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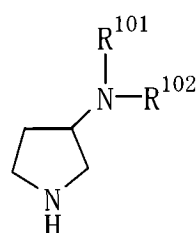
权利要求书5页 说明书189页

(54) 发明名称

可用作单胺再摄取抑制剂的 N, N- 取代的
3- 氨基吡咯烷化合物

(57) 摘要

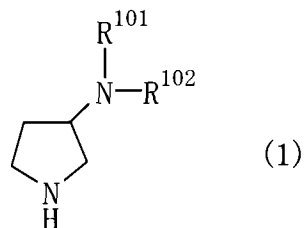
本发明提供了通式 (1) 的吡咯烷化合物：



或它们的盐, 其中 R¹⁰¹ 和
(1)

R¹⁰² 各自独立地是苯基或吡啶基, 该苯基或吡啶基可以具有一个或多个取代基, 所述取代基选自卤素原子和任选被一个或多个卤素原子取代的低级烷基等。本发明的吡咯烷化合物或它们的盐可用于制备具有更宽治疗范围并且在短期给药后能够显示出充分的治疗效果的药物制剂。

1. 通式 (1) 的吡咯烷化合物：



或它们的盐，

其中 R^{102} 是下列基团 (2)-(4)、(7)-(14)、(16)-(19)、(21)-(32) 和 (40)-(50) 之一：

- (2) 吡啶基，
- (3) 苯并噻吩基，
- (4) 吲哚基，
- (7) 苯并呋喃基，
- (8) 喹啉基，
- (9) 噻唑基，
- (10) 嘧啶基，
- (11) 吡嗪基，
- (12) 苯并噻唑基，
- (13) 噻吩并 [3,2-b] 吡啶基，
- (14) 噻吩基，
- (16) 四氢吡喃基，
- (17) 吡咯基，
- (18) 2,4-二氢 -1,3- 苯并二氧杂环己烯基，
- (19) 2,3-二氢苯并呋喃基，
- (21) 吡唑基，
- (22) 哒嗪基，
- (23) 二氢吲哚基，
- (24) 噻吩并 [2,3-b] 吡啶基，
- (25) 噻吩并 [3,2-d] 嘧啶基，
- (26) 噻吩并 [3,2-e] 嘧啶基，
- (27) 1H- 吡唑并 [3,4-b] 吡啶基，
- (28) 异喹啉基，
- (29) 2,3-二氢 -1,4- 苯并噁嗪基，
- (30) 喹喔啉基，
- (31) 喹唑啉基，
- (32) 1,2,3,4- 四氢喹啉基，
- (40) 1,3- 苯并间二氧杂环戊烯基，
- (41) 2,3-二氢 -1,4- 苯并二氧杂环己烯基，
- (42) 3,4-二氢 -1,5- 苯并二氧杂环庚烯基，
- (43) 二氢吡啶基，

- (44) 1,2- 二氢喹啉基,
- (45) 1,2,3,4- 四氢异喹啉基,
- (46) 苯并噁唑基,
- (47) 苯并异噻唑基,
- (48) 吡唑基,
- (49) 苯并咪唑基, 和
- (50) 咪唑基,

基团 (2)-(4)、(7)-(14)、(16)-(19)、(21)-(32) 和 (40)-(50) 各自可以在环烷基、芳环或杂环上具有一个或多个选自下列 (1-1) 到 (1-37) 中的取代基:

- (1-1) 卤素原子,
- (1-2) 任选被一个或多个卤素原子取代的 C_{1-6} 烷硫基,
- (1-3) 任选被一个或多个卤素原子取代的 C_{1-6} 烷基,
- (1-4) 任选被一个或多个卤素原子取代的 C_{1-6} 烷氧基,
- (1-5) 硝基,
- (1-6) C_{1-6} 烷氧基羰基,
- (1-7) 任选被一个或两个 C_{1-6} 烷基取代的氨基,
- (1-8) C_{1-6} 烷基磺酰基,
- (1-9) 氰基,
- (1-10) 羧基,
- (1-11) 羟基,
- (1-12) 噻吩基,
- (1-13) 噁唑基,
- (1-14) 萘基,
- (1-15) 苯甲酰基,
- (1-16) 在苯环上任选被 1-3 个卤素原子取代的苯氧基,
- (1-17) 苯基 C_{1-6} 烷氧基,
- (1-18) C_{1-6} 烷酰基,
- (1-19) 在苯环上任选被 1-5 个选自卤素原子、 C_{1-6} 烷氧基、氰基、 C_{1-6} 烷酰基和 C_{1-6} 烷基中的取代基取代的苯基,
- (1-20) 苯基 C_{1-6} 烷基,
- (1-21) 氰基 C_{1-6} 烷基,
- (1-22) 5-7 员饱和杂环基取代的磺酰基, 该杂环基团在杂环上含有一个或两个选自氮、氧和硫中的杂原子,
- (1-23) 在噻唑环上任选被一个或两个 C_{1-6} 烷基取代的噻唑基,
- (1-24) 咪唑基,
- (1-25) 在氨基上任选被一个或两个 C_{1-6} 烷基取代的氨基 C_{1-6} 烷基,
- (1-26) 吡咯烷基 C_{1-6} 烷氧基,
- (1-27) 异噁唑基,
- (1-28) 环烷基羰基,

(1-29) 萘氧基,

(1-30) 吡啶基,

(1-31) 呋喃基,

(1-32) 苯硫基,

(1-33) 氧代基,

(1-34) 氨基甲酰基,

(1-35) 含有一个或两个选自氮、氧和硫中的杂原子的 5 到 7 员饱和杂环基,该杂环基任选被 1-3 个选自下列之中的取代基取代:氧代基; C_{1-6} 烷基; C_{1-6} 烷酰基;苯基 C_{1-6} 烷基;在苯环上任选被 1-3 个选自卤素原子和 C_{1-6} 烷氧基中的基团取代的苯基;和吡啶基,

(1-36) 氧撑基团和

(1-37) C_{1-6} 醇基,和

R^{101} 是 (1) 苯基,且基团 (1) 在苯环上可以具有一个或多个选自基团 (1-1) 到 (1-32)、(1-34) 和 (1-35) 中的取代基。

2. 根据权利要求 1 所述的通式 (1) 的吡咯烷化合物或它们的盐,其中:

R^{101} 是:

(1) 苯基,

且基团 (1) 在苯环上可以具有 1-3 个选自如权利要求 1 所定义的基团 (1-1) 到 (1-32)、(1-34) 和 (1-35) 中的取代基。

3. 根据权利要求 2 所述的通式 (1) 的吡咯烷化合物或它们的盐,其中:

R^{101} 是:

(1) 苯基,

且基团 (1) 可以在苯环上具有 1-3 个选自 (1-1) 卤素原子和 (1-3) 任选被 1-3 个卤素原子取代的 C_{1-6} 烷基中的取代基。

4. 根据权利要求 3 所述的通式 (1) 的吡咯烷化合物或它们的盐,其中:

R^{102} 是:

(2) 吡啶基,

(9) 噻唑基,

(10) 嘧啶基,

(11) 吡嗪基,

(14) 噻吩基,

(48) 呋唑基,

基团 (2)、(9)、(10)、(11)、(14) 和 (48) 各自可以在杂环上具有 1-3 个选自如权利要求 1 所定义的基团 (1-1) 到 (1-37) 中的取代基。

5. 根据权利要求 4 所述的通式 (1) 的吡咯烷化合物或它们的盐,其中:

R^{101} 是:

单卤代苯基,二卤代苯基,或被 1 个卤素原子和一个 C_{1-6} 烷基取代的苯基,

R^{102} 是:

(2) 吡啶基,

(9) 噻唑基,

- (10) 嘧啶基,
- (11) 吡嗪基,
- (14) 噻吩基,
- (48) 吡唑基,

基团 (2)、(9)、(10)、(11)、(14) 和 (48) 各自可以在杂环上具有 1 或 2 个选自 (1-1) 卤素原子, (1-3) 任选被一个或多个卤素原子取代的 C_{1-6} 烷基和 (1-9) 氰基中的取代基。

6. 根据权利要求 5 所述的通式 (1) 的吡咯烷化合物或它们的盐, 选自下列化合物:

- (3- 氯 -4- 氟苯基)-(S)-吡咯烷-3-基噻唑-2-基胺,
- (4- 氟苯基)-(S)-吡咯烷-3-基噻唑-2-基胺,
- (3,4-二氯苯基)-(S)-吡咯烷-3-基噻唑-2-基胺,
- (3,4-二氯苯基)嘧啶-5-基-(S)-吡咯烷-3-基胺,
- (3- 氯 -4- 氟苯基)吡嗪-2-基-(S)-吡咯烷-3-基胺,
- (3- 氯 -4- 氟苯基)-(5- 氯吡啶-2-基)-(S)-吡咯烷-3-基胺,
- (3- 氯 -4- 氟苯基)吡啶-2-基-(S)-吡咯烷-3-基胺,
- (3- 氯 -4- 氟苯基)吡啶-3-基-(S)-吡咯烷-3-基胺,
- (3- 氯 -4- 氟苯基)-(6- 氟吡啶-3-基)-(S)-吡咯烷-3-基胺,
- (3,4-二氯苯基)吡啶-3-基-(S)-吡咯烷-3-基胺,
- (3- 氯 -4- 氟苯基)-(S)-吡咯烷-3-基噻吩-3-基胺,
- (3- 氯 -4- 氟苯基)-(5- 氟吡啶-3-基)-(S)-吡咯烷-3-基胺,
- (4- 氟-3- 甲基苯基)-(5- 氟吡啶-3-基)-(S)-吡咯烷-3-基胺, 和
- (3- 氯 -4- 氟苯基)-(1- 甲基-1H-吡唑-5-基)-(S)-吡咯烷-3-基胺。

7. 药物组合物, 包括作为活性成分的根据权利要求 1 所述的通式 (1) 的吡咯烷化合物或它们的盐和可药用载体。

8. 用于由 5-羟色胺、去甲肾上腺素或多巴胺的神经传递减少所引起的疾病的预防和/或治疗剂, 包括作为活性成分的根据权利要求 1 所述的通式 (1) 的吡咯烷化合物或它们的盐。

9. 根据权利要求 8 所述的预防和/或治疗剂, 其中所述疾病选自高血压; 抑郁症; 焦虑症; 恐惧症; 外伤后应激综合症; 急性应激综合症; 回避性人格障碍; 身体畸形病; 早熟性射精; 饮食障碍; 肥胖; 酒精、古柯碱、海洛因、苯巴比妥、烟碱和苯二氮草类的化学依赖性; 群集性头痛; 偏头痛; 疼痛症; 阿尔茨海默氏病; 强迫-强制症; 恐慌症; 记忆障碍; 帕金森氏病; 内分泌疾病; 血管痉挛; 小脑性共济失调; 胃肠道疾病; 精神分裂症的阴性综合症; 经前期综合征; 纤维肌痛综合症; 压力性尿失禁; 多发性抽动症; 拔毛发癖; 盗癖; 男性阳痿; 注意力缺乏活动亢进症(抗利尿激素); 慢性发作性偏头痛; 慢性疲劳; 猝倒; 睡眠无呼吸综合征和头痛。

10. 根据权利要求 8 所述的预防和/或治疗剂, 其中所述疾病选自:

抑郁症, 包括: 主要抑郁症; 双向 1 型障碍; 双向 2 型障碍; 混合性发作; 心情恶劣症; 快速循环型精神障碍; 非典型抑郁症; 季节性情感障碍; 产后抑郁症; 未成年人抑郁症; 复发性短暂性抑郁症; 难治性抑郁/慢性抑郁症; 双重抑郁; 酒精诱发的情绪障碍; 混合性焦虑与抑郁症; 由选自库兴氏病、甲状腺功能减退、甲状旁腺机能亢进综合症、阿狄森氏病、停

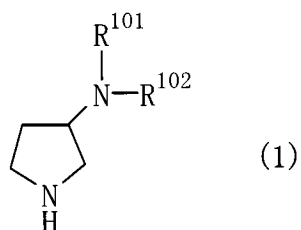
经和泌乳综合症、帕金森氏病、阿尔茨海默氏病、脑内出血、糖尿病、慢性疲劳综合症和癌症中的各种身体疾病诱发的抑郁；中年抑郁症；高龄抑郁症；儿童和青春期抑郁症；干扰素诱发的抑郁症；调节性疾病诱发的抑郁症；和焦虑症，包括调节障碍诱发的焦虑症，选自头颅外伤、脑感染和内耳损伤中的神经病诱发的焦虑症。

11. 根据权利要求 1-6 的任一项所述的通式 (1) 的吡咯烷化合物或它们的盐作为药物的用途。

12. 根据权利要求 1-6 的任一项所述的通式 (1) 的吡咯烷化合物或它们的盐作为 5-羟色胺再摄取抑制剂和 / 或去甲肾上腺素再摄取抑制剂和 / 或多巴胺再摄取抑制剂的用途。

13. 治疗或预防 5-羟色胺、去甲肾上腺素或多巴胺神经传递减少诱发的疾病的方法，包括将根据权利要求 1-6 的任一项所述的通式 (1) 的吡咯烷化合物或它们的盐给药于人或动物。

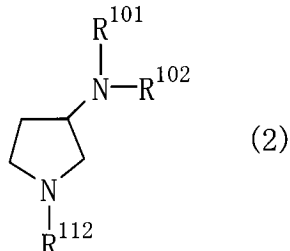
14. 制备通式 (1) 的吡咯烷化合物或它们的盐的方法：



其中 R^{101} 和 R^{102} 如权利要求 1 所定义，

该方法包括：

(1) 使通式 (2) 的化合物进行消去反应以除去氨基保护基：



其中 R^{101} 和 R^{102} 如权利要求 1 所定义，且 R^{112} 是氨基保护基。

可用作单胺再摄取抑制剂的 N, N- 取代的 3- 氨基吡咯烷化合物

[0001] 本申请是申请日为 2006 年 05 月 12 日和发明名称为“可用作单胺再摄取抑制剂的 N, N- 取代的 3- 氨基吡咯烷化合物”的 200680016402.4 号发明专利申请的分案申请。

技术领域

[0002] 本发明涉及吡咯烷化合物。

背景技术

[0003] 三类单胺, 分别称之为 5- 羟色胺、去甲肾上腺素和多巴胺, 在生物体中起神经递质的作用。因此, 具有单胺再摄取抑制效应的药物广泛用作中枢和周围神经系统疾病的治疗药物。

[0004] 目前用于治疗抑郁症的许多药物选择地抑制去甲肾上腺素或 5- 羟色胺再摄取。这些药物的实例包括丙咪嗪 (第一代抗抑郁药), 麦普替林 (第二代抗抑郁药), 选择性 5- 羟色胺摄取抑制剂比如氟苯氧丙胺 (SSRI, 第三代抗抑郁药), 5- 羟色胺和 / 或去甲肾上腺素再摄取抑制剂比如文拉法辛 (SNRI, 第四代抗抑郁药) 等等 (参见 Sadanori Miura, Rinshoseishinyakuri (日本临床精神药理学杂志), 2000, 3 :311-318)。

[0005] 然而, 这些药物需要至少三周才显示出它们的治疗效果, 此外, 这些药物在约 30% 的抑郁症病人中未能显示出足够的效果 (参见 Phil Skolnick, 欧洲药理学杂志, 2001, 375 :31-40)。

发明内容

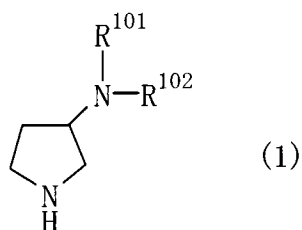
[0006] 本发明的一个目的是提供比已知的抗抑郁药具有更广的治疗谱、并且能够在短期给药之后显示出充分的治疗效果的药物制剂。

[0007] 为了实现上述目的本发明人进行了广泛研究, 发现用下式 (1) 表示的吡咯烷化合物可用于生产这种需要的药物制剂。基于该发现, 完成了本发明。

[0008] 本发明提供了如在下列项 1 到项 14 中所述的吡咯烷化合物, 包含所述化合物的组合物, 包含所述化合物的药剂, 所述化合物的用途, 治疗疾病的方法以及生产所述化合物的方法。

[0009] 项 1. 通式 (1) 的吡咯烷化合物:

[0010]



[0011] 或它们的盐,

- [0012] 其中 R^{101} 和 R^{102} 各自独立地是下列基团 (1)–(86) 之一：
- [0013] (1) 苯基，
- [0014] (2) 吡啶基，
- [0015] (3) 苯并噻吩基，
- [0016] (4) 吲哚基，
- [0017] (5) 2,3-二氢-1H-茛基，
- [0018] (6) 萘基，
- [0019] (7) 苯并呋喃基，
- [0020] (8) 喹啉基，
- [0021] (9) 噻唑基，
- [0022] (10) 嘧啶基，
- [0023] (11) 吡嗪基，
- [0024] (12) 苯并噻唑基，
- [0025] (13) 噻吩并 [3,2-b] 吡啶基，
- [0026] (14) 噻吩基，
- [0027] (15) 环烷基，
- [0028] (16) 四氢吡喃基，
- [0029] (17) 吡咯基，
- [0030] (18) 2,4-二氢-1,3-苯并二氧杂环己烯基，
- [0031] (19) 2,3-二氢苯并呋喃基，
- [0032] (20) 9H-茛基，
- [0033] (21) 吡唑基，
- [0034] (22) 哒嗪基，
- [0035] (23) 二氢吲哚基，
- [0036] (24) 噻吩并 [2,3-b] 吡啶基，
- [0037] (25) 噻吩并 [3,2-d] 嘧啶基，
- [0038] (26) 噻吩并 [3,2-e] 嘧啶基，
- [0039] (27) 1H-吡唑并 [3,4-b] 吡啶基，
- [0040] (28) 异喹啉基，
- [0041] (29) 2,3-二氢-1,4-苯并噁嗪基 (benzoxadiny1)，
- [0042] (30) 喹喔啉基，
- [0043] (31) 喹唑啉基，
- [0044] (32) 1,2,3,4-四氢喹啉基，
- [0045] (33) 环烷基低级烷基，
- [0046] (34) 低级烷硫基低级烷基，
- [0047] (35) 在氨基上任选被一个或两个低级烷基取代的氨基取代的低级烷基，
- [0048] (36) 苯氧基低级烷基，
- [0049] (37) 吡啶氧基低级烷基，
- [0050] (38) 低级炔基，

- [0051] (39) 苯基低级烯基,
- [0052] (40) 1,3- 苯并间二氧杂环戊烯基,
- [0053] (41) 2,3- 二氢 -1,4- 苯并二氧杂环己烯基,
- [0054] (42) 3,4- 二氢 -1,5- 苯并二氧杂环庚烯基 (benzodioxepinyl),
- [0055] (43) 二氢吡啶基,
- [0056] (44) 1,2- 二氢喹啉基,
- [0057] (45) 1,2,3,4- 四氢异喹啉基,
- [0058] (46) 苯并噁唑基,
- [0059] (47) 苯并异噻唑基,
- [0060] (48) 呋唑基,
- [0061] (49) 苯并咪唑基,
- [0062] (50) 咪唑基,
- [0063] (51) 1,2,3,4- 四氢萘基低级烷基,
- [0064] (52) 咪唑并 [1,2-a] 吡啶基低级烷基,
- [0065] (53) 噻唑基低级烷基,
- [0066] (54) 四氢吡喃基低级烷基,
- [0067] (55) 哌啶基低级烷基,
- [0068] (56) 二苯基低级烷氧基取代的低级烷基,
- [0069] (57) 低级烷氧基羰基取代的低级烷基,
- [0070] (58) 苯基低级烷氧基羰基取代的低级烷基,
- [0071] (59) 羟基取代的低级烷基,
- [0072] (60) 低级烷氧基低级烷基,
- [0073] (61) 羧基低级烷基,
- [0074] (62) 在氨基甲酰基上任选被一个或两个低级烷基取代的氨基甲酰基取代的低级烷基,
- [0075] (63) 低级烯基,
- [0076] (64) 吗啉基羰基低级烷基,
- [0077] (65) 苯甲酰基低级烷基,
- [0078] (66) 苯硫基低级烷基,
- [0079] (67) 萘硫基低级烷基,
- [0080] (68) 环烷硫基低级烷基,
- [0081] (69) 吡啶基硫基低级烷基,
- [0082] (70) 嘧啶基硫基低级烷基,
- [0083] (71) 呋喃硫基低级烷基,
- [0084] (72) 噻吩硫基低级烷基,
- [0085] (73) 1,3,4- 噻二唑硫基低级烷基,
- [0086] (74) 苯并咪唑硫基低级烷基,
- [0087] (75) 苯并噻唑硫基低级烷基,
- [0088] (76) 四唑硫基低级烷基,

- [0089] (77) 苯并噁唑硫基低级烷基，
- [0090] (78) 噻唑硫基低级烷基，
- [0091] (79) 咪唑硫基低级烷基，
- [0092] (80) 在氨基上任选被一个或两个低级烷基取代的氨基取代的低级烷硫基，
- [0093] (81) 苯基取代的低级烷硫基低级烷基，
- [0094] (82) 呋喃基取代的低级烷硫基低级烷基，
- [0095] (83) 吡啶基取代的低级烷硫基低级烷基，
- [0096] (84) 羟基取代的低级烷硫基低级烷基，
- [0097] (85) 苯氧基取代的低级烷硫基低级烷基，和
- [0098] (86) 低级烷氧基羰基取代的低级烷硫基低级烷基，
- [0099] 基团 (1)-(32)，(37)，(39)-(56)，(64)-(79)，(81)-(83) 和 (85) 各自可以在环烷基、芳环或杂环上具有一个或多个选自下列 (1-1)-(1-37) 中的取代基：
- [0100] (1-1) 卤素原子，
- [0101] (1-2) 任选被一个或多个卤素原子取代的低级烷硫基，
- [0102] (1-3) 任选被一个或多个卤素原子取代的低级烷基，
- [0103] (1-4) 任选被一个或多个卤素原子取代的低级烷氧基，
- [0104] (1-5) 硝基，
- [0105] (1-6) 低级烷氧基羰基，
- [0106] (1-7) 任选被一个或两个低级烷基取代的氨基，
- [0107] (1-8) 低级烷基磺酰基，
- [0108] (1-9) 氰基，
- [0109] (1-10) 羧基，
- [0110] (1-11) 羟基，
- [0111] (1-12) 噻吩基，
- [0112] (1-13) 噁唑基，
- [0113] (1-14) 萘基，
- [0114] (1-15) 苯甲酰基，
- [0115] (1-16) 在苯环上任选被 1-3 个卤素原子取代的苯氧基，
- [0116] (1-17) 苯基低级烷氧基，
- [0117] (1-18) 低级烷酰基，
- [0118] (1-19) 在苯环上任选被 1-5 个选自卤素原子，低级烷氧基，氰基，低级烷酰基和低级烷基中的取代基取代的苯基，
- [0119] (1-20) 苯基低级烷基，
- [0120] (1-21) 氰基低级烷基，
- [0121] (1-22) 5-7 员饱和杂环基取代的磺酰基，该杂环基团在杂环上含有一个或两个选自氮、氧和硫中的杂原子，
- [0122] (1-23) 在噻唑环上任选被一个或两个低级烷基取代的噻唑基，
- [0123] (1-24) 咪唑基，
- [0124] (1-25) 在氨基上任选被一个或两个低级烷基取代的氨基低级烷基，

- [0125] (1-26) 吡咯烷基低级烷氧基，
[0126] (1-27) 异噁唑基，
[0127] (1-28) 环烷基羰基，
[0128] (1-29) 萘氧基，
[0129] (1-30) 吡啶基，
[0130] (1-31) 呋喃基，
[0131] (1-32) 苯硫基，
[0132] (1-33) 氧代基，
[0133] (1-34) 氨基甲酰基，
[0134] (1-35) 含有一个或两个选自氮、氧和硫中的杂原子的 5 到 7 员饱和杂环基，该杂环基任选被 1-3 个选自下列之中的取代基取代：氧代基；低级烷基；低级烷酰基；苯基低级烷基；在苯环上任选被 1-3 个选自卤素原子和低级烷氧基中的基团取代的苯基；和吡啶基，
[0135] (1-36) 氧撑基团和
[0136] (1-37) 低级醇基 (alkoxido)，
[0137] 前提条件是 R^{101} 和 R^{102} 不同时是未取代的苯基。
[0138] 项 2、根据项 1 所述的通式 (1) 的吡咯烷化合物或它们的盐，其中
[0139] R^{101} 是
[0140] (1) 苯基，
[0141] (3) 苯并噻吩基，
[0142] (4) 吲哚基，
[0143] (5) 2,3-二氢-1H-茚基，
[0144] (6) 萘基，
[0145] (7) 苯并呋喃基，
[0146] (8) 喹啉基，
[0147] (12) 苯并噻唑基，
[0148] (18) 2,4-二氢-1,3-苯并二氧杂环己烯基，
[0149] (19) 2,3-二氢苯并呋喃基，
[0150] (20) 9H-芴基，
[0151] (23) 二氢吲哚基，
[0152] (28) 异喹啉基，
[0153] (29) 2,3-二氢-1,4-苯并噁嗪基 (benzoxadiny1)，
[0154] (30) 喹喔啉基，
[0155] (31) 喹唑啉基，
[0156] (32) 1,2,3,4-四氢喹啉基，
[0157] (40) 1,3-苯并间二氧杂环戊烯基，
[0158] (41) 2,3-二氢-1,4-苯并二氧杂环己烯基，
[0159] (42) 3,4-二氢-1,5-苯并二氧杂环庚烯基 (benzodioxepiny1)，
[0160] (44) 1,2-二氢喹啉基，
[0161] (45) 1,2,3,4-四氢异喹啉基，

[0162] (46) 苯并噁唑基,

[0163] (47) 苯并异噁唑基,

[0164] (48) 呔唑基或

[0165] (49) 苯并咪唑基,

[0166] 上述各基团可以在芳环或杂环上可以具有 1-3 个选自如项 1 所定义的基团 (1-1) 到 (1-37) 中的取代基。

[0167] 项 3、根据项 2 所述的通式 (1) 的吡咯烷化合物或它们的盐, 其中

[0168] R^{101} 是

[0169] (1) 苯基或

[0170] (3) 苯并噁吩基,

[0171] 上述各基团可以在芳环或杂环上具有 1-3 个选自 (1-1) 卤素原子和 (1-3) 任选被 1-3 个卤素原子取代的低级烷基中的取代基。

[0172] 项 4、根据项 3 所述的通式 (1) 的吡咯烷化合物或它们的盐, 其中

[0173] R^{102} 是

[0174] (1) 苯基,

[0175] (2) 吡啶基,

[0176] (9) 噻唑基,

[0177] (10) 嘧啶基,

[0178] (11) 吡嗪基,

[0179] (14) 噻吩基,

[0180] (48) 呔唑基,

[0181] (59) 羟基取代的低级烷基或

[0182] (60) 低级烷氧基低级烷基,

[0183] 基团 (1), (2), (9), (10), (11), (14) 和 (48) 各自可以在芳环或杂环上具有 1-3 个选自如项 1 所定义的基团 (1-1) 到 (1-37) 中的取代基。

[0184] 项 5、根据项 4 所述的通式 (1) 的吡咯烷化合物或它们的盐, 其中

[0185] R^{101} 是

[0186] 单卤代苯基, 二卤代苯基, 或被 1 个卤素原子和一个低级烷基取代的苯基,

[0187] R^{102} 是

[0188] (1) 苯基,

[0189] (2) 吡啶基,

[0190] (9) 噻唑基,

[0191] (10) 嘧啶基,

[0192] (11) 吡嗪基,

[0193] (14) 噻吩基,

[0194] (48) 呔唑基,

[0195] (59) 羟基取代的低级烷基或

[0196] (60) 低级烷氧基低级烷基,

[0197] 基团 (1), (2), (9), (10), (11), (14) 和 (48) 各自可以在芳环或杂环上具有 1 或

2 个选自 (1-1) 卤素原子, (1-3) 任选被一个或多个卤素原子取代的低级烷基和 (1-9) 氰基中的取代基。

[0198] 项 6、根据项 5 所述的通式 (1) 的吡咯烷化合物或它们的盐, 选自下列化合物:

[0199] (4- 氯苯基) 苯基-(S)- 吡咯烷-3- 基胺,

[0200] (4- 氟苯基) 苯基-(S)- 吡咯烷-3- 基胺,

[0201] (3,4- 二氟苯基) 苯基-(S)- 吡咯烷-3- 基胺,

[0202] 双-(4- 氟苯基)-(S)- 吡咯烷-3- 基胺,

[0203] (3,4- 二氟苯基)-(4- 氟苯基)-(S)- 吡咯烷-3- 基胺,

[0204] (3- 氯-4- 氟苯基)-(S)- 吡咯烷-3- 基-对- 甲苯胺,

[0205] 4-[(S)-(4- 氟-3- 甲基苯基) 吡咯烷-3- 基氨基]- 苄腈,

[0206] 双-(3- 氟苯基)-(S)- 吡咯烷-3- 基胺,

[0207] (3- 氯-4- 氟苯基)-(S)- 吡咯烷-3- 基噻唑-2- 基胺,

[0208] (4- 氟苯基)-(S)- 吡咯烷-3- 基噻唑-2- 基胺,

[0209] (3,4- 二氯苯基)-(S)- 吡咯烷-3- 基噻唑-2- 基胺,

[0210] (3,4- 二氯苯基) 嘧啶-5- 基-(S)- 吡咯烷-3- 基胺,

[0211] (3- 氯-4- 氟苯基) 吡嗪-2- 基-(S)- 吡咯烷-3- 基胺,

[0212] (3- 氯-4- 氟苯基)-(5- 氯吡啶-2- 基)-(S)- 吡咯烷-3- 基胺,

[0213] (3- 氯-4- 氟苯基) 吡啶-2- 基-(S)- 吡咯烷-3- 基胺,

[0214] (3- 氯-4- 氟苯基) 吡啶-3- 基-(S)- 吡咯烷-3- 基胺,

[0215] (3- 氯-4- 氟苯基)-(6- 氟吡啶-3- 基)-(S)- 吡咯烷-3- 基胺,

[0216] (3,4- 二氯苯基) 吡啶-3- 基-(S)- 吡咯烷-3- 基胺,

[0217] (3- 氯-4- 氟苯基)-(S)- 吡咯烷-3- 基噻吩-3- 基胺,

[0218] (3- 氯-4- 氟苯基)-(5- 氟吡啶-3- 基)-(S)- 吡咯烷-3- 基胺,

[0219] (4- 氟-3- 甲基苯基)-(5- 氟吡啶-3- 基)-(S)- 吡咯烷-3- 基胺,

[0220] 2-[(S)-(3- 氯-4- 氟苯基) 吡咯烷-3- 基氨基] 乙醇,

[0221] 1-[(S)-(3- 氯-4- 氟苯基) 吡咯烷-3- 基氨基]-2- 甲基- 丙烷-2- 醇,

[0222] (3- 氯-4- 氟苯基)-(2- 甲氧基乙基)-(S)- 吡咯烷-3- 基胺,

[0223] 3-[(S)-(3- 氯-4- 氟苯基) 吡咯烷-3- 基氨基]- 丙烷-1- 醇,

[0224] (3- 氯-4- 氟苯基)-(3- 甲氧基丙基)-(S)- 吡咯烷-3- 基胺,

[0225] (3- 氯-4- 氟苯基)-(1- 甲基-1H- 吡唑-5- 基)-(S)- 吡咯烷-3- 基胺,

[0226] 苯并 [b] 噻吩-6- 基-(S)- 吡咯烷-3- 基噻吩-3- 基胺, 和

[0227] 苯并 [b] 噻吩-5- 基-(S)- 吡咯烷-3- 基噻吩-3- 基胺。

[0228] 项 7、药物组合物, 包括作为活性成分的根据项 1 所述的通式 (1) 的吡咯烷化合物或它们的盐和可药用载体。

[0229] 项 8、由 5- 羟色胺、去甲肾上腺素或多巴胺的神经传递减少所引起的疾病的预防和 / 或治疗剂, 包括作为活性成分的项 1 所述的通式 (1) 的吡咯烷化合物或它们的盐。

[0230] 项 9、根据项 8 所述的预防和 / 或治疗剂, 其中所述疾病选自高血压; 抑郁症; 焦虑症; 恐惧症; 外伤后应激综合症; 急性应激综合症; 回避性人格障碍; 身体畸形病; 早熟性射精; 饮食障碍; 肥胖; 酒精、古柯碱、海洛因、苯巴比妥、烟碱和苯二氮草类的化学依赖

性；群集性头痛；偏头痛；疼痛症；阿尔茨海默氏病；强迫－强制症；恐慌症；记忆障碍；帕金森氏病；内分泌疾病；血管痉挛；小脑性共济失调；胃肠道疾病；精神分裂症的阴性综合症；经前期综合征；纤维肌痛综合症；压力性尿失禁；多发性抽动症；拔毛发癖；盗癖；男性阳萎；注意力缺乏活动亢进症（抗利尿激素）；慢性发作性偏头痛；慢性疲劳；猝倒；睡眠无呼吸综合征和头痛。

[0231] 项 10、根据项 8 所述的预防和 / 或治疗剂，其中所述疾病选自：

[0232] 抑郁症，包括：主要抑郁症；双向 1 型障碍；双向 2 型障碍；混合性发作；心情恶劣症；快速循环型精神障碍 (rapid cycler)；非典型抑郁症；季节性情感障碍；产后抑郁症；未成年人抑郁症；复发性短暂性抑郁症；难治性抑郁 / 慢性抑郁症；双重抑郁；酒精诱发的情绪障碍；混合性焦虑与抑郁症；由选自库兴氏病，甲状腺功能减退，甲状旁腺机能亢进综合症，阿狄森氏病，停经和泌乳综合症，帕金森氏病，阿尔茨海默氏病，脑内出血，糖尿病，慢性疲劳综合症和癌症中的各种身体疾病诱发的抑郁；中年抑郁症；高龄抑郁症；儿童和青春期抑郁症；干扰素诱发的抑郁症；调节障碍诱发的抑郁症；和

[0233] 焦虑症，包括调节障碍诱发的焦虑症，选自头颅外伤、脑感染和内耳损伤中的神经病诱发的焦虑症。

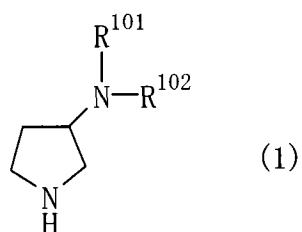
[0234] 项 11、根据项 1-6 的任一项所述的通式 (1) 的吡咯烷化合物或它们的盐作为药物的用途。

[0235] 项 12、根据项 1-6 的任一项所述的通式 (1) 的吡咯烷化合物或它们的盐作为 5-羟色胺再摄取抑制剂和 / 或去甲肾上腺素再摄取抑制剂和 / 或多巴胺再摄取抑制剂的用途。

[0236] 项 13、治疗或预防 5-羟色胺、去甲肾上腺素或多巴胺神经传递减少诱发的疾病的方法，包括将根据项 1-6 的任一项所述的通式 (1) 的吡咯烷化合物或它们的盐给药于人或动物。

[0237] 项 14、制备通式 (1) 的吡咯烷化合物或它们的盐的方法：

[0238]

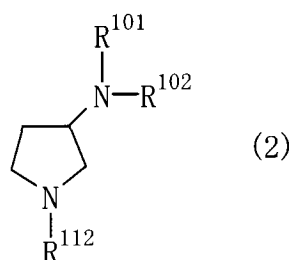


[0239] 其中 R¹⁰¹ 和 R¹⁰² 如项 1 所定义，

[0240] 该方法包括：

[0241] (1) 让通式 (2) 的化合物进行消除反应，以除去氨基保护基：

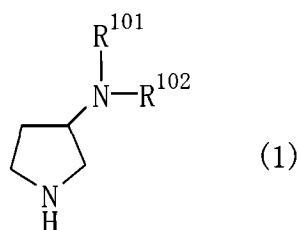
[0242]



[0243] 其中 R¹⁰¹ 和 R¹⁰² 如项 1 所定义，R¹¹² 是氨基保护基。

[0244] 优选的吡咯烷化合物 (1) 的实例包括通式 (1) 表示的化合物：

[0245]



[0246] 和它们的盐，

[0247] 其中 R¹⁰¹ 是

[0248] (1) 苯基，

[0249] (3) 苯并噻吩基，

[0250] (4) 吲哚基，

[0251] (5) 2,3-二氢-1H-茛基，

[0252] (6) 蔡基，

[0253] (7) 苯并呋喃基，

[0254] (8) 喹啉基，

[0255] (12) 苯并噻唑基，

[0256] (18) 2,4-二氢-1,3-苯并二氧杂环己烯基，

[0257] (19) 2,3-二氢苯并呋喃基，

[0258] (20) 9H-芴基，

[0259] (23) 二氢吲哚基，

[0260] (28) 异喹啉基，

[0261] (29) 2,3-二氢-1,4-苯并噁嗪基 (benzoxadiny),

[0262] (30) 喹喔啉基，

[0263] (31) 喹唑啉基，

[0264] (32) 1,2,3,4-四氢喹啉基，

[0265] (40) 1,3-苯并间二氧杂环戊烯基，

[0266] (41) 2,3-二氢-1,4-苯并二氧杂环己烯基，

[0267] (42) 3,4-二氢-1,5-苯并二氧杂环庚烯基 (benzodioxepinyl),

[0268] (44) 1,2-二氢喹啉基，

[0269] (45) 1,2,3,4-四氢异喹啉基，

[0270] (46) 苯并噁唑基，

[0271] (47) 苯并异噻唑基，

[0272] (48) 吲唑基或

[0273] (49) 苯并咪唑基，

[0274] 上述各基团可以在芳环或杂环上具有 1-5 个 (优选 1-3 个) 选自下列 (1-1) 到 (1-37) 中的取代基：

[0275] (1-1) 卤素原子，

[0276] (1-2) 任选被一个或多个 (优选 1-3 个) 卤素原子取代的低级烷硫基，

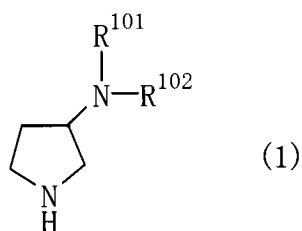
- [0277] (1-3) 任选被一个或多个 (优选 1-3 个) 卤素原子取代的低级烷基,
- [0278] (1-4) 任选被一个或多个 (优选 1-4 个) 卤素原子取代的低级烷氧基,
- [0279] (1-5) 硝基,
- [0280] (1-6) 低级烷氧基羰基,
- [0281] (1-7) 任选被一个或两个低级烷基取代的氨基,
- [0282] (1-8) 低级烷基磺酰基,
- [0283] (1-9) 氰基,
- [0284] (1-10) 羧基,
- [0285] (1-11) 羟基,
- [0286] (1-12) 噻吩基,
- [0287] (,1-13) 噁唑基,
- [0288] (1-14) 萘基,
- [0289] (1-15) 苯甲酰基,
- [0290] (1-16) 在苯环上任选被 1-3 个卤素原子取代的苯氧基,
- [0291] (1-17) 苯基低级烷氧基,
- [0292] (1-18) 低级烷酰基,
- [0293] (1-19) 在苯环上任选被 1-5 个 (优选 1-3 个) 选自卤素原子,低级烷氧基,氰基,低级烷酰基和低级烷基中的取代基取代的苯基,
- [0294] (1-20) 苯基低级烷基,
- [0295] (1-21) 氰基低级烷基,
- [0296] (1-22) 5-7 员饱和杂环基取代的磺酰基,该杂环基在杂环上含有 1 或 2 个氮原子 (优选哌啶基磺酰基),
- [0297] (1-23) 在噻唑环上任选被一个或两个低级烷基取代的噻唑基,
- [0298] (1-24) 咪唑基,
- [0299] (1-25) 在氨基上任选被一个或两个低级烷基取代的氨基低级烷基,
- [0300] (1-26) 吡咯烷基低级烷氧基,
- [0301] (1-27) 异噁唑基,
- [0302] (1-28) 环烷基羰基,
- [0303] (1-29) 萘氧基,
- [0304] (1-30) 吡啶基,
- [0305] (1-31) 呋喃基,
- [0306] (1-32) 苯硫基,
- [0307] (1-33) 氧代基,
- [0308] (1-34) 氨基甲酰基,
- [0309] (1-35) 含有一个或两个氮原子的 5 到 7 员饱和杂环基 (优选吡咯烷基,哌嗪基或哌啶基),该杂环基任选被 1-3 个选自下列之中的取代基取代:氧代基;低级烷基;低级烷酰基;苯基低级烷基;任选被 1-3 个选自卤素原子和低级烷氧基中的基团取代的苯基;和吡啶基,
- [0310] (1-36) 氧撑基团和

[0311] (1-37) 低级醇基 (alkoxido),

[0312] 前提条件是 R^{101} 和 R^{102} 不同时是未取代的苯基。

[0313] 更优选的吡咯烷化合物 (1) 的实例包括通式 (1) 表示的化合物:

[0314]



[0315] 和它们的盐,

[0316] 其中 R^{101} 是

[0317] (1) 苯基或

[0318] (3) 苯并噻吩基,

[0319] 上述各基团可以在芳环或杂环上具有一个或两个选自 (1-1) 卤素原子和 (1-3) 任选被 1-3 个卤素原子取代的低级烷基中的取代基, 和

[0320] R^{102} 是

[0321] (1) 苯基,

[0322] (2) 吡啶基,

[0323] (3) 苯并噻吩基,

[0324] (4) 吲哚基,

[0325] (5) 2,3-二氢-1H-茛基,

[0326] (6) 萘基,

[0327] (7) 苯并呋喃基,

[0328] (8) 喹啉基,

[0329] (9) 噻唑基,

[0330] (10) 嘧啶基,

[0331] (11) 吡嗪基,

[0332] (12) 苯并噻唑基,

[0333] (13) 噻吩并 [3,2-b] 吡啶基,

[0334] (14) 噻吩基,

[0335] (15) 环烷基,

[0336] (16) 四氢吡喃基,

[0337] (17) 吡咯基,

[0338] (18) 2,4-二氢-1,3-苯并二氧杂环己烯基,

[0339] (19) 2,3-二氢苯并呋喃基,

[0340] (20) 9H-芴基,

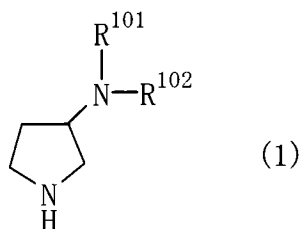
[0341] (21) 吡唑基,

[0342] (22) 哒嗪基,

[0343] (23) 二氢吲哚基,

- [0344] (24) 噻吩并 [2,3-b] 吡啶基,
- [0345] (25) 噻吩并 [3,2-d] 嘧啶基,
- [0346] (26) 噻吩并 [3,2-e] 嘧啶基,
- [0347] (27) 1H- 吡唑并 [3,4-b] 吡啶基,
- [0348] (28) 异喹啉基,
- [0349] (29) 2,3- 二氢 -1,4- 苯并噁嗪基 (benzoxadiny),
- [0350] (30) 喹喔啉基,
- [0351] (31) 喹唑啉基,
- [0352] (32) 1,2,3,4- 四氢喹啉基,
- [0353] (40) 1,3- 苯并间二氧杂环戊烯基,
- [0354] (41) 2,3- 二氢 -1,4- 苯并二氧杂环己烯基,
- [0355] (42) 3,4- 二氢 -1,5- 苯并二氧杂环庚烯基 (benzodioxepinyl),
- [0356] (43) 二氢吡啶基,
- [0357] (44) 1,2- 二氢喹啉基,
- [0358] (45) 1,2,3,4- 四氢异喹啉基,
- [0359] (46) 苯并噁唑基,
- [0360] (47) 苯并异噁唑基,
- [0361] (48) 呋唑基,
- [0362] (49) 苯并咪唑基,
- [0363] (50) 咪唑基,
- [0364] (59) 羟基取代的低级烷基或
- [0365] (60) 低级烷氧基低级烷基,
- [0366] 基团 (1) 到 (50) 各自可以在芳环或杂环上具有 1-5 个 (优选 1-3 个) 选自下列 (1-1) 到 (1-37) 中的取代基:
- [0367] (1-1) 卤素原子,
- [0368] (1-2) 任选被一个或多个 (优选 1-3 个) 卤素原子取代的低级烷硫基,
- [0369] (1-3) 任选被一个或多个 (优选 1-3 个) 卤素原子取代的低级烷基,
- [0370] (1-4) 任选被一个或多个 (优选 1-4 个) 卤素原子取代的低级烷氧基,
- [0371] (1-5) 硝基,
- [0372] (1-6) 低级烷氧基羰基,
- [0373] (1-7) 任选被一个或两个低级烷基取代的氨基,
- [0374] (1-8) 低级烷基磺酰基,
- [0375] (1-9) 氰基,
- [0376] (1-10) 羧基,
- [0377] (1-11) 羟基,
- [0378] (1-12) 噻吩基,
- [0379] (1-13) 噁唑基,
- [0380] (1-14) 萘基,
- [0381] (1-15) 苯甲酰基,

- [0382] (1-16) 在苯环上任选被 1-3 个卤素原子取代的苯氧基，
- [0383] (1-17) 苯基低级烷基氧基，
- [0384] (1-18) 低级烷基酰基，
- [0385] (1-19) 在苯环上任选被 1-5 个（优选 1-3 个）选自卤素原子，低级烷基氧基，氰基，低级烷基酰基和低级烷基中的取代基取代的苯基，
- [0386] (1-20) 苯基低级烷基，
- [0387] (1-21) 氰基低级烷基，
- [0388] (1-22) 5-7 员饱和杂环基取代的磺酰基，该杂环基在杂环上含有 1 或 2 个氮原子（优选哌啶基磺酰基），
- [0389] (1-23) 在噻唑环上任选被一个或两个低级烷基取代的噻唑基，
- [0390] (1-24) 咪唑基，
- [0391] (1-25) 在氨基上任选被一个或两个低级烷基取代的氨基低级烷基，
- [0392] (1-26) 吡咯烷基低级烷基氧基，
- [0393] (1-27) 异噁唑基，
- [0394] (1-28) 环烷基羰基，
- [0395] (1-29) 蔡氧基，
- [0396] (1-30) 吡啶基，
- [0397] (1-31) 呋喃基，
- [0398] (1-32) 苯硫基，
- [0399] (1-33) 氧代基，
- [0400] (1-34) 氨基甲酰基，
- [0401] (1-35) 含有一个或两个氮原子的 5 到 7 员饱和杂环基（优选吡咯烷基，哌嗪基或哌啶基），该杂环基任选被 1-3 个选自下列之中的取代基取代：氧代基；低级烷基；低级烷基酰基；苯基低级烷基；任选被 1-3 个选自卤素原子和低级烷基氧基中的基团取代的苯基；和吡啶基，
- [0402] (1-36) 氧撑基团和
- [0403] (1-37) 低级醇基 (alkoxido)，
- [0404] 前提条件是 R^{101} 和 R^{102} 不同时是未取代的苯基。
- [0405] 特别优选的吡咯烷化合物 (1) 的实例包括通式 (1) 表示的化合物：
- [0406]



- [0407] 和它们的盐，
- [0408] 其中 R^{101} 是
- [0409] (1) 在苯环上被一个或两个选自 (1-1) 卤素原子和 (1-3) 任选被 1-3 个卤素原子取代的低级烷基中的取代基取代的苯基，和

[0410] R^{102} 是

[0411] (1) 苯基,

[0412] (2) 吡啶基,

[0413] (9) 噻唑基,

[0414] (10) 嘧啶基,

[0415] (11) 吡嗪基,

[0416] (14) 噻吩基,

[0417] (48) 呋唑基,

[0418] (59) 羟基取代的低级烷基或

[0419] (60) 低级烷氧基低级烷基,

[0420] 基团 (1), (2), (9), (10), (11), (14) 和 (48) 各自可以在芳环或杂环上具有一个或两个选自下列之中的取代基:

[0421] (1-1) 卤素原子,

[0422] (1-3) 任选被 1-3 个卤素原子取代的低级烷基和

[0423] (1-9) 氰基。

[0424] 特别优选的本发明的吡咯烷化合物的实例如下所示:

[0425] (4-氯苯基)苯基-(S)-吡咯烷-3-基胺,

[0426] (4-氟苯基)苯基-(S)-吡咯烷-3-基胺,

[0427] (3,4-二氟苯基)苯基-(S)-吡咯烷-3-基胺,

[0428] 双-(4-氟苯基)-(S)-吡咯烷-3-基胺,

[0429] (3,4-二氟苯基)-(4-氟苯基)-(S)-吡咯烷-3-基胺,

[0430] (3-氯-4-氟苯基)-(S)-吡咯烷-3-基-对-甲苯胺,

[0431] 4-[(S)-(4-氟-3-甲基苯基)吡咯烷-3-基氨基]-苄腈,

[0432] 双-(3-氟苯基)-(S)-吡咯烷-3-基胺,

[0433] (3-氯-4-氟苯基)-(S)-吡咯烷-3-基噻唑-2-基胺,

[0434] (4-氟苯基)-(S)-吡咯烷-3-基噻唑-2-基胺,

[0435] (3,4-二氯苯基)-(S)-吡咯烷-3-基噻唑-2-基胺,

[0436] (3,4-二氯苯基)嘧啶-5-基-(S)-吡咯烷-3-基胺,

[0437] (3-氯-4-氟苯基)吡嗪-2-基-(S)-吡咯烷-3-基胺,

[0438] (3-氯-4-氟苯基)-(5-氯吡啶-2-基)-(S)-吡咯烷-3-基胺,

[0439] (3-氯-4-氟苯基)吡啶-2-基-(S)-吡咯烷-3-基胺,

[0440] (3-氯-4-氟苯基)吡啶-3-基-(S)-吡咯烷-3-基胺,

[0441] (3-氯-4-氟苯基)-(6-氟吡啶-3-基)-(S)-吡咯烷-3-基胺,

[0442] (3,4-二氯苯基)吡啶-3-基-(S)-吡咯烷-3-基胺,

[0443] (3-氯-4-氟苯基)-(S)-吡咯烷-3-基噻吩-3-基胺,

[0444] (3-氯-4-氟苯基)-(5-氟吡啶-3-基)-(S)-吡咯烷-3-基胺,

[0445] (4-氟-3-甲基苯基)-(5-氟吡啶-3-基)-(S)-吡咯烷-3-基胺,

[0446] 2-[(S)-(3-氯-4-氟苯基)吡咯烷-3-基氨基]乙醇,

[0447] 1-[(S)-(3-氯-4-氟苯基)吡咯烷-3-基氨基]-2-甲基-丙烷-2-醇,

- [0448] (3-氯-4-氟苯基)-(2-甲氧基乙基)-(S)-吡咯烷-3-基胺,
[0449] 3-[(S)-(3-氯-4-氟苯基)吡咯烷-3-基氨基]-丙烷-1-醇,
[0450] (3-氯-4-氟苯基)-(3-甲氧基丙基)-(S)-吡咯烷-3-基胺,
[0451] (3-氯-4-氟苯基)-(1-甲基-1H-吡唑-5-基)-(S)-吡咯烷-3-基胺,
[0452] 苯并[b]噻吩-6-基-(S)-吡咯烷-3-基噻吩-3-基胺,和
[0453] 苯并[b]噻吩-5-基-(S)-吡咯烷-3-基噻吩-3-基胺。
[0454] 通式(1)中的基团的具体例子如下所示。

[0455] 卤素原子的实例包括氟,氯,溴和碘。

[0456] 任选被一个或多个卤素原子取代的低级烷硫基的实例包括任选被1-3个卤素原子取代的直链或支链 C_{1-6} 烷硫基,如甲硫基,乙硫基,正丙硫基,异丙硫基,正丁基硫基,异丁基硫基,叔丁基硫基,仲丁基硫基,正戊基硫基,异戊基硫基,新戊基硫基,正己基硫基,异己基硫基,3-甲基戊基硫基,三氟甲基硫基,三氯甲基硫基,氯甲基硫基,溴甲基硫基,氟甲基硫基,碘甲基硫基,二氟甲基硫基,二溴甲基硫基,2-氯乙基硫基,2,2,2-三氟乙基硫基,2,2,2-三氯乙基硫基,3-氯丙基硫基,2,3-二氯丙基硫基,4,4,4-三氯丁基硫基,4-氟丁基硫基,5-氯戊基硫基,3-氯-2-甲基丙基硫基,5-溴己基硫基,5,6-二溴己基硫基等等。

[0457] 任选被一个或多个卤素原子取代的低级烷基的实例包括任选被1-4个卤素原子取代的直链或支链 C_{1-6} 烷基,如甲基,乙基,正丙基,异丙基,正丁基,异丁基,叔丁基,仲丁基,正戊基,异戊基,新戊基,正己基,异己基,3-甲基戊基,三氟甲基,三氯甲基,氯甲基,溴甲基,氟甲基,碘甲基,二氟甲基,二溴甲基,2-氯乙基,2,2,2-三氟乙基,2,2,2-三氯乙基,3-氯丙基,2,3-二氯丙基,4,4,4-三氯丁基,4-氟丁基,5-氯戊基,3-氯-2-甲基丙基,5-溴己基,5,6-二溴己基,1,1,2,2-四氟乙基等。

[0458] 任选被一个或多个卤素原子取代的低级烷氧基的实例包括任选被1-4个卤素原子取代的直链或支链 C_{1-6} 烷氧基,如甲氧基,乙氧基,正丙氧基,异丙氧基,正丁氧基,异丁氧基,叔丁氧基,仲丁氧基,正戊氧基,异戊氧基,新戊氧基,正己氧基,异己基氧基,3-甲基戊氧基,三氟甲氧基,三氯甲氧基,氯甲氧基,溴甲氧基,氟甲氧基,碘甲氧基,二氟甲氧基,二溴甲氧基,2-氯乙氧基,2,2,2-三氟乙氧基,2,2,2-三氯乙氧基,3-氯丙氧基,2,3-二氯丙氧基,4,4,4-三氯丁氧基,4-氟丁氧基,5-氯戊氧基,3-氯-2-甲基丙氧基,5-溴己氧基,5,6-二溴己氧基,1,1,2,2-四氟乙氧基等。

[0459] 低级烷氧基羰基的实例包括烷氧基羰基,其中该烷氧基结构部分是直链或支链 C_{1-6} 烷氧基,如甲氧基羰基,乙氧基羰基,正丙氧基羰基,异丙氧基羰基,正丁氧基羰基,异丁氧基羰基,叔丁氧基羰基,仲丁氧基羰基,正戊氧基羰基,新戊氧基羰基,正己氧基羰基,异己氧基羰基,3-甲基戊氧基羰基等。

[0460] 低级烷基的实例包括直链或支链 C_{1-6} 烷基,如甲基,乙基,正丙基,异丙基,正丁基,异丁基,叔丁基,仲丁基,正戊基,异戊基,新戊基,正己基,异己基,3-甲基戊基等。

[0461] 低级烷酰基的实例包括直链或支链 C_{1-6} 烷酰基,如甲酰基,乙酰基,丙酰基,丁酰基,异丁酰基,戊酰基,叔丁基羰基,己酰基等。

[0462] 低级烷基磺酰基的实例包括直链或支链 C_{1-6} 烷基磺酰基,如甲基磺酰基,乙基磺酰基,正丙基磺酰基,异丙基磺酰基,正丁基磺酰基,异丁基磺酰基,叔丁基磺酰基,仲丁基磺酰基,正戊基磺酰基,异戊基磺酰基,新戊基磺酰基,正己基磺酰基,异己基磺酰基,3-甲基

戊基磺酰基等等。

[0463] 在苯环上任选被 1-3 个卤素原子取代的苯氧基的实例包括苯氧基, 2- 氟苯氧基, 3- 氟苯氧基, 4- 氟苯氧基, 2- 氯苯氧基, 3- 氯苯氧基, 4- 氯苯氧基, 2- 溴苯氧基, 3- 溴苯氧基, 4- 溴苯氧基, 2- 碘苯氧基, 3- 碘苯氧基, 4- 碘苯氧基, 2, 3- 二氟苯氧基, 3, 4- 二氟苯氧基, 3, 5- 二氟苯氧基, 2, 4- 二氟苯氧基, 2, 6- 二氟苯氧基, 2, 3- 二氯苯氧基, 3, 4- 二氯苯氧基, 3, 5- 二氯苯氧基, 2, 4- 二氯苯氧基, 2, 6- 二氯苯氧基, 3, 4, 5- 三氟苯氧基, 3, 4, 5- 三氯苯氧基, 2, 4, 6- 三氟苯氧基, 2, 4, 6- 三氯苯氧基, 2- 氟-4- 溴苯氧基, 4- 氯-3- 氟苯氧基, 2, 3, 4- 三氯苯氧基等等。

[0464] 苯基低级烷氧基的实例包括其中烷氧基结构部分是直链或支链 C_{1-6} 烷氧基的苯基烷氧基, 如苄氧基, 2- 苯基乙氧基, 1- 苯基乙氧基, 3- 苯基丙氧基, 4- 苯基丁氧基, 5- 苯基戊氧基, 6- 苯基己氧基, 1, 1- 二甲基-2- 苯基乙氧基, 2- 甲基-3- 苯基丙氧基等。

[0465] 苯基低级烷基的实例包括其中烷基结构部分是直链或支链 C_{1-6} 烷基的苯基烷基, 如苄基, 1- 苯乙基, 2- 苯乙基, 3- 苯基丙基, 2- 苯基丙基, 4- 苯基丁基, 5- 苯基戊基, 4- 苯基戊基, 6- 苯基己基, 2- 甲基-3- 苯基丙基, 1, 1- 二甲基-2- 苯基乙基等。

[0466] 氰基低级烷基的实例包括其中烷基结构部分是直链或支链 C_{1-6} 烷基的氰基烷基, 如氰基甲基, 2- 氰基乙基, 1- 氰基乙基, 3- 氰基丙基, 4- 氰基丁基, 1, 1- 二甲基-2- 氰基乙基, 5- 氰基戊基, 6- 氰基己基, 1- 氰基异丙基, 2- 甲基-3- 氰基丙基等。

[0467] 任选在噻唑环上被一个或两个低级烷基取代的噻唑基的实例包括在噻唑环上任选被一个或两个直链或支链 C_{1-6} 烷基取代的噻唑基, 如 (2-, 4-, 或 5-) 噻唑基, 2- 甲基-(4-, 或 5-) 噻唑基, 4- 甲基-(2- 或 5-) 噻唑基, 2- 乙基-(4- 或 5-) 噻唑基, 4- 正丙基-(2- 或 5-) 噻唑基, 5- 正丁基-(2- 或 4-) 噻唑基, 2- 正戊基-(4- 或 5-) 噻唑基, 4- 正己基-(2- 或 5-) 噻唑基, 2, 4- 二甲基-5- 噻唑基等。

[0468] 在氨基上任选被一个或两个低级烷基取代的氨基低级烷基的实例包括其中烷基结构部分是直链或支链 C_{1-6} 烷基并且在氨基上任选被一个或两个直链或支链 C_{1-6} 烷基取代的氨基烷基; 如氨基甲基, 2- 氨基乙基, 1- 氨基乙基, 3- 氨基丙基, 4- 氨基丁基, 5- 氨基戊基, 6- 氨基己基, 1, 1- 二甲基-2- 氨基乙基, 2- 甲基-3- 氨基丙基, 甲基氨基甲基, 2- 乙基氨基乙基, 3- 丙基氨基丙基, 3- 异丙基氨基丙基, 4- 丁基氨基丁基, 5- 戊基氨基戊基, 6- 己基氨基己基, 2- 二甲基氨基乙基, 2- 二异丙基氨基丙基, 3- 二甲基氨基丙基, 二异丙基氨基甲基, 3- 二异丙基氨基丙基, (N- 乙基-N- 丙基氨基) 甲基, 2-(N- 甲基-N- 己基氨基) 甲基等。

[0469] 吡咯烷基低级烷氧基的实例包括其中烷氧基结构部分是直链或支链 C_{1-6} 烷氧基的吡咯烷基烷氧基, 如 (1-, 2-, 或 3-) 吡咯烷基甲氧基, 2-[(1-, 2-, 或 3-) 吡咯烷基] 乙氧基, 1-[(1-, 2-, 或 3-) 吡咯烷基] 乙氧基, 3-[(1-, 2-, 或 3-) 吡咯烷基] 丙氧基, 4-[(1-, 2-, 或 3-) 吡咯烷基] 丁氧基, 5-[(1-, 2-, 或 3-) 吡咯烷基] 戊氧基, 6-[(1-, 2-, 或 3-) 吡咯烷基] 己氧基, 1, 1- 二甲基-2-[(1-, 2-, 或 3-) 吡咯烷基] 乙氧基, 2- 甲基-3-[(1-, 2-, 或 3-) 吡咯烷基] 丙氧基等。

[0470] 环烷基的实例包括 C_{3-8} 环烷基, 如环丙基, 环丁基, 环戊基, 环己基, 环庚基, 环辛基等。

[0471] 环烷基羰基的实例包括其中环烷基结构部分是 C_{3-8} 环烷基的环烷基羰基, 比如环

丙基羰基,环丁基羰基,环戊基羰基,环己基羰基,环庚基羰基,环辛基羰基等。

[0472] 低级烷氧基的实例包括直链或支链 C_{1-6} 烷氧基,如甲氧基,乙氧基,正丙氧基,异丙氧基,正丁氧基,异丁氧基,叔丁氧基,仲丁氧基,正戊氧基,异戊氧基,新戊氧基,正己氧基,异己基氧基,3-甲基戊氧基等。

[0473] 低级烷硫基的实例包括直链或支链 C_{1-6} 烷硫基,如甲硫基,乙硫基,正丙硫基,异丙硫基,正丁基硫基,异丁硫基,叔丁基硫基,仲丁基硫基,正戊基硫基,异戊基硫基,新戊基硫基,正己基硫基,异己基硫基,3-甲基戊基硫基等。

[0474] 在苯环上任选被 1-3 个选自卤素原子和低级烷氧基中的基团取代的苯基的实例包括在苯环上任选被 1-3 个选自卤素原子和直链或支链 C_{1-6} 烷氧基中的基团取代的苯基,如苯基,2-甲氧基苯基,3-甲氧基苯基,4-甲氧基苯基,2-乙氧基苯基,3-乙氧基苯基,4-乙氧基苯基,4-异丙氧基苯基,3-丁氧基苯基,4-戊氧基苯基,4-己氧基苯基,3,4-二甲氧基苯基,3,4-二乙氧基苯基,2,4-二甲氧基苯基,2,5-二甲氧基苯基,2,6-二甲氧基苯基,3,4,5-三甲氧基苯基,2-甲氧基-4-氟苯基,4-氟苯基,2,5-二氟苯基,2,4-二氟苯基,3,4-二氟苯基,3,5-二氟苯基,2,6-二氟苯基,2-氯苯基,3-氯苯基,4-氯苯基,2,3-二氯苯基,2,4-二氯苯基,2,5-二氯苯基,3,4-二氯苯基,2,6-二氯苯基,3-氟苯基,2-氟苯基,3-溴苯基,4-碘苯基,2-溴苯基,4-溴苯基,3,5-二氯苯基,2,4,6-三氟苯基,2-氯苯基,3-氯苯基,4-氯苯基,2-碘苯基,3-碘苯基,2,3-二溴苯基,2,4-二碘苯基,2,4,6-三氯苯基等。

[0475] 在杂环上含有一个或两个选自氮、氧和硫中的杂原子的 5-7 员饱和杂环基的实例包括吡咯烷基,哌嗪基,哌啶基,吗啉代,硫代吗啉基,高哌嗪基,高哌啶基,咪唑烷基,噻唑烷基,异噻唑烷基,噁唑烷基,异噁唑烷基,异噻唑烷基和吡唑烷基。

[0476] 上述被 1-3 个选自氧代;低级烷基;低级链烷酰基;苯基低级烷基;在苯环上任选被 1-3 个选自卤素原子和低级烷氧基中的基团取代的苯基;和吡啶基中的基团取代的杂环基的实例包括:

[0477] 被 1-3 个选自氧代基团;直链或支链 C_{1-6} 烷基;直链或支链 C_{1-6} 烷酰基;其中烷基结构部分是直链或支链 C_{1-6} 烷基的苯基烷基;在苯环上任选被 1-3 个选自卤素原子和直链或支链 C_{1-6} 烷氧基中的基团取代的苯基;和吡啶基基团中的基团取代的上述杂环基;

[0478] 例如 2-氧代-(1-,3-,4-,或 5-)吡咯烷基,2-氧代-(1-,3-,4-,5-,或 6-)哌嗪基,4-甲基-(1-,2-,或 3-)哌嗪基,4-乙酰基-(1-,2-,或 3-)哌嗪基,4-乙基-(1-,2-,或 3-)哌嗪基,2-甲基-(1-,2-,3-,4-,或 5-)吡咯烷基,2-甲基-(1-,2-,3-,4-,5-,或 6-)哌啶基,2,4-二甲基-(1-,2-,3-,5-,或 6-)哌啶基,3-甲基-(1-,2-,3-,4-,或 5-)吡咯烷基,2,3,4-三甲基-(1-,2-,3-,5-,或 6-)哌嗪基,4-乙酰基-3-甲基-(1-,2-,3-,5-,或 6-)哌嗪基,3-甲基-(2-,3-,4-,5-,或 6-)吗啉代,2-乙酰基-(2-,3-,4-,5-,或 6-)吗啉代,4-(2-苯基乙基)-(1-,2-,或 3-)哌嗪基,4-(3,4-二氯苯基)-(1-,2-,3-,或 4-)哌嗪基,4-(4-甲氧基苯基)-(1-,2-,或 3-)哌嗪基,4-(2-氯苯基)-(1-,2-,或 3-)哌嗪基,4-[(2-,3-,或 4-)吡啶基]-(1-,2-,或 3-)哌嗪基,4-苯基-(1-,2-,或 3-)哌嗪基,4-苄基-(1-,2-,或 3-)哌啶基,4-(3,4-二氯苯基)-(1-,2-,或 3-)吗啉代,2-(4-甲氧基苯基)-(1-,2-,3-,4-,或 5-)吡咯烷基,4-(2-氯苯基)-(1-,2-,或 3-)哌啶基,4-[(2-,3-,或 4-)吡啶基]-(1-,2-,或 3-)哌啶基,4-苯基-(1-,2-,或 3-)哌啶基,4-苯基-3-甲基-(1-,2-,3-,5-,或 6-)哌嗪基,4-[(2-,3-,或 4-)吡啶基]-2-乙酰基-(1-,2-,3-,5-,或 6-)哌嗪基等。

[0479] 环烷基低级烷基的实例包括其中环烷基结构部分是 C_{3-8} 环烷基和烷基结构部分是直链或支链 C_{1-6} 烷基的环烷基烷基, 如环丙基甲基, 环己基甲基, 2- 环丙基乙基, 1- 环丁基乙基, 环戊基甲基, 3- 环戊基丙基, 4- 环己基丁基, 5- 环庚基戊基, 6- 环辛基己基, 1, 1- 二甲基 -2- 环己基乙基, 2- 甲基 -3- 环丙基丙基等。

[0480] 低级烷硫基低级烷基的实例包括其中烷硫基结构部分是直链或支链 C_{1-6} 烷硫基和烷基结构部分是直链或支链 C_{1-6} 烷基的烷硫基烷基, 如甲基硫基甲基, 2- 甲基硫基乙基, 1- 乙基硫基乙基, 2- 乙基硫基乙基, 3- 正丁基硫基丙基, 4- 正丙基硫基丁基, 1, 1- 二甲基 -2- 正戊基硫基乙基, 5- 正己基硫基戊基, 6- 甲基硫基己基, 1- 乙基硫基异丙基, 2- 甲基 -3- 甲基硫基丙基等。

[0481] 苯氧基低级烷基的实例包括其中烷基结构部分是直链或支链 C_{1-6} 烷基的苯氧基烷基, 如苯氧基甲基, 1- 苯氧基乙基, 2- 苯氧基乙基, 3- 苯氧基丙基, 2- 苯氧基丙基, 4- 苯氧基丁基, 5- 苯氧基戊基, 4- 苯氧基戊基, 6- 苯氧基己基, 2- 甲基 -3- 苯氧基丙基, 1, 1- 二甲基 -2- 苯氧基乙基等。

[0482] 吡啶基氧基低级烷基的实例包括其中烷基结构部分是直链或支链 C_{1-6} 烷基的吡啶氧基烷基, 比如 [2-, 3-, 或 4-] 吡啶基氧基] 甲基, 1-[2-, 3-, 或 4-] 吡啶基氧基] 乙基, 2-[2-, 3-, 或 4-] 吡啶基氧基] 乙基, 3-[2-, 3-, 或 4-] 吡啶基氧基] 丙基, 2-[2-, 3-, 或 4-] 吡啶基氧基] 丙基, 4-[2-, 3-, 或 4-] 吡啶基氧基] 丁基, 5-[2-, 3-, 或 4-] 吡啶基氧基] 戊基, 4-[2-, 3-, 或 4-] 吡啶基氧基] 戊基, 6-[2-, 3-, 或 4-] 吡啶基氧基] 己基, 2- 甲基 -3-[2-, 3-, 或 4-] 吡啶基氧基] 丙基, 1, 1- 二甲基 -2-[2-, 3-, 或 4-] 吡啶基氧基] 乙基等。

[0483] 低级炔基的实例包括 C_{2-6} 直链或支链炔基, 如乙炔基, (1- 或 2-) 丙炔基, 1- 甲基 -(1- 或 2-) 丙炔基, 1- 乙基 -(1- 或 2-) 丙炔基, (1-, 2- 或 3-) 丁炔基和 (1-, 2-, 3- 或 4-) 戊炔基, (1-, 2-, 3-, 4- 或 5-) 己炔基等。

[0484] 苯基低级烯基的实例包括其中烯基结构部分是直链或支链 C_{2-6} 烯基基团的含有 1-3 个双键的苯基烯基, 如苯乙烯基, 3- 苯基 -2- 丙烯基 (俗名: 肉桂基), 4- 苯基 -2- 丁烯基, 4- 苯基 -3- 丁烯基, 5- 苯基 -4- 戊烯基, 5- 苯基 -3- 戊烯基, 6- 苯基 -5- 己烯基, 6- 苯基 -4- 己烯基, 6- 苯基 -3- 己烯基, 4- 苯基 -1, 3- 丁间二烯基, 6- 苯基 -1, 3, 5- 己三烯基等。

[0485] 环烷基低级烷基的实例包括其中环烷基结构部分是以上定义的 C_{3-8} 环烷基和烷基结构部分是以上定义的直链或支链 C_{1-6} 烷基的环烷基烷基。

[0486] 低级烷硫基低级烷基的实例包括其中烷硫基结构部分是以上定义的直链或支链 C_{1-6} 烷硫基和烷基结构部分是以上定义的直链或支链 C_{1-6} 烷基的烷硫基烷基。

[0487] 在氨基上任选被一个或两个低级烷基取代的氨基取代的低级烷基的实例包括在氨基上任选被一个或两个直链或支链 C_{1-6} 烷基取代的氨基取代的烷基, 其中烷基结构部分是以上定义的直链或支链 C_{1-6} 烷基。

[0488] 苯氧基低级烷基的实例包括其中烷基结构部分是以上定义的直链或支链 C_{1-6} 烷基的苯氧基烷基。

[0489] 吡啶基氧基低级烷基的实例包括其中烷基结构部分是以上定义的直链或支链 C_{1-6} 烷基的吡啶基氧基烷基。

[0490] 1,2,3,4- 四氢萘基低级烷基的实例包括其中烷基结构部分是以上定义的直链或支链 C_{1-6} 烷基的 1,2,3,4- 四氢萘基烷基。

[0491] 咪唑并 [1,2-a] 吡啶基低级烷基的实例包括其中烷基结构部分是以上定义的直链或支链 C_{1-6} 烷基的咪唑并 [1,2-a] 吡啶基烷基。

[0492] 噻唑基低级烷基的实例包括其中烷基结构部分是以上定义的直链或支链 C_{1-6} 烷基的噻唑基烷基。

[0493] 四氢吡喃基低级烷基的实例包括其中烷基结构部分是以上定义的直链或支链 C_{1-6} 烷基的四氢吡喃基烷基。

[0494] 哌啶基低级烷基的实例包括其中烷基结构部分是以上定义的直链或支链 C_{1-6} 烷基的哌啶基烷基。

[0495] 二苯基低级烷氧基取代的低级烷基的实例包括其中烷氧基结构部分是以上定义的直链或支链 C_{1-6} 烷氧基和烷基结构部分是以上定义的直链或支链 C_{1-6} 烷基的二苯基烷氧基取代的烷基。

[0496] 低级烷氧基羰基取代的低级烷基的实例包括其中烷氧基结构部分是以上定义的直链或支链 C_{1-6} 烷氧基和烷基结构部分是以上定义的直链或支链 C_{1-6} 烷基的烷氧基羰基取代的烷基。

[0497] 苯基低级烷氧基羰基取代的低级烷基的实例包括其中烷氧基结构部分是以上定义的直链或支链 C_{1-6} 烷氧基和烷基结构部分是以上定义的直链或支链 C_{1-6} 烷基的苯基烷氧基羰基取代的烷基。

[0498] 羟基取代的低级烷基的实例包括具有 1 到 3 个羟基的、其中烷基结构部分是以上定义的直链或支链 C_{1-6} 烷基的羟基取代的烷基,如羟甲基,1- 羟乙基,2- 羟乙基,2,3- 二羟基丙基,3- 羟丙基,2- 羟丙基,4- 羟基丁基,3,4- 二羟基丁基,5- 羟基戊基,4- 羟基戊基,6- 羟基己基,2,2- 二甲基 -3- 羟丙基,1,1- 二甲基 -2- 羟乙基,2,3,4- 三羟基丁基等。

[0499] 低级烷氧基低级烷基的实例包括其中烷氧基结构部分是以上定义的直链或支链 C_{1-6} 烷氧基和烷基结构部分是以上定义的直链或支链 C_{1-6} 烷基的烷氧基烷基,如甲氧基甲基,1- 甲氧基乙基,2- 甲氧基乙基,2- 乙氧基丙基,3- 甲氧基丙基,3- 乙氧基丙基,3- 丙氧基丙基,4- 甲氧基丁基,3- 甲氧基丁基,5- 甲氧基戊基,4- 乙氧基戊基,6- 甲氧基己基,2,2- 二甲基 -3- 甲氧基丙基,1,1- 二甲基 -2- 甲氧基乙基等。

[0500] 羧基低级烷基的实例包括其中烷基结构部分是以上定义的直链或支链 C_{1-6} 烷基的羧基烷基。

[0501] 在氨基甲酰基上任选被一个或两个低级烷基取代的氨基甲酰基取代的低级烷基的实例包括在氨基甲酰基上任选被一个或两个直链或支链 C_{1-6} 烷基取代的氨基甲酰基取代的烷基,其中烷基结构部分是以上定义的直链或支链 C_{1-6} 烷基。

[0502] 吗啉基羰基低级烷基的实例包括其中烷基结构部分是以上定义的直链或支链 C_{1-6} 烷基的吗啉基羰基烷基。

[0503] 苯甲酰基低级烷基的实例包括其中烷基结构部分是以上定义的直链或支链 C_{1-6} 烷基的苯甲酰基烷基。

[0504] 苯硫基低级烷基的实例包括其中烷基结构部分是以上定义的直链或支链 C_{1-6} 烷基的苯硫基烷基。

[0505] 萘硫基低级烷基的实例包括其中烷基结构部分是以上定义直链或支链 C_{1-6} 烷基的萘硫基烷基。

[0506] 环烷硫基低级烷基的实例包括其中烷基结构部分是以上定义直链或支链 C_{1-6} 烷基的环烷硫基烷基。

[0507] 吡啶基硫基低级烷基的实例包括其中烷基结构部分是以上定义直链或支链 C_{1-6} 烷基的吡啶基硫基烷基。

[0508] 嘧啶基硫基低级烷基的实例包括其中烷基结构部分是以上定义直链或支链 C_{1-6} 烷基的嘧啶基硫基烷基。

[0509] 呋喃硫基低级烷基的实例包括其中烷基结构部分是以上定义直链或支链 C_{1-6} 烷基的呋喃硫基烷基。

[0510] 噻吩硫基低级烷基的实例包括其中烷基结构部分是以上定义直链或支链 C_{1-6} 烷基的噻吩硫基烷基。

[0511] 1,3,4-噻二唑硫基低级烷基的实例包括其中烷基结构部分是以上定义直链或支链 C_{1-6} 烷基的 1,3,4-噻二唑硫基烷基。

[0512] 苯并咪唑硫基低级烷基的实例包括其中烷基结构部分是以上定义直链或支链 C_{1-6} 烷基的苯并咪唑硫基烷基。

[0513] 苯并噻唑硫基低级烷基的实例包括其中烷基结构部分是以上定义直链或支链 C_{1-6} 烷基的苯并噻唑硫基烷基。

[0514] 四唑硫基低级烷基的实例包括其中烷基结构部分是以上定义直链或支链 C_{1-6} 烷基的四唑硫基烷基。

[0515] 苯并噁唑硫基低级烷基的实例包括其中烷基结构部分是以上定义直链或支链 C_{1-6} 烷基的苯并噁唑硫基烷基。

[0516] 噻唑硫基低级烷基的实例包括其中烷基结构部分是以上定义直链或支链 C_{1-6} 烷基的噻唑硫基烷基。

[0517] 咪唑硫基低级烷基的实例包括其中烷基结构部分是以上定义直链或支链 C_{1-6} 烷基的咪唑硫基烷基。

[0518] 任选在氨基上被一个或两个低级烷基取代的氨基取代的低级烷硫基低级烷基的实例包括在氨基上任选被一个或两个直链或支链 C_{1-6} 烷基取代的氨基取代的烷硫基烷基，其中烷硫基结构部分是以上定义直链或支链 C_{1-6} 烷硫基和烷基结构部分是以上定义直链或支链 C_{1-6} 烷基。

[0519] 苯基取代的低级烷硫基低级烷基的实例包括其中烷硫基结构部分是以上定义直链或支链 C_{1-6} 烷硫基和烷基结构部分是以上定义直链或支链 C_{1-6} 烷基的苯基取代的烷硫基烷基。

[0520] 呋喃基取代的低级烷硫基低级烷基的实例包括其中烷硫基结构部分是以上定义直链或支链 C_{1-6} 烷硫基和烷基结构部分是以上定义直链或支链 C_{1-6} 烷基的呋喃基取代的烷硫基烷基。

[0521] 吡啶基取代的低级烷硫基低级烷基的实例包括其中烷硫基结构部分是以上定义直链或支链 C_{1-6} 烷硫基和烷基结构部分是以上定义直链或支链 C_{1-6} 烷基的吡啶基取代的烷硫基烷基。

[0522] 羟基取代的低级烷硫基低级烷基的实例包括其中烷硫基结构部分是以上定义的直链或支链 C_{1-6} 烷硫基和烷基结构部分是以上定义的直链或支链 C_{1-6} 烷基的羟基取代的烷硫基烷基。

[0523] 苯氧基取代的低级烷硫基低级烷基的实例包括其中烷硫基结构部分是以上定义的直链或支链 C_{1-6} 烷硫基和烷基结构部分是以上定义的直链或支链 C_{1-6} 烷基的苯氧基取代的烷硫基烷基。

[0524] 低级烷氧基羰基取代的低级烷硫基低级烷基的实例包括其中烷氧基结构部分是以上定义的直链或支链 C_{1-6} 烷氧基, 烷硫基结构部分是以上定义的直链或支链 C_{1-6} 烷硫基和烷基结构部分是以上定义的直链或支链 C_{1-6} 烷基的烷氧基羰基取代的烷硫基烷基。

[0525] 低级烯基的实例包括直链或支链 C_{2-6} 烯基, 如乙烯基, 1- 丙烯基, 烯丙基, 1- 甲代烯丙基, (1-, 2- 或 3-) 丁烯基, (1-, 2-, 3- 或 4-) 戊烯基和 (1-, 2-, 3-, 4- 或 5-) 己烯基。

[0526] 二氢吡啶基的实例包括 1, 2- 二氢吡啶基, 3, 4- 二氢吡啶基等。

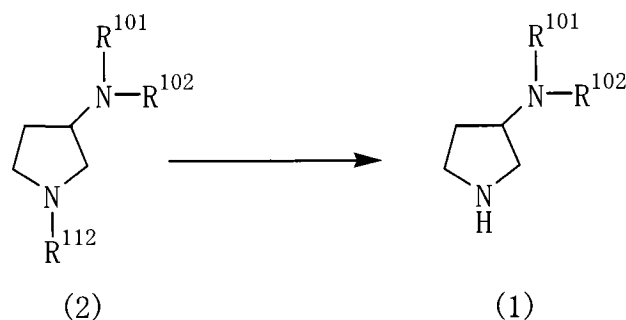
[0527] 5-7 员饱和杂环基 (该杂环基团含有一个或两个选自氮、氧和硫中的杂原子) 取代的磺酰基的实例包括吡咯烷基磺酰基, 哌嗪基磺酰基, 哌啶基磺酰基, 吗啉代磺酰基, 硫代吗啉基磺酰基, 高哌嗪基磺酰基, 高哌啶基磺酰基, 咪唑烷基磺酰基, 噻唑烷基磺酰基, 异噻唑烷基磺酰基, 噁唑烷基磺酰基, 异噁唑烷基磺酰基, 异噻唑烷基磺酰基, 吡唑烷基磺酰基等。

[0528] 低级醇基 (alkoxido) 的实例包括直链或支链 C_{1-6} 醇基, 如甲醇基 (methoxido), 乙醇基 (ethoxido) 等。

[0529] 通式 (1) 表示的吡咯烷化合物可以通过多种方法制备, 例如通过按照以下反应路线 1 的方法。

[0530] [反应路线 1]

[0531]



[0532] 其中 R^{101} 和 R^{102} 如以上所定义, R^{112} 是氨基保护基。

[0533] 吡咯烷化合物 (1) 可以通过让化合物 (2) 进行消除反应以除去氨基保护基来制备。

[0534] 可在这里使用的氨基保护基包括低级烷氧基羰基, 低级烷酰基, 芳氧基羰基, 芳基取代的低级烷基等。

[0535] 低级烷氧基羰基的实例包括直链或支链 C_{1-6} 烷氧基羰基, 如甲氧基羰基, 乙氧基羰基, 丙氧基羰基, 丁氧基羰基, 叔丁氧基羰基, 戊氧基羰基, 己氧基羰基等。

[0536] 低级烷酰基的实例包括直链或支链 C_{1-6} 烷酰基, 如甲酰基, 乙酰基, 丙酰基, 丁酰基, 异丁酰基, 戊酰基, 叔丁基羰基, 己酰基等。

[0537] 芳氧基羰基的实例包括任选被 1-3 个取代基取代的苯氧基羰基；任选被 1-3 个取代基取代的萘氧基羰基等。芳基的取代基的实例包括甲基，乙基，丙基，正丁基，仲丁基，叔丁基，正戊基，正己基，羟甲基，2-羟乙基，1-羟乙基，3-羟丙基，2,3-二羟基丙基，4-羟基丁基，1,1-二甲基-2-羟乙基，5,5,4-三羟基戊基，5-羟基戊基，6-羟基己基，1-羟基异丙基，2-甲基-3-羟丙基，三氟甲基，三氯甲基，氯甲基，溴甲基，氟甲基，碘甲基，二氟甲基，二溴甲基，2-氯乙基，2,2,2-三氟乙基，2,2,2-三氯乙基，3-氯丙基，2,3-二氯丙基，4,4,4-三氯丁基，4-氟丁基，5-氯戊基，3-氯-2-甲基丙基，5-溴己基，5,6-二氯己基，3-羟基-2-氯丙基，或任选被 1-3 个选自卤素原子和羟基中的基团取代的类似直链或支链 C_{1-6} 烷基；甲氧基，乙氧基，丙氧基，正丁氧基，仲丁氧基，叔丁氧基，正戊氧基，正己氧基，羟基甲氧基，2-羟基乙氧基，1-羟基乙氧基，3-羟基丙氧基，2,3-二羟基丙氧基，4-羟基丁氧基，1,1-二甲基-2-羟基乙氧基，5,5,4-三羟基戊氧基，5-羟基戊氧基，6-羟基己氧基，1-羟基异丙氧基，2-甲基-3-羟基丙氧基，三氟甲氧基，三氯甲氧基，氯甲氧基，溴甲氧基，氟甲氧基，碘甲氧基，二氟甲氧基，二溴甲氧基，2-氯乙氧基，2,2,2-三氟乙氧基，2,2,2-三氯乙氧基，3-氯丙氧基，2,3-二氯丙氧基，4,4,4-三氯丁氧基，4-氟丁氧基，5-氯戊氧基，3-氯-2-甲基丙氧基，5-溴己氧基，5,6-二氯己氧基，3-羟基-2-氯丙氧基，或任选被 1-3 个选自卤素原子和羟基中的基团取代的类似直链或支链 C_{1-6} 烷氧基；卤素原子，如氟，溴，氯和碘等。当存在两个或多个取代基时，该取代基可以是相同的或不同的。

[0538] 芳基取代的低级烷基的实例包括苄基，2-苯基乙基，1-苯基乙基，3-苯基丙基，4-苯基丁基，5-苯基戊基，6-苯基己基，1,1-二甲基-2-苯基乙基，2-甲基-3-苯基丙基， α -萘基甲基， β -萘基甲基，2-(α -萘基)乙基，1-(β -萘基)乙基，3-(α -萘基)丙基，4-(β -萘基)丁基，5-(α -萘基)戊基，6-(β -萘基)己基，1,1-二甲基-2-(α -萘基)乙基，2-甲基-3-(β -萘基)丙基，任选被 1-3 个取代基取代的类似苯基取代的直链或支链 C_{1-6} 烷基；或任选被 1-3 个取代基取代的类似萘基取代的直链或支链 C_{1-6} 烷基。芳基的取代基的实例包括甲基，乙基，丙基，正丁基，仲丁基，叔丁基，正戊基，正己基，羟甲基，2-羟乙基，1-羟乙基，3-羟丙基，2,3-二羟基丙基，4-羟基丁基，1,1-二甲基-2-羟乙基，5,5,4-三羟基戊基，5-羟基戊基，6-羟基己基，1-羟基异丙基，2-甲基-3-羟丙基，三氟甲基，三氯甲基，氯甲基，溴甲基，氟甲基，碘甲基，二氟甲基，二溴甲基，2-氯乙基，2,2,2-三氟乙基，2,2,2-三氯乙基，3-氯丙基，2,3-二氯丙基，4,4,4-三氯丁基，4-氟丁基，5-氯戊基，3-氯-2-甲基丙基，5-溴己基，5,6-二氯己基，3-羟基-2-氯丙基，或者任选被 1-3 个选自卤素原子和羟基中的基团取代的类似直链或支链 C_{1-6} 烷基；甲氧基，乙氧基，丙氧基，正丁氧基，仲丁氧基，叔丁氧基，正戊氧基，正己氧基，羟基甲氧基，2-羟基乙氧基，1-羟基乙氧基，3-羟基丙氧基，2,3-二羟基丙氧基，4-羟基丁氧基，1,1-二甲基-2-羟基乙氧基，5,5,4-三羟基戊氧基，5-羟基戊氧基，6-羟基己氧基，1-羟基异丙氧基，2-甲基-3-羟基丙氧基，三氟甲氧基，三氯甲氧基，氯甲氧基，溴甲氧基，氟甲氧基，碘甲氧基，二氟甲氧基，二溴甲氧基，2-氯乙氧基，2,2,2-三氟乙氧基，2,2,2-三氯乙氧基，3-氯丙氧基，2,3-二氯丙氧基，4,4,4-三氯丁氧基，4-氟丁氧基，5-氯戊氧基，3-氯-2-甲基丙氧基，5-溴己氧基，5,6-二氯己氧基，3-羟基-2-氯丙氧基，或者任选被 1-3 个选自卤素原子和羟基中的基团取代的直链或支链 C_{1-6} 烷氧基；卤素原子如氟，溴，氯和碘等。当存在两个或多个取代基时，该取代基可以是相同的或不同的。

[0539] 由化合物 (2) 制备化合物 (1) 的反应在适合的溶剂中或没有溶剂的情况下在酸或碱性化合物的存在下进行。该反应在下文称之为“反应 A”。

[0540] 有用的溶剂的实例包括水；低级醇，如甲醇，乙醇，异丙醇和叔丁醇；酮，如丙酮和甲基乙基酮；醚，如二乙醚，二噁烷，四氢呋喃，单甘醇二甲醚和二甘醇二甲醚；脂族酸，如乙酸和甲酸；酯，如乙酸甲酯和乙酸乙酯；卤代烃，如氯仿，二氯甲烷，二氯乙烷和四氯化碳；酰胺，例如 N, N- 二甲基甲酰胺，N, N- 二甲基乙酰胺和 N- 甲基吡咯烷酮；二甲亚砜；六甲基磷酸三酰胺；以及这些溶剂的混合物。

[0541] 有用的酸的实例包括无机酸比如盐酸，硫酸和氢溴酸；和有机酸比如甲酸，乙酸，三氟乙酸和对甲苯磺酸。

[0542] 有用的碱性化合物的实例包括碳酸盐比如碳酸钠，碳酸钾，碳酸氢钠和碳酸氢钾；和金属氢氧化物比如氢氧化钠，氢氧化钾，氢氧化钙和氢氧化锂。

[0543] 酸或碱性化合物通常以至少约 1 摩尔，优选约 1 到约 10 摩尔 / 每摩尔的化合物 (2) 的量使用。然而，酸还可以相对于化合物 (2) 的很大过量使用。

[0544] 该反应有利地通常在大约 0 到约 200°C，优选在大约 0 到约 150°C 的温度下进行，通常在约 10 分钟到约 30 小时内结束。

[0545] 当化合物 (2) 的 R¹¹² 是芳基取代的低级烷基时，还可以通过这种化合物 (2) 的还原来制备化合物 (1)。

[0546] 还原反应例如可以通过在适合的溶剂中在催化剂的存在下的催化氢化来进行。

[0547] 有用的溶剂的实例包括水；乙酸；醇，比如甲醇，乙醇和异丙醇；烃，比如正己烷和环己烷；醚，比如二噁烷，四氢呋喃，二乙醚和乙二醇二甲醚；酯，比如乙酸乙酯和乙酸甲酯；非质子性极性溶剂，比如二甲基甲酰胺；和这些溶剂的混合物。

[0548] 有用的催化剂的实例包括钯，钯黑，钯碳，铂，氧化铂，亚铬酸铜，拉内镍和它们的混合物。催化剂优选以约 0.02 到约 1 倍的化合物 (2) 重量的量使用。

[0549] 还原反应的反应温度通常约 -20 到约 100°C，优选约 0 到约 80°C，氢气压力通常是 1 到 10 个大气压。反应通常在约 0.5 到约 20 小时内结束。

[0550] 当化合物 (2) 的 R¹¹² 是芳基取代的低级烷基时，化合物 (2) 可以通过步骤 (i) 在适合的溶剂中用脱烷基化剂处理化合物 (2)；和 (ii) 在适合的溶剂中加热所得化合物来起反应，形成化合物 (1)。

[0551] 用于步骤 (i) 的反应的溶剂可以与用于反应 (A) 的任何溶剂相同。

[0552] 有用的脱烷基化剂的实例包括甲酸酯比如氯甲酸 1- 氯乙基酯，氯甲酸乙酯和氯甲酸叔丁基酯。脱烷基化剂通常以至少约 1 摩尔，优选约 1 摩尔到约 10 摩尔 / 每摩尔的化合物 (2) 的量使用。

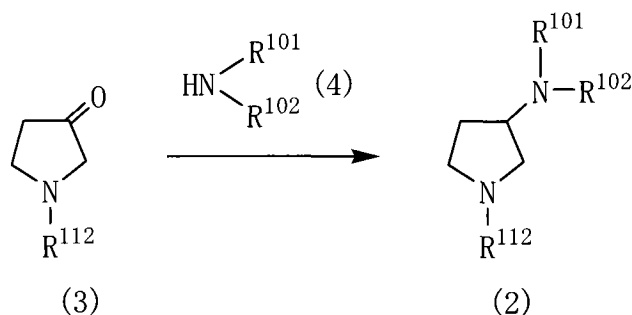
[0553] 该反应有利地通常在约 0 到约 150°C，优选在室温到约 100°C 的温度下进行，通常在约 1 到约 25 小时内完成。

[0554] 用于步骤 (ii) 的溶剂的实例包括醇比如甲醇，乙醇和异丙醇。通常在约 0 到约 150°C，优选室温到约 100°C 下加热约 1 到约 10 小时。

[0555] 用作起始原料的通式 (2) 的化合物可以容易地制备，例如通过反应路线 2 所示的方法：

[0556] [反应路线 2]

[0557]

[0558] 其中 R¹⁰¹、R¹⁰² 和 R¹¹² 如以上所定义。

[0559] 化合物 (3) 与化合物 (4) 的反应例如在没有溶剂的情况下或在适合的溶剂中在还原剂的存在下进行。

[0560] 对于该反应, 化合物 (4) 通常以至少约 1 摩尔 / 每摩尔的化合物 (3), 优选以相对于化合物 (3) 的很大过量使用。

[0561] 有用的溶剂的实例包括水; 低级醇比如甲醇, 乙醇, 异丙醇, 丁醇, 叔丁醇和乙二醇; 乙腈; 脂族酸比如甲酸和乙酸; 醚比如二乙醚, 四氢呋喃, 二噁烷, 单甘醇二甲醚和二甘醇二甲醚; 芳族烃比如苯, 甲苯和二甲苯; 卤代烃比如二氯甲烷, 二氯乙烷和四氯化碳; 和这些溶剂的混合物。

[0562] 还原剂的实例包括脂族酸比如甲酸; 脂族酸碱金属盐比如甲酸钠; 氢化物还原剂比如硼氢化钠, 氰基硼氢化钠, 三乙酰氧基硼氢化钠, 氢化锂铝或这些氢化物还原剂的混合物; 催化氢化还原剂比如钯黑, 钯碳, 氧化铂, 铂黑和拉内镍。

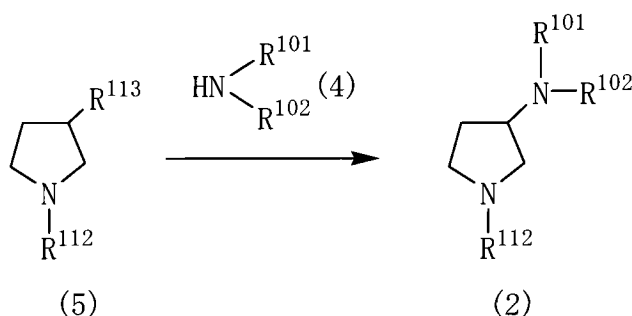
[0563] 当脂族酸或脂族酸碱金属盐用作还原剂时, 适合的温度通常是室温到约 200℃, 优选约 50 到约 150℃。反应通常在约 10 分钟到约 10 小时内完成。脂族酸或脂族酸碱金属盐优选以相对于化合物 (3) 的很大过量使用。

[0564] 当氢化物还原剂用作还原剂时, 适合的反应温度通常是约 -80 到约 100℃, 优选约 -80 到约 70℃。反应通常在约 30 分钟到约 60 小时内结束。氢化物还原剂通常以约 1 到约 20 摩尔 / 每摩尔的化合物 (3), 优选约 1 到约 6 摩尔 / 每摩尔的化合物 (3) 的量使用。尤其当氢化锂铝用作氢化物还原剂时, 优选使用醚类, 比如二乙醚, 四氢呋喃, 二噁烷, 单甘醇二甲醚和二甘醇二甲醚以及芳族烃, 比如苯, 甲苯和二甲苯, 或这些溶剂的混合物作为溶剂。在反应体系中可以添加胺, 如三甲胺, 三乙胺和 N-乙基二异丙基胺, 或添加分子筛, 如 3A 类分子筛 (MS-3A) 和 4A 类分子筛 (MS-4A)。

[0565] 当使用催化氢化还原剂作为还原剂时, 反应通常在大约 -30 到约 100℃, 优选约 0 到约 60℃ 下, 在约大气压到约 20 个大气压, 并且优选约大气压到约 10 个大气压的氢气氛围中, 或在氢给体如甲酸、甲酸铵、环己烯和水合肼的存在下进行。反应通常在约 1 到约 12 小时内结束。催化氢化还原剂通常以化合物 (3) 的约 0.1 到约 40wt%, 优选约 1 到约 20wt% 的量使用。

[0566] [反应路线 3]

[0567]



[0568] 其中 R^{101} 、 R^{102} 和 R^{112} 如以上所定义； R^{113} 表示低级烷基磺酰氧基，在苯环上任选被一个或多个低级烷基取代的苯基磺酰氧基，或卤素原子。

[0569] 低级烷基磺酰基氧基由 C_{1-6} 烷基和磺酰氧基组成，实例包括甲烷磺酰氧基，乙烷磺酰氧基，丙烷磺酰氧基，丁烷磺酰氧基，戊烷磺酰氧基和己烷磺酰氧基。

[0570] 在苯环上任选被一个或多个低级烷基取代的苯基磺酰氧基是可以被 1-3 个直链或支链 C_{1-6} 烷基取代的苯磺酰氧基，如苯磺酰氧基，邻甲苯磺酰氧基，间甲苯磺酰基氧基，对甲苯磺酰基氧基，2-乙基苯磺酰氧基，3-乙基苯磺酰氧基，4-乙基苯磺酰氧基，2-丙基苯磺酰氧基，3-丙基苯磺酰氧基，4-丙基苯磺酰氧基，2,3-二甲基苯磺酰氧基，2,4-二甲基苯磺酰氧基和 2,4,6-三甲基苯磺酰氧基。

[0571] 卤素原子的实例包括氟，氯，溴和碘。

[0572] 化合物 (4) 与化合物 (5) 的反应在适合的溶剂中在碱性化合物的存在下进行。

[0573] 有用的惰性溶剂的实例包括水；芳族烃比如苯，甲苯和二甲苯；醚比如二乙醚，四氢呋喃，二噁烷，2-甲氧基乙醇，单甘醇二甲醚和二甘醇二甲醚；卤代烃比如二氯甲烷，二氯乙烷，氯仿和四氯化碳；低级醇比如甲醇，乙醇，异丙醇，丁醇，叔丁醇和乙二醇；脂族酸比如乙酸；酯比如乙酸乙酯和乙酸甲酯；酮比如丙酮和甲基乙基酮；乙腈，吡啶，N-甲基吡咯烷酮，二甲亚砜，N,N-二甲基甲酰胺和六甲基磷酰胺；和这些溶剂的混合物。

[0574] 碱性化合物的实例包括碳酸盐比如碳酸钠，碳酸钾，碳酸氢钠，碳酸氢钾和碳酸铯；碱金属氢氧化物比如氢氧化钠，氢氧化钾和氢氧化钙；磷酸盐比如磷酸钾和磷酸钠；碱金属氢化物比如氢化钠和氢化钾；碱金属比如钾和钠；氨基钠；金属醇化物比如甲醇钠，乙醇钠和正丁醇钠，叔丁醇钠和叔丁醇钾；有机碱比如吡啶，咪唑，N-乙基二异丙基胺，二甲基氨基吡啶，三乙胺，三甲胺，二甲苯胺，N-甲基吗啉，1,5-二氮杂双环 [4.3.0] 壬烯-5 (DBN)，1,8-二氮杂双环 [5.4.0] 十一碳烯-7 (DBU) 和 1,4-二氮杂双环 [2.2.2] 辛烷 (DABCO)；和这些碱性化合物的混合物。

[0575] 化合物 (5) 通常以至少约 0.1 摩尔 / 每摩尔的化合物 (4)，优选约 0.1 到约 10 摩尔 / 每摩尔的化合物 (4) 的量使用。

[0576] 碱性化合物通常以至少约 1 摩尔 / 每摩尔的化合物 (4)，优选约 1 摩尔到约 10 摩尔 / 每摩尔的化合物 (4) 的量使用。

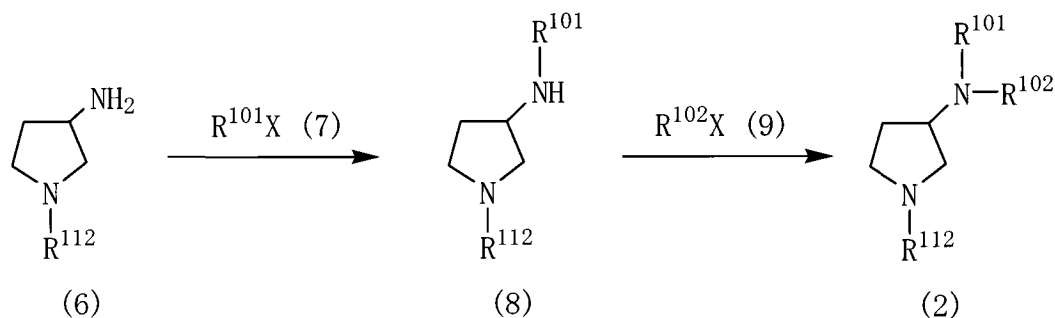
[0577] 对于该反应，化合物 (4) 可以很大过量使用，而不添加碱性化合物。

[0578] 可以将碱金属卤化物，比如碘化钠和碘化钾加入到反应系统中。

[0579] 反应通常在大约 0 到约 200℃，优选在大约 0 到约 150℃ 的温度下进行，通常在约 5 分钟到约 80 小时内完成。

[0580] 反应路线 4

[0581]



[0582] 其中 R^{101} 、 R^{102} 和 R^{112} 如以上所定义, X 表示卤素原子。

[0583] 化合物 (6) 和 (7) 之间的反应以及化合物 (8) 和 (9) 之间的反应在与反应路线 3 所示的化合物 (5) 和 (4) 之间的反应相同的条件下进行。

[0584] 当化合物 (6) 的 R^{101} 或 R^{102} 表示 (1)-(14)、(17)-(32) 和 (40)-(50) 所示的任何基团时, 化合物 (6) 和化合物 (7) 之间的反应在适合的溶剂中在碱性化合物和催化剂的存在下进行。类似地, 当化合物 (8) 的 R^{101} 或 R^{102} 表示 (1)-(14)、(17)-(32) 和 (40)-(50) 所示的任何基团时, 化合物 (8) 和化合物 (9) 之间的反应在适合的溶剂中在碱性化合物和催化剂的存在下进行。

[0585] 用于该反应的溶剂和碱性化合物各自可以与用于反应路线 3 所示的化合物 (5) 和 (4) 之间的反应的那些相同。

[0586] 催化剂的实例包括钯化合物比如乙酸钯, 双(三丁基锡)/双(二苄叉基丙酮)钯, 碘化亚铜/2,2'-联吡啶, 双(二苄叉基丙酮)钯, 三(二苄叉基丙酮)二钯, [1,1'-双(二苯基膦基)二茂铁]二氯钯(II)和四(三苯膦)钯; 联萘化合物例如 R-2,2'-双(二苯基膦基)-1,1'-联萘(R-BINAP), S-2,2'-双(二苯基膦基)-1,1'-联萘(S-BINAP)以及 RAC-2,2'-双(二苯基膦基)-1,1'-联萘(RAC-BINAP); 氧杂蒽化合物例如 4,5-双(二苯基膦基)-9,9-二甲基氧杂蒽; 硼酸盐例如四氟硼酸三-叔丁基膦; 2,2-双(二苯基咪唑烷叉基(imidazolidinylidene)); 和它们的混合物。

[0587] 碱性化合物通常以至少约 0.5 摩尔/每摩尔的化合物 (6) 或 (8), 优选约 0.5 到约 40 摩尔/每摩尔的化合物 (6) 或 (8) 的量使用。

[0588] 催化剂可以化合物 (6) 或 (8) 的通常催化量使用。

[0589] 化合物 (7) 和 (9) 通常分别地以至少约 0.5 摩尔/每摩尔的化合物 (6) 和 (8), 优选约 0.5 到约 3 摩尔/每摩尔的化合物 (6) 和 (8) 的量使用。

[0590] 这些反应有利地通常在室温到约 200°C, 优选在室温到约 150°C 的温度下进行, 通常在约 0.5 到约 20 小时内完成。

[0591] 当化合物 (6) 的 R^{101} 或 R^{102} 表示 (1)-(14)、(17)-(32) 和 (40)-(50) 所示的任何基团时, 化合物 (6) 和化合物 (7) 之间的反应在适合的溶剂中在碱性化合物、碘化亚铜和乙二醇的存在下进行。类似地, 当化合物 (8) 的 R^{101} 或 R^{102} 表示 (1)-(14)、(17)-(32) 和 (40)-(50) 所示的任何基团时, 化合物 (8) 和化合物 (9) 之间的反应在适合的溶剂中在碱性化合物、碘化亚铜和乙二醇的存在下进行。

[0592] 用于该反应的溶剂和碱性化合物各自可以与用于反应路线 3 所示的化合物 (5) 和 (4) 之间的反应的那些相同。

[0593] 碘化亚铜和乙二醇通常各自可以约 0.01 到 3 摩尔, 优选约 0.05 到约 1 摩尔 / 每摩尔的化合物 (6) 或 (7) 的量使用。

[0594] 化合物 (7) 和 (9) 通常分别地以至少约 1 摩尔 / 每摩尔的化合物 (6) 和 (8), 优选约 1 到约 2 摩尔 / 每摩尔的化合物 (6) 和 (8) 的量使用。

[0595] 这些反应有利地通常在室温到约 200°C, 优选在室温到约 150°C 的温度下进行, 通常在约 0.5 到约 50 小时内完成。

[0596] 当化合物 (6) 的 R^{101} 或 R^{102} 表示 (1)-(14)、(17)-(32) 和 (40)-(50) 所示的任何基团时, 化合物 (6) 和化合物 (7) 之间的反应在适合的溶剂中在硅烷化合物如双(三甲基甲硅烷基)氨基钠的存在下进行。类似地, 当化合物 (8) 的 R^{101} 或 R^{102} 表示 (1)-(14)、(17)-(32) 和 (40)-(50) 所示的任何基团时, 化合物 (8) 和化合物 (9) 之间的反应在适合的溶剂中在硅烷化合物例如双(三甲基甲硅烷基)氨基钠的存在下进行。

[0597] 用于该反应的溶剂可以与用于反应路线 3 所示的化合物 (5) 和 (4) 之间的反应的溶剂相同。

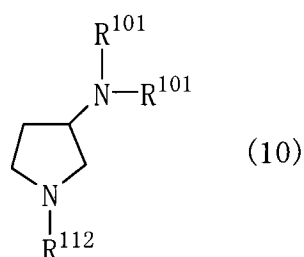
[0598] 硅烷化合物通常以约 0.1 到约 3 摩尔, 优选约 0.1 到约 2 摩尔 / 每摩尔的化合物 (6) 或 (7) 的量使用。

[0599] 化合物 (7) 和 (9) 通常分别地以至少约 1 摩尔 / 每摩尔的化合物 (6) 和 (8), 优选约 1 到约 2 摩尔 / 每摩尔的化合物 (6) 和 (8) 的量使用。

[0600] 这些反应有利地通常在大约 0 到约 200°C, 优选在大约 0 到约 150°C 的温度下进行, 通常在约 0.5 到约 20 小时内结束。

[0601] 取决于所使用的化合物 (7) 的类型, 化合物 (6) 和化合物 (7) 的反应产生了以下所示的化合物 (10), 而不是化合物 (8) :

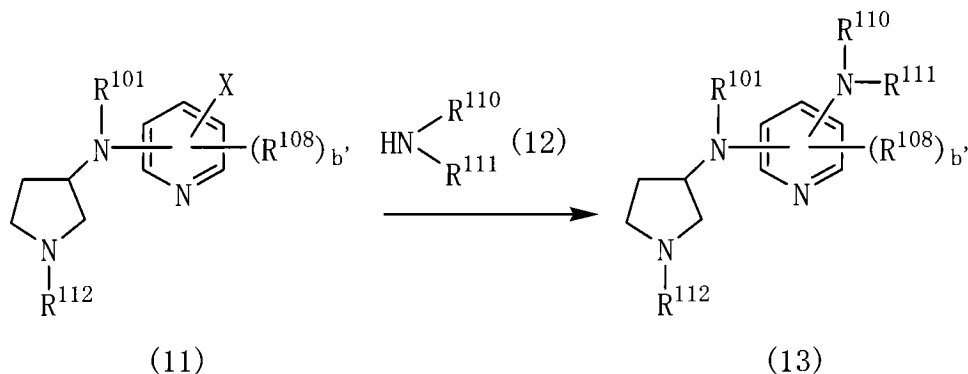
[0602]



[0603] 其中 R^{101} 和 R^{112} 如以上所定义。

[0604] [反应路线 5]

[0605]



[0606] 其中 R^{101} 和 X 如以上所定义, R^{108} 表示如通式 (1) 中所定义的 (1-1)-(1-37) 所示

的任何基团, R^{110} 和 R^{111} 与它们所键接的氮原子连在一起, 形成含有一个氮原子的 5-7 员饱和杂环基, 所述杂环基可以具有 1 个选自氮、氧和硫中的杂原子, 该杂环基任选被 1-3 个选自下列之中的取代基取代: 氧代基; 低级烷基; 低级烷酰基; 苯基低级烷基; 在苯环上任选被 1-3 个选自卤素原子和低级烷氧基中的基团取代的苯基; 和吡啶基,

[0607] b' 表示 0-3 的整数。

[0608] 可含有一个或两个选自氮、氧和硫中的杂原子的 5-7 员的含 1 个氮原子的饱和杂环基的实例包括吡咯烷基, 哌嗪基, 哌啶基, 吗啉代, 硫代吗啉基, 高哌嗪基, 高哌啶基, 咪唑烷基, 噻唑烷基, 异噻唑烷基, 噁唑烷基, 异噁唑烷基, 异噻唑烷基和吡唑烷基。

[0609] 上述被 1-3 个选自氧代; 低级烷基; 低级烷酰基; 苯基低级烷基; 在苯环上任选被 1-3 个选自卤素原子和低级烷氧基中的基团取代的苯基; 和吡啶基中的基团取代的杂环基的实例包括:

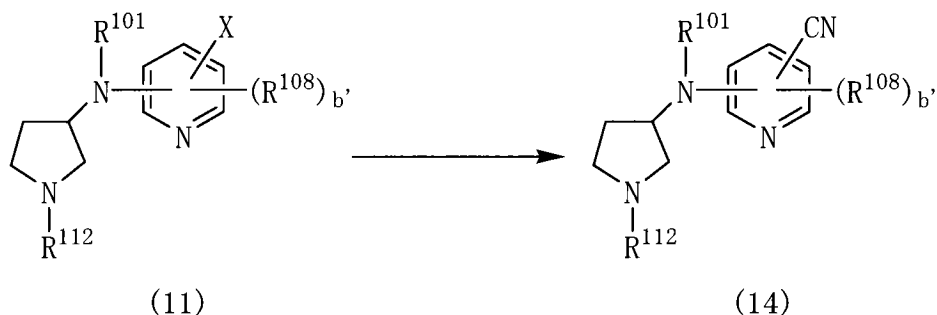
[0610] 被 1-3 个选自氧代基团; 直链或支链 C_{1-6} 烷基; 直链或支链 C_{1-6} 烷酰基; 其中烷基结构部分是直链或支链 C_{1-6} 烷基的苯基烷基; 在苯环上任选被 1-3 个选自卤素原子和直链或支链 C_{1-6} 烷氧基中的基团取代的苯基; 和吡啶基基团中的基团取代的上述杂环基;

[0611] 例如 2-氧代-(1-, 3-, 4-, 或 5-) 吡咯烷基, 2-氧代-(1-, 3-, 4-, 5-, 或 6-) 哌嗪基, 4-甲基-(1-, 2-, 或 3-) 哌嗪基, 4-乙酰基-(1-, 2-, 或 3-) 哌嗪基, 4-乙基-(1-, 2-, 或 3-) 哌嗪基, 2-甲基-(1-, 2-, 3-, 4-, 或 5-) 吡咯烷基, 2-甲基-(1-, 2-, 3-, 4-, 5-, 或 6-) 哌啶基, 2, 4-二甲基-(1-, 2-, 3-, 5-, 或 6-) 哌啶基, 3-甲基-(1-, 2-, 3-, 4-, 或 5-) 吡咯烷基, 2, 3, 4-三甲基-(1-, 2-, 3-, 5-, 或 6-) 哌嗪基, 4-乙酰基-3-甲基-(1-, 2-, 3-, 5-, 或 6-) 哌嗪基, 3-甲基-(2-, 3-, 4-, 5-, 或 6-) 吗啉代, 2-乙酰基-(2-, 3-, 4-, 5-, 或 6-) 吗啉代, 4-(2-苯基乙基)-(1-, 2-, 或 3-) 哌嗪基, 4-(3, 4-二氯苯基)-(1-, 2-, 3-, 或 4-) 哌嗪基, 4-(4-甲氧基苯基)-(1-, 2-, 或 3-) 哌嗪基, 4-(2-氯苯基)-(1-, 2-, 或 3-) 哌嗪基, 4-[(2-, 3-, 或 4-) 吡啶基]-(1-, 2-, 或 3-) 哌嗪基, 4-苯基-(1-, 2-, 或 3-) 哌嗪基, 4-苄基-(1-, 2-, 或 3-) 哌啶基, 4-(3, 4-二氯苯基)-(1-, 2-, 或 3-) 吗啉代, 2-(4-甲氧基苯基)-(1-, 2-, 3-, 4-, 或 5-) 吡咯烷基, 4-(2-氯苯基)-(1-, 2-, 或 3-) 哌啶基, 4-[(2-, 3-, 或 4-) 吡啶基]-(1-, 2-, 或 3-) 哌啶基, 4-苯基-3-甲基-(1-, 2-, 3-, 5-, 或 6-) 哌嗪基, 4-[(2-, 3-, 或 4-) 吡啶基]-2-乙酰基-(1-, 2-, 3-, 5-, 或 6-) 哌嗪基等。

[0612] 化合物 (11) 和化合物 (12) 之间反应在与反应路线 4 所示的化合物 (6) 和 (7) 之间的反应相同的条件下进行。

[0613] [反应路线 6]

[0614]



[0615] 其中 R^{101} 、 R^{108} 、 b' 和 X 如以上所定义。

[0616] 化合物 (14) 通过让化合物 (11) 与金属氰化物在适合的溶剂中在催化剂的存在下反应来制备。

[0617] 金属氰化物的实例包括氰化钠, 氰化钾, 氰化锌, 氰化铜等。

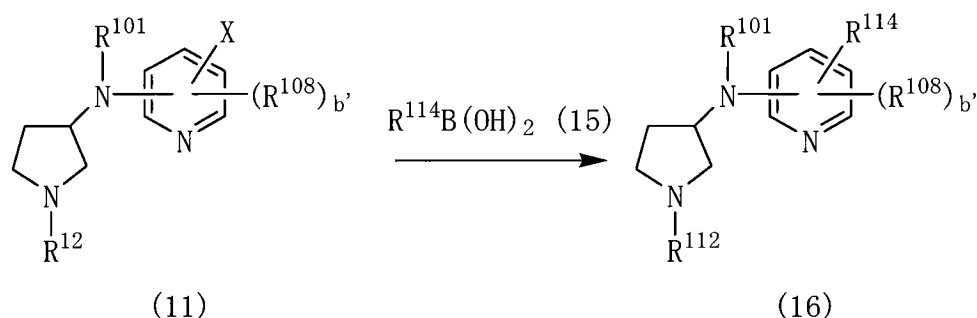
[0618] 用于反应的溶剂和催化剂可以各自与用于反应路线 4 所示的化合物 (6) 和 (7) 之间的反应的那些相同。催化剂可以化合物 (11) 的通常催化量使用。

[0619] 金属氰化物通常以至少约 1 摩尔 / 每摩尔的化合物 (11), 优选约 1 到约 3 摩尔 / 每摩尔的化合物 (11) 的量使用。

[0620] 反应有利地通常在室温到约 200°C, 优选在室温到约 150°C 的温度下进行, 通常在约 0.5 到约 20 小时内完成。

[0621] [反应路线 7]

[0622]

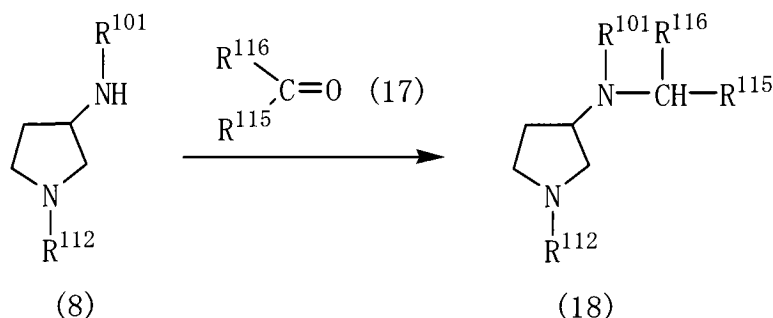


[0623] 其中 R^{101} 、 R^{108} 、 b' 和 X 如以上所定义, R^{114} 表示通式 (1) 中 (1-3)、(1-12)、(1-14)、(1-19)、(1-23)、(1-30) 和 (1-31) 所示的任何基团。

[0624] 化合物 (11) 和化合物 (15) 之间反应在与反应路线 4 所示的化合物 (6) 和 (7) 之间的反应相同的条件下进行。

[0625] [反应路线 8]

[0626]

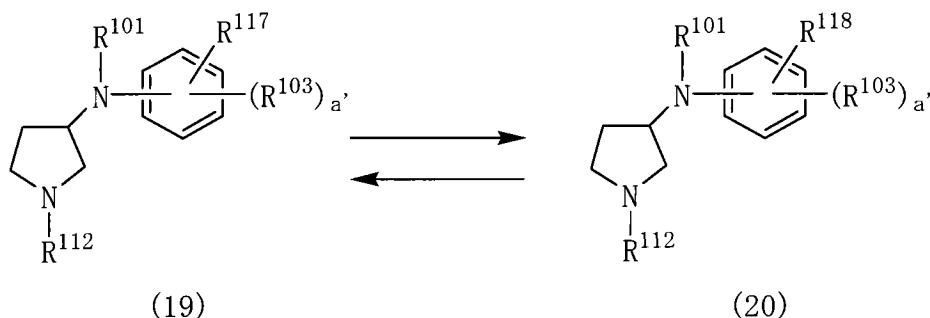


[0627] 其中 R^{101} 和 R^{112} 如以上所定义; R^{115} 表示苯基, 苯基低级烷基, 环烷基, 环烷基低级烷基, 低级烷硫基低级烷基, 在氨基上任选被一个或两个低级烷基取代的氨基取代的低级烷基, 苯氧基低级烷基, 或吡啶基低级烷基; R^{116} 表示氢原子或低级烷基。 R^{115} 和 R^{116} 另外可以连在一起形成环烷基, 前提是在化合物 (18) 的侧链 $-(R^{101})CH(R^{116})(R^{115})$ 中的 $CH(R^{116})(R^{115})$ 部分的碳原子的总数不超过 6。

[0628] 化合物 (8) 和化合物 (17) 之间的反应在与反应路线 2 所示的化合物 (3) 和 (4) 之间的反应相同的条件下进行, 只是化合物 (17) 的用量通常为至少 1 摩尔 / 每摩尔的化合物 (8), 优选 1 到 5 摩尔 / 每摩尔的化合物 (8)。

[0629] [反应路线 9]

[0630]



[0631] 其中 R^{101} 和 R^{112} 如以上所定义； a' 表示 0-4 的整数； R^{103} 表示通式 (1) 中所定义的 (1-1)-(1-37) 所示的任何基团， R^{117} 表示低级烷氧基羰基； R^{118} 表示羧基。

[0632] 化合物 (20) 通过化合物 (19) 的水解来制备。

[0633] 化合物 (19) 在酸或碱性化合物的存在下在适合的溶剂中或在没有溶剂的情况下水解。

[0634] 有用的溶剂的实例包括水；低级醇，如甲醇，乙醇，异丙醇和叔丁醇；酮，如丙酮和甲基乙基酮；醚，如二乙醚，二噁烷，四氢呋喃，单甘醇二甲醚和二甘醇二甲醚；脂族酸，如乙酸和甲酸；酯，如乙酸甲酯和乙酸乙酯；卤代烃，如氯仿，二氯甲烷，二氯乙烷和四氯化碳；二甲亚砆，N,N-二甲基甲酰胺和六甲基磷酰三胺；以及这些溶剂的混合物。

[0635] 有用的酸的实例包括无机酸比如盐酸，硫酸和氢溴酸；以及有机酸比如甲酸，乙酸，三氟乙酸和磺酸类如对甲苯磺酸。这些酸可以单独或结合使用。

[0636] 碱性化合物的实例包括碳酸盐比如碳酸钠，碳酸钾，碳酸氢钠和碳酸氢钾；碱金属氢氧化物比如氢氧化钠，氢氧化钾和氢氧化锂；碱土金属氢氧化物比如氢氧化钙；和其它类似碱性化合物。这些碱性化合物可以单独或结合使用。

[0637] 水解反应有利地通常在大约 0 到约 200°C，优选在大约 0 到约 150°C 的温度下进行，通常在约 10 分钟到约 30 小时内结束。

[0638] 化合物 (19) 通过让化合物 (20) 与通式 (21) 所示的化合物反应来制备：

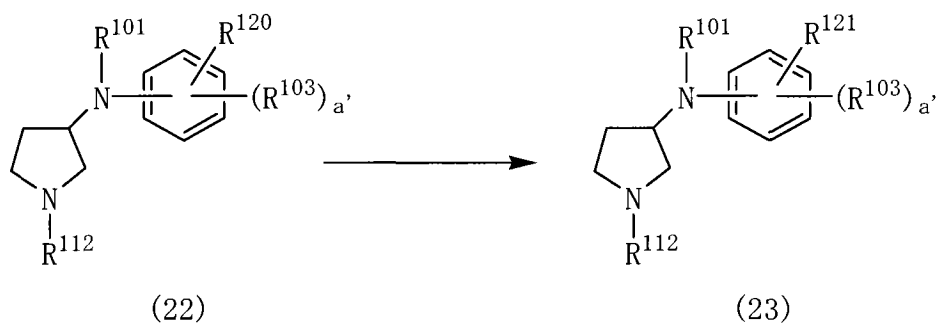
[0639] $R^{119}OH$ (21)

[0640] 其中 R^{119} 表示低级烷基。

[0641] 通常选择用于酯化反应的条件适用于化合物 (20) 和 (21) 之间的反应。例如，化合物 (20) 和 (21) 之间的反应可以在无机酸如盐酸和硫酸；或卤化剂如亚硫酸氯，三氯化磷，五氯化磷和三氯化磷的存在下进行。化合物 (21) 以相对于化合物 (20) 的很大过量使用。该反应有利地通常在大约 0 到约 150°C，优选在大约 0 到约 100°C 的温度下进行，通常在约 1 到约 10 小时内完成。

[0642] [反应路线 10]

[0643]



[0644] 其中 R^{101} 、 R^{103} 、 a' 和 R^{112} 如以上所定义, R^{120} 表示低级烷硫基; R^{121} 表示低级烷基磺酰基。

[0645] 由化合物 (22) 制备化合物 (23) 的反应在适合的溶剂中在氧化剂的存在下进行。

[0646] 有用的溶剂的实例包括水; 脂族酸比如甲酸, 乙酸和三氟乙酸; 醇如甲醇和乙醇; 卤代烃比如氯仿和二氯甲烷; 和这些溶剂的混合物。

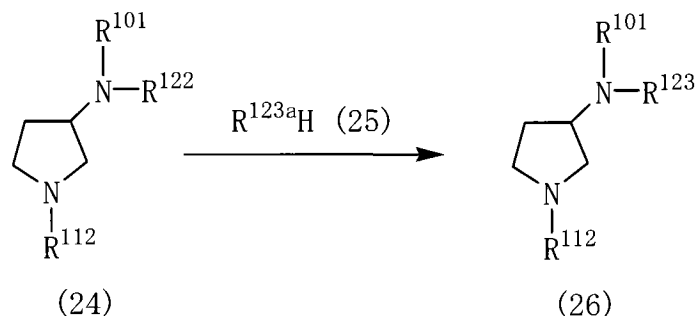
[0647] 有用的氧化剂的实例包括过酸比如过甲酸, 过乙酸, 过三氟乙酸, 过苯甲酸, 间-氯过苯甲酸和邻-羧基过苯甲酸; 过氧化氢; 偏高碘酸钠; 重铬酸盐比如重铬酸, 重铬酸钠和重铬酸钾; 高锰酸盐比如高锰酸, 高锰酸钠和高锰酸钾; 铅盐比如四乙酸铅。

[0648] 氧化剂通常以至少约 2 摩尔 / 每摩尔的化合物 (22), 优选约 2 到 4 摩尔 / 每摩尔的化合物 (22) 的量使用。

[0649] 该反应通常在约 -10 到约 150°C , 优选在约 -10 到约 100°C 的温度下进行, 通常在约 1 到约 10 小时内完成。

[0650] [反应路线 11]

[0651]



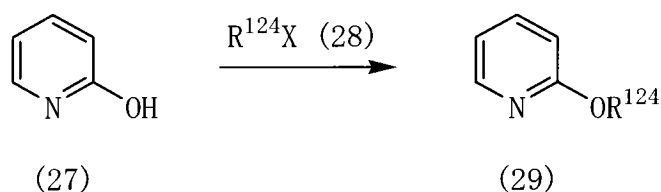
[0652] 其中 R^{101} 和 R^{112} 如以上所定义, R^{122} 表示含有一个或多个卤素原子的低级烷基; R^{123} 表示在氨基上任选被一个或两个低级烷基取代的氨基取代的低级烷基; R^{123a} 表示在氨基上任选被一个或两个低级烷基取代的氨基。

[0653] 化合物 (24) 和化合物 (25) 之间反应在与反应路线 3 所示的化合物 (5) 和 (4) 之间的反应相同的条件下进行。

[0654] 用作起始原料的化合物 (7) 和化合物 (9) 可以容易地制备, 例如通过以下反应路线所示的方法:

[0655] [反应路线 12]

[0656]



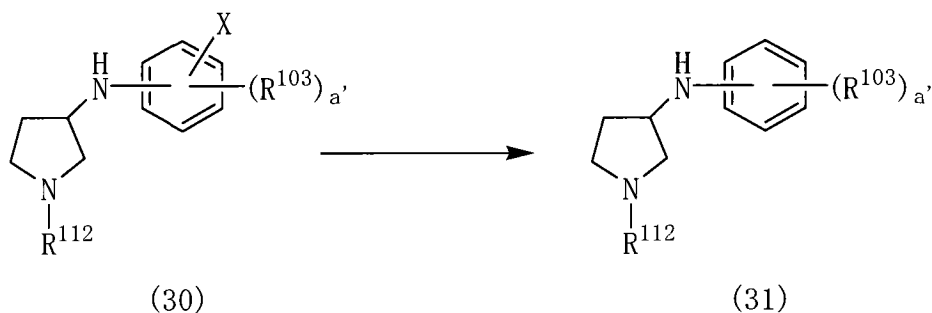
[0657] 其中 X 如以上所定义, R^{124} 表示含有一个或多个卤素原子的低级烷基。

[0658] 化合物 (27) 和化合物 (28) 之间反应在与反应路线 3 所示的化合物 (5) 和 (4) 之间的反应相同的条件下进行。

[0659] 作为起始原料的化合物 (8) 例如可以通过以下反应路线 13 所示的方法来制备：

[0660] [反应路线 13]

[0661]



[0662] 其中 R^{103} 、 a' 、X 和 R^{112} 如以上所定义。

[0663] 由化合物 (30) 制备化合物 (31) 的反应例如在还原剂的存在下在没有溶剂的情况下或在适合的溶剂中进行。

[0664] 有用的溶剂的实例包括水；低级醇比如甲醇, 乙醇, 异丙醇, 丁醇, 叔丁醇和乙二醇；乙腈；脂族酸比如甲酸和乙酸；醚比如二乙醚, 四氢呋喃, 二噁烷, 单甘醇二甲醚和二甘醇二甲醚；芳族烃比如苯, 甲苯和二甲苯；卤代烃比如二氯甲烷, 二氯乙烷, 氯仿和四氯化碳；和这些溶剂的混合物。

[0665] 还原剂的实例包括催化氢化还原剂比如钨黑, 钨碳, 氧化铂, 铂黑和拉内镍等等。

[0666] 催化氢化还原剂通常以化合物 (30) 的约 0.1 到 40wt%, 优选约 0.1 到约 20wt% 的量使用。

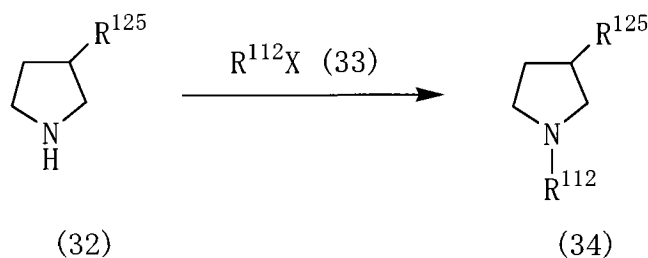
[0667] 反应有利地通过将碱性化合物如氢氧化钠添加到反应系统中来进行。

[0668] 反应通常在大约 -30 到约 100°C , 优选在大约 0 到约 60°C 的温度, 在大气压到约 20 个大气压, 优选大气压到约 10 个大气压的氢气氛围中进行。反应通常在约 1 到约 12 小时内结束。

[0669] 用作起始原料的化合物 (3), (5) 和 (6) 可以容易地通过例如以下所示的反应路线来制备：

[0670] [反应路线 14]

[0671]



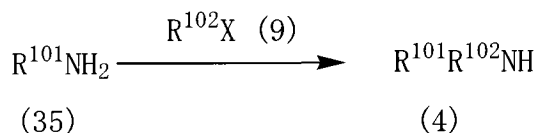
[0672] 其中 R^{112} 和 X 如以上所定义, R^{125} 表示氧代基, R^{113} 表示的基团, 或氨基, R^{113} 如以上所定义。

[0673] 化合物 (32) 和化合物 (33) 之间的反应在与以上反应路线 3 所示的化合物 (5) 和 (4) 之间的反应相同的条件下进行。

[0674] 用作起始原料的化合物 (4) 例如可以通过以下反应路线所示的方法来制备:

[0675] [反应路线 15]

[0676]



[0677] 其中 R^{101} 、 R^{102} 和 X 如以上所定义。

[0678] 化合物 (35) 与化合物 (9) 的反应在与反应路线 4 所示的化合物 (6) 与化合物 (7) 的反应相同的条件下进行。

[0679] R^{112} 是氢原子的化合物 (2), (8), (13), (14), (16), (18), (19), (20), (23) 和 (26) 可以通过用氢置换在反应路线 2-11 所示的各反应中用作起始原料的化合物 (3), (5), (6), (8), (11), (19), (20), (22) 和 (24) 中的 R^{112} , 使用这样获得的化合物作为起始原料, 并且在与反应路线 2-11 所示的反应相同的条件下让起始原料反应来制备。

[0680] 如果在反应路线 3-11 所示的反应中使用旋光物作为起始原料 (化合物 (5), (6), (8), (11), (19), (20), (22) 和 (24)), 旋光活性化合物 (2), (8), (13), (14), (16), (18), (19), (20), (23) 和 (26) 可以通过让该化合物在与反应路线 3-11 所示的反应相同的条件下反应来制备。

[0681] 还可以使用没有进行分离的反应路线 2-11 的反应中产生的化合物 (2), (8), (13), (14), (16), (18), (19), (20), (23) 或 (26) 作为反应路线 1 的反应中的起始原料来制备本发明的化合物 (1)。

[0682] 可以从反应混合物中分离和提纯根据以上反应路线获得的每一目标化合物, 例如, 在冷却反应混合物后, 进行诸如过滤、浓缩、提取之类的分离程序, 分离出粗反应产物, 然后用诸如柱色谱法、重结晶之类的标准提纯工序提纯粗反应产物。

[0683] 根据本发明的通式 (1) 化合物包括它们的立体异构体和旋光异构体。

[0684] 在起始化合物和本发明的目的吡咯烷化合物中, 具有一个或多个碱性基团的那些化合物适于和普通的可药用酸形成盐。这种酸的实例包括盐酸, 氢溴酸, 硝酸, 硫酸, 磷酸和其它无机酸; 甲磺酸, 对甲苯磺酸, 乙酸, 柠檬酸, 酒石酸, 马来酸, 富马酸, 苹果酸, 乳酸和其它有机酸等等。

[0685] 在起始化合物和本发明的目的吡咯烷化合物中, 具有一个或多个酸性基团的那些化合物适于和普通的可药用碱性化合物形成盐。这种碱性化合物的实例包括氢氧化钠, 氢

氧化钾,氢氧化钙,碳酸钠,碳酸钾,碳酸氢钠,碳酸氢钾等等。

[0686] 另外,其中溶剂化物(例如水合物,乙醇化物等)加入到每一反应式所示的起始化合物和目的化合物中的这种形式的化合物被归入每一通式中。

[0687] 以下说明含有本发明的化合物作为活性成分的药物制剂。

[0688] 这种药物制剂通过采用常用的稀释剂和/或赋形剂例如填料、增量剂(extender)、粘结剂、润湿剂、崩解剂、表面活性剂、润滑剂等将本发明的化合物配制成标准药物制剂而获得。

[0689] 这种药物制剂的形式可以根据治疗目的从各种形式中选择。典型实例包括片剂,药丸,粉末,溶液,悬浮液,乳液,颗粒,胶囊剂,栓剂,注射剂(溶液,悬浮液等),等等。

[0690] 为了形成片剂,可以使用各种已知的载体,例如包括:乳糖,白糖,氯化钠,葡萄糖,尿素,淀粉,碳酸钙,高岭土,结晶纤维素和其它赋形剂;水,乙醇,丙醇,净糖浆,葡萄糖溶液,淀粉溶液,明胶溶液,羧甲基纤维素,虫胶,甲基纤维素,磷酸钾,聚乙烯吡咯烷酮和其它粘结剂;干燥淀粉,海藻酸钠,琼脂粉,昆布多糖粉,碳酸氢钠,碳酸钙,聚氧乙烯脱水山梨糖醇的脂肪酸酯,十二烷基硫酸钠,硬脂酸甘油酯,淀粉,乳糖和其它崩解剂;白糖,硬脂精,可可脂,氢化油和其它崩解抑制剂;季铵碱,十二烷基硫酸钠和其它吸收促进剂;甘油,淀粉和其它润湿剂;淀粉,乳糖,高岭土,膨润土,胶态硅酸和其它吸附剂;净化滑石粉,硬脂酸酯,硼酸粉,聚乙二醇和其它润滑剂;等等。

[0691] 这种片剂根据需要可以用典型的膜料包衣,以制备例如糖衣片,明胶包衣片剂,肠溶衣片剂,薄膜包衣片剂,双层或多层片剂等。

[0692] 为了形成药丸,可以使用各种已知的载体,例如包括:葡萄糖,乳糖,淀粉,可可脂,氢化植物油,高岭土,滑石和其它赋形剂;阿拉伯树胶粉,黄芪胶粉,明胶,乙醇和其它粘结剂;昆布多糖,琼脂和其它崩解剂;等等。

[0693] 为了形成栓剂,可以使用各种已知的载体,例如包括:聚乙二醇,可可脂,高级醇,高级醇的酯,明胶,半合成甘油酯等。

[0694] 为了形成注射剂,将溶液、乳液或悬浮液灭菌,优选制成与血液等渗。可以使用各种已知的广泛使用的稀释剂来制备溶液、乳液或悬浮液。这种稀释剂的实例包括水,乙醇,丙二醇,乙氧基化异硬脂基醇,多氧化(polyoxylated)异硬脂基醇,聚氧化乙烯脱水山梨糖醇的脂肪酸酯等。在这种情况下,该药物制剂可以含有足以制备等渗溶液的量的氯化钠,葡萄糖或甘油,并且可以含有典型的增溶剂,缓冲剂,止痛剂等,如果必要,进一步含有着色剂,防腐剂,香味剂,甜味剂等,和/或其它药物。

[0695] 本发明的化合物在药物制剂中的比例没有限制,可以从宽范围中适当选择。通常优选该药物制剂含有1-70wt%的本发明的化合物。

[0696] 本发明药物制剂的给药途径没有限制,该制剂通过适于制剂形式、病人年龄和性别、疾病状况和其它条件的途径给药。例如,片剂,药丸,溶液,悬浮液,乳液,颗粒和胶囊可以口服给药。根据需要,注射剂可以单独静脉内给药,或与常用注射输液如葡萄糖溶液、氨基酸溶液等混合后静脉内给药,或单独肌肉注射、皮内注射、皮下注射或腹膜内注射。栓剂直肠内给药。

[0697] 药物制剂的剂量适宜地根据使用方法、病人年龄和性别、疾病的严重程度和其它条件来选择,通常是约0.001到约100mg/kg体重/天,优选0.001到50mg/kg体重/天,按

一次或分剂量给药。

[0698] 因为剂量根据各种条件而改变,小于以上范围的剂量可能是足够的,或者可以需要大于以上范围的剂量。

[0699] [本发明的效果]

[0700] 本发明的吡咯烷化合物具有抑制一种、两种或三种单胺(,即 5-羟色胺,去甲肾上腺素,多巴胺)的再摄取的效果。

[0701] 在活体外或体外实验中,与已知的具有单胺摄取抑制活性的化合物相比,本发明的吡咯烷化合物显示出明显更强的对这三种单胺之一的摄取抑制活性。在微量渗析研究中,与已知的具有单胺摄取抑制活性的化合物相比,本发明的吡咯烷化合物也显示出明显更强的提高大鼠脑内的这三种单胺之一的水平的效果。

[0702] 本发明的吡咯烷化合物比已知的抗抑郁药具有更广的医疗范围。

[0703] 即使在短期给药之后,本发明的吡咯烷化合物也显示出足够的治疗效果。

[0704] 本发明的吡咯烷化合物具有优异的生物利用率,很小的肝内代谢酶抑制活性,很小的副作用,并且非常安全。

[0705] 本发明的吡咯烷化合物在用于筛选抗抑郁药的小鼠强迫游泳试验/悬尾试验中显示出很强的活性。本发明的吡咯烷化合物在用于筛选抗抑郁药的大鼠强迫游泳试验中也显示出很强的活性。本发明的吡咯烷化合物在用于筛选抗抑郁药的利血平诱导低体温模型中也显示出很强的活性。

[0706] 本发明的吡咯烷化合物在小鼠大理石掩盖行为试验和属于焦虑或应激相关疾病模型的条件恐惧应激模型中也显示出强劲活性。

[0707] 本发明的吡咯烷化合物具有抑制一种、两种或三种单胺(也就是 5-羟色胺,去甲肾上腺素,多巴胺)再摄取的效果,因此可有效治疗由 5-羟色胺、去甲肾上腺素或多巴胺的神经传递减少所引起的各种疾病。

[0708] 这种疾病的实例包括高血压,抑郁症(例如,主要抑郁症,1型双向性障碍,2型双向性障碍,混合型急性发作,精神抑郁症,快速循环,非典型抑郁症,季节性情感障碍,产后抑郁症,未成年人抑郁症,复发性短暂抑郁症,难治性抑郁/慢性抑郁症,双重抑郁,酒精诱发的情绪障碍,混合型焦虑与抑郁症;由各种身体疾病比如库兴氏病,甲状腺功能减退,甲状旁腺机能亢进综合症,阿狄森氏病,停经和泌乳综合症,帕金森氏病,阿尔茨海默氏病,脑内出血,糖尿病,慢性疲劳综合症和癌症诱发的抑郁症;中年抑郁症,高龄抑郁症,儿童和青春期抑郁症,药物如干扰素诱发的抑郁症,调节障碍诱发的抑郁症,调节障碍诱发的焦虑,由各种身体疾病(例如,神经病(头颅外伤,脑感染,内耳损伤),心血管失调(心跳停止,异常心律),内分泌病症(肾上腺功能亢进(hyperfunction),恶性突眼(exophthalmia)),呼吸问题(哮喘,慢性阻塞性肺病))诱发的焦虑,全身化焦虑症,恐惧(例如,陌生环境恐怖症,社会恐怖病和简单恐怖病),外伤后应激综合症,急性应激综合症,逃避型人格障碍,身体畸形病,早熟型射精,饮食障碍(例如,神经性厌食症和食欲过盛nervosa),肥胖,化学品依赖性(例如,酒精,古柯碱,海洛因,苯巴比妥,烟碱和苯二氮草类),群集性头痛,偏头痛,疼痛病症,阿尔茨海默氏病,强迫-强制症,恐慌症,记忆障碍(例如,痴呆,遗忘症和衰老相关性认知衰退(ARCD)),帕金森氏病(例如,由帕金森氏病引起的痴呆,神经安定药诱发的帕金森氏综合征,迟发性运动障碍),内分泌疾病(例如,高催乳素

血症),血管痉挛(尤其,大脑血液循环系统),小脑性共济失调,胃肠道疾病(包括运动和分泌方面的变化),精神分裂症的阴性综合症,经前期综合征,纤维肌痛综合症,压力性尿失禁,多发性抽动症,拔毛发癖,盗癖,男性阳痿,注意力缺乏活动亢进症(抗利尿激素),慢性发作性偏头痛,慢性疲劳,猝倒,睡眠无呼吸综合征和头痛(与血管病有关)。

具体实施方式

[0709] 以下说明制备实施例、参比实施例、实施例和药物学试验。

[0710] 制备实施例 1

[0711] 将本发明的化合物(100g)、40g Avicel(商品名,Asahi kasei Corporation 生产)、30g 玉米淀粉和 2g 硬脂酸镁混合,研磨,然后使用用于糖衣片剂的 10.0mm 直径的冲头压片。这样获得的片剂用薄膜包衣剂包衣,形成含有上述成分的薄膜包衣片剂,所用薄膜包衣剂包括 10g 的 TC-5(商品名,Shin-Etsu Chemical Co.,Ltd.,羟丙基甲基纤维素),3g 的聚乙二醇(polyethylene glycol)6000,40g 的蓖麻油以及适量的乙醇。

[0712] 参比实施例 1

[0713] 3-[(3,4-二氯苯基)-(4-氟苯基)氨基]吡咯烷-1-羧酸叔丁基酯的合成

[0714] 将氢化钠(0.19g,60%,在油中)加入到 10mL 的二甲亚砜(DMSO)中,并在 60℃ 下搅拌一小时。随后,将 1.0g 的(3,4-二氯苯基)-(4-氟苯基)胺加入到该混合物中,并在 60℃ 下搅拌一小时。将含有 2.0g 的 3-(甲苯-4-磺酰氧基)吡咯烷-1-羧酸叔丁基酯的二甲亚砜溶液逐渐地加入到该混合物中并在 60℃ 下搅拌 15 小时。将乙酸乙酯加入到反应溶液中。然后用水清洗该溶液,用硫酸镁干燥。用减压馏出溶剂,残留物通过硅胶柱层析(正己烷:乙酸乙酯=20:1)来提纯。用减压馏出洗脱剂溶剂,从而获得 0.29g 的棕色油状的 3-[(3,4-二氯苯基)-(4-氟苯基)氨基]吡咯烷-1-羧酸叔丁基酯。

[0715] $^1\text{H-NMR}(\text{CDCl}_3)$ δ ppm:

[0716] 1.43(9H, s), 1.74-1.92(1H, m), 2.04-2.22(1H, m), 3.10-3.35(3H, m), 3.61-3.85(1H, m), 4.31-4.48(1H, m), 6.42(1H, dd = 2.9Hz, J = 8.9Hz), 6.67(1H, d, J = 2.8Hz), 6.90-7.22(5H, m).

[0717] 参比实施例 2

[0718] 3(S)-[(3,4-二氯苯基)苯基氨基]吡咯烷-1-羧酸叔丁基酯的合成

[0719] 将氢化钠(0.36g,60%,在油中)加入到 20mL 的二甲亚砜(DMSO)中,并在 60℃ 下搅拌一小时。随后,将 2.0g 的 3,4-二氯苯基-苯胺加入到该混合物中,并在 60℃ 下搅拌一小时。将含有 1.5g 的 3(R)-甲烷磺酰氧基吡咯烷-1-羧酸叔丁基酯的 DMSO 溶液逐渐加入到该混合物中并在 60℃ 下搅拌 15 小时。将乙酸乙酯加入到反应溶液中,然后用水清洗反应溶液,用硫酸镁干燥。用减压馏出溶剂,残留物通过硅胶柱层析(正己烷:乙酸乙酯=20:1)来提纯。用减压馏出洗脱剂溶剂,从而获得 0.13g 的浅棕色无定形固体 3(S)-[(3,4-二氯苯基)-苯基氨基]吡咯烷-1-羧酸叔丁基酯。

[0720] $^1\text{H-NMR}(\text{CDCl}_3)$ δ ppm:

[0721] 1.42(9H, s), 1.73-1.93(1H, m), 2.05-2.23(1H, m), 3.10-3.36(3H, m), 3.61-3.83(1H, m), 4.33-4.50(1H, m), 6.48(1H, dd, J = 2.9Hz, J = 10.3Hz), 6.74(1H, d, J = 2.8Hz), 6.96-7.07(2H, m), 7.16-7.34(2H, m), 7.35-7.46(2H, m).

[0722] 参比实施例 3

[0723] ((S)-1-苄基吡咯烷-3-基)-(3-氟苯基)胺的合成

[0724] 将含有 2.2g 的 (S)-1-苄基吡咯烷-3-基胺 (12.5mmol), 2.2g 的 3-溴氟苯 (12.5mmol), 0.31g 的 2,2-双(二苯基膦基)-1,1-联萘 (BINAP, 0.51mmol), 0.14g 的双(二苄叉基丙酮)钯 ($\text{Pd}(\text{dba})_2$, 0.22mmol) 和 1.3g 的叔丁醇钠 (13.2mmol) 的甲苯溶液在回流下在氮气氛中加热 3 小时。将反应溶液过滤以除去不溶物质, 将乙酸乙酯和水加入到滤液中, 以便使溶液分层。有机层用水清洗, 在减压下馏出溶剂, 残留物通过硅胶柱层析来提纯 (正己烷:乙酸乙酯 = 20:1 $\rightarrow$ 1:1)。在减压下馏出洗脱溶剂, 从而获得 3.0g 的无色油状 ((S)-1-苄基吡咯烷-3-基)-(3-氟苯基)胺。

[0725] $^1\text{H-NMR}(\text{CDCl}_3)$ δ ppm:

[0726] 1.59-1.78 (2H, m), 2.21-2.38 (1H, m), 2.39-2.50 (1H, m), 2.55 (1H, dd, $J = 3.3\text{Hz}$, $J = 9.7\text{Hz}$), 2.71-2.85 (2H, m), 3.63 (2H, s), 3.90-4.10 (1H, m), 6.24 (1H, dt, $J = 2.3\text{Hz}$, $J = 11.6\text{Hz}$), 6.29-6.41 (2H, m), 7.02-7.11 (1H, m), 7.21-7.39 (5H, m).

[0727] 参比实施例 4

[0728] ((S)-1-苄基吡咯烷-3-基)-苯胺的合成

[0729] 按照参比实施例 3 同样的方法, 使用 (S)-1-苄基吡咯烷-3-基胺和溴苯合成 ((S)-1-苄基吡咯烷-3-基)-苯胺。

[0730] 棕色油性物质

[0731] $^1\text{H-NMR}(\text{CDCl}_3)$ δ ppm:

[0732] 1.56-1.78 (2H, m), 2.22-2.39 (1H, m), 2.41-2.58 (1H, m), 2.70-2.84 (2H, m), 3.63 (2H, s), 4.01 (1H, s), 6.57 (2H, d, $J = 8.5\text{Hz}$), 6.64-6.73 (1H, m), 7.11-7.19 (2H, m), 7.21-7.36 (5H, m).

[0733] 参比实施例 5

[0734] ((S)-1-苄基吡咯烷-3-基)-(3-氟苯基)-(4-三氟甲基苯基)胺的合成

[0735] 将含有 0.7g 的 ((S)-1-苄基吡咯烷-3-基)-(3-氟苯基)胺 (2.6mmol), 0.59g 的 4-溴次苄基三氟 (2.6mmol), 65mg 的 BINAP (0.1mmol), 23mg 的乙酸钯 (0.1mmol) 和 0.28g 的叔丁醇钠 (2.9mmol) 在回流下在氮气氛中加热 3 小时。将反应溶液过滤以除去不溶物质, 将乙酸乙酯和水加入到滤液中, 以便使溶液分层。然后用水清洗有机层, 用硫酸镁干燥。在减压下馏出溶剂, 通过硅胶柱层析提纯残留物 (正己烷:乙酸乙酯 = 20:1 $\rightarrow$ 10:1)。在减压下馏出洗脱溶剂, 从而获得 0.48g 的无色油状 ((S)-1-苄基吡咯烷-3-基)-(3-氟苯基)-(4-三氟甲基苯基)胺。

[0736] $^1\text{H-NMR}(\text{CDCl}_3)$ δ ppm:

[0737] 1.82-2.01 (1H, m), 2.17-2.31 (1H, m), 2.61-2.78 (3H, m), 3.45 (1H, d, $J = 12.9\text{Hz}$), 3.64 (1H, d, $J = 12.9\text{Hz}$), 4.55 (1H, m), 6.78-6.86 (3H, m), 6.88-6.96 (2H, m), 7.19-7.36 (6H, m).

[0738] 参比实施例 6

[0739] 3(S)-(3-氯-4-氟苯基氨基)吡咯烷-1-羧酸叔丁基酯的合成

[0740] 在 50mL 的含有 5.0g 的 3(S)-氨基吡咯烷-1-羧酸叔丁基酯 (27mmol) 和 5.7g 的 4-溴-2-氯-1-氟代苯 (27mmol) 的甲苯溶液中添加 1.7g 的 BINAP (2.7mmol), 0.30g 的乙

酸钡 (1.3mmol) 和 3.5g 的叔丁醇钠 (36mmol)。将该混合物在回流下在氮气氛围中加热 8 小时,然后冷却到室温。将水加入到反应溶液中,再用乙酸乙酯萃取。在用硫酸钠干燥和减压浓缩之后,通过硅胶柱层析来提纯(正己烷:乙酸乙酯=4:1)残留物。在减压下馏出溶剂,残留物从二乙醚中再结晶,从而获得 4.76g 的白色粉状 3(S)-(3-氯-4-氟苯基氨基)吡咯烷-1-羧酸叔丁基酯。

[0741] $^1\text{H-NMR}(\text{CDCl}_3)$ δ ppm :

[0742] 1.47(9H, s), 1.78-1.96(1H, m), 2.10-2.28(1H, m), 2.10-2.28(1H, m), 3.11-3.30(1H, m), 3.30-3.56(2H, m), 3.57-3.79(2H, m), 3.85-4.03(1H, m), 6.38-6.47(1H, m), 6.60(1H, dd, $J = 6.0\text{Hz}$, $J = 2.9\text{Hz}$), 6.90-7.00(1H, m).

[0743] 参比实施例 7

[0744] 3(S)-(3-氯-4-氟苯基氨基)吡咯烷-1-羧酸叔丁基酯的合成

[0745] 向 50mL 的含有 15.0g 的 3(S)-氨基吡咯烷-1-羧酸叔丁基酯 (80.5mmol) 和 24.8g 的 2-氯-1-氟-4-碘代苯 (96.7mmol) 的异丙醇溶液添加 1.54g 的碘化铜 (I) (8.1mmol), 9.0mL 的乙二醇 (10.1mmol) 和 34.2g 的磷酸钾 (161mmol), 并且在氮气氛围中回流加热 46 小时。将反应溶液冷却到室温,使用赛力特硅藻土过滤。过滤器中剩余的物质用乙酸乙酯清洗,滤液和洗液一起在减压下浓缩,残留物通过硅胶柱层析法提纯(正己烷:乙酸乙酯=4:1)。在减压下馏出溶剂,残留物从二乙醚中再结晶,从而获得 15.9g 的白色粉状 3(S)-(3-氯-4-氟苯基氨基)吡咯烷-1-羧酸叔丁基酯。

[0746] $^1\text{H-NMR}(\text{CDCl}_3)$ δ ppm :

[0747] 1.47(9H, s), 1.78-1.96(1H, m), 2.10-2.28(1H, m), 2.10-2.28(1H, m), 3.11-3.30(1H, m), 3.30-3.56(2H, m), 3.57-3.79(2H, m), 3.85-4.03(1H, m), 6.38-6.47(1H, m), 6.60(1H, dd, $J = 6.0\text{Hz}$, $J = 2.9\text{Hz}$), 6.90-7.00(1H, m).

[0748] 参比实施例 8

[0749] 3(S)-(3-氰基苯基氨基)吡咯烷-1-羧酸叔丁基酯的合成

[0750] 向含有 2.82g 的 3(S)-氨基吡咯烷-1-羧酸叔丁基酯 (15mmol) 和 1.82g 的 3-溴苄腈 (10mmol) 的甲苯溶液 (7mL) 添加 68.5mg 的 BINAP (0.11mmol), 22.5mg 的乙酸钡 (0.1mmol) 和 3.91g 的碳酸铯 (12mmol)。将该混合物在回流下在氮气氛围中加热 8 小时。在冷却到室温之后,将水加入到反应溶液中,再用二氯甲烷萃取。在用硫酸钠干燥和减压浓缩之后,残留物然后通过硅胶柱层析来提纯(正己烷:乙酸乙酯=4:1)。在减压下将提纯产物浓缩至干燥,从而获得 1.56g 的浅黄色粉状的 3(S)-(3-氰基苯基氨基)吡咯烷-1-羧酸叔丁基酯。

[0751] $^1\text{H-NMR}(\text{CDCl}_3)$ δ ppm :

[0752] 1.46(9H, s), 1.8-2.0(1H, m), 2.1-2.3(1H, m), 3.1-3.6(3H, m), 3.6-3.8(1H, m), 3.9-4.1(2H, m), 6.7-6.9(2H, m), 6.99(1H, d, $J = 7.6\text{Hz}$), 7.23(1H, dd, $J = 7.6\text{Hz}$, $J = 8.4\text{Hz}$).

[0753] 参比实施例 9

[0754] 3(S)-(3-氯-4-甲氧基苯基氨基)吡咯烷-1-羧酸叔丁基酯的合成

[0755] 向 5mL 的含有 0.20g 的 3(S)-氨基吡咯烷-1-羧酸叔丁基酯 (1.1mmol) 和 0.238g 的 2-氯-3-溴茴香醚 (1.1mmol) 的甲苯溶液添加 67.0mg 的 BINAP (0.11mmol), 24mg 的三

(二苄叉基丙酮)二钯(0.027mmol)和144mg的叔丁醇钠(1.5mmol)。将该混合物在氮气氛中在100℃下回流加热一小时。在冷却到室温之后,使用赛力特硅藻土过滤反应溶液。在减压下馏出滤液,残留物通过硅胶柱层析法提纯(正己烷:乙酸乙酯=10:1→3:1)。在减压下将提纯产物浓缩至干燥,从而获得0.28g的浅黄色无定形固体3(S)-(3-氯-4-甲氧基苯基氨基)吡咯烷-1-羧酸叔丁基酯。

[0756] $^1\text{H-NMR}(\text{CDCl}_3)$ δ ppm:

[0757] 1.47(9H, s), 1.80-1.90(1H, m), 2.10-2.20(1H, m), 3.10-3.25(1H, m), 3.38-3.75(3H, m), 3.83(3H, s), 3.92-3.96(1H, m), 6.47(1H, dd, $J = 2.8\text{Hz}$, $J = 8.8\text{Hz}$), 6.67(1H, d, $J = 2.8\text{Hz}$), 6.81(1H, d, $J = 8.8\text{Hz}$).

[0758] 参比实施例10

[0759] 3(S)-(4-甲氧基苯基氨基)吡咯烷-1-羧酸叔丁基酯的合成

[0760] 向10mL的含有0.28g的3(S)-(3-氯-4-甲氧基苯基氨基)吡咯烷-1-羧酸叔丁基酯的乙醇溶液添加0.2mL的5N氢氧化钠溶液和0.1g10%钯碳。催化还原在室温和大气压力(常压)下进行。在使用赛力特硅藻土过滤反应溶液并在减压下浓缩。将水加入到残留物中,再用二氯甲烷萃取。用硫酸镁干燥萃取物,在减压下浓缩至干燥,从而获得0.25g的浅黄色无定形固体3(S)-(4-甲氧基苯基氨基)吡咯烷-1-羧酸叔丁基酯。

[0761] $^1\text{H-NMR}(\text{CDCl}_3)$ δ ppm:

[0762] 1.46(9H, s), 1.79-1.88(1H, m), 2.10-2.22(1H, m), 3.12-3.25(1H, m), 3.30-3.52(3H, m), 3.60-3.75(4H, m), 3.88-4.00(1H, m), 6.50-6.58(2H, m), 6.72-6.80(2H, m).

[0763] 参比实施例11

[0764] 3(S)-[双-(3-氟苯基)氨基]吡咯烷-1-羧酸叔丁基酯的合成

[0765] 向10mL的含有1.0g的3(S)-氨基吡咯烷-1-羧酸叔丁基酯(5.3mmol)和2.3g的3-溴-1-氟代苯(13mmol)的甲苯溶液添加32mg的四氟硼酸·三叔丁基膦(0.11mmol), 24mg的乙酸钯(0.11mmol)和1.5g的叔丁醇钠(5.30mmol)。将该混合物在回流下在氮气氛中加热8小时。在冷却到室温之后,将水加入到反应溶液中,再用乙酸乙酯萃取。在用硫酸钠干燥和减压浓缩之后,残留物然后通过硅胶柱层析来提纯(正己烷:乙酸乙酯=4:1)。在减压下将提纯产物浓缩至干燥,从而获得1.56g的黄色油状的3(S)-[双-(3-氟苯基)氨基]吡咯烷-1-羧酸叔丁基酯。

[0766] $^1\text{H-NMR}(\text{CDCl}_3)$ δ ppm:

[0767] 1.43(9H, s), 1.78-1.95(1H, m), 2.02-2.26(1H, m), 3.12-3.39(3H, m), 3.65-3.83(1H, m), 4.35-4.51(1H, m), 6.61(2H, dt, $J = 2.1\text{Hz}$, $J = 11.0\text{Hz}$), 6.61-6.68(2H, m), 6.77(2H, t, $J = 8.0\text{Hz}$), 7.18-7.31(2H, m).

[0768] 参比实施例12

[0769] 3(S)-[(3,4-二氯苯基)-噻唑-2-基氨基]吡咯烷-1-羧酸叔丁基酯的合成

[0770] 向150mL的含有20.0g的3(S)-(3,4-二氯苯基氨基)吡咯烷-1-羧酸叔丁基酯(60.4mmol)和15.0g的2-溴噻唑(91.5mmol)的甲苯溶液添加1.86g的四氟硼酸·三叔丁基膦(6.4mmol), 2.88g的三(二苄叉基丙酮)二钯(3.15mmol)和11.6g的叔丁醇钠(120mmol)。将该混合物在回流下在氮气氛中加热9小时。将反应溶液冷却到室温,使用赛

力特硅藻土过滤。将水加入到滤液中,再用乙酸乙酯萃取。在用硫酸钠干燥和减压浓缩之后,残留物然后通过硅胶柱层析来提纯(正己烷:乙酸乙酯=4:1)。在减压下将提纯产物浓缩至干燥,从而获得7.94g的黄色粉状的3(S)-[(3,4-二氯苯基)-噻唑-2-基氨基]吡咯烷-1-羧酸叔丁基酯。

[0771] $^1\text{H-NMR}(\text{CDCl}_3)$ δ ppm:

[0772] 1.43(9H, s), 1.83-2.03(1H, m), 2.11-2.35(1H, m), 3.18-3.42(3H, m), 3.73-3.87(1H, m), 4.97-5.09(1H, m), 6.53(1H, d, $J = 3.5\text{Hz}$), 7.14(1H, dd, $J = 2.5\text{Hz}$, $J = 8.5\text{Hz}$), 7.22(1H, brs), 7.39(1H, d, $J = 2.5\text{Hz}$), 7.56(1H, brd, $J = 8.5\text{Hz}$).

[0773] 参比实施例 13

[0774] 3(S)-[(3-氯-4-氟苯基)吡啶-3-基氨基]吡咯烷-1-羧酸叔丁基酯的合成

[0775] 向10mL的含有1.0g的3(S)-[(3-氯-4-氟苯基氨基)吡咯烷-1-羧酸叔丁基酯(3.2mmol)和0.75g的3-溴吡啶(4.75mmol)的甲苯溶液添加50mg的9,9-二甲基-4,5-双(二苯基膦基)氧杂蒽(XANTPHOS, 0.09mmol), 21.4mg的乙酸钯(0.10mmol)和11.6g的叔丁醇钠(120mmol)。将该混合物在回流下在氮气氛围中加热9小时。在冷却到室温之后,使用赛力特硅藻土过滤反应溶液。将水加入到滤液中,再用乙酸乙酯萃取。在用硫酸钠干燥和减压浓缩之后,然后通过硅胶柱层析法来提纯(正己烷:乙酸乙酯=1:1)残留物。在减压下浓缩该提纯产物,从而获得1.14g的浅黄色油状3(S)-[(3-氯-4-氟苯基)吡啶-3-基氨基]吡咯烷-1-羧酸叔丁基酯。

[0776] $^1\text{H-NMR}(\text{CDCl}_3)$ δ ppm:

[0777] 1.43(9H, s), 1.79-1.98(1H, m), 2.08-2.29(1H, m), 3.12-3.41(3H, m), 3.65-3.85(1H, m), 4.38-4.51(1H, m), 6.83-6.91(1H, m), 7.00-7.23(4H, m[包括7.04ppm(dd, $J = 2.7\text{Hz}$, $J = 6.4\text{Hz}$)]), 8.14(1H, s), 8.22(1H, d, $J = 4.4\text{Hz}$).

[0778] 参比实施例 14

[0779] 3(S)-[(3-氯-4-氟苯基)环己基氨基]吡咯烷-1-羧酸叔丁基酯的合成

[0780] 将3mL的含有0.60g的3(S)-[(3-氯-4-氟苯基)氨基]吡咯烷-1-羧酸叔丁基酯(1.9mmol)和0.56g的环己酮(5.7mmol)的乙酸溶液在室温下搅拌过夜。向该混合物添加1.21g的三乙酰氧基硼氢化钠(5.7mmol),之后在室温下搅拌8小时。将二氯甲烷加入到反应溶液中,反应溶液用水和饱和碳酸氢钠水溶液清洗,然后用硫酸镁干燥。用减压馏出溶剂,残留物通过硅胶柱层析(正己烷:乙酸乙酯=10:1)来提纯。在减压下从提纯产物中馏出溶剂,从而获得0.24g的无色油状3(S)-[(3-氯-4-氟苯基)环己基氨基]吡咯烷-1-羧酸叔丁基酯。

[0781] $^1\text{H-NMR}(\text{CDCl}_3)$ δ ppm:

[0782] 0.81-1.32(6H, m), 1.44(9H, s), 1.60-2.00(6H, m), 2.79-2.93(1H, m), 2.98-3.10(1H, m), 3.16-3.31(1H, m), 3.35-3.70(2H, m), 3.35-3.70(2H, m), 3.85-4.07(1H, m), 6.85-7.13(3H, m).

[0783] 参比实施例 15

[0784] 3(S)-[(4-羧基苯基)-(3-氯-4-氟苯基)氨基]吡咯烷-1-羧酸叔丁基酯的合成

[0785] 向含有1.7g的3(S)-[(3-氯-4-氟苯基)-(4-乙氧基羰基苯基)氨基]吡咯

烷-1-羧酸叔丁基酯 (3.7mmol) 的乙醇溶液添加 6mL 的 5N 氢氧化钠溶液,随后在室温下搅拌 15 小时。将二氯甲烷和乙酸加入到该反应溶液中,以使反应溶液呈酸性。用水洗三次和用饱和碳酸氢钠水溶液清洗一次后,在减压下馏出溶剂,从而获得 1.50g 的白色粉状的 3(S)-[(4-羧基苯基)-(3-氯-4-氟苯基)氨基]吡咯烷-1-羧酸叔丁基酯。

[0786] $^1\text{H-NMR}$ (DMSO-d_6) δ ppm :

[0787] 1.33(9H, s), 1.72-1.88(1H, m), 2.06-2.26(1H, m), 2.99-3.23(3H, m), 3.61(1H, dd, $J = 6.4\text{Hz}$, $J = 11.3\text{Hz}$), 4.53-4.69(1H, m), 6.57-6.65(2H, m), 7.19-7.28(1H, m), 7.46-7.58(2H, m), 7.68-7.78(2H, m), 12.3(1H, brs).

[0788] 参比实施例 16

[0789] 3(S)-[(3-氯-4-氟苯基)-(4-甲磺酰基苯基)氨基]吡咯烷-1-羧酸叔丁基酯的合成

[0790] 在 0°C 下向含有 0.45g 的 3(S)-[(3-氯-4-氟苯基)-(4-甲烷磺酰胺基苯基)氨基]吡咯烷-1-羧酸叔丁基酯 (1.0mmol) 的二氯甲烷溶液添加 0.54g 的间氯过苯甲酸 (3.1mmol),接着在 0°C 搅拌 2 小时。该反应溶液用水清洗,用硫酸镁干燥,并在减压下馏出溶剂。随后,残留物通过硅胶柱层析法提纯(正己烷:乙酸乙酯 = 5:1 $\rightarrow$ 1:1)。在减压下从提纯产物中馏出溶剂,从而获得 0.42g 的浅黄色油状 3(S)-[(3-氯-4-氟苯基)-(4-甲磺酰基苯基)氨基]吡咯烷-1-羧酸叔丁基酯。

[0791] $^1\text{H-NMR}$ (CDCl_3) δ ppm :

[0792] 1.43(9H, s), 1.80-1.91(1H, m), 2.11-2.29(1H, m), 3.01(3H, s), 3.16-3.40(3H, m), 3.70-3.86(1H, m), 4.49-4.61(1H, m), 6.62(2H, d, $J = 9.0\text{Hz}$), 7.03(1H, ddd, $J = 2.6\text{Hz}$, $J = 4.1\text{Hz}$, $J = 8.6\text{Hz}$), 7.01-7.06(1H, m), 7.19-7.23(1H, m), 7.24-7.31(1H, m), 7.66-7.74(2H, m).

[0793] 参比实施例 17

[0794] 3(S)-[(3-氯-4-氟苯基)-(6-氰基吡啶-2-基)氨基]吡咯烷-1-羧酸叔丁基酯的合成

[0795] 将 3(S)-[(6-溴吡啶-2-基)-(3-氯-4-氟苯基)氨基]吡咯烷-1-羧酸叔丁基酯 (500mg, 1.06mmol), 氰化锌 (250mg, 2.12mmol) 和四(三苯膦)钯 (122mg, 0.106mmol) 悬浮于 8mL 的二甲基甲酰胺 (DMF) 中,随后在氮气氛围中在 110°C 搅拌 9 小时。在冷却到室温之后,将乙酸乙酯和水加入到反应溶液中,以使该溶液分层。然后用水清洗有机层,用硫酸镁干燥。在减压下馏出溶剂,通过硅胶柱层析提纯残留物(正己烷:乙酸乙酯 = 6:1 $\rightarrow$ 3:1)。在减压下从提纯产物中馏出溶剂,从而获得 398mg 的无色油状 3(S)-[(3-氯-4-氟苯基)-(6-氰基吡啶-2-基)氨基]吡咯烷-1-羧酸叔丁基酯。

[0796] $^1\text{H-NMR}$ (CDCl_3) δ ppm :

[0797] 1.44(9H, s), 1.74-1.84(1H, m), 2.03-2.24(1H, m), 3.08-3.32(3H, m), 3.76-3.86(1H, m), 5.28-5.38(1H, m), 6.21(1H, d, $J = 8.7\text{Hz}$), 7.04-7.11(2H, m), 7.23-7.42(3H, m).

[0798] 参比实施例 18

[0799] 3(S)-{[(3-氯-4-氟苯基)-[5-(4-氟苯基)吡啶-2-基]氨基]吡咯烷-1-羧酸叔丁基酯的合成

[0800] 将 3(S)-[(5-溴吡啶-2-基)-(3-氯-4-氟苯基)氨基]吡咯烷-1-羧酸叔丁基酯 (300mg, 0.64mmol), 4-氟苯基硼酸 (98mg, 0.7mmol), 四(三苯膦)钯 (23mg, 0.02mmol) 和 2M 碳酸钠水溶液 (0.83mL) 加入到甲苯 (3mL) 中, 接着在氮气氛围中在 100℃ 搅拌 10 小时。在冷却到室温之后, 将乙酸乙酯和水加入到反应溶液中, 以使反应溶液分层。有机层用饱和盐水清洗, 后面用硫酸钠干燥。用减压馏出溶剂, 残留物通过硅胶柱层析 (正己烷: 乙酸乙酯 = 5:1) 来提纯。在减压下从提纯产物中馏出溶剂, 从而获得 255mg 的白色固体 3(S)-[(3-氯-4-氟苯基)-[5-(4-氟苯基)吡啶-2-基]氨基]吡咯烷-1-羧酸叔丁基酯。

[0801] $^1\text{H-NMR}(\text{CDCl}_3)$ δ ppm:

[0802] 1.44(9H, s), 1.78-1.89(1H, m), 2.05-2.23(1H, m), 3.07-3.31(3H, m), 3.85(1H, dd, $J = 7.1, 10.8\text{Hz}$), 5.31-5.42(1H, m), 6.08(1H, d, $J = 8.8\text{Hz}$), 7.06-7.14(3H, m), 7.20-7.28(2H, m), 7.41-7.50(3H, m), 8.37-8.41(1H, m).

[0803] 参比实施例 19

[0804] 3(S)-[(3-氯-4-氟苯基)-(4-噻吩-3-基苯基)氨基]吡咯烷-1-羧酸叔丁基酯的合成

[0805] 使用 3(S)-[(4-溴苯基)-(3-氯-4-氟苯基)氨基]吡咯烷-1-羧酸叔丁基酯和 3-噻吩硼酸, 按照与参比实施例 9 相同的方式合成 3(S)-[(3-氯-4-氟苯基)-(4-噻吩-3-基苯基)氨基]吡咯烷-1-羧酸叔丁基酯。

[0806] 油性无色物质

[0807] $^1\text{H-NMR}(\text{CDCl}_3)$ δ ppm:

[0808] 1.43(9H, s), 1.83-1.88(1H, m), 2.05-2.20(1H, m), 3.18-3.31(3H, m), 3.63-3.84(1H, m), 4.40-4.51(1H, m), 6.71-6.80(1H, m), 6.85-6.88(2H, m), 6.94(1H, dd, $J = 2.8\text{Hz}$, $J = 6.4\text{Hz}$), 7.05-7.10(1H, m), 7.30-7.45(3H, m), 7.50-7.55(2H, m).

[0809] 参比实施例 20

[0810] (S)-[(3-氯-4-氟苯基)-[6-(4-甲基哌嗪-1-基)吡啶-2-基]氨基]吡咯烷-1-羧酸叔丁基酯的合成

[0811] 将 3(S)-[(6-溴吡啶-2-基)-(3-氯-4-氟苯基)氨基]吡咯烷-1-羧酸叔丁基酯 (200mg, 0.43mmol), 1-甲基哌嗪 (0.61mL, 0.55mmol), 9,9-二甲基-4,5-双(二苯基膦基)氧杂蒽 (XANTPHOS, 12mg, 0.02mmol), 三(二苄叉基丙酮)二钯 (9mg, 0.01mmol) 和叔丁醇钠 (61mg, 0.63mmol) 加入到甲苯 (5mL) 中, 接着在氮气氛围中在 100℃ 搅拌 8 小时。通过过滤除去不溶物质, 所形成的滤液在减压下浓缩。残留物通过硅胶柱硅胶柱层析法 (正己烷: 乙酸乙酯 = 4:1) 提纯。在减压下从提纯产物中馏出溶剂, 从而获得 102mg 的无色油状 (S)-[(3-氯-4-氟苯基)-[6-(4-甲基哌嗪-1-基)吡啶-2-基]氨基]吡咯烷-1-羧酸叔丁基酯。

[0812] $^1\text{H-NMR}(\text{CDCl}_3)$ δ ppm:

[0813] 1.44(9H, s), 1.74-1.89(1H, m), 2.03-2.21(1H, m), 2.36(3H, s), 2.51-2.55(4H, m), 3.08-3.31(3H, m), 3.54(4H, brs), 3.64-3.90(1H, m), 5.10-5.23(1H, m), 5.32(1H, d, $J = 8.1\text{Hz}$), 6.01(1H, d, $J = 8.1\text{Hz}$), 7.03-7.08(1H, m), 7.19-7.25(3H, m).

[0814] 参比实施例 21

[0815] 3(S)-[(3-氯-4-氟苯基)-(4-哌啶-1-基苯基)氨基]吡咯烷-1-羧酸叔丁基酯的合成

[0816] 使用 3(S)-[(4-溴苯基)-(3-氯-4-氟苯基)氨基]吡咯烷-1-羧酸叔丁基酯和哌啶,按照与参比实施例 11 相同的方式合成 3(S)-[(3-氯-4-氟苯基)-(4-哌啶-1-基苯基)氨基]吡咯烷-1-羧酸叔丁基酯。

[0817] 油性无色物质

[0818] $^1\text{H-NMR}(\text{CDCl}_3)$ δ ppm :

[0819] 1.43(9H, s), 1.55-1.62(2H, m), 1.68-1.73(4H, m), 1.74-1.90(1H, m), 2.02-2.18(1H, m), 3.16-3.29(7H, m), 3.61-3.81(1H, m), 4.23-4.38(1H, m), 6.40-6.46(1H, m), 6.59-6.62(1H, m), 6.86-6.92(5H, m).

[0820] 参比实施例 22

[0821] 3(S)-[(3-氯-4-氰基苯基)-(3-氯-4-氟苯基)氨基]吡咯烷-1-羧酸叔丁基酯的合成

[0822] 使用注射器,向含有 3(S)-[(3-氯-4-氟苯基)氨基]吡咯烷-1-羧酸叔丁基酯(0.50g, 1.6mmol)和 2-氯-4-氟苄腈(0.30g, 1.9mmol)的无水甲苯溶液添加含有双(三甲基甲硅烷基)氨基钠(1.1M)的 1.45mL 四氢呋喃溶液。将该混合物在回流下在氮气氛围中加热 8 小时,再冷却到室温。将水加入到反应溶液中,再用二乙醚萃取。在用硫酸钠干燥和减压浓缩之后,残留物通过硅胶柱层析来提纯(正己烷:乙酸乙酯=4:1)。将该提纯产物在减压下浓缩至干燥,从而获得 0.56g 的白色无定形固体 3(S)-[(3-氯-4-氰基苯基)-(3-氯-4-氟苯基)氨基]吡咯烷-1-羧酸叔丁基酯。

[0823] $^1\text{H-NMR}(\text{CDCl}_3)$ δ ppm :

[0824] 1.43(9H, s), 1.76-1.93(1H, m), 2.11-2.27(1H, m), 3.15-3.39(3H, m), 3.66-3.87(1H, m), 4.39-4.55(1H, m), 6.42(1H, dd, $J = 2.5\text{Hz}$, $J = 9.0\text{Hz}$), 6.57(1H, d, $J = 2.5\text{Hz}$), 6.98-7.04(1H, m), 7.20(1H, dd, $J = 2.5\text{Hz}$, $J = 6.5\text{Hz}$), 7.23-7.32(1H, m), 7.40(1H, d, $J = 8.5\text{Hz}$).

[0825] 参比实施例 23

[0826] 2-(4-氯丁氧基)吡啶的合成

[0827] 向含有 2-吡啶酚(10g, 105mmol)和 1-溴-4-氯丁烷(36mL, 315mmol)的 DMF 溶液(110mL)添加碳酸钾(16g, 116mmol),随后在室温下搅拌 8 小时。将水(300mL)加入到该反应溶液中,然后用乙酸乙酯(300mL)萃取。有机层用水(300mL)洗两次,再用硫酸镁干燥。用减压馏出溶剂,残留物然后通过硅胶柱层析(正己烷:乙酸乙酯=5:1)来提纯。该提纯产物在减压下浓缩,从而获得 3.32g 的无色油状 2-(4-氯丁氧基)吡啶。

[0828] 参比实施例 24

[0829] 3(S)-[4-(吡啶-2-基氧基)丁基氨基]吡咯烷-1-羧酸叔丁基酯的合成

[0830] 将 3(S)-氨基吡咯烷-1-羧酸叔丁基酯(0.93g, 5.0mmol), 2-(4-氯丁氧基)吡啶(0.93g, 5.0mmol), 碳酸钾(0.83g, 6.0mmol)和碘化钠(0.83g, 5.5mmol)悬浮于乙腈(20mL)中,并回流加热为 24 小时。在冷却到室温之后,将水(50mL)加入到反应溶液中,再用乙酸乙酯(50mL)萃取。然后用水清洗有机层两次,用硫酸镁干燥。用减压馏出溶剂,残留物然后通过硅胶柱层析法(正己烷:乙酸乙酯=3:1)来提纯。该提纯产物在减压下浓缩,从而获

得 372mg 的无色油状 3(S)-[4-(吡啶-2-基氧基)丁基氨基]吡咯烷-1-羧酸叔丁基酯。

[0831] $^1\text{H-NMR}(\text{CDCl}_3)$ δ ppm :

[0832] 1.46 (9H, s), 1.5-1.9 (6H, m), 1.95-2.15 (1H, m), 2.68 (2H, t, $J = 7\text{Hz}$), 2.95-3.15 (1H, m), 3.25-3.65 (4H, m), 4.30 (2H, t, $J = 6.5\text{Hz}$), 6.71 (1H, d, $J = 8.5\text{Hz}$), 6.85 (1H, dd, $J = 5.5\text{Hz}$, $J = 6.5\text{Hz}$), 7.5-7.65 (1H, m), 8.14 (1H, dd, $J = 2\text{Hz}$, $J = 5\text{Hz}$).

[0833] 参比实施例 25

[0834] 3(S)-[(3-氯-4-氟苯基)-(3-氯丙基)氨基]吡咯烷-1-羧酸叔丁基酯的合成

[0835] 将 3(S)-[(3-氯-4-氟苯基)氨基]吡咯烷-1-羧酸叔丁基酯 (3g, 9.5mmol), 1-溴-3-氯丙烷 (4.7mL, 48mmol) 和碳酸钾 (1.97g, 14.3mmol) 悬浮于 N-甲基吡咯烷酮 (NMP, 15mL), 随后在 100℃ 搅拌 8 小时。在冷却到室温之后, 将水加入到反应溶液中, 再用乙酸乙酯萃取。用硫酸钠干燥有机层, 之后, 在减压下馏出溶剂。残留物通过硅胶柱层析法 (正己烷:乙酸乙酯 = 3:1) 提纯, 该提纯产物在减压下浓缩, 从而获得 1.0g 的无色油状 3(S)-[(3-氯-4-氟苯基)-(3-氯丙基)氨基]吡咯烷-1-羧酸叔丁基酯。

[0836] $^1\text{H-NMR}(\text{CDCl}_3)$ δ ppm :

[0837] 1.46 (9H, s), 1.7-2.1 (4H, m), 3.1-3.35 (4H, m), 3.35-3.7 (4H, m), 3.8-4.1 (1H, m), 6.7-6.9 (1H, m), 6.9-7.1 (2H, m).

[0838] 参比实施例 26

[0839] 3(S)-[(3-氯-4-氟苯基)-(3-二甲基氨基丙基)氨基]吡咯烷-1-羧酸叔丁基酯的合成

[0840] 将 3(S)-[(3-氯-4-氟苯基)-(3-氯丙基)氨基]吡咯烷-1-羧酸叔丁基酯 (0.5g, 1.24mmol), 50% 二甲胺溶液 (1mL) 和碘化钠 (0.37g, 2.5mmol) 悬浮于 DMF (3mL), 随后在 60℃ 搅拌 4 小时。在冷却到室温之后, 将水加入到反应溶液中, 再用乙酸乙酯萃取。用硫酸钠干燥有机层, 然后在减压下馏出溶剂。残留物与碱性硅胶柱层析法 (乙酸乙酯) 提纯, 该提纯产物然后在减压下浓缩, 从而获得 0.36g 的无色油状 3(S)-[(3-氯-4-氟苯基)-(3-二甲基氨基丙基)氨基]吡咯烷-1-羧酸叔丁基酯。

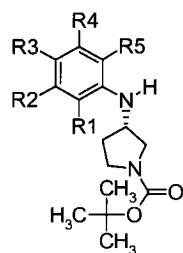
[0841] $^1\text{H-NMR}(\text{CDCl}_3)$ δ ppm :

[0842] 1.46 (9H, s), 1.5-1.75 (4H, m), 1.75-2.1 (2H, m), 2.19 (6H, s), 3.0-3.3 (4H, m), 3.3-3.75 (2H, m), 3.8-4.2 (1H, m), 6.6-6.8 (1H, m), 6.8-7.1 (2H, m).

[0843] 按照上述参比实施例同样的方法制备以下所示的化合物。

[0844] 表 1

[0845]

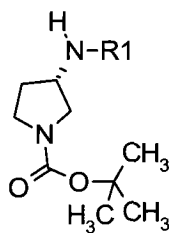


[0846]

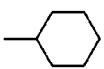
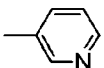
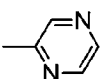
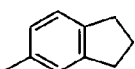
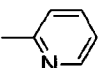
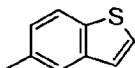
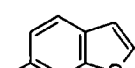
参比实 施例	R1	R2	R3	R4	R5	NMR
27	-H	-H	-H	-H	-H	¹ H-NMR (CDCl ₃) δppm 1.46 (9H, s), 1.85-1.95 (1H, m), 2.15-2.23 (1H, m), 3.18-3.26 (1H, m), 3.39-3.51 (2H, m), 3.62-3.75 (2H, m), 4.00-4.05 (1H, m), 6.60 (2H, d, J=7.8Hz), 6.69-6.73 (1H, m), 7.15-7.20 (2H, m).
28	-H	-H	-OCH ₃	-H	-H	¹ H-NMR (CDCl ₃) δppm 1.46 (9H, s), 1.79-1.88 (1H, m), 2.10-2.22 (1H, m), 3.12-3.25 (1H, m), 3.30-3.52 (3H, m), 3.60-3.75 (4H, m), 3.88-4.00 (1H, m), 6.50-6.58 (2H, m), 6.72-6.80 (2H, m).
29	-H	-H	-CH ₃	-H	-H	¹ H-NMR (CDCl ₃) δppm 1.46 (9H, s), 1.80-1.92 (1H, m), 2.10-2.22 (1H, m), 2.24 (3H, s), 3.15-3.23 (1H, m), 3.35-3.75 (4H, m), 3.95-4.05 (1H, m), 6.51-6.55 (2H, m), 6.95-7.05 (2H, m).
30	-H	-H	-OCH ₃	-Cl	-H	¹ H-NMR (CDCl ₃) δppm 1.47 (9H, s), 1.80-1.90 (1H, m), 2.10-2.20 (1H, m), 3.10-3.25 (1H, m), 3.38-3.75 (3H, m), 3.83 (3H, s), 3.92-3.96 (1H, m), 6.47 (1H, dd, J=2.8, 8.8Hz), 6.67 (1H, d, J=2.8Hz), 6.81 (1H, d, J=8.8Hz).
31	-H	-H	-F	-H	-H	¹ H-NMR (CDCl ₃) δppm 1.46 (9H, s), 1.75-1.82 (1H, m), 2.00-2.24 (1H, m), 3.03-3.79 (5H, m), 3.80-4.05 (1H, m), 6.51-6.57 (2H, m), 6.90 (2H, dd, J=8.5Hz, 8.5Hz).
32	-H	-H	-H	-F	-H	¹ H-NMR (CDCl ₃) δppm 1.47 (9H, s), 1.80-1.99 (1H, m), 2.10-2.26 (1H, m), 3.11-3.35 (1H, m), 3.38-3.57 (2H, m), 3.61-3.77 (1H, m), 3.79-3.91 (1H, m), 3.94-4.08 (1H, m), 6.29 (1H, dt, J=2.3Hz and 11.4Hz), 6.33-6.39 (1H, m), 6.40-6.47 (1H, m), 7.04-7.16 (1H, m).
33	-H	-H	-F	-Cl	-H	¹ H-NMR (CDCl ₃) δppm 1.47 (9H, s), 1.78-1.96 (1H, m), 2.10-2.28 (1H, m), 2.10-2.28 (1H, m), 3.11-3.30 (1H, m), 3.30-3.56 (2H, m), 3.57-3.79 (2H, m), 3.85-4.03 (1H, m), 6.38-6.47 (1H, m), 6.60 (1H, dd, J=6.0Hz and 2.9Hz), 6.90-7.00 (1H, m).
34	-H	-H	-F	-CH ₃	-H	¹ H-NMR (CDCl ₃) δppm 1.46 (9H, s), 1.7-1.9 (1H, m), 2.1-2.2 (1H, m), 2.21 (3H, s), 3.1-3.3 (1H, m), 3.3-3.8 (4H, m), 3.8-4.1 (1H, m), 6.3-6.5 (2H, m), 6.83 (1H, dd, J = 8.9 Hz, J = 8.9 Hz).
35	-H	-H	-H	-CN	-H	¹ H-NMR (CDCl ₃) δppm 1.46 (9H, s), 1.8-2.0 (1H, m), 2.1-2.3 (1H, m), 3.1-3.6 (3H, m), 3.6-3.8 (1H, m), 3.9-4.1 (2H, m), 6.7-6.9 (2H, m), 6.99 (1H, d, J = 7.6 Hz), 7.23 (1H, dd, J = 7.6 Hz, J = 8.4 Hz).
36	-H	-H	-F	-CF ₃	-H	¹ H-NMR (CDCl ₃) δppm 1.47 (9H, s), 1.76-1.96 (1H, m), 2.11-2.27 (1H, m), 3.13-3.32 (1H, m), 3.37-3.53 (2H, m), 3.61-3.84 (2H, m), 3.92-4.06 (1H, m), 6.66-6.76 (2H, m), 7.02 (1H, dd, J=9.5Hz, 9.5Hz).
37	-H	-H	-Cl	-Cl	-H	¹ H-NMR (CDCl ₃) δppm 1.47 (9H, s), 1.80-1.92 (1H, brs), 2.11-2.26 (1H, m), 3.15-3.30 (1H, m), 3.40-3.55 (2H, m), 3.60-3.75 (1H, m), 3.79-3.89 (1H, m), 3.91-4.04 (1H, m), 6.42 (1H, dd, J=2.7Hz and 8.7Hz), 6.66 (1H, d, J=2.7Hz), 7.19 (1H, d, J=8.6Hz).

[0847] 表 2

[0848]

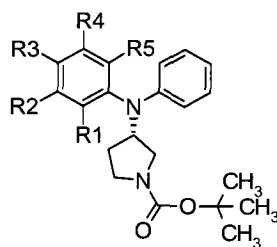


[0849]

Ref. Ex. No.	R1	NMR
38		¹ H-NMR (CDCl ₃) δppm 1.20-1.30 (2H, m), 1.46 (9H, s), 1.50-1.70 (5H, m), 1.80-1.92 (2H, m), 2.05-2.12 (1H, m), 2.92-3.05 (1H, m), 3.06-3.15 (1H, m), 3.25-3.65 (4H, m).
39		¹ H-NMR (CDCl ₃) δppm 1.00-1.30 (5H, m), 1.46 (9H, s), 1.47-1.96 (6H, m), 2.00-2.10 (1H, m), 2.40-2.50 (1H, m), 2.91-3.02 (1H, m), 3.25-3.35 (1H, m), 3.38-3.65 (3H, m).
40		¹ H-NMR (CDCl ₃) δppm 1.47 (9H, s), 1.8-2.0 (1H, m), 2.1-2.3 (1H, m), 3.1-3.3 (1H, m), 3.4-3.6 (2H, m), 3.6-3.8 (2H, m), 3.9-4.1 (1H, m), 6.88 (1H, d, J = 8.3 Hz), 7.0-7.2 (1H, m), 6.8-7.1 (2H, m), 7.9-8.0 (1H, m), 8.03 (1H, s)
41		¹ H-NMR (CDCl ₃) δppm 1.47 (9H, s), 1.82-2.00 (1H, m), 2.18-2.32 (1H, m), 3.14-3.37 (1H, m), 3.39-3.56 (2H, m), 3.73 (1H, dd, J=6.0Hz, 11.5Hz), 4.37-4.52 (1H, m), 4.59-4.71 (1H, m), 7.84 (1H, d, J=2.5Hz), 7.90 (1H, d, J=1.0Hz), 8.00 (1H, brs).
42		¹ H-NMR (CDCl ₃) δppm 1.46 (9H, s), 1.79-1.95 (1H, m), 1.97-2.24 (3H, m), 2.82 (4H, dd, J=7.5Hz, 14.5Hz), 3.13-3.29 (1H, m), 3.36-3.81 (4H, m), 3.95-4.08 (1H, m), 6.42 (1H, dd, J=2.0Hz, 8.0Hz), 6.52 (1H, brs), 7.04 (1H, d, J=8.0Hz).
43		¹ H-NMR (CDCl ₃) δppm 1.46 (9H, s), 1.73-2.01 (1H, m), 2.15-2.31 (1H, m), 3.12-3.35 (1H, m), 3.38-3.59 (2H, m), 3.65-3.79 (1H, m), 4.27-4.42 (1H, m), 4.48-4.65 (1H, m), 6.35-6.42 (1H, m), 6.56-6.64 (1H, m), 7.38-7.46 (1H, m), 8.04-8.15 (2H, m)
44		¹ H-NMR (CDCl ₃) δppm 1.46 (9H, s), 1.55-1.71 (1H, m), 1.74-2.01 (1H, m), 2.16-2.29 (1H, m), 3.19-3.36 (1H, m), 3.40-3.59 (1H, m), 3.63-3.85 (2H, m), 4.01-4.19 (1H, m), 6.71 (1H, dd, J=2.2Hz and 8.6Hz), 6.99 (1H, d, J=2.2Hz), 7.13-7.21 (1H, m), 7.35-7.43 (1H, m), 7.59-7.68 (1H, m)
45		¹ H-NMR (CDCl ₃) δppm 1.46 (9H, s), 1.88-2.01 (1H, m), 2.19-2.29 (1H, m), 3.20-3.36 (1H, m), 3.41-3.59 (2H, m), 3.68-3.90 (2H, m), 4.03-4.18 (1H, m), 6.69 (1H, dd, J=2.1Hz and 8.6Hz), 7.03 (1H, d, J=2.0Hz), 7.11 (1H, d, J=5.2Hz), 7.17 (1H, d, J=5.3Hz), 7.59 (1H, d, J=8.4Hz)

[0850] 表 3

[0851]



[0852]

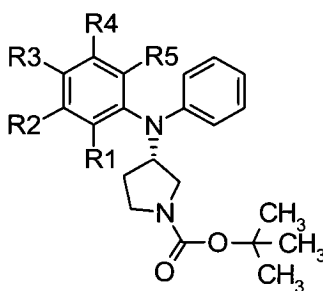
参比实例	R1	R2	R3	R4	R5	NMR
46	-H	-H	-Cl	-Cl	-H	¹ H-NMR (CDCl ₃) δppm 1.42 (9H, s), 1.73-1.93 (1H, m), 2.05-2.23 (1H, m), 3.10-3.36 (3H, m), 3.61-3.83 (1H, m), 4.33-4.50 (1H, m), 6.48 (1H, dd, J=2.9Hz and J=10.3Hz), 6.74

[0853]

47	-H	-H	-SCH ₃	-H	-H	(1H, d, J=2.8Hz), 6.96-7.07 (2H, m), 7.16-7.34 (2H, m), 7.35-7.46 (2H, m). ¹ H-NMR (CDCl ₃) δppm 1.42 (9H, s), 1.75-1.92 (1H, m), 2.00-2.20 (1H, m), 2.46 (3H, s), 3.09-3.33 (3H, m), 3.62-3.83 (1H, m), 4.38-4.55 (1H, m), 6.77-6.88 (4H, m), 6.97-7.08 (1H, m), 7.18-7.33 (4H, m)
48	-H	-H	-Cl	-H	-H	¹ H-NMR (CDCl ₃) δppm 1.42 (9H, s), 1.78-1.87 (1H, m), 2.05-2.16 (1H, m), 3.13-3.27 (3H, m), 3.68-3.79 (1H, m), 4.39-4.45 (1H, m), 6.68-6.75 (2H, m), 6.90 (2H, d, J=7.7Hz), 7.05-7.15 (1H, m), 7.16-7.25 (2H, m), 7.30-7.40 (2H, m).
49	-H	-H	-H	-Cl	-Cl	¹ H-NMR (CDCl ₃) δppm 1.36-1.49 (9H, m), 1.80-1.98 (1H, m), 2.03-2.29 (1H, m), 3.19-3.41 (3H, m), 3.64-3.89 (1H, m), 4.44-4.59 (1H, m), 6.52 (2H, d, J=8.2Hz), 6.74-6.85 (1H, m), 7.12-7.33 (4H, m), 7.46-7.52 (1H, m)
50	-H	-H	-OCF ₃	-H	-H	¹ H-NMR (CDCl ₃) δppm 1.42 (9H, s), 1.76-1.91 (1H, m), 2.02-2.21 (1H, m), 3.08-3.86 (4H, m), 4.38-4.53 (1H, m), 6.76 (2H, d, J=9.0Hz), 6.90-6.96 (2H, m), 7.03-7.22 (3H, m), 7.29-7.40 (2H, m)
51	-H	-H	-CO ₂ CH ₃	-H	-H	¹ H-NMR (CDCl ₃) δppm 1.42 (9H, s), 1.73-1.92 (1H, m), 2.08-2.28 (1H, m), 3.12-3.34 (3H, m), 3.69-3.88 (4H, m with s at Φ3.84), 4.49-4.65 (1H, m), 6.50-6.59 (2H, m), 7.08-7.16 (2H, m), 7.31-7.51 (3H, m), 7.82 (2H, d, J=6.1Hz)
52	-H	-Cl	-H	-Cl	-H	¹ H-NMR (CDCl ₃) δppm 1.42 (9H, s), 1.73-1.89 (1H, m), 2.02-2.21 (1H, m), 3.09-3.33 (3H, m), 3.62-3.85 (1H, m), 4.35-4.45 (1H, m), 6.42 (2H, d, J=1.6Hz), 6.74 (1H, s), 7.02-7.11 (2H, m), 7.30-7.50 (3H, m)
53	-H	-H	-NO ₂	-H	-H	¹ H-NMR (CDCl ₃) δppm 1.42 (9H, s), 1.78-1.95 (1H, m), 2.09-2.28 (1H, m), 3.10-3.38 (3H, m), 3.71-3.92 (1H, m), 4.52-4.69 (1H, m), 6.48-6.55 (2H, m), 7.08-7.18 (2H, m), 7.39-7.58 (3H, m), 8.04 (2H, d, J=8.1Hz)
54	-H	-H	-CH ₃	-H	-H	¹ H-NMR (CDCl ₃) δppm 1.42 (9H, s), 1.80-1.88 (1H, m), 2.00-2.15 (1H, m), 2.34 (3H, s), 3.18-3.25 (3H, m), 3.65-3.80 (1H, m), 4.40-4.50 (1H, m), 6.73 (2H, d, J=8.1Hz), 6.85-6.90 (3H, m), 7.10-7.26 (4H, m).
55	-H	-H	-CHO	-H	-H	¹ H-NMR (CDCl ₃) δppm 1.42 (9H, s), 1.80-1.88 (1H, m), 2.10-2.20 (1H, m), 3.15-3.30 (3H, m), 3.70-3.85 (1H, m), 4.55-4.65 (1H, m), 6.59 (2H, d, J=8.4Hz), 7.10-7.15 (2H, m), 7.40-7.60 (3H, m), 7.60-7.70 (2H, m), 9.75 (1H, s).
56	-H	-H	-Br	-H	-H	¹ H-NMR (CDCl ₃) δppm 1.41 (9H, s), 1.80-1.88 (1H, m), 2.05-2.20 (1H, m), 3.15-3.30 (3H, m), 3.65-3.75 (1H, m), 4.38-4.46 (1H, m), 6.65 (2H, d, J=8.9Hz), 6.94 (2H, d, J=8.5Hz), 7.10-7.40 (5H, m).
57	-H	-H	-OCH ₃	-Cl	-H	¹ H-NMR (CDCl ₃) δppm 1.43 (9H, s), 1.80-1.88 (1H, m), 2.05-2.15 (1H, m), 3.15-3.30 (3H, m), 3.65-3.80 (1H, m), 3.90 (3H, s), 4.38-4.44 (1H, m), 6.65-6.70 (2H, m), 6.82-6.90 (3H, m), 7.07 (1H, s), 7.15-7.25 (2H, m).

[0854] 表 4

[0855]



[0856]

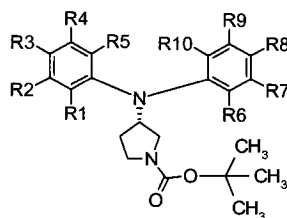
参比实 施例	R1	R2	R3	R4	R5	NMR
58	-H	-H	-OCH ₃	-H	-H	¹ H-NMR (CDCl ₃) δppm 1.42 (9H, s), 1.80-1.86 (1H, m), 2.00-2.12 (1H, m), 3.15-3.26 (3H, m), 3.65-3.78 (1H, m), 3.82 (3H, s), 4.40-4.50 (1H, m), 6.63 (2H, d, J=7.6Hz), 6.75-6.80 (1H, m), 6.86-6.95 (2H, m), 7.00 (2H, d, J=7.6Hz), 7.10-7.20 (2H, m).

[0857]

59	-H	-H	-OC ₂ H ₅	-Cl	-H	¹ H-NMR (CDCl ₃) δppm 1.43 (9H, s), 1.47 (3H, t, J=7.0Hz), 1.75-1.92 (1H, m), 2.01-2.21 (1H, m), 3.11-3.36 (3H, m), 3.64-3.83 (1H, m), 4.10 (2H, q, J=7.0Hz), 4.36-4.51 (1H, m), 6.67-6.74 (2H, m), 6.83-6.93 (3H, m), 7.04-7.08 (2H, m), 7.14-7.27 (2H, m)...
60	-H	-H	-OC ₃ H ₇	-Cl	-H	¹ H-NMR (CDCl ₃) δppm 1.08 (3H, t, J=7.4Hz), 1.43 (9H, s), 1.79-1.95 (1H, m), 1.96-2.20 (1H, m), 3.15-3.38 (3H, m), 3.60-3.85 (1H, m), 3.98 (2H, t, J=6.5Hz), 4.37-4.51 (1H, m), 6.66-6.73 (2H, m), 6.81-6.93 (3H, m), 7.03-7.09 (1H, m), 7.14-7.28 (2H, m)
61	-H	-H	-F	-CH ₃	-H	¹ H-NMR (CDCl ₃) δppm 1.43 (9H, s), 1.7-1.9 (1H, m), 2.0-2.2 (1H, m), 2.24 (3H, s), 3.1-3.4 (3H, m), 3.6-3.8 (1H, m), 4.4-4.6 (1H, m), 6.69 (2H, d, J = 7.9 Hz), 6.7-7.1 (4H, m), 7.1-7.3 (2H, m)
62	-H	-OCH ₃	-F	-F	-H	¹ H-NMR (CDCl ₃) δppm 1.43 (9H, s), 1.7-1.9 (1H, m), 2.0-2.2 (1H, m), 3.1-3.4 (3H, m), 3.6-3.8 (1H, m), 3.76 (3H, s), 4.3-4.5 (1H, m), 6.0-6.3 (2H, m), 6.92 (2H, d, J = 7.5 Hz), 7.0-7.2 (1H, m), 7.2-7.4 (2H, m)
63	-H	-H	-F	-H	-H	¹ H-NMR (CDCl ₃) δppm 1.42 (9H, s), 1.75-1.92 (1H, m), 2.00-2.24 (1H, m), 3.10-3.32 (3H, m), 3.61-3.83 (1H, m), 4.41-4.53 (1H, m), 6.72(2H,d, J=8.2Hz), 6.85-7.10 (5H, m), 7.16-7.28 (2H, m)
64	-H	-H	-H	-H	-Cl	¹ H-NMR (CDCl ₃) δppm 1.30-1.50 (total 9H, m with two ss at δ1.41 and 1.44), 1.79-1.96 (1H, m), 2.06-2.32 (1H, m), 3.12-3.41 (3H, m), 3.64-3.91 (1H, m), 4.41-4.60 (1H, m), 6.52(2H, d, J=8.2Hz), 6.70-6.81 (1H, m), 7.21-7.41 (5H, m), 7.47-7.58 (1H, m)
65	-H	-H	-H	-Cl	-H	¹ H-NMR (CDCl ₃) δppm 1.43 (9H, s), 1.78-1.88 (1H, m), 2.07-2.20 (1H, m), 3.15-3.31 (3H, m), 3.65-3.74 (1H, m), 4.40-4.51 (1H, m), 6.55 (2H,dd, J=1.2Hz and 4.8Hz), 6.67 (1H, t, J=1.2Hz), 6.80-6.85 (1H, m), 6.98-7.03 (1H, m), 7.07-7.14 (1H, m), 7.21-7.28 (1H, m), 7.34-7.43 (1H, m)

[0858] 表 5

[0859]



[0860]

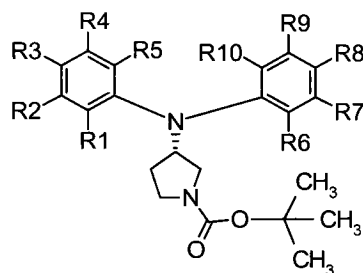
参比实例	R1	R2	R3	R4	R5	R6	R7	R8	R9	R10	NMR
66	-H	-H	-Cl	-Cl	-H	-H	-H	-F	-H	-H	¹ H-NMR (CDCl ₃) δppm 1.43 (9H, s), 1.73-1.91 (1H, m), 2.01-2.21 (1H, m), 3.09-3.38 (3H, m), 3.60-3.82 (1H, m), 4.29-4.48 (1H, m), 6.41 (1H, dd, J=2.9Hz and J=8.9Hz), 6.67 (1H, d, J=2.8Hz), 6.90-7.22 (5H, m)
67	-H	-H	-Cl	-Cl	-H	-F	-H	-H	-H	-H	¹ H-NMR (CDCl ₃) δppm 1.42 (9H, s), 1.73-1.92 (1H, m), 2.05-2.28 (1H, m), 3.12-3.35 (3H, m), 3.63-3.86 (1H, m), 4.35-4.51 (1H, m), 6.39 (1H, dd, J=2.9Hz and 9.0Hz), 6.66 (1H, d, J=2.7Hz), 7.08-7.28 (4H, m), 7.31-7.45 (1H, m)
68	-H	-H	-H	-F	-H	-H	-H	-Cl	-H	-H	¹ H-NMR (CDCl ₃) δppm 1.43 (9H, s), 1.74-1.91 (1H, m), 2.02-2.21 (1H, m), 3.10-3.35 (3H, m), 3.62-3.82 (1H, m), 4.39-4.51 (1H, m), 6.39 (1H, dt, J=1.4Hz and J=11.7Hz), 6.47 (1H, d, J=8.3Hz), 6.55-6.65 (1H, m), 6.89-6.98 (2H, m), 7.09-7.21 (1H, m), 7.29-7.38 (2H, m)
69	-H	-H	-H	-F	-H	-H	-H	-F	-H	-H	¹ H-NMR (CDCl ₃) δppm 1.43 (9H, s), 1.74-1.92 (1H, m), 2.06-2.29 (1H, m), 3.08-3.89 (4H, m), 4.35-4.51 (1H, m), 6.27 (1H, dt, J=2.3Hz and J=12.3Hz), 6.35 (1H, d, J=7.0Hz), 6.41-6.53 (1H, m), 7.01-7.21 (5H, m)

[0861]

70	-H -H -H -F	-H -H -H	-SCH ₃ -H -H	¹ H-NMR (CDCl ₃) δppm 1.43 (9H, s), 1.75-1.91 (1H, m), 2.01-2.21 (1H, m), 2.50 (1H, s), 3.11-3.32 (3H, m), 3.63-3.83 (1H, m), 4.38-4.51 (1H, m), 6.34 (1H, dt, J=2.3Hz and J=12.1Hz), 6.42 (1H, d, J=8.4Hz), 6.48-6.58 (1H, m), 6.92-7.01 (2H, m), 7.05-7.18 (1H, m), 7.22-7.31 (2H, m)
71	-H -H -F -H	-H -H -H	-Cl -H -H	¹ H-NMR (CDCl ₃) δppm 1.42 (9H, s), 1.75-1.92 (1H, m), 2.01-2.20 (1H, m), 3.10-3.33 (3H, m), 3.61-3.81 (1H, m), 4.32-4.99 (1H, m), 6.61 (2H, d, J=8.8Hz), 6.94-7.19 (6H, m)
72	-H -H -F -H	-H -H -H	-F -H -H	¹ H-NMR (CDCl ₃) δppm 1.42 (9H, s), 1.80-1.88 (1H, m), 2.00-2.15 (1H, m), 3.10-3.30 (3H, m), 3.60-3.75 (1H, m), 4.30-4.38 (1H, m), 6.75-6.85 (4H, m), 6.90-7.00 (4H, m)
73	-H -H -H -F	-H -H -F	-H -H -H	¹ H-NMR (CDCl ₃) δppm 1.43 (9H, s), 1.78-1.95 (1H, m), 2.02-2.26 (1H, m), 3.12-3.39 (3H, m), 3.65-3.83 (1H, m), 4.35-4.51 (1H, m), 6.61 (2H, dt, J=2.1Hz and J=11.0Hz), 6.61-6.68 (2H, m), 6.77 (2H, t, J=8.0Hz), 7.18-7.31 (2H, m)
74	-H -H -F -Cl	-H -H -F	-H -H -H	¹ H-NMR (CDCl ₃) δppm 1.43 (9H, s), 1.75-1.92 (1H, m), 2.02-2.35 (1H, m), 3.12-3.38 (3H, m), 3.63-3.85 (1H, m), 4.35-4.50 (1H, m), 6.38 (1H, dt, J=2.3Hz and 11.7Hz), 6.90 (1H, ddd, J=4.2Hz, J=4.2Hz and J=8.8Hz), 7.08 (1H, dd, J=2.6Hz and J=6.5Hz), 7.11-7.22 (1H, m)
75	-H -H -F -CH ₃ -H -H -CH ₃ -F	-H -H -H	-H -H -H	¹ H-NMR (CDCl ₃) δppm 1.43 (9H, s), 1.8-2.0 (1H, m), 2.0-2.2 (1H, m), 2.21 (6H, s), 3.1-3.4 (3H, m), 3.6-3.8 (1H, m), 4.3-4.5 (1H, m), 6.6-6.7 (4H, m), 6.8-7.0 (2H, m)
76	-H -H -F -CH ₃ -H -H -F	-H -H -H	-H -H -H	¹ H-NMR (CDCl ₃) δppm 1.43 (9H, s), 1.7-1.9 (1H, m), 2.0-2.2 (1H, m), 2.27 (3H, s), 3.1-3.4 (3H, m), 3.6-3.8 (1H, m), 4.3-4.5 (1H, m), 6.26 (1H, d, J=12.4 Hz), 6.3-6.5 (2H, m), 6.8-7.2 (4H, m)

[0862] 表 6

[0863]



[0864]

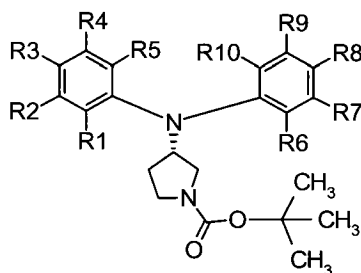
参比实 施例	R1	R2	R3	R4	R5	R6	R7	R8	R9	R10	NMR
77	-H	-H	-F	-Cl	-H	-H	-CH ₃	-H	-H	-H	¹ H-NMR (CDCl ₃) δppm 1.43 (9H, s), 1.7-1.9 (1H, m), 2.0-2.2 (1H, m), 2.40 (3H, s), 3.1-3.4 (3H, m), 3.6-3.8 (1H, m), 4.3-4.5 (1H, m), 6.6-6.8 (3H, m), 6.85 (1H, d, J=6.4 Hz), 6.92 (1H, d, J=7.3 Hz), 6.9-7.1 (1H, m), 7.1-7.3 (1H, m)
78	-H	-H	-H	-F	-H	-H	-CH ₃	-H	-H	-H	¹ H-NMR (CDCl ₃) δppm 1.43 (9H, s), 1.7-1.9 (1H, m), 2.0-2.2 (1H, m), 2.34 (3H, s), 3.1-3.4 (3H, m), 3.6-3.8 (1H, m), 4.3-4.5 (1H, m), 6.33 (1H, d, J=12.2 Hz), 6.42 (1H, d, J=8.3 Hz), 6.4-6.6 (1H, m), 6.8-6.9 (2H, m), 7.0-7.2 (2H, m), 7.2-7.3 (1H, m)
79	-H	-H	-F	-CH ₃	-H	-H	-H	-F	-H	-H	¹ H-NMR (CDCl ₃) δppm 1.43 (9H, s), 1.7-1.9 (1H, m), 2.0-2.2 (1H, m), 2.22 (3H, s), 3.1-3.4 (3H, m), 3.6-3.8 (1H, m), 4.3-4.5 (1H, m), 6.6-6.8 (4H, m), 6.8-7.1 (3H, m)
80	-H	-H	-H	-CH ₃	-H	-H	-H	-F	-H	-H	¹ H-NMR (CDCl ₃) δppm 1.43 (9H, s), 1.7-1.9 (1H, m), 2.0-2.2 (1H, m), 2.27 (3H, s), 3.1-3.4 (3H, m), 3.6-3.8 (1H, m), 4.4-4.6 (1H, m), 6.54 (2H, d, J=6.5 Hz), 6.74 (1H, d, J=7.1 Hz), 6.8-7.2 (5H, m)

[0865]

81	-H -H -H	-F	-H -H -H	-CH ₃	-H -H	¹ H-NMR (CDCl ₃) δppm 1.42 (9H, s), 1.7-1.9 (1H, m), 2.0-2.2 (1H, m), 2.38 (3H, s), 3.1-3.4 (3H, m), 3.6-3.8 (1H, m), 4.3-4.5 (1H, m), 6.28 (1H, d, J=12.5 Hz), 6.3-6.5 (2H, m), 6.96 (2H, d, J = 8.2 Hz), 7.0-7.3 (3H, m)
82	-H -H -CH ₃	-Cl	-H -H -F	-H	-H -H	¹ H-NMR (CDCl ₃) δppm 1.43 (9H, s), 1.7-1.9 (1H, m), 2.0-2.2 (1H, m), 2.37 (3H, s), 3.1-3.4 (3H, m), 3.6-3.8 (1H, m), 4.3-4.5 (1H, m), 6.38 (1H, d, J = 11.9 Hz), 6.46 (1H, d, J = 8.3 Hz), 6.57 (1H, dd, J = 8.1 Hz, 7.8 Hz), 6.82 (1H, d, J = 8.1 Hz), 7.02 (1H, s), 7.1-7.3 (2H, m)
83	-H -H -Cl	-CH ₃	-H -H -F	-H	-H -H	¹ H-NMR (CDCl ₃) δppm 1.43 (9H, s), 1.7-1.9 (1H, m), 2.0-2.2 (1H, m), 2.35 (3H, s), 3.1-3.4 (3H, m), 3.6-3.8 (1H, m), 4.3-4.5 (1H, m), 6.36 (1H, d, J = 11.9 Hz), 6.43 (1H, d, J = 8.3 Hz), 6.55 (1H, dd, J = 8.0 Hz, 8.1 Hz), 6.80 (1H, d, J = 8.3 Hz), 6.89 (1H, s), 7.1-7.2 (1H, m), 7.3-7.4 (1H, m)
84	-H -H -F	-Cl	-H -H -Cl	-F	-H -H	¹ H-NMR (CDCl ₃) δppm 1.75-1.92 (1H, m), 2.03-2.22 (1H, m), 3.11-3.39 (3H, m), 3.61-3.79 (1H, m), 4.26-4.42 (1H, m), 6.42-6.75 (2H, m), 6.87-6.91 (2H, m), 7.06 (1H, dd, J=8.5Hz, 8.5Hz).
85	-H -H -H	-F	-H -H -CN	-H	-H -H	¹ H-NMR (CDCl ₃) δppm 1.43 (9H, s), 1.8-1.9 (1H, m), 2.1-2.3 (1H, m), 3.1-3.4 (3H, m), 3.6-3.8 (1H, m), 4.4-4.5 (1H, m), 6.68 (1H, d, J = 10.2 Hz), 6.75 (1H, d, J = 8.0 Hz), 6.9-7.0 (3H, m), 7.1-7.4 (3H, m)

[0866] 表 7

[0867]



[0868]

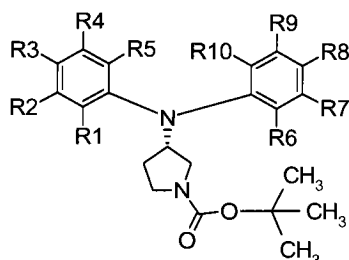
参比实 施例	R1	R2	R3	R4	R5	R6	R7	R8	R9	R10	NMR
86	-H	-H	-F	-Cl	-H	-H	-CN	-H	-H	-H	¹ H-NMR (CDCl ₃) δppm 1.44 (9H, s), 1.7-1.9 (1H, m), 2.0-2.2 (1H, m), 3.1-3.4 (3H, m), 3.6-3.8 (1H, m), 4.3-4.5 (1H, m), 6.7-6.9 (2H, m), 6.9-7.0 (1H, m), 7.0-7.4 (4H, m),
87	-H	-H	-F	-Cl	-H	-H	-H	-OCH ₃	-H	-H	¹ H-NMR (CDCl ₃) δppm 1.43 (9H, s), 1.75-1.91 (1H, m), 2.02-2.18 (1H, m), 3.11-3.35 (3H, m), 3.60-3.79 (1H, m), 3.83 (3H, s), 4.29-4.42 (1H, m), 6.44 (1H, dt, J=3.5Hz and J=8.9Hz), 6.61 (1H, dd, J=2.8Hz and J=6.1Hz), 6.86-7.01 (5H, m)
88	-H	-H	-F	-Cl	-H	-H	-H	-CH ₃	-H	-H	¹ H-NMR (CDCl ₃) δppm 1.43 (9H, s), 1.75-1.91 (1H, m), 2.02-2.20 (1H, m), 2.37 (1H, s), 3.11-3.38 (3H, m), 3.60-3.83 (1H, m), 4.29-4.49 (1H, m), 6.56 (1H, dt, J=3.6Hz and J=9.0Hz), 6.74 (1H, dd, J=2.9Hz and J=6.3Hz), 6.86 (2H, d, J=8.3Hz), 6.91-7.02 (1H, m), 7.11-7.21 (2H, m)
89	-H	-H	-F	-Cl	-H	-H	-H	-OC ₂ H ₅	-H	-H	¹ H-NMR (CDCl ₃) δppm 1.32-1.50 (12H, m, with s at δ1.42 and t at δ 1.43, J=7.0Hz), 1.74-1.91 (1H, m), 2.01-2.18 (1H, m), 3.10-3.32 (3H, m), 3.58-3.81 (1H, m), 4.06 (2H, q, J=7.0Hz), 4.28-4.42 (1H, m), 6.44 (1H, dt, J=3.2Hz and J=9.0Hz), 6.61 (1H, dd, J=2.9Hz and J=6.1Hz), 6.84-7.01 (5H, m) with at δ6.96, J=2.5Hz)

[0869]

90	-H -H -F	-Cl	-H -H -H	-C ₂ H ₅	-H -H	¹ H-NMR (CDCl ₃) δppm 1.25 (3H, t, J=7.5Hz), 1.43 (9H, s), 1.72-1.91 (1H, m), 2.00-2.20 (1H, m), 2.64 (2H, q, J=7.5Hz), 3.10-3.46 (3H, m), 3.60-3.81 (1H, m), 4.30-4.49 (1H, m), 6.53-6.61 (1H, m), 6.76 (1H, dd, J=2.9Hz and J=6.3Hz), 6.87 (1H, d, J=8.2Hz), 6.91-7.03 (1H, m), 7.12-7.22 (2H, m)
91	-H -H -F	-Cl	-H -H -H	-CO ₂ C ₂ H ₅	-H -H	¹ H-NMR (CDCl ₃) δppm 1.35 (3H, t, J=7.1Hz), 1.43 (9H, s), 1.78-1.95 (1H, m), 2.09-2.27 (1H, m), 3.11-3.39 (3H, m), 3.69-3.85 (1H, m), 4.32 (2H, q, J=7.1Hz), 4.93-4.61 (1H, m), 6.57 (2H, d, J=8.9Hz), 6.96-7.04 (1H, m), 7.14-7.29 (2H, m), 7.81-7.94 (2H, m)
92	-H -H -F	-Cl	-H -H -H	-CO ₂ H	-H -H	¹ H-NMR (DMSO-d ₆) δppm 1.33 (9H, s), 1.72-1.88 (1H, m), 2.06-2.26 (1H, m), 2.99- 3.23 (3H, m), 3.61 (1H, dd, J=6.4Hz and J=11.3Hz), 4.53- 4.69 (1H, m), 6.57-6.65 (2H, m), 7.19-7.28 (1H, m), 7.46- 7.58 (2H, m), 7.68-7.78 (2H, m), 12.3 (1H, brs)
93	-H -H -CH ₃	-H	-H -H -H	-F	-H -H	¹ H-NMR (CDCl ₃) δppm 1.42 (9H, s), 1.74-1.92 (1H, m), 2.00-2.20 (1H, m), 2.30 (3H, s), 3.13-3.32 (3H, m), 3.62-3.80 (1H, m), 4.33-4.48 (1H, m), 6.74 (2H, d, J=8.5Hz), 6.80-6.88 (2H, m), 6.90- 7.02 (2H, m), 7.03-7.13 (2H, m).

[0870] 表 8

[0871]



[0872]

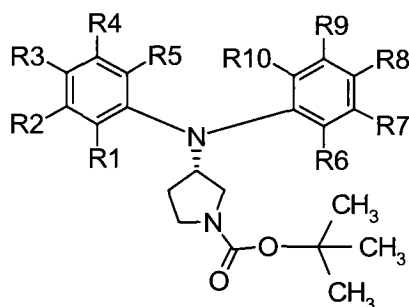
参比实 施例	R1	R2	R3	R4	R5	R6	R7	R8	R9	R10	NMR
94	-H	-H	-F	-Cl	-H	-H	-H	-N(CH ₃) ₂	-H	-H	¹ H-NMR (CDCl ₃) δppm 1.43 (9H, s), 1.70-1.87 (1H, m), 2.00-2.13 (1H, m), 2.97 (6H, s), 3.10-3.29 (3H, m), 3.59-3.77 (1H, m), 4.28-4.38 (1H, m), 6.41 (1H, dt, J=3.4, 9.1Hz), 6.57-6.61 (1H, m), 6.68-6.72 (2H, m), 6.84-6.94 (3H, m).
95	-H	-H	-F	-Cl	-H	-H	-H	-CN	-H	-H	¹ H-NMR (CDCl ₃) δppm 1.43 (9H, s), 1.79-1.92 (1H, m), 2.09-2.17 (1H, m), 3.11- 3.32 (3H, m), 3.70-3.89 (1H, m), 4.45-4.53 (1H, m), 6.56 (2H, d, J=9.0Hz), 7.02 (1H, ddd, J=2.6, 4.2, 8.7Hz), 7.18- 7.28 (2H, m), 7.43 (2H, d, J=7.9Hz).
96	-H	-H	-F	-Cl	-H	-H	-H	-CF ₃	-H	-H	¹ H-NMR (CDCl ₃) δppm 1.43 (9H, s), 1.78-1.90 (1H, m), 2.09-2.23 (1H, m), 3.12- 3.34 (3H, m), 3.65-3.80 (1H, m), 4.40-4.52 (1H, m), 6.64 (2H, d, J=8.8Hz), 7.02 (1H, ddd, J=2.7, 4.1, 8.6Hz), 7.15- 7.25 (2H, m), 7.42 (2H, d, J=7.7Hz).
97	-H	-H	-F	-Cl	-H	-H	-OCH ₃	-H	-H	-H	¹ H-NMR (CDCl ₃) δppm 1.43 (9H, s), 1.82-1.90 (1H, m), 2.04-2.18 (1H, m), 3.15- 3.32 (3H, m), 3.65-3.80 (1H, m), 3.76 (3H, s), 4.33-4.43 (1H, m), 6.35 (1H, t, J=2.3Hz), 6.59 (1H, dd, J=1.8, 8.2Hz), 6.74-6.79 (1H, m), 6.95 (1H, dd, J=2.7, 6.4Hz), 7.02-7.10 (1H, m), 7.15-7.22 (1H, m).

[0873]

98	-H -H -F	-Cl -H -H -OC ₂ H ₅ -H	-H -H	¹ H-NMR (CDCl ₃) δppm 1.38 (3H, t, J=7.0Hz), 1.43 (9H, s), 1.80-1.90 (1H, m), 2.03-2.18 (1H, m), 3.16-3.32 (3H, m), 3.60-3.69 (1H, m), 3.96 (2H, q, J=7.0), 4.31-4.41 (1H, m), 6.37 (1H, t, J=2.2Hz), 6.41 (1H, dd, J=1.58, 8.0Hz), 6.59 (1H, d, J=8.1Hz), 6.75 (1H, ddd, J=2.9, 3.9, 8.8Hz), 6.93 (1H, dd, J=2.8, 6.4Hz), 7.00-7.08 (1H, m), 7.14-7.25 (1H, m).
99	-H -H -F	-Cl -H -H -SCH ₃ -H	-H -H	¹ H-NMR (CDCl ₃) δppm 1.43 (9H, s), 1.78-1.92 (1H, m), 2.04-2.20 (1H, m), 2.44 (3H, s), 3.11-3.33 (3H, m), 3.60-3.80 (1H, m), 4.31-4.45 (1H, m), 6.57 (1H, ddd, J=0.8, 2.3, 8.1Hz), 6.70 (1H, t, 1.9Hz), 6.76 (1H, ddd, J=2.8, 4.0, 8.9Hz), 6.90-6.96 (2H, m), 7.03-7.11 (1H, m), 7.16-7.23 (1H, m).
100	-H -H -F	-CH ₃ -H -H -H	-NO ₂ -H -H	¹ H-NMR (CDCl ₃) δppm 1.43 (9H, s), 1.80-1.90 (1H, m), 2.01-2.20 (1H, m), 2.31 (3H, s), 3.18-3.38 (3H, m), 3.70-3.88 (1H, m), 4.50-4.59 (1H, m), 6.50 (2H, d, J=9.5Hz), 6.85-6.97 (2H, m), 7.07- 7.15 (1H, m), 8.03 (2H, d, J=7.9Hz).
101	-H -H -F	-CH ₃ -H -H -H	-CN -H -H	¹ H-NMR (CDCl ₃) δppm 1.43 (9H, s), 1.81-1.93 (1H, m), 2.08-2.20 (1H, m), 2.35 (3H, s), 3.18-3.30 (3H, m), 3.65-3.78 (1H, m), 4.45-4.55 (1H, m), 6.50 (2H, d, J=9.5Hz), 6.83-6.99 (2H, m), 7.03- 7.15 (1H, m), 7.32-7.43 (2H, m).

[0874] 表 9

[0875]



[0876]

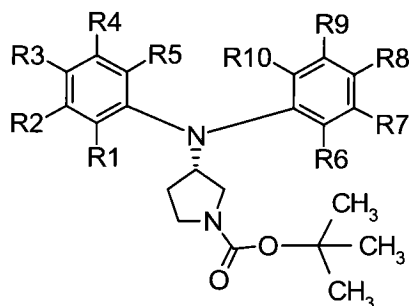
参比实 施例	R1	R2	R3	R4	R5	R6	R7	R8	R9	R10	NMR
102	-H	-H	-F	-CH ₃	-H	-H	-CH ₃	-H	-H	-H	¹ H-NMR (CDCl ₃) δppm 1.43 (9H, s), 1.79-1.90 (1H, m), 2.00-2.18 (1H, m), 2.24 (3H, s), 2.27 (3H, s), 3.12-3.30 (3H, m), 3.62-3.71 (1H, m), 4.39-4.50 (1H, m), 6.50-6.52 (2H, m), 6.68-6.72 (1H, m), 6.77-6.84 (2H, m), 6.93-7.01 (1H, m), 7.06-7.11 (1H, m).
103	-H	-H	-F	-Cl	-H	-H	-H	-C ₃ H ₇	-H	-H	¹ H-NMR (CDCl ₃) δppm 0.96 (3H, t, J=7.3Hz), 1.43 (9H, s), 1.61-1.70 (2H, m), 1.76-1.89 (1H, m), 2.01-2.18 (1H, m), 2.51-2.65 (2H, m), 3.11-3.35 (3H, m), 3.62-3.82 (1H, m), 4.31-4.43 (1H, m), 6.55-6.59 (1H, m), 6.76 (1H, dd, J=2.9Hz and 6.3Hz), 6.86 (2H, d, J=8.2Hz), 6.97 (1H, q, J=9.1Hz), 7.11-7.19 (2H, m).
104	-H	-H	-F	-Cl	-H	-H	-H	-C(CH ₃) ₃	-H	-H	¹ H-NMR (CDCl ₃) δppm 1.31 (9H, s), 1.43 (9H, s), 1.78-1.89 (1H, m), 2.02-2.19 (1H, m), 3.11-3.34 (3H, m), 3.62-3.80 (1H, m), 4.32-4.45 (1H, m), 6.59-6.65 (1H, m), 6.79-6.88 (2H, m with dd at δ6.81, J=2.8Hz and 6.3Hz), 6.99 (1H, q, J=8.9Hz), 7.29- 7.38 (2H, m).
105	-H	-H	-F	-Cl	-H	-H	-H	-SCH ₃	-H	-H	¹ H-NMR (CDCl ₃) δppm 1.43 (9H, s), 1.79-1.89 (1H, m), 2.03-2.09 (1H, m), 2.51 (3H, s), 3.13-3.34 (3H, m), 3.63-3.80 (1H, m), 6.65-6.69 (1H, m), 6.80-6.86 (3H, m), 7.02 (1H, q, J=8.81Hz), 7.21- 7.27 (2H, m).
106	-H	-H	-F	-Cl	-H	-H	-H	-SO ₂ CH ₃	-H	-H	¹ H-NMR (CDCl ₃) δppm

[0877]

										1.43 (9H, s), 1.80-1.91 (1H, m), 2.11-2.29 (1H, m), 3.01 (3H, s), 3.16-3.40 (3H, m), 3.70-3.86 (1H, m), 4.49-4.61 (1H, m), 6.62 (2H, d, J= 9.0Hz), 7.03 (1H, ddd, J=2.6Hz, 4.1Hz and 8.6Hz), 7.01-7.06 (1H,m), 7.19-7.23 (1H, m), 7.24-7.31 (1H, m), 7.66-7.74 (2H, m)	
107	-H	-H	-H	-SCH ₃	-H	-H	-H	-F	-H	-H	¹ H-NMR (CDCl ₃) δppm 1.43 (9H, s), 1.78-1.91 (1H, m), 2.02-2.18 (1H, m), 2.40 (3H, s), 3.11-3.30 (3H, m), 3.71-3.80 (1H, m), 4.35-4.50 (1H, m), 6.45 (1H, dd, J=2.0, 8.1Hz), 6.56 (1H, brs), 6.75 (1H, d, J=7.9Hz), 6.97-7.15 (5H, m).
108	-H	-H	-H	-NO ₂	-H	-H	-CH ₃	-F	-H	-H	¹ H-NMR (CDCl ₃) δppm 1.43 (9H, s), 1.78-1.91 (1H, m), 2.08-2.23 (1H, m), 2.29 (3H, s), 3.14-3.33 (3H, m), 3.71-3.82 (1H, m), 4.45-4.55 (1H, m), 6.75-6.84 (1H, m), 6.89-6.99 (2H, m), 7.03-7.28 (2H, m), 7.41-7.55 (1H, m), 7.55-7.58 (1H, m).
109	-H	-H	-F	-CH ₃	-H	-H	-OCH ₃	-H	-H	-H	¹ H-NMR (CDCl ₃) δppm 1.43 (9H, s), 1.78-1.90 (1H, m), 2.02-2.19 (1H, m), 2.24 (3H, s), 3.13-3.30 (3H, m), 3.63-3.82 (1H, m), 3.73 (3H, s), 4.39-4.52 (1H, m), 6.19 (1H, s), 6.25-6.28 (1H, m), 6.38-6.41 (1H, m), 6.80-6.91 (2H, m), 6.92-7.06 (1H, m), 7.07-7.13 (1H, m).

[0878] 表 10

[0879]

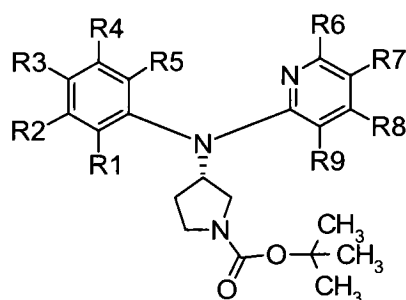


[0880]

参比实 施例	R1	R2	R3	R4	R5	R6	R7	R8	R9	R10	NMR
110	-H	-H	-Cl	-Cl	-H	-H	-F	-H	-H	-H	¹ H-NMR (CDCl ₃) δppm 1.43 (9H, s), 1.78-1.92 (1H, m), 2.03-2.23 (1H, m), 3.12-3.36 (3H, m), 3.61-3.82 (1H, m), 4.31-4.50 (1H, m), 6.57 (1H, dt, J=2.2Hz and 10.7Hz), 6.61-6.66 (1H,m), 6.69 (1H, dd, J=2.7Hz and 8.7Hz), 6.75-6.85 (1H, m), 6.95 (1H,d,J=2.7Hz), 7.19-7.39 (2H, m)
111	-H	-H	-F	-Cl	-H	-H	-H		-H	-H	¹ H-NMR (CDCl ₃) δppm 1.43 (9H, s), 1.59-1.75 (3H, m), 1.79-1.92 (3H, m), 1.95-2.15 (2H, m), 3.11-3.32 (3H, m), 3.58-3.79 (2H, m), 3.89-3.99 (1H, m), 4.30-4.43 (1H, m), 5.30 (1H, s), 6.43-6.44 (1H, m), 6.62-6.67 (1H, m), 6.85-6.97 (3H, m), 7.02-7.10 (2H, m)
112	-H	-H	-F	-CF ₃	-H	-H	-Cl	-F	-H	-H	¹ H-NMR (CDCl ₃) δppm 1.43(9H,s), 1.76-1.91(1H,m), 2.03-2.09(1H,m), 3.11-3.37(3H,m), 3.61-3.79(1H,m), 4.32-4.45(1H,m), 6.73-6.79(1H,m), 6.93-6.98(2H,m), 7.01-7.04(1H,m), 7.05-7.16(2H,m)

[0881] 表 11

[0882]

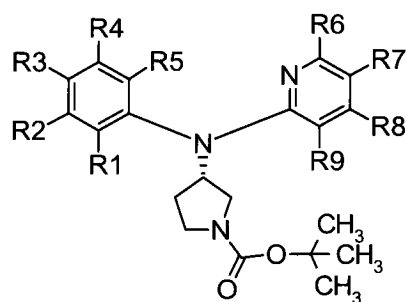


[0883]

参比实 施例	R1	R2	R3	R4	R5	R6	R7	R8	R9	NMR
113	-H	-H	-H	-H	-H	-H	-H	-H	-H	¹ H-NMR (CDCl ₃) δppm 1.42 (9H, s), 1.68-1.72 (1H, m), 1.99-2.21 (1H, m), 3.06-3.31 (3H, m), 3.83 (1H, dd, J=7.2Hz and 10.7Hz), 5.32-5.49 (1H, m), 5.96 (1H, d, J=6.0Hz), 6.52-6.65 (1H, m), 7.10-7.29 (3H, m), 7.31-7.52 (3H, m), 8.15- 8.23 (1H, m)
114	-H	-F	-H	-H	-H	-H	-H	-H	-H	¹ H-NMR (CDCl ₃) δppm 1.43 (9H, s), 1.75-1.94 (1H, m), 2.09-2.38 (1H, m), 3.12-3.49 (3H, m), 3.70-3.85 (1H, m), 4.40-4.60 (1H, m), 6.49-6.61 (2H, m), 6.68-6.79 (1H, m), 7.16-7.31 (3H, m), 8.27(1H, s), 8.36-8.44(1H, m)
115	-H	-Cl	-F	-H	-H	-H	-H	-H	-H	¹ H-NMR (CDCl ₃) δppm 1.45 (9H, s), 1.70-1.89 (1H, m), 2.02-2.25 (1H, m), 3.04-3.49 (3H, m), 3.84 (1H, dd, J=7.1Hz and 10.8Hz), 5.30-5.49 (1H, m), 6.02 (1H, d, J=8.6Hz), 6.58-6.72 (1H, m), 7.02-7.39 (4H, m), 8.16-8.28 (1H, m)
116	-H	-H	-H	-H	-H	-CH ₃	-H	-H	-H	¹ H-NMR (CDCl ₃) δppm 1.43 (9H, s), 1.68-1.89 (1H, m), 2.00-2.20 (1H, m), 2.43 (3H, d, J=4.6Hz), 3.09-3.30 (3H, m), 3.72-3.95 (1H, m), 5.39-5.58 (1H, m), 5.74 (1H, d, J=8.5Hz), 6.33-6.53 (1H, m), 7.05-7.20 (3H, m), 7.29-7.50 31H, m)
117	-H	-H	-H	-H	-H	-H	-CH ₃	-H	-H	¹ H-NMR (CDCl ₃) δppm 1.42 (9H, s), 1.68-1.85 (1H, m), 1.95-2.20 (4H, m with s at δ2.17), 3.03-3.31 (3H, m), 3.75-3.88 (1H, m), 5.24- 5.47 (1H, m), 5.92 (1H, d, J=8.6Hz), 7.07 (1H, d, J=8.6Hz), 7.11-7.19 (2H, m), 7.29-7.31 (3H, m), 8.00 (1H, d, J=5.2Hz)
118	-H	-H	-H	-H	-H	-H	-H	-CH ₃	-H	¹ H-NMR (CDCl ₃) δppm 1.42 (9H, s), 1.65-1.87 (1H, m), 1.95-2.12 (1H, m), 2.17 (3H, s), 3.05-3.31 (3H, m), 3.78-3.88 (1H, m), 5.21- 5.45 (1H, m), 5.92 (1H, d, J=8.6Hz), 7.07 (1H, d, J=8.6Hz), 7.10-7.20 (2H, m), 7.28-7.31 (3H, m), 7.96- 8.05 (1H, m)
119	-H	-Cl	-F	-H	-H	-H	-CH ₃	-H	-H	¹ H-NMR (CDCl ₃) δppm 1.43 (9H, s), 1.69-1.71 (1H, m), 1.90-2.10 (1H, m), 2.19 (3H, s), 3.01-3.36 (3H, m), 3.76-3.86 (1H, m), 5.19-5.36 (1H, m), 5.96 (1H, d, J=8.6Hz), 7.01-7.06(1H, m), 7.07- 7.17 (2H, m), 7.18-7.26 (2H, m), 8.01 (1H, d, J=12.5Hz)
120	-H	-Cl	-F	-H	-H	-H	-H	-CH ₃	-H	¹ H-NMR (CDCl ₃) δppm 1.43 (9H, s), 1.68-1.81 (1H, m), 2.02-2.20 (4H, m with s at δ2.12), 3.04-3.32 (3H, m), 3.78-3.84 (1H, m), 5.29- 5.42 (1H, m), 5.80 (1H, s), 6.40-6.53(1H, m), 7.02-7.10 (1H, m), 7.11-7.25 (2H, m), 8.05 (1H, dd, J=5.0Hz and 12.2Hz)

[0884] 表 12

[0885]

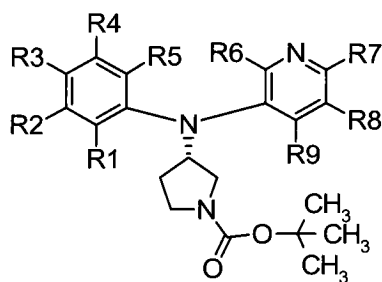


[0886]

参比实 施例	R1	R2	R3	R4	R5	R6	R7	R8	R9	NMR
121	-H	-Cl	-F	-H	-H	-CH ₃	-H	-H	-H	¹ H-NMR (CDCl ₃) δppm 1.44 (9H, s), 1.68-1.82 (1H, m), 2.00-2.19 (1H, m), 2.39-2.49 (3H, m), 3.02-3.37 (3H, m), 3.74-3.84 (1H, m), 5.32-5.51 (1H, m), 5.70-5.81 (1H, m), 6.41-6.57 (1H, m), 7.04 (1H, ddd, J=2.6Hz, 4.3Hz and 8.7Hz), 7.10-7.30 (3H, m)
122	-H	-Cl	-F	-H	-H	-H	-Cl	-H	-H	¹ H-NMR (CDCl ₃) δppm 1.43 (9H, s), 1.62-1.82 (1H, m), 2.01-2.22 (1H, m), 3.03-3.31 (3H, m), 3.79 (1H, dd, J=7.0, 10.8Hz), 5.21- 5.27 (1H, m), 5.96 (1H, d, J=9.0Hz), 7.04 (1H, ddd, J=2.6, 4.2, 8.6), 7.20-7.26 (4H, m), 8.12-8.14 (1H, m).
123	-H	-CF ₃	-F	-H	-H	-H	-H	-H	-H	¹ H-NMR (CDCl ₃) δppm 1.43 (9H, s), 1.63-1.79 (1H, m), 2.02-2.26 (1H, m), 3.03-3.35 (3H, m), 3.84 (1H, dd, J=7.0Hz, 11.0Hz), 5.30-5.41 (1H, m), 5.97 (1H, d, J=8.5Hz), 6.62-6.73 (1H, m), 7.26-7.47 (4H, m), 8.18-8.26 (1H, m).
124	-H	-CH ₃	-F	-H	-H	-H	-Cl	-H	-H	¹ H-NMR (CDCl ₃) δppm 1.43 (9H, s), 1.68-1.82 (1H, m), 2.00-2.19 (1H, m), 2.29 (3H, s), 3.10-3.29 (3H, m), 3.79 (1H, dd, J=7.1, 10.8Hz), 5.15-5.32 (1H, m), 5.93 (1H, d, J=9.1Hz), 6.90-6.99 (2H, m), 7.01-7.21 (2H, m), 8.11-8.12 (1H, m).
125	-H	-H	-F	-H	-H	-H	-Cl	-H	-H	¹ H-NMR (CDCl ₃) δppm 1.42 (9H, s), 1.73-1.82 (1H, m), 2.00-2.17 (1H, m), 3.06-3.29 (3H, m), 3.79 (1H, dd, J=7.1, 10.8Hz), 5.15- 5.32 (1H, m), 5.92 (1H, d, J=9.0Hz), 7.07-7.27 (5H, m), 8.12 (1H, d, J=4.7).
126	-H	-Cl	-F	-H	-H	-H	-H	-CF ₃	-H	¹ H-NMR (CDCl ₃) δppm 1.43 (9H, s), 1.7-1.9 (1H, m), 2.0-2.2 (1H, m), 3.0-3.4 (3H, m), 3.7-3.9 (1H, m), 5.2-5.4 (1H, m), 6.15 (1H, s), 6.82 (1H, d, J = 5.0 Hz), 7.0-7.1 (1H, m), 7.2-7.4 (2H, m), 8.3-8.4 (1H, m)
127	-H	-Cl	-F	-H	-H	-OCH ₃	-H	-H	-H	¹ H-NMR (CDCl ₃) δppm 1.43 (9H, s), 1.7-1.9 (1H, m), 2.0-2.2 (1H, m), 3.1-3.4 (3H, m), 3.7-3.9 (1H, m), 3.90 (3H, s), 5.1-5.3 (1H, m), 5.51 (1H, d, J = 8.1 Hz), 6.09 (1H, d, J = 8.3 Hz), 7.0-7.1 (1H, m), 7.2-7.4 (3H, m)

[0887] 表 13

[0888]

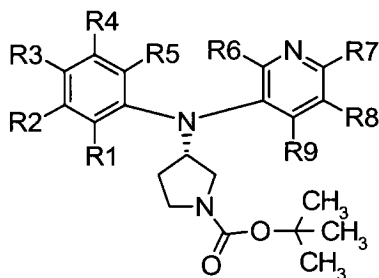


[0889]

参比实 施例	R1	R2	R3	R4	R5	R6	R7	R8	R9	NMR
128	-H	-Cl	-F	-H	-H	-H	-H	-H	-H	¹ H-NMR (CDCl ₃) δppm 1.43 (9H, s), 1.79-1.98 (1H, m), 2.08-2.29 (1H, m), 3.12-3.41 (3H, m), 3.65-3.85 (1H, m), 4.38-4.51 (1H, m), 6.83-6.91 (1H, m), 7.00-7.23 (4H, m with dd at δ7.04, J=2.7Hz and J=6.4Hz), 8.14(1H, s), 8.22 (1H, d, J=4.4Hz)
129	-H	-CH ₃	-F	-H	-H	-H	-H	-H	-H	¹ H-NMR (CDCl ₃) δppm 1.43 (9H, s), 1.7-1.9 (1H, m), 2.0-2.2 (1H, m), 2.26 (3H, s), 3.1-3.4 (3H, m), 3.6-3.8 (1H, m), 4.3-4.5 (1H, m), 6.8-7.1 (5H, m), 7.9-8.1 (2H, m)
130	-H	-H	-H	-H	-H	-H	-F	-H	-H	¹ H-NMR (CDCl ₃) δppm 1.43 (9H, s), 1.73-1.96 (1H, m), 2.01-2.29 (1H, m), 3.11-3.40 (3H, m), 3.64-3.86 (1H, m), 4.37-4.56 (1H, m), 6.79-6.94 (3H, m), 7.02-7.15 (1H, m), 7.19-7.40 (3H, m), 7.80 (1H, brs)
131	-H	-Cl	-F	-H	-H	-H	-OCH ₃	-H	-H	¹ H-NMR (CDCl ₃) δppm 1.43 (9H, s), 1.7-1.9 (1H, m), 2.0-2.2 (1H, m), 3.1-3.4 (3H, m), 3.6-3.8 (1H, m), 3.96 (3H, s), 4.3-4.5 (1H, m), 6.50 (1H, d, J = 9.0 Hz), 6.67 (1H, d, J = 6.0 Hz), 6.78 (1H, d, J = 8.8 Hz), 6.9-7.0 (1H, m), 7.26 (1H, d, J = 8.8 Hz), 7.92 (1H, s)
132	-H	-Cl	-H	-H	-H	-H	-H	-H	-H	¹ H-NMR (CDCl ₃) δppm 1.41 (9H, s), 1.7-1.9 (1H, m), 2.1-2.3 (1H, m), 3.1-3.4 (3H, m), 3.7-3.9 (1H, m), 4.4-4.6 (1H, m), 6.71 (1H, d, J = 6.9 Hz), 6.83 (1H, s), 7.03 (1H, dd, J = 6.9 Hz, J = 7.8 Hz), 7.1-7.3 (2H, m), 8.24 (1H, s), 8.36 (1H, s)

[0890] 表 14

[0891]



[0892]

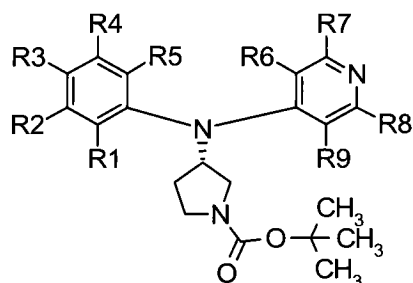
参比实 施例	R1	R2	R3	R4	R5	R6	R7	R8	R9	NMR
133	-H	-F	-F	-H	-H	-H	-H	-H	-H	¹ H-NMR (CDCl ₃) δppm 1.43 (9H, s), 1.8-2.0 (1H, m), 2.1-2.3 (1H, m), 3.1- 3.4 (3H, m), 3.6-3.8 (1H, m), 4.4-4.5 (1H, m), 6.6-6.7 (1H, m), 6.7-6.9 (1H, m), 7.0-7.3 (3H, m), 8.16 (1H, d, J = 6.6 Hz), 8.25 (1H, s)
134	-H	-F	-Cl	-H	-H	-H	-H	-H	-H	¹ H-NMR (CDCl ₃) δppm

[0893]

										1.42 (9H, s), 1.8-1.9 (1H, m), 2.1-2.3 (1H, m), 3.1-3.4 (3H, m), 3.7-3.9 (1H, m), 4.4-4.5 (1H, m), 6.47 (1H, d, J = 8.1 Hz), 6.54 (1H, d, J = 11.2 Hz), 7.2-7.4 (3H, m), 8.30 (1H, s), 8.45 (1H, s)
135	-H	-Cl	-Cl	-H	-H	-H	-H	-H	-H	¹ H-NMR (CDCl ₃) δppm 1.43 (9H, s), 1.8-1.9 (1H, m), 2.1-2.3 (1H, m), 3.1-3.4 (3H, m), 3.7-3.9 (1H, m), 4.4-4.5 (1H, m), 6.63 (1H, d, J = 8.7 Hz), 6.90 (1H, s), 7.2-7.4 (3H, m), 8.27 (1H, s), 8.41 (1H, s)
136	-H	-CF ₃	-F	-H	-H	-H	-H	-H	-H	¹ H-NMR (CDCl ₃) δppm 1.43 (9H, s), 1.74-1.94 (1H, m), 2.06-2.28 (1H, m), 3.12-3.38 (3H, m), 3.65-3.82 (1H, m), 4.38-4.56 (1H, m), 7.01-7.25 (5H, m), 8.16 (1H, s), 8.28 (1H, d, J=4.5Hz).
137	-H	-H	-F	-H	-H	-H	-H	-H	-H	¹ H-NMR (CDCl ₃) δppm 1.43 (9H, s), 1.79-1.97 (1H, m), 2.03-2.23 (1H, m), 3.11-3.29 (3H, m), 3.63-3.79 (1H, m), 4.38-4.50 (1H, m), 6.83-6.92 (1H, m), 7.01-7.12 (5H, m), 8.01-8.10 (2H, m).

[0894] 表 15

[0895]

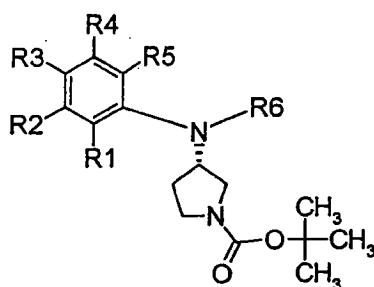


[0896]

参比实 施例	R1	R2	R3	R4	R5	R6	R7	R8	R9	NMR
138	-H	-H	-H	-H	-H	-H	-H	-H	-H	¹ H-NMR (CDCl ₃) δppm 1.42 (9H, s), 1.77-1.92 (1H, m), 1.95-2.27 (1H, m), 3.10-3.38 (3H, m), 3.68-3.89 (1H, m), 4.41-4.61 (1H, m), 6.32-6.40 (2H, m), 7.08-7.15 (2H, m), 7.38-7.54 (3H, m), 8.12-8.22 (1H, m)
139	-H	-Cl	-F	-H	-H	-H	-H	-H	-H	¹ H-NMR (CDCl ₃) δppm 1.43 (9H, s), 1.73-1.95 (1H, m), 2.07-2.27 (1H, m), 3.12-3.38 (3H, m), 3.65-3.84 (1H, m), 4.41-4.61 (1H, m), 6.32-6.41 (2H, m), 6.99-7.08 (1H, m), 7.18-7.32 (2H, m with dd at δ7.21, J=2.5Hz and J=6.6Hz), 8.12-8.31 (2H, m)
140	-H	-Cl	-F	-H	-H	-H	-H	-CH ₃	-H	¹ H-NMR (CDCl ₃) δppm 1.43 (9H, s), 1.8-2.0 (1H, m), 2.1-2.3 (1H, m), 2.40 (3H, s), 3.1-3.4 (3H, m), 3.7-3.9 (1H, m), 4.4-4.6 (1H, m), 6.1-6.3 (2H, m), 6.9-7.1 (1H, m), 7.1-7.3 (2H, m), 8.12 (1H, d, J = 5.0 Hz)

[0897] 表 16

[0898]

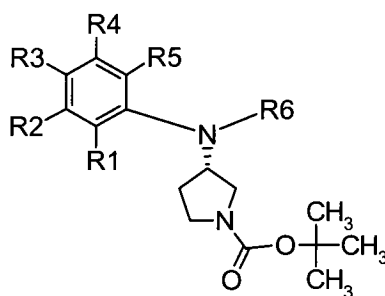


[0899]

Ref. Ex. No.	R1	R2	R3	R4	R5	R6	NMR
141	-H	-H	-F	-H	-H		¹ H-NMR (CDCl ₃) δppm 0.80-1.36 (6H, m), 1.44 (9H, s), 1.61-1.99 (6H, m), 2.75-2.93 (1H, m), 2.95-3.09 (1H, m), 3.15-3.31 (1H, m), 3.33-3.68 (2H, m), 3.87-4.07 (1H, m), 6.86-6.98 (2H, m), 6.98-7.07 (2H, m)
142	-H	-H	-F	-H	-H		¹ H-NMR (CDCl ₃) δppm 1.44 (9H, s), 1.61-1.81 (3H, m), 1.89-2.01 (1H, m), 2.95-3.70 (7H, m), 3.88-4.01 (1H, m), 6.88-7.10 (4H, m)
143	-H	-H	-F	-Cl	-H		¹ H-NMR (CDCl ₃) δppm 1.19-1.74 (18H, m with s at δ1.46), 1.89-2.02 (1H, m), 2.97-3.63 (5H, m), 3.71-3.91 (1H, m), 6.89-7.07 (2H, m), 7.10 (1H, d, J=6.4Hz)
144	-H	-H	-F	-H	-H		¹ H-NMR (CDCl ₃) δppm 1.43 (9H, s), 1.8-2.0 (1H, m), 2.0-2.2 (1H, m), 3.1-3.4 (3H, m), 3.6-3.8 (1H, m), 4.2-4.4 (1H, m), 5.95 (2H, s), 6.4-6.5 (2H, m), 6.6-6.8 (3H, m), 6.8-7.0 (2H, m)
145	-H	-H	-F	-Cl	-H		¹ H-NMR (CDCl ₃) δppm 1.44 (9H, s), 1.7-1.9 (1H, m), 2.0-2.2 (1H, m), 3.1-3.4 (3H, m), 3.6-3.8 (1H, m), 4.2-4.4 (1H, m), 6.00 (2H, s), 6.4-6.5 (3H, m), 6.66 (1H, d, J = 6.2 Hz), 6.7-7.0 (2H, m)
146	-H	-H	-H	-F	-H		¹ H-NMR (CDCl ₃) δppm 1.43 (9H, s), 1.8-1.9 (1H, m), 2.0-2.2 (1H, m), 3.1-3.4 (3H, m), 3.6-3.8 (1H, m), 4.3-4.5 (1H, m), 6.02 (2H, s), 6.27 (1H, d, J = 12.6 Hz), 6.37 (1H, d, J = 8.5 Hz), 6.4-6.5 (1H, m), 6.5-6.7 (2H, m), 6.8-6.9 (1H, m), 7.0-7.2 (1H, m)
147	-H	-H	-F	-Cl	-H		¹ H-NMR (CDCl ₃) δppm 1.43 (9H, s), 1.78-1.90 (1H, m), 2.04-2.16 (3H, m), 2.79-2.95 (4H, m), 3.13-3.32 (3H, m), 3.61-3.80 (1H, m), 4.27-4.45 (1H, m), 6.50-6.57 (1H, m), 6.61-6.79 (2H, m), 6.83 (1H, s), 6.88-7.02 (1H, m), 7.13-7.22 (1H, m)
148	-H	-H	-F	-Cl	-H		¹ H-NMR (CDCl ₃) δppm 1.45 (9H, s), 1.7-1.9 (1H, m), 2.0-2.2 (1H, m), 3.1-3.4 (3H, m), 3.6-3.8 (1H, m), 4.27 (4H, s), 4.3-4.5 (1H, m), 6.4-6.6 (3H, m), 6.68 (1H, d, J = 6.2 Hz), 6.84 (1H, dd, J = 9.1 Hz, J = 9.1 Hz), 6.9-7.0 (1H, m)
149	-H	-H	-H	-H	-H		¹ H-NMR (CDCl ₃) δppm : 1.41 (9H, s), 1.8-2.0 (1H, m), 2.05-2.3 (1H, m), 3.1-3.4 (3H, m), 3.7-3.95 (1H, m), 4.5-4.7 (1H, m), 6.85-7.0 (3H, m), 7.08 (1H, dd, J = 7, 7Hz), 7.2-7.5 (5H, m), 7.6-7.8 (3H, m)
150	-H	-H	-H	-H	-H		¹ H-NMR (CDCl ₃) δppm : 1.40 (9H, d, J = 4.5Hz), 1.65-1.9 (1H, m), 2.0-2.25 (1H, m), 3.05-3.4 (3H, m), 3.7-4.0 (1H, m), 4.6-4.8 (1H, m), 6.54 (2H, d, J = 8Hz), 6.65-6.8 (1H, m), 7.0-7.25 (2H, m), 7.31 (1H, d, J = 7Hz), 7.35-7.6 (3H, m), 7.75-8.0 (3H, m)

[0900] 表 17

[0901]

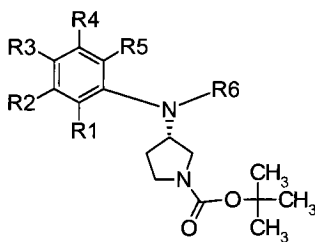


[0902]

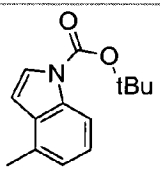
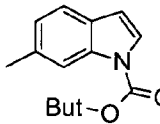
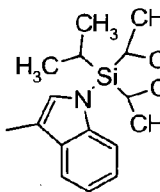
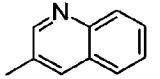
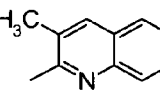
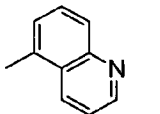
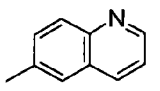
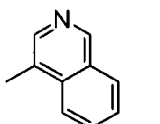
参比实 施例	R1	R2	R3	R4	R5	R6	NMR
151	-H	-H	-H	-H	-H		¹ H-NMR (CDCl ₃) δppm : 1.40 (9H, s), 1.75-2.0 (1H, m), 2.0-2.25 (1H, m), 3.1-3.4 (3H, m), 3.65-3.9 (1H, m), 4.45-4.65 (1H, m), 6.65 (2H, d, J = 8Hz), 6.7-6.85 (2H, m), 7.00 (1H, dd, J = 2, 8.5Hz), 7.1-7.25 (2H, m), 7.34 (1H, d, J = 2Hz), 7.50 (1H, dd, J = 3.5, 8.5Hz), 7.65 (1H, bs).
152	-H	-H	-F	-Cl	-H		¹ H-NMR (CDCl ₃) δppm 1.40 (9H, s), 1.7-1.9 (1H, m), 2.1-2.3 (1H, m), 3.1-3.4 (3H, m), 3.6-3.9 (1H, m), 4.3-4.5 (1H, m), 6.4-6.6 (1H, m), 6.64 (1H, s), 6.76 (1H, d, J = 7.4 Hz), 6.8-7.1 (2H, m), 7.31 (1H, s), 7.52 (1H, dd, J = 8.9 Hz, J = 9.0 Hz), 7.67 (1H, s)
153	-H	-H	-F	-Cl	-H		¹ H-NMR (CDCl ₃) δppm 1.41 (9H, s), 1.7-1.9 (1H, m), 2.1-2.3 (1H, m), 3.1-3.4 (3H, m), 3.6-3.8 (1H, m), 4.3-4.5 (1H, m), 6.5-6.7 (1H, m), 6.76 (1H, d, J = 6.2 Hz), 6.9-7.1 (2H, m), 7.2-7.3 (1H, m), 7.4-7.6 (2H, m), 7.8-7.9 (1H, m)
154	-H	-H	-H	-H	-H		¹ H-NMR (CDCl ₃) δppm : 1.41 (9H, s), 1.8-2.0 (1H, m), 2.0-2.25 (1H, m), 3.1-3.4 (3H, m), 3.65-3.95 (1H, m), 4.4-4.65 (1H, m), 6.82 (2H, dd, J = 1, 8.5Hz), 6.95 (2H, dd, J = 2, 8.5Hz), 7.15-7.3 (3H, m), 7.36 (1H, d, J = 5.5Hz), 7.47 (1H, d, J = 2Hz), 7.73 (1H, dd, J = 2.5, 8.5Hz).
155	-H	-H	-H	-H	-H		¹ H-NMR (CDCl ₃) δppm : 1.41 (9H, s), 1.75-1.95 (1H, m), 2.0-2.25 (1H, m), 3.1-3.4 (3H, m), 3.7-3.95 (1H, m), 4.5-4.75 (1H, m), 6.59 (2H, d, J = 8Hz), 6.7-6.8 (1H, m), 7.05-7.25 (4H, m), 7.3-7.5 (2H, m), 7.86 (1H, d, J = 8Hz).
156	-H	-H	-H	-H	-H		¹ H-NMR (CDCl ₃) δppm : 1.40 (9H, s), 1.75-2.0 (1H, m), 2.0-2.25 (1H, m), 3.1-3.4 (3H, m), 3.7-3.9 (1H, m), 4.45-4.65 (1H, m), 6.76 (2H, d, J = 8Hz), 6.89 (1H, dd, J = 7.5, 7.5Hz), 6.99 (1H, dd, J = 2.5, 8.5Hz), 7.15-7.3 (3H, m), 7.4-7.5 (2H, m), 7.82 (1H, dd, J = 3.5, 8.5Hz).
157	-H	-H	-F	-Cl	-H		¹ H-NMR (CDCl ₃) δppm : 1.41 (9H, s), 1.75-2.0 (1H, m), 2.0-2.25 (1H, m), 3.15-3.4 (3H, m), 3.65-3.9 (1H, m), 4.35-4.55 (1H, m), 6.55-6.7 (1H, m), 6.82 (1H, dd, J = 3, 6.5Hz), 6.85-7.1 (2H, m), 7.30 (1H, d, J = 5.5Hz), 7.41 (1H, d, J = 5.5Hz), 7.48 (1H, d, J = 2Hz), 7.76 (1H, d, J = 9Hz).

[0903] 表 18

[0904]

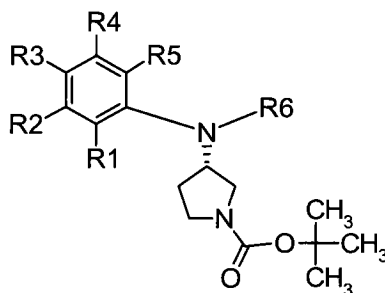


[0905]

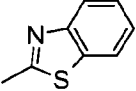
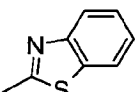
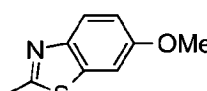
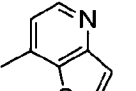
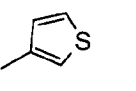
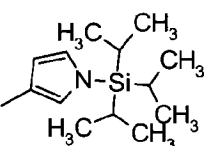
参比实 施例	R1	R2	R3	R4	R5	R6	NMR
158	-H	-H	-F	-Cl	-H		¹ H-NMR (CDCl ₃) δppm : 1.41 (9H, s), 1.68 (9H, s), 1.7-1.95 (1H, m), 2.0-2.2 (1H, m), 3.1-3.3 (3H, m), 3.65-3.9 (1H, m), 4.4-4.6 (1H, m), 6.26 (1H, d, J = 4Hz), 6.35-6.45 (1H, m), 6.60 (1H, dd, J = 3, 6Hz), 6.8-6.95 (1H, m), 6.99 (1H, d, J = 7.5Hz), 7.25-7.4 (1H, m), 7.53 (1H, br), 8.15 (1H, d, J = 8.5Hz).
159	-H	-H	-F	-Cl	-H		¹ H-NMR (CDCl ₃) δppm : 1.41 (9H, s), 1.63 (9H, s), 1.8-2.0 (1H, m), 2.0-2.25 (1H, m), 3.15-3.4 (3H, m), 3.65-3.85 (1H, m), 4.35-4.45 (1H, m), 6.5-6.65 (2H, m), 6.6-6.8 (1H, m), 6.86 (1H, dd, J = 2, 8.5Hz), 6.9-7.0 (1H, m), 7.45-7.55 (1H, m), 7.55-7.65 (1H, m), 7.86 (1H, br).
160	-H	-H	-F	-Cl	-H		¹ H-NMR (CDCl ₃) δppm : 1.17 (18H, d, J = 7.5Hz), 1.40 (9H, s), 1.71 (3H, qq, J = 7.5, 7.5Hz), 1.75-1.95 (1H, m), 2.0-2.25 (1H, m), 3.05-3.35 (3H, m), 3.65-3.95 (1H, m), 4.4-4.6 (1H, m), 6.35-6.5 (1H, m), 6.6-6.75 (1H, m), 6.8-6.95 (1H, m), 7.0-7.3 (4H, m), 7.52 (1H, d, J = 8Hz).
161	-H	-H	-F	-Cl	-H		¹ H-NMR (CDCl ₃) δppm : 1.42 (9H, s), 1.8-2.0 (1H, m), 2.1-2.3 (1H, m), 3.2-3.5 (3H, m), 3.7-3.9 (1H, m), 4.4-4.6 (1H, m), 6.8-7.0 (1H, m), 7.0-7.2 (2H, m), 7.4-7.8 (4H, m), 8.02 (1H, d, J = 8.2 Hz), 8.41 (1H, s)
162	-H	-H	-F	-Cl	-H		¹ H-NMR (CDCl ₃) δppm : 1.45 (9H, s), 1.90 (3H, s), 2.1-2.2 (1H, m), 2.2-2.3 (1H, m), 3.2-3.5 (3H, m), 3.8-4.0 (1H, m), 4.8-5.0 (1H, m), 6.8-7.0 (1H, m), 7.0-7.1 (2H, m), 7.3-7.5 (1H, m), 7.5-7.7 (2H, m), 7.76 (1H, d, J = 5.9 Hz), 7.9-8.0 (1H, m)
163	-H	-H	-F	-Cl	-H		¹ H-NMR (CDCl ₃) δppm : 1.39 (9H, d, J = 7.5Hz), 1.65-1.85 (1H, m), 1.95-2.2 (1H, m), 3.05-3.35 (3H, m), 3.6-3.95 (1H, m), 4.5-4.75 (1H, m), 6.25-6.4 (1H, m), 6.57 (1H, dd, J = 3, 6Hz), 6.75-7.0 (1H, m), 7.3-7.45 (2H, m), 7.78 (1H, dd, J = 7.5, 7.5Hz), 8.05-8.25 (2H, m), 8.95 (1H, d, J = 3.5Hz).
164	-H	-H	-H	-H	-H		¹ H-NMR (CDCl ₃) δppm : 1.39 (9H, d, J = 6Hz), 1.65-1.85 (1H, m), 1.95-2.25 (1H, m), 3.05-3.35 (3H, m), 3.7-3.95 (1H, m), 4.6-4.8 (1H, m), 6.54 (2H, d, J = 8Hz), 6.65-6.8 (1H, m), 7.05-7.2 (2H, m), 7.3-7.45 (2H, m), 7.77 (1H, dd, J = 7.5, 7.5Hz), 8.1-8.25 (2H, m), 8.93 (1H, d, J = 3.5Hz).
165	-H	-H	-F	-Cl	-H		¹ H-NMR (CDCl ₃) δppm : 1.40 (9H, s), 1.7-1.9 (1H, m), 2.0-2.3 (1H, m), 3.1-3.4 (3H, m), 3.7-3.9 (1H, m), 4.5-4.8 (1H, m), 6.3-6.5 (1H, m), 6.5-6.7 (1H, m), 6.8-7.0 (1H, m), 7.5-7.8 (3H, m), 8.08 (1H, d, J = 6.7 Hz), 8.37 (1H, s), 9.28 (1H, s)

[0906] 表 19

[0907]

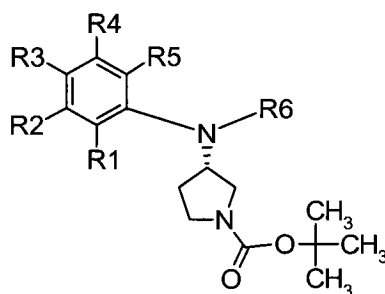


[0908]

参比实 施例	R1	R2	R3	R4	R5	R6	NMR
166	-H	-H	-H	-H	-H		¹ H-NMR (CDCl ₃) δppm 1.43 (9H, s), 1.8-2.0 (1H, m), 2.1-2.4 (1H, m), 3.1-3.4 (3H, m), 3.7-3.9 (1H, m), 5.3-5.5 (1H, m), 7.0-7.1 (1H, m), 7.2-7.4 (3H, m), 7.45 (1H, d, J = 7.7 Hz), 7.4-7.6 (3H, m), 7.61 (1H, dd, J = 8.2 Hz, J = 8.5 Hz)
167	-H	-H	-F	-Cl	-H		¹ H-NMR (CDCl ₃) δppm 1.44 (9H, s), 1.8-2.0 (1H, m), 2.2-2.4 (1H, m), 3.2-3.5 (3H, m), 3.8-4.0 (1H, m), 5.2-5.4 (1H, m), 7.0-7.4 (4H, m), 7.40 (1H, d, J = 8.6 Hz), 7.50 (1H, d, J = 7.7 Hz), 7.62 (1H, dd, J = 8.2 Hz, J = 8.6 Hz)
168	-H	-H	-F	-Cl	-H		¹ H-NMR (CDCl ₃) δppm 1.43 (9H, s), 1.8-2.0 (1H, m), 2.2-2.4 (1H, m), 3.2-3.5 (3H, m), 3.80 (3H, s), 3.8-4.0 (1H, m), 5.2-5.4 (1H, m), 6.92 (1H, d, J = 8.6 Hz), 7.03 (1H, s), 7.1-7.3 (2H, m), 7.39 (1H, d, J = 8.6 Hz), 7.52 (1H, dd, J = 9.0 Hz, J = 9.0 Hz)
169	-H	-H	-F	-Cl	-H		¹ H-NMR (CDCl ₃) δppm 1.44 (9H, s), 1.9-2.1 (1H, m), 2.1-2.3 (1H, m), 3.2-3.4 (3H, m), 3.7-3.9 (1H, m), 4.6-4.8 (1H, m), 6.77 (1H, d, J = 5.6 Hz), 7.1-7.2 (2H, m), 7.29 (1H, d, J = 6.4 Hz), 7.37 (1H, d, J = 5.6 Hz), 7.45 (1H, d, J = 5.6 Hz), 8.49 (1H, d, J = 5.6 Hz)
170	-H	-H	-H	-F	-H		¹ H-NMR (CDCl ₃) δppm 1.43 (9H, s), 1.82-2.00 (1H, m), 2.03-2.25 (1H, m), 3.10-3.39 (3H, m), 4.32-4.50 (1H, m), 6.37 (1H, dt, J=2.3Hz and 12.2Hz), 6.41-6.57 (2H, m), 6.76 (1H, dd, J=1.4Hz and J=5.1Hz), 6.96 (1H, dd, J=1.4Hz and J=3.1Hz), 7.06-7.18 (1H, m...)
171	-H	-H	-F	-Cl	-H		¹ H-NMR (CDCl ₃) δppm 1.11 (18H, d, J=7.4Hz), 1.43 (9H, s), 1.77-2.21 (2H, m), 3.07-3.35 (3H, m), 3.59-3.82 (1H, m), 4.26-4.42 (1H, m), 5.97-6.02 (1H, m), 6.43-6.58 (2H, m), 6.62-6.70 (1H, m), 6.76 (1H, s), 6.83-6.95 (1H, m)

[0909] 表 20

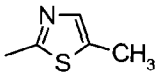
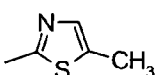
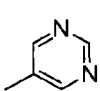
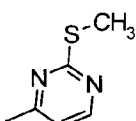
[0910]



[0911]

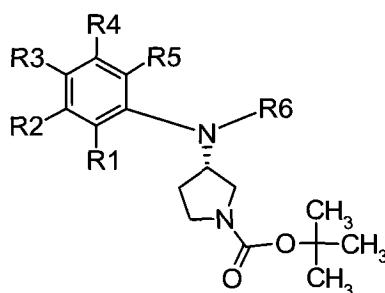
参比实 施例	R1	R2	R3	R4	R5	R6	NMR
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[0912]

172	-H	-H	-Cl	-Cl	-H		¹ H-NMR (CDCl ₃) δppm 1.42(9H,s), 1.81-2.01(1H,m), 2.03-2.31(1H,m), 2.23(3H,d,J=1.0Hz), 3.12-3.38(3H,m), 3.69-3.85(1H,m), 4.89- 5.01(1H,m), 6.85(1H,brs), 7.11(1H,dd,J=2.5Hz,8.5Hz), 7.37(1H,d,J=2.5Hz), 7.51-7.54(1H,m)
173	-H	-H	-F	-Cl	-H		¹ H-NMR (CDCl ₃) δppm 1.43 (9H, s), 1.81-2.00 (1H, m), 2.10-2.40 (1H, m), 3.11-3.41 (3H, m), 3.68-3.88 (1H, m), 4.99-5.13 (1H, m), 6.51 (1H, d, J=3.5Hz), 7.12-7.31 (3H, m), 7.35 (1H, dd, J=6.5Hz and J=2.5Hz)
174	-H	-H	-Cl	-Cl	-H		¹ H-NMR (CDCl ₃) δppm 1.43(9H,s), 1.83-2.03(1H,m), 2.11-2.35(1H,m), 3.18- 3.42(3H,m), 3.73-3.87(1H,m), 4.97-5.09(1H,m), 6.53(1H,d,J=3.5Hz), 7.14(1H,dd,J=2.5Hz,8.5Hz), 7.22(1H,brs), 7.39(1H,d,J=2.5Hz), 7.56(1H,brd,J=8.5Hz)
175	-H	-H	-F	-Cl	-H		¹ H-NMR (CDCl ₃) δppm 1.42(9H,s), 1.80-2.03(1H,m), 2.08-2.22(1H,m), 2.22(3H,s), 3.13-3.38(3H,m), 3.68-3.85(1H,m), 4.98(1H,tt,J=6.5Hz,6.5Hz), 6.84(1H,brs), 7.11-7.23(2H,m), 7.33(1H,dd,J=2.5Hz,6.5Hz)
176	-H	-H	-F	-H	-H		¹ H-NMR (CDCl ₃) δppm 1.42(9H,s), 1.76-2.03(1H,m), 2.08-2.33(1H,m), 3.08- 3.42(3H,m), 3.71-3.87(1H,m), 5.03-5.20(1H,m), 6.47(1H,d,J=3.5Hz), 7.11-7.32(5H,m)
177	-H	-H	-F	-Cl	-H		¹ H-NMR (CDCl ₃) δppm 1.43 (9H, s), 1.80-2.00 (1H, m), 2.10-2.31 (1H, m), 3.18-3.42 (3H, m), 3.63-3.80 (1H, m), 4.38-4.50 (1H, m), 6.95-7.05(1H, m), 7.14-7.30 (2H, m with dd at δ7.17, J=2.6Hz and 6.4Hz), 8.12 (2H, s), 8.72 (1H,s)
178	-H	-H	-F	-Cl	-H		¹ H-NMR (CDCl ₃) δppm 1.44 (9H, s), 1.70-1.90 (1H, m), 2.02-2.21 (1H, m), 3.09-3.41 (3H, m), 3.75-3.90 (1H, m), 5.21-5.38 (1H, m), 6.62 (1H, s), 6.99-7.09 (1H, m), 7.15-7.29 (2H, m), 8.21-8.41 (2H, m)
179	-H	-H	-F	-Cl	-H		¹ H-NMR (CDCl ₃) δppm 1.43 (9H, s), 1.7-1.9 (1H, m), 2.1-2.3 (1H, m), 2.53 (3H, s), 3.1-3.4 (3H, m), 3.7-3.9 (1H, m), 5.3-5.5 (1H, m), 5.56 (1H, d, J = 5.7 Hz), 7.0-7.1 (1H, m), 7.2-7.3 (2H, m), 7.91(1H, d, J = 5.7 Hz)

[0913] 表 21

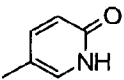
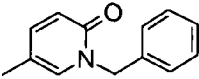
[0914]



[0915]

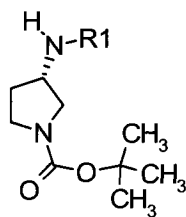
参比实 施例	R1	R2	R3	R4	R5	R6	NMR
180	-H	-H	-F	-Cl	-H		¹ H-NMR (CDCl ₃) δppm 1.43 (9H, s), 1.71-1.90 (1H, m), 2.01-2.25 (1H, m), 3.08-3.40 (3H, m), 3.71-3.89 (1H, m), 5.12-5.39 (1H, m), 7.05-7.13 (1H, m), 7.23-7.33(2H, m), 7.49 (1H, s), 7.90 (1H,s), 8.09 (1H,s)

[0916]

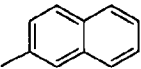
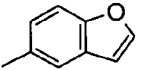
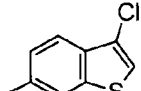
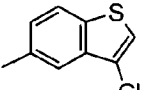
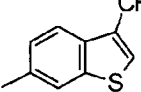
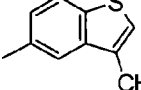
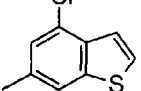
181	-H -H -F -H -H		¹ H-NMR (CDCl ₃) δppm 1.43 (9H, s), 1.69-1.87 (1H, m), 2.00-2.21 (1H, m), 3.05-3.34 (3H, m), 3.71-3.87 (1H, m), 5.13-5.27 (1H, m), 7.17 (4H, d, J=5.5Hz), 7.44 (1H, s), 7.85 (1H, s), 8.08 (1H, s).
182	-H -H -F -Cl -H		¹ H-NMR (CDCl ₃) δppm 1.40 (9H, s), 1.8-1.9 (1H, m), 2.0-2.2 (1H, m), 3.1-3.4 (3H, m), 3.6-3.8 (1H, m), 4.2-4.4 (1H, m), 6.5-6.6 (1H, m), 6.62 (1H, dd, J = 10.0 Hz, J = 9.8 Hz), 6.72 (1H, d, J = 6.0 Hz), 6.9-7.1 (1H, m), 7.2-7.3 (2H, m), 13.17 (1H, brs)
183	-H -H -F -Cl -H		¹ H-NMR (CDCl ₃) δppm 1.44 (9H, s), 1.7-1.9 (1H, m), 2.0-2.2 (1H, m), 3.0-3.4 (3H, m), 3.6-3.8 (1H, m), 4.2-4.4 (1H, m), 4.9-5.3 (2H, m), 6.4-6.5 (1H, m), 6.6-6.7 (2H, m), 6.7-7.1 (3H, m), 7.2-7.4 (5H, m)

[0917] 表 22

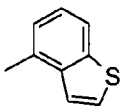
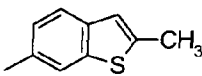
[0918]



[0919]

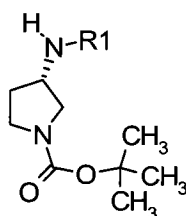
参比实施例	R1	NMR
184		¹ H-NMR (CDCl ₃) δppm: 1.47 (9H, s), 2.04 (1H, br), 2.15-2.35 (1H, m), 3.2-3.4 (1H, m), 3.4-3.6 (2H, m), 3.65-3.95 (2H, m), 4.17 (1H, br), 6.81 (1H, d, J = 2.3Hz), 6.86 (1H, dd, J = 2.4, 8.7Hz), 7.15-7.3 (1H, m), 7.37 (1H, dd, J = 7.8, 7.8Hz), 7.55-7.7 (3H, m).
185		¹ H-NMR (CDCl ₃) δppm : 1.47 (9H, s), 1.91 (1H, br), 2.1-2.3 (1H, m), 3.1-3.35 (1H, m), 3.35-3.85 (4H, m), 4.05 (1H, br), 6.55-6.7 (2H, m), 6.77 (1H, d, J = 2.3Hz), 7.31 (1H, d, J = 8.8Hz), 7.54 (1H, d, J = 2.0Hz).
186		¹ H-NMR (CDCl ₃) δppm: 1.47 (9H, s), 1.93 (1H, br), 2.15-2.3 (1H, m), 3.15-3.4 (1H, m), 3.4-3.6 (2H, m), 3.65-3.85 (1H, m), 3.85-4.0 (1H, m), 4.0-4.2 (1H, m), 6.75 (1H, dd, J = 2.1, 8.7Hz), 6.9-7.0 (2H, m), 7.60 (1H, d, J = 8.6Hz).
187		¹ H-NMR (CDCl ₃) δppm: 1.47 (9H, s), 1.85-2.05 (1H, m), 2.15-2.35 (1H, m), 3.2-3.4 (1H, m), 3.4-3.6 (2H, m), 3.65-3.9 (2H, m), 4.16 (1H, br), 6.76 (1H, dd, J = 2.2, 8.6Hz), 6.96 (1H, d, J = 2.3Hz), 7.26 (1H, s), 7.59 (1H, d, J = 8.6Hz).
188		¹ H-NMR (CDCl ₃) δppm: 1.47 (9H, s), 1.85-2.0 (1H, m), 2.1-2.3 (1H, m), 2.36 (3H, d, J = 1.1Hz), 3.1-3.35 (1H, m), 3.4-3.6 (2H, m), 3.65-3.85 (2H, m), 4.0-4.2 (1H, m), 6.71 (1H, dd, J = 2.2, 8.6Hz), 6.76 (1H, d, J = 0.8Hz), 7.01 (1H, d, J = 2.1Hz), 7.49 (1H, d, J = 8.6Hz).
189		¹ H-NMR (CDCl ₃) δppm: 1.47 (9H, s), 1.85-2.0 (1H, m), 2.15-2.3 (1H, m), 2.37 (3H, s), 3.15-3.35 (1H, m), 3.4-3.6 (2H, m), 3.65-3.85 (2H, m), 4.05-4.25 (1H, m), 6.72 (1H, dd, J = 2.2, 8.6Hz), 6.85 (1H, d, J = 2.1Hz), 7.03 (1H, s), 7.61 (1H, d, J = 8.5Hz).
190		¹ H-NMR (CDCl ₃) δppm: 1.65 (9H, s), 2.04 (1H, br), 2.1-2.3 (1H, m), 3.15-3.35 (1H, m), 3.35-3.6 (2H, m), 3.6-3.8 (1H, m), 3.8-3.95 (1H, m), 3.95-4.1 (1H, m), 6.71 (1H, d, J = 1.9Hz), 6.90 (1H, d, J = 1.5Hz), 7.15 (1H, d, J = 5.5Hz), 7.30 (1H, d, J = 5.7Hz).

[0920]

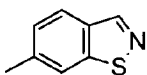
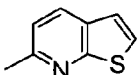
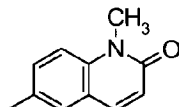
191		¹ H-NMR (CDCl ₃) δppm: 1.47 (9H, s), 1.9-2.1 (1H, m), 2.05-2.35 (1H, m), 3.2-3.65 (3H, m), 3.65-3.9 (1H, m), 4.0-4.3 (2H, m), 6.53 (1H, d, J = 7.4Hz), 7.15-7.4 (4H, m).
192		¹ H-NMR (CDCl ₃) δppm: 1.47 (9H, s), 1.91 (1H, br), 2.0-2.3 (1H, m), 2.51 (3H, d, J = 0.9Hz), 3.15-3.35 (1H, m), 3.35-3.6 (2H, m), 3.6-3.85 (2H, m), 4.07 (1H, br), 6.62 (1H, dd, J = 2.2, 8.5Hz), 6.80 (1H, s), 6.93 (1H, d, J = 2.1Hz), 7.42 (1H, d, J = 8.5Hz).

[0921] 表 23

[0922]

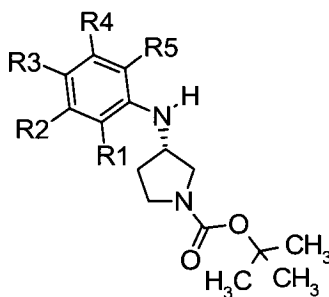


[0923]

Ref. Ex. No.	R1	NMR
193		¹ H-NMR (CDCl ₃) δppm: 1.47 (9H, s), 1.97 (1H, br), 2.15-2.3 (1H, m), 3.15-3.4 (1H, m), 3.4-3.6 (2H, m), 3.65-3.85 (1H, m), 4.0-4.25 (2H, m), 6.70 (1H, dd, J = 2.0, 8.7Hz), 6.96 (1H, d, J = 1.5Hz), 7.79 (1H, d, J = 8.7Hz), 8.65 (1H, s).
194		¹ H-NMR (CDCl ₃) δppm: 1.47 (9H, s), 1.8-2.0 (1H, m), 2.15-2.35 (1H, m), 3.15-3.6 (3H, m), 3.7-3.85 (1H, m), 4.4-4.65 (2H, m), 6.43 (1H, d, J = 8.6Hz), 7.07 (2H, s), 7.76 (1H, d, J = 8.6Hz).
195		¹ H-NMR (CDCl ₃) δppm: 1.47 (9H, s), 1.93 (1H, br), 2.17-2.29 (1H, m), 3.27 (1H, br), 3.49 (2H, br), 3.69 (3H, s), 3.92 (2H, br), 4.08 (1H, br), 6.69 (1H, d, J = 9.6 Hz), 6.71 (1H, d, J = 2.9 Hz), 6.91 (1H, dd, J = 9.0 Hz), 7.23 (1H, d, J = 2.9, 9.0 Hz), 7.55 (1H, d, J = 9.6 Hz).

[0924] 表 24

[0925]



[0926]

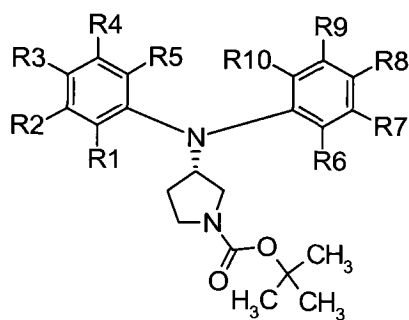
参比实施例	R1	R2	R3	R4	R5	NMR
196	-H	-H	-F	-F	-H	¹ H-NMR (CDCl ₃) δppm: 1.47(9H, s), 1.76-1.95(1H, m), 2.09-2.25(1H, m), 3.11-3.32(1H, m), 3.36-3.56 (2H, m), 3.58-3.78(2H, m), 3.85-4.03(1H, m), 6.19-6.30(1H, m), 6.34-6.43(1H, m), 6.96 (1H, dd, J=9.0, 19.0Hz)
197	-H	-Cl	-H	-Cl	-H	¹ H-NMR (CDCl ₃) δppm: 1.47 (9H, s), 1.77-1.95 (1H, m), 2.02-2.27 (1H, m), 3.15-3.75 (3H, m), 3.87-4.02 (2H, m), 6.45-6.46 (2H, m), 6.68-6.70 (1H, m).
198	-H	-H	-Cl	-CH ₃	-H	¹ H-NMR (DMSO-d ₆) δppm : 1.39 (9H, s), 1.64-1.85 (1H, m), 2.00-2.18 (1H, m), 2.21 (3H, s), 2.97-3.10 (1H, m), 3.22-3.39 (2H, m), 3.42-3.60 (1H, m), 3.78-3.96 (1H, m), 5.89 (1H, d, J = 6.8 Hz), 6.43

[0927]

						(1H, dd, J = 8.6, 2.5 Hz), 6.55 (1H, d, J = 2.5 Hz), 7.06 (1H, d, J = 8.6 Hz).
199	-H	-OCH ₃	-F	-F	-H	¹ H-NMR (DMSO-d ₆) δppm : 1.39 (9H, s), 1.60--1.82 (1H, m), 1.93-2.17 (1H, m), 2.92-3.10 (1H, m), 3.20-3.44 (1H, m), 3.48-3.57 (1H, m), 3.75 (3H, s), 3.80-4.00 (1H, m), 6.01-6.19 (2H, m).
200	-H	-F	-F	-F	-H	¹ H-NMR (CDCl ₃) δppm: 1.47 (9H, s), 1.74--1.92 (1H, m), 2.08-2.21 (1H, m), 3.08-3.28 (1H, m), 3.33-3.51 (2H, m), 3.61-3.95 (2H, m), 6.08-6.21 (2H, m).
201	-H	-F	-Cl	-F	-H	¹ H-NMR (CDCl ₃) δppm: 1.45 (9H, s), 1.78--1.93 (1H, m), 2.03-2.24 (1H, m), 3.09-3.31 (1H, m), 3.36-3.52 (2H, m), 3.60-3.75 (1H, m), 3.85-4.08 (1H, m), 6.15-6.24 (2H, m).
202	-H	-H	-CH ₃	-F	-H	¹ H-NMR (CDCl ₃) δppm: 1.46 (9H, s), 1.87 (1H, br), 2.14-2.23 (1H, m), 2.15 (3H, d, J = 1.4 Hz), 3.21 (1H, br), 3.45 (2H, br), 3.68 (2H, br), 3.97 (1H, br), 6.26-6.31 (2H, m), 6.95 (1H, dd, J = 8.5, 10.7 Hz).
203	-H	-H	-Cl	-H	-H	¹ H-NMR (CDCl ₃) δppm 1.46 (9H, s), 1.78-1.96 (1H, m), 2.10-2.20(1H,m), 3.11-3.30 (1H, m), 3.40-3.56 (2H, m), 3.60-3.80(2H, m), 3.85-4.03 (1H, m), 6.52 (2H, d, J=8.7Hz), 7.12 (1H, d, 8.7Hz)

[0928] 表 25

[0929]

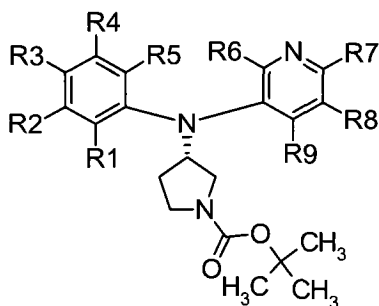


[0930]

参比实施例	R1	R2	R3	R4	R5	R6	R7	R8	R9	R10	NMR
204	-H	-H	-F	-Cl	-H	-CH ₃	-H	-F	-H	-H	¹ H-NMR (CDCl ₃) δppm; {1.42 (s), 1.44 (s) total 9H, 1:1}, 1.71-1.89 (1H, m), 2.03-2.19 (1H, m), 2.08 (3H, s), 3.12-3.36 (3H, m), 3.61-3.82(1H, m), 4.32-4.45 (1H, m), 6.23-6.29 (1H, m), 6.46 (1H, dd, J=3.0, 6.0Hz), 6.86-7.07 (4H, m)
205	-H	-H	-F	-F	-H	-H	-F	-F	-H	-H	¹ H-NMR (CDCl ₃) δppm; 1.43(9H, s), 1.73-1.92(1H, m), 2.00-2.22(1H, m), 3.11-3.36(3H, m), 3.59-3.78 (1H, m), 4.25-4.41(1H, m), 6.51-6.72(4H, m), 7.09(2H, dd, J=8.5, 18.0Hz)

[0931] 表 26

[0932]

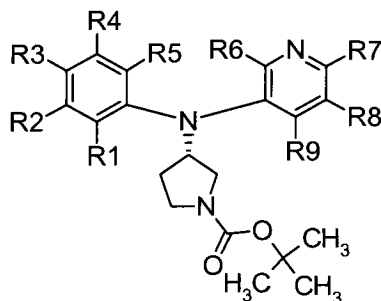


[0933]

参比实施例	R1	R2	R3	R4	R5	R6	R7	R8	R9	NMR
206	-H	-Cl	-Cl	-H	-H	-H	-H	-H	-H	¹ H-NMR (CDCl ₃) δppm; 1.43 (9H, s), 1.79-1.90 (1H, m), 2.10-2.20 (1H, m), 3.15-3.33 (3H, m), 3.67-3.84 (1H, m), 4.39-4.52 (1H, m), 6.63 (1H, dd, J=2.7, 8.8Hz), 6.89 (1H, d, J=2.7Hz), 7.24-7.32 (3H, m), 8.28 (1H, brs), 8.42 (1H, brs).
207	-H	-Cl	-F	-H	-H	-H	-H	-H	-CH ₃	¹ H-NMR (CDCl ₃) δppm; 1.44 (9H, s), 1.74-1.89 (1H, m), 2.04-2.20 (1H, m), 2.12 (3H, s), 3.13-3.21 (1H, m), 3.24-3.38 (2H, m), 3.69-3.85 (1H, m), 4.39-4.55 (1H, m), 6.25-6.36 (1H, m), 6.52 (1H, dd, J=3.1, 6.0Hz), 6.90-6.98 (1H, m), 7.25-7.28 (1H, m), 8.30 (1H, s), 8.48 (1H, d, J=4.8Hz).
208	-H	-Cl	-Cl	-H	-H	-H	-H	-H	-CH ₃	¹ H-NMR (CDCl ₃) δppm; 1.43 (9H, s), 1.70-1.86 (1H, m), 2.04-2.28 (1H, m), 2.12 (3H, s), 3.14-3.21 (1H, m), 3.23-3.35 (2H, m), 3.68-3.84 (1H, m), 4.43-4.51-5.35 (1H, m), 6.29 (1H, d, 8.7Hz), 6.56 (1H, d, J=2.9Hz), 7.16-7.20 (1H, m), 7.27-7.30 (1H, m), 8.29 (1H, s), 8.50 (1H, d, J=4.7Hz).

[0934] 表 27

[0935]

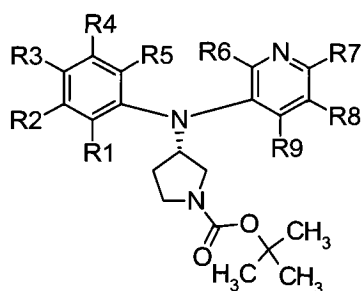


[0936]

参比实施例	R1	R2	R3	R4	R5	R6	R7	R8	R9	NMR
209	-H	-Cl	-H	-Cl	-H	-H	-H	-H	-H	¹ H-NMR (CDCl ₃) δppm : 1.43 (9H, s), 1.72-1.89 (1H, m), 2.08-2.24 (1H, m), 3.09-3.32 (3H, m), 3.67-3.84 (1H, m), 4.38-4.52 (1H, m), 6.52-6.53 (2H, m), 6.87-6.89 (1H, m), 7.35-7.40 (2H, m), 8.34-8.35 (1H, m), 8.54-8.56 (1H, m).
210	-H	-CH ₃	-Cl	-H	-H	-H	-H	-H	-H	¹ H-NMR (CDCl ₃) δppm : 1.43 (9H, s), 1.79-1.92 (1H, m), 2.04-2.22 (1H, m), 2.34 (3H, s), 3.15-3.38 (3H, m), 6.76 (1H, dd, J = 8.4, 2.5 Hz), 6.85 (1H, d, J = 2.5 Hz), 6.97-7.05 (1H, m), 6.87-6.89 (1H, dd, J = 8.4, 4.6 Hz), 7.27-7.35 (1H, m), 8.09-8.145 (1H, m), 8.18 (1H, d, J = 3.8 Hz).
211	-H	-Cl	-F	-H	-H	-H	-H	-F	-H	¹ H-NMR (CDCl ₃) δppm: 1.43 (9H, s), 1.8-1.95 (1H, m), 2.05-2.3 (1H, m), 3.15-3.4 (3H, m), 3.65-3.8 (1H, m), 4.35-4.5 (1H, m), 6.59 (1H, d, J = 10.2Hz), 6.95-7.05 (1H, m), 7.1-7.3 (2H, m), 7.84 (1H, br), 7.96 (1H, d, J = 2.1Hz).
212	-H	-CH ₃	-F	-H	-H	-H	-H	-F	-H	¹ H-NMR (CDCl ₃) δppm: 1.43 (9H, s), 1.8-1.95 (1H, m), 2.05-2.25 (1H, m), 2.29 (3H, s), 3.15-3.35 (3H, m), 3.65-3.8 (1H, m), 4.35-4.5 (1H, m), 6.45-6.55 (1H, m), 6.85-6.95 (2H, m), 7.0-7.15 (1H, m), 7.79 (1H, br), 7.87 (1H, d, J = 1.9Hz).
213	-H	-H	-F	-H	-H	-H	-H	-F	-H	¹ H-NMR (CDCl ₃) δppm: 1.43 (9H, s), 1.8-1.95 (1H, m), 2.05-2.25 (1H, m), 3.1-3.35 (3H, m), 3.65-3.8 (1H, m), 4.35-4.5 (1H, m), 6.45-6.55 (1H, m), 7.05-7.2 (4H, m), 7.80 (1H, br), 7.88 (1H, d, J = 2.1Hz).

[0937] 表 28

[0938]

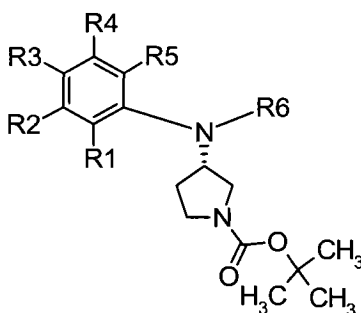


[0939]

参比实施例	R1	R2	R3	R4	R5	R6	R7	R8	R9	NMR
214	-H	-Cl	-F	-H	-H	-H	-H	-F	-H	¹ H-NMR (CDCl ₃) δppm: 1.43 (9H, s), 1.8-1.95 (1H, m), 2.05-2.3 (1H, m), 3.15-3.4 (3H, m), 3.65-3.8 (1H, m), 4.35-4.5 (1H, m), 6.59 (1H, d, J = 10.2Hz), 6.95-7.05 (1H, m), 7.1-7.3 (2H, m), 7.84 (1H, br), 7.96 (1H, d, J = 2.1Hz).
215	-H	-CH ₃	-F	-H	-H	-H	-H	-F	-H	¹ H-NMR (CDCl ₃) δppm: 1.43 (9H, s), 1.8-1.95 (1H, m), 2.05-2.25 (1H, m), 2.29 (3H, s), 3.15-3.35 (3H, m), 3.65-3.8 (1H, m), 4.35-4.5 (1H, m), 6.45-6.55 (1H, m), 6.85-6.95 (2H, m), 7.0-7.15 (1H, m), 7.79 (1H, br), 7.87 (1H, d, J = 1.9Hz).
216	-H	-H	-F	-H	-H	-H	-H	-F	-H	¹ H-NMR (CDCl ₃) δppm: 1.43 (9H, s), 1.8-1.95 (1H, m), 2.05-2.25 (1H, m), 3.1-3.35 (3H, m), 3.65-3.8 (1H, m), 4.35-4.5 (1H, m), 6.45-6.55 (1H, m), 7.05-7.2 (4H, m), 7.80 (1H, br), 7.88 (1H, d, J = 2.1Hz).

[0940] 表 29

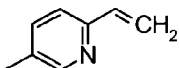
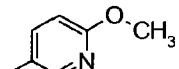
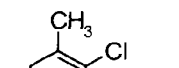
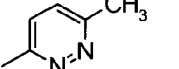
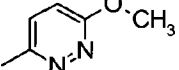
[0941]



[0942]

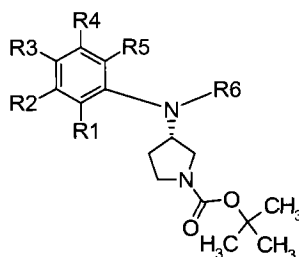
参比实施例	R1	R2	R3	R4	R5	R6	NMR
217	-H	-H	-Cl	-Cl	-H		¹ H-NMR (CDCl ₃) δppm: 1.43 (9H, s), 1.75-1.89 (1H, m), 2.03-2.20 (1H, m), 3.08-3.33 (3H, m), 3.80 (1H, dd, J=7.1, 10.9Hz), 5.17-5.29 (1H, m), 6.00 (1H, d, J=9.0Hz), 7.03 (1H, dd, J=2.4, 8.4Hz), 7.25 (1H, dd, J=2.2, 9.0Hz), 7.29 (1H, d, J=2.2Hz), 7.52-7.57 (1H, dd, J=4.7, 8.3Hz), 8.13 (1H, d, J=4.7Hz).
218	-H	-H	-F	-Cl	-H		¹ H-NMR (CDCl ₃) δppm: 1.44 (9H, s), 1.80-2.21 (2H, m), 3.20-3.47 (3H, m), 3.57-3.78 (1H, m), 4.68-4.74 (1H, m), 6.85-7.03 (4H, m), 7.55-7.59 (1H, m), 8.29-8.32 (1H, m).
219	-H	-H	-F	-Cl	-H		¹ H-NMR (CDCl ₃) δppm: 1.44 (9H, s), 1.71-1.89 (1H, m), 2.04-2.28 (1H, m), 3.10-3.34 (3H, m), 3.85 (1H, dd, J=7.5, 10.3Hz), 5.35-5.43 (1H, m), 6.08 (1H, d, J=8.8Hz), 7.07-7.12 (1H, m), 7.26-7.36 (5H, m), 7.46-7.51 (2H, m), 8.42 (1H, d, J=5.9Hz).

[0943]

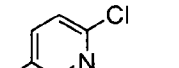
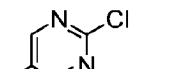
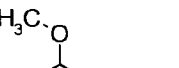
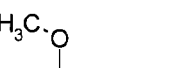
220	-H	-H	-F	-Cl	-H		¹ H-NMR (CDCl ₃) δppm: 1.43 (9H, s), 1.80-1.93 (1H, m), 2.05-2.21 (1H, m), 3.14-3.35 (3H, m), 3.67-3.82 (1H, m), 4.35-4.46 (1H, m), 5.36 (1H, d, J=10.8Hz), 6.05 (1H, d, J=17.4Hz), 6.75 (1H, dd, J=10.8, 17.4Hz), 6.83-6.89 (1H, m), 7.02-7.19 (3H, m), 7.24 (1H, d, J=8.6Hz), 8.09 (1H, s).
221	-H	-H	-Cl	-Cl	-H		¹ H-NMR (CDCl ₃) δppm: 1.32 (9H, s), 1.75-1.89 (1H, m), 2.08-2.20 (1H, m), 3.07-3.32 (3H, m), 3.67-3.81 (1H, m), 3.97 (3H, s), 4.38-4.46 (1H, m), 6.42 (1H, dd, J=2.9, 9.0Hz), 6.66 (1H, d, J=2.9Hz), 6.81 (1H, dd, J=3.1, 8.4Hz), 7.17 (1H, d, J=6.8Hz), 7.30 (1H, dd, J=2.7, 8.8Hz), 7.94 (1H, d, 2.3Hz).
222	-H	-H	-F	-Cl	-H		¹ H-NMR (CDCl ₃) δppm: 1.43 (9H, s), 1.80-1.93 (1H, m), 2.15-2.20 (1H, m), 2.29 (3H, s), 3.18-3.39 (3H, m), 3.63-3.77 (1H, m), 4.41 (1H, brs), 6.85-6.91 (2H, m), 7.03-7.07 (1H, m), 7.11-7.18 (1H, m), 7.73 (1H, brs).
223	-H	-H	-F	-Cl	-H		¹ H-NMR (CDCl ₃) δppm: 1.43 (9H, s), 1.78-1.92 (1H, m), 2.09-2.36 (1H, m), 2.55 (3H, s), 3.15-3.32 (3H, m), 3.68-3.99 (1H, m), 5.31-5.52 (1H, m), 6.24 (1H, d, J=9.2Hz), 6.96 (1H, d, J=9.2Hz), 7.06 (1H, ddd, J=2.6, 4.2, 8.6Hz), 7.15-7.27 (1H, m), 7.55-7.59 (1H, m).
224	-H	-H	-F	-Cl	-H		¹ H-NMR (CDCl ₃) δppm: 1.43 (9H, s), 1.78-1.97 (1H, m), 2.08-2.36 (1H, m), 3.12-3.32 (3H, m), 3.67-3.96 (1H, m), 4.05 (3H, s), 5.14-5.33 (1H, m), 6.39 (1H, d, J=9.6Hz), 6.72 (1H, d, J=9.6Hz), 7.07 (1H, ddd, J=2.6, 4.2, 8.6Hz), 7.11-7.32 (2H, m).

[0944] 表 30

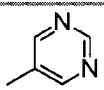
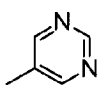
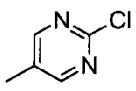
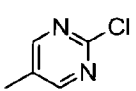
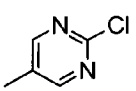
[0945]



[0946]

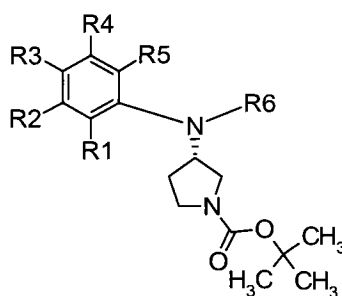
参比实施例	R1	R2	R3	R4	R5	R6	NMR
225	-H	-H	-F	-Cl	-H		¹ H-NMR (CDCl ₃) δppm: 1.43 (9H, s), 1.81-1.95 (1H, m), 2.10-2.35 (1H, m), 3.12-3.30 (3H, m), 3.74-3.95 (1H, m), 5.34-5.45 (1H, m), 6.31 (1H, d, J=9.4Hz), 7.06-7.10 (2H, m), 7.21-7.33 (2H, m).
226	-H	-H	-F	-Cl	-H		¹ H-NMR (CDCl ₃) δppm: 1.43 (9H, s), 1.84-1.99 (1H, m), 2.10-2.29 (1H, m), 3.12-3.38 (3H, m), 3.70-3.76 (1H, m), 4.36-4.45 (1H, m), 7.02 (1H, ddd, J=2.7, 4.1, 8.6Hz), 7.20 (1H, dd, J=2.5, 6.4Hz), 7.21-7.28 (1H, m), 7.97 (2H, m).
227	-H	-H	-F	-Cl	-H		¹ H-NMR (CDCl ₃) δppm: 1.44 (9H, s), 1.80-1.95 (1H, m), 2.04-2.20 (1H, m), 3.20-3.40 (3H, m), 3.70 (6H, s), 3.77-3.88 (1H, m), 5.21-5.30 (1H, m), 5.46 (1H, s), 7.02 (1H, ddd, J=2.5, 4.3, 8.7Hz), 7.13-7.19 (1H, m), 7.24 (1H, dd, J=2.4, 6.6Hz).
228	-H	-H	-F	-Cl	-H		¹ H-NMR (CDCl ₃) δppm: 1.43 (9H, s), 1.70-1.88 (1H, m), 1.97-2.20 (1H, m), 3.07-3.30 (3H, m), 3.72-3.82 (1H, m), 3.83 (3H, s), 3.96 (3H, s), 4.86 (1H, s), 5.37-5.41 (1H, m), 7.05 (1H, ddd, J=2.6, 4.2, 8.7Hz), 7.21-7.31 (2H, m).

[0947]

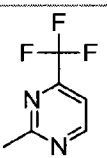
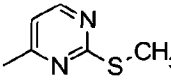
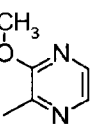
229	-H	-H	-F	-H	-H		¹ H-NMR (CDCl ₃) δppm: 1.43 (9H, s), 1.86-1.96 (1H, m), 2.16-2.28 (1H, m), 3.10-3.35 (3H, m), 3.72-3.77 (1H, m), 4.41-4.51 (1H, m), 7.09-7.17 (4H, m), 8.07 (2H, s), 8.64 (1H, s).
230	-H	-H	-F	-CH ₃	-H		¹ H-NMR (CDCl ₃) δppm: 1.43 (9H, s), 1.85-1.97 (1H, m), 2.05-2.28 (1H, m), 2.29 (3H, s), 3.20-3.35 (3H, m), 3.70-3.78 (1H, m), 4.43-4.47 (1H, m), 6.89-7.97 (2H, m), 7.06-7.13 (1H, m), 8.06 (2H, s), 8.63 (1H, s).
231	-H	-H	-Cl	-Cl	-H		¹ H-NMR (CDCl ₃) δppm: 1.43 (9H, s), 1.81-1.96 (1H, m), 2.10-2.31 (1H, m), 3.15-3.39 (3H, m), 3.63-3.78 (1H, m), 4.37-4.45 (1H, m), 6.90 (1H, dd, J=2.5, 8.6Hz), 7.16 (1H, d, J=2.4Hz), 7.51 (1H, d, J=8.3Hz), 8.05 (2H, s).
232	-H	-H	-F	-H	-H		¹ H-NMR (CDCl ₃) δppm: 1.42 (9H, s), 1.78-1.93 (1H, m), 2.10-2.26 (1H, m), 3.09-3.37 (3H, m), 3.63-3.70 (1H, m), 4.37-4.45 (1H, m), 7.07-7.29 (4H, m), 7.92 (2H, s).
233	-H	-H	-F	-CH ₃	-H		¹ H-NMR (CDCl ₃) δppm: 1.43 (9H, s), 1.81-1.95 (1H, m), 2.05-2.27 (1H, m), 2.29 (3H, s), 3.19-3.43 (3H, m), 3.65-3.80 (1H, m), 4.35-4.43 (1H, m), 6.90-6.97 (2H, m), 7.07-7.13 (1H, m), 7.91 (2H, s).

[0948] 表 31

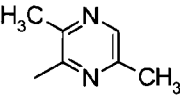
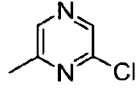
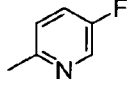
[0949]



[0950]

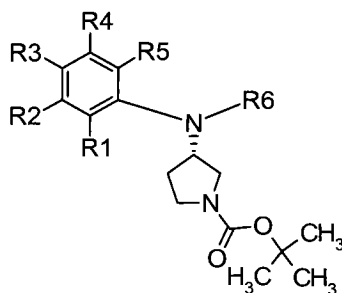
参比实施例	R1	R2	R3	R4	R5	R6	NMR
234	-H	-H	-F	-Cl	-H		¹ H-NMR (CDCl ₃) δppm: 1.44 (9H, s), 1.74-1.90 (1H, m), 2.08-2.26 (1H, m), 3.09-3.35 (3H, m), 3.78-3.88 (1H, m), 5.20-5.35 (1H, m), 6.92 (1H, d, J=4.8Hz), 7.04 (1H, ddd, J=2.5, 4.2, 8.7Hz), 7.20-7.25 (2H, m), 8.47 (1H, d, J=4.6Hz).
235	-H	-H	-Cl	-Cl	-H		¹ H-NMR (CDCl ₃) δppm: 1.43 (9H, s), 1.77-1.88 (1H, m), 2.05-2.28 (1H, m), 2.52 (3H, s), 3.15-3.33 (3H, m), 3.70-3.90 (1H, m), 5.28-5.43 (1H, m), 5.60 (1H, d, J=6.0Hz), 7.03 (1H, dd, J=2.4, 8.5Hz), 7.29 (1H, d, J=2.4Hz), 7.58 (1H, d, J=8.3Hz), 7.90 (1H, d, J=6.0Hz).
236	-H	-H	-Cl	-Cl	-H		¹ H-NMR (CDCl ₃) δppm: 1.44 (9H, s), 1.75-1.88 (1H, m), 2.05-2.20 (1H, m), 3.12-3.36 (3H, m), 3.77-3.87 (1H, m), 5.24-5.34 (1H, m), 6.62 (1H, brs), 7.02 (1H, dd, J=2.4, 8.5Hz), 7.27 (1H, d, J=2.4Hz), 7.51 (1H, dd, J=4.1, 8.4Hz), 8.32 (2H, brs).
237	-H	-H	-F	-Cl	-H		¹ H-NMR (CDCl ₃) δppm: 1.44 (9H, s), 1.87-1.96 (1H, m), 2.04-2.20 (1H, m), 3.15-3.39 (3H, m), 3.61 (3H, s), 3.72-3.84 (1H, m), 4.77-4.86 (1H, m), 6.96 (1H, ddd, J=2.6, 4.3, 8.7Hz), 7.06 (1H, dd, J=2.6, 8.5Hz), 7.11 (1H, dd, J=2.6, 6.6Hz), 7.65 (1H, brs), 7.79 (1H, d, J=4.4Hz).

[0951]

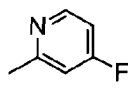
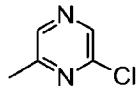
238	-H	-H	-F	-Cl	-H		¹ H-NMR (CDCl ₃) δppm: 1.42 (9H, s), 1.90-2.20 (2H, m), 2.00 (3H, s), 2.48 (3H, s), 3.22-3.45 (3H, m), 3.61-3.82 (1H, m), 4.67-4.76 (1H, m), 6.80-6.84 (1H, m), 6.95-7.02 (1H, m), 7.08 (1H, t, J=8.6Hz), 8.04 (1H, d, J=5.2Hz).
239	-H	-H	-F	-Cl	-H		¹ H-NMR (CDCl ₃) δppm: 1.44 (9H, s), 1.78-1.86 (1H, m), 2.05-2.24 (1H, m), 3.08-3.31 (3H, m), 3.80 (1H, dd, J=7.0, 9.0Hz), 5.17-5.23 (1H, m), 7.10 (1H, ddd, J=2.6, 3.9, 8.7Hz), 7.26-7.32 (3H, m), 7.88 (1H, s).
240	-H	-H	-Cl	-Cl	-H		¹ H-NMR (CDCl ₃) δppm: 1.44 (9H, s), 1.77-1.87 (1H, m), 2.04-2.21 (1H, m), 3.11-3.35 (3H, m), 3.75-3.86 (1H, m), 5.14-5.23 (1H, m), 7.07 (1H, dd, J=2.4, 8.5Hz), 7.33 (1H, d, J=2.4Hz), 7.51 (1H, d, J=1.1Hz), 7.58 (1H, dd, J=3.9, 8.2Hz), 7.90 (1H, s), 8.09 (1H, s).
241	-H	-H	-Cl	-Cl	-H		¹ H-NMR (CDCl ₃) δppm: 1.44 (9H, s), 1.73-1.80 (1H, m), 2.01-2.18 (1H, m), 3.03-3.33 (3H, m), 3.81 (1H, dd, J=6.1, 10.7Hz), 5.13-5.22 (1H, m), 6.06 (1H, dd, J=3.4, 9.2Hz), 7.02 (1H, dd, J=2.4, 8.4Hz), 7.06-7.12 (1H, m), 7.28 (1H, d, J=2.4Hz), 7.50-7.55 (1H, m), 8.06 (1H, brs).

[0952] 表 32

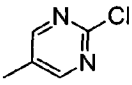
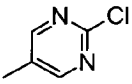
[0953]



[0954]

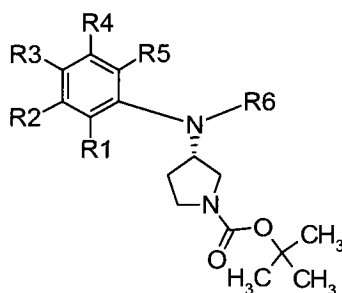
参比实施例	R1	R2	R3	R4	R5	R6	NMR
242	-H	-H	-Cl	-Cl	-H		¹ H-NMR (CDCl ₃) δppm: 1.43 (9H, s), 1.75-1.84 (1H, m), 2.04-2.18 (1H, m), 3.03-3.33 (3H, m), 3.77-3.85 (1H, m), 5.29-5.38 (1H, m), 5.68 (1H, dd, J=2.1, 12.0Hz), 6.38-6.46 (1H, m), 7.03 (1H, dd, J=2.4, 8.5Hz), 7.29 (1H, d, J=2.3Hz), 7.54-7.59 (1H, m), 8.10-8.18 (1H, m).
243	-H	-H	-Cl	-Cl	-H		¹ H-NMR (CDCl ₃) δppm: 1.43 (9H, s), 1.72-1.86 (1H, m), 2.04-2.22 (1H, m), 3.08-3.33 (3H, m), 3.83 (1H, dd, J=7.1, 10.8Hz), 5.28-5.37 (1H, m), 6.04 (1H, d, J=8.6Hz), 6.63-6.68 (1H, m), 7.03 (1H, dd, J=2.4, 8.5Hz), 7.27-7.35 (2H, m), 7.51-7.56 (1H, m), 8.17-8.22 (1H, m).
244	-H	-H	-F	-Cl	-H		¹ H-NMR (CDCl ₃) δppm: 1.44 (9H, s), 1.73-1.90 (1H, m), 2.05-2.22 (1H, m), 3.08-3.34 (3H, m), 3.82 (1H, dd, J=7.2, 10.7Hz), 5.16-5.25 (1H, m), 7.08-7.14 (1H, m), 7.27-7.33 (2H, m), 7.49 (1H, s), 7.89 (1H, brs), 8.09 (1H, brs).
245	-H	-H	-Cl	-Cl	-H		¹ H-NMR (CDCl ₃) δppm: 1.44 (9H, s), 1.76-1.89 (1H, m), 2.05-2.28 (1H, m), 3.10-3.35 (3H, m), 3.77-3.87 (1H, m), 5.14-5.25 (1H, m), 7.08 (1H, dd, J=2.4, 8.5Hz), 7.34 (1H, d, J=2.3Hz), 7.52 (1H, s), 7.59 (1H, dd, J=4.0, 8.2Hz), 8.10 (1H, brs), 8.66 (1H, brs).
246	-H	-H	-Cl	-Cl	-H		¹ H-NMR (CDCl ₃) δppm: 1.44 (9H, s), 1.75-1.86 (1H, m), 2.09-2.28 (1H, m), 3.12-3.34 (3H, m), 3.80 (1H, dd, J=7.1, 10.0Hz), 5.13-5.24 (1H, m), 7.07 (1H, dd, J=2.4, 8.5Hz), 7.32-7.34 (2H, m), 7.59 (1H, d, J=8.0Hz), 8.49 (1H, s).
247	-H	-H	-Cl	-Cl	-H		¹ H-NMR (CDCl ₃) δppm: 1.43 (9H, s), 1.82-1.95 (1H, m), 2.09-2.25 (1H, m), 3.13-3.37 (3H, m), 3.70-3.80 (1H, m), 4.41-4.50 (1H, m), 6.86 (1H, dd, J=2.5, 8.6Hz), 7.13 (1H, d, J=2.5Hz), 7.48 (1H, d, J=8.8Hz), 8.22 (2H, s), 8.82 (1H, s).

[0955]

248	-H	-H	-Cl	-Cl	-H		¹ H-NMR (CDCl ₃) δppm: 1.44 (9H, s), 1.74-1.88 (1H, m), 2.05-2.20 (1H, m), 3.10-3.38 (3H, m), 3.77-3.87 (1H, m), 5.22-5.34 (1H, m), 6.63 (1H, brs), 7.02 (1H, dd, J=2.4, 8.5Hz), 7.28 (1H, d, J=2.4Hz), 7.51 (1H, dd, J=4.3, 8.4Hz), 8.32 (2H, brs).
249	-H	-H	-Cl	-Cl	-H		¹ H-NMR (CDCl ₃) δppm: 1.43 (9H, s), 1.79-1.90 (1H, m), 2.04-2.27 (1H, m), 3.14-3.36 (3H, m), 3.67-3.80 (1H, m), 4.36-4.45 (1H, m), 6.89 (1H, dd, J=2.5, 8.5Hz), 7.16 (1H, d, J=2.3Hz), 7.51 (1H, d, J=8.4Hz), 8.05 (1H, brs).
250	-H	-H	-F	-Cl	-H		¹ H-NMR (CDCl ₃) δppm: 1.43 (9H, s), 1.80-1.98 (1H, m), 2.11-2.28 (1H, m), 3.15-3.39 (3H, m), 3.68-3.78 (1H, m), 4.36-4.45 (1H, m), 6.99-7.05 (1H, m), 7.18-7.27 (2H, m), 7.97 (2H, s).

[0956] 表 33

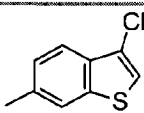
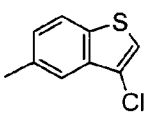
[0957]



[0958]

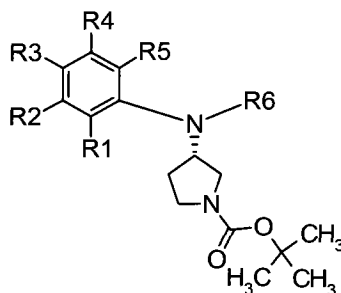
参比实施例	R1	R2	R3	R4	R5	R6	NMR
251	-H	-H	-F	-F	-H		¹ H-NMR (CDCl ₃) δppm: 1.43(9H, s), 1.79-1.97(1H, m), 2.01-2.22(1H, m), 3.08-3.38(3H, m), 3.60-3.78 (1H, m), 4.25-4.41(1H, m), 6.42-6.62(2H, m), 6.66(1H, dd, J=1.5, 5.0Hz), 6.78(1H, dd, J=1.5, 3.0Hz), 6.91-7.07(1H, m), 7.30 (1H, d, J=3.0Hz)
252	-H	-H	-Cl	-CH ₃	-H		¹ H-NMR (CDCl ₃) δppm: 1.43 (9H, s), 1.78-1.97 (1H, m), 2.03-2.20 (1H, m), 2.29 (3H, s), 3.18-3.38 (3H, m), 3.61-3.82 (1H, m), 4.34-4.43 (1H, m), 6.54-6.73 (4H, m), 7.11-7.30 (2H, m).
253	-H	-Cl	-H	-Cl	-H		¹ H-NMR (CDCl ₃) δppm: 1.44 (9H, s), 1.78--1.94 (1H, m), 2.04-2.20 (1H, m), 3.13-3.34 (3H, m), 3.67-3.80 (1H, m), 4.29-4.45 (1H, m), 6.48 (2H, d, J = 1.7 Hz), 6.72-6.83 (2H, m), 7.04 (1H, dd, J = 3.1, 1.7 Hz), 7.37-7.42 (1H, m).
254	-H	-H	-F	-H	-H		¹ H-NMR (CDCl ₃) δppm: 1.43 (9H, s), 1.82-2.00 (1H, m), 2.01-2.23 (1H, m), 3.10-3.40 (3H, m), 3.61-3.79 (1H, m), 4.26-4.42 (1H, m), 6.41-6.44 (1H, m), 6.50 (1H, dd, J= 1.5, 5.0Hz), 6.89-7.02 (4H, m), 7.18 (1h, brs)
255	-H	-H	-Cl	-Cl	-H		¹ H-NMR (CDCl ₃) δppm: 1.43 (9H, s), 1.81-1.98 (1H, m), 2.05-2.24 (1H, m), 3.12-3.38 (3H, m), 3.63-3.82 (1H, m), 4.30-4.46 (1H, m), 6.50 (1H, dd, J = 3.0, 9.0Hz), 6.72-6.76 (2H, m), 6.96 (1H, dd, J=1.5, 3.0Hz), 7.20 (1H, brd, J = 9.5Hz), 7.36 (1H, brs)
256	-H	-H	-F	-Cl	-H		¹ H-NMR (CDCl ₃) δppm: 1.27-1.52 (11H, m), 1.62-1.82 (3H, m), 1.90-2.05 (1H, m), 2.95-3.69 (7H, m), 3.85-4.05 (3H, m), 6.95-7.00 (1H, m), 7.00-7.16 (2H, m).
257	-H	-H	-F	-Cl	-H		¹ H-NMR (CDCl ₃) δppm: 1.15-1.35 (2H, m), 1.46 (9H, s), 1.52-1.73 (3H, m), 1.76-2.05 (2H, m), 2.91 (2H, d, J = 6.7 Hz), 3.08-3.35 (4H, m), 3.35-3.65 (2H, m), 3.80-4.00 (3H, m), 6.76-6.88 (1H, m), 6.95-7.10 (2H, m).
258	-H	-H	-F	-Cl	-H		¹ H-NMR (CDCl ₃) δppm: 1.42 (9H, s), 1.8-1.95 (1H, m), 2.1-2.25 (1H, m), 3.15-3.35 (3H, m), 3.65-3.85 (1H, m), 4.45-4.6 (1H, m), 6.7-6.8 (1H, m), 6.9-7.0 (2H, m), 7.0-7.1 (1H, m), 7.21 (1H, s), 7.31 (1H, d, J = 1.7Hz), 7.65-7.8 (1H, m).

[0959]

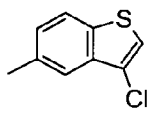
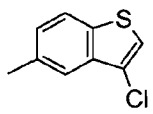
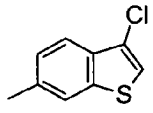
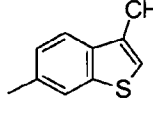
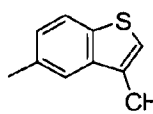
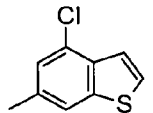
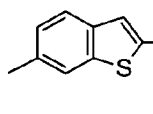
259	-H -H -H -H -H		¹ H-NMR (CDCl ₃) δppm: 1.42 (9H, s), 1.8-1.95 (1H, m), 2.1-2.25 (1H, m), 3.15-3.35 (3H, m), 3.65-3.9 (1H, m), 4.45-4.6 (1H, m), 6.85-7.0 (3H, m), 7.05-7.2 (2H, m), 7.25-7.4 (3H, m), 7.6-7.75 (1H, m).
260	-H -H -F -Cl -H		¹ H-NMR (CDCl ₃) δppm: 1.42 (9H, s), 1.8-2.0 (1H, m), 2.1-2.3 (1H, m), 3.15-3.4 (3H, m), 3.65-3.85 (1H, m), 4.4-4.6 (1H, m), 6.65-6.75 (1H, m), 6.86 (1H, dd, J = 2.9, 6.3Hz), 6.95 (1H, dd, J = 2.2, 8.6Hz), 6.95-7.1 (1H, m), 7.35 (1H, s), 7.42 (1H, d, J = 2.1Hz), 7.74 (1H, d, J = 8.6Hz).

[0960] 表 34

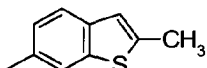
[0961]



[0962]

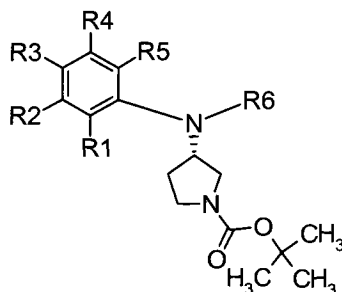
参比实施例	R1	R2	R3	R4	R5	R6	NMR
261	-H	-H	-H	-H	-H		¹ H-NMR (CDCl ₃) δppm: 1.41 (9H, s), 1.8-2.0 (1H, m), 2.05-2.3 (1H, m), 3.15-3.4 (3H, m), 3.7-3.9 (1H, m), 4.5-4.7 (1H, m), 6.8-6.9 (2H, m), 6.9-7.1 (2H, m), 7.2-7.35 (3H, m), 7.42 (1H, d, J = 2.1Hz), 7.65-7.75 (1H, m).
262	-H	-H	-F	-H	-H		¹ H-NMR (CDCl ₃) δppm: 1.42 (9H, s), 1.8-2.0 (1H, m), 2.05-2.3 (1H, m), 3.15-3.4 (3H, m), 3.7-3.85 (1H, m), 4.45-4.6 (1H, m), 6.80 (1H, dd, J = 2.3, 8.8Hz), 6.9-7.1 (4H, m), 7.2-7.35 (2H, m), 7.62 (1H, d, J = 8.6Hz).
263	-H	-H	-F	-H	-H		¹ H-NMR (CDCl ₃) δppm: 1.43 (9H, s), 1.8-1.95 (1H, m), 2.05-2.25 (1H, m), 3.1-3.4 (3H, m), 3.65-3.9 (1H, m), 4.4-4.6 (1H, m), 6.82 (1H, dd, J = 2.0, 8.8Hz), 6.95-7.2 (6H, m), 7.55-7.7 (1H, m).
264	-H	-H	-H	-H	-H		¹ H-NMR (CDCl ₃) δppm: 1.41 (9H, s), 1.8-1.95 (1H, m), 2.05-2.25 (1H, m), 2.42 (3H, d, J = 0.6Hz), 3.15-3.35 (3H, m), 3.7-3.9 (1H, m), 4.45-4.65 (1H, m), 6.75-6.85 (2H, m), 6.9-7.05 (3H, m), 7.15-7.3 (2H, m), 7.45 (1H, d, J = 1.9Hz), 7.63 (1H, dd, J = 3.9, 8.5Hz).
265	-H	-H	-H	-H	-H		¹ H-NMR (CDCl ₃) δppm: 1.40 (9H, d, J = 2.9Hz), 1.8-1.95 (1H, m), 2.05-2.25 (1H, m), 2.39 (3H, d, J = 0.8Hz), 3.15-3.35 (3H, m), 3.7-3.9 (1H, m), 4.45-4.65 (1H, m), 6.65-6.75 (2H, m), 6.8-6.9 (1H, m), 7.01 (1H, dd, J = 1.8, 8.5Hz), 7.11 (1H, bs), 7.15-7.3 (2H, m), 7.39 (1H, d, J = 1.9Hz), 7.81 (1H, dd, J = 3.6, 8.4Hz).
266	-H	-H	-H	-H	-H		¹ H-NMR (CDCl ₃) δppm: 1.42 (9H, s), 1.8-1.95 (1H, m), 2.05-2.25 (1H, m), 3.15-3.35 (3H, m), 3.7-3.9 (1H, m), 4.45-4.6 (1H, m), 6.87 (1H, d, J = 1.9Hz), 6.93 (2H, dd, J = 1.0, 8.5Hz), 7.05-7.15 (1H, m), 7.23 (1H, s), 7.25-7.4 (4H, m).
267	-H	-H	-H	-H	-H		¹ H-NMR (CDCl ₃) δppm: 1.41 (9H, s), 1.75-1.95 (1H, m), 2.0-2.2 (1H, m), 2.57 (3H, s), 3.15-3.35 (3H, m), 3.7-3.9 (1H, m), 4.45-4.6 (1H, m), 6.75 (2H, d, J = 7.8Hz), 6.8-7.0 (3H, m), 7.15-7.3 (2H, m), 7.39 (1H, d, J = 1.7Hz), 7.58 (1H, dd, J = 3.8, 8.2Hz).

[0963]

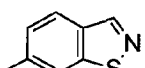
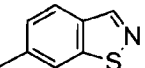
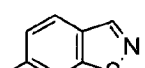
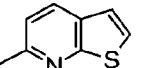
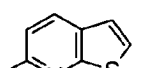
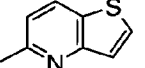
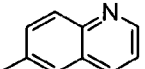
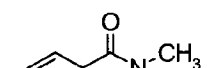
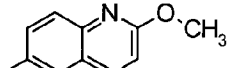
268	-H -H -F -H -H		¹ H-NMR (CDCl ₃) δppm: 1.42 (9H, s), 1.75-1.95 (1H, m), 2.0-2.2 (1H, m), 2.55 (3H, d, J = 1.0Hz), 3.15-3.35 (3H, m), 3.657-3.85 (1H, m), 4.35-4.55 (1H, m), 6.75-6.9 (4H, m), 6.9-7.05 (2H, m), 7.26 (1H, s), 7.51 (1H, d, J = 8.6Hz).
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[0964] 表 35

[0965]

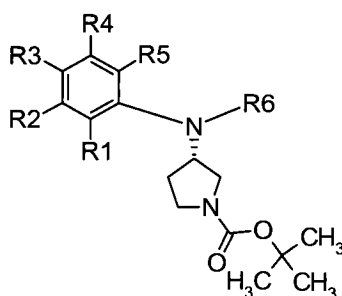


[0966]

参比实施例	R1	R2	R3	R4	R5	R6	NMR
269	-H	-H	-F	-Cl	-H		¹ H-NMR (CDCl ₃) δppm: 1.44 (9H, s), 1.8-1.95 (1H, m), 2.1-2.3 (1H, m), 3.15-3.4 (3H, m), 3.7-3.9 (1H, m), 4.45-4.6 (1H, m), 6.71 (1H, dd, J = 2.1, 8.9Hz), 6.9-7.05 (1H, m), 7.1-7.3 (3H, m), 7.81 (1H, d, J = 8.8Hz), 8.72 (1H, s).
270	-H	-H	-H	-H	-H		¹ H-NMR (CDCl ₃) δppm: 1.43 (9H, s), 1.8-2.0 (1H, m), 2.1-2.25 (1H, m), 3.15-3.35 (3H, m), 3.75-3.95 (1H, m), 4.5-4.65 (1H, m), 6.69 (1H, dd, J = 2.2, 8.9Hz), 7.05-7.15 (3H, m), 7.3-7.4 (1H, m), 7.4-7.5 (2H, m), 7.76 (1H, d, J = 7.7Hz), 8.68 (1H, bs).
271	-H	-H	-F	-H	-H		¹ H-NMR (CDCl ₃) δppm: 1.43 (9H, s), 1.8-1.95 (1H, m), 2.1-2.3 (1H, m), 3.1-3.35 (3H, m), 3.7-3.9 (1H, m), 4.5-4.65 (1H, m), 6.65 (1H, dd, J = 2.2, 9.0Hz), 7.05-7.2 (5H, m), 7.75 (1H, d, J = 8.3Hz), 8.67 (1H, s).
272	-H	-H	-H	-H	-H		¹ H-NMR (CDCl ₃) δppm: 1.43 (9H, s), 1.7-1.9 (1H, m), 2.05-2.25 (1H, m), 3.1-3.35 (3H, m), 3.8-3.95 (1H, m), 5.4-5.55 (1H, m), 6.03 (1H, d, J = 8.9Hz), 7.0-7.05 (1H, m), 7.05-7.1 (1H, m), 7.1-7.2 (2H, m), 7.35-7.55 (3H, m), 7.58 (1H, d, J = 8.9Hz).
273	-H	-H	-F	-H	-H		¹ H-NMR (CDCl ₃) δppm: 1.43 (9H, s), 1.7-1.9 (1H, m), 2.05-2.25 (1H, m), 3.05-3.35 (3H, m), 3.8-3.95 (1H, m), 5.4-5.55 (1H, m), 6.02 (1H, d, J = 8.9Hz), 7.0-7.2 (6H, m), 7.60 (1H, d, J = 8.8Hz).
274	-H	-H	-H	-H	-H		¹ H-NMR (CDCl ₃) δppm: 1.43 (9H, s), 1.7-1.9 (1H, m), 2.05-2.25 (1H, m), 3.1-3.35 (3H, m), 3.8-3.95 (1H, m), 5.4-5.55 (1H, m), 6.06 (1H, d, J = 9.0Hz), 7.15-7.2 (2H, m), 7.3-7.55 (4H, m), 7.55-7.65 (1H, m), 7.67 (1H, d, J = 10.0Hz).
275	-H	-H	-F	-Cl	-H		¹ H-NMR (CDCl ₃) δppm: 1.43 (9H, s), 1.85-2.00 (1H, m), 2.08-2.26 (1H, m), 3.16-3.40 (3H, m), 3.68-3.90 (1H, m), 4.50-4.61 (1H, m), 6.88-6.96 (1H, m), 7.05-7.20 (4H, m), 7.35 (1H, dd, J = 4.2, 8.3Hz), 7.88-8.05 (2H, m), 8.76 (1H, d, J = 2.9Hz).
276	-H	-H	-F	-CH ₃	-H		¹ H-NMR (CDCl ₃) δppm: 1.43 (9H, s), 1.75-1.88 (1H, m), 2.12 (1H, br), 2.28 (3H, s), 2.85 (2H, t, J = 6.6 Hz), 3.10 (3H, s), 3.19-3.28 (3H, m), 3.48 (2H, t, J = 6.6 Hz), 3.69-3.83 (1H, m), 4.49-4.55 (1H, m), 6.22 (1H, d, J = 12.3 Hz), 6.49 (1H, dd, J = 8.1, 8.6 Hz), 6.87-6.95 (2H, m), 7.03-7.09 (1H, m), 7.87 (1H, dd, J = 8.7, 8.7 Hz).
277	-H	-H	-F	-Cl	-H		¹ H-NMR (CDCl ₃) δppm: 1.41 (9H, s), 1.83-1.95 (1H, m), 2.15 (1H, br), 3.22-3.34 (3H, m), 3.69-3.85 (1H, m), 4.06 (3H, s), 4.47 (1H, br), 6.65-6.70 (1H, m), 6.85 (1H, dd, J = 2.8, 6.3 Hz), 6.90 (1H, d, J = 8.8 Hz), 6.99-7.05 (1H, m), 7.17 (1H, dd, J = 2.5, 8.9 Hz), 7.26-7.27 (1H, m), 7.77-7.90 (2H, m).

[0967] 表 36

[0968]

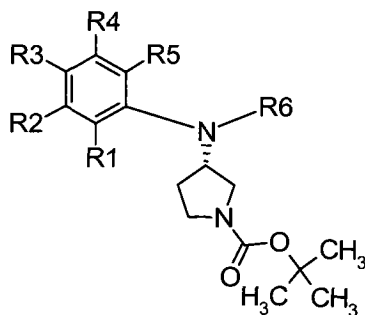


[0969]

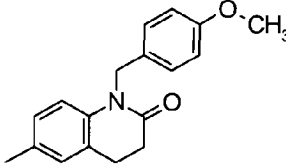
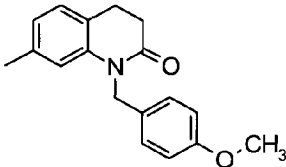
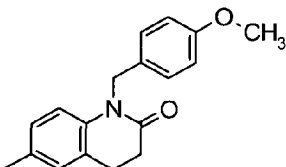
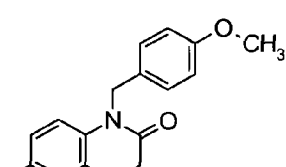
参比实施例	R1	R2	R3	R4	R5	R6	NMR
278	-H	-H	-F	-Cl	-H		¹ H-NMR (CDCl ₃) δppm: 1.43(9H, s), 1.78-1.90 (1H, m), 2.04-2.17 (1H, m), 2.66 (2H, dd, J = 6.7, 7.7 Hz), 2.86 (2H, dd, J = 6.7, 7.7 Hz), 3.19-3.29 (3H, m), 3.36 (3H, s), 3.66-3.78 (1H, m), 4.35-4.41 (1H, m), 6.60 (1H, ddd, J = 3.0, 3.8, 9.0 Hz), 6.75-6.78 (2H, m), 6.86 (1H, dd, J = 1.9, 8.6 Hz), 6.93-7.02 (2H, m).
279	-H	-H	-F	-H	-H		¹ H-NMR (CDCl ₃) δppm: 1.43 (9H, s), 1.78-1.91 (1H, m), 2.05-2.17 (1H, m), 2.62 (2H, dd, J = 6.1, 8.3 Hz), 2.82 (2H, dd, J = 6.1, 8.3 Hz), 3.26 (3H, br), 3.33 (3H, s), 3.69-3.79 (1H, m), 4.41 (1H, br), 6.62 (1H, br), 6.72 (1H, dd, J = 2.5, 8.7 Hz), 6.84-6.91 (3H, m), 6.93-7.03 (2H, m).
280	-H	-H	-F	-Cl	-H		¹ H-NMR (CDCl ₃) δppm: 1.41 (9H, s), 1.81-1.93 (1H, m), 2.13-2.18 (1H, m), 3.24-3.31 (3H, m), 3.67-3.81 (1H, m), 3.72 (3H, s), 4.41-4.45 (1H, m), 6.62-6.67 (1H, m), 6.73 (1H, d, J = 9.4 Hz), 6.81 (1H, dd, J = 2.7, 6.2 Hz), 6.82-7.05 (1H, m), 7.14-7.18 (2H, m), 7.27-7.32 (1H, m), 7.59 (1H, d, J = 9.4 Hz).
281	-H	-H	-CH ₃	-F	-H		¹ H-NMR (CDCl ₃) δppm: 1.43(9H, s), 1.78-1.91 (1H, m), 2.08-2.18 (1H, m), 2.18 (3H, s), 2.66 (2H, dd, J = 6.6, 7.6 Hz), 2.86 (2H, dd, J = 6.6, 7.6 Hz), 3.18-3.27 (3H, m), 3.36 (3H, s), 3.68-3.78 (1H, m), 4.38-4.44 (1H, m), 6.36-6.43 (2H, m), 6.79 (1H, d, J = 2.2 Hz), 6.87-7.02 (3H, m).
282	-H	-H	-CH ₃	-F	-H		¹ H-NMR (CDCl ₃) δppm: 1.41 (9H, s), 1.60-1.72 (1H, m), 2.15 (1H, br), 2.20 (3H, s), 3.24-3.32 (3H, m), 3.72 (3H, s), 3.75-3.81 (1H, m), 4.46 (1H, br), 6.40-6.45 (2H, m), 6.72 (1H, d, J = 9.5 Hz), 7.02 (1H, br), 7.18-7.21 (2H, m), 7.31-7.34 (1H, m), 7.58 (1H, dd, J = 2.9, 9.4 Hz).
283	-H	-H	-F	-CH ₃	-H		¹ H-NMR (CDCl ₃) δppm: 1.43 (9H, s), 1.78-1.90 (1H, m), 2.02-2.13 (1H, m), 2.24 (3H, s), 2.62 (2H, dd, J = 5.4, 8.0 Hz), 2.79-2.84 (2H, m), 3.19-3.29 (3H, m), 3.32 (3H, s), 3.98-3.79 (1H, m), 4.35-4.46 (1H, m), 6.58 (1H, br), 6.70-6.76 (3H, m), 6.84-6.99 (2H, m).
284	-H	-H	-F	-CH ₃	-H		¹ H-NMR (CDCl ₃) δppm: 1.42 (9H, s), 1.80-1.92 (1H, m), 2.08-2.18 (1H, m), 2.24 (3H, s), 3.24-3.31 (3H, m), 3.69 (3H, s), 3.75-3.81 (1H, m), 4.44 (1H, br), 6.69 (1H, d, J = 9.4 Hz), 6.74-6.79 (2H, m), 6.96-7.01 (3H, m), 7.21-6.79 (1H, m), 7.55 (1H, d, J = 9.4 Hz).

[0970] 表 37

[0971]

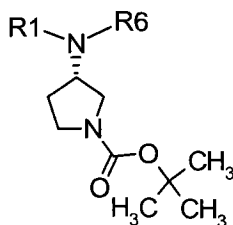


[0972]

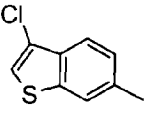
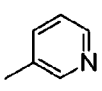
参比实施例	R1	R2	R3	R4	R5	R6	NMR
285	-H	-H	-F	-Cl	-H		¹ H-NMR (CDCl ₃) δppm: 1.42 (9H, s), 1.77-1.82 (1H, m), 2.06-2.10 (1H, m), 2.72-2.80 (2H, m), 2.86-2.91 (2H, m), 3.15-3.27 (3H, m), 3.64-3.73 (1H, m), 3.78 (3H, s), 4.34 (1H, br), 5.09 (2H, br), 6.53-6.89 (7H, m), 6.97-7.00 (1H, m), 7.14-7.17 (2H, m).
286	-H	-H	-F	-H	-H		¹ H-NMR (CDCl ₃) δppm: 1.42 (9H, s), 1.61-1.73 (1H, m), 1.90-2.00 (1H, m), 2.74 (2H, dd, J = 5.8, 7.9 Hz), 2.87 (2H, dd, J = 5.8, 7.9 Hz), 3.10-3.23 (3H, m), 3.56-3.68 (1H, m), 3.77 (3H, s), 4.23-4.28 (1H, m), 4.81 (1H, d, J = 15.5 Hz), 5.02 (1H, d, J = 15.5 Hz), 6.12 (1H, d, J = 2.3 Hz), 6.37 (1H, d, J = 8.4 Hz), 6.72-6.99 (9H, m).
287	-H	-H	-CH ₃	-F	-H		¹ H-NMR (CDCl ₃) δppm: 1.42 (9H, s), 1.76-1.86 (1H, m), 2.04-2.11 (1H, m), 2.18 (3H, s), 2.75-2.79 (2H, m), 2.88-2.93 (2H, m), 3.13-3.25 (3H, m), 3.66-3.76 (1H, m), 3.78 (3H, s), 4.34-4.38 (1H, m), 5.09 (2H, s), 6.36 (2H, m), 6.70-6.74 (2H, m), 6.83-6.91 (3H, m), 6.99 (1H, br), 7.17 (1H, d, J = 8.6 Hz).
288	-H	-H	-F	-CH ₃	-H		¹ H-NMR (CDCl ₃) δppm: 1.42 (9H, s), 1.76-1.85 (1H, m), 2.01-2.09 (1H, m), 2.22 (3H, s), 2.71-2.75 (2H, m), 2.84-2.88 (2H, m), 3.13-3.28 (3H, m), 3.63-3.75 (1H, m), 3.77 (3H, s), 4.33-4.37 (1H, m), 5.06 (2H, s), 6.47-6.53 (2H, m), 6.69-6.85 (5H, m), 6.91-6.95 (1H, m), 7.14 (2H, d, J = 8.5 Hz).

[0973] 表 38

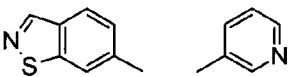
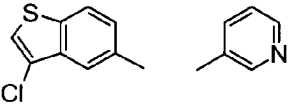
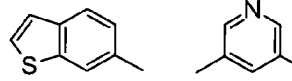
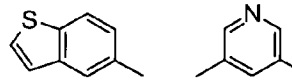
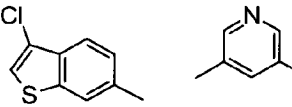
[0974]



[0975]

参比实施例	R1	R6	NMR
289			¹ H-NMR (CDCl ₃) δppm: 1.41 (9H, s), 1.8-2.0 (1H, m), 2.1-2.3 (1H, m), 3.15-3.4 (3H, m), 3.7-3.9 (1H, m), 4.45-4.6 (1H, m), 7.0-7.1 (2H, m), 7.1-7.2 (1H, m), 7.28 (1H, s), 7.45 (1H, d, J = 1.6Hz), 7.75-7.8 (1H, m), 8.1-8.3 (2H, m).

[0976]

290		¹ H-NMR (CDCl ₃) δppm: 1.42 (9H, s), 1.8-2.0 (1H, m), 2.1-2.3 (1H, m), 3.15-3.4 (3H, m), 3.7-3.9 (1H, m), 4.5-4.7 (1H, m), 6.78 (1H, dd, J = 2.0, 8.9Hz), 7.28 (1H, s), 7.3-7.4 (2H, m), 7.86 (1H, d, J = 9.4Hz), 8.37 (1H, s), 8.45-8.55 (1H, m), 8.75 (1H, s).
291		¹ H-NMR (CDCl ₃) δppm: 1.40 (9H, s), 1.8-2.0 (1H, m), 2.1-2.3 (1H, m), 3.15-3.4 (3H, m), 3.7-3.9 (1H, m), 4.5-4.65 (1H, m), 6.95-7.2 (3H, m), 7.38 (1H, s), 7.53 (1H, d, J = 2.0Hz), 7.75-7.9 (1H, m), 8.05-8.2 (2H, m).
292		¹ H-NMR (CDCl ₃) δppm: 1.40 (9H, s), 1.8-2.0 (1H, m), 2.1-2.3 (1H, m), 3.1-3.4 (3H, m), 3.7-3.9 (1H, m), 4.45-4.6 (1H, m), 6.45-6.6 (1H, m), 7.09 (1H, dd, J = 1.9, 8.4Hz), 7.38 (1H, d, J = 5.4Hz), 7.54 (1H, d, J = 5.4Hz), 7.65 (1H, d, J = 1.7Hz), 7.8-7.95 (3H, m).
293		¹ H-NMR (CDCl ₃) δppm: 1.42 (9H, s), 1.8-2.0 (1H, m), 2.1-2.3 (1H, m), 3.1-3.4 (3H, m), 3.7-3.9 (1H, m), 4.45-4.6 (1H, m), 6.45-6.6 (1H, m), 7.07 (1H, dd, J = 2.0, 8.4Hz), 7.3-7.4 (1H, m), 7.55 (1H, d, J = 5.4Hz), 7.59 (1H, d, J = 2.0Hz), 7.8-7.9 (2H, m), 7.96 (1H, d, J = 5.4Hz).
294		¹ H-NMR (CDCl ₃) δppm: 1.40 (9H, s), 1.8-2.0 (1H, m), 2.1-2.3 (1H, m), 3.1-3.4 (3H, m), 3.7-3.9 (1H, m), 4.45-4.6 (1H, m), 6.5-6.65 (1H, m), 7.18 (1H, dd, J = 1.9, 8.5Hz), 7.40 (1H, s), 7.59 (1H, d, J = 1.7Hz), 7.8-8.0 (3H, m).

[0977] 实施例 1

[0978] (3,4-二氯苯基)苯基吡咯烷-3-基胺二盐酸盐的合成

[0979] 将含有 3-氧代吡咯烷-1-羧酸叔丁基酯 (0.67g) 和 (3,4-二氯苯基)苯胺 (0.94g) 的乙酸溶液 (15mL) 在室温下搅拌过夜。向该混合物添加 1.5g 的三乙酰氧基硼氢化钠, 随后在室温下搅拌 8 小时。将二氯甲烷加入到反应溶液中, 用水洗, 随后用硫酸镁干燥。用减压馏出溶剂, 残留物然后通过硅胶柱层析法 (正己烷: 乙酸乙酯 = 20:1) 来提纯。在减压下从该提纯产物中馏出溶剂, 将该残留物溶于 1N 盐酸-乙醇中, 回流加热一小时。将反应溶液浓缩至干燥, 从而获得 50mg 的棕色无定形固体 (3,4-二氯苯基)苯基吡咯烷-3-基胺二盐酸盐。

[0980] ¹H-NMR (DMSO-d₆) δ ppm:

[0981] 1.50-1.68 (1H, m), 2.10-2.29 (1H, m), 2.74-2.90 (1H, m), 3.02-3.22 (2H, m), 3.51-3.66 (1H, m), 4.61-4.79 (1H, m), 6.58 (1H, dd, J = 2.9Hz, J = 9.0Hz), 6.87 (1H, d, J = 2.9Hz), 7.13-7.19 (2H, m), 7.29-7.44 (2H, m), 7.45-7.54 (2H, m), 9.03 (2H, brs).

[0982] 实施例 2

[0983] (S)-(3,4-二氯苯基)苯基吡咯烷-3-基胺·二盐酸盐的合成

[0984] 将 3(S)-[(3,4-二氯苯基)苯基氨基]吡咯烷-1-羧酸叔丁基酯 (0.13g) 溶于 1N 盐酸-乙醇中, 回流加热一小时。将反应溶液浓缩至干燥, 从而获得 0.11 的棕色无定形固体 (3,4-二氯苯基)苯基吡咯烷-3-基胺盐酸盐。

[0985] ¹H-NMR (DMSO-d₆) δ ppm:

[0986] 1.50-1.68 (1H, m), 2.10-2.29 (1H, m), 2.75-2.90 (1H, m), 3.02-3.23 (2H, m), 3.51-3.65 (1H, m), 4.60-4.80 (1H, m), 6.58 (1H, dd, J = 2.9Hz, J = 9.0Hz), 6.87 (1H, d, J = 2.9Hz), 7.12-7.19 (2H, m), 7.29-7.44 (2H, m), 7.45-7.54 (2H, m), 9.05 (2H, brs).

[0987] 实施例 3

[0988] (3-氟苯基)-(S)-吡咯烷-3-基-(4-三氟甲基苯基)胺富马酸氢盐的合成

[0989] 向含有 ((S)-1-苄基吡咯烷-3-基)-(3-氟苯基)-(4-三氟甲基苯基)胺 (0.48g,

1.1mmol) 的 1,2-二氯甲烷溶液 (1mL) 添加氯甲酸 1-氯乙基酯 (0.82g, 5.8mmol)。将该混合物在室温下搅拌 15 小时并回流加热 3 小时。在减压下馏出溶剂, 然后将 5mL 甲醇加入到该残留物中并回流加热 3 小时。在减压下馏出溶剂后, 然后将残留物溶于二氯甲烷, 用饱和碳酸氢钠水溶液清洗。用硫酸镁干燥, 之后, 在减压下馏出溶剂。将残留物溶于乙醇, 然后添加富马酸 (128mg, 1.1mmol), 获得均匀的溶液。在减压下馏出溶剂, 通过过滤分离出由添加二氯甲烷到残留物中所产生的晶体, 再干燥, 获得 0.24g 的浅棕色粉状的 (3-氟苯基)-(S)-吡咯烷-3-基-(4-三氟甲基苯基) 胺富马酸氢盐。

[0990] 熔点 144.0-146.2°C。

[0991] 实施例 4

[0992] (3-氯-4-氟苯基)-(4-甲磺酰基苯基)-(S)-吡咯烷-3-基胺盐酸盐的合成

[0993] 将 3(S)-[(3-氯-4-氟苯基)-(4-甲磺酰基苯基)氨基]吡咯烷-1-羧酸叔丁基酯 (0.42g, 0.9mmol) 加入到 4N 盐酸/乙酸乙酯中, 随后在室温下搅拌一小时。在减压下将反应溶液浓缩到干燥, 从而获得 0.35g 的白色粉状的 (3-氯-4-氟苯基)-(4-甲磺酰基苯基)-(S)-吡咯烷-3-基胺盐酸盐。

[0994] $^1\text{H-NMR}$ (DMSO- d_6) δ ppm :

[0995] 1.56-1.68 (1H, m), 2.19-2.29 (1H, m), 2.82-2.94 (1H, m), 3.08 (3H, s), 3.10-3.20 (2H, m), 3.57-3.68 (1H, m), 4.70-4.85 (1H, m), 6.69-6.75 (2H, m), 7.32-7.37 (1H, m), 7.58-7.64 (1H, m), 7.65-7.69 (3H, m), 9.10-9.45 (2H, m).

[0996] 实施例 5

[0997] (3-氯-4-氟苯基)-[4-(吡啶-2-基氧基)丁基]-(S)-吡咯烷-3-基胺富马酸氢盐的合成

[0998] 向含有 3(S)-[4-(吡啶-2-基氧基)丁基氨基]吡咯烷-1-羧酸叔丁基酯 (0.2g, 0.6mmol) 和 4-溴-2-氯-1-氟代苯 (0.8mL, 0.65mmol) 的甲苯溶液 (4mL) 添加四氟硼酸·三-叔丁基膦 (14mg, 0.05mmol), 三(二苄叉基丙酮)二钯 (11mg, 0.012mmol) 和叔丁醇钠 (110mg, 1.2mmol), 在氮气气氛中回流加热 12 小时。在冷却到室温之后, 将水加入到反应溶液中, 再用乙酸乙酯萃取。该萃取物用硫酸镁干燥, 并在减压下浓缩, 残留物然后通过硅胶柱层析法 (正己烷:乙酸乙酯 = 3:1) 提纯。在减压下从提纯产物中馏出溶剂。将残留物溶于 0.4mL 二氯甲烷, 再添加三氟乙酸 (0.06mL, 0.8mmol), 随后在室温下搅拌 3 小时。在减压下浓缩后, 残留物通过 HPLC 提纯。收集目标级分, 之后, 在减压下馏出溶剂, 将 10% 碳酸钾水溶液加入到残留物中, 随后用二氯甲烷萃取。该萃取物用硫酸镁干燥并在减压下浓缩, 再将含有富马酸 (8.1mg) 的乙醇溶液加入到该残留物 (乙醇溶液) 中, 从而获得均匀的溶液。在减压下浓缩, 之后, 将水 (3mL) 加入到残留物中, 随后冷冻干燥, 从而获得 19mg 的白色固体 (3-氯-4-氟苯基)-[4-(吡啶-2-基氧基)丁基]-(S)-吡咯烷-3-基胺富马酸氢盐。

[0999] $^1\text{H-NMR}$ (DMSO- d_6) δ ppm :

[1000] 1.45-1.55 (2H, m), 1.65-1.8 (2H, m), 1.8-1.95 (1H, m), 2.05-2.15 (1H, m), 2.6-4.05 (11H, m), 4.25 (2H, t, $J = 6.5\text{Hz}$), 4.3-4.4 (1H, m), 6.55 (4H, s), 6.77 (1H, d, $J = 8.5\text{Hz}$), 6.8-6.9 (1H, m), 6.9-7.0 (1H, m), 7.03 (1H, dd, $J = 3\text{Hz}$, $J = 6.5\text{Hz}$), 7.22 (1H, dd, $J = 9\text{Hz}$, $J = 9\text{Hz}$), 7.65-7.7 (1H, m), 8.1-8.15 (1H, m).

[1001] 实施例 6

[1002] (3-氯-4-氟苯基)-(3-甲基硫烷基丙基)-(S)-吡咯烷-3-基胺盐酸盐的合成

[1003] 将含有 0.60g 的 3(S)-[(3-氯-4-氟苯基)氨基]吡咯烷-1-羧酸叔丁基酯 (0.60g, 1.9mmol) 和 3-甲基硫基丙醛 (0.6g, 5.7mmol) 的乙酸溶液 (3mL) 在室温下搅拌过夜。将三乙酰氧基氢硼化钠 (0.81g, 3.8mmol) 加入到该混合物中, 随后在室温下搅拌 15 小时。将二氯甲烷加入到反应溶液中, 然后用水和饱和碳酸氢钠水溶液清洗反应溶液, 再用硫酸镁干燥。在减压下馏出溶剂, 然后将残留物溶于 1N 盐酸-乙醇 (10mL), 再回流加热一小时。将反应溶液浓缩至干燥, 从而获得 0.16g 的黄色无定形固体 (3-氯-4-氟苯基)-(3-甲基硫基丙基)-(S)-吡咯烷-3-基胺盐酸盐。

[1004] $^1\text{H-NMR}$ (DMSO- d_6) δ ppm :

[1005] 1.52-1.70 (2H, m), 1.80-2.18 (包括 5H, m [2.07ppm(s)]), 2.40-2.51 (2H, m), 2.84-3.49 (6H, m), 4.29-4.49 (1H, m), 6.85-6.95 (1H, m), 7.05-7.35 (2H, m), 9.30-9.79 (2H, m).

[1006] 实施例 7

[1007] (3-氯-4-氟苯基)吡啶-3-基-(S)-吡咯烷-3-基胺二甲烷磺酸盐的合成

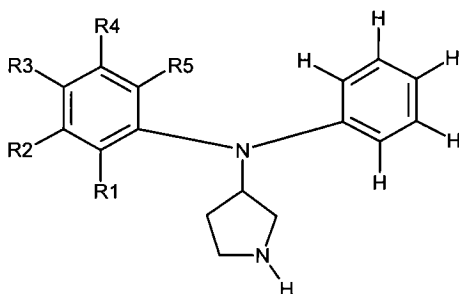
[1008] 向含有 3(S)-[(3-氯-4-氟苯基)吡啶-3-基氨基]吡咯烷-1-羧酸叔丁基酯 (16.0g, 41mmol) 的二氯甲烷溶液 (100mL) 添加三氟乙酸 (20mL), 随后在室温下搅拌 3 小时。在减压下馏出溶剂, 将饱和碳酸氢钠水溶液加入到该残留物中, 以使该残留物呈碱性, 随后用二氯甲烷萃取。萃取物用硫酸镁干燥, 在减压下馏出溶剂, 该残留物通过碱性硅胶柱层析法 (二氯甲烷: 甲醇 = 10:1) 来提纯。在减压下从提纯产物中馏出溶剂。向含有该残留物的乙醇溶液添加甲磺酸 (9.2g), 然后在减压下馏出溶剂。该残留物从乙醇中再结晶出来, 从而获得 16.9g 的白色粉状的 (3-氯-4-氟苯基)吡啶-3-基-(S)-吡咯烷-3-基胺二甲烷磺酸盐。

[1009] 熔点 194.0-195.0°C。

[1010] 使用相应起始化合物, 按照与以上实施例相同的方式可以制备下表所示的实施例 8 到 1180 的化合物。在下表中, 实际上形成了具有诸如晶形, m. p. (熔点), 盐, $^1\text{H-NMR}$ 和 MS (质谱) 之类的物理性能的化合物。

[1011] 表 39

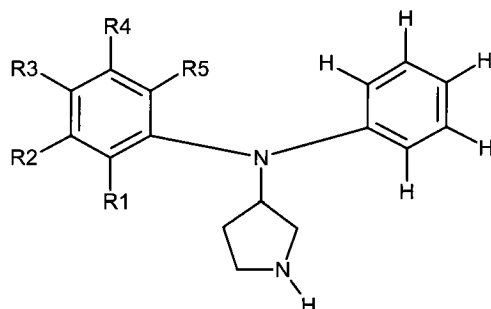
[1012]



	实施例	R1	R2	R3	R4	R5	M.p. (°C)	盐
[1013]	8	-H	-H	-Cl	-H	-H	173.7-175.0	富马酸盐
	9	-Cl	-Cl	-H	-H	-H	160.3-162.6	富马酸盐
	10	-H	-Cl	-H	-H	-H	144.2-146.7	富马酸盐

[1014] 表 40

[1015]

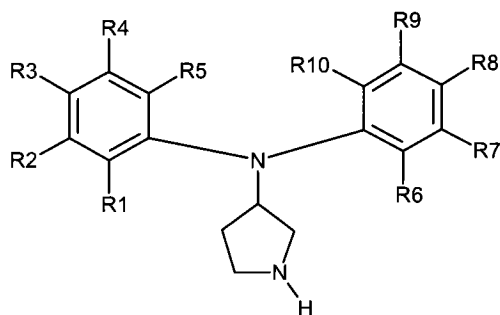


[1016]

实施例	R1	R2	R3	R4	R5	NMR	盐
11	-H	-H	-Cl	-Cl	-H	1H-NMR (DMSO-d6) δ ppm 1.50-1.68 (1H, m), 2.10-2.29 (1H, m), 2.74-2.90 (1H, m), 3.02-3.22 (2H, m), 3.51-3.66 (1H, m), 4.61-4.79 (1H, m), 6.58 (1H, dd, J=2.9Hz and 9.0Hz), 6.87 (1H, d, J=2.9Hz), 7.13-7.19 (2H, m), 7.29-7.44(2H, m), 7.45-7.54 (2H, m),	2 盐酸盐
12	-H	-H	-Cl	-Cl	-H	1H-NMR (DMSO-d6) δ ppm 1.49-1.68 (1H, m), 2.05-2.25 (1H, m), 2.69-2.82 (1H, m), 2.92-3.15 (2H, m), 3.44-3.60 (1H, m), 4.55-4.74 (1H, m), 6.44(2H, s), 6.57 (1H, dd, J=2.9Hz and 9.0Hz), 6.85 (1H, d, J=2.8Hz), 7.11-7.21 (2H, m), 7.29-7.41 (2H, m), 7.43- 7.54 (2H, m)	富马酸盐

[1017] 表 41

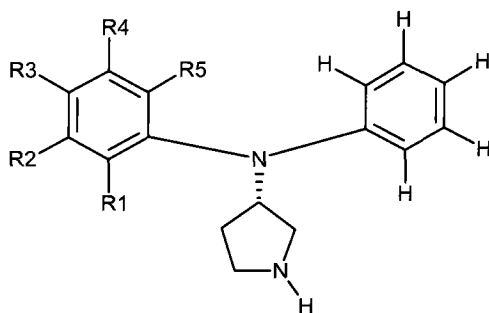
[1018]



	实施例	R1	R2	R3	R4	R5	R6	R7	R8	R9	R10	熔点 (°C)	盐
[1019]	13	-H	-H	-F	-H	-H	-H	-H	-F	-H	-H	155.4-156.4	富马酸盐
	14	-H	-H	-F	-H	-H	-H	-H	-Cl	-Cl	-H	178.7-180.1	富马酸盐
	15	-H	-H	-H	-H	-F	-H	-H	-Cl	-Cl	-H	156.6-158.7	富马酸盐
	16	-H	-F	-H	-H	-H	-H	-Cl	-Cl	-H	-H	156.4-158.5	富马酸盐

[1020] 表 42

[1021]

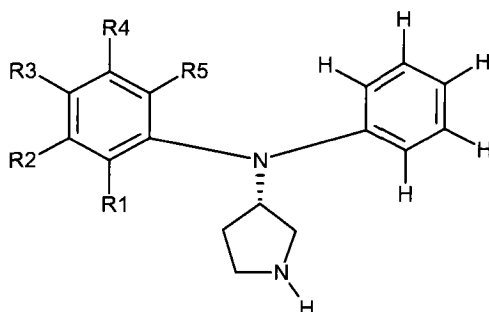


[1022]

实施例	R1	R2	R3	R4	R5	熔点 (°C)	盐
17	-H	-H	-Cl	-H	-H	152.0-153.0	富马酸盐
18	-H	-Cl	-Cl	-H	-H	144.0-147.9	富马酸盐
19	-H	-H	-SCH ₃	-H	-H	152.9-155.5	富马酸盐
20	-H	-H	-F	-H	-H	143.0-145.0	富马酸盐
21	-Cl	-H	-H	-H	-H	138.1-141.8	富马酸盐
22	-H	-H	-CH ₃	-H	-H	141.7-143.8	富马酸盐
23	-Cl	-Cl	-H	-H	-H	130.2-132.2	富马酸盐
24	-H	-H	-OCF ₃	-H	-H	131.2-133.6	富马酸盐
25	-H	-Cl	-H	-H	-H	146.6-149.1	富马酸盐
26	-H	-H	-CF ₃	-H	-H	120.3-124.6	富马酸盐
27	-H	-H	-OCH ₃	-H	-H	137.5-139.2	富马酸盐
28	-H	-H	-NO ₂	-H	-H	153.0-135.5	富马酸盐
29	-H	-OCH ₃	-H	-H	-H	135.3-140.7	富马酸盐
30	-H	-H	-CO ₂ CH ₃	-H	-H	147.5-149.0	富马酸盐
31	-H	-Cl	-H	-Cl	-H	164.8-166.8	富马酸盐
32	-H	-H	-Br	-H	-H	156-158	富马酸盐
33	-H	-H	-SO ₂ CH ₃	-H	-H	184.5-185.8	(dec.) 富马酸盐
34	-H	-F	-F	-H	-H	137.5-138.5	富马酸盐
35	-H	-H	-CN	-H	-H	146.7-149.6	富马酸盐
36	-H	-Cl	-OCH ₃	-H	-H	142-144	富马酸盐
37	-H	-H	-H	-F	-H	144.2-145.2	富马酸盐
38	-H	-F	-Cl	-H	-H	155.4-158.4	富马酸盐
39	-H	-Cl	-OC ₂ H ₅	-H	-H	135.0-137.2	富马酸盐
40	-H	-Cl	-OC ₃ H ₇	-H	-H	129.6-132.4	富马酸盐

[1023] 表 43

[1024]

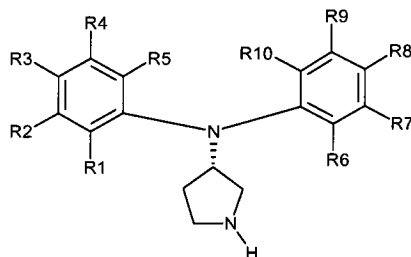


[1025]

实施例	R1	R2	R3	R4	R5	NMR	盐
41	-H	-Cl	-Cl	-H	-H	1H-NMR (DMSO-d6) δ ppm 1.50-1.68 (1H, m), 2.10-2.29 (1H, m), 2.75-2.90 (1H, m), 3.02-3.23 (2H, m), 3.51-3.65 (1H, m), 4.60-4.80 (1H, m), 6.58 (1H, dd, J=2.9Hz and 9.0Hz), 6.87 (1H, d, J=2.9Hz), 7.12-7.19 (2H, m), 7.29-7.44 (2H, m), 7.45-7.54 (2H, m), 9.05 (2H, brs)	盐酸盐
42	-H	-H	-NH ₂	-H	-H	1H-NMR (DMSO-d6) δ ppm 1.52-1.69 (1H, m), 2.09-2.24 (1H, m), 2.71-2.86 (1H, m), 3.00-3.21 (2H, m), 3.48-3.62 (1H, m), 4.52-4.75 (1H, m), 6.82-6.90 (2H, m), 6.98-7.08 (2H, m), 7.14-7.23 (1H, m), 7.24-7.32 (2H, m), 7.35-7.44 (2H, m), 9.30-10.9 (5H, m)	2 盐酸盐
43	-H	-H	-N(CH ₃) ₂	-H	-H	1H-NMR (DMSO-d6) δ ppm 1.50-1.70 (1H, m), 2.09-2.27 (1H, m), 2.69-2.87 (1H, m), 2.92-3.24 (8H, m with s at δ 3.01), 4.60-4.77 (1H, m), 6.83 (2H, d, J=8.6Hz), 6.90-7.20 (3H, m), 7.22-7.70 (4H, m), 9.12-9.60 (2H, m)	2 盐酸盐
44	-H	-Cl	-F	-H	-H	1H-NMR (DMSO-d6) δ ppm 1.50-1.68 (1H, m), 2.05-2.20 (1H, m), 2.72-2.86 (1H, m), 2.96-3.13 (2H, m), 3.43-3.57 (1H, m), 4.52-4.69 (1H, m), 6.45 (2H, s), 6.77-6.86 (1H, m), 6.97 (2H, d, J=8.2Hz), 7.05 (1H, dd, J=2.8Hz and 6.4Hz), 7.09-7.17 (1H, m), 7.26-7.41 (3H, m)	富马酸盐
45	-H	-H	-CO ₂ H	-H	-H	1H-NMR (DMSO-d6) δ ppm 1.50-1.70 (1H, m), 2.14-2.30 (1H, m), 2.70-2.90 (1H, m), 2.99-3.22 (2H, m), 3.51-3.70 (1H, m), 4.69-4.89 (1H, m), 6.54-6.64 (2H, m), 7.19-7.29 (2H, m), 7.38-7.48 (1H, m), 7.49-7.59 (2H, m), 7.68-7.79 (2H, m), 9.34(2H,brs), 12.32 (1H, brs)	盐酸盐
46	-H	-CH ₃	-F	-H	-H	1H-NMR (DMSO-d6) δ ppm 1.5-1.7 (1H, m), 2.0-2.2 (1H, m), 2.20 (3H, s), 2.7-2.9 (1H, m), 3.0-3.2 (2H, m), 3.5-3.6 (1H, m), 4.5-4.7 (1H, m), 6.44 (2H, s), 6.6-6.8 (2H, m), 6.8-6.9 (2H, m), 6.9-7.0 (1H, m), 7.0-7.3 (3H, m)	富马酸盐
47	-H	-F	-F	-OCH ₃	-H	1H-NMR (DMSO-d6) δ ppm 1.5-1.7 (1H, m), 2.0-2.2 (1H, m), 2.7-2.9 (1H, m), 3.0-3.2 (2H, m), 3.5-3.7 (1H, m), 3.77 (3H, s), 4.6-4.8 (1H, m), 6.2-6.4 (2H, m), 6.47 (2H, s), 7.00 (2H, d, J = 7.6 Hz), 7.15 (1H, dd, J = 7.3 Hz, J = 7.3 Hz), 7.3-7.5 (2H, m)	富马酸盐

[1026] 表 44

[1027]

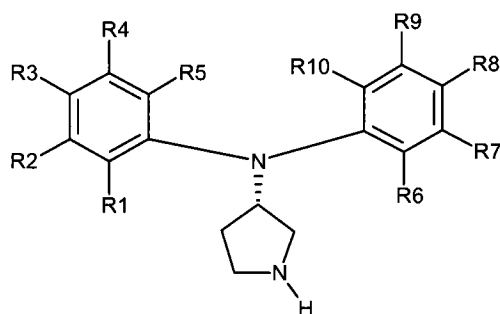


[1028]

实施例	R1	R2	R3	R4	R5	R6	R7	R8	R9	R10	熔点 (°C)	盐
48	-H	-H	-F	-H	-H	-H	-H	-F	-H	-H	156.0-157.0	富马酸盐
49	-H	-H	-F	-H	-H	-H	-H	-Cl	-Cl	-H	170.5-171.8	富马酸盐
50	-H	-H	-H	-H	-F	-H	-H	-Cl	-Cl	-H	133.1-135.8	富马酸盐
51	-H	-H	-Cl	-H	-H	-H	-F	-H	-H	-H	154.3-155.6	富马酸盐
52	-H	-H	-F	-H	-H	-H	-F	-H	-H	-H	143.2-144.4	富马酸盐
53	-H	-H	-CF ₃	-H	-H	-H	-F	-H	-H	-H	144.0-146.2	2 富马酸盐
54	-H	-H	-SCH ₃	-H	-H	-H	-F	-H	-H	-H	161.1-163.2	富马酸盐
55	-H	-H	-F	-H	-H	-H	-H	-Cl	-H	-H	174.1-176.2	富马酸盐
56	-H	-H	-F	-H	-H	-H	-F	-F	-H	-H	148.6-151.3	富马酸盐
57	-H	-H	-F	-H	-H	-H	-Cl	-F	-H	-H	176.7-178.4	富马酸盐
58	-H	-H	-F	-H	-H	-H	-F	-Cl	-H	-H	163.1-164.1	富马酸盐
59	-H	-H	-H	-F	-H	-H	-Cl	-F	-H	-H	149.0-152.0	富马酸盐
60	-H	-CH ₃	-H	-H	-H	-H	-H	-F	-H	-H	142-143	富马酸盐
61	-H	-Cl	-F	-H	-H	-H	-H	-OCH ₃	-H	-H	133.1-135.1	富马酸盐
62	-H	-H	-CH ₃	-H	-H	-H	-Cl	-F	-H	-H	144.0-146.0	富马酸盐
63	-H	-Cl	-F	-H	-H	-H	-H	-OC ₂ H ₅	-H	-H	138.0-141.0	富马酸盐
64	-H	-H	-SCH ₃	-H	-H	-H	-H	-F	-Cl	-H	136.7-139.0	富马酸盐
65	-H	-H	-C ₃ H ₇	-H	-H	-H	-H	-F	-Cl	-H	136.6-138.0	富马酸盐
66	-H	-H	-C(CH ₃) ₃	-H	-H	-H	-H	-F	-Cl	-H	132.0-134.8	富马酸盐
67	-H	-Cl	-F	-H	-H	-H	-Cl	-F	-H	-H	165-167	富马酸盐
68	-H	-H	-F	-Cl	-H	-H	-H	-OH	-H	-H	191.5-194.5	富马酸盐
69	-H	-H	-F	-H	-H	-H	-H	-CH ₃	-H	-H	145-148	富马酸盐

[1029] 表 45

[1030]

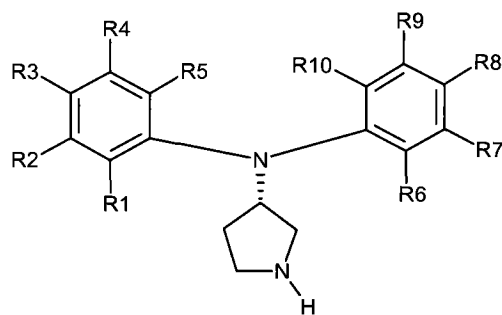


[1031]

实施例	R1	R2	R3	R4	R5	R6	R7	R8	R9	R10	熔点 (°C)	盐
70	-H	-H	-Br	-H	-H	-H	-H	-F	-Cl	-H	141-143	富马酸盐
71	-H	-H	-3-噻吩基	-H	-H	-H	-Cl	-F	-H	-H	158-160	富马酸盐
72	-H	-CF ₃	-F	-H	-H	-H	-H	-F	-Cl	-H	105-108	2 富马酸盐
73	-H	-H	-CN	-H	-H	-H	-Cl	-F	-H	-H	174-175	富马酸盐
74	-H	-H	-CF ₃	-H	-H	-H	-Cl	-F	-H	-H	169-170	富马酸盐
75	-H	-H	-N(CH ₃) ₂	-H	-H	-H	-Cl	-F	-H	-H	153-154	富马酸盐
76	-H	-OCH ₃	-H	-H	-H	-H	-Cl	-F	-H	-H	135-137	富马酸盐
77	-H	-OC ₂ H ₅	-H	-H	-H	-H	-Cl	-F	-H	-H	155-156	富马酸盐
78	-H	-H	-NO ₂	-H	-H	-H	-CH ₃	-F	-H	-H	162-164	富马酸盐
79	-H	-H	-CN	-H	-H	-H	-CH ₃	-F	-H	-H	169-170	富马酸盐
80	-H	-CH ₃	-H	-H	-H	-H	-CH ₃	-F	-H	-H	129-130	富马酸盐
81	-H	-H	-F	-H	-H	-H	-SCH ₃	-H	-H	-H	156-158	富马酸盐
82	-H	-NO ₂	-H	-H	-H	-H	-CH ₃	-F	-H	-H	108-110	富马酸盐
83	-H	-OCH ₃	-H	-H	-H	-H	-H	-F	-CH ₃	-H	140-142	富马酸盐
84	-H	-H	-OC ₂ H ₅	-H	-H	-H	-H	-F	-CH ₃	-H	112-113	富马酸盐
85	-H	-F	-H	-H	-H	-H	-F	-H	-H	-H	149.0-153.0 (dec.)	富马酸盐
86	-H	-SCH ₃	-H	-H	-H	-H	-Cl	-F	-H	-H	143-144	富马酸盐

[1032] 表 46

[1033]

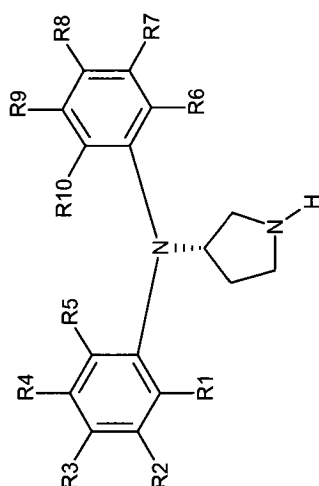


[1034]

实施例	R1	R2	R3	R4	R5	R6	R7	R8	R9	R10	熔点 (°C)	盐
87	-H	-H		-H	-H	-H	-H	-F	-Cl	-H	199-203	3 盐酸盐
88	-H	-H		-H	-H	-H	-Cl	-F	-H	-H	108-110	富马酸盐
89	-H	-H		-H	-H	-H	-H	-F	-Cl	-H	198-201	3 盐酸盐
90	-H	-H		-H	-H	-H	-H	-F	-Cl	-H	115-117	

[1035]

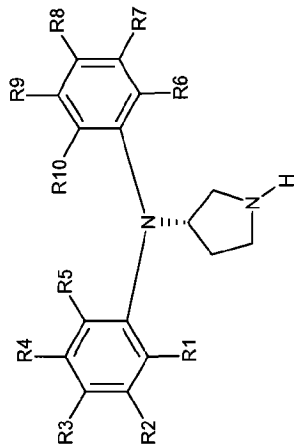
表 47



实施例	R1	R2	R3	R4	R5	R6	R7	R8	R9	R10	NMR	盐
91	-H	-F	-H	-H	-H	-H	-Cl	-Cl	-H	-H	¹ H-NMR (DMSO-d ₆) δppm 1.49-1.69 (1H, m), 2.03-2.22 (1H, m), 2.73-2.86 (1H, m), 2.92-3.10 (2H, m), 3.42-3.58 (1H, m), 4.54-4.72 (1H, m), 6.73-6.91 (3H, m with dd at δ6.82, J=2.7Hz and 8.8Hz, and dt at δ6.88, J=2.4Hz and 11.1Hz), 6.93-7.01 (1H, m), 7.14 (1H, d, J=2.7Hz), 7.32-7.43 (1H, m), 7.51 (1H, d, J=8.8Hz)	富马酸盐
92	-H	-CH ₃	-F	-H	-H	-H	-CH ₃	-F	-H	-H	¹ H-NMR (DMSO-d ₆) δppm 1.5-1.7 (1H, m), 2.0-2.2 (1H, m), 2.17 (6H, s), 2.7-2.9 (1H, m), 3.0-3.2 (2H, m), 3.5-3.6 (1H, m), 4.5-4.7 (1H, m), 6.44 (2H, s), 6.7-6.9 (4H, m), 7.05 (2H, dd, J = 9.1 Hz, J = 9.1 Hz)	富马酸盐
93	-H	-F	-H	-H	-H	-H	-CH ₃	-F	-H	-H	¹ H-NMR (DMSO-d ₆) δppm 1.5-1.7 (1H, m), 2.0-2.2 (1H, m), 2.23 (3H, s), 2.7-2.9 (1H, m), 3.0-3.2 (2H, m), 3.5-3.6 (1H, m), 4.5-4.7 (1H, m), 6.3-6.6 (3H, m), 6.44 (2H, s), 7.0-7.2 (3H, m), 7.22 (1H, dd, J = 9.2 Hz, J = 8.9 Hz)	富马酸盐
94	-H	-CH ₃	-H	-H	-H	-H	-Cl	-F	-H	-H	¹ H-NMR (DMSO-d ₆) δppm 1.5-1.7 (1H, m), 2.0-2.2 (1H, m), 2.27 (3H, s), 2.7-2.9 (1H, m), 3.0-3.2 (2H, m), 3.5-3.6 (1H, m), 4.5-4.7 (1H, m), 6.45 (2H, s), 6.7-7.1 (5H, m), 7.2-7.4 (2H, m)	富马酸盐
95	-H	-CH ₃	-H	-H	-H	-H	-F	-H	-H	-H	¹ H-NMR (DMSO-d ₆) δppm 1.5-1.7 (1H, m), 2.0-2.2 (1H, m), 2.30 (3H, s), 2.7-2.9 (1H, m), 3.0-3.2 (2H, m), 3.5-3.6 (1H, m), 4.5-4.7 (1H, m), 6.3-6.6 (3H, m), 6.43 (2H, s), 6.8-7.0 (2H, m), 7.1-7.3 (2H, m), 7.33 (1H, dd, J = 7.7 Hz, J = 7.7 Hz)	富马酸盐
96	-H	-H	-F	-H	-H	-H	-CH ₃	-F	-H	-H	¹ H-NMR (DMSO-d ₆) δppm 1.5-1.7 (1H, m), 2.0-2.2 (1H, m), 2.48 (3H, s), 2.7-2.9 (1H, m), 3.0-3.2 (2H, m), 3.5-3.6 (1H, m), 4.5-4.7 (1H, m), 6.43 (2H, s), 6.7-6.9 (4H, m), 7.0-7.2 (3H, m)	富马酸盐

[1036]

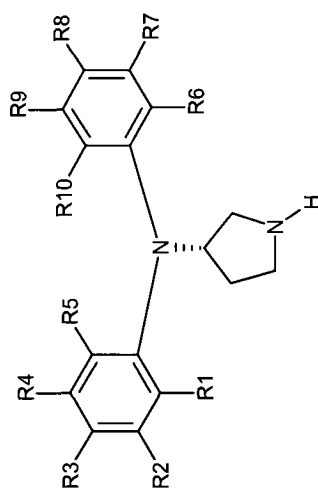
表 48



实施例	R1	R2	R3	R4	R5	R6	R7	R8	R9	R10	NMR	盐
97	-H	-H	-CH ₃	-H	-H	-H	-F	-H	-H	-H	¹ H-NMR (DMSO-d ₆) δppm 1.5-1.7 (1H, m), 2.0-2.2 (1H, m), 2.33 (3H, s), 2.7-2.9 (1H, m), 3.0-3.2 (2H, m), 3.5-3.6 (1H, m), 4.5-4.7 (1H, m), 6.3-6.6 (3H, m), 6.43 (2H, s), 7.05 (2H, d, J = 8.1 Hz), 7.1-7.2 (1H, m), 7.28 (2H, d, J = 8.1 Hz)	富马酸盐
98	-H	-Cl	-CH ₃	-H	-H	-H	-F	-H	-H	-H	¹ H-NMR (DMSO-d ₆) δppm 1.5-1.7 (1H, m), 2.0-2.2 (1H, m), 2.32 (3H, s), 2.7-2.9 (1H, m), 3.0-3.2 (2H, m), 3.5-3.6 (1H, m), 4.5-4.7 (1H, m), 6.4-6.7 (3H, m), 6.43 (2H, s), 6.98 (1H, d, J = 8.1 Hz), 7.16 (1H, s), 7.2-7.3 (1H, m), 7.38 (1H, d, J = 8.1 Hz)	富马酸盐
99	-H	-Cl	-F	-H	-H	-H	-H	-	-H	-H	¹ H-NMR (DMSO-d ₆) δppm 1.18 (3H, t, J=7.6Hz), 1.49-1.68 (1H, m), 2.01-2.19 (1H, m), 2.60 (2H, q, J=7.6Hz), 2.69-2.81 (1H, m), 2.92-3.14 (2H, m), 3.40-3.55 (1H, m), 4.50-4.69 (1H, m), 6.44 (2H, s), 6.63-6.71 (1H, m), 6.89 (1H, dd, J=2.8Hz and 6.3Hz), 7.00 (2H, d, J=8.3Hz), 7.19-7.29 (2H, m)	富马酸盐
100	-H	-F	-H	-H	-H	-H	-CH ₃	-Cl	-H	-H	¹ H-NMR (DMSO-d ₆) δppm 1.5-1.7 (1H, m), 2.0-2.2 (1H, m), 2.30 (3H, s), 2.7-2.9 (1H, m), 3.0-3.2 (2H, m), 3.5-3.6 (1H, m), 4.5-4.7 (1H, m), 6.4-6.7 (3H, m), 6.46 (2H, s), 6.93 (1H, d, J = 8.5 Hz), 7.12 (1H, s), 7.2-7.3 (1H, m), 7.43 (1H, d, J = 8.5 Hz)	富马酸盐
101	-H	-F	-H	-H	-H	-H	-CN	-H	-H	-H	¹ H-NMR (DMSO-d ₆) δppm 1.5-1.7 (1H, m), 2.1-2.3 (1H, m), 2.8-3.0 (1H, m), 3.0-3.2 (2H, m), 3.5-3.7 (1H, m), 4.6-4.8 (1H, m), 6.48 (2H, s), 6.7-7.0 (3H, m), 7.1-7.2 (1H, m), 7.3-7.5 (4H, m)	富马酸盐
102	-H	-H	-F	-Cl	-H	-H	-CN	-H	-H	-H	¹ H-NMR (DMSO-d ₆) δppm 1.5-1.7 (1H, m), 2.0-2.2 (1H, m), 2.7-2.9 (1H, m), 3.0-3.2 (2H, m), 3.6-3.8 (1H, m), 4.6-4.8 (1H, m), 6.44 (2H, s), 6.93 (1H, d, J = 8.4 Hz), 7.1-7.2 (1H, m), 7.19 (1H, s), 7.27 (1H, d, J = 7.6 Hz), 7.37 (1H, dd, J = 7.6 Hz, J = 8.2 Hz), 7.4-7.6 (2H, m)	富马酸盐

[1037]

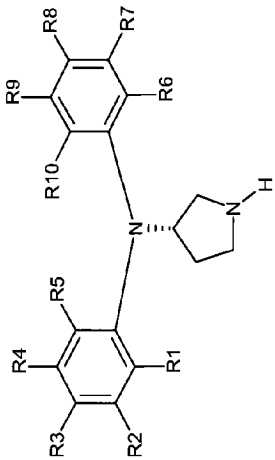
表 49



实施例	R1	R2	R3	R4	R5	R6	R7	R8	R9	R10	NMR	盐
103	-H	-H	-CO ₂ C ₂ H ₅	-H	-H	-H	-Cl	-F	-H	-H	¹ H-NMR (DMSO-d ₆) δppm 1.26 (3H, t, J=7.1Hz), 1.55-1.68 (1H, m), 2.18-2.29 (1H, m), 2.83-2.92 (1H, m), 3.07-3.19 (2H, m), 3.58-3.68 (1H, m), 4.23 (2H, q, J=7.1Hz), 4.71-4.82 (1H, m), 6.65 (2H, d, J=9.0Hz), 7.28-7.34 (1H, m), 7.55-7.64 (2H, m), 7.76 (2H, d, J=9.0Hz), 8.90-9.51 (2H, br)	盐酸盐
104	-H	-H	-CO ₂ H	-H	-H	-H	-Cl	-F	-H	-H	¹ H-NMR (DMSO-d ₆) δppm 1.52-1.70 (1H, m), 2.15-2.21 (1H, m), 2.81-2.92 (1H, m), 3.06-3.18 (2H, m), 3.53-3.67 (1H, m), 4.65-4.80 (1H, m), 6.64 (1H, d, J=9.0Hz), 7.25-7.33 (1H, m), 7.52-7.62 (2H, m), 7.75 (2H, d, J=9.0Hz), 8.50-10.50 (1H, br), 11.00-13.00 (2H, br)	盐酸盐
105	-H	-H	-SO ₂ CH ₃	-H	-H	-H	-Cl	-F	-H	-H	¹ H-NMR (DMSO-d ₆) δppm 1.56-1.68 (1H, m), 2.19-2.29 (1H, m), 2.82-2.94 (1H, m), 3.08 (3H, s), 3.10-3.20 (2H, m), 3.57-3.68 (1H, m), 4.70-4.85 (1H, m), 6.69-6.75 (2H, m), 7.32-7.37 (1H, m), 7.58-7.64 (1H, m), 7.65-7.69 (3H, m), 9.10-9.45 (2H, m)	盐酸盐
106	-H	-H	-N(CH ₃) ₂	-H	-H	-H	-CH ₃	-F	-H	-H	¹ H-NMR (DMSO-d ₆) δppm 1.52-1.70 (1H, m), 2.08-2.25 (1H, m), 2.24 (3H, s), 2.73-2.87 (1H, m), 3.03 (6H, s), 3.02-3.19 (2H, m), 3.50-3.67 (1H, m), 4.65-4.76 (1H, m), 6.73 (2H, d, J=9.1Hz), 7.00-7.20 (2H, m), 7.25 (1H, t, J=9.1Hz), 7.56 (2H, d, J=7.2Hz), 9.47 (1H, brs), 9.58 (1H, brs).	2 盐酸盐

[1038]

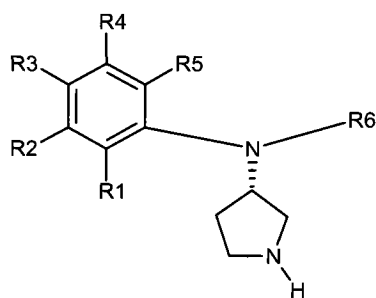
表 50



实施例	R1	R2	R3	R4	R5	R6	R7	R8	R9	R10	NMR
107	-H	-Cl	-F	-H	-H	-H	-H	O ₂ S(1-pyrrolidinyl)	-H	-H	¹ H-NMR (CDCl ₃) δppm 1.56-1.86 (5H, m), 2.17-2.30 (1H, m), 2.96 (1H, dd, J=7.4, 11.5Hz), 3.08-3.21 (6H, m), 3.52 (1H, dd, J=6.8, 11.4Hz), 4.58-4.72 (1H, m), 6.62 (2H, d, J=9.0Hz), 7.02-7.09 (1H, m), 7.21-7.30 (2H, m), 7.59 (2H, d, J=9.0Hz).

[1039] 表 51

[1040]

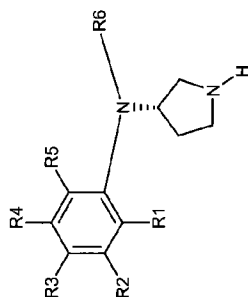


[1041]

实施例	R1	R2	R3	R4	R5	R6	熔点 (°C)	盐
108	-H	-Cl	-F	-H	-H		126-129	
109	-H	-H	-H	-H	-H		141-142	富马酸盐
110	-H	-H	-H	-H	-H		148-150	富马酸盐
111	-H	-Cl	-F	-H	-H		144-146 (dec.)	富马酸盐
112	-H	-H	-F	-Cl	-H		168-170	富马酸盐
113	-H	-H	-H	-H	-H		133-135	富马酸盐
114	-H	-H	-F	-H	-H		131.6-133.3	富马酸盐
115	-H	-H	-F	-H	-H		133.2-135.6	富马酸盐
116	-H	-H	-H	-H	-H		158-160	盐酸盐

[1042]

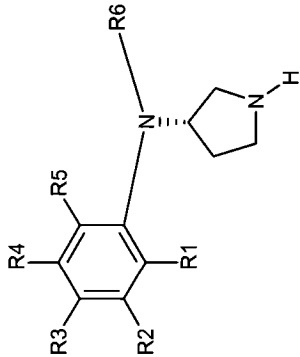
表 52



实施例	R1	R2	R3	R4	R5	R6	NMR	盐
117	-H	-H	-F	-H	-H		¹ H-NMR (DMSO-d ₆) δppm 1.5-1.7 (1H, m), 2.0-2.2 (1H, m), 2.7-2.9 (1H, m), 3.0-3.2 (2H, m), 3.4-3.5 (1H, m), 4.4-4.6 (1H, m), 6.02 (2H, s), 6.43 (2H, s), 6.54 (1H, d, J = 8.2 Hz), 6.69 (1H, s), 6.7-6.8 (2H, m), 6.90 (1H, d, J = 8.2 Hz), 7.0-7.1 (2H, m)	富马酸盐
118	-H	-H	-F	-Cl	-H		¹ H-NMR (DMSO-d ₆) δppm 1.5-1.7 (1H, m), 2.0-2.2 (1H, m), 2.7-2.9 (1H, m), 3.0-3.2 (2H, m), 3.5-3.6 (1H, m), 4.5-4.7 (1H, m), 6.06 (2H, s), 6.44 (2H, s), 6.5-6.7 (2H, m), 6.7-6.8 (2H, m), 6.96 (1H, d, J = 8.2 Hz), 7.12 (1H, s), 7.1-7.3 (1H, m)	富马酸盐
119	-H	-H	-H	-F	-H		¹ H-NMR (DMSO-d ₆) δppm 1.5-1.7 (1H, m), 2.0-2.2 (1H, m), 2.7-2.9 (1H, m), 2.9-3.1 (2H, m), 3.4-3.6 (1H, m), 4.5-4.7 (1H, m), 6.08 (2H, s), 6.3-6.5 (3H, m), 6.44 (2H, s), 6.67 (1H, d, J = 8.1 Hz), 6.82 (1H, s), 6.99 (1H, d, J = 8.1 Hz), 7.0-7.2 (1H, m)	富马酸盐
120	-H	-H	-H	-Cl	-H		¹ H-NMR (DMSO-d ₆) δppm 1.5-1.7 (1H, m), 2.0-2.2 (1H, m), 2.7-2.9 (1H, m), 3.0-3.2 (2H, m), 3.4-3.6 (1H, m), 4.24 (4H, s), 4.5-4.7 (1H, m), 6.45 (2H, s), 6.5-6.7 (2H, m), 6.70 (1H, s), 6.7-6.8 (1H, m), 6.91 (1H, d, J = 8.5 Hz), 7.20 (1H, dd, J = 9.1 Hz, J = 9.1 Hz)	富马酸盐
121	-H	-H	-F	-Cl	-H		¹ H-NMR (DMSO-d ₆) δppm 1.5-1.7 (1H, m), 2.1-2.3 (1H, m), 2.7-2.9 (1H, m), 3.0-3.2 (2H, m), 3.5-3.7 (1H, m), 4.6-4.8 (1H, m), 6.45 (2H, s), 6.9-7.0 (1H, m), 7.08 (1H, d, J = 8.5 Hz), 7.23 (1H, dd, J = 9.1 Hz, J = 9.1 Hz), 7.42 (1H, d, J = 5.4 Hz), 7.66 (1H, s), 7.80 (1H, s), 8.02 (1H, d, J = 8.5 Hz)	富马酸盐
122	-H	-H	-F	-Cl	-H		¹ H-NMR (DMSO-d ₆) δppm 1.5-1.7 (1H, m), 2.1-2.3 (1H, m), 2.7-2.9 (1H, m), 3.0-3.2 (2H, m), 3.5-3.7 (1H, m), 4.6-4.8 (1H, m), 6.46 (2H, s), 6.5-6.6 (1H, m), 6.7-6.8 (1H, m), 6.96 (1H, d, J = 2.2 Hz), 7.09 (1H, d, J = 8.7 Hz), 7.18 (1H, dd, J = 9.1 Hz, J = 9.1 Hz), 7.50 (1H, d, J = 2.2 Hz), 7.67 (1H, d, J = 8.7 Hz), 8.05 (1H, d, J = 2.2 Hz)	富马酸盐

[1043]

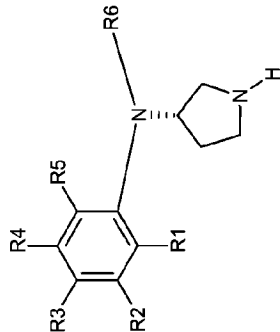
表 53

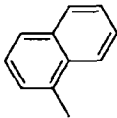
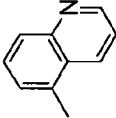
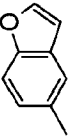


实施例	R1	R2	R3	R4	R5	R6	NMR
123	-H	-Cl	-F	-H	-H		¹H-NMR (CDCl₃) δppm 1.7-1.9 (2H, m), 2.0-2.25 (1H, m), 2.8-3.0 (3H, m), 3.05-3.25 (1H, m), 4.35-4.6 (1H, m), 6.24 (1H, d, J = 1Hz), 6.4-6.5 (1H, m), 6.65-6.75 (1H, m), 6.8-7.0 (2H, m), 7.1-7.2 (1H, m), 7.22 (1H, d, J = 7.5Hz), 7.36 (1H, d, J = 8Hz), 8.43 (1H, br).
124	-H	-H	-H	-H	-H		¹H-NMR (CDCl₃) δppm 1.68 (1H, br), 1.8-1.95 (1H, m), 2.0-2.2 (1H, m), 2.86 (2H, t, J = 7.5Hz), 2.99 (1H, dd, J = 5.5, 12Hz), 3.13 (1H, dd, J = 6.5, 11.5Hz), 4.5-4.6 (1H, m), 6.2-6.3 (1H, m), 6.6-6.75 (3H, m), 6.92 (1H, d, J = 7.5Hz), 7.05-7.25 (4H, m), 7.35 (1H, d, J = 8Hz), 8.34 (1H, br).
125	-H	-Cl	-F	-H	-H		¹H-NMR (CDCl₃) δppm 1.65-1.9 (2H, m), 2.0-2.2 (1H, m), 2.8-3.0 (3H, m), 3.05-3.2 (1H, m), 4.25-4.4 (1H, m), 6.4-6.5 (1H, m), 6.57 (1H, d, J = 3H), 6.67 (1H, dd, J = 3, 6Hz), 6.75-6.85 (1H, m), 6.90 (1H, dd, J = 9, 9Hz), 7.13 (1H, s), 7.2-7.3 (1H, m), 7.64 (1H, d, J = 8.5Hz), 8.38 (1H, br).
126	-H	-Cl	-F	-H	-H		¹H-NMR(CDCl₃) δppm 1.74-1.91(1H,m), 2.03-2.18(1H,m), 2.82-3.00(3H,m), 3.14(1H,dd,J=6.5Hz,11.5Hz), 4.30-4.40(1H,m), 6.39-6.46(1H,m), 6.55(1H,d,J=3.0Hz), 6.63(1H,dd,J=3.0Hz,3.0Hz), 6.83-6.91(1H,m), 7.18-7.41(3H,m), 8.50(1H,br)

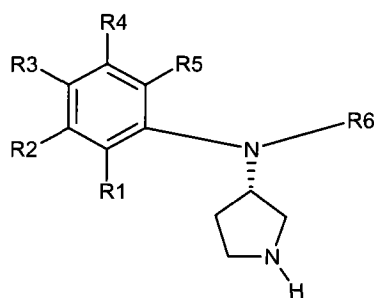
[1044]

表 54



实施例	R1	R2	R3	R4	R5	R6	NMR	盐
127	-H	-H	-H	-H	-H		¹H-NMR (DMSO-d₆) δppm 1.4-1.6 (1H, m), 2.05-2.25 (1H, m), 2.8-2.95 (1H, m), 3.0-3.2 (2H, m), 3.55-3.7 (1H, m), 4.8-5.0 (1H, m), 6.47 (2H, s), 6.53 (2H, d, J = 8Hz), 6.68 (1H, dd, J = 7.5, 7.5Hz), 7.0-7.2 (2H, m), 7.4-7.7 (4H, m), 7.7-7.85 (1H, m), 8.02 (2H, d, J = 7.5, 7.5Hz).	富马酸盐
128	-H	-H	-F	-Cl	-H		¹H-NMR (DMSO-d₆) δppm 1.35-1.55 (1H, m), 2.0-2.2 (1H, m), 2.25-5.45 (8H, m), 6.3-6.45 (1H, m), 6.48 (2H, s), 6.77 (1H, dd, J = 3, 6Hz), 7.14 (1H, dd, J = 9, 9Hz), 7.55 (1H, dd, J = 4, 8.5Hz), 7.62 (1H, dd, J = 1, 7.5Hz), 7.88 (1H, dd, J = 7.5, 7.5Hz), 8.12 (1H, d, J = 8.5Hz), 8.22 (1H, d, J = 8Hz), 8.96 (1H, dd, J = 1.5, 4Hz).	富马酸盐
129	-H	-H	-H	-H	-H		¹H-NMR (DMSO-d₆) δppm 1.45-1.8 (1H, m), 1.95-2.25 (1H, m), 2.6-4.8 (8H, m), 6.44 (2H, s), 6.67 (2H, d, J = 8Hz), 6.77 (1H, dd, J = 7.5, 7.5Hz), 6.96 (1H, dd, J = 1, 2Hz), 7.06 (1H, dd, J = 2, 8.5Hz), 7.16 (2H, dd, J = 7.5, 8.5Hz), 7.47 (1H, d, J = 2Hz), 7.65 (1H, d, J = 8.5Hz), 8.04 (1H, d, J = 2Hz).	富马酸盐

[1045] 表 55
[1046]

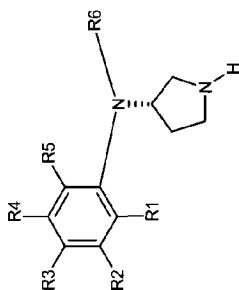


[1047]

实施例	R1	R2	R3	R4	R5	R6	熔点 (°C)	盐
130	-H	-Cl	-F	-H	-H		183-186	盐酸盐
131	-H	-Cl	-F	-H	-H		128.0-129.9	富马酸盐
132	-H	-H	-F	-H	-H		172-176	2 盐酸盐
133	-H	-Cl	-F	-H	-H		183-186	2 盐酸盐
134	-H	-Cl	-Cl	-H	-H		209-211	2 甲磺酸盐
135	-H	-Cl	-Cl	-H	-H		193-195	2 甲磺酸盐
136	-H	-Cl	-Cl	-H	-H		122-126	2 盐酸盐
137	-H	-Cl	-F	-H	-H		137.0-140.0	富马酸盐
138	-H	-H	-F	-H	-H		115-119 (dec.)	富马酸盐
139	-H	-Cl	-F	-H	-H		162.0-164.0	富马酸盐

[1048]

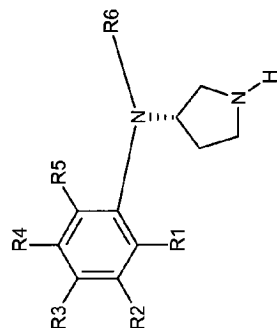
表 56



实施例	R1	R2	R3	R4	R5	R6	NMR	盐
140	-H	-CH ₃	-F	-H	-H		¹ H-NMR (DMSO-d ₆) δppm 1.8-2.0 (1H, m), 2.2-2.4 (1H, m), 2.27 (3H, s), 3.1-3.3 (3H, m), 3.5-3.7 (1H, m), 4.8-5.0 (1H, m), 6.79 (1H, d, J = 3.7 Hz), 7.23 (1H, d, J = 3.7 Hz), 7.3-7.4 (1H, m), 7.43 (1H, d, J = 7.5 Hz), 9.25 (1H, brs), 9.44 (1H, brs)	2 盐酸盐
141	-H	-Cl	-F	-H	-H		¹ H-NMR (DMSO-d ₆) δppm 1.79-1.98 (1H, m), 2.14-2.33 (1H, m), 2.19 (3H, d, J=1.0Hz), 2.98-3.39 (2H, m), 3.46-3.63 (1H, m), 4.71-4.90 (1H, m), 6.93 (1H, d, J = 1.0Hz), 7.50-7.65 (2H, m), 7.84 (1H, dd, J=2.5Hz, 6.5Hz), 9.05 (1H, br), 9.24 (1H, br).	2 盐酸盐
142	-H	-Cl	-F	-H	-H		¹ H-NMR (DMSO-d ₆) δppm 1.55-1.72 (1H, m), 2.05-2.29 (1H, m), 2.82-2.95 (1H, m), 3.02-3.14 (2H, m), 3.51-3.65 (1H, m), 4.65-4.83 (1H, m), 6.51 (4H, s), 7.20-7.29 (1H, m), 7.46-7.60 (2H, m with dd, J=2.6Hz and 6.7Hz), 8.24 (2H, s), 8.68 (1H, s).	2 富马酸盐
143	-H	-Cl	-F	-H	-H		¹ H-NMR (DMSO-d ₆) δppm 1.6-1.7 (1H, m), 2.1-2.2 (1H, m), 2.57 (3H, s), 2.9-3.1 (1H, m), 3.1-3.2 (2H, m), 3.6-3.8 (1H, m), 5.2-5.4 (1H, m), 5.87 (1H, d, J = 6.1 Hz), 7.4-7.5 (1H, m), 7.65 (1H, dd, J = 8.9 Hz, J = 8.9 Hz), 7.8-7.9 (1H, m), 8.01 (1H, d, J = 6.1 Hz), 9.39 (1H, brs), 9.59 (1H, brs)	2 盐酸盐
144	-H	-Cl	-F	-H	-H		¹ H-NMR (DMSO-d ₆) δppm 1.66-1.88 (1H, m), 2.10-2.29 (1H, m), 2.96-3.30 (3H, m), 3.48-3.64 (1H, m), 4.95-5.09 (1H, m), 7.38-7.49 (1H, m), 7.53 (1H, d, J=1.5Hz), 7.55-7.66 (1H, m), 7.7 (1H, dd, J = 2.5Hz and 6.8Hz), 7.94 (1H, d, J=2.7Hz), 8.19-8.26 (1H, m), 9.30 (1H, brs), 9.62 (1H, brs)	2 盐酸盐

[1049]

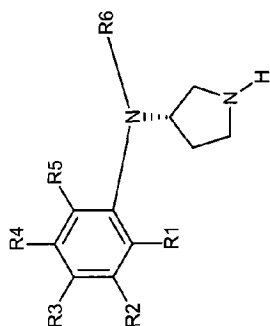
表 57



实施例	R1	R2	R3	R4	R5	R6	NMR	盐
145	-H	-Cl	-F	-H	-H		H-NMR (DMSO-d ₆) δppm 1.8-2.0 (1H, m), 2.2-2.4 (1H, m), 3.1-3.4 (3H, m), 3.5-3.7 (1H, m), 5.0-5.2 (1H, m), 5.0-5.2 (1H, m), 7.11 (1H, dd, J = 7.3 Hz, J = 7.7 Hz), 7.32 (1H, dd, J = 7.3 Hz, J = 8.2 Hz), 7.6-7.8 (4H, m), 7.9-8.1 (1H, m), 9.22 (1H, m), 9.46 (1H, brs)	2 盐酸盐
146	-H	-Cl	-F	-H	-H		H-NMR (DMSO-d ₆) δppm 1.8-2.0 (1H, m), 2.2-2.4 (1H, m), 2.57 (3H, s), 3.1-3.4 (3H, m), 3.5-3.7 (1H, m), 3.72 (3H, s), 4.9-5.1 (1H, m), 6.92 (1H, d, J = 8.8 Hz), 7.31 (1H, s), 7.52 (1H, d, J = 8.8 Hz), 7.6-7.7 (2H, m), 7.9-8.1 (1H, m), 9.17 (1H, brs), 9.42 (1H, brs)	2 盐酸盐
147	-H	-H	-H	-H	-H		H-NMR (DMSO-d ₆) δppm 1.8-2.0 (1H, m), 2.2-2.4 (1H, m), 3.1-3.4 (3H, m), 3.6-3.7 (1H, m), 5.0-5.2 (1H, m), 5.0-5.2 (1H, m), 7.08 (1H, dd, J = 7.2 Hz, J = 7.9 Hz), 7.31 (1H, dd, J = 7.2 Hz, J = 8.2 Hz), 7.5-7.8 (7H, m), 9.28 (1H, brs), 9.50 (1H, brs)	2 盐酸盐
148	-H	-Cl	-F	-H	-H		H-NMR (DMSO-d ₆) δppm 1.6-1.8 (1H, m), 2.3-2.4 (1H, m), 2.9-3.1 (1H, m), 3.1-3.2 (2H, m), 3.7-3.8 (1H, m), 5.1-5.2 (1H, m), 7.39 (1H, d, J = 7.2 Hz), 7.55 (1H, d, J = 5.7 Hz), 7.7-7.8 (2H, m), 8.08 (1H, d, J = 7.2 Hz), 8.22 (1H, d, J = 5.7 Hz), 8.69 (1H, d, J = 7.0 Hz), 9.43 (1H, brs), 9.59 (1H, brs)	2 盐酸盐

[1050]

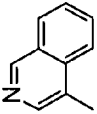
表 58

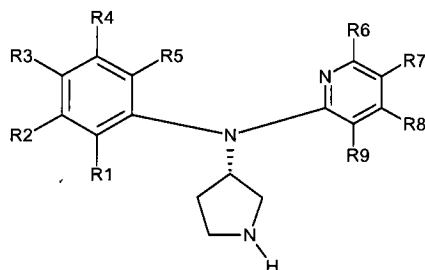


实施例	R1	R2	R3	R4	R5	R6	NMR	盐
149	-H	-Cl	-F	-H	-H		¹ H-NMR (DMSO-d ₆) δppm 1.6-1.8 (1H, m), 2.2-2.4 (1H, m), 2.9-3.1 (1H, m), 3.1-3.3 (2H, m), 3.6-3.8 (1H, m), 4.8-5.0 (1H, m), 7.3-7.4 (1H, m), 7.56 (1H, dd, J = 9.0 Hz), 7.6-7.7 (1H, m), 7.7-7.9 (2H, m), 8.08 (1H, d, J = 7.8 Hz), 8.22 (1H, d, J = 8.4 Hz), 8.27 (1H, s), 8.67 (1H, s), 9.57 (1H, brs), 9.64 (1H, brs)	2 盐酸盐
150	-H	-Cl	-F	-H	-H		¹ H-NMR (DMSO-d ₆) δppm 1.82 (3H, s), 1.9-2.1 (1H, m), 2.2-2.3 (1H, m), 3.1-3.2 (1H, m), 3.2-3.3 (1H, m), 3.4-3.5 (1H, m), 3.6-3.8 (1H, m), 4.9-5.0 (1H, m), 7.0-7.1 (1H, m), 7.3-7.4 (2H, m), 7.4-7.5 (1H, m), 7.68 (1H, dd, J = 8.0 Hz, J = 8.3 Hz), 7.81 (1H, d, J = 7.2 Hz), 7.92 (1H, d, J = 8.3 Hz), 8.04 (1H, s), 8.94 (1H, brs), 9.11 (1H, brs)	2 盐酸盐
151	-H	-CH ₃	-F	-H	-H		¹ H-NMR (CDCl ₃) δppm 1.8-2.0 (1H, m), 2.32 (3H, s), 2.4-2.5 (1H, m), 3.1-3.3 (1H, m), 3.4-3.5 (1H, m), 3.5-3.7 (1H, m), 4.1-4.3 (1H, m), 5.2-5.4 (1H, m), 7.0-7.3 (3H, m), 7.5-7.7 (2H, m), 7.89 (1H, d, J = 7.9 Hz), 8.04 (1H, s), 8.47 (1H, d, J = 8.3 Hz), 8.87 (1H, s), 9.72 (1H, brs), 10.28 (1H, brs)	2 盐酸盐

[1051]

[1052] 表 59
[1053]

152	-H	-Cl	-F	-H	-H		1H-NMR (DMSO-d6) δppm 1.6-1.8 (1H, m), 2.2-2.4 (1H, m), 2.9-3.1 (1H, m), 3.1-3.3 (2H, m), 3.6-3.8 (1H, m), 4.8-5.0 (1H, m), 6.3-6.4 (1H, m), 6.48 (2H, s), 6.7-6.8 (1H, m), 7.15 (1H, dd, J = 9.0 Hz, J = 9.0 Hz), 7.6-7.8 (3H, m), 8.1-8.3 (1H, m), 8.51 (1H, s), 9.41 (1H, s)	富马酸盐
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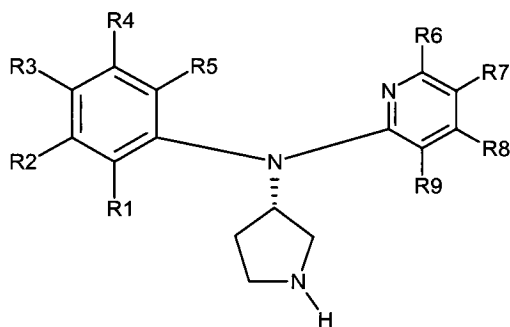


[1054]

实施例	R1	R2	R3	R4	R5	R6	R7	R8	R9	熔点 (°C)	盐
153	-H	-H	-H	-H	-H	-H	-H	-H	-H	208.0-211.0 (dec.)	2 盐酸盐
154	-H	-Cl	-F	-H	-H	-H	-H	-H	-H	152.4-154.4	富马酸盐
155	-H	-Cl	-F	-H	-H	-H	-CH ₃	-H	-H	141.8-143.1	富马酸盐
156	-H	-Cl	-F	-H	-H	-H	-H	-CH ₃	-H	138.6-140.2	富马酸盐
157	-H	-Cl	-F	-H	-H	-H	-H	-H	-H	207.0-208.0	2 甲磺酸盐
158	-H	-Cl	-F	-H	-H	-H	-3-噻吩基	-H	-H	148-151	2 盐酸盐
159	-H	-Cl	-F	-H	-H	-H	-4-吡啶基	-H	-H	157-158	3 盐酸盐
160	-H	-Cl	-F	-H	-H	-H	-C ₆ H ₅	-H	-H	150-153	2 盐酸盐
161	-H	-Cl	-F	-H	-H	-H	-H	-H	-F	83-85	2 盐酸盐
162	-H	-Cl	-F	-H	-H	-H	-H	-F	-H	150-153	2 盐酸盐
163	-H	-Cl	-F	-H	-H	-H	-CF ₃	-H	-H	87-89	盐酸盐
164	-H	-Cl	-F	-H	-H	-H	-H	-OCH ₃	-H	153-156	2 盐酸盐
165	-H	-Cl	-F	-H	-H	-Br	-H	-H	-H	220-223	盐酸盐
166	-H	-Cl	-F	-H	-H	-Cl	-H	-H	-H	219-220	盐酸盐
167	-H	-Cl	-F	-H	-H	-H	-C ₂ H ₅	-H	-H	112-115	富马酸盐
168	-H	-Cl	-F	-H	-H	-2-噻吩基	-H	-H	-H	98-103	盐酸盐
169	-H	-Cl	-F	-H	-H	-3-噻吩基	-H	-H	-H	95-98	盐酸盐
170	-H	-Cl	-F	-H	-H	-H	-H	-Cl	-H	125-128	2 盐酸盐
171	-H	-Cl	-Cl	-H	-H	-H	-F	-H	-H	111-115	2 盐酸盐
172	-H	-Cl	-Cl	-H	-H	-H	-Br	-H	-H	115-118	2 盐酸盐
173	-H	-Cl	-Cl	-H	-H	-H	-H	-H	-F	75-80	2 盐酸盐
174	-H	-Cl	-Cl	-H	-H	-H	-H	-F	-H	125-128	2 盐酸盐

[1055] 表 60

[1056]



[1057]

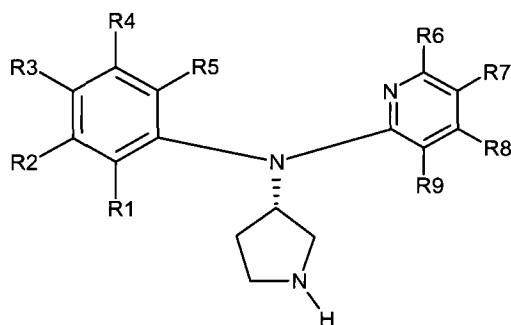
实施例	R1	R2	R3	R4	R5	R6	R7	R8	R9	熔点 (°C)	盐
175	-H	-Cl	-Cl	-H	-H	-H	-H	-OCH ₃	-H	160-165	2 盐酸盐
176	-H	-Cl	-F	-H	-H	-H	-CN	-H	-H	211-213	盐酸盐
177	-H	-Cl	-Cl	-H	-H	-H	-CN	-H	-H	126-130	2 盐酸盐
178	-H	-Cl	-Cl	-H	-H	-H	-H	-CH ₃	-H	204-207	2 盐酸盐

[1058]

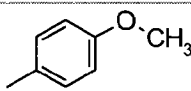
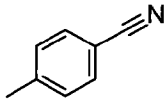
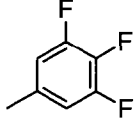
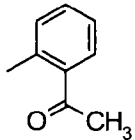
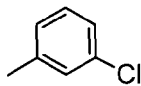
179	-H	-Cl	-Cl	-H	-H	-H	-CF ₃	-H	-H	100-105	2 盐酸盐
180	-H	-Cl	-Cl	-H	-H	-H	-OCH ₃	-H	-H	190-195	2 盐酸盐
181	-H	-Cl	-Cl	-H	-H	-H	-H	-CN	-H	135-138	2 盐酸盐
182	-H	-Cl	-F	-H	-H	-H	-Cl	-H	-H	163-165	富马酸盐
183	-H	-Cl	-F	-H	-H	-H	-Cl	-H	-H	190-191	2 盐酸盐
184	-H	-H	-F	-H	-H	-H	-Cl	-H	-H	95-97	富马酸盐
185	-H	-CH ₃	-F	-H	-H	-H	-Cl	-H	-H	156-157	富马酸盐
186	-H	-Cl	-F	-H	-H	-H	-Br	-H	-H	159-160	富马酸盐
187	-H	-H	-F	-H	-H	-H	-H	-H	-H	226-228	2 盐酸盐
188	-H	-H	-Cl	-Cl	-H	-H	-H	-H	-H	135-138	2 盐酸盐
189	-H	-H	-Cl	-Cl	-H	-H	-Cl	-H	-H	123-125	2 盐酸盐
190	-H	-H	-F	-Cl	-H	-H	-3-呋喃基	-H	-H	157-160	2 盐酸盐
191	-H	-H	-F	-Cl	-H	-H	-2-噻吩基	-H	-H	152-155	2 盐酸盐
192	-H	-H	-F	-Cl	-H	-H	-F	-H	-H	115-120	2 盐酸盐

[1059] 表 61

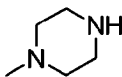
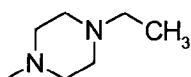
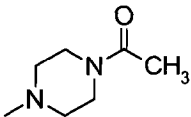
[1060]



[1061]

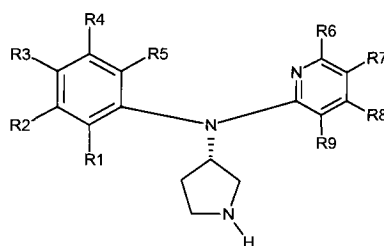
实施例	R1	R2	R3	R4	R5	R6	R7	R8	R9	熔点 (°C)	盐
193	-H	-Cl	-F	-H	-H	-H		-H	-H	143-145	2 盐酸盐
194	-H	-Cl	-F	-H	-H	-H		-H	-H	145-146	2 盐酸盐
195	-H	-Cl	-F	-H	-H	-H		-H	-H	113-116	2 盐酸盐
196	-H	-Cl	-F	-H	-H	-H		-H	-H	128-130	2 盐酸盐
197	-H	-Cl	-F	-H	-H	-H		-H	-H	116-120	2 盐酸盐
198	-H	-H	-F	-H	-H	-H		-H	-H	132-135	2 盐酸盐

[1062]

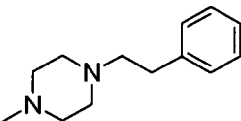
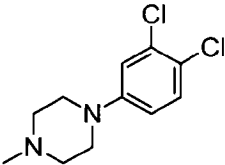
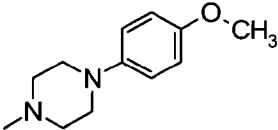
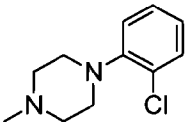
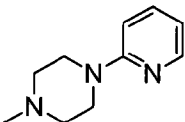
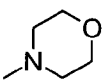
199	-H	-Cl	-F	-H	-H	-H		-H	-H	142-145	3 盐酸盐
200	-H	-Cl	-F	-H	-H	-H		-H	-H	212-215	4 盐酸盐
201	-H	-Cl	-F	-H	-H	-H		-H	-H	208-211	4 盐酸盐
202	-H	-Cl	-F	-H	-H	-H		-H	-H	200-203	3 盐酸盐

[1063] 表 62

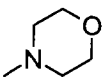
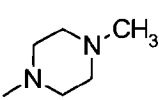
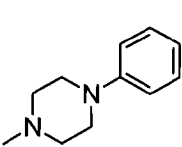
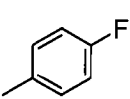
[1064]



[1065]

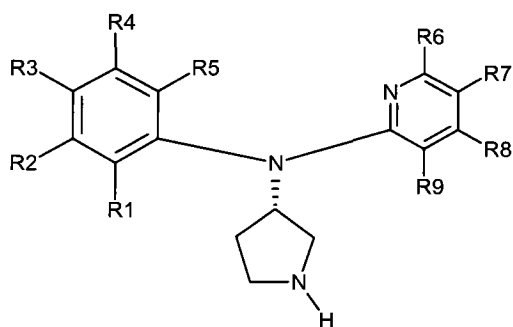
实施例	R1	R2	R3	R4	R5	R6	R7	R8	R9	熔点 (°C)	盐
203	-H	-Cl	-F	-H	-H	-H		-H	-H	160-162	4 盐酸盐
204	-H	-Cl	-F	-H	-H	-H		-H	-H	167-170	2 盐酸盐
205	-H	-Cl	-F	-H	-H	-H		-H	-H	200-203	3 盐酸盐
206	-H	-Cl	-F	-H	-H	-H		-H	-H	243-246	3 盐酸盐
207	-H	-Cl	-F	-H	-H	-H		-H	-H	145-147	4 盐酸盐
208	-H	-H	-F	-Cl	-H	-H		-H	-H	143-145	3 盐酸盐

[1066]

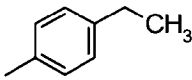
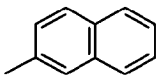
209	-H	-H	-F	-H	-H	-H		-H	-H	131-133	3 盐酸盐
210	-H	-H	-F	-Cl	-H	-H		-H	-H	184-186	3 盐酸盐
211	-H	-H	-F	-Cl	-H	-H		-H	-H	160-162	3 盐酸盐
212	-H	-H	-F	-Cl	-H	-H		-H	-H	133-135	2 盐酸盐

[1067] 表 63

[1068]

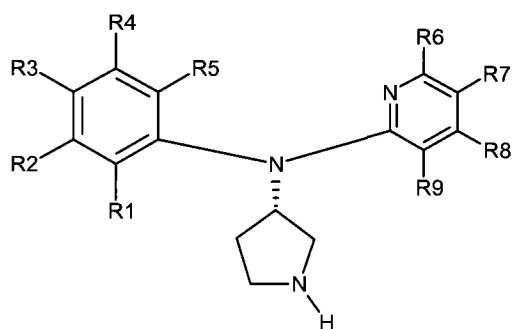


[1069]

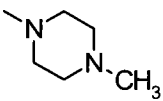
实施例	R1	R2	R3	R4	R5	R6	R7	R8	R9	熔点 (°C)	盐
213	-H	-Cl	-F	-H	-H	-H		-H	-H	128-131	2 盐酸盐
214	-H	-Cl	-F	-H	-H	-H		-H	-H	164-166	2 盐酸盐

[1070] 表 64

[1071]

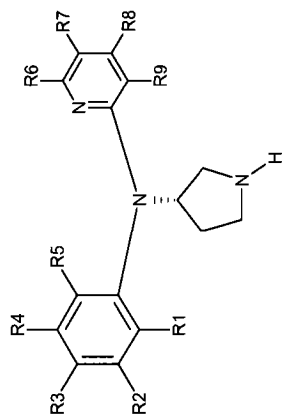


[1072]

实施例	R1	R2	R3	R4	R5	R6	R7	R8	R9	熔点 (°C)	盐
215	-H	-Cl	-F	-H	-H		-H	-H	-H	181-183	4 盐酸盐

[1074]

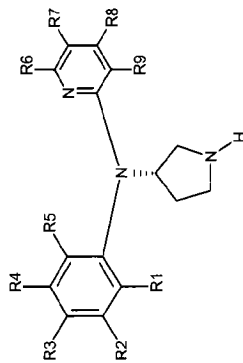
表 65



实施例	R1	R2	R3	R4	R5	R6	R7	R8	R9	NMR	盐
216	-H	-Cl	-F	-H	-H	-H	-H	-H	-H	¹ H-NMR (DMSO-d ₆) δppm 1.59-1.82 (1H, m), 2.11-2.35 (1H, m), 2.85-3.28 (3H, m), 3.50-3.71 (1H, m), 5.01-5.21 (1H, m), 6.25-6.46 (1H, m), 6.82-6.92 (1H, m), 7.33-7.50 (1H, m), 7.55-7.70 (2H, m), 7.74 (1H, dd, J=2.4Hz and 6.7Hz), 8.11-8.21 (1H, m), 9.20-9.75 (2H, m)	2 盐酸盐
217	-H	-H	-H	-H	-H	-CH ₃	-H	-H	-H	¹ H-NMR (DMSO-d ₆) δppm 1.60-1.79 (1H, m), 2.13-2.30 (1H, m), 2.50 (1H, s), 2.86-3.02 (1H, m), 3.05-3.20 (2H, m), 3.59-3.64 (1H, m), 5.29-5.45 (1H, m), 5.80-6.00 (1H, m), 6.68 (1H, d, J=7.2Hz), 7.32 (1H, d, J=7.2Hz), 7.41-7.51 (2H, m), 7.53-7.61 (2H, m), 9.49 (2H, brs)	盐酸盐
218	-H	-H	-H	-H	-H	-H	-CH ₃	-H	-H	¹ H-NMR (DMSO-d ₆) δppm 1.61-1.79 (1H, m), 2.19 (3H, s), 2.23-2.39 (1H, m), 2.85-3.20 (3H, m), 3.59-3.74 (1H, m), 5.05-5.22 (1H, m), 6.20-6.40 (1H, m), 7.32-7.41 (2H, m), 7.46-7.62 (4H, m), 7.94-7.99 (1H, m), 9.30-9.65 (2H, br)	2 盐酸盐
219	-H	-H	-H	-H	-H	-H	-H	-CH ₃	-H	¹ H-NMR (DMSO-d ₆) δppm 1.60-1.80 (1H, m), 2.19 (3H, s), 2.24-2.48 (1H, m), 2.81-3.00 (1H, m), 3.02-3.19 (2H, m), 3.58-3.64 (1H, m), 6.30 (1H, d, J=8.8Hz), 7.32-7.42 (2H, m), 7.49-7.68 (4H, m), 7.93-8.01 (1H, m), 9.50 (2H, brs)	2 盐酸盐
220	-H	-Cl	-F	-H	-H	-CH ₃	-H	-H	-H	¹ H-NMR (DMSO-d ₆) δppm 1.52-1.76 (1H, m), 1.92-2.18 (1H, m), 2.32 (3H, s), 2.90-3.22 (3H, m), 3.50-3.72 (1H, m), 5.05-5.25 (1H, m), 5.72-5.90 (1H, m), 6.35-6.70 (3H, m), 7.11-7.75 (3H, m)	富马酸盐
221	-H	-CF ₃	-F	-H	-H	-H	-H	-H	-H	¹ H-NMR (DMSO-d ₆) δppm 1.65-1.83 (1H, m), 2.16-2.31 (1H, m), 3.00-3.31 (3H, m), 3.52-3.67 (1H, m), 5.03-5.16 (1H, m), 6.25 (1H, d, J=8.5Hz), 6.80-6.85 (1H, m), 7.52-7.59 (1H, m), 7.67-7.81 (1H, m), 7.84 (1H, d, J=6.5Hz), 8.19-8.22 (1H, m), 9.07 (1H, br), 9.34 (1H, br)	2 盐酸盐

[1075]

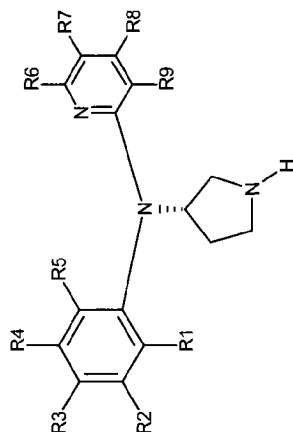
表 66



实施例	R1	R2	R3	R4	R5	R6	R7	R8	R9	NMR	盐
222	-H	-Cl	-F	-Cl	-H	-H	-H	-CF ₃	-H	¹ H-NMR (DMSO-d ₆) δppm 1.7-1.8 (1H, m), 2.1-2.3 (1H, m), 3.0-3.2 (2H, m), 3.2-3.3 (1H, m), 3.5-3.7 (1H, m), 5.1-5.2 (1H, m), 6.24 (1H, s), 7.03 (1H, d, J = 5.3 Hz), 7.4-7.5 (1H, m), 7.63 (1H, dd, J = 9.0 Hz, J = 9.0 Hz), 7.7-7.8 (1H, m), 8.47 (1H, d, J = 5.3 Hz), 9.21 (1H, brs), 9.53 (1H, brs)	2 盐酸盐
223	-H	-Cl	-F	-H	-H	-OCH ₃	-H	-H	-H	¹ H-NMR (DMSO-d ₆) δppm 1.6-1.7 (1H, m), 2.1-2.2 (1H, m), 2.9-3.1 (1H, m), 3.1-3.2 (2H, m), 3.6-3.8 (1H, m), 3.85 (3H, s), 5.1-5.2 (1H, m), 5.52 (1H, d, J = 8.0 Hz), 6.12 (1H, d, J = 7.8 Hz), 7.3-7.4 (2H, m), 7.5-7.7 (2H, m), 9.25 (1H, brs), 9.45 (1H, brs)	2 盐酸盐
224	-H	-CH ₃	-F	-H	-H	-H	-H	-H	-Cl	¹ H-NMR (CDCl ₃) δppm 2.1-2.4 (2H, m), 2.23 (3H, s), 3.2-3.3 (1H, m), 3.4-3.6 (2H, m), 3.6-3.8 (1H, m), 4.7-4.9 (1H, m), 6.7-7.1 (4H, m), 7.57 (1H, d, J = 7.1 Hz), 8.52 (1H, d, J = 3.9 Hz), 9.53 (1H, brs), 10.10 (1H, brs)	2 盐酸盐
225	-H	-CH ₃	-F	-H	-H	-H	-H	-H	-H	¹ H-NMR (CDCl ₃) δppm 1.8-2.0 (1H, m), 2.35 (3H, s), 2.5-2.7 (1H, m), 3.1-3.4 (2H, m), 3.4-3.6 (1H, m), 4.1-4.3 (1H, m), 5.3-5.5 (1H, m), 6.47 (1H, d, J = 8.9 Hz), 7.05 (1H, s), 7.2-7.4 (3H, m), 7.78 (1H, dd, J = 8.9 Hz, J = 7.6 Hz), 8.25 (1H, d, J = 4.7 Hz), 9.51 (1H, brs), 10.39 (1H, brs)	2 盐酸盐
226	-H	-H	-F	-H	-H	-H	-CH ₃	-H	-H	¹ H-NMR (CDCl ₃) δppm 1.8-2.0 (1H, m), 2.31 (3H, s), 2.35 (3H, s), 2.6-2.7 (1H, m), 3.1-3.3 (1H, m), 3.3-3.4 (1H, m), 3.4-3.6 (1H, m), 4.1-4.3 (1H, m), 5.3-5.5 (1H, m), 6.42 (1H, d, J = 9.3 Hz), 7.1-7.4 (3H, m), 7.61 (1H, d, J = 9.3 Hz), 8.04 (1H, s), 9.51 (1H, brs), 10.47 (1H, brs)	2 盐酸盐
227	-H	-CH ₃	-F	-H	-H	-CH ₃	-H	-H	-H	¹ H-NMR (CDCl ₃) δppm 1.8-2.0 (1H, m), 2.36 (3H, s), 2.4-2.5 (1H, m), 2.92 (3H, s), 3.2-3.4 (2H, m), 3.4-3.6 (1H, m), 4.1-4.3 (1H, m), 6.0-6.1 (1H, m), 6.20 (1H, d, J = 8.9 Hz), 6.73 (1H, d, J = 7.1 Hz), 7.1-7.3 (3H, m), 7.5-7.7 (1H, m), 9.29 (1H, brs), 10.98 (1H, brs)	2 盐酸盐

[1076]

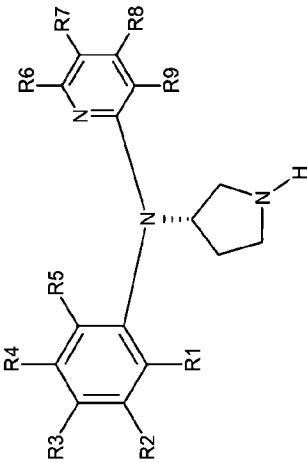
表 67



实施例	R1	R2	R3	R4	R5	R6	R7	R8	R9	NMR	盐
228	-H	-CH ₃	-F	-H	-H	-OCH ₃	-H	-H	-H	¹ H-NMR (CDCl ₃) δppm 1.9-2.1 (1H, m), 2.26 (3H, s), 2.2-2.4 (1H, m), 3.2-3.5 (3H, m), 3.8-3.9 (1H, m), 3.90 (3H, s), 5.0-5.2 (1H, m), 5.58 (1H, d, J = 8.1 Hz), 6.08 (1H, d, J = 8.0 Hz), 6.9-7.1 (3H, m), 7.22 (1H, dd, J = 8.0 Hz, J = 8.1 Hz), 9.74 (1H, brs), 10.18 (1H, brs)	2 盐酸盐
229	-H	-CH ₃	-F	-H	-H	-H	-H	-CH ₃	-H	¹ H-NMR (CDCl ₃) δppm 1.9-2.0 (1H, m), 2.31 (3H, s), 2.37 (3H, s), 2.6-2.7 (1H, m), 3.1-3.3 (1H, m), 3.3-3.4 (1H, m), 3.4-3.6 (1H, m), 4.1-4.3 (1H, m), 5.4-5.6 (1H, m), 6.18 (1H, s), 6.84 (1H, d, J = 6.3 Hz), 7.2-7.4 (3H, m), 8.11 (1H, d, J = 6.3 Hz), 9.55 (1H, brs), 10.64 (1H, brs)	2 盐酸盐
230	-H	-CH ₃	-F	-H	-H	-H	-H	-H	-CH ₃	¹ H-NMR (CDCl ₃) δppm 1.96 (3H, s), 2.0-2.1 (1H, m), 2.27 (3H, s), 2.4-2.6 (1H, m), 3.4-3.7 (3H, m), 3.8-4.0 (1H, m), 5.3-5.5 (1H, m), 7.0-7.3 (3H, m), 7.3-7.5 (1H, m), 7.89 (1H, d, J = 7.0 Hz), 8.50 (1H, d, J = 5.1 Hz), 9.77 (1H, brs), 10.39 (1H, brs)	2 盐酸盐
231	-H	-Cl	-F	-H	-H	-H	-Cl	-H	-Cl	¹ H-NMR (CDCl ₃) δppm 1.65-1.81 (1H, m), 1.99-2.09 (1H, m), 2.81-3.11 (4H, m), 4.50-4.61 (1H, m), 6.80-6.87 (1H, m), 7.00 (1H, dd, J=2.8, 6.4Hz), 7.05 (1H, t, d, J=8.7Hz), 7.61 (1H, d=2.3Hz), 8.26 (1H, d, J=2.3Hz)	
232	-H	-Cl	-F	-H	-H	-H	-CN	-H	-H	¹ H-NMR (CDCl ₃) δppm 1.63-1.77 (1H, m), 2.01-2.15 (1H, m), 2.78-2.96 (3H, m), 3.28-3.35 (1H, m), 5.02-5.16 (1H, m), 6.03 (1H, d, J=9.0Hz), 7.02-7.10 (1H, m), 7.24-7.32 (2H, m), 7.44 (1H, dd, J=2.3, 9.0Hz), 8.46 (1H, d, J=2.3Hz)	
233	-H	-Cl	-F	-H	-H	-CN	-H	-H	-H	¹ H-NMR (CDCl ₃) δppm 1.82-1.95 (1H, m), 2.19-2.25 (1H, m), 3.11-3.29 (3H, m), 3.62-3.70 (1H, m), 5.01-5.11 (1H, m), 6.27 (1H, d, J=8.8Hz), 7.06 (1H, d, J=7.3Hz), 7.10-7.15 (1H, m), 7.23-7.31 (2H, m), 7.39 (1H, dd, J=7.3, 8.8Hz)	

[1077]

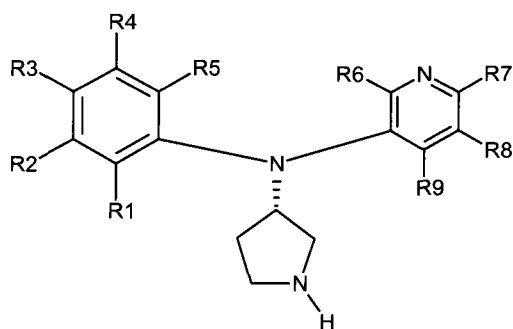
表 68



实施例	R1	R2	R3	R4	R5	R6	R7	R8	R9	NMR	盐
234	-H	-Cl	-Cl	-H	-H	-H	-H	-Cl	-H	¹ H-NMR (DMSO-d ₆) δppm 1.68-1.82 (1H, m), 2.11-2.24 (1H, m), 3.01-3.14 (2H, m), 3.15-3.29 (1H, m), 3.48-3.65 (1H, m), 4.98-5.10 (1H, m), 6.21 (1H, s), 6.88 (1H, d, J=5.4Hz), 7.35-7.40 (1H, m), 7.76 (1H, d, J=1.7Hz), 7.82 (1H, d, J=8.4Hz), 8.21 (1H, d, J=5.4Hz), 9.19 (1H, brs), 9.55 (1H, brs).	2 盐酸盐
235	-H	-Cl	-F	-H	-H	-H	-H	-H	-Cl	¹ H-NMR (CDCl ₃) δppm 1.74 (1H, brs), 2.30 (1H, brs), 3.34 (1H, brs), 3.55 (2H, brs), 3.73 (1H, brs), 4.79 (1H, brs), 6.90-7.13 (4H, m), 7.60 (1H, d, J=7.7Hz), 8.58 (1H, s), 9.48 (1H, brs), 10.38 (1H, brs).	盐酸盐
236	-H	-Cl	-F	-H	-H	-H	-3-吡啶基	-H	-H	¹ H-NMR (DMSO-d ₆) δppm 1.65-1.90 (1H, m), 2.13-2.31 (1H, m), 2.99-3.28 (3H, m), 3.58-3.72 (1H, m), 5.13-5.28 (1H, m), 6.26 (1H, d, J=9.0Hz), 7.45 (1H, ddd, J=2.6, 4.3, 8.6Hz), 7.65 (1H, t, J=9.0Hz), 7.76 (1H, dd, J=2.5, 6.7Hz), 8.02 (1H, dd, J=2.5, 9.0Hz), 8.11 (1H, dd, J=5.7, 8.1Hz), 8.78-8.87 (3H, m), 9.25 (1H, s), 9.60 (1H, brs), 9.85 (1H, brs).	2 盐酸盐

[1078] 表 69

[1079]

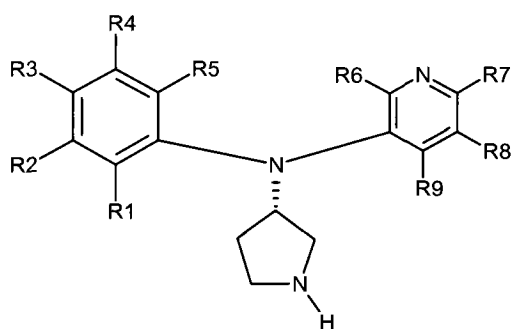


[1080]

实施例	R1	R2	R3	R4	R5	R6	R7	R8	R9	熔点 (°C)	盐
237	-H	-Cl	-F	-H	-H	-H	-H	-H	-H	194.0-195.0	2 甲磺酸盐
238	-H	-Cl	-F	-H	-H	-H	-C ₆ H ₅	-H	-H	158-161	2 盐酸盐
239	-H	-Cl	-F	-H	-H	-H	-F	-H	-H	75-80	2 盐酸盐
240	-H	-Cl	-F	-H	-H	-H	-F	-H	-H	121-123	富马酸盐
241	-H	-Cl	-Cl	-H	-H	-H	-CN	-H	-H	150-155	2 盐酸盐
242	-H	-Cl	-Cl	-H	-H	-H	-H	-H	-H	108-110	盐酸盐
243	-H	-H	-F	-H	-H	-H	-H	-H	-H	232-234	2 盐酸盐
244	-H	-Cl	-F	-H	-H	-H	-Cl	-H	-H	136-137	富马酸盐
245	-H	-Cl	-F	-H	-H	-H	-H	-4-吡啶基	-H	200-205	3 盐酸盐

[1081] 表 70

[1082]

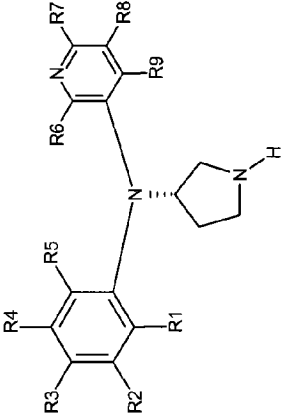


[1083]

实施例	R1	R2	R3	R4	R5	R6	R7	R8	R9	熔点 (°C)	盐
246	-H	-Cl	-F	-H	-H	-H	-H		-H	252-257	4 盐酸盐
247	-H	-H	-F	-Cl	-H	-H		-H	-H	223-225	3 盐酸盐
248	-H	-H	-F	-Cl	-H	-H		-H	-H	155-157	2 盐酸盐

[1084]

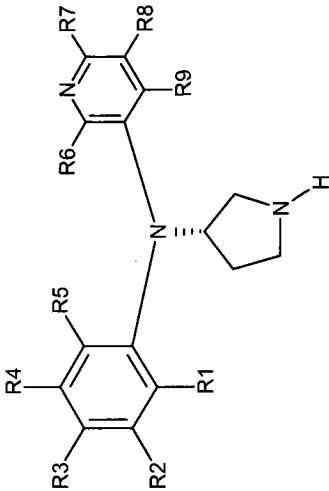
表 71



实施例	R1	R2	R3	R4	R5	R6	R7	R8	R9	NMR	盐
249	-H	-H	-H	-H	-H	-H	-H	-H	-H	¹ H-NMR (DMSO-d ₆) δppm 1.50-1.70 (1H, m), 2.10-2.31 (1H, m), 2.75-2.90 (1H, m), 3.00-3.22 (2H, m), 3.51-3.68 (1H, m), 4.60-4.80 (1H, m), 6.47 (2H, s), 7.01-7.10 (2H, m), 7.13-7.30 (3H, m), 7.32-7.45 (2H, m), 8.07 (1H, d, J=2.7Hz), 8.13 (1H, dd, J=1.4Hz and 4.5Hz) ¹ H-NMR (DMSO-d ₆) δppm 1.51-1.74 (1H, m), 2.13-2.35 (1H, m), 2.80-2.99 (1H, m), 3.01-3.20 (2H, m), 3.52-3.72 (1H, m), 4.75-4.94 (1H, m), 7.39-7.48 (1H, m), 7.59-7.69 (2H, m), 7.71-7.81 (2H, m), 8.19-8.29 (2H, m)	富马酸盐
250	-H	-Cl	-F	-H	-H	-H	-H	-H	-H	¹ H-NMR (DMSO-d ₆) δppm 1.50-1.71 (1H, m), 2.05-2.28 (1H, m), 2.75-2.92 (1H, m), 3.00-3.24 (2H, m), 3.45-3.62 (1H, m), 4.52-4.78 (1H, m), 6.86-6.98 (2H, m), 7.01-7.11 (1H, m), 7.15 (1H, dd, J=3.4Hz and 7.2Hz), 7.28-7.39 (2H, m), 7.48-7.62 (1H, m), 7.84-7.93 (1H, m), 9.20-9.80 (2H, m)	2 盐酸盐
251	-H	-F	-H	-H	-H	-H	-H	-H	-H	¹ H-NMR (DMSO-d ₆) δppm 1.62-1.81 (1H, m), 2.20-2.37 (1H, m), 2.88-3.24 (3H, m), 3.56-3.72 (1H, m), 5.10-5.27 (1H, m), 6.27 (1H, d, J=8.6Hz), 6.82-6.92 (1H, m), 7.37 (2H, d, J=7.1Hz), 7.49-7.72 (4H, m with d at δ7.58, J=7.6Hz), 8.15 (1H, dd, J=1.2Hz and 5.6Hz), 9.30-9.80 (2H, m)	2 盐酸盐
252	-H	-H	-H	-H	-H	-H	-F	-H	-H	¹ H-NMR (DMSO-d ₆) δppm 1.50-1.71 (1H, m), 2.05-2.28 (1H, m), 2.75-2.92 (1H, m), 3.00-3.24 (2H, m), 3.45-3.62 (1H, m), 4.52-4.78 (1H, m), 6.86-6.98 (2H, m), 7.01-7.11 (1H, m), 7.15 (1H, dd, J=3.4Hz and 7.2Hz), 7.28-7.39 (2H, m), 7.48-7.62 (1H, m), 7.84-7.93 (1H, m), 9.20-9.80 (2H, m)	盐酸盐
253	-H	-CH ₃	-F	-H	-H	-H	-H	-H	-H	¹ H-NMR (DMSO-d ₆) δppm 1.5-1.7 (1H, m), 2.0-2.2 (1H, m), 2.27 (3H, s), 2.36 (6H, s), 2.8-3.0 (1H, m), 3.0-3.3 (2H, m), 3.6-3.7 (1H, m), 4.7-4.9 (1H, m), 7.2-7.4 (3H, m), 7.55 (1H, d, J = 8.9 Hz), 7.75 (1H, d, J = 8.9 Hz), 8.14 (1H, s), 8.22 (1H, d, J = 5.1 Hz), 8.83 (2H, brs)	2 甲磺酸盐
254	-H	-Cl	-F	-H	-H	-H	-OCH ₃	-H	-H	¹ H-NMR (DMSO-d ₆) δppm 1.5-1.7 (1H, m), 2.1-2.2 (1H, m), 2.7-2.9 (1H, m), 3.0-3.2 (2H, m), 3.5-3.6 (1H, m), 3.86 (3H, s), 4.6-4.7 (1H, m), 6.46 (2H, s), 6.5-6.7 (1H, m), 6.85 (1H, d, J = 9.1 Hz), 6.90 (1H, d, J = 8.7 Hz), 7.21 (1H, dd, J = 9.1 Hz, J = 9.1 Hz), 7.56 (1H, d, J = 8.7 Hz), 8.03 (1H, s)	富马酸盐

[1085]

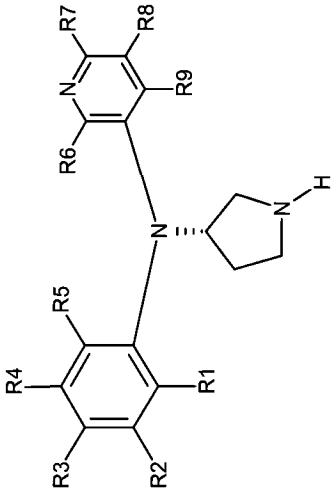
表 72



实施例	R1	R2	R3	R4	R5	R6	R7	R8	R9	NMR	盐
255	-H	-F	-F	-H	-H	-H	-H	-H	-H	¹ H-NMR (DMSO-d ₆) δppm 1.6-1.8 (1H, m), 2.2-2.3 (1H, m), 2.9-3.0 (1H, m), 3.0-3.2 (2H, m), 3.6-3.8 (1H, m), 4.8-4.9 (1H, m), 7.23 (1H, d, J = 8.7 Hz), 7.5-7.8 (4H, m), 8.21 (1H, s), 8.36 (1H, d, J = 5.1 Hz), 9.49 (1H, brs), 9.55 (1H, brs)	2 盐酸盐
256	-H	-Cl	-Cl	-H	-H	-H	-H	-H	-H	¹ H-NMR (DMSO-d ₆) δppm 1.6-1.8 (1H, m), 2.2-2.3 (1H, m), 2.9-3.0 (1H, m), 3.1-3.2 (2H, m), 3.6-3.8 (1H, m), 4.8-4.9 (1H, m), 7.26 (1H, d, J = 8.6 Hz), 7.6-7.8 (4H, m), 8.32 (1H, s), 8.34 (1H, d, J = 4.6 Hz), 9.38 (1H, brs), 9.50 (1H, brs)	2 盐酸盐
257	-H	-CF ₃	-F	-H	-H	-H	-H	-H	-H	¹ H-NMR (DMSO-d ₆) δppm 1.52-1.72 (1H, m), 2.19-2.35 (1H, m), 2.84-3.01 (1H, m), 3.05-3.21 (2H, m), 3.59-3.73 (1H, m), 4.81-4.94 (1H, m), 7.61 (1H, dd, J = 2.0 Hz, 8.5 Hz), 7.71-7.76 (3H, m), 7.82 (1H, d, J = 7.0 Hz), 8.26-8.29 (2H, m), 9.40 (1H, br), 9.50 (1H, br)	2 盐酸盐
258	-H	-Cl	-H	-H	-H	-H	-H	-H	-H	¹ H-NMR (DMSO-d ₆) δppm 1.6-1.8 (1H, m), 2.2-2.3 (1H, m), 2.8-2.9 (1H, m), 3.0-3.2 (2H, m), 3.5-3.7 (1H, m), 4.8-5.0 (1H, m), 7.29 (1H, d, J = 7.8 Hz), 7.47 (1H, s), 7.5-7.7 (3H, m), 7.76 (1H, d, J = 8.9 Hz), 8.21 (1H, s), 8.29 (1H, d, J = 5.3 Hz), 9.5-9.8 (2H, br)	2 盐酸盐
259	-H	-Cl	-F	-H	-H	-H	-H	-Br	-H	¹ H-NMR (DMSO-d ₆) δppm 1.5-1.7 (1H, m), 2.1-2.3 (1H, m), 2.8-3.0 (1H, m), 3.0-3.2 (2H, m), 3.5-3.7 (1H, m), 4.7-4.9 (1H, m), 7.2-7.4 (1H, m), 7.50 (1H, s), 7.56 (1H, dd, J = 9.0 Hz, J = 9.0 Hz), 7.6-7.7 (1H, m), 7.97 (1H, s), 8.23 (1H, s), 9.41 (1H, brs), 9.51 (1H, brs)	2 盐酸盐

[1086]

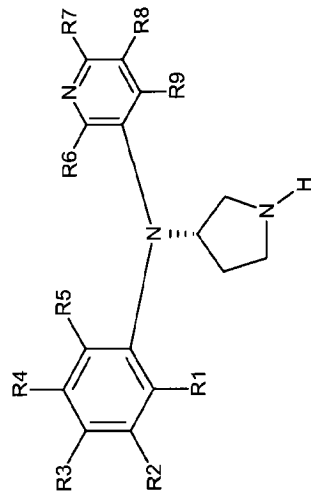
表 73



实施例	R1	R2	R3	R4	R5	R6	R7	R8	R9	NMR	盐
260	-H	-Cl	-F	-H	-H	-H	-H	-COC ₆ H ₅	-H	H-NMR (DMSO-d ₆) δppm 1.6-1.8 (1H, m), 2.2-2.4 (1H, m), 2.9-3.0 (1H, m), 3.1-3.2 (2H, m), 3.5-3.7 (1H, m), 4.8-5.0 (1H, m), 7.3-7.4 (1H, m), 7.5-7.9 (8H, m), 8.37 (1H, s), 8.39 (1H, s), 9.4-9.7 (2H, br)	2 盐酸盐
261	-H	-Cl	-F	-H	-H	-H	-H	-C ₆ H ₅	-H	H-NMR (DMSO-d ₆) δppm 1.6-1.8 (1H, m), 2.2-2.4 (1H, m), 2.9-3.0 (1H, m), 3.1-3.2 (2H, m), 3.6-3.8 (1H, m), 4.9-5.1 (1H, m), 7.4-7.5 (1H, m), 7.5-7.6 (3H, m), 7.62 (1H, dd, J = 8.9 Hz, J = 8.9 Hz), 7.7-7.8 (1H, m), 7.79 (2H, d, J = 8.3 Hz), 7.87 (1H, s), 8.00 (1H, s), 8.57 (1H, s), 9.46 (1H, brs), 9.58 (1H, brs)	2 盐酸盐
262	-H	-Cl	-F	-H	-H	-H	-H	-SCH ₃	-H	H-NMR (DMSO-d ₆) δppm 1.5-1.7 (1H, m), 2.1-2.3 (1H, m), 2.55 (3H, s), 2.8-3.0 (1H, m), 3.0-3.2 (2H, m), 3.5-3.7 (1H, m), 4.7-4.9 (1H, m), 4.7-4.9 (1H, m), 7.2-7.3 (1H, m), 7.33 (1H, s), 7.5-7.6 (2H, m), 7.81 (1H, s), 8.10 (1H, s), 9.22 (1H, brs), 9.36 (1H, brs)	2 盐酸盐
263	-H	-Cl	-F	-H	-H	-H	-H	-SC ₆ H ₅	-H	H-NMR (DMSO-d ₆) δppm 1.5-1.7 (1H, m), 2.1-2.3 (1H, m), 2.8-2.9 (1H, m), 3.0-3.2 (2H, m), 3.5-3.7 (1H, m), 4.7-4.9 (1H, m), 6.77 (1H, s), 7.2-7.3 (1H, m), 7.40 (5H, s), 7.4-7.6 (2H, m), 8.01 (1H, s), 8.08 (1H, s), 9.38 (1H, brs), 9.46 (1H, brs)	2 盐酸盐
264	-H	-Cl	-F	-H	-H	-H	-Cl	-Cl	-H	H-NMR (DMSO-d ₆) δppm 1.5-1.7 (1H, m), 2.1-2.3 (1H, m), 2.8-2.9 (1H, m), 3.0-3.2 (2H, m), 3.5-3.7 (1H, m), 4.7-4.9 (1H, m), 7.2-7.4 (1H, m), 7.44 (1H, s), 7.54 (1H, dd, J = 9.0 Hz, J = 9.0 Hz), 7.6-7.7 (1H, m), 7.75 (1H, s), 9.36 (2H, brs)	2 盐酸盐

[1087]

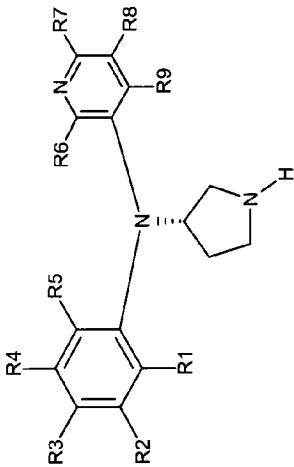
表 74



实施例	R1	R2	R3	R4	R5	R6	R7	R8	R9	NMR	盐
265	-H	-Cl	-F	-H	-H	-H	-H	-C ₂ H ₅	-H	¹ H-NMR (DMSO-d ₆) δppm 1.16 (3H, t, J = 7.0 Hz), 1.5-1.7 (1H, m), 2.2-2.3 (1H, m), 2.69 (2H, q, J = 7.0 Hz), 2.8-2.9 (1H, m), 3.0-3.2 (2H, m), 3.5-3.7 (1H, m), 4.8-5.0 (1H, m), 7.2-7.3 (1H, m), 7.59 (1H, s), 7.6-7.7 (2H, m), 7.95 (1H, s), 8.19 (1H, s), 9.42 (1H, brs), 9.55 (1H, brs)	2 盐酸盐
266	-H	-Cl	-F	-H	-H	-H	-H	-Cl	-H	¹ H-NMR (DMSO-d ₆) δppm 1.5-1.7 (1H, m), 2.1-2.3 (1H, m), 2.8-2.9 (1H, m), 3.0-3.2 (2H, m), 3.5-3.7 (1H, m), 4.7-4.9 (1H, m), 7.2-7.3 (1H, m), 7.33 (1H, s), 7.55 (1H, dd, J = 9.0 Hz, J = 9.0 Hz), 7.6-7.7 (1H, m), 7.92 (1H, s), 8.13 (1H, s), 9.44 (1H, brs), 9.53 (1H, brs)	2 盐酸盐
267	-H	-Cl	-F	-H	-H	-H	-H	-CN	-H	¹ H-NMR (DMSO-d ₆) δppm 1.5-1.7 (1H, m), 2.1-2.3 (1H, m), 2.44 (6H, s), 2.8-3.0 (1H, m), 3.1-3.2 (2H, m), 3.6-3.8 (1H, m), 4.7-4.9 (1H, m), 7.2-7.3 (1H, m), 7.5-7.7 (2H, m), 7.67 (1H, s), 8.17 (1H, s), 8.45 (1H, s), 8.79 (1H, brs), 8.84 (1H, brs)	2 甲磺酸盐
268	-H	-Cl	-F	-H	-H	-H	-CN	-H	-H	¹ H-NMR (DMSO-d ₆) δppm 1.60-1.78 (1H, m), 2.18-2.32 (1H, m), 2.83-2.99 (1H, m), 3.05-3.19 (2H, m), 3.55-3.70 (1H, m), 4.75-4.87 (1H, m), 7.05 (1H, dd, J=3.0, 8.9Hz), 7.32-7.43 (1H, m), 7.64 (1H, t, J=9.0Hz), 7.74 (1H, dd, J=2.5, 6.7Hz), 7.78 (1H, d, J=8.9Hz), 8.03 (1H, d, J=2.9Hz), 9.25 (1H, brs), 9.38 (1H, brs)	2 盐酸盐
269	-H	-Cl	-F	-H	-H	-H	-CN	-H	-H	¹ H-NMR (CDCl ₃) δppm 1.67-1.81 (1H, m), 2.10-2.25 (1H, m), 2.83-2.89 (1H, m), 2.90-3.00 (2H, m), 3.27-3.34 (1H, m), 4.35-4.52 (1H, m), 6.86 (1H, dd, J=3.0, 5.4Hz), 7.05-7.10 (1H, m), 7.23-7.28 (1H, m), 7.30 (1H, d, J=8.8Hz), 7.44 (1H, d, J=8.8Hz), 8.00 (1H, d, J=3.0Hz)	2 盐酸盐

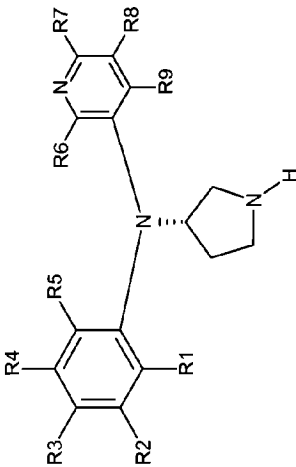
[1088]

表 75



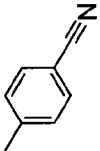
实施例	R1	R2	R3	R4	R5	R6	R7	R8	R9	NMR	盐
270	-H	-Cl	-Cl	-H	-H	-H	-CN	-H	-H	¹ H-NMR (CDCl ₃) δppm 1.70-1.82 (1H, m), 2.11-2.25 (1H, m), 2.83-2.90 (1H, m), 2.94-3.00 (2H, m), 3.26-3.33 (1H, m), 4.35-4.50 (1H, m), 6.90 (1H, dd, J=3.0, 8.8Hz), 7.04 (1H, dd, J=2.4, 8.5Hz), 7.28 (1H, d, J=2.8Hz), 7.45 (1H, d, J=8.8Hz), 7.59 (1H, d, J=8.5Hz), 8.03 (1H, d, J=2.8Hz).	2 甲磺酸盐
271	-H	-H	-Cl	-F	-H	-H	-H	-H	-H	¹ H-NMR (DMSO-d ₆) δppm 1.6-1.8 (1H, m), 2.2-2.3 (1H, m), 2.36 (6H, s), 2.9-3.0 (1H, m), 3.1-3.3 (2H, m), 3.6-3.8 (1H, m), 4.8-4.9 (1H, m), 7.09 (1H, d, J = 8.5 Hz), 7.4-7.5 (1H, m), 7.7-7.9 (3H, m), 8.30 (1H, s), 8.36 (1H, d, J = 6.1Hz), 8.76 (1H, brs), 8.84 (1H, brs)	

表 76



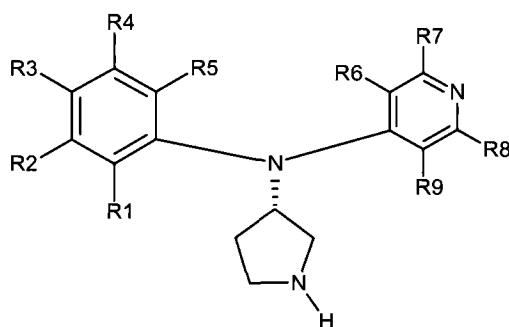
实施例	R1	R2	R3	R4	R5	R6	R7	R8	R9	NMR
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[1089]

272	-H	-Cl	-F	-H	-H	-H	-H	-H	-H		-H	$^1\text{H-NMR (CDCl}_3\text{) } \delta\text{ppm}$
												1.67-1.81 (1H, m), 2.08-2.19 (1H, m), 2.87-3.00 (3H, m), 3.24-3.31 (1H, m), 4.40-4.48 (1H, m), 6.95-7.05 (1H, m), 7.16-7.24 (3H, m), 7.61 (2H, d, $J=8.3\text{Hz}$), 7.74 (2H, d, $J=8.3\text{Hz}$), 8.12 (1H, d, $J=2.6\text{Hz}$), 8.43 (1H, d, $J=1.5\text{Hz}$).

[1090] 表 77

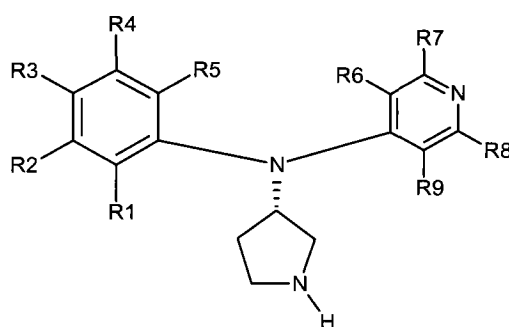
[1091]



实施例	R1	R2	R3	R4	R5	R6	R7	R8	R9	熔点 (°C)	盐
[1092]	273	-H	-Cl	-Cl	-H	-H	-H	-H	-H	229-231	2 盐酸盐

[1093] 表 78

[1094]

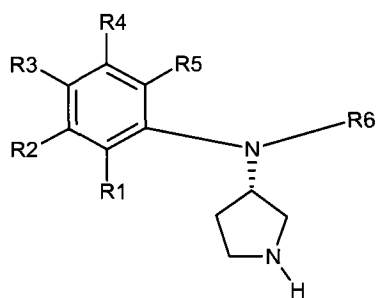


[1095]

实施例	R1	R2	R3	R4	R5	R6	R7	R8	R9	NMR	盐
274	-H	-H	-H	-H	-H	-H	-H	-H	-H	1H-NMR (DMSO-d6) δppm 1.52-1.71 (1H, m), 2.21-2.39 (1H, m), 2.40-2.99 (1H, m), 3.00-3.25 (2H, m), 3.61-3.78 (1H, m), 4.98-5.12 (1H, m), 6.55-7.10 (2H, m), 7.35-7.45 (2H, m), 7.53-7.71 (3H, m), 8.22-8.38 (2H, m), 9.80 (2H, brs), 14.45 (1H, brs)	盐酸盐
275	-H	-Cl	-F	-H	-H	-H	-H	-H	-H	1H-NMR (DMSO-d6) δppm 1.56-1.76 (1H, m), 2.20-2.38 (1H, m), 2.89-3.02 (1H, m), 3.03-3.20 (2H, m), 3.60-3.75 (1H, m), 4.94-5.11 (1H, m), 6.70-7.15 (2H, m), 7.41-7.53 (1H, m), 7.66-7.76 (1H, m), 7.85 (1H, dd, J=2.5Hz and 6.9Hz), 8.33 (2H, d, J=7.0Hz), 9.44-9.80 (2H, m)	2 盐酸盐
276	-H	-Cl	-F	-H	-H	-H	-CH ₃	-H	-H	H-NMR (DMSO-d6) δppm 1.6-1.8 (1H, m), 2.2-2.4 (1H, m), 2.50 (3H, s), 2.8-3.0 (1H, m), 3.1-3.2 (2H, m), 3.6-3.8 (1H, m), 4.9-5.1 (1H, m), 6.4-7.0 (2H, m), 7.4-7.5 (1H, m), 7.69 (1H, dd, J = 9.0 Hz, J = 9.0 Hz), 7.8-7.9 (1H, m), 8.20 (1H, d, J = 5.5 Hz), 9.54 (1H, brs), 9.70 (1H, brs)	2 盐酸盐

[1096] 表 79

[1097]

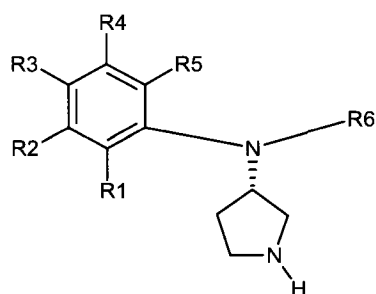


[1098]

实施例	R1	R2	R3	R4	R5	R6	熔点 (°C)	盐
277	-H	-H	-H	-H	-H		124.7-126.7	富马酸盐
278	-H	-Cl	-F	-H	-H		135.0-136.0	富马酸盐
279	-H	-F	-H	-H	-H		139.0-141.0	富马酸盐

[1099] 表 80

[1100]

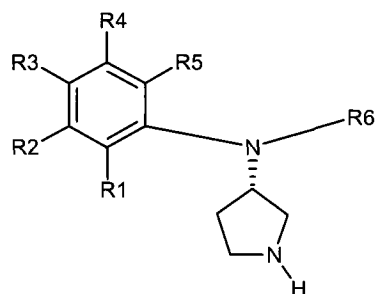


[1101]

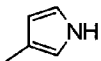
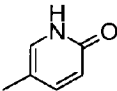
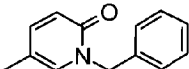
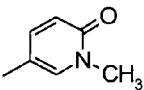
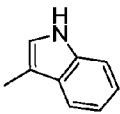
实施例	R1	R2	R3	R4	R5	R6	NMR	盐
280	-H	-H	-F	-H	-H		¹ H-NMR (DMSO-d ₆) δppm 0.99-1.50 (2H, m), 1.51-2.20 (4H, m), 2.80-3.65 (7H, m), 3.60-3.99 (2H, m), 4.10-4.81 (1H, m), 7.01-7.99 (4H, m), 9.15-9.90 (2H, m)	盐酸盐

[1102] 表 81

[1103]

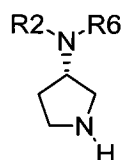


[1104]

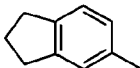
实施例	R1	R2	R3	R4	R5	R6	NMR	盐
281	-H	-Cl	-F	-H	-H		¹ H-NMR (DMSO-d ₆) δppm 1.68-1.83 (1H, m), 2.05-2.22 (1H, m), 2.75-3.20 (3H, m), 3.41-3.59 (1H, m), 4.51-4.72 (1H, m), 5.80-5.90 (1H, m), 6.57-6.65 (1H, m), 6.69-6.79 (2H, m), 6.80-6.88 (1H, m), 7.09-7.19 (1H, m), 9.10-9.50 (2H, m), 11.05 (1H, brs)	2 盐酸盐
282	-H	-Cl	-F	-H	-H		¹ H-NMR (DMSO-d ₆) δppm 1.6-1.8 (1H, m), 2.1-2.2 (1H, m), 2.8-3.0 (1H, m), 3.1-3.3 (2H, m), 3.4-3.6 (1H, m), 4.6-4.7 (1H, m), 6.56 (1H, d, J = 9.6 Hz), 6.7-6.8 (1H, m), 6.94 (1H, d, J = 9.2 Hz), 7.25 (1H, dd, J = 9.2 Hz, J = 9.0 Hz), 7.43 (1H, d, J = 9.6 Hz), 7.58 (1H, s), 8.90 (2H, brs)	2 氢溴酸盐
283	-H	-Cl	-F	-H	-H		¹ H-NMR (DMSO-d ₆) δppm 1.6-1.8 (1H, m), 2.1-2.2 (1H, m), 2.8-3.0 (1H, m), 3.0-3.2 (2H, m), 3.4-3.6 (1H, m), 4.5-4.7 (1H, m), 5.04 (1H, d, J = 14.5 Hz), 5.12 (1H, d, J = 14.5 Hz), 6.48 (2H, s), 6.49 (1H, d, J = 9.5 Hz), 6.6-6.7 (1H, m), 6.8-6.9 (1H, m), 7.1-7.5 (7H, m), 7.94 (1H, s)	富马酸盐
284	-H	-Cl	-F	-H	-H		¹ H-NMR (DMSO-d ₆) δppm 1.6-1.8 (1H, m), 2.1-2.2 (1H, m), 2.8-3.0 (1H, m), 3.0-3.2 (2H, m), 3.42 (3H, s), 3.4-3.6 (1H, m), 4.5-4.7 (1H, m), 6.46 (1H, d, J = 9.5 Hz), 6.6-6.7 (1H, m), 6.8-6.9 (1H, m), 7.22 (1H, dd, J = 9.1 Hz, J = 9.1 Hz), 7.30 (1H, d, J = 9.5 Hz), 7.87 (1H, s), 9.42 (1H, brs), 9.49 (1H, brs)	2 盐酸盐
285	-H	-Cl	-F	-H	-H		¹ H-NMR (CDCl ₃) δppm : 1.65-2.0 (2H, m), 2.05-2.25 (1H, m), 2.7-3.05 (3H, m), 3.1-3.3 (1H, m), 4.4-4.55 (1H, m), 6.4-6.55 (1H, m), 6.65-6.75 (1H, m), 6.86 (1H, dd, J = 9, 9Hz), 7.0-7.1 (2H, m), 7.1-7.45 (4H, m), 8.51 (1H, br).	

[1105] 表 82

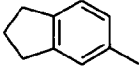
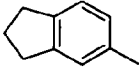
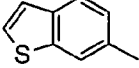
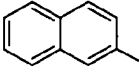
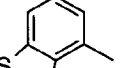
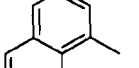
[1106]



[1107]

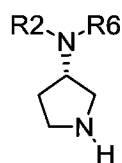
实施例	R2	R6	NMR	盐
286			¹ H-NMR (DMSO-d ₆) δppm 1.56-1.76 (1H, m), 2.01-2.17 (2H, m), 2.21-2.35 (1H, m), 2.76-3.01 (5H, m), 3.05-3.25 (2H, m), 3.59-3.74 (1H, m), 4.79-4.91 (1H, m), 7.07 (1H, dd, J = 1.5Hz, 7.5Hz), 7.20 (1H, s), 7.42-7.53 (2H, m), 7.70-7.76 (1H, m), 8.06 (1H, d, J = 3.0Hz), 8.19 (1H, d, J = 5.0Hz), 9.46 (1H, br), 9.52 (1H, br).	2 盐酸盐

[1108]

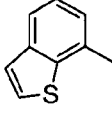
287			1H-NMR (DMSO-d6) δ ppm 1.62-1.81 (1H, m), 1.99-2.15 (2H, m), 2.20-2.37 (1H, m), 2.84-3.21 (7H, m), 3.57-3.73 (1H, m), 5.10-5.26 (1H, m), 6.38 (1H, d, J=8.5Hz), 6.90 (1H, dd, J=6.5Hz, 6.5Hz), 7.11 (1H, dd, J=1.5Hz, 8.0Hz), 7.24 (1H, s), 7.44 (1H, d, J=8.0Hz), 7.68 (1H, dd, J=7.5Hz, 7.5Hz), 8.12 (1H, dd, J=1.5Hz, 5.5Hz), 9.42 (1H, br), 9.51 (1H, br).	2 盐酸盐
288			1H-NMR (DMSO-d6) δ ppm 1.64-1.85 (1H, m), 1.99-2.25 (3H, m), 2.85-3.28 (7H, m), 3.47-3.63 (1H, m), 5.02-5.15 (1H, m), 7.09 (1H, dd, J=2.0Hz, 8.0Hz), 7.22 (1H, s), 7.38-7.43 (2H, m), 7.88 (1H, d, J=2.5Hz), 8.19-8.21 (1H, m), 9.26 (1H, br), 9.54 (1H, br).	2 盐酸盐
289			1H-NMR (DMSO-d6) δ ppm 1.66-1.71 (1H, m), 2.15-2.25 (1H, m), 2.82-2.91 (1H, m), 3.01-3.14 (2H, m), 3.54-3.62 (1H, m), 4.70-4.85 (1H, m), 6.47 (2H, s), 7.09 (1H, dd, J=1.9Hz and 8.5Hz), 7.12-7.16 (1H, m), 7.20-7.26 (1H, m), 7.45 (1H, d, J=5.4Hz), 7.77 (1H, d, J=5.4Hz), 7.85-7.88 (1H, m), 7.91 (1H, d, J=8.5Hz), 8.04-8.09 (2H, m)	富马酸盐
290			1H-NMR (DMSO-d6) δ ppm : 1.55-1.8 (1H, m), 2.1-2.35 (1H, m), 2.75-4.5 (7H, m), 4.65-4.9 (1H, m), 6.46 (2H, s), 7.09 (1H, dd, J=2.5, 9Hz), 7.2-7.35 (2H, m), 7.35-7.55 (2H, m), 7.60 (1H, d, J=2Hz), 7.75-7.95 (3H, m), 8.1-8.25 (2H, m).	富马酸盐
291			1H-NMR (DMSO-d6) δ ppm : 1.45-1.7 (1H, m), 2.1-2.3 (1H, m), 2.6-4.3 (7H, m), 4.75-4.95 (1H, m), 6.48 (2H, s), 6.85-6.95 (1H, m), 7.1-7.25 (2H, m), 7.25-7.4 (1H, m), 7.51 (1H, dd, J=7.5, 7.5Hz), 7.78 (1H, d, J=5.5Hz), 7.85-8.0 (2H, m), 8.10 (1H, d, J=8Hz).	富马酸盐
292			1H-NMR (DMSO-d6) δ ppm : 1.4-1.7 (1H, m), 2.0-2.3 (1H, m), 2.6-4.65 (7H, m), 4.85-5.0 (1H, m), 6.49 (2H, s), 6.8-6.9 (1H, m), 7.12 (1H, dd, J=4.5, 8.5), 7.45-7.7 (4H, m), 7.77 (1H, d, J=8Hz), 7.84 (1H, d, J=3Hz), 7.91 (1H, dd, J=1, 4.5Hz), 7.99-8.1 (2H, m).	富马酸盐

[1109] 表 83

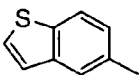
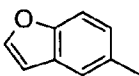
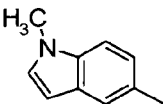
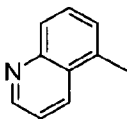
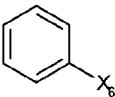
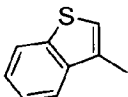
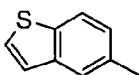
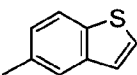
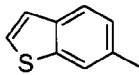
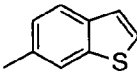
[1110]



[1111]

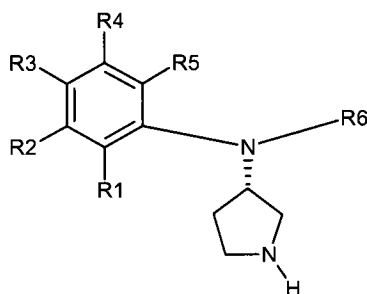
实施例 R2	R6	NMR	盐
293			富马酸盐
		1H-NMR (DMSO-d6) δ ppm : 1.55-1.75 (1H, m), 2.15-2.3 (1H, m), 2.55-4.55 (7H, m), 4.75-4.9 (1H, m), 6.48 (2H, s), 6.95-7.05 (1H, m), 7.1-7.25 (1H, m), 7.38 (1H, d, J=7.5Hz), 7.45-7.6 (2H, m), 7.75 (1H, d, J=5.5Hz), 7.85-8.05 (3H, m).	

[1112]

294			1H-NMR (DMSO-d6) δ ppm 1.59-1.69 (1H, m), 2.21-2.49 (1H, m), 2.82-3.24 (3H, m), 3.61-3.75 (1H, m), 4.84-5.02 (1H, m), 7.90 (1H, d, J=2.0Hz), 7.92 (1H, d, J=5.5Hz), 8.14 (1H, d, J=2.8Hz), 8.19 (1H, d, J=5.5Hz), 8.24 (1H, d, J=8.5Hz)	2 盐酸盐
295			1H-NMR (CDCl3) δ ppm : 1.7-1.9 (2H, m), 2.16 (1H, dt, J = 7.5, 7.5Hz), 2.85-3.0 (3H, m), 3.21 (1H, dd, J = 6.5, 11.5Hz), 4.45 (1H, tt, J = 6.5, 6.5Hz), 6.77 (1H, dd, J = 1, 2Hz), 6.8-6.9 (1H, m), 7.0-7.1 (2H, m), 7.38 (1H, d, J = 2Hz), 7.55 (1H, d, J = 8.5Hz), 7.68 (1H, d, J = 2Hz), 7.99 (1H, dd, J = 1.5, 4.5Hz), 8.04 (1H, d, J = 3Hz).	
296			1H-NMR (CDCl3) δ ppm : 1.75-1.95 (1H, m), 2.05-2.4 (2H, m), 2.88 (2H, t, J = 7.5Hz), 2.98 (1H, dd, J = 5.5, 11.5Hz), 3.17 (1H, dd, J = 6.5, 12Hz), 3.83 (3H, s), 4.35-4.5 (1H, m), 6.48 (1H, dd, J = 0.5, 3Hz), 6.75-6.85 (1H, m), 6.9-7.05 (2H, m), 7.11 (1H, d, J = 3Hz), 7.3-7.45 (2H, m), 7.92 (1H, dd, J = 1.5, 4.5Hz), 8.03 (1H, d, J = 3Hz).	
297			1H-NMR (DMSO-d6) δ ppm : 1.3-1.65 (1H, m), 2.0-2.25 (1H, m), 2.6-5.65 (8H, m), 6.46 (2H, s), 6.54 (2H, d, J = 8Hz), 6.71 (1H, dd, J = 7.5, 7.5Hz), 7.12 (2H, dd, J = 7.5, 8.5Hz), 7.52 (1H, dd, J = 4, 8.5Hz), 7.59 (1H, dd, J = 1, 7.5Hz), 7.87 (1H, dd, J = 7.5, 8.5Hz), 8.09 (1H, d, J = 8.5Hz), 8.15-8.25 (1H, m), 8.93 (1H, dd, J = 1.5, 4Hz).	富马酸盐
298			1H-NMR (DMSO-d6) δ ppm : 1.55-1.75 (1H, m), 2.15-2.35 (1H, m), 2.6-5.75 (8H, m), 6.50 (2H, s), 6.95-7.05 (1H, m), 7.1-7.2 (1H, m), 7.3-7.5 (3H, m), 7.9-8.0 (3H, m), 8.0-8.1 (1H, m).	富马酸盐
299			1H-NMR (DMSO-d6) δ ppm : 1.65-1.85 (1H, m), 2.15-2.35 (1H, m), 2.85-3.05 (1H, m), 3.05-3.3 (2H, m), 3.5-3.7 (1H, m), 4.7-4.9 (1H, m), 6.9-7.05 (2H, m), 7.38 (2H, d, J = 5.5Hz), 7.55 (2H, d, J = 1.5Hz), 7.76 (2H, d, J = 5.5Hz), 7.91 (2H, d, J = 8.5Hz), 9.28 (1H, br), 9.50 (1H, br).	盐酸盐
300			1H-NMR (DMSO-d6) δ ppm : 1.65-1.85 (1H, m), 2.15-2.35 (1H, m), 2.8-3.05 (1H, m), 3.05-3.25 (2H, m), 3.35-3.8 (1H, m), 4.75-4.9 (1H, m), 6.9-7.0 (2H, m), 7.39 (2H, d, J = 5.5Hz), 7.64 (2H, d, J = 5.5Hz), 7.70 (2H, s), 7.79 (2H, d, J = 8.5Hz), 9.24 (1H, br), 9.43 (1H, br).	盐酸盐

[1113] 表 84

[1114]

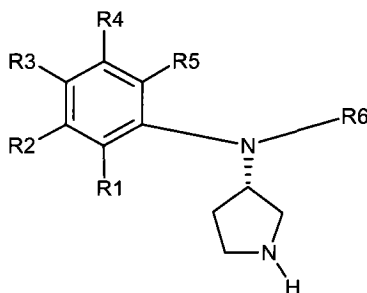


[1115]

实施例	R1	R2	R3	R4	R5	R6	熔点 (°C)	盐
301	-H	-Cl	-F	-H	-H	-环-C ₆ H ₁₁	194.9-196.1 (dec.)	盐酸盐
302	-H	-Cl	-F	-H	-H	-CH ₂ -环-C ₆ H ₁₁	158.5-161.0	盐酸盐

[1116] 表 85

[1117]

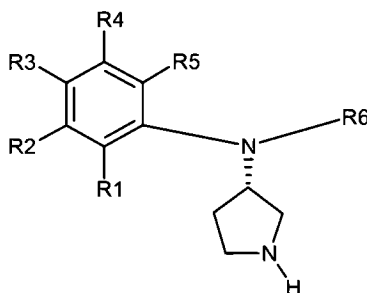


[1118]

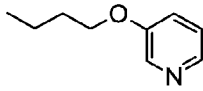
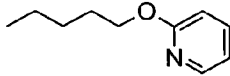
实施例	R1	R2	R3	R4	R5	R6	NMR	盐
303	-H	-Cl	-F	-H	-H	-cyclo-C ₆ H ₁₁	¹ H-NMR (DMSO-d ₆) δppm 0.80-1.09 (3H, m), 1.15-1.38 (2H, m), 1.42-1.58 (2H, m), 1.60-1.87 (5H, m), 1.88-2.05 (1H, m), 2.81-3.12 (3H, m), 3.12-3.29 (1H, m), 4.09-4.25 (1H, m), 7.00-7.10 (1H, m), 7.20 (1H, dd, J=2.6Hz and 6.7Hz), 7.24-7.34 (1H, m),	富马酸盐
304	-H	-H	-F	-H	-H	-环-C ₆ H ₁₁	¹ H-NMR (DMSO-d ₆) δppm 0.59-1.55 (8H, m), 1.58-2.43 (5H, m), 2.81-4.11 (4H, m), 4.40-5.22 (1H, m), 7.00-8.20 (4H, m), 9.25-10.45 (2H, m)	盐酸盐
305	-H	-Cl	-F	-H	-H	-(CH ₂) ₃ SCH ₃	¹ H-NMR (DMSO-d ₆) δppm 1.52-1.70 (2H, m), 1.80-2.18 (5H, m with s at δ2.07), 2.40-2.51 (2H, m), 2.84-3.49 (6H, m), 4.29-4.49 (1H, m), 6.85-6.95 (1H, m), 7.05-7.35 (2H, m), 9.30-9.79 (2H, m)	盐酸盐
306	-H	-Cl	-F	-H	-H	-环-C ₅ H ₉	¹ H-NMR (DMSO-d ₆) δppm 1.15-1.88 (9H, m), 1.95-2.18 (1H, m), 2.71-3.49 (4H, m), 3.60-3.85 (1H, m), 4.35-4.55 (1H, m), 7.05-7.55 (3H, m), 9.01-9.45 (2H, m)	盐酸盐
307	-H	-Cl	-F	-H	-H	-(CH ₂) ₃ NHCH ₃	¹ H-NMR (DMSO-d ₆) δppm 1.5-3.5 (14H, m), 3.7-3.9 (1H, m), 4.1-4.6 (2H, m), 5-5.75 (1H, brs), 6.8-7.1 (1H, m), 7.1-7.3 (2H, m), 8.7-9.7 (2H, m)	3 盐酸盐
308	-H	-Cl	-F	-H	-H	-(CH ₂) ₃ N(CH ₃) ₂	¹ H-NMR (DMSO-d ₆) δppm 1.7-2.3 (3H, m), 2.70 (3H, s), 2.72 (3H, s), 2.9-3.4 (8H, m), 4.38 (1H, m), 6.8-7.0 (1H, m), 7.1-7.2 (1H, m), 7.28 (1H, t, J=9.1Hz), 9.2-9.4 (1H, brs), 9.6-9.8 (1H, brs), 10.3-10.6 (1H, brs)	3 盐酸盐

[1119] 表 86

[1120]

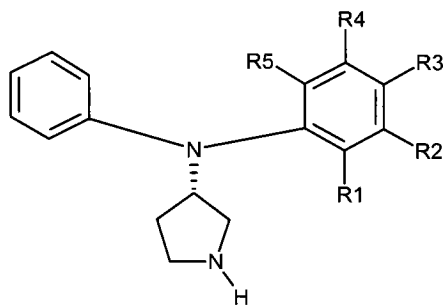


[1121]

实施例	R1	R2	R3	R4	R5	R6	NMR	盐
309	-H	-Cl	-F	-H	-H	$-(CH_2)_2OC_6H_5$	¹ H-NMR (DMSO-d ₆) δppm : 1.85-2.1 (1H, m), 2.1-2.3 (1H, m), 2.95-3.25 (2H, m), 3.25-3.55 (2H, m), 3.67 (2H, t, J = 5.5Hz), 3.85-4.1 (3H, m), 4.4-4.6 (2H, m), 6.8-7.0 (4H, m), 7.1-7.2 (1H, m), 7.2-7.35 (3H, m), 9.43 (1H, br), 9.60 (1H, br).	2 盐酸盐
310	-H	-Cl	-F	-H	-H		¹ H-NMR (DMSO-d ₆) δppm : 1.8-1.95 (3H, m), 2.05-2.15 (1H, m), 2.6-3.95 (11H, m), 4.07 (2H, t, J = 6Hz), 4.35-4.45 (1H, m), 6.57 (4H, s), 6.9-6.95 (1H, m), 7.12 (1H, dd, J = 3, 6.5Hz), 7.26 (1H, dd, J = 9, 9Hz), 7.32 (1H, dd, J = 4.5, 8.5Hz), 7.38 (1H, dd, J = 1.5, 8.5Hz), 8.17 (1H, dd, J = 3.5, 3.5Hz), 8.31 (1H, d, J = 3Hz).	2 富马酸盐
311	-H	-Cl	-F	-H	-H		¹ H-NMR (DMSO-d ₆) δppm : 1.45-1.55 (2H, m), 1.65-1.8 (2H, m), 1.8-1.95 (1H, m), 2.05-2.15 (1H, m), 2.6-4.05 (11H, m), 4.25 (2H, t, J = 6.5Hz), 4.3-4.4 (1H, m), 6.55 (4H, s), 6.77 (1H, d, J = 8.5Hz), 6.8-6.9 (1H, m), 6.9-7.0 (1H, m), 7.03 (1H, dd, J = 3, 6.5Hz), 7.22 (1H, dd, J = 9, 9Hz), 7.65-7.7 (1H, m), 8.1-8.15 (1H, m).	2 富马酸盐

[1122] 表 87

[1123]



[1124]

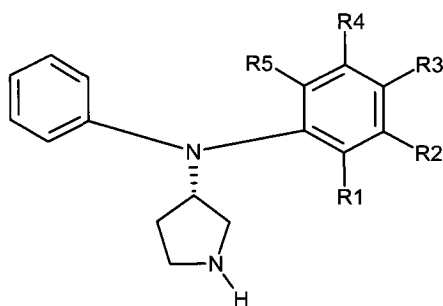
实施例	R1	R2	R3	R4	R5	MS (M+1)
312	-H	-H	$-OC_2H_5$	-H	-H	283
313	$-CH_3$	-H	-H	-H	-H	253
314	-H	-H	$-CF_3$	-H	-H	307
315	-H	-H	-CN	-H	-H	264
316	-H	$-NO_2$	-H	-H	-H	284
317	-H	-H	$-NO_2$	-H	-H	284

[1125]

318	-H	-H	-N(CH ₃) ₂	-H	-H	282
319	-H	-CH ₃	-H	-H	-H	253
320	-OCH ₃	-H	-H	-H	-H	269
321	-H	-OCH ₃	-H	-H	-H	269
322	-H	-OC ₂ H ₅	-H	-H	-H	283
323	-H	-OCF ₃	-H	-H	-H	323
324	-H	-SCH ₃	-H	-H	-H	285
325	-H	-N(CH ₃) ₂	-H	-H	-H	282
326	-CN	-H	-H	-H	-H	264
327	-H	-H	-SCH ₃	-H	-H	285
328	-H	-CF ₃	-H	-H	-H	307
329	-CH ₃	-H	-F	-H	-H	271
330	-H	-CF ₃	-Cl	-H	-H	341
331	-H	-H	-CH ₃	-H	-H	253
332	-H	-Cl	-H	-Cl	-H	307
333	-H	-H	-COC ₆ H ₅	-H	-H	343
334	-H	-H	-CH(CH ₃) ₂	-H	-H	281
335	-H	-H	-OC ₆ H ₅	-H	-H	331
336	-H	-H	-OC ₆ H ₁₃	-H	-H	339
337	-H	-H	-C ₂ H ₅	-H	-H	267
338	-H	-H	-OCH ₂ C ₆ H ₅	-H	-H	345
339	-H	-CF ₃	-F	-H	-H	325
340	-H	-CF ₃	-H	-CF ₃	-H	375
341	-H	-H	-OCH ₃	-H	-H	269
342	-CH ₃	-CH ₃	-H	-H	-H	267
343	-C ₂ H ₅	-H	-H	-H	-H	267
344	-H	-F	-H	-H	-OCH ₃	287
345	-H	-H	-COCH ₃	-H	-H	281
346	-H	-COCH ₃	-H	-H	-H	281
347	-CH ₃	-H	-Cl	-H	-H	287
348	-H	-Cl	-Cl	-H	-H	307

[1126] 表 88

[1127]



[1128]

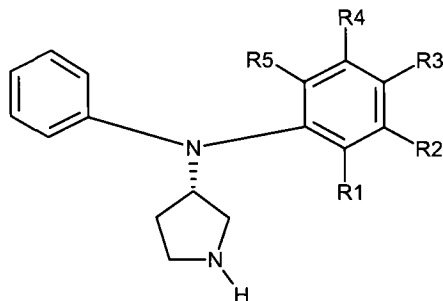
实施例	R1	R2	R3	R4	R5	MS (M+1)
349	-H	-F	-F	-H	-H	275
350	-H	-F	-H	-F	-H	275
351	-H	-H	-CF ₃	-F	-H	325
352	-H	-CF ₃	-H	-F	-H	325
353	-H	-CF ₃	-CH ₃	-H	-H	321
354	-H	-SCF ₃	-H	-H	-H	339
355	-H	-CF ₃	-OCH ₃	-H	-H	337

[1129]

356	-H	-CH ₃	-N(CH ₃) ₂	-CH ₃	-H	310
357	-H	-CH(CH ₃) ₂	-H	-H	-H	281
358	-H	-H	-SC ₂ H ₅	-H	-H	299
359	-H	-H	-N(C ₂ H ₅) ₂	-H	-H	310
360	-H	-OCH(CH ₃) ₂	-H	-H	-H	297
361	-H	-F	-H	-Cl	-H	291
362	-H	-CH ₃	-H	-CH ₃	-H	
363	-H	-F	-CH ₃	-H	-H	271
364	-H	-F	-Cl	-H	-H	291
365	-H	-C ₆ H ₅	-H	-H	-H	315
366	-H	-F	-H	-H	-H	257
367	-H	-Cl	-CH ₃	-H	-H	287
368	-H	-F	-F	-F	-H	293
369	-H	-F	-H	-H	-CH ₃	271
370	-F	-H	-H	-CH ₃	-H	271
371	-H	-F	-OCH ₃	-H	-H	287
372	-H	-CH ₃	-Cl	-H	-H	287
373	-H	-H	-C ₃ H ₇	-H	-H	281
374	-OCH ₃	-H	-H	-CH ₃	-H	283
375	-CH ₃	-Cl	-H	-H	-H	287
376	-H	-H	-CH ₂ C ₆ H ₅	-H	-H	329
377	-H	-Cl	-H	-H	-OCH ₃	303
378	-CH ₃	-F	-CH ₃	-H	-H	285
379	-H	-CH ₂ CH ₂ CN	-H	-H	-H	292
380	-H	-H	-CH ₂ CH ₂ CN	-H	-H	292
381	-H	-Cl	-H	-H	-CH ₃	287
382	-H	-OCHF ₂	-H	-H	-H	305
383	-H	-C ₂ H ₅	-H	-H	-H	267
384	-H	-F	-OCH ₃	-F	-H	305
385	-CH ₃	-H	-CH ₃	-H	-H	267

[1130] 表 89

[1131]



[1132]

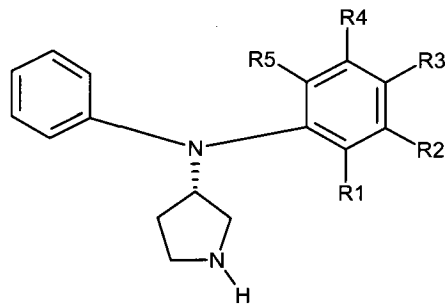
实施例	R1	R2	R3	R4	R5	MS (M+1)
386	-H	-F	-F	-OCH ₃	-H	305
387	-H	-Cl	-H	-H	-H	273
388	-CH ₃	-H	-H	-CH ₃	-H	267
389	-H	-CH ₃	-CH ₃	-H	-H	267
390	-H	-OCH ₃	-OCH ₃	-OCH ₃	-H	329
391	-H	-CN	-F	-H	-H	282
392	-CH(CH ₃) ₂	-H	-H	-CH ₃	-H	295
393	-H	-H	-COC ₂ H ₅	-H	-H	295
394	-H	-H	-CF ₃	-H	-F	325
395	-F	-H	-CF ₃	-F	-H	343
396	-H	-CO ₂ C ₂ H ₅	-Cl	-H	-H	345

[1133]

397	-CH ₂ C ₆ H ₅	-H	-H	-H	-H	329
398	-H	-CH ₃	-OCH ₃	-H	-H	283
399	-H	-H	-C ₆ H ₅	-H	-H	315
400	-H	-Cl	-CN	-H	-H	298
401	-H	-CH ₃	-F	-CH ₃	-H	285
402	-H	-H	-OCF ₂ CHF ₂	-H	-H	355
403	-H	-H	-OH	-H	-H	255

[1134] 表 90

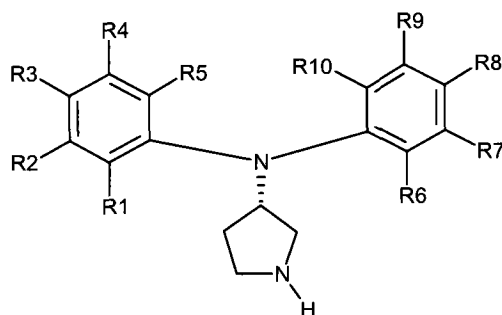
[1135]



实施例	R1	R2	R3	R4	R5	MS (M+1)
404	-H	-H		-H	-H	322
405	-H		-H	-H	-H	336
406	-H	-H		-H	-H	306
407	-H	-H		-H	-H	305
408	-H	-H		-H	-H	352
409	-H	-H		-H	-H	306
410	-H	-H		-H	-H	307
411	-H		-H	-H	-H	349

[1137] 表 91

[1138]

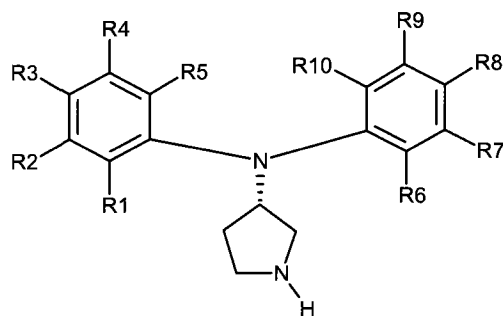


[1139]

实施例	R1	R2	R3	R4	R5	R6	R7	R8	R9	R10	MS (M+1)
412	-H	-Cl	-F	-H	-H	-H	-H	-OC ₂ H ₅	-H	-H	335
413	-H	-Cl	-F	-H	-H	-CH ₃	-H	-H	-H	-H	305
414	-H	-Cl	-F	-H	-H	-H	-H	-CF ₃	-H	-H	359
415	-H	-Cl	-F	-H	-H	-H	-H	-CN	-H	-H	316
416	-H	-Cl	-F	-H	-H	-H	-H	-N(CH ₃) ₂	-H	-H	334
417	-H	-Cl	-F	-H	-H	-H	-CH ₃	-H	-H	-H	305
418	-H	-Cl	-F	-H	-H	-H	-CO ₂ C ₂ H ₅	-H	-H	-H	363
419	-H	-Cl	-F	-H	-H	-OCH ₃	-H	-H	-H	-H	321
420	-H	-Cl	-F	-H	-H	-H	-OCH ₃	-H	-H	-H	321
421	-H	-Cl	-F	-H	-H	-H	-OC ₂ H ₅	-H	-H	-H	335
422	-H	-Cl	-F	-H	-H	-H	-OCF ₃	-H	-H	-H	375
423	-H	-Cl	-F	-H	-H	-H	-SCH ₃	-H	-H	-H	337
424	-H	-CH ₃	-F	-H	-H	-H	-H	-OC ₂ H ₅	-H	-H	315
425	-H	-CH ₃	-F	-H	-H	-CH ₃	-H	-H	-H	-H	285
426	-H	-CH ₃	-F	-H	-H	-H	-H	-CF ₃	-H	-H	339
427	-H	-CH ₃	-F	-H	-H	-H	-H	-CN	-H	-H	296
428	-H	-CH ₃	-F	-H	-H	-H	-NO ₂	-H	-H	-H	316
429	-H	-CH ₃	-F	-H	-H	-H	-H	-NO ₂	-H	-H	316
430	-H	-CH ₃	-F	-H	-H	-H	-H	-N(CH ₃) ₂	-H	-H	314
431	-H	-CH ₃	-F	-H	-H	-H	-CH ₃	-H	-H	-H	285
432	-H	-CH ₃	-F	-H	-H	-OCH ₃	-H	-H	-H	-H	301
433	-H	-CH ₃	-F	-H	-H	-H	-OCH ₃	-H	-H	-H	301
434	-H	-CH ₃	-F	-H	-H	-H	-OC ₂ H ₅	-H	-H	-H	315
435	-H	-CH ₃	-F	-H	-H	-H	-OCF ₃	-H	-H	-H	355
436	-H	-CH ₃	-F	-H	-H	-H	-SCH ₃	-H	-H	-H	317
437	-H	-H	-F	-H	-H	-H	-H	-OC ₂ H ₅	-H	-H	301
438	-CH ₃	-H	-H	-H	-H	-H	-H	-F	-H	-H	271
439	-H	-H	-CF ₃	-H	-H	-H	-H	-F	-H	-H	325
440	-H	-H	-F	-H	-H	-H	-H	-CN	-H	-H	282
441	-H	-NO ₂	-H	-H	-H	-H	-H	-F	-H	-H	302
442	-H	-H	-NO ₂	-H	-H	-H	-H	-F	-H	-H	302
443	-H	-H	-N(CH ₃) ₂	-H	-H	-H	-H	-F	-H	-H	300
444	-H	-CH ₃	-H	-H	-H	-H	-H	-F	-H	-H	271
445	-OCH ₃	-H	-H	-H	-H	-H	-H	-F	-H	-H	287
446	-H	-OCH ₃	-H	-H	-H	-H	-H	-F	-H	-H	287

[1140] 表 92

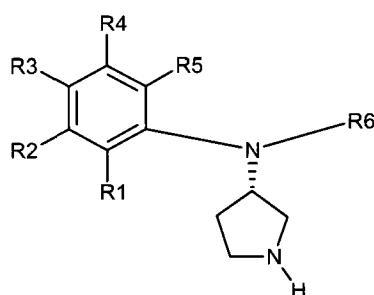
[1141]



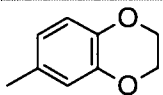
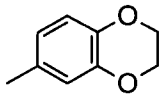
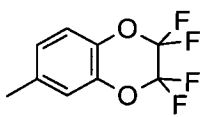
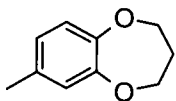
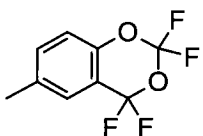
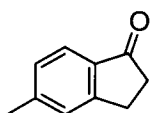
实施例	R1	R2	R3	R4	R5	R6	R7	R8	R9	R10	MS (M+1)
447	-H	-OC ₂ H ₅	-H	-H	-H	-H	-H	-F	-H	-H	301
448	-H	-OCF ₃	-H	-H	-H	-H	-H	-F	-H	-H	341
449	-H	-SCH ₃	-H	-H	-H	-H	-H	-F	-H	-H	303
450	-H	-N(CH ₃) ₂	-H	-H	-H	-H	-Cl	-F	-H	-H	334
[1142] 451	-H	-Cl	-F	-H	-H	-CN	-H	-H	-H	-H	316
452	-H	-Cl	-F	-H	-H	-H	-H	-SCH ₃	-H	-H	337
453	-H	-N(CH ₃) ₂	-H	-H	-H	-H	-CH ₃	-F	-H	-H	314
454	-H	-CH ₃	-F	-H	-H	-H	-H	-SCH ₃	-H	-H	317
455	-H	-N(CH ₃) ₂	-H	-H	-H	-H	-H	-F	-H	-H	300
456	-H	-H	-F	-H	-H	-H	-H	-SCH ₃	-H	-H	303

[1143] 表 93

[1144]

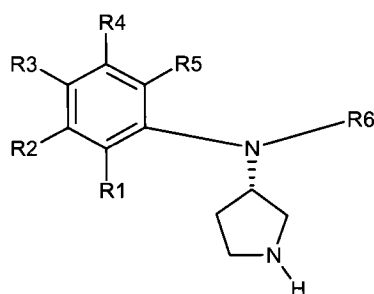


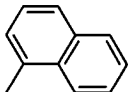
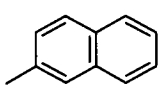
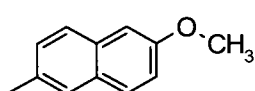
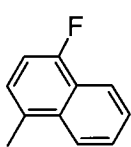
实施例	R1	R2	R3	R4	R5	R6	MS (M+1)
457	-H	-H	-H	-H	-H		283
458	-H	-H	-H	-H	-H		283
[1145] 459	-H	-H	-H	-H	-H		319
460	-H	-Cl	-F	-H	-H		349
461	-H	-H	-H	-H	-H		297

[1146]	462	-H	-CH ₃	-F	-H	-H		329
	463	-H	-H	-F	-H	-H		315
	464	-H	-H	-H	-H	-H		369
	465	-H	-H	-H	-H	-H		311
	466	-H	-H	-H	-H	-H		369
	467	-H	-H	-H	-H	-H		293

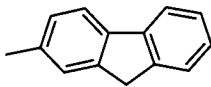
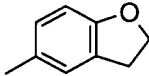
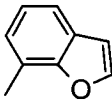
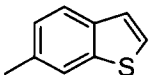
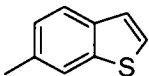
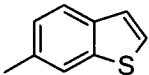
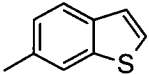
[1147] 表 94

[1148]



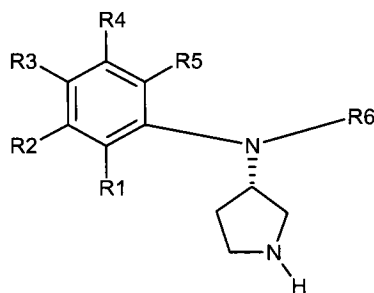
实施例	R1	R2	R3	R4	R5	R6	MS (M+1)
468	-H	-H	-H	-H	-H		289
469	-H	-H	-H	-H	-H		289
[1149]	470	-H	-H	-H	-H		319
	471	-H	-H	-H	-H		307

[1150]

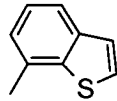
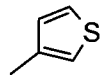
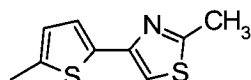
472	-H	-H	-H	-H	-H		327
473	-H	-H	-H	-H	-H		281
474	-H	-H	-H	-H	-H		279
475	-H	-Cl	-F	-H	-H		347
476	-H	-H	-H	-H	-H		295
477	-H	-CH ₃	-F	-H	-H		327
478	-H	-H	-F	-H	-H		313

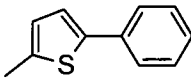
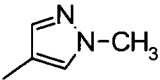
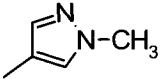
[1151] 表 95

[1152]



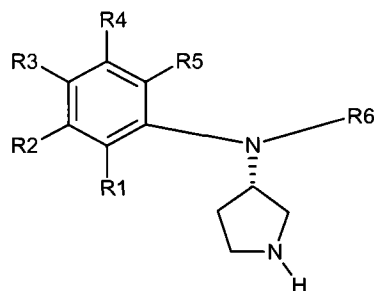
[1153]

实施例	R1	R2	R3	R4	R5	R6	MS (M+1)
479	-H	-H	-H	-H	-H		295
480	-H	-Cl	-F	-H	-H		297
481	-H	-Cl	-F	-H	-H		394

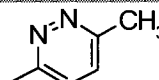
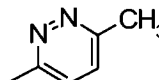
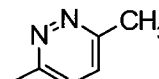
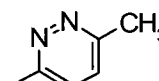
[1154]	482	-H	-H	-H	-H	-H		321
	483	-H	-H	-H	-H	-H		246
	484	-H	-Cl	-F	-H	-H		298
	485	-H	-CH ₃	-F	-H	-H		278
	486	-H	-H	-H	-H	-H		243
	487	-H	-H	-F	-H	-H		261

[1155] 表 96

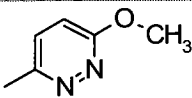
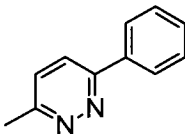
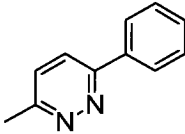
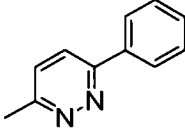
[1156]



[1157]

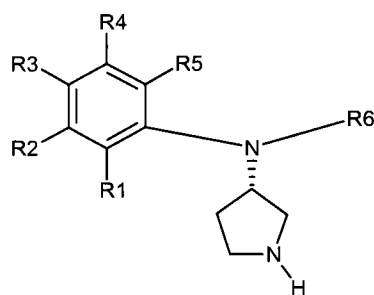
实施例	R1	R2	R3	R4	R5	R6	MS (M+1)
488	-H	-H	-H	-H	-H		255
489	-H	-Cl	-F	-H	-H		307
490	-H	-CH ₃	-F	-H	-H		287
491	-H	-H	-F	-H	-H		273

[1158]

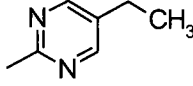
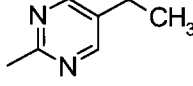
492	-H	-CH ₃	-F	-H	-H		303
493	-H	-H	-H	-H	-H		317
494	-H	-Cl	-F	-H	-H		369
495	-H	-CH ₃	-F	-H	-H		349

[1159] 表 97

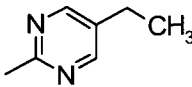
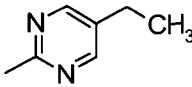
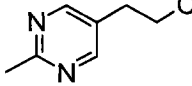
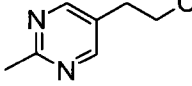
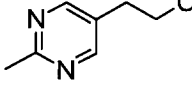
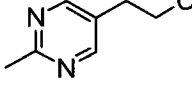
[1160]



[1161]

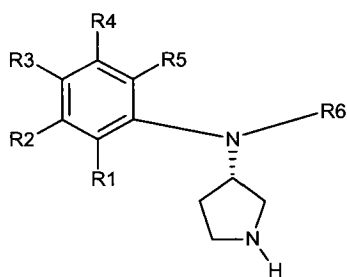
实施例	R1	R2	R3	R4	R5	R6	MS (M+1)
496	-H	-H	-H	-H	-H		241
497	-H	-Cl	-F	-H	-H		293
498	-H	-CH ₃	-F	-H	-H		273
499	-H	-H	-H	-H	-H		269
500	-H	-H	-F	-H	-H		287

[1162]

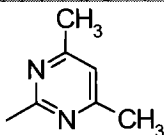
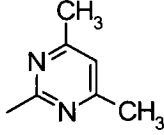
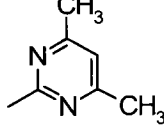
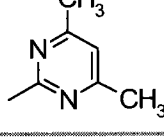
501	-H	-CH ₃	-F	-H	-H		301
502	-H	-Cl	-F	-H	-H		321
503	-H	-H	-H	-H	-H		283
504	-H	-Cl	-F	-H	-H		335
505	-H	-H	-F	-H	-H		301
506	-H	-CH ₃	-F	-H	-H		315

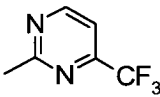
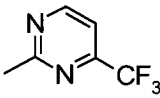
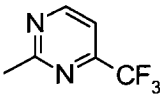
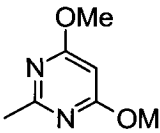
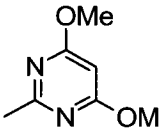
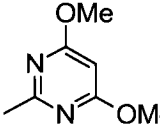
[1163] 表 98

[1164]



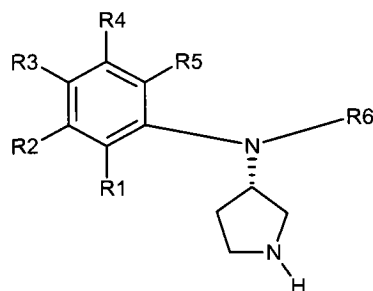
[1165]

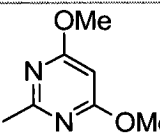
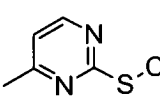
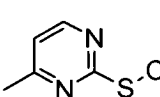
实施例	R1	R2	R3	R4	R5	R6	MS (M+1)
507	-H	-H	-H	-H	-H		269
508	-H	-Cl	-F	-H	-H		321
509	-H	-CH ₃	-F	-H	-H		301
510	-H	-H	-F	-H	-H		287

[1166]	511	-H	-Cl	-F	-H	-H		361
	512	-H	-CH ₃	-F	-H	-H		341
	513	-H	-H	-F	-H	-H		327
	514	-H	-H	-H	-H	-H		301
	515	-H	-Cl	-F	-H	-H		353
	516	-H	-CH ₃	-F	-H	-H		333

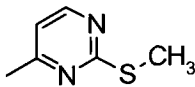
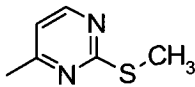
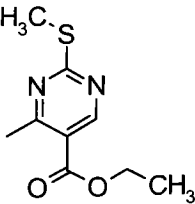
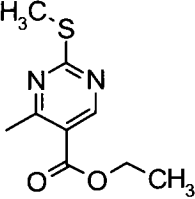
[1167] 表 99

[1168]



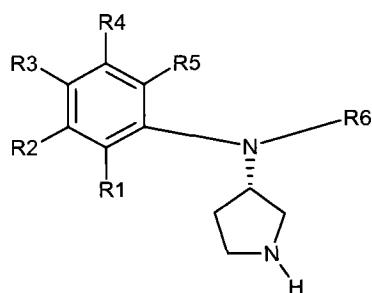
实施例	R1	R2	R3	R4	R5	R6	MS
							(M+1)
[1169]	517	-H	-H	-F	-H	-H	 319
	518	-H	-H	-H	-H	-H	 287
	519	-H	-Cl	-F	-H	-H	 339

[1170]

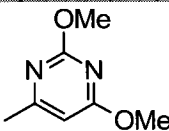
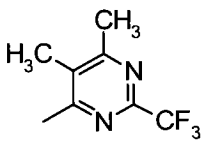
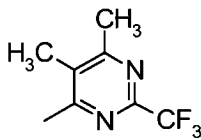
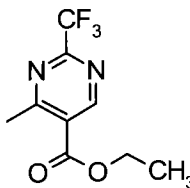
520	-H	-CH ₃	-F	-H	-H		319
521	-H	-H	-F	-H	-H		305
522	-H	-Cl	-F	-H	-H		411
523	-H	-CH ₃	-F	-H	-H		391

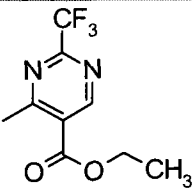
[1171] 表 100

[1172]



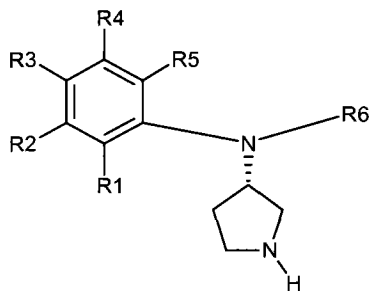
[1173]

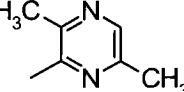
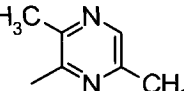
实施例	R1	R2	R3	R4	R5	R6	MS (M+1)
524	-H	-Cl	-F	-H	-H		353
525	-H	-H	-H	-H	-H		337
526	-H	-CH ₃	-F	-H	-H		369
527	-H	-H	-F	-H	-H		399

[1174]	528	-H	-CH ₃	-F	-H	-H		413
	529	-H	-H	-H	-H	-H		241
	530	-H	-CH ₃	-F	-H	-H		273
	531	-H	-H	-F	-H	-H		259
	532	-H	-Cl	-F	-H	-H		293

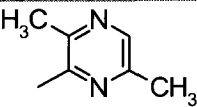
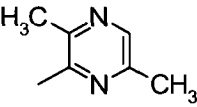
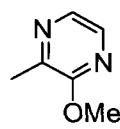
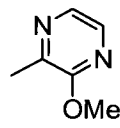
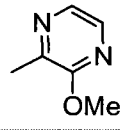
[1175] 表 101

[1176]



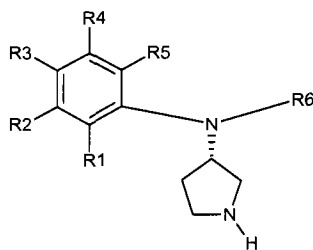
实施例	R1	R2	R3	R4	R5	R6	MS (M+1)
533	-H	-H	-H	-H	-H		241
534	-H	-Cl	-F	-H	-H		293
535	-H	-CH ₃	-F	-H	-H		273
536	-H	-H	-F	-H	-H		259
537	-H	-H	-H	-H	-H		269
538	-H	-Cl	-F	-H	-H		321

[1178]

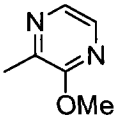
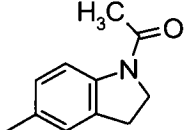
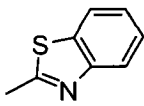
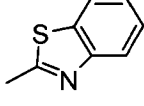
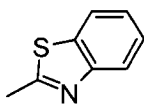
539	-H	-CH ₃	-F	-H	-H		301
540	-H	-H	-F	-H	-H		287
541	-H	-H	-H	-H	-H		271
542	-H	-Cl	-F	-H	-H		323
543	-H	-CH ₃	-F	-H	-H		303

[1179] 表 102

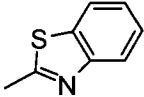
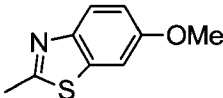
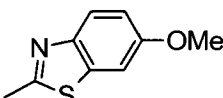
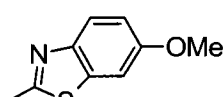
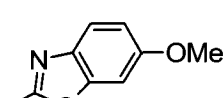
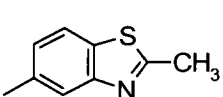
[1180]



[1181]

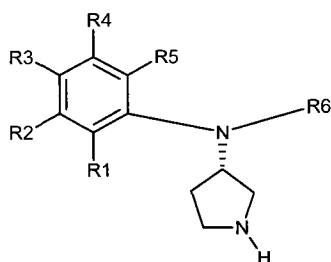
实施例	R1	R2	R3	R4	R5	R6	MS (M+1)
544	-H	-H	-F	-H	-H		289
545	-H	-H	-H	-H	-H		322
546	-H	-H	-H	-H	-H		296
547	-H	-Cl	-F	-H	-H		348
548	-H	-CH ₃	-F	-H	-H		328

[1182]

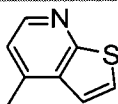
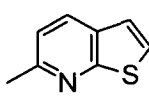
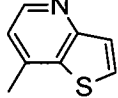
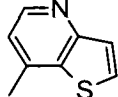
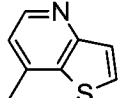
549	-H	-H	-F	-H	-H		314
550	-H	-H	-H	-H	-H		326
551	-H	-Cl	-F	-H	-H		378
552	-H	-CH ₃	-F	-H	-H		358
553	-H	-H	-F	-H	-H		344
554	-H	-H	-H	-H	-H		310

[1183] 表 103

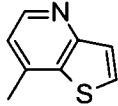
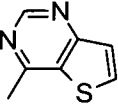
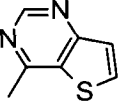
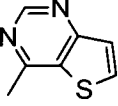
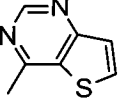
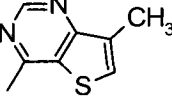
[1184]



[1185]

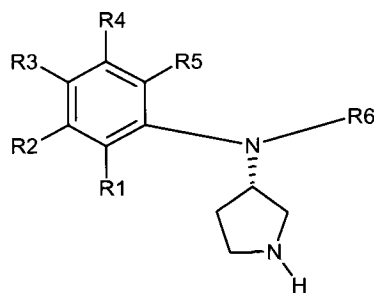
实施例	R1	R2	R3	R4	R5	R6	MS (M+1)
555	-H	-H	-H	-H	-H		296
556	-H	-H	-H	-H	-H		296
557	-H	-H	-H	-H	-H		296
558	-H	-Cl	-F	-H	-H		348
559	-H	-CH ₃	-F	-H	-H		328

[1186]

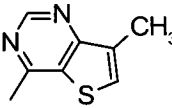
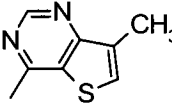
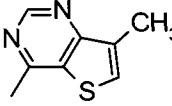
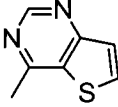
560	-H	-H	-F	-H	-H		314
561	-H	-H	-H	-H	-H		297
562	-H	-Cl	-F	-H	-H		349
563	-H	-CH ₃	-F	-H	-H		329
564	-H	-H	-F	-H	-H		315
565	-H	-H	-H	-H	-H		311

[1187] 表 104

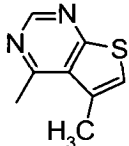
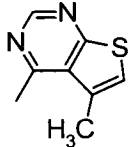
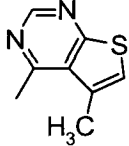
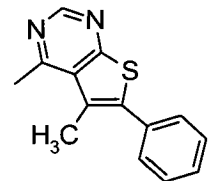
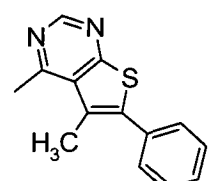
[1188]



[1189]

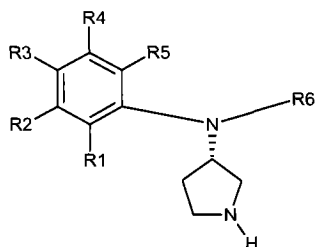
实施例	R1	R2	R3	R4	R5	R6	MS (M+1)
566	-H	-Cl	-F	-H	-H		363
567	-H	-CH ₃	-F	-H	-H		343
568	-H	-H	-F	-H	-H		329
569	-H	-H	-F	-H	-H		315

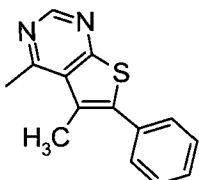
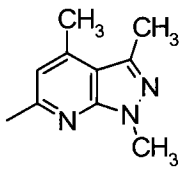
[1190]

570	-H	-Cl	-F	-H	-H		363
571	-H	-CH ₃	-F	-H	-H		343
572	-H	-H	-F	-H	-H		329
573	-H	-H	-H	-H	-H		387
574	-H	-Cl	-F	-H	-H		439

[1191] 表 105

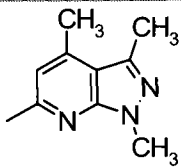
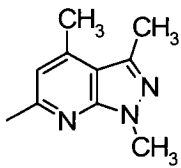
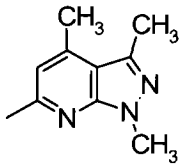
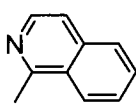
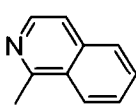
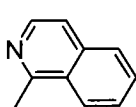
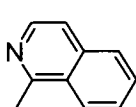
[1192]



实施例	R1	R2	R3	R4	R5	R6	MS (M+1)
575	-H	-CH ₃	-F	-H	-H		419
576	-H	-H	-H	-H	-H		322

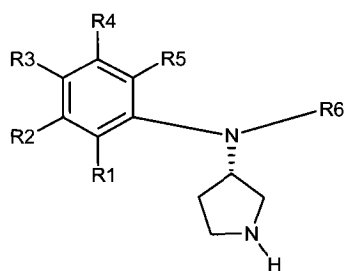
[1193]

[1194]

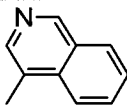
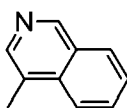
577	-H	-Cl	-F	-H	-H		374
578	-H	-CH ₃	-F	-H	-H		354
579	-H	-H	-F	-H	-H		340
580	-H	-H	-H	-H	-H		290
581	-H	-Cl	-F	-H	-H		342
582	-H	-CH ₃	-F	-H	-H		322
583	-H	-H	-F	-H	-H		308

[1195] 表 106

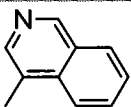
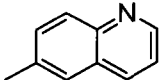
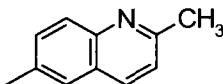
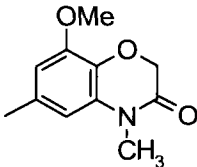
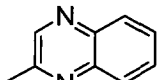
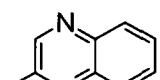
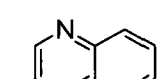
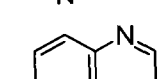
[1196]



[1197]

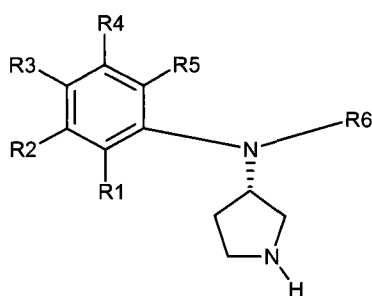
实施例	R1	R2	R3	R4	R5	R6	MS (M+1)
584	-H	-H	-H	-H	-H		290
585	-H	-H	-F	-H	-H		308

[1198]

586	-H	-Cl	-F	-H	-H		342
587	-H	-H	-H	-H	-H		290
588	-H	-H	-H	-H	-H		304
589	-H	-H	-H	-H	-H		310
590	-H	-H	-H	-H	-H		354
591	-H	-H	-H	-H	-H		291
592	-H	-Cl	-F	-H	-H		343
593	-H	-CH ₃	-F	-H	-H		323
594	-H	-H	-H	-H	-H		291

[1199] 表 107

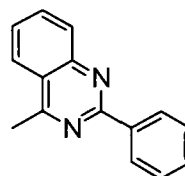
[1200]



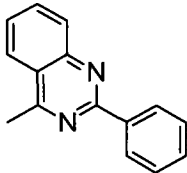
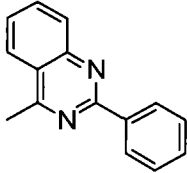
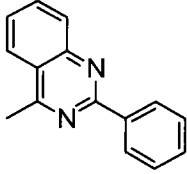
实施例	R1	R2	R3	R4	R5	R6	MS (M+1)
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595	-H	-H	-H	-H	-H		367
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[1201]

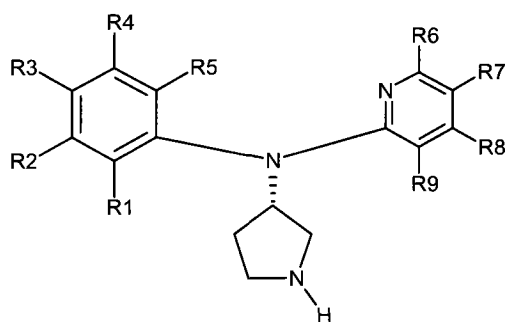


[1202]

596	-H	-Cl	-F	-H	-H		419
597	-H	-CH ₃	-F	-H	-H		399
598	-H	-H	-F	-H	-H		385

[1203] 表 108

[1204]



[1205]

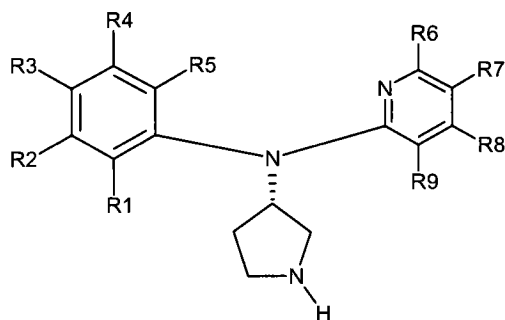
实施例	R1	R2	R3	R4	R5	R6	R7	R8	R9	MS (M+1)
599	-H	-Cl	-F	-H	-H	-H	-NO ₂	-H	-H	337
600	-H	-Cl	-F	-H	-H	-H	-CO ₂ CH ₃	-H	-H	350
601	-H	-Cl	-F	-H	-H	-H	-H	-H	-CF ₃	360
602	-H	-Cl	-F	-H	-H	-H	-Cl	-H	-H	326
603	-H	-Cl	-F	-H	-H	-H	-H	-H	-Cl	326
604	-H	-Cl	-F	-H	-H	-OCH ₃	-H	-H	-H	322
605	-H	-Cl	-F	-H	-H	-H	-H	-H	-H	292
606	-H	-Cl	-F	-H	-H	-H	-CH ₃	-H	-H	306
607	-H	-Cl	-F	-H	-H	-H	-H	-CH ₃	-H	306
608	-H	-Cl	-F	-H	-H	-H	-H	-CF ₃	-H	360
609	-H	-Cl	-F	-H	-H	-CH ₃	-H	-H	-H	306
610	-H	-Cl	-F	-H	-H	-H	-CF ₃	-H	-H	360
611	-H	-H	-H	-H	-H	-H	-NO ₂	-H	-H	285
612	-H	-H	-H	-H	-H	-H	-CO ₂ CH ₃	-H	-H	298
613	-H	-H	-H	-H	-H	-H	-H	-H	-CF ₃	308
614	-H	-H	-H	-H	-H	-H	-Cl	-H	-H	274
615	-H	-H	-H	-H	-H	-H	-H	-H	-Cl	274
616	-H	-H	-H	-H	-H	-H	-H	-H	-H	240
617	-H	-H	-H	-H	-H	-H	-CH ₃	-H	-H	254
618	-H	-H	-H	-H	-H	-H	-H	-CH ₃	-H	254

[1206]

619	-H	-H	-H	-H	-H	-H	-H	-CF ₃	-H	308
620	-H	-H	-H	-H	-H	-CH ₃	-H	-H	-H	254
621	-H	-H	-H	-H	-H	-OCH ₃	-H	-H	-H	270
622	-H	-H	-H	-H	-H	-H	-H	-H	-CH ₃	254
623	-H	-H	-H	-H	-H	-H	-CF ₃	-H	-H	308
624	-H	-CH ₃	-F	-H	-H	-H	-NO ₂	-H	-H	317
625	-H	-CH ₃	-F	-H	-H	-H	-CO ₂ CH ₃	-H	-H	330
626	-H	-CH ₃	-F	-H	-H	-H	-H	-H	-CF ₃	340
627	-H	-CH ₃	-F	-H	-H	-H	-H	-H	-NO ₂	317
628	-H	-CH ₃	-F	-H	-H	-H	-Cl	-H	-H	306
629	-H	-CH ₃	-F	-H	-H	-H	-H	-H	-Cl	306
630	-H	-CH ₃	-F	-H	-H	-H	-H	-H	-H	272
631	-H	-CH ₃	-F	-H	-H	-H	-CH ₃	-H	-H	286
632	-H	-CH ₃	-F	-H	-H	-H	-H	-CH ₃	-H	286
633	-H	-CH ₃	-F	-H	-H	-H	-H	-CF ₃	-H	340
634	-H	-CH ₃	-F	-H	-H	-CH ₃	-H	-H	-H	286
635	-H	-CH ₃	-F	-H	-H	-OCH ₃	-H	-H	-H	302

[1207] 表 109

[1208]



[1209]

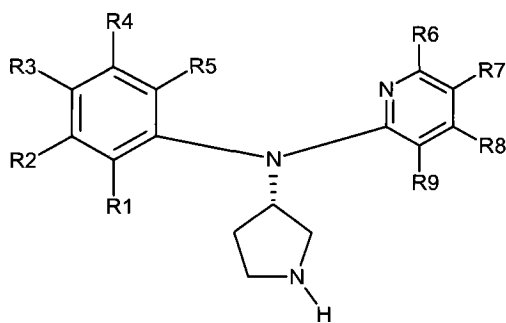
实施例	R1	R2	R3	R4	R5	R6	R7	R8	R9	MS (M+1)
636	-H	-CH ₃	-F	-H	-H	-H	-H	-H	-CH ₃	286
637	-H	-CH ₃	-F	-H	-H	-H	-CF ₃	-H	-H	340
638	-H	-H	-F	-H	-H	-H	-NO ₂	-H	-H	303
639	-H	-H	-F	-H	-H	-H	-CO ₂ CH ₃	-H	-H	316
640	-H	-H	-F	-H	-H	-H	-H	-H	-CF ₃	326
641	-H	-H	-F	-H	-H	-H	-Cl	-H	-H	292
642	-H	-H	-F	-H	-H	-H	-H	-H	-Cl	292
643	-H	-H	-F	-H	-H	-H	-H	-H	-H	258
644	-H	-H	-F	-H	-H	-H	-CH ₃	-H	-H	272
645	-H	-H	-F	-H	-H	-H	-H	-CH ₃	-H	272
646	-H	-H	-F	-H	-H	-H	-H	-CF ₃	-H	326
647	-H	-H	-F	-H	-H	-CH ₃	-H	-H	-H	272
648	-H	-H	-F	-H	-H	-OCH ₃	-H	-H	-H	288
649	-H	-H	-F	-H	-H	-H	-CF ₃	-H	-H	326
650	-H	-Cl	-F	-H	-H	-CH ₃	-H	-CF ₃	-H	374
651	-H	-Cl	-F	-H	-H	-H	-H	-NO ₂	-H	337
652	-H	-Cl	-F	-H	-H	-H	-H	-OCH ₃	-H	322

[1210]

653	-H	-Cl	-F	-H	-H	-H	-H	-C ₂ H ₅	-H	320
654	-H	-H	-H	-H	-H	-CH ₃	-H	-CF ₃	-H	322
655	-H	-H	-H	-H	-H	-H	-H	-NO ₂	-H	285
656	-H	-H	-H	-H	-H	-H	-H	-OCH ₃	-H	270
657	-H	-H	-H	-H	-H	-H	-H	-C ₂ H ₅	-H	268
658	-H	-CH ₃	-F	-H	-H	-CH ₃	-H	-CF ₃	-H	354
659	-H	-CH ₃	-F	-H	-H	-H	-H	-NO ₂	-H	317
660	-H	-CH ₃	-F	-H	-H	-H	-H	-OCH ₃	-H	302
661	-H	-CH ₃	-F	-H	-H	-H	-H	-C ₂ H ₅	-H	300
662	-H	-H	-F	-H	-H	-CH ₃	-H	-CF ₃	-H	340
663	-H	-H	-F	-H	-H	-H	-H	-NO ₂	-H	303
664	-H	-H	-F	-H	-H	-H	-H	-OCH ₃	-H	288
665	-H	-H	-F	-H	-H	-H	-H	-C ₂ H ₅	-H	286

[1211] 表 110

[1212]

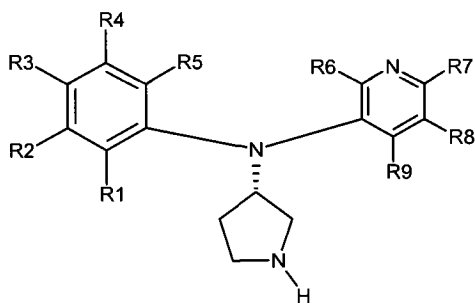


[1213]

实施例	R1	R2	R3	R4	R5	R6	R7	R8	R9	MS (M+1)
666	-H	-H	-H	-H	-H	-H	-H		-H	309

[1214] 表 111

[1215]



[1216]

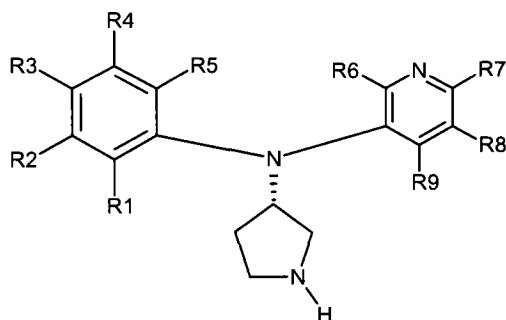
实施例	R1	R2	R3	R4	R5	R6	R7	R8	R9	MS (M+1)
667	-H	-Cl	-F	-H	-H	-H	-H	-H	-H	292
668	-H	-H	-H	-H	-H	-H	-H	-H	-H	240
669	-H	-H	-H	-H	-H	-H	-NO ₂	-H	-H	285
670	-H	-H	-H	-H	-H	-CH ₃	-CH ₃	-H	-H	268
671	-H	-CH ₃	-F	-H	-H	-H	-H	-H	-H	272
672	-H	-CH ₃	-F	-H	-H	-H	-NO ₂	-H	-H	317

[1217]

673	-H	-H	-F	-H	-H	-H	-H	-H	-H	258
674	-H	-H	-F	-H	-H	-H	-NO ₂	-H	-H	303
675	-H	-H	-F	-H	-H	-CH ₃	-CH ₃	-H	-H	286
676	-H	-Cl	-F	-H	-H	-H	-CH ₃	-H	-H	306
677	-H	-Cl	-F	-H	-H	-H	-OCH ₃	-H	-H	322
678	-H	-Cl	-F	-H	-H	-H	-H	-OCH ₃	-H	322
679	-H	-H	-H	-H	-H	-H	-CH ₃	-H	-H	254
680	-H	-H	-H	-H	-H	-H	-H	-OCH ₃	-H	270
681	-H	-CH ₃	-F	-H	-H	-H	-CH ₃	-H	-H	286
682	-H	-CH ₃	-F	-H	-H	-H	-H	-OCH ₃	-H	302
683	-H	-H	-F	-H	-H	-H	-CH ₃	-H	-H	272
684	-H	-H	-F	-H	-H	-H	-H	-OCH ₃	-H	288
685	-H	-H	-OC ₂ H ₅	-H	-H	-H	-H	-H	-H	284
686	-CH ₃	-H	-H	-H	-H	-H	-H	-H	-H	254
687	-H	-H	-CF ₃	-H	-H	-H	-H	-H	-H	308
688	-H	-H	-CN	-H	-H	-H	-H	-H	-H	265
689	-H	-NO ₂	-H	-H	-H	-H	-H	-H	-H	285
690	-H	-H	-NO ₂	-H	-H	-H	-H	-H	-H	285
691	-H	-H	-N(CH ₃) ₂	-H	-H	-H	-H	-H	-H	283
692	-H	-CF ₃	-H	-H	-H	-H	-H	-H	-H	308
693	-CH ₃	-H	-F	-H	-H	-H	-H	-H	-H	272
694	-H	-CF ₃	-Cl	-H	-H	-H	-H	-H	-H	342
695	-H	-H	-CH ₃	-H	-H	-H	-H	-H	-H	254
696	-H	-H	-C(CH ₃) ₃	-H	-H	-H	-H	-H	-H	296
697	-H	-Cl	-H	-Cl	-H	-H	-H	-H	-H	308
698	-H	-H	-SCH ₃	-H	-H	-H	-H	-H	-H	286
699	-H	-H	-COC ₆ H ₅	-H	-H	-H	-H	-H	-H	344
700	-H	-H	-CH(CH ₃) ₂	-H	-H	-H	-H	-H	-H	282
701	-H	-H	-OC ₆ H ₅	-H	-H	-H	-H	-H	-H	332
702	-H	-H	-OC ₆ H ₁₃	-H	-H	-H	-H	-H	-H	340
703	-H	-H	-C ₆ H ₁₃	-H	-H	-H	-H	-H	-H	324
704	-H	-H	-C ₂ H ₅	-H	-H	-H	-H	-H	-H	268

[1218] 表 112

[1219]



[1220]

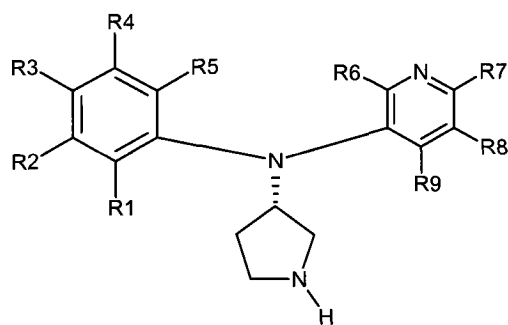
实施例	R1	R2	R3	R4	R5	R6	R7	R8	R9	MS (M+1)
705	-H	-H	-OCH ₂ C ₆ H ₅	-H	-H	-H	-H	-H	-H	346
706	-H	-CF ₃	-F	-H	-H	-H	-H	-H	-H	326
707	-H	-CF ₃	-H	-CF ₃	-H	-H	-H	-H	-H	376
708	-H	-OCH ₃	-H	-H	-OCH ₃	-H	-H	-H	-H	300
709	-Cl	-H	-H	-H	-H	-H	-H	-H	-H	274

[1221]

710	-H	-H	-OCH ₃	-H	-H	-H	-H	-H	-H	270
711	-CH ₃	-CH ₃	-H	-H	-H	-H	-H	-H	-H	268
712	-C ₂ H ₅	-H	-H	-H	-H	-H	-H	-H	-H	268
713	-H	-F	-H	-H	-OCH ₃	-H	-H	-H	-H	288
714	-H	-H	-COCH ₃	-H	-H	-H	-H	-H	-H	282
715	-H	-COCH ₃	-H	-H	-H	-H	-H	-H	-H	282
716	-CH ₃	-H	-Cl	-H	-H	-H	-H	-H	-H	288
717	-H	-Cl	-Cl	-H	-H	-H	-H	-H	-H	308
718	-H	-F	-F	-H	-H	-H	-H	-H	-H	276
719	-H	-F	-H	-F	-H	-H	-H	-H	-H	276
720	-H	-H	-CF ₃	-F	-H	-H	-H	-H	-H	326
721	-H	-CF ₃	-H	-F	-H	-H	-H	-H	-H	326
722	-H	-CF ₃	-CH ₃	-H	-H	-H	-H	-H	-H	322
723	-H	-SCF ₃	-H	-H	-H	-H	-H	-H	-H	340
724	-H	-CF ₃	-OCH ₃	-H	-H	-H	-H	-H	-H	338
725	-H	-CH ₃	-N(CH ₃) ₂	-CH ₃	-H	-H	-H	-H	-H	311
726	-H	-CH(CH ₃) ₂	-H	-H	-H	-H	-H	-H	-H	282
727	-H	-H	-SC ₂ H ₅	-H	-H	-H	-H	-H	-H	300
728	-H	-H	-N(C ₂ H ₅) ₂	-H	-H	-H	-H	-H	-H	311
729	-H	-OCH(CH ₃) ₂	-H	-H	-H	-H	-H	-H	-H	298
730	-H	-H	-OCHF ₂	-H	-H	-H	-H	-H	-H	306
731	-H	-F	-H	-Cl	-H	-H	-H	-H	-H	292
732	-H	-CH ₃	-OCH ₃	-CH ₃	-H	-H	-H	-H	-H	298
733	-H	-CH ₃	-H	-CH ₃	-H	-H	-H	-H	-H	268
734	-H	-F	-CH ₃	-H	-H	-H	-H	-H	-H	272
735	-H	-F	-Cl	-H	-H	-H	-H	-H	-H	292
736	-H	-C ₆ H ₅	-H	-H	-H	-H	-H	-H	-H	316
737	-H	-F	-H	-H	-H	-H	-H	-H	-H	258
738	-H	-Cl	-CH ₃	-H	-H	-H	-H	-H	-H	288
739	-H	-F	-F	-F	-H	-H	-H	-H	-H	294
740	-H	-F	-H	-H	-CH ₃	-H	-H	-H	-H	272
741	-F	-H	-H	-CH ₃	-H	-H	-H	-H	-H	272
742	-H	-F	-OCH ₃	-H	-H	-H	-H	-H	-H	288

[1222] 表 113

[1223]



[1224]

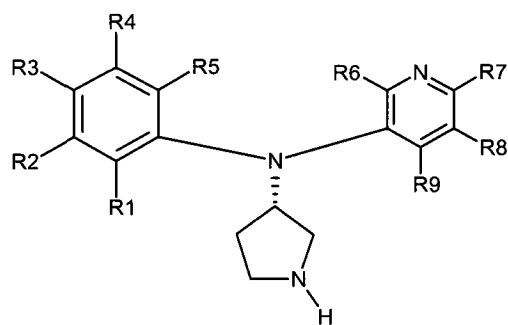
实施例	R1	R2	R3	R4	R5	R6	R7	R8	R9	MS (M+1)
743	-H	-CH ₃	-Cl	-H	-H	-H	-H	-H	-H	288
744	-H	-H	-C ₃ H ₇	-H	-H	-H	-H	-H	-H	282

[1225]

745	-OCH ₃	-H	-H	-CH ₃	-H	-H	-H	-H	-H	284
746	-CH ₃	-Cl	-H	-H	-H	-H	-H	-H	-H	288
747	-H	-H	-CH ₂ C ₆ H ₅	-H	-H	-H	-H	-H	-H	330
748	-H	-Cl	-H	-H	-OCH ₃	-H	-H	-H	-H	304
749	-CH ₃	-F	-CH ₃	-H	-H	-H	-H	-H	-H	286
750	-H	-CH ₂ CH ₂ CN	-H	-H	-H	-H	-H	-H	-H	293
751	-H	-H	-CH ₂ CH ₂ CN	-H	-H	-H	-H	-H	-H	293
752	-H	-Cl	-H	-H	-CH ₃	-H	-H	-H	-H	288
753	-H	-OCHF ₂	-H	-H	-H	-H	-H	-H	-H	306
754	-H	-C ₂ H ₅	-H	-H	-H	-H	-H	-H	-H	268
755	-H	-F	-OCH ₃	-F	-H	-H	-H	-H	-H	306
756	-H	-F	-F	-H	-OCH ₃	-H	-H	-H	-H	306
757	-CH ₃	-H	-CH ₃	-H	-H	-H	-H	-H	-H	268
758	-H	-F	-F	-OCH ₃	-H	-H	-H	-H	-H	306
759	-H	-OCH ₃	-OCH ₃	-H	-H	-H	-H	-H	-H	300
760	-H	-Cl	-H	-H	-H	-H	-H	-H	-H	274
761	-CH ₃	-H	-H	-CH ₃	-H	-H	-H	-H	-H	268
762	-H	-CH ₃	-CH ₃	-H	-H	-H	-H	-H	-H	268
763	-H	-CN	-F	-H	-H	-H	-H	-H	-H	283
764	-CH(CH ₃) ₂	-H	-H	-CH ₃	-H	-H	-H	-H	-H	296
765	-H	-NO ₂	-F	-H	-H	-H	-H	-H	-H	303
766	-CH ₂ C ₆ H ₅	-H	-H	-H	-H	-H	-H	-H	-H	330
767	-H	-CH ₃	-OCH ₃	-H	-H	-H	-H	-H	-H	284
768	-H	-H	-C ₆ H ₅	-H	-H	-H	-H	-H	-H	316
769	-H	-Cl	-CN	-H	-H	-H	-H	-H	-H	299
770	-H	-CH ₃	-F	-CH ₃	-H	-H	-H	-H	-H	286
771	-H	-H	-OCF ₂ CHF ₂	-H	-H	-H	-H	-H	-H	356
772	-H	-H	-OH	-H	-H	-H	-H	-H	-H	256

[1226] 表 114

[1227]



[1228]

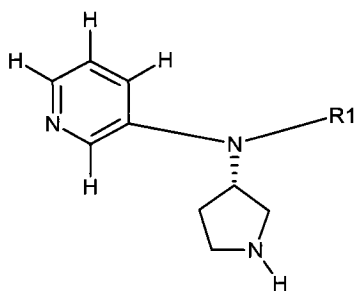
实施例	R1	R2	R3	R4	R5	R6	R7	R8	R9	MS (M+1)
773	-H		-H	-H	-H	-H	-H	-H	-H	337

[1229]

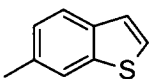
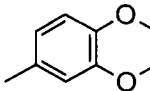
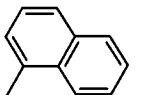
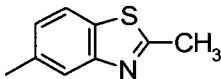
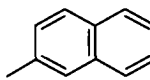
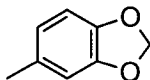
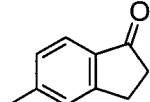
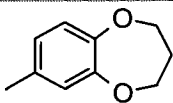
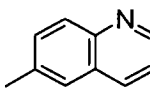
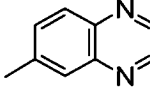
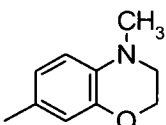
774	-H	-H		-H	-H	-H	-H	-H	-H	307
775	-H	-H		-H	-H	-H	-H	-H	-H	353
776	-H	-H		-H	-H	-H	-H	-H	-H	308
777	-H		-H	-H	-H	-H	-H	-H	-H	350

[1230] 表 115

[1231]



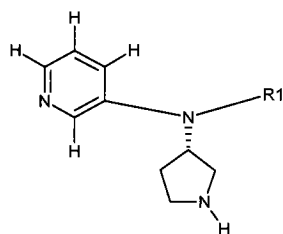
[1232]

实施例	R1	MS (M+1)
778		296
779		298
780		290
781		311
782		290
783		284
784		294
785		312
786		291
787		292
788		311

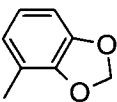
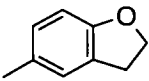
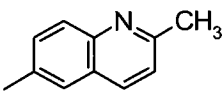
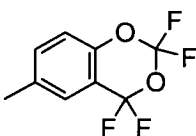
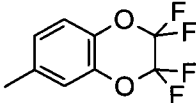
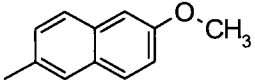
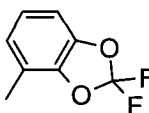
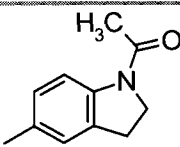
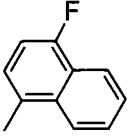
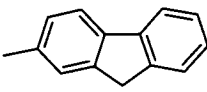
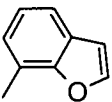
[1233]

[1234] 表 116

[1235]



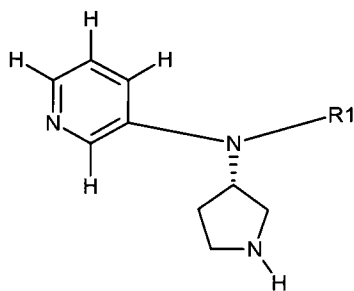
[1236]

实施例	R1	MS (M+1)
789		284
790		282
791		305
792		370
793		370
794		320
795		320
796		323
797		308
798		328
799		280

[1237]

[1238] 表 117

[1239]



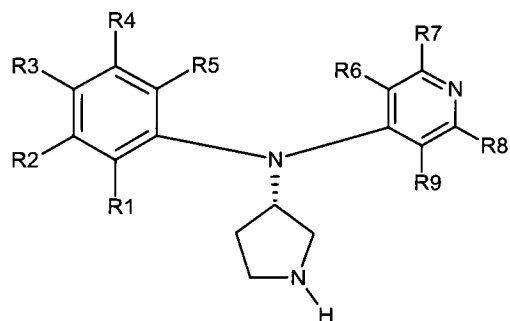
[1240]

实施例	R1	MS (M+1)
800		279
801		353
802		355
803		310
804		297
805		297

[1241]

[1242] 表 118

[1243]

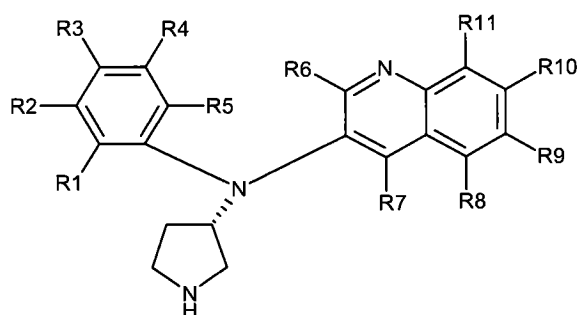


[1244]

实施例	R1	R2	R3	R4	R5	R6	R7	R8	R9	MS (M+1)
806	-H	-Cl	-F	-H	-H	-H	-H	-CH ₃	-H	306
807	-H	-Cl	-F	-H	-H	-H	-2-吡啶基	-2-吡啶基	-H	446
808	-H	-H	-H	-H	-H	-H	-H	-CH ₃	-H	254
809	-H	-H	-H	-H	-H	-H	-H	-H	-CH ₃	254
810	-H	-H	-H	-H	-H	-H	-2-吡啶基	-2-吡啶基	-H	394
811	-H	-CH ₃	-F	-H	-H	-H	-H	-CH ₃	-H	286
812	-H	-CH ₃	-F	-H	-H	-H	-2-吡啶基	-2-吡啶基	-H	426
813	-H	-H	-F	-H	-H	-H	-2-吡啶基	-2-吡啶基	-H	412

[1245] 表 119

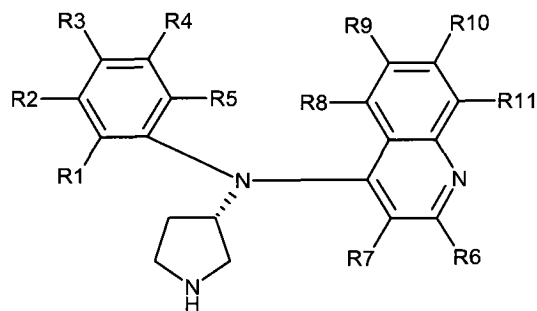
[1246]



实施例	R1	R2	R3	R4	R5	R6	R7	R8	R9	R10	R11	MS (M+1)
814	-H	-Cl	-F	-H	-H	-H	-H	-H	-H	-H	-H	342
815	-H	-H	-H	-H	-H	-H	-H	-H	-H	-H	-H	290
816	-H	-CH ₃	-F	-H	-H	-H	-H	-H	-H	-H	-H	322
817	-H	-H	-F	-H	-H	-H	-H	-H	-H	-H	-H	308

[1248] 表 120

[1249]

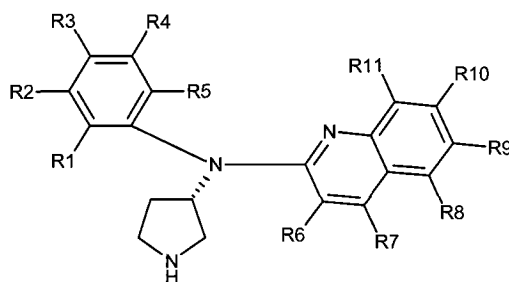


[1250]

实施例	R1	R2	R3	R4	R5	R6	R7	R8	R9	R10	R11	MS (M+1)
818	-H	-Cl	-F	-H	-H	-CH ₃	-H	-H	-H	-H	-H	356
819	-H	-Cl	-F	-H	-H	-H	-H	-H	-H	-H	-H	342
820	-H	-Cl	-F	-H	-H	-H	-H	-H	-H	-CF ₃	-H	410
821	-H	-Cl	-F	-H	-H	-C ₆ H ₅	-H	-H	-H	-H	-H	418
822	-H	-Cl	-F	-H	-H	-H	-H	-H	-H	-Cl	-H	376
823	-H	-Cl	-F	-H	-H	-CF ₃	-H	-H	-H	-H	-H	410
824	-H	-Cl	-F	-H	-H	-H	-H	-H	-H	-H	-CF ₃	410
825	-H	-H	-H	-H	-H	-CH ₃	-H	-H	-H	-H	-H	304
826	-H	-H	-H	-H	-H	-H	-H	-H	-H	-H	-H	290
827	-H	-H	-H	-H	-H	-H	-H	-H	-H	-CF ₃	-H	358
828	-H	-H	-H	-H	-H	-C ₆ H ₅	-H	-H	-H	-H	-H	366
829	-H	-H	-H	-H	-H	-H	-H	-H	-H	-Cl	-H	324
830	-H	-H	-H	-H	-H	-CF ₃	-H	-H	-H	-H	-H	358
831	-H	-H	-H	-H	-H	-H	-H	-H	-H	-H	-CF ₃	358
832	-H	-CH ₃	-F	-H	-H	-CH ₃	-H	-H	-H	-H	-H	336
833	-H	-CH ₃	-F	-H	-H	-H	-H	-H	-H	-H	-H	322
834	-H	-CH ₃	-F	-H	-H	-H	-H	-H	-H	-CF ₃	-H	390
835	-H	-CH ₃	-F	-H	-H	-C ₆ H ₅	-H	-H	-H	-H	-H	398
836	-H	-CH ₃	-F	-H	-H	-H	-H	-H	-H	-Cl	-H	356
837	-H	-CH ₃	-F	-H	-H	-CF ₃	-H	-H	-H	-H	-H	390
838	-H	-CH ₃	-F	-H	-H	-H	-H	-H	-H	-H	-CF ₃	390
839	-H	-H	-F	-H	-H	-CH ₃	-H	-H	-H	-H	-H	322
840	-H	-H	-F	-H	-H	-H	-H	-H	-H	-H	-H	308
841	-H	-H	-F	-H	-H	-H	-H	-H	-H	-CF ₃	-H	376
842	-H	-H	-F	-H	-H	-C ₆ H ₅	-H	-H	-H	-H	-H	384
843	-H	-H	-F	-H	-H	-H	-H	-H	-H	-Cl	-H	342
844	-H	-H	-F	-H	-H	-CF ₃	-H	-H	-H	-H	-H	376
845	-H	-H	-F	-H	-H	-H	-H	-H	-H	-H	-CF ₃	376
846	-H	-Cl	-F	-H	-H	-H	-H	-H	-CF ₃	-H	-H	410
847	-H	-H	-H	-H	-H	-H	-H	-H	-F	-H	-F	326
848	-H	-H	-H	-H	-H	-H	-H	-H	-CF ₃	-H	-H	358
849	-H	-CH ₃	-F	-H	-H	-H	-H	-H	-F	-H	-F	358
850	-H	-CH ₃	-F	-H	-H	-H	-H	-H	-CF ₃	-H	-H	390
851	-H	-H	-F	-H	-H	-H	-H	-H	-F	-H	-F	344
852	-H	-H	-F	-H	-H	-H	-H	-H	-CF ₃	-H	-H	376
853	-H	-H	-H	-H	-H	-OCH ₃	-H	-H	-H	-H	-H	320

[1251] 表 121

[1252]



[1253]

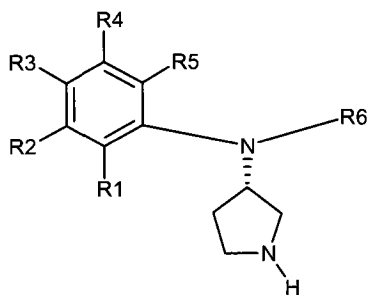
实施例	R1	R2	R3	R4	R5	R6	R7	R8	R9	R10	R11	MS (M+1)
854	-H	-H	-F	-Cl	-H	-H	-H	-H	-H	-H	-H	342

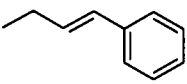
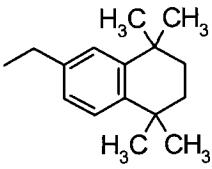
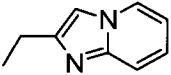
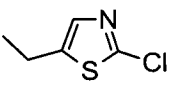
[1254]

855	-H	-H	-F	-Cl	-H	-CH ₃	-H	-H	-H	-H	-H	356
856	-H	-H	-F	-Cl	-H	-OCH ₃	-H	-H	-H	-H	-H	372
857	-H	-H	-F	-Cl	-H	-H	-CH ₃	-H	-H	-H	-H	356
858	-H	-H	-F	-Cl	-H	-H	-H	-NO ₂	-H	-H	-F	405
859	-H	-H	-F	-Cl	-H	-CH ₂ C ₆ H ₅	-H	-H	-H	-H	-H	432
860	-H	-H	-F	-Cl	-H	-H	-H	-H	-OCH ₃	-H	-H	372
861	-H	-H	-F	-Cl	-H	-H	-OCH ₃	-H	-H	-H	-H	372
862	-H	-H	-F	-Cl	-H	-H	-H	-H	-H	-OCH ₃	-H	372
863	-H	-H	-H	-H	-H	-H	-H	-H	-H	-H	-H	290
864	-H	-H	-H	-H	-H	-CH ₃	-H	-H	-H	-H	-H	304
865	-H	-H	-H	-H	-H	-OCH ₃	-H	-H	-H	-H	-H	320
866	-H	-H	-H	-H	-H	-H	-CH ₃	-H	-H	-H	-H	304
867	-H	-H	-H	-H	-H	-H	-H	-NO ₂	-H	-H	-F	353
868	-H	-H	-H	-H	-H	-CH ₂ C ₆ H ₅	-H	-H	-H	-H	-H	380
869	-H	-H	-H	-H	-H	-H	-H	-H	-OCH ₃	-H	-H	320
870	-H	-H	-H	-H	-H	-H	-OCH ₃	-H	-H	-H	-H	320
871	-H	-H	-H	-H	-H	-H	-H	-H	-H	-OCH ₃	-H	320
872	-H	-H	-F	-CH ₃	-H	-H	-H	-H	-H	-H	-H	322
873	-H	-H	-F	-CH ₃	-H	-CH ₃	-H	-H	-H	-H	-H	336
874	-H	-H	-F	-CH ₃	-H	-OCH ₃	-H	-H	-H	-H	-H	352
875	-H	-H	-F	-CH ₃	-H	-H	-CH ₃	-H	-H	-H	-H	336
876	-H	-H	-F	-CH ₃	-H	-H	-H	-NO ₂	-H	-H	-F	385
877	-H	-H	-F	-CH ₃	-H	-H	-H	-H	-OCH ₃	-H	-H	352
878	-H	-H	-F	-CH ₃	-H	-H	-H	-H	-H	-OCH ₃	-H	352
879	-H	-H	-F	-H	-H	-H	-H	-H	-H	-H	-H	308
880	-H	-H	-F	-H	-H	-CH ₃	-H	-H	-H	-H	-H	322
881	-H	-H	-F	-H	-H	-OCH ₃	-H	-H	-H	-H	-H	338
882	-H	-H	-F	-H	-H	-H	-CH ₃	-H	-H	-H	-H	322
883	-H	-H	-F	-H	-H	-H	-H	-NO ₂	-H	-H	-F	371
884	-H	-H	-F	-H	-H	-H	-H	-H	-OCH ₃	-H	-H	338
885	-H	-H	-F	-H	-H	-H	-OCH ₃	-H	-H	-H	-H	338
886	-H	-H	-F	-H	-H	-H	-H	-H	-H	-OCH ₃	-H	338
887	-H	-H	-H	-H	-H	-H	-OC ₂ H ₅	-H	-H	-H	-H	334

[1255] 表 122

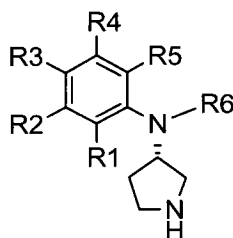
[1256]



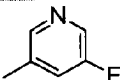
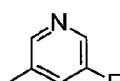
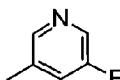
实施例	R1	R2	R3	R4	R5	R6	MS (M+1)
888	-H	-H	-F	-H	-H		297
889	-H	-H	-F	-Cl	-H	-CH ₂ C≡CH	253
890	-H	-H	-F	-Cl	-H		415
[1257]							
891	-H	-H	-F	-Cl	-H		345
892	-H	-H	-F	-Cl	-H		346

[1258] 表 123

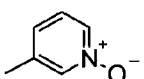
[1259]



[1260]

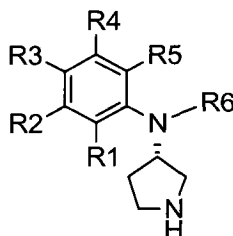
实施例	R1	R2	R3	R4	R5	R6	NMR	盐
893	-H	-H	-F	-Cl	-H		¹ H-NMR (DMSO-d ₆) δppm : 1.55-1.75 (1H, m), 2.2-2.35 (1H, m), 2.38 (6H, s), 2.85-3.0 (1H, m), 3.1-3.2 (2H, m), 3.6-3.75 (1H, m), 4.17 (1H, br), 4.77 (1H, tt, J = 7.7, 7.7Hz), 7.21 (1H, dt, J = 4.0, 7.1Hz), 7.25-7.35 (1H, m), 7.55-7.65 (2H, m), 7.86 (1H, bs), 8.14 (1H, d, J = 2.3Hz), 8.76 (2H, br).	2 甲磺酸盐
894	-H	-H	-F	-Cl	-H		¹ H-NMR (DMSO-d ₆)δppm : 1.55-1.75 (1H, m), 2.15-2.3 (1H, m), 2.8-3.0 (1H, m), 3.05-3.2 (2H, m), 3.61 (1H, dd, J = 7.1, 11.8), 4.74 (1H, tt, J = 7.5, 7.5Hz), 7.10 (1H, ddd, J = 2.4, 2.4, 12.0Hz), 7.25-7.35 (1H, m), 7.45-7.65 (2H, m), 7.82 (1H, s), 8.05 (1H, d, J = 2.2Hz), 9.1-9.55 (2H, m).	盐酸盐
895	-H	-H	-F	-CH ₃	-H		¹ H-NMR (DMSO-d ₆)δppm : 1.55-1.75 (1H, m), 2.15-2.35 (4H, m), 2.75-2.95 (1H, m), 3.0-3.2 (2H, m), 3.55-3.7 (1H, m), 4.76 (1H, tt, J = 7.6, 7.6Hz), 5.38 (1H, br), 7.05-7.25 (2H, m), 7.25-7.4 (2H, m), 7.75 (1H, dd, J = 1.2, 2.3Hz), 8.07 (1H, d, J = 1.8Hz), 9.43 (2H, br).	2 盐酸盐

[1261]

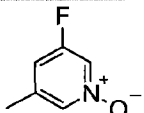
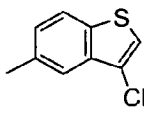
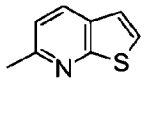
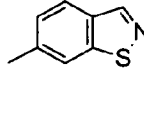
896	-H	-H	-F	-Cl	-H		¹ H-NMR (DMSO-d ₆)δppm : 1.55-1.75 (1H, m), 2.15-2.3 (1H, m), 2.8-3.0 (1H, m), 3.0-3.2 (2H, m), 3.55-3.7 (1H, m), 4.75 (1H, tt, J = 7.6, 7.6Hz), 5.04 (1H, br), 6.9-7.05 (1H, m), 7.3-7.5 (2H, m), 7.62 (1H, dd, J = 9.0, 9.0Hz), 7.71 (1H, dd, J = 2.4, 6.7Hz), 7.95-8.15 (2H, m), 9.40 (2H, br).	2 盐酸盐
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[1262] 表 124

[1263]

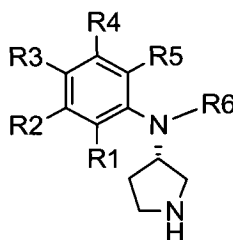


[1264]

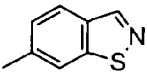
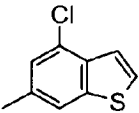
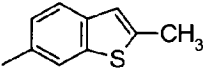
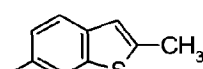
实施例	R1	R2	R3	R4	R5	R6	NMR	盐
897	-H	-H	-F	-Cl	-H		¹ H-NMR (DMSO-d ₆)δppm : 1.5-1.7 (1H, m), 2.15-2.3 (1H, m), 2.8-2.95 (1H, m), 3.0-3.2 (2H, m), 3.5-3.65 (1H, m), 4.39 (1H, br), 4.70 (1H, tt, J = 7.8, 7.8Hz), 6.68 (1H, d, J = 11.3Hz), 7.35-7.45 (1H, m), 7.46 (1H, s), 7.61 (1H, dd, J = 9.0, 9.0Hz), 7.71 (1H, dd, J = 2.6, 6.8Hz), 7.95-8.05 (1H, m), 9.27 (2H, br).	2 盐酸盐
898	-H	-H	-F	-Cl	-H		¹ H-NMR (DMSO-d ₆)δppm : 1.55-1.75 (1H, m), 2.05-2.3 (1H, m), 2.8-3.0 (1H, m), 3.05-3.3 (2H, m), 3.5-3.7 (1H, m), 4.78 (1H, tt, J = 7.3, 7.3Hz), 6.8-6.9 (1H, m), 7.1-7.2 (2H, m), 7.34 (1H, dd, J = 9.0, 9.0Hz), 7.44 (1H, d, J = 2.1Hz), 7.97 (1H, s), 8.08 (1H, d, J = 8.7Hz), 9.29 (1H, br), 9.44 (1H, br).	盐酸盐
899	-H	-H	-F	-H	-H		¹ H-NMR (DMSO-d ₆)δppm : 1.55-1.75 (1H, m), 2.1-2.25 (1H, m), 2.85-3.05 (1H, m), 3.1-3.25 (2H, m), 3.6-3.75 (1H, m), 3.8-5.0 (1H, m), 5.28 (1H, tt, J = 8.2, 8.2Hz), 6.06 (1H, d, J = 8.9Hz), 7.22 (1H, d, J = 5.9Hz), 7.35-7.5 (5H, m), 7.85 (1H, d, J = 8.9Hz), 9.34 (2H, br).	2 盐酸盐
900	-H	-H	-H	-H	-H		¹ H-NMR (DMSO-d ₆)δppm : 1.55-1.8 (1H, m), 2.2-2.35 (1H, m), 2.8-2.95 (1H, m), 3.0-3.25 (2H, m), 3.6-3.75 (1H, m), 4.10 (1H, br), 4.75-4.9 (1H, m), 6.68 (1H, dd, J = 2.1, 8.9Hz), 7.15-7.3 (2H, m), 7.3-7.45 (1H, m), 7.45-7.6 (3H, m), 7.93 (1H, d, J = 8.9Hz), 8.87 (1H, s), 9.26 (1H, br), 9.38 (1H, br).	2 盐酸盐

[1265] 表 125

[1266]

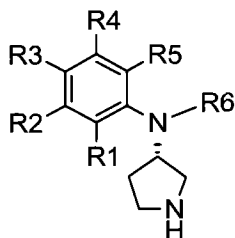


[1267]

实施例	R1	R2	R3	R4	R5	R6	NMR	盐
901	-H	-H	-F	-H	-H		¹ H-NMR (DMSO-d ₆)δppm : 1.6-1.75 (1H, m), 2.2-2.35 (1H, m), 2.8-2.95 (1H, m), 3.05-3.25 (2H, m), 3.6-3.75 (1H, m), 4.47 (1H, br), 4.80 (1H, tt, J = 7.6, 7.6Hz), 6.66 (1H, dd, J = 2.2, 8.9Hz), 7.25-7.4 (4H, m), 7.48 (1H, d, J = 1.8Hz), 7.92 (1H, d, J = 9.0Hz), 8.85 (1H, s), 9.34 (1H, br), 9.45 (1H, br).	2 盐酸盐
902	-H	-H	-H	-H	-H		¹ H-NMR (DMSO-d ₆)δppm : 1.6-1.75 (1H, m), 2.15-2.3 (1H, m), 2.90 (1H, dd, J = 8.0, 11.6Hz), 3.05-3.2 (2H, m), 3.62 (1H, dd, J = 6.9, 11.6Hz), 4.7-4.85 (1H, m), 6.92 (1H, d, J = 1.8Hz), 7.04 (2H, d, J = 7.7Hz), 7.17 (1H, dd, J = 7.3, 7.3Hz), 7.35-7.45 (3H, m), 7.63 (1H, d, J = 1.3Hz), 7.76 (1H, d, J = 5.5Hz), 9.23 (2H, br).	盐酸盐
903	-H	-H	-H	-H	-H		¹ H-NMR (DMSO-d ₆)δppm : 1.6-1.75 (1H, m), 2.1-2.25 (1H, m), 2.55 (3H, d, J = 0.9Hz), 2.8-2.95 (1H, m), 3.0-3.25 (2H, m), 3.5-3.65 (1H, m), 4.72 (1H, tt, J = 7.3, 7.3Hz), 6.80 (2H, d, J = 7.7Hz), 6.85-7.0 (2H, m), 7.10 (1H, s), 7.2-7.3 (2H, m), 7.63 (1H, d, J = 1.9Hz), 7.69 (1H, d, J = 8.5Hz), 9.17 (1H, br), 9.34 (1H, br).	盐酸盐
904	-H	-H	-F	-H	-H		¹ H-NMR (DMSO-d ₆)δppm : 1.6-1.75 (1H, m), 2.1-2.25 (1H, m), 2.53 (3H, d, J = 0.7Hz), 2.8-2.95 (1H, m), 3.0-3.25 (2H, m), 3.5-3.65 (1H, m), 4.69 (1H, tt, J = 7.1, 7.1Hz), 6.86 (1H, dd, J = 2.1, 8.5Hz), 6.9-7.05 (2H, m), 7.05 (1H, s), 7.1-7.2 (2H, m), 7.54 (1H, d, J = 1.9Hz), 7.62 (1H, d, J = 8.6Hz), 9.30 (1H, br), 9.45 (1H, br).	盐酸盐

[1268] 表 126

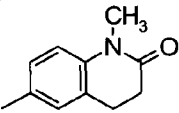
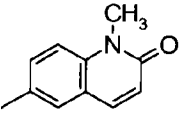
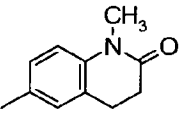
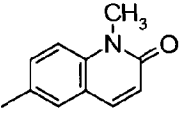
[1269]



[1270]

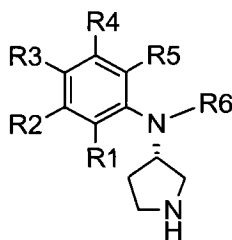
实施例	R1	R2	R3	R4	R5	R6	NMR	盐
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[1271]

905	-H	-H	-CH ₃	-F	-H		¹ H-NMR (DMSO-d ₆)δppm : 1.58-1.71 (1H, m), 2.12 (3H, s), 2.19-2.23 (1H, m), 2.55 (2H, dd, J = 7.0, 8.0 Hz, with DMSO-d ₆), 2.78-2.89 (1H, m), 2.86 (2H, dd, J = 7.0, 8.0 Hz), 3.08-3.22 (2H, m), 3.27 (3H, s), 3.48-3.62 (1H, m, with H ₂ O), 4.59-4.69 (1H, m), 6.44 (1H, dd, J = 2.3, 8.3 Hz), 6.52 (1H, dd, J = 2.3, 12.8 Hz), 7.02-7.16 (4H, m), 9.34 (2H, br).	盐酸盐
906	-H	-H	-CH ₃	-F	-H		¹ H-NMR (DMSO-d ₆)δppm : 1.59-1.72 (1H, m), 2.13 (3H, d, J = 0.86 Hz), 2.17-2.27 (1H, m), 2.82-2.91 (1H, m), 3.09-3.20 (2H, m), 3.61-3.63 (1H, m, with H ₂ O), 3.63 (3H, s), 4.66-4.73 (1H, m), 6.47 (1H, dd, J = 2.3, 8.5 Hz), 6.58 (1H, dd, J = 2.3, 12.6 Hz), 6.65 (1H, d, J = 9.5 Hz), 7.11 (1H, dd, J = 8.5, 8.9 Hz), 7.36 (1H, dd, J = 2.5, 8.9 Hz), 7.56-7.60 (2H, m), 7.89 (1H, d, J = 9.5 Hz), 9.33 (1H, br), 9.41 (1H, br).	盐酸盐
907	-H	-H	-F	-CH ₃	-H		¹ H-NMR (DMSO-d ₆)δppm : 1.59-1.72 (1H, m), 2.09-2.19 (1H, m), 2.19 (3H, d, J = 1.4 Hz), 2.48-2.51 (2H, m, with DMSO-d ₆), 2.78-2.90 (1H, m), 2.81 (2H, dd, J = 6.8, 8.0 Hz), 3.09-3.19 (2H, m), 3.22 (3H, s), 3.40-3.54 (1H, m, with H ₂ O), 4.56-4.66 (1H, m), 6.75-6.80 (1H, m), 6.83-6.85 (2H, m), 6.90 (1H, dd, J = 2.6, 6.8 Hz), 7.02-7.11 (2H, m), 9.29 (1H, br), 9.40 (1H, br).	盐酸盐
908	-H	-H	-F	-CH ₃	-H		¹ H-NMR (DMSO-d ₆)δppm : 1.62-1.75 (1H, m), 2.14-2.26 (1H, m), 2.20 (3H, d, J = 1.6 Hz), 2.85-2.95 (1H, m), 3.11-3.43 (2H, m), 3.53-3.69 (1H, m, with H ₂ O), 3.59 (3H, s), 4.64-4.73 (1H, m), 6.61 (1H, d, J = 9.4 Hz), 6.82-6.87 (1H, m), 6.95 (1H, dd, J = 2.6, 6.8 Hz), 7.11 (1H, dd, J = 9.0, 9.1 Hz), 7.16 (1H, dd, J = 2.6, 9.1 Hz), 7.38 (1H, d, J = 2.6 Hz), 7.48 (1H, d, J = 9.1 Hz), 7.86 (1H, d, J = 9.4 Hz), 9.35 (1H, br), 9.48 (1H, br).	盐酸盐

[1272] 表 127

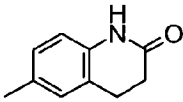
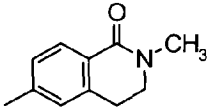
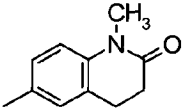
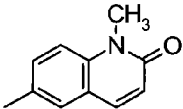
[1273]



[1274]

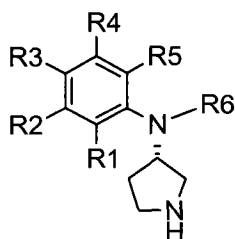
实施例	R1	R2	R3	R4	R5	R6	NMR	盐
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[1275]

909	-H	-H	-F	-CH ₃	-H		¹ H-NMR (DMSO-d ₆)δppm : 1.58-1.71 (1H, m), 2.08-2.17 (1H, m), 2.17 (3H, d, J = 1.5 Hz), 2.42 (2H, dd, J = 6.9, 8.0 Hz), 2.81-2.89 (1H, m), 2.83 (2H, dd, J = 6.9, 8.0 Hz), 3.08-3.14 (2H, m), 3.16-3.56 (1H, m, with H ₂ O), 4.52-4.61 (1H, m), 6.63-6.69 (1H, m), 6.79 (1H, dd, J = 2.6, 6.9 Hz), 6.84-6.86 (3H, m), 7.02 (1H, dd, J = 9.1, 9.1 Hz), 9.17 (1H, br), 9.29 (1H, br), 10.07 (1H, s).	盐酸盐
910	-H	-H	-F	-CH ₃	-H		¹ H-NMR (DMSO-d ₆)δppm : 1.56-1.69 (1H, m), 2.16-2.65 (1H, m), 2.63 (3H, d, J = 1.5 Hz), 2.78-2.89 (1H, m), 2.83 (2H, dd, J = 6.5, 6.5 Hz), 2.96 (3H, s), 3.07-3.19 (2H, m), 3.37-3.45 (2H, m, with H ₂ O), 3.56-3.66 (1H, m), 4.71-4.80 (1H, m), 6.41 (1H, d, J = 2.4 Hz), 6.47 (1H, dd, J = 2.4, 8.7 Hz), 7.07-7.12 (1H, m), 7.20 (1H, dd, J = 2.4, 7.0 Hz), 7.29 (1H, dd, J = 8.9, 9.2 Hz), 7.64 (1H, d, J = 8.7 Hz), 9.11 (1H, br), 9.19 (1H, br).	盐酸盐
911	-H	-H	-F	-Cl	-H		¹ H-NMR (DMSO-d ₆)δppm : 1.58-1.71 (1H, m), 2.15-2.22 (1H, m), 2.55 (2H, dd, J = 6.4, 8.3 Hz), 2.81-2.89 (1H, m), 2.86 (2H, dd, J = 6.4, 8.3 Hz), 3.12-3.17 (2H, m), 3.26 (3H, s), 3.55 (1H, dd, J = 6.9, 11.7 Hz), 4.60-4.70 (1H, m), 6.69 (1H, ddd, J = 3.0, 3.9, 9.1 Hz), 6.93 (1H, dd, J = 3.0, 6.3 Hz), 7.03-7.06 (2H, m), 7.15 (1H, d, J = 9.3 Hz), 7.27 (1H, dd, J = 9.1, 9.1 Hz), 9.17 (2H, br).	盐酸盐
912	-H	-H	-F	-Cl	-H		¹ H-NMR (DMSO-d ₆)δppm : 1.62-1.72 (1H, m), 2.17-2.27 (1H, m), 2.83-2.94 (1H, m), 3.12-3.19 (1H, m), 3.54-3.60 (1H, m), 3.63 (3H, s), 4.67-4.77 (1H, m), 6.66 (1H, d, J = 9.5 Hz), 6.74 (1H, ddd, J = 3.1, 3.8, 9.1 Hz), 6.99 (1H, dd, J = 3.1, 6.3 Hz), 7.29 (1H, dd, J = 9.1, 9.1 Hz), 7.37 (1H, dd, J = 2.6, 8.9 Hz), 7.56-7.60 (2H, m), 7.88 (1H, d, J = 9.5 Hz), 9.13 (1H, br), 9.21 (1H, br).	盐酸盐

[1276] 表 128

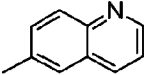
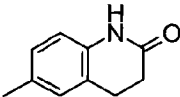
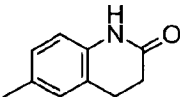
[1277]



[1278]

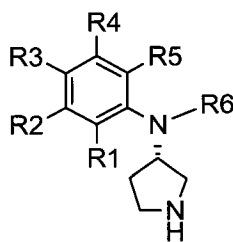
实施例	R1	R2	R3	R4	R5	R6	NMR	盐
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[1279]

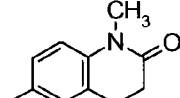
913	-H	-Cl	-F	-H	-H		¹ H-NMR (DMSO-d ₆)δppm; 1.65-1.82(1H, m), 2.19- 2.40(1H, m), 2.90-3.10(1H, m), 3.10-3.20(2H, m), 3.65- 3.80(1H, m), 4.80-4.90(1H, m), 7.30-7.45 (2H, m), 7.52(1H, d, J=2.5Hz), 7.55- 7.69 (2H, m), 7.88(1H, dd, J=8.4, 5.1Hz), 8.15(1H, d, J=9.4Hz), 8.83(1H, d, J=8.4Hz), 8.94(1H, d, J=4.1Hz), 9.45(1H, bs), 9.62(1H, bs)	2 盐酸盐
914	-H	-H	-F	-Cl	-H		¹ H-NMR (DMSO-d ₆)δppm : 1.56-1.70 (1H, m), 2.12-2.22 (1H, m), 2.46 (2H, dd, J = 7.1, 8.0 Hz), 2.80-2.90 (1H, m), 2.88 (2H, dd, J = 7.1, 8.0 Hz), 3.09-3.16 (2H, m), 3.50-3.60 (1H, m), 4.58-4.68 (1H, m), 6.61 (1H, ddd, J = 3.4, 3.5, 9.1 Hz), 6.86 (1H, dd, J = 2.9, 6.3 Hz), 6.91-7.00 (3H, m), 7.23 (1H, dd, J = 9.1, 9.1 Hz), 8.80 (2 H, br), 10.19 (1H, s).	2 三氟乙酸盐
915	-H	-H	-F	-H	-H		¹ H-NMR (DMSO-d ₆)δppm : 1.59-1.66 (1H, m), 2.10-2.20 (1H, m), 2.43 (2H, dd, J = 7.0, 8.1 Hz), 2.84 (2H, dd, J = 7.0, 8.1 Hz), 2.84-2.92 (1H, m), 3.11-3.21 (2H, m), 3.47- 3.55(1H, m), 4.54-4.64 (1H, m), 6.79-6.89 (5H, m), 7.09 (2H, dd, J = 8.8, 8.9 Hz), 8.71 (2H, br), 10.10 (1H, s).	2 三氟乙酸盐

[1280] 表 129

[1281]



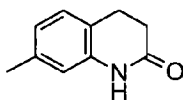
[1282]

实施例	R1	R2	R3	R4	R5	R6	NMR	盐
916	-H	-H	-F	-H	-H		¹ H-NMR (DMSO-d ₆)δppm : 1.60-1.71 (1H, m), 2.12-2.22 (1H, m), 2.49-2.54 (2H, m, with DMSO-d ₆), 2.82 (2H, dd, J = 7.4, 8.0), 2.84-2.91 (1H, m), 3.12-3.16 (2H, m), 3.23 (3H, s), 3.45-3.55 (1H, m), 4.56-4.65 (1H, m), 6.87- 6.95 (4H, m), 7.06 (1H, d, J = 9.4 Hz), 7.14 (2H, dd, J = 8.8,	盐酸盐

[1283]

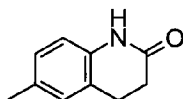
8.9 Hz), 8.67 (2H, br).

917 -H -H -F -H -H



¹H-NMR (DMSO-d₆)δppm :
 1.58-1.73 (1H, m), 2.10-2.31 (1H, m), 2.41 (2H, dd, J = 7.0, 8.0 Hz), 2.80 (2H, dd, J = 7.0, 8.0 Hz), 2.82-3.14 (1H, m), 3.14 (2H, br), 3.46-3.56 (1H, m), 4.54-4.62 (1H, m), 6.31 (1H, d, J = 2.2 Hz), 6.47 (1H, dd, J = 2.2, 8.1 Hz), 7.01-7.10 (3H, m), 7.21 (2H, dd, J = 8.7, 8.8 Hz), 8.83 (2H, br), 9.88 (1H, s).

盐酸盐

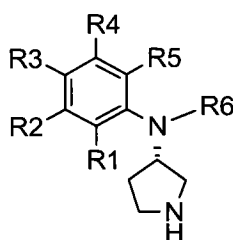
918 -H -F -CH₃ -H -H

¹H-NMR (DMSO-d₆)δppm :
 1.60-1.70 (1H, m), 2.10 (3H, s), 2.13-2.21 (1H, m), 2.43-2.48 (2H, m), 2.79-2.90 (1H, m), 2.87 (2H, dd, J = 7.1, 8.0 Hz), 3.11 (2H, br), 3.48-3.55 (1H, m), 4.56-4.66 (1H, m), 6.37 (1H, dd, J = 2.4, 8.4 Hz), 6.44 (1H, dd, J = 2.4, 13.0 Hz), 6.90-7.08 (4H, m), 9.22 (1H, br), 9.32 (1H, br), 10.19 (1H, s).

盐酸盐

[1284] 表 130

[1285]



[1286]

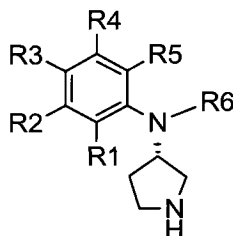
实施例	R1	R2	R3	R4	R5	R6	NMR	盐
919	-H	-CH ₃	-F	-H	-H		¹ H-NMR (DMSO-d ₆)δppm : 1.53-1.65 (1H, m), 2.14-2.21 (1H, m), 2.14 (3H, d, J = 1.6 Hz), 2.44-2.49 (2H, m, with DMSO-d ₆), 2.63-2.69 (2H, m), 2.85 (1H, dd, J = 7.8, 11.6 Hz), 3.13-3.17 (2H, m), 3.28 (3H, s), 3.59 (1H, dd, J = 6.9, 11.6 Hz), 4.57-4.67 (1H, m), 6.33-6.39 (1H, m), 6.51 (1H, dd, J = 3.1, 6.4 Hz), 6.91-6.97 (2H, m), 7.15 (1H, d, J = 8.1 Hz), 7.38 (1H, t, J = 8.1 Hz), 9.03 (2H, br).	盐酸盐
920	-H	-Cl	-F	-H	-H		¹ H-NMR (DMSO-d ₆)δppm : 1.58-1.71 (1H, m), 2.15-2.25 (1H, m), 2.82-2.92 (1H, m), 3.11-3.16 (2H, m), 3.37 (3H, s, with H ₂ O), 3.54-	2 盐酸盐

[1287]

3.60 (1H, m), 4.65-4.74 (1H, m),
6.54 (1H, d, J = 9.6 Hz), 6.64-6.69
(1H, m), 6.93 (1H, dd, J = 2.9, 6.3
Hz), 7.22-7.30 (2H, m), 7.37 (1H,
d, J = 8.7 Hz), 7.53 (1H, d, J = 2.2
Hz), 7.88 (1H, d, J = 9.6 Hz), 9.04
(1H, br), 9.13 (1H, br), 11.86 (1H,
s).

[1288] 表 131

[1289]

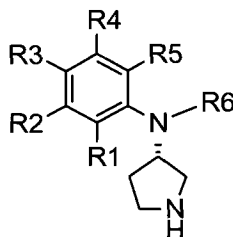


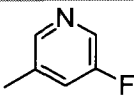
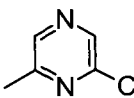
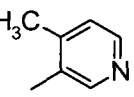
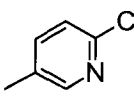
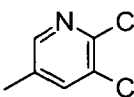
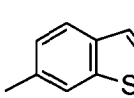
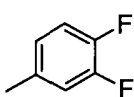
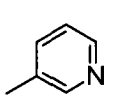
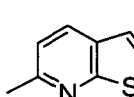
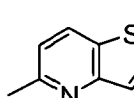
[1290]

实施例	R1	R2	R3	R4	R5	R6	NMR	盐
921	-H	-H	-F	-Cl	-H		¹ H-NMR (DMSO-d ₆)δppm : 1.18-1.35 (2H, m), 1.66-1.90 (3H, m), 1.95-2.12 (1H, m), 2.88-3.46 (7H, m), 3.83 (2H, dd, J = 3.2, 11.1 Hz), 4.18-4.36 (1H, brs), 7.11-7.30 (1H, m), 7.30-7.50 (2H, m), 9.25-9.65 (2H, br).	盐酸盐
922	-H	-H	-F	-Cl	-H		¹ H-NMR (DMSO-d ₆)δppm : 1.08-1.29 (2H, m), 1.45-1.70 (3H, m), 1.79-2.14 (2H, m), 2.85-3.40 (8H, m), 3.73-3.85 (2H, m), 4.28-4.46 (1H, m), 6.91-7.08 (1H, m), 7.11-7.35 (2H, m), 9.00-9.85 (2H, m).	盐酸盐
923	-H	-H	-Cl	-CH ₃	-H		¹ H-NMR (DMSO-d ₆)δppm : 1.57-1.75 (1H, m), 2.19--2.35 (1H, m), 2.37 (3H, s), 2.83-2.96 (1H, m), 3.00-3.19 (2H, m), 3.58-3.74 (1H, m), 4.80-4.95 (1H, m), 7.22 (1H, dd, J = 8.4, 2.4 Hz), 7.40 (1H, d, J = 2.4 Hz), 7.55-7.66 (2H, m), 7.77 (1H, dd, J = 8.9, 5.3 Hz), 8.17 (1H, J = 2.7 Hz), 8.24 (1H, d, J = 5.3 Hz), 9.62 (2H, br).	2 盐酸盐
924	-H	-H	-F	-Cl	-H		¹ H-NMR (DMSO-d ₆)δppm : 1.76-1.93 (6H, m), 2.07-2.09 (1H, m), 2.94 (1H, br), 3.10 (1H, br), 3.13 (2H, s), 3.34-3.71 (6H, m, with H ₂ O), 4.36-4.42 (1H, m), 7.02-7.07 (1H, m), 7.24-7.51 (5H, m), 7.77 (2H, br), 9.06 (1H, br), 9.40 (1H, br).	盐酸盐

[1291] 表 132

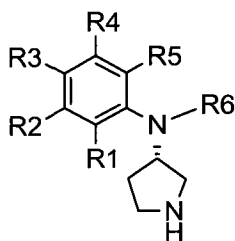
[1292]

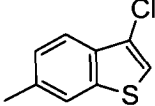
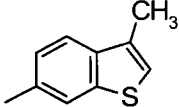
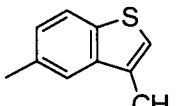
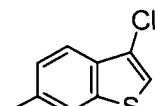


实施例	R1	R2	R3	R4	R5	R6	熔点 (°C)	盐
925	-H	-H	-F	-H	-H		195.5-198.5	2 盐酸盐
926	-H	-H	-Cl	-Cl	-H		102-105	盐酸盐
927	-H	-H	-Cl	-Cl	-H		119-122	2 盐酸盐
928	-H	-H	-Cl	-Cl	-H		123-124	2 盐酸盐
929	-H	-H	-Cl	-Cl	-H		191-193	盐酸盐
[1293] 930	-H	-H	-F	-Cl	-H		150-156	2 盐酸盐
931	-H	-F	-F	-H	-H		153-155	富马酸盐
932	-H	-Cl	-H	-Cl	-H		174.7-176.7	2 盐酸盐
933	-H	-H	-H	-H	-H		227-228.5	2 盐酸盐
934	-H	-H	-H	-H	-H		241.5-243.5	2 盐酸盐

[1294] 表 133

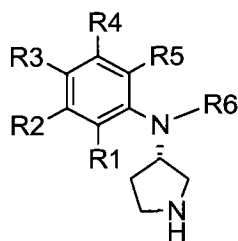
[1295]

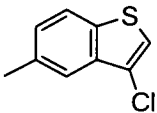
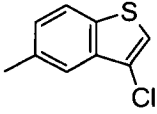
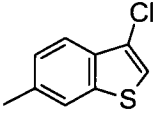


实施例	R1	R2	R3	R4	R5	R6	熔点 (°C)	盐
935	-H	-H	-F	-H	-H		133-135	富马酸盐
936	-H	-Cl	-Cl	-H	-H		134-136	富马酸盐
937	-H	-F	-F	-H	-H		138-141	富马酸盐
938	-H	-H	-Cl	-CH ₃	-H		110.3-111.9	富马酸盐
[1296] 939	-H	-Cl	-H	-Cl	-H		179.2-181.1	富马酸盐
940	-H	-H	-F	-Cl	-H		203.5-206	盐酸盐
941	-H	-H	-H	-H	-H		141-144	富马酸盐
942	-H	-H	-H	-H	-H		135-161	富马酸盐
943	-H	-H	-H	-H	-H		155-156	盐酸盐

[1297] 表 134

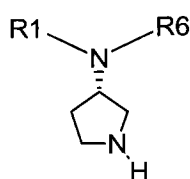
[1298]



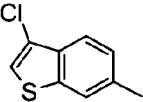
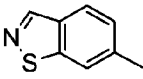
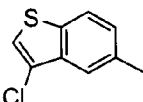
实施例	R1	R2	R3	R4	R5	R6	熔点 (°C)	盐
944	-H	-H	-H	-H	-H		160-180	盐酸盐
[1299]	945	-H	-H	-F	-H		155.5-164.5	盐酸盐
	946	-H	-H	-F	-H		161-167.5	盐酸盐

[1300] 表 135

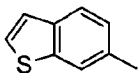
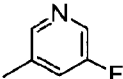
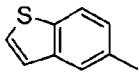
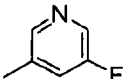
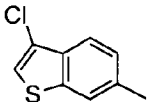
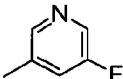
[1301]



[1302]

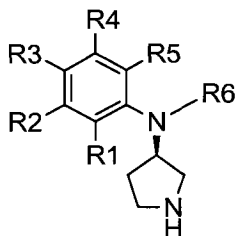
实施例	R1	R6	NMR	盐
947			¹ H-NMR (DMSO-d ₆)δppm : 1.6-1.8 (1H, m), 2.25-2.4 (1H, m), 2.85-3.0 (1H, m), 3.0-3.2 (2H, m), 3.25-4.45 (2H, m), 4.9-5.0 (1H, m), 7.45 (1H, dd, J = 1.8, 8.5Hz), 7.58 (1H, dd, J = 2.3, 8.8Hz), 7.72 (1H, dd, J = 5.3, 8.8Hz), 7.98 (1H, d, J = 8.5Hz), 8.08 (1H, s), 8.16 (1H, d, J = 1.6Hz), 8.22 (1H, d, J = 2.8Hz), 8.25 (1H, d, J = 5.0Hz), 9.45 (1H, br), 9.58 (1H, br).	2 盐酸盐
948			¹ H-NMR (DMSO-d ₆)δppm : 1.6-1.8 (1H, m), 2.25-2.4 (1H, m), 2.85-3.25 (3H, m), 3.6-3.8 (1H, m), 4.97 (1H, tt, J = 7.7, 7.7Hz), 7.32 (1H, dd, J = 1.7, 8.6Hz), 7.65-7.8 (2H, m), 8.16 (1H, s), 8.3-8.4 (3H, m), 9.17 (1H, d, J = 0.7Hz), 9.3-9.8 (2H, m).	2 盐酸盐
949			¹ H-NMR (DMSO-d ₆)δppm : 1.55-1.75 (1H, m), 2.25-2.4 (1H, m), 2.7-5.3 (1H, br), 2.85-3.0 (1H, m), 3.05-3.25 (2H, m), 3.65-3.8 (1H, m), 4.95 (1H, tt, J = 7.7, 7.7Hz), 7.45 (1H, dd, J = 1.9, 8.6Hz), 7.55-7.6 (1H, m), 7.74 (1H, dd, J = 5.3, 8.8Hz), 7.81 (1H, d, J = 1.8Hz), 8.09 (1H, s), 8.19 (1H, d, J = 2.8Hz), 8.23 (1H, d, J = 5.2Hz), 8.33 (1H, d, J = 8.6Hz), 9.44 (1, br), 9.62 (1H, br).	2 盐酸盐

[1303]

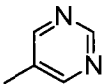
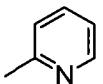
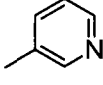
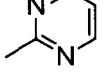
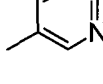
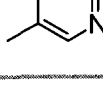
950			¹ H-NMR (DMSO-d ₆)δppm : 1.55-1.75 (1H, m), 2.2-2.35 (1H, m), 2.8-3.0 (1H, m), 3.0-3.25 (2H, m), 3.55-3.75 (1H, m), 4.35-5.5 (2H, m), 7.20 (1H, d, J = 12.2Hz), 7.28 (1H, dd, J = 1.8, 8.5Hz), 7.55 (1H, d, J = 5.4Hz), 7.7-7.8 (1H, m), 7.91 (1H, d, J = 5.4Hz), 8.0-8.1 (2H, m), 8.10 (1H, d, J = 2.2Hz), 9.32 (1H, br), 9.47 (1H, br).	2 盐酸盐
951			¹ H-NMR (DMSO-d ₆)δppm : 1.55-1.8 (1H, m), 2.2-2.35 (1H, m), 2.8-3.0 (1H, m), 3.0-3.2 (2H, m), 3.6-3.75 (1H, m), 4.3-5.0 (2H, m), 7.1-7.25 (1H, m), 7.27 (1H, dd, J = 2.0, 8.5Hz), 7.51 (1H, d, J = 5.5Hz), 7.76 (1H, d, J = 1.1Hz), 7.87 (1H, d, J = 1.9Hz), 7.91 (1H, d, J = 5.4Hz), 8.08 (1H, d, J = 2.2Hz), 8.20 (1H, d, J = 8.5Hz), 9.27 (1H, br), 9.43 (1H, br).	2 盐酸盐
952			¹ H-NMR (DMSO-d ₆)δppm : 1.6-1.75 (1H, m), 2.2-2.35 (1H, m), 2.85-3.0 (1H, m), 3.0-3.2 (2H, m), 3.6-3.75 (1H, m), 4.32 (1H, br), 4.85 (1H, tt, J = 7.7, 7.7Hz), 7.19 (1H, ddd, J = 2.4, 2.4, 12.0Hz), 7.37 (1H, dd, J = 1.9, 8.5Hz), 7.8-7.85 (1H, m), 7.92 (1H, d, J = 8.5Hz), 8.02 (1H, s), 8.05-8.15 (2H, m), 9.21 (1H, br), 9.33 (1H, br).	2 盐酸盐

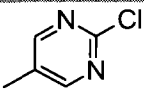
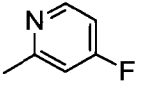
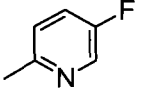
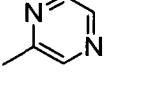
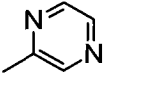
[1304] 表 136

[1305]



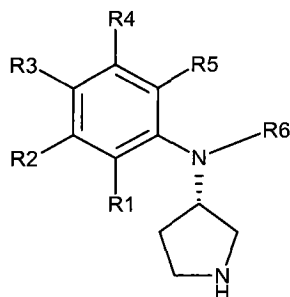
[1306]

实施例	R1	R2	R3	R4	R5	R6	熔点 (°C)	盐
953	-H	-H	-Cl	-Cl	-H		96-98	2 盐酸盐
954	-H	-H	-Cl	-Cl	-H		126-129	2 盐酸盐
955	-H	-H	-Cl	-Cl	-H		139-143	2 盐酸盐
956	-H	-H	-Cl	-Cl	-H		117-120	2 盐酸盐
957	-H	-H	-Cl	-Cl	-H		155-159	盐酸盐
958	-H	-H	-F	-Cl	-H		101-103	盐酸盐

[1307]	959	-H	-H	-F	-Cl	-H		157-160	盐酸盐
	960	-H	-H	-Cl	-Cl	-H		151-153	2 盐酸盐
	961	-H	-H	-Cl	-Cl	-H		96-98	盐酸盐
	962	-H	-H	-F	-Cl	-H		119-123	2 盐酸盐
	963	-H	-H	-Cl	-Cl	-H		120-124	2 盐酸盐

[1308] 表 137

[1309]



[1310]

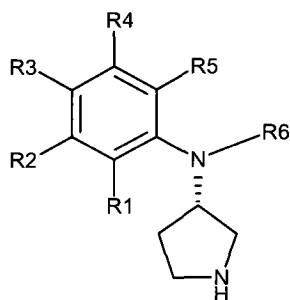
实施例	R1	R2	R3	R4	R5	R6	NMR	盐
964	-H	-Cl	-F	-H	-H	-(CH ₂) ₂ OCH(C ₆ H ₅) ₂	¹ H-NMR (CDCl ₃)δppm; 1.99-2.18 (2H, m), 3.13-3.34 (2H, m), 3.38-3.47 (7H, m), 4.23-4.35 (1H, m), 5.25 (1H, s), 6.71-6.78 (1H, m), 6.92-7.00 (2H, m), 7.18-7.33 (10H, m)	—
965	-H	-Cl	-F	-H	-H	-CH ₂ CO ₂ C ₂ H ₅	¹ H-NMR (DMSO-d ₆)δppm ; 1.15 (3H, t, J = 7.1 Hz), 2.05-2.36 (2H, m), 3.04-3.22 (1H, m), 3.22-3.72 (4H, m), 3.71-4.50 (3H, m), 5.34 (1H, brs), 7.52-7.69 (2H, m), 7.87-7.98 (1H, m), 9.10-9.70 (2H, m).	盐酸盐
966	-H	-Cl	-F	-H	-H	-(CH ₂) ₂ OH	¹ H-NMR (CDCl ₃)δppm; 1.25 (1H, s), 1.80-1.94 (1H, m), 2.04-2.19 (1H, m), 2.97-3.74 (9H, m), 4.05-4.14 (1H, m), 6.76 (1H, ddd, J = 8.9, 3.6, 2.9 Hz), 6.92 (1H, dd, J = 6.2, 2.9 Hz), 7.03 (1H, dd, J = 8.9, 8.8 Hz)	—
967	-H	-Cl	-F	-H	-H	-CH ₂ C(CH ₃) ₂ OH	¹ H-NMR (DMSO-d ₆)δppm ; 1.01 (3H, s), 1.04 (3H, s), 1.88-2.15 (2H, m), 3.03-3.22 (4H, m), 3.22-3.45 (2H, m), 3.45-3.55 (5H, m; including 1H, quint at 4.30), 7.01-7.10 (1H, m), 7.23 (1H, t, J = 9.1 Hz), 7.25-7.32 (1H, m).	草酸盐

[1311]

968	-H	-Cl	-F	-H	-H	-(CH ₂) ₂ OCH ₃	¹ H-NMR (DMSO-d ₆) δppm ; 1.82-2.00 (1H, m), 2.06-2.20 (1H, m), 2.90-3.19 (2H, m), 3.24 (3H, s), 3.26-3.50 (6H, m), 4.44 (1H, quint, J = 8.2 Hz), 6.89 (1H, td, J = 3.3, 9.1 Hz), 7.07 (1H, dd, J = 3.3, 9.1 Hz), 7.25 (1H, t, J = 9.1 Hz), 9.34 (1H, br), 9.52 (1H, br).	盐酸盐
969	-H	-Cl	-F	-H	-H	-CH ₂ CO ₂ H	¹ H-NMR (DMSO-d ₆) δppm ; 2.05-2.34 (2H, m), 2.80-4.40 (5H, m), 5.22 (1H, brs), 7.51-7.71 (2H, m), 7.89 (1H, dd, J = 1.8, 5.3 Hz), 7.15-7.65 (2H, br), 9.85-11.65 (2H, br).	盐酸盐
970	-H	-Cl	-F	-H	-H	-CH ₂ CONH ₂	¹ H-NMR (DMSO-d ₆) δppm ; 2.09-2.31 (2H, m), 2.63 (3H, d, J = 4.6 Hz), 3.05-3.25 (1H, m), 3.25-3.54 (3H, m), 3.54-3.79 (1H, m), 5.27 (1H, brs), 7.50-7.70 (2H, m), 7.80-7.97 (1H, m), 8.92 (1H, brs), 9.36-9.85 (2H, m), 9.80-11.10 (1H, br).	盐酸盐
971	-H	-Cl	-F	-H	-H	-CH ₂ CONHCH ₃		

[1312] 表 138

[1313]



[1314]

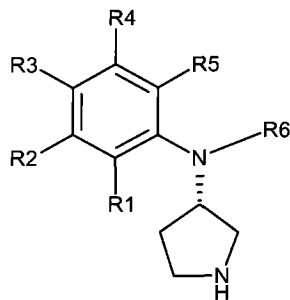
实施例	R1	R2	R3	R4	R5	R6	NMR	盐
972	-H	-Cl	-F	-H	-H	-CH ₂ CON(CH ₃) ₂	¹ H-NMR (DMSO-d ₆) δppm ; 2.07-2.40 (2H, m), 2.89 (3H, s), 2.90 (3H, s), 3.02-3.24 (1H, m), 3.24-3.83 (4H, m), 5.63 (1H, brs), 7.53-7.69 (2H, m), 7.83-7.93 (1H, m), 9.32-9.75 (2H, m), 9.82-10.50 (1H, m).	盐酸盐
973	-H	-Cl	-F	-H	-H	-CH ₂ CH=CH ₂	¹ H-NMR (DMSO-d ₆) δppm ; 1.76-1.95 (1H, m), 2.10-2.25 (1H, m), 2.85-3.02 (1H, m), 3.02-3.19 (1H, m), 3.25-3.50 (2H, m), 3.89 (2H, brs), 4.59 (1H, quint, J = 7.8 Hz), 5.05-5.20 (2H, m), 5.76-5.94 (1H, m), 6.69-6.82 (1H, m), 6.88-6.97 (1H, m), 7.23 (1H, t, J = 9.2 Hz), 8.90-9.95 (2H, br).	盐酸盐
974	-H	-Cl	-F	-H	-H	-(CH ₂) ₃ OH	¹ H-NMR (DMSO-d ₆) δppm ; 1.49-2.79 (2H, m), 1.81-2.04 (2H, m), 2.05-2.20 (1H, m), 2.82-3.20 (2H, m), 3.20-3.50 (6H, m), 4.33-4.52 (1H, m), 6.84-7.04 (1H, m), 7.04-7.21 (1H, m), 7.22-7.35 (1H, m), 9.15-9.75 (2H, m).	盐酸盐
975	-H	-Cl	-F	-H	-H	-(CH ₂) ₂ C(CH ₃) ₂ OH		

[1315]

976	-H	-Cl	-F	-H	-H	-(CH ₂) ₃ OCH ₃	¹ H-NMR (DMSO-d ₆)δppm; 1.55-1.72 (2H, m), 1.80-1.99 (1H, m), 2.04-2.20 (1H, m), 2.93 (1H, dd, J = 9.4, 11.6 Hz), 3.05-3.50 (10H, m), 4.40 (1H, quint, J = 7.9 Hz), 5.25-8.20 (6H, m; including 6.80-6.90 (1H, m), 7.00-7.10 (1H, m), and 7.26 (1H, t, J = 9.1Hz).	草酸盐
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[1316] 表 139

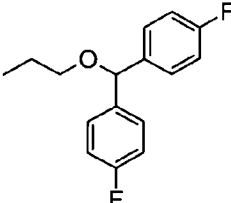
[1317]



[1318]

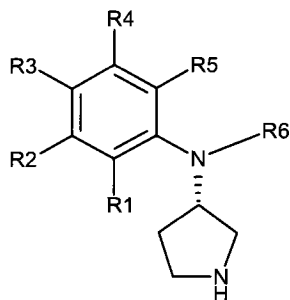
实施例	R1	R2	R3	R4	R5	R6	NMR	盐
977	-H	-Cl	-F	-H	-H		¹ H-NMR (CDCl ₃)δppm; 1.58-1.71 (1H, m), 2.03-2.18 (2H, m), 2.79 (1H, dd, J = 11.2, 4.3 Hz), 2.91 (1H, ddd, J = 11.2, 8.2, 6.2 Hz), 3.03-3.15 (2H, m), 4.25-4.35 (1H, m), 6.88-6.92 (1H, m), 6.97-7.15 (3H, m), 7.25 (1H, dd, J = 8.7, 8.7 Hz), 7.49 (1H, ddd, J = 8.7, 4.2, 2.6 Hz), 7.66 (1H, dd, J = 6.5, 2.6 Hz)	—
978	-H	-Cl	-F	-H	-H		¹ H-NMR (CDCl ₃)δppm; 1.59 (1H, s), 1.66-1.81 (1H, m), 2.00-2.16 (1H, m), 2.83-2.93 (3H, m), 3.12 (1H, dd, J = 11.5, 6.6 Hz), 3.22 (1H, t, J = 8.7 Hz), 4.20-4.31 (1H, m), 4.62 (1H, t, J = 8.7 Hz), 6.44 (1H, ddd, J = 9.1, 3.6, 3.0 Hz), 6.62 (1H, dd, J = 6.2, 3.0 Hz), 6.75-6.85 (2H, m), 6.86-6.94 (2H, m)	—
979	-H	-Cl	-F	-H	-H			
980	-H	-Cl	-F	-H	-H		¹ H-NMR (CDCl ₃)δppm; 1.64-1.84 (2H, m), 2.07-2.19 (1H, m), 2.87-3.02 (3H, m), 3.21 (1H, dd, J = 11.5, 6.7 Hz), 4.34-4.44 (1H, m), 6.81 (1H, ddd, J = 8.9, 4.1, 2.8 Hz), 6.90-6.95 (2H, m), 7.00 (1H, dd, J = 6.5, 2.8 Hz), 7.07 (1H, dd, J = 8.9, 8.7 Hz), 7.30-7.34 (1H, m), 7.39-7.45 (2H, m), 7.49-7.61 (4H, m)	草酸盐
981	-H	-Cl	-F	-H	-H		¹ H-NMR (CDCl ₃)δppm; 1.66-1.82 (1H, m), 1.98-2.12 (1H, m), 2.83-3.20 (5H, m), 3.40-3.52 (4H, m), 4.02-4.15 (1H, m), 5.23 (1H, s), 6.67 (1H, ddd, J = 8.9, 3.6, 3.0 Hz), 6.89 (1H, dd, J = 6.2, 3.0 Hz), 6.96 (1H, dd, J = 8.9, 8.8 Hz), 7.16-7.21 (4H, m), 7.25-7.32 (4H, m)	—

[1319]

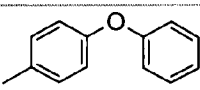
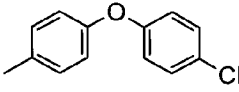
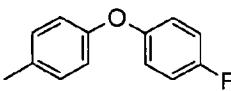
982	-H	-Cl	-F	-H	-H		¹ H-NMR (CDCl ₃)δppm; 1.67-1.82 (1H, m), 1.98-2.13 (1H, m), 2.83-3.20 (4H, m), 3.24 (1H, br), 3.40-3.52 (4H, m), 4.03-4.15 (1H, m), 5.26 (1H, s), 6.67 (1H, ddd, J = 9.0, 3.6, 3.0 Hz), 6.89 (1H, dd, J = 6.2, 3.0 Hz), 6.91-7.05 (5H, m), 7.20-7.29 (4H, m)	—
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[1320] 表 140

[1321]

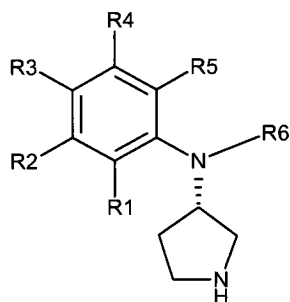


[1322]

实施例	R1	R2	R3	R4	R5	R6	NMR	盐
983	-H	-Cl	-F	-H	-H		¹ H-NMR (CDCl ₃)δppm; 1.68-1.82 (2H, m), 2.03-2.17 (1H, m), 2.83-2.95 (3H, m), 3.16 (1H, dd, J = 11.6, 6.7 Hz), 4.25-4.35 (1H, m), 6.58 (1H, ddd, J = 9.0, 3.9, 2.9 Hz), 6.78 (1H, dd, J = 6.3, 2.9 Hz), 6.94-7.06 (7H, m), 7.09-7.16 (1H, m), 7.32-7.40 (2H, m)	草酸盐
984	-H	-Cl	-F	-H	-H		¹ H-NMR (CDCl ₃)δppm; 1.67-1.90 (2H, m), 2.04-2.18 (1H, m), 2.80-3.01 (3H, m), 3.05-3.30 (1H, m), 4.20-4.44 (1H, m), 6.58-6.69 (1H, m), 6.78-6.82 (1H, m), 6.84-7.00 (7H, m), 7.27-7.34 (2H, m)	—
985	-H	-Cl	-F	-H	-H		¹ H-NMR (CDCl ₃)δppm; 1.66-1.80 (2H, m), 2.02-2.17 (1H, m), 2.80-2.95 (3H, m), 3.03-3.26 (1H, m), 4.24-4.37 (1H, m), 6.54-6.62 (1H, m), 6.74-6.81 (1H, m), 6.83-7.10 (9H, m)	—

[1323] 表 141

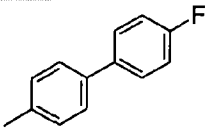
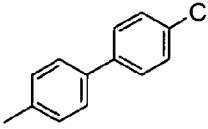
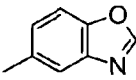
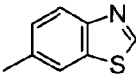
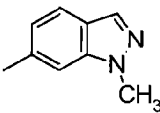
[1324]



[1325]

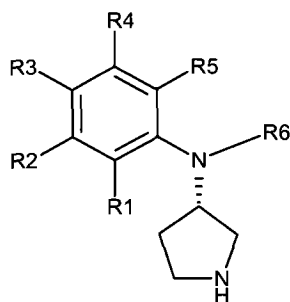
实施例	R1	R2	R3	R4	R5	R6	NMR	盐
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[1326]

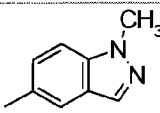
986	-H	-Cl	-F	-H	-H		¹ H-NMR (CDCl ₃)δppm; 1.70-1.84 (2H, m), 2.06-2.20 (1H, m), 2.86-2.98 (3H, m), 3.18-3.26 (1H, m), 4.33-4.45 (1H, m), 6.78-6.85 (1H, m), 6.87-6.94 (2H, m), 6.98-7.02 (1H, m), 7.04-7.16 (3H, m), 7.43-7.55 (4H, m)	—
987	-H	-Cl	-F	-H	-H		¹ H-NMR (CDCl ₃)δppm; 1.68 (1H, s), 1.69-1.83 (1H, m), 2.04-2.20 (1H, m), 2.75-2.97 (3H, m), 3.22 (1H, dd, J = 11.5, 6.8 Hz), 4.34-4.45 (1H, m), 6.84 (1H, ddd, J = 8.8, 4.1, 2.7 Hz), 6.85-6.92 (2H, m), 7.03 (1H, dd, J = 6.5, 2.7 Hz), 7.10 (1H, dd, J = 8.8, 8.7 Hz), 7.34-7.41 (2H, m), 7.43-7.52 (4H, m)	—
988	-H	-Cl	-F	-H	-H			2 三氟乙酸盐
989	-H	-Cl	-F	-H	-H		¹ H-NMR (CDCl ₃)δppm; 1.85-2.1 (1H, m), 2.15-2.35 (1H, m), 2.35-2.95 (1H, m), 3.14 (1H, br), 3.33 (2H, br), 3.59 (1H, br), 4.55-4.8 (1H, m), 6.8-6.95 (1H, m), 7.01 (1H, dd, J = 2.7, 6.3Hz), 7.05-7.2 (2H, m), 7.55 (1H, d, J = 2.0Hz), 8.06 (1H, d, J = 8.8Hz), 8.97 (1H, s), 9.86 (2H, br).	2 三氟乙酸盐
990	-H	-Cl	-F	-H	-H		¹ H-NMR (DMSO-d ₆)δppm ; 1.6-1.8 (1H, m), 2.15-2.3 (1H, m), 2.85-3.0 (1H, m), 3.05-3.25 (2H, m), 3.55-3.7 (1H, m), 4.03 (3H, s), 4.76 (1H, tt, J = 7.2, 7.2Hz), 5.28 (1H, br), 6.8-6.9 (1H, br), 6.8-6.9 (1H, m), 7.08 (1H, dd, J = 2.9, 6.4Hz), 7.32 (1H, dd, J = 9.0, 9.0Hz), 7.44 (1H, s), 7.71 (1H, d, J = 8.6Hz), 8.01 (1H, s), 9.36 (1H, br), 9.52 (1H, br).	2 盐酸盐

[1327] 表 142

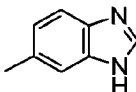
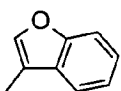
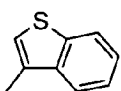
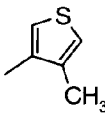
[1328]



[1329]

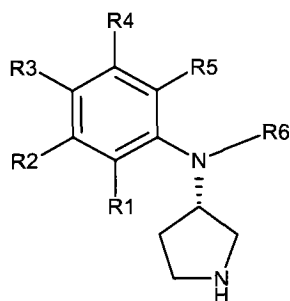
实施例	R1	R2	R3	R4	R5	R6	NMR	盐
991	-H	-Cl	-F	-H	-H		¹ H-NMR (DMSO-d ₆)δppm ; 1.5-1.75 (1H, m), 2.1-2.3 (1H, m), 2.75-2.95 (1H, m), 2.95-3.25 (2H, m), 3.45-3.65 (1H, m), 3.65-4.35 (4H, m), 4.72 (1H, tt, J = 7.2, 7.2Hz), 6.59 (1H, ddd, J = 3.5, 3.5,	盐酸盐

[1330]

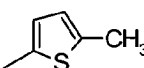
						9.1Hz), 6.79 (1H, dd, J = 3.0, 6.3Hz), 7.1-7.25 (2H, m), 7.67 (1H, d, J = 1.5Hz), 7.75 (1H, d, J = 8.8Hz), 8.08 (1H, d, J = 0.4Hz), 9.31 (1H, br), 9.42 (1H, br).		
992	-H	-Cl	-F	-H	-H			
993	-H	-Cl	-F	-H	-H			
994	-H	-Cl	-F	-H	-H		¹ H-NMR (CDCl ₃)δppm; 1.85-2.05 (1H, m), 2.2-2.35 (1H, m), 3.1-3.25 (1H, m), 3.25-3.4 (2H, m), 3.55-3.7 (1H, m), 4.79 (1H, tt, J = 6.8, 6.8Hz), 6.60 (1H, ddd, J = 3.4, 3.4, 9.0Hz), 6.76 (1H, dd, J = 3.0, 6.0Hz), 6.95 (1H, dd, J = 8.8, 8.8Hz), 7.25-7.45 (4H, m), 7.85 (1H, dd, J = 1.2, 7.6Hz), 9.07 (1H, br), 9.24 (1H, br), 10.44 (1H, br).	2 三氟乙酸盐
995	-H	-Cl	-F	-H	-H		¹ H-NMR (CDCl ₃)δppm; 1.8-2.05 (4H, m), 2.15-2.35 (1H, m), 3.0-3.2 (1H, m), 3.25-3.45 (2H, m), 3.5-3.7 (1H, m), 4.64 (1H, tt, J = 6.8, 6.8Hz), 6.46 (1H, ddd, J = 3.4, 3.4, 9.1Hz), 6.60 (1H, dd, J = 3.0, 6.1Hz), 6.96 (1H, dd, J = 8.8, 8.8Hz), 7.05-7.15 (2H, m), 8.85-9.65 (2H, m), 10.42 (1H, br).	2 三氟乙酸盐

[1331] 表 143

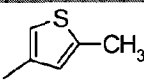
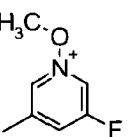
[1332]



[1333]

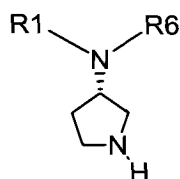
实施例	R1	R2	R3	R4	R5	R6	NMR	盐
996	-H	-Cl	-F	-H	-H			
997	-H	-Cl	-F	-H	-H		¹ H-NMR (CDCl ₃)δppm; 2.05-2.2 (1H, m), 2.2-2.35 (1H, m), 2.44 (3H, d, J = 1.0Hz), 3.15-3.45 (3H, m), 3.5-3.7 (1H, m), 4.59 (1H, tt, J = 6.6, 6.6Hz), 6.55-6.65 (2H, m), 6.69 (1H, ddd, J = 3.4, 9.0Hz), 6.84 (1H, dd, J = 3.0, 6.1Hz), 7.00 (1H, dd, J = 8.7, 8.7Hz), 9.14 (2H, br), 9.52 (1H, br).	2 三氟乙酸盐

[1334]

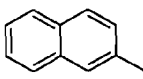
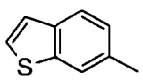
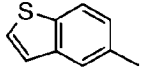
998	-H	-Cl	-F	-H	-H		¹ H-NMR (DMSO-d ₆)δppm ; 1.6-1.75 (1H, 富马酸盐 m), 2.05-2.2 (1H, m), 2.39 (3H, d, J = 0.7Hz), 2.86 (1H, dd, J = 7.4, 11.5Hz), 2.95-3.15 (2H, m), 3.50 (1H, dd, J = 7.0, 11.5Hz), 3.65-6.1 (4H, m), 6.46 (2H, s), 6.50 (1H, s), 6.7-6.85 (1H, m), 6.9-7.0 (2H, m), 7.27 (1H, dd, J = 9.1, 9.1Hz).	
999	-H	-Cl	-F	-H	-H			2 三氟乙酸盐

[1335] 表 144

[1336]

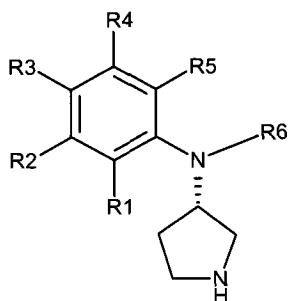


[1337]

实施例	R1	R6	NMR	盐
1000			¹ H-NMR (DMSO-d ₆)δppm ; 1.7-1.85 (1H, m), 2.15-2.3 (1H, 富马酸盐 m), 2.9-3.2 (3H, m), 3.63 (1H, dd, J = 7.0, 11.5Hz), 4.73 (1H, tt, J = 7.3, 7.3Hz), 6.47 (2H, s), 6.82 (1H, dd, J = 1.4, 5.1Hz), 6.95 (1H, dd, J = 2.4, 9.0Hz), 7.26 (1H, dd, J = 1.4, 3.1Hz), 7.25-7.35 (2H, m), 7.35-7.45 (1H, m), 7.59 (1H, dd, J = 3.1, 5.1Hz), 7.7-7.8 (3H, m), 10.3 (3H, br).	富马酸盐
1001			¹ H-NMR (DMSO-d ₆)δppm ; 1.6-1.9 (1H, m), 2.0-2.35 (1H, 富马酸盐 m), 2.65-5.55 (8H, m), 6.48 (2H, s), 6.68 (1H, dd, J = 1.4, 5.1Hz), 6.92 (1H, dd, J = 2.1, 8.6Hz), 7.04 (1H, dd, J = 1.4, 3.0Hz), 7.35 (1H, d, J = 5.5Hz), 7.50 (1H, dd, J = 3.1, 5.1Hz), 7.55-7.65 (2H, m), 7.75 (1H, d, J = 8.6Hz).	富马酸盐
1002			¹ H-NMR (DMSO-d ₆)δppm ; 1.55-1.9 (1H, m), 2.0-2.25 (1H, 富马酸盐 m), 2.3-5.45 (8H, m), 6.48 (2H, s), 6.59 (1H, dd, J = 1.4, 5.1Hz), 6.92 (1H, dd, J = 1.4, 3.0Hz), 6.99 (1H, dd, J = 2.2, 8.7Hz), 7.38 (1H, d, J = 5.4Hz), 7.45 (1H, dd, J = 3.1, 5.1Hz), 7.54 (1H, d, J = 2.1Hz), 7.75 (1H, d, J = 5.4Hz), 7.91 (1H, d, J = 8.6Hz).	富马酸盐

[1338] 表 145

[1339]



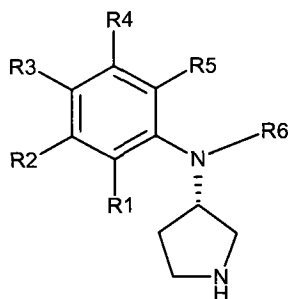
[1340]	实施例	R1	R2	R3	R4	R5	R6	MS(M+1)
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[1341]

1003	-H	-Cl	-F	-H	-H	-(CH ₂) ₂ CO ₂ CH ₃	
1004	-H	-Cl	-F	-H	-H	-(CH ₂) ₂ CO ₂ C ₂ H ₅	
1005	-H	-Cl	-F	-H	-H	-(CH ₂) ₂ CO ₂ CH ₂ C ₆ H ₅	
1006	-H	-Cl	-F	-H	-H	-(CH ₂) ₂ CON(CH ₃) ₂	314
1007	-H	-Cl	-F	-H	-H	-(CH ₂) ₂ COCH ₃	
1008	-H	-Cl	-F	-H	-H	-(CH ₂) ₂ COC ₂ H ₅	
1009	-H	-Cl	-F	-H	-H	-(CH ₂) ₂ COC ₆ H ₅	
1010	-H	-Cl	-F	-H	-H	-(CH ₂) ₂ CH(OH)CH ₃	
1011	-H	-Cl	-F	-H	-H	-(CH ₂) ₂ CH(OH)C ₂ H ₅	
1012	-H	-Cl	-F	-H	-H	-(CH ₂) ₂ CH(OH)C ₆ H ₅	
1013	-H	-Cl	-F	-H	-H	-(CH ₂) ₂ CH(OH)(CH ₃) ₂	
1014	-H	-Cl	-F	-H	-H	-(CH ₂) ₃ SC ₆ H ₅	365
1015	-H	-Cl	-F	-H	-H	-(CH ₂) ₃ S(CH ₂) ₂ N(C ₂ H ₅) ₂	
1016	-H	-Cl	-F	-H	-H	-(CH ₂) ₃ S(CH ₂) ₂ CH ₃	331
1017	-H	-Cl	-F	-H	-H	-(CH ₂) ₃ SCH ₂ C ₆ H ₅	379
1018	-H	-Cl	-F	-H	-H	-(CH ₂) ₃ S(CH ₂) ₂ C ₆ H ₅	393
1019	-H	-Cl	-F	-H	-H	-(CH ₂) ₃ S(CH ₂) ₂ NH ₂	
1020	-H	-Cl	-F	-H	-H	-(CH ₂) ₃ SC ₂ H ₅	
1021	-H	-Cl	-F	-H	-H	-(CH ₂) ₃ S(CH ₂) ₂ OH	333
1022	-H	-Cl	-F	-H	-H	-(CH ₂) ₃ S(CH ₂) ₂ CO ₂ CH ₃	375
1023	-H	-Cl	-F	-H	-H	-(CH ₂) ₃ SCH ₂ CO ₂ CH ₃	361
1024	-H	-Cl	-F	-H	-H	-(CH ₂) ₃ S-cyclo-C ₃ H ₉	357
1025	-H	-Cl	-F	-H	-H	-(CH ₂) ₃ S-cyclo-C ₆ H ₁₁	371
1026	-H	-Cl	-F	-H	-H	-(CH ₂) ₃ S(CH ₂) ₃ C ₆ H ₅	407
1027	-H	-Cl	-F	-H	-H	-(CH ₂) ₃ S(CH ₂) ₂ OC ₆ H ₅	409

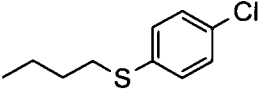
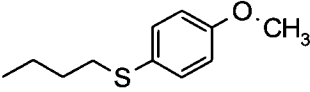
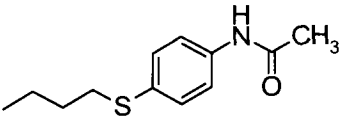
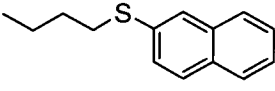
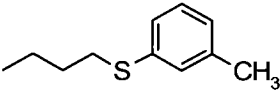
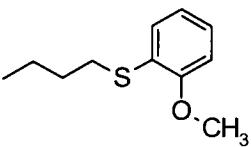
[1342] 表 146

[1343]



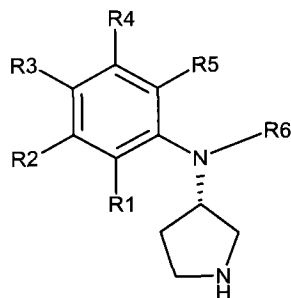
[1344]

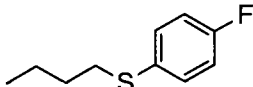
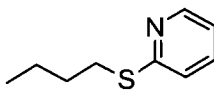
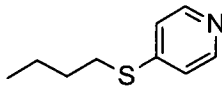
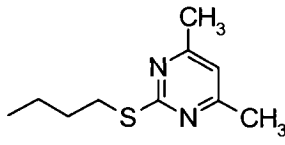
实施例	R1	R2	R3	R4	R5	R6	MS(M+1)
1028	-H	-Cl	-F	-H	-H		
1029	-H	-Cl	-F	-H	-H		380
1030	-H	-Cl	-F	-H	-H		379
1031	-H	-Cl	-F	-H	-H		399

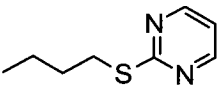
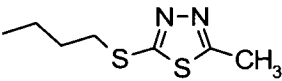
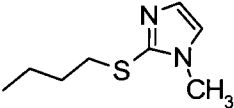
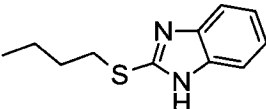
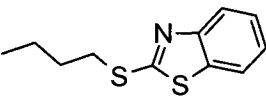
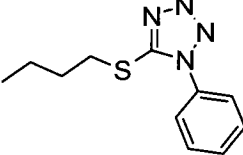
[1345]	1032	-H	-Cl	-F	-H	-H		
	1033	-H	-Cl	-F	-H	-H		
	1034	-H	-Cl	-F	-H	-H		422
	1035	-H	-Cl	-F	-H	-H		
	1036	-H	-Cl	-F	-H	-H		
	1037	-H	-Cl	-F	-H	-H		395

[1346] 表 147

[1347]

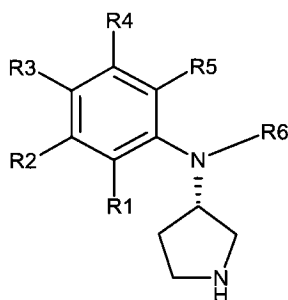


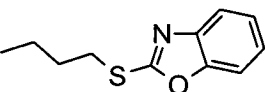
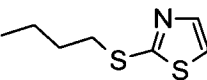
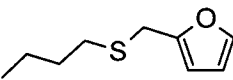
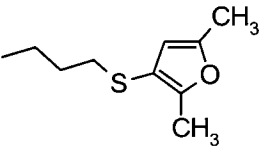
实施例	R1	R2	R3	R4	R5	R6	MS(M+1)
1038	-H	-Cl	-F	-H	-H		
1039	-H	-Cl	-F	-H	-H		366
1040	-H	-Cl	-F	-H	-H		366
1041	-H	-Cl	-F	-H	-H		395

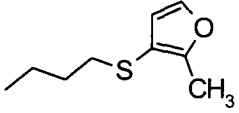
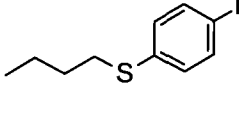
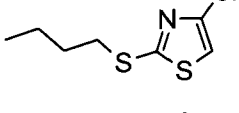
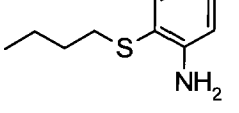
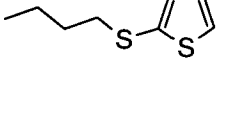
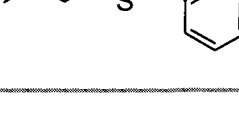
[1349]	1042	-H	-Cl	-F	-H	-H		367
	1043	-H	-Cl	-F	-H	-H		387
	1044	-H	-Cl	-F	-H	-H		369
	1045	-H	-Cl	-F	-H	-H		405
	1046	-H	-Cl	-F	-H	-H		422
	1047	-H	-Cl	-F	-H	-H		433

[1350] 表 148

[1351]

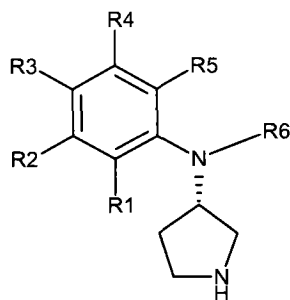


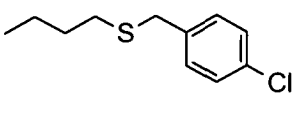
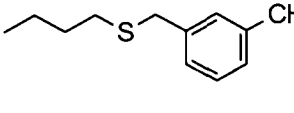
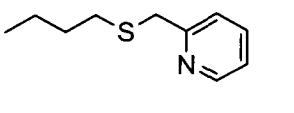
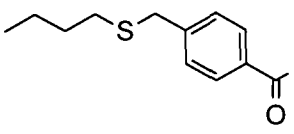
实施例	R1	R2	R3	R4	R5	R6	MS(M+1)
1048	-H	-Cl	-F	-H	-H		406
1049	-H	-Cl	-F	-H	-H		
[1352]							
1050	-H	-Cl	-F	-H	-H		369
1051	-H	-Cl	-F	-H	-H		

	1052	-H	-Cl	-F	-H	-H		369
	1053	-H	-Cl	-F	-H	-H		
	1054	-H	-Cl	-F	-H	-H		386
[1353]	1055	-H	-Cl	-F	-H	-H		
	1056	-H	-Cl	-F	-H	-H		371
	1057	-H	-Cl	-F	-H	-H		409

[1354] 表 149

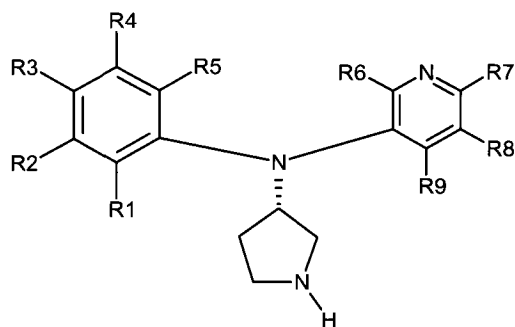
[1355]



实施例	R1	R2	R3	R4	R5	R6	MS(M+1)
1058	-H	-Cl	-F	-H	-H		413
1059	-H	-Cl	-F	-H	-H		393
[1356]							
1060	-H	-Cl	-F	-H	-H		
1061	-H	-Cl	-F	-H	-H		

[1357] 表 150

[1358]

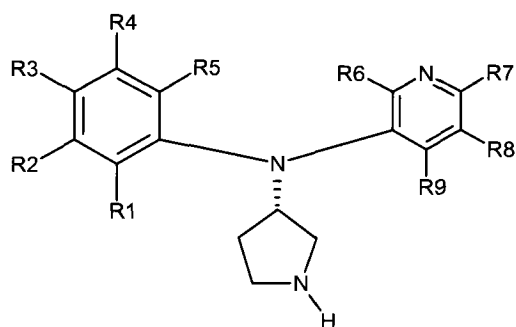


[1359]

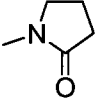
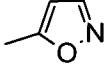
实施例	R1	R2	R3	R4	R5	R6	R7	R8	R9	MS(M+1)
1062	-H	-H	-CF ₃	-H	-H	-H	-H	-F	-H	326
1063	-H	-H	-N(CH ₃) ₂	-H	-H	-H	-H	-F	-H	301
1064	-H	-OCH ₃	-H	-H	-H	-H	-H	-F	-H	288
1065	-H	-OC ₂ H ₅	-H	-H	-H	-H	-H	-F	-H	302
1066	-H	-SCH ₃	-H	-H	-H	-H	-H	-F	-H	304
1067	-H	-CF ₃	-Cl	-H	-H	-H	-H	-F	-H	360
1068	-H	-H	-CH ₃	-H	-H	-H	-H	-F	-H	272
1069	-Cl	-Cl	-H	-H	-H	-H	-H	-F	-H	
1070	-H	-H	-SCH ₃	-H	-H	-H	-H	-F	-H	304
1071	-H	-H	-CH(CH ₃) ₂	-H	-H	-H	-H	-F	-H	300
1072	-H	-H	-OC ₆ H ₅	-H	-H	-H	-H	-F	-H	350
1073	-H	-H	-C ₂ H ₅	-H	-H	-H	-H	-F	-H	286
1074	-H	-CF ₃	-F	-H	-H	-H	-H	-F	-H	344
1075	-F	-CF ₃	-H	-H	-H	-H	-H	-F	-H	
1076	-Cl	-H	-H	-H	-H	-H	-H	-F	-H	292
1077	-H	-H	-OCH ₃	-H	-H	-H	-H	-F	-H	288
1078	-CH ₃	-CH ₃	-H	-H	-H	-H	-H	-F	-H	286
1079	-C ₂ H ₅	-H	-H	-H	-H	-H	-H	-F	-H	286
1080	-H	-Cl	-Cl	-H	-H	-H	-H	-F	-H	326
1081	-H	-F	-F	-H	-H	-H	-H	-F	-H	294
1082	-H	-F	-H	-F	-H	-H	-H	-F	-H	294
1083	-H	-H	-CF ₃	-F	-H	-H	-H	-F	-H	344
1084	-CF ₃	-F	-H	-H	-H	-H	-H	-F	-H	
1085	-F	-H	-CF ₃	-H	-H	-H	-H	-F	-H	344
1086	-H	-CF ₃	-H	-F	-H	-H	-H	-F	-H	344
1087	-H	-CF ₃	-CH ₃	-H	-H	-H	-H	-F	-H	340
1088	-H	-CF ₃	-OCH ₃	-H	-H	-H	-H	-F	-H	356
1089	-H	-CH ₃	-N(CH ₃) ₂	-CH ₃	-H	-H	-H	-F	-H	329
1090	-H	-CH(CH ₃) ₂	-H	-H	-H	-H	-H	-F	-H	300
1091	-H	-F	-Br	-H	-H	-H	-H	-F	-H	
1092	-H	-F	-H	-Cl	-H	-H	-H	-F	-H	310
1093	-H	-CH ₃	-OCH ₃	-CH ₃	-H	-H	-H	-F	-H	316
1094	-H	-CH ₃	-H	-CH ₃	-H	-H	-H	-F	-H	286

[1360] 表 151

[1361]

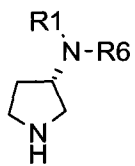


[1362]

实施例	R1	R2	R3	R4	R5	R6	R7	R8	R9	MS(M+1)
1095	-H	-F	-CH ₃	-H	-H	-H	-H	-F	-H	290
1096	-H	-F	-Cl	-H	-H	-H	-H	-F	-H	310
1097	-H	-F	-F	-H	-F	-H	-H	-F	-H	
1098	-F	-H	-F	-H	-H	-H	-H	-F	-H	
1099	-H	-F	-H	-H	-F	-H	-H	-F	-H	294
1100	-H	-F	-H	-H	-H	-H	-H	-F	-H	276
1101	-H	-Cl	-CH ₃	-H	-H	-H	-H	-F	-H	306
1102	-H	-F	-F	-F	-H	-H	-H	-F	-H	312
1103	-F	-F	-H	-H	-H	-H	-H	-F	-H	294
1104	-H	-F	-OCH ₃	-H	-H	-H	-H	-F	-H	306
1105	-H	-CH ₃	-Cl	-H	-H	-H	-H	-F	-H	306
1106	-H	-H	-C ₃ H ₇	-H	-H	-H	-H	-F	-H	300
1107	-H	-C ₂ H ₅	-H	-H	-H	-H	-H	-F	-H	
1108	-H	-OCH ₃	-OCH ₃	-H	-H	-H	-H	-F	-H	318
1109	-H	-Cl	-H	-H	-H	-H	-H	-F	-H	292
1110	-H	-CH ₃	-CH ₃	-H	-H	-H	-H	-F	-H	286
1111	-H	-CH ₃	-OCH ₃	-H	-H	-H	-H	-F	-H	302
1112	-H	-CH ₃	-F	-CH ₃	-H	-H	-H	-F	-H	304
1113	-H	-H	-Cl	-H	-H	-H	-H	-F	-H	292
1114	-H	-H	-H	-H	-H	-H	-H	-F	-H	258
1115	-H	-H	-F	-H	-H	-H	-H	-F	-H	276
1116	-H	-H		-H	-H	-H	-H	-F	-H	341
1117	-H	-H		-H	-H	-H	-H	-F	-H	325
1118	-H		-H	-H	-H	-H	-H	-F	-H	

[1363] 表 152

[1364]

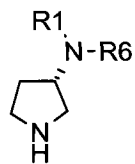


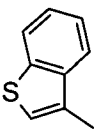
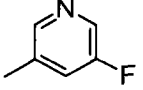
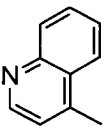
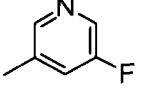
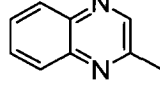
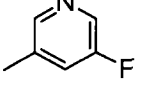
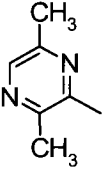
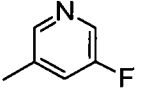
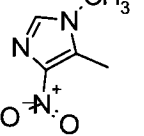
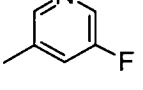
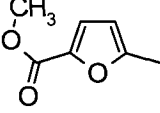
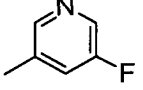
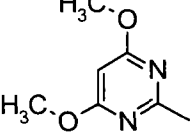
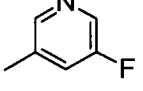
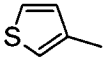
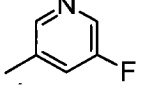
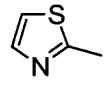
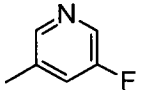
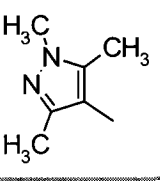
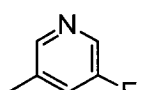
实施例	R1	R6	MS(M+1)
1119			293
1120			259
1121			260
1122			309
1123			309
1124			
1125			260
1126			323
1127			309
1128			

[1365]

[1366] 表 153

[1367]

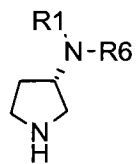


实施例	R1	R6	MS(M+1)
1129			314
1130			309
1131			310
1132			288
1133			
1134			
1135			320
1136			264
1137			265
1138			

[1368]

[1369] 表 154

[1370]

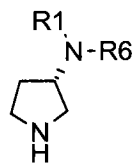


实施例	R1	R6	MS(M+1)
1139			
1140			288
1141			323
1142			377
1143			315
1144			323
1145			
1146			339
1147			377
1148			

[1371]

[1372] 表 155

[1373]

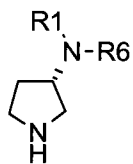


实施例	R1	R6	MS(M+1)
1149			
1150			314
1151			316
1152			308
1153			329
1154			308
1155			302
1156			330
1157			309
1158			310

[1374]

[1375] 表 156

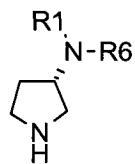
[1376]



实施例	R1	R6	MS(M+1)
1159			329
1160			302
1161			300
1162			323
1163			338
[1377] 1164			341
1165			326
1166			346
1167			314
1168			298

[1378] 表 157

[1379]

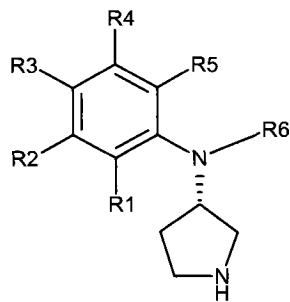


[1380]

实施例	R1	R6	MS(M+1)
1169			315
1170			339
1171			353
1172			
1173			298

[1381] 表 158

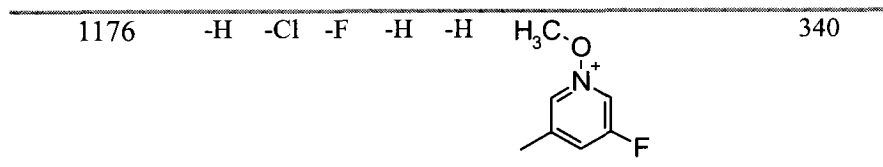
[1382]



[1383]

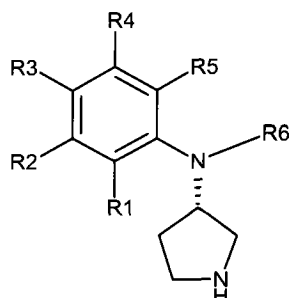
实施例	R1	R2	R3	R4	R5	R6	MS(M+1)
1174	-H	-Cl	-F	-H	-H		344
1175	-H	-Cl	-F	-H	-H		332

[1384]



[1385] 表 159

[1386]



[1387]

实施例	R1	R2	R3	R4	R5	R6	NMR	盐
1177	-H	-H	-F	-Cl	-H		$^1\text{H-NMR}$ (DMSO- d_6) δ ppm: 1.55-1.75 (1H, m), 2.1-2.25 (1H, m), 2.8-2.95 (1H, m), 3.0-3.25 (2H, m), 3.5-3.65 (1H, m), 4.19 (3H, s), 4.64 (1H, tt, $J = 7.3, 7.3\text{Hz}$), 5.01 (1H, br), 6.60 (1H, ddd, $J = 3.5, 3.5, 9.1\text{Hz}$), 6.81 (1H, dd, $J = 3.0, 6.3\text{Hz}$), 6.96 (1H, dd, $J = 2.0, 9.0\text{Hz}$), 7.22 (1H, dd, $J = 9.1, 9.1\text{Hz}$), 7.61 (1H, d, $J = 1.5\text{Hz}$), 7.68 (1H, d, $J = 9.0\text{Hz}$), 8.39 (1H, s), 9.28 (1H, br), 9.39 (1H, br).	2 盐酸盐
1178	-H	-H	-F	-Cl	-H		$^1\text{H-NMR}$ (DMSO- d_6) δ ppm: 1.6-1.75 (1H, m), 2.1-2.3 (1H, m), 2.8-3.0 (1H, m), 3.05-3.25 (2H, m), 3.5-3.65 (1H, m), 4.18 (3H, s), 4.72 (1H, tt, $J = 7.3, 7.3\text{Hz}$), 5.88 (1H, br), 6.67 (1H, dd, $J = 1.9, 8.9\text{Hz}$), 6.8-6.9 (1H, m), 7.07 (1H, dd, $J = 2.9, 6.4\text{Hz}$), 7.25-7.4 (2H, m), 7.73 (1H, dd, $J = 0.3, 8.9\text{Hz}$), 8.42 (1H, s), 9.43 (1H, br), 9.56 (1H, br).	2 盐酸盐
1179	-H	-H	-H	-H	-H		$^1\text{H-NMR}$ (DMSO- d_6) δ ppm: 1.6-1.8 (1H, m), 2.1-2.25 (1H, m), 2.8-2.95 (1H, m), 3.0-3.25 (2H, m), 3.5-3.65 (1H, m), 4.0-4.5 (4H, m), 4.70 (1H, tt, $J = 7.3, 7.3\text{Hz}$), 6.70 (2H, d, $J = 7.9\text{Hz}$), 6.80 (1H, dd, $J = 7.3, 7.3\text{Hz}$), 6.92 (1H, dd, $J = 2.0, 9.0\text{Hz}$), 7.1-7.25 (2H, m), 7.55 (1H, d, $J = 1.4\text{Hz}$), 7.64 (1H, d, $J = 9.0\text{Hz}$), 8.36 (1H, s), 9.30 (1H, br), 9.47 (1H, br).	2 盐酸盐
1180	-H	-H	-H	-H	-H		$^1\text{H-NMR}$ (DMSO- d_6) δ ppm: 1.6-1.8 (1H, m), 2.1-2.25 (1H, m), 2.8-3.0 (1H, m), 3.0-3.25 (2H, m), 3.5-3.65 (1H, m), 4.15 (3H, s), 4.22 (1H, br), 4.73 (1H, tt, $J = 7.3, 7.3\text{Hz}$), 6.60 (1H, dd, $J = 1.8, 8.9\text{Hz}$), 6.91 (2H, d, $J = 7.6\text{Hz}$), 7.02 (1H, dd, $J = 7.3, 7.3\text{Hz}$), 7.22 (1H, s), 7.25-7.4 (2H, m), 7.66 (1H, d, $J = 8.9\text{Hz}$), 8.37 (1H, s), 9.26 (1H, br), 9.42 (1H, br).	2 盐酸盐

[1388] 药理学试验 1

[1389] 试验化合物对 5-羟色胺 (5-HT) 摄取到大鼠脑突触体的抑制活性的评价

[1390] 将雄性 Wistar 大鼠斩首, 取出脑, 切取前皮层。分离的前皮层用 Potter 型均化

器在 20 倍体积（按重量计）的 0.32M 蔗糖溶液中均化。该匀浆在 4℃ 在 1000g 下离心 10 分钟，上层清液然后在 4℃ 在 20000g 下离心 20 分钟。将颗粒再悬浮于含有 10mM 葡萄糖，145mM 氯化钠，4.5mM 氯化钾，1.2mM 氯化镁和 1.5mM 氯化钙的孵育缓冲液（20mM HEPES 缓冲剂（pH7.4））中，并用作粗突触体级分。

[1391] 在 96 孔圆底板的每一孔内，将该摄取反应混合物悬浮于含有优降宁（终浓度 10 μ M）和抗坏血酸钠（终浓度 0.2mg/ml）的 200 μ l 的最终容积中。

[1392] 每一孔内添加溶剂、未标记的 5-羟色胺和系列稀释的试验化合物，再添加最终容积的 1/10 容积的突触体级分。在 37℃ 预孵育 10 分钟后，通过在 37℃ 下添加氚标记的 5-HT 溶液（最终浓度 8nM）来启动摄取。通过用 96 孔玻璃纤维过滤板在真空下过滤 10 分钟之后停止摄取。用冷生理盐水清洗过滤器并干燥后，添加 Microscint-0 (Perkin-Elmer)，测定过滤器上的余留放射性。

[1393] 仅有溶剂的总摄取活性被确定为 100%，具有未标记 5-HT 的非特异性摄取活性（最终浓度 10 μ M）被确定 0%。根据试验化合物的浓度和它们的抑制活性计算 50% 抑制浓度。表 160 示出了结果。

[1394] 表 160

[1395]

试验化合物	50%抑制浓度 (nM)
实施例 5 的化合物	1.6
实施例 7 的化合物	3.0
实施例 19 的化合物	0.7
实施例 40 的化合物	0.8
实施例 73 的化合物	0.6
实施例 90 的化合物	1.2

[1396]

实施例 114 的化合物	0.8
实施例 131 的化合物	0.6
实施例 145 的化合物	0.6
实施例 149 的化合物	1.2
实施例 151 的化合物	0.8
实施例 154 的化合物	0.8

实施例 268 的化合物	0.8
实施例 278 的化合物	2.2
实施例 306 的化合物	1.4
实施例 894 的化合物	2.6
实施例 895 的化合物	3.0
实施例 896 的化合物	2.5
实施例 899 的化合物	0.7
实施例 900 的化合物	1.5
实施例 901 的化合物	0.7
实施例 903 的化合物	1.2
实施例 912 的化合物	1.0
实施例 913 的化合物	0.8
实施例 917 的化合物	0.7
实施例 930 的化合物	0.8
实施例 934 的化合物	1.8
实施例 961 的化合物	2.8
实施例 963 的化合物	1.0
实施例 967 的化合物	0.9
实施例 989 的化合物	0.6

[1397] 药理学试验 2

[1398] 试验化合物对去甲肾上腺素 (NE) 摄取到大鼠脑突触体的抑制活性的评价

[1399] 将雄性 Wistar 大鼠斩首, 取出脑, 切取海马。分离的海马用 Potter 型均化器在 20 倍体积 (按重量计) 的 0.32M 蔗糖溶液中均化。该匀浆在 4℃ 在 1000g 下离心 10 分钟, 上层清液然后在 4℃ 在 20000g 下离心 20 分钟。将颗粒再悬浮于含有 10mM 葡萄糖, 145mM 氯化钠, 4.5mM 氯化钾, 1.2mM 氯化镁和 1.5mM 氯化钙的孵育缓冲液 (20mMHEPES 缓冲剂 (pH7.4)) 中, 并用作粗突触体级分。

[1400] 在 96 孔圆底板的每一孔内, 将该摄取反应混合物悬浮于含有优降宁 (终浓度

10 μ M) 和抗坏血酸钠 (终浓度 0.2mg/ml) 的 200 μ l 的最终容积中。

[1401] 每一孔内添加溶剂、未标记的 NE 和系列稀释的试验化合物,再添加最终容积的 1/10 容积的突触体级分。在 37℃ 预孵育 10 分钟后,通过在 37℃ 下添加氚标记的 NE 溶液 (最终浓度 12nM) 来启动摄取。通过用 96 孔玻璃纤维过滤板在真空下过滤 10 分钟之后停止摄取。用冷生理盐水清洗过滤器并干燥后,添加 Microscint-0 (Perkin-Elmer),测定过滤器上的余留放射性。

[1402] 仅有溶剂的总摄取活性被确定为 100%,具有未标记 NE 的非特异性摄取活性 (最终浓度 10 μ M) 被确定 0%。根据试验化合物的浓度和它们的抑制活性计算 50%抑制浓度。

表 161 示出了结果。

[1403] 表 161

[1404]

试验化合物	50%抑制浓度 (nM)
实施例 1 的化合物	0.6
实施例 7 的化合物	0.4
实施例 20 的化合物	0.8
实施例 22 的化合物	2.2
实施例 44 的化合物	0.4
实施例 90 的化合物	0.7
实施例 98 的化合物	0.3
实施例 114 的化合物	0.4
实施例 116 的化合物	0.1
实施例 131 的化合物	0.2
实施例 154 的化合物	0.2
实施例 188 的化合物	0.1
实施例 223 的化合物	0.2
实施例 242 的化合物	0.2
实施例 244 的化合物	0.5
实施例 256 的化合物	0.1

实施例 278 的化合物	0.3
实施例 289 的化合物	0.1
实施例 306 的化合物	0.8

[1405]

实施例 894 的化合物	0.3
实施例 895 的化合物	0.5
实施例 896 的化合物	0.9
实施例 900 的化合物	0.6
实施例 903 的化合物	0.7
实施例 913 的化合物	0.8
实施例 922 的化合物	0.5
实施例 930 的化合物	1.0
实施例 951 的化合物	0.5
实施例 961 的化合物	0.7
实施例 963 的化合物	0.8
实施例 967 的化合物	0.1
实施例 989 的化合物	0.3
实施例 990 的化合物	0.8
实施例 1000 的化合物	0.4
实施例 1001 的化合物	0.1
实施例 1002 的化合物	0.1

[1406] 药理学试验 3

[1407] 试验化合物对多巴胺 (DA) 摄取到大鼠脑突触体的抑制活性的评价

[1408] 将雄性 Wistar 大鼠斩首, 取出脑, 切取纹状体 (striata)。分离的纹状体用 Potter 型均化器在 20 倍体积 (按重量计) 的 0.32M 蔗糖溶液中均化。该匀浆在 4°C 在 1000g 下离心 10 分钟, 上层清液然后在 4°C 在 20000g 下离心 20 分钟。将颗粒再悬浮于含有 10mM 葡萄糖, 145mM 氯化钠, 4.5mM 氯化钾, 1.2mM 氯化镁和 1.5mM 氯化钙的孵育缓冲液 (20mM HEPES

缓冲剂 (pH7.4)) 中, 并用作粗突触体级分。

[1409] 在 96 孔圆底板的每一孔内, 将该摄取反应混合物悬浮于含有优降宁 (终浓度 $10 \mu\text{M}$) 和抗坏血酸钠 (终浓度 0.2mg/ml) 的 $200 \mu\text{l}$ 的最终容积中。

[1410] 每一孔内添加溶剂、未标记的 DA 和系列稀释的试验化合物, 再添加最终容积的 $1/10$ 容积的突触体级分。在 37°C 预孵育 10 分钟后, 通过在 37°C 下添加氚标记的 DA 溶液 (最终浓度的 2nM) 来启动摄取。通过用 96 孔玻璃纤维过滤板在真空下过滤 10 分钟之后停止摄取。用冷生理盐水清洗过滤器并干燥后, 添加 Microscint-0 (Perkin-Elmer), 测定过滤器上的余留放射性。

[1411] 仅有溶剂的摄取活性被确定为 100%, 具有未标记 DA 的非特异性摄取活性 (最终浓度 $10 \mu\text{M}$) 被确定 0%。根据试验化合物的浓度和它们的抑制活性计算 50% 抑制浓度。表 162 示出了结果。

[1412] 表 162

[1413]

试验化合物	50%抑制浓度 (nM)
实施例 7 的化合物	45.0
实施例 44 的化合物	8.7
实施例 46 的化合物	9.3
实施例 73 的化合物	9.0
实施例 90 的化合物	4.8
实施例 114 的化合物	32.5
实施例 116 的化合物	8.9
实施例 154 的化合物	9.2
实施例 200 的化合物	3.8
实施例 201 的化合物	4.3
实施例 268 的化合物	6.5
实施例 270 的化合物	8.2
实施例 272 的化合物	30.0
实施例 273 的化合物	32.9
实施例 278 的化合物	34.7

实施例 289 的化合物	30.6
实施例 294 的化合物	24.0
实施例 299 的化合物	48.6
实施例 300 的化合物	9.6
实施例 894 的化合物	9.4
实施例 895 的化合物	38.0
实施例 912 的化合物	30.2
实施例 913 的化合物	6.5
实施例 930 的化合物	6.8
实施例 951 的化合物	29.8
实施例 961 的化合物	9.6
实施例 963 的化合物	47.1
实施例 967 的化合物	25.4
实施例 989 的化合物	5.8
实施例 990 的化合物	26.0
实施例 1001 的化合物	16.4
实施例 1002 的化合物	32.9

[1414] 药理学试验 4

[1415] 强迫游泳试验

[1416] 强迫游泳试验根据改良的Porsolt, R. D. 等人的方法进行 (Porsolt, R. D. 等人, 小鼠的绝望行为: 抗抑郁药的初筛试验. Arch. Int. Pharmacodyn., 229, 第 327-336 页 (1977))。

[1417] 将试验化合物悬浮于 5% 阿拉伯树胶 / 生理盐溶液 (w/v), 然后口服给药于雄性 ICR 小鼠 (由 Clea Japan Inc. 提供, 5-6 周龄)。在给药后 1 小时, 将小鼠扔进含有温度维持在 21-25°C、深度 9.5cm 的水的水槽内。然后, 迫使小鼠游泳 6 分钟。在该试验的最后 4 分钟期间, 测定小鼠不运动的时间 (即不动时间)。使用 SCANETMV-20AQ 系统 (Melquest Co., Ltd. 的产品名) 分析和测定不动时间。

[1418] 在本试验中, 试验化合物治疗的动物显示了不动时间的减少。因此, 可以看出试验化合物可有效作为抗抑郁药。