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(73) 专利权人 盐野义制药株式会社

地址 日本大阪府

专利权人 株式会社医药分子设计研究所

(72) 发明人 板井昭子 武藤进 德山龙光

深泽弘志 大原孝文 加藤辉和

(74) 专利代理机构 中国专利代理(香港)有限公司

司 72001

代理人 邹锋 李连涛

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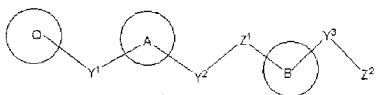
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(54) 发明名称

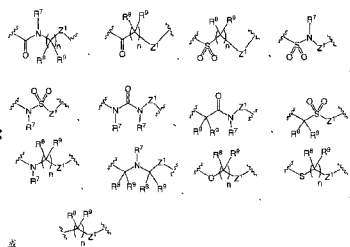
具有 PPAR 激动活性的衍生物

(57) 摘要

本发明涉及式 (I) 的化合物、其可药用盐或

溶剂化物,  其

中: 环 Q 为任选被取代的单环芳基、任选被取代的单环杂芳基、任选被取代的稠合芳基或任选被取代的稠合杂芳基, Y¹ 为键或 -NR⁶- 等, 环 A 为任选被取代的非芳香族杂环二基, 式 -Y²Z¹- 的基团为

下式的基团:  其中

R⁷ 各自独立地为氢、任选被取代的低级烷基等, R⁸ 和 R⁹ 各自独立地为氢或任选被取代的低级烷基, n 为 1-3 的整数, Z¹ 为键、-O-、-S- 或 -NR⁹-, 环 B 为任选被取代的芳香族碳环二基或任选被取代的芳香族杂环二基, Y³ 为键、任选地被 -O- 插入的任选被取代的低级亚烷基、任选被取代的低级亚烯基等, 和 Z² 为 COOR³ 等。

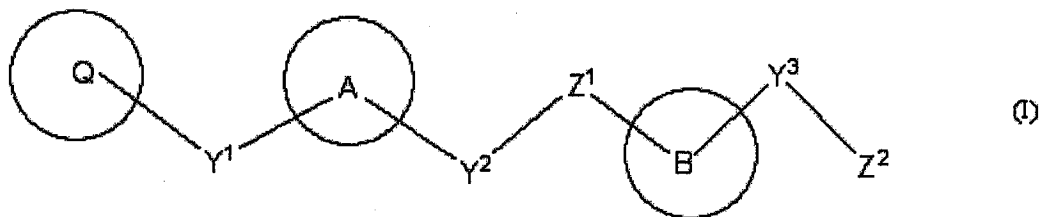
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(51) Int. Cl.

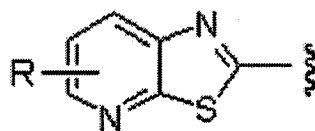
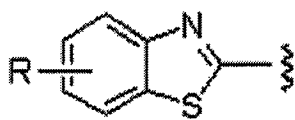
A61P 9/10 (2006.01)

1. 式 (I) 的化合物、或其可药用盐,

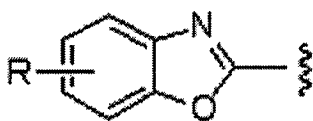


其中

环 Q 是下式的基团:



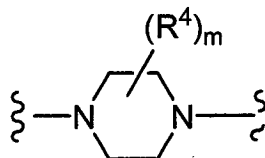
或



R 是任选被取代的 C1-C10 烷基, 取代基是卤素; 卤素; 或任选被取代的 C1-C10 烷氧基, 取代基是卤素;

Y^1 为键,

环 A 为下式的基团:

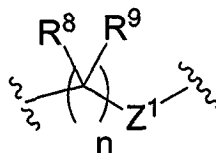


R^4 各自独立地为任选被取代的 C1-C10 烷基,

R^4 的所述 C1-C10 烷基的取代基选自卤素; 羟基; 任选被取代的 C1-C10 烷氧基, 取代基是苯基; C2-C10 炔基氧基; 任选被取代的氨基, 取代基是 C1-C10 烷基; 巯基; C1-C10 烷硫基; 酰基; 酰氧基; 亚氨基; 羧基; C1-C10 烷氧基羰基; 氨基甲酰基; 硫代氨基甲酰基; 任选被取代的氨基甲酰氧基, 取代基是 C1-C10 烷基; 硫代氨基甲酰氧基; 氨基磺酰基; C1-C10 烷基磺酰基; C1-C10 烷基磺酰氧基; 氰基; 硝基; C3-C9 环烷基; C3-C9 环烷氧基; 苯基; 苯氧基; 苯硫基; 苯基磺酰基; 苯基磺酰氧基; 吗啉代; C1-C10 亚烷基; C1-C10 亚烷基二氧基; 和氧代,

m 为 1 或 2 的整数,

式 $-Y^2Z^1-$ 的基团为下式的基团:



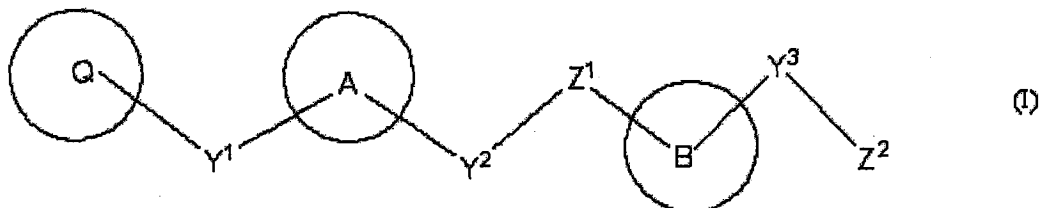
R^8 和 R^9 各自独立地为氢或 C1-C10 烷基,

n 为 1 或 2 的整数,

Z^1 为键或 $-O-$,

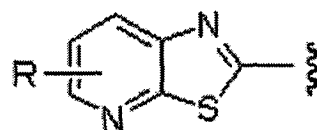
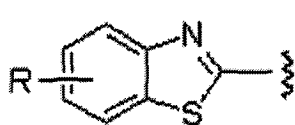
环 B 为任选被取代的亚苯基,取代基选自卤素、C1-C10 烷基和 C1-C10 烷氧基,
 Y^3 为任选被取代的 C1-C10 亚烷基或 -O- 任选被取代的 C1-C10 亚烷基,
 Y^3 的所述 C1-C10 亚烷基的取代基选自卤素和 C1-C10 亚烷基,和
 Z^2 为 $COOR^3$,其中 R^3 为氢或 C1-C10 烷基。

2. 式 (I) 的化合物、或其可药用盐,

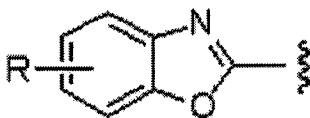


其中,

环 Q 是下式的基团:



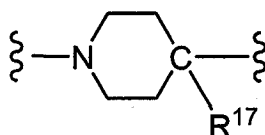
或



R 是任选被取代的 C1-C10 烷基,取代基是卤素;卤素;或任选被取代的 C1-C10 烷氧基,取代基是卤素;

Y^1 为键,

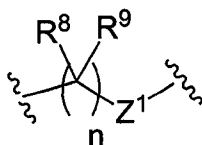
环 A 为下式的基团:



R^{17} 为任选被取代的 C1-C10 烷基,取代基是任选被 C1-C10 烷氧基取代的亚氨基;或任选被取代的非芳香族杂环,所述杂环选自吡咯烷基、哌啶基、哌啶子基、和吗啉代,取代基为氧代;

来自 N 的键结合于 Y^1 并且来自 C 的键结合于 Y^2 ,

式 $-Y^2Z^1-$ 的基团为下式的基团:



R^8 和 R^9 各自独立地为氢或 C1-C10 烷基,

n 为 2,

Z^1 为 -O-,

环 B 为任选被取代的亚苯基,取代基选自卤素、C1-C10 烷基和 C1-C10 烷氧基,

Y^3 为任选被取代的 C1-C10 亚烷基或 -O- 任选被取代的 C1-C10 亚烷基,

Y^3 的所述 C1-C10 亚烷基的取代基选自卤素和 C1-C10 亚烷基, 和
 Z^2 为 $COOR^3$, 其中 R^3 为氢或 C1-C10 烷基。

3. 一种药物组合物, 其包括权利要求 1 或 2 中任一项的化合物或其可药用盐作为活性成分。

具有 PPAR 激动活性的衍生物

技术领域

[0001] 本发明涉及具有过氧化物酶体增植物激活受体（以下称为 PPAR）的激动活性并且可用作药物的化合物。

背景技术

[0002] 作为胞内颗粒的过氧化物酶体是细胞质中的小颗粒，包含过氧化氢酶和一组氧化酶。使过氧化物酶体增殖的过氧化物酶体增植物被认为是体内重要的脂类代谢控制因子。由过氧化物酶体增植物激活的核受体 PPAR 已证明是涉及内分泌、新陈代谢、炎症等的多功能受体。因此，认为配体能够作为各种药物应用，并且最近研究人员的数量在增加。

[0003] 已经从各种动物器官发现了 PPAR 的亚型基因，并且形成一个家族。在哺乳动物中，PPAR 被分为三个 PPAR 亚型（PPAR α 、PPAR δ （也称为 PPAR β ）和 PPAR γ 。

[0004] 认为用作抗高脂血症药物的贝特类药物，通过 PPAR α 激活介导的基因群转录增强，表现出改善血清脂质的活性。另外，已经提出 PPAR α 可能涉及骨代谢和非甾体抗炎药活性的表达。

[0005] 作为胰岛素抗性改善药的噻唑烷二酮（thiazolidindion）化合物是 PPAR γ 的配体。由于这些化合物表现出降血糖作用、降脂血作用、脂肪细胞分化诱导作用等，预计将 PPAR γ 激动剂开发为糖尿病、高脂血症、肥胖症等的治疗剂。此外、预计 PPAR γ 激动剂为用于慢性胰腺炎、炎症性结肠炎、肾小球硬化症、阿尔茨海默氏病、银屑病、帕金森综合征、巴塞杜氏病、慢性类风湿性关节炎、癌症（乳癌、结肠癌、前列腺癌等）、不育症等的治疗剂。

[0006] 据报道，其中 PPAR δ 在脂肪细胞中特异性过度表达的转基因小鼠难以发胖等。因此，PPAR δ 激动剂可用作抗肥胖药或抗糖尿病药。另外，提出了 PPAR δ 激动剂作为用于结肠癌、骨质疏松症、不育症、银屑病、多发性硬化等的治疗剂的可能性。

[0007] 基于这些发现，预计 PPAR 激动剂可用于治疗或预防高脂血症、糖尿病、高血糖症、胰岛素抗性、肥胖症、动脉硬化、动脉粥样硬化、高血压、X 综合征、炎症、变应性疾病（炎症性结肠炎、慢性类风湿性关节炎、慢性胰腺炎、多发性硬化、肾小球硬化症、银屑病等）、骨质疏松症、不育症、癌症、阿尔茨海默氏病、帕金森综合征、巴塞杜氏病等（非专利文献 1）。

[0008] 专利文献 1 公开了可用作抗肥胖药物等的包含哌嗪的苯并噻唑衍生物。然而，其完全没有公开 PPAR 激动活性。

[0009] 专利文献 2 公开了作为抗病毒药物的包含哌嗪或哌啶的苯并噻唑或苯并噁唑衍生物。然而，其完全没有公开 PPAR 激动活性。

[0010] 专利文献 3 公开了作为 PPAR γ 激动剂的包含吡咯烷的苯并噻唑衍生物。然而，其没有公开包含哌嗪或哌啶的化合物。

[0011] 专利文献 4 和 5 公开了具有抗变应性作用等的包含哌嗪的化合物。非专利文献 2 公开了作为糖蛋白 IIb/IIIa 拮抗剂的包含哌嗪的化合物。专利文献 6 公开了作为 CB 1 拮抗剂的包含哌嗪的化合物。然而，其完全没有公开 PPAR 激动活性。

[0012] 专利文献 7 和 8 公开了作为 PPAR 调节剂的包含哌嗪或哌啶的化合物。然而，这些

化合物的特征在于在哌嗪和苯基之间有磺酰基作为连接基。

[0013] [专利文献 1]W0 00/006558

[0014] [专利文献 2]EP 398425

[0015] [专利文献 3]W0 97/31907

[0016] [专利文献 4]JP1992-345765

[0017] [专利文献 5]JP1997-208570

[0018] [专利文献 6]W0 2006/060461

[0019] [专利文献 7]W0 2004/092117

[0020] [专利文献 8]W0 2005/115983

[0021] [非专利文献 1]Current Medicinal Chemistry, 2003, Vol. 10, p. p. 267-280

[0022] [非 专 利 文 献 2]Bioorganic&Medical Chemistry Letters, 1998, Vol. 8, p. p. 1531-1536。

发明内容

[0023] 本发明要解决的问题

[0024] 本发明的目的是提供良好的 PPAR 激动剂。

[0025] 解决问题的方法

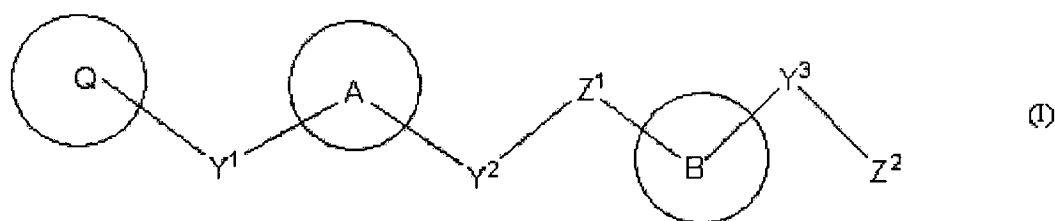
[0026] 本发明人深入研究以合成优异的 PPAR 激动剂,并且通过使用计算机化的分子设计技术作为发现候选化合物的方法,寻找具有所期望的药理学活性的化合物。本发明人执行了从基于在 PDB(Protein Data Bank) 中登记结构的过氧化物酶体增殖物激活受体的三维结构的三维化合物数据库自动搜索化合物程序,并且通过实质上的筛选,从在商业化合物的数据库中登记的化合物中选择具有作为 PPAR 激动剂潜力的化合物。根据被选化合物的骨架,本发明人合成了许多衍生物并且对合成的衍生物进行试验,例如试验 PPAR δ 、 α 和 γ 的转录激活、试验细胞毒性等。本发明人选择了具有较强的和所期望的药理学活性的化合物,并且进一步制备它们的衍生物,以完成本发明。另外,本发明人发现,本发明的化合物具有 PPAR 转录活性,较少的药物代谢酶抑制性和良好的代谢稳定性和可溶性。此外,本发明的化合物毒性较低,并且被认为对于药物用途足够安全。

[0027] 本发明包括以下。

[0028] (1). 式的化合物 (I) :

[0029] [式 1]

[0030]



[0031] 其可药用盐或溶剂化物,

[0032] 其中

[0033] 环 Q 为任选被取代的单环芳基、任选被取代的单环杂芳基、任选被取代的稠合芳

基或任选被取代的稠合杂芳基,条件是环 Q 不是未被取代的 11H-二苯并 [b, e]-氮杂 草 -6-基,

[0034] Y^1 为键、 $-NR^6-$ 或 $-NR^6-CO-$, 其中 R^6 为氢或任选被取代的低级烷基,

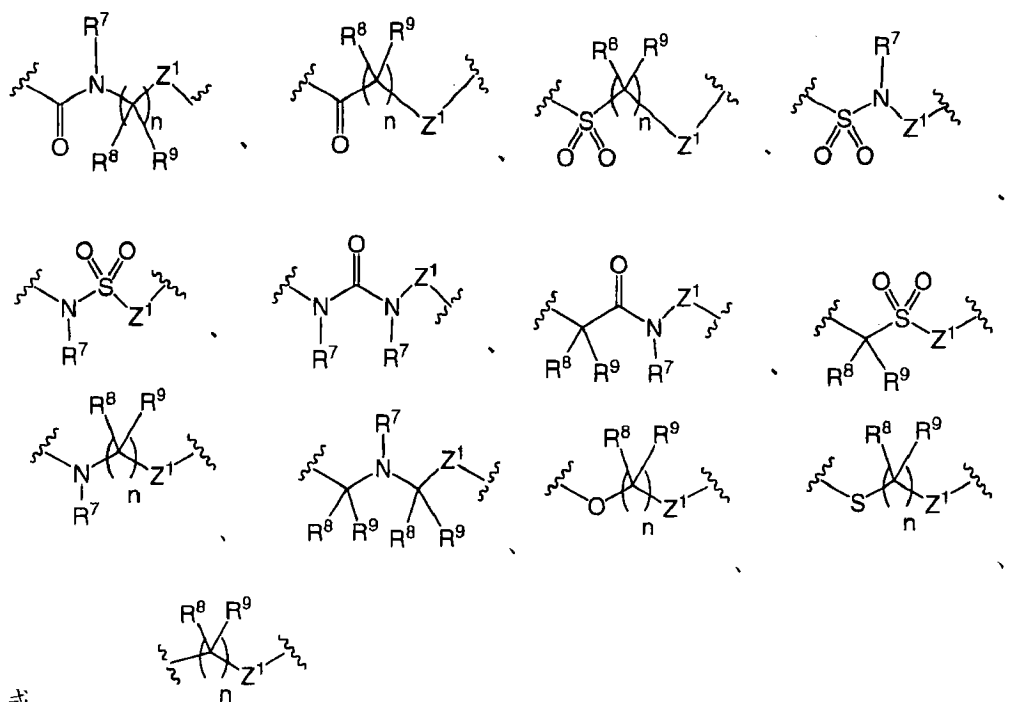
[0035] 条件是,当环 Q 为未被取代的单环芳基时, Y^1 为 $-NR^6-CO-$, 和当环 Q 为单环芳基和 Y^1 为键时,环 Q 是被烷基卤化物取代的苯基,

[0036] 环 A 为任选被取代的非芳香族杂环二基,条件是当 Y^1 为键时,环 Q 结合于环 A 的氮原子,

[0037] 式 $-Y^2Z^1-$ 的基团为下式的基团:

[0038] [式 2]

[0039]



或

[0040] 条件是,式 $-Y^2Z^1-$ 的基团不是 $-SO_2-$, 并且当环 Q 为未被取代的苯并噻唑 -2-基或未被取代的苯并噁唑 -2-基时,式 $-Y^2Z^1-$ 的基团不是 $-CH_2-CH_2-O-$ 或 $-O-$,

[0041] R^7 各自独立地为氢、任选被取代的低级烷基或任选被取代的环烷基,

[0042] R^8 和 R^9 各自独立地为氢或任选被取代的低级烷基,

[0043] n 为 0 到 3 的整数,

[0044] Z^1 为键、 $-O-$ 、 $-S-$ 或 $-NR^9-$, 其中 R^9 为氢、任选被取代的低级烷基、任选被取代的酰基、任选被取代的低级烷基磺酰基或任选被取代的芳基磺酰基,

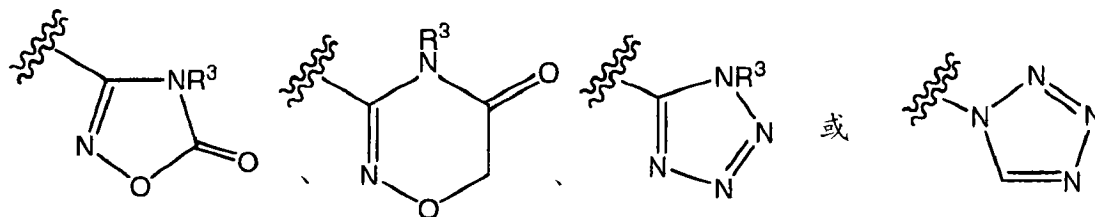
[0045] 环 B 为任选被取代的芳香族碳环二基或任选被取代的芳香族杂环二基,

[0046] Y^3 为键、任选地被 $-O-$ 插入的任选被取代的低级亚烷基、任选地被 $-O-$ 插入的亚环烷基或任选被取代的低级亚烯基,

[0047] Z^2 为 $COOR^3$ 、 $C(=NR^3)NR^{14}OR^{15}$ 、 $CONHCN$ 或下式的基团:

[0048] [式 3]

[0049]

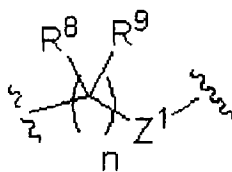


[0050] R^3 、 R^{14} 和 R^{15} 各自独立地为氢、任选被取代的低级烷基、任选被取代的低级烯基、任选被取代的芳基或任选被取代的杂芳基,和

[0051] 条件是排除如下化合物:其中式 $-Y^2Z^1-$ 的基团为下式的基团:

[0052] [式 4]

[0053]



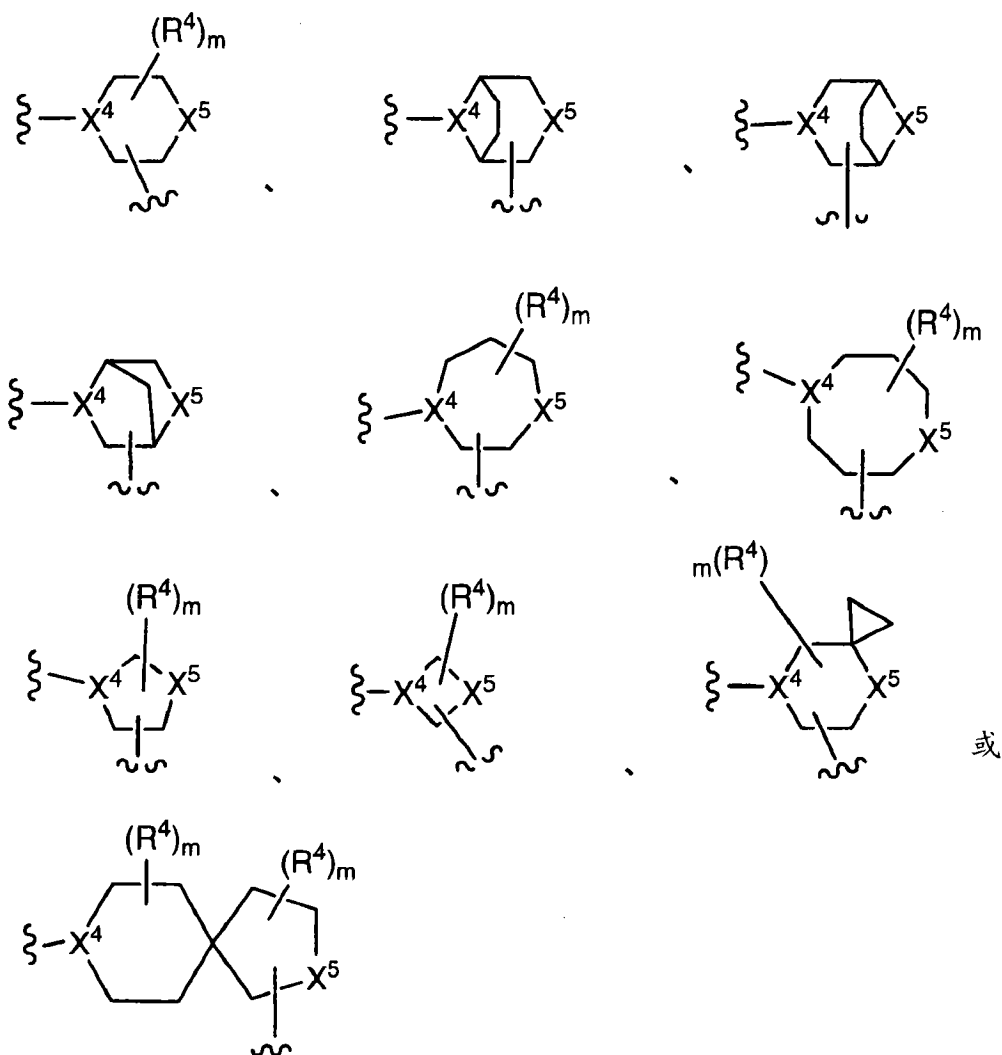
[0054] n 为 0 和 Z^1 为键。

[0055] (2). (1) 的化合物、其可药用盐或溶剂化物,其中

[0056] 环 A 为下式的基团:

[0057] [式 5]

[0058]



[0059] 其中

[0060] X^4 为 N 或 CR^5 , 其中 R^5 为氢或任选被取代的低级烷基,

[0061] X^5 为 O、S、 NR^{16} 或 $CR^{17}R^{18}$, 其中 R^{16} 到 R^{18} 各自独立地为氢、任选被取代的低级烷基、氰基、任选被取代的非芳香族杂环、任选被取代的杂芳基、任选被取代的氨基、任选被取代的低级烷氧基、芳基低级烷基或任选被取代的环烷基, 条件是排除其中 X^4 为 CR^5 和 X^5 为 $CR^{17}R^{18}$ 的化合物,

[0062] R^4 各自独立地为卤素、任选被取代的低级烷基、任选被取代的低级烯基、任选被取代的低级炔基、任选被取代的低级烷氧基或任选被取代的芳基,

[0063] m 为 0 到 2 的整数,

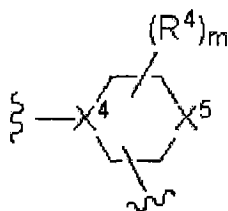
[0064] 来自 X^4 的键结合于 Y^1 并且另一个键结合于 Y^2 , 和当 X^5 为 NR^{16} 或 $CR^{17}R^{18}$ 时, 另一个键可结合于 X^5 。

[0065] (3). (1) 的化合物、其可药用盐或溶剂化物, 其中

[0066] 环 A 为下式的基团:

[0067] [式 6]

[0068]



[0069] X^4 为 N 或 CR^5 , 其中 R^5 为氢或任选被取代的低级烷基,

[0070] X^5 为 NR^{16} 或 $CR^{17}R^{18}$, 其中 R^{16} 到 R^{18} 各自独立地为氢、任选被取代的低级烷基、氰基、任选被取代的非芳香族杂环、任选被取代的杂芳基、任选被取代的氨基、任选被取代的低级烷氧基、芳基低级烷基或任选被取代的环烷基,

[0071] R^4 各自独立地为卤素、任选被取代的低级烷基、任选被取代的低级烯基、任选被取代的低级炔基、任选被取代的低级烷氧基或任选被取代的芳基,

[0072] m 为 0 到 2 的整数,

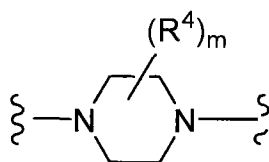
[0073] 来自 X^4 的键结合于 Y^1 并且另一个键结合于 Y^2 , 另一个键可结合于 X^5 。

[0074] (4). (1) 的化合物、其可药用盐或溶剂化物, 其中

[0075] 环 A 为下式的基团:

[0076] [式 7]

[0077]



[0078] R^4 各自独立地为卤素、任选被取代的低级烷基、任选被取代的低级烯基、任选被取代的低级炔基或任选被取代的低级烷氧基, 和

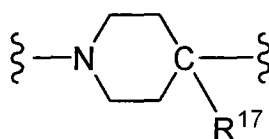
[0079] m 为 1 或 2 的整数。

[0080] (5). (1) 的化合物、其可药用盐或溶剂化物, 其中

[0081] 环 A 为下式的基团:

[0082] [式 8]

[0083]



[0084] R^{17} 为任选被取代的低级烷基、氰基、任选被取代的非芳香族杂环、任选被取代的杂芳基、任选被取代的氨基、任选被取代的低级烷氧基、芳基低级烷基或任选被取代的环烷基,

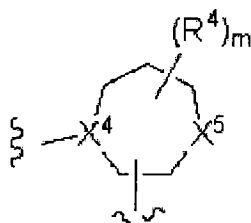
[0085] 来自 N 的键结合于 Y^1 并且来自 C 的键结合于 Y^2 。

[0086] (6). (1) 的化合物、其可药用盐或溶剂化物, 其中

[0087] 环 A 为下式的基团:

[0088] [式 9]

[0089]



[0090] X^4 为 N 或 CR^5 , 其中 R^5 为氢或任选被取代的低级烷基,

[0091] X^5 为 NR^{16} 或 $CR^{17}R^{18}$, 其中 R^{16} 到 R^{18} 各自独立地为氢、任选被取代的低级烷基、氰基、任选被取代的非芳香族杂环、任选被取代的杂芳基、任选被取代的氨基、任选被取代的低级烷氧基、芳基低级烷基或任选被取代的环烷基, 条件是排除如下化合物: 其中 X^4 为 CR^5 和 X^5 为 $CR^{17}R^{18}$,

[0092] R^4 各自独立地为卤素、任选被取代的低级烷基、任选被取代的低级烯基、任选被取代的低级炔基、任选被取代的低级烷氧基或任选被取代的芳基,

[0093] m 为 0 到 2 的整数,

[0094] 来自 X^4 的键结合于 Y^1 并且另一个键结合于 Y^2 , 和另一个键可结合于 X^5 。

[0095] (7). (1) 或 (2) 的化合物、其可药用盐或溶剂化物, 其中环 Q 为被取代的稠合杂芳基。

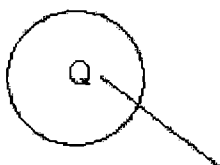
[0096] (8). (1) 或 (2) 的化合物、其可药用盐或溶剂化物, 其中环 Q 为被取代的苯并呋喃基、被取代的苯并噻吩基、被取代的苯并吡咯基、被取代的苯并噁唑基、被取代的苯并异噁唑基、被取代的苯并噻唑基、被取代的苯并异噻唑基、被取代的苯并咪唑基或被取代的苯并吡唑基。

[0097] (9). (1) 或 (2) 的化合物、其可药用盐或溶剂化物, 其中

[0098] 下式的基团:

[0099] [式 10]

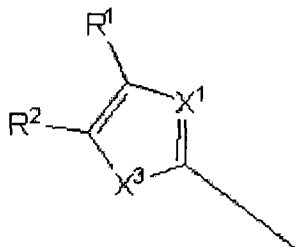
[0100]



[0101] 是下式的基团:

[0102] [式 11]

[0103]



[0104] R^1 为氢、卤素、羟基、任选被取代的低级烷基、任选被取代的低级烯基、任选被取代的低级炔基、任选被取代的低级烷氧基或任选被取代的芳基,

[0105] R^2 为卤素、任选被取代的烷基、任选被取代的芳基、任选被取代的芳氧基、任选被

取代的芳硫基或任选被取代的杂芳基,或

[0106] R^1 和 R^2 可与相邻的碳原子以及包括 X^1 和 X^3 作为组成原子的 5 元环一起形成被取代的稠合杂芳基,

[0107] X^1 为 N 或 CR^{10} , 和

[0108] X^3 为 NR^{11} 、O 或 S, 其中 R^{10} 和 R^{11} 各自独立地为氢或任选被取代的低级烷基。

[0109] (11). (1) 或 (2) 的化合物、其可药用盐或溶剂化物, 其中

[0110] 下式的基团:

[0111] [式 12]

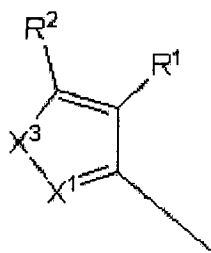
[0112]



[0113] 是下式的基团:

[0114] [式 13]

[0115]



[0116] R^1 为氢、卤素、羟基、任选被取代的低级烷基、任选被取代的低级烯基、任选被取代的低级炔基或任选被取代的低级烷氧基,

[0117] R^2 为卤素、任选被取代的烷基、任选被取代的芳基、任选被取代的芳氧基、任选被取代的芳硫基或任选被取代的杂芳基,或

[0118] R^1 和 R^2 可与相邻的碳原子以及包括 X^1 和 X^3 作为组成原子的 5 元环一起形成被取代的稠合杂芳基,

[0119] X^1 为 N 或 CR^{12} , 和

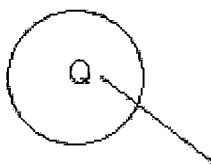
[0120] X^3 为 NR^{13} 、O 或 S, 其中 R^{12} 和 R^{13} 各自独立地为氢或任选被取代的低级烷基。

[0121] (12). (1) 或 (2) 的化合物、其可药用盐或溶剂化物, 其中

[0122] 下式的基团:

[0123] [式 14]

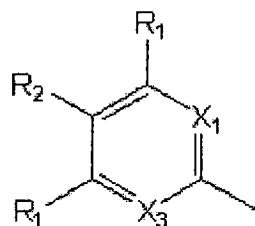
[0124]



[0125] 是下式的基团:

[0126] [式 15]

[0127]



[0128] R^1 各自独立地为氢、卤素、羟基、任选被取代的低级烷基、任选被取代的低级烯基、任选被取代的低级炔基或任选被取代的低级烷氧基，

[0129] R^2 为卤素、任选被取代的烷基、任选被取代的芳基、任选被取代的芳氧基、任选被取代的芳硫基或任选被取代的杂芳基，

[0130] X^1 为 N 或 CR^{19} ，和

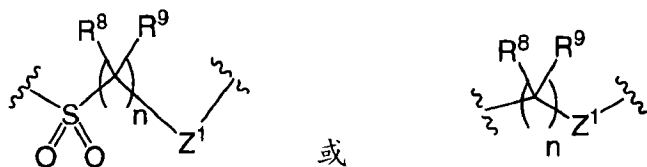
[0131] X^3 为 N 或 CR^{20} ，其中 R^{19} 和 R^{20} 各自独立地为氢或任选被取代的低级烷基，条件是 X^1 或 X^3 为 N。

[0132] (13). (1) 或 (2) 的化合物、其可药用盐或溶剂化物，其中

[0133] 式 $-Y^2Z^1-$ 的基团为下式的基团：

[0134] [式 16]

[0135]



[0136] R^8 和 R^9 各自独立地为氢或低级烷基，

[0137] n 为 0 到 2 的整数，和

[0138] Z^1 为键、 $-O-$ 或 $-S-$ 。

[0139] (14). (1) 或 (2) 的化合物、其可药用盐或溶剂化物，其中环 B 为任选被取代的亚苯基、任选被取代的吡啶二基、任选被取代的苯并呋喃二基、任选被取代的苯并噻吩二基、任选被取代的呋喃二基或任选被取代的噻吩二基。

[0140] (15). (1) 或 (2) 的化合物、其可药用盐或溶剂化物，其中 Y^3 为键、任选被取代的低级亚烷基、 $-O-$ 任选被取代的低级亚烷基或任选被取代的低级亚烯基。

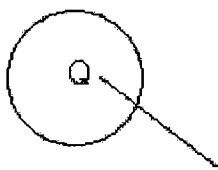
[0141] (16). (1) 或 (2) 的化合物、其可药用盐或溶剂化物，其中 Z^2 为 $COOR^3$ ，其中 R^3 为氢或任选被取代的低级烷基。

[0142] (17). (1) 的化合物、其可药用盐或溶剂化物，其中

[0143] 下式的基团：

[0144] [式 17]

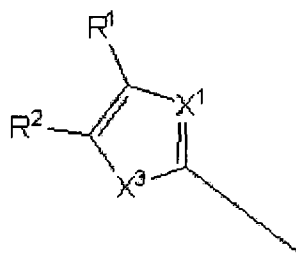
[0145]



[0146] 是下式的基团：

[0147] [式 18]

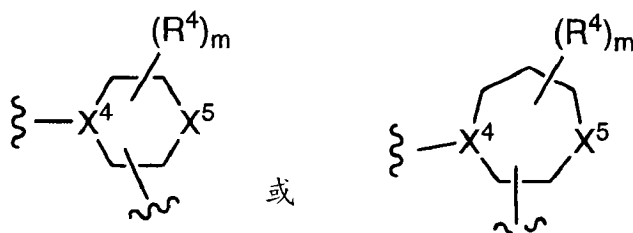
[0148]

[0149] R^1 为氢,[0150] R^2 为任选被取代的芳基或[0151] R^1 和 R^2 可与相邻的碳原子以及包括 X^1 和 X^3 作为组成原子的 5 元环一起形成被取代的稠合杂芳基,[0152] X^1 为 N 或 CR^{10} , 其中 R^{10} 为氢,[0153] X^3 为 O 或 S,[0154] Y^1 为键,

[0155] 环 A 为下式的基团:

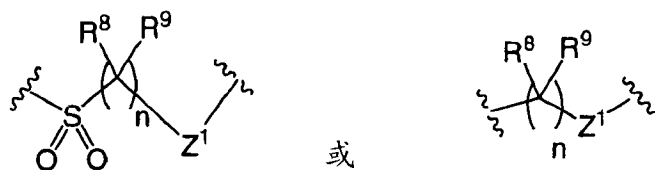
[0156] [式 19]

[0157]

[0158] X^4 为 N,[0159] X^5 为 NR^{16} 或 $CR^{17}R^{18}$, 其中 R^{16} 到 R^{18} 各自独立地为氢、任选被取代的低级烷基、氰基、任选被取代的非芳香族杂环、任选被取代的杂芳基、任选被取代的氨基、任选被取代的低级烷氧基、芳基低级烷基或任选被取代的环烷基,[0160] R^4 各自独立地为卤素、任选被取代的低级烷基、任选被取代的低级烯基、任选被取代的低级炔基、任选被取代的低级烷氧基或任选被取代的芳基,[0161] m 为 0 到 2 的整数,[0162] 来自 X^4 的键结合于 Y^1 并且另一个键结合于 Y^2 , 和另一个键可结合于 X^5 ,[0163] 式 $-Y^2Z^1-$ 的基团为下式的基团:

[0164] [式 20]

[0165]

[0166] R^8 和 R^9 各自独立地为氢或低级烷基,[0167] n 为 0 到 2 的整数,

[0168] Z^1 为键、-O- 或 -S-,

[0169] 环 B 为任选被取代的亚苯基、任选被取代的呋喃二基或任选被取代的噻吩二基,

[0170] 环 B 的所述亚苯基、呋喃二基或噻吩二基的取代基选自卤素、低级烷基和低级烷氧基,

[0171] Y^3 为键、任选被取代的低级亚烷基、-O- 任选被取代的低级亚烷基或任选被取代的低级亚烯基,

[0172] Y^3 的所述低级亚烷基或低级亚烯基的取代基选自卤素和低级亚烷基, 和

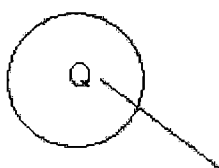
[0173] Z^2 为 COOR^3 , 其中 R^3 为氢或低级烷基。

[0174] (18). (1) 的化合物、其可药用盐或溶剂化物, 其中

[0175] 下式的基团:

[0176] [式 21]

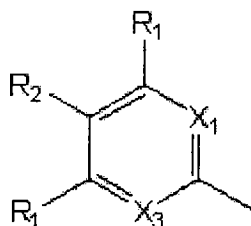
[0177]



[0178] 是下式的基团:

[0179] [式 22]

[0180]



[0181] R^1 各自独立地为氢、卤素、羟基、任选被取代的低级烷基、任选被取代的低级烯基、任选被取代的低级炔基或任选被取代的低级烷氧基,

[0182] R^2 为任选被取代的烷基或任选被取代的芳基,

[0183] X^1 为 N 或 CR^{19} ,

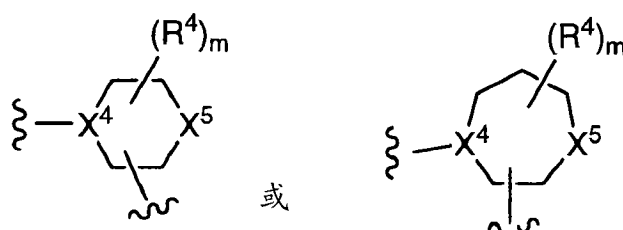
[0184] X^3 为 N 或 CR^{20} , 其中 R^{19} 和 R^{20} 各自独立地为氢或任选被取代的低级烷基, 条件是 X^1 或 X^3 为 N,

[0185] Y^1 为键,

[0186] 环 A 为下式的基团:

[0187] [式 23]

[0188]



[0189] X^4 为 N,

[0190] X^5 为 NR^{16} 或 $CR^{17}R^{18}$, 其中 R^{16} 到 R^{18} 各自独立地为氢、任选被取代的低级烷基、氰基、任选被取代的非芳香族杂环、任选被取代的杂芳基、任选被取代的氨基、任选被取代的低级烷氧基、芳基低级烷基或任选被取代的环烷基,

[0191] R^4 各自独立地为卤素、任选被取代的低级烷基、任选被取代的低级烯基、任选被取代的低级炔基、任选被取代的低级烷氧基或任选被取代的芳基,

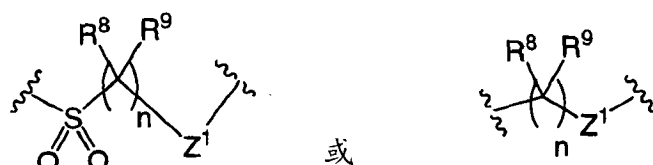
[0192] m 为 0 到 2 的整数,

[0193] 来自 X^4 的键结合于 Y^1 并且另一个键结合于 Y^2 , 和另一个键可结合于 X^5 ,

[0194] 式 $-Y^2Z^1-$ 的基团为下式的基团:

[0195] [式 24]

[0196]



[0197] R^8 和 R^9 各自独立地为氢或低级烷基,

[0198] n 为 0 到 2 的整数,

[0199] Z^1 为键、 $-O-$ 或 $-S-$,

[0200] 环 B 为任选被取代的亚苯基、任选被取代的呋喃二基或任选被取代的噻吩二基,

[0201] 环 B 的所述亚苯基、呋喃二基或噻吩二基的取代基选自卤素、低级烷基和低级烷氧基,

[0202] Y^3 为键、任选被取代的低级亚烷基、 $-O-$ 任选被取代的低级亚烷基或任选被取代的低级亚烯基,

[0203] Y^3 的所述低级亚烷基或低级亚烯基的取代基选自卤素和低级亚烷基, 和

[0204] Z^2 为 $COOR^3$, 其中 R^3 为氢或低级烷基。

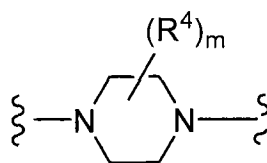
[0205] (19). (1) 的化合物、其可药用盐或溶剂化物, 其中

[0206] Y^1 为键,

[0207] 环 A 为下式的基团:

[0208] [式 25]

[0209]



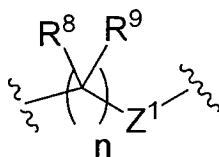
[0210] R^4 各自独立地为卤素、任选被取代的低级烷基、任选被取代的低级烯基、任选被取代的低级炔基或任选被取代的低级烷氧基,

[0211] m 为 1 或 2 的整数,

[0212] 式 $-Y^2Z^1-$ 的基团为下式的基团:

[0213] [式 26]

[0214]



[0215] R^8 和 R^9 各自独立地为氢或低级烷基,

[0216] n 为 1 或 2 的整数,

[0217] Z^1 为键或 $-O-$,

[0218] 环 B 为任选被取代的亚苯基,

[0219] Y^3 为任选被取代的低级亚烷基或 $-O-$ 任选被取代的低级亚烷基,

[0220] Y^3 的所述低级亚烷基的取代基选自卤素和低级亚烷基, 和

[0221] Z^2 为 $COOR^3$, 其中 R^3 为氢或低级烷基。

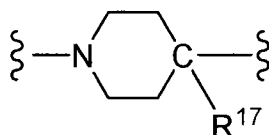
[0222] (20). (1) 的化合物、其可药用盐或溶剂化物, 其中

[0223] Y^1 为键,

[0224] 环 A 为下式的基团:

[0225] [式 27]

[0226]



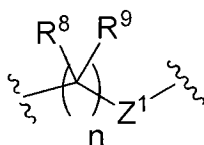
[0227] R^{17} 为任选被取代的低级烷基、氰基、任选被取代的非芳香族杂环、任选被取代的杂芳基、任选被取代的氨基、任选被取代的低级烷氧基、芳基低级烷基或任选被取代的环烷基,

[0228] 来自 N 的键结合于 Y^1 并且来自 C 的键结合于 Y^2 ,

[0229] 式 $-Y^2Z^1-$ 的基团为下式的基团:

[0230] [式 28]

[0231]



[0232] R^8 和 R^9 各自独立地为氢或低级烷基,

[0233] n 为 2,

[0234] Z^1 为 $-O-$,

[0235] 环 B 为任选被取代的亚苯基,

[0236] Y^3 为任选被取代的低级亚烷基或 $-O-$ 任选被取代的低级亚烷基, 和

[0237] Y^3 的所述低级亚烷基的取代基选自卤素和低级亚烷基, 和

[0238] Z^2 为 $COOR^3$, 其中 R^3 为氢或低级烷基。

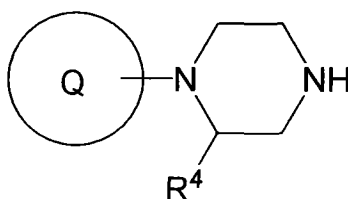
[0239] (21) 药物组合物, 其包括 (1) 到 (20) 中任一项的化合物、其可药用盐或溶剂化物作为活性成分。

[0240] (22) 用于预防和 / 或治疗涉及过氧化物酶体增植物激活受体的疾病的药物组合物, 其包括 (1) 到 (20) 中任一项的化合物、其可药用盐或溶剂化物作为活性成分。

[0241] (23) 下式的化合物：

[0242] [式 29]

[0243]



[0244] 其盐或溶剂化物，

[0245] 其中

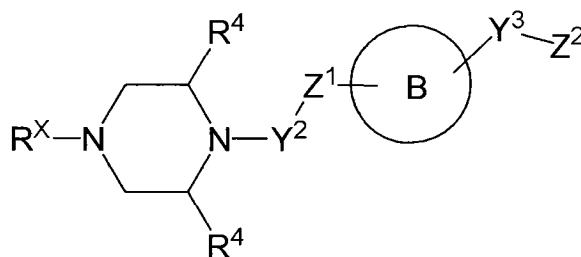
[0246] 环 Q 具有与 (1) 中定义的相同的含义，和

[0247] R^4 为卤素、任选被取代的低级烷基、任选被取代的低级烯基、任选被取代的低级炔基或任选被取代的低级烷氧基。

[0248] (24) 下式的化合物：

[0249] [式 30]

[0250]



[0251] 其盐或溶剂化物，

[0252] 其中

[0253] Y^2 、 Z^1 、环 B、 Y^3 和 Z^2 具有与 (1) 中定义的相同的含义，

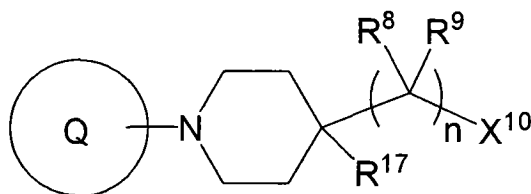
[0254] R^4 各自独立地为卤素、任选被取代的低级烷基、任选被取代的低级烯基、任选被取代的低级炔基、任选被取代的低级烷氧基或任选被取代的芳基，和

[0255] R^X 为氢或氨基保护基。

[0256] (25) 下式的化合物：

[0257] [式 31]

[0258]



[0259] 其盐或溶剂化物，

[0260] 其中

[0261] 环 Q 具有与 (1) 中定义的相同的含义，

[0262] R^{17} 为任选被取代的低级烷基、氰基、任选被取代的非芳香族杂环、任选被取代的杂芳基、任选被取代的氨基、任选被取代的低级烷氧基、芳基低级烷基或任选被取代的环烷

基,

[0263] R^8 和 R^9 各自独立地为氢或低级烷基,

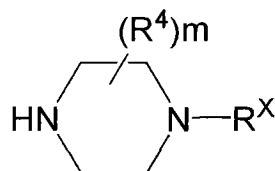
[0264] n 为 1 到 3 的整数, 和

[0265] X^{10} 为卤素或羟基。

[0266] (26) 下式的化合物:

[0267] [式 32]

[0268]



[0269] 其盐或溶剂化物,

[0270] 其中

[0271] R^4 各自独立地为卤素、任选被取代的低级烷基、任选被取代的低级烯基、任选被取代的低级炔基或任选被取代的低级烷氧基,

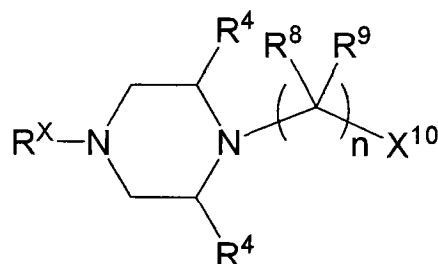
[0272] m 为 1 或 2, 和

[0273] R^X 为氢或氨基保护基。

[0274] (27) 下式的化合物:

[0275] [式 33]

[0276]



[0277] 其盐或溶剂化物,

[0278] 其中

[0279] R^4 各自独立地为卤素、任选被取代的低级烷基、任选被取代的低级烯基、任选被取代的低级炔基或任选被取代的低级烷氧基,

[0280] R^8 和 R^9 各自独立地为氢或低级烷基,

[0281] n 为 1 到 3 的整数,

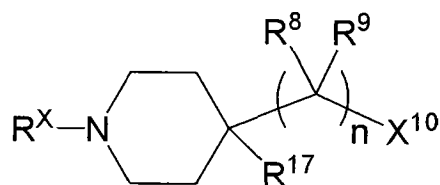
[0282] R^X 为氢或氨基保护基, 和

[0283] X^{10} 为羟基或卤素。

[0284] (28) 下式的化合物:

[0285] [式 34]

[0286]



[0287] 其盐或溶剂化物，

[0288] 其中

[0289] R^{17} 为任选被取代的低级烷基、氰基、任选被取代的非芳香族杂环、任选被取代的杂芳基、任选被取代的氨基、任选被取代的低级烷氧基、芳基低级烷基或任选被取代的环烷基，

[0290] R^8 和 R^9 各自独立地为氢或低级烷基，

[0291] n 为 1 到 3 的整数，

[0292] X^{10} 为卤素或羟基，和

[0293] R^X 为氢或氨基保护基。

[0294] 此外，本发明提供一种 PPAR 激活的方法，其特征在于给予上述的化合物、其可药用盐或溶剂化物。具体地，其为用于高脂血症、糖尿病、肥胖症、动脉硬化、动脉粥样硬化、高血糖和 / 或 X 综合症的治疗方法和 / 或预防方法。

[0295] 作为另一个实施方案，本发明提供上述化合物、其可药用盐或溶剂化物生产用于 PPAR 激活的药物的用途，例如用于治疗 and / 或预防高脂血症、糖尿病、肥胖症、动脉硬化、动脉粥样硬化、高血糖和 / 或 X 综合症的药物。

[0296] 发明效果

[0297] 如以下试验结果所示，本发明的化合物具有 PPAR 激动活性并且作为药物非常有用，尤其是作为用于治疗 and / 或预防高脂血症、糖尿病、肥胖症、动脉硬化、动脉粥样硬化、高血糖和 / 或 X 综合症的药物。

[0298] 发明详述

[0299] 以下说明用于本说明书的各个术语。各个术语在本说明书中具有相同的含义，无论是单独使用各个术语或与另外的术语一起使用。

[0300] 术语“单环芳基”是指 C6 到 C12 单环芳香族碳环。其实例包括苯基等。

[0301] 术语“稠合芳基”是指芳香族碳环，其中 1 到 4 个单环的芳香族碳环（C6 到 C12 单环芳香族碳环）与 C6 到 C12 单环芳香族碳环稠合。其实例包括萘基、蒽基、菲基等。键可以连接于任何这些环。更优选萘基。

[0302] 术语“芳基”是指上述的“单环芳基”和“稠合芳基”。

[0303] 术语“芳烷基”是指被 1 到 3 个上述“芳基”取代的上述“烷基”。其实例包括苯甲基、苯乙基、苯丙基、三苯甲基等。

[0304] 术语“单环杂芳基”是指 4 到 8 元的单环芳香族杂环，在环中具有一个或多个选自 O、S 和 N 的杂原子。其实例包括吡咯基、咪唑基、吡啶基、哒嗪基、嘧啶基、吡嗪基、三唑基、三嗪基、四唑基、异噁唑基、噁唑基、噁二唑基、异噻唑基、噻唑基、噻二唑基、呋喃基、噻吩基等。特别优选 5 或 6 元的单环芳香族杂环。

[0305] 术语“稠合杂芳基”是指衍生自稠合的芳香族杂环的基团，其中芳香族碳环（衍生自上述“芳基”的芳香族碳环）或芳香族杂环（在环中具有一个或多个选自 O、S 和 N 的杂

原子的 4 到 8 元芳香族杂环)与衍生自上述“单环杂芳基”的单环芳香族杂环稠合。其实例包括吡啶基、异吡啶基、吡嗪基、中氮茛基、喹啉基、异喹啉基、1,2-二氮杂萘基、2,3-二氮杂萘基、喹啉基、1,5-二氮杂萘基、喹啉基、prinylyl、蝶啶基、苯并吡喃基、苯并咪唑基、苯并异噁唑基、苯并噁唑基、苯并噁二唑基、苯并异噻唑基、苯并噻唑基、苯并噻二唑基、苯并呋喃基、异构苯并呋喃基、苯并噻吩基、苯并三唑基、咪唑并吡啶基、三唑并吡啶基、咪唑并噻唑基、吡啶并哒嗪基 (pyradinopyridazinyl)、喹啉基、四氢喹啉基、四氢苯并噻吩基、呋唑基、吡啶基、咕吨基、吩噻嗪基、dphenoxathiinyl、吩噻嗪基、二苯并呋喃基等。在“稠合杂芳基”的情况中,键可以连接于任何这些环。尤其优选其中苯环与 5 或 6 元单环芳香族杂环稠合的稠合的稠合杂芳基 (condensed fused heteroaryl)。

[0306] 术语“杂芳基”是指上述的“单环杂芳基”和“稠合杂芳基”。

[0307] 术语“杂芳烷基”是指被 1 到 3 个上述“杂芳基”取代的上述“烷基”。

[0308] 术语“非芳香族杂环”是指稠合的非芳香族杂环,其中芳香族碳环(衍生自上述“芳基”的芳香族碳环)、芳香族杂环(在环中具有一个或多个选自 O、S 和 N 的杂原子的 4 到 8 元的芳香族杂环)、单环的非芳香族杂环(衍生自上述“单环非芳香族杂环”的单环的非芳香族杂环)或环烷烃(衍生自以下“环烷基”的环)与在环中具有一个或多个选自 O、S 和 N 的杂原子的 4 到 8 元单环的非芳香族杂环或上述“单环的非芳香族杂环”稠合。其实例包括二氢吡啶基、二氧杂环己基、硫杂环丙基、氧杂环丙基 (oxyranyl)、氧杂硫杂环戊基 (oxathiolanyl)、氮杂环丁基、硫杂环己基 (thianyl)、吡咯烷基、吡咯啉基、咪唑烷基、咪唑啉基、吡唑烷基、吡唑啉基、哌啶基、哌啶子基、哌嗪基、piperadino、吗啉基、吗啉代、oxadiadinylyl、二氢吡啶基等。

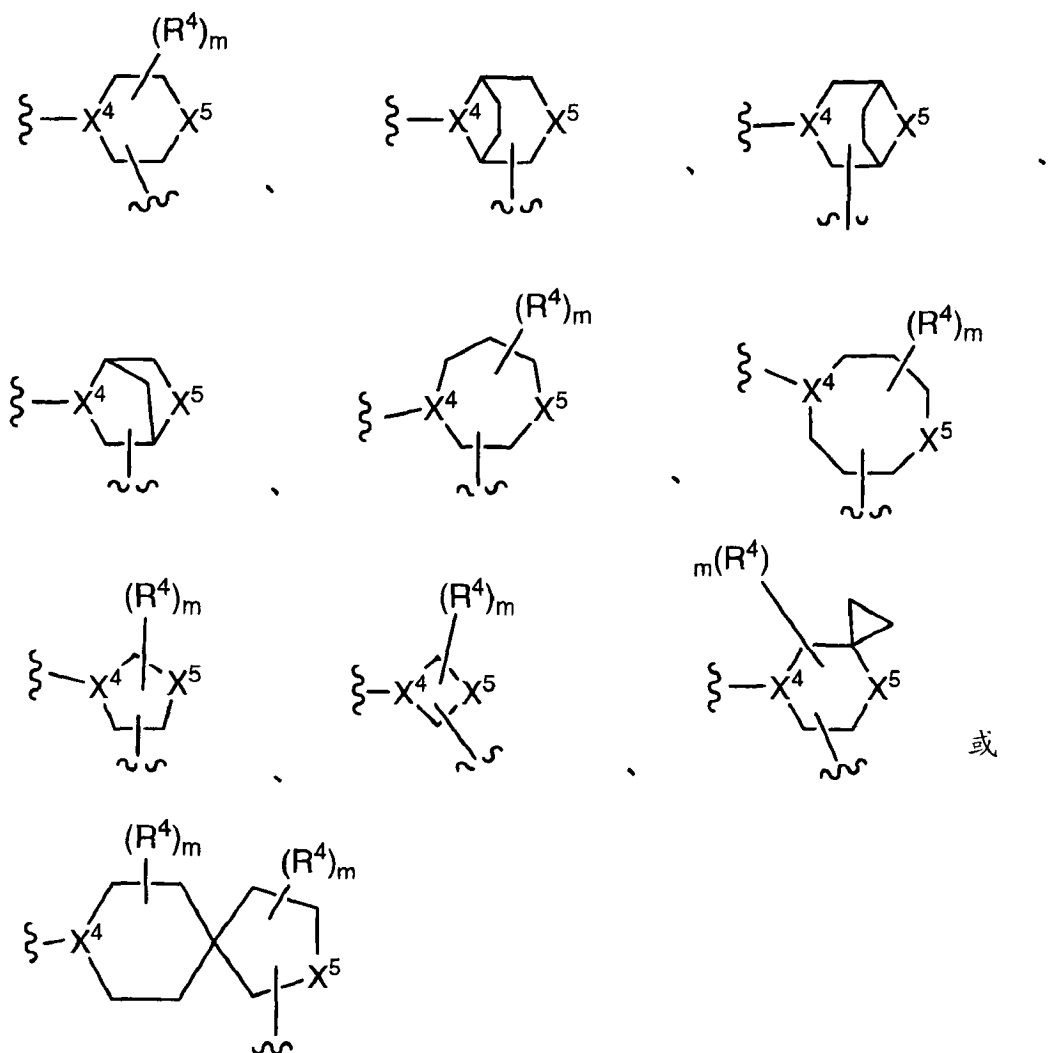
[0309] 术语“杂环”包括上述的“杂芳基”和“非芳香族杂环”。实例包括吗啉代、哌啶子基、piperadino、呋喃基、噻吩基、吡啶基等。

[0310] 术语“非芳香族杂环二基”包括通过从在环中具有一个或多个选自 O、S 和 N 的杂原子的 4 到 10 元的非芳香族杂环除去 2 个氢原子衍生的二价基团。非芳香族杂环可以通过亚烷基桥接。优选的实例包括哌啶二基、piperadine 二基、吗啉二基、二噁烷二基、吡咯烷二基、吡咯啉二基、咪唑啉二基、咪唑烷二基等。环 A 的“非芳香族杂环二基”的实例包括以下基团。

[0311] 下式的基团:

[0312] [式 35]

[0313]



[0314] 其中

[0315] X^4 为 N 或 CR^5 , 其中 R^5 为氢或任选被取代的低级烷基,

[0316] X^5 为 O、S、 NR^{16} 或 $CR^{17}R^{18}$, 其中 R^{16} 到 R^{18} 各自独立地为氢、任选被取代的低级烷基、任选被取代的非芳香族杂环、任选被取代的杂芳基、任选被取代的氨基、任选被取代的低级烷氧基、芳基低级烷基或任选被取代的环烷基, 条件是排除以下化合物: 其中 X^4 为 CR^5 和 X^5 为 $CR^{17}R^{18}$,

[0317] R^4 各自独立地为卤素、任选被取代的低级烷基、任选被取代的低级烯基、任选被取代的低级炔基、任选被取代的低级烷氧基或任选被取代的芳基, 和

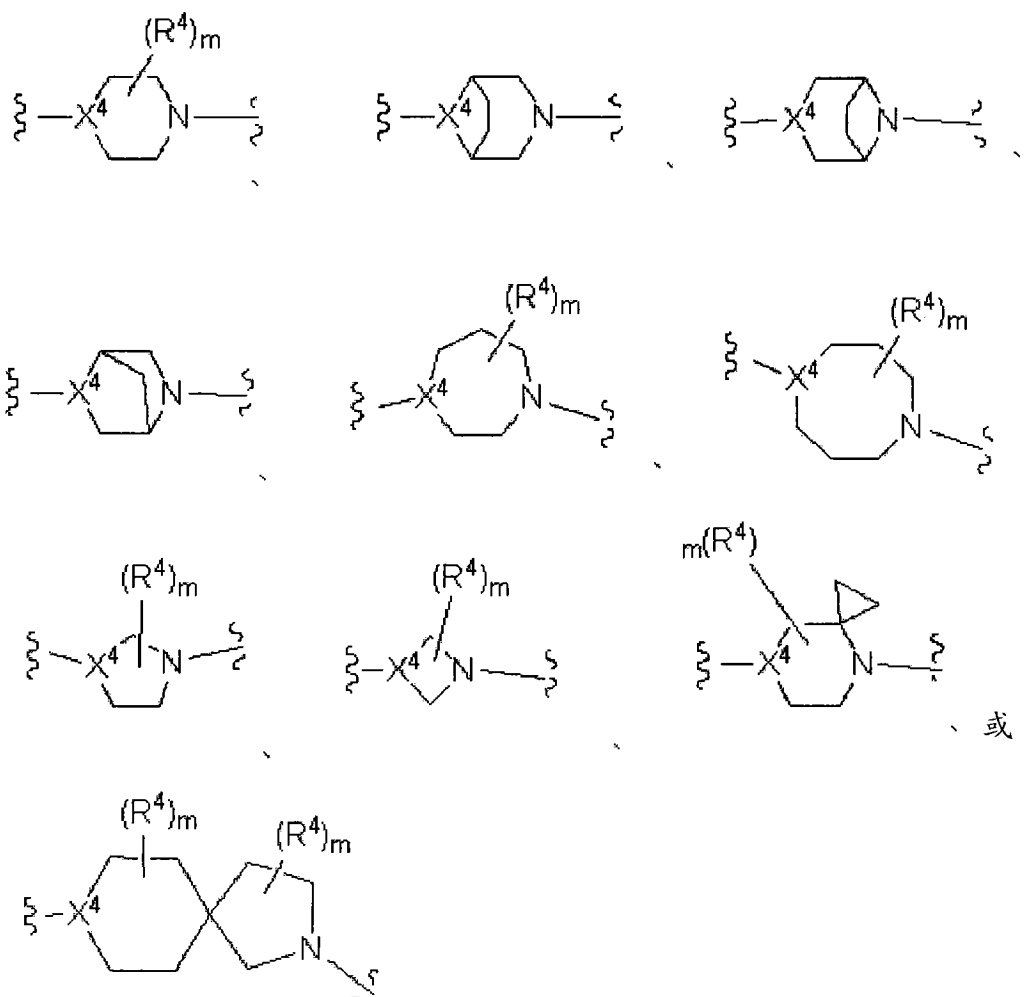
[0318] m 为 0 到 2 的整数,

[0319] 来自 X^4 的键结合于 Y^1 和另一个键结合于 Y^2 , 和当 X^5 为 NR^{16} 或 $CR^{17}R^{18}$ 时, 另一个键可结合于 X^5 。另一个键优选结合于 X^5 。

[0320] “当 X^5 为 NR^{16} 时, 另一个键可结合于 X^5 ” 意思如下。

[0321] [式 36]

[0322]

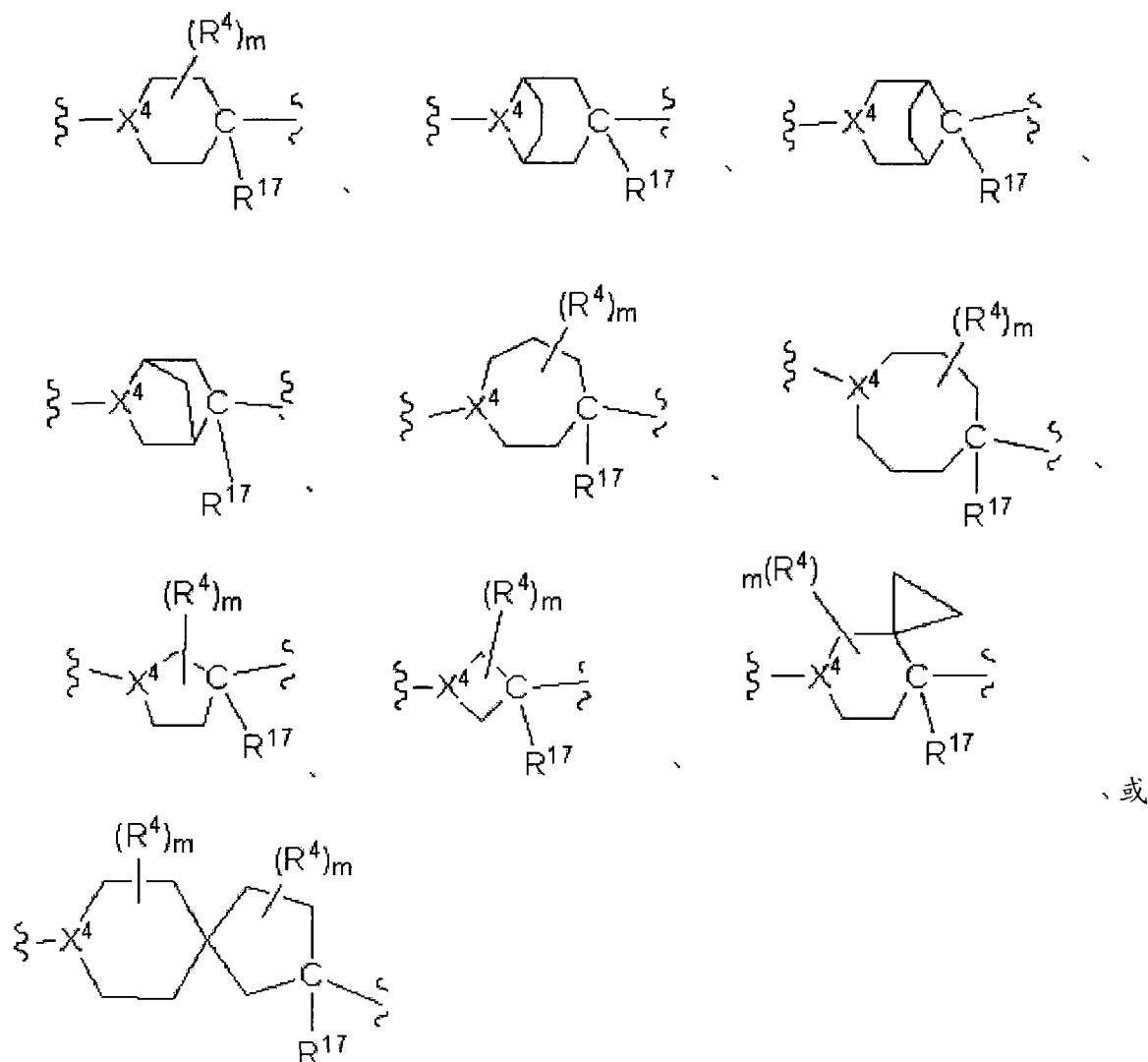


[0323] 其中各个符号具有与上述定义相同的含义。

[0324] “当 X^5 为 $CR^{17}R^{18}$ 时, 另一个键可结合于 X^5 ” 意思如下。

[0325] [式 37]

[0326]



[0327] 其中各个符号具有与上述定义相同的含义。

[0328] 术语“芳香族碳环二基”包括通过从上述的“芳基”除去氢原子衍生的二价基团。其实例包括亚苯基、亚萘基等。更优选亚苯基。

[0329] 术语“芳香族杂环二基”包括通过从上述的“杂芳基”除去氢原子衍生的二价基团。实例包括吡咯二基、咪唑二基、吡唑二基、吡啶二基、哒嗪二基、嘧啶二基、吡嗪二基、三唑二基、三嗪二基、异噻唑二基、噻唑二基、噁二唑二基、异噻唑二基、噻唑二基、噻二唑二基、呋喃二基、噻吩二基、吡啶二基、苯并呋喃二基、苯并噻吩二基等。优选吡啶二基、苯并呋喃二基、苯并噻吩二基、呋喃二基或噻吩二基。尤其优选单环的芳香族杂环二基。更优选呋喃二基（尤其是呋喃-2,5-二基）或噻吩二基（尤其是噻吩-2,5-二基）。

[0330] 术语“低级烷基”是指 C1 到 C10、优选 C1 到 C6、并且更优选 C1 到 C4 的直链或支链烷基。实例包括甲基、乙基、正丙基、异丙基、正丁基、异丁基、仲丁基、叔丁基、正戊基、异戊基、新戊基、己基、异己基、正庚基、异庚基、正辛基、异辛基、正壬基、正癸基等。

[0331] 术语“低级烯基”是指在任意的位置具有一个或多个双键的 C2 到 C10、优选 C2 到 C6、并且更优选 C2 到 C4 的直链或支链烯基。实例包括乙烯基、丙烯基、异丙烯基、丁烯基、异丁烯基、异戊二烯基、丁间二烯基、戊烯基、异戊烯基、戊二烯基、己烯基、异己烯基、己二烯基、庚烯基、辛烯基、壬烯基、癸烯基等。

[0332] 术语“低级炔基”是指 C2 到 C10、优选 C2 到 C6、并且更优选 C2 到 C4 的直链或支链炔基。实例包括乙炔基、丙炔基、丁炔基、戊炔基、己炔基、庚炔基、辛炔基、壬炔基、癸炔基等。这些基团在任意的位置具有一个或多个三键并且可具有双键。

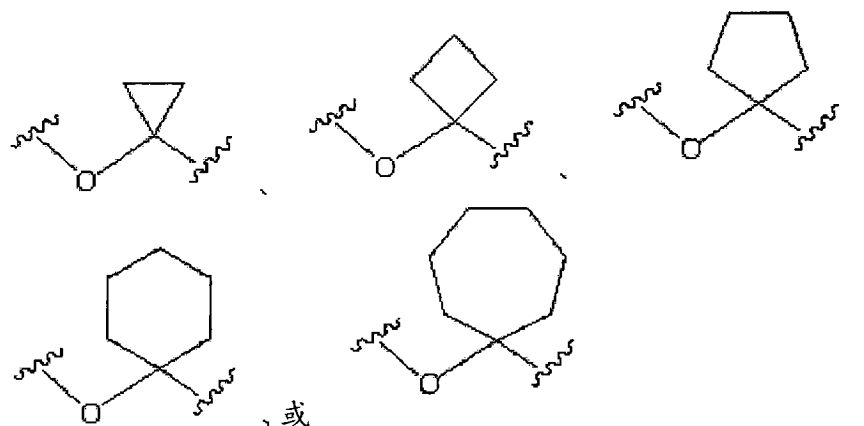
[0333] 术语“环烷基”包括 C3 到 C9 并且优选 C3 到 C6 环烷基。实例包括环丙基、环丁基、环戊基、环己基、环庚基、环辛基等。

[0334] 术语“亚环烷基”包括 C3 到 C9 并且优选 C3 到 C6 亚环烷基。实例包括亚环丙基、亚环丁基、亚环戊基、亚环己基、亚环庚基、亚环辛基等。尤其优选亚环丙基。

[0335] “任选地被 -O- 插入的亚环烷基”是指亚环烷基，为任选地被 1 或 2 个 -O- 插入的上述“亚环烷基”。实例包括下式的基团：

[0336] [式 38]

[0337]



[0338] 术语“酰基”包括 (a) 被上述“烷基”或“烯基”取代的羰基，(b) 被上述“环烷基”取代的羰基，(c) 被上述“芳基”取代的羰基或 (d) 甲酰基。实例包括甲酰基、乙酰基、丙酰基、丁酰基、异丁酰基、戊酰基、新戊酰基、己酰基、丙烯酰基、丙炔酰基、异丁烯酰基、巴豆酰基、环丙基羰基、环己基羰基、环辛基羰基、苯甲酰基等。

[0339] 术语“低级亚烷基”包括是指 C1 到 10、优选 C1 到 6、并且更优选 C1 到 3 的直链或支链亚烷基。实例包括亚甲基、亚乙基、1,3-亚丙基、1,4-亚丁基、1,5-亚戊基、1,6-亚己基、甲基亚甲基、亚丙基、二甲基亚甲基、1,1-二甲基亚乙基、1,2-二甲基亚乙基等。尤其优选亚甲基、亚乙基或二甲基亚甲基。

[0340] “任选地被 -O- 插入的低级亚烷基”是指亚烷基，为任选地被 1 到 3 个 -O- 插入的上述“亚烷基”。还包括在末端插入 -O- 的亚烷基。实例包括 -O-CH₂-、-CH₂-O-、-CH₂-O-CH₂-、-O-CH₂-CH₂-、-CH₂-CH₂-O-、-O-CH(CH₃)-、-O-C(CH₃)₂-、-O-CH₂-CH₂-O-、-O-CH(CH₃)-O-、-O-C(CH₃)₂-O- 等。

[0341] “-O- 任选被取代的低级亚烷基”是指 -O- 插入在末端的亚烷基。

[0342] 术语“低级亚烯基”包括是指在任意的位置具有一个或多个双键的 C2 到 C10、优选 C2 到 C6、并且更优选 C2 到 C4 的直链或支链亚烯基。实例包括亚乙烯基、亚丙烯基等。

[0343] 术语“卤素”是指氟、氯、溴或碘。特别地，优选氟、氯或溴。

[0344] “低级烷氧基”的烷基部分与上述“低级烷基”相同。

[0345] “任选被取代的低级烷基”、“任选被取代的低级烷基磺酰基”、“任选被取代的低级烯基”、“任选被取代的低级炔基”、“任选被取代的低级亚烷基”、“任选被取代的低级亚

烯基”、“任选被取代的低级烷氧基”或“任选被取代的酰基”的取代基的实例包括卤素、羟基、任选被取代的低级烷氧基、任选被取代的低级炔氧基、任选被取代的氨基、巯基、任选被取代的低级烷硫基、酰基、酰氧基、任选被取代的亚胺基、羧基、任选被取代的低级烷氧基羰基、任选被取代的氨基甲酰基、任选被取代的硫代氨基甲酰基、任选被取代的氨基甲酰氧基、任选被取代的硫代氨基甲酰氧基、任选被取代的氨基磺酰基、任选被取代的低级烷基磺酰基、任选被取代的低级烷基磺酰氧基、氰基、硝基、任选被取代的环烷基、任选被取代的环烷氧基、任选被取代的芳基、任选被取代的芳氧基、任选被取代的芳硫基、任选被取代的芳基磺酰基、任选被取代的芳基磺酰氧基、任选被取代的杂环、任选被取代的杂环氧基、任选被取代的低级亚烷基、任选被取代的低级亚烷基二氧基和氧代。它们可以在任意的位置被选自上述的一个或多个基团取代。在任选被取代的低级亚烷基或任选被取代的低级亚烷基二氧基为取代基的情况中，两个键结合于一个碳原子形成螺环，或者结合于不同的原子并且与相邻的碳原子一起形成环。

[0346] “杂环氧基”的杂环部分与上述“杂环”相同。

[0347] “任选被取代的单环芳基”、“任选被取代的单环杂芳基”、“任选被取代的芳基”、“任选被取代的芳烷基”、“任选被取代的芳氧基”、“任选被取代的芳硫基”、“任选被取代的杂芳基”、“任选被取代的杂芳烷基”、“任选被取代的杂芳氧基”、“任选被取代的杂芳硫基”、“被取代的稠合芳基”、“被取代的稠合杂芳基”、“任选被取代的芳基磺酰基”、“任选被取代的芳香族碳环二基”、“任选被取代的芳香族杂环二基”或“任选被取代的非芳香族杂环二基”的取代基的实例包括任选被取代的低级烷基、任选被取代的低级烯基、任选被取代的低级炔基、任选被取代的低级烯基氧基、卤素、羟基、任选被取代的低级烷氧基、任选被取代的低级炔氧基、任选被取代的氨基、巯基、任选被取代的低级烷硫基、酰基、酰氧基、任选被取代的亚胺基、羧基、任选被取代的低级烷氧基羰基、任选被取代的氨基甲酰基、任选被取代的硫代氨基甲酰基、任选被取代的氨基甲酰氧基、任选被取代的硫代氨基甲酰氧基、任选被取代的氨基磺酰基、任选被取代的低级烷基磺酰基、任选被取代的低级烷基磺酰氧基、氰基、硝基、任选被取代的环烷基、任选被取代的环烷氧基、任选被取代的芳基、任选被取代的芳氧基、任选被取代的芳硫基、任选被取代的芳基磺酰基、任选被取代的芳基磺酰氧基、任选被取代的杂环、任选被取代的杂环氧基、任选被取代的低级亚烷基和任选被取代的低级亚烷基二氧基。它们可以在任意的位置被选自上述的一个或多个基团取代。在任选被取代的低级亚烷基或任选被取代的低级亚烷基二氧基为取代基的情况中，键可结合于不同的原子，并且可与相邻碳原子的一起形成环。

[0348] 上述取代基的优选实例包括卤素、羟基、任选被取代的低级烷基（取代基为卤素或羟基）、任选被取代的低级烯基（取代基为卤素或羟基）、任选被取代的低级烷氧基（取代基为卤素或芳基）、羧基、低级烷氧基羰基、任选被取代的氨基甲酰基（取代基为低级烷基或芳基）、任选被取代的氨基（取代基为酰基或低级烷基）、巯基、低级烷硫基、酰基、酰氧基、氰基、硝基、芳基、杂环、低级亚烷基和低级亚烷基二氧基。特别优选卤素或任选被取代的低级烷基（取代基为卤素）。

[0349] “被取代的苯并呋喃基”、“被取代的苯并噁吩基”、“被取代的 benzopyronyl”、“被取代的苯并噁唑基”、“被取代的苯并异噁唑基”、“被取代的苯并噻唑基”、“被取代的苯并异噻唑基”、“被取代的苯并咪唑基”或“被取代的苯并吡唑基”的取代基为与上述“被取代的

稠合杂芳基”的取代基相同。

[0350] “任选被取代的亚苯基”的取代基与“任选被取代的芳香族碳环二基”的取代基相同。

[0351] “任选被取代的吡啶二基”、“任选被取代的苯并呋喃二基”、“任选被取代的苯并噻吩二基”、“任选被取代的呋喃二基”或“任选被取代的噻吩二基”的取代基与上述“任选被取代的芳香族杂环二基”的取代基相同。

[0352] “任选被取代的非芳香族杂环二基”的取代基的实例包括卤素、羟基、任选被取代的低级烷氧基、任选被取代的低级炔氧基、任选被取代的氨基、巯基、任选被取代的低级烷硫基、酰基、酰氧基、任选被取代的亚胺基、羧基、任选被取代的低级烷氧基羰基、任选被取代的氨基甲酰基、任选被取代的硫代氨基甲酰基、任选被取代的氨基甲酰氧基、任选被取代的硫代氨基甲酰氧基、任选被取代的氨基磺酰基、任选被取代的低级烷基磺酰基、任选被取代的低级烷基磺酰氧基、氰基、硝基、任选被取代的环烷基、任选被取代的环烷氧基、任选被取代的芳基、任选被取代的芳氧基、任选被取代的芳硫基、任选被取代的芳基磺酰基、任选被取代的芳基磺酰氧基、任选被取代的杂环、任选被取代的杂环氧基、任选被取代的低级亚烷基、任选被取代的低级亚烷基二氧基和氧代。它可以在任意的位置任选地被选自上述的一个或多个基团取代。在任选被取代的低级亚烷基或任选被取代的低级亚烷基二氧基为取代基的情况中，两个键结合于一个碳原子形成螺环，或者结合于不同的原子并且与相邻的碳原子一起形成环。

[0353] “任选被取代的低级炔氧基”、“任选被取代的低级烷硫基”、“任选被取代的低级烷氧基羰基”、“任选被取代的低级烷基磺酰氧基”、“任选被取代的环烷基”、“任选被取代的环烷氧基”、“任选被取代的芳基磺酰基”、“任选被取代的芳基磺酰氧基”、“任选被取代的杂环”、“任选被取代的杂环氧基”或“任选被取代的低级亚烷基二氧基”的取代基与上述“任选被取代的低级烷基”的取代基相同。

[0354] “任选被取代的氨基”、“任选被取代的亚胺基”、“任选被取代的氨基甲酰基”、“任选被取代的硫代氨基甲酰基”、“任选被取代的氨基甲酰氧基”、“任选被取代的硫代氨基甲酰氧基”或“任选被取代的氨基磺酰基”的取代基与上述“任选被取代的低级烷基”的取代基相同。这些取代基可为氮原子上的单取代或二取代。特别优选低级烷基、芳基、杂环、酰基、低级烷氧基羰基、低级烷基磺酰基或芳基磺酰基。

[0355] 以下说明式 (I) 的化合物的各个取代基的优选实施方案。

[0356] 环 Q 为任选被取代的单环芳基、任选被取代的单环杂芳基、任选被取代的稠合芳基或任选被取代的稠合杂芳基。优选的实例包括被一个或多个 R^2 取代并且任选被其它基团取代的单环芳基、被一个或多个 R^2 取代并且任选被其它基团取代的单环杂芳基，其中每个 R^2 为卤素、任选被取代的烷基、任选被取代的芳基、任选被取代的芳烷基、任选被取代的芳氧基、任选被取代的芳硫基、任选被取代的杂芳基、任选被取代的杂芳烷基、任选被取代的杂芳氧基或任选被取代的杂芳硫基、被取代的稠合芳基或被取代的稠合杂芳基。特别优选被一个 R^2 取代并且任选被其它基团取代的单环杂芳基，其中 R^2 为卤素、任选被取代的烷基或任选被取代的芳基、被取代的稠合芳基或被取代的稠合杂芳基。

[0357] “并且任选被其它基团取代的”是指除了取代基 R^2 之外，任选被取代。所述取代基可为与 R^2 相同的取代基。

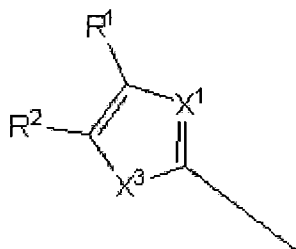
[0358] 被取代的稠合杂芳基的实例包括被取代的苯并呋喃基、被取代的苯并噻吩基、被取代的 benzopyronyl、被取代的苯并噁唑基、被取代的苯并异噁唑基、被取代的苯并噻唑基、被取代的苯并异噻唑基、被取代的苯并咪唑基、被取代的苯并吡唑基等。特别优选被取代的苯并噻唑基,其中取代基为卤素、任选被取代的低级烷基、任选被取代的低级烷氧基、芳基、低级烷基磺酰基或任选被取代的氨基甲酰基。

[0359] 特别优选的环 Q 的实例包括以下。

[0360] 下式的基团:

[0361] [式 39]

[0362]



[0363] R^1 为氢、卤素、羟基、任选被取代的低级烷基、任选被取代的低级烯基、任选被取代的低级炔基、任选被取代的低级烷氧基或任选被取代的芳基,

[0364] R^2 为卤素、任选被取代的烷基、任选被取代的芳基、任选被取代的芳氧基、任选被取代的芳硫基或任选被取代的杂芳基,或

[0365] R^1 和 R^2 可以与相邻碳原子一起形成任选被取代的环,

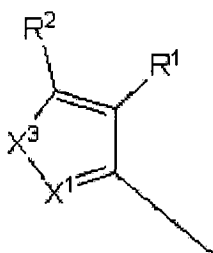
[0366] X^1 为 N 或 CR^{10} , 和

[0367] X^3 为 NR^{11} 、O 或 S, 其中 R^{10} 和 R^{11} 各自独立地为氢或任选被取代的低级烷基,

[0368] 下式的基团:

[0369] [式 40]

[0370]



[0371] R^1 为氢、卤素、羟基、任选被取代的低级烷基、任选被取代的低级烯基、任选被取代的低级炔基或任选被取代的低级烷氧基,

[0372] R^2 为卤素、任选被取代的烷基、任选被取代的芳基、任选被取代的芳氧基、任选被取代的芳硫基或任选被取代的杂芳基,或

[0373] R^1 和 R^2 可以与相邻碳原子一起形成任选被取代的环,

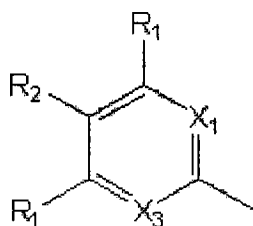
[0374] X^1 为 N 或 CR^{12} , 和

[0375] X^3 为 NR^{13} 、O 或 S, 其中 R^{12} 和 R^{13} 各自独立地为氢或任选被取代的低级烷基, 或

[0376] 下式的基团:

[0377] [式 41]

[0378]



[0379] R^1 各自独立地为氢、卤素、羟基、任选被取代的低级烷基、任选被取代的低级烯基、任选被取代的低级炔基或任选被取代的低级烷氧基，

[0380] R^2 为卤素、任选被取代的烷基、任选被取代的芳基、任选被取代的芳氧基、任选被取代的芳硫基或任选被取代的杂芳基，

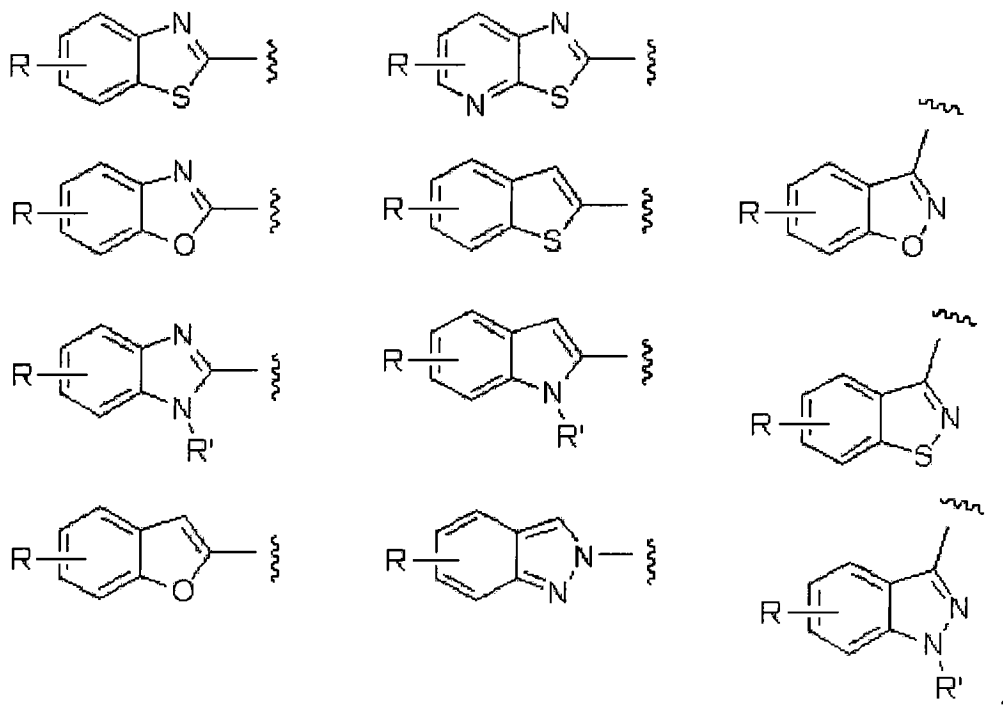
[0381] X^1 为 N 或 CR^{19} ，和

[0382] X^3 为 N 或 CR^{20} ，其中 R^{19} 和 R^{20} 各自独立地为氢或任选被取代的低级烷基，条件是 X^1 或 X^3 为 N。

[0383] 以下实施方案优选作为环 Q 的“被取代的稠合杂芳基”。

[0384] [式 42]

[0385]



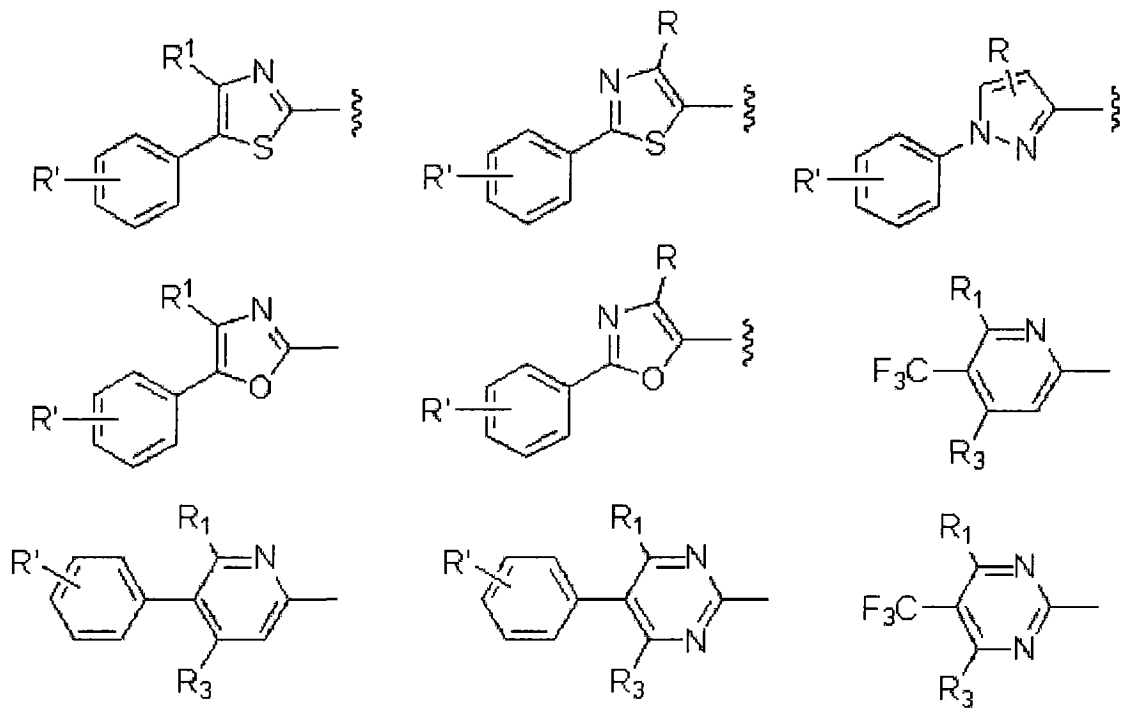
[0386] R 为任选被取代的低级烷基、任选被取代的低级烯基、任选被取代的低级炔基、任选被取代的低级烯基氧基、卤素、羟基、任选被取代的低级烷氧基、任选被取代的低级炔氧基、任选被取代的氨基、巯基、任选被取代的低级烷硫基、酰基、酰氧基、任选被取代的亚胺基、羧基、任选被取代的低级烷氧基羰基、任选被取代的氨基甲酰基、任选被取代的硫代氨基甲酰基、任选被取代的氨基甲酰氧基、任选被取代的硫代氨基甲酰氧基、任选被取代的氨基磺酰基、任选被取代的低级烷基磺酰基、任选被取代的低级烷基磺酰氧基、氰基、硝基、任选被取代的环烷基、任选被取代的环烷氧基、任选被取代的芳基、任选被取代的芳氧基、任选被取代的芳硫基、任选被取代的芳基磺酰基、任选被取代的芳基磺酰氧基、任选被取代的杂环、任选被取代的杂环氧基，

[0387] R' 为氢或具有与上述 R 相同的含义, 并且, 条件是当 R' 具有与上述 R 相同的含义时, R 可为氢。

[0388] 以下实施方案也优选作为环 Q 的“被一个或多个 R² 取代并且任选被其它基团取代的单环杂芳基”。

[0389] [式 43]

[0390]



[0391] R¹ 为氢、卤素、羟基、任选被取代的低级烷基、任选被取代的低级烯基、任选被取代的低级炔基、任选被取代的低级烷氧基或任选被取代的芳基, 和

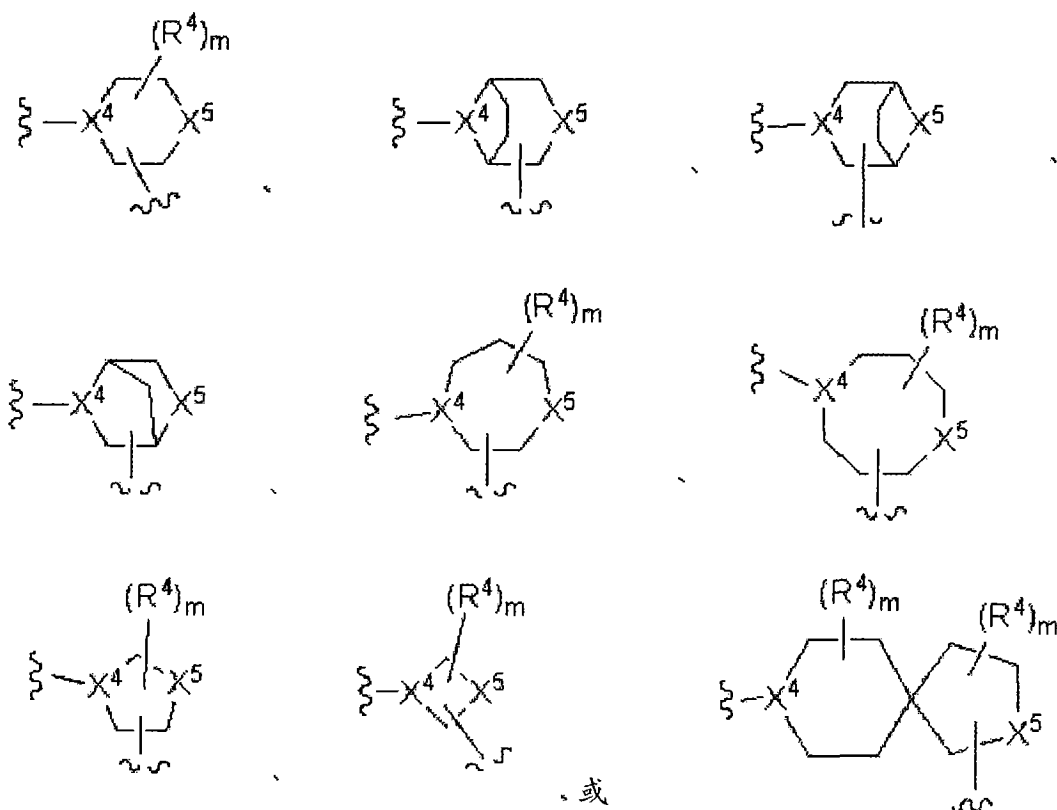
[0392] R 和 R' 各自独立地为氢、卤素、羟基、任选被取代的低级烷氧基、任选被取代的低级炔基氧基、任选被取代的氨基、巯基、任选被取代的低级烷硫基、酰基、酰氧基、任选被取代的亚胺基、羧基、任选被取代的低级烷氧基羰基、任选被取代的氨基甲酰基、任选被取代的硫代氨基甲酰基、任选被取代的氨基甲酰氧基、任选被取代的硫代氨基甲酰氧基、任选被取代的氨基磺酰基、任选被取代的低级烷基磺酰基、任选被取代的低级烷基磺酰氧基、氰基、硝基、任选被取代的环烷基、任选被取代的环烷氧基、任选被取代的芳基、任选被取代的芳氧基、任选被取代的芳硫基、任选被取代的芳基磺酰基、任选被取代的芳基磺酰氧基、任选被取代的杂环、任选被取代的杂环基氧基等。

[0393] Y¹ 为键、-NR⁶- 或 -NR⁶-CO-, 其中 R⁶ 为氢或任选被取代的低级烷基。特别优选为键。

[0394] 环 A 为任选被取代的非芳香族杂环二基, 条件是当 Y¹ 为键时, 环 Q 结合于环 A 的氮原子。特别优选的实例包括下式的基团:

[0395] [式 44]

[0396]



[0397] 其中

[0398] X^4 为 N 或 CR^5 , 其中 R^5 为氢或任选被取代的低级烷基,

[0399] X^5 为 O、S、 NR^{16} 或 $CR^{17}R^{18}$, 其中 R^{16} 到 R^{18} 各自独立地为氢、任选被取代的低级烷基、氰基、任选被取代的非芳香族杂环、任选被取代的杂芳基、任选被取代的氨基、任选被取代的低级烷氧基、芳基低级烷基或任选被取代的环烷基, 条件是排除以下化合物: 其中 X^4 为 CR^5 和 X^5 为 $CR^{17}R^{18}$,

[0400] R^4 各自独立地为卤素、任选被取代的低级烷基、任选被取代的低级烯基、任选被取代的低级炔基、任选被取代的低级烷氧基或任选被取代的芳基, 和

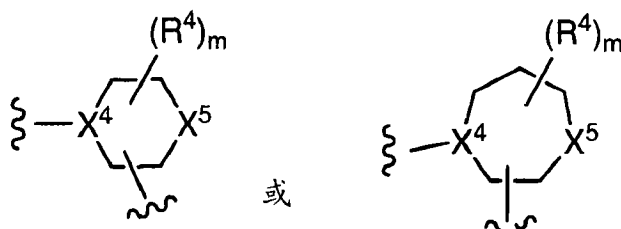
[0401] m 为 0 到 2 的整数,

[0402] 来自 X^4 的键结合于 Y^1 和另一个键结合于 Y^2 , 并且当 X^5 为 NR^{16} 或 $CR^{17}R^{18}$ 时, 另一个键可结合于 X^5 。

[0403] 更优选的实例包括下式的基团:

[0404] [式 45]

[0405]



[0406] 其中

[0407] X^4 为 N 或 CR^5 , 其中 R^5 为氢或任选被取代的低级烷基,

[0408] X^5 为 NR^{16} 或 $CR^{17}R^{18}$, 其中 R^{16} 到 R^{18} 各自独立地为氢、任选被取代的低级烷基、氰基、

任选被取代的非芳香族杂环、任选被取代的杂芳基、任选被取代的氨基、任选被取代的低级烷氧基、芳基低级烷基或任选被取代的环烷基,条件是排除以下化合物:其中 X^4 为 CR^5 和 X^5 为 $CR^{17}R^{18}$,

[0409] R^4 各自独立地为卤素、任选被取代的低级烷基、任选被取代的低级烯基、任选被取代的低级炔基、任选被取代的低级烷氧基或任选被取代的芳基,

[0410] m 为 0 到 2 的整数,

[0411] 来自 X^4 的键结合于 Y^1 和另一个键结合于 Y^2 , 并且当 X^5 为 NR^{16} 或 $CR^{17}R^{18}$ 时, 另一个键可结合于 X^5 。

[0412] 更优选的实例包括下式的基团:

[0413] [式 46]

[0414]



[0415] 其中

[0416] X^4 为 N,

[0417] X^5 为 NR^{16} 或 $CR^{17}R^{18}$, 其中 R^{16} 到 R^{18} 各自独立地为氢、任选被取代的低级烷基、氰基、任选被取代的非芳香族杂环、任选被取代的杂芳基、任选被取代的氨基、任选被取代的低级烷氧基、芳基低级烷基或任选被取代的环烷基,

[0418] R^4 各自独立地为卤素、任选被取代的低级烷基、任选被取代的低级烯基、任选被取代的低级炔基、任选被取代的低级烷氧基或任选被取代的芳基,

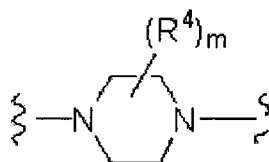
[0419] m 为 0 到 2 的整数,

[0420] 来自 X^4 的键结合于 Y^1 和另一个键结合于 Y^2 。

[0421] 特别优选的 m 的实例包括 1 和 2。特别地, R^4 各自独立地为任选被取代的低级烷基并且优选的实例包括 C1 到 C4 直链或支链烷基。更优选的实例包括下式的基团:

[0422] [式 47]

[0423]



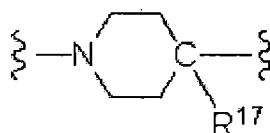
[0424] R^4 各自独立地为卤素、任选被取代的低级烷基、任选被取代的低级烯基、任选被取代的低级炔基或任选被取代的低级烷氧基, 和

[0425] m 为 1 或 2 的整数, 或

[0426] 下式的基团:

[0427] [式 48]

[0428]



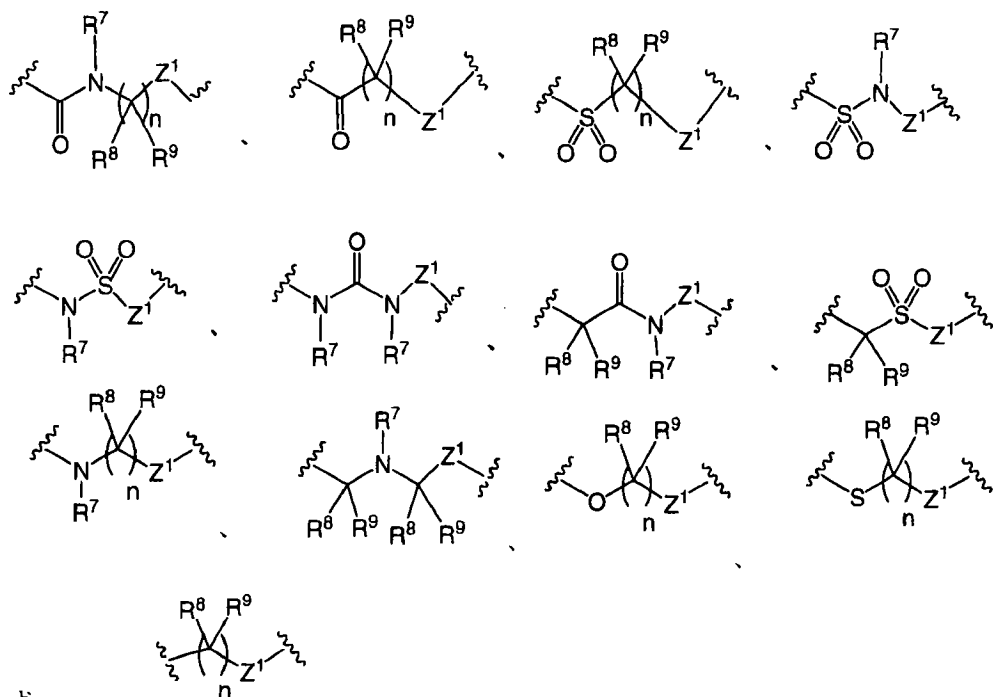
[0429] R^{17} 为任选被取代的低级烷基、氰基、任选被取代的非芳香族杂环、任选被取代的杂芳基、任选被取代的氨基、任选被取代的低级烷氧基、芳基低级烷基或任选被取代的环烷基，

[0430] 来自 N 的键结合于 Y^1 并且来自 C 的键结合于 Y^2 。

[0431] 式 $-Y^2Z^1-$ 的基团为下式的基团：

[0432] [式 49]

[0433]



或

[0434] R^7 各自独立地为氢、任选被取代的低级烷基或任选被取代的环烷基，

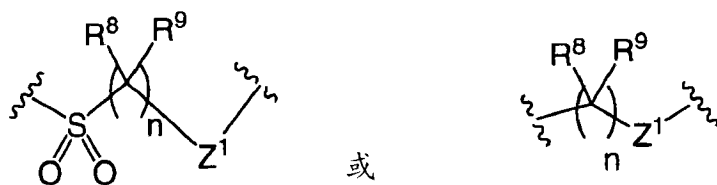
[0435] R^8 和 R^9 各自独立地为氢或任选被取代的低级烷基，

[0436] n 为 0 到 3 的整数，

[0437] Z^1 为键、 $-O-$ 、 $-S-$ 或 $-NR^9-$ ，其中 R^9 为氢、任选被取代的低级烷基、任选被取代的酰基、任选被取代的低级烷基磺酰基或任选被取代的芳基磺酰基。特别优选的实例包括下式的基团：

[0438] [式 50]

[0439]



[0440] R^8 和 R^9 各自独立地为氢或低级烷基，

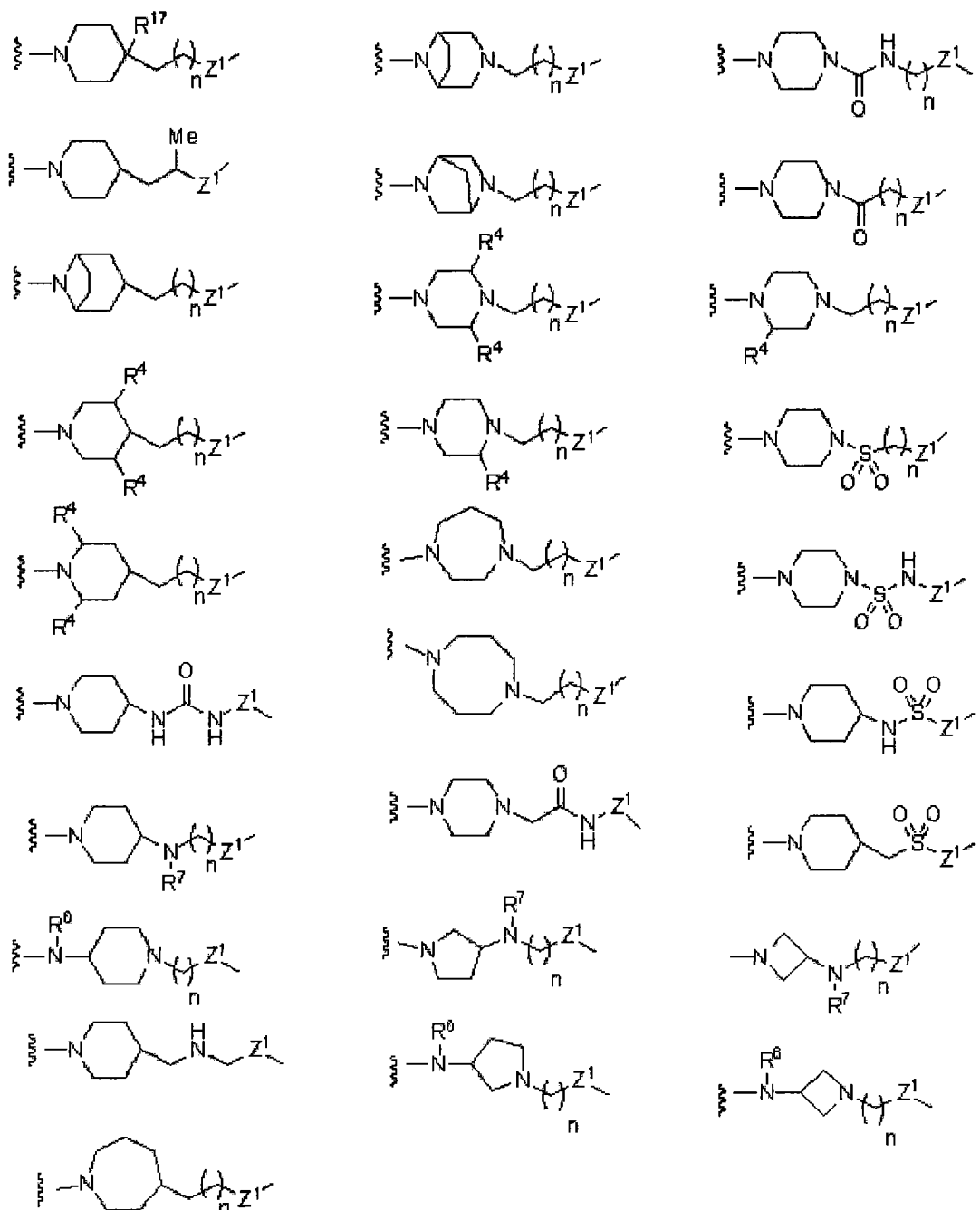
[0441] n 为 0 到 2 的整数，和

[0442] Z^1 为键、-O- 或 -S-。

[0443] 以下实施方案也优选作为式 $-Y^1-$ 环 A- Y^2-Z^1- 的基团。

[0444] [式 51]

[0445]



[0446] R^{17} 为氢、任选被取代的低级烷基、氰基、任选被取代的非芳香族杂环、任选被取代的杂芳基、任选被取代的氨基、任选被取代的低级烷氧基、芳基低级烷基或任选被取代的环烷基，

[0447] R^6 为氢或任选被取代的低级烷基，

[0448] R^7 为氢、任选被取代的低级烷基或任选被取代的环烷基，

[0449] R^4 各自独立地为卤素、任选被取代的低级烷基、任选被取代的低级烯基、任选被取代的低级炔基、任选被取代的低级烷氧基或任选被取代的芳基，

[0450] Z^1 为键、O、S 或 NR^9 ，其中 R^9 为氢、任选被取代的低级烷基、任选被取代的酰基、任选被取代的低级烷基磺酰基或任选被取代的芳基磺酰基，

[0451] n 为 0 到 3 的整数。

[0452] R^{17} 特别地为非芳香族杂环。优选的实例包括吡咯烷基、哌啶基、氮杂环庚烷基、吗啉基等。

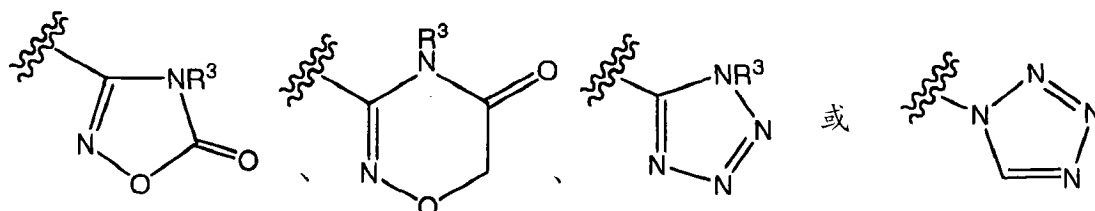
[0453] 环 B 为任选被取代的芳香族碳环二基或任选被取代的芳香族杂环二基。特别优选的实例包括任选被取代的亚苯基、任选被取代的呋喃二基和任选被取代的噻吩二基，和所述亚苯基、呋喃二基或噻吩二基的取代基选自卤素、低级烷基和低级烷氧基。

[0454] Y^3 为键、任选地被 -O- 插入的任选被取代的低级亚烷基、任选地被 -O- 插入的亚环烷基或任选被取代的低级亚烯基。特别优选的实例包括键、任选被取代的低级亚烷基、-O- 任选被取代的低级亚烷基和任选被取代的低级亚烯基，和所述低级亚烷基或低级亚烯基的取代基选自低级亚烷基和卤素。

[0455] Z^2 为 $COOR^3$ 、 $C(=NR^3)NR^{14}OR^{15}$ 、 $CONHCN$ 或下式的基团：

[0456] [式 52]

[0457]

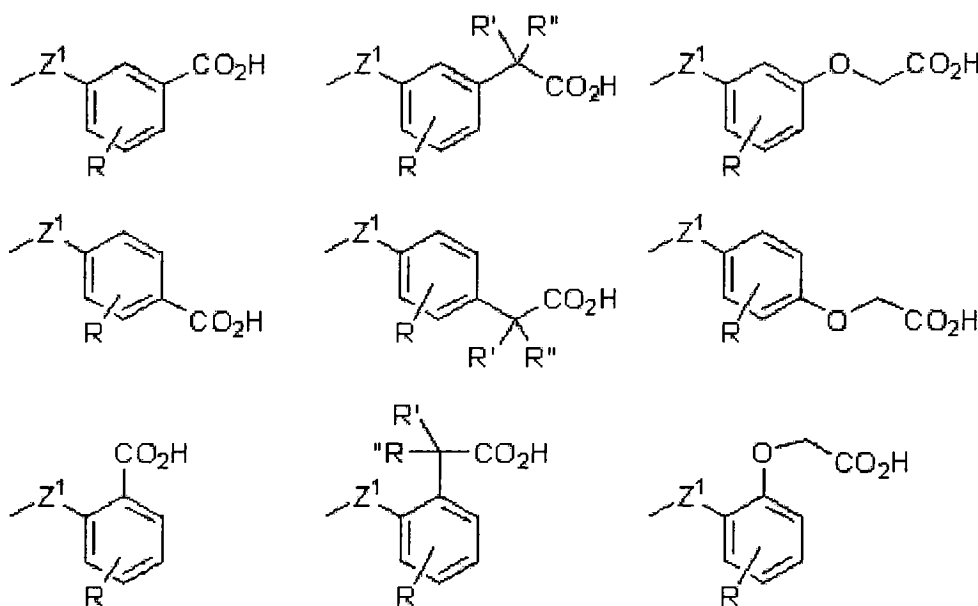


[0458] R^3 、 R^{14} 和 R^{15} 各自独立地为氢、任选被取代的低级烷基、任选被取代的低级烯基、任选被取代的芳基或任选被取代的杂芳基。特别优选的实例包括 $COOR^3$ ，其中 R^3 为氢或任选被取代的低级烷基。

[0459] 以下实施方案也优选作为式 $-Z^1-$ 环 B- y^3-Z^2 的基团。

[0460] [式 53]

[0461]



[0462] Z^1 为键、-O-、-S- 或 $-NR^9$ ，其中 R^9 为氢、任选被取代的低级烷基、任选被取代的酰

基、任选被取代的低级烷基磺酰基或任选被取代的芳基磺酰基,和

[0463] R、R' 和 R'' 各自独立地为氢、卤素、羟基、任选被取代的低级烷氧基、任选被取代的低级炔氧基、任选被取代的氨基、巯基、任选被取代的低级烷基硫基、酰基、酰氧基、任选被取代的亚胺基、羧基、任选被取代的低级烷氧基羰基、任选被取代的氨基甲酰基、任选被取代的硫代氨基甲酰基、任选被取代的氨基甲酰氧基、任选被取代的硫代氨基甲酰氧基、任选被取代的氨基磺酰基、任选被取代的低级烷基磺酰基、任选被取代的低级烷基磺酰氧基、氰基、硝基、任选被取代的环烷基、任选被取代的环烷氧基、任选被取代的芳基、任选被取代的芳氧基、任选被取代的芳硫基、任选被取代的芳基磺酰基、任选被取代的芳基磺酰氧基、任选被取代的杂环、任选被取代的杂环基氧基、任选被取代的低级亚烷基、任选被取代的低级亚烷基二氧基或氧代。

[0464] 本发明的化合物包括各个化合物的可生产的和可药用的盐。可药用盐的实例包括无机酸盐、有机酸盐、有机盐基团的盐、碱金属盐和碱土金属盐,无机酸例如盐酸、硫酸、硝酸、磷酸等,有机酸例如对甲苯磺酸、甲磺酸、草酸、柠檬酸等,有机盐基团例如铵、三甲基铵或三乙基铵,碱金属例如钠或钾,碱土金属例如钙、镁等。

[0465] 本发明的化合物包括其溶剂化物,并且可以有任何数量的溶剂分子与化合物 (I) 配位。优选水合物。

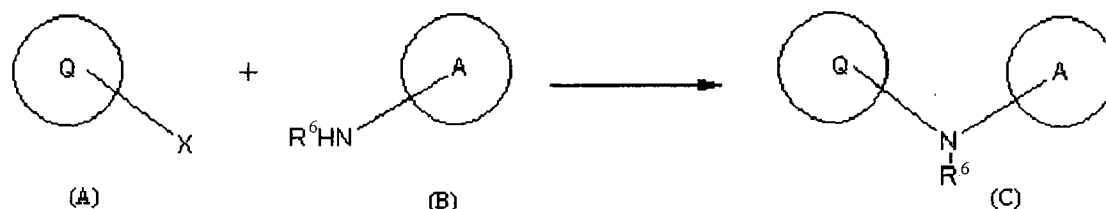
[0466] 当本发明的化合物 (I) 具有不对称碳原子时,其包含消旋体和所有的立体异构体(非对映异构体、对映体等)。当本发明的化合物 (I) 具有双键并且在双键的取代基位置上有几何异构体时,其包括两种异构体。

[0467] 生产本发明的化合物的通用方法描述如下。

[0468] 步骤 A

[0469] [式 54]

[0470]



[0471] 其中 X 为卤素等,和其它符号具有与上述 (1) 定义的相同的含义。

[0472] 这个步骤是通过使化合物 (A) 和 (B) 反应生产化合物 (C) 的方法。

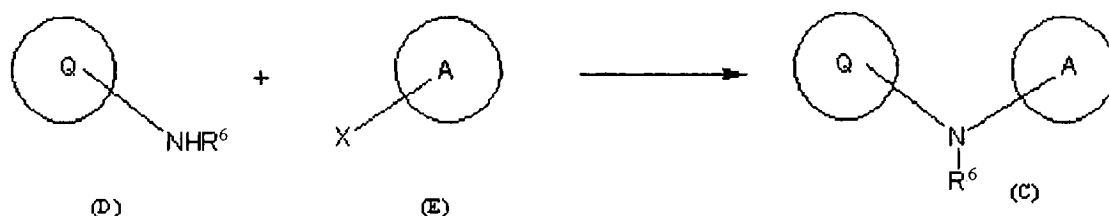
[0473] 这个步骤特别优选尤其在碱的存在下进行。碱的实例包括碳酸钾、碳酸钠、碳酸氢钠、氢氧化钠、氢化钠、三乙胺、N,N-二异丙基乙胺等。反应溶剂的实例包括 N,N-二甲基甲酰胺、四氢呋喃、二噁烷、二氯甲烷、乙腈、二甲亚砜等。反应可以在室温到 100℃ 进行。

[0474] 可将酸加成盐用作化合物 (B)。在该情况下,增加用于反应中的碱的量。

[0475] 步骤 B

[0476] [式 55]

[0477]



[0478] 其中 X 为卤素等,和其它符号具有与上述 (1) 定义的相同的含义。

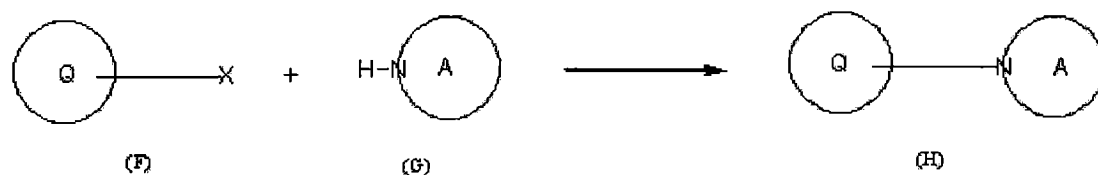
[0479] 这个步骤是通过使化合物 (D) 和 (E) 反应生产化合物 (C) 的方法。

[0480] 这个步骤可以在与步骤 B 相同的条件下进行。

[0481] 步骤 C

[0482] [式 56]

[0483]



[0484] 其中 X 为卤素等,和其它符号具有与上述 (1) 定义的相同的含义。

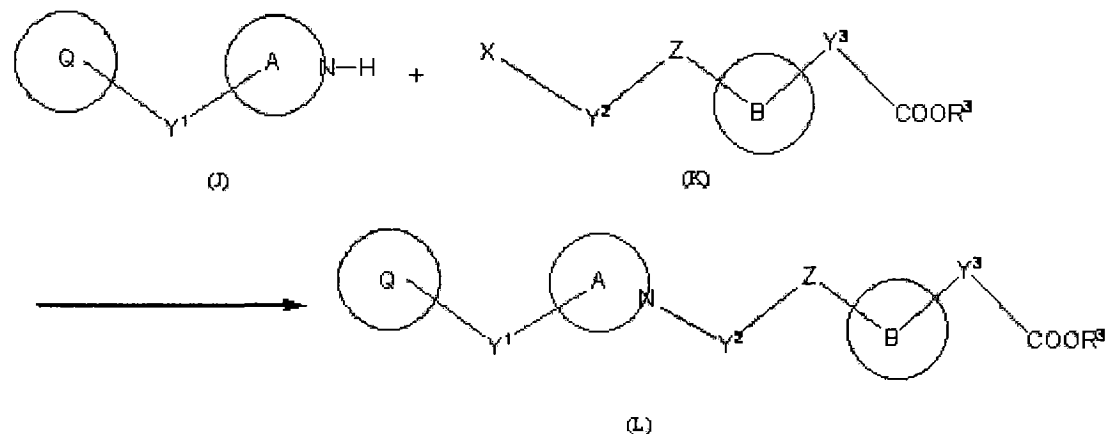
[0485] 这个步骤是通过使化合物 (F) 和 (G) 反应生产化合物 (H) 的方法。

[0486] 这个步骤可以在与步骤 A 和 B 相同的条件下进行。

[0487] 步骤 D

[0488] [式 57]

[0489]



[0490] 其中 X 为卤素等,和其它符号具有与上述 (1) 定义的相同的含义。

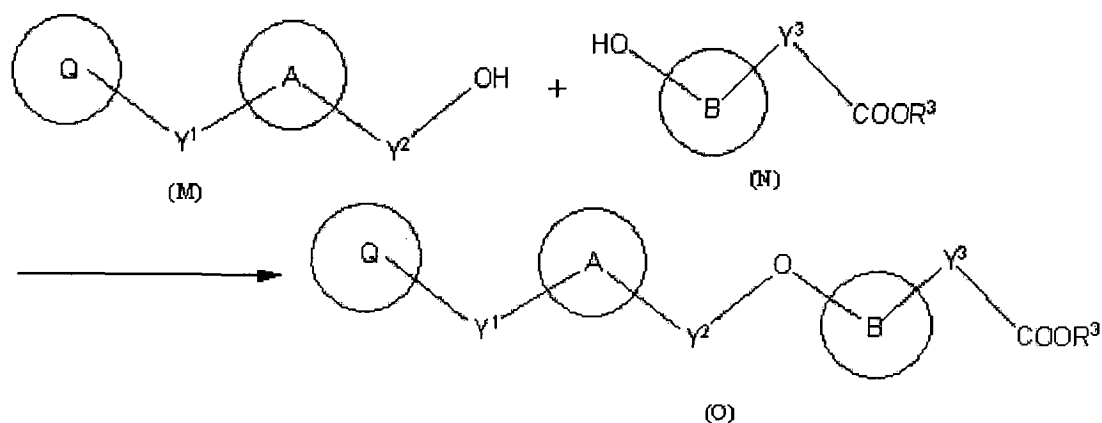
[0491] 这个步骤是通过使化合物 (J) 和 (K) 反应生产化合物 (L) 的方法。

[0492] 这个步骤可以在与步骤 A、B 和 C 相同的条件下进行。

[0493] 步骤 E

[0494] [式 58]

[0495]



[0496] 其中各个符号具有与上述 (1) 中定义的相同的含义。

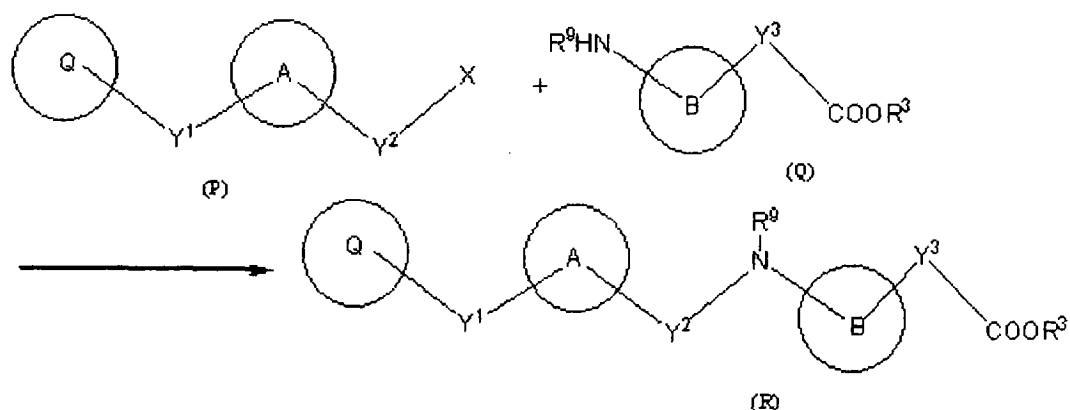
[0497] 这个步骤是通过使化合物 (M) 和 (N) 反应生产化合物 (O) 的方法。

[0498] 这个步骤可以通过在偶氮二羧酸酯和三苯基膦的存在下通过 Mitsunobu 反应进行。代替偶氮二羧酸酯,可使用 1,1-偶氮二羰基二哌啶,N,N,N',N'-四甲基偶氮二甲酰胺等。代替三苯基膦,可使用三丁基膦等。反应溶剂的实例包括四氢呋喃、甲苯、苯等。反应可以在室温下进行。

[0499] 步骤 F

[0500] [式 59]

[0501]



[0502] 其中 X 为卤素等,和其它符号具有与上述 (1) 定义的相同的含义。

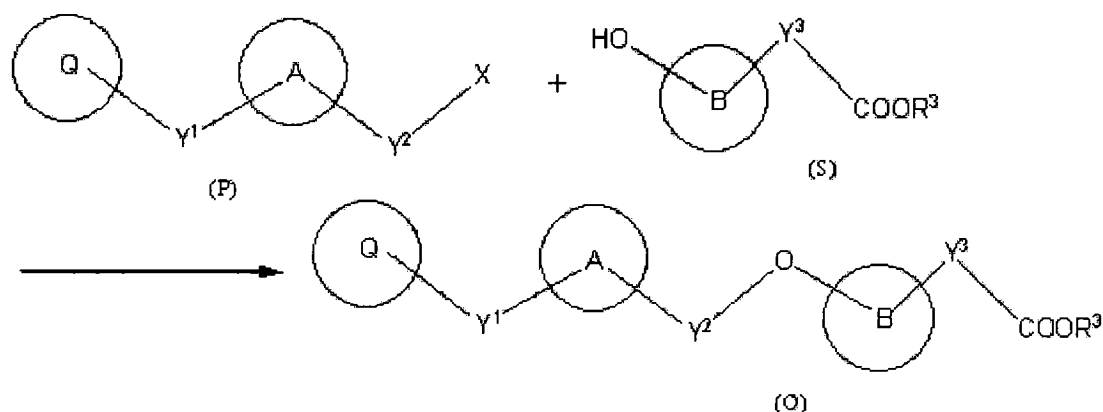
[0503] 这个步骤是通过使化合物 (P) 和 (Q) 反应生产化合物 (R) 的方法。

[0504] 这个步骤可以在与步骤 A、B、C 和 D 相同的条件下进行。

[0505] 步骤 G

[0506] [式 60]

[0507]



[0508] 其中 X 为卤素等,和其它符号具有与上述 (1) 定义的相同的含义。

[0509] 这个步骤是通过使化合物 (P) 和 (S) 反应生产化合物 (O) 的方法。

[0510] 这个步骤可以在与步骤 A、B、C、D 和 F 相同的条件下进行。

[0511] 当通过上述任何步骤得到的化合物为 COOR^3 酯时,这个化合物通过通常的方法水解,得到 COOH 羧酸。

[0512] 如有必要,在上述生产方法的适当的步骤中,可以通过公知的有机合成反应将任何取代基转化为不同的取代基。

[0513] 例如,当任何化合物具有卤素时,将其与醇在溶剂例如 DMF、四氢呋喃等中在碱例如氢氧化钠、氢氧化钾等和脱酸试剂例如碱金属氢氧化物、碱金属碳酸氢盐、碱金属碳酸盐、有机碱等的存在下在 -20°C 到 100°C 反应,得到取代基转化为低级烷氧基的化合物。

[0514] 当任何化合物具有烷基羟基时,其与氧化剂例如重铬酸吡啶鎓、琼斯试剂、二氧化锰、高锰酸钾、四氧化钨等在溶剂例如二甲基甲酰胺、四氢呋喃、二氯甲烷、苯、丙酮等中反应,得到取代基转化为羧基的化合物。

[0515] 如有必要,使其在化合物的氨基或羟基在适当的步骤中通过通常的方法保护之后进行反应,然后在适当的步骤中通过用酸或碱处理脱保护。

[0516] 作为氨基保护基,可使用邻苯二甲酰亚胺、低级烷氧基羰基(如,丁氧基羰基(Boc)),低级烯基氧基羰基,卤代烷氧基羰基,芳基低级烷氧基羰基,三烷基甲硅烷基,低级烷基磺酰基,卤代低级烷基磺酰基,芳基磺酰基,低级烷基羰基,芳基羰基,芳基低级烷基(如,苯甲基)等。

[0517] 作为羟基保护基,可使用烷基(如,叔丁基),芳烷基(三苯基甲基或苯甲基),三烷基甲硅烷基(如,叔丁基二甲基甲硅烷基或三异丙基甲硅烷基),烷基二芳基甲硅烷基(如,叔丁基二苯基甲硅烷基),三芳烷基甲硅烷基(如,三苯基甲硅烷基),烷氧基烷基(如,甲氧基甲基、1-乙氧基乙基或 1-甲基-1-甲氧基乙基),烷氧基烷氧基烷基(如,甲氧基乙氧基甲基),烷硫基烷基(如,甲硫基甲基),四氢吡喃基(如,四氢吡喃-2-基或 4-甲氧基四氢吡喃-4-基),四氢噻喃基(如,四氢噻喃-2-基),四氢呋喃基(如,四氢呋喃-2-基),四氢噻吩基(如,四氢噻吩-2-基),芳烷氧基烷基(如,苯甲基氧基甲基)烷基磺酰基,酰基,对甲苯磺酰基等。

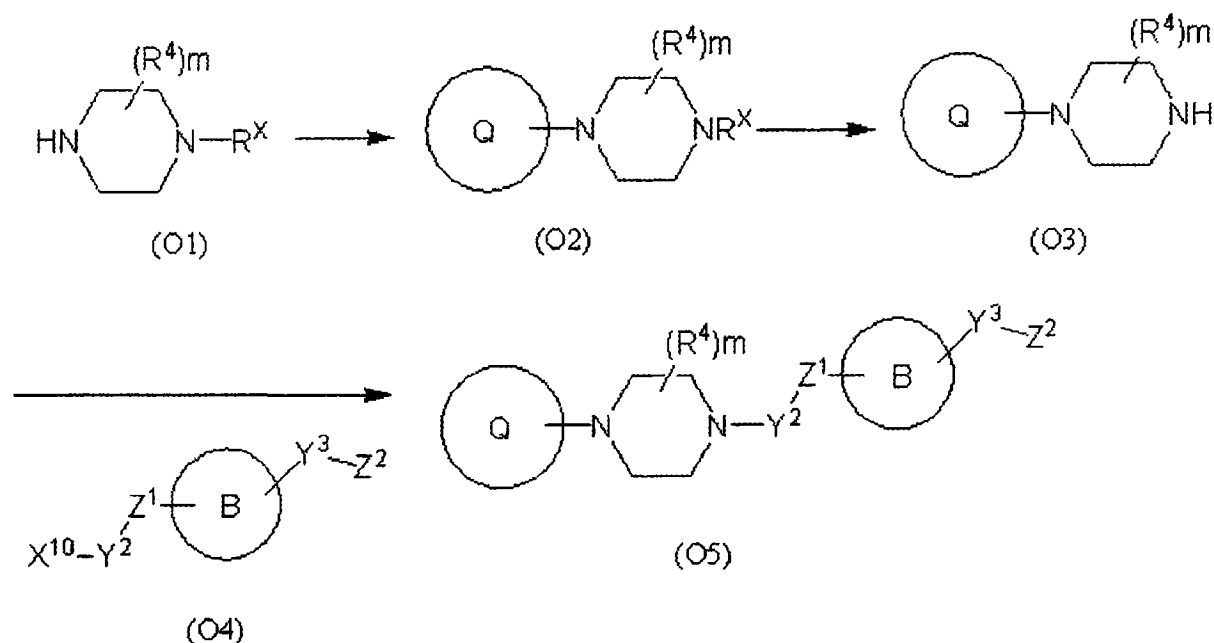
[0518] 脱保护反应在溶剂例如四氢呋喃、二甲基甲酰胺、乙醚、二氯甲烷、甲苯、苯、二甲苯、环己烷、己烷、氯仿、乙酸乙酯、乙酸丁酯、戊烷、庚烷、二噁烷、丙酮、乙腈或其混合溶剂中通过使用碱例如胍、吡啶、氢氧化钠、氢氧化钾等或酸例如盐酸、三氟乙酸、氢氟酸等进

行。

[0519] 步骤 H

[0520] [式 61]

[0521]



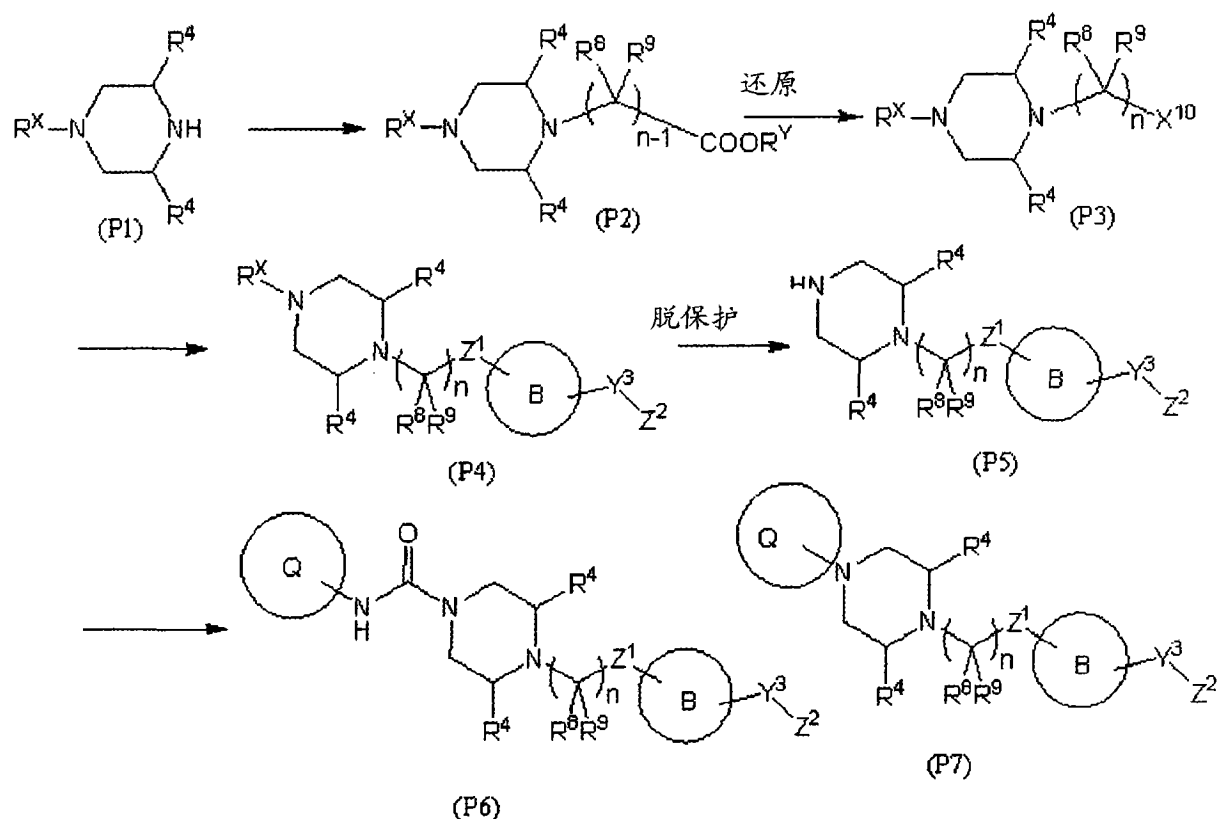
[0522] 其中 R^X 为氨基保护基（如，苯甲基或叔丁氧羰基）等， X^{10} 为卤素，并且其它符号具有与上述相同的含义。

[0523] 化合物 (O1) 在碱的存在下与具有环 Q 的衍生物反应得到化合物 (O2)。除去得到的化合物 (O2) 的保护基并将该化合物与化合物 (O4) 反应，得到化合物 (O5)。

[0524] 步骤 I

[0525] [式 62]

[0526]



[0527] 其中 R^{X} 为氨基保护基（如，苯甲基或叔丁氧羰基）等， R^{Y} 为低级烷基等， X^{10} 为羟基， Z^1 为 O, S 或 NR^9 ，和其它符号具有与上述相同的含义。

[0528] 式 $\text{X}-\text{C}(\text{R}^8\text{R}^9)_{n-1}-\text{COOR}^{\text{Y}}$ 的化合物在碱（如，碳酸钾）的存在下与化合物 (P1) 反应，得到化合物 (P2)。作为溶剂，可使用二甲基甲酰胺等。

[0529] 将得到的化合物 (P2) 还原，得到化合物 (P3)。还原可使用氢化铝锂等进行。

[0530] 得到的化合物 (P3) 与甲磺酰氯等反应，将 X^{10} 转化为离去基团并且与具有环 B 的化合物偶联。

[0531] 然后，通过 R^{X} 的脱保护得到化合物 (P5) 并使其与苯基异氰酸酯衍生物等反应，得到化合物 (P6)。

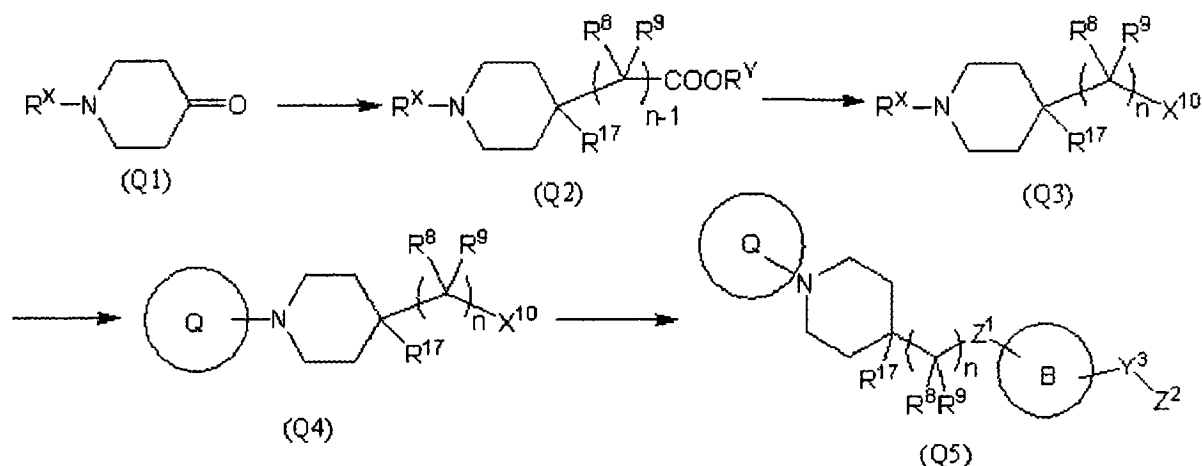
[0532] 通过与具有环 Q 的化合物反应还可以得到化合物 (P7)。

[0533] 可以通过将化合物 (P3) 的 X^{10} 转化为卤素并与具有环 B 的化合物反应得到其中 Z^1 为 $-\text{S}-$ 或 $-\text{NR}^9-$ 的化合物。

[0534] 步骤 J

[0535] [式 63]

[0536]



[0537] 其中 R^X 为氨基保护基（如，苯甲基或叔丁氧羰基）等， R^Y 为低级烷基等， X^{10} 为羟基或卤素， Z^1 为 $-O-$ 、 $-S-$ 或 $-NR^9-$ ，并且其它符号具有与上述相同的含义。

[0538] 在将化合物 (Q1) 转化为化合物 (Q2) 之后，将 $COOR^Y$ 还原。还原可以用氢化铝锂等进行。然后，进行 R^X 的脱保护。当保护基为苯甲基时，脱保护通过催化还原等进行。在脱保护之后，具有环 Q 的化合物在碱（如，碳酸钾）的存在下反应，得到化合物 (Q4)。然后，具有环 B 的化合物与得到的化合物 (Q4) 反应，得到化合物 (Q5)。也可以通过将化合物 (Q4) 的 X^{10} 转化为卤素并且与具有环 B 的化合物反应得到其中 Z^1 为 $-S-$ 或 $-NR^9-$ 的化合物。

[0539] 本发明的 PPAR 激动剂的药物组合物可以有效地对涉及 PPAR 的所有疾病起作用，并且特别是用于预防和/或治疗高脂血症、脂质代谢障碍、脂类代谢异常、低 HDL、高 LDL、高 VLDL、高 TG、糖尿病、高血糖症、抗胰岛素性、肥胖症、食欲过盛、动脉硬化、动脉粥样硬化、高血压、X 综合症、局部缺血性疾病、炎症、变应性疾病（如，炎症性肠病、类风湿性关节炎、慢性胰腺炎、多发性硬化、肾小球硬化症、银屑病或湿疹）、骨质疏松症、不育症、癌症（如，乳腺癌、结肠癌、直肠癌、卵巢癌、或肺癌）、阿尔茨海默氏病、帕金森综合征或巴塞杜氏病。特别地，在具有 PPAR 激动活性的本发明的化合物中，具有 PPAR δ 选择性激动活性的化合物可以是好的药物。理由是，例如，可以预计其具有高的 HDL 增加活性或能减轻副作用。

[0540] 此外，本发明的化合物具有好的特性，例如，

[0541] a) 弱的 CYP 酶抑制作用

[0542] b) 高的水溶性

[0543] c) 好的药物处置例如高生物利用度

[0544] d) 低的贫血诱导活性等毒性，或

[0545] e) 高的代谢稳定性。

[0546] 当将本发明的化合物作为 PPAR 激动剂的药物组合物给予时，其可以口服或非肠道给予。对于口服给予，本发明的化合物可以作为通过通常方法制备的任何通常制剂形式使用，例如片剂、颗粒、粉剂、胶囊、丸剂、溶液、糖浆、口腔含片、舌下含片等。对于非肠道给予，本发明的化合物可以作为通常制剂的任何形式给予，例如注射剂如肌肉给予和静脉内给予、栓剂、透皮治疗剂、吸入剂等。本发明的化合物优选作为口服药物，因为其具有高的口服生物利用度。

[0547] 如有必要，可通过将治愈有效量的本发明化合物与各种可药用赋形剂（例如，粘合剂、润湿剂、崩解剂、润滑剂、稀释剂等）合并生产本发明的制剂。在制剂为注射剂时，可

通过用适当的载体进行灭菌处理生产本发明的混配物。

[0548] 例如,赋形剂为乳糖、蔗糖、葡萄糖、淀粉、碳酸钙、结晶纤维素等。粘合剂为甲基纤维素、羧甲基纤维素、羟丙基纤维素、明胶、聚乙烯基吡咯烷酮等。崩解剂为羧甲基纤维素、羧基甲基纤维素钠、淀粉、海藻酸钠、粉末琼脂、月桂基硫酸钠等。润滑剂为滑石、硬脂酸镁、聚乙二醇等。作为栓剂的基质,可使用可可脂、聚乙二醇、甲基纤维素等。当将本发明生产为液体药物、乳液注射剂或悬浮液注射剂时,可以适当地加入通常使用的增溶剂、助悬剂、乳化剂、稳定剂、防腐剂、等渗剂等。在口服给予的情况中,可加入甜味剂、调味剂等。

[0549] 本发明的化合物作为 PPAR 激动剂的药物组合物的剂量优选根据以下情况确定:年龄、体重、疾病的类型、患者的状况、给予途径等。在对成年人口服给予的情况中,通常为 0.05 到 100mg/kg/天并且优选为 0.1 到 10mg/kg/天。在非肠道给予的情况中,尽管取决于给药途径有明显不同,但通常为 0.005 到 10mg/kg/天并且优选为 0.01 到 10mg/kg/天。可以将其分开并且以每天一次到几次给予。

[0550] 实施例

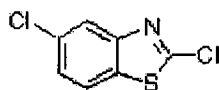
[0551] 提供以下实施例用于更详细地说明本发明,而不是限制本发明。

[0552] 通过美国专利申请公开 no US2004-0224997 或 WO 95/22531 中所述的方法得到参考例 1 到 6 的化合物。

[0553] 参考例 1

[0554] [式 64]

[0555]

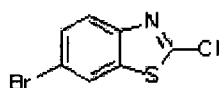


[0556] 收率:88%, $^1\text{H-NMR}(\text{CDCl}_3)$: δ 7.41 (1H, dd, $J = 8.5, 2.0\text{Hz}$), 7.45 (1H, d, $J = 8.5\text{Hz}$), 7.95 (1H, d, $J = 2.0\text{Hz}$).

[0557] 参考例 2

[0558] [式 65]

[0559]

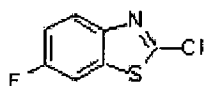


[0560] 收率:90%, $^1\text{H-NMR}(\text{CDCl}_3)$: δ 7.60 (1H, dd, $J = 8.5, 2.0\text{Hz}$), 7.82 (1H, d, $J = 8.5\text{Hz}$), 7.93 (1H, d, $J = 2.0\text{Hz}$).

[0561] 参考例 3

[0562] [式 66]

[0563]

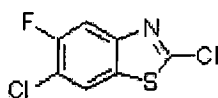


[0564] 收率:76%, $^1\text{H-NMR}(\text{CDCl}_3)$: δ 7.23 (1H, td, $J = 8.0, 2.5\text{Hz}$), 7.48 (1H, dd, $J = 8.0, 2.5\text{Hz}$), 7.91 (1H, dd, $J = 8.0, 4.0\text{Hz}$).

[0565] 参考例 4

[0566] [式 67]

[0567]

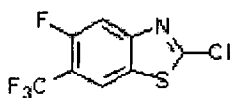


[0568] 收率:65%, $^1\text{H-NMR}$ (CDCl_3): δ 7.73 (1H, d, $J = 7.0\text{Hz}$), 7.82 (1H, d, $J = 9.0\text{Hz}$)。

[0569] 参考例 5

[0570] [式 68]

[0571]

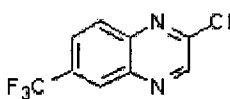


[0572] 收率:89%, $^1\text{H-NMR}$ (CDCl_3): δ 7.78 (1H, d, $J = 6.5\text{Hz}$), 8.06 (1H, d, $J = 10.5\text{Hz}$)。

[0573] 参考例 6

[0574] [式 69]

[0575]



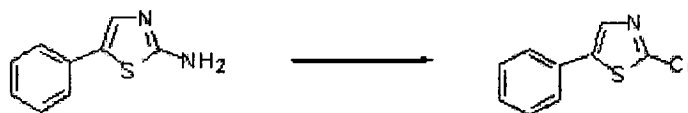
[0576] 收率:66%, $^1\text{H-NMR}$ (CDCl_3): δ 8.00 (1H, d, $J = 8.5\text{Hz}$), 8.17 (1H, d, $J = 8.5\text{Hz}$), 8.45 (1H, s), 8.89 (1H, s)。

[0577] 参考例 7

[0578] 2-氯-5-苯基噻唑的制备

[0579] [式 70]

[0580]



[0581] 在冰冷却下向 Journal of Medicinal Chemistry, 1983, Vol. 26(8), 1158-1163 中所述的 2-氨基-5-苯基噻唑 (1.00g; 5.67mmol)、氯化铜 (II) 二水合物 (1.94g; 11.3mmol)、浓盐酸 (8ml) 和乙酸 (8ml) 的混合物中加入亚硝酸钠 (0.47g; 6.80mmol)。将混合物在 40℃ 搅拌 1 小时。在使反应混合物回到室温之后, 加入水和氯仿并且萃取。有机层用盐水洗涤, 用无水硫酸钠干燥, 并且减压蒸发。残余物通过硅胶柱色谱法纯化 (二氯甲烷), 得到 2-氯-5-苯基噻唑, 为浅黄色晶体 (0.68g; 62%)。

[0582] $^1\text{H-NMR}$ (CDCl_3): δ 7.32-7.53 (5H, m), 7.71 (1H, s)。

[0583] 参考例 8

[0584] [3-(甲氧基甲氧基)-4-甲基苯基]乙腈的制备

[0585] [式 71]

[0586]



[0587] 在冰冷却下向 W02004/022551 中所述的 3-(甲氧基甲氧基)-4-甲基苯甲醇 (9.80g; 53.78mmol)、三乙胺 (7.90ml; 56.47mmol) 和无水 THF (50ml) 的混合物中滴加甲磺酰氯 (4.40ml; 56.47mmol)。将混合物在相同的温度搅拌 1.5 小时。收集沉淀物并且在减

压下浓缩。然后,向残余物中加入氰化钠(7.91g;0.161mol)和无水N,N-二甲基甲酰胺(50ml)。将混合物在室温搅拌3天。向反应溶液加入水和乙酸乙酯。分离有机层,用盐水洗涤,用无水硫酸钠干燥,并且减压蒸发。残余物通过硅胶柱色谱法纯化(己烷:乙酸乙酯=3:1),得到[3-(甲氧基甲氧基)-4-甲基苯基]乙腈,为带黑色的棕色油状物(7.87g;77%)。

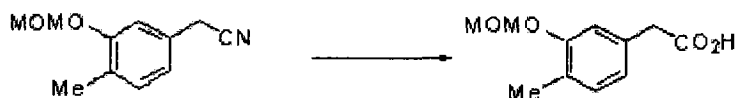
[0588] $^1\text{H-NMR}(\text{CDCl}_3)$: δ 2.23(3H, s), 3.49(3H, s), 3.70(2H, s), 5.21(2H, s), 6.89(1H, dd, $J = 7.5, 1.5\text{Hz}$), 6.98(1H, d, $J = 1.5\text{Hz}$), 7.14(1H, d, $J = 7.5\text{Hz}$)。

[0589] 参考例 9

[0590] 3-(甲氧基甲氧基)-4-甲基苯基乙酸的制备

[0591] [式 72]

[0592]



[0593] 将[3-(甲氧基甲氧基)-4-甲基苯基]乙腈(7.87g;41.2mmol)、氢氧化钠(8.30g;210mmol)、水(30ml)和乙醇(70ml)的混合物回流5小时。将反应溶液减压浓缩。向其中加入水和乙酸乙酯并且反萃取。通过加入2N-盐酸使水层变为 $\text{pH} = 7$ 。向其中加入乙酸乙酯并且萃取。有机层用盐水洗涤,用无水硫酸钠干燥,并且减压蒸发,得到3-(甲氧基甲氧基)-4-甲基苯基乙酸,为带浅黑色的棕色油状物(5.52g;64%)。

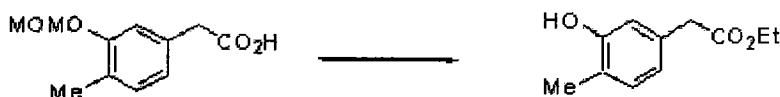
[0594] $^1\text{H-NMR}(\text{CDCl}_3)$: δ 2.22(3H, s), 3.48(3H, s), 3.59(2H, s), 5.19(2H, s), 6.83(1H, dd, $J = 7.5, 1.5\text{Hz}$), 6.95(1H, d, $J = 1.5\text{Hz}$), 7.13(1H, d, $J = 7.5\text{Hz}$), 9.83(1H, brs)。

[0595] 参考例 10

[0596] [3-羟基-4-甲基苯基]乙酸乙酯的制备

[0597] [式 73]

[0598]



[0599] 将[3-(甲氧基甲氧基)-4-甲基]苯基乙酸(5.52g;26.3mmol)、浓盐酸(2ml)和乙醇(20ml)的混合物回流3小时。在冷却之后,将反应溶液减压浓缩。向残余物中加入饱和碳酸氢钠水溶液到 $\text{pH} = 7$ 。向其中加入乙酸乙酯并且萃取。有机层用盐水洗涤,用无水硫酸钠干燥,并且减压蒸发。残余物通过硅胶柱色谱法纯化(己烷:乙酸乙酯=3:1),得到3-羟基-4-甲基苯基乙酸乙酯,为浅黄色油状物(2.40g;47%)。

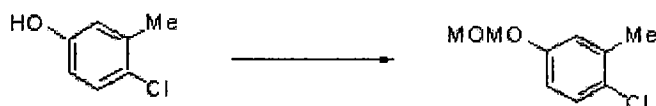
[0600] $^1\text{H-NMR}(\text{CDCl}_3)$: δ 1.26(3H, t, $J = 7\text{Hz}$), 2.21(3H, s), 3.53(2H, s), 4.14(2H, q, $J = 7\text{Hz}$), 5.13(1H, s), 6.72(1H, s), 6.74(1H, d, $J = 7.5\text{Hz}$), 7.05(1H, d, $J = 7.5\text{Hz}$)。

[0601] 参考例 11

[0602] 2-氯-5-(甲氧基乙氧基)甲苯的制备

[0603] [式 74]

[0604]



[0605] 在室温向 4-氯-3-甲基甲酚 (15.0g ;0.105mol)、N,N-二异丙基乙基胺 (23.3ml ;0.137mol) 和 THF(150ml) 的混合物中滴加氯甲基甲基醚 (9.50ml ;0.126mol)。将混合物在 60℃ 搅拌 27.5 小时。将反应溶液倾倒在冰水中并且用乙酸乙酯萃取。有机层用盐水洗涤,用无水硫酸钠干燥,并且减压蒸发。残余物通过硅胶柱色谱法纯化 (己烷:乙酸乙酯=5 : 1),得到 2-氯-5-(甲氧基乙氧基) 甲苯,为暗红褐色油状物 (17.7g ;90%)。

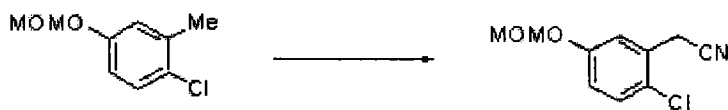
[0606] $^1\text{H-NMR}(\text{CDCl}_3)$: δ 2.34(3H, s), 3.47(3H, s), 5.13(2H, s), 6.81(1H, dd, $J = 8.5$, 3.0Hz), 6.92(1H, d, $J = 3.0\text{Hz}$), 7.22(1H, d, $J = 8.5\text{Hz}$)。

[0607] 参考例 12

[0608] [2-氯-5-(甲氧基甲氧基) 苯基] 乙腈的制备

[0609] [式 75]

[0610]



[0611] 将 2-氯-5-(甲氧基乙氧基) 甲苯 (5.00g ;26.8mmol), N-溴代琥珀酰亚胺 (4.77g ;26.8mmol) 和 2,2-偶氮二(异丁腈) (0.09g ;0.53mmol) 在四氯化碳 (25ml) 中的混合物回流 2 小时。在空气冷却和过滤沉淀物之后,将滤液减压浓缩。向残余物中加入氰化钠 (2.77g ;80.4mmol) 和无水 N,N-二甲基甲酰胺 (30ml)。将混合物在室温搅拌 2 小时。向反应溶液加入水和乙酸乙酯并且萃取。有机层用盐水洗涤,用无水硫酸钠干燥,并且减压蒸发。残余物通过硅胶柱色谱法纯化 (己烷:乙酸乙酯=6 : 1 $\rightarrow$ 4 : 1),得到 [2-氯-5-(甲氧基甲氧基) 苯基] 乙腈,为无色油状物 (2.64g ;47%)。

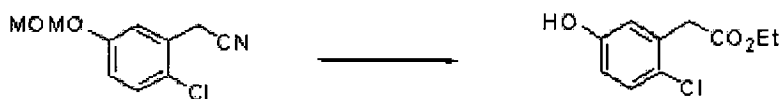
[0612] $^1\text{H-NMR}(\text{CDCl}_3)$: δ 3.48(3H, s), 3.80(2H, s), 5.17(2H, s), 6.99(1H, dd, $J = 9.0$, 3.0Hz), 7.19(1H, d, $J = 3.0\text{Hz}$), 7.32(1H, d, $J = 9.0\text{Hz}$)。

[0613] 参考例 13

[0614] [2-氯-5-羟基苯基] 乙酸乙酯的制备

[0615] [式 76]

[0616]



[0617] 将 [2-氯-5-(甲氧基甲氧基) 苯基] 乙腈 (2.60g ;12.3mmol), 氢氧化钠 (2.46g ;61.5mmol), 水 (10.4ml) 和乙醇 (33.8ml) 的混合物在 80℃ 搅拌 3 小时。在冷却之后,减压蒸发溶剂。向残余物中加入水和 2N-盐酸到变为酸性并且用乙酸乙酯萃取。有机层用盐水洗涤,用无水硫酸钠干燥,并且减压蒸发。向残余物中加入浓盐酸 (0.65ml) 和乙醇 (15ml)。将混合物在 80℃ 搅拌 8 小时。在冷却之后,将反应溶液减压浓缩。残余物通过硅胶柱色谱法纯化 (己烷:乙酸乙酯=2 : 1),得到 [2-氯-5-羟基苯基] 乙酸乙酯,为无色油状物 (0.69g ;26%)。

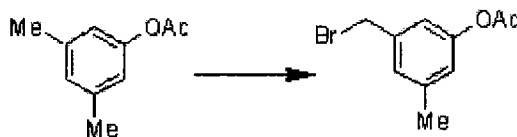
[0618] $^1\text{H-NMR}(\text{CDCl}_3)$: δ 1.28(3H, t, $J = 7.0\text{Hz}$), 3.70(2H, s), 4.20(2H, q, $J = 7.0\text{Hz}$), 5.66(1H, s), 6.64(1H, dd, $J = 8.5$, 3.0Hz), 6.73(1H, d, $J = 3.0\text{Hz}$), 7.18(1H, d, $J = 8.5\text{Hz}$)。

[0619] 参考例 14

[0620] [3- 溴甲基 -5- 甲基] 苯氧基乙酸酯的制备

[0621] [式 77]

[0622]



[0623] 其通过 W02004/022551 的参考例 77 中所述的方法合成。

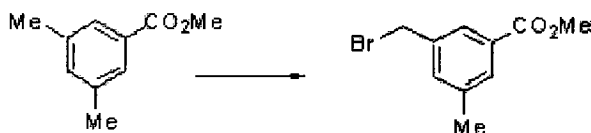
[0624] $^1\text{H-NMR}$ (CDCl_3) : δ 2.29 (3H, s), 2.35 (3H, s), 4.44 (2H, s), 6.85 (1H, s), 6.94 (1H, s), 7.08 (1H, s)。

[0625] 参考例 15

[0626] 3- 溴甲基 -5- 甲基苯甲酸甲基酯的制备

[0627] [式 78]

[0628]



[0629] 将 3,5- 二甲基甲基苯甲酸酯 (5.00g ; 30.5mmol), N- 溴代琥珀酰亚胺 (5.69g ; 32.0mmol) 和 2,2- 偶氮二 (异丁腈) (0.10g ; 0.61mmol) 在四氯化碳 (25ml) 中的混合物回流 1 小时。在冷却和过滤沉淀物之后,将滤液减压浓缩。残余物通过硅胶柱色谱法纯化 (己烷 : 乙酸乙酯 = 10 : 1), 得到 3- 溴甲基 -5- 甲基甲基苯甲酸酯,为无色油状物 (3.78g ; 51%)。

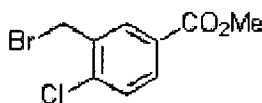
[0630] $^1\text{H-NMR}$ (CDCl_3) : δ 2.40 (3H, s), 3.92 (3H, s), 4.49 (2H, s), 7.40 (1H, s), 7.79 (1H, s), 7.89 (1H, s)。

[0631] 参考例 16 和 17 的化合物通过与参考例 15 相似的方法得到。

[0632] 参考例 16

[0633] [式 79]

[0634]

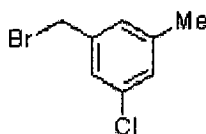


[0635] 收率 : 56%, $^1\text{H-NMR}$ (CDCl_3) : δ 3.93 (3H, s), 4.61 (2H, s), 7.47 (1H, d, $J = 8.5\text{Hz}$), 7.91 (1H, dd, $J = 8.5, 2\text{Hz}$), 8.11 (1H, d, $J = 2\text{Hz}$)。

[0636] 参考例 17

[0637] [式 80]

[0638]



[0639] 收率 : 75%, $^1\text{H-NMR}$ (CDCl_3) : δ 2.33 (3H, s), 4.40 (2H, s), 7.08 (1H, s), 7.10 (1H, s), 7.18 (1H, s)。

[0640] 参考例 18

[0641] [(3-氯-5-甲基)苯基]乙腈的制备

[0642] [式 81]

[0643]



[0644] 将 (3-溴甲基-5-氯) 甲苯 (1.67g ;7.62mmol), 氰化钠 (0.42g ;8.51mmol) 和无水 N,N-二甲基甲酰胺 (15ml) 的混合物在 40℃ 搅拌 2 小时。向反应溶液加入水和乙酸乙酯并且萃取。有机层用盐水洗涤, 用无水硫酸钠干燥, 并且减压蒸发。残余物通过硅胶柱色谱法纯化 (二氯甲烷), 得到 [(3-氯-5-甲基) 苯基] 乙腈, 为浅黄色油状物 (0.75g ;59%)。

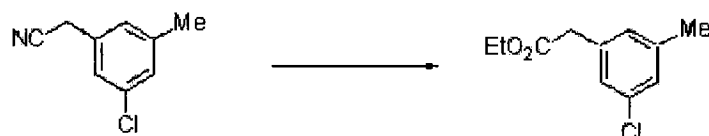
[0645] $^1\text{H-NMR}$ (CDCl_3) : δ 2.35 (3H, s), 3.69 (2H, s), 7.04 (1H, s), 7.12 (1H, s), 7.14 (1H, s)。

[0646] 参考例 19

[0647] (3-氯-5-甲基) 苯基乙酸乙酯的制备

[0648] [式 82]

[0649]



[0650] 向 [(3-氯-5-甲基苯基)] 乙腈 (0.38g ;2.29mmol) 加入 2N 氢氧化钠水溶液 (2.1ml) 和乙醇 (5ml)。将混合物在 80℃ 搅拌 1 小时。将反应溶液减压浓缩。向残余物中加入水和 2N-HCl 水溶液到变为中性。向其中加入乙酸乙酯并且萃取。有机层用盐水洗涤, 用无水硫酸钠干燥, 并且减压蒸发, 得到无色晶体。向其中加入浓硫酸 (0.02ml) 和乙醇 (2ml), 并将混合物回流 5 小时。将反应溶液减压浓缩。向残余物中加入水和 2N-氢氧化钠水溶液到变为中性。向其中加入乙酸乙酯并且萃取。有机层用盐水洗涤, 用无水硫酸钠干燥, 并且减压蒸发。残余物通过硅胶柱色谱法纯化 (己烷: 乙酸乙酯 = 6 : 1), 得到 3-氯-5-甲基苯基乙酸乙酯, 为无色油状物 (0.31g ;63%)。

[0651] $^1\text{H-NMR}$ (CDCl_3) : δ 1.26 (3H, t, $J = 7.2\text{Hz}$), 2.32 (3H, s), 3.53 (2H, s), 4.16 (2H, q, $J = 7.2\text{Hz}$), 6.97 (1H, s), 7.08 (2H, s)。

[0652] 参考例 20

[0653] [3-溴甲基-5-氯] 苯基乙酸乙酯的制备

[0654] [式 83]

[0655]



[0656] 将 3-氯-5-甲基苯基乙酸乙酯 (0.20g ;0.958mmol), N-溴代琥珀酰亚胺 (0.21g ;1.21mmol) 和 2,2-偶氮二 (异丁腈) (0.01g ;0.037mmol) 在四氯化碳 (2ml) 中的混合物

回流 2 小时。在冷却和过滤沉淀物之后,将滤液减压浓缩。残余物通过硅胶柱色谱法纯化(己烷:乙酸乙酯=20:1),得到 3-溴甲基-5-氯苯基乙酸乙酯,为无色油状物(0.16g;57%)。

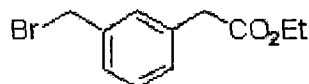
[0657] $^1\text{H-NMR}(\text{CDCl}_3)$: δ 1.27(3H, t, $J = 7.2\text{Hz}$), 3.58(2H, s), 4.17(2H, t, $J = 7.2\text{Hz}$), 4.42(2H, s), 7.20(1H, s), 7.22(1H, s), 7.30(1H, s)。

[0658] 如上合成参考例 21 和 22 的化合物。

[0659] 参考例 21

[0660] [式 84]

[0661]

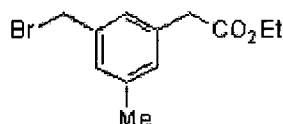


[0662] 收率:56%, $^1\text{H-NMR}(\text{CDCl}_3)$: δ 1.26(3H, t, $J = 7.0\text{Hz}$), 3.61(2H, s), 4.16(2H, q, $J = 7.0\text{Hz}$), 4.48(2H, s), 7.18-7.38(4H, m)。

[0663] 参考例 22

[0664] [式 85]

[0665]



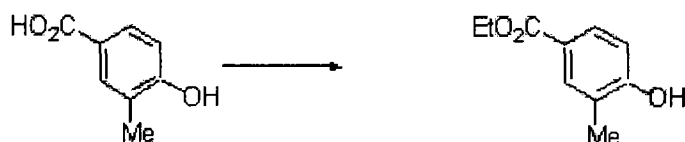
[0666] 收率:70%, $^1\text{H-NMR}(\text{CDCl}_3)$: δ 1.28(3H, t, $J = 7\text{Hz}$), 3.51(3H, s), 3.59(2H, s), 4.17(2H, q, $J = 7\text{Hz}$), 4.45(2H, s), 7.04(1H, s), 7.12(2H, s)。

[0667] 参考例 23

[0668] 4-羟基-3-甲基苯甲酸乙酯的制备

[0669] [式 86]

[0670]



[0671] 将 4-羟基-3-甲基苯甲酸(3.01g;19.78mmol),浓硫酸(0.20ml)和乙醇(40ml)的混合物回流 6 小时。将反应溶液减压浓缩。向残余物中加入水和 2N-氢氧化钠水溶液到变为中性。加入乙酸乙酯并且萃取。有机层用盐水洗涤,用无水硫酸钠干燥,并且减压蒸发,得到 4-羟基-3-甲基苯甲酸乙酯,为黄色晶体(3.40g,95%)。

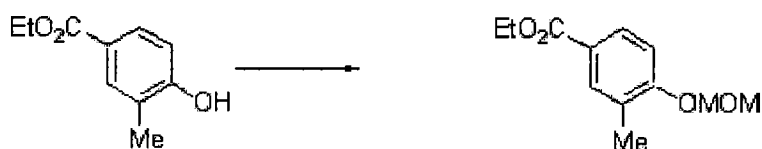
[0672] $^1\text{H-NMR}(\text{CDCl}_3)$: δ 1.38(3H, t, $J = 7.2\text{Hz}$), 2.28(3H, s), 4.35(2H, q, $J = 7.2\text{Hz}$), 5.75(1H, s), 6.81(1H, d, $J = 8.1\text{Hz}$), 8.40(1H, d, $J = 8.1\text{Hz}$), 7.84(1H, s)。

[0673] 参考例 24

[0674] 4-(甲氧基甲氧基)-3-甲基苯甲酸乙酯的制备

[0675] [式 87]

[0676]



[0677] 将 4-羟基-3-甲基苯甲酸乙酯 (2.15g ;11.93mmol), 甲氧基甲氧基氯 (1.60ml ; 21.2mmol), 二异丙基乙基胺 (4.10ml ;23.9mmol) 和 THF (40ml) 的混合物在 60℃ 回流 9 小时。在冷却之后, 向反应溶液加入水和乙酸乙酯并且萃取。有机层用盐水洗涤, 用无水硫酸钠干燥, 并且减压蒸发。残余物通过硅胶柱色谱法纯化 (己烷: 乙酸乙酯 = 20 : 1), 得到 4-(甲氧基甲氧基)-3-甲基苯甲酸乙酯, 为无色油状物 (1.94g ;73%)。

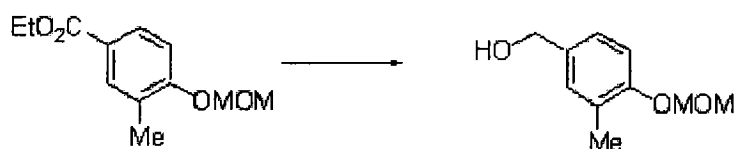
[0678] $^1\text{H-NMR}$ (CDCl_3) : δ 1.38 (3H, t, $J = 7.2\text{Hz}$), 2.27 (3H, s), 3.49 (3H, s), 4.34 (2H, q, $J = 7.2\text{Hz}$), 5.26 (2H, s), 7.05 (1H, d, $J = 9.3\text{Hz}$), 7.84-7.86 (2H, m)。

[0679] 参考例 25

[0680] [4-(甲氧基甲氧基)-3-甲基]苯甲醇的制备

[0681] [式 88]

[0682]



[0683] 在 0℃ 向氢化铝锂 (0.26g ;6.76mmol) 在无水 THF (5ml) 中的悬浮液滴加 4-(甲氧基甲氧基)-3-甲基苯甲酸乙酯 (1.02g ;4.55mmol) 和无水 THF (10ml) 的混合物。在相同的温度搅拌 1 小时之后, 向反应溶液滴加 2N-氢氧化钠水溶液。将残余物过滤。向滤液加入乙酸乙酯和盐水。分离有机层并且用无水硫酸钠干燥和减压蒸发溶剂。残余物通过硅胶柱色谱法纯化 (己烷: 乙酸乙酯 = 3 : 1), 得到 [4-(甲氧基甲氧基)-3-甲基]苯甲醇, 为无色油状物 (0.80g ;97%)。

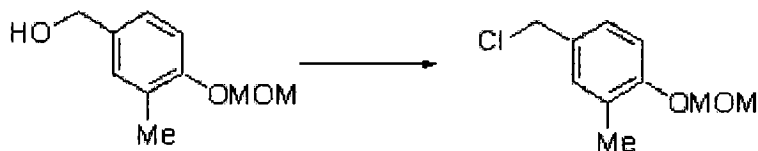
[0684] $^1\text{H-NMR}$ (CDCl_3) : δ 1.63 (1H, brs), 2.25 (3H, s), 3.48 (3H, s), 4.59 (2H, d, $J = 3.9\text{Hz}$), 5.20 (2H, s), 7.01-7.17 (3H, m)。

[0685] 参考例 26

[0686] 5-氯甲基-2-(甲氧基甲氧基)甲苯的制备

[0687] [式 89]

[0688]



[0689] 在冰冷却下向 [4-(甲氧基甲氧基)-3-甲基]苯甲醇 (0.49g ;2.69mmol), 三乙胺 (0.42ml ;3.01mmol) 和二氯甲烷 (14ml) 的混合物中滴加甲磺酰氯 (0.23ml ;2.97mmol)。将混合物搅拌 4.5 小时。将反应溶液减压浓缩。残余物通过硅胶柱色谱法纯化 (己烷: 乙酸乙酯 = 6 : 1), 得到 5-氯甲基-2-(甲氧基甲氧基)甲苯, 为带浅黑色的棕色油状物 (0.53g ;99%)。

[0690] $^1\text{H-NMR}$ (CDCl_3) : δ 2.25 (3H, s), 3.48 (3H, s), 4.54 (2H, s), 5.20 (2H, s), 7.02 (1H, d, $J = 8.4\text{Hz}$), 7.14-7.18 (2H, m)。

[0691] 参考例 27

[0692] 通过参考 Synthetic Communications, 2004, Vol. 34, 4111 到 4118 合成以下化合物。

[0693] 2-(N-氯乙酰胺)丁酸甲酯的合成

[0694] [式 90]

[0695]



[0696] 在冰冷却下向 2-氨基丁酸 (10.0g ;96.97mmol) 的甲醇 (65ml) 溶液中滴加亚硫酸氯 (30ml ;411.28mmol)。将混合物在室温搅拌 18 小时。将反应溶液减压浓缩。向残余物中加入二异丙醚 (20ml)。将混合物在减压下共沸,得到无色晶体。

[0697] 向上述晶体 (5.00g) 加入水 (15ml) 和碳酸氢钠 (6.66g ;79.28mmol) 并且在冰冷却下滴加氯乙酰氯 (2.6ml ;32.64mmol) 的甲苯 (10ml) 溶液。将混合物在室温搅拌 18 小时。将反应溶液分离并将有机层用无水硫酸钠干燥。减压蒸发溶剂。残余物通过硅胶柱色谱法纯化 (己烷:乙酸乙酯=2:1),得到 2-(N-氯乙酰胺)丁酸甲酯,为无色油状物 (4.75g ;75%)。

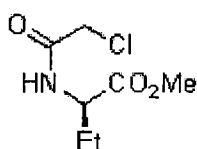
[0698] $^1\text{H-NMR}$ (CDCl₃) : δ 0.94 (3H, t, $J = 7.2\text{Hz}$), 1.74-1.86 (1H, m), 1.8-2.02 (1H, m), 3.78 (3H, s), 4.08 (2H, s), 4.59 (1H, q, $J = 6.6\text{Hz}$), 7.07 (1H, s)。

[0699] 如上得到参考例 28 到 37 的化合物。

[0700] 参考例 28

[0701] [式 91]

[0702]

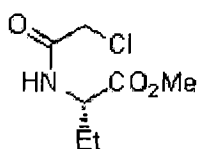


[0703] 收率:74%, $^1\text{H-NMR}$ (CDCl₃) : δ 0.94 (3H, t, $J = 7.5\text{Hz}$), 1.70-2.00 (2H, m), 3.78 (3H, s), 4.09 (2H, s), 4.54-4.63 (1H, m), 7.10 (1H, brs)。

[0704] 参考例 29

[0705] [式 92]

[0706]

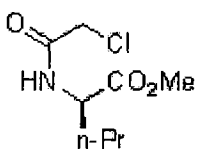


[0707] 收率:70%, $^1\text{H-NMR}$ (CDCl₃) : δ 0.94 (3H, t, $J = 7.5\text{Hz}$), 1.65-2.00 (2H, m), 3.78 (3H, s), 4.11 (2H, s), 4.50-4.65 (1H, m), 7.09 (1H, brs)。

[0708] 参考例 30

[0709] [式 93]

[0710]

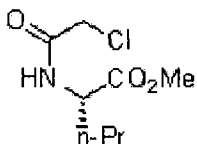


[0711] 收率:97%, $^1\text{H-NMR}$ (CDCl_3): δ 0.95 (3H, t, $J = 7.2\text{Hz}$), 1.26-1.41 (2H, m), 1.66-1.78 (1H, m), 1.81-1.89 (1H, m), 3.77 (3H, s), 4.08 (2H, s), 4.62 (1H, dt, $J = 7.8\text{Hz}$), 7.03 (1H, s)。

[0712] 参考例 31

[0713] [式 94]

[0714]

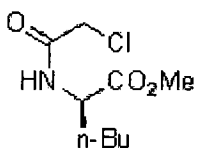


[0715] 收率:91%, $^1\text{H-NMR}$ (CDCl_3): δ 0.95 (3H, t, $J = 7.5\text{Hz}$), 1.24-1.43 (2H, m), 1.66-1.78 (1H, m), 1.81-1.93 (1H, m), 3.77 (3H, s), 4.08 (2H, s), 4.62 (1H, q, $J = 7.5\text{Hz}$), 7.02 (1H, s)。

[0716] 参考例 32

[0717] [式 95]

[0718]

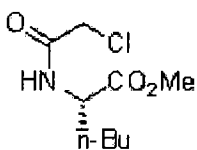


[0719] 收率:99%, $^1\text{H-NMR}$ (CDCl_3): δ 0.91 (3H, t, $J = 7\text{Hz}$), 1.23-1.40 (4H, m), 1.67-1.80 (1H, m), 1.81-1.96 (1H, m), 3.77 (3H, s), 4.08 (2H, s), 4.57-4.65 (1H, m), 7.03 (1H, brs)。

[0720] 参考例 33

[0721] [式 96]

[0722]

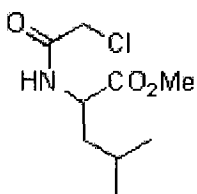


[0723] 收率:86%, $^1\text{H-NMR}$ (CDCl_3): δ 0.91 (3H, t, $J = 7\text{Hz}$), 1.23-1.40 (4H, m), 1.65-1.80 (1H, m), 1.82-1.95 (1H, m), 3.77 (3H, s), 4.08 (2H, s), 4.55-4.65 (1H, m), 7.02 (1H, brs)。

[0724] 参考例 34

[0725] [式 97]

[0726]

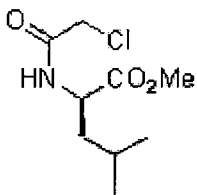


[0727] 收率:93%, $^1\text{H-NMR}$ (CDCl_3): δ 0.96 (6H, d, $J = 6.0\text{Hz}$), 1.58–1.74 (3H, m), 3.76 (3H, s), 4.08 (2H, s), 4.66 (1H, t, $J = 8.4\text{Hz}$), 6.90 (1H, br)。

[0728] 参考例 35

[0729] [式 98]

[0730]

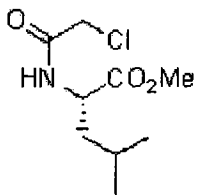


[0731] 收率:定量收率, $^1\text{H-NMR}$ (CDCl_3): δ 0.96 (6H, d, $J = 6.0\text{Hz}$), 1.54–1.78 (3H, m), 3.76 (3H, s), 4.08 (2H, s), 4.60–4.70 (1H, m), 6.83–6.95 (1H, m)。

[0732] 参考例 36

[0733] [式 99]

[0734]

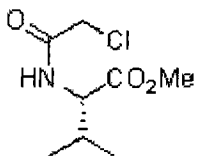


[0735] 收率:93%, $^1\text{H-NMR}$ (CDCl_3): δ 0.95 (6H, d, $J = 6\text{Hz}$), 1.56–1.75 (3H, m), 3.76 (3H, s), 4.08 (2H, s), 4.60–4.70 (1H, m), 6.93 (1H, brs)。

[0736] 参考例 37

[0737] [式 100]

[0738]



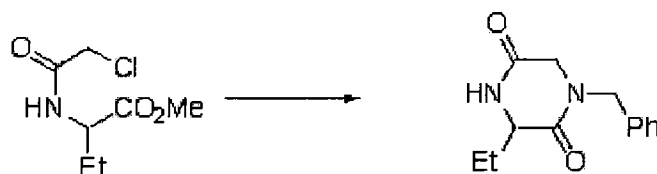
[0739] 收率:90%, $^1\text{H-NMR}$ (CDCl_3): δ 0.96 (6H, t, $J = 6.5\text{Hz}$), 2.16–2.30 (1H, m), 3.77 (3H, s), 4.10 (2H, s), 4.51–4.60 (1H, m), 7.04 (1H, brs)。

[0740] 参考例 38

[0741] 1-苯甲基-3-乙基哌嗪-2,5-二酮的合成

[0742] [式 101]

[0743]



[0744] 将 2-(N-氯乙酰胺)丁酸甲酯 (4.00g ;20.71mmol), 三乙胺 (8.8ml ;63.14mmol), 苯甲胺 (2.8ml ;25.64mmol) 和甲醇 (45ml) 的混合物回流 16 小时。将反应溶液减压浓缩。向残余物加入水和乙酸乙酯并且萃取。向有机层加入 1N 盐酸以分层。向有机层加入碳酸氢钠水溶液到变为中性。有机层用盐水洗涤, 用无水硫酸钠干燥, 并且减压蒸发。残余物用二异丙醚洗涤, 得到 1-苯甲基-3-乙基哌嗪-2,5-二酮, 为无色晶体 (1.58g ;33%)。

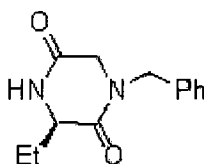
[0745] $^1\text{H-NMR}$ (CDCl₃) : δ 0.98 (3H, t, $J = 7.2\text{Hz}$), 1.71-2.02 (2H, m), 3.84 (2H, dd, $J = 0.9, 5.1\text{Hz}$), 4.03-4.08 (1H, m), 4.51 (1H, d, $J = 14.4\text{Hz}$), 4.71 (1H, d, $J = 14.4\text{Hz}$), 7.25-7.36 (5H, m)。

[0746] 如上得到参考例 39 到 48 的化合物。

[0747] 参考例 39

[0748] [式 102]

[0749]

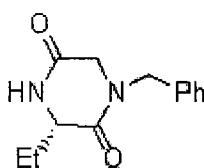


[0750] 收率:44%, $^1\text{H-NMR}$ (CDCl₃) : δ 0.98 (3H, t, $J = 7.5\text{Hz}$), 1.83-2.03 (2H, m), 3.83 (2H, d, $J = 5.5\text{Hz}$), 4.00-4.10 (1H, m), 4.50 (1H, d, $J = 14.5\text{Hz}$), 4.71 (1H, d, $J = 14.5\text{Hz}$), 7.05 (1H, brs), 7.23-7.40 (5H, m)。

[0751] 参考例 40

[0752] [式 103]

[0753]

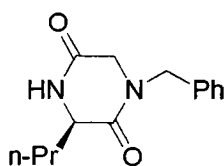


[0754] 收率:32%, $^1\text{H-NMR}$ (CDCl₃) : δ 0.98 (3H, t, $J = 7.5\text{Hz}$), 1.85-2.05 (2H, m), 3.83 (2H, dd, $J = 6, 1\text{Hz}$), 4.02-4.10 (1H, m), 4.50 (1H, d, $J = 14.5\text{Hz}$), 4.71 (1H, d, $J = 14.5\text{Hz}$), 6.95 (1H, brs), 7.20-7.40 (5H, m)。

[0755] 参考例 41

[0756] [式 104]

[0757]



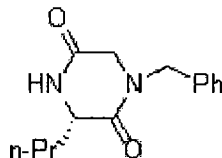
[0758] 收率:41%, $^1\text{H-NMR}$ (CDCl₃) : δ 0.97 (3H, t, $J = 7.2\text{Hz}$), 1.36-1.48 (2H, m),

1.82-1.90 (2H, m), 3.83 (2H, dd, $J = 0.9, 5.4\text{Hz}$), 4.07 (1H, td, $J = 2.6, 5.7\text{Hz}$), 4.60 (2H, dd, $J = 14.1, 39.9\text{Hz}$), 7.24-7.38 (5H, m)。

[0759] 参考例 42

[0760] [式 105]

[0761]

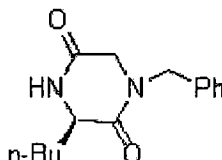


[0762] 收率:45%, $^1\text{H-NMR}(\text{CDCl}_3)$: δ 0.97 (3H, t, $J = 7.2\text{Hz}$), 1.36-1.48 (2H, m), 1.82-1.90 (2H, m), 3.83 (2H, dd, $J = 0.9, 5.4\text{Hz}$), 4.04-4.09 (1H, m), 4.53 (1H, d, $J = 14.4\text{Hz}$), 4.67 (1H, d, $J = 14.4\text{Hz}$), 7.24-7.39 (5H, m)。

[0763] 参考例 43

[0764] [式 106]

[0765]

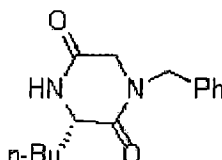


[0766] 收率:49%, $^1\text{H-NMR}(\text{CDCl}_3)$: δ 0.85-1.00 (3H, m), 1.24-1.45 (4H, m), 1.80-1.96 (2H, m), 3.83 (2H, d, $J = 6\text{Hz}$), 4.02-4.12 (1H, m), 4.53 (1H, d, $J = 14.5\text{Hz}$), 4.67 (1H, d, $J = 14.5\text{Hz}$), 6.68 (1H, brs), 7.21-7.40 (5H, m)。

[0767] 参考例 44

[0768] [式 107]

[0769]

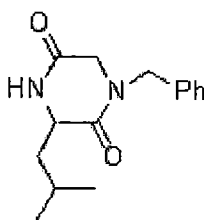


[0770] 收率:43%, $^1\text{H-NMR}(\text{CDCl}_3)$: δ 0.85-0.95 (3H, m), 1.30-1.50 (4H, m), 1.80-1.98 (2H, m), 3.72-3.91 (2H, m), 4.04-4.10 (1H, m), 4.53 (1H, d, $J = 14.5\text{Hz}$), 4.67 (1H, d, $J = 14.5\text{Hz}$), 6.45 (1H, brs), 7.23-7.40 (5H, m)。

[0771] 参考例 45

[0772] [式 108]

[0773]



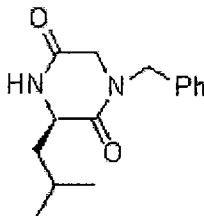
[0774] 收率:34%, $^1\text{H-NMR}(\text{CDCl}_3)$: δ 0.97 (6H, dd, $J = 6.0, 8.1\text{Hz}$), 1.61-1.73 (2H, m),

1.76-1.88 (1H, m), 3.83 (2H, d, $J = 6.3\text{Hz}$), 4.02-4.07 (1H, m), 4.59 (2H, q, $J = 14.7\text{Hz}$), 6.65 (1H, s), 7.23-7.35 (5H, m)。

[0775] 参考例 46

[0776] [式 109]

[0777]

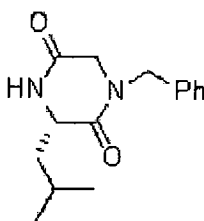


[0778] 收率:55%, $^1\text{H-NMR}(\text{CDCl}_3)$: δ 0.96 (3H, d, $J = 6.5\text{Hz}$), 0.98 (3H, d, $J = 6.5\text{Hz}$), 1.58-1.89 (3H, m), 3.80 (1H, d, $J = 17.5\text{Hz}$), 3.83 (1H, d, $J = 17.5\text{Hz}$), 4.01-4.10 (1H, m), 4.55 (1H, d, $J = 14.5\text{Hz}$), 4.65 (1H, d, $J = 14.5\text{Hz}$), 6.66 (1H, s), 7.21-7.40 (5H, m)。

[0779] 参考例 47

[0780] [式 110]

[0781]

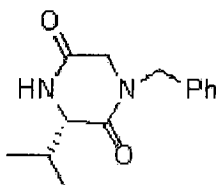


[0782] 收率:50%, $^1\text{H-NMR}(\text{CDCl}_3)$: δ 0.90-1.05 (6H, m), 1.58-1.90 (3H, m), 3.83 (2H, d, $J = 6.5\text{Hz}$), 4.02-4.10 (1H, m), 4.54 (1H, d, $J = 14.5\text{Hz}$), 4.65 (1H, d, $J = 14.5\text{Hz}$), 6.75 (1H, brs), 7.20-7.40 (5H, m)。

[0783] 参考例 48

[0784] [式 111]

[0785]



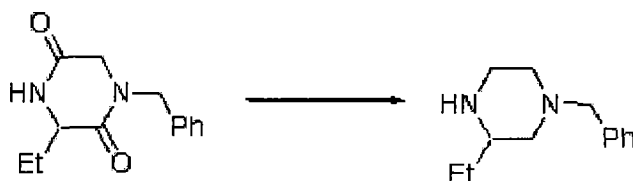
[0786] 收率:12%, $^1\text{H-NMR}(\text{CDCl}_3)$: δ 0.88 (3H, d, $J = 6.5\text{Hz}$), 1.02 (3H, d, $J = 6.5\text{Hz}$), 2.42-2.55 (1H, m), 3.83 (2H, d, $J = 11\text{Hz}$), 3.90-3.96 (1H, m), 4.45 (1H, d, $J = 14\text{Hz}$), 4.77 (1H, d, $J = 14\text{Hz}$), 6.43 (1H, brs), 7.21-7.45 (5H, m)。

[0787] 参考例 49

[0788] 1-苯甲基-3-乙基哌嗪的合成

[0789] [式 112]

[0790]



[0791] 在冰冷却下向氢化铝锂 (0.87g ;22.9mmol) 在无水的 THF (20ml) 中的悬浮液滴加 1- 苯甲基 -3- 乙基哌嗪 -2,5- 二酮 (1.50g ;6.46mmol) 的无水 THF (10ml) 溶液。在室温搅拌 18 小时之后,在冰冷却下顺序地滴加水 (0.25ml) 和 THF (5ml) 的混合物和 2N- 氢氧化钠水溶液 (0.5ml)。将混合物在室温搅拌 1 小时。在过滤氢氧化铝之后,将滤液减压浓缩。向残余物中加入乙酸乙酯和盐水以分层。有机层用无水硫酸钠干燥。减压蒸发溶剂,得到 1- 苯甲基 -3- 乙基哌嗪,为浅黄色油状物 (1.29g ;98%)。

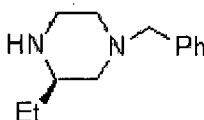
[0792] $^1\text{H-NMR}(\text{CDCl}_3)$: δ 0.90 (3H, t, $J = 7.5\text{Hz}$), 1.30-1.40 (2H, m), 1.70 (1H, t, $J = 10.8\text{Hz}$), 2.01 (1H, dt, $J = 3.6, 10.8\text{Hz}$), 2.61-2.70 (1H, m), 2.73-2.89 (2H, m), 2.92-3.00 (1H, m), 3.49 (2H, dt, $J = 6.9\text{Hz}$), 3.68 (1H, t, $J = 5.7\text{Hz}$), 7.23-7.31 (5H, m)。

[0793] 如上得到参考例 50 到 60 的化合物。

[0794] 参考例 50

[0795] [式 113]

[0796]

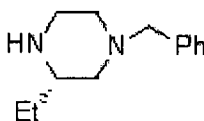


[0797] 收 率 :96 % , $^1\text{H-NMR}(\text{CDCl}_3)$: δ 0.90 (3H, t, $J = 7.5\text{Hz}$), 1.29-1.36 (2H, m), 1.70 (1H, t, $J = 10.5\text{Hz}$), 2.01 (1H, td, $J = 11, 3.5\text{Hz}$), 2.60-3.00 (5H, m), 3.46 (1H, d, $J = 13\text{Hz}$), 3.53 (1H, d, $J = 13\text{Hz}$), 7.20-7.40 (5H, m)。

[0798] 参考例 51

[0799] [式 114]

[0800]

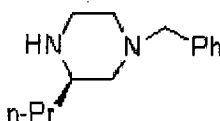


[0801] 收 率 :89 % , $^1\text{H-NMR}(\text{CDCl}_3)$: δ 0.90 (3H, t, $J = 7.5\text{Hz}$), 1.35 (2H, quant, $J = 7.5\text{Hz}$), 1.70 (1H, t, $J = 10.5\text{Hz}$), 2.01 (1H, td, $J = 11, 3.5\text{Hz}$), 2.60-3.00 (5H, m), 3.46 (1H, d, $J = 13\text{Hz}$), 3.53 (1H, d, $J = 13\text{Hz}$), 7.20-7.40 (5H, m)。

[0802] 参考例 52

[0803] [式 115]

[0804]



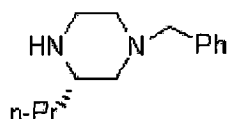
[0805] 收 率 :73 % , $^1\text{H-NMR}(\text{CDCl}_3)$: δ 0.89 (3H, t, $J = 6.9\text{Hz}$), 1.29-1.40 (4H, m), 1.69 (1H, t, $J = 9.9\text{Hz}$), 2.00 (1H, td, $J = 3.6, 10.5\text{Hz}$), 2.73-2.99 (5H, m), 3.49 (2H, d, J

= 5.4Hz), 7.21-7.35 (5H, m)。

[0806] 参考例 53

[0807] [式 116]

[0808]

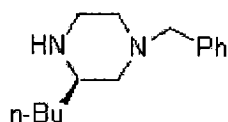


[0809] 收率:68%, $^1\text{H-NMR}$ (CDCl₃): δ 0.89 (3H, t, J = 6.8Hz), 1.26-1.40 (4H, m), 1.69 (1H, t, J = 9.9Hz), 2.00 (1H, td, J = 3.6, 10.8Hz), 2.72-2.95 (5H, m), 3.49 (2H, d, J = 5.1Hz), 7.23-7.32 (5H, m)。

[0810] 参考例 54

[0811] [式 117]

[0812]

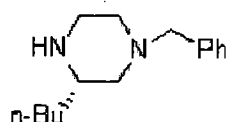


[0813] 收率: 定量收率 (quant. %), $^1\text{H-NMR}$ (CDCl₃): δ 0.88 (3H, t, J = 6.5Hz), 1.20-1.40 (6H, m), 1.50 (1H, brs), 1.70 (1H, t, J = 10Hz), 2.00 (1H, td, J = 11, 4Hz), 2.65-3.00 (5H, m), 3.46 (1H, d, J = 13Hz), 3.52 (1H, d, J = 13Hz), 7.20-7.40 (5H, m)。

[0814] 参考例 55

[0815] [式 118]

[0816]

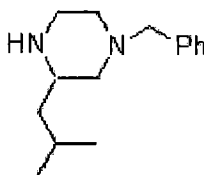


[0817] 收率: 定量收率, $^1\text{H-NMR}$ (CDCl₃): δ 0.88 (3H, d, J = 6.5Hz), 1.20-1.39 (6H, m), 1.70 (1H, t, J = 10Hz), 2.00 (1H, td, J = 11, 4Hz), 2.65-3.00 (5H, m), 3.46 (1H, d, J = 13Hz), 3.52 (1H, d, J = 13Hz), 7.20-7.40 (5H, m)。

[0818] 参考例 56

[0819] [式 119]

[0820]

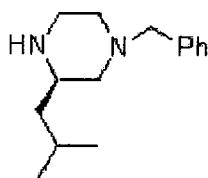


[0821] 收率:88%, $^1\text{H-NMR}$ (CDCl₃): δ 0.88 (6H, dd, J = 5.1, 6.6Hz), 1.09-1.26 (2H, m), 1.59-1.72 (3H, m), 2.00 (1H, dt, J = 3.9, 10.8Hz), 2.74-2.84 (3H, m), 2.88-2.94 (2H, m), 3.49 (2H, d, J = 7.5Hz), 7.31 (3H, s), 7.32 (2H, s)。

[0822] 参考例 57

[0823] [式 120]

[0824]

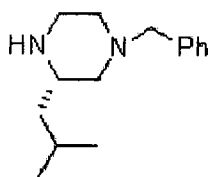


[0825] 收率：定量收率， $^1\text{H-NMR}$ (CDCl_3) : δ 0.87 (3H, d, $J = 6.5\text{Hz}$), 0.89 (3H, d, $J = 6.5\text{Hz}$), 1.05-1.29 (2H, m), 1.57-1.74 (2H, m), 2.00 (1H, td, $J = 10.5, 4.0\text{Hz}$), 2.70-2.99 (5H, m), 3.43 (1H, d, $J = 13.0\text{Hz}$), 3.50 (1H, d, $J = 13.0\text{Hz}$), 7.20-7.38 (5H, m)。

[0826] 参考例 58

[0827] [式 121]

[0828]

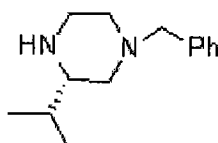


[0829] 收率：90%， $^1\text{H-NMR}$ (CDCl_3) : δ 0.87 (3H, d, $J = 5\text{Hz}$), 0.89 (3H, d, $J = 5\text{Hz}$), 1.16-1.30 (2H, m), 1.58-1.74 (2H, m), 2.00 (1H, td, $J = 11, 4\text{Hz}$), 2.70-3.00 (5H, m), 3.45 (1H, d, $J = 13\text{Hz}$), 3.52 (1H, d, $J = 13\text{Hz}$), 7.20-7.40 (5H, m)。

[0830] 参考例 59

[0831] [式 122]

[0832]

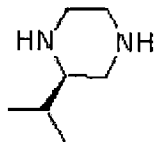


[0833] 收率：92%， $^1\text{H-NMR}$ (CDCl_3) : δ 0.88 (3H, d, $J = 6.5\text{Hz}$), 0.93 (3H, d, $J = 6.5\text{Hz}$), 1.55 (1H, sextet, $J = 6.5\text{Hz}$), 1.78 (1H, t, $J = 10.5\text{Hz}$), 1.97 (1H, td, $J = 11, 3.5\text{Hz}$), 2.67-3.03 (5H, m), 3.44 (1H, d, $J = 13\text{Hz}$), 3.56 (1H, d, $J = 13\text{Hz}$), 7.20-7.40 (5H, m)。

[0834] 参考例 60

[0835] [式 123]

[0836]



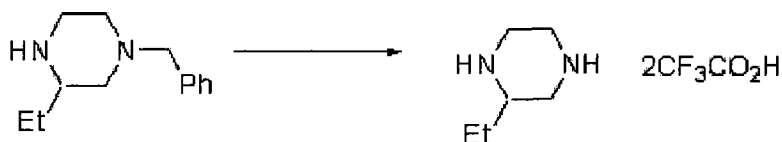
[0837] 收率：80%， $^1\text{H-NMR}$ (CDCl_3) : δ 0.91 (3H, d, $J = 7.0\text{Hz}$), 0.94 (3H, d, $J = 7.0\text{Hz}$), 1.43-1.60 (1H, m), 2.27-2.37 (1H, m), 2.38-2.48 (1H, m), 2.65-2.85 (2H, m), 2.86-2.94 (1H, m), 2.96-3.06 (2H, m)。

[0838] 参考例 61

[0839] 3-乙基哌嗪二(三氟乙酸盐)的合成

[0840] [式 124]

[0841]



[0842] 将 1- 苯甲基 -3- 乙基哌嗪 (1.16g ;5.68mmol), 5 % 钨碳 (0.11g), 三氟乙酸 (1.1ml ;14.8mmol) 和甲醇 (30ml) 的混合物在氢气的存在下在室温搅拌 17 小时。将反应溶液过滤并且将滤液减压浓缩。残余物用二异丙醚洗涤, 得到 3- 乙基哌嗪二 (三氟乙酸盐), 为无色晶体 (1.65g ;85%)。

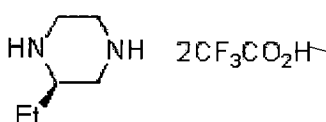
[0843] $^1\text{H-NMR}$ (D₂O) : δ 0.74 (3H, t, $J = 7.5\text{Hz}$), 1.44–1.54 (2H, m), 2.90 (1H, dd, $J = 12.0\text{Hz}$), 3.07–3.15 (2H, m), 3.20–3.34 (1H, m), 3.43–3.51 (3H, m)。

[0844] 如上得到参考例 62 到 71 的化合物。

[0845] 参考例 62

[0846] [式 125]

[0847]

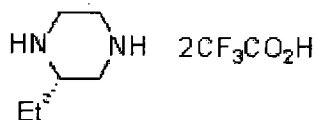


[0848] 收率 :88%, $^1\text{H-NMR}$ (DMSO- d_6) : δ 0.94 (3H, t, $J = 7.5\text{Hz}$), 1.60 (2H, quant, $J = 7.5\text{Hz}$), 2.93 (1H, t, $J = 12.5\text{Hz}$), 3.00–3.65 (6H, m), 9.24 (2H, brs)。

[0849] 参考例 63

[0850] [式 126]

[0851]

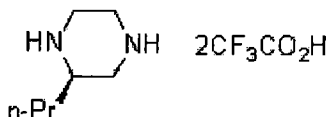


[0852] 收率 :80%, $^1\text{H-NMR}$ (DMSO- d_6) : δ 0.94 (3H, t, $J = 7.5\text{Hz}$), 1.61 (2H, quant, $J = 7.5\text{Hz}$), 2.93 (1H, t, $J = 12.5\text{Hz}$), 3.00–3.60 (6H, m), 9.27 (2H, brs)。

[0853] 参考例 64

[0854] [式 127]

[0855]

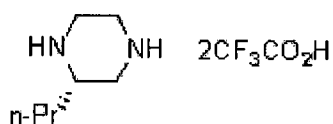


[0856] 收率 :59%, $^1\text{H-NMR}$ (D₂O) : δ 0.76 (3H, t, $J = 7.5\text{Hz}$), 1.25 (2H, m), 1.53 (2H, q, $J = 7.5\text{Hz}$), 3.00 (1H, t, $J = 12.9\text{Hz}$), 3.13–3.29 (2H, m), 3.39–3.48 (1H, m), 3.52–3.59 (3H, m)。

[0857] 参考例 65

[0858] [式 128]

[0859]

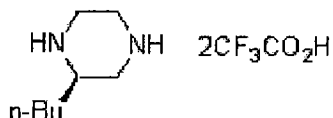


[0860] 收率:61 %, $^1\text{H-NMR}$ (D_2O) : δ 0.79 (3H, t, $J = 7.2\text{Hz}$), 1.22–1.35 (2H, m), 1.52–1.60 (2H, m), 3.03 (1H, dd, $J = 12.2\text{Hz}$), 3.16–3.32 (2H, m), 3.40–3.51 (1H, m), 3.55–3.63 (3H, m)。

[0861] 参考例 66

[0862] [式 129]

[0863]

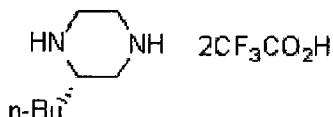


[0864] 收率:76 %, $^1\text{H-NMR}$ (DMSO-d_6) : δ 0.88 (3H, t, $J = 7\text{Hz}$), 1.20–1.40 (4H, m), 1.48–1.70 (2H, m), 2.96 (1H, t, $J = 12.5\text{Hz}$), 3.05–3.28 (2H, m), 3.30–3.44 (1H, m), 3.45–3.60 (3H, m), 9.39 (2H, brs)。

[0865] 参考例 67

[0866] [式 130]

[0867]

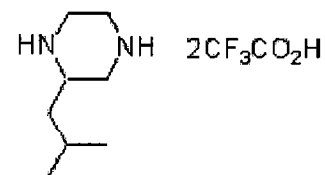


[0868] 收率:74 %, $^1\text{H-NMR}$ (DMSO-d_6) : δ 0.87 (3H, t, $J = 7.5\text{Hz}$), 1.20–1.40 (4H, m), 1.45–1.67 (2H, m), 2.94 (1H, t, $J = 7\text{Hz}$), 3.16 (2H, quant, $J = 12.5\text{Hz}$), 3.29–2.65 (4H, m), 9.35 (2H, brs)。

[0869] 参考例 68

[0870] [式 131]

[0871]

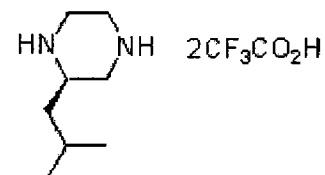


[0872] 收率:78 %, $^1\text{H-NMR}$ (D_2O) : δ 0.82 (6H, dd, $J = 1.8, 6.0\text{Hz}$), 1.49 (2H, t, $J = 6.9\text{Hz}$), 1.54–1.65 (1H, m), 3.06 (1H, dd, $J = 11.7\text{Hz}$), 3.20–3.37 (2H, m), 3.48–3.55 (1H, m), 3.57–3.66 (3H, m)。

[0873] 参考例 69

[0874] [式 132]

[0875]

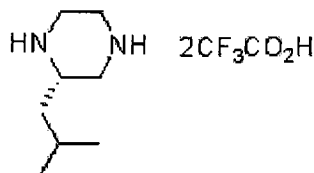


[0876] $^1\text{H-NMR}$ (CDCl_3) : δ 0.87 (3H, d, $J = 6.5\text{Hz}$), 0.89 (3H, d, $J = 6.5\text{Hz}$), 1.44 (2H, t, $J = 7.0\text{Hz}$), 1.61–1.78 (1H, m), 2.85–3.00 (1H, m), 3.03–3.32 (2H, m), 3.35–3.59 (4H, m), 9.34 (2H, brs)。

[0877] 参考例 70

[0878] [式 133]

[0879]

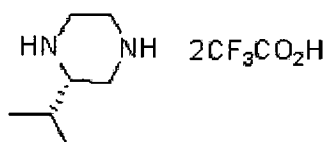


[0880] 收率 :82%, $^1\text{H-NMR}$ (DMSO-d_6) :0.88 (6H, t, $J = 6.5\text{Hz}$), 1.43 (2H, t, $J = 6.5\text{Hz}$), 1.70 (1H, quant, $J = 6.5\text{Hz}$), 2.90 (1H, t, $J = 13\text{Hz}$), 3.00–3.28 (2H, m), 3.35–3.55 (4H, m), 9.17 (2H, brs)。

[0881] 参考例 71

[0882] [式 134]

[0883]



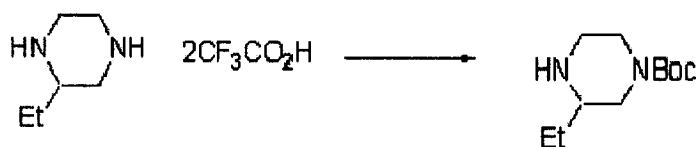
[0884] 收率 :49%, $^1\text{H-NMR}$ (DMSO-d_6) :0.94 (3H, d, $J = 7\text{Hz}$), 0.98 (3H, d, $J = 7\text{Hz}$), 1.84–1.98 (1H, m), 2.94 (1H, t, $J = 12.5\text{Hz}$), 3.05–3.25 (3H, m), 3.47 (2H, d, $J = 10.5\text{Hz}$), 3.52 (1H, d, $J = 15\text{Hz}$), 9.12 (2H, brs)。

[0885] 参考例 72

[0886] 1-叔丁氧羰基-3-乙基哌嗪的合成

[0887] [式 135]

[0888]



[0889] 在冰冷却下向 3-乙基哌嗪二(三氟乙酸盐) (0.51g ;1.47mmol) 和乙腈 (10ml) 的混合物中加入三乙胺 (0.62ml ;4.45mmol) 和二碳酸二叔丁基酯 (0.35g ;1.59mmol)。将混合物在室温搅拌 17 小时。将反应溶液减压浓缩。向残余物中加入乙酸乙酯和水并且萃取。有机层用盐水洗涤,用无水硫酸钠干燥,并且减压蒸发。残余物通过硅胶柱色谱法纯化(氯仿:甲醇 = 20 : 1),得到 1-叔丁氧羰基-3-乙基哌嗪,为无色晶体 (0.27g ;85%)。

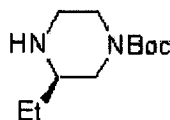
[0890] $^1\text{H-NMR}$ (CDCl_3) : δ 1.03 (3H, t, $J = 7.5\text{Hz}$), 1.47 (9H, s), 1.60–1.81 (2H, m), 2.96 (3H, br), 3.26 (2H, d, $J = 12.6\text{Hz}$), 4.08 (2H, d, $J = 14.1\text{Hz}$)。

[0891] 如上得到参考例 73 到 83 的化合物。

[0892] 参考例 73

[0893] [式 136]

[0894]

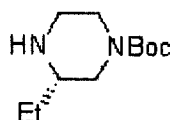


[0895] 收率:99%, $^1\text{H-NMR}$ (CDCl_3): 0.95 (3H, t, $J = 7.5\text{Hz}$), 1.30-1.45 (2H, m), 1.46 (9H, s), 1.67 (1H, brs), 2.30-2.55 (2H, m), 2.68-2.90 (2H, m), 2.91-3.01 (1H, m), 3.80-4.05 (2H, m)。

[0896] 参考例 74

[0897] [式 137]

[0898]

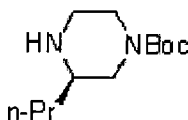


[0899] 收率:80%, $^1\text{H-NMR}$ (CDCl_3): 0.95 (3H, t, $J = 7.5\text{Hz}$), 1.30-1.45 (2H, m), 1.46 (9H, s), 1.69 (1H, brs), 2.30-2.55 (2H, m), 2.68-2.88 (2H, m), 2.90-3.00 (1H, m), 3.85-4.02 (2H, m)。

[0900] 参考例 75

[0901] [式 138]

[0902]

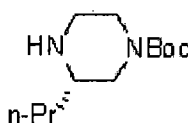


[0903] 收率:定量收率, $^1\text{H-NMR}$ (CDCl_3 , 328K): 0.94 (3H, t, $J = 6.9\text{Hz}$), 1.29-1.46 (4H, m), 1.46 (9H, s), 2.64-2.86 (3H, m), 2.96-3.14 (2H, m), 3.64-4.04 (2H, m)。

[0904] 参考例 76

[0905] [式 139]

[0906]

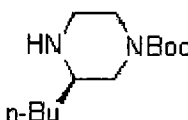


[0907] 收率:定量收率, $^1\text{H-NMR}$ (CDCl_3 , 328K): 0.94 (3H, t, $J = 6.9\text{Hz}$), 1.36-1.60 (4H, m), 1.47 (9H, s), 2.82-2.93 (3H, m), 3.12-3.21 (2H, m), 3.99-4.10 (2H, m)。

[0908] 参考例 77

[0909] [式 140]

[0910]

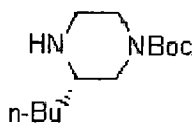


[0911] 收率:96%, $^1\text{H-NMR}$ (CDCl_3): 0.90 (3H, t, $J = 6\text{Hz}$), 1.25-1.40 (6H, m), 1.46 (9H, s), 1.54 (1H, brs), 2.30-2.60 (2H, m), 2.67-2.86 (2H, m), 2.90-2.99 (1H, m), 3.80-4.05 (2H, m)。

[0912] 参考例 78

[0913] [式 141]

[0914]

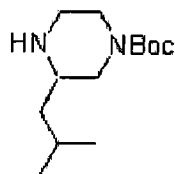


[0915] 收率 :94 % , $^1\text{H-NMR}$ (CDC13) :0.85-0.95 (3H, m) , 1.25-1.40 (6H, m) , 1.46 (9H, s) , 1.56 (1H, brs) , 2.30-3.00 (5H, m) , 3.80-4.05 (2H, m) 。

[0916] 参考例 79

[0917] [式 142]

[0918]

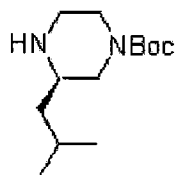


[0919] 收 率 :90 % , $^1\text{H-NMR}$ (CDC13) :0.94 (6H, dd, $J = 3.3, 6.3\text{Hz}$) , 1.47 (9H, s) , 1.43-1.54 (2H, m) , 1.68-1.79 (1H, m) , 2.97 (2H, dt, $J = 3.3, 12.3\text{Hz}$) , 3.08 (1H, br) , 3.22-3.28 (2H, m) , 4.08 (2H, d, $J = 13.8\text{Hz}$) 。

[0920] 参考例 80

[0921] [式 143]

[0922]

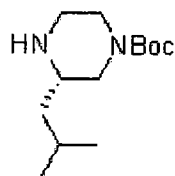


[0923] 收 率 :74 % , $^1\text{H-NMR}$ (CDC13) :0.90 (3H, d, $J = 6.5\text{Hz}$) , 0.93 (3H, d, $J = 6.5\text{Hz}$) , 1.11-1.30 (2H, m) , 1.47 (9H, s) , 1.60-1.78 (1H, m) , 2.41 (1H, brs) , 2.56-2.87 (3H, m) , 2.90-3.00 (1H, m) , 3.82-4.03 (2H, m) 。

[0924] 参考例 81

[0925] [式 144]

[0926]

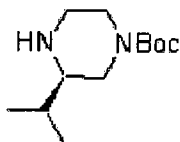


[0927] 收率 :99 % , $^1\text{H-NMR}$ (CDC13) :0.92 (6H, t, $J = 7\text{Hz}$) , 1.15-1.30 (2H, m) , 1.46 (9H, s) , 1.47 (1H, brs) , 1.62-1.76 (1H, m) , 2.30-2.52 (1H, m) , 2.58-3.00 (4H, m) , 3.82-4.04 (2H, m) 。

[0928] 参考例 82

[0929] [式 145]

[0930]

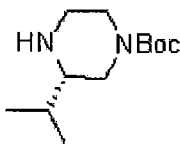


[0931] 收率:59%, $^1\text{H-NMR}$ (CDCl_3): 0.95 (3H, d, $J = 13.5\text{Hz}$), 0.96 (3H, d, $J = 13.5\text{Hz}$), 1.46 (9H, s), 1.47–1.69 (1H, m), 2.22–2.35 (1H, m), 2.38–2.63 (1H, brs), 2.65–2.86 (2H, m), 2.93–3.04 (1H, m), 3.80–4.17 (2H, m)。

[0932] 参考例 83

[0933] [式 146]

[0934]



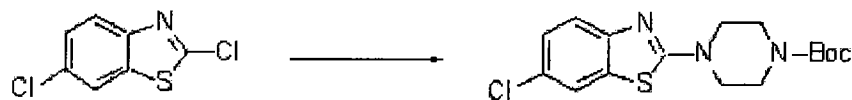
[0935] 收率:75%, $^1\text{H-NMR}$ (CDCl_3): 0.94 (3H, d, $J = 2.5\text{Hz}$), 0.96 (3H, d, $J = 2.5\text{Hz}$), 1.46 (9H, s), 1.53–1.70 (2H, m), 2.24–2.35 (1H, m), 2.36–2.65 (1H, m), 2.66–2.86 (2H, m), 2.93–3.04 (1H, m), 3.80–4.16 (2H, m)。

[0936] 参考例 84

[0937] 4-(6-氯苯并噻唑-2-基)哌嗪-1-羧酸叔丁基酯的制备

[0938] [式 147]

[0939]



[0940] 将 2,6-二氯苯并噻唑 (1.00g; 4.90mmol)、1-哌嗪-叔丁基酯 (0.96g; 5.15mmol)、碳酸钾 (0.71g; 5.15mmol) 和无水 N,N -二甲基甲酰胺 (10ml) 的混合物在室温搅拌 14 小时和在 50°C 搅拌 3 小时。向反应溶液加入水。收集沉淀物并且用二异丙醚洗涤, 得到 4-(6-氯苯并噻唑-2-基)哌嗪-1-羧酸叔丁基酯, 为带浅黑色的褐色晶体 (1.50g; 87%)。

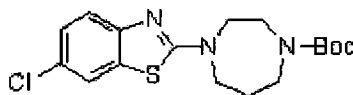
[0941] $^1\text{H-NMR}$ ($\text{DMSO}-d_6$): δ 1.43 (9H, s), 3.44–3.53 (4H, m), 3.55–3.60 (4H, m), 7.30 (1H, dd, $J = 8, 2\text{Hz}$), 7.44 (1H, d, $J = 8\text{Hz}$), 7.93 (1H, d, $J = 2\text{Hz}$)。

[0942] 通过与参考例 84 相似的方法得到参考例 85 到 154 的化合物。

[0943] 参考例 85

[0944] [式 148]

[0945]

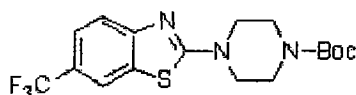


[0946] 收率:97%, $^1\text{H-NMR}$ (CDCl_3): δ 1.42 (9H, d, $J = 8.4\text{Hz}$), 2.01–2.07 (2H, m), 3.36 (1H, t, $J = 6.0\text{Hz}$), 3.44 (1H, t, $J = 5.7\text{Hz}$), 3.63–3.76 (6H, m), 7.24 (1H, dd, $J = 8.7, 2.1\text{Hz}$), 7.43 (1H, d, $J = 8.4\text{Hz}$), 7.55 (1H, d, $J = 2.4\text{Hz}$)。

[0947] 参考例 86

[0948] [式 149]

[0949]

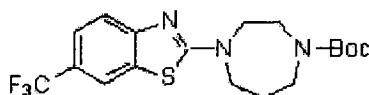


[0950] 收率 :51 % , $^1\text{H-NMR}$ (DMSO-d_6) : δ 1.43 (9H, s) , 3.44-3.53 (4H, m) , 3.55-3.65 (4H, m) , 7.58 (2H, s) , 8.27 (1H, s) 。

[0951] 参考例 87

[0952] [式 150]

[0953]

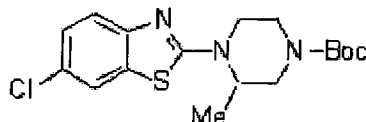


[0954] 收率 :47 % , $^1\text{H-NMR}$ (CDCl_3) : δ 1.44 (9H, s) , 2.06 (2H, quant, $J = 6\text{Hz}$) , 3.35-3.50 (2H, m) , 3.60-3.85 (6H, m) , 7.50-7.60 (2H, m) , 7.85 (1H, s) 。

[0955] 参考例 88

[0956] [式 151]

[0957]

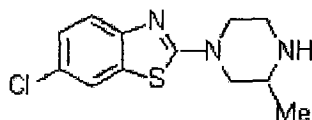


[0958] 收率 :43 % , $^1\text{H-NMR}$ (CDCl_3) : δ 1.29 (3H, d, $J = 7\text{Hz}$) , 1.49 (9H, s) , 2.85-3.10 (1H, m) , 3.10-3.30 (1H, m) , 3.40 (1H, td, $J = 13, 3.5\text{Hz}$) , 3.75-4.25 (4H, m) , 7.24 (1H, dd, $J = 8.5, 2\text{Hz}$) , 7.44 (1H, d, $J = 8.5\text{Hz}$) , 7.56 (1H, d, $J = 2\text{Hz}$) 。

[0959] 参考例 89

[0960] [式 152]

[0961]

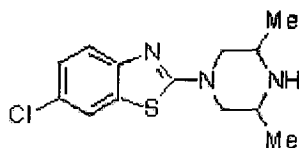


[0962] 收率 :69 % , $^1\text{H-NMR}$ (CDCl_3) : δ 1.16 (3H, d, $J = 6\text{Hz}$) , 1.76 (1H, brs) , 2.80 (1H, dd, $J = 12, 12\text{Hz}$) , 2.90-2.95 (1H, m) , 3.00 (1H, dd, $J = 12, 3\text{Hz}$) , 3.15 (1H, td, $J = 12, 3\text{Hz}$) , 3.21 (1H, dd, $J = 12, 3\text{Hz}$) , 3.84-4.00 (2H, m) , 7.24 (1H, dd, $J = 8.5, 2.5\text{Hz}$) , 7.44 (1H, d, $J = 8.5\text{Hz}$) , 7.56 (1H, d, $J = 2.5\text{Hz}$) 。

[0963] 参考例 90

[0964] [式 153]

[0965]

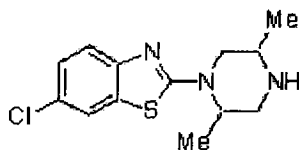


[0966] 收率 :90 % , $^1\text{H-NMR}$ (CDCl_3) : δ 1.15 (6H, d, $J = 6\text{Hz}$) , 1.61 (1H, brs) , 2.73 (2H, dd, $J = 12.5, 10\text{Hz}$) , 2.95-3.10 (2H, m) , 3.94 (2H, dd, $J = 12.5, 2.5\text{Hz}$) , 7.23 (1H, dd, $J = 8.5, 2\text{Hz}$) , 7.42 (1H, d, $J = 2\text{Hz}$) , 7.55 (1H, d, $J = 8.5\text{Hz}$) 。

[0967] 参考例 91

[0968] [式 154]

[0969]

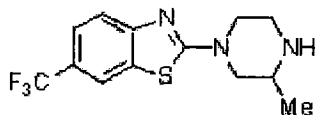


[0970] 收率:40%, $^1\text{H-NMR}(\text{CDCl}_3)$: δ 1.27 (3H, d, $J = 7\text{Hz}$), 1.37 (3H, d, $J = 7\text{Hz}$), 2.64 (1H, dd, $J = 12, 2.5\text{Hz}$), 3.20-3.35 (1H, m), 3.42 (1H, dd, $J = 12, 4.5\text{Hz}$), 3.50-3.65 (2H, m), 4.10-4.25 (1H, m), 7.23 (1H, dd, $J = 8.5, 2\text{Hz}$), 7.42 (1H, d, $J = 8.5\text{Hz}$), 7.54 (1H, d, $J = 2\text{Hz}$)。

[0971] 参考例 92

[0972] [式 155]

[0973]

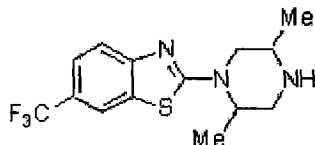


[0974] 收率:87%, $^1\text{H-NMR}(\text{CDCl}_3)$: δ 1.16 (3H, d, $J = 6\text{Hz}$), 1.62 (1H, brs), 2.84 (1H, t, $J = 10.5\text{Hz}$), 2.90-3.00 (1H, m), 3.01 (1H, dd, $J = 12, 3\text{Hz}$), 3.14 (1H, dt, $J = 12, 2.5\text{Hz}$), 3.25 (1H, td, $J = 12, 3.5\text{Hz}$), 4.01 (2H, t, $J = 12\text{Hz}$), 7.52 (1H, d, $J = 8.5\text{Hz}$), 7.57 (1H, d, $J = 8.5\text{Hz}$), 7.85 (1H, s)。

[0975] 参考例 93

[0976] [式 156]

[0977]

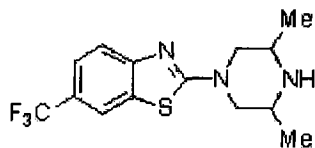


[0978] 收率:8%, $^1\text{H-NMR}(\text{CDCl}_3)$: δ 1.27 (3H, d, $J = 6.5\text{Hz}$), 1.40 (3H, d, $J = 6.5\text{Hz}$), 1.65 (1H, brs), 2.66 (1H, dd, $J = 13, 2\text{Hz}$), 3.25-3.40 (1H, m), 3.43 (1H, dd, $J = 13, 4.5\text{Hz}$), 3.61 (2H, d, $J = 3\text{Hz}$), 4.20-4.28 (1H, m), 7.51 (1H, d, $J = 8.5\text{Hz}$), 7.56 (1H, d, $J = 8.5\text{Hz}$), 7.84 (1H, s)。

[0979] 参考例 94

[0980] [式 157]

[0981]

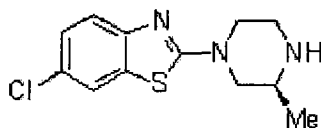


[0982] 收率:38%, $^1\text{H-NMR}(\text{CDCl}_3)$: δ 1.16 (6H, d, $J = 6.5\text{Hz}$), 1.54 (1H, brs), 2.76 (1H, d, $J = 12.5\text{Hz}$), 2.80 (1H, d, $J = 12.5\text{Hz}$), 2.95-3.08 (2H, m), 3.95-4.03 (2H, m), 7.52 (1H, d, $J = 8.5\text{Hz}$), 7.57 (1H, d, $J = 8.5\text{Hz}$), 7.85 (1H, s)。

[0983] 参考例 95

[0984] [式 158]

[0985]

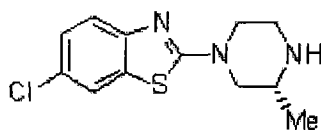


[0986] 收率:71%, $^1\text{H-NMR}(\text{CDCl}_3)$: δ 1.15(3H, d, $J = 6.3\text{Hz}$), 2.80(1H, dd, $J = 12.3\text{Hz}$), 2.88-3.02(2H, m), 3.08-3.23(2H, m), 3.94(2H, dd, $J = 12.3\text{Hz}$), 7.24(1H, dd, $J = 2.1, 8.7\text{Hz}$), 7.43(1H, d, $J = 8.7\text{Hz}$), 7.56(1H, d, $J = 2.1\text{Hz}$)。

[0987] 参考例 96

[0988] [式 159]

[0989]

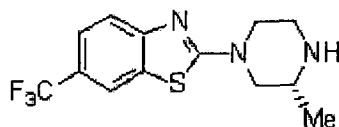


[0990] 收率:77%, $^1\text{H-NMR}(\text{CDCl}_3)$: δ 1.15(3H, d, $J = 6.0\text{Hz}$), 2.80(1H, dd, $J = 12.3\text{Hz}$), 2.89-3.02(2H, m), 3.10-3.23(2H, m), 3.95(2H, t, $J = 12.3\text{Hz}$), 7.24(1H, dd, $J = 2.4, 8.4\text{Hz}$), 7.44(1H, d, $J = 8.4\text{Hz}$), 7.56(1H, d, $J = 2.4\text{Hz}$)。

[0991] 参考例 97

[0992] [式 160]

[0993]

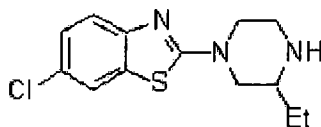


[0994] 收率:48%, $^1\text{H-NMR}(\text{CDCl}_3)$: δ 1.16(3H, d, $J = 6.0\text{Hz}$), 2.86(1H, d, $J = 12.0\text{Hz}$), 2.88-3.03(2H, m), 3.11-3.16(1H, m), 3.23(1H, dt, $J = 3.3, 12.0\text{Hz}$), 4.01(2H, t, $J = 12.6\text{Hz}$), 7.51-7.59(2H, m), 7.85(1H, s)。

[0995] 参考例 98

[0996] [式 161]

[0997]

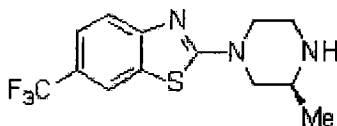


[0998] 收率:63%, $^1\text{H-NMR}(\text{CDCl}_3)$: δ 1.01(3H, t, $J = 7.2\text{Hz}$), 1.44-1.53(2H, m), 2.67-2.76(1H, m), 2.80-2.88(1H, m), 2.91-3.00(1H, m), 3.10-3.20(2H, m), 3.91-4.01(2H, m), 7.24(1H, dd, $J = 2.1, 8.7\text{Hz}$), 7.43(1H, d, $J = 8.7\text{Hz}$), 7.55(1H, d, $J = 2.1\text{Hz}$), 8.02(1H, s)。

[0999] 参考例 99

[1000] [式 162]

[1001]

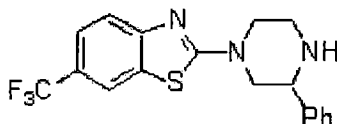


[1002] 收率: 定量收率, $^1\text{H-NMR}$ (CDCl_3): δ 1.16 (3H, d, $J = 6\text{Hz}$), 1.75 (1H, brs), 2.80-3.05 (3H, m), 3.08-3.18 (1H, m), 3.25 (1H, dd, $J = 12, 3.5\text{Hz}$), 4.00 (2H, t, $J = 12\text{Hz}$), 7.53 (1H, d, $J = 8.5\text{Hz}$), 7.55 (1H, d, $J = 8.5\text{Hz}$), 7.85 (1H, s)。

[1003] 参考例 100

[1004] [式 163]

[1005]

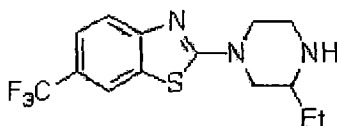


[1006] 收率: 定量收率, $^1\text{H-NMR}$ (CDCl_3): δ 1.98 (1H, brs), 3.06-3.30 (3H, m), 3.38 (1H, dd, $J = 12, 3.5\text{Hz}$), 3.93 (1H, dd, $J = 10.5, 3\text{Hz}$), 4.05-4.18 (2H, m), 7.30-7.60 (7H, m), 7.86 (1H, s)。

[1007] 参考例 101

[1008] [式 164]

[1009]

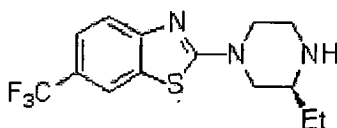


[1010] 收率: 定量收率, $^1\text{H-NMR}$ (CDCl_3): δ 1.02 (3H, t, $J = 7.5\text{Hz}$), 1.38-1.60 (2H, m), 1.75 (1H, brs), 2.65-2.80 (1H, m), 2.85-3.00 (2H, m), 3.10-3.20 (1H, m), 3.25 (1H, td, $J = 12, 3.5\text{Hz}$), 3.95-4.10 (2H, m), 7.52 (1H, dd, $J = 8.5, 1.5\text{Hz}$), 7.57 (1H, d, $J = 8.5\text{Hz}$), 7.85 (1H, d, $J = 1.5\text{Hz}$)。

[1011] 参考例 102

[1012] [式 165]

[1013]

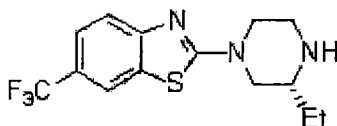


[1014] 收率: 93%, $^1\text{H-NMR}$ (CDCl_3): δ 1.02 (3H, t, $J = 7.5\text{Hz}$), 1.38-1.60 (2H, m), 1.78 (1H, brs), 2.67-2.78 (1H, m), 2.82-3.03 (2H, m), 3.09-3.32 (2H, m), 3.95-4.10 (2H, m), 7.52 (1H, d, $J = 8.5\text{Hz}$), 7.70 (1H, d, $J = 8.5\text{Hz}$), 7.85 (1H, s)。

[1015] 参考例 103

[1016] [式 166]

[1017]

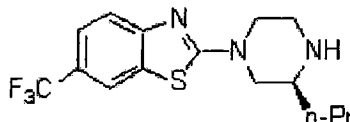


[1018] 收率:定量收率, $^1\text{H-NMR}$ (CDCl_3): δ 1.02 (3H, t, $J = 7.5\text{Hz}$), 1.38-1.60 (2H, m), 1.83 (1H, brs), 2.65-2.78 (1H, m), 2.85-3.03 (2H, m), 3.10-3.18 (1H, m), 3.24 (1H, td, $J = 12, 3.5\text{Hz}$), 3.93-4.10 (2H, m), 7.52 (1H, dd, $J = 8.5, 1.5\text{Hz}$), 7.57 (1H, d, $J = 8.5\text{Hz}$), 7.85 (1H, d, $J = 1.5\text{Hz}$)。

[1019] 参考例 104

[1020] [式 167]

[1021]

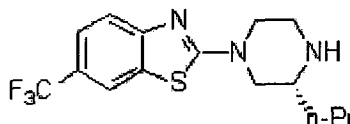


[1022] 收率:84 %, $^1\text{H-NMR}$ (CDCl_3): δ 0.90-1.05 (3H, m), 1.35-1.54 (4H, m), 1.55-1.66 (2H, m), 2.75-3.02 (3H, m), 3.14 (1H, dt, $J = 12, 2\text{Hz}$), 3.25 (1H, td, $J = 12.5, 3.5\text{Hz}$), 4.01 (1H, t, $J = 11.5\text{Hz}$), 7.52 (1H, dd, $J = 8.5, 1.5\text{Hz}$), 7.57 (1H, d, $J = 8.5\text{Hz}$), 7.85 (1H, d, $J = 1.5\text{Hz}$)。

[1023] 参考例 105

[1024] [式 168]

[1025]

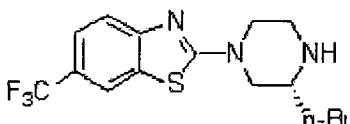


[1026] 收率:87 %, $^1\text{H-NMR}$ (CDCl_3): δ 0.96-0.99 (3H, m), 1.42-1.50 (4H, m), 2.83-3.01 (3H, m), 3.12-3.29 (2H, m), 4.01 (2H, t, $J = 9.9\text{Hz}$), 7.51-7.59 (2H, m), 7.85 (1H, s), 8.02 (1H, s)。

[1027] 参考例 106

[1028] [式 169]

[1029]

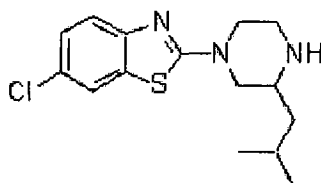


[1030] 收率:定量收率, $^1\text{H-NMR}$ (CDCl_3): δ 0.94 (3H, t, $J = 7.5\text{Hz}$), 1.29-1.54 (6H, m), 1.56-1.70 (2H, m), 2.73-3.05 (3H, m), 3.13 (1H, dt, $J = 12, 2\text{Hz}$), 3.25 (1H, td, $J = 12, 3.5\text{Hz}$), 4.01 (1H, t, $J = 10\text{Hz}$), 7.52 (1H, dd, $J = 8.5, 1.5\text{Hz}$), 7.57 (1H, d, $J = 8.5\text{Hz}$), 7.85 (1H, d, $J = 1.5\text{Hz}$)。

[1031] 参考例 107

[1032] [式 170]

[1033]

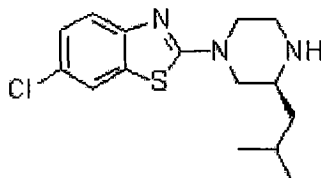


[1034] 收率:56%,¹H-NMR(CDC13): δ 0.95(6H, dd, $J = 6.6, 8.4\text{Hz}$), 1.25-1.33(2H, m), 1.71-1.80(1H, m), 2.77-2.92(2H, m), 2.96-3.00(1H, m), 3.10-3.24(2H, m), 3.95(2H, d, $J = 10.5\text{Hz}$), 7.24(1H, dd, $J = 2.1, 8.4\text{Hz}$), 7.44(1H, d, $J = 8.4\text{Hz}$), 7.56(1H, d, $J = 2.1\text{Hz}$)。

[1035] 参考例 108

[1036] [式 171]

[1037]

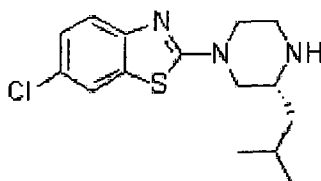


[1038] 收率:定量收率,¹H-NMR(CDC13): δ 0.93(3H, d, $J = 6.5\text{Hz}$), 0.96(3H, d, $J = 6.5\text{Hz}$), 1.26-1.35(2H, m), 1.68(1H, brs), 1.69-1.83(1H, m), 2.73-3.03(3H, m), 3.07-3.25(2H, m), 3.90-4.00(2H, m), 7.23(1H, dd, $J = 8.5, 2\text{Hz}$), 7.44(1H, d, $J = 8.5\text{Hz}$), 7.55(1H, d, $J = 2\text{Hz}$)。

[1039] 参考例 109

[1040] [式 172]

[1041]

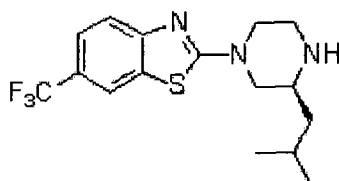


[1042] 收率:定量收率,¹H-NMR(CDC13): δ 0.93(3H, d, $J = 6.5\text{Hz}$), 0.96(3H, d, $J = 6.5\text{Hz}$), 1.20-1.38(2H, m), 1.60-1.84(2H, m), 2.72-3.03(2H, m), 3.05-3.26(2H, m), 3.87-4.02(2H, m), 7.23(1H, dd, $J = 8.5, 2.0\text{Hz}$), 7.43(1H, d, $J = 8.5\text{Hz}$), 7.55(1H, d, $J = 2.0\text{Hz}$)。

[1043] 参考例 110

[1044] [式 173]

[1045]

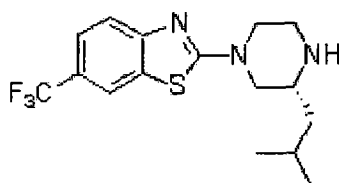


[1046] 收率:定量收率,¹H-NMR(CDC13): δ 0.94(3H, d, $J = 6.5\text{Hz}$), 0.97(3H, d, $J = 6.5\text{Hz}$), 1.27-1.37(2H, m), 1.66(1H, brs), 1.70-1.83(1H, m), 2.80-3.03(3H, m), 3.09-3.30(2H, m), 3.95-4.05(2H, m), 7.52(1H, d, $J = 8.5\text{Hz}$), 7.57(1H, d, $J = 8.5\text{Hz}$), 7.85(1H, s)。

[1047] 参考例 111

[1048] [式 174]

[1049]

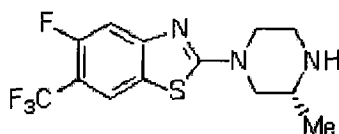


[1050] 收率:91%, $^1\text{H-NMR}$ (CDCl_3): δ 0.94 (3H, d, $J = 6.5\text{Hz}$), 0.97 (3H, d, $J = 6.5\text{Hz}$), 1.27-1.36 (2H, m), 1.62-1.84 (2H, m), 2.81-3.03 (2H, m), 3.09-3.30 (2H, m), 3.94-4.07 (2H, m), 7.52 (1H, d, $J = 8.5\text{Hz}$), 7.57 (1H, d, $J = 8.5\text{Hz}$), 7.85 (1H, s)。

[1051] 参考例 112

[1052] [式 175]

[1053]

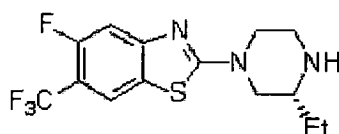


[1054] 收率:91%, $^1\text{H-NMR}$ (CDCl_3): δ 1.16 (3H, d, $J = 6\text{Hz}$), 1.58 (1H, brs), 2.80-3.03 (3H, m), 3.07-3.17 (1H, m), 3.24 (1H, td, $J = 12, 3.5\text{Hz}$), 3.99 (2H, t, $J = 11\text{Hz}$), 7.26 (1H, d, $J = 12\text{Hz}$), 7.75 (1H, d, $J = 6.5\text{Hz}$)。

[1055] 参考例 113

[1056] [式 176]

[1057]

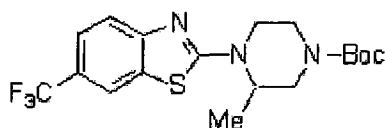


[1058] 收率:91%, $^1\text{H-NMR}$ (CDCl_3): δ 1.02 (3H, t, $J = 7.5\text{Hz}$), 1.37-1.62 (2H, m), 1.90 (1H, brs), 2.64-2.78 (1H, m), 2.84-3.03 (2H, m), 3.10-3.20 (1H, m), 3.21-3.32 (1H, m), 3.92-4.09 (2H, m), 7.27 (1H, d, $J = 12.5\text{Hz}$), 7.76 (1H, d, $J = 6.5\text{Hz}$)。

[1059] 参考例 114

[1060] [式 177]

[1061]

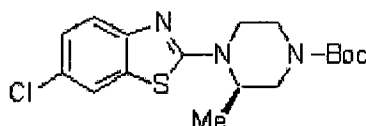


[1062] 收率:75%, $^1\text{H-NMR}$ (CDCl_3): δ 1.32 (3H, d, $J = 6.5\text{Hz}$), 1.50 (9H, s), 2.90-3.30 (2H, m), 3.44 (1H, td, $J = 12.5, 3.5\text{Hz}$), 3.80-4.40 (4H, m), 7.53 (1H, dd, $J = 8.5, 1.5\text{Hz}$), 7.57 (1H, d, $J = 8.5\text{Hz}$), 7.86 (1H, d, $J = 1.5\text{Hz}$)。

[1063] 参考例 115

[1064] [式 178]

[1065]

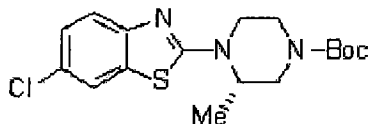


[1066] 收率:61%, ¹H-NMR(CDCl₃): δ 1.29(3H, d, J = 6Hz), 1.49(9H, s), 2.90-3.30(2H, m), 3.34-3.48(1H, m), 3.80-4.30(4H, m), 7.25(1H, dd, J = 8.5, 2Hz), 7.44(1H, d, J = 8.5Hz), 7.57(1H, d, J = 2Hz)。

[1067] 参考例 116

[1068] [式 179]

[1069]

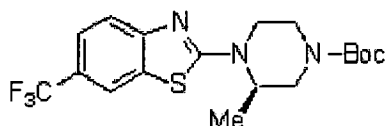


[1070] 收率:31%, ¹H-NMR(CDCl₃): δ 1.30(3H, d, J = 6.5Hz), 1.49(9H, s), 2.91-3.29(2H, m), 3.33-3.47(1H, m), 3.76-4.34(4H, m), 7.25(1H, dd, J = 8.5, 2.0Hz), 7.44(1H, d, J = 8.5Hz), 7.57(1H, d, J = 2.0Hz)。

[1071] 参考例 117

[1072] [式 180]

[1073]

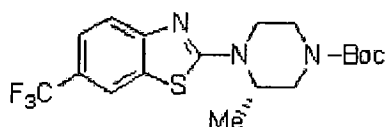


[1074] 收率:65%, ¹H-NMR(CDCl₃): δ 1.31(3H, d, J = 6.5Hz), 1.50(9H, s), 2.90-3.30(2H, m), 3.44(1H, td, J = 12.5, 3.5Hz), 3.85-4.35(4H, m), 7.53(1H, dd, J = 8.5, 1.5Hz), 7.58(1H, d, J = 8.5Hz), 7.86(1H, d, J = 1.5Hz)。

[1075] 参考例 118

[1076] [式 181]

[1077]

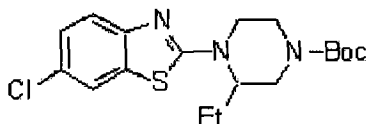


[1078] 收率:50%, ¹H-NMR(CDCl₃): δ 1.32(3H, d, J = 6.5Hz), 1.50(9H, s), 2.85-3.27(2H, m), 3.32-3.52(1H, m), 3.82-4.38(4H, m), 7.54(1H, d, J = 8.5Hz), 7.58(1H, d, J = 8.5Hz), 7.86(1H, s)。

[1079] 参考例 119

[1080] [式 182]

[1081]

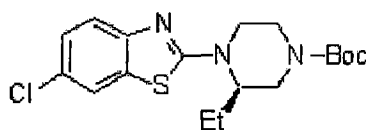


[1082] 收率:22%, ¹H-NMR(CDCl₃): δ 1.00(3H, t, J = 7.5Hz), 1.49(9H, s), 1.63-1.78(2H, m), 2.83-3.17(2H, m), 3.26-3.41(1H, m), 3.82-4.31(4H, m), 7.23(1H, dd, J = 8.5, 2.0Hz), 7.41(1H, d, J = 8.5Hz), 7.53(1H, d, J = 2.0Hz)。

[1083] 参考例 120

[1084] [式 183]

[1085]

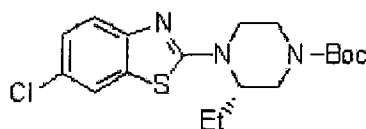


[1086] 收 率 :41 % , $^1\text{H-NMR}$ (CDCl_3) : δ 1.00 (3H, t, $J = 7.5\text{Hz}$), 1.49 (9H, s), 1.72 (2H, quant, $J = 7.5\text{Hz}$), 2.90-3.20 (3H, m), 3.26-3.42 (1H, m), 3.85-4.00 (2H, m), 4.10-4.30 (1H, m), 7.24 (1H, dd, $J = 8.5, 2\text{Hz}$), 7.41 (1H, d, $J = 8.5\text{Hz}$), 7.55 (1H, d, $J = 2\text{Hz}$)。

[1087] 参考例 121

[1088] [式 184]

[1089]

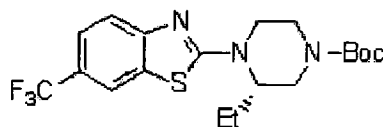


[1090] 收 率 :25 % , $^1\text{H-NMR}$ (CDCl_3) : δ 1.00 (3H, t, $J = 7.5\text{Hz}$), 1.49 (9H, s), 1.63-1.78 (2H, m), 2.82-3.19 (2H, m), 3.26-3.43 (1H, m), 3.80-4.30 (4H, m), 7.23 (1H, dd, $J = 8.5, 2.0\text{Hz}$), 7.41 (1H, d, $J = 8.5\text{Hz}$), 7.54 (1H, d, $J = 2.0\text{Hz}$)。

[1091] 参考例 122

[1092] [式 185]

[1093]

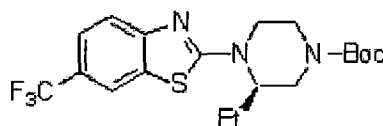


[1094] 收 率 :67 % , $^1\text{H-NMR}$ (CDCl_3) : δ 1.01 (3H, t, $J = 7.5\text{Hz}$), 1.49 (9H, s), 1.68-1.80 (2H, m), 2.90-3.20 (2H, m), 3.32-3.46 (1H, m), 3.90-4.32 (4H, m), 7.54 (1H, d, $J = 8.5\text{Hz}$), 7.55 (1H, d, $J = 8.5\text{Hz}$), 7.85 (1H, s)。

[1095] 参考例 123

[1096] [式 186]

[1097]

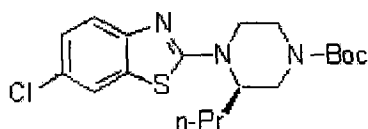


[1098] 收 率 :60 % , $^1\text{H-NMR}$ (CDCl_3) : δ 1.01 (3H, t, $J = 7.5\text{Hz}$), 1.49 (9H, s), 1.74 (2H, quant, $J = 7.5\text{Hz}$), 2.90-3.20 (2H, m), 3.33-3.46 (1H, m), 3.92-4.31 (4H, m), 7.50-7.58 (2H, m), 7.85 (1H, s)。

[1099] 参考例 124

[1100] [式 187]

[1101]

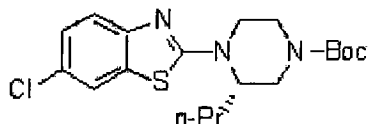


[1102] 收率:43%, $^1\text{H-NMR}(\text{CDCl}_3)$: δ 0.96 (3H, t, $J = 7.0\text{Hz}$), 1.25-1.75 (4H, m), 1.49 (9H, s), 2.84-3.18 (2H, m), 3.36 (1H, td, $J = 12.5, 3.0\text{Hz}$), 3.85-4.32 (4H, m), 7.24 (1H, dd, $J = 8.5, 2.0\text{Hz}$), 7.41 (1H, d, $J = 8.5\text{Hz}$), 7.55 (1H, d, $J = 2.0\text{Hz}$)。

[1103] 参考例 125

[1104] [式 188]

[1105]

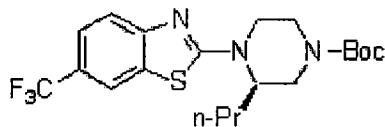


[1106] 收率:33%, $^1\text{H-NMR}(\text{CDCl}_3, 328\text{K})$: δ 0.96 (3H, t, $J = 7.2\text{Hz}$), 1.36-1.49 (2H, m), 1.49 (9H, s), 1.59-1.71 (2H, m), 2.98 (1H, t, $J = 11.1\text{Hz}$), 3.10 (1H, d, $J = 11.1\text{Hz}$), 3.36 (1H, dt, $J = 3.3, 13.2\text{Hz}$), 3.93-4.12 (4H, m), 7.22 (1H, s), 7.41 (1H, d, $J = 8.4\text{Hz}$), 7.54 (1H, s)。

[1107] 参考例 126

[1108] [式 189]

[1109]

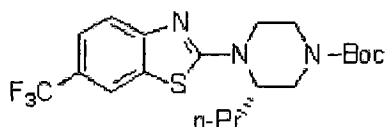


[1110] 收率:40%, $^1\text{H-NMR}(\text{CDCl}_3)$: δ 0.97 (3H, t, $J = 7.0\text{Hz}$), 1.20-1.55 (2H, m), 1.50 (9H, s), 1.56-1.77 (2H, m), 2.83-3.21 (2H, m), 3.40 (1H, td, $J = 13.0, 3.0\text{Hz}$), 3.88-4.35 (4H, m), 7.52 (1H, d, $J = 8.5\text{Hz}$), 7.56 (1H, d, $J = 8.5\text{Hz}$), 7.84 (1H, s)。

[1111] 参考例 127

[1112] [式 190]

[1113]

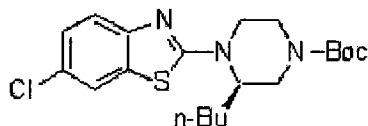


[1114] 收率:64%, $^1\text{H-NMR}(\text{CDCl}_3, 328\text{K})$: δ 0.97 (3H, t, $J = 7.2\text{Hz}$), 1.27-1.49 (2H, m), 1.49 (9H, s), 1.69 (2H, br), 2.99 (1H, t, $J = 11.7\text{Hz}$), 3.11 (1H, d, $J = 12.6\text{Hz}$), 3.39 (1H, td, $J = 12.6\text{Hz}$), 3.97-4.14 (4H, m), 7.53 (2H, s, $J = \text{Hz}$), 7.83 (1H, s)。

[1115] 参考例 128

[1116] [式 191]

[1117]



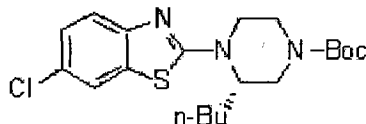
[1118] 收率:18%, $^1\text{H-NMR}(\text{CDCl}_3)$: δ 0.85-0.97 (3H, m), 1.30-1.45 (4H, m), 1.49 (9H,

s), 1.59-1.75 (2H, m), 2.86-3.19 (2H, m), 3.30-3.43 (1H, m), 3.90-4.30 (4H, m), 7.24 (1H, dd, $J = 8.5, 2\text{Hz}$), 7.42 (1H, d, $J = 8.5\text{Hz}$), 7.55 (1H, d, $J = 2\text{Hz}$)。

[1119] 参考例 129

[1120] [式 192]

[1121]

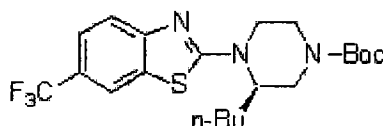


[1122] 收率: 50%, $^1\text{H-NMR}$ (CDCl_3): δ 0.84-0.98 (3H, m), 1.25-1.75 (15H, m), 2.85-3.20 (2H, m), 3.30-3.45 (1H, m), 3.90-4.30 (4H, m), 7.24 (1H, dd, $J = 9, 2\text{Hz}$), 7.42 (1H, d, $J = 9\text{Hz}$), 7.55 (1H, d, $J = 2\text{Hz}$)。

[1123] 参考例 130

[1124] [式 193]

[1125]

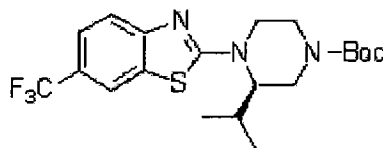


[1126] 收率: 58%, $^1\text{H-NMR}$ (CDCl_3): δ 0.85-0.97 (3H, m), 1.30-1.45 (4H, m), 1.50 (9H, s), 1.63-1.78 (2H, m), 2.85-3.20 (2H, m), 3.33-3.43 (1H, m), 3.95-4.35 (4H, m), 7.50-7.58 (2H, m), 7.85 (1H, s)。

[1127] 参考例 131

[1128] [式 194]

[1129]

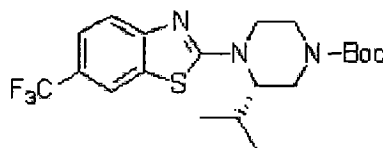


[1130] 收率: 11%, $^1\text{H-NMR}$ (CDCl_3): δ 0.92 (3H, d, $J = 6.5\text{Hz}$), 1.13 (3H, d, $J = 6.5\text{Hz}$), 1.49 (9H, s), 2.07-2.27 (1H, m), 2.70-3.15 (2H, m), 3.25-3.44 (1H, m), 3.59-3.75 (1H, m), 3.95-4.46 (3H, m), 7.52 (1H, s), 7.53 (1H, s), 7.83 (1H, s)。

[1131] 参考例 132

[1132] [式 195]

[1133]

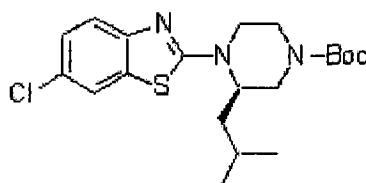


[1134] 收率: 31%, $^1\text{H-NMR}$ (CDCl_3): δ 0.91 (3H, d, $J = 6.5\text{Hz}$), 1.13 (3H, d, $J = 6.5\text{Hz}$), 1.49 (9H, s), 2.12-2.24 (1H, m), 2.84-3.13 (2H, m), 3.27-3.43 (1H, m), 3.60-3.75 (1H, m), 4.02-4.40 (3H, m), 7.53 (2H, s), 7.83 (1H, s)。

[1135] 参考例 133

[1136] [式 196]

[1137]

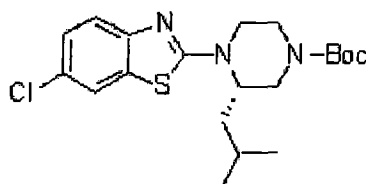


[1138] 收率:26%, $^1\text{H-NMR}$ (CDCl_3): δ 0.98 (3H, d, $J = 6.5\text{Hz}$), 1.00 (3H, d, $J = 6.5\text{Hz}$), 1.33–1.75 (3H, m), 1.49 (9H, s), 2.84–3.22 (2H, m), 3.37 (1H, td, $J = 13.0, 3.5\text{Hz}$), 3.88–4.32 (4H, m), 7.24 (1H, dd, $J = 8.5, 2.0\text{Hz}$), 7.42 (1H, d, $J = 8.5\text{Hz}$), 7.56 (1H, d, $J = 2.0\text{Hz}$)。

[1139] 参考例 134

[1140] [式 197]

[1141]

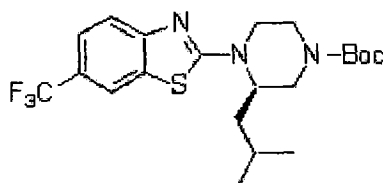


[1142] 收率:54%, $^1\text{H-NMR}$ (CDCl_3): δ 0.90–1.05 (6H, m), 1.35–1.48 (2H, m), 1.49 (9H, s), 1.58–1.73 (1H, m), 2.85–3.20 (2H, m), 3.30–3.43 (1H, m), 3.90–4.30 (4H, m), 7.35 (1H, dd, $J = 8.5, 2\text{Hz}$), 7.41 (1H, d, $J = 8.5\text{Hz}$), 7.57 (1H, d, $J = 2\text{Hz}$)。

[1143] 参考例 135

[1144] [式 198]

[1145]

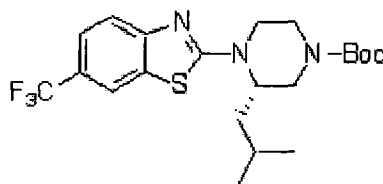


[1146] 收率:43%, $^1\text{H-NMR}$ (CDCl_3): δ 0.99 (3H, d, $J = 6.5\text{Hz}$), 1.00 (3H, d, $J = 6.5\text{Hz}$), 1.37–1.52 (1H, m), 1.49 (9H, s), 1.57–1.75 (2H, m), 2.84–3.23 (2H, m), 3.40 (1H, td, $J = 13.0, 3.5\text{Hz}$), 3.94–4.35 (4H, m), 7.48–7.58 (2H, m), 7.85 (1H, s)。

[1147] 参考例 136

[1148] [式 199]

[1149]

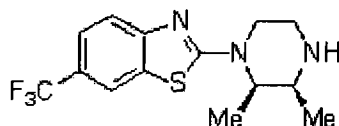


[1150] 收率:57%, $^1\text{H-NMR}$ ($\text{CDCl}_3, 328\text{K}$): δ 1.00 (6H, t, $J = 6.0\text{Hz}$), 1.40–1.52 (1H, m), 1.49 (9H, s), 1.60–1.69 (2H, m), 2.99 (1H, t, $J = 10.8\text{Hz}$), 3.12 (1H, d, $J = 10.8\text{Hz}$), 3.40 (1H, dt, $J = 3.6, 12.9\text{Hz}$), 3.98–4.13 (4H, m), 7.49–7.56 (2H, m), 7.84 (1H, s)。

[1151] 参考例 137

[1152] [式 200]

[1153]

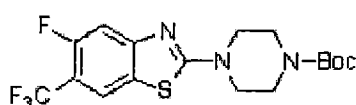


[1154] 收率:46%, ¹H-NMR(CDCl₃): δ 1.10(3H, d, J = 7.0Hz), 1.26(3H, d, J = 7.0Hz), 2.98(1H, td, J = 12.5, 3.5Hz), 3.06-3.17(2H, m), 3.35(1H, td, J = 12.5, 3.5Hz), 3.75-3.93(1H, m), 4.00-4.18(1H, m), 7.46-7.62(2H, m), 7.85(1H, s)。

[1155] 参考例 138

[1156] [式 201]

[1157]

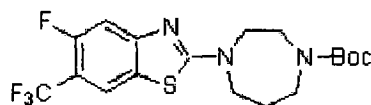


[1158] 收率:96%, ¹H-NMR(CDCl₃): δ 1.49(9H, s), 3.54-3.70(8H, m), 7.29(1H, d, J = 7.0Hz), 7.78(1H, d, J = 11.5Hz)。

[1159] 参考例 139

[1160] [式 202]

[1161]

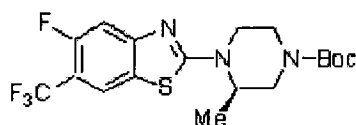


[1162] 收率:90%, ¹H-NMR(CDCl₃): δ 1.43(9H, s), 2.00-2.13(2H, m), 3.32-3.54(2H, m), 3.62-3.89(6H, m), 7.28(1H, d, J = 7.0Hz), 7.75(1H, d, J = 11.5Hz)。

[1163] 参考例 140

[1164] [式 203]

[1165]

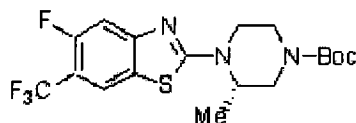


[1166] 收率:64%, ¹H-NMR(CDCl₃): δ 1.32(3H, d, J = 7.0Hz), 1.50(9H, s), 2.94-3.15(2H, m), 3.44(1H, td, J = 12.5, 3.5Hz), 3.77-4.42(4H, m), 7.28(1H, d, J = 12.0Hz), 7.77(1H, d, J = 7.0Hz)。

[1167] 参考例 141

[1168] [式 204]

[1169]



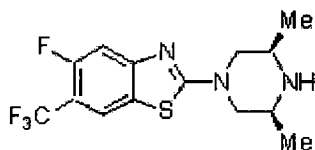
[1170] 收率:57%, ¹H-NMR(CDCl₃): δ 1.32(3H, d, J = 7.0Hz), 1.50(9H, s), 2.88-3.32(2H, m), 3.45(1H, td, J = 12.5, 3.5Hz), 3.75-4.36(4H, m), 7.29(1H, d, J =

12.0Hz), 7.77 (1H, d, $J = 7.0\text{Hz}$)。

[1171] 参考例 142

[1172] [式 205]

[1173]

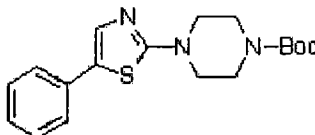


[1174] 收率:93%, $^1\text{H-NMR}(\text{CDCl}_3)$: δ 1.17 (6H, d, $J = 6.0\text{Hz}$), 2.76 (1H, d, $J = 12.5\text{Hz}$), 2.81 (1H, d, $J = 12.5\text{Hz}$), 2.94-3.08 (2H, m), 3.97 (2H, d, $J = 12.5\text{Hz}$), 7.27 (1H, d, $J = 11.5\text{Hz}$), 7.75 (1H, d, $J = 7.0\text{Hz}$)。

[1175] 参考例 143

[1176] [式 206]

[1177]

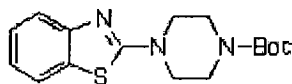


[1178] 收率:55%, $^1\text{H-NMR}(\text{CDCl}_3)$: δ 1.49 (9H, s), 3.43-3.66 (8H, m), 7.22 (1H, t, $J = 7.5\text{Hz}$), 7.33 (2H, t, $J = 7.5\text{Hz}$), 7.41 (1H, s), 7.43 (2H, d, $J = 7.5\text{Hz}$)。

[1179] 参考例 144

[1180] [式 207]

[1181]

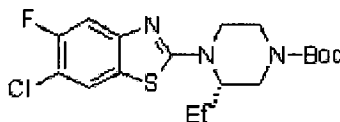


[1182] 收率:78%, $^1\text{H-NMR}(\text{CDCl}_3)$: δ 1.49 (9H, s), 3.55-3.67 (8H, m), 7.10 (1H, td, $J = 8.0, 1.0\text{Hz}$), 7.31 (1H, td, $J = 8.0, 1.0\text{Hz}$), 7.57 (1H, dd, $J = 8.0, 1.0\text{Hz}$), 7.61 (1H, dd, $J = 8.0, 1.0\text{Hz}$)。

[1183] 参考例 145

[1184] [式 208]

[1185]

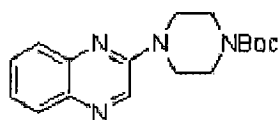


[1186] 收率:42%, $^1\text{H-NMR}(\text{CDCl}_3)$: δ 1.00 (3H, t, $J = 7.5\text{Hz}$), 1.49 (9H, s), 1.64-1.79 (2H, m), 2.85-3.19 (2H, m), 3.28-3.44 (1H, m), 3.83-4.33 (4H, m), 7.27 (1H, d, $J = 10.0\text{Hz}$), 7.55 (1H, d, $J = 7.0\text{Hz}$)。

[1187] 参考例 146

[1188] [式 209]

[1189]

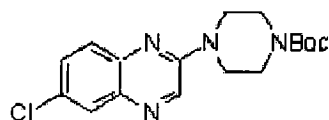


[1190] 收率:60%, $^1\text{H-NMR}(\text{CDCl}_3)$: δ 1.50 (9H, s), 3.55-3.68 (4H, m), 3.73-3.85 (4H, m), 7.37-7.47 (1H, m), 7.59 (1H, td, $J = 8.0, 1.0\text{Hz}$), 7.69 (1H, dd, $J = 8.0, 1.0\text{Hz}$), 7.89 (1H, dd, $J = 8.0, 1.0\text{Hz}$), 8.58 (1H, s)。

[1191] 参考例 147

[1192] [式 210]

[1193]

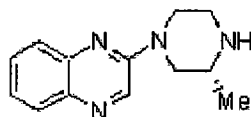


[1194] 收率:60%, $^1\text{H-NMR}(\text{CDCl}_3)$: δ 1.50 (9H, s), 3.56-3.67 (4H, m), 3.73-3.84 (4H, m), 7.53 (1H, dd, $J = 9.0, 2.0\text{Hz}$), 7.62 (1H, d, $J = 9.0\text{Hz}$), 7.88 (1H, d, $J = 2.0\text{Hz}$), 8.57 (1H, s)。

[1195] 参考例 148

[1196] [式 211]

[1197]

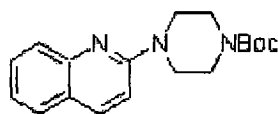


[1198] 收率:70%, $^1\text{H-NMR}(\text{CDCl}_3)$: δ 1.20 (3H, d, $J = 6.5\text{Hz}$), 2.68 (1H, dd, $J = 13.0, 10.5\text{Hz}$), 2.86-3.22 (4H, m), 4.37-4.48 (2H, m), 7.35-7.44 (1H, m), 7.53-7.62 (1H, m), 7.68 (1H, dd, $J = 8.5, 1.5\text{Hz}$), 7.88 (1H, dd, $J = 8.5, 1.5\text{Hz}$), 8.58 (1H, s)。

[1199] 参考例 149

[1200] [式 212]

[1201]

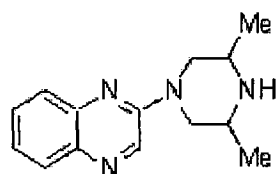


[1202] 收率:27%, $^1\text{H-NMR}(\text{CDCl}_3)$: δ 1.50 (9H, s), 3.53-3.64 (4H, m), 3.68-3.78 (4H, m), 6.98 (1H, d, $J = 9.0\text{Hz}$), 7.25 (1H, td, $J = 8.0, 1.5\text{Hz}$), 7.55 (1H, td, $J = 8.0, 1.5\text{Hz}$), 7.61 (1H, d, $J = 8.0\text{Hz}$), 7.71 (1H, d, $J = 8.0\text{Hz}$), 7.92 (1H, d, $J = 9.0\text{Hz}$)。

[1203] 参考例 150

[1204] [式 213]

[1205]



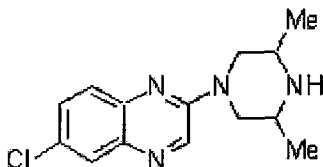
[1206] 收率:51%, $^1\text{H-NMR}(\text{CDCl}_3)$: δ 1.20 (6H, d, $J = 6.0\text{Hz}$), 2.58 (1H, d, $J = 12.5\text{Hz}$),

2.62 (1H, d, $J = 12.5$ Hz), 2.93–3.07 (2H, m), 4.43 (2H, dd, $J = 12.5, 2.0$ Hz), 7.38 (1H, td, $J = 8.5, 1.5$ Hz), 7.57 (1H, td, $J = 8.5, 1.5$ Hz), 7.68 (1H, dd, $J = 8.5, 1.5$ Hz), 7.87 (1H, dd, $J = 8.5, 1.5$ Hz), 8.58 (1H, s)。

[1207] 参考例 151

[1208] [式 214]

[1209]

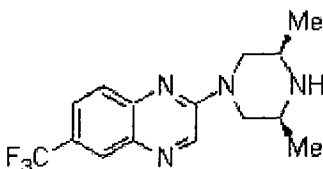


[1210] 收率:88%, $^1\text{H-NMR}$ (CDCl_3): δ 1.20 (6H, d, $J = 6.5$ Hz), 2.58 (1H, d, $J = 13.0$ Hz), 2.62 (1H, d, $J = 13.0$ Hz), 2.92–3.07 (2H, m), 4.42 (2H, dd, $J = 13.0, 2.0$ Hz), 7.50 (1H, dd, $J = 9.0, 2.0$ Hz), 7.60 (1H, d, $J = 9.0$ Hz), 7.85 (1H, d, $J = 2.0$ Hz), 8.57 (1H, s)。

[1211] 参考例 152

[1212] [式 215]

[1213]

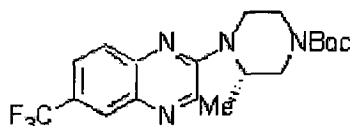


[1214] 收率:定量收率, $^1\text{H-NMR}$ (CDCl_3): δ 1.21 (6H, d, $J = 6.0$ Hz), 2.62 (1H, d, $J = 12.5$ Hz), 2.66 (1H, d, $J = 12.5$ Hz), 2.92–3.06 (2H, m), 4.49 (2H, dd, $J = 12.5, 2.0$ Hz), 7.71–7.75 (2H, m), 8.14 (1H, s), 8.63 (1H, s)。

[1215] 参考例 153

[1216] [式 216]

[1217]

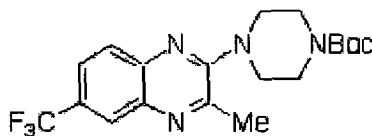


[1218] 收率:52%, $^1\text{H-NMR}$ (CDCl_3): δ 1.31 (3H, d, $J = 6.5$ Hz), 1.51 (9H, s), 2.95–3.19 (1H, m), 3.21–3.31 (1H, m), 3.32–3.45 (1H, m), 3.92–4.41 (3H, m), 4.68–4.82 (1H, m), 7.72 (1H, s), 7.73 (1H, s), 8.17 (1H, s), 8.60 (1H, s)。

[1219] 参考例 154

[1220] [式 217]

[1221]



[1222] 收率:72%, $^1\text{H-NMR}$ (CDCl_3): δ 1.50 (9H, s), 2.73 (3H, s), 3.37–3.46 (4H, m), 3.62–3.70 (4H, m), 7.76 (1H, d, $J = 9.0$ Hz), 7.89 (1H, d, $J = 9.0$ Hz), 8.19 (1H, s)。

[1223] 参考例 155

[1224] 4-(6-氯苯并噻唑-2-基)哌嗪二盐酸盐的制备

[1225] [式 218]

[1226]



[1227] 向 4N 的氢氯酸-二噁烷溶液加入 4-(6-氯苯并噻唑-2-基)哌嗪-1-羧酸叔丁基酯 (1.50g ; 4.239mmol)。将混合物在 60℃ 搅拌 1 小时。将反应溶液减压浓缩并将残余物用乙酸乙酯洗涤,得到 4-(6-氯苯并噻唑-2-基)哌嗪二盐酸盐,为无色晶体 (1.40g ; 100%)。

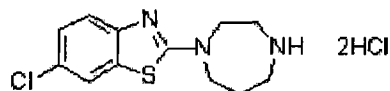
[1228] $^1\text{H-NMR}$ (DMSO- d_6) : δ 3.15-3.25 (4H, m), 3.84 (4H, t, $J = 5\text{Hz}$), 6.88 (1H, brs), 7.34 (1H, dd, $J = 8.5, 2\text{Hz}$), 7.50 (1H, d, $J = 8.5\text{Hz}$), 7.99 (1H, d, $J = 2\text{Hz}$), 9.71 (2H, brs)。

[1229] 通过与参考例 155 相似的方法得到参考例 156 到 194 的化合物。

[1230] 参考例 156

[1231] [式 219]

[1232]

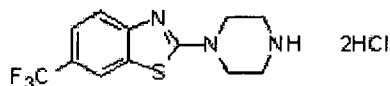


[1233] 收率:100%, $^1\text{H-NMR}$ (DMSO- d_6) : δ 2.13-2.20 (2H, m), 3.20-3.22, (2H, m), 3.33-3.35 (2H, m), 3.68-3.72 (2H, m), 3.98-4.00 (2H, m), 7.33 (1H, dd, $J = 8.7\text{Hz}, 2.4\text{Hz}$), 7.47 (1H, d, $J = 9.0\text{Hz}$), 7.97 (1H, d, $J = 2.1\text{Hz}$), 9.35 (2H, br-s)。

[1234] 参考例 157

[1235] [式 220]

[1236]

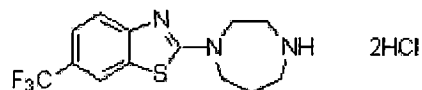


[1237] 收率:99%, $^1\text{H-NMR}$ (DMSO- d_6) : δ 3.26 (4H, t, $J = 5\text{Hz}$), 3.90 (4H, t, $J = 5\text{Hz}$), 7.64 (2H, s), 8.34 (1H, s), 8.65 (1H, brs), 9.77 (2H, s)。

[1238] 参考例 158

[1239] [式 221]

[1240]

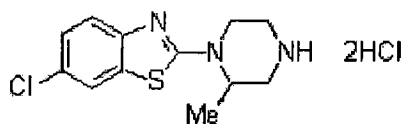


[1241] 收率:99%, $^1\text{H-NMR}$ (DMSO- d_6) : δ 2.10-2.25 (2H, m), 3.20-3.30 (2H, m), 3.30-3.40 (2H, m), 3.70-3.80 (2H, m), 4.00-4.10 (2H, m), 6.64 (1H, brs), 7.60 (2H, s), 8.30 (1H, s), 9.47 (2H, s)。

[1242] 参考例 159

[1243] [式 222]

[1244]

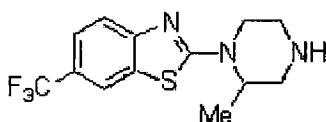


[1245] 收率:91%, $^1\text{H-NMR}$ (DMSO-d_6): δ 1.39 (3H, d, $J = 7\text{Hz}$), 3.03-3.18 (1H, m), 3.25-3.40 (4H, m), 3.95-4.05 (1H, m), 4.44-4.55 (1H, m), 7.34 (1H, dd, $J = 8.5, 2\text{Hz}$), 7.49 (1H, d, $J = 8.5\text{Hz}$), 7.96 (1H, d, $J = 2\text{Hz}$), 9.09 (1H, brs), 9.55 (2H, brs)。

[1246] 参考例 160

[1247] [式 223]

[1248]

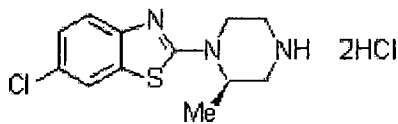


[1249] 收率:82%, $^1\text{H-NMR}$ (CDCl_3): δ 1.40 (3H, d, $J = 6.5\text{Hz}$), 1.67 (1H, brs), 2.77-2.95 (2H, m), 3.05-3.15 (2H, m), 3.40 (1H, td, $J = 12.5, 3.5\text{Hz}$), 3.87 (1H, dd, $J = 12.5, 3.5\text{Hz}$), 4.15-4.30 (1H, m), 7.51 (1H, dd, $J = 8.5, 1\text{Hz}$), 7.56 (1H, d, $J = 8.5\text{Hz}$), 7.84 (1H, d, $J = 1\text{Hz}$)。

[1250] 参考例 161

[1251] [式 224]

[1252]

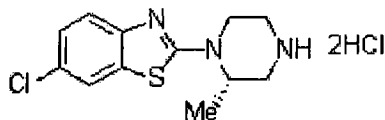


[1253] 收率:定量收率, $^1\text{H-NMR}$ (DMSO-d_6): δ 1.42 (3H, d, $J = 7\text{Hz}$), 2.95-3.15 (1H, m), 3.15-3.40 (3H, m), 3.48-3.65 (1H, m), 3.95 (1H, m), 4.40-4.55 (1H, m), 7.33 (1H, dd, $J = 8.5, 2\text{Hz}$), 7.48 (1H, d, $J = 8.5\text{Hz}$), 7.98 (1H, d, $J = 2\text{Hz}$), 8.16 (1H, brs), 9.51 (1H, brs), 9.94 (1H, brs)。

[1254] 参考例 162

[1255] [式 225]

[1256]

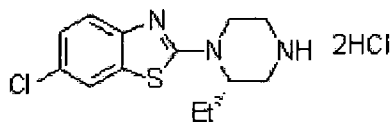


[1257] 收率:94%, $^1\text{H-NMR}$ (DMSO-d_6): δ 1.42 (3H, d, $J = 7.0\text{Hz}$), 2.98-3.15 (1H, m), 3.16-3.38 (3H, m), 3.47-3.63 (1H, m), 3.96-4.08 (1H, m), 4.40-4.53 (1H, m), 5.10 (1H, s), 7.33 (1H, dd, $J = 8.5, 2.0\text{Hz}$), 7.49 (1H, d, $J = 8.5\text{Hz}$), 7.97 (1H, d, $J = 2.0\text{Hz}$), 9.35-9.53 (1H, br), 9.82-9.98 (1H, br)。

[1258] 参考例 163

[1259] [式 226]

[1260]

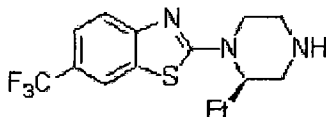


[1277] 收率：定量收率，¹H-NMR(DMSO-d₆)：δ 0.90(3H, t, J = 7.5Hz), 1.84-2.05(2H, m), 2.94-3.62(5H, m), 4.07-4.26(2H, m), 6.71(1H, brs), 7.32(1H, dd, J = 8.5, 2.0Hz), 7.46(1H, d, J = 8.5Hz), 7.96(1H, d, J = 2.0Hz), 9.35-9.58(1H, m), 9.73-9.95(1H, m)。

[1278] 参考例 168

[1279] [式 231]

[1280]

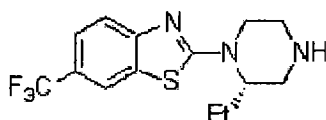


[1281] 收率：定量收率，¹H-NMR(CDCl₃)：δ 0.98(3H, t, J = 7.5Hz), 1.61(1H, brs), 1.90(2H, quant, J = 7.5Hz), 2.89(1H, td, J = 12, 3.5Hz), 2.95-3.13(3H, m), 3.37(1H, td, J = 12.5, 3.5Hz), 3.83-3.94(1H, m), 3.95-4.06(1H, m), 7.45-7.56(2H, m), 7.83(1H, s)。

[1282] 参考例 169

[1283] [式 232]

[1284]

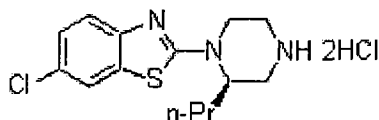


[1285] 收率：定量收率，¹H-NMR(CDCl₃)：δ 0.98(3H, t, J = 7.5Hz), 1.72(1H, brs), 1.91(2H, quant, J = 7.5Hz), 2.89(1H, td, J = 12.5, 3.5Hz), 2.95-3.13(3H, m), 3.38(1H, td, J = 12.5, 3.5Hz), 3.84-3.95(1H, m), 3.95-4.08(1H, m), 7.50(1H, d, J = 8.5Hz), 7.54(1H, d, J = 8.5Hz), 7.83(1H, s)。

[1286] 参考例 170

[1287] [式 233]

[1288]

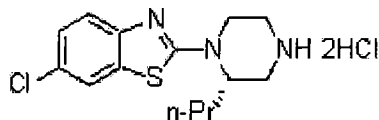


[1289] 收率：定量收率，¹H-NMR(DMSO-d₆)：δ 0.92(3H, t, J = 7.0Hz), 1.20-1.45(2H, m), 1.78-1.92(2H, q, J = 7.5Hz), 2.97-3.38(4H, m), 3.42-3.59(1H, m), 4.04-4.17(1H, m), 4.22-4.34(1H, m), 5.64(1H, br), 7.31(1H, dd, J = 8.5, 2.5Hz), 7.45(1H, d, J = 8.5Hz), 7.96(1H, d, J = 2.5Hz), 9.04-9.20(1H, m), 9.50-9.64(1H, m)。

[1290] 参考例 171

[1291] [式 234]

[1292]

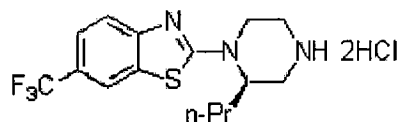


[1293] 收率:定量收率, $^1\text{H-NMR}$ (CDCl_3): δ 0.99 (3H, t, $J = 6.6\text{Hz}$), 1.26-1.49 (4H, m), 2.11 (2H, br), 3.63-3.83 (3H, m), 4.10 (1H, br), 4.51 (1H, br), 4.64 (1H, br), 7.22 (1H, s), 7.56-7.63 (2H, m)。

[1294] 参考例 172

[1295] [式 235]

[1296]

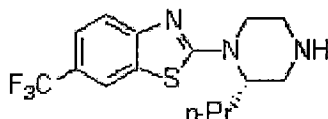


[1297] 收率:定量收率, $^1\text{H-NMR}$ (DMSO-d_6): δ 0.93 (3H, t, $J = 7.5\text{Hz}$), 1.18-1.46 (2H, m), 1.80-1.95 (2H, m), 3.00-3.40 (4H, m), 3.45-3.62 (1H, m), 4.12-4.24 (1H, m), 4.29-4.42 (1H, m), 7.54-7.65 (2H, m), 8.31 (1H, s), 9.14-9.32 (1H, m), 9.60-9.72 (1H, m)。

[1298] 参考例 173

[1299] [式 236]

[1300]

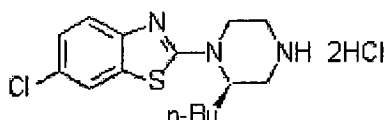


[1301] 收率:定量收率, $^1\text{H-NMR}$ (CDCl_3): δ 1.00 (3H, t, $J = 6.0\text{Hz}$), 1.26-1.54 (4H, m), 2.17 (2H, br), 3.63-3.86 (3H, m), 4.11 (1H, br), 4.54 (1H, br), 4.70 (1H, br), 7.50 (1H, d, $J = 7.5\text{Hz}$), 7.72 (1H, d, $J = 7.5\text{Hz}$), 7.91 (1H, s)。

[1302] 参考例 174

[1303] [式 237]

[1304]

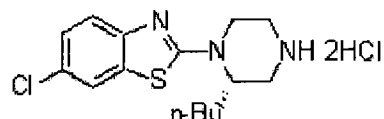


[1305] 收率:定量收率, $^1\text{H-NMR}$ (DMSO-d_6): δ 0.87 (3H, t, $J = 7\text{Hz}$), 1.20-1.39 (4H, m), 1.78-1.95 (2H, m), 3.00-3.15 (1H, m), 3.15-3.40 (3H, m), 3.42-3.55 (1H, m), 4.07-4.20 (1H, m), 4.20-4.30 (1H, m), 4.55 (1H, brs), 7.31 (1H, dd, $J = 8.5, 2\text{Hz}$), 7.44 (1H, d, $J = 8.5\text{Hz}$), 7.95 (1H, d, $J = 2\text{Hz}$), 9.00 (1H, brs), 9.48 (1H, brs)。

[1306] 参考例 175

[1307] [式 238]

[1308]

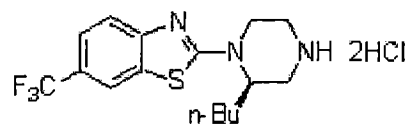


[1309] 收率:定量收率, $^1\text{H-NMR}$ (DMSO-d_6): δ 0.87 (3H, t, $J = 7\text{Hz}$), 1.18-1.40 (4H, m), 1.77-1.98 (2H, m), 2.95-3.14 (1H, m), 3.14-3.37 (3H, m), 3.40-3.51 (1H, m), 4.08-4.20 (1H, m), 4.20-4.31 (1H, m), 6.89 (1H, brs), 7.31 (1H, dd, $J = 8.5, 2\text{Hz}$), 7.44 (1H, d, $J = 8.5\text{Hz}$), 7.95 (1H, d, $J = 2\text{Hz}$), 9.25 (1H, brs), 9.62 (1H, brs)。

[1310] 参考例 176

[1311] [式 239]

[1312]

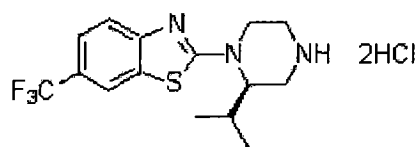


[1313] 收率: 定量收率, $^1\text{H-NMR}$ (DMSO-d_6): δ 0.85–0.90 (3H, m), 1.20–1.40 (4H, m), 1.85–2.00 (2H, m), 3.00–3.59 (5H, m), 4.15–4.23 (1H, m), 4.24–4.35 (1H, m), 7.60 (2H, s), 8.29 (1H, s), 9.36 (2H, brs), 9.75 (1H, s)。

[1314] 参考例 177

[1315] [式 240]

[1316]

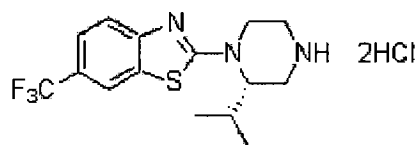


[1317] 收率: 定量收率, $^1\text{H-NMR}$ (DMSO-d_6): δ 0.86 (3H, d, $J = 6.5\text{Hz}$), 1.04 (3H, d, $J = 6.5\text{Hz}$), 3.00-3.35 (4H, m), 3.38-3.60 (2H, m), 3.87-4.02 (1H, m), 4.16-4.31 (1H, m), 5.20 (1H, br), 7.57 (1H, d, $J = 8.5\text{Hz}$), 7.61 (1H, d, $J = 8.5\text{Hz}$), 8.29 (1H, s), 9.05-9.22 (1H, m), 9.37-9.50 (1H, m)。

[1318] 参考例 178

[1319] [式 241]

[1320]

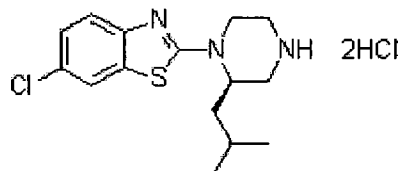


[1321] 收率:93%,¹H-NMR(DMSO-d₆): δ 0.86(3H, d, J = 6.5Hz), 1.00(3H, d, J = 6.5Hz), 2.50-2.60(1H, m), 3.03-3.31(3H, m), 3.44-3.60(2H, m), 3.90-4.00(1H, m), 4.20-4.30(1H, m), 7.54-7.63(2H, m), 8.29(1H, s), 9.23(1H, brs), 9.48(2H, brs)。

[1322] 参考例 179

[1323] [式 242]

[1324]

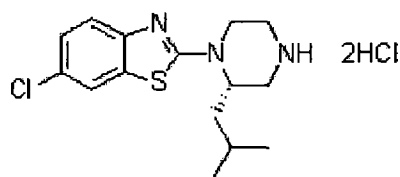


[1325] 收率:96%, ¹H-NMR(DMSO-d₆): δ 0.95(6H, d, J = 6.5Hz), 1.50-1.90(3H, m), 2.96-3.37(4H, m), 3.40-3.60(1H, m), 4.03-4.16(1H, m), 4.27-4.40(1H, m), 6.30(1H, br), 7.32(1H, dd, J = 8.5, 2.0Hz), 7.45(1H, d, J = 8.5Hz), 7.97(1H, d, J = 2.0Hz), 9.10-9.32(1H, m), 9.52-9.75(1H, m)。

[1326] 参考例 180

[1327] [式 243]

[1328]

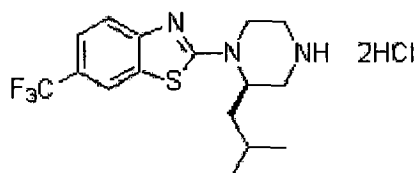


[1329] 收率:定量收率, $^1\text{H-NMR}$ (DMSO-d_6): δ 0.94 (6H, d, $J = 6.5\text{Hz}$), 1.52-1.94 (3H, m), 2.95-3.35 (4H, m), 3.45-3.57 (1H, m), 4.04-4.16 (1H, m), 4.29-4.40 (1H, m), 7.32 (1H, dd, $J = 8.5, 2\text{Hz}$), 7.45 (1H, d, $J = 8.5\text{Hz}$), 7.97 (1H, d, $J = 2\text{Hz}$), 9.45 (1H, brs), 9.81 (1H, brs), 9.84 (1H, brs)。

[1330] 参考例 181

[1331] [式 244]

[1332]

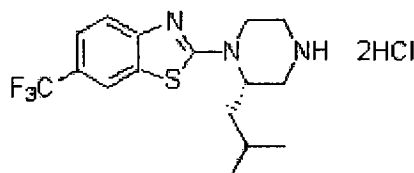


[1333] 收率:定量收率, $^1\text{H-NMR}$ (DMSO-d_6): δ 0.96 (6H, d, $J = 6.5\text{Hz}$), 1.50-1.90 (3H, m), 2.99-3.39 (4H, m), 3.46-3.63 (1H, m), 4.08-4.22 (1H, m), 4.35-4.48 (1H, m), 6.11 (1H, brs), 7.60 (2H, s), 8.31 (1H, s), 9.10-9.29 (1H, m), 9.54-9.67 (1H, m)。

[1334] 参考例 182

[1335] [式 245]

[1336]

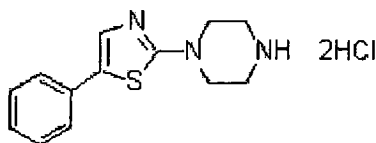


[1337] 收率:97%, $^1\text{H-NMR}$ (CDCl_3): δ 1.04 (6H, s), 1.68 (1H, br), 1.98 (1H, br), 2.07 (1H, br), 3.54 (3H, br), 3.71 (1H, br), 3.98 (1H, s), 4.46 (2H, br), 7.52 (1H, d, $J = 7.5\text{Hz}$), 7.65 (1H, d, $J = 7.5\text{Hz}$), 7.90 (1H, s)。

[1338] 参考例 183

[1339] [式 246]

[1340]

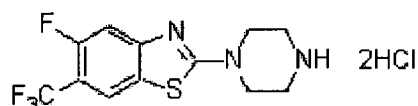


[1341] 收率:94%, $^1\text{H-NMR}$ (DMSO-d_6): δ 3.24 (4H, t, $J = 5.0\text{Hz}$), 3.74 (4H, t, $J = 5.0\text{Hz}$), 5.12 (1H, s), 7.26 (1H, t, $J = 7.5\text{Hz}$), 7.39 (2H, t, $J = 7.5\text{Hz}$), 7.51 (2H, d, $J = 7.5\text{Hz}$), 7.71 (1H, s), 9.58 (2H, s)。

[1342] 参考例 184

[1343] [式 247]

[1344]

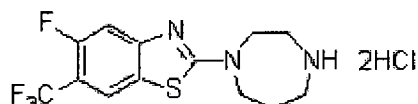


[1345] 收率:96%, $^1\text{H-NMR}$ (DMSO-d_6): δ 3.17-3.34 (4H, m), 3.83-3.96 (4H, m), 5.12 (1H, brs), 7.55 (1H, d, $J = 12.5\text{Hz}$), 8.36 (1H, d, $J = 7.5\text{Hz}$), 9.69 (2H, brs)。

[1346] 参考例 185

[1347] [式 248]

[1348]

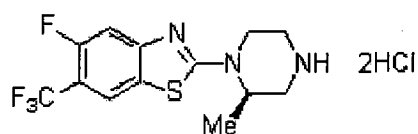


[1349] 收率:92%, $^1\text{H-NMR}$ (DMSO-d_6): δ 2.14-2.27 (2H, m), 3.16-3.30 (2H, m), 3.31-3.43 (2H, m), 3.66-3.84 (2H, m), 3.97-4.13 (2H, m), 4.78 (1H, brs), 7.53 (1H, d, $J = 12.5\text{Hz}$), 8.32 (1H, d, $J = 7.5\text{Hz}$), 9.53 (2H, brs)。

[1350] 参考例 186

[1351] [式 249]

[1352]

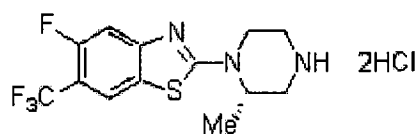


[1353] 收率:89%, $^1\text{H-NMR}$ (CDCl_3): δ 1.44 (3H, d, $J = 7.0\text{Hz}$), 3.00-3.13 (1H, m), 3.14-3.40 (3H, m), 3.53-3.69 (1H, m), 4.02-4.15 (1H, m), 4.46-4.60 (1H, m), 6.90 (1H, brs), 7.55 (1H, d, $J = 12.5\text{Hz}$), 8.35 (1H, d, $J = 7.0\text{Hz}$), 9.50 (1H, br), 9.94 (1H, br)。

[1354] 参考例 187

[1355] [式 250]

[1356]

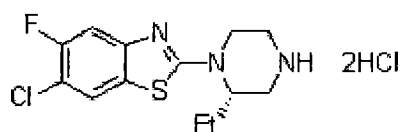


[1357] 收率:83%, $^1\text{H-NMR}$ (DMSO-d_6): δ 1.44 (3H, d, $J = 7.0\text{Hz}$), 3.01-3.19 (1H, m), 3.20-3.45 (3H, m), 3.51-3.70 (1H, m), 4.01-4.16 (1H, m), 4.45-4.62 (1H, m), 5.95 (1H, brs), 7.55 (1H, d, $J = 12.5\text{Hz}$), 8.35 (1H, d, $J = 7.5\text{Hz}$), 9.49 (1H, br), 9.89 (1H, br)。

[1358] 参考例 188

[1359] [式 251]

[1360]



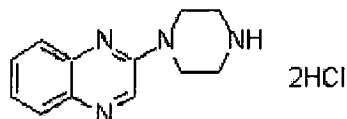
[1361] 收率:83%, $^1\text{H-NMR}$ (DMSO-d_6): δ 0.90 (3H, t, $J = 7.5\text{Hz}$), 1.80-2.00 (2H, m),

2.97-3.40 (4H, m), 3.41-3.56 (1H, m), 4.06-4.26 (2H, m), 7.49 (1H, d, $J = 10.5\text{Hz}$), 8.10 (1H, d, $J = 7.5\text{Hz}$), 9.02-9.25 (1H, m), 9.43-9.65 (1H, m)。

[1362] 参考例 189

[1363] [式 252]

[1364]

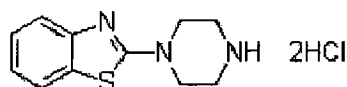


[1365] 收率：定量收率, $^1\text{H-NMR}$ (DMSO- d_6) : δ 3.16-3.32 (4H, m), 3.98-4.12 (4H, m), 7.42-7.51 (1H, m), 7.60-7.72 (2H, m), 7.88 (1H, d, $J = 8.0\text{Hz}$), 8.90 (1H, s), 9.54 (2H, s)。

[1366] 参考例 190

[1367] [式 253]

[1368]

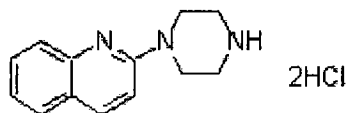


[1369] 收率：92%, $^1\text{H-NMR}$ (DMSO- d_6) : δ 2.19-3.32 (4H, m), 3.80-3.90 (4H, m), 7.15 (1H, td, $J = 8.0, 1.0\text{Hz}$), 7.34 (1H, td, $J = 8.0, 1.0\text{Hz}$), 7.54 (1H, dd, $J = 8.0, 1.0\text{Hz}$), 7.85 (1H, dd, $J = 8.0, 1.0\text{Hz}$), 9.65 (2H, s)。

[1370] 参考例 191

[1371] [式 254]

[1372]

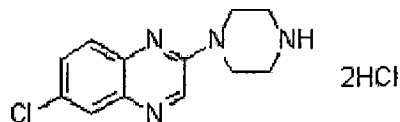


[1373] 收率：91%, $^1\text{H-NMR}$ (DMSO- d_6) : δ 3.30 (4H, s), 3.80 (1H, br), 4.16 (4H, s), 7.38-7.60 (2H, m), 7.68-7.81 (1H, m), 7.84-7.97 (1H, m), 8.16 (1H, br), 8.32-8.52 (1H, m), 9.57 (2H, brs)。

[1374] 参考例 192

[1375] [式 255]

[1376]

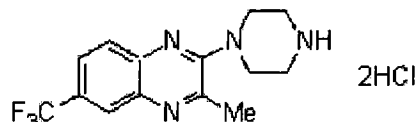


[1377] 收率：63%, $^1\text{H-NMR}$ (DMSO- d_6) : δ 3.24 (4H, s), 3.87 (1H, brs), 4.03 (4H, s), 7.66 (2H, s), 7.93 (1H, s), 8.92 (1H, s), 9.38 (2H, brs)。

[1378] 参考例 193

[1379] [式 256]

[1380]

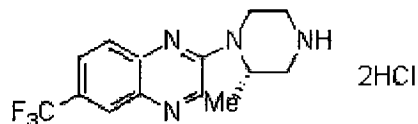


[1381] 收率:82%, $^1\text{H-NMR}$ (DMSO-d_6): δ 2.71 (3H, s), 3.24-3.35 (4H, m), 3.62-3.73 (4H, m), 7.91 (1H, d, $J = 9.0\text{Hz}$), 7.97 (1H, d, $J = 9.0\text{Hz}$), 8.23 (1H, s), 9.32 (2H, brs)。

[1382] 参考例 194

[1383] [式 257]

[1384]



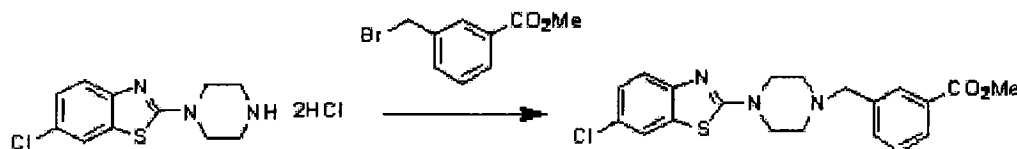
[1385] 收率:80%, $^1\text{H-NMR}$ (DMSO-d_6): δ 1.39 (3H, d, $J = 7.0\text{Hz}$), 3.00-3.16 (1H, m), 3.18-3.54 (5H, m), 4.68 (1H, d, $J = 14.0\text{Hz}$), 5.05-5.17 (1H, m), 7.79 (1H, d, $J = 8.5\text{Hz}$), 7.89 (1H, d, $J = 8.5\text{Hz}$), 8.20 (1H, s), 8.97 (1H, s), 9.19 (1H, brs), 9.53 (1H, brs)。

[1386] 实施例 1

[1387] 3-[[4-(6-氯苯并噻唑-2-基)哌嗪-1-基]甲基]苯甲酸甲基酯的制备

[1388] [式 258]

[1389]



[1390] 将 4-(6-氯苯并噻唑-2-基)哌嗪二盐酸盐 (3.00g; 9.18mmol), 3-(溴甲基)丁酸甲酯 (2.31g; 10.1mmol), 碳酸钾 (3.81g; 27.6mmol) 和无水 N,N-二甲基甲酰胺 (30ml) 的混合物在室温搅拌 14 小时。向反应溶液加入水。收集沉淀物并且用二异丙醚洗涤, 得到 3-[[4-(6-氯苯并噻唑-2-基)哌嗪-1-基]甲基]苯甲酸甲基酯, 为无色晶体 (3.06g; 83%)。

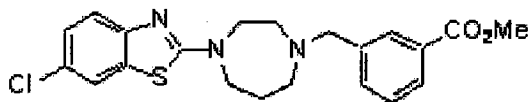
[1391] $^1\text{H-NMR}$ (CDCl_3): δ 2.58 (4H, t, $J = 5\text{Hz}$), 3.61 (2H, s), 3.64 (4H, t, $J = 5\text{Hz}$), 3.93 (3H, s), 7.23 (1H, dd, $J = 8.5, 2\text{Hz}$), 7.35-7.45 (1H, m), 7.43 (1H, d, $J = 8.5\text{Hz}$), 7.55 (1H, d, $J = 2\text{Hz}$), 7.55-7.60 (1H, m), 7.96 (1H, d, $J = 7.5\text{Hz}$), 8.01 (1H, s)。

[1392] 通过与实施例 1 相似的方法得到实施例 2 到 127 的化合物。

[1393] 实施例 2

[1394] [式 259]

[1395]

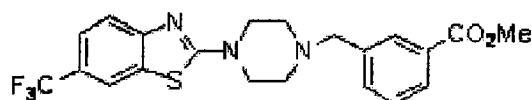


[1396] 收率:88%, $^1\text{H-NMR}$ (CDCl_3): δ 2.01-2.05 (2H, m), 2.69 (2H, t, $J = 5.4\text{Hz}$), 2.80-2.83 (2H, m), 3.67 (2H, s), 3.72-3.78 (4H, m), 3.92 (3H, s), 7.23 (1H, dd, $J = 8.7\text{Hz}$, 2.1Hz), 7.37-7.44 (2H, m), 7.53 (1H, s), 7.55 (1H, d, $J = 2.1\text{Hz}$), 7.94 (1H, d, $J = 7.5\text{Hz}$), 7.99 (1H, s)。

[1397] 实施例 3

[1398] [式 260]

[1399]

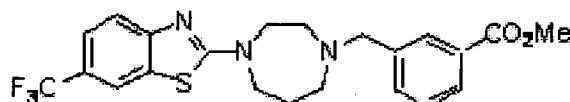


[1400] 收率:73%, ¹H-NMR(CDCl₃): δ 2.60(4H, t, J = 5Hz), 3.62(2H, s), 3.67(4H, t, J = 5Hz), 3.97(3H, s), 7.43(1H, t, J = 7.5Hz), 7.50-7.60(3H, m), 7.85(1H, s), 7.97(1H, d, J = 7.5Hz), 8.02(1H, s)。

[1401] 实施例 4

[1402] [式 261]

[1403]

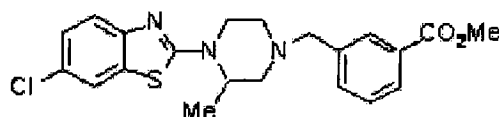


[1404] 收率: 定量收率 (q. y), ¹H-NMR(CDCl₃): δ 2.00-2.20(2H, m), 2.70(2H, t, J = 5.5Hz), 2.83(2H, t, J = 5.5Hz), 3.69(2H, s), 3.70-3.85(4H, m), 3.92(3H, s), 7.40(1H, t, J = 7.5Hz), 7.50-7.60(3H, m), 7.84(1H, s), 7.94(1H, d, J = 7.5Hz), 7.99(1H, s)。

[1405] 实施例 5

[1406] [式 262]

[1407]

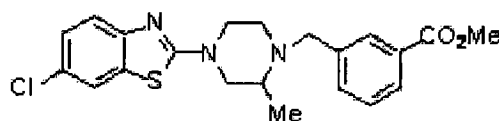


[1408] 收率:97%, ¹H-NMR(CDCl₃): δ 1.41(3H, d, J = 6Hz), 2.28(1H, td, J = 11.5, 3.5Hz), 2.36(1H, dd, J = 11.5, 3.5Hz), 2.69(1H, d, J = 11.5Hz), 2.90(1H, d, J = 11.5Hz), 3.40-3.55(2H, m), 3.63(1H, d, J = 12.5Hz), 3.80-3.90(1H, m), 3.93(3H, s), 4.10-4.25(1H, m), 7.22(1H, dd, J = 8.5, 2Hz), 7.42(1H, d, J = 8.5Hz), 7.43(1H, t, J = 7.5Hz), 7.54(1H, d, J = 2Hz), 7.58(1H, d, J = 7.5Hz), 7.95(1H, d, J = 7.5Hz), 8.02(1H, s)。

[1409] 实施例 6

[1410] [式 263]

[1411]

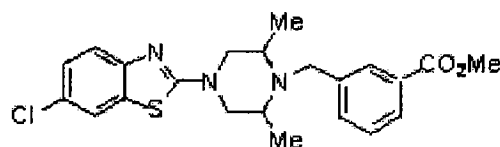


[1412] 收率: 定量收率 (q. y), ¹H-NMR(CDCl₃): δ 1.23(3H, d, J = 6Hz), 2.25-2.35(1H, m), 2.60-2.73(1H, m), 2.73-2.82(1H, m), 3.17(1H, dd, J = 12.5, 9Hz), 3.33(1H, d, J = 13.5Hz), 3.35-3.45(1H, m), 3.65-3.75(1H, m), 3.85-3.90(1H, m), 3.93(3H, s), 4.08(1H, d, J = 13.5Hz), 7.22(1H, dd, J = 8.5, 2Hz), 7.41(1H, t, J = 7.5Hz), 7.43(1H, d, J = 8.5Hz), 7.54(1H, d, J = 2Hz), 7.56(1H, d, J = 7.5Hz), 7.94(1H, d, J = 7.5Hz), 8.01(1H, s)。

[1413] 实施例 7

[1414] [式 264]

[1415]

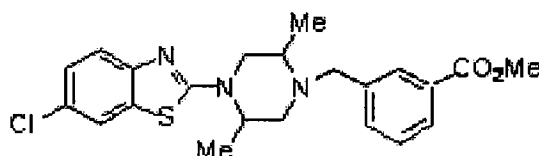


[1416] 收率:83%, $^1\text{H-NMR}(\text{CDCl}_3)$: δ 1.15(6H, d, $J = 6\text{Hz}$), 2.75-2.85(2H, m), 3.06(2H, dd, $J = 13, 12.5\text{Hz}$), 3.80-3.92(4H, m), 3.92(3H, s), 7.24(1H, dd, $J = 8.5, 2\text{Hz}$), 7.37(1H, d, $J = 7.5\text{Hz}$), 7.43(1H, d, $J = 8.5\text{Hz}$), 7.55(1H, d, $J = 2\text{Hz}$), 7.62(1H, d, $J = 7.5\text{Hz}$), 7.89(1H, d, $J = 7.5\text{Hz}$), 8.04(1H, s)。

[1417] 实施例 8

[1418] [式 265]

[1419]

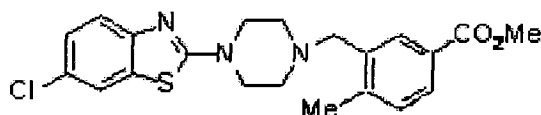


[1420] 收率:79%, $^1\text{H-NMR}(\text{CDCl}_3)$: δ 1.10(3H, d, $J = 6.5\text{Hz}$), 1.38(3H, d, $J = 6.5\text{Hz}$), 2.31(1H, d, $J = 12\text{Hz}$), 2.91(1H, dd, $J = 12, 4\text{Hz}$), 3.10-3.20(1H, m), 3.59(2H, t, $J = 14\text{Hz}$), 3.71(2H, t, $J = 14\text{Hz}$), 3.93(3H, s), 4.16-4.28(1H, m), 7.22(1H, dd, $J = 8.5, 2\text{Hz}$), 7.42(1H, d, $J = 8.5\text{Hz}$), 7.43(1H, d, $J = 7.5\text{Hz}$), 7.53(1H, d, $J = 2\text{Hz}$), 7.61(1H, d, $J = 7.5\text{Hz}$), 7.95(1H, d, $J = 7.5\text{Hz}$), 8.06(1H, s)。

[1421] 实施例 9

[1422] [式 266]

[1423]

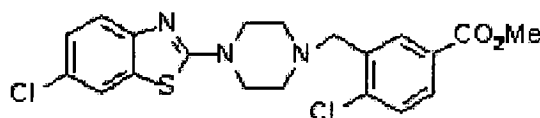


[1424] 收率:92%, $^1\text{H-NMR}(\text{CDCl}_3)$: δ 2.45(3H, s), 2.58(4H, t, $J = 5\text{Hz}$), 3.55(2H, s), 3.61(4H, t, $J = 5\text{Hz}$), 3.91(3H, s), 7.23(1H, dd, $J = 8.5, 2\text{Hz}$), 7.24(1H, d, $J = 8\text{Hz}$), 7.43(1H, d, $J = 8.5\text{Hz}$), 7.55(1H, d, $J = 2\text{Hz}$), 7.87(1H, dd, $J = 8, 1.5\text{Hz}$), 7.92(1H, d, $J = 1.5\text{Hz}$)。

[1425] 实施例 10

[1426] [式 267]

[1427]

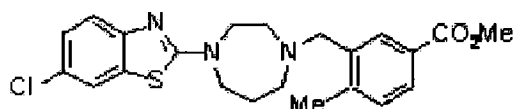


[1428] 收率:93%, $^1\text{H-NMR}(\text{CDCl}_3)$: δ 2.66(4H, t, $J = 5\text{Hz}$), 3.66(4H, t, $J = 5\text{Hz}$), 3.71(2H, s), 3.96(3H, s), 7.24(1H, dd, $J = 8.5, 2\text{Hz}$), 7.44(1H, d, $J = 8.5\text{Hz}$), 7.45(1H, d, $J = 8\text{Hz}$), 7.55(1H, d, $J = 2\text{Hz}$), 7.88(1H, dd, $J = 8, 2\text{Hz}$), 8.15(1H, d, $J = 2\text{Hz}$)。

[1429] 实施例 11

[1430] [式 268]

[1431]

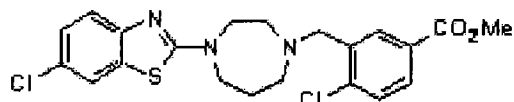


[1432] 收率:79%, $^1\text{H-NMR}(\text{CDCl}_3)$: δ 1.99-2.05 (2H, m), 2.40 (3H, s), 2.69 (2H, t, $J = 5.1\text{Hz}$), 2.79-2.82 (2H, m), 3.61 (2H, s), 3.71-3.75 (4H, m), 3.90 (3H, s), 7.21-7.25 (2H, m), 7.42 (1H, d, $J = 8.4\text{Hz}$), 7.55 (1H, d, $J = 2.4\text{Hz}$), 7.38-7.87 (1H, m), 7.92 (1H, s)。

[1433] 实施例 12

[1434] [式 269]

[1435]

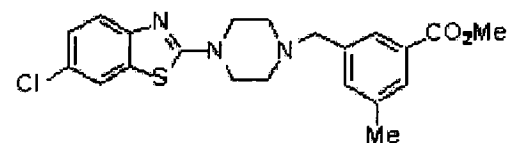


[1436] 收率:79%, $^1\text{H-NMR}(\text{CDCl}_3)$: δ 2.03-2.10 (2H, m), 2.75 (2H, t, $J = 5.4\text{Hz}$), 2.87-2.90 (2H, m), 3.73-3.80 (6H, m), 3.92 (3H, s), 7.22-7.26 (1H, m), 7.41 (1H, s), 7.44 (1H, s), 7.55 (1H, d, $J = 2.1\text{Hz}$), 7.87 (1H, dd, $J = 8.4\text{Hz}, 2.1\text{Hz}$), 8.15 (1H, d, $J = 2.1\text{Hz}$)。

[1437] 实施例 13

[1438] [式 270]

[1439]

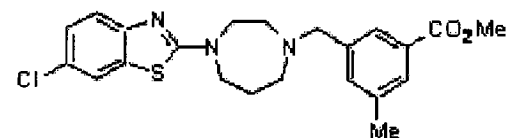


[1440] 收率:90%, $^1\text{H-NMR}(\text{CDCl}_3)$: δ 2.38 (3H, s), 2.57 (4H, t, $J = 5\text{Hz}$), 3.51 (2H, s), 3.64 (4H, t, $J = 5\text{Hz}$), 3.92 (3H, s), 7.23 (1H, dd, $J = 8.5, 2\text{Hz}$), 7.37 (1H, s), 7.43 (1H, d, $J = 8.5\text{Hz}$), 7.55 (1H, d, $J = 2\text{Hz}$), 7.78 (1H, s), 7.80 (1H, s)。

[1441] 实施例 14

[1442] [式 271]

[1443]

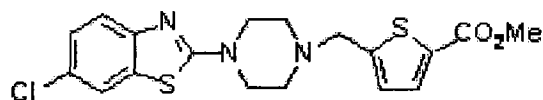


[1444] 收率:90%, $^1\text{H-NMR}(\text{CDCl}_3)$: δ 1.59 (3H, s), 2.00-2.06 (2H, m), 2.39 (3H, s), 2.69 (2H, t, $J = 5.4\text{Hz}$), 2.79-2.82 (2H, m), 3.64 (2H, s), 3.74-3.77 (4H, m), 7.23 (1H, dd, $J = 8.4\text{Hz}, 1.8\text{Hz}$), 7.35 (1H, s), 7.42 (1H, d, $J = 8.4\text{Hz}$), 7.55 (1H, d, $J = 1.8\text{Hz}$), 7.75 (1H, s), 7.78 (1H, s)。

[1445] 实施例 15

[1446] [式 272]

[1447]

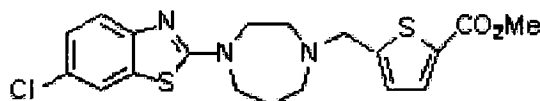


[1448] $^1\text{H-NMR}$ (CDCl_3) : δ 2.65 (4H, t, $J = 5.1\text{Hz}$), 3.64-3.67 (4H, m), 3.78 (2H, s), 3.88 (3H, s), 6.93 (1H, d, $J = 3.3\text{Hz}$), 7.24 (1H, dd, $J = 8.7, 2.1\text{Hz}$), 7.44 (1H, d, $J = 8.7\text{Hz}$), 7.56 (1H, d, $J = 2.1\text{Hz}$), 7.67 (1H, d, $J = 3.3\text{Hz}$)。

[1449] 实施例 16

[1450] [式 273]

[1451]

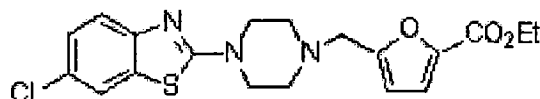


[1452] 收率: 65%, $^1\text{H-NMR}$ (CDCl_3) : δ 2.01-2.08 (2H, m), 2.71-2.75 (2H, m), 2.85-2.89 (2H, m), 3.72-3.76 (2H, m), 3.79-3.82 (2H, m), 3.86 (2H, s), 3.87 (3H, s), 6.89 (1H, d, $J = 3.9\text{Hz}$), 7.23 (1H, dd, $J = 8.7\text{Hz}, 2.1\text{Hz}$), 7.42 (1H, d, $J = 8.7\text{Hz}$), 7.55 (1H, d, $J = 2.4\text{Hz}$), 7.65 (1H, d, $J = 3.9\text{Hz}$)。

[1453] 实施例 17

[1454] [式 274]

[1455]

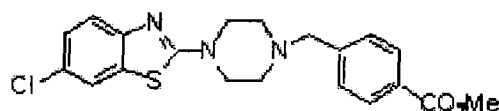


[1456] $^1\text{H-NMR}$ (CDCl_3) : δ 1.37 (3H, t, $J = 7\text{Hz}$), 2.65 (4H, t, $J = 5\text{Hz}$), 3.65 (4H, t, $J = 5\text{Hz}$), 3.69 (2H, s), 4.36 (2H, q, $J = 7\text{Hz}$), 6.37 (1H, d, $J = 3.5\text{Hz}$), 7.13 (1H, d, $J = 3.5\text{Hz}$), 7.24 (1H, dd, $J = 8.5, 2\text{Hz}$), 7.43 (1H, d, $J = 8.5\text{Hz}$), 7.55 (1H, d, $J = 2\text{Hz}$)。

[1457] 实施例 18

[1458] [式 275]

[1459]

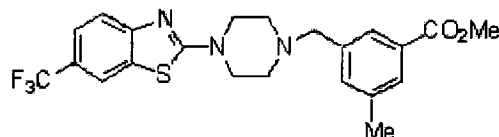


[1460] $^1\text{H-NMR}$ (CDCl_3) : δ 2.56-2.60 (4H, m), 3.62-3.66 (6H, m), 3.92 (3H, s), 7.24 (1H, dd, $J = 8.7, 2.1\text{Hz}$), 7.42-7.44 (3H, m), 7.55 (1H, d, $J = 2.1\text{Hz}$), 8.01 (2H, d, $J = 8.4\text{Hz}$)。

[1461] 实施例 19

[1462] [式 276]

[1463]

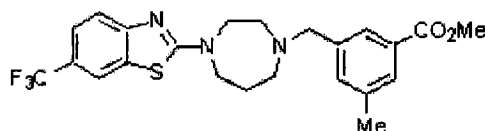


[1464] 收率: 76%, $^1\text{H-NMR}$ (CDCl_3) : δ 2.41 (3H, s), 2.59 (4H, t, $J = 5\text{Hz}$), 3.58 (2H, s), 3.69 (4H, t, $J = 5\text{Hz}$), 3.96 (3H, s), 7.37 (1H, s), 7.50-7.60 (2H, m), 7.79 (1H, s), 7.80 (1H, s), 7.85 (1H, s)。

[1465] 实施例 20

[1466] [式 277]

[1467]

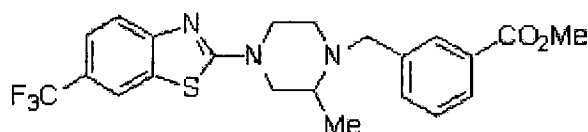


[1468] 收率:74%, $^1\text{H-NMR}(\text{CDCl}_3)$: δ 2.00-2.10 (2H, m), 2.38 (3H, s), 2.70 (2H, t, $J = 5\text{Hz}$), 2.82 (2H, t, $J = 5\text{Hz}$), 3.65 (2H, s), 3.70-3.90 (4H, m), 3.91 (3H, s), 7.34 (1H, s), 7.50-7.60 (2H, m), 7.75 (1H, s), 7.79 (1H, s), 7.85 (1H, s)。

[1469] 实施例 21

[1470] [式 278]

[1471]

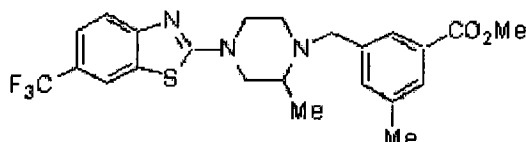


[1472] 收率:98%, $^1\text{H-NMR}(\text{CDCl}_3)$: δ 1.24 (3H, d, $J = 6.5\text{Hz}$), 2.25-2.37 (1H, m), 2.64-2.75 (1H, m), 2.75-2.83 (1H, m), 3.23 (1H, dd, $J = 13, 9\text{Hz}$), 3.29 (1H, d, $J = 13.5\text{Hz}$), 3.40-3.50 (1H, m), 3.70-3.80 (1H, m), 3.87-3.95 (1H, m), 3.93 (3H, s), 4.08 (1H, d, $J = 13.5\text{Hz}$), 7.42 (1H, t, $J = 7.5\text{Hz}$), 7.50-7.60 (3H, m), 7.84 (1H, s), 7.95 (1H, d, $J = 8\text{Hz}$), 8.01 (1H, s)。

[1473] 实施例 22

[1474] [式 279]

[1475]

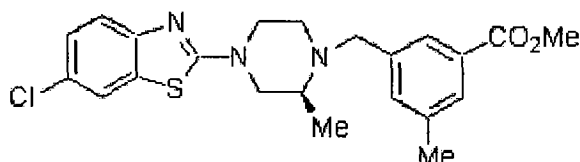


[1476] 收率:85%, $^1\text{H-NMR}(\text{CDCl}_3)$: δ 1.24 (3H, d, $J = 6.5\text{Hz}$), 2.23-2.35 (1H, m), 2.41 (3H, s), 2.60-2.73 (1H, m), 2.80 (1H, dt, $J = 12, 3.5\text{Hz}$), 3.21 (1H, d, $J = 13\text{Hz}$), 3.24 (1H, d, $J = 13.5\text{Hz}$), 3.39-3.50 (1H, m), 3.70-3.80 (1H, m), 3.91 (3H, s), 3.91-3.95 (1H, m), 4.05 (1H, d, $J = 13.5\text{Hz}$), 7.36 (1H, s), 7.51 (1H, d, $J = 8.5\text{Hz}$), 7.55 (1H, d, $J = 8.5\text{Hz}$), 7.77 (1H, s), 7.80 (1H, s), 7.84 (1H, s)。

[1477] 实施例 23

[1478] [式 280]

[1479]



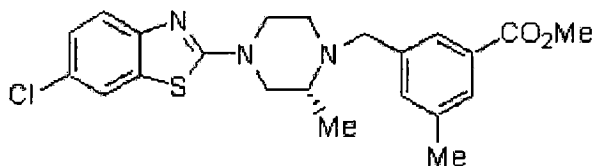
[1480] 收率:96%, $^1\text{H-NMR}(\text{CDCl}_3)$: δ 1.24 (3H, d, $J = 6.3\text{Hz}$), 2.24-2.32 (1H, m), 2.40 (3H, s), 2.63-2.68 (1H, m), 2.78 (1H, dt, $J = 3.6, 12.0\text{Hz}$), 3.17 (1H, dd, $J = 9.0\text{Hz}$), 3.22 (1H, d, $J = 13.2\text{Hz}$), 3.35-3.43 (1H, m), 3.71 (1H, dt, $J = 3.3, 12.6\text{Hz}$), 3.88 (1H, dd, $J = 3.0, 15.0\text{Hz}$), 3.91 (3H, s), 4.05 (1H, d, $J = 13.2\text{Hz}$), 7.23 (1H, dd, $J = 2.4, 8.4\text{Hz}$),

7.36(1H, s), 7.43(1H, d, $J = 8.4\text{Hz}$), 7.54(1H, d, $J = 2.4\text{Hz}$), 7.76(1H, s), 7.79(1H, s)。

[1481] 实施例 24

[1482] [式 281]

[1483]

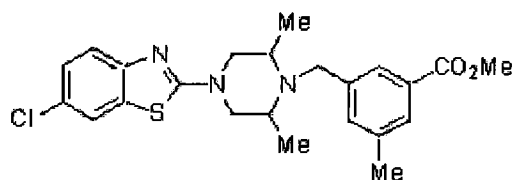


[1484] 收率:98%, $^1\text{H-NMR}(\text{CDCl}_3)$: δ 1.24(3H, d, $J = 6.3\text{Hz}$), 2.28(1H, ddd, $J = 3.3, 8.7, 9.6\text{Hz}$), 2.40(3H, s), 2.62-2.68(1H, m), 2.78(1H, dt, $J = 3.6, 12.0\text{Hz}$), 3.17(1H, dd, $J = 8.7, 12.6\text{Hz}$), 3.22(1H, d, $J = 12.9\text{Hz}$), 3.39(1H, m), 3.71(1H, d, $J = 12.3\text{Hz}$), 3.88(1H, dd, $J = 3.3, 13.2\text{Hz}$), 3.92(3H, s), 4.05(1H, d, $J = 13.2\text{Hz}$), 7.23(1H, dd, $J = 2.1, 8.4\text{Hz}$), 7.36(1H, s), 7.43(1H, d, $J = 8.4\text{Hz}$), 7.54(1H, d, $J = 2.1\text{Hz}$), 7.76(1H, s), 7.79(1H, s)。

[1485] 实施例 25

[1486] [式 282]

[1487]

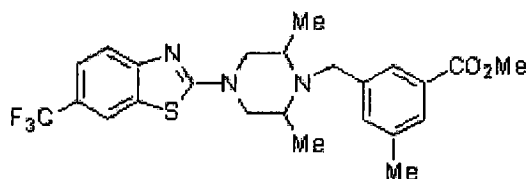


[1488] 收率:86%, $^1\text{H-NMR}(\text{CDCl}_3)$: δ 1.11(6H, d, $J = 6\text{Hz}$), 2.40(3H, s), 2.70-2.85(2H, m), 3.00-3.15(2H, m), 3.83(2H, s), 3.83-3.90(2H, m), 3.91(3H, s), 7.23(1H, dd, $J = 8.5, 2\text{Hz}$), 7.40(1H, s), 7.43(1H, d, $J = 8.5\text{Hz}$), 7.55(1H, d, $J = 2\text{Hz}$), 7.72(1H, s), 7.84(1H, s)。

[1489] 实施例 26

[1490] [式 283]

[1491]

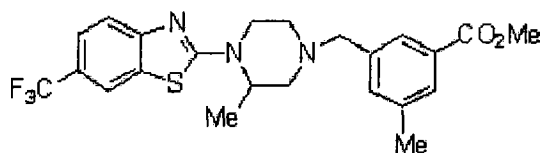


[1492] 收率:67%, $^1\text{H-NMR}(\text{CDCl}_3)$: δ 1.13(6H, d, $J = 6.5\text{Hz}$), 2.40(3H, s), 2.75-2.88(2H, m), 3.05-3.18(2H, m), 3.84(2H, s), 3.91(3H, s), 3.91-3.95(2H, m), 7.40(1H, s), 7.52(1H, d, $J = 8.5\text{Hz}$), 7.57(1H, d, $J = 8.5\text{Hz}$), 7.72(1H, s), 7.84(2H, s)。

[1493] 实施例 27

[1494] [式 284]

[1495]

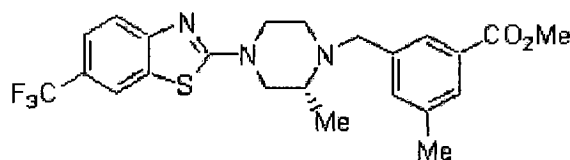


[1496] 收率:75%, $^1\text{H-NMR}(\text{CDCl}_3)$: δ 1.42(3H, d, $J = 6.5\text{Hz}$), 2.26(1H, td, $J = 11.5, 3.5\text{Hz}$), 2.36(1H, dd, $J = 11.5, 3.5\text{Hz}$), 2.41(3H, s), 2.65-2.75(1H, m), 2.85-2.95(1H, m), 3.47(1H, d, $J = 13.5\text{Hz}$), 3.48-3.55(1H, m), 3.60(1H, d, $J = 13.5\text{Hz}$), 3.80-3.90(1H, m), 3.91(3H, s), 4.20-4.30(1H, m), 7.38(1H, s), 7.51(1H, dd, $J = 8.5, 2\text{Hz}$), 7.56(1H, d, $J = 8.5\text{Hz}$), 7.77(1H, s), 7.83(1H, d, $J = 2\text{Hz}$), 7.84(1H, s)。

[1497] 实施例 28

[1498] [式 285]

[1499]

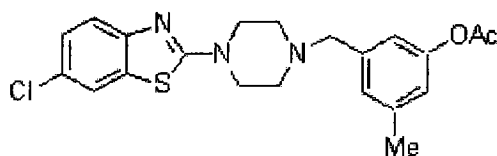


[1500] 收率:78%, $^1\text{H-NMR}(\text{CDCl}_3)$: δ 1.24(3H, t, $J = 6.0\text{Hz}$), 2.24-2.36(1H, m), 2.41(3H, s), 2.61-2.73(1H, m), 2.75-2.84(1H, m), 3.21(1H, d, $J = 13.0\text{Hz}$), 3.24(1H, d, $J = 13.5\text{Hz}$), 3.38-3.51(1H, m), 3.71-3.82(1H, m), 3.88-3.98(1H, m), 3.92(3H, s), 4.05(1H, d, $J = 13.0\text{Hz}$), 7.36(1H, s), 7.51(1H, d, $J = 8.5$), 7.56(1H, d, $J = 8.5\text{Hz}$), 7.77(1H, s), 7.80(1H, s), 7.84(1H, s)。

[1501] 实施例 29

[1502] [式 286]

[1503]

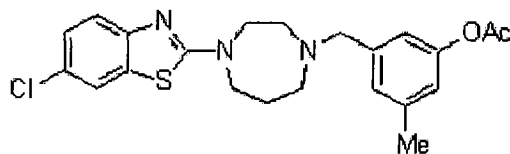


[1504] 收率:58%, $^1\text{H-NMR}(\text{DMSO}-d_6)$: δ 2.25(3H, s), 2.31(3H, s), 2.51(4H, t, $J = 5\text{Hz}$), 3.51(2H, s), 3.57(4H, t, $J = 5\text{Hz}$), 6.85(1H, s), 6.89(1H, s), 7.04(1H, s), 7.28(1H, dd, $J = 8.5, 2.5\text{Hz}$), 7.42(1H, d, $J = 8.5\text{Hz}$), 7.91(1H, d, $J = 2.5\text{Hz}$)。

[1505] 实施例 30

[1506] [式 287]

[1507]

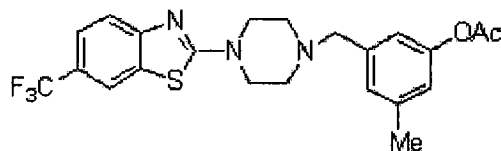


[1508] 收率:89%, $^1\text{H-NMR}(\text{CDCl}_3)$: δ 1.99-2.06(2H, m), 2.29(3H, s), 2.34(3H, s), 2.68(2H, t, $J = 5.7\text{Hz}$), 2.78-2.82(2H, m), 3.61(2H, s), 3.72-3.78(4H, m), 6.79(1H, s), 6.88(1H, s), 6.98(1H, s), 7.22(1H, dd, $J = 7.5\text{Hz}, 3.3\text{Hz}$), 7.42(1H, d, $J = 6.3\text{Hz}$), 7.54(1H, d, $J = 2.1\text{Hz}$)。

[1509] 实施例 31

[1510] [式 288]

[1511]

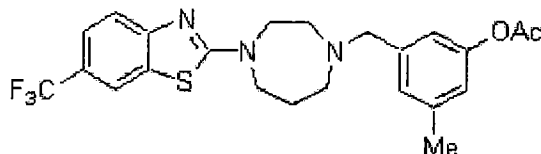


[1512] 收率:71%, $^1\text{H-NMR}(\text{CDCl}_3)$: δ 2.30 (3H, s), 2.36 (3H, s), 2.59 (4H, t, $J = 5\text{Hz}$), 3.53 (2H, s), 3.68 (4H, t, $J = 5\text{Hz}$), 6.83 (1H, s), 6.90 (1H, s), 7.02 (1H, s), 7.50–7.60 (2H, m), 7.85 (1H, s)。

[1513] 实施例 32

[1514] [式 289]

[1515]

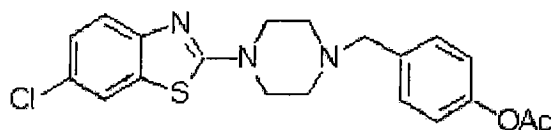


[1516] 收率:65%, $^1\text{H-NMR}(\text{CDCl}_3)$: δ 1.95–2.10 (2H, m), 2.28 (3H, s), 2.34 (3H, s), 2.69 (2H, t, $J = 5\text{Hz}$), 2.83 (2H, t, $J = 5\text{Hz}$), 3.61 (2H, s), 3.70–3.85 (4H, m), 6.80 (1H, s), 6.89 (1H, s), 6.99 (1H, s), 7.48–7.60 (2H, m), 7.85 (1H, s)。

[1517] 实施例 33

[1518] [式 290]

[1519]

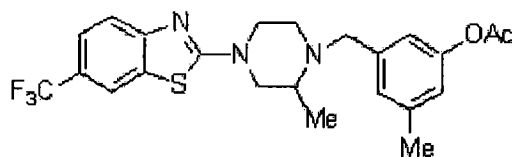


[1520] 收率:69%, $^1\text{H-NMR}(\text{CDCl}_3)$: δ 2.31 (3H, s), 2.57 (4H, t, $J = 5.1\text{Hz}$), 3.55 (2H, s), 3.63 (4H, t, $J = 5.1\text{Hz}$), 7.06 (2H, d, $J = 8.1\text{Hz}$), 7.24 (1H, dd, $J = 8.4, 2.1\text{Hz}$), 7.35 (2H, d, $J = 8.1\text{Hz}$), 7.43 (1H, d, $J = 8.4\text{Hz}$), 7.55 (1H, d, $J = 2.1\text{Hz}$)。

[1521] 实施例 34

[1522] [式 291]

[1523]

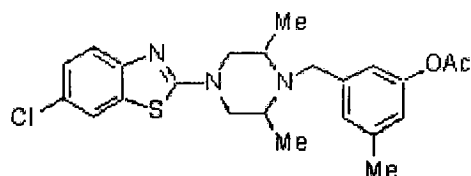


[1524] 收率:56%, $^1\text{H-NMR}(\text{CDCl}_3)$: δ 1.22 (3H, d, $J = 6\text{Hz}$), 2.24–2.35 (1H, m), 2.29 (3H, s), 2.35 (3H, s), 2.62–2.72 (1H, m), 2.83 (1H, dt, $J = 12, 4\text{Hz}$), 3.15–3.25 (2H, m), 3.40–3.50 (1H, m), 3.70–3.80 (1H, m), 3.87–3.95 (1H, m), 4.03 (1H, d, $J = 13.5\text{Hz}$), 6.81 (1H, s), 6.90 (1H, s), 7.01 (1H, s), 7.52 (1H, d, $J = 8.5\text{Hz}$), 7.56 (1H, d, $J = 8.5\text{Hz}$), 7.84 (1H, s)。

[1525] 实施例 35

[1526] [式 292]

[1527]

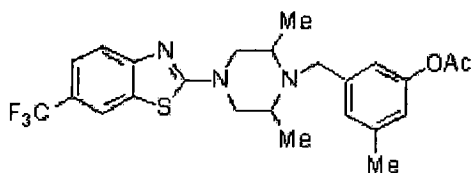


[1528] 收率:41%, $^1\text{H-NMR}$ (CDCl_3): δ 1.10 (6H, d, $J = 6\text{Hz}$), 2.29 (3H, s), 2.34 (3H, s), 2.70–2.85 (2H, m), 3.00–3.10 (2H, m), 3.79 (2H, s), 3.80–3.90 (2H, m), 6.76 (1H, s), 6.95 (1H, s), 7.02 (1H, s), 7.23 (1H, dd, $J = 8.5, 2\text{Hz}$), 7.43 (1H, d, $J = 8.5\text{Hz}$), 7.55 (1H, d, $J = 2\text{Hz}$)。

[1529] 实施例 36

[1530] [式 293]

[1531]

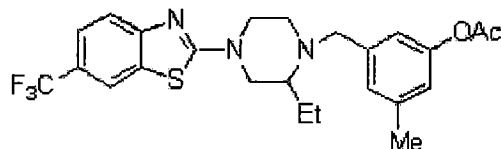


[1532] 收率:63%, $^1\text{H-NMR}$ (CDCl_3): δ 1.11 (6H, d, $J = 6\text{Hz}$), 2.30 (3H, s), 2.35 (3H, s), 2.70–2.86 (2H, m), 3.00–3.15 (2H, m), 3.80 (2H, s), 3.85–3.95 (2H, m), 6.77 (1H, s), 6.95 (1H, s), 7.02 (1H, s), 7.52 (1H, d, $J = 8.5\text{Hz}$), 7.57 (1H, d, $J = 8.5\text{Hz}$), 7.85 (1H, s)。

[1533] 实施例 37

[1534] [式 294]

[1535]

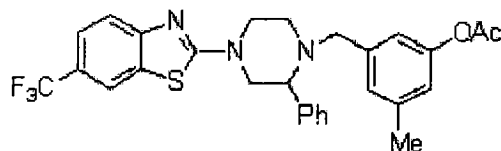


[1536] 收率:53%, $^1\text{H-NMR}$ (CDCl_3): δ 1.02 (3H, t, $J = 7.5\text{Hz}$), 1.55–1.78 (2H, m), 2.30 (3H, s), 2.30–2.35 (1H, m), 2.36 (3H, s), 2.49–2.60 (1H, m), 2.78–2.90 (1H, m), 3.26 (1H, d, $J = 13.5\text{Hz}$), 3.38–3.46 (1H, m), 3.46–3.58 (1H, m), 3.63–3.72 (1H, m), 3.85 (1H, dd, $J = 13, 3.5\text{Hz}$), 3.98 (1H, d, $J = 13.5\text{Hz}$), 6.81 (1H, s), 6.91 (1H, s), 7.02 (1H, s), 7.51 (1H, dd, $J = 8.5, 1.5\text{Hz}$), 7.56 (1H, d, $J = 8.5\text{Hz}$), 7.843 (1H, d, $J = 1.5\text{Hz}$)。

[1537] 实施例 38

[1538] [式 295]

[1539]

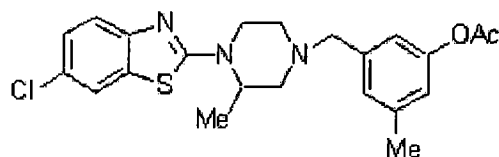


[1540] 收率:69%, $^1\text{H-NMR}$ (CDCl_3): δ 2.25–2.35 (1H, m), 2.30 (3H, s), 2.34 (3H, s), 2.86 (1H, d, $J = 13.5\text{Hz}$), 3.02 (1H, d, $J = 11.5\text{Hz}$), 3.25–3.50 (3H, m), 3.82 (1H, d, $J = 13.5\text{Hz}$), 4.00–4.10 (2H, m), 6.79 (1H, s), 6.82 (1H, s), 6.93 (1H, s), 7.30–7.45 (3H, m), 7.48–7.55 (4H, m), 7.84 (1H, d, $J = 0.5\text{Hz}$)。

[1541] 实施例 39

[1542] [式 296]

[1543]

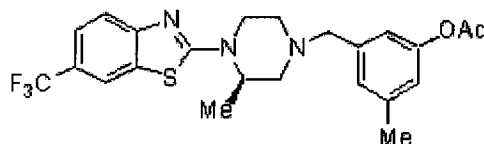


[1544] 收率:48%, $^1\text{H-NMR}$ (CDCl_3): δ 1.40 (3H, d, $J = 6.5\text{Hz}$), 2.15–2.30 (2H, m), 2.31 (3H, s), 2.36 (3H, s), 2.68–2.75 (1H, m), 2.85–2.95 (1H, m), 3.38–3.60 (3H, m), 3.80–3.90 (1H, m), 4.15–4.25 (1H, m), 6.81 (1H, s), 6.92 (1H, s), 7.02 (1H, s), 7.23 (1H, dd, $J = 8.5, 2\text{Hz}$), 7.42 (1H, d, $J = 8.5\text{Hz}$), 7.54 (1H, d, $J = 2\text{Hz}$)。

[1545] 实施例 40

[1546] [式 297]

[1547]

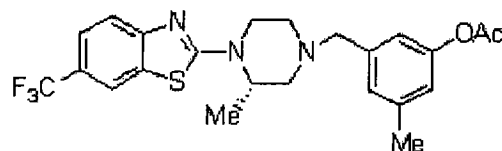


[1548] 收率:81%, $^1\text{H-NMR}$ (CDCl_3): δ 1.42 (3H, d, $J = 6.5\text{Hz}$), 2.18–2.29 (1H, m), 2.30 (3H, s), 2.30–2.35 (1H, m), 2.36 (3H, s), 2.75 (1H, d, $J = 11.5\text{Hz}$), 2.92 (1H, d, $J = 11.5\text{Hz}$), 3.43 (1H, d, $J = 13.5\text{Hz}$), 3.52 (1H, td, $J = 12.5, 3.5\text{Hz}$), 3.57 (1H, d, $J = 13.5\text{Hz}$), 3.91 (1H, d, $J = 12.5\text{Hz}$), 4.17–4.30 (1H, m), 6.81 (1H, s), 6.92 (1H, s), 7.02 (1H, s), 7.51 (1H, d, $J = 8.5\text{Hz}$), 7.55 (1H, d, $J = 8.5\text{Hz}$), 7.84 (1H, s)。

[1549] 实施例 41

[1550] [式 298]

[1551]

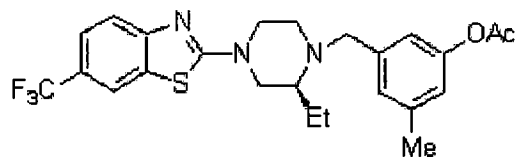


[1552] 收率:57%, $^1\text{H-NMR}$ (CDCl_3): δ 1.42 (3H, d, $J = 6.5\text{Hz}$), 2.18–2.38 (2H, m), 2.30 (3H, s), 2.36 (3H, s), 2.70–2.80 (1H, m), 2.86–2.97 (1H, m), 3.38–3.61 (3H, m), 3.85–3.97 (1H, m), 4.17–4.30 (1H, m), 6.82 (1H, s), 6.92 (1H, s), 7.03 (1H, s), 7.48–7.59 (2H, m), 7.84 (1H, s)。

[1553] 实施例 42

[1554] [式 299]

[1555]



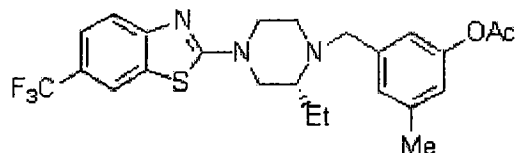
[1556] 收率:63%, $^1\text{H-NMR}$ (CDCl_3): δ 1.02 (3H, t, $J = 7.5\text{Hz}$), 1.60–1.75 (2H, m),

2.30 (3H, s), 2.30-2.35 (1H, m), 2.36 (3H, s), 2.48-2.58 (1H, m), 2.79-2.90 (1H, m), 3.26 (1H, d, $J = 13.5\text{Hz}$), 3.38-3.58 (2H, m), 3.63-3.73 (1H, m), 3.80-3.90 (1H, m), 3.98 (1H, d, $J = 13.5\text{Hz}$), 6.81 (1H, s), 6.91 (1H, s), 7.02 (1H, s), 7.51 (1H, d, $J = 8.5\text{Hz}$), 7.55 (1H, d, $J = 8.5\text{Hz}$), 7.84 (1H, s)。

[1557] 实施例 43

[1558] [式 300]

[1559]

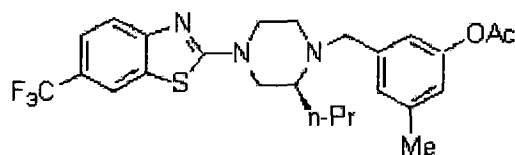


[1560] 收率:79%, $^1\text{H-NMR}(\text{CDCl}_3)$: δ 1.02 (3H, t, $J = 7.5\text{Hz}$), 1.57-1.80 (2H, m), 2.21 (3H, s), 2.21-2.35 (1H, m), 2.36 (3H, s), 2.50-2.60 (1H, m), 2.80-2.90 (1H, m), 3.26 (1H, d, $J = 13.5\text{Hz}$), 3.38-3.60 (2H, m), 3.63-3.74 (1H, m), 3.85 (1H, dd, $J = 12.5, 3.5\text{Hz}$), 3.98 (1H, d, $J = 13.5\text{Hz}$), 6.81 (1H, s), 6.91 (1H, s), 7.02 (1H, s), 7.53 (1H, d, $J = 8.5\text{Hz}$), 7.55 (1H, d, $J = 8.5\text{Hz}$), 7.84 (1H, s)。

[1561] 实施例 44

[1562] [式 301]

[1563]

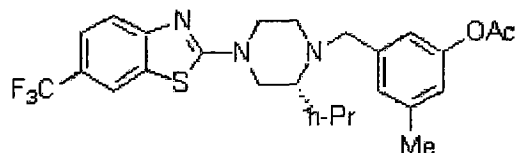


[1564] 收率:63%, $^1\text{H-NMR}(\text{CDCl}_3)$: δ 1.20 (3H, t, $J = 7.5\text{Hz}$), 1.30-1.70 (4H, m), 2.29 (3H, s), 2.29-2.35 (1H, m), 2.36 (3H, s), 2.55-2.65 (1H, m), 2.79-2.89 (1H, m), 3.28 (1H, d, $J = 13.5\text{Hz}$), 3.41 (1H, dd, $J = 13, 7.5\text{Hz}$), 3.50-3.60 (1H, m), 3.60-3.70 (1H, m), 3.84 (1H, dd, $J = 13, 3\text{Hz}$), 3.97 (1H, d, $J = 13.5\text{Hz}$), 6.81 (1H, s), 6.90 (1H, s), 7.02 (1H, s), 7.51 (1H, dd, $J = 8.5, 1.5\text{Hz}$), 7.56 (1H, d, $J = 8.5\text{Hz}$), 7.83 (1H, d, $J = 1.5\text{Hz}$)。

[1565] 实施例 45

[1566] [式 302]

[1567]

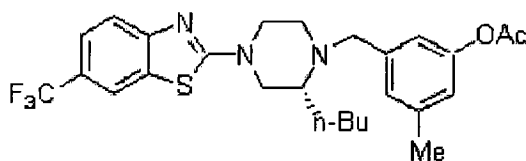


[1568] 收率:62%, $^1\text{H-NMR}(\text{CDCl}_3)$: δ 0.95 (3H, t, $J = 7.2\text{Hz}$), 1.36-1.43 (2H, m), 1.50-1.66 (2H, m), 2.30 (3H, s), 2.35 (3H, s), 2.32-2.39 (1H, m), 2.58-2.63 (1H, m), 2.80-2.87 (1H, m), 3.28 (1H, d, $J = 13.5\text{Hz}$), 3.41 (1H, dd, $J = 7.5, 12.6\text{Hz}$), 3.50-3.59 (1H, m), 3.62-3.68 (1H, m), 3.84 (1H, dd, $J = 3.0, 12.6\text{Hz}$), 3.97 (1H, d, $J = 13.5\text{Hz}$), 6.81 (1H, s), 6.90 (1H, s), 7.01 (1H, s), 7.53-7.55 (2H, m), 7.83 (1H, s)。

[1569] 实施例 46

[1570] [式 303]

[1571]

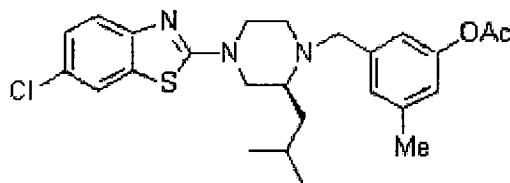


[1572] 收率:70%, $^1\text{H-NMR}$ (CDCl_3): δ 0.93 (3H, t, $J = 7.5\text{Hz}$), 1.23–1.75 (6H, m), 2.30 (3H, s), 2.30–2.34 (1H, m), 2.35 (3H, s), 2.54–2.64 (1H, m), 2.79–2.89 (1H, m), 3.27 (1H, d, $J = 13.5\text{Hz}$), 3.41 (1H, dd, $J = 12.5, 7.5\text{Hz}$), 3.49–3.60 (1H, m), 3.61–3.71 (1H, m), 3.84 (1H, dd, $J = 12.5, 2.5\text{Hz}$), 3.97 (1H, d, $J = 13.5\text{Hz}$), 6.81 (1H, s), 6.90 (1H, s), 7.02 (1H, s), 7.51 (1H, dd, $J = 8.5, 1.5\text{Hz}$), 7.56 (1H, d, $J = 8.5\text{Hz}$), 7.84 (1H, d, $J = 1.5\text{Hz}$)。

[1573] 实施例 47

[1574] [式 304]

[1575]

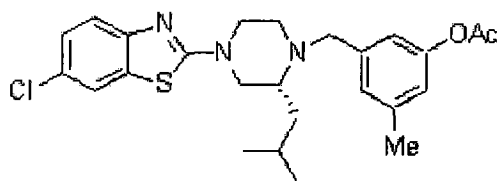


[1576] 收率:69%, $^1\text{H-NMR}$ (CDCl_3): δ 0.91 (3H, d, $J = 6.5\text{Hz}$), 0.95 (3H, d, $J = 6.5\text{Hz}$), 1.33–1.45 (1H, m), 1.45–1.58 (1H, m), 1.62–1.77 (1H, m), 2.29 (3H, s), 2.35 (3H, s), 2.36–2.45 (1H, m), 2.62–2.73 (1H, m), 2.77–2.88 (1H, m), 3.33 (1H, d, $J = 13.5\text{Hz}$), 3.35 (1H, dd, $J = 13, 7\text{Hz}$), 3.58 (2H, t, $J = 5.5\text{Hz}$), 3.75 (1H, dd, $J = 13, 3.5\text{Hz}$), 3.90 (1H, d, $J = 13.5\text{Hz}$), 6.80 (1H, s), 6.90 (1H, s), 7.02 (1H, s), 7.23 (1H, dd, $J = 8.5, 2\text{Hz}$), 7.42 (1H, d, $J = 8.5\text{Hz}$), 7.54 (1H, d, $J = 2\text{Hz}$)。

[1577] 实施例 48

[1578] [式 305]

[1579]

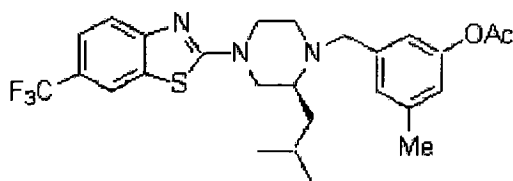


[1580] 收率:49%, $^1\text{H-NMR}$ (CDCl_3): δ 0.92 (3H, d, $J = 6.5\text{Hz}$), 0.95 (3H, d, $J = 6.5\text{Hz}$), 1.32–1.60 (2H, m), 1.62–1.78 (1H, m), 2.29 (3H, s), 2.31–2.46 (1H, m), 2.35 (3H, s), 2.62–2.72 (1H, m), 2.75–2.88 (1H, m), 3.29–3.42 (2H, m), 3.58 (2H, t, $J = 5.0\text{Hz}$), 3.75 (1H, dd, $J = 13.0, 3.5\text{Hz}$), 3.90 (1H, d, $J = 13.5\text{Hz}$), 6.80 (1H, s), 6.91 (1H, s), 7.02 (1H, s), 7.23 (1H, dd, $J = 8.5, 2.0\text{Hz}$), 7.43 (1H, d, $J = 8.5\text{Hz}$), 7.54 (1H, d, $J = 2.0\text{Hz}$)。

[1581] 实施例 49

[1582] [式 306]

[1583]

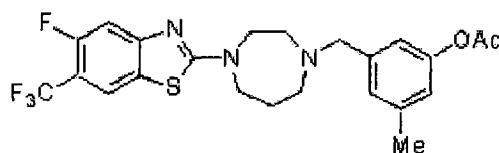


[1584] 收率:72%, $^1\text{H-NMR}$ (CDCl_3): δ 0.92 (3H, d, $J = 7.5\text{Hz}$), 0.95 (3H, d, $J = 7.5\text{Hz}$), 1.33-1.45 (1H, m), 1.46-1.60 (1H, m), 1.64-1.78 (1H, m), 2.30 (3H, s), 2.35 (3H, s), 2.36-2.46 (1H, m), 2.63-2.75 (1H, m), 2.77-2.88 (1H, m), 3.35 (1H, d, $J = 13.5\text{Hz}$), 3.40 (1H, dd, $J = 13, 6.5\text{Hz}$), 3.55-3.70 (2H, m), 3.79 (1H, dd, $J = 12, 3\text{Hz}$), 3.90 (1H, d, $J = 13.5\text{Hz}$), 6.81 (1H, s), 6.91 (1H, s), 7.02 (1H, s), 7.51 (1H, dd, $J = 8.5, 1.5\text{Hz}$), 7.55 (1H, d, $J = 8.5\text{Hz}$), 7.83 (1H, d, $J = 1.5\text{Hz}$)。

[1585] 实施例 50

[1586] [式 307]

[1587]

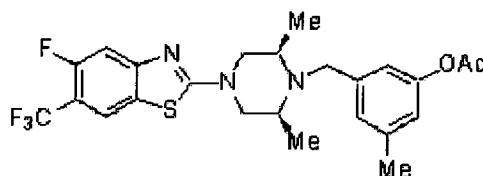


[1588] 收率:65%, $^1\text{H-NMR}$ (CDCl_3): δ 1.98-2.08 (2H, m), 2.28 (3H, s), 2.34 (3H, s), 2.65-2.74 (2H, m), 2.78-2.85 (2H, m), 3.61 (2H, s), 3.65-3.88 (4H, m), 6.80 (1H, s), 6.88 (1H, s), 6.99 (1H, s), 7.27 (1H, d, $J = 12.0\text{Hz}$), 7.75 (1H, d, $J = 7.0\text{Hz}$)。

[1589] 实施例 51

[1590] [式 308]

[1591]

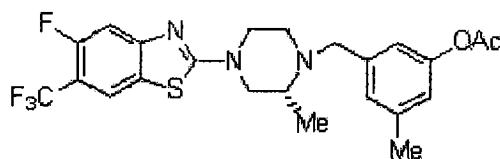


[1592] 收率:57%, $^1\text{H-NMR}$ (CDCl_3): δ 1.11 (6H, d, $J = 6.0\text{Hz}$), 2.29 (3H, s), 2.34 (3H, s), 2.71-2.86 (2H, m), 3.07 (1H, d, $J = 13.0\text{Hz}$), 3.10 (1H, d, $J = 13.0\text{Hz}$), 3.79 (2H, s), 3.88 (2H, d, $J = 13.0\text{Hz}$), 6.77 (1H, s), 6.96 (1H, s), 7.01 (1H, s), 7.26 (1H, d, $J = 11.5\text{Hz}$), 7.73 (1H, d, $J = 7.0\text{Hz}$)。

[1593] 实施例 52

[1594] [式 309]

[1595]



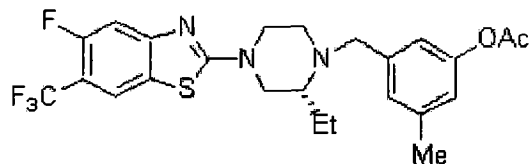
[1596] 收率:57%, $^1\text{H-NMR}$ (CDCl_3): δ 1.21 (3H, d, $J = 6\text{Hz}$), 2.24-2.29 (1H, m), 2.30 (3H, s), 2.36 (3H, s), 2.60-2.72 (1H, m), 2.83 (1H, dt, $J = 12, 3.5\text{Hz}$), 3.18 (1H, d, $J = 13.5\text{Hz}$), 3.18-3.25 (1H, m), 3.48-3.51 (1H, m), 3.67-3.80 (1H, m), 3.85-3.95 (1H, m), 4.02 (1H, d, J

= 13.5Hz), 6.81 (1H, s), 6.90 (1H, s), 7.01 (1H, s), 7.26 (1H, d, $J = 12\text{Hz}$), 7.73 (1H, d, $J = 7\text{Hz}$)。

[1597] 实施例 53

[1598] [式 310]

[1599]

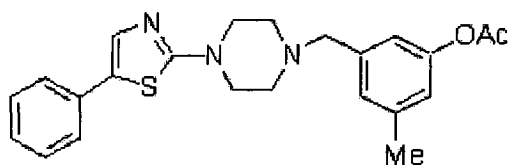


[1600] 收率:65%, $^1\text{H-NMR}(\text{CDCl}_3)$: δ 1.02 (3H, t, $J = 7.5\text{Hz}$), 1.50–1.78 (2H, m), 2.26–2.42 (1H, m), 2.30 (3H, s), 2.36 (3H, s), 2.48–2.59 (1H, m), 2.78–2.89 (1H, m), 3.27 (1H, d, $J = 13.5\text{Hz}$), 3.38–3.58 (2H, m), 3.61–3.72 (1H, m), 3.78–3.89 (1H, m), 3.98 (1H, d, $J = 13.5\text{Hz}$), 6.81 (1H, s), 6.90 (1H, s), 7.01 (1H, s), 7.26 (1H, d, $J = 12.0\text{Hz}$), 7.74 (1H, d, $J = 7.0\text{Hz}$)。

[1601] 实施例 54

[1602] [式 311]

[1603]

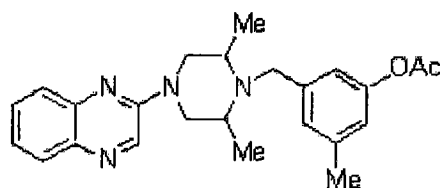


[1604] 收率:61%, $^1\text{H-NMR}(\text{CDCl}_3)$: δ 2.29 (3H, s), 2.36 (3H, s), 2.58 (4H, t, $J = 5.0\text{Hz}$), 3.52 (2H, s), 3.53 (4H, t, $J = 5.0\text{Hz}$), 6.82 (1H, s), 6.90 (1H, s), 7.02 (1H, s), 7.17–7.24 (1H, m), 7.27–7.37 (2H, m), 7.38–7.47 (3H, m)。

[1605] 实施例 55

[1606] [式 312]

[1607]

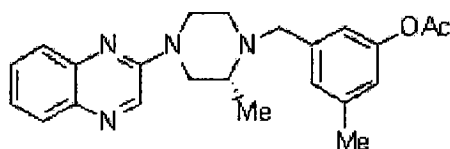


[1608] 收率:49%, $^1\text{H-NMR}(\text{CDCl}_3)$: δ 1.15 (6H, d, $J = 6.0\text{Hz}$), 2.30 (3H, s), 2.35 (3H, s), 2.68–2.83 (2H, m), 2.94 (1H, d, $J = 13.0\text{Hz}$), 2.97 (1H, d, $J = 13.0\text{Hz}$), 3.80 (2H, s), 4.33 (2H, d, $J = 14.0\text{Hz}$), 6.76 (1H, s), 6.97 (1H, s), 7.04 (1H, s), 7.34–7.43 (1H, m), 7.52–7.61 (1H, m), 7.67 (1H, d, $J = 8.0, 1.5\text{Hz}$), 7.87 (1H, dd, $J = 8.0, 1.5\text{Hz}$), 8.56 (1H, s)。

[1609] 实施例 56

[1610] [式 313]

[1611]

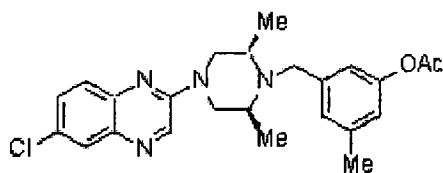


[1612] 收率:56%, $^1\text{H-NMR}$ (CDCl_3): δ 1.21 (3H, d, $J = 6.0\text{Hz}$), 1.18–2.30 (1H, m), 2.28 (3H, s), 2.35 (3H, s), 2.52–2.65 (1H, m), 2.78–2.89 (1H, m), 3.05–3.20 (2H, m), 3.27–3.41 (1H, m), 3.97–4.12 (2H, m), 4.15–4.25 (1H, m), 6.80 (1H, s), 6.92 (1H, s), 7.01 (1H, s), 7.32–7.40 (1H, m), 7.50–7.59 (1H, m), 7.67 (1H, dd, $J = 8.0, 1.5\text{Hz}$), 7.87 (1H, dd, $J = 8.0, 1.5\text{Hz}$), 8.53 (1H, s)。

[1613] 实施例 57

[1614] [式 314]

[1615]

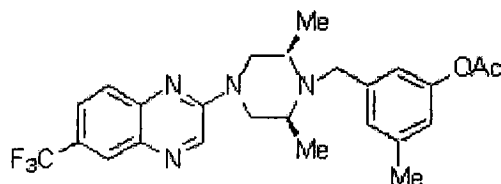


[1616] 收率:55%, $^1\text{H-NMR}$ (CDCl_3): δ 1.14 (6H, d, $J = 6.0\text{Hz}$), 2.29 (3H, s), 2.35 (3H, s), 2.68–2.82 (2H, m), 2.94 (1H, d, $J = 13.0\text{Hz}$), 2.98 (1H, d, $J = 13.0\text{Hz}$), 3.80 (2H, s), 4.30 (2H, d, $J = 13.0\text{Hz}$), 6.76 (1H, s), 6.97 (1H, s), 7.03 (1H, s), 7.50 (1H, dd, $J = 9.0, 2.5\text{Hz}$), 7.59 (1H, d, $J = 9.0\text{Hz}$), 7.85 (1H, d, $J = 2.5\text{Hz}$), 8.54 (1H, s)。

[1617] 实施例 58

[1618] [式 315]

[1619]

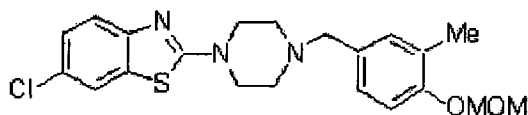


[1620] 收率:34%, $^1\text{H-NMR}$ (CDCl_3): δ 1.13 (6H, d, $J = 6.0\text{Hz}$), 2.28 (3H, s), 2.34 (3H, s), 2.65–2.79 (2H, m), 2.95 (1H, d, $J = 13.0\text{Hz}$), 2.98 (1H, d, $J = 13.0\text{Hz}$), 3.78 (2H, s), 4.34 (2H, d, $J = 13.0\text{Hz}$), 6.77 (1H, s), 6.98 (1H, s), 7.02 (1H, s), 7.67–7.73 (2H, m), 8.13 (1H, s), 8.58 (1H, s)。

[1621] 实施例 59

[1622] [式 316]

[1623]

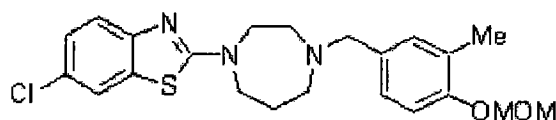


[1624] 收率:92%, $^1\text{H-NMR}$ (CDCl_3): δ 2.25 (3H, s), 2.56 (4H, t, $J = 5.1\text{Hz}$), 3.48 (2H, s), 3.50 (3H, s), 3.63 (4H, t, $J = 5.1\text{Hz}$), 5.20 (2H, s), 7.00 (1H, d), 7.08 (1H, d, 8.1Hz), 7.12 (1H, s), 7.23 (1H, dd, $J = 8.7, 2.1\text{Hz}$), 7.43 (1H, d, $J = 8.7\text{Hz}$), 7.53 (1H, d, 2.1Hz)。

[1625] 实施例 60

[1626] [式 317]

[1627]

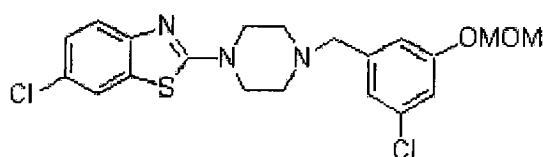


[1628] 收率:90%, $^1\text{H-NMR}(\text{CDCl}_3)$: δ 1.98-2.05 (2H, m), 2.24 (3H, s), 2.68 (2H, t, $J = 5.4\text{Hz}$), 2.79 (2H, t, $J = 4.8\text{Hz}$), 3.49 (3H, s), 3.55 (2H, s), 3.71-3.78 (4H, m), 5.19 (2H, s), 6.98 (1H, s), 7.07 (2H, m), 7.22 (1H, dd, $J = 2.1\text{Hz}$), 7.42 (1H, d, $J = 8.7\text{Hz}$), 7.54 (1H, d, $J = 2.1\text{Hz}$)。

[1629] 实施例 61

[1630] [式 318]

[1631]

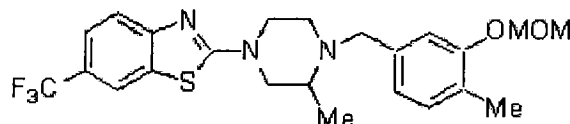


[1632] 收率:60%, $^1\text{H-NMR}(\text{CDCl}_3)$: δ 2.57 (4H, t, $J = 5.1\text{Hz}$), 3.48 (3H, s), 3.50 (2H, s), 3.64 (4H, t, $J = 5.1\text{Hz}$), 5.17 (2H, s), 6.91 (1H, s), 6.97-7.01 (2H, m), 7.24 (1H, dd, $J = 2.1\text{Hz}$), 7.44 (1H, d, $J = 8.7\text{Hz}$), 7.56 (1H, d, $J = 2.1\text{Hz}$)。

[1633] 实施例 62

[1634] [式 319]

[1635]

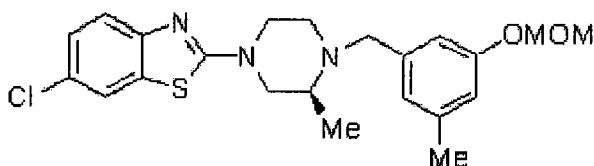


[1636] 收率:70%, $^1\text{H-NMR}(\text{CDCl}_3)$: δ 1.22 (3H, d, $J = 6.5\text{Hz}$), 2.24 (3H, s), 2.24-2.35 (1H, m), 2.60-2.70 (1H, m), 2.78-2.88 (1H, m), 3.19 (1H, dt, $J = 13, 4.5\text{Hz}$), 3.24 (1H, d, $J = 13\text{Hz}$), 3.38-3.50 (1H, m), 3.50 (3H, s), 3.70-3.80 (1H, m), 3.85-3.93 (1H, m), 4.01 (1H, d, $J = 13\text{Hz}$), 5.21 (2H, s), 6.89 (1H, d, $J = 7.5\text{Hz}$), 7.02 (1H, s), 7.10 (1H, d, $J = 7.5\text{Hz}$), 7.50 (1H, d, $J = 8.5\text{Hz}$), 7.53 (1H, d, $J = 8.5\text{Hz}$), 7.83 (1H, s)。

[1637] 实施例 63

[1638] [式 320]

[1639]



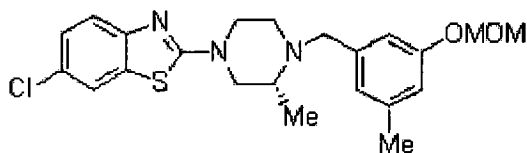
[1640] 收率:92%, $^1\text{H-NMR}(\text{CDCl}_3)$: δ 1.22 (3H, d, $J = 6.0\text{Hz}$), 2.23-2.33 (1H, m), 2.33 (3H, s), 2.60-2.67 (1H, m), 2.83 (1H, dt, $J = 3.3, 12.0\text{Hz}$), 3.16 (2H, dd, $J = 4.2, 13.2\text{Hz}$), 3.44-3.35 (1H, m), 3.49 (3H, s), 3.71 (1H, d, $J = 12.0\text{Hz}$), 3.86 (1H, dd, $J = 2.1, 12.6\text{Hz}$), 3.99 (1H, d, $J = 13.2\text{Hz}$), 5.17 (2H, s), 6.77 (1H, s), 6.80 (1H, s), 6.83 (1H, s),

7.23(1H, dd, $J = 2.1, 8.7\text{Hz}$), 7.42(1H, d, $J = 8.7\text{Hz}$), 7.54(1H, d, $J = 2.1\text{Hz}$)。

[1641] 实施例 64

[1642] [式 321]

[1643]

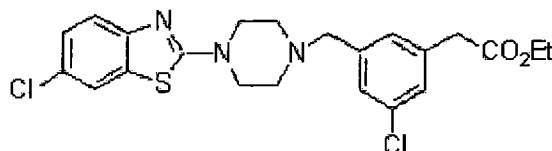


[1644] 收率:95%, $^1\text{H-NMR}(\text{CDCl}_3)$: δ 1.22(3H, d, $J = 6.0\text{Hz}$), 2.25–2.31(1H, m), 2.33(3H, s), 2.60–2.67(1H, m), 2.83(1H, dt, $J = 3.6, 12.0\text{Hz}$), 3.16(2H, dt, $J = 3.6, 13.5\text{Hz}$), 3.44–3.35(1H, m), 3.49(3H, s), 3.71(1H, dt, $J = 3.0, 12.3\text{Hz}$), 3.86(1H, ddd, $J = 1.5, 3.6, 12.6\text{Hz}$), 3.99(1H, d, $J = 13.5\text{Hz}$), 5.16(2H, s), 6.77(1H, s), 6.80(1H, s), 6.83(1H, s), 7.23(1H, dd, $J = 2.1, 8.7\text{Hz}$), 7.42(1H, d, $J = 8.7\text{Hz}$), 7.54(1H, d, $J = 2.1\text{Hz}$)。

[1645] 实施例 65

[1646] [式 322]

[1647]

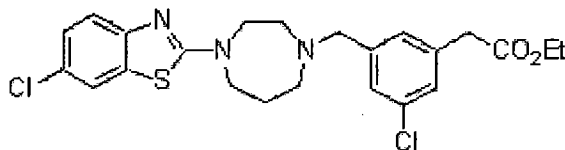


[1648] 收率:38%, $^1\text{H-NMR}(\text{CDCl}_3)$: δ 1.27(3H, t, $J = 7.2\text{Hz}$), 2.57(4H, t, $J = 4.8\text{Hz}$), 3.52(2H, s), 3.59(2H, s), 3.64(4H, t, $J = 4.8\text{Hz}$), 4.17(2H, q, $J = 7.2\text{Hz}$), 7.14(1H, s), 7.20(1H, s), 7.23(1H, dd, $J = 7.8, 2.4\text{Hz}$), 7.26(1H, s), 7.43(1H, d, $J = 7.8\text{Hz}$), 7.56(1H, d, $J = 2.4\text{Hz}$)。

[1649] 实施例 66

[1650] [式 323]

[1651]

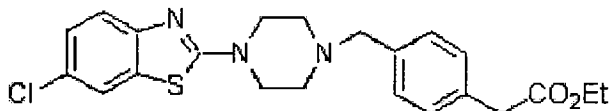


[1652] 收率:60%, $^1\text{H-NMR}(\text{CDCl}_3)$: δ 1.26(3H, t, $J = 7.2\text{Hz}$), 1.98–2.06(2H, m), 2.68(2H, t, $J = 5.4\text{Hz}$), 2.80(2H, t, $J = 5.4\text{Hz}$), 3.56(2H, s), 3.60(2H, s), 3.71–3.78(4H, m), 4.16(2H, q, $J = 7.2\text{Hz}$), 7.12(1H, s), 7.18(1H, s), 7.23(1H, dd, $J = 8.4, 2.1\text{Hz}$), 7.25(1H, s), 7.42(1H, d, $J = 8.4\text{Hz}$), 7.55(1H, d, $J = 2.1\text{Hz}$)。

[1653] 实施例 67

[1654] [式 324]

[1655]

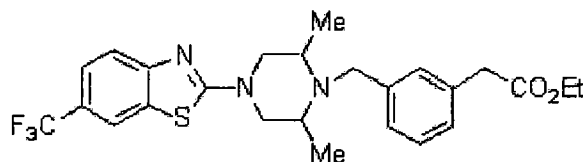


[1656] 收率:89%, $^1\text{H-NMR}(\text{CDCl}_3)$: δ 1.26(3H, t, $J = 7\text{Hz}$), 2.57(4H, t, $J = 5\text{Hz}$), 3.55(2H, s), 3.61(2H, s), 3.62(4H, t, $J = 5\text{Hz}$), 4.15(2H, q, $J = 7\text{Hz}$), 7.23(1H, dd, $J = 8.5, 2\text{Hz}$), 7.25-7.35(4H, m), 7.42(1H, d, $J = 8.5\text{Hz}$), 7.55(1H, d, $J = 2\text{Hz}$)。

[1657] 实施例 68

[1658] [式 325]

[1659]

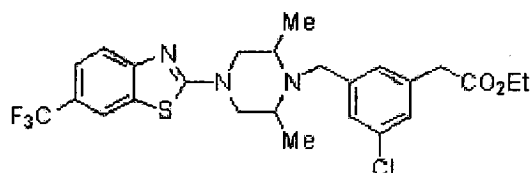


[1660] 收率:79%, $^1\text{H-NMR}(\text{CDCl}_3)$: δ 1.13(6H, d, $J = 6\text{Hz}$), 1.25(3H, t, $J = 7\text{Hz}$), 2.73-2.90(2H, m), 3.05-3.15(2H, m), 3.61(2H, s), 3.85(2H, s), 3.85-3.95(2H, m), 4.14(2H, q, $J = 7\text{Hz}$), 7.10-7.35(4H, m), 7.52(1H, d, $J = 8.5\text{Hz}$), 7.56(1H, d, $J = 8.5\text{Hz}$), 7.84(1H, s)。

[1661] 实施例 69

[1662] [式 326]

[1663]

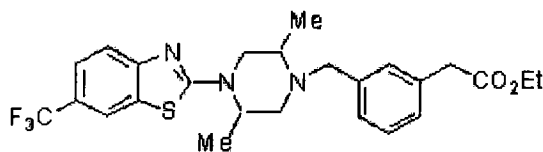


[1664] 收率:54%, $^1\text{H-NMR}(\text{CDCl}_3)$: δ 1.09(6H, d, $J = 6.5\text{Hz}$), 1.26(3H, t, $J = 7\text{Hz}$), 2.70-2.95(2H, m), 3.10(2H, dd, $J = 13, 13\text{Hz}$), 3.58(2H, s), 3.78(s), 3.86-3.96(2H, m), 4.15(2H, q, $J = 7\text{Hz}$), 7.14(1H, s), 7.17(1H, s), 7.33(s), 7.53(1H, d, $J = 8.5\text{Hz}$), 7.57(1H, d, $J = 8.5\text{Hz}$), 7.85(1H, s)。

[1665] 实施例 70

[1666] [式 327]

[1667]

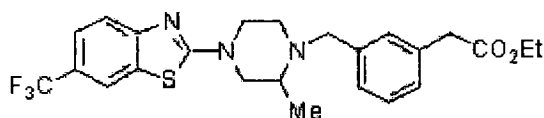


[1668] 收率:71%, $^1\text{H-NMR}(\text{CDCl}_3)$: δ 1.08(3H, d, $J = 6.5\text{Hz}$), 1.25(3H, t, $J = 7\text{Hz}$), 1.40(3H, d, $J = 6.5\text{Hz}$), 2.25-2.35(1H, m), 2.90(1H, dd, $J = 12, 4\text{Hz}$), 3.10-3.20(1H, m), 3.52(1H, d, $J = 13.5\text{Hz}$), 3.62(2H, s), 3.63-3.78(3H, m), 4.16(2H, q, $J = 7\text{Hz}$), 4.20-4.35(1H, m), 7.20-7.35(4H, m), 7.45-7.56(2H, m), 7.82(1H, s)。

[1669] 实施例 71

[1670] [式 328]

[1671]

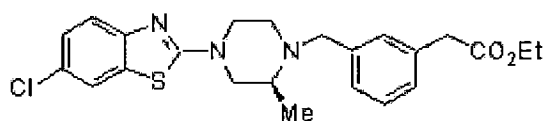


[1672] 收率:92%, $^1\text{H-NMR}$ (CDCl_3): δ 1.23 (3H, d, $J = 6\text{Hz}$), 1.25 (3H, t, $J = 7\text{Hz}$), 2.23-2.35 (1H, m), 2.60-2.75 (1H, m), 2.83 (1H, dt, $J = 12, 4\text{Hz}$), 3.20 (1H, d, $J = 12.5\text{Hz}$), 3.22 (1H, d, $J = 13\text{Hz}$), 3.38-3.50 (1H, m), 3.62 (2H, s), 3.70-3.80 (1H, m), 3.85-3.95 (1H, m), 4.05 (1H, d, $J = 13\text{Hz}$), 4.16 (2H, q, $J = 7\text{Hz}$), 7.15-7.35 (4H, m), 7.45-7.60 (2H, m), 7.84 (1H, s)。

[1673] 实施例 72

[1674] [式 329]

[1675]

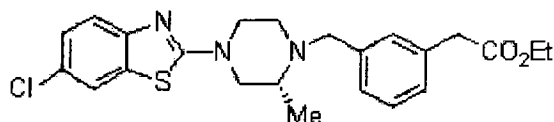


[1676] 收率:88%, $^1\text{H-NMR}$ (CDCl_3): δ 1.23 (3H, t, $J = 7.2\text{Hz}$), 1.26 (3H, t, $J = 6.9\text{Hz}$), 2.27 (1H, ddd, $J = 3.3, 8.7, 9.9\text{Hz}$), 2.61-2.67 (1H, m), 2.80 (1H, dt, $J = 3.3, 11.7\text{Hz}$), 3.21 (2H, d, $J = 13.5\text{Hz}$), 3.34-3.43 (1H, m), 3.62 (2H, s), 3.71 (1H, d, $J = 12.6\text{Hz}$), 3.87 (1H, dd, $J = 2.1, 12.6\text{Hz}$), 4.05 (1H, d, $J = 13.5\text{Hz}$), 4.16 (2H, q, $J = 7.2\text{Hz}$), 7.18-7.32 (5H, m), 7.42 (1H, d, $J = 8.7\text{Hz}$), 7.54 (1H, d, $J = 2.4\text{Hz}$)。

[1677] 实施例 73

[1678] [式 330]

[1679]

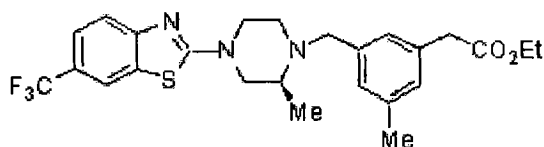


[1680] 收率:93%, $^1\text{H-NMR}$ (CDCl_3): δ 1.24 (3H, t, $J = 6.0\text{Hz}$), 1.26 (3H, t, $J = 7.2\text{Hz}$), 2.27 (1H, ddd, $J = 3.3, 8.7, 9.9\text{Hz}$), 2.62-2.67 (1H, m), 2.80 (1H, dt, $J = 3.6, 12.0\text{Hz}$), 3.21 (2H, d, $J = 13.5\text{Hz}$), 3.39-3.42 (1H, m), 3.62 (2H, s), 3.71 (1H, dt, $J = 12.0\text{Hz}$), 3.87 (1H, dd, $J = 2.1, 12.6\text{Hz}$), 4.06 (1H, d, $J = 13.5\text{Hz}$), 4.16 (2H, q, $J = 7.2\text{Hz}$), 7.18-7.32 (5H, m), 7.42 (1H, d, $J = 8.4\text{Hz}$), 7.54 (1H, d, $J = 2.1\text{Hz}$)。

[1681] 实施例 74

[1682] [式 331]

[1683]



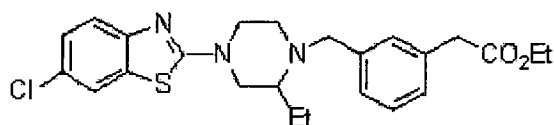
[1684] 收率:82%, $^1\text{H-NMR}$ (CDCl_3): δ 1.23 (3H, d, $J = 6\text{Hz}$), 1.26 (3H, t, $J = 7\text{Hz}$), 2.20-2.35 (1H, m), 2.34 (3H, s), 2.58-2.71 (1H, m), 2.82 (1H, dt, $J = 12, 4\text{Hz}$), 3.16 (1H, d, $J = 13.5\text{Hz}$), 3.16-3.25 (1H, m), 3.38-3.50 (1H, m), 3.58 (2H, s), 3.70-3.80 (1H, m), 3.86-3.96 (1H, m), 4.03 (1H, d, $J = 13.5\text{Hz}$), 4.15 (2H, q, $J = 7\text{Hz}$), 7.01 (1H, s), 7.05 (2H,

s), 7.51 (1H, d, $J = 8.5\text{Hz}$), 7.55 (1H, d, $J = 8.5\text{Hz}$), 7.84 (1H, s)。

[1685] 实施例 75

[1686] [式 332]

[1687]

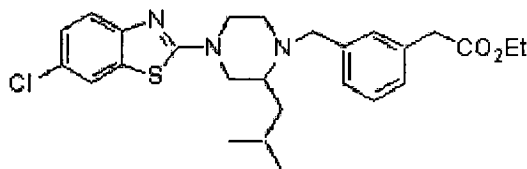


[1688] 收率:92%, $^1\text{H-NMR}(\text{CDCl}_3)$: δ 1.02 (3H, t, $J = 7.2\text{Hz}$), 1.26 (3H, t, $J = 7.2\text{Hz}$), 1.61-1.74 (2H, m), 2.29-2.37 (1H, m), 2.50-2.55 (1H, m), 2.79-2.84 (1H, m), 3.29 (1H, d, $J = 13.5\text{Hz}$), 3.37 (1H, dd, $J = 8.1, 12.9\text{Hz}$), 3.40-3.50 (1H, m), 3.62 (3H, s), 3.80 (1H, dd, $J = 3.3, 12.9\text{Hz}$), 4.01 (1H, d, $J = 13.5\text{Hz}$), 4.16 (2H, t, $J = 7.2\text{Hz}$), 7.18 (5H, m), 7.42 (1H, d, $J = 8.7\text{Hz}$), 7.54 (1H, d, $J = 2.1\text{Hz}$)。

[1689] 实施例 76

[1690] [式 333]

[1691]

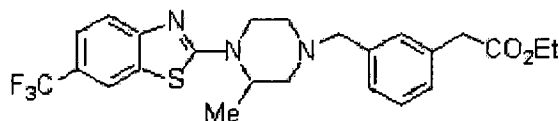


[1692] 收率:90%, $^1\text{H-NMR}(\text{CDCl}_3)$: δ 0.93 (6H, dd, $J = 6.3, 11.7\text{Hz}$), 1.26 (3H, t, $J = 7.2\text{Hz}$), 1.35-1.44 (1H, m), 1.50-1.56 (1H, m), 1.65-1.76 (1H, m), 2.37-2.44 (1H, m), 2.67-2.72 (1H, m), 2.78-2.85 (1H, m), 3.36 (1H, d, $J = 12.9\text{Hz}$), 3.39 (1H, d, $J = 13.2\text{Hz}$), 3.58 (2H, t, $J = 4.8\text{Hz}$), 3.61 (2H, s), 3.75 (1H, dd, $J = 3.3, 12.9\text{Hz}$), 3.93 (1H, d, $J = 13.2\text{Hz}$), 4.16 (2H, q, $J = 7.2\text{Hz}$), 7.17-7.31 (5H, m), 7.42 (1H, d, $J = 8.7\text{Hz}$), 7.54 (1H, d, $J = 1.8\text{Hz}$)。

[1693] 实施例 77

[1694] [式 334]

[1695]

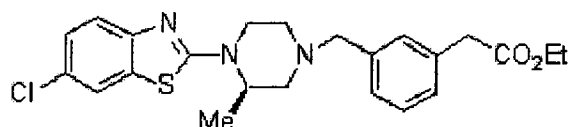


[1696] 收率:68%, $^1\text{H-NMR}(\text{CDCl}_3)$: δ 1.26 (3H, t, $J = 7\text{Hz}$), 1.42 (3H, d, $J = 6.5\text{Hz}$), 2.25 (1H, td, $J = 11.5, 3.5\text{Hz}$), 2.32 (1H, dd, $J = 11.5, 4\text{Hz}$), 2.74 (1H, d, $J = 11.5\text{Hz}$), 2.91 (1H, dt, $J = 11.5, 2\text{Hz}$), 3.46 (1H, d, $J = 13.5\text{Hz}$), 3.52 (1H, td, $J = 11.5, 4\text{Hz}$), 3.59 (1H, d, $J = 13.5\text{Hz}$), 3.62 (2H, s), 3.85-4.00 (1H, m), 4.15 (2H, q, $J = 7\text{Hz}$), 4.20-4.30 (1H, m), 7.15-7.33 (4H, m), 7.51 (1H, d, $J = 8.5\text{Hz}$), 7.55 (1H, d, $J = 8.5\text{Hz}$), 7.84 (1H, s)。

[1697] 实施例 78

[1698] [式 335]

[1699]

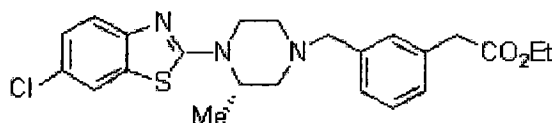


[1700] 收率:86%, ¹H-NMR(CDC13): δ 1.25(3H, t, J = 7Hz), 1.40(3H, d, J = 6.5Hz), 2.24(1H, td, J = 11.5, 3.5Hz), 2.33(1H, dd, J = 11.5, 3.5Hz), 2.72(1H, d, J = 11Hz), 2.91(1H, d, J = 11Hz), 3.43(1H, d, J = 13.5Hz), 3.49(1H, td, J = 11.5, 3.5Hz), 3.59(1H, d, J = 13.5Hz), 3.62(2H, s), 3.80-3.90(1H, m), 4.10-4.18(1H, m), 4.19(2H, q, J = 7Hz), 7.15-7.35(5H, m), 7.42(1H, d, J = 7.5Hz), 7.54(1H, d, J = 2Hz)。

[1701] 实施例 79

[1702] [式 336]

[1703]

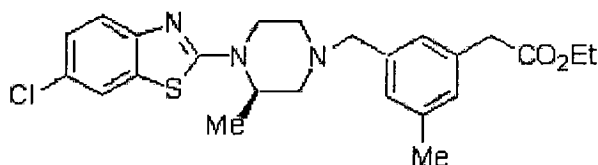


[1704] 收率:71%, ¹H-NMR(CDC13): δ 1.26(3H, t, J = 7.0Hz), 1.40(3H, d, J = 7.0Hz), 2.17-2.38(2H, m), 2.68-2.77(1H, m), 2.88-2.96(1H, m), 3.41-3.67(5H, m), 3.82-3.92(1H, m), 4.07-4.23(1H, m), 4.16(2H, q, J = 7.0Hz), 7.16-7.34(5H, m), 7.42(1H, d, J = 8.5Hz), 7.54(1H, d, J = 2.0Hz)。

[1705] 实施例 80

[1706] [式 337]

[1707]

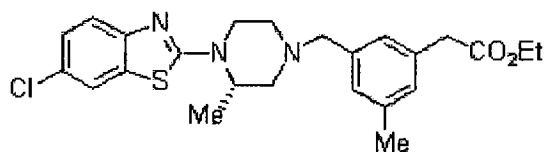


[1708] 收率:85%, ¹H-NMR(CDC13): δ 1.26(3H, t, J = 7Hz), 1.40(3H, d, J = 6.5Hz), 2.23(1H, td, J = 11.5, 3.5Hz), 2.27-2.33(1H, m), 2.34(3H, s), 2.72(1H, d, J = 11.5Hz), 2.90(1H, d, J = 11.5Hz), 3.41(1H, d, J = 13.5Hz), 3.45-3.54(1H, m), 3.55(1H, d, J = 13.5Hz), 3.58(2H, s), 3.85(1H, d, J = 12Hz), 4.10-4.15(1H, m), 4.16(2H, q, J = 7Hz), 7.01(1H, s), 7.07(1H, s), 7.08(1H, s), 7.22(1H, dd, J = 8.5, 2Hz), 7.42(1H, d, J = 8.5Hz), 7.54(1H, d, J = 2Hz)。

[1709] 实施例 81

[1710] [式 338]

[1711]



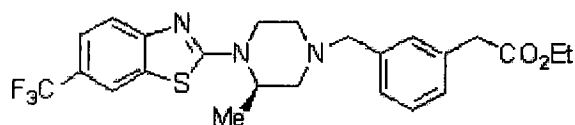
[1712] 收率:74%, ¹H-NMR(CDC13): δ 1.26(3H, t, J = 7.0Hz), 1.40(3H, d, J = 7.0Hz), 2.16-2.37(5H, m), 2.68-2.77(1H, m), 2.86-2.96(1H, m), 3.36-3.62(5H, m), 3.80-3.90(1H, m), 4.15(3H, m), 7.01(1H, s), 7.04-7.10(2H, m), 7.23(1H, dd, J = 8.5, 2.0Hz), 7.42(1H, d,

$J = 8.5\text{Hz}$), $7.54(1\text{H}, \text{d}, J = 2.0\text{Hz})$ 。

[1713] 实施例 82

[1714] [式 339]

[1715]

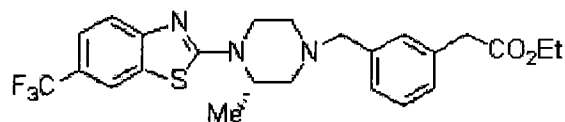


[1716] 收率:83%, $^1\text{H-NMR}(\text{CDCl}_3)$: δ 1.26(3H, t, $J = 7\text{Hz}$), 1.42(3H, d, $J = 6.5\text{Hz}$), 2.25(1H, dt, $J = 12.5, 3.5\text{Hz}$), 2.33(1H, dd, $J = 11, 3.5\text{Hz}$), 2.73(1H, d, $J = 11\text{Hz}$), 2.93(1H, d, $J = 11\text{Hz}$), 3.42-3.60(3H, m), 3.62(2H, s), 3.85-3.97(1H, m), 4.16(2H, q, $J = 7\text{Hz}$), 4.18-4.28(1H, m), 7.18-7.35(4H, m), 7.51(1H, d, $J = 8.5\text{Hz}$), 7.56(1H, d, $J = 8.5\text{Hz}$), 7.84(1H, s)。

[1717] 实施例 83

[1718] [式 340]

[1719]

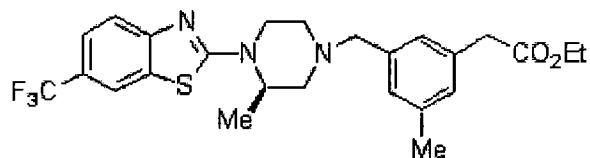


[1720] 收率:72%, $^1\text{H-NMR}(\text{CDCl}_3)$: δ 1.26(3H, t, $J = 7.0\text{Hz}$), 1.42(3H, d, $J = 6.5\text{Hz}$), 2.25(1H, td, $J = 11.5, 3.5\text{Hz}$), 2.34(1H, dd, $J = 11.5, 3.5\text{Hz}$), 2.74(1H, d, $J = 11.5\text{Hz}$), 2.93(1H, d, $J = 11.5\text{Hz}$), 3.42-3.66(5H, m), 3.91(1H, d, $J = 11.5\text{Hz}$), 4.08-4.29(3H, m), 7.16-7.35(4H, m), 7.47-7.60(2H, m), 7.84(1H, s)。

[1721] 实施例 84

[1722] [式 341]

[1723]

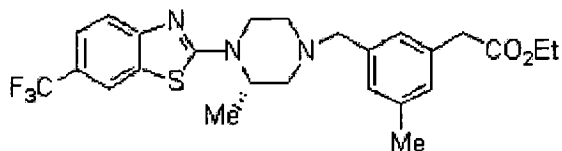


[1724] 收率:74%, $^1\text{H-NMR}(\text{CDCl}_3)$: δ 1.26(3H, t, $J = 7\text{Hz}$), 1.42(3H, d, $J = 6.5\text{Hz}$), 2.18-2.34(2H, m), 2.35(3H, s), 2.74(1H, d, $J = 11\text{Hz}$), 2.92(1H, d, $J = 11.5\text{Hz}$), 3.42(1H, d, $J = 13.5\text{Hz}$), 3.53(1H, td, $J = 11.5, 3.5\text{Hz}$), 3.56(1H, d, $J = 13.5\text{Hz}$), 3.58(2H, s), 3.91(1H, d, $J = 12\text{Hz}$), 4.15(2H, q, $J = 7\text{Hz}$), 4.15-4.30(1H, m), 7.02(1H, s), 7.07(1H, s), 7.09(1H, s), 7.51(1H, d, $J = 8.5\text{Hz}$), 7.55(1H, d, $J = 8.5\text{Hz}$), 7.84(1H, s)。

[1725] 实施例 85

[1726] [式 342]

[1727]

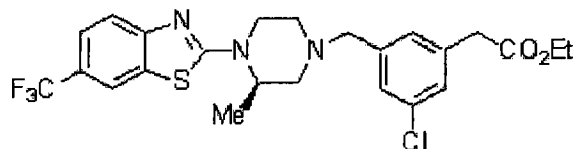


[1728] 收率:69%, ¹H-NMR(CDC13): δ 1.26(3H, t, $J = 7.0\text{Hz}$), 1.43(3H, d, $J = 6.5\text{Hz}$), 2.17-2.39(5H, m), 2.70-2.79(1H, m), 2.87-2.97(1H, m), 3.43(1H, d, $J = 13.0\text{Hz}$), 3.46-3.62(4H, m), 3.85-3.97(1H, m), 4.16(2H, q, $J = 7.0\text{Hz}$), 4.17-4.29(1H, m), 7.02(1H, s), 7.05-7.11(2H, m), 7.47-7.59(2H, m), 7.84(1H, s)。

[1729] 实施例 86

[1730] [式 343]

[1731]

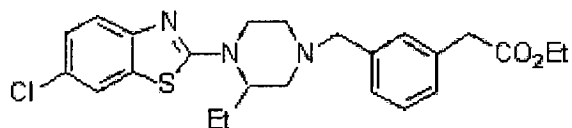


[1732] 收率:86%, ¹H-NMR(CDC13): δ 1.27(3H, t, $J = 7\text{Hz}$), 1.43(3H, d, $J = 6.5\text{Hz}$), 2.26(1H, td, $J = 12, 3.5\text{Hz}$), 2.36(1H, dd, $J = 11, 3.5\text{Hz}$), 2.72(1H, d, $J = 11\text{Hz}$), 2.91(1H, d, $J = 11\text{Hz}$), 3.44(1H, d, $J = 13.5\text{Hz}$), 3.52(1H, td, $J = 12.5, 3.5\text{Hz}$), 3.55(1H, d, $J = 13.5\text{Hz}$), 3.59(2H, s), 3.86-3.96(1H, m), 4.16(2H, q, $J = 7\text{Hz}$), 4.20-4.30(1H, m), 7.17(1H, s), 7.20(1H, s), 7.29(1H, s), 7.51(1H, d, $J = 8.5\text{Hz}$), 7.56(1H, d, $J = 8.5\text{Hz}$), 7.84(1H, s)。

[1733] 实施例 87

[1734] [式 344]

[1735]

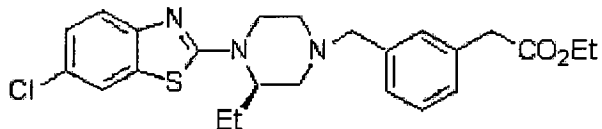


[1736] 收率:41%, ¹H-NMR(CDC13): δ 0.87(3H, t, $J = 7.5\text{Hz}$), 1.26(3H, t, $J = 7.0\text{Hz}$), 1.80-2.02(2H, m), 2.16-2.30(2H, m), 2.79-2.94(2H, m), 3.38-3.52(2H, m), 3.54-3.65(3H, m), 3.76-3.88(1H, m), 3.94-4.06(1H, m), 4.15(2H, q, $J = 7.0\text{Hz}$), 7.15-7.34(5H, m), 7.39(1H, d, $J = 8.5\text{Hz}$), 7.52(1H, d, $J = 2.0\text{Hz}$)。

[1737] 实施例 88

[1738] [式 345]

[1739]

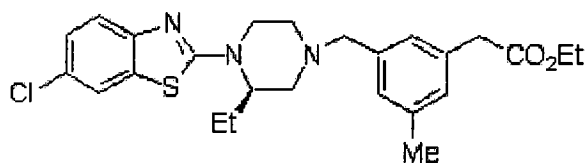


[1740] 收率:79%, ¹H-NMR(CDC13): δ 0.87(3H, t, $J = 7.5\text{Hz}$), 1.26(3H, t, $J = 7\text{Hz}$), 1.85-2.00(2H, m), 2.18-2.29(2H, m), 2.80-2.84(2H, m), 3.42(1H, d, $J = 13.5\text{Hz}$), 3.44(1H, td, $J = 12.5, 3.5\text{Hz}$), 3.59(1H, d, $J = 13.5\text{Hz}$), 3.62(2H, s), 3.70-3.86(1H, m), 3.95-4.05(1H, m), 4.15(2H, q, $J = 7\text{Hz}$), 7.15-7.33(5H, m), 7.39(1H, d, $J = 8.5\text{Hz}$), 7.52(1H, d, $J = 2\text{Hz}$)。

[1741] 实施例 89

[1742] [式 346]

[1743]

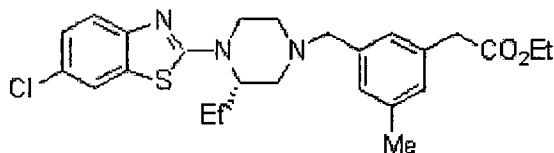


[1744] 收率:25%,¹H-NMR(CDCl₃): δ 0.88(3H, t, J = 7.5Hz), 1.26(3H, t, J = 7Hz), 1.83-2.03(2H, m), 2.22(2H, td, J = 12.5, 3.5Hz), 2.34(3H, s), 2.80-2.92(2H, m), 3.38(1H, d, J = 13.5Hz), 3.45(1H, td, J = 12.5, 3.5Hz), 3.55(1H, d, J = 13.5Hz), 3.57(2H, s), 3.75-3.88(1H, m), 3.95-4.03(1H, m), 4.15(2H, q, J = 7Hz), 7.01(1H, s), 7.05(1H, s), 7.06(1H, s), 7.21(1H, dd, J = 8.5, 2Hz), 7.39(1H, d, J = 8.5Hz), 7.52(1H, d, J = 2Hz)。

[1745] 实施例 90

[1746] [式 347]

[1747]

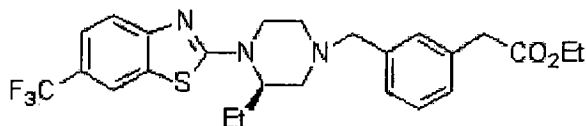


[1748] 收率:67%,¹H-NMR(CDCl₃): δ 0.88(3H, t, J = 7.5Hz), 1.26(3H, t, J = 7.0Hz), 1.80-2.03(2H, m), 2.22(2H, td, J = 11.5, 3.5Hz), 2.34(3H, s), 2.80-2.93(2H, m), 3.38(1H, d, J = 13.0Hz), 3.46(1H, td, J = 12.5, 3.0Hz), 3.56(1H, d, J = 13.0Hz), 3.57(2H, s), 3.76-3.87(1H, m), 3.94-4.05(1H, m), 4.15(2H, q, J = 7.0Hz), 7.01(1H, s), 7.06(2H, s), 7.22(1H, dd, J = 8.5, 2.0Hz), 7.39(1H, d, J = 8.5Hz), 7.52(1H, d, J = 2.0Hz)。

[1749] 实施例 91

[1750] [式 348]

[1751]

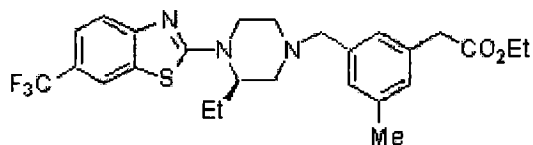


[1752] 收率:80%,¹H-NMR(CDCl₃): δ 0.88(3H, t, J = 7.5Hz), 1.26(3H, t, J = 7Hz), 1.96(2H, quant, J = 7.5Hz), 2.19-2.30(2H, m), 2.82-2.95(2H, m), 3.44(1H, d, J = 13.5Hz), 3.49(1H, td, J = 12.5, 3.5Hz), 3.59(1H, d, J = 13.5Hz), 3.62(2H, s), 3.73-3.83(1H, m), 4.00-4.10(1H, m), 4.17(2H, q, J = 7Hz), 7.15-7.33(4H, m), 7.48-7.55(2H, m), 7.82(1H, s)。

[1753] 实施例 92

[1754] [式 349]

[1755]



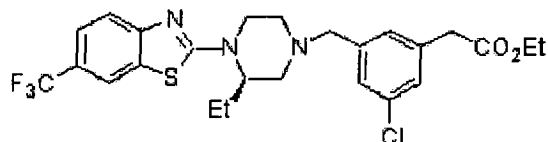
[1756] 收率:53%,¹H-NMR(CDCl₃): δ 0.89(3H, t, J = 7.5Hz), 1.20(3H, t, J =

7Hz), 1.87-2.03 (2H, m), 2.24 (2H, td, $J = 11, 3.5\text{Hz}$), 2.34 (3H, s), 2.82-2.95 (2H, m), 3.38 (1H, d, $J = 13\text{Hz}$), 3.49 (1H, td, $J = 13, 3.5\text{Hz}$), 3.56 (1H, d, $J = 13\text{Hz}$), 3.57 (2H, s), 3.80-3.95 (1H, m), 4.00-4.10 (1H, m), 4.16 (2H, q, $J = 7\text{Hz}$), 7.01 (1H, s), 7.05 (1H, s), 7.06 (1H, s), 7.48-7.55 (2H, m), 7.82 (1H, s)。

[1757] 实施例 93

[1758] [式 350]

[1759]

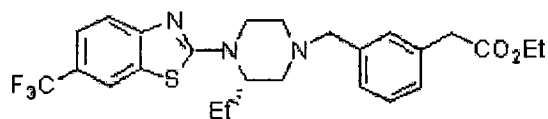


[1760] 收率:74%, $^1\text{H-NMR}(\text{CDCl}_3)$: δ 0.90 (3H, t, $J = 7.5\text{Hz}$), 1.27 (3H, t, $J = 7\text{Hz}$), 1.94 (2H, quant, $J = 7.5\text{Hz}$), 2.20-2.32 (2H, m), 2.80-2.93 (2H, m), 3.41 (1H, d, $J = 13.5\text{Hz}$), 3.49 (1H, td, $J = 12.5, 3.5\text{Hz}$), 3.55 (1H, d, $J = 13.5\text{Hz}$), 3.59 (2H, s), 3.85-3.95 (1H, m), 4.00-4.10 (1H, m), 4.17 (2H, q, $J = 7\text{Hz}$), 7.14 (1H, s), 7.20 (1H, s), 7.28 (1H, s), 7.45-7.56 (2H, m), 7.82 (1H, s)。

[1761] 实施例 94

[1762] [式 351]

[1763]

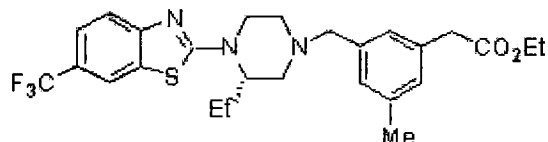


[1764] 收率:85%, $^1\text{H-NMR}(\text{CDCl}_3)$: δ 0.88 (3H, t, $J = 7.5\text{Hz}$), 1.20 (3H, t, $J = 7\text{Hz}$), 1.94 (2H, quant, $J = 7.5\text{Hz}$), 2.19-2.30 (2H, m), 2.80-2.95 (2H, m), 3.43 (1H, d, $J = 13.5\text{Hz}$), 3.51 (1H, td, $J = 12.5, 3.5\text{Hz}$), 3.59 (1H, d, $J = 13.5\text{Hz}$), 3.62 (2H, s), 3.80-3.95 (1H, m), 4.00-4.10 (1H, m), 4.15 (2H, q, $J = 7\text{Hz}$), 7.15-7.33 (4H, m), 7.50 (1H, d, $J = 8.5\text{Hz}$), 7.52 (1H, d, $J = 8.5\text{Hz}$), 7.82 (1H, s)。

[1765] 实施例 95

[1766] [式 352]

[1767]

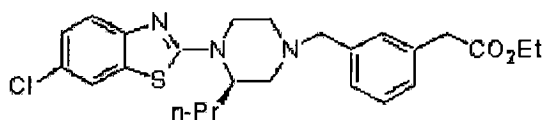


[1768] 收率:73%, $^1\text{H-NMR}(\text{CDCl}_3)$: δ 0.88 (3H, t, $J = 7.5\text{Hz}$), 1.26 (3H, t, $J = 7\text{Hz}$), 1.95 (2H, quant, $J = 7.5\text{Hz}$), 2.15-2.28 (2H, m), 2.34 (3H, s), 2.82-2.93 (2H, m), 3.39 (1H, d, $J = 13.5\text{Hz}$), 3.48 (1H, td, $J = 12.5, 3.5\text{Hz}$), 3.55 (1H, d, $J = 13.5\text{Hz}$), 3.57 (2H, s), 3.80-3.95 (1H, m), 3.98-4.10 (1H, m), 4.15 (2H, q, $J = 7\text{Hz}$), 7.01 (1H, s), 7.06 (2H, s), 7.52 (2H, s), 7.82 (1H, s)。

[1769] 实施例 96

[1770] [式 353]

[1771]

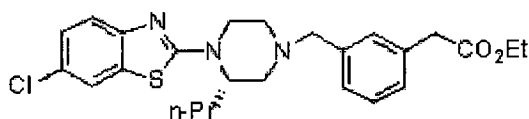


[1772] 收率:67%, $^1\text{H-NMR}$ (CDCl_3): δ 0.93 (3H, t, $J = 7.5\text{Hz}$), 1.19–1.35 (2H, m), 1.26 (3H, t, $J = 7.0\text{Hz}$), 1.73–2.00 (2H, m), 2.15–2.30 (2H, m), 2.81 (1H, d, $J = 11.5\text{Hz}$), 2.88 (1H, d, $J = 11.0\text{Hz}$), 3.42 (1H, d, $J = 13.5\text{Hz}$), 3.46 (1H, td, $J = 12.5, 3.5\text{Hz}$), 3.58 (1H, d, $J = 13.5\text{Hz}$), 3.61 (2H, s), 3.84–4.05 (2H, m), 4.16 (2H, q, $J = 7.0\text{Hz}$), 7.14–7.34 (5H, m), 7.39 (1H, d, $J = 8.5\text{Hz}$), 7.52 (1H, d, $J = 2.0\text{Hz}$)。

[1773] 实施例 97

[1774] [式 354]

[1775]

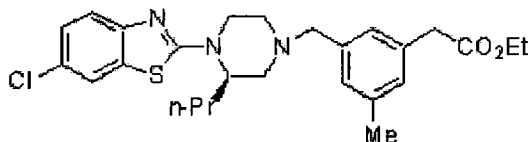


[1776] 收率:64%, $^1\text{H-NMR}$ (CDCl_3): δ 0.93 (3H, t, $J = 7.2\text{Hz}$), 1.21–1.31 (5H, m), 1.78–1.96 (2H, m), 2.19–2.28 (2H, m), 2.81 (1H, d, $J = 11.4\text{Hz}$), 2.88 (1H, d, $J = 11.4\text{Hz}$), 3.42 (1H, d, $J = 13.2\text{Hz}$), 3.47 (1H, td, $J = 3.3, 12.6\text{Hz}$), 3.59 (1H, d, $J = 13.2\text{Hz}$), 3.62 (2H, s), 3.90 (1H, s), 4.00 (1H, d, $J = 12.6\text{Hz}$), 4.16 (2H, q, $J = 7.2\text{Hz}$), 7.19–7.33 (5H, m), 7.39 (1H, d, $J = 8.4\text{Hz}$), 7.53 (1H, d, $J = 2.1\text{Hz}$)。

[1777] 实施例 98

[1778] [式 355]

[1779]

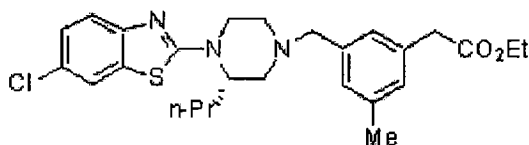


[1780] 收率:58%, $^1\text{H-NMR}$ (CDCl_3): δ 0.34 (3H, t, $J = 7.0\text{Hz}$), 1.19–1.35 (2H, m), 1.26 (3H, t, $J = 7.0\text{Hz}$), 1.72–2.02 (2H, m), 2.15–2.29 (2H, m), 2.34 (3H, s), 2.81 (1H, d, $J = 11.5\text{Hz}$), 2.89 (1H, d, $J = 11.5\text{Hz}$), 3.37 (1H, d, $J = 13.5\text{Hz}$), 3.47 (1H, td, $J = 13.5, 3.0\text{Hz}$), 3.57 (1H, d, $J = 13.5\text{Hz}$), 3.57 (2H, s), 3.83–3.93 (1H, m), 3.94–4.04 (1H, m), 4.16 (2H, q, $J = 7.0\text{Hz}$), 7.01 (1H, s), 7.05 (2H, s), 7.22 (1H, dd, $J = 8.5, 2.0\text{Hz}$), 7.39 (1H, d, $J = 8.5\text{Hz}$), 7.52 (1H, d, $J = 2.0\text{Hz}$)。

[1781] 实施例 99

[1782] [式 356]

[1783]



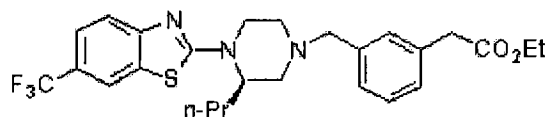
[1784] 收率:68%, $^1\text{H-NMR}$ (CDCl_3): δ 0.94 (3H, t, $J = 7.5\text{Hz}$), 1.24–1.31 (5H, m), 1.73–1.85 (1H, m), 1.89–2.01 (1H, m), 2.17–2.27 (2H, m), 2.34 (3H, s), 2.81 (1H, d, $J = 11.4\text{Hz}$), 2.88 (1H, d, $J = 11.1\text{Hz}$), 3.37 (1H, d, $J = 13.5\text{Hz}$), 3.47 (1H, dt, $J = 3.3,$

12.6Hz), 3.57(1H, d, $J = 13.5\text{Hz}$), 3.57(2H, s), 3.89(1H, s), 3.99(1H, d, $J = 12.0\text{Hz}$), 4.16(2H, q, $J = 7.2\text{Hz}$), 7.01(1H, s), 7.06(2H, s), 7.22(1H, dd, $J = 2.1, 8.4\text{Hz}$), 7.39(1H, d, $J = 8.4\text{Hz}$), 7.52(1H, d, $J = 2.1\text{Hz}$)。

[1785] 实施例 100

[1786] [式 357]

[1787]

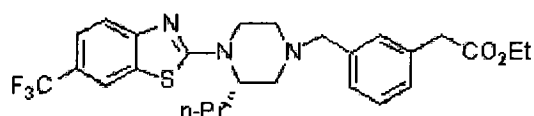


[1788] 收率:69%, $^1\text{H-NMR}(\text{CDCl}_3)$: δ 0.93(3H, t, $J = 7.0\text{Hz}$), 1.18-1.35(2H, m), 1.26(3H, t, $J = 7.0\text{Hz}$), 1.76-1.99(2H, m), 2.16-2.29(2H, m), 2.82(1H, d, $J = 11.5\text{Hz}$), 2.89(1H, d, $J = 11.5\text{Hz}$), 3.42(1H, d, $J = 13.5\text{Hz}$), 3.49(1H, td, $J = 13.0, 3.5\text{Hz}$), 3.59(1H, d, $J = 13.5\text{Hz}$), 3.62(2H, s), 3.90-4.09(2H, m), 4.16(2H, q, $J = 7.0\text{Hz}$), 7.15-7.34(4H, m), 7.49(1H, d, $J = 8.5\text{Hz}$), 7.53(1H, d, $J = 8.5\text{Hz}$), 7.81(1H, s)。

[1789] 实施例 101

[1790] [式 358]

[1791]

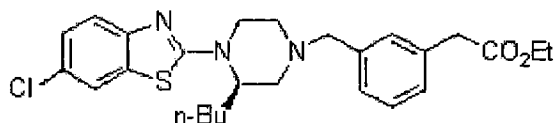


[1792] 收率:80%, $^1\text{H-NMR}(\text{CDCl}_3)$: δ 0.94(3H, t, $J = 7.2\text{Hz}$), 1.24-1.31(5H, m), 1.83-1.91(2H, m), 2.20-2.29(2H, m), 2.83(1H, d, $J = 11.4\text{Hz}$), 2.90(1H, d, $J = 11.4\text{Hz}$), 3.34(1H, d, $J = 13.5\text{Hz}$), 3.50(1H, td, $J = 3.6, 12.6\text{Hz}$), 3.60(1H, d, $J = 13.5\text{Hz}$), 3.62(2H, s), 3.97(1H, s), 4.05(1H, d, $J = 12.6\text{Hz}$), 4.16(2H, q, $J = 7.2\text{Hz}$), 7.19-7.33(4H, m), 7.51(2H, s), 7.82(1H, s)。

[1793] 实施例 102

[1794] [式 359]

[1795]

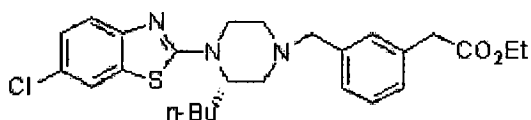


[1796] 收率:79%, $^1\text{H-NMR}(\text{CDCl}_3)$: δ 0.87(3H, t, $J = 7\text{Hz}$), 1.15-1.40(7H, m), 1.74-2.00(2H, m), 2.17-2.29(2H, m), 2.77-2.94(2H, m), 3.41(1H, d, $J = 13.5\text{Hz}$), 3.46(1H, td, $J = 13, 3.5\text{Hz}$), 3.59(1H, d, $J = 13.5\text{Hz}$), 3.61(2H, s), 3.80-3.93(1H, m), 3.95-4.08(1H, m), 4.16(2H, q, $J = 7\text{Hz}$), 7.15-7.32(5H, m), 7.39(1H, d, $J = 9\text{Hz}$), 7.52(1H, d, $J = 2\text{Hz}$)。

[1797] 实施例 103

[1798] [式 360]

[1799]

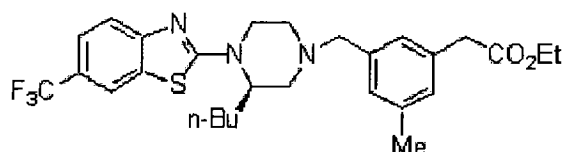


[1800] 收率:75%, $^1\text{H-NMR}(\text{CDCl}_3)$: δ 0.87 (3H, t, $J = 7\text{Hz}$), 1.15-1.40 (7H, m), 1.76-2.01 (2H, m), 2.20-2.30 (2H, m), 2.77-2.93 (2H, m), 3.42 (1H, d, $J = 13.5\text{Hz}$), 3.46 (1H, td, $J = 13, 3.5\text{Hz}$), 3.59 (1H, d, $J = 13.5\text{Hz}$), 3.61 (2H, s), 3.80-3.92 (1H, m), 3.95-4.06 (1H, m), 4.16 (2H, q, $J = 7\text{Hz}$), 7.16-7.33 (5H, m), 7.39 (1H, d, $J = 9\text{Hz}$), 7.52 (1H, d, $J = 2\text{Hz}$)。

[1801] 实施例 104

[1802] [式 361]

[1803]

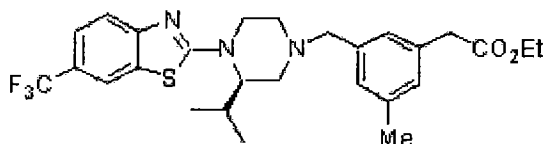


[1804] 收率:75%, $^1\text{H-NMR}(\text{CDCl}_3)$: δ 0.88 (3H, t, $J = 7\text{Hz}$), 1.15-1.40 (7H, m), 1.75-2.03 (2H, m), 2.17-2.30 (2H, m), 2.34 (3H, s), 2.80-2.96 (2H, m), 3.37 (1H, d, $J = 13.5\text{Hz}$), 3.50 (1H, td, $J = 13, 3.5\text{Hz}$), 3.57 (2H, s), 3.58 (1H, d, $J = 13.5\text{Hz}$), 3.85-4.00 (1H, m), 4.00-4.10 (1H, m), 4.15 (2H, q, $J = 7\text{Hz}$), 7.01 (1H, s), 7.05 (1H, s), 7.07 (1H, s), 7.45-7.55 (2H, m), 7.82 (1H, s)。

[1805] 实施例 105

[1806] [式 362]

[1807]

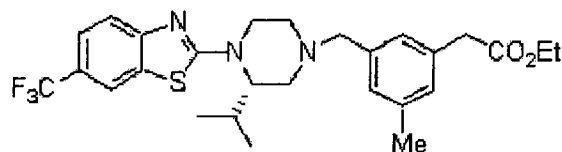


[1808] 收率:44%, $^1\text{H-NMR}(\text{CDCl}_3)$: δ 0.90 (3H, d, $J = 6.5\text{Hz}$), 0.91 (3H, d, $J = 6.5\text{Hz}$), 1.26 (3H, t, $J = 7.0\text{Hz}$), 2.12 (1H, dd, $J = 11.5, 3.5\text{Hz}$), 2.23 (1H, td, $J = 11.5, 3.5\text{Hz}$), 2.34 (3H, s), 2.56-2.72 (1H, m), 2.88 (1H, d, $J = 11.5\text{Hz}$), 2.98 (1H, d, $J = 11.5\text{Hz}$), 3.34 (1H, d, $J = 13.0\text{Hz}$), 3.40-3.65 (2H, m), 3.56 (1H, d, $J = 13.0\text{Hz}$), 3.57 (2H, s), 4.08-4.22 (1H, m), 4.15 (2H, q, $J = 7.0\text{Hz}$), 7.01 (1H, s), 7.05 (2H, s), 7.49 (2H, s), 7.79 (1H, s)。

[1809] 实施例 106

[1810] [式 363]

[1811]



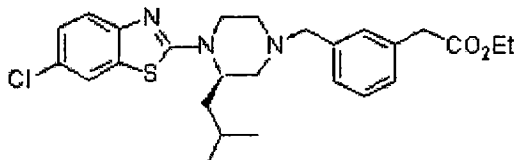
[1812] 收率:70%, $^1\text{H-NMR}(\text{CDCl}_3)$: δ 0.90 (3H, d, $J = 2.5\text{Hz}$), 0.91 (3H, d, $J = 2.5\text{Hz}$), 1.26 (3H, t, $J = 7\text{Hz}$), 2.12 (1H, dd, $J = 11.5, 3.5\text{Hz}$), 2.23 (1H, td, $J = 11.5, 3.5\text{Hz}$),

2.34(3H, s), 2.55-2.73(1H, m), 2.88(1H, d, $J = 9.5\text{Hz}$), 2.98(1H, d, $J = 9.5\text{Hz}$), 3.34(1H, d, $J = 13\text{Hz}$), 3.40-3.54(1H, m), 3.56(1H, d, $J = 13\text{Hz}$), 3.57(2H, s), 3.57-3.60(1H, m), 4.11-4.15(1H, m), 4.16(2H, q, $J = 7\text{Hz}$), 7.01(1H, s), 7.04(1H, s), 7.05(1H, s), 7.49-7.50(2H, m), 7.79(1H, s)。

[1813] 实施例 107

[1814] [式 364]

[1815]

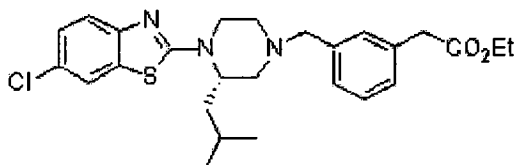


[1816] 收率:73%, $^1\text{H-NMR}(\text{CDCl}_3)$: δ 0.93(6H, d, $J = 6.5\text{Hz}$), 1.26(3H, t, $J = 7.0\text{Hz}$), 1.32-1.53(1H, m), 1.54-1.67(1H, m), 1.85-1.98(1H, m), 2.24(2H, td, $J = 11.5, 3.5\text{Hz}$), 2.79(1H, d, $J = 11.5\text{Hz}$), 2.89(1H, d, $J = 11.5\text{Hz}$), 3.40(1H, d, $J = 13.5\text{Hz}$), 3.47(1H, td, $J = 13.0, 3.5\text{Hz}$), 3.61(1H, d, $J = 13.5\text{Hz}$), 3.61(2H, s), 3.88-4.08(2H, m), 4.16(2H, q, $J = 7.0\text{Hz}$), 7.15-7.33(5H, m), 7.39(1H, d, $J = 8.5\text{Hz}$), 7.53(1H, d, $J = 2.0\text{Hz}$)。

[1817] 实施例 108

[1818] [式 365]

[1819]

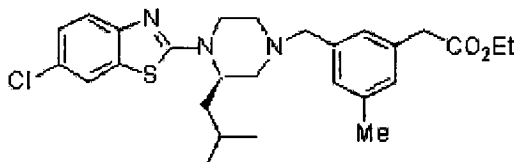


[1820] 收率:81%, $^1\text{H-NMR}(\text{CDCl}_3)$: δ 0.93(6H, d, $J = 6.5\text{Hz}$), 1.26(3H, t, $J = 7\text{Hz}$), 1.38-1.47(1H, m), 1.55-1.67(1H, m), 1.85-1.96(1H, m), 2.19-2.30(2H, m), 2.78(1H, d, $J = 11.5\text{Hz}$), 2.88(1H, d, $J = 11.5\text{Hz}$), 3.40(1H, d, $J = 13.5\text{Hz}$), 3.47(1H, td, $J = 13.5\text{Hz}$), 3.60(1H, d, $J = 13.5\text{Hz}$), 3.61(2H, s), 3.90-4.08(2H, m), 4.15(2H, q, $J = 7\text{Hz}$), 7.15-7.35(5H, m), 7.39(1H, d, $J = 8.5\text{Hz}$), 7.53(1H, d, $J = 2\text{Hz}$)。

[1821] 实施例 109

[1822] [式 366]

[1823]

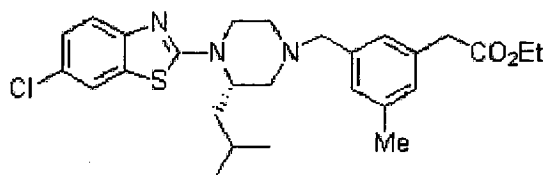


[1824] 收率:63%, $^1\text{H-NMR}(\text{CDCl}_3)$: δ 0.93(3H, d, $J = 6.5\text{Hz}$), 0.94(3H, d, $J = 6.5\text{Hz}$), 1.26(3H, t, $J = 7.0\text{Hz}$), 1.36-1.64(2H, m), 1.88-2.02(1H, m), 2.13-2.44(2H, m), 2.34(3H, s), 2.79(1H, d, $J = 11.0\text{Hz}$), 2.89(1H, d, $J = 11.0\text{Hz}$), 3.35(1H, d, $J = 13.5\text{Hz}$), 3.41-3.68(2H, m), 3.57(2H, s), 3.86-4.09(2H, m), 4.16(2H, q, $J = 7.0\text{Hz}$), 7.01(1H, s), 7.04(1H, s), 7.06(1H, s), 7.22(1H, dd, $J = 8.5, 2.0\text{Hz}$), 7.39(1H, d, $J = 8.5\text{Hz}$), 7.53(1H, d, $J = 2.0\text{Hz}$)。

[1825] 实施例 110

[1826] [式 367]

[1827]

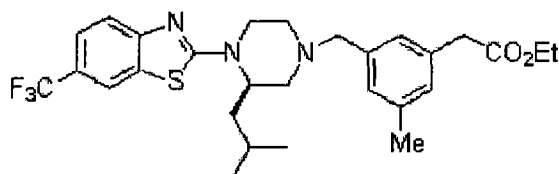


[1828] 收率:81%, $^1\text{H-NMR}$ (CDCl_3): δ 0.92 (3H, d, $J = 3\text{Hz}$), 0.95 (3H, d, $J = 3\text{Hz}$), 1.26 (3H, t, $J = 7\text{Hz}$), 1.39-1.65 (2H, m), 1.90-2.02 (1H, m), 2.15-2.32 (2H, m), 2.34 (3H, s), 2.78 (1H, d, $J = 11.5\text{Hz}$), 2.89 (1H, d, $J = 11.5\text{Hz}$), 3.35 (1H, d, $J = 13.5\text{Hz}$), 3.48 (1H, td, $J = 13, 3.5\text{Hz}$), 3.57 (2H, s), 3.59 (1H, d, $J = 13.5\text{Hz}$), 3.86-4.08 (2H, m), 4.15 (2H, q, $J = 7\text{Hz}$), 7.01 (1H, s), 7.04 (1H, s), 7.06 (1H, s), 7.21 (1H, dd, $J = 8.5, 2\text{Hz}$), 7.39 (1H, d, $J = 8.5\text{Hz}$), 7.53 (1H, d, $J = 2\text{Hz}$)。

[1829] 实施例 111

[1830] [式 368]

[1831]

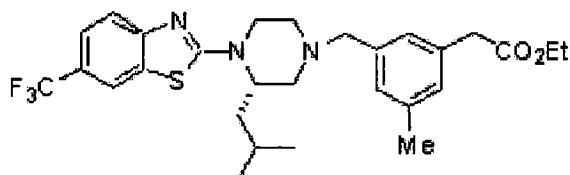


[1832] 收率:47%, $^1\text{H-NMR}$ (CDCl_3): δ 0.94 (3H, d, $J = 6.5\text{Hz}$), 0.95 (3H, d, $J = 6.5\text{Hz}$), 1.27 (3H, t, $J = 7.0\text{Hz}$), 1.38-1.67 (2H, m), 1.89-2.04 (1H, m), 2.14-2.38 (2H, m), 2.34 (3H, s), 2.80 (1H, d, $J = 11.5\text{Hz}$), 2.90 (1H, d, $J = 11.5\text{Hz}$), 3.35 (1H, d, $J = 13.5\text{Hz}$), 3.44-3.64 (2H, m), 3.57 (2H, s), 3.94-4.21 (2H, m), 4.16 (2H, q, $J = 7.0\text{Hz}$), 7.01 (1H, s), 7.06 (2H, s), 7.49 (1H, d, $J = 8.5\text{Hz}$), 7.53 (1H, d, $J = 8.5\text{Hz}$), 7.82 (1H, s)。

[1833] 实施例 112

[1834] [式 369]

[1835]

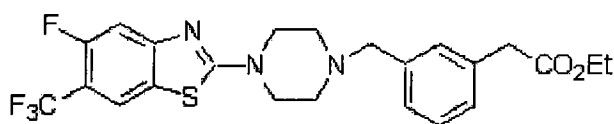


[1836] 收率:80%, $^1\text{H-NMR}$ (CDCl_3): δ 0.94 (6H, dd, $J = 3.0, 6.3\text{Hz}$), 1.26 (3H, t, $J = 7.2\text{Hz}$), 1.44-1.48 (1H, m), 1.56-1.62 (1H, m), 1.91-2.00 (1H, m), 2.18-2.26 (2H, m), 2.34 (3H, s), 2.80 (1H, d, $J = 11.4\text{Hz}$), 2.91 (1H, d, $J = 11.4\text{Hz}$), 3.36 (1H, d, $J = 13.2\text{Hz}$), 3.52 (1H, dt, $J = 3.6, 12.6\text{Hz}$), 3.57 (2H, s), 3.60 (1H, d, $J = 13.2\text{Hz}$), 4.04 (2H, br), 4.16 (2H, q, $J = 7.2\text{Hz}$), 7.01 (1H, s), 7.04 (1H, s), 7.06 (1H, s), 7.2 (2H, s), 7.83 (1H, s)。

[1837] 实施例 113

[1838] [式 370]

[1839]

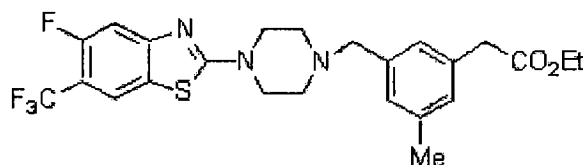


[1840] 收率:69%, $^1\text{H-NMR}$ (CDCl_3): δ 1.26 (3H, t, $J = 7.0\text{Hz}$), 2.59 (4H, t, $J = 5.0\text{Hz}$), 3.57 (2H, s), 3.62 (2H, s), 3.68 (4H, t, $J = 5.0\text{Hz}$), 4.16 (2H, q, $J = 7.0\text{Hz}$), 7.18-7.34 (5H, m), 7.75 (1H, d, $J = 7.0\text{Hz}$)。

[1841] 实施例 114

[1842] [式 371]

[1843]

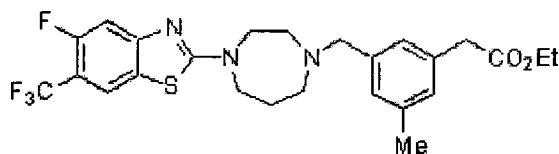


[1844] 收率:72%, $^1\text{H-NMR}$ (CDCl_3): δ 1.26 (3H, t, $J = 7.0\text{Hz}$), 2.34 (3H, s), 2.58 (4H, t, $J = 5.0\text{Hz}$), 3.52 (2H, s), 3.58 (2H, s), 3.68 (4H, t, $J = 5.0\text{Hz}$), 4.16 (2H, q, $J = 7.0\text{Hz}$), 7.00-7.12 (3H, m), 7.26 (1H, d, $J = 11.5\text{Hz}$), 7.75 (1H, d, $J = 7.0\text{Hz}$)。

[1845] 实施例 115

[1846] [式 372]

[1847]

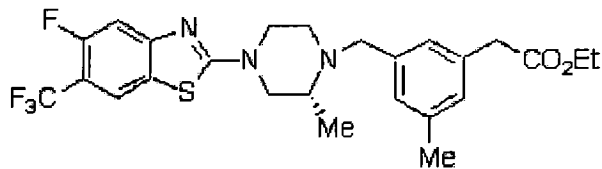


[1848] 收率:41%, $^1\text{H-NMR}$ (CDCl_3): δ 1.25 (3H, t, $J = 7.0\text{Hz}$), 1.96-2.08 (2H, m), 2.32 (3H, s), 2.69 (2H, t, $J = 5.0\text{Hz}$), 2.75-2.85 (2H, m), 3.56 (2H, s), 3.60 (2H, s), 3.61-3.89 (4H, m), 4.15 (2H, q, $J = 7.0\text{Hz}$), 6.50-7.07 (3H, m), 7.26 (1H, d, $J = 12.0\text{Hz}$), 7.73 (1H, d, $J = 7.0\text{Hz}$)。

[1849] 实施例 116

[1850] [式 373]

[1851]

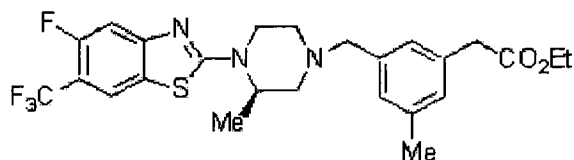


[1852] 收率:80%, $^1\text{H-NMR}$ (CDCl_3): δ 1.23 (3H, d, $J = 6\text{Hz}$), 1.26 (3H, t, $J = 7\text{Hz}$), 2.23-2.33 (1H, m), 2.34 (3H, s), 2.69-2.70 (1H, m), 2.82 (1H, dt, $J = 12, 4\text{Hz}$), 3.17 (1H, d, $J = 13\text{Hz}$), 3.18-3.26 (1H, m), 3.36-3.48 (1H, m), 3.58 (2H, s), 3.70-3.80 (1H, m), 3.85-3.95 (1H, m), 4.02 (1H, d, $J = 13\text{Hz}$), 4.13 (2H, q, $J = 7\text{Hz}$), 7.01 (1H, s), 7.04 (1H, s), 7.05 (1H, s), 7.26 (1H, d, $J = 12\text{Hz}$), 7.73 (1H, d, $J = 7\text{Hz}$)。

[1853] 实施例 117

[1854] [式 374]

[1855]

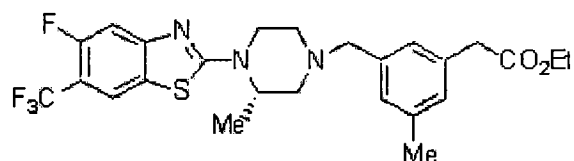


[1856] 收率:63%, $^1\text{H-NMR}$ (CDCl_3): δ 1.26 (3H, t, $J = 7.0\text{Hz}$), 1.43 (3H, d, $J = 7.0\text{Hz}$), 2.17-2.37 (2H, m), 2.34 (3H, s), 2.71-2.79 (1H, m), 2.87-2.98 (1H, m), 3.43 (1H, d, $J = 13.0\text{Hz}$), 3.46-3.60 (2H, m), 3.58 (2H, s), 3.83-3.94 (1H, m), 4.15-4.28 (1H, m), 4.16 (2H, q, $J = 7.0\text{Hz}$), 7.02 (1H, s), 7.06 (1H, s), 7.08 (1H, s), 7.26 (1H, d, $J = 11.5\text{Hz}$), 7.74 (1H, d, $J = 7.0\text{Hz}$)。

[1857] 实施例 118

[1858] [式 375]

[1859]

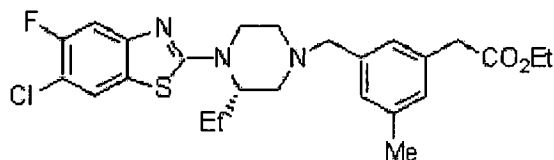


[1860] 收率:60%, $^1\text{H-NMR}$ (CDCl_3): δ 1.26 (3H, t, $J = 7.0\text{Hz}$), 1.43 (3H, d, $J = 7.0\text{Hz}$), 2.16-2.36 (2H, m), 2.34 (3H, s), 2.70-2.79 (1H, m), 2.87-2.98 (1H, m), 3.43 (1H, d, $J = 13.0\text{Hz}$), 3.45-3.61 (4H, m), 3.84-3.94 (1H, m), 4.14-4.28 (1H, m), 4.16 (2H, q, $J = 7.0\text{Hz}$), 7.01 (1H, s), 7.04-7.12 (2H, m), 7.26 (1H, d, $J = 11.5\text{Hz}$), 7.74 (1H, d, $J = 7.0\text{Hz}$)。

[1861] 实施例 119

[1862] [式 376]

[1863]

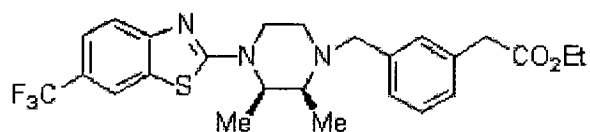


[1864] 收率:90%, $^1\text{H-NMR}$ (CDCl_3): δ 0.87 (3H, t, $J = 7.5\text{Hz}$), 1.25 (3H, t, $J = 7.0\text{Hz}$), 1.82-2.03 (2H, m), 2.14-2.53 (2H, m), 2.33 (3H, s), 2.78-2.93 (2H, m), 3.37 (1H, d, $J = 13.5\text{Hz}$), 3.45 (1H, td, $J = 12.5, 3.5\text{Hz}$), 3.55 (1H, d, $J = 13.5\text{Hz}$), 3.57 (2H, s), 3.76-3.88 (1H, m), 3.90-4.03 (1H, m), 4.15 (2H, q, $J = 7.0\text{Hz}$), 7.00 (1H, s), 7.03-7.09 (2H, m), 7.24 (1H, d, $J = 10.5\text{Hz}$), 7.49 (1H, d, $J = 7.0\text{Hz}$)。

[1865] 实施例 120

[1866] [式 377]

[1867]



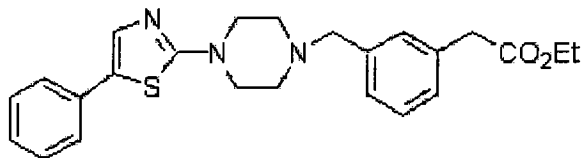
[1868] 收率:18%, $^1\text{H-NMR}$ (CDCl_3): δ 1.20 (3H, d, $J = 6.5\text{Hz}$), 1.25 (3H, t, $J = 7.0\text{Hz}$), 1.36 (3H, d, $J = 6.5\text{Hz}$), 2.15 (1H, td, $J = 12.0, 3.5\text{Hz}$), 2.60-2.72 (1H, m), 2.74-2.84 (1H,

m), 2.98 (1H, d, $J = 13.5$ Hz), 3.40 (1H, td, $J = 12.5, 3.5$ Hz), 3.62 (2H, s), 3.67-3.81 (1H, m), 4.03-4.22 (4H, m), 7.13-7.34 (4H, m), 7.50 (1H, dd, $J = 8.5, 1.5$ Hz), 7.55 (1H, d, $J = 8.5$ Hz), 7.82 (1H, d, $J = 1.5$ Hz)。

[1869] 实施例 121

[1870] [式 378]

[1871]

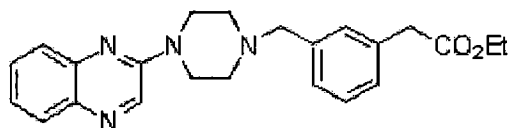


[1872] 收率:73%, $^1\text{H-NMR}$ (CDCl₃): δ 1.26 (3H, t, $J = 7.0$ Hz), 2.58 (4H, t, $J = 5.0$ Hz), 3.54 (4H, t, $J = 5.0$ Hz), 3.56 (2H, s), 3.62 (2H, s), 4.16 (2H, q, $J = 7.0$ Hz), 7.17-7.24 (2H, m), 7.25-7.37 (5H, m), 7.39-7.45 (2H, m), 7.40 (1H, s)。

[1873] 实施例 122

[1874] [式 379]

[1875]

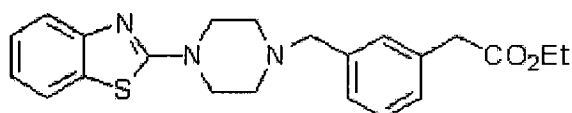


[1876] 收率:56%, $^1\text{H-NMR}$ (CDCl₃): δ 1.26 (3H, t, $J = 7.0$ Hz), 2.61 (4H, t, $J = 5.0$ Hz), 3.57 (2H, s), 3.63 (2H, s), 3.81 (4H, t, $J = 5.0$), 4.16 (2H, q, $J = 7.0$ Hz), 7.14-7.34 (4H, m), 7.35-7.43 (1H, m), 7.53-7.62 (1H, m), 7.68 (1H, dd, $J = 8.0, 1.5$ Hz), 7.87 (1H, dd, $J = 8.0, 1.5$ Hz), 8.57 (1H, s)。

[1877] 实施例 123

[1878] [式 380]

[1879]

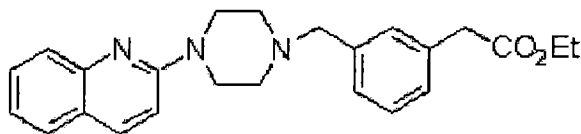


[1880] 收率:70%, $^1\text{H-NMR}$ (CDCl₃): δ 1.26 (3H, t, $J = 7.0$ Hz), 2.58 (4H, t, $J = 5.0$ Hz), 3.56 (2H, s), 3.62 (2H, s), 3.65 (4H, t, $J = 5.0$ Hz), 4.16 (2H, q, $J = 7.0$ Hz), 7.07 (1H, t, $J = 7.5$ Hz), 7.16-7.34 (5H, m), 7.55 (1H, d, $J = 8.0$ Hz), 7.59 (1H, d, $J = 8.0$ Hz)。

[1881] 实施例 124

[1882] [式 381]

[1883]



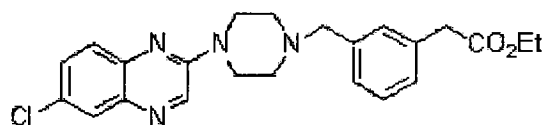
[1884] 收率:66%, $^1\text{H-NMR}$ (CDCl₃): δ 1.26 (3H, t, $J = 7.0$ Hz), 2.59 (4H, t, $J = 5.0$ Hz), 3.57 (2H, s), 3.63 (2H, s), 3.76 (4H, t, $J = 5.0$ Hz), 4.16 (2H, q, $J = 7.0$ Hz), 6.97 (1H, d, $J = 9.0$ Hz), 7.17-7.38 (5H, m), 7.48-7.64 (2H, m), 7.69 (1H, d, $J = 8.5$ Hz), 7.88 (1H, d, $J =$

9.0Hz)。

[1885] 实施例 125

[1886] [式 382]

[1887]

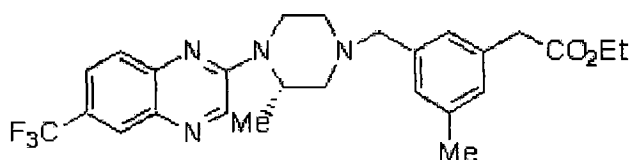


[1888] 收率:88%, $^1\text{H-NMR}$ (CDCl_3): δ 1.26 (3H, t, $J = 7.0\text{Hz}$), 2.60 (4H, t, $J = 5.0\text{Hz}$), 3.57 (2H, s), 3.63 (2H, s), 3.80 (4H, t, $J = 5.0\text{Hz}$), 4.16 (2H, q, $J = 7.0\text{Hz}$), 7.16-7.35 (4H, m), 7.50 (1H, dd, $J = 9.0, 2.5\text{Hz}$), 7.59 (1H, d, $J = 9.0\text{Hz}$), 7.85 (1H, d, $J = 2.5\text{Hz}$), 8.55 (1H, s)。

[1889] 实施例 126

[1890] [式 383]

[1891]

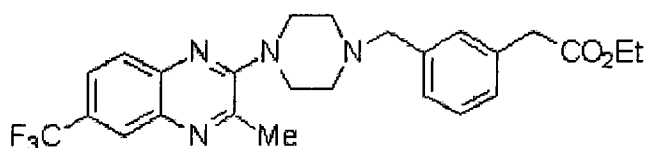


[1892] 收率:80%, $^1\text{H-NMR}$ (CDCl_3): δ 1.26 (3H, t, $J = 7.0\text{Hz}$), 1.39 (3H, d, $J = 7.0\text{Hz}$), 2.20 (1H, t, $J = 11.5, 3.5\text{Hz}$), 2.25-2.37 (4H, m), 2.82 (1H, d, $J = 11.5\text{Hz}$), 3.00 (1H, d, $J = 11.5\text{Hz}$), 3.31-3.46 (2H, m), 3.53-3.63 (3H, m), 4.16 (2H, q, $J = 7.0\text{Hz}$), 4.33-4.43 (1H, m), 4.64-4.77 (1H, m), 7.02 (1H, s), 7.09 (1H, s), 7.11 (1H, s), 7.70 (2H, s), 8.14 (1H, s), 8.58 (1H, s)。

[1893] 实施例 127

[1894] [式 384]

[1895]



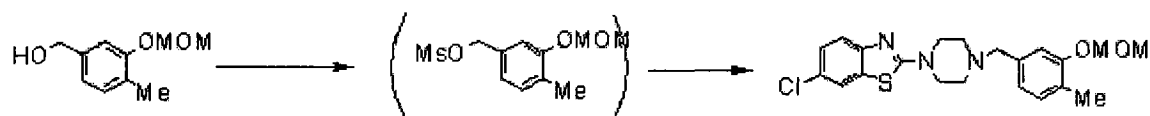
[1896] 收率:90%, $^1\text{H-NMR}$ (CDCl_3): δ 1.26 (3H, t, $J = 7.0\text{Hz}$), 2.66 (4H, t, $J = 5.0\text{Hz}$), 2.70 (3H, s), 3.47 (4H, t, $J = 5.0\text{Hz}$), 3.60 (2H, s), 3.63 (2H, s), 4.16 (2H, q, $J = 7.0\text{Hz}$), 7.16-7.34 (4H, m), 7.74 (1H, d, $J = 8.5\text{Hz}$), 7.87 (1H, d, $J = 8.5\text{Hz}$), 8.16 (1H, s)。

[1897] 实施例 128

[1898] 6-氯-2-[4-(3-甲氧基甲氧基-4-甲基苯基)哌嗪-1-基]苯并噻唑的制备

[1899] [式 385]

[1900]



[1901] 在冰冷却下向 W02004/022551 的参考例 68 中所述的 [3-(甲氧基甲氧基)-4-甲基] 苯甲醇 (1.23g ;6.75mmol), 三乙胺 (0.55ml ;7.09mmol) 和 THF(12ml) 的混合物中滴加甲磺酰氯 (0.55ml ;7.09mmol)。将混合物搅拌 1 小时, 并将反应溶液减压浓缩。向残余物中加入 4-(6-氯苯并噻唑-2-基) 哌嗪二盐酸盐 (2.10g ;6.43mmol), 碳酸钾 (2.67g ;19.3mmol) 和无水 N,N-二甲基甲酰胺 (20ml)。将混合物在室温搅拌 14 小时。向反应溶液加入水, 和收集沉淀物并且用二异丙醚洗涤, 得到 6-氯-2-[4-(3-甲氧基甲氧基-4-甲基苯基) 哌嗪-1-基] 苯并噻唑, 为无色晶体 (1.70g ;63%)。

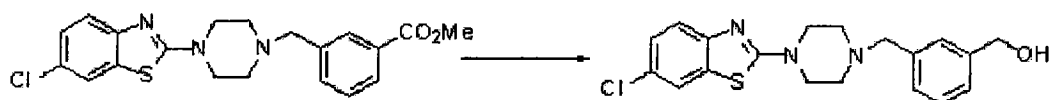
[1902] $^1\text{H-NMR}(\text{CDCl}_3)$: δ 2.24(3H, s), 2.57(4H, t, $J = 5\text{Hz}$), 3.50(3H, s), 3.52(2H, s), 3.63(4H, t, $J = 5\text{Hz}$), 5.22(2H, s), 6.89(1H, d, $J = 7.5\text{Hz}$), 7.03(1H, s), 7.10(1H, d, $J = 7.5\text{Hz}$), 7.23(1H, dd, $J = 8.5, 2\text{Hz}$), 7.45(1H, d, $J = 8.5\text{Hz}$), 7.59(1H, d, $J = 2\text{Hz}$)。

[1903] 实施例 129

[1904] 3-[4-[(6-氯苯并噻唑-2-基) 哌嗪-1-基] 甲基] 苯甲醇的制备

[1905] [式 386]

[1906]



[1907] 在冰冷却下向氢化铝锂 (0.52g ;13.7mmol) 在无 THF(27ml) 中的悬浮液滴加 3-[[4-(6-氯苯并噻唑-2-基) 哌嗪-1-基] 甲基] 苯甲酸甲酯 (2.76g ;6.87mmol) 的无水 THF(27ml) 溶液。在室温搅拌 1 小时之后, 在冰冷却下向其中顺序地滴加水 / THF(0.25ml/5mL) 的混合物和 2N-氢氧化钠水溶液 (0.5ml)。将混合物在室温搅拌 1 小时。在过滤氢氧化铝之后, 将滤液减压浓缩。向残余物中加入乙酸乙酯和盐水以分层。有机层用无水硫酸钠干燥。减压蒸发溶剂, 得到黄色晶体。将晶体用二异丙醚洗涤, 得到 3-[4-[(6-氯苯并噻唑-2-基) 哌嗪-1-基] 甲基] 苯甲醇, 为浅黄色晶体 (2.35g ;92%)。

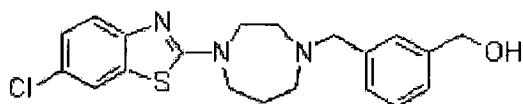
[1908] $^1\text{H-NMR}(\text{CDCl}_3)$: 1.83(1H, t, $J = 5.5\text{Hz}$), 2.57(4H, t, $J = 5\text{Hz}$), 3.51(2H, s), 3.63(4H, t, $J = 5\text{Hz}$), 4.71(2H, d, $J = 5.5\text{Hz}$), 7.23(1H, dd, $J = 8.5, 2\text{Hz}$), 7.25-7.38(4H, m), 7.42(1H, d, $J = 8.5\text{Hz}$), 7.55(1H, d, $J = 2\text{Hz}$)。

[1909] 通过与实施例 129 相似的方法得到实施例 130 到 153 的化合物。

[1910] 实施例 130

[1911] [式 387]

[1912]

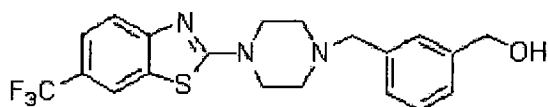


[1913] 收率 :100%, $^1\text{H-NMR}(\text{CDCl}_3)$; δ 1.65(1H, brs), 1.98-2.05(2H, m), 2.70(2H, t, $J = 5.1\text{Hz}$), 2.79-2.82(2H, m), 3.65(2H, s), 3.71-3.77(4H, m), 4.69(2H, s), 7.23(1H, dd, $J = 8.7\text{Hz}, 2.4\text{Hz}$), 7.26-7.34(4H, m), 7.43(1H, d, $J = 8.4\text{Hz}$), 7.55(1H, d, $J = 2.1\text{Hz}$)。

[1914] 实施例 131

[1915] [式 388]

[1916]

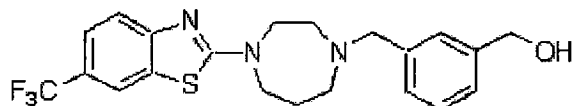


[1917] 收率:100%, $^1\text{H-NMR}(\text{CDCl}_3)$; δ 1.26 (1H, brs), 2.59 (4H, t, $J = 5\text{Hz}$), 3.58 (2H, s), 3.68 (4H, t, $J = 5\text{Hz}$), 4.72 (2H, s), 7.20–7.40 (4H, m), 7.50–7.60 (2H, m), 7.84 (1H, s)。

[1918] 实施例 132

[1919] [式 389]

[1920]

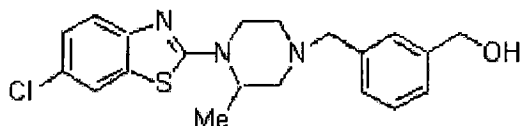


[1921] 收率:60%, $^1\text{H-NMR}(\text{DMSO}-d_6)$; δ 1.88–1.99 (2H, m), 2.58–2.67 (2H, m), 2.74–2.84 (2H, m), 3.62 (2H, s), 3.63–3.85 (4H, m), 4.47 (2H, d, $J = 5.5\text{Hz}$), 5.16 (1H, t, $J = 5.5\text{Hz}$), 7.13–7.20 (2H, m), 7.22–7.30 (2H, m), 7.52–7.57 (2H, m), 8.22 (1H, s)。

[1922] 实施例 133

[1923] [式 390]

[1924]

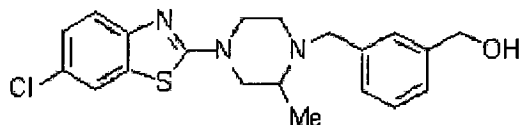


[1925] 收率:96%, $^1\text{H-NMR}(\text{CDCl}_3)$; δ 1.41 (3H, d, $J = 6.5\text{Hz}$), 1.63 (1H, brs), 2.25 (1H, td, $J = 11.5, 3.5\text{Hz}$), 2.33 (1H, dd, $J = 11.5, 3.5\text{Hz}$), 2.72 (1H, d, $J = 11.5\text{Hz}$), 2.86–2.95 (1H, m), 3.47 (1H, td, $J = 12.5, 3.5\text{Hz}$), 3.48 (1H, d, $J = 13.5\text{Hz}$), 3.60 (1H, d, $J = 13.5\text{Hz}$), 3.85 (1H, d, $J = 12.5\text{Hz}$), 4.10–4.25 (1H, m), 4.72 (2H, s), 7.22 (1H, dd, $J = 8.5, 2\text{Hz}$), 7.25–7.40 (4H, m), 7.42 (1H, d, $J = 8.5\text{Hz}$), 7.54 (1H, d, $J = 2\text{Hz}$)。

[1926] 实施例 134

[1927] [式 391]

[1928]

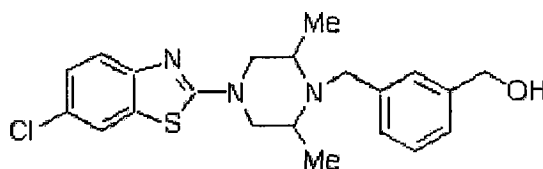


[1929] 收率:98%, $^1\text{H-NMR}(\text{CDCl}_3)$; δ 1.23 (3H, d, $J = 6.5\text{Hz}$), 1.55–1.70 (1H, m), 2.22–2.32 (1H, m), 2.60–2.70 (1H, m), 2.75–2.85 (1H, m), 3.10–3.20 (1H, m), 3.22 (1H, d, $J = 13.5\text{Hz}$), 3.35–3.45 (1H, m), 3.65–3.75 (1H, m), 3.83–3.90 (1H, m), 4.06 (1H, d, $J = 13.5\text{Hz}$), 4.71 (2H, s), 7.20–7.35 (5H, m), 7.42 (1H, d, $J = 8.5\text{Hz}$), 7.54 (1H, d, $J = 2\text{Hz}$)。

[1930] 实施例 135

[1931] [式 392]

[1932]

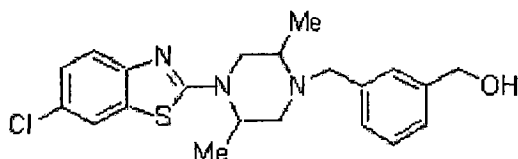


[1933] 收率:定量收率 (q. y.), $^1\text{H-NMR}(\text{CDCl}_3)$; δ 1.12 (6H, d, $J = 6\text{Hz}$), 1.64 (1H, brs), 2.75-2.85 (2H, m), 3.05 (2H, dd, $J = 13, 12.5\text{Hz}$), 3.85 (2H, s), 3.80-3.90 (2H, m), 4.70 (2H, s), 7.23 (1H, dd, $J = 8.5, 2\text{Hz}$), 7.25-7.28 (1H, m), 7.30-7.35 (2H, m), 7.38 (1H, s), 7.42 (1H, d, $J = 8.5\text{Hz}$), 7.55 (1H, d, $J = 2\text{Hz}$)。

[1934] 实施例 136

[1935] [式 393]

[1936]

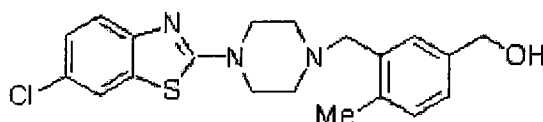


[1937] 收率:定量收率 (q. y.), $^1\text{H-NMR}(\text{CDCl}_3)$; δ 1.08 (3H, d, $J = 6.5\text{Hz}$), 1.38 (3H, d, $J = 6.5\text{Hz}$), 1.74 (1H, brs), 2.33 (1H, d, $J = 11.5\text{Hz}$), 2.89 (1H, dd, $J = 11.5, 4\text{Hz}$), 3.06-3.19 (1H, m), 3.53 (1H, d, $J = 14.5\text{Hz}$), 3.60-3.75 (3H, m), 4.15-4.28 (1H, m), 4.70 (2H, s), 7.21 (1H, dd, $J = 8.5, 2\text{Hz}$), 7.25-7.35 (4H, m), 7.40 (1H, d, $J = 8.5\text{Hz}$), 7.53 (1H, d, $J = 2\text{Hz}$)。

[1938] 实施例 137

[1939] [式 394]

[1940]

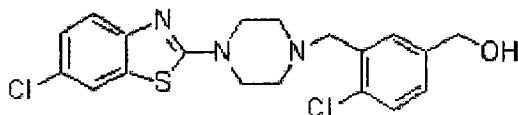


[1941] 收率:60%, $^1\text{H-NMR}(\text{CDCl}_3)$; δ 1.71 (1H, brs), 2.38 (3H, s), 2.58 (4H, t, $J = 5\text{Hz}$), 3.52 (2H, s), 3.61 (4H, t, $J = 5\text{Hz}$), 4.67 (2H, s), 7.15-7.20 (2H, m), 7.23 (1H, dd, $J = 8.5, 2\text{Hz}$), 7.25-7.28 (1H, m), 7.43 (1H, d, $J = 8.5\text{Hz}$), 7.55 (1H, d, $J = 2\text{Hz}$)。

[1942] 实施例 138

[1943] [式 395]

[1944]

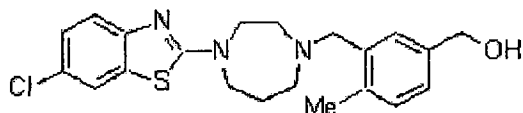


[1945] 收率:39%, $^1\text{H-NMR}(\text{CDCl}_3)$; δ 1.80 (1H, brs), 2.65 (4H, t, $J = 5\text{Hz}$), 3.65 (4H, t, $J = 5\text{Hz}$), 3.68 (2H, s), 4.70 (2H, s), 7.23 (1H, dd, $J = 8, 2\text{Hz}$), 7.24 (1H, dd, $J = 8.5, 2\text{Hz}$), 7.36 (1H, d, $J = 8\text{Hz}$), 7.42 (1H, d, $J = 8.5\text{Hz}$), 7.48 (1H, d, $J = 2\text{Hz}$), 7.55 (1H, d, $J = 2\text{Hz}$)。

[1946] 实施例 139

[1947] [式 396]

[1948]

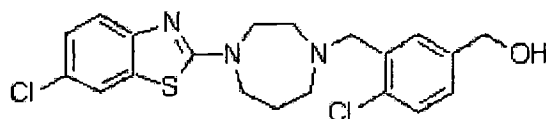


[1949] 收率:92%, $^1\text{H-NMR}(\text{CDCl}_3)$; δ 1.66-1.73, (1H, br-s), 1.97-2.04 (2H, m), 2.33 (3H, s), 2.69 (2H, t, $J = 5.4\text{Hz}$), 2.78-2.81 (2H, m), 3.59 (2H, s), 3.70-3.75 (4H, m), 4.65 (2H, s), 7.16-7.17 (2H, m), 7.23 (1H, dd, $J = 8.7\text{Hz}, 2.1\text{Hz}$), 7.28 (1H, s), 7.43 (1H, d, $J = 8.7\text{Hz}$), 7.55 (1H, d, $J = 2.4\text{Hz}$)。

[1950] 实施例 140

[1951] [式 397]

[1952]

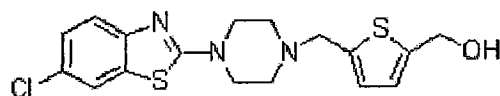


[1953] 收率:100%, $^1\text{H-NMR}(\text{CDCl}_3)$; δ 1.70-1.88 (1H, br-s), 1.98-2.07 (2H, m), 2.75 (2H, t, $J = 5.4\text{Hz}$), 2.84-2.89 (2H, m), 3.72-3.84 (6H, m), 4.68 (2H, s), 7.17-7.25 (2H, m), 7.33 (1H, d, $J = 8.1\text{Hz}$), 7.44 (1H, d, $J = 8.1\text{Hz}$), 7.50 (1H, d, $J = 2.1\text{Hz}$), 7.55 (1H, d, $J = 2.4\text{Hz}$)。

[1954] 实施例 141

[1955] [式 398]

[1956]

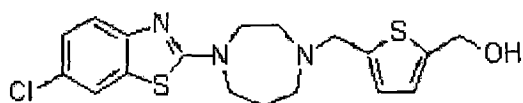


[1957] 收率:30%, $^1\text{H-NMR}(\text{CDCl}_3)$; δ 1.90 (1H, brs), 2.62 (4H, t, $J = 5\text{Hz}$), 3.64 (4H, t, $J = 5\text{Hz}$), 3.74 (2H, s), 4.79 (2H, s), 6.79 (1H, d, $J = 3.5\text{Hz}$), 6.85 (1H, d, $J = 3.5\text{Hz}$), 7.23 (1H, dd, $J = 8.5, 2\text{Hz}$), 7.43 (1H, d, $J = 8.5\text{Hz}$), 7.55 (1H, d, $J = 2\text{Hz}$)。

[1958] 实施例 142

[1959] [式 399]

[1960]

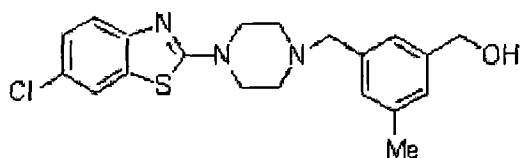


[1961] 收率:80%, $^1\text{H-NMR}(\text{CDCl}_3)$; δ 1.86 (1H, s), 2.00-2.07 (2H, m), 2.71-2.74 (2H, m), 2.84-2.87 (2H, m), 3.73 (2H, t, $J = 6.0\text{Hz}$), 3.77-3.80 (2H, m), 3.82 (2H, s), 4.78 (2H, s), 6.76 (1H, d, $J = 3.3\text{Hz}$), 6.84 (1H, d, $J = 3.3\text{Hz}$), 7.23 (1H, dd, $J = 8.7, 2.4\text{Hz}$), 7.42 (1H, d, $J = 9.0\text{Hz}$), 7.55 (1H, d, $J = 2.4\text{Hz}$)。

[1962] 实施例 143

[1963] [式 400]

[1964]

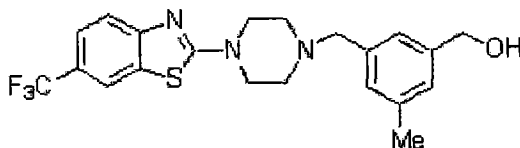


[1965] 收率:90%, $^1\text{H-NMR}$ (CDCl_3); δ 1.81 (1H, brs), 2.36 (3H, s), 2.57 (4H, t, $J = 5\text{Hz}$), 3.53 (2H, s), 3.63 (4H, t, $J = 5\text{Hz}$), 4.67 (2H, s), 7.08 (1H, s), 7.11 (1H, s), 7.13 (1H, s), 7.23 (1H, dd, $J = 8.5, 2\text{Hz}$), 7.43 (1H, d, $J = 8.5\text{Hz}$), 7.55 (1H, d, $J = 2\text{Hz}$)。

[1966] 实施例 144

[1967] [式 401]

[1968]

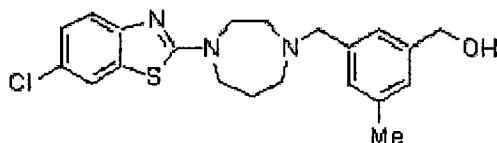


[1969] 收率:定量收率 (q. y.), $^1\text{H-NMR}$ (CDCl_3); δ 1.79 (1H, t, $J = 4.5\text{Hz}$), 2.36 (3H, s), 2.59 (4H, t, $J = 5\text{Hz}$), 3.54 (2H, s), 3.68 (4H, t, $J = 5\text{Hz}$), 4.67 (2H, d, $J = 4.5\text{Hz}$), 7.09 (1H, s), 7.11 (1H, s), 7.14 (1H, s), 7.45-7.60 (2H, m), 7.84 (1H, s)。

[1970] 实施例 145

[1971] [式 402]

[1972]

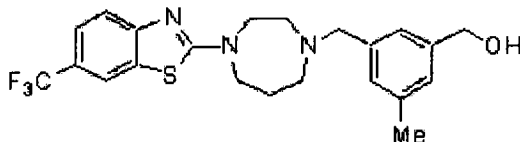


[1973] 收率:93%, $^1\text{H-NMR}$ (CDCl_3); δ 1.70 (1H, s), 1.99-2.06 (2H, m), 2.35 (3H, s), 2.70 (2H, t, $J = 5.4\text{Hz}$), 2.79-2.82 (2H, m), 3.61 (2H, s), 3.71-3.77 (4H, m), 4.65 (2H, s), 7.07 (1H, s), 7.09 (1H, s), 7.13 (1H, s), 7.23 (1H, dd, $J = 8.7\text{Hz}$, $J = 2.1\text{Hz}$), 7.43 (1H, d, $J = 8.7\text{Hz}$), 7.55 (1H, d, $J = 2.1\text{Hz}$)。

[1974] 实施例 146

[1975] [式 403]

[1976]

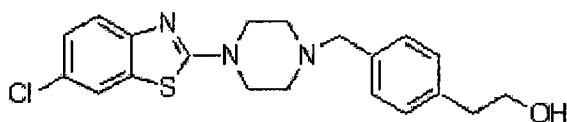


[1977] 收率:定量收率 (q. y.), $^1\text{H-NMR}$ (CDCl_3); δ 1.77 (1H, brs), 1.95-2.10 (2H, m), 2.34 (3H, s), 2.68 (2H, t, $J = 5.5\text{Hz}$), 2.82 (2H, t, $J = 5.5\text{Hz}$), 3.61 (2H, s), 3.70-3.85 (4H, m), 4.65 (2H, s), 7.06 (1H, s), 7.08 (1H, s), 7.13 (1H, s), 7.45-7.60 (2H, m), 7.84 (1H, s)。

[1978] 实施例 147

[1979] [式 404]

[1980]

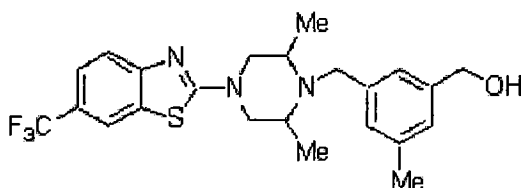


[1981] 收率:80%, $^1\text{H-NMR}$ (DMSO-d_6): δ 1.59 (1H, brs), 2.57 (4H, t, $J = 5\text{Hz}$), 2.88 (2H, t, $J = 6.5\text{Hz}$), 3.55 (2H, s), 3.63 (4H, t, $J = 5\text{Hz}$), 3.88 (2H, t, $J = 6.5\text{Hz}$), 7.20 (2H, d, $J = 7.5\text{Hz}$), 7.26 (1H, dd, $J = 8.5, 2\text{Hz}$), 7.29 (2H, d, $J = 7.5\text{Hz}$), 7.43 (1H, d, $J = 8.5\text{Hz}$), 7.55 (1H, d, $J = 2\text{Hz}$)。

[1982] 实施例 148

[1983] [式 405]

[1984]

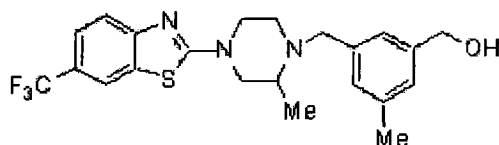


[1985] 收率:46%, $^1\text{H-NMR}$ (CDCl_3): δ 1.14 (6H, d, $J = 6\text{Hz}$), 1.68 (1H, brs), 2.30 (3H, s), 2.70-2.87 (2H, m), 3.03-3.15 (2H, m), 3.82 (2H, s), 3.85-3.95 (2H, m), 4.66 (2H, s), 7.05 (1H, s), 7.11 (1H, s), 7.17 (1H, s), 7.51 (1H, d, $J = 8.5\text{Hz}$), 7.55 (1H, d, $J = 8.5\text{Hz}$), 7.84 (1H, s)。

[1986] 实施例 149

[1987] [式 406]

[1988]

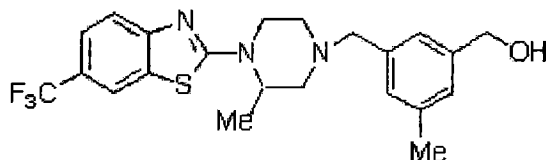


[1989] 收率:95%, $^1\text{H-NMR}$ (CDCl_3): δ 1.24 (3H, d, $J = 6\text{Hz}$), 1.69 (1H, brs), 2.20-2.35 (1H, m), 2.36 (3H, s), 2.60-2.72 (1H, m), 2.82 (1H, dt, $J = 12, 3.5\text{Hz}$), 3.15-3.25 (2H, m), 3.35-3.48 (1H, m), 3.70-3.80 (1H, m), 3.85-3.95 (1H, m), 4.04 (1H, d, $J = 13.5\text{Hz}$), 4.67 (2H, s), 7.00-7.15 (3H, m), 7.52 (1H, dd, $J = 8.5, 1\text{Hz}$), 7.56 (1H, d, $J = 8.5\text{Hz}$), 7.83 (1H, d, $J = 1\text{Hz}$)。

[1990] 实施例 150

[1991] [式 407]

[1992]

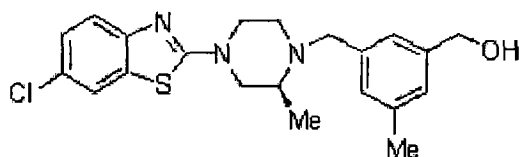


[1993] 收率:定量收率, $^1\text{H-NMR}$ (DMSO-d_6): δ 1.30 (3H, d, $J = 7\text{Hz}$), 2.05-2.25 (2H, m), 2.27 (3H, s), 2.65-2.75 (1H, m), 2.80-2.95 (1H, m), 3.30-3.85 (3H, m), 4.15-4.30 (1H, m), 4.43 (2H, d, $J = 5.5\text{Hz}$), 4.48 (1H, t, $J = 5\text{Hz}$), 5.21 (1H, t, $J = 5.5\text{Hz}$), 7.00 (2H, s), 7.06 (1H, s), 7.54 (2H, s), 8.19 (1H, s)。

[1994] 实施例 151

[1995] [式 408]

[1996]

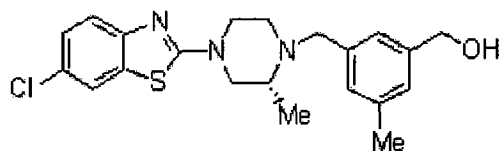


[1997] 收率:45%, $^1\text{H-NMR}$ (CDCl_3): δ 1.23 (3H, d, $J = 6.3\text{Hz}$), 2.26 (1H, ddd, $J = 3.3, 9.5, 12.3\text{Hz}$), 2.36 (3H, s), 2.60–2.66 (1H, m), 2.80 (1H, dt, $J = 3.3, 12.0\text{Hz}$), 3.17 (2H, d, $J = 13.2\text{Hz}$), 3.20–3.33 (1H, m), 3.71 (1H, dt, $J = 2.1, 12.0\text{Hz}$), 3.87 (1H, dd, $J = 2.1, 12.6\text{Hz}$), 4.03 (1H, d, $J = 13.2\text{Hz}$), 4.67 (2H, s), 7.09 (2H, s), 7.14 (1H, s), 7.23 (1H, dd, $J = 2.1, 8.4\text{Hz}$), 7.42 (1H, d, $J = 8.4\text{Hz}$), 7.54 (1H, d, $J = 2.1\text{Hz}$)。

[1998] 实施例 152

[1999] [式 409]

[2000]

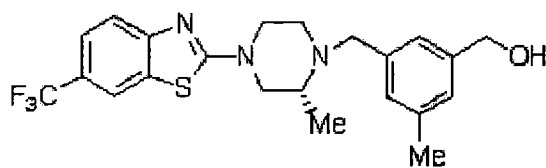


[2001] 收率:54%, $^1\text{H-NMR}$ (CDCl_3): δ 1.24 (3H, d, $J = 6.3\text{Hz}$), 2.23–2.31 (1H, m), 2.36 (3H, s), 2.60–2.66 (1H, m), 2.81 (1H, dt, $J = 3.3, 11.7\text{Hz}$), 3.18 (2H, d, $J = 12.9\text{Hz}$), 3.34–3.42 (1H, m), 3.71 (1H, d, $J = 12.9\text{Hz}$), 3.87 (1H, d, $J = 10.2\text{Hz}$), 4.04 (1H, d, $J = 13.5\text{Hz}$), 4.67 (2H, s), 7.09 (2H, s), 7.14 (1H, s), 7.23 (1H, dd, $J = 2.4, 8.4\text{Hz}$), 7.43 (1H, d, $J = 8.4\text{Hz}$), 7.55 (1H, d, $J = 2.4\text{Hz}$)。

[2002] 实施例 153

[2003] [式 410]

[2004]



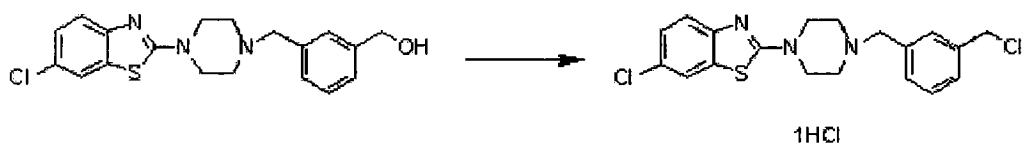
[2005] 收率:84%, $^1\text{H-NMR}$ (CDCl_3): δ 1.24 (3H, d, $J = 6.0\text{Hz}$), 1.63–1.73 (1H, m), 2.23–2.34 (1H, m), 2.37 (3H, s), 2.59–2.72 (1H, m), 2.78–2.88 (1H, m), 3.15–3.26 (1H, m), 3.19 (1H, d, $J = 13.0\text{Hz}$), 3.37–3.48 (1H, m), 3.72–3.83 (1H, m), 3.86–3.97 (1H, m), 4.04 (1H, d, $J = 13.0\text{Hz}$), 4.67 (2H, d, $J = 4.5\text{Hz}$), 7.07–7.17 (3H, m), 7.48–7.59 (2H, m), 7.84 (1H, s)。

[2006] 实施例 154

[2007] 6-氯[4-(3-氯甲基苯甲基)哌嗪-1-基]苯并噻唑单盐酸盐的制备

[2008] [式 411]

[2009]



[2010] 在室温向 3-[4-[(6-氯苯并噻唑-2-基)哌嗪-1-基]甲基]苯甲醇 (2.35g; 6.29mmol) 加入亚硫酸氯 (12ml)。将混合物在 60℃ 搅拌 1 小时。将反应溶液减压浓缩。向得到的残余物加入冰水和 10% 氢氧化钠水溶液到变为中性。收集沉淀物, 得到 6-氯 [4-(3-氯甲基苯甲基) 哌嗪-1-基] 苯并噻唑单盐酸盐, 为无色晶体 (2.50g; 93%)。

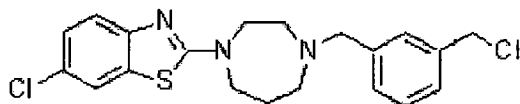
[2011] $^1\text{H-NMR}$ (DMSO- d_6) : δ 3.20-3.30 (2H, m), 3.35-3.45 (2H, m), 3.55-3.75 (2H, m), 4.10-4.25 (2H, m), 4.35-4.40 (2H, m), 4.80 (2H, s), 7.34 (1H, dd, $J = 8.5, 2\text{Hz}$), 7.45-7.60 (3H, m), 7.60-7.70 (2H, m), 8.00 (1H, d, $J = 2\text{Hz}$), 11.45 (1H, brs)。

[2012] 通过与实施例 154 相似的方法得到实施例 155 到 178 的化合物。

[2013] 实施例 155

[2014] [式 412]

[2015]

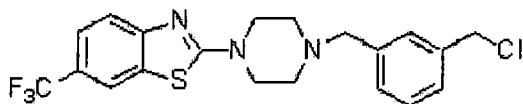


[2016] 收率: 77%, $^1\text{H-NMR}$ (CDCl_3) : δ 1.99-2.06 (2H, m), 2.69 (2H, t, $J = 5.4\text{Hz}$), 2.80-2.83 (2H, m), 3.65 (2H, s), 3.72-3.79 (4H, m), 4.58 (2H, s), 7.21-7.31 (4H, m), 7.36 (1H, s), 7.42 (1H, d, $J = 8.4\text{Hz}$), 7.55 (1H, d, $J = 2.4\text{Hz}$)。

[2017] 实施例 156

[2018] [式 413]

[2019]

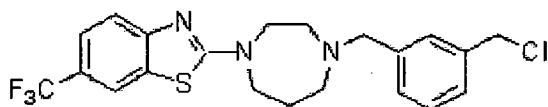


[2020] 收率: 77%, $^1\text{H-NMR}$ (CDCl_3) : δ 2.60 (4H, t, $J = 5\text{Hz}$), 3.59 (2H, s), 3.70 (4H, t, $J = 5\text{Hz}$), 4.60 (2H, s), 7.25-7.40 (4H, m), 7.50-7.60 (2H, m), 7.85 (1H, s)。

[2021] 实施例 157

[2022] [式 414]

[2023]

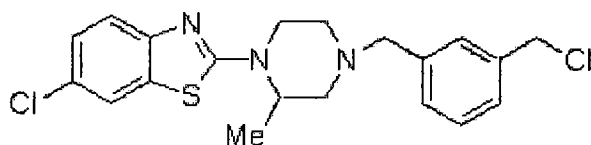


[2024] 收率: 95%, $^1\text{H-NMR}$ (CDCl_3) : δ 1.95-2.12 (2H, m), 2.61-2.71 (2H, m), 2.77-2.88 (2H, m), 3.66 (2H, s), 3.68-3.90 (4H, m), 4.58 (2H, s), 7.22-7.40 (4H, m), 7.48-7.60 (2H, m), 7.85 (1H, s)。

[2025] 实施例 158

[2026] [式 415]

[2027]

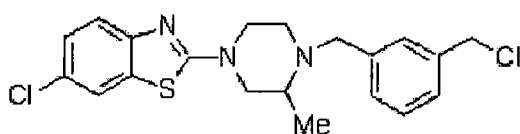


[2028] 收率:95%, $^1\text{H-NMR}(\text{CDCl}_3)$; δ 1.41(3H, d, $J = 6.5\text{Hz}$), 2.25(1H, td, $J = 11, 3\text{Hz}$), 2.34(1H, dd, $J = 11, 3\text{Hz}$), 2.71(1H, d, $J = 11\text{Hz}$), 2.92(1H, d, $J = 11\text{Hz}$), 3.47(1H, d, $J = 13.5\text{Hz}$), 3.49(1H, td, $J = 12, 3\text{Hz}$), 3.62(1H, d, $J = 13.5\text{Hz}$), 3.87(1H, d, $J = 12\text{Hz}$), 4.15-4.25(1H, m), 4.60(2H, s), 7.22(1H, dd, $J = 8.5, 2\text{Hz}$), 7.30-7.38(3H, m), 7.38-7.42(1H, m), 7.42(1H, d, $J = 8.5\text{Hz}$), 7.54(1H, d, $J = 2\text{Hz}$)。

[2029] 实施例 159

[2030] [式 416]

[2031]

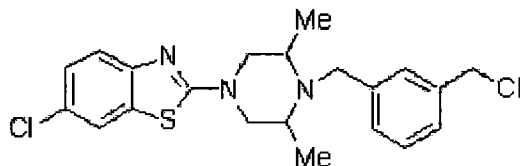


[2032] 收率:63%, $^1\text{H-NMR}(\text{CDCl}_3)$; δ 1.23(3H, d, $J = 6\text{Hz}$), 2.24-2.34(1H, m), 2.60-2.73(1H, m), 2.75-2.85(1H, m), 3.13-3.23(1H, m), 3.22(1H, d, $J = 13.5\text{Hz}$), 3.34-3.44(1H, m), 3.66-3.76(1H, m), 3.84-3.92(1H, m), 4.06(1H, d, $J = 13.5\text{Hz}$), 4.60(2H, s), 7.23(1H, dd, $J = 8.5, 2\text{Hz}$), 7.25-7.40(4H, m), 7.43(1H, d, $J = 8.5\text{Hz}$), 7.55(1H, d, $J = 2\text{Hz}$)。

[2033] 实施例 160

[2034] [式 417]

[2035]

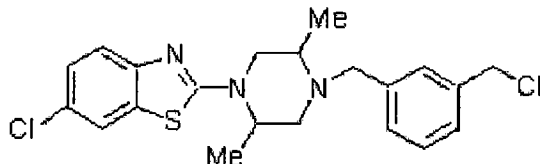


[2036] 收率:71%, $^1\text{H-NMR}(\text{CDCl}_3)$; δ 1.11(6H, d, $J = 6\text{Hz}$), 2.70-2.85(2H, m), 3.06(2H, dd, $J = 13, 13\text{Hz}$), 3.84(2H, s), 3.85-3.90(2H, m), 4.60(2H, s), 7.20-7.45(6H, m), 7.55(1H, d, $J = 2\text{Hz}$)。

[2037] 实施例 161

[2038] [式 418]

[2039]



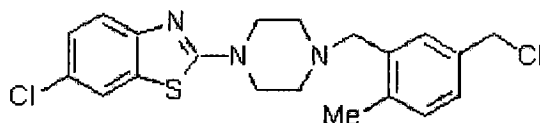
[2040] 收率:90%, $^1\text{H-NMR}(\text{CDCl}_3)$; δ 1.09(3H, d, $J = 6.5\text{Hz}$), 1.39(3H, d, $J = 6.5\text{Hz}$), 2.32(1H, d, $J = 10.5\text{Hz}$), 2.89(1H, dd, $J = 12, 4\text{Hz}$), 3.08-3.20(1H, m), 3.52(1H, d, $J = 13.5\text{Hz}$), 3.64(1H, d, $J = 12\text{Hz}$), 3.70(1H, d, $J = 13.5\text{Hz}$), 3.73(1H, dd, $J = 12, 4\text{Hz}$), 4.15-4.30(1H, m), 4.60(2H, s), 7.23(1H, dd, $J = 8.5, 2\text{Hz}$), 7.25-7.35(3H, m), 7.41(1H, d,

$J = 8.5\text{Hz}$), $7.44(1\text{H}, \text{s})$, $7.53(1\text{H}, \text{d}, J = 2\text{Hz})$ 。

[2041] 实施例 162

[2042] [式 419]

[2043]

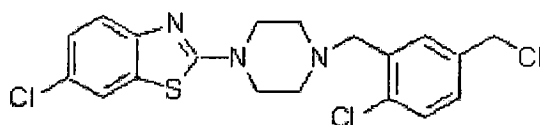


[2044] 收率:85%, $^1\text{H-NMR}(\text{CDCl}_3)$; δ 2.38(3H, s), 2.58(4H, t, $J = 5\text{Hz}$), 3.52(2H, s), 3.63(4H, t, $J = 5\text{Hz}$), 4.60(2H, s), 7.15-7.30(4H, m), 7.44(1H, d, $J = 8\text{Hz}$), 7.56(1H, d, $J = 2\text{Hz}$)。

[2045] 实施例 163

[2046] [式 420]

[2047]

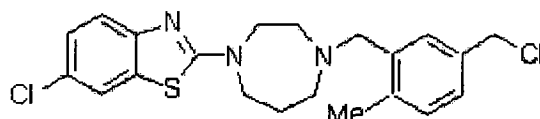


[2048] 收率:68%, $^1\text{H-NMR}(\text{CDCl}_3)$; δ 2.66(4H, t, $J = 5\text{Hz}$), 3.66(4H, t, $J = 5\text{Hz}$), 3.68(2H, s), 4.58(2H, s), 7.20-7.25(2H, m), 7.37(1H, d, $J = 8\text{Hz}$), 7.44(1H, d, $J = 8.5\text{Hz}$), 7.55(1H, d, $J = 2\text{Hz}$), 7.56(1H, d, $J = 2\text{Hz}$)。

[2049] 实施例 164

[2050] [式 421]

[2051]

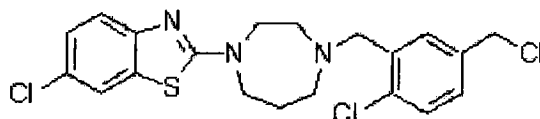


[2052] 收率:99%, $^1\text{H-NMR}(\text{CDCl}_3)$; δ 1.97-2.05(2H, m), 2.33(3H, s), 2.67(2H, t, $J = 5.4\text{Hz}$), 2.79-2.82(2H, m), 3.58(2H, s), 3.72-3.77(4H, m), 4.56(2H, s), 7.12-7.25(3H, m), 7.30(1H, d, $J = 1.8\text{Hz}$), 7.42(1H, d, $J = 8.4\text{Hz}$), 7.55(1H, d, $J = 2.4\text{Hz}$)。

[2053] 实施例 165

[2054] [式 422]

[2055]

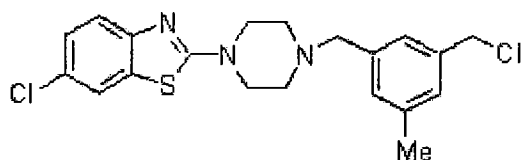


[2056] 收率:81%, $^1\text{H-NMR}(\text{CDCl}_3)$; δ 2.01-2.09(2H, m), 2.75(2H, t, $J = 5.1\text{Hz}$), 2.87-2.90(2H, m), 3.74-3.83(6H, m), 4.54(2H, s), 7.20-7.25(2H, m), 7.33(1H, d, $J = 8.4\text{Hz}$), 7.43(1H, d, $J = 9.0\text{Hz}$), 7.52(1H, d, $J = 2.1\text{Hz}$), 7.55(1H, d, $J = 2.1\text{Hz}$)。

[2057] 实施例 166

[2058] [式 423]

[2059]

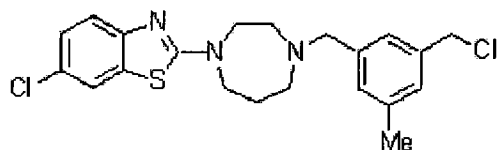


[2060] 收率:85%, $^1\text{H-NMR}(\text{CDCl}_3)$; δ 2.36(3H, s), 2.58(4H, t, $J = 5\text{Hz}$), 3.53(2H, s), 3.64(4H, t, $J = 5\text{Hz}$), 4.56(2H, s), 7.12(1H, s), 7.13(1H, s), 7.17(1H, s), 7.23(1H, dd, $J = 8.5, 2\text{Hz}$), 7.43(1H, d, $J = 8.5\text{Hz}$), 7.55(1H, d, $J = 2\text{Hz}$)。

[2061] 实施例 167

[2062] [式 424]

[2063]

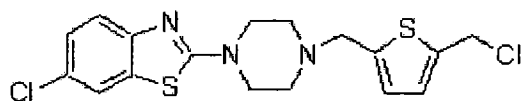


[2064] 收率:91%, $^1\text{H-NMR}(\text{CDCl}_3)$; δ 1.98-2.06(2H, m), 2.34(3H, s), 2.69(2H, t, $J = 5.4\text{Hz}$), 2.78-2.83(2H, m), 3.61(2H, s), 3.72-3.78(4H, m), 4.55(2H, s), 7.09-7.11(2H, m), 7.14(1H, s), 7.23(1H, dd, $J = 8.4, 2.1\text{Hz}$), 7.43(1H, d, $J = 8.7\text{Hz}$), 7.55(1H, d, $J = 2.1\text{Hz}$)。

[2065] 实施例 168

[2066] [式 425]

[2067]

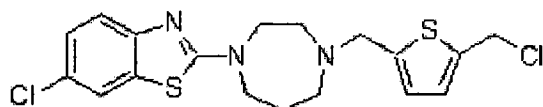


[2068] 收率:45%, $^1\text{H-NMR}(\text{DMSO}-d_6)$; δ 2.55(4H, t, $J = 5\text{Hz}$), 3.57(4H, t, $J = 5\text{Hz}$), 3.74(2H, s), 4.99(2H, s), 6.86(1H, d, $J = 3.5\text{Hz}$), 7.04(1H, d, $J = 3.5\text{Hz}$), 7.28(1H, dd, $J = 8.5, 2\text{Hz}$), 7.42(1H, d, $J = 8.5\text{Hz}$), 7.91(1H, d, $J = 2\text{Hz}$)。

[2069] 实施例 169

[2070] [式 426]

[2071]

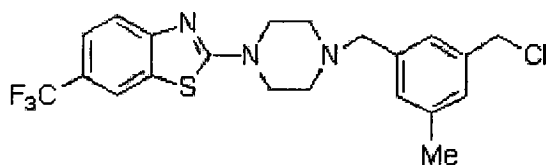


[2072] 收率:45%, $^1\text{H-NMR}(\text{CDCl}_3)$; δ 2.00-2.07(2H, m), 2.71-2.74(2H, m), 2.84-2.87(2H, m), 3.73(2H, t, $J = 6.0\text{Hz}$), 3.75-3.81(2H, m), 3.81(2H, s), 4.76(2H, s), 6.73(1H, d, $J = 3.3\text{Hz}$), 6.91(1H, d, $J = 3.3\text{Hz}$), 7.23(1H, dd, $J = 8.7, 2.4\text{Hz}$), 7.42(1H, d, $J = 8.4\text{Hz}$), 7.55(1H, d, $J = 2.1\text{Hz}$)。

[2073] 实施例 170

[2074] [式 427]

[2075]

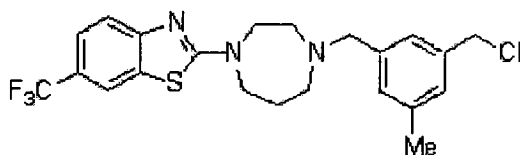


[2076] 收率:59%, $^1\text{H-NMR}$ (CDCl_3); δ 2.37 (3H, s), 2.59 (4H, t, $J = 5\text{Hz}$), 3.54 (2H, s), 3.69 (4H, t, $J = 5\text{Hz}$), 4.57 (2H, s), 7.12 (1H, s), 7.13 (1H, s), 7.17 (1H, s), 7.50–7.60 (2H, m), 7.85 (1H, s)。

[2077] 实施例 171

[2078] [式 428]

[2079]

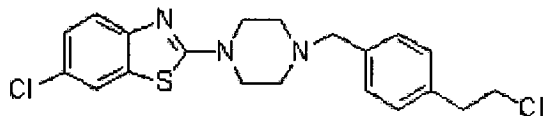


[2080] 收率:71%, $^1\text{H-NMR}$ (CDCl_3); δ 1.95–2.10 (2H, m), 2.34 (3H, s), 2.70 (2H, t, $J = 5.5\text{Hz}$), 2.82 (2H, t, $J = 5.5\text{Hz}$), 3.61 (2H, s), 3.70–3.90 (4H, m), 4.54 (2H, s), 7.05–7.14 (2H, m), 7.15 (1H, s), 7.48–7.60 (2H, m), 7.85 (1H, s)。

[2081] 实施例 172

[2082] [式 429]

[2083]

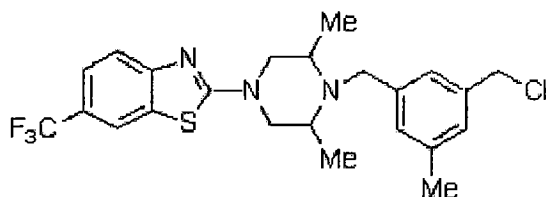


[2084] 收率:77%, $^1\text{H-NMR}$ (CDCl_3); δ 2.57 (4H, t, $J = 5\text{Hz}$), 3.07 (2H, t, $J = 7.5\text{Hz}$), 3.55 (2H, s), 3.63 (4H, t, $J = 5\text{Hz}$), 3.72 (2H, t, $J = 7.5\text{Hz}$), 7.19 (2H, d, $J = 8\text{Hz}$), 7.23 (1H, dd, $J = 8.5, 2\text{Hz}$), 7.29 (2H, d, $J = 8\text{Hz}$), 7.43 (1H, d, $J = 8.5\text{Hz}$), 7.55 (1H, d, $J = 2\text{Hz}$)。

[2085] 实施例 173

[2086] [式 430]

[2087]

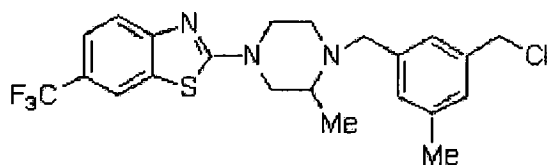


[2088] 收率:91%, $^1\text{H-NMR}$ (CDCl_3); δ 1.12 (6H, d, $J = 6\text{Hz}$), 2.35 (3H, s), 2.68–2.86 (2H, m), 3.05–3.15 (2H, m), 3.81 (2H, s), 3.85–3.98 (2H, m), 4.56 (2H, s), 7.07 (1H, s), 7.14 (1H, s), 7.21 (1H, s), 7.52 (1H, d, $J = 8.5\text{Hz}$), 7.57 (1H, d, $J = 8.5\text{Hz}$), 7.84 (1H, s)。

[2089] 实施例 174

[2090] [式 431]

[2091]

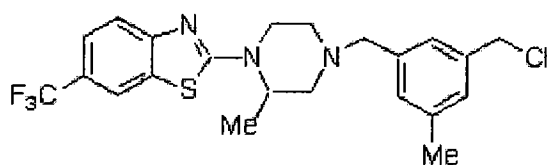


[2092] 收率:74%, $^1\text{H-NMR}$ (CDCl_3): δ 1.24 (3H, d, $J = 6\text{Hz}$), 2.23–2.35 (1H, m), 2.36 (3H, s), 2.60–2.70 (1H, m), 2.80 (1H, dt, $J = 13, 3.5\text{Hz}$), 3.17 (1H, d, $J = 13.5\text{Hz}$), 3.18–3.26 (1H, m), 3.38–3.50 (1H, m), 3.72–3.80 (1H, m), 3.87–3.95 (1H, m), 4.03 (1H, d, $J = 13.5\text{Hz}$), 4.56 (2H, s), 7.11 (2H, s), 7.17 (1H, s), 7.53 (1H, d, $J = 8.5\text{Hz}$), 7.56 (1H, d, $J = 8.5\text{Hz}$), 7.84 (1H, s)。

[2093] 实施例 175

[2094] [式 432]

[2095]

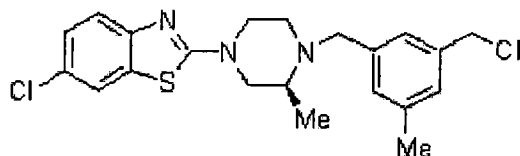


[2096] 收率:81%, $^1\text{H-NMR}$ (CDCl_3): δ 1.43 (3H, d, $J = 6.5\text{Hz}$), 2.26 (1H, td, $J = 11.5, 3.5\text{Hz}$), 2.30–2.36 (1H, m), 2.37 (3H, s), 2.73 (1H, d, $J = 11.5\text{Hz}$), 2.93 (1H, d, $J = 11.5\text{Hz}$), 3.43 (1H, d, $J = 13.5\text{Hz}$), 3.54 (1H, td, $J = 12.5, 3.5\text{Hz}$), 3.58 (1H, d, $J = 13.5\text{Hz}$), 3.85–3.98 (1H, m), 4.20–4.30 (1H, m), 4.57 (2H, s), 7.12 (2H, s), 7.21 (1H, s), 7.51 (1H, dd, $J = 8.5, 1.5\text{Hz}$), 7.56 (1H, d, $J = 8.5\text{Hz}$), 7.84 (1H, d, $J = 1.5\text{Hz}$)。

[2097] 实施例 176

[2098] [式 433]

[2099]

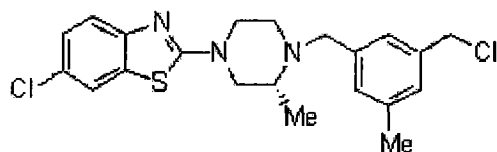


[2100] 收率:83%, $^1\text{H-NMR}$ (CDCl_3): δ 1.23 (3H, d, $J = 6.0\text{Hz}$), 2.23–2.31 (1H, m), 2.36 (3H, s), 2.61–2.83 (1H, m), 2.80 (1H, dt, $J = 3.6, 11.7\text{Hz}$), 3.13–3.20 (2H, m), 3.35–3.43 (1H, m), 3.72 (1H, dt, $J = 2.7\text{Hz}$), 3.87 (1H, dd, $J = 1.8, 12.3\text{Hz}$), 4.03 (1H, d, $J = 13.2\text{Hz}$), 4.56 (2H, s), 7.11 (2H, s), 7.16 (1H, s), 7.23 (1H, dd, $J = 2.1, 8.7\text{Hz}$), 7.43 (1H, d, $J = 8.7\text{Hz}$), 7.54 (1H, d, $J = 2.1\text{Hz}$)。

[2101] 实施例 177

[2102] [式 434]

[2103]



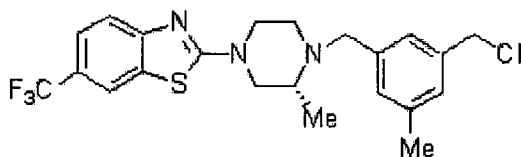
[2104] 收率:77%, $^1\text{H-NMR}$ (CDCl_3): δ 1.23 (3H, d, $J = 6.0\text{Hz}$), 2.27 (1H, ddd, $J = 3.3, 8.7, 9.9\text{Hz}$), 2.35 (3H, s), 2.61–2.67 (1H, m), 2.80 (1H, dt, $J = 3.6, 12.0\text{Hz}$),

3.13-3.20 (2H, m), 3.35-3.43 (1H, m), 3.72 (1H, d, $J = 12.6\text{Hz}$), 3.87 (1H, dd, $J = 1.8, 12.6\text{Hz}$), 4.03 (1H, d, $J = 13.2\text{Hz}$), 4.56 (2H, s), 7.11 (2H, s), 7.16 (1H, s), 7.23 (1H, dd, $J = 1.8, 8.7\text{Hz}$), 7.53 (1H, d, $J = 8.7\text{Hz}$), 7.54 (1H, d, $J = 1.8\text{Hz}$)。

[2105] 实施例 178

[2106] [式 435]

[2107]



[2108] 收率:60%, $^1\text{H-NMR}(\text{CDCl}_3)$: δ 1.24 (3H, d, $J = 6.0\text{Hz}$), 2.23-2.34 (1H, m), 2.36 (3H, s), 2.60-2.72 (1H, m), 2.77-2.87 (1H, m), 3.14-3.27 (2H, m), 3.38-3.51 (1H, m), 3.72-3.82 (1H, m), 3.87-3.98 (1H, m), 4.04 (1H, d, $J = 13.0\text{Hz}$), 4.56 (2H, s), 7.12 (2H, s), 7.17 (1H, s), 7.48-7.59 (2H, m), 7.84 (1H, s)。

[2109] 实施例 179

[2110] {3-[[4-(6-氯苯并噻唑-2-基)哌嗪-1-基]甲基]苯基}乙腈的制备

[2111] [式 436]

[2112]



[2113] 将 6-氯 [4-(3-氯甲基苯甲基)哌嗪-1-基]苯并噻唑单盐酸盐 (0.50g; 1.27mmol) 和氰化钠 (0.19g; 3.82mmol) 在无水 N,N-二甲基甲酰胺 (5ml) 中的混合物在 40°C 搅拌 1.5 小时。在冷却之后,向反应溶液加入水和乙酸乙酯。分离有机层并且用盐水洗涤,用无水硫酸钠干燥,并且减压蒸发和沉淀物用二异丙醚洗涤,得到 {3-[[4-(6-氯苯并噻唑-2-基)哌嗪-1-基]甲基]苯基}乙腈,为带浅黑色的褐色晶体 (0.35g; 72%)。

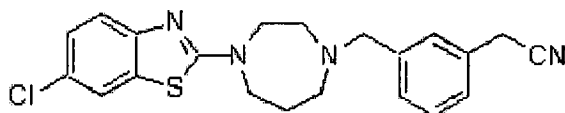
[2114] $^1\text{H-NMR}(\text{CDCl}_3)$: δ 2.58 (4H, t, $J = 5\text{Hz}$), 3.57 (2H, s), 3.67 (4H, t, $J = 5\text{Hz}$), 3.77 (2H, s), 7.24 (1H, dd, $J = 8.5, 2\text{Hz}$), 7.25-7.40 (4H, m), 7.43 (1H, d, $J = 8.5\text{Hz}$), 7.55 (1H, d, $J = 2\text{Hz}$)。

[2115] 通过与实施例 179 相似的方法得到实施例 180 到 203 的化合物。

[2116] 实施例 180

[2117] [式 437]

[2118]

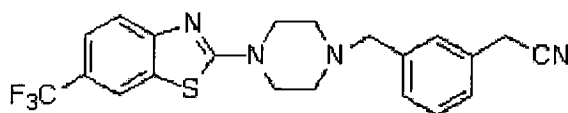


[2119] 收率:95%, $^1\text{H-NMR}(\text{CDCl}_3)$: δ 1.98-2.06 (2H, m), 2.69 (2H, t, $J = 5.4\text{Hz}$), 2.79-2.83 (2H, m), 3.65 (2H, s), 3.72-3.80 (6H, m), 7.21-7.25 (2H, m), 7.29-7.33 (3H, m), 7.43 (1H, d, $J = 8.7\text{Hz}$), 7.55 (1H, d, $J = 2.4\text{Hz}$)。

[2120] 实施例 181

[2121] [式 438]

[2122]

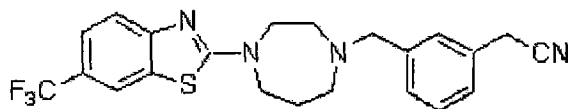


[2123] 收率:99%, $^1\text{H-NMR}$ (CDCl_3) ; δ 2.59 (4H, t, $J = 5\text{Hz}$), 3.58 (2H, s), 3.69 (4H, t, $J = 5\text{Hz}$), 3.77 (2H, s), 7.20-7.40 (4H, m), 7.50-7.60 (2H, m), 7.85 (1H, d, $J = 0.5\text{Hz}$)。

[2124] 实施例 182

[2125] [式 439]

[2126]

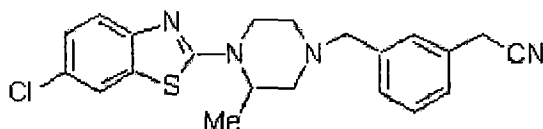


[2127] 收 率 : 74 % , $^1\text{H-NMR}$ (CDCl_3) ; δ 1.98-2.10 (2H, m) , 2.64-2.74 (2H, m) , 2.77-2.88 (2H, m) , 3.65 (2H, s) , 3.68-3.90 (4H, m) , 3.74 (2H, s) , 7.18-7.38 (4H, m) , 7.48-7.59 (2H, m) , 7.84 (1H, s) 。

[2128] 实施例 183

[2129] [式 440]

[2130]

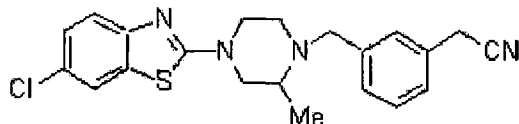


[2131] 收率:68%, $^1\text{H-NMR}(\text{CDCl}_3)$; δ 1.41 (3H, d, $J = 6.5\text{Hz}$), 2.26 (1H, td, $J = 11, 2.5\text{Hz}$), 2.35 (1H, dd, $J = 11, 4\text{Hz}$), 2.71 (1H, d, $J = 11\text{Hz}$), 2.89 (1H, d, $J = 11\text{Hz}$), 3.47 (1H, d, $J = 13\text{Hz}$), 3.50 (1H, td, $J = 13, 3\text{Hz}$), 3.61 (1H, d, $J = 13\text{Hz}$), 3.77 (2H, s), 3.87 (1H, d, $J = 13\text{Hz}$), 4.15-4.25 (1H, m), 7.23 (1H, dd, $J = 8.5, 2\text{Hz}$), 7.25-7.30 (1H, m), 7.30-7.40 (3H, m), 7.42 (1H, d, $J = 8.5\text{Hz}$), 7.55 (1H, d, $J = 2\text{Hz}$)。

[2132] 实施例 184

[2133] [式 441]

[2134]

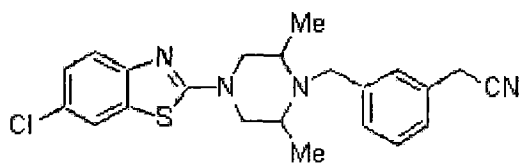


[2135] 收 率 :86 % , $^1\text{H-NMR}$ (CDCl_3) ; δ 1.23 (3H, d, $J = 6.5\text{Hz}$) , 2.23-2.35 (1H, m) , 2.58-2.72 (1H, m) , 2.72-2.85 (1H, m) , 3.10-3.20 (1H, m) , 3.22 (1H, d, $J = 13.5\text{Hz}$) , 3.33-3.45 (1H, m) , 3.60-3.75 (1H, m) , 3.76 (2H, s) , 3.83-3.93 (1H, m) , 4.06 (1H, d, $J = 13.5\text{Hz}$) , 7.23 (1H, dd, $J = 8.5, 2\text{Hz}$) , 7.25-7.35 (4H, m) , 7.43 (1H, d, $J = 8.5\text{Hz}$) , 7.55 (1H, d, $J = 2\text{Hz}$) 。

[2136] 实施例 185

[2137] [式 442]

[2138]

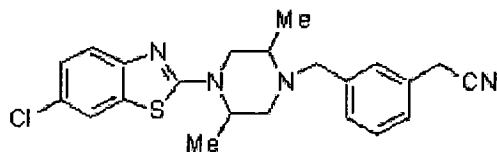


[2139] 收率:59%, $^1\text{H-NMR}(\text{CDCl}_3)$; δ 1.10 (6H, d, $J = 6\text{Hz}$), 2.70-2.85 (2H, m), 3.05 (2H, dd, $J = 13, 13\text{Hz}$), 3.76 (2H, s), 3.83 (2H, s), 3.88 (2H, dd, $J = 13, 2\text{Hz}$), 7.18 (1H, d, $J = 7\text{Hz}$), 7.25 (1H, dd, $J = 8.5, 2\text{Hz}$), 7.30-7.40 (3H, m), 7.43 (1H, d, $J = 8.5\text{Hz}$), 7.55 (1H, d, $J = 2\text{Hz}$)。

[2140] 实施例 186

[2141] [式 443]

[2142]

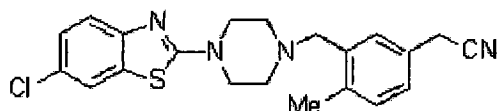


[2143] 收率:97%, $^1\text{H-NMR}(\text{CDCl}_3)$; δ 1.09 (3H, d, $J = 6.5\text{Hz}$), 1.39 (3H, d, $J = 6.5\text{Hz}$), 2.31 (1H, d, $J = 11.5\text{Hz}$), 2.90 (1H, dd, $J = 11.5, 4\text{Hz}$), 3.08-3.20 (1H, m), 3.53 (1H, t, $J = 14\text{Hz}$), 3.64 (1H, d, $J = 12.5\text{Hz}$), 3.70 (1H, d, $J = 14\text{Hz}$), 3.72 (1H, dd, $J = 12.5, 4\text{Hz}$), 3.76 (2H, s), 4.18-4.30 (1H, m), 7.21 (1H, dd, $J = 8.5, 2\text{Hz}$), 7.21-7.25 (1H, m), 7.30-7.40 (3H, m), 7.41 (1H, d, $J = 8.5\text{Hz}$), 7.53 (1H, d, $J = 2\text{Hz}$)。

[2144] 实施例 187

[2145] [式 444]

[2146]

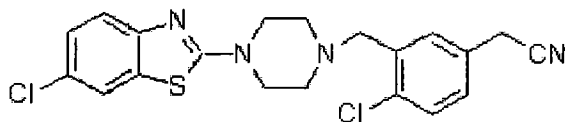


[2147] 收率:35%, $^1\text{H-NMR}(\text{CDCl}_3)$; δ 2.37 (3H, s), 2.58 (4H, t, $J = 5\text{Hz}$), 3.52 (2H, s), 3.63 (4H, t, $J = 5\text{Hz}$), 3.73 (2H, s), 7.10-7.30 (4H, m), 7.43 (1H, d, $J = 8.5\text{Hz}$), 7.55 (1H, d, $J = 2\text{Hz}$)。

[2148] 实施例 188

[2149] [式 445]

[2150]

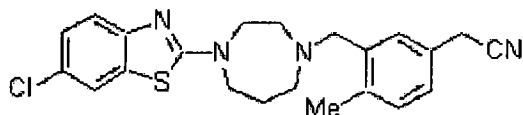


[2151] 收率:69%, $^1\text{H-NMR}(\text{CDCl}_3)$; δ 2.65 (4H, t, $J = 5\text{Hz}$), 3.66 (4H, t, $J = 5\text{Hz}$), 3.68 (2H, s), 3.76 (2H, s), 7.19 (1H, dd, $J = 8, 2\text{Hz}$), 7.24 (1H, dd, $J = 8.5, 2\text{Hz}$), 7.38 (1H, d, $J = 8\text{Hz}$), 7.44 (1H, d, $J = 8.5\text{Hz}$), 7.51 (1H, d, $J = 2\text{Hz}$), 7.56 (1H, d, $J = 2\text{Hz}$)。

[2152] 实施例 189

[2153] [式 446]

[2154]

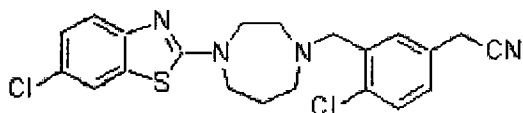


[2155] 收率:78%, $^1\text{H-NMR}(\text{CDCl}_3)$; δ 1.99-2.05 (2H, m), 2.32 (3H, s), 2.67 (2H, t, $J = 5.4\text{Hz}$), 2.79-2.83 (2H, m), 3.58 (2H, s), 3.70 (2H, s), 3.72-3.78 (4H, m), 7.13-7.14 (2H, m), 7.21-7.26 (2H, m), 7.42 (1H, d, $J = 8.4\text{Hz}$), 7.55 (1H, d, $J = 2.1\text{Hz}$)。

[2156] 实施例 190

[2157] [式 447]

[2158]

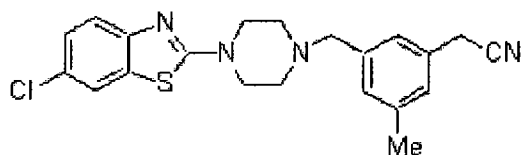


[2159] 收率:99%, $^1\text{H-NMR}(\text{CDCl}_3)$; δ 2.03-2.07 (2H, m), 2.75 (2H, t, $J = 5.4\text{Hz}$), 2.87-2.90 (2H, m), 3.70 (2H, s), 3.75 (2H, s), 3.75 (2H, t, $J = 6.0\text{Hz}$), 3.82 (2H, t, $J = 5.1\text{Hz}$), 7.16 (1H, dd, $J = 8.1, 2.1\text{Hz}$), 7.23 (1H, dd, $J = 8.4\text{Hz}, 2.1\text{Hz}$), 7.35 (1H, d, $J = 8.4\text{Hz}$), 7.42 (1H, d, $J = 8.4\text{Hz}$), 7.49 (1H, d, $J = 2.4\text{Hz}$), 7.56 (1H, d, $J = 2.1\text{Hz}$)。

[2160] 实施例 191

[2161] [式 448]

[2162]

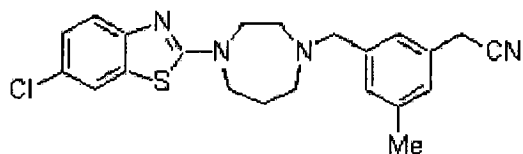


[2163] 收率:78%, $^1\text{H-NMR}(\text{CDCl}_3)$; δ 2.36 (3H, s), 2.57 (4H, t, $J = 5\text{Hz}$), 3.51 (2H, s), 3.64 (4H, t, $J = 5\text{Hz}$), 3.72 (2H, s), 7.06 (1H, s), 7.10 (1H, s), 7.11 (1H, s), 7.23 (1H, dd, $J = 8.5, 2\text{Hz}$), 7.42 (1H, d, $J = 8.5\text{Hz}$), 7.55 (1H, d, $J = 2\text{Hz}$)。

[2164] 实施例 192

[2165] [式 449]

[2166]

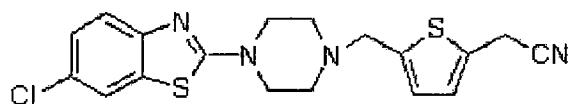


[2167] 收率:定量收率 (q. y.), $^1\text{H-NMR}(\text{CDCl}_3)$; δ 1.99-2.06 (2H, m), 2.35 (3H, s), 2.67 (2H, t, $J = 5.4\text{Hz}$), 2.78-2.82 (2H, m), 3.60 (2H, s), 3.70-3.78 (6H, m), 7.04 (1H, s), 7.09 (2H, s), 7.23 (1H, dd, $J = 8.7, 2.1\text{Hz}$), 7.43 (1H, d, $J = 8.7\text{Hz}$), 7.55 (1H, d, $J = 2.1\text{Hz}$)。

[2168] 实施例 193

[2169] [式 450]

[2170]

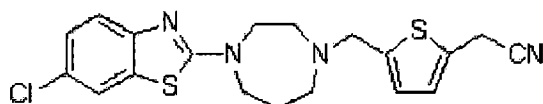


[2171] 收率:68%, $^1\text{H-NMR}(\text{CDCl}_3)$; δ 2.50-2.60 (4H, m), 3.50-3.60 (4H, m), 3.72 (2H, s), 4.24 (2H, s), 6.88 (1H, d, $J = 3\text{Hz}$), 6.91 (1H, d, $J = 3\text{Hz}$), 7.28 (1H, dd, $J = 8.5, 1.5\text{Hz}$), 7.42 (1H, d, $J = 8.5\text{Hz}$), 7.91 (1H, d, $J = 1.5\text{Hz}$)。

[2172] 实施例 194

[2173] [式 451]

[2174]

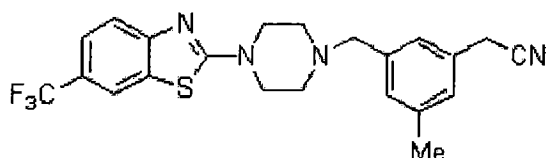


[2175] 收率:32%, $^1\text{H-NMR}(\text{CDCl}_3)$; δ 1.99-2.07 (2H, m), 2.70-2.74 (2H, m), 2.83-2.87 (2H, m), 3.73 (2H, t, $J = 6.0\text{Hz}$), 3.77-3.80 (2H, m), 3.80 (2H, s), 3.86 (2H, s), 6.76 (1H, d, $J = 3.3\text{Hz}$), 6.88 (1H, td, $J = 3.3, 0.9\text{Hz}$), 7.23 (1H, dd, $J = 8.7, 2.1\text{Hz}$), 7.42 (1H, d, $J = 8.4\text{Hz}$), 7.55 (1H, d, $J = 2.4\text{Hz}$)。

[2176] 实施例 195

[2177] [式 452]

[2178]

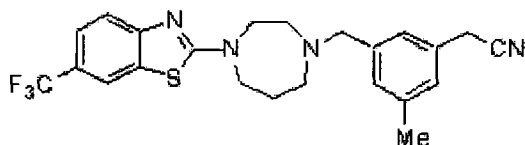


[2179] 收率:93%, $^1\text{H-NMR}(\text{CDCl}_3)$; δ 2.27 (3H, s), 2.58 (4H, t, $J = 5\text{Hz}$), 3.53 (2H, s), 3.69 (4H, t, $J = 5\text{Hz}$), 3.72 (2H, s), 7.07 (1H, s), 7.11 (1H, s), 7.12 (1H, s), 7.52 (1H, d, $J = 8.5\text{Hz}$), 7.57 (1H, d, $J = 8.5\text{Hz}$), 7.85 (1H, s)。

[2180] 实施例 196

[2181] [式 453]

[2182]

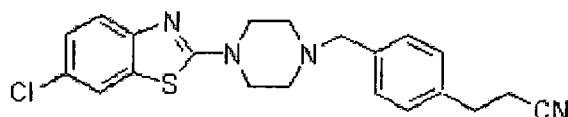


[2183] 收率:86%, $^1\text{H-NMR}(\text{CDCl}_3)$; δ 1.95-2.10 (2H, m), 2.34 (3H, s), 2.69 (2H, t, $J = 5.5\text{Hz}$), 2.82 (2H, t, $J = 5.5\text{Hz}$), 3.61 (2H, s), 3.69 (2H, s), 3.70-3.90 (4H, m), 7.04 (1H, s), 7.08 (1H, s), 7.09 (1H, s), 7.51 (1H, d, $J = 8.5\text{Hz}$), 7.56 (1H, d, $J = 8.5\text{Hz}$), 7.85 (1H, s)。

[2184] 实施例 197

[2185] [式 454]

[2186]



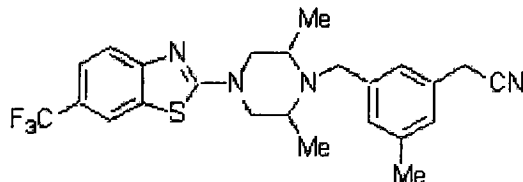
[2187] 收率:85%, $^1\text{H-NMR}(\text{DMSO}-d_6)$; δ 2.45-2.55 (4H, m), 2.81 (2H, t, $J = 5\text{Hz}$),

2.87 (2H, t, $J = 5\text{Hz}$), 3.52 (2H, s), 3.56 (4H, t, $J = 5.5\text{Hz}$), 7.20–7.35 (5H, m), 7.42 (1H, d, $J = 8.5\text{Hz}$), 7.91 (1H, d, $J = 2\text{Hz}$)。

[2188] 实施例 198

[2189] [式 455]

[2190]

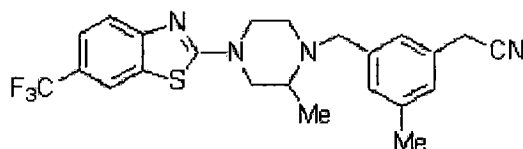


[2191] 收率:84%, $^1\text{H-NMR}$ (CDCl_3): δ 1.12 (6H, d, $J = 6\text{Hz}$), 2.36 (3H, s), 2.75–2.87 (2H, m), 3.10 (1H, d, $J = 13\text{Hz}$), 3.13 (1H, d, $J = 13\text{Hz}$), 3.71 (2H, s), 3.79 (2H, s), 3.92 (2H, dd, $J = 13, 2\text{Hz}$), 7.00 (1H, s), 7.14 (1H, s), 7.16 (1H, s), 7.52 (1H, dd, $J = 8.5, 1\text{Hz}$), 7.57 (1H, d, $J = 8.5\text{Hz}$), 7.84 (1H, d, $J = 1\text{Hz}$)。

[2192] 实施例 199

[2193] [式 456]

[2194]

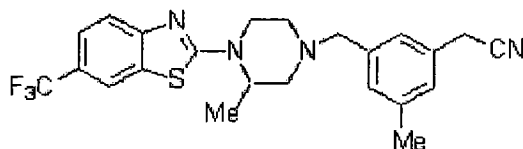


[2195] 收率:86%, $^1\text{H-NMR}$ (CDCl_3): δ 1.23 (3H, d, $J = 6\text{Hz}$), 2.20–2.35 (1H, m), 2.36 (3H, s), 2.61–2.73 (1H, m), 2.80 (1H, dt, $J = 12, 3.5\text{Hz}$), 3.15–3.28 (2H, m), 3.40–3.50 (1H, m), 3.71 (2H, s), 3.71–3.81 (1H, m), 3.87–3.97 (1H, m), 4.02 (1H, d, $J = 13.5\text{Hz}$), 7.05 (1H, s), 7.11 (2H, s), 7.50 (1H, d, $J = 8.5\text{Hz}$), 7.56 (1H, d, $J = 8.5\text{Hz}$), 7.84 (1H, s)。

[2196] 实施例 200

[2197] [式 457]

[2198]

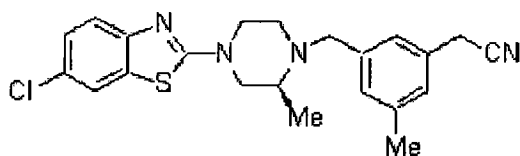


[2199] 收率:79%, $^1\text{H-NMR}$ (CDCl_3): δ 1.43 (3H, d, $J = 6.5\text{Hz}$), 2.26 (1H, td, $J = 11.5, 3.5\text{Hz}$), 2.30–2.33 (1H, m), 2.34 (3H, s), 2.72 (1H, d, $J = 11\text{Hz}$), 2.91 (1H, d, $J = 11.5\text{Hz}$), 3.45 (1H, d, $J = 13.5\text{Hz}$), 3.54 (1H, td, $J = 13, 3.5\text{Hz}$), 3.58 (1H, d, $J = 13.5\text{Hz}$), 3.72 (2H, s), 3.92 (1H, d, $J = 13\text{Hz}$), 4.20–4.30 (1H, m), 7.06 (1H, s), 7.13 (1H, s), 7.15 (1H, s), 7.51 (1H, d, $J = 8.5\text{Hz}$), 7.56 (1H, d, $J = 8.5\text{Hz}$), 7.84 (1H, s)。

[2200] 实施例 201

[2201] [式 458]

[2202]

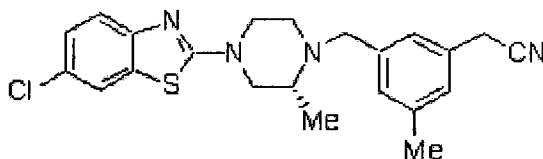


[2203] 收率:90%, $^1\text{H-NMR}$ (CDCl_3): δ 1.22 (3H, d, $J = 6.3\text{Hz}$), 2.23–2.32 (1H, m), 2.36 (3H, s), 2.59–2.69 (1H, m), 2.78 (1H, dt, $J = 3.6, 8.1\text{Hz}$), 3.17 (2H, dt, $J = 3.6, 13.5\text{Hz}$), 3.35–3.44 (1H, m), 3.70–3.75 (1H, m), 3.71 (2H, s), 3.85–3.90 (1H, m), 4.02 (1H, s), 7.05 (1H, s), 7.11 (2H, s), 7.23 (1H, dd, $J = 2.1, 8.7\text{Hz}$), 7.43 (1H, d, $J = 8.7\text{Hz}$), 7.55 (1H, d, $J = 2.1\text{Hz}$)。

[2204] 实施例 202

[2205] [式 459]

[2206]

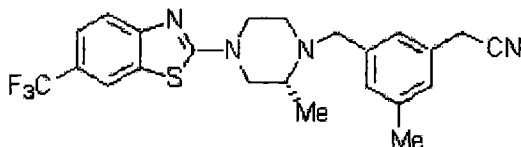


[2207] 收率:98%, $^1\text{H-NMR}$ (CDCl_3): δ 1.22 (3H, d, $J = 6.3\text{Hz}$), 2.23–2.32 (1H, m), 2.36 (3H, s), 2.62–2.66 (1H, m), 2.78 (1H, dt, $J = 3.9, 11.7\text{Hz}$), 3.17 (2H, dt, $J = 3.9, 13.5\text{Hz}$), 3.35–3.44 (1H, m), 3.71 (2H, s), 3.70–3.74 (1H, m), 3.87 (1H, dd, $J = 2.1, 12.6\text{Hz}$), 4.02 (1H, d, $J = 13.5\text{Hz}$), 7.05 (1H, s), 7.11 (2H, s), 7.23 (1H, dd, $J = 2.1, 8.4\text{Hz}$), 7.43 (1H, d, $J = 8.4\text{Hz}$), 7.55 (1H, d, $J = 2.1\text{Hz}$)。

[2208] 实施例 203

[2209] [式 460]

[2210]



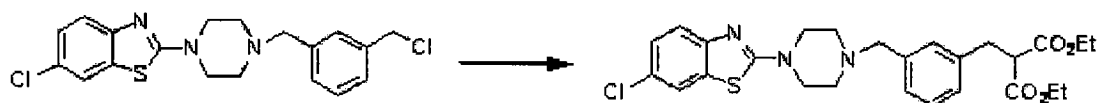
[2211] 收率:85%, $^1\text{H-NMR}$ (CDCl_3): δ 1.24 (3H, d, $J = 6.5\text{Hz}$), 2.23–2.34 (1H, m), 2.37 (3H, s), 2.60–2.73 (1H, m), 2.80 (1H, dt, $J = 12.0, 3.5\text{Hz}$), 3.13–3.27 (2H, m), 3.39–3.51 (1H, m), 3.70–3.83 (3H, m), 3.87–3.97 (1H, m), 4.03 (1H, d, $J = 13.5\text{Hz}$), 7.06 (1H, s), 7.11 (2H, s), 7.48–7.59 (2H, m), 7.84 (1H, s)。

[2212] 实施例 204

[2213] 2-{3-[4-(6-氯苯并噻唑-2-基)哌嗪-1-基甲基]苯甲基}丙二酸二乙酯的制备

[2214] [式 461]

[2215]



[2216] 在冰冷却下向氢化钠 (0.15g; 60%, 3.81mmol) 的无水 THF 悬浮液滴加丙二酸二乙酯 (0.58ml; 3.81mmol)。将混合物在室温搅拌 30 分钟。向反应溶液加入 6-氯 [4-(3-氯

甲基苯甲基)哌嗪-1-基]苯并噻唑单盐酸盐(0.50g;1.27mmol)。将混合物在相同的温度搅拌 14.5 小时和在 50℃ 搅拌 38 小时。向反应溶液加入水和乙酸乙酯并且萃取。有机层用盐水洗涤,用无水硫酸钠干燥,并且减压蒸发。残余物通过硅胶柱色谱法纯化(己烷:乙酸乙酯=3:1),得到 2-{3-[4-(6-氯苯并噻唑-2-基)哌嗪-1-基甲基]苯甲基}丙二酸二乙酯,为无色油状物(0.38g;58%)。

[2217] $^1\text{H-NMR}$ (DMSO-d_6): δ 1.10 (6H, t, $J = 7\text{Hz}$), 2.49 (4H, t, $J = 5\text{Hz}$), 3.08 (2H, d, $J = 8\text{Hz}$), 3.50 (2H, s), 3.56 (4H, t, $J = 5\text{Hz}$), 3.81 (1H, t, $J = 8\text{Hz}$), 4.06 (4H, q, $J = 7\text{Hz}$), 7.10–7.20 (3H, m), 7.24 (1H, d, $J = 7.5\text{Hz}$), 7.28 (1H, dd, $J = 8.5, 2\text{Hz}$), 7.42 (1H, d, $J = 8.5\text{Hz}$), 7.91 (1H, d, $J = 2\text{Hz}$)。

[2218] 通过与实施例 204 相似的方法得到实施例 205 和 206 的化合物。

[2219] 实施例 205

[2220] [式 462]

[2221]

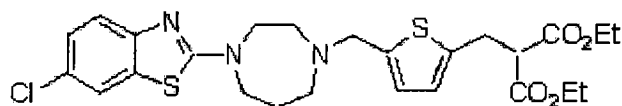


[2222] 收率:46%, $^1\text{H-NMR}$ (CDCl_3): δ 1.26 (6H, t, $J = 7\text{Hz}$), 2.59 (4H, t, $J = 5\text{Hz}$), 3.38 (2H, d, $J = 7.5\text{Hz}$), 3.60–3.68 (5H, m), 3.69 (2H, s), 4.24 (4H, q, $J = 7\text{Hz}$), 6.68 (1H, d, $J = 3\text{Hz}$), 6.71 (1H, d, $J = 3\text{Hz}$), 7.25 (1H, dd, $J = 9, 2\text{Hz}$), 7.43 (1H, d, $J = 9\text{Hz}$), 7.55 (1H, d, $J = 2\text{Hz}$)。

[2223] 实施例 206

[2224] [式 463]

[2225]



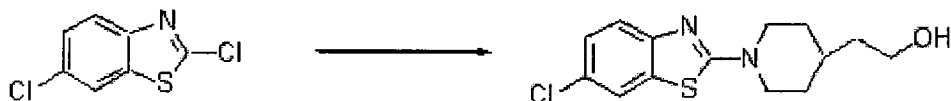
[2226] 收率:5%, $^1\text{H-NMR}$ (CDCl_3): δ 1.21–1.32 (6H, m), 2.00–2.05 (2H, m), 2.70 (2H, t, $J = 5.4\text{Hz}$), 2.81–2.84 (2H, m), 3.36–3.38 (2H, m), 3.62–3.82 (7H, m), 4.14–4.24 (4H, m), 6.65–6.68 (2H, m), 7.22 (1H, dd, $J = 9.0, 1.8\text{Hz}$), 7.42 (1H, d, $J = 8.4\text{Hz}$), 7.54 (1H, d, $J = 1.8\text{Hz}$)。

[2227] 参考例 195

[2228] 6-氯-2-[4-(2-羟基乙基)哌啶-1-基]苯并噻唑的制备

[2229] [式 464]

[2230]



[2231] 将 2,6-二氯苯并噻唑(3.00g;14.7mmol),4-哌啶乙醇(2.09g;16.2mmol),碳酸钾(2.33g;16.2mmol)和无水 N,N-二甲基甲酰胺(15ml)的混合物在室温搅拌 16 小时。向反应溶液加入水和乙酸乙酯。分离有机层,用盐水洗涤,用无水硫酸钠干燥,并且减压蒸发。沉淀物用二异丙醚洗涤,得到 6-氯-2-[4-(2-羟基乙基)哌啶-1-基]苯并噻唑,为绿色

晶体 (2.92g; 67%)。

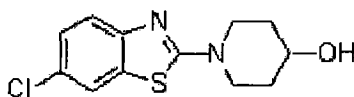
[2232] $^1\text{H-NMR}$ (CDCl_3) : δ 1.26-1.44 (3H, m), 1.57 (2H, q, $J = 6.5\text{Hz}$), 1.68-1.91 (3H, m), 3.06-3.19 (2H, m), 3.74 (2H, q, $J = 6.5\text{Hz}$), 4.07-4.17 (2H, m), 7.22 (1H, dd, $J = 8.5, 2.0\text{Hz}$), 7.42 (1H, d, $J = 8.5\text{Hz}$), 7.54 (1H, d, $J = 2.0\text{Hz}$)。

[2233] 通过与参考例 195 相似的方法得到参考例 196 到 211 的化合物。

[2234] 参考例 196

[2235] [式 465]

[2236]

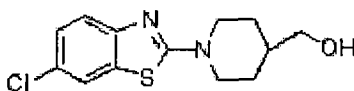


[2237] 收率: 64%, $^1\text{H-NMR}$ (CDCl_3) : δ 1.60-1.75 (3H, m), 1.95-2.18 (2H, m), 3.34-3.48 (2H, m), 3.87-4.10 (3H, m), 7.23 (1H, dd, $J = 8.5, 2\text{Hz}$), 7.43 (1H, d, $J = 8.5\text{Hz}$), 7.53 (1H, d, $J = 2\text{Hz}$)。

[2238] 参考例 197

[2239] [式 466]

[2240]

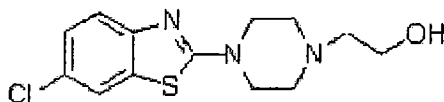


[2241] 收率: 100%, $^1\text{H-NMR}$ (DMSO-d_6) : δ 1.15-1.25 (2H, m), 1.60-1.75 (1H, m), 1.75-1.85 (2H, m), 3.05-3.20 (2H, m), 3.25-3.30 (2H, m), 3.95-4.10 (2H, m), 4.56 (1H, brs), 7.27 (1H, dd, $J = 8.5, 2\text{Hz}$), 7.40 (1H, d, $J = 8.5\text{Hz}$), 7.88 (1H, d, $J = 2\text{Hz}$)。

[2242] 参考例 198

[2243] [式 467]

[2244]

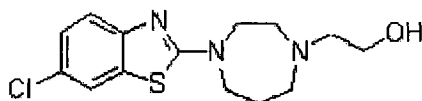


[2245] 收率: 95%, $^1\text{H-NMR}$ (CDCl_3) : δ 1.65 (1H, s), 2.60-2.67 (6H, m), 3.63-3.69 (6H, m), 7.23 (1H, d, $J = 8.5, 2.0\text{Hz}$), 7.44 (1H, d, $J = 8.5\text{Hz}$), 7.57 (1H, d, $J = 2.0\text{Hz}$)。

[2246] 参考例 199

[2247] [式 468]

[2248]

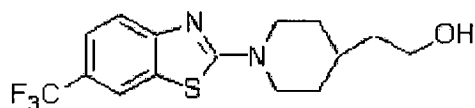


[2249] 收率: 99%, $^1\text{H-NMR}$ (CDCl_3) : δ 2.00-2.07 (2H, m), 2.69 (2H, t, $J = 5.1\text{Hz}$), 2.76 (2H, t, $J = 5.4\text{Hz}$), 2.89-2.93 (2H, m), 2.96 (1H, s), 3.60 (2H, t, $J = 5.4\text{Hz}$), 3.73 (2H, t, $J = 6.0\text{Hz}$), 3.80-3.83 (2H, m), 7.24 (1H, dd, $J = 7.8, 2.1\text{Hz}$), 7.42 (1H, d, $J = 8.7\text{Hz}$), 7.55 (1H, d, $J = 2.1\text{Hz}$)。

[2250] 参考例 200

[2251] [式 469]

[2252]

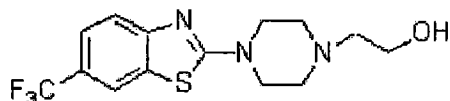


[2253] 收率:48%, $^1\text{H-NMR}$ (CDCl_3): δ 1.28-1.46 (2H, m), 1.58 (2H, q, $J = 6.5\text{Hz}$), 1.72-1.94 (3H, m), 3.11-3.24 (2H, m), 3.76 (2H, t, $J = 6.5\text{Hz}$), 4.11-4.22 (2H, m), 7.48-7.57 (2H, m), 7.83 (1H, s)。

[2254] 参考例 201

[2255] [式 470]

[2256]

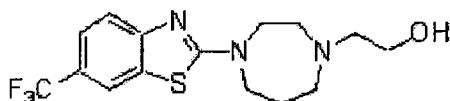


[2257] 收率:70%, $^1\text{H-NMR}$ (DMSO-d_6): δ 2.49 (2H, t, $J = 6\text{Hz}$), 2.57 (4H, t, $J = 5\text{Hz}$), 3.55 (2H, t, $J = 6\text{Hz}$), 3.62 (4H, t, $J = 5\text{Hz}$), 4.51 (1H, brs), 7.57 (2H, s), 8.25 (1H, s)。

[2258] 参考例 202

[2259] [式 471]

[2260]

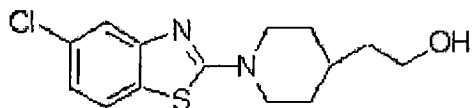


[2261] 收率:85%, $^1\text{H-NMR}$ (DMSO-d_6): δ 1.83-1.90 (2H, m), 2.55 (2H, t, $J = 5.5\text{Hz}$), 2.67 (2H, t, $J = 5\text{Hz}$), 2.87 (2H, t, $J = 5\text{Hz}$), 3.47 (2H, q, $J = 5.5\text{Hz}$), 3.60-3.80 (4H, m), 4.39 (1H, t, $J = 5.5\text{Hz}$), 7.55 (1H, s), 7.95 (1H, s), 8.21 (1H, s)。

[2262] 参考例 203

[2263] [式 472]

[2264]

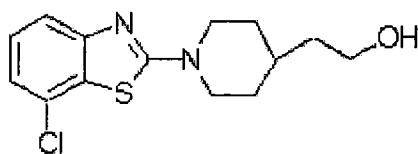


[2265] 收率:63%, $^1\text{H-NMR}$ (CDCl_3): δ 1.23-1.44 (3H, m), 1.53-1.63 (2H, m), 1.68-1.90 (3H, m), 3.08-3.20 (2H, m), 3.75 (2H, q, $J = 6.0\text{Hz}$), 4.08-4.18 (2H, m), 7.02 (1H, dd, $J = 8.5, 2.0\text{Hz}$), 7.46 (1H, d, $J = 8.5\text{Hz}$), 7.49 (1H, d, $J = 2.0\text{Hz}$)。

[2266] 参考例 204

[2267] [式 473]

[2268]

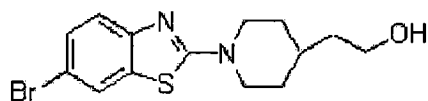


[2269] 收率:36%, $^1\text{H-NMR}$ (CDCl_3): δ 1.25-1.45 (3H, m), 1.57 (2H, q, $J = 6.5\text{Hz}$), 1.70-1.91 (3H, m), 3.08-3.23 (2H, m), 3.75 (2H, t, $J = 6.5\text{Hz}$), 4.08-4.21 (2H, m), 7.04 (1H, dd, $J = 8.0, 1.0\text{Hz}$), 7.21 (1H, t, $J = 8.0\text{Hz}$), 7.39 (1H, dd, $J = 8.0, 1.0\text{Hz}$)。

[2270] 参考例 205

[2271] [式 474]

[2272]

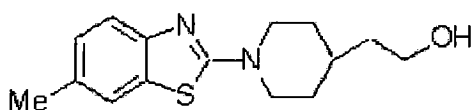


[2273] 收率:52%, $^1\text{H-NMR}$ (CDCl_3); δ 1.26 (1H, t, $J = 6.5\text{Hz}$), 1.27-1.44 (2H, m), 1.57 (2H, q, $J = 6.5\text{Hz}$), 1.68-1.91 (3H, m), 3.06-3.19 (2H, m), 3.75 (2H, q, $J = 6.5\text{Hz}$), 4.05-4.19 (2H, m), 7.35-7.40 (2H, m), 7.68 (1H, s)。

[2274] 参考例 206

[2275] [式 475]

[2276]

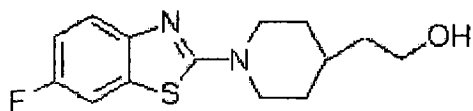


[2277] 收率:31%, $^1\text{H-NMR}$ (CDCl_3); δ 1.22 (1H, t, $J = 5.0\text{Hz}$), 1.27-1.45 (2H, m), 1.57 (2H, q, $J = 5.0\text{Hz}$), 1.65-1.90 (3H, m), 2.38 (3H, s), 3.03-3.19 (2H, m), 3.75 (2H, q, $J = 5.0\text{Hz}$), 4.06-4.17 (2H, m), 7.08 (1H, d, $J = 8.0\text{Hz}$), 7.39 (1H, s), 7.42 (1H, d, $J = 8.0\text{Hz}$)。

[2278] 参考例 207

[2279] [式 476]

[2280]

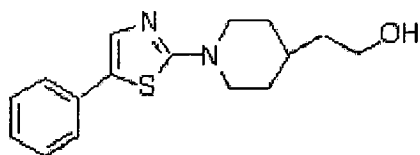


[2281] 收率:9%, $^1\text{H-NMR}$ (CDCl_3); δ 1.23-1.45 (3H, m), 1.52-1.64 (2H, m), 1.67-1.94 (3H, m), 3.40-3.22 (2H, m), 3.68-3.83 (2H, m), 4.03-4.17 (2H, m), 7.00 (1H, td, $J = 8.5, 2.5\text{Hz}$), 7.29 (1H, dd, $J = 8.5, 2.5\text{Hz}$), 7.40 (1H, dd, $J = 8.5, 4.0\text{Hz}$)。

[2282] 参考例 208

[2283] [式 477]

[2284]

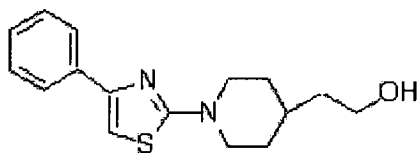


[2285] 收率:48%, $^1\text{H-NMR}$ (DMSO-d_6); δ 1.12-1.29 (2H, m), 1.40 (2H, q, $J = 6.5\text{Hz}$), 1.57-1.81 (3H, m), 2.95-3.10 (2H, m), 3.47 (2H, q, $J = 6.5\text{Hz}$), 3.84-3.97 (2H, m), 4.40 (1H, t, $J = 6.5\text{Hz}$), 7.20 (1H, t, $J = 7.5\text{Hz}$), 7.35 (2H, t, $J = 7.5\text{Hz}$), 7.44 (2H, d, $J = 7.5\text{Hz}$), 7.57 (1H, s)。

[2286] 参考例 209

[2287] [式 478]

[2288]

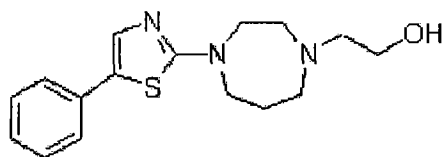


[2289] 收率:88%, $^1\text{H-NMR}$ (CDCl_3): δ 1.14-1.32 (2H, m), 1.40 (2H, q, $J = 6.5\text{Hz}$), 1.54-1.83 (3H, m), 2.95-3.08 (2H, m), 3.47 (2H, q, $J = 6.5\text{Hz}$), 3.88-4.00 (2H, m), 4.40 (1H, t, $J = 6.5\text{Hz}$), 7.22 (1H, s), 7.27 (1H, t, $J = 7.5\text{Hz}$), 7.38 (2H, t, $J = 7.5\text{Hz}$), 7.87 (2H, d, $J = 7.5\text{Hz}$)。

[2290] 参考例 210

[2291] [式 479]

[2292]

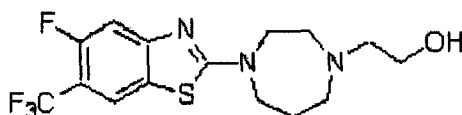


[2293] 收率:71%, $^1\text{H-NMR}$ (DMSO-d_6): δ 1.82-1.93 (2H, m), 2.55 (2H, t, $J = 6.0\text{Hz}$), 2.62-2.70 (2H, m), 2.78-2.86 (2H, m), 3.47 (2H, q, $J = 6.0\text{Hz}$), 3.59 (2H, t, $J = 6.0\text{Hz}$), 3.61-3.68 (2H, m), 4.38 (1H, t, $J = 6.0\text{Hz}$), 7.18 (1H, t, $J = 7.5\text{Hz}$), 7.34 (2H, t, $J = 7.5\text{Hz}$), 7.45 (2H, d, $J = 7.5\text{Hz}$), 7.57 (1H, s)。

[2294] 参考例 211

[2295] [式 480]

[2296]



[2297] 收率:93%, $^1\text{H-NMR}$ (DMSO-d_6): δ 1.80-2.01 (2H, m), 2.57 (2H, t, $J = 6.0\text{Hz}$), 2.64-2.77 (2H, m), 2.82-2.96 (2H, m), 3.42-3.53 (2H, m), 3.45-3.94 (4H, br), 4.34-4.46 (1H, m), 7.45 (1H, d, $J = 7.0\text{Hz}$), 8.23 (1H, d, $J = 12.5\text{Hz}$)。

[2298] 参考例 212

[2299] 6-氯-2-[4-(2-氯乙基)哌啶-1-基]苯并噻唑的制备

[2300] [式 481]

[2301]



[2302] 向 6-氯-2-[4-(2-羟基乙基)哌啶-1-基]苯并噻唑 (1.20g; 4.03mmol) 加入亚硫酸氯 (10ml)。将混合物在 60℃ 搅拌 1 小时。将反应溶液倾倒在冰水中。向其中加入 5N 氢氧化钠水溶液以中和并且收集沉淀物。沉淀物用二异丙醚洗涤, 得到 6-氯-2-[4-(2-氯乙基)哌啶-1-基]苯并噻唑, 为无色晶体 (0.98g; 77%)。

[2303] $^1\text{H-NMR}$ (CDCl_3): δ 1.25-1.44 (2H, m), 1.70-1.94 (5H, m), 3.08-3.22 (2H, m), 3.62 (2H, t, $J = 6.5\text{Hz}$), 4.07-4.20 (2H, m), 7.23 (1H, dd, $J = 8.5, 2.0\text{Hz}$), 7.43 (1H, d, $J =$

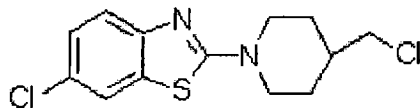
8.5Hz), 7.55(1H, d, $J = 2.0$)。

[2304] 通过与参考例 212 相似的方法得到参考例 213 到 225 的化合物。

[2305] 参考例 213

[2306] [式 482]

[2307]

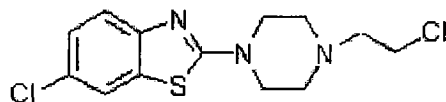


[2308] 收率: 定量收率 (q. y.), $^1\text{H-NMR}$ (DMSO- d_6): δ 1.20-1.42 (2H, m), 1.80-2.00 (3H, m), 3.10-3.25 (2H, m), 3.60 (2H, d, $J = 6.5\text{Hz}$), 4.00-4.10 (2H, m), 7.28 (1H, dd, $J = 8.5, 2\text{Hz}$), 7.41 (1H, d, $J = 8.5\text{Hz}$), 7.90 (1H, d, $J = 2\text{Hz}$)。

[2309] 参考例 214

[2310] [式 483]

[2311]

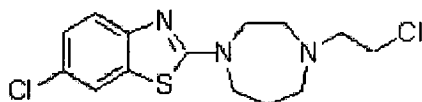


[2312] 收率: 95%, $^1\text{H-NMR}$ (CDCl_3): δ 2.63-2.72 (4H, m), 2.80 (2H, t, $J = 7.0\text{Hz}$), 3.58-3.73 (6H, m), 7.23 (1H, dd, $J = 8.5, 2.0\text{Hz}$), 7.44 (1H, d, $J = 8.5\text{Hz}$), 7.56 (1H, d, $J = 2.0\text{Hz}$)。

[2313] 参考例 215

[2314] [式 484]

[2315]

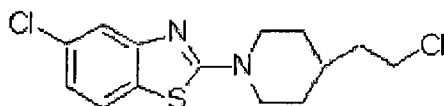


[2316] 收率: 58%, $^1\text{H-NMR}$ (CDCl_3): δ 1.98-2.06 (2H, m), 2.78 (2H, t, $J = 5.4\text{Hz}$), 2.90-2.96 (4H, m), 3.56 (2H, t, $J = 7.2\text{Hz}$), 3.72 (2H, t, $J = 6.0\text{Hz}$), 3.78-3.81 (2H, m), 7.23 (1H, dd, $J = 8.4, 2.1\text{Hz}$), 7.42 (1H, d, $J = 8.4\text{Hz}$), 7.55 (1H, d, $J = 2.1\text{Hz}$)。

[2317] 参考例 216

[2318] [式 485]

[2319]

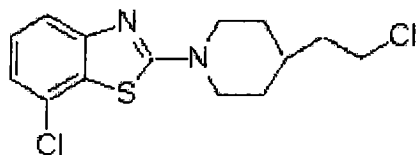


[2320] 收率: 68%, $^1\text{H-NMR}$ (CDCl_3): δ 1.25-1.43 (2H, m), 1.70-1.94 (5H, m), 3.08-3.22 (2H, m), 3.62 (2H, t, $J = 6.5\text{Hz}$), 4.08-4.22 (2H, m), 7.03 (1H, dd, $J = 8.5, 2.0\text{Hz}$), 7.46 (1H, d, $J = 8.5\text{Hz}$), 7.52 (1H, d, $J = 2.0\text{Hz}$)。

[2321] 参考例 217

[2322] [式 486]

[2323]

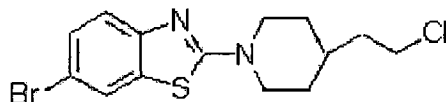


[2324] 收率:90%, $^1\text{H-NMR}$ (CDCl_3); δ 1.26-1.44 (2H, m), 1.71-1.93 (5H, m), 3.08-3.23 (2H, m), 3.62 (2H, t, $J = 6.5\text{Hz}$), 4.10-4.22 (2H, m), 7.04 (1H, d, $J = 8.0\text{Hz}$), 7.22 (1H, t, $J = 8.0\text{Hz}$), 7.40 (1H, d, $J = 8.0\text{Hz}$)。

[2325] 参考例 218

[2326] [式 487]

[2327]

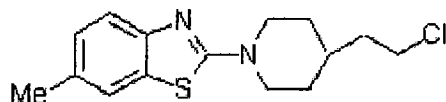


[2328] 收率:95%, $^1\text{H-NMR}$ (CDCl_3); δ 1.25-1.43 (2H, m), 1.71-1.92 (5H, m), 3.07-3.23 (2H, m), 3.61 (2H, t, $J = 6.5\text{Hz}$), 4.06-4.21 (2H, m), 7.35-7.43 (2H, m), 7.69 (1H, s)。

[2329] 参考例 219

[2330] [式 488]

[2331]

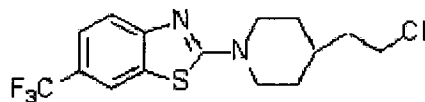


[2332] 收率:65%, $^1\text{H-NMR}$ (CDCl_3); δ 1.22-1.41 (2H, m), 1.68-1.90 (5H, m), 2.38 (3H, s), 3.02-3.18 (2H, m), 3.59 (2H, t, $J = 6.5\text{Hz}$), 4.05-4.18 (2H, m), 7.06-7.12 (1H, m), 7.36-7.39 (1H, m), 7.43 (1H, d, $J = 8.0\text{Hz}$)。

[2333] 参考例 220

[2334] [式 489]

[2335]

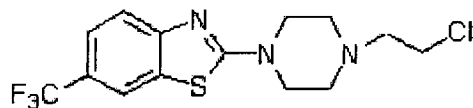


[2336] 收率:91%, $^1\text{H-NMR}$ (CDCl_3); δ 1.27-1.45 (2H, m), 1.72-1.95 (5H, m), 3.12-3.27 (2H, m), 3.62 (2H, t, $J = 6.5\text{Hz}$), 4.12-4.26 (2H, m), 7.49-7.59 (2H, m), 7.84 (1H, s)。

[2337] 参考例 221

[2338] [式 490]

[2339]

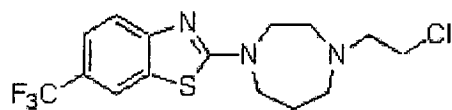


[2340] 收率:42%, $^1\text{H-NMR}$ (CDCl_3); δ 2.68 (4H, t, $J = 5\text{Hz}$), 2.81 (2H, t, $J = 7\text{Hz}$), 3.63 (2H, t, $J = 7\text{Hz}$), 3.71 (4H, t, $J = 5\text{Hz}$), 7.53 (1H, d, $J = 8.5\text{Hz}$), 7.58 (1H, d, $J = 8.5\text{Hz}$), 7.86 (1H, s)。

[2341] 参考例 222

[2342] [式 491]

[2343]

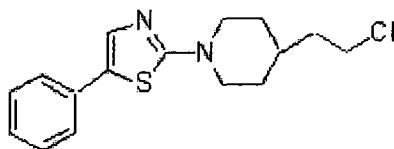


[2344] 收率:23%, $^1\text{H-NMR}$ (CDCl_3); δ 1.94-2.07 (2H, m), 2.70-2.80 (2H, m), 2.83-2.99 (4H, m), 3.50-3.58 (2H, m), 3.64-3.88 (4H, m), 7.48-7.60 (2H, m), 7.84 (1H, s)。

[2345] 参考例 223

[2346] [式 492]

[2347]

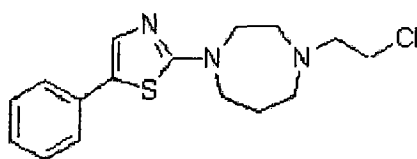


[2348] 收率:89%, $^1\text{H-NMR}$ (CDCl_3); δ 1.27-1.44 (2H, m), 1.72-1.88 (5H, m), 2.99-3.13 (2H, m), 3.62 (2H, t, $J = 6.5\text{Hz}$), 3.99-4.10 (2H, m), 7.17-7.24 (1H, m), 7.30-7.37 (2H, m), 7.38-7.45 (3H, m)。

[2349] 参考例 224

[2350] [式 493]

[2351]

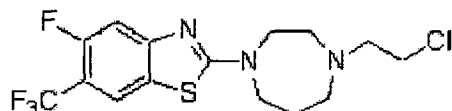


[2352] 收率:35%, $^1\text{H-NMR}$ (DMSO-d_6); δ 1.81-1.94 (2H, m), 2.66-2.76 (2H, m), 2.77-2.93 (4H, m), 3.55-3.72 (6H, m), 7.18 (1H, t, $J = 7.5\text{Hz}$), 7.34 (2H, t, $J = 7.5\text{Hz}$), 7.44 (2H, d, $J = 7.5\text{Hz}$), 7.57 (1H, s)。

[2353] 参考例 225

[2354] [式 494]

[2355]



[2356] 收率:定量收率, $^1\text{H-NMR}$ (CDCl_3); δ 1.95-2.10 (2H, m), 2.73-2.84 (2H, m), 2.85-3.01 (4H, m), 3.56 (2H, t, $J = 7.0\text{Hz}$), 3.66-3.89 (4H, m), 7.27 (1H, d, $J = 11.5\text{Hz}$), 7.75 (1H, d, $J = 7.0\text{Hz}$)。

[2357] 参考例 226

[2358] 2-氯-1-[4-(6-氯苯并噻唑-2-基)哌嗪-1-基]乙烷-1-酮的制备

[2359] [式 495]

[2360]



[2361] 在冰冷却下向 4-(6-氯苯并噻唑-2-基)哌嗪二盐酸盐 (0.50g ;1.53mmol)、三乙胺 (0.32ml ;2.25mmol) 和无水 THF (10ml) 的混合物中滴加氯乙酰氯 (0.18ml ;2.25mmol)。将混合物在室温搅拌 24 小时。向反应溶液加入水和乙酸乙酯并且萃取。有机层用盐水洗涤,用无水硫酸钠干燥,并且减压蒸发。沉淀物用己烷洗涤,得到 2-氯-1-[4-(6-氯苯并噻唑-2-基)哌嗪-1-基]乙烷-1-酮,为带浅黑色的褐色晶体 (0.15g ;30%)。

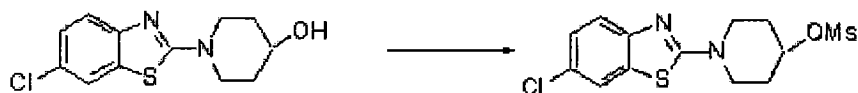
[2362] $^1\text{H-NMR}(\text{CDCl}_3)$: δ 3.61-3.81 (8H, m), 4.12 (2H, s), 7.28 (1H, dd, $J = 8.5, 2.0\text{Hz}$), 7.47 (1H, d, $J = 8.5\text{Hz}$), 7.60 (1H, d, $J = 2.0\text{Hz}$)。

[2363] 参考例 227

[2364] 甲磺酸 [(6-氯苯并噻唑-2-基)哌啶-4-基]酯的制备

[2365] [式 496]

[2366]



[2367] 在冰冷却下向 1-(6-氯苯并噻唑-2-基)哌啶-4-醇 (1.43g ;5.32mmol)、三乙胺 (0.78ml ;5.59mmol) 和无水 THF (30ml) 的混合物中滴加甲磺酰氯 (0.43ml ;5.59mmol)。将混合物在室温搅拌 30 分钟。将反应溶液减压浓缩。向残余物加入水并且收集沉淀物,得到 [(6-氯苯并噻唑-1-基)哌啶-4-基]甲磺酸酯,为带浅黑色的褐色晶体 (1.66g ;90%)。

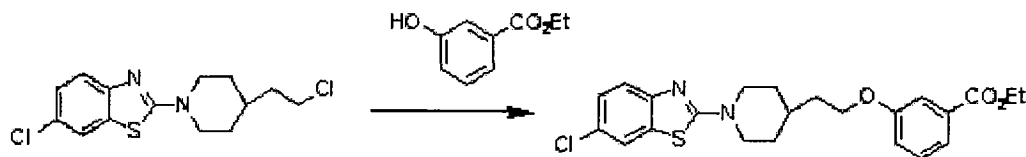
[2368] $^1\text{H-NMR}(\text{CDCl}_3)$: δ 1.97-2.20 (4H, m), 3.08 (3H, s), 3.57-3.68 (2H, m), 3.80-3.91 (2H, m), 4.97-5.08 (1H, m), 7.25 (1H, dd, $J = 8.5, 2.0\text{Hz}$), 7.44 (1H, d, $J = 8.5\text{Hz}$), 7.57 (1H, d, $J = 2.0\text{Hz}$)。

[2369] 实施例 207

[2370] 3-{2-[1-(6-氯苯并噻唑-2-基)哌啶-4-基]乙氧基}苯甲酸乙酯

[2371] [式 497]

[2372]



[2373] 将 6-氯-2-[4-(2-氯乙基)哌啶-1-基]苯并噻唑 (0.50g ;1.59mmol)、碳酸铯 (0.78g ;2.39mmol)、3-羟基苯甲酸乙酯 (0.40g ;2.39mmol) 和无水 N,N-二甲基甲酰胺 (5ml) 的混合物在 60℃ 搅拌 9 小时。使反应溶液回到室温。向其中加入水和乙酸乙酯并用乙酸乙酯萃取。有机层用盐水洗涤,用无水硫酸钠干燥,并且减压蒸发。残余物通过硅胶柱色谱法纯化 (二氯甲烷),得到 3-{2-[1-(6-氯苯并噻唑-2-基)哌啶-4-基]乙氧基}苯甲酸乙酯,为无色晶体 (0.43g ;62%)。

[2374] $^1\text{H-NMR}(\text{CDCl}_3)$: δ 1.30-1.51 (5H, m), 1.74-1.97 (5H, m), 3.09-3.22 (2H, m), 4.04-4.18 (4H, m), 4.38 (2H, q, $J = 7.0\text{Hz}$), 7.09 (1H, dd, $J = 8.0, 1.5\text{Hz}$), 7.23 (1H, dd, $J = 8.5, 2.0\text{Hz}$), 7.35 (1H, t, $J = 8.0\text{Hz}$), 7.42 (1H, d, $J = 8.5\text{Hz}$), 7.52-7.58 (2H, m), 7.65 (1H,

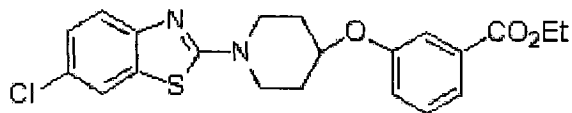
dd, $J = 8.0, 1.5\text{Hz}$).

[2375] 通过与实施例 207 相似的方法得到实施例 208 到 253 的化合物。

[2376] 实施例 208

[2377] [式 498]

[2378]

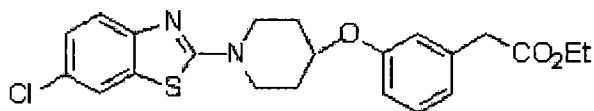


[2379] 收率:39%, $^1\text{H-NMR}(\text{CDCl}_3)$; δ 1.40 (3H, t, $J = 7.0\text{Hz}$), 1.92-2.16 (4H, m), 3.60-3.72 (2H, m), 3.80-3.92 (2H, m), 4.38 (2H, q, $J = 7.0\text{Hz}$), 4.65-4.74 (1H, m), 7.13 (1H, m), 7.24 (1H, dd, $J = 8.5, 2.0\text{Hz}$), 7.37 (1H, t, $J = 8.0\text{Hz}$), 7.44 (1H, d, $J = 8.5\text{Hz}$), 7.56 (1H, d, $J = 2.0\text{Hz}$), 7.58-7.63 (1H, m), 7.67 (1H, m)。

[2380] 实施例 209

[2381] [式 499]

[2382]

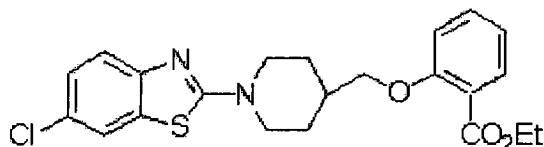


[2383] 收率:16%, $^1\text{H-NMR}(\text{CDCl}_3)$; δ 1.26 (3H, t, $J = 7.0\text{Hz}$), 1.90-2.12 (4H, m), 3.56-3.70 (4H, m), 3.78-3.90 (2H, m), 4.16 (2H, q, $J = 7.0\text{Hz}$), 4.61 (1H, m), 6.80-6.93 (3H, m), 7.20-7.28 (2H, m), 7.43 (1H, d, $J = 8.5\text{Hz}$), 7.55 (1H, d, $J = 2.0\text{Hz}$)。

[2384] 实施例 210

[2385] [式 500]

[2386]

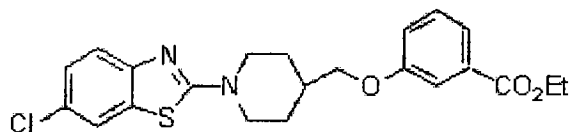


[2387] 收率:39%, $^1\text{H-NMR}(\text{CDCl}_3)$; δ 1.34 (3H, t, $J = 7\text{Hz}$), 1.45-1.65 (2H, m), 1.95-2.10 (2H, m), 2.10-2.25 (1H, m), 3.10-3.30 (2H, m), 3.92 (2H, d, $J = 6\text{Hz}$), 4.15-4.25 (2H, m), 4.32 (2H, q, $J = 7\text{Hz}$), 6.93 (1H, d, $J = 7.5\text{Hz}$), 6.98 (1H, td, $J = 7.5, 1\text{Hz}$), 7.24 (1H, dd, $J = 8.5, 2\text{Hz}$), 7.43 (1H, d, $J = 8.5\text{Hz}$), 7.46 (1H, td, $J = 7.5, 1\text{Hz}$), 7.55 (1H, d, $J = 2\text{Hz}$), 7.80 (1H, dd, $J = 7.5, 1\text{Hz}$)。

[2388] 实施例 211

[2389] [式 501]

[2390]



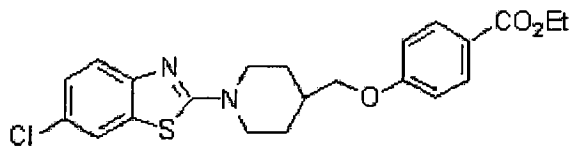
[2391] 收率:39%, $^1\text{H-NMR}(\text{CDCl}_3)$; δ 1.40 (3H, t, $J = 7\text{Hz}$), 1.45-1.60 (2H, m), 1.95-2.05 (2H, m), 2.05-2.20 (1H, m), 3.10-3.25 (2H, m), 3.90 (2H, d, $J = 6\text{Hz}$),

4.15-4.25 (2H, m), 4.37 (2H, q, $J = 7\text{Hz}$), 7.09 (1H, dd, $J = 8, 1.5\text{Hz}$), 7.23 (1H, dd, $J = 8.5, 2\text{Hz}$), 7.34 (1H, t, $J = 8\text{Hz}$), 7.43 (1H, d, $J = 8.5\text{Hz}$), 7.55 (1H, d, $J = 1.5\text{Hz}$), 7.56 (1H, d, $J = 2\text{Hz}$), 7.64 (1H, dd, $J = 8, 1.5\text{Hz}$)。

[2392] 实施例 212

[2393] [式 502]

[2394]

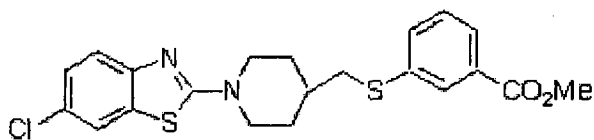


[2395] 收率: 52%, $^1\text{H-NMR}$ (CDCl_3): δ 1.38 (3H, t, $J = 7\text{Hz}$), 1.45-1.60 (2H, m), 1.90-2.05 (2H, m), 2.05-2.20 (1H, m), 3.10-3.25 (2H, m), 3.90 (2H, d, $J = 6\text{Hz}$), 4.10-4.25 (2H, m), 4.35 (2H, q, $J = 7\text{Hz}$), 6.89 (2H, d, $J = 9\text{Hz}$), 7.24 (1H, dd, $J = 8.5, 2\text{Hz}$), 7.43 (1H, d, $J = 8.5\text{Hz}$), 7.55 (1H, d, $J = 2\text{Hz}$), 7.99 (2H, d, $J = 9\text{Hz}$)。

[2396] 实施例 213

[2397] [式 503]

[2398]

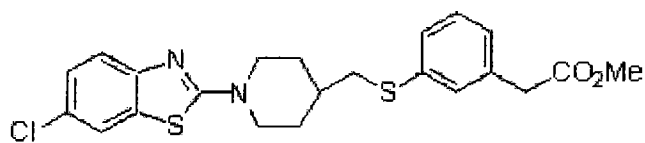


[2399] 收率: 63%, $^1\text{H-NMR}$ (DMSO-d_6): δ 1.25-1.45 (2H, m), 1.70-1.85 (1H, m), 1.85-2.00 (2H, m), 3.03 (2H, d, $J = 7\text{Hz}$), 3.08-3.24 (2H, m), 3.86 (3H, s), 3.95-4.10 (2H, m), 7.27 (1H, dd, $J = 8.5, 2\text{Hz}$), 7.40 (1H, d, $J = 8.5\text{Hz}$), 7.48 (1H, t, $J = 8\text{Hz}$), 7.64 (1H, d, $J = 8\text{Hz}$), 7.75 (1H, d, $J = 8\text{Hz}$), 7.84 (1H, s), 7.88 (1H, d, $J = 2\text{Hz}$)。

[2400] 实施例 214

[2401] [式 504]

[2402]

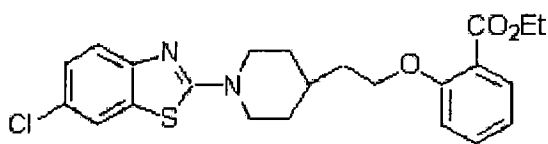


[2403] 收率: 79%, $^1\text{H-NMR}$ (CDCl_3): δ 1.30-1.50 (2H, m), 1.75-2.00 (1H, m), 1.95-2.05 (2H, m), 2.89 (2H, d, $J = 7\text{Hz}$), 3.05-3.18 (2H, m), 3.60 (2H, s), 3.70 (3H, s), 4.05-4.20 (2H, m), 7.20-7.30 (5H, m), 7.42 (1H, d, $J = 8.5\text{Hz}$), 7.54 (1H, d, $J = 2\text{Hz}$)。

[2404] 实施例 215

[2405] [式 505]

[2406]



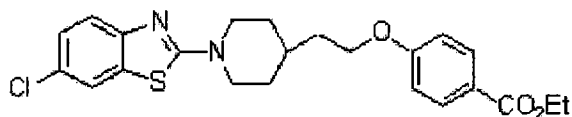
[2407] 收率: 86%, $^1\text{H-NMR}$ (CDCl_3): δ 1.25-1.50 (5H, m), 1.77-2.00 (5H, m),

3.06-3.23 (2H, m), 4.05-4.20 (4H, m), 4.35 (2H, q, $J = 7.0\text{Hz}$), 6.93-7.04 (2H, m), 7.22 (1H, dd, $J = 8.5, 2.0\text{Hz}$), 7.37-7.49 (2H, m), 7.54 (1H, d, $J = 2.0\text{Hz}$), 7.78 (1H, dd, $J = 8.0, 1.5\text{Hz}$)。

[2408] 实施例 216

[2409] [式 506]

[2410]

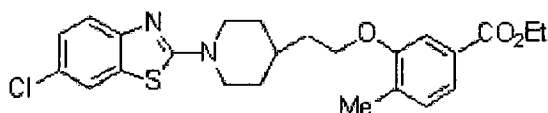


[2411] 收率: 65%, $^1\text{H-NMR}$ (CDCl_3); δ 1.34-1.53 (5H, m), 1.76-1.98 (5H, m), 3.09-3.24 (2H, m), 4.06-4.23 (4H, m), 4.35 (2H, q, $J = 7.0\text{Hz}$), 6.91 (2H, d, $J = 8.5\text{Hz}$), 7.23 (1H, dd, $J = 8.5, 2.0\text{Hz}$), 7.42 (1H, d, $J = 8.5\text{Hz}$), 7.55 (1H, d, $J = 2.0\text{Hz}$), 8.00 (2H, d, $J = 8.5\text{Hz}$)。

[2412] 实施例 217

[2413] [式 507]

[2414]



[2415] 收率: 72%, $^1\text{H-NMR}$ (CDCl_3); δ 1.40 (3H, t, $J = 7.0\text{Hz}$), 1.33-1.52 (2H, m), 1.79-1.98 (5H, m), 2.27 (3H, s), 3.08-3.21 (2H, m), 4.07-4.18 (4H, m), 4.37 (2H, q, $J = 7.0\text{Hz}$), 7.19 (1H, dd, $J = 7.5, 1.5\text{Hz}$), 7.23 (1H, dd, $J = 8.5, 2.0\text{Hz}$), 7.42 (1H, d, $J = 8.5\text{Hz}$), 7.47 (1H, d, $J = 1.5\text{Hz}$), 7.55 (1H, d, $J = 2.0\text{Hz}$), 7.57 (1H, dd, $J = 7.5, 1.5\text{Hz}$)。

[2416] 实施例 218

[2417] [式 508]

[2418]

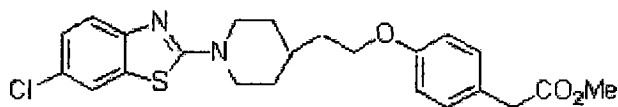


[2419] 收率: 46%, $^1\text{H-NMR}$ (CDCl_3); δ 1.24 (3H, t, $J = 7.0\text{Hz}$), 1.23-1.44 (2H, m), 1.67-1.92 (5H, m), 3.02-3.16 (2H, m), 3.57 (2H, s), 3.98 (2H, t, $J = 6.0\text{Hz}$), 4.02-4.15 (2H, m), 4.14 (2H, q, $J = 7.0\text{Hz}$), 6.75-6.90 (3H, m), 7.16-7.26 (2H, m), 7.41 (1H, d, $J = 8.5\text{Hz}$), 7.51 (1H, d, $J = 2.0\text{Hz}$)。

[2420] 实施例 219

[2421] [式 509]

[2422]



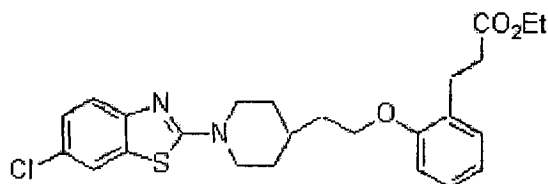
[2423] 收率: 17%, $^1\text{H-NMR}$ (CDCl_3); δ 1.23-1.44 (2H, m), 1.67-1.90 (5H, m), 3.02-3.16 (2H, m), 3.55 (2H, s), 3.67 (3H, s), 3.98 (2H, t, $J = 6.0\text{Hz}$), 4.02-4.14 (2H, m), 6.84 (2H, d, $J = 8.5\text{Hz}$), 7.18 (2H, d, $J = 8.5\text{Hz}$), 7.20 (1H, dd, $J = 8.5, 2.0\text{Hz}$), 7.40 (1H,

d, $J = 8.5\text{Hz}$), 7.51 (1H, d, $J = 2.0$)。

[2424] 实施例 220

[2425] [式 510]

[2426]



[2427] 收率: 58%, $^1\text{H-NMR}$ (CDCl_3); δ 1.23 (3H, t, $J = 7.0\text{Hz}$), 1.33-1.50 (2H, m), 1.74-1.96 (5H, m), 2.60 (2H, t, $J = 8.0\text{Hz}$), 2.95 (2H, t, $J = 8.0\text{Hz}$), 3.08-3.22 (2H, m), 4.02-4.19 (6H, m), 6.83 (1H, d, $J = 7.5\text{Hz}$), 6.88 (1H, td, $J = 7.5, 1.0\text{Hz}$), 7.14-7.20 (2H, m), 7.23 (1H, dd, $J = 8.5, 2.0\text{Hz}$), 7.42 (1H, d, $J = 8.5\text{Hz}$), 7.55 (1H, d, $J = 2.0\text{Hz}$)。

[2428] 实施例 221

[2429] [式 511]

[2430]



[2431] 收率: 71%, $^1\text{H-NMR}$ (CDCl_3); δ 1.24 (3H, t, $J = 7.0\text{Hz}$), 1.31-1.49 (2H, m), 1.73-1.95 (5H, m), 2.62 (2H, t, $J = 8.0\text{Hz}$), 2.93 (2H, t, $J = 8.0\text{Hz}$), 3.08-3.21 (2H, m), 4.02 (2H, t, $J = 6.0\text{Hz}$), 4.07-4.20 (2H, m), 4.13 (2H, q, $J = 7.0\text{Hz}$), 6.71-6.84 (3H, m), 7.16-7.25 (2H, m), 7.42 (1H, d, $J = 8.5\text{Hz}$), 7.54 (1H, d, $J = 2.0\text{Hz}$)。

[2432] 实施例 222

[2433] [式 512]

[2434]

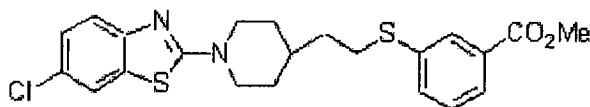


[2435] 收率: 58%, $^1\text{H-NMR}$ (CDCl_3); δ 1.30-1.47 (2H, m), 1.72-1.95 (5H, m), 2.60 (2H, t, $J = 8.0\text{Hz}$), 2.90 (2H, t, $J = 8.0\text{Hz}$), 3.08-3.20 (2H, m), 3.67 (3H, s), 4.01 (2H, t, $J = 6.0\text{Hz}$), 4.06-4.18 (2H, m), 6.82 (2H, d, $J = 8.5\text{Hz}$), 7.12 (2H, d, $J = 8.5\text{Hz}$), 7.23 (1H, dd, $J = 8.5, 2.0\text{Hz}$), 7.42 (1H, d, $J = 8.5\text{Hz}$), 7.54 (1H, d, $J = 2.0\text{Hz}$)。

[2436] 实施例 223

[2437] [式 513]

[2438]



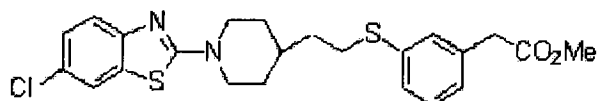
[2439] 收率: 58%, $^1\text{H-NMR}$ (CDCl_3); δ 1.24-1.43 (2H, m), 1.61-1.92 (5H, m), 2.97-3.20 (4H, m), 3.93 (3H, s), 4.06-4.18 (2H, m), 7.23 (1H, dd, $J = 8.5, 2.0\text{Hz}$), 7.36 (1H, t, $J = 7.5\text{Hz}$), 7.41 (1H, d, $J = 8.5\text{Hz}$), 7.49 (1H, dt, $J = 7.5, 1.5\text{Hz}$), 7.54 (1H, d, $J =$

2.0Hz), 7.84(1H, dt, $J = 7.5, 1.5\text{Hz}$), 7.98(1H, t, $J = 1.5\text{Hz}$)。

[2440] 实施例 224

[2441] [式 514]

[2442]

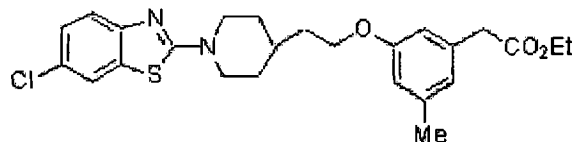


[2443] 收率: 45%, $^1\text{H-NMR}$ (DMSO-d_6): δ 1.12-1.30 (2H, m), 1.50-1.61 (2H, m), 1.65-1.86 (3H, m), 2.96-3.21 (4H, m), 3.61 (3H, s), 3.67 (2H, s), 3.94-4.07 (2H, m), 7.06 (1H, d, $J = 7.0\text{Hz}$), 7.18-7.32 (4H, m), 7.39 (1H, d, $J = 8.5\text{Hz}$), 7.88 (1H, d, $J = 2.0\text{Hz}$)。

[2444] 实施例 225

[2445] [式 515]

[2446]



[2447] 收率: 50%, $^1\text{H-NMR}$ (CDCl_3): δ 1.26 (3H, t, $J = 7.2\text{Hz}$), 1.39-1.46 (2H, m), 1.73-1.80 (1H, m), 1.89 (3H, d, $J = 12.3\text{Hz}$), 2.31 (3H, s), 3.54 (3H, s), 4.01 (2H, t, $J = 6.0\text{Hz}$), 4.05-4.15 (2H, m), 4.15 (2H, q, $J = 7.2\text{Hz}$), 4.10-4.12 (2H, m), 6.58-6.67 (2H, m), 6.69 (1H, m), 7.22 (1H, dd, $J = 8.7, 2.1\text{Hz}$), 7.42 (1H, d, $J = 8.7\text{Hz}$), 7.54 (1H, d, $J = 2.1\text{Hz}$)。

[2448] 实施例 226

[2449] [式 516]

[2450]

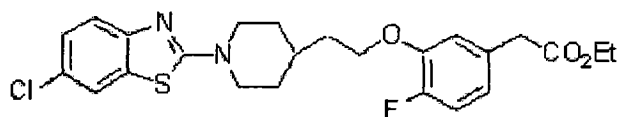


[2451] 收率: 53%, $^1\text{H-NMR}$ (CDCl_3): δ 1.26 (3H, t, $J = 7.0\text{Hz}$), 1.31-1.51 (2H, m), 1.76-1.98 (5H, m), 3.07-3.23 (2H, m), 3.57 (2H, s), 4.04-4.20 (6H, m), 6.81 (1H, dd, $J = 7.5, 1.5\text{Hz}$), 6.87 (1H, d, $J = 1.5\text{Hz}$), 7.19-7.34 (2H, m), 7.42 (1H, d, $J = 8.5\text{Hz}$), 7.53 (1H, d, $J = 2.0\text{Hz}$)。

[2452] 实施例 227

[2453] [式 517]

[2454]



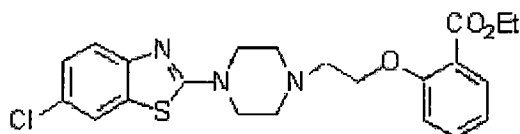
[2455] 收率: 93%, $^1\text{H-NMR}$ (CDCl_3): δ 1.26 (3H, t, $J = 7\text{Hz}$), 1.30-1.50 (1H, m), 1.75-2.00 (4H, m), 3.05-3.23 (2H, m), 3.55 (2H, s), 4.05-4.15 (6H, m), 4.18 (2H, q, $J = 7\text{Hz}$), 6.75-6.85 (1H, m), 6.91 (1H, dd, $J = 8, 2\text{Hz}$), 6.92 (1H, dd, $J = 11, 2\text{Hz}$), 7.22 (1H, dd,

$J = 8.5, 2\text{Hz}$), $7.42 (1\text{H}, \text{d}, J = 8.5\text{Hz})$, $7.54 (1\text{H}, \text{d}, J = 2\text{Hz})$ 。

[2456] 实施例 228

[2457] [式 518]

[2458]

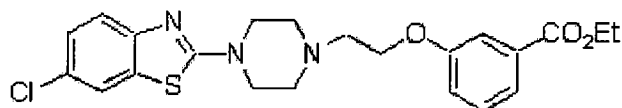


[2459] 收率: 67%, $^1\text{H-NMR}(\text{CDCl}_3)$; δ 1.39 (3H, t, $J = 7.0\text{Hz}$), 2.77 (4H, t, $J = 5.0\text{Hz}$), 2.93 (2H, t, $J = 5.5\text{Hz}$), 3.65 (4H, t, $J = 5.0\text{Hz}$), 4.21 (2H, t, $J = 5.5\text{Hz}$), 4.35 (2H, q, $J = 7.0\text{Hz}$), 6.98 (1H, d, $J = 7.5\text{Hz}$), 7.00 (1H, t, $J = 7.5\text{Hz}$), 7.24 (1H, dd, $J = 8.5, 2.0\text{Hz}$), 7.44 (1H, d, $J = 8.5\text{Hz}$), 7.46 (1H, t, $J = 7.5\text{Hz}$), 7.56 (1H, d, $J = 2.0\text{Hz}$), 7.79 (1H, dd, $J = 7.5, 2.0\text{Hz}$)。

[2460] 实施例 229

[2461] [式 519]

[2462]

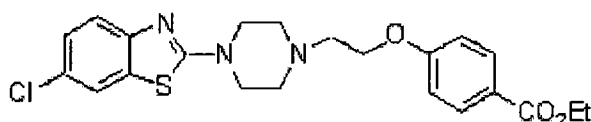


[2463] 收率: 76%, $^1\text{H-NMR}(\text{CDCl}_3)$; δ 1.40 (3H, t, $J = 7.0\text{Hz}$), 2.73 (4H, t, $J = 5.0\text{Hz}$), 2.90 (2H, t, $J = 5.5\text{Hz}$), 3.67 (4H, t, $J = 5.0\text{Hz}$), 4.19 (2H, t, $J = 5.5\text{Hz}$), 4.38 (2H, q, $J = 7.0\text{Hz}$), 7.11 (1H, dd, $J = 8.0, 2.5\text{Hz}$), 7.24 (1H, dd, $J = 8.5, 2.0\text{Hz}$), 7.35 (1H, t, $J = 8.0\text{Hz}$), 7.44 (1H, d, $J = 8.5\text{Hz}$), 7.56 (1H, d, $J = 2.0\text{Hz}$), 7.58 (1H, s), 7.66 (1H, dd, $J = 8.0, 2.5\text{Hz}$)。

[2464] 实施例 230

[2465] [式 520]

[2466]

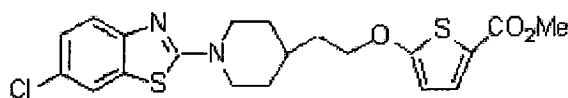


[2467] 收率: 82%, $^1\text{H-NMR}(\text{CDCl}_3)$; δ 1.38 (3H, t, $J = 7.0\text{Hz}$), 2.73 (4H, t, $J = 5.0\text{Hz}$), 2.90 (2H, t, $J = 5.5\text{Hz}$), 3.66 (4H, t, $J = 5.0\text{Hz}$), 4.19 (2H, t, $J = 5.5\text{Hz}$), 4.35 (2H, q, $J = 7.0\text{Hz}$), 6.93 (2H, d, $J = 9.0\text{Hz}$), 7.24 (1H, dd, $J = 8.5, 2.0\text{Hz}$), 7.43 (1H, d, $J = 8.5\text{Hz}$), 7.56 (1H, d, $J = 2.0\text{Hz}$), 8.00 (2H, d, $J = 9.0\text{Hz}$)。

[2468] 实施例 231

[2469] [式 521]

[2470]



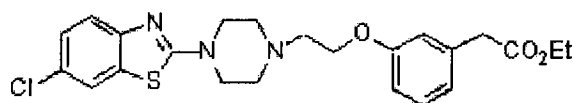
[2471] 收率: 18%, $^1\text{H-NMR}(\text{CDCl}_3)$; δ 1.27-1.48 (2H, m), 1.64-1.95 (5H, m), 3.05-3.19 (2H, m), 3.84 (3H, s), 4.06-4.19 (4H, m), 6.22 (1H, d, $J = 4.0\text{Hz}$), 7.22 (1H, dd, J

= 8.5, 2.0Hz), 7.42 (1H, d, J = 8.5Hz), 7.51-7.27 (2H, m)。

[2472] 实施例 232

[2473] [式 522]

[2474]

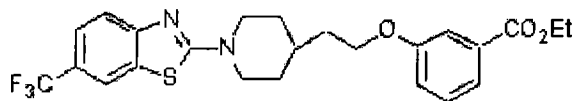


[2475] 收率:46%, $^1\text{H-NMR}$ (CDCl_3) ; δ 1.26 (3H, t, J = 7.0Hz), 2.72 (4H, t, J = 5.0Hz), 2.87 (2H, t, J = 5.5Hz), 3.58 (2H, s), 3.66 (4H, t, J = 5.0Hz), 4.14 (2H, t, J = 5.5Hz), 4.15 (2H, q, J = 7.0Hz), 6.79-6.91 (3H, m), 7.23 (1H, d, J = 8.0Hz), 7.24 (1H, dd, J = 8.5, 2.0Hz), 7.44 (1H, d, J = 8.5Hz), 7.56 (1H, d, J = 2.0Hz)。

[2476] 实施例 233

[2477] [式 523]

[2478]

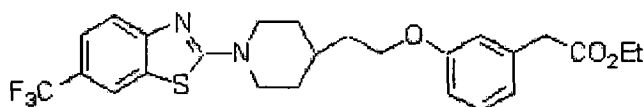


[2479] 收率:81%, $^1\text{H-NMR}$ (CDCl_3) ; δ 1.32-1.51 (5H, m), 1.74-1.99 (5H, m), 3.11-3.27 (2H, m), 4.04-4.24 (4H, m), 4.38 (2H, q, J = 7.0Hz), 7.06-7.13 (1H, m), 7.35 (1H, t, J = 8.0Hz), 7.48-7.57 (3H, m), 7.65 (1H, d, J = 8.0Hz), 7.84 (1H, s)。

[2480] 实施例 234

[2481] [式 524]

[2482]

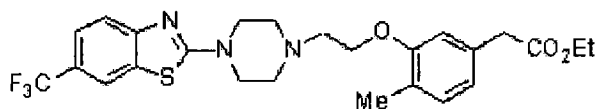


[2483] 收率:58%, $^1\text{H-NMR}$ (CDCl_3) ; δ 1.26 (3H, t, J = 7.0Hz), 1.31-1.50 (2H, m), 1.72-1.98 (5H, m), 3.12-3.25 (2H, m), 3.59 (2H, s), 4.04 (2H, t, J = 6.0Hz), 4.10-4.24 (4H, m), 6.77-6.91 (3H, m), 7.23 (1H, t, J = 7.5Hz), 7.48-7.59 (2H, m), 7.84 (1H, s)。

[2484] 实施例 235

[2485] [式 525]

[2486]



[2487] 收率:51%, $^1\text{H-NMR}$ (DMSO-d_6) : δ 1.26 (3H, t, J = 7Hz), 2.20 (3H, s), 2.77 (4H, t, J = 5Hz), 2.92 (2H, t, J = 5.5Hz), 3.56 (2H, s), 3.70 (4H, t, J = 5Hz), 4.13 (2H, t, J = 5.5Hz), 4.16 (2H, q, J = 7Hz), 6.75-6.80 (2H, m), 7.08 (1H, d, J = 7Hz), 7.52 (1H, dd, J = 8.5, 1.5Hz), 7.55 (1H, d, J = 8.5Hz), 7.85 (1H, d, J = 0.5Hz)。

[2488] 实施例 236

[2489] [式 526]

[2490]



[2491] 收率:49 %, $^1\text{H-NMR}$ (CDCl_3) ; δ 1.26 (3H, t, $J = 7.0\text{Hz}$), 1.32-1.51 (2H, m), 1.78-2.00 (5H, m), 3.12-3.27 (2H, m), 3.57 (2H, s), 4.05-4.24 (6H, m), 6.81 (1H, dd, $J = 8.0, 2.0\text{Hz}$), 6.87 (1H, d, $J = 2.0\text{Hz}$), 7.30 (1H, d, $J = 8.0\text{Hz}$), 7.47-7.59 (2H, m), 7.83 (1H, s)。

[2492] 实施例 237

[2493] [式 527]

[2494]

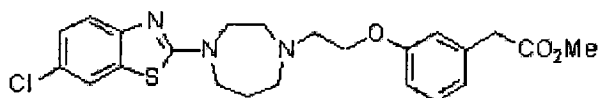


[2495] 收率:39 %, $^1\text{H-NMR}$ (CDCl_3) ; δ 1.27 (3H, t, $J = 7.0\text{Hz}$), 1.30-1.48 (2H, m), 1.72-1.94 (5H, m), 3.08-3.21 (2H, m), 3.72 (2H, s), 3.97-4.04 (2H, m), 4.07-4.19 (2H, m), 4.19 (2H, q, $J = 7.0\text{Hz}$), 6.76 (1H, dd, $J = 8.5, 3.0\text{Hz}$), 6.84 (1H, d, $J = 3.0\text{Hz}$), 7.23 (1H, dd, $J = 8.5, 2.0\text{Hz}$), 7.27 (1H, d, $J = 8.5\text{Hz}$), 7.42 (1H, d, $J = 8.5\text{Hz}$), 7.54 (1H, d, $J = 2.0\text{Hz}$)。

[2496] 实施例 238

[2497] [式 528]

[2498]

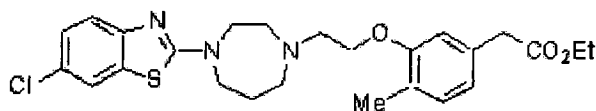


[2499] 收率:69 %, $^1\text{H-NMR}$ (CDCl_3) ; δ 2.00-2.08 (2H, m), 2.84 (2H, t, $J = 8.4\text{Hz}$), 2.96-3.02 (4H, m), 3.59 (2H, s), 3.69 (3H, s), 3.73 (2H, t, $J = 6.0\text{Hz}$), 3.79-3.84 (2H, m), 4.07 (2H, t, $J = 5.4\text{Hz}$), 6.79-6.88 (3H, m), 7.20-7.27 (2H, m), 7.43 (1H, d, $J = 8.4\text{Hz}$), 7.55 (1H, d, $J = 2.1\text{Hz}$)。

[2500] 实施例 239

[2501] [式 529]

[2502]

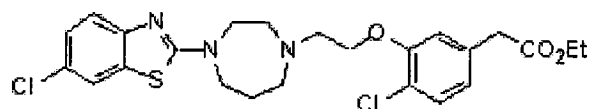


[2503] 收率:49 %, $^1\text{H-NMR}$ (CDCl_3) ; δ 1.25 (3H, t, $J = 7\text{Hz}$), 1.98-2.08 (2H, m), 2.18 (3H, s), 2.82-2.90 (2H, m), 2.98-3.05 (4H, m), 3.55 (2H, s), 3.73 (2H, t, $J = 5.5\text{Hz}$), 3.75-3.85 (2H, m), 4.05-4.10 (2H, m), 4.15 (2H, q, $J = 7\text{Hz}$), 6.74 (1H, s), 6.76 (1H, d, $J = 7.5\text{Hz}$), 7.07 (1H, d, $J = 7.5\text{Hz}$), 7.22 (1H, dd, $J = 8.5, 2\text{Hz}$), 7.43 (1H, d, $J = 8.5\text{Hz}$), 7.54 (1H, d, $J = 2\text{Hz}$)。

[2504] 实施例 240

[2505] [式 530]

[2506]

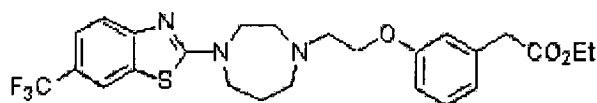


[2507] 收率:45%, $^1\text{H-NMR}$ (CDCl_3); δ 1.25 (3H, t, $J = 7\text{Hz}$), 1.95-2.10 (2H, m), 2.88 (2H, t, $J = 5.5\text{Hz}$), 3.00-3.10 (4H, m), 3.55 (2H, s), 3.73 (2H, t, $J = 5.5\text{Hz}$), 3.75-3.85 (2H, m), 4.10-4.15 (2H, m), 4.15 (2H, q, $J = 7\text{Hz}$), 6.80 (1H, dd, $J = 8, 2\text{Hz}$), 6.85 (1H, d, $J = 2\text{Hz}$), 7.22 (1H, dd, $J = 8.5, 2.5\text{Hz}$), 7.29 (1H, d, $J = 8\text{Hz}$), 7.42 (1H, d, $J = 8.5\text{Hz}$), 7.54 (1H, d, $J = 2.5\text{Hz}$)。

[2508] 实施例 241

[2509] [式 531]

[2510]

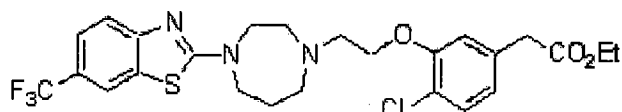


[2511] 收率:74%, $^1\text{H-NMR}$ (CDCl_3); δ 1.25 (3H, t, $J = 7.0\text{Hz}$), 1.20-2.11 (2H, m), 2.79-2.90 (2H, m), 2.93-3.06 (4H, m), 3.57 (2H, s), 3.69-3.90 (4H, m), 4.04-4.12 (2H, m), 4.15 (2H, q, $J = 7.0\text{Hz}$), 6.76-6.90 (3H, m), 7.22 (1H, t, $J = 8.0\text{Hz}$), 7.48-7.59 (2H, m), 7.84 (1H, s)。

[2512] 实施例 242

[2513] [式 532]

[2514]

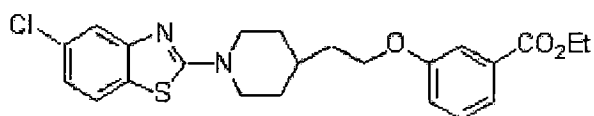


[2515] 收率:42%, $^1\text{H-NMR}$ (CDCl_3); δ 1.25 (3H, t, $J = 7.0\text{Hz}$), 1.99-2.09 (2H, m), 2.86-2.94 (2H, m), 3.02-3.12 (4H, m), 3.55 (2H, s), 3.69-3.90 (4H, m), 4.10-4.20 (4H, m), 6.81 (1H, dd, $J = 8.0, 2.0\text{Hz}$), 6.87 (1H, d, $J = 2.0\text{Hz}$), 7.29 (1H, d, $J = 8.0\text{Hz}$), 7.48-7.59 (2H, m), 7.84 (1H, s)。

[2516] 实施例 243

[2517] [式 533]

[2518]

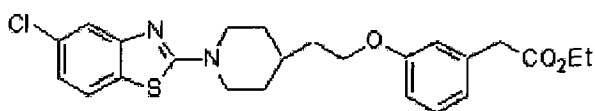


[2519] 收率:51%, $^1\text{H-NMR}$ (CDCl_3); δ 1.31-1.49 (5H, m), 1.75-1.96 (5H, m), 3.09-3.22 (2H, m), 4.05-4.19 (4H, m), 4.38 (2H, q, $J = 7.0\text{Hz}$), 7.02 (1H, dd, $J = 8.0, 2.0\text{Hz}$), 7.09 (1H, ddd, $J = 8.0, 2.5, 1.0\text{Hz}$), 7.35 (1H, t, $J = 8.0\text{Hz}$), 7.47 (1H, d, $J = 8.0\text{Hz}$), 7.50 (1H, d, $J = 2.0\text{Hz}$), 7.56 (1H, dd, $J = 2.5, 1.5\text{Hz}$), 7.65 (1H, dt, $J = 8.0, 1.5, 1.0\text{Hz}$)。

[2520] 实施例 244

[2521] [式 534]

[2522]

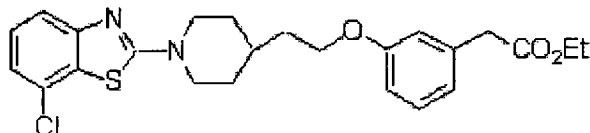


[2523] 收率:44 %, $^1\text{H-NMR}(\text{CDCl}_3)$; δ 1.26 (3H, t, $J = 6.5\text{Hz}$), 1.30-1.48 (2H, m), 1.72-1.95 (5H, m), 3.08-3.21 (2H, m), 3.58 (2H, s), 4.03 (2H, t, $J = 6.0\text{Hz}$), 4.08-4.21 (2H, m), 4.15 (2H, q, $J = 6.5\text{Hz}$), 6.76-6.90 (3H, m), 7.02 (1H, dd, $J = 8.5, 2.0\text{Hz}$), 7.22 (1H, d, $J = 7.5\text{Hz}$), 7.47 (1H, d, $J = 8.5\text{Hz}$), 7.50 (1H, d, $J = 2.0\text{Hz}$)。

[2524] 实施例 245

[2525] [式 535]

[2526]



[2527] 收率:57 %, $^1\text{H-NMR}(\text{CDCl}_3)$; δ 1.26 (3H, t, $J = 7.0\text{Hz}$), 1.31-1.48 (2H, m), 1.71-1.96 (5H, m), 3.09-3.22 (2H, m), 3.58 (2H, s), 4.03 (2H, t, $J = 6.0\text{Hz}$), 4.09-4.21 (4H, m), 6.77-6.91 (3H, m), 7.03 (1H, dd, $J = 8.0, 1.0\text{Hz}$), 7.17-7.28 (2H, m), 7.40 (1H, dd, $J = 8.0, 1.0\text{Hz}$)。

[2528] 实施例 246

[2529] [式 536]

[2530]



[2531] 收率:81 %, $^1\text{H-NMR}(\text{CDCl}_3)$; δ 1.32-1.50 (5H, m), 1.75-1.95 (5H, m), 3.09-3.21 (2H, m), 4.05-4.18 (4H, m), 4.38 (2H, q, $J = 7.0\text{Hz}$), 7.06-7.12 (1H, m), 7.32-7.39 (3H, m), 7.54-7.58 (1H, m), 7.62-7.67 (1H, m), 7.67-7.69 (1H, m)。

[2532] 实施例 247

[2533] [式 537]

[2534]



[2535] 收率:44 %, $^1\text{H-NMR}(\text{CDCl}_3)$; δ 1.26 (3H, t, $J = 7.0\text{Hz}$), 1.31-1.48 (2H, m), 1.73-1.96 (5H, m), 3.08-3.20 (2H, m), 3.58 (2H, s), 4.00-4.18 (4H, m), 4.16 (2H, q, $J = 7.0\text{Hz}$), 6.78-6.90 (3H, m), 7.20-7.28 (1H, m), 7.36 (2H, m), 7.69 (1H, m)。

[2536] 实施例 248

[2537] [式 538]

[2538]



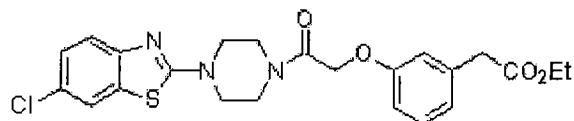
[2539] 收率:48 %, $^1\text{H-NMR}(\text{CDCl}_3)$; δ 1.26 (3H, t, $J = 7.0\text{Hz}$), 1.30-1.49 (2H, m),

1.72-1.95 (5H, m), 2.39 (3H, s), 3.06-3.19 (2H, m), 3.58 (2H, s), 3.98-4.21 (6H, m), 6.77-6.91 (3H, m), 7.06-7.12 (1H, m), 7.23 (1H, t, $J = 7.5\text{Hz}$), 7.37-7.47 (2H, m)。

[2540] 实施例 249

[2541] [式 539]

[2542]

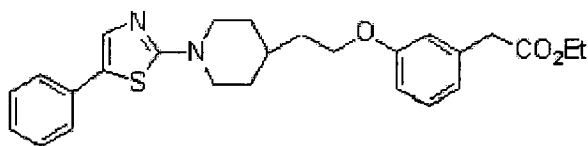


[2543] 收率:54%, $^1\text{H-NMR}(\text{CDCl}_3)$; δ 1.25 (3H, t, $J = 7.0\text{Hz}$), 3.56-3.82 (10H, m), 4.14 (2H, q, $J = 7.0\text{Hz}$), 4.74 (2H, s), 6.83-6.96 (3H, m), 7.22-7.29 (2H, m), 7.45 (1H, d, $J = 8.5\text{Hz}$), 7.58 (1H, d, $J = 2.0\text{Hz}$)。

[2544] 实施例 250

[2545] [式 540]

[2546]

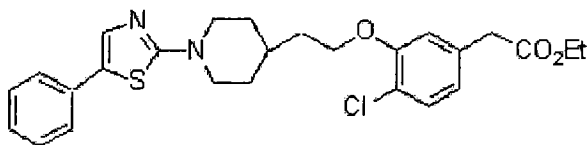


[2547] 收率:49%, $^1\text{H-NMR}(\text{CDCl}_3)$; δ 1.26 (3H, t, $J = 7.0\text{Hz}$), 1.31-1.50 (2H, m), 1.73-1.93 (5H, m), 2.99-3.12 (2H, m), 3.58 (2H, s), 3.98-4.09 (4H, m), 4.15 (2H, q, $J = 7.0\text{Hz}$), 6.78-6.90 (3H, m), 7.16-7.47 (7H, m)。

[2548] 实施例 251

[2549] [式 541]

[2550]

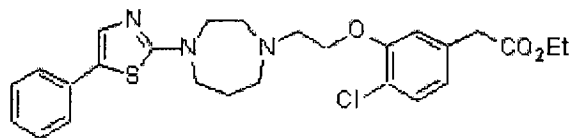


[2551] 收率:54%, $^1\text{H-NMR}(\text{CDCl}_3)$; δ 1.26 (3H, t, $J = 7.0\text{Hz}$), 1.35-1.52 (2H, m), 1.78-1.97 (5H, m), 3.01-3.14 (2H, m), 3.58 (2H, s), 3.99-4.21 (6H, m), 6.81 (1H, dd, $J = 8.0, 2.0\text{Hz}$), 6.87 (1H, d, $J = 2.0\text{Hz}$), 7.16-7.24 (1H, m), 7.27-7.37 (3H, m), 7.38-7.47 (3H, m)。

[2552] 实施例 252

[2553] [式 542]

[2554]



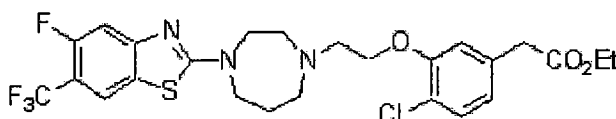
[2555] 收率:58%, $^1\text{H-NMR}(\text{DMSO-d}_6)$; δ 1.18 (3H, t, $J = 7.0\text{Hz}$), 1.83-1.95 (2H, m), 2.74-2.84 (2H, m), 2.89-3.01 (4H, m), 3.56-3.72 (6H, m), 4.08 (2H, q, $J = 7.0\text{Hz}$), 4.09-4.17 (2H, m), 6.84 (1H, dd, $J = 8.0, 1.5\text{Hz}$), 7.09 (1H, d, $J = 1.5\text{Hz}$), 7.18 (1H, t, $J =$

7.5Hz), 7.29–7.38 (3H, m), 7.44 (2H, d, $J = 7.5\text{Hz}$), 7.57 (1H, s) .

[2556] 实施例 253

[2557] [式 543]

[2558]



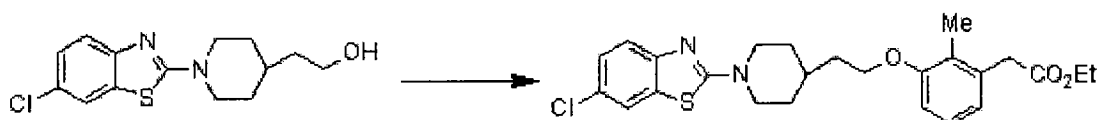
[2559] 收 率 :31 % , $^1\text{H-NMR}$ (CDCl_3) : δ 1.24 (3H, t, $J = 7.0\text{Hz}$) , 1.95–2.08 (2H, m) , 2.88 (2H, t, $J = 5.5\text{Hz}$) , 2.98–3.12 (4H, m) , 3.55 (2H, s) , 3.60–3.90 (4H, m) , 4.06–4.19 (4H, m) , 6.79 (1H, dd, $J = 8.0, 1.5\text{Hz}$) , 6.86 (1H, d, $J = 1.5\text{Hz}$) , 7.25 (1H, d, $J = 12.0\text{Hz}$) , 7.27 (1H, d, $J = 8.0\text{Hz}$) , 7.72 (1H, d, $J = 7.0\text{Hz}$) 。

[2560] 实施例 254

[2561] 3-{2-[(6-氯苯并噻唑-2-基) 哌啶-4-基] 乙氧基}-2-甲基苯基乙酸乙酯的制备

[2562] [式 544]

[2563]



[2564] 在氩气和冰冷却下向 6-氯-2-[4-(2-羟基乙基)哌啶-1-基]苯并噻唑 (0.17g; 0.562mmol), W02004/0225 的参考例 67 所述的 [3-羟基-2-甲基]苯基乙酸乙酯 (510.11g; 0.552mmol), 1,1-偶氮二羧基二哌啶 (0.21g; 0.844mmol) 和无水 THF (6ml) 的混合物中滴加三丁基膦 (0.21ml; 0.841mmol)。在相同的温度搅拌反应溶液 2.5 小时之后, 向其中加入水和乙酸乙酯。分离有机层, 用盐水洗涤, 用无水硫酸钠干燥, 并且减压蒸发。残余物通过硅胶柱色谱法纯化 (己烷: 乙酸乙酯 = 10 : 1 → 5 : 1), 得到 3-{2-[(6-氯苯并噻唑-2-基) 哌啶-4-基]乙氧基}-2-甲基苯基乙酸乙酯, 为无色油状物 (0.16g; 59%)。

[2565] $^1\text{H-NMR}(\text{CDCl}_3)$: δ 1.26 (3H, t, $J = 7.2\text{Hz}$), 1.38–1.47 (2H, m), 1.78–1.93 (5H, m), 2.18 (3H, s), 3.14 (2H, td, $J = 12.6, 2.4\text{Hz}$), 3.64 (2H, s), 4.02 (2H, t, $J = 5.7\text{Hz}$), 4.10–4.16 (2H, m), 4.15 (2H, t, $J = 7.2\text{Hz}$), 6.80 (2H, q, $J = 7.8\text{Hz}$), 7.11 (1H, t, $J = 7.8\text{Hz}$), 7.23 (1H, dd, $J = 8.4, 1.8\text{Hz}$), 7.42 (1H, d, $J = 8.4\text{Hz}$), 7.54 (1H, d, $J = 1.8\text{Hz}$)。

[2566] 通过与实施例 254 相似的方法得到实施例 255 和 256 的化合物。

[2567] 实施例 255

[2568] [式 545]

[2569]

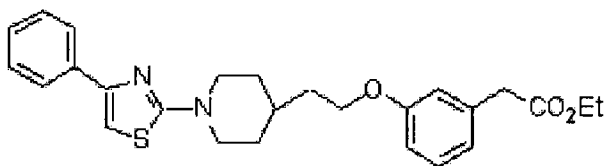


[2570] 收 率 :39 % , $^1\text{H-NMR}$ (CDCl_3) ; δ 1.26 (3H, t, $J = 7.0\text{Hz}$) , 1.28-1.50 (2H, m) , 1.70-1.98 (5H, m) , 3.04-3.21 (2H, m) , 3.58 (2H, s) , 3.97-4.22 (4H, m) , 4.15 (2H, q, $J = 7.0\text{Hz}$) , 6.75-6.92 (3H, m) , 7.00 (1H, td, $J = 9.0, 3.0\text{Hz}$) , 7.23 (1H, t, $J = 8.0\text{Hz}$) , 7.29 (1H, dd, $J = 9.0, 3.0\text{Hz}$) , 7.44 (1H, dd, $J = 9.0, 5.0\text{Hz}$) 。

[2571] 实施例 256

[2572] [式 546]

[2573]



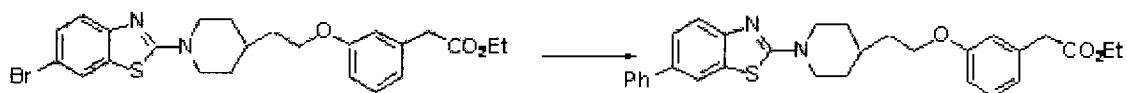
[2574] 收率:22%, $^1\text{H-NMR}$ (CDCl_3): δ 1.24 (3H, t, $J = 7.0\text{Hz}$), 1.26-1.50 (2H, m), 1.68-1.92 (5H, m), 2.94-3.09 (2H, m), 3.58 (2H, m), 3.94-4.13 (4H, m), 4.14 (2H, q, $J = 7.0\text{Hz}$), 6.72 (1H, s), 6.75-6.93 (3H, m), 7.24 (2H, m), 7.35 (2H, t, $J = 7.0\text{Hz}$), 7.83 (2H, d, $J = 7.0\text{Hz}$)。

[2575] 实施例 257

[2576] 3-{2-[(6-苯基苯并噻唑-2-基)哌啶-4-基]乙氧基}苯基乙酸乙酯的制备

[2577] [式 547]

[2578]



[2579] 将 3-{2-[(6-溴苯并噻唑-2-基)哌啶-4-基]乙氧基}苯基乙酸乙酯 (0.30g; 0.596mmol), 苯基硼酸 (0.09g; 0.775mmol), 四(三苯膦)合钯(0) (0.03g; 0.03mmol), 碳酸铯 (0.25g; 0.775mmol) 和二噁烷 (3ml) 的混合物在氩气下回流 3 小时。将反应溶液冷却到室温并且减压浓缩。残余物通过硅胶柱色谱法纯化 (己烷:乙酸乙酯 = 3:1), 得到 3-{2-[(6-苯基苯并噻唑-2-基)哌啶-4-基]乙氧基}苯基乙酸乙酯, 为无色晶体 (0.08g; 26%)。

[2580] $^1\text{H-NMR}$ (CDCl_3): δ 1.25 (3H, t, $J = 7.0\text{Hz}$), 1.28-1.48 (2H, m), 1.66-1.96 (5H, m), 3.04-3.21 (2H, m), 3.57 (2H, s), 3.94-4.07 (2H, m), 4.08-4.25 (4H, m), 6.73-6.92 (3H, m), 7.17-7.34 (2H, m), 7.36-7.47 (2H, m), 7.48-7.64 (4H, m), 7.79 (1H, d, $J = 2.0\text{Hz}$)。

[2581] 实施例 258

[2582] 3-{[4-(6-氯苯并噻唑-2-基)哌嗪-1-基]甲基}-5-甲基苯酚的制备

[2583] [式 548]

[2584]



[2585] 将乙酸 3-{[4-(6-氯苯并噻唑-2-基)哌嗪-1-基]甲基}-5-甲基苯基酯 (1.97g; 4.88mmol), 2N-氢氧化钠水溶液 (10ml) 和甲醇 (20ml) 的混合物在 40℃ 搅拌 1 小时。减压蒸发溶剂。向残余物中加入水和 2N-盐酸直到为中性。向其中加入乙酸乙酯并用乙酸乙酯萃取。有机层用盐水洗涤, 用无水硫酸钠干燥, 并且减压蒸发。残余物通过硅胶柱色谱法纯化 (乙酸乙酯), 得到 3-{[4-(6-氯苯并噻唑-2-基)哌嗪-1-基]甲基}-5-甲基苯酚, 为无色的无定形固体 (1.83g; 100%)。

[2586] $^1\text{H-NMR}$ (CDCl_3): δ 2.29 (3H, s), 2.57 (4H, t, $J = 5\text{Hz}$), 3.47 (2H, s), 3.67 (4H, t,

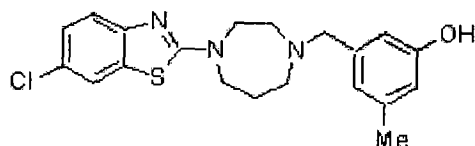
$J = 5\text{Hz}$), 6.59 (1H, s), 6.67 (2H, s), 7.23 (1H, dd, $J = 8.5, 2\text{Hz}$), 7.45 (1H, d, $J = 8.5\text{Hz}$), 7.55 (1H, d, $J = 2\text{Hz}$)。

[2587] 通过与实施例 258 相似的方法得到实施例 259 到 286 的化合物。

[2588] 实施例 259

[2589] [式 549]

[2590]

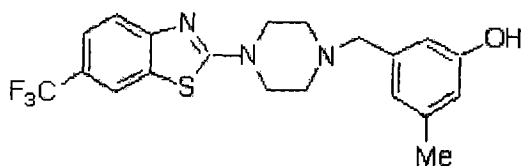


[2591] 收率:85%, $^1\text{H-NMR}(\text{CDCl}_3)$; δ 1.74 (1H, brs), 1.96-2.05 (2H, m), 2.26 (3H, s), 2.67 (2H, t, $J = 5.1\text{Hz}$), 2.75-2.79 (2H, m), 3.52 (2H, s), 3.68-3.74 (4H, m), 6.55 (1H, s), 6.61 (1H, s), 6.65 (1H, s), 7.22 (1H, dd, $J = 8.7, 2.1\text{Hz}$), 7.43 (1H, d, $J = 8.4\text{Hz}$), 7.54 (1H, d, $J = 2.1\text{Hz}$)。

[2592] 实施例 260

[2593] [式 550]

[2594]

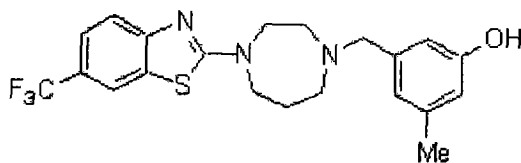


[2595] 收率:100%, $^1\text{H-NMR}(\text{CDCl}_3)$; δ 2.29 (3H, s), 2.61 (4H, t, $J = 5\text{Hz}$), 3.50 (2H, s), 3.71 (4H, t, $J = 5\text{Hz}$), 6.60 (1H, s), 6.69 (2H, s), 7.52 (1H, d, $J = 7.5\text{Hz}$), 7.58 (1H, d, $J = 7.5\text{Hz}$), 7.85 (1H, s)。

[2596] 实施例 261

[2597] [式 551]

[2598]

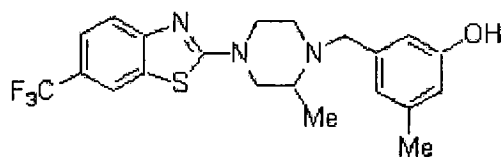


[2599] 收率:71%, $^1\text{H-NMR}(\text{CDCl}_3)$; δ 2.00-2.10 (2H, m), 2.28 (3H, s), 2.65-2.75 (2H, m), 2.80-2.90 (2H, m), 3.57 (2H, s), 3.70-3.90 (4H, m), 6.56 (1H, s), 6.65-6.70 (2H, m), 7.45-7.60 (2H, m), 7.85 (1H, s)。

[2600] 实施例 262

[2601] [式 552]

[2602]

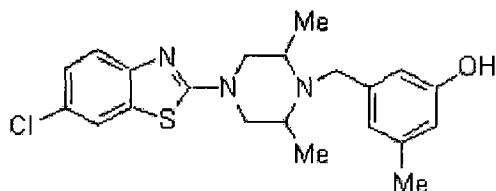


[2603] 收率:99 %, $^1\text{H-NMR}(\text{CDCl}_3)$: δ 1.22(3H, d, $J = 6\text{Hz}$), 1.64(1H, brs), 2.25-2.29(1H, m), 2.30(3H, s), 2.60-2.70(1H, m), 2.80-2.83(1H, m), 3.13(1H, d, $J = 13.5\text{Hz}$), 3.17-3.25(1H, m), 3.40-3.50(1H, m), 3.73-3.83(1H, m), 3.85-3.95(1H, m), 3.98(1H, d, $J = 13.5\text{Hz}$), 6.57(1H, s), 6.66(1H, s), 6.69(1H, s), 7.52(1H, d, $J = 8.5\text{Hz}$), 7.57(1H, d, $J = 8.5\text{Hz}$), 7.84(1H, s)。

[2604] 实施例 263

[2605] [式 553]

[2606]

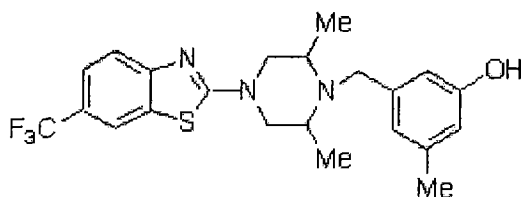


[2607] 收率: 定量收率, $^1\text{H-NMR}(\text{CDCl}_3)$: δ 1.11(6H, d, $J = 6\text{Hz}$), 2.28(3H, s), 2.70-2.85(2H, m), 2.95-3.10(2H, m), 3.70-3.90(4H, m), 6.53(1H, s), 6.68(1H, s), 6.72(1H, s), 7.23(1H, dd, $J = 8.5, 2\text{Hz}$), 7.43(1H, d, $J = 8.5\text{Hz}$), 7.55(1H, d, $J = 2\text{Hz}$)。

[2608] 实施例 264

[2609] [式 554]

[2610]

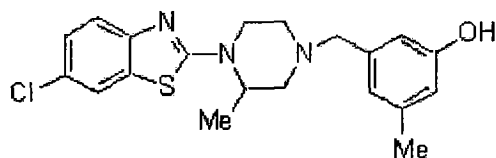


[2611] 收率: 定量收率, $^1\text{H-NMR}(\text{CDCl}_3)$: δ 1.10(6H, d, $J = 6\text{Hz}$), 2.28(3H, s), 2.70-2.85(2H, m), 3.00-3.15(2H, m), 3.75(2H, s), 3.82-3.94(2H, m), 5.53(1H, brs), 6.52(1H, s), 6.69(1H, s), 6.72(1H, s), 7.51(1H, d, $J = 8.5\text{Hz}$), 7.56(1H, d, $J = 8.5\text{Hz}$), 7.84(1H, s)。

[2612] 实施例 265

[2613] [式 555]

[2614]

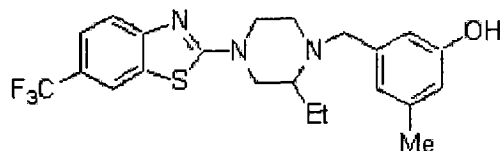


[2615] 收率: 定量收率, $^1\text{H-NMR}(\text{CDCl}_3)$: δ 1.42(3H, d, $J = 7\text{Hz}$), 2.20-2.28(1H, m), 2.28(3H, s), 2.30-2.45(1H, m), 2.70-2.85(1H, m), 2.90-3.00(1H, m), 3.43(1H, d, $J = 13.5\text{Hz}$), 3.45-3.55(1H, m), 3.58(1H, d, $J = 13.5\text{Hz}$), 3.80-3.90(1H, m), 4.15-4.25(1H, m), 6.60(1H, s), 6.66(1H, s), 6.77(1H, s), 7.22(1H, dd, $J = 8.5, 2\text{Hz}$), 7.43(1H, d, $J = 8.5\text{Hz}$), 7.54(1H, d, $J = 2\text{Hz}$)。

[2616] 实施例 266

[2617] [式 556]

[2618]

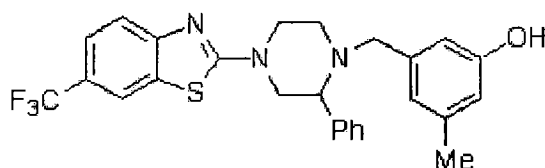


[2619] 收率:定量收率, $^1\text{H-NMR}$ (CDCl_3): δ 1.01 (3H, t, $J = 7.5\text{Hz}$), 1.55–1.78 (2H, m), 2.29 (3H, s), 2.30–2.40 (1H, m), 2.48–2.56 (1H, m), 2.79–2.83 (1H, m), 3.18 (1H, d, $J = 13.5\text{Hz}$), 3.37–3.56 (2H, m), 3.65–3.77 (1H, m), 3.82 (1H, dd, $J = 13, 3\text{Hz}$), 3.93 (1H, d, $J = 13.5\text{Hz}$), 6.57 (1H, s), 6.67 (1H, s), 6.70 (1H, s), 7.52 (1H, dd, $J = 8.5, 1.5\text{Hz}$), 7.57 (1H, d, $J = 8.5\text{Hz}$), 7.84 (1H, d, $J = 1.5\text{Hz}$)。

[2620] 实施例 267

[2621] [式 557]

[2622]

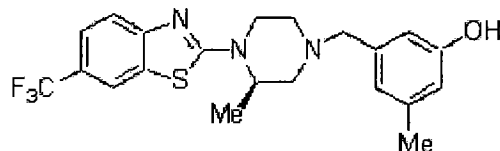


[2623] 收率:99%, $^1\text{H-NMR}$ (CDCl_3): δ 2.27 (3H, s), 2.27–2.35 (1H, m), 2.77 (1H, d, $J = 13.5\text{Hz}$), 3.02 (1H, d, $J = 11.5\text{Hz}$), 3.28–3.50 (3H, m), 3.75 (1H, d, $J = 13.5\text{Hz}$), 3.98 (1H, d, $J = 11\text{Hz}$), 4.10–4.18 (1H, m), 5.61 (1H, brs), 6.54 (1H, s), 6.61 (1H, s), 6.64 (1H, s), 7.30–7.43 (3H, m), 7.45–7.60 (4H, m), 7.86 (1H, s)。

[2624] 实施例 268

[2625] [式 558]

[2626]

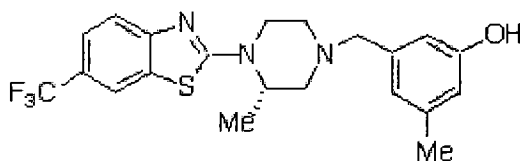


[2627] 收率:96%, $^1\text{H-NMR}$ (CDCl_3): δ 1.42 (3H, d, $J = 6.5\text{Hz}$), 2.18 (1H, td, $J = 12, 3.5\text{Hz}$), 2.29 (3H, s), 2.29–2.40 (1H, m), 2.74 (1H, d, $J = 11.5\text{Hz}$), 2.89 (1H, d, $J = 11.5\text{Hz}$), 3.39 (1H, d, $J = 13\text{Hz}$), 3.47 (1H, d, $J = 13\text{Hz}$), 3.55 (1H, td, $J = 12.5, 3.5\text{Hz}$), 3.90 (1H, d, $J = 13\text{Hz}$), 4.16–4.29 (1H, m), 6.58 (1H, s), 6.69 (1H, s), 6.70 (1H, s), 7.51 (1H, dd, $J = 8.5, 1.5\text{Hz}$), 7.57 (1H, d, $J = 8.5\text{Hz}$), 7.84 (1H, d, $J = 1.5\text{Hz}$)。

[2628] 实施例 269

[2629] [式 559]

[2630]



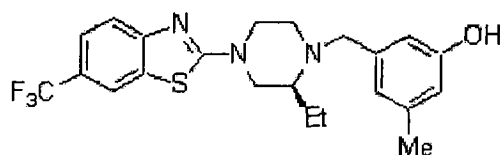
[2631] 收率:定量收率, $^1\text{H-NMR}$ (CDCl_3): δ 1.43 (3H, d, $J = 6.5\text{Hz}$), 2.14–2.41 (5H, m), 2.71–2.80 (1H, m), 2.86–2.92 (1H, m), 3.35–3.59 (3H, m), 3.85–3.97 (1H, m), 4.17–4.29 (1H,

m), 6.58 (1H, s), 6.69 (1H, s), 6.72 (1H, s), 7.48–7.60 (2H, m), 7.84 (1H, s)。

[2632] 实施例 270

[2633] [式 560]

[2634]

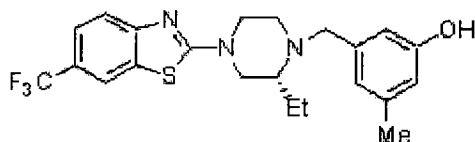


[2635] 收率:96%, $^1\text{H-NMR}$ (CDCl₃): δ 1.00 (3H, t, $J = 7.5\text{Hz}$), 1.55–1.75 (2H, m), 2.29 (3H, s), 2.29–2.38 (1H, m), 2.47–2.57 (1H, m), 2.78–2.88 (1H, m), 3.17 (1H, d, $J = 13.5\text{Hz}$), 3.37–3.55 (2H, m), 3.65–3.85 (2H, m), 3.93 (1H, d, $J = 13.5\text{Hz}$), 6.57 (1H, s), 6.67 (1H, s), 6.69 (1H, s), 7.52 (1H, d, $J = 8.5\text{Hz}$), 7.57 (1H, d, $J = 8.5\text{Hz}$), 7.84 (1H, s)。

[2636] 实施例 271

[2637] [式 561]

[2638]

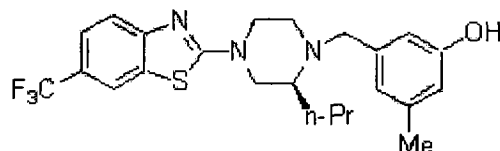


[2639] 收率:92%, $^1\text{H-NMR}$ (CDCl₃): δ 1.01 (3H, t, $J = 7.5\text{Hz}$), 1.57–1.79 (2H, m), 2.29 (3H, s), 2.29–2.40 (1H, m), 2.46–2.58 (1H, m), 2.77–2.89 (1H, m), 3.18 (1H, d, $J = 13\text{Hz}$), 3.32–3.58 (2H, m), 3.65–3.87 (2H, m), 3.93 (1H, d, $J = 13\text{Hz}$), 6.57 (1H, s), 6.67 (1H, s), 6.69 (1H, s), 7.52 (1H, d, $J = 8.5\text{Hz}$), 7.57 (1H, d, $J = 8.5\text{Hz}$), 7.84 (1H, s)。

[2640] 实施例 272

[2641] [式 562]

[2642]

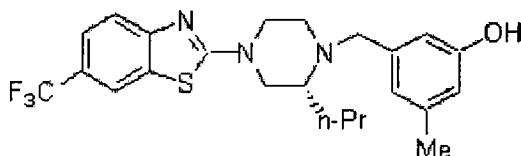


[2643] 收率:95%, $^1\text{H-NMR}$ (CDCl₃): δ 0.93 (3H, t, $J = 7.5\text{Hz}$), 1.30–1.70 (4H, m), 2.29 (3H, s), 2.29–2.39 (1H, m), 2.55–2.65 (1H, m), 2.79–2.88 (1H, m), 3.19 (1H, d, $J = 13.5\text{Hz}$), 3.41 (1H, dd, $J = 12.5, 8\text{Hz}$), 3.48–3.58 (1H, m), 3.65–3.75 (1H, m), 3.82 (1H, dd, $J = 12.5, 2.5\text{Hz}$), 3.92 (1H, d, $J = 13.5\text{Hz}$), 6.57 (1H, s), 6.68 (1H, s), 6.70 (1H, s), 7.51 (1H, dd, $J = 8.5, 1.5\text{Hz}$), 7.55 (1H, d, $J = 8.5\text{Hz}$), 7.84 (1H, d, $J = 1.5\text{Hz}$)。

[2644] 实施例 273

[2645] [式 563]

[2646]

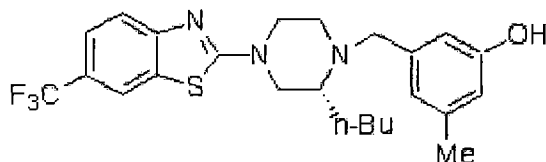


[2647] 收率:98%, $^1\text{H-NMR}(\text{CDCl}_3)$: δ 0.93 (3H, t, $J = 7.5\text{Hz}$), 1.30-1.41 (1H, m), 1.48-1.63 (3H, m), 2.29 (3H, s), 2.29-2.36 (1H, m), 2.56-2.62 (1H, m), 2.79-2.86 (1H, m), 3.19 (1H, d, $J = 13.5\text{Hz}$), 3.41 (1H, dd, $J = 7.8, 12.9\text{Hz}$), 3.50-3.57 (1H, m), 3.69-3.81 (2H, m), 3.92 (1H, d, $J = 13.5\text{Hz}$), 6.67 (1H, s), 6.68 (2H, s), 7.50-7.59 (2H, m), 7.84 (1H, s)。

[2648] 实施例 274

[2649] [式 564]

[2650]

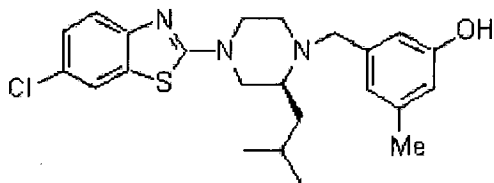


[2651] 收率:98%, $^1\text{H-NMR}(\text{CDCl}_3)$: δ 0.91 (3H, t, $J = 7\text{Hz}$), 1.26-1.75 (6H, m), 2.30 (3H, s), 2.30-2.40 (1H, m), 2.52-2.63 (1H, m), 2.77-2.87 (1H, m), 3.19 (1H, d, $J = 13.5\text{Hz}$), 3.35-3.45 (1H, m), 3.47-3.57 (1H, m), 3.65-3.75 (1H, m), 3.81 (1H, dd, $J = 12.5, 2.5\text{Hz}$), 3.92 (1H, d, $J = 13.5\text{Hz}$), 5.49 (1H, brs), 6.57 (1H, s), 6.67 (1H, s), 6.69 (1H, s), 7.52 (1H, dd, $J = 8.5, 1.5\text{Hz}$), 7.57 (1H, d, $J = 8.5\text{Hz}$), 7.84 (1H, d, $J = 1.5\text{Hz}$)。

[2652] 实施例 275

[2653] [式 565]

[2654]

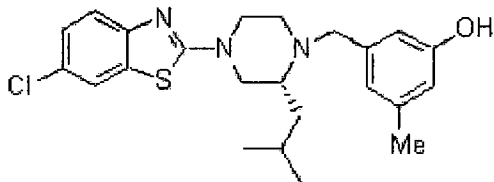


[2655] 收率:96%, $^1\text{H-NMR}(\text{CDCl}_3)$: δ 0.91 (3H, d, $J = 6.5\text{Hz}$), 0.95 (3H, d, $J = 6.5\text{Hz}$), 1.32-1.46 (1H, m), 1.47-1.59 (1H, m), 1.62-1.78 (1H, m), 2.29 (3H, s), 2.33-2.45 (1H, m), 2.62-2.74 (1H, m), 2.75-2.87 (1H, m), 3.27 (1H, d, $J = 13.5\text{Hz}$), 3.36 (1H, dd, $J = 12.5, 7.5\text{Hz}$), 3.55-3.65 (2H, m), 3.70-3.79 (1H, m), 3.86 (1H, d, $J = 13.5\text{Hz}$), 6.56 (1H, s), 6.69 (2H, s), 7.22 (1H, dd, $J = 8.5, 2\text{Hz}$), 7.43 (1H, d, $J = 8.5\text{Hz}$), 7.54 (1H, d, $J = 2\text{Hz}$)。

[2656] 实施例 276

[2657] [式 566]

[2658]



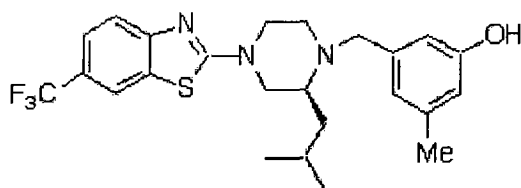
[2659] 收率:定量收率, $^1\text{H-NMR}(\text{CDCl}_3)$: δ 0.91 (3H, d, $J = 6.5\text{Hz}$), 0.95 (3H, d, $J = 6.5\text{Hz}$), 1.30-1.59 (2H, m), 1.62-1.79 (1H, m), 2.18 (1H, s), 2.29 (3H, s), 2.30-2.45 (1H, m), 2.60-2.72 (1H, m), 2.75-2.88 (1H, m), 3.27 (1H, d, $J = 13.5\text{Hz}$), 3.29-3.42 (1H, m), 3.53-3.65 (2H, m), 3.74 (1H, dd, $J = 12.5, 3.5\text{Hz}$), 3.86 (1H, d, $J = 13.5\text{Hz}$), 6.56 (1H, s), 6.67 (1H, s), 6.70 (1H, s), 7.23 (1H, dd, $J = 8.5, 2.0\text{Hz}$), 7.43 (1H, d, $J = 8.5\text{Hz}$), 7.54 (1H,

d, $J = 2.0\text{Hz}$)。

[2660] 实施例 277

[2661] [式 567]

[2662]

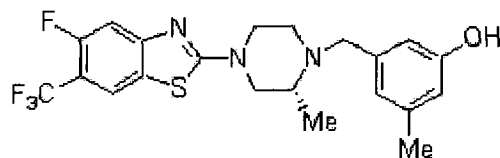


[2663] 收率:98%, $^1\text{H-NMR}$ (CDCl_3) : δ 0.91 (3H, d, $J = 6.5\text{Hz}$), 0.95 (3H, d, $J = 6.5\text{Hz}$), 1.37-1.45 (1H, m), 1.46-1.60 (1H, m), 1.64-1.77 (1H, m), 2.29 (3H, s), 2.36-2.47 (1H, m), 2.64-2.75 (1H, m), 2.78-2.90 (1H, m), 3.29 (1H, d, $J = 13.5\text{Hz}$), 3.42 (1H, dd, $J = 12.5, 7.5\text{Hz}$), 3.65 (2H, t, $J = 5\text{Hz}$), 3.78 (1H, dd, $J = 13, 3\text{Hz}$), 3.86 (1H, d, $J = 13.5\text{Hz}$), 6.57 (1H, s), 6.70 (2H, s), 7.51 (1H, dd, $J = 8.5, 1.5\text{Hz}$), 7.57 (1H, d, $J = 8.5\text{Hz}$), 7.84 (1H, d, $J = 1.5\text{Hz}$)。

[2664] 实施例 278

[2665] [式 568]

[2666]

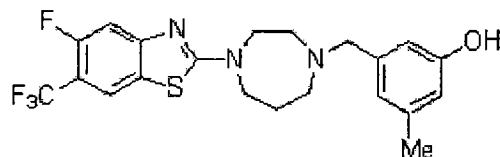


[2667] 收率:99%, $^1\text{H-NMR}$ (CDCl_3) : δ 1.21 (3H, d, $J = 6\text{Hz}$), 2.22-2.28 (1H, m), 2.29 (3H, s), 2.59-2.70 (1H, m), 2.83 (1H, dt, $J = 12, 3.5\text{Hz}$), 3.13 (1H, d, $J = 13.5\text{Hz}$), 3.21 (1H, dd, $J = 11, 8.5\text{Hz}$), 3.39-3.50 (1H, m), 3.72-3.83 (1H, m), 3.84-3.93 (1H, m), 3.97 (1H, d, $J = 13.5\text{Hz}$), 6.56 (1H, s), 6.65 (1H, s), 6.70 (1H, s), 7.26 (1H, d, $J = 11.5\text{Hz}$), 7.73 (1H, d, $J = 7\text{Hz}$)。

[2668] 实施例 279

[2669] [式 569]

[2670]

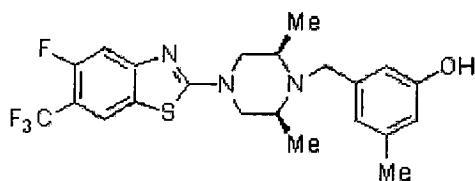


[2671] 收率: 定量收率, $^1\text{H-NMR}$ (CDCl_3) : δ 2.00-2.14 (2H, m), 2.22 (3H, s), 2.68-2.93 (4H, m), 3.53-3.95 (6H, m), 6.60 (2H, s), 6.72 (1H, s), 7.24 (1H, d, $J = 11.5\text{Hz}$), 7.72 (1H, d, $J = 7.0\text{Hz}$), 7.85 (1H, s)。

[2672] 实施例 280

[2673] [式 570]

[2674]

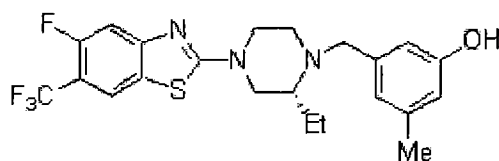


[2675] 收率:89%, $^1\text{H-NMR}$ (CDCl_3): δ 1.13 (6H, d, $J = 6.0\text{Hz}$), 2.29 (3H, s), 2.72-2.88 (2H, m), 3.01-3.19 (2H, m), 3.77 (2H, s), 3.89 (2H, d, $J = 12.0\text{Hz}$), 6.52 (1H, s), 6.70 (1H, s), 6.72 (1H, s), 7.27 (1H, d, $J = 11.5\text{Hz}$), 7.75 (1H, d, $J = 6.5\text{Hz}$)。

[2676] 实施例 281

[2677] [式 571]

[2678]

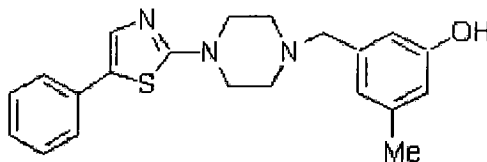


[2679] 收率:95%, $^1\text{H-NMR}$ (CDCl_3): δ 1.01 (3H, t, $J = 7.5\text{Hz}$), 1.48-1.80 (2H, m), 2.25-2.40 (1H, m), 2.30 (3H, s), 2.46-2.58 (1H, m), 2.78-2.89 (1H, m), 3.19 (1H, d, $J = 13.5\text{Hz}$), 3.32-3.57 (2H, m), 3.64-3.75 (1H, m), 3.76-3.87 (1H, m), 3.93 (1H, d, $J = 13.5\text{Hz}$), 6.57 (1H, s), 6.67 (1H, s), 6.70 (1H, s), 7.27 (1H, d, $J = 11.5\text{Hz}$), 7.74 (1H, d, $J = 7.0\text{Hz}$)。

[2680] 实施例 282

[2681] [式 572]

[2682]

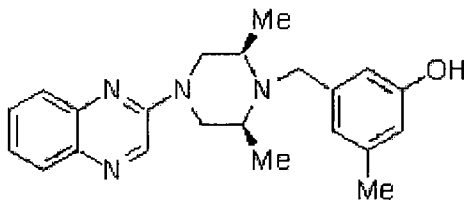


[2683] 收率: 定量收率, $^1\text{H-NMR}$ (CDCl_3): δ 2.23 (3H, s), 2.62-2.80 (4H, m), 3.52-3.73 (6H, m), 6.63 (1H, s), 6.65 (1H, s), 6.78 (1H, s), 7.20 (1H, t, $J = 7.5\text{Hz}$), 7.31 (2H, t, $J = 7.5\text{Hz}$), 7.35-7.44 (3H, m), 8.70 (1H, brs)。

[2684] 实施例 283

[2685] [式 573]

[2686]

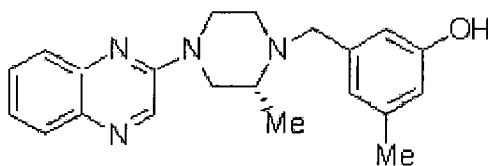


[2687] 收率:93%, $^1\text{H-NMR}$ (CDCl_3): δ 1.13 (6H, d, $J = 6.0\text{Hz}$), 2.29 (3H, s), 2.65-2.80 (2H, m), 2.90 (2H, t, $J = 11.5\text{Hz}$), 3.76 (2H, s), 4.29 (2H, d, $J = 13.0\text{Hz}$), 6.54 (1H, s), 6.70 (1H, s), 6.75 (1H, s), 7.34-7.43 (1H, m), 7.53-7.62 (1H, m), 7.69 (1H, d, $J = 8.0\text{Hz}$), 7.88 (1H, d, $J = 8.0\text{Hz}$), 8.55 (1H, s)。

[2688] 实施例 284

[2689] [式 574]

[2690]

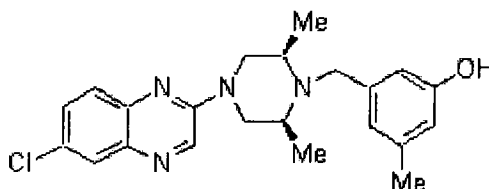


[2691] 收率:93%, $^1\text{H-NMR}$ (CDCl_3): δ 1.25 (3H, d, $J = 5.5\text{Hz}$), 2.21-2.34 (1H, m), 2.29 (3H, s), 2.54-2.70 (1H, m), 2.83-2.94 (1H, m), 3.07-3.22 (1H, m), 3.14 (1H, d, $J = 13.5\text{Hz}$), 3.30-3.45 (1H, m), 4.02 (1H, d, $J = 13.5\text{Hz}$), 4.06-4.17 (1H, m), 4.18-4.28 (1H, m), 6.58 (1H, s), 6.66-6.74 (2H, m), 7.34-7.43 (1H, m), 7.53-7.61 (1H, m), 7.68 (1H, dd, $J = 8.5, 1.0\text{Hz}$), 7.88 (1H, dd, $J = 8.5, 1.0\text{Hz}$), 8.55 (1H, s)。

[2692] 实施例 285

[2693] [式 575]

[2694]

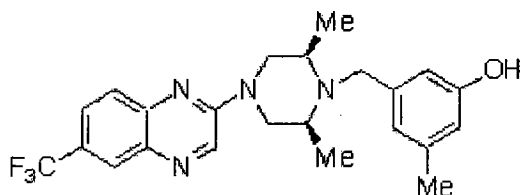


[2695] 收率:88%, $^1\text{H-NMR}$ (CDCl_3): δ 1.16 (6H, d, $J = 6.0\text{Hz}$), 2.29 (3H, s), 2.65-2.83 (2H, m), 2.94 (2H, t, $J = 11.5\text{Hz}$), 3.77 (2H, s), 4.30 (2H, d, $J = 14.0\text{Hz}$), 6.52 (1H, s), 6.72 (1H, s), 6.75 (1H, s), 7.50 (1H, dd, $J = 9.0, 2.5\text{Hz}$), 7.60 (1H, d, $J = 9.0\text{Hz}$), 7.85 (1H, d, $J = 2.5\text{Hz}$), 8.54 (1H, s)。

[2696] 实施例 286

[2697] [式 576]

[2698]



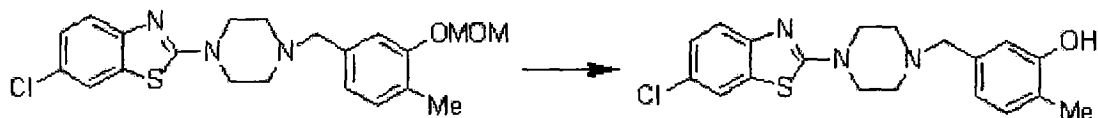
[2699] 收率:97%, $^1\text{H-NMR}$ (CDCl_3): δ 1.17 (6H, d, $J = 6.0\text{Hz}$), 2.28 (3H, s), 2.66-2.83 (2H, m), 2.90-3.06 (2H, m), 3.79 (2H, s), 4.34 (2H, d, $J = 13.0\text{Hz}$), 6.55 (1H, s), 6.69 (1H, s), 6.75 (1H, s), 7.72 (2H, s), 8.14 (1H, s), 8.59 (1H, s)。

[2700] 实施例 287

[2701] 5-([4-(6-氯苯并噻唑-2-基)哌嗪-1-基]甲基)-2-甲基苯酚的制备

[2702] [式 577]

[2703]



[2704] 将6-氯-2-[4-(2-甲氧基甲氧基-3-甲基苯基)哌嗪-1-基]苯并噻唑(1.70g; 4.067mmol)和4N氢氯酸/二噁烷溶液(8.5ml)的混合物在60℃搅拌2小时。在冷却之后,将反应溶液减压浓缩。向残余物中加入饱和碳酸氢钠水溶液到碱性并且用乙酸乙酯萃取。有机层用盐水洗涤,用无水硫酸钠干燥,并且减压蒸发。沉淀物用二异丙醚洗涤,得到5-{[4-(6-氯苯并噻唑-2-基)哌嗪-1-基]甲基}-2-甲基苯酚,为无色晶体(1.33g; 87%)。

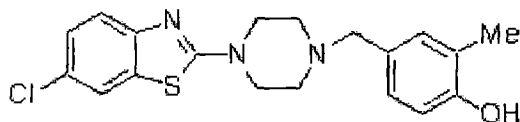
[2705] $^1\text{H-NMR}(\text{CDCl}_3)$: δ 2.24(3H, s), 2.55(4H, t, $J = 5\text{Hz}$), 3.46(2H, s), 3.63(4H, t, $J = 5\text{Hz}$), 5.95(1H, brs), 6.76(1H, d, $J = 7.5\text{Hz}$), 6.81(1H, s), 7.07(1H, d, $J = 7.5\text{Hz}$), 7.23(1H, dd, $J = 8, 2\text{Hz}$), 7.45(1H, d, $J = 8\text{Hz}$), 7.55(1H, d, $J = 2\text{Hz}$)。

[2706] 通过与实施例 287 相似的方法得到实施例 288 到 292 的化合物。

[2707] 实施例 288

[2708] [式 578]

[2709]

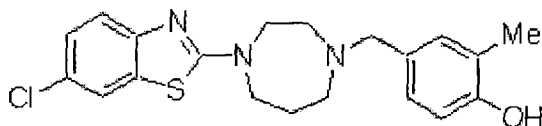


[2710] 收率:100%, $^1\text{H-NMR}(\text{DMSO}-d_6)$: δ 2.12(3H, s), 3.08-3.18(2H, m), 3.39(2H, d, $J = 12.0\text{Hz}$), 3.65(2H, t, $J = 12.0\text{Hz}$), 4.13-4.21(4H, m), 6.85(1H, d, $J = 8.4\text{Hz}$), 7.22(1H, d, $J = 8.4\text{Hz}$), 7.28(1H, s), 7.28(1H, m), 7.49(1H, d, $J = 8.7\text{Hz}$), 7.99(1H, d, $J = 2.1\text{Hz}$)。

[2711] 实施例 289

[2712] [式 579]

[2713]

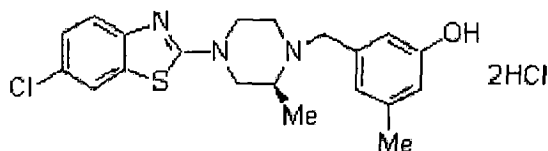


[2714] 收率:80%, $^1\text{H-NMR}(\text{DMSO}-d_6)$: δ 2.12(3H, s), 2.16-2.26(2H, m), 3.03-3.15(2H, m), 3.49-3.76(4H, m), 4.02(4H, s), 6.83(1H, d, $J = 8.1\text{Hz}$), 7.19(1H, d, $J = 8.1\text{Hz}$), 7.25(1H, s), 7.31(1H, dd, $J = 2.4, 8.7\text{Hz}$), 7.45(1H, d, $J = 9.7\text{Hz}$), 7.95(1H, d, $J = 2.4\text{Hz}$)。

[2715] 实施例 290

[2716] [式 580]

[2717]

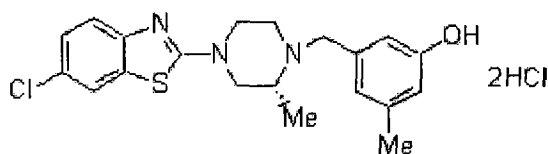


[2718] 收率:77%, $^1\text{H-NMR}(\text{DMSO}-d_6)$: δ 1.59(3H, d, $J = 6.3\text{Hz}$), 2.24(3H, s), 3.12(2H, br), 3.54(1H, br), 3.65(2H, br), 3.89-3.96(1H, m), 4.09(1H, d, $J = 14.1\text{Hz}$), 4.21(1H, d, $J = 12.9\text{Hz}$), 4.63(1H, d, $J = 11.2\text{Hz}$), 6.68(1H, s), 6.81(1H, s), 6.88(1H, s), 7.34(1H, dd, $J = 2.1, 8.7\text{Hz}$), 7.50(1H, d, $J = 8.7\text{Hz}$), 8.00(1H, d, $J = 2.1\text{Hz}$), 11.6(1H, s)。

[2719] 实施例 291

[2720] [式 581]

[2721]

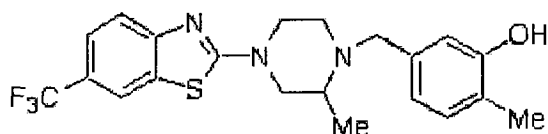


[2722] 收率:84%, $^1\text{H-NMR}$ (DMSO-d_6): δ 1.58 (3H, d, $J = 6.0\text{Hz}$), 2.24 (3H, s), 3.16 (2H, br), 3.53 (1H, br), 3.64 (1H, br), 3.89-3.96 (2H, m), 4.08 (1H, d, $J = 12.9\text{Hz}$), 4.21 (1H, d, $J = 12.9\text{Hz}$), 4.63 (1H, d, $J = 12.0\text{Hz}$), 6.68 (1H, s), 6.81 (1H, s), 6.87 (1H, s), 7.34 (1H, dd, $J = 2.1, 8.7\text{Hz}$), 7.50 (1H, d, $J = 8.7\text{Hz}$), 8.00 (1H, d, $J = 2.1\text{Hz}$), 11.6 (1H, br)。

[2723] 实施例 292

[2724] [式 582]

[2725]



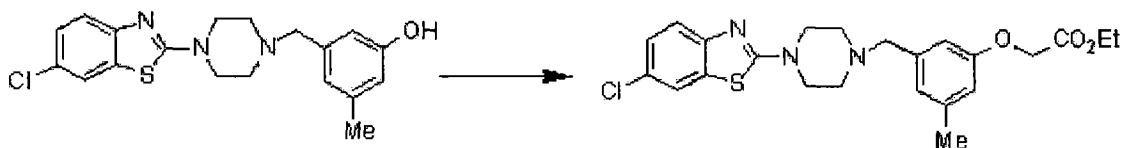
[2726] 收率:84%, $^1\text{H-NMR}$ (CDCl_3): δ 1.21 (3H, d, $J = 6\text{Hz}$), 2.24 (3H, s), 2.25-2.33 (1H, m), 2.59-2.70 (1H, m), 2.81 (1H, dt, $J = 12, 3\text{Hz}$), 3.14 (1H, d, $J = 13.5\text{Hz}$), 3.15-3.25 (1H, m), 3.39-3.50 (1H, m), 3.73-3.83 (1H, m), 3.84-3.94 (1H, m), 3.98 (1H, d, $J = 13.5\text{Hz}$), 5.18 (1H, brs), 6.79 (1H, d, $J = 7.5\text{Hz}$), 6.80 (1H, s), 7.07 (1H, d, $J = 7.5\text{Hz}$), 7.51 (1H, d, $J = 8.5\text{Hz}$), 7.57 (1H, d, $J = 8.5\text{Hz}$), 7.84 (1H, s)。

[2727] 实施例 293

[2728] {3-[[4-(6-氯苯并噻唑-2-基)哌嗪-1-基]甲基]-5-甲基}苯氧基乙酸乙酯的制备

[2729] [式 583]

[2730]



[2731] 将 3-[[4-(6-氯苯并噻唑-2-基)哌嗪-1-基]甲基]-5-甲基苯酚 (0.50g; 1.34mmol), 溴乙酸乙酯 (bromoethyl acetate) (0.22ml; 2.01mmol) 和碳酸铯 (0.65g; 2.01mmol) 在无水 N,N -二甲基甲酰胺 (5ml) 中的混合物在 50°C 搅拌 17 小时。向反应溶液加入水和乙酸乙酯并且萃取。有机层用盐水洗涤, 用无水硫酸钠干燥, 并且减压蒸发。残余物通过硅胶柱色谱法纯化 (己烷: 乙酸乙酯 = 2 : 1), 得到 {3-[[4-(6-氯苯并噻唑-2-基)哌嗪-1-基]甲基]-5-甲基}苯氧基乙酸乙酯, 为浅黄色油状物 (0.48g; 78%)。

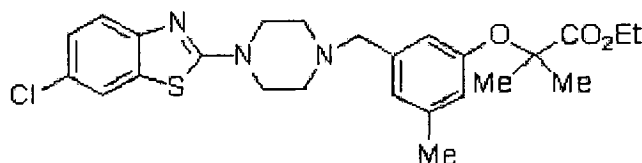
[2732] $^1\text{H-NMR}$ (CDCl_3): δ 1.28 (3H, t, $J = 7\text{Hz}$), 2.32 (3H, s), 2.56 (4H, t, $J = 5\text{Hz}$), 3.49 (2H, s), 3.63 (4H, t, $J = 5\text{Hz}$), 4.27 (2H, q, $J = 7\text{Hz}$), 4.61 (2H, s), 6.64 (1H, s), 6.74 (1H, s), 6.78 (1H, s), 7.23 (1H, dd, $J = 8.5, 2\text{Hz}$), 7.43 (1H, d, $J = 8.5\text{Hz}$), 7.55 (1H, d, $J = 2\text{Hz}$)。

[2733] 通过与实施例 293 相似的方法得到实施例 294 到 329 的化合物。

[2734] 实施例 294

[2735] [式 584]

[2736]

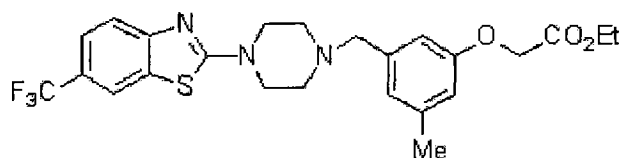


[2737] 收率:84%, $^1\text{H-NMR}(\text{CDCl}_3)$; δ 1.27 (3H, t, $J = 7\text{Hz}$), 1.59 (6H, s), 2.29 (3H, s), 2.55 (4H, t, $J = 5\text{Hz}$), 3.46 (2H, s), 3.62 (4H, t, $J = 5\text{Hz}$), 4.26 (2H, q, $J = 7\text{Hz}$), 6.55 (1H, s), 6.60 (1H, s), 6.77 (1H, s), 7.23 (1H, dd, $J = 8.5, 2\text{Hz}$), 7.42 (1H, d, $J = 8.5\text{Hz}$), 7.55 (1H, d, $J = 2\text{Hz}$)。

[2738] 实施例 295

[2739] [式 585]

[2740]

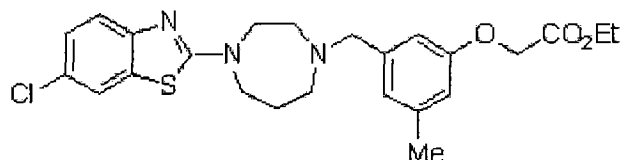


[2741] 收率:78%, $^1\text{H-NMR}(\text{CDCl}_3)$; δ 1.31 (3H, t, $J = 7\text{Hz}$), 2.32 (3H, s), 2.58 (4H, t, $J = 5\text{Hz}$), 3.50 (2H, s), 3.68 (4H, t, $J = 5\text{Hz}$), 4.28 (2H, q, $J = 7\text{Hz}$), 4.62 (2H, s), 6.65 (1H, s), 6.74 (1H, s), 6.78 (1H, s), 7.50-7.60 (2H, m), 7.85 (1H, s)。

[2742] 实施例 296

[2743] [式 586]

[2744]

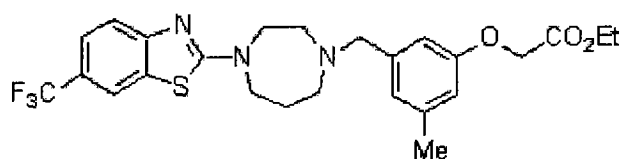


[2745] 收率:93%, $^1\text{H-NMR}(\text{CDCl}_3)$; δ 1.30 (3H, t, $J = 6.9\text{Hz}$), 1.98-2.05 (2H, m), 2.30 (3H, s), 2.67 (2H, t, $J = 5.1\text{Hz}$), 2.77-2.81 (2H, m), 3.57 (2H, s), 3.71-3.75 (4H, m), 4.27 (2H, q, $J = 7.2\text{Hz}$), 4.60 (2H, s), 6.63 (1H, s), 6.73 (1H, s), 6.76 (1H, s), 7.23 (1H, dd, $J = 8.7, 2.4\text{Hz}$), 7.42 (1H, d, $J = 8.4\text{Hz}$), 7.55 (1H, d, $J = 2.1\text{Hz}$)。

[2746] 实施例 297

[2747] [式 587]

[2748]



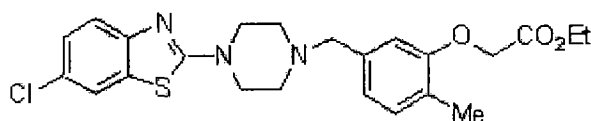
[2749] 收率:66%, $^1\text{H-NMR}(\text{CDCl}_3)$; δ 1.29 (3H, t, $J = 7\text{Hz}$), 1.98-2.06 (2H, m), 2.30 (3H, s), 2.68 (2H, t, $J = 5.5\text{Hz}$), 2.81 (2H, t, $J = 5.5\text{Hz}$), 3.57 (2H, s), 3.70-3.85 (4H, m), 4.27 (2H, q, $J = 7\text{Hz}$), 4.60 (2H, s), 6.63 (1H, s), 6.73 (1H, s), 6.76 (1H, s), 7.48-7.58 (2H,

m), 7.84 (1H, s)。

[2750] 实施例 298

[2751] [式 588]

[2752]

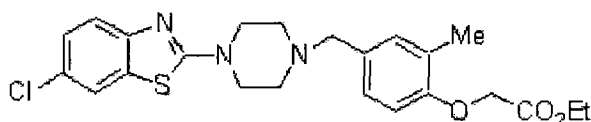


[2753] 收率:68%, $^1\text{H-NMR}$ (CDCl_3) ; δ 1.29 (3H, t, $J = 7\text{Hz}$), 2.28 (3H, s), 2.55 (4H, t, $J = 5\text{Hz}$), 3.50 (2H, s), 3.62 (4H, t, $J = 5\text{Hz}$), 4.26 (2H, q, $J = 7\text{Hz}$), 4.65 (2H, s), 6.74 (1H, s), 6.84 (1H, d, $J = 7.5\text{Hz}$), 7.10 (1H, d, $J = 7.5\text{Hz}$), 7.23 (1H, dd, $J = 8.5, 2\text{Hz}$), 7.43 (1H, d, $J = 8.5\text{Hz}$), 7.55 (1H, d, $J = 2\text{Hz}$)。

[2754] 实施例 299

[2755] [式 589]

[2756]

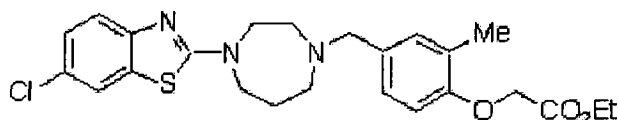


[2757] 收率:84%, $^1\text{H-NMR}$ (CDCl_3) ; δ 1.30 (3H, t, $J = 7.2\text{Hz}$), 2.30 (3H, s), 2.55 (4H, t, $J = 5.1\text{Hz}$), 3.46 (2H, s), 3.62 (4H, t, $J = 5.1\text{Hz}$), 4.27 (2H, q, $J = 7.2\text{Hz}$), 4.64 (2H, s), 6.66 (1H, dd, $J = 8.1\text{Hz}$), 7.07 (1H, d, $J = 8.1\text{Hz}$), 7.13 (1H, s), 7.23 (1H, dd, $J = 8.4, 2.1\text{Hz}$), 7.43 (1H, dd, $J = 8.1\text{Hz}$), 7.55 (1H, d, $J = 2.1\text{Hz}$)。

[2758] 实施例 300

[2759] [式 590]

[2760]

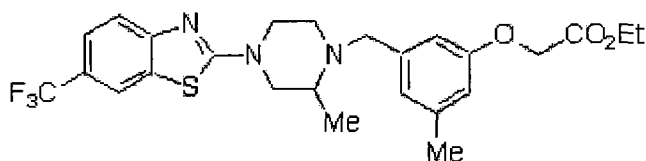


[2761] 收率:90%, $^1\text{H-NMR}$ (CDCl_3) ; δ 1.30 (3H, t, $J = 7.2\text{Hz}$), 1.98-2.05 (2H, m), 2.28 (3H, s), 2.67 (2H, t, $J = 5.1\text{Hz}$), 2.78 (2H, t, $J = 5.1\text{Hz}$), 3.54 (2H, s), 3.71-3.78 (4H, m), 4.27 (2H, q, $J = 7.2\text{Hz}$), 4.63 (2H, s), 6.64 (1H, d, $J = 8.1\text{Hz}$), 7.05 (1H, d, $J = 8.1\text{Hz}$), 7.11 (1H, s), 7.22 (1H, dd, $J = 8.7, 2.1\text{Hz}$), 7.42 (1H, d, $J = 8.7\text{Hz}$), 7.54 (1H, d, $J = 2.1\text{Hz}$)。

[2762] 实施例 301

[2763] [式 591]

[2764]



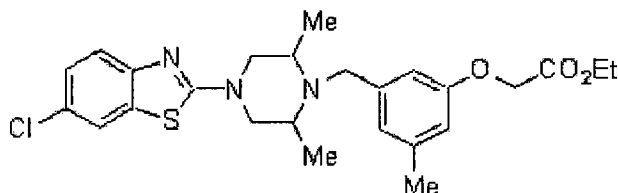
[2765] 收率:92%, $^1\text{H-NMR}$ (CDCl_3) ; δ 1.21 (3H, d, $J = 6\text{Hz}$), 1.31 (3H, t, $J = 7\text{Hz}$), 2.20-2.32 (1H, m), 2.33 (3H, s), 2.60-2.70 (1H, m), 2.77-2.85 (1H, m), 3.05-3.25 (2H,

m), 3.35-3.50 (1H, m), 3.70-3.80 (1H, m), 3.85-3.95 (1H, m), 3.98 (1H, d, $J = 13.5\text{Hz}$), 4.28 (2H, q, $J = 7\text{Hz}$), 4.61 (2H, s), 6.63 (1H, s), 6.75 (1H, s), 6.78 (1H, s), 7.53 (1H, d, $J = 8.5\text{Hz}$), 7.56 (1H, d, $J = 8.5\text{Hz}$), 7.84 (1H, s)。

[2766] 实施例 302

[2767] [式 592]

[2768]

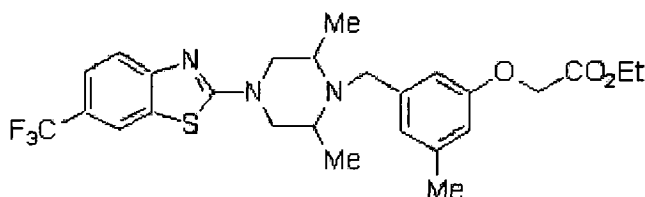


[2769] 收率:74%, $^1\text{H-NMR}(\text{CDCl}_3)$: δ 1.10 (6H, d, $J = 6\text{Hz}$), 1.30 (3H, t, $J = 7\text{Hz}$), 2.31 (3H, s), 2.70-2.85 (2H, m), 3.01 (1H, d, $J = 10.5\text{Hz}$), 3.05 (1H, d, $J = 10.5\text{Hz}$), 3.76 (2H, s), 3.80-3.90 (2H, m), 4.27 (2H, q, $J = 7\text{Hz}$), 4.60 (2H, s), 6.57 (1H, s), 6.78 (1H, s), 6.83 (1H, s), 7.23 (1H, dd, $J = 8.5, 2\text{Hz}$), 7.43 (1H, d, $J = 8.5\text{Hz}$), 7.55 (1H, d, $J = 2\text{Hz}$)。

[2770] 实施例 303

[2771] [式 593]

[2772]

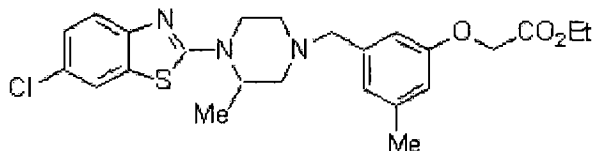


[2773] 收率:93%, $^1\text{H-NMR}(\text{CDCl}_3)$: δ 1.12 (6H, d, $J = 6\text{Hz}$), 1.30 (3H, t, $J = 7\text{Hz}$), 2.31 (3H, s), 2.70-2.90 (2H, m), 3.00-3.15 (2H, m), 3.77 (2H, s), 3.85-3.95 (2H, m), 4.27 (2H, q, $J = 7\text{Hz}$), 4.60 (2H, s), 6.57 (1H, s), 6.78 (1H, s), 6.84 (1H, s), 7.52 (1H, d, $J = 8.5\text{Hz}$), 7.56 (1H, d, $J = 8.5\text{Hz}$), 7.84 (1H, s)。

[2774] 实施例 304

[2775] [式 594]

[2776]

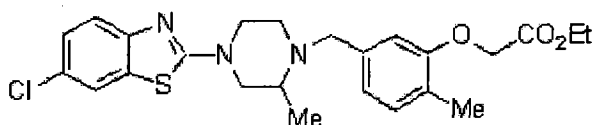


[2777] 收率:95%, $^1\text{H-NMR}(\text{CDCl}_3)$: δ 1.30 (3H, t, $J = 7\text{Hz}$), 1.41 (3H, d, $J = 7\text{Hz}$), 2.21 (1H, td, $J = 12, 3.5\text{Hz}$), 2.25-2.35 (1H, m), 2.32 (3H, s), 2.73 (1H, d, $J = 11\text{Hz}$), 2.90 (1H, d, $J = 11\text{Hz}$), 3.38 (1H, d, $J = 13.5\text{Hz}$), 3.48 (1H, td, $J = 12, 3.5\text{Hz}$), 3.52 (1H, d, $J = 13.5\text{Hz}$), 3.85 (1H, d, $J = 12\text{Hz}$), 4.15-4.25 (1H, m), 4.27 (2H, q, $J = 7\text{Hz}$), 4.61 (2H, s), 6.64 (1H, s), 6.76 (1H, s), 6.78 (1H, s), 7.22 (1H, dd, $J = 8, 2\text{Hz}$), 7.42 (1H, d, $J = 8\text{Hz}$), 7.54 (1H, d, $J = 2\text{Hz}$)。

[2778] 实施例 305

[2779] [式 595]

[2780]

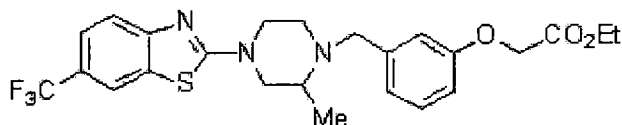


[2781] 收率:43%, $^1\text{H-NMR}$ (CDCl_3): δ 1.21 (3H, d, $J = 6\text{Hz}$), 1.30 (3H, t, $J = 7\text{Hz}$), 2.20-2.27 (1H, m), 2.28 (3H, s), 2.60-2.70 (1H, m), 2.75-2.85 (1H, m), 3.10-3.25 (2H, m), 3.35-3.50 (1H, m), 3.68-3.78 (1H, m), 3.85-3.95 (1H, m), 4.01 (1H, d, $J = 13\text{Hz}$), 4.27 (2H, q, $J = 7\text{Hz}$), 4.65 (2H, s), 6.74 (1H, s), 6.85 (1H, d, $J = 7.5\text{Hz}$), 7.11 (1H, d, $J = 7.5\text{Hz}$), 7.53 (1H, d, $J = 8.5\text{Hz}$), 7.56 (1H, d, $J = 8.5\text{Hz}$), 7.84 (1H, s)。

[2782] 实施例 306

[2783] [式 596]

[2784]

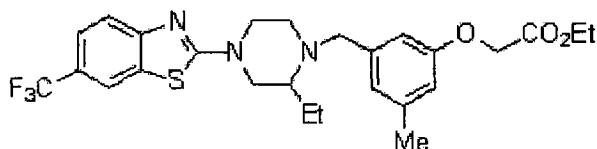


[2785] 收率:79%, $^1\text{H-NMR}$ (CDCl_3): δ 1.22 (3H, d, $J = 6.5\text{Hz}$), 1.31 (3H, t, $J = 7\text{Hz}$), 2.23-2.35 (1H, m), 2.60-2.73 (1H, m), 2.75-2.90 (1H, m), 3.15-3.25 (2H, m), 3.40-3.50 (1H, m), 3.70-3.82 (1H, m), 3.85-3.95 (1H, m), 4.03 (1H, d, $J = 13.5\text{Hz}$), 4.28 (2H, q, $J = 7\text{Hz}$), 4.63 (2H, s), 6.80 (1H, dd, $J = 8, 1.5\text{Hz}$), 6.93-7.02 (2H, m), 7.25 (1H, t, $J = 8\text{Hz}$), 7.53 (1H, d, $J = 8.5\text{Hz}$), 7.56 (1H, d, $J = 8.5\text{Hz}$), 7.84 (1H, s)。

[2786] 实施例 307

[2787] [式 597]

[2788]

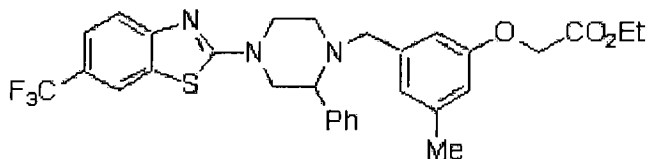


[2789] 收率:81%, $^1\text{H-NMR}$ (CDCl_3): δ 1.02 (3H, t, $J = 7.5\text{Hz}$), 1.31 (3H, t, $J = 7\text{Hz}$), 1.58-1.79 (2H, m), 2.31 (3H, s), 2.31-2.38 (1H, m), 2.47-2.58 (1H, m), 2.78-2.88 (1H, m), 3.23 (1H, d, $J = 13.5\text{Hz}$), 3.36-3.58 (2H, m), 3.64-3.75 (1H, m), 3.84 (1H, d, $J = 11\text{Hz}$), 3.95 (1H, d, $J = 13.5\text{Hz}$), 4.28 (2H, q, $J = 7\text{Hz}$), 4.62 (2H, s), 6.63 (1H, s), 6.77 (1H, s), 6.78 (1H, s), 7.51 (1H, d, $J = 8.5\text{Hz}$), 7.56 (1H, d, $J = 8.5\text{Hz}$), 7.84 (1H, s)。

[2790] 实施例 308

[2791] [式 598]

[2792]



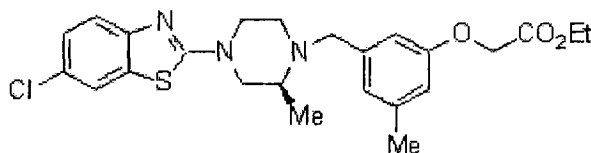
[2793] 收率:91%, $^1\text{H-NMR}$ (CDCl_3): δ 1.31 (3H, t, $J = 7\text{Hz}$), 2.25-2.35 (4H, m), 2.82 (1H,

d, $J = 13.5\text{Hz}$), 3.01 (1H, d, $J = 11.5\text{Hz}$), 3.25–3.50 (3H, m), 3.79 (1H, d, $J = 13.5\text{Hz}$), 4.00–4.10 (2H, m), 4.28 (2H, q, $J = 7\text{Hz}$), 4.60 (2H, s), 6.59 (1H, s), 6.70 (1H, s), 6.72 (1H, s), 7.30–7.45 (3H, m), 7.50–7.58 (4H, m), 7.84 (1H, s)。

[2794] 实施例 309

[2795] [式 599]

[2796]

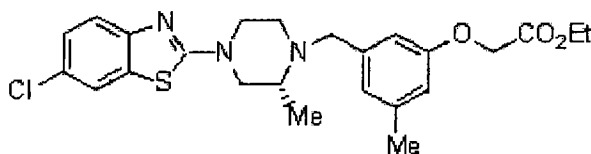


[2797] 收率:90%, $^1\text{H-NMR}$ (CDCl₃): δ 1.21 (3H, d, $J = 6.3\text{Hz}$), 1.31 (3H, t, $J = 7.2\text{Hz}$), 2.22–2.31 (1H, m), 2.32 (3H, s), 2.58–2.68 (1H, m), 2.83 (1H, dt, $J = 3.3, 12.3\text{Hz}$), 3.12–3.19 (2H, m), 3.34–3.43 (1H, m), 3.71 (1H, d, $J = 12.3\text{Hz}$), 3.86 (1H, d, $J = 10.5\text{Hz}$), 3.99 (1H, d, $J = 13.5\text{Hz}$), 4.28 (2H, q, $J = 7.2\text{Hz}$), 4.61 (2H, s), 6.63 (1H, s), 6.75 (1H, s), 6.78 (1H, s), 7.23 (1H, d, $J = 2.4, 8.7\text{Hz}$), 7.43 (1H, d, $J = 8.7\text{Hz}$), 7.55 (1H, d, $J = 2.4\text{Hz}$)。

[2798] 实施例 310

[2799] [式 600]

[2800]

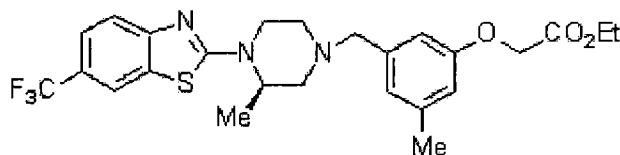


[2801] 收率:70%, $^1\text{H-NMR}$ (CDCl₃): δ 1.21 (3H, d, $J = 6.3\text{Hz}$), 1.30 (3H, t, $J = 7.2\text{Hz}$), 2.23–2.32 (1H, m), 2.32 (3H, s), 2.58–2.67 (1H, m), 2.80 (1H, d, $J = 3.3, 12.3\text{Hz}$), 3.12–3.19 (2H, m), 3.35–3.42 (1H, m), 3.71 (1H, dt, $J = 12.0\text{Hz}$), 3.86 (1H, dt, $J = 12.0\text{Hz}$), 3.99 (1H, d, $J = 13.2\text{Hz}$), 4.28 (2H, q, $J = 7.2\text{Hz}$), 4.61 (2H, s), 6.63 (1H, s), 6.75 (1H, s), 6.78 (1H, s), 7.23 (1H, dd, $J = 2.1, 8.7\text{Hz}$), 7.43 (1H, d, $J = 8.7\text{Hz}$), 7.54 (1H, d, $J = 2.1\text{Hz}$)。

[2802] 实施例 311

[2803] [式 601]

[2804]

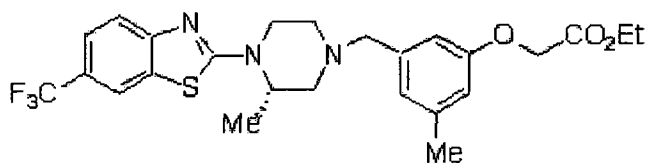


[2805] 收率:89%, $^1\text{H-NMR}$ (CDCl₃): δ 1.30 (3H, t, $J = 7\text{Hz}$), 1.43 (3H, d, $J = 6.5\text{Hz}$), 2.23 (1H, td, $J = 12, 3.5\text{Hz}$), 2.31 (3H, s), 2.31–2.40 (1H, m), 2.73 (1H, d, $J = 11\text{Hz}$), 2.91 (1H, d, $J = 11\text{Hz}$), 3.40 (1H, d, $J = 13\text{Hz}$), 3.46–3.51 (1H, m), 3.53 (1H, d, $J = 13\text{Hz}$), 3.85–3.95 (1H, m), 4.20–4.27 (1H, m), 4.28 (2H, q, $J = 7\text{Hz}$), 4.62 (2H, s), 6.65 (1H, s), 6.77 (1H, s), 6.79 (1H, s), 7.52 (1H, d, $J = 8.5\text{Hz}$), 7.56 (1H, d, $J = 8.5\text{Hz}$), 7.84 (1H, s)。

[2806] 实施例 312

[2807] [式 602]

[2808]

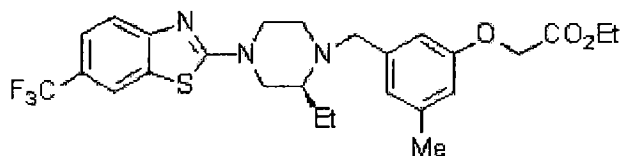


[2809] 收率:84%, $^1\text{H-NMR}$ (CDCl_3): δ 1.31 (3H, t, $J = 7.0\text{Hz}$), 1.43 (3H, d, $J = 6.5\text{Hz}$), 2.16-2.28 (1H, m), 2.30-2.39 (1H, m), 2.33 (3H, s), 2.70-2.78 (1H, m), 2.87-2.96 (1H, m), 3.40 (1H, d, $J = 13.5\text{Hz}$), 3.45-3.58 (2H, m), 3.86-3.97 (1H, m), 4.18-4.30 (1H, m), 4.28 (2H, q, $J = 7.0\text{Hz}$), 4.62 (2H, s), 6.65 (1H, s), 6.75-6.82 (2H, m), 7.48-7.60 (2H, m), 7.84 (1H, s)。

[2810] 实施例 313

[2811] [式 603]

[2812]

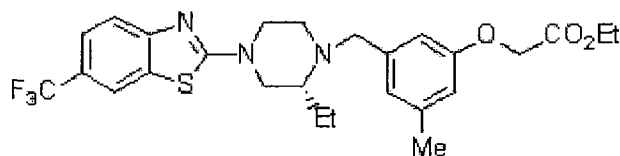


[2813] 收率:86%, $^1\text{H-NMR}$ (CDCl_3): δ 1.02 (3H, t, $J = 7.5\text{Hz}$), 1.31 (3H, t, $J = 7\text{Hz}$), 1.57-1.78 (2H, m), 2.30-2.33 (1H, m), 2.34 (3H, s), 2.48-2.60 (1H, m), 2.78-2.90 (1H, m), 3.17 (1H, d, $J = 13.5\text{Hz}$), 3.37-3.58 (2H, m), 3.62-3.73 (1H, m), 3.79-3.88 (1H, m), 3.95 (1H, d, $J = 13.5\text{Hz}$), 4.28 (2H, q, $J = 7\text{Hz}$), 4.61 (2H, s), 6.63 (1H, s), 6.76 (1H, s), 6.78 (1H, s), 7.51 (1H, d, $J = 8.5\text{Hz}$), 7.55 (1H, d, $J = 8.5\text{Hz}$), 7.83 (1H, s)。

[2814] 实施例 314

[2815] [式 604]

[2816]

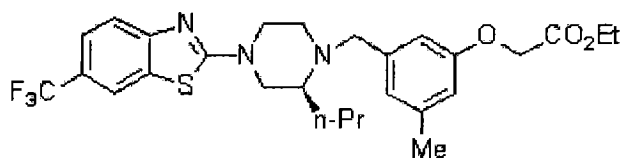


[2817] 收率:85%, $^1\text{H-NMR}$ (CDCl_3): δ 1.02 (3H, t, $J = 7.5\text{Hz}$), 1.29 (3H, t, $J = 7\text{Hz}$), 1.58-1.78 (2H, m), 2.04 (3H, s), 2.05-2.15 (1H, m), 2.48-2.58 (1H, m), 2.79-2.89 (1H, m), 3.23 (1H, d, $J = 13.5\text{Hz}$), 3.42 (1H, dd, $J = 12.5, 8\text{Hz}$), 3.47-3.56 (1H, m), 3.63-3.72 (1H, m), 3.80-3.90 (1H, m), 3.95 (1H, d, $J = 13.5\text{Hz}$), 4.27 (2H, q, $J = 7\text{Hz}$), 4.61 (2H, s), 6.63 (1H, s), 6.77 (1H, s), 6.78 (1H, s), 7.52 (1H, d, $J = 8.5\text{Hz}$), 7.56 (1H, d, $J = 8.5\text{Hz}$), 7.83 (1H, s)。

[2818] 实施例 315

[2819] [式 605]

[2820]

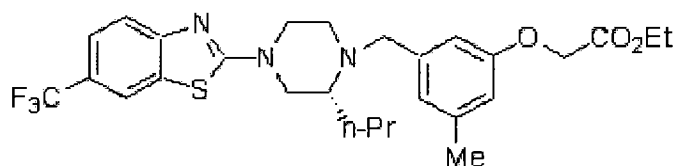


[2821] 收率:60%, $^1\text{H-NMR}$ (CDCl_3): δ 0.95 (3H, t, $J = 7.0\text{Hz}$), 1.22-1.68 (4H, m), 1.31 (3H, t, $J = 7.0\text{Hz}$), 2.27-2.40 (1H, m), 2.32 (3H, s), 2.54-2.65 (1H, m), 2.76-2.89 (1H, m), 3.25 (1H, d, $J = 13.5\text{Hz}$), 3.41 (1H, dd, $J = 13.0, 7.5\text{Hz}$), 3.48-3.59 (1H, m), 3.60-3.71 (1H, m), 3.83 (1H, dd, $J = 12.5, 3.5\text{Hz}$), 3.93 (1H, d, $J = 13.5\text{Hz}$), 4.28 (2H, q, $J = 7.0\text{Hz}$), 4.61 (2H, s), 6.63 (1H, s), 6.76 (1H, s), 6.78 (1H, s), 7.52 (1H, d, $J = 8.5\text{Hz}$), 7.56 (1H, d, $J = 8.5\text{Hz}$), 7.83 (1H, s)。

[2822] 实施例 316

[2823] [式 606]

[2824]

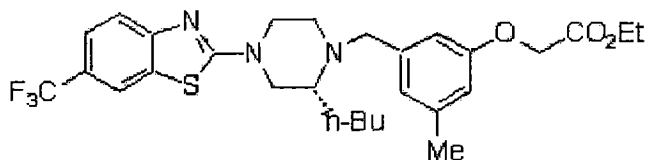


[2825] 收率:90%, $^1\text{H-NMR}$ (CDCl_3): δ 0.95 (3H, t, $J = 7.2\text{Hz}$), 1.31 (3H, t, $J = 7.2\text{Hz}$), 1.33-1.62 (4H, m), 2.32 (3H, s), 2.32-2.38 (1H, m), 2.57-2.62 (1H, m), 2.79-2.86 (1H, m), 3.24 (1H, d, $J = 13.5\text{Hz}$), 3.41 (1H, dd, $J = 7.8, 12.6\text{Hz}$), 3.38-3.44 (1H, m), 3.64-3.69 (1H, m), 3.83 (1H, dd, $J = 3.0, 12.6\text{Hz}$), 3.93 (1H, d, $J = 13.5\text{Hz}$), 4.28 (2H, q, $J = 7.2\text{Hz}$), 4.61 (2H, s), 6.63 (1H, s), 6.77 (2H, d, $J = 6.3\text{Hz}$), 7.53-7.55 (2H, m), 7.83 (1H, s)。

[2826] 实施例 317

[2827] [式 607]

[2828]

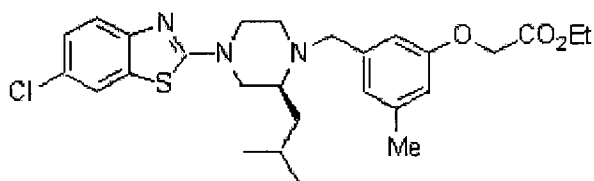


[2829] 收率:64%, $^1\text{H-NMR}$ (CDCl_3): δ 0.93 (3H, t, $J = 7.0\text{Hz}$), 1.22-1.75 (6H, m), 1.31 (3H, t, $J = 7.0\text{Hz}$), 2.27-2.39 (1H, m), 2.32 (3H, s), 2.51-2.64 (1H, m), 2.76-2.88 (1H, m), 3.24 (1H, d, $J = 13.0\text{Hz}$), 3.41 (1H, dd, $J = 13.0, 7.5\text{Hz}$), 3.47-3.59 (1H, m), 3.61-3.72 (1H, m), 3.84 (1H, dd, $J = 13.0, 3.0\text{Hz}$), 3.94 (1H, d, $J = 13.0\text{Hz}$), 4.28 (2H, q, $J = 7.0\text{Hz}$), 4.61 (2H, s), 6.63 (1H, s), 6.76 (1H, s), 6.78 (1H, s), 7.51 (1H, d, $J = 8.5\text{Hz}$), 7.56 (1H, d, $J = 8.5\text{Hz}$), 7.84 (1H, s)。

[2830] 实施例 318

[2831] [式 608]

[2832]

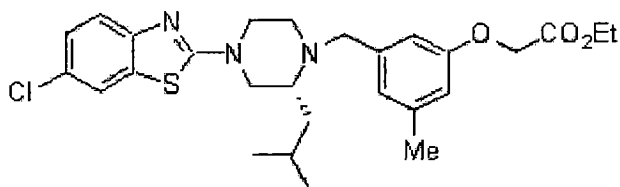


[2833] 收率:83%, $^1\text{H-NMR}$ (CDCl_3): δ 0.91 (3H, d, $J = 6.5\text{Hz}$), 0.95 (3H, d, $J = 6.5\text{Hz}$), 1.30 (3H, t, $J = 7\text{Hz}$), 1.35-1.45 (1H, m), 1.46-1.58 (1H, m), 1.65-1.80 (1H, m), 2.32 (3H, s), 2.33-2.44 (1H, m), 2.62-2.73 (1H, m), 2.75-2.86 (1H, m), 3.30 (1H, d, $J = 13.5\text{Hz}$), 3.35 (1H, dd, $J = 13, 6.5\text{Hz}$), 3.58 (2H, t, $J = 5\text{Hz}$), 3.75 (1H, dd, $J = 13, 6.5\text{Hz}$), 3.87 (1H, d, $J = 13.5\text{Hz}$), 4.28 (2H, q, $J = 7\text{Hz}$), 4.61 (2H, s), 6.62 (1H, s), 6.76 (1H, s), 6.78 (1H, s), 7.23 (1H, dd, $J = 8.5, 2\text{Hz}$), 7.42 (1H, d, $J = 8.5\text{Hz}$), 7.54 (1H, d, $J = 2\text{Hz}$)。

[2834] 实施例 319

[2835] [式 609]

[2836]

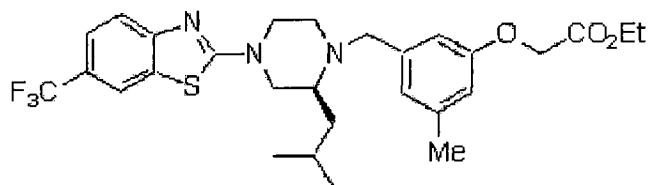


[2837] 收率:68%, $^1\text{H-NMR}$ (CDCl_3): δ 0.92 (3H, d, $J = 6.5\text{Hz}$), 0.95 (3H, d, $J = 7.0\text{Hz}$), 1.20-1.44 (1H, m), 1.30 (3H, t, $J = 6.5\text{Hz}$), 1.45-1.80 (2H, m), 2.27-2.47 (1H, m), 2.32 (3H, s), 2.61-2.72 (1H, m), 2.75-2.88 (1H, m), 3.25-3.41 (2H, m), 3.58 (2H, t, $J = 5.0\text{Hz}$), 3.75 (1H, dd, $J = 12.5, 3.5\text{Hz}$), 3.87 (1H, d, $J = 13.5\text{Hz}$), 4.28 (2H, q, $J = 7.0\text{Hz}$), 4.61 (2H, s), 6.62 (1H, s), 6.76 (1H, s), 6.78 (1H, s), 7.23 (1H, dd, $J = 8.0, 2.0\text{Hz}$), 7.42 (1H, d, $J = 8.0\text{Hz}$), 7.54 (1H, d, $J = 2.0\text{Hz}$)。

[2838] 实施例 320

[2839] [式 610]

[2840]

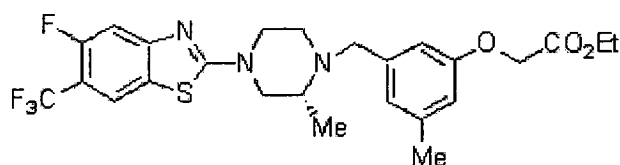


[2841] 收率:85%, $^1\text{H-NMR}$ (CDCl_3): δ 0.92 (3H, d, $J = 6.5\text{Hz}$), 0.95 (3H, d, $J = 6.5\text{Hz}$), 1.31 (3H, t, $J = 7\text{Hz}$), 1.34-1.45 (1H, m), 1.45-1.55 (1H, m), 1.65-1.80 (1H, m), 2.32 (3H, s), 2.35-2.46 (1H, m), 2.64-2.75 (1H, m), 2.78-2.88 (1H, m), 3.32 (1H, d, $J = 13.5\text{Hz}$), 3.42 (1H, dd, $J = 13, 6.5\text{Hz}$), 3.60-3.67 (2H, m), 3.79 (1H, dd, $J = 13, 3.5\text{Hz}$), 3.87 (1H, d, $J = 13.5\text{Hz}$), 4.28 (2H, q, $J = 7\text{Hz}$), 4.61 (2H, s), 6.63 (1H, s), 6.77 (1H, s), 6.79 (1H, s), 7.51 (1H, d, $J = 8.5\text{Hz}$), 7.56 (1H, d, $J = 8.5\text{Hz}$), 7.83 (1H, s)。

[2842] 实施例 321

[2843] [式 611]

[2844]

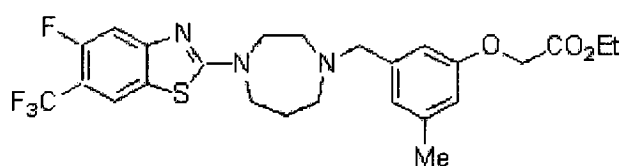


[2845] 收率:98%, $^1\text{H-NMR}$ (CDCl_3): δ 1.21 (3H, d, $J = 6\text{Hz}$), 1.31 (3H, t, $J = 7\text{Hz}$), 2.20-2.32 (1H, m), 2.32 (3H, s), 2.59-2.70 (1H, m), 2.75-2.88 (1H, m), 3.16 (1H, d, $J = 13.5\text{Hz}$), 3.17-3.25 (1H, m), 3.48-3.50 (1H, m), 3.69-3.80 (1H, m), 3.85-3.95 (1H, m), 3.98 (1H, d, $J = 13.5\text{Hz}$), 4.28 (2H, q, $J = 7\text{Hz}$), 4.62 (2H, s), 6.63 (1H, s), 6.75 (1H, s), 6.78 (1H, s), 7.26 (1H, d, $J = 12\text{Hz}$), 7.74 (1H, d, $J = 7\text{Hz}$)。

[2846] 实施例 322

[2847] [式 612]

[2848]

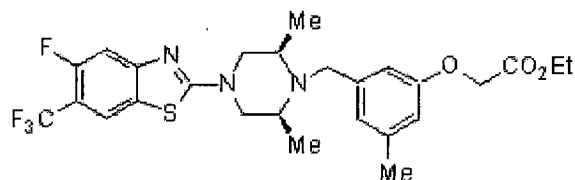


[2849] 收率:69%, $^1\text{H-NMR}$ (CDCl_3): δ 1.30 (3H, t, $J = 7.0\text{Hz}$), 1.96-2.08 (2H, m), 2.30 (3H, s), 2.63-2.71 (2H, m), 2.74-2.84 (2H, m), 3.57 (2H, s), 3.60-3.89 (4H, m), 4.27 (2H, q, $J = 7.0\text{Hz}$), 4.60 (2H, s), 6.62 (1H, s), 6.73 (1H, s), 6.75 (1H, s), 7.27 (1H, d, $J = 7.0\text{Hz}$), 7.75 (1H, d, $J = 11.5\text{Hz}$)。

[2850] 实施例 323

[2851] [式 613]

[2852]

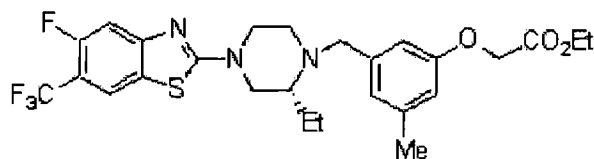


[2853] 收率:75%, $^1\text{H-NMR}$ (CDCl_3): δ 1.12 (6H, d, $J = 6.0\text{Hz}$), 1.30 (3H, t, $J = 7.0\text{Hz}$), 2.32 (3H, s), 2.72-2.86 (2H, m), 3.07 (1H, d, $J = 13.0\text{Hz}$), 3.11 (1H, d, $J = 13.0\text{Hz}$), 3.77 (2H, s), 3.89 (2H, d, $J = 11.0\text{Hz}$), 4.28 (2H, q, $J = 7.0\text{Hz}$), 4.60 (2H, s), 6.57 (1H, s), 6.78 (1H, s), 6.84 (1H, s), 7.27 (1H, d, $J = 11.5\text{Hz}$), 7.75 (1H, d, $J = 6.0\text{Hz}$)。

[2854] 实施例 324

[2855] [式 614]

[2856]



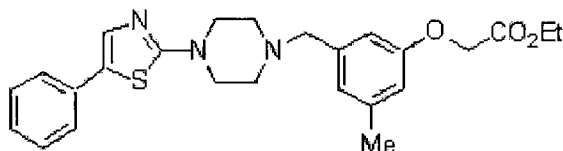
[2857] 收率:79%, $^1\text{H-NMR}$ (CDCl_3): δ 1.01 (3H, t, $J = 7.5\text{Hz}$), 1.31 (3H, t, $J = 7.0\text{Hz}$), 1.50-1.80 (2H, m), 2.26-2.39 (1H, m), 2.32 (3H, s), 2.47-2.58 (1H, m), 2.77-2.88 (1H, m), 3.24 (1H, d, $J = 13.5\text{Hz}$), 3.36-3.57 (2H, m), 3.61-3.73 (1H, m), 3.77-3.88 (1H, m),

3.94 (1H, d, $J = 13.5$ Hz), 4.28 (2H, q, $J = 7.0$ Hz), 4.61 (2H, s), 6.62 (1H, s), 6.73–6.82 (2H, m), 7.26 (1H, d, $J = 11.5$ Hz), 7.74 (1H, d, $J = 7.0$ Hz)。

[2858] 实施例 325

[2859] [式 615]

[2860]

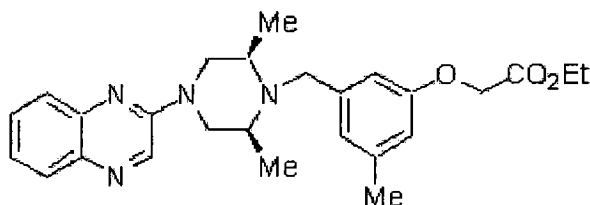


[2861] 收率:71%, $^1\text{H-NMR}$ (CDCl_3): δ 1.29 (3H, t, $J = 7.0$ Hz), 2.31 (3H, s), 2.54 (4H, t, $J = 5.0$ Hz), 3.47 (2H, s), 3.52 (4H, t, $J = 5.0$ Hz), 4.26 (2H, q, $J = 7.0$ Hz), 4.60 (2H, s), 6.64 (1H, s), 6.74 (1H, s), 6.78 (1H, s), 7.18 (1H, tt, $J = 7.5, 1.5$ Hz), 7.26–7.35 (2H, m), 7.37–7.44 (3H, m)。

[2862] 实施例 326

[2863] [式 616]

[2864]

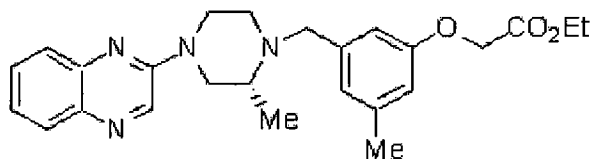


[2865] 收率:74%, $^1\text{H-NMR}$ (CDCl_3): δ 1.15 (6H, d, $J = 7.0$ Hz), 1.30 (3H, t, $J = 7.0$ Hz), 2.32 (3H, s), 2.68–2.83 (2H, m), 2.93 (1H, d, $J = 13.0$ Hz), 2.96 (1H, d, $J = 13.0$ Hz), 3.78 (2H, s), 4.26–4.38 (2H, m), 4.27 (2H, q, $J = 7.0$ Hz), 4.61 (2H, s), 6.57 (1H, s), 6.80 (1H, s), 6.86 (1H, s), 7.34–7.43 (1H, m), 7.52–7.62 (1H, m), 7.67 (1H, dd, $J = 8.5, 1.5$ Hz), 7.87 (1H, dd, $J = 8.5, 1.5$ Hz), 8.56 (1H, s)。

[2866] 实施例 327

[2867] [式 617]

[2868]

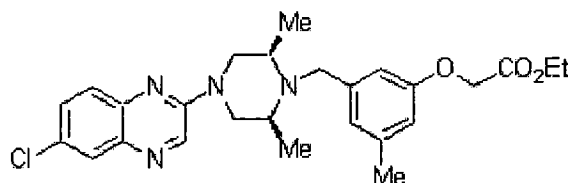


[2869] 收率:79%, $^1\text{H-NMR}$ (CDCl_3): δ 1.25 (3H, d, $J = 6.0$ Hz), 1.31 (3H, t, $J = 7.0$ Hz), 2.20–2.32 (1H, m), 2.33 (3H, s), 2.55–2.68 (1H, m), 2.85 (1H, dt, $J = 12.0, 3.5$ Hz), 3.14 (1H, d, $J = 13.0$ Hz), 3.16 (1H, d, $J = 13.5$ Hz), 3.30–3.43 (1H, m), 4.02 (1H, d, $J = 13.0$ Hz), 4.04–4.15 (1H, m), 4.17–4.26 (1H, m), 4.28 (2H, q, $J = 7.0$ Hz), 4.62 (2H, s), 6.63 (1H, s), 6.77 (1H, s), 6.80 (1H, s), 7.34–7.42 (1H, m), 7.52–7.61 (1H, m), 7.67 (1H, dd, $J = 8.5, 1.5$ Hz), 7.87 (1H, dd, $J = 8.5, 1.5$ Hz), 8.55 (1H, s)。

[2870] 实施例 328

[2871] [式 618]

[2872]

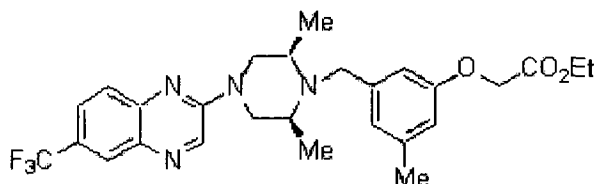


[2873] 收率:74%, $^1\text{H-NMR}$ (CDCl_3): δ 1.15 (6H, d, $J = 6.0\text{Hz}$), 1.30 (3H, t, $J = 7.0\text{Hz}$), 2.32 (3H, s), 2.67-2.81 (2H, m), 2.93 (1H, d, $J = 13.0\text{Hz}$), 2.97 (1H, d, $J = 13.0\text{Hz}$), 3.78 (2H, s), 4.24-4.35 (2H, m), 4.27 (2H, q, $J = 7.0\text{Hz}$), 4.61 (2H, s), 6.66 (1H, s), 6.79 (1H, s), 6.86 (1H, s), 7.50 (1H, dd, $J = 9.5, 2.0\text{Hz}$), 7.59 (1H, d, $J = 9.5\text{Hz}$), 7.85 (1H, d, $J = 2.0\text{Hz}$), 8.54 (1H, s)。

[2874] 实施例 329

[2875] [式 619]

[2876]



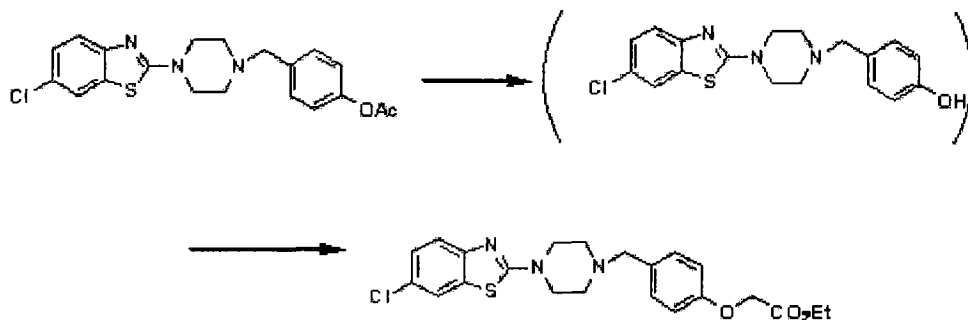
[2877] 收率:51%, $^1\text{H-NMR}$ (CDCl_3): δ 1.15 (6H, d, $J = 6.0\text{Hz}$), 1.29 (3H, t, $J = 7.0\text{Hz}$), 2.31 (3H, s), 2.65-2.79 (2H, m), 2.95 (1H, d, $J = 13.0\text{Hz}$), 2.99 (1H, d, $J = 13.0\text{Hz}$), 3.76 (2H, s), 4.26 (2H, q, $J = 7.0\text{Hz}$), 4.35 (2H, d, $J = 12.0\text{Hz}$), 4.62 (2H, s), 6.58 (1H, s), 6.79 (1H, s), 6.86 (1H, s), 7.69 (1H, s), 7.70 (1H, s), 8.13 (1H, s), 8.59 (1H, s)。

[2878] 实施例 330

[2879] 4-[[4-(6-氯苯并噻唑-2-基)哌嗪-1-基]甲基]苯氧基乙酸乙酯的制备

[2880] [式 620]

[2881]



[2882] 将乙酸 4-[[4-(6-氯苯并噻唑-2-基)哌嗪-1-基]甲基]苯基酯 (0.33g; 0.834mmol), 氢氧化锂 (0.04g; 0.831mmol) 和 THF (8ml) 的混合物在室温搅拌 5 小时。减压蒸发溶剂。向残余物中加入溴乙酸乙酯 (0.14ml; 1.26mmol), 碳酸铯 (0.41g; 1.26mmol) 和无水 N,N-二甲基甲酰胺 (4ml)。将混合物在室温搅拌 17 小时。向反应溶液加入水和乙酸乙酯并用乙酸乙酯萃取。有机层用盐水洗涤, 用无水硫酸钠干燥, 并且减压蒸发。残余物通过硅胶柱色谱法纯化 (己烷: 乙酸乙酯 = 2:1), 得到 4-[[4-(6-氯苯并噻唑-2-基)哌嗪-1-基]甲基]苯氧基乙酸乙酯, 为无色油状物 (0.35g; 93%)。

[2883] $^1\text{H-NMR}$ (CDCl_3): δ 1.31 (3H, t, $J = 7.2\text{Hz}$), 2.55 (4H, t, $J = 5.1\text{Hz}$), 3.50 (2H, s),

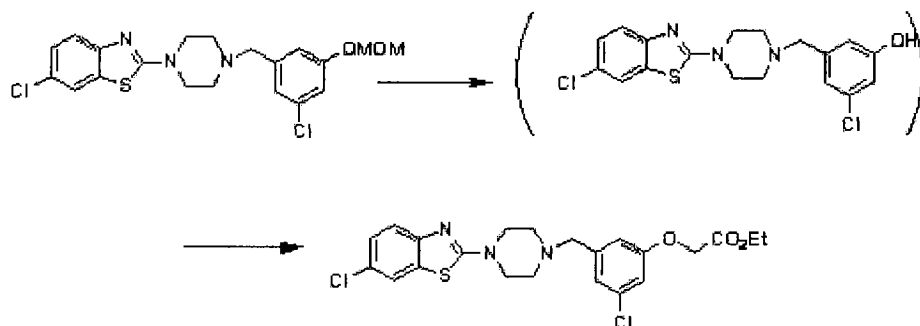
3.62(4H, t, $J = 5.1\text{Hz}$), 4.28(2H, q, $J = 7.2\text{Hz}$), 4.66(2H, s), 6.88(1H, d, $J = 8.1\text{Hz}$), 7.22-7.26(4H, m), 7.43(1H, d, $J = 8.1\text{Hz}$), 7.55(1H, d, $J = 2.1\text{Hz}$)。

[2884] 实施例 331

[2885] 3-氯-5-[[4-(6-氯苯并噻唑-2-基)哌嗪-1-基]甲基]苯氧基乙酸乙酯的制备

[2886] [式 621]

[2887]



[2888] 将 3-氯-5-[4-(2-甲氧基甲氧基-3-甲基苯基)哌嗪-1-基]苯并噻唑 (0.15g; 0.346mmol) 和 4N 氢氯酸/二噁烷溶液 (8.5ml) 的混合物在 60℃ 搅拌 2 小时。在冷却之后, 将反应溶液减压浓缩。向残余物中加入溴乙酸乙酯 (0.05ml; 0.451mmol), 碳酸铯 (0.50g; 1.56mmol) 和无水 N,N-二甲基甲酰胺 (3ml)。将混合物在室温搅拌 17 小时。向反应溶液加入水和乙酸乙酯并且用乙酸乙酯萃取。有机层用盐水洗涤, 用无水硫酸钠干燥, 并且减压蒸发。残余物通过硅胶柱色谱法纯化 (己烷: 乙酸乙酯 = 2 : 1), 得到 3-氯-5-[[4-(6-氯苯并噻唑-2-基)哌嗪-1-基]甲基]苯氧基乙酸乙酯, 为无色油状物 (0.13g; 77%)。

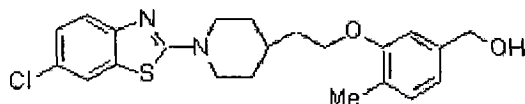
[2889] $^1\text{H-NMR}$ (CDCl_3): δ 1.31(3H, t, $J = 6.9\text{Hz}$), 2.56(4H, t, $J = 5.1\text{Hz}$), 3.49(2H, s), 3.63(4H, t, $J = 5.1\text{Hz}$), 4.28(2H, q, $J = 6.9\text{Hz}$), 4.61(2H, s), 6.87(1H, t, $J = 1.5\text{Hz}$), 6.84(1H, s), 6.99(1H, t, $J = 1.5\text{Hz}$), 7.24(1H, dd, $J = 2.1, 8.7\text{Hz}$), 7.44(1H, d, $J = 8.7\text{Hz}$), 7.55(1H, dd, $J = 2.1\text{Hz}$)。

[2890] 实施例 332

[2891] 以实施例 217 的化合物作为原料通过与实施例 129 相似的方法得到以下化合物。

[2892] [式 622]

[2893]



[2894] 收率: 84%, $^1\text{H-NMR}$ (CDCl_3): δ 1.31-1.50(2H, m), 1.65(1H, s), 1.74-1.96(5H, m), 2.21(3H, s), 3.07-3.20(2H, m), 4.02-4.18(4H, m), 4.65(2H, d, $J = 5.5\text{Hz}$), 6.83(1H, d, $J = 7.5\text{Hz}$), 6.86(1H, s), 7.12(1H, d, $J = 7.5\text{Hz}$), 7.22(1H, dd, $J = 8.5, 2.0\text{Hz}$), 7.42(1H, d, $J = 8.5\text{Hz}$), 7.54(1H, d, $J = 2.0\text{Hz}$)。

[2895] 实施例 333

[2896] 以实施例 332 的化合物作为原料通过与实施例 154 相似的方法得到以下化合物。

[2897] [式 623]

[2898]



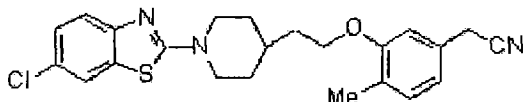
[2899] 收率:79%, $^1\text{H-NMR}(\text{CDCl}_3)$; δ 1.33-1.52(2H, m), 1.78-1.98(5H, m), 2.21(3H, s), 3.08-3.21(2H, m), 4.03-4.17(4H, m), 4.50(2H, s), 6.82-6.90(2H, m), 7.11(1H, d, $J = 7.5\text{Hz}$), 7.22(1H, dd, $J = 8.5, 2.0\text{Hz}$), 7.42(1H, d, $J = 8.5\text{Hz}$), 7.55(1H, d, $J = 2.0\text{Hz}$)。

[2900] 实施例 334

[2901] 以实施例 333 的化合物作为原料通过与实施例 179 相似的方法得到以下化合物。

[2902] [式 624]

[2903]



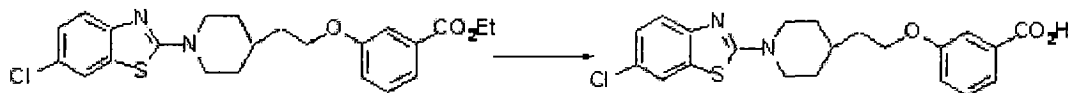
[2904] 收率:96%, $^1\text{H-NMR}(\text{CDCl}_3)$; δ 1.34-1.52(2H, m), 1.77-1.97(5H, m), 2.21(3H, s), 3.08-3.22(2H, m), 3.72(2H, s), 4.01-4.19(4H, m), 6.75-6.81(2H, m), 7.13(1H, d, $J = 7.5\text{Hz}$), 7.23(1H, dd, $J = 8.5, 2.0\text{Hz}$), 7.42(1H, d, $J = 8.5\text{Hz}$), 7.55(1H, d, $J = 2.0\text{Hz}$)。

[2905] 实施例 335

[2906] 3-{2-[1-(6-氯苯并噻唑-2-基)哌啶-4-基]乙氧基}苯甲酸的制备

[2907] [式 625]

[2908]



[2909] 将 3-{2-[1-(6-氯苯并噻唑-2-基)哌啶-4-基]乙氧基}苯甲酸乙酯 (0.30g; 6.671mmol), 2N-氢氧化钠水溶液 (1.5ml) 和甲醇 (3ml) 的混合物在 60°C 搅拌 1 小时。将反应溶液减压浓缩。向残余物中加入水和 2N 盐酸直到为中性。收集沉淀物并且用水和二异丙醚洗涤, 得到 3-{2-[1-(6-氯苯并噻唑-2-基)哌啶-4-基]乙氧基}苯甲酸, 为无色晶体 (0.26g; 93%)。

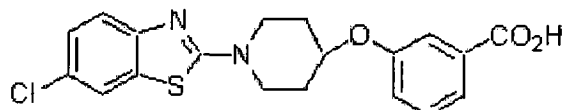
[2910] $^1\text{H-NMR}(\text{DMSO}-d_6)$: δ 1.20-1.39(2H, m), 1.66-1.93(5H, m), 3.10-3.26(2H, m), 3.94-4.16(4H, m), 7.20(1H, dd, $J = 8.5, 2.5\text{Hz}$), 7.27(1H, d, $J = 8.5, 2.0\text{Hz}$), 7.36-7.47(3H, m), 7.52(1H, d, $J = 7.5\text{Hz}$), 7.89(1H, d, $J = 2.0\text{Hz}$)。

[2911] 通过与实施例 335 相似的方法得到实施例 336 到 489 的化合物。

[2912] 实施例 336

[2913] [式 626]

[2914]

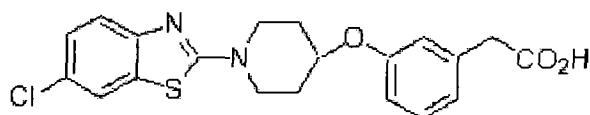


[2915] 收率:18%, $^1\text{H-NMR}(\text{DMSO}-d_6)$: δ 1.68-1.84(2H, m), 2.00-2.15(2H, m), 3.50-3.64(2H, m), 3.78-3.92(2H, m), 4.68-4.81(1H, m), 7.12-7.18(1H, m), 7.26-7.39(2H, m), 7.43(1H, d, $J = 8.5\text{Hz}$), 7.48-7.55(2H, m), 7.91(1H, d, $J = 2.0\text{Hz}$)。

[2916] 实施例 337

[2917] [式 627]

[2918]

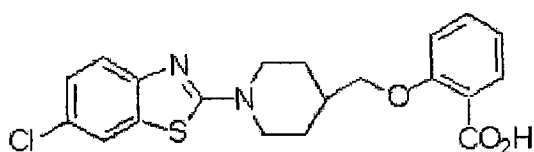


[2919] 收率:27%, $^1\text{H-NMR}$ (DMSO-d_6): δ 1.66-1.83 (2H, m), 2.00-2.15 (2H, m), 3.48-3.64 (4H, m), 3.78-3.93 (2H, m), 4.62-4.75 (1H, m), 6.80-6.98 (3H, m), 7.19-7.28 (1H, m), 7.29 (1H, dd, $J = 8.5, 2.5\text{Hz}$), 7.44 (1H, d, $J = 8.5\text{Hz}$), 7.90 (1H, d, $J = 2.5\text{Hz}$), 12.29 (1H, s)。

[2920] 实施例 338

[2921] [式 628]

[2922]

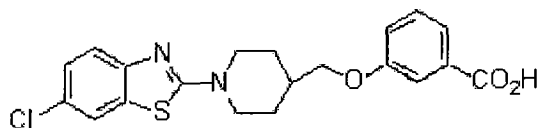


[2923] 收率:84%, $^1\text{H-NMR}$ (DMSO-d_6): δ 1.35-1.55 (2H, m), 1.85-2.00 (2H, m), 2.00-2.20 (1H, m), 3.10-3.30 (2H, m), 3.94 (2H, d, $J = 6\text{Hz}$), 4.00-4.15 (2H, m), 6.98 (1H, t, $J = 7.5\text{Hz}$), 7.10 (1H, d, $J = 7.5\text{Hz}$), 7.27 (1H, dd, $J = 8.5, 2\text{Hz}$), 7.41 (1H, d, $J = 8.5\text{Hz}$), 7.47 (1H, t, $J = 7.5\text{Hz}$), 7.61 (1H, d, $J = 7.5\text{Hz}$), 7.89 (1H, d, $J = 2\text{Hz}$), 12.50 (1H, brs)。

[2924] 实施例 339

[2925] [式 629]

[2926]

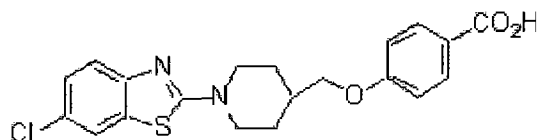


[2927] 收率:84%, $^1\text{H-NMR}$ (DMSO-d_6): δ 1.30-1.50 (2H, m), 1.80-1.95 (2H, m), 2.00-2.15 (1H, m), 3.15-3.30 (2H, m), 3.93 (2H, d, $J = 6\text{Hz}$), 4.00-4.15 (2H, m), 7.20 (1H, dd, $J = 8, 2.5\text{Hz}$), 7.27 (1H, dd, $J = 8.5, 2\text{Hz}$), 7.35-7.45 (3H, m), 7.52 (1H, d, $J = 8\text{Hz}$), 7.88 (1H, d, $J = 2\text{Hz}$), 13.0 (1H, brs)。

[2928] 实施例 340

[2929] [式 630]

[2930]

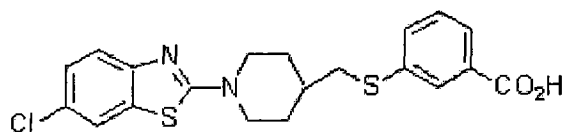


[2931] 收率:59%, $^1\text{H-NMR}$ (DMSO-d_6): δ 1.30-1.50 (2H, m), 1.85-1.95 (2H, m), 2.00-2.20 (1H, m), 3.00-3.20 (2H, m), 3.96 (2H, d, $J = 6.5\text{Hz}$), 4.04-4.14 (2H, m), 7.00 (2H, d, $J = 8\text{Hz}$), 7.28 (1H, dd, $J = 8.5, 1.5\text{Hz}$), 7.41 (1H, d, $J = 8.5\text{Hz}$), 7.87 (2H, d, $J = 8\text{Hz}$), 7.89 (1H, d, $J = 1.5\text{Hz}$)。

[2932] 实施例 341

[2933] [式 631]

[2934]

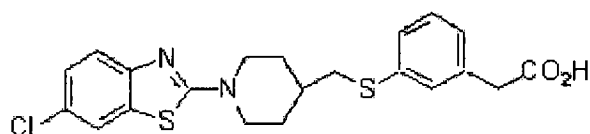


[2935] 收率:88%, $^1\text{H-NMR}$ (DMSO-d_6): δ 1.20-1.45 (2H, m), 1.70-1.90 (1H, m), 1.90-2.05 (2H, m), 3.02 (2H, d, $J = 7\text{Hz}$), 3.10-3.25 (2H, m), 3.95-4.10 (2H, m), 7.70 (1H, dd, $J = 8.5, 2\text{Hz}$), 7.40 (1H, d, $J = 8.5\text{Hz}$), 7.44 (1H, t, $J = 7.5\text{Hz}$), 7.59 (1H, d, $J = 7.5\text{Hz}$), 7.73 (1H, d, $J = 7.5\text{Hz}$), 7.83 (1H, s), 7.88 (1H, d, $J = 2\text{Hz}$), 13.40 (1H, brs)。

[2936] 实施例 342

[2937] [式 632]

[2938]

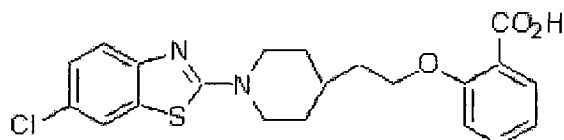


[2939] 收率:32%, $^1\text{H-NMR}$ (CDCl_3): δ 1.30-1.48 (2H, m), 1.70-1.90 (1H, m), 1.85-2.05 (2H, m), 2.88 (2H, d, $J = 7\text{Hz}$), 3.02-3.15 (2H, m), 3.63 (2H, s), 4.05-4.18 (2H, m), 7.05-7.15 (1H, m), 7.24 (1H, dd, $J = 8.5, 2\text{Hz}$), 7.25-7.30 (3H, m), 7.42 (1H, d, $J = 8.5\text{Hz}$), 7.53 (1H, d, $J = 2\text{Hz}$)。

[2940] 实施例 343

[2941] [式 633]

[2942]

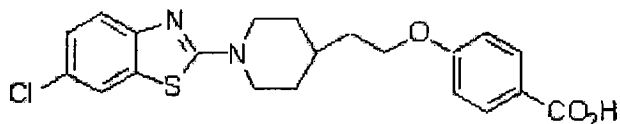


[2943] 收率:88%, $^1\text{H-NMR}$ (DMSO-d_6): δ 1.20-1.38 (2H, m), 1.71 (2H, q, $J = 6.0\text{Hz}$), 1.78-1.94 (3H, m), 3.09-3.23 (2H, m), 3.95-4.07 (2H, m), 4.10 (2H, t, $J = 6.0\text{Hz}$), 6.99 (1H, td, $J = 7.5, 1.5\text{Hz}$), 7.14 (1H, d, $J = 7.5\text{Hz}$), 7.27 (1H, dd, $J = 8.5, 2.0\text{Hz}$), 7.40 (1H, d, $J = 8.5\text{Hz}$), 7.48 (1H, td, $J = 1.5, 7.5\text{Hz}$), 7.60 (1H, dd, $J = 7.5, 1.5\text{Hz}$), 7.88 (1H, d, $J = 2.0\text{Hz}$), 12.55 (1H, br)。

[2944] 实施例 344

[2945] [式 634]

[2946]

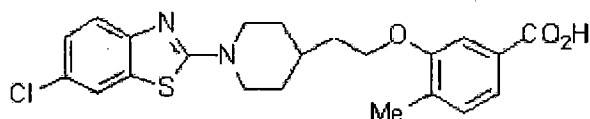


[2947] 收率:82%, $^1\text{H-NMR}$ (DMSO-d_6): δ 1.20-1.39 (2H, m), 1.68-1.92 (5H, m), 3.10-3.26 (2H, m), 3.08-4.08 (2H, m), 4.12 (2H, t, $J = 6.0\text{Hz}$), 7.03 (2H, d, $J = 9.0\text{Hz}$), 7.27 (1H, dd, $J = 8.5, 2.0\text{Hz}$), 7.40 (1H, d, $J = 8.5\text{Hz}$), 7.88 (1H, d, $J = 2.0\text{Hz}$), 7.88 (2H, d, $J = 9.0\text{Hz}$), 12.62 (1H, br)。

[2948] 实施例 345

[2949] [式 635]

[2950]



[2951] 收率:75%, $^1\text{H-NMR}$ (DMSO-d_6): δ 1.22-1.40 (2H, m), 1.70-1.92 (5H, m), 2.21 (3H, s), 3.12-3.24 (2H, m), 3.96-4.08 (2H, m), 4.09 (2H, t, $J = 6.0\text{Hz}$), 7.25 (1H, d, $J = 8.0\text{Hz}$), 7.27 (1H, dd, $J = 8.5, 2.0\text{Hz}$), 7.40 (1H, d, $J = 8.5\text{Hz}$), 7.43 (2H, m), 7.88 (1H, d, $J = 2.0\text{Hz}$)。

[2952] 实施例 346

[2953] [式 636]

[2954]



[2955] 收率:78%, $^1\text{H-NMR}$ (DMSO-d_6): δ 1.18-1.38 (2H, m), 1.64-1.91 (5H, m), 3.11-3.24 (2H, m), 3.52 (2H, s), 3.96-4.07 (4H, m), 6.78-6.87 (3H, m), 7.21 (1H, t, $J = 7.5\text{Hz}$), 7.27 (1H, dd, $J = 8.5, 2.0\text{Hz}$), 7.40 (1H, d, $J = 8.5\text{Hz}$), 7.88 (1H, d, $J = 2.0\text{Hz}$), 12.31 (1H, brs)。

[2956] 实施例 347

[2957] [式 637]

[2958]



[2959] 收率:84%, $^1\text{H-NMR}$ (DMSO-d_6): δ 1.19-1.39 (2H, m), 1.64-1.92 (5H, m), 3.09-3.28 (2H, m), 3.47 (2H, s), 3.95-4.10 (4H, m), 6.80 (2H, d, $J = 8.5\text{Hz}$), 7.15 (2H, d, $J = 8.5\text{Hz}$), 7.27 (1H, dd, $J = 8.5, 2.0\text{Hz}$), 7.40 (1H, d, $J = 8.5\text{Hz}$), 7.88 (1H, d, $J = 2.0\text{Hz}$)。

[2960] 实施例 348

[2961] [式 638]

[2962]

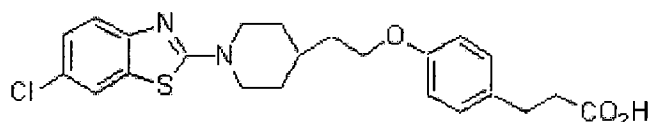


[2963] 收率:35%, $^1\text{H-NMR}$ (CDCl_3): δ 1.18-1.37 (2H, m), 1.68-1.91 (5H, m), 2.77 (2H, t, $J = 7.5\text{Hz}$), 3.09-3.43 (4H, m), 3.94-4.06 (4H, m), 6.71-6.83 (3H, m), 7.16 (1H, t, $J = 8.0\text{Hz}$), 7.27 (1H, dd, $J = 8.5, 2.0\text{Hz}$), 7.40 (1H, d, $J = 8.5\text{Hz}$), 7.88 (1H, d, $J = 2.0\text{Hz}$)。

[2964] 实施例 349

[2965] [式 639]

[2966]

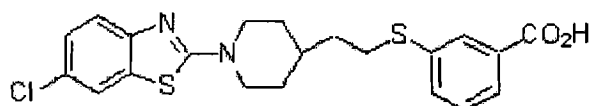


[2967] 收率:27%, $^1\text{H-NMR}$ (DMSO-d_6): δ 1.18-1.42 (2H, m), 1.68-1.94 (5H, m), 2.47 (2H, t, $J = 7.5\text{Hz}$), 2.80 (2H, t, $J = 7.5\text{Hz}$), 3.10-3.23 (2H, m), 3.96-4.10 (4H, m), 6.84 (1H, t, $J = 7.5\text{Hz}$), 6.96 (1H, d, $J = 7.5\text{Hz}$), 7.12-7.21 (2H, m), 7.27 (1H, dd, $J = 8.5, 2.0\text{Hz}$), 7.40 (1H, d, $J = 8.5\text{Hz}$), 7.88 (1H, d, $J = 2.0\text{Hz}$), 12.09 (1H, s)。

[2968] 实施例 350

[2969] [式 640]

[2970]

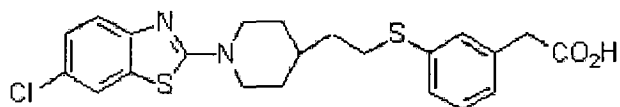


[2971] 收率:27%, $^1\text{H-NMR}$ (DMSO-d_6): δ 1.14-1.31 (2H, m), 1.50-1.61 (2H, m), 1.64-1.86 (3H, m), 2.96-3.22 (4H, m), 3.93-4.03 (2H, m), 7.23-7.36 (3H, m), 7.39 (1H, d, $J = 8.5\text{Hz}$), 7.67 (1H, d, $J = 7.0\text{Hz}$), 7.81 (1H, s), 7.88 (1H, d, $J = 2.0\text{Hz}$)。

[2972] 实施例 351

[2973] [式 641]

[2974]

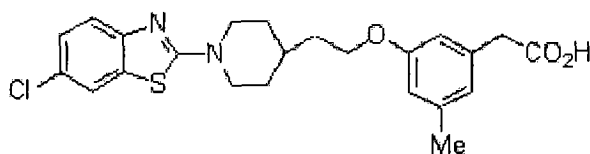


[2975] 收率:72%, $^1\text{H-NMR}$ (DMSO-d_6): δ 1.12-1.32 (2H, m), 1.50-1.63 (2H, m), 1.64-1.87 (3H, m), 2.95-3.06 (2H, m), 3.07-3.22 (2H, m), 3.55 (2H, s), 3.92-4.08 (2H, m), 4.05 (1H, d, $J = 2.0\text{Hz}$), 7.17-7.31 (4H, m), 7.39 (1H, d, $J = 8.5\text{Hz}$), 7.87 (1H, d, $J = 7.5\text{Hz}$), 12.36 (1H, brs)。

[2976] 实施例 352

[2977] [式 642]

[2978]

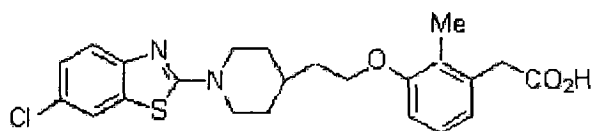


[2979] 收率:65%, $^1\text{H-NMR}$ (CDCl_3): δ 1.33 (2H, m), 1.73-1.90 (5H, m), 2.31 (3H, s), 3.14 (2H, t, $J = 12.6\text{Hz}$), 3.58 (2H, s), 4.01 (2H, t, $J = 5.7\text{Hz}$), 4.11 (2H, d, $J = 14.1\text{Hz}$), 6.65 (2H, s), 6.70 (1H, s), 7.23 (1H, dd, $J = 8.4, 2.1\text{Hz}$), 7.43 (1H, d, $J = 8.4\text{Hz}$), 7.54 (1H, d, $J = 2.1\text{Hz}$)。

[2980] 实施例 353

[2981] [式 643]

[2982]

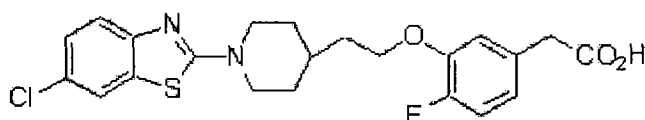


[2983] 收率:90%, $^1\text{H-NMR}$ (DMSO-d_6): δ 1.23-1.36 (2H, m), 1.72-1.87 (5H, m), 2.07 (3H, s), 3.15-3.23 (2H, m), 3.56 (2H, s), 4.01 (4H, t, $J = 5.7\text{Hz}$), 6.77 (1H, d, $J = 8.1\text{Hz}$), 6.87 (1H, d, $J = 8.1\text{Hz}$), 7.07 (1H, t, $J = 8.1\text{Hz}$), 7.28 (1H, dd, $J = 8.7, 2.1\text{Hz}$), 7.40 (1H, d, $J = 8.7\text{Hz}$), 7.89 (1H, d, $J = 2.1\text{Hz}$)。

[2984] 实施例 354

[2985] [式 644]

[2986]

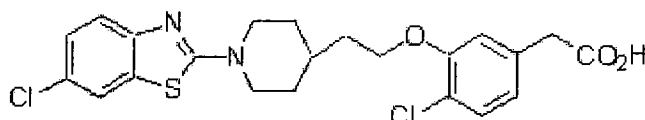


[2987] 收率:65%, $^1\text{H-NMR}$ (DMSO-d_6): δ 1.20-1.35 (1H, m), 1.65-1.90 (6H, m), 3.10-3.25 (2H, m), 3.54 (2H, s), 3.95-4.15 (4H, m), 6.75-6.85 (1H, m), 7.10 (1H, dd, $J = 8, 3.5\text{Hz}$), 7.14 (1H, d, $J = 8\text{Hz}$), 7.24 (1H, dd, $J = 8.5, 2\text{Hz}$), 7.40 (1H, d, $J = 8.5\text{Hz}$), 7.88 (1H, d, $J = 2\text{Hz}$), 12.34 (1H, brs)。

[2988] 实施例 355

[2989] [式 645]

[2990]

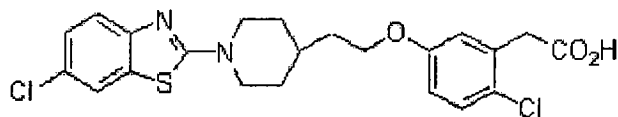


[2991] 收率:36%, $^1\text{H-NMR}$ (DMSO-d_6): δ 1.20-1.39 (2H, m), 1.66-1.93 (5H, m), 3.08-3.23 (2H, m), 3.40 (2H, s), 3.94-4.13 (4H, m), 6.76-6.84 (1H, m), 7.06 (1H, s), 7.23-7.32 (2H, m), 7.36-7.43 (1H, m), 7.87 (1H, d, $J = 2.0\text{Hz}$)。

[2992] 实施例 356

[2993] [式 646]

[2994]

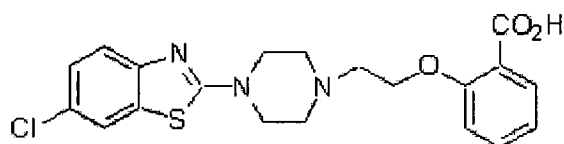


[2995] 收率:59%, $^1\text{H-NMR}$ (DMSO-d_6): δ 1.17-1.37 (2H, m), 1.62-1.91 (5H, m), 3.09-3.25 (2H, m), 3.34 (2H, s), 3.92-4.07 (4H, m), 6.75 (1H, dd, $J = 8.5, 3.0\text{Hz}$), 6.92 (1H, d, $J = 3.0\text{Hz}$), 7.21 (1H, d, $J = 8.5\text{Hz}$), 7.27 (1H, dd, $J = 8.5, 2.0\text{Hz}$), 7.40 (1H, d, $J = 8.5\text{Hz}$), 7.88 (1H, d, $J = 2.0\text{Hz}$)。

[2996] 实施例 357

[2997] [式 647]

[2998]

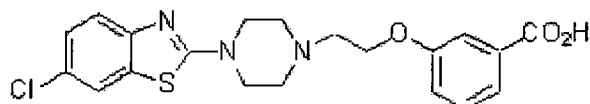


[2999] 收率:63%, $^1\text{H-NMR}$ (DMSO-d_6): δ 2.69 (4H, t, $J = 4.5\text{Hz}$), 2.80 (2H, t, $J = 5.5\text{Hz}$), 3.56 (4H, t, $J = 4.5\text{Hz}$), 4.22 (2H, t, $J = 5.5\text{Hz}$), 7.01 (1H, t, $J = 7.5\text{Hz}$), 7.16 (1H, d, $J = 7.5\text{Hz}$), 7.29 (1H, dd, $J = 8.5, 2.0\text{Hz}$), 7.43 (1H, d, $J = 8.5\text{Hz}$), 7.48 (1H, t, $J = 7.5\text{Hz}$), 7.61 (1H, d, $J = 7.5\text{Hz}$), 7.91 (1H, d, $J = 2.0\text{Hz}$)。

[3000] 实施例 358

[3001] [式 648]

[3002]

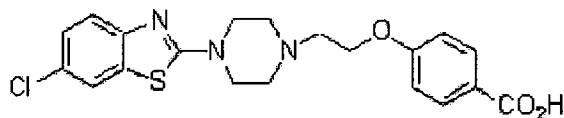


[3003] 收率:31%, $^1\text{H-NMR}$ (DMSO-d_6): δ 2.65 (4H, t, $J = 5.0\text{Hz}$), 2.80 (2H, t, $J = 5.5\text{Hz}$), 3.57 (4H, t, $J = 5.0\text{Hz}$), 4.15 (2H, t, $J = 5.5\text{Hz}$), 7.10 (1H, d, $J = 8.0\text{Hz}$), 7.27-7.36 (2H, m), 7.41-7.52 (3H, m), 7.91 (1H, d, $J = 2.2\text{Hz}$)。

[3004] 实施例 359

[3005] [式 649]

[3006]

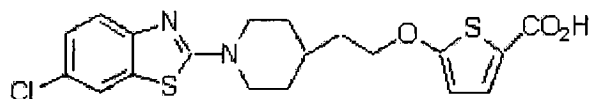


[3007] 收率:50%, $^1\text{H-NMR}$ (DMSO-d_6): δ 2.64 (4H, t, $J = 5.0\text{Hz}$), 2.80 (2H, t, $J = 5.5\text{Hz}$), 3.57 (4H, t, $J = 5.0\text{Hz}$), 4.20 (2H, t, $J = 5.5\text{Hz}$), 7.03 (2H, d, $J = 9\text{Hz}$), 7.29 (1H, dd, $J = 8.5, 2.0\text{Hz}$), 7.42 (1H, d, $J = 8.5\text{Hz}$), 7.87 (2H, d, $J = 9.0\text{Hz}$), 7.91 (1H, d, $J = 2.0\text{Hz}$)。

[3008] 实施例 360

[3009] [式 650]

[3010]

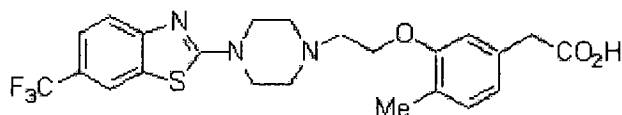


[3011] 收率:29%, $^1\text{H-NMR}$ (DMSO-d_6): δ 1.18-1.36 (2H, m), 1.68-1.88 (5H, m), 3.00-3.25 (2H, m), 3.94-4.07 (2H, m), 4.20 (2H, t, $J = 6.0\text{Hz}$), 6.41 (1H, d, $J = 4.0\text{Hz}$), 7.27 (1H, dd, $J = 8.5, 2.0\text{Hz}$), 7.40 (1H, d, $J = 8.5\text{Hz}$), 7.44 (1H, d, $J = 4.0\text{Hz}$), 7.88 (1H, d, $J = 2.0\text{Hz}$)。

[3012] 实施例 361

[3013] [式 651]

[3014]



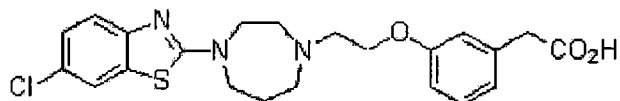
[3015] 收率:64%, $^1\text{H-NMR}$ (DMSO-d_6): δ 2.13 (3H, s), 2.68 (4H, t, $J = 5\text{Hz}$), 2.82 (2H, t,

J = 5.5Hz), 3.47 (2H, s), 3.63 (4H, t, J = 5Hz), 4.10 (2H, t, J = 5.5Hz), 6.72 (1H, d, J = 8Hz), 6.86 (1H, s), 7.05 (1H, d, J = 7.5Hz), 7.57 (2H, s), 8.25 (1H, s), 12.50 (1H, brs)。

[3016] 实施例 362

[3017] [式 652]

[3018]

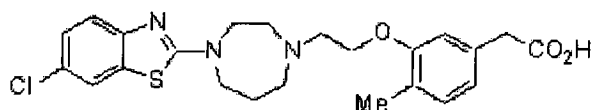


[3019] 收率:25%, $^1\text{H-NMR}$ (DMSO-d_6): δ 1.88-1.94 (2H, m), 2.73-2.75 (2H, m), 2.87 (2H, t, $J = 5.1\text{Hz}$), 2.92-2.95 (2H, m), 3.25 (2H, s), 3.67-3.72 (4H, m), 4.01 (2H, t, $J = 5.7\text{Hz}$), 6.68-6.82 (3H, m), 7.10 (1H, t, $J = 7.5\text{Hz}$), 7.26 (1H, dd, $J = 8.7, 2.1\text{Hz}$), 7.40 (1H, d, $J = 8.7\text{Hz}$), 7.88 (1H, d, $J = 2.1\text{Hz}$)。

[3020] 实施例 363

[3021] [式 653]

[3022]

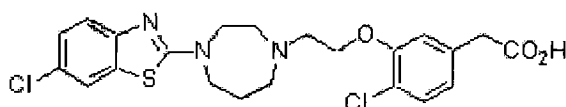


[3023] 收率:68%, $^1\text{H-NMR}$ (DMSO-d_6): δ 1.85-1.95 (2H, m), 2.09 (3H, s), 2.75-2.82 (2H, m), 2.92 (2H, t, $J = 5.5\text{Hz}$), 2.95-3.02 (2H, m), 3.49 (2H, s), 3.60-3.75 (4H, m), 4.03 (2H, t, $J = 5.5\text{Hz}$), 6.71 (1H, d, $J = 7.5\text{Hz}$), 6.83 (1H, s), 7.03 (1H, d, $J = 7.5\text{Hz}$), 7.26 (1H, dd, $J = 8.5, 2\text{Hz}$), 7.39 (1H, d, $J = 8.5\text{Hz}$), 7.87 (1H, d, $J = 2\text{Hz}$), 12.37 (1H, brs)。

[3024] 实施例 364

[3025] [式 654]

[3026]

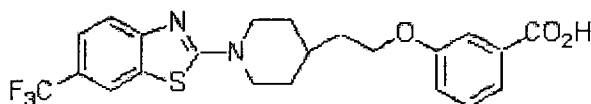


[3027] 收率:67%, $^1\text{H-NMR}$ (DMSO- d_6): δ 1.85-1.95(2H, m), 2.75-2.85(2H, m), 2.93(2H, t, $J = 5.5\text{Hz}$), 2.95-3.05(2H, m), 3.55(2H, s), 3.60-3.80(4H, m), 4.12(2H, t, $J = 5.5\text{Hz}$), 6.83(1H, dd, $J = 8, 1.5\text{Hz}$), 7.07(1H, d, $J = 1.5\text{Hz}$), 7.25(1H, dd, $J = 8.5, 2\text{Hz}$), 7.33(1H, d, $J = 8\text{Hz}$), 7.39(1H, d, $J = 8.5\text{Hz}$), 7.87(1H, d, $J = 2\text{Hz}$), 12.37(1H, brs)。

[3028] 实施例 365

[3029] [式 655]

[3030]



[3031] 收 率 :45 % , $^1\text{H-NMR}$ (DMSO-d_6) : δ 1.20-1.39 (2H, m) , 1.65-1.94 (5H, m) , 3.17-3.32 (2H, m) , 3.99-4.12 (4H, m) , 6.92-6.99 (1H, m) , 7.23 (1H, t, $J = 7.5\text{Hz}$) , 7.40-7.48 (2H, m) , 7.51-7.59 (2H, m) , 8.21 (1H, s) 。

[3032] 实施例 366

[3033] [式 656]

[3034]

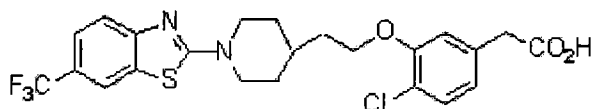


[3035] 收率:48%, $^1\text{H-NMR}$ (DMSO-d_6): δ 1.18-1.38 (2H, m), 1.63-1.94 (5H, m), 3.13-3.30 (2H, m), 3.32 (2H, s), 3.93-4.13 (4H, m), 6.70-6.85 (3H, m), 7.13 (1H, t, $J = 8.0\text{Hz}$), 7.49-7.60 (2H, m), 8.21 (1H, s)。

[3036] 实施例 367

[3037] [式 657]

[3038]

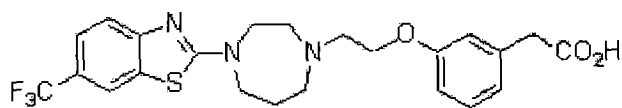


[3039] 收率:82%, $^1\text{H-NMR}$ (DMSO-d_6): δ 1.17-1.42 (2H, m), 1.68-1.96 (5H, m), 3.13-3.30 (2H, m), 3.43 (2H, s), 3.95-4.19 (4H, m), 6.81 (1H, d, $J = 7.5\text{Hz}$), 7.07 (1H, s), 7.28 (1H, d, $J = 7.5\text{Hz}$), 7.49-7.61 (2H, m), 8.21 (1H, s)。

[3040] 实施例 368

[3041] [式 658]

[3042]

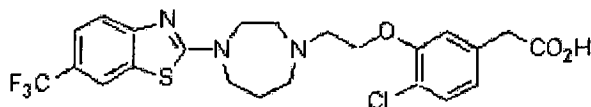


[3043] 收率:77%, $^1\text{H-NMR}$ (DMSO-d_6): δ 1.85-2.00 (2H, m), 2.68-2.81 (2H, m), 2.82-3.03 (4H, m), 3.51 (2H, s), 3.60-3.89 (4H, m), 3.97-4.09 (2H, m), 6.75-6.90 (3H, m), 7.19 (1H, t, $J = 8.0\text{Hz}$), 7.50-7.60 (2H, m), 8.22 (1H, s), 12.26 (1H, br)。

[3044] 实施例 369

[3045] [式 659]

[3046]

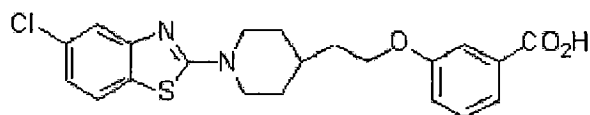


[3047] 收率:78%, $^1\text{H-NMR}$ (DMSO-d_6): δ 1.84-1.98 (2H, m), 2.74-2.85 (2H, m), 2.86-3.07 (4H, m), 3.56 (2H, s), 3.60-3.85 (4H, m), 4.06-4.18 (2H, m), 6.83 (1H, dd, $J = 8.0, 2.0\text{Hz}$), 7.07 (1H, d, $J = 2.0\text{Hz}$), 7.33 (1H, d, $J = 8.0\text{Hz}$), 7.51-7.57 (2H, m), 8.22 (1H, s), 12.35 (1H, br)。

[3048] 实施例 370

[3049] [式 660]

[3050]

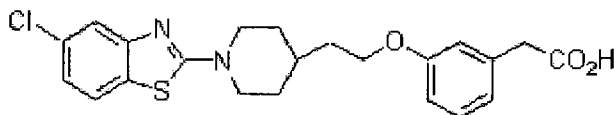


[3051] 收率:68%, $^1\text{H-NMR}$ (CDCl_3): δ 1.19-1.39 (2H, m), 1.64-1.92 (5H, m), 3.12-3.27 (2H, m), 3.96-4.08 (4H, m), 6.80-6.87 (1H, m), 7.06 (1H, dd, $J = 8.0, 2.0\text{Hz}$), 7.15 (1H, t, $J = 8.0\text{Hz}$), 7.38-7.47 (3H, m), 7.76 (1H, d, $J = 8.0\text{Hz}$)。

[3052] 实施例 371

[3053] [式 661]

[3054]

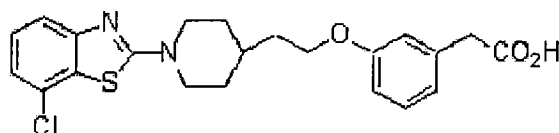


[3055] 收率:87%, $^1\text{H-NMR}$ (DMSO-d_6): δ 1.19-1.40 (2H, m), 1.63-1.92 (5H, m), 3.10-3.27 (2H, m), 3.51 (2H, s), 3.94-4.10 (4H, m), 6.77-6.86 (3H, m), 7.07 (1H, dd, $J = 8.5, 2.0\text{Hz}$), 7.20 (1H, t, $J = 7.5\text{Hz}$), 7.44 (1H, d, $J = 2.0\text{Hz}$), 7.76 (1H, d, $J = 8.5\text{Hz}$), 12.33 (1H, br)。

[3056] 实施例 372

[3057] [式 662]

[3058]

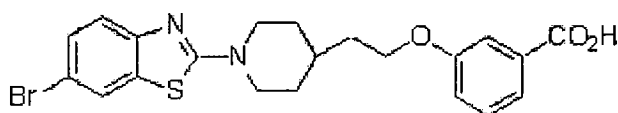


[3059] 收率:36%, $^1\text{H-NMR}$ (DMSO-d_6): δ 1.20-1.39 (2H, m), 1.63-1.93 (5H, m), 3.12-3.28 (2H, m), 3.53 (2H, s), 3.95-4.12 (4H, m), 6.78-6.88 (3H, m), 7.13 (1H, dd, $J = 8.0, 1.0\text{Hz}$), 7.20 (1H, t, $J = 7.5\text{Hz}$), 7.31 (1H, d, $J = 8.0\text{Hz}$), 7.39 (1H, dd, $J = 8.0, 1.0\text{Hz}$), 12.31 (1H, s)。

[3060] 实施例 373

[3061] [式 663]

[3062]

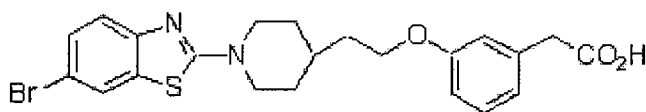


[3063] 收率:89%, $^1\text{H-NMR}$ (DMSO-d_6): δ 1.19-1.39 (2H, m), 1.65-1.93 (5H, m), 3.10-3.25 (2H, m), 3.96-4.09 (4H, m), 6.87-6.94 (1H, m), 7.20 (1H, t, $J = 8.0\text{Hz}$), 7.31-7.48 (4H, m), 8.00 (1H, d, $J = 2.0\text{Hz}$)。

[3064] 实施例 374

[3065] [式 664]

[3066]



[3067] 收率:58%, $^1\text{H-NMR}$ (DMSO-d_6): δ 1.18-1.37 (2H, m), 1.63-1.91 (5H, m), 3.10-3.26 (4H, m), 3.92-4.07 (4H, m), 6.63-6.84 (3H, m), 7.08 (1H, t, $J = 8.0\text{Hz}$), 7.31-7.42 (2H, m), 7.99 (1H, d, $J = 2.0\text{Hz}$)。

[3068] 实施例 375

[3069] [式 665]

[3070]



[3071] 收率:46%, $^1\text{H-NMR}$ (DMSO-d_6): δ 1.18-1.36 (2H, m), 1.61-1.90 (5H, m), 2.32 (3H, s), 3.04-3.19 (2H, m), 3.39 (2H, s), 3.91-4.07 (4H, m), 6.72-6.86 (3H, m), 7.06 (1H, d, $J = 8.5\text{Hz}$), 7.16 (1H, t, $J = 8.0\text{Hz}$), 7.31 (1H, d, $J = 8.5\text{Hz}$), 7.53 (1H, s)。

[3072] 实施例 376

[3073] [式 666]

[3074]

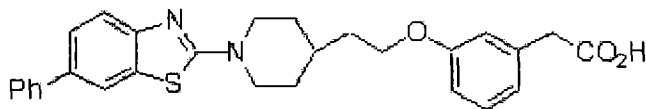


[3075] 收率:83%, $^1\text{H-NMR}$ (DMSO-d_6): δ 1.18-1.39 (2H, m), 1.63-1.92 (5H, m), 3.07-3.24 (2H, m), 3.52 (2H, s), 3.93-4.09 (4H, m), 6.77-6.78 (3H, m), 7.10 (1H, td, $J = 9.0, 2.5\text{Hz}$), 7.21 (1H, t, $J = 8.0\text{Hz}$), 7.41 (1H, dd, $J = 9.0, 4.5\text{Hz}$), 7.69 (1H, dd, $J = 9.0, 2.5\text{Hz}$), 12.34 (1H, br)。

[3076] 实施例 377

[3077] [式 667]

[3078]

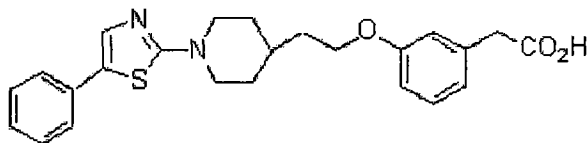


[3079] 收率:51%, $^1\text{H-NMR}$ (DMSO-d_6): δ 1.18-1.35 (2H, m), 1.63-1.93 (5H, m), 3.09-3.26 (2H, m), 3.52 (2H, s), 3.95-4.13 (4H, m), 6.77-6.90 (3H, m), 7.20 (1H, t, $J = 8.0\text{Hz}$), 7.31 (1H, t, $J = 8.0\text{Hz}$), 7.43 (2H, t, $J = 8.0\text{Hz}$), 7.48 (1H, d, $J = 8.5\text{Hz}$), 7.57 (1H, d, $J = 8.5\text{Hz}$), 7.66 (2H, d, $J = 8.0\text{Hz}$), 8.07 (1H, s), 12.31 (1H, br)。

[3080] 实施例 378

[3081] [式 668]

[3082]

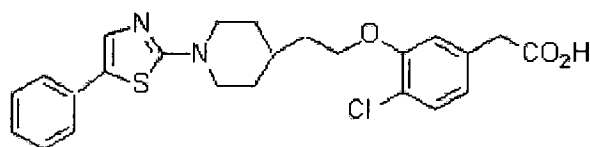


[3083] 收率:77%, $^1\text{H-NMR}$ (DMSO-d_6): δ 1.19-1.40 (2H, m), 1.64-1.91 (5H, m), 2.98-3.14 (2H, m), 3.53 (2H, s), 3.86-4.10 (4H, m), 6.78-6.90 (3H, m), 7.16-7.26 (2H, m), 7.31-7.34 (2H, m), 7.44-7.50 (2H, m), 7.58 (1H, s), 12.30 (1H, s)。

[3084] 实施例 379

[3085] [式 669]

[3086]

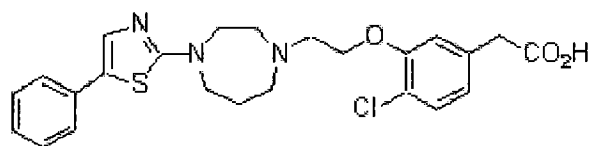


[3087] 收率:76%, $^1\text{H-NMR}$ (DMSO-d_6): δ 1.22-1.41 (2H, m), 1.68-1.90 (5H, m), 2.97-3.13 (2H, m), 3.56 (2H, s), 3.86-3.99 (2H, m), 4.06-4.16 (2H, m), 6.84 (1H, dd, $J = 8.0, 1.5\text{Hz}$), 7.09 (1H, d, $J = 1.5\text{Hz}$), 7.20 (1H, t, $J = 7.5\text{Hz}$), 7.31-7.41 (3H, m), 7.43-7.51 (2H, m), 7.58 (1H, s)。

[3088] 实施例 380

[3089] [式 670]

[3090]

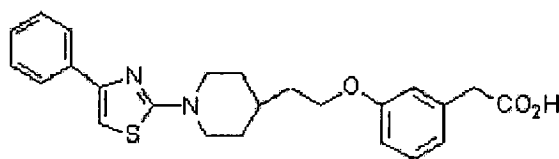


[3091] 收率:69%, $^1\text{H-NMR}$ (DMSO-d_6): δ 1.83-1.95 (2H, m), 2.73-2.83 (2H, m), 2.87-3.00 (4H, m), 3.52-3.71 (6H, m), 4.12 (2H, m), 6.83 (1H, d, $J = 7.0\text{Hz}$), 7.08 (1H, s), 7.18 (1H, t, $J = 7.5\text{Hz}$), 7.28-7.38 (3H, m), 7.40-7.47 (2H, m), 7.56 (1H, s)。

[3092] 实施例 381

[3093] [式 671]

[3094]

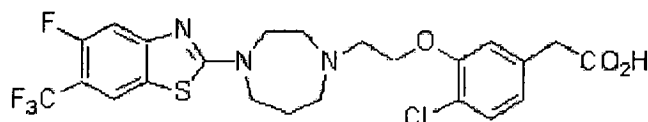


[3095] 收率:79%, $^1\text{H-NMR}$ (DMSO-d_6): δ 1.20-1.41 (2H, m), 1.65-1.93 (5H, m), 3.05 (2H, m), 3.53 (2H, s), 3.90-4.10 (4H, m), 6.76-6.87 (3H, m), 7.16-7.32 (3H, m), 7.38 (2H, t, $J = 7.5\text{Hz}$), 7.85 (2H, d, $J = 7.5\text{Hz}$), 12.29 (1H, s)。

[3096] 实施例 382

[3097] [式 672]

[3098]

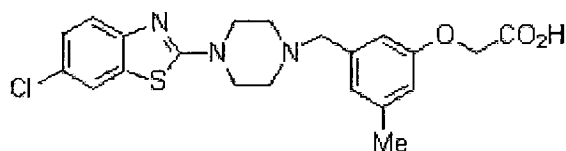


[3099] 收率:54%, $^1\text{H-NMR}$ (CDCl_3): 1.88-2.03 (2H, m), 2.73-3.04 (6H, m), 3.30 (2H, s), 3.47-3.84 (4H, m), 3.86-4.02 (2H, m), 6.59 (1H, d, $J = 8.0\text{Hz}$), 6.68 (1H, s), 7.07 (1H, d, $J = 8.0\text{Hz}$), 7.20 (1H, d, $J = 11.5\text{Hz}$), 7.68 (1H, d, $J = 7.0\text{Hz}$)。

[3100] 实施例 383

[3101] [式 673]

[3102]

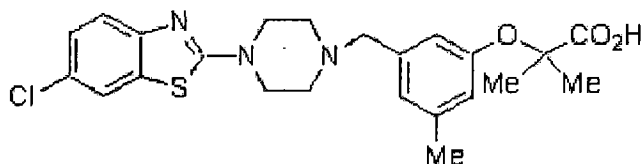


[3103] 收率:12%, $^1\text{H-NMR}$ (DMSO-d_6): δ 2.25 (3H, s), 2.45-2.55 (4H, m), 3.44 (2H, s), 3.50-3.60 (4H, m), 4.47 (2H, s), 6.59 (1H, s), 6.65 (1H, s), 7.00 (1H, s), 7.28 (1H, dd, $J = 8.5, 2\text{Hz}$), 7.42 (1H, d, $J = 8.5\text{Hz}$), 7.90 (1H, d, $J = 2\text{Hz}$)。

[3104] 实施例 384

[3105] [式 674]

[3106]

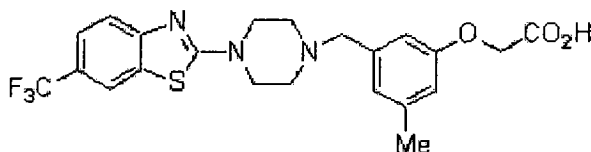


[3107] 收率:68%, $^1\text{H-NMR}$ (CDCl_3): δ 1.60 (6H, s), 2.23 (3H, s), 2.65 (4H, t, $J = 5\text{Hz}$), 3.57 (2H, s), 3.62 (4H, t, $J = 5\text{Hz}$), 6.19 (1H, brs), 6.70-6.88 (3H, m), 7.24 (1H, dd, $J = 8.5, 2\text{Hz}$), 7.42 (1H, d, $J = 8.5\text{Hz}$), 7.54 (1H, d, $J = 2\text{Hz}$)。

[3108] 实施例 385

[3109] [式 675]

[3110]

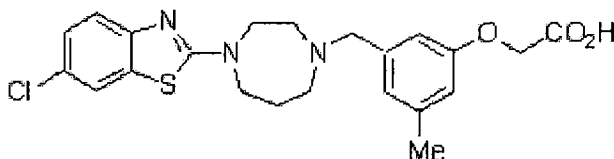


[3111] 收率:64%, $^1\text{H-NMR}$ (DMSO-d_6): δ 2.24 (3H, s), 2.51 (4H, t, $J = 5.5\text{Hz}$), 3.43 (2H, s), 3.62 (4H, t, $J = 5.5\text{Hz}$), 4.10 (2H, s), 6.53 (1H, s), 6.61 (1H, s), 6.64 (1H, s), 7.57 (2H, s), 8.24 (1H, s)。

[3112] 实施例 386

[3113] [式 676]

[3114]

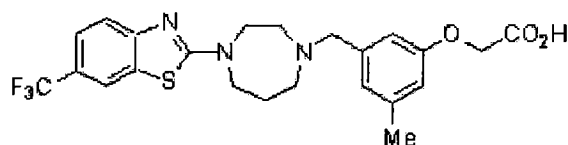


[3115] 收率:96%, $^1\text{H-NMR}$ (DMSO-d_6): δ 1.89-1.97 (2H, m), 2.23 (3H, s), 2.60 (2H, t, $J = 4.2\text{Hz}$), 2.74-2.77 (2H, m), 3.55 (2H, s), 3.68-3.70 (4H, m), 4.56 (2H, s), 6.58 (1H, s), 6.65 (1H, s), 6.70 (1H, s), 7.26 (1H, dd, $J = 9.0, 2.1\text{Hz}$), 7.39 (1H, d, $J = 8.7\text{Hz}$), 7.86 (1H, d, $J = 2.4\text{Hz}$)。

[3116] 实施例 387

[3117] [式 677]

[3118]

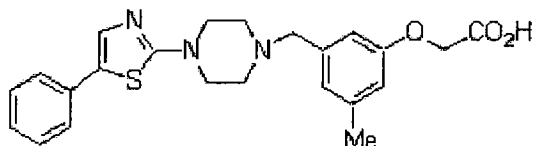


[3119] 收率:98%, $^1\text{H-NMR}$ (DMSO-d_6): δ 1.85-2.00 (2H, m), 2.20 (3H, s), 2.55-2.65 (2H, m), 2.70-2.83 (2H, m), 3.52 (2H, s), 3.55-3.85 (4H, m), 4.14 (2H, s), 6.52 (1H, s), 6.58-6.65 (2H, m), 7.55 (2H, s), 8.22 (1H, s)。

[3120] 实施例 388

[3121] [式 678]

[3122]

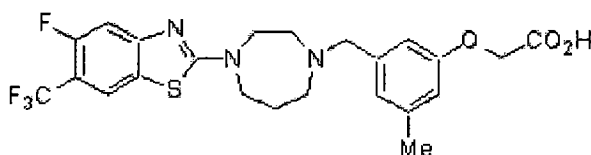


[3123] 收率:59%, $^1\text{H-NMR}$ (CD_3OD): δ 2.29 (3H, s), 2.60 (4H, t, $J = 5.0\text{Hz}$), 3.46-3.57 (6H, m), 4.36 (2H, s), 6.69 (1H, s), 6.75 (2H, s), 7.21 (1H, t, $J = 7.5\text{Hz}$), 7.33 (2H, t, $J = 7.5\text{Hz}$), 7.41 (1H, s), 7.45 (2H, d, $J = 7.5\text{Hz}$)。

[3124] 实施例 389

[3125] [式 679]

[3126]

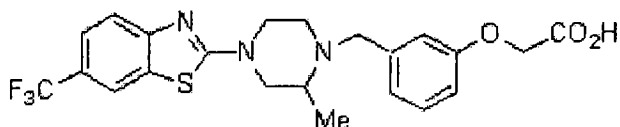


[3127] 收率:67%, $^1\text{H-NMR}$ (CD_3OD): δ 1.98-2.12 (2H, m), 2.27 (3H, s), 2.70-2.81 (2H, m), 2.84-2.94 (2H, m), 3.65 (2H, s), 3.67-3.93 (4H, m), 4.39 (2H, s), 6.67 (1H, s), 6.73 (1H, s), 6.74 (1H, s), 7.27 (1H, d, $J = 12.0\text{Hz}$), 7.96 (1H, d, $J = 7.0\text{Hz}$)。

[3128] 实施例 390

[3129] [式 680]

[3130]

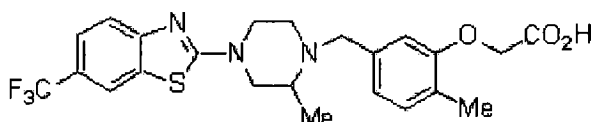


[3131] 收率:97%, $^1\text{H-NMR}$ (DMSO-d_6): δ 1.15 (3H, d, $J = 6\text{Hz}$), 2.18-2.33 (1H, m), 2.58-2.70 (1H, m), 2.70-2.83 (1H, m), 3.15-3.30 (2H, m), 3.35-3.50 (1H, m), 3.65-3.80 (1H, m), 3.83 (1H, d, $J = 11\text{Hz}$), 3.93 (1H, d, $J = 14\text{Hz}$), 4.65 (2H, s), 6.78 (1H, d, $J = 8\text{Hz}$), 6.90-6.95 (2H, m), 7.24 (1H, t, $J = 8\text{Hz}$), 7.56 (2H, s), 8.24 (1H, s), 13.0 (1H, brs)。

[3132] 实施例 391

[3133] [式 681]

[3134]

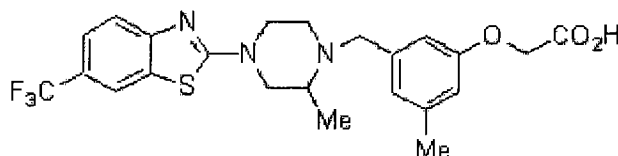


[3135] 收率:86%, $^1\text{H-NMR}$ (DMSO- d_6): δ 1.13 (3H, d, $J = 6\text{Hz}$), 2.17 (3H, s), 2.20-2.30 (1H, m), 2.55-2.65 (1H, m), 2.68-2.80 (1H, m), 3.15-3.50 (3H, m), 3.65-3.75 (1H, m), 3.82 (1H, d, $J = 9\text{Hz}$), 3.88 (1H, d, $J = 13.5\text{Hz}$), 4.68 (2H, s), 6.80 (1H, s), 6.83 (1H, d, $J = 7.5\text{Hz}$), 7.09 (1H, d, $J = 7.5\text{Hz}$), 7.56 (2H, s), 8.23 (1H, s), 12.30 (1H, brs)。

[3136] 实施例 392

[3137] [式 682]

[3138]

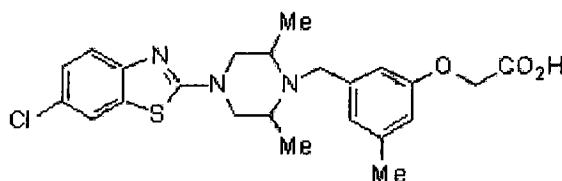


[3139] 收率:86%, $^1\text{H-NMR}$ (DMSO- d_6): δ 1.14 (3H, d, $J = 6\text{Hz}$), 2.20-2.25 (1H, m), 2.26 (3H, s), 2.55-2.65 (1H, m), 2.70-2.80 (1H, m), 3.10-3.50 (3H, m), 3.70-3.82 (3H, m), 4.63 (2H, s), 6.61 (1H, s), 6.70 (1H, s), 6.75 (1H, s), 7.55-7.59 (2H, m), 8.24 (1H, s), 12.9 (1H, brs)。

[3140] 实施例 393

[3141] [式 683]

[3142]

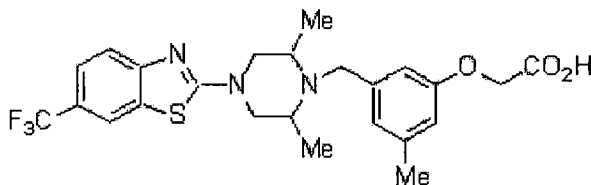


[3143] 收率:73%, $^1\text{H-NMR}$ (DMSO- d_6): δ 1.03 (6H, d, $J = 6\text{Hz}$), 2.25 (3H, s), 2.60-2.80 (2H, m), 2.95-3.10 (2H, m), 3.71 (2H, s), 3.80-3.85 (2H, m), 4.61 (2H, s), 6.55 (1H, s), 6.76 (2H, s), 7.28 (1H, dd, $J = 8.5, 2\text{Hz}$), 7.42 (1H, d, $J = 8.5\text{Hz}$), 7.90 (1H, d, $J = 2\text{Hz}$), 12.95 (1H, s)。

[3144] 实施例 394

[3145] [式 684]

[3146]

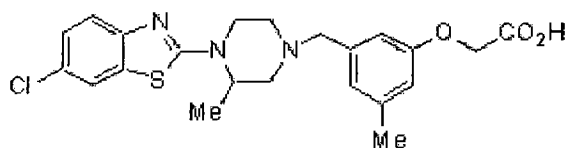


[3147] 收率:82%, $^1\text{H-NMR}$ (DMSO- d_6): δ 1.04 (6H, d, $J = 6\text{Hz}$), 2.25 (3H, s), 2.70-2.80 (2H, m), 2.95-3.15 (2H, m), 3.71 (2H, s), 3.80-3.95 (2H, m), 4.61 (2H, s), 6.55 (1H, s), 6.76 (2H, s), 7.57 (2H, s), 8.24 (1H, s), 12.94 (1H, brs)。

[3148] 实施例 395

[3149] [式 685]

[3150]

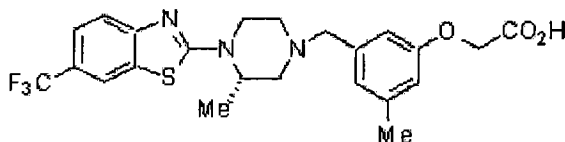


[3151] 收率:72%, $^1\text{H-NMR}$ (DMSO- d_6): δ 1.31 (3H, d, $J = 6.5\text{Hz}$), 2.02-2.24 (2H, m), 2.25 (3H, s), 2.70 (1H, d, $J = 11\text{Hz}$), 2.88 (1H, d, $J = 12\text{Hz}$), 3.20-3.35 (1H, m), 3.37 (1H, d, $J = 13.5\text{Hz}$), 3.51 (1H, d, $J = 13.5\text{Hz}$), 3.77 (1H, d, $J = 13\text{Hz}$), 4.10-4.25 (1H, m), 4.60 (2H, s), 6.61 (1H, s), 6.70 (1H, s), 6.73 (1H, s), 7.26 (1H, dd, $J = 8.5, 2\text{Hz}$), 7.40 (1H, d, $J = 8.5\text{Hz}$), 7.88 (1H, d, $J = 2\text{Hz}$), 13.00 (1H, brs)。

[3152] 实施例 396

[3153] [式 686]

[3154]

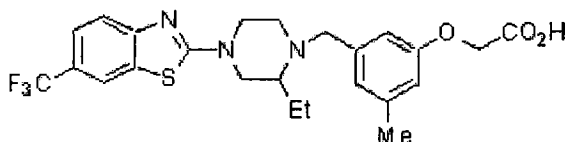


[3155] 收率:76%, $^1\text{H-NMR}$ (DMSO- d_6): δ 1.34 (3H, d, $J = 6.5\text{Hz}$), 2.06-2.30 (5H, m), 2.73 (1H, d, $J = 10.5\text{Hz}$), 2.90 (1H, d, $J = 10.5\text{Hz}$), 3.30-3.56 (3H, m), 3.84 (1H, d, $J = 11.5\text{Hz}$), 4.19-4.32 (1H, m), 4.38 (2H, s), 6.58 (1H, s), 6.67 (1H, s), 6.70 (1H, s), 7.56 (2H, s), 8.24 (1H, s)。

[3156] 实施例 397

[3157] [式 687]

[3158]

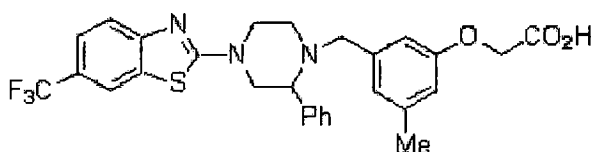


[3159] 收率:82%, $^1\text{H-NMR}$ (CDCl₃): δ 0.97 (3H, t, $J = 7.5\text{Hz}$), 1.62-1.85 (2H, m), 2.28 (3H, s), 2.80-3.00 (3H, m), 3.55 (1H, d, $J = 13\text{Hz}$), 3.65-3.77 (1H, m), 3.77-3.90 (3H, m), 4.23 (1H, d, $J = 13\text{Hz}$), 4.65 (2H, s), 6.63 (1H, s), 6.80 (1H, s), 7.01 (1H, s), 7.53 (1H, d, $J = 8.5\text{Hz}$), 7.56 (1H, d, $J = 8.5\text{Hz}$), 7.84 (1H, s)。

[3160] 实施例 398

[3161] [式 688]

[3162]



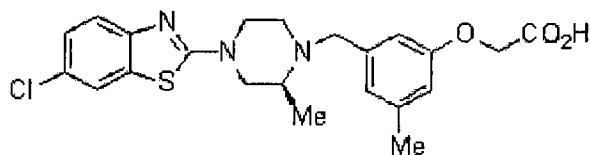
[3163] 收率:92%, $^1\text{H-NMR}$ (CDCl₃): δ 2.27 (3H, s), 2.27-2.40 (1H, m), 2.90 (1H, d, $J = 13.5\text{Hz}$), 3.06 (1H, d, $J = 11.5\text{Hz}$), 3.32-3.55 (3H, m), 3.80 (1H, d, $J = 13.5\text{Hz}$), 3.95-4.10 (2H, m), 5.30 (2H, s), 6.63 (1H, s), 6.66 (1H, s), 6.72 (1H, s), 7.30-7.45 (3H, m),

7.45-7.60 (4H, m), 7.82 (1H, s)。

[3164] 实施例 399

[3165] [式 689]

[3166]

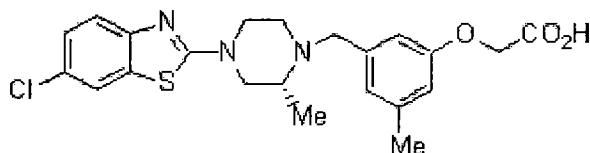


[3167] 收率:81%, $^1\text{H-NMR}$ (CDCl_3): δ 1.32 (3H, d, $J = 6.6\text{Hz}$), 2.26 (3H, s), 2.76 (1H, s), 2.93-3.02 (2H, m), 3.37 (1H, d, $J = 12.9\text{Hz}$), 3.49-3.56 (1H, m), 3.70 (2H, s), 3.87 (1H, d, $J = 10.8\text{Hz}$), 4.25 (1H, d, $J = 12.9\text{Hz}$), 4.63 (2H, s), 6.62 (1H, s), 6.77 (1H, s), 6.99 (1H, s), 7.24 (1H, dd, $J = 2.1, 8.7\text{Hz}$), 7.42 (1H, d, $J = 8.7\text{Hz}$), 7.54 (1H, d, $J = 2.1\text{Hz}$)。

[3168] 实施例 400

[3169] [式 690]

[3170]

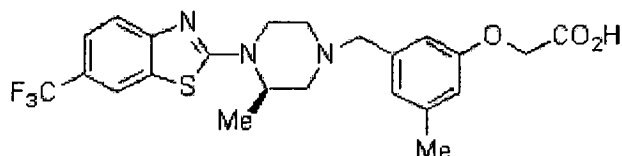


[3171] 收率:80%, $^1\text{H-NMR}$ (CDCl_3): δ 1.33 (3H, d, $J = 6.0\text{Hz}$), 2.27 (3H, s), 2.76 (1H, br), 2.93-3.02 (2H, m), 3.38 (1H, d, $J = 12.6\text{Hz}$), 3.49-3.56 (1H, m), 3.71 (2H, s), 3.87 (1H, d, $J = 11.1\text{Hz}$), 4.25 (1H, d, $J = 12.6\text{Hz}$), 4.63 (2H, s), 6.62 (1H, s), 6.77 (1H, s), 6.99 (1H, s), 7.24 (1H, dd, $J = 1.8, 8.7\text{Hz}$), 7.42 (1H, d, $J = 8.7\text{Hz}$), 7.54 (1H, d, $J = 1.8\text{Hz}$)。

[3172] 实施例 401

[3173] [式 691]

[3174]

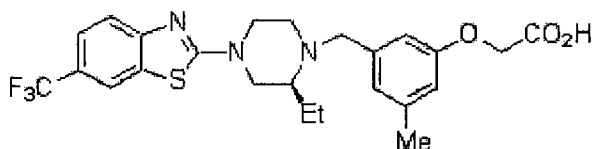


[3175] 收率:88%, $^1\text{H-NMR}$ (CDCl_3): δ 1.41 (3H, d, $J = 6.5\text{Hz}$), 2.29 (3H, s), 2.35 (1H, td, $J = 12, 3.5\text{Hz}$), 2.48 (1H, dd, $J = 12, 4\text{Hz}$), 2.91 (1H, d, $J = 12\text{Hz}$), 3.26 (1H, d, $J = 11.5\text{Hz}$), 3.52 (1H, d, $J = 13\text{Hz}$), 3.54-3.65 (1H, m), 3.80 (1H, d, $J = 13\text{Hz}$), 3.89 (1H, d, $J = 13\text{Hz}$), 4.25-4.36 (1H, m), 4.62 (2H, s), 6.69 (1H, s), 6.75 (1H, s), 6.86 (1H, s), 7.52 (1H, d, $J = 8.5\text{Hz}$), 7.56 (1H, d, $J = 8.5\text{Hz}$), 7.83 (1H, s)。

[3176] 实施例 402

[3177] [式 692]

[3178]

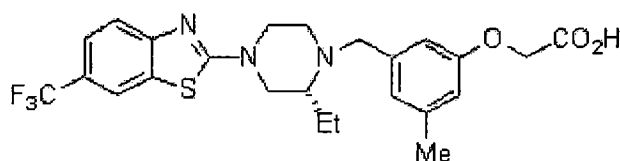


[3179] 收率:94%, $^1\text{H-NMR}$ (CDCl_3): δ 0.96 (3H, t, $J = 7\text{Hz}$), 1.60-1.86 (2H, m), 2.29 (3H, s), 2.75-2.86 (1H, m), 2.87-3.00 (1H, m), 3.00-3.10 (1H, m), 3.51 (1H, d, $J = 13\text{Hz}$), 3.65-3.80 (1H, m), 3.80-3.93 (3H, m), 4.28 (1H, d, $J = 13\text{Hz}$), 4.63 (1H, d, $J = 16.5\text{Hz}$), 4.71 (1H, d, $J = 16.5\text{Hz}$), 6.63 (1H, s), 6.81 (1H, s), 7.02 (1H, s), 7.53 (1H, d, $J = 8.5\text{Hz}$), 7.57 (1H, d, $J = 8.5\text{Hz}$), 7.84 (1H, s)。

[3180] 实施例 403

[3181] [式 693]

[3182]

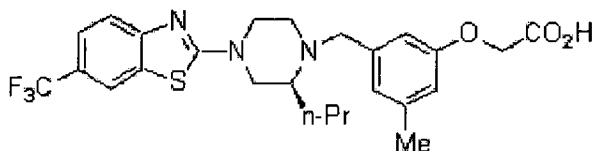


[3183] 收率:86%, $^1\text{H-NMR}$ (CDCl_3): δ 0.96 (3H, t, $J = 7.5\text{Hz}$), 1.62-1.86 (2H, m), 2.28 (3H, s), 2.76-2.88 (1H, m), 2.89-3.00 (1H, m), 3.01-3.13 (1H, m), 3.52 (1H, d, $J = 13\text{Hz}$), 3.65-3.93 (4H, m), 4.30 (1H, d, $J = 13\text{Hz}$), 4.63 (1H, d, $J = 16.5\text{Hz}$), 4.72 (1H, d, $J = 16.5\text{Hz}$), 6.63 (1H, s), 6.82 (1H, s), 7.03 (1H, s), 7.49-7.60 (2H, m), 7.84 (1H, s)。

[3184] 实施例 404

[3185] [式 694]

[3186]

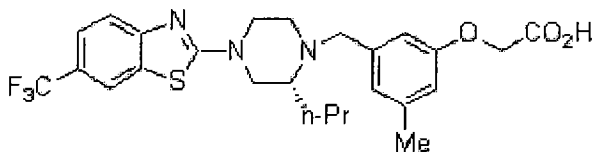


[3187] 收率:68%, $^1\text{H-NMR}$ (DMSO-d_6): δ 0.89 (3H, t, $J = 7.0\text{Hz}$), 1.22-1.69 (4H, m), 2.22-2.37 (1H, m), 2.24 (3H, s), 2.49-2.62 (1H, m), 2.68-2.82 (1H, m), 3.28 (1H, d, $J = 13.5\text{Hz}$), 3.38-3.68 (3H, m), 3.69-3.80 (1H, m), 3.83 (1H, d, $J = 13.5\text{Hz}$), 4.28 (2H, s), 6.53 (1H, s), 6.64 (1H, s), 6.67 (1H, s), 7.53 (1H, d, $J = 8.5\text{Hz}$), 7.57 (1H, d, $J = 8.5\text{Hz}$), 8.22 (1H, s)。

[3188] 实施例 405

[3189] [式 695]

[3190]



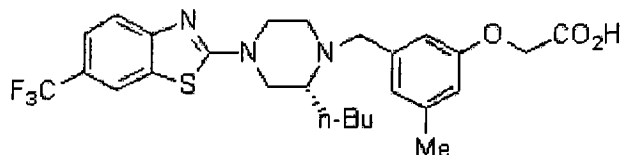
[3191] 收率:87%, $^1\text{H-NMR}$ (CDCl_3): δ 0.90 (3H, t, $J = 7.2\text{Hz}$), 1.19-1.28 (1H, m), 1.45-1.52 (1H, m), 1.65 (2H, br), 2.78 (3H, s), 2.93 (2H, br), 3.05 (1H, br), 3.52 (1H, d, J

= 12.6Hz), 3.67-3.74 (1H, m), 3.81-3.91 (3H, m), 4.30 (1H, d), 4.66 (2H, q, $J = 11.1\text{Hz}$), 6.62 (1H, s), 6.81 (1H, s), 7.03 (1H, s), 7.52-7.61 (2H, m), 7.84 (1H, s)。

[3192] 实施例 406

[3193] [式 696]

[3194]

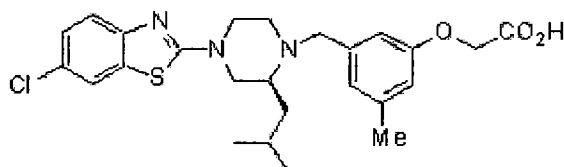


[3195] 收率:82%, $^1\text{H-NMR}$ (DMSO- d_6): δ 0.88 (3H, t, $J = 6.5\text{Hz}$), 1.18-1.70 (6H, m), 2.23 (3H, s), 2.24-2.37 (1H, m), 2.48-2.60 (1H, m), 2.67-2.80 (1H, m), 3.27 (1H, d, $J = 13.5\text{Hz}$), 3.36-3.82 (4H, m), 3.83 (1H, d, $J = 13.5\text{Hz}$), 4.31 (2H, s), 6.54 (1H, s), 6.65 (1H, s), 6.67 (1H, s), 7.53 (1H, d, $J = 9.0\text{Hz}$), 7.56 (1H, d, $J = 9.0\text{Hz}$), 8.22 (1H, s)。

[3196] 实施例 407

[3197] [式 697]

[3198]

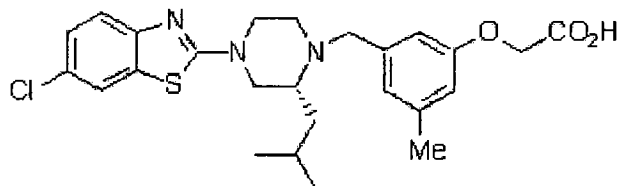


[3199] 收率:70%, $^1\text{H-NMR}$ (DMSO- d_6): δ 0.88 (6H, t, $J = 6.5\text{Hz}$), 1.21-1.35 (1H, m), 1.45-1.58 (1H, m), 1.58-1.73 (1H, m), 2.23 (3H, s), 2.32-2.43 (1H, m), 2.59-2.80 (2H, m), 3.35 (1H, d, $J = 13.5\text{Hz}$), 3.37-3.45 (1H, m), 3.45-3.60 (2H, m), 3.60-3.71 (1H, m), 3.77 (1H, d, $J = 13.5\text{Hz}$), 4.19 (2H, s), 6.51 (1H, s), 6.63 (1H, s), 6.66 (1H, s), 7.27 (1H, dd, $J = 8.5, 2\text{Hz}$), 7.40 (1H, d, $J = 8.5\text{Hz}$), 7.88 (1H, d, $J = 2\text{Hz}$)。

[3200] 实施例 408

[3201] [式 698]

[3202]

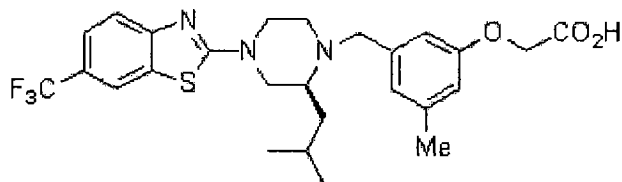


[3203] 收率:77%, $^1\text{H-NMR}$ (DMSO- d_6): δ 0.87 (3H, d, $J = 6.5\text{Hz}$), 0.89 (3H, d, $J = 6.5\text{Hz}$), 1.21-1.36 (1H, m), 1.43-1.57 (1H, m), 1.58-1.73 (1H, m), 2.23 (3H, s), 2.30-2.43 (1H, m), 2.60-2.79 (2H, m), 3.34 (1H, d, $J = 13.5\text{Hz}$), 3.35-3.72 (4H, m), 3.77 (1H, d, $J = 13.5\text{Hz}$), 4.25 (2H, s), 6.53 (1H, s), 6.64 (1H, s), 6.70 (1H, s), 7.27 (1H, dd, $J = 8.5, 2.0\text{Hz}$), 7.40 (1H, d, $J = 8.5\text{Hz}$), 7.88 (1H, d, $J = 2.0\text{Hz}$)。

[3204] 实施例 409

[3205] [式 699]

[3206]

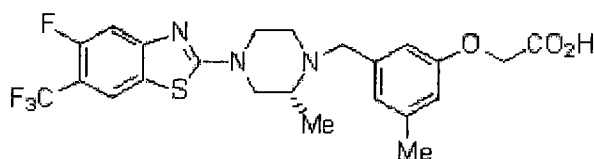


[3207] 收率:76%, $^1\text{H-NMR}$ (CDCl_3): δ 0.77 (3H, d, $J = 6.5\text{Hz}$), 0.92 (3H, d, $J = 6.5\text{Hz}$), 1.40-1.75 (3H, m), 2.25 (3H, s), 2.80-3.05 (3H, m), 3.46 (1H, d, $J = 13\text{Hz}$), 3.60-3.95 (4H, m), 4.22 (1H, d, $J = 13\text{Hz}$), 4.56 (1H, d, $J = 16\text{Hz}$), 4.65 (1H, d, $J = 16\text{Hz}$), 6.63 (1H, s), 6.77 (1H, s), 7.01 (1H, s), 7.52 (1H, d, $J = 8.5\text{Hz}$), 7.59 (1H, d, $J = 8.5\text{Hz}$), 7.83 (1H, s)。

[3208] 实施例 410

[3209] [式 700]

[3210]

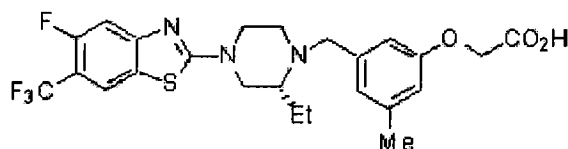


[3211] 收率:79%, $^1\text{H-NMR}$ (CDCl_3): δ 1.33 (3H, d, $J = 6.5\text{Hz}$), 2.28 (3H, s), 2.70-2.83 (1H, m), 2.92-3.08 (2H, m), 3.38 (1H, d, $J = 13\text{Hz}$), 3.54-3.65 (1H, m), 3.70-3.82 (2H, m), 3.87-3.97 (1H, m), 4.25 (1H, d, $J = 13\text{Hz}$), 4.60 (1H, d, $J = 16.5\text{Hz}$), 4.67 (1H, d, $J = 16.5\text{Hz}$), 6.64 (1H, s), 6.78 (1H, s), 6.99 (1H, s), 7.26 (1H, d, $J = 11.5\text{Hz}$), 7.74 (1H, d, $J = 7\text{Hz}$)。

[3212] 实施例 411

[3213] [式 701]

[3214]

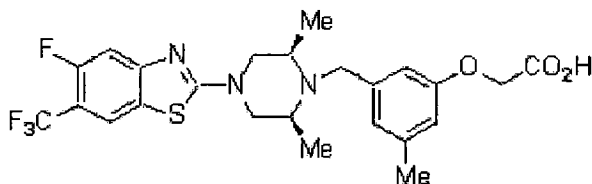


[3215] 收率:93%, $^1\text{H-NMR}$ (CDCl_3): δ 0.92 (3H, t, $J = 7.0\text{Hz}$), 1.42-1.74 (2H, m), 2.13 (3H, s), 2.27-2.57 (2H, m), 2.62-2.82 (1H, m), 3.08-3.24 (1H, m), 3.35-3.77 (4H, m), 3.80-3.97 (1H, m), 4.37 (2H, s), 6.58 (1H, s), 6.63 (1H, s), 6.74 (1H, s), 7.20 (1H, d, $J = 11.5\text{Hz}$), 7.66 (1H, d, $J = 7.0\text{Hz}$)。

[3216] 实施例 412

[3217] [式 702]

[3218]

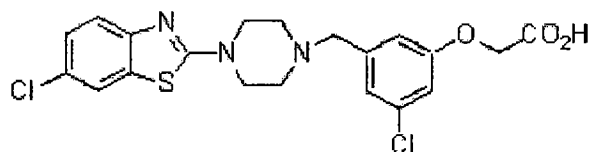


[3219] 收率:80%, $^1\text{H-NMR}$ (CDCl_3): δ 1.18 (6H, d, $J = 6.0\text{Hz}$), 2.25 (3H, s), 2.78-2.94 (2H, m), 3.13-3.29 (2H, m), 3.78-3.94 (4H, m), 4.54 (2H, s), 6.61 (1H, s), 6.74 (1H, s), 6.80 (1H, s), 7.24 (1H, d, $J = 11.5\text{Hz}$), 7.72 (1H, d, $J = 7.0\text{Hz}$)。

[3220] 实施例 413

[3221] [式 703]

[3222]

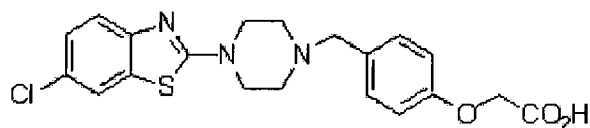


[3223] 收率:82%, $^1\text{H-NMR}$ (DMSO-d_6): δ 3.52 (2H, s), 3.57 (8H, s), 4.65 (2H, s), 6.87 (2H, s), 6.98 (1H, s), 7.29 (1H, d, $J = 8.7, 2.4\text{Hz}$), 7.42 (1H, dd, $J = 8.7\text{Hz}$), 7.91 (1H, d, $J = 2.4\text{Hz}$)。

[3224] 实施例 414

[3225] [式 704]

[3226]

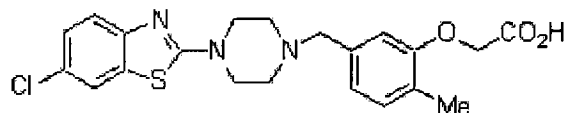


[3227] 收率:83%, $^1\text{H-NMR}$ (DMSO-d_6): δ 2.40-2.55 (4H, m), 3.46 (2H, s), 3.53-3.56 (4H, m), 4.55 (2H, s), 6.85 (2H, d, $J = 8.4\text{Hz}$), 7.22 (2H, d, $J = 8.4\text{Hz}$), 7.28 (1H, dd, $J = 8.4, 2.4\text{Hz}$), 7.42 (1H, d, $J = 8.4\text{Hz}$), 7.90 (1H, d, $J = 2.4\text{Hz}$)。

[3228] 实施例 415

[3229] [式 705]

[3230]

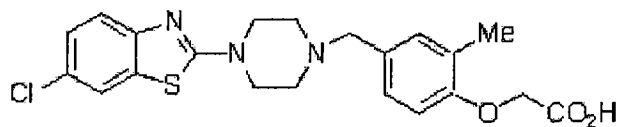


[3231] 收率:51%, $^1\text{H-NMR}$ (DMSO-d_6): δ 2.16 (3H, s), 2.40-2.55 (4H, m), 3.47 (2H, s), 3.50-3.60 (4H, m), 4.67 (2H, s), 6.75-6.85 (2H, m), 7.08 (1H, d, $J = 7.5\text{Hz}$), 7.27 (1H, dd, $J = 8.5, 1\text{Hz}$), 7.41 (1H, d, $J = 8\text{Hz}$), 7.88 (1H, d, $J = 2\text{Hz}$), 12.9 (1H, brs)。

[3232] 实施例 416

[3233] [式 706]

[3234]

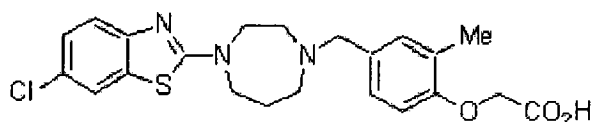


[3235] 收率:92%, $^1\text{H-NMR}$ (DMSO-d_6): δ 2.19 (3H, s), 2.50-2.55 (4H, m), 3.52 (4H, s), 3.55-3.58 (4H, m), 6.76 (1H, d, $J = 8.4\text{Hz}$), 7.07 (1H, d, $J = 8.4\text{Hz}$), 7.11 (1H, s), 7.28 (1H, dd, $J = 8.7, 1.5\text{Hz}$), 7.42 (1H, d, $J = 8.7\text{Hz}$), 7.90 (1H, d, $J = 1.5\text{Hz}$)。

[3236] 实施例 417

[3237] [式 707]

[3238]

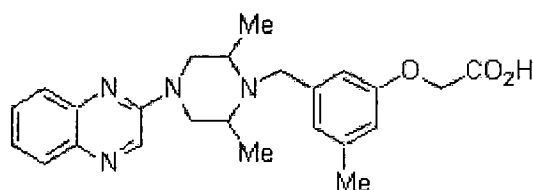


[3239] 收率:91%, $^1\text{H-NMR}$ (DMSO-d_6): δ 1.90 (2H, m), 2.14 (3H, s), 2.58 (2H, m), 2.73 (2H, m), 3.50 (2H, s), 3.65-3.70 (4H, m), 4.49 (2H, s), 6.68 (1H, d, $J = 8.4\text{Hz}$), 7.01 (1H, d, $J = 8.4\text{Hz}$), 7.05 (1H, s), 7.26 (1H, dd, $J = 8.7, 2.1\text{Hz}$), 7.40 (1H, d, $J = 8.7\text{Hz}$), 7.88 (1H, d, $J = 2.1\text{Hz}$)。

[3240] 实施例 418

[3241] [式 708]

[3242]

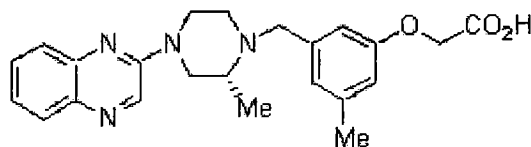


[3243] 收率:28%, $^1\text{H-NMR}$ (CDCl_3): δ 1.33 (6H, d, $J = 6.0\text{Hz}$), 2.27 (3H, s), 2.87-3.04 (2H, m), 3.12-3.29 (2H, m), 4.02 (2H, s), 4.30 (2H, d, $J = 13.0\text{Hz}$), 4.59 (2H, s), 6.70 (2H, s), 6.83 (1H, s), 7.35-7.44 (1H, m), 7.52-7.61 (1H, m), 7.65 (1H, d, $J = 7.0\text{Hz}$), 7.86 (1H, d, $J = 7.0\text{Hz}$), 8.51 (1H, s)。

[3244] 实施例 419

[3245] [式 709]

[3246]

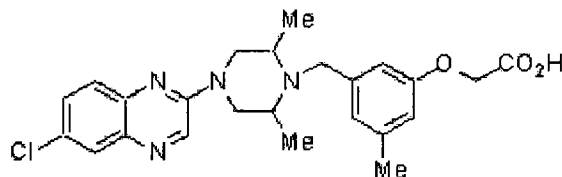


[3247] 收率:37%, $^1\text{H-NMR}$ (CDCl_3): δ 1.37 (3H, d, $J = 6.5\text{Hz}$), 2.26 (3H, s), 2.84-3.23 (3H, m), 3.45 (1H, d, $J = 13.0\text{Hz}$), 3.71-4.14 (4H, m), 4.34 (1H, d, $J = 13.0\text{Hz}$), 4.62 (1H, d, $J = 16.0\text{Hz}$), 4.69 (1H, d, $J = 16.0\text{Hz}$), 6.60 (1H, s), 6.81 (1H, s), 7.12 (1H, s), 7.37-7.47 (1H, m), 7.53-7.63 (1H, m), 7.67 (1H, d, $J = 8.0\text{Hz}$), 7.89 (1H, d, $J = 8.0\text{Hz}$), 8.52 (1H, s)。

[3248] 实施例 420

[3249] [式 710]

[3250]



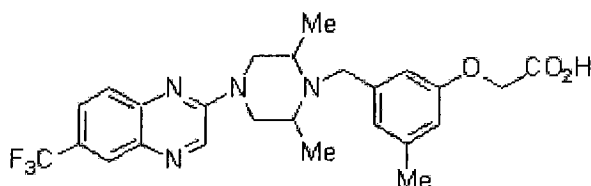
[3251] 收率:55%, $^1\text{H-NMR}$ (CDCl_3): δ 1.24 (6H, d, $J = 6.0\text{Hz}$), 2.20 (3H, s), 2.77-2.92 (2H, m), 3.03-3.18 (2H, m), 3.89 (2H, s), 4.23 (2H, d, $J = 11.5\text{Hz}$), 4.48 (2H, s), 6.61 (1H, s), 6.69 (1H, s), 6.78 (1H, s), 7.46 (1H, dd, $J = 9.0, 2.0\text{Hz}$), 7.54 (1H, d, $J =$

9.0Hz), 7.81 (1H, d, $J = 2.0\text{Hz}$), 8.47 (1H, s)。

[3252] 实施例 421

[3253] [式 711]

[3254]

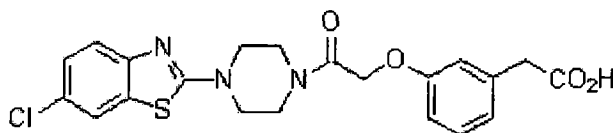


[3255] 收率: 60%, $^1\text{H-NMR}$ (CDCl_3): δ 1.32 (6H, d, $J = 6.0\text{Hz}$), 2.27 (3H, s), 2.85-3.00 (2H, m), 3.16-3.30 (2H, m), 3.98 (2H, s), 4.29-4.41 (2H, m), 4.60 (2H, s), 6.67 (1H, s), 6.73 (1H, s), 6.83 (1H, s), 7.65-7.75 (2H, m), 8.12 (1H, s), 8.57 (1H, s)。

[3256] 实施例 422

[3257] [式 712]

[3258]

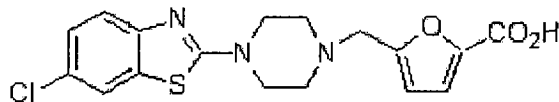


[3259] 收率: 46%, $^1\text{H-NMR}$ (DMSO-d_6): δ 3.53 (2H, s), 3.54-3.74 (8H, m), 4.87 (2H, s), 6.79-6.90 (3H, m), 7.22 (1H, t, $J = 7.5\text{Hz}$), 7.32 (1H, dd, $J = 8.5, 2.0\text{Hz}$), 7.46 (1H, d, $J = 8.5\text{Hz}$), 7.94 (1H, d, $J = 2.0\text{Hz}$), 12.31 (1H, br)。

[3260] 实施例 423

[3261] [式 713]

[3262]

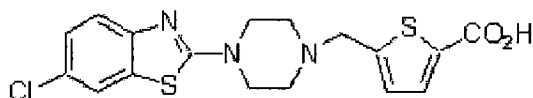


[3263] 收率: 21%, $^1\text{H-NMR}$ (DMSO-d_6): δ 2.45-2.55 (4H, m), 3.33 (2H, s), 3.55-3.60 (4H, m), 6.50-6.60 (1H, m), 7.15-7.20 (1H, m), 7.29 (1H, dd, $J = 8.5, 2\text{Hz}$), 7.43 (1H, d, $J = 8.5\text{Hz}$), 7.92 (1H, d, $J = 2.5\text{Hz}$)。

[3264] 实施例 424

[3265] [式 714]

[3266]

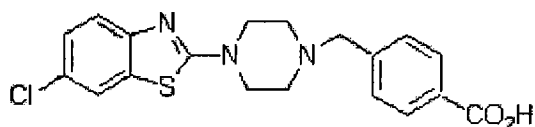


[3267] 收率: 76%, $^1\text{H-NMR}$ (DMSO-d_6): δ 2.58 (4H, s), 3.35 (2H, s), 3.59 (2H, s), 3.81 (2H, s), 7.06 (1H, d, $J = 3.6\text{Hz}$), 7.29 (1H, dd, $J = 8.7, 2.1\text{Hz}$), 7.43 (1H, d, $J = 8.4\text{Hz}$), 7.60 (1H, d, $J = 3.3\text{Hz}$), 7.91 (1H, d, $J = 2.1\text{Hz}$), 12.99 (1H, brs)。

[3268] 实施例 425

[3269] [式 715]

[3270]

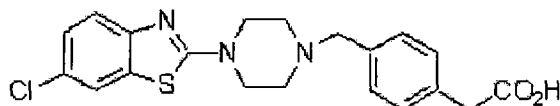


[3271] 收率:76%, $^1\text{H-NMR}$ (DMSO-d_6): δ 1.25 (2H, m), 3.30 (2H, m), 3.62 (2H, m), 4.20 (2H, m), 4.45 (2H, brs), 7.33 (1H, dd, $J = 8.4, 1.8\text{Hz}$), 7.49 (1H, d, $J = 8.7\text{Hz}$), 7.69-7.71 (2H, m), 7.98 (1H, d, $J = 1.8\text{Hz}$), 8.02 (2H, d, $J = 8.1\text{Hz}$)。

[3272] 实施例 426

[3273] [式 716]

[3274]

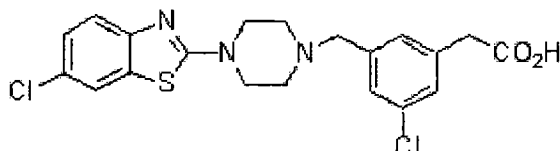


[3275] 收率:81%, $^1\text{H-NMR}$ (DMSO-d_6): δ 2.45-2.50 (4H, m), 3.45-3.60 (8H, m), 7.15-7.35 (5H, m), 7.42 (1H, d, $J = 8.5\text{Hz}$), 7.91 (1H, d, $J = 2\text{Hz}$), 12.31 (1H, brs)。

[3276] 实施例 427

[3277] [式 717]

[3278]

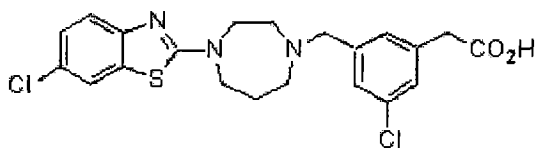


[3279] 收率:94%, $^1\text{H-NMR}$ (DMSO-d_6): δ 2.50-2.55 (4H, m), 3.52 (4H, s), 3.57 (4H, s), 7.17 (1H, s), 7.24 (2H, s), 7.29 (1H, dd, $J = 2.1, 8.4\text{Hz}$), 7.42 (1H, d, $J = 8.4\text{Hz}$), 7.91 (1H, d, $J = 2.1\text{Hz}$)。

[3280] 实施例 428

[3281] [式 718]

[3282]

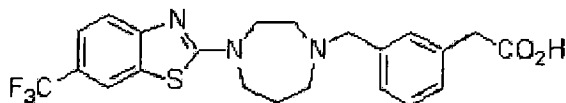


[3283] 收率:86%, $^1\text{H-NMR}$ (DMSO-d_6): δ 1.92 (2H, s), 2.61 (2H, s), 2.77 (2H, s), 3.53 (2H, s), 3.61 (2H, s), 3.60-3.65 (4H, m), 7.15 (1H, s), 7.21 (1H, s), 7.22 (1H, s), 7.26 (1H, dd, $J = 8.4, 2.1\text{Hz}$), 7.40 (1H, d, $J = 8.4\text{Hz}$), 7.88 (1H, d, $J = 2.1\text{Hz}$)。

[3284] 实施例 429

[3285] [式 719]

[3286]



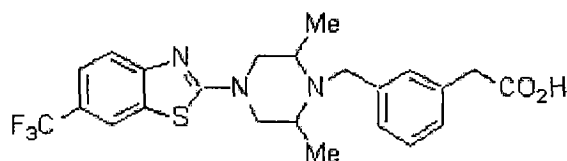
[3287] 收率:18%, $^1\text{H-NMR}$ (DMSO-d_6): δ 1.85-2.00 (2H, m), 2.57-2.68 (2H, m), 2.74-2.85 (2H, m), 3.52 (2H, s), 3.61 (2H, s), 3.62-3.85 (4H, m), 7.09-7.31 (4H, m),

7.52-7.58 (2H, m), 8.22 (1H, s)。

[3288] 实施例 430

[3289] [式 720]

[3290]

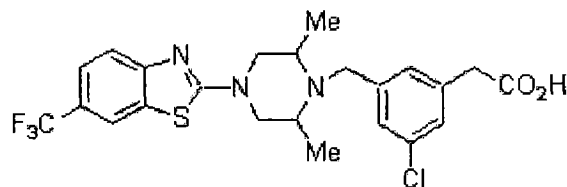


[3291] 收率:95%, ¹H-NMR(DMSO-d₆): δ 1.05 (6H, d, J = 6.5Hz), 2.65-2.80 (2H, m), 3.04-3.15 (2H, m), 3.55 (2H, s), 3.79 (2H, s), 3.83-3.95 (2H, m), 7.05-7.15 (1H, m), 7.20-7.30 (3H, m), 7.57 (2H, s), 8.24 (1H, s), 12.27 (1H, brs)。

[3292] 实施例 431

[3293] [式 721]

[3294]

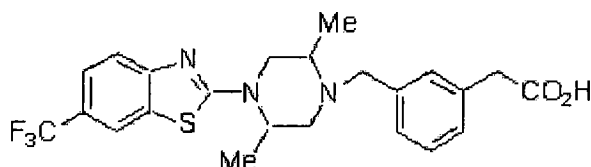


[3295] 收率:61%, ¹H-NMR(CDCl₃): δ 1.08 (6H, d, J = 6.5Hz), 2.74-2.86 (2H, m), 3.08 (1H, d, J = 13Hz), 3.12 (1H, d, J = 13Hz), 3.62 (2H, s), 3.78 (2H, s), 3.86-3.95 (2H, m), 7.16-7.18 (2H, m), 7.34 (1H, s), 7.52 (1H, d, J = 8.5Hz), 7.57 (1H, d, J = 8.5Hz), 7.84 (1H, s)。

[3296] 实施例 432

[3297] [式 722]

[3298]

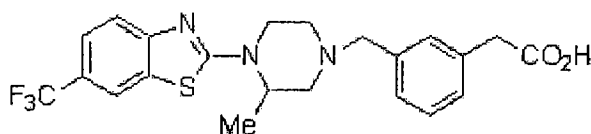


[3299] 收率:87%, ¹H-NMR(DMSO-d₆): δ 1.01 (3H, d, J = 6.5Hz), 1.33 (3H, d, J = 6.5Hz), 2.25-2.35 (1H, m), 2.75-2.85 (1H, m), 3.08-3.20 (1H, m), 3.49 (1H, d, J = 14Hz), 3.56 (2H, s), 3.63-3.75 (3H, m), 4.23-4.35 (1H, m), 7.10-7.20 (1H, m), 7.20-7.35 (3H, m), 7.50-7.60 (2H, m), 8.21 (1H, s), 12.23 (1H, brs)。

[3300] 实施例 433

[3301] [式 723]

[3302]



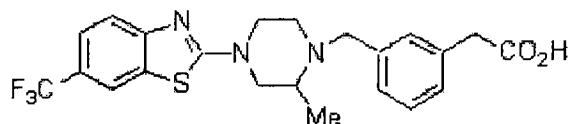
[3303] 收率:87%, ¹H-NMR(DMSO-d₆): δ 1.33 (3H, d, J = 6.5Hz), 2.10-2.30 (2H, m),

2.72 (1H, d, $J = 11.5\text{Hz}$), 2.94 (1H, d, $J = 12\text{Hz}$), 3.35-3.50 (2H, m), 3.57 (2H, s), 3.60 (1H, d, $J = 13.5\text{Hz}$), 3.75-3.90 (1H, m), 4.20-4.30 (1H, m), 7.15-7.32 (4H, m), 7.56 (2H, s), 8.22 (1H, s), 12.28 (1H, brs)。

[3304] 实施例 434

[3305] [式 724]

[3306]

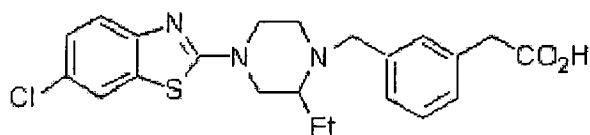


[3307] 收率:82%, $^1\text{H-NMR}$ (DMSO- d_6): δ 1.16 (3H, d, $J = 6\text{Hz}$), 2.15-2.35 (1H, m), 2.55-2.68 (1H, m), 2.70-2.80 (1H, m), 3.15-3.30 (2H, m), 3.35-3.50 (1H, m), 3.56 (2H, s), 3.70-3.80 (1H, m), 3.80-3.90 (1H, m), 3.97 (1H, d, $J = 13.5\text{Hz}$), 7.10-7.35 (4H, m), 7.56 (2H, s), 8.23 (1H, s), 12.29 (1H, brs)。

[3308] 实施例 435

[3309] [式 725]

[3310]

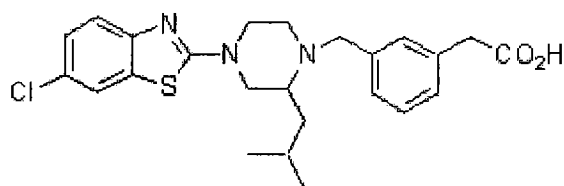


[3311] 收率:98%, $^1\text{H-NMR}$ (CDCl $_3$): δ 1.00 (3H, t, $J = 7.5\text{Hz}$), 1.59-1.69 (1H, m), 1.73-1.80 (1H, m), 2.37-2.45 (1H, m), 2.54-2.59 (1H, m), 2.80-2.86 (1H, m), 3.34-3.54 (3H, m), 3.59-3.63 (1H, m), 3.63 (2H, s), 3.79 (1H, dd, $J = 2.7, 13.2\text{Hz}$), 4.04 (1H, d, $J = 13.2\text{Hz}$), 7.20-7.29 (5H, m), 7.42 (1H, d, $J = 8.7\text{Hz}$), 7.53 (1H, d, $J = 2.1\text{Hz}$)。

[3312] 实施例 436

[3313] [式 726]

[3314]

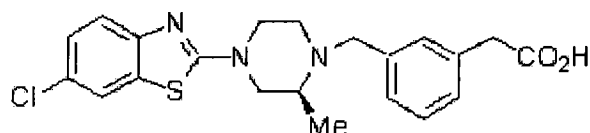


[3315] 收率:96%, $^1\text{H-NMR}$ (CDCl $_3$): δ 0.92 (6H, dd, $J = 6.3, 16.2\text{Hz}$), 1.38-1.47 (1H, m), 1.51-1.59 (1H, m), 1.64-1.75 (1H, m), 2.43-2.51 (1H, m), 2.71-2.76 (1H, m), 2.79-2.87 (1H, m), 3.40 (2H, dt, $J = 3.0, 13.2\text{Hz}$), 3.57-3.64 (2H, m), 3.63 (2H, s), 3.76 (1H, dd, $J = 3.0, 12.9\text{Hz}$), 3.99 (1H, d, $J = 13.2\text{Hz}$), 7.21-7.31 (5H, m), 7.43 (1H, d, $J = 8.4\text{Hz}$), 7.53 (1H, d, $J = 2.4\text{Hz}$)。

[3316] 实施例 437

[3317] [式 727]

[3318]

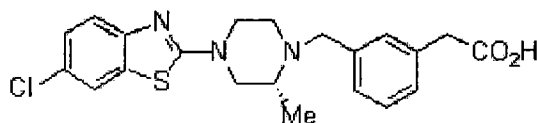


[3319] 收率:89%, $^1\text{H-NMR}$ (CDCl_3): δ 1.25 (3H, d, $J = 6.0\text{Hz}$), 2.30–2.38 (1H, m), 2.68–2.74 (1H, m), 2.83 (1H, dt, $J = 3.9, 12.0\text{Hz}$), 3.18–3.28 (2H, m), 3.39–3.49 (1H, m), 3.63 (2H, s), 3.63–3.70 (1H, m), 3.86 (1H, dd, $J = 2.4, 12.0\text{Hz}$), 4.10 (1H, d, $J = 13.2\text{Hz}$), 7.19–7.30 (5H, m), 7.43 (1H, d, $J = 8.4\text{Hz}$), 7.53 (1H, d, $J = 2.4\text{Hz}$)。

[3320] 实施例 438

[3321] [式 728]

[3322]

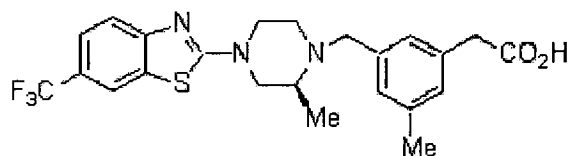


[3323] 收率:91%, $^1\text{H-NMR}$ (CDCl_3): δ 1.30 (3H, d, $J = 6.0\text{Hz}$), 2.40 (1H, t, $J = 9.6\text{Hz}$), 2.78 (1H, br), 2.88 (1H, br), 3.33 (2H, d, $J = 12.6\text{Hz}$), 3.48–3.54 (1H, m), 3.64 (2H, s), 3.72 (1H, d, $J = 13.2\text{Hz}$), 3.89 (1H, d, $J = 10.2\text{Hz}$), 4.16 (1H, d, $J = 13.2\text{Hz}$), 7.22–7.33 (5H, m), 7.43 (1H, d, $J = 8.7\text{Hz}$), 7.54 (1H, d, $J = 2.1\text{Hz}$)。

[3324] 实施例 439

[3325] [式 729]

[3326]

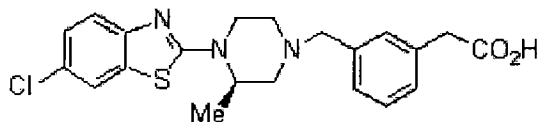


[3327] 收率:96%, $^1\text{H-NMR}$ (CDCl_3): δ 1.26 (3H, d, $J = 6\text{Hz}$), 2.25–2.40 (4H, m), 2.65–2.75 (1H, m), 2.80–2.90 (1H, m), 3.20 (1H, d, $J = 13\text{Hz}$), 3.25–3.30 (1H, m), 3.45–3.53 (1H, m), 3.61 (2H, s), 3.68–3.80 (1H, m), 3.84–3.95 (1H, m), 4.07 (1H, d, $J = 13\text{Hz}$), 7.03 (2H, s), 7.10 (1H, s), 7.51 (1H, d, $J = 8.5\text{Hz}$), 7.53 (1H, d, $J = 8.5\text{Hz}$), 7.83 (1H, s)。

[3328] 实施例 440

[3329] [式 730]

[3330]

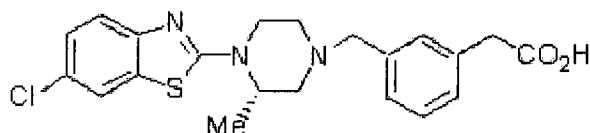


[3331] 收率:67%, $^1\text{H-NMR}$ ($\text{DMSO}-d_6$): δ 1.31 (3H, d, $J = 6.5\text{Hz}$), 2.03–2.25 (2H, m), 2.70 (1H, d, $J = 11.5\text{Hz}$), 2.91 (1H, d, $J = 12\text{Hz}$), 3.35–3.43 (2H, m), 3.56 (2H, s), 3.56–3.65 (1H, m), 3.79 (1H, d, $J = 11\text{Hz}$), 4.15–4.25 (1H, m), 7.15 (1H, d, $J = 7\text{Hz}$), 7.20–7.33 (4H, m), 7.41 (1H, d, $J = 8.5\text{Hz}$), 7.89 (1H, d, $J = 1.5\text{Hz}$), 12.30 (1H, brs)。

[3332] 实施例 441

[3333] [式 731]

[3334]

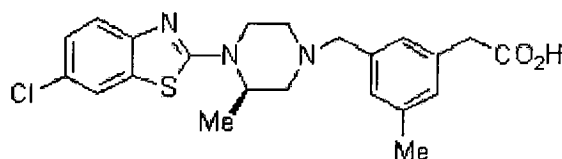


[3335] 收率:86%, $^1\text{H-NMR}$ (CDCl_3): δ 1.37 (3H, d, $J = 7.0\text{Hz}$), 2.23 (1H, td, $J = 11.0, 3.5\text{Hz}$), 2.31 (1H, dd, $J = 11.0, 3.5\text{Hz}$), 2.71 (1H, d, $J = 11.0\text{Hz}$), 2.91 (1H, d, $J = 11.0\text{Hz}$), 3.44 (1H, d, $J = 13.5\text{Hz}$), 3.47 (1H, td, $J = 12.5, 3.5\text{Hz}$), 3.60 (1H, d, $J = 11.0\text{Hz}$), 3.64 (2H, s), 3.83 (1H, d, $J = 12.5\text{Hz}$), 4.09-4.21 (1H, m), 7.14-7.33 (5H, m), 7.42 (1H, d, $J = 8.5\text{Hz}$), 7.53 (1H, d, $J = 2.0\text{Hz}$).

[3336] 实施例 442

[3337] [式 732]

[3338]

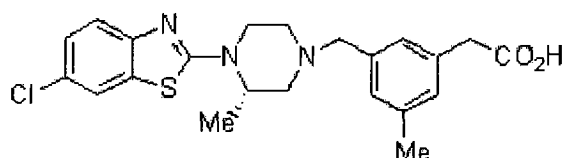


[3339] 收率:94%, $^1\text{H-NMR}$ (CDCl_3): δ 1.37 (3H, d, $J = 6.5\text{Hz}$), 2.23 (1H, td, $J = 11.5, 3.5\text{Hz}$), 2.25-2.30 (1H, m), 2.32 (3H, s), 2.71 (1H, d, $J = 11.5\text{Hz}$), 2.91 (1H, d, $J = 11\text{Hz}$), 3.39 (1H, d, $J = 13.5\text{Hz}$), 3.45-3.54 (1H, m), 3.55 (1H, d, $J = 13.5\text{Hz}$), 3.60 (2H, s), 3.83 (1H, d, $J = 11.5\text{Hz}$), 4.10-4.20 (1H, m), 7.01 (1H, s), 7.06 (1H, s), 7.09 (1H, s), 7.23 (1H, dd, $J = 8.5, 2\text{Hz}$), 7.42 (1H, d, $J = 8.5\text{Hz}$), 7.54 (1H, d, $J = 2\text{Hz}$).

[3340] 实施例 443

[3341] [式 733]

[3342]

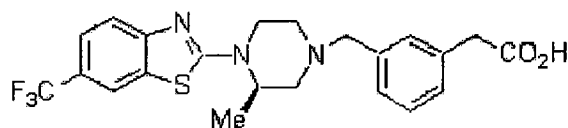


[3343] 收率:82%, $^1\text{H-NMR}$ (CDCl_3): δ 1.37 (3H, d, $J = 6.5\text{Hz}$), 2.13-2.36 (5H, m), 2.70 (1H, d, $J = 11.5\text{Hz}$), 2.89 (1H, d, $J = 11.5\text{Hz}$), 3.32-3.62 (5H, m), 3.76-3.87 (1H, m), 4.07-4.22 (1H, m), 6.99 (1H, s), 7.05 (1H, s), 7.07 (1H, s), 7.22 (1H, dd, $J = 8.5, 2.0\text{Hz}$), 7.42 (1H, d, $J = 8.5\text{Hz}$), 7.53 (1H, d, $J = 2.0\text{Hz}$).

[3344] 实施例 444

[3345] [式 734]

[3346]



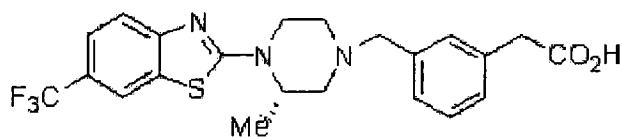
[3347] 收率:87%, $^1\text{H-NMR}$ (DMSO-d_6): δ 1.33 (3H, d, $J = 6.5\text{Hz}$), 2.10-2.30 (2H, m), 2.72 (1H, d, $J = 11.5\text{Hz}$), 2.93 (1H, d, $J = 11.5\text{Hz}$), 3.30-3.50 (2H, m), 3.56 (2H, s), 3.59 (1H, d, $J = 13.5\text{Hz}$), 3.86 (1H, d, $J = 12.5\text{Hz}$), 4.20-4.30 (1H, m), 7.10-7.35 (4H, m),

7.56 (2H, s), 8.24 (1H, s), 12.43 (1H, brs)。

[3348] 实施例 445

[3349] [式 735]

[3350]

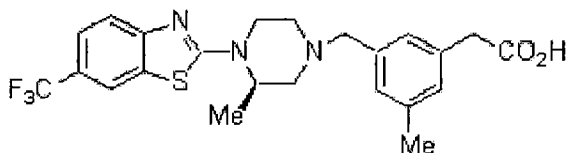


[3351] 收率:96%, $^1\text{H-NMR}$ (CDCl_3): δ 1.34 (3H, d, $J = 6.5\text{Hz}$), 2.14 (1H, td, $J = 11.5, 3.5\text{Hz}$), 2.25 (1H, dd, $J = 11.5, 3.5\text{Hz}$), 2.66 (1H, d, $J = 11.5\text{Hz}$), 2.83 (1H, d, $J = 11.5\text{Hz}$), 3.37 (1H, d, $J = 13.5\text{Hz}$), 3.38-3.55 (4H, m), 3.82 (1H, d, $J = 11.5\text{Hz}$), 4.08-4.22 (1H, m), 7.10 (1H, s), 7.14-7.23 (3H, m), 7.45-7.56 (2H, m), 7.81 (1H, s)。

[3352] 实施例 446

[3353] [式 736]

[3354]

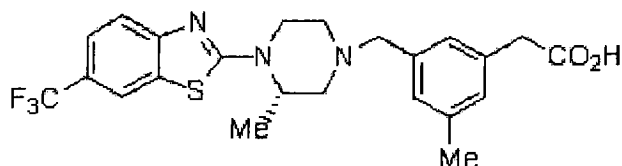


[3355] 收率:98%, $^1\text{H-NMR}$ (CDCl_3): δ 1.39 (3H, d, $J = 6.5\text{Hz}$), 2.23 (1H, td, $J = 12, 3.5\text{Hz}$), 2.25-2.31 (1H, m), 2.32 (3H, s), 2.73 (1H, d, $J = 11.5\text{Hz}$), 2.92 (1H, d, $J = 12\text{Hz}$), 3.41 (1H, d, $J = 13\text{Hz}$), 3.45-3.55 (1H, m), 3.56 (1H, d, $J = 13\text{Hz}$), 3.59 (2H, s), 3.88 (1H, d, $J = 12\text{Hz}$), 4.17-4.28 (1H, m), 7.01 (1H, s), 7.06 (1H, s), 7.09 (1H, s), 7.51 (1H, d, $J = 8.5\text{Hz}$), 7.55 (1H, d, $J = 8.5\text{Hz}$), 7.83 (1H, s)。

[3356] 实施例 447

[3357] [式 737]

[3358]

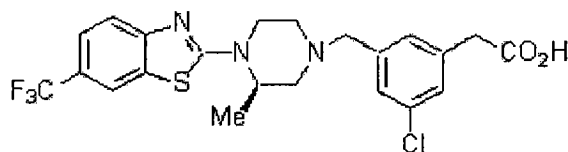


[3359] 收率:72%, $^1\text{H-NMR}$ (CDCl_3): δ 1.39 (3H, d, $J = 6.5\text{Hz}$), 2.13-2.34 (5H, m), 2.71 (1H, d, $J = 11.5\text{Hz}$), 2.90 (1H, d, $J = 11.5\text{Hz}$), 3.39 (1H, d, $J = 13.0\text{Hz}$), 3.43-3.60 (4H, m), 3.87 (1H, d, $J = 12.5\text{Hz}$), 4.13-4.26 (1H, m), 6.99 (1H, s), 7.05 (2H, s), 7.46-7.58 (2H, m), 7.83 (1H, s)。

[3360] 实施例 448

[3361] [式 738]

[3362]

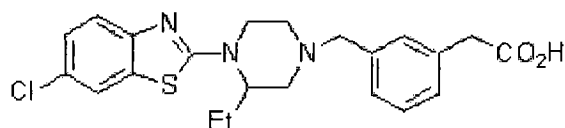


[3363] 收率:90%, $^1\text{H-NMR}$ (CDCl_3): δ 1.40 (3H, d, $J = 6.5\text{Hz}$), 2.26 (1H, td, $J = 12, 3.5\text{Hz}$), 2.35 (1H, dd, $J = 11.5, 3.5\text{Hz}$), 2.72 (1H, d, $J = 11.5\text{Hz}$), 2.91 (1H, d, $J = 12\text{Hz}$), 3.43 (1H, d, $J = 13.5\text{Hz}$), 3.52 (1H, td, $J = 12.5, 3.5\text{Hz}$), 3.57 (1H, d, $J = 13.5\text{Hz}$), 3.64 (2H, s), 3.85-3.95 (1H, m), 4.19-4.30 (1H, m), 7.18 (1H, s), 7.21 (1H, s), 7.29 (1H, s), 7.51 (1H, d, $J = 8.5\text{Hz}$), 7.57 (1H, d, $J = 8.5\text{Hz}$), 7.84 (1H, s)。

[3364] 实施例 449

[3365] [式 739]

[3366]

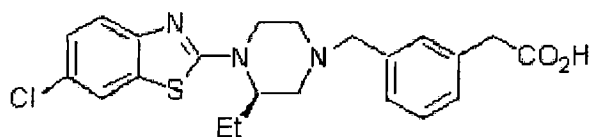


[3367] 收率:68%, $^1\text{H-NMR}$ (CDCl_3): δ 0.85 (3H, t, $J = 7.5\text{Hz}$), 1.82-1.99 (2H, m), 2.17-2.29 (2H, m), 2.78-2.92 (2H, m), 3.37-3.51 (1H, m), 3.42 (1H, d, $J = 13.0\text{Hz}$), 3.59 (1H, d, $J = 13.0\text{Hz}$), 3.65 (2H, s), 3.76-3.87 (1H, m), 3.93-4.04 (1H, m), 7.16-7.34 (5H, m), 7.39 (1H, d, $J = 8.5\text{Hz}$), 7.52 (1H, d, $J = 2.0\text{Hz}$)。

[3368] 实施例 450

[3369] [式 740]

[3370]

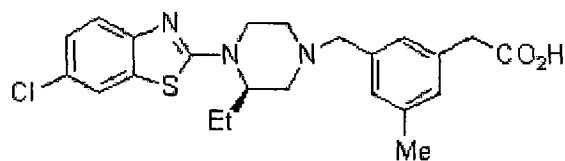


[3371] 收率:95%, $^1\text{H-NMR}$ ($\text{DMSO}-d_6$): δ 0.79 (3H, t, $J = 7.5\text{Hz}$), 1.72-1.95 (2H, m), 2.07-2.20 (2H, m), 2.81 (1H, d, $J = 11\text{Hz}$), 2.89 (1H, d, $J = 11\text{Hz}$), 3.25-3.39 (2H, m), 3.40 (1H, d, $J = 13.5\text{Hz}$), 3.55 (2H, s), 3.59 (1H, d, $J = 13.5\text{Hz}$), 3.80-3.95 (1H, m), 7.13-7.34 (5H, m), 7.38 (1H, d, $J = 8.5\text{Hz}$), 7.87 (1H, d, $J = 2\text{Hz}$), 12.45 (1H, brs)。

[3372] 实施例 451

[3373] [式 741]

[3374]

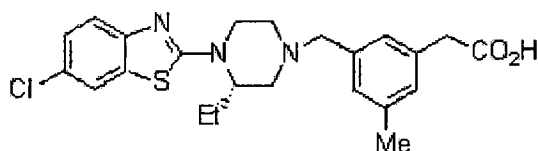


[3375] 收率:96%, $^1\text{H-NMR}$ (CDCl_3): δ 0.86 (3H, t, $J = 7.5\text{Hz}$), 1.80-2.00 (2H, m), 2.16-2.29 (2H, m), 2.33 (3H, s), 2.79-2.94 (2H, m), 3.38 (1H, d, $J = 13.5\text{Hz}$), 3.50 (1H, td, $J = 12.5, 3.5\text{Hz}$), 3.57 (1H, d, $J = 13.5\text{Hz}$), 3.61 (2H, s), 3.75-3.87 (1H, m), 3.93-4.03 (1H, m), 7.02 (1H, s), 7.06 (1H, s), 7.08 (1H, s), 7.21 (1H, dd, $J = 8.5, 2\text{Hz}$), 7.39 (1H, d, $J = 8.5\text{Hz}$), 7.52 (1H, d, $J = 2\text{Hz}$)。

[3376] 实施例 452

[3377] [式 742]

[3378]

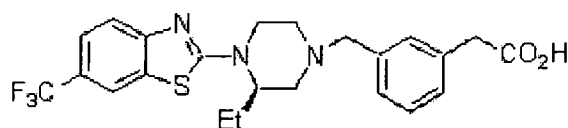


[3379] 收率:77%, $^1\text{H-NMR}$ (DMSO- d_6): δ 0.80 (3H, t, $J = 7.5\text{Hz}$), 1.67-1.97 (2H, m), 2.03-2.19 (2H, m), 2.28 (3H, s), 2.81 (1H, d, $J = 11.5\text{Hz}$), 2.89 (1H, d, $J = 11.0\text{Hz}$), 3.27-3.44 (2H, m), 3.48 (2H, s), 3.55 (1H, d, $J = 13.5\text{Hz}$), 3.81-3.95 (2H, m), 6.96 (1H, s), 7.02 (2H, s), 7.26 (1H, dd, $J = 8.5, 2.0\text{Hz}$), 7.38 (1H, d, $J = 8.5\text{Hz}$), 7.87 (1H, d, $J = 2.0\text{Hz}$)。

[3380] 实施例 453

[3381] [式 743]

[3382]

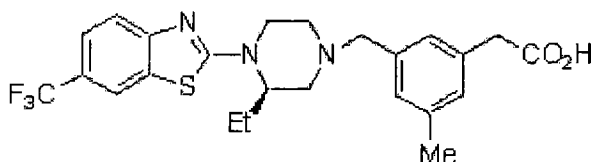


[3383] 收率:96%, $^1\text{H-NMR}$ (DMSO- d_6): δ 0.80 (3H, t, $J = 7.5\text{Hz}$), 1.76-1.96 (2H, m), 2.09-2.20 (2H, m), 2.82 (1H, d, $J = 11.5\text{Hz}$), 2.89 (1H, d, $J = 11.5\text{Hz}$), 3.30-3.42 (2H, m), 3.43 (1H, d, $J = 13.5\text{Hz}$), 3.56 (2H, s), 3.60 (1H, d, $J = 13.5\text{Hz}$), 3.88-4.00 (1H, m), 7.12-7.32 (4H, m), 7.51 (1H, d, $J = 8.5\text{Hz}$), 7.56 (1H, d, $J = 8.5\text{Hz}$), 8.21 (1H, s), 12.3 (1H, brs)。

[3384] 实施例 454

[3385] [式 744]

[3386]

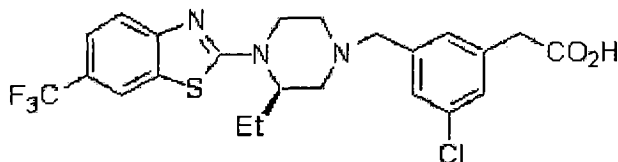


[3387] 收率:89%, $^1\text{H-NMR}$ (CDCl $_3$): δ 0.87 (3H, t, $J = 7.5\text{Hz}$), 1.85-2.00 (2H, m), 2.23 (2H, td, $J = 12.5, 3.5\text{Hz}$), 2.34 (3H, s), 2.81-2.96 (2H, m), 3.38 (1H, d, $J = 13.5\text{Hz}$), 3.49 (1H, td, $J = 12.5, 3.5\text{Hz}$), 3.58 (1H, d, $J = 13.5\text{Hz}$), 3.62 (2H, s), 3.80-3.95 (1H, m), 3.97-4.10 (1H, m), 7.02 (1H, s), 7.06 (1H, s), 7.08 (1H, s), 7.46-7.50 (2H, m), 7.81 (1H, s)。

[3388] 实施例 455

[3389] [式 745]

[3390]



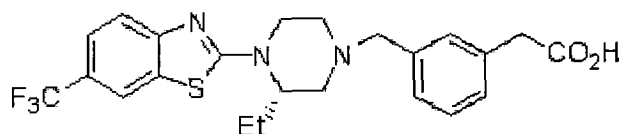
[3391] 收率:89%, $^1\text{H-NMR}$ (CDCl $_3$): δ 0.88 (3H, t, $J = 7.5\text{Hz}$), 1.93 (2H, quant, $J = 7.5\text{Hz}$), 2.19-2.32 (2H, m), 2.78-2.93 (2H, m), 3.40 (1H, d, $J = 13.5\text{Hz}$), 3.49 (1H, td, $J = 12.5, 3.5\text{Hz}$), 3.57 (1H, d, $J = 13.5\text{Hz}$), 3.64 (2H, s), 3.84-3.95 (1H, m), 3.96-4.10 (1H, m),

7.16 (1H, s), 7.22 (1H, s), 7.28 (1H, s), 7.45-7.57 (2H, m), 7.82 (1H, s)。

[3392] 实施例 456

[3393] [式 746]

[3394]

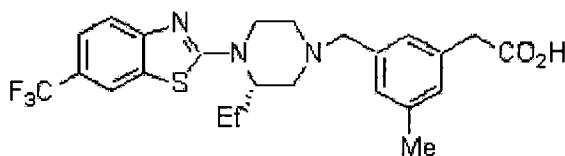


[3395] 收率:93%, $^1\text{H-NMR}$ (CDCl₃): δ 0.86 (3H, t, $J = 7.5\text{Hz}$), 1.92 (2H, quant, $J = 7.5\text{Hz}$), 2.15-2.31 (2H, m), 2.80-2.96 (2H, m), 3.42 (1H, d, $J = 13\text{Hz}$), 3.48 (1H, td, $J = 12.5, 3\text{Hz}$), 3.61 (1H, d, $J = 13\text{Hz}$), 3.66 (2H, s), 3.80-3.95 (1H, m), 3.96-4.10 (1H, m), 7.15-7.33 (4H, m), 7.49 (1H, d, $J = 8.5\text{Hz}$), 7.50 (1H, d, $J = 8.5\text{Hz}$), 7.81 (1H, s)。

[3396] 实施例 457

[3397] [式 747]

[3398]

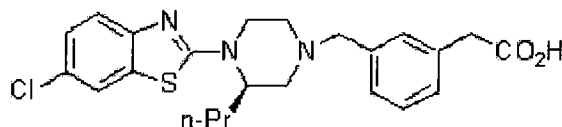


[3399] 收率:96%, $^1\text{H-NMR}$ (CDCl₃): δ 0.87 (3H, t, $J = 7.5\text{Hz}$), 1.85-2.00 (2H, m), 2.15-2.28 (2H, m), 2.34 (3H, s), 2.80-2.95 (2H, m), 3.39 (1H, d, $J = 13\text{Hz}$), 3.51 (1H, td, $J = 13, 3.5\text{Hz}$), 3.58 (1H, d, $J = 13\text{Hz}$), 3.62 (2H, s), 3.80-3.95 (1H, m), 3.96-4.10 (1H, m), 7.02 (1H, s), 7.06 (1H, s), 7.08 (1H, s), 7.50 (1H, d, $J = 8.5\text{Hz}$), 7.53 (1H, d, $J = 8.5\text{Hz}$), 7.81 (1H, s)。

[3400] 实施例 458

[3401] [式 748]

[3402]

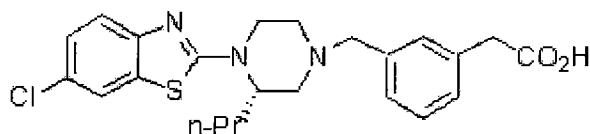


[3403] 收率:98%, $^1\text{H-NMR}$ (CDCl₃): δ 0.87 (3H, t, $J = 7.5\text{Hz}$), 1.11-1.28 (2H, m), 1.68-1.88 (2H, m), 2.20-2.18 (2H, m), 2.64-2.79 (2H, m), 3.23-3.48 (5H, m), 3.74-3.96 (2H, m), 6.98-7.23 (5H, m), 7.35 (1H, d, $J = 8.5\text{Hz}$), 7.49 (1H, d, $J = 2.0\text{Hz}$)。

[3404] 实施例 459

[3405] [式 749]

[3406]



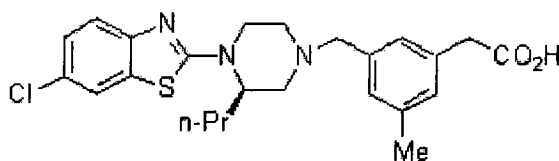
[3407] 收率:98%, $^1\text{H-NMR}$ (CDCl₃): δ 0.91 (3H, t, $J = 7.2\text{Hz}$), 1.19-1.29 (2H, m), 1.77-1.94 (2H, m), 2.18-2.28 (2H, m), 2.81 (1H, d, $J = 11.1\text{Hz}$), 2.89 (1H, d, $J = 11.1\text{Hz}$), 3.40-3.47 (2H, m), 3.61 (1H, d, $J = 13.2\text{Hz}$), 3.66 (2H, s), 3.90 (1H, s), 3.99 (1H, d, $J =$

12.0Hz), 7.20-7.31 (5H, m), 7.39 (1H, d, $J = 8.7\text{Hz}$), 7.52 (1H, d, $J = 2.1\text{Hz}$)。

[3408] 实施例 460

[3409] [式 750]

[3410]

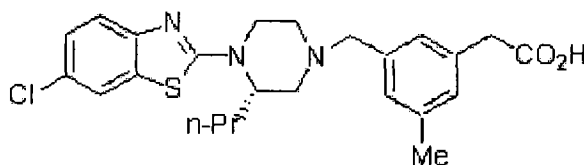


[3411] 收率:69%, $^1\text{H-NMR}(\text{CDCl}_3)$: δ 0.92 (3H, t, $J = 7.0\text{Hz}$), 1.16-1.34 (2H, m), 1.68-2.00 (2H, m), 2.12-2.27 (2H, m), 2.32 (3H, s), 2.79 (1H, d, $J = 11.5\text{Hz}$), 2.86 (1H, d, $J = 11.5\text{Hz}$), 3.35 (1H, d, $J = 13.5\text{Hz}$), 3.39-3.62 (2H, m), 3.58 (2H, s), 3.82-4.03 (2H, m), 6.99 (1H, s), 7.03 (1H, s), 7.06 (1H, s), 7.21 (1H, dd, $J = 8.5, 2.0\text{Hz}$), 7.39 (1H, d, $J = 8.5\text{Hz}$), 7.52 (1H, d, $J = 2.0\text{Hz}$)。

[3412] 实施例 461

[3413] [式 751]

[3414]

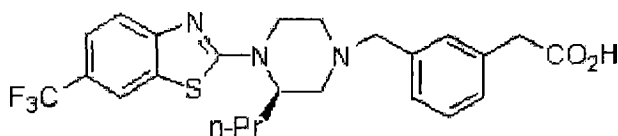


[3415] 收率:91%, $^1\text{H-NMR}(\text{CDCl}_3)$: δ 0.92 (3H, t, $J = 7.2\text{Hz}$), 1.20-1.30 (2H, m), 1.75-1.84 (1H, m), 1.87-1.97 (1H, m), 2.18-2.28 (2H, m), 2.34 (3H, s), 2.86 (2H, dd, $J = 11.1\text{Hz}$), 3.37 (1H, d, $J = 13.2\text{Hz}$), 3.48 (1H, dt, $J = 3.3, 12.6\text{Hz}$), 3.61 (1H, d, $J = 12.1\text{Hz}$), 3.62 (2H, s), 3.90 (1H, s), 3.99 (1H, d, $J = 11.1\text{Hz}$), 7.02 (1H, s), 7.07 (2H, s), 7.22 (1H, dd, $J = 2.1, 8.7\text{Hz}$), 7.40 (1H, d, $J = 8.7\text{Hz}$), 7.52 (1H, d, $J = 2.1\text{Hz}$)。

[3416] 实施例 462

[3417] [式 752]

[3418]

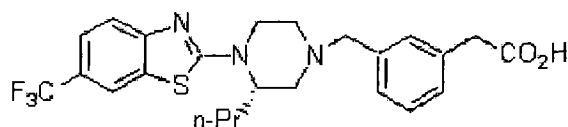


[3419] 收率:70%, $^1\text{H-NMR}(\text{CDCl}_3)$: δ 0.92 (3H, t, $J = 7.0\text{Hz}$), 1.18-1.35 (2H, m), 1.75-1.98 (2H, m), 2.15-2.29 (2H, m), 2.81 (1H, d, $J = 11.5\text{Hz}$), 2.88 (1H, d, $J = 11.5\text{Hz}$), 3.41 (1H, d, $J = 13.0\text{Hz}$), 3.48 (1H, td, $J = 12.5, 3.0\text{Hz}$), 3.58 (1H, d, $J = 13.0\text{Hz}$), 3.62 (2H, s), 3.89-4.09 (2H, m), 7.14-7.32 (4H, m), 7.49 (1H, d, $J = 8.5\text{Hz}$), 7.53 (1H, d, $J = 8.5\text{Hz}$), 7.81 (1H, s)。

[3420] 实施例 463

[3421] [式 753]

[3422]

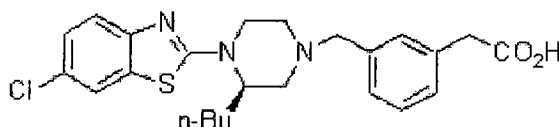


[3423] 收率:81%, $^1\text{H-NMR}$ (CDCl_3): δ 0.92 (3H, t, $J = 7.2\text{Hz}$), 1.21-1.31 (2H, m), 1.80-1.94 (2H, m), 2.20-2.29 (2H, m), 2.82 (1H, d, $J = 11.4\text{Hz}$), 2.91 (1H, d, $J = 11.1\text{Hz}$), 3.43 (1H, d, $J = 13.2\text{Hz}$), 3.50 (1H, dt, $J = 3.0, 12.6\text{Hz}$), 3.61 (1H, d, $J = 13.2\text{Hz}$), 3.67 (2H, s), 3.99 (1H, d, $J = 14.1\text{Hz}$), 4.06 (1H, s), 7.20-7.34 (4H, m), 7.52 (2H, s), 7.82 (1H, s)。

[3424] 实施例 464

[3425] [式 754]

[3426]

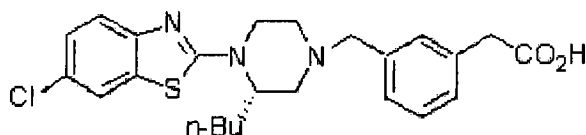


[3427] 收率:81%, $^1\text{H-NMR}$ (CDCl_3): δ 0.86 (3H, t, $J = 7.5\text{Hz}$), 1.14-1.38 (4H, m), 1.74-1.99 (2H, m), 2.16-2.30 (2H, m), 2.81 (1H, d, $J = 11.5\text{Hz}$), 2.89 (1H, d, $J = 11.5\text{Hz}$), 3.42 (1H, d, $J = 13\text{Hz}$), 3.46 (1H, td, $J = 13.5, 3.5\text{Hz}$), 3.60 (1H, d, $J = 13\text{Hz}$), 3.66 (2H, s), 3.80-3.93 (1H, m), 3.95-4.06 (1H, m), 7.15-7.35 (5H, m), 7.40 (1H, d, $J = 8.5\text{Hz}$), 7.52 (1H, d, $J = 2.5\text{Hz}$)。

[3428] 实施例 465

[3429] [式 755]

[3430]

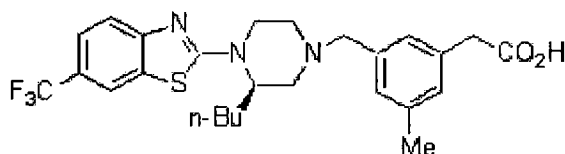


[3431] 收率:91%, $^1\text{H-NMR}$ (CDCl_3): δ 0.86 (3H, t, $J = 7.5\text{Hz}$), 1.13-1.40 (4H, m), 1.74-2.00 (2H, m), 2.16-2.30 (2H, m), 2.82 (1H, d, $J = 12\text{Hz}$), 2.88 (1H, d, $J = 11.5\text{Hz}$), 3.41 (1H, d, $J = 13.5\text{Hz}$), 3.41-3.51 (1H, m), 3.60 (1H, d, $J = 13.5\text{Hz}$), 3.66 (2H, s), 3.80-3.92 (1H, m), 3.94-4.05 (1H, m), 7.16-7.34 (5H, m), 7.39 (1H, d, $J = 8.5\text{Hz}$), 7.52 (1H, d, $J = 2\text{Hz}$)。

[3432] 实施例 466

[3433] [式 756]

[3434]



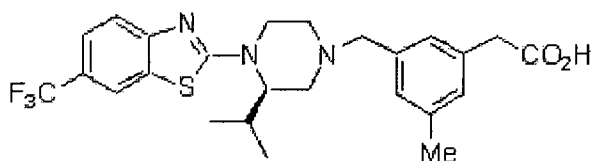
[3435] 收率:81%, $^1\text{H-NMR}$ (CDCl_3): δ 0.87 (3H, t, $J = 7.5\text{Hz}$), 1.17-1.39 (4H, m), 1.75-2.03 (2H, m), 2.17-2.30 (2H, m), 2.34 (3H, s), 2.83 (1H, d, $J = 11.5\text{Hz}$), 2.91 (1H, d, $J = 10.5\text{Hz}$), 3.38 (1H, d, $J = 13.5\text{Hz}$), 3.44-3.55 (1H, m), 3.58 (1H, d, $J = 13.5\text{Hz}$), 3.62 (2H, s), 3.85-3.97 (1H, m), 4.00-4.10 (1H, m), 7.02 (1H, s), 7.06 (1H, s), 7.07 (1H, s), 7.51 (2H,

s), 7.82 (1H, s)。

[3436] 实施例 467

[3437] [式 757]

[3438]

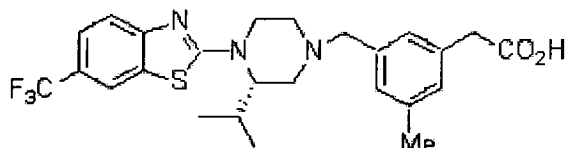


[3439] 收率:53%, $^1\text{H-NMR}$ (DMSO- d_6): δ 0.87 (3H, d, $J = 6.5\text{Hz}$), 0.89 (3H, d, $J = 6.5\text{Hz}$), 2.02-2.25 (2H, m), 2.29 (3H, s), 2.45-3.05 (4H, m), 3.10 (1H, d, $J = 13.0\text{Hz}$), 3.35-3.58 (2H, m), 3.53 (2H, s), 4.01-4.22 (1H, m), 6.96 (1H, s), 7.00 (1H, s), 7.03 (1H, s), 7.49 (2H, s), 7.78 (1H, s)。

[3440] 实施例 468

[3441] [式 758]

[3442]

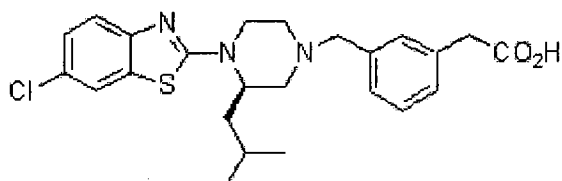


[3443] 收率:70%, $^1\text{H-NMR}$ (DMSO- d_6): δ 0.85 (6H, t, $J = 7.5\text{Hz}$), 2.00 (1H, d, $J = 11.5\text{Hz}$), 2.14 (1H, t, $J = 11.5\text{Hz}$), 2.28 (3H, s), 2.50-2.57 (1H, m), 2.93 (2H, t, $J = 11.5\text{Hz}$), 3.32 (1H, d, $J = 13.5\text{Hz}$), 3.32-3.48 (1H, m), 3.49 (2H, s), 3.57 (1H, d, $J = 13.5\text{Hz}$), 3.58-3.65 (1H, m), 3.95-4.10 (1H, m), 6.97 (1H, s), 7.02 (2H, s), 7.49 (1H, d, $J = 8.5\text{Hz}$), 7.55 (1H, d, $J = 8.5\text{Hz}$), 8.18 (1H, s), 12.4 (1H, brs)。

[3444] 实施例 469

[3445] [式 759]

[3446]

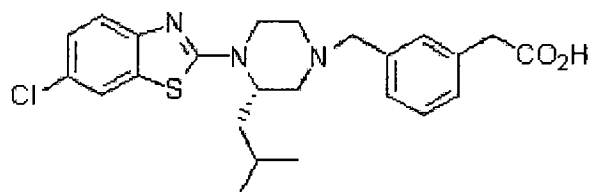


[3447] 收率:67%, $^1\text{H-NMR}$ (DMSO- d_6): δ 0.88 (3H, d, $J = 6.5\text{Hz}$), 0.90 (3H, d, $J = 6.5\text{Hz}$), 1.32-1.58 (2H, m), 1.80-1.96 (1H, m), 2.05-2.23 (2H, m), 2.75 (1H, d, $J = 10.5\text{Hz}$), 2.89 (1H, d, $J = 11.5\text{Hz}$), 3.30-3.53 (2H, m), 3.48 (2H, s), 3.59 (1H, d, $J = 13.5\text{Hz}$), 3.80-4.08 (2H, m), 7.10-7.30 (5H, m), 7.38 (1H, d, $J = 8.5\text{Hz}$), 7.87 (1H, d, $J = 2.0\text{Hz}$)。

[3448] 实施例 470

[3449] [式 760]

[3450]

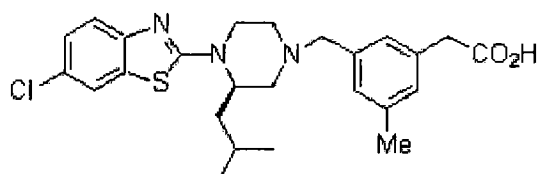


[3451] 收率:88%, $^1\text{H-NMR}$ (CDCl_3): δ 0.90 (6H, dd, $J = 6, 2\text{Hz}$), 1.30–1.59 (2H, m), 1.80–1.95 (1H, m), 2.08–2.24 (2H, m), 2.75 (1H, d, $J = 11.5\text{Hz}$), 2.91 (1H, d, $J = 11.5\text{Hz}$), 3.20–3.37 (1H, m), 3.38 (1H, d, $J = 13.5\text{Hz}$), 3.55 (2H, s), 3.62 (1H, d, $J = 13.5\text{Hz}$), 3.80–3.96 (1H, m), 3.97–4.10 (1H, m), 7.10–7.32 (5H, m), 7.38 (1H, d, $J = 8.5\text{Hz}$), 7.89 (1H, d, $J = 2\text{Hz}$), 12.43 (1H, brs)。

[3452] 实施例 471

[3453] [式 761]

[3454]

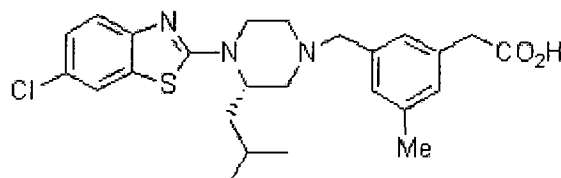


[3455] 收率:62%, $^1\text{H-NMR}$ (CDCl_3): δ 0.91 (3H, d, $J = 6.5\text{Hz}$), 0.93 (3H, d, $J = 6.5\text{Hz}$), 1.34–1.64 (2H, m), 1.85–2.00 (1H, m), 2.11–2.38 (2H, m), 2.31 (3H, s), 2.77 (1H, d, $J = 11.0\text{Hz}$), 2.86 (1H, d, $J = 10.5\text{Hz}$), 3.32 (1H, d, $J = 13.0\text{Hz}$), 3.38–3.64 (2H, m), 3.56 (2H, s), 3.83–4.07 (2H, m), 6.98 (1H, s), 7.01 (1H, s), 7.05 (1H, s), 7.21 (1H, dd, $J = 8.5, 2.0\text{Hz}$), 7.39 (1H, d, $J = 8.5\text{Hz}$), 7.52 (1H, d, $J = 2.0\text{Hz}$)。

[3456] 实施例 472

[3457] [式 762]

[3458]

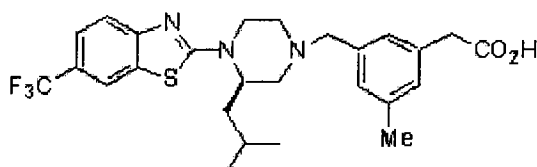


[3459] 收率:92%, $^1\text{H-NMR}$ (CDCl_3): δ 0.90 (6H, t, $J = 6\text{Hz}$), 1.42–1.53 (2H, m), 1.93–2.01 (1H, m), 2.02–2.12 (2H, m), 2.29 (3H, s), 2.75 (1H, d, $J = 11.5\text{Hz}$), 2.91 (1H, d, $J = 11.5\text{Hz}$), 3.31 (1H, d, $J = 13.5\text{Hz}$), 3.32–3.50 (1H, m), 3.51 (2H, s), 3.61 (1H, d, $J = 13.5\text{Hz}$), 3.87–4.04 (2H, m), 6.97 (1H, s), 7.02 (1H, s), 7.04 (1H, s), 7.27 (1H, dd, $J = 8.5, 2\text{Hz}$), 7.38 (1H, d, $J = 8.5\text{Hz}$), 7.89 (1H, d, $J = 2\text{Hz}$), 12.28 (1H, brs)。

[3460] 实施例 473

[3461] [式 763]

[3462]

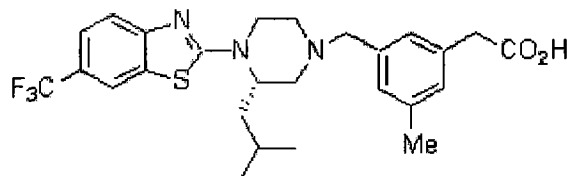


[3463] 收率:99%, $^1\text{H-NMR}(\text{CDCl}_3)$: δ 0.90 (3H, d, $J = 6.0\text{Hz}$), 0.92 (3H, d, $J = 6.0\text{Hz}$), 1.34-1.64 (2H, m), 1.84-1.98 (1H, m), 2.07-2.30 (2H, m), 2.26 (3H, s), 2.74 (1H, d, $J = 11.0\text{Hz}$), 2.82 (1H, d, $J = 10.5\text{Hz}$), 3.28 (1H, d, $J = 13.5\text{Hz}$), 3.35-3.54 (4H, m), 3.87-4.07 (2H, m), 6.91 (1H, s), 6.93 (1H, s), 7.02 (1H, s), 7.50 (2H, s), 7.81 (1H, s)。

[3464] 实施例 474

[3465] [式 764]

[3466]

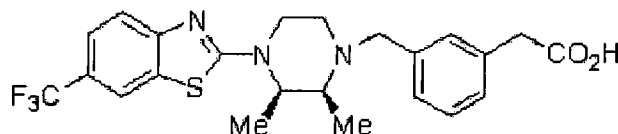


[3467] 收率:98%, $^1\text{H-NMR}(\text{CDCl}_3)$: δ 0.93 (6H, dd, $J = 3.6, 6.3\text{Hz}$), 1.42-1.50 (1H, m), 1.55-1.64 (1H, m), 1.90-1.99 (1H, m), 2.23 (2H, td, $J = 3.6, 11.4\text{Hz}$), 2.34 (3H, s), 2.81 (1H, d, $J = 11.4\text{Hz}$), 2.92 (1H, d, $J = 10.2\text{Hz}$), 3.37 (1H, d, $J = 13.2\text{Hz}$), 3.52 (1H, td, $J = 3.3, 12.9\text{Hz}$), 3.62 (1H, d, $J = 13.2\text{Hz}$), 3.62 (2H, s), 4.04 (2H, br), 7.02 (1H, s), 7.07 (2H, s), 7.52 (2H, s), 7.82 (1H, s)。

[3468] 实施例 475

[3469] [式 765]

[3470]

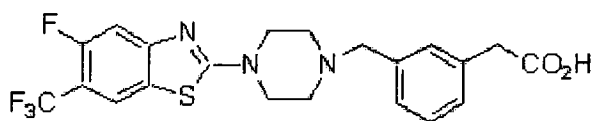


[3471] 收率:62%, $^1\text{H-NMR}(\text{CDCl}_3)$: δ 1.23 (3H, d, $J = 6.5\text{Hz}$), 1.38 (3H, d, $J = 6.5\text{Hz}$), 2.11-2.26 (1H, m), 2.65-2.89 (2H, m), 2.98-3.15 (1H, m), 3.35-3.52 (1H, m), 3.67 (2H, s), 3.68-3.82 (1H, m), 4.03-4.22 (2H, m), 7.17-7.36 (4H, m), 7.48-7.60 (2H, m), 7.83 (1H, s)。

[3472] 实施例 476

[3473] [式 766]

[3474]

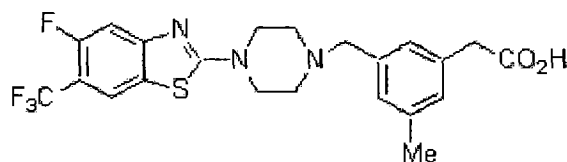


[3475] 收率:80%, $^1\text{H-NMR}(\text{DMSO-d}_6)$: δ 2.43-2.58 (4H, m), 3.54 (2H, s), 3.57 (2H, s), 3.58-3.70 (4H, m), 7.13-7.34 (4H, m), 7.47 (1H, d, $J = 12.5\text{Hz}$), 8.27 (1H, d, $J = 7.5\text{Hz}$), 12.28 (1H, s)。

[3476] 实施例 477

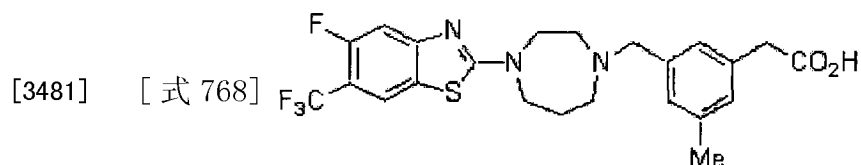
[3477] [式 767]

[3478]



[3479] 收率:92%, $^1\text{H-NMR}$ (CDCl_3): δ 2.28 (3H, s), 2.50-2.62 (4H, m), 3.47 (2H, s), 3.52 (2H, s), 3.58-3.68 (4H, m), 6.97 (2H, s), 7.04 (1H, s), 7.25 (1H, d, $J = 11.5\text{Hz}$), 7.73 (1H, d, $J = 7.0\text{Hz}$)。

[3480] 实施例 478

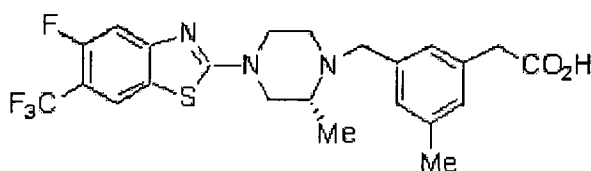


[3482] 收率:59%, $^1\text{H-NMR}$ (CD_3OD): δ 2.06-2.18 (2H, m), 2.31 (3H, s), 2.87-2.97 (2H, m), 2.99-3.08 (2H, m), 3.52 (2H, s), 3.70-3.98 (4H, m), 3.82 (2H, s), 7.07 (2H, s), 7.11 (1H, s), 7.29 (1H, d, $J = 12.0\text{Hz}$), 7.98 (1H, d, $J = 7.0\text{Hz}$)。

[3483] 实施例 479

[3484] [式 769]

[3485]

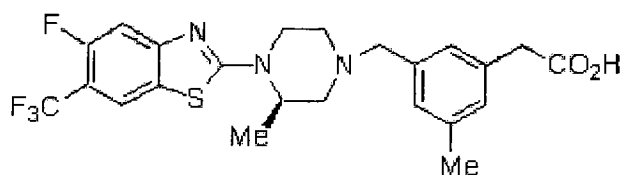


[3486] 收率:85%, $^1\text{H-NMR}$ (DMSO-d_6): δ 1.15 (3H, d, $J = 6\text{Hz}$), 2.16-2.27 (1H, m), 2.28 (3H, s), 2.55-2.68 (1H, m), 2.69-2.80 (1H, m), 3.17 (1H, d, $J = 13.5\text{Hz}$), 3.18-3.26 (1H, m), 3.35-3.48 (1H, m), 3.49 (2H, s), 3.65-3.79 (1H, m), 3.80-3.90 (1H, m), 3.92 (1H, d, $J = 13.5\text{Hz}$), 6.96 (1H, s), 7.00 (1H, s), 7.01 (1H, s), 7.45 (1H, d, $J = 12\text{Hz}$), 8.25 (1H, d, $J = 8\text{Hz}$), 12.40 (1H, brs)。

[3487] 实施例 480

[3488] [式 770]

[3489]

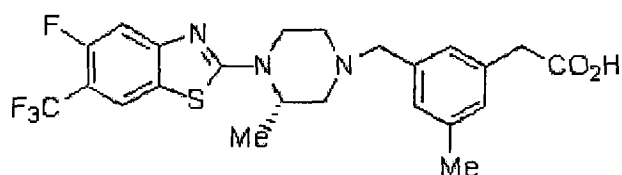


[3490] 收率:67%, $^1\text{H-NMR}$ (CDCl_3): δ 1.39 (3H, d, $J = 7.0\text{Hz}$), 2.14-2.35 (2H, m), 2.32 (3H, s), 2.72 (1H, d, $J = 11.0\text{Hz}$), 2.91 (1H, d, $J = 11.0\text{Hz}$), 3.40 (1H, d, $J = 14.0\text{Hz}$), 3.43-3.62 (2H, m), 3.58 (2H, s), 3.86 (1H, d, $J = 12.5\text{Hz}$), 4.12-4.28 (1H, m), 6.99 (1H, s), 7.02-7.10 (2H, m), 7.25 (1H, d, $J = 11.5\text{Hz}$), 7.73 (1H, d, $J = 7.0\text{Hz}$)。

[3491] 实施例 481

[3492] [式 771]

[3493]

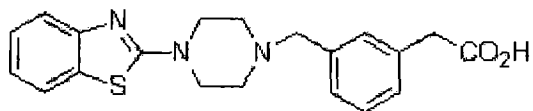


[3494] 收率:78%, $^1\text{H-NMR}$ (CDCl_3): δ 1.38 (3H, d, $J = 7.0\text{Hz}$), 2.12-2.35 (2H, m), 2.30 (3H, s), 2.70 (1H, d, $J = 11.5\text{Hz}$), 2.88 (1H, d, $J = 11.5\text{Hz}$), 3.32-3.60 (5H, m), 3.84 (1H, d, $J = 11.5\text{Hz}$), 4.10-4.25 (1H, m), 6.97 (1H, s), 7.04 (2H, s), 7.24 (1H, d, $J = 12.0\text{Hz}$), 7.73 (1H, d, $J = 7.0\text{Hz}$)。

[3495] 实施例 482

[3496] [式 772]

[3497]

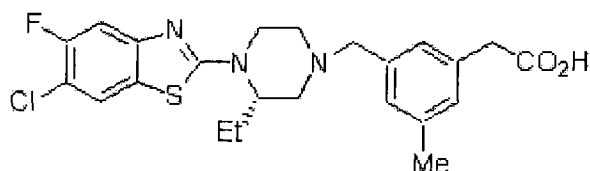


[3498] 收率:82%, $^1\text{H-NMR}$ (DMSO-d_6): δ 2.45-2.60 (4H, m), 3.48-3.63 (8H, m), 7.06 (1H, td, $J = 7.5, 1.0\text{Hz}$), 7.13-7.33 (5H, m), 7.45 (1H, d, $J = 7.5\text{Hz}$), 7.76 (1H, d, $J = 7.5\text{Hz}$), 12.32 (1H, brs)。

[3499] 实施例 483

[3500] [式 773]

[3501]

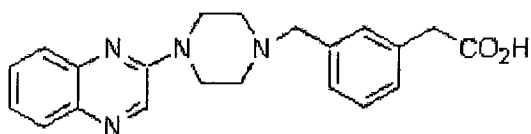


[3502] 收率:60%, $^1\text{H-NMR}$ (CDCl_3): δ 0.85 (3H, t, $J = 7.5\text{Hz}$), 1.80-2.00 (2H, m), 2.12-2.26 (2H, m), 2.31 (3H, s), 2.77-2.91 (2H, m), 3.36 (1H, d, $J = 13.5\text{Hz}$), 3.36-3.62 (2H, m), 3.57 (2H, s), 3.75-3.87 (1H, m), 3.88-4.02 (1H, m), 6.98 (1H, s), 7.04 (2H, s), 7.24 (1H, d, $J = 10.5\text{Hz}$), 7.51 (1H, d, $J = 7.0\text{Hz}$)。

[3503] 实施例 484

[3504] [式 774]

[3505]

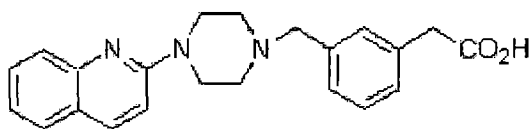


[3506] 收率:67%, $^1\text{H-NMR}$ (CDCl_3): δ 2.75 (4H, t, $J = 5.0\text{Hz}$), 3.68 (4H, s), 3.85 (4H, t, $J = 5.0\text{Hz}$), 7.13-7.21 (1H, m), 7.22-7.34 (2H, m), 7.37-7.46 (2H, m), 7.54-7.64 (1H, m), 7.69 (1H, dd, $J = 8.0, 1.0\text{Hz}$), 7.89 (1H, dd, $J = 8.0, 1.0\text{Hz}$), 8.56 (1H, s)。

[3507] 实施例 485

[3508] [式 775]

[3509]

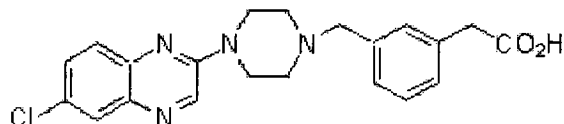


[3510] 收率:57%, $^1\text{H-NMR}(\text{CDCl}_3)$: δ 2.82(4H, t, $J = 4.5\text{Hz}$), 3.66(2H, s), 3.74(2H, s), 3.83(4H, t, $J = 4.5\text{Hz}$), 6.93(1H, d, $J = 9.0\text{Hz}$), 7.07-7.15(1H, m), 7.20-7.31(3H, m), 7.47(1H, s), 7.54(1H, td, $J = 8.0, 1.5\text{Hz}$), 7.60(1H, d, $J = 8.0$), 7.70(1H, d, $J = 8.0\text{Hz}$), 7.89(1H, d, $J = 9.0\text{Hz}$)。

[3511] 实施例 486

[3512] [式 776]

[3513]

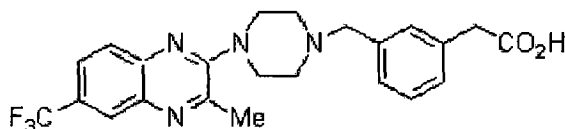


[3514] 收率:42%, $^1\text{H-NMR}(\text{CDCl}_3)$: δ 2.65-2.77(4H, m), 3.64(4H, s), 3.76-3.88(4H, m), 7.13-7.32(3H, m), 7.38(1H, s), 7.50(1H, dd, $J = 9.0, 2.0\text{Hz}$), 7.59(1H, d, $J = 9.0\text{Hz}$), 7.86(1H, d, $J = 2.0\text{Hz}$), 8.53(1H, s)。

[3515] 实施例 487

[3516] [式 777]

[3517]

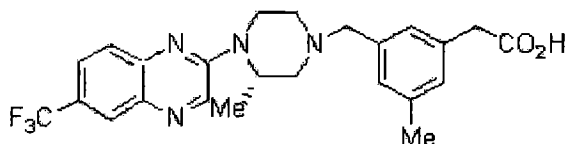


[3518] 收率:81%, $^1\text{H-NMR}(\text{CDCl}_3)$: δ 2.60-2.74(4H, m), 2.63(3H, s), 3.35-3.49(4H, m), 3.52(2H, s), 3.54(2H, s), 7.05-7.23(3H, m), 7.29(1H, s), 7.69(1H, d, $J = 9.0\text{Hz}$), 7.80(1H, d, $J = 9.0\text{Hz}$), 8.14(1H, s)。

[3519] 实施例 488

[3520] [式 778]

[3521]

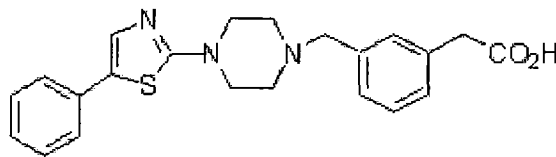


[3522] 收率:79%, $^1\text{H-NMR}(\text{CDCl}_3)$: δ 1.35(3H, d, $J = 6.5\text{Hz}$), 2.12-2.35(5H, m), 2.79(1H, d, $J = 11.5\text{Hz}$), 2.99(1H, d, $J = 11.5\text{Hz}$), 3.27-3.43(2H, m), 3.50-3.62(3H, m), 4.35(1H, d, $J = 12.5\text{Hz}$), 4.59-4.72(1H, m), 6.98(1H, s), 7.05(1H, s), 7.08(1H, s), 7.70(2H, s), 8.13(1H, s), 8.56(1H, s)。

[3523] 实施例 489

[3524] [式 779]

[3525]



[3526] 收率:76%, $^1\text{H-NMR}(\text{CD}_3\text{OD})$: δ 2.69-2.78(4H, m), 3.52-3.60(4H, m), 3.61(2H,

s), 3.71 (2H, s), 7.18-7.39 (7H, m), 7.42-7.50 (3H, m)。

[3527] 实施例 490

[3528] 3-[[4-(6-氯苯并噻唑-2-基)哌嗪-1-基]甲基]苯基乙酸

[3529] [式 780]

[3530]



[3531] 将 {3-[[4-(6-氯苯并噻唑-2-基)哌嗪-1-基]甲基]苯基} 乙腈 (0.35g; 0.914mmol), 浓硫酸 (2ml) 和水 (2ml) 的混合物在 80℃ 搅拌 2 小时。在空气冷却之后, 5N-氢氧化钠水溶液向其中加入直到为碱性。向其中加入乙酸乙酯并且反萃取。用 2N-盐酸使水层变为中性, 并且用乙酸乙酯萃取。有机层用盐水洗涤, 用无水硫酸钠干燥, 并且减压蒸发, 得到 3-[[4-(6-氯苯并噻唑-2-基)哌嗪-1-基]甲基]苯基乙酸, 为无色的无定形固体 (0.08g; 22%)。

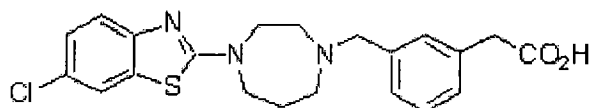
[3532] $^1\text{H-NMR}$ (DMSO- d_6): δ 2.45-2.50 (4H, m), 3.53 (2H, s), 3.53-3.65 (6H, m), 7.10-7.35 (5H, m), 7.42 (1H, d, $J = 8.5\text{Hz}$), 7.91 (1H, d, $J = 2\text{Hz}$), 12.28 (1H, brs)。

[3533] 通过与实施例 490 相似的方法得到实施例 491 到 512 的化合物。

[3534] 实施例 491

[3535] [式 781]

[3536]

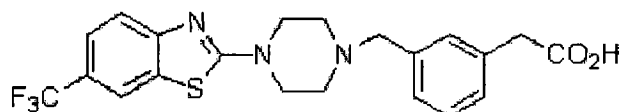


[3537] 收率: 43%, $^1\text{H-NMR}$ (DMSO- d_6): δ 1.90-1.96 (2H, m), 2.61 (2H, t, $J = 4.8\text{Hz}$), 2.77-2.80 (2H, m), 3.57-3.62 (4H, m), 3.62-3.71 (4H, m), 7.12-7.16 (2H, m), 7.21-7.28 (3H, m), 7.40 (1H, d, $J = 8.5\text{Hz}$), 7.88 (1H, d, $J = 2.4\text{Hz}$)。

[3538] 实施例 492

[3539] [式 782]

[3540]

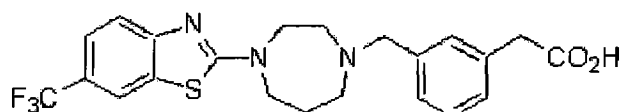


[3541] 收率: 78%, $^1\text{H-NMR}$ (DMSO- d_6): δ 2.52 (4H, t, $J = 5\text{Hz}$), 3.54 (2H, s), 3.57 (2H, s), 3.63 (4H, t, $J = 5\text{Hz}$), 7.10-7.35 (4H, m), 7.57 (2H, s), 8.24 (1H, s), 12.31 (1H, s)。

[3542] 实施例 493

[3543] [式 783]

[3544]



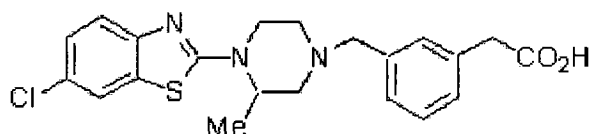
[3545] 收率: 18%, $^1\text{H-NMR}$ (DMSO- d_6): δ 1.85-2.00 (2H, m), 2.57-2.68 (2H, m), 2.74-2.85 (2H, m), 3.52 (2H, s), 3.61 (2H, s), 3.62-3.85 (4H, m), 7.09-7.31 (4H, m),

7.52-7.58 (2H, m), 8.22 (2H, s)。

[3546] 实施例 494

[3547] [式 784]

[3548]

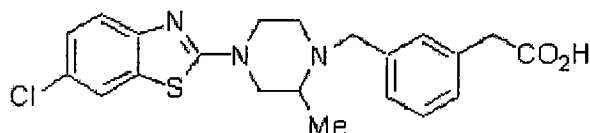


[3549] 收率:79%, $^1\text{H-NMR}$ (DMSO- d_6): δ 1.31 (3H, d, $J = 6.5\text{Hz}$), 2.15 (1H, td, $J = 12, 3.5\text{Hz}$), 2.22 (1H, dd, $J = 11.5, 3.5\text{Hz}$), 2.70 (1H, d, $J = 11.5\text{Hz}$), 2.91 (1H, d, $J = 12\text{Hz}$), 3.41 (1H, td, $J = 12, 3.5\text{Hz}$), 3.44 (1H, d, $J = 13.5\text{Hz}$), 3.56 (2H, s), 3.59 (1H, d, $J = 13.5\text{Hz}$), 3.80 (1H, d, $J = 12\text{Hz}$), 4.10-4.30 (1H, m), 7.10-7.35 (5H, m), 7.41 (1H, d, $J = 8.5\text{Hz}$), 7.90 (1H, d, $J = 2\text{Hz}$), 12.40 (1H, brs)。

[3550] 实施例 495

[3551] [式 785]

[3552]

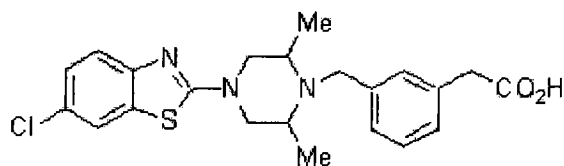


[3553] 收率:69%, $^1\text{H-NMR}$ (DMSO- d_6): δ 1.05-1.25 (3H, m), 2.15-2.30 (1H, s), 2.50-2.65 (1H, m), 2.65-2.80 (1H, m), 3.05-3.40 (3H, m), 3.57 (2H, s), 3.60-3.70 (1H, m), 3.70-3.85 (1H, m), 3.90-4.00 (1H, m), 7.05-7.35 (5H, m), 7.41 (1H, d, $J = 8.5\text{Hz}$), 7.90 (1H, s), 12.29 (1H, s)。

[3554] 实施例 496

[3555] [式 786]

[3556]

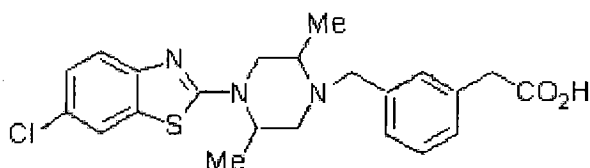


[3557] 收率:92%, $^1\text{H-NMR}$ (DMSO- d_6): δ 1.04 (6H, d, $J = 6\text{Hz}$), 2.60-2.80 (2H, m), 2.95-3.10 (2H, m), 3.53 (2H, s), 3.77 (2H, s), 3.77-3.87 (2H, m), 7.00-7.10 (1H, m), 7.20-7.30 (4H, m), 7.42 (1H, d, $J = 8.5\text{Hz}$), 7.90 (1H, d, $J = 2\text{Hz}$), 12.5 (1H, brs)。

[3558] 实施例 497

[3559] [式 787]

[3560]



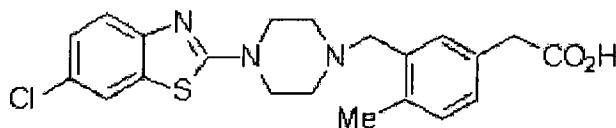
[3561] 收率:76%, $^1\text{H-NMR}$ (DMSO- d_6): δ 1.00 (3H, d, $J = 6\text{Hz}$), 1.30 (3H, d, $J = 6\text{Hz}$),

2.30 (1H, d, $J = 9.5\text{Hz}$), 2.70–2.85 (1H, m), 3.05–3.15 (1H, m), 3.40–3.45 (1H, m), 3.49 (2H, s), 3.62 (2H, s), 3.63–3.70 (1H, m), 4.10–4.30 (1H, m), 7.05–7.10 (1H, m), 7.20–7.35 (4H, m), 7.38 (1H, d, $J = 9\text{Hz}$), 7.87 (1H, d, $J = 2\text{Hz}$)。

[3562] 实施例 498

[3563] [式 788]

[3564]

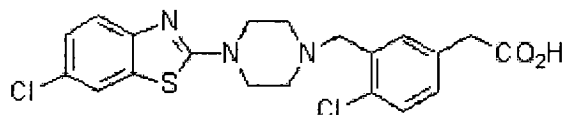


[3565] 收率:42%, $^1\text{H-NMR}$ (DMSO- d_6): 2.31 (3H, s), 2.50 (4H, t, $J = 5\text{Hz}$), 3.47 (2H, s), 3.52 (2H, s), 3.55 (4H, t, $J = 5\text{Hz}$), 7.00–7.18 (3H, m), 7.28 (1H, dd, $J = 8.5, 2\text{Hz}$), 7.42 (1H, d, $J = 8.5\text{Hz}$), 7.91 (1H, d, $J = 2\text{Hz}$), 12.25 (1H, brs)。

[3566] 实施例 499

[3567] [式 789]

[3568]

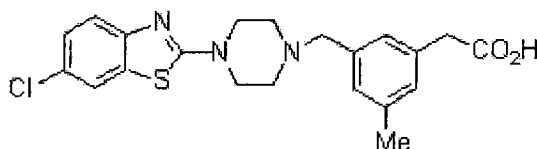


[3569] 收率:39%, $^1\text{H-NMR}$ (DMSO- d_6): δ 2.58 (4H, t, $J = 5\text{Hz}$), 3.58 (4H, t, $J = 5\text{Hz}$), 3.61 (2H, s), 3.62 (2H, s), 7.19 (1H, dd, $J = 8, 2\text{Hz}$), 7.29 (1H, dd, $J = 8.5, 1.5\text{Hz}$), 7.39 (1H, d, $J = 8.5\text{Hz}$), 7.42 (1H, d, $J = 8\text{Hz}$), 7.43 (1H, d, $J = 1.5\text{Hz}$), 7.91 (1H, d, $J = 2\text{Hz}$), 12.41 (1H, brs)。

[3570] 实施例 500

[3571] [式 790]

[3572]

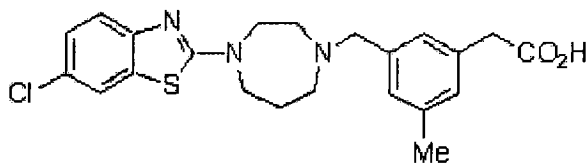


[3573] 收率:68%, $^1\text{H-NMR}$ (CDCl_3): δ 2.32 (3H, s), 2.67 (4H, t, $J = 5\text{Hz}$), 3.59 (2H, s), 3.61 (2H, s), 3.67 (4H, t, $J = 5\text{Hz}$), 6.99 (1H, s), 7.04 (1H, s), 7.14 (1H, s), 7.24 (1H, dd, $J = 8.5, 2\text{Hz}$), 7.43 (1H, d, $J = 8.5\text{Hz}$), 7.55 (1H, d, $J = 2\text{Hz}$)。

[3574] 实施例 501

[3575] [式 791]

[3576]



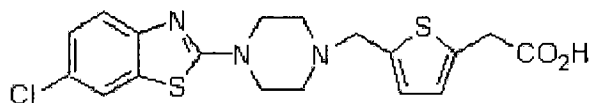
[3577] 收率:73%, $^1\text{H-NMR}$ (DMSO- d_6): δ 1.88–1.94 (2H, m), 2.25 (3H, s), 2.60 (2H, t, $J = 4.5\text{Hz}$), 2.74–2.78 (2H, m), 3.48 (2H, s), 3.56 (2H, s), 3.66–3.73 (4H, m), 6.94–6.98 (3H, m),

7.26 (1H, dd, $J = 8.7, 2.1$ Hz), 7.40 (1H, d, $J = 8.4$ Hz), 7.88 (1H, d, $J = 2.1$ Hz)。

[3578] 实施例 502

[3579] [式 792]

[3580]

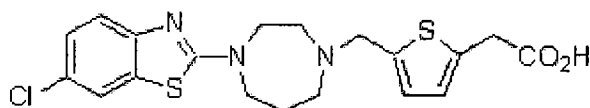


[3581] 收率:67%, $^1\text{H-NMR}$ (CDCl_3): δ 2.71 (4H, t, $J = 5$ Hz), 3.67 (4H, t, $J = 5$ Hz), 3.78 (2H, s), 3.81 (2H, s), 6.78 (2H, s), 7.24 (1H, dd, $J = 8.5, 2$ Hz), 7.43 (1H, d, $J = 8.5$ Hz), 7.56 (1H, d, $J = 2$ Hz)。

[3582] 实施例 503

[3583] [式 793]

[3584]

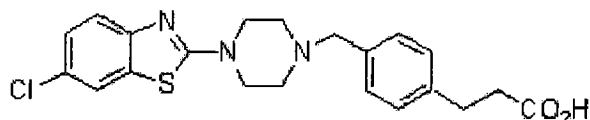


[3585] 收率:46%, $^1\text{H-NMR}$ (CDCl_3): δ 2.16-2.20 (2H, m), 2.91-2.95 (2H, m), 3.03-3.06 (2H, m), 3.68 (2H, t, $J = 6.0$ Hz), 3.79 (2H, s), 3.90-3.91 (2H, m), 3.97 (2H, s), 6.75 (1H, d, $J = 3.6$ Hz), 6.77 (1H, d, $J = 3.3$ Hz), 7.24 (1H, dd, $J = 9.0, 2.4$ Hz), 7.43 (1H, d, $J = 9.0$ Hz), 7.55 (1H, d, $J = 2.1$ Hz)。

[3586] 实施例 504

[3587] [式 794]

[3588]

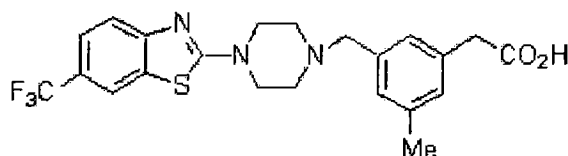


[3589] 收率:2%, $^1\text{H-NMR}$ (DMSO-d_6): δ 2.40-2.50 (4H, m), 2.53 (2H, t, $J = 7.5$ Hz), 2.81 (2H, t, $J = 7.5$ Hz), 3.50 (2H, s), 3.55 (4H, t, $J = 5$ Hz), 7.19 (2H, d, $J = 8$ Hz), 7.23 (2H, d, $J = 8$ Hz), 7.29 (1H, dd, $J = 8.5, 2$ Hz), 7.41 (1H, d, $J = 8.5$ Hz), 7.90 (1H, d, $J = 2$ Hz), 12.05 (1H, brs)。

[3590] 实施例 505

[3591] [式 795]

[3592]

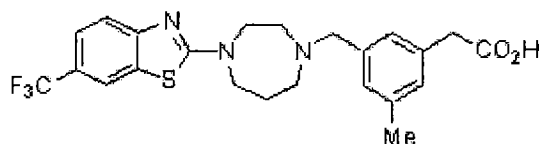


[3593] 收率:70%, $^1\text{H-NMR}$ (DMSO-d_6): δ 2.28 (3H, s), 2.45-2.55 (4H, m), 3.49 (2H, s), 3.51 (2H, s), 3.60-3.65 (4H, m), 6.97 (1H, s), 7.02 (2H, s), 7.57 (2H, s), 8.25 (1H, s), 12.4 (1H, brs)。

[3594] 实施例 506

[3595] [式 796]

[3596]

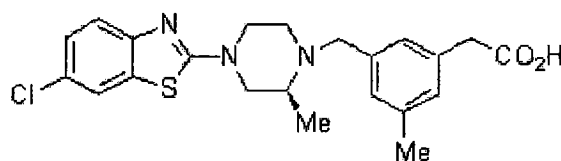


[3597] 收率:55%, $^1\text{H-NMR}$ (DMSO- d_6): δ 1.85–2.00 (2H, m), 2.25 (3H, s), 2.55–2.70 (2H, m), 2.70–2.85 (2H, m), 3.49 (2H, s), 3.57 (2H, s), 3.60–3.85 (4H, m), 6.94 (1H, s), 6.99 (2H, s), 7.55 (2H, s), 8.22 (1H, s), 12.4 (1H, brs)。

[3598] 实施例 507

[3599] [式 797]

[3600]

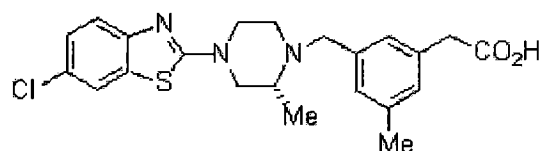


[3601] 收率:99%, $^1\text{H-NMR}$ (CDCl₃): δ 1.24 (3H, d, $J = 6.0\text{Hz}$), 2.26–2.33 (1H, m), 2.33 (3H, s), 2.64–2.71 (1H, m), 2.82 (1H, dt, $J = 3.6, 12.0\text{Hz}$), 3.19 (2H, d, $J = 12.9\text{Hz}$), 3.38–3.45 (1H, m), 3.61 (2H, s), 3.70 (1H, dt, $J = 3.6, 12.9\text{Hz}$), 3.86 (1H, dd, $J = 2.1, 11.7\text{Hz}$), 4.05 (1H, d, $J = 12.9\text{Hz}$), 7.03 (2H, d, $J = 4.5\text{Hz}$), 7.09 (1H, s), 7.23 (1H, dd, $J = 2.1, 8.7\text{Hz}$), 7.43 (1H, d, $J = 8.7\text{Hz}$), 7.54 (1H, d, $J = 2.1\text{Hz}$)。

[3602] 实施例 508

[3603] [式 798]

[3604]

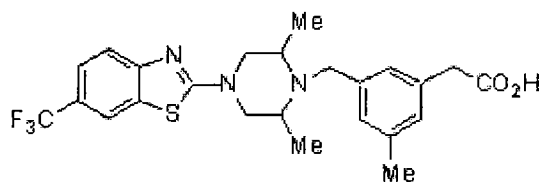


[3605] 收率:93%, $^1\text{H-NMR}$ (CDCl₃): δ 1.24 (3H, d, $J = 6.3\text{Hz}$), 2.27–2.37 (1H, m), 2.33 (3H, s), 2.56–2.71 (1H, m), 2.83 (1H, dt, $J = 3.3, 12.0\text{Hz}$), 3.19 (2H, d, $J = 13.2\text{Hz}$), 3.38–3.47 (1H, m), 3.60 (2H, s), 3.70 (1H, dt, $J = 4.8, 12.6\text{Hz}$), 3.86 (1H, dd, $J = 2.7, 12.6\text{Hz}$), 4.06 (1H, d, $J = 13.2\text{Hz}$), 7.03 (2H, s), 7.09 (1H, s), 7.23 (1H, dd, $J = 2.1, 8.7\text{Hz}$), 7.43 (1H, d, $J = 8.7\text{Hz}$), 7.54 (1H, d, $J = 2.1\text{Hz}$)。

[3606] 实施例 509

[3607] [式 799]

[3608]

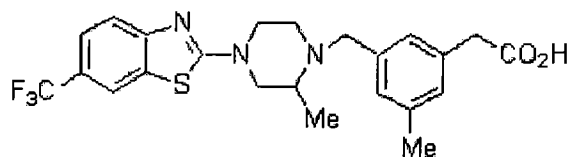


[3609] 收率:95%, $^1\text{H-NMR}$ (DMSO- d_6): δ 1.04 (6H, d, $J = 6\text{Hz}$), 2.26 (3H, s), 2.60–2.80 (2H, m), 3.07 (1H, d, $J = 13\text{Hz}$), 3.09 (1H, d, $J = 13\text{Hz}$), 3.48 (2H, s), 3.73 (2H, s), 3.80–3.90 (2H, m), 6.88 (1H, s), 7.05 (2H, s), 7.55 (2H, s), 8.22 (1H, s), 12.21 (1H, brs)。

[3610] 实施例 510

[3611] [式 800]

[3612]

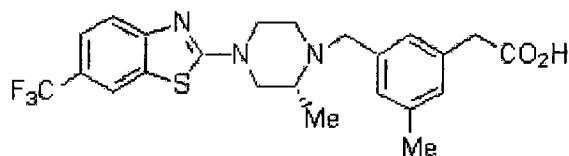


[3613] 收率:82%, $^1\text{H-NMR}$ (DMSO-d_6): δ 1.15 (3H, d, $J = 6.5\text{Hz}$), 2.18-2.25 (1H, m), 2.28 (3H, s), 2.55-2.68 (1H, m), 2.68-2.80 (1H, m), 3.15-3.48 (3H, m), 3.50 (2H, s), 3.70-3.76 (1H, m), 3.80-3.90 (1H, m), 3.93 (1H, d, $J = 13.5\text{Hz}$), 6.96 (1H, s), 7.02 (2H, s), 7.56 (2H, s), 8.23 (1H, s), 12.43 (1H, brs)。

[3614] 实施例 511

[3615] [式 801]

[3616]

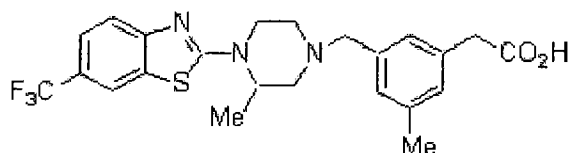


[3617] 收率:64%, $^1\text{H-NMR}$ (CDCl_3): δ 1.23 (3H, d, $J = 6.5\text{Hz}$), 2.22-2.40 (4H, m), 2.60-2.74 (1H, m), 2.76-2.89 (1H, m), 3.10-3.31 (2H, m), 3.38-3.52 (1H, m), 3.59 (2H, s), 3.67-3.80 (1H, m), 3.84-3.96 (1H, m), 4.04 (1H, d, $J = 13.0\text{Hz}$), 6.97-7.12 (3H, m), 7.47-7.60 (2H, m), 7.83 (1H, s)。

[3618] 实施例 512

[3619] [式 802]

[3620]



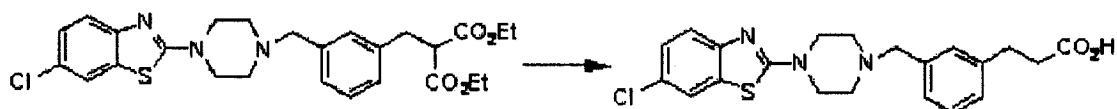
[3621] 收率:93%, $^1\text{H-NMR}$ (DMSO-d_6): δ 1.33 (3H, d, $J = 6.5\text{Hz}$), 2.05-2.28 (2H, m), 2.29 (3H, s), 2.72 (1H, d, $J = 11\text{Hz}$), 2.93 (1H, d, $J = 11\text{Hz}$), 3.25-3.50 (2H, m), 3.51 (2H, s), 3.51-3.60 (1H, m), 3.86 (1H, d, $J = 11\text{Hz}$), 4.20-4.35 (1H, m), 6.97 (1H, s), 7.05 (2H, s), 7.56 (2H, s), 8.24 (1H, s), 12.43 (1H, brs)。

[3622] 实施例 513

[3623] 3-{3-[4-(6-氯苯并噻唑-2-基)哌嗪-1-基]甲基}苯基丙酸的制备

[3624] [式 803]

[3625]



[3626] 向 2-{3-[4-(6-氯苯并噻唑-2-基)哌嗪-1-基甲基]苯基}丙二酸二乙酯

(0.38g ;0.736mmol) 加入 6N- 盐酸。将混合物回流 2 小时。在冷却之后,向其中加入饱和碳酸氢钠水溶液到变为中性。向其中加入乙酸乙酯并且用乙酸乙酯萃取。有机层用盐水洗涤,用无水硫酸钠干燥,并且减压蒸发。残余物用二异丙醚洗涤,得到 3-{3-[4-(6- 氯苯并噻唑-2- 基) 哌嗪-1- 基] 甲基} 苯基丙酸,为无色晶体 (0.08g ;22%)。

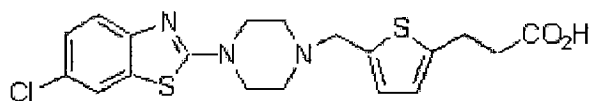
[3627] $^1\text{H-NMR}$ (DMSO-d_6) : δ 2.50-2.52 (4H, m), 2.53 (2H, t, $J = 7.5\text{Hz}$), 2.82 (2H, t, $J = 7.5\text{Hz}$), 3.51 (2H, s), 3.57 (4H, t, $J = 5\text{Hz}$), 7.10-7.20 (3H, m), 7.24 (1H, d, $J = 7.5\text{Hz}$), 7.28 (1H, dd, $J = 8.5, 2\text{Hz}$), 7.42 (1H, d, $J = 8.5\text{Hz}$), 7.91 (1H, d, $J = 2\text{Hz}$), 12.15 (1H, brs)。

[3628] 通过与实施例 513 相似的方法得到实施例 514 的化合物。

[3629] 实施例 514

[3630] [式 804]

[3631]



[3632] 收率 :55 %, $^1\text{H-NMR}$ (CDCl_3) : δ 2.63 (4H, t, $J = 5\text{Hz}$), 2.72 (2H, t, $J = 7.5\text{Hz}$), 3.13 (2H, t, $J = 7.5\text{Hz}$), 3.64 (4H, t, $J = 5\text{Hz}$), 3.72 (2H, s), 6.68 (1H, d, $J = 3.5\text{Hz}$), 6.73 (1H, d, $J = 3.5\text{Hz}$), 7.24 (1H, dd, $J = 8.5, 2\text{Hz}$), 7.43 (1H, d, $J = 8.5\text{Hz}$), 7.55 (1H, d, $J = 2\text{Hz}$)。

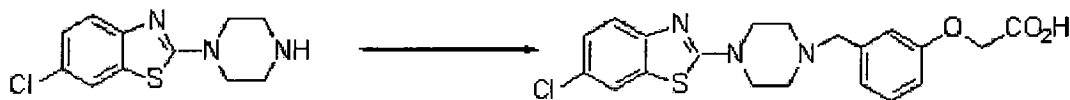
[3633] 实施例 515

[3634] 3-{3-[4-(6- 氯苯并噻唑-2- 基) 哌嗪-1- 基] 甲基} 苯氧基乙酸的制备 [0141]

[3635] 通过与参考例 155 相似的方法得到以下化合物。

[3636] [式 805]

[3637]



[3638] 收率 :55 %, $^1\text{H-NMR}$ (DMSO-d_6) : δ 2.50-2.55 (4H, m), 3.51 (2H, s), 3.55-3.65 (4H, m), 4.61 (2H, s), 6.75-7.00 (3H, m), 7.20-7.35 (2H, m), 7.42 (1H, d, $J = 8\text{Hz}$), 7.90 (1H, d, $J = 2\text{Hz}$)。

[3639] 实施例 516

[3640] 3-{2-[1-(6- 氯苯并噻唑-2- 基) 哌啶-4- 基] 乙氧基}-4- 甲基苯基乙酸的制备

[3641] [式 806]

[3642]



[3643] 将 [3-{2-[1-(6- 氯苯并噻唑-2- 基) 哌啶-4- 基] 乙氧基}-4- 甲基苯基] 乙腈 (1.14g ;2.68mmol), 氢氧化钠 (0.54g ;13.5mmol), 水 (1.6ml) 和乙醇 (21ml) 的混合物在 80°C 搅拌 6 小时。反应溶液减压浓缩并且用 2N- 盐酸调节为 $\text{pH} = 7$ 。收集沉淀物,得到 3-{2-[1-(6- 氯苯并噻唑-2- 基) 哌啶-4- 基] 乙氧基}-4- 甲基苯基乙酸,为无色晶体 (0.63g ;53%)。

[3644] $^1\text{H-NMR}$ (DMSO-d_6) : δ 1.20-1.38 (2H, m), 1.67-1.91 (5H, m), 2.09 (3H, s),

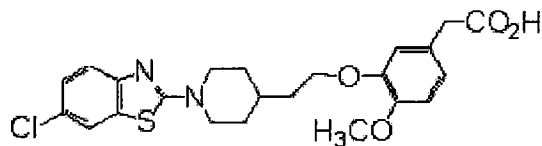
3.10-3.25 (4H, m), 3.93-4.06 (4H, m), 6.54 (1H, d, $J = 7.5\text{Hz}$), 6.82 (1H, s), 6.92 (1H, d, $J = 7.5\text{Hz}$), 7.27 (1H, dd, $J = 8.5, 2.0\text{Hz}$), 7.40 (1H, d, $J = 8.5\text{Hz}$), 7.88 (1H, d, $J = 2.0\text{Hz}$)。

[3645] 本发明包括通过相似的方法合成的以下化合物。

[3646] 实施例 517

[3647] [式 807]

[3648]

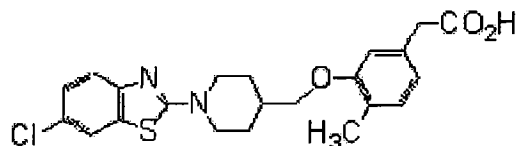


[3649] $m/z = 461 (M+H)^+$

[3650] 实施例 518

[3651] [式 808]

[3652]

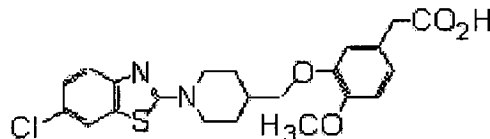


[3653] $m/z = 431 (M+H)^+$

[3654] 实施例 519

[3655] [式 809]

[3656]

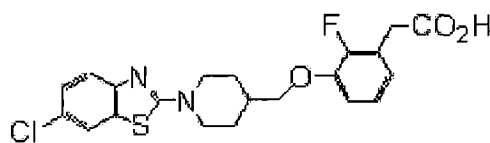


[3657] $m/z = 447 (M+H)^+$

[3658] 实施例 520

[3659] [式 810]

[3660]

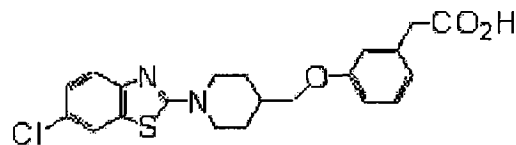


[3661] $m/z = 435 (M+H)^+$

[3662] 实施例 521

[3663] [式 811]

[3664]

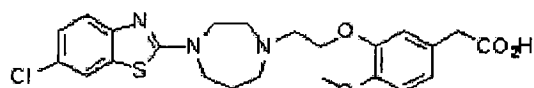


[3665] $R_f = 0.49 (\text{AcOEt})$

[3666] 实施例 522

[3667] [式 812]

[3668]

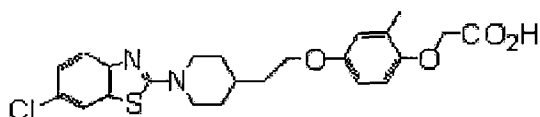


[3669] ^1H NMR (DMSO- d_6) : δ 12.9 (br, 1H), 7.86 (s, 1H), 7.39 (d, 1H, $J = 6.3\text{Hz}$), 7.25 (d, 1H, $J = 6.3\text{Hz}$), 6.88 (s, 1H), 6.87 (d, 1H, $J = 6.0\text{Hz}$), 6.77 (d, 1H, $J = 6.0\text{Hz}$), 4.01 (m, 2H), 3.72 (s, 3H), 3.67 (br, 4H), 3.46 (s, 2H), 2.94 (s, 2H), 2.87 (t, 2H, $J = 4.2\text{Hz}$), 2.75 (br, 2H), 1.90 (s, 2H)。

[3670] 实施例 523

[3671] [式 813]

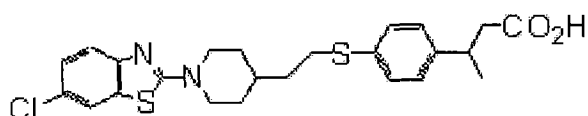
[3672]

[3673] $m/z = 461 (M+H)^+$

[3674] 实施例 524

[3675] [式 814]

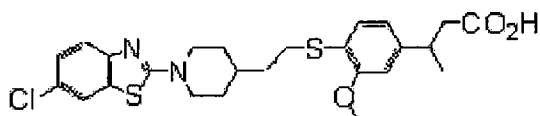
[3676]

[3677] $m/z = 475 (M+H)^+$

[3678] 实施例 525

[3679] [式 815]

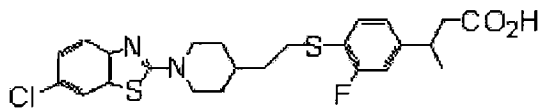
[3680]

[3681] $m/z = 505 (M+H)^+$

[3682] 实施例 526

[3683] [式 816]

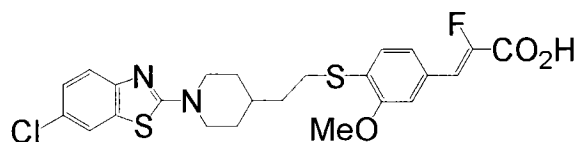
[3684]

[3685] $m/z = 493 (M+H)^+$

[3686] 实施例 527

[3687] [式 817]

[3688]

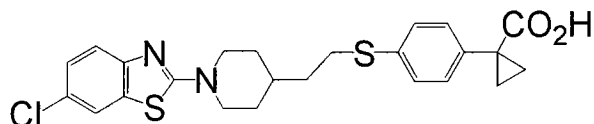


[3689] MS (ESI)m/e, C₂₄H₂₅ClFN₂O₃S₂ (MH)⁺ 计算值 :507. 1, 实测值 :507

[3690] 实施例 528

[3691] [式 818]

[3692]

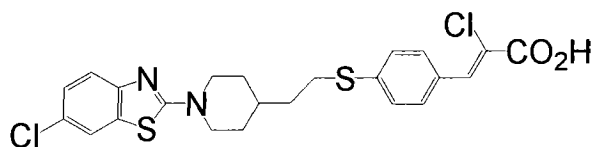


[3693] MS (ESI)m/e, C₂₄H₂₆ClN₂O₂S₂ (MH)⁺ 计算值 :473. 1, 实测值 :473

[3694] 实施例 529

[3695] [式 819]

[3696]

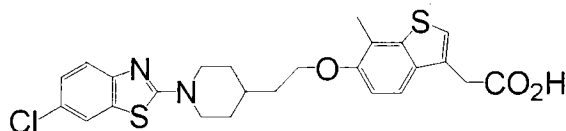


[3697] MS (ESI)m/e, C₂₃H₂₃Cl₂N₂O₂S₂ (MH)⁺ 计算值 :493. 1, 实测值 :493

[3698] 实施例 530

[3699] [式 820]

[3700]

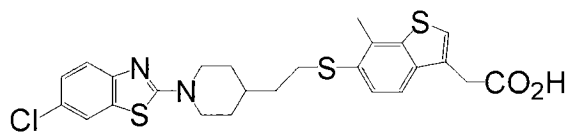


[3701] MS (ESI)m/e, C₂₅H₂₆ClN₂O₃S₂ (MH)⁺ 计算值 :501. 1, 实测值 :501. 4

[3702] 实施例 531

[3703] [式 821]

[3704]

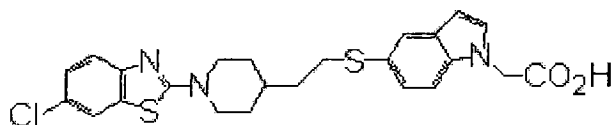


[3705] MS (ESI)m/e, C₂₅H₂₆ClN₂O₂S₃ (MH)⁺ 计算值 :517. 1, 实测值 :517. 4

[3706] 实施例 532

[3707] [式 822]

[3708]

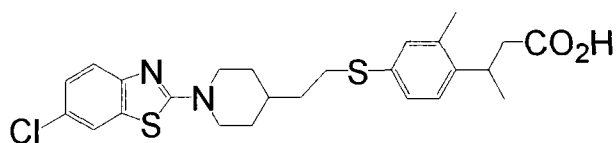


[3709] MS (ESI)m/e, C₂₄H₂₅ClN₃O₂S₂ (MH)⁺ 计算值 :486. 1, 实测值 :486. 4

[3710] 实施例 533

[3711] [式 823]

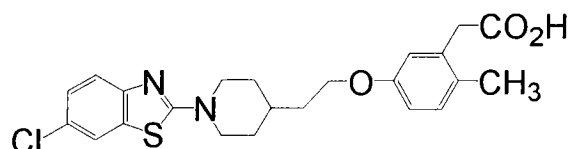
[3712]

[3713] $m/z = 489 (M+H)^+$

[3714] 实施例 534

[3715] [式 824]

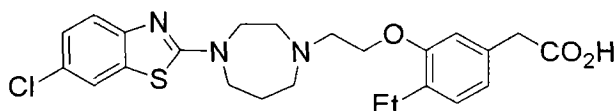
[3716]

[3717] $m/z = 445 (M+H)^+$

[3718] 实施例 535

[3719] [式 825]

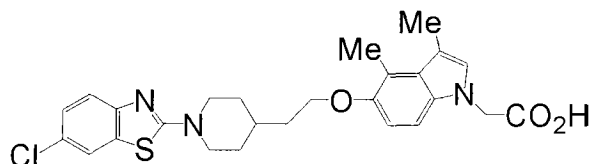
[3720]

[3721] MS (ESI) m/e , $C_{24}H_{29}ClN_3O_3S (MH)^+$ 计算值 :474. 2, 实测值 :474. 4

[3722] 实施例 536

[3723] [式 826]

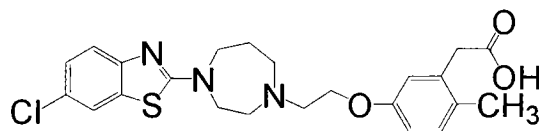
[3724]

[3725] MS (ESI) m/e , $C_{26}H_{29}ClN_3O_3S (MH)^+$ 计算值 :498. 2, 实测值 :498

[3726] 实施例 537

[3727] [式 827]

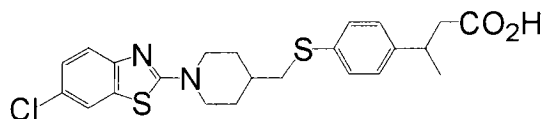
[3728]

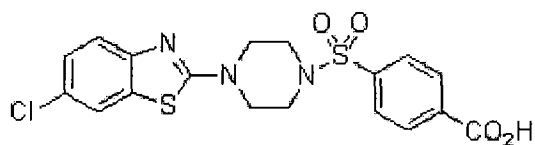
[3729] $m/z = 460 (M+H)^+$

[3730] 实施例 538

[3731] [式 828]

[3732]



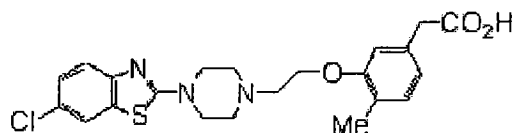


[3757] MS (ESI) m/z 438 [M+H]⁺

[3758] 实施例 545

[3759] [式 835]

[3760]

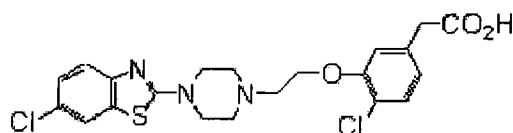


[3761] m/z = 446 (M+H)⁺

[3762] 实施例 546

[3763] [式 836]

[3764]

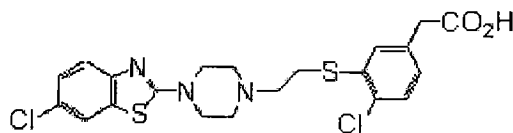


[3765] m/z = 466 (M+H)⁺

[3766] 实施例 547

[3767] [式 837]

[3768]

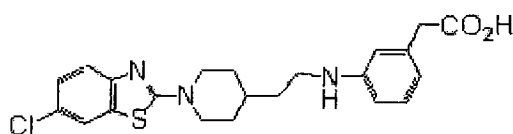


[3769] m/z = 482 (M+H)⁺

[3770] 实施例 548

[3771] [式 838]

[3772]

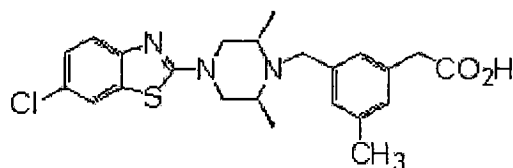


[3773] m/z = 430 (M+H)⁺

[3774] 实施例 549

[3775] [式 839]

[3776]

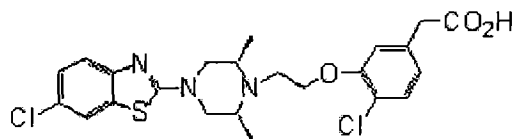


[3777] m/z = 444 (M+H)⁺

[3778] 实施例 550

[3779] [式 840]

[3780]

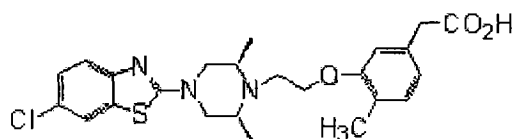


[3781] $m/z = 494 (M+H)^+$

[3782] 实施例 551

[3783] [式 841]

[3784]

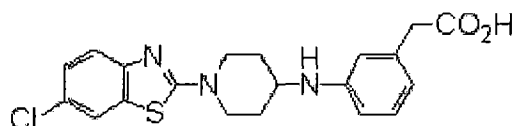


[3785] $m/z = 474 (M+H)^+$

[3786] 实施例 552

[3787] [式 842]

[3788]

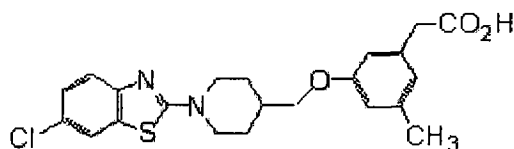


[3789] $m/z = 402 (M+H)^+$

[3790] 实施例 553

[3791] [式 843]

[3792]

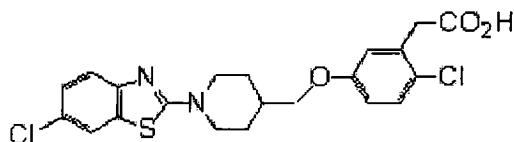


[3793] $m/z = 431 (M+H)^+$

[3794] 实施例 554

[3795] [式 844]

[3796]

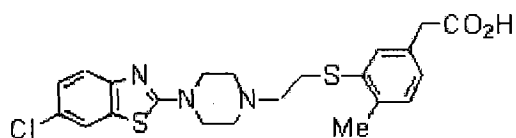


[3797] $m/z = 451 (M+H)^+$

[3798] 实施例 555

[3799] [式 845]

[3800]



[3801] $m/z = 462 (M+H)^+$

[3802] 实施例 556

[3803] [式 846]

[3804]

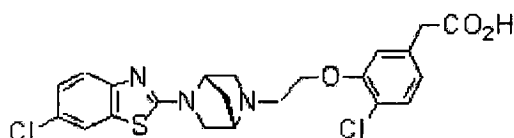


[3805] $m/z = 478 (M+H)^+$

[3806] 实施例 557

[3807] [式 847]

[3808]



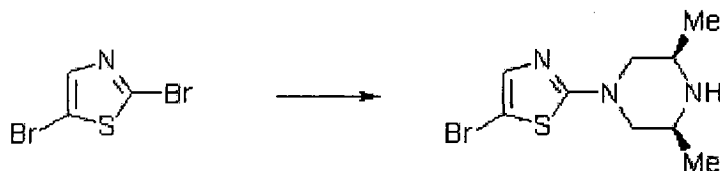
[3809] $m/z = 478 (M+H)^+$

[3810] 参考例 228

[3811] 1-(5-溴噻唑-2-基)-3,5-二甲基哌嗪的制备

[3812] [式 848]

[3813]



[3814] 将 2,5-二溴噻唑 (29.5g), 2,6-二甲基哌嗪 (13.8g), 碳酸钾 (20.1g) 和二甲基甲酰胺 (150mL) 的混合物在 60℃ 搅拌 6 小时。向反应溶液加入水并且用乙酸乙酯萃取。有机层用水和盐水洗涤, 和用硫酸钠干燥。减压蒸发溶剂, 得到标题化合物 (21.5g)。收率: 64%。

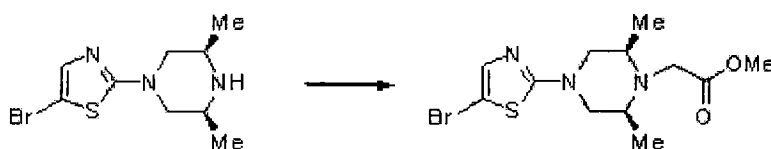
[3815] $^1\text{H-NMR}(\text{CDCl}_3) \delta$: 1.14 (6H, d, $J = 6.3\text{Hz}$), 2.05 (1H, br), 2.59-2.63 (2H, m), 2.98-3.02 (2H, m), 3.70-3.74 (2H, m), 7.06 (1H, s)。

[3816] 参考例 229

[3817] [4-(5-溴噻唑-2-基)-2,6-二甲基哌嗪-1-基] 乙酸甲基酯的制备

[3818] [式 849]

[3819]



[3820] 将 1-(5-溴噻唑-2-基)-3,5-二甲基哌嗪 (21.5g), 溴乙酸甲基酯 (8.8mL), 碳酸钾 (12.9g) 和二甲基甲酰胺 (150mL) 的混合物在 60℃ 搅拌 2.5 小时。向反应溶液加入水并且用乙酸乙酯萃取。有机层用水和盐水洗涤, 并用硫酸镁干燥。减压蒸发溶剂。残余物通过硅胶柱色谱法纯化, 得到标题化合物 (20.1g)。收率: 74%。

[3821] $^1\text{H-NMR}$ (CDCl_3) δ : 1.17 (6H, d, $J = 6.0\text{Hz}$), 2.80-2.84 (2H, m), 3.13-3.16 (2H, m), 3.65 (2H, s), 3.65-3.68 (2H, m), 3.73 (3H, s), 7.08 (1H, s)。

[3822] 参考例 230

[3823] 2-[4-(5-溴噻唑-2-基)-2,6-二甲基哌嗪-1-基]乙醇的制备

[3824] [式 850]

[3825]



[3826] 在 -78℃ 向 [4-(5-溴噻唑-2-基)-2,6-二甲基哌嗪-1-基]乙酸甲基酯 (20.1g) 的四氢呋喃 (300mL) 溶液中滴加二异丁基氢化铝 (1M 甲苯溶液, 200mL)。将混合物在 -78℃ 搅拌 3.5 小时。向反应溶液加入氯化铵水溶液 (150mL) 和乙醚 (45mL)。过滤不溶性物质。滤液用乙醚萃取。有机层用水和盐水洗涤, 并且用硫酸镁干燥。减压蒸发溶剂。残余物通过硅胶柱色谱法纯化, 得到标题化合物 (13.2g)。收率: 71%。

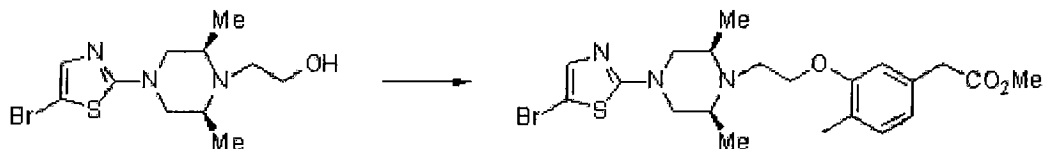
[3827] $^1\text{H-NMR}$ (CDCl_3) δ : 1.17 (6H, d, $J = 5.8\text{Hz}$), 2.44 (1H, br), 2.84 (6H, dd, $J = 16.9, 11.1\text{Hz}$), 3.60-3.64 (4H, m), 7.06 (1H, s)。

[3828] 参考例 231

[3829] [3-[2-[4-(5-溴噻唑-2-基)-2,6-二甲基哌嗪-1-基]乙氧基]-4-甲基苯基]乙酸甲基酯的制备

[3830] [式 851]

[3831]



[3832] 在 0℃ 向 2-[4-(5-溴噻唑-2-基)-2,6-二甲基哌嗪-1-基]乙醇 (9.87g), 三乙胺 (8.6mL) 和二氯甲烷 (100mL) 的混合物中滴加甲磺酰氯 (2.9mL)。在 0℃ 搅拌 0.5 小时之后, 向反应溶液加入水并用氯仿萃取。有机层用水和盐水洗涤, 并且用硫酸镁干燥。减压蒸发溶剂。将得到的残余物溶解于乙腈 (100mL)。向其中加入 (3-羟基-4-甲基苯基)乙酸甲基酯 (5.0g) 和碳酸铯 (12.0g) 并且在 60℃ 搅拌 1 小时。反应溶液用乙酸乙酯稀释并且过滤不溶性物质。将滤液减压蒸发。残余物通过硅胶柱色谱法纯化, 得到标题化合物 (8.49g)。收率: 57%。

[3833] $^1\text{H-NMR}$ (CDCl_3) δ : 1.27 (6H, d, $J = 6.6\text{Hz}$), 2.20 (3H, s), 2.87-2.91 (4H, m),

3. 25-3. 27 (2H, m), 3. 60 (2H, s), 3. 68 (2H, brm), 3. 71 (3H, s), 4. 03-4. 05 (2H, m), 6. 75 (1H, d, $J = 1.4\text{Hz}$), 6. 79 (1H, dd, $J = 7.7, 1.4\text{Hz}$), 7. 07 (1H, s), 7. 10 (1H, d, $J = 7.7\text{Hz}$)。

[3834] 参考例 232

[3835] [3-[2-[4-(5-溴噻唑-2-基)-2,6-二甲基哌嗪-1-基]乙氧基]-4-甲基苯基]乙酸的制备

[3836] [式 852]

[3837]



[3838] 将 [3-[2-[4-(5-溴噻唑-2-基)-2,6-二甲基哌嗪-1-基]乙氧基]-4-甲基苯基]乙酸甲基酯 (8.49g), 2N 氢氧化钠水溶液 (22mL), 甲醇 (50mL) 和四氢呋喃 (50mL) 的混合物在室温搅拌 1.5 小时。向反应溶液加入水和盐水。混合物用乙酸乙酯洗涤。水层用 2N 盐酸中和并且用氯仿萃取。有机层用水和盐水洗涤, 并且用硫酸镁干燥。减压蒸发溶剂, 残余物用二异丙醚洗涤, 得到标题化合物 (5.81g)。收率: 71%。

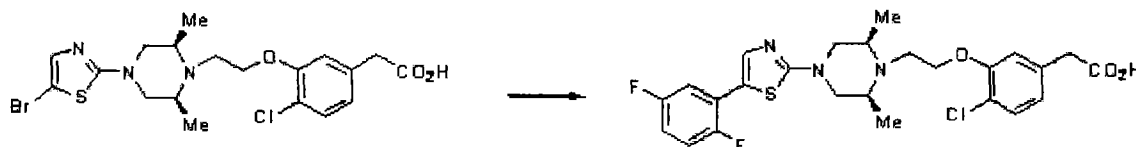
[3839] $^1\text{H-NMR}$ (DMSO- d_6) δ : 1.16 (6H, d, $J = 5.5\text{Hz}$), 2.13 (3H, s), 2.71-2.83 (4H, m), 3.12-3.14 (2H, m), 3.52 (2H, s), 3.65-3.68 (2H, m), 3.99-4.01 (2H, m), 6.74 (1H, d, $J = 7.4\text{Hz}$), 6.87 (1H, s), 7.07 (1H, d, $J = 7.4\text{Hz}$), 8.34 (1H, s)。

[3840] 实施例 558

[3841] [3-[2-[4-[5-(2,5-二氟苯基)噻唑-2-基]-2,6-二甲基哌嗪-1-基]乙氧基]-4-甲基苯基]乙酸的制备

[3842] [式 853]

[3843]



[3844] 使用微波反应设备使 [3-[2-[4-(5-溴噻唑-2-基)-2,6-二甲基哌嗪-1-基]乙氧基]-4-甲基苯基]乙酸 (400mg), 2,5-二氟苯基硼酸 (270mg), 四(三苯膦)合钯 (100mg), 1M 碳酸钠 (4.3mL) 和二甲基甲酰胺 (8mL) 的混合物在 180°C 反应 5 分钟。向反应溶液加入水并且用氯仿萃取。有机层用水和盐水洗涤, 并且用硫酸镁干燥。减压蒸发溶剂。残余物通过硅胶柱色谱法纯化, 得到标题化合物 (369mg)。收率: 87%。

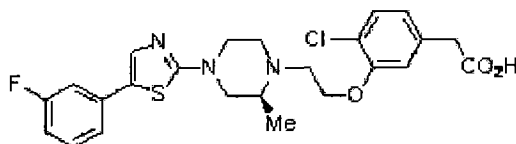
[3845] MS (ESI) m/z 502 $[M+H]$

[3846] 通过与如上相似的方法得到以下化合物。

[3847] 实施例 559

[3848] [式 854]

[3849]

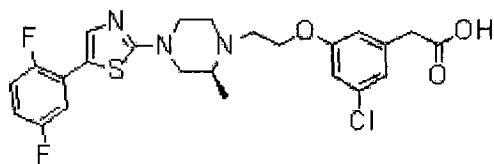


[3850] MS (ESI) m/z 508 [M+]

[3851] 实施例 560

[3852] [式 855]

[3853]

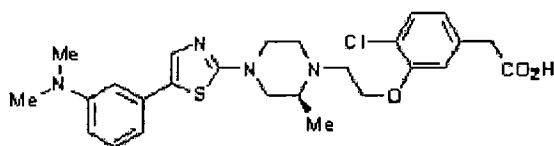


[3854] MS (ESI) m/z 508 [M+]

[3855] 实施例 561

[3856] [式 856]

[3857]

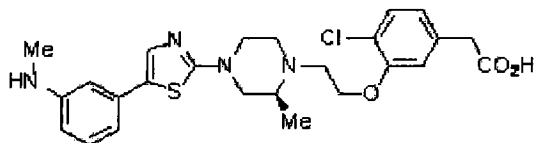


[3858] MS (ESI) m/z 515, 517 [M+H] +

[3859] 实施例 562

[3860] [式 857]

[3861]

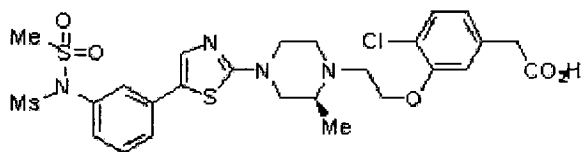


[3862] MS (ESI) m/z 501, 503 [M+H] +

[3863] 实施例 563

[3864] [式 858]

[3865]

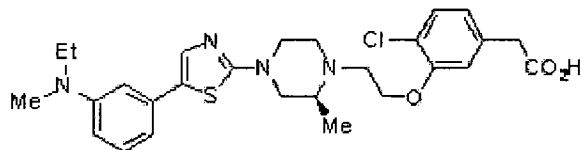


[3866] MS (ESI) m/z 579, 581 [M+H] +

[3867] 实施例 564

[3868] [式 859]

[3869]

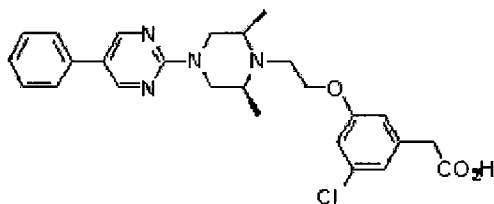


[3870] MS (ESI) m/z 529, 531 [M+H] +

[3871] 实施例 565

[3872] [式 860]

[3873]

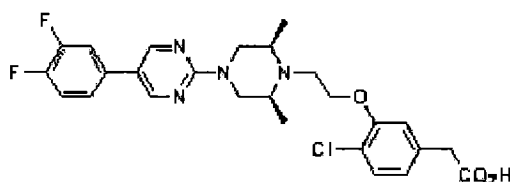


[3874] $^1\text{H-NMR}$ (DMSO- d_6) δ : 1.11 (6H, d, $J = 5.1\text{Hz}$), 2.60–2.70 (2H, m), 3.00–3.05 (2H, m), 3.55 (2H, s), 3.96–4.05 (2H, m), 4.32–4.45 (2H, m), 6.80–6.96 (3H, m), 8.44 (2H, s)。

[3875] 实施例 566

[3876] [式 861]

[3877]

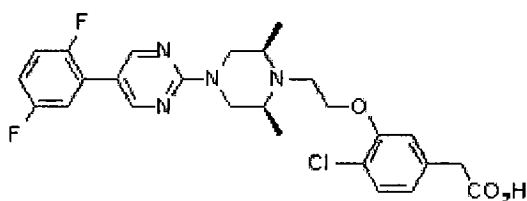


[3878] $^1\text{H-NMR}$ (DMSO- d_6) δ : 1.17 (6H, d, $J = 4.9\text{Hz}$), 2.64–2.74 (4H, m), 3.09–3.18 (2H, m), 3.55 (2H, s), 4.03–4.10 (2H, m), 4.48–4.60 (2H, m), 6.83 (1H, dd, $J = 8.0, 0.8\text{Hz}$), 7.09 (1H, d, $J = 1.1\text{Hz}$), 7.33 (1H, d, $J = 8.0\text{Hz}$), 7.47–7.83 (3H, m), 8.71 (2H, s)。

[3879] 实施例 567

[3880] [式 862]

[3881]

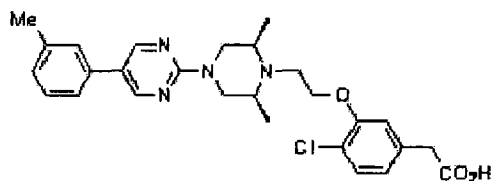


[3882] $^1\text{H-NMR}$ (DMSO- d_6) δ : 1.17 (6H, d, $J = 4.4\text{Hz}$), 2.64–2.76 (4H, m), 3.10–3.18 (2H, m), 3.56 (2H, s), 4.04–4.11 (2H, m), 4.49–4.60 (2H, m), 6.83 (1H, d, $J = 8.0\text{Hz}$), 7.07–7.59 (5H, m), 8.59 (2H, s)。

[3883] 实施例 568

[3884] [式 863]

[3885]

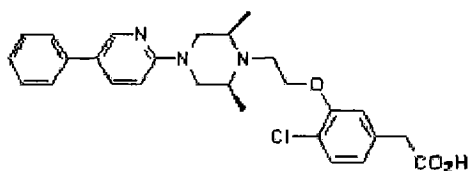


[3886] $^1\text{H-NMR}$ (CDCl $_3$) δ : 1.31 (6H, d, $J = 5.8\text{Hz}$), 2.40 (3H, s), 2.90–3.08 (4H, m), 3.35–3.42 (2H, m), 3.54 (2H, s), 4.08–4.16 (2H, m), 4.52–4.67 (2H, m), 6.79–7.34 (7H, m), 8.52 (2H, s)。

[3887] 实施例 569

[3888] [式 864]

[3889]

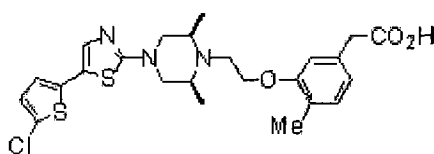


[3890] $^1\text{H-NMR}$ (丙酮) δ : 8.62 (2.0H, s), 7.61–7.59 (2.0H, m), 7.45 (2.0H, dd, $J = 7.55$, 7.55Hz), 7.37–7.28 (2.0H, m), 7.14 (1.0H, d, $J = 1.89\text{Hz}$), 6.89 (1.0H, dd, $J = 8.10$, 1.89Hz), 4.64 (2.0H, d, $J = 11.81\text{Hz}$), 4.16 (2.0H, dd, $J = 6.11$, 6.11Hz), 3.59 (2.0H, s), 3.24 (2.0H, dd, $J = 6.11$, 6.11Hz), 2.93–2.64 (4.0H, m), 1.25 (6.0H, d, $J = 6.04\text{Hz}$)。

[3891] 实施例 570

[3892] [式 865]

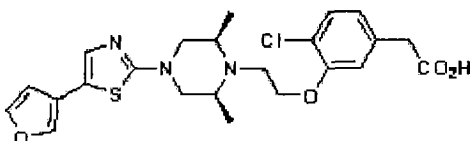
[3893]

[3894] MS (ESI) m/z 508 $[\text{M}+\text{H}]^+$

[3895] 实施例 571

[3896] [式 866]

[3897]

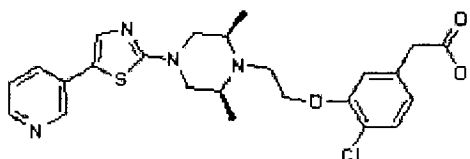


[3898] $^1\text{H-NMR}$ (DMSO- d_6) δ : 7.81 (1H, s), 7.67 (1H, s), 7.32–7.29 (2H, m), 7.07 (1H, s), 6.81 (1H, d, $J = 8.8\text{Hz}$), 6.75 (1H, s), 4.06–4.03 (2H, m), 3.67 (2H, d, $J = 10.8\text{Hz}$), 3.52 (2H, s), 3.12–3.09 (2H, m), 2.82–2.69 (4H, m), 1.13 (6H, d, $J = 5.7\text{Hz}$)。

[3899] 实施例 572

[3900] [式 867]

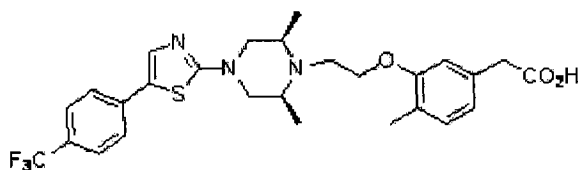
[3901]

[3902] MS (ESI) m/z 525 $[\text{M}+\text{H}]^+$

[3903] 实施例 573

[3904] [式 868]

[3905]

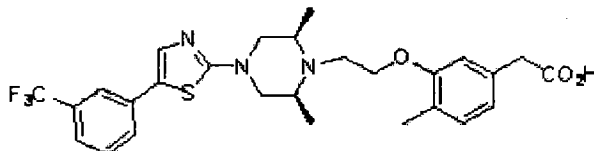


[3906] $^1\text{H-NMR}$ (DMSO- d_6) δ :7.79 (1.0H, s), 7.70–7.64 (4.0H, m), 7.03 (1.0H, d, $J = 7.56\text{Hz}$), 6.85 (1.0H, s), 6.71 (1.0H, d, $J = 7.56\text{Hz}$), 3.99 (2.0H, dd, $J = 5.49, 5.49\text{Hz}$), 3.79 (2.0H, d, $J = 9.06\text{Hz}$), 3.47 (2.0H, s), 3.15–3.11 (2.0H, m), 2.89–2.78 (4.0H, m), 2.11 (3.0H, s), 1.17 (6.0H, d, $J = 5.22\text{Hz}$)。

[3907] 实施例 574

[3908] [式 869]

[3909]

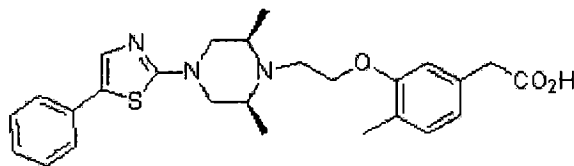


[3910] $^1\text{H-NMR}$ (DMSO- d_6) δ :7.83–7.70 (3.0H, m), 7.63–7.50 (2.0H, m), 7.03 (1.0H, d, $J = 7.69\text{Hz}$), 6.85 (1.0H, s), 6.70 (1.0H, d, $J = 7.69\text{Hz}$), 4.02–3.96 (2.0H, m), 3.79 (2.0H, d, $J = 9.06\text{Hz}$), 3.47 (2.0H, s), 3.17–3.10 (2.0H, m), 2.91–2.76 (4.0H, m), 2.12 (3.0H, s), 1.26–1.11 (6.0H, d, $J = 6.0\text{Hz}$)。

[3911] 实施例 575

[3912] [式 870]

[3913]

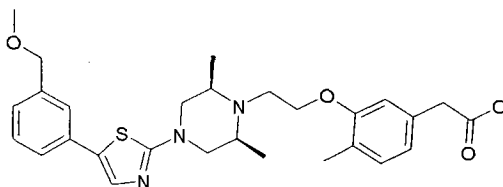


[3914] $^1\text{H-NMR}$ (DMSO- d_6) δ :7.58 (1.0H, s), 7.46 (2.0H, d, $J = 7.42\text{Hz}$), 7.35 (2.0H, dd, $J = 7.42, 7.42\text{Hz}$), 7.21 (1.0H, dd, $J = 7.42, 7.42\text{Hz}$), 7.03 (1.0H, d, $J = 7.80\text{Hz}$), 6.85 (1.0H, s), 6.70 (1.0H, d, $J = 7.80\text{Hz}$), 4.01–3.97 (2.0H, m), 3.76 (2.0H, d, $J = 10.99\text{Hz}$), 3.45 (2.0H, s), 3.14–3.11 (2.0H, m), 2.89–2.74 (4.0H, m), 2.11 (3.0H, s), 1.17 (6.0H, d, $J = 5.49\text{Hz}$)。

[3915] 实施例 576

[3916] [式 871]

[3917]

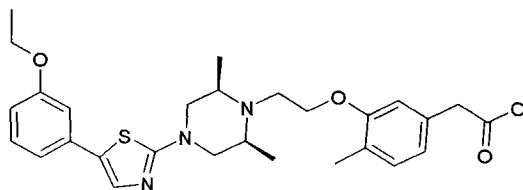


[3918] $^1\text{H-NMR}$ (CDCl $_3$) δ 1.17 (6H, m), 2.12 (3H, s), 2.82 (4H, m), 2.13 (2H, br), 3.30 (3H, d, $J = 2.1\text{Hz}$), 3.49 (2H, s), 3.77 (2H, d, $J = 10.2\text{Hz}$), 3.99 (2H, br), 4.41 (2H, s), 6.71 (1H, brd), 6.85 (1H, brd), 7.04 (1H, brd), 7.15 (1H, brd), 7.30–7.41 (3H, m), 7.60 (1H, d, 1.8Hz)。

[3919] 实施例 577

[3920] [式 872]

[3921]

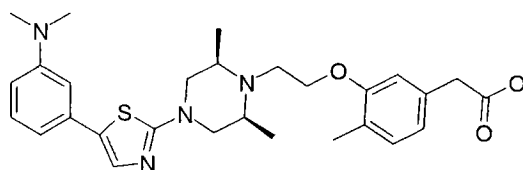


[3922] $^1\text{H-NMR}$ (DMSO- d_6) δ 1.16 (6H, d, $J = 6.0\text{Hz}$), 1.33 (3H, t, $J = 6.9\text{Hz}$), 2.12 (3H, s), 2.74–2.90 (4H, m), 3.13 (2H, t, $J = 5.1\text{Hz}$), 3.49 (2H, s), 3.76 (2H, d, $J = 10.5\text{Hz}$), 3.97–4.08 (4H, m), 6.72 (1H, d, $J = 7.8\text{Hz}$), 6.78 (1H, dd, $J = 8.4\text{Hz}, 2.4\text{Hz}$), 6.85 (1H, s), 6.98–7.06 (3H, m), 7.24 (1H, t, $J = 8.1\text{Hz}$), 7.61 (1H, s)。

[3923] 实施例 578

[3924] [式 873]

[3925]

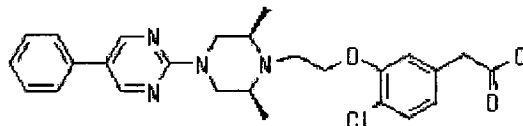


[3926] $^1\text{H-NMR}$ (DMSO- d_6) δ 1.16 (6H, d, $J = 5.7\text{Hz}$), 2.12 (3H, s), 2.72–2.91 (4H, m), 2.91 (6H, s), 3.12 (2H, brs), 3.49 (2H, s), 3.76 (2H, d, $J = 10.5\text{Hz}$), 3.99 (2H, brs), 6.57–6.61 (1H, m), 6.70–6.77 (3H, m), 6.85 (1H, s), 7.05 (1H, d, $J = 7.5\text{Hz}$), 7.15 (1H, t, $J = 7.8\text{Hz}$), 7.54 (1H, s)。

[3927] 实施例 579

[3928] [式 874]

[3929]

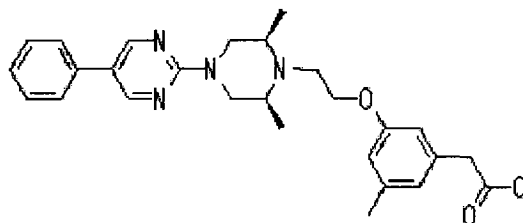


[3930] $^1\text{H-NMR}$ (丙酮) δ : 8.62 (2.0H, s), 7.61–7.59 (2.0H, m), 7.45 (2.0H, dd, $J = 7.55, 7.55\text{Hz}$), 7.37–7.28 (2.0H, m), 7.14 (1.0H, d, $J = 1.89\text{Hz}$), 6.89 (1.0H, dd, $J = 8.10, 1.89\text{Hz}$), 4.64 (2.0H, d, $J = 11.81\text{Hz}$), 4.16 (2.0H, dd, $J = 6.11, 6.11\text{Hz}$), 3.59 (2.0H, s), 3.24 (2.0H, dd, $J = 6.11, 6.11\text{Hz}$), 2.93–2.64 (4.0H, m), 1.25 (6.0H, d, $J = 6.04\text{Hz}$)。

[3931] 实施例 580

[3932] [式 875]

[3933]



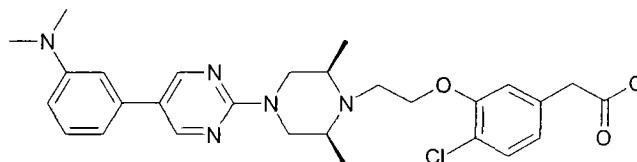
[3934] $^1\text{H-NMR}$ (DMSO- d_6) δ : 8.69 (2.0H, s), 7.63 (2.0H, d, $J = 7.42\text{Hz}$), 7.45 (2.0H, dd, $J = 7.42, 7.42\text{Hz}$), 7.35 (1.0H, d, $J = 7.42\text{Hz}$), 6.62 (3.0H, s), 4.53 (2.0H, d, $J = 8.79\text{Hz}$),

3.96 (2.0H, dd, $J = 6.48, 6.48\text{Hz}$), 3.45 (2.0H, s), 3.03 (2.0H, dd, $J = 6.48, 6.48\text{Hz}$), 2.67 (4.0H, d, $J = 7.97\text{Hz}$), 2.23 (3.0H, s), 1.14 (6.0H, d, $J = 4.94\text{Hz}$)。

[3935] 实施例 581

[3936] [式 876]

[3937]



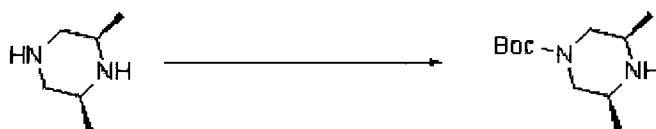
[3938] $^1\text{H-NMR}$ (DMSO- d_6) δ : 8.65 (2.0H, s), 7.32 (1.0H, d, $J = 8.23\text{Hz}$), 7.23 (1.0H, dd, $J = 8.10, 8.10\text{Hz}$), 7.09 (1.0H, d, $J = 1.65\text{Hz}$), 6.87-6.81 (3.0H, m), 6.72-6.67 (1.0H, m), 4.52 (2.0H, d, $J = 9.61\text{Hz}$), 4.07 (2.0H, dd, $J = 5.40, 5.40\text{Hz}$), 3.55 (2.0H, s), 3.13 (2.0H, dd, $J = 5.40, 5.40\text{Hz}$), 2.93 (6.0H, s), 2.73-2.62 (4.0H, m), 1.18 (6.0H, d, $J = 6.04\text{Hz}$)。

[3939] 参考例 233

[3940] 3,5-二甲基羰基哌嗪-1-羧酸叔丁基酯的制备

[3941] [式 877]

[3942]



[3943] 在冰冷却下向 2,6-二甲基哌嗪 (10.0g) 在二氯甲烷 (200mL) 的混合物中加入二碳酸二叔丁基酯 (19.1g)。在室温搅拌 17 小时之后,向反应溶液加入水并且用二氯甲烷萃取。有机层用盐水洗涤,并且用硫酸镁干燥。减压蒸发溶剂,得到标题化合物 (18.7g)。收率:100%。

[3944] $^1\text{H-NMR}$ (CDCl $_3$) δ 1.15 (6H, d, $J = 6.3$), 1.32 (2H, m), 1.49 (9H, s), 2.43 (1H, m), 2.85 (2H, m), 3.99 (1H, m)。

[3945] 参考例 234

[3946] 4-甲氧基羰基甲基-3,5-二甲基哌嗪-1-羧酸叔丁基酯的制备

[3947] [式 878]

[3948]



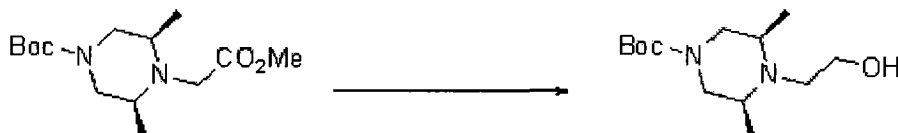
[3949] 将 3,5-二甲基羰基哌嗪-1-羧酸叔丁基酯 (18.7g), 碳酸钾 (14.5g), 溴乙酸甲基酯 (14.7g), DMF (90mL) 的混合物在 60℃ 搅拌 3 小时。向反应溶液加入水并且用乙酸乙酯萃取。有机层用水和盐水洗涤,并且用硫酸镁干燥。减压蒸发溶剂,得到标题化合物。这个化合物不经进一步纯化用于下一步反应。

[3950] 参考例 235

[3951] 4-(2-羟基乙基)-3,5-二甲基哌嗪-1-羧酸叔丁基酯的制备

[3952] [式 879]

[3953]



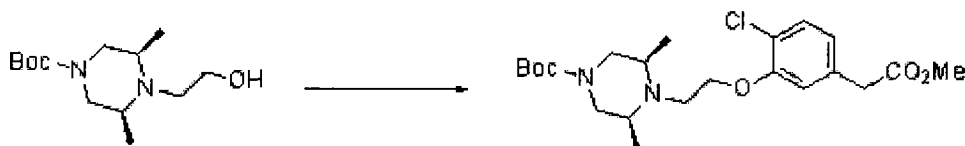
[3954] 将得自上述反应的 3,5-二甲基羰基哌嗪-1-羧酸叔丁基酯溶解于 THF (300mL) 并且在冰冷却下向其中加入氢化铝锂 (3.31g)。在 0℃ 搅拌 1 小时之后, 顺序地加入水和 2N 氢氧化钠水溶液。在过滤不溶性物质之后, 将滤液减压浓缩, 得到标题化合物 (20.3g)。收率: 90%。

[3955] 参考例 236

[3956] 4-[2-(5-羰基甲基-2-氯苯氧基)乙基]-3,5-二甲基哌嗪-1-羧酸叔丁基酯的制备

[3957] [式 880]

[3958]



[3959] 将 4-(2-羟基乙基)-3,5-二甲基哌嗪-1-羧酸叔丁基酯 (3.0g), 三乙胺 (1.76g), 甲磺酰氯 (1.60g) 和二氯甲烷 (60mL) 的混合物在冰冷却下搅拌 1.5 小时。向反应溶液加入水并且用乙酸乙酯萃取。有机层用水和盐水洗涤, 并且用硫酸镁干燥。减压蒸发溶剂。将得到的残余物溶解于乙腈 (60mL), 并且向其中加入 (4-氯-3-羟基苯基) 乙酸甲基酯 (2.33g) 和碳酸铯 (4.54g)。将混合物在 60℃ 搅拌 5 小时。在过滤不溶性物质之后, 将滤液浓缩并将得到的残余物通过硅胶柱色谱法纯化, 得到标题化合物 (3.58g)。收率: 70%。

[3960] $^1\text{H-NMR}$ (DMSO- d_6) δ : 1.09 (6H, d, $J = 6.0$), 1.40 (9H, s), 2.40-2.50 (2H, m), 2.52-2.61 (2H, m), 3.08-3.12 (2H, m), 3.64 (3H, s), 3.71 (2H, 2), 3.77 (2H, m), 4.02-4.09 (2H, m), 6.87 (1H, d, $J = 8.0$), 7.13 (1H, s), 7.37 (1H, d, $J = 8.0$)。

[3961] 参考例 237 [4-氯-3-[2-(2,6-二甲基哌嗪-1-基)乙氧基]苯基]乙酸甲基酯的制备

[3962] [式 881]

[3963]



[3964] 将 4-[2-(5-羰基甲基-2-氯苯氧基)乙基]-3,5-二甲基哌嗪-1-羧酸叔丁基酯 (400mg) 的 4N 氢氯酸-二噁烷溶液 (4mL) 在室温搅拌 2 小时。向反应溶液加入水和乙酸乙酯。混合物用碳酸钠中和。混合物用乙酸乙酯萃取并将有机层用盐水洗涤。减压蒸发溶剂, 得到标题化合物 (291mg)。收率: 94%。

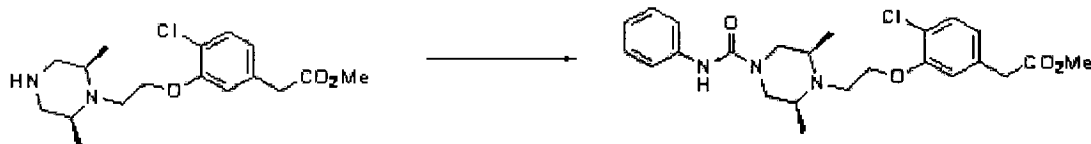
[3965] $^1\text{H-NMR}$ (DMSO- d_6) δ : 1.02 (3H, d, $J = 6.3$), 2.22-2.29 (2H, m), 2.50-2.54 (2H, m), 2.72-2.76 (2H, m), 3.03-3.07 (2H, m), 4.03-4.07 (2H, m), 6.87 (1H, d, $J = 8.2$), 7.13 (1H, s), 7.37 (1H, d, $J = 8.2$)。

[3966] 实施例 582

[3967] [4-氯-3-[2-(2,6-二甲基-4-苯基氨基甲酰基哌嗪-1-基)乙氧基]苯基]乙酸甲基酯的制备

[3968] [式 882]

[3969]



[3970] 将 [4-氯-3-[2-(2,6-二甲基哌嗪-1-基)乙氧基]苯基]乙酸甲基酯 (50mg), 苯基异氰酸酯 (19mg), 碳酸钾 (41mg) 和二氯甲烷 (2mL) 的混合物在室温搅拌 3 小时。在过滤不溶性物质之后, 将滤液减压浓缩。残余物通过硅胶柱色谱法纯化, 得到标题化合物 (52m)。收率: 77%。

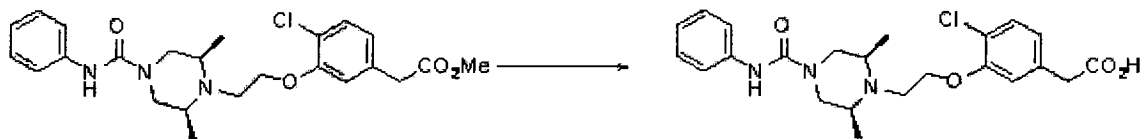
[3971] $^1\text{H-NMR}$ (DMSO- d_6) δ : 1.15 (6H, d, $J = 5.8$), 2.11 (2H, brm), 2.57 (2H, brm), 2.67 (2H, brm), 3.13 (2H, brm), 3.64 (3H, s), 3.71 (2H, s), 4.04-4.09 (2H, m), 6.86-6.97 (2H, m), 7.14 (1H, s), 7.22-7.25 (2H, m), 7.36-7.47 (3H, m), 8.48 (1H, s)。

[3972] 实施例 583

[3973] [4-氯-3-[2-(2,6-二甲基-4-苯基氨基甲酰基哌嗪-1-基)乙氧基]苯基]乙酸的制备

[3974] [式 883]

[3975]



[3976] 将 [4-氯-3-[2-(2,6-二甲基-4-苯基氨基甲酰基哌嗪-1-基)乙氧基]苯基]乙酸甲基酯 (50mg), 2N 氢氧化钠 (0.1mL) 和四氢呋喃 (1mL) 的混合物在室温搅拌 4 小时。在用 2N 盐酸中和之后, 混合物用乙酸乙酯萃取。有机层用盐水洗涤, 并且用硫酸镁干燥。减压蒸发溶剂。残余物通过硅胶柱色谱法纯化, 得到标题化合物 (18mg)。收率: 37%。

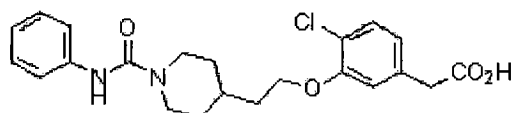
[3977] $^1\text{H-NMR}$ (DMSO- d_6) δ : 1.12 (6H, d, $J = 5.8\text{Hz}$), 2.42-2.70 (4H, m), 3.06-3.16 (2H, m), 3.56 (2H, s), 3.93-4.11 (4H, m), 6.81-7.47 (6H, m), 8.46 (1H, s)。

[3978] 通过与如上相似的方法得到以下化合物。

[3979] 实施例 584

[3980] [式 884]

[3981]



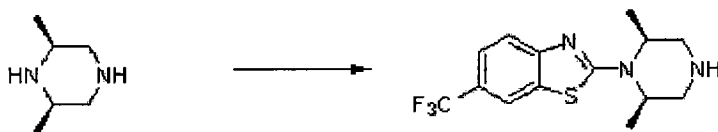
[3982] $^1\text{H-NMR}$ (DMSO- d_6) δ : 1.10-1.29 (2H, m), 1.70-1.83 (4H, m), 2.73-2.87 (2H, m), 3.59 (2H, s), 4.07-4.20 (4H, m), 6.83-7.51 (6H, m), 8.46 (1H, s)。

[3983] 参考例 238

[3984] 2-(2,6-二甲基哌嗪-1-基)-6-三氟甲基苯并噻唑的制备

[3985] [式 885]

[3986]



[3987] 在 -78°C 向顺式-2,6-二甲基哌嗪 (247mg) 的四氢呋喃 (5mL) 溶液中加入 $n\text{-BuLi}$ (2.67M 己烷溶液, 1.62mL)。将混合物在室温搅拌 30 分钟, 并且向其中加入三甲基硅烷基氯 (0.27mL)。在搅拌 40 分钟之后, 向其中加入 2-氯-6-三氟甲基苯并噻唑 (500mg) 的四氢呋喃 (2mL) 溶液并将混合物搅拌 2 小时。向反应溶液加入水并且用乙酸乙酯萃取。有机层用水洗涤并且用碳酸钠干燥。残余物通过硅胶柱色谱法纯化, 得到标题化合物 (367mg)。收率: 54%。

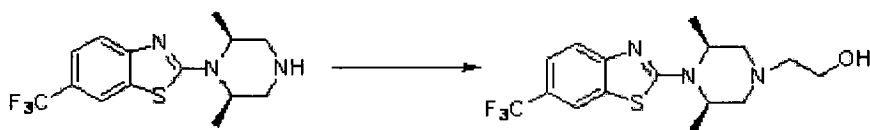
[3988] $^1\text{H-NMR}$ (CDCl_3) δ : 1.47 (6H, d, $J = 6.87\text{Hz}$), 2.13 (2H, s), 2.91-3.10 (4H, m), 4.14-4.23 (2H, m), 7.51-7.59 (2H, m), 7.85 (1H, s)。

[3989] 参考例 239

[3990] 2-[3,5-二甲基-4-(6-三氟甲基苯并噻唑-2-基)哌嗪-1-基]乙醇的制备

[3991] [式 886]

[3992]



[3993] 将 2-(2,6-二甲基哌嗪-1-基)-6-三氟甲基苯并噻唑 (360mg), (2-溴乙氧基)-叔丁基二甲基甲硅烷 (257 μL), 碳酸钾 (157mg) 和二甲基甲酰胺 (2mL) 的混合物在 60°C 搅拌 20 小时。向反应溶液加入水并且用乙酸乙酯萃取。有机层用水洗涤并且用碳酸钠干燥。在蒸发溶剂之后, 残余物通过硅胶柱色谱法纯化, 得到标题化合物 (265mg)。收率: 65%。

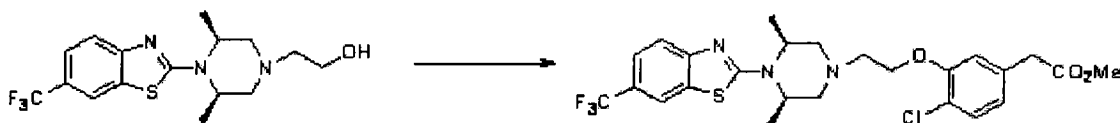
[3994] $^1\text{H-NMR}$ (CDCl_3) δ : 1.53 (6H, d, $J = 6.59\text{Hz}$), 2.54-2.57 (2H, br m), 2.67-2.70 (2H, br m), 2.80-2.90 (2H, br m), 3.74-3.77 (2H, br m), 4.29-4.32 (2H, br m), 7.52-7.61 (2H, m), 7.87 (1H, s)。

[3995] 实施例 585

[3996] [4-氯-3-[2-[3,5-二甲基-4-(6-三氟甲基苯并噻唑-2-基)哌嗪-1-基]乙氧基]苯基]乙酸甲基酯的制备

[3997] [式 887]

[3998]



[3999] 向 2-[3,5-二甲基-4-(6-三氟甲基苯并噻唑-2-基)哌嗪-1-基]乙醇 (138mg) 的二氯甲烷 (3mL) 溶液中加入甲磺酰氯 (45 μL) 和三乙胺 (107 μL)。将混合物在室温搅拌 1 小时。向反应溶液加入水并且用氯仿萃取。有机层用水和盐水洗涤, 并且用硫酸钠干燥。

减压蒸发溶剂。向得到的残余物加入二甲基甲酰胺 (2mL), 碳酸铯 (248mg) 和 (4-氯-3-羟基苯基) 乙酸甲基酯 (92mg)。将混合物在 60℃ 搅拌 2 小时。向反应溶液加入 2N 盐酸以中和并且用乙酸乙酯萃取。有机层用水洗涤并且用硫酸镁干燥。残余物通过硅胶柱色谱法纯化, 得到标题化合物 (178mg)。收率: 89%。

[4000] 实施例 586

[4001] [4-氯-3-[2-[3,5-二甲基-4-(6-三氟甲基苯并噻唑-2-基)哌嗪-1-基]乙氧基]苯基]乙酸的制备

[4002] [式 888]

[4003]



[4004] 将 [4-氯-3-[2-[3,5-二甲基-4-(6-三氟甲基苯并噻唑-2-基)哌嗪-1-基]乙氧基]苯基]乙酸甲基酯 (178mg), 2N 氢氧化钠水溶液 (0.66mL), 四氢呋喃 (2mL) 和甲醇 (2mL) 的混合物在室温搅拌 2 小时。混合物用 2N 盐酸中和并且用乙酸乙酯萃取。有机层用水洗涤并且用硫酸钠干燥。减压蒸发溶剂, 并且残余物通过硅胶柱色谱法纯化, 得到标题化合物 (83mg)。收率: 48%。

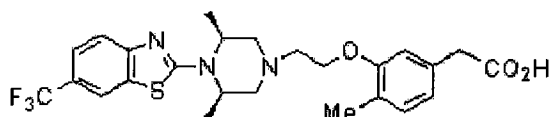
[4005] MS(ESI) m/z 528 [M+H]⁺

[4006] 通过与如上相似的方法得到以下化合物。

[4007] 实施例 587

[4008] [式 889]

[4009]



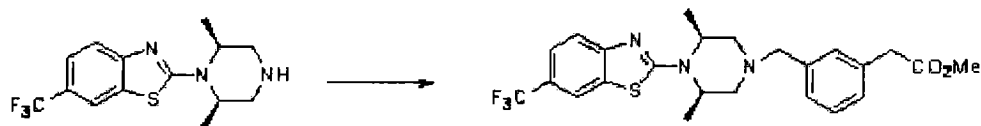
[4010] MS(ESI) m/z 508 [M+H]⁺

[4011] 实施例 588

[4012] [3-[3,5-二甲基-4-(6-三氟甲基苯并噻唑-2-基)哌嗪-1-基甲基]苯基]乙酸甲基酯的制备

[4013] [式 890]

[4014]



[4015] 将 2-(2,6-二甲基哌嗪-1-基)-6-三氟甲基苯并噻唑 (163mg), (3-溴甲基苯基) 乙酸甲基酯 (126mg), 碳酸钾 (75mg) 和二甲基甲酰胺 (4mL) 的混合物在室温搅拌 18 小时。向反应溶液加入水并且用乙酸乙酯萃取。有机层用水洗涤并且用硫酸钠干燥。减压蒸发溶剂, 并将残余物通过硅胶柱色谱法纯化, 得到标题化合物 (171mg)。收率: 65%。

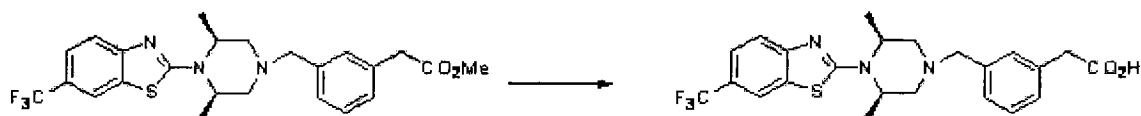
[4016] 实施例 589

[4017] [3-[3,5-二甲基-4-(6-三氟甲基苯并噻唑-2-基)哌嗪-1-基甲基]苯基]乙

酸的制备

[4018] [式 891]

[4019]



[4020] 将 [3-[3,5-二甲基-4-(6-三氟甲基苯并噻唑-2-基)哌嗪-1-基甲基]苯基]乙酸甲基酯 (171mg), 2N 氢氧化钠 (1mL) 和甲醇 (2mL) 的混合物在室温搅拌 1 小时。混合物用 2N 盐酸中和并且用乙酸乙酯萃取。减压蒸发溶剂, 并将残余物通过硅胶柱色谱法纯化, 得到标题化合物 (82mg)。收率: 52%。

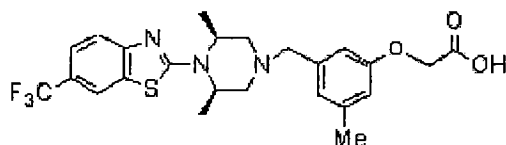
[4021] MS (ESI) m/z 464 [M+H]⁺

[4022] 通过与如上相似的方法得到以下化合物。

[4023] 实施例 590

[4024] [式 892]

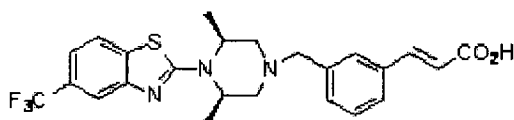
[4025]

[4026] MS (ESI) m/z 494 [M+H]⁺

[4027] 实施例 591

[4028] [式 893]

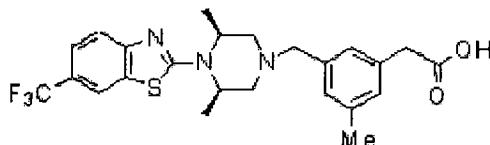
[4029]

[4030] MS (ESI) m/z 475 [M+H]⁺

[4031] 实施例 592

[4032] [式 894]

[4033]

[4034] MS (ESI) m/z 478 [M+H]⁺

[4035] 参考例 240

[4036] 4-甲氧基羧基甲叉基哌啶-1-羧酸叔丁基酯的制备

[4037] [式 895]

[4038]



[4039] 在 0℃ 向氢化钠 (4.02g) 在四氢呋喃 (300mL) 中的悬浮液加入磷酸基乙酸三甲基

酯。在 0℃ 搅拌 1 小时之后,向其中加入 1-Boc-4-哌啶酮 (20g) 的四氢呋喃 (150mL) 溶液。在 50℃ 搅拌 1.5 小时之后,向反应溶液加入水并且用乙酸乙酯萃取。有机层用水和盐水洗涤,并且用硫酸钠干燥。减压蒸发溶剂,并将残余物通过硅胶柱色谱法纯化,得到标题化合物 (27.0g)。收率:100%。

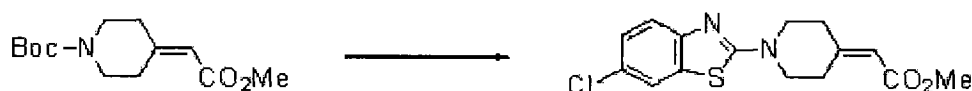
[4040] $^1\text{H-NMR}(\text{CDCl}_3)$ δ : 1.47 (9H, s), 2.27-2.29 (2H, m), 2.93-2.94 (2H, m), 3.47-3.51 (4H, m), 3.70 (3H, s), 5.72 (1H, s)。

[4041] 参考例 241

[4042] [1-(6-氯苯并噻唑-2-基)哌啶-4-亚基]乙酸甲基酯的制备

[4043] [式 896]

[4044]



[4045] 将 4-羧基甲叉基哌啶-1-羧酸叔丁基酯 (8.00g) 的 4N 氢氯酸/二噁烷 (80mL) 溶液在室温搅拌 1 小时。减压蒸发溶剂并将残余物溶解于二甲基甲酰胺 (60mL)。在 0℃ 向其中加入碳酸钾 (8.65g) 和 2,6-二氯苯并噻唑 (6.39g)。在 50℃ 搅拌 1 小时和在 60℃ 搅拌 3 小时之后,向其中加入水并且用乙酸乙酯萃取。有机层用水和盐水洗涤,并且用硫酸钠干燥。减压蒸发溶剂,并将残余物通过硅胶柱色谱法纯化,得到标题化合物 (9.48g)。收率:94%。

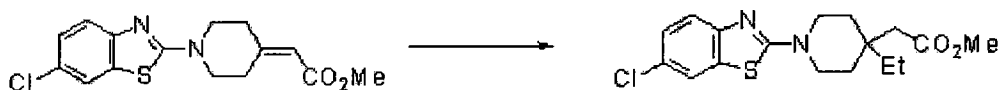
[4046] $^1\text{H-NMR}(\text{CDCl}_3)$ δ : 2.47-2.49 (2H, m), 3.14-3.19 (2H, m), 3.72 (3H, s), 3.70-3.77 (4H, m), 5.81 (1H, s), 7.25 (1H, dd, $J = 8.5, 2.2\text{Hz}$), 7.46 (1H, d, $J = 8.8\text{Hz}$), 7.57 (1H, d, $J = 2.2\text{Hz}$)。

[4047] 参考例 242

[4048] [1-(6-氯苯并噻唑-2-基)-4-乙基哌啶-4-基]乙酸甲基酯的制备

[4049] [式 897]

[4050]



[4051] 将碘化铜 (1.77g) 悬浮在四氢呋喃 (18mL) 中,并且在 -30℃ 向其中加入乙基溴化镁 (1.0M 四氢呋喃溶液, 18.6mL)。在 -25℃ 搅拌 0.5 小时之后,将反应溶液冷却到 -78℃。向混合物滴加 [1-(6-氯苯并噻唑-2-基)哌啶-4-亚基]乙酸甲基酯 (1.00g) 的四氢呋喃 (10mL) 溶液,然后加入三甲基甲硅烷基三氟甲磺酸酯 (1.12mL)。在 -78℃ 搅拌 2 小时之后,向其中加入碳酸氢钠水溶液。在过滤不溶性物质之后,滤液用乙酸乙酯萃取。有机层用水和盐水洗涤,并且用硫酸镁干燥。减压蒸发溶剂,并将残余物通过硅胶柱色谱法纯化,得到标题化合物 (979mg)。收率:90%。

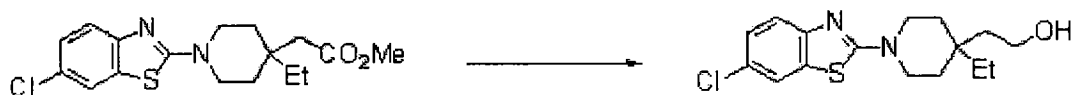
[4052] $^1\text{H-NMR}(\text{CDCl}_3)$ δ : 0.93 (3H, t, $J = 7.6\text{Hz}$), 1.67-1.75 (6H, m), 2.42 (2H, s), 3.57-3.68 (4H, m), 3.70 (3H, s), 7.26 (1H, dd, $J = 8.5, 2.2\text{Hz}$), 7.47 (1H, d, $J = 8.5\text{Hz}$), 7.58 (1H, d, $J = 2.2\text{Hz}$)。

[4053] 参考例 243

[4054] 2-[1-(6-氯苯并噻唑-2-基)-4-乙基哌啶-4-基]乙醇的制备

[4055] [式 898]

[4056]



[4057] 将氢化铝锂 (202mg) 悬浮在四氢呋喃 (10mL) 中。在 0℃ 向其中加入 [1-(6-氯苯并噻唑-2-基)-4-乙基哌啶-4-基] 乙酸甲基酯 (940mg) 的四氢呋喃 (10mL) 溶液。在 0℃ 搅拌 1 小时之后, 向反应溶液顺序地加入水 (0.2mL), 10% 氢氧化钠 (0.2mL) 和水 (0.6mL)。过滤不溶性物质并将滤液用乙酸乙酯萃取。有机层用水和盐水洗涤, 并且用硫酸钠干燥。减压蒸发溶剂, 并将残余物通过硅胶柱色谱法纯化, 得到标题化合物 (790mg)。收率: 91%。

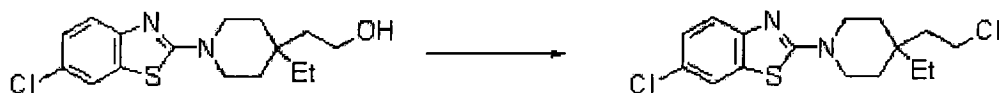
[4058] $^1\text{H-NMR}$ (CDCl_3) δ : 0.87 (3H, t, $J = 7.5\text{Hz}$), 1.44 (2H, q, $J = 7.5\text{Hz}$), 1.58-1.60 (4H, m), 1.68 (2H, t, $J = 7.5\text{Hz}$), 1.81 (1H, br), 3.60-3.62 (4H, m), 3.71-3.74 (2H, m), 7.23 (1H, dd, $J = 8.8, 2.2\text{Hz}$), 7.44 (1H, d, $J = 8.8\text{Hz}$), 7.55 (1H, d, $J = 2.2\text{Hz}$)。

[4059] 参考例 244

[4060] 6-氯-2-[4-(2-氯乙基)-4-乙基哌啶-1-基] 苯并噻唑的制备

[4061] [式 899]

[4062]



[4063] 将 2-[1-(6-氯苯并噻唑-2-基)-4-乙基哌啶-4-基] 乙醇 (764mg) 和亚硫酸氯 (4mL) 的混合物在 60℃ 搅拌 1.5 小时。向反应溶液加入冰并且用乙酸乙酯萃取。有机层用碳酸氢钠和盐水洗涤并且用硫酸钠干燥。减压蒸发溶剂, 并将残余物通过硅胶柱色谱法纯化, 得到标题化合物 (739mg)。收率: 92%。

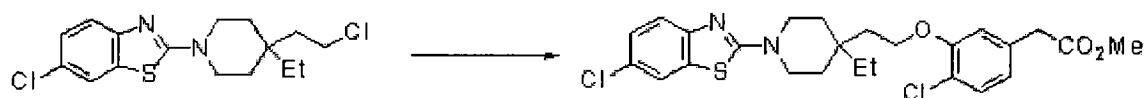
[4064] $^1\text{H-NMR}$ (CDCl_3) δ : 0.91 (3H, t, $J = 7.6\text{Hz}$), 1.47 (2H, q, $J = 7.6\text{Hz}$), 1.60-1.63 (4H, m), 1.92-1.94 (2H, m), 3.53-3.56 (2H, m), 3.62-3.65 (4H, m), 7.26 (1H, dd, $J = 8.5, 2.2\text{Hz}$), 7.47 (1H, d, $J = 8.5\text{Hz}$), 7.58 (1H, d, $J = 2.2\text{Hz}$)。

[4065] 实施例 593

[4066] [4-氯-3-[2-[1-(6-氯苯并噻唑-2-基)-4-乙基哌啶-4-基] 乙氧基] 苯基] 乙酸甲基酯的制备

[4067] [式 900]

[4068]



[4069] 将 6-氯-2-[4-(2-氯乙基)-4-乙基哌啶-1-基] 苯并噻唑 (150mg), (4-氯-3-羟基苯基) 乙酸甲基酯 (176mg), 碳酸铯 (285mg) 和二甲基甲酰胺 (2mL) 的混合物在 75℃ 搅拌 24 小时。向反应溶液加入水并且用乙酸乙酯萃取。有机层用盐水洗涤, 并且用硫酸钠干燥。减压蒸发溶剂, 并将残余物通过硅胶柱色谱法纯化, 得到标题化合物 (174mg)。收率: 79%。

[4070] $^1\text{H-NMR}$ (CDCl_3) δ : 0.94 (3H, t, $J = 7.6\text{Hz}$), 1.52-1.78 (8H, m), 3.59 (2H, s),

3.60-3.63 (2H, m), 3.68-3.70 (2H, m), 3.72 (3H, s), 4.09-4.18 (2H, m), 6.80-6.88 (2H, m), 6.98-6.98 (1H, m), 7.27-7.32 (1H, m), 7.48 (1H, d, $J = 8.5\text{Hz}$), 7.57 (1H, d, $J = 1.9\text{Hz}$)。

[4071] 实施例 594

[4072] [4-氯-3-[2-[1-(6-氯苯并噻唑-2-基)-4-乙基哌啶-4-基]乙氧基]苯基]乙酸的制备

[4073] [式 901]

[4074]



[4075] 将 [4-氯-3-[2-[1-(6-氯苯并噻唑-2-基)-4-乙基哌啶-4-基]乙氧基]苯基]乙酸甲基酯 (152mg), 2N 氢氧化钠水溶液 (0.45mL), 四氢呋喃 (1mL) 和甲醇 (1mL) 的混合物在室温搅拌 2 小时。反应溶液用 2N 盐酸中和并且用乙酸乙酯萃取。有机层用水和盐水洗涤, 并且用硫酸钠干燥。减压蒸发溶剂, 并将残余物通过硅胶柱色谱法纯化, 得到标题化合物 (53mg)。收率 :36%。

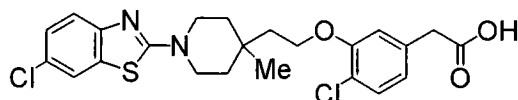
[4076] MS (ESI) m/z 493 $[M+H]^+$

[4077] 通过与如上相似的方法得到以下化合物。

[4078] 实施例 595

[4079] [式 902]

[4080]

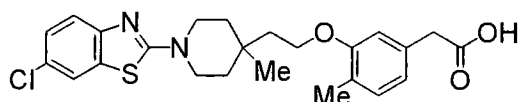


[4081] MS (ESI) m/z 479 $[M+H]^+$

[4082] 实施例 596

[4083] [式 903]

[4084]

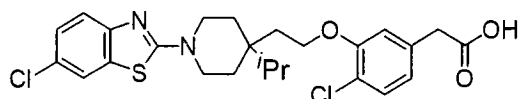


[4085] MS (ESI) m/z 459 $[M+H]^+$

[4086] 实施例 597

[4087] [式 904]

[4088]

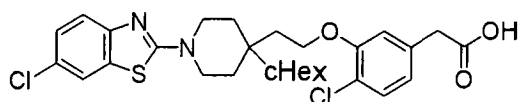


[4089] MS (ESI) m/z 507 $[M+H]^+$

[4090] 实施例 598

[4091] [式 905]

[4092]

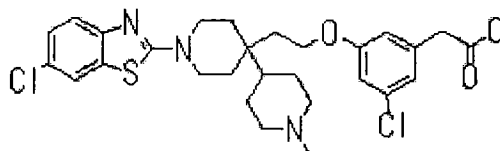


[4093] MS (ESI) m/z 547 $[M+H]^+$

[4094] 实施例 599

[4095] [式 906]

[4096]

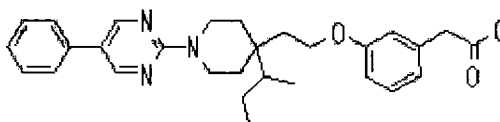


[4097] MS (ESI) m/z 564 $[M+H]^+$

[4098] 实施例 600

[4099] [式 907]

[4100]

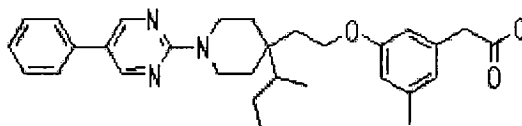


[4101] $^1\text{H-NMR}$ (丙酮- d_6) δ : 8.65 (1H, s), 7.60–7.63 (2H, m), 7.48 (2H, t, $J = 7.55\text{Hz}$), 7.36 (1H, t, $J = 7.55\text{Hz}$), 7.20–7.25 (1H, m), 6.97 (1H, s), 6.84–6.87 (2H, m), 4.19–4.27 (2H, m), 4.14 (2H, t, $J = 7.42\text{Hz}$), 3.65–3.72 (2H, m), 3.62 (2H, s), 2.05–2.10 (2H, m), 1.57–1.79 (7H, m), 0.96–1.00 (6H, m)。

[4102] 实施例 601

[4103] [式 908]

[4104]

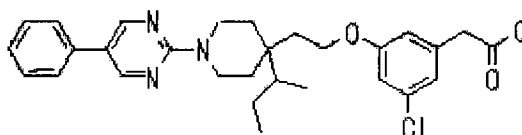


[4105] $^1\text{H-NMR}$ (丙酮- d_6) δ : 8.65 (1H, s), 7.62–7.65 (2H, m), 7.48 (2H, t, $J = 7.55\text{Hz}$), 7.36 (1H, t, $J = 7.55\text{Hz}$), 6.76 (1H, s), 6.72 (2H, s), 4.19–4.27 (2H, m), 4.14 (2H, t, $J = 7.42\text{Hz}$), 3.65–3.72 (2H, m), 3.62 (2H, s), 2.25 (3H, s), 2.05–2.10 (2H, m), 1.57–1.79 (7H, m), 0.96–1.00 (6H, m)。

[4106] 实施例 602

[4107] [式 909]

[4108]



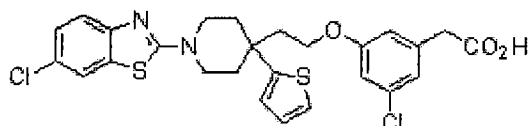
[4109] $^1\text{H-NMR}$ (丙酮) δ : 8.65 (1H, s), 7.62–7.65 (2H, m), 7.48 (2H, t, $J = 7.55\text{Hz}$), 7.36 (1H, t, $J = 7.55\text{Hz}$), 6.76 (1H, s), 6.72 (2H, s), 4.19–4.27 (2H, m), 4.14 (2H, t, $J = 7.42\text{Hz}$), 3.65–3.72 (2H, m), 3.62 (2H, s), 2.05–2.10 (2H, m), 1.57–1.79 (7H, m),

0.96-1.00 (6H, m)。

[4110] 实施例 603

[4111] [式 910]

[4112]

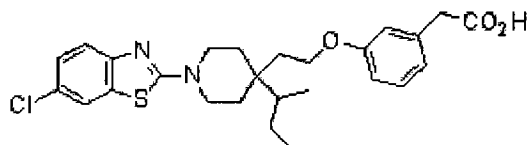


[4113] MS (ESI) m/z 547 $[M+H]^+$

[4114] 实施例 604

[4115] [式 911]

[4116]

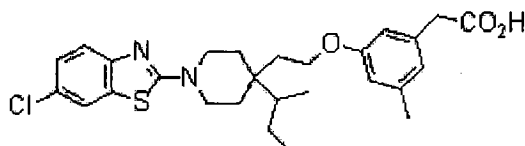


[4117] $^1\text{H-NMR}$ (CDCl₃) δ : 0.87-1.98 (15H, m), 3.44-3.78 (6H, m), 4.03 (3H, t, $J = 7.1\text{Hz}$), 6.78-7.45 (7H, m), 7.54 (1H, d, $J = 1.9\text{Hz}$)。

[4118] 实施例 605

[4119] [式 912]

[4120]

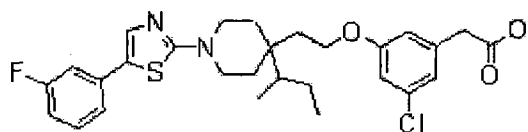


[4121] $^1\text{H-NMR}$ (CDCl₃) δ : 0.83-1.99 (15H, m), 2.30 (3H, s), 3.47-3.79 (6H, m), 4.02 (2H, t, $J = 7.1\text{Hz}$), 6.62 (2H, s), 6.69 (1H, s), 7.22-7.26 (1H, m), 7.46 (1H, d, $J = 9.1\text{Hz}$), 7.54 (1H, d, $J = 2.2\text{Hz}$)。

[4122] 实施例 606

[4123] [式 913]

[4124]

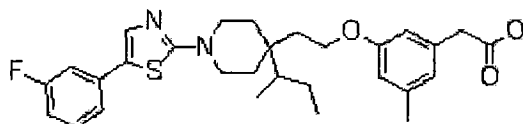


[4125] $^1\text{H-NMR}$ (CDCl₃) δ : 7.42 (1.0H, s), 7.29-7.24 (1.0H, m), 7.17 (1.0H, ddd, $J = 7.97, 1.30, 1.30\text{Hz}$), 7.10 (1.0H, ddd, $J = 9.89, 2.13, 2.13\text{Hz}$), 6.93-6.85 (2.0H, m), 6.80 (1.0H, dd, $J = 1.92, 1.92\text{Hz}$), 6.72 (1.0H, dd, $J = 1.79, 1.79\text{Hz}$), 4.03 (2.0H, dd, $J = 7.14, 7.14\text{Hz}$), 3.67-3.57 (4.0H, m), 3.47-3.39 (2.0H, m), 1.93 (2.0H, dd, $J = 7.14, 7.14\text{Hz}$), 1.82-1.77 (2.0H, m), 1.67-1.54 (4.0H, m), 1.50-1.42 (1.0H, m), 0.98-0.90 (6.0H, m)。

[4126] 实施例 607

[4127] [式 914]

[4128]

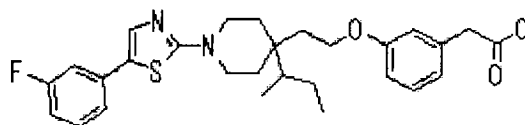


[4129] $^1\text{H-NMR}$ (CDCl₃) δ : 7.42 (1.0H, s), 7.30 (1.0H, dd, $J = 5.63, 2.06\text{Hz}$), 7.17 (1.0H, d, $J = 8.79\text{Hz}$), 7.12-7.07 (1.0H, m), 6.92-6.85 (1.0H, m), 6.69 (1.0H, s), 6.63 (2.0H, d, $J = 4.67\text{Hz}$), 4.04 (2.0H, dd, $J = 7.00, 7.00\text{Hz}$), 3.68-3.57 (4.0H, m), 3.47-3.39 (2.0H, m), 2.31 (3.0H, s), 1.95-1.54 (8.0H, m), 1.49-1.42 (1.0H, m), 0.97-0.90 (6.0H, m)。

[4130] 实施例 608

[4131] [式 915]

[4132]

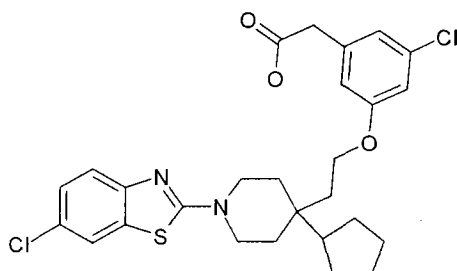


[4133] $^1\text{H-NMR}$ (丙酮) δ : 7.60 (1.0H, d, $J = 1.65\text{Hz}$), 7.42-7.33 (1.0H, m), 7.30-7.18 (3.0H, m), 6.99-6.92 (2.0H, m), 6.89-6.83 (2.0H, m), 4.15-4.09 (2.0H, m), 3.72-3.47 (6.0H, m), 1.85-1.56 (6.0H, m), 1.31-1.27 (3.0H, m), 0.99-0.92 (6.0H, m)。

[4134] 实施例 609

[4135] [式 916]

[4136]



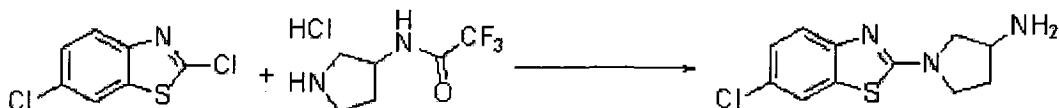
[4137] $^1\text{H-NMR}$ (DMSO- d_6) δ 1.25 (2H, br), 1.46-1.64 (10H, m), 1.94 (2H, t, $J = 6.9\text{Hz}$), 2.12 (1H, m), 3.43-3.52 (2H, m), 3.56 (2H, s), 3.70-3.80 (2H, br), 4.02 (3H, 2H, $J = 6.9\text{Hz}$), 6.83 (1H, s), 6.90 (1H, s), 6.96 (1H, s), 7.25-7.29 (1H, m), 7.40 (1H, d, $J = 8.7\text{Hz}$), 7.89 (1H, d, $J = 2.4\text{Hz}$)。

[4138] 参考例 245

[4139] 1-(6-氯苯并噻唑-2-基)吡咯烷-3-基胺的制备

[4140] [式 917]

[4141]



[4142] 将 2,6-二氯苯并噻唑 (2.00g), 3-(三氟乙酰胺)吡咯烷盐酸盐 (2.14g), 碳酸钾 (4.06g) 和二甲基甲酰胺 (15mL) 的混合物在 60°C 搅拌 2 小时。向反应溶液加入水并且用

乙酸乙酯萃取。有机层用水和盐水洗涤,并且用硫酸镁干燥。减压蒸发溶剂,并将残余物用正己烷洗涤。将得到的纯化产物溶解于四氢呋喃(20mL)和甲醇(10mL)。向其中加入 2N 氢氧化钠并将混合物搅拌 2.5 小时。减压蒸发溶剂。向其中加入水并用乙酸乙酯萃取。有机层用水和盐水洗涤,并且用硫酸钠干燥。减压蒸发溶剂,得到标题化合物(2.49g)。收率:100%。

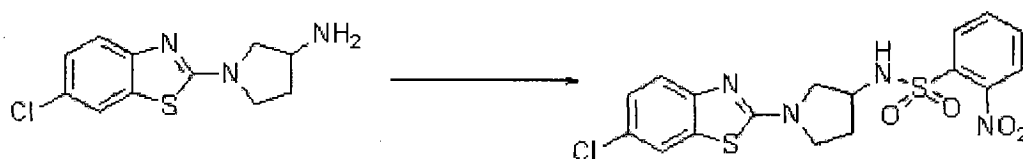
[4143] $^1\text{H-NMR}$ (DMSO- d_6) δ : 1.72-1.80(2H, m), 3.45-3.63(5H, m), 7.26(1H, dd, $H = 2.0$, 8.0), 7.41(1H, d, $J = 8.5$), 7.88(1H, d, $J = 2.0$)。

[4144] 参考例 246

[4145] N-[1(6-氯苯并噻唑-2-基)吡咯烷-3-基]-2-硝基苯磺酰胺的制备

[4146] [式 918]

[4147]



[4148] 将 1-(6-氯苯并噻唑-2-基)吡咯烷-3-基胺(2.49g), 2-硝基苯磺酰氯(2.40g), 三乙胺(3.02mL)和二甲基甲酰胺(15mL)的混合物在 60℃ 搅拌 3 小时。向反应溶液加入水并且用乙酸乙酯萃取。有机层用水和盐水洗涤,并且用硫酸钠干燥。减压蒸发溶剂,并将残余物通过硅胶柱色谱法纯化,得到标题化合物(2.01g)。收率:47%。

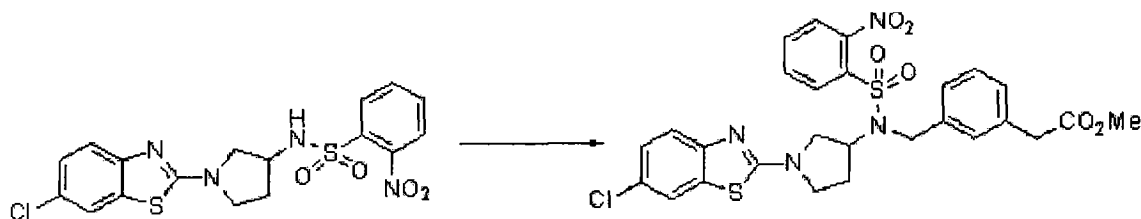
[4149] $^1\text{H-NMR}$ (DMSO- d_6) δ : 1.99-2.03(1H, m), 2.19-2.23(1H, m), 3.55-3.63(4H, m), 4.07-4.09(1H, m), 7.30(1H, dd, $J = 8.5$, 2.2Hz), 7.45(1H, d, $J = 8.8\text{Hz}$), 7.90-7.94(3H, m), 8.01-8.10(2H, m)。

[4150] 参考例 247

[4151] [3-[[[1-(6-氯苯并噻唑-2-基)吡咯烷-3-基]-(2-硝基苯磺酰基)氨基]甲基]苯基]乙酸甲基酯的制备

[4152] [式 919]

[4153]



[4154] 将 N-[1(6-氯苯并噻唑-2-基)吡咯烷-3-基]-2-硝基苯磺酰胺(500mg)溶解于二甲基甲酰胺(5mL)。向其中加入氢化钠(60%, 油, 50mg)并将混合物在室温搅拌 1 小时。向其中加入 (3-溴甲基苯基)乙酸甲基酯(305mg)并将混合物搅拌 16 小时。向反应溶液加入水并且用乙酸乙酯萃取。有机层用水和盐水洗涤,并且用硫酸镁干燥。减压蒸发溶剂,并将残余物通过硅胶柱色谱法纯化,得到标题化合物(412mg)。收率:60%。

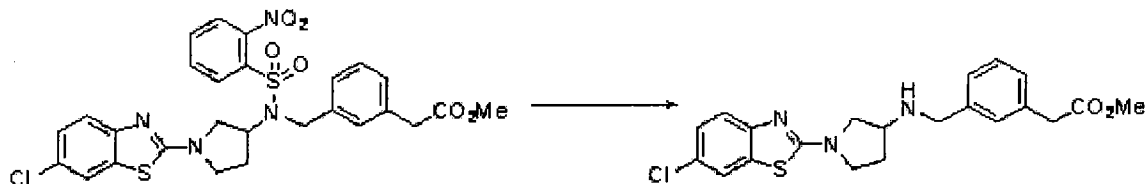
[4155] $^1\text{H-NMR}$ (CDCl_3) δ : 2.11-2.19(1H, m), 2.34-2.37(1H, m), 3.53-3.59(6H, m), 3.69(3H, s), 3.78-3.81(1H, m), 4.53-4.63(2H, m), 7.07-7.19(4H, m), 7.25-7.32(1H, m), 7.50-7.58(3H, m), 7.65-7.67(2H, m), 7.85(1H, d, $J = 7.7\text{Hz}$)。

[4156] 实施例 610

[4157] [3-[[1-(6-氯苯并噻唑-2-基)吡咯烷-3-基氨基]甲基]苯基]乙酸甲基酯的制备

[4158] [式 920]

[4159]



[4160] 将 [3-[[[1-(6-氯苯并噻唑-2-基)吡咯烷-3-基]-(2-硝基苯磺酰基)氨基]甲基]苯基]乙酸甲基酯 (412mg), 巯基乙酸 (95 μ L), 1,8-二氮杂双环 [5,4,0]-7-十一碳烯 (4mL) 和二甲基甲酰胺 (4mL) 的混合物在室温搅拌 1 小时。向反应溶液加入水并且用乙酸乙酯萃取。有机层用水和盐水洗涤, 并且用硫酸钠干燥。减压蒸发溶剂, 并将残余物通过硅胶柱色谱法纯化, 得到标题化合物 (204mg)。收率 :71%。

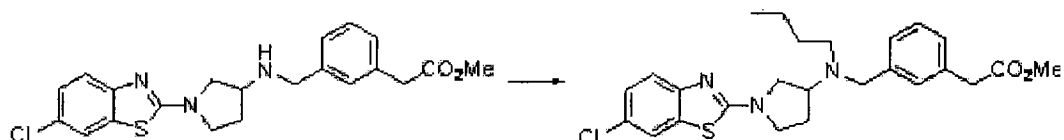
[4161] $^1\text{H-NMR}$ (CDCl_3) δ : 2.11-2.14 (1H, m), 2.27-2.32 (1H, m), 3.49-3.59 (2H, m), 3.63 (2H, s), 3.70 (3H, s), 3.74-3.82 (2H, m), 3.89 (2H, s), 7.23 (2H, dd, $J = 8.5, 2.2\text{Hz}$), 7.31-7.33 (3H, m), 7.45 (1H, d, $J = 8.5\text{Hz}$), 7.46 (1H, s), 7.54 (1H, d, $J = 2.2\text{Hz}$), 8.02 (1H, brs)。

[4162] 实施例 611

[4163] [3-[[丁基 [1-(6-氯苯并噻唑-2-基)吡咯烷-3-基]氨基]甲基]苯基]乙酸甲基酯的制备

[4164] [式 921]

[4165]



[4166] 将 [3-[[1-(6-氯苯并噻唑-2-基)吡咯烷-3-基氨基]甲基]苯基]乙酸甲基酯 (68mg), 1-碘丁烷 (37 μ L), 碳酸钾 (45mg) 和二甲基甲酰胺 (1mL) 的混合物在 80 $^{\circ}\text{C}$ 搅拌 3.5 小时。向反应溶液加入水并且用乙酸乙酯萃取。有机层用水和盐水洗涤, 并且用硫酸钠干燥。残余物通过硅胶柱色谱法纯化, 得到标题化合物 (28mg)。收率 :36%。

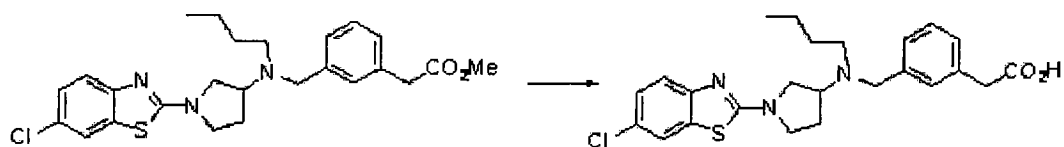
[4167] $^1\text{H-NMR}$ (CDCl_3) δ : 0.90 (3H, t, $J = 7.3\text{Hz}$), 1.24-1.36 (2H, m), 1.47-1.50 (2H, m), 2.54-2.56 (2H, m), 3.51-3.71 (14H, m), 7.21-7.29 (5H, m), 7.50 (1H, d, $J = 8.8\text{Hz}$), 7.58 (1H, d, $J = 2.2\text{Hz}$)。

[4168] 实施例 612

[4169] [3-[[丁基 [1-(6-氯苯并噻唑-2-基)吡咯烷-3-基]氨基]甲基]苯基]乙酸的制备

[4170] [式 922]

[4171]



[4172] 将 [3-[[丁基 [1-(6-氯苯并噻唑-2-基) 吡咯烷-3-基] 氨基] 甲基] 苯基] 乙酸甲基酯 (28mg), 2N 氢氧化钠 (0.15mL), 四氢呋喃 (1mL) 和甲醇 (0.5mL) 的混合物在室温搅拌 1 小时。混合物用 2N 盐酸中和并且减压浓缩。溶液用乙酸乙酯萃取。有机层用水和盐水洗涤, 并且用硫酸钠干燥, 得到标题化合物 (19mg)。收率 :68%。

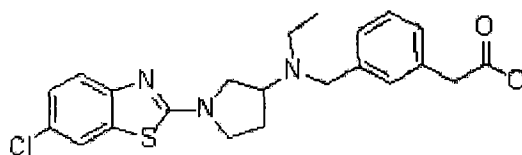
[4173] MS(ESI)m/z 458 [M+H]⁺

[4174] 通过与如上相似的方法得到以下化合物。

[4175] 实施例 613

[4176] [式 923]

[4177]

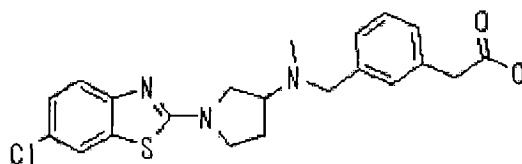


[4178] MS(ESI)m/z 430 [M+H]⁺

[4179] 实施例 614

[4180] [式 924]

[4181]

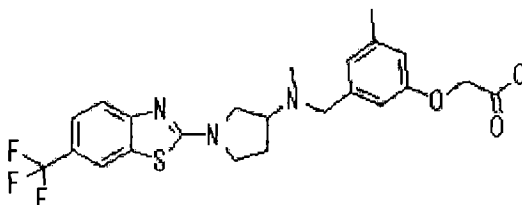


[4182] MS(ESI)m/z 416 [M+H]⁺

[4183] 实施例 615

[4184] [式 925]

[4185]

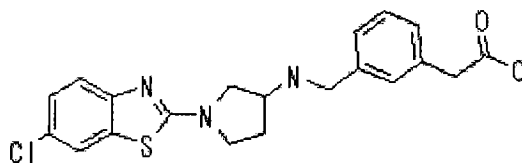


[4186] MS(ESI)m/z 480 [M+H]⁺

[4187] 实施例 616

[4188] [式 926]

[4189]



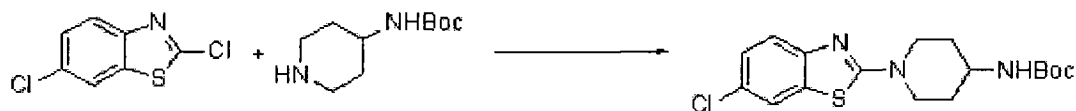
[4190] MS(ESI) m/z 402 $[M+H]^+$

[4191] 参考例 248

[4192] [1-(6-氯苯并噻唑-2-基)哌啶-4-基]氨基甲酸叔丁酯的制备

[4193] [式 927]

[4194]



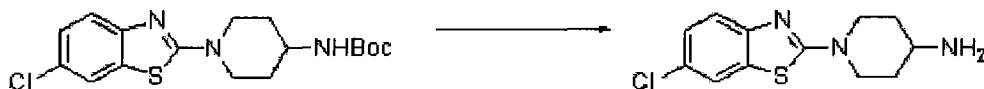
[4195] 将 4-Boc-氨基哌啶 (3.23g), 2,6-二氯苯并噻唑 (3.29g), 碳酸钾 (6.68g) 和二甲基甲酰胺 (20mL) 的混合物在 60℃ 搅拌 16 小时。向反应溶液加入水。收集沉淀物并将得到的化合物不经进一步纯化用于下一步反应。

[4196] 参考例 249

[4197] 1-(6-氯苯并噻唑-2-基)哌啶-4-基胺的合成

[4198] [式 928]

[4199]



[4200] 将得自上述反应的 [1-(6-氯苯并噻唑-2-基)哌啶-4-基]氨基甲酸叔丁酯溶解于氯仿。向其中加入 4N 的氢氯酸/二噁烷溶液并将混合物在室温搅拌 16 小时。将溶剂减压浓缩。向其中加入水并用乙酸乙酯洗涤。水层用 2N 氢氧化钠中和并且用乙酸乙酯萃取。有机层用硫酸镁洗涤并且减压蒸发溶剂, 得到标题化合物 (3.31g)。收率: 77%。

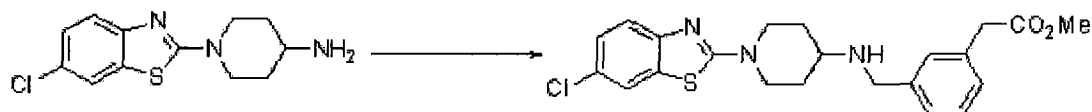
[4201] $^1\text{H-NMR}$ (DMSO-d_6) δ : 1.24-1.33 (4H, m), 3.20-3.30 (3H, m), 3.90-3.95 (2H, m), 7.27 (1H, dd, $J = 8.5, 2.2\text{Hz}$), 7.40 (1H, d, $J = 8.8\text{Hz}$), 7.88 (1H, d, $J = 2.2\text{Hz}$)。

[4202] 实施例 617

[4203] [3-[[1-(6-氯苯并噻唑-2-基)哌啶-4-基氨基]甲基]苯基]乙酸甲基酯的制备

[4204] [式 929]

[4205]



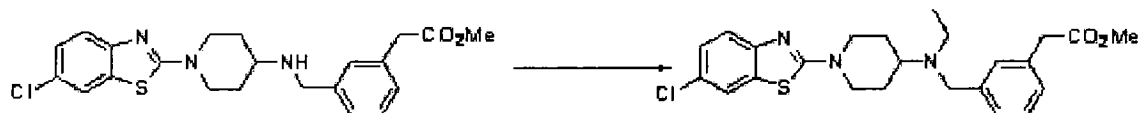
[4206] 将 1-(6-氯苯并噻唑-2-基)哌啶-4-基胺 (500mg), (3-溴甲基苯基)乙酸甲基酯 (454mg), 碳酸钾 (284mg) 和二甲基甲酰胺 (6mL) 的混合物在室温搅拌 1 小时。向反应溶液加入水并且用乙酸乙酯萃取。有机层用水和盐水洗涤, 并且用硫酸钠干燥。减压蒸发溶剂, 并将残余物通过硅胶柱色谱法纯化, 得到标题化合物 (434mg)。收率: 55%。

[4207] 实施例 618

[4208] [3-[[[1-(6-氯苯并噻唑-2-基)哌啶-4-基]乙基氨基]甲基]苯基]乙酸甲基酯的制备

[4209] [式 930]

[4210]



[4211] 将 [3-[[[1-(6-氯苯并噻唑-2-基)哌啶-4-基氨基]甲基]苯基]乙酸甲基酯 (110mg), 碘甲烷 (800mg), 碳酸钾 (71mg) 和二甲基甲酰胺 (2mL) 的混合物在 80℃ 搅拌 5 小时。向反应溶液加入水并且用乙酸乙酯萃取。有机层用水和盐水洗涤, 并且用硫酸钠干燥。减压蒸发溶剂, 并将残余物通过硅胶柱色谱法纯化, 得到标题化合物 (65mg)。收率: 56%。

[4212] $^1\text{H-NMR}$ (CDCl_3) δ : 1.03-1.07 (3H, br m), 1.63-1.66 (2H, br m), 1.89-1.92 (2H, br m), 2.58-2.62 (1H, br m), 2.91 (2H, s), 2.98 (2H, s), 3.09-3.13 (2H, m), 3.64-3.67 (2H, br m), 3.71 (3H, s), 4.20-4.23 (2H, br m), 7.25-7.28 (5H, m), 7.44 (1H, d, $J = 8.5\text{Hz}$), 7.57 (1H, d, $J = 10.0\text{Hz}$)。

[4213] 实施例 619

[4214] [3-[[[1-(6-氯苯并噻唑-2-基)哌啶-4-基]乙基氨基]甲基]苯基]乙酸的制备

[4215] [式 931]

[4216]



[4217] 将 [3-[[[1-(6-氯苯并噻唑-2-基)哌啶-4-基]乙基氨基]甲基]苯基]乙酸甲基酯 (65mg), 2N 氢氧化钠 (0.36mL), 四氢呋喃 (1mL) 和甲醇 (1mL) 的混合物在室温搅拌 1 小时。溶液用 2N 盐酸中和并且用乙酸乙酯萃取。有机层用水和盐水洗涤, 并且用硫酸钠干燥。减压蒸发溶剂并将得到的残余物用乙酸乙酯和正己烷的混合溶剂洗涤, 得到标题化合物 (19mg)。收率: 30%。

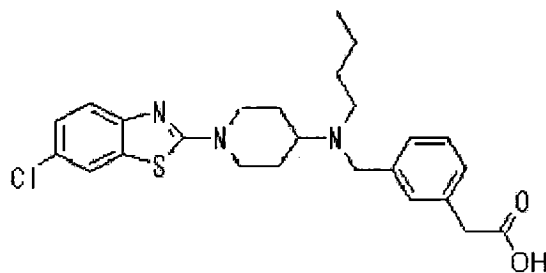
[4218] MS (ESI) m/z 444 $[\text{M}+\text{H}]^+$

[4219] 通过与如上相似的方法得到以下化合物。

[4220] 实施例 620

[4221] [式 932]

[4222]

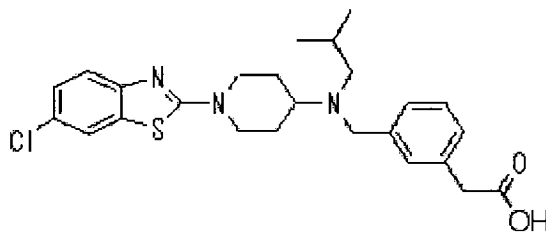


[4223] MS (ESI) m/z 472 $[\text{M}+\text{H}]^+$

[4224] 实施例 621

[4225] [式 933]

[4226]

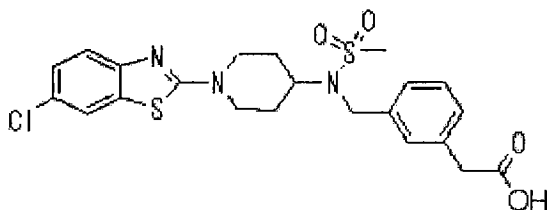


[4227] MS (ESI) m/z 472 $[M+H]^+$

[4228] 实施例 622

[4229] [式 934]

[4230]



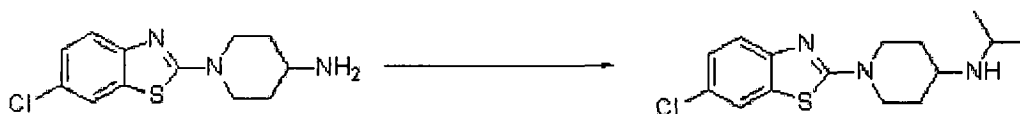
[4231] MS (ESI) m/z 494 $[M+H]^+$

[4232] 参考例 250

[4233] [1-(6-氯苯并噻唑-2-基)哌啶-4-基]异丙基胺的制备

[4234] [式 935]

[4235]



[4236] 将 1-(6-氯苯并噻唑-2-基)哌啶-4-基胺 (335mg), 丙酮 (92u1), 乙酸 (0.1mL) 和甲醇 (3mL) 的混合物在室温搅拌 5 分钟。向反应溶液加入三乙酰氧基硼氢化钠 (332mg)。将混合物在室温搅拌 16 小时。将反应溶液减压浓缩。向其中加入碳酸氢钠水溶液并用乙酸乙酯萃取。有机层用水和盐水洗涤, 并且用硫酸钠干燥。减压蒸发溶剂, 并将残余物通过硅胶柱色谱法纯化, 得到标题化合物 (160mg)。收率: 41%。

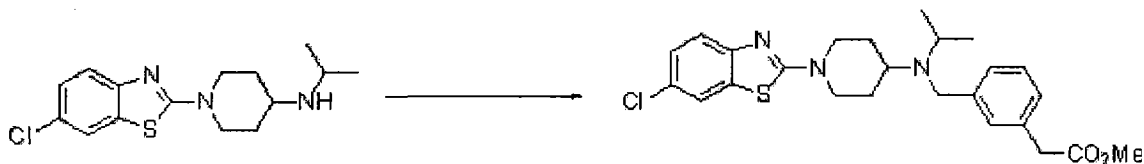
[4237] $^1\text{H-NMR}$ (CDCl_3) δ : 1.11 (6H, d, $J = 6.3\text{Hz}$), 1.48-1.51 (2H, m), 2.01-2.05 (2H, m), 2.84-2.91 (1H, m), 3.00-3.08 (1H, m), 3.14-3.24 (2H, m), 4.08-4.16 (2H, m), 7.23 (1H, dd, $J = 8.5, 2.2\text{Hz}$), 7.42 (1H, d, $J = 8.5\text{Hz}$), 7.55 (1H, d, $J = 2.2\text{Hz}$)。

[4238] 实施例 623

[4239] [3-[[[1-(6-氯苯并噻唑-2-基)哌啶-4-基]异丙基氨基]甲基]苯基]乙酸甲基酯的制备

[4240] [式 936]

[4241]



[4242] 将 [1-(6-氯苯并噻唑-2-基)哌啶-4-基]异丙基胺 (159mg), (3-溴甲基苯基)乙酸甲基酯 (138mg), 碳酸钾 (107mg) 和二甲基甲酰胺 (2mL) 的混合物在 80℃ 搅拌 8 小时。

向反应溶液加入水并且用乙酸乙酯萃取。有机层用水和盐水洗涤,并且用硫酸镁干燥。减压蒸发溶剂,并将残余物通过硅胶柱色谱法纯化,得到标题化合物(90mg)。收率:37%。

[4243] 实施例 624

[4244] [3-[[[1-(6-氯苯并噻唑-2-基)哌啶-4-基]异丙基氨基]甲基]苯基]乙酸的制备

[4245] [式 937]

[4246]



[4247] 将[3-[[[1-(6-氯苯并噻唑-2-基)哌啶-4-基]异丙基氨基]甲基]苯基]乙酸甲基酯(90mg), 2N氢氧化钠(0.5mL), 四氢呋喃(2mL)和甲醇(1mL)的混合物在室温搅拌1小时。在用2N盐酸中和之后,将反应溶液减压浓缩并用乙酸乙酯萃取。有机层用水和盐水洗涤,并且用硫酸镁干燥。减压蒸发溶剂,并将残余物通过硅胶柱色谱法纯化,得到标题化合物(28mg)。收率:32%。

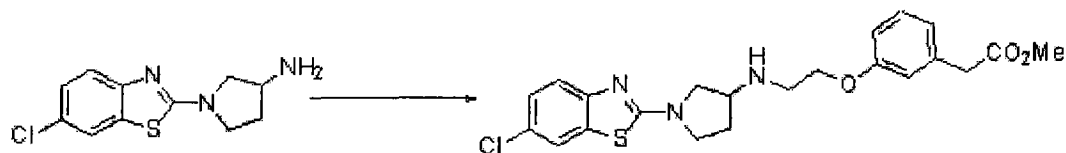
[4248] MS(ESI)m/z 458[M+H]⁺

[4249] 实施例 625

[4250] [3-[2-[1-(6-氯苯并噻唑-2-基)吡咯烷-3-基氨基]乙氧基]苯基]乙酸甲基酯的制备

[4251] [式 938]

[4252]



[4253] 将1-(6-氯苯并噻唑-2-基)吡咯烷-3-基胺(190mg), [3-(2-溴乙氧基)苯基]乙酸甲基酯(205mg)和碳酸钾(114mg)的混合物在80℃搅拌2小时。向反应溶液,加入水并且用乙酸乙酯萃取。有机层用水和盐水洗涤,并且用硫酸钠干燥。减压蒸发溶剂,并将残余物通过硅胶柱色谱法纯化,得到标题化合物(174mg)。收率:52%。

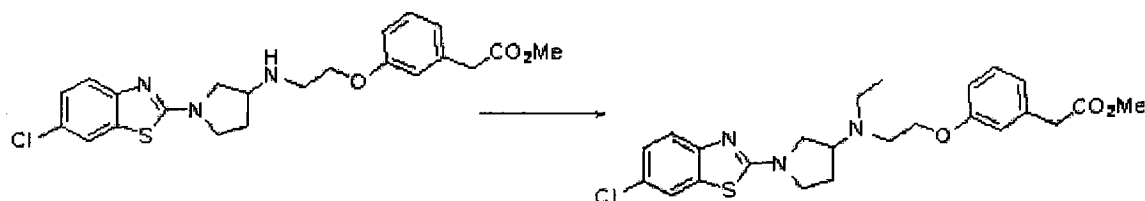
[4254] ¹H-NMR(CDCl₃) δ :2.01-2.06(1H, m), 2.31-2.36(1H, m), 3.09(2H, t, J = 4.9Hz), 3.48-3.50(1H, m), 3.62(2H, s), 3.64-3.80(4H, m), 3.72(3H, s), 4.12(2H, t, J = 4.9Hz), 6.83-6.91(3H, m), 7.24-7.28(3H, m), 7.50(1H, d, J = 8.5Hz), 7.59(1H, d, J = 1.9Hz)。

[4255] 实施例 626

[4256] [3-[2-[[1-(6-氯苯并噻唑-2-基)吡咯烷-3-基]乙基氨基]乙氧基]苯基]乙酸甲基酯的制备

[4257] [式 939]

[4258]



[4259] 将 [3-[2-[1-(6-氯苯并噻唑-2-基)吡咯烷-3-基氨基]乙氧基]苯基]乙酸甲基酯 (174mg), 碘乙烷 (68uL), 碳酸钾 (81mg) 和二甲基甲酰胺 (2mL) 的混合物在 80℃ 搅拌 6.5 小时。向反应溶液加入水并且用乙酸乙酯萃取。有机层用水和盐水洗涤, 并且用硫酸钠干燥。减压蒸发溶剂, 并将残余物通过硅胶柱色谱法纯化, 得到标题化合物 (101mg)。收率: 55%。

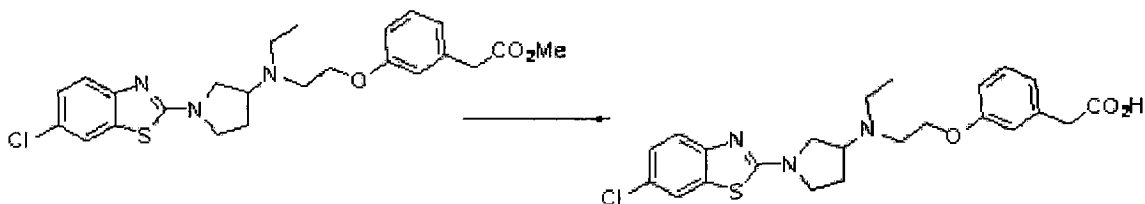
[4260] $^1\text{H-NMR}$ (CDCl_3) δ : 1.14 (3H, t, $J = 6.7\text{Hz}$), 2.08-2.11 (1H, m), 2.29-2.32 (1H, m), 2.79-2.81 (2H, m), 2.98-3.03 (2H, m), 3.46-3.86 (5H, m), 3.62 (2H, s), 3.71 (3H, s), 4.05-4.08 (2H, m), 6.82-6.90 (3H, m), 7.23-7.29 (2H, m), 7.50 (1H, d, $J = 8.8\text{Hz}$), 7.59 (1H, d, $J = 1.9\text{Hz}$)。

[4261] 实施例 627

[4262] [3-[2-[[1-(6-氯苯并噻唑-2-基)吡咯烷-3-基]乙基氨基]乙氧基]苯基]乙酸的制备

[4263] [式 940]

[4264]



[4265] 将 [3-[2-[[1-(6-氯苯并噻唑-2-基)吡咯烷-3-基]乙基氨基]乙氧基]苯基]乙酸甲基酯 (101mg), 2N 氢氧化钠水溶液 (0.535mL), 四氢呋喃 (1mL) 和甲醇 (0.5mL) 的混合物在室温搅拌 1 小时。将反应溶液减压浓缩并用乙酸乙酯萃取。有机层用水和盐水洗涤, 并且用硫酸钠干燥。减压蒸发溶剂, 并将残余物用乙酸乙酯/正己烷洗涤, 得到标题化合物 (13mg)。收率: 14%。

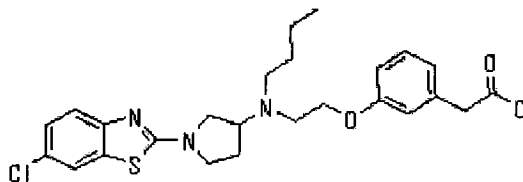
[4266] MS (ESI) m/z 459 $[\text{M}+\text{H}]^+$

[4267] 通过与如上相似的方法得到以下化合物。

[4268] 实施例 628

[4269] [式 941]

[4270]

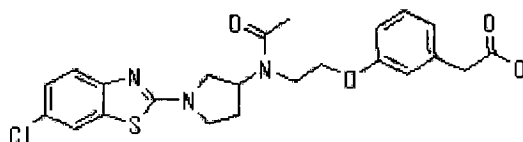


[4271] MS (ESI) m/z 487 $[\text{M}+\text{H}]^+$

[4272] 实施例 629

[4273] [式 942]

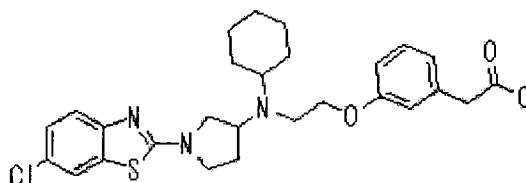
[4274]

[4275] MS (ESI) m/z 473 $[M+H]^+$

[4276] 实施例 630

[4277] [式 943]

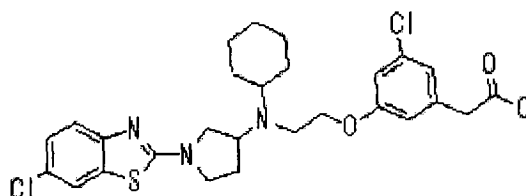
[4278]

[4279] MS (ESI) m/z 516 $[M+H]^+$

[4280] 实施例 631

[4281] [式 944]

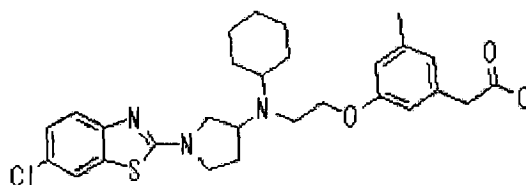
[4282]

[4283] MS (ESI) m/z 548 $[M+H]^+$

[4284] 实施例 632

[4285] [式 945]

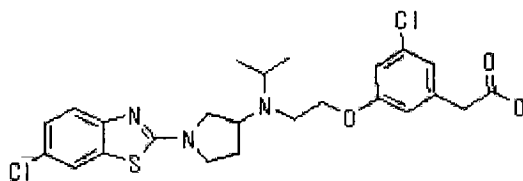
[4286]

[4287] MS (ESI) m/z 528 $[M+H]^+$

[4288] 实施例 633

[4289] [式 946]

[4290]

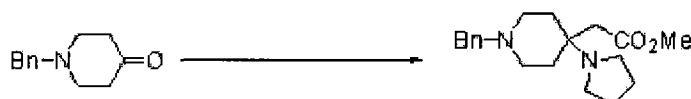
[4291] MS (ESI) m/z 508 $[M+H]^+$

[4292] 参考例 251

[4293] (1- 苯甲基 -4- 吡咯烷 -1- 基哌啶 -4- 基) 乙酸甲基酯的制备

[4294] [式 947]

[4295]



[4296] 将 1- 苯甲基 -4- 哌啶酮 (3mL), 吡咯烷 (6.95mL) 和 甲苯 (30mL) 的混合物回流 1 小时。减压蒸发溶剂。向残余物中加入乙酸 (0.96mL)。将混合物在室温搅拌 5 分钟。向反应溶液加入锌 (1.37g) 和溴乙酸甲基酯 (2.17mL)。将混合物在室温搅拌 2 小时。向反应溶液加入碳酸钠水溶液 (20mL) 并且用乙酸乙酯萃取。有机层用水和盐水洗涤, 并且用硫酸钠干燥。减压蒸发溶剂, 并将残余物通过硅胶柱色谱法纯化, 得到标题化合物 (2.77g)。收率: 52%。

[4297] $^1\text{H-NMR}(\text{CDCl}_3)$ δ : 1.71-1.73 (4H, m), 1.81-1.84 (4H, m), 2.45-2.56 (10H, m), 3.55-3.58 (2H, m), 3.69 (3H, s), 7.26-7.36 (5H, m)。

[4298] 参考例 252

[4299] 2-(1- 苯甲基 -4- 吡咯烷 -1- 基哌啶 -4- 基) 乙醇的制备

[4300] [式 948]

[4301]



[4302] 将氢化铝锂 (324mg) 悬浮在四氢呋喃 (25mL) 中。在 0℃ 向其中加入 (1- 苯甲基 -4- 吡咯烷 -1- 基哌啶 -4- 基) 乙酸甲基酯 (2.70g) 的四氢呋喃 (25mL) 溶液。在 0℃ 搅拌 1 小时之后, 向反应溶液顺序地加入水 (0.35mL), 10% 氢氧化钠水溶液 (0.35mL) 和水 (1.05mL)。过滤不溶性物质并将滤液用乙酸乙酯萃取。有机层用水和盐水洗涤, 并且用硫酸钠干燥。减压蒸发溶剂, 得到标题化合物。得到的目标化合物不经进一步纯化用于下一步反应。

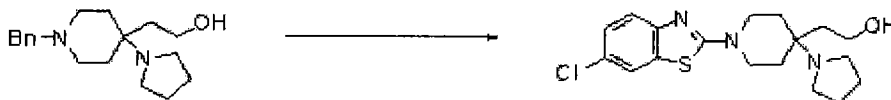
[4303] $^1\text{H-NMR}(\text{CDCl}_3)$ δ : 1.74-1.76 (6H, m), 1.89-1.94 (4H, m), 2.06-2.17 (2H, m), 2.80-2.83 (6H, m), 3.54 (3H, s), 3.85-3.87 (2H, m), 7.33 (5H, t, $J = 3.6\text{Hz}$)。

[4304] 参考例 253

[4305] 2-[1-(6- 氯苯并噻唑 -2- 基)-4- 吡咯烷 -1- 基哌啶 -4- 基] 乙醇的制备

[4306] [式 949]

[4307]



[4308] 将上述得到的 2-(1- 苯甲基 -4- 吡咯烷 -1- 基哌啶 -4- 基) 乙醇溶解于甲醇 (60mL)。向其中加入 Pd/C (600mg) 并将混合物在氢气气氛下搅拌 19 小时。过滤不溶性物质并将滤液减压浓缩。向得到的残余物加入二甲基甲酰胺 (30mL), 碳酸钾 (1.24g) 和 2, 6- 二氯苯并噻唑 (1.83g)。将混合物在 60℃ 搅拌 21 小时。向反应溶液加入水并且用乙酸乙酯萃取。有机层用水和盐水洗涤, 并且用硫酸钠干燥。减压蒸发溶剂, 并将残余物通过硅胶柱色谱法纯化, 得到标题化合物 (2.58g)。收率: 83%。

[4309] $^1\text{H-NMR}(\text{CDCl}_3)$ δ : 1.83-1.86 (4H, m), 2.00-2.01 (6H, m), 2.91-2.98 (4H, m),

3.29-3.38 (2H, m), 3.92-4.05 (4H, m), 7.26 (1H, d, $J = 2.2\text{Hz}$), 7.45 (1H, t, $J = 7.8\text{Hz}$), 7.59 (1H, d, $J = 2.2\text{Hz}$)。

[4310] 实施例 634

[4311] [3-氯-5-[2-[1-(6-氯苯并噻唑-2-基)-4-吡咯烷-1-基哌啶-4-基]乙醇]苯基]乙酸甲基酯的制备

[4312] [式 950]

[4313]



[4314] 将 2-[1-(6-氯苯并噻唑-2-基)-4-吡咯烷-1-基哌啶-4-基]乙醇 (1.60g), 三正丁基膦 (1.15mL), 1,1'-(偶氮二羰基)二哌啶 (1.16g) 和四氢呋喃 (25mL) 的混合物在室温搅拌 1 小时。过滤不溶性物质。向滤液加入碳酸氢钠水溶液并且用乙酸乙酯萃取。有机层用水和盐水洗涤, 并且用硫酸钠干燥。减压蒸发溶剂, 并将残余物通过硅胶柱色谱法纯化, 得到标题化合物 (874mg)。收率: 36%。

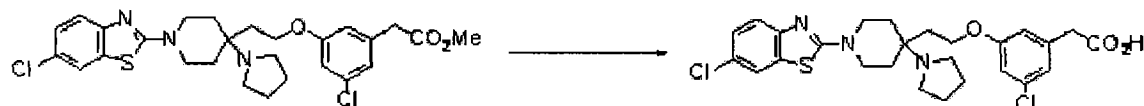
[4315] $^1\text{H-NMR}$ (CDCl_3) δ : 1.77-1.81 (6H, m), 1.94-2.03 (4H, m), 2.69-2.72 (4H, m), 3.53-3.77 (4H, m), 3.56 (2H, s), 3.72 (3H, s), 4.01 (2H, m), 6.75-6.84 (3H, m), 7.25 (1H, dd, $J = 8.7, 2.1\text{Hz}$), 7.44 (1H, d, $J = 8.8\text{Hz}$), 7.57 (1H, d, $J = 2.2\text{Hz}$)。

[4316] 实施例 635

[4317] [3-氯-5-[2-[1-(6-氯苯并噻唑-2-基)-4-吡咯烷-1-基哌啶-4-基]乙醇]苯基]乙酸的制备

[4318] [式 951]

[4319]



[4320] 将 [3-氯-5-[2-[1-(6-氯苯并噻唑-2-基)-4-吡咯烷-1-基哌啶-4-基]乙醇]苯基]乙酸甲基酯 (851mg), 2N 氢氧化钠 (2.33mL), 四氢呋喃 (5mL) 和甲醇 (5mL) 的混合物在室温搅拌 0.5 小时。混合物用 2N 盐酸中和并且用乙酸乙酯萃取。有机层用水和盐水洗涤, 并且用硫酸镁干燥。减压蒸发溶剂, 并将残余物用己烷洗涤, 得到标题化合物 (725mg)。收率: 88%。

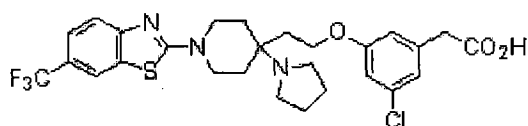
[4321] MS (ESI) m/z 534 $[\text{M}+\text{H}]^+$

[4322] 通过与如上相似的方法得到以下化合物。

[4323] 实施例 636

[4324] [式 952]

[4325]

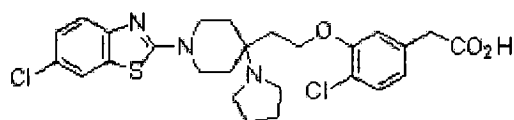


[4326] MS (ESI) m/z 568 $[\text{M}+\text{H}]^+$

[4327] 实施例 637

[4328] [式 953]

[4329]

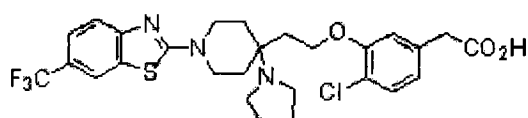


[4330] MS (ESI) m/z 534 $[M+H]^+$

[4331] 实施例 638

[4332] [式 954]

[4333]

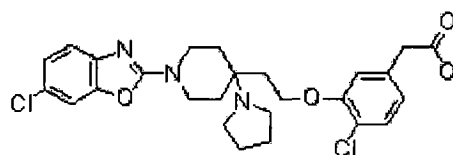


[4334] MS (ESI) m/z 568 $[M+H]^+$

[4335] 实施例 639

[4336] [式 955]

[4337]

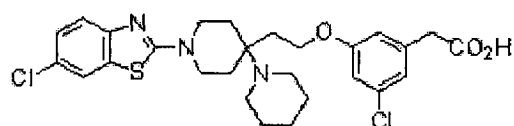


[4338] MS (ESI) m/z 520 $[M+H]^+$

[4339] 实施例 640

[4340] [式 956]

[4341]

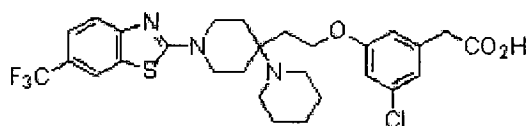


[4342] MS (ESI) m/z 548 $[M+H]^+$

[4343] 实施例 641

[4344] [式 957]

[4345]

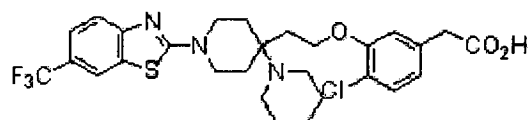


[4346] MS (ESI) m/z 582 $[M+H]^+$

[4347] 实施例 642

[4348] [式 958]

[4349]

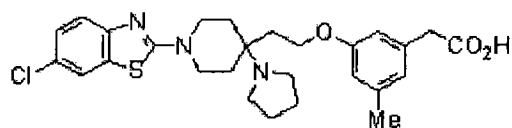


[4350] MS (ESI) m/z 582 $[M+H]^+$

[4351] 实施例 643

[4352] [式 959]

[4353]

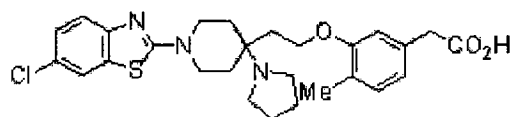


[4354] MS (ESI) m/z 514 $[M+H]^+$

[4355] 实施例 644

[4356] [式 960]

[4357]

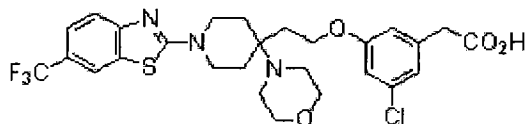


[4358] MS (ESI) m/z 514 $[M+H]^+$

[4359] 实施例 645

[4360] [式 961]

[4361]

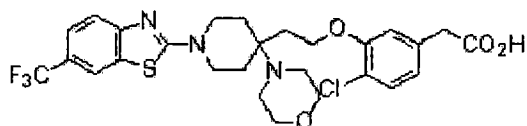


[4362] MS (ESI) m/z 584 $[M+H]^+$

[4363] 实施例 646

[4364] [式 962]

[4365]

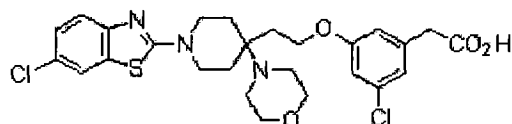


[4366] MS (ESI) m/z 584 $[M+H]^+$

[4367] 实施例 647

[4368] [式 963]

[4369]

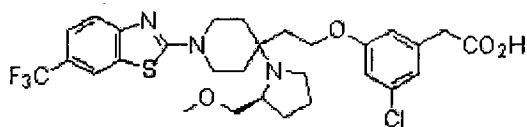


[4370] MS (ESI) m/z 550 $[M+H]^+$

[4371] 实施例 648

[4372] [式 964]

[4373]

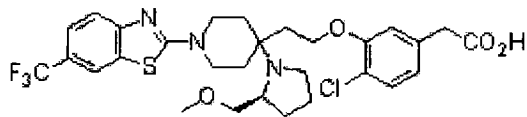


[4374] MS (ESI) m/z 612 $[M+H]^+$

[4375] 实施例 649

[4376] [式 965]

[4377]

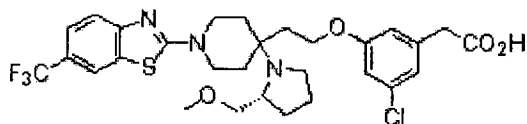


[4378] MS (ESI) m/z 612 $[M+H]^+$

[4379] 实施例 650

[4380] [式 966]

[4381]

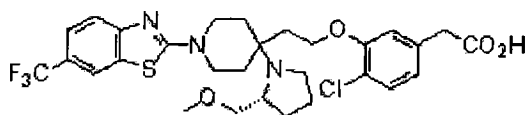


[4382] MS (ESI) m/z 612 $[M+H]^+$

[4383] 实施例 651

[4384] [式 967]

[4385]

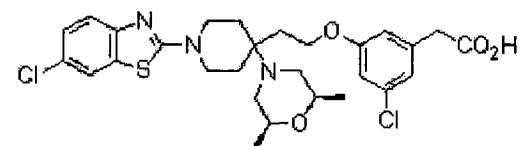


[4386] MS (ESI) m/z 612 $[M+H]^+$

[4387] 实施例 652

[4388] [式 968]

[4389]

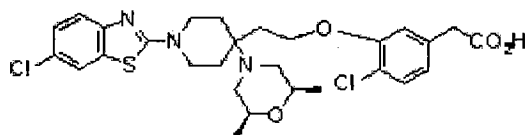


[4390] MS (ESI) m/z 578 $[M+H]^+$

[4391] 实施例 653

[4392] [式 969]

[4393]

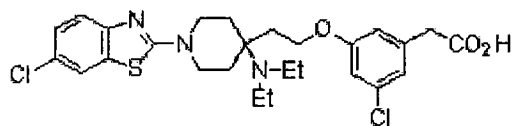


[4394] MS(ESI) m/z 578 $[M+H]^+$

[4395] 实施例 654

[4396] [式 970]

[4397]

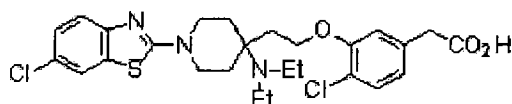


[4398] $^1\text{H-NMR}$ (CDCl_3) δ : 1.08 (6H, t, $J = 7.1\text{Hz}$), 1.65–1.77 (2H, m), 1.92–2.05 (4H, m), 2.65 (4H, q, $J = 7.1\text{Hz}$), 3.54–3.77 (6H, m), 4.01 (2H, t, $J = 6.6\text{Hz}$), 6.70 (1H, s), 6.78 (1H, s), 6.87 (1H, s), 7.22 (1H, dd, $J = 8.5, 2.2\text{Hz}$), 7.43 (1H, d, $J = 8.5\text{Hz}$), 7.54 (1H, d, $J = 2.2\text{Hz}$)。

[4399] 实施例 655

[4400] [式 971]

[4401]

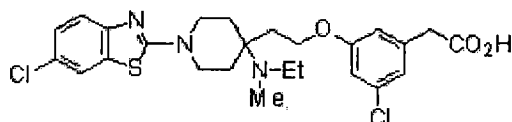


[4402] $^1\text{H-NMR}$ (CDCl_3) δ : 1.07 (6H, t, $J = 7.0\text{Hz}$), 1.70–2.10 (6H, m), 2.66 (4H, q, $J = 7.0\text{Hz}$), 3.56–3.79 (6H, m), 4.05–4.13 (2H, m), 6.76–6.85 (2H, m), 7.19–7.30 (2H, m), 7.42 (1H, d, $J = 8.5\text{Hz}$), 7.53 (1H, d, $J = 1.6\text{Hz}$)。

[4403] 实施例 656

[4404] [式 972]

[4405]

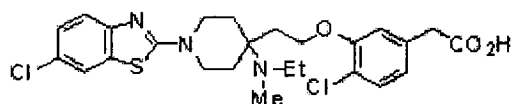


[4406] $^1\text{H-NMR}$ (CDCl_3) δ : 1.08 (3H, t, $J = 6.9\text{Hz}$), 1.64–2.03 (6H, m), 2.26 (3H, s), 2.53 (2H, q, $J = 6.9\text{Hz}$), 3.52–3.68 (6H, m), 3.96–4.03 (2H, m), 6.68–6.88 (3H, m), 7.22 (1H, dd, $J = 8.5, 2.2\text{Hz}$), 7.43 (1H, d, $J = 8.8\text{Hz}$), 7.54 (1H, d, $J = 2.2\text{Hz}$)。

[4407] 实施例 657

[4408] [式 973]

[4409]

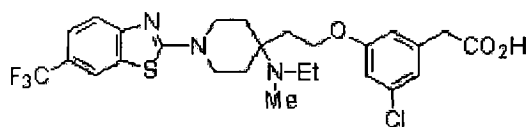


[4410] $^1\text{H-NMR}$ (CDCl_3) δ : 1.05 (3H, t, $J = 7.1\text{Hz}$), 1.64–2.03 (6H, m), 2.23 (3H, s), 2.44–2.56 (2H, m), 3.45–3.68 (6H, m), 3.98–4.08 (2H, m), 6.68–6.85 (2H, m), 7.18–7.25 (2H, m), 7.41 (1H, d, $J = 8.8\text{Hz}$), 7.52 (1H, d, $J = 1.4\text{Hz}$)。

[4411] 实施例 658

[4412] [式 974]

[4413]

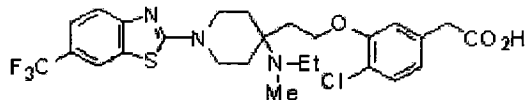


[4414] $^1\text{H-NMR}(\text{CDCl}_3)$ δ :1.08 (3H, t, $J = 7.1\text{Hz}$), 1.64–2.06 (6H, m), 2.26 (3H, s), 2.52 (2H, q, $J = 7.1\text{Hz}$), 3.56 (2H, s), 3.60–3.80 (4H, m), 4.00 (2H, t, $J = 6.7\text{Hz}$), 6.68–6.89 (3H, m), 7.49–7.58 (2H, m), 7.83 (1H, s)。

[4415] 实施例 659

[4416] [式 975]

[4417]

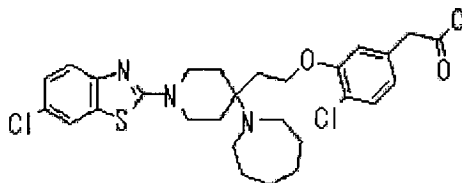


[4418] $^1\text{H-NMR}(\text{CDCl}_3)$ δ :1.07 (3H, t, $J = 6.9\text{Hz}$), 1.70–2.07 (6H, m), 2.25 (3H, s), 2.52 (2H, q, $J = 6.9\text{Hz}$), 3.53 (2H, s), 3.59–3.76 (5H, m), 4.03–4.10 (2H, m), 6.74–6.84 (2H, m), 7.23–7.28 (1H, m), 7.47–7.57 (2H, m), 7.82 (1H, s)。

[4419] 实施例 660

[4420] [式 976]

[4421]

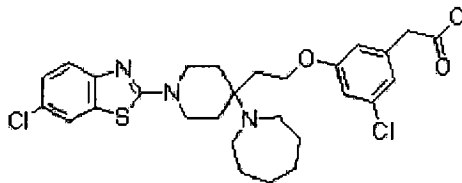


[4422] $^1\text{H-NMR}(\text{CDCl}_3)$ δ :7.54 (1.0H, d, $J = 1.92\text{Hz}$), 7.42 (1.0H, d, $J = 8.79\text{Hz}$), 7.31–7.29 (1.0H, m), 7.24–7.21 (1.0H, m), 6.85–6.79 (2.0H, m), 4.09 (2.0H, dd, $J = 7.14, 7.14\text{Hz}$), 3.78–3.58 (6.0H, m), 2.79–2.73 (4.0H, br m), 2.10–1.52 (14.0H, m)。

[4423] 实施例 661

[4424] [式 977]

[4425]

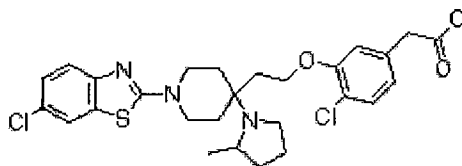


[4426] $^1\text{H-NMR}(\text{CDCl}_3)$ δ :7.54 (1.0H, d, $J = 2.20\text{Hz}$), 7.43 (1.0H, d, $J = 8.24\text{Hz}$), 7.25–7.20 (1.0H, m), 6.87 (1.0H, s), 6.78 (1.0H, s), 6.70 (1.0H, s), 3.99 (2.0H, dd, $J = 7.00, 7.00\text{Hz}$), 3.77–3.56 (6.0H, m), 2.76–2.72 (4.0H, m), 2.13–1.91 (10.0H, m), 1.73–1.56 (4.0H, m)。

[4427] 实施例 662

[4428] [式 978]

[4429]

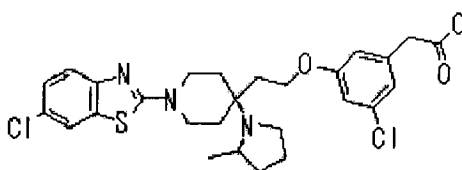


[4430] $^1\text{H-NMR}(\text{CDCl}_3)$ δ :7.53(1.0H, d, $J = 1.92\text{Hz}$), 7.41(1.0H, d, $J = 8.79\text{Hz}$), 7.26-7.20(2.0H, m), 6.86(1.0H, s), 6.76(1.0H, d, $J = 8.52\text{Hz}$), 4.17-4.10(2.0H, m), 3.92-3.84(1.0H, m), 3.81-3.40(4.0H, m), 3.33-3.24(2.0H, m), 2.97-2.89(1.0H, m), 2.76-2.66(1.0H, m), 2.19-1.61(8.0H, m), 1.54-1.42(2.0H, m), 1.04(3.0H, d, $J = 6.30\text{Hz}$)。

[4431] 实施例 663

[4432] [式 979]

[4433]

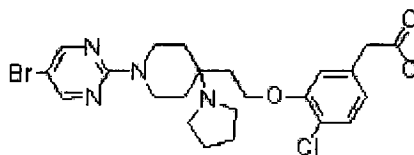


[4434] MS(ESI) m/z 548 $[\text{M}+\text{H}]^+$

[4435] 实施例 664

[4436] [式 980]

[4437]

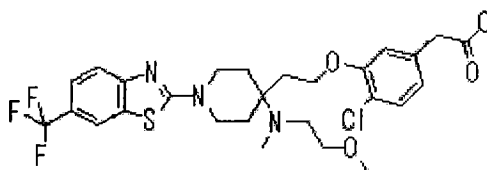


[4438] MS(ESI) m/z 525 $[\text{M}+\text{H}]^+$

[4439] 实施例 665

[4440] [式 981]

[4441]

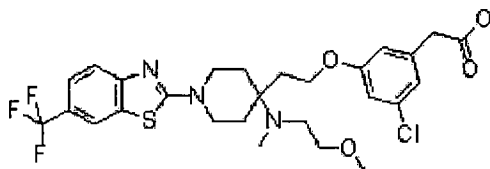


[4442] $^1\text{H-NMR}(\text{CDCl}_3)$ δ :7.83(1.0H, d, $J = 1.24\text{Hz}$), 7.55(1.0H, d, $J = 8.51\text{Hz}$), 7.50(1.0H, dd, $J = 8.78, 1.24\text{Hz}$), 7.30(1.0H, d, $J = 8.10\text{Hz}$), 6.85(1.0H, d, $J = 1.78\text{Hz}$), 6.80(1.0H, dd, $J = 8.10, 1.78\text{Hz}$), 4.15-4.10(2.0H, m), 3.79-3.61(6.0H, m), 3.47(2.0H, t, $J = 6.45\text{Hz}$), 3.36(3.0H, s), 2.71(4.0H, t, $J = 6.45\text{Hz}$), 2.07-1.98(4.0H, m), 1.82-1.71(2.0H, m)。

[4443] 实施例 666

[4444] [式 982]

[4445]



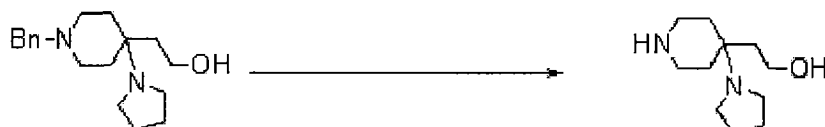
[4446] $^1\text{H-NMR}$ (CDCl₃) δ : 7.83 (1.0H, d, $J = 0.89\text{Hz}$), 7.56 (1.0H, d, $J = 8.85\text{Hz}$), 7.51 (1.0H, dd, $J = 8.85, 0.89\text{Hz}$), 6.88-6.87 (1.0H, m), 6.79 (1.0H, dd, $J = 1.92, 0.96\text{Hz}$), 6.71-6.69 (1.0H, m), 4.02 (2.0H, t, $J = 6.31\text{Hz}$), 3.79-3.63 (4.0H, m), 3.57 (2.0H, s), 3.46 (2.0H, t, $J = 6.24\text{Hz}$), 3.35 (3.0H, s), 2.68 (3.0H, t, $J = 6.24\text{Hz}$), 2.31 (3.0H, s), 2.07-1.91 (4.0H, m), 1.77-1.64 (2.0H, m)。

[4447] 参考例 254

[4448] 2-(4-吡咯烷-1-基哌啶-4-基)乙醇的制备

[4449] [式 983]

[4450]



[4451] 将 2-(1-苯甲基-4-吡咯烷-1-基哌啶-4-基)乙醇 (9.28g), 10% Pd/C (1.86g) 和甲醇 (100mL) 的混合物在氢气 (4atm) 下搅拌 3 天。过滤不溶性物质并将滤液浓缩, 得到标题化合物 (6.30g)。收率: 99%。

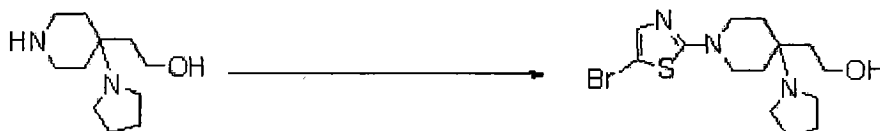
[4452] $^1\text{H-NMR}$ (DMSO- d_6) δ : 1.76-1.79 (6H, m), 1.88-1.91 (4H, m), 2.77-2.80 (4H, m), 3.02-3.05 (2H, br m), 3.15-3.18 (2H, br m), 3.53-3.55 (2H, br m)。

[4453] 参考例 255

[4454] 2-[1-(5-溴噻唑-2-基)-4-吡咯烷-1-基哌啶-4-基]乙醇的制备

[4455] [式 984]

[4456]



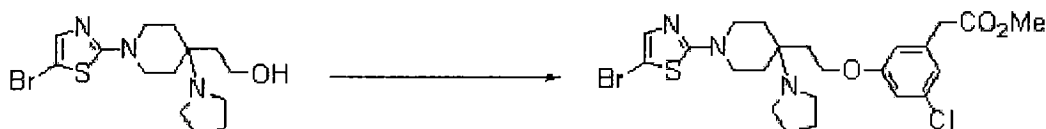
[4457] 将 2-(4-吡咯烷-1-基哌啶-4-基)乙醇 (4.11g), 2,5-二溴噻唑 (5.03g), 碳酸钾 (3.43g) 和二甲基甲酰胺 (75mL) 的混合物在 60℃ 搅拌 16 小时。向反应溶液加入水并且用乙酸乙酯萃取。有机层用水和盐水洗涤, 并用硫酸镁干燥。减压蒸发溶剂, 并将残余物通过硅胶柱色谱法纯化, 得到标题化合物 (3.88g)。收率: 52%。

[4458] 实施例 667

[4459] [3-[2-[1-(5-溴噻唑-2-基)-4-吡咯烷-1-基哌啶-4-基]乙氧基]-5-氯苯基]乙酸甲基酯的制备

[4460] [式 985]

[4461]



[4462] 将 2-[1-(5-溴噻唑-2-基)-4-吡咯烷-1-基哌啶-4-基]乙醇 (1.30g), (3-氯-5-羟基苯基)乙酸 (796mg), 三正丁基膦 (0.99mL), 1,1'-(偶氮二羰基)二哌啶 (1.00g) 和四氢呋喃 (20mL) 的混合物在室温搅拌 4 小时。向反应溶液加入水并且用乙酸乙酯萃取。有机层用水和盐水洗涤, 并且用硫酸镁干燥。减压蒸发溶剂, 并将残余物通过硅胶柱色谱法纯化, 得到标题化合物 (1.45g)。收率: 74%。

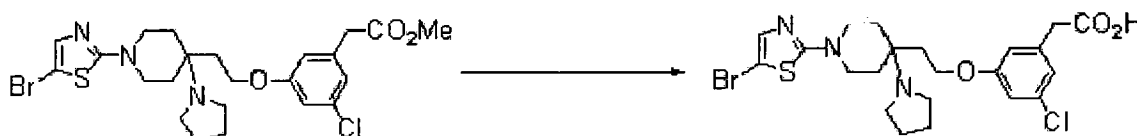
[4463] $^1\text{H-NMR}(\text{CDCl}_3)$ δ : 1.71-1.85 (8H, m), 2.09-2.10 (2H, m), 2.69-2.71 (4H, br m), 3.48-3.53 (4H, m), 3.61 (2H, s), 3.71 (3H, s), 4.12-4.16 (2H, m), 6.83 (2H, dd, $J = 8.0$, 2.2Hz), 7.07 (1H, d, $J = 2.2\text{Hz}$), 7.31 (1H, d, $J = 8.0\text{Hz}$)。

[4464] 实施例 668

[4465] [3-[2-[1-(5-溴噻唑-2-基)-4-吡咯烷-1-基哌啶-4-基]乙氧基]-5-氯苯基]乙酸的制备

[4466] [式 986]

[4467]



[4468] 将 [3-[2-[1-(5-溴噻唑-2-基)-4-吡咯烷-1-基哌啶-4-基]乙氧基]-5-氯苯基]乙酸甲基酯 (1.45g), 2N 氢氧化钠 (3.3mL), 四氢呋喃 (15mL) 和甲醇 (15mL) 的混合物在室温搅拌 3 小时。向反应溶液加入水并用氯仿洗涤。水层用 2N 盐酸中和并且用氯仿萃取。有机层用水和盐水洗涤, 并且用硫酸镁干燥。减压蒸发溶剂, 并将残余物通过硅胶柱色谱法纯化, 得到标题化合物 (916mg)。收率: 65%。

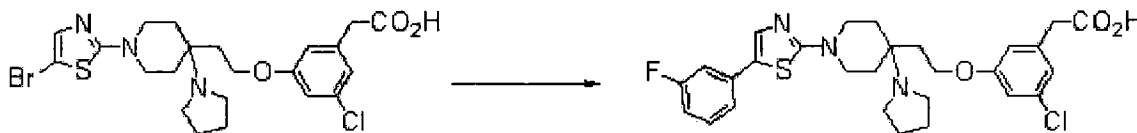
[4469] $^1\text{H-NMR}(\text{DMSO-d}_6)$ δ : 1.75-1.89 (10H, m), 2.64-2.67 (4H, m), 3.33-3.36 (2H, m), 3.34 (2H, s), 3.51-3.55 (2H, m), 4.11-4.14 (2H, m), 6.85 (1H, dd, $J = 7.8$, 2.1Hz), 7.10 (1H, d, $J = 2.1\text{Hz}$), 7.19 (1H, s), 7.34 (1H, d, $J = 7.8\text{Hz}$)。

[4470] 实施例 669

[4471] [3-氯-5-[2-[1-[5-(3-氟苯基)噻唑-2-基]-4-吡咯烷-1-基哌啶-4-基]乙氧基]苯基]乙酸的制备

[4472] [式 987]

[4473]



[4474] 使用微波反应器使 [3-[2-[1-(5-溴噻唑-2-基)-4-吡咯烷-1-基哌啶-4-基]乙氧基]-5-氯苯基]乙酸 (60mg), 3-氟苯基硼酸 (32mg), 四(三苯膦)合钯 (13mg), 1M 碳酸钠 (0.55mL) 和二甲基甲酰胺 (1mL) 的混合物在 180°C 反应 5 分钟。过滤不溶性物质。向滤液加入甲酸。减压蒸发溶剂并将残余物通过高效液相色谱法纯化, 得到标题化合物 (14.4mg)。收率: 24%。

[4475] $^1\text{H-NMR}(\text{DMSO-d}_6)$ δ : 8.18 (1H, s), 7.69 (1H, s), 7.39-7.26 (3H, m), 7.01 (1H, m), 6.90 (1H, d, $J = 10.8\text{Hz}$), 6.82 (1H, s), 4.53 (2H, m), 3.58-3.54 (4H, m), 2.64 (2H, s),

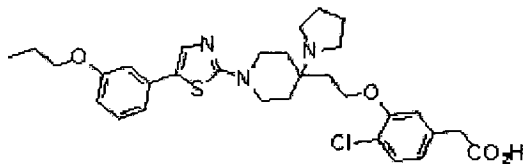
1. 94-1. 69 (8H, m)。

[4476] 通过与如上相似的方法得到以下化合物。

[4477] 实施例 670

[4478] [式 988]

[4479]

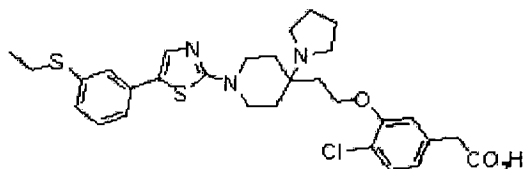


[4480] MS (ESI) m/z 584 [M+]

[4481] 实施例 671

[4482] [式 989]

[4483]

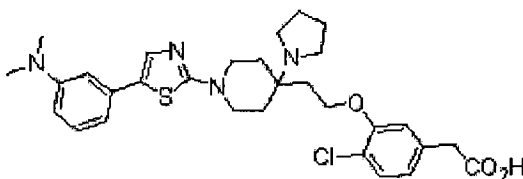


[4484] MS (ESI) m/z 586 [M+]

[4485] 实施例 672

[4486] [式 990]

[4487]

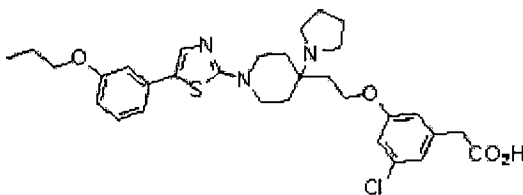


[4488] MS (ESI) m/z 569 [M+]

[4489] 实施例 673

[4490] [式 991]

[4491]

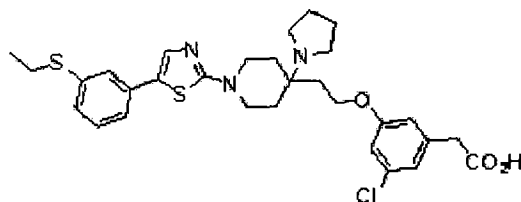


[4492] MS (ESI) m/z 584 [M+]

[4493] 实施例 674

[4494] [式 992]

[4495]

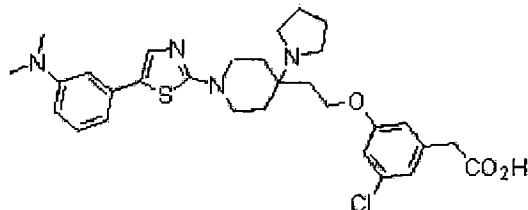


[4496] MS(ESI) m/z 586 [M+]

[4497] 实施例 675

[4498] [式 993]

[4499]

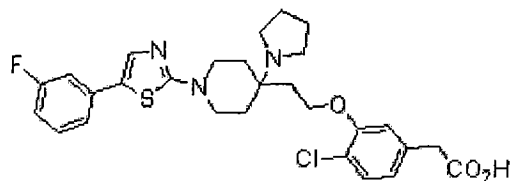


[4500] MS(ESI) m/z 569 [M+]

[4501] 实施例 676

[4502] [式 994]

[4503]

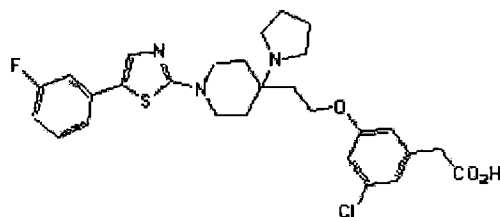


[4504] MS(ESI) m/z 546 [M+H]⁺

[4505] 实施例 677

[4506] [式 995]

[4507]

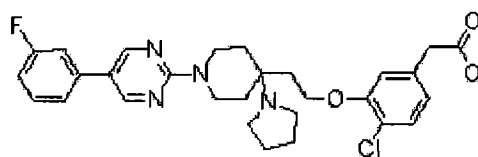


[4508] ¹H-NMR(DMSO- d_6) δ : 8.18(1H, s), 7.69(1H, s), 7.39-7.26(3H, m), 7.01(1H, m), 6.90(1H, d, $J = 10.8$ Hz), 6.82(1H, s), 4.53(2H, m), 3.58-3.54(4H, m), 2.64(2H, s), 1.94-1.69(8H, m)。

[4509] 实施例 678

[4510] [式 996]

[4511]

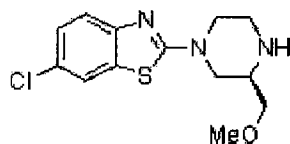


[4512] MS(ESI)m/z 540 [M+H]⁺

[4513] 参考例 256

[4514] [式 997]

[4515]

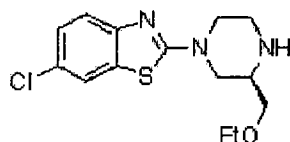


[4516] ¹H-NMR(CDC13) δ 2.93-3.18(4H, m), 3.29(1H, td, J = 12.0, 3.2Hz), 3.35-3.42(1H, m), 3.39(3H, s), 3.48(1H, dd, J = 9.2, 3.6Hz), 3.91(1H, d, J = 12.0Hz), 3.99(1H, d, J = 12.0Hz), 7.24(1H, dd, J = 8.8, 2.4Hz), 7.44(1H, d, J = 8.8Hz), 7.56(1H, d, J = 2.4Hz)。

[4517] 参考例 257

[4518] [式 998]

[4519]

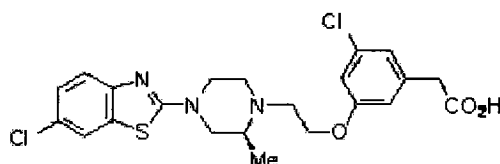


[4520] ¹H-NMR(CDC13) δ 1.22(3H, t, J = 7.2Hz), 2.92-3.02(2H, m), 3.04-3.11(1H, m), 3.12-3.17(1H, m), 3.26(1H, td, J = 12.0, 3.2Hz), 3.39(1H, dd, J = 9.2, 7.2Hz), 3.48-3.59(3H, m), 3.91(1H, brd, J = 12.0Hz), 3.98(1H, brd, J = 12.0Hz), 7.24(1H, dd, J = 8.8, 2.0Hz), 7.44(1H, d, J = 8.8Hz), 7.56(1H, d, J = 2.0Hz)。

[4521] 实施例 679

[4522] [式 999]

[4523]

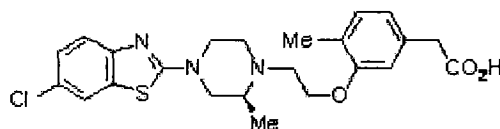


[4524] TLC Rf 0.13(MeOH-CHCl3, 1 : 10)

[4525] 实施例 680

[4526] [式 1000]

[4527]

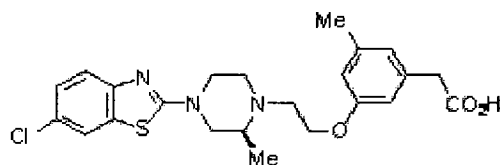


[4528] mp 109-112

[4529] 实施例 681

[4530] [式 1001]

[4531]

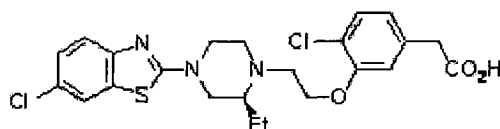


[4532] mp 92-98

[4533] 实施例 682

[4534] [式 1002]

[4535]

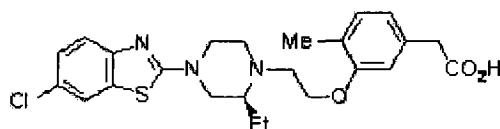


[4536] TLC Rf 0.15 (MeOH-CHCl₃, 1 : 10)

[4537] 实施例 683

[4538] [式 1003]

[4539]

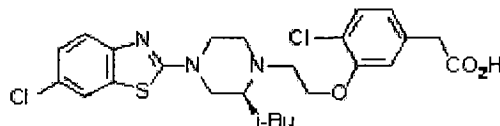


[4540] TLC Rf 0.23 (MeOH-CHCl₃, 1 : 10)

[4541] 实施例 684

[4542] [式 1004]

[4543]

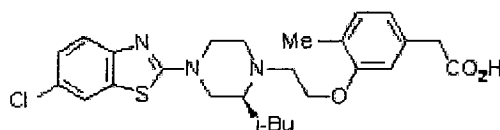


[4544] Rf 0.12 (MeOH-CHCl₃, 1 : 10)

[4545] 实施例 685

[4546] [式 1005]

[4547]

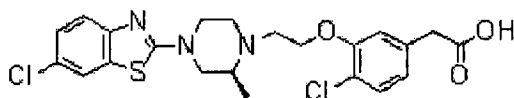


[4548] Rf 0.24 (MeOH-CHCl₃, 1 : 10)

[4549] 实施例 686

[4550] [式 1006]

[4551]

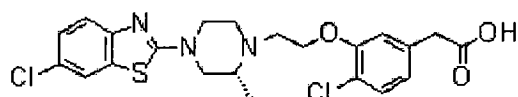


[4552] MS (ESI) m/z 480 [M+H]⁺

[4553] 实施例 687

[4554] [式 1007]

[4555]



[4556] MS (ESI) m/z 480 $[M+H]^+$

[4557] 实施例 688

[4558] [式 1008]

[4559]

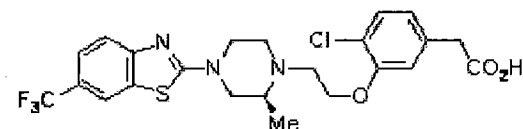


[4560] MS (ESI) m/z 479 $[M+H]^+$

[4561] 实施例 689

[4562] [式 1009]

[4563]

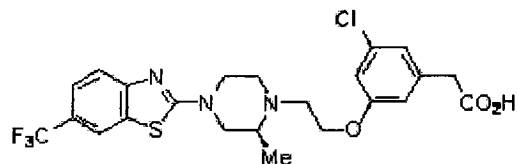


[4564] MS (ESI) m/z 514, 516 $[M+H]^+$

[4565] 实施例 690

[4566] [式 1010]

[4567]

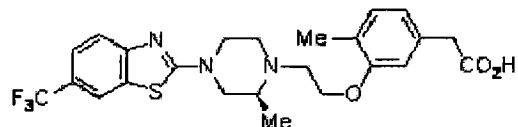


[4568] MS (ESI) m/z 514, 516 $[M+H]^+$

[4569] 实施例 691

[4570] [式 1011]

[4571]

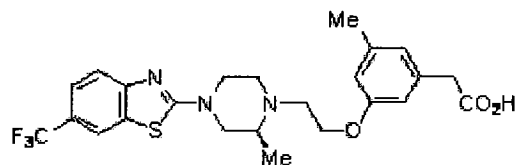


[4572] MS (ESI) m/z 494 $[M+H]^+$

[4573] 实施例 692

[4574] [式 1012]

[4575]

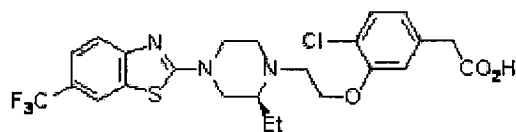


[4576] MS (ESI) m/z 494 $[M+H]^+$

[4577] 实施例 693

[4578] [式 1013]

[4579]

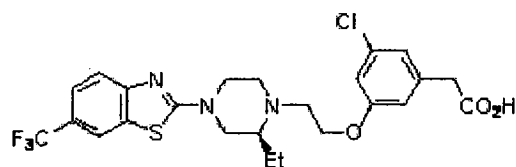


[4580] MS (ESI) m/z 528, 530 $[M+H]^+$

[4581] 实施例 694

[4582] [式 1014]

[4583]

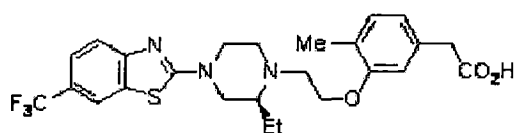


[4584] MS (ESI) m/z 528, 530 $[M+H]^+$

[4585] 实施例 695

[4586] [式 1015]

[4587]

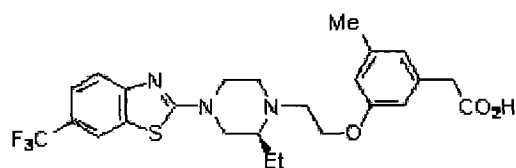


[4588] MS (ESI) m/z 508 $[M+H]^+$

[4589] 实施例 696

[4590] [式 1016]

[4591]



[4592] MS (ESI) m/z 508 $[M+H]^+$

[4593] 实施例 697

[4594] [式 1017]

[4595]



[4596] MS (ESI) m/z 480 $[M+H]^+$

[4597] 实施例 698

[4598] [式 1018]

[4599]

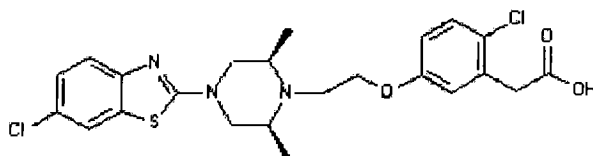


[4600] $^1\text{H-NMR}$ (300MHz, CDCl_3) : 1.46 (3H, d, $J = 6.9\text{Hz}$), 2.53-2.60 (1H, m), 2.73-2.77 (1H, m), 3.06 (2H, s), 3.16-3.20 (1H, m), 3.27-3.31 (1H, m), 3.55-3.60 (1H, m), 3.60 (2H, s), 3.89-3.94 (1H, m), 4.29 (3H, m), 6.84 (1H, d, $J = 8.1\text{Hz}$), 6.87 (1H, s), 7.25 (1H, dd, $J = 8.7\text{Hz}$, 2.1Hz), 7.31 (1H, d, $J = 8.1\text{Hz}$), 7.44 (1H, d, $J = 8.7\text{Hz}$), 7.56 (1H, d, $J = 2.1\text{Hz}$)。

[4601] 实施例 699

[4602] [式 1019]

[4603]

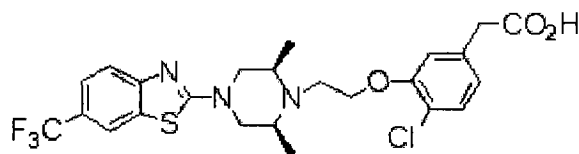


[4604] MS (ESI) m/z 494 $[\text{M}+\text{H}]^+$

[4605] 实施例 700

[4606] [式 1020]

[4607]

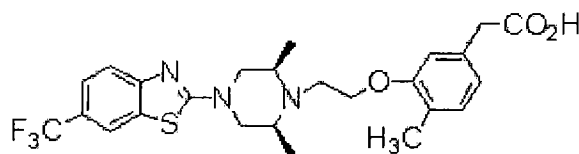


[4608] MS (ESI) m/z 528 $[\text{M}+\text{H}]^+$

[4609] 实施例 701

[4610] [式 1021]

[4611]

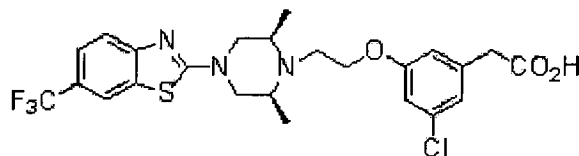


[4612] MS (ESI) m/z 508 $[\text{M}+\text{H}]^+$

[4613] 实施例 702

[4614] [式 1022]

[4615]

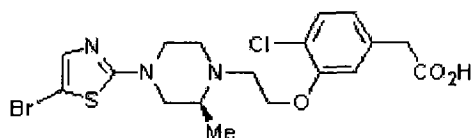


[4616] MS (ESI) m/z 528 $[\text{M}+\text{H}]^+$

[4617] 实施例 703

[4618] [式 1023]

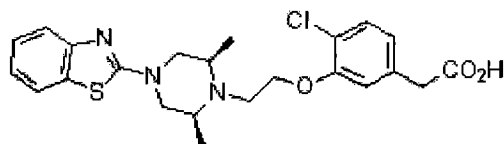
[4619]

[4620] MS(ESI)m/z 474, 476, 478 [M+H]⁺

[4621] 实施例 704

[4622] [式 1024]

[4623]

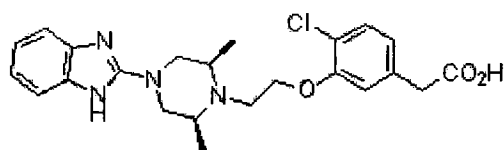


[4624] ¹H-NMR(DMSO-d₆) δ : 1.18 (6H, d, J = 4.7Hz), 2.80-2.95 (4H, m), 3.10-3.19 (2H, m), 3.55 (2H, s), 3.85 (2H, d, J = 9.9Hz), 4.03-4.11 (2H, m), 6.83 (1H, d, J = 8.2Hz), 7.02-7.11 (2H, m), 7.22-7.48 (3H, m), 7.75 (1H, d, J = 8.0Hz)。

[4625] 实施例 705

[4626] [式 1025]

[4627]

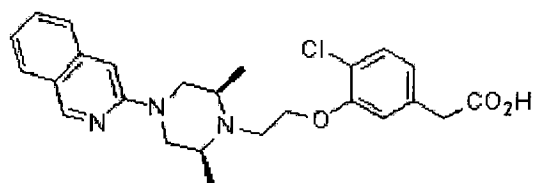


[4628] ¹H-NMR(DMSO-d₆) δ : 1.16 (6H, d, J = 5.8Hz), 2.61-2.85 (5H, m), 3.07-3.16 (3H, m), 3.55 (2H, s), 3.89-4.11 (5H, m), 6.79-7.36 (8H, m)。

[4629] 实施例 706

[4630] [式 1026]

[4631]

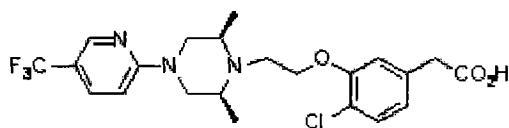


[4632] ¹H-NMR(DMSO-d₆) δ : 1.22 (6H, d, J = 6.0Hz), 2.58-2.84 (4H, m), 3.09-3.19 (2H, m), 3.52 (2H, s), 4.06-4.14 (2H, m), 4.34-4.46 (2H, m), 6.84 (1H, d, J = 8.2Hz), 7.09-7.74 (7H, m), 8.03 (1H, d, J = 9.1Hz)。

[4633] 实施例 707

[4634] [式 1027]

[4635]



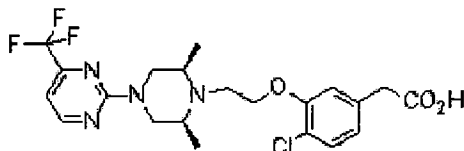
[4636] ¹H-NMR(丙酮) δ : 8.38-8.35 (1.0H, m), 7.71 (1.0H, dd, J = 9.34, 2.20Hz),

7.31 (1.0H, dd, $J = 7.97, 1.65\text{Hz}$), 7.13 (1.0H, d, $J = 1.92\text{Hz}$), 6.97-6.87 (2.0H, m), 4.33 (2.0H, d, $J = 12.64\text{Hz}$), 4.17 (2.0H, dd, $J = 5.91, 5.91\text{Hz}$), 3.61 (2.0H, s), 3.25-3.23 (2.0H, m), 2.83-2.67 (4.0H, m), 1.24 (6.0H, d, $J = 6.00\text{Hz}$)。

[4637] 实施例 708

[4638] [式 1028]

[4639]

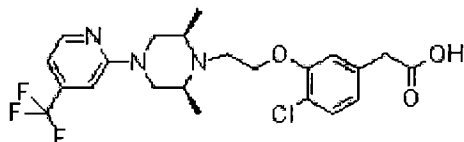


[4640] $^1\text{H-NMR}$ (DMSO- d_6) δ : 8.66 (1.0H, d, $J = 4.94\text{Hz}$), 7.31 (1.0H, d, $J = 8.10\text{Hz}$), 7.08 (1.0H, s), 6.99 (1.0H, d, $J = 4.94\text{Hz}$), 6.82 (1.0H, d, $J = 8.10\text{Hz}$), 4.45 (2.0H, d, $J = 8.24\text{Hz}$), 4.08-3.99 (3.0H, m), 3.53 (2.0H, s), 3.13 (2.0H, dd, $J = 5.63, 5.63\text{Hz}$), 2.76-2.65 (4.0H, m), 1.16 (6.0H, d, $J = 6.32\text{Hz}$)。

[4641] 实施例 709

[4642] [式 1029]

[4643]

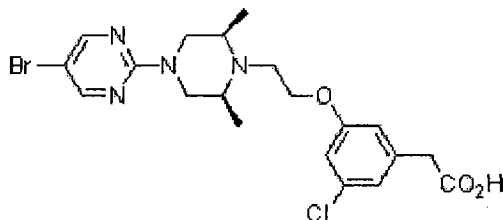


[4644] $^1\text{H-NMR}$ (丙酮) δ : 8.14 (1.0H, d, $J = 2.54\text{Hz}$), 7.60 (1.0H, dd, $J = 9.13, 2.54\text{Hz}$), 7.40 (1.0H, s), 7.34 (1.0H, d, $J = 7.69\text{Hz}$), 7.25 (1.0H, dd, $J = 7.69, 7.69\text{Hz}$), 7.15 (1.0H, d, $J = 7.69\text{Hz}$), 6.81 (1.0H, d, $J = 9.13\text{Hz}$), 4.13 (2.0H, d, $J = 11.54\text{Hz}$), 3.81 (2.0H, s), 3.62 (2.0H, s), 2.76-2.62 (4.0H, m), 1.07 (6.0H, d, $J = 5.77\text{Hz}$)。

[4645] 实施例 710

[4646] [式 1030]

[4647]

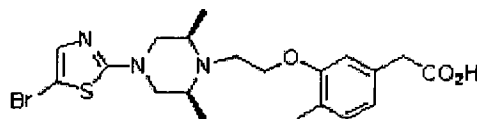


[4648] $^1\text{H-NMR}$ (DMSO- d_6) δ : 1.14 (6H, d, $J = 5.1\text{Hz}$), 2.60-2.76 (2H, m), 3.00-3.10 (2H, m), 3.55 (2H, s), 3.97-4.06 (2H, m), 4.46-4.60 (2H, m), 6.80-6.96 (3H, m), 7.30-7.67 (3H, m), 8.69 (2H, s)。

[4649] 实施例 711

[4650] [式 1031]

[4651]

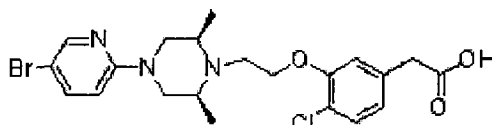


[4652] $^1\text{H-NMR}$ (DMSO- d_6) δ : 7.18-7.18 (1.0H, m), 7.04 (1.0H, d, $J = 7.28\text{Hz}$), 6.84 (1.0H, s), 6.71 (1.0H, d, $J = 7.28\text{Hz}$), 3.98 (2.0H, dd, $J = 5.10, 5.10\text{Hz}$), 3.64 (2.0H, d, $J = 10.99\text{Hz}$), 3.48 (2.0H, s), 3.10 (2.0H, dd, $J = 5.10, 5.10\text{Hz}$), 2.84-2.69 (4.0H, m), 2.11 (3.0H, s), 1.14 (6.0H, d, $J = 5.77\text{Hz}$)。

[4653] 实施例 712

[4654] [式 1032]

[4655]

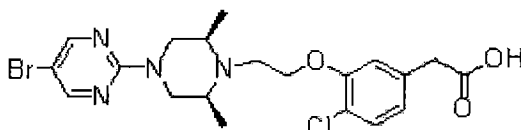


[4656] $^1\text{H-NMR}$ (丙酮) δ : 8.12 (1.0H, d, $J = 2.68\text{Hz}$), 7.59 (1.0H, dd, $J = 9.13, 2.68\text{Hz}$), 7.32 (1.0H, d, $J = 8.11\text{Hz}$), 7.13 (1.0H, d, $J = 1.92\text{Hz}$), 6.90 (1.0H, dd, $J = 8.11, 1.92\text{Hz}$), 6.80 (1.0H, d, $J = 9.13\text{Hz}$), 4.18-4.13 (4.0H, m), 3.63 (2.0H, s), 3.22 (2.0H, dd, $J = 6.04, 6.04\text{Hz}$), 2.85-2.78 (2.0H, m), 2.62-2.53 (2.0H, m), 1.23 (6.0H, d, $J = 6.04\text{Hz}$)。

[4657] 实施例 713

[4658] [式 1033]

[4659]

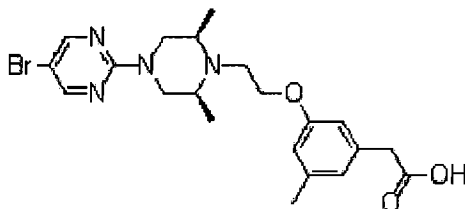


[4660] $^1\text{H-NMR}$ (丙酮) δ : 8.34 (2.0H, s), 7.30 (1.0H, d, $J = 8.04\text{Hz}$), 7.13 (1.0H, d, $J = 1.65\text{Hz}$), 6.90 (1.0H, dd, $J = 8.04, 1.65\text{Hz}$), 4.49 (2.0H, d, $J = 12.36\text{Hz}$), 4.15 (2.0H, dd, $J = 5.91, 5.91\text{Hz}$), 3.60 (2.0H, s), 3.23 (2.0H, dd, $J = 6.04, 6.04\text{Hz}$), 2.82-2.60 (4.0H, m), 1.22 (6.0H, d, $J = 6.04\text{Hz}$)。

[4661] 实施例 714

[4662] [式 1034]

[4663]

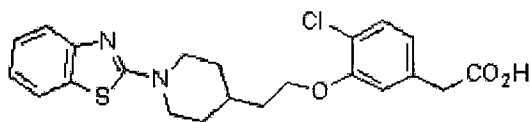


[4664] $^1\text{H-NMR}$ (DMSO- d_6) δ : 8.44 (2.0H, s), 6.61 (3.0H, s), 4.43-4.33 (2.0H, m), 3.95 (2.0H, dd, $J = 6.59, 6.59\text{Hz}$), 3.43 (2.0H, s), 3.03 (2.0H, dd, $J = 6.00, 6.00\text{Hz}$), 2.63 (4.0H, d, $J = 6.90\text{Hz}$), 2.23 (3.0H, s), 1.12 (6.0H, d, $J = 5.22\text{Hz}$)。

[4665] 实施例 715

[4666] [式 1035]

[4667]

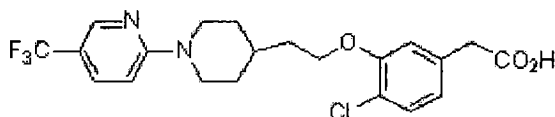


[4668] $^1\text{H-NMR}$ (DMSO-d_6) δ : 1.23–1.41 (2H, m), 1.70–1.92 (5H, m), 3.09–3.23 (2H, m), 3.57 (2H, s), 3.98–4.15 (4H, m), 6.81–7.46 (6H, m), 7.74 (1H, d, $J = 8.0\text{Hz}$).

[4669] 实施例 716

[4670] [式 1036]

[4671]

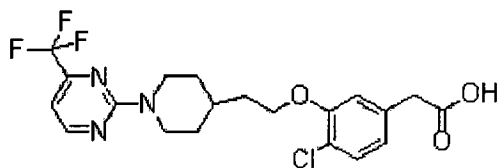


[4672] $^1\text{H-NMR}$ (丙酮) δ : 8.37 (1.0H, s), 7.71 (1.0H, dd, $J = 9.06, 2.47\text{Hz}$), 7.33 (1.0H, d, $J = 7.97\text{Hz}$), 7.12 (1.0H, d, $J = 1.65\text{Hz}$), 6.93–6.89 (2.0H, m), 4.55–4.50 (2.0H, m), 4.19 (2.0H, dd, $J = 6.32, 6.32\text{Hz}$), 3.62 (2.0H, s), 2.96–2.92 (3.0H, m), 1.96–1.79 (4.0H, m), 1.37–1.24 (2.0H, m)。

[4673] 实施例 717

[4674] [式 1037]

[4675]

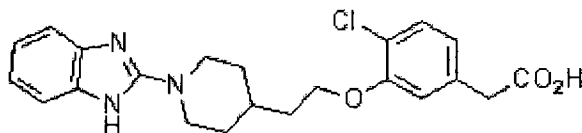


[4676] $^1\text{H-NMR}$ (DMSO-d_6) δ : 8.65 (1.0H, d, $J = 4.67\text{Hz}$), 7.33 (1.0H, d, $J = 8.11\text{Hz}$), 7.08 (1.0H, s), 6.95 (1.0H, d, $J = 4.67\text{Hz}$), 6.83 (1.0H, d, $J = 8.11\text{Hz}$), 4.64 (2.0H, d, $J = 12.42\text{Hz}$), 4.10 (2.0H, dd, $J = 6.59, 6.59\text{Hz}$), 3.55 (2.0H, s), 3.40–3.25 (1.0H, m), 2.96 (2.0H, dd, $J = 12.42, 12.42\text{Hz}$), 1.91–1.72 (4.0H, m), 1.24–1.15 (2.0H, m)。

[4677] 实施例 718

[4678] [式 1038]

[4679]

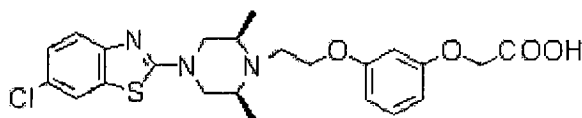


[4680] $^1\text{H-NMR}$ (DMSO-d_6) δ : 1.13–1.36 (2H, m), 1.67–1.87 (5H, m), 2.86–3.00 (2H, m), 3.56 (2H, s), 4.05–4.16 (5H, m), 6.80–7.36 (7H, m)。

[4681] 实施例 719

[4682] [式 1039]

[4683]

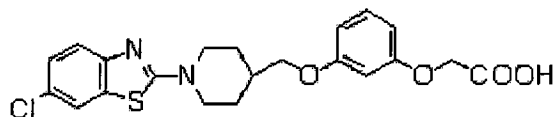


[4684] ¹H-NMR (300MHz, CDC13) :1.40 (6H, m), 3.27-3.44 (6H, m), 3.93-3.98 (2H, m), 4.14 (2H, m), 4.53 (2H, s), 6.47-6.55 (3H, m), 7.13-7.26 (2H, m), 7.43 (1H, d, J = 8.1Hz), 7.55 (1H, s)。

[4685] 实施例 720

[4686] [式 1040]

[4687]

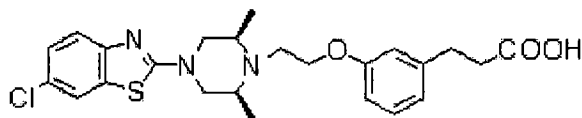


[4688] $^1\text{H-NMR}$ (300MHz, CDCl_3) : 1.98–2.17 (5H, m), 3.21–3.29 (2H, m), 3.84 (2H, d, $J = 6.0\text{Hz}$), 4.23 (2H, m), 4.65 (2H, s), 6.49–6.56 (3H, m), 7.20 (1H, t, $J = 8.1\text{Hz}$), 7.26–7.29 (2H, m), 7.55 (1H, d, $J = 2.1\text{Hz}$)。

[4689] 实施例 721

[4690] [式 1041]

[4691]

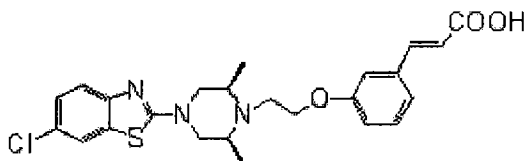


[4692] $^1\text{H-NMR}$ (300MHz, CDCl_3) : 1.28 (6H, m), 2.64 (2H, t, $J = 7.5\text{Hz}$), 2.91 (2H, t, $J = 7.5\text{Hz}$), 2.99 (4H, m), 3.24 (2H, m), 3.87-3.91 (2H, m), 4.05 (2H, m), 6.70-6.73 (2H, m), 6.80 (1H, d, $J = 7.5\text{Hz}$), 7.19 (1H, t, $J = 7.5\text{Hz}$), 7.22-7.25 (1H, m), 7.43 (1H, d, $J = 8.4\text{Hz}$), 7.54 (1H, d, $J = 2.1\text{Hz}$)。

[4693] 实施例 722

[4694] [式 1042]

[4695]

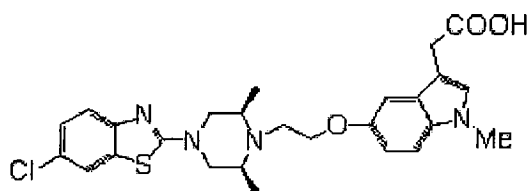


[4696] ¹H-NMR (300MHz, CDC13) :1. 27 (6H, m), 2. 99 (4H, m), 3. 23 (2H, m), 3. 89–3. 93 (2H, m), 4. 09 (2H, m), 6. 43 (1H, d, J = 15. 9Hz), 6. 92 (1H, dd, J = 8. 1Hz, 2. 1Hz), 7. 04 (1H, s), 7. 14 (1H, d, J = 8. 1Hz), 7. 24 (1H, dd, J = 8. 7Hz, 2. 1Hz), 7. 31 (1H, t, J = 8, 1Hz), 7. 44 (1H, d, J = 8. 7Hz), 7. 56 (1H, d, J = 2. 1Hz), 7. 71 (1H, d, J = 15. 9Hz)。

[4697] 实施例 723

[4698] [式 1043]

[4699]

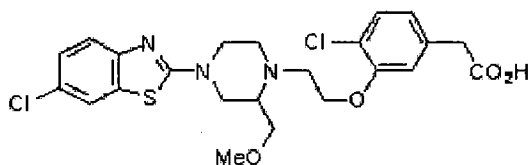


[4700] $^1\text{H-NMR}$ (300MHz, CDCl_3) : 1.35 (6H, m), 2.53 (4H, m), 3.15 (2H, m), 3.71 (3H, s), 3.90–3.94 (2H, m), 4.14 (2H, m), 6.81 (1H, dd, $J = 8.7\text{Hz}, 2.1\text{Hz}$), 7.01–7.02 (2H, m), 7.14 (1H, d, $J = 8.7\text{Hz}$), 7.24 (1H, dd, $J = 8.7\text{Hz}$), 7.44 (1H, d, $J = 8.7\text{Hz}$), 7.54 (1H, d, $J = 2.1\text{Hz}$)。

[4701] 实施例 724

[4702] [式 1044]

[4703]

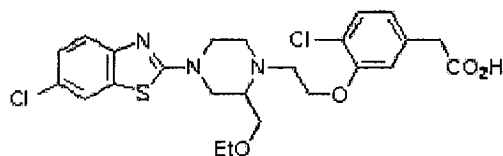


[4704] TLC Rf 0.13 (MeOH-CHCl_3 , 1 : 10)

[4705] 实施例 725

[4706] [式 1045]

[4707]

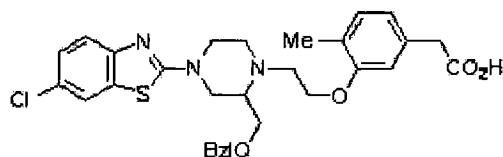


[4708] TLC Rf 0.20 (MeOH-CHCl_3 , 1 : 10)

[4709] 实施例 726

[4710] [式 1046]

[4711]

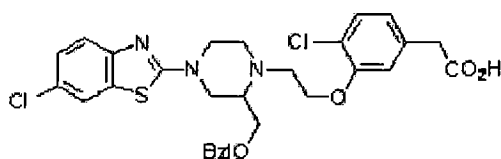


[4712] TLC Rf 0.30 (MeOH-CHCl_3 , 1 : 10)

[4713] 实施例 727

[4714] [式 1047]

[4715]

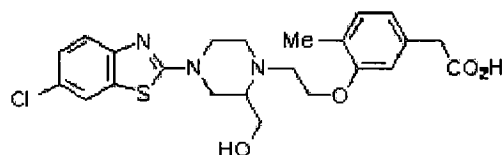


[4716] TLC Rf 0.31 (MeOH-CHCl_3 , 1 : 10)

[4717] 实施例 728

[4718] [式 1048]

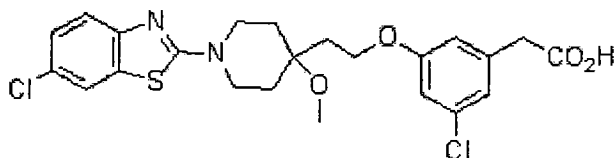
[4719]

[4720] TLC Rf 0.23 (MeOH-CHCl₃, 1 : 5)

[4721] 实施例 729

[4722] [式 1049]

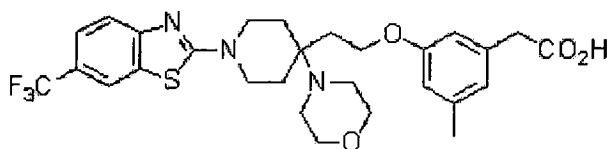
[4723]

[4724] MS (ESI) m/z 495 [M+H]⁺

[4725] 实施例 730

[4726] [式 1050]

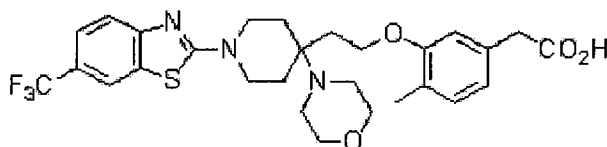
[4727]

[4728] MS (ESI) m/z 564 [M+H]⁺

[4729] 实施例 731

[4730] [式 1051]

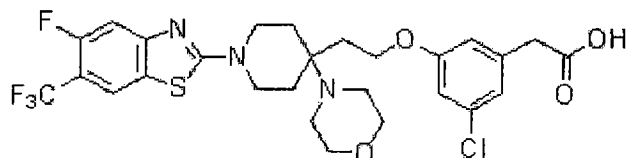
[4731]

[4732] MS (ESI) m/z 564 [M+H]⁺

[4733] 实施例 732

[4734] [式 1052]

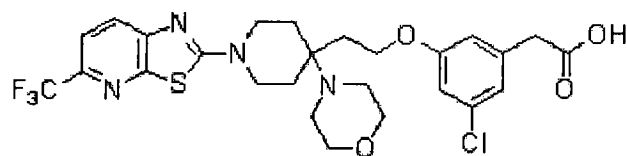
[4735]

[4736] MS (ESI) m/z 602 [M+H]⁺

[4737] 实施例 733

[4738] [式 1053]

[4739]

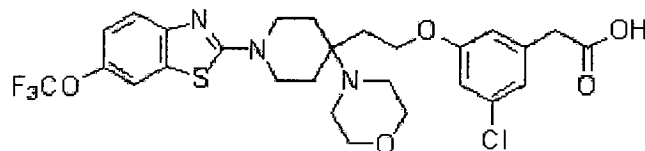


[4740] MS (ESI) m/z 585 $[M+H]^+$

[4741] 实施例 734

[4742] [式 1054]

[4743]

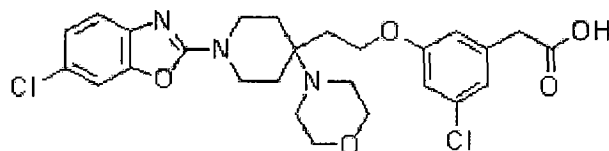


[4744] MS (ESI) m/z 600 $[M+H]^+$

[4745] 实施例 735

[4746] [式 1055]

[4747]

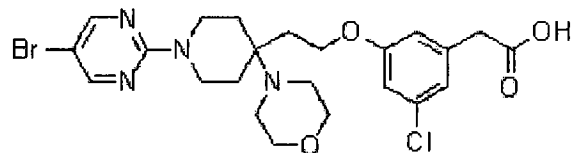


[4748] MS (ESI) m/z 534 $[M+H]^+$

[4749] 实施例 736

[4750] [式 1056]

[4751]

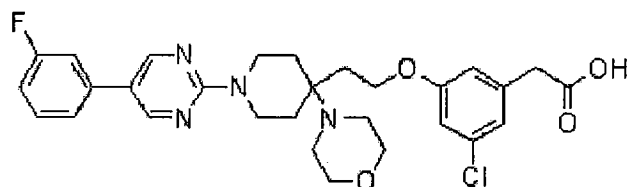


[4752] MS (ESI) m/z 539 $[M+H]^+$

[4753] 实施例 737

[4754] [式 1057]

[4755]

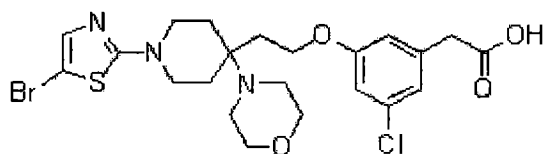


[4756] MS (ESI) m/z 555 $[M+H]^+$

[4757] 实施例 738

[4758] [式 1058]

[4759]

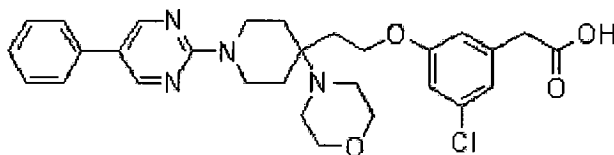


[4760] MS (ESI) m/z 544 [M+H]⁺

[4761] 实施例 739

[4762] [式 1059]

[4763]

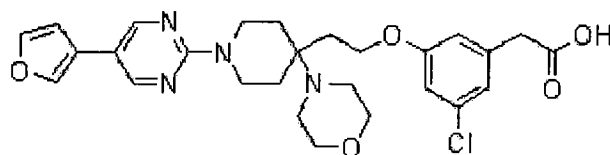


[4764] MS (ESI) m/z 537 [M+H]⁺

[4765] 实施例 740

[4766] [式 1060]

[4767]

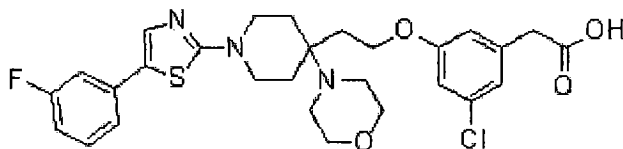


[4768] MS (ESI) m/z 527 [M+H]⁺

[4769] 实施例 741

[4770] [式 1061]

[4771]

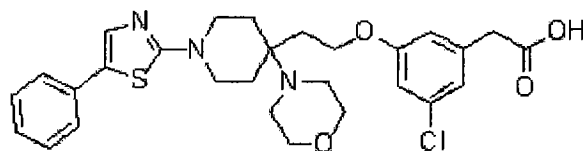


[4772] MS (ESI) m/z 560 [M+H]⁺

[4773] 实施例 742

[4774] [式 1062]

[4775]

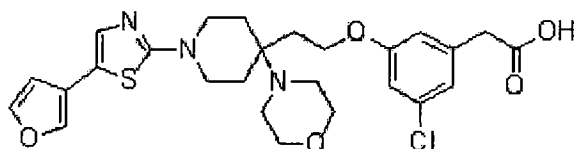


[4776] MS (ESI) m/z 542 [M+H]⁺

[4777] 实施例 743

[4778] [式 1063]

[4779]

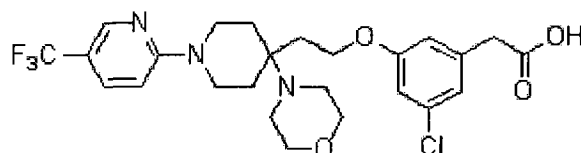


[4780] MS (ESI) m/z 532 $[M+H]^+$

[4781] 实施例 744

[4782] [式 1064]

[4783]

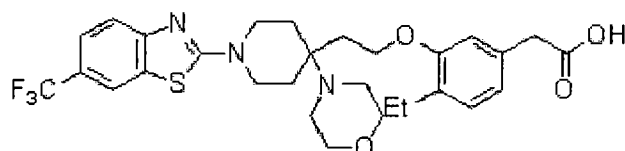


[4784] MS (ESI) m/z 528 $[M+H]^+$

[4785] 实施例 745

[4786] [式 1065]

[4787]

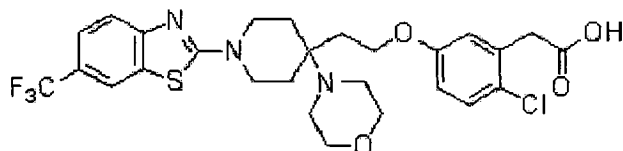


[4788] MS (ESI) m/z 578 $[M+H]^+$

[4789] 实施例 746

[4790] [式 1066]

[4791]

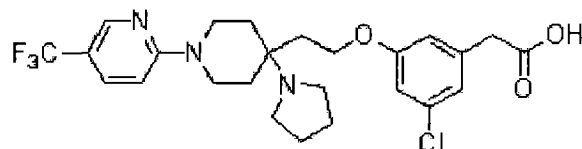


[4792] MS (ESI) m/z 584 $[M+H]^+$

[4793] 实施例 747

[4794] [式 1067]

[4795]

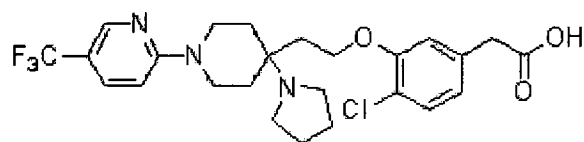


[4796] MS (ESI) m/z 512 $[M+H]^+$

[4797] 实施例 748

[4798] [式 1068]

[4799]

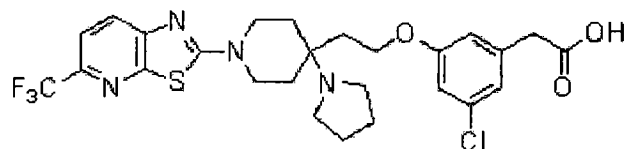


[4800] MS (ESI) m/z 512 $[M+H]^+$

[4801] 实施例 749

[4802] [式 1069]

[4803]

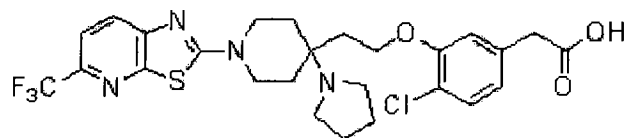


[4804] MS (ESI) m/z 569 $[M+H]^+$

[4805] 实施例 750

[4806] [式 1070]

[4807]

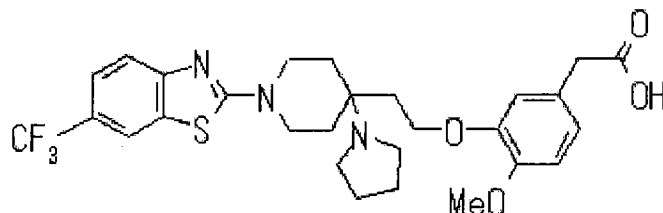


[4808] MS (ESI) m/z 569 $[M+H]^+$

[4809] 实施例 751

[4810] [式 1071]

[4811]

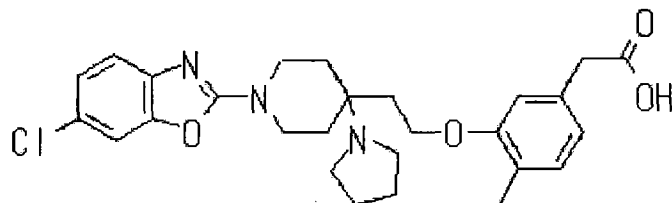


[4812] TLC : (SiO₂) CHCl₃-MeOH (10 : 1) R_f = 0.1

[4813] 实施例 752

[4814] [式 1072]

[4815]

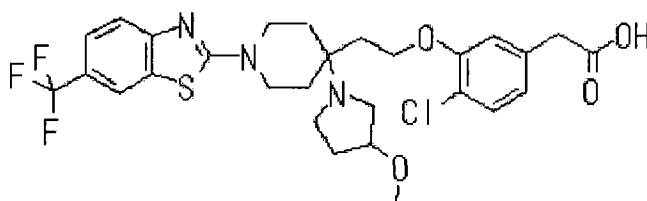


[4816] ¹H-NMR (DMSO-*d*₆) δ : 7.56 (1.0H, d, J = 1.92Hz), 7.26 (1.0H, d, J = 8.51Hz), 7.19 (1.0H, dd, J = 8.51, 4.25Hz), 7.04 (1.0H, d, J = 7.41Hz), 6.86 (1.0H, s), 6.71 (1.0H, d, J = 7.41Hz), 4.06-4.03 (2.0H, m), 3.84-3.80 (2.0H, m), 3.65-3.48 (2.0H, m), 2.68 (4.0H, br s), 2.10 (2.0H, s), 2.03-1.67 (6.0H, m), 1.06 (3.0H, d, J = 6.04Hz)。

[4817] 实施例 753

[4818] [式 1073]

[4819]

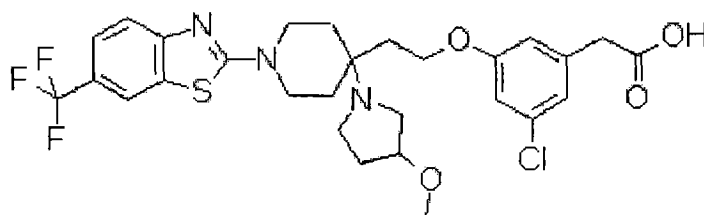


[4820] $^1\text{H-NMR}$ (CDCl_3) δ : 7.84–7.82 (1.0H, m), 7.64–7.49 (2.0H, m), 6.93–6.76 (3.0H, m), 4.22–4.11 (1.0H, m), 3.99–3.37 (9.0H, m), 3.31 (3.0H, s), 3.09–2.95 (1.0H, m), 2.89–2.64 (3.0H, m), 2.31–1.12 (8.0H, m)。

[4821] 实施例 754

[4822] [式 1074]

[4823]

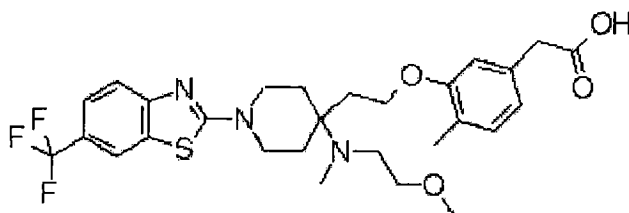


[4824] $^1\text{H-NMR}$ (CDCl_3) δ : 7.86–7.82 (1.0H, m), 7.59–7.48 (2.0H, m), 6.89–6.85 (1.0H, m), 6.80–6.77 (1.0H, m), 6.73–6.69 (1.0H, m), 4.05 (2.0H, dd, $J = 6.59, 6.59\text{Hz}$), 3.95–3.87 (1.0H, m), 3.79–3.60 (4.0H, m), 3.56 (2.0H, s), 3.31 (3.0H, s), 3.01 (1.0H, dd, $J = 7.68, 5.49\text{Hz}$), 2.83–2.69 (3.0H, m), 2.07–1.68 (8.0H, m)。

[4825] 实施例 755

[4826] [式 1075]

[4827]

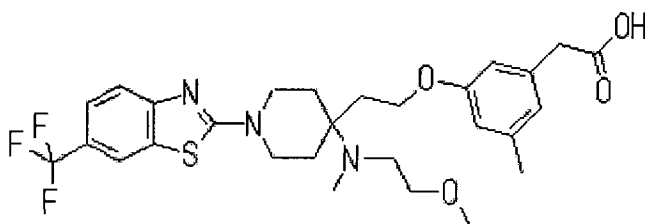


[4828] $^1\text{H-NMR}$ (CDCl_3) δ : 7.83 (1.0H, s), 7.58–7.48 (2.0H, m), 7.07 (1.0H, d, $J = 7.41\text{Hz}$), 6.79–6.70 (2.0H, m), 4.04 (2.0H, dd, $J = 6.59, 6.59\text{Hz}$), 3.83–3.56 (6.0H, m), 3.47 (2.0H, dd, $J = 6.59, 6.59\text{Hz}$), 3.36 (3.0H, s), 2.70 (2.0H, dd, $J = 6.59, 6.59\text{Hz}$), 2.33 (3.0H, s), 2.17 (3.0H, s), 2.06–1.95 (4.0H, m), 1.84–1.70 (2.0H, m)。

[4829] 实施例 756

[4830] [式 1076]

[4831]

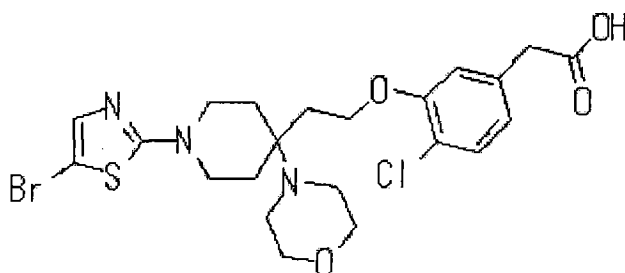


[4832] ¹H-NMR(CDC13) δ :7.83(1.0H, br s), 7.57-7.48(2.0H, m), 6.68(1.0H, s), 6.62-6.58(2.0H, m), 4.00(2.0H, dd, J = 6.59, 6.59Hz), 3.82-3.61(4.0H, m), 3.55(2.0H, s), 3.47(2.0H, dd, J = 6.31, 6.31Hz), 3.35(3.0H, s), 2.68(2.0H, dd, J = 6.31, 6.31Hz), 2.31(3.0H, s), 2.29(3.0H, s), 2.04-1.91(4.0H, m), 1.80-1.66(2.0H, m)。

[4833] 实施例 757

[4834] [式 1077]

[4835]

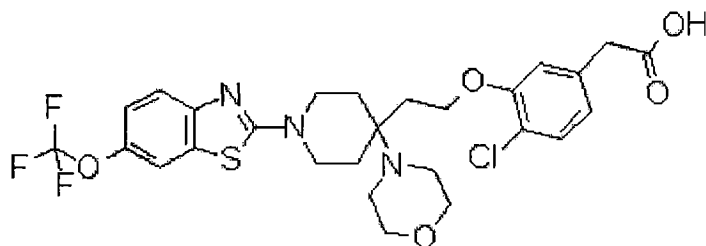


[4836] ¹H-NMR(CDCl₃) δ :7.31 (1.0H, d, J = 8.23Hz), 7.08 (1.0H, s), 6.93-6.87 (1.0H, m), 6.83 (1.0H, dd, J = 8.23, 1.65Hz), 4.30-4.07 (2.0H, m), 3.89-3.66 (4.0H, m), 3.65-3.55 (4.0H, m), 3.53-3.34 (4.0H, m), 2.87-2.52 (4.0H, m), 2.32-1.62 (6.0H, m)。

[4837] 实施例 758

[4838] [式 1078]

[4839]

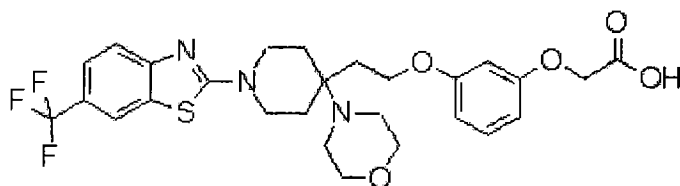


[4840] $^1\text{H-NMR}$ (CDCl_3) δ : 7.55–7.44 (2.0H, m), 7.31 (1.0H, d, $J = 8.23\text{Hz}$), 7.19–7.13 (1.0H, m), 6.93–6.80 (2.0H, m), 4.32–4.08 (2.0H, m), 3.91–3.57 (10.0H, m), 2.91–2.51 (4.0H, m), 2.33–1.61 (6.0H, m)。

[4841] 实施例 759

[4842] [式 1079]

[4843]



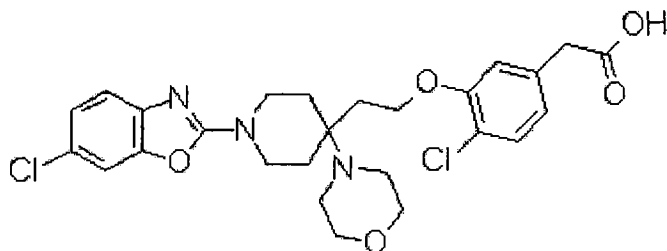
[4844] $^1\text{H-NMR}$ (DMSO-d_6) δ : 8.22 (1.0H, s), 7.59–7.52 (2.0H, m), 7.13 (1.0H, dd, J =

8.51, 8.51Hz), 6.54-6.49 (1.0H, m), 6.46-6.41 (3.0H, m), 4.57-4.47 (2.0H, m), 4.00 (2.0H, dd, $J = 7.14, 7.14\text{Hz}$), 3.82-3.67 (2.0H, m), 3.63-3.44 (6.0H, m), 2.60-2.53 (4.0H, m), 2.01 (2.0H, d, $J = 12.90\text{Hz}$), 1.90 (2.0H, dd, $J = 7.14, 7.14\text{Hz}$), 1.77-1.63 (2.0H, m)。

[4845] 实施例 760

[4846] [式 1080]

[4847]

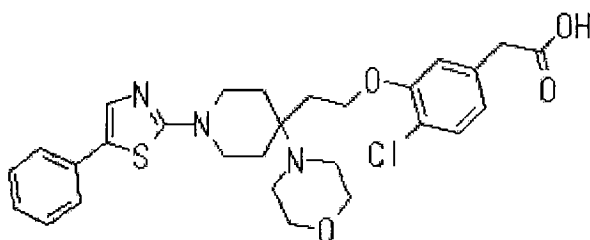


[4848] $^1\text{H-NMR}$ (DMSO- d_6) δ : 7.55 (1.0H, d, $J = 2.20\text{Hz}$), 7.30 (1.0H, d, $J = 8.23\text{Hz}$), 7.24 (1.0H, d, $J = 8.23\text{Hz}$), 7.20-7.14 (1.0H, m), 7.07 (1.0H, s), 6.82 (1.0H, d, $J = 9.61\text{Hz}$), 4.12-4.00 (2.0H, m), 3.83-3.71 (2.0H, m), 3.63-3.51 (8.0H, m), 2.58-2.53 (4.0H, m), 2.03-1.89 (4.0H, m), 1.77-1.65 (2.0H, m)。

[4849] 实施例 761

[4850] [式 1081]

[4851]

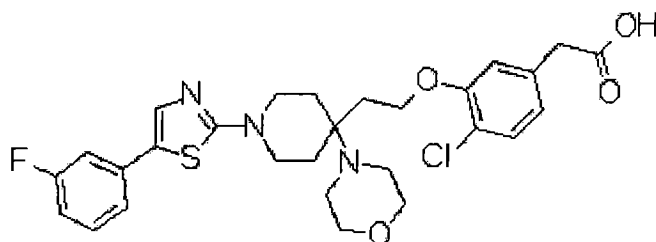


[4852] $^1\text{H-NMR}$ (DMSO- d_6) δ : 12.36 (1.0H, br s), 7.59 (1.0H, s), 7.46 (2.0H, d, $J = 7.41\text{Hz}$), 7.38-7.31 (3.0H, m), 7.20 (1.0H, dd, $J = 7.41, 7.41\text{Hz}$), 7.10 (1.0H, d, $J = 1.65\text{Hz}$), 6.83 (1.0H, dd, $J = 7.41, 1.65\text{Hz}$), 4.11 (2.0H, dd, $J = 6.59, 6.59\text{Hz}$), 3.63-3.53 (8.0H, m), 3.47-3.39 (2.0H, m), 2.60-2.53 (4.0H, m), 2.05-1.90 (4.0H, m), 1.80-1.66 (2.0H, m)。

[4853] 实施例 762

[4854] [式 1082]

[4855]



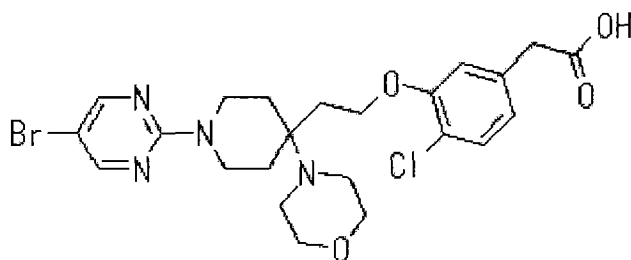
[4856] $^1\text{H-NMR}$ (DMSO- d_6) δ : 7.70 (1.0H, s), 7.42-7.30 (3.0H, m), 7.25 (1.0H, d, $J = 8.23\text{Hz}$), 7.10 (1.0H, d, $J = 1.92\text{Hz}$), 7.06-6.97 (1.0H, m), 6.83 (1.0H, dd, $J = 8.23, 1.92\text{Hz}$), 4.11 (2.0H, dd, $J = 6.59, 6.59\text{Hz}$), 3.63-3.54 (8.0H, m), 3.47-3.40 (2.0H, m),

2.60-2.53 (4.0H, m), 2.06-1.90 (4.0H, m), 1.80-1.66 (2.0H, m)。

[4857] 实施例 763

[4858] [式 1083]

[4859]

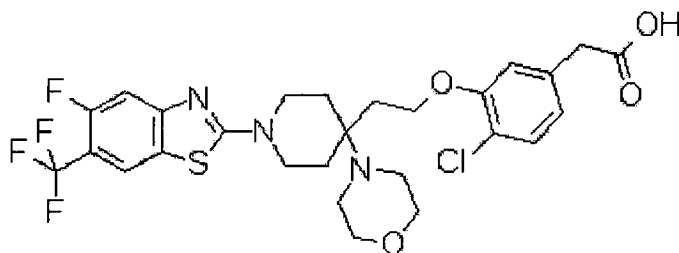


[4860] $^1\text{H-NMR}$ (CDCl_3) δ : 8.29 (2.0H, s), 7.31 (1.0H, d, $J = 8.23\text{Hz}$), 6.91 (1.0H, s), 6.85-6.82 (1.0H, m), 4.31-4.16 (2.0H, m), 4.00-3.70 (6.0H, m), 3.69-3.60 (4.0H, m), 2.98-2.69 (4.0H, m), 2.29-1.60 (6.0H, m)。

[4861] 实施例 764

[4862] [式 1084]

[4863]

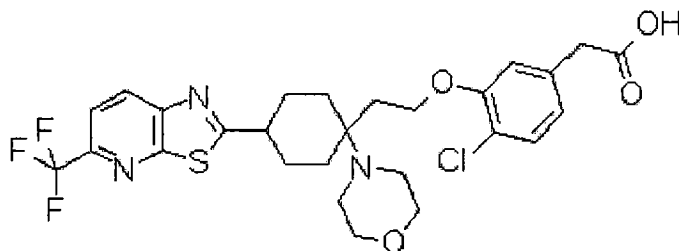


[4864] $^1\text{H-NMR}$ (DMSO-d_6) δ : 8.23 (1.0H, d, $J = 7.41\text{Hz}$), 7.44 (1.0H, d, $J = 12.35\text{Hz}$), 7.31 (1.0H, d, $J = 8.23\text{Hz}$), 7.08 (1.0H, d, $J = 2.20\text{Hz}$), 6.82 (1.0H, dd, $J = 8.23, 2.20\text{Hz}$), 4.10 (2.0H, dd, $J = 7.14, 7.14\text{Hz}$), 3.65-3.50 (6.0H, m), 3.49-3.12 (4.0H, m), 2.60-2.53 (4.0H, m), 2.10-1.89 (4.0H, m), 1.82-1.68 (2.0H, m)。

[4865] 实施例 765

[4866] [式 1085]

[4867]

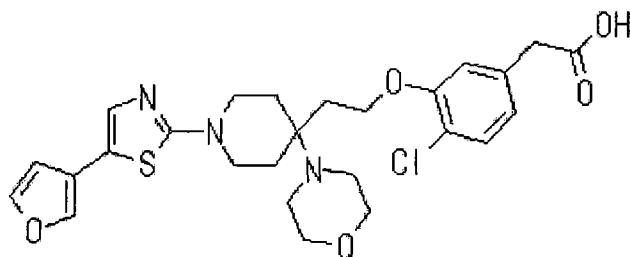


[4868] $^1\text{H-NMR}$ (DMSO-d_6) δ : 7.86 (1.0H, d, $J = 8.51\text{Hz}$), 7.76 (1.0H, d, $J = 8.51\text{Hz}$), 7.31 (1.0H, d, $J = 7.96\text{Hz}$), 7.08 (1.0H, d, $J = 1.92\text{Hz}$), 6.83 (1.0H, dd, $J = 7.96, 1.92\text{Hz}$), 4.10 (2.0H, dd, $J = 6.86, 6.86\text{Hz}$), 3.67-3.52 (6.0H, m), 3.44-3.22 (4.0H, m), 2.62-2.54 (4.0H, m), 2.10-1.92 (4.0H, m), 1.83-1.68 (2.0H, m)。

[4869] 实施例 766

[4870] [式 1086]

[4871]

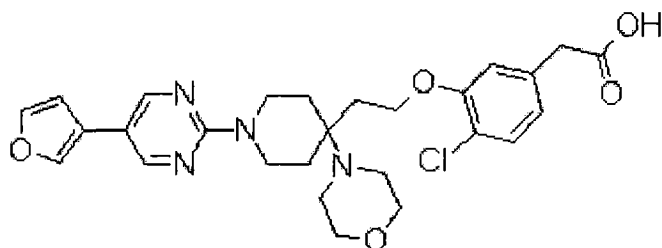


[4872] $^1\text{H-NMR}$ (DMSO- d_6) δ : 7.83 (1.0H, s), 7.71–7.67 (1.0H, m), 7.33–7.31 (2.0H, m), 7.09 (1.0H, s), 6.83 (1.0H, d, $J = 7.96\text{Hz}$), 6.78 (1.0H, s), 4.10 (2.0H, dd, $J = 6.86, 6.86\text{Hz}$), 3.63–3.46 (6.0H, m), 3.45–3.24 (4.0H, m), 2.61–2.52 (4.0H, m), 2.03–1.89 (4.0H, m), 1.78–1.65 (2.0H, m), 1.04 (2.7H, d, $J = 6.04\text{Hz}$)。

[4873] 实施例 767

[4874] [式 1087]

[4875]

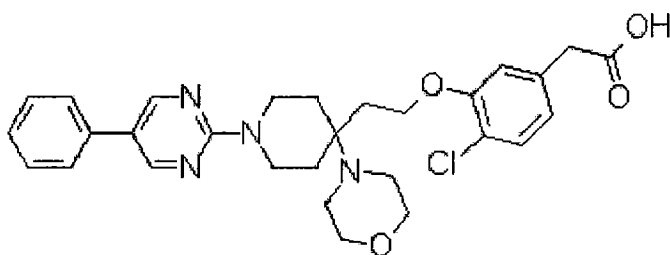


[4876] $^1\text{H-NMR}$ (DMSO- d_6) δ : 12.37 (1.0H, br s), 8.61 (2.0H, s), 8.10 (1.0H, s), 7.75–7.72 (1.0H, m), 7.32 (1.0H, d, $J = 8.23\text{Hz}$), 7.08 (1.0H, s), 6.93 (1.0H, s), 6.82 (1.0H, d, $J = 8.23\text{Hz}$), 4.16–3.96 (4.0H, m), 3.64–3.47 (8.0H, m), 2.62–2.53 (4.0H, m), 2.00–1.86 (4.0H, m), 1.67–1.52 (2.0H, m)。

[4877] 实施例 768

[4878] [式 1088]

[4879]

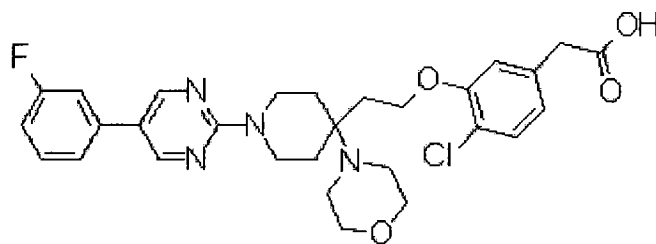


[4880] $^1\text{H-NMR}$ (DMSO- d_6) δ : 12.40 (1.0H, br s), 8.69 (2.0H, s), 7.63 (2.0H, d, $J = 7.72\text{Hz}$), 7.43 (2.0H, dd, $J = 7.72, 7.72\text{Hz}$), 7.34–7.31 (2.0H, m), 7.08 (1.0H, d, $J = 1.85\text{Hz}$), 6.82 (1.0H, dd, $J = 8.23, 1.85\text{Hz}$), 4.20–4.06 (4.0H, m), 3.63–3.52 (8.0H, m), 2.62–2.54 (4.0H, m), 2.02–1.87 (4.0H, m), 1.68–1.54 (2.0H, m)。

[4881] 实施例 769

[4882] [式 1089]

[4883]

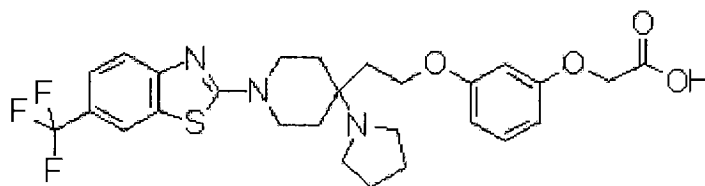


[4884] $^1\text{H-NMR}$ (DMSO- d_6) δ : 8.73 (2.0H, s), 7.57-7.42 (3.0H, m), 7.31 (1.0H, d, J = 8.23Hz), 7.19-7.07 (2.0H, m), 6.82 (1.0H, d, J = 8.23Hz), 4.20-4.06 (4.0H, m), 3.63-3.51 (8.0H, m), 2.63-2.55 (4.0H, m), 2.01-1.87 (4.0H, m), 1.67-1.54 (2.0H, m)。

[4885] 实施例 770

[4886] [式 1090]

[4887]

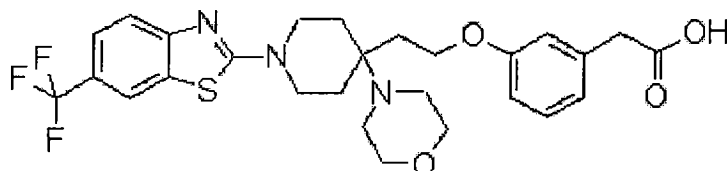


[4888] $^1\text{H-NMR}$ (DMSO- d_6) δ : 8.21 (1.0H, s), 7.58-7.51 (2.0H, m), 7.12 (1.0H, dd, J = 8.56, 8.56Hz), 6.54-6.40 (2.0H, m), 4.56-4.41 (1.0H, m), 4.08-3.97 (3.0H, m), 3.84-3.69 (2.0H, m), 3.59-3.46 (2.0H, m), 2.71-2.60 (4.0H, m), 2.00-1.81 (4.0H, m), 1.79-1.65 (6.0H, m)。

[4889] 实施例 771

[4890] [式 1091]

[4891]



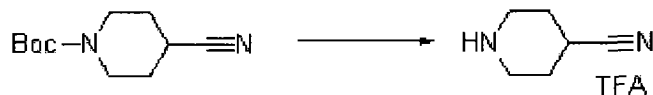
[4892] $^1\text{H-NMR}$ (CDCl $_3$) δ : 7.85 (1.0H, s), 7.62-7.49 (2.0H, m), 7.31-7.20 (1.0H, m), 6.94-6.76 (3.0H, m), 4.14-3.95 (2.0H, m), 3.84-3.58 (8.0H, m), 2.72-2.55 (4.0H, m), 2.12-1.90 (4.0H, m), 1.88-1.69 (2.0H, m)。

[4893] 参考例 258

[4894] 哌啶-4-甲腈三氟乙酸盐的制备

[4895] [式 1092]

[4896]



[4897] 将 4-氰基哌啶-1-羧酸叔丁基酯 (5.35g) 加入到三氟乙酸 (20mL) 中并将混合物在室温搅拌 10 分钟。将三氟乙酸减压蒸发, 得到标题化合物, 为无色晶体 (5.62g)。收率: 99%。

[4898] $^1\text{H-NMR}$ (DMSO- d_6) δ : 1.83-1.96 (2H, m), 2.08-2.14 (2H, m), 3.00-3.08 (2H, m),

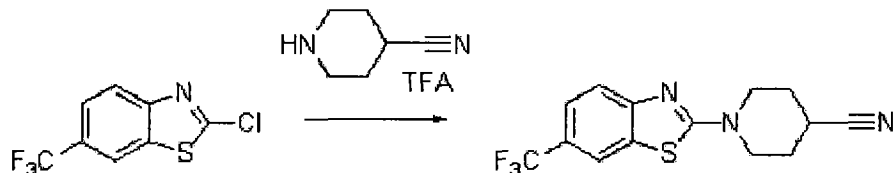
3.14-3.26 (2H, m), 3.41 (1H, br s)。

[4899] 参考例 259

[4900] 1-(6-三氟甲基苯并噻唑-2-基)哌啶-4-甲腈的制备

[4901] [式 1093]

[4902]



[4903] 将 2-氯-6-三氟苯并噻唑 (5.84g), 哌啶-4-甲腈三氟乙酸盐 (5.62g), 碳酸钾 (10.39g) 和二甲基亚砜 (50mL) 在 60℃ 搅拌 6 小时。向反应溶液加入水并且用乙酸乙酯萃取。有机层用水和盐水洗涤, 并且用硫酸镁干燥。减压蒸发溶剂, 并将残余物用异丙基醚洗涤, 得到标题化合物, 为无色晶体 (6.84g)。收率: 89%。

[4904] $^1\text{H-NMR}(\text{CDCl}_3)$ δ : 1.99-2.17 (4H, m), 2.97-3.05 (1H, m), 3.68-3.76 (2H, m), 3.87-3.95 (2H, m), 7.55-7.63 (2H, m), 7.89-7.90 (1H, m)。

[4905] 参考例 260

[4906] 4-[2-(叔丁基二甲基甲硅烷基氧基)乙基]-1-(6-三氟甲基苯并噻唑-2-基)哌啶-4-甲腈的制备

[4907] [式 1094]

[4908]



[4909] 在 -15℃ 向 1-(6-三氟甲基苯并噻唑-2-基)哌啶-4-甲腈 (1.00g) 的四氢呋喃 (10mL) 溶液中加入二(三甲基甲硅烷基)氨基锂 (3.21mL)。向反应溶液加入 (2-溴乙氧基)-叔丁基二甲基甲硅烷 (689 μL)。将混合物在 0℃ 搅拌 3 小时。向反应溶液加入盐水并且用乙酸乙酯萃取。有机层用水和盐水洗涤, 并且用硫酸镁干燥。减压蒸发溶剂并将得到的残余物通过硅胶柱色谱法纯化, 得到标题化合物 (1.23g)。收率: 82%。

[4910] $^1\text{H-NMR}(\text{CDCl}_3)$ δ : 0.10 (6H, s), 0.93 (9H, s), 1.71-1.81 (2H, m), 1.88 (2H, t, $J = 6.0\text{Hz}$), 2.17-2.21 (2H, m), 3.49-3.59 (2H, m), 3.94 (2H, t, $J = 6.0\text{Hz}$), 4.11-4.23 (2H, m), 7.55-7.62 (2H, m), 7.89-7.89 (1H, m)。

[4911] 参考例 261

[4912] 4-(2-羟基乙基)-1-(6-三氟甲基苯并噻唑-2-基)哌啶-4-甲腈的制备

[4913] [式 1095]

[4914]



[4915] 向 4-[2-(叔丁基二甲基甲硅烷基氧基)乙基]-1-(6-三氟甲基苯并噻唑-2-基)哌啶-4-甲腈 (510mg) 加入四甲基氟化铵 (1M 四氢呋喃溶液, 1.63mL)。将混合物在 0℃ 搅拌 0.5 小时。向反应溶液加入柠檬酸水溶液并且用乙酸乙酯萃取。有机层用水和盐水洗

涤,并且用硫酸钠干燥。减压蒸发溶剂,并将残余物通过硅胶柱色谱法纯化,得到标题化合物(366mg)。收率:95%。

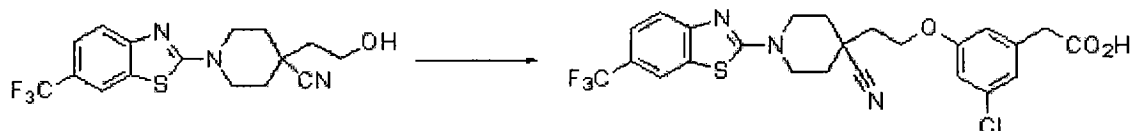
[4916] $^1\text{H-NMR}$ (丙酮) δ : 1.82-1.99(4H, m), 2.20-2.25(2H, m), 3.44-3.54(2H, m), 3.89(2H, t, $J = 5.9\text{Hz}$), 4.25-4.29(2H, m), 7.62-7.63(2H, m), 8.13-8.16(1H, br m)。

[4917] 实施例 772

[4918] [3-氯-5-[2-[4-氰基-1-(6-三氟甲基苯并噻唑-2-基)哌啶-4-基]乙氧基]苯基]乙酸的制备

[4919] [式 1096]

[4920]



[4921] 根据实施例 585 和 586 的方法从 4-(2-羟基乙基)-1-(6-三氟甲基苯并噻唑-2-基)哌啶-4-甲腈合成上述化合物。

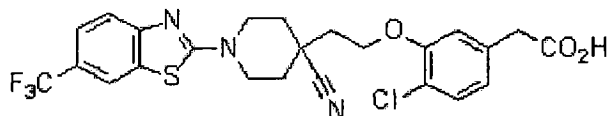
[4922] MS(ESI)m/z 524[M+H]⁺

[4923] 通过与如上相似的方法得到以下化合物。

[4924] 实施例 773

[4925] [式 1097]

[4926]



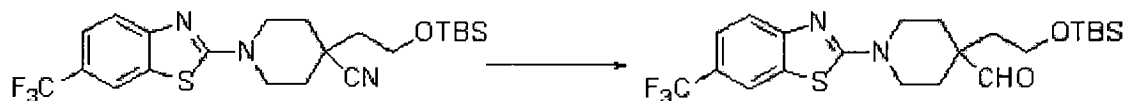
[4927] MS(ESI)m/z 524[M+H]⁺

[4928] 参考例 262

[4929] 4-[2-(叔丁基二甲基甲硅烷基氧基)乙基]-1-(6-三氟甲基苯并噻唑-2-基)哌啶-4-甲醛的制备

[4930] [式 1098]

[4931]



[4932] 在 0℃ 向 4-[2-(叔丁基二甲基甲硅烷基氧基)乙基]-1-(6-三氟甲基苯并噻唑-2-基)哌啶-4-甲腈(600mg)的 1,2-二甲氧基乙烷(12mL)溶液中加入二异丁基氢化铝(1.0M 甲苯溶液,6.39mL)。将混合物搅拌 4 小时。向反应溶液加入柠檬酸水溶液并且用乙酸乙酯萃取。有机层顺序地用柠檬酸水溶液,水和盐水洗涤,并且用硫酸镁干燥。减压蒸发溶剂,并将残余物通过硅胶柱色谱法纯化,得到标题化合物(526mg)。收率:87%。

[4933] $^1\text{H-NMR}$ (CDCl_3) δ : 0.05(6H, s), 0.90(9H, s), 1.64-1.74(2H, m), 1.85(2H, t, $J = 5.8\text{Hz}$), 2.13-2.19(2H, m), 3.40-3.50(2H, m), 3.68(2H, t, $J = 5.8\text{Hz}$), 3.93-4.00(2H, m), 7.52-7.59(2H, m), 7.85-7.88(1H, br m), 9.57-9.60(1H, br m)。

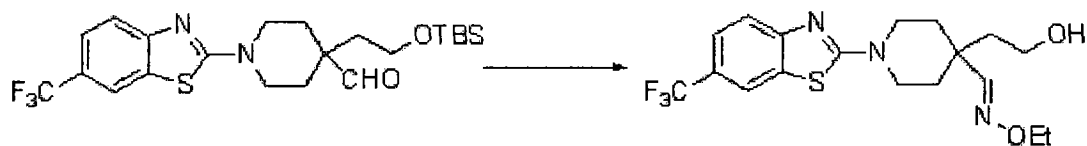
[4934] 参考例 263

[4935] N-[4-(2-羟基乙基)-1-(6-三氟甲基苯并噻唑-2-基)哌啶-4-基]甲亚胺酸乙

基酯 (formimido ethyl ester) 的制备

[4936] [式 1099]

[4937]



[4938] 向 4-[2-(叔丁基二甲基甲硅烷基氧基)乙基]-1-(6-三氟甲基苯并噻唑-2-基)哌啶-4-甲醛 (500mg) 的四氢呋喃 (20mL) 溶液中加入乙氧基胺盐酸盐 (124mg)。将混合物在 60℃ 搅拌 4 小时。减压蒸发溶剂。向残余物中加入四丁基氟化铵 (1M 四氢呋喃溶液, 1.59mL)。将混合物在 0℃ 搅拌 0.5 小时, 在室温搅拌 1 小时并且在 40℃ 搅拌 2 小时。向反应溶液加入柠檬酸水溶液并且用乙酸乙酯萃取。有机层用盐水洗涤, 并且用硫酸镁干燥。减压蒸发溶剂, 并将残余物通过硅胶柱色谱法纯化, 得到标题化合物 (394mg)。收率: 93%。

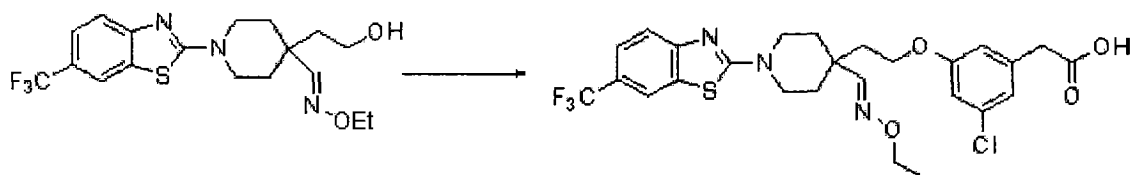
[4939] $^1\text{H-NMR}$ (CDCl_3) δ : 1.28 (3H, t, $J = 7.0\text{Hz}$), 1.68-1.77 (2H, m), 1.80 (2H, t, $J = 6.7\text{Hz}$), 2.03-2.10 (2H, m), 3.47-3.56 (2H, m), 3.74-3.80 (2H, m), 3.92-3.99 (2H, m), 4.13 (2H, q, $J = 7.0\text{Hz}$), 7.33-7.36 (1H, br m), 7.52-7.59 (2H, m), 7.84-7.88 (1H, br m)。

[4940] 实施例 774

[4941] [3-氯-5-[2-[4-乙氧基亚氨基-1-(6-三氟甲基苯并噻唑-2-基)哌啶-4-基]乙氧基]苯基]乙酸的制备

[4942] [式 1100]

[4943]



[4944] 根据实施例 585 和 586 的方法从 N-[4-(2-羟基乙基)-1-(6-三氟甲基苯并噻唑-2-基)哌啶-4-基]甲亚胺酸乙基酯 (formimido ethyl ester) 合成上述化合物。

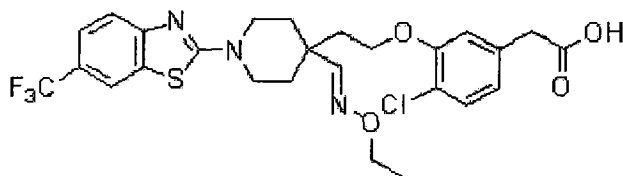
[4945] MS (ESI) m/z 570 $[\text{M}+\text{H}]^+$

[4946] 通过与如上相似的方法得到以下化合物。

[4947] 实施例 775

[4948] [式 1101]

[4949]

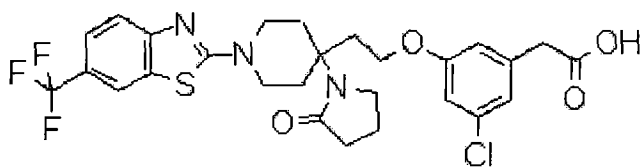


[4950] MS (ESI) m/z 570 $[\text{M}+\text{H}]^+$

[4951] 实施例 776

[4952] [式 1102]

[4953]

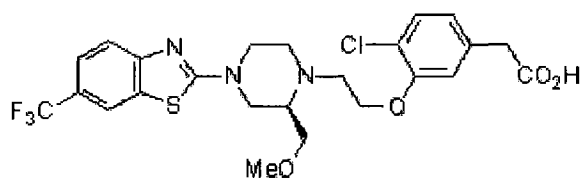


[4954] MS (FABMS) m/z 582 $[M+H]^+$

[4955] 实施例 777

[4956] [式 1103]

[4957]

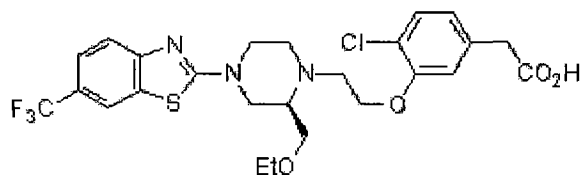


[4958] TLC_{Rf} = 0.61 (MeOH : CHCl₃ = 1 : 15)

[4959] 实施例 778

[4960] [式 1104]

[4961]

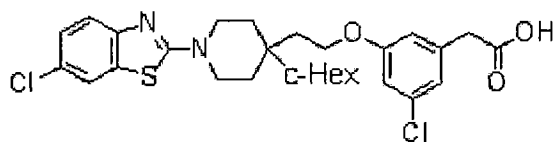


[4962] TLC_{Rf} = 0.63 (MeOH : CHCl₃ = 1 : 15)

[4963] 实施例 779

[4964] [式 1105]

[4965]

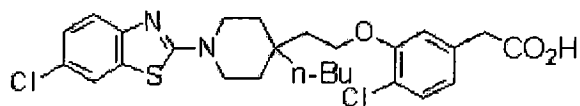


[4966] MS (ESI) m/z 547 $[M+H]^+$

[4967] 实施例 780

[4968] [式 1106]

[4969]

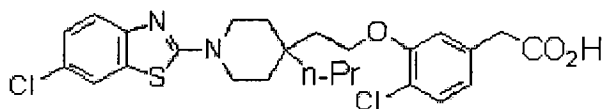


[4970] MS (ESI) m/z 521 $[M+H]^+$

[4971] 实施例 781

[4972] [式 1107]

[4973]

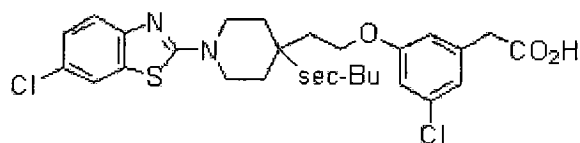


[4974] MS (ESI) m/z 507 $[M+H]^+$

[4975] 实施例 782

[4976] [式 1108]

[4977]

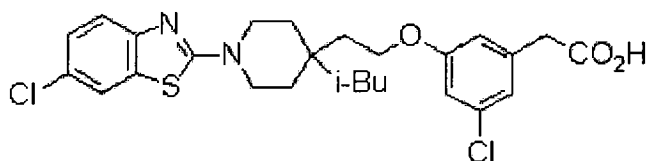


[4978] MS (ESI) m/z 521 $[M+H]^+$

[4979] 实施例 783

[4980] [式 1109]

[4981]

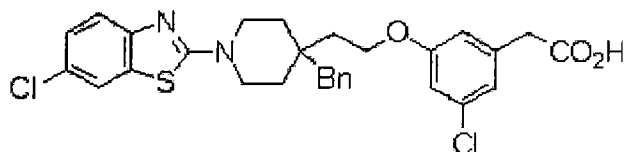


[4982] MS (ESI) m/z 521 $[M+H]^+$

[4983] 实施例 784

[4984] [式 1110]

[4985]

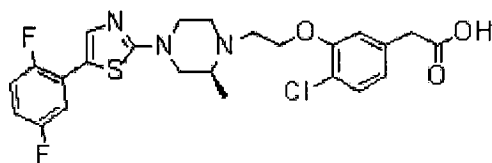


[4986] MS (ESI) m/z 555 $[M+H]^+$

[4987] 实施例 785

[4988] [式 1111]

[4989]

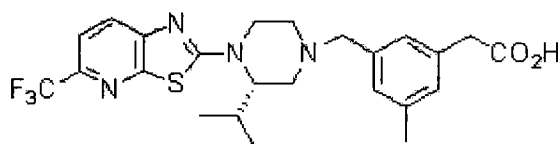


[4990] MS (ESI) m/z 508 $[M+H]^+$

[4991] 实施例 786

[4992] [式 1112]

[4993]

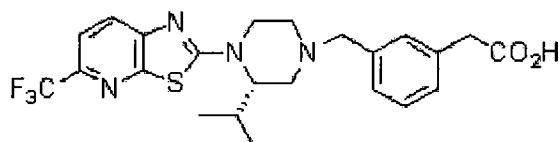


[4994] MS (ESI) m/z 493 $[M+H]^+$

[4995] 实施例 787

[4996] [式 1113]

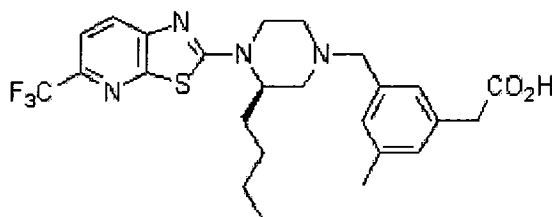
[4997]

[4998] MS(ESI) m/z 479 $[M+H]^+$

[4999] 实施例 788

[5000] [式 1114]

[5001]

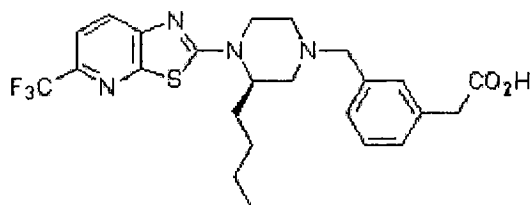


[5002] $^1\text{H-NMR}$ (DMSO- d_6) δ : 7.88 (1.0H, d, $J = 8.51\text{Hz}$), 7.78 (1.0H, d, $J = 8.51\text{Hz}$), 7.05 (2.0H, d, $J = 5.21\text{Hz}$), 7.00 (1.0H, s), 4.22-3.91 (1.0H, m), 3.65-3.36 (4.0H, m), 2.97 (1.0H, d, $J = 11.53\text{Hz}$), 2.83 (1.0H, d, $J = 11.53\text{Hz}$), 2.31 (3.0H, s), 2.21-2.16 (3.0H, m), 2.02-1.93 (1.0H, m), 1.83-1.78 (1.0H, m), 1.38-1.16 (4.0H, m), 0.86 (3.0H, t, $J = 7.27\text{Hz}$)。

[5003] 实施例 789

[5004] [式 1115]

[5005]

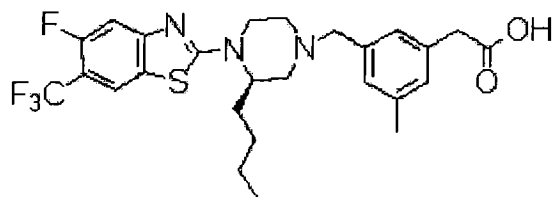


[5006] $^1\text{H-NMR}$ (DMSO- d_6) δ : 7.88 (1.0H, d, $J = 8.23\text{Hz}$), 7.78 (1.0H, d, $J = 8.23\text{Hz}$), 7.34-7.18 (4.0H, m), 4.06 (1.0H, br s), 3.61-3.41 (5.0H, m), 2.96 (1.0H, d, $J = 11.80\text{Hz}$), 2.84 (1.0H, d, $J = 11.80\text{Hz}$), 2.19-2.17 (2.0H, m), 1.92-1.84 (2.0H, m), 1.32-1.21 (4.0H, m), 0.86 (3.0H, t, $J = 7.27\text{Hz}$)。

[5007] 实施例 790

[5008] [式 1116]

[5009]



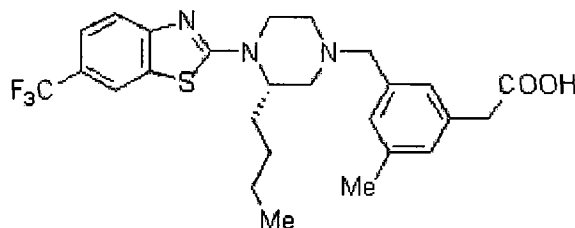
[5010] $^1\text{H-NMR}$ (DMSO- d_6) δ : 12.32 (1.0H, br s), 8.26 (1.0H, d, $J = 7.41\text{Hz}$), 7.46 (1.0H, d, $J = 12.08\text{Hz}$), 7.05 (2.0H, d, $J = 5.76\text{Hz}$), 7.00 (1.0H, s), 4.07-4.04 (1.0H, m), 3.58-3.40 (5.0H, m), 2.95 (1.0H, d, $J = 12.08\text{Hz}$), 2.82 (1.0H, d, $J = 12.08\text{Hz}$), 2.31 (3.0H, s)

s), 2.22-2.11 (2.0H, m), 2.02-1.92 (1.0H, m), 1.78-1.74 (1.0H, m), 1.30-1.22 (4.0H, m), 0.86 (3.0H, t, $J = 7.27\text{Hz}$)。

[5011] 实施例 791

[5012] [式 1117]

[5013]

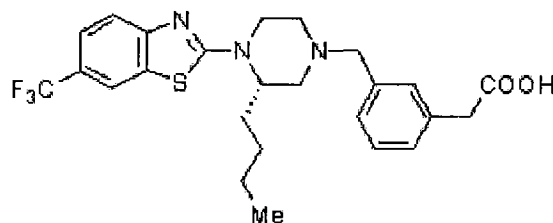


[5014] $^1\text{H-NMR}$ (300MHz, DMSO-d_6) : δ 0.83 (3H, t, $J = 7.2\text{Hz}$), 1.13-1.20 (2H, m), 1.27-1.34 (2H, m), 1.71-1.94 (2H, m), 2.09-2.19 (2H, m), 2.28 (3H, s), 2.78-2.94 (2H, m), 3.32-3.61 (5H, m), 3.99 (2H, m), 6.97-7.02 (3H, m), 7.50-7.57 (2H, m), 8.22 (1H, s)。

[5015] 实施例 792

[5016] [式 1118]

[5017]

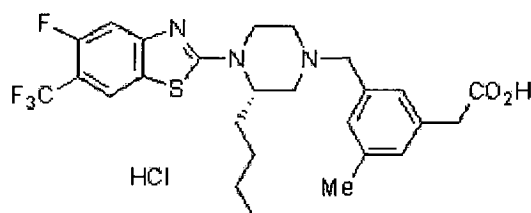


[5018] $^1\text{H-NMR}$ (300MHz, DMSO-d_6) : δ 0.83 (3H, t, $J = 7.2\text{Hz}$), 1.13-1.20 (2H, m), 1.27-1.36 (2H, m), 1.72-1.94 (2H, m), 2.12-2.15 (2H, m), 2.78-2.92 (2H, m), 3.37-3.61 (5H, m), 3.99 (2H, m), 7.16-7.29 (4H, m), 7.50-7.57 (2H, m), 8.21 (1H, s)。

[5019] 实施例 793

[5020] [式 1119]

[5021]

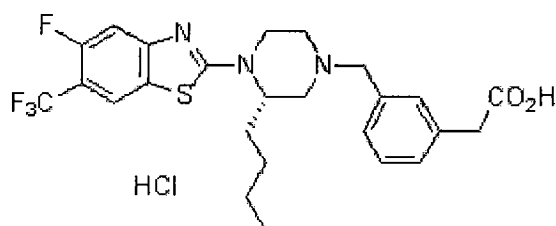


[5022] $^1\text{H-NMR}$ (300MHz, DMSO-d_6) : δ 0.81 (3H, t, $J = 7.2\text{Hz}$), 1.07-1.17 (2H, m), 1.25-1.32 (2H, m), 1.68-1.77 (2H, m), 2.09-2.18 (2H, m), 2.26 (3H, s), 2.75-2.93 (2H, m), 3.26-3.42 (3H, m), 3.48 (2H, s), 3.57 (1H, d, $J = 13.5\text{Hz}$), 3.97 (1H, m), 6.95-7.02 (3H, m), 7.41 (1H, d, $J = 12.3\text{Hz}$), 8.22 (1H, d, $J = 6.6\text{Hz}$), 12.24 (1H, br)。

[5023] 实施例 794

[5024] [式 1120]

[5025]

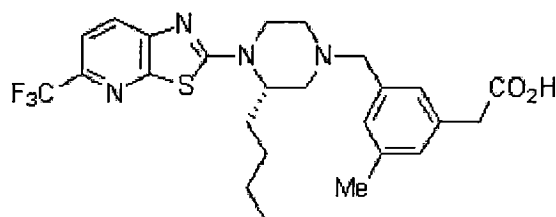


[5026] $^1\text{H-NMR}$ (300MHz, DMSO-d_6) : δ 0.81 (3H, t, $J = 7.2\text{Hz}$), 1.13-1.31 (4H, m), 1.75-1.95 (2H, m), 2.10-2.13 (2H, m), 2.76-2.90 (1H, m), 3.21-4.37 (8H, m), 7.15-7.59 (5H, m), 8.21-8.30 (1H, m), 12.34 (1H, br)。

[5027] 实施例 795

[5028] [式 1121]

[5029]

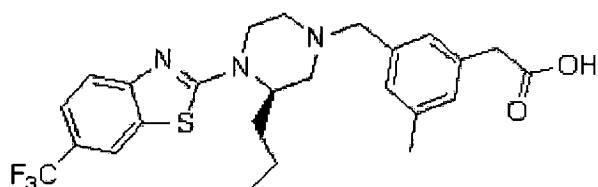


[5030] $^1\text{H-NMR}$ (300MHz, CDCl_3) : δ 0.88 (3H, t, $J = 7.2\text{Hz}$), 1.21-1.39 (4H, m), 1.94 (2H, m), 2.27 (2H, m), 2.36 (3H, s), 2.91 (2H, m), 3.45 (3H, m), 3.64 (2H, s), 4.11 (2H, m), 7.06-7.11 (3H, m), 7.58 (1H, d, $J = 8.4\text{Hz}$), 7.71 (1H, d, $J = 8.4\text{Hz}$)。

[5031] 实施例 796

[5032] [式 1122]

[5033]

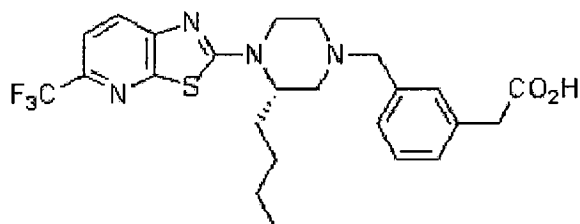


[5034] $^1\text{H-NMR}$ (DMSO-d_6) δ : 8.24 (1H, s), 7.58-7.55 (2H, m), 7.06 (2H, s), 7.00 (1H, s), 4.09-3.95 (2H, m), 3.64-3.32 (2H, m), 3.53 (2H, s), 2.94 (1H, d, $J = 11.2\text{Hz}$), 2.82 (1H, d, $J = 11.4\text{Hz}$), 2.31 (3H, s), 2.19-2.14 (2H, m), 1.98-1.89 (1H, m), 1.80-1.71 (1H, m), 1.27-1.19 (2H, m), 0.92 (3H, t, $J = 7.3\text{Hz}$)。

[5035] 实施例 797

[5036] [式 1123]

[5037]



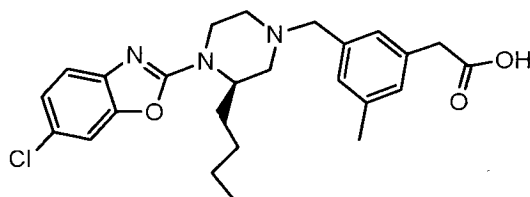
[5038] $^1\text{H-NMR}$ (300MHz, CDCl_3) : δ 0.87 (3H, t, $J = 7.2\text{Hz}$), 1.20-1.38 (4H, m), 1.92 (2H, m), 2.27 (2H, m), 2.89 (2H, m), 3.50 (3H, m), 3.67 (2H, s), 4.11 (2H, m), 7.31 (4H, m), 7.57 (1H,

d, $J = 8.4\text{Hz}$), 7.70 (1H, d, $J = 8.4\text{Hz}$)。

[5039] 实施例 798

[5040] [式 1124]

[5041]

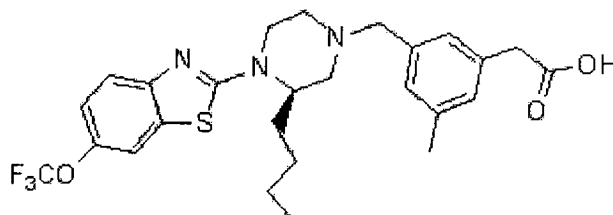


[5042] $^1\text{H-NMR}$ (DMSO- d_6) δ : 7.55 (1H, d, $J = 2.0\text{Hz}$), 7.26-7.17 (2H, m), 7.04 (1H, s), 7.02 (1H, s), 6.97 (1H, s), 4.13 (1H, s), 3.95 (1H, d, $J = 12.3\text{Hz}$), 3.50 (2H, s), 3.48 (2H, dd, $J = 58.3, 14.7\text{Hz}$), 2.90 (1H, d, $J = 12.1\text{Hz}$), 2.76 (1H, d, $J = 12.1\text{Hz}$), 2.28 (3H, s), 2.15-2.09 (2H, m), 1.92-1.83 (1H, m), 1.79-1.70 (1H, m), 1.31-1.26 (2H, m), 1.16-1.10 (2H, m), 0.83 (3H, t, $J = 7.3\text{Hz}$)。

[5043] 实施例 799

[5044] [式 1125]

[5045]

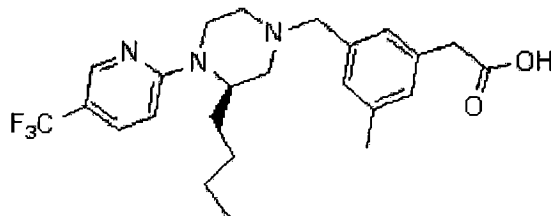


[5046] $^1\text{H-NMR}$ (DMSO- d_6) δ : 7.88 (1H, s), 7.45 (1H, d, $J = 8.8\text{Hz}$), 7.24 (1H, d, $J = 9.1\text{Hz}$), 7.03 (1H, s), 7.01 (1H, s), 6.97 (1H, s), 3.99-3.90 (2H, m), 3.50 (2H, s), 3.49 (2H, dd, $J = 58.4, 12.7\text{Hz}$), 2.91 (1H, d, $J = 11.5\text{Hz}$), 2.79 (1H, d, $J = 11.5\text{Hz}$), 2.28 (3H, s), 2.15-2.09 (2H, m), 1.97-1.91 (1H, m), 1.73-1.67 (1H, m), 1.32-1.26 (2H, m), 1.19-1.13 (2H, m), 0.84 (3H, t, $J = 7.1\text{Hz}$)。

[5047] 实施例 800

[5048] [式 1126]

[5049]

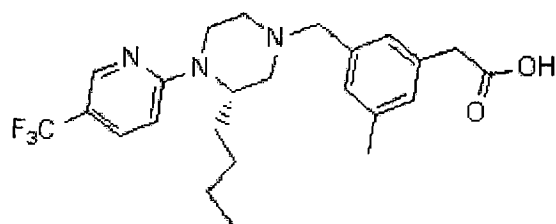


[5050] $^1\text{H-NMR}$ (DMSO- d_6) δ : 8.40 (1H, s), 7.77 (1H, dd, $J = 9.3, 2.6\text{Hz}$), 7.05 (2H, d, $J = 6.2\text{Hz}$), 6.99 (1H, s), 6.88 (1H, d, $J = 9.1\text{Hz}$), 4.41 (1H, s), 4.25 (1H, d, $J = 10.0\text{Hz}$), 3.63-3.29 (2H, m), 3.51 (2H, s), 3.14 (1H, t, $J = 11.3\text{Hz}$), 2.93 (1H, d, $J = 10.2\text{Hz}$), 2.81 (1H, d, $J = 11.8\text{Hz}$), 2.30 (3H, s), 2.11-1.88 (3H, m), 1.53-1.48 (1H, m), 1.32-1.23 (2H, m), 1.16-1.06 (2H, m), 0.84 (3H, t, $J = 7.3\text{Hz}$)。

[5051] 实施例 801

[5052] [式 1127]

[5053]

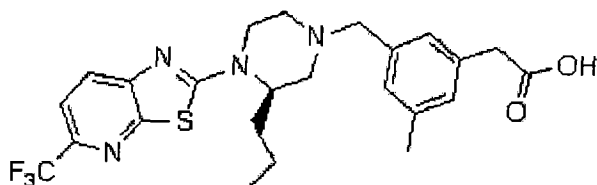


[5054] $^1\text{H-NMR}$ (DMSO- d_6) δ : 8.37 (1H, s), 7.74 (1H, dd, $J = 9.1, 2.5\text{Hz}$), 7.03 (2H, d, $J = 6.6\text{Hz}$), 6.97 (1H, s), 6.85 (1H, d, $J = 9.3\text{Hz}$), 4.38 (1H, s), 4.22 (1H, d, $J = 11.6\text{Hz}$), 3.50 (2H, s), 3.44 (2H, dd, $J = 87.8, 13.2\text{Hz}$), 3.12 (1H, t, $J = 11.3\text{Hz}$), 2.91 (1H, d, $J = 11.0\text{Hz}$), 2.79 (1H, d, $J = 11.3\text{Hz}$), 2.28 (3H, s), 1.51-1.45 (1H, m), 1.28-1.21 (2H, m), 1.13-1.06 (2H, m), 0.81 (3H, t, $J = 7.3\text{Hz}$)。

[5055] 实施例 802

[5056] [式 1128]

[5057]

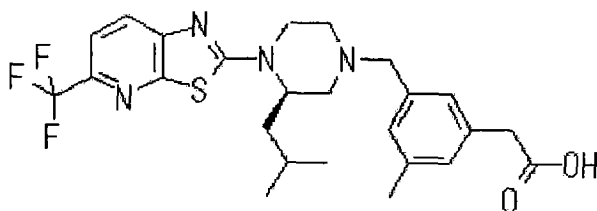


[5058] $^1\text{H-NMR}$ (DMSO- d_6) δ : 7.87 (1H, d, $J = 8.6\text{Hz}$), 7.78 (1H, d, $J = 8.6\text{Hz}$), 7.05 (2H, s), 7.00 (1H, s), 4.13-4.02 (2H, m), 3.63-3.34 (2H, m), 3.51 (2H, s), 2.96 (1H, d, $J = 11.4\text{Hz}$), 2.83 (1H, d, $J = 11.9\text{Hz}$), 2.31 (3H, s), 2.21-2.15 (2H, m), 1.95-1.87 (1H, m), 1.84-1.76 (1H, m), 1.27-1.18 (2H, m), 0.92 (3H, t, $J = 7.3\text{Hz}$)。

[5059] 实施例 803

[5060] [式 1129]

[5061]

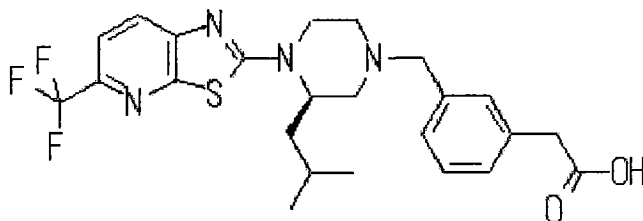


[5062] $^1\text{H-NMR}$ (CDCl $_3$) δ : 7.71 (1.0H, d, $J = 8.23\text{Hz}$), 7.58 (1.0H, d, $J = 8.23\text{Hz}$), 7.17-7.00 (3.0H, m), 4.22-4.01 (2.0H, m), 3.67-3.29 (5.0H, m), 3.07-2.72 (2.0H, m), 2.38-2.19 (5.0H, m), 2.03-1.90 (1.0H, m), 1.75-1.56 (2.0H, m), 1.55-1.40 (1.0H, m), 1.02-0.88 (6.0H, m)。

[5063] 实施例 804

[5064] [式 1130]

[5065]

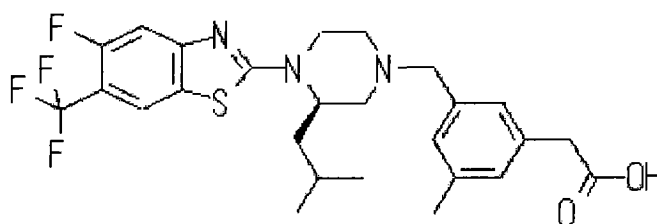


[5066] $^1\text{H-NMR}$ (CDCl_3) δ : 7.70 (1.0H, d, $J = 8.51\text{Hz}$), 7.57 (1.0H, d, $J = 8.51\text{Hz}$), 7.37-7.20 (4.0H, m), 4.22-4.03 (2.0H, m), 3.74-3.38 (5.0H, m), 3.13-2.74 (2.0H, m), 2.43-2.18 (2.0H, m), 2.00-1.85 (1.0H, m), 1.80-1.58 (1.0H, m), 1.50-1.41 (1.0H, m), 0.98-0.89 (6.0H, m)。

[5067] 实施例 805

[5068] [式 1131]

[5069]

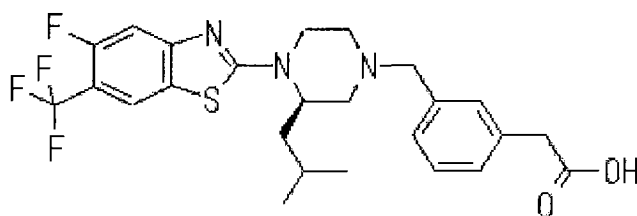


[5070] $^1\text{H-NMR}$ (DMSO-d_6) δ : 8.25 (1.0H, d, $J = 7.41\text{Hz}$), 7.42 (1.0H, d, $J = 12.90\text{Hz}$), 7.05-6.95 (3.0H, m), 4.17-3.88 (2.0H, m), 3.59 (2.0H, d, $J = 14.00\text{Hz}$), 3.49 (2.0H, s), 3.45-3.19 (2.0H, m), 2.93 (1.0H, d, $J = 11.53\text{Hz}$), 2.76 (1.0H, d, $J = 11.53\text{Hz}$), 2.28 (3.0H, s), 2.23-2.07 (2.0H, m), 1.98-1.87 (1.0H, m), 1.59-1.34 (1.6H, m), 0.93-0.87 (6.0H, m)。

[5071] 实施例 806

[5072] [式 1132]

[5073]

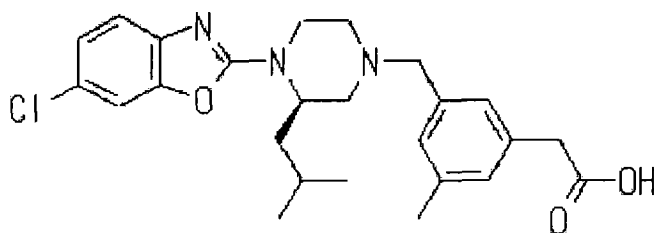


[5074] $^1\text{H-NMR}$ (DMSO-d_6) δ : 8.24 (1.0H, d, $J = 7.41\text{Hz}$), 7.42 (1.0H, d, $J = 12.62\text{Hz}$), 7.32-7.13 (4.0H, m), 4.24-3.82 (2.0H, m), 3.63 (1.0H, d, $J = 13.72\text{Hz}$), 3.56 (2.0H, s), 3.53-3.36 (3.0H, m), 2.93 (1.0H, d, $J = 11.53\text{Hz}$), 2.77 (1.0H, d, $J = 11.53\text{Hz}$), 2.23-2.11 (2.0H, m), 1.95-1.80 (1.0H, m), 1.64-1.50 (1.0H, m), 1.48-1.32 (1.0H, m), 0.94-0.86 (6.0H, m)。

[5075] 实施例 807

[5076] [式 1133]

[5077]

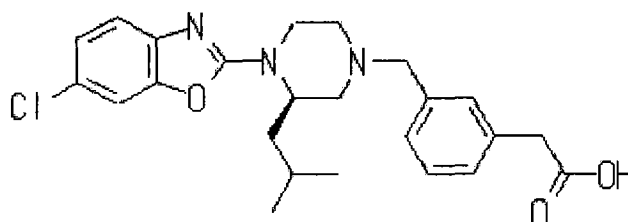


[5078] $^1\text{H-NMR}$ (CDCl_3) δ : 7.29–7.19 (3.0H, m), 7.17–7.02 (3.0H, m), 4.43–4.25 (1.0H, m), 4.16–4.01 (1.0H, m), 3.67–3.35 (4.0H, m), 3.11–2.69 (2.0H, m), 2.41–2.16 (5.0H, m), 1.85–1.70 (2.0H, m), 1.53–1.39 (1.0H, m), 0.98–0.86 (6.0H, m)。

[5079] 实施例 808

[5080] [式 1134]

[5081]

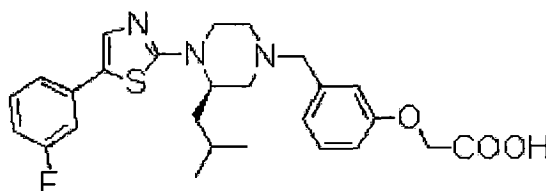


[5082] $^1\text{H-NMR}$ (CDCl_3) δ : 7.40–7.19 (6.0H, m), 7.14 (1.0H, dd, $J = 8.51, 1.92\text{Hz}$), 4.49–4.24 (1.0H, m), 4.22–4.01 (1.0H, m), 3.71–3.39 (4.0H, m), 2.99–2.71 (2.0H, m), 2.53–1.69 (4.0H, m), 1.55–1.39 (1.0H, m), 0.96–0.89 (6.0H, m)。

[5083] 实施例 809

[5084] [式 1135]

[5085]



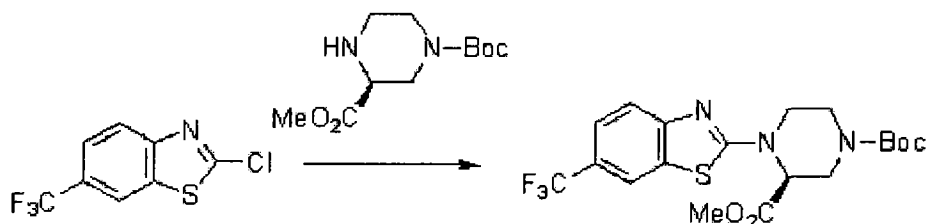
[5086] $\text{TLC}_{\text{Rf}} = 0.55$ ($\text{MeOH} : \text{CHCl}_3 = 1 : 10$)

[5087] 参考例 264

[5088] (S)-4-(6-三氟甲基苯并噻唑-2-基)哌嗪-1,3-二羧酸-1-叔丁基酯-3-甲基酯

[5089] [式 1136]

[5090]



[5091] 将 2-氯-6-三氟甲基苯并噻唑 (2.79g), (S)-4-N-Boc-哌嗪羧酸甲基酯 (3.10g), 碳酸钾 (1.95g) 和二甲基甲酰胺 (20mL) 在 55°C 搅拌 16 小时和在 90°C 搅拌 7 小时。向反应溶液加入水并且用乙酸乙酯萃取。有机层用盐水洗涤, 并且用硫酸镁干燥。减压蒸发溶

剂,并将残余物通过硅胶柱色谱法纯化,得到标题化合物 (1.40g)。收率:27%。

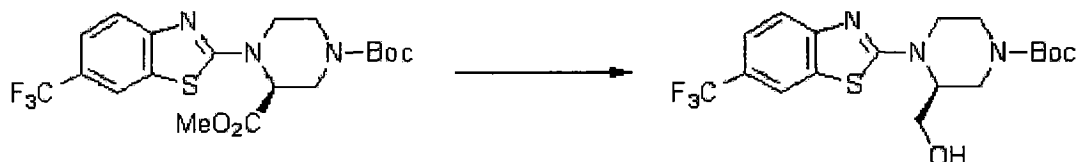
[5092] $^1\text{H-NMR}$ (CDCl_3) δ : 1.47 (9H, s), 2.97-3.18 (1H, m), 3.20-3.38 (1H, m), 3.58-3.81 (2H, m), 3.76 (3H, s), 4.09-4.37 (1H, m), 4.61-4.77 (1H, m), 5.06 (1H, brs), 7.55 (1H, d, $J = 8.4, 1.2\text{Hz}$), 7.61 (1H, d, $J = 8.4\text{Hz}$), 7.90 (1H, d, $J = 1.2\text{Hz}$)。

[5093] 参考例 265

[5094] (S)-3-羟基甲基-4-(6-三氟甲基苯并噻唑-2-基)哌嗪-1-羧酸叔丁基酯的制备

[5095] [式 1137]

[5096]



[5097] 向 (S)-4-(6-三氟甲基苯并噻唑-2-基)哌嗪-1,3-二羧酸-1-叔丁基酯-3-甲基酯 (1.18g) 的四氢呋喃 (10mL) 溶液中加入硼氢化锂 (65.7mg)。将混合物搅拌 20 小时。向反应溶液加入氯化铵水溶液并且用乙酸乙酯萃取。有机层用盐水洗涤,并且用硫酸镁干燥。减压蒸发溶剂,并将残余物通过硅胶柱色谱法纯化,得到标题化合物 (840mg)。收率:76%。

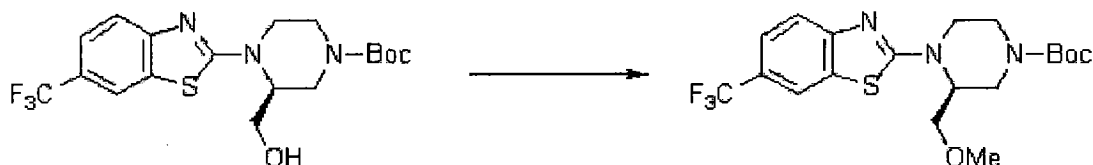
[5098] $^1\text{H-NMR}$ (CDCl_3) δ : 1.50 (9H, s), 3.03-3.30 (2H, m), 3.35-3.55 (1H, m), 3.68-4.00 (3H, m), 4.00-4.43 (3H, m), 7.51-7.59 (2H, m), 7.87 (1H, d, $J = 0.8\text{Hz}$)。

[5099] 参考例 266

[5100] (S)-3-甲氧基甲基-4-(6-三氟甲基苯并噻唑-2-基)哌嗪-1-羧酸叔丁基酯的制备

[5101] [式 1138]

[5102]



[5103] 向 (S)-3-羟基甲基-4-(6-三氟甲基苯并噻唑-2-基)哌嗪-1-羧酸叔丁基酯 (209mg) 的二甲基甲酰胺 (2mL) 溶液中顺序地加入碘甲烷 (0.5mL) 和氢化钠 (62.4mg)。将混合物在室温搅拌 24 小时。向反应溶液加入冰水并且用乙酸乙酯萃取。有机层用盐水洗涤,并且用硫酸镁干燥。减压蒸发溶剂,并将残余物通过硅胶柱色谱法纯化,得到标题化合物 (167mg)。收率:77%。

[5104] $^1\text{H-NMR}$ (CDCl_3) δ : 1.50 (9H, s), 2.96-3.19 (2H, m), 3.34-3.45 (1H, m), 3.38 (3H, s), 3.57 (2H, d, $J = 6.9\text{Hz}$), 3.94-4.06 (1H, m), 4.20-4.33 (3H, m), 7.53 (1H, dd, $J = 8.7, 1.5\text{Hz}$), 7.58 (1H, d, $J = 8.7\text{Hz}$), 7.86 (1H, d, $J = 1.5\text{Hz}$)。

[5105] 参考例 267

[5106] 2-((S)-2-甲氧基甲基哌嗪-1-基)-6-三氟甲基苯并噻唑的制备

[5107] [式 1139]

[5108]



[5109] 向 (S)-3-甲氧基甲基-4-(6-三氟甲基苯并噻唑-2-基)哌嗪-1-羧酸叔丁基酯 (167mg) 的二氯甲烷 (1.5mL) 溶液中加入三氟乙酸 (0.3mL)。将混合物在室温搅拌 20 小时。将反应溶液减压浓缩。向其中加入饱和碳酸氢钠水溶液并用乙酸乙酯萃取。有机层用盐水洗涤, 并且用硫酸镁干燥。减压蒸发溶剂, 得到标题化合物 (123mg)。收率: 96%。

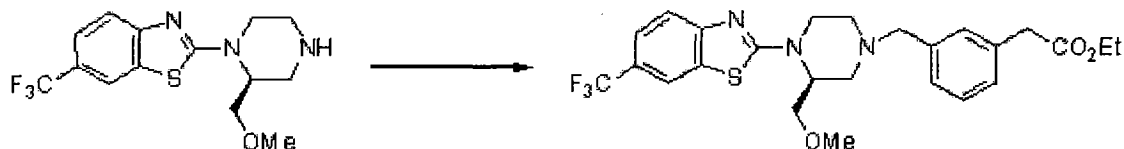
[5110] $^1\text{H-NMR}$ (CDCl₃) δ : 2.84-2.96 (3H, m), 3.01 (1H, dd, $J = 12.0, 3.9\text{Hz}$), 3.06-3.16 (1H, m), 3.26 (1H, d, $J = 12.9\text{Hz}$), 3.39 (1H, s), 3.46 (1H, dd, $J = 12.0, 3.3\text{Hz}$), 3.66 (1H, dd, $J = 12.4, 5.1\text{Hz}$), 3.91 (1H, dd, $J = 12.4, 7.2\text{Hz}$), 3.90-3.96 (1H, m), 4.12-4.21 (1H, m), 7.52 (1H, dd, $J = 8.4, 2.1\text{Hz}$), 7.56 (1H, d, $J = 8.4\text{Hz}$), 7.85 (1H, d, $J = 2.1\text{Hz}$)。

[5111] 参考例 268

[5112] [3-[(S)-3-甲氧基甲基-4-(6-三氟甲基苯并噻唑-2-基)哌嗪-1-基甲基]苯基]乙酸乙酯的制备

[5113] [式 1140]

[5114]



[5115] 将 2-((S)-2-甲氧基甲基哌嗪-1-基)-6-三氟甲基苯并噻唑 (123mg), (3-溴甲基苯基) 乙酸乙酯 (104mg), 碳酸钾 (259mg) 和二甲基甲酰胺 (1.5mL) 的混合物在室温搅拌 2 小时。向反应溶液加入水并且用乙酸乙酯萃取。有机层用盐水洗涤, 并且用硫酸镁干燥。减压蒸发溶剂, 并将残余物通过硅胶柱色谱法纯化, 得到标题化合物 (169mg)。收率: 90%。

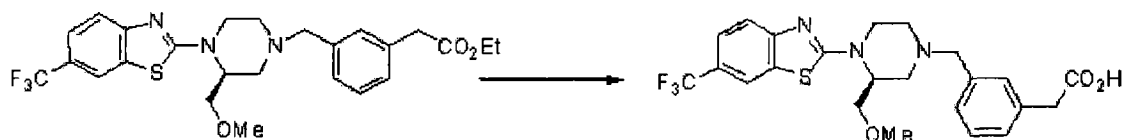
[5116] $^1\text{H-NMR}$ (CDCl₃) δ : 1.26 (3H, t, $J = 7.2\text{Hz}$), 2.20-2.32 (2H, m), 2.90 (1H, brd, $J = 10.8\text{Hz}$), 3.04 (1H, d, $J = 11.7\text{Hz}$), 3.36 (3H, s), 3.39-3.64 (3H, m), 3.62 (2H, s), 3.70 (1H, dd, $J = 9.0, 6.0\text{Hz}$), 3.83 (1H, t, $J = 9.0\text{Hz}$), 4.03 (1H, brd, $J = 12.6\text{Hz}$), 4.16 (2H, q, $J = 7.2\text{Hz}$), 4.13-4.24 (1H, m), 7.18-7.33 (4H, m), 7.51 (1H, dd, $J = 8.4, 1.8\text{Hz}$), 7.56 (1H, d, $J = 8.4\text{Hz}$), 7.83 (1H, d, $J = 1.8\text{Hz}$)。

[5117] 实施例 810

[5118] [3-[(S)-3-甲氧基甲基-4-(6-三氟甲基苯并噻唑-2-基)哌嗪-1-基甲基]苯基]乙酸的制备

[5119] [式 1141]

[5120]



[5121] 将 [3-[(S)-3-甲氧基甲基-4-(6-三氟甲基苯并噻唑-2-基)哌嗪-1-基甲基]苯基]乙酸乙酯 (167mg), 2N 氢氧化钠水溶液 (0.8mL), 四氢呋喃 (1.2mL) 和甲醇 (1.2mL) 的混合物在室温搅拌 16 小时。将反应溶液减压浓缩。向残余物中加入 2N 盐酸并且用乙酸乙酯萃取。有机层用盐水洗涤, 并且用硫酸镁干燥。减压蒸发溶剂, 得到标题化合物 (153mg)。收率: 97%。

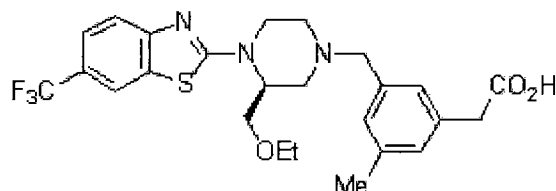
[5122] TLC_{Rf} = 0.40 (MeOH : CHCl₃ = 1 : 10)

[5123] 通过与如上相似的方法得到以下化合物。

[5124] 实施例 811

[5125] [式 1142]

[5126]

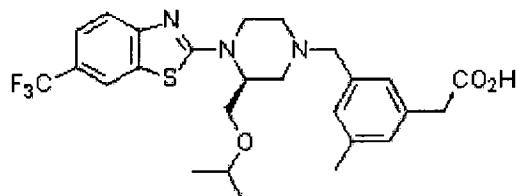


[5127] TLC_{Rf} = 0.33 (MeOH : CHCl₃ = 1 : 10)

[5128] 实施例 812

[5129] [式 1143]

[5130]

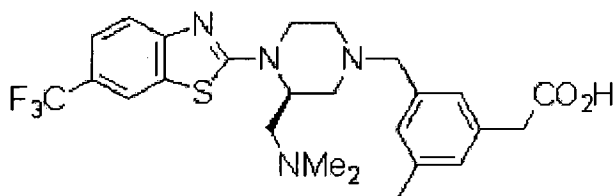


[5131] TLC_{Rf} = 0.52 (MeOH : CHCl₃ = 1 : 15)

[5132] 实施例 813

[5133] [式 1144]

[5134]

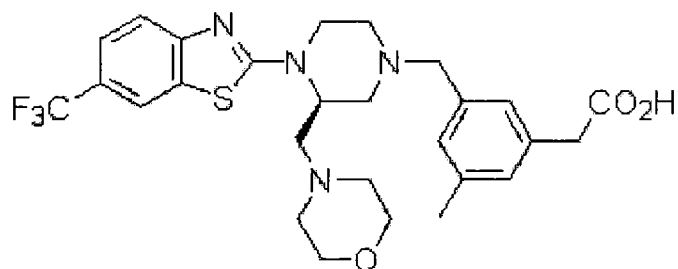


[5135] TLC_{Rf} = 0.088 (MeOH : CHCl₃ = 1 : 5)

[5136] 实施例 814

[5137] [式 1145]

[5138]

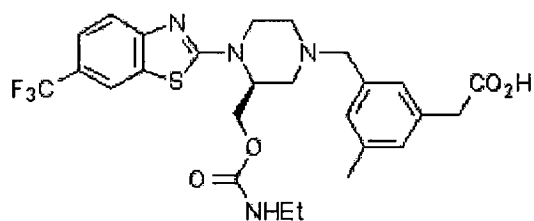


[5139] TLC_{Rf} = 0.17 (MeOH : CHCl₃ = 1 : 15)

[5140] 实施例 815

[5141] [式 1146]

[5142]

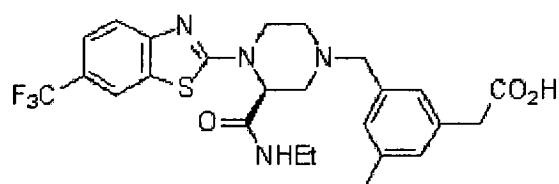


[5143] TLC_{Rf} = 0.29 (MeOH : CHCl₃ = 1 : 15)

[5144] 实施例 816

[5145] [式 1147]

[5146]

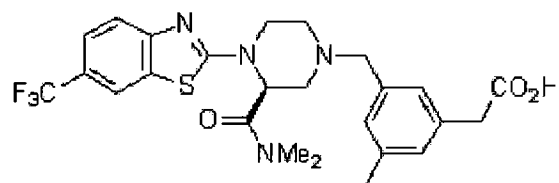


[5147] TLC_{Rf} = 0.23 (MeOH : CHCl₃ = 1 : 15)

[5148] 实施例 817

[5149] [式 1148]

[5150]

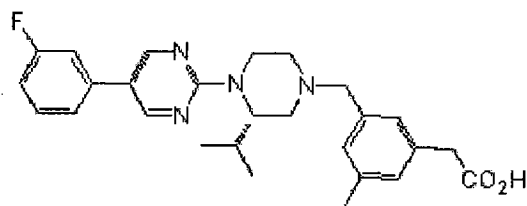


[5151] TLC_{Rf} = 0.28 (MeOH : CHCl₃ = 1 : 15)

[5152] 实施例 818

[5153] [式 1149]

[5154]

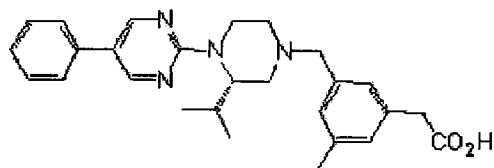


[5155] MS (ESI) ;m/z 463 [M+H]⁺

[5156] 实施例 819

[5157] [式 1150]

[5158]

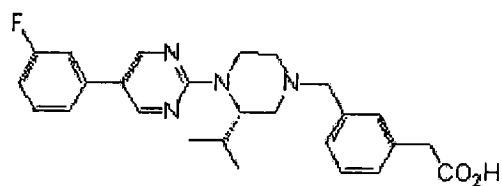


[5159] MS (ESI) ;m/z 445 [M+H]⁺

[5160] 实施例 820

[5161] [式 1151]

[5162]

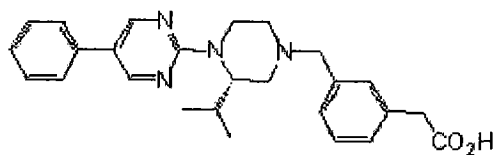


[5163] MS (ESI) ;m/z 449 [M+H]⁺

[5164] 实施例 821

[5165] [式 1152]

[5166]

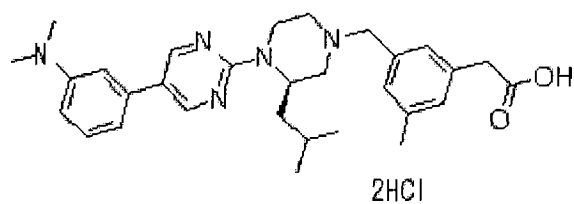


[5167] MS (ESI) ;m/z 431 [M+H]⁺

[5168] 实施例 822

[5169] [式 1153]

[5170]

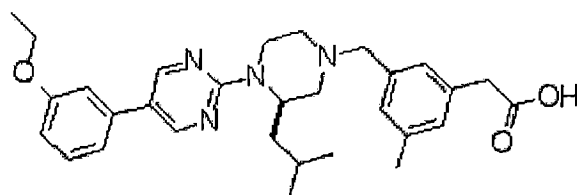


[5171] TLC : (SiO₂) AcOEt- 己烷 (3 : 1) R_f = 0.21

[5172] 实施例 823

[5173] [式 1154]

[5174]

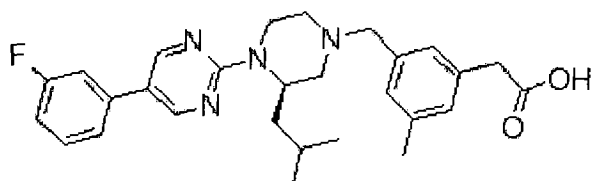


[5175] TLC : (SiO₂) AcOEt R_f = 0.46

[5176] 实施例 824

[5177] [式 1155]

[5178]

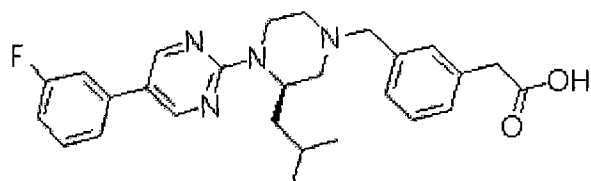


[5179] TLC : (SiO₂) AcOEt R_f = 0.45

[5180] 实施例 825

[5181] [式 1156]

[5182]

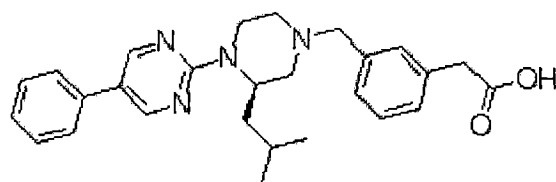


[5183] TLC : (SiO₂) AcOEt R_f = 0.67

[5184] 实施例 826

[5185] [式 1157]

[5186]

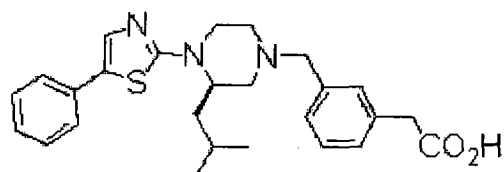


[5187] TLC : (SiO₂) AcOEt R_f = 0.60

[5188] 实施例 827

[5189] [式 1158]

[5190]

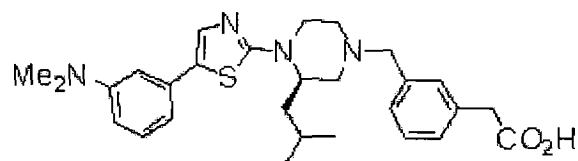


[5191] TLC : (SiO₂) AcOEt- 己烷 (1 : 1) R_f = 0.18

[5192] 实施例 828

[5193] [式 1159]

[5194]

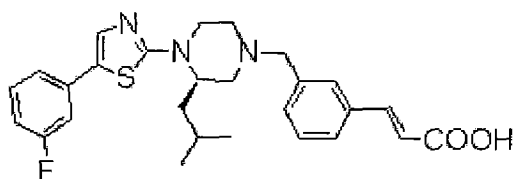


[5195] TLC : (SiO₂) AcOEt- 己烷 (1 : 1) R_f = 0.25

[5196] 实施例 829

[5197] [式 1160]

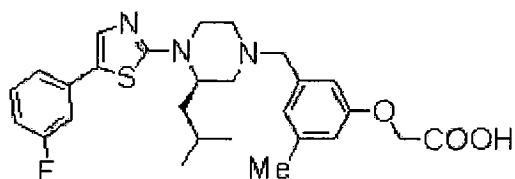
[5198]

[5199] TLC : (SiO₂) AcOEt- 己烷 (1 : 1) R_f = 0.34

[5200] 实施例 830

[5201] [式 1161]

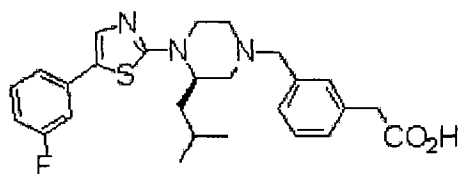
[5202]

[5203] TLC : (SiO₂) AcOEt R_f = 0.29

[5204] 实施例 831

[5205] [式 1162]

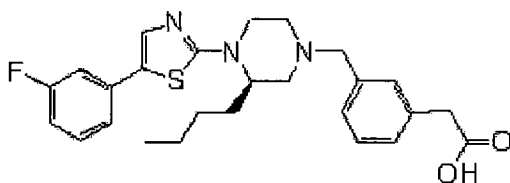
[5206]

[5207] TLC : (SiO₂) AcOEt R_f = 0.25

[5208] 实施例 832

[5209] [式 1163]

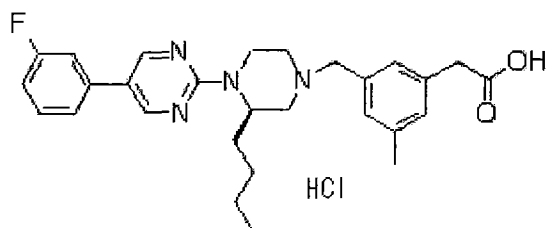
[5210]

[5211] MS (ESI) m/z 468 [M+H]⁺

[5212] 实施例 833

[5213] [式 1164]

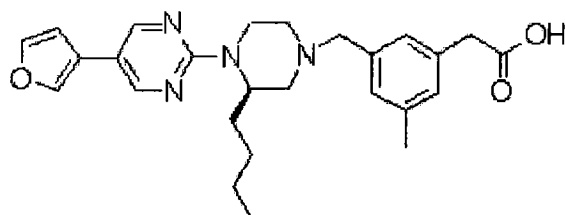
[5214]

[5215] MS (ESI) m/z 477 [M+H]⁺

[5216] 实施例 834

[5217] [式 1165]

[5218]

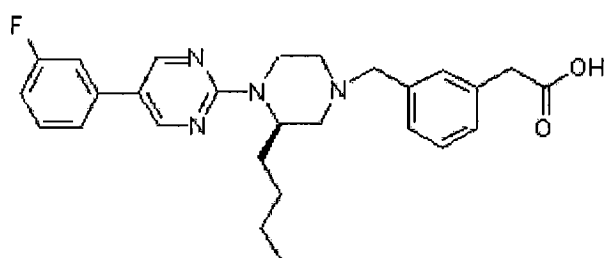


[5219] MS (ESI) m/z 449 $[M+H]^+$

[5220] 实施例 835

[5221] [式 1166]

[5222]

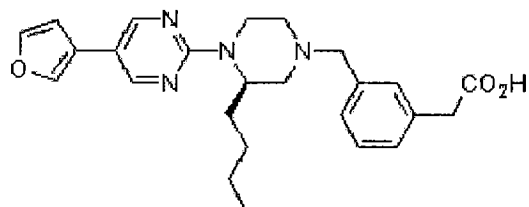


[5223] MS (ESI) m/z 463 $[M+H]^+$

[5224] 实施例 836

[5225] [式 1167]

[5226]

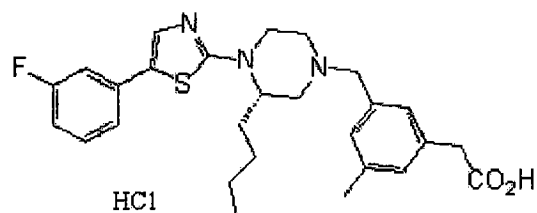


[5227] MS (ESI) m/z 435 $[M+H]^+$

[5228] 实施例 837

[5229] [式 1168]

[5230]



[5231] MS (ESI) m/z 483 $[M+H]^+$

[5232] 实施例 838

[5233] [式 1169]

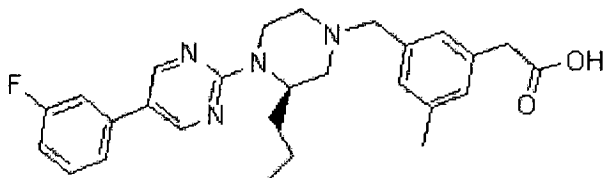
[5234]

1.82-1.95 (2H, m), 3.00-3.15 (2H, m), 3.24-3.39 (3H, m), 3.62 (2H, s), 4.25-4.40 (2H, m), 4.81-4.86 (1H, m), 5.05 (1H, m), 7.18 (1H, m), 7.39-7.60 (7H, m), 8.82 (2H, s), 10.62 (2H, br), 12.45 (1H, br)。

[5248] 实施例 842

[5249] [式 1173]

[5250]

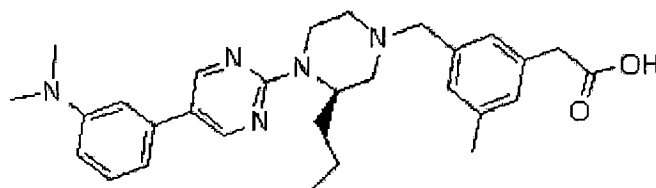


[5251] $^1\text{H-NMR}$ (DMSO- d_6) δ : 8.72 (2H, s), 7.52-7.48 (3H, m), 7.14-7.11 (1H, m), 7.03 (2H, s), 6.96 (1H, s), 4.73 (1H, s), 4.56 (1H, d, $J = 12.3\text{Hz}$), 3.56-3.31 (2H, m), 3.51 (2H, s), 3.19-3.15 (1H, m), 2.90 (1H, d, $J = 9.9\text{Hz}$), 2.79 (1H, d, $J = 11.0\text{Hz}$), 2.29 (3H, s), 2.03 (2H, s), 1.86-1.83 (1H, m), 1.65-1.62 (1H, m), 1.18-1.15 (2H, m), 0.88 (3H, t, $J = 7.1\text{Hz}$)。

[5252] 实施例 843

[5253] [式 1174]

[5254]

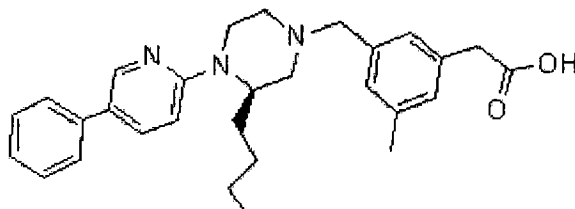


[5255] $^1\text{H-NMR}$ (DMSO- d_6) δ : 8.65 (2H, s), 7.23 (1H, t, $J = 8.2\text{Hz}$), 7.03 (2H, s), 6.96 (1H, s), 6.88 (1H, s), 6.87 (1H, d, $J = 7.8\text{Hz}$), 6.69 (1H, d, $J = 9.3\text{Hz}$), 4.72 (1H, s), 4.54 (1H, d, $J = 10.0\text{Hz}$), 3.59-3.32 (2H, m), 3.51 (2H, s), 3.15 (1H, t, $J = 10.0\text{Hz}$), 2.94 (6H, s), 2.91-2.88 (1H, m), 2.77 (1H, t, $J = 11.0\text{Hz}$), 2.29 (3H, s), 2.05-1.97 (2H, m), 1.89-1.81 (1H, m), 1.65-1.58 (1H, m), 1.18-1.14 (2H, m), 0.88 (3H, t, $J = 7.3\text{Hz}$)。

[5256] 实施例 844

[5257] [式 1175]

[5258]

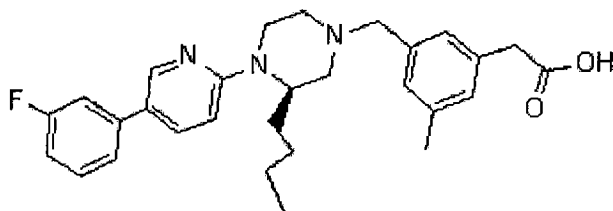


[5259] $^1\text{H-NMR}$ (DMSO- d_6) δ : 8.42 (1H, d, $J = 2.7\text{Hz}$), 7.82 (1H, dd, $J = 8.9, 2.6\text{Hz}$), 7.62 (1H, d, $J = 1.4\text{Hz}$), 7.59 (1H, s), 7.42 (2H, t, $J = 7.5\text{Hz}$), 7.29 (1H, d, $J = 7.4\text{Hz}$), 7.04 (2H, d, $J = 8.8\text{Hz}$), 6.97 (1H, s), 6.81 (1H, d, $J = 9.1\text{Hz}$), 4.31 (1H, s), 4.14 (1H, d, $J = 10.9\text{Hz}$), 3.62-3.33 (2H, m), 3.50 (2H, s), 3.14-3.06 (1H, m), 2.91 (1H, d, $J = 10.0\text{Hz}$), 2.80 (1H, d, $J = 10.0\text{Hz}$), 2.29 (3H, s), 2.09 (1H, t, $J = 10.0\text{Hz}$), 2.01-1.92 (2H, m), 1.47-1.38 (1H, m), 1.29-1.23 (2H, m), 1.15-1.07 (2H, m), 0.82 (3H, t, $J = 7.1\text{Hz}$)。

[5260] 实施例 845

[5261] [式 1176]

[5262]

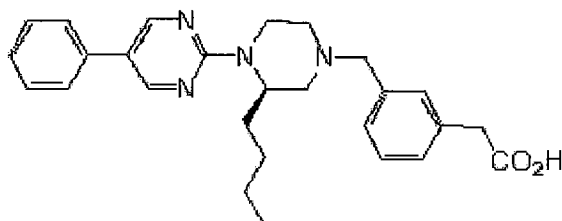


[5263] $^1\text{H-NMR}$ (DMSO-d_6) δ : 8.47 (1H, d, $J = 2.5\text{Hz}$), 7.87 (1H, dd, $J = 8.9, 2.7\text{Hz}$), 7.46 (3H, t, $J = 8.8\text{Hz}$), 7.05 (1H, s), 7.02 (1H, s), 6.97 (1H, s), 6.81 (1H, d, $J = 9.1\text{Hz}$), 4.32 (1H, s), 4.16 (1H, d, $J = 12.6\text{Hz}$), 3.63–3.28 (2H, m), 3.50 (2H, s), 3.10 (1H, t, $J = 12.6\text{Hz}$), 2.92 (1H, d, $J = 9.9\text{Hz}$), 2.80 (1H, d, $J = 10.9\text{Hz}$), 2.29 (3H, s), 2.09 (1H, t, $J = 9.4\text{Hz}$), 1.98–1.91 (2H, m), 1.44–1.39 (1H, m), 1.31–1.22 (2H, m), 1.15–1.06 (2H, m), 0.82 (3H, t, $J = 7.2\text{Hz}$).

[5264] 实施例 846

[5265] [式 1177]

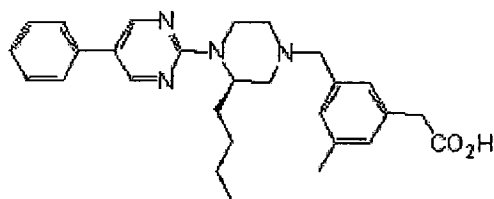
[5266]

[5267] MS (ESI) ; m/z 445 $[\text{M}+\text{H}]^+$

[5268] 实施例 847

[5269] [式 1178]

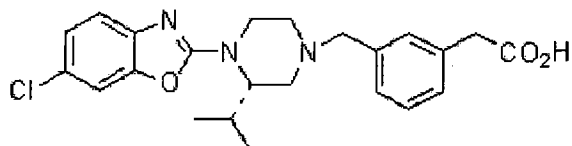
[5270]

[5271] MS (ESI) m/z 459 $[\text{M}+\text{H}]^+$

[5272] 实施例 848

[5273] [式 1179]

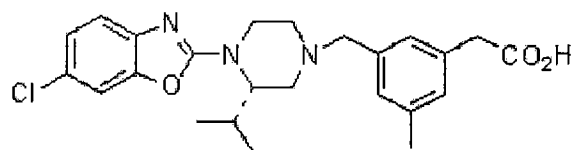
[5274]

[5275] MS (ESI) m/z 426 $[\text{M}-\text{H}]^-$

[5276] 实施例 849

[5277] [式 1180]

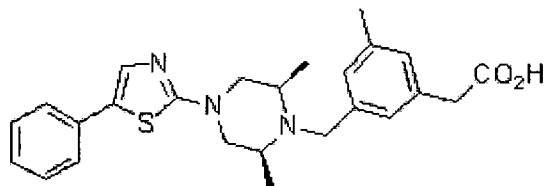
[5278]

[5279] MS (ESI) m/z 440 $[M-H]^-$

[5280] 实施例 850

[5281] [式 1181]

[5282]

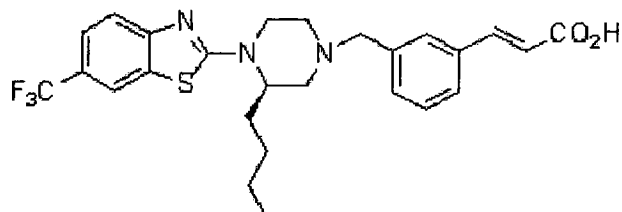


[5283] $^1\text{H-NMR}$ (DMSO-d_6) δ : 1.03 (6H, d, $J = 6.0\text{ Hz}$), 2.27 (3H, s), 2.63–2.80 (2H, m), 2.85–2.97 (2H, m), 3.49 (2H, s), 3.69–3.78 (4H, m), 6.86–7.61 (9H, m)。

[5284] 实施例 851

[5285] [式 1182]

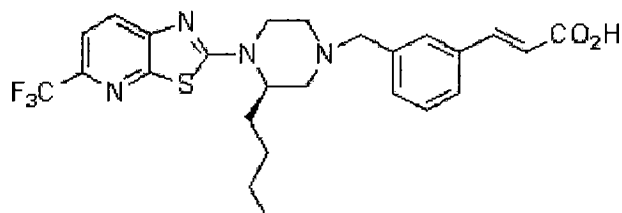
[5286]

[5287] TLC R_f 0.64 (己烷 : AcOEt = 1 : 1)

[5288] 实施例 852

[5289] [式 1183]

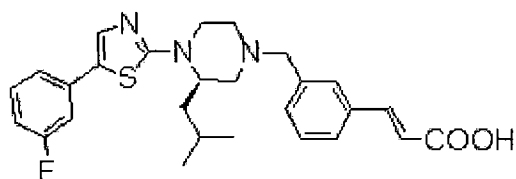
[5290]

[5291] TLC R_f 0.70 (己烷 : AcOEt = 1 : 1)

[5292] 实施例 853

[5293] [式 1184]

[5294]



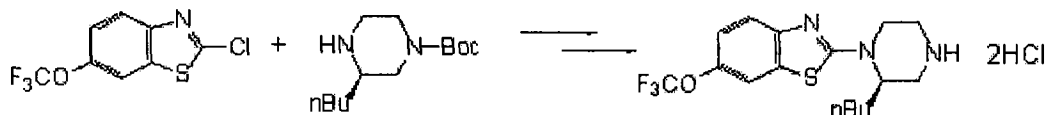
[5295] TLC:(SiO₂)AcOEt-己烷(1:1)R_f=0.34

[5296] 参考例 269

[5297] 2-((R)-2-丁基哌嗪-1-基)-6-三氟甲氧基苯并噻唑二盐酸盐的制备

[5298] [式 1185]

[5299]



[5300] 用 2-氯-6-三氟甲基苯并噻唑和哌嗪-1-羧酸叔丁基酯作为原料通过与参考例 84 或 155 相似的方法合成上述化合物。

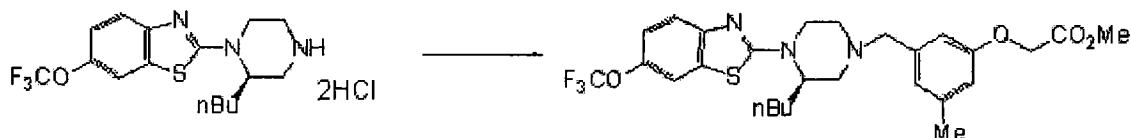
[5301] ¹H-NMR(DMSO-d₆) δ :0.90(3H, t, J = 7.0Hz), 1.31-1.37(4H, m), 1.85-1.95(2H, m), 3.03-3.18(1H, m), 3.25-3.39(3H, m), 3.42-3.55(1H, m), 4.13-4.33(2H, m), 7.31(1H, dd, J = 8.5, 1.8Hz), 7.54(1H, d, J = 8.5Hz), 7.99(1H, d, J = 1.8Hz), 9.14(1H, br s), 9.57(1H, br s)。

[5302] 参考例 270

[5303] [3-[(R)-3-丁基-4-(6-三氟甲氧基苯并噻唑-2-基)-哌嗪-1-基甲基]-5-甲基苯氧基]乙酸甲基酯的制备

[5304] [式 1186]

[5305]



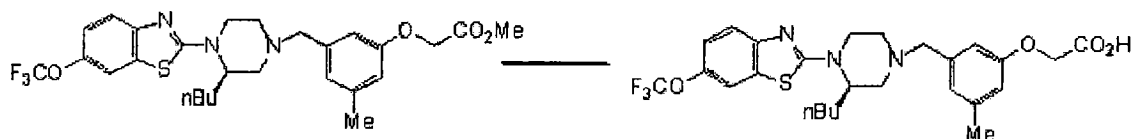
[5306] 将 2-((R)-2-丁基哌嗪-1-基)-6-三氟甲氧基苯并噻唑二盐酸盐(170mg), (3-氯甲基-5-甲基苯氧基)乙酸甲基酯(108mg), 碳酸钾(270mg), 碘化钾(65mg) 和二甲基甲酰胺(4mL) 的混合物在室温搅拌 24 小时。向反应溶液加入水并且用乙酸乙酯萃取。有机层用水和盐水洗涤, 并且用硫酸镁干燥。减压蒸发溶剂, 并将残余物通过硅胶柱色谱法纯化, 得到标题化合物(203mg)。收率:94%。

[5307] TLC R_f 0.62(AcOEt/正己烷=1/5)。

[5308] 实施例 854

[5309] [3-[(R)-3-丁基-4-(6-三氟甲氧基苯并噻唑-2-基)-哌嗪-1-基甲基]-5-甲基苯氧基]乙酸的制备

[5310] [式 1187]



[5311] 将 [3-[(R)-3-丁基-4-(6-三氟甲氧基苯并噻唑-2-基)-哌嗪-1-基甲基]-5-甲基苯氧基]乙酸甲基酯(203mg)、2N 氢氧化钠(0.46mL)、四氢呋喃(2mL) 和甲醇(2mL) 的混合物在室温搅拌 16 小时。向反应溶液加入水和氯仿。混合物用 2N 盐酸中和。反应溶液用氯仿萃取。有机层用盐水洗涤, 并且用硫酸镁干燥。减压蒸发溶剂, 得到标题化合物(182mg)。收率:91%。

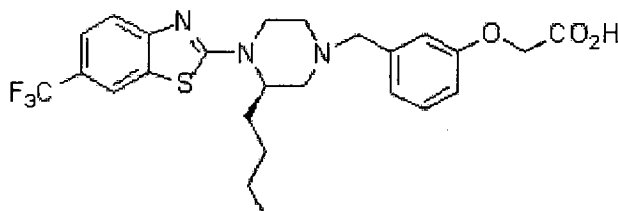
[5312] $^1\text{H-NMR}$ (DMSO- d_6) δ :7.90 (1.0H, d, $J = 1.65\text{Hz}$), 7.48 (1.0H, d, $J = 8.78\text{Hz}$), 7.25 (1.0H, dd, $J = 8.78, 1.65\text{Hz}$), 6.74 (1.0H, s), 6.67 (1.0H, s), 6.61 (1.0H, s), 4.48 (2.0H, s), 4.06-3.80 (1.0H, m), 3.72-3.20 (3.0H, m), 2.90 (1.0H, d, $J = 12.62\text{Hz}$), 2.81

[5313] 通过与如上相似的方法得到以下化合物。

[5314] 实施例 855

[5315] [式 1188]

[5316]

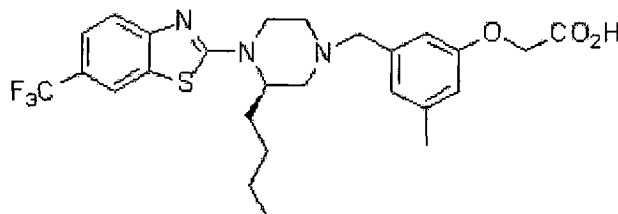


[5317] MS (ESI) m/z 508 $[\text{M}+\text{H}]^+$

[5318] 实施例 856

[5319] [式 1189]

[5320]

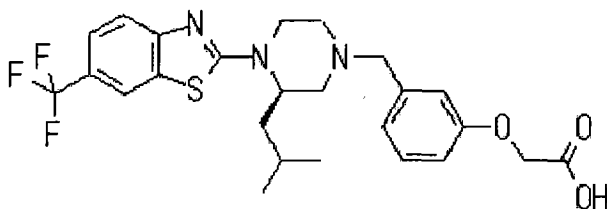


[5321] $^1\text{H-NMR}$ (DMSO- d_6) δ :8.23 (1.0H, s), 7.58-7.54 (2.0H, m), 6.74 (1.0H, s), 6.68 (1.0H, s), 6.62 (1.0H, s), 4.48 (2.0H, s), 4.11-3.87 (1.0H, m), 3.58-3.33 (3.0H, m), 2.94 (1.0H, d, $J = 12.42\text{Hz}$), 2.83 (1.0H, d, $J = 12.42\text{Hz}$), 2.27 (3.0H, s), 2.16-2.12 (2.0H, m), 2.01-1.92 (1.0H, m), 1.80-1.76 (1.0H, m), 1.34-1.21 (4.0H, m), 0.86 (3.0H, t, $J = 7.22\text{Hz}$)。

[5322] 实施例 857

[5323] [式 1190]

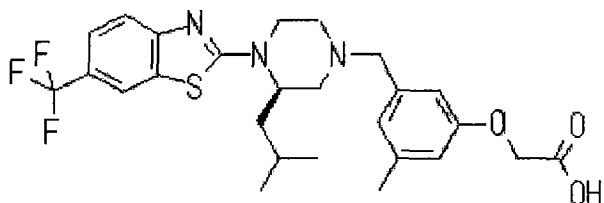
[5324]



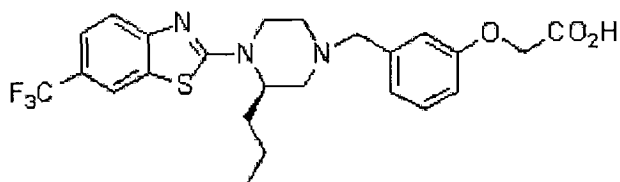
[5325] $^1\text{H-NMR}$ (DMSO- d_6) δ :8.22 (1.0H, s), 7.59-7.49 (2.0H, m), 7.24 (1.0H, dd, $J = 7.72, 7.72\text{Hz}$), 6.95-6.87 (2.0H, m), 6.82-6.76 (1.0H, m), 4.60 (2.0H, s), 4.20-3.89 (2.0H, m), 3.57 (1.0H, d, $J = 13.76\text{Hz}$), 3.47-3.22 (2.0H, m), 2.96-2.70 (2.0H, m), 2.24-2.08 (2.0H, m), 1.93-1.79 (1.5H, br m), 1.70-1.56 (1.2H, br m), 1.52-1.37 (1.4H, br m), 0.92 (6.0H, d, $J = 6.55\text{Hz}$)。

[5326] 实施例 858

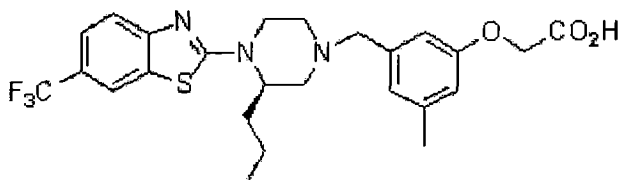
[5328]



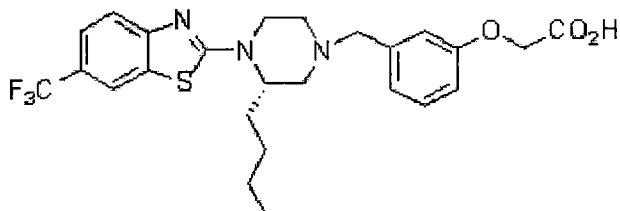
[5332]



[5336]



[5340]



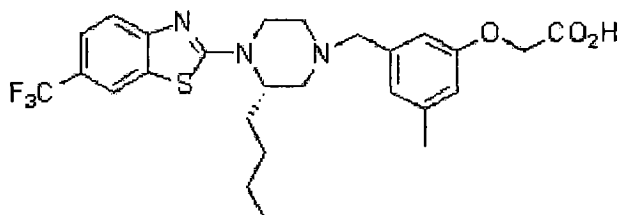
334

7.26 (1H, t, $J = 7.8\text{Hz}$), 7.51–7.58 (2H, m), 8.22 (1H, s), 13.00 (1H, br s)。

[5342] 实施例 862

[5343] [式 1195]

[5344]

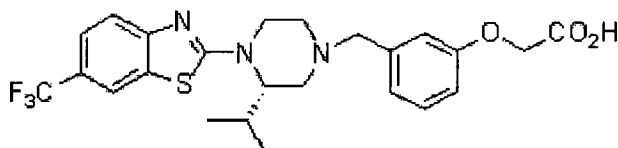


[5345] $^1\text{H-NMR}$ (300MHz, DMSO-d_6) δ 0.84 (3H, t, $J = 7.2\text{Hz}$), 1.15–1.36 (4H, m), 1.73–1.97 (2H, m), 2.11–2.16 (2H, m), 2.27 (3H, s), 2.79–2.92 (2H, m), 3.33–3.57 (3H, m), 4.02 (2H, m), 4.62 (2H, s), 6.63 (1H, s), 6.69 (1H, s), 6.76 (1H, s), 7.51–7.58 (2H, m), 8.22 (1H, s), 12.98 (1H, br s)。

[5346] 实施例 863

[5347] [式 1196]

[5348]

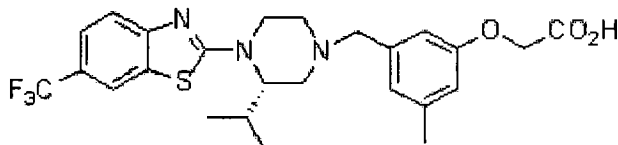


[5349] MS (ESI) 492 $[\text{M-H}]^-$

[5350] 实施例 864

[5351] [式 1197]

[5352]

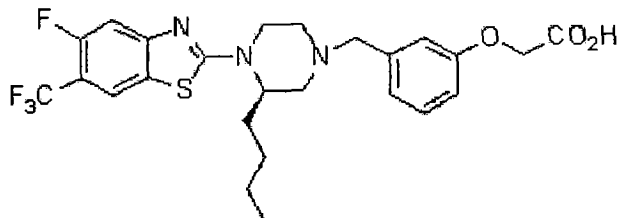


[5353] MS (ESI) 506 $[\text{M-H}]^-$

[5354] 实施例 865

[5355] [式 1198]

[5356]

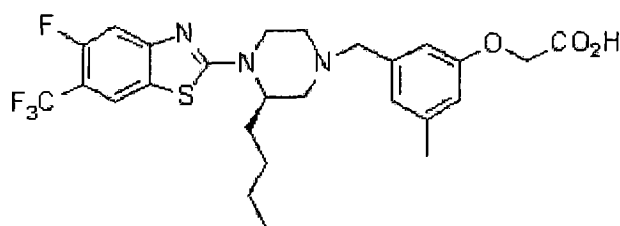


[5357] $^1\text{H-NMR}$ (300MHz, DMSO-d_6) δ 0.84 (3H, t, $J = 7.2\text{Hz}$), 1.15–1.35 (4H, m), 1.77–1.95 (2H, m), 2.10–2.18 (2H, m), 2.80–2.92 (2H, m), 3.25–3.59 (3H, m), 4.01 (2H, m), 4.61 (2H, s), 6.80 (1H, d, $J = 7.8\text{Hz}$), 6.89 (1H, s), 6.92 (1H, d, $J = 7.8\text{Hz}$), 7.25 (1H, t, $J = 7.8\text{Hz}$), 7.43 (1H, d, $J = 12.3\text{Hz}$), 8.23 (1H, d, $J = 7.5\text{Hz}$)。

[5358] 实施例 866

[5359] [式 1199]

[5360]

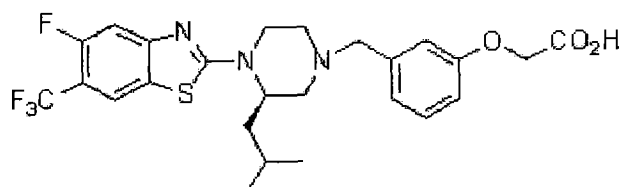


[5361] $^1\text{H-NMR}$ (300MHz, DMSO- d_6) δ 0.84 (3H, t, $J = 7.2\text{Hz}$), 1.15–1.35 (4H, m), 1.74–1.99 (2H, m), 2.11–2.14 (2H, m), 2.26 (3H, s), 2.79–2.92 (2H, m), 3.33–3.57 (3H, m), 3.99 (2H, m), 4.61 (2H, s), 6.63 (1H, s), 6.69 (1H, s), 6.75 (1H, s), 7.43 (1H, d, $J = 12.3\text{Hz}$), 8.23 (1H, d, $J = 7.5\text{Hz}$).

[5362] 实施例 867

[5363] [式 1200]

[5364]

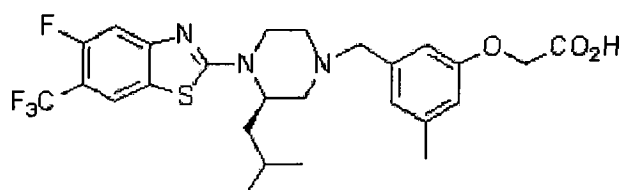


[5365] $^1\text{H-NMR}$ (DMSO- d_6) δ : 8.24 (1.0H, d, $J = 7.72\text{Hz}$), 7.42 (1.0H, d, $J = 12.59\text{Hz}$), 7.24 (1.0H, dd, $J = 7.72, 7.72\text{Hz}$), 6.95–6.86 (2.0H, m), 6.82–6.75 (1.0H, m), 4.55 (2.0H, s), 4.11–3.86 (2.0H, m), 3.60–3.20 (3.0H, m), 2.90 (1.0H, d, $J = 12.25\text{Hz}$), 2.77 (1.0H, d, $J = 12.25\text{Hz}$), 2.25–2.06 (2.0H, m), 1.92–1.76 (1.0H, m), 1.70–1.54 (1.0H, m), 1.53–1.35 (1.0H, m), 0.95–0.88 (6.0H, m).

[5366] 实施例 868

[5367] [式 1201]

[5368]

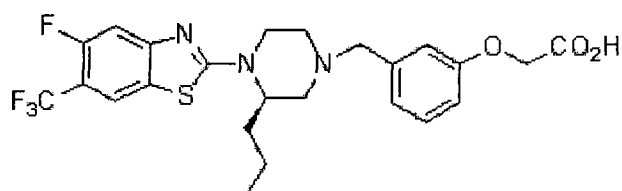


[5369] $^1\text{H-NMR}$ (DMSO- d_6) δ : 8.24 (1.0H, d, $J = 7.39\text{Hz}$), 7.42 (1.0H, d, $J = 12.59\text{Hz}$), 6.75 (1.0H, s), 6.68 (1.0H, s), 6.62 (1.0H, s), 4.61 (2.0H, s), 4.19–3.89 (2.0H, m), 3.59–3.21 (3.0H, m), 2.90 (1.0H, d, $J = 10.74\text{Hz}$), 2.83–2.71 (1.0H, m), 2.26 (3.0H, s), 2.21–2.08 (2.0H, m), 1.96–1.83 (1.0H, m), 1.65–1.52 (1.0H, m), 1.51–1.36 (1.0H, m), 0.95–0.88 (6.0H, m).

[5370] 实施例 869

[5371] [式 1202]

[5372]

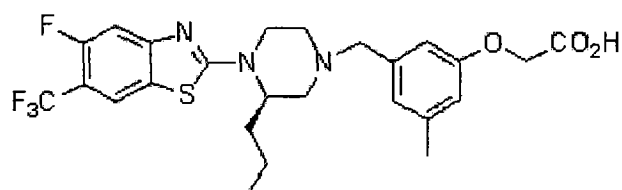


[5373] $^1\text{H-NMR}$ (DMSO-d_6) δ : 8.23 (1.0H, d, $J = 7.39\text{Hz}$), 7.43 (1.0H, d, $J = 12.42\text{Hz}$), 7.25 (1.0H, dd, $J = 7.72, 7.72\text{Hz}$), 6.96–6.88 (2.0H, m), 6.80 (1.0H, dd, $J = 8.31, 2.27\text{Hz}$), 4.64 (2.0H, s), 4.15–3.89 (2.0H, m), 3.60–3.22 (3.0H, m), 2.89 (1.0H, d, $J = 11.92\text{Hz}$), 2.82 (2.0H, d, $J = 11.92\text{Hz}$), 2.23–2.07 (2.0H, m), 1.90–1.76 (2.0H, m), 1.31–1.14 (2.0H, m), 0.90 (3.0H, t, $J = 7.30\text{Hz}$)。

[5374] 实施例 870

[5375] [式 1203]

[5376]

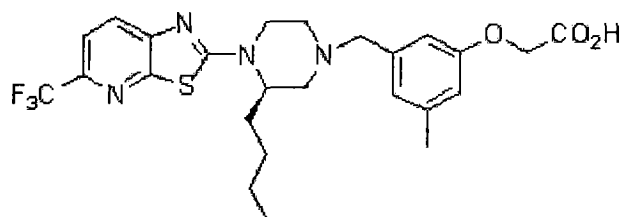


[5377] $^1\text{H-NMR}$ (DMSO-d_6) δ : 8.23 (1.0H, d, $J = 7.22\text{Hz}$), 7.43 (1.0H, d, $J = 12.42\text{Hz}$), 6.75 (1.0H, s), 6.69 (1.0H, s), 6.63 (1.0H, s), 4.62 (2.0H, s), 4.17–3.86 (2.0H, m), 3.57–3.22 (3.0H, m), 2.89 (1.0H, d, $J = 11.58\text{Hz}$), 2.81 (1.0H, d, $J = 11.58\text{Hz}$), 2.26 (3.0H, s), 2.19–2.07 (2.0H, m), 1.97–1.71 (2.0H, m), 1.31–1.15 (2.0H, m), 0.90 (3.0H, t, $J = 7.30\text{Hz}$)。

[5378] 实施例 871

[5379] [式 1204]

[5380]

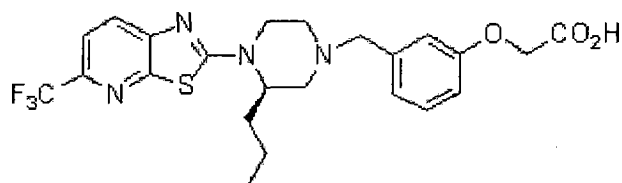


[5381] $^1\text{H-NMR}$ (DMSO-d_6) δ : 7.87 (1.0H, d, $J = 8.73\text{Hz}$), 7.77 (1.0H, d, $J = 8.39\text{Hz}$), 6.71 (1.0H, s), 6.64 (1.0H, s), 6.57 (1.0H, s), 4.28 (2.0H, s), 3.53–3.39 (6.0H, m), 3.00–2.71 (2.0H, m), 2.30–2.26 (3.0H, m), 2.18–2.15 (2.0H, m), 1.36–1.17 (4.0H, m), 0.87 (3.0H, t, $J = 7.13\text{Hz}$)。

[5382] 实施例 872

[5383] [式 1205]

[5384]

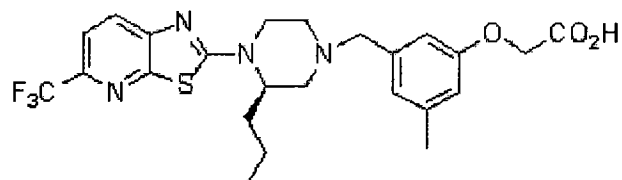


[5385] MS (ESI) 493 [M-H] -

[5386] 实施例 873

[5387] [式 1206]

[5388]

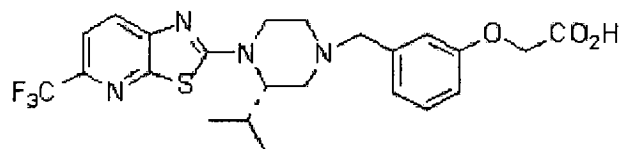


[5389] MS (ESI) 507 [M-H] -

[5390] 实施例 874

[5391] [式 1207]

[5392]

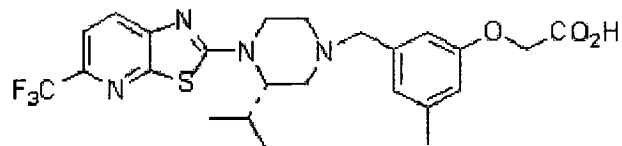


[5393] MS (ESI) m/z 493 [M-H] -

[5394] 实施例 875

[5395] [式 1208]

[5396]

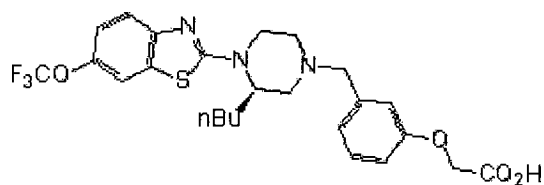


[5397] MS (ESI) m/z 507 [M-H] -

[5398] 实施例 876

[5399] [式 1209]

[5400]

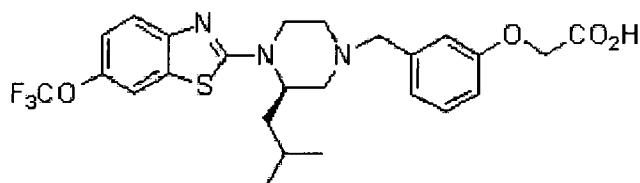


[5401] MS (ESI) m/z 524 [M+H] +

[5402] 实施例 877

[5403] [式 1210]

[5404]

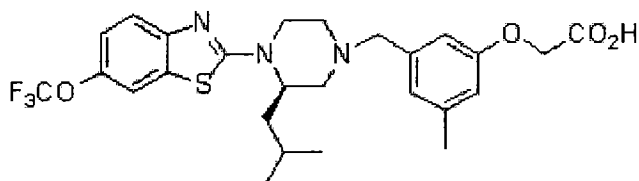


[5405] $^1\text{H-NMR}$ (DMSO- d_6) δ : 7.89 (1.0H, d, $J = 2.18\text{Hz}$), 7.45 (1.0H, d, $J = 8.73\text{Hz}$), 7.29–7.20 (2.0H, m), 6.95–6.88 (2.0H, m), 6.80 (1.0H, dd, $J = 8.73, 2.18\text{Hz}$), 4.64 (2.0H, s), 4.11–4.01 (1.0H, m), 3.97–3.85 (1.0H, m), 3.56 (1.0H, d, $J = 13.76\text{Hz}$), 3.44–3.29 (2.0H, m), 2.88 (1.0H, d, $J = 10.74\text{Hz}$), 2.78 (1.0H, d, $J = 10.74\text{Hz}$), 2.22–2.06 (2.0H, m), 1.90–1.76 (1.0H, m), 1.67–1.54 (1.0H, m), 1.50–1.37 (1.0H, m), 0.91 (6.0H, d, $J = 6.55\text{Hz}$).

[5406] 实施例 878

[5407] [式 1211]

[5408]

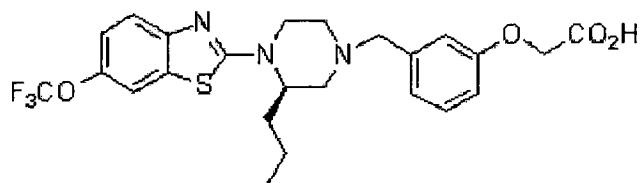


[5409] $^1\text{H-NMR}$ (DMSO- d_6) δ : 7.89 (1.0H, d, $J = 2.18\text{Hz}$), 7.45 (1.0H, d, $J = 8.73\text{Hz}$), 7.23 (1.0H, dd, $J = 8.73, 2.18\text{Hz}$), 6.75 (1.0H, s), 6.68 (1.0H, s), 6.62 (1.0H, s), 4.61 (2.0H, s), 4.09–4.00 (1.0H, m), 3.96–3.86 (1.0H, m), 3.55 (2.0H, d, $J = 13.26\text{Hz}$), 3.50–3.14 (1.0H, m), 2.89 (1.0H, d, $J = 11.92\text{Hz}$), 2.77 (1.0H, d, $J = 11.92\text{Hz}$), 2.26 (3.0H, s), 2.21–2.08 (2.0H, m), 1.96–1.83 (1.0H, m), 1.62–1.36 (2.0H, m), 0.94–0.88 (6.0H, m).

[5410] 实施例 879

[5411] [式 1212]

[5412]

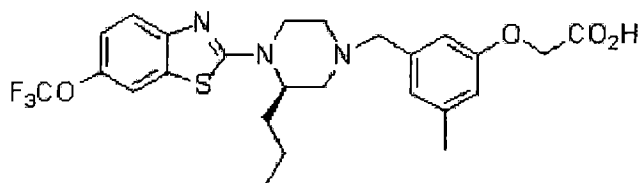


[5413] $^1\text{H-NMR}$ (300MHz, DMSO- d_6) δ 0.90 (3H, t, $J = 7.2\text{Hz}$), 1.14–1.28 (2H, m), 1.72–1.90 (2H, m), 2.12–2.18 (2H, m), 2.79–2.89 (2H, m), 3.33–3.58 (3H, m), 3.89–4.00 (2H, m), 4.66 (2H, s), 6.80 (1H, dd, $J = 8.1\text{Hz}, 1.8\text{Hz}$), 6.90–6.94 (2H, m), 7.22–7.28 (2H, m), 7.45 (1H, d, $J = 8.7\text{Hz}$), 7.88 (1H, s), 12.98 (1H, br s).

[5414] 实施例 880

[5415] [式 1213]

[5416]

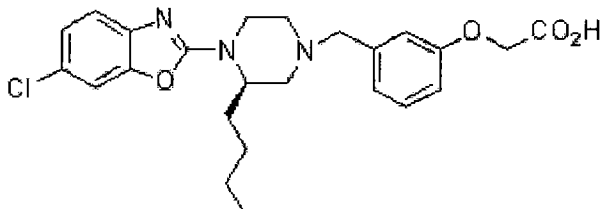


[5417] $^1\text{H-NMR}$ (300MHz, DMSO- d_6) δ 0.88 (3H, t, $J = 7.5\text{Hz}$), 1.21 (2H, m), 1.71-1.91 (2H, m), 2.10-2.13 (2H, m), 2.24 (3H, s), 2.76-2.88 (2H, m), 3.30-3.53 (3H, m), 3.87-3.98 (2H, m), 4.60 (2H, s), 6.61 (1H, s), 6.67 (1H, s), 6.73 (1H, s), 7.21 (1H, d, $J = 8.7\text{Hz}$), 7.43 (1H, d, $J = 8.7\text{Hz}$), 7.85 (1H, s), 13.02 (1H, br s)。

[5418] 实施例 881

[5419] [式 1214]

[5420]

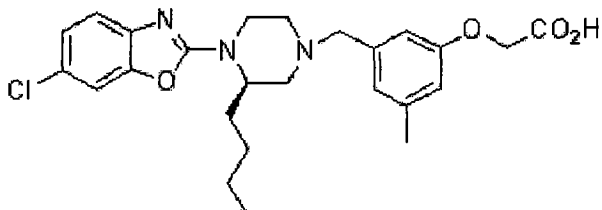


[5421] $^1\text{H-NMR}$ (DMSO- d_6) δ :7.54 (1H, s), 7.28-7.15 (2H, m), 6.74 (1H, s), 6.94-6.89 (2H, m), 6.80 (1H, d, $J = 7.8\text{Hz}$), 4.64 (2H, s), 4.13 (1H, s), 3.95 (1H, m), 3.57-3.32 (3H, m), 2.90-2.76 (2H, m), 2.19-2.11 (2H, m), 1.85-1.80 (2.0H, m), 1.28 (2H, q, $J = 7.2\text{Hz}$), 1.13 (2H, q, $J = 7.5\text{Hz}$), 0.83 (3H, t, $J = 7.2\text{Hz}$)。

[5422] 实施例 882

[5423] [式 1215]

[5424]

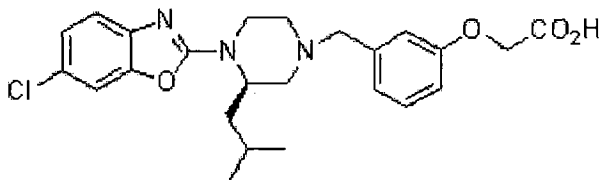


[5425] $^1\text{H-NMR}$ (DMSO- d_6) δ :7.54 (1H, d, $J = 1.85\text{Hz}$), 7.20 (2H, d, $J = 8.4\text{Hz}$), 6.74 (1H, s), 6.68 (1H, s), 6.62 (1H, s), 4.62 (2H, s), 4.14-3.92 (2H, m), 3.52 (1H, d, $J = 13.8\text{Hz}$), 2.90-2.75 (2H, m), 2.26 (3H, s), 2.15-2.11 (2H, m), 1.80 (2.0H, m), 1.26 (2H, t, $J = 7.2\text{Hz}$), 0.85 (7.0H, t, $J = 5.96\text{Hz}$)。

[5426] 实施例 883

[5427] [式 1216]

[5428]

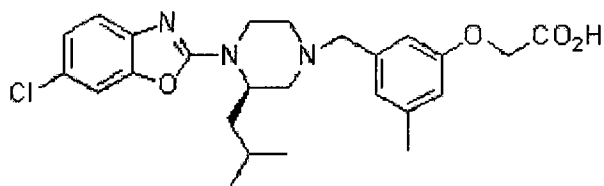


[5429] $^1\text{H-NMR}$ (DMSO- d_6) δ :7.54 (1.0H, d, $J = 2.18\text{Hz}$), 7.28-7.21 (2.0H, m), 7.17 (1.0H, dd, $J = 8.23, 2.18\text{Hz}$), 6.94-6.87 (2.0H, m), 6.79 (1.0H, dd, $J = 8.23, 2.18\text{Hz}$), 4.63 (2.0H, s), 4.29-4.21 (1.0H, m), 3.94 (1.0H, d, $J = 13.93\text{Hz}$), 3.54 (1.0H, d, $J = 13.93\text{Hz}$), 3.45-3.24 (2.0H, m), 2.86 (1.0H, d, $J = 10.74\text{Hz}$), 2.75 (1.3H, d, $J = 10.74\text{Hz}$), 2.30-2.05 (2.0H, m), 1.81-1.62 (2.0H, m), 1.47-1.35 (1.0H, m), 0.93-0.86 (6.0H, m)。

[5430] 实施例 884

[5431] [式 1217]

[5432]

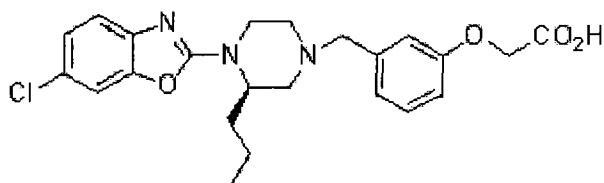


[5433] $^1\text{H-NMR}$ (DMSO-d_6) δ : 7.54 (1.0H, d, $J = 1.85\text{Hz}$), 7.24 (1.0H, d, $J = 8.56\text{Hz}$), 7.17 (1.0H, dd, $J = 8.56, 1.85\text{Hz}$), 6.74 (1.0H, s), 6.68 (1.0H, s), 6.62 (1.0H, s), 4.62 (2.0H, s), 4.29–4.20 (1.0H, m), 3.94 (1.0H, d, $J = 12.25\text{Hz}$), 3.52 (1.0H, d, $J = 13.76\text{Hz}$), 3.45–3.36 (2.0H, m), 2.87 (1.0H, d, $J = 10.58\text{Hz}$), 2.74 (1.0H, d, $J = 10.58\text{Hz}$), 2.26 (3.0H, s), 2.20–2.05 (2.0H, m), 1.80–1.62 (2.0H, m), 1.49–1.34 (1.0H, m), 0.90 (7.0H, t, $J = 5.96\text{Hz}$).

[5434] 实施例 885

[5435] [式 1218]

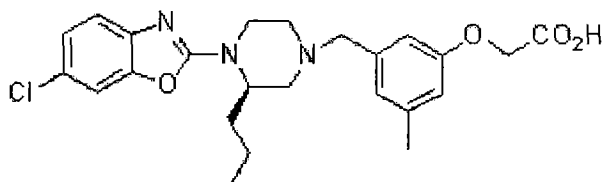
[5436]

[5437] MS (ESI) m/z 442 $[\text{M-H}]^-$

[5438] 实施例 886

[5439] [式 1219]

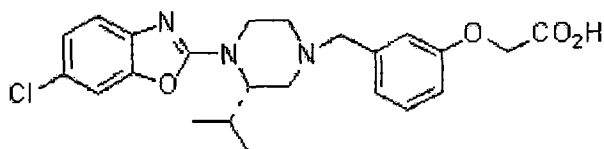
[5440]

[5441] MS (ESI) m/z 456 $[\text{M-H}]^-$

[5442] 实施例 887

[5443] [式 1220]

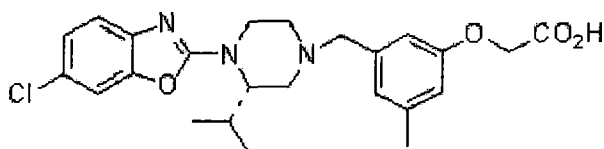
[5444]

[5445] MS (ESI) m/z 442 $[\text{M-H}]^-$

[5446] 实施例 888

[5447] [式 1221]

[5448]

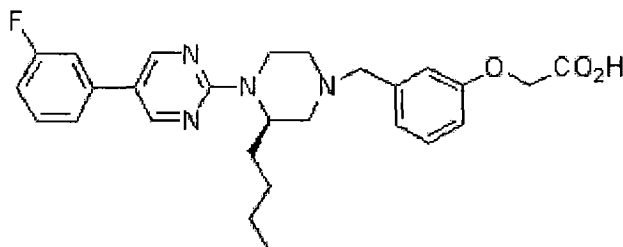


[5449] MS(ESI) m/z 456 $[M-H]^-$

[5450] 实施例 889

[5451] [式 1222]

[5452]

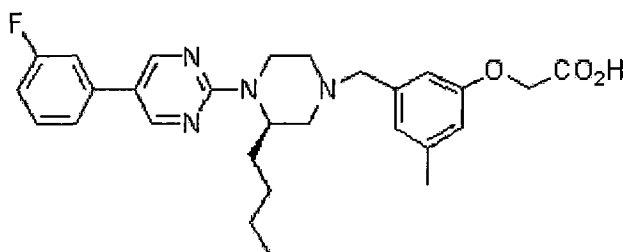


[5453] $^1\text{H-NMR}$ (DMSO-d_6) δ : 8.74 (2H, s), 7.55–7.45 (3H, m), 7.24 (1H, t, $J = 8.1\text{Hz}$), 7.14 (1H, m), 6.95–6.90 (2H, m), 6.80 (1H, dd, $J = 8.1, 2.4\text{Hz}$), 4.74 (1H, s), 4.64 (2H, s), 4.55 (1H, m), 3.57–3.53 (2H, m), 3.15 (1H, m), 2.89–2.79 (2H, m), 2.06–2.01 (2H, m), 1.84 (1H, m), 1.68 (1H, m), 1.27 (2H, q, $J = 7.2\text{Hz}$), 1.17 (2H, q, $J = 7.2\text{Hz}$), 0.82 (3H, t, $J = 7.1\text{Hz}$)。

[5454] 实施例 890

[5455] [式 1223]

[5456]

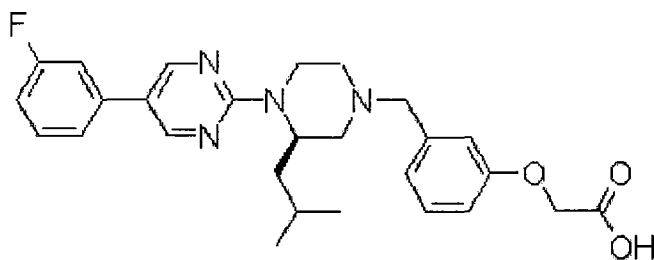


[5457] $^1\text{H-NMR}$ (DMSO-d_6) δ : 8.74 (2H, s), 7.55–7.45 (3H, m), 7.24 (1H, t, $J = 8.1\text{Hz}$), 6.75 (1H, s), 6.68 (1H, s), 6.62 (1H, s), 4.74 (1H, s), 4.64 (2H, s), 4.55 (1H, m), 3.57–3.53 (2H, m), 3.15 (1H, m), 2.89–2.79 (2H, m), 2.25 (3H, s), 2.06–2.01 (2H, m), 1.84 (1H, m), 1.68 (1H, m), 1.27 (2H, q, $J = 7.2\text{Hz}$), 1.17 (2H, q, $J = 7.2\text{Hz}$), 0.82 (3H, t, $J = 7.1\text{Hz}$)。

[5458] 实施例 891

[5459] [式 1224]

[5460]

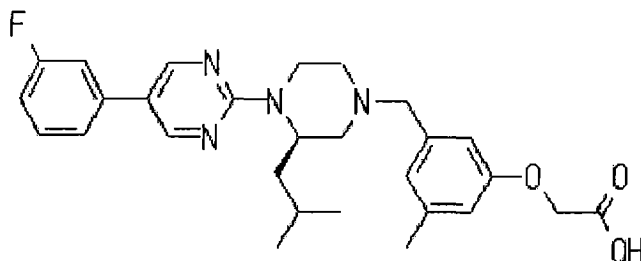


[5461] $^1\text{H-NMR}$ (DMSO- d_6) δ : 8.73 (2.0H, s), 7.57–7.42 (3.0H, m), 7.25 (1.0H, dd, J = 7.89, 7.89Hz), 7.18–7.09 (1.0H, m), 6.96–6.87 (2.0H, m), 6.80 (1.0H, dd, J = 7.89, 2.52Hz), 4.92–4.83 (1.0H, m), 4.66–4.52 (3.0H, m), 3.53 (1.0H, d, J = 13.60Hz), 3.48–3.07 (2.0H, m), 2.86 (1.0H, d, J = 11.25Hz), 2.77 (1.0H, d, J = 11.25Hz), 2.11–1.94 (2.0H, m), 1.74–1.61 (2.0H, m), 1.46–1.34 (1.0H, m), 0.93–0.86 (6.0H, m)。

[5462] 实施例 892

[5463] [式 1225]

[5464]

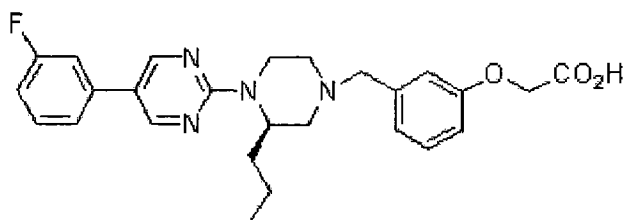


[5465] $^1\text{H-NMR}$ (DMSO- d_6) δ : 8.73 (2.0H, s), 7.58–7.42 (3.0H, m), 7.18–7.09 (1.0H, m), 6.76 (1.0H, s), 6.69 (1.0H, s), 6.62 (1.0H, s), 4.91–4.81 (1.0H, m), 4.64–4.52 (3.0H, m), 3.51 (1.0H, d, J = 13.60Hz), 3.47–3.09 (2.0H, m), 2.92–2.82 (1.0H, m), 2.80–2.71 (1.0H, m), 2.26 (3.0H, s), 2.08–1.95 (2.0H, m), 1.81–1.69 (1.0H, m), 1.66–1.53 (1.0H, m), 1.49–1.35 (1.0H, m), 0.93–0.86 (6.0H, m)。

[5466] 实施例 893

[5467] [式 1226]

[5468]

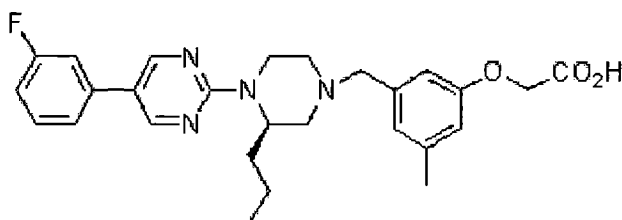


[5469] $^1\text{H-NMR}$ (DMSO- d_6) δ : 8.74 (2H, s), 7.55–7.45 (3H, m), 7.25 (1H, t, J = 8.0Hz), 7.14 (1H, m), 6.94–6.90 (2H, m), 6.79 (1H, dd, J = 8.1, 2.4Hz), 4.78 (1H, s), 4.64 (2H, s), 4.59 (1H, m), 3.57–3.10 (3H, m), 2.89–2.79 (2H, m), 2.08–2.04 (2H, m), 1.77 (2H, m), 1.17 (2H, q, J = 7.2Hz), 0.87 (3H, t, J = 7.1Hz)。

[5470] 实施例 894

[5471] [式 1227]

[5472]

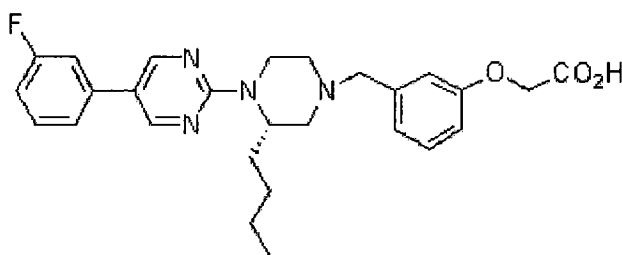


[5473] $^1\text{H-NMR}$ (DMSO- d_6) δ : 8.74 (2H, s), 7.55-7.45 (3H, m), 7.25 (1H, t, $J = 8.0\text{Hz}$), 6.75 (1H, s), 6.68 (1H, s), 6.62 (1H, s), 4.78 (1H, s), 4.64 (2H, s), 4.59 (1H, m), 3.57-3.10 (3H, m), 2.89-2.79 (2H, m), 2.26 (3H, s), 2.08-2.04 (2H, m), 1.77 (2H, m), 1.17 (2H, q, $J = 7.2\text{Hz}$), 0.87 (3H, t, $J = 7.1\text{Hz}$).

[5474] 实施例 895

[5475] [式 1228]

[5476]

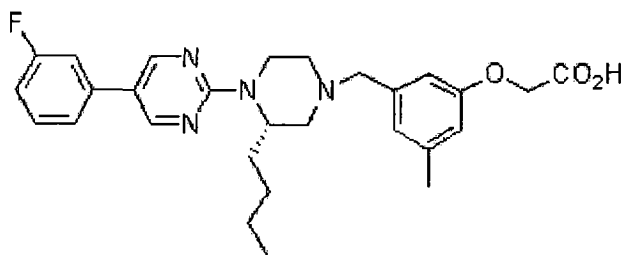


[5477] $^1\text{H-NMR}$ (300MHz, DMSO- d_6) δ 0.83 (3H, t, $J = 7.2\text{Hz}$), 1.13-1.33 (4H, m), 1.62-1.91 (2H, m), 1.98-2.04 (2H, m), 2.79-2.90 (2H, m), 3.12-3.56 (3H, m), 4.52-4.57 (3H, m), 4.74 (1H, m), 6.77 (1H, d, $J = 7.8\text{Hz}$), 6.88 (1H, s), 6.91 (1H, d, $J = 7.8\text{Hz}$), 7.11-7.16 (1H, m), 7.23 (1H, t, $J = 7.8\text{Hz}$), 7.43-7.55 (3H, m), 8.73 (2H, s).

[5478] 实施例 896

[5479] [式 1229]

[5480]

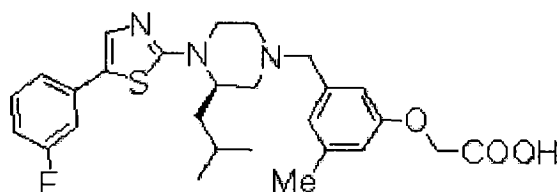


[5481] $^1\text{H-NMR}$ (300MHz, DMSO- d_6) δ 0.83 (3H, t, $J = 7.2\text{Hz}$), 1.06-1.33 (4H, m), 1.61-1.91 (2H, m), 1.98-2.05 (2H, m), 2.26 (3H, s), 2.78-2.90 (2H, m), 3.11-3.55 (3H, m), 4.55 (1H, d, $J = 12.3\text{Hz}$), 4.61 (2H, s), 4.72 (1H, m), 6.62 (1H, s), 6.69 (1H, s), 6.76 (1H, s), 7.14 (1H, m), 7.45-7.55 (3H, m), 8.73 (2H, s), 12.94 (1H, br s).

[5482] 实施例 897

[5483] [式 1230]

[5484]

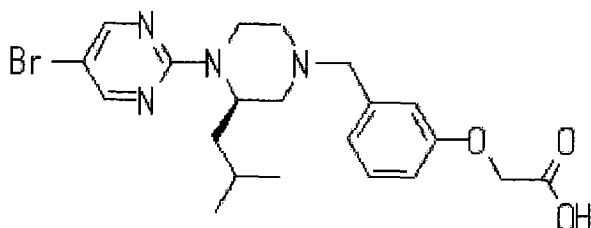


[5485] TLC : (SiO₂) AcOEt R_f = 0.29

[5486] 实施例 898

[5487] [式 1231]

[5488]

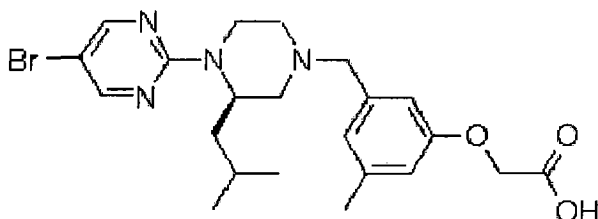


[5489] ¹H-NMR (DMSO-d₆) δ : 8.42 (2.0H, s), 7.24 (1.0H, dd, J = 7.72, 7.72Hz), 6.94-6.86 (2.0H, m), 6.79 (1.0H, dd, J = 8.56, 1.85Hz), 4.76-4.67 (1.0H, m), 4.64 (2.0H, s), 4.40 (1.0H, d, J = 12.93Hz), 3.51 (1.0H, d, J = 13.60Hz), 3.42-3.21 (1.0H, m), 3.18-3.05 (1.0H, m), 2.83 (1.0H, d, J = 11.25Hz), 2.74 (1.0H, d, J = 11.25Hz), 2.09-1.90 (2.0H, m), 1.72-1.52 (2.0H, m), 1.41-1.30 (1.0H, m), 0.89-0.83 (6.0H, m)。

[5490] 实施例 899

[5491] [式 1232]

[5492]

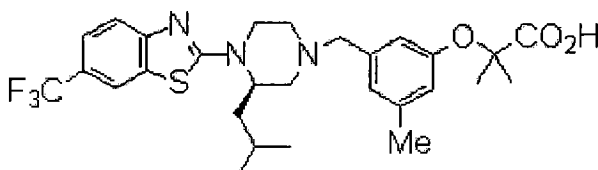


[5493] ¹H-NMR (DMSO-d₆) δ : 8.42 (2.0H, s), 6.74 (1.0H, s), 6.67 (1.0H, s), 6.61 (1.0H, s), 4.76-4.66 (1.0H, br m), 4.60 (2.0H, s), 4.40 (1.0H, d, J = 13.26Hz), 3.49 (1.0H, d, J = 13.93Hz), 3.45-3.20 (1.0H, m), 3.18-3.05 (1.0H, m), 2.83 (1.0H, d, J = 12.09Hz), 2.77-2.69 (1.0H, m), 2.25 (3.0H, s), 2.04-1.96 (2.0H, m), 1.77-1.65 (1.0H, m), 1.60-1.47 (1.0H, m), 1.44-1.28 (1.0H, m), 0.90-0.83 (6.0H, m)。

[5494] 实施例 900

[5495] [式 1233]

[5496]



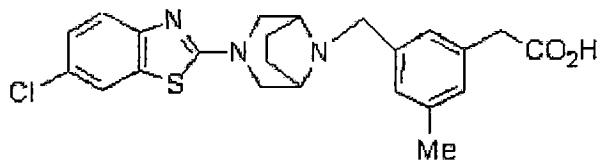
[5497] ¹H-NMR (DMSO-d₆) δ : 8.22 (1H, s), 7.59-7.53 (2H, m), 6.75 (1H, s), 6.68 (1H,

s), 6.54 (1H, s), 4.21-3.89 (2H, m), 3.55-3.30 (3H, m), 2.92-2.75 (2H, m), 2.24 (3H, s), 2.18-2.02 (2H, m), 1.83 (1H, m), 1.65-1.38 (2H, m), 1.51 (6H, s), 0.93-0.91 (6H, m)。

[5498] 实施例 901

[5499] [式 1234]

[5500]

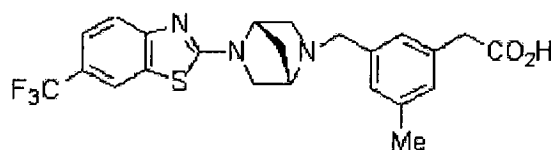


[5501] MS (ESI) m/z 442 [M+H]⁺

[5502] 实施例 902

[5503] [式 1235]

[5504]

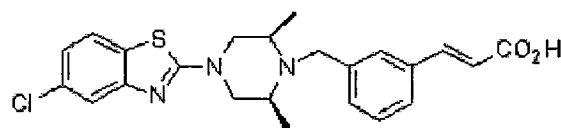


[5505] MS (ESI) m/z 462 [M+H]⁺

[5506] 实施例 903

[5507] [式 1236]

[5508]

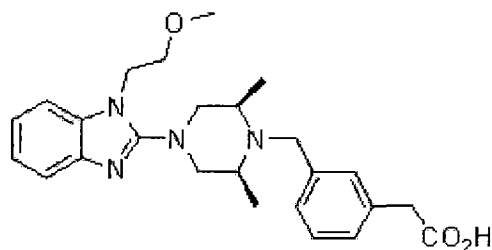


[5509] MS (ESI) m/z 442 [M+H]⁺

[5510] 实施例 904

[5511] [式 1237]

[5512]

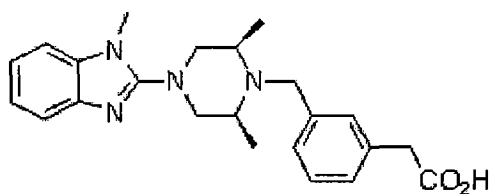


[5513] ¹H-NMR (DMSO-d₆) δ : 1.01 (6H, d, J = 5.5 Hz), 2.70-2.87 (4H, m), 3.22 (3H, s), 3.47 (2H, d, J = 10.2 Hz), 3.55 (2H, s), 3.71-3.83 (4H, m), 4.15-4.24 (2H, m), 7.04-7.45 (8H, m)。

[5514] 实施例 905

[5515] [式 1238]

[5516]

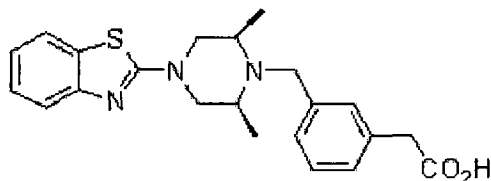


[5517] $^1\text{H-NMR}$ (DMSO-d_6) δ : 1.03 (6H, d, $J = 5.2\text{Hz}$), 2.70-2.88 (4H, m), 3.45 (2H, d, $J = 11.0\text{Hz}$), 3.55 (2H, s), 3.60 (3H, s), 3.81 (2H, s), 7.04-7.42 (8H, m)。

[5518] 实施例 906

[5519] [式 1239]

[5520]

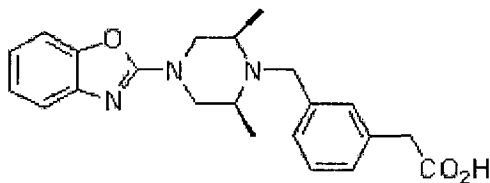


[5521] $^1\text{H-NMR}$ (DMSO-d_6) δ : 1.04 (6H, d, $J = 6.0\text{Hz}$), 2.66-2.79 (2H, m), 3.01 (2H, t, $J = 11.7\text{Hz}$), 3.54 (3H, s), 3.76-3.88 (4H, m), 7.02-7.31 (6H, m), 7.44 (1H, d, $J = 8.0\text{Hz}$), 7.75 (1H, d, $J = 7.7\text{Hz}$)。

[5522] 实施例 907

[5523] [式 1240]

[5524]

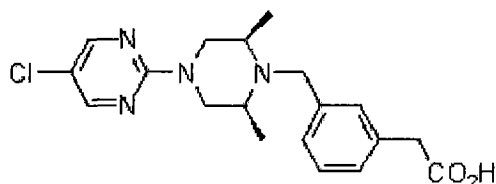


[5525] $^1\text{H-NMR}$ (DMSO-d_6) δ : 1.04 (6H, d, $J = 6.0\text{Hz}$), 2.63-2.76 (2H, m), 2.93-3.04 (2H, m), 3.53 (2H, s), 3.78 (2H, s), 3.90-3.98 (2H, m), 6.98-7.41 (8H, m)。

[5526] 实施例 908

[5527] [式 1241]

[5528]

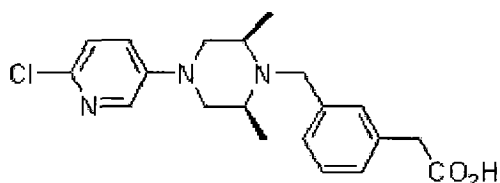


[5529] $^1\text{H-NMR}$ (DMSO-d_6) δ : 1.01 (6H, d, $J = 6.0\text{Hz}$), 2.50-2.58 (2H, m), 2.80 (2H, dd, $J = 12.6, 10.4\text{Hz}$), 3.52 (2H, s), 3.75 (2H, s), 4.34 (2H, dd, $J = 12.6, 1.6\text{Hz}$), 7.05-7.27 (4H, m), 8.44 (2H, s)。

[5530] 实施例 909

[5531] [式 1242]

[5532]

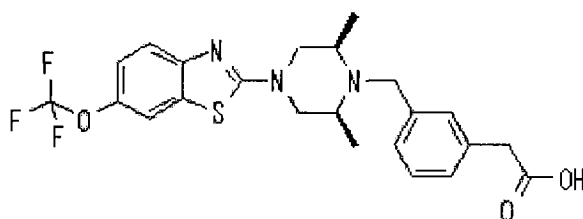


[5533] $^1\text{H-NMR}$ (DMSO- d_6) δ : 1.02 (6H, d, $J = 6.0\text{Hz}$), 2.47–2.55 (2H, m), 2.61–2.74 (2H, m), 3.52 (2H, s), 3.60–3.67 (2H, m), 3.76 (2H, s), 7.07–7.45 (6H, m), 8.07 (1H, d, $J = 3.3\text{Hz}$)。

[5534] 实施例 910

[5535] [式 1243]

[5536]

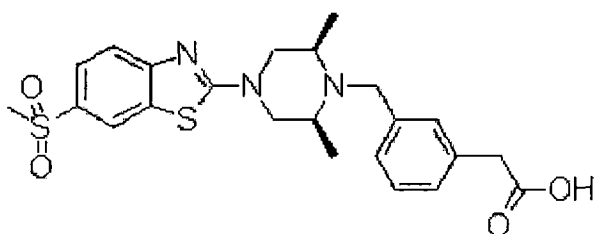


[5537] $^1\text{H-NMR}$ (丙酮) δ : 7.76 (1.0H, s), 7.50 (1.0H, d, $J = 9.06\text{Hz}$), 7.41 (1.0H, s), 7.35 (1.0H, d, $J = 7.42\text{Hz}$), 7.30–7.22 (2.0H, m), 7.16 (1.0H, d, $J = 7.42\text{Hz}$), 3.94 (2.0H, dd, $J = 12.71, 2.33\text{Hz}$), 3.86 (2.0H, s), 3.62 (2.0H, s), 3.10 (2.0H, dd, $J = 12.71, 10.16\text{Hz}$), 2.87–2.77 (2.0H, m), 1.12 (6.0H, d, $J = 6.00\text{Hz}$)。

[5538] 实施例 911

[5539] [式 1244]

[5540]

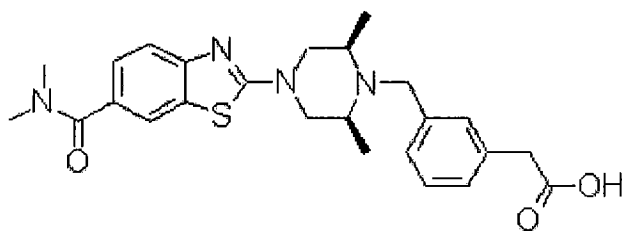


[5541] $^1\text{H-NMR}$ (丙酮) δ : 8.27 (1.0H, d, $J = 1.80\text{Hz}$), 7.82 (1.0H, dd, $J = 8.46, 1.80\text{Hz}$), 7.58 (1.0H, d, $J = 8.46\text{Hz}$), 7.41 (1.0H, s), 7.35 (1.0H, d, $J = 7.42\text{Hz}$), 7.27 (1.0H, dd, $J = 7.42, 7.42\text{Hz}$), 7.17 (1.0H, d, $J = 7.42\text{Hz}$), 4.00 (2.0H, d, $J = 12.64\text{Hz}$), 3.87 (2.0H, s), 3.63 (2.0H, s), 3.21–3.07 (5.0H, m), 2.89–2.78 (2.0H, m), 1.13 (6.0H, d, $J = 6.32\text{Hz}$)。

[5542] 实施例 912

[5543] [式 1245]

[5544]

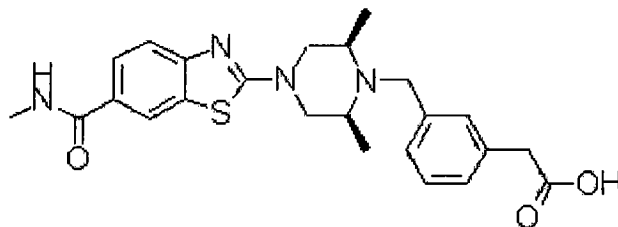


[5545] $^1\text{H-NMR}$ (丙酮) δ : 7.81 (1.0H, s), 7.47-7.33 (4.0H, m), 7.26 (1.0H, dd, $J = 7.54, 7.54\text{Hz}$), 7.16 (1.0H, d, $J = 7.54\text{Hz}$), 3.96 (2.0H, d, $J = 12.91\text{Hz}$), 3.86 (2.0H, s), 3.62 (2.0H, s), 3.15-3.01 (8.0H, m), 2.92-2.78 (2.0H, m), 1.12 (6.0H, d, $J = 6.04\text{Hz}$)。

[5546] 实施例 913

[5547] [式 1246]

[5548]

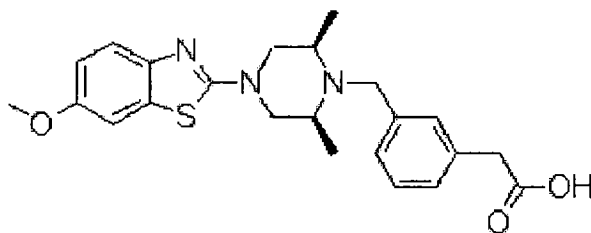


[5549] $^1\text{H-NMR}$ (丙酮) δ : 8.23 (1.0H, s), 7.82 (1.0H, d, $J = 8.52\text{Hz}$), 7.64 (1.0H, br s), 7.48-7.23 (4.0H, m), 7.16 (1.0H, d, $J = 7.14\text{Hz}$), 3.96 (2.0H, d, $J = 12.64\text{Hz}$), 3.86 (2.0H, s), 3.62 (2.0H, s), 3.11 (2.0H, dd, $J = 11.40, 11.40\text{Hz}$), 2.93-2.76 (5.0H, m), 1.12 (6.0H, d, $J = 6.32\text{Hz}$)。

[5550] 实施例 914

[5551] [式 1247]

[5552]

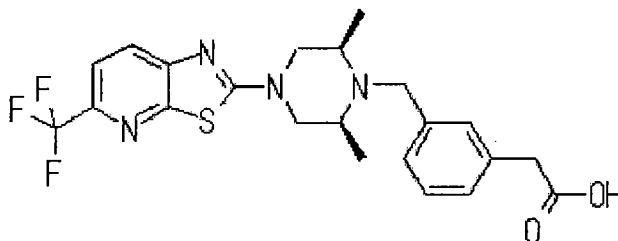


[5553] $^1\text{H-NMR}$ (丙酮) δ : 7.42-7.31 (4.0H, m), 7.26 (1.0H, dd, $J = 7.42, 7.42\text{Hz}$), 7.16 (1.0H, d, $J = 7.42\text{Hz}$), 6.90 (1.0H, dd, $J = 8.79, 2.75\text{Hz}$), 3.90-3.84 (4.0H, m), 3.80 (3.0H, s), 3.60 (2.0H, s), 3.01 (2.0H, dd, $J = 12.77, 10.30\text{Hz}$), 2.83-2.72 (2.0H, m), 1.11 (6.0H, d, $J = 6.00\text{Hz}$)。

[5554] 实施例 915

[5555] [式 1248]

[5556]

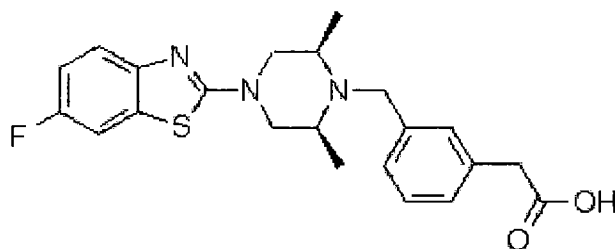


[5557] $^1\text{H-NMR}$ (丙酮) δ : 7.83 (1.0H, d, $J = 8.24\text{Hz}$), 7.73 (1.0H, d, $J = 8.24\text{Hz}$), 7.42 (1.0H, s), 7.36 (1.0H, d, $J = 7.55\text{Hz}$), 7.27 (1.0H, dd, $J = 7.55, 7.55\text{Hz}$), 7.17 (1.0H, d, $J = 7.55\text{Hz}$), 4.05 (2.0H, d, $J = 13.05\text{Hz}$), 3.88 (2.0H, s), 3.63 (2.0H, s), 3.21 (2.0H, dd, $J = 13.05, 10.30\text{Hz}$), 1.14 (6.0H, d, $J = 6.32\text{Hz}$)。

[5558] 实施例 916

[5559] [式 1249]

[5560]

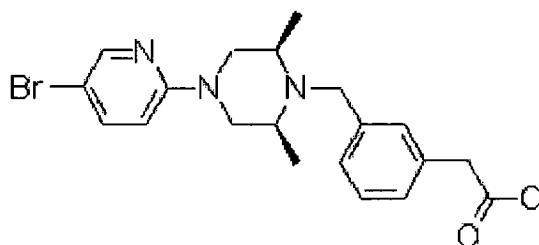


[5561] $^1\text{H-NMR}$ (DMSO- d_6) δ : 7.70 (1.0H, dd, $J = 8.52, 2.75\text{Hz}$), 7.43 (1.0H, dd, $J = 9.06, 4.94\text{Hz}$), 7.28–7.20 (3.0H, m), 7.16–7.05 (2.0H, m), 3.83–3.78 (4.0H, m), 3.52 (2.0H, s), 3.01 (2.0H, dd, $J = 11.54, 11.54\text{Hz}$), 2.77–2.69 (2.0H, m), 1.04 (6.0H, d, $J = 6.04\text{Hz}$)。

[5562] 实施例 917

[5563] [式 1250]

[5564]

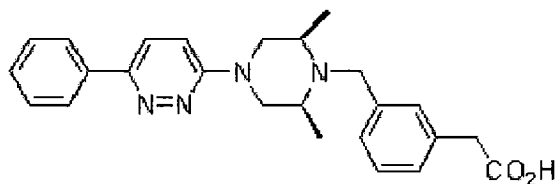


[5565] $^1\text{H-NMR}$ (丙酮) δ : 8.30 (1.0H, d, $J = 5.22\text{Hz}$), 7.31 (1.0H, d, $J = 7.97\text{Hz}$), 7.13 (1.0H, d, $J = 1.92\text{Hz}$), 7.05 (1.0H, s), 6.89 (1.0H, dd, $J = 7.97, 1.92\text{Hz}$), 6.80 (1.0H, d, $J = 5.22\text{Hz}$), 4.32 (2.0H, d, $J = 13.73\text{Hz}$), 4.16 (2.0H, dd, $J = 6.04, 6.04\text{Hz}$), 3.23 (2.0H, dd, $J = 6.04, 6.04\text{Hz}$), 2.89–2.79 (2.0H, m), 2.70–2.61 (2.0H, m), 1.25 (6.0H, d, $J = 6.04\text{Hz}$)。

[5566] 实施例 918

[5567] [式 1251]

[5568]

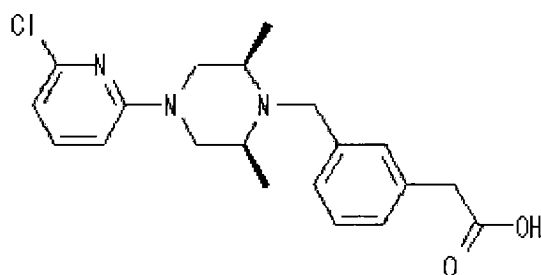


[5569] $^1\text{H-NMR}$ (DMSO- d_6) δ : 1.05 (7H, d, $J = 6.0\text{Hz}$), 2.58–2.87 (4H, m), 3.54 (2H, s), 3.77 (2H, s), 4.23–4.34 (2H, m), 7.05–7.53 (8H, m), 7.90–8.06 (3H, m)。

[5570] 实施例 919

[5571] [式 1252]

[5572]

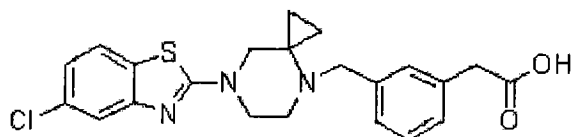


[5573] $^1\text{H-NMR}$ (丙酮) δ : 7.50 (1.0H, dd, $J = 7.97, 7.97\text{Hz}$), 7.40 (1.0H, s), 7.34 (1.0H, d, $J = 7.42\text{Hz}$), 7.25 (1.0H, dd, $J = 7.42, 7.42\text{Hz}$), 7.15 (1.0H, d, $J = 7.42\text{Hz}$), 6.75 (1.0H, d, $J = 7.97\text{Hz}$), 6.59 (1.0H, d, $J = 7.97\text{Hz}$), 4.13 (2.0H, d, $J = 11.54\text{Hz}$), 3.82 (2.0H, s), 3.61 (2.0H, s), 2.80–2.62 (4.0H, m), 1.08 (6.0H, d, $J = 5.77\text{Hz}$)。

[5574] 实施例 920

[5575] [式 1253]

[5576]

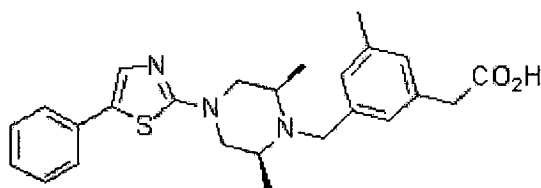


[5577] MS (ESI) m/z 428 $[\text{M}+\text{H}]^+$

[5578] 实施例 921

[5579] [式 1254]

[5580]

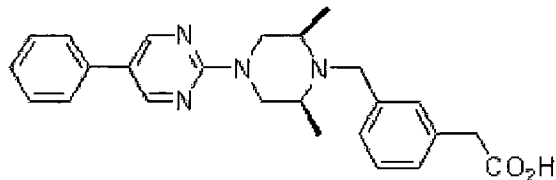


[5581] $^1\text{H-NMR}$ (DMSO- d_6) δ : 1.03 (6H, d, $J = 6.0\text{Hz}$), 2.27 (3H, s), 2.63–2.80 (2H, m), 2.85–2.97 (2H, m), 3.49 (2H, s), 3.69–3.78 (4H, m), 6.86–7.61 (9H, m)。

[5582] 实施例 922

[5583] [式 1255]

[5584]

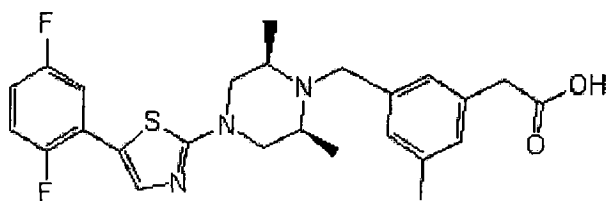


[5585] $^1\text{H-NMR}$ (DMSO- d_6) δ : 1.04 (6H, d, $J = 6.0\text{Hz}$), 2.52–2.62 (2H, m), 2.84 (2H, dd, $J = 12.9, 10.4\text{Hz}$), 3.54 (2H, s), 3.77 (2H, s), 4.44–4.52 (2H, m), 7.07–7.64 (9H, m), 8.69 (2H, s)。

[5586] 实施例 923

[5587] [式 1256]

[5588]

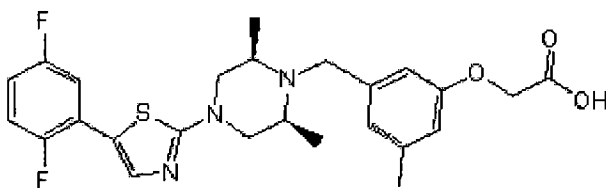


[5589] $^1\text{H-NMR}$ (DMSO-d_6) δ : 7.77 (1H, s), 7.59–7.53 (1H, m), 7.37–7.29 (1H, m), 7.14–7.06 (3H, m), 6.89 (1H, s), 3.78–3.73 (4H, m), 3.49 (2H, s), 2.94 (2H, t, $J = 12.6\text{Hz}$), 2.74–2.68 (2H, m), 2.27 (3H, s), 1.03 (6H, d, $J = 6.3\text{Hz}$)。

[5590] 实施例 924

[5591] [式 1257]

[5592]

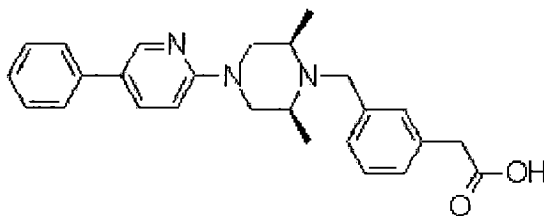


[5593] $^1\text{H-NMR}$ (DMSO-d_6) δ : 7.77 (1H, s), 7.59–7.53 (1H, m), 7.37–7.29 (1H, m), 7.14–7.06 (3H, m), 6.76 (2H, s), 6.54 (1H, s), 4.60 (2H, s), 3.79–3.70 (4H, m), 2.93 (2H, t, $J = 10.5\text{Hz}$), 2.70 (2H, brs), 2.25 (3H, s), 1.02 (6H, d, $J = 6.0\text{Hz}$)。

[5594] 实施例 925

[5595] [式 1258]

[5596]

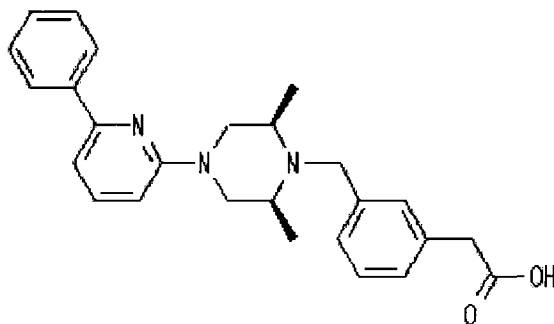


[5597] $^1\text{H-NMR}$ (丙酮) δ : 8.43 (1.0H, d, $J = 2.54\text{Hz}$), 7.81 (1.0H, dd, $J = 9.00, 2.54\text{Hz}$), 7.61–7.58 (2.0H, m), 7.45–7.24 (6.0H, m), 7.16 (1.0H, d, $J = 7.69\text{Hz}$), 6.91 (1.0H, d, $J = 9.00\text{Hz}$), 4.25 (2.0H, d, $J = 11.81\text{Hz}$), 3.84 (2.0H, s), 3.63 (2.0H, s), 2.90–2.63 (4.0H, m), 1.10 (6.0H, d, $J = 5.22\text{Hz}$)。

[5598] 实施例 926

[5599] [式 1259]

[5600]

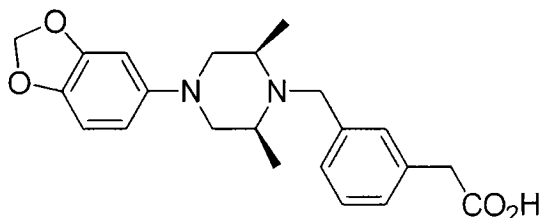


[5601] $^1\text{H-NMR}$ (丙酮) δ : 8.09–8.07 (2.0H, m), 7.60 (1.0H, dd, $J = 7.76, 7.76\text{Hz}$), 7.48–7.34 (5.0H, m), 7.26 (1.0H, dd, $J = 7.76, 7.76\text{Hz}$), 7.20–7.13 (2.0H, m), 6.79 (1.0H, d, $J = 8.79\text{Hz}$), 4.32 (2.0H, d, $J = 11.81\text{Hz}$), 3.83 (2.0H, s), 3.62 (2.0H, s), 2.93–2.67 (4.0H, m), 1.10 (2.0H, d, $J = 5.70\text{Hz}$)。

[5602] 实施例 927

[5603] [式 1260]

[5604]

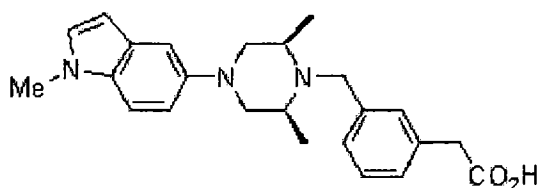


[5605] $^1\text{H-NMR}$ (DMSO- d_6) δ : 1.00 (6H, d, $J = 6.0\text{Hz}$), 2.35 (3H, t, $J = 10.7\text{Hz}$), 2.61–2.73 (2H, m), 3.53 (2H, s), 3.75 (2H, s), 5.90 (2H, s), 6.32 (1H, dd, $J = 8.5, 1.6\text{Hz}$), 6.65–6.78 (2H, m), 7.05–7.28 (4H, m)。

[5606] 实施例 928

[5607] [式 1261]

[5608]

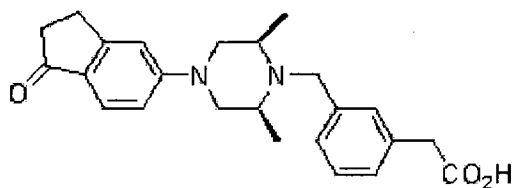


[5609] $^1\text{H-NMR}$ (DMSO- d_6) δ : 1.03 (7H, d, $J = 6.0\text{Hz}$), 2.35–2.46 (2H, m), 2.68–2.81 (2H, m), 3.55 (2H, s), 3.72 (3H, s), 3.79 (2H, s), 6.27 (1H, d, $J = 2.2\text{Hz}$), 6.90–7.31 (8H, m)。

[5610] 实施例 929

[5611] [式 1262]

[5612]

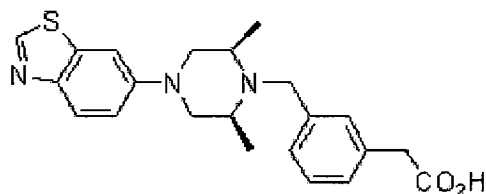


[5613] $^1\text{H-NMR}$ (DMSO- d_6) δ : 1.03 (6H, d, $J = 5.2\text{Hz}$), 2.61–2.76 (4H, m), 2.92–3.00 (2H, m), 3.53 (2H, s), 3.75 (2H, s), 3.83 (2H, d, $J = 10.7\text{Hz}$), 6.93–7.28 (6H, m), 7.42 (1H, d, $J = 8.5\text{Hz}$)。

[5614] 实施例 930

[5615] [式 1263]

[5616]

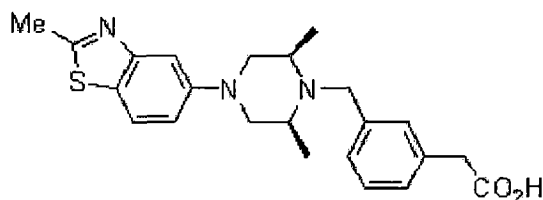


[5617] $^1\text{H-NMR}$ (DMSO- d_6) δ : 1.04 (6H, d, $J = 6.0\text{Hz}$), 2.50–2.58 (2H, m), 2.66–2.78 (2H, m), 3.54 (2H, s), 3.66 (2H, d, $J = 11.5\text{Hz}$), 3.78 (2H, s), 7.06–7.31 (5H, m), 7.59 (1H, d, $J = 2.2\text{Hz}$), 7.87 (1H, d, $J = 9.1\text{Hz}$), 9.07 (1H, s)。

[5618] 实施例 931

[5619] [式 1264]

[5620]

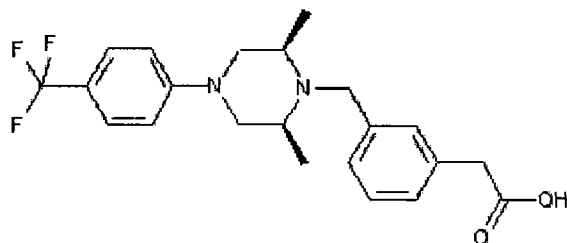


[5621] $^1\text{H-NMR}$ (DMSO- d_6) δ : 1.04 (6H, d, $J = 6.0\text{Hz}$), 2.45–2.75 (7H, m), 3.54 (2H, s), 3.61 (2H, d, $J = 10.7\text{Hz}$), 3.78 (2H, s), 7.06–7.39 (6H, m), 7.78 (1H, d, $J = 8.8\text{Hz}$)。

[5622] 实施例 932

[5623] [式 1265]

[5624]

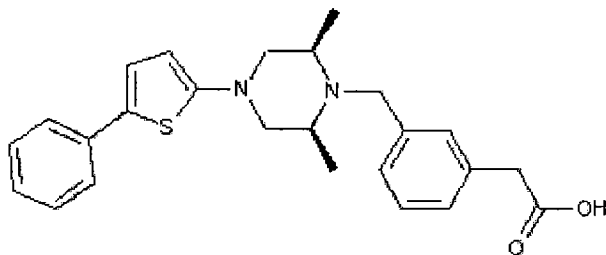


[5625] $^1\text{H-NMR}$ (丙酮) δ : 7.49 (2.0H, d, $J = 8.66\text{Hz}$), 7.40 (1.0H, s), 7.35 (1.0H, d, $J = 7.42\text{Hz}$), 7.26 (1.0H, dd, $J = 7.42, 7.42\text{Hz}$), 7.16 (1.0H, d, $J = 7.42\text{Hz}$), 7.08 (2.0H, d, $J = 8.66\text{Hz}$), 3.83 (2.0H, s), 3.75 (2.0H, d, $J = 10.71\text{Hz}$), 3.62 (2.0H, s), 2.84–2.66 (4.0H, m), 1.09 (6.0H, d, $J = 5.77\text{Hz}$)。

[5626] 实施例 933

[5627] [式 1266]

[5628]



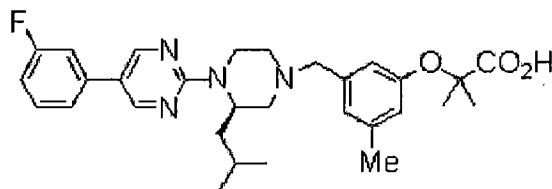
[5629] $^1\text{H-NMR}$ (丙酮) δ : 7.53–7.49 (2.0H, m), 7.41 (1.0H, s), 7.37–7.32 (3.0H, m),

7. 29 (1. 0H, d, J = 4. 39Hz), 7. 25 (1. 0H, d, J = 7. 42Hz), 7. 20-7. 13 (3. 0H, m), 6. 17 (1. 0H, d, J = 3. 85Hz), 3. 85 (2. 0H, s), 3. 63 (2. 0H, s), 3. 43 (2. 0H, d, J = 9. 61Hz), 2. 86-2. 83 (2. 0H, m), 2. 70-2. 66 (2. 0H, m), 1. 09 (6. 0H, d, J = 6. 32Hz)。

[5630] 实施例 934

[5631] [式 1267]

[5632]

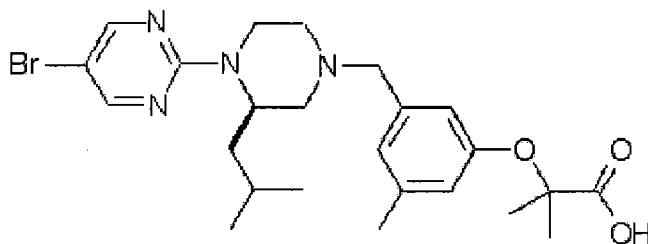


[5633] $^1\text{H-NMR}$ (DMSO- d_6) δ : 8. 72 (2H, s), 7. 59-7. 40 (2H, m), 7. 13 (1H, t, J = 8. 1Hz), 6. 75 (1H, s), 6. 66 (1H, s), 6. 54 (1H, s), 4. 86 (1H, br-s), 4. 56 (1H, d, J = 12. 9Hz), 3. 48-3. 13 (3H, m), 2. 86-2. 72 (2H, m), 2. 23 (3H, s), 2. 10-1. 90 (2H, m), 1. 39 (1H, m), 0. 91-0. 87 (6H, m)。

[5634] 实施例 935

[5635] [式 1268]

[5636]

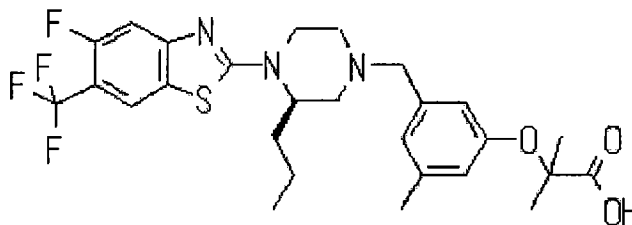


[5637] $^1\text{H-NMR}$ (DMSO- d_6) δ : 8. 72 (2H, s), 6. 75 (1H, s), 6. 66 (1H, s), 6. 54 (1H, s), 4. 86 (1H, br-s), 4. 56 (1H, d, J = 12. 9Hz), 3. 48-3. 13 (3H, m), 2. 86-2. 72 (2H, m), 2. 23 (3H, s), 2. 10-1. 90 (2H, m), 1. 39 (1H, m), 0. 91-0. 87 (6H, m)。

[5638] 实施例 936

[5639] [式 1269]

[5640]

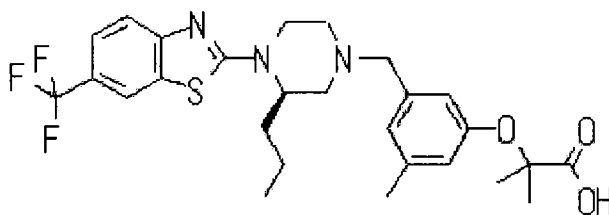


[5641] $^1\text{H-NMR}$ (DMSO- d_6) δ : 8. 23 (1. 0H, d, J = 7. 22Hz), 7. 42 (1. 0H, d, J = 12. 42Hz), 6. 73 (1. 0H, s), 6. 65 (1. 0H, s), 6. 54 (1. 0H, s), 4. 15-3. 86 (2. 0H, m), 3. 53-3. 20 (3. 0H, m), 2. 92-2. 75 (2. 0H, m), 2. 24 (3. 0H, s), 2. 20-2. 05 (2. 0H, m), 1. 92-1. 70 (2. 0H, m), 1. 52-1. 48 (6. 0H, m), 1. 30-1. 14 (2. 0H, m), 0. 90 (3. 0H, t, J = 7. 30Hz)。

[5642] 实施例 937

[5643] [式 1270]

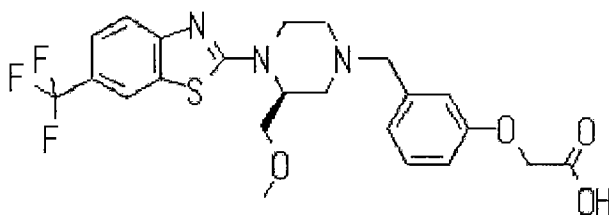
[5644]

[5645] MS (ESI) 534 [M-H]⁻

[5646] 实施例 938

[5647] [式 1271]

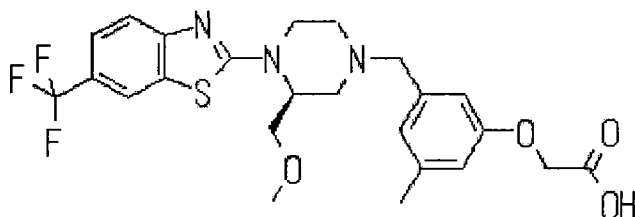
[5648]

[5649] MS (ESI) 494 [M-H]⁻

[5650] 实施例 939

[5651] [式 1272]

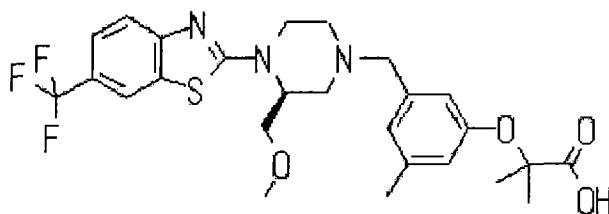
[5652]

[5653] MS (ESI) 508 [M-H]⁻

[5654] 实施例 940

[5655] [式 1273]

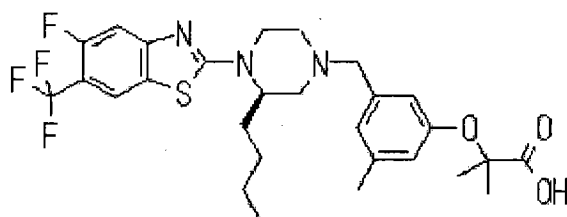
[5656]

[5657] MS (ESI) 536 [M-H]⁻

[5658] 实施例 941

[5659] [式 1274]

[5660]

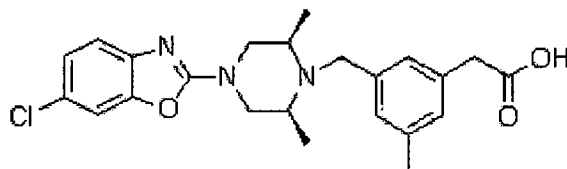


[5661] $^1\text{H-NMR}$ (300MHz, DMSO- d_6) δ 0.85 (3H, t, $J = 7.2\text{Hz}$), 1.13-1.35 (4H, m), 1.50 (6H, s), 1.75-1.94 (2H, m), 2.12-2.17 (2H, m), 2.24 (3H, s), 2.78-2.90 (2H, m), 3.33-3.53 (3H, m), 4.02 (2H, m), 6.54 (1H, s), 6.65 (1H, s), 6.74 (1H, s), 7.43 (1H, d, $J = 12.0\text{Hz}$), 8.23 (1H, d, $J = 7.2\text{Hz}$), 12.97 (1H, br s)。

[5662] 实施例 942

[5663] [式 1275]

[5664]

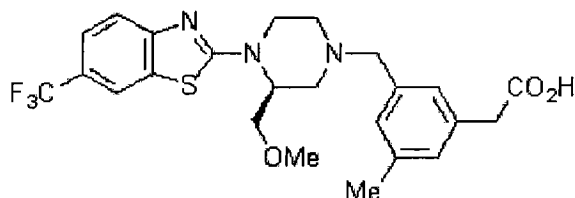


[5665] MS (ESI) m/z 428 $[\text{M}+\text{H}]^+$

[5666] 实施例 943

[5667] [式 1276]

[5668]

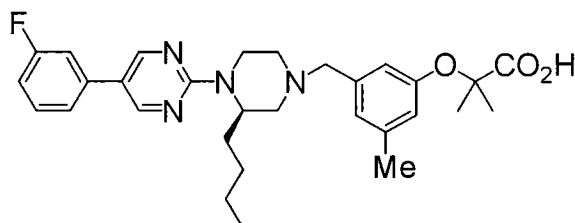


[5669] TLC_{Rf} = 0.55 (MeOH : CHCl₃ = 1 : 10)

[5670] 实施例 944

[5671] [式 1277]

[5672]



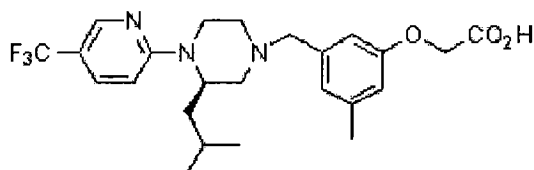
[5673] $^1\text{H-NMR}$ (300MHz, DMSO- d_6) δ 0.83 (3H, t, $J = 7.2\text{Hz}$), 1.06-1.33 (4H, m), 1.51 (6H, s), 1.61-1.91 (2H, m), 1.98-2.05 (2H, m), 2.26 (3H, s), 2.78-2.90 (2H, m), 3.11-3.55 (3H, m), 4.55 (1H, d, $J = 12.3\text{Hz}$), 4.72 (1H, m), 6.54 (1H, s), 6.66 (1H, s), 6.75 (1H, s), 7.14 (1H, m), 7.45-7.55 (3H, m), 8.72 (2H, s)。

[5674] 本发明包括通过与上述相似的方法合成的以下化合物。

[5675] 化合物 I-1

[5676] [式 1278]

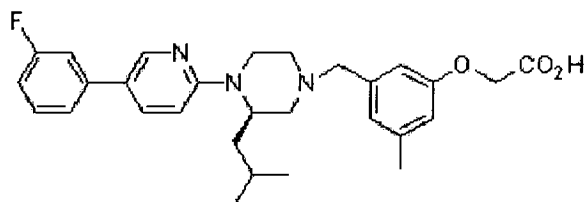
[5677]



[5678] 化合物 I-2

[5679] [式 1279]

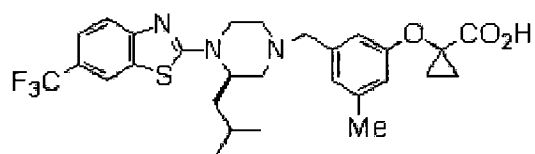
[5680]



[5681] 化合物 I-3

[5682] [式 1280]

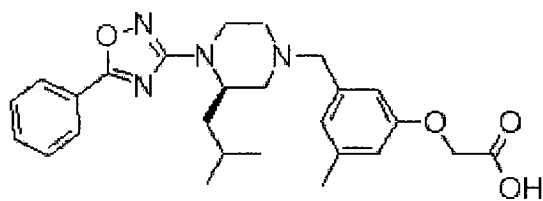
[5683]



[5684] 化合物 I-4

[5685] [式 1281]

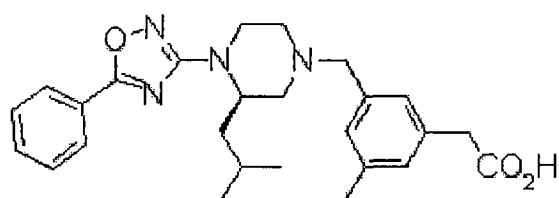
[5686]



[5687] 化合物 I-5

[5688] [式 1282]

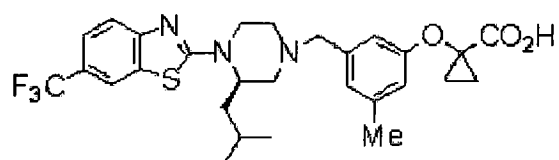
[5689]



[5690] 化合物 I-6

[5691] [式 1283]

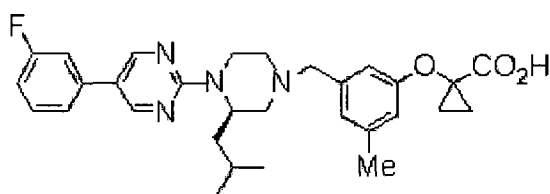
[5692]



[5693] 化合物 I-7

[5694] [式 1284]

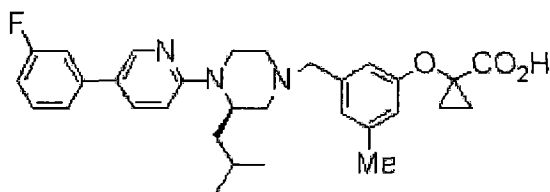
[5695]



[5696] 化合物 I-8

[5697] [式 1285]

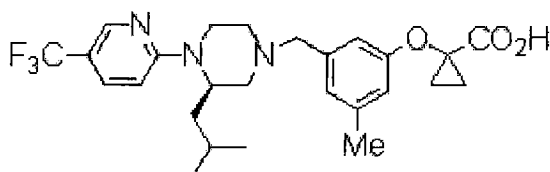
[5698]



[5699] 化合物 I-9

[5700] [式 1286]

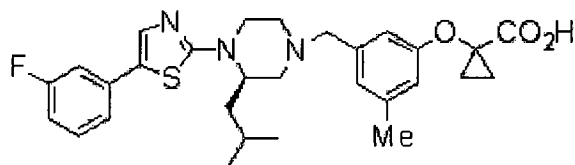
[5701]



[5702] 化合物 I-10

[5703] [式 1287]

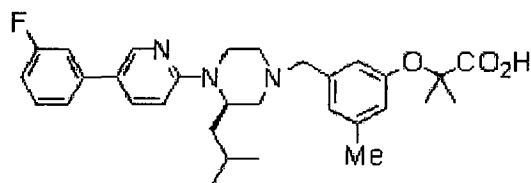
[5704]



[5705] 化合物 I-11

[5706] [式 1288]

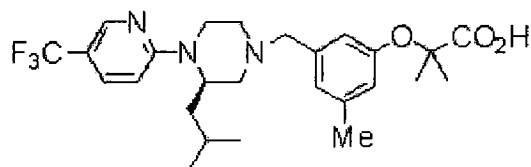
[5707]



[5708] 化合物 I-12

[5709] [式 1289]

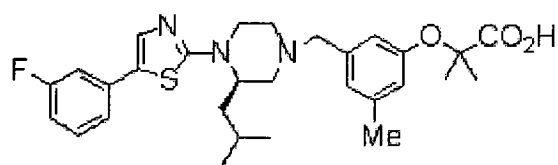
[5710]



[5711] 化合物 I-13

[5712] [式 1290]

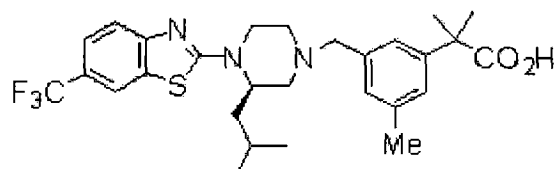
[5713]



[5714] 化合物 I-14

[5715] [式 1291]

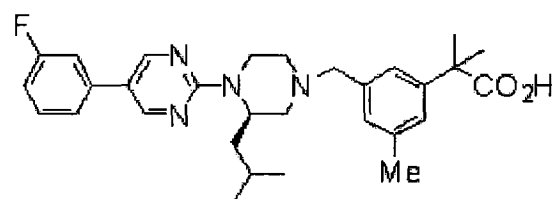
[5716]



[5717] 化合物 I-15

[5718] [式 1292]

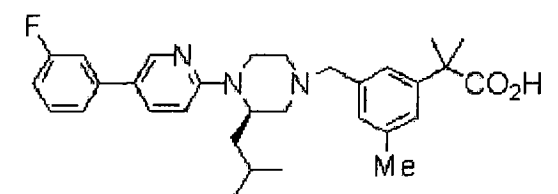
[5719]



[5720] 化合物 I-16

[5721] [式 1293]

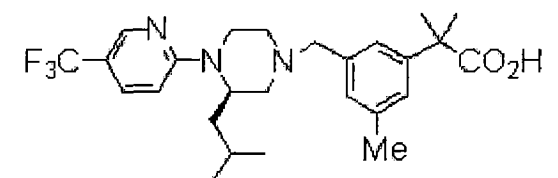
[5722]



[5723] 化合物 I-17

[5724] [式 1294]

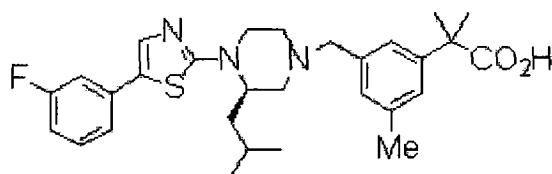
[5725]



[5726] 化合物 I-18

[5727] [式 1295]

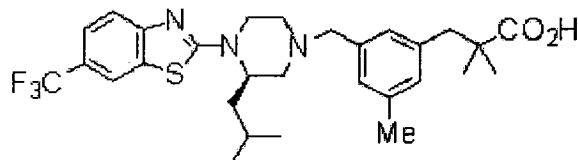
[5728]



[5729] 化合物 I-19

[5730] [式 1296]

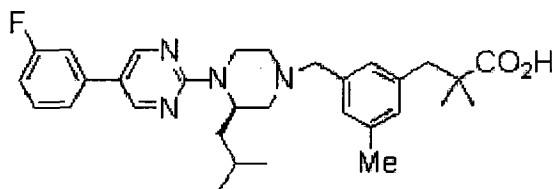
[5731]



[5732] 化合物 I-20

[5733] [式 1297]

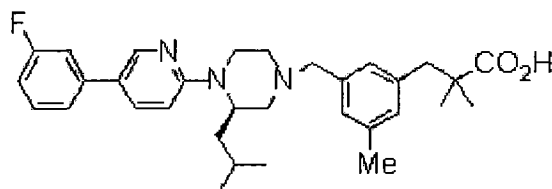
[5734]



[5735] 化合物 I-21

[5736] [式 1298]

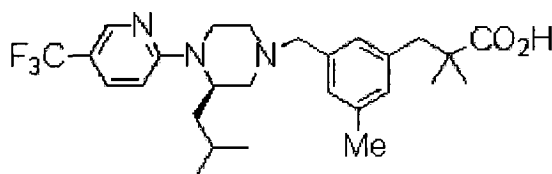
[5737]



[5738] 化合物 I-22

[5739] [式 1299]

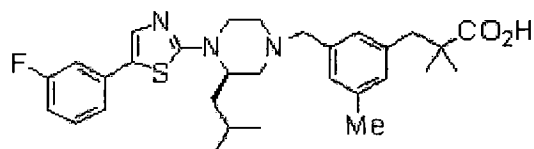
[5740]



[5741] 化合物 I-23

[5742] [式 1300]

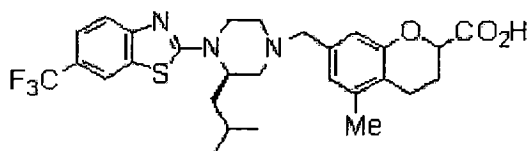
[5743]



[5744] 化合物 I-24

[5745] [式 1301]

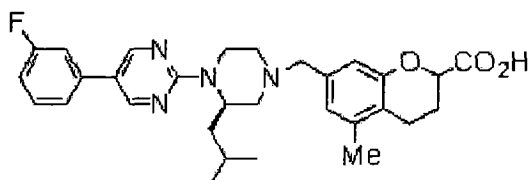
[5746]



[5747] 化合物 I-25

[5748] [式 1302]

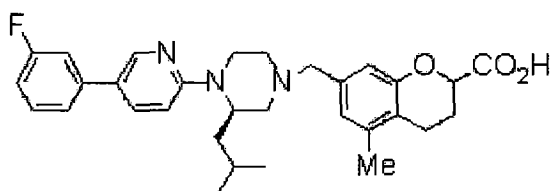
[5749]



[5750] 化合物 I-26

[5751] [式 1303]

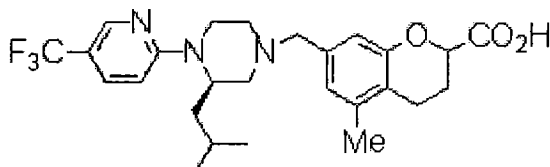
[5752]



[5753] 化合物 I-27

[5754] [式 1304]

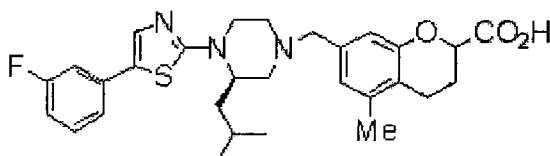
[5755]



[5756] 化合物 I-28

[5757] [式 1305]

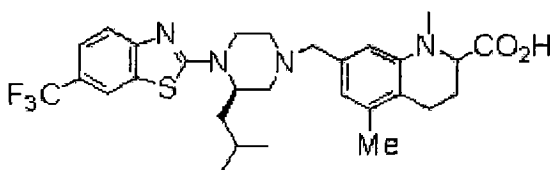
[5758]



[5759] 化合物 I-29

[5760] [式 1306]

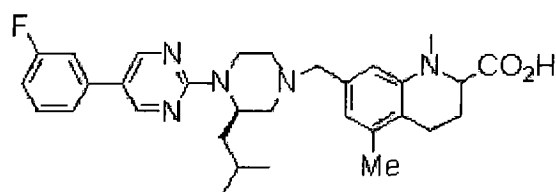
[5761]



[5762] 化合物 I-30

[5763] [式 1307]

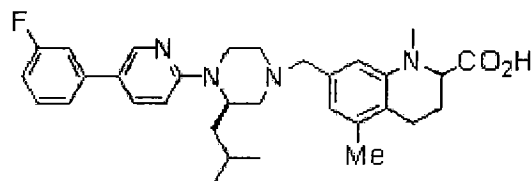
[5764]



[5765] 化合物 I-31

[5766] [式 1308]

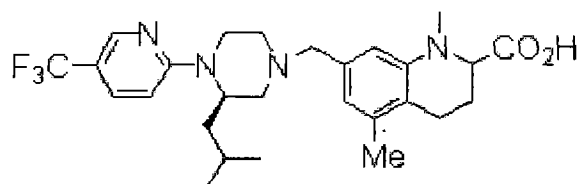
[5767]



[5768] 化合物 I-32

[5769] [式 1309]

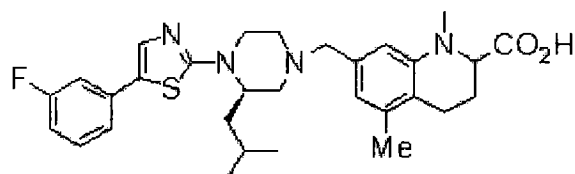
[5770]



[5771] 化合物 I-33

[5772] [式 1310]

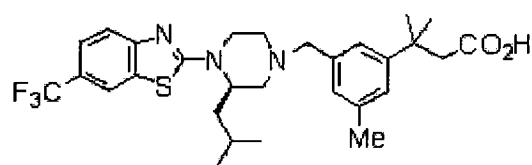
[5773]



[5774] 化合物 I-34

[5775] [式 1311]

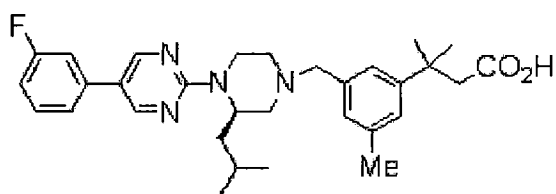
[5776]



[5777] 化合物 I-35

[5778] [式 1312]

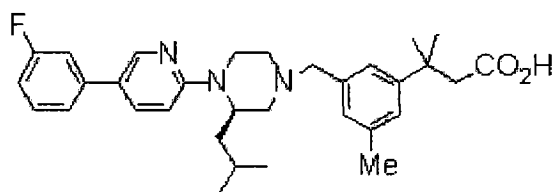
[5779]



[5780] 化合物 I-36

[5781] [式 1313]

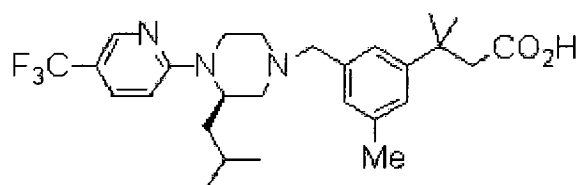
[5782]



[5783] 化合物 I-37

[5784] [式 1314]

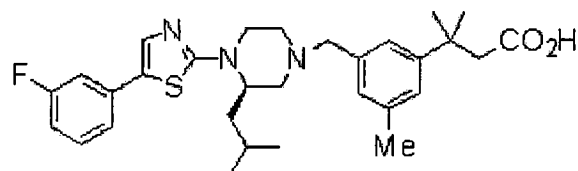
[5785]



[5786] 化合物 I-38

[5787] [式 1315]

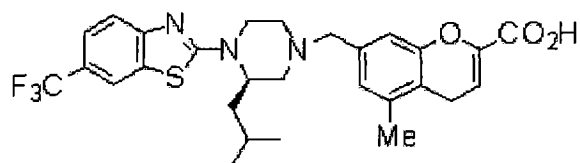
[5788]



[5789] 化合物 I-39

[5790] [式 1316]

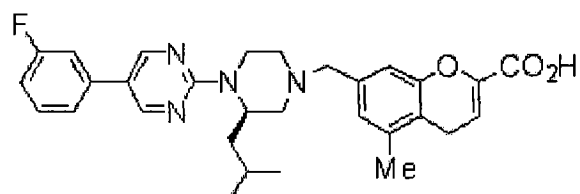
[5791]



[5792] 化合物 I-40

[5793] [式 1317]

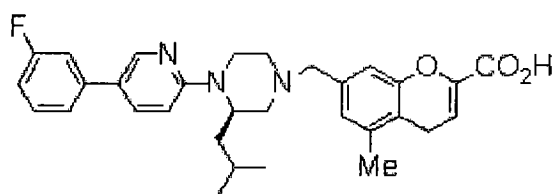
[5794]



[5795] 化合物 I-41

[5796] [式 1318]

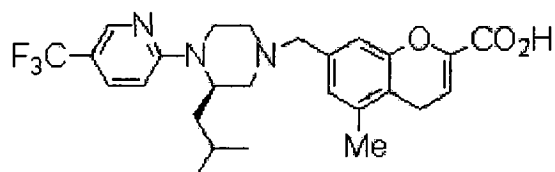
[5797]



[5798] 化合物 I-42

[5799] [式 1319]

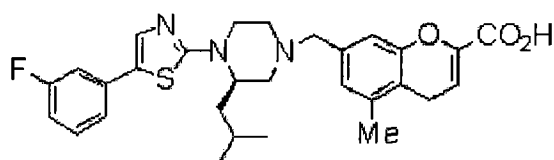
[5800]



[5801] 化合物 I-43

[5802] [式 1320]

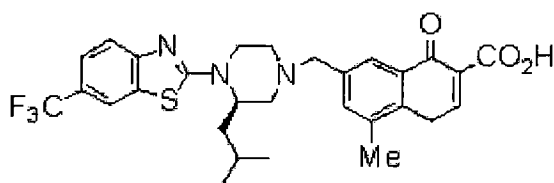
[5803]



[5804] 化合物 I-44

[5805] [式 1321]

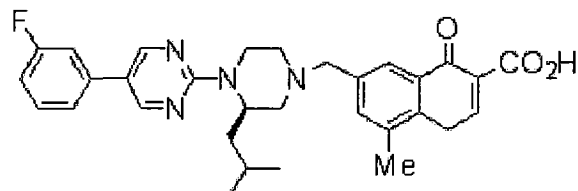
[5806]



[5807] 化合物 I-45

[5808] [式 1322]

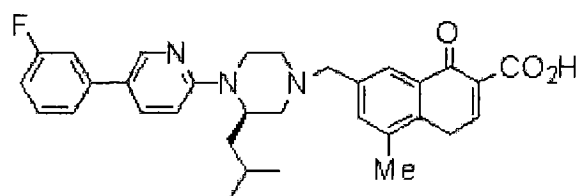
[5809]



[5810] 化合物 I-46

[5811] [式 1323]

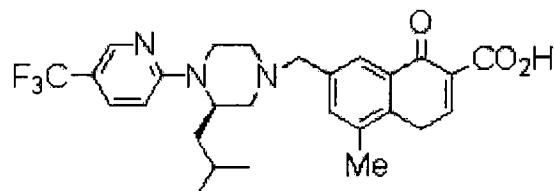
[5812]



[5813] 化合物 I-47

[5814] [式 1324]

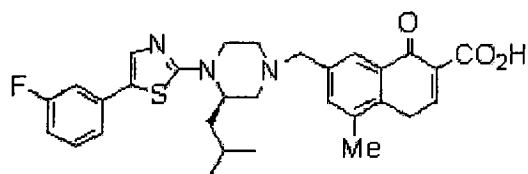
[5815]



[5816] 化合物 I-48

[5817] [式 1325]

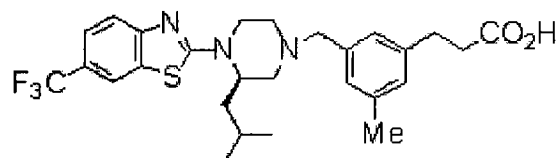
[5818]



[5819] 化合物 I-49

[5820] [式 1326]

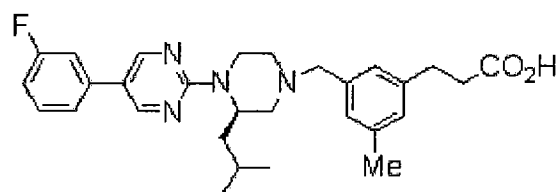
[5821]



[5822] 化合物 I-50

[5823] [式 1327]

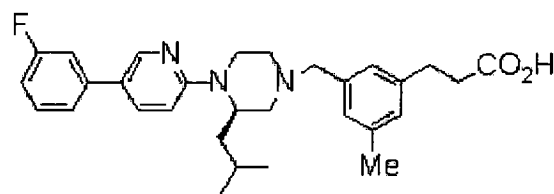
[5824]



[5825] 化合物 I-51

[5826] [式 1328]

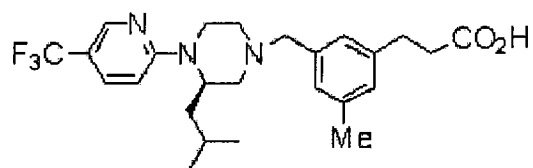
[5827]



[5828] 化合物 I-52

[5829] [式 1329]

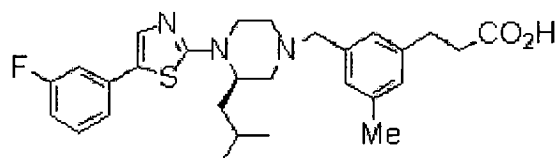
[5830]



[5831] 化合物 I-53

[5832] [式 1330]

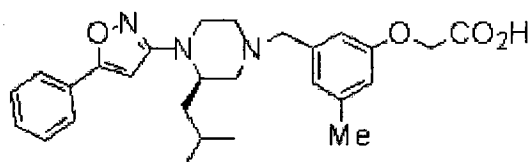
[5833]



[5834] 化合物 I-54

[5835] [式 1331]

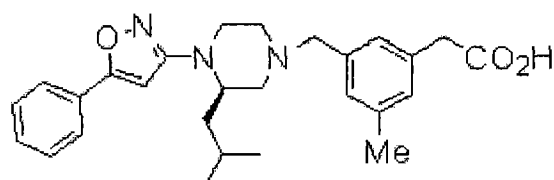
[5836]



[5837] 化合物 I-55

[5838] [式 1332]

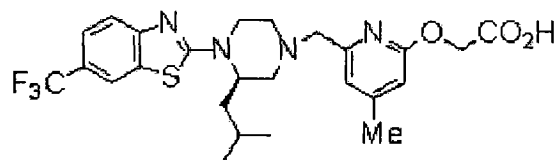
[5839]



[5840] 化合物 I-56

[5841] [式 1333]

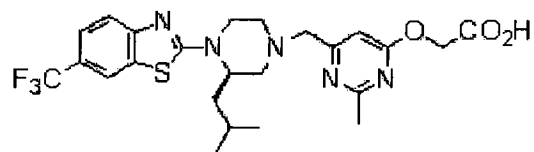
[5842]



[5843] 化合物 I-57

[5844] [式 1334]

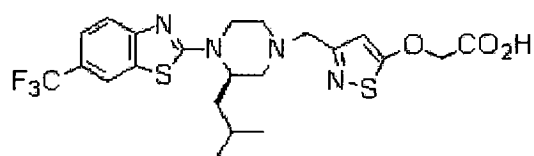
[5845]



[5846] 化合物 I-58

[5847] [式 1335]

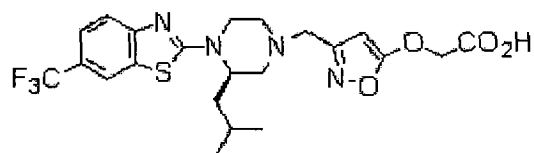
[5848]



[5849] 化合物 I-59

[5850] [式 1336]

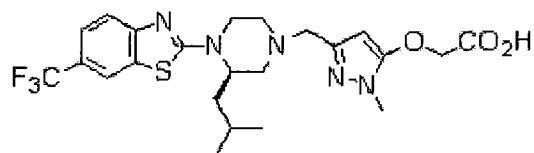
[5851]



[5852] 化合物 I-60

[5853] [式 1337]

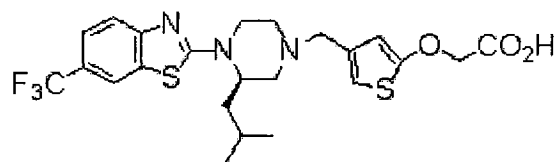
[5854]



[5855] 化合物 I-61

[5856] [式 1338]

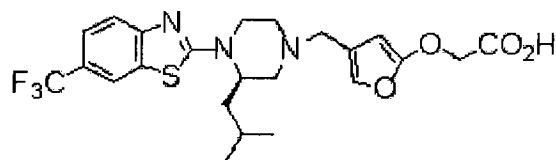
[5857]



[5858] 化合物 I-62

[5859] [式 1339]

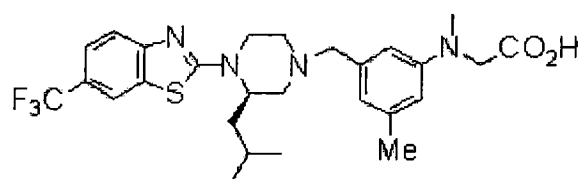
[5860]



[5861] 化合物 I-63

[5862] [式 1340]

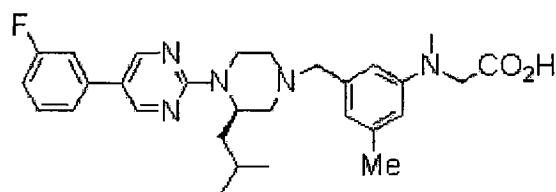
[5863]



[5864] 化合物 I-64

[5865] [式 1341]

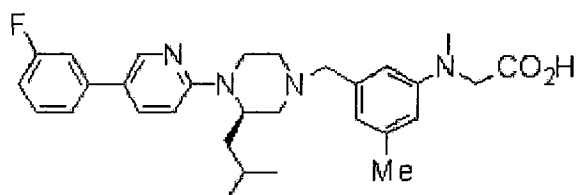
[5866]



[5867] 化合物 I-65

[5868] [式 1342]

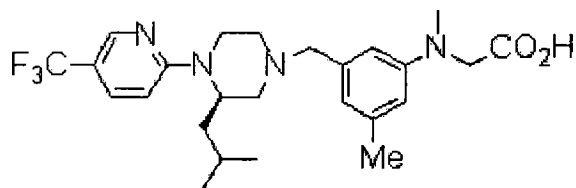
[5869]



[5870] 化合物 I-66

[5871] [式 1343]

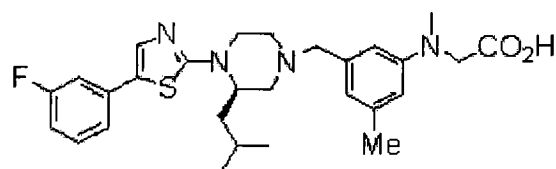
[5872]



[5873] 化合物 I-67

[5874] [式 1344]

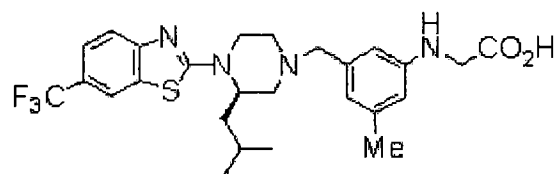
[5875]



[5876] 化合物 I-68

[5877] [式 1345]

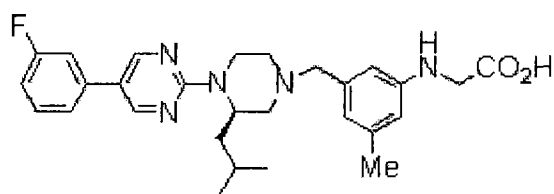
[5878]



[5879] 化合物 I-69

[5880] [式 1346]

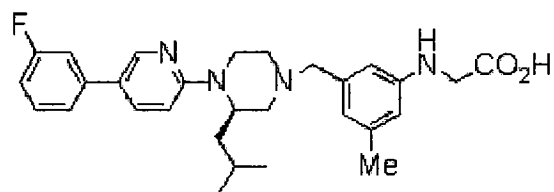
[5881]



[5882] 化合物 I-70

[5883] [式 1347]

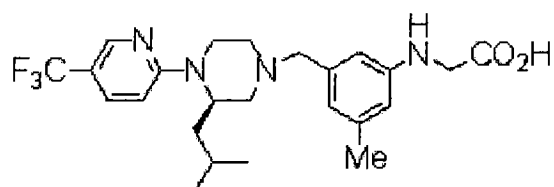
[5884]



[5885] 化合物 I-71

[5886] [式 1348]

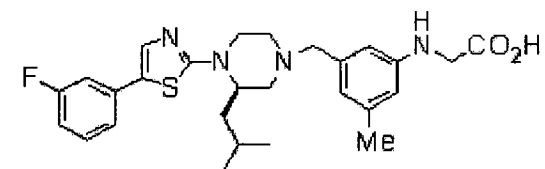
[5887]



[5888] 化合物 I-72

[5889] [式 1349]

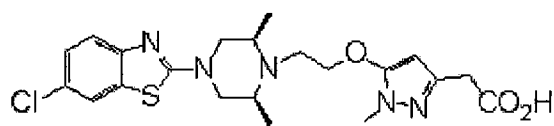
[5890]



[5891] 化合物 I-73

[5892] [式 1350]

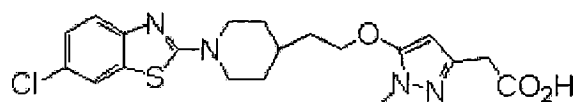
[5893]



[5894] 化合物 I-74

[5895] [式 1351]

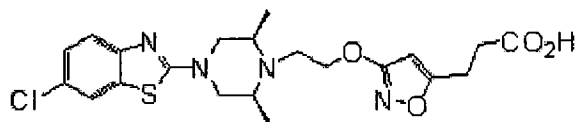
[5896]



[5897] 化合物 I-75

[5898] [式 1352]

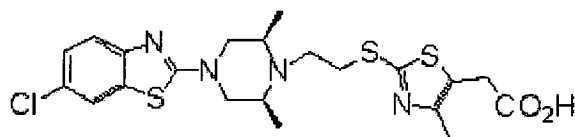
[5899]



[5900] 化合物 I-76

[5901] [式 1353]

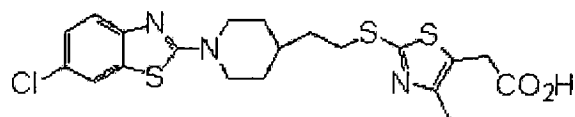
[5902]



[5903] 化合物 I-77

[5904] [式 1354]

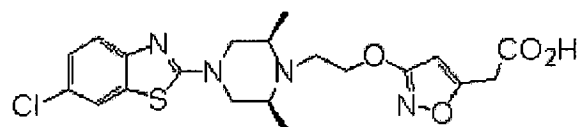
[5905]



[5906] 化合物 I-78

[5907] [式 1355]

[5908]



[5909] 化合物 I-79

[5910] [式 1356]

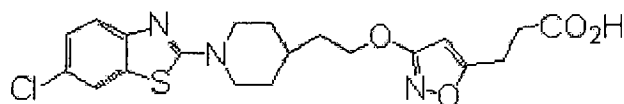
[5911]



[5912] 化合物 I-80

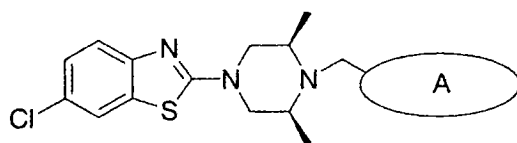
[5913] [式 1357]

[5914]



[5915] [表 1]

[5916]

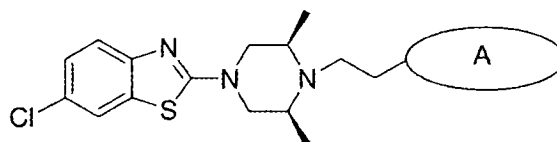


[5917]

No.	A
X-1	
X-2	
X-3	
X-4	
X-5	

[5918] [表 2]

[5919]

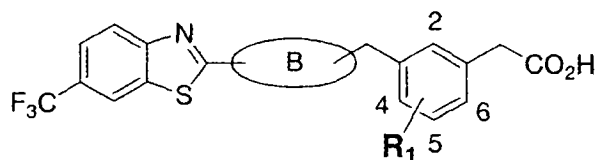


[5920]

No.	A	No.	A
X-6		X-11	
X-7		X-12	
X-8		X-13	
X-9		X-14	
X-10		X-15	

[5921] [表 3]

[5922]

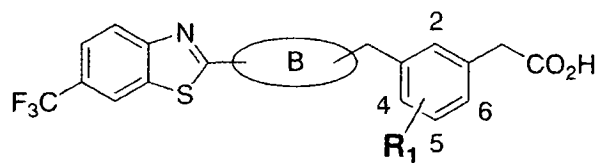


[5923]

No.	R1	B	No.	R1	B
Y-1	H		Y-18	5-Me	
Y-2	H		Y-19	5-Me	
Y-3	H		Y-20	5-Me	
Y-4	H		Y-21	5-Me	
Y-5	H		Y-22	5-Me	
Y-6	H		Y-23	5-Me	
Y-7	H		Y-24	5-Me	
Y-8	H		Y-25	5-Me	
Y-9	H		Y-26	5-Me	
Y-10	H		Y-27	5-Me	

[5924] [表 4]

[5925]

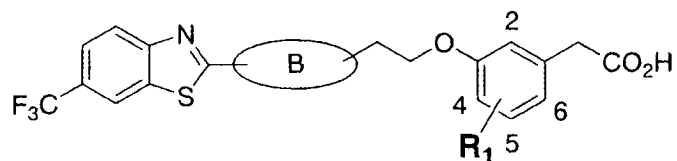


[5926]

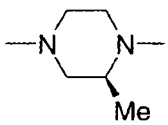
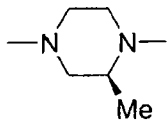
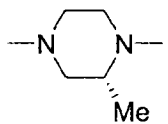
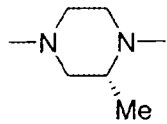
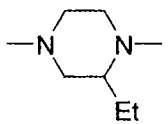
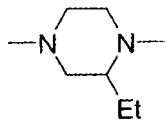
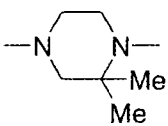
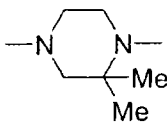
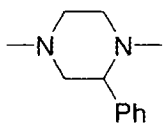
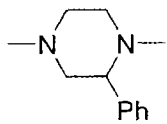
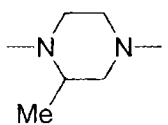
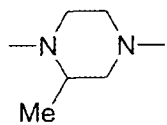
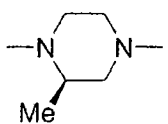
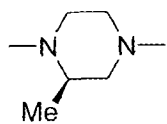
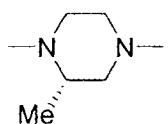
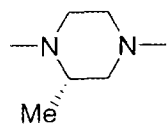
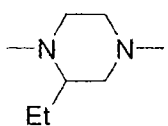
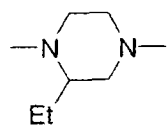
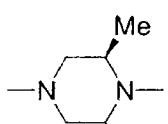
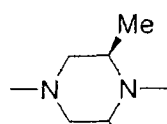
No.	R1	B	No.	R1	B
Y-11	H		Y-28	5-Me	
Y-12	H		Y-29	5-Me	
Y-13	H		Y-30	5-Me	
Y-14	H		Y-31	5-Me	
Y-15	H		Y-32	5-Me	
Y-16	H		Y-33	5-Me	
Y-17	H		Y-34	5-Me	

[5927] [表 5]

[5928]

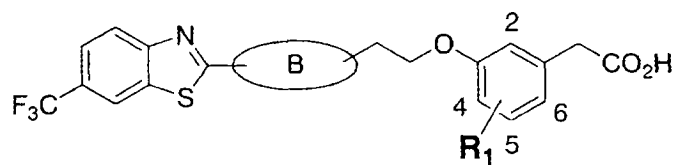


[5929]

No.	R1	B	No.	R1	B
Y-35	H		Y-52	4 - Cl	
Y-36	H		Y-53	4 - Cl	
Y-37	H		Y-54	4 - Cl	
Y-38	H		Y-55	4 - Cl	
Y-39	H		Y-56	4 - Cl	
Y-40	H		Y-57	4 - Cl	
Y-41	H		Y-58	4 - Cl	
Y-42	H		Y-59	4 - Cl	
Y-43	H		Y-60	4 - Cl	
Y-44	H		Y-61	4 - Cl	

[5930] [表 6]

[5931]

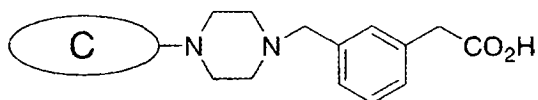


[5932]

No.	R1	B	No.	R1	B
Y-45	H		Y-62	4 - Cl	
Y-46	H		Y-63	4 - Cl	
Y-47	H		Y-64	4 - Cl	
Y-48	H		Y-65	4 - Cl	
Y-49	H		Y-66	4 - Cl	
Y-50	H		Y-67	4 - Cl	
Y-51	H		Y-68	4 - Cl	

[5933] [表 7]

[5934]

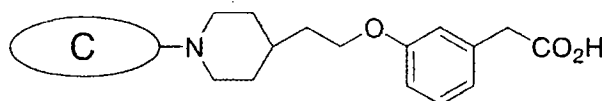


[5935]

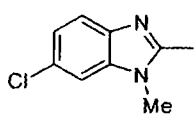
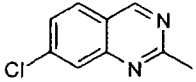
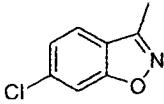
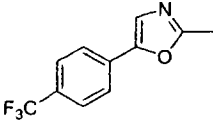
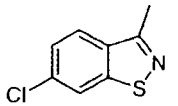
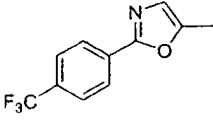
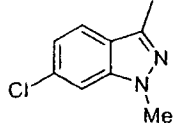
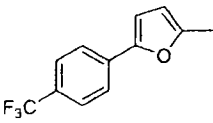
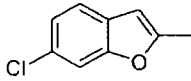
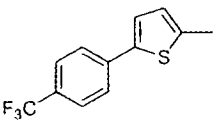
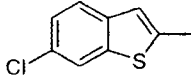
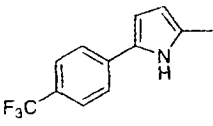
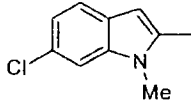
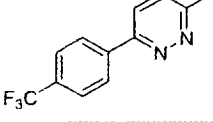
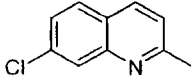
No.	C	No.	C
Z-1		Z-9	
Z-2		Z-10	
Z-3		Z-11	
Z-4		Z-12	
Z-5		Z-13	
Z-6		Z-14	
Z-7		Z-15	
Z-8			

[5936] [表 8]

[5937]



[5938]

No.	C	No.	C
Z-16		Z-24	
Z-17		Z-25	
Z-18		Z-26	
Z-19		Z-27	
Z-20		Z-28	
Z-21		Z-29	
Z-22		Z-30	
Z-23			

[5939] 试验例 1 试验 PPAR δ 和 α 的转录活性

[5940] 采用通常用于检测核受体活性的嵌合转录因子试验来测量 PPAR 转录活性。具体地,将两个质粒瞬时转染给 CHO 细胞,一个质粒表达酵母转录因子 GAL4 的 DNA 结合结构域与受体的配体结合结构域的融合蛋白,和另一个质粒为报道质粒。将有在报道质粒上的编码的 GAL4 的识别序列的启动子的活性用作评价受体活性的参数。

[5941] 质粒:通过使用 Human Universal Quick-Clone cDNA (CLONTECH) 的 PCR 扩增得到人 PPAR δ (hPPAR δ) 或 α (hPPAR α) (δ :aa 139-C 端; α :aa167-C 端) 的配体结合结构域。将各个扩增的 cDNA 亚克隆到 pCR2.1-TOPO 载体 (Invitrogen) 中并且通过 DNA 序列证实 cDNA 克隆的同一性。然后,将各个得到的 cDNA 片段亚克隆到 pBIND 载体 (Promega) 中,以构建表达具有酵母转录因子 GAL4 的 DNA 结合结构域的融合蛋白的质粒。将 pG5luc 载体 (Promega) 用作报道质粒。

[5942] 细胞培养和转染:将 CHO 细胞在 10% FBS- α MEM 中培养。使用 96 孔板 (Costar),将用胰蛋白酶处理分散的 CHO 细胞以 20000 细胞每孔和通过上述方法得到的两种质粒以

25ng 每孔用 FuGene Reagent (Roche) 转染, 根据生产者的说明进行。

[5943] 转录活性的测量: 将如上转染的 CHO 细胞以 100 μ l 每孔分配到其中预先点有溶解于 DMSO 0.5 μ l 中的试验化合物的孔中。在将细胞和试验化合物在 CO2 培养箱中一起培养 24 小时之后, 通过每孔加入 100 μ l 的荧光素酶底物 PicaGene LT2.0 (Toyo ink) 测量荧光素酶活性。使用 LUMINOUS CT-9000D (DIA-IATRON) 测量活性。

[5944] 对于 PPAR δ , 使用 Excel 程序计算表现 1/2 最大荧光素酶活性的试验化合物浓度, 以得到试验化合物的 PPAR δ 活性的 EC₅₀ 值。结果如表 9 中所示。

[5945] [表 9]

[5946]

实施例编号	EC ₅₀ (μ M)		
	hPPAR δ	hPPAR α	hPPAR γ
474	0.0045	0.35	0.20
503	0.91	1.5	>10
519	0.02	0.54	0.8
562	0.029	>10	1.9
590	0.026	>10	>10
597	0.0075	0.27	0.69
612	0.049	0.57	2.2
630	0.023	2.6	4.2
652	0.28	>10	>10
679	0.013	0.96	0.58
699	0.041	1.00	0.76
707	0.019	2.50	3.30
854	0.0044	>10	>10

[5947] 试验例 2 试验 CYP2C9 酶的抑制

[5948] 抑制 CYP2C9 酶的试验使用人肝微粒体进行并且将作为 CYP2C9 的典型反应的甲苯磺丁脲 4 位的水合活性作为一个参数。

[5949] 反应条件如下: 底物, 5 μ M 甲苯磺丁脲 (¹⁴C 标记的化合物); 反应时间, 30 分钟; 反应温度, 37°C; 蛋白质浓度, 0.25mg/ml (人肝微粒体, 15pol, 批号 210296、XenoTech)。

[5950] 向 HEPES Buffer (pH 7.4) 加入蛋白质 (人肝微粒体)、药物溶液和具有上述成分的底物。向其中加入作为反应的辅酶的 NADPH, 以开始反应。在反应固定的时间之后, 向其中加入 2N 盐酸溶液并通过除去蛋白将反应终止。将剩余的底物药物和产生的代谢物用氯仿萃取。除去溶剂并将残余物再溶解在甲醇中。将该溶液在 TLC 上点板, 用氯仿: 甲醇: 乙酸 = 90: 10: 1 展开, 连接在显像板上约 14-20 小时并且通过 BAS2000 分析。对于代谢物 (甲苯磺丁脲 4-位水合物质) 的产生活性, 将在溶解药物的溶剂加入到反应试样中的

情况下的活性用作对照 (100%)。计算在将试验药物溶液加入到反应的情况中的剩余活性 (%), 以证实本发明的化合物对 CYP2C9 酶的抑制有很少影响。

[5951] 试验例 3 试验代谢稳定性

[5952] 试验在肝微粒体中的代谢稳定性: 向 tris-HCl 缓冲液 (pH 7.4) 加入 NADPH (在氧化代谢的情况中最终浓度为 1mM)、肝微粒体 (最终浓度为 0.5mg 蛋白 /ml) 和各种化合物 (最终浓度为 2 μ M)。将混合物在 37°C 反应 0 和 30 分钟。在被结合的葡糖醛酸的情况中, 加入 UDPGA (最终浓度为 5mM) 代替 NADPH。通过加入基于反应溶液的 1 体积份为 2 体积份的乙腈 / 甲醇 = 1/1 (v/v) 终止反应, 然后通过 HPLC 测量离心的上清液中的化合物。通过比较 0 和 30 分钟之间的数值, 计算通过代谢反应而消失的化合物的量, 以证实本发明化合物的代谢稳定性。

[5953] 试验例 4 试验溶解性

[5954] 将本发明的化合物和试验溶剂 (JP-2 溶液, 和包含 20mM 牛磺胆酸钠的 JP-2 溶液) 在 37°C 搅拌 3 小时。将混合物用 0.45 μ m 过滤器过滤并且用 HPLC 方法测量滤液的浓度, 以证实本发明化合物的溶解性。

[5955] 试验例 5 试验毒性

[5956] 将本发明的化合物 (30 到 300mg/kg/天) 给予大鼠。在给予之后, 检查大鼠的死亡数、状态、食物摄入和体重并且进行组织病理学检查。

[5957] 另外, 作为血液学检查, 在给予之后的几天, 收集血液并且在血液处理之后测量 PT、APTT 和 Fbg。测量外源性凝血因子 (F-III、F-V、F-VII、F-X) 和内源性凝血因子 (F-VIII、F-IX、F-XI、F-XII) 的活性。通过在向大鼠血浆加入对于各个测量对象 (Dade Boehringer Marburg) 来说具有不充分因子的血浆并且预培养之后测量 PT (外源) 或 APTT (内源) 的方法测量外源或内源凝血因子的凝固时间。混合对照大鼠的血浆并且用将血浆用作为标准物质的 Owren's Veronal Buffer 顺序双倍稀释的稀释物作出校准曲线。通过因子不充分血浆 (factor deficient plasma) 的凝固时间的方法测量的凝固时间和校准曲线计算活性百分比, 并且通过与未经处理大鼠的血浆相比的活性百分数评价各个凝血因子的活性。

[5958] 如上所述, 确定本发明化合物的毒性。