, 29.52, 29.49, 29.37, 22.71, 14.14.

TM-122

^{1}H NMR ($CDCl_3$, 300 MHz) δ 12.87 (s, OH), 7.30-7.23 (m, 5H), 7.08 (s, 1H), 6.23 (b, OH), 5.91 (b, OH), 3.95 (s, 2H), 2.80 (m, 2H), 1.66 (m, 2H), 1.26 (m, 14H), 0.87 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 206.22, 149.32, 148.16, 140.24, 130.93, 128.69, 128.43, 126.15, 122.93, 119.41, 112.92, 38.00, 35.26, 31.92, 31.61, 29.59, 29.50, 29.43, 29.35, 25.01, 22.70, 14.14.

TM-123

^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.20 (m, 5H), 6.59 (s, 1H), 5.22 (b, 2OH), 4.69 (b, OH), 3.99 (t, 2H), 2.55 (t, 2H), 1.96 (m, 2H), 1.58 (m, 2H), 1.25 (m, 32H), 0.88 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 144.74, 140.30, 139.55, 132.16, 128.69, 127.84, 126.39, 123.24, 120.95, 119.06, 44.58, 34.68, 31.95, 31.93, 30.15, 29.95, 29.73, 29.69, 29.63, 29.56, 29.48, 29.39, 29.36, 27.90, 22.84, 22.71, 14.13.

TM-125

^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.36 (M, 2h), 7.28-7.17 (M, 5h), 7.06 (D, 2h), 6.59 (s 1H), 5.30 (b, OH), 5.12 (b, OH), 4.79 (b, OH), 3.98 (t, 1H), 3.87 (d, 2H), 1.93 (m, 2H), 1.20 (m, 16H), 0.88 (t, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 144.47, 140.65, 140.38, 139.72, 132.49, 131.46, 130.27, 128.75, 127.81, 126.51, 123.69, 119.91, 119.85, 118.93, 44.58, 35.34, 34.60, 31.91, 29.65, 29.62, 29.56, 29.35, 27.88, 22.69, 21.04, 14.14.

TM-126

^{1}H NMR ($CDCl_3$, 300 MHz) δ 12.57, 7.61 (d, 2H), 7.35 (d, 2H), 7.23 (m, 1H), 7.15 (m, 4H), 7.03 (s, 1H), 6.04 (b, OH), 5.62 (b, OH), 3.00 (m, 1H),

2.63 (m, 4H), 1.90 (m, 2H), 1.31 (6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 200.26, 153.10, 149.56, 148.24, 142.24, 135.70, 130.89, 129.37, 128.40, 128.25, 126.44, 126.08, 125.69, 120.07, 112.56, 35.38, 34.23, 31.16, 29.12, 23.78.

TM-127

^{1}H NMR ($CDCl_3$, 300 MHz) δ 12.54 (s, OH), 7.72 (m, 4H), 7.65-7.45 (m, 4H), 7.32-7.15 (m, 5H), 7.05 (s, 1H), 6.10 (b, OH), 5.69 (b, OH), 2.65 (4H), 1.91 (m, 2H), 1.66 (m, 2H), 1.50 (m, 2H), 1.27 (m, 10H), 0.89 (m, 3H).

TM-128

^{1}H NMR ($CDCl_3$, 300 MHz) δ 12.36 (s, OH), 7.64 (d, 2H), 7.52 (d, 2H), 7.27-7.23 (m, 2H), 7.19-7.13 (m, 3H), 6.90 (1H), 6.11 (b, OH), 5.65 (b, OH), 2.61 (m, 4H), 1.88 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 199.22, 149.60, 148.72, 142.10, 136.81, 131.63, 130.96, 130.51, 128.37, 128.29, 126.47, 125.75, 120.51, 112.27, 35.40, 31.11, 29.11.

TM-129

^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.37 (s, 1H), , 5.30 (b, OH), 5.10 (b, OH), 4.95 (b, OH), 2.50 (t, 2H), 2.38 (d, 2H), 1.68 (m, 5H), 1.55 (m, 4H), 1.20 (m, 20H), 0.90 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 139.90, 139.80, 131.61, 128.81, 128.71, 128.06, 127.85, 126.41, 122.15, 120.59, 119.06, 38.74, 37.55, 33.30, 31.94, 30.48, 30.15, 29.67, 29.56, 29.48, 29.37, 26.55, 26.32, 25.71, 22.71, 14.14, 14.05.

TM-130

^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.31-7.15 (m, 5H), 6.26 (s, 1H), 5.06 (b, OH), 5.00 (b, OH), 4.79 (b, OH), 2.71 (t, 2H), 2.56 (t, 2H), 2.37 (t, 2H), 1.84 (m, 2H), 1.43 (m, 2H), 1.26 (m, 16H), 0.88 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 142.51, 142.29, 140.99, 133.21, 129.38, 128.43, 128.32, 125.77,

119.57, 108.03, 35.94, 32.45, 31.94, 31.69, 31.54, 29.70, 29.67, 29.56, 29.38, 25.31, 22.71, 14.15.

TM-132

^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.30-7.25 (m, 2H), 7.20-7.15 (m, 3H), 7.13-7.05 (m, 4H), 6.48 (s, 1H), 5.20 (b, OH), 4.97 (b, OH), 4.62 (b, OH), 3.88 (s, 2H), 2.67 (t, 2H), 2.58 (t, 2H), 2.43 (d, 2H), 1.91 (m, 2H), 1.82 (m, 1H), 0.88 (d, 6H).

TM-133

^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.29-7.22 (m, 2H), 7.19-7.17 (m, 3H), 7.10-7.03 (m, 8H), 6.46 (s, 1H), 5.24 (b, OH), 4.99 (b, OH), 4.66 (b, OH), 3.88 (s, 2H), 3.85 (s, 2H), 2.63 (t, 2H), 2.56 (t, 2H), 2.29 (s, 3H), 1.90 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 142.34, 139.88, 139.68, 137.99, 137.51, 135.54, 129.24, 129.13, 128.75, 128.48, 128.44, 128.30, 125.70, 121.81, 120.67, 119.01, 41.08, 35.90, 35.46, 31.50, 28.92, 21.00.

TM-140

^{1}H NMR ($CDCl_3$, 300 MHz) δ 12.56 (s, OH), 7.62 (m, 2H), 7.45 (m, 2H), 7.29-7.20 (m, 6H), 7.06 (m, 2H), 7.01 (m, 3H), 6.12 (b, OH), 5.90 (b, OH), 3.95 (s, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 198.97, 160.96, 155.61, 149.82, 148.20, 140.17, 132.16, 131.49, 131.10, 130.04, 128.70, 128.39, 126.48, 126.10, 124.54, 120.09, 119.28, 117.22, 35.12.

TM-142

^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.54-7.45 (m, 4H), 7.38 (m, 1H), 7.29-7.15 (m, 9H), 6.49 (s, 1H), 5.22 (b, 3OH), 3.88 (s, 2H), 3.86 (s, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 140.81, 140.08, 139.31, 139.13, 132.41, 128.90, 128.70,

128.63, 128.49, 127.28, 127.08, 126.94, 126.31, 122.86, 119.69, 119.64, 36.94, 35.49.

TM-143

^{1}H NMR ($CDCl_3$, 300 MHz) δ 12.70 (s, OH), 7.22-7.20 (m, 2H), 7.16-7.12 (m, 3H), 6.94 (s, 1H), 6.75 (d, 1H), 6.06 (s, OH), 5.63 (s, OH), 5.09 (s, OH), 3.84 (s, 2H), 2.99 (m, 1H), 2.20 (s, 3H), 1.12 (d, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 197.42, 162.94, 157.62, 154.58, 151.95, 149.52, 146.35, 140.75, 133.76, 130.71, 130.55, 129.74, 128.71, 128.34, 126.34, 125.99, 120.52, 112.77, 36.75, 36.06, 24.09, 15.36.

TM-144

^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.23 (d, 1H), 7.64 (dd, 1H), 7.28-7.14 (m, 5H), 7.01 (s, 1H), 6.96 (s, 1H), 6.84 (d, 1H), 6.26 (s, 1H), 5.52 (b, OH), 5.30 (b, OH), 4.96 (b, OH), 3.95 (s, 2H), 3.87 (s, 2H), 3.15 (m, 1H), 2.08 (s, 3H), 1.11 (d, 6H).

TM-145

^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.93 (d, 1H), 7.34 (d, 1H), 7.26-7.23 (m, 2H), 7.17 (m, 3H), 7.01 (s, 1H), 6.98 (dd, 1H), 6.93 (s, 1H), 6.28 (s, 1H), 5.61 (b, OH), 5.36 (b, OH), 5.04 (b, OH), 3.95 (s, 2H), 3.88 (s, 2H), 3.15 (m, 1H), 2.06 (s, 3H), 1.11 (d, 6H).

TM-146

^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.59 (d, 1H), 8.26 (dd, 1H), 7.26-7.22 (m, 2H), 7.20-7.14 (m, 3H), 6.98 (d, 1H), 6.73 (d, 1H), 6.24 (s, 1H), 5.90 (b, OH), 5.59 (b, OH), 5.36 (b, OH), 3.95 (d, 2H), 3.89 (d, 2H), 3.16 (m, 1H), 2.04 (s, 3H), 1.13 (d, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 161.31, 150.21, 147.72, 141.19, 141.12, 140.88, 140.29, 135.48, 133.50, 132.21, 129.01,

128.58, 128.50, 127.18, 126.29, 124.00 (q), 122.26, 119.66, 119.31, 119.19, 115.08, 35.92, 34.69, 31.62, 23.67, 15.40.

TM-147

^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.43 (d, 1H), 8.38 (d, 1H), 8.11 (d, 1H), 7.99 (s, 1H), 7.76 (m, 1H), 7.62 (m, 1H), 7.18 (m, 5H), 7.00 (s, 1H), 6.94 (s, 1H), 6.29 (s, 1H), 6.10 (b, 3H), 3.96 (s, 2H), 3.90 (s, 2H), 3.12 (m, 1H), 2.00 (s, 3H), 1.04 (d, 6H).

TM-148

^{1}H NMR ($CDCl_3$, 300 MHz) δ 12.52 (s, OH), 8.28 (d, 1H), 7.73 (dd, 1H), 7.25-7.20 (m, 2H), 7.17-7.11 (m, 4H), 7.03 (s, 1H), 6.88 (d, 1H), 6.59 (s, 1H), 6.39 (b, OH), 6.02 (b, OH), 3.86 (s, 2H), 2.95 (m, 1H), 2.17 (s, 3H), 1.09 (d, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 202.45, 153.58, 152.93, 149.86, 149.24, 147.06, 139.98, 139.43, 135.27, 131.04, 130.99, 130.96, 130.79, 128.67, 128.33, 127.44, 126.57, 126.13, 123.83 (q), 120.00, 118.22, 117.66, 113.79, 34.98, 31.62, 22.68, 15.54.

TM-149

^{1}H NMR ($CDCl_3$, 300 MHz) δ 12.58 (s, OH), 7.99 (d, 1H), 7.43 (d, 1H), 7.22 (m, 2H), 7.16-7.12 (m, 4H), 7.02 (m, 1.5H), 6.98 (d, 0.5H), 6.61 (s, 1H), 6.44 (b, OH), 6.08 (b, OH), 3.87 (s, 2H), 2.96 (m, 1H), 2.15 (s, 3H), 1.09 (d, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 202.50, 161.03, 153.17, 149.86, 149.27, 147.16, 142.03, 139.98, 135.11, 130.97, 130.90, 128.67, 128.33, 128.26, 127.43, 126.77, 126.31, 126.11, 123.48, 120.00, 118.33, 118.27, 116.28 (q), 113.81, 34.95, 31.62, 30.34, 15.61.

TM-150

^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.08 (d, 1H), 7.75 (m, 2H), 7.57 (m, 1H), 7.40 (m, 1H), 7.23-7.16 (m, 5H), 7.04 (s, 1H), 6.93 (s, 1H), 6.91 (d, 1H), 6.33 (s, 1H), 5.90 (b, 3H), 3.93 (s, 2H), 3.89 (s, 2H), 3.16 (m, 1H), 2.00 (s, 3H), 1.08 (d, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 162.06, 150.46, 146.65, 146.16, 141.445, 141.40, 140.83, 140.51, 134.17, 132.54, 132.14, 130.30, 128.56, 128.38, 127.60, 127.44, 127.07, 125.96, 125.39, 124.91, 122.61, 119.37, 119.22, 118.80, 111.19, 35.74, 32.03, 31.59, 28.75, 23.59.

TM-153

^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.08 (d, 1H), 7.54 (m, 2H), 7.57 (m, 1H), 7.40 (m, 1H), 7.22 (m, 6H), 6.98 (m, 3H), 6.52 (s, 1H), 5.50 (b, 3H), 3.92 (s, 2H), 3.90 (s, 2H), 3.11 (m, 1H), 1.13 (d, 6H).

TM-154

^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.41 (d, 1H), 8.35 (d, 1H), 8.11 (d, 1H), 7.76 (m, 1H), 7.26 (s, 1H), 7.20 (m, 4H), 7.12 (m, 1H), 7.05 (m, 1H), 6.86 (d, 1H), 6.50 (s, 1H), 6.40 (b, 3H), 6.32 (d, 1H), 3.95 (s, 2H), 3.92 (s, 2H), 2.94 (m, 1H), 1.09 (d, 6H).

TM-155

^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.57 (d, 1H), 8.24 (dd, 1H), 7.29 (m, 3H), 7.20 (m, 3H), 7.09 (dd, 1H), 6.86 (d, 1H), 6.81 (d, 1H), 6.51 (s, 1H), 5.45 (b, 1H), 5.19 (b, 1H), 4.91 (b, 1H), 3.93 (s, 2H), 3.92 (s, 2H), 3.00 (m, 1H), 1.16 (d, 6H).

TM-156

^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.41 (m, 1H), 8.08 (d, 1H), 7.70 (m, 1H), 7.60 (m, 1H), 7.30 (b, 3OH), 7.14 (m, 4H), 7.07 (m, 1H), 7.00 (s, 1H),

6.93 (s, 1H), 6.26 (s, 1H), 3.96 (d, 2H), 3.89 (s, 2H), 3.12 (m, 1H), 1.97 (s, 3H), 1.04 (d, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 167.86, 163.30, 150.12, 150.05, 147.40, 147.30, 142.25, 142.14, 141.16, 135.97, 133.22, 132.40, 131.22, 130.92, 128.80, 128.58, 128.19, 126.93, 126.70, 125.72, 122.46, 122.10, 120.97, 119.35, 118.74, 118.01, 102.90, 31.64, 30.34, 28.91, 28.68, 23.59.

TM-158

^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.33-7.16 (m, 5H), 7.07-6.91 (m, 4H), 6.77 (s, 1H), 5.44 (b, 2OH), 5.36 (b, OH), 3.87 (s, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 157.36, 155.48, 142.11, 138.71, 134.99, 132.58, 131.77, 130.08, 129.94, 129.67, 123.05, 120.22, 118.99, 118.68, 34.45.

TM-159

^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.33-7.27 (m, 2H), 7.16 (m, 2H), 7.07 (m, 1H), 6.99-6.91 (4H), 6.54 (s, 1H), 5.18 (b, 3OH), 3.89 (s, 2H), 3.11 (m, 1H), 1.23 (d, 6H).

TM-160

^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.32-7.26 (m, 2H), 7.17 (d, 2H), 7.08 (m, 1H), 7.00-6.92 (m, 4H), 6.44 (s, 1H), 5.05 (b, 3OH), 3.89 (s, 2H), 2.40 (d, 2H), 1.85 (m, 1H), 0.91 (d, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 157.35, 155.62, 140.83, 140.00, 135.12, 129.69, 123.10, 122.81, 119.19, 118.88, 118.68, 38.79, 35.41, 29.08, 22.48.

TM-163

^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.30-7.25 (m, 4H), 7.19-7.14 (m, 5H), 7.07 (m, 1H), 6.98-6.91 (m, 4H), 6.47 (s, 1H), 5.30 (b, OH), 4.98 (b, OH), 4.78 (b, OH), 3.87 (s, 2H), 2.65 (t, 2H), 2.56 (t, 2H), 1.92 (pent, 2H); ^{13}C

NMR ($CDCl_3$, 75 MHz) δ 157.27, 155.67, 142.26, 140.66, 140.00, 134.92, 132.13, 129.70, 128.43, 128.33, 125.75, 123.13, 121.77, 120.63, 119.16, 119.09, 118.70, 35.44, 35.41, 31.48, 28.89.

TM-165

^1H NMR ($CDCl_3$, 300 MHz) δ 12.60 (s, OH), 7.93 (s, 1H), 7.89-7.84 (m, 3H), 7.73 (d, 2H), 7.63 (d, 1H), 7.50-7.47 (m, 2H), 7.41-7.37 (m, 3H), 7.19 (t, 1H), 7.08 (d, 2H), 7.04 (d, 2H), 6.26 (b, OH), 5.82 (b, OH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 199.24, 161.26, 155.38, 150.48, 147.30, 134.01, 133.35, 132.50, 132.06, 131.52, 130.06, 128.05, 127.93, 127.84, 127.64, 127.28, 126.73, 126.26, 126.11, 124.64, 120.56, 120.25, 117.24, 113.26.

TM-166

^1H NMR ($CDCl_3$, 300 MHz) δ 12.67 (s, OH), 7.67 (d, 2H), 7.41 (m, 2H), 7.19 (d, 2H), 7.10 (d, 2H), 7.05 (d, 2H), 6.51 (d, 2H), 6.16 (b, OH), 5.80 (b, OH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 199.18, 161.10, 155.57, 151.36, 149.85, 132.18, 131.45, 131.34, 130.08, 126.26, 124.59, 120.14, 117.28, 113.26, 107.01

TM-167

^1H NMR ($CDCl_3$, 300 MHz) δ 12.68 (s, OH), 7.90 (d, 2H), 7.69-7.66 (m, 3H), 7.55-7.40 (m, 4H), 7.38-7.32 (m, 2H), 7.24 (s, 1H), 7.16 (t, 1H), 7.03 (d, 2H), 6.96 (d, 2H), 5.91 (b, OH), 5.81 (b, OH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 199.26, 161.16, 155.37, 150.87, 147.48, 133.98, 133.64, 132.10, 131.99, 131.51, 131.45, 130.02, 128.56, 128.40, 128.03, 127.46, 126.34, 126.08, 125.79, 125.48, 124.58, 120.22, 119.12, 117.20, 113.09.

TM-168

^{1}H NMR ($CDCl_3$, 300 MHz) δ 12.95 (s, OH), 12.89 (s, OH), 8.12 (s, 1H), 7.87 (m, 3H), 7.76 (s, 1H), 7.70 (dd, 1H), 7.64-7.62 (m, 3H), 7.48 (t, 1H), 7.34 (m, 2H), 7.22 (m, 1H), 6.88-6.85 (m, 4H), 5.84 (b, OH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 200.12, 198.80, 161.53, 155.49, 155.35, 155.02, 134.91, 134.30, 133.07, 132.64, 131.95, 131.32, 131.08, 130.45, 130.10, 128.84, 128.52, 128.48, 127.88, 127.28, 125.00, 124.75, 120.26, 116.97, 112.43, 112.32.

TM-169

^{1}H NMR ($CDCl_3$, 300 MHz) δ 12.95 (s, OH), 12.89 (s, OH), 8.11 (s, 1H), 7.88-7.84 (m, 3H), 7.74 (s, 1H), 7.70 (dd, 1H), 7.64-7.55 (m, 3H), 7.47 (t, 1H), 7.34 (m, 2H), 7.21 (m, 1H), 6.88-6.84 (m, 4H), 5.91 (b, OH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 200.09, 198.77, 161.49, 155.48, 155.34, 154.99, 134.87, 134.25, 133.05, 132.63, 131.91, 131.31, 131.04, 130.43, 130.08, 128.82, 128.48, 128.46, 127.84, 127.25, 124.98, 124.73, 120.24, 116.93, 112.40, 112.29.

TM-170

^{1}H NMR ($CDCl_3$, 300 MHz) δ 12.86 (s, 2OH), 7.68 (s, 1H), 7.64 (d, 4H), 7.43 (m, 4H), 7.22 (t, 2H), 7.08 (d, 4H), 7.02 (d, 4H), 5.70 (b, OH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 199.38, 161.95, 155.74, 155.70, 133.43, 132.82, 131.81, 131.75, 130.66, 125.27, 120.53, 117.64, 112.72.

TM-171

^{1}H NMR ($CDCl_3$, 300 MHz) δ 12.93 (s, OH), 12.88 (s, OH), 7.74-7.71 (m, 3H), 7.67-7.59 (m, 6H), 7.53-7.43 (m, 3H), 7.22-7.09 (m, 3H), 6.99 (d, 2H), 6.94 (d, 2H), 5.66 (b, OH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 199.84, 198.90, 161.67, 155.38, 155.12, 145.31, 139.69, 135.80, 133.03, 132.48, 131.44,

131.21, 130.07, 129.68, 129.10, 128.42, 127.34, 127.06, 124.78, 120.11, 117.08, 112.38, 112.27.

TM-172

^{1}H NMR ($CDCl_3$, 300 MHz) δ 13.09 (s, OH), 12.82 (s, OH), 7.53 (d, 2H), 7.47-7.41 (m, 3H), 7.23 (m, 1H), 7.10 (d, 1H), 7.05 (d, 2H), 6.94 (d, 2H), 6.84 (d, 1H), 6.63 (dd, 1H), 5.63 (s, OH), 5.47 (s, OH), 3.02 (m, 1H), 1.13 (d, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 203.38, 199.15, 161.91, 158.39, 155.82, 155.75, 150.44, 133.25, 133.112, 131.94, 131.49, 130.59, 130.14, 128.86, 125.18, 120.51, 117.60, 114.15, 113.71, 112.66, 112.35, 30.48, 24.36.

TM-175

^{1}H NMR ($CDCl_3$, 300 MHz) δ 12.96 (s, 2OH), 8.11 (s, 2H), 7.83-7.75 (m, 7H), 7.69 (d, 2H), 7.52 (m, 4H), 5.71 (b, OH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 200.22, 155.46, 134.80, 134.33, 133.07, 132.94, 132.01, 130.14, 129.00, 128.42, 128.31, 127.80, 127.00, 124.83, 112.62.

TM-176

^{1}H NMR ($CDCl_3$, 300 MHz) δ 13.10 (s, 2OH), 11.01 (s, 1H), 8.05 (m, 4H), 7.60 (m, 4H), 5.32 (s, OH).

TM-177

^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.26-7.15 (m, 6H), 6.94-6.92 (m, 2H), 6.68-6.61 (m, 3H), 6.48 (s, 1H), 4.52 (b, 4H), 3.90 (s, 2H), 3.85 (s, 2H), 3.25 (m, 1H), 1.19 (d, 6H).

TM-178

^{1}H NMR ($CDCl_3$, 300 MHz) δ 13.41 (s, OH), 9.48 (s, 1H), 8.17 (m, 1H), 8.07-7.98 (m, 3H), 7.56 (m, 4H), 5.30 (s, OH), 4.06 (s, 3H); ^{13}C NMR

($CDCl_3$, 75 MHz) δ 186.26, 185.51, 167.24, 166.94, 155.70, 153.51, 153.06, 152.07, 137.37, 137.14, 136.59, 129.03, 128.08, 127.60, 127.23, 126.96, 125.63, 125.53, 122.73, 122.37, 122.09, 113.55, 61.46.

TM-179

^1H NMR ($CDCl_3$, 300 MHz) δ 13.16 (s, OH), 12.97 (s, OH), 9.68 (s, 1H), 8.02 (d, 1H), 7.90 (d, 3H), 7.55 (m, 4H), 7.17 (d, 3H), 7.03 (d, 2H), 5.60 (s, OH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 199.11, 185.50, 166.90, 161.76, 156.34, 155.77, 155.39, 153.38, 136.66, 134.05, 132.74, 132.18, 131.48, 130.22, 128.01, 127.24, 125.27, 124.87, 122.22, 120.38, 117.22, 113.26, 111.20.

TM-180

^1H NMR ($CO(CD_3)_2$, 300 MHz) δ 12.88 (s, 1H), 12.61 (s, 1H), 9.71 (s, 1H), 8.24 (m, 2H), 8.09-7.99 (m, 3H), 7.64 (m, 2H), 7.47 (d, 2H), 7.41 (d, 1H), 7.25 (dd, 1H), 3.24 (m, 4H), 1.59 (m, 6H); ^{13}C NMR ($CO(CD_3)_2$, 75 MHz) δ 200.15, 186.80, 167.94, 161.00, 159.68, 154.37, 137.39, 134.91, 134.72, 134.48, 133.19, 132.76, 129.12, 128.39, 126.02, 123.50, 122.81, 120.29, 120.12, 117.76, 114.37, 112.10, 47.28, 26.36, 24.34.

TM-183

^1H NMR ($CDCl_3$, 300 MHz) δ 13.28 (s, OH), 13.24 (s, OH), 9.58 (s, 1H), 7.92 (d, 2H), 7.69 (t, 3H), 7.58 (t, 1H), 7.46 (m, 4H), 7.16 (d, 4H), 5.66 (s, OH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 198.90, 181.53, 161.97, 156.76, 156.29, 155.64, 155.44, 150.20, 140.48, 133.90, 132.77, 132.36, 131.16, 130.21, 128.88, 126.03, 124.90, 122.05, 120.44, 117.22, 113.13, 111.98, 111.55; ^{13}C NMR ($CO(CD_3)_2$, 75 MHz) δ 207.06, 198.90, 181.53, 161.97, 156.76, 156.29, 155.64, 155.44, 150.20, 140.48, 133.90, 132.77, 132.36, 131.16, 130.21, 128.88, 126.03, 124.90, 122.05, 120.44, 117.22, 113.13, 111.98, 111.55.

TM-190

^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.69 (b, OH), 7.99 (s, 1H), 7.79 (dd, 1H), 7.40 (s, 1H), 7.38 (d, 1H), 7.24-7.17 (m, 4H), 6.81 (s, 1H), 6.68 (b, OH), 4.82 (s, 2H), 3.96-3.81 (m, 4H), 3.32-3.23 (m, 2H), 3.07-2.98 (m, 6H), 2.87-2.82 (m, 2H), 1.66 (m, 4H), 1.47 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 168.73, 149.43, 143.15, 139.34, 135.43, 133.94, 133.28, 131.98, 130.55, 129.86, 128.86, 128.71, 128.53, 127.15, 126.79, 126.57, 115.91, 115.24, 113.89, 84.72, 47.01, 38.78, 28.87, 28.32, 25.14, 23.45.

TM-191

^{1}H NMR (CD_3OD, 300 MHz) δ 7.57-7.51 (m, 2H), 7.31-7.26 (m, 2H), 7.18-7.14 (m, 9H), 4.77 (m, 2H), 4.40 (s, 2H), 4.10 (t, 1H), 3.80 (m, 2H), 3.60-3.53 (m, 4H), 3.00 (m, 4H), 2.92 (m, 6H), 1.77 (m, 2H).

TM-193

^{1}H NMR ($CDCl_3$, 300 MHz) δ 10.34 (s, OH), 8.82 (s, 1H), 7.60 (d, 1H), 7.51 (s, 1H), 7.35 (d, 1H), 7.31 (s, 1H), 7.18-7.15 (m, 2H), 7.10 (m, 1H), 7.05-7.02 (m, 1H), 5.68 (s, 1H), 4.88 (s, 2H), 4.34 (s, 2H), 3.90 (t, 2H), 3.73 (s, 2H), 3.46 (t, 2H), 3.06 (2H), 3.00-2.92 (m, 4H), 1.65 (m, 4H), 1.43 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.67, 151.08, 145.60, 139.15, 134.94, 133.83, 133.37, 132.70, 130.85, 129.57, 128.90, 127.10, 126.60, 126.31, 125.72, 120.04, 112.14, 110.62, 47.27, 46.96, 43.66, 43.46, 28.92, 28.54, 25.13, 23.46.

TM-194

^{1}H NMR ($CDCl_3$, 300 MHz) δ 10.15 (s, OH), 8.74 (s, 1H), 7.69 (d, 1H), 7.63 (s, 1H), 7.30 (m, 2H), 7.16-7.12 (m, 2H), 7.10-7.08 (m, 1H), 7.04-7.01 (m, 1H), 6.04 (s, 1H), 4.84 (s, 2H), 4.32 (s, 2H), 3.86 (t, 2H), 3.43 (t, 2H), 3.04 (t, 2H), 2.92 (t, 2H), 2.74 (t, 2H), 1.74 (m, 1H), 0.87 (d, 6H); ^{13}C NMR

($CDCl_3$, 75 MHz) δ 169.46, 150.70, 145.59, 139.16, 138.64, 133.80, 133.58, 132.74, 130.89, 129.62, 128.89, 127.06, 126.56, 126.31, 125.65, 125.08, 120.12, 112.28, 110.01, 50.58, 47.26, 43.56, 28.87, 28.52, 19.89.

TM-197

^1H NMR ($CO(CD_3)_2$, 300 MHz) δ 7.65-7.63 (m, 3H), 7.45 (m, 1H), 7.41-7.37 (m, 2H), 7.30 (s, 0.5H), 7.21-7.14 (m, 7H), 6.83 (s, 0.5H), 4.89-4.86 (m, 3H), 4.39 (s, 1H), 3.87 (m, 3.5H), 3.52 (t, 0.5H), 3.26 (m, 1H), 3.17-3.11 (m, 4H), 2.93 (t, 1H), 2.76 (m, 2H).

TM-198

^1H NMR ($CO(CD_3)_2$, 300 MHz) δ 9.74 (b, 1H), 9.41 (s, 1H), 9.11 (s, 1H), 7.66-7.60 (m, 4H), 7.44-7.13 (m, 13H), 6.83 (s, 1H), 6.55 (t, 1H), 4.83 (s, 2H), 4.20 (t, 2H), 3.85 (m, 2H), 3.59 (m, 2H), 3.41 (m, 1H), 3.25 (m, 2H), 3.05 (m, 2H), 2.91 (m, 2H).

TM-199

^1H NMR ($CO(CD_3)_2$, 300 MHz) δ 10.12 (b, OH), 9.08 (s, 1H), 8.57 (s, 1H), 7.47 (d, 1H), 7.40 (m, 2H), 7.24 (d, 1H), 7.14-7.04 (m, 9H), 6.62 (d, 1H), 6.53 (b, 1H), 4.78 (s, 2H), 4.41 (s, 2H), 4.06 (m, 1H), 3.84 (t, 2H), 3.54 (t, 2H), 3.02 (m, 2H), 2.95-2.89 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 167.46, 148.30, 143.51, 143.07, 140.52, 139.87, 135.40, 130.88, 130.75, 130.52, 130.32, 129.75, 129.32, 128.88, 127.50, 127.40, 127.08, 125.91, 125.76, 118.62, 116.09, 115.80, 86.37, 66.10, 52.00, 48.17, 48.08, 44.60, 39.81.

TM-1202

^1H NMR ($CO(CD_3)_2$, 300 MHz) δ 9.24-8.58 (b, OH), 7.61-7.59 (m, 2H), 7.39-7.30 (m, 4H), 7.21-7.14 (m, 7H), 6.84 (s, 2H), 4.85 (s, 1H), 4.82 (s,

1H), 4.52 (s, 1H), 3.88 (s, 1H), 3.88-3.71 (m, 3H), 3.53-3.25 (m, 10H), 3.30-2.86 (m, 6H).

TM-1205

^{1}H NMR ($CO(CD_3)_2$, 300 MHz) δ 9.17 (b, 2OH), 7.66-7.64 (m, 2H), 7.35-7.33 (m, 2H), 7.23-7.11 (m, 10H), 6.53 (b, 1H), 4.86 (s, 2H), 3.82 (m, 2H), 3.38 (m, 2H), 3.14 (m, 2H), 2.98 (m, 2H), 2.88-2.74 (m, 7H); ^{13}C NMR ($CO(CD_3)_2$, 75 MHz) δ 169.23, 150.40, 146.72, 140.27, 139.69, 139.50, 139.48, 135.09, 134.51, 130.28, 129.58, 129.49, 129.18, 129.11, 127.09, 127.04, 125.83, 125.74, 120.95, 115.35, 113.88, 52.34, 47.30, 45.30, 36.52, 35.26, 35.01, 20.84.

TM-1206

^{1}H NMR ($CO(CD_3)_2$, 300 MHz) δ 10.12 (b, OH), 9.06 (b, OH), 8.48 (b, OH), 7.65 (d, 1H), 7.63 (s, 1H), 7.51 (m, 1H), 7.41-7.32 (m, 3H), 7.23-7.14 (m, 8H), 6.50 (t, 1H), 4.88 (s, 2H), 3.87 (t, 2H), 3.17 (t, 2H), 3.05 (t, 2H), 2.90-2.89 (m, 2H), 2.84 (s, 3H), 2.78 (t, 2H), 2.64 (t, 2H), 1.87 (m, 2H); ^{13}C NMR ($CO(CD_3)_2$, 75 MHz) δ 169.36, 150.76, 146.87, 142.57, 140.43, 139.95, 139.67, 135.34, 134.60, 130.39, 129.62, 129.34, 129.22, 129.18, 128.27, 127.15, 126.66, 125.96, 125.84, 121.42, 121.09, 115.29, 113.69, 53.35, 50.48, 49.56, 45.42, 38.70, 36.67, 35.04, 33.39, 20.83.

TM-1209

^{1}H NMR ($CO(CD_3)_2$, 300 MHz) δ 10.14 (b, OH), 9.07 (b, OH), 8.52 (b, OH), 7.65-7.61 (m, 2H), 7.40 (s, 1H), 7.39 (d, 1H), 7.24 (d, 2H), 7.18-7.14 (m, 6H), 6.53 (t, 1H), 4.90 (s, 2H), 4.40 (s, 2H), 3.88 (t, 2H), 3.53 (t, 2H), 3.18 (t, 2H), 3.08 (m, 2H), 2.92 (m, 2H), 2.77 (t, 2H); ^{13}C NMR ($CO(CD_3)_2$, 75 MHz) δ 169.31, 151.01, 147.08, 140.45, 139.94, 138.68, 135.29, 134.65, 134.29, 133.00, 132.44, 131.44, 130.42, 129.67, 129.14, 127.52, 127.29,

127.11, 125.97, 125.77, 121.45, 114.32, 113.77, 48.12, 45.16, 45.06, 44.60, 35.91.

TM-1212

^{1}H NMR ($CO(CD_3)_2$, 300 MHz) δ 10.11 (b, OH), 9.06 (b, OH), 8.54 (b, OH), 7.97 (d, 2H), 7.68-7.64 (m, 2H), 7.40-7.39 (m, 2H), 7.22 (d, 2H), 7.12 (m, 4H), 7.00-6.96 (m, 4H), 6.55 (t, 1H), 4.91 (s, 2H), 4.37 (s, 2H), 3.87 (t, 2H), 3.50 (t, 2H), 3.17 (t, 2H), 3.05 (m, 2H), 2.90 (t, 2H), 2.80 (t, 2H); ^{13}C NMR ($CO(CD_3)_2$, 75 MHz) δ 169.29, 162.75, 154.84, 150.92, 147.02, 140.44, 139.89, 136.15, 135.26, 132.89, 131.39, 130.41, 129.63, 127.49, 127.25, 127.07, 125.97, 125.80, 121.41, 120.90, 117.80, 114.21, 113.80, 48.08, 45.36, 44.56, 35.94, 26.54, 20.83.

TM-1214

^{1}H NMR ($CO(CD_3)_2$, 300 MHz) δ 10.01 (b, OH), 8.90 (b, OH), 7.46-7.30 (m, 2H), 7.19-6.98 (m, 7H), 6.72 (b, 1H), 4.77 (s, 2H), 4.29 (s, 2H), 3.81 (m, 2H), 3.40 (t, 2H), 2.94 (m, 2H), 2.87 (m, 2H).

TM-1217

^{1}H NMR ($CO(CD_3)_2$, 300 MHz) δ 10.22 (b, OH), 9.15 (b, OH), 8.43 (b, OH), 7.65 (m, 2H), 7.40 (d, 1H), 7.38 (s, 1H), 7.24-7.13 (m, 5H), 6.49 (t, NH), 6.33 (m, NH), 4.90 (s, 2H), 3.90 (t, 2H), 3.14 (t, 2H), 3.07 (t, 2H), 2.94 (m, 2H), 2.77 (t, 2H), 2.60 (d, 3H); ^{13}C NMR ($CO(CD_3)_2$, 75 MHz) δ 169.71, 150.94, 146.71, 140.43, 139.93, 139.67, 135.34, 134.44, 130.36, 129.61, 129.21, 127.14, 125.95, 125.86, 120.97, 116.15, 113.10, 45.42, 45.32, 36.65.

TM-1218

^{1}H NMR ($CO(CD_3)_2$, 300 MHz) δ 10.02 (b, 1H), 9.04 (b, 2H), 7.69-7.64 (m, 3H), 7.43 (m, 2H), 7.12 (m, 4H), 6.91-6.82 (m, 1H), 6.67-6.43 (m,

3H), 5.13 (s, 1H), 4.93 (d, 2H), 4.37 (s, 2H), 3.87 (t, 2H), 3.50 (m, 2H), 3.24 (m, 2H), 3.05 (m, 2H), 2.91 (m, 2H), 2.71 (m, 2H); ^{13}C NMR ($CO(CD_3)_2$, 75 MHz) δ 169.24, 150.75, 146.99, 145.72, 144.85, 144.35, 141.05, 140.32, 139.87, 135.46, 135.40, 135.19, 134.59, 134.19, 132.86, 129.61, 127.48, 127.23, 127.06, 121.34, 114.14, 96.30, 96.16, 48.08, 44.56, 36.05, 28.70.

TM-1219

^{1}H NMR ($CO(CD_3)_2$, 300 MHz) δ 9.07 (b, 1H), 7.58-7.09 (m, 18H), 6.58 (s, 1H), 4.89 (s, 2H), 4.35 (s, 2H), 3.81 (t, 2H), 3.64 (m, 2H), 3.19 (m, 2H), 2.99 (m, 2H), 2.82 (m, 4H); ^{13}C NMR ($CO(CD_3)_2$, 75 MHz) δ 169.24, 150.83, 147.02, 141.42, 140.35, 139.83, 139.72, 138.84, 135.31, 135.18, 134.61, 134.16, 132.84, 132.66, 130.84, 130.62, 130.38, 130.16, 129.66, 129.43, 127.98, 127.61, 127.23, 125.96, 125.78, 121.39, 114.17, 48.07, 45.32, 44.55, 39.75, 36.22, 23.23, 20.83, 14.34.

TM-1220

^{1}H NMR ($CO(CD_3)_2$, 300 MHz) δ 9.17 (b, OH), 7.71-7.36 (m, 13H), 7.12 (m, 5H), 5.62 (s, 2H), 4.89 (s, 2H), 4.19 (m, 2H), 3.80 (m, 2H), 3.49 (m, 2H), 3.01 (m, 2H), 2.90 (m, 2H); ^{13}C NMR ($CO(CD_3)_2$, 75 MHz) δ 169.23, 150.77, 146.99, 141.21, 140.67, 140.30, 140.04, 137.54, 135.30, 135.04, 134.60, 134.14, 132.81, 130.34, 129.68, 129.58, 129.23, 128.14, 127.54, 127.50, 127.22, 127.02, 126.07, 125.81, 121.37, 114.12, 113.91, 48.05, 47.34, 44.54, 39.75, 28.58.

TM-1225

^{1}H NMR ($CO(CD_3)_2$, 300 MHz) δ 10.26 (s, OH), 8.30 (b, 1H), 7.98 (s, 1H), 7.85 (m, 2H), 7.69 (m, 3H), 7.46-7.37 (m, 4H), 7.13 (m, 4H), 4.42 (s, 2H), 3.56 (t, 2H), 2.90 (t, 2H); ^{13}C NMR ($CO(CD_3)_2$, 75 MHz) δ 170.93, 156.31, 141.14, 138.16, 134.56, 134.49, 133.32, 129.74, 129.68, 128.07, 127.97, 127.48, 127.41, 127.18, 127.01, 122.87, 121.07, 47.99, 44.51, 20.83.

TM-1226

^{1}H NMR ($CO(CD_3)_2$, 300 MHz) δ 9.10 (b, OH), 7.66-7.61 (m, 2H), 7.44 (d, 1H), 7.38 (s, 1H), 7.31-7.20 (m, 5H), 6.36 (b, 1H), 4.93 (s, 2H), 3.90 (m, 2H), 3.28 (t, 2H), 3.08 (m, 2H), 2.85 (t, 2H), 2.77 (s, 3H), 2.59 (s, 3H); ^{13}C NMR ($CO(CD_3)_2$, 75 MHz) δ 169.60, 150.64, 146.63, 140.77, 139.62, 136.93, 135.53, 134.35, 130.46, 129.66, 129.41, 129.25, 127.16, 126.39, 126.31, 120.90, 116.09, 113.37, 35.38, 35.08, 20.84.

TM-1227

^{1}H NMR ($CO(CD_3)_2$, 300 MHz) δ 9.33 (b, OH), 7.99 (b, 1H), 7.64-7.62 (m, 2H), 7.42-7.22 (m, 12H), 4.94 (s, 2H), 4.32 (s, 2H), 3.89 (m, 2H), 3.26 (m, 2H), 3.07 (m, 2H), 2.94 (m, 2H), 2.75 (s, 3H), 2.68 (s, 3H); ^{13}C NMR ($CO(CD_3)_2$, 75 MHz) δ 169.50, 163.05, 150.92, 147.04, 140.76, 139.59, 137.48, 136.92, 135.49, 134.67, 130.46, 129.64, 129.23, 129.09, 128.49, 127.15, 126.37, 126.29, 121.37, 115.35, 113.52, 54.58, 52.31, 35.37, 35.06, 34.73, 20.83.

TW-1- 5-苄基-4′-(5-苯基-戊基)-联苯-2, 3, 4-三醇

^{1}H NMR (CD_3COCD_3, 300 MHz) δ (ppm) 7.34-7.19 (m, 14H), 6.64 (s, 1H), 5.56 (s, 1H), 5.43 (s, 1H), 5.36 (s, 1H), 4.0 (s, 2H), 2.67-2.70 (m, 4H), 1.85-1.65 (m, 4H), 1.41-1.26 (m, 4H); ^{13}C NMR (CD_3COCD_3) δ (ppm) 142.79, 142.10, 141.86, 140.73, 138.87, 134.32, 132.35, 131.56, 129.18, 128.71, 128.33, 126.04, 125.60, 121.88, 120.38, 120.07, 35.95, 35.61, 31.41, 29.14, 21.06, 14.19.

TW-2- 5-苄基-4′-癸基-联苯-2, 3, 4-三醇

^{1}H NMR (CD_3COCD_3, 300 MHz) δ (ppm) 7.36-7.20 (m, 9H), 6.63 (s, 1H), 5.39 (s, 1H), 5.31 (s, 1H), 5.26 (s, 1H), 4.0 (s, 2H), 2.65 (t, 2H), 1.62-1.58 (m, 4H), 1.34-1.27 (m, 14H), 0.99-0.88 (m, 3H); ^{13}C NMR (CD_3COCD_3) δ (ppm) 142.36, 141.76, 140.68, 138.68, 134.16, 131.55, 129.28, 128.70, 128.46, 126.07, 121.81, 120.28, 120.07, 31.91, 31.60, 31.50, 29.63, 29.60, 29.53, 29.38, 29.35.

TW-3- 5-苄基-4′-叔丁基-联苯-2, 3, 4-三醇

^{1}H NMR (CD_3COCD_3, 300 MHz) δ (ppm) 7.50 (d, 2H), 7.38 (d, 2H), 7.21-7.20 (m, 5H), 6.64 (s, 1H), 5.36 (s, 1H), 5.30 (s, 1H), 5.25 (s, 1H), 4.0 (s, 2H), 1.38 (s, 9H); ^{13}C NMR (CD_3COCD_3) δ (ppm) 141.77, 140.64, 138.73,

133.99, 131.53, 128.71, 128.50, 128.46, 126.16, 126.06, 121.86, 120.26, 120.13, 35.61, 34.59, 31.31.

TW-4- 4′-叔丁基-5-异丙基-联苯-2,3,4-三醇

^{1}H NMR (CD_3COCD_3, 300 MHz) δ (ppm) 7.42-7.31 (m, 4H), 6.72 (s, 1H), 5.70 (s, 1H), 5.64 (s, 1H), 5.37 (s, 1H), 3.33-3.20 (m, 1H), 2.70 (q, 2H), 1.73-1.63 (m, 2H), 1.41-1.20 (m, 16H), 0.95 (t, 3H); ^{13}C NMR (CD_3COCD_3) δ (ppm) 142.31, 141.32, 137.88, 134.51, 131.10, 129.28, 128,76, 127.65, 120.20, 117.78, 35.69, 31.93, 31.52, 29.64, 29.56, 29.42, 29.37, 26.85.

TW-5- 4′-癸基-5-异丙基-联苯-2,3,4-三醇

^{1}H NMR (CD_3COCD_3, 300 MHz) δ (ppm) 7.52 (d, 2H), 7.40 (d, 2H), 6.68 (s, 1H), 5.43 (s, 2H), 5.21 (s, 1H), 3.31-3.21 (m, 1H), 1.39 (s, 9H), 1.26 (d, 6H); ^{13}C NMR (CD_3COCD_3) δ (ppm) 150.17, 140.43, 137.84, 134.32, 131.09, 128.53, 126.26, 117.67, 120.01, 34.62, 31.33, 26.88, 22.73.

TW-6- 5-(3-苯基-丙基)-4′-十一烷基-联苯-2,3,4-三醇

^{1}H NMR (CD_3COCD_3, 300 MHz) δ (ppm) 7.39-7.14 (m, 9H), 6.56 (s, 1H), 5.51 (s, 1H), 5.45 (s, 1H), 5.28 (s, 1H), 2.76-2.55 (m, 6H), 2.05-1.95 (m, 2H), 1.77-1.56 (m, 2H), 1.48-1.23 (m, 16H), 0.93 (t, 3H); ^{13}C NMR (CD_3COCD_3) δ (ppm) 142.77, 142.36, 141.85, 138.12, 134.28, 131.26, 129.30, 129.13, 128.68, 128.25, 125.63, 121.21, 120.11, 31.91, 31.53, 31.50, 29.65, 29.62, 29.54, 29.38, 29.35, 29.12.

TW-7- 5-[2-(4-叔丁基-苯基)-乙基]-4′-十一烷基-联苯-2,3,4-三醇

^{1}H NMR (CD_3COCD_3, 300 MHz) δ (ppm) 7.52-7.18 (m, 8H), 6.57 (s, 1H), 5.45 (s, 1H), 5.33 (s, 1H), 5.29 (s, 1H), 2.71-2.60 (m, 4H), 2.68 (t, 2H), 1.92-1.60 (m, 2H), 1.50-1.22 (m, 21H), 0.93 (t, 3H); ^{13}C NMR (CD_3COCD_3) δ (ppm) 148.63, 142.29, 141.73, 139.13, 138.22, 134.24, 131.36, 130.55, 129.56, 128.66, 128.23, 125.20, 121.42, 120.90, 120.09, 31.91, 31.86, 31.51, 31.42, 29.64, 29.60, 29.53, 29.39, 29.35, 22.70, 14.14.

TW-8- 5-(4-叔丁基-苄基)-4′-十一烷基-联苯-2,3,4-三醇

^{1}H NMR (CD_3COCD_3, 300 MHz) δ (ppm): 7.42-7.25 (m, 8H), 6.71 (s, 1H), 5.55 (s, 1H), 5.41 (s, 1H), 5.36 (s, 1H), 4.16 (s, 2H), 2.70 (t, 2H), 1.70 (m, 2H), 1.36 (m, 23H), 0.96 (t, 3H); ^{13}C NMR (CD_3COCD_3) δ (ppm):149.28, 142.72, 142.22, 139.22, 137.96, 134.71, 132.05, 129.65, 129.20, 128.72, 125.86, 122.40, 120.91, 120.71, 36.14, 35.63, 34.80, 32.89, 32.07, 31.96, 31.84, 30.12, 30.09, 30.01, 29.87, 29.82, 23.17, 14.62.

TW-9- 5-(4-异丙基-苄基)-4′-十一烷基-联苯-2,3,4-三醇

^{1}H NMR (CD_3COCD_3, 300 MHz) δ (ppm) 7.39-7.15 (m, 8H), 6.67 (s, 1H), 5.39 (s, 1H), 5.29 (s, 1H), 5.27 (s, 1H), 4.0 (s, 2H), 2.94-2.84 (m, 1H), 2.66 (t, 2H), 1.67-1.62 (m, 2H), 1.36-1.23 (m, H), 0.91 (t, 3H); ^{13}C NMR (CD_3COCD_3) δ (ppm) 146.61, 142.29, 141.70, 138.71, 137.84, 134.23, 131.58, 129.22, 128.71, 128.52, 126.57, 121.84, 120.37, 120.21, 35.68, 35.31, 33.68, 31.91, 31.50, 29.64, 29.61, 29.53, 29.39, 29.35, 24.03, 22.70, 14.13.

TW-10- 5-苄基-4′-十一烷基-联苯-2,3,4-三醇

^{1}H NMR (CD_3COCD_3, 300 MHz) δ (ppm) 7.30-6.85 (m, 9H), 6.46 (s, 1H), 5.53 (s, 1H), 5.03 (s, 1H), 3.70 (s, 2H), 2.75 (t, 2H), 1.74-1.69 (m, 2H), 1.52-1.24 (m, 14H), 0.95 (t, 3H); ^{13}C NMR (CD_3COCD_3) δ (ppm) 143.34, 142.91, 141.24, 140.70, 131.72, 131.31, 130.65, 129.42, 129.21, 128.75, 128.06, 125.66, 120.96, 109.3, 38.83, 35.71, 31.93, 31.41, 29.71, 29.66, 29.55, 29.38, 22.70, 14.14.

TW-11- 5-苄基-4′-(3-苯基-丙基)-联苯-2,3,4-三醇

^{1}H NMR (CD_3COCD_3, 300 MHz) δ (ppm) 7.60-7.21 (m, 14H), 6.68 (s, 1H), 5.63 (s, 1H), 5.54 (s, 1H), 5.32 (s, 1H), 4.03 (s, 2H), 3.00 (s, 1H); ^{13}C NMR (CD_3COCD_3) δ (ppm) 141.80, 141.57, 141.09, 140.60, 138.73, 134.56, 131.57, 129.26, 128.81, 128.68, 128.46, 128.41, 128.38, 126.08, 126.01, 121.87, 120.31, 120.13, 37.78, 37.53, 35.62.

TW-12- 5,4′-二苄基-联苯-2,3,4-三醇

^{1}H NMR (CD_3COCD_3, 300 MHz) δ (ppm) 7.40-7.19 (m, 14H), 6.64 (m, 1H), 5.44 (s, 1H), 5.36 (s, 1H), 5.27 (s, 1H), 4.03 (s, 2h), 3.95 (s, 2H); ^{13}C NMR (CD_3COCD_3) δ (ppm) 141.81, 140.77, 140.57, 140.49, 138.73, 134.74, 131.60, 131.59, 129.56, 129.05, 128.58, 128.54, 128.51, 128.20, 126.12, 126.08, 121.85, 120.21, 120.17, 41.63, 35.62.

TW-13- 5-甲基-4′-十一烷基-联苯-2,3,4-三醇

^{1}H NMR (CD_3COCD_3, 300 MHz) δ (ppm) 7.31 (d, 2H), 7.18 (d, 2H), 6.49 (s, 1H), 5.38 (s, 1H), 5.21 (s, 1H), 4.92 (s, 1H), 2.68 (t, 2H), 2.01 (s, 3H), 1.74-1.61 (m, 2H), 1.41-1.28 (m, 16H), 0.90 (t, 3H); ^{13}C NMR (CD_3COCD_3) δ (ppm) 143.16, 142.84, 140.49, 132.19, 130.37, 129.38, 128.96, 128.04, 35.77, 31.94, 31.40, 29.69, 29.65, 29.63, 29.44, 29.35, 29.27, 22.70, 19.77, 14.14.

TW-14- 5-(2-异丙基-苄基)-4′-十一烷基-联苯-2,3,4-三醇

^{1}H NMR (CD_3COCD_3, 300 MHz) δ (ppm) 7.40-7.10 (m, 8H), 6.4 (s, 1H), 5.38 (s, 1H), 5.37 (s, 1H), 5.22 (s, 1H), 4.0 (s, 2H), 3.27-3.20 (m, 1H), 2.64 (t, 2H), 1.65-1.58 (m, 2H), 1.46-1.21 (m, 20H), 0.91 (t, 3H); ^{13}C NMR (CD_3COCD_3) δ (ppm) 147.31, 142.30, 141.58, 138.42, 136.51, 134.18, 131.30, 129.93, 129.24, 128.68, 126.82, 125.73, 125.42, 121.30, 120.24, 119.98, 35.65, 32.20, 31.92, 31.47, 29.70, 29.64, 29.60, 29.53, 29.38, 29.34, 28.83, 23.77, 22.70, 14.14.

TW-15- N-[2-氯-4-(4-氯-苯磺酰基)-苯基]-2,3,4-三羟基-5-苯乙基-苯甲酰胺

^{1}H NMR (CD_3COCD_3, 300 MHz) δ (ppm) 12.30 (s, 1H), 7.72-7.21 (m, 14H), 6.58 (s, 1H), 5.91 (s, 1H), 5.67 (s, 1H), 2.96 (s, 4H), 2.7 (t, 2H), 1.74-1.68 (m, 2H), 1.58-1.21 (m, 14H), 0.91 (t, 3H); ^{13}C NMR (CD_3COCD_3) δ (ppm) 148.15, 146.44, 143.58, 141.94, 140.24, 138.22, 135.86, 131.59, 128.93, 128.72, 128.31, 127.78, 127.45, 127.05, 125.96, 124.24, 121.18, 119.45, 117.57, 36.19, 36.11, 31.92, 31.74, 31.62, 29.63, 29.55, 29.42, 29.36, 22.71, 14.15.

TW-16- N-[2-氯-4-(4-氯-苯磺酰基)-苯基]-2,3,4-三羟基-5-苄基-苯甲酰胺

^{1}H NMR (CD_3COCD_3, 300 MHz) δ (ppm) 11.80 (s, 1H), 9.07 (d, 2H), 8.29 (s, 1H), 7.95 (d, 2H), 7.61-7.14 (m, 10H), 7.65 (s, 1H), 6.63 (s, 1H), 5.86 (s, 1H), 2.95 (s, 4H); ^{13}C NMR (CD_3COCD_3) δ (ppm) 148.42, 147.22, 141.50, 140.94, 140.30, 139.53, 134.99, 131.66, 130.05, 129.79, 129.26, 128.61, 128.30, 126.02, 123.37, 120.67, 120.14, 117.42, 106.16, 35.74, 31.71.

TW-20- N-(4-苯氧基-苯基)-2,3,4-三羟基-5-苯乙基-苯甲酰胺

^{1}H NMR (CD_3COCD_3, 300 MHz) δ (ppm) 11.29 (s, 1H), 7.51-7.02 (m, 15H), 6.57 (s, 1H), 5.91 (s, 1H), 5.69 (s, 1H), 2.94 (s, 4H); ^{13}C NMR (CD_3COCD_3) δ (ppm) 168.33, 157.21, 154.36, 148.11, 146.42, 141.93, 131.89, 131.57, 129.78, 128.89, 128.29, 125.92, 123.35, 122.92, 119.50, 119.42, 118.72, 117.52, 106.45, 36.16, 31.75.

TW-21- N-(3-苯磺酰基-苯基)-2,3,4-三羟基-5-苯乙基-苯甲酰胺

^{1}H NMR (CD_3COCD_3, 300 MHz) δ (ppm) 12.0 (s, 1H), 8.15-7.21 (m, 15H), 6.72 (s, 1H), 6.00 (s, 1H), 5.79 (s, 1H), 2.89 (s, 4H); ^{13}C NMR (CD_3COCD_3) δ (ppm) 148.50, 147.20, 142.11, 142.0, 133.49, 131.52, 131.20, 129.42, 128.88, 128.30, 127.66, 125.92, 124.62, 120.05, 119.68, 118.21, 36.15, 31.58.

TW-22- N-(3-苯磺酰基-苯基)-5-[2-(4-叔丁基-苯基)-乙基]-2,3,4-三羟基-苯甲酰胺

^{1}H NMR (CD_3COCD_3, 300 MHz) δ (ppm) 12.08 (s, 1H), 8.19 (d; 2H), 7.97 (t, 3H), 7.72 (d, 1H), 7.62-7.16 (m, 10H), 6.89 (s, 1H), 5.96 (s, 1H), 5.73 (s, 1H), 2.89 (s, 1H), 1.32 (s, 9H); ^{13}C NMR (CD_3COCD_3) δ (ppm) 168.68, 148.74, 148.35, 146.91, 142.14, 141.02, 138.86, 138.19, 133.44, 131.56, 130.93, 130.20, 129.40, 128.84, 128.21, 127.65, 125.72, 125.20, 123.60, 120.34, 119.62, 117.65, 106.24, 35.64, 34.35, 31.60, 31.41.

TW-23- 5-[2-(4-叔丁基-苯基)-乙基]-N-[2-氯-3-(4-氯-苯磺酰基)-苯基]-2,3,4-三羟基-苯甲酰胺

^{1}H NMR (CD_3COCD_3, 300 MHz) δ (ppm) 11.82 (s, 1H), 9.08 (s, 1H), 8.37 (s, 1H), 7.95 (d, 2H), 7.67-7.15 (m, 10H), 6.74 (s, 1H), 5.94 (s, 1H), 5.64 (s, 1H), 2.94 (s, 4H), 1.29 (s, 9H); ^{13}C NMR (CD_3COCD_3) δ (ppm) 168.10, 148.84, 148.45, 147.44, 141.02, 140.32, 139.57, 138.47, 135.03, 131.69, 130.09, 129.29, 128.26, 128.14, 125.25, 123.39, 120.66, 120.52, 117.23, 106.22, 35.20, 34.36, 31.58, 31.37.

TW-24- N-(3-异丙基-苯基)-2,3,4-三羟基-5-苯乙基-苯甲酰胺

^{1}H NMR (CD_3COCD_3, 300 MHz) δ (ppm) 7.37-7.08 (m, 10H), 6.57 (s, 1H), 5.91 (br, 2H), 3.92-3.78 (m, 5H), 1.31 (d, 6H); ^{13}C NMR (CD_3COCD_3) δ (ppm) 168.34, 150.10, 148.11, 146.52, 141.95, 136.64, 131.57, 129.04, 128.90, 128.27, 125.92, 123.30, 119.40, 119.05, 118.54, 117.57, 106.67, 36.17, 34.13, 31.70, 23.93.

TW-25- N-(4-叔丁基-苄基)-2,3,4-三羟基-5-苯乙基-苯甲酰胺

^{1}H NMR (CD_3COCD_3, 300 MHz) δ (ppm) 12.66 (s, 1H), 7.46-7.15 (m, 9H), 6.46 (s, 1H), 6.12 (s, 1H), 5.83 (s, 1H), 5.65 (s, 1H), 4.58 (d, 2H), 2.87 (s, 4H), 1.36 (s, 9H); ^{13}C NMR (CD_3COCD_3) δ (ppm) 169.77, 150.98, 147.95, 146.01, 141.92, 134.41, 131.42, 128.70, 128.41, 127.81, 125.81, 119.20, 117.30, 106.23, 43.25, 36.23, 24.58, 31.80, 31.33.

TW-26- N-[2-氯-3-(4-氯-苯磺酰基)-苯基]-2,3,4-三羟基-5-(4-异丙基-苄基)-苯甲酰胺

^{1}H NMR (CD_3COCD_3, 300 MHz) δ (ppm) 11.81 (s, 1H), 9.02 (s, 1H), 8.33 (s, 1H), 7.93 (d, 2H), 7.74-6.95 (m, 8H), 6.55 (s, 1H), 6.08 (s, 1H), 5.60 (s, 1H), 3.97 (s, 2H), 2.96-2.85 (m, 1H), 1.28 (d, 6H).

TW-27

^{1}H NMR (CD_3COCD_3, 300 MHz) δ (ppm) 11.98 (s, 1H), 7.78 (s, 1H), 7.50-7.18 (m, 8H), 6.52 (s, 1H), 5.99 (s, 1H), 5.74 (s, 1H), 2.93 (s, 4H); ^{13}C NMR (CD_3COCD_3) δ (ppm) 168.27, 148.10, 146.82, 141.85, 136.25, 132.91, 131.58, 130.58, 128.93, 128.30, 125.95, 122.44, 121.98, 119.71, 106.17, 36.11, 31.65.

TW-28

^{1}H NMR (CD_3COCD_3, 300 MHz,) δ (ppm) 10.60 (s, 1H), 7.69 (d, 2H), 7.50 (s, 1H), 7.42-7.09 (m, 8H), 6.59 (s, 1H), 5.91 (s, 1H), 5.68 (s, 1H), 2.95 (s, 4H), 2.28 (s, 3H); ^{13}C NMR (CD_3COCD_3) δ (ppm) 168.52, 148.27, 146.42, 141.78, 134.37, 131.60, 131.05, 130.63, 128.77, 128.27, 126.72, 126.28, 125.83, 124.42, 119.43, 117.42, 106.45, 36.00, 31.83, 17.90.

TW-29- N-[4-(4-叔丁基-苯磺酰基)-3-三氟甲基-苯基]-2,3,4-三羟基-5-苯乙基-苯甲酰胺

^{1}H NMR (CD_3COCD_3, 300 MHz) δ (ppm) 11.67 (s, 1H), 8.39 (d, 1H), 8.05 (d, 1H), 7.85 (d, 2H), 7.70 (d, 2H), 7.49 (d, 2H), 7.32-7.17 (m, 6H), 6.62 (s, 1H), 5.96 (s, 1H), 5.64 (s, 1H), 2.92 (s, 4H), 1.33 (s, 9H); ^{13}C NMR (CD3COCD3) δ (ppm) 168.59, 157.34, 141.88, 141.75, 138.14, 134.69, 133.93, 131.55, 129.00, 128.29, 127.60, 126.07, 125.92, 122.60, 119.95, 118.10, 105.93, 36.03, 35.31, 31.41, 31.00.

TW-30- N-[4-(4-叔丁基-苯磺酰基)-3-三氟甲基-苯基]-2,3,4-三羟基-5-(4-叔丁基-苯乙基)-苯甲酰胺

^{1}H NMR (CD_3COCD_3, 300 MHz) δ (ppm) 11.77 (s, 1H), 8.42 (d, 1H), 8.14 (s, 1H), 8.03 (d, 2H), 7.79 (d, 2H), 7.50 (d, 2H), 7.30 (d, 2H), 7.14 (d, 2H), 6.86 (s, 1H), 5.94 (s, 1H), 5.62 (s, 1H), 2.91 (s, 4H), 1.33 (s, 9H), 1.31 (s,

9H); ^{13}C NMR (CD3COCD3) δ (ppm) 168.60, 157.31, 148.90, 148.43, 147.30, 141.67, 138.66, 138.17, 134.82, 133.90, 131.64, 128.78, 128.21, 126.06, 125.21, 122.80, 120.59, 117.71, 105.97, 35.54, 35.21, 34.37, 31.78, 31.39, 31.00.

TW-31- N-(3-苯磺酰基-苯基)-2,3-二羟基-5-苯乙基-苯甲酰胺

^{1}H NMR (CD_3COCD_3, 300 MHz) δ (ppm) 11.85 (br, 1H), 8.48 (s, 1H), 8.18 (s, 1H), 8.15 (d, 1H), 7.94 (d, 2H), 7.73 (d, 1H), 7.56-7.23 (m, 8H), 7.17 (d, 2H), 6.95 (d, 1H), 6.82 (s, 1H), 2.90-2.80 (m, 4H); ^{13}C NMR (CD_3COCD_3) δ (ppm) 169.75, 147.34, 145.59, 142.00, 141.44, 140.90, 138.15, 133.53, 132.67, 130.20, 129.43, 128.75, 128.32, 127.72, 127.57, 126.00, 123.70, 119.67, 119.40, 116.33, 113.47, 37.80, 37.07.

TW-32- N-[(4-异丙基-苯磺酰基)-苯基]-N-乙基-2,3-二羟基-5-苯乙基-苯甲酰胺

^{1}H NMR (CD_3COCD_3, 300 MHz) δ (ppm) 10.74 (s, 1H), 7.92 (d, 2H), 7.79 (d, 2H), 7.30-7.18 (m, 7H), 6.93 (d, 2H), 6.61 (d, 2H), 5.86 (d, 2H), 5.69 (s, 1H), 5.32 (s, 1H), 3.96 (q, 2H), 2.88-2.81 (m, 1H), 2.32-2.07 (m, 4H), 1.28-1.18 (m, 9H); ^{13}C NMR (CD_3COCD_3) δ (ppm) 171.07, 155.10, 147.85, 146.18, 145.24, 140.99, 140.48, 138.17, 131.42, 128.90, 128.43, 128.31, 137.89, 127.77, 127.50, 125.98, 120.89, 118.06, 115.19, 46.54, 37.58, 37.00, 34.08, 23.50, 14.14.

TW-33- N-[(4-异丙基-苯磺酰基)-苯基]-N-乙基-2,3,4-三羟基-5-苯乙基-苯甲酰胺

^{1}H NMR (CD_3COCD_3, 300 MHz) δ (ppm) 11.54 (s, 1H), 7.92 (d, 2H), 7.80 (d, 2H), 7.43-7.16 (m, 8H), 6.98 (d, 2H), 5.81(s, 1H), 5.63 (s, 1H), 5.46 (s, 1H), 3.94 (q, 2H), 2.95-2.87 (m, 1H), 2.33-2.17 (m, 4H), 1.27-1.18 (m, 9H); ^{13}C NMR (CD_3COCD_3) δ (ppm) 171.38, 155.11, 148.24, 147.68, 145.21, 141.53, 140.26, 138.26, 131.29, 128.95, 128.45, 128.26, 127.90, 127.74, 127.51, 125.85, 122.76, 118.36, 46.54, 35.87, 34.09, 31.03, 23.51, 12.81.

TW-34- N-[2-氯-5-(4-氯-苯磺酰基)-苯基]-2,3-二羟基-苯乙基-苯甲酰胺

^{1}H NMR (CD_3COCD_3, 300 MHz) δ (ppm) 11.60 (s, 1H), 9.08 (d, 1H), 8.51 (s, 1H), 7.95 (d, 2H), 7.71 (dd, 1H), 7.62-7.12 (m, 9H), 7.02 (s, 1H), 6.67 (s, 1H), 5.82 (s, 1H), 2.92 (s, 4H); ^{13}C NMR (CD_3COCD_3) δ (ppm) 168.13, 147.60, 145.97, 141.07, 140.96, 140.3, 139.49, 134.80, 132.94, 130.13, 129.83, 129.29, 128.56, 128.51, 128.39, 126.17, 123.74, 120.83, 118.85, 115.63, 113.35, 37.81, 37.25.

TW-35- N-[2-氯-5-(4-氯-苯磺酰基)-苯基]-2,3,4-三羟基-5-(2-异丙基-苄基)-苯甲酰胺

^{1}H NMR (CD_3COCD_3, 300 MHz) δ (ppm) 11.80 (s, 1H), 9.08 (d, 2H), 8.22 (s, 1H), 7.92 (d, 2H), 7.63 (dd, 1H), 7.50-7.11 (m, 8H), 6.35 (s, 1H), 6.06 (s, 1H), 5.70 (s, 1H), 4.03 (s, 2H), 3.02 (m, 1H), 1.17 (d, 6H); ^{13}C NMR (CD_3COCD_3) δ (ppm) 167.85, 148.40, 147.55, 146.77, 140.97, 140.47, 139.57, 135.42, 135.03, 131.47, 130.75, 129.89, 129.77, 129.25, 128.09, 127.31, 126.01, 125.74, 123.12, 120.37, 119.83, 116.68, 106.23, 31.61, 28.96, 23.94.

TW-36- N-[4-(4-叔丁基-苯磺酰基)-3-三氟甲基-苯基]-2,3,4-三羟基-5-(2-异-丙基-苄基)-苯甲酰胺

^{1}H NMR (CD_3COCD_3, 300 MHz) δ (ppm) 11.83 (s, 1H), 8.36 (d, 1H), 8.17 (s, 1H), 8.00 (s, 1H), 7.91 (d, 1H), 7.76 (d, 2H), 7.49 (d, 2H), 7.37-7.07 (m, 4H), 6.72 (s, 1H), 6.01 (s, 1H), 5.70 (s, 1H), 4.03 (s, 2H), 3.18 (h, 1H), 1.32 (s, 9H), 0.92 (d, 6H); ^{13}C NMR (CD_3COCD_3) δ (ppm) 168.58, 157.29, 148.53, 147.25, 147.10, 141.67, 138.17, 136.14, 134.75, 133.80, 129.70, 127.59, 127.12, 126.04, 125.86, 125.51, 122.75, 119.77, 117.82, 106.31, 35.20, 31.57, 31.00, 28.86, 21.07.

TW-37- N-[(2-叔丁基-苯磺酰基)-苯基]-2,3,4-三羟基-5-(2-异丙基-苯基)-苯甲酰胺

^{1}H NMR (CD_3COCD_3, 300 MHz) δ (ppm) 12.02 (s, 1H), 7.93 (d, 1H), 7.78 (d, 1H), 7.69-7.03 (m, 9H), 6.59 (s, 1H), 5.95 (s, 1H), 5.63 (s, 1H), 4.04 (s, 2H), 3.17 (h, 1H), 1.57 (s, 9H), 1.22 (d, 6H); ^{13}C NMR (CD_3COCD_3) δ (ppm) 168.32, 152.04, 148.48, 147.30, 146.70, 142.30, 142.00, 139.20, 136.02, 133.22, 133.00, 131.63, 129.87, 129.11, 128.44, 127.20, 126.19, 125.90, 120.19, 119.60, 117.17, 106.49, 37.30, 32.19, 31.54, 28.90, 23.82.

TW-38- N-[(2-叔丁基-苯磺酰基)-苯基]-2,3,4-三羟基-5-(4-叔丁基-苯乙基)-苯甲酰胺

^{1}H NMR (CD_3COCD_3, 300 MHz) δ (ppm) 11.96 (s, 1H), 7.96 (d, 1H), 7.88 (s, 1H), 7.80 (d, 2H), 7.70 (d, 2H), 7.52 (t, 1H), 7.36-7.25 (m, 4H), 7.16 (d, 2H), 6.77 (s, 1H), 5.89 (s, 1H), 5.58 (s, 1H), 2.91 (s, 4H), 1.58 (s, 9H), 1.21 (s, 9H); ^{13}C NMR (CD_3COCD_3) δ (ppm) 168.43, 151.14, 148.90, 148.37, 147.20, 141.72, 140.30, 139.60, 139.23, 133.20, 133.00, 132.20, 129.15,

128.48, 128.26, 126.20, 125.23, 120.30, 120.24, 117.20, 106.30, 37.33, 35.56, 35.02, 32.20, 31.74, 31.40.

TW-39- N-[2-氯-5-(4-氯-苯磺酰基)-苯基]-2,3,4-三羟基-5-(4-叔丁基-苄基)-苯甲酰胺

^{1}H NMR (CD_3COCD_3, 300 MHz) δ (ppm) 11.82 (s, 1H), 9.10 (s, 1H), 8.37 (s, 1H), 7.91 (d, 2H), 7.62-7.15 (m, 8H), 6.69 (s, 1H), 5.94 (s, 1H), 5.68 (s, 1H), 3.97 (s, 2H), 1.33 (s, 9H), 1.32 (s, 9H).

TW-40- N-[4-(4-叔丁基-苯磺酰基)-3-三氟甲基-苯基]-2,3,4-三羟基-5-(4-叔丁基-苄基)-苯甲酰胺

^{1}H NMR (CD_3COCD_3, 300 MHz) δ (ppm) 11.76 (s, 1H), 8.39-7.17 (m, 12H), 7.0 (s, 1H), 5.98 (s, 1H), 3.90 (s, 1H), 3.95 (s, 2H), 1.33 (s, 9H), 1.31 (s, 9H); ^{13}C NMR (CD_3COCD_3) δ (ppm) 168.57, 157.32, 149.16, 148.54, 147.30, 141.80, 138.17, 137.00, 134.66, 133.86, 131.74, 129.58, 128.29, 126.07, 125.41, 122.77, 120.08, 118.39, 106.43, 35.21, 34.63, 34.38, 31.36, 31.00, 29.72.

TW-41- N-[4-(2-叔丁基-苯磺酰基)-苯基]-2,3,4-三羟基-5-(4-叔丁基-苄基)-苯甲酰胺

^{1}H NMR (CD_3COCD_3, 300 MHz) δ (ppm) 12.02 (s, 1H), 8.10 (s, 1H), 7.95 (d, 1H), 7.72-7.14 (m, 9H), 6.95 (d, 1H), 5.94 (s, 1H), 5.67 (s, 1H), 3.96 (s, 2H), 1.57 (s, 9H), 1.31 (s, 9H); ^{13}C NMR (CD_3COCD_3) δ (ppm) 168.44, 151.14, 149.14, 148.56, 140.85, 137.10, 133.20, 133.05, 131.76, 129.16, 128.41, 128.25, 126.21, 125.41, 120.41, 120.35, 119.79, 118.02, 106.46, 37.33, 34.62, 34.40, 32.18, 31.38.

TW-42- N-[4-(2-叔丁基-苯磺酰基)-苯基]-2,3,4-三羟基-5-(2-异-己基-苄基)-苯甲酰胺

^{1}H NMR (CD_3COCD_3, 300 MHz) δ (ppm) 12.04 (s, 1H), 7.94-7.03 (m, 13H), 6.69 (s, 1H), 5.96 (s, 1H), 5.67 (s, 1H), 4.0 (s, 2H), 2.65-2.61 (m, 2H), 1.56 (s, 9H), 1.61-1.45 (m, 3H), 0.94 (d, 6H); ^{13}C NMR (CD_3COCD_3) δ (ppm) 168.41, 151.13, 148.40, 146.88, 141.53, 140.78, 140.00, 138.97, 137.15, 133.20, 133.03, 121.65, 129.59, 129.38, 129.14, 128.32, 126.72, 126.20, 125.95, 120.31, 119.38, 117.58, 40.17, 37.31, 32.17, 31.60, 30.83, 29.71, 28.25.

TW-43- N-[2-氯-5-(4-氯-苯磺酰基)-苯基]-2,3,4-三羟基-5-(3-氯-苯乙基)-苯甲酰胺

^{1}H NMR (CD_3COCD_3, 300 MHz) δ (ppm) 11.76 (s, 1H), 9.38 (s, 1H), 8.36 (s, 1H), 7.94 (d, 2H), 7.66-6.0 (m, 8H), 6.67 (s, 1H), 6.28 (s, 1H), 6.12 (s, 1H), 2.90 (s, 4H); ^{13}C NMR (CD_3COCD_3) δ (ppm) 168.01, 148.53, 147.42, 143.61, 140.75, 140.29, 139.40, 134.94, 133.97, 131.77, 130.08, 129.76, 129.48, 129.21, 128.60, 128.55, 126.86, 126.13, 123.43, 120.69, 119.77, 117.50, 106.23, 35.36, 31.59.

TW-44

^{1}H NMR (CD_3COCD_3, 300 MHz) δ (ppm) 9.09 (s, 1H), 8.56 (s, 1H), 7.95 (d, 2H), 7.68-7.50 (m, 4H), 6.85 (s, 1H), 5.6-4.9 (br, 1H), 3.73 (t, 2H), 3.47 (t, 2H), 2.65 (q, 2H), 1.99 (h, 2H), 1.75 (h, 2H), 1.24 (t, 3H); ^{13}C NMR (CD_3COCD_3) δ (ppm) 168.16, 148.31, 147.48, 140.87, 140.31, 139.48, 135.13, 131.67, 130.13, 129.80, 129.27, 128.40, 123.36, 122.93, 120.67, 116.27, 106.34, 62.03, 33.67, 31.04, 29.17, 22.80, 14.10.

TW-45- N-[2-氯-5-(4-氯-苯磺酰基)-苯基]-2,3,4-三羟基-5-乙基-苯甲酰胺

^{1}H NMR (CD_3COCD_3, 300 MHz) δ (ppm) 11.81 (s, 1H), 9.11 (d, 1H), 8.52 (s, 1H), 7.96 (d, 2H), 7.70-7.51 (m, 4H), 6.88 (s, 1H), 5.96 (s, 1H), 5.72 (s, 1H), 2.69 (q, 2H), 1.25 (t, 3H); ^{13}C NMR (CD_3COCD_3) δ (ppm) 168.18, 148.34, 147.19, 141.01, 140.33, 139.55, 135.10, 131.62, 130.12, 129.81, 129.29, 128.28, 123.37, 122.91, 120.65, 116.12, 106.12, 106.33, 22.81, 14.19.

TW-46/51- N-[2-氯-5-(4-氯-苯磺酰基)-苯基]-2,3,4-三羟基-苯甲酰胺

^{1}H NMR (CD_3COCD_3, 300 MHz) δ (ppm) 12.00 (s, 1H), 9.12 (d, 1H), 8.66 (s, 1H), 7.88-7.42 (m, 6H), 7.08 (d, 1H), 6.61 (d, 1H), 5.88 (s, 1H), 5.68 (s, 1H); ^{13}C NMR (CD_3COCD_3) δ (ppm) 168.08, 151.30, 149.82, 142.30, 140.3, 135.4, 133.60, 131.2, 130.2, 129.7, 128.4, 123.6, 121.02, 117.76, 108.03, 106.4.

TW-47- N-[2-氯-5-(4-氯-苯磺酰基)-苯基]-2,3,4-三羟基-5-异

-己基-苯甲酰胺

^{1}H NMR (CD_3COCD_3, 300 MHz) δ (ppm) 11.67 (s, 1H), 9.06 (d, 1H), 8.53 (s, 1H), 7.92 (d, 2H), 7.70-7.26 (m, 4H), 6.86 (s, 1H), 6.19 (s, 1H), 6.09 (s, 1H), 2.57 (t, 2H), 1.61-1.52 (m, 3H), 1.27-1.20 (m, 2H), 0.87 (d, 6H); ^{13}C NMR (CD_3COCD_3) δ (ppm) 168.15, 148.20, 147.55, 140.86, 140.32, 139.48, 135.12, 131.16, 130.14, 129.81, 129.28, 128.49, 123.41, 121.66, 120.73, 117.15, 106.15, 38.63, 29.88, 27.90, 27.56, 22.64.

TW-48- N-[(4-氯-苯磺酰基)-苯基]-2,3,4-三羟基-苯甲酰胺

^{1}H NMR (CD_3COCD_3, 300 MHz) δ (ppm) 12.29 (s, 1H), 9.84 (s, 1H), 8.53-7.34 (m, 12H), 6.50 (s, 1H); ^{13}C NMR (CD_3COCD_3) δ (ppm) 169.92, 151.81, 150.97, 143.43, 142.91, 140.25, 134.33, 133.54, 130.91, 130.46, 128.45, 126.23, 123.81, 120.48, 119.47, 108.08, 107.96.

TW-49- N-[2-氯-5-(4-氯-苯磺酰基)-苯基]-2,3,4-三羟基-5-(2-异-己基-苄基)-苯甲酰胺

^{1}H NMR (CD_3COCD_3, 300 MHz) δ (ppm) 11.79 (s, 1H), 9.09 (s, 1H), 8.25 (s, 1H), 7.93 (d, 2H), 7.68-7.10 (m, 8H), 6.42 (s, 2H), 6.04 (s, 1H), 5.69 (s, 1H), 4.00 (s, 2H), 2.54 (t, 2H), 1.60-1.29 (m, 5H), 0.92 (d, 6H); ^{13}C NMR (CD_3COCD_3) δ (ppm) 167.85, 148.36, 146.90, 141.80, 140.98, 140.27, 139.57, 136.54, 135.04, 131.51, 130.56, 129.92, 128.07, 126.91, 126.09, 123.14, 120.08, 119.87, 116.85, 106.37, 40.39, 31.50, 30.70, 28.13, 22.49.

TW-50- 4-(2-异-丙基-苄基)-2,3,4-三醇

^{1}H NMR (CD_3COCD_3, 300 MHz) δ (ppm) 7.39-7.08 (m, 4H), 6.41-6.30 (m, 2H), 5.31 (s, 1H), 5.16 (s, 1H), 5.08 (s, 1H), 4.0 (s, 2H), 3.14 (h, 1H), 1.21 (d, 6H); ^{13}C NMR (CD_3COCD_3) δ (ppm) 147.48, 142.14, 142.01, 136.15, 131.84, 129.58, 127.11, 125.95, 125.66, 120.86, 120.10, 107.44, 32.74, 28.83, 23.68.

TW-52- N-苯基-2,3,4-三羟基-5-(2-异-丙基-苄基)-苯甲酰胺

^{1}H NMR (CD_3COCD_3, 300 MHz) δ (ppm) 12.42 (s, 1H), 7.74-7.11 (m, 10H), 6.57 (s, 1H), 5.96 (d, 1H), 5.72 (d, 1H), 4.05 (s, 2H), 3.18 (h, 1H), 1.24 (d, 6H); ^{13}C NMR (CD_3COCD_3) δ (ppm) 168.32, 148.40, 147.28, 146.23, 136.53, 136.15, 131.59, 129.91, 129.13, 127.12, 125.88, 125.52, 125.20, 121.15, 119.24, 117.04, 106.83, 31.59, 28.89, 23.83.

TW-53- N-(2-氯-苯基)-2,3,4-三羟基-5-(2-异-丙基-苄基)-苯甲酰胺

^{1}H NMR (CD_3COCD_3, 300 MHz) δ (ppm) 12.19 (s, 1H), 8.40 (dd, 1H), 8.18 (s, 1H), 7.38-7.07 (m, 7H), 6.45 (s, 1H), 6.01 (s, 1H), 5.68 (s, 1H), 4.04 (s, 2H), 3.07 (h, 1H), 1.20 (d, 6H); ^{13}C NMR (CD_3COCD_3) δ (ppm) 167.94, 148.33, 147.49, 146.32, 135.58, 133.78, 131.42, 130.66, 129.03, 127.79, 127.28, 125.99, 125.72, 124.93, 123.45, 121.29, 120.04, 116.80, 106.76, 31.65, 28.97, 23.95.

TW-54- N-[2-甲基-4-(2-叔丁基-苯磺酰基)-苯基]-2,3,4-三羟基-5-(2-异-丙基-苄基)-苯甲酰胺

^{1}H NMR (CD_3COCD_3, 300 MHz) δ (ppm) 11.98 (s, 1H), 8.25 (d, 1H), 7.87 (d, 1H), 7.67-7.16 (m, 10H), 6.33 (s, 1H), 6.05 (s, 1H), 5.70 (s, 1H), 4.03 (s, 2H), 3.21 (h, 1H), 2.07 (s, 3H), 1.59 (s, 9H), 1.18 (d, 6H); ^{13}C NMR (CD3COCD3) δ (ppm) 167.95, 151.04, 148.36, 147.57, 146.57, 140.26, 139.12, 138.74, 135.62, 133.04, 132.86, 131.52, 130.70, 129.06, 129.0, 127.33, 126.47, 126.12, 125.94, 125.71, 120.94, 120.17, 116.46, 106.47, 37.28, 32.20, 31.60, 28.93, 23.95, 17.40.

TW-55- N-甲基-2,3,4-三羟基-5-(2-异丙基-苄基)-苯甲酰胺

^{1}H NMR (CD_3COCD_3, 300 MHz) δ (ppm) 12.83 (s, 1H), 7.35-7.09 (m, 4H), 6.36 (s, 1H), 5.94 (s, 1H), 5.91 (s, 1H), 5.71 (s, 1H), 4.0 (s, 2H), 3.12 (h, 1H), 2.93 (d, 3H), 1.19 (d, 6H); ^{13}C NMR (CD_3COCD_3) δ (ppm) 170.56, 148.00, 147.41, 145.63, 136.30, 131.38, 130.15, 127.96, 125.76, 125.52, 118.88, 116.59, 106.59, 31.55, 28.83, 26.26, 23.78.

TW-56- N-(苯磺酰基-苯基)-2,3,4-三羟基-5-苄基-苯甲酰胺

^{1}H NMR (CD_3COCD_3, 300 MHz) δ (ppm) 9.89 (s, 1H), 8.30 (s, 1H), 8.10-6.94 (m, 17H), 3.92 (s, 2H); ^{13}C NMR (CD_3COCD_3) δ (ppm) 170.59, 150.82, 149.61, 143.80, 143.40, 142.20, 137.54, 134.07, 130.37, 129.54, 128.99, 128.26, 126.55, 121.88, 121.79, 120.26, 120.13, 36.12.

TW-58- N-[3-甲基-4-(2-叔丁基-苯磺酰基)-苯基]-2,3,4-三羟基-5-(2-异丙基-苄基)-苯甲酰胺

^{1}H NMR (CD_3COCD_3, 300 MHz) δ (ppm) 12.01 (s, 1H), 7.97 (d, 1H), 7.88 (s, 1H), 7.70 (d, 1H), 7.42-7.05 (m, 12H), 6.65 (s, 1H), 6.03 (s, 1H), 5.76 (s, 1H), 4.04 (s, 2H), 3.34-3.20 (m, 1H), 2.31 (s, 3H), 1.66 (s, 9H), 1.25 (d,

6H); ^{13}C NMR (CD_3COCD_3) δ (ppm) 168.50, 150.59, 148.49, 147.15, 141.03, 141.00, 139.29, 136.51, 132.45, 130.18, 129.83, 129.80, 129.16, 127.06, 126.06, 125.86, 125.52, 123.85, 119.57, 117.51, 117.26, 106.63, 37.32, 31.95, 31.57, 28.48, 23.80, 20.42.

TW-59- N-[3-氯-4-(2-叔丁基-苯磺酰基)-苯基]-2,3,4-三羟基-5-(2-异丙基-苄基)-苯甲酰胺

^{1}H NMR (CD_3COCD_3, 300 MHz) δ (ppm) 12.01 (s, 1H), 8.13 (d, 1H), 8.02 (s, 1H), 7.83 (s, 1H), 7.68-6.92 (m, 7H), 6.68 (s, 1H), 6.03 (s, 1H), 5.73 (s, 1H), 4.04 (s, 2H), 3.19 (h, 1H), 1.66 (s, 9H), 1.25 (d, 6H); ^{13}C NMR (CD_3COCD_3) δ (ppm) 168.47, 150.44, 148.47, 147.25, 147.01, 142.09, 140.66, 136.13, 135.47, 133.67, 132.52, 131.60, 130.20, 129.77, 129.00, 127.13, 126.02, 125.87, 125.53, 123.02, 119.75, 117.90, 117.76, 37.17, 31.87, 31.56, 28.87, 23.78.

TW-60- N-[2-氯-4-(4-溴-苯磺酰基)-苯基]-2,3,4-三羟基-5-(4-叔丁基-苯乙基)-苯甲酰胺

^{1}H NMR (CD_3COCD_3, 300 MHz) δ (ppm) 11.79 (s, 1H), 9.08 (d, 1H), 8.40 (s, 1H), 7.87 (d, 2H), 7.72-7.08 (m, 9H), 6.76 (s, 1H), 6.09 (s, 1H), 5.86 (s, 1H), 2.93 (s, 4H), 1.32 (s, 9H); ^{13}C NMR (CD_3COCD_3) δ (ppm) 168.10, 148.80, 148.41, 147.36, 140.87, 140.05, 138.50, 135.03, 132.80, 131.70, 130.10, 129.32, 128.90, 128.80, 128.35, 128.13, 125.23, 123.40, 120.66, 120.54, 117.30, 106.22, 35.20, 34.34, 31.56, 31.36.

TW-61- N-[2-氯-4-(4-溴-苯磺酰基)-苯基]-2,3,4-三羟基-5-(2-异丙基-苄基)-苯甲酰胺

^{1}H NMR (CD_3COCD_3, 300 MHz) δ (ppm) 11.87 (s, 1H), 9.08 (d, 1H), 8.23 (s, 1H), 7.86-6.36 (m, 10H), 6.35 (s, 1H), 6.18 (s, 1H), 5.88 (s, 1H), 4.02 (s, 2H), 3.02 (h, 1H), 1.21 (d, 6H); ^{13}C NMR (CD_3COCD_3) δ (ppm) 167.86, 148.40, 147.53, 146.90, 140.85, 140.05, 135.44, 135.03, 132.75, 131.50, 130.74, 129.90, 127.30, 128.87, 128.16, 127.29, 126.00, 125.73, 123.14, 120.40, 119.81, 116.71, 106.21, 31.60, 28.95, 23.94.

TW-62- N-[4-(3-甲基-苯基氨磺酰基)-苯基]-2,3,4-三羟基-5-(2-异丙基-苄基)-苯甲酰胺

^{1}H NMR (CD_3COCD_3, 300 MHz) δ (ppm) 12.01 (s, 1H), 7.73-6.71 (m, 12H), 6.54 (s, 1H), 6.43 (s, 1H), 5.93 (s, 1H), 5.62 (s, 1H), 4.04 (s, 2H), 3.12 (h, 1H), 2.29 (s, 3H), 1.22 (d, 6H); ^{13}C NMR (CD_3COCD_3) δ (ppm) 168.31,

149.03, 148.72, 146.02, 141.98, 138.29, 137.57, 137.17, 133.85, 132.40, 128.80, 128.51, 127.54, 126.03, 125.19, 124.62, 124.55, 120.64, 120.28, 118.52, 116.78, 107.00, 31.45, 28.91, 23.39, 20.91.

TW-63- N-[4-(2-叔丁基-苯亚磺酰基)-苯基]-2,3,4-三羟基-5-(2-异丙基-苄基)-苯甲酰胺

^{1}H NMR (CD_3COCD_3, 300 MHz) δ (ppm) 11.86 (s, 1H), 8.37 (s, 1H), 7.71 (d, 1H), 7.62-6.95 (m, 12H), 6.34 (s, 1H), 6.20 (s, 1H), 3.98 (s, 2H), 3.16 (h, 1H), 1.57 (s, 9H), 1.23 (d, 6H); ^{13}C NMR (CD_3COCD_3) δ (ppm) 168.26, 148.89, 148.23, 147.13, 146.98, 143.78, 140.29, 139.24, 135.32, 131.78, 131.55, 129.73, 129.60, 127.87, 126.90, 126.64, 126.17, 125.73, 125.34, 121.07, 119.38, 118.27, 107.03, 36.46, 32.78, 31.63, 28.77, 23.71.

TW-64- N-[4-(3-甲基-苯基氨磺酰基)-苯基]-2,3,4-三羟基-5-苄基-苯甲酰胺

^{1}H NMR (CD_3COCD_3, 300 MHz) δ (ppm) 12.21 (s, 1H), 9.83 (s, 1H), 8.91 (s, 1H), 8.31 (s, 1H), 8.01 (s, 1H), 7.87-6.88 (m, 14H), 3.93 (s, 2H), 2.25 (s, 3H); ^{13}C NMR (CD_3COCD_3) δ (ppm) 170.47, 150.76, 149.52, 143.11, 142.23, 139.75, 138.80, 135.75, 133.40, 129.80, 129.28, 128.98, 128.95, 126.54, 126.02, 122.14, 121.44, 120.24, 120.11, 118.59, 107.37, 36.14, 21.41.

TW-65- N-[4-(3-甲基-苯基氨磺酰基)-苯基]-2,3,4-三羟基-苯甲酰胺

^{1}H NMR (CD_3COCD_3, 300 MHz) δ (ppm) 12.16 (s, 1H), 9.77 (s, 1H), 8.90 (s, 1H), 8.48 (s, 1H), 7.91-6.86 (m, 10H), 6.45 (d, 1H), 2.23 (s, 3H); ^{13}C NMR (CD_3COCD_3) δ (ppm) 170.23, 152.03, 151.16, 143.18, 139.76, 138.82, 135.73, 133.71, 129.82, 126.02, 122.11, 121.38, 119.54, 118.56, 108.20, 108.02, 21.42.

TW-66- N-[4-(4-氯-苯基氨磺酰基)-苯基]-2,3,4-三羟基-苯甲酰胺 ^{1}H NMR (CD_3COCD_3, 300 MHz) δ (ppm) 12.15 (s, 1H), 9.81 (s, 1H), 9.15 (s, 1H), 8.53 (s, 1H), 7.95-7.25 (m, 9H), 6.47 (d, 1H); ^{13}C NMR (CD_3COCD_3) δ (ppm) 170.20, 152.00, 151.15, 143.40, 137.77, 135.17, 133.68, 133.00, 130.15, 129.00, 123.14, 122.51, 121.43, 119.56, 108.19.

TW-68- N-[4-(4-氯-苯磺酰基)-苯基]-2,3,4-三羟基-苯甲酰胺

^{1}H NMR (CD_3COCD_3, 300 MHz) δ (ppm) 12.13 (s, 1H), 9.90 (s, 1H), 8.52 (s, 1H), 8.03-7.91 (m, 7H), 7.68 (d, 2H), 7.46 (d, 1H), 6.49 (d, 1H); ^{13}C NMR (CD_3COCD_3) δ (ppm) 170.27, 151.99, 151.22, 144.11, 142.18, 139.90, 136.90, 133.68, 130.57, 130.13, 129.66, 121.85, 119.62, 108.16, 108.06.

TW-69- N-[4-(3-异丙基-苯基氨磺酰基)-苯基]-2,3,4-三羟基-苯甲酰胺

^{1}H NMR (CD_3COCD_3, 300 MHz) δ (ppm) 12.20 (s, 1H), 9.79 (s, 1H), 8.90 (s, 1H), 8.48 (s, 1H), 8.02-7.70 (m, 5H), 7.45 (d, 1H), 7.17-6.98 (m, 4H), 6.47 (d, 1H), 2.90-2.75 (m, 1H), 1.16 (d, 6H); ^{13}C NMR (CD_3COCD_3) δ (ppm) 170.21, 152.02, 151.138, 150.76, 143.17, 138.81, 135.64, 133.69, 129.88, 129.02, 123.44, 121.31, 119.67, 119.57, 119.17, 108.16, 108.06, 34.67, 24.14.

TW-70- N-[4-(2-异丙基-苯基氨磺酰基)-苯基]-2,3,4-三羟基-苯甲酰胺

^{1}H NMR (CD_3COCD_3, 300 MHz) δ (ppm) 12.25 (s, 1H), 9.84 (s, 1H), 8.50 (s, 1H), 8.42 (s, 1H), 7.94 (d, 2H), 7.86 (s, 1H), 7.71-7.11 (m, 7H), 6.48 (d, 1H), 3.38-3.28 (m, 1H), 1.03 (d, 6H); ^{13}C NMR (CD_3COCD_3) δ (ppm) 170.23, 152.06, 151.14, 146.34, 143.06, 136.42, 134.19, 133.71, 129.02, 128.29, 128.13, 127.19, 126.81, 121.34, 119.50, 108.16, 108.02, 27.89, 23.95.

TW-71- N-[4-(3-异丙基-苯基氨磺酰基)-苯基]-2,3,4-三羟基-5-苄基-苯甲酰胺

^{1}H NMR (CD_3COCD_3, 300 MHz) δ (ppm) 12.23 (s, 1H), 9.83 (s, 1H), 8.90 (s, 1H), 8.31 (s, 1H), 8.01 (s, 1H), 7.85-7.61 (m, 4H), 7.46 (s, 1H), 7.16-6.98 (m, 8H), 3.93 (s, 2H), 2.90-2.75 (m, 1H), 1.16 (d, 6H); ^{13}C NMR (CD_3COCD_3) δ (ppm) 170.48, 150.78, 149.51, 143.10, 142.22, 138.81, 135.67, 133.39, 129.87, 129.27, 128.99, 126.53, 123.44, 121.38, 120.21, 120.09, 119.69, 119.19, 107.33, 36.13, 34.66, 24.24.

TW-73- N-[3-(2-异丙基-苯基氨磺酰基)-苯基]-2,3,4-三羟基-苯甲酰胺

^{1}H NMR (CD_3COCD_3, 300 MHz) δ (ppm) 12.37 (s, 1H), 9.79 (s, 1H), 8.57 (s, 1H), 8.45 (s, 1H), 8.25 (s, 1H), 8.24 (d, 1H), 7.54 (s, 1H), 7.52-7.10 (m, 7H), 6.47 (d, 1H), 2.94 (h, 1H), 1.02 (d, 6H).

TW-74- N-[3-(3-异丙基-苯基氨磺酰基)-苯基]-2,3,4-三羟基-苯甲酰胺

^{1}H NMR (CD_3COCD_3, 300 MHz) δ (ppm) 12.33 (s, 1H), 9.77 (s, 1H), 9.02 (s, 1H), 8.41-6.90 (m, 11H), 6.43 (d, 1H), 2.82 (h, 1H), 1.15 (d, 6H); ^{13}C NMR (CD_3COCD_3) δ (ppm) 170.23, 152.12, 151.05, 150.78, 141.47, 139.82, 138.64, 133.71, 130.22, 129.89, 125.60, 123.56, 123.41, 120.36, 119.84, 119.40, 119.32, 108.04, 107.97, 34.68, 24.12.

TW-75- N-[4-(3-异丙基-苯基氨磺酰基)-苯基]-2,3,4-三羟基-5-(2-异丙基-苄基)-苯甲酰胺

^{1}H NMR (CD_3COCD_3, 300 MHz) δ (ppm) 12.17 (s, 1H), 9.79 (s, 1H), 8.88 (s, 1H), 8.31 (s, 1H), 8.01 (s, 1H), 7.84-7.74 (m, 4H), 7.31-6.93 (m, 10H), 4.0 (s, 2H), 3.36 (h, 1H), 2.79 (h, 1H), 1.21 (d, 6H), 0.89 (d, 6H); ^{13}C NMR (CD_3COCD_3) δ (ppm) 170.41, 150.76, 149.10, 147.38, 143.09, 138.81, 138.18, 135.67, 129.86, 129.82, 128.98, 127.19, 126.29, 125.70, 123.44, 121.39, 120.39, 119.70, 119.20, 108.41, 34.66, 32.47, 32.18, 24.13, 23.93.

TW-76- N-[4-(2-异丙基-苯基氨磺酰基)-苯基]-2,3,4-三羟基-5-(2-异丙基-苄基)-苯甲酰胺

^{1}H NMR (CD_3COCD_3, 300 MHz) δ (ppm) 12.08 (s, 1H), 7.89 (s, 1H), 7.69-7.57 (m, 4H), 7.39-7.06 (m, 8H), 6.61 (s, 1H), 6.47 (s, 1H), 6.04 (s, 1H), 5.78 (s, 1H), 4.04 (s, 2H), 3.36 (h, 1H), 2.82 (h, 1H), 1.21 (d, 6H), 1.02 (d, 6H); ^{13}C NMR (CD_3COCD_3) δ (ppm) 168.74, 148.84, 147.67, 147.13, 143.18, 141.46, 136.49, 135.08, 132.74, 131.96, 130.19, 128.88, 127.53, 127.49, 126.84, 126.52, 126.20, 125.88, 125.85, 120.42, 119.90, 117.69, 106.88, 31.86, 29.21, 27.79, 24.11, 23.57.

TW-78- N-[4-(-2-叔丁基-苯磺酰基)-苯基]-5-萘-1-基甲基-苯甲酰胺

^{1}H NMR (CD_3COCD_3, 300 MHz) δ (ppm) 12.21 (s, 1H), 9.87 (s, 1H), 8.46 (s, 1H), 8.24 (d, 1H), 8.08 (s, 1H), 7.95-7.15 (m, 15H), 4.42 (s, 2H), 1.57 (s, 9H); ^{13}C NMR (CD_3COCD_3) δ (ppm) 168.41, 151.27, 150.72, 149.64, 143.25, 141.83, 139.36, 137.70, 134.77, 134.03, 133.89, 133.46, 132.97, 129.98, 129.45, 128.93, 127.51, 127.31, 126.77, 126.42, 124.66, 121.61, 120.56, 119.08, 107.65, 37.83, 32.51.

TW-79- N-[2-甲基-5-(3-异丙基-苯基氨磺酰基)-苯基]-2,3,4-

三羟基-5-(2-异丙基-苄基)-苯甲酰胺

^{1}H NMR (CD_3COCD_3, 300 MHz) δ (ppm) 12.10 (s, 1H), 8.51 (s, 1H), 7.50-6.71 (m, 16H), 6.35 (s, 1H), 6.16 (s, 1H), 6.03 (s, 1H), 4.03 (s, 2H), 3.06 (h, 1H), 2.81 (h, 1H), 2.07 (s, 3H), 1.19 (d, 6H), 1.13 (g, 6H); ^{13}C NMR (CD_3COCD_3) δ (ppm) 167.97, 150.34, 148.36, 147.56, 146.67, 136.21, 135.80, 135.64, 133.76, 131.59, 130.78, 130.61, 129.15, 127.24, 125.91, 125.65, 123.83, 123.62, 120.73, 120.06, 120.00, 119.24, 116.57, 106.41, 33.88, 31.62, 28.91, 23.93, 23.91, 17.57.

TW-80- N-[2-甲基-5-(4-氯-苯基氨磺酰基)-苯基]-2,3,4-三羟基-5-(2-异丙基-苯基)-苯甲酰胺

^{1}H NMR (CD_3COCD_3, 300 MHz) δ (ppm) 12.04 (s, 1H), 9.31 (s, 1H), 9.22 (s, 1H), 8.33 (s, 1H), 8.12 (s, 1H), 8.00 (s, 1H), 7.53 (d, 1H), 7.41-7.08 (m, 9H), 4.03 (s, 2H), 3.28 (h, 1H), 2.28 (s, 3H), 1.21 (d, 6H); ^{13}C NMR (CD_3COCD_3) δ (ppm) 169.58, 150.03, 149.18, 147.71, 138.68, 138.55, 137.88, 137.73, 137.46, 133.25, 131.88, 130.08, 130.00, 127.43, 126.40, 125.96, 124.91, 124.39, 123.04, 121.49, 120.28, 120.02, 107.66, 32.61, 24.06, 23.29, 18.21.

TW-81- N-[4-(2-异丙基-苯基氨磺酰基)-苯基]-2,3,4-三羟基-5-萘-1-基甲基-苯甲酰胺

^{1}H NMR (CD_3COCD_3, 300 MHz) δ (ppm) 12.27 (s, 1H), 9.73 (s, 1H), 8.44 (s, 1H), 8.37 (s, 1H), 8.25 (d, 1H), 8.08 (s, 1H), 7.93 (s, 1H), 7.83-7.08 (m, 14H), 4.42 (s, 2H), 3.376 (h, 1H), 1.01 (d, 6H); ^{13}C NMR (CD_3COCD_3) δ (ppm) 168.62, 150.73, 149.58, 146.33, 142.93, 137.72, 136.43, 134.76, 134.16, 133.45, 132.97, 129.44, 128.96, 128.28, 128.12, 127.82, 127.49, 127.17, 126.77, 126.41, 126.39, 121.65, 121.41, 121.31, 120.50, 119.05, 107.64, 32.53, 27.87, 23.93.

TW-82- N-苯基-2,3,4-三羟基-5-苄基-苯甲酰胺

^{1}H NMR (CD_3COCD_3, 300 MHz) δ (ppm) 12.61 (s, 1H), 9.58 (s, 1H), 8.17 (s, 1H), 7.92 (s, 1H), 7.71 (d, 2H), 7.48 (s, 1H), 7.39-7.13 (m, 8H), 3.95 (s, 2H); ^{13}C NMR (CD_3COCD_3) δ (ppm) 170.30, 150.79, 149.00, 142.38, 139.02, 133.38, 129.50, 129.30, 128.97, 126.50, 125.19, 122.27, 119.89, 119.82, 107.58, 36.17.

TW-83- N-[2-氯-5-(4-氯-苯磺酰基)-苯基]-2,3,4-三羟基-5-萘-1-基甲基-苯甲酰胺

^{1}H NMR (CD_3COCD_3, 300 MHz) δ (ppm) 11.25 (s, 1H), 9.58 (s, 1H), 8.84 (s, 1H), 8.66 (s, 1H), 8.15-7.16 (m, 16H), 4.43 (s, 2H); ^{13}C NMR (CD_3COCD_3) δ (ppm) 168.49, 149.37, 148.95, 141.68, 141.21, 140.42, 137.31, 136.95, 136.87, 134.94, 133.32, 133.08, 131.47, 130.74, 130.39, 129.48, 127.80, 127.75, 126.83, 126.51, 126.46, 124.99, 124.88, 123.24, 123.06, 121.10, 120.34, 108.57, 32.54.

TW-85- N-(3-苯磺酰基)-苯基-2,3,4-三羟基-5-(2-异丙基-苄基)-苯甲酰胺

^{1}H NMR (CD_3COCD_3, 300 MHz) δ (ppm) 12.29 (s, 1H), 9.85 (s, 1H), 8.33 (s, 1H), 8.32 (s, 1H), 8.05-6.98 (m, 14H), 4.02 (s, 2H), 3.39-3.30 (m, 1H), 1.22 (d, 6H); ^{13}C NMR (CD_3COCD_3) δ (ppm) 170.48, 150.65, 149.45, 147.38, 143.34, 142.80, 140.15, 138.19, 134.30, 133.33, 130.84, 130.41, 129.82, 128.40, 127.18, 126.50, 126.28, 125.69, 123.83, 120.65, 120.22, 119.70, 107.36, 32.47, 23.92, 14.48.

TW-86- N-[2-乙基-5-(2-异丙基-苯基氨磺酰基)-苯基]-2,3,4-三羟基-5-(2-异丙基-苄基)-苯甲酰胺

^{1}H NMR (CD_3COCD_3, 300 MHz) δ (ppm) 12.13 (s, 1H), 8.53 (s, 1H), 7.52 (s, 1H), 7.45-6.96 (m, 11H), 6.72 (s, 1H), 6.24 (s 3H), 4.04 (s, 2H), 3.21-3.17 (m, 2H), 2.40 (s, 3H), 1.20-0.94 (m, 15H); ^{13}C NMR (CD_3COCD_3) δ (ppm) 168.08, 148.41, 147.65, 146.78, 142.97, 139.33, 137.75, 135.72, 135.02, 132.50, 131.66, 130.80, 128.88, 127.28, 127.04, 126.45, 126.07, 125.91, 125.68, 124.11, 121.29, 120.14, 116.25, 106.38, 31.64, 28.92, 27.37, 24.29, 23.95, 23.22, 13.31.

TW-87- N-[2-乙基-(4-氯-苯磺酰基)-苯基]-2,3,4-三羟基-5-(2-异丙基-苄基)-苯甲酰胺

^{1}H NMR (CD_3COCD_3, 300 MHz) δ (ppm) 12.09 (s, 1H), 8.64 (s, 1H), 7.92 (d, 2H), 7.68 (d, 1H), 7.50-7.18 (m, 10H), 6.29 (s, 1H), 6.01 (s, 1H), 5.67 (s, 1H), 4.04 (s, 2H), 3.25 (h, 1H), 2.72 (q, 2H), 1.21 (d, 6H), 1.06 (t, 3H); ^{13}C NMR (CD_3COCD_3) δ (ppm) 168.04, 148.41, 147.65, 146.36, 140.13, 139.86, 139.65, 135.58, 135.35, 131.53, 130.79, 129.61, 129.55, 129.14, 127.33, 125.91, 125.73, 124.05, 121.58, 120.06, 116.07, 106.29, 31.62, 28.93, 24.29, 23.93, 13.18.

TW-88- N-[2-乙基-5-(4-氯-苯基氨磺酰基)苯基]-2,3,4-三羟基-5-(2-异丙基-苄基)-苯甲酰胺

^{1}H NMR (CD_3COCD_3, 300 MHz) δ (ppm) 12.13 (s, 1H), 8.56 (s, 1H), 7.65-7.05 (m, 13H), 6.31 (s, 1H), 6.22 (s, 1H), 6.11 (s, 1H), 4.03 (s, 2H), 3.03 (h, 1H), 2.72 (q, 2H), 1.20 (d, 6H), 1.06 (t, 3H); ^{13}C NMR (CD_3COCD_3) δ (ppm) 168.10, 148.34, 147.63, 146.75, 139.29, 136.98, 135.62, 135.09, 134.90, 131.60, 131.02, 130.77, 129.40, 128.95, 127.30, 125.91, 125.71, 123.94, 123.26, 120.91, 120.21, 116.26, 106.35, 31.62, 30.96, 24.16, 13.08.

TW-89- N-[4-(吡啶-2-磺酰基)-苯基]-2,3,4-三羟基-5-苄基-苯甲酰胺

^{1}H NMR (CD_3COCD_3, 300 MHz) δ (ppm) 12.19 (s, 1H), 9.94 (s, 1H), 8.68 (d, 1H), 8.34-7.15 (m, 15H), 3.94 (s, 2H); ^{13}C NMR (CD_3COCD_3) δ (ppm) 170.62, 151.32, 150.83, 149.64, 144.28, 142.23, 139.50, 134.80, 133.43, 130.82, 129.28, 128.99, 128.10, 126.56, 122.54, 121.58, 121.48, 120.31, 120.16, 107.37, 36.14.

TW-90- N-[4-(2-叔丁基苯磺酰基)-苯基]-2,3,4-三羟基-5-萘-2-基-苯甲酰胺

^{1}H NMR (CD_3COCD_3, 300 MHz) δ (ppm) 12.38 (s, 1H), 10.08 (s, 1H), 8.37 (s, 1H), 8.28 (s, 1H), 8.08-7.53 (m, 17H), 1.58 (s, 9H); ^{13}C NMR (CD_3COCD_3) δ (ppm) 170.61, 151.44, 151.30, 148.96, 143.28, 141.80, 139.49, 134.42, 134.14, 134.04, 133.91, 133.71, 129.99, 128.97, 128.80, 128.54, 128.06, 127.31, 126.90, 126.64, 121.67, 121.58, 121.44, 120.56, 108.05, 37.84, 32.51.

TW-91- N-[2-氯-5-(4-氯-苯磺酰基)-苯基]-2,3,4-三羟基-5-萘-2-基-苯甲酰胺

^{1}H NMR (CD_3COCD_3, 300 MHz) δ (ppm) 11.54 (s, 1H), 10.14 (s, 1H), 8.82 (s, 1H), 8.53 (s, 1H), 8.29 (s, 1H), 8.11-7.49 (m, 14H); ^{13}C NMR (CD_3COCD_3) δ (ppm) 168.41, 150.02, 149.09, 141.70, 141.23, 140.50, 137.04, 136.31, 134.46, 133.80, 133.37, 133.04, 131.75, 130.79, 130.45, 128.88, 128.69, 128.61, 128.41, 128.29, 126.93, 126.69, 125.70, 125.10, 122.11, 121.89, 109.11.

TW-92- N-[4-(2-叔丁基-苯磺酰基)-苯基]-2,3,4-三羟基-5-萘-2-基甲基-苯甲酰胺

^{1}H NMR (CD_3COCD_3, 300 MHz) δ (ppm) 12.28 (s, 1H), 9.91 (s, 1H), 8.47-7.27 (m, 18H), 4.32-4.13 (m, 2H), 1.57 (s, 9H); ^{13}C NMR (CD_3COCD_3) δ (ppm) 170.52, 151.28, 151.11, 149.85, 143.22, 141.81, 139.40, 139.26, 134.33, 134.02, 133.90, 133.55, 129.98, 129.11, 128.79, 128.52, 127.60, 126.64, 121.65, 120.68, 120.42, 118.40, 107.64, 107.46, 37.83, 37.41, 32.51.

TW-94

^{1}H NMR (CD_3COCD_3, 300 MHz) δ (ppm) 11.88 (s. 1H), 8.68 (d, 1H), 8.21-8.16 (m, 2H), 7.97-7.25 (m, 10H), 6.87 (s, 1H), 6.10 (s, 1H), 5.82 (s, 1H), 3.97 (s, 2H), 2.23 (s, 3H); ^{13}C NMR (CD_3COCD_3) δ (ppm) 168.50, 159.19, 150.88, 148.87, 147.31, 140.59, 140.04, 138.59, 134.58, 132.10, 131.46, 129.53, 129.41, 129.00, 128.45, 127.32, 126.80, 122.54, 120.53, 117.83, 107.05, 35.40, 17.97.

TW-95-1

^{1}H NMR (CD_3COCD_3, 300 MHz) δ (ppm) 10.19 (s, 1H), 8.62-7.25 (m, 19H), 4.43 (s, 2H), 4.04 (s, 3H), 3.95 (s, 3H), 3.89 (s, 3H); ^{13}C NMR (CD_3COCD_3) δ (ppm) 167.77, 162.97, 155.81, 151.00, 145.79, 143.35, 142.45, 142.21, 135.88, 135.76, 135.09, 134.46, 134.19, 130.83, 129.32, 129.22, 128.84, 128.74, 127.42, 127.34, 127.20, 127.15, 126.90, 125.96, 125.54, 125.52, 125.37, 125.32, 124.26, 124.01, 123.79, 120.19, 119.84, 62.52, 61.38, 61.33, 32.95.

TW-95

^{1}H NMR (CD_3COCD_3, 300 MHz) δ (ppm) 12.06 (s, 1H), 9.83 (s, 1H), 8.83-7.33 (m, 23H), 4.22 (s, 2H); ^{13}C NMR (CD_3COCD_3) δ (ppm) 174.2, 172.1, 150.65, 144.27, 143.32, 137.68, 136.75, 136.33, 135.22, 134.76, 133.47, 132.95, 131.46, 130.29, 129.89, 129.78, 129.69, 129.47, 129.344, 129.04, 128.95, 128.06, 127.49, 126.81, 126.76, 126.40, 126.30, 126.18, 125.60, 124.79, 124.67, 121.76, 120.63, 119.17, 32.51.

TW-98

^{1}H NMR (CD_3COCD_3, 300 MHz) δ (ppm) 12.42 (s, 1H), 10.01 (s, 1H), 8.37-7.40 (m, 17H), 1.57 (s, 9H); ^{13}C NMR (CD_3COCD_3) δ (ppm) 170.09, 151.20, 150.80, 148.96, 142.87, 138.90, 136.49, 134.11, 133.57, 133.44, 133.14, 132.94, 129.50, 128.44, 128.20, 128.06, 126.83, 126.20, 126.08, 125.80, 121.08, 120.63, 119.88, 107.14, 37.33.

TW-100

^{1}H NMR (CD_3COCD_3, 300 MHz) δ (ppm) 12.11 (s, 1H), 8.15 (s, 1H), 7.98 (s, 1H), 7.95 (s, 1H), 7.78-7.12 (m, 14H), 6.36 (s, 1H), 5.74 (s, 1H), 1.56 (s, 9H); ^{13}C NMR (CD_3COCD_3) δ (ppm) 170.373, 151.65, 151.33, 143.16, 141.79, 141.21, 140.51, 140.30, 139.70, 134.07, 133.94, 130.16, 128.97, 127.33, 125.19, 124.90, 124.08, 122.60, 122.50, 121.93, 121.84, 119.29, 114.51, 108.43, 79.20, 37.85, 32.52.

TW-108

^{1}H NMR (CD_3COCD_3, 300 MHz) δ (ppm) 12.18 (s, 1H), 10.33 (s, 1H), 8.31-7.43 (m, 17H), 1.60 (s, 9H); ^{13}C NMR (CD_3COCD_3) δ (ppm) 151.36, 143.03, 138.32, 134.74, 134.10, 133.98, 133.49, 132.71, 130.03, 129.32, 129.03, 128.97, 128.47, 127.34, 127.29, 126.81, 125.97, 125.89, 121.95, 121.85, 119.14, 117.39, 37.87, 32.52.

TW-109

^{1}H NMR (CD_3COCD_3, 300 MHz) δ (ppm) 11.71 (s, 1H), 10.09 (s, 1H), 8.76 (s, 1H), 8.56 (s, 1H), 8.08 (s, 1H), 8.20-7.54 (m, 24 H); ^{13}C NMR (CD_3COCD_3) δ (ppm) 152.3, 148.90, 141.71, 141.23, 140.52, 134.97, 132.43, 131.81, 130.80, 130.56, 130.47, 130.11, 129.28, 128.57, 127.76, 127.03, 126.76, 126.53, 126.42, 121.42, 108.79.

TW-115

^{1}H NMR (CD_3COCD_3, 300 MHz) δ (ppm) 12.44 (s, 1H), 10.60 (s, 1H), 9.40 (s, 1H), 8.35 (s, 1H), 8.32-7.44 (m, 15H); ^{13}C NMR (CD_3COCD_3) δ (ppm) 170.19, 151.67, 141.38, 138.30, 137.84, 137.21, 135.52, 133.94, 133.48, 132.85, 131.68, 128.85, 128.54, 128.26, 127.17, 126.70, 126.30, 124.07, 123.15, 122.91, 121.50, 120.23, 114.53, 107.17.

TW-121

^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 12.44 (s, 1H), 10.21 (s, 1H), 9.02 (s, 1H), 8.40 (d, 2H), 7.94-7.0 (m, 14H), 3.30 (hex, 1H), 0.95 (d, 6H); ^{13}C NMR ($CDCl_3$) δ (ppm) 170.30, 151.69, 148.57, 146.37, 142.82, 141.12, 140.23, 136.77, 134.19, 129.05, 128.31, 128.26, 128.17, 127.22, 126.83, 125.18, 124.90, 124.09, 122.61, 122.48, 121.76, 119.21, 114.50, 108.41, 27.91, 23.97.

TW-127

^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 12.10 (s, 1H), 8.06 (s, 1H), 7.81-6.61 (m, 13H), 7.07 (s, 1H), 6.06 (s, 1H), 5.77 (s, 1H), 4.20-4.07 (m, 1H), 4.04 (s, 2H), 3.54 (s, 3H), 3.10-2.95 (m, 1H), 3.05 (q, 2H), 1.23 (d, 6H); ^{13}C NMR ($CDCl_3$) δ (ppm) 172.18, 169.23, 149.23, 147.95, 147.81, 141.80, 137.00, 135.60, 135.36, 132.38, 130.47, 130.09, 129.34, 129.02, 128.04, 127.80, 126.59, 126.21, 121.08, 120.36, 118.60, 107.37, 61.27, 57.45, 53.35, 40.03, 32.16, 29.60, 23.32.

TW-130

^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 12.41 (s, 1H), 7.15-7.02 (m, 8H), 6.35 (d, 2H), 6.17 (s, 1H), 6.00 (s, 1H), 5.32 (s, 1H), 4.94-4.83 (m, 1H), 4.07-3.94 (m, 2H), 3.43 (s, 1H), 3.20-3.08 (m, 2H); ^{13}C NMR ($CDCl_3$) δ (ppm) 172.44, 170.25, 148.76, 147.88, 147.02, 136.89, 136.09, 132.05, 130.62, 130.01, 129.74, 129.45, 127.95, 127.61, 126.41, 126.08, 119.88, 117.94, 106.83, 53.80, 53.24, 38.48, 32.29, 29.50, 24.46.

TW-132

^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 12.10 (s, 1H), 8.22 (s, 1H), 7.86-7.05 (m, 8H), 6.68 (s, 1H), 6.21 (s, 1H), 6.01 (s, 1H), 5.27 (d, 1H), 4.03 (s,

2H), 3.95-3.87 (m, 1H), 3.38 (s, 1H), 3.20-3.14 (m, 1H), 1.75-1.68 (m, 2H), 1.26 (d, 6H).

TW-133

^{1}H NMR (CD_3COCD_3, 300 MHz,) δ (ppm) 12.25 (s, 1H), 9.83 (s, 1H), 8.51 (s, 1H), 8.33 (s, 1H), 7.83-6.98 (m, 15H), 5.14-5.09 (t, 1H), 4.02 (s, 2H), 3.53 (s, 3H), 3.32-3.28 (m, 1H), 1.31 (d, 6H); ^{13}C NMR (CD_3COCD_3) δ (ppm) 170.57, 169.96, 150.15, 149.05, 146.92, 142.35, 137.73, 136.46, 136.31, 132.87, 129.34, 129.03, 128.73, 128.31, 127.69, 126.72, 125.83, 125.23, 120.94, 120.84, 119.90, 119.25, 107.06, 60.17, 60.06, 52.37, 32.00, 23.46.

TW-134

^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 12.01 (s, 1H), 7.89-7.23 (m, 13H), 6.86 (s, 1H), 6.50 (s, 1H), 5.45 (s, 1H), 4.01 (s, 2H), 1.56 (s, 9H); ^{13}C NMR ($CDCl_3$) δ (ppm) 168.37, 151.13, 148.61, 146.90, 140.70, 140.06, 139.09, 133.20, 133.01, 131.78, 129.13, 128.65, 128.51, 128.40, 126.30, 126.19, 120.33, 119.63, 117.81, 106.59, 37.31, 35.12, 32.17.

TW-137

^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 12.06 (s, 1H), 7.87-7.06 (m, 9H), 6.83 (s, 1H), 6.08 (s, 1H), 5.81 (s, 1H), 5.32-5.27 (m, 1H), 4.04 (s, 2H), 3.95-3.78 (m, 1H), 3.70-3.54 (m, 2H), 3.5 (s, 3H), 3.20-3.15 (m, 2H), 1.76-1.56 (m, 1H), 1.00-0.87 (m, 12H); ^{13}C NMR ($CDCl_3$) δ (ppm) 171.83, 168.37, 148.48, 147.21, 146.85, 140.95, 136.10, 134.88, 131.64, 129.74, 128.52, 127.12, 125.86, 125.51, 120.18, 119.60, 117.42, 106.53, 61.06, 52.40, 31.57, 28.86, 23.77, 22.63, 18.93, 17.32, 14.11.

TW-138

^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 12.30 (s, 1H), 10.61 (s, 1H), 9.61 (s, 1H), 8.39-7.55 (m, 14H); ^{13}C NMR ($CDCl_3$) δ (ppm) 170.17, 138.34, 137.85, 136.52, 135.71, 133.83, 133.79, 132.61, 131.70, 131.11, 128.92, 128.73, 128.31, 128.26, 127.86, 127.30, 126.93, 126.62, 125.77, 124.12, 123.18, 122.93, 121.18, 120.98, 114.65.

TW-141

^{1}H NMR (CD_3COCD_3, 300 MHz,) δ (ppm) 12.74 (s, 1H), 10.50 (s, 1H), 9.75 (s, 1H), 9.30 (s, 1H), 8.52-7.14 (m, 13H), 4.42 (s, 2H), 3.57 (t, 2H), 2.91 (s, 2H), 1.66 (s, 9H).

TW-142

^{1}H NMR (CD_3COCD_3, 300 MHz,) δ (ppm) 11.98 (s, 1H), 8.16 (s, 1H), 8.00-6.34 (m, 16H), 4.04 (s, 2H), 3.87-3.67 (m, 1H), 2.96-2.74 (m, 1H), 2.70 (s, 3H), 1.21 (d, 6H); ^{13}C NMR (CD_3COCD_3) δ (ppm) 208.07, 171.70, 171.60, 168.89, 149.03, 147.76, 147.62, 141.92, 136.71, 135.57, 133.80, 132.17, 130.09, 129.40, 129.37, 128.69, 127.76, 127.45, 126.23, 125.87, 120.77, 119.97, 118.47, 107.18, 60.68, 58.46, 38.90, 32.06, 30.11, 28.86, 24.20, 21.48, 14.60.

TW-144

^{1}H NMR (CD_3COCD_3, 300 MHz,) δ (ppm) 12.07 (s, 1H), 7.88 (s, 1H), 7.70 (d, 2H), 7.57 (d, 2H), 7.39-7.07 (m, 11H), 6.62 (s, 1H), 6.11 (s, 1H), 5.85 (s, 1H), 4.04 (s, 2H), 3.54 (s, 4H), 3.10-2.87 (m, 2H), 0.91 (d, 6H); ^{13}C NMR (CD_3COCD_3) δ (ppm) 171.30, 168.43, 148.51, 147.32, 146.90, 141.00, 136.17, 134.83, 131.64, 129.86, 129.38, 128.62, 128.37, 127.32, 127.16, 125.88, 125.55, 120.27, 119.61, 117.44, 106.55, 56.64, 53.44, 39.34, 31.59, 28.89, 23.80, 22.66, 14.14.

TW-147

^{1}H NMR (CD_3COCD_3, 300 MHz,) δ (ppm) 12.02 (s, 1H), 8.20-6.80 (m, 15H), 4.01 (s, 3H).

TW-148

^{1}H NMR (CD_3COCD_3, 300 MHz,) δ (ppm) 11.67 (s, 1H), 9.31 (s, 1H), 7.98-7.05 (m, 15H), 3.96 (s, 2H), 3.76-3.64 (m, 2H), 2.48 (d, 2H), 2.21 (t, 2H), 1.57 (s, 9H), 1.31-1.22 (m, 4H); ^{13}C NMR (CD_3COCD_3) δ (ppm) 166.61, 154.04, 151.14, 149.04, 140.68, 139.98, 139.61, 139.55, 133.26, 129.15, 128.98, 128.30, 128.255, 128.17, 126.30, 126.12, 121.68, 121.30, 119.51, 115.10, 112.80, 56.71, 46.58, 42.48, 37.20, 32.20, 31.60, 22.66, 14.13.

TW-159

^{1}H NMR (CD_3COCD_3, 300 MHz,) δ (ppm) 12.84 (s, 1H), 9.08 (s, 1H), 7.97-7.05 (m, 15H), 6.23 (s, 1H), 5.23 (s, 1H), 2.94 (t, 2H), 2.58 (t, 2H), 1.75-1.63 (m, 2H), 1.67 (s, 9H).

TW-160

^{1}H NMR (CD_3COCD_3, 300 MHz,) δ (ppm) 10.6 (s, 1H), 8.07-7.10 (m, 16H), 2.92 (t, 2H), 2.56 (t, 2H), 1.58 (s, 9H), 1.57-1.45 (m, 4H).

TW-161

^{1}H NMR (CD_3COCD_3, 300 MHz,) δ (ppm) 12.58 (s, 1H), 10.64 (s, 1H), 8.73 (s, 1H), 8.05-6.83 (m, 16H), 3.18 (t, 2H), 2.87 (t, 2H), 1.57 (s, 9H), 1.54-1.34 (m, 2H); ^{13}C NMR (CD_3COCD_3) δ (ppm) 167.94, 150.35, 146.39, 141.66, 140.62, 139.18, 138.64, 133.13, 132.99, 131.02, 129.01, 128.58, 128.27, 128.18, 128.04, 127.96, 126.34, 126.12, 120.98, 119.14, 117.61, 116.50, 114.71, 67.28, 44.30, 34.90, 29.59.

TW-164

^{1}H NMR (CD_3COCD_3, 300 MHz,) δ (ppm) 10.76 (s, 1H), 8.40 (s, 1H), 7.95 (s, 1H), 7.60-7.12 (m 10H), 4.19 (s, 2H), 3.68-3.72 (m, 6H), 2.95-2.76 (m, 6H); ^{13}C NMR (CD_3COCD_3) δ (ppm) 165.13, 147.75, 137.84, 136.46, 133.85, 133.15, 132.47, 129.54, 127.52, 127.36, 126.97, 124.74, 122.40, 120.99, 119.45, 116.73, 66.14, 55.79, 48.12, 46.78, 44.48, 28.89, 18.95.

TW-166

^{1}H NMR (CD_3COCD_3, 300 MHz,) δ (ppm) 7.99-7.15 (m, 22H), 3.63 (t, 2H), 2.93 (t, 2H).

TW-167

^{1}H NMR (CD_3COCD_3, 300 MHz,) δ (ppm) 8.31 (s, 1H), 7.84-6.93 (m, 17H), 3.30-3.24 (m, 8H), 2.89 (s, 4H), 1.31 (s, 9H); ^{13}C NMR (CD_3COCD_3) δ (ppm) 168.96, 151.02, 149.44, 147.81, 146.24, 141.62, 138.61, 133.50, 131.41, 129.67, 129.50, 129.16, 128.58, 125.70, 121.33, 121.13, 120.09, 117.38, 116.58, 114.10, 49.56, 46.49, 37.70, 34.81, 31.81, 25.49.

TW-168

^{1}H NMR (CD_3COCD_3, 300 MHz,) δ (ppm) 11.67 (s, 1H), 10.17 (s, 1H), 8.06-7.00 (m, 15H), 3.72-3.78 (m, 4H), 3.31-3.05 (m, 2H), 2.91-2.84 (m, 4H), 1.29 (s, 9H); ^{13}C NMR (CD_3COCD_3) δ (ppm) 169.41, 158.20, 148.78, 148.03, 146.55, 142.90, 139.05, 138.84, 133.09, 131.55, 130.98, 129.22, 129.15, 128.44, 125.46, 121.48, 121.18, 120.36, 117.93, 115.40, 113.88, 108.43, 49.29, 46.19, 39.15, 31.21, 28.86, 24.00, 22.80.

TW-169

^{1}H NMR (CD_3COCD_3, 300 MHz,) δ (ppm) 11.69 (s, 1H), 8.30 (d, 2H), 8.27 (s, 1H), 7.83 (s, 3H), 7.20 (d, 2H), 6.92 (d, 2H), 6.74 (s, 1H), 6.58 (s,

1H), 5.93 (t, 1H), 4.02-3.96 (m, 4H), 3.10-2.98 (m, 4H), 2.88 (s, 4H), 1.31 (s, 9H); ^{13}C NMR (CD_3COCD_3) δ (ppm) 168.93. 161.43, 158.19, 149.40, 147.89, 147.28, 141.49, 138.55, 133.50, 131.51, 131.33, 129.35, 129.20, 128.58, 125.70, 121.10, 120.06, 116.31, 113.91, 110.99, 46.31, 43.16, 39.11, 37.69, 31.79.

TW-170

^{1}H NMR (CD_3COCD_3, 300 MHz,) δ (ppm) 11.78 (s, 1H), 8.27 (s, 1H), 7.80-7.21 (m, 15H), 6.94 (s, 1H), 5.88 (s, 1H), 3.84-3.74 (m, 2H), 2.90 (s, 4H), 2.53 (d, 2H), 2.31-2.19 (m, 5H), 1.33 (s, 9H); ^{13}C NMR (CD_3COCD_3) δ (ppm) 168.99, 149.41, 147.91, 146.25, 141.13, 140.10, 138.63, 133.50, 132.33, 131.34, 129.40, 129.27, 128.72, 128.60, 126.50, 125.71, 121.17, 120.02, 116.34, 113.95, 46.88, 42.98, 37.72, 34.82, 31.82, 31.61.

TW-171

^{1}H NMR (CD_3COCD_3, 300 MHz,) δ (ppm) 11.06 (s, 1H), 7.85-6.97 (m, 15H), 6.31 (s, 1H), 4.27 (s, 2H), 3.39 (t, 2H), 3.21-3.17 (m, 8H), 2.95 (t, 2H).

TW-172

^{1}H NMR (CD_3COCD_3, 300 MHz,) δ (ppm) 10.63 (s, 1H), 8.21-7.09 (m, 20H), 4.12-4.03 (m, 2H), 3.65-3.54 (m, 2H), 3.15-2.95 (m, 2H), 2.75 (d, 2H), 1.76-1.56 (m, 3H).

TW-173

^{1}H NMR (CD_3COCD_3, 300 MHz,) δ (ppm) 10.67 (s, 1H), 8.10-6.67 (m, 21H), 4.28 (s, 2h), 3:50-3.37 (m, 6H), 2.95-2.90 (m, 4H), 2.70-2.65 (m, 3H); ^{13}C NMR (CD_3COCD_3) δ (ppm) 168.60, 147.50, 144.02, 139.95, 133.63, 132.40, 132.24, 130.61, 129.42, 129.31, 129.18, 128.91, 128.28, 127.50, 127.03, 126.80, 126.56, 121.58, 118.95, 117.54, 117.28, 115.67, 48.52, 48.01, 45.22, 44.25, 31.36.

TW-174

^{1}H NMR (CD_3COCD_3, 300 MHz,) δ (ppm) 10.86 (s, 1H), 8.23-6.65 (m, 16H), 4.29 (s, 2H), 3.80-3.54 (m, 7H), 1.74-1.45 (m, 4H), 1.31 (s, 9H).

TW-175

^{1}H NMR (CD_3COCD_3, 300 MHz,) δ (ppm 10.59 (s, 1H), 9.01 (s, 1H), 8.07-6.36 (m, 18H), 4.20 (s, 2H), 3.79-3.69 (m, 2H), 3.40-3.32 (m, 6H), 1.79-1.58 (m, 3H).

TW-183- 3-[2-(4-叔丁基-苯基)-乙基]-2-羟基-5-萘-2-基-苯甲酸

^{1}H NMR (300 MHz, CD_3COCD_3): δ (ppm) 11.2 (br, 1H), 8.2-6.85 (m, 14H), 2.83-2.42 (m, 4H), 1.15 (s, 9H); ^{13}C NMR (CD_3COCD_3): δ (ppm) 181.2, 148.3, 138.87, 137.24, 135.6, 134.85, 133.54, 132.17, 131.19, 130.56, 129.45, 128.92, 128.28, 128.12, 127.98, 127.44, 127.13, 125.99, 125.64, 125.44, 125.34, 125.24, 125.03, 124.65, 123.68, 38.51, 34.66, 32.04, 31.37.

TW-184- N-[-4-(4-联苯-2-基-乙基-哌嗪-1-基)-苯基]-2,3-二羟基-5-萘-2-基-苯甲酰胺

^{1}H NMR (300 MHz, CD_3COCD_3): δ (ppm) 8.1 (d, J = 3.2 Hz, 1H), 7.95-7.26 (m, 21H), 6.90 (d, J = 7.1 Hz, 2H), 3.49 (s, 2H), 3.14 (t, J = 5.4 Hz, 4H), 2.53 (t, J = 5.3 Hz, 4H); ^{13}C NMR (CD_3COCD_3): δ (ppm) 168.3, 149.36, 148.81, 146.313, 142.77, 141.38, 137.49, 135.355, 133.58, 132.48, 132.38, 130.15, 129.67, 129.51, 129.16, 128.58, 128.01, 127.85, 127.65, 127.14, 126.92, 126.87, 126.48, 126.00, 125.32, 125.16, 122.91, 117.55, 115.28, 114.83, 114.55, 59.73, 52.60, 49.20.

TW-189- 2-羟基-5-萘-1-基-3-苯乙基-苯甲酸

^{1}H NMR (300 MHz, CD_3COCD_3): δ (ppm) 11.3 (br, 1H), 8.16 (d, J = 2.3 Hz, 1H), 8.05-7.18 (m, 14H), 3.05(m, 4H); ^{13}C NMR (CD_3COCD_3): δ (ppm) 173.38, 160.72, 142.89, 138.20, 135.85, 134.78, 133.41, 132.48, 131.31, 131.00, 129.42, 129.35, 129.15, 128.95, 128.42, 127.78, 127.40, 126.68, 125.82, 125.67, 36.38, 32.78.

TW-190- 2-羟基-5-萘-1-基-3-{2-[4-(4-苯基-丁基氨磺酰基)-苯基]-乙基}-苯甲酸

^{1}H NMR (300 MHz, CD_3COCD_3): δ (ppm) 8.22 (s, 1H), 8.13 (s, 1H), 8.03-6.95 (m, 16H), 6.35 (s, 1H), 3.14 (m, 4H), 2.82 (m, 2H), 2.46 (m, 2H), 1.53-1.62 (m, 4H); ^{13}C NMR (CD_3COCD_3): δ (ppm) 160.11, 147.23, 142.611, 139.03, 137.64, 134.97, 134.29, 132.88, 130.03, 129.90, 129.58, 129.53, 128.88, 128.70, 128.52, 127.91, 127.33, 126.68, 126.16, 126.00, 125.35, 125.07, 43.16, 43.07, 35.54, 35.39, 31.91, 23.50.

TW-194- 4-氯-3-(甲基-苯乙基-氨磺酰基)-5-[(萘-2-羰基)-氨基]-苯甲酸

^{1}H NMR (300 MHz, CD_3COCD_3): δ (ppm) 9.35 (s, 1H), 9.12 (s, 1H), 8.80 (s, 1H), 8.46 (s, 1H), 8.12-7.22 (m, 11H), 3.78 (m, 2H), 3.03 (s, 3H), 2.94 (m, 2H); ^{13}C NMR (CD_3COCD_3): δ (ppm) 165.96, 165.47, 138.97, 138.93, 138.28, 135.58, 133.06, 131.78, 130.13, 129.57, 129.28, 128.12, 129.01, 128.77, 128.70, 128.61, 128.52, 128.28, 128.21, 127.43, 126.77, 124.41, 51.59, 34.65, 34.48.

TW-195- 4-氯-3-(4-氟-苯甲酰基氨基)-5-(甲基-苯乙基-氨磺酰基)-苯甲酸

^{1}H NMR (300 MHz, CD_3COCD_3): δ (ppm) 9.33 (s, 1H), 8.53 (s, 1H), 8.47 (s, 1H), 8.02 (m, 2H), 7.30-7.11 (m, 7H), 3.62 (t, J= 6.8 Hz, 3H), 2.98 (s, 3H), 2.89 (t, J = 5.4 Hz, 3H); ^{13}C NMR (CD_3COCD_3): δ (ppm) 164.87, 164.10, 130.30, 130.17, 129.10, 128.88, 128.14, 127.39, 126.94, 126.26, 116.66, 116.37, 52.04, 35.15, 34.98.

TW-196- 3-[(苯并呋喃-2-羰基)-氨基]-4-氯-5-(甲基-苯乙基-氨磺酰基)-苯甲酸

^{1}H NMR (300 MHz, CD_3COCD_3): δ (ppm) 10.51 (s, 1H), 8.44 (s, 1H), 8.32 (s, 1H), 7.82-7.16 (m, 9H), 3.62 (t, J= 6.8 Hz, 3H), 2.98 (s, 3H), 2.89 (t, J = 5.4 Hz, 3H); ^{13}C NMR (CD_3COCD_3): δ (ppm) 166.07, 157.82, 155.41, 148.61, 139.10, 139.01, 137.91, 132.36, 131.83, 130.70, 129.55, 129.22, 128.50, 127.86, 127.22, 124.93, 124.03, 112.91, 112.61, 52.00, 35.28, 34.62.

TW-198- 3-[(联苯-4-羰基)-氨基]-4-氯-5-(甲基-苯乙基-氨磺酰基)-苯甲酸

^{1}H NMR (300 MHz, CD_3COCD_3): δ (ppm) 9.42 (s, 1H), 9.05 (s, 1H), 8.51 (s, 1H), 8.22-7.12 (m, 15H), 3.54 (m, 2H), 3.09 (s, 3H), 2.96 (m, 3H); ^{13}C NMR (CD_3COCD_3): δ (ppm) 165.56, 165.43, 145.19, 140.02, 138.93, 138.23, 133.17, 130.04, 129.45, 129.26, 129.12, 128.77, 128.71, 128.62, 128.24, 127.57, 127.50, 126.77, 51.88, 34.63, 34.48.

TW-199- 4-氯-3-(甲基-苯乙基-氨磺酰基)-5-{4-(4-苯基-哌啶-1-磺酰基)-苯甲酰基氨基 }-苯甲酸

^{1}H NMR (300 MHz, CD_3COCD_3): δ (ppm) 9.67 (s, 1H), 8.95 (s, 1H), 8.51 (s, 1H), 8.51 (d, J = 8.1 Hz, 2H), 8.02 (d, J = 7.5 Hz, 2H), 7.32-7.19 (m, 10H), 3.9 (m, 2H), 3.58 (m, 2H), 3.31 (s, 3H), 2.96 (m, 2H), 2.43 (m, 4H), 1.84 (m, 4H); ^{13}C NMR (CD_3COCD_3): δ (ppm) 165.20, 165.00, 145.73, 140.18, 139.18, 138.92, 138.31, 137.97, 137.86, 130.01, 129.97, 129.47, 129.12, 129.02, 128.82, 128.88, 128.47, 127.11, 126.78, 126.75, 51.92, 47.18, 41.74, 34.78, 34.65, 34.52, 32.86.

TW-200- 3-(4-苯甲酰基-苯甲酰基氨基)-4-氯-5-(甲基-苯乙基-氨磺酰基)苯甲酸

^{1}H NMR (300 MHz, CD_3COCD_3): δ (ppm) 9.56 (s, 1H), 9.00 (s, 1H), 8.53 (s, 1H), 8.32-7.65 (m, 9H), 7.32-6.93 (m, 5H), 3.55 (m, 2H), 3.02(s, 3H), 2.89 (m, 2H); ^{13}C NMR (CD_3COCD_3): δ (ppm) 181.3, 138.94, 137.45, 133.30, 130.25, 129.80, 129.13, 128.96, 128.28, 128.18, 126.80, 51.89, 34.66, 34.51.

TW-201- 3-苯甲酰基氨基-4-氯-5-(甲基-苯乙基-氨磺酰基)-苯甲酸

^{1}H NMR (300 MHz, CD_3COCD_3): δ (ppm) 9.37 (s, 1H), 9.04 (s, 1H), 8.47 (s, 1H), 8.21-7.13 (m, 10H), 3.63 (m, 2H), 3.02 (s, 3H), 2.89 (m, 2H); ^{13}C NMR (CD_3COCD_3): δ (ppm) 165.87, 165.30, 138.93, 138.23, 134.47, 132.75, 129.88, 129.18, 129.11, 128.76, 128.23, 128.00, 126.76, 51.87, 34.62, 34.47.

TW-202- 4-氯-3-[4-(3,4-二氢-1H-异喹啉-2-磺酰基)-苯甲酰基氨基]-5-(甲基-苯乙基-氨磺酰基)-苯甲酸

^{1}H NMR (300 MHz, CD_3COCD_3): δ (ppm) 9.63 (s, 1H), 8.92 (s, 1H), 8.50 (s, 1H), 8.29 (d, J = 8.1 Hz, 2H), 8.07 (d, J = 8.0 Hz, 2H), 7.34-7.03 (m, 8H), 4.33 (s, 2H), 3.54 (m, 2H), 3.45 (m, 4H), 3.10 (s, 3H), 3.10-3.01 (m, 2H); ^{13}C NMR (CD_3COCD_3): δ (ppm) 165.19, 164.96, 140.40, 139.15, 138.91, 138.41, 137.93, 133.57, 132.12, 129.95, 129.20, 129.11, 129.05, 128.77, 128.41, 127.13, 126.77, 126.65, 51.89, 47.87, 44.22, 34.62, 34.49.

TW-203- 4-氯-3-(甲基-苯乙基-氨磺酰基)-5-{4[甲基-(3-苯基-丙基)-氨磺酰基]-苯甲酰基氨基}-苯甲酸

^{1}H NMR (300 MHz, CD_3COCD_3): δ (ppm) 9.63 (s, 1H), 8.82 (s, 1H), 8.49 (s, 1H), 8.23 (d, J = 7.5 Hz, 2H), 7.93 (d, J = 7.6 Hz, 2H), 7.34-6.90 (m, 10H), 3.42-3.02 (m, 8H), 2.74 (s, 3H), 2.65 (s, 3H), 1.90-1.78 (m, 2H); ^{13}C NMR (CD_3COCD_3): δ (ppm) 164.32, 142.05, 141.17, 139.00, 138.02, 137.73, 129.17, 129.05, 128.77, 127.99, 126.68, 126.12, 51.86, 50.06, 34.88, 34.66, 32.87, 30.12.

TW-204- 4-氯-3-(4-甲氧基-苯甲酰基氨基)-5-(甲基-苯乙基-氨磺酰基)-苯甲酸

^{1}H NMR (300 MHz, CD_3COCD_3): δ (ppm) 9.20 (s, 1H), 9.06 (s, 1H), 8.46 (s, 1H), 8.06 (d, J = 7.5 Hz, 2H), 7.34-7.02 (m, 7H), 3.91 (s, 3H), 3.57 (m, 2H), 3.02 (s, 3H), 2.95 (m, 2H); ^{13}C NMR (CD_3COCD_3): δ (ppm) 165.31, 163.53, 138.92, 138.42, 129.97, 129.77, 128.76, 127.87, 126.76, 126.43, 114.37, 55.47, 51.86, 34.62, 34.45.

TW-205- 3-[(金刚烷-1-羰基)-氨基]-4-氯-5-(甲基-苯乙基-氨磺酰基)-苯甲酸

^{1}H NMR (300 MHz, CD_3COCD_3): δ (ppm) 9.0 (s, 1H), 8.41 (m, 2H), 7.44-7.23 (m, 5H), 3.52 (m, 2H), 3.01 (s, 3H), 2.89 (m, 2H), 2.04 (s, 10H), 1.74 (s, 3H); ^{13}C NMR (CD_3COCD_3): δ (ppm) 176.13, 165.36, 138.88, 138.65, 138.12, 129.80, 129.08, 128.70, 128.00, 127.44, 127.21, 126.76, 51.77, 42.29, 39.17, 36.55, 34.54, 34.37.

TM-1230- 2-[5-(3,4-二氢-1H-异喹啉-2-磺酰基)-2,3,4-三羟基-苯甲酰基]-1,2,3,4-四氢-异喹啉-7-磺酸(3-苯甲酰基-苯基)-酰胺

^{1}H NMR ($CDCl_3$, 300 MHz) δ 10.4 (s, 1H), 8.52 (s, 1H), 8.00-6.97 (m, 17H), 6.68 (1H), 6.28 (s, 1H), 4.85-4.63 (m, 2H), 4.28 (s, 1H), 3.79 (m, 3H), 3.38 (s, 1H), 3.22-3.09 (m, 2H), 2.95-2.87 (m, 3H); ^{1}H NMR ($CO(CD_3)_2$, 300 MHz) δ 9.27 (b, 1H), 7.70-7.66 (m, 4.5H), 7.61-7.59 (m, 2.5H), 7.56-7.47 (m, 7H), 7.38 (m, 3H), 7.29 (s, 0.5H), 7.12 (b, 2H), 6.82 (s, 0.5H), 4.84 (d, 2H), 4.38 (s, 1H), 3.83 (m, 2H), 3.02 (m, 1H), 2.90 (m, 3H); ^{13}C NMR ($CO(CD_3)_2$, 75 MHz) δ 195.8, 169.1, 167.5, 150.5, 148.2, 141.3, 139.2, 138.8, 138.5, 138.0, 135.2, 133.4, 130.5, 130.3, 129.7, 129.2, 127.4, 126.4, 125.8, 125.3, 122.2, 115.8, 48.0, 44.5, 39.7.

TM-1231- 2,3,4-三羟基-5-异丙基-N-萘-2-基-苯-磺酰胺

^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.55 (s, 1H), 7.74-7.67 (m, 3H), 7.51 (d, 1H), 7.43 (m, 2H), 7.16 (dd, 1H), 7.05 (s, 1H), 6.90 (s, 1H), 5.86 (s, 1H), 5.54

(s, 1H), 3.05 (hept, 1H), 0.99 (d, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 147.1, 141.4, 133.8, 133.4, 131.9, 131.5, 129.8, 128.7, 128.0, 127.9, 127.1, 126.3, 122.4, 121.0, 117.1, 112.9, 26.9, 22.4.

TM-1232- 2,3,4-三羟基-5-异丙基-N-甲基-N-萘-2-基-苯磺酰胺

^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.48 (s, 1H), 7.83 (m, 1H), 7.80 (d, 1H), 7.74 (m, 1H), 7.53 (d, 1H), 7.51-7.48 (m, 2H), 7.27 (dd, 1H), 6.63 (s, 1H), 5.91 (b, 1H), 5.51 (b, 1H), 3.26 (s, 3H), 3.14 (hept, 1H), 1.02 (d, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 146.9, 141.7, 138.9, 133.5, 132.7, 131.4, 129.2, 128.26, 128.2, 128.0, 127.0, 126.96, 125.6, 125.4, 117.5, 110.8, 38.5, 26.9, 22.5.

TM-1233- N-乙基-2,3,4-三羟基-5-异丙基-N-萘-2-基-苯磺酰胺

^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.48 (s, 1H), 7.82-7.72 (m, 3H), 7.55 (s, 1H), 7.48 (m, 2H), 7.13 (dd, 1H), 6.76 (s, 1H), 5.88 (s, 1H), 5.48 (b, 1H), 3.66 (q, 2H), 3.17 (hept, 1H), 1.10-1.06 (m, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 146.9, 141.4, 135.8, 133.5, 133.0, 131.5, 129.3, 128.4, 128.3, 128.2, 127.9, 127.1, 126.9, 126.6, 117.2, 112.8, 45.8, 26.9, 22.6, 14.1.

TM-1234- 2,3,4-三羟基-5-异丙基-N-萘-2-基-N-丙基-苯磺酰胺

^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.55 (s, 1H), 7.80-7.71 (m, 3H), 7.59 (s, 1H), 7.49-7.44 (m, 2H), 7.16 (dd, 1H), 6.77 (s, 1H), 6.18 (b, 1H), 5.89 (b, 1H), 3.58 (t, 2H), 3.19 (hept, 1H), 1.44 (hex, 2H), 1.09 (d, 6H), 0.90 (t, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 146.9, 141.5, 136.1, 133.5, 133.0, 131.4, 129.2, 128.24, 128.19, 127.9, 127.0, 126.8, 126.4, 117.2, 112.7, 52.5, 26.9, 22.5, 21.6.

TM-1235- 2,3,4-三羟基-5,N-二异丙基-N-萘-2-基-苯磺酰胺

^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.58 (b, 1H), 7.85-7.75 (m, 3H), 7.54 (s, 1H), 7.52-7.47 (m, 2H), 7.12 (dd, 1H), 7.00 (s, 1H), 5.93 (b, 1H), 5.58 (b, 1H), 4.65 (hept, 1H), 3.24 (hept, 1H), 1.18 (d, 6H), 1.11 (d, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 146.5, 141.2, 133.4, 133.3, 132.1, 131.8, 131.4, 129.9, 129.0, 128.4, 127.9, 127.4, 126.8, 116.9, 115.6, 52.1, 27.0, 22.7, 22.3.

TM-1236-2,3,4-三羟基-N-异丁基-5-异丙基-N-萘-2-基-苯磺酰胺

^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.53 (s, 1H), 7.83-7.73 (m, 3H), 7.59 (s, 1H), 7.50-7.47 (m, 2H), 7.18 (dd, 1H), 6.73 (s, 1H), 5.94 (b, 1H), 5.55 (b, 1H), 3.39 (d, 2H), 3.18 (m, 1H), 1.63 (m, 1H), 1.09 (d, 6H), 0.92 (d, 6H); ^{13}C NMR

($CDCl_3$, 75 MHz) δ 146.7, 141.5, 136.6, 133.6, 133.0, 131.4, 129.3, 128.3, 128.2, 128.1, 128.0, 127.1, 126.9, 126.4, 117.2, 112.8, 58.3, 27.1, 27.0, 22.6, 20.2.

TM-1237- 2,3,4-三羟基-5-异丙基-N-苯乙基-苯磺酰胺

^1H NMR ($CDCl_3$, 300 MHz) δ 8.70 (b, 1H), 7.30-7.20 (m, 3H), 7.06 (d, 2H), 6.96 (s, 1H), 5.92 (b, 1H), 5.65 (b, 1H), 4.49 (t, 1H), 3.27-3.16 (m, 3H), 2.76 (t, 2H), 1.21 (d, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 147.2, 141.5, 137.7, 131.8, 129.0, 128.9, 128.8, 127.1, 116.6, 113.8, 44.3, 35.6, 27.2, 22.5.

TM-1238- N-乙基-2,3,4-三羟基-5-异丙基-N-苯乙基-苯磺酰胺

^1H NMR ($CDCl_3$, 300 MHz) δ 9.00, 7.31-7.23 (m, 3H), 7.18-7.14 (m, 2H), 6.95 (s, 1H), 5.94 (b, 1H), 5.70 (b, 1H), 3.36 (t, 2H), 3.26 (t, 2H), 3.18 (m, 1H), 2.84 (t, 2H), 1.20 (d, 6H), 1.11 (t, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 146.6, 141.4, 138.5, 131.6, 129.0, 128.9, 128.6, 126.9, 116.2, 114.4, 49.0, 43.2, 35.7, 27.2, 22.6, 13.9.

TM-1239- 2-[5-(3,4-二氢-1H-异喹啉-2-磺酰基)-2,3,4-三羟基-苯甲酰基]-1,2,3,4-四氢-异喹啉-7-磺酸 [2-(4-叔丁基-苯基)-乙基]-酰胺 ^1H NMR ($CO(CD_3)_2$, 300 MHz) δ 10.13 (b, 1H), 9.06 (b, 1H), 8.50 (b, 1H), 7.72-7.70 (m, 2H), 7.41 (m, 3H), 7.30 (m, 2H), 7.14-7.07 (m, 5H), 6.45 (t, 1H), 4.92 (s, 2H), 4.39 (s, 2H), 3.86 (m, 2H), 3.52 (t, 2H), 3.11 (m, 2H), 2.93 (m, 4H), 2.74 (m, 2H), 1.27 (s, 9H); ^{13}C NMR ($CO(CD_3)_2$, 75 MHz) δ 169.2, 167.5, 150.8, 149.7, 147.0, 140.4, 139.8, 136.4, 135.3, 134.2, 132.8, 130.4, 129.6, 129.2, 127.4, 127.2, 126.0, 121.4, 48.0, 45.4, 44.5, 36.1, 31.6, 31.6.

TM-1240- 2-[2,3,4-三羟基-5-(4-苯基-丁基氨磺酰基)-苯甲酰基]-1,2,3,4-四氢-异喹啉-7-磺酸苯乙基-酰胺

^1H NMR ($CDCl_3$, 300 MHz) δ 10.14 (b, 1H), 8.30 (b, 1H), 7.59 (d, 1H), 7.55 (s, 1H), 7.38 (s, 1H), 7.25-7.19 (m, 6H), 7.15 (m, 1H), 7.08-7.06 (m, 4H), 6.55 (b, 1H), 5.24 (t, 1H), 5.01 (t, 1H), 4.76 (s, 2H), 3.81 (m, 2H), 3.15 (m, 2H), 2.98 (m, 2H), 2.88 (m, 2H), 2.76 (m, 2H), 2.52 (m, 2H), 1.57-1.48 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.9, 150.7, 145.4, 142.0, 139.7, 138.5, 138.1, 134.1, 133.6, 129.8, 129.1, 129.0, 128.6, 127.0, 126.2, 126.0, 125.4, 120.6, 116.2, 111.2, 44.7, 43.4, 36.2, 35.5, 29.2, 28.5.

TM-1241- 2-{2,3,4-三羟基-5-[甲基-(4-苯基-丁基)-氨磺酰基]-苯甲酰基}-1,2,3,4-四氢-异喹啉-7-磺酸甲基-苯乙基-酰胺

^1H NMR ($CDCl_3$, 300 MHz) δ 9.78 (b, 1H), 8.78 (b, 1H), 7.56 (d, 1H), 7.47 (s, 1H), 7.28-7.23 (m, 6H), 7.18-7.13 (m, 6H), 6.32 (b, 1H), 4.81 (s, 2H),

3.85 (m, 2H), 3.26 (m, 2H), 3.06-3.00 (m, 4H), 2.85 (t, 2H), 2.74 (s, 3H), 2.70 (s, 3H), 2.61 (t, 2H), 1.64-1.56 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.7, 150.4, 145.7, 142.0, 139.5, 138.4, 136.6, 133.9, 133.8, 129.9, 129.0, 128.8, 128.6, 126.8, 126.1, 126.0, 125.6, 120.0, 113.6, 111.5, 52.0, 50.0, 35.5, 35.4, 35.1, 34.7, 29.2, 28.3, 27.2, 14.4.

TM-1242- 2-{5-[乙基-(4-苯基-丁基)-氨磺酰基]-2,3,4-三羟基-苯甲酰基}-1,2,3,4-四氢-异喹啉-7-磺酸乙基-苯乙基-酰胺

^{1}H NMR ($CDCl_3$, 300 MHz) δ 10.10 (b, 1H), 8.90 (b, 1H), 7.61 (d, 1H), 7.52 (s, 1H), 7.34-7.23 (m, 8H), 7.18-7.12 (m, 6H), 4.82 (s, 2H), 3.87 (m, 2H), 3.35 (m, 2H), 3.26-3.16 (m, 6H), 3.02 (m, 2H), 2.88 (m, 2H), 2.61 (m, 2H), 1.60 (m, 4H), 1.15-1.06 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.7, 150.1, 145.5, 142.0, 139.3, 138.7, 138.6, 133.7, 129.8, 129.0, 128.8, 128.6, 126.8, 126.1, 125.7, 125.3, 119.8, 116.0, 111.6, 49.3, 47.6, 43.3, 42.9, 36.1, 35.5, 29.1, 28.4, 28.2, 14.3, 14.1.

TM-1243- 6-(2,3,4-三羟基-5-异丙基-苯磺酰基氨基)-萘-2-甲酸

^{1}H NMR ($CO(CD_3)_2$, 300 MHz) δ 9.43 (b, 1H), 8.56 (s, 1H), 8.20 (b, 1H), 8.02-7.98 (m, 2H), 7.87 (d, 1H), 7.76 (s, 1H), 7.51 (dd, 1H), 7.08 (s, 1H), 3.13 (m, 1H), 1.06 (d, 6H); ^{13}C NMR ($CO(CD_3)_2$, 75 MHz) δ 167.6, 149.4, 143.6, 138.6, 136.9, 133.3, 131.5, 130.6, 128.5, 128.2, 127.0, 122.3, 117.7, 117.3, 114.7, 27.3, 22.3.

TM-1244- 6-[乙基-(2,3,4-三羟基-5-异丙基-苯磺酰基)-氨基]-萘-2-甲酸乙酯

^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.60 (s, 1H), 8.47 (s, 1H), 8.09 (d, 1H), 7.91 (d, 1H), 7.79 (d, 1H), 7.62 (s, 1H), 7.23 (d, 1H), 6.73 (s, 1H), 5.91 (s, 1H), 5.49 (s, 1H), 4.45 (q, 2H), 3.69 (q, 2H), 3.18 (hept, 1H), 1.45 (t, 3H), 1.13-1.08 (m, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 166.8, 147.0, 141.5, 138.1, 135.6, 132.0, 131.5, 130.8, 130.6, 128.8, 128.4, 127.4, 126.3, 117.1, 112.5, 61.6, 45.7, 26.9, 22.6, 14.6, 14.1.

TM-1245- 6-(2,3,4-三羟基-5-异丙基-苯磺酰基氨基)-萘-2-甲酸苯乙基-酰胺

^{1}H NMR (CD_3OD, 300 MHz) δ 8.15 (s, 1H), 7.78-7.69 (m, 3H), 7.53 (s, 1H), 7.29 (dd, 1H), 7.23 (m, 4H), 7.15 (m, 1H), 6.94 (s, 1H), 3.58 (t, 2H), 3.03 (m, 1H), 2.89 (t, 2H), 0.98 (d, 6H).

TM-1246- 6-(2,3,4-三羟基-5-异丙基-苯磺酰基氨基)-萘-2-甲酸(3-苯基-丙基)-酰胺

^{1}H NMR ($CO(CD_3)_2$, 300 MHz) δ 9.41 (s, 1H), 8.63 (s, 1H), 8.34 (s, 1H), 8.21 (s, 2H), 7.99 (t, 1H), 7.93 (d, 1H), 7.86 (d, 1H), 7.80 (d, 1H), 7.73 (s, 1H), 7.47 (dd, 1H), 7.24 (m, 4H), 7.15 (m, 1H), 7.08 (s, 1H), 3.48 (m, 2H), 3.10 (m, 1H), 2.71 (t, 2H), 1.95 (pent, 2H), 1.05 (d, 6H); ^{13}C NMR ($CO(CD_3)_2$, 75 MHz) δ 167.6, 149.3, 143.6, 142.9, 137.9, 135.9, 133.3, 132.4, 130.9, 130.7, 129.2, 129.1, 128.2, 128.0, 127.99, 126.6, 125.7, 122.3, 117.7, 117.6, 114.8, 40.2, 33.9, 32.2, 27.2, 22.7.

TM-1247- 6-(2,3,4-三羟基-5-异丙基-苯磺酰基氨基)-萘-2-甲酸(4-苯基-丁基)-酰胺

^{1}H NMR ($CO(CD_3)_2$, 300 MHz) δ 9.32 (s, 1H), 8.59 (s, 1H), 8.34 (s, 1H), 8.10 (dd, 1H), 7.92-7.80 (m, 4H), 7.72 (d, 1H), 7.45 (dd, 1H), 7.25-7.20 (m, 4H), 7.15 (m, 1H), 7.04 (s, 1H), 3.47 (m, 2H), 3.11 (m, 1H), 2.66 (t, 2H), 1.70 (m, 4H), 1.04 (d, 6H); ^{13}C NMR ($CO(CD_3)_2$, 75 MHz) δ 167.5, 149.3, 143.6, 143.3, 137.8, 135.8, 133.2, 132.5, 130.9, 130.7, 129.2, 129.0, 128.2, 128.1, 128.0, 126.4, 125.7, 122.4, 117.7, 114.7, 40.4, 36.1, 27.2, 22.7.

TM-1248- 2-(2,3,4-三羟基-5-苯基氨磺酰基-苯甲酰基)-1,2,3,4-四氢-异喹啉-7-磺酸苯乙基-酰胺

^{1}H NMR ($CDCl_3$, 300 MHz) δ 10.25 (b, 1H), 8.15 (b, 1H), 7.57 (m, 2H), 7.48 (s, 1H), 7.20-7.05 (m, 12H), 6.50 (b, 1H), 5.30 (m, 1H), 4.61 (s, 2H), 3.64 (m, 2H), 3.17 (m, 2H), 2.88 (m, 2H), 2.76 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 168.9, 148.1, 146.4, 134.2, 133.8, 131.6, 131.1, 129.0, 127.8, 127.7, 126.9, 126.7, 125.6, 121.0, 118.6, 113.7, 106.9, 27.4, 22.6.

TM-1249- 2-{2,3,4-三羟基-5-[甲基-(4-苯基-丁基)-氨磺酰基]-苯甲酰基}-1,2,3,4-四氢-异喹啉-7-磺酸苯乙基-酰胺

^{1}H NMR ($CO(CD_3)_2$, 300 MHz) δ 10.39 (b, 1H), 8.56 (b, 1H), 7.63 (d, 1H), 7.50 (s, 1H), 7.36 (s, 1H), 7.25-7.16 (m, 6H), 7.19 (m, 1H), 7.08-7.02 (m, 4H), 6.68 (b, 1H), 5.40 (t, 1H), 4.76 (s, 2H), 3.81 (m, 2H), 3.15 (m, 2H), 2.98 (m, 2H), 2.88 (m, 2H), 2.76 (m, 2H), 2.52 (m, 2H), 2.32 (s, 3H), 1.57-1.48 (m, 4H); ^{13}C NMR ($CO(CD_3)_2$, 75 MHz) δ 169.9, 150.7, 145.4, 142.0, 139.7, 138.5, 138.1, 134.1, 133.6, 129.8, 129.1, 129.0, 128.6, 127.0, 126.2, 126.0, 125.4, 120.6, 116.2, 111.2, 44.7, 43.4, 36.2, 35.5, 29.2, 28.5.

TM-1250- 2,3,4-三羟基-5-异丙基-N-萘-2-基-苯甲酰胺

^{1}H NMR ($CDCl_3$, 300 MHz) δ 12.40 (s, 1H), 8.09 (d, 1H), 8.01 (s, 1H), 7.81-7.75 (m, 3H), 7.54 (dd, 1H), 7.44 (m, 2H), 6.91 (s, 1H), 6.01 (b, 2OH), 3.24 (m, 1H), 1.27 (d, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 168.9, 148.1, 146.4, 134.2, 133.8, 131.6, 131.1, 129.0, 127.8, 127.7, 126.9, 126.7, 125.6, 121.0, 118.6, 113.7, 106.9, 27.4, 22.6.

TM-1251- 2-{5-[乙基-(3-苯基-丙基)-氨磺酰基]-2,3,4-三羟基-苯甲酰基}-1,2,3,4-四氢-异喹啉-7-磺酸苯乙基-酰胺

^{1}H NMR ($CO(CD_3)_2$, 300 MHz) δ 10.53 (b, 1H), 8.45 (b, 1H), 7.66 (d, 1H), 7.64 (s, 1H), 7.39 (d, 1H), 7.35 (s, 1H), 7.24-7.13 (m, 11H), 6.49 (t, 1H), 4.88 (s, 2H), 3.86 (t, 2H), 3.36-3.28 (m, 4H), 3.15 (m, 2H), 3.04 (m, 2H), 2.77 (t, 2H), 2.61 (t, 2H), 1.87 (pent, 2H), 1.11 (t, 3H); ^{13}C NMR ($CO(CD_3)_2$, 75 MHz) δ 169.4, 150.6, 146.7, 142.5, 140.4, 139.9, 139.7, 135.3, 134.5, 130.4, 129.6, 129.2, 129.1, 127.1, 126.6, 126.0, 125.8, 120.9, 117.6, 113.4, 55.0, 47.8, 45.4, 45.3, 43.9, 43.3, 36.6, 33.5, 31.2, 14.5.

TM-1252- 2-{2,3,4-三羟基-5-[(3-苯基-丙基)-丙基-氨磺酰基]-苯甲酰基}-1,2,3,4-四氢-异喹啉-7-磺酸苯乙基-酰胺

^{1}H NMR ($CO(CD_3)_2$, 300 MHz) δ 9.25 (b, 2OH), 7.66 (d, 1H), 7.64 (s, 1H), 7.38 (d, 1H), 7.36 (s, 1H), 7.23-7.10 (m, 11H), 6.52 (b, 1H), 4.87 (s, 2H), 3.85 (m, 2H), 3.31-3.20 (m, 4H), 3.17 (t, 2H), 3.02 (m, 2H), 2.77 (t, 2H), 2.59 (t, 2H), 1.86 (m, 2H), 1.55 (m, 2H), 0.84 (t, 3H); ^{13}C NMR ($CO(CD_3)_2$, 75 MHz) δ 169.4, 150.6, 146.7, 142.4, 140.4, 139.9, 139.6, 135.2, 134.5, 130.4, 129.58, 129.18, 129.14, 129.12, 127.1, 126.6, 125.9, 125.8, 120.9, 117.5, 113.5, 50.6, 48.4, 45.4, 36.6, 33.5, 22.6, 11.4.

TM-1253- 6-(2-羟基-5-异丙基-苯磺酰基氨基)-萘-2-甲酸(3-苯基-丙基)-酰胺

^{1}H NMR ($CO(CD_3)_2$, 300 MHz) δ 8.32 (s, 1H), 7.96 (t, 1H), 7.93 (dd, 1H), 7.84 (d, 1H), 7.77 (d, 1H), 7.74 (d, 1H), 7.65 (d, 1H), 7.53 (dd, 1H), 7.29-7.22 (m, 6H), 7.19-7.13 (m, 2H), 6.90 (d, 1H), 3.47 (m, 2H), 2.78 (m, 1H), 2.71 (m, 2H), 1.95 (m, 2H), 1.10 (d, 6H); ^{13}C NMR ($CO(CD_3)_2$, 75 MHz) δ 167.4, 154.0, 142.9, 140.7, 138.0, 135.9, 133.9, 132.3, 130.8, 130.5, 129.2, 129.1, 128.1, 128.0, 127.9, 126.6, 125.7, 124.7, 121.9, 118.2, 116.7, 40.2, 33.9, 33.7, 32.1, 24.1.

TM-1254- 6-[甲基-(2,3,4-三羟基-5-异丙基-苯磺酰基)-氨基]-萘-2-甲酸苯乙基-丙基-酰胺

^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.38 (s, 1H), 7.75-7.66 (m, 2.5H), 7.50 (s, 1H), 7.42-7.31 (m, 4.5H), 7.21 (m, 2H), 6.88 (s, 1H), 6.53 (d, 1H), 6.30 (d,

1H), 6.24 (s, 1H), 3.77 (m, 1H), 3.60 (m, 1H), 3.49 (m, 1H), 3.23 (s, 3H), 3.14-3.05 (m, 3H), 2.78 (m, 1H), 1.78 (m, 1H), 1.50 (m, 1H), 1.03 (m, 1.5H), 0.96 (d, 6H), 0.67 (m, 1.5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.8, 147.1, 141.8, 139.6, 139.0, 137.7, 134.7, 133.1, 131.6, 131.4, 129.2, 128.9, 128.6, 128.2, 127.7, 126.7, 126.5, 125.8, 125.6, 124.9, 124.7, 117.0, 110.2, 53.4, 51.4, 50.5, 46.8, 46.4, 38.0, 34.9, 33.7, 26.5, 22.2.

TM-1255- 6-[甲基-(2,3,4-三羟基-5-异丙基-苯磺酰基)-氨基]-萘-2-甲酸环己基甲基-酰胺

^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.38 (s, 1H), 8.21 (s, 1H), 7.83-7.75 (m, 3H), 7.54 (d, 1H), 7.33 (dd, 1H), 6.60 (s, 1H), 6.48 (t, 1H), 6.15 (s, 1H), 6.03 (s, 1H), 3.34 (t, 2H), 3.26 (s, 3H), 3.14 (m, 1H), 1.83-1.66 (m, 7H), 1.21 (m, 2H), 1.06-0.95 (m, 8H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 167.5, 147.0, 141.6, 140.2, 134.4, 132.6, 131.5, 131.3, 129.8, 128.4, 127.9, 126.9, 125.9, 124.8, 124.3, 117.0, 110.2, 53.4, 46.4, 38.0, 30.9, 26.6, 26.3, 25.8, 22.6.

TM-1256- 6-[丙基-(2,3,4-三羟基-5-异丙基-苯磺酰基)-氨基]-萘-2-甲酸(3-苯基-丙基)-酰胺

^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.37 (b, 1H), 8.10 (s, 1H), 7.84 (d, 1H), 7.74 (m, 2H), 7.59 (s, 1H), 7.35-7.21 (m, 6H), 6.72 (s, 1H), 6.19 (t, 1H), 5.85 (b, 2H), 3.61-3.54 (m, 4H), 3.19 (m, 1H), 2.03 (m, 2H), 1.46 (m, 2H), 1.09 (d, 6H), 0.92 (t, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 167.3, 146.8, 141.5, 141.4, 137.6, 134.5, 132.6, 131.8, 131.3, 129.9, 128.6, 128.4, 128.0, 127.6, 127.1, 126.9, 126.1, 124.3, 116.8, 112.3, 52.1, 40.1, 33.6, 31.0, 26.7, 22.3, 21.4, 11.0.

TM-1257-2,3,4-三羟基-N-(4-羟基-萘-2-基)-5-异丙基-苯磺酰胺

^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.69 (s, 1H), 8.16 (d, 1H), 7.45-7.37 (m, 3H), 7.09 (m, 1H), 6.81 (s, 2H), 6.26 (s, 1H), 6.12 (s, 1H), 5.69 (s, 1H), 2.97 (m, 1H), 0.92 (d, 6H).

TM-1258- 6-[甲基-(2,3,4-三羟基-5-异丙基-苯磺酰基)-氨基]-萘-2-甲酸甲基-苯乙基-酰胺

^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.34 (s, 1H), 7.76-7.69 (m, 1.4H), 7.62 (d, 1H), 7.48 (d, 1H), 7.40-7.27 (m, 4H), 7.22 (m, 2H), 7.13 (d, 0.6H), 6.92 (s, 1H), 6.72 (s, 1H), 6.51 (s, 1H), 6.44 (s, 1H), 3.80 (t, 1H), 3.51 (t, 1H), 3.21 (s, 3H), 3.19 (s, 1.4H), 3.09 (m, 1H), 3.04 (m, 1H), 2.88-2.81 (m, 2.6H), 0.95 (d, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 172.1, 147.3, 141.8, 139.6, 138.6, 137.5, 134.0, 133.8, 133.2, 133.0, 131.4, 129.1, 128.8, 128.6, 128.5, 128.0, 127.5, 126.7, 126.5, 126.3, 125.8, 124.7, 124.4, 116.9, 110.1, 52.8, 49.5, 38.3, 37.9, 34.3, 33.2, 33.0, 26.4, 22.1, 22.0.

TM-1259- 6-[甲基-(2,3,4-三羟基-5-异丙基-苯磺酰基)-氨基]-萘-2-甲酸苄基-苯乙基-酰胺

^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.37 (d, 1H), 7.82 (s, 0.5H), 7.69 (d, 2H), 7.50-7.20 (m, 11.5H), 7.10 (s, 1H), 6.85 (s, 1H), 6.54 (s, 1H), 6.14 (s, 1H), 6.09 (s, 1H), 4.89 (s, 1H), 4.33 (s, 1H), 3.73 (m, 1H), 3.42 (m, 1H), 3.23 (s, 3H), 3.11-3.02 (m, 2H), 2.76 (m, 1H), 0.96 (d, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 172.1, 147.0, 141.6, 139.6, 138.9, 137.6, 137.0, 136.4, 134.2, 133.2, 131.5, 131.3, 129.2, 128.8, 128.6, 128.2, 127.7, 126.8, 126.6, 126.5, 126.1, 125.8, 124.9, 124.6, 124.5, 117.0, 110.2, 53.4, 49.6, 47.5, 46.8, 38.0, 34.4, 33.4, 26.5, 22.1.

TM-1260- 6-[甲基-(2,3,4-三羟基-5-异丙基-苯磺酰基)-氨基]-萘-2-甲酸异丁基-酰胺

^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.35 (s, 1H), 8.22 (s, 1H), 7.78 (m, 3H), 7.54 (d, 1H), 7.33 (dd, 1H), 6.44 (t, 1H), 6.11 (s, 1H), 5.95 (s, 1H), 3.33 (t, 2H), 3.26 (s, 3H), 3.13 (m, 1H), 1.95 (m, 1H), 1.01 (d, 6H), 1.00 (d, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 167.5, 147.0, 141.5, 140.2, 134.4, 132.7, 131.5, 131.3, 129.8, 128.4, 127.9, 126.9, 125.9, 124.8, 124.3, 117.0, 110.3, 47.5, 38.0, 28.6, 26.6, 22.2, 20.2.

TM-1261- 6-[丙基-(2,3,4-三羟基-5-异丙基-苯磺酰基)-氨基]-萘-2-甲酸甲基-苯乙基-酰胺

^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.41 (s, 1H), 7.76 (m, 1H), 7.66 (m, 1H), 7.56 (s, 1H), 7.32-7.20 (m, 7H), 6.94 (s, 1H), 6.71 (s, 1H), 6.13 (s, 1H), 6.04 (s, 1H), 3.83 (m, 1H), 3.57 (m, 3H), 3.16 (m, 3H), 3.04 (m, 1H), 2.89 (m, 2H), 1.44 (m, 2H), 1.08 (d, 6H), 0.91 (t, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 146.7, 141.4, 131.3, 129.4, 128.9, 128.7, 127.8, 127.7, 126.9, 116.7, 112.3, 52.1, 26.6, 22.3, 21.4, 11.0; ^{1}H NMR ($CO(CD_3)_2$, 300 MHz) δ 8.45 (s, 1H), 8.30 (s, 1H), 8.26 (s, 1H), 7.91 (m, 2H), 7.74 (s, 1H), 7.51 (s, 1H), 7.35-7.23 (m, 5H), 7.04 (s, 1H), 6.68 (s, 1H), 3.79 (m, 1H), 3.70 (m, 2H), 3.57 (m, 1H), 3.20 (m, 2H), 2.99 (m, 4H), 1.45 (m, 2H), 1.06 (d, 6H), 0.91 (t, 3H).

TM-1262- N-丁基-2,3,4-三羟基-5-异丙基-N-萘-2-基-苯磺酰胺

^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.47 (s, 1H), 7.83-7.74 (m, 3H), 7.57 (s, 1H), 7.50 (m, 2H), 7.16 (dd, 1H), 6.76 (s, 1H), 5.91 (b, 1H), 5.53 (b, 1H), 3.61 (t, 2H), 3.19 (m, 1H), 1.38-1.32 (m, 4H), 1.10 (d, 6H), 0.85 (t, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 146.4, 141.1, 135.9, 133.2, 132.7, 131.1, 129.0, 128.0, 127.9, 127.7, 126.8, 126.6, 126.2, 116.9, 112.5, 50.2, 30.0, 26.7, 22.3, 19.6, 13.5.

TM-1263- 6-[丙基-(2,3,4-三羟基-5-异丙基-苯磺酰基)-氨基]-萘-2-甲酸苯乙基-丙基-酰胺

^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.46 (s, 1H), 7.77-7.69 (m, 3H), 7.57 (s, 1H), 7.46-7.43 (m, 1H), 7.34 (m, 2H), 7.22 (m, 4H), 6.91 (s, 1H), 6.72 (s, 1H), 5.91 (s, 1H), 5.55 (d, 1H), 3.77 (m, 1H), 3.58 (m, 3H), 3.20 (m, 1H), 3.18 (m, 1H), 3.16 (m, 2H), 3.03 (m, 1H), 1.75 (m, 1H), 1.48 (m, 3H), 1.09 (d, 7.4H), 0.92 (t, 3H), 0.71 (m, 1.6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.7, 146.8, 141.5, 139.0, 137.7, 137.0, 135.0, 133.2, 131.9, 131.4, 129.4, 128.9, 128.6, 128.3, 127.8, 127.7, 127.1, 126.7, 126.5, 125.9, 125.6, 124.7, 124.5, 116.8, 112.3, 52.1, 51.4, 50.5, 46.8, 46.4, 34.9, 33.7, 26.6, 22.3, 21.4, 11.0.

TM-1264- 6-[丙基-(2,3,4-三羟基-5-异丙基-苯磺酰基)-氨基]-萘-2-甲酸(2-联苯-4-基-乙基)-酰胺

^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.45 (s, 1H), 8.22 (s, 1H), 7.85 (d, 1H), 7.78 (s, 2H), 7.61-7.57 (m, 5H), 7.45 (t, 2H), 7.35-7.33 (m, 3H), 7.22 (dd, 1H), 6.72 (s, 1H), 6.32 (t, 1H), 5.85 (s, 1H), 5.41 (s, 1H), 3.82 (q, 2H), 3.58 (t, 2H), 3.18 (m, 1H), 3.03 (t, 2H), 1.45 (m, 2H), 1.09 (d, 6H), 0.91 (t, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 167.2, 147.5, 146.4, 141.1, 140.7, 139.6, 137.9, 137.7, 134.6, 132.7, 131.9, 131.1, 130.0, 129.3, 128.8, 128.6, 128.0, 127.6, 127.5, 127.3, 127.2, 127.0, 127.0, 124.2, 116.8, 112.3, 52.1, 41.3, 35.3, 26.7, 22.3, 21.4, 11.0.

TM-1265- 6-[丙基-(2,3,4-三羟基-5-异丙基-苯磺酰基)-氨基]-萘-2-甲酸甲基-(3-苯基-丙基)-酰胺

^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.44 (d, 1H), 7.82 (s, 1H), 7.76 (m, 2H), 7.59 (s, 1H), 7.46 (t, 1H), 7.30 (m, 2H), 7.20 (dd, 1H), 7.10 (m, 2H), 6.99 (m, 1H), 6.74 (s, 1H), 5.96 (s, 1H), 5.69 (s, 1H), 3.64 (m, 1H), 3.58 (t, 2H), 3.31 (t, 1H), 3.18 (m, 1H), 3.13 (m, 2H), 2.96 (m, 1H), 2.75 (m, 1H), 2.44 (m, 1H), 2.05 (m, 1H), 1.90 (m, 1H), 1.46 (m, 2H), 1.10 (d, 6H), 0.93 (t, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 146.7, 141.4, 140.4, 137.0, 134.6, 133.3, 131.9, 131.3, 129.4, 128.4, 128.0, 127.8, 127.0, 126.0, 116.7, 112.3, 52.1, 47.5, 37.6, 28.5, 26.6, 22.3, 21.3, 11.0.

TM-1266- 6-(2,3,4-三羟基-5-异丙基-苯磺酰基氨基)-萘-2-甲酸苯乙基-丙基-酰胺

^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.45 (b, 1H), 7.55 (s, 1H), 7.33-7.18 (m, 9H), 7.01 (m, 1H), 6.96 (s, 1H), 6.85 (m, 1H), 6.60 (b, 1H), 6.11 (b, 1H), 3.78 (m, 1H), 3.60 (m, 1H), 3.48 (m, 1H), 3.05 (m, 3H), 2.77 (m, 1H), 1.79 (m, 1H), 1.49 (m, 1H), 0.98 (d, 6H), 0.68 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 173.1, 147.6, 141.3, 138.8, 137.5, 135.6, 133.7, 132.5, 129.9, 128.8, 126.8, 124.2, 122.1, 117.8, 114.3, 51.8, 47.2, 34.8, 33.8, 26.7, 22.3, 20.8.

TM-1267- 6-(2,3,4-三羟基-5-异丙基-苯磺酰基氨基)-萘-2-甲酸苄基-苯乙基-酰胺

^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.43 (s, 1H), 7.72 (s, 1H), 7.62 (s, 1H), 7.39-6.94 (m, 16H), 6.80 (s, 1H), 6.45 (s, 1H), 6.10 (s, 1H), 4.88 (m, 1H), 4.30 (m, 1H), 3.73 (m, 1H), 3.41 (m, 1H), 3.00 (m, 2H), 2.74 (m, 1H), 0.95 (d, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 173.0, 147.4, 141.3, 138.5, 137.3, 136.3, 135.7, 135.5, 133.7, 133.5, 131.7, 131.4, 129.7, 129.4, 128.9, 128.6, 128.1, 127.8, 127.5, 126.9, 126.5, 126.2, 125.7, 124.0, 121.9, 117.6, 113.9, 53.7, 49.9, 47.9, 47.0, 34.3, 33.2, 26.5, 22.1.

TM-1269- 2-(2,3,4-三羟基-5-异丙基-苯甲酰基)-1,2,3,4-四氢-异喹啉-7-磺酸苯乙基-酰胺

^{1}H NMR ($CDCl_3$, 300 MHz) δ 10.2 (b, 1H), 7.63 (dd, 1H), 7.52 (s, 1H), 7.31-7.19 (m, 4H), 7.07 (m, 2H), 6.78 (s, 1H), 5.90 (b, 2H), 4.86 (s, 2H), 4.56 (t, 1H), 3.92 (t, 2H), 3.25 (m, 1H), 3.22 (m, 2H), 3.06 (t, 2H), 2.78 (t, 2H), 1.24 (d, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 172.2, 145.5, 145.1, 139.6, 138.2, 137.7, 134.2, 131.9, 129.7, 128.8, 128.7, 126.8, 126.4, 125.5, 125.2, 116.8, 109.1, 47.8, 44.3, 35.9, 31.7, 29.1, 26.8, 22.7.

TM-1271- 乙酸 2,3-二乙酰氧基-6-(3,4-二氢-1H-异喹啉-2-磺酰基)-4-{7-[2-(4-硝基-苯基)-乙基氨磺酰基]-3,4-二氢-1H-异喹啉-2-羰基}-苯基酯

^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.08 (t, 2H), 7.87 (s, 0.5H), 7.78 (s, 0.5H), 7.69-7.62 (m, 1.5H), 7.54 (s, 0.5H), 7.31-7.24 (m, 4H), 7.20-7.14 (m, 3H), 7.12 (m, 1H), 7.04 (m, 1H), 4.93-4.85 (m, 2H), 4.63 (s, 1H), 4.38 (m, 2H), 3.68 (m, 2H), 3.51 (m, 2H), 3.25 (m, 2H), 3.00 (m, 2H), 2.92 (m, 4H), 2.40 (s, 3H), 2.30, 2.38 (s, 3H), 2.23, 2.09 (s, 3H).

TM-1276- 2-[2,3,4-三羟基-5-(3-苯基-丙基氨磺酰基)-苯甲酰基]-1,2,3,4-四氢-异喹啉-7-磺酸[2-(4-硝基-苯基)-乙基]-酰胺

^{1}H NMR ($CO(CD_3)_2$, 300 MHz) δ 9.00 (b, 3OH), 8.08 (m, 2H), 7.61 (m, 2H), 7.38 (m, 4H), 7.12 (m, 4H), 6.61 (m, 1H), 4.90 (s, 2H), 4.38 (s, 2H), 3.86 (m, 2H), 3.52 (m, 2H), 3.26 (m, 2H), 3.03 (m, 2H), 2.94 (m, 4H); ^{13}C NMR ($CO(CD_3)_2$, 75 MHz) δ 169.1, 150.5, 147.8, 147.3, 146.9, 140.3, 139.6, 135.0, 134.5, 134.0, 132.6, 130.8, 130.4, 129.5, 127.4, 127.1, 127.0, 125.8, 125.7, 124.0, 121.3, 114.0, 113.9, 60.5, 48.0, 44.5, 44.0, 36.2.

TM-1277- 乙酸 2,3-二乙酰氧基-6-{7-[2-(4-硝基-苯基)-乙基氨磺酰基]-3,4-二氢-1H-异喹啉-2-羰基}-4-(3-苯基-丙基氨磺酰基)-苯基酯

^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.08 (m, 2H), 7.87 (s, 0.6H), 7.79 (s, 0.5H), 7.69-7.62 (m, 1.8H), 7.54 (s, 0.5H), 7.31-7.24 (m, 3H), 7.20-7.09 (m, 3.4H), 7.05-7.01 (m, 1.2H), 4.93-4.74 (m, 3H), 4.63 (s, 1H), 4.38 (s, 2H), 3.68 (m, 2H), 3.51 (m, 2H), 3.25 (m, 2H), 3.00-2.87 (m, 4H), 2.40 (s, 3H), 2.30 (s, 1.5H), 2.28 (s, 1.5H), 2.23 (s, 2H), 2.09 (s, 1H).

TM-1278- 2,3,4-三羟基-5-[甲基-(3-苯基-丙基)-氨磺酰基]-苯甲酸甲酯

^{1}H NMR ($CDCl_3$, 300 MHz) δ 11.44 (b, 1H), 7.86 (s, 1H), 7.23-7.21 (m, 2H), 7.16 (m, 1H), 7.07 (d, 2H), 4.12 (s, 3H), 2.94 (t, 2H), 2.60 (t, 2H), 1.79 (m, 2H).

TM-1282- 2-(5-苄基氨磺酰基-2,3,4-三羟基-苯甲酰基)-1,2,3,4-四氢-异喹啉-7-磺酸苯乙基-酰胺

^{1}H NMR ($CO(CD_3)_2$, 300 MHz) δ 10.29 (b, 1H), 9.16 (s, 1H), 8.39 (s, 1H), 7.65 (m, 2H), 7.41 (m, 2H), 7.31 (m, 3H), 7.21-7.13 (m, 7H), 6.91 (t, 1H), 6.48 (t, 1H), 4.89 (s, 2H), 4.18 (d, 2H), 3.88 (t, 2H), 3.15 (q, 2H), 3.07 (t, 2H), 2.77 (t, 2H); ^{13}C NMR ($CO(CD_3)_2$, 75 MHz) δ 169.8, 151.0, 146.6, 140.4, 139.9, 139.6, 138.3, 135.3, 134.4, 130.4, 129.6, 129.2, 129.1, 128.6, 128.1, 127.1, 126.0, 125.8, 120.7, 117.9, 112.8, 47.7, 45.4, 45.3.

实施例 2

荧光偏振结合测定

体外 Bcl-2 结合测定

将使用 6-羧基荧光素琥珀酰亚胺基酯(FAM)在 N-末端上标记的 21-残基 Bid BH3 肽(QEDIIRNIARHLAQVGDSMDR)(SEQ ID NO:1)用作荧光标记(Flu-Bid-21)。已经证实该荧光肽具有 K_d 为 15.74 nM 的高结合亲和力。在本测定法中使用的 Bcl-2 为重组的 His-融合可溶性蛋白。

将溶于 DMSO 的测试化合物和在测定缓冲液(100 mM 磷酸钾, pH 7.5; 100 μg/ml 牛血清丙种球蛋白; 0.02%叠氮化纳, 购自 Invitrogen Corporation, Life Technologies)中 Bcl-2 蛋白质(0.120 μM)与 Flu-Bid-21 肽(0.010 μM)预温育的 5 μl 样品加入到 Dynex 96-孔黑色圆底平板(Fisher Scientific)中, 以便产生 125 μl 的终体积。对每次测定而言,每个测定平板上均包括含有 Bcl-2 和 Flu-Bid-21 肽(相当于 0%抑制)的结合肽和仅含 Flu-Bid-21 (相当于 100%抑制)的游离肽对照品。在结合达到平衡时的 4 小时温育后, 使用 Ultra 平板读数器(Tecan U.S. Inc., Research Triangle Park, NC)在 485 nm 的激发波长和 530 nm 的发射波长处测定以毫极化(milipolarization)单位计的极化值(mP)。使用非线性最小二乘法分析和用 GraphPad Prism®软件拟合的曲线从曲线图中确定 IC_{50}, 即取代 50%结合肽时的抑制剂浓度 。将未标记的 Bid 肽用作阳性对照。使用我们研发的 FP 测定等式计算 K_i 值(Nikolovska-Coleska 等, Anal. Biochem., 2004, 印刷中)。计算 K_i 值的程序可以以免费的形式从互联网上获得: http://sw16.im.med.umich.edu/software/calc_ki/。

体外 BcI-XL 结合测定

为了测定与 Bcl-xL 蛋白质的结合亲和力, 使用不含 C-末端疏水尾的人 Bcl-xL 重组 His-标记的蛋白质并用 6-羧基荧光素琥珀酰亚胺基酯(FAM)标记的 Bak-16mer BH3 肽。这种肽已经表现出 K_d= 9.79 nM

的结合亲和力。按照与对 Bcl-2 蛋白质所述相同的方式，使用与 60 nM Bcl-xL 和 5 nM Flu-Bak 肽预温育的复合物在含有 50 mM Tris-Bis, pH 7.4; 0.01%牛血清丙种球蛋白的测定缓冲液中进行竞争性结合测定。

使用荧光偏振测定法测试实施例 1 中所述化合物与 Bcl-2 的结合亲和力。下列化合物具有 1.0 μM 或 1.0 μM 以下的对 Bcl-2 的 IC_{50}值: TM-1216, 197, 1213, 1203, 1207, 1208, 1209, 1210, 1211, 1205, 1206, 190, 192, 121 和 122; 和 TW-37, 38, 45, 46, 47, 60, 61, 159, 164, 165, 166, 169,和 172。下列化合物具有高于 1.0 μM 的对 Bcl-2 的 IC_{50}值: TM-174, 175, 176, 178, 1214, 1215, 194, 195, 196, 198, 193, 1212, 199, 1200, 1202, 1217, 1201, 105, 106, 107, 108, 129 和 142; 和 TW-1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 24, 25, 27, 28, 21, 16, 17, 20, 22, 23, 34, 35, 39, 41, 42, 55, 52, 53, 56, 160, 161, 162, 163, 167, 170, 173 和 174。下列化合物具有 1.0 μM 或 1.0 μM 以下的对 Bcl-xL 的 IC_{50}值: TM-171。下列化合物具有高于 1.0 μM 的对 Bcl-xL 的 IC_{50}值: TM-174, 175, 176, 178, 1214, 1215, 194, 1216, 195, 198, 193, 190, 192, 1201, 105, 106, 107, 129, 142, 159, 1210, 199, 1200, 1202, 1217, 1205, 1206, 162, 163, 133, 165, 167, 168, 169, 183, 180, 196, 197, 1213, 1203, 108, 121, 122, 140, 141, 157, 1207, 1208, 1209, 1211, 1212 和 179。

实施例 3

通过 NMR 证实 TW-37 与 Bcl-2 的结合

使用 ^{15}N 异核单量子结合光谱(HSQC) NMR 法测定 TW-3 与 Bcl-2 结合。

使用 ^{15}N 均匀标记用于 NMR 研究的蛋白质样品用于筛选，并且使用 ^{15}N 和 ^{13}C 均匀双重标记以便按照 M. Jansson 等 J. Biomol. NMR, 7:131-141 (1996),和 M. L. Cai 等 J. Biomol. NMR, 11:97-102 (1998) 所述的方法进行结构表征。

由于在脉冲场梯度(PFG)中和 pH 7.2 下进行 NMR 实验，所以将具有水回转的HSQC用于使信号强度最大化(S. Grzesiek和A. Bax, J. Am. Chem. Soc, 115:12593-12594 (1993)；和 G.S. Sheppard 等 Abstracts of Papers of the Amer. Chem. Soc, 213:81 (1997))，并且将来自水信号的破坏减小到最低限度。在添加抑制剂浓溶液前(游离 Bc1-2)和之后记录 Bc1-2 的 HSQC 光谱。将两种光谱进行比较以便鉴定通过添加抑制剂诱导的化学位移。使用 nmrPipe、pipp 和 nmrDraw 软件进行数据处理(参见 D.S. Garrett 等 J. Magn. Reson. Ser., B 95:214-220 (1991)；和 F. Delaglio 等 J. Biomol. NMR, 6:277-293 (1995))。将移位的峰与指定的表进行交叉参考，以便揭示出受存在的棉酚化合物影响的残基。因结合 TW-37 而受影响的残基如附图 1 中所示，该附图表示 TW-37 与 Bc1-2 中的 BH3 结合位点结合。

实施例 4

TW-37 对人癌细胞中细胞生长的抑制

为了测试本发明化合物对人癌细胞中细胞生长抑制的作用，将 TW-37 给予 5 种不同的癌细胞系。将 LnCap、PC-3 和 DU145c 前列腺癌细胞系和 2LMP 和 MCF-10A 乳腺癌细胞系各自接种在含有增加浓度的 TW-37 的 96-孔平板中。然后将细胞在 37℃与 5% CO_2 下孵育 5 天，随后使用 MTT 检测细胞存活率。将未处理的细胞用作 100%生长。TW-37 抑制各细胞系的细胞生长，其中 IC_{50} 在约 1-5 μM 的范围(附图 2)。这些数据表明 TW-37 能够抑制人癌细胞中的细胞生长。

测试本发明的其它化合物对 PC-3 细胞的细胞生长的作用。如上所述使 PC-3 细胞生长并且加入增加浓度的化合物。然后使用 WST 检测细胞存活率(附图 3)。结果表明所有测试化合物均具有抑制前列腺癌细胞生长的能力，其中大部分化合物具有约 0.5-10 μM 的 IC_{50}。

还测试了本发明的化合物对 MDA-MB-231(2LMP)细胞的细胞生长的作用。如上所述使 PC-3 细胞生长并且加入增加浓度的化合物。然后使用 WST 检测细胞存活率。结果表明所有测试化合物均具有抑制前列

腺癌细胞生长的能力，其中大部分化合物具有约 0.1-20 μM 的 IC_{50}。在此范围内的那些化合物为：TM-103, 104, 105, 106, 107, 108, 109, 110, 111, 121, 122, 125, 126, 127, 128, 129, 130, 132, 133,134, 135, 136, 137, 140, 141, 142, 144, 145, 146, 147, 148, 149, 150, 152, 153, 154, 155, 156, 165, 166, 167, 168, 169, 170 和 171，高于 20 μM 的那些化合物为：TM-124 和 143。

实施例 5

TW-37 诱导前列腺癌 PC-3 细胞中的细胞凋亡

用 TW-37 将 6-孔平板中的 PC-3 细胞处理 45 小时并且通过膜联蛋白 V-FITC 染色和流式细胞计量术分析细胞凋亡。结果表明增加浓度的 TW-37 诱导 PC-3 细胞中的细胞凋亡水平增加，其中 2.5 μM TW-37 产生约 35%的细胞凋亡性细胞(附图 4)。这些结果证实 TW-37 能够诱导癌细胞中的细胞凋亡。

实施例 6

TW-37 活化前列腺癌 PC-3 细胞中的天冬氨酸特异性半胱氨酸蛋白酶（caspase）-3

为了测试前列腺癌细胞中细胞凋亡的诱导是否由天冬氨酸特异性半胱氨酸蛋白酶途径介导，用 TW-37 将 PC-3 细胞和 PrEC(人正常前列腺上皮细胞)处理 48 小时，然后用 CaspGlow 红色活性天冬氨酸特异性半胱氨酸蛋白酶-3 染色试剂盒(Bio Vision, Inc.)染色，其中罗丹宁-DEVD-FMK (SEQ ID NO: 1)与细胞凋亡性细胞中的活性天冬氨酸特异性半胱氨酸蛋白酶-3 共价结合。在并联的试管中加入特异性天冬氨酸特异性半胱氨酸蛋白酶-3 抑制剂 Z-DEVD-FMK (1 μg/ml)以便抑制天冬氨酸特异性半胱氨酸蛋白酶-3 活化。在红色通道内通过流式细胞计量术分析细胞并且将结果表示为具有活性天冬氨酸特异性半胱氨酸蛋白酶-3 的细胞百分比(附图 5)。结果证实用 TW-37 处理 PC-3 细胞导致细胞内的天冬氨酸特异性半胱氨酸蛋白酶-3 活化，其中 5 μM TW-37 导

致约 60%的具有活化的天冬氨酸特异性半胱氨酸蛋白酶-3 的细胞(附图 5)。添加天冬氨酸特异性半胱氨酸蛋白酶抑制剂 Z-DEVD-FMK 阻断了天冬氨酸特异性半胱氨酸蛋白酶-3 的活化。TW-37 对正常前列腺上皮细胞无作用。这些结果表明人癌细胞中天冬氨酸特异性半胱氨酸蛋白酶-3 诱导的细胞凋亡由天冬氨酸特异性半胱氨酸蛋白酶途径介导，并且该作用对癌细胞具有特异性。

实施例 7

TW-37 促进乳腺癌 MDA-231 细胞中顺铂-诱导的细胞凋亡

使用 TW-37 和顺铂(CDDP)的组合测试具有式 I 的化合物增加化疗药诱导的细胞凋亡的能力。CDDP 为 DNA 损伤剂并且可以有效诱导 MDA-231 乳腺癌细胞中的细胞凋亡，且还为临床使用的癌症化疗药。

用单独的 CDDP 和 TW-37 或其组合将 MDA-231 细胞处理 42 小时并且分析细胞存活率。接触 CDDP 导致细胞存活率下降，其中 IC_{50} 约为 0.75 μM (附图 6)。添加 0.2 μM 或 0.3 μM TW-37 促进了 CDDP 诱导的细胞死亡，其中 0.3 μM TW-37 将 CDDP 的 IC_{50} 降低了约一半(附图 6)。结果证实 TW-37 可有效强化 CDDP 在 MDA-231 细胞中诱导细胞死亡的活性。

实施例 8

TW-37 对裸鼠异种移植物模型或前列腺癌中肿瘤生长的抑制

为了测试 TW-37 在体内控制肿瘤生长中的能力，使用裸鼠异种移植物模型。使用 i.v. q.d.x5，持续 3 周的 4-6 周龄雌性 Balb/c 小鼠测定 TW-37 的最大耐受剂量(MTD)。在该方案中将 TW-37 的 MTD 测定为 80 mg/kg。将 TAXOTERE (TXT)和顺铂(CDDP)用作阳性对照。就 PC-3 肿瘤模型而言，将 5 x 10^6 PC-3 细胞注入 NCr-nu 雄性裸鼠两侧胁腹。测试四分之一-MTD 和一半-MTD 剂量，即 20 和 40 mg/kg，i.v. q.d.x5，持续 3 周。当肿瘤生长至约 50-60 mm^3，将小鼠随机分成：(1) 对照组；(2) TW-37 治疗组(20 mg/kg，i.v. q.d.5 x 3 周)；(3) TW-37

治疗组(40 mg/kg, i.v. q.d.5 x 3周); (4) TXT组(7.5 mg/kg i.v. 每周1次，持续3周); (5) CDDP组(5 mg/kg i.v.)。将肿瘤尺寸每周测定2次，并且计算为：肿瘤体积= (A X B^2)/2，其中A和B分别为肿瘤长度和宽度(以mm计)。结果如附图7中所示。结果证实TW-37能够显著抑制体内的肿瘤生长，其中40 mg/ml TW-37与TAXOTERE同样有效。

TAXOTERE和顺铂在用于癌症治疗时均具有毒性副作用。为了比较TW-37与这些已知抗癌剂的毒性副作用，监测上述研究中使用的动物的体重以便评价作为毒性征兆的体重减轻。结果如附图8中所示。结果证实TAXOTERE在35天治疗过程中使体重轻度减轻，而顺铂在截至到3周治疗时使体重明显减轻，五周后几乎恢复到对照组的水平。TW-37在整个实验过程中对体重几乎没有影响，表明TW-37在使用过程中不可能具有显著的细胞毒性副作用。

实施例9

TW-37增强TAXOTERE对裸鼠异种移植物模型或前列腺癌中肿瘤生长的抑制

将前列腺癌PC-3异种移植物模型用于测试TW-37增强TAXOTERE在抑制肿瘤生长方面的活性的能力。当肿瘤生长至约50-60 mm^3，将小鼠随机分成：(1) 对照组(6只小鼠/12个肿瘤); (2) TW-37治疗组(40 mg/kg, i.v. q.d.5 x 3周); (3) TXT组(7.5 mg/kg i.v. 每周1次，持续3周); (4) 联合用药组：TW-37 + TXT (5只小鼠/10个肿瘤)。将肿瘤尺寸每周测定2次并且计算为：肿瘤体积= (A X B^2)/2，其中A和B分别为肿瘤长度和宽度(以mm计)。

结果如附图9中所示。与对照组相比，TW-37在40 mg/kg下显著抑制了肿瘤生长($p<0.001$, 双道ANOVA, n=10)。表8中概括了如所述计算的肿瘤生长抑制(T/C)和肿瘤生长延迟(T-C)值(Corbett, Transplantable syngeneic rodent tumors. Tumor Models in Cancer Research, ed. B. A. Teicher. 2002, Totowa: Humana Press. Pp.

41-71)（圆括号中的数字为剂量 mg/kg 体重）。就 40 mg/kg TW-37 而言，T/C 值为 34.5%；就 7.5 mg/kg TXT 而言，为 55.1%，并且就 11mg/kg TXT 而言，为 32.1%。因此，在 NCI 标准下，40 mg/kg TW-37 和 11 mg/kg TXT 在这种模型中具有显著性活性(T/C <42%)，而 7.5 mg/kg TXT 没有(T/C >42%)。11 mg/kg 接近 MTD 剂量并且 7.5 mg/kg 在该动物模型中为 TXT 的亚适剂量。更为有意义的是，TW-37 与亚适剂量的 TXT(7.5mg/kg)的联合用药导致 T/C = 19.6%。另外，这种联合治疗在某些动物中使得肿瘤完全消退，而在单一药物治疗过程中未观察到这一结果。因此，联合疗法的有效性比单独治疗更为显著($p<0.0001$，双道 ANOVA，n=10)。

表 5

	TW-37	TXT (7.5 mg/kg)	TXT (11 mg/kg)	TXT (7.5 mg/kg) + TW-37
T/C (%)	34.5	55.1	32.1	19.6
T-C（天）	37	30	32	-
完全的肿瘤消退	0/10	0/10	0/10	2/10

为了监测毒性，测定动物体重并且绘制在附图 10 中。正如可以观察到的，TW-37 治疗的小鼠在治疗过程中未表现出明显的体重减轻。TXT 治疗或与 TW-37 联合用药导致在治疗终止后可逆的体重减轻。联合疗法不会产生比单独 TXT 更为严重的毒性($p < 0.05$，双道 ANOVA)。

由于完整地描述了本发明，所以本领域技术人员可以理解可以在广泛和不影响本发明范围或其任何实施方案的条件、组成和其它参数等效范围内实施本发明。将本文引述的所有专利、专利申请和公开文献完整地引入本文作为参考。

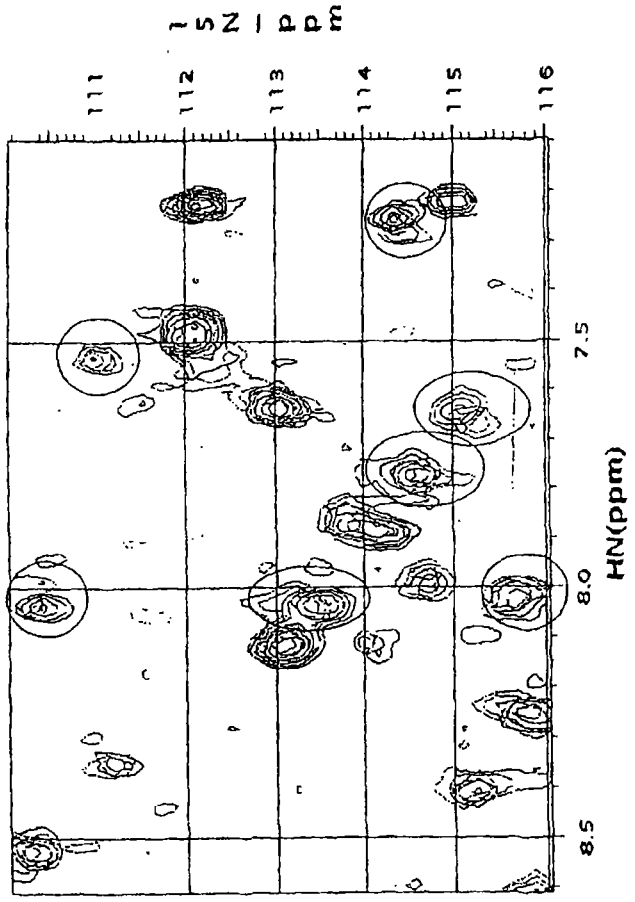


图1

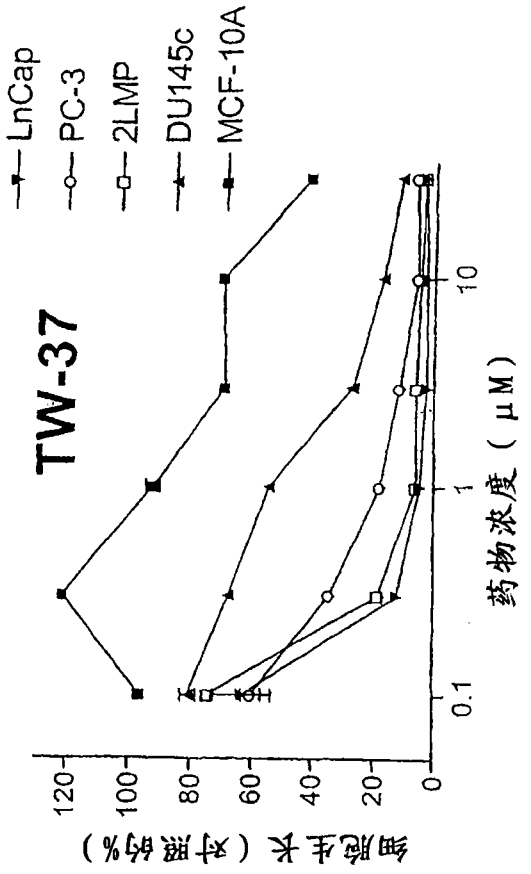

TW-37
LnCap
PC-3
2LMP
DU145c
MCF-10A
细胞生长（对照的%）
药物浓度（μM）
0
20
40
60
80
100
120
0.1
1
10

图2

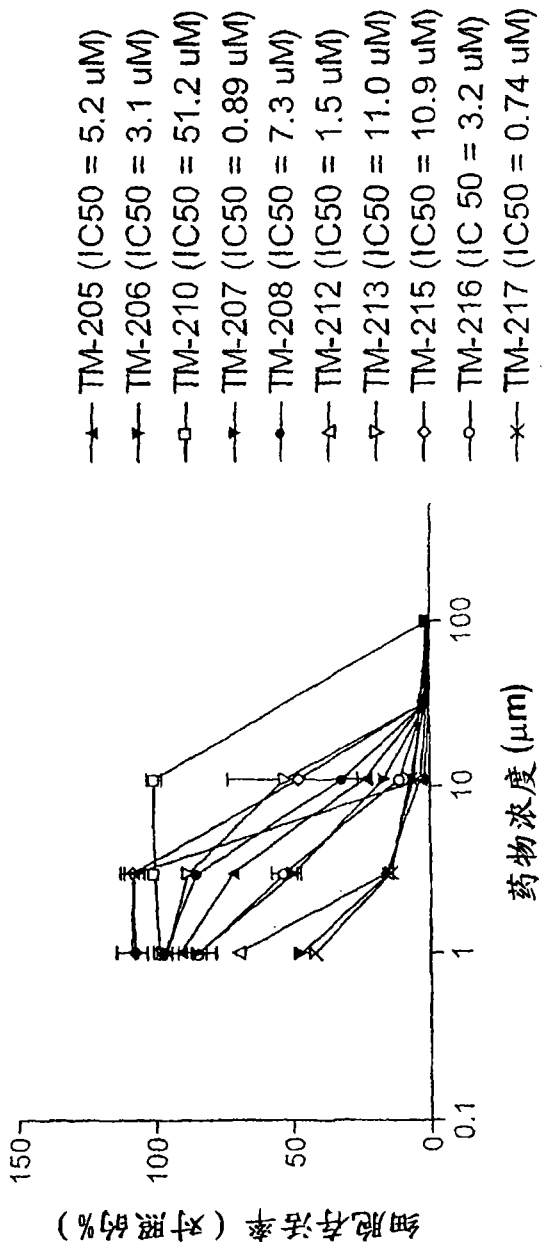

TM-205 (IC50 = 5.2 uM)
TM-206 (IC50 = 3.1 uM)
TM-210 (IC50 = 51.2 uM)
TM-207 (IC50 = 0.89 uM)
TM-208 (IC50 = 7.3 uM)
TM-212 (IC50 = 1.5 uM)
TM-213 (IC50 = 11.0 uM)
TM-215 (IC50 = 10.9 uM)
TM-216 (IC 50 = 3.2 uM)
TM-217 (IC50 = 0.74 uM)
细胞存活率（对照的%）
150
100
50
0
0.1
1
10
100
药物浓度 (μm)

图 3

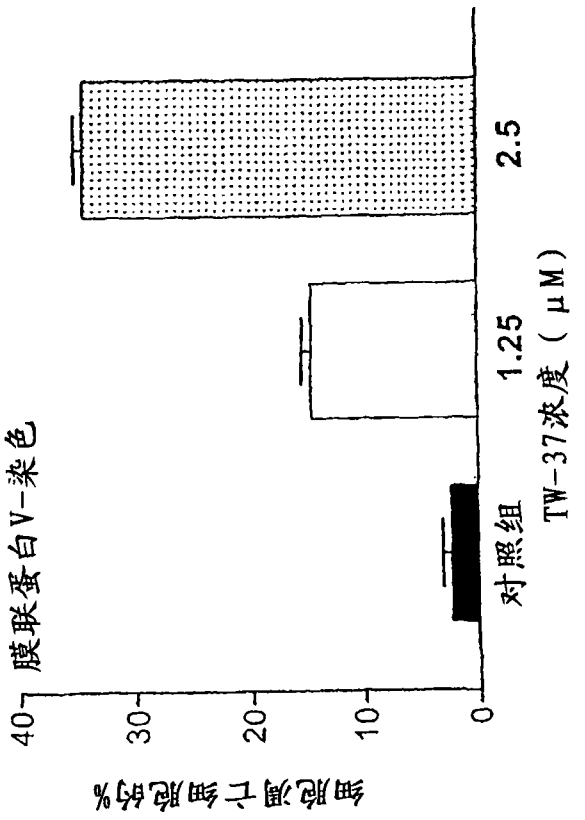


图4

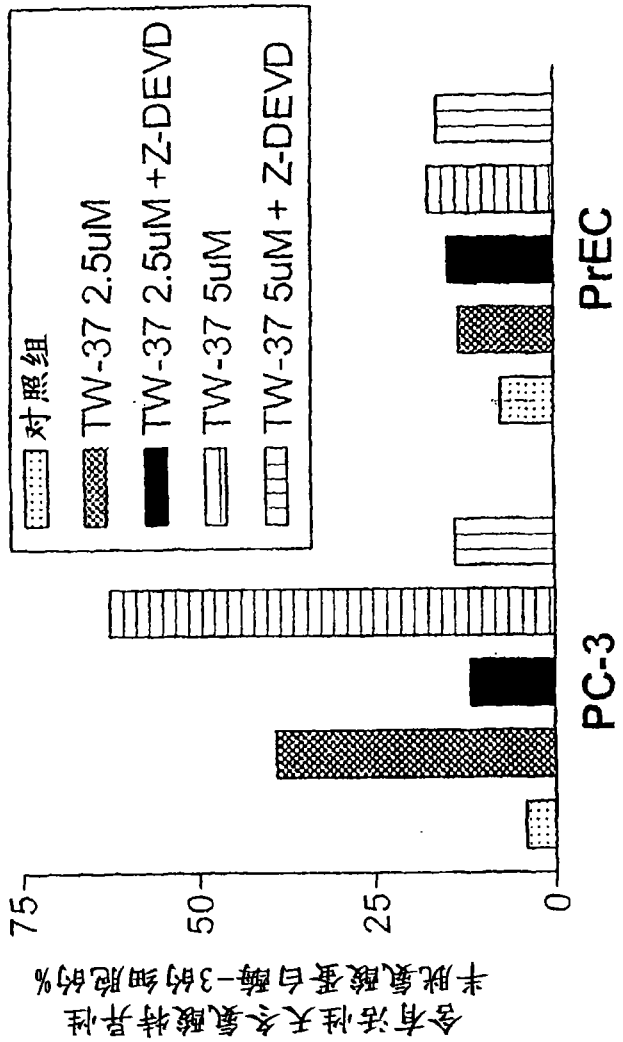

含有活性天冬氨酸特异性
半胱氨酸蛋白酶-3的细胞的%
75
50
25
0
PC-3
PrEC
对照组
TW-37 2.5uM
TW-37 2.5uM +Z-DEVD
TW-37 5uM
TW-37 5uM + Z-DEVD

图5

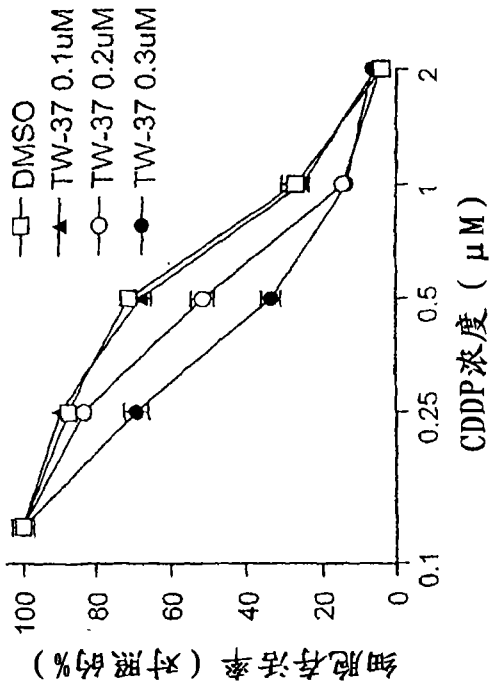

DMSO
TW-37 0.1uM
TW-37 0.2uM
TW-37 0.3uM
细胞存活率（对照的%）
100
80
60
40
20
0
0.1
0.25
0.5
1
2
CDDP浓度（μM）

图6

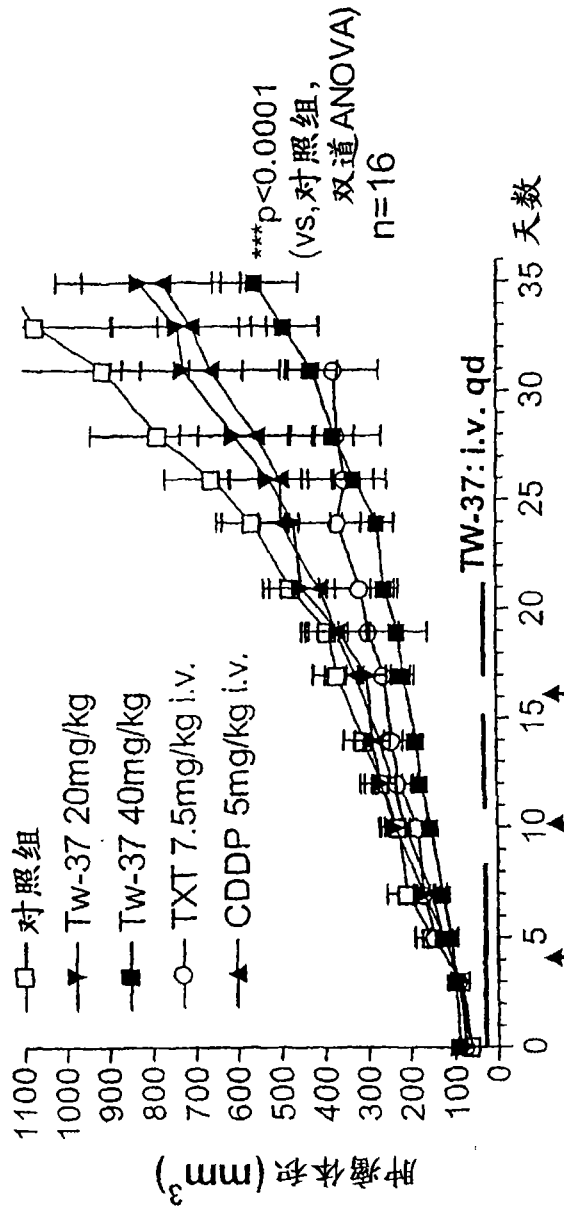

肿瘤体积 (mm^3)
1100
1000
900
800
700
600
500
400
300
200
100
0
5
10
15
20
25
30
35
天数
TXT
TXT
TXT
TXT
TW-37: i.v. qd
对照组
Tw-37 20mg/kg
Tw-37 40mg/kg
TXT 7.5mg/kg i.v.
CDDP 5mg/kg i.v.
***p<0.0001
(vs,对照组,
双道ANOVA)
n=16

图 7

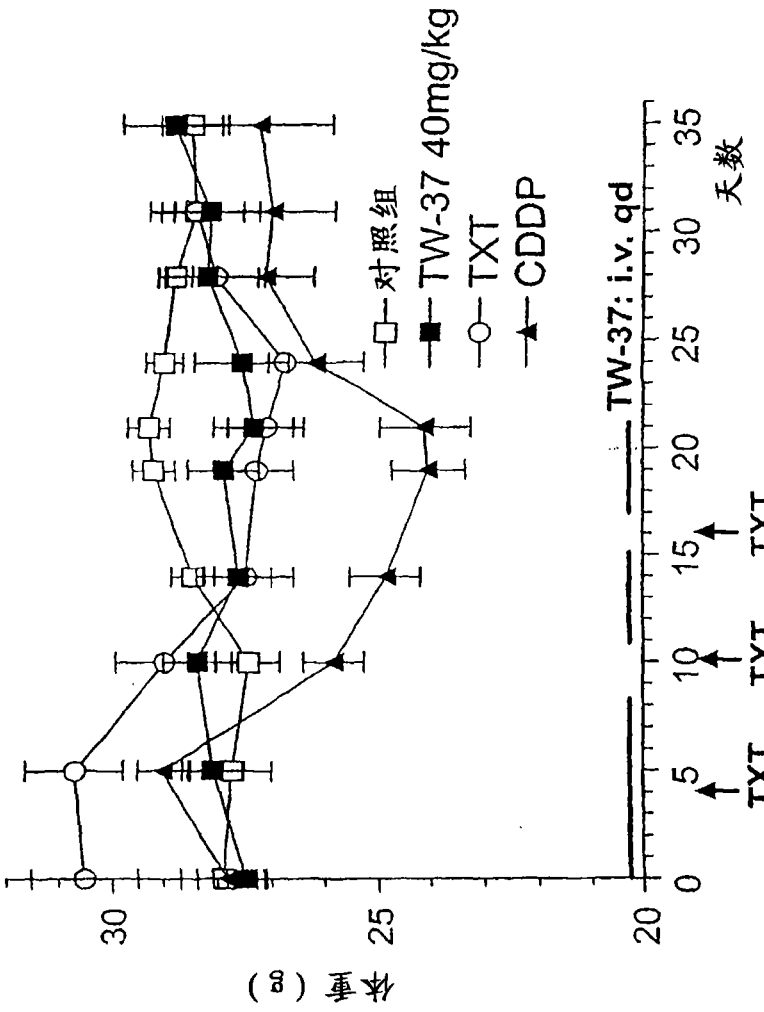

体重（g）
30
25
20
0
5
10
15
20
25
30
35
天数
TXT
TXT
TXT
TW-37: i.v. qd
对照组
TW-37 40mg/kg
TXT
CDDP

图8

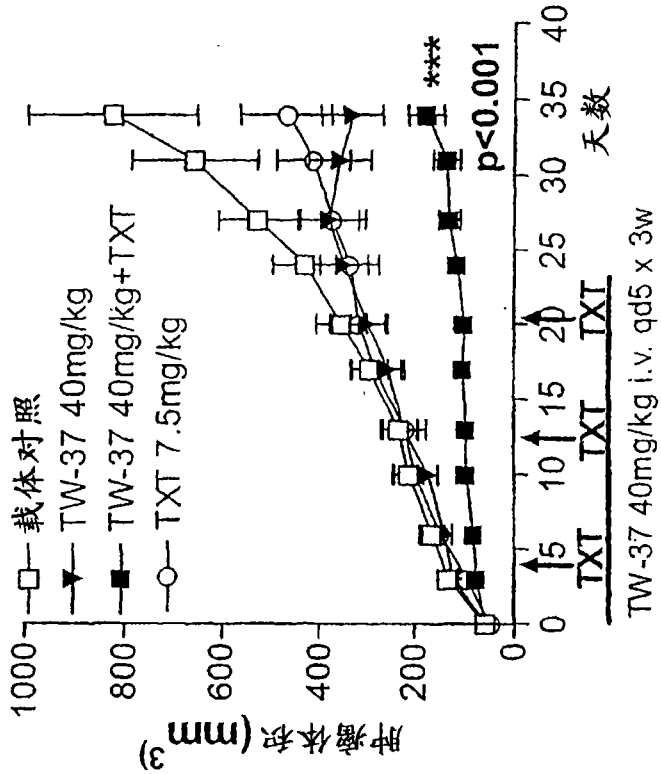

载体对照
TW-37 40mg/kg
TW-37 40mg/kg+TXT
TXT 7.5mg/kg
肿瘤体积 (mm3)
1000
800
600
400
200
0
***
p<0.001
0
5
10
15
20
25
30
35
40
天数
TXT
TXT
TXT
TW-37 40mg/kg i.v. qd5 x 3w

图9

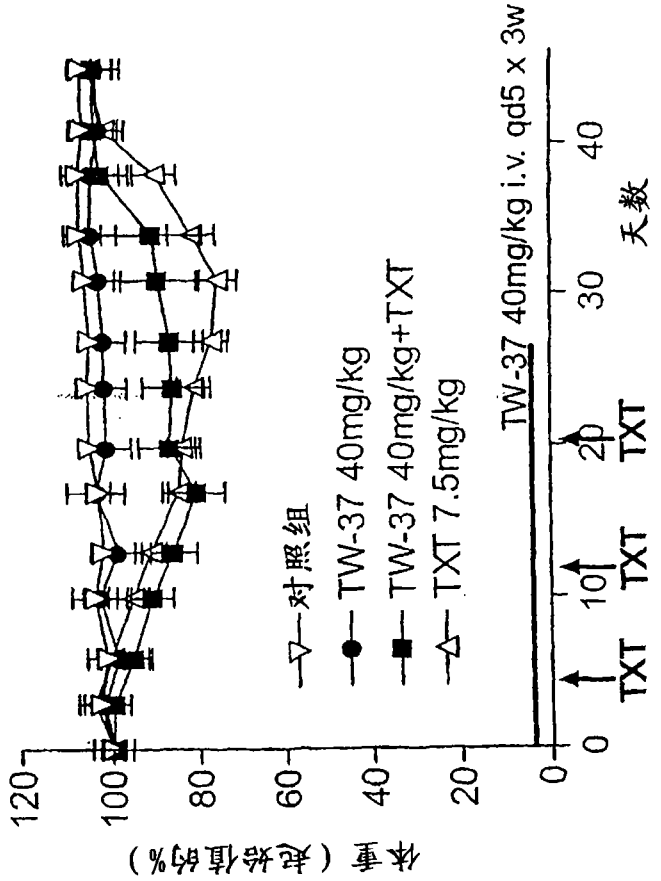

体重（起始值的%）
120
100
80
60
40
20
0
对照组
TW-37 40mg/kg
TW-37 40mg/kg+TXT
TXT 7.5mg/kg
TW-37 40mg/kg i.v. qd5 x 3w
0
10
20
30
40
天数
TXT
TXT
TXT

图10