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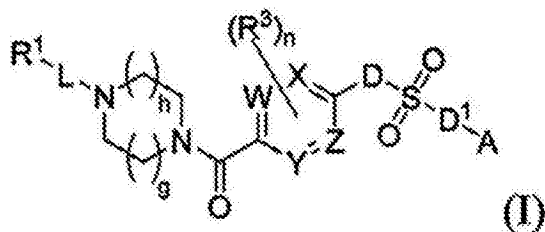
(54)发明名称

治疗性化合物和组合物

(57)摘要

本文描述了化合物和包含调节丙酮酸激酶
M2(PKM2)的化合物的组合物。本文还描述了在治
疗癌症中使用调节PKM2的化合物的方法。

1. 式 (I) 化合物或其药学上可接受的盐,



其中:

W、X、Y和Z是CH;

D为NR^b;

D¹为键;

A是未被取代的喹啉基;

L是键或-(CR^cR^c)_m-;

R¹选自C₁-C₁₂烷基、C₃-C₁₂环烷基、苯基、萘基、蒽基、杂芳基和杂环基;其每个被0-5次出现的R^d取代;

每个R³独立地选自卤素、卤代C₁-C₁₂烷基、C₁-C₁₂烷基、羟基和-OR^a;

每个R^a独立地选自C₁-C₁₂烷基、酰基、羟基C₁-C₁₂烷基和卤代C₁-C₁₂烷基;

每个R^b独立地选自氢和C₁-C₁₂烷基;

每个R^c独立地选自氢、卤素、C₁-C₁₂烷基;

每个R^d独立地选自卤素、C₁-C₁₂烷基;

n是0,1或2;

m是1或2;

h是1;及

g是1,

其中,

杂芳基是指5-14元芳族环系统,其为含1-3个环杂原子的5-8元单环,或含1-6个环杂原子的8-12元双环,或含1-9个环杂原子的11-14元三环,所述环杂原子独立地选自O、N和S;以及

杂环基是指在环结构中包括1-4个独立选自O、N和S的杂原子的3元至14元非芳族环结构。

2. 权利要求1所述的化合物或其药学上可接受的盐,其中R^b是H、甲基或乙基。

3. 权利要求1所述的化合物或其药学上可接受的盐,其中L是键。

4. 权利要求3所述的化合物或其药学上可接受的盐,其中R¹是被0-5次出现的R^d取代的C₁-C₁₂烷基、苯基、萘基、蒽基或杂芳基。

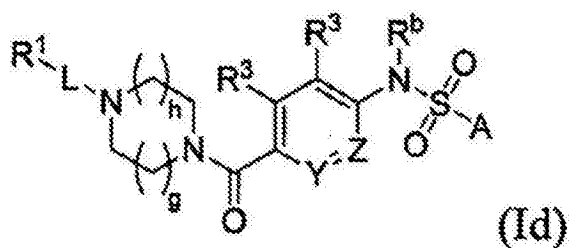
5. 权利要求1所述的化合物或其药学上可接受的盐,其中L是-(CR^cR^c)_m-。

6. 权利要求5所述的化合物或其药学上可接受的盐,其中R¹是被0-5次出现的R^d取代的C₃-C₁₂环烷基、苯基、萘基、蒽基、杂芳基或杂环基。

7. 权利要求3-6中任一项所述的化合物或其药学上可接受的盐,其中n是0。

8. 权利要求3-6中任一项所述的化合物或其药学上可接受的盐,其中n是1且R³是CH₃、CH₂CH₃、OCH₃、OCH₂CH₃、OH、F、Cl或CF₃。

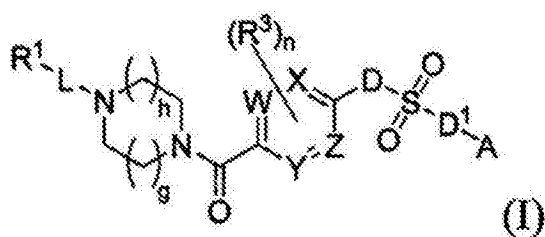
9. 权利要求1-6中任一项的化合物或其药学上可接受的盐,其中所述的化合物为式(Id)化合物:



其中A是未被取代的喹啉基。

10. 权利要求1-6中任一项的化合物或其药学上可接受的盐,其中所述杂环基为3-7元环。

11. 权利要求1的化合物或其药学上可接受的盐,



其中

W、X、Y和Z是CH;

D为NR^b;

D¹为键;

A是未被取代的喹啉基;

L是-CH₂-;

R¹选自苯基、吡啶基、环丙基、环戊基、环己基和四氢呋喃基;其每个被0-5次出现的R^d取代;

每个R³独立地选自Cl和甲基;

每个R^b为氢;

每个R^d独立地选自Cl和F;

n是0或1;

h是1;及

g是1。

12. 一种药物组合物,其包含权利要求1-11中任一项的化合物或其药学上可接受的盐。

13. 权利要求1-11中任一项的式(I)化合物或其药学上可接受的盐或包含权利要求1-11中任一项的化合物或其药学上可接受的盐的药物组合物在制备用于在需要其的受试者中调节PKM2活性或用于治疗与PKM2功能有关的疾病或紊乱的药物中的应用,其中所述的疾病或紊乱选自癌症、肥胖症、糖尿病、动脉粥样硬化、再狭窄和自身免疫疾病。

14. 权利要求1-11中任一项的式(I)化合物或其药学上可接受的盐或包含权利要求1-11中任一项的化合物或其药学上可接受的盐的药物组合物在制备用于在需要其的受试者中治疗与PKM2活性有关的癌症的药物中的用途。

治疗性化合物和组合物

[0001] 本申请是2010年6月29日递交的申请号为201080037700.8,发明名称为“治疗性化合物和组合物”的分案申请。

[0002] 优先权声明

[0003] 本申请要求于2009年6月29日提交的U.S.S.N.61/221,430和于2010年1月5日提交的U.S.S.N.61/292,360的优先权,其每个通过引用整体并入本文。

[0004] 发明背景

[0005] 癌细胞主要依赖于糖酵解以产生用于生物合成脂质和核苷酸的细胞能量和生物化学中间体,而成人组织的大部分“正常”细胞利用有氧呼吸。细胞代谢中癌细胞和正常细胞之间的基本差异(被称为Warburg效应)已经用于诊断目的,但是仍未用于治疗利益。

[0006] 丙酮酸激酶(PK)是一种在糖酵解期间将磷酸烯醇丙酮酸转化为丙酮酸的代谢酶。四种PK同种型存在于哺乳动物中:L和R同种型在肝和红细胞中表达,M1同种型在大多数成人组织中表达,且M2同种型是胚胎发育期间表达的M1的剪接变体。所有肿瘤细胞专门表达胚胎M2同种型。PK的M1和M2同种型之间的众所周知的差异为:M2是通过上游糖酵解中间体-果糖-1,6-二磷酸(FBP)依赖于变构活化的低活性酶,而M1是组成型活性酶。

[0007] 所有肿瘤细胞专门表达丙酮酸激酶的胚胎M2同种型,表明PKM2作为潜在靶用于癌症治疗。PKM2也在脂肪组织和活化的T-细胞中表达。因此,调节(例如抑制或活化)PKM2可在治疗例如肥胖症、糖尿病、自身免疫病症和增殖依赖性疾病例如良性前列腺增生(BPH)中有效。丙酮酸激酶的现有抑制剂并不具有选择性,使其难以治疗与丙酮酸激酶功能有关的疾病。

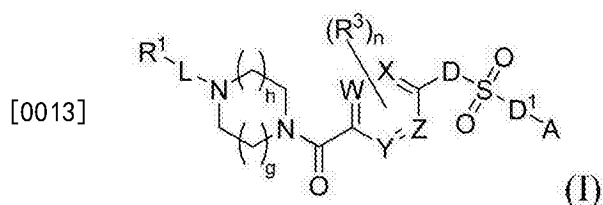
[0008] 此外,结合PKM2的磷酸酪氨酸肽导致FBP从PKM2解离并且将PKM2从活性四聚体形式构象变化为非活性形式。结合PKM2并且将酶锁定于活性构象中的化合物将导致将生物化学中间体从糖酵解分流到核苷酸和脂质的生物合成所需要的PKM2的别构调控的损失。因此,PKM2的活化(即,PKM2活化剂)还可抑制癌细胞、活化的免疫细胞和脂肪细胞的生长和增殖。

[0009] 对疾病例如癌症、糖尿病、肥胖症、自身免疫病症、增殖依赖性疾病(例如,BPH)和其它与丙酮酸激酶(例如,PKM2)功能有关的疾病的新疗法有持续需求。

[0010] 发明概述

[0011] 本文描述的是调节丙酮酸激酶M2(PKM2)的化合物和其药学上可接受的盐、溶剂合物和水合物,例如活化PKM2的化合物。还提供了包含本文提供的化合物的药物组合物及此类组合物在治疗与丙酮酸激酶功能(例如,PKM2功能)有关的疾病和病症(包括例如,癌症、糖尿病、肥胖症、自身免疫病症和良性前列腺增生(BPH))的方法中的用途。

[0012] 在一个实施方案中,提供的是一种药物组合物,其包含式(I)的化合物或药学上可接受的盐:



[0014] 其中：

[0015] W、X、Y和Z各自独立地选自CH或N；

[0016] D和D¹各自独立地选自键或NR^b；

[0017] A是任选取代的芳基或任选取代的杂芳基；

[0018] L是键、-C(O)-、-(CR^cR^c)_m-、-OC(O)-、-(CR^cR^c)_m-OC(O)-、-(CR^cR^c)_m-C(O)-、-NR^bC(S)-或-NR^bC(O)-（其中与R¹的连接点是在左手侧上）；

[0019] R¹选自烷基、环烷基、芳基、杂芳基和杂环基；其每个被0-5次出现的R^d取代；

[0020] 每个R³独立地选自卤素、卤代烷基、烷基、羟基和-OR^a，或两个相邻的R³与它们所连接的碳原子一起形成任选取代的杂环基；每个R^a独立地选自烷基、酰基、羟基烷基和卤代烷基；

[0021] 每个R^b独立地选自氢和烷基；

[0022] 每个R^c独立地选自氢、卤素、烷基、烷氧基和卤代烷氧基或两个R^c与它们所连接的碳原子一起形成任选取代的环烷基；

[0023] 每个R^d独立地选自卤素、卤代烷基、卤代烷氧基、烷基、炔基、硝基、氰基、羟基、-C(O)R^a、-OC(O)R^a、-C(O)OR^a、-SR^a、-NR^aR^b和-OR^a，或两个R^d与它们所连接的碳原子一起形成任选取代的杂环基；

[0024] n是0、1或2；

[0025] m是1、2或3；

[0026] h是0、1、2；及

[0027] g是0、1或2。

[0028] 在另一实施方案中，提供的是治疗或预防本文所述（例如治疗）的疾病、病症或障碍的方法，其包括施用本文提供的化合物、其药学上可接受的盐或其药物组合物。

[0029] 在另一实施方案中，提供的是在需要其的患者中调节（例如，增加或减少）PKM2活性和/或糖酵解（例如，在患者中调节细胞的内源性能力以下调PKM2）的水平的方法。该方法包括给需要其的患者施用有效量的本文所述的化合物的步骤，由此在患者中调节（例如，增加或减少）PKM2活性和/或糖酵解的水平。在一些实施方案中，本文所述的化合物或组合物用于以其活性构象维持PKM2或在增殖细胞中活化丙酮酸激酶活性作为在患者中将葡萄糖代谢产物转入分解代谢而非合成代谢的方法。

[0030] 在另一实施方案中，提供的是在需要其的患者中抑制细胞增殖的方法。该方法包括给需要其的患者施用有效量的本文所述的化合物的步骤，由此在患者中抑制细胞增殖。例如，这种方法可在经历有氧糖酵解的PKM2依赖性细胞中抑制转化细胞（例如癌细胞）的生长，或普遍抑制生长。

[0031] 在另一实施方案中，提供的是在需要其的患者中治疗罹患或易患与PKM2功能有关的疾病或障碍的患者的方法。该方法包括给需要其的患者施用有效量的本文所述的化合

物,由此在患者中治疗、预防或缓解疾病或障碍。在某些实施方案中,在药物组合物中提供该调节剂。在某些实施方案中,该方法包括鉴定或选择将从调节(例如,活化)PKM2中受益的患者。例如,该患者可基于在用于治疗与PKM2功能有关的癌症的患者的细胞中的PKM2活性水平而被鉴定。在另一实施方案中,所选患者是罹患或易患本文所鉴定的障碍或疾病,例如由不需要的细胞生长或增殖(例如癌症、肥胖症、糖尿病、动脉粥样硬化、再狭窄和自身免疫疾病)表征的障碍的患者。

[0032] 在另一实施方案中,本文所述的化合物以足以增加乳酸盐生成或氧化磷酸化的剂量和频率施用。

[0033] 附图简述

[0034] 图1表示示例性化合物和该化合物的相应活性的表。

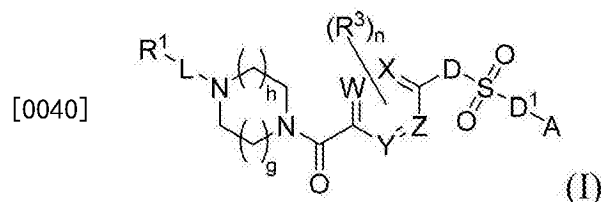
[0035] 详述

[0036] 在下面描述中显示的或在附图中阐述的构造的细节和组分的布置并不旨在限制。可用多种方式实施或进行实施方案。同样,本文所用的措辞和术语是出于描述的目的且不应被视作限制。使用“包括”、“包含”或“具有”、“含有”、“涵盖”及本文的变更意指包括下文列出的条目和其等价物以及其它条目。

[0037] 化合物

[0038] 本文描述的是调节PKM2、例如活化PKM2的化合物和组合物。调节PKM2、例如活化PKM2的化合物可用于治疗病症例如肿瘤性障碍(例如,癌症)或脂肪相关障碍(例如,肥胖症)。

[0039] 在一个实施方案中,提供的是式(I)化合物或其药学上可接受的盐,或包含式(I)化合物或其药学上可接受的盐的药物组合物:



[0041] 其中：

[0042] W、X、Y和Z各自独立地选自CH或N:

[0043] D和D¹各自独立地选自键或NR^b;

[0044] A是任选取代的芳基或任选取代的杂芳基:

[0045] L是键、 $-\text{C}(\text{O})-$ 、 $-(\text{CR}^{\text{c}}\text{R}^{\text{c}})_m-$ 、 $-\text{OC}(\text{O})-$ 、 $-(\text{CR}^{\text{c}}\text{R}^{\text{c}})_m-\text{OC}(\text{O})-$ 、 $-(\text{CR}^{\text{c}}\text{R}^{\text{c}})_m-\text{C}(\text{O})-$ 、 $-\text{NR}^{\text{b}}\text{C}(\text{S})-$ 或 $-\text{NR}^{\text{b}}\text{C}(\text{O})-$ (其中与 R^1 的连接点是在左手侧上)；

[0046] R¹选自烷基、环烷基、芳基、杂芳基和杂环基;其每个被0-5次出现的R^d取代;

[0047] 每个R³独立地选自卤素、卤代烷基、烷基、羟基和-OR^a,或两个相邻的R³与它们所连接的碳原子一起形成任选取代的杂环基;

[0048] 每个R^a独立地选自烷基、酰基、羟基烷基和卤代烷基；

[0049] 每个R^b独立地选自氢和烷基:

[0050] 每个R^c独立地选自氢、卤素、烷基、烷氧基和卤代烷氧基或两个R^c与它们所连接的碳原子一起形成任选取代的环烷基；

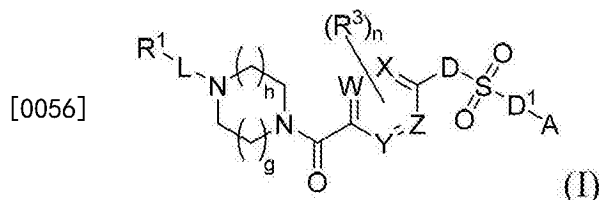
[0051] 每个 R^d 独立地选自卤素、卤代烷基、卤代烷氧基、烷基、炔基、硝基、氰基、羟基、 $-C(O)R^a$ 、 $-OC(O)R^a$ 、 $-C(O)OR^a$ 、 $-SR^a$ 、 $-NR^aR^b$ 和 $-OR^a$ ，或两个 R^d 与它们所连接的碳原子一起形成任选取代的杂环基；

[0052] n 是0、1或2；

[0053] m 是1、2或3；

[0054] h 是0、1、2；及

[0055] g 是0、1或2。在某些实施方案中，提供的是式(I)化合物或其药学上可接受的盐：



[0057] 其中：

[0058] W 、 X 、 Y 和 Z 各自独立地选自 CH 或 N ；

[0059] D 和 D^1 各自独立地选自键或 NR^b ；

[0060] A 是任选取代的二环杂芳基；

[0061] L 是键、 $-C(O)-$ 、 $-(CR^cR^c)_m-$ 、 $-OC(O)-$ 、 $-(CR^cR^c)_m-OC(O)-$ 、 $-(CR^cR^c)_m-C(O)-$ 、 $-NR^bC(S)-$ 或 $-NR^bC(O)-$ ；

[0062] R^1 选自烷基、环烷基、芳基、杂芳基和杂环基；其每个被0-5次出现的 R^d 取代；

[0063] 每个 R^3 独立地选自卤素、卤代烷基、烷基、羟基和 $-OR^a$ 或两个相邻的 R^3 与它们所连接的碳原子一起形成任选取代的环基；每个 R^a 独立地选自烷基、酰基、羟基烷基和卤代烷基；

[0064] 每个 R^b 独立地选自氢和烷基；

[0065] 每个 R^c 独立地选自氢、卤素、烷基、烷氧基和卤代烷氧基或两个 R^c 与它们所连接的碳原子一起形成任选取代的环烷基；

[0066] 每个 R^d 独立地选自卤素、卤代烷基、卤代烷氧基、烷基、炔基、硝基、氰基、羟基、 $-C(O)R^a$ 、 $-OC(O)R^a$ 、 $-C(O)OR^a$ 、 $-SR^a$ 、 $-NR^aR^b$ 和 $-OR^a$ ，或两个 R^d 与它们所连接的碳原子一起形成任选取代的杂环基；

[0067] n 是0、1或2；

[0068] m 是1、2或3；

[0069] h 是0、1、2；及

[0070] g 是0、1或2。在一些实施方案中， h 是1。在一些实施方案中， h 是2。

[0071] 在一些实施方案中， g 是1。在一些实施方案中， g 是2。

[0072] 在一些实施方案中， h 和 g 均是1。在一些实施方案中， h 是1且 g 是2。在一些实施方案中， g 是1且 h 是2。

[0073] 在一些实施方案中， W 、 X 、 Y 和 Z 是 CH 。在一些实施方案中， W 、 X 、 Y 和 Z 中的至少一个是 N 。在一些实施方案中， W 、 X 、 Y 和 Z 中的至少两个是 N 。在一些实施方案中， W 、 X 、 Y 和 Z 中的至少三个是 N 。

[0074] 在一些实施方案中， W 、 X 、 Y 、 Z 与它们所连接的碳形成吡啶基环。在一些实施方案

中,W、X、Y、Z与它们所连接的碳形成嘧啶基环。在一些实施方案中,W、X、Y、Z与它们所连接的碳形成哒嗪基环。

[0075] 在一些实施方案中,W、X和Y是CH且Z是N。

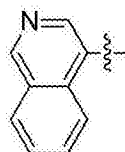
[0076] 在一些实施方案中,X、Y和Z是CH且W是N。

[0077] 在一些实施方案中,D是NR^b且D¹是键。在一些实施方案中,D是键且D¹是NR^b。在一些实施方案中,D和D¹两者是NR^b。在一些实施方案中,R^b是烷基(例如,甲基或乙基)。在一些实施方案中,R^b是氢(H)。

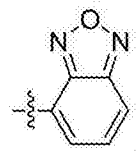
[0078] 在一些实施方案中,A是9-10元二环杂芳基(例如,喹啉基、喹喔啉基、噌啉基、异喹啉基、吲哚基、苯并噁唑基、吡咯并吡啶基、吡咯并嘧啶基、苯并咪唑基、苯并噻唑基或苯并噁唑基)。在一些实施方案中,A是含氮9-10元二环杂芳基。在一些实施方案中,A是任选取代的喹啉基(例如,8-喹啉基或4-喹啉基)、任选取代的喹喔啉基(例如,5-喹喔啉基)、任选取代的噌啉基(例如,4-噌啉基或8-噌啉基)、任选取代的噌啉基(例如,8-噌啉基)、任选取代的异喹啉基、任选取代的吲哚基(7-吲哚基)、任选取代的苯并噁唑基(例如,7-苯并噁唑基)、任选取代的吡咯并吡啶基(例如,4-吡咯并吡啶基)、任选取代的吡咯并嘧啶基(例如,4-吡咯并嘧啶基)、任选取代的苯并咪唑基(例如,7-苯并咪唑基)、任选取代的苯并噻唑基(例如,4-苯并噻唑基、2-甲基-4-苯并噻唑基或7-苯并噻唑基)、或任选取代的苯并噁唑基(例如,4-苯并噁唑基)。在一些实施方案中,A任选地被卤素取代。在一些实施方案中,A是



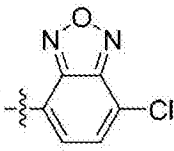
在一些实施方案中,A是



在一些实施方案中,A是任选取代的



在一些实施方案中,A是



[0079] 在一些实施方案中,L是键。

[0080] 在一些实施方案中,L是-(CR^cR^c)_m-且m是1。在这些实施方案的一些方面,每个R^c是氢。在这些实施方案的一些方面,一个R^c是烷基(例如,甲基或乙基)而另一个R^c是氢。在这些实施方案的一些方面,一个R^c是卤素(例如,氟)而一个R^c是氢。在这些实施方案的一些方面,两个R^c均是卤素(例如,氟)。在这些实施方案的一些方面,一个R^c是烷氧基(例如,甲氧基或乙氧基)而一个R^c是氢。在这些实施方案的一些方面,两个R^c均是烷氧基(例如,甲氧基或乙氧基)。在这些实施方案的一些方面,两个R^c与它们所连接的碳一起形成环烷基(例如,环丙基)。

[0081] 在一些实施方案中,L是-(CR^cR^c)_m-且m是2。在这些实施方案的一些方面,每个R^c是氢。在这些实施方案的一些方面,1个R^c是烷基(例如,甲基或乙基)而其它R^c中的每一个是氢。在这些实施方案的一些方面,两个R^c与它们所连接的碳一起形成环烷基(例如,环丙基)而其它两个R^c中的每一个是氢。

[0082] 在一些实施方案中,L是-(CR^cR^c)_m-且m是3。在这些实施方案的某些方面,每个R^c是氢。

[0083] 在一些实施方案中,L是-C(O)-。

[0084] 在一些实施方案中, L是 $-O-C(O)-$ 。

[0085] 在一些实施方案中, L是 $NR^bC(O)-$ 且 R^b 是H。在一些实施方案中, L是 $NR^bC(S)-$ 且 R^b 是H。

[0086] 在一些实施方案中, L是 $-(CR^cR^c)_m-C(O)-$ 且m是1。在这些实施方案的一些方面, 每个 R^c 是氢。在这些实施方案的一些方面, 一个 R^c 是烷基(例如, 甲基或乙基) 而一个 R^c 是氢。在这些实施方案的一些方面, 两个 R^c 均是烷基(例如, 甲基或乙基)。

[0087] 在一些实施方案中, L是 $-(CR^cR^c)_m-C(O)-$ 且m是2。在这些实施方案的一些方面, 每个 R^c 是氢。

[0088] 在一些实施方案中, L是 $-(CR^cR^c)_m-C(O)-$ 且m是3。在这些实施方案的一些方面, 每个 R^c 是氢。

[0089] 在一些实施方案中, R^1 是被0-5次出现的 R^d 取代的烷基(例如, 甲基、乙基、正丙基、异丙基或正丁基)。在一些实施方案中, R^1 是甲基、乙基、正丙基、异丙基或正丁基。在一些实施方案中, R^1 是乙基或丙基(正丙基或异丙基)。在这些实施方案的一些方面, L是键、 $-CH_2-$ 、 $-C(O)-$ 或 $-O(CO)-$ 。在这些实施方案的一些方面, L是 $-O(CO)-$ 。

[0090] 在一些实施方案中, R^1 是被1次出现的 R^d 取代的烷基(例如, 甲基、乙基、正丙基、异丙基或正丁基)。在一些实施方案中, R^1 是被1次出现的 R^d 取代的甲基、乙基或正丙基。在这些实施方案的一些方面, R^d 是卤素(例如, 氟或氯)。在这些实施方案的一些方面, R^d 是 $-C(O)OR^a$ 。在这些实施方案的一些方面, R^a 是烷基(例如, 甲基或乙基)。在这些实施方案的一些方面, L是 $-NHC(O)-$ 。

[0091] 在一些实施方案中, R^1 是被2次出现的 R^d 取代的烷基(例如, 甲基、乙基、正丙基、异丙基或正丁基)。在一些实施方案中, R^1 是被2次出现的 R^d 取代的甲基、乙基或正丙基。在一些实施方案中, R^1 是被2次出现的 R^d 取代的正丙基。在这些实施方案的一些方面, 1个 R^d 是氰基而另一个 R^d 是 $-NR^aR^b$ 。在这些实施方案的一些方面, R^a 和 R^b 是氢。在这些实施方案的一些方面, L是 $-CH_2-$ 。

[0092] 在一些实施方案中, R^1 是被0-5次出现的 R^d 取代的杂芳基(例如, 含S单环杂芳基、含N单环杂芳基或含N二环杂芳基)。在一些实施方案中, R^1 是被0-5次出现的 R^d 取代的5-8元单环杂芳基(例如, 噻吩基、吡啶基、嘧啶基或吡嗪基(pyrazyl))。在一些实施方案中, R^1 是被0-5次出现的 R^d 取代的吡啶基(例如, 2-吡啶基、3-吡啶基或4-吡啶基)、被0-5次出现的 R^d 取代的嘧啶基(例如, 2-嘧啶基或5-嘧啶基)或被0-5次出现的 R^d 取代的吡嗪基(例如, 2-吡嗪基)。在一些实施方案中, R^1 是被0-5次出现的 R^d 取代的噻唑基(例如, 2-噻唑基或5-噻唑基)。在一些实施方案中, R^1 是被0-5次出现的 R^d 取代的嘧啶基(例如, 2-嘧啶基)。在一些实施方案中, R^1 是被0-5次出现的 R^d 取代的噻二唑基(例如, 4-噻二唑基)。在一些实施方案中, R^1 是被0-5次出现的 R^d 取代的吡咯基(例如, 2-吡咯基)。在这些实施方案的一些方面, L是键、 $-CH_2-$ 、 $-C(O)-$ 或 $-O(CO)-$ 。在一些实施方案中, R^1 是吡啶基(例如, 2-吡啶基、3-吡啶基或4-吡啶基)。

[0093] 在一些实施方案中, R^1 是被1次出现的 R^d 取代的吡啶基(例如, 2-吡啶基、3-吡啶基或4-吡啶基)。在这些实施方案的一些方面, R^d 是 $-OC(O)R^a$ 。在这些实施方案的一些方面, R^d 是 $-OR^a$ 。在这些实施方案的一些方面, R^d 是 $-C(O)OR^a$ 。在这些实施方案的一些方面, R^d 是烷基(例如, 甲基或乙基)。在这些实施方案的一些方面, R^d 是卤代烷基(例如, 三氟甲基)。在这些

实施方案的一些方面, R^d 是卤素 (例如, 氟或氯)。在这些实施方案的一些方面, R^a 是烷基 (例如, 甲基或乙基)。在这些实施方案的一些方面, L 是 $-\text{CH}_2-$ 。在一些实施方案中, R^1 是被 2 次出现的 R^d 取代的吡啶基 (例如, 2-吡啶基、3-吡啶基或 4-吡啶基)。在这些实施方案的一些方面, 一个 R^d 是 $-\text{C}(\text{O})\text{OR}^a$ 而另一个 R^d 是 $-\text{OR}^a$ 。在这些实施方案的一些方面, R^a 是烷基 (例如, 甲基或乙基)。在这些实施方案的一些方面, 两个 R^d 均是卤素 (例如, 氟或氯)。在这些实施方案的一些方面, L 是 $-\text{CH}_2-$ 。

[0094] 在一些实施方案中, R^1 是嘧啶基 (例如, 2-嘧啶基或 5-嘧啶基)。在这些实施方案的一些方面, L 是键。

[0095] 在一些实施方案中, R^1 是被 1 次出现的 R^d 取代的嘧啶基 (例如, 2-嘧啶基或 5-嘧啶基)。在这些实施方案的一些方面, R^d 是卤素 (例如, 氟或氯)。

[0096] 在一些实施方案中, R^1 是吡嗪基 (例如, 2-吡嗪基)。在这些实施方案的一些方面, L 是键。

[0097] 在一些实施方案中, R^1 是噻唑基 (例如, 2-噻唑基、4-噻唑基或 5-噻唑基)。在这些实施方案的一些方面, L 是 $-\text{C}(\text{O})-$ 。

[0098] 在一些实施方案中, R^1 是被 1 次出现的 R^d 取代的噻唑基 (例如, 2-噻唑基、4-噻唑基或 5-噻唑基)。在这些实施方案的一些方面, R^d 是烷基 (例如, 甲基或乙基)。在这些实施方案的一些方面, L 是 $-\text{C}(\text{O})-$ 。

[0099] 在一些实施方案中, R^1 是被 0-5 次出现的 R^d 取代的噻吩基 (例如, 2-噻吩基)。在一些实施方案中, R^1 是噻吩基。

[0100] 在一些实施方案中, R^1 是噻二唑基 (例如, 4-噻二唑基)。

[0101] 在一些实施方案中, R^1 是吡咯基 (例如, 2-吡咯基)。

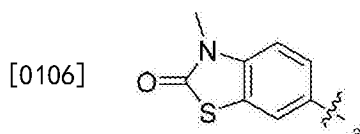
[0102] 在一些实施方案中, R^1 是被 0-5 次出现的 R^d 取代的环烷基 (例如, 环丙基、环戊基或环己基)。在一些实施方案中, R^1 是环丙基。在一些实施方案中, R^1 是环己基。在一些实施方案中, R^1 是环戊基。在这些实施方案的一些方面, L 是 $-\text{CH}_2-\text{C}(\text{O})-$ 。在一些实施方案中, R^1 是被 0-5 次出现的 R^d 取代的芳基。在这些实施方案的一些方面, L 是键、 $-\text{CH}_2-$ 、 $-\text{C}(\text{O})-$ 或 $-\text{O}(\text{C}(\text{O})-)$ 。

[0103] 在一些实施方案中, R^1 是芳基 (例如, 苯基)。在一些实施方案中, R^1 是苯基。在这些实施方案的一些方面, L 是键、 $-\text{CH}_2-$ 、 $-\text{C}(\text{O})-$ 或 $-\text{O}(\text{C}(\text{O})-)$ 。

[0104] 在一些实施方案中, R^1 是被 1 次出现的 R^d 取代的苯基。在这些实施方案的一些方面, R^d 是邻位取代的。在这些实施方案的一些方面, R^d 是间位取代的。在这些实施方案的一些方面, R^d 是对位取代的。在这些实施方案的一些方面, R^d 是卤素 (例如, 氟、溴或氯)。在这些实施方案的一些方面, R^d 是烷基 (例如, 甲基、乙基、异丙基、叔丁基、正丁基或正戊基)。在这些实施方案的一些方面, R^d 是卤代烷基 (例如, 三氟甲基)。在这些实施方案的一些方面, R^d 是 $-\text{OR}^a$ 。在这些实施方案的一些方面, R^d 是 $-\text{C}(\text{O})\text{R}^a$ 。在这些实施方案的一些方面, R^d 是 $-\text{SR}^a$ 。在这些实施方案的一些方面, R^d 是 $-\text{C}(\text{O})\text{OR}^a$ 。在这些实施方案的一些方面, R^d 是氰基。在这些实施方案的一些方面, R^d 是 $-\text{NR}^a\text{R}^b$ 。在这些实施方案的一些方面, R^d 是卤代烷氧基 (例如, 二氟甲氧基或三氟甲氧基)。在这些实施方案的一些方面, R^d 是羟基。在这些实施方案的一些方面, R^d 是 $-\text{OC}(\text{O})\text{R}^a$ 。在这些实施方案的一些方面, R^d 是炔基 (例如, 1-己炔基)。在这些实施方案的一些方面, R^d 是卤代烷基 (例如, 三氟甲基)。在这些实施方案的一些方面, R^a 是烷基 (例如, 甲基、乙基、正丙基、异丙基、正丁基、异丁基、叔丁基或正戊基)。在这些实施方案的一些方面,

R^a 是羟基烷基(例如,2-羟基乙基)。在这些实施方案的一些方面, R^a 和 R^b 是烷基(例如,甲基或乙基)。在这些实施方案的一些方面, R^a 是酰基(例如,乙酰基)且 R^b 是氢。在这些实施方案的一些方面,L是键、 $-\text{CH}_2-$ 、 $-\text{C}(\text{O})-$ 或 $-\text{O}(\text{CO})-$ 。

[0105] 在一些实施方案中, R^1 是被2次出现的 R^d 取代的苯基。在这些实施方案的一些方面,两个 R^d 均是卤素(例如,氟或氯)。在这些实施方案的一些方面,两个 R^d 均是烷基(例如,甲基或乙基)。在这些实施方案的一些方面,1个 R^d 是烷基(例如,甲基或乙基)而另一个是 $-\text{OR}^a$ 。在这些实施方案的一些方面,1个 R^d 是卤素(例如,氟或氯)而另一个 R^d 是 $-\text{OR}^a$ 。在这些实施方案的一些方面,两个 R^d 均是 $-\text{OR}^a$ 。在这些实施方案的一些方面,1个 R^d 是卤素(例如,氟或氯)而另一个 R^d 是羟基。在这些实施方案的一些方面,1个 R^d 是卤素(例如,氟或氯)而另一个是卤代烷基(例如,三氟甲基)。在这些实施方案的一些方面,1个 R^d 是 $-\text{OR}^a$ 而另一个 R^d 是 $-\text{C}(\text{O})\text{OR}^a$ 。在这些实施方案的一些方面,1个 R^d 是 $-\text{OR}^a$ 而另一个 R^d 是羟基。在这些实施方案的一些方面,1个 R^d 是烷基(例如,甲基或乙基)而另一个 R^d 是羟基。在这些实施方案的一些方面,两个 R^d 均是羟基。在这些实施方案的一些方面,1个 R^d 是卤素(例如,氟)而另一个 R^d 是卤代烷基(例如,三氟甲基)。在这些实施方案的一些方面,两个 R^d 均是羟基。在这些实施方案的一些方面,一个 R^d 是卤代烷基(例如,三氟甲基)而另一个 R^d 是烷基(例如,甲基)。在这些实施方案的一些方面,两个 R^d 与它们所连接的碳原子一起形成任选取代的杂环基。在这些实施方案的一些方面,两个 R^d 与它们所连接的碳原子一起形成任选取代的5-7元杂环基。在这些实施方案的一些方面,两个 R^d 与它们所连接的苯基环一起形成下列结构:



[0107] 在这些实施方案的一些方面, R^a 是烷基(例如,甲基或乙基)。在这些实施方案的一些方面,L是键、 $-\text{CH}_2-$ 、 $-\text{C}(\text{O})-$ 或 $-\text{O}(\text{CO})-$ 。

[0108] 在一些实施方案中, R^1 是被3次出现的 R^d 取代的苯基。在这些实施方案的一些方面,3个 R^d 是卤素(例如,氟或氯)。在这些实施方案的一些方面,2个 R^d 是卤素(例如,氟或氯)且1个 R^d 是羟基。在这些实施方案的一些方面,1个 R^d 是卤素(例如,氟或氯),1个 R^d 是烷基(例如,甲基)且1个 R^d 是羟基。在这些实施方案的一些方面,3个 R^d 是烷基(例如,甲基或乙基)。在这些实施方案的一些方面,2个 R^d 是烷基(例如,甲基或乙基)且1个 R^d 是羟基。在这些实施方案的一些方面,2个 R^d 是卤素(例如,氟或氯)且1个 R^d 是 $-\text{OR}^a$ 。在这些实施方案的一些方面, R^a 是烷基(例如,甲基或乙基)。在这些实施方案的一些方面,1个 R^d 是羟基且2个 R^d 是 $-\text{OR}^a$ 。在这些实施方案的一些方面, R^a 是烷基(例如,甲基或乙基)。在这些实施方案的一些方面,3个 R^d 是 $-\text{OR}^a$ 。在这些实施方案的一些方面,3个 R^d 是卤素(例如,氟或氯)。在这些实施方案的一些方面, R^a 是烷基(例如,甲基或乙基)。在这些实施方案的一些方面,L是键、 $-\text{CH}_2-$ 、 $-\text{C}(\text{O})-$ 或 $-\text{O}(\text{CO})-$ 。

[0109] 在一些实施方案中, R^1 是被4次出现的 R^d 取代的苯基。在这些实施方案的一些方面,1个 R^d 是羟基,1个 R^d 是烷基(例如,甲基或乙基)且2个 R^d 是 $-\text{OR}^a$ 。在这些实施方案的一些方面, R^a 是烷基(例如,甲基或乙基)。在这些实施方案的一些方面,L是键、 $-\text{CH}_2-$ 、 $-\text{C}(\text{O})-$ 或 $-\text{O}(\text{CO})-$ 。

[0110] 在一些实施方案中, R^1 是被0-5次出现的 R^d 取代的杂环基。

[0111] 在一些实施方案中, R^1 是被 0-5 次出现的 R^d 取代的四氢呋喃基 (例如, 2-四氢呋喃基或 3-四氢呋喃基)。在这些实施方案的一些方面, R^1 是四氢呋喃基 (例如, 2-四氢呋喃基或 3-四氢呋喃基)。在这些实施方案的一些方面, L 是 $-C(O)-$ 。

[0112] 在一些实施方案中, R^1 是被 0-5 次出现的 R^d 取代的氮杂环丁烷基 (例如, 3-氮杂环丁烷基)。在一些实施方案中, R^1 是氮杂环丁烷基 (例如, 3-氮杂环丁烷基)。在一些实施方案中, R^1 是被 1 次出现的 R^d 取代的氮杂环丁烷基 (例如, 3-氮杂环丁烷基)。在这些实施方案的一些方面, R^d 是烷基 (例如, 甲基或乙基)。在这些实施方案的一些方面, L 是 $-C(O)-$ 。

[0113] 在一些实施方案中, R^1 是被 0-5 次出现的 R^d 取代的 10-14 元二环芳基。在一些实施方案中, R^d 是被 0-5 次出现的 R^d 取代的萘基。在一些实施方案中, R^d 是萘基。

[0114] 在一些实施方案中, L 是键、 $-(CR^cR^c)_m-$ 、 $-NR^bC(O)-$ 、 $-(CR^cR^c)_m-C(O)-$ 、 $-C(O)-$ 或 $-O(CO)-$ 。

[0115] 在一些实施方案中, L 是键且 R^1 是被 0-5 次出现的 R^d 取代的烷基、芳基或杂芳基。在这些实施方案的一些方面, R^1 的烷基、芳基或杂芳基如上文的实施方案和方面中的任一个所述。

[0116] 在一些实施方案中, L 是 $-(CR^cR^c)_m-$ 且 R^1 是被 0-5 次出现的 R^d 取代的环烷基、芳基、杂芳基或杂环基。在这些实施方案的一些方面, R^1 的环烷基、芳基、杂芳基或杂环基如上文的实施方案和方面中的任一个所述。

[0117] 在一些实施方案中, L 是 $-NR^bC(O)-$ 且 R^b 是氢; 且 R^1 是被 0-5 次出现的 R^d 取代的芳基。在这些实施方案的一些方面, R^1 的芳基如上文的实施方案和方面中的任一个所述。

[0118] 在一些实施方案中, L 是 $-(CR^cR^c)_m-C(O)-$ 且 R^1 是被 0-5 次出现的 R^d 取代的环烷基、芳基或杂芳基。在这些实施方案的一些方面, R^1 的环烷基、芳基或杂芳基如上文的实施方案和方面中的任一个所述。

[0119] 在一些实施方案中, L 是 $-C(O)-$ 且 R^1 是被 0-5 次出现的 R^d 取代的芳基、烷基或杂芳基。在这些实施方案的一些方面, R^1 的芳基、烷基或杂芳基如上文的实施方案和方面中的任一个所述。

[0120] 在一些实施方案中, L 是 $-OC(O)-$ 且 R^1 是被 0-5 次出现的 R^d 取代的烷基、芳基或杂环基。在这些实施方案的一些方面, R^1 的烷基、芳基或杂环基如上文的实施方案和方面中的任一个所述。

[0121] 在一些实施方案中, L 是 $-(CR^cR^c)_m-OC(O)-$ 且 R^1 是被 0-5 次出现的 R^d 取代的杂环基或环烷基。在这些实施方案的一些方面, R^1 的杂环基或环烷基如上文的实施方案和方面中的任一个所述。

[0122] 在一些实施方案中, n 是 0。在一些实施方案中, n 是 1。

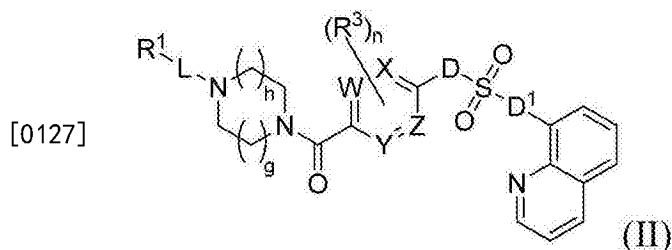
[0123] 在一些实施方案中, R^3 是烷基 (例如, 甲基或乙基)。在一些实施方案中, R^3 是 $-OR^a$ 。在这些实施方案的一些方面, R^a 是烷基 (例如, 甲基或乙基)。在一些实施方案中, R^3 是卤素 (例如, 氟或氯)。在一些实施方案中, R^3 是羟基。在一些实施方案中, R^3 是卤代烷基 (例如, 三氟甲基)。

[0124] 在一些实施方案中, n 是 2。

[0125] 在一些实施方案中, 两个相邻的 R^3 与它们所连接的碳原子一起形成杂环基环。在一些实施方案中, 两个 R^3 均是 $-OR^a$ 。在一些实施方案中, 两个相邻的 R^3 与它们所连接的碳原



[0126] 在某些实施方案中,化合物为式(II)或其药学上可接受的盐:



[0128] 其中L、R¹、R³、R^a、R^b、R^c、R^d、Y、Z、m、h和g如上文式(I)中或本文所述的实施方案或方面中的任一个所定义。

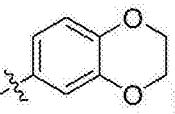
[0129] 在某些实施方案中,A是被1或2次出现的R²任选取代的芳基(例如,苯基或萘基),其中每个R²独立地选自卤素、卤代烷基、芳基、杂芳基、烷基、-OR^a、-COOR^c、或-CONR^cR^c;且D、D¹、L、R¹、R³、R^a、R^b、R^c、R^d、X、Y、Z、W、n、m、h和g如上文式(I)中或本文所述的实施方案或方面中的任一个所定义。在这些实施方案的一些方面,D和D¹是N。在这些实施方案的一些方面,W、X、Y和Z中的至少一个是N。在这些实施方案的一些方面,W、Y和Z中的一个N;h是1且g是1。

[0130] 在某些实施方案中,A是杂芳基(例如,含N单环杂芳基或含N二环杂芳基);且D、D¹、L、R¹、R³、R^a、R^b、R^c、R^d、X、Y、Z、W、n、m、h和g如上文式(I)中或本文所述的实施方案或方面中的任一个所定义。在一些实施方案中,A是5-8元单环杂芳基(例如,吡啶基、嘧啶基或吡嗪基);且D、D¹、L、R¹、R³、R^a、R^b、R^c、R^d、X、Y、Z、W、n、m、h和g如上文式(I)中或本文所述的实施方案或方面中的任一个所定义。在一些实施方案中,A是5-8元含N单环杂芳基;且D、D¹、L、R¹、R³、R^a、R^b、R^c、R^d、X、Y、Z、W、n、m、h和g如上文式(I)中或本文所述的实施方案或方面中的任一个所定义。在一些实施方案中,A是任选取代的吡啶基(例如,2-吡啶基、3-吡啶基或4-吡啶基)、任选取代的嘧啶基(例如,2-嘧啶基或5-嘧啶基),或任选取代的吡嗪基(例如,2-吡嗪基);且L、R¹、R³、R^a、R^b、R^c、R^d、Y、Z、m、h和g如上文式(I)中或本文所述的实施方案或方面中的任一个所定义。

[0131] 在一些实施方案中,A被1次出现的R²取代;且D、D¹、L、R¹、R³、R^a、R^b、R^c、R^d、X、Y、Z、W、n、m、h和g如上文式(I)中或本文所述的实施方案或方面中的任一个所定义。在这些实施方案的一些方面,R²是烷基(例如,甲基或乙基)。在这些实施方案的一些方面,R²是卤素。在这些实施方案的一些方面,R²是氟(F)。在这些实施方案的一些方面,R²是溴(Br)。在这些实施方案的一些方面,R²是氯(Cl)。在这些实施方案的一些方面,R²是-OR^a。在这些实施方案的一些方面,R^a是烷基(例如,甲基)。

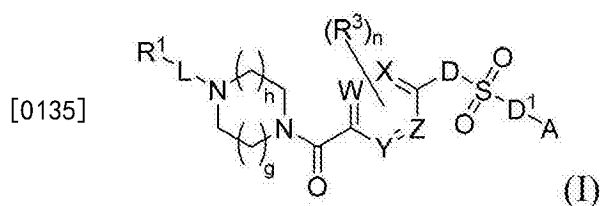
[0132] 在一些实施方案中,A被2次出现的R²取代;且D、D¹、L、R¹、R³、R^a、R^b、R^c、R^d、X、Y、Z、W、n、m、h和g如上文式(I)中或本文所述的实施方案或方面中的任一个所定义。在这些实施方案的一些方面,两个R²均是卤素(例如,氟或氟和氯)。在这些实施方案的一些方面,两个R²均是烷基(例如,甲基)。在这些实施方案的一些方面,两个R²均是-OR^a。在这些实施方案的一些方面,一个R²是卤素而另一个是-OR^a。在这些实施方案的一些方面,一个R²是溴(BR)而另一

个是 $-OR^a$ 。在这些实施方案的一些方面,一个 R^2 是氯(Cl)而另一个是 $-OR^a$ 。在这些实施方案的一些方面,一个 R^2 是氟(F)而另一个是 $-OR^a$ 。在这些实施方案的一些方面, R^a 是烷基(例如,甲基或乙基)。在这些实施方案的一些方面,两个 R^2 均是 $-OR^a$ 。在这些实施方案的一些方面,两个 $-OR^a$ 与它们所连接的碳原子一起形成杂环基。

[0133] 在一些实施方案中,A是且D、 D^1 、L、 R^1 、 R^3 、 R^a 、 R^b 、 R^c 、 R^d 、X、Y、Z、W、n、m、

h和g如上文式(I)中或本文所述的实施方案或方面中的任一个所定义。

[0134] 在另一实施方案中,提供的是式(I)化合物或其药学上可接受的盐,或包含式(I)化合物或其药学上可接受的盐的药物组合物:



[0136] 其中:

[0137] W、X、Y和Z各自独立地选自CH或N;

[0138] D和 D^1 各自独立地选自键或 NR^b ;

[0139] A是任选取代的芳基或任选取代的杂芳基;

[0140] L是键、 $-C(O)-$ 、 $-(CR^cR^c)_m-$ 、 $-OC(O)-$ 或 $-C(O)NR^b-$;

[0141] R^1 独立地选自烷基、环烷基、芳基、杂芳基和杂环基;其每个被0-3次出现的 R^d 取代;

[0142] 每个 R^3 独立地选自卤素、卤代烷基、烷基、羟基和 $-OR^a$ 或两个相邻的 R^3 与它们所连接的碳原子一起形成任选取代的环基;

[0143] 每个 R^a 独立地选自烷基和卤代烷基;

[0144] 每个 R^b 独立地选自氢和烷基;

[0145] 每个 R^c 独立地选自氢、卤素、烷基、烷氧基和卤代烷氧基或两个 R^c 与它们所连接的碳原子一起形成任选取代的环烷基;

[0146] 每个 R^d 独立地选自卤素、卤代烷基、烷基、硝基、氰基和 $-OR^a$,或两个 R^d 与它们所连接的碳原子一起形成任选取代的杂环基;

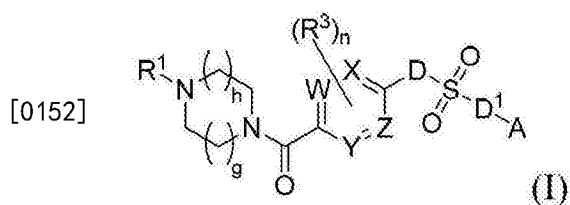
[0147] n是0、1或2;

[0148] m是1、2或3;

[0149] h是0、1、2;及

[0150] g是0、1或2。在实施方案的某些方面中,A、D、 D^1 、L、 R^1 、 R^3 、 R^a 、 R^b 、 R^c 、 R^d 、X、Y、Z、W、n、m、h和g如本文所述的实施方案或方面中的任一个所定义。

[0151] 在另一实施方案中,提供的是式(I)化合物或其药学上可接受的盐,或包含式(I)化合物或其药学上可接受的盐的药物组合物:



[0153] 其中：

[0154] W、X、Y和Z各自独立地选自CH或N；

[0155] D和D¹各自独立地选自键或NR^c；

[0156] A是任选取代的芳基或任选取代的杂芳基；

[0157] R¹独立地选自烷基、任选取代的芳基和任选取代的杂芳基；

[0158] 每个R³独立地选自卤素、卤代烷基、烷基和-OR^a；

[0159] 每个R^a独立地选自烷基、卤代烷基和任选取代的杂芳基；

[0160] 每个R^b独立地为烷基；

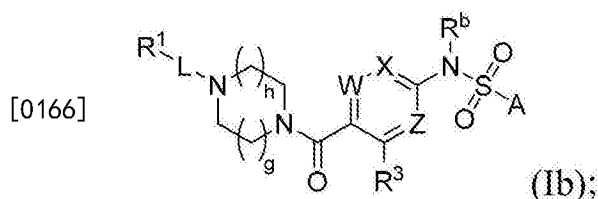
[0161] 每个R^c独立地选自氢或烷基；

[0162] n是0、1或2；

[0163] h是0、1、2；及

[0164] g是0、1或2。在实施方案的某些方面中，A、D、D¹、L、R¹、R³、R^a、R^b、R^c、R^d、X、Y、Z、W、n、m、h和g如本文所述的实施方案或方面中的任一个所定义。

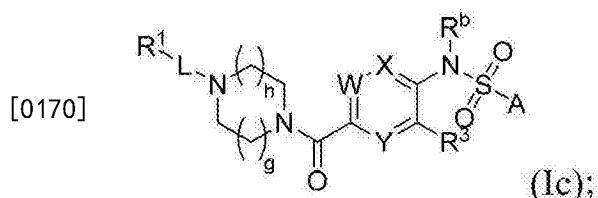
[0165] 在另一实施方案中，提供的是式 (Ib) 的化合物或药学上可接受的盐或包含式 (Ib) 的化合物或药学上可接受的盐的药物组合物：



[0167] 其中A、L、R¹、R³、R^a、R^b、R^c、R^d、W、X、Z、m、h和g如上文式 (I) 中或本文所述的实施方案或方面中的任一个所定义。

[0168] 在一些实施方案中，X、W和Z是CH。在一些实施方案中，X、W和Z中的一个N且X、W和Z中的其它两个是CH。

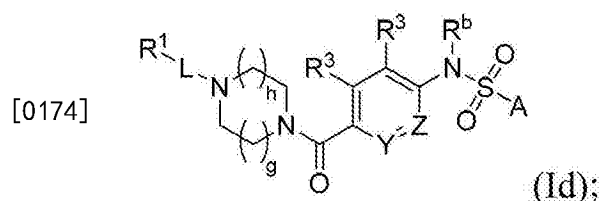
[0169] 在另一实施方案中，提供了包含式 (Ic) 的化合物或药学上可接受的盐的药物组合物或包含式 (Ic) 的化合物或药学上可接受的盐的药物组合物：



[0171] 其中A、L、R¹、R³、R^a、R^b、R^c、R^d、W、X、Y、m、h和g如上文式 (I) 中或本文所述的实施方案或方面中的任一个所定义。

[0172] 在一些实施方案中，X、Y和W是CH。在一些实施方案中，X、Y和W中的一个N且X、Y和W中的其它两个是CH。

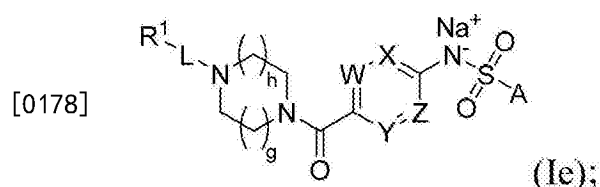
[0173] 在另一实施方案中,提供的是式 (Id) 的化合物或药学上可接受的盐或包含式 (Id) 的化合物或药学上可接受的盐的药物组合物:



[0175] 其中A、L、R¹、R³、R^a、R^b、R^c、R^d、Y、Z、m、h和g如上文式 (I) 中或本文所述的实施方案或方面中的任一个所定义。

[0176] 在一些实施方案中,Y和Z是CH。在一些实施方案中,Y和Z中的一个N且Y和Z中的一个CH。

[0177] 在另一实施方案中,提供的是式 (Ie) 的化合物或药学上可接受的盐或包含式 (Ie) 的化合物或药学上可接受的盐的药物组合物:



[0179] 其中A、L、R¹、R³、R^a、R^b、R^c、R^d、W、X、Y、Z、m、h和g如上文式 (I) 中或本文所述的实施方案或方面中的任一个所定义。

[0180] 在某些实施方案中,式I的示例性化合物包括图1和实施例中所所述的化合物。在一些实施方案中,本文所述的化合物通过与FBP结合口袋相互作用(例如,结合)来调节PKM2。例如,本文所述的化合物可与FBP结合竞争PKM2。

[0181] 在一些实施方案中,本文所述的化合物具有一种或多种本文所述的性质,例如一种或多种下列性质:其是别构调节剂(例如,活化剂);其调节FBP(例如,促进)的释放;其是FBP的调节剂(例如,激动剂),例如,结合亲和性与结合FBP亲和性相比较低、大约相同或较高的激动剂;其调节(例如,促进)四聚体PKM2的溶出;其调节(例如,促进)四聚体PKM2的装配;其相比于PK的至少一种其它同种型选择性调节(例如,活化)PKM2,例如,其对于PKM2较PKR、PKM1或PKL具有选择性;其对于PKM2的亲和性大于其对于PK的至少一种其它同种型(例如,PKR、PKM1或PKL)的亲和性。

[0182] 在另一实施方案中,用于本文所述的方法和组合物的PKM2的活化剂具有一种或多种下列机理或性质:

[0183] a. 其为PKM2的别构活化剂;

[0184] b. 其调节(例如,稳定)FBP在PKM2的结合口袋中的结合;

[0185] c. 其调节(例如,促进)从PKM2的结合口袋释放FBP;

[0186] d. 其为FBP的调节剂(例如,激动剂),例如类似物,例如,结合PKM2亲和性与结合FBP亲和性相比较低、大约相同或较高的激动剂;

[0187] e. 其调节(例如,促进)四聚体PKM2的溶出;

[0188] f. 其调节(例如,促进)四聚体PKM2的装配;

[0189] g. 其调节(例如,稳定)PKM2的四聚体构象;

[0190] h. 其调节 (例如, 促进) 含有多肽的磷酸酪氨酸与PKM2的结合;

[0191] i. 其调节 (例如, 促进) 含有多肽的磷酸酪氨酸诱导FBP从PKM2释放的能力, 例如通过诱导PKM2的构象 (例如Lys 433的位置) 的变化, 由此阻碍FBP的释放;

[0192] k. 其结合或改变Lys 433相对于FBP结合口袋的位置;

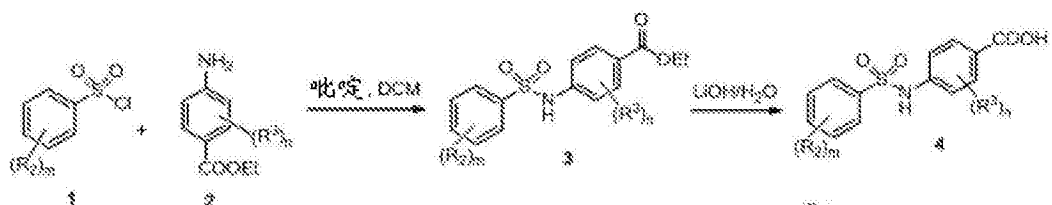
[0193] l. 其相比于PK的至少一种其它同种型选择性调节 (例如, 活化) PKM2, 例如, 其对于PKM2较PKR、PKM1或PKL中的一种或多种具有选择性;

[0194] m. 其对于PKM2的亲合性大于其对于PK的至少一种其它同种型 (例如, PKR、PKM1或PKL) 的亲合性。

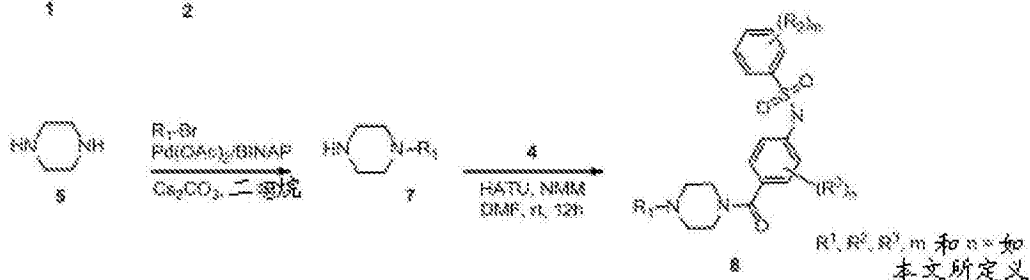
[0195] 可测试本文所述的化合物活化PKM2的能力。为了简单起见, 这些化合物的活化活性被表示为图1和整篇申请中的AC₅₀。示例性化合物示于图1。如图1所示, “A”是指EC₅₀ < 100nM的PKM2活化剂。“B”是指EC₅₀为100nM至500nM的PKM2活化剂。“C”是指EC₅₀为500nM至1000nM的PKM2活化剂。“D”是指1μM至10μM之间的EC₅₀的PKM2活化剂。“E”是指不可用的数据。

[0196] 本文所述的化合物可使用多种合成技术制备。

[0197] 流程1.



[0198]



[0199] 上文流程1是示例性流程, 描述本文所述的某些化合物的代表性合成。将磺酰氯1与胺2在标准偶合条件下反应以生成酯3。使用氢氧化锂水解3而产生羧酸4。将哌嗪 (5) 与适当的溴化物在标准钯偶合条件下反应以提供7。然后将羧酸4与哌嗪衍生物7反应以生成最终化合物8。

[0200] 如熟练技术人员可理解, 合成本文式的化合物的方法将对本领域普通技术人员而言是明显的。此外, 各种合成步骤可以替代顺序进行以便得到所需化合物。用于合成本文所述的化合物的合成化学转化和保护基团方法 (保护和脱保护) 为本领域所已知, 并且包括, 例如, 如在R.Larock, Comprehensive Organic Transformations, VCH Publishers (1989); T.W.Greene和P.G.M.Wuts, Protective Groups in Organic Synthesis, 第2版, John Wiley and Sons (1991); L.Fieser和M.Fieser, Fieser and Fieser's Reagents for Organic Synthesis, John Wiley and Sons (1994); 和L.Paquette编辑, Encyclopedia of Reagents for Organic Synthesis, John Wiley and Sons (1995) 及其后续版本中所述的方法。

[0201] 本文提供的化合物可包含一个或多个不对称中心并且由此表现为消旋化合物和外消旋混合物、单一对映体、单独非对映体和非对映体混合物。这些化合物的所有此类异构

形式被明确地包括在本发明范围之内。除非另有说明,当化合物由未详细说明立体化学的结构命名或描述并且具有一个或多个手性中心时,应理解代表化合物的所有可能立体异构体。本文提供的化合物还可包含可限制键旋转的键合(例如,碳-碳键)或取代基,例如由存在环或双键而引起的限制。因此,明确包括所有反式/顺式和E/Z异构体。

[0202] 本文提供的化合物(例如式I化合物)还可包含一种或多种同位素取代。例如,H可以是任何同位素形式,包括 ^1H 、 ^2H (D或氘)和 ^3H (T或氚);C可以是任何同位素形式,包括 ^{12}C 、 ^{13}C 和 ^{14}C ;O可以是任何同位素形式,包括 ^{16}O 和 ^{18}O ;等等。本文提供的化合物还可以多种互变异构形式呈现,在此类情况下,明确包括本文所述的化合物的所有互变异构形式,即使可以表示仅仅一种单一互变异构形式(例如,环系统的烷基化可在多个位点发生烷基化;所有此类反应产物明确地包括)。此类化合物的所有异构形式明确地包括。本文所述的化合物的所有晶体形式明确地包括。

[0203] 本文提供的化合物包括化合物自身,以及其盐和前药(如果适用的话)。例如,盐可在阴离子和本文所述的化合物上的带正电的取代基(例如,氨基)之间形成。适宜的阴离子包括氯离子、溴离子、碘离子、硫酸根、硝酸根、磷酸根、柠檬酸根、甲磺酸根、三氟乙酸根和乙酸根。同样,盐还可在阳离子和本文所述的化合物上的带负电的取代基(例如,羧酸根)之间形成。适宜的阳离子包括钠离子、钾离子、镁离子、钙离子和铵离子例如四甲基铵离子。前药的实例包括酯和其它药学上可接受的衍生物,其经向受治疗者施用后能够提供活性化合物。

[0204] 可通过添加适当官能度对本文提供的化合物进行修饰以增强选定的生物性质(例如靶向特定组织)。此类修饰为本领域所已知并且包括增加进入给定生物隔室的生物穿透(例如,血液、淋巴系统、中枢神经系统),增加口服利用度,增加溶解度以允许通过注射施用,改变代谢以及改变排泄速率。

[0205] 在替代实施方案中,本文所述的化合物可用作平台或支架,该平台或支架可在用于制备化合物的衍生物和/或化学文库的组合化学技术中应用。化合物的此类衍生物和文库具有生物活性并且可用于鉴定和设计具有特定活性的化合物。适于利用本文所述的化合物的组合技术为本领域所已知(如由Obrecht,D.和Villalagrodo,J.M.,Solid-Supported Combinatorial and Parallel Synthesis of Small-Molecular-Weight Compound Libraries,Pergamon-Elsevier Science Limited(1998)示例),并且包括例如“混合裂分(split and pool)”或“平行(parallel)”合成技术、固相和溶液相技术以及编码技术(参见,例如,Czarnik,A.W.,Curr.Opin.Chem.Bio.,(1997)1,60。因此,一个实施方案涉及使用本文所述的化合物以产生衍生物或化学文库的方法,其包括:1)提供包含多个孔的主体;2)在每个孔中提供一种或多种由本文所述的方法鉴定的化合物;3)在每个孔中提供其它一种或多种化学品;4)从每个孔中分离所得的一种或多种产物。替代实施方案涉及使用本文所述的化合物以产生衍生物或化学文库的方法,其包括:1)提供一种或多种连接至固体载体的本文所述的化合物;2)用一种或多种其它化学品处理一种或多种连接至固体载体的由本文所述的方法鉴定的化合物;3)从每个孔中分离所得的一种或多种产物。在上述方法中,“标签”或鉴定剂或标记部分可连接至本文所述的化合物或其衍生物和/或与本文所述的化合物或其衍生物分离,以促进所需产物或其中间体的示踪、鉴定或分离。此类部分为本领域所已知。用于前述方法的化学品可包括,例如溶剂、试剂、催化剂、保护基团和脱保护基团试

剂等。此类化学品的实例为在本文提及的各种合成和保护基化学教科书和论文中出现的化学品。

[0206] 定义

[0207] 术语“卤代”或“卤素”是指任何氟、氯、溴或碘的任何基团。

[0208] 术语“烷基”是指可以是直链或支链的烃链,包含所示数目的碳原子。例如,C₁-C₁₂烷基表示该基团可在其中含有1至12个(含)碳原子。术语“卤代烷基”是指其中一个或多个氢原子被卤素取代的烷基,并包括其中所有氢被卤素取代的烷基部分(如,全氟烷基)。术语“芳基烷基”或“芳烷基”是指烷基氢原子被芳基取代的烷基部分。芳烷基包括其中不止一个氢原子被芳基取代的基团。“芳基烷基”或“芳烷基”的实例包括苄基、2-苯基乙基、3-苯基丙基、9-苊基、二苯甲基和三苯甲基。

[0209] 术语“亚烷基”是指二价烷基、例如-CH₂-、-CH₂CH₂-和-CH₂CH₂CH₂-。

[0210] 术语“链烯基”是指包含2-12个碳原子且含有一个或多个双键的直链或支链烃链。链烯基例如包括但不限于烯丙基、丙烯基、2-丁烯基、3-己烯基和3-辛烯基。双键碳之一可任选是链烯基取代基的连接点。术语“炔基”是指包含2-12个碳原子且特征在于含有一个或多个三键的直链或支链烃链。术语“炔基”是指包含2-12个碳原子且特征在于含有一个或多个三键的直链或支链烃链。炔基例如包括但不限于乙炔基、炔丙基和3-己炔基。三键碳之一可任选是炔基取代基的连接点。

[0211] 术语“烷基氨基”和“二烷基氨基”分别是指-NH(烷基)和-NH(烷基)₂。术语“芳烷基氨基”是指-NH(芳烷基)基团。术语烷基氨基烷基是指(烷基)NH-烷基-基团；术语二烷基氨基烷基是指(烷基)₂N-烷基-基团。术语“烷氧基”是指-O-烷基基团。术语“巯基”是指SH基团。术语“硫代烷氧基”是指-S-烷基基团。术语硫代芳基氧基是指-S-芳基基团。

[0212] 术语“芳基”是指芳香性单环、双环或三环烃环系统,其中能够取代的任何环原子可被取代(例如,被一种或多种取代基)。芳基部分例如包括但不限于苯基、萘基和蒽基。

[0213] 本文所用的术语“环烷基”包括含有3-12个碳的饱和的环状、双环、三环或多环非芳族烃基。任何可取代的环原子可被取代(例如,被一种或多种取代基)。环烷基可包含稠环或螺环。稠环是公用碳原子的环。环烷基部分的实例包括但不限于环丙基、环己基、甲基环己基、金刚烷基和降冰片基。

[0214] 术语“杂环基”或“杂环基团”是指3元至14元三环非芳族环结构(例如,3元至14元环,更优选3元至7元环),其环结构包括1-4个独立选自O、N和S的杂原子。杂环基或杂环基可包含稠环或螺环。杂环还可以是多环,每个基团具有例如5-7个环成员。术语“杂环基”或“杂环基团”包括饱和和部分饱和的杂环基结构。术语“杂芳基”是指5-14元(即,5-8元单环、8-12元双环或11-14元三环)芳族环系统,如果是单环,则含1-3个环杂原子,如果是双环,则含1-6个环杂原子,如果是三环,则含1-9个环杂原子,所述环杂原子独立地选自O、N和S(例如,如果是单环、双环或三环则分别含1-3、1-6或1-9个N、O或S的环杂原子)。任何可取代的环原子可被取代(例如,被一个或多个取代基)。杂环基和杂芳基包括例如,噻吩、噻蒎、呋喃、吡喃、异苯并呋喃、色原烯、氧杂蒎、氧硫杂蒎、吡咯、咪唑、吡啶、异噁唑、异噻唑、吡啶、吡嗪、嘧啶、哒嗪、吲哚、异吲哚、吲唑、嘌呤、喹啉、异喹啉、喹啉、酞嗪、茶啖、喹噁啉、喹啉、噌啉、喋啖、卟啉、卟啉、菲啖吡啖、嘧啖、菲咯啉、吩嗪、吩吡嗪、吩噻嗪、呋咱、吩噻嗪、吡咯烷、氧杂环戊烷(oxolane)、硫杂环戊烷(thiolane)、噁唑、哌啖、哌嗪、吗啉、内酯、内酰胺

例如氮杂环丁酮和吡咯酮、磺内酰胺、磺内酯等。杂环或杂芳基环可在一个或多个位置被如本文所述的取代基取代,所述取代基例如卤素、烷基、芳烷基、链烯基、炔基、环烷基、羟基、氨基、硝基、硫氢基、亚氨基、酰氨基、磷酸酯、膦酸酯、亚膦酸酯、羰基、羧基、甲硅烷基、醚、烷硫基、磺酰基、酮、醛、酯、杂环基、芳族或杂芳族部分、 $-\text{CF}_3$ 、 $-\text{CN}$ 或等。

[0215] 本文所述的术语“杂环基烷基”是指被杂环基团取代的烷基。

[0216] 术语“环烯基”是指含有5-12个碳、优选5-8个碳的部分饱和的、非芳族的、单环、双环或三环的烃基。不饱和碳可任选是环烯基取代基的连接点。任何可取代的环原子可被取代(例如,被一种或多种取代基)。环烯基可包含稠环或螺环。稠环是共享公用碳原子的环。环烯基部分的实例包括但不限于环己烯基、环己二烯基或降冰片烯基。

[0217] 术语“杂环烯基”是指部分饱和的非芳族5-10元单环、8-12元双环或11-14元三环环系统,如果是单环,则含1-3个环杂原子,如果是双环,则含1-6个环杂原子,如果是三环,则含1-9个环杂原子,所述环杂原子独立地选自O、N和S(例如,如果是单环、双环或三环则分别含1-3、1-6或1-9个N、O或S的环杂原子)。不饱和的碳原子或杂原子可任选是杂环烯基取代基的连接点。任何可取代的环原子可被取代(例如,被一种或多种取代基)。杂环烯基可包含稠环。稠环是共享公用碳原子的环。杂环烯基的实例包括但不限于四氢吡啶基和二氢吡喃基。

[0218] 本文所用的术语“杂芳烷基(hetaralkyl)”和“杂芳烷基”是指被杂芳基取代的烷基。本文提供的化合物的环杂原子包括N-O、S(O)和S(O)₂。

[0219] 术语“氧代”指氧原子,当连接于碳时其形成羰基,当连接于氮时形成N-氧化物,当连接于硫时形成亚砷或砷。

[0220] 术语“酰基”是指烷基羰基、环烷基羰基、芳基羰基、杂环基羰基或杂芳基羰基取代基,其中任一基团还可被进一步取代(例如,被一种或多种取代基)。

[0221] 术语“取代基”是指“取代”于烷基、环烷基、链烯基、炔基、杂环基、杂环烯基、环烯基、芳基或杂芳基上任何可取代原子处的基团。任何可取代的原子可被取代。除非另有说明,此类取代基包括但不限于烷基(例如,C₁、C₂、C₃、C₄、C₅、C₆、C₇、C₈、C₉、C₁₀、C₁₁、C₁₂直链或支链烷基)、环烷基、卤代烷基(例如,全氟烷基例如CF₃)、芳基、杂芳基、芳烷基、杂芳烷基、杂环基、链烯基、炔基、环烯基、杂环烯基、烷氧基、卤代烷氧基(例如,全氟烷氧基例如OCF₃)、卤素、羟基、羧基、羧酸酯、氰基、硝基、氨基、烷基氨基、SO₃H、硫酸酯、磷酸酯、亚甲基二氧基(-O-CH₂-O-其中氧与邻近的原子相连)、亚乙基二氧基、氧代(不是杂芳基上的取代基)、硫酮(例如,C=S)(不是杂芳基上的取代基)、亚氨基(烷基、芳基、芳烷基)、S(O)_n烷基(其中n是0-2)、S(O)_n芳基(其中n是0-2)、S(O)_n杂芳基(其中n是0-2)、S(O)_n杂环基(其中n是0-2)、胺(单-、二-、烷基、环烷基、芳烷基、杂芳烷基、芳基、杂芳基及其组合)、酯(烷基、芳烷基、杂芳烷基、芳基、杂芳基)、酰胺(单-、二-、烷基、芳烷基、杂芳烷基、芳基、杂芳基及其组合)、磺酰胺(单-、二-、烷基、芳烷基、杂芳烷基及其组合)。在一个方面,基团上的取代基独立地是任何一个单一取代基,或上述取代基的任何子集。在另一个方面,取代基自身可以被任一上述取代基取代。

[0222] 术语“选择性”是指对PKM2的调节(例如,活化)为对PKM1的至少2倍、3倍、4倍、5倍、6倍或10倍。

[0223] 本文所用的术语“活化剂”是指(可测量地)增加丙酮酸激酶(例如,PKM2)的活性或

使丙酮酸激酶(例如,PKM2)活性增加至大于PKM2的基态活性水平的水平的试剂。例如,活化剂可模拟由天然配体(例如,FBP)引起的效应。由本文提供的化合物引起的活化剂效应可与由天然配体引起的活化效应相比为相同或较高或较低水平,但是引起相同类型的效应。可评价本文提供的化合物以当施用所述化合物时通过直接或间接测量丙酮酸激酶的活性而确定是否其为活化剂。可测量本文提供的化合物例如相对于对照物质的活性。在某些情况下,所测的测试化合物的活性是针对活化PKM2。可例如通过监测物质例如ATP或NADH的浓度测量PKM2的活性。

[0224] 缩写Me、Et、Ph、Tf、Nf、Ts、Ms分别表示甲基、乙基、苯基、三氟甲磺酰基、九氟磺酰基、对甲苯磺酰基和甲磺酰基。本领域中具有普通技能的有机化学师所用的更综合的缩写列表出现在Journal of Organic Chemistry的每卷的第一期中;该列表通常示于标题为标准缩写列表(Standard List of Abbreviations)的表中。所述列表中所含的缩写以及本领域中具有普通技能的有机化学师所用的所有缩写由此通过引用并入。

[0225] 评价化合物的方法

[0226] 可以通过本领域已知的方法评价本文所述的化合物调节PKM2(例如,活化PKM2)的能力。在一些实施方案中,在丝氨酸缺陷条件下评价本文所述的化合物调节PKM2(例如活化PKM2)的能力。在一些实施方案中,示例性方法包括将化合物与允许评估调节(例如,活化)PKM2的能力的基于细胞的测定相接触。例如,可将候选化合物与细胞相接触,并且测量氧消耗量或乳酸盐生成量。细胞的磷酸烯醇丙酮酸的变化、甘油-磷酸的变化、核糖或脱氧核糖的变化、脂质合成的变化或葡萄糖转化为脂质或核酸或氨基酸或蛋白质的变化也可用于评价化合物调节PKM2(例如,活化PKM2)的能力。该评价也可包括测量丙酮酸的变化或测定线粒体膜电势的改变,例如通过荧光电位器染料来测量。

[0227] 筛选/测试测定法中测定的PKM酶的活性可通过例如监测存在于反应混合物中的底物(例如,ATP或NADH)的浓度来测量。通过乳酸脱氢酶将由丙酮酸激酶的酶活性产生的丙酮酸转化为乳酸,其需要消耗NADH($\text{NADH} \rightarrow \text{NAD}^+$)。因此,PKM2的活性可通过监测NADH的消耗量经由例如荧光测定法来间接测量。此外,PKM2酶的活性可通过测量ATP的生成来直接监测,由于当磷酸烯醇丙酮酸转化为丙酮酸时ATP生成。用于在反应混合物中监测底物的方法包括例如,吸光度、荧光、拉曼散射、磷光、发光、荧光素酶测定法和放射性。

[0228] 筛选程序需要反应混合物中存在特定组分。测定中所用的组分包括例如,二磷酸核苷(例如,ADP)、磷酸烯醇丙酮酸、NADH、乳酸脱氢酶、FBP、还原剂(例如,二硫苏糖醇)、去污剂(例如,Brij 35)、甘油和溶剂(例如,DMSO)。示例性反应条件存在于表1中。

[0229] 表1

[0230]

反应条件的组分	活化测定中的量
ADP	0.1–5.0mM
磷酸烯醇丙酮酸	0.1–5.0mM
NADH	10–1000 μ M
乳酸脱氢酶	0.1–10个单位
果糖-1,6-二磷酸	0
DTT	0.1–50mM

Brij 35	0.01-1%
甘油	0.1-10%
丙酮酸激酶M2 (用于筛选)	1-100pg
DMSO	1-10%

[0231] 在一些实施方案中,可在细胞/立体测定中评价化合物例如本文所述的化合物。例如,用本文所述的化合物(即,PKM2活化剂)处理细胞,并且评价化合物,例如评价其进入细胞并且结合PKM2、从而诱导PKM2的活化构象的能力。然后可用PBS冲洗过量未结合的化合物,例如通过在干冰上快速冷冻将细胞溶解,然后添加含去污剂的溶解缓冲液。然后可除去在其中活化的PKM2保持完整的溶解产物,并且加至化学品混合物(包括测量丙酮酸激酶活性所必需的化学品)。该测量可与另一个测量(例如与LDHa酶偶合的测定)偶合。然后可将所测量的丙酮酸激酶活性的量归一化为溶解产物中的总蛋白含量,并且与添加至细胞中的PKM2活化剂的浓度有关。这可以允许获得AC₅₀(PKM2被活化50%的浓度)。与模拟物处理的细胞相比,也可计算出活性的总倍数增加,并且可使用“活化的最大水平”区分完全活化PKM2的化合物与仅部分活化PKM2的化合物。在从组织(例如,在细胞肿瘤中)测量PKM2活性的情况下,可向包含感兴趣的组织/肿瘤的动物给药化合物。在其中已感兴趣的组织/肿瘤中实现暴露的特定时段后,组织/肿瘤然后可从动物中收集,快速冷冻,然后溶解,匀浆化。丙酮酸激酶活性在该溶解产物的量然后可被如上所述定量。

[0232] 用于本文所述的筛选/测试方法的PKM1和PKM2可通过本领域已知的任何方法产生,以用于表达重组蛋白质。例如,编码所需多肽的核酸可被引入到各种细胞类型或无细胞系统中用于表达。可产生真核细胞(例如,COS、HEK293T、CHO和NIH细胞系)和原核细胞(例如,大肠杆菌)表达系统,在其中PKM序列被引入到质粒或其它载体中,然后被用于转化活细胞。其中PKM cDNA包含整个开放阅读框或其生物活性片段的构建体以正确定向被插入到表达质粒中并且可用于蛋白质表达。原核细胞和真核细胞表达系统允许表达并恢复融合蛋白,其中PKM蛋白被共价连接至氨基末端或羧基末端侧上的标签分子,其促进鉴定和/或纯化。可使用的标签的实例包括六聚组氨酸、HA、FLAG和c-myc表位标签。酶促裂解或化学裂解位点可在PKM蛋白质与标签分子之间被工程化以使标签可在纯化之后被移除。

[0233] 用作PKM2活化剂的化合物显示PKM2酶在FBP不存在下的特异性和活化的水平为在FBP存在下的10%、15%、20%、25%、30%、35%、40%、45%、50%、55%、60%、65%、70%、75%、80%、85%、90%、95%、99%或100%。此外,可在磷酸酪氨酸肽的存在或不存在下评价化合物。结合PKM2的磷酸酪氨酸肽导致FBP与PKM2的解离以及PKM2从活性四聚体形式至无活性形式的构象变化。结合PKM2并且甚至在磷酸酪氨酸肽存在下以活性构象锁定酶的化合物将导致将生物化学中间体从糖酵解分流至其它中间体的生物合成中所需的PKM2的别构调控的损失。反过来,这将导致抑制癌细胞、活化免疫细胞和脂肪细胞的生长。

[0234] 治疗方法

[0235] 在一个实施方案中,提供的是用于治疗或预防如本文所述的(例如,治疗)的疾病、病症或障碍的方法,所述方法包括施用化合物、化合物的药学上可接受的盐或包含本文所述的化合物(例如,式(I)、(I-a)、(II)或在图1中的化合物)的药物组合物。

[0236] 可向在培养物中的细胞例如体外或离体施用、或向受试者例如体内施用本文所述的化合物和组合物以治疗、预防和/或诊断多种障碍,包括下文所述的那些障碍。

[0237] 如本文所用的,术语“治疗”被定义为为了治愈、医治、缓和、减轻、改变、治疗、缓解、改善或影响障碍、一种或多种障碍的症状或易患障碍的体质(例如,以预防障碍的至少一种症状或以延迟障碍的至少一种症状),向受试者(例如患者)单独或与第二化合物组合地应用或施用化合物,或向来自具有障碍(例如,本文所述的障碍)、障碍的症状、或易患障碍的体质的受试者(例如患者)的分离的组织或细胞(例如细胞系)应用或施用化合物。

[0238] 如本文所用的,化合物有效治疗障碍的量或“治疗有效量”是指化合物经向受试者施用单次或多次剂量后在治疗细胞或在治愈、缓和、减轻或改善具有障碍的受试者中有效(优于在不存在此类治疗下所预期的)的量。

[0239] 如本文所用的,化合物有效预防障碍的量或化合物的“预防有效量”是指经向受试者施用单次或多次剂量施用后在预防或延迟障碍或障碍的症状发作或复发中有效的量。

[0240] 如本文所用的,术语“受试者”旨在包括人和非人动物。示例性人受试者包括具有障碍(例如本文所述的障碍)的人患者或正常受试者。术语“非人动物”包括所有脊椎动物,例如非哺乳动物(例如鸡、两栖动物、爬行动物)和哺乳动物,例如非人灵长类动物、家养动物和/或农业有用的动物,例如羊、狗、猫、牛、猪等。

[0241] 肿瘤性障碍

[0242] 本文所述的化合物或组合物可用于治疗肿瘤性障碍。“肿瘤性障碍”是特征在于具有自发生长或复制的能力的细胞的疾病或病症,例如特征在于增殖性细胞生长的异常状态或病症。示例性肿瘤性障碍包括:癌、肉瘤、转移性障碍(例如,从前列腺、结肠、肺、乳房和肝来源产生的肿瘤)、造血肿瘤性障碍(例如白血病、转移性肿瘤)。流行性癌包括:乳腺癌、前列腺癌、结肠癌、肺癌、肝癌和胰脏癌。用化合物治疗可以是有效缓解肿瘤性障碍的至少一种症状(例如细胞增殖减少、肿瘤质量下降等)的量。

[0243] 所公开的方法用于预防和治疗癌症,包括例如实体瘤、软组织肿瘤和其转移灶。所公开的方法也用于治疗非实体瘤。示例性实体肿瘤包括各种器官系统的恶性肿瘤(例如,肉瘤、腺癌和癌),例如肺、乳房、淋巴样、胃肠道(例如结肠)和泌尿生殖道(例如肾脏、泌尿道上皮或睾丸肿瘤)、咽、前列腺和卵巢的恶性肿瘤。示例性腺癌包括结肠直肠癌、肾细胞癌、肝癌、肺非小细胞癌和小肠癌。

[0244] 其它示例性癌包括:成人急性成淋巴细胞性白血病;儿童急性成淋巴细胞性白血病;成人急性髓样白血病;肾上腺皮质癌;儿童肾上腺皮质癌;AIDS相关淋巴瘤;AIDS相关恶性肿瘤;直肠癌;儿童小脑星形细胞瘤;儿童大脑星形细胞瘤;肝外胆管癌症;膀胱癌;儿童膀胱癌;骨肉瘤/恶性纤维组织细胞瘤;儿童脑干神经胶质瘤;成人脑瘤;儿童脑瘤,脑干神经胶质瘤;儿童脑瘤,小脑星形细胞瘤;儿童脑瘤,大脑星形细胞瘤/恶性神经胶质瘤;儿童脑瘤,室管膜瘤;儿童脑瘤,髓母细胞瘤;儿童脑瘤,幕上原始神经外胚叶瘤;儿童脑瘤,视通路和下丘脑神经胶质瘤;脑瘤儿童(其它);乳腺癌;妊娠期乳腺癌;儿童乳腺癌;男性乳腺癌;儿童支气管腺瘤/类癌;儿童类癌瘤;胃肠类癌瘤;肾上腺皮质癌;胰岛细胞癌;原发灶不明癌;儿童原发性中枢神经系统淋巴瘤;小脑星形细胞瘤;儿童大脑星形细胞瘤/恶性神经胶质瘤;宫颈癌;儿童癌症;慢性淋巴细胞性白血病;慢性髓性白血病;慢性骨髓增殖性障碍;髓鞘透明细胞肉瘤;结肠癌;儿童结直肠癌;皮肤T细胞淋巴瘤;子宫内膜癌;儿童室管膜瘤;卵巢上皮癌;食管癌;儿童食管癌;尤因氏瘤;颅外胚细胞瘤儿童;性腺外胚细胞瘤;肝外胆管癌;眼癌,眼内黑素瘤;眼癌,视网膜母细胞瘤;胆囊癌;胃癌;儿童胃癌;胃肠类癌瘤;儿童颅

外胚细胞瘤;性腺外胚细胞瘤;卵巢胚细胞瘤;妊娠期滋养细胞瘤;儿童脑干神经胶质瘤;儿童视通路和下丘脑神经胶质瘤;毛细胞白血病;头颈癌;成人(原发性)肝细胞(肝)癌;儿童(原发性)肝细胞(肝)癌;成人霍奇金淋巴瘤;儿童霍奇金淋巴瘤;妊娠期霍奇金淋巴瘤;下咽癌;儿童下丘脑和视通路神经胶质瘤;眼内黑素瘤;胰岛细胞癌(内分泌胰腺);卡波西肉瘤;肾癌;喉癌;喉癌儿童;成人急性成淋巴细胞性白血病;儿童急性成淋巴细胞性白血病;成人急性髓样白血病;儿童急性髓样白血病;慢性淋巴细胞性白血病;慢性骨髓性白血病;毛细胞白血病;唇和口腔癌;成人(原发性)肝癌;儿童(原发性)肝癌;非小细胞肺癌;小细胞肺癌;成人急性成淋巴细胞性白血病;儿童急性成淋巴细胞性白血病;慢性淋巴细胞性白血病;AIDS相关淋巴瘤;(原发性)中枢神经系统淋巴瘤;皮肤T细胞淋巴瘤;成人霍奇金淋巴瘤;儿童霍奇金淋巴瘤;妊娠期霍奇金淋巴瘤;成人非霍奇金淋巴瘤;儿童非霍奇金淋巴瘤;妊娠期非霍奇金淋巴瘤;原发性中枢神经系统淋巴瘤;瓦尔登斯特伦巨球蛋白血症;男性乳腺癌;成人恶性间皮瘤;儿童恶性间皮瘤;恶性胸腺瘤;儿童髓母细胞瘤;黑素瘤;眼内黑素瘤;梅克尔细胞癌;恶性间皮瘤;原发灶不明转移性颈鳞癌;儿童多发性内分泌腺瘤综合征;多发性骨髓瘤/浆细胞肿瘤;草样真菌病;骨髓增生异常综合征;慢性髓性白血病;儿童急性髓样白血病;多发性骨髓瘤;慢性骨髓增殖性障碍;鼻腔和鼻旁窦癌;鼻咽癌;儿童鼻咽癌;神经母细胞瘤;成人非霍奇金淋巴瘤;儿童非霍奇金淋巴瘤;妊娠期非霍奇金淋巴瘤;非小细胞肺癌;儿童卵巢癌;口腔和唇癌;口咽癌;骨肉瘤/骨恶性纤维组织细胞瘤;卵巢癌儿童;卵巢上皮癌;卵巢胚细胞瘤;卵巢低度恶性潜在肿瘤;胰腺癌;胰腺癌儿童;胰岛细胞胰腺癌;鼻旁窦和鼻腔癌;甲状旁腺癌;阴茎癌;嗜铬细胞癌;儿童松果体和幕上原始神经外胚叶瘤;垂体瘤;浆细胞肿瘤/多发性骨髓瘤;胸膜肺母细胞瘤;妊娠期乳癌;妊娠期霍奇金淋巴瘤;妊娠期非霍奇金淋巴瘤;原发性中枢神经系统淋巴瘤;成人原发性肝癌;儿童原发性肝癌;前列腺癌;直肠癌;肾细胞(肾)癌;儿童肾细胞癌;肾盂和输尿管移行细胞癌;视网膜母细胞瘤;儿童横纹肌肉瘤;涎腺癌;儿童涎腺癌;肉瘤,尤因氏瘤;卡波西氏肉瘤;肉瘤(骨肉瘤)/骨恶性纤维组织细胞瘤;肉瘤,儿童横纹肌肉瘤;成人软组织肉瘤;儿童软组织肉瘤;赛扎里综合征;皮肤癌;儿童皮肤癌;皮肤癌(黑素瘤);梅克尔细胞皮肤癌;小细胞肺癌;小肠癌;成人软组织肉瘤;儿童软组织肉瘤;转移性原发不明颈鳞癌;胃癌;儿童胃癌;儿童幕上原始神经外胚叶瘤;皮肤T细胞淋巴瘤;睾丸癌;儿童胸腺癌;恶性胸腺癌;甲状腺癌;儿童甲状腺癌;肾盂和输尿管的移行细胞癌;妊娠期滋养细胞癌;儿童未知原发灶癌;儿童罕见癌;输尿管和肾盂移行细胞癌;尿道癌;子宫肉瘤;阴道癌;视通路和下丘脑神经胶质瘤儿童;外阴癌;瓦尔登斯特伦巨球蛋白血症;和肾母细胞瘤。根据本文所述的方法也可治疗或预防前述癌的转移。

[0245] 癌症联合疗法

[0246] 在一些实施方案中,本文所述的化合物与一种或多种其它癌症治疗一起施用。示例性癌症治疗包括,例如:化疗、靶向疗法例如抗体疗法、免疫疗法和激素疗法。如下提供这些治疗中的每种治疗的实例。

[0247] 化疗

[0248] 在一些实施方案中,本文所述的化合物与一种或多种化疗一起施用。化疗是用可以破坏癌细胞的药物治疗癌症。“化疗”通常是指相比于靶向疗法通常快速影响分裂细胞的细胞毒药物。化疗药物以各种可能方法干扰细胞分裂,例如干扰DNA复制或新形成的染色体

的分离。大多数化疗形式靶向所有快速分裂的细胞并且对癌细胞不具有特异性,尽管由于很多癌细胞不能修复DNA损伤而正常细胞通常可以修复DNA损伤,可产生一些程度的特异性。

[0249] 用于癌症疗法的化疗剂的实例包括,例如抗代谢药(例如甲酸、嘌呤和嘧啶衍生物)和烷化剂(例如,氮芥、亚硝基脲、铂、烷基磺酸酯、胍类、三氮烯类、氮丙啶类、纺锤体毒剂、细胞毒剂、拓扑异构酶抑制剂及其它)。示例性试剂包括阿柔比星、放线菌素、阿曲替诺因(Alitretinon)、六甲蜜胺、氨基嘌呤、氨基酮戊酸、氨柔比星、安吡啶、阿那格雷、三氧化二砷、门冬酰胺酶、阿曲生坦、贝罗替康(Belotecan)、贝沙罗汀、苯达莫司汀(endamustine)、博来霉素、硼替佐米、白消安、喜树碱、卡培他滨、卡铂、卡波醌、卡莫氟、卡莫司汀塞来昔布、苯丁酸氮芥、甲川氯、顺铂、克拉屈滨、氯法拉滨、克立他酶(Crisantaspase)、环磷酰胺、阿糖胞苷、达卡巴嗪、更生霉素、柔红霉素、地西他滨、秋水仙胺、多西他赛、多柔比星、乙法昔罗、Elesclomol、依沙芦星、依诺他滨、表柔比星、雌莫司汀、依托格鲁、依托泊苷、氟尿苷、氟达拉滨、氟尿嘧啶(5FU)、福莫司汀、吉西他滨、卡氮芥糯米纸胶囊剂(Gliadel)植入剂、羟基脲(Hydroxycarbamide)、羟基脲(Hydroxyurea)、伊达比星、异环磷酰胺、伊立替康、伊罗夫文、伊沙匹隆、Larotaxel、左亚叶酸、多柔比星脂质体、柔红霉素脂质体、氯尼达明、洛莫司汀、硫蒽酮、甘露舒凡、马索罗酚、美法仑、疏嘌呤、美司钠、甲氨蝶呤、氨基酮戊酸甲酯、二溴甘露醇、米托胍脲、米托坦、丝裂霉素、米托蒽醌、奈达铂、尼莫司汀、Oblimersen、Omacetaxine、Ortataxel、奥利沙伯、紫杉醇、培门冬酶、培美曲塞、喷司他丁、吡柔比星、Pixantrone、普卡霉素、吡吩姆钠、泼尼莫司汀、丙卡巴肼、雷替曲塞、雷莫司汀、卢比替康、Sapacitabine、司莫司汀、Sitimagene ceradenovec、沙铂、链脲菌素、他拉泊芬、替加氟-尿嘧啶、替莫泊芬、替莫唑胺、替尼泊苷、Tasetaxel、睾内酯、四硝酸盐、噻替派、噻唑羧胺核苷(Tiazofurin)、硫鸟嘌呤、替吡法尼(Tipifarnib)、托泊替康、曲贝替定、三亚胺醌、三乙撑密胺、三铂(Triplatin)、维A酸(Tretinoin)、曲奥舒凡、曲磷胺、乌拉莫司汀、戊柔比星、维替泊芬、长春碱、长春新碱、长春他辛、长春氟宁、长春瑞滨、伏立诺他(Vorinostat)、左柔比星和其它本文所述的细胞生长抑制剂或细胞毒剂。

[0250] 由于一些药物共同施用的作用优于单独施用,所以通常同时给予两种或更多种药物。通常,两种或更多种化疗剂用作联合化疗。在一些实施方案中,化疗剂(包括联合化疗)可用于与本文所述的化合物联合。

[0251] 靶向疗法

[0252] 在一些实施方案中,本文所述的化合物与一种或多种靶向疗法一起施用。靶向疗法指定试剂对癌细胞的失调蛋白具有特异性的用途。小分子靶向疗法药物通常是在癌细胞内的突变蛋白、过表达蛋白或在其它方面关键的蛋白上的酶结构域的抑制剂。最突出的实例是酪氨酸激酶抑制剂例如Axitinib、博舒替尼(Bosutinib)、西地替尼、达沙替尼、埃罗替尼、伊马替尼、吉非替尼、拉帕替尼、来他替尼、尼罗替尼、Semaxanib、索拉非尼、舒尼替尼和凡德他尼,且也是细胞周期蛋白依赖性激酶抑制剂例如Alvociclib和Seliciclib。单克隆抗体疗法是另一种策略,其中治疗剂为特异性结合在癌细胞表面上的蛋白质的抗体。实例包括通常用于乳癌的抗-HER2/neu抗体曲妥珠单抗(HERCEPTIN®),和通常用于多种B细胞恶性肿瘤的抗-CD20抗体利妥昔单抗和托西莫单抗。其它示例性抗体包括西妥昔单抗、帕尼单抗、曲妥珠单抗、阿伦单抗、贝伐单抗、依决洛单抗和吉妥珠单抗。示例性融合蛋白

包括Aflibercept和地尼白介素(Denileukin diftitox)。在一些实施方案中,靶向疗法可用于与本文所述的化合物联合。

[0253] 靶向疗法也可包括可结合细胞表面受体或肿瘤周围受侵袭的细胞外基质的作为“归巢装置”的小肽。与这些肽(例如,RGD)连接的放射性核素最终杀死癌细胞(如果核素在细胞附近衰变的话)。此类疗法的实例包括BEXXAR®。

[0254] 免疫疗法

[0255] 在一些实施方案中,本文所述的化合物与一种或多种免疫疗法一起施用。癌症免疫疗法是指设计用于诱导患者自身免疫系统以与肿瘤斗争的一组不同的治疗策略。用于产生对抗肿瘤的免疫反应的现代方法包括浅性膀胱癌的血管内BCG免疫疗法,以及使用干扰素和其它细胞因子以在肾细胞癌和黑素瘤患者中诱导免疫反应。

[0256] 异基因造血干细胞移植可视为一种免疫疗法形式,因为供者的免疫细胞将经常以移植抗肿瘤效应攻击肿瘤。在一些实施方案中,免疫治疗剂可用于与本文所述的化合物联合。

[0257] 激素疗法

[0258] 在一些实施方案中,本文所述的化合物与一种或多种激素疗法一起施用。可通过提供或拦阻某些激素抑制一些癌症的生长。激素敏感性肿瘤的共有实例包括某些类型的乳腺癌和前列腺癌。移除或拦阻雌激素或睾酮通常为一种重要的其它治疗。在某些癌症中,施用激素激动剂例如孕激素可以是治疗有益的。在一些实施方案中,激素疗法剂可用于与本文所述的化合物联合。

[0259] 肥胖症和脂肪障碍

[0260] 本文所述的化合物或组合物可用于治疗或预防肥胖症,例如在人受试者中,例如儿童或成人受试者。“肥胖症”是指其中受试者的体重指数大于或等于30的病症。很多本文所述的化合物可用于治疗或预防超重病症。“超重”是指其中受试者的体重指数大于或等于25.0的病症。体重指数(BMI)和其它定义是根据“NIH Clinical Guidelines on the Identification and Evaluation, and Treatment of Overweight and Obesity in Adults”(1998)。用化合物的治疗可以为有效改变受试者重量例如至少2%、5%、7%、10%、12%、15%、20%、25%、30%、35%、40%、45%、50%或55%的量。用化合物的治疗可以为有效减少受试者的体重指数例如至低于30、28、27、25、22、20或18。化合物可用于治疗或预防异常或不适当体重增长、代谢速率、或脂肪沉积,例如,厌食症、食欲亢进、肥胖症、糖尿病或高脂血症(例如,升高的甘油三酯和/或升高的胆固醇),以及脂肪或脂质代谢的障碍。

[0261] 可施用本文所述的化合物或组合物以治疗与Prader-Willi综合征(PWS)有关的肥胖症。PWS为与肥胖症(例如,病态肥胖症)有关的遗传性障碍。

[0262] 本文所述的化合物或组合物可用于减少体脂肪,预防增加的体脂肪,减少胆固醇(例如,总胆固醇和/或总胆固醇与HDL胆固醇的比率),和/或减少具有PWS相关肥胖症的个体的食欲,和/或减少并发症共病例如糖尿病、心血管疾病和中分。

[0263] 组合物和施用途径

[0264] 本文所述的组合物包括本文所述的化合物(例如,本文所述的化合物),以及其它治疗剂(如果存在),以有效实现疾病或疾病症状(包括本文所述的那些)的调节。

[0265] 术语“药学上可接受的载体或佐剂”是指可与本文提供的化合物一起被施用于患

者,且不破坏其药理活性,并且当以足以递送治疗量的化合物的剂量施用时为无毒的载体或佐剂。

[0266] 可用于本文提供的药物组合物的药学上可接受的载体、佐剂和媒介物包括但不限于离子交换剂、氧化铝、硬脂酸铝、卵磷脂、自乳化给药系统(SEDDS)例如d- α -生育酚聚乙二醇1000琥珀酸酯、用于药物剂型例如吐温或其它类似聚合物递送基质的表面活性剂、血清蛋白例如人血清蛋白、缓冲物质例如磷酸盐、甘氨酸、山梨酸、山梨酸钾、饱和的植物脂肪酸的部分甘油酯混合物、水、盐或电解质例如硫酸精蛋白、磷酸氢二钠、磷酸氢钾、氯化钠、锌盐、胶体硅、三硅酸镁、聚乙烯吡咯烷酮、基于纤维素的物质、聚乙二醇、羧甲基纤维素钠、聚丙烯酸酯、蜡、聚乙烯-聚氧丙烯嵌段聚合物、聚乙二醇和羊毛脂。环糊精例如 α -、 β -和 γ -环糊精、或化学修饰的衍生物例如羟基烷基环糊精(包括2-和3-羟基丙基- β -环糊精)、或其它利于增加递送本文所述的式的化合物的可溶性衍生物。

[0267] 本文提供的药物组合物可经口服、胃肠外、吸入喷雾、局部、直肠、鼻、口腔、阴道或植入贮器的形式施用,但是优选口服施用或注射施用。本文提供的药物组合物可包含任何无毒的常规药学上可接受的载体、佐剂或媒介物。在一些情况下,可用药学上可接受的酸、碱或缓冲液调节制剂的pH以增加所配制化合物或其递送形式的稳定性。本文所用的胃肠外施用包括皮下、皮内、静脉内、肌内、关节内、动脉内、滑膜内、胸骨内、鞘内、病灶内和颅内注射或输注技术。

[0268] 药用组合物可以是无菌注射制剂,例如,可注射的无菌水性或油性混悬液。按照本领域已知技术,采用适宜的分散剂或湿润剂(如吐温80)和悬浮剂可以制得该混悬液。无菌注射剂也可以是在一种无毒的胃肠外稀释剂或溶剂如1,3-丁二醇溶液中的无菌注射溶液或混悬液。可接受的媒介物和溶剂中可包括甘露醇、水、林格氏溶液和等渗氯化钠溶液。另外,无菌的不挥发油通常用作溶剂或混悬介质。因此,可采用的任何非刺激性不挥发油包括合成的单甘油酯或二甘油酯。脂肪酸如油酸及其甘油酯衍生物均可用于注射液制剂,如药学上可接受的天然油如橄榄油或蓖麻油,尤其是其聚氧乙烯化的衍生物。这些油溶液或混悬液也可含有长链醇稀释剂或分散剂、或羧甲基纤维素或常用于配制药学上可接受的剂型(例如乳剂和/或混悬剂)的类似分散剂。其它常用的表面活性剂例如吐温或司盘和/或其它常用于制备药学上可接受的固体、液体或其它剂型的类似乳化剂或生物利用度增强剂可用于配制的目的。

[0269] 本文提供的药物组合物可采用任何口服可接受的剂型经口服施用,其中包括但不限于:胶囊剂、片剂、乳剂和水性混悬液、分散液和溶液。在口服使用的片剂的情况下,常用的载体包括乳糖和玉米淀粉。通常也加入润滑剂如硬脂酸镁。对胶囊形式的口服施用有用的稀释剂包括乳糖和干燥玉米淀粉。当口服施用水性混悬剂和/或乳剂时,可悬浮或溶解于油相中的活性成分与乳化剂和/或悬浮剂联合。如果需要,可加入某些甜味剂和/或芳香剂和/或着色剂。

[0270] 本文提供的药物组合物也可以混悬剂形式经直肠施用。通过将本文提供的化合物与适宜的非刺激性赋形剂混合可制得这些组合物,通过将本文提供的化合物与适宜的非刺激性赋形剂混合可制得这些组合物,因此在直肠中溶解并释放活性组分。此类物质包括但不限于可可脂、蜂蜡和聚乙二醇。

[0271] 当所需治疗包括可通过局部涂敷容易接近的面积或器官时,局部施用本文提供的

药物组合物是有用的。对于局部涂敷至皮肤而言,药物组合物应配制成适宜的软膏形式,该软膏包含悬浮或溶解于载体中的活性组分。用于局部施用本文提供的化合物的载体包括但不限于:矿物油、液体凡士林、白凡士林、丙二醇、聚氧乙烯聚氧丙烯化合物、乳化蜡和水。可选地,药用组合物可配制成适宜的洗剂或霜剂,其中所含的活性化合物与适宜的乳化剂一起悬浮或溶解于适宜载体中。适宜的载体包括但不限于矿物油、脱水山梨醇单硬脂酸、聚山梨醇酯60、十六烷基酯蜡、鲸蜡硬脂醇(cetearyl alcohol)、2-辛基十二烷醇、苯甲醇和水。本文提供的药物组合物也可通过直肠栓剂或适宜的灌肠剂局部应用于下肠道。本发明也包括局部透皮贴剂。

[0272] 本文提供的药物组合物也可通过鼻气溶胶或吸入施用。此类组合物根据药物制剂领域的已知技术可制备,并且可制备为盐水溶液,采用苯甲醇或其它合适的防腐剂、可增加生物利用度的吸收促进剂、碳氟化合物、和/或其它本领域已知的助溶剂或分散剂。

[0273] 当本文提供的组合物包含本文所述式的化合物与一种或多种其它治疗剂或预防剂的组合时,化合物与其它试剂两者应以通常施用于单一疗法方案中的剂量的约1至100%、更优选约5至95%的剂量水平存在。其它试剂可作为多个剂量方案的部分与本文提供的化合物单独施用。可选地,那些试剂可以是单个剂型的部分,与本文提供的化合物在单一组合物中混合。

[0274] 本文所述的化合物可通过静脉内、动脉内、经皮、腹膜内、肌肉或皮下注射施用;或通过口服、经颊、经鼻、经粘膜、局部、在眼用制剂中或通过吸入施用,剂量范围为约0.5至约100mg/kg体重,可选的剂量为1mg至1000mg/剂量,每4至120小时服用一次,或根据特定药物的需要。本文的方法涵盖施用有效量的化合物或组合物以实现所需或所述效应。通常,将每天约1次至约6次或可选地以连续输注形式施用本文提供的药物组合物。此类施用可用作慢性或急性疗法。可与载体材料组合以产生单一剂型的活性成分的量将根据待治疗的宿主和特定的施用方式而变化。典型的制剂将包含约5%至约95%活性化合物(w/w)。可选地,此类制剂包含约20%至约80%活性化合物。

[0275] 可以需要低于或高于上述量的剂量。任何具体患者的特定剂量和治疗方案将取决于多种因素,所述因素包括所用的特定化合物的活性、年龄、体重、一般健康状况、性别、饮食、施用时间、排泄速率、药物联用、疾病、病症或症状的严重度或病程、患者易患疾病、病症或症状的体质和治疗医师的判断。

[0276] 经改善患者的病症之后,如果需要,可以施用维持剂量的本文提供的化合物、组合物或联合。随后,施用的剂量或频率、或两者作为症状的函数可减至当该症状已被缓和至所需水平时保持经改善的病症的水平。然而,如果疾病症状有任何复发,则患者就需要长时间的间歇治疗。

[0277] 患者选择和监测

[0278] 本文所述的化合物可调节PKM2。因此,可使用本文所述的化合物选择用于治疗的患者和/或受试者,通过首先评价患者和/或受试者以确定该受试者是否需要调节PKM2,并且如果确定该受试者需要调节PKM2,那么给该受试者施用本文所述的化合物。

[0279] 可使用本领域已知的方法例如通过测量患者中PKM2的存在和/或活性,将受试者评价为需要调节PKM2。在一些实施方案中,在癌症中评价PKM2的活性和/或水平。

[0280] 可以监测接受本文所述的化合物的患者,例如监测病症和/或不良反应的改善。可

以评价患者的病症的改善,例如通过监测癌症(例如,肿瘤)的生长、生长缺乏或消退。在一些实施方案中,使用溶血参数的放射学测定或评价来评价患者。

实施例

[0281] 实施例1.PKM2测定。

[0282] 程序:

[0283] ●在反应缓冲液中稀释PKM2储备酶溶液

[0284] ●首先将2μL化合物加至每孔中,然后加入180μL反应混合物。

[0285] ●将反应混合物与化合物(不含ADP)在4℃孵育30分钟。

[0286] ●将板重新平衡至室温,然后加入20μL ADP以启动反应。

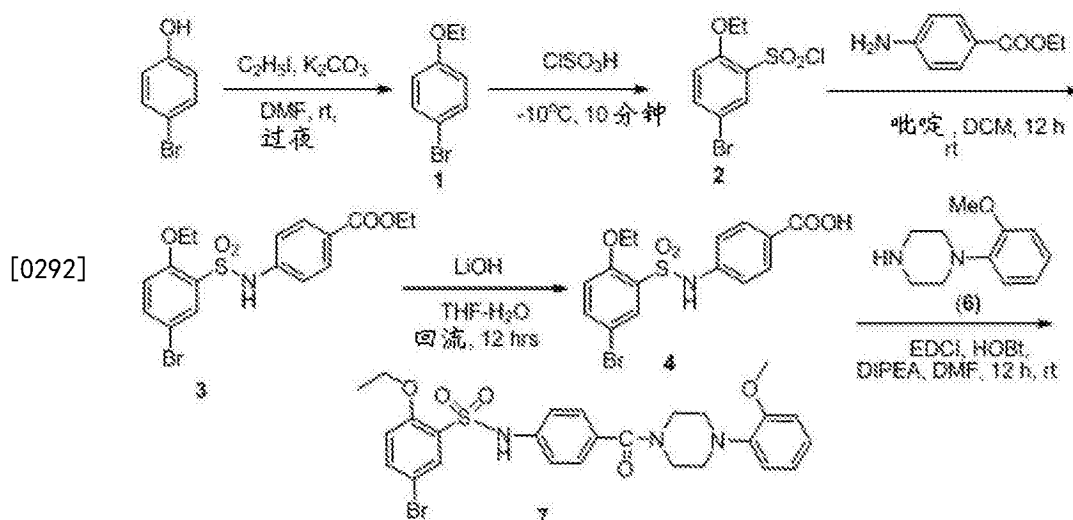
[0287] ●以室温(25℃)和340nm波长下的吸光度变化测量反应进展。

[0288] 反应混合物:在反应缓冲液中的PKM2(50ng/孔)、ADP(0.7mM)、PEP(0.15mM)、NADH(180μM)、LDH(2单位)

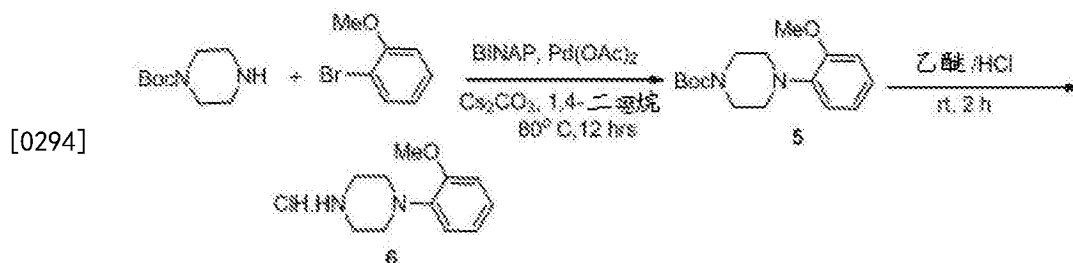
[0289] 反应缓冲液:100mM KCl、50mM Tris pH 7.5、5mM MgCl₂、1mM DTT、0.03%BSA。

[0290] 实施例2:化合物及其制备

[0291] 流程2:



[0293] 化合物6:



[0295] 化合物1的一般程序:向4-溴苯酚(5.0,0.0289摩尔,1eq)在DMF(50mL)中的溶液,加入碳酸钾(9.970g,0.0722摩尔,2.5eq),然后加入碘乙烷(4.70mL,0.0578摩尔,2eq),搅拌过夜。通过TLC监控反应的进程。原料耗尽后,用水(25mL)淬灭反应混合物,用乙酸乙酯萃取(2×50mL)。将合并的有机层用盐水(40mL)溶液洗涤。经Na₂SO₄干燥乙酸乙酯层,在减压下浓缩。通过柱色谱法(9:1,乙酸乙酯/己烷)纯化粗产物,获得化合物1(5.0g,86.2%)。MS

(201.06) 202.1 (M+1)。

[0296] 化合物2的一般程序:将化合物1装入两颈烧瓶(2.00g,0.0099摩尔,1eq)中。在10℃、经10min内缓慢加入氯磺酸(25mL,0.358摩尔,36eq)。将所得混合物在相同温度下搅拌10min。原料耗尽后,将反应混合物倒入冰冷水(100mL)中,用乙酸乙酯萃取。用水洗涤有机层,经Na₂SO₄干燥,在减压下浓缩。通过柱纯化(60-120目硅胶,5%乙酸乙酯-己烷)获得为固体状的所需产物2(3g,43.3%)。

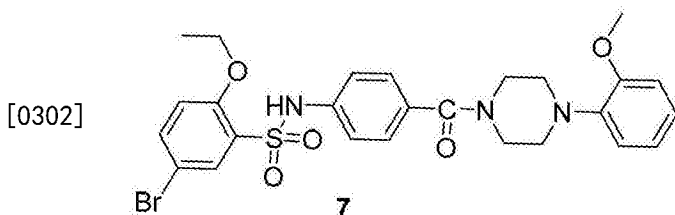
[0297] 化合物3的一般程序:在0℃、向4-氨基苯甲酸乙酯(300mg,1.81mmol,1eq)在DCM/吡啶的1:1混合物(5mL/5mL)中的溶液加入5-溴-2-乙氧基苯-1-磺酰氯(化合物2,654mg,2.17mmol,1.2eq)在DCM(5mL/5mL)中的溶液。然后将反应混合物在室温搅拌过夜。反应结束后,用DCM稀释反应混合物,用水洗涤,经硫酸钠干燥,在减压下浓缩。然后用乙醚、然后用正己烷洗涤粗产物,干燥,得到为灰白色固体状的化合物3(0.600g,77%)。

[0298] ¹H NMR(200MHz,DMSO-d₆) 1.30(t,3H),1.58(t,3H),4.20-4.40(m,4H),6.82(d,1H),7.10-7.20(m,2H),7.56-7.60(dd,1H),7.90-8.00(m,3H)。

[0299] 化合物4的一般程序:将4-(5-溴-2-乙氧基苯基亚磺酰氨基)苯甲酸乙酯(化合物3,600mg,0.0014摩尔,1eq)溶于THF-H₂O(1:1,30mL/30mL)中。然后将LiOH·H₂O(0.293g,0.007摩尔,5eq)加至上述反应混合物中并且在回流下搅拌过夜。原料耗尽后,在减压下除去溶剂以获得粗产物。用乙酸乙酯洗涤粗产物。用柠檬酸(pH=4)酸化水层,再次用乙酸乙酯萃取(2×25mL)。将合并的有机层经Na₂SO₄干燥,在减压下浓缩。将所得酸用己烷进一步洗涤,得到纯化合物4(0.500g,89%)。

[0300] MS(400.24) 397.9(M-2峰,负离子模式);¹H NMR(200MHz,DMSO-d₆) 1.20(t,3H),4.18(q,2H),7.10(d,1H),7.10-7.20(d,3H),7.60-8.0(m,4H),10.6(s,1H),12.6(bs,1H)。

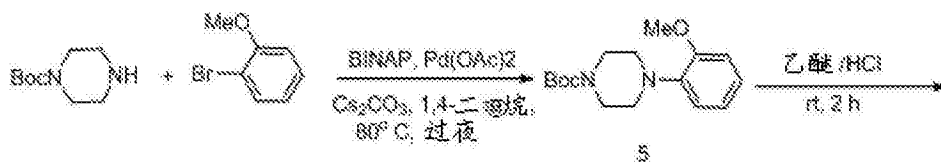
[0301] 化合物7的一般程序:在0℃、向4-(5-溴-2-乙氧基苯基亚磺酰氨基)苯甲酸(化合物4,0.300g,0.00074摩尔,1eq)在DMF(25mL)中的溶液加入EDCI(0.157g,0.00082摩尔,1.1eq)、HOBt(0.126g,0.00082摩尔,1.1eq)和DIPEA(0.48mL,0.0026摩尔,3.5eq),搅拌15分钟。然后在0℃加入1-2-(甲氧基苯基)哌嗪(化合物6,0.171g,0.00074摩尔,1eq)的溶液,然后将所得混合物在室温搅拌过夜。反应结束后,加入水(30mL),用乙酸乙酯萃取(2×30mL)。将合并的有机层经无水Na₂SO₄干燥,在减压下浓缩。将粗产物溶解于EtOAc中,加入戊烷,得到为白色固体状的化合物7,将其过滤并干燥(200mg,46.5%收率)。



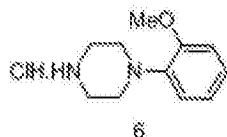
[0303] ¹H NMR(500MHz,DMSO-d₆) 1.30(t,3H),2.80-3.0(bs,4H),3.30-3.60(bm,4H),3.78(s,3H),4.20(q,2H),6.80-7.00(m,4H),7.10-7.20(m,3H),7.30-7.34(d,2H),7.70-7.75(dd,1H),7.80(d,1H),10.35(s,1H);MS 574.0;MS基峰为574.0;HPLC纯度97.80%。

[0304] 化合物6的合成:

[0305] 流程3:



[0306]



[0307] 化合物5的一般程序:在两颈圆底烧瓶中,在N₂气氛下将哌嗪-1-羧酸叔丁酯(4.97g,0.0267摩尔,1eq)、2-溴茴香醚(5.0g,0.0267摩尔,1eq)和CS₂CO₃(21.7g,0.0668摩尔,2.5eq)装入脱气的1,4-二噁烷(100mL)。然后在N₂气氛下将BINAP(1.49g,0.00240摩尔,0.09eq)和Pd(OAc)₂(0.96g,0.00042摩尔,0.016eq)加至反应混合物,在80℃搅拌过夜。通过TLC监控反应的进程。原料耗尽后,在减压下馏出过量溶剂,将残余物用水稀释,用乙酸乙酯萃取。分离有机层,经Na₂SO₄干燥,在减压下浓缩。通过柱色谱法(硅胶60-120,5-6%,乙酸乙酯/己烷)纯化粗产物,得到为粘稠油状的所需产物5(2.8g,36%)。

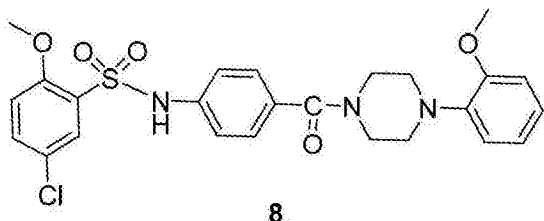
[0308] ¹H NMR(500MHz,CDC1₃):1.42(s,9H),3.0(m,4H),3.60(m,4H),3.84(s,3H),6.80-7.00(m,4H);MS 293.1(M+1峰)。

[0309] 化合物6的一般程序:在两颈RB烧瓶中,用乙醚-HCl(10mL)处理4-(2-甲氧基苯基)哌嗪-1-羧酸叔丁酯(化合物5,0.600g,0.00205摩尔,1eq)。将所得混合物搅拌过夜。如TLC所示原料耗尽后,在减压下除去乙醚,获得固体材料。用乙酸乙酯洗涤固体材料,干燥,获得为白色固体状的胺化合物6(0.425g,90.08%)。

[0310] 利用上述程序,用各种磺酰氯代替化合物2来制备下列类似物。

[0311] 5-氯-2-甲氧基-N-(4-(4-(2-甲氧基苯基)哌嗪-1-羰基)苯基)苯-磺酰胺(8)

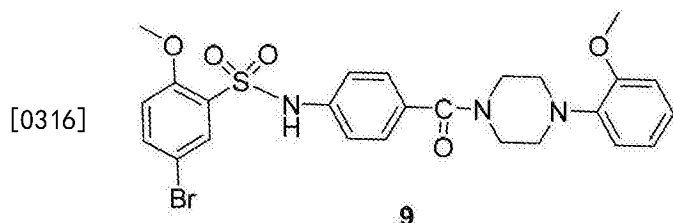
[0312]



[0313] 如流程2中所示,由市售可得的2-甲氧基-5-氯苯磺酰氯制备化合物8。

[0314] ¹H NMR(500MHz,DMSO-d₆)2.8-3.0(bm,4H),3.40-3.78(m,4H),3.80(s,3H),3.84(s,3H),6.80-7.00(m,4H),7.12(d,2H),7.21(d,1H),7.30(d,2H),7.65(dd,1H),7.74(d,1H);MS基峰为m/z 516;HPLC纯度:94.33%

[0315] 5-溴-2-甲氧基-N-(4-(4-(2-甲氧基苯基)哌嗪-1-羰基)苯基)苯-磺酰胺(9)

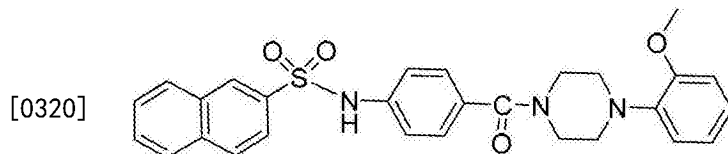


[0317] 由4-溴苯酚制备相应的磺酰氯。将4-溴苯酚O-甲基化,然后氯磺酸反应,得到2-甲

氧基-5-溴苯磺酰氯,如流程2中所提供,利用该磺酰氯以生成化合物9。

[0318] ^1H NMR (500MHz, DMSO- d_6) 2.90-3.00 (bm, 4H), 3.40-3.78 (m, 4H), 3.80 (s, 3H), 3.84 (s, 3H), 6.80-7.00 (m, 4H), 7.10-7.18 (m, 3H), 7.30 (d, 2H), 7.70 (dd, 1H), 7.74 (d, 1H); MS基峰为562.0; HPLC纯度: 94.36%

[0319] N-(4-(4-(2-甲氧基苯基)哌嗪-1-羰基)苯基)萘-2-磺酰胺 (10)

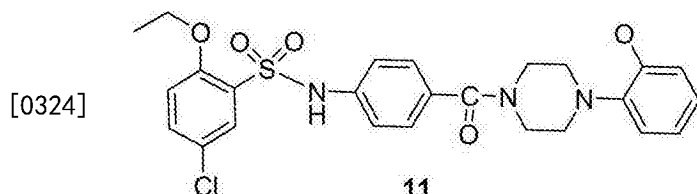


10

[0321] 用市售可得的萘-2-磺酰氯代替所用化合物2以提供10。

[0322] ^1H NMR (500MHz, DMSO- d_6) 2.80-3.00 (bm, 4H), 3.40-3.78 (m, 4H), 3.80 (s, 3H), 6.80-7.00 (m, 4H), 7.10-7.30 (m, 4H), 7.60-7.80 (m, 3H), 8.00-8.20 (m, 3H), 8.50 (s, 1H), 10.7 (s, 1H); MS基峰为504.2; HPLC纯度: 93.65% (UPLC)

[0323] 5-氯-2-乙氧基-N-(4-(4-(2-甲氧基苯基)哌嗪-1-羰基)苯基)苯-磺酰胺 (11)

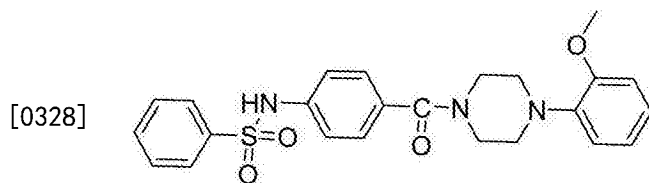


11

[0325] 由4-氯苯酚制备相应的磺酰氯。将4-氯苯酚O-乙基化,然后在适当的条件下进行氯磺酸反应,提供2-乙氧基-5-氯苯磺酰氯,如流程2中所示,利用该磺酰氯制备化合物11。

[0326] ^1H NMR (500MHz, DMSO- d_6) 1.30 (t, 3H), 2.80-3.0 (bs, 4H), 3.40-3.78 (bm, 4H), 3.80 (s, 3H), 4.20 (q, 2H), 6.80-7.00 (m, 4H), 7.16 (d, 2H), 7.20 (d, 1H), 7.38 (d, 2H), 7.60 (d, 1H), 7.80 (s, 1H), 10.20 (s, 1H); MS基峰为530.1; HPLC纯度97.48%

[0327] N-(4-(4-(2-甲氧基苯基)哌嗪-1-羰基)苯基)苯-磺酰胺 (12)

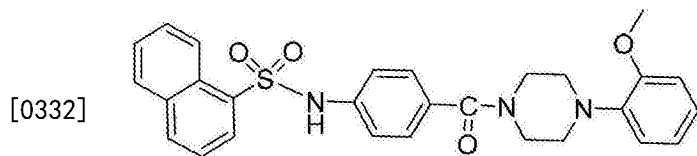


12

[0329] 按照流程2,使用苯磺酰氯制备化合物12。

[0330] ^1H NMR (500MHz, DMSO- d_6) 2.90-3.00 (bs, 4H), 3.40-3.78 (bm, 4H), 3.80 (s, 3H), 6.84-6.98 (m, 4H), 7.15 (d, 2H), 7.30 (d, 2H), 7.56-7.64 (m, 3H), 7.80 (d, 2H), 10.6 (s, 1H); MS基峰为452.6; HPLC纯度96.90%。

[0331] N-(4-(4-(2-甲氧基苯基)哌嗪-1-羰基)苯基)萘-1-磺酰胺 (13)

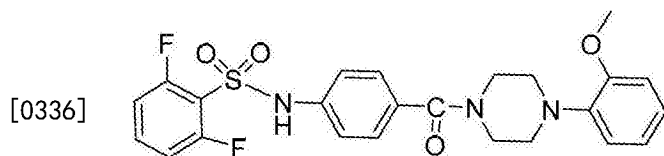


13

[0333] 按照流程2,使用市售可得的萘-1-磺酰氯制备化合物13。

[0334] ^1H NMR (500MHz, DMSO- d_6) 2.90-3.00 (bs, 4H), 3.40-3.78 (bm, 4H), 3.80 (s, 3H), 6.84-6.98 (m, 4H), 7.10 (d, 2H), 7.24 (d, 2H), 7.62-7.78 (m, 3H), 8.08 (d, 1H), 8.23 (d, 1H), 8.28 (d, 1H), 8.72 (d, 1H), 10.98 (s, 1H); MS基峰为502.1; HPLC纯度96.59%。

[0335] 2,6-二氟-N-(4-(4-(2-甲氧基苯基)哌嗪-1-羰基)苯基)苯磺酰胺 (14)

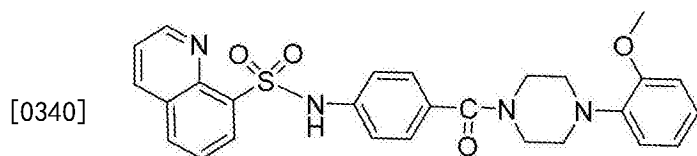


14

[0337] 按照流程2,使用市售可得的2,6-二氟苯磺酰氯制备化合物14。

[0338] ^1H NMR (500MHz, DMSO- d_6) 2.90-3.00 (bs, 4H), 3.40-3.78 (bm, 4H), 3.80 (s, 3H), 6.84-7.00 (m, 4H), 7.20 (d, 2H), 7.30 (t, 2H), 7.38 (d, 2H), 7.68-7.74 (m, 1H), 11.2 (s, 1H); MS基峰为488.1; HPLC纯度97.16%。

[0339] N-(4-(4-(2-甲氧基苯基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (15)

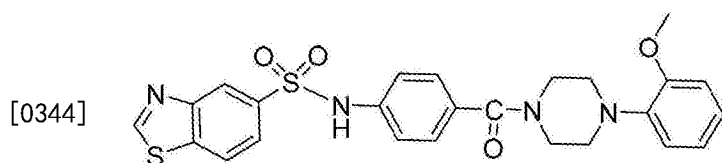


15

[0341] 按照流程2,使用市售可得的喹啉-8-磺酰氯制备化合物15。

[0342] ^1H NMR (500MHz, DMSO- d_6) 2.90-3.00 (bs, 4H), 3.40-3.78 (bm, 4H), 3.80 (s, 3H), 6.82 (d, 2H), 6.90-7.00 (m, 2H), 7.15-7.20 (2doublets, 4H), 7.70-7.78 (m, 2H), 8.24 (d, 1H), 8.40 (d, 1H), 8.50 (d, 1H), 9.15 (bs, 1H), 10.42 (s, 1H); MS基峰为503.2; HPLC纯度97.11%。

[0343] N-(4-(4-(2-甲氧基苯基)哌嗪-1-羰基)苯基)苯并[d]噻唑-5-磺酰胺 (17)

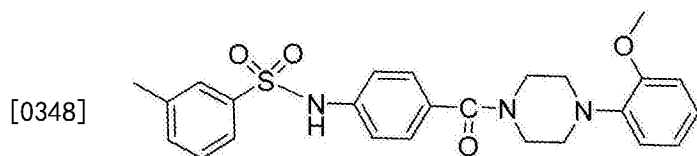


17

[0345] 按照流程2方案,由市售可得的苯并噻唑-6-磺酰氯制备化合物17。

[0346] ^1H NMR (500MHz, DMSO- d_6) 2.90-3.00 (bs, 4H), 3.40-3.78 (bm, 4H), 3.80 (s, 3H), 6.82-7.00 (m, 4H), 7.20 (d, 2H), 7.38 (d, 2H), 7.90 (d, 1H), 8.22 (d, 1H), 8.78 (s, 1H), 9.60 (s, 1H), 10.70 (s, 1H); MS基峰为509.1; HPLC纯度97.29%。

[0347] N-(4-(4-(2-甲氧基苯基)哌嗪-1-羰基)苯基)-3,5-二甲基苯磺酰胺 (18)

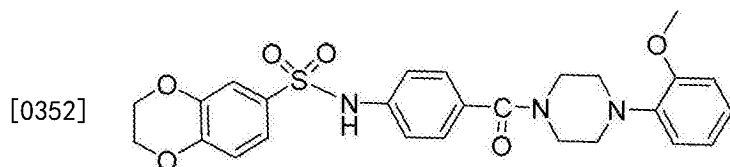


18

[0349] 按照流程2中提供的方案,由市售可得3,5-二甲基苯磺酰氯制备化合物18。

[0350] ^1H NMR (500MHz, DMSO- d_6) 2.35 (s, 6H), 2.80-2.90 (m, 4H), 3.42-3.78 (bm, 4H), 3.80 (s, 3H), 6.88 (bs, 2H), 6.92-7.00 (m, 2H), 7.15 (d, 2H), 7.26 (s, 1H), 7.33 (d, 2H), 7.42 (s, 2H), 10.5 (s, 1H); MS基峰为480.3; HPLC纯度98.56%。

[0351] N-(4-(4-(2-甲氧基苯基)哌嗪-1-羰基)苯基)2,3-二氢苯并[b][1,4]二氧杂环己烯-6-磺酰胺 (19)

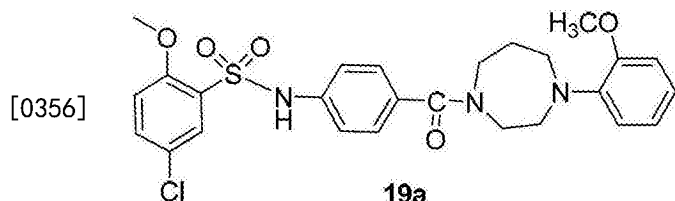


19

[0353] 按照流程2中提供的方案,由市售可得2,3-二氢苯并二氧杂-6-磺酰氯制备化合物19。

[0354] ^1H NMR (500MHz, DMSO- d_6) 2.80-3.00 (m, 4H), 3.42-3.78 (bm, 4H), 3.80 (s, 3H), 4.25 (m, 4H), 6.86-6.88 (m, 2H), 6.92-6.98 (m, 2H), 7.00 (d, 1H), 7.15 (d, 2H), 7.24 (s, 1H), 7.26-7.30 (dd, 1H), 7.34 (d, 2H), 10.5 (s, 1H); MS基峰为510.3; HPLC纯度97.02%。

[0355] 5-氯-2-甲氧基-N-(4-(4-(2-甲氧基苯基)-1,4-二氮杂环庚烷-1-羰基)苯基)苯磺酰胺 (19a)

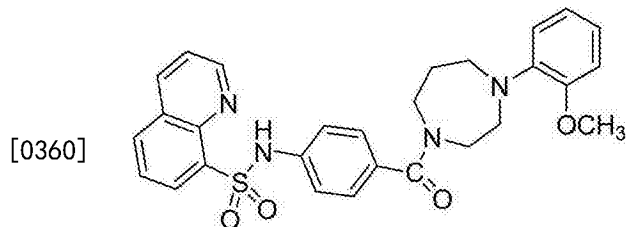


19a

[0357] 根据流程2制备化合物19a。通过如流程3中提供的Buchwald反应,用N-boc-高哌嗪代替N-Boc-哌嗪以制备N-2-甲氧基苯基-高哌嗪中间体。

[0358] ^1H NMR (500MHz, DMSO- d_6) 1.70 (s, 1H), 1.90 (s, 1H), 3.10-3.40 (m, 9H), 3.60-3.80 (m, 2H), 3.82 (s, 3H), 6.70-6.82 (m, 4H), 6.96-7.30 (m, 5H), 7.66 (t, 1H), 7.74 (s, 1H), 10.40 (d, 1H); MS基峰为530.1; HPLC纯度95.89%。

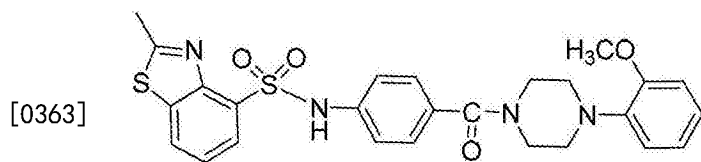
[0359] N-(4-(4-(2-甲氧基苯基)-1,4-二氮杂环庚烷-1-羰基)苯基)喹啉-8-磺酰胺 (19b)



19b

[0361] ^1H NMR (500MHz, DMSO- d_6) 1.70 (s, 1H), 1.90 (s, 1H), 3.10-3.40 (m, 8H), 3.58-3.80 (m, 3H), 6.58 (d, 1H), 6.70-7.20 (m, 7H), 7.80 (m, 2H), 8.30 (t, 1H), 8.40 (d, 1H), 8.56 (t, 1H), 9.18 (s, 1H), 10.40 (d, 1H); MS基峰为517.2; HPLC纯度97.60%。

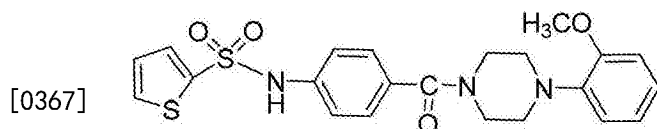
[0362] N-(4-(4-(2-甲氧基苯基)哌嗪-1-羰基)苯基)2-甲基苯并[d]噻唑-4-磺酰胺 (35)

**35**

[0364] 根据U.S. 专利4,643,759制备2-甲基苯并噻唑-4-磺酰氯。按照流程2中所述的一般程序制备化合物35。

[0365] ^1H NMR (500MHz, DMSO- d_6) 2.80 (s, 3H), 3.00 (bs, 4H), 3.40-3.78 (m, 4H), 3.80 (s, 3H), 6.90 (s, 2H), 6.90-7.0 (m, 2H), 7.18 (d, 2H), 7.30 (d, 2H), 7.82 (d, 1H), 8.04 (d, 1H), 8.60 (s, 1H), 10.6 (1H); MS基峰为523.4; LCMS纯度97.38%

[0366] N-(4-(4-(2-甲氧基苯基)哌嗪-1-羰基)苯基)噻吩-2-磺酰胺 (36)

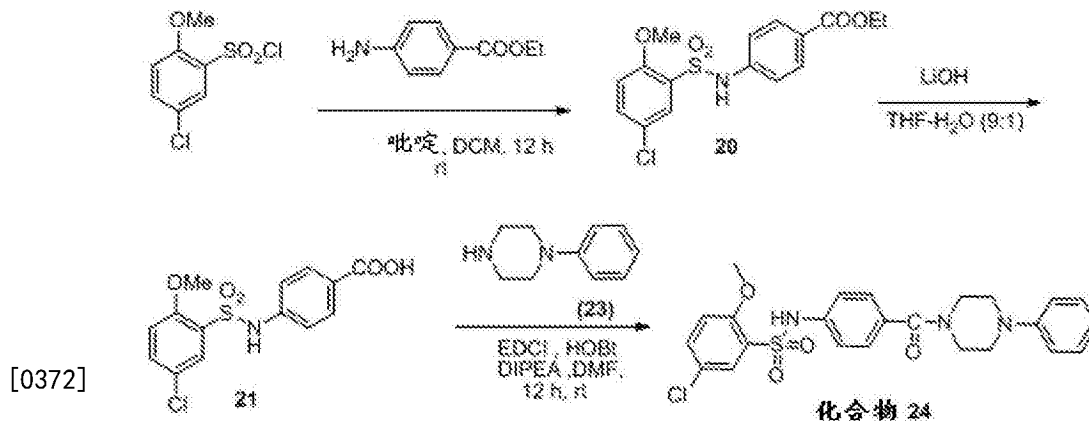
**36**

[0368] 根据流程2中所述的一般程序,由市售可得的噻吩-2-磺酰氯制备化合物36。

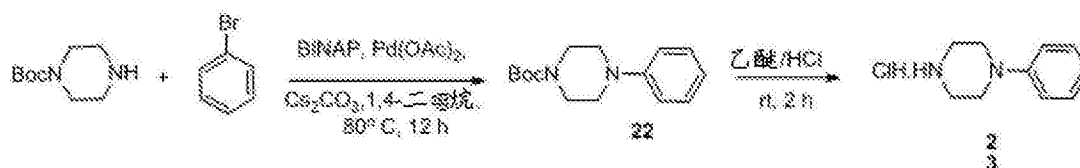
[0369] ^1H NMR (500MHz, DMSO- d_6) 2.90-3.00 (bs, 4H), 3.30-3.78 (bm, 4H), 3.80 (s, 3H), 6.80-6.90 (m, 2H), 6.90-7.0 (m, 2H), 7.18 (d, 1H), 7.20 (d, 2H), 7.40 (d, 2H), 7.60 (s, 1H), 7.94 (d, 1H), 10.70 (s, 1H); MS基峰为458.2; HPLC纯度95.02%.

[0370] 苯基类似物的合成:

[0371] 流程4



化合物 22:



[0373] 用于合成化合物20的程序:于0℃、在氮气气氛下向2-甲氧基-5-氯苯磺酰氯(878mg,0.00362摩尔,1.5eq)在二氯甲烷中的溶液加入4-氨基苯甲酸乙酯(400mg,0.00242

摩尔, 1eq) 在1:1比率的吡啶和DCM (5mL/5mL) 中的溶液。将反应混合物在室温搅拌过夜。通过TLC监控反应进程。结束后, 用DCM稀释反应混合物, 用水洗涤两次, 用无水硫酸钠干燥。浓缩有机层, 干燥, 用乙醚、然后用正己烷洗涤, 干燥, 以提供为灰白色固体状的20 (0.8g, 89% 收率)。

[0374] ^1H NMR (500MHz, CDCl_3) 1.34 (t, 3H), 4.0 (s, 3H), 4.22–4.32 (q, 2H), 6.90 (d, 1H), 7.16 (d, 2H), 7.20 (s, 1H), 7.84 (s, 1H), 7.92 (d, 2H)。

[0375] 用于合成化合物21的程序: 将LiOH (226mg, 0.0049摩尔, 4eq) 加至化合物20 (500mg, 0.0013摩尔, 1eq) 在THF- H_2O 混合物 (1:1比率, 30ml/30ml) 中的溶液, 在回流加热过热。通过TLC监控反应进程。结束后, 将反应混合物用柠檬酸酸化至pH 4, 用乙酸乙酯萃取。用水洗涤乙酸乙酯层, 经硫酸钠干燥, 蒸馏。干燥所得固体21, 其不需纯化即可用于下一步骤 (400mg, 87% 收率)。

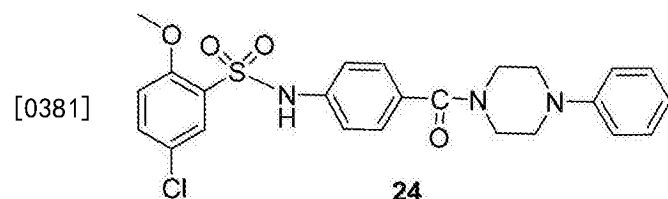
[0376] ^1H NMR (500MHz, $\text{DMSO}-d_6$) 3.82 (s, 3H), 7.10–7.22 (m, 3H), 7.62 (d, 1H), 7.88–7.92 (m, 3H), 10.64 (s, 1H), 12.70 (s, 1H)。

[0377] 用于合成化合物22的程序: 利用溴苯代替2-溴茴香醚, 按照与化合物5类似的程序进行化合物22的合成。MS 263 (M+1峰)。

[0378] 用于合成化合物23的程序: 将化合物22 (500mg) 溶解于30ml乙醚/ HCl 中, 在氮气气氛下于室温搅拌2小时。在减压下蒸馏反应混合物以除去乙醚, 用戊烷洗涤, 经硫酸钠干燥, 获得化合物23 (300mg, 97% 收率)。

[0379] ^1H NMR (500MHz, $\text{DMSO}-d_6$) 3.10–3.20 (m, 4H), 3.40–3.42 (m, 4H), 6.80 (t, 1H), 7.00 (d, 2H), 7.22 (t, 2H), 9.0 (bs, 1H), 9.40 (bs, 2H)。

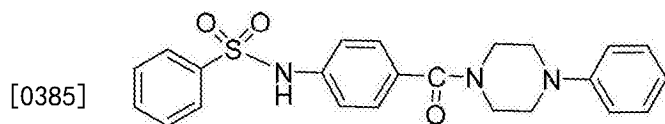
[0380] 用于合成化合物24的合成: 于0℃、在氮气气氛下向化合物21 (100mg, 0.00029摩尔, 1eq) 在DMF (10mL) 中的搅拌溶液加入EDCI (62mg, 0.00032摩尔, 1.1eq)、HOBt (50mg, 0.00032摩尔, 1.1eq) 和DIPEA (0.16ml, 0.00088摩尔, 3eq)。将反应混合物于0℃搅拌5分钟, 然后在室温搅拌30分钟。于0℃、将化合物23 (59mg, 0.00029摩尔, 1eq) 溶于DMF和半当量的DIPEA中的溶液缓慢加至上述反应混合物, 将在室温搅拌过夜。通过TLC监控反应。结束后, 用水洗涤反应混合物, 用乙酸乙酯萃取。将有机层经硫酸钠干燥, 在真空下浓缩。通过用乙酸乙酯/己烷溶剂混合物纯化粗产物, 获得收率为24.6%的化合物24 (35mg)。



[0382] ^1H NMR (500MHz, $\text{DMSO}-d_6$) 3.10–3.20 (bs, 4H), 3.40–3.78 (bm, 4H), 3.82 (s, 3H), 6.80 (t, 1H), 6.90 (d, 2H), 7.14 (d, 2H), 7.20 (t, 3H), 7.30 (d, 2H), 7.62–7.66 (dd, 1H), 7.74 (d, 1H), 10.40 (s, 1H); MS基峰为486.0; HPLC纯度97.34%。

[0383] **按照与流程4中所述的方案类似的方案, 制备化合物25至30。

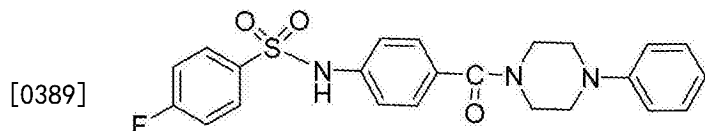
[0384] N-(4-(4-苯基哌嗪-1-羰基)苯基)苯磺酰胺 (25)

**25**

[0386] 按照与流程4中所示的方案类似的方案,使用苯磺酰氯制备化合物25。

[0387] ^1H NMR (500MHz, DMSO- d_6) 3.10-3.20 (bs, 4H), 3.40-3.78 (bm, 4H), 6.80 (t, 1H), 6.92 (d, 2H), 7.10-7.35 (m, 6H), 7.50-7.70 (m, 3H), 7.80 (d, 2H), 10.60 (s, 1H); MS基峰为422.0; HPLC纯度97.92%。

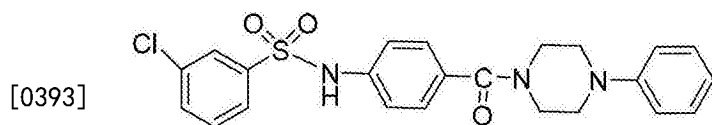
[0388] 4-氟-N-(4-(4-苯基哌嗪-1-羰基)苯基)苯磺酰胺 (26)

**26**

[0390] 按照与流程4中提供的程序类似的程序,使用4-氟苯磺酰氯制备化合物26。

[0391] ^1H NMR (500MHz, DMSO- d_6) 3.10-3.20 (bs, 4H), 3.40-3.80 (bm, 4H), 6.80 (t, 1H), 6.94 (d, 2H), 7.14 (d, 2H), 7.20 (t, 2H), 7.32 (d, 2H), 7.35 (t, 2H), 7.80-7.90 (m, 2H), 10.6 (s, 1H); MS基峰为440.1; HPLC纯度96.72%。

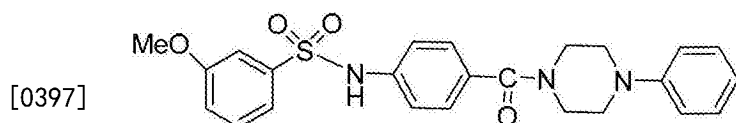
[0392] 3-氯-N-(4-(4-苯基哌嗪-1-羰基)苯基)苯磺酰胺 (27)

**27**

[0394] 按照与流程4中提供的程序类似的程序,使用市售的3-氯苯磺酰氯制备化合物27。

[0395] ^1H NMR (500MHz, DMSO- d_6) 3.10-3.20 (bs, 4H), 3.40-3.80 (bm, 4H), 6.80 (t, 1H), 7.00 (d, 2H), 7.18-7.22 (m, 4H), 7.38 (d, 2H), 7.60 (t, 1H), 7.70-7.80 (m, 3H), 10.6 (s, 1H); MS基峰为456.2; HPLC纯度97.25%。

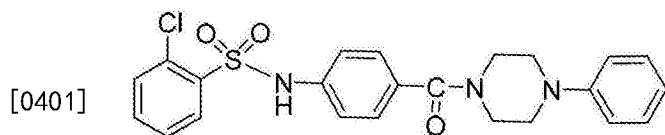
[0396] 3-甲氧基-N-(4-(4-苯基哌嗪-1-羰基)苯基)苯磺酰胺 (28)

**28**

[0398] 根据流程4中提供给的一般程序,使用3-甲氧基苯磺酰氯制备化合物28。

[0399] ^1H NMR (500MHz, DMSO- d_6) 3.10-3.20 (bs, 4H), 3.40-3.78 (bm, 4H), 3.80 (s, 3H), 6.80 (t, 1H), 6.95 (d, 2H), 7.14-7.24 (m, 5H), 7.28 (bs, 1H), 7.32-7.40 (m, 3H), 7.50 (t, 1H), 10.6 (s, 1H); MS基峰为452.2; HPLC纯度93.60%。

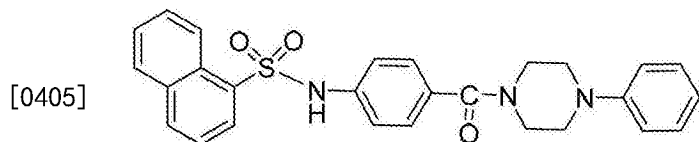
[0400] 2-氯-N-(4-(4-苯基哌嗪-1-羰基)苯基)苯磺酰胺 (29)

**29**

[0402] 根据流程4中提供的一般程序,使用市售可得2-氯苯磺酰氯制备化合物29。

[0403] ^1H NMR (500MHz, DMSO- d_6) 3.10-3.20 (bs, 4H), 3.40-3.78 (bm, 4H), 6.80 (t, 1H), 6.95 (d, 2H), 7.16-7.38 (m, 6H), 7.58 (t, 1H), 7.64 (d, 2H), 8.10 (d, 1H), 10.90 (s, 1H); MS基峰为456.2; HPLC纯度99.21%。

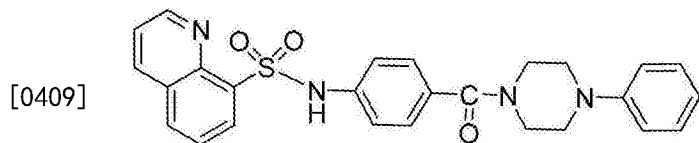
[0404] N-(4-(4-苯基哌嗪-1-羰基)苯基)萘-1-磺酰胺 (30)

**30**

[0406] 根据流程4中提供的一般程序,使用市售可得萘-1-磺酰氯制备化合物30。

[0407] ^1H NMR (500MHz, DMSO- d_6) 3.10-3.20 (bs, 4H), 3.40-3.78 (bm, 4H), 6.80 (t, 1H), 6.95 (d, 2H), 7.08 (d, 2H), 7.10-7.30 (m, 4H), 7.70-7.80 (m, 3H), 8.10 (d, 1H), 8.20-8.30 (m, 2H), 8.76 (d, 1H), 11.0 (s, 1H); MS基峰为472.3; HPLC纯度99.14%。

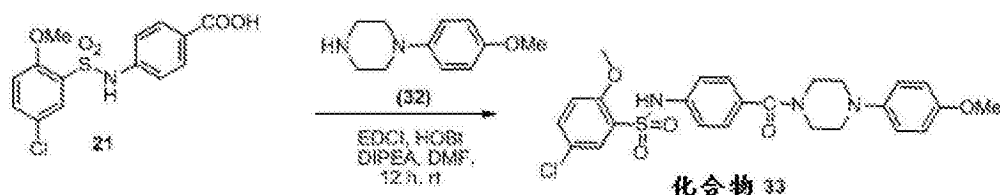
[0408] N-(4-(4-苯基哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (30a)

**30a**

[0410] ^1H NMR (500MHz, DMSO- d_6) 3.00-3.20 (bm, 4H), 3.30-3.70 (bs, 4H), 6.80 (t, 1H), 6.90 (d, 2H), 7.10-7.22 (m, 6H), 7.70-7.80 (m, 2H), 8.30 (d, 1H), 8.44 (d, 1H), 8.56 (d, 1H), 9.18 (d, 1H), 10.42 (s, 1H); MS基峰为473.2; HPLC纯度98.50%。

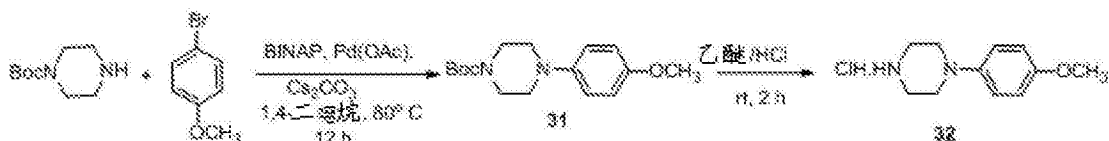
[0411] 4-甲氧基苯基类似物的合成

[0412] 流程5:



[0413]

化合物 31:



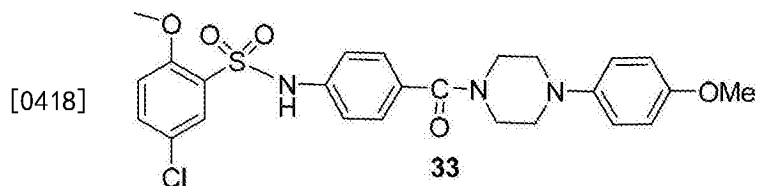
[0414] 化合物31的合成:

[0415] 向4-溴茴香醚 (2.0g, 0.0106摩尔, 1eq) 在1,4-二噁烷 (30mL) 中的溶液, 在室温下

鼓入N₂气体30分钟,然后添加Cs₂CO₃ (7.64g,0.023摩尔,2.2eq)、BINAP (598mg,0.00096摩尔,0.09eq)、Pd(OAc)₂ (38mg,0.00017摩尔,0.016eq)和四丁基碘化铵(15mg)。将反应混合物再用氮气净化另外15分钟,然后添加N-Boc-哌嗪(2.38g,0.0128摩尔,1.2eq)。将反应混合物在80℃加热过夜,通过TLC监控。在减压下馏去过量溶剂,将残余物用水稀释,用乙酸乙酯萃取。分离有机层,再次用水洗涤一次,经硫酸钠干燥,浓缩。通过使用60-120目硅胶(15%乙酸乙酯/己烷)的柱色谱法纯化粗物质,得到1.5g(48.3%收率)化合物31。

[0416] 化合物32的合成:将化合物31于室温在60ml乙醚/HCl中搅拌2小时。在减压下除去过量溶剂,用正己烷洗涤所得固体,干燥,获得780mg(99.7%收率)化合物32。

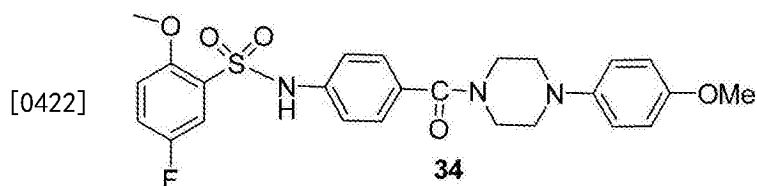
[0417] 5-氯-2-甲氧基-N-(4-(4-(4-甲氧基苯基)哌嗪-1-羰基)苯基)苯磺酰胺(33)



[0419] 按照流程4中对于化合物24所述的方案,制备化合物33。

[0420] ¹H NMR (500MHz, DMSO-d₆) 3.00 (bs, 4H), 3.40-3.70 (m, 7H), 3.80 (s, 3H), 6.80-6.90 (dd, 4H), 7.14 (d, 2H), 7.22 (d, 1H), 7.30 (d, 2H), 7.62-7.66 (dd, 1H), 7.74 (d, 1H), 10.4 (s, 1H); MS基峰为557.1; HPLC纯度94.14%。

[0421] 5-氟-2-甲氧基-N-(4-(4-(4-甲氧基苯基)哌嗪-1-羰基)苯基)苯磺酰胺(34)

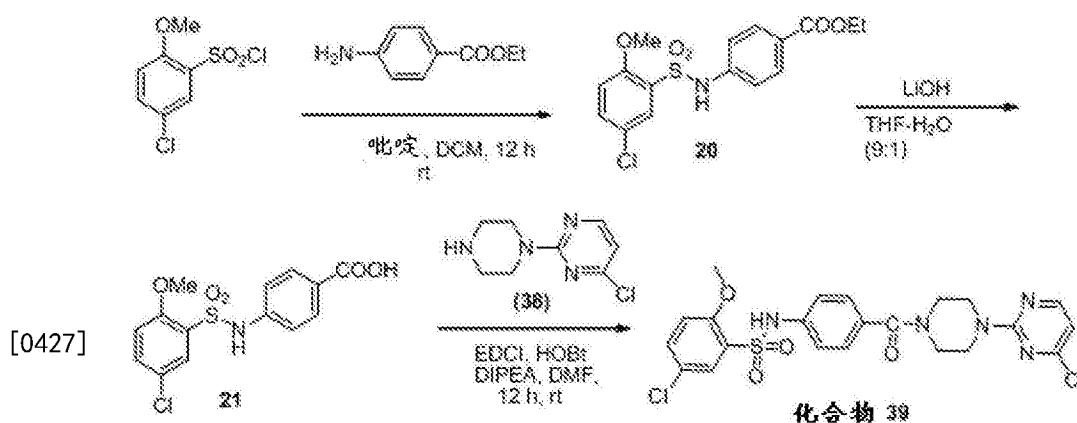


[0423] 按照流程4中提供的一般方案,由2-甲氧基-4-氟苯磺酰氯开始制备化合物34。

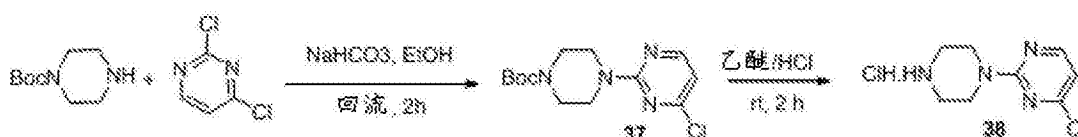
[0424] ¹H NMR (500MHz, DMSO-d₆) 3.00 (bs, 4H), 3.40-3.70 (m, 7H), 3.82 (s, 3H), 6.80-6.90 (dd, 4H), 7.14 (d, 2H), 7.20 (dd, 1H), 7.30 (d, 2H), 7.46-7.49 (m, 1H), 7.60 (dd, 1H), 10.4 (s, 1H); MS基峰为500.2; HPLC纯度95.48%。

[0425] 4-氯嘧啶类似物的合成:

[0426] 流程6:



化合物 38:



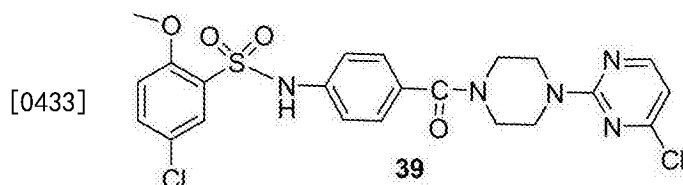
[0428] 化合物37的制备:将2,4-二氯嘧啶(801mg,0.0053mol,1eq)、N-Boc-哌嗪(1.0gm,0.0053mol,1eq)和碳酸氢钠(903mg,0.0107mol,2eq)溶解于乙醇(50ml)中,回流搅拌1h。通过TLC监控反应进程。除去过量溶剂,溶解于水中,用DCM萃取。用水洗涤有机层,用硫酸钠干燥,在减压下浓缩。使用15%乙酸乙酯-己烷将粗产物在硅胶(60-120目)上纯化,得到偶联产物化合物37(230mg)。

[0429] ^1H NMR (500MHz, CDCl_3) 1.5 (s, 9H), 3.5 (m, 4H), 3.80 (m, 4H), 6.80 (d, 1H), 8.20 (d, 1H)。

[0430] 化合物38的制备:在氮气气氛下、将化合物37在20ml乙醚/HCl中的溶液在室温搅拌1h。在减压下馏去过量溶剂,将粗物质用正戊烷洗涤,干燥,得到定量收率的180mg化合物38。

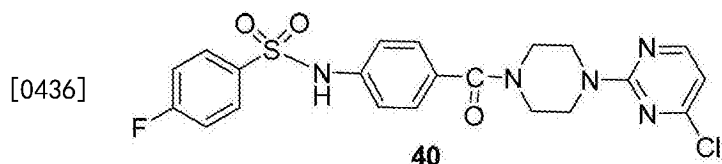
[0431] 化合物39的制备:于0℃、在氮气气氛下向化合物21(109mg,0.31mmol,1.0eq)在DMF(15mL)中的搅拌溶液加入EDCI(67mg,0.35mmol,1.1eq)、HOBT(53.7mg,0.35,1.1eq)和DIPEA(2.0eq)。将反应混合物在室温搅拌30分钟。于0℃、将化合物38(75mg,0.319mmol,1eq)在5ml DMF和1.5eq DIPEA中的溶液缓慢加至反应混合物,在室温搅拌12h。通过TLC监控反应。结束后,用水淬灭反应混合物,用乙酸乙酯萃取。分离有机层,经硫酸钠干燥,在减压下浓缩。使用2%MeOH-DCM将粗产物在硅胶柱(60-120目)纯化,得到收率为18%的30mg化合物39。

[0432] 5-氯-N-(4-(4-(4-氯嘧啶-2-基)哌嗪-1-羰基)苯基)-2-甲氧基苯磺酰胺(39)



[0434] ^1H NMR (500MHz, $\text{DMSO}-d_6$) 3.35-3.60 (bs, 4H), 3.70-3.78 (bm, 4H), 3.80 (s, 3H), 6.78 (d, 1H), 7.16 (d, 2H), 7.22 (d, 1H), 7.36 (d, 2H), 7.66 (d, 1H), 7.80 (s, 1H), 8.18 (s, 1H), 10.50 (s, 1H); MS基峰为522.1; HPLC纯度96.50%。

[0435] N-(4-(4-(4-氯嘧啶-2-基)哌嗪-1-羰基)苯基)-4-氟苯磺酰胺 (40)

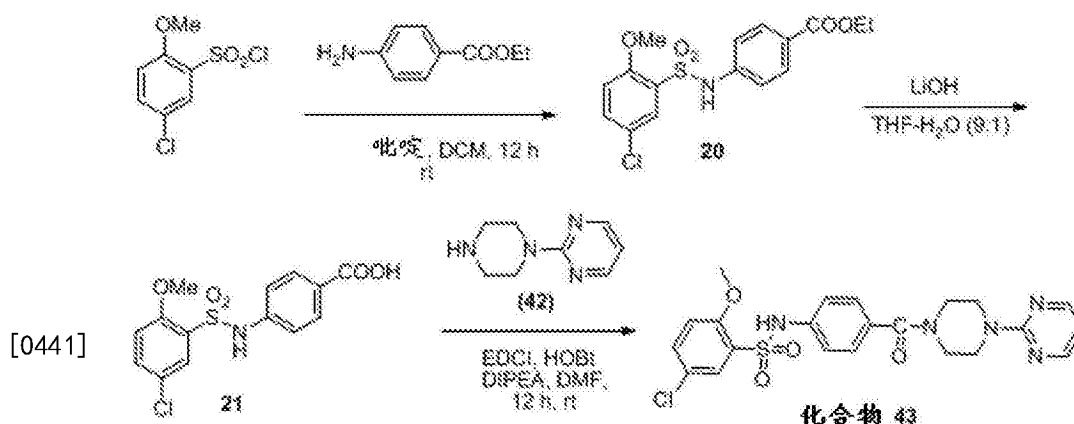


[0437] 由4-氟苯磺酰氯开始,通过按照如流程6中提供的对于化合物38与嘧啶的偶联所建立的方案以及随后通过如流程4中所述的一般程序分步制备化合物40。

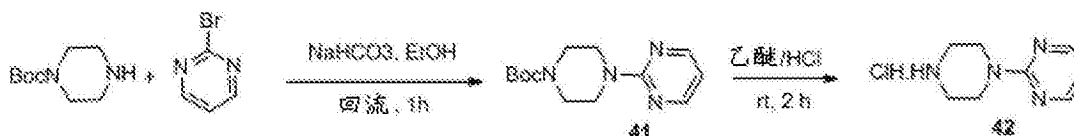
[0438] ^1H NMR (500MHz, DMSO- d_6) 3.35-3.60 (bs, 4H), 3.70-3.78 (bm, 4H), 6.78 (d, 1H), 7.18 (d, 2H), 7.38 (d, 2H), 7.42 (d, 2H), 7.82 (d, 2H), 8.38 (d, 1H), 10.60 (s, 1H); MS基峰为 476.2; HPLC纯度97.89%。

[0439] 2-嘧啶类似物的合成

[0440] 流程7:



化合物 42:



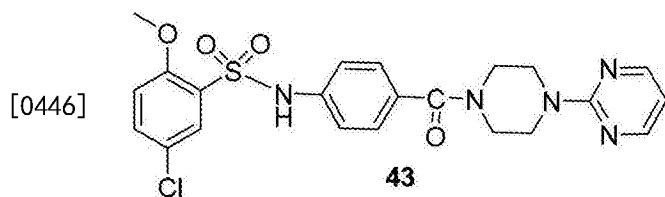
[0442] 化合物41的制备:向2-溴嘧啶 (500mg, 0.003144摩尔, 1eq) 在乙醇 (50ml) 中的溶液加入碳酸氢钠 (528mg, 0.0062摩尔, 2eq), 然后加入N-Boc-哌嗪 (585mg, 0.0031摩尔, 1.0eq)。将反应混合物在回流下搅拌1h, 通过TLC监控。结束后, 在减压下除去过滤溶剂。用水稀释粗物质, 用乙酸乙酯萃取。将有机层经硫酸钠干燥, 浓缩。将粗物质用己烷洗涤, 干燥, 获得400mg化合物41 (48%收率)。

[0443] 化合物42的制备:将化合物41 (400mg) 在乙醚/HCl (30ml) 中的溶液在室温搅拌2h, 通过TLC监控。2小时后, 在减压下浓缩反应混合物, 得到化合物42 (300mg, 98%收率), 其随后用己烷洗涤, 不需进一步纯化即可使用。

[0444] 化合物43的制备:于0℃、向化合物21 (100mg, 0.00029摩尔, 1eq) 在DMF (15mL) 中的溶液加入EDCI (61.5mg, 0.00032摩尔, 1.1)、HOBT (49.28mg, 0.00032摩尔, 1.1eq) 和1.5当量的DIPEA, 在室温搅拌30分钟。于0℃、向其中加入化合物42在DMF (5ml) 和2eq DIPEA中的溶液, 在室温搅拌过夜。用水淬灭反应混合物, 用乙酸乙酯萃取。用水洗涤有机层, 经硫酸钠干燥, 在减压下浓缩以提供粗产物。用3%MeOH/DCM将粗物质在硅胶 (230-400目) 柱上纯化, 得

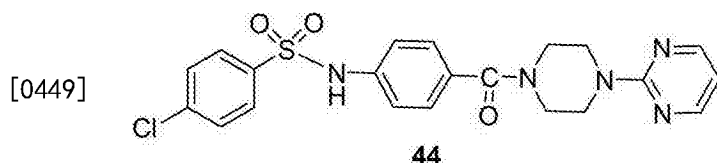
到收率为31.6%的化合物43 (45mg)。

[0445] 5-氯-2-甲氧基-N-(4-(4-(嘧啶-2-基)哌嗪-1-羰基)苯基)苯磺酰胺 (43)



[0447] ^1H NMR (500MHz, DMSO- d_6) 3.35-3.70 (bm, 4H), 3.70-3.80 (bm, 4H), 3.82 (s, 3H), 6.62 (d, 1H), 7.15 (d, 2H), 7.22 (d, 1H), 7.34 (d, 2H), 7.62-7.66 (dd, 1H), 7.75 (d, 1H), 8.40 (s, 2H), 10.5 (s, 1H); MS基峰为488.3; HPLC纯度97.47%.

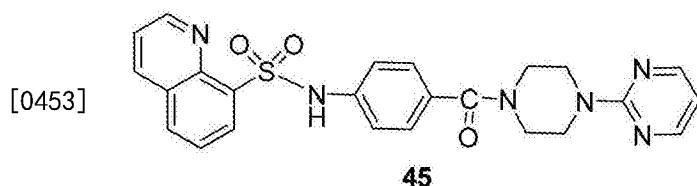
[0448] 4-氯-N-(4-(4-(嘧啶-2-基)哌嗪-1-羰基)苯基)苯磺酰胺 (44)



[0450] 按照流程7中所述的方案和利用流程4中所述的一般程序,由4-氯苯磺酰氯制备化合物44。

[0451] ^1H NMR (500MHz, DMSO- d_6) 3.35-3.70 (bm, 4H), 3.70-3.80 (bm, 4H), 6.62 (t, 1H), 7.18 (d, 2H), 7.38 (d, 2H), 7.62 (d, 2H), 7.80 (d, 2H), 8.40 (d, 2H), 10.62 (s, 1H); MS基峰为458.2; HPLC纯度98.41%.

[0452] N-(4-(4-(嘧啶-2-基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (45)

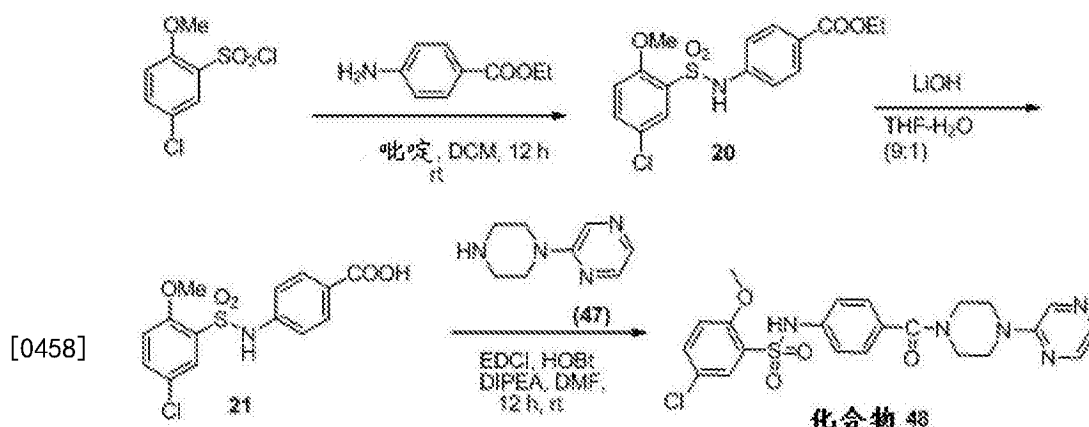


[0454] 使用流程4中所提供的一般程序,按照流程7中所述的方案由4-氯苯磺酰氯制备化合物45。

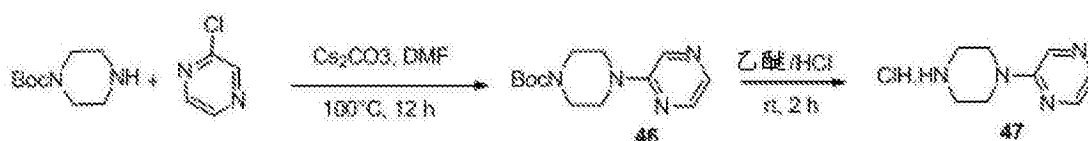
[0455] ^1H NMR (500MHz, DMSO- d_6) 3.30-3.80 (bm, 8H), 6.62 (t, 1H), 7.18 (d, 2H), 7.22 (d, 2H), 7.64-7.80 (m, 2H), 8.30 (d, 1H), 8.38 (d, 2H), 8.42 (d, 1H), 8.58 (d, 1H), 9.18 (d, 1H), 10.42 (s, 1H); MS基峰为475.2; HPLC纯度99.52%.

[0456] 吡嗪类似物的合成:

[0457] 流程8:



化合物 47:

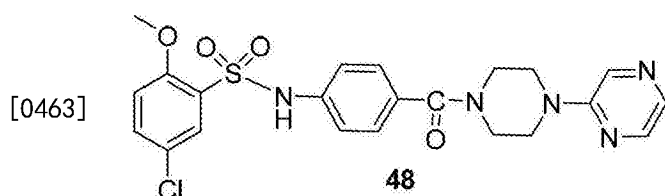


[0459] 化合物46的制备:向2-氯吡嗪(500mg,0.0027摩尔,1eq)在DMF(20ml)中的溶液加入碳酸铯(1.7g,0.0052摩尔,2eq),然后加入N-Boc-哌嗪(506.8mg,0.0027摩尔,1.0eq)。将反应混合物在100℃加热12h,通过TLC监控。结束后,在减压下除去过量溶剂,用水稀释粗物质,用乙酸乙酯萃取。将有机层经硫酸钠干燥,浓缩。洗涤粗物质,使用30%乙酸乙酯-己烷在硅胶(60-120目)上纯化,提供400mg化合物46(44.1%收率)。

[0460] 化合物47的制备:将化合物46(250mg)在乙醚/HCl(30ml)中的溶液在室温搅拌1h,通过TLC监控。1h后,在减压下浓缩反应混合物,得到化合物47(200mg,98%收率),其用己烷洗涤,不需进一步纯化即可使用。

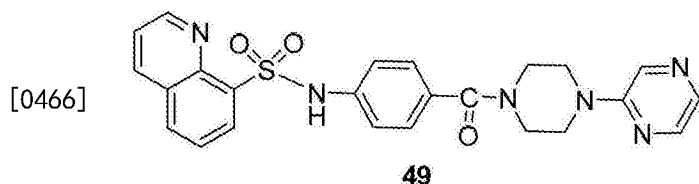
[0461] 化合物48的制备:于0℃、向化合物21(100mg,0.00029摩尔,1eq)在DMF(15mL)中的溶液加入EDCI(61.5mg,0.00032摩尔,1.1)、HOBT(49.28mg,0.00032摩尔,1.1eq)和1.5当量的DIPEA,在室温搅拌30分钟。于0℃、向其中加入化合物47(58.7mg,0.00029摩尔,1eq)在DMF(5ml)和3eq.DIPEA中的溶液,在室温搅拌12h。用水淬灭反应混合物,用乙酸乙酯萃取。用水洗涤有机层,经硫酸钠干燥,在减压下浓缩以提供粗产物。随后用乙酸乙酯将粗物质在硅胶(60-120目)上纯化,得到收率为31.6%的化合物48(45mg)。

[0462] 5-氯-2-甲氧基-N-(4-(4-(吡嗪-2-基)哌嗪-1-羰基)苯基)苯磺酰胺(48)



[0464] ^1H NMR(500MHz,DMSO- d_6) 3.35-3.70(bm,8H),3.82(s,3H),7.14(d,2H),7.22(d,1H),7.33(d,2H),7.62-7.68(dd,1H),7.74(d,1H),7.86(d,1H),8.10(bs,1H),8.30(s,1H),10.56(s,1H);MS基峰为488.2;HPLC纯度92.55%。

[0465] N-(4-(4-(吡嗪-2-基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺(49)

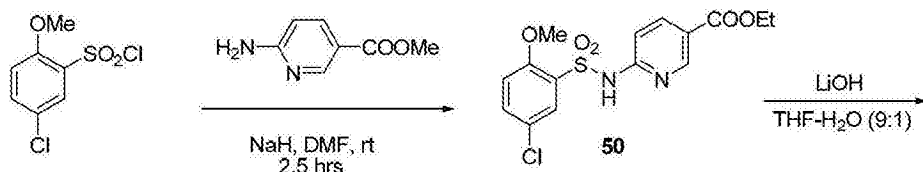


[0467] 利用流程4中所提供的一般程序,如流程8中所述,由喹啉-8-磺酰氯制备化合物49。

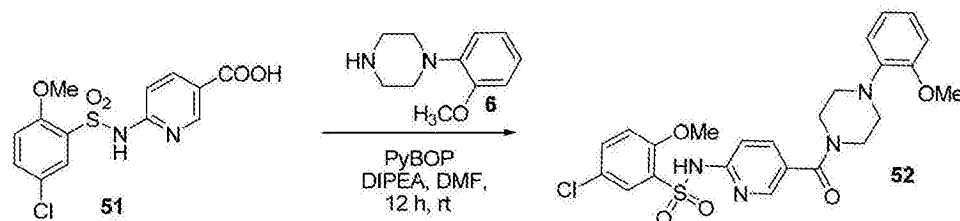
[0468] ^1H NMR (500MHz, DMSO- d_6) 3.35-3.70 (bm, 8H), 7.12 (d, 2H), 7.22 (d, 2H), 7.68-7.78 (m, 2H), 7.84 (s, 1H), 8.08 (s, 1H), 8.24 (d, 2H), 8.42 (d, 1H), 8.52 (d, 1H), 9.19 (s, 1H), 10.50 (s, 1H); MS基峰为475.2; HPLC纯度98.10%。

[0469] 吡啶类似物的合成

[0470] 流程9:



[0471]

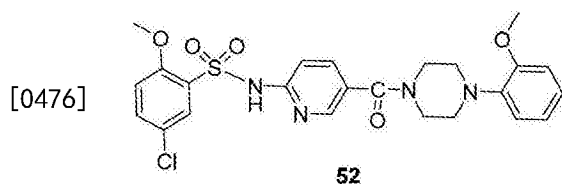


[0472] 化合物50的制备:向NaH (94mg, 3.94mmol, 2eq) 在DMF (20mL) 中的悬液加入2-氨基-吡啶-5-羧酸甲酯 (300mg, 1.97mmol, 1eq), 在室温搅拌30分钟。在室温缓慢加入5-氯-2-甲氧基苯磺酰氯 (570mg, 2.36mmol, 1.2eq) 溶液, 再搅拌2h。通过TLC监控反应, 显示剩余50%原料, 继续反应未能显示有所改善。用水淬灭反应混合物, 用乙酸乙酯萃取。分离有机层, 经硫酸钠干燥, 在减压下浓缩。包含50%初始酯的粗产物50不需进一步纯合即可用于下一步骤。

[0473] 化合物51的制备:向化合物50 (270mg) 在THF/ H_2O 中的溶液加入氢氧化锂 (0.160g, 5eq, 3.786mmol)。将所得反应物加热回流, 搅拌4h。结束后, 将反应混合物用水稀释, 用乙醚洗涤。用柠檬酸酸化水层, 用乙酸乙酯萃取。分离有机层, 经硫酸钠干燥, 在减压下浓缩。粗酸51 (90mg, 36%收率) 不需进一步纯化即可使用。

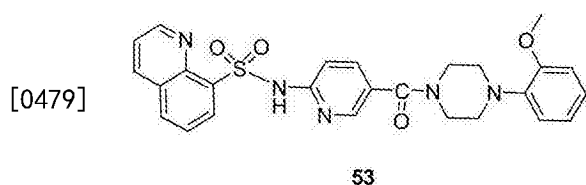
[0474] 化合物52的制备:于0℃、向化合物51 (90mg, 0.263mmol, 1eq) 在DMF (15mL) 中的溶液加入PyBOP (205mg, 0.395mmol, 1.5eq), 搅拌5分钟。于0℃、向其中加入化合物6 (60.2mg, 0.2635mmol, 1eq) 在5mL DMF和3eq DIPEA中的溶液, 在室温搅拌过夜。结束后, 真空除去过量溶剂, 将残余物用水稀释, 用乙酸乙酯萃取。分离有机层, 用水洗涤, 经硫酸钠干燥, 在减压下浓缩。使用1-2% MeOH/DCM通过硅胶柱色谱法 (60-120目) 纯化粗产物, 得到收率为33%的化合物52 (45mg)。

[0475] 5-氯-2-甲氧基-N-(5-(4-(2-甲氧基苯基)哌嗪-1-羰基)吡啶-2-基)苯磺酰胺 (52)



[0477] ^1H NMR (500MHz, DMSO- d_6) 3.00 (bs, 4H), 3.40-3.78 (bm, 4H), 3.9 (s, 6H), 6.90 (s, 2H), 6.92-7.00 (m, 2H), 7.20 (d, 1H), 7.60-7.62 (m, 1H), 7.80-7.82 (m, 2H), 8.18 (s, 1H), 11.4 (bs, 1H); MS基峰为517.2; HPLC纯度97.65%.

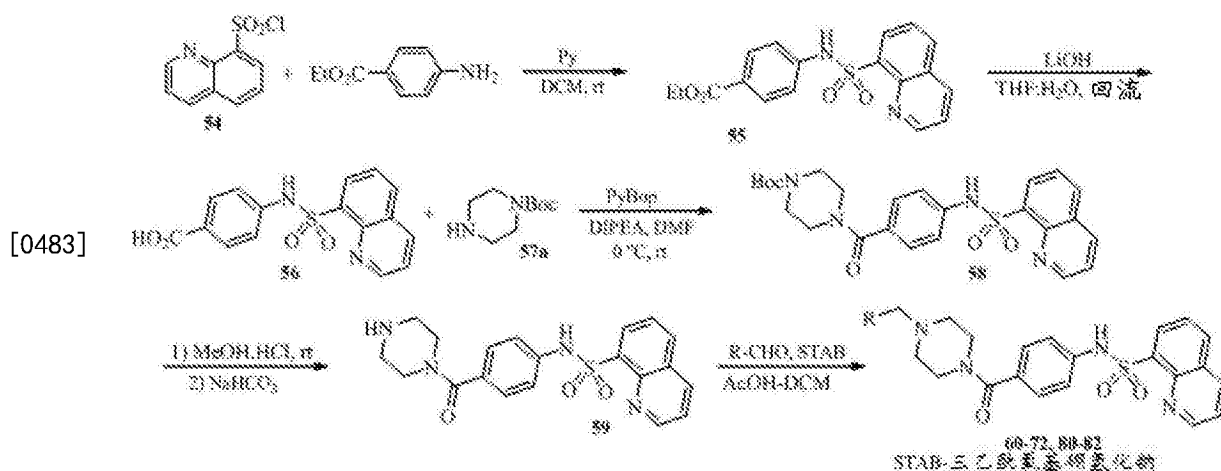
[0478] N-(5-(4-(2-甲氧基苯基)哌嗪-1-羰基)吡啶-2-基)喹啉-8-磺酰胺 (53)



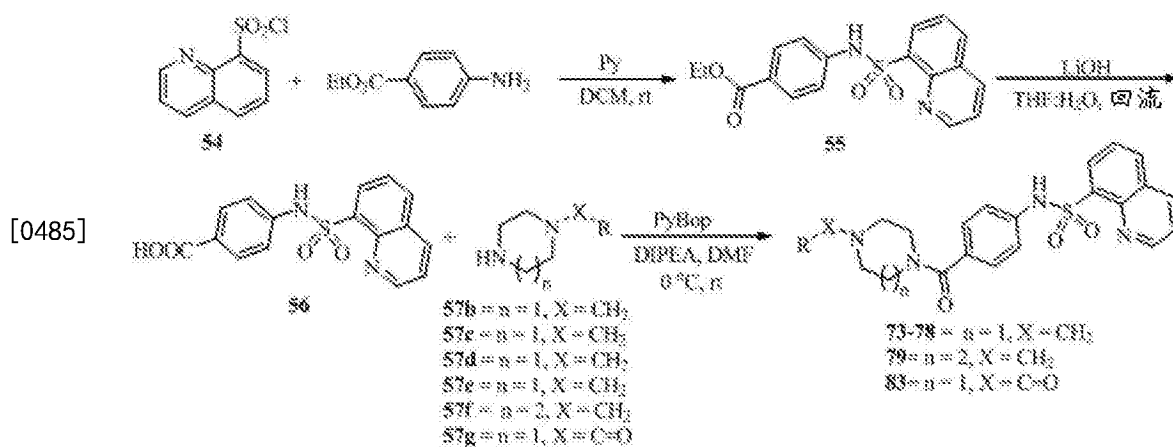
[0480] ^1H NMR (500MHz, DMSO- d_6) 2.90 (bs, 4H), 3.40-3.70 (bm, 4H), 3.80 (s, 3H), 6.80-7.20 (m, 5H), 7.60-7.80 (m, 3H), 8.10 (s, 1H), 8.30 (d, 1H), 8.50 (d, 2H), 9.0 (s, 1H); MS基峰为504.2; HPLC纯度98.92%.

[0481] 苄基类似物的合成

[0482] 流程10

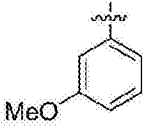
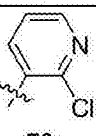


[0484] 流程11

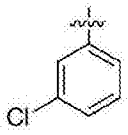
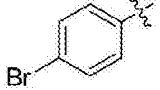
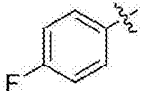
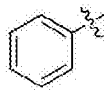
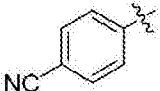
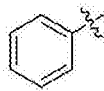
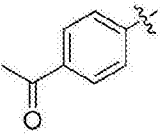
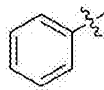
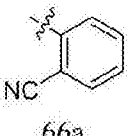
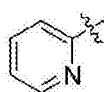
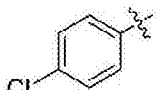
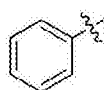
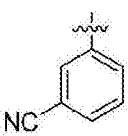
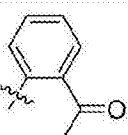
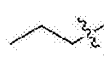
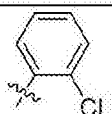
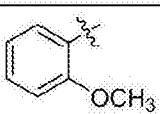


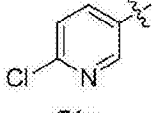
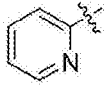
[0486] 表2

[0487]

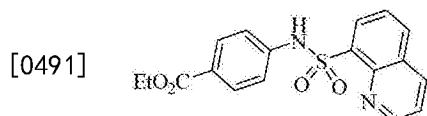
S. No.	R	R'	n		S. No.	R	R'	n
60	 60a	H	1		72	 72a	H	1

[0488]

61	 61a	H	1		73	 73a	H	1
62	 62a	H	1		74	 74a	H	1
63	 63a	H	1		75	 75a	H	1
64	 64a	H	1		76	 75a	Na ⁺	1
65	 65a	H	1		77	 75a	CH ₃ SO ₃ ⁻	1
66	 66a	H	1		78	 78a	H	1
67	 67a	H	1		79	 75a	H	2
68	 68a	H	1		80	 80a	H	1
69	 69a	H	1		81	 81a	H	1
70	 70a	H	1		82	 82a	H	1

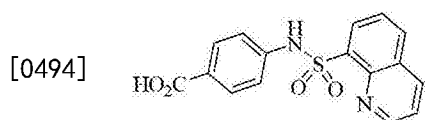
		70a				82a		
[0489]	71		H	1	83		H	1
		71a				83a		

[0490] 化合物55的制备:



[0492] 于室温、在N₂气氛下向4-氨基苯甲酸乙酯(16g, 96.85mmol)在DCM和吡啶的混合物(1:1)中的溶液加入磺酰氯54(27.56g, 121.07mmol)。将所得混合物搅拌16h。反应结束后, 将粗混合物用DCM稀释, 用水洗涤, 然后用1N HCl洗涤。然后将所得有机层经Na₂SO₄干燥, 在减压下浓缩, 得到收率为98%的产物55(34g)。

[0493] 化合物56的制备:

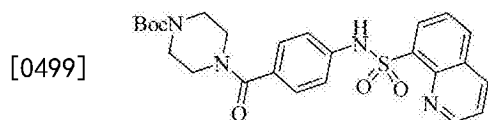


[0495] 向磺酰胺55(34g, 95.5mmol)在THF和水(1:1)中的溶液加入LiOH(20g, 47.66mmol)。将反应混合物在80℃搅拌过夜。反应结束后, 将粗混合物用EtOAc洗涤。用柠檬酸酸化水层, 过滤。然后将所得固体用Et₂O洗涤, 在减压下与甲苯共沸, 得到酸产物56(30g, 95.8%收率)。

[0496] 化合物57b-57f的一般程序(流程11): 向N-Boc哌嗪在DMF中的溶液加入相应的溴化物R-Br(R=20-23, 参见表1), 然后添加K₂CO₃。将反应混合物在80℃搅拌3天。反应结束后, 在减压下除去DMF, 将所得残余物用水稀释, 用EtOAc稀释。用水洗涤有机层, 经Na₂SO₄干燥, 浓缩。通过柱色谱法纯化残余物, 得到收率良好的产物57b-57f。

[0497] 化合物57g的制备(流程2): 通过按照流程10中对于制备化合物58所述的类似程序, 通过使用胺N-Boc哌嗪, 由2-吡啶甲酸(1.0g, 8.12mmol)进行化合物57g的合成, 得到收率为76.10%的产物57g(1.80g)。

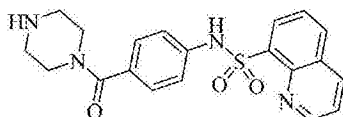
[0498] 化合物58的制备:



[0500] 于0℃、向酸56(2.0g, 6.09mmol)在DMF中的溶液加入PyBoP(苯并三唑-1-基-氧基-三-(二甲基氨基)-磷六氟磷酸酯)(4.75g, 9.14mmol), 搅拌5分钟。然后于0℃在N₂气氛下加入胺57a(1.13g, 6.09mmol), 在室温搅拌过夜。反应结束后, 将所得混合物用水稀释, 用EtOAc萃取。用水洗涤有机层, 经Na₂SO₄干燥, 在减压下蒸发。通过柱色谱法(硅胶, 60-120目; MeOH-DCM, 2:8)纯化残余物, 得到收率为66%的产物58(2.0g)。

[0501] 化合物6的制备:

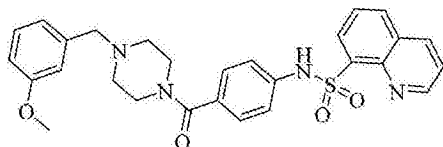
[0502]



[0503] 向MeOH·HCl的溶液加入经Boc保护的胺5 (2gm, 4.03mmol), 将所得混合物搅拌1h。反应结束后, 在减压下除去溶剂, 用水洗涤, 然后加入NaHCO₃, 用DCM萃取。将有机层经Na₂SO₄干燥, 在减压下蒸发, 得到产物6 (1.5gm, 94.30% 收率)。

[0504] 化合物60的制备:

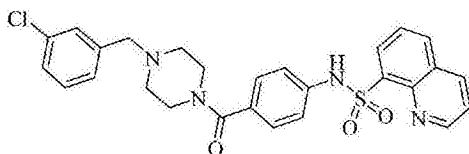
[0505]



[0506] 于室温。向胺59 (0.1g, 0.25mmol) 和醛60a (0.04g, 0.27mmol) 在DCM中的溶液加入乙酸 (0.2mL), 将所得混合物搅拌30min。然后加入STAB (0.26g, 1.26mmol), 将所得混合物在50℃搅拌1h。反应结束后, 将粗混合物用DCM稀释, 用水洗涤, 经Na₂SO₄干燥, 在减压下浓缩。通过柱色谱法 (硅胶, 60-120目; MeOH-DCM, 2:8) 纯化残余物, 得到产物60 (0.05g, 38.40% 收率)。¹H NMR (400MHz, CDCl₃) δ2.40 (br d, 4H), 3.38 (br s, 2H), 3.48 (s, 2H), 3.68 (br s, 2H), 3.80 (s, 3H), 6.79 (d, 1H), 6.84 (s, 2H), 7.04 (d, 2H), 7.18 (d, 2H), 7.20-7.28 (m, 2H), 7.59-7.64 (m, 2H), 8.03 (d, 1H), 8.28 (d, 1H), 8.36 (d, 1H), 8.58 (s, 1H), 9.18 (s, 1H); MS: 517 (M+1 峰)。

[0507] 化合物61的制备:

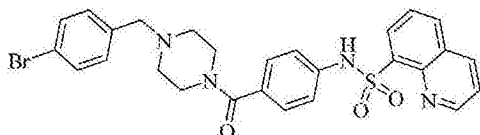
[0508]



[0509] 使用化合物59 (0.10g, 0.25mmol) 并且按照对于化合物60所述的类似程序 (通过使用醛61a) 进行化合物61的合成, 得到收率为30.40%的产物61 (0.040g)。¹H NMR (400MHz, CDCl₃) δ2.40 (br d, 4H), 3.38 (br s, 2H), 3.56 (s, 2H), 3.68 (br s, 2H), 7.06 (d, 2H), 7.18 (d, 3H), 7.25 (d, 4H), 7.42 (d, 2H), 7.59-7.66 (m, 2H), 8.03 (d, 1H), 8.27 (d, 1H), 8.35 (d, 1H), 8.58 (s, 1H), 9.18 (s, 1H); MS: 521 (M+1 峰)。

[0510] 化合物62的制备:

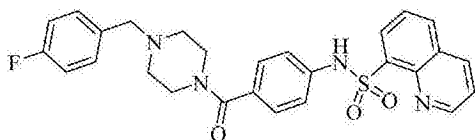
[0511]



[0512] 使用化合物59 (0.08g, 0.20mmol) 并且按照对于化合物60所述的类似程序 (通过使用醛62a) 进行化合物62的合成, 得到收率为35.00%的产物62 (0.040g)。¹H NMR (400MHz, CDCl₃) δ2.40 (br d, 4H), 3.39 (br s, 2H), 3.43 (s, 2H), 3.67 (br s, 2H), 7.02 (d, 2H), 7.15-7.21 (m, 2H), 7.48-7.63 (m, 2H), 8.03 (d, 1H), 8.31 (d, 2H), 8.39 (d, 1H), 8.58 (s, 1H), 9.18 (s, 1H); MS: 567 (M+2 峰)。

[0513] 化合物63的制备:

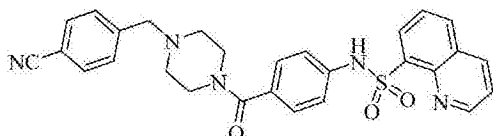
[0514]



[0515] 按照对于化合物60所述的类似程序(通过使用醛63a),由化合物59(0.08g, 0.20mmol)进行化合物63的合成,得到收率为59.00%的产物63(0.06g)。¹H NMR(400MHz, CDCl₃) δ2.40(br d, 4H), 3.39(br s, 2H), 3.43(s, 2H), 3.67(br s, 2H), 7.02(t, 2H), 7.05(d, 2H), 7.19(d, 2H), 7.21(s, 2H), 7.49-7.63(m, 2H), 7.51-7.66(m, 5H), 8.03(d, 1H), 8.31(d, 2H), 8.39(d, 1H), 8.58(s, 1H), 9.18(s, 1H); MS: 505 (M+1峰)。

[0516] 化合物64的制备:

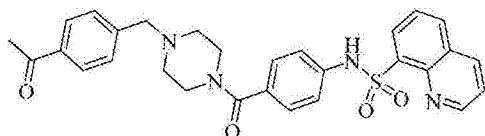
[0517]



[0518] 按照对于化合物60所述的类似程序(通过使用醛64a),由化合物59(0.08g, 0.20mmol)进行化合物64的合成,得到收率为48.54%的产物64(0.05g)。¹H NMR(400MHz, CDCl₃) δ2.40(br s, 4H), 3.39(br s, 2H), 3.58(s, 2H), 3.71(br s, 2H), 7.08(d, 2H), 7.16(d, 2H), 7.43(d, 1H), 7.51(d, 1H), 7.59-7.68(m, 4H), 8.04(d, 1H), 8.31(d, 2H), 8.39(d, 1H), 8.58(s, 1H), 9.18(s, 1H); MS: 512 (M+1峰)。

[0519] 化合物65的制备:

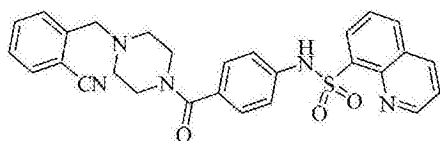
[0520]



[0521] 按照对于化合物60所述的类似程序(通过使用醛65a),由化合物59(0.08g, 0.20mmol)进行化合物65的合成,得到收率为28.00%的产物65(0.03g)。¹H NMR(400MHz, CDCl₃) δ2.39(br d, 4H), 2.58(s, 3H), 3.29(br s, 2H), 3.59(s, 2H), 3.76(br s, 2H), 7.06(d, 2H), 7.21(d, 2H), 7.51-7.68(m, 2H), 7.80(d, 2H), 8.03(d, 1H), 8.31(d, 2H), 8.39(d, 1H), 8.58(s, 1H), 9.18(s, 1H); MS: 529 (M+1峰)。

[0522] 化合物66的制备:

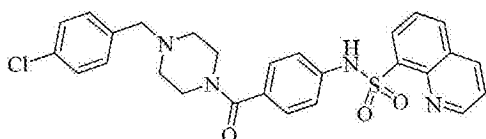
[0523]



[0524] 按照对于化合物60所述的类似程序(通过使用醛66a),由化合物59(0.08g, 0.20mmol)进行化合物66的合成,得到收率为38.80%的产物(0.04g)。¹H NMR(400MHz, CDCl₃) δ2.40(br s, 4H), 3.39(br s, 2H), 3.53(s, 2H), 3.71(br s, 2H), 7.06(d, 2H), 7.15(d, 2H), 7.43(t, 1H), 7.51-7.66(m, 5H), 8.03(d, 1H), 8.31(d, 2H), 8.39(d, 1H), 8.58(s, 1H), 9.18(s, 1H); MS: 512 (M+1峰)。

[0525] 化合物67的制备:

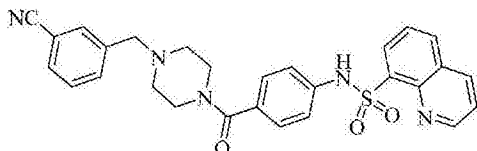
[0526]



[0527] 按照对于化合物60所述的类似程序(通过使用醛67a),由化合物59(0.08g, 0.20mmol)进行化合物67的合成,得到收率为38%的产物(0.04g)。¹H NMR(400MHz, CDCl₃) δ 2.42(br d, 4H), 3.38(br s, 2H), 3.56(s, 2H), 3.68(br s, 2H), 7.06(d, 2H), 7.18(d, 2H), 7.42(d, 2H), 7.49(d, 1H), 7.59–7.68(m, 4H), 8.03(d, 1H), 8.27(d, 1H), 8.35(d, 1H), 8.58(s, 1H), 9.18(s, 1H); MS: 521 (M+1峰)。

[0528] 化合物68的制备:

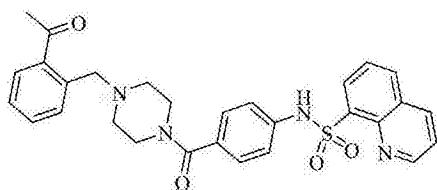
[0529]



[0530] 按照对于化合物60所述的类似程序(通过使用醛68a),由化合物59(0.08g, 0.20mmol)进行化合物68的合成,得到收率为38%的产物(0.04g)。¹H NMR(400MHz, CDCl₃) δ 2.43(br d, 4H), 3.41(br s, 2H), 3.68(br s, 4H), 7.06(d, 2H), 7.15(d, 2H), 7.35–7.42(m, 1H), 7.50–7.69(m, 5H), 8.03(d, 1H), 8.31(d, 2H), 8.39(d, 1H), 8.58(s, 1H), 9.18(s, 1H); MS: 512 (M+1峰)。

[0531] 化合物69的制备:

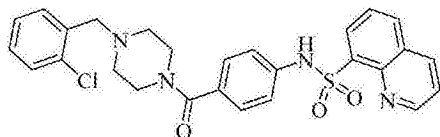
[0532]



[0533] 按照对于化合物60所述的类似程序(通过使用醛69a),由化合物59(0.08g, 0.20mmol)进行化合物69的合成,得到收率为37.70%的产物(0.04g)。¹H NMR(400MHz, CDCl₃) δ 2.39(br s, 4H), 2.52(s, 3H), 3.26(br s, 2H), 3.61(br s, 2H), 3.65(s, 2H), 7.06(d, 2H), 7.15(d, 2H), 7.29–7.39(m, 3H), 7.58–7.63(m, 2H), 7.80(d, 1H), 8.03(d, 1H), 8.31(d, 2H), 8.39(d, 1H), 8.58(s, 1H), 9.18(s, 1H); MS: 529 (M+1峰)。

[0534] 化合物70的制备:

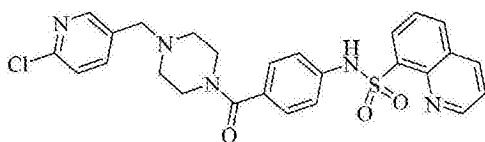
[0535]



[0536] 按照对于化合物60所述的类似程序(通过使用醛70a),由化合物6(0.08gm, 0.20mmol)进行化合物70的合成,得到收率为28.50%的产物(0.03gm)。¹H NMR(400MHz, CDCl₃) δ 2.42(br d, 4H), 3.35(br s, 2H), 3.60(s, 2H), 3.68(br s, 2H), 7.03(d, 2H), 7.08–7.26(m, 4H), 7.32(d, 1H), 7.39(d, 1H), 7.54–7.60(m, 2H), 8.03(d, 1H), 8.28(d, 1H), 8.37(d, 1H), 8.58(s, 1H), 9.18(s, 1H); MS: 521 (M+1峰)。

[0537] 化合物71的制备:

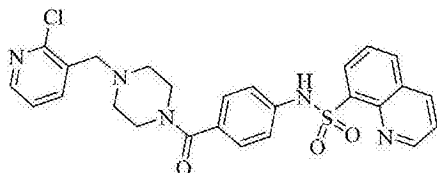
[0538]



[0539] 按照对于化合物60所述的类似程序(通过使用醛71a),由化合物59(0.08g, 0.20mmol)进行化合物71的合成,得到收率为57.00%的所需产物(0.06g)。¹H NMR(400MHz, CDCl₃) δ2.39(br d, 4H), 3.38(br s, 2H), 3.43(s, 2H), 3.63(br s, 2H), 7.06(d, 2H), 7.17(d, 2H), 7.21-7.29(m, 2H), 7.58-7.63(m, 3H), 8.03(d, 1H), 8.31(d, 2H), 8.39(d, 1H), 8.58(s, 1H), 9.18(s, 1H); MS: 522 (M+峰)。

[0540] 化合物72的合成:

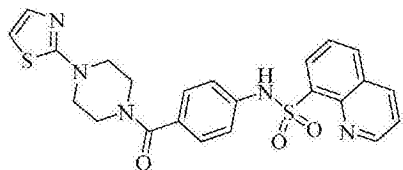
[0541]



[0542] 按照对于化合物7a所述的类似程序(通过使用醛72a),由化合物59(0.08g, 0.20mmol)进行化合物72的合成,得到收率为38.80%的产物(0.04g)。¹H NMR(400MHz, CDCl₃): δ2.45(br s, 4H), 3.41(br s, 2H), 3.60(s, 2H), 3.68(br s, 2H), 7.06(d, 2H), 7.15(d, 2H), 7.21-7.29(m, 1H), 7.58-7.63(m, 2H), 7.80(d, 1H), 8.03(d, 1H), 8.31(d, 2H), 8.39(d, 1H), 8.58(s, 1H), 9.18(s, 1H); MS: 522 (M+峰)。

[0543] 化合物73的制备:

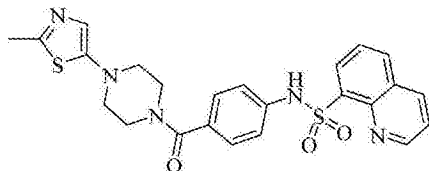
[0544]



[0545] 按照流程10中对于化合物58所述的类似程序(通过使用胺57b),由化合物56(0.08g, 0.24mmol)进行化合物73的合成,得到收率为73.27%的产物73(0.08g)。¹H NMR(400MHz, CDCl₃): δ3.44(br s, 4H), 3.62(s, 2H), 3.76(br s, 4H), 6.84(d, 1H), 7.12(d, 2H), 7.21(d, 2H), 7.37(d, 1H), 7.60-7.66(m, 2H), 8.04(d, 1H), 8.32(d, 1H), 8.39(d, 1H), 9.18(d, 1H); MS: 480 (M+1峰)。

[0546] 化合物74的制备:

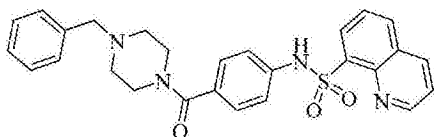
[0547]



[0548] 按照流程10中对于化合物58所述的类似程序(通过使用胺57c),由化合物56(0.18g, 0.54mmol)进行化合物74的合成,得到收率为33.45%的产物74(0.09g)。¹H NMR(400MHz, DMSO-d₆): δ2.45(s, 3H), 2.99(br s, 4H), 3.55(br s, 4H), 6.78(s, 1H), 7.14(dd, 4H), 7.66-7.75(m, 2H), 8.26(d, 1H), 8.41(d, 1H), 8.50(d, 1H), 9.16(d, 1H); MS: 480 (M+1峰)。

[0549] 化合物75的制备:

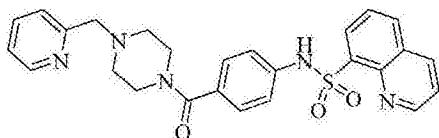
[0550]



[0551] 按照流程10中对于化合物58所述的类似程序(通过使用胺57d),由化合物56(0.15g,0.47mmol)进行化合物75的合成,得到收率为43.85%的产物75(0.10g)。¹H NMR(400MHz,CDCl₃): δ 2.40(br d,4H),3.38(br s,2H),3.52(s,2H),3.73(br s,2H),7.07(d,2H),7.18(d,2H),7.22-7.38(m,8H),7.59-7.63(m,2H),8.02(d,1H),8.32(d,1H),8.39(d,1H),9.18(d,1H),8.58(s,1H),9.18(s,1H);MS:487(M+1峰)。

[0552] 化合物76的制备:

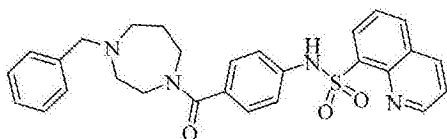
[0553]



[0554] 按照流程10中对于化合物58所述的类似程序(通过使用胺57e),由化合物56(0.23g,0.70mmol)进行化合物76的合成,得到收率为26.31%的产物76(0.06g)。¹H NMR(400MHz,CDCl₃): δ 3.15(br s,4H),3.82(br s,4H),4.21(s,2H),7.12(dd,4H),7.41(t,1H),7.52-7.67(m,3H),7.82(t,1H),8.04(d,1H),8.31(d,1H),8.39(d,1H),8.63(d,2H),9.16(d,1H);MS:480(M+1峰);MS:488(M+1峰)。

[0555] 化合物77的制备:

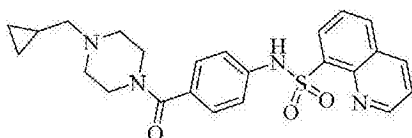
[0556]



[0557] 按照流程10中对于化合物58所述的类似程序(通过使用胺57f),由化合物56(0.17g,0.51mmol)进行化合物77的合成,得到收率为21.14%的产物77(0.07g)。¹H NMR(400MHz,CDCl₃): δ 1.71(br s,1H),1.80(br s,1H),2.53(br d,2H),2.71(br d,2H),3.38(br s,2H),3.57-3.69(m,4H),7.02(t,2H),7.16(t,2H),7.59-7.63(m,2H),8.01(d,1H),8.31(d,1H),8.39(d,1H),8.48(s,1H),9.16(d,1H);MS:480(M+1峰);MS:501(M+1峰)。

[0558] 化合物78的制备:

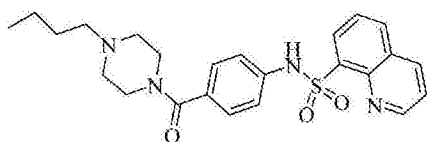
[0559]



[0560] 按照流程10中对于化合物60所述的类似程序(通过使用醛24),由化合物59(0.07g,0.16mmol)进行化合物78的合成,得到收率为48.61%的所需产物(0.035g)。¹H NMR(400MHz,CDCl₃): δ 0.04(d,2H),0.54(d,2H),0.80-0.90(m 1H),2.24(d,2H),2.48(br d,4H),3.39(br s,2H),3.78(br s,2H),7.12(dd,4H),7.49-7.64(m,2H),8.04(d,1H),8.31(d,1H),8.39(d,1H),8.58(s,1H),9.16(d,1H);MS:480(M+1峰);MS:451(M+1峰)。

[0561] 化合物81的制备:

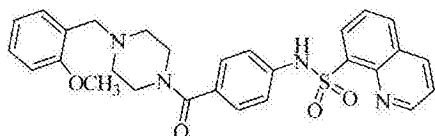
[0562]



[0563] 按照流程10中对于化合物60所述的类似程序(通过使用醛81a),由化合物6(0.1g, 0.23mmol)进行化合物81的合成,得到收率为43.26%的产物81(0.045g)。¹H NMR (400MHz, CDCl₃): δ0.91 (t, 3H), 1.25-1.39 (m, 2H), 1.40-1.49 (m, 2H), 2.30 (t, 2H), 2.42 (br s, 4H), 3.39 (br s, 2H), 3.70 (br s, 2H), 7.05 (d, 2H), 7.16 (d, 2H), 7.59-7.64 (m, 2H), 8.02 (d, 1H), 8.32 (d, 1H), 8.38 (d, 1H), 8.58 (br s, 1H), 9.16 (d, 1H); MS: 480 (M+1峰); MS: 453 (M+1峰)。

[0564] 化合物82的制备:

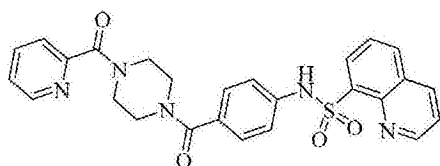
[0565]



[0566] 按照流程10中对于化合物60所述的类似程序(通过使用醛82a),由化合物59(0.08g, 0.20mmol)进行化合物82的合成,得到收率为48.73%的产物(0.06g)。¹H NMR (400MHz, CDCl₃): δ2.39 (br s, 2H), 2.56 (br s, 2H), 3.39 (br s, 2H), 3.59 (s, 2H), 3.75 (br s, 2H), 3.81 (s, 3H), 6.85 (d, 1H), 6.92 (t, 1H), 7.08 (d, 2H), 7.17 (d, 2H), 7.24-7.31 (m, 2H), 8.02 (d, 1H), 8.32 (d, 1H), 8.38 (d, 1H), 8.58 (br s, 1H), 9.17 (d, 1H); MS: 480 (M+1峰); MS: 517 (M+1峰)。

[0567] 化合物83的制备:

[0568]



[0569] 按照流程10中对于化合物58所述的类似程序(通过使用胺57g),由化合物56(0.14gm, 0.43mmol)进行化合物83的合成,得到收率为22.72%的产物(0.05gm)。¹H NMR (400MHz, CDCl₃): δ3.62 (br s, 8H), 7.05 (d, 2H), 7.19 (d, 2H), 7.38 (t, 1H), 7.59-7.64 (m, 2H), 7.69 (d, 1H), 7.80 (t, 1H), 8.02 (d, 1H), 8.32 (d, 1H), 8.38 (d, 1H), 8.58 (br s, 1H), 9.17 (d, 1H); MS: 480 (M+1峰); MS: 502 (M+1峰)。

[0570] 钠盐76的制备:

[0571] 于室温向磺酰胺75(0.05g, 0.10mmol)在甲醇中的溶液加入NaOH(0.04g, 0.10mmol),将所得混合物搅拌2h。反应结束后,在减压下除去相应的溶剂。然后添加Et₂O(5mL),随后将其除去。添加和除去Et₂O进行数次,得到收率为84.61%的为固体状的所需产物(0.04g)。¹H NMR (400MHz, DMSO-d₆): δ3.40 (br s, 2H), 3.59 (br s, 8H), 6.77 (d, 1H), 6.89 (d, 1H), 7.18-7.29 (m, 2H), 7.50-7.60 (m, 2H), 7.99 (d, 1H), 8.25-8.32 (m, 2H), 8.98 (d, 1H); MS: 509 (M+1峰)。

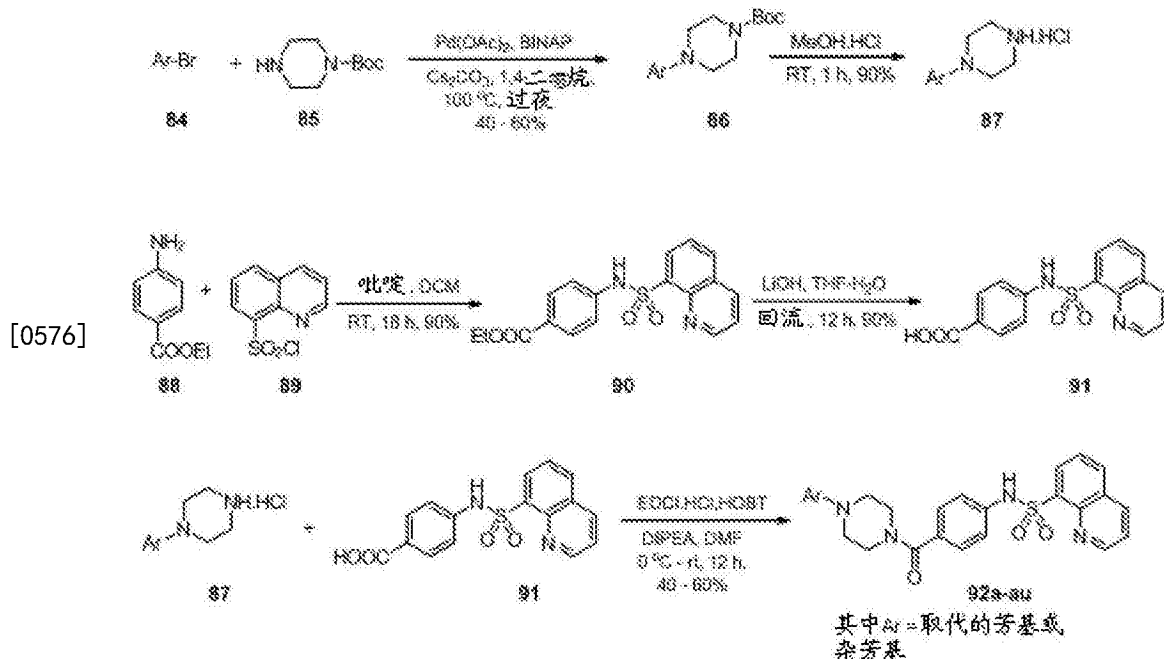
[0572] 甲磺酸盐77的制备:

[0573] 于室温向磺酰胺75(0.05g, 0.10mmol)在DCM中的溶液加入CH₃SO₃H(0.10g, 0.10mmol),将所得混合物搅拌2h。反应结束后,在减压下除去相应的溶剂,然后添加Et₂O(5mL),随后将其除去。添加和除去Et₂O进行数次(3×5mL),得到收率为59.32%的所需产物

(0.035gm)。¹H NMR (400MHz, CDCl₃) : δ 3.02 (br s, 3H), 3.25 (br s, 3H), 4.23 (s, 2H), 7.17 (dd, 4H), 7.62–7.69 (m, 2H), 8.22 (d, 1H), 8.32 (d, 1H), 8.38 (d, 1H), 9.10 (d, 1H); MS: 487 (M⁺峰)。

[0574] N⁴-芳基/杂芳基哌嗪类似物的合成

[0575] 流程12



[0577] 化合物86的一般程序:于室温、将氮气鼓入芳基溴(84, 2.15mmol)在1,4-二噁烷(20ml)中的搅拌溶液,持续30min。将BINAP(0.134g, 0.215mmol)、醋酸铯(0.0096g, 0.043mmol)和碳酸铯(1.40g, 4.3mmol)加至反应混合物,将氮气鼓入持续另外20min,最终加入N-Boc哌嗪(85, 0.4g, 2.15mmol),于100℃在氮气气氛下搅拌过夜。反应结束后(通过TLC监控),在真空下浓缩反应混合物。将残余物溶解于水中,用乙酸乙酯萃取(3×50ml)。合并的有机萃取液用盐水(20ml)洗涤,经无水硫酸钠干燥,过滤,在减压下浓缩。然后通过使用10%乙酸乙酯-己烷的柱色谱法(60–120硅胶)纯化粗产物,得到化合物86(40–60%)。

[0578] 化合物87的一般程序:将N¹-Boc-N⁴-芳基哌嗪(86, 1.075mmol)装入圆底烧瓶中,加入甲醇-HCl(20ml, 20%),其导致形成均质溶液,在室温搅拌1h。反应结束后(通过TLC监控),在真空下除去溶剂。重复用乙酸乙酯洗涤粗产物,然后充分干燥,获得为白色固体状的化合物87(90%)。

[0579] 用于制备4-(喹啉-8-亚磺酰氨基)苯甲酸乙酯90的程序:在氮气气氛下向4-氨基苯甲酸乙酯(88, 5.0g, 30.16mmol)在DCM-吡啶(50:50ml)的1:1混合物中的溶液加入喹啉-8-磺酰氯(89, 8.24g, 36.19mmol)。将所得溶液在室温搅拌过夜。反应结束后(通过TLC监控),将所得混合物用二氯甲烷(150ml)稀释,用水(3×50ml)、1N HCl溶液(3×50ml)和盐水(50ml)洗涤。将合并的有机萃取液经无水硫酸钠干燥,过滤,在真空下浓缩。将粗产物与甲苯共蒸馏,除去吡啶残余部分,干燥,得到为灰白色固体状的磺酰胺90(11.58g, 90%),因此不需进一步纯化即可用于下一步骤。

[0580] 化合物90的分析数据:¹H NMR (500MHz, CDCl₃) δ: 1.20 (3H, t), 4.19 (2H, q), 7.20 (2H, m), 7.60–7.80 (4H, m), 8.30 (1H, m), 8.40–8.50 (2H, m), 9.10 (1H, m), 10.8 (1H, s); MS: m/

z 357.4 (M+1)⁺.

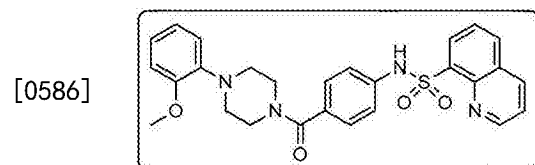
[0581] 用于制备4-(喹啉-8-亚磺酰氨基)苯甲酸91的程序:将4-(喹啉-8-亚磺酰氨基)苯甲酸乙酯(90,10g,28.08mmol)溶解于THF-水(100:100ml)的混合物中,维持在室温。向该溶液加入LiOH(5.89g,14.0mmol),将所得溶液回流过夜。然后将反应混合物用乙酸乙酯洗涤(3×50ml),然后用稀HCl酸化。过滤所得悬浮液,将残余物与甲苯共蒸馏。然后在真空下干燥该产物,得到为灰白色固体状的羧酸91(8.28g,90%)。

[0582] 化合物91的分析数据:¹H NMR(500MHz,CDCl₃) δ:7.10(2H,m),7.60-7.80(4H,m),8.25(1H,m),8.40-8.60(2H,m),9.10(1H,m),10.7(1H,bs),12.6(1H,bs);MS:m/z 329.3 (M+1)⁺.

[0583] 化合物92的一般程序:于0℃、在氮气气氛下向羧酸(91,0.61mmol)在DMF中的搅拌溶液加入EDCI(0.129g,0.671mmol)、HOBt(0.91g,0.671mmol)和DIPEA(0.31ml,1.83mmol),将所得溶液在室温搅拌30min。然后在0℃加入胺盐酸盐(87,0.61mmol),在室温搅拌过夜。反应结束后(通过TLC监控),将反应混合物倒入1.0M HCl中,用EtOAc萃取。用饱和NaHCO₃溶液洗涤有机层,经NaSO₄干燥,过滤。通过旋转蒸发除去溶剂,通过硅胶层析法(60-120硅胶,2%MeOH-DCM)或制备型HPLC分离产物,得到为灰白色固体状的酰胺(92a-as)(40-60%)。

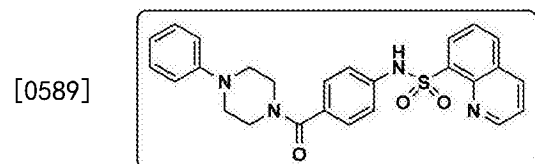
[0584] 化合物(92at,92au和92av)的一般程序:向N⁴-芳基哌嗪类似物(0.39mmol)在甲醇-DCM混合物(对于钠盐)或DCM(对于甲磺酸盐)中的溶液加入氢氧化钠在甲醇(0.39mmol)或甲磺酰氯(0.39mmol)中的溶液。将反应混合物搅拌过夜,在减压下蒸发溶剂。然后将粗残余物相继用乙醚和正戊烷洗涤,得到为白色固体状的所需盐。

[0585] N-(4-(4-(2-甲氧基苯基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺(92a):



[0587] ¹H NMR(500MHz,DMSO-d₆) δ:10.42(s,1H),9.15(bs,1H),8.50(d,1H),8.40(d,1H),8.24(d,1H),7.70-7.80(m,2H),7.15-7.20(dd,4H),6.90-7.00(m,2H),6.82(d,2H),3.80(s,3H),3.40-3.78(bm,4H),2.80-3.00(bs,4H);HPLC纯度:97.11%;MS,m/z实测值503.2 (M+1)⁺.

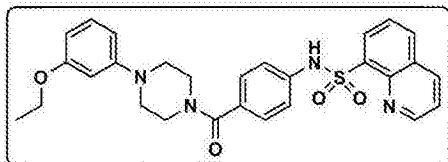
[0588] N-(4-(4-苯基哌嗪-1-羰基)苯基)喹啉-8-磺酰胺(92b):



[0590] ¹H NMR(500MHz,DMSO-d₆) δ:10.42(s,1H),9.18(d,1H),8.56(d,1H),8.44(d,1H),8.30(d,1H),7.70-7.80(m,2H),7.10-7.22(m,6H),6.90(d,2H),6.80(t,1H),3.30-3.70(bs,4H),3.00-3.20(bm,4H);HPLC纯度98.50%;MS,m/z实测值473.2 (M+1)⁺.

[0591] N-(4-(4-(3-乙氧基苯基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺(92c):

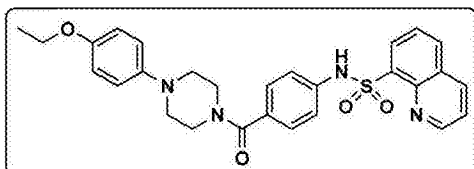
[0592]



[0593] ^1H NMR (400MHz, CDCl_3) δ : 9.18 (d, 1H), 8.60 (s, 1H), 8.35 (d, 1H), 8.30 (d, 1H), 8.10 (d, 1H), 7.65 (m, 2H), 7.05–7.20 (m, 5H), 6.50 (m, 3H), 4.00 (q, 2H), 3.40–3.90 (bs, 4H), 3.00–3.20 (bm, 4H), 1.40 (t, 3H); HPLC纯度99.74%:MS, m/z 实测值517.40 ($M+1$) $^+$.

[0594] N-(4-(4-(4-乙氧基苯基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (92d):

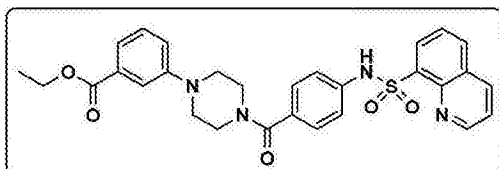
[0595]



[0596] ^1H NMR (400MHz, CDCl_3) δ : 9.18 (d, 1H), 8.60 (s, 1H), 8.35 (d, 1H), 8.30 (d, 1H), 8.05 (d, 1H), 7.60 (m, 2H), 7.20 (d, 2H), 7.10 (d, 2H), 6.85 (m, 4H), 4.00 (q, 2H), 3.40–3.90 (bm, 4H), 3.00 (bm, 4H), 1.4 (t, 3H); HPLC纯度99.36%:MS, m/z 实测值517.40 ($M+1$) $^+$.

[0597] 3-(4-(4-(喹啉-8-亚磺酰氨基)苯甲酰基)哌嗪-1-基)苯甲酸乙酯 (92e):

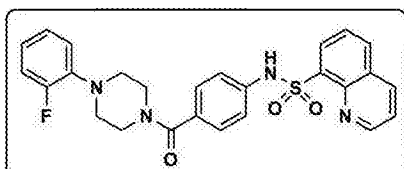
[0598]



[0599] ^1H NMR (400MHz, CDCl_3) δ : 9.20 (d, 1H), 8.60 (s, 1H), 8.40 (d, 1H), 8.30 (d, 1H), 8.05 (d, 1H), 7.60 (m, 4H), 7.30 (m, 1H), 7.20 (d, 2H), 7.10 (m, 3H), 4.40 (q, 2H), 3.40–3.90 (bm, 4H), 3.20 (bm, 4H), 1.4 (t, 3H); HPLC纯度99.65%:MS, m/z 实测值545.35 ($M+1$) $^+$.

[0600] N-(4-(4-(2-氟苯基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (92f):

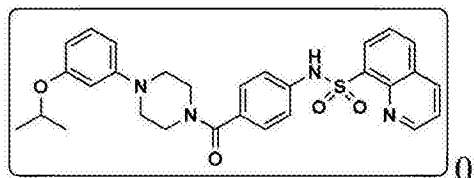
[0601]



[0602] ^1H NMR (400MHz, CDCl_3) δ : 9.15 (d, 1H), 8.60 (s, 1H), 8.40 (d, 1H), 8.30 (d, 1H), 8.05 (d, 1H), 7.60 (m, 2H), 7.20 (m, 3H), 7.10 (d, 2H), 6.65 (d, 1H), 6.55 (m, 2H), 3.40–3.80 (bm, 4H), 3.15 (bm, 4H); HPLC纯度99.16%:MS, m/z 实测值491.35 ($M+1$) $^+$.

[0603] N-(4-(4-(3-异丙氧基苯基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (92g):

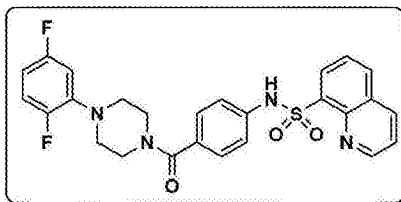
[0604]



[0605] ^1H NMR (400MHz, CDCl_3) δ : 9.15 (d, 1H), 8.60 (s, 1H), 8.40 (d, 1H), 8.30 (d, 1H), 8.05 (d, 1H), 7.60 (m, 2H), 7.20 (m, 2H), 7.15 (m, 1H), 7.10 (d, 2H), 6.45 (m, 3H), 3.40–3.80 (bm, 4H), 3.15 (bm, 4H); HPLC纯度99.45%:MS, m/z 实测值531.40 ($M+1$) $^+$.

[0606] N-(4-(4-(2,5-二氟苯基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (92h) :

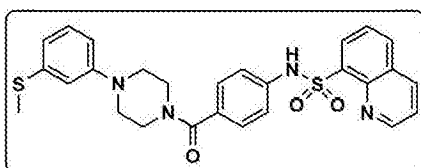
[0607]



[0608] ^1H NMR (400MHz, CDCl_3) δ : 9.15 (d, 1H), 8.60 (s, 1H), 8.35 (d, 1H), 8.30 (d, 1H), 8.05 (d, 1H), 7.60 (m, 2H), 7.20 (m, 2H), 7.10 (d, 2H), 6.95 (m, 1H), 6.60 (m, 2H), 3.45-3.90 (bm, 4H), 3.00 (bm, 4H); HPLC纯度99.94%:MS, m/z 实测值509.30 ($M+1$) $^+$.

[0609] N-(4-(4-(3-(甲硫基)苯基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (92i) :

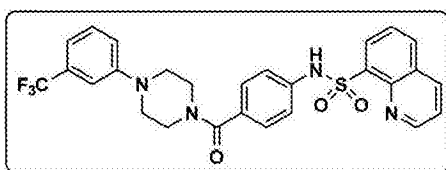
[0610]



[0611] ^1H NMR (400MHz, CDCl_3) δ : 9.15 (d, 1H), 8.60 (s, 1H), 8.35 (d, 1H), 8.30 (d, 1H), 8.05 (d, 1H), 7.60 (m, 2H), 7.20 (m, 3H), 7.10 (d, 2H), 6.80 (m, 2H), 6.65 (d, 1H), 3.45-3.90 (bm, 4H), 3.10 (bm, 4H), 2.45 (s, 3H); HPLC纯度99.98%:MS, m/z 实测值519.30 ($M+1$) $^+$.

[0612] N-(4-(4-(3-(三氟甲基)苯基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (92j) :

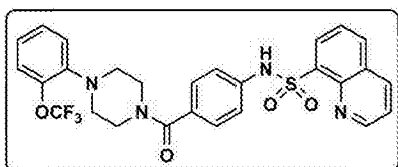
[0613]



[0614] ^1H NMR (400MHz, CDCl_3) δ : 9.15 (d, 1H), 8.60 (s, 1H), 8.35 (d, 1H), 8.30 (d, 1H), 8.05 (d, 1H), 7.60 (m, 2H), 7.50 (d, 2H), 7.20 (m, 2H), 7.10 (d, 2H), 6.90 (d, 2H), 3.45-3.90 (bm, 4H), 3.10 (bm, 4H); HPLC纯度99.63%:MS, m/z 实测值541.25 ($M+1$) $^+$.

[0615] N-(4-(4-(2-(三氟甲氧基)苯基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (92k) :

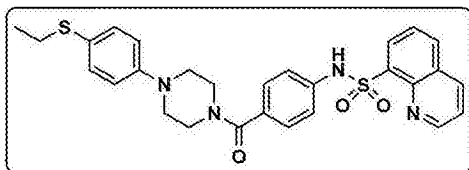
[0616]



[0617] ^1H NMR (400MHz, CDCl_3) δ : 9.15 (d, 1H), 8.55 (s, 1H), 8.35 (d, 1H), 8.30 (d, 1H), 8.05 (d, 1H), 7.60 (m, 2H), 7.20 (m, 4H), 6.95-7.15 (m, 4H), 3.45-3.90 (bm, 4H), 3.10 (bm, 4H); HPLC纯度99.89%:MS, m/z 实测值557.35 ($M+1$) $^+$.

[0618] N-(4-(4-(4-(乙硫基)苯基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (92l) :

[0619]

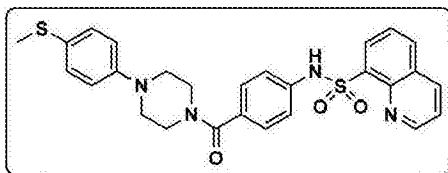


[0620] ^1H NMR (400MHz, CDCl_3) δ : 9.15 (d, 1H), 8.55 (s, 1H), 8.35 (d, 1H), 8.30 (d, 1H), 8.05 (d, 1H), 7.60 (m, 2H), 7.3 (d, 2H), 7.20 (d, 2H), 7.10 (d, 2H), 6.80 (d, 2H), 3.45-3.90 (bm,

4H), 3.10 (bm, 4H), 2.90 (q, 2H), 1.15 (t, 3H); HPLC纯度98.53%; MS, m/z实测值533.35 (M+1)⁺.

[0621] N-(4-(4-(4-(甲硫基)苯基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (92m):

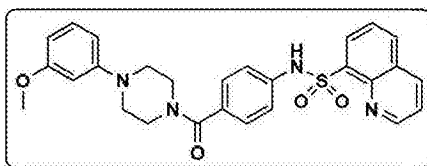
[0622]



[0623] ¹H NMR (400MHz, DMSO-d₆) δ: 10.40 (s, 1H), 9.15 (s, 1H), 8.50 (d, 1H), 8.40 (d, 1H), 8.30 (d, 1H), 7.70 (m, 2H), 7.20 (m, 6H), 6.85 (d, 2H), 3.20-3.70 (bm, 4H), 3.05 (bm, 4H), 2.35 (s, 3H); HPLC纯度91.00%; MS, m/z实测值518.50 (M+1)⁺.

[0624] N-(4-(4-(3-(甲氧基)苯基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (92n):

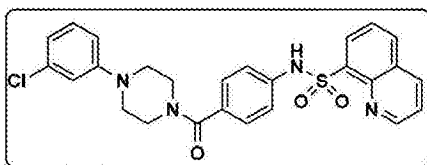
[0625]



[0626] ¹H NMR (400MHz, DMSO-d₆) δ: 10.45 (s, 1H), 9.05 (d, 1H), 8.50 (d, 1H), 8.45 (d, 1H), 8.30 (d, 1H), 7.70 (m, 2H), 7.00-7.20 (m, 5H), 6.50 (d, 1H), 6.40 (s, 1H), 6.35 (d, 1H), 3.65 (s, 3H), 3.20-3.70 (bm, 4H), 3.05 (bm, 4H); LCMS纯度100.00%; MS, m/z实测值503.35 (M+1)⁺.

[0627] N-(4-(4-(3-(氯)苯基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (92o):

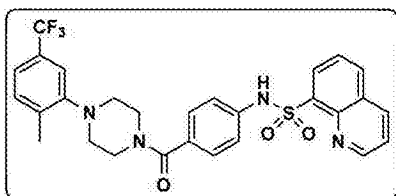
[0628]



[0629] ¹H NMR (400MHz, CDCl₃) δ: 9.15 (s, 1H), 8.60 (s, 1H), 8.35 (d, 1H), 8.30 (d, 1H), 8.05 (d, 1H), 7.60 (m, 2H), 7.10-7.20 (m, 5H), 6.85 (m, 2H), 6.75 (d, 1H), 3.40-3.85 (bm, 4H), 3.10 (bm, 4H); LCMS纯度97.15%; MS, m/z实测值507.30 (M+1)⁺.

[0630] N-(4-(4-(3-(甲基)-5-(三氟甲基)苯基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (92p):

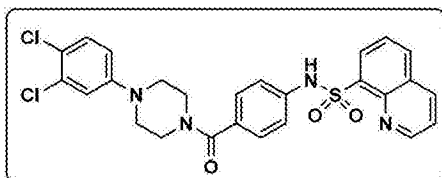
[0631]



[0632] ¹H NMR (400MHz, CDCl₃) δ: 9.15 (d, 1H), 8.55 (s, 1H), 8.35 (d, 1H), 8.30 (d, 1H), 8.05 (d, 1H), 7.60 (m, 2H), 7.20-7.30 (m, 4H), 7.15 (s, 1H), 7.10 (d, 2H), 3.40-3.85 (bm, 4H), 2.85 (bm, 4H), 2.35 (s, 3H); LCMS纯度99.65%; MS, m/z实测值555.35 (M+1)⁺.

[0633] N-(4-(4-(3,4-(二氯)苯基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (92q):

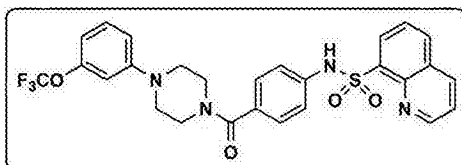
[0634]



[0635] ^1H NMR (400MHz, DMSO- d_6) δ : 10.45 (s, 1H), 9.15 (s, 1H), 8.50 (d, 1H), 8.40 (d, 1H), 8.30 (d, 1H), 7.75 (m, 2H), 7.4 (d, 1H), 7.10–7.20 (m, 5H), 6.90 (d, 1H), 3.20–3.65 (bm, 4H), 3.10 (bs, 4H); HPLC纯度93.48%; MS, m/z 实测值542.35 ($M+1$) $^+$.

[0636] N-(4-(4-(3-(三氟甲氧基)苯基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (92r):

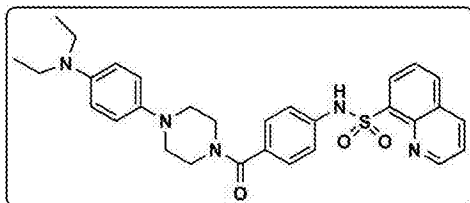
[0637]



[0638] ^1H NMR (400MHz, CDCl_3) δ : 9.15 (d, 1H), 8.55 (s, 1H), 8.35 (d, 1H), 8.30 (d, 1H), 8.05 (d, 1H), 7.60 (m, 2H), 7.20 (d, 2H), 7.10 (m, 4H), 6.85 (d, 2H), 3.40–3.90 (bm, 4H), 3.10 (bs, 4H); HPLC纯度90.37%; MS, m/z 实测值557.50 ($M+1$) $^+$.

[0639] N-(4-(4-(4-(N,N-二乙基氨基)苯基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (92s):

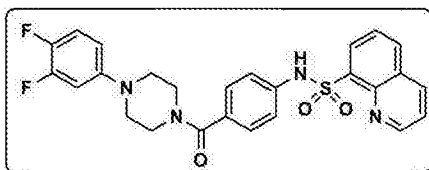
[0640]



[0641] ^1H NMR (400MHz, CDCl_3) δ : 9.15 (d, 1H), 8.55 (s, 1H), 8.35 (d, 1H), 8.30 (d, 1H), 8.05 (d, 1H), 7.60 (m, 2H), 7.20 (d, 2H), 7.10 (d, 2H), 6.85 (d, 2H), 6.65 (d, 2H), 3.40–3.90 (bm, 4H), 3.3 (q, 4H), 2.80–3.10 (bm, 4H), 1.1 (t, 6H); HPLC纯度97.59%; MS, m/z 实测值544.50 ($M+1$) $^+$.

[0642] N-(4-(4-(3,4-(二氟)苯基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (92t):

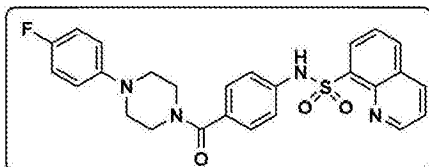
[0643]



[0644] ^1H NMR (400MHz, CDCl_3) δ : 9.15 (d, 1H), 8.55 (s, 1H), 8.35 (d, 1H), 8.30 (d, 1H), 8.05 (d, 1H), 7.60 (m, 2H), 7.20 (d, 2H), 7.10 (d, 2H), 7.05 (m, 1H), 6.65 (m, 1H), 6.55 (d, 1H), 3.40–3.90 (bm, 4H), 3.00 (bs, 4H); HPLC纯度99.73%; MS, m/z 实测值509.55 ($M+1$) $^+$.

[0645] N-(4-(4-(4-(氟)苯基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (92u):

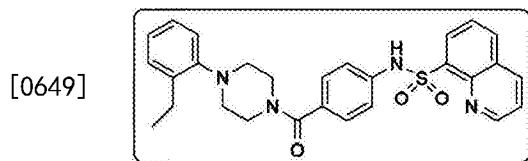
[0646]



[0647] ^1H NMR (400MHz, CDCl_3) δ : 9.15 (d, 1H), 8.55 (s, 1H), 8.35 (d, 1H), 8.30 (d, 1H), 8.05 (d, 1H), 7.60 (m, 2H), 7.20 (d, 2H), 7.10 (d, 2H), 6.95 (m, 2H), 6.85 (m, 2H), 3.40–3.90 (bm,

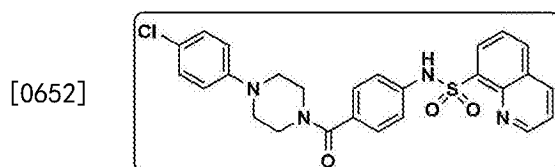
4H), 3.00 (bs, 4H); HPLC纯度97.39%; MS, m/z实测值491.25 (M+1)⁺.

[0648] N-(4-(4-(2-(乙基)苯基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (92v):



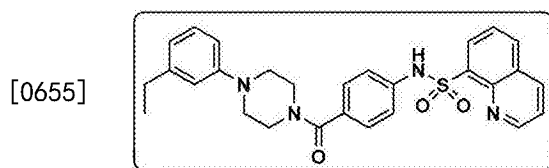
[0650] ¹H NMR (400MHz, CDCl₃) δ: 9.15 (d, 1H), 8.55 (s, 1H), 8.35 (d, 1H), 8.30 (d, 1H), 8.05 (d, 1H), 7.60 (m, 2H), 7.05-7.30 (m, 7H), 7.00 (d, 1H), 3.40-3.90 (bm, 4H), 2.80 (bm, 4H), 2.7 (q, 2H), 1.20 (t, 3H); HPLC纯度98.85%; MS, m/z实测值501.05 (M+1)⁺.

[0651] N-(4-(4-(4-(氯)苯基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (92w):



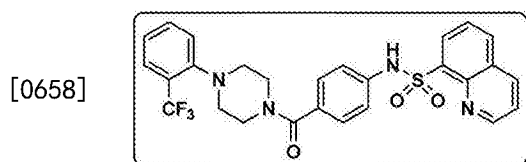
[0653] ¹H NMR (400MHz, CDCl₃) δ: 9.15 (d, 1H), 8.55 (s, 1H), 8.35 (d, 1H), 8.30 (d, 1H), 8.05 (d, 1H), 7.60 (m, 2H), 7.20 (m, 4H), 7.10 (d, 2H), 6.80 (d, 2H), 3.40-3.90 (bm, 4H), 3.10 (bm, 4H); LCMS纯度99.88%; MS, m/z实测值507.25 (M+1)⁺.

[0654] N-(4-(4-(3-(乙基)苯基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (92x):



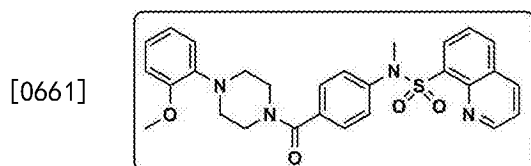
[0656] ¹H NMR (400MHz, CDCl₃) δ: 9.15 (d, 1H), 8.55 (s, 1H), 8.35 (d, 1H), 8.30 (d, 1H), 8.05 (d, 1H), 7.60 (m, 2H), 7.20 (m, 3H), 7.10 (d, 2H), 6.75 (m, 3H), 3.40-3.90 (bm, 4H), 3.10 (bm, 4H), 2.6 (q, 2H), 1.2 (t, 3H); LCMS纯度96.79%; MS, m/z实测值501.30 (M+1)⁺.

[0657] N-(4-(4-(3-(三氟甲基)苯基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (92y):



[0659] ¹H NMR (400MHz, CDCl₃) δ: 9.15 (d, 1H), 8.55 (s, 1H), 8.35 (d, 1H), 8.30 (d, 1H), 8.05 (d, 1H), 7.60 (m, 2H), 7.50 (m, 2H), 7.25 (m, 2H), 7.20 (m, 2H), 7.10 (d, 2H), 3.40-3.90 (bm, 4H), 2.90 (bm, 4H); HPLC纯度99.65%; MS, m/z实测值541.15 (M+1)⁺.

[0660] N-(4-(4-(2-甲氧基苯基)哌嗪-1-羰基)苯基)-N-甲基喹啉-8-磺酰胺 (92z):

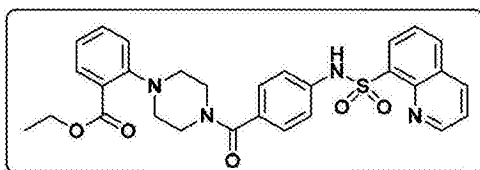


[0662] ¹H NMR (500MHz, DMSO-d₆) δ: 9.05 (s, 1H), 8.55 (m, 1H), 8.3 (m, 2H), 7.7 (m, 2H), 7.25 (m, 4H), 6.95 (m, 2H), 6.85 (m, 2H), 3.78 (s, 3H), 3.6 (s, 3H), 3.30-3.80 (bm, 4H), 2.80-3.00

(bm, 4H); HPLC纯度97.68%; MS, m/z实测值517.3 (M+1)⁺.

[0663] 2-(4-(4-(N-甲基喹啉-8-亚磺酰氨基)苯甲酰基)哌嗪-1-基)苯甲酸乙酯 (92aa):

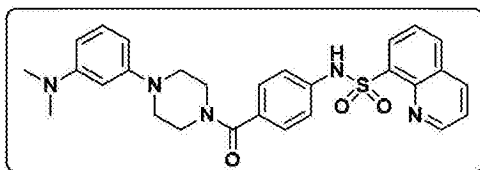
[0664]



[0665] ¹H NMR (400MHz, DMSO-d₆) δ: 10.43 (s, 1H), 9.18 (s, 1H), 8.55 (d, 1H), 8.41 (d, 1H), 8.23 (d, 1H), 7.7 (m, 2H), 7.55 (m, 1H), 7.41 (m, 1H), 7.25 (m, 6H), 4.22 (q, 2H), 3.30-3.80 (bm, 4H), 2.80-3.00 (bm, 4H), 1.25 (t, 3H); LCMS纯度97.43%; MS, m/z实测值545.1 (M+1)⁺, 567.1 (M+23).

[0666] N-(4-(4-(3-(二甲基氨基)苯基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (92ab):

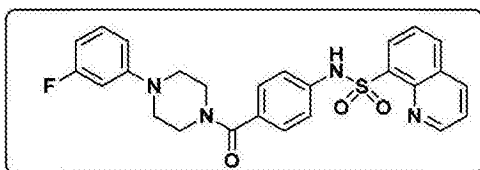
[0667]



[0668] ¹H NMR (400MHz, DMSO-d₆) δ: 9.11-9.16 (d, 1H), 8.54 (bs, 1H), 8.22-8.55 (d, 2H), 8.02-8.06 (d, 1H), 7.55-7.64 (m, 2H), 7.02-7.32 (m, 6H), 6.20-6.54 (m, 2H), 3.20-3.94 (m, 4H), 3.00-3.22 (bs, 4H), 2.84-2.94 (s, 6H); LCMS纯度98.33%; MS, m/z实测值516.3 (M+1)⁺, 538.3 (M+23).

[0669] N-(4-(4-(3-氟苯基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (92ac):

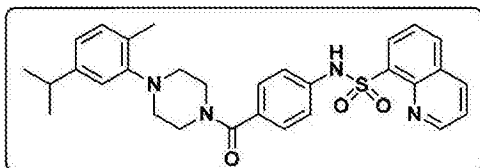
[0670]



[0671] ¹H NMR (400MHz, DMSO-d₆) δ: 9.10-9.15 (d, 1H), 8.22-8.40 (m, 2H), 7.98-8.11 (d, 1H), 7.52-7.66 (m, 2H), 7.02-7.28 (m, 6H), 6.42-6.64 (m, 3H), 3.42-3.84 (bd, 4H), 3.00-3.22 (m, 4H); LCMS纯度93.74%; MS, m/z实测值491.3 (M+1)⁺.

[0672] N-(4-(4-(5-异丙基-2-甲基苯基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (92ad):

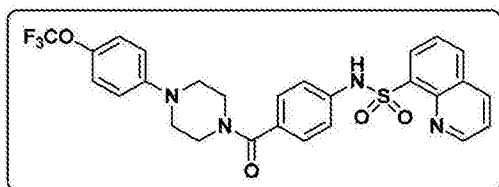
[0673]



[0674] ¹H NMR (400MHz, DMSO-d₆) δ: 9.18 (d, 1H), 8.54 (bs, 1H), 8.24-8.38 (dd, 2H), 8.00-8.15 (d, 1H), 7.54-7.66 (m, 2H), 7.18-7.26 (m, 2H), 7.02-7.14 (m, 3H), 6.86-6.94 (m, 2H), 3.42-3.92 (bd, 4H), 2.80-2.98 (m, 2H), 2.22 (s, 3H), 1.14-1.24 (d, 6H), 0.80-0.92 (m, 1H); HPLC纯度98.76%:

[0675] N-(4-(4-(4-(三氟甲氧基)苯基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (92ae):

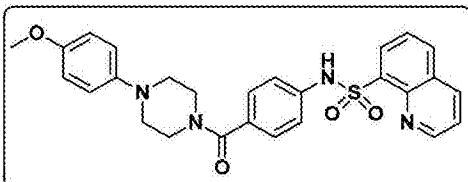
[0676]



[0677] ^1H NMR (400MHz, DMSO- d_6) δ : 9.18 (d, 1H), 8.58 (bs, 1H), 8.23–8.38 (dd, 2H), 8.00–8.15 (d, 1H), 7.52–7.68 (m, 2H), 7.14–7.24 (m, 6H), 6.80–6.89 (d, 2H), 3.42–3.92 (bd, 4H), 3.00–3.18 (bs, 4H); HPLC纯度98.77%:

[0678] N-(4-(4-(4-甲氧基苯基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (92af):

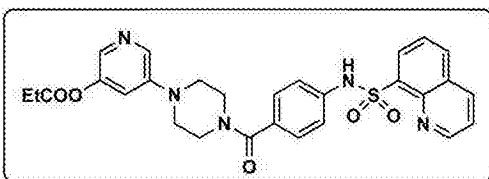
[0679]



[0680] ^1H NMR (400MHz, DMSO- d_6) δ : 10.41 (s, 1H), 9.17 (s, 1H), 8.21–8.45 (ddd, 3H), 7.63–7.78 (m, 2H), 7.12–7.24 (m, 4H), 6.78–6.94 (d, 4H), 3.82 (s, 3H), 3.22–3.54 (m, 4H), 2.84–3.08 (m, 4H); LCMS纯度=93.70%; MS, m/z实测值503.1 (M+1) $^+$.

[0681] 丙酸5-(4-(4-(喹啉-8-亚磺酰氨基)苯甲酰基)哌嗪-1-基)吡啶-3-基酯 (92ag):

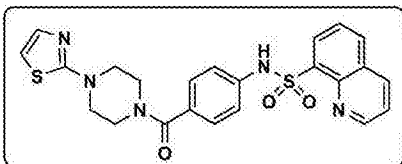
[0682]



[0683] ^1H NMR (400MHz, CDCl_3) δ : 10.42 (s, 1H), 9.15 (s, 1H), 8.40–8.54 (dt, 2H), 8.24–8.28 (d, 1H), 7.60–7.72 (m, 3H), 7.05–7.22 (m, 4H), 4.21–4.38 (q, 2H), 3.3–3.8 (m, 8H), 1.25 (t, 3H); LCMS纯度:98.85%; MS, m/z实测值546.3 (M+1) $^+$.

[0684] N-(4-(4-(噻唑-2-基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (92ah):

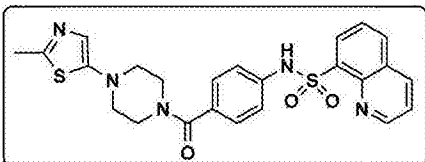
[0685]



[0686] ^1H NMR (400MHz, CDCl_3) δ : 9.15 (d, 1H), 8.40 (d, 1H), 8.30 (d, 1H), 8.05 (d, 1H), 7.60 (m, 2H), 7.35 (d, 1H), 7.20 (d, 2H), 7.10 (d, 2H), 6.7 (d, 1H), 3.3–3.8 (m, 8H); HPLC纯度: 99.79%; MS, m/z实测值480.2 (M+1) $^+$.

[0687] N-(4-(4-(2-甲基噻唑-5-基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (92ai):

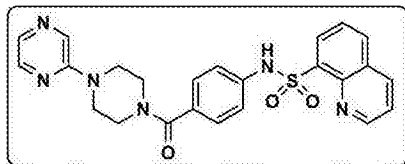
[0688]



[0689] ^1H NMR (400MHz, CDCl_3) δ : 10.42 (s, 1H), 9.15 (d, 1H), 8.45 (d, 1H), 8.40 (d, 1H), 8.15 (d, 1H), 7.70 (m, 2H), 7.20 (d, 2H), 7.15 (d, 2H), 6.8 (s, 1H), 3.5 (bm, 4H), 2.95 (bm, 4H), 2.4 (s, 3H); HPLC纯度:95.78%; MS, m/z实测值494.3 (M+1) $^+$.

[0690] N-(4-(4-(吡嗪-2-基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (92aj) :

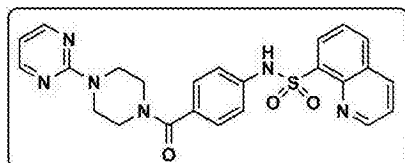
[0691]



[0692] ^1H NMR (500MHz, DMSO- d_6) δ : 10.42 (s, 1H), 9.15 (s, 1H), 8.52 (d, 1H), 8.44 (d, 1H), 8.3 (m, 2H), 8.1 (s, 1H), 7.86 (s, 1H), 7.74 (m, 2H), 7.23 (d, 2H), 7.14 (d, 2H), 3.3-3.7 (m, 8H); HPLC纯度: 98.10%; MS, m/z 实测值 475.2 ($M+1$) $^+$.

[0693] N-(4-(4-(嘧啶-2-基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (92ak) :

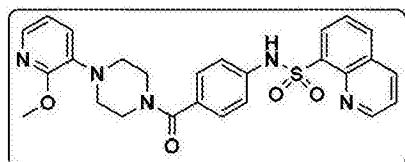
[0694]



[0695] ^1H NMR (500MHz, DMSO- d_6) δ : 10.42 (s, 1H), 9.15 (s, 1H), 8.52 (d, 1H), 8.45 (d, 1H), 8.35 (d, 2H), 8.30 (d, 1H), 7.75 (m, 2H), 7.20 (d, 2H), 7.15 (d, 2H), 7.80 (t, 1H), 3.3-3.8 (m, 8H); HPLC纯度: 99.52%; MS, m/z 实测值 475.2 ($M+1$) $^+$.

[0696] N-(4-(4-(2-甲氧基吡啶-3-基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (92a1) :

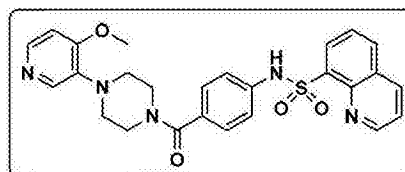
[0697]



[0698] ^1H NMR (500MHz, DMSO- d_6) 2.80-3.00 (4H, m), 3.40-3.85 (4H, m), 3.85 (3H, s), 6.91 (1H, m), 7.11-7.20 (5H, m), 7.70-7.75 (3H, m), 8.27-8.29 (1H, m), 8.41-8.53 (2H, m), 9.12 (1H, m), 10.44 (1H, s). MS 504.1 ($M+1$) $^+$.

[0699] N-(4-(4-(4-甲氧基吡啶-3-基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (92am) :

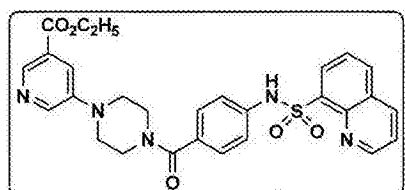
[0700]



[0701] ^1H NMR (400MHz, CDCl_3) δ : 9.18 (d, 1H), 8.60 (bs, 1H), 8.25-8.40 (m, 3H), 8.05 (d, 1H), 7.65 (m, 2H), 7.20 (d, 2H), 7.15 (d, 2H), 7.10 (d, 1H), 4.10 (s, 3H), 3.40-3.80 (bm, 4H), 3.10 (bm, 4H); HPLC纯度: 97.14%; LCMS, m/z 实测值 504.35 ($M+1$) $^+$.

[0702] N-(4-(4-(5-(乙氧基羰基)吡啶-3-基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (92an) :

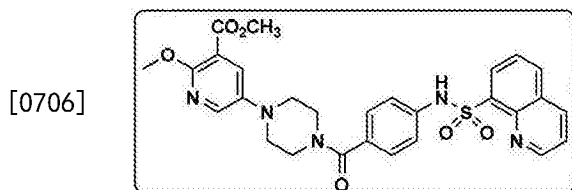
[0703]



[0704] ^1H NMR (400MHz, DMSO- d_6) δ : 10.45 (s, 1H), 9.15 (d, 1H), 8.55 (m, 3H), 8.45 (d, 1H),

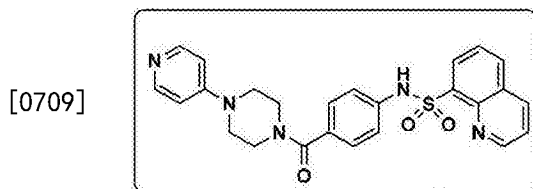
8.30 (d, 1H), 7.70 (m, 2H), 7.65 (s, 1H), 7.20 (d, 2H), 7.10 (d, 2H), 4.30 (q, 2H), 3.4-3.8 (bm, 4H), 3.1 (bm, 4H), 1.3 (t, 3H); LCMS纯度: 98.85%; MS, m/z实测值546.35 (M+1)⁺.

[0705] N-(4-(4-(5-(甲氧基羰基)-6-甲氧基)吡啶-3-基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (92ao):



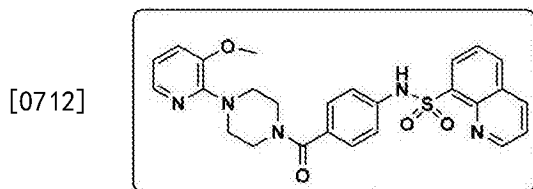
[0707] ¹H NMR (400MHz, CDCl₃) δ: 9.18 (d, 1H), 8.60 (bs, 1H), 8.35 (d, 1H), 8.30 (d, 1H), 8.05 (d, 1H), 7.95 (d, 1H), 7.80 (d, 1H), 7.60 (m, 2H), 7.20 (d, 2H), 7.10 (d, 2H), 4.00 (s, 3H), 3.9 (s, 3H), 3.4-3.8 (bm, 4H), 3.1 (bm, 4H); HPLC纯度: 94.72%; MS, m/z实测值562.18 (M+1)⁺.

[0708] N-(4-(4-(吡啶-4-基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (92ap):



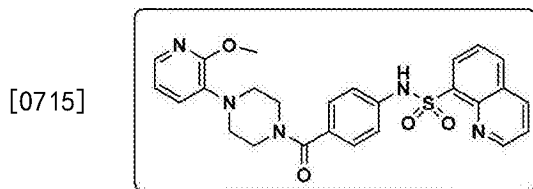
[0710] ¹H NMR (400MHz, CDCl₃) δ: 9.2 (s, 1H), 8.22-8.40 (m, 4H), 8.00-8.04 (m, 1H), 7.54-7.62 (m, 2H), 7.05-7.22 (dd, 4H), 6.60-6.68 (d, 1H), 3.2-3.8 (m, 8H); LCMS纯度: 97.37%; LCMS, m/z实测值474.05 (M+1)⁺.

[0711] N-(4-(4-(3-甲氧基吡啶-2-基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (92aq):



[0713] ¹H NMR (400MHz, CDCl₃) δ: 10.22 (s, 1H), 9.14 (d, 1H), 8.22-8.50 (ddd, 3H), 7.62-7.78 (m, 3H), 7.11-7.22 (m, 5H), 6.82-6.86 (d, 1H), 3.7 (s, 3H), 3.2-3.8 (m, 8H); LCMS纯度: 97.96%; LCMS, m/z实测值504.3 (M+1)⁺.

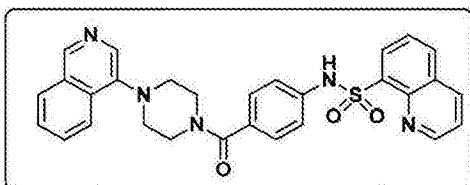
[0714] N-(4-(4-(2-甲氧基吡啶-3-基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (92ar):



[0716] ¹H NMR (400MHz, CDCl₃) δ: 10.21 (s, 1H), 9.12-9.13 (d, 1H), 8.27-8.53 (ddd, 3H), 7.70-7.75 (m, 3H), 7.13-7.20 (m, 5H), 6.87-6.90 (dd, 1H), 3.85 (s, 3H), 3.29-3.50 (m, 4H), 2.92 (bm, 4H); LCMS纯度97.11%; LCMS, m/z实测值504.3 (M+1)⁺.

[0717] N-(4-(4-(异喹啉-4-基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (92as):

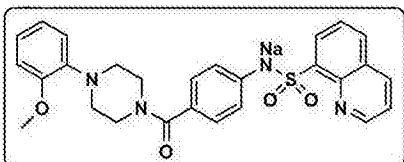
[0718]



[0719] ^1H NMR (400MHz, DMSO- d_6) δ : 9.18 (d, 1H), 9.01 (s, 1H), 8.52–8.58 (s, 1H), 8.25–8.41 (dd, 2H), 7.98–8.18 (m, 4H), 7.54–7.78 (m, 4H), 7.22–7.28 (d, 2H), 7.02–7.16 (d, 2H), 3.82–3.98 (m, 4H), 2.94–3.22 (bs, 4H); HPLC纯度94.23%; MS m/z 实测值524.25 ($M+1$) $^+$.

[0720] (4-(4-(2-甲氧基苯基)哌嗪-1-羰基)苯基)(喹啉-8-基磺酰基)酰胺钠(92at):

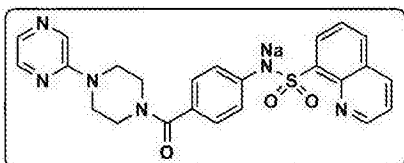
[0721]



[0722] ^1H NMR (400MHz, DMSO- d_6) δ : 9.00 (s, 1H), 8.40 (m, 2H), 8.00 (d, 1H), 7.60 (m, 2H), 6.90–7.00 (m, 4H), 6.80 (m, 4H), 3.75 (s, 3H), 3.55 (bs, 4H), 2.90 (bs, 4H); LCMS纯度: 95.17%; MS, m/z 实测值503.25 ($M-\text{Na}+1$) $^+$.

[0723] (4-(4-(吡嗪-2-基)哌嗪-1-羰基)苯基)(喹啉-8-基磺酰基)酰胺钠(92au):

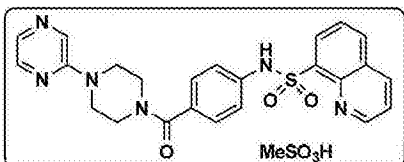
[0724]



[0725] ^1H NMR (400MHz, DMSO- d_6) δ : 9.05 (s, 1H), 8.40 (m, 2H), 8.30 (s, 1H), 8.10 (m, 2H), 7.85 (s, 1H), 7.60 (m, 2H), 7.05 (d, 2H), 6.85 (d, 2H), 3.50 (bs, 8H); LCMS纯度: 98.60%; MS, m/z 实测值475.15 ($M-\text{Na}+1$) $^+$.

[0726] N-(4-(4-(吡嗪-2-基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺甲磺酸盐(92av):

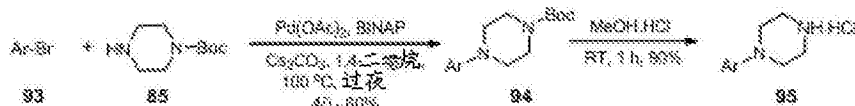
[0727]



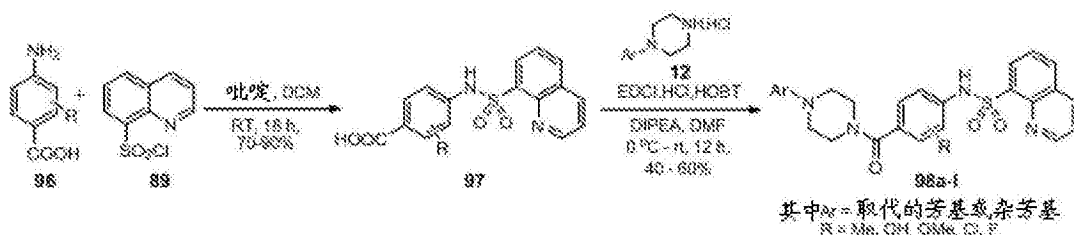
[0728] ^1H NMR (400MHz, DMSO- d_6) δ : 10.45 (s, 1H), 9.05 (d, 1H), 8.52 (d, 1H), 8.40 (d, 1H), 8.30 (m, 2H), 8.10 (s, 1H), 7.85 (s, 1H), 7.70 (m, 2H), 7.20 (d, 2H), 7.10 (d, 2H), 3.50 (bm, 8H), 2.4 (s, 3H); LCMS纯度: 98.41%; MS, m/z 实测值475.15 ($M-\text{MsSO}_3\text{H}+1$) $^+$.

[0729] 具有取代的苯基中心环的N4-芳基/杂芳基哌嗪类似物的合成.

[0730] 流程13



[0731]



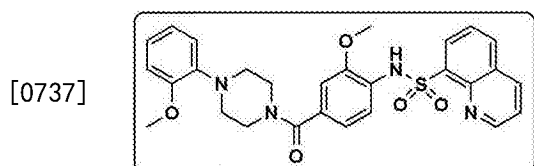
[0732] 化合物94的一般程序:于室温、将氮气鼓入芳基溴(93,2.15mmol)在1,4-二噁烷(20ml)中的搅拌溶液,持续30min。将BINAP(0.134g,0.215mmol)、醋酸钯(0.0096g,0.043mmol)和碳酸铯(1.40g,4.3mmol)加至反应混合物,将氮气鼓入持续另外20min,最终加入N-Boc哌嗪(85,0.4g,2.15mmol),于100℃在氮气气氛下搅拌过夜。反应结束后(通过TLC监控),在真空下浓缩反应混合物。将残余物溶解于水中,用乙酸乙酯萃取(3×50ml)。合并的有机萃取液用盐水(20ml)洗涤,经无水硫酸钠干燥,过滤,在减压下浓缩。然后通过使用10%乙酸乙酯-己烷的柱色谱法(60-120硅胶)纯化粗产物,得到化合物(94)(40-60%)。

[0733] 化合物(95)的一般程序:将N¹-Boc-N⁴-芳基哌嗪(94,1.075mmol)装入圆底烧瓶中,加入甲醇-HCl(20ml,20%),其导致形成均质溶液,在室温搅拌1h。反应结束后(通过TLC监控),在真空下除去溶剂。重复用乙酸乙酯洗涤粗产物,然后充分干燥,获得为白色固体状的盐酸盐(95)(90%)。

[0734] 化合物97的一般程序:在氮气气氛下向胺(96,30.16mmol)在DCM-吡啶(50:50ml)的1:1混合物中的溶液加入喹啉-8-磺酰氯(89,8.24g,36.19mmol)。将所得溶液在室温搅拌过夜。反应结束后(通过TLC监控),将所得混合物用二氯甲烷(150ml)稀释,用水(3×50ml)、1N HCl溶液(3×50ml)和盐水(50ml)洗涤。将合并的有机萃取液经无水硫酸钠干燥,过滤,在真空下浓缩。将粗产物与甲苯共蒸馏,除去吡啶残余部分,干燥,得到为灰白色固体状的磺酰胺(97)(70-90%),因此不需进一步纯化即可用于下一步骤。

[0735] 化合物98a-1的一般程序:于0℃、在氮气气氛下向羧酸(97,0.61mmol)在DMF中的搅拌溶液加入EDCI(0.129gm,0.671mmol)、HOBt(0.91gm,0.671mmol)和DIPEA(0.31ml,1.83mmol),将所得溶液在室温搅拌30min。然后在0℃加入胺盐酸盐(95,0.61mmol),在室温搅拌过夜。反应结束后(通过TLC监控),将反应混合物倒入1.0M HCl中,用EtOAc萃取。用饱和NaHCO₃溶液洗涤有机层,经NaSO₄干燥,过滤。通过旋转蒸发除去溶剂,通过硅胶层析法(60-120硅胶,2%MeOH-DCM)或制备型HPLC分离产物,得到为灰白色固体状的酰胺(98a-1)(40-60%)。

[0736] N-(4-(4-(2-甲氧基苯基)哌嗪-1-羰基)-2-甲氧基苯基)喹啉-8-磺酰胺(98a):

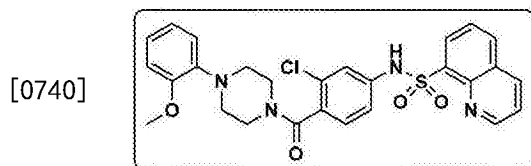


[0737]

[0738] ¹H NMR(400MHz,DMSO-d₆) δ:10.30(s,1H),9.10(d,1H),8.52(d,1H),8.45(d,1H),8.30(d,1H),7.72(m,2H),6.95(m,5H),6.80(s,1H),6.65(d,1H),3.80(s,3H),3.65(bs,

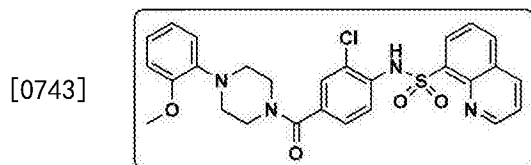
2H), 3.60 (s, 3H), 3.10 (bs, 2H), 2.95 (bs, 2H), 2.80 (bs, 2H); HPLC纯度99.73%; MS, m/z实测值533.30 (M+1)⁺.

[0739] N-(4-(4-(2-甲氧基苯基)哌嗪-1-羰基)-3-氯苯基)喹啉-8-磺酰胺 (98b):



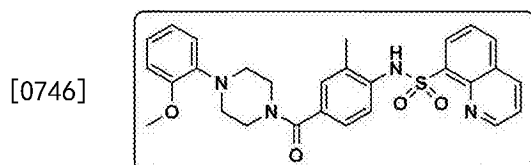
[0741] ¹H NMR (400MHz, DMSO-d₆) δ: 10.60 (s, 1H), 9.10 (d, 1H), 8.55 (d, 1H), 8.45 (d, 1H), 8.30 (d, 1H), 7.75 (m, 2H), 7.20 (m, 3H), 6.95 (m, 4H), 3.80 (s, 3H), 3.70 (bs, 2H), 3.10 (bs, 2H), 2.95 (bs, 2H), 2.80 (bs, 2H); HPLC纯度94.42%; MS, m/z实测值537.25 (M+1)⁺.

[0742] N-(4-(4-(2-甲氧基苯基)哌嗪-1-羰基)-2-氯苯基)喹啉-8-磺酰胺 (98c):



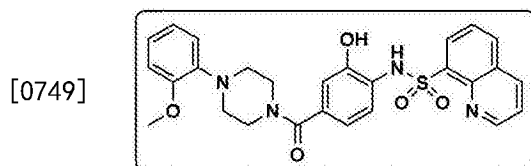
[0744] ¹H NMR (400MHz, DMSO-d₆) δ: 10.50 (bs, 1H), 9.10 (d, 1H), 8.58 (d, 1H), 8.35 (m, 2H), 7.75 (m, 2H), 7.50 (d, 1H), 7.40 (s, 1H), 7.30 (d, 1H), 6.95 (m, 3H), 6.85 (m, 1H), 3.80 (s, 3H), 3.30-3.75 (bm, 4H), 2.95 (bm, 4H); LCMS纯度97.99%; MS, m/z实测值537.20 (M+1)⁺.

[0745] N-(4-(4-(2-甲氧基苯基)哌嗪-1-羰基)-2-甲基苯基)喹啉-8-磺酰胺 (98d):



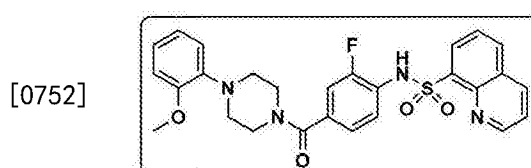
[0747] ¹H NMR (400MHz, DMSO-d₆) δ: 9.40 (s, 1H), 9.14 (d, 1H), 8.56 (d, 1H), 8.30 (d, 1H), 8.25 (d, 1H), 7.70 (m, 2H), 7.15 (s, 1H), 6.90-7.10 (m, 4H), 6.83 (m, 2H), 3.75 (s, 3H), 3.30-3.75 (bm, 4H), 2.95 (bm, 4H), 2.05 (s, 3H); HPLC纯度99.11%; MS, m/z实测值517.14 (M+1)⁺.

[0748] N-(4-(4-(2-甲氧基苯基)哌嗪-1-羰基)-2-羟基苯基)喹啉-8-磺酰胺 (98e):



[0750] ¹H NMR (400MHz, DMSO-d₆) δ: 10.2 (s, 1H), 9.98 (s, 1H), 9.15 (d, 1H), 8.52 (d, 1H), 8.40 (d, 1H), 8.30 (d, 1H), 7.70 (m, 2H), 6.80-6.98 (m, 5H), 6.70 (s, 1H), 6.55 (d, 1H), 3.75 (s, 3H), 3.30-3.60 (bm, 4H), 2.85 (bm, 4H); HPLC纯度95.25%; MS, m/z实测值519.14 (M+1)⁺.

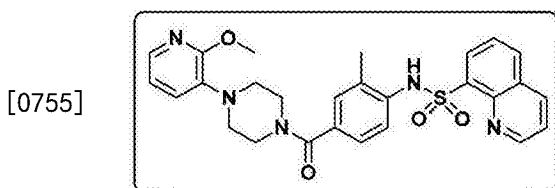
[0751] N-(4-(4-(2-甲氧基苯基)哌嗪-1-羰基)-2-氟苯基)喹啉-8-磺酰胺 (98f):



[0753] ¹H NMR (400MHz, CDCl₃) δ: 9.15 (d, 1H), 8.40 (d, 1H), 8.30 (d, 1H), 8.05 (d, 1H), 7.80

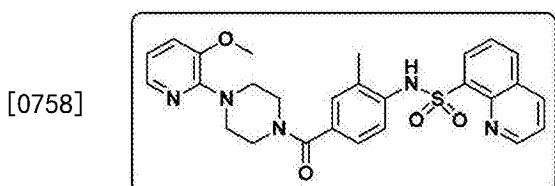
(t, 1H), 7.60 (m, 2H), 7.13–7.25 (m, 3H), 7.10 (d, 1H), 6.95 (m, 3H), 3.90 (s, 3H), 3.65–4.05 (bm, 4H), 3.30 (bm, 4H); LCMS纯度99.50%; MS, m/z实测值521.10 (M+1)⁺.

[0754] N-(4-(4-(2-甲氧基吡啶-3-基)哌嗪-1-羰基)-2-甲基苯基)喹啉-8-磺酰胺 (98g):



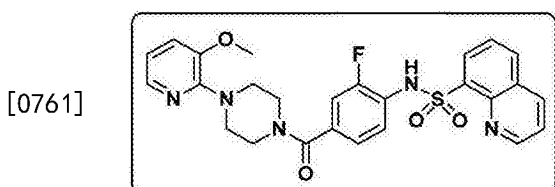
[0756] ¹H NMR (400MHz, DMSO-d₆) δ: 9.16 (s, 1H), 8.40–8.51 (d, 1H), 8.20–8.38 (m, 2H), 8.02–8.11 (d, 1H), 7.82–8.88 (d, 1H), 7.56–7.66 (m, 2H), 7.34–7.38 (m, 2H), 7.02–7.18 (d, 2H), 6.84–6.88 (d, 1H), 4.02 (s, 3H), 3.78–3.96 (bs, 2H), 3.58–3.62 (bs, 2H), 2.84–3.12 (bs, 4H), 2.22 (s, 3H); HPLC纯度90.41%; MS, m/z实测值518.20 (M+1)⁺.

[0757] N-(4-(4-(3-甲氧基吡啶-2-基)哌嗪-1-羰基)-2-甲基苯基)喹啉-8-磺酰胺 (98h):



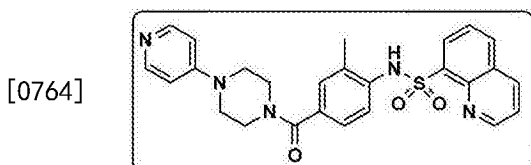
[0759] ¹H NMR (400MHz, DMSO-d₆) δ: 9.16 (d, 1H), 8.40–8.51 (d, 1H), 8.23–8.31 (d, 1H), 8.19 (s, 1H), 8.02–8.11 (d, 1H), 7.82–8.84 (m, 1H), 7.52–7.64 (m, 2H), 7.28–7.32 (m, 1H), 7.11–7.18 (s, 1H), 6.98–7.02 (t, 1H), 6.82–6.88 (m, 1H), 3.88 (s, 3H), 3.78–3.84 (bs, 2H), 3.26–3.64 (bs, 6H), 2.24 (s, 3H); LCMS纯度96.68%, LCMS, m/z实测值518.2 (M+1)⁺.

[0760] N-(2-氟-4-(4-(3-甲氧基吡啶-2-基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (98i):



[0762] ¹H NMR (400MHz, DMSO-d₆) δ: 9.18 (d, 1H), 8.88 (s, 1H), 8.38–8.42 (d, 1H), 8.20–8.28 (m, 2H), 8.02–8.13 (d, 2H), 7.72–7.80 (t, 1H), 7.56–7.62 (m, 2H), 6.84–2.12 (dd, 2H), 6.70–6.78 (d, 1H), 3.92 (s, 3H), 3.48–3.82 (bs, 4H), 3.00–3.18 (bs, 4H); LCMS纯度96.76%, LCMS, m/z实测值522.2 (M+1)⁺.

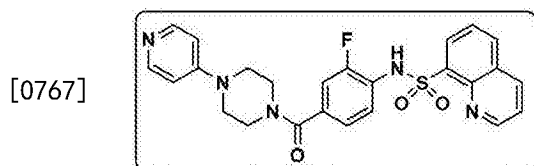
[0763] N-(4-(4-(吡啶-4-基)哌嗪-1-羰基)-2-甲基苯基)喹啉-8-磺酰胺 (98j):



[0765] ¹H NMR (400MHz, CDCl₃) δ: 9.10 (d, 1H), 8.45 (d, 1H), 8.30 (m, 4H), 8.15 (d, 1H), 7.60 (m, 2H), 7.35 (d, 1H), 7.15 (d, 1H), 7.05 (d, 1H), 6.65 (d, 2H), 3.45–3.90 (bm, 4H), 3.30 (bm,

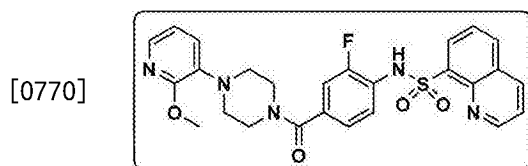
4H), 2.22 (s, 3H); LCMS纯度100.00%; MS, m/z实测值488.30 (M+1)⁺.

[0766] N-(4-(4-(2-甲氧基吡啶-3-基)哌嗪-1-羰基)-2-氟苯基)喹啉-8-磺酰胺 (98k):



[0768] ¹H NMR (400MHz, CDCl₃) δ: 9.10 (d, 1H), 8.40 (d, 1H), 8.30 (m, 3H), 8.05 (d, 1H), 7.80 (m, 1H), 7.60 (m, 2H), 7.05 (d, 1H), 6.95 (d, 1H), 6.80 (d, 2H), 3.45-3.90 (bm, 4H), 3.30 (bm, 4H); LCMS纯度99.81%; MS, m/z实测值492.30 (M+1)⁺.

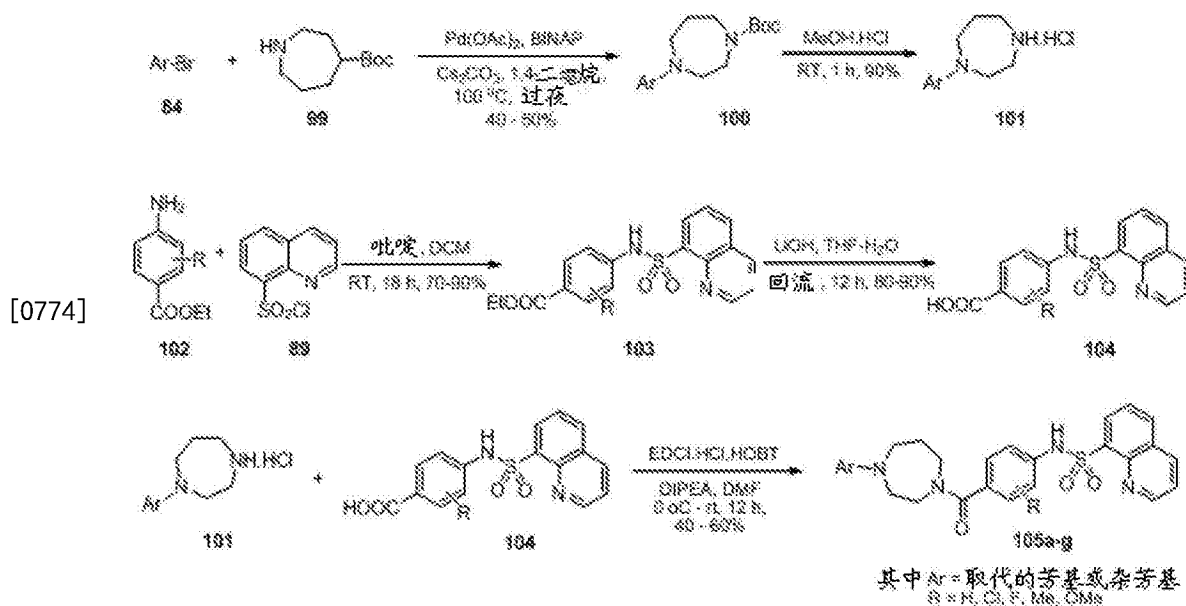
[0769] N-(4-(4-(2-甲氧基吡啶-3-基)哌嗪-1-羰基)-2-氟苯基)喹啉-8-磺酰胺 (98l):



[0771] ¹H NMR (400MHz, CDCl₃) δ: 9.18 (d, 1H), 8.90 (bs, 1H), 8.40 (d, 1H), 8.30 (d, 1H), 8.05 (d, 1H), 7.85 (m, 1H), 7.75 (m, 1H), 7.60 (m, 2H), 7.05 (m, 1H), 6.95 (d, 1H), 6.80 (m, 1H), 4.00 (s, 3H), 3.45-3.90 (bm, 4H), 3.00 (bm, 4H); HPLC纯度96.60%; MS, m/z实测值522.25 (M+1)⁺.

[0772] N4-芳基/杂芳基高哌嗪类似物的合成

[0773] 流程14



[0775] 化合物(100)的一般程序:于室温、将氮气鼓入芳基溴(84, 2.15mmol)在1,4-二噁烷(20ml)中的搅拌溶液,持续30min。将BINAP(0.134g, 0.215mmol)、醋酸钯(0.0096g, 0.043mmol)和碳酸铯(1.40g, 4.3mmol)加至反应混合物,将氮气鼓入持续另外20min,最终加入N-Boc哌嗪(99, 0.428g, 2.15mmol),于100℃在氮气气氛下搅拌过夜。反应结束后(通过TLC监控),在真空下浓缩反应混合物。将残余物溶解于水中,用乙酸乙酯萃取(3×50ml)。合并的有机萃取液用盐水(20ml)洗涤,经无水硫酸钠干燥,过滤,在减压下浓缩。然后通过使用10%乙酸乙酯-己烷的柱色谱法(60-120硅胶)纯化粗产物,得到化合物(100) (40-50%)。

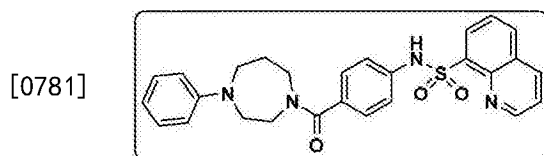
[0776] 化合物(101)的一般程序:将N¹-Boc-N⁴-芳基高哌嗪(100,1.070mmol)装入圆底烧瓶中,加入甲醇-HCl(20ml,20%),其导致形成均质溶液,在室温搅拌1h。反应结束后(通过TLC监控),在真空下除去溶剂。重复用乙酸乙酯洗涤粗产物,然后充分干燥,获得为白色固体状的化合物(101)(90%)。

[0777] 化合物103的一般程序:在氮气气氛下向胺(102,30.16mmol)在DCM-吡啶(50:50ml)的1:1混合物中的溶液加入喹啉-8-磺酰氯(89,8.24g,36.19mmol)。将所得溶液在室温搅拌过夜。反应结束后(通过TLC监控),将所得混合物用二氯甲烷(150ml)稀释,用水(3×50ml)、1N HCl溶液(3×50ml)和盐水(50ml)洗涤。将合并的有机萃取液经无水硫酸钠干燥,过滤,在真空下浓缩。将粗产物与甲苯共蒸馏,除去吡啶残余部分,干燥,得到为灰白色固体状的磺酰胺(103)(70-90%),因此不需进一步纯化即可用于下一步骤。

[0778] 用于制备4-(喹啉-8-亚磺酰氨基)苯甲酸(104)的程序:将酯(103,5g,14.04mmol)溶解于THF-水(100:100ml)的混合物中,维持在室温。向该溶液加入LiOH(3.0g,7.0mmol),将所得溶液回流过夜。然后将反应混合物用乙酸乙酯洗涤(3×50ml),然后用稀HCl酸化。过滤所得悬浮液,将残余物与甲苯共蒸馏。然后在真空下干燥该产物,得到为灰白色固体状的羧酸(104)(80-90%)。

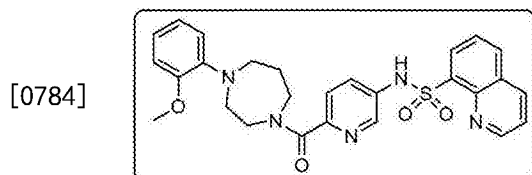
[0779] 化合物105a-g的一般程序:于0℃、在氮气气氛下向羧酸(104,0.61mmol)在DMF中的搅拌溶液加入EDCI(0.129gm,0.671mmol)、HOBT(0.91gm,0.671mmol)和DIPEA(0.31ml,1.83mmol),将所得溶液在室温搅拌30min。然后在0℃加入胺盐酸盐(101,0.61mmol),在室温搅拌过夜。反应结束后(通过TLC监控),将反应混合物倒入1.0MHCl中,用EtOAc萃取。用饱和NaHCO₃溶液洗涤有机层,经NaSO₄干燥,过滤。通过旋转蒸发除去溶剂,通过硅胶层析法(60-120硅胶,2%MeOH-DCM)或制备型HPLC分离产物,得到为灰白色固体状的酰胺(105a-g)(40-60%)。

[0780] N-(4-(4-苯基-1,4-二氮杂环庚烷-1-羰基)苯基)喹啉-8-磺酰胺(105a):



[0782] ¹H NMR(400MHz,DMSO-d₆) δ:10.20(s,1H),9.10(s,1H),8.52(d,1H),8.40(d,1H),8.30(d,1H),7.70(m,2H),6.85-7.20(m,5H),6.40-6.75(m,4H),3.10-3.70(m,8H),1.82(bm,2H);HPLC纯度:95.19%;MS,m/z实测值487.30(M+1)⁺.

[0783] N-(6-(4-(2-甲氧基苯基)-1,4-二氮杂环庚烷-1-羰基)吡啶-3-基)喹啉-8-磺酰胺(105b):

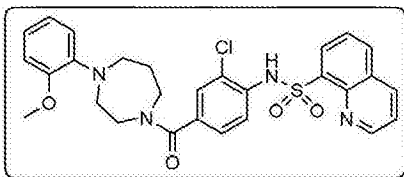


[0785] ¹H NMR(400MHz,DMSO-d₆) δ:9.15-9.19(m,1H),8.32-8.42(m,2H),8.20-8.26(d,1H),8.10-8.16(m,1H),7.58-7.74(m,5H),7.20-7.28(m,1H),6.92-7.18(m,2H),4.15-4.20(m,4H),3.81-3.88(m,4H),3.82(s,3H),2.42-2.58(m,2H);LCMS纯度99.92%;MS,m/z实测

值518.5 (M+1)⁺.

[0786] N-(2-氯-4-(4-(2-甲氧基苯基)-1,4-二氮杂环庚烷-1-羰基)苯基)喹啉-8-磺酰胺 (105c):

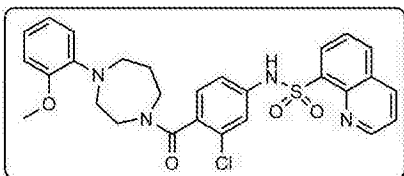
[0787]



[0788] ¹H NMR (400MHz, DMSO-d₆) δ: 9.15 (d, 1H), 8.08-8.92 (m, 1H), 8.40-8.52 (m, 1H), 8.20-8.26 (d, 1H), 8.02-8.06 (d, 1H), 7.68-7.82 (dd, 1H), 7.54-7.62 (m, 2H), 6.84-7.05 (m, 5H), 6.66-6.68 (d, 1H), 3.82 (s, 3H), 3.74-3.78 (m, 2H), 3.41-3.54 (m, 2H), 3.21-3.36 (m, 3H), 3.16-3.19 (bs, 3H), 2.00-2.11 (bs, 1H), 1.82-1.98 (bs, 1H); LCMS纯度97.10%; LCMS, m/z实测值551.4 (M+1)⁺.

[0789] N-(3-氯-4-(4-(2-甲氧基苯基)-1,4-二氮杂环庚烷-1-羰基)苯基)喹啉-8-磺酰胺 (105d):

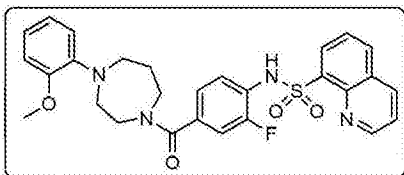
[0790]



[0791] ¹H NMR (400MHz, DMSO-d₆) δ: 9.15 (s, 1H), 8.32-8.44 (m, 3H), 8.05-8.10 (m, 1H), 7.60-7.72 (m, 2H), 7.22-7.32 (m, 2H), 7.12 (s, 1H), 6.88-7.05 (m, 3H), 6.80-6.84 (m, 1H), 3.74-3.91 (m, 2H), 3.41 (s, 3H), 3.14-3.42 (m, 6H), 1.82-1.86 (m, 2H); LCMS纯度99.47%; MS, m/z实测值551.4 (M+1)⁺.

[0792] N-(2-氟-4-(4-(2-甲氧基苯基)-1,4-二氮杂环庚烷-1-羰基)苯基)喹啉-8-磺酰胺 (105e):

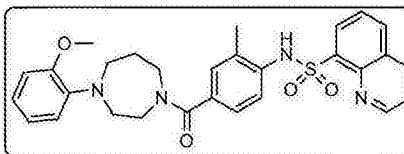
[0793]



[0794] ¹H NMR (400MHz, DMSO-d₆) δ: 9.15 (s, 1H), 8.32-8.44 (d, 2H), 8.02-8.07 (t, 1H), 7.70-7.84 (m, 1H), 7.51-7.62 (m, 3H), 7.37-7.40 (m, 2H), 6.82-7.10 (m, 4H), 3.91-4.15 (m, 2H), 3.78-3.88 (m, 2H), 3.82 (s, 3H), 3.62-3.70 (m, 2H), 3.52-3.58 (m, 2H), 2.35-4.2 (m, 2H); LCMS纯度99.01%; MS, m/z实测值535.5 (M+1)⁺.

[0795] N-(4-(4-(2-甲氧基苯基)-1,4-二氮杂环庚烷-1-羰基)-2-甲基苯基)喹啉-8-磺酰胺 (105f):

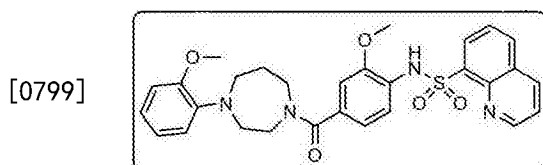
[0796]



[0797] ¹H NMR (400MHz, DMSO-d₆) δ: 9.25 (s, 1H), 9.10 (d, 1H), 8.54-8.58 (d, 1H), 8.22-

8.30 (dd, 2H), 7.68–7.76 (m, 2H), 6.78–7.18 (m, 7H), 3.81 (s, 3H), 3.20–3.64 (m, 8H), 2.15 (s, 3H), 1.82 (bm, 2H); LCMS 纯度: 99.67%; MS, m/z 实测值 531.4 (M+1)⁺.

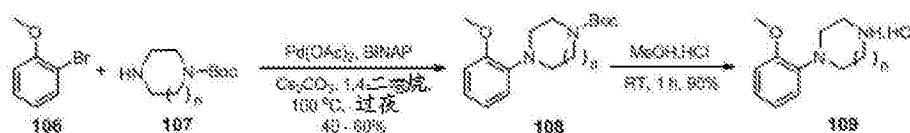
[0798] N-(2-甲氧基-4-(4-(2-甲氧基苯基)-1,4-二氮杂环庚烷-1-羰基)苯基)喹啉-8-磺酰胺 (105g):



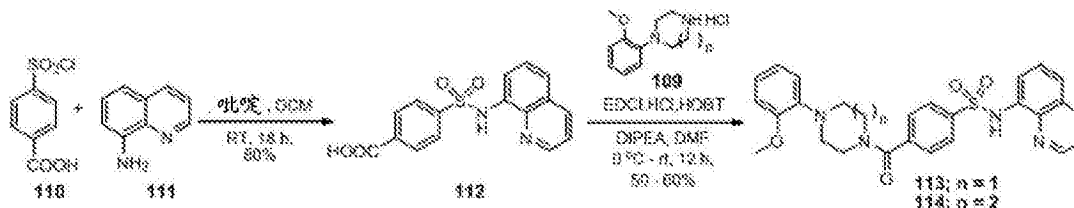
[0800] ¹H NMR (400MHz, DMSO-d₆) δ: 9.17 (d, 1H), 8.44 (s, 1H), 8.34–8.58 (dd, 2H), 8.02–8.10 (d, 1H), 7.56–7.64 (t, 2H), 6.82–6.94 (m, 4H), 6.66–6.68 (m, 1H), 6.24–6.38 (m, 1H), 3.81 (s, 3H), 3.64 (s, 3H), 3.58–3.60 (m, 2H), 3.24–3.40 (m, 4H), 3.04–3.22 (m, 2H), 1.82 (bm, 2H); LCMS 纯度: 94.21%; MS, m/z 实测值 547.3 (M+1)⁺.

[0801] N4-芳基/杂芳基哌嗪/高哌嗪反磺酰胺类似物的合成

[0802] 流程15



[0803]



[0804] 化合物(108)的一般程序:于室温、将氮气鼓入芳基溴(106,0.4g,2.15mmol) in 1,4-二噁烷(20ml)中的搅拌溶液,持续30min。将BINAP(0.134g,0.215mmol)、醋酸钯(0.0096g,0.043mmol)和碳酸铯(1.40g,4.3mmol)加至反应混合物,将氮气鼓入持续另外20min,最终加入N-Boc哌嗪(107,2.15mmol),于100℃在氮气气氛下搅拌过夜。反应结束后(通过TLC监控),在真空下浓缩反应混合物。将残余物溶解于水中,用乙酸乙酯萃取(3×50ml)。合并的有机萃取液用盐水(20ml)洗涤,经无水硫酸钠干燥,过滤,在减压下浓缩。然后通过使用10%乙酸乙酯-己烷的柱色谱法(60–120硅胶)纯化粗产物,得到化合物(108)(40–60%)。

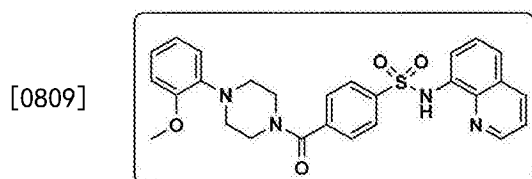
[0805] 化合物(109)的一般程序:将化合物108(1.075mmol)装入圆底烧瓶中,加入甲醇-HCl(20ml,20%),其导致形成均质溶液,在室温搅拌1h。反应结束后(通过TLC监控),在真空下除去溶剂。重复用乙酸乙酯洗涤粗产物,然后充分干燥,获得为白色固体状的化合物(109)(90%)。

[0806] 化合物112的一般程序:在氮气气氛下向(4-氯磺酰基)苯甲酸(110,1.6g,7.27mmol)在DCM-吡啶(50:50ml)的1:1混合物中的溶液加入8-氨基喹啉(111,1.15g,8.0mmol)。将所得溶液在室温搅拌过夜。反应结束后(通过TLC监控),将所得混合物用二氯甲烷(150ml)稀释,用水(3×50ml)、1N HCl溶液(3×50ml)和盐水(50ml)洗涤。将合并的有机萃取液经无水硫酸钠干燥,过滤,在真空下浓缩。将粗产物与甲苯共蒸馏,除去吡啶残余

部分,干燥,得到为灰白色固体状的磺酰胺(112)(1.9g,80%),因此不需进一步纯化即可用于下一步骤。

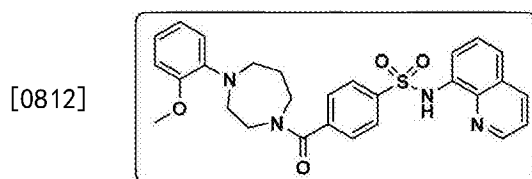
[0807] 化合物113/114的一般程序:于0℃、在氮气气氛下向羧酸(112,0.61mmol)在DMF中的搅拌溶液加入EDCI(0.129gm,0.671mmol)、HOBT(0.91gm,0.671mmol)和DIPEA(0.31ml,1.83mmol),将所得溶液在室温搅拌30min。然后在0℃加入胺盐酸盐(109,0.61mmol),在室温搅拌过夜。反应结束后(通过TLC监控),将反应混合物倒入1.0M HCl中,用EtOAc萃取。用饱和NaHCO₃溶液洗涤有机层,经NaSO₄干燥,过滤。通过旋转蒸发除去溶剂,通过硅胶层析法(60-120硅胶,2%MeOH-DCM)或制备型HPLC分离产物,得到为灰白色固体状的酰胺(113/114)(50-60%)。

[0808] 4-(4-(2-甲氧基苯基)哌嗪-1-羰基)-N-(喹啉-8-基)苯磺酰胺(113):



[0810] ¹H NMR(400MHz,DMSO-d₆) δ:10.18(s,1H),8.92(s,1H),8.54-8.56(d,1H),7.89-7.93(d,2H),7.66-7.94(m,2H),7.44-7.57(m,4H),6.94-6.98(m,2H),6.83-6.86(m,2H),3.78(s,3H),3.61-3.69(m,2H),3.20-3.54(m,2H),2.91-2.94(bs,2H),1.82-1.86(bs,2H);HPLC纯度99.01%;MS,m/z实测值503.3(M+1)⁺。

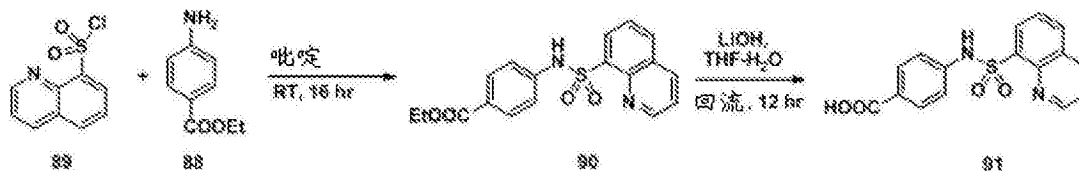
[0811] 4-(4-(2-甲氧基苯基)-1,4-二氮杂环庚烷-1-羰基)-N-(喹啉-8-基)苯磺酰胺(114):



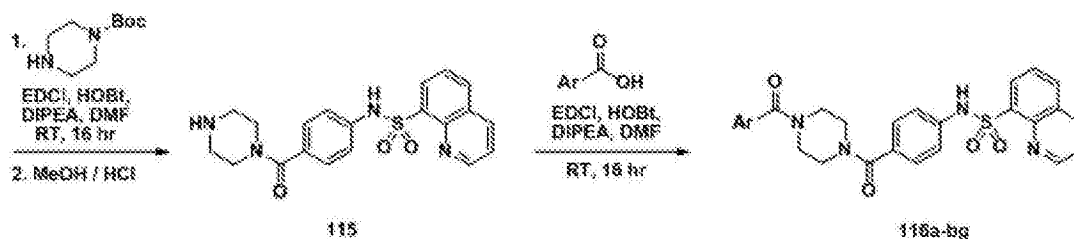
[0813] ¹H NMR(400MHz,DMSO-d₆) δ:9.25(s,1H),8.78(s,1H),8.15(d,1H),7.80-7.99(m,3H),7.38-7.59(m,4H),7.15-7.27(m,2H),6.80-7.00(m,3H),3.74-3.91(m,2H),3.41(s,3H),3.14-3.42(m,6H),1.82-1.86(m,2H);LCMS纯度99.97%;MS,m/z实测值517.3(M+1)⁺。

[0814] 具有取代的苯基环的基于哌嗪的化合物的合成

[0815] 流程16



[0816]



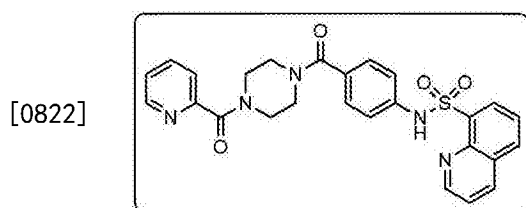
[0817] 4-(喹啉-8-亚磺酰氨基)苯甲酸乙酯(90):于0℃、在氮气气氛下向4-氨基苯甲酸乙酯(5gm, 30.3mmol)的搅拌溶液加入吡啶(50ml), 搅拌10min。然后在相同温度下将喹啉-8-磺酰氯89(8.94gm, 39.4mmol)加至反应混合物。将所得混合物在RT搅拌16h。反应结束后, 在减压下除去溶剂。通过与甲苯共馏除去痕量的吡啶。将乙醚加至所得残余物中, 滤出固体产物, 空气干燥。所得粗产物(8.0gm, 74%)不需进一步纯化即可用于下一步骤。

[0818] 4-(喹啉-8-亚磺酰氨基)苯甲酸(91):于RT、在氮气气氛下向4-(喹啉-8-亚磺酰氨基)苯甲酸乙酯90(8gm, 22.4mmol)在THF:H₂O(1:1)中的搅拌溶液加入固体LiOH(9.4gm, 224mmol)。然后将溶液回流6h。反应结束后, 将反应混合物用乙酸乙酯洗涤(2×100ml), 除去非极性杂质。用柠檬酸溶液酸化水层(pH 4)。将所得沉淀滤去, 空气干燥。通过与甲苯共蒸馏除去痕量水。所得灰白色固体(5.9gm, 80%)不需进一步纯化即可用于下一步骤。

[0819] N-(4-(哌嗪-1-羰基)苯基)喹啉-8-磺酰胺(115):将EDCI(3.8g, 19.8mmol)和HOBT(2.67g, 19.8mmol)加至酸91(6.5g, 19.8mmol)在无水DMF中的搅拌溶液。将混合物的温度降至0℃, 此时在氮气气氛下加入DIPEA(11ml, 59.45mmol), 将所得溶液(或悬浮液)在室温搅拌30min。然后于0℃加入Boc-哌嗪(3.68g, 19.8mmol)。然后将反应混合物升至室温, 搅拌过夜。反应结束后, 将反应混合物用水稀释, 用乙酸乙酯萃取(3×70ml)。将有机层用水洗涤(3×50ml), 经无水硫酸钠干燥, 过滤, 经旋转蒸发仪浓缩, 得到粗产物。通过柱色谱法(60-120硅胶, 2%MeOH-DCM)纯化粗产物, 得到为灰白色固体状的纯产物Boc-115(8.0g, 82%), 将其于RT用甲醇HCl(100ml)处理2h。Boc-基团完全断裂后, 在低压下除去溶剂, 得到为HCl盐的纯产物。用乙醚洗涤盐的水溶液, 用NaHCO₃(pH 10)碱化。然后将所需产物分配至乙酸乙酯中, 用无水Na₂SO₄干燥, 在低压下除去溶剂, 得到为灰白色固体状的游离胺115(6.0g, 95%)。

[0820] 合成酰胺116a-bg的一般程序:将EDCI(48mg, 0.2525mmol)和HOBT(34mg, 0.2525mmol)加至Ar-COOH(0.2525mmol)在无水DMF中的搅拌溶液。将混合物的温度降至0℃, 此时在氮气气氛下加入DIPEA(139μl, 0.7575mmol), 将所得溶液(或悬浮液)在室温搅拌30min。然后于0℃加入胺115(100mg, 0.2525mmol)。然后将反应混合物升至室温, 搅拌过夜。反应结束后, 将反应混合物用水稀释, 用乙酸乙酯萃取(3×15ml)。将有机层用水洗涤(3×10ml), 经无水硫酸钠干燥, 过滤, 经旋转蒸发仪浓缩, 得到粗产物。通过柱色谱法或制备型HPLC纯化粗产物, 获得收率为55-69%的纯产物。

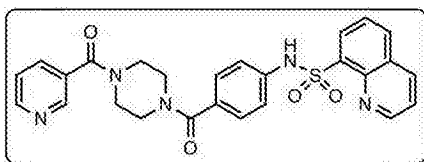
[0821] N-(4-(4-吡啶甲酰基哌嗪-1-羰基)苯基)喹啉-8-磺酰胺(116a):



[0823] ¹H NMR(400MHz, DMSO-d₆) δ: 3.2-3.8(m, 8H), 7.0-7.2(m, 4H), 7.4-7.6(m, 2H), 7.7(m, 2H), 7.9(m, 1H), 8.3(m, 1H), 8.4-8.6(m, 3H), 9.1(d, 1H), 10.2-10.4(s, 1H); HPLC纯度: 95.7%; LCMS, m/z实测值502.1(M+1)⁺.

[0824] N-(4-(4-烟酰基哌嗪-1-羰基)苯基)喹啉-8-磺酰胺(116b):

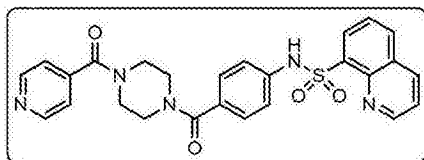
[0825]



[0826] ^1H NMR (400MHz, CDCl_3) δ : 3.2–3.8 (m, 8H), 7.0–7.2 (m, 4H), 7.4 (m, 1H), 7.6–7.8 (m, 3H), 8.0 (m, 1H), 8.3 (m, 2H), 8.4–8.6 (m, 3H), 9.1 (d, 1H), 10.2–10.4 (s, 1H); HPLC纯度: 96.7%; LCMS, m/z 实测值502.2 ($\text{M}+1$) $^+$.

[0827] N-(4-(4-(2-甲基烟酰基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (116c):

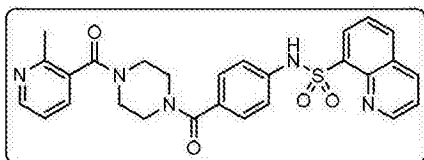
[0828]



[0829] ^1H NMR (400MHz, CDCl_3) δ : 3.2–3.8 (m, 8H), 7.0–7.2 (m, 4H), 7.6 (m, 2H), 8.0 (m, 1H), 8.2–8.4 (m, 2H), 8.6 (m, 3H), 9.1 (m, 2H), 10.2–10.4 (s, 1H); HPLC纯度: 98.8%; LCMS, m/z 实测值502.1 ($\text{M}+1$) $^+$.

[0830] N-(4-(4-(2-甲基烟酰基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (116d):

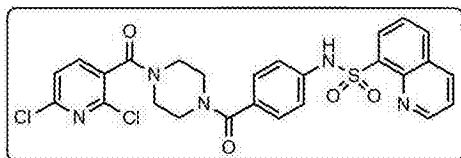
[0831]



[0832] ^1H NMR (400MHz, $\text{DMSO}-d_6$) δ : 3.2 (s, 3H), 3.3–3.8 (m, 8H), 7.0–7.2 (m, 4H), 7.4 (m, 1H), 7.6–7.9 (m, 3H), 8.2 (m, 1H), 8.4–8.6 (m, 3H), 9.1 (m, 1H), 10.4 (s, 1H); HPLC纯度: 99.2%; LCMS, m/z 实测值516.4 ($\text{M}+1$) $^+$.

[0833] N-(4-(4-(2,6-二氯烟酰基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (116e):

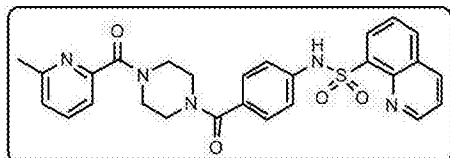
[0834]



[0835] ^1H NMR (400MHz, $\text{DMSO}-d_6$) δ : 3.2 (s, 3H), 3.3–3.8 (m, 8H), 7.0–7.4 (m, 4H), 7.6 (m, 3H), 8.0 (m, 1H), 8.2 (m, 2H), 8.6 (m, 1H), 9.1 (m, 1H), 10.4 (s, 1H); HPLC纯度: 98.8%; LCMS, m/z 实测值570.3 ($\text{M}+1$) $^+$.

[0836] N-(4-(4-(6-甲基吡啶甲酰基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (116f):

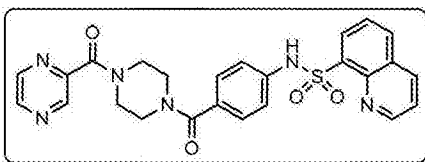
[0837]



[0838] ^1H NMR (400MHz, $\text{DMSO}-d_6$) δ : 2.5 (s, 3H), 3.3–3.8 (m, 8H), 7.0–7.3 (m, 5H), 7.4 (m, 1H), 7.6–7.8 (m, 3H), 8.0 (m, 1H), 8.2–8.4 (m, 1H), 8.6 (m, 1H), 10.4 (s, 1H); HPLC纯度: 99.9%; LCMS, m/z 实测值516.1 ($\text{M}+1$) $^+$.

[0839] N-(4-(4-(吡啶-2-羰基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (116g):

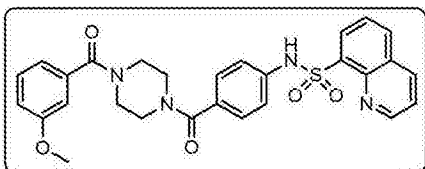
[0840]



[0841] ^1H NMR (400MHz, CDCl_3) δ : 3.3–3.8 (m, 8H), 7.0–7.2 (m, 4H), 7.6 (m, 2H), 8.0 (m, 1H), 8.2–8.4 (m, 2H), 8.2–8.4 (m, 1H), 8.6 (m, 2H), 9.0 (s, 1H), 9.2 (m, 1H); HPLC纯度: 97.5%; LCMS, m/z 实测值 503.2 ($M+1$) $^+$.

[0842] N-(4-(4-(3-甲氧基苯甲酰基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (116h):

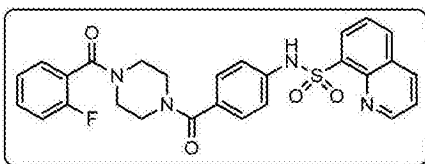
[0843]



[0844] ^1H NMR (400MHz, $\text{DMSO}-d_6$) δ : 3.3–3.8 (m, 8H), 3.9 (s, 3H), 6.9–7.0 (m, 3H), 7.2 (m, 4H), 7.4 (m, 1H), 7.9 (m, 2H), 8.2 (m, 1H), 8.4–8.6 (m, 2H), 9.1 (s, 1H), 10.5 (s, 1H); HPLC纯度: 97.3%; LCMS, m/z 实测值 531.3 ($M+1$) $^+$.

[0845] N-(4-(4-(2-氟苯甲酰基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (116i):

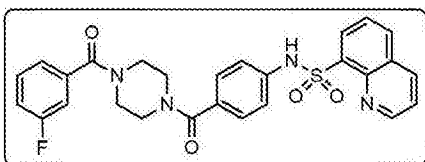
[0846]



[0847] ^1H NMR (400MHz, $\text{DMSO}-d_6$) δ : 3.2 (m, 4H), 3.4 (m, 2H), 3.6 (m, 2H), 7.0–7.5 (m, 8H), 7.7 (m, 2H), 8.2 (m, 1H), 8.4–8.6 (m, 2H), 9.1 (m, 1H), 10.5 (s, 1H); HPLC纯度: 97.3%; LCMS, m/z 实测值 519.3 ($M+1$) $^+$.

[0848] N-(4-(4-(3-氟苯甲酰基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (116j):

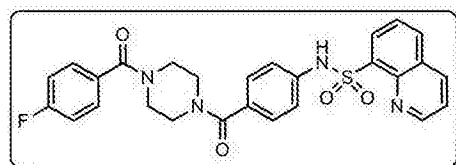
[0849]



[0850] ^1H NMR (400MHz, $\text{DMSO}-d_6$) δ : 3.2–3.8 (m, 8H), 7.0–7.2 (m, 6H), 7.4 (m, 2H), 7.8 (m, 2H), 8.2–8.5 (m, 3H), 9.1 (m, 1H), 10.5 (s, 1H); HPLC纯度: 97.3%; LCMS, m/z 实测值 519.3 ($M+1$) $^+$.

[0851] N-(4-(4-(4-氟苯甲酰基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (116k):

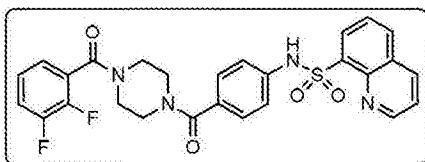
[0852]



[0853] ^1H NMR (400MHz, $\text{DMSO}-d_6$) δ : 3.2–3.8 (m, 8H), 7.0–7.2 (m, 6H), 7.4 (m, 2H), 7.8 (m, 2H), 8.2–8.5 (m, 3H), 9.1 (m, 1H), 10.5 (s, 1H); HPLC纯度: 97.3%; LCMS, m/z 实测值 519.3 ($M+1$) $^+$.

[0854] N-(4-(4-(2,3-二氟苯甲酰基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (116l):

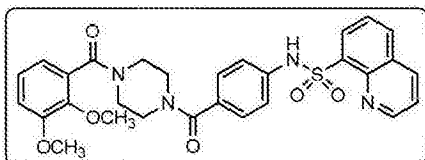
[0855]



[0856] ^1H NMR (400MHz, DMSO- d_6) δ : 3.2 (m, 4H), 3.6 (m, 4H), 7.0–7.4 (m, 6H), 7.5–7.8 (m, 3H), 8.2 (m, 1H), 8.4–8.6 (m, 2H), 9.1 (m, 1H), 10.5 (s, 1H); HPLC纯度: 94.3%; LCMS, m/z 实测值 537.3 ($M+1$) $^+$.

[0857] N-(4-(4-(2,3-二甲氧基苯甲酰基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (116m):

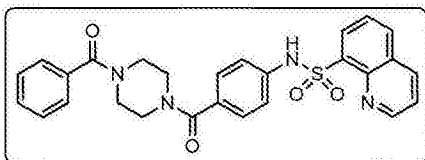
[0858]



[0859] ^1H NMR (400MHz, DMSO- d_6) δ : 3.2 (m, 4H), 3.6 (m, 4H), 3.7 (s, 3H), 3.8 (s, 3H), 6.8 (m, 1H), 7.0–7.2 (m, 6H), 7.6–7.8 (m, 2H), 8.2 (m, 1H), 8.4–8.6 (m, 2H), 9.1 (m, 1H), 10.5 (s, 1H); HPLC纯度: 97.2%; LCMS, m/z 实测值 561.1 ($M+1$) $^+$.

[0860] N-(4-(4-苯甲酰基哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (116n):

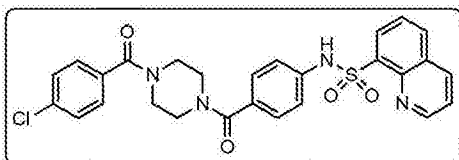
[0861]



[0862] ^1H NMR (400MHz, DMSO- d_6) δ : 3.2–3.8 (s, 8H), 6.8 (m, 1H), 7.0–7.2 (m, 6H), 7.6–7.8 (m, 2H), 8.2 (m, 2H), 8.4–8.6 (m, 2H), 9.1 (m, 1H), 10.5 (s, 1H); HPLC纯度: 98.2%; LCMS, m/z 实测值 501.2 ($M+1$) $^+$.

[0863] N-(4-(4-(4-氯苯甲酰基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (116o):

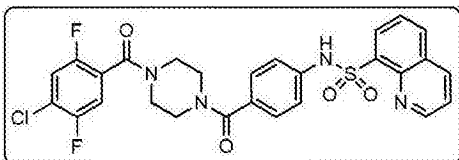
[0864]



[0865] ^1H NMR (400MHz, DMSO- d_6) δ : 3.2–3.8 (m, 8H), 7.0–7.2 (m, 4H), 7.2–7.6 (m, 4H), 7.6–7.8 (m, 2H), 8.2–8.6 (m, 3H), 9.1 (m, 1H), 10.5 (s, 1H); HPLC纯度: 99.7%; LCMS, m/z 实测值 535.0 ($M+1$) $^+$.

[0866] N-(4-(4-(4-氯-2,5-二氟苯甲酰基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (116p):

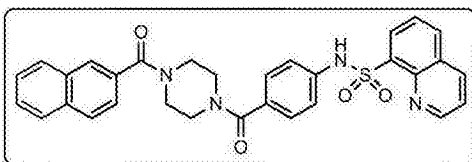
[0867]



[0868] ^1H NMR (400MHz, DMSO- d_6) δ : 3.2–3.8 (m, 8H), 7.0–7.2 (m, 4H), 7.6–7.8 (m, 4H), 8.2–8.6 (m, 3H), 9.1 (m, 1H), 10.5 (s, 1H); HPLC纯度: 99.7%; LCMS, m/z 实测值 555.4 ($M+1$) $^+$.

[0869] N-(4-(4-(2-萘甲酰基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (116r):

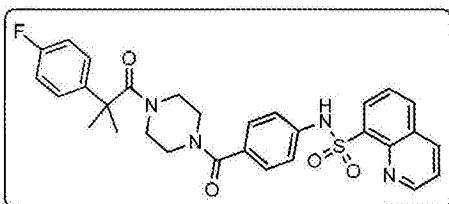
[0870]



[0871] ^1H NMR (400MHz, CDCl_3) δ : 3.2–3.8 (m, 8H), 7.0–7.2 (m, 4H), 7.4–7.6 (m, 5H), 7.8 (m, 4H), 8.0 (m, 1H), 8.2–8.4 (m, 2H), 9.1 (m, 1H), 10.5 (s, 1H); HPLC纯度: 98.4%; LCMS, m/z 实测值 551.4 ($M+1$) $^+$.

[0872] N-(4-(4-(2-(4-氟苯基)-2-甲基丙酰基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (116s):

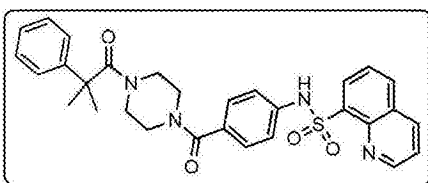
[0873]



[0874] ^1H NMR (400MHz, $\text{DMSO}-d_6$) δ : 1.2 (s, 6H), 3.2–3.8 (m, 8H), 7.0–7.2 (m, 8H), 7.6–7.8 (m, 2H), 8.2–8.6 (m, 3H), 9.1 (m, 1H), 10.5 (s, 1H); HPLC纯度: 98.4%; LCMS, m/z 实测值 561.4 ($M+1$) $^+$.

[0875] N-(4-(4-(2-甲基-2-苯基丙酰基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (116t):

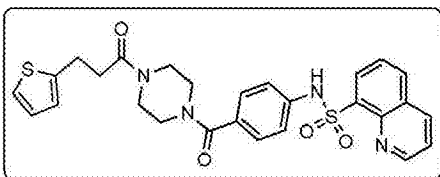
[0876]



[0877] ^1H NMR (400MHz, CD_3OD) δ : 3.2–3.8 (m, 8H), 3.9 (s, 2H), 7.2–7.4 (m, 9H), 7.6–7.8 (m, 2H), 8.2 (m, 1H), 8.4 (m, 2H), 9.1 (m, 1H), 10.5 (s, 1H); HPLC纯度: 99.4%; LCMS, m/z 实测值 515.3 ($M+1$) $^+$.

[0878] N-(4-(4-(3-(噻吩-2-基)丙酰基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (116u):

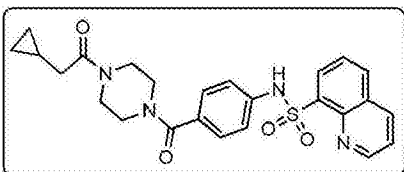
[0879]



[0880] ^1H NMR (400MHz, $\text{DMSO}-d_6$) δ : 2.4–2.6 (m, 3H), 2.7 (m, 2H), 3.0 (m, 2H), 3.2–3.6 (m, 5H), 6.9 (m, 2H), 7.0–7.2 (m, 4H), 7.4 (m, 1H), 7.8 (m, 2H), 8.2–8.6 (m, 3H), 9.1 (m, 1H), 10.5 (s, 1H); HPLC纯度: 98.0%; LCMS, m/z 实测值 535.1 ($M+1$) $^+$.

[0881] N-(4-(4-(2-环丙基乙酰基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (116v):

[0882]

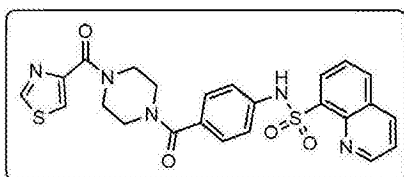


[0883] ^1H NMR (400MHz, CDCl_3) δ : 0.2 (m, 2H), 0.6 (m, 2H), 1.0 (m, 1H), 3.3–3.8 (m, 8H), 7.0–7.2 (m, 4H), 7.6 (m, 2H), 8.0 (m, 1H), 8.2–8.4 (m, 2H), 9.1 (m, 1H), 10.5 (s, 1H); HPLC纯度:

99.9% ; LCMS, m/z 实测值 479.4 ($M+1$)⁺.

[0884] N-(4-(4-(噻唑-4-羰基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (116w) :

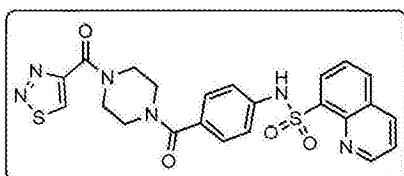
[0885]



[0886] ¹H NMR (400MHz, CDCl₃) δ : 3.3-3.8 (m, 8H), 7.0-7.2 (m, 4H), 7.6-7.8 (m, 2H), 8.0-8.2 (m, 2H), 8.4-8.6 (m, 2H), 9.1 (m, 2H), 10.5 (s, 1H); HPLC 纯度: 98.2%; LCMS, m/z 实测值 508.1 ($M+1$)⁺.

[0887] N-(4-(4-(1,2,3-噻二唑-4-羰基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (116x) :

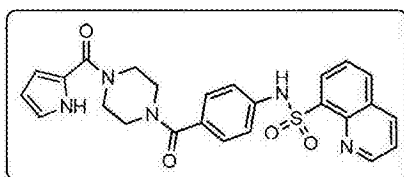
[0888]



[0889] ¹H NMR (400MHz, DMSO-d₆) δ : 3.3-3.8 (m, 8H), 7.0-7.2 (m, 4H), 7.6-7.8 (m, 2H), 8.2-8.6 (m, 3H), 9.1 (m, 1H), 9.6 (s, 1H), 10.5 (s, 1H); HPLC 纯度: 98.2%; LCMS, m/z 实测值 508.1 ($M+1$)⁺.

[0890] N-(4-(4-(1H-吡咯-2-羰基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (116y) :

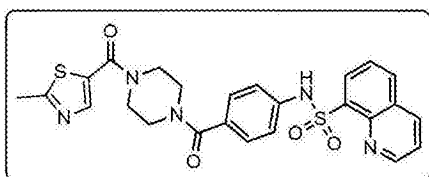
[0891]



[0892] ¹H NMR (400MHz, DMSO-d₆) δ : 3.2-3.8 (m, 8H), 6.0 (m, 1H), 6.4 (m, 1H), 6.8 (m, 1H), 7.0-7.2 (m, 4H), 7.6-7.8 (m, 2H), 8.2 (m, 1H), 8.4-8.6 (m, 2H), 9.1 (m, 1H), 10.5 (s, 1H), 11.4 (s, 1H); HPLC 纯度: 99.2%; LCMS, m/z 实测值 490.3 ($M+1$)⁺.

[0893] N-(4-(4-(2-甲基噻唑-5-羰基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (116z) :

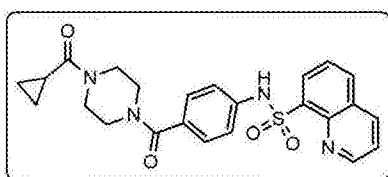
[0894]



[0895] ¹H NMR (400MHz, CDCl₃) δ : 2.3 (s, 3H), 3.6-3.8 (m, 8H), 7.0-7.2 (m, 5H), 7.6 (m, 2H), 8.0 (m, 1H), 8.2-8.4 (m, 2H), 9.1 (m, 1H); HPLC 纯度: 99.7%; LCMS, m/z 实测值 521.6 ($M+1$)⁺.

[0896] N-(4-(4-(环丙烷羰基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (116aa) :

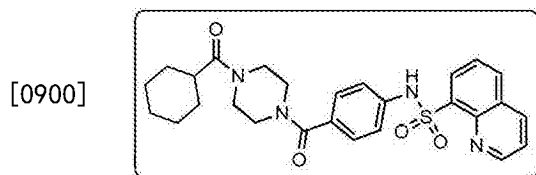
[0897]



[0898] ¹H NMR (400MHz, DMSO-d₆) δ : 0.6-0.8 (m, 2H), 2.0 (m, 1H), 3.2-3.8 (m, 8H), 7.0-7.2 (m, 4H), 7.6-7.8 (m, 2H), 8.2 (m, 1H), 8.4-8.6 (m, 2H), 9.1 (m, 1H), 10.5 (s, 1H); HPLC 纯度:

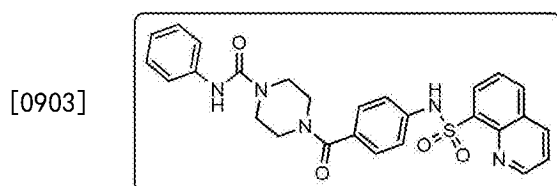
99.0% ; LCMS, m/z 实测值 465.35 ($M+1$)⁺.

[0899] N-(4-(4-(环己烷羰基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (116ab) :



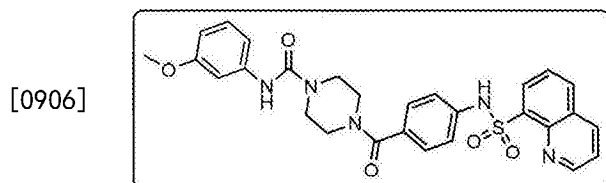
[0901] ¹H NMR (400MHz, DMSO-d₆) δ : 1.0-1.2 (m, 5H), 1.6-1.8 (m, 5H), 2.5 (m, 1H), 3.2-3.8 (m, 8H), 7.0-7.2 (m, 4H), 7.6-7.8 (m, 2H), 8.2 (m, 1H), 8.4-8.6 (m, 2H), 9.1 (m, 1H), 10.5 (s, 1H); HPLC 纯度: 93.0%; LCMS, m/z 实测值 507.15 ($M+1$)⁺.

[0902] N-苯基-4-(4-(喹啉-8-亚磺酰氨基)苯甲酰基)哌嗪-1-羧酰胺 (116ac) :



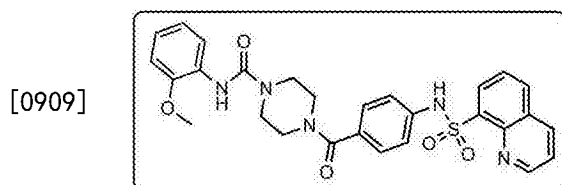
[0904] ¹H NMR (400MHz, DMSO-d₆) δ : 3.2-3.8 (m, 8H), 7.0-7.2 (m, 6H), 7.4 (m, 2H), 7.6 (m, 2H), 8.2 (m, 2H), 8.4-8.6 (m, 2H), 9.1 (m, 1H), 10.5 (s, 1H); HPLC 纯度: 99.4%; LCMS, m/z 实测值 516.4 ($M+1$)⁺.

[0905] N-(3-甲氧基苯基)-4-(4-(喹啉-8-亚磺酰氨基)苯甲酰基)哌嗪-1-羧酰胺 (116ad) :



[0907] ¹H NMR (400MHz, DMSO-d₆) δ : 3.8 (m, 8H), 3.9 (s, 3H), 6.48 (s, 1H), 7.23 (m, 7H), 7.9 (m, 2H), 8.3 (s, 1H), 8.4-8.6 (d, 2H), 8.72 (s, 1H), 9.24 (s, 1H), 10.53 (s, 1H); HPLC 纯度: 95.27%; MS, m/z 实测值 546.16 ($M+1$)⁺.

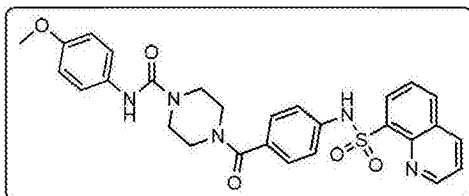
[0908] N-(2-甲氧基苯基)-4-(4-(喹啉-8-亚磺酰氨基)苯甲酰基)哌嗪-1-羧酰胺 (116ae) :



[0910] ¹H NMR (400MHz, DMSO-d₆) δ : 3.8 (m, 8H), 3.9 (s, 3H), 6.8 (d, 2H), 6.98 (d, 2H), 7.23 (m, 4H), 7.9 (m, 4H), 8.42 (d, 1H), 8.6 (d, 1H), 8.72 (d, 1H), 9.24 (s, 1H), 10.53 (s, 1H); HPLC 纯度: 97.73%; MS, m/z 实测值 546.14 ($M+1$)⁺.

[0911] N-(4-甲氧基苯基)-4-(4-(喹啉-8-亚磺酰氨基)苯甲酰基)哌嗪-1-羧酰胺 (116af) :

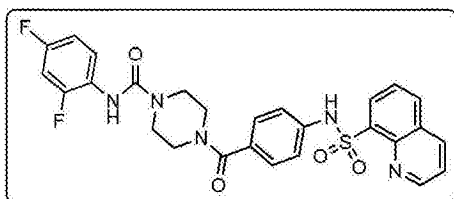
[0912]



[0913] ^1H NMR (400MHz, DMSO- d_6) δ : 3.8 (m, 8H), 3.9 (s, 3H), 5.9 (s, 1H), 6.8 (d, 2H), 6.98 (d, 2H), 7.23 (m, 6H), 7.9 (m, 2H), 8.2–8.6 (m, 4H), 9.24 (s, 1H), 10.53 (s, 1H); HPLC纯度: 98.22%; MS, m/z 实测值546.17 ($M+1$) $^+$.

[0914] N-(2,4-二氟苯基)-4-(4-(喹啉-8-亚磺酰氨基)苯甲酰基)哌嗪-1-羧酰胺 (116ag):

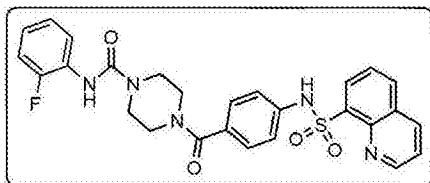
[0915]



[0916] ^1H NMR (400MHz, DMSO- d_6) δ : 3.4 (m, 8H), 7.9 (m, 7H), 7.5 (m, 2H), 8.2–8.5 (d, 3H), 9.24 (s, 1H); HPLC纯度: 95.79%; MS, m/z 实测值552.19 ($M+1$) $^+$.

[0917] N-(2-氟苯基)-4-(4-(喹啉-8-亚磺酰氨基)苯甲酰基)哌嗪-1-羧酰胺 (116ah):

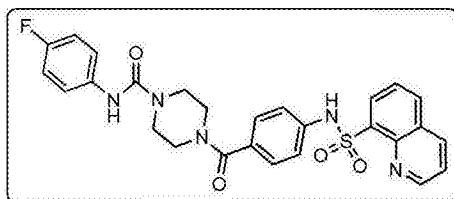
[0918]



[0919] ^1H NMR (400MHz, DMSO- d_6) δ : 3.8 (m, 8H), 7.2 (m, 7H), 7.6 (s, 1H), 7.9 (d, 2H), 8.2–8.6 (d, 4H), 9.24 (s, 1H), 10.53 (s, 1H); HPLC纯度: 95.38%; MS, m/z 实测值534.22 ($M+1$) $^+$.

[0920] N-(4-氟苯基)-4-(4-(喹啉-8-亚磺酰氨基)苯甲酰基)哌嗪-1-羧酰胺 (116ai):

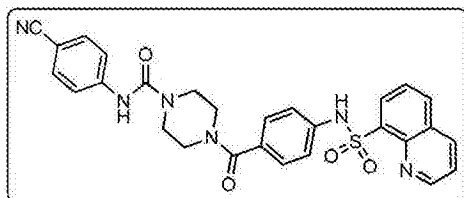
[0921]



[0922] ^1H NMR (400MHz, DMSO- d_6) δ : 3.8 (m, 8H), 7.2 (m, 5H), 7.42 (d, 2H), 7.6 (d, 2H), 8.2–8.6 (d, 4H), 10.53 (s, 1H), 9.24 (s, 1H); HPLC纯度: 98.92%; MS, m/z 实测值532.42 ($M+1$) $^+$.

[0923] N-(4-氰基苯基)-4-(4-(喹啉-8-亚磺酰氨基)苯甲酰基)哌嗪-1-羧酰胺 (116aj):

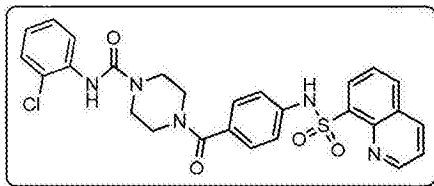
[0924]



[0925] ^1H NMR (400MHz, DMSO- d_6) δ : 3.8 (m, 8H), 7.23 (d, 4H), 7.9 (m, 6H), 8.42 (d, 1H), 8.2 (d, 1H), 8.15 (d, 1H), 9.23 (s, 1H), 9.1 (s, 1H), 10.53 (s, 1H); HPLC纯度: 97.97%; MS, m/z 实测值541.30 ($M+1$) $^+$.

[0926] N-(2-氯苯基)-4-(4-(喹啉-8-亚磺酰氨基)苯甲酰基)哌嗪-1-羧酰胺 (116ak) :

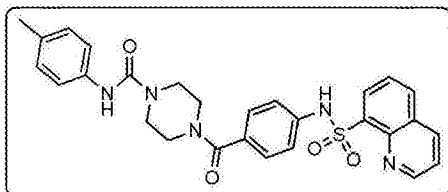
[0927]



[0928] ^1H NMR (400MHz, DMSO- d_6) δ : 3.3 (m, 8H), 7.2 (m, 6H), 7.3 (d, 4H), 7.9 (m, 2H), 8.42 (d, 2H), 8.5 (d, 1H), 8.52 (d, 1H), 9.24 (s, 1H), 10.53 (s, 1H); HPLC纯度: 97.73%; MS, m/z 实测值 546.14 ($M+1$) $^+$.

[0929] 4-(4-(喹啉-8-亚磺酰氨基)苯甲酰基)-N-(对甲苯基)哌嗪-1-羧酰胺 (116al) :

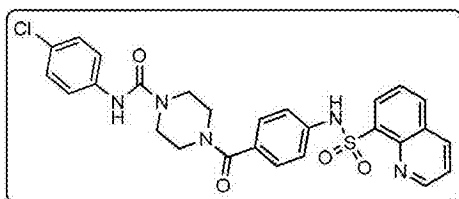
[0930]



[0931] ^1H NMR (400MHz, DMSO- d_6) δ : 2.2 (s, 3H), 3.8 (m, 8H), 7.1-7.3 (m, 7H), 7.9 (m, 2H), 8.23-8.4 (d, 4H), 9.1 (s, 1H), 10.53 (s, 1H); HPLC纯度: 98.27%; MS, m/z 实测值 530.19 ($M+1$) $^+$.

[0932] N-(4-氯苯基)-4-(4-(喹啉-8-亚磺酰氨基)苯甲酰基)哌嗪-1-羧酰胺 (116am) :

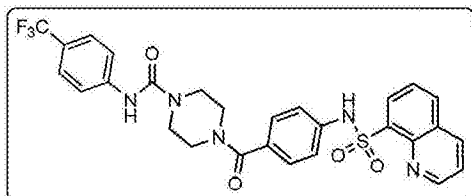
[0933]



[0934] ^1H NMR (400MHz, DMSO- d_6) δ : 3.3 (m, 8H), 7.2 (m, 6H), 7.4 (d, 2H), 7.9 (m, 2H), 8.42 (d, 2H), 8.5 (d, 1H), 8.62 (d, 1H), 9.24 (s, 1H), 10.43 (s, 1H); HPLC纯度: 97.92%; MS, m/z 实测值 550.14 ($M+1$) $^+$.

[0935] 4-(4-(喹啉-8-亚磺酰氨基)苯甲酰基)-N-(4-(三氟甲基)苯基)哌嗪-1-羧酰胺 (116an) :

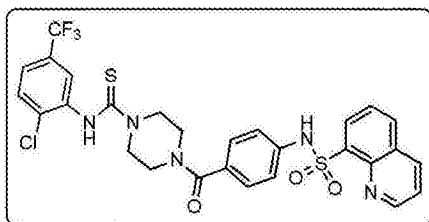
[0936]



[0937] ^1H NMR (400MHz, DMSO- d_6) δ : 3.3 (m, 8H), 7.4 (m, 6H), 7.5 (d, 2H), 8.0 (m, 2H), 8.6 (d, 2H), 8.7 (d, 1H), 8.8 (d, 1H), 9.24 (s, 1H), 10.43 (s, 1H); HPLC纯度: 97.90%; MS, m/z 实测值 584.05 ($M+1$) $^+$.

[0938] N-(2-氯-5-(三氟甲基)苯基)-4-(4-(喹啉-8-亚磺酰氨基)苯甲酰基)哌嗪-1-硫代羧酰胺 (116ao) :

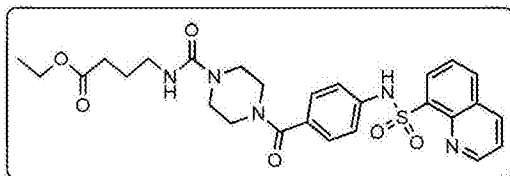
[0939]



[0940] ^1H NMR (400MHz, DMSO- d_6) δ : 3.2–3.8 (m, 8H), 7.0–7.2 (m, 4H), 7.6–7.8 (m, 5H), 8.2 (m, 1H), 8.4–8.6 (m, 2H), 9.1 (m, 1H), 9.4 (m, 1H), 10.5 (s, 1H); HPLC纯度: 96.1%; LCMS, m/z 实测值 634.17 ($M+1$) $^+$.

[0941] 4-(4-(4-(喹啉-8-亚磺酰氨基)苯甲酰基)哌嗪-1-羧酰胺基)丁酸乙酯 (116ap):

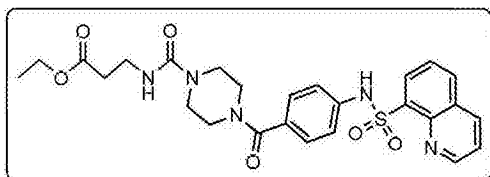
[0942]



[0943] ^1H NMR (400MHz, CDCl_3) δ : 1.2 (t, 3H), 1.8 (q, 2H), 2.4 (t, 2H), 3.2–3.8 (m, 8H), 3.6 (m, 2H), 4.1 (m, 2H), 5.0 (m, 1H), 7.0–7.2 (m, 4H), 7.6 (m, 2H), 8.0 (m, 1H), 8.4 (m, 2H), 8.6 (m, 1H), 9.1 (m, 1H); HPLC纯度: 98.7%; LCMS, m/z 实测值 554.19 ($M+1$) $^+$.

[0944] 3-(4-(4-(喹啉-8-亚磺酰氨基)苯甲酰基)哌嗪-1-羧酰胺基)丙酸乙酯 (116aq):

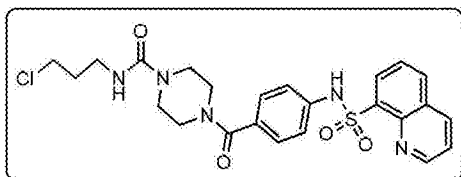
[0945]



[0946] ^1H NMR (400MHz, CD_3OD) δ : 1.2 (t, 3H), 2.5 (t, 2H), 3.2–3.8 (m, 8H), 3.6 (m, 2H), 4.1 (m, 2H), 7.2 (m, 4H), 7.6 (m, 2H), 8.2 (m, 1H), 8.4 (m, 2H), 9.1 (m, 1H); HPLC纯度: 99.3%; LCMS, m/z 实测值 540.1 ($M+1$) $^+$.

[0947] N-(3-氯丙基)-4-(4-(喹啉-8-亚磺酰氨基)苯甲酰基)哌嗪-1-羧酰胺 (116ar):

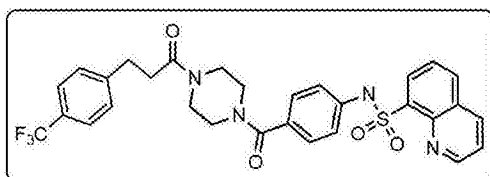
[0948]



[0949] ^1H NMR (400MHz, CD_3OD) δ : 2.5 (m, 2H), 3.6 (t, 2H), 3.8 (t, 3H), 3.2–3.8 (m, 8H), 7.2 (m, 4H), 7.6 (m, 2H), 8.2 (m, 1H), 8.4 (m, 2H), 9.1 (m, 1H); HPLC纯度: 98.3%; LCMS, m/z 实测值 517.1 ($M+1$) $^+$.

[0950] N-(4-(4-(3-(4-(三氟甲基)苯基)丙酰基)哌嗪-1-羧基)苯基)喹啉-8-磺酰胺 (116as):

[0951]

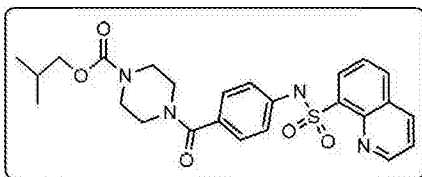


[0952] ^1H NMR (400MHz, DMSO- d_6) δ : 2.7 (t, 2H), 2.9 (t, 2H), 3.2–3.8 (m, 8H), 7.2 (m, 4H),

7.5 (m, 2H), 7.6–7.8 (m, 4H), 8.3 (m, 1H), 8.4–8.6 (m, 2H), 9.1 (m, 1H), 10.5 (s, 1H); HPLC纯度: 99.0%; LCMS, m/z 实测值 597.45 ($M+1$)⁺.

[0953] 4-(4-(喹啉-8-亚磺酰氨基)苯甲酰基)哌嗪-1-羧酸异丁酯 (116at):

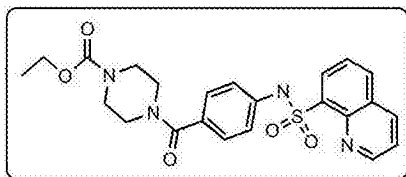
[0954]



[0955] ¹H NMR (400MHz, DMSO-d₆) δ: 0.8–0.91 (t, 6H), 1.90 (m, 1H), 3.4–3.6 (m, 8H), 3.8 (d, 2H), 7.0–7.2 (m, 4H), 7.6–7.8 (m, 2H), 8.2 (m, 1H), 8.4–8.6 (m, 2H), 9.1 (m, 1H), 10.5 (s, 1H); HPLC纯度: 99.91%; LCMS, m/z 实测值 497.18 ($M+1$)⁺.

[0956] 4-(4-(喹啉-8-亚磺酰氨基)苯甲酰基)哌嗪-1-羧酸乙酯 (116au):

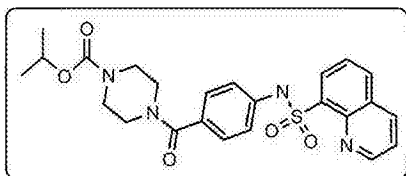
[0957]



[0958] ¹H NMR (400MHz, DMSO-d₆) δ: 1.3 (t, 3H), 3.4–3.6 (m, 8H), 4.1 (q, 2H), 7.2 (m, 4H), 7.7–7.8 (m, 2H), 8.2 (m, 1H), 8.5–8.6 (m, 2H), 9.2 (m, 1H), 10.4 (s, 1H); HPLC纯度: 99.65%; LCMS, m/z 实测值 469.10 ($M+1$)⁺.

[0959] 4-(4-(喹啉-8-亚磺酰氨基)苯甲酰基)哌嗪-1-羧酸异丙酯 (116av):

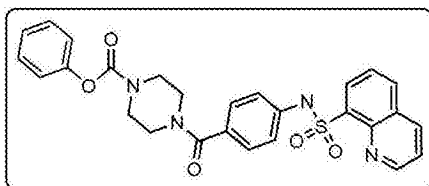
[0960]



[0961] ¹H NMR (400MHz, DMSO-d₆) δ: 1.02–1.21 (m, 6H), 4.81–4.9 (m, 1H), 7.0–7.2 (m, 4H), 7.6–7.8 (m, 2H), 8.2 (m, 1H), 8.4–8.6 (m, 2H), 9.1 (m, 1H), 10.5 (s, 1H); HPLC纯度: 94.12%; LCMS, m/z 实测值 481.51 ($M-1$)⁺.

[0962] 4-(4-(喹啉-8-亚磺酰氨基)苯甲酰基)哌嗪-1-羧酸苯酯 (116aw):

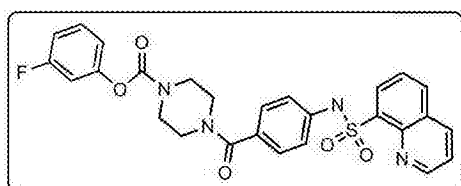
[0963]



[0964] ¹H NMR (400MHz, DMSO-d₆) δ: 3.4–3.8 (m, 8H), 7.0–7.2 (m, 7H), 7.4–7.6 (m, 2H), 7.8–7.85 (m, 2H), 8.2–8.6 (m, 3H), 9.1 (m, 1H), 10.5 (s, 1H); HPLC纯度: 99.71%; LCMS, m/z 实测值 517.25 ($M+1$)⁺.

[0965] 4-(4-(喹啉-8-亚磺酰氨基)苯甲酰基)哌嗪-1-羧酸3-氟苯酯 (116ax):

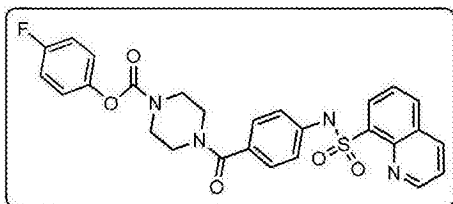
[0966]



[0967] ^1H NMR (400MHz, DMSO- d_6) δ : 3.4–3.8 (m, 8H), 7.0–7.2 (m, 7H), 7.4–7.6 (m, 1H), 7.8–7.85 (m, 2H), 8.2–8.6 (m, 3H), 9.1 (m, 1H), 10.5 (s, 1H); HPLC纯度: 95.75%; LCMS, m/z 实测值 535.25 ($M+1$) $^+$.

[0968] 4-(4-(喹啉-8-亚磺酰氨基)苯甲酰基)哌嗪-1-羧酸4-氟苯酯 (116ay):

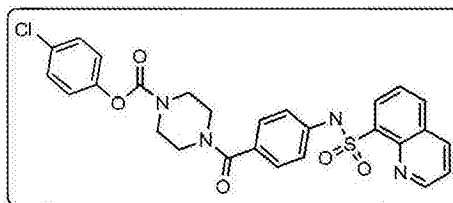
[0969]



[0970] ^1H NMR (400MHz, DMSO- d_6) δ : 3.4–3.8 (m, 8H), 7.0–7.2 (m, 8H), 7.8–7.85 (m, 2H), 8.2–8.6 (m, 3H), 9.1 (m, 1H), 10.5 (s, 1H); HPLC纯度: 95.05%; LCMS, m/z 实测值 535.27 ($M+1$) $^+$.

[0971] 4-(4-(喹啉-8-亚磺酰氨基)苯甲酰基)哌嗪-1-羧酸4-氯苯酯 (116az):

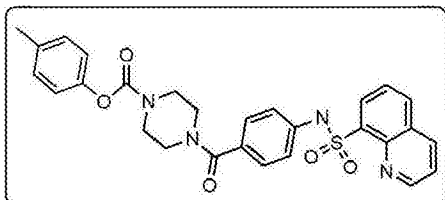
[0972]



[0973] ^1H NMR (400MHz, DMSO- d_6) δ : 3.4–3.8 (m, 8H), 7.0–7.2 (m, 6H), 7.4 (d, 2H), 7.7 (m, 2H), 8.3–8.5 (m, 3H), 9.2 (m, 1H), 10.5 (s, 1H); HPLC纯度: 99.41%; LCMS, m/z 实测值 549.56 (M) $^+$.

[0974] 4-(4-(喹啉-8-亚磺酰氨基)苯甲酰基)哌嗪-1-羧酸对甲苯酯 (116ba):

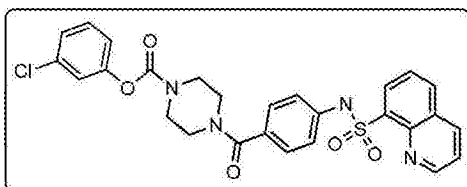
[0975]



[0976] ^1H NMR (400MHz, DMSO- d_6) δ : 2.2 (s, 3H), 3.2–3.8 (m, 8H), 7.0 (m, 2H), 7.2 (m, 6H), 7.6–7.8 (m, 2H), 8.3 (m, 1H), 8.4–8.6 (m, 2H), 9.1 (m, 1H), 10.5 (s, 1H); HPLC纯度: 99.5%; LCMS, m/z 实测值 531.58 ($M+1$) $^+$.

[0977] 4-(4-(喹啉-8-亚磺酰氨基)苯甲酰基)哌嗪-1-羧酸3-氯苯酯 (116bb):

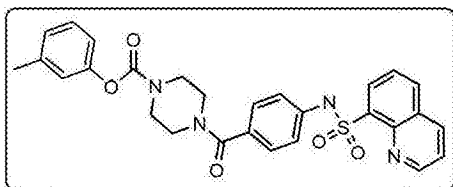
[0978]



[0979] ^1H NMR (400MHz, DMSO- d_6) δ : 3.4–3.8 (m, 8H), 7.0–7.2 (m, 8H), 7.6–7.8 (m, 2H), 8.2–8.6 (m, 3H), 9.1 (m, 1H), HPLC纯度: 99.79%; LCMS, m/z 实测值 549.58 (M) $^+$.

[0980] 4-(4-(喹啉-8-亚磺酰氨基)苯甲酰基)哌嗪-1-羧酸间甲苯酯 (116bc):

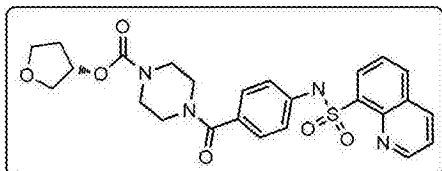
[0981]



[0982] ^1H NMR (400MHz, DMSO- d_6) δ : 2.23–2.4 (t, 3H), 3.4–3.8 (t, 8H), 6.82–6.98 (m, 6H), 7.0–7.2 (m, 6H), 7.6–7.8 (m, 2H), 8.2–8.6 (m, 3H), 9.1 (m, 1H); HPLC纯度: 99.26%; LCMS, m/z 实测值 531.16 ($M+1$) $^+$.

[0983] (S)-4-(4-(喹啉-8-亚磺酰氨基)苯甲酰基)哌嗪-1-羧酸四氢呋喃-3-酯 (116bd):

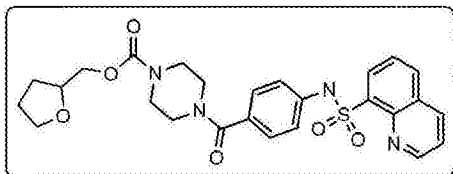
[0984]



[0985] ^1H NMR (400MHz, DMSO- d_6) δ : 2.23–2.4 (m, 2H), 2.6–2.98 (m, 4H), 3.4–3.8 (t, 8H), 3.8–3.95 (m, 4H), 5.23–5.35 (m, 1H), 7.0–7.2 (m, 4H), 7.6–7.8 (m, 2H), 8.0–8.1 (d, 2H), 8.32–8.45 (dd, 2H), 9.1 (m, H); HPLC纯度: 96.89%; LCMS, m/z 实测值 533.05 ($M+23$) $^+$.

[0986] 4-(4-(喹啉-8-亚磺酰氨基)苯甲酰基)哌嗪-1-羧酸(四氢呋喃-2-基)甲酯 (116be):

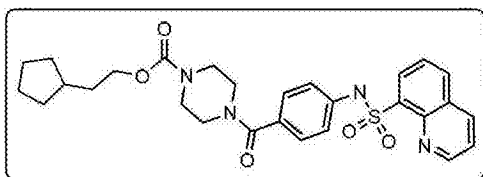
[0987]



[0988] ^1H NMR (400MHz, DMSO- d_6) δ : 2.23–2.4 (m, 3H), 3.4–3.8 (t, 8H), 3.8–3.95 (m, 4H), 7.0–7.2 (m, 4H), 7.6–7.8 (m, 2H), 8.0–8.1 (d, 2H), 8.32–8.45 (dd, 3H), 9.1 (m, 1H); HPLC纯度: 99.84%; LCMS, m/z 实测值 525.10 ($M+1$) $^+$.

[0989] 4-(4-(喹啉-8-亚磺酰氨基)苯甲酰基)哌嗪-1-羧酸2-环戊基乙酯 (116bf):

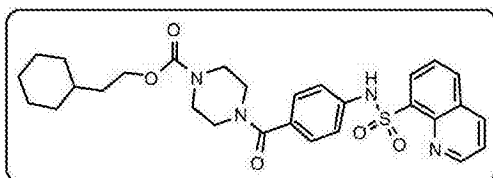
[0990]



[0991] ^1H NMR (400MHz, DMSO- d_6) δ : 1.2–1.32 (d, 4H), 2.0–2.12 (m, 8H), 3.4–3.8 (t, 8H), 4.62–4.72 (m, 1H), 7.0–7.2 (m, 6H), 7.6–7.8 (m, 2H), 8.0–8.1 (d, 2H), 8.32–8.45 (dd, 3H), 9.1 (m, 1H); HPLC纯度: 99.89%; LCMS, m/z 实测值 537.10 ($M+1$) $^+$.

[0992] 4-(4-(喹啉-8-亚磺酰氨基)苯甲酰基)哌嗪-1-羧酸2-环己基乙酯 (116bg):

[0993]

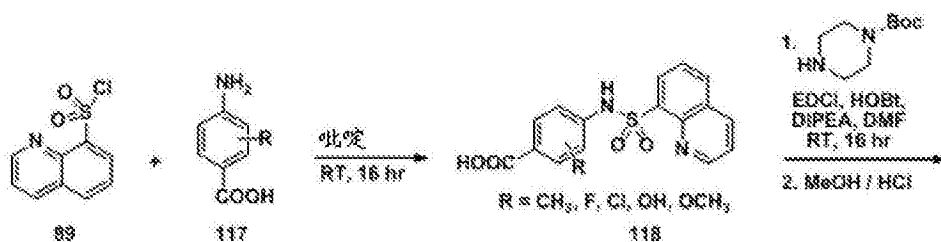


[0994] ^1H NMR (400MHz, CDCl_3) δ : 1.0 (m, 2H), 1.2 (m, 7H), 1.5 (m, 1H), 1.6 (m, 5H), 3.2–3.8 (m, 8H), 7.0–7.2 (m, 4H), 7.6–7.8 (m, 2H), 8.0 (m, 1H), 8.2–8.4 (m, 2H), 8.6 (m, 2H), 9.1 (m,

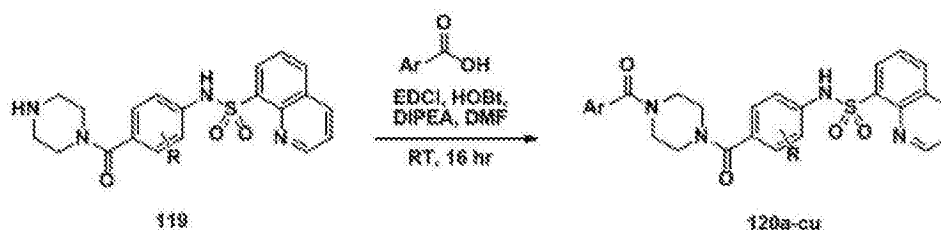
1H); HPLC纯度: 99.6%; LCMS, m/z 实测值 551.45 (M+1)⁺.

[0995] 具有3-甲基、2-甲基、3-氟、3-氯、3-羟基或3-甲氧基取代的苯基环的哌嗪衍生物的合成

[0996] 流程17



[0997]



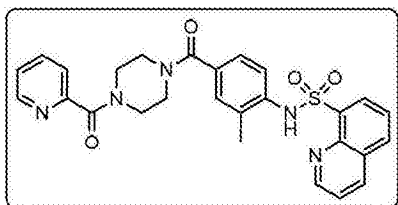
[0998] 合成磺酰胺118的一般程序: 于0℃、在氮气气氛下向胺7 (30.3mmol) 的搅拌溶液加入吡啶 (50ml), 搅拌10min。然后在相同温度下将喹啉-8-磺酰氯89 (8.94gm, 39.4mmol) 加至反应混合物。将所得混合物在RT搅拌16h。反应结束后, 在减压下除去溶剂。通过与甲苯共馏除去痕量的吡啶。将乙醚加至所得残余物中, 滤出固体产物, 空气干燥。所得粗产物 (8.0gm, 74%) 不需进一步纯化即可用于下一步骤。

[0999] 合成磺酰胺119的一般程序: 将EDCI (3.8g, 19.8mmol) 和HOBT (2.67g, 19.8mmol) 加至酸118 (19.8mmol) 在无水DMF中的搅拌溶液。将混合物的温度降至0℃, 此时在氮气气氛下加入DIPEA (11ml, 59.45mmol), 将所得溶液 (或悬浮液) 在室温搅拌30min。然后于0℃加入Boc-哌嗪 (3.68g, 19.8mmol)。然后将反应混合物升至室温, 搅拌过夜。反应结束后, 将反应混合物用水稀释, 用乙酸乙酯萃取 (3×50ml)。经无水硫酸钠干燥, 过滤, 经旋转蒸发仪浓缩, 得到粗产物。通过柱色谱法 (60-120硅胶, 2% MeOH-DCM) 纯化粗产物, 得到为灰白色固体状的纯产物Boc-119 (81%), 将其于RT用甲醇HCl (100ml) 处理2h。Boc-基团完全断裂后, 在低压下除去溶剂, 得到为HCl盐的纯产物。用乙醚洗涤盐的水溶液, 用NaHCO₃ (pH 10) 碱化。然后将所需产物分配至乙酸乙酯中, 用无水Na₂SO₄干燥, 在低压下除去溶剂, 得到为灰白色固体状的游离胺119 (95%)。

[1000] 合成酰胺120a-cu的一般程序: 将EDCI (48mg, 0.2525mmol) 和HOBT (34mg, 0.2525mmol) 加至Ar-COOH (0.2525mmol) 在无水DMF中的搅拌溶液。将混合物的温度降至0℃, 此时在氮气气氛下加入DIPEA (139μl, 0.7575mmol), 将所得溶液 (或悬浮液) 在室温搅拌30min。然后于0℃加入胺119 (100mg, 0.2525mmol)。然后将反应混合物升至室温, 搅拌过夜。反应结束后, 将反应混合物用水稀释, 用乙酸乙酯萃取 (3×15ml)。将有机层用水洗涤 (3×10ml), 经无水硫酸钠干燥, 过滤, 经旋转蒸发仪浓缩, 得到粗产物。通过柱色谱法或制备型HPLC纯化粗产物, 获得收率为52-68%的纯产物。

[1001] N-(2-甲基-4-(4-吡啶甲酰基哌嗪-1-基) 苯基) 喹啉-8-磺酰胺 (120a):

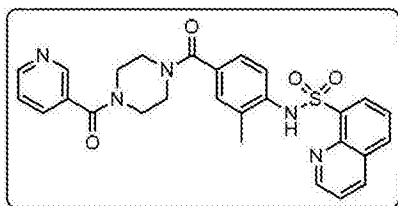
[1002]



[1003] ^1H NMR (400MHz, CD_3OD) δ : 2.1 (s, 3H), 3.2–3.8 (m, 8H), 7.0–7.2 (m, 3H), 7.6–7.8 (m, 4H), 8.0 (m, 1H), 8.2–8.4 (m, 2H), 8.6 (m, 2H), 9.1 (m, 1H); HPLC纯度: 97.9%; LCMS, m/z 实测值 516.1 ($\text{M}+1$) $^+$.

[1004] N-(2-甲基-4-(4-(烟酰基哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (120b):

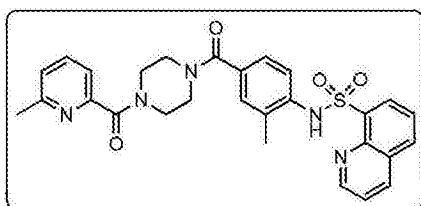
[1005]



[1006] ^1H NMR (400MHz, CDCl_3) δ : 2.1 (s, 3H), 3.2–3.8 (m, 8H), 7.0–7.2 (m, 3H), 7.6–7.8 (m, 4H), 8.2 (m, 1H), 8.6 (m, 2H), 8.9 (m, 2H), 9.1 (m, 1H), 10.5 (s, 1H); HPLC纯度: 99.3%; LCMS, m/z 实测值 516.1 ($\text{M}+1$) $^+$.

[1007] N-(2-甲基-4-(4-(6-甲基吡啶甲酰基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (120c):

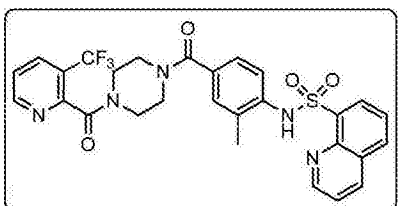
[1008]



[1009] ^1H NMR (400MHz, CDCl_3) δ : 2.1 (s, 3H), 2.3 (s, 3H), 3.2–3.8 (m, 8H), 7.0–7.2 (m, 3H), 7.6–7.8 (m, 4H), 8.2 (m, 1H), 8.6 (m, 1H), 8.9 (m, 2H), 9.1 (m, 1H), 10.5 (s, 1H); HPLC纯度: 95.5.0%; LCMS, m/z 实测值 530.2 ($\text{M}+1$) $^+$.

[1010] N-(2-甲基-4-(4-(3-(三氟甲基)吡啶甲酰基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (120d):

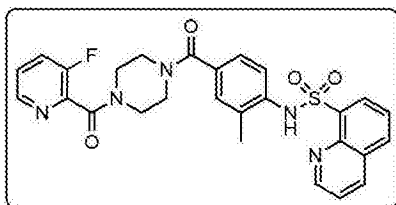
[1011]



[1012] ^1H NMR (400MHz, CDCl_3) δ : 2.1 (s, 3H), 3.2–3.8 (m, 8H), 7.0–7.2 (m, 2H), 7.4–7.6 (m, 4H), 8.2 (m, 2H), 8.4 (m, 2H), 8.6–8.8 (m, 2H), 9.1 (m, 1H); HPLC纯度: 97.2.0%; LCMS, m/z 实测值 584.1 ($\text{M}+1$) $^+$.

[1013] N-(4-(4-(3-氟吡啶甲酰基)哌嗪-1-羰基)-2-甲基苯基)喹啉-8-磺酰胺 (120e):

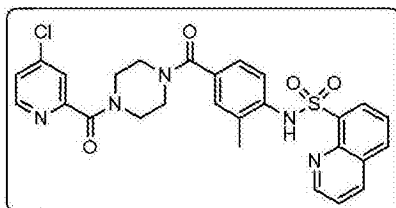
[1014]



[1015] ^1H NMR (400MHz, CDCl_3) δ : 2.1 (s, 3H), 3.2–3.8 (m, 8H), 7.0–7.2 (m, 2H), 7.4–7.6 (m, 5H), 8.2 (m, 1H), 8.4 (m, 3H), 9.1 (m, 1H); HPLC纯度: 99.6.0%; LCMS, m/z 实测值 534.1 ($\text{M}+1$) $^+$.

[1016] N-(4-(4-(4-chloropyridin-2-yl)pyrimidin-1-yl)-2-methylphenyl)quinoline-8-sulfonamide (120f):

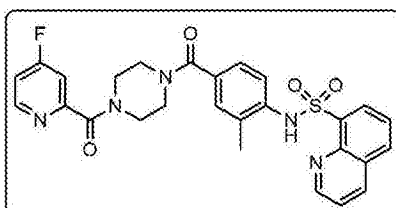
[1017]



[1018] ^1H NMR (400MHz, CDCl_3) δ : 2.1 (s, 3H), 3.2–3.8 (m, 8H), 7.0–7.2 (m, 2H), 7.4 (m, 1H), 7.5–7.8 (m, 4H), 8.0 (m, 1H), 8.2 (m, 2H), 8.6 (m, 1H), 9.1 (m, 1H); HPLC纯度: 93.4%; LCMS, m/z 实测值 550.1 ($\text{M}+1$) $^+$.

[1019] N-(4-(4-(4-fluoropyridin-2-yl)pyrimidin-1-yl)-2-methylphenyl)quinoline-8-sulfonamide (120g):

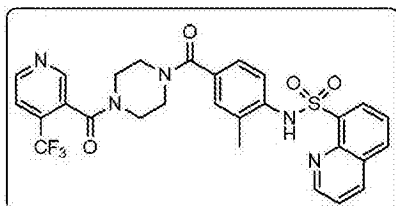
[1020]



[1021] ^1H NMR (400MHz, CDCl_3) δ : 2.1 (s, 3H), 3.2–3.8 (m, 8H), 7.0 (m, 2H), 7.4 (m, 1H), 7.5–7.8 (m, 4H), 8.0 (m, 1H), 8.2–8.4 (m, 3H), 9.1 (m, 1H); HPLC纯度: 99.2%; LCMS, m/z 实测值 534.1 ($\text{M}+1$) $^+$.

[1022] N-(2-methyl-4-(4-(4-(trifluoromethyl)pyridin-2-yl)pyrimidin-1-yl)phenyl)quinoline-8-sulfonamide (120h):

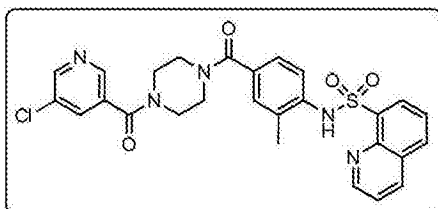
[1023]



[1024] ^1H NMR (400MHz, CDCl_3) δ : 2.1 (s, 3H), 3.2–3.8 (m, 8H), 7.0 (m, 2H), 7.4 (m, 1H), 7.5–7.6 (m, 3H), 8.4 (m, 3H), 8.7 (s, 1H), 8.8 (m, 1H), 9.1 (m, 1H); HPLC纯度: 95.0%; LCMS, m/z 实测值 584.1 ($\text{M}+1$) $^+$.

[1025] N-(4-(4-(5-chloropyridin-2-yl)pyrimidin-1-yl)-2-methylphenyl)quinoline-8-sulfonamide (120i):

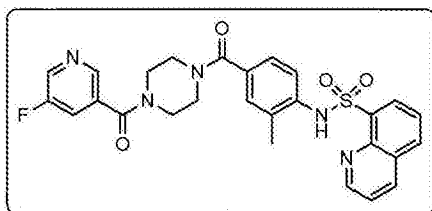
[1026]



[1027] ^1H NMR (400MHz, CDCl_3) δ : 2.1 (s, 3H), 3.2–3.8 (m, 8H), 7.0 (m, 3H), 7.4 (m, 1H), 7.6–7.8 (m, 2H), 8.1 (m, 1H), 8.2 (m, 2H), 8.8 (m, 2H), 9.1 (m, 1H); HPLC纯度: 98.1%; LCMS, m/z 实测值 550.1 ($\text{M}+1$) $^+$.

[1028] N-(4-(4-(5-氟烟酰基)哌嗪-1-羰基)-2-甲基苯基)喹啉-8-磺酰胺 (120j):

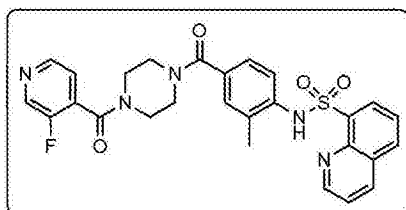
[1029]



[1030] ^1H NMR (400MHz, CDCl_3) δ : 2.1 (s, 3H), 3.2–3.8 (m, 8H), 7.0 (m, 2H), 7.2–7.4 (m, 2H), 7.6–7.8 (m, 2H), 8.0–8.6 (m, 5H), 9.1 (m, 1H); HPLC纯度: 99.1%; LCMS, m/z 实测值 534.3 ($\text{M}+1$) $^+$.

[1031] N-(4-(4-(3-氟异烟酰基)哌嗪-1-羰基)-2-甲基苯基)喹啉-8-磺酰胺 (120k):

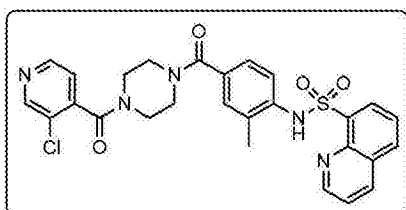
[1032]



[1033] ^1H NMR (400MHz, CDCl_3) δ : 2.1 (s, 3H), 3.2–3.8 (m, 8H), 7.0 (m, 2H), 7.2–7.4 (m, 2H), 7.6–7.8 (m, 2H), 8.0 (m, 1H), 8.2–8.6 (m, 4H), 9.1 (m, 1H); HPLC纯度: 95.3%; LCMS, m/z 实测值 534.1 ($\text{M}+1$) $^+$.

[1034] N-(4-(4-(3-氯异烟酰基)哌嗪-1-羰基)-2-甲基苯基)喹啉-8-磺酰胺 (120l):

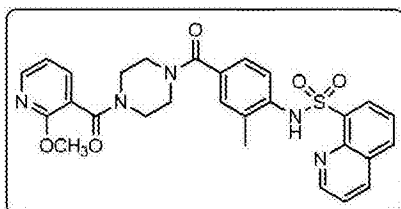
[1035]



[1036] ^1H NMR (400MHz, CDCl_3) δ : 2.1 (s, 3H), 3.2–3.8 (m, 8H), 7.0 (m, 1H), 7.2–7.4 (m, 4H), 7.6–7.8 (m, 2H), 8.0 (m, 1H), 8.2–8.6 (m, 3H), 9.1 (m, 1H); HPLC纯度: 99.8%; LCMS, m/z 实测值 550.3 ($\text{M}+1$) $^+$.

[1037] N-(4-(4-(2-甲氧基烟酰基)哌嗪-1-羰基)-2-甲基苯基)喹啉-8-磺酰胺 (120m):

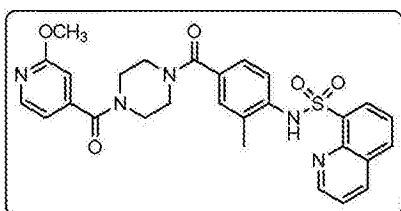
[1038]



[1039] ^1H NMR (400MHz, CDCl_3) δ : 2.1 (s, 3H), 3.2-3.8 (m, 8H), 7.2-7.4 (m, 4H), 7.6-7.8 (m, 3H), 8.0 (m, 1H), 8.2-8.6 (m, 3H), 9.1 (m, 1H); HPLC纯度: 99.3%; LCMS, m/z 实测值 546.3 ($M+1$) $^+$.

[1040] N-(4-(4-(2-甲氧基异烟酰基)哌嗪-1-羰基)-2-甲基苯基)喹啉-8-磺酰胺 (120n):

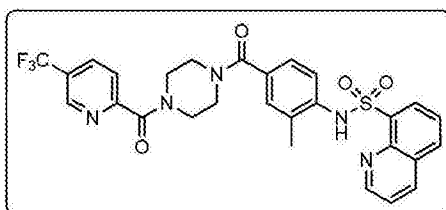
[1041]



[1042] ^1H NMR (400MHz, CDCl_3) δ : 2.1 (s, 3H), 3.2-3.8 (m, 8H), 6.7-7.0 (m, 4H), 7.2 (m, 1H), 7.6 (m, 2H), 8.0 (m, 1H), 8.2-8.6 (m, 3H), 9.1 (m, 1H); HPLC纯度: 98.8%; LCMS, m/z 实测值 546.3 ($M+1$) $^+$.

[1043] N-(2-甲基-4-(4-(5-(三氟甲基)吡啶甲酰基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (120o):

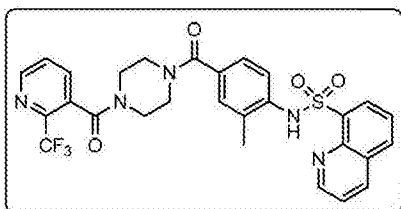
[1044]



[1045] ^1H NMR (400MHz, CDCl_3) δ : 2.1 (s, 3H), 3.2-3.8 (m, 8H), 7.0 (m, 2H), 7.2 (m, 1H), 7.6 (m, 2H), 7.8 (m, 1H), 8.0 (m, 2H), 8.3-8.5 (m, 2H), 8.8 (s, 1H), 9.1 (m, 1H); HPLC纯度: 91.8%; LCMS, m/z 实测值 584.4 ($M+1$) $^+$.

[1046] N-(2-甲基-4-(4-(2-(三氟甲基)烟酰基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (120p):

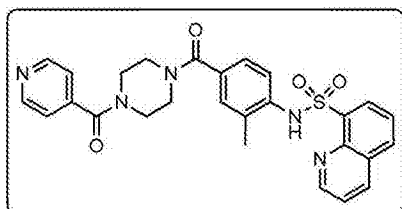
[1047]



[1048] ^1H NMR (400MHz, CDCl_3) δ : 2.1 (s, 3H), 3.2-3.8 (m, 8H), 7.0 (m, 3H), 7.4 (m, 1H), 7.6 (m, 4H), 8.0 (m, 1H), 8.3-8.5 (m, 1H), 8.8 (s, 1H), 9.1 (m, 1H); HPLC纯度: 99.2%; LCMS, m/z 实测值 584.3 ($M+1$) $^+$.

[1049] N-(4-(4-异烟酰基哌嗪-1-羰基)-2-甲基苯基)喹啉-8-磺酰胺 (120q):

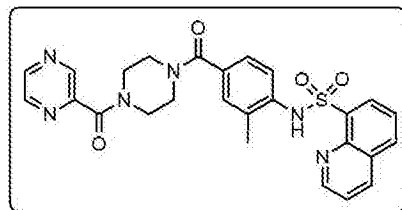
[1050]



[1051] ^1H NMR (400MHz, CDCl_3) δ : 2.1 (s, 3H), 3.2–3.8 (m, 8H), 7.0 (m, 3H), 7.4 (m, 2H), 7.6 (m, 2H), 8.3 (m, 2H), 8.5 (m, 2H), 9.1 (m, 1H); HPLC纯度: 94.5%; LCMS, m/z 实测值 516.34 ($M+1$) $^+$.

[1052] N-(2-甲基-4-(4-(吡嗪-2-羰基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (120r):

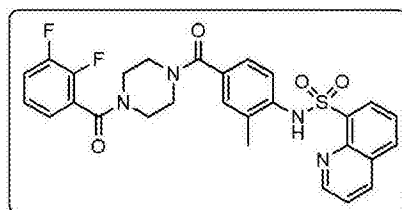
[1053]



[1054] ^1H NMR (400MHz, CDCl_3) δ : 2.1 (s, 3H), 3.2–3.8 (m, 8H), 7.0–7.2 (m, 2H), 7.4 (m, 1H), 7.6 (m, 2H), 8.0 (m, 1H), 8.3 (m, 2H), 8.6 (m, 1H), 8.8 (m, 1H), 9.0 (s, 1H), 9.1 (m, 1H); HPLC纯度: 99.4%; LCMS, m/z 实测值 517.15 ($M+1$) $^+$.

[1055] N-(4-(4-(2,3-二氟苯甲酰基)哌嗪-1-羰基)-2-甲基苯基)喹啉-8-磺酰胺 (120s):

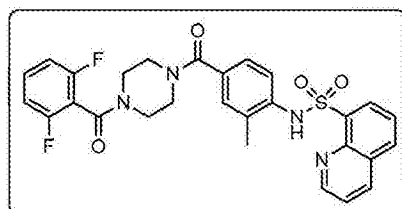
[1056]



[1057] ^1H NMR (400MHz, CD_3OD) δ : 2.1 (s, 3H), 3.2–3.8 (m, 8H), 7.0 (m, 1H), 7.2 (m, 4H), 7.4 (m, 1H), 8.7 (m, 2H), 8.2–8.5 (m, 3H), 9.1 (m, 1H); HPLC纯度: 98.6%; LCMS, m/z 实测值 551.35 ($M+1$) $^+$.

[1058] N-(4-(4-(2,6-二氟苯甲酰基)哌嗪-1-羰基)-2-甲基苯基)喹啉-8-磺酰胺 (120t):

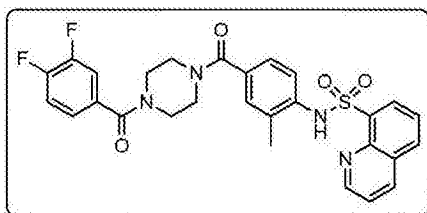
[1059]



[1060] ^1H NMR (400MHz, CD_3OD) δ : 2.1 (s, 3H), 3.2–3.8 (m, 8H), 7.0–7.2 (m, 5H), 7.5 (m, 2H), 7.7 (m, 2H), 8.2–8.5 (m, 3H), 9.1 (m, 1H); HPLC纯度: 96.4%; LCMS, m/z 实测值 551.35 ($M+1$) $^+$.

[1061] N-(4-(4-(3,4-二氟苯甲酰基)哌嗪-1-羰基)-2-甲基苯基)喹啉-8-磺酰胺 (120u):

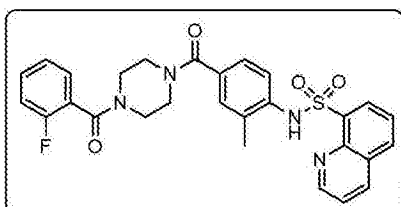
[1062]



[1063] ^1H NMR (400MHz, CD_3OD) δ : 2.1 (s, 3H), 3.2–3.8 (m, 8H), 7.0 (m, 2H), 7.2–7.5 (m, 5H), 7.7 (m, 2H), 8.2–8.5 (m, 3H), 9.1 (m, 1H); HPLC纯度: 97.9%; LCMS, m/z 实测值 551.35 ($\text{M}+1$) $^+$.

[1064] N-(4-(4-(2-氟苯甲酰基)哌嗪-1-羰基)-2-甲基苯基)喹啉-8-磺酰胺 (120v):

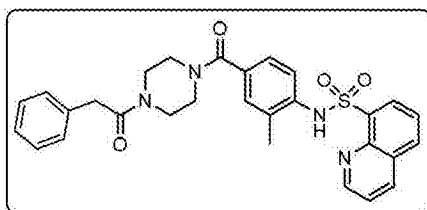
[1065]



[1066] ^1H NMR (400MHz, CDCl_3) δ : 2.1 (s, 3H), 3.2–3.8 (m, 8H), 7.0–7.2 (m, 4H), 7.2–7.5 (m, 3H), 7.7 (m, 2H), 8.0–8.5 (m, 3H), 9.1 (m, 1H); HPLC纯度: 93.6%; LCMS, m/z 实测值 533.27 ($\text{M}+1$) $^+$.

[1067] N-(2-甲基-4-(4-(2-苯基乙酰基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (120w):

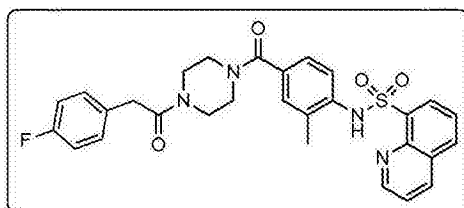
[1068]



[1069] ^1H NMR (400MHz, CDCl_3) δ : 2.1 (s, 3H), 3.2–3.8 (m, 8H), 3.9 (m, 2H), 7.0 (m, 1H), 7.2–7.5 (m, 7H), 7.7 (m, 2H), 8.2–8.5 (m, 4H), 9.1 (m, 1H); HPLC纯度: 94.6%; LCMS, m/z 实测值 529.35 ($\text{M}+1$) $^+$.

[1070] N-(4-(4-(2-(4-氟苯基)乙酰基)哌嗪-1-羰基)-2-甲基苯基)喹啉-8-磺酰胺 (120x):

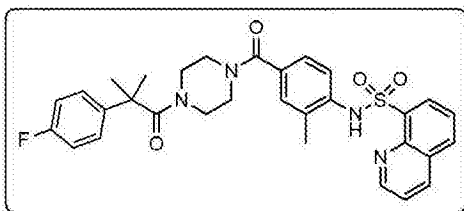
[1071]



[1072] ^1H NMR (400MHz, CD_3OD) δ : 2.1 (s, 3H), 3.2–3.8 (m, 8H), 7.0–7.5 (m, 7H), 7.7 (m, 2H), 8.2–8.5 (m, 3H), 9.1 (m, 1H); HPLC纯度: 95.1%; LCMS, m/z 实测值 547.0 ($\text{M}+1$) $^+$.

[1073] N-(4-(4-(2-(4-氟苯基)-2-甲基丙酰基)哌嗪-1-羰基)-2-甲基苯基)喹啉-8-磺酰胺 (120y):

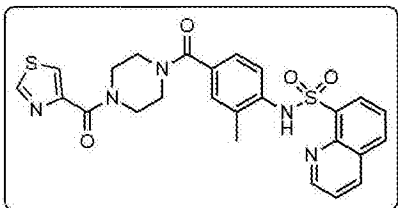
[1074]



[1075] ^1H NMR (400MHz, CDCl_3) δ : 1.6 (s, 6H), 2.1 (s, 3H), 3.2–3.8 (m, 8H), 6.9–7.0 (m, 3H), 7.2–7.5 (m, 3H), 7.7 (m, 2H), 8.2–8.5 (m, 4H), 9.1 (m, 1H); HPLC纯度: 99.1%; LCMS, m/z 实测值 575.1 ($M+1$) $^+$.

[1076] N-(2-甲基-4-(4-(噻唑-4-羰基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (120z):

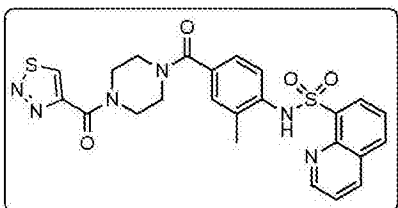
[1077]



[1078] ^1H NMR (400MHz, CD_3OD) δ : 2.1 (s, 3H), 3.2–3.8 (m, 8H), 7.0–7.2 (m, 3H), 7.6–7.8 (m, 2H), 8.1–8.5 (m, 4H), 9.1 (m, 2H); HPLC纯度: 98.6%; LCMS, m/z 实测值 522.05 ($M+1$) $^+$.

[1079] N-(4-(4-(1,2,3-噻二唑-4-羰基)哌嗪-1-羰基)-2-甲基苯基)喹啉-8-磺酰胺 (120aa):

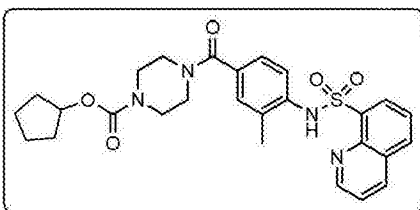
[1080]



[1081] ^1H NMR (400MHz, $\text{DMSO}-d_6$) δ : 2.1 (s, 3H), 3.2–3.8 (m, 8H), 7.0–7.2 (m, 3H), 7.4–7.6 (m, 2H), 7.7 (m, 2H), 8.2–8.5 (m, 3H), 9.1 (m, 1H), 9.4 (s, 1H), 9.6 (s, 1H); HPLC纯度: 99.1%; LCMS, m/z 实测值 523.15 ($M+1$) $^+$.

[1082] 4-(3-甲基-4-(喹啉-8-亚磺酰氨基)苯甲酰基)哌嗪-1-羧酸环戊酯 (120ab):

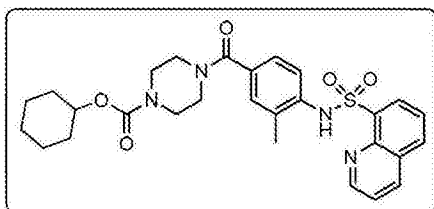
[1083]



[1084] ^1H NMR (400MHz, CDCl_3) δ : 1.4–1.9 (m, 8H), 2.1 (s, 3H), 3.2–3.8 (m, 8H), 5.1 (s, 1H), 7.0–7.2 (m, 1H), 7.4 (m, 3H), 7.7 (m, 1H), 8.2 (m, 1H), 8.2–8.4 (m, 2H), 9.1 (m, 1H); HPLC纯度: 97.4%; LCMS, m/z 实测值 523.30 ($M+1$) $^+$.

[1085] 4-(3-甲基-4-(喹啉-8-亚磺酰氨基)苯甲酰基)哌嗪-1-羧酸环己酯 (120ac):

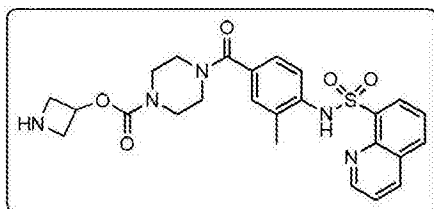
[1086]



[1087] ^1H NMR (400MHz, CDCl_3) δ : 0.9 (m, 1H), 1.2–1.7 (m, 10H), 2.1 (s, 3H), 3.2–3.8 (m, 8H), 5.1 (s, 1H), 7.0–7.4 (m, 3H), 7.6 (m, 2H), 8.1 (m, 1H), 8.2–8.4 (m, 2H), 9.1 (m, 1H); HPLC 纯度: 99.0%; LCMS, m/z 实测值 537.19 ($M+1$) $^+$.

[1088] 4-(3-甲基-4-(喹啉-8-亚磺酰氨基)苯甲酰基)哌嗪-1-羧酸氮杂环丁烷-3-基酯 (120ad):

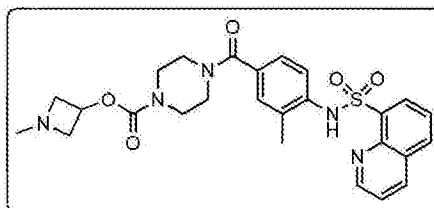
[1089]



[1090] ^1H NMR (400MHz, $\text{DMSO}-d_6$) δ : 0.9 (m, 1H), 1.2–1.7 (m, 4H), 2.1 (s, 3H), 3.2–3.8 (m, 8H), 5.1 (s, 1H), 7.0–7.4 (m, 3H), 7.6 (m, 2H), 8.3 (m, 2H), 8.6 (m, 1H), 9.1 (m, 1H); HPLC 纯度: 92.9%; LCMS, m/z 实测值 510.31 ($M+1$) $^+$.

[1091] 4-(3-甲基-4-(喹啉-8-亚磺酰氨基)苯甲酰基)哌嗪-1-羧酸1-甲基氮杂环丁烷-3-基酯 (120ae):

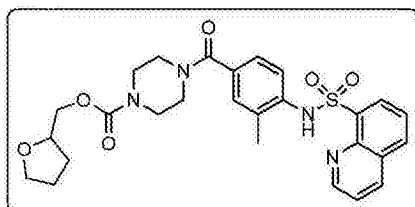
[1092]



[1093] ^1H NMR (400MHz, $\text{DMSO}-d_6$) δ : 2.0 (s, 3H), 2.1 (s, 3H), 2.9 (m, 4H), 3.2–3.8 (m, 8H), 5.1 (s, 1H), 7.0–7.4 (m, 3H), 7.8 (m, 2H), 8.3 (m, 2H), 8.6 (m, 1H), 9.1 (m, 1H), 9.4 (s, 1H); HPLC 纯度: 92.0%; LCMS, m/z 实测值 524.05 ($M+1$) $^+$.

[1094] 4-(3-甲基-4-(喹啉-8-亚磺酰氨基)苯甲酰基)哌嗪-1-羧酸(四氢呋喃-2-基)甲酯 (120af):

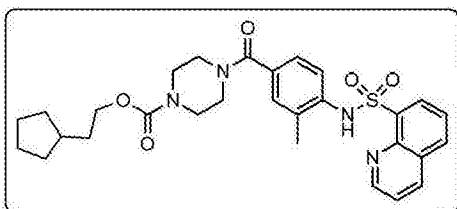
[1095]



[1096] ^1H NMR (400MHz, CDCl_3) δ : 1.1 (m, 2H), 1.8–2.0 (m, 4H), 2.1 (s, 3H), 2.9 (m, 4H), 3.2–3.8 (m, 8H), 5.1 (s, 1H), 7.0–7.2 (m, 2H), 7.2–7.4 (m, 1H), 7.6 (m, 2H), 8.0–8.4 (m, 3H), 9.1 (m, 1H); HPLC 纯度: 99.40%; LCMS, m/z 实测值 539.15 ($M+1$) $^+$.

[1097] 2-环戊基乙基4-(3-甲基-4-(喹啉-8-亚磺酰氨基)苯甲酰基)哌嗪-1-羧酸酯 (120ag):

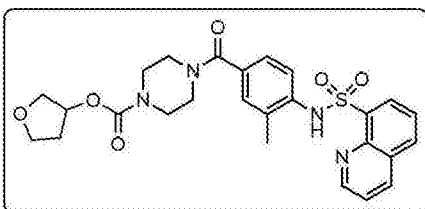
[1098]



[1099] ^1H NMR (400MHz, CDCl_3) δ : 1.2 (m, 4H), 1.4–1.6 (m, 8H), 2.0 (m, 1H), 2.1 (s, 3H), 3.2–3.8 (m, 8H), 5.1 (s, 1H), 7.0–7.2 (m, 2H), 7.2–7.4 (m, 1H), 7.6 (m, 2H), 8.0–8.4 (m, 3H), 9.1 (m, 1H); HPLC纯度: 99.50%; LCMS, m/z 实测值 551.1 ($M+1$) $^+$.

[1100] 4-(3-甲基-4-(喹啉-8-亚磺酰氨基)苯甲酰基)哌嗪-1-羧酸四氢呋喃-3-基酯 (120ah):

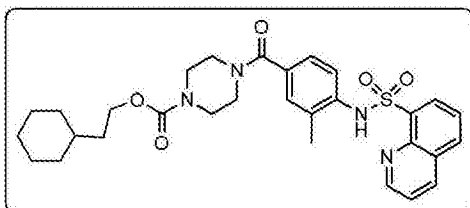
[1101]



[1102] ^1H NMR (400MHz, CDCl_3) δ : 2.0 (m, 2H), 2.2 (s, 3H), 2.5 (s, 1H), 3.2–3.8 (m, 8H), 4.0 (m, 4H), 5.1 (s, 1H), 7.0–7.2 (m, 1H), 7.2–7.4 (m, 2H), 7.6 (m, 2H), 8.0–8.4 (m, 3H), 9.1 (m, 1H); HPLC纯度: 99.50%; LCMS, m/z 实测值 525.05 ($M+1$) $^+$.

[1103] 4-(3-甲基-4-(喹啉-8-亚磺酰氨基)苯甲酰基)哌嗪-1-羧酸2-环己基乙酯 (120ai):

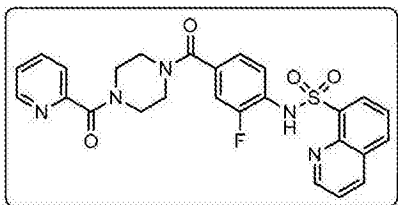
[1104]



[1105] ^1H NMR (400MHz, CDCl_3) δ : 2.0 (m, 2H), 2.2 (s, 3H), 2.5 (s, 1H), 3.2–3.8 (m, 8H), 4.0 (m, 4H), 5.1 (s, 1H), 7.0–7.2 (m, 1H), 7.2–7.4 (m, 2H), 7.6 (m, 2H), 8.0–8.4 (m, 3H), 9.1 (m, 1H); HPLC纯度: 99.50%; LCMS, m/z 实测值 525.05 ($M+1$) $^+$.

[1106] N-(2-氟-4-(4-吡啶甲酰基哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (120aj):

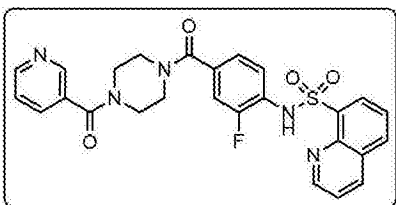
[1107]



[1108] ^1H NMR (400MHz, CDCl_3) δ : 1.1 (m, 7H), 1.6–1.8 (m, 5H), 2.1 (s, 3H), 3.2–3.8 (m, 8H), 4.7 (m, 1H), 7.0–7.2 (m, 2H), 7.4–7.6 (m, 3H), 8.0–8.4 (m, 3H), 9.1 (m, 1H); HPLC纯度: 99.60%; LCMS, m/z 实测值 565.45 ($M+1$) $^+$.

[1109] N-(2-氟-4-(4-烟酰基哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (120ak):

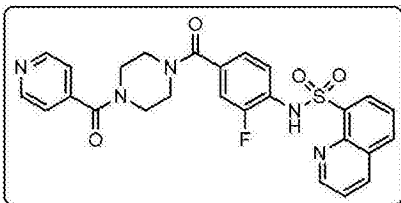
[1110]



[1111] ^1H NMR (400MHz, DMSO- d_6) δ : 3.2–3.8 (m, 8H), 7.0–7.2 (m, 2H), 7.4–7.6 (m, 3H), 8.0–8.4 (m, 3H), 8.7 (m, 3H), 8.9 (m, 1H), 9.1 (m, 1H); HPLC纯度: 94.6%; LCMS, m/z 实测值 520.25 ($M+1$) $^+$.

[1112] N-(2-氟-4-(4-异烟酰基哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (120a1):

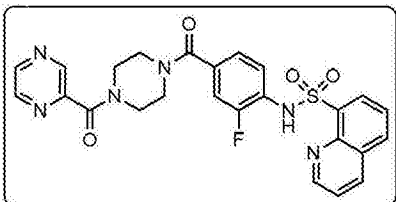
[1113]



[1114] ^1H NMR (400MHz, DMSO- d_6) δ : 3.2–3.8 (m, 8H), 7.0–7.2 (m, 2H), 7.4–7.6 (m, 3H), 8.0–8.4 (m, 3H), 8.7 (m, 3H), 8.9 (m, 1H), 9.1 (m, 1H), 10.5 (s, 1H); HPLC纯度: 93.8%; LCMS, m/z 实测值 518.46 ($M+1$) $^+$.

[1115] N-(2-氟-4-(4-(吡嗪-2-羰基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (120am):

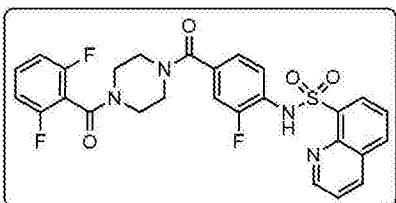
[1116]



[1117] ^1H NMR (400MHz, DMSO- d_6) δ : 3.2–3.8 (m, 8H), 7.0–7.4 (m, 3H), 7.6–7.8 (m, 2H), 8.0–8.4 (m, 2H), 8.7 (m, 3H), 9.1 (m, 1H), 10.0 (s, 1H); HPLC纯度: 99.8%; LCMS, m/z 实测值 521.24 ($M+1$) $^+$.

[1118] N-(4-(4-(2,6-二氟苯甲酰基)哌嗪-1-羰基)-2-氟苯基)喹啉-8-磺酰胺 (120an):

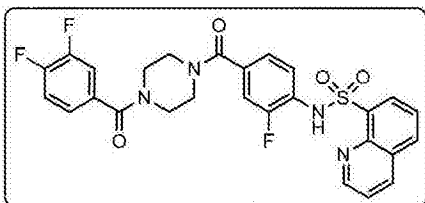
[1119]



[1120] ^1H NMR (400MHz, DMSO- d_6) δ : 3.2–3.8 (m, 8H), 7.0–7.4 (m, 3H), 7.6–7.8 (m, 5H), 8.0–8.4 (m, 3H), 9.1 (m, 1H), 10.0 (s, 1H); HPLC纯度: 99.8%; LCMS, m/z 实测值 555.21 ($M+1$) $^+$.

[1121] N-(4-(4-(3,4-二氟苯甲酰基)哌嗪-1-羰基)-2-氟苯基)喹啉-8-磺酰胺 (120ao):

[1122]

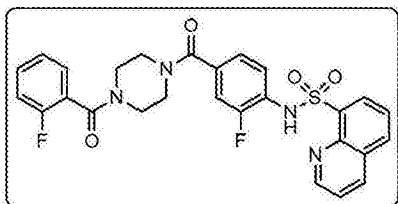


[1123] ^1H NMR (400MHz, DMSO- d_6) δ : 3.2–3.8 (m, 8H), 7.0–7.4 (m, 4H), 7.6–7.8 (m, 4H), 8.0–

8.4 (m, 2H), 8.7 (m, 1H), 9.1 (m, 1H), 10.0 (s, 1H); HPLC纯度: 97.9%; LCMS, m/z 实测值 555.14 (M+1)⁺.

[1124] N-(2-氟-4-(4-(2-氟苯甲酰基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (120ap): 108

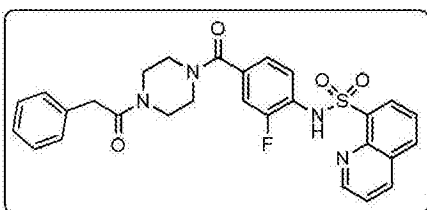
[1125]



[1126] ¹H NMR (400MHz, CDCl₃) δ: 3.2-3.8 (m, 8H), 7.0-7.2 (m, 3H), 7.2-7.4 (m, 4H), 7.6-7.8 (m, 2H), 8.0-8.4 (m, 2H), 8.9 (s, 1H), 9.1 (m, 1H); HPLC纯度: 97.8%; LCMS, m/z 实测值 537.21 (M+1)⁺.

[1127] N-(2-氟-4-(4-(2-苯基乙酰基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (120aq):

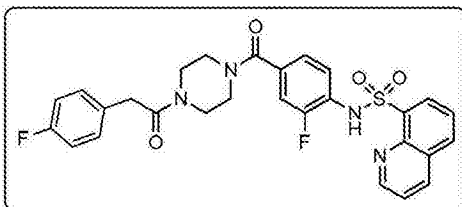
[1128]



[1129] ¹H NMR (400MHz, CDCl₃) δ: 2.4 (s, 2H), 7.0-7.2 (m, 3H), 7.2-7.4 (m, 4H), 7.6-7.8 (m, 4H), 8.0-8.4 (m, 2H), 9.1 (m, 1H); HPLC纯度: 98.4%; LCMS, m/z 实测值 533.26 (M+1)⁺.

[1130] N-(2-氟-4-(4-(2-(4-氟苯基)乙酰基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (120ar):

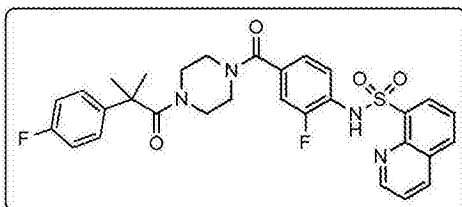
[1131]



[1132] ¹H NMR (400MHz, CD₃OD) δ: 3.2-3.8 (m, 8H), 3.9 (s, 2H), 7.0-7.2 (m, 4H), 7.2-7.4 (m, 2H), 7.6-7.8 (m, 3H), 8.2 (m, 1H), 8.4 (m, 2H), 9.1 (m, 1H); HPLC纯度: 93.1%; LCMS, m/z 实测值 551.23 (M+1)⁺.

[1133] N-(2-氟-4-(4-(2-(4-氟苯基)-2-甲基丙酰基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (120as):

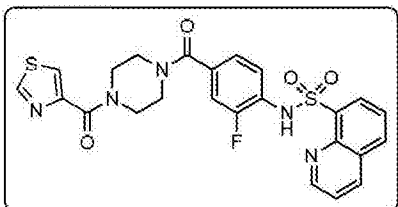
[1134]



[1135] ¹H NMR (400MHz, CDCl₃) δ: 1.3 (s, 6H), 3.2-3.8 (m, 8H), 7.0-7.2 (m, 3H), 7.2-7.4 (m, 2H), 7.6-7.8 (m, 3H), 8.2 (m, 1H), 8.4 (m, 2H), 8.9 (s, 1H), 9.1 (m, 1H); HPLC纯度: 98.3%; LCMS, m/z 实测值 579.22 (M+1)⁺.

[1136] N-(2-氟-4-(4-(噻唑-4-羰基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (120at):

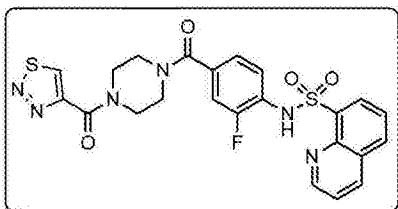
[1137]



[1138] ^1H NMR (400MHz, DMSO- d_6) δ : 3.2-3.8 (m, 8H), 7.0-7.2 (m, 3H), 7.2-7.4 (m, 2H), 7.6-7.8 (m, 3H), 8.2 (m, 1H), 8.9 (m, 2H), 9.0 (s, 1H), 9.5 (d, 1H); HPLC纯度: 91.6%; LCMS, m/z 实测值 526.19 ($M+1$) $^+$.

[1139] N-(4-(4-(1,2,3-噻二唑-4-羰基)哌嗪-1-羰基)-2-氟苯基)喹啉-8-磺酰胺 (120au):

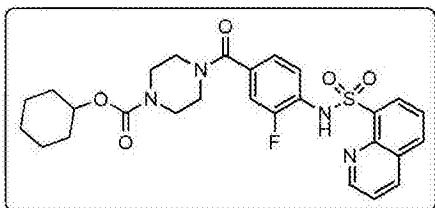
[1140]



[1141] ^1H NMR (400MHz, DMSO- d_6) δ : 3.2-3.8 (m, 8H), 7.0-7.2 (m, 3H), 7.6-7.8 (m, 2H), 8.2-8.4 (m, 3H), 9.0 (m, 1H), 9.5 (s, 1H); HPLC纯度: 91.6%; LCMS, m/z 实测值 526.19 ($M+1$) $^+$.

[1142] 4-(3-氟-4-(喹啉-8-亚磺酰氨基)苯甲酰基)哌嗪-1-羧酸环己酯 (120av):

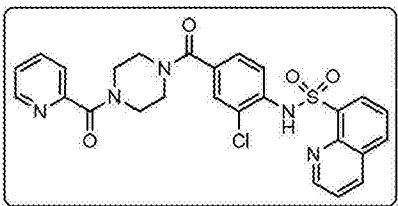
[1143]



[1144] ^1H NMR (400MHz, DMSO- d_6) δ : 1.2-1.8 (m, 10H), 3.2-3.8 (m, 8H), 4.8 (m, 1H), 7.0-7.2 (m, 2H), 7.6-7.8 (m, 3H), 8.2 (m, 1H), 8.2-8.4 (m, 2H), 8.9 (m, 1H), 9.0 (s, 1H), 9.5 (d, 1H); HPLC纯度: 91.6%; LCMS, m/z 实测值 526.19 ($M+1$) $^+$.

[1145] N-(2-氯-4-(4-吡啶甲酰基哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (120aw):

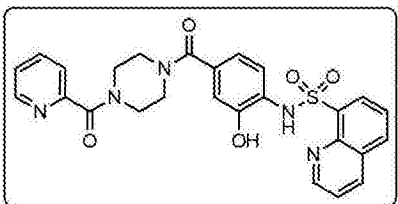
[1146]



[1147] ^1H NMR (400MHz, DMSO- d_6) δ : 3.2-3.8 (m, 8H), 7.0-7.2 (m, 2H), 7.6-7.8 (m, 3H), 8.2 (m, 3H), 8.2-8.4 (m, 2H), 8.9 (m, 1H), 9.0 (s, 1H), 10.5 (s, 1H); HPLC纯度: 99.1%; LCMS, m/z 实测值 537.1 ($M+1$) $^+$.

[1148] N-(2-羟基-4-(4-吡啶甲酰基哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (120ax):

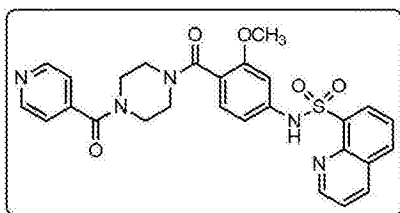
[1149]



[1150] ^1H NMR (400MHz, DMSO- d_6) δ : 3.2–3.8 (m, 8H), 4.8 (s, 1H), 7.0–7.2 (m, 2H), 7.6–7.8 (m, 3H), 8.2 (m, 3H), 8.2–8.4 (m, 2H), 8.9 (m, 1H), 9.0 (s, 1H), 10.5 (s, 1H); HPLC纯度: 98.1%; LCMS, m/z 实测值518.2 ($M+1$) $^+$.

[1151] N-(4-(4-异烟酰基哌嗪-1-羰基)-3-甲氧基苯基)喹啉-8-磺酰胺 (120ay):

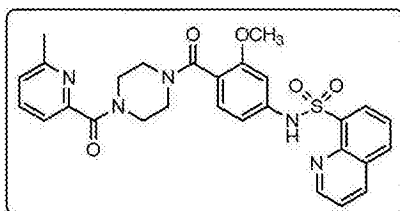
[1152]



[1153] ^1H NMR (400MHz, DMSO- d_6) δ : 3.2–3.8 (m, 8H), 6.4 (m, 1H), 7.0–7.2 (m, 2H), 7.6–7.8 (m, 2H), 8.0 (m, 1H), 8.2–8.4 (m, 3H), 8.8 (s, 1H), 8.9 (s, 1H), 9.0 (s, 1H); HPLC纯度: 95.0%; LCMS, m/z 实测值532.2 ($M+1$) $^+$.

[1154] N-(3-甲氧基-4-(4-(6-甲基吡啶甲酰基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (120az):

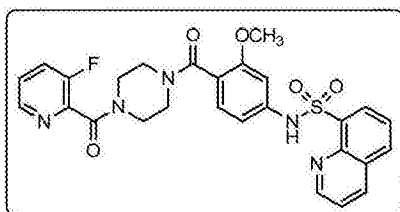
[1155]



[1156] ^1H NMR (400MHz, CD_3OD) δ : 2.2 (s, 3H), 3.2–3.8 (m, 8H), 3.9 (s, 3H), 6.7 (m, 3H), 7.2 (m, 2H), 7.6–7.8 (m, 3H), 8.0 (m, 1H), 8.2–8.4 (m, 2H), 9.0 (s, 1H); HPLC纯度: 98.8%; LCMS, m/z 实测值546.2 ($M+1$) $^+$.

[1157] N-(4-(4-(3-氟吡啶甲酰基)哌嗪-1-羰基)-3-甲氧基苯基)喹啉-8-磺酰胺 (120ba):

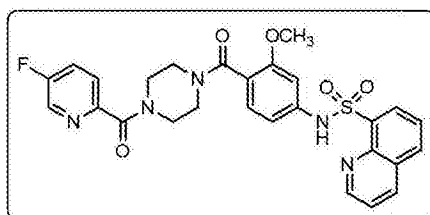
[1158]



[1159] ^1H NMR (400MHz, DMSO- d_6) δ : 3.2–3.8 (m, 8H), 3.9 (s, 3H), 6.7–7.0 (m, 3H), 7.2 (m, 2H), 7.6–7.8 (m, 3H), 8.1 (s, 1H), 8.4 (m, 2H), 9.0 (s, 1H); HPLC纯度: 98.8%; LCMS, m/z 实测值550.2 ($M+1$) $^+$.

[1160] N-(4-(4-(5-氟吡啶甲酰基)哌嗪-1-羰基)-3-甲氧基苯基)喹啉-8-磺酰胺 (120bb):

[1161]

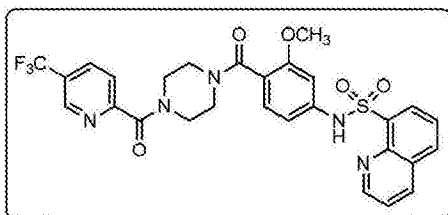


[1162] ^1H NMR (400MHz, CDCl_3) δ : 3.2–3.8 (m, 8H), 3.9 (s, 3H), 6.7–7.0 (m, 3H), 7.2 (m, 2H),

7.6–7.8 (m, 3H), 8.1 (s, 1H), 8.4 (m, 1H), 9.0 (s, 1H), 9.3 (s, 1H), 10.5 (s, 1H); HPLC纯度: 98.9%; LCMS, m/z 实测值 550.2 (M+1)⁺.

[1163] N-(3-甲氧基-4-(4-(5-(三氟甲基)吡啶甲酰基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (120bc):

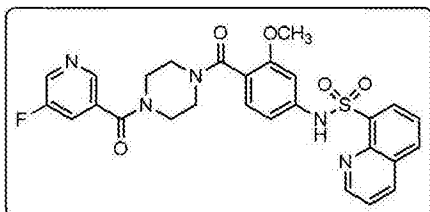
[1164]



[1165] ¹H NMR (400MHz, CDCl₃) δ: 3.2–3.8 (m, 8H), 3.9 (s, 3H), 6.6–6.9 (m, 3H), 7.2 (m, 2H), 7.6–7.8 (m, 3H), 8.2–8.4 (m, 2H), 8.9 (m, 1H), 9.0 (s, 1H); HPLC纯度: 99.2%; LCMS, m/z 实测值 600.3 (M+1)⁺.

[1166] N-(4-(4-(5-氟烟酰基)哌嗪-1-羰基)-3-甲氧基苯基)喹啉-8-磺酰胺 (120bd):

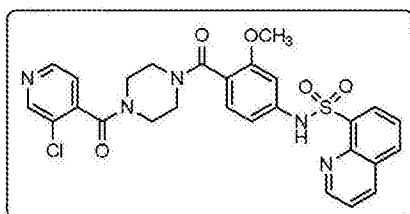
[1167]



[1168] ¹H NMR (400MHz, CDCl₃) δ: 3.2–3.8 (m, 8H), 3.9 (s, 3H), 6.4 (m, 1H), 7.0 (m, 2H), 7.6 (m, 3H), 8.0 (m, 1H), 8.2–8.6 (m, 4H), 9.1 (m, 1H); HPLC纯度: 99.5%; LCMS, m/z 实测值 550.3 (M+1)⁺.

[1169] N-(4-(4-(3-氯异烟酰基)哌嗪-1-羰基)-3-甲氧基苯基)喹啉-8-磺酰胺 (120be):

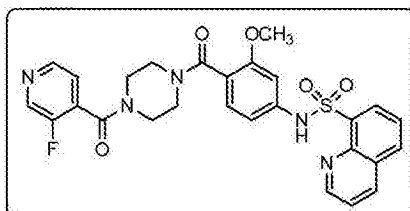
[1170]



[1171] ¹H NMR (400MHz, CDCl₃) δ: 3.2–3.8 (m, 8H), 3.9 (s, 3H), 6.4 (m, 1H), 7.0 (m, 2H), 7.6 (m, 3H), 8.0 (m, 1H), 8.2–8.4 (m, 2H), 8.6–8.8 (m, 2H), 9.1 (m, 1H); HPLC纯度: 98.2%; LCMS, m/z 实测值 566.25 (M+1)⁺.

[1172] N-(4-(4-(3-氟异烟酰基)哌嗪-1-羰基)-3-甲氧基苯基)喹啉-8-磺酰胺 (120bf):

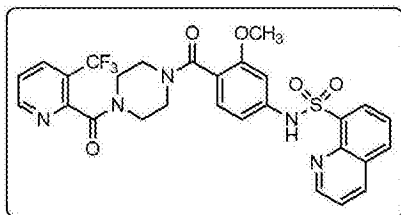
[1173]



[1174] ¹H NMR (400MHz, CDCl₃) δ: 3.2–3.8 (m, 8H), 3.9 (s, 3H), 6.4 (m, 1H), 7.0 (m, 2H), 7.6 (m, 3H), 8.0 (m, 1H), 8.2–8.4 (m, 2H), 8.6–8.8 (m, 2H), 9.1 (m, 1H); HPLC纯度: 98.9%; LCMS, m/z 实测值 550.35 (M+1)⁺.

[1175] N-(4-(4-(5-氯烟酰基)哌嗪-1-羰基)-3-甲氧基苯基)喹啉-8-磺酰胺 (120bg):

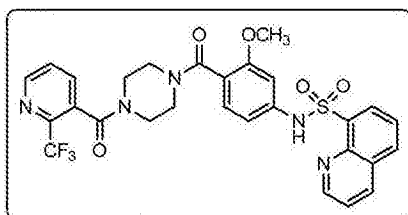
[1188]



[1189] ^1H NMR (400MHz, CDCl_3) δ : 3.2–3.8 (m, 8H), 3.9 (s, 3H), 6.4 (m, 1H), 7.0 (m, 2H), 7.6–7.8 (m, 3H), 8.0 (m, 1H), 8.2–8.4 (m, 2H), 8.8 (m, 1H), 9.1 (m, 1H); HPLC纯度: 92.08%; LCMS, m/z 实测值566.3 ($M+1$) $^+$.

[1190] N-(3-甲氧基-4-(4-(2-(三氟甲基)烟酰基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (120b1):

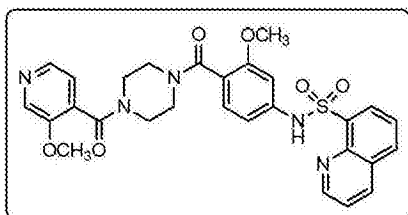
[1191]



[1192] ^1H NMR (400MHz, CDCl_3) δ : 3.2–3.8 (m, 8H), 3.9 (s, 3H), 6.4 (m, 1H), 7.0 (m, 2H), 7.6–7.8 (m, 4H), 8.0 (m, 1H), 8.2–8.4 (m, 2H), 8.8 (m, 1H), 9.1 (m, 1H); HPLC纯度: 96.5%; LCMS, m/z 实测值600.3 ($M+1$) $^+$.

[1193] N-(3-甲氧基-4-(4-(3-甲氧基异烟酰基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (120bm):

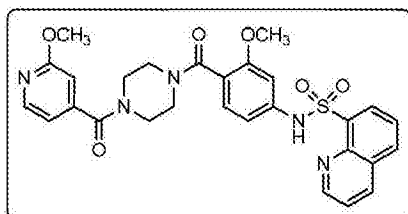
[1194]



[1195] ^1H NMR (400MHz, CDCl_3) δ : 3.2–3.8 (m, 8H), 3.9 (s, 3H), 6.4 (m, 1H), 7.0 (m, 3H), 7.6–7.8 (m, 3H), 8.0 (m, 1H), 8.2–8.4 (m, 2H), 8.8 (m, 1H), 9.1 (m, 1H); HPLC纯度: 93.2%; LCMS, m/z 实测值562.3 ($M+1$) $^+$.

[1196] N-(3-甲氧基-4-(4-(2-甲氧基异烟酰基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (120bn):

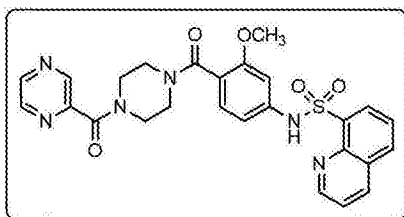
[1197]



[1198] ^1H NMR (400MHz, CDCl_3) δ : 3.2–3.8 (m, 8H), 3.9 (s, 3H), 6.4 (m, 1H), 7.0 (m, 3H), 7.6–7.8 (m, 2H), 8.0 (m, 1H), 8.2–8.4 (m, 3H), 8.8 (m, 1H), 9.1 (m, 1H); HPLC纯度: 98.5%; LCMS, m/z 实测值562.4 ($M+1$) $^+$.

[1199] N-(3-甲氧基-4-(4-(吡嗪-2-羰基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (120bo):

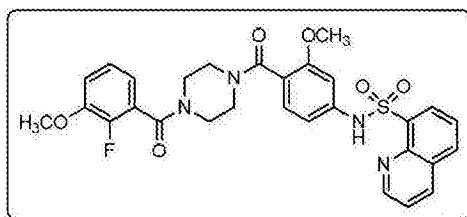
[1200]



[1201] ^1H NMR (400MHz, CDCl_3) δ : 3.2–3.8 (m, 8H), 3.9 (s, 3H), 6.4 (m, 1H), 7.0 (m, 2H), 7.6–7.8 (m, 2H), 8.0 (m, 1H), 8.2–8.4 (m, 4H), 9.1 (s, 1H), 9.2 (s, 1H); HPLC纯度: 98.9%; LCMS, m/z 实测值 533.1 ($M+1$) $^+$.

[1202] N-(4-(4-(2-氟-3-甲氧基苯甲酰基)哌嗪-1-羰基)-3-甲氧基苯基)喹啉-8-磺酰胺 (120bp):

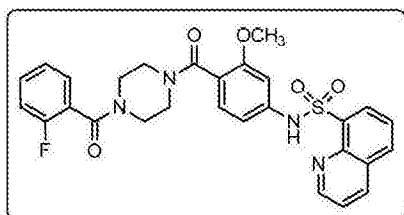
[1203]



[1204] ^1H NMR (400MHz, CDCl_3) δ : 3.2–3.8 (m, 8H), 3.9 (s, 3H), 4.0 (s, 3H), 6.4 (m, 1H), 7.0 (m, 3H), 7.2 (m, 2H), 7.6 (m, 2H), 8.0 (m, 1H), 8.4 (m, 2H), 9.1 (s, 1H); HPLC纯度: 99.3%; LCMS, m/z 实测值 579.2 ($M+1$) $^+$.

[1205] N-(4-(4-(2-氟苯甲酰基)哌嗪-1-羰基)-3-甲氧基苯基)喹啉-8-磺酰胺 (120bq):

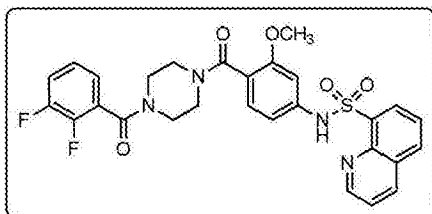
[1206]



[1207] ^1H NMR (400MHz, CDCl_3) δ : 3.2–3.8 (m, 8H), 3.9 (s, 3H), 6.4 (m, 1H), 7.2–7.4 (m, 6H), 8.8 (m, 1H), 8.0 (m, 3H), 8.6 (s, 1H), 9.1 (s, 1H); HPLC纯度: 99.5%; LCMS, m/z 实测值 549.2 ($M+1$) $^+$.

[1208] N-(4-(4-(2,3-二氟苯甲酰基)哌嗪-1-羰基)-3-甲氧基苯基)喹啉-8-磺酰胺 (120br):

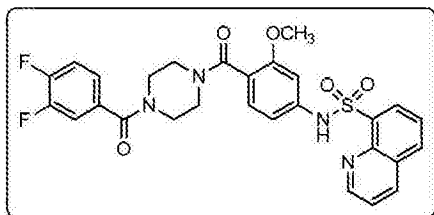
[1209]



[1210] ^1H NMR (400MHz, CDCl_3) δ : 3.2–3.8 (m, 8H), 3.9 (s, 3H), 6.4 (m, 1H), 7.0–7.4 (m, 5H), 7.6 (m, 2H), 8.0 (m, 1H), 8.4 (m, 2H), 8.6 (s, 1H), 9.1 (s, 1H); HPLC纯度: 96.1%; LCMS, m/z 实测值 567.1 ($M+1$) $^+$.

[1211] N-(4-(4-(3,4-二氟苯甲酰基)哌嗪-1-羰基)-3-甲氧基苯基)喹啉-8-磺酰胺 (120bs):

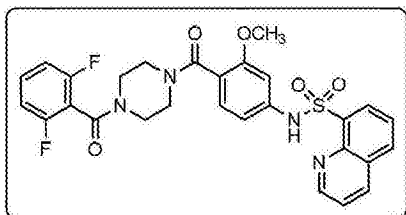
[1212]



[1213] ^1H NMR (400MHz, CDCl_3) δ : 3.2–3.8 (m, 8H), 3.9 (s, 3H), 6.4 (m, 1H), 7.0–7.4 (m, 5H), 7.6 (m, 2H), 8.0 (m, 1H), 8.4 (m, 2H), 8.6 (s, 1H), 9.1 (s, 1H); HPLC纯度: 98.9%; LCMS, m/z 实测值 567.1 ($M+1$) $^+$.

[1214] N-(4-(4-(2,6-二氟苯甲酰基)哌嗪-1-羰基)-3-甲氧基苯基)喹啉-8-磺酰胺 (120bt):

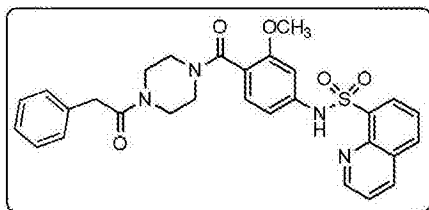
[1215]



[1216] ^1H NMR (400MHz, CDCl_3) δ : 3.2–3.8 (m, 8H), 3.9 (s, 3H), 6.4 (m, 1H), 7.0–7.4 (m, 4H), 7.6 (m, 3H), 8.0 (m, 1H), 8.4 (m, 2H), 9.1 (s, 1H); HPLC纯度: 98.4%; LCMS, m/z 实测值 567.0 ($M+1$) $^+$.

[1217] N-(3-甲氧基-4-(4-(2-苯基乙酰基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (120bu):

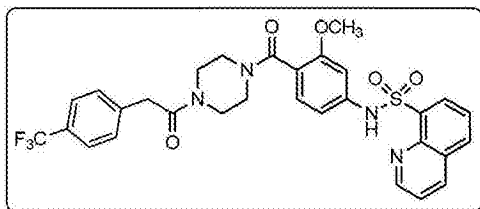
[1218]



[1219] ^1H NMR (400MHz, CDCl_3) δ : 3.2–3.8 (m, 8H), 3.9 (s, 3H), 6.4 (m, 1H), 7.0 (m, 2H), 7.2–7.4 (m, 5H), 7.6 (m, 2H), 8.0 (m, 1H), 8.4 (m, 2H), 9.1 (s, 1H); HPLC纯度: 99.7%; LCMS, m/z 实测值 545.2 ($M+1$) $^+$.

[1220] N-(3-甲氧基-4-(4-(2-(4-(三氟甲基)苯基)乙酰基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (120bv):

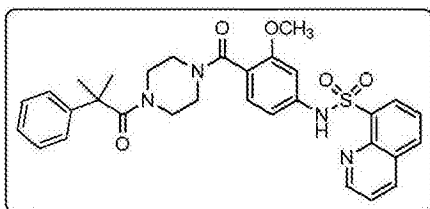
[1221]



[1222] ^1H NMR (400MHz, CDCl_3) δ : 3.2–3.8 (m, 8H), 3.9 (s, 3H), 6.4 (m, 1H), 7.0 (m, 3H), 7.2–7.4 (m, 2H), 7.6 (m, 3H), 8.0 (m, 1H), 8.4 (m, 2H), 8.6 (s, 1H), 9.1 (s, 1H); HPLC纯度: 99.1%; LCMS, m/z 实测值 613.1 ($M+1$) $^+$.

[1223] N-(3-甲氧基-4-(4-(2-甲基-2-苯基丙酰基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (120bw):

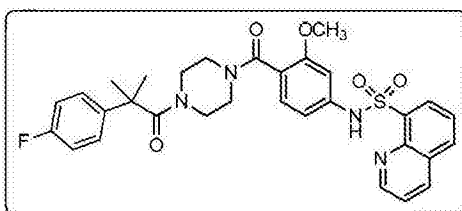
[1224]



[1225] ^1H NMR (400MHz, CDCl_3) δ : 3.2–3.8 (m, 8H), 3.9 (s, 3H), 6.4 (m, 1H), 6.9–7.0 (m, 2H), 7.2–7.4 (m, 4H), 7.6 (m, 2H), 8.0 (m, 1H), 8.4 (m, 2H), 8.6 (s, 1H), 9.1 (s, 1H); HPLC纯度: 95.3%; LCMS, m/z 实测值 573.45 ($M+1$) $^+$.

[1226] N-(4-(4-(2-(4-氟苯基)-2-甲基丙酰基)哌嗪-1-羰基)-3-甲氧基苯基)喹啉-8-磺酰胺 (120bx):

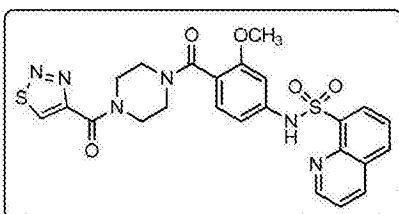
[1227]



[1228] ^1H NMR (400MHz, CDCl_3) δ : 3.2–3.8 (m, 8H), 3.9 (s, 3H), 6.4 (m, 1H), 6.9–7.2 (m, 5H), 7.6 (m, 2H), 8.0 (m, 1H), 8.4 (m, 2H), 8.6 (s, 1H), 9.1 (s, 1H); HPLC纯度: 99.1%; LCMS, m/z 实测值 591.3 ($M+1$) $^+$.

[1229] N-(4-(4-(1,2,3-噻二唑-4-羰基)哌嗪-1-羰基)-3-甲氧基苯基)喹啉-8-磺酰胺 (120by):

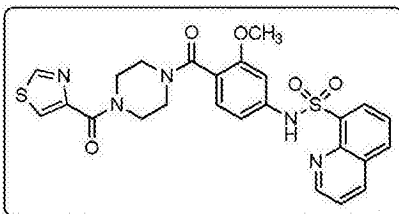
[1230]



[1231] ^1H NMR (400MHz, CDCl_3) δ : 3.2–3.8 (m, 8H), 3.9 (s, 3H), 6.4 (m, 1H), 6.9–7.2 (m, 2H), 7.6 (m, 2H), 8.0 (m, 1H), 8.4 (m, 2H), 8.6 (s, 1H), 9.1 (m, 1H); HPLC纯度: 99.0%; LCMS, m/z 实测值 539.3 ($M+1$) $^+$.

[1232] N-(3-甲氧基-4-(4-(噻唑-4-羰基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (120bz):

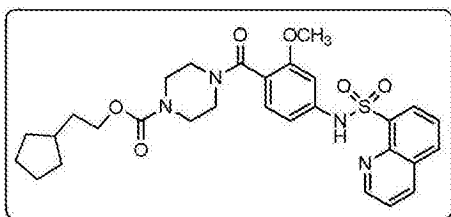
[1233]



[1234] ^1H NMR (400MHz, CDCl_3) δ : 3.2–3.8 (m, 8H), 3.9 (s, 3H), 6.4 (m, 1H), 6.9–7.2 (m, 2H), 7.6 (m, 2H), 8.0 (m, 1H), 8.4 (m, 1H), 8.6 (s, 1H), 8.8 (s, 1H), 9.1 (m, 1H); HPLC纯度: 99.6%; LCMS, m/z 实测值 538.3 ($M+1$) $^+$.

[1235] 4-(2-甲氧基-4-(喹啉-8-亚磺酰氨基)苯甲酰基)哌嗪-1-羧酸2-环戊基乙酯 (120ca):

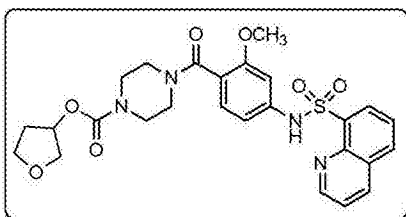
[1236]



[1237] ^1H NMR (400MHz, CDCl_3) δ : 1.2 (m, 4H), 1.6 (m, 8H), 3.2–3.8 (m, 8H), 3.9 (s, 3H), 4.7 (m, 1H), 6.4 (m, 1H), 6.9–7.2 (m, 2H), 7.6 (m, 2H), 8.0 (m, 1H), 8.4 (m, 1H), 8.6 (s, 1H), 8.8 (s, 1H), 9.1 (m, 1H); HPLC纯度: 99.8%; LCMS, m/z 实测值 567.1 ($M+1$) $^+$.

[1238] 4-(2-甲氧基-4-(喹啉-8-亚磺酰氨基)苯甲酰基)哌嗪-1-羧酸四氢呋喃-3-基酯 (120cb):

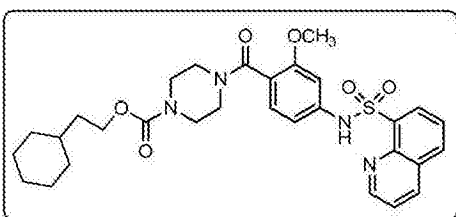
[1239]



[1240] ^1H NMR (400MHz, CDCl_3) δ : 2.0 (m, 2H), 2.2 (m, 1H), 3.0–3.6 (m, 4H), 3.2–3.8 (m, 8H), 3.9 (s, 3H), 5.2 (s, 1H), 6.4 (m, 1H), 6.9–7.2 (m, 2H), 7.6 (m, 2H), 8.0 (m, 1H), 8.4 (m, 1H), 8.6 (s, 1H), 8.8 (s, 1H), 9.1 (m, 1H); HPLC纯度: 96.2%; LCMS, m/z 实测值 541.05 ($M+1$) $^+$.

[1241] 4-(2-甲氧基-4-(喹啉-8-亚磺酰氨基)苯甲酰基)哌嗪-1-羧酸2-环己基乙酯 (120cc):

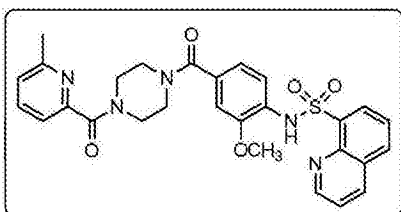
[1242]



[1243] ^1H NMR (400MHz, CDCl_3) δ : 1.2 (m, 10H), 1.6–1.8 (m, 4H), 3.2–3.8 (m, 8H), 3.9 (s, 3H), 4.7 (s, 1H), 6.4 (m, 1H), 6.9–7.0 (m, 2H), 7.6 (m, 2H), 8.0 (m, 1H), 8.2–8.4 (m, 2H), 8.6 (s, 1H), 9.1 (m, 1H); HPLC纯度: 97.7%; LCMS, m/z 实测值 581.4 ($M+1$) $^+$.

[1244] N-(2-甲氧基-4-(4-(6-甲基吡啶甲酰基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (120cd):

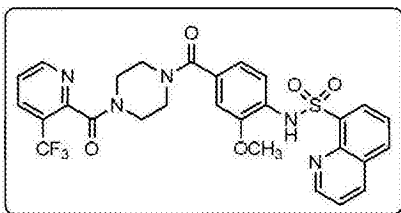
[1245]



[1246] ^1H NMR (400MHz, CDCl_3) δ : 2.1 (s, 3H), 3.2–3.8 (m, 8H), 3.9 (s, 3H), 6.7 (s, 1H), 6.9 (m, 1H), 7.2 (m, 1H), 7.4–7.8 (m, 5H), 8.0 (m, 1H), 8.2–8.4 (m, 2H), 8.8 (s, 1H), 9.1 (m, 1H); HPLC纯度: 99.6%; LCMS, m/z 实测值 546.3 ($M+1$) $^+$.

[1247] N-(2-甲氧基-4-(4-(3-(三氟甲基)吡啶甲酰基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (120ce):

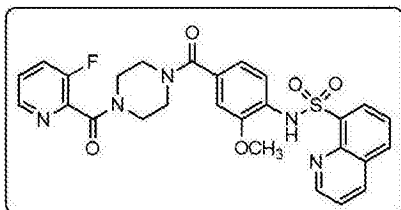
[1248]



[1249] ^1H NMR (400MHz, CDCl_3) δ : 3.2–3.8 (m, 8H), 3.9 (s, 3H), 6.7 (s, 1H), 6.9 (m, 1H), 7.4–7.7 (m, 4H), 8.0 (m, 2H), 8.2–8.4 (m, 2H), 8.8 (s, 1H), 9.1 (m, 1H); HPLC纯度: 99.9%; LCMS, m/z 实测值 600.3 ($M+1$) $^+$.

[1250] N-(4-(4-(3-氟吡啶甲酰基)哌嗪-1-羰基)-2-甲氧基苯基)喹啉-8-磺酰胺 (120cf):

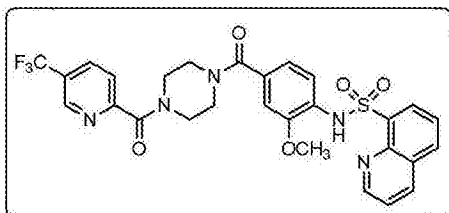
[1251]



[1252] ^1H NMR (400MHz, CDCl_3) δ : 3.2–3.8 (m, 8H), 3.9 (s, 3H), 6.9 (m, 2H), 7.4–7.7 (m, 5H), 8.0 (m, 2H), 8.2–8.4 (m, 2H), 8.8 (s, 1H), 9.1 (m, 1H); HPLC纯度: 99.8%; LCMS, m/z 实测值 550.3 ($M+1$) $^+$.

[1253] N-(2-甲氧基-4-(4-(5-(三氟甲基)吡啶甲酰基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (120cg):

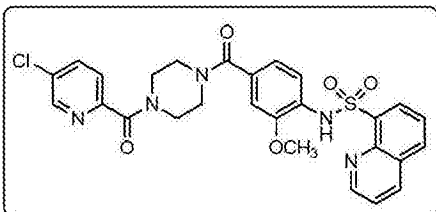
[1254]



[1255] ^1H NMR (400MHz, CDCl_3) δ : 3.2–3.8 (m, 8H), 3.9 (s, 3H), 6.9 (m, 2H), 7.6–7.8 (m, 4H), 8.0 (m, 2H), 8.2–8.4 (m, 2H), 8.8 (s, 1H), 8.9 (m, 1H), 9.1 (m, 1H); HPLC纯度: 99.6%; LCMS, m/z 实测值 600.3 ($M+1$) $^+$.

[1256] N-(4-(4-(5-氯吡啶甲酰基)哌嗪-1-羰基)-2-甲氧基苯基)喹啉-8-磺酰胺 (120ch):

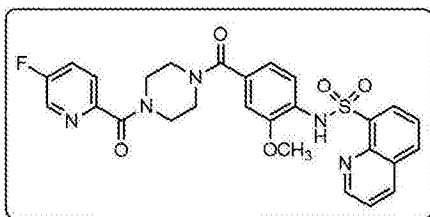
[1257]



[1258] ^1H NMR (400MHz, CDCl_3) δ : 3.2–3.8 (m, 8H), 3.9 (s, 3H), 6.9 (m, 2H), 7.6–7.8 (m, 5H), 8.0 (m, 1H), 8.2–8.4 (m, 2H), 8.8 (s, 1H), 8.9 (m, 1H), 9.1 (m, 1H); HPLC纯度: 99.3%; LCMS, m/z 实测值 566.3 ($M+1$) $^+$.

[1259] N-(4-(4-(5-氟吡啶甲酰基)哌嗪-1-羰基)-2-甲氧基苯基)喹啉-8-磺酰胺 (120ci):

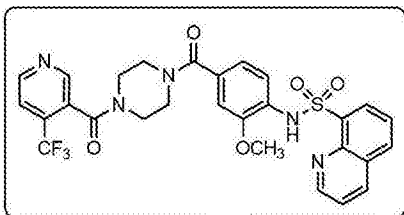
[1260]



[1261] ^1H NMR (400MHz, CDCl_3) δ : 3.2–3.8 (m, 8H), 3.9 (s, 3H), 6.9 (m, 2H), 7.6–7.8 (m, 5H), 8.0 (m, 1H), 8.2–8.4 (m, 3H), 8.8 (s, 1H), 9.1 (m, 1H); HPLC纯度: 99.4%; LCMS, m/z 实测值 550.3 ($M+1$) $^+$.

[1262] N-(2-甲氧基-4-(4-(4-(三氟甲基)烟酰基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (120cj):

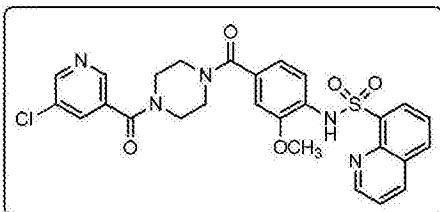
[1263]



[1264] ^1H NMR (400MHz, CDCl_3) δ : 3.2–3.8 (m, 8H), 3.9 (s, 3H), 6.9 (m, 2H), 7.6–7.8 (m, 4H), 8.2–8.4 (m, 2H), 8.6 (s, 1H), 8.8 (m, 2H), 9.1 (m, 1H); HPLC纯度: 99.9%; LCMS, m/z 实测值 600.3 ($M+1$) $^+$.

[1265] N-(4-(4-(5-氯烟酰基)哌嗪-1-羰基)-2-甲氧基苯基)喹啉-8-磺酰胺 (120ck):

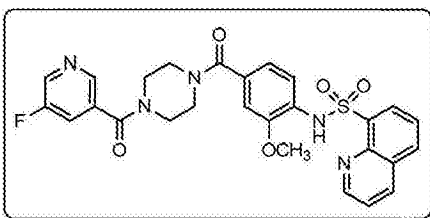
[1266]



[1267] ^1H NMR (400MHz, CDCl_3) δ : 3.2–3.8 (m, 8H), 3.9 (s, 3H), 6.9 (m, 2H), 7.6–7.8 (m, 4H), 8.0 (m, 1H), 8.4–8.6 (m, 2H), 8.7 (s, 1H), 8.8 (s, 1H), 9.1 (m, 1H); HPLC纯度: 95.7%; LCMS, m/z 实测值 566.3 ($M+1$) $^+$.

[1268] N-(4-(4-(5-氟烟酰基)哌嗪-1-羰基)-2-甲氧基苯基)喹啉-8-磺酰胺 (120cl):

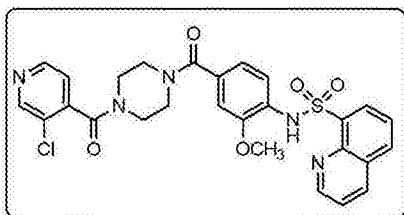
[1269]



[1270] ^1H NMR (400MHz, CDCl_3) δ : 3.2–3.8 (m, 8H), 3.9 (s, 3H), 6.9 (m, 2H), 7.6–7.8 (m, 4H), 8.0 (m, 1H), 8.4–8.6 (m, 2H), 8.7 (s, 1H), 8.8 (s, 1H), 9.1 (m, 1H); HPLC纯度: 89.4%; LCMS, m/z 实测值 550.3 ($M+1$) $^+$.

[1271] N-(4-(4-(3-氯异烟酰基)哌嗪-1-羰基)-2-甲氧基苯基)喹啉-8-磺酰胺 (120cm):

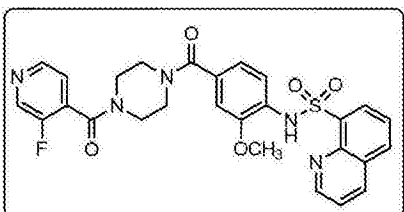
[1272]



[1273] ^1H NMR (400MHz, CDCl_3) δ : 3.2–3.8 (m, 8H), 3.9 (s, 3H), 6.9 (m, 2H), 7.6–7.8 (m, 3H), 8.0 (m, 1H), 8.4–8.6 (m, 4H), 8.9 (s, 1H), 9.1 (m, 1H); HPLC纯度: 98.5%; LCMS, m/z 实测值 566.3 ($M+1$) $^+$.

[1274] N-(4-(4-(3-氟异烟酰基)哌嗪-1-羰基)-2-甲氧基苯基)喹啉-8-磺酰胺 (120cn):

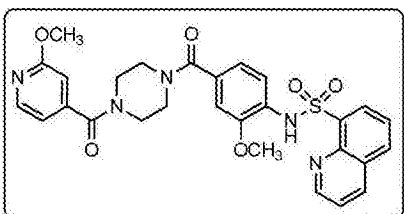
[1275]



[1276] ^1H NMR (400MHz, CDCl_3) δ : 3.2–3.8 (m, 8H), 3.9 (s, 3H), 6.9 (m, 2H), 7.6–7.8 (m, 4H), 8.0 (m, 1H), 8.4–8.6 (m, 3H), 8.9 (s, 1H), 9.1 (m, 1H); HPLC纯度: 94.9%; LCMS, m/z 实测值 550.3 ($M+1$) $^+$.

[1277] N-(2-甲氧基-4-(4-(2-甲氧基异烟酰基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (120co):

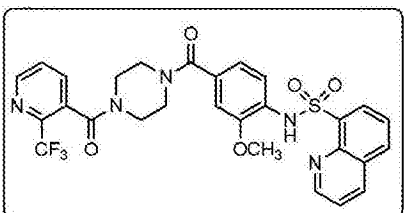
[1278]



[1279] ^1H NMR (400MHz, CDCl_3) δ : 3.2–3.8 (m, 8H), 3.8 (s, 3H), 3.9 (s, 3H), 6.6–6.9 (m, 4H), 7.6–7.8 (m, 3H), 8.0 (m, 1H), 8.2–8.4 (m, 3H), 8.9 (s, 1H), 9.1 (m, 1H); HPLC纯度: 97.3%; LCMS, m/z 实测值 562.3 ($M+1$) $^+$.

[1280] N-(2-甲氧基-4-(4-(2-(三氟甲基)烟酰基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (120cp):

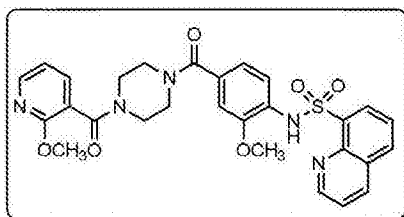
[1281]



[1282] ^1H NMR (400MHz, CDCl_3) δ : 3.2–3.8 (m, 8H), 3.9 (s, 3H), 6.6 (s, 1H), 6.9 (m, 1H), 7.6–7.8 (m, 5H), 8.0 (m, 1H), 8.2–8.4 (m, 2H), 8.9 (s, 1H), 9.1 (m, 1H); HPLC纯度: 99.7%; LCMS, m/z 实测值 600.3 ($M+1$) $^+$.

[1283] N-(2-甲氧基-4-(4-(2-甲氧基烟酰基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (120cq):

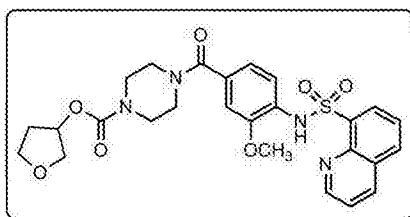
[1284]



[1285] ^1H NMR (400MHz, CDCl_3) δ : 3.2–3.8 (m, 8H), 3.8 (s, 3H), 3.9 (s, 3H), 6.6 (s, 1H), 6.9 (m, 1H), 7.6–7.8 (m, 4H), 8.0 (m, 1H), 8.2–8.4 (m, 3H), 8.9 (s, 1H), 9.1 (m, 1H); HPLC纯度: 99.8%; LCMS, m/z 实测值562.4 ($M+1$) $^+$.

[1286] 4-(3-甲氧基-4-(喹啉-8-亚磺酰氨基)苯甲酰基)哌嗪-1-羧酸四氢呋喃-3-基酯 (120cr):

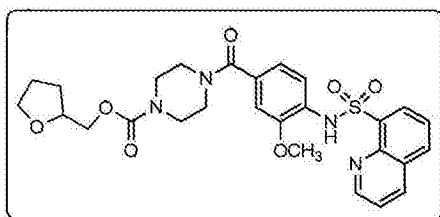
[1287]



[1288] ^1H NMR (400MHz, CDCl_3) δ : 2.2 (m, 2H), 3.2–3.8 (m, 8H), 3.9 (s, 3H), 4.0 (m, 2H), 5.0 (m, 1H), 6.9 (m, 2H), 7.6–7.8 (m, 3H), 8.0 (m, 1H), 8.2–8.4 (m, 2H), 9.1 (m, 1H); HPLC纯度: 98.1%; LCMS, m/z 实测值541.0 ($M+1$) $^+$.

[1289] 4-(3-甲氧基-4-(喹啉-8-亚磺酰氨基)苯甲酰基)哌嗪-1-羧酸(四氢呋喃-2-基)甲酯 (120cs):

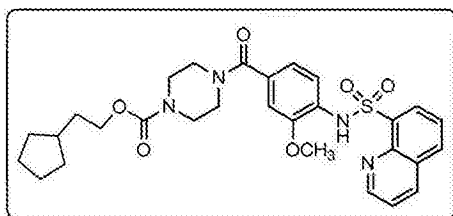
[1290]



[1291] ^1H NMR (400MHz, CDCl_3) δ : 1.2 (m, 2H), 1.2 (m, 2H), 1.6 (m, 1H), 2.0 (m, 2H), 3.2–3.8 (m, 8H), 3.9 (s, 3H), 4.0 (m, 2H), 6.9–7.0 (m, 2H), 7.6–7.8 (m, 3H), 8.0 (m, 1H), 8.2–8.4 (m, 2H), 9.1 (m, 1H); HPLC纯度: 99.0%; LCMS, m/z 实测值555.1 ($M+1$) $^+$.

[1292] 4-(3-甲氧基-4-(喹啉-8-亚磺酰氨基)苯甲酰基)哌嗪-1-羧酸2-环戊基乙酯 (120ct):

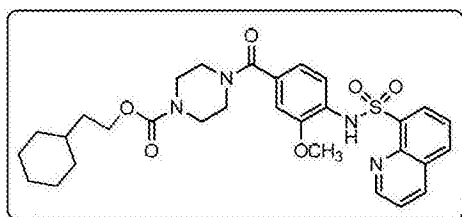
[1293]



[1294] ^1H NMR (400MHz, CDCl_3) δ : 1.2 (m, 6H), 1.6 (m, 12H), 2.0 (m, 2H), 3.2–3.8 (m, 8H), 3.9 (s, 3H), 4.0 (m, 2H), 6.9–7.0 (m, 2H), 7.6–7.8 (m, 3H), 8.0 (m, 1H), 8.2–8.4 (m, 2H), 9.1 (m, 1H); HPLC纯度: 99.0%; LCMS, m/z 实测值589.1 ($M+1$) $^+$.

[1295] 4-(3-甲氧基-4-(喹啉-8-亚磺酰氨基)苯甲酰基)哌嗪-1-羧酸2-环己基乙酯 (120cu):

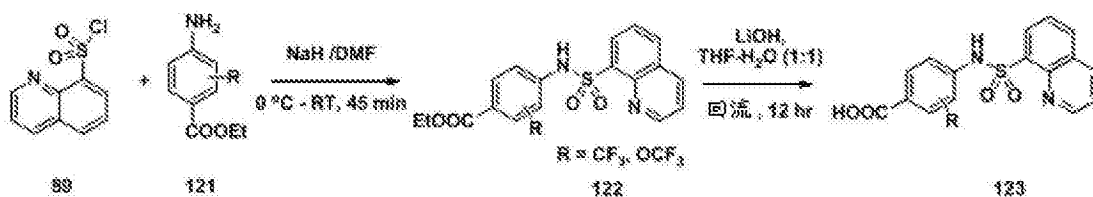
[1296]



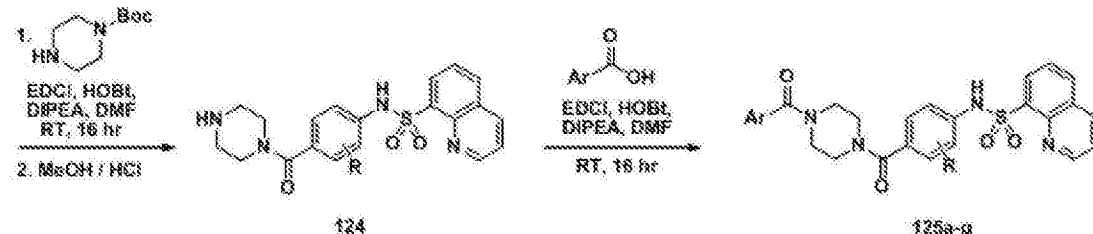
[1297] ^1H NMR (400MHz, CDCl_3) δ : 1.0 (m, 2H), 1.2 (m, 6H), 1.6 (m, 6H), 3.2-3.8 (m, 8H), 3.9 (s, 3H), 4.6 (m, 1H), 6.9-7.0 (m, 2H), 7.6-7.8 (m, 3H), 8.0 (m, 1H), 8.2-8.4 (m, 2H), 9.1 (m, 1H); HPLC纯度: 98.3%; LCMS, m/z 实测值 581.4 ($M+1$) $^+$.

[1298] 具有3-三氟甲基或3-三氟甲氧基取代的苯基环的哌嗪衍生物的合成

[1299] 流程18



[1300]



[1301] 合成磺酰胺122的一般程序:于0℃、在氮气气氛下向胺121 (30.3mmol) 在DMF (20ml pergm) 中的搅拌溶液分批加入氢化钠 (90.9mmol), 在RT搅拌10min。然后于0℃将喹啉-8-磺酰氯89 (8.94gm, 39.4mmol) 加至反应混合物。将所得混合物在RT再搅拌16h。反应结束后, 在减压下除去大部分溶剂。将残余物用冰水-EtOAc混合物稀释, 用 NaH_2PO_4 饱和溶液将pH升至7.0。然后将产物萃取于EtOAc中, 用水和盐水洗涤, 经硫酸钠干燥, 在减压下除去溶剂。所得粗产物 (80%) 不需进一步纯化即可用于下一步骤。

[1302] 合成水解产物123的一般程序:于RT、在氮气气氛下向磺酰胺122 (22.4mmol) 在THF:H₂O (1:1) 中的搅拌溶液加入固体LiOH (9.4gm, 224mmol)。然后将溶液回流6h。反应结束后, 将反应混合物用乙酸乙酯洗涤 (2×100ml), 除去非极性杂质。用柠檬酸溶液酸化水层 (pH 4)。将所得沉淀滤去, 空气干燥。通过与甲苯共蒸馏除去痕量水。所得灰白色固体 (80%) 不需进一步纯化即可用于下一步骤。

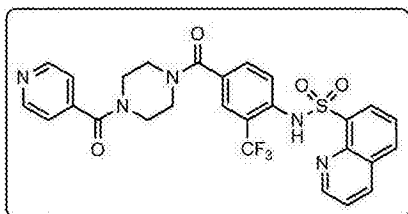
[1303] 合成磺酰胺124的一般程序:将EDCI (3.8g, 19.8mmol) 和HOBT (2.67g, 19.8mmol) 加至酸123 (19.8mmol) 在无水DMF中的搅拌溶液。将混合物的温度降至0℃, 此时在氮气气氛下加入DIPEA (11ml, 59.45mmol), 将所得溶液 (或悬浮液) 在室温搅拌30min。然后于0℃加入Boc-哌嗪 (3.68g, 19.8mmol)。然后将反应混合物升至室温, 搅拌过夜。反应结束后, 将反应混合物用水稀释, 用乙酸乙酯萃取 (3×70ml)。将有机层用水洗涤 (3×50ml), 经无水硫酸钠干燥, 过滤, 经旋转蒸发仪浓缩, 得到粗产物。通过柱色谱法 (60-120硅胶, 2% MeOH-DCM) 纯化粗产物, 得到为灰白色固体状的纯产物Boc-125 (8.0g, 82%), 将其于RT用甲醇HCl (100ml) 处理2h。Boc-基团完全断裂后, 在低压下除去溶剂, 得到为HCl盐的纯产物。用乙醚

洗涤盐的水溶液,用 NaHCO_3 (pH 10) 碱化。然后将所需产物分配至乙酸乙酯中,用无水 Na_2SO_4 干燥,在低压下除去溶剂,得到为灰白色固体状的游离胺125 (6.0g, 95%)。

[1304] 合成酰胺125a-g的一般程序:将EDCI (48mg, 0.2525mmol) 和HOBt (34mg, 0.2525mmol) 加至Ar-COOH (0.2525mmol) 在无水DMF中的搅拌溶液。将混合物的温度降至0℃,此时在氮气气氛下加入DIPEA (139μl, 0.7575mmol), 将所得溶液(或悬浮液)在室温搅拌30min。然后于0℃加入胺124 (100mg, 0.2525mmol)。然后将反应混合物升至室温,搅拌过夜。反应结束后,将反应混合物用水稀释,用乙酸乙酯萃取(3×15ml)。将有机层用水洗涤(3×10ml),经无水硫酸钠干燥,过滤,经旋转蒸发仪浓缩,得到粗产物。通过柱色谱法或制备型HPLC纯化粗产物,获得收率为52-70%的纯产物。

[1305] N-(4-(4-异烟酰基哌嗪-1-羰基)-2-(三氟甲基)苯基)喹啉-8-磺酰胺 (125a):

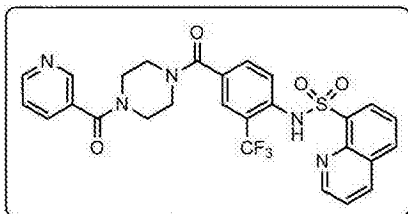
[1306]



[1307] ^1H NMR (400MHz, CDCl_3) δ : 3.2-3.8 (m, 8H), 7.2 (m, 2H), 7.4-7.7 (m, 4H), 8.0 (m, 2H), 8.4-8.8 (m, 4H), 9.1 (m, 1H); HPLC纯度: 99.0%; LCMS, m/z 实测值 570.1 ($\text{M}+1$) $^+$.

[1308] N-(4-(4-烟酰基哌嗪-1-羰基)-2-(三氟甲基)苯基)喹啉-8-磺酰胺 (125b):

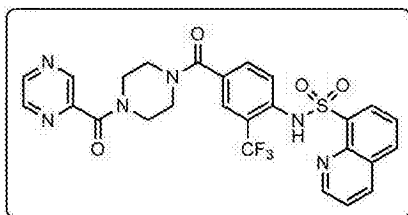
[1309]



[1310] ^1H NMR (400MHz, CDCl_3) δ : 3.2-3.8 (m, 8H), 7.2 (m, 2H), 7.4-7.9 (m, 5H), 8.0-8.4 (m, 2H), 8.4-8.8 (m, 3H), 9.1 (m, 1H); HPLC纯度: 98.4%; LCMS, m/z 实测值 570.1 ($\text{M}+1$) $^+$.

[1311] N-(4-(4-(吡嗪-2-羰基)哌嗪-1-羰基)-2-(三氟甲基)苯基)喹啉-8-磺酰胺 (125c):

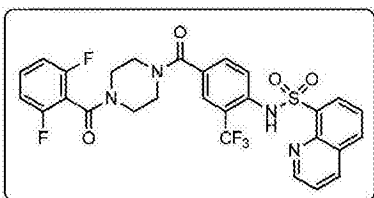
[1312]



[1313] ^1H NMR (400MHz, CDCl_3) δ : 3.2-3.8 (m, 8H), 7.4-7.9 (m, 5H), 8.0-8.4 (m, 2H), 8.4-8.8 (m, 3H), 9.1 (m, 2H); HPLC纯度: 90.0%; LCMS, m/z 实测值 571.1 ($\text{M}+1$) $^+$.

[1314] N-(4-(4-(2,6-二氟苯甲酰基)哌嗪-1-羰基)-2-(三氟甲基)苯基)喹啉-8-磺酰胺 (125d):

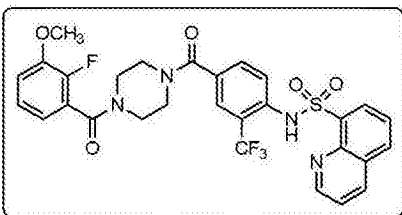
[1315]



[1316] ^1H NMR (400MHz, CDCl_3) δ : 3.2–3.8 (m, 8H), 7.0 (m, 1H), 7.2–7.9 (m, 6H), 8.2–8.8 (m, 3H), 9.1 (m, 2H); HPLC纯度: 90.0%; LCMS, m/z 实测值 571.1 ($\text{M}+1$) $^+$.

[1317] N-(4-(4-(2-氟-3-甲氧基苯甲酰基)哌嗪-1-羰基)-2-(三氟甲基)苯基)喹啉-8-磺酰胺 (125e):

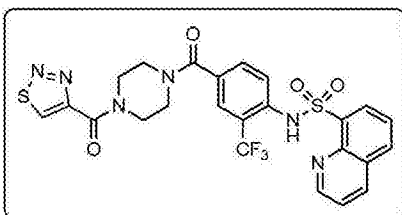
[1318]



[1319] ^1H NMR (400MHz, CDCl_3) δ : 3.2–3.8 (m, 8H), 3.9 (s, 3H), 6.9–7.2 (m, 2H), 7.4–7.9 (m, 5H), 8.0–8.6 (m, 3H), 9.1 (m, 2H); HPLC纯度: 99.0%; LCMS, m/z 实测值 617.1 ($\text{M}+1$) $^+$.

[1320] N-(4-(4-(1,2,3-噻二唑-4-羰基)哌嗪-1-羰基)-2-(三氟甲基)苯基)喹啉-8-磺酰胺 (125f):

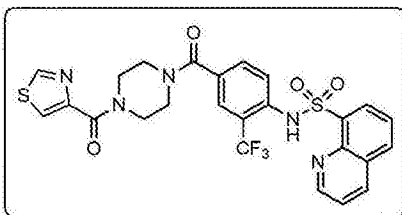
[1321]



[1322] ^1H NMR (400MHz, CDCl_3) δ : 3.2–3.8 (m, 8H), 7.4–7.9 (m, 4H), 8.1–8.6 (m, 3H), 9.0 (m, 2H), 9.2 (s, 1H); HPLC纯度: 99.0%; LCMS, m/z 实测值 557.1 ($\text{M}+1$) $^+$.

[1323] N-(4-(4-(噻唑-4-羰基)哌嗪-1-羰基)-2-(三氟甲基)苯基)喹啉-8-磺酰胺 (125g):

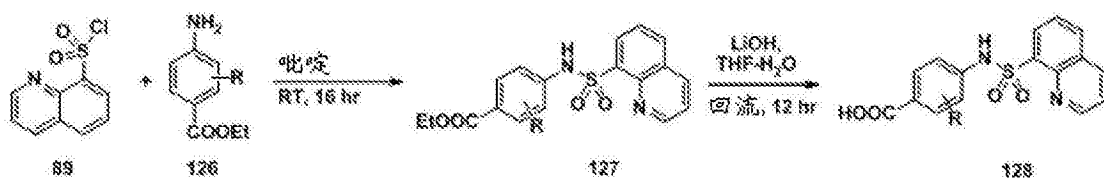
[1324]



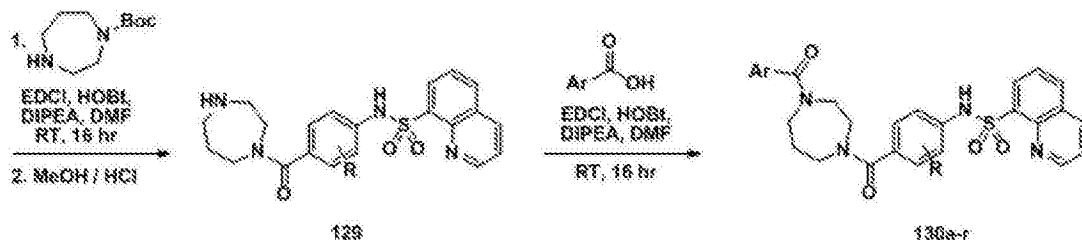
[1325] ^1H NMR (400MHz, CDCl_3) δ : 3.2–3.8 (m, 8H), 7.4–7.9 (m, 3H), 8.1–8.6 (m, 4H), 8.8 (s, 1H), 9.0 (m, 1H); HPLC纯度: 99.3%; LCMS, m/z 实测值 576.1 ($\text{M}+1$) $^+$.

[1326] 合成高哌嗪化合物

[1327] 流程19



[1328]



[1329] 合成磺酰胺127的一般程序:于0℃、在氮气气氛下向胺126 (30.3mmol) 的搅拌溶液加入吡啶 (50ml), 搅拌10min。然后在相同温度下将喹啉-8-磺酰氯89 (8.94gm, 39.4mmol) 加至反应混合物。将所得混合物在RT搅拌16h。反应结束后, 在减压下除去溶剂。通过与甲苯共馏除去痕量的吡啶。将乙醚加至所得残余物中, 滤出固体产物, 空气干燥。所得粗产物 (8.0gm, 74%) 不需进一步纯化即可用于下一步骤。

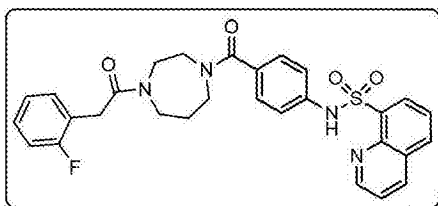
[1330] 合成酸128的一般程序:于RT、在氮气气氛下向磺酰胺127 (22.4mmol) 在THF:H₂O (1:1) 中的溶液加入固体LiOH (9.4gm, 224mmol)。然后将溶液回流6h。反应结束后, 将反应混合物用乙酸乙酯洗涤 (2×100ml), 除去非极性杂质。用柠檬酸溶液酸化水层 (pH 4)。将所得沉淀滤去, 空气干燥。通过与甲苯共蒸馏除去痕量水。所得灰白色固体 (80%) 不需进一步纯化即可用于下一步骤。

[1331] 合成胺129的一般程序:将EDCI (3.8g, 19.8mmol) 和HOBT (2.67g, 19.8mmol) 加至酸128 (19.8mmol) 在无水DMF中的搅拌溶液。将混合物的温度降至0℃, 此时在氮气气氛下加入DIPEA (11ml, 59.45mmol), 将所得溶液 (或悬浮液) 在室温搅拌30min。然后于0℃加入Boc-哌嗪 (3.68g, 19.8mmol)。然后将反应混合物升至室温, 搅拌过夜。反应结束后, 将反应混合物用水稀释, 用乙酸乙酯萃取 (3×70ml)。将有机层用水洗涤 (3×50ml), 经无水硫酸钠干燥, 过滤, 经旋转蒸发仪浓缩, 得到粗产物。通过柱色谱法 (60-120硅胶, 2% MeOH-DCM) 纯化粗产物, 得到为灰白色固体状的纯产物Boc-129 (85%), 将其于RT用甲醇HCl (100ml) 处理2h。Boc-基团完全断裂后, 在低压下除去溶剂, 得到纯产物为灰白色固体状的Boc-115 (8.0g, 82%), 将其于RT用甲醇HCl (100ml) 处理2h。Boc-基团完全断裂后, 在低压下除去溶剂, 得到为HCl盐的纯产物。用乙醚洗涤盐的水溶液, 用NaHCO₃ (pH 10) 碱化。然后将所需产物分配至乙酸乙酯中, 用无水Na₂SO₄干燥, 在低压下除去溶剂, 得到为灰白色固体状的游离胺129 (92%)。

[1332] 合成酰胺130a-r的一般程序:将EDCI (48mg, 0.2525mmol) 和HOBT (34mg, 0.2525mmol) 加至Ar-COOH (0.2525mmol) 在无水DMF中的搅拌溶液。将混合物的温度降至0℃, 此时在氮气气氛下加入DIPEA (139μl, 0.7575mmol), 将所得溶液 (或悬浮液) 在室温搅拌30min。然后于0℃加入胺129 (0.2525mmol)。然后将反应混合物升至室温, 搅拌过夜。反应结束后, 将反应混合物用水稀释, 用乙酸乙酯萃取 (3×15ml)。将有机层用水洗涤 (3×10ml), 经无水硫酸钠干燥, 过滤, 经旋转蒸发仪浓缩, 得到粗产物。通过柱色谱法或制备型HPLC纯化粗产物, 获得收率为54-72%的纯产物。

[1333] N-(4-(4-(2-(2-氟苯基)乙酰基)-1,4-二氮杂环庚烷-1-羰基)苯基)喹啉-8-磺酰胺 (130a):

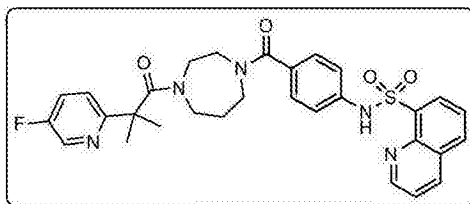
[1334]



[1335] ^1H NMR (400MHz, DMSO-d_6) δ : 3.0–3.8 (m, 10H), 7.0–7.4 (m, 8H), 7.5–7.8 (m, 2H), 8.0–8.4 (m, 3H), 9.1 (m, 1H); HPLC纯度: 98.1%; LCMS, m/z 实测值 547.4 ($\text{M}+1$) $^+$.

[1336] N-(4-(4-(2-(5-氟吡啶-2-基)-2-甲基丙酰基)-1,4-二氮杂环庚烷-1-羰基)苯基)喹啉-8-磺酰胺 (130b):

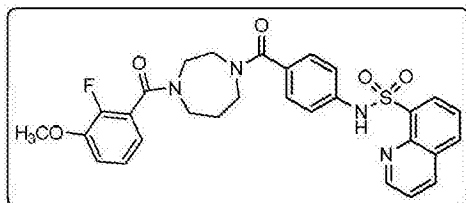
[1337]



[1338] ^1H NMR (400MHz, DMSO-d_6) δ : 1.4 (s, 6H), 3.0–3.8 (m, 10H), 7.0–7.2 (m, 6H), 7.6–7.8 (m, 2H), 8.0–8.4 (m, 3H), 9.1 (m, 1H); HPLC纯度: 98.6%; LCMS, m/z 实测值 575.4 ($\text{M}+1$) $^+$.

[1339] N-(4-(4-(2-氟-3-甲氧基苯甲酰基)-1,4-二氮杂环庚烷-1-羰基)苯基)喹啉-8-磺酰胺 (130c):

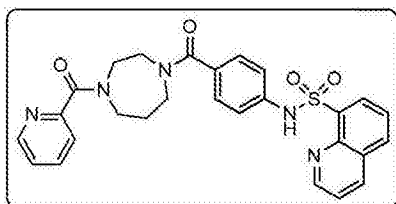
[1340]



[1341] ^1H NMR (400MHz, DMSO-d_6) δ : 3.0–3.8 (m, 10H), 3.9 (s, 3H), 6.9–7.2 (m, 7H), 7.6–7.8 (m, 2H), 8.2–8.4 (m, 3H), 9.1 (m, 1H); HPLC纯度: 98.2%; LCMS, m/z 实测值 561.5 ($\text{M}+1$) $^+$.

[1342] N-(4-(4-吡啶甲酰基)-1,4-二氮杂环庚烷-1-羰基)苯基)喹啉-8-磺酰胺 (130d):

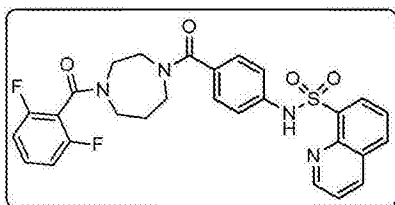
[1343]



[1344] ^1H NMR (400MHz, DMSO-d_6) δ : 1.4–1.6 (m, 2H), 3.0–3.8 (m, 8H), 7.0–8.0 (m, 8H), 8.2–8.4 (m, 5H), 9.1 (m, 1H); HPLC纯度: 99.4%; LCMS, m/z 实测值 516.0 ($\text{M}+1$) $^+$.

[1345] N-(4-(4-(2,6-二氟苯甲酰基)-1,4-二氮杂环庚烷-1-羰基)苯基)喹啉-8-磺酰胺 (130e):

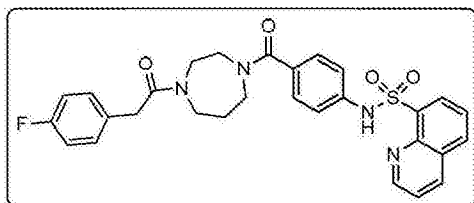
[1346]



[1347] ^1H NMR (400MHz, DMSO-d₆) δ : 1.4–1.6 (m, 2H), 3.0–3.8 (m, 8H), 7.0–8.0 (m, 8H), 8.2–8.4 (m, 4H), 9.1 (m, 1H); HPLC纯度: 98.7%; LCMS, m/z 实测值 551.3 (M+1)⁺.

[1348] N-(4-(4-(2-(4-氟苯基)乙酰基)-1,4-二氮杂环庚烷-1-羰基)苯基)喹啉-8-磺酰胺 (130f):

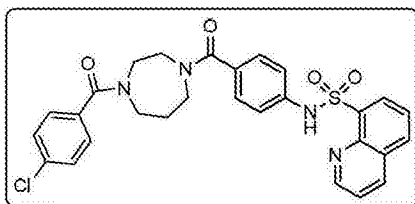
[1349]



[1350] ^1H NMR (400MHz, DMSO-d₆) δ : 1.4–1.6 (m, 2H), 3.0–3.8 (m, 8H), 7.0–8.0 (m, 8H), 8.2–8.4 (m, 5H), 9.1 (m, 1H); HPLC纯度: 99.6%; LCMS, m/z 实测值 547.2 (M+1)⁺.

[1351] N-(4-(4-(4-氯苯甲酰基)-1,4-二氮杂环庚烷-1-羰基)苯基)喹啉-8-磺酰胺 (130g):

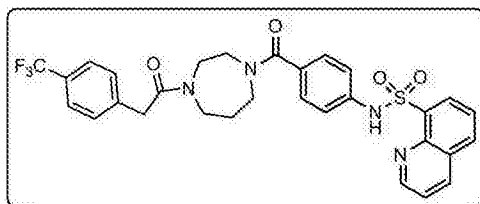
[1352]



[1353] ^1H NMR (400MHz, DMSO-d₆) δ : 1.4–1.6 (m, 2H), 3.0–3.8 (m, 8H), 7.0–8.0 (m, 8H), 8.2–8.4 (m, 5H), 9.1 (m, 1H); HPLC纯度: 99.4%; LCMS, m/z 实测值 549.3 (M+1)⁺.

[1354] N-(4-(4-(2-(4-(三氟甲基)苯基)乙酰基)-1,4-二氮杂环庚烷-1-羰基)苯基)喹啉-8-磺酰胺 (130h):

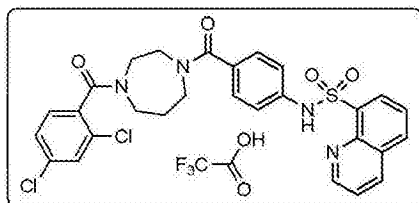
[1355]



[1356] ^1H NMR (400MHz, DMSO-d₆) δ : 1.4–1.6 (m, 2H), 3.0–3.8 (m, 8H), 7.0–8.0 (m, 8H), 8.2–8.4 (m, 5H), 9.1 (m, 1H); HPLC纯度: 99.2%; LCMS, m/z 实测值 597.2 (M+1)⁺.

[1357] N-(4-(4-(2,4-二氯苯甲酰基)-1,4-二氮杂环庚烷-1-羰基)苯基)喹啉-8-磺酰胺 2,2,2-三氟乙酸盐 (130i):

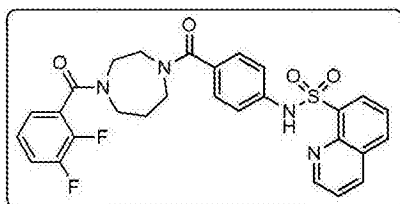
[1358]



[1359] ^1H NMR (400MHz, DMSO- d_6) δ : 1.4–1.6 (m, 2H), 3.0–3.8 (m, 8H), 7.0–8.0 (m, 8H), 8.2–8.4 (m, 3H), 8.5 (s, 1H), 9.1 (m, 1H); HPLC纯度: 94.4%; LCMS, m/z 实测值582.47 ($M+1$) $^+$.

[1360] N-(4-(4-(2,3-二氟苯甲酰基)-1,4-二氮杂环庚烷-1-羰基)苯基)喹啉-8-磺酰胺 (130j):

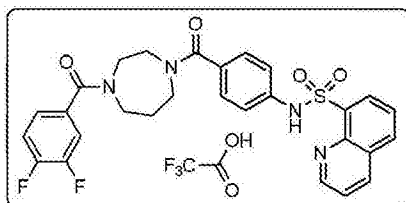
[1361]



[1362] ^1H NMR (400MHz, CD $_3$ OD) δ : 1.4–1.6 (m, 2H), 3.0–3.8 (m, 8H), 7.0–8.0 (m, 8H), 8.2–8.4 (m, 4H), 9.1 (m, 1H); HPLC纯度: 98.6%; LCMS, m/z 实测值549.5 ($M-1$) $^+$.

[1363] N-(4-(4-(3,4-二氟苯甲酰基)-1,4-二氮杂环庚烷-1-羰基)苯基)喹啉-8-磺酰胺 2,2,2-三氟乙酸盐 (130k):

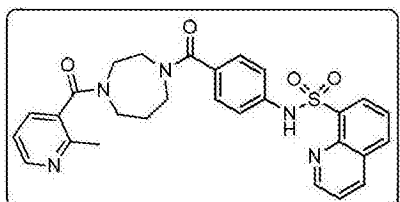
[1364]



[1365] ^1H NMR (400MHz, CD $_3$ OD) δ : 1.4–1.6 (m, 2H), 3.0–3.8 (m, 8H), 7.0–8.0 (m, 8H), 8.2–8.4 (m, 4H), 9.1 (m, 1H); HPLC纯度: 99.4%; LCMS, m/z 实测值549.3 ($M-1$) $^+$.

[1366] N-(4-(4-(2-甲基烟酰基)-1,4-二氮杂环庚烷-1-羰基)苯基)喹啉-8-磺酰胺 (130l):

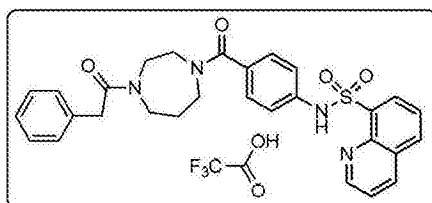
[1367]



[1368] ^1H NMR (400MHz, CD $_3$ OD) δ : 1.4–1.6 (m, 2H), 2.1 (s, 3H), 3.0–3.8 (m, 8H), 7.0–8.0 (m, 8H), 8.2–8.4 (m, 4H), 9.1 (m, 1H); HPLC纯度: 98.0%; LCMS, m/z 实测值530.4 ($M+1$) $^+$.

[1369] N-(4-(4-(2-苯基乙酰基)-1,4-二氮杂环庚烷-1-羰基)苯基)喹啉-8-磺酰胺 2,2,2-三氟乙酸盐 (130m):

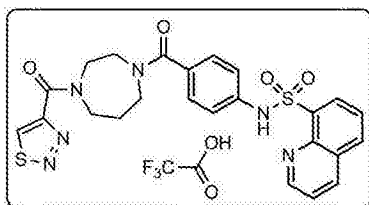
[1370]



[1371] ^1H NMR (400MHz, CD $_3$ OD) δ : 1.4–1.6 (m, 2H), 1.6–2.0 (s, 2H), 3.0–3.8 (m, 8H), 7.0–8.0 (m, 8H), 8.2–8.4 (m, 6H), 9.1 (m, 1H); HPLC纯度: 98.8%; LCMS, m/z 实测值529.1 ($M+1$) $^+$.

[1372] N-(4-(4-(1,2,3-噻二唑-4-羰基)-1,4-二氮杂环庚烷-1-羰基)苯基)喹啉-8-磺酰胺 2,2,2-三氟乙酸盐 (130n):

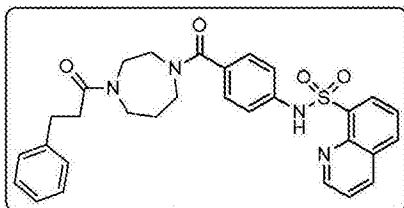
[1373]



[1374] ^1H NMR (400MHz, CD_3OD) δ : 1.4–1.6 (m, 2H), 3.0–3.8 (m, 8H), 7.0–8.0 (m, 6H), 8.2–8.4 (m, 4H), 9.1 (s, 1H); HPLC纯度: 98.5%; LCMS, m/z 实测值 523.1 ($\text{M}+1$) $^+$.

[1375] N-(4-(4-(3-苯基丙酰基)-1,4-二氮杂环庚烷-1-羰基)苯基)喹啉-8-磺酰胺 (130o):

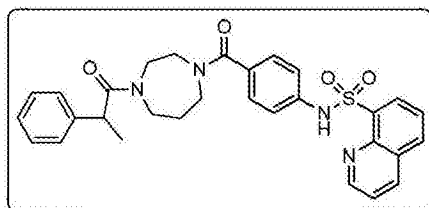
[1376]



[1377] ^1H NMR (400MHz, CD_3OD) δ : 1.4–1.6 (m, 2H), 1.7 (t, 2H), 1.8 (t, 2H), 3.0–3.8 (m, 8H), 7.0–8.0 (m, 8H), 8.2–8.4 (m, 6H), 9.1 (s, 1H); HPLC纯度: 98.2%; LCMS, m/z 实测值 543.1 ($\text{M}+1$) $^+$.

[1378] N-(4-(4-(2-苯基丙酰基)-1,4-二氮杂环庚烷-1-羰基)苯基)喹啉-8-磺酰胺 (130p):

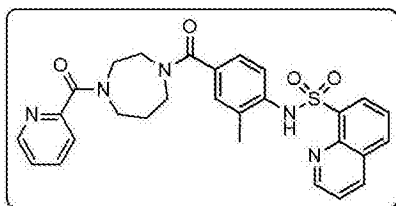
[1379]



[1380] ^1H NMR (400MHz, DMSO-d_6) δ : 1.2 (s, 3H), 1.3 (m, 2H), 3.0–3.8 (m, 8H), 4.0 (m, 1H), 7.0–8.0 (m, 8H), 8.2–8.4 (m, 6H), 9.1 (s, 1H); HPLC纯度: 97.1%; LCMS, m/z 实测值 543.1 ($\text{M}+1$) $^+$.

[1381] N-(2-甲基-4-(4-吡啶甲酰基-1,4-二氮杂环庚烷-1-羰基)苯基)喹啉-8-磺酰胺 (130q):

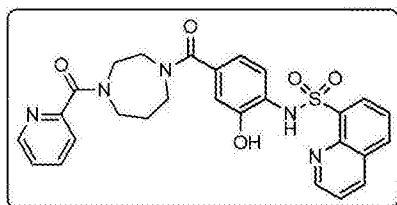
[1382]



[1383] ^1H NMR (400MHz, DMSO-d_6) δ : 1.2 (s, 3H), 1.3 (m, 2H), 3.0–3.8 (m, 8H), 7.0–8.0 (m, 8H), 8.2–8.4 (m, 4H), 9.1 (s, 1H); HPLC纯度: 96.3%; LCMS, m/z 实测值 530.1 ($\text{M}+1$) $^+$.

[1384] N-(2-羟基-4-(4-吡啶甲酰基-1,4-二氮杂环庚烷-1-羰基)苯基)喹啉-8-磺酰胺 (130r):

[1385]

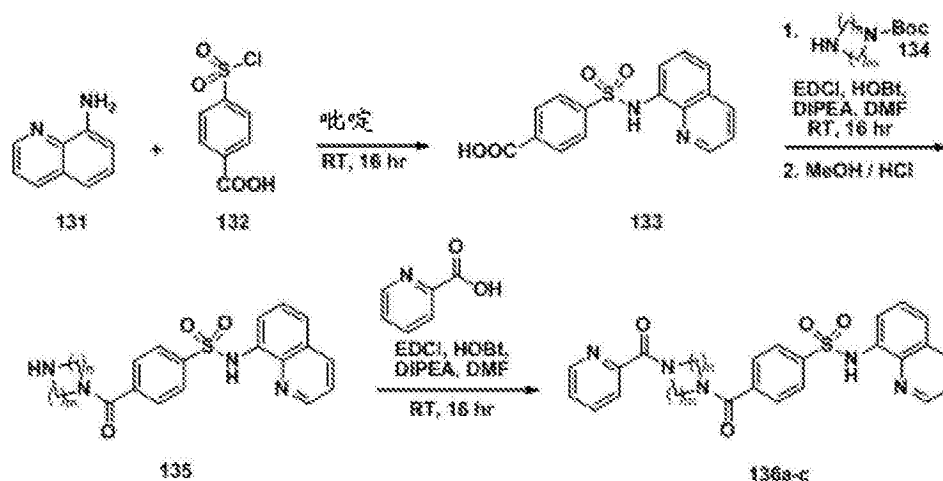


[1386] ^1H NMR (400MHz, DMSO-d_6) δ : 1.3-1.8 (m, 2H), 3.0-3.8 (m, 8H), 5.8 (s, 1H), 7.0-8.0 (m, 8H), 8.2-8.4 (m, 4H), 9.1 (s, 1H); 10.2 (s, 1H), HPLC纯度: 98.0%; LCMS, m/z 实测值 532.2 ($M+1$) $^+$.

[1387] 基于哌嗪的反磺酰胺的合成

[1388] 流程20

[1389]



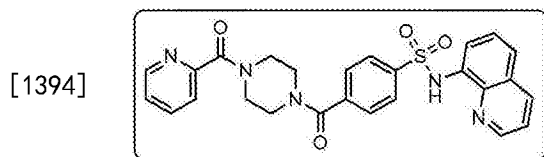
[1390] 合成磺酰胺133的一般程序:于0℃、在氮气气氛下向喹啉-8-胺131 (30.3mmol) 的搅拌溶液加入吡啶 (50ml), 搅拌10min。然后在相同温度下将4-(氯磺酰基) 苯甲酸 (132, 30.3mmol) 加至反应混合物。将所得混合物在RT搅拌16h。反应结束后, 在减压下除去溶剂。通过与甲苯共馏除去痕量的吡啶。将乙醚加至所得残余物中, 滤出固体产物, 空气干燥。所得粗产物 (74%) 不需进一步纯化即可用于下一步骤。

[1391] 合成磺酰胺135的一般程序:将EDCI (3.8g, 19.8mmol) 和HOBT (2.67g, 19.8mmol) 加至酸133 (6.5g, 19.8mmol) 在无水DMF中的搅拌溶液。将混合物的温度降至0℃, 此时在氮气气氛下加入DIPEA (11ml, 59.45mmol), 将所得溶液 (或悬浮液) 在室温搅拌30min。然后于0℃加入仲胺134 (19.8mmol)。然后将反应混合物升至室温, 搅拌过夜。反应结束后, 将反应混合物用水稀释, 用乙酸乙酯萃取 (3×70ml)。将有机层用水洗涤 (3×50ml), 经无水硫酸钠干燥, 过滤, 经旋转蒸发仪浓缩, 得到粗产物。通过柱色谱法 (60-120硅胶, 2% MeOH-DCM) 纯化粗产物, 得到为灰白色固体状的纯产物Boc-135 (83%), 将其于RT用甲醇HCl (100ml) 处理2h。Boc-基团完全断裂后, 在低压下除去溶剂, 得到为HCl盐的纯产物。用乙醚洗涤盐的水溶液, 用 NaHCO_3 (pH 10) 碱化。然后将所需产物分配至乙酸乙酯中, 用无水 Na_2SO_4 干燥, 在低压下除去溶剂, 得到为灰白色固体状的游离胺135 (95%)。

[1392] 合成酰胺136a-c的一般程序:将EDCI (48mg, 0.2525mmol) 和HOBT (34mg, 0.2525mmol) 加至吡啶甲酸 (0.2525mmol) 在无水DMF中的搅拌溶液。将混合物的温度降至0℃, 此时在氮气气氛下加入DIPEA (139 μ l, 0.7575mmol), 将所得溶液 (或悬浮液) 在室温搅拌30min。然后于0℃加入胺135 (100mg, 0.2525mmol)。然后将反应混合物升至室温, 搅拌过夜。

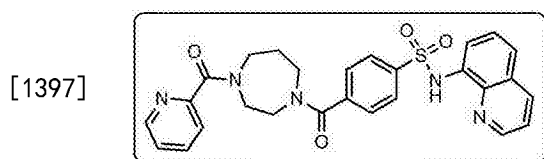
反应结束后,将反应混合物用水稀释,用乙酸乙酯萃取 ($3 \times 15\text{ml}$)。将有机层用水洗涤 ($3 \times 10\text{ml}$),经无水硫酸钠干燥,过滤,经旋转蒸发仪浓缩,得到粗产物。通过柱色谱法或制备型 HPLC 纯化粗产物,获得收率为 55-76% 的纯产物。

[1393] 4-(4-吡啶甲酰基哌嗪-1-羰基)-N-(喹啉-8-基)苯磺酰胺 (136a):



[1395] ^1H NMR (400MHz, DMSO-d_6) δ : 1.4-1.6 (m, 2H), 3.2-3.8 (m, 8H), 7.0-8.0 (m, 10H), 8.2 (m, 1H), 8.5 (d, 2H), 8.8 (d, 2H), 10.2 (s, 1H); HPLC 纯度: 99.4%; LCMS, m/z 实测值 502.1 ($\text{M}+1$) $^+$.

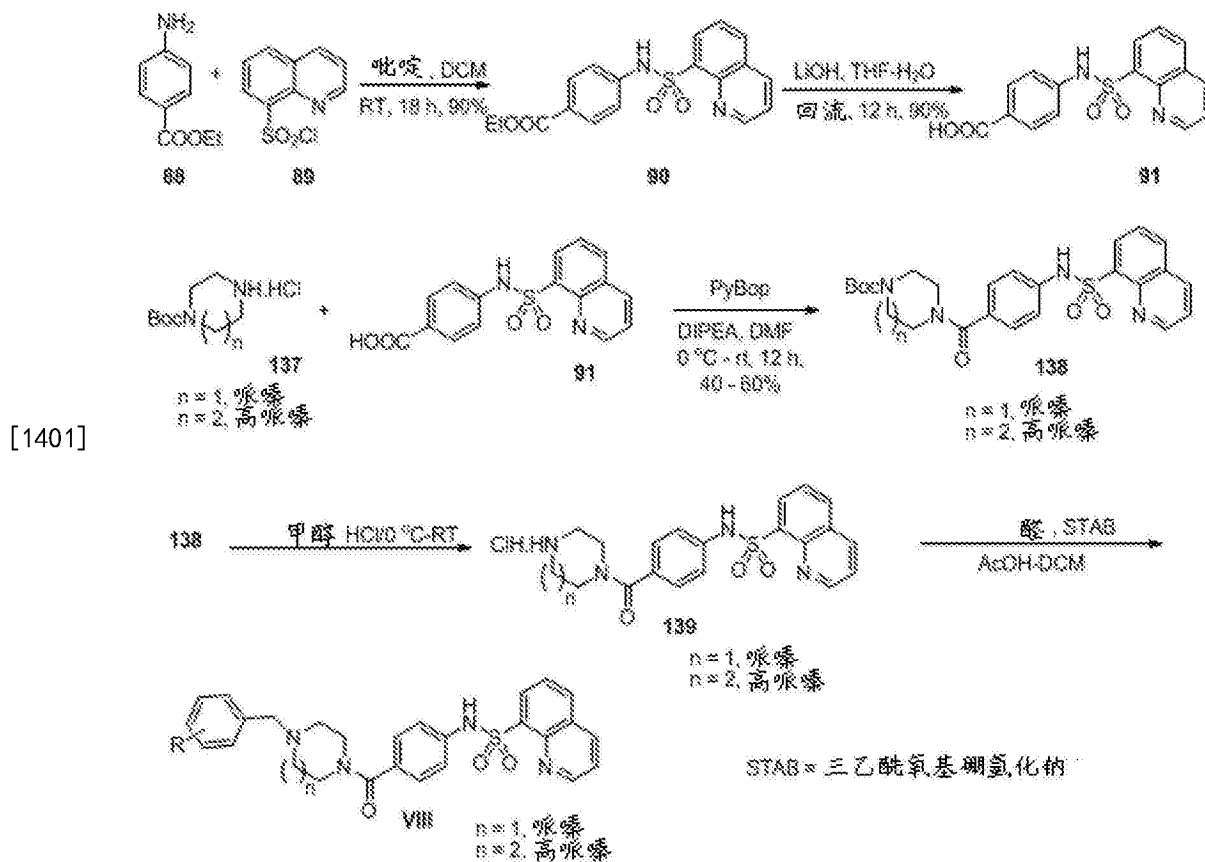
[1396] 4-(4-吡啶甲酰基-1,4-二氮杂环庚烷-1-羰基)-N-(喹啉-8-基)苯磺酰胺 (136b):



[1398] ^1H NMR (400MHz, DMSO-d_6) δ : 3.2 (m, 2H), 3.5 (m, 2H), 3.8 (m, 6H), 7.0-7.4 (m, 6H), 7.6-8.0 (m, 4H), 8.2-9.0 (m, 4H), 10.2 (s, 1H); HPLC 纯度: 97.8%; LCMS, m/z 实测值 516.2 ($\text{M}+1$) $^+$.

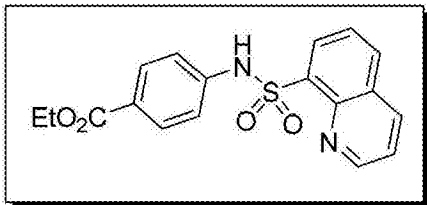
[1399] 具有取代的苯基环的基于苄基系列-哌嗪的化合物的合成

[1400] 流程 21



[1402] 4-(喹啉-8-亚磺酰氨基)苯甲酸乙酯(90)的合成:

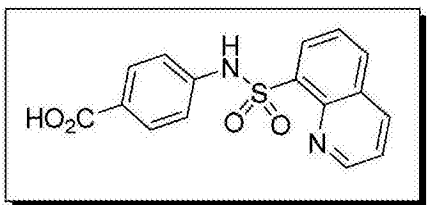
[1403]



[1404] 于室温、在 N_2 气氛下向胺88(16gm, 96.85mmol)在DCM和吡啶的(1:1)混合物中的溶液加入磺酰氯89(27.56gm, 121.07mmol)。将所得混合物搅拌16h。反应结束后,将粗混合物用DCM稀释,用水、然后用1N HCl洗涤。然后将有机层经 Na_2SO_4 干燥,在减压下浓缩,得到收率为98%的产物90(34gm)。

[1405] 4-(喹啉-8-亚磺酰氨基)苯甲酸(91)的合成:

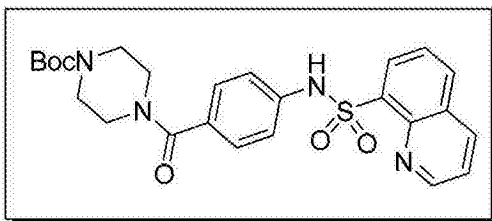
[1406]



[1407] 向磺酰胺90(34gm, 95.5mmol)在THF和水(1:1)中的溶液加入LiOH(20gm, 47.66mmol),将所得混合物在80℃搅拌过夜。反应结束后,将粗混合物用EtOAc洗涤。用柠檬酸酸化水层,过滤。由此获得的固体用Et₂O洗涤,在减压下与甲苯共沸,得到酸91(30gm, 95.8%收率),其不需进一步纯化即可用于下一步骤。

[1408] 4-(4-(喹啉-8-亚磺酰氨基)苯甲酰基)哌嗪-1-羧酸叔丁酯(138)的合成:

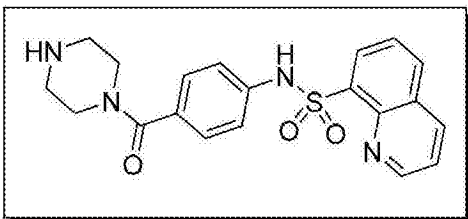
[1409]



[1410] 于0℃、向酸91(2gm, 6.09mmol)在DMF中的溶液加入PyBoP(苯并三唑-1-基-氧基-三-(二甲基氨基)-磷六氟磷酸酯)(4.75gm, 9.14mmol),搅拌5分钟。然后在 N_2 气氛下、在相同温度下将Boc保护的哌嗪/高哌嗪137(1.13gm, 6.09mmol)加至反应混合物,在室温搅拌过夜。反应结束后,用水稀释混合物,用EtOAc萃取。用水洗涤有机层,经 Na_2SO_4 干燥,在减压下蒸发。通过柱色谱法(硅胶, 60-120目; MeOH-DCM, 2:8)纯化残余物,得到收率为66%的产物138(2gm)。

[1411] N-(4-(哌嗪-1-羰基)苯基)喹啉-8-磺酰胺(139)的合成:

[1412]



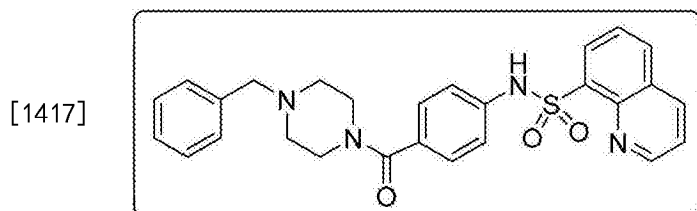
[1413] 向MeOH.HCl的溶液加入Boc保护的胺138(2gm, 4.03mmol),将所得混合物搅拌1h。反应结束后,在减压下除去溶剂,用水洗涤,然后加入 $NaHCO_3$,用DCM萃取。将有机层经 Na_2SO_4

干燥,在减压下蒸发,得到产物139 (1.5gm,94.30%收率)。

[1414] 合成化合物(VIII-1)-(VIII-216)的一般程序:

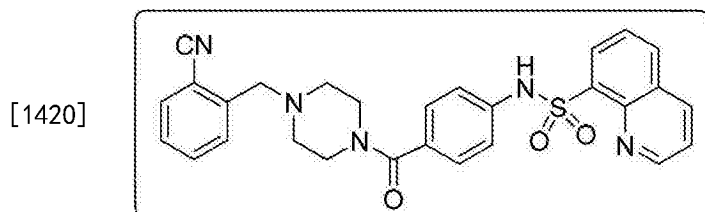
[1415] 于室温、向胺139 (0.25mmol)和适当醛(0.27mmol)在DCM中的溶液加入乙酸(0.2mL),将所得混合物搅拌30min。然后将STAB(0.26gm,1.26mmol)加至反应混合物,将所得混合物于50℃搅拌1h。反应结束后,将粗混合物用DCM稀释,用水洗涤,经Na₂SO₄干燥,在减压下浓缩。通过柱色谱法(硅胶,60-120目;MeOH-DCM,2:8)纯化残余物,得到收率为32-45%的产物(VIII-1)-(VIII-216)。

[1416] N-(4-(4-苄基哌嗪-1-羰基)苯基)喹啉-8-磺酰胺(VIII-1):



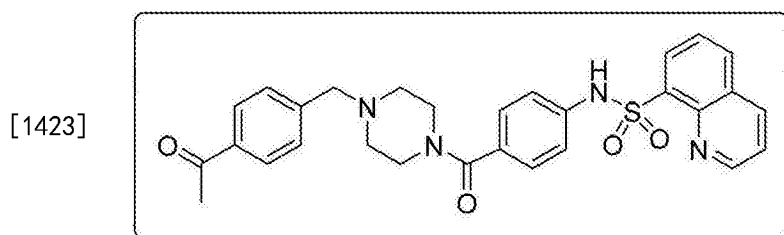
[1418] ¹H NMR (400MHz, CDCl₃) δ: 1.8 (s, 2H), 2.40 (br d, 4H), 3.38 (br d, 2H), 3.48 (d, 2H), 6.79-7.04 (m, 6H), 7.1-7.2 (m, 4H), 7.59-7.64 (m, 2H), 8.03-8.28 (m, 2H), 9.18 (s, 1H), 10.4 (s, 1H); HPLC纯度:98.7%; LCMS:487 (M+1)。

[1419] N-(4-(4-(2-氰基苄基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺(VIII-2):



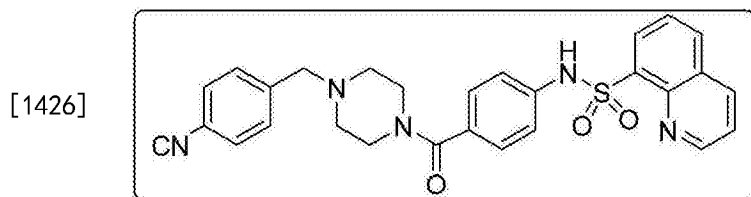
[1421] ¹H NMR (400MHz, CDCl₃) δ: 1.8 (s, 2H), 2.40 (br d, 4H), 3.38 (br d, 2H), 3.48 (d, 2H), 6.79-7.04 (m, 6H), 7.1-7.2 (m, 4H), 7.59-8.1 (m, 4H), 9.18 (s, 1H); HPLC纯度:99.2%; LCMS:512.3 (M+1)。

[1422] N-(4-(4-(4-乙酰基苄基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺(VIII-3):



[1424] ¹H NMR (400MHz, CDCl₃) δ: 1.8 (s, 2H), 2.6 (s, 3H), 2.40 (br d, 4H), 3.38 (br d, 2H), 3.48 (d, 2H), 6.79-7.04 (m, 6H), 7.1-7.2 (m, 4H), 7.60-7.71 (m, 2H), 8.01-8.28 (m, 2H), 9.18 (s, 1H); HPLC纯度:97.8%; LCMS:529.2 (M+1)。

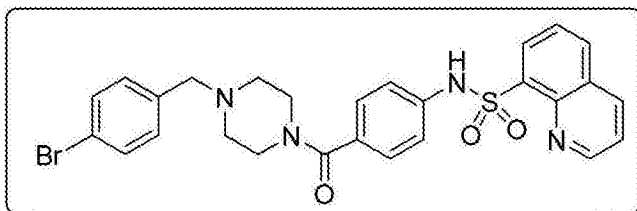
[1425] N-(4-(4-(4-氰基苄基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺(VIII-4):



[1427] ^1H NMR (400MHz, CDCl_3) δ : 1.8 (s, 2H), 2.40 (br d, 4H), 3.38 (br d, 2H), 3.48 (d, 2H), 6.79–7.04 (m, 6H), 7.1–7.2 (m, 4H), 7.59–7.64 (m, 2H), 8.03–8.28 (m, 2H), 9.18 (s, 1H); HPLC纯度: 97.8%; LCMS: 512.3 (M+1)。

[1428] N-(4-(4-(4-溴苄基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (VIII-5):

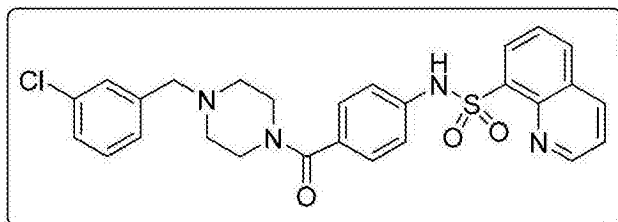
[1429]



[1430] ^1H NMR (400MHz, CDCl_3) δ : 1.8 (s, 2H), 2.40 (br d, 4H), 3.38 (br d, 2H), 3.48 (d, 2H), 6.79–7.04 (m, 6H), 7.1–7.2 (m, 4H), 7.59–7.64 (m, 2H), 8.03–8.28 (m, 2H), 10.4 (s, 1H); HPLC纯度: 98.3%; LCMS: 566.1 (M+1)。

[1431] N-(4-(4-(3-氯苄基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (VIII-6):

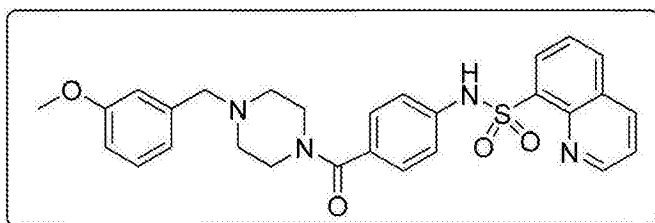
[1432]



[1433] ^1H NMR (400MHz, CDCl_3) δ : 1.8 (s, 2H), 2.40 (br d, 4H), 3.38 (br d, 2H), 3.48 (d, 2H), 6.8–7.04 (m, 4H), 7.1–7.2 (m, 3H), 7.59–7.64 (m, 4H), 8.0–8.6 (m, 3H), 10.4 (s, 1H); HPLC纯度: 96.5%; LCMS: 522.1 (M+1)。

[1434] N-(4-(4-(3-甲氧基苄基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (VIII-7):

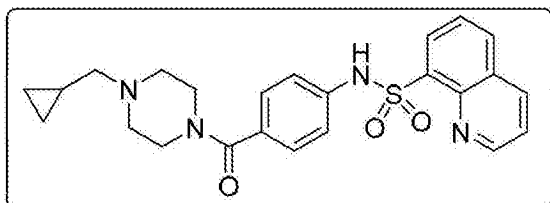
[1435]



[1436] ^1H NMR (400MHz, CDCl_3) δ : 2.40 (s, 2H), 3.9 (s, 3H), 3.68 (br s, 4H), 3.4–3.6 (m, 4H), 7.06 (m, 4H), 7.18 (m, 3H), 7.25 (m, 2H), 7.42 (m, 2H), 8.58 (s, 1H), 9.18 (s, 1H); HPLC纯度: 97.8%; LCMS: 517.1 (M+1)。

[1437] N-(4-(4-(环丙基甲基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (VIII-8):

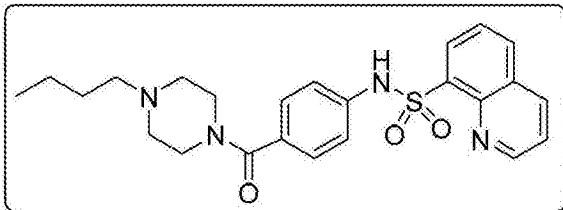
[1438]



[1439] ^1H NMR (400MHz, $\text{DMSO}-d_6$) δ : 1.2 (t, 2H), 1.3 (t, 2H), 1.31–1.35 (m, 1H), 2.40 (s, 2H), 3.68 (br s, 4H), 3.4–3.6 (m, 4H), 7.06 (m, 6H), 7.25–7.42 (m, 3H), 9.18 (s, 1H), 10.4 (s, 1H); HPLC纯度: 97.81%; LCMS: 451.3 (M+1)。

[1440] N-(4-(4-丁基哌嗪-1-羰基)苯基)喹啉-8-磺酰胺(VIII-9):

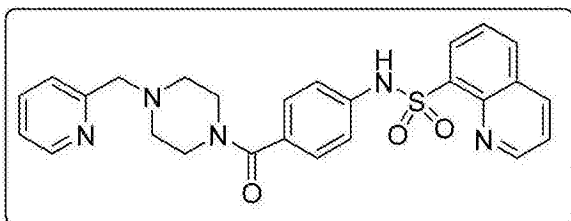
[1441]



[1442] ^1H NMR (400MHz, DMSO- d_6) δ : 1.25-1.3 (m, 2H), 1.38-1.35 (m, 2H), 1.5 (t, 3H), 2.40 (s, 2H), 3.68 (br s, 4H), 3.4-3.6 (m, 4H), 7.06 (m, 6H), 7.25-7.42 (m, 3H), 9.18 (s, 1H), 10.4 (s, 1H); HPLC纯度: 99.7%; LCMS: 453.2 (M+1)。

[1443] N-(4-(4-(吡啶-2-基甲基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺(VIII-10):

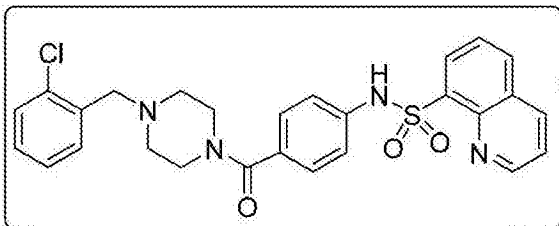
[1444]



[1445] ^1H NMR (400MHz, DMSO- d_6) δ : 2.5 (s, 2H), 3.68 (br s, 4H), 3.4-3.6 (m, 4H), 7.0-7.4 (m, 8H), 7.3-7.4 (m, 3H), 9.18 (s, 1H), 10.4 (s, 1H); HPLC纯度: 95.8%; LCMS: 488.1 (M+1)。

[1446] N-(4-(4-(2-氯苄基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺(VIII-11):

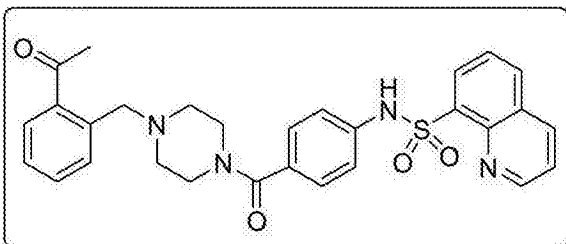
[1447]



[1448] ^1H NMR (400MHz, DMSO- d_6) δ : 2.5 (s, 2H), 3.68 (br s, 4H), 3.4-3.6 (m, 4H), 7.0-7.4 (m, 6H), 7.3-7.4 (m, 4H), 8.0-8.35 (m, 3H), 9.18 (s, 1H), 10.4 (s, 1H); HPLC纯度: 98.8%; LCMS: 522.1 (M+1)。

[1449] N-(4-(4-(2-乙酰基苄基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺(VIII-12):

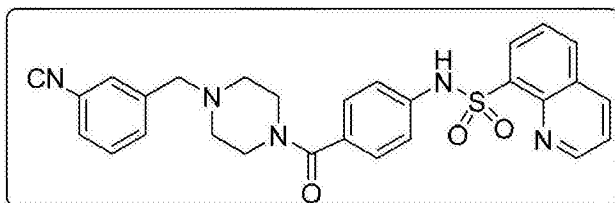
[1450]



[1451] ^1H NMR (400MHz, CDCl_3) δ : 1.8 (s, 2H), 2.6 (s, 3H), 2.40 (br d, 4H), 3.38 (br d, 2H), 3.48 (d, 2H), 7.0-7.4 (m, 6H), 7.45-7.7 (m, 4H), 8.0-8.4 (m, 3H), 9.18 (s, 1H), 10.4 (s, 1H); HPLC纯度: 98.3%; LCMS: 529.2 (M+1)。

[1452] N-(4-(4-(3-氰基苄基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺(VIII-13):

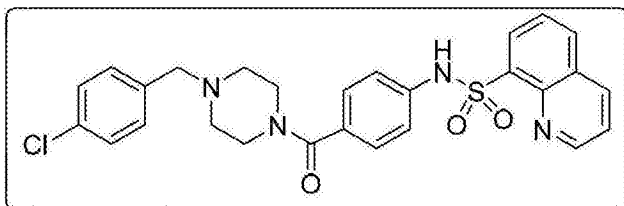
[1453]



[1454] ^1H NMR (400MHz, CDCl_3) δ : 1.8 (s, 2H), 2.40 (br d, 4H), 3.38 (br d, 2H), 3.48 (d, 2H), 6.79–7.04 (m, 6H), 7.1–7.2 (m, 4H), 7.59–8.1 (m, 4H), 10.35 (s, 1H); HPLC纯度: 99.2%; MS: 512.3 (M+1)。

[1455] N-(4-(4-(4-氯苄基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (VIII-14):

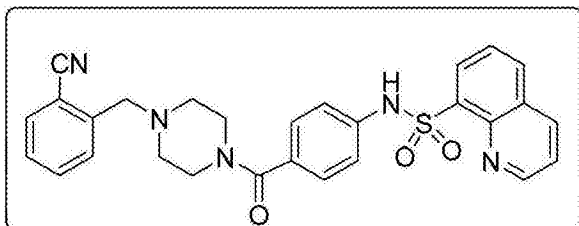
[1456]



[1457] ^1H NMR (400MHz, CDCl_3) δ : 1.8 (s, 2H), 2.40 (br d, 4H), 3.38 (br d, 2H), 3.48 (d, 2H), 6.79–7.04 (m, 6H), 7.1–7.2 (m, 4H), 7.59–7.64 (m, 2H), 8.03–8.28 (m, 2H), 10.4 (s, 1H); HPLC纯度: 98.3%; LCMS: 522.3 (M+1)。

[1458] N-(4-(4-(2-氰基苄基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (VIII-15):

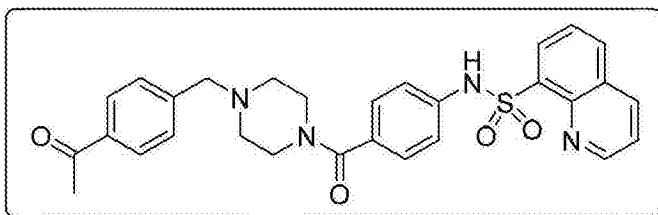
[1459]



[1460] ^1H NMR (400MHz, DMSO-d_6) δ : 2.5 (s, 2H), 3.68 (br s, 4H), 3.4–3.6 (m, 4H), 7.0–7.4 (m, 6H), 7.3–7.4 (m, 4H), 8.0–8.35 (m, 3H), 9.18 (s, 1H), 10.4 (s, 1H); HPLC纯度: 99.1%; LCMS: 512.3 (M+1)。

[1461] N-(4-(4-(4-乙酰基苄基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (VIII-16):

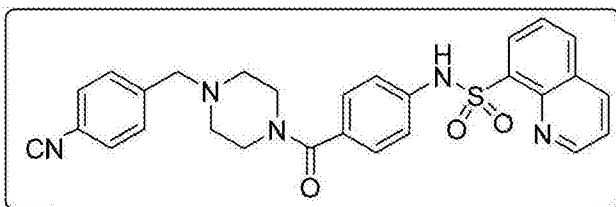
[1462]



[1463] ^1H NMR (400MHz, CDCl_3) δ : 1.8 (s, 2H), 2.6 (s, 3H), 2.40 (br d, 4H), 3.38 (br d, 2H), 3.48 (d, 2H), 6.79–7.04 (m, 6H), 7.1–7.2 (m, 4H), 7.6–7.7 (m, 2H), 8.0–8.28 (m, 2H), 10.3 (s, 1H); HPLC纯度: 97.8%; LCMS: 529.2 (M+1)。

[1464] N-(4-(4-(4-氰基苄基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (VIII-17):

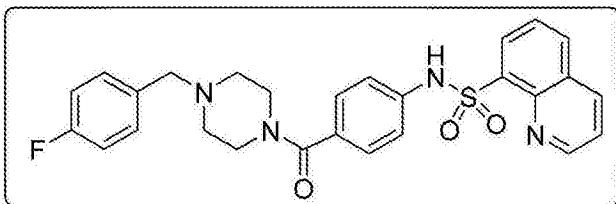
[1465]



[1466] ^1H NMR (400MHz, CDCl_3) δ : 1.8 (s, 2H), 2.40 (br d, 4H), 3.38 (br d, 2H), 3.48 (d, 2H), 6.79–7.04 (m, 6H), 7.1–7.2 (m, 4H), 7.59–7.64 (m, 2H), 8.03–8.28 (m, 2H), 10.3 (s, 1H); HPLC纯度: 97.8%; LCMS: 512.3 ($\text{M}+1$)。

[1467] N-(4-(4-(4-氟苄基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (VIII-18):

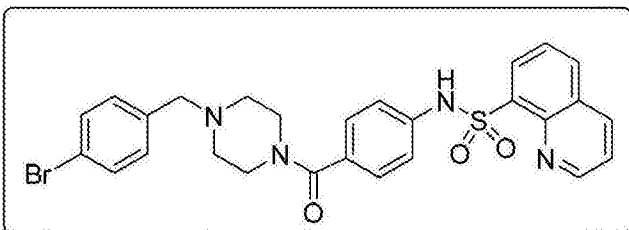
[1468]



[1469] ^1H NMR (400MHz, CDCl_3) δ : 2.38 (br d, 4H), 3.31 (br s, 2H), 3.41 (s, 2H), 3.64 (br s, 2H), 6.94 (t, 2H), 7.02 (d, 2H), 7.17 (d, 2H), 7.20–7.26 (m, 2H), 7.56–7.64 (m, 2H), 8.03 (d, 1H), 8.28 (d, 1H), 8.38 (d, 1H), 8.58 (s, 1H), 9.18 (s, 1H); HPLC纯度: 97.62%; LCMS: 505 (M^+)。

[1470] N-(4-(4-(4-溴苄基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (VIII-19):

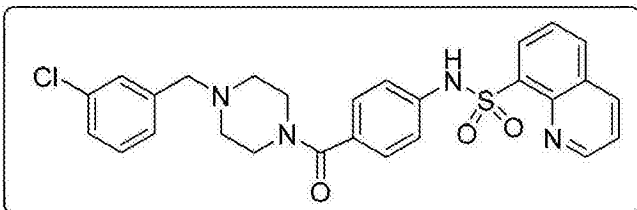
[1471]



[1472] ^1H NMR (400MHz, CDCl_3) δ : 2.38 (br d, 4H), 3.31 (br s, 2H), 3.41 (s, 2H), 3.64 (br s, 2H), 6.94 (d, 2H), 7.06 (t, 4H), 7.40 (d, 2H), 7.56–7.63 (m, 2H), 8.01 (d, 1H), 8.28 (d, 1H), 8.38 (d, 1H), 8.56 (s, 1H), 9.18 (s, 1H); HPLC纯度: 94.21%; LCMS: 567 (M^+)。

[1473] N-(4-(4-(3-氯苄基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (VIII-20):

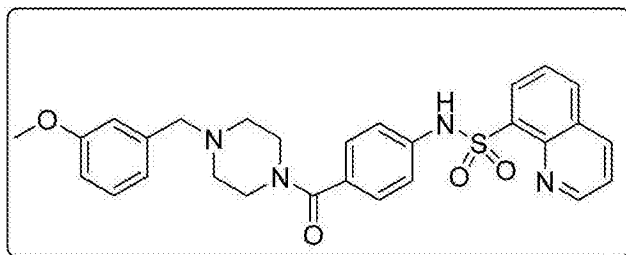
[1474]



[1475] ^1H NMR (400MHz, CDCl_3) δ : 2.38 (br d, 4H), 3.31 (br s, 2H), 3.41 (s, 2H), 3.64 (br s, 2H), 7.01 (d, 2H), 7.16 (t, 3H), 7.21–7.28 (m, 5H), 7.56–7.62 (m, 2H), 8.01 (d, 1H), 8.28 (d, 1H), 8.38 (d, 1H), 8.56 (s, 1H), 9.18 (s, 1H); HPLC纯度: 99.41%; LCMS: 567 (M^+2)。

[1476] N-(4-(4-(3-甲氧基苄基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (VIII-21):

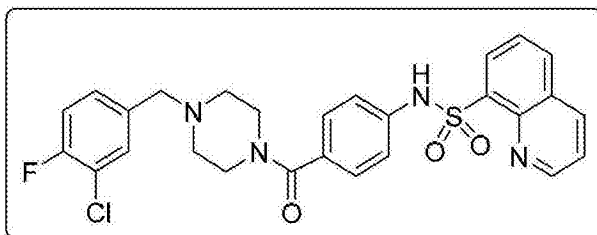
[1477]



[1478] ^1H NMR (400MHz, CDCl_3) δ : 2.38 (br d, 4H), 3.38 (br s, 2H), 3.46 (s, 2H), 3.72 (br s, 2H), 3.82 (s, 3H), 6.79 (d, 1H), 6.82 (s, 2H), 7.10 (q, 4H), 7.21–7.29 (m, 2H), 7.59–7.66 (m, 2H), 8.01 (d, 1H), 8.28 (d, 1H), 8.38 (d, 1H), 8.56 (s, 1H), 9.18 (s, 1H); HPLC纯度: 98.26%; LCMS: 539 ($\text{M}^+ + 23$).

[1479] N-(4-(4-(3-氯-4-氟苄基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (VIII-22):

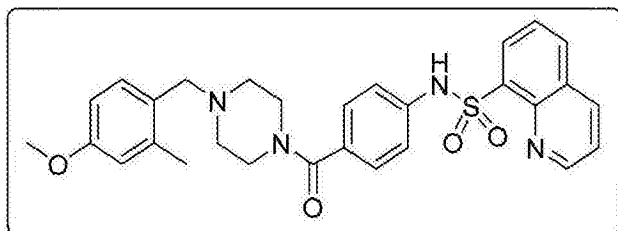
[1480]



[1481] ^1H NMR (400MHz, CDCl_3) δ : 3.10 (br s, 4H), 3.84 (br s, 4H), 4.19 (s, 2H), 7.16 (d, 2H), 7.21 (d, 2H), 7.28–7.34 (m, 1H), 7.44 (d, 1H), 7.60–7.68 (m, 2H), 8.10 (d, 1H), 8.36 (d, 1H), 8.41 (d, 1H), 9.18 (d, 1H); HPLC纯度: 96.82%; LCMS: 539 (M^+).

[1482] N-(4-(4-(4-methoxy-2-methylbenzyl)piperidin-1-yl)benzoyl)benzyl quinoline-8-sulfonamide (VIII-23):

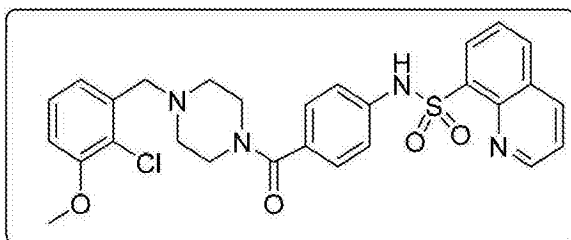
[1483]



[1484] ^1H NMR (400MHz, CDCl_3) δ : 2.38 (s, 3H), 2.80 (br s, 4H), 3.80 (s, 3H), 3.88 (br s, 4H), 4.20 (s, 2H), 6.78 (d, 2H), 7.10 (d, 2H), 7.20 (d, 2H), 7.25 (d, 2H), 7.60–7.65 (m, 2H), 8.03 (d, 1H), 8.32 (d, 1H), 8.38 (d, 1H), 9.18 (d, 1H); HPLC纯度: 96.98%; LCMS: 531 ($\text{M}^+ + 1$).

[1485] N-(4-(4-(2-chloro-3-methoxybenzyl)piperidin-1-yl)benzoyl)benzyl quinoline-8-sulfonamide (VIII-24):

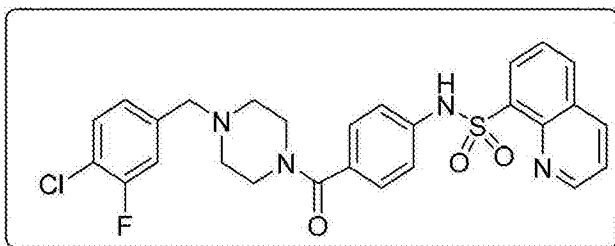
[1486]



[1487] ^1H NMR (400MHz, CDCl_3) δ : 2.41 (br s, 4H), 3.18 (br s, 4H), 3.81 (br s, 3H), 3.98 (s, 2H), 7.02 (d, 1H), 7.13 (d, 2H), 7.18–7.22 (m, 2H), 7.30 (t, 1H), 7.60–7.67 (m, 2H), 8.04 (d, 1H), 8.36 (d, 1H), 8.38 (d, 1H), 9.18 (d, 1H); HPLC纯度: 99.46%; LCMS: 551 (M^+).

[1488] N-(4-(4-(4-chloro-3-fluorobenzyl)piperidin-1-yl)benzoyl)benzyl quinoline-8-sulfonamide (VIII-25):

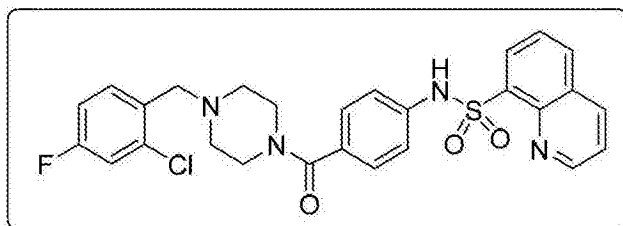
[1489]



[1490] ^1H NMR (400MHz, CDCl_3) δ : 3.15 (br s, 4H), 3.84 (br s, 4H), 4.19 (s, 2H), 7.13–7.24 (m, 6H), 7.48 (t, 1H), 7.61–7.68 (m, 2H), 8.10 (d, 1H), 8.34 (d, 1H), 8.41 (d, 1H), 9.18 (d, 1H); HPLC纯度: 99.24%; LCMS: 539 (M^+).

[1491] N-(4-(4-(2-chloro-3-fluorophenyl)piperidin-1-yl)benzoyl)quinoline-8-sulfonamide (VIII-26):

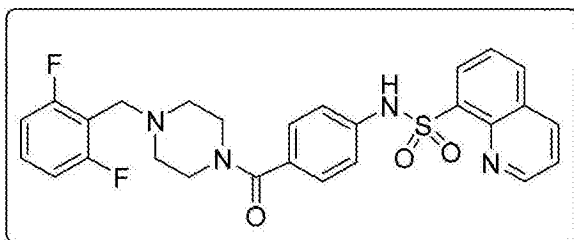
[1492]



[1493] ^1H NMR (400MHz, CDCl_3) δ : 2.37 (s, 4H), 3.21 (br s, 2H), 3.78 (br s, 2H), 4.39 (s, 2H), 7.18 (d, 2H), 7.21 (d, 2H), 7.61–7.65 (m, 2H), 8.05 (d, 1H), 8.36 (d, 1H), 8.41 (d, 1H), 9.18 (d, 1H); HPLC纯度: 99.56%; LCMS: 539 (M^+).

[1494] N-(4-(4-(2,6-difluorophenyl)piperidin-1-yl)benzoyl)quinoline-8-sulfonamide (VIII-27):

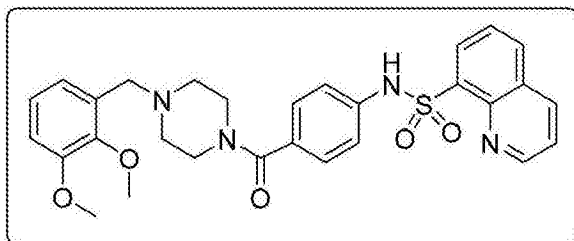
[1495]



[1496] ^1H NMR (400MHz, CDCl_3) δ : 3.07 (br s, 4H), 3.81 (s, 4H), 4.38 (s, 2H), 7.06 (t, 2H), 7.12 (d, 2H), 7.18 (d, 2H), 7.54 (s, 1H), 7.60–7.64 (m, 2H), 8.01 (d, 1H), 8.36 (d, 1H), 8.38 (d, 1H), 9.18 (d, 1H); HPLC纯度: 98.26%; LCMS: 523 ($\text{M}^+ + 1$).

[1497] N-(4-(4-(2,3-dimethoxyphenyl)piperidin-1-yl)benzoyl)quinoline-8-sulfonamide (VIII-28):

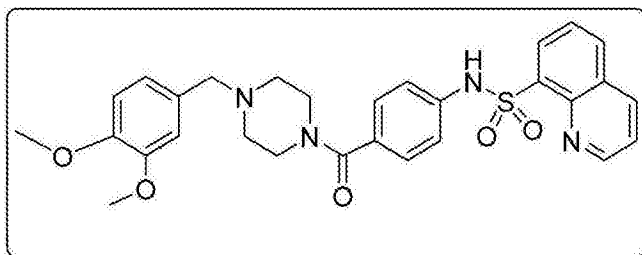
[1498]



[1499] ^1H NMR (400MHz, CDCl_3) δ : 2.63 (br s, 4H), 3.57 (br s, 4H), 3.90 (d, 6H), 4.18 (s, 2H), 6.98 (d, 2H), 7.00 (d, 1H), 7.14–7.19 (m, 6H), 7.58–7.64 (m, 2H), 8.06 (d, 1H), 8.38 (d, 1H), 8.40 (d, 1H), 9.18 (d, 1H); HPLC纯度: 99.41%; LCMS: 547 ($\text{M}^+ + 1$).

[1500] N-(4-(4-(3,4-dimethoxyphenyl)piperidin-1-yl)benzoyl)quinoline-8-sulfonamide (VIII-29):

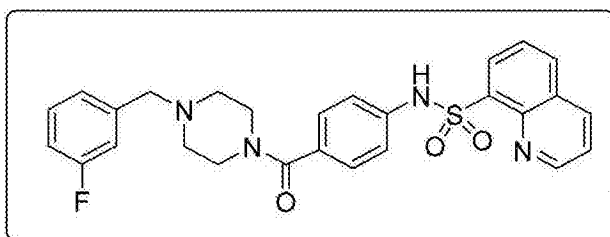
[1501]



[1502] ^1H NMR (400MHz, CDCl_3) δ : 2.63 (br s, 4H), 3.57 (br s, 4H), 3.90 (d, 6H), 4.18 (s, 2H), 6.83 (s, 2H), 7.00 (s, 1H), 7.14 (d, 2H), 7.21 (d, 2H), 7.62–7.68 (m, 2H), 8.04 (d, 1H), 8.38 (d, 1H), 8.40 (d, 1H), 9.18 (d, 1H); HPLC纯度: 92.46%; LCMS: 547 (M^+ +1)。

[1503] N-(4-(4-(3-氟苄基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (VIII-30):

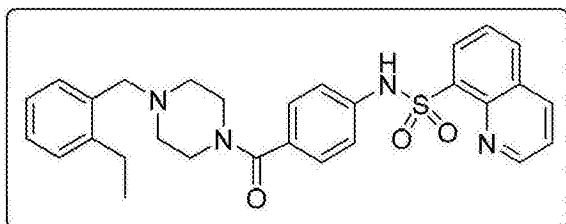
[1504]



[1505] ^1H NMR (400MHz, CDCl_3) δ : 3.09 (br s, 4H), 3.85 (s, 4H), 4.19 (s, 2H), 6.94 (d, 2H), 7.06–7.21 (m, 6H), 7.40–7.44 (m, 1H), 7.62–7.68 (m, 2H), 8.08 (d, 1H), 8.38 (d, 1H), 8.40 (d, 1H), 9.18 (d, 1H); HPLC纯度: 98.92%; LCMS: 505 (M^+ +1)。

[1506] N-(4-(4-(2-乙基苄基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (VIII-31):

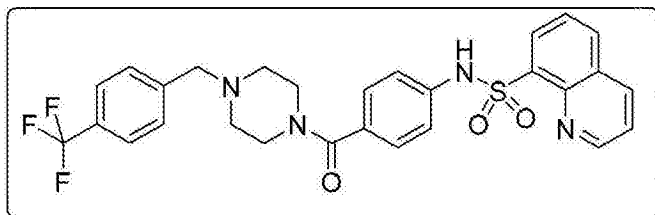
[1507]



[1508] ^1H NMR (400MHz, CDCl_3) δ : 1.22 (t, 3H), 2.41 (br s, 4H), 2.68 (q, 2H), 3.64 (br s, 4H), 7.06 (d, 2H), 7.20 (d, 2H), 7.22–7.26 (m, 2H), 7.40 (d, 2H), 7.61–7.68 (m, 2H), 8.01 (d, 1H), 8.32 (d, 1H), 8.41 (d, 1H), 9.18 (d, 1H); HPLC纯度: 99.22%; LCMS: 515 (M^+ +1)。

[1509] N-(4-(4-(4-(三氟甲基)苄基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (VIII-32):

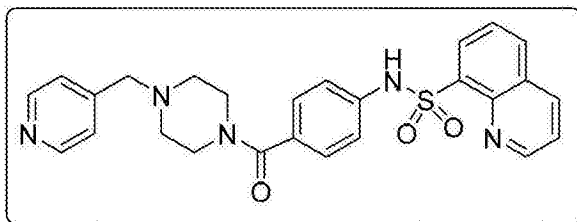
[1510]



[1511] ^1H NMR (400MHz, CDCl_3) δ : 3.18 (br s, 4H), 3.83 (br s, 4H), 4.25 (s, 2H), 7.06 (d, 2H), 7.22 (d, 2H), 7.56 (d, 2H), 7.60–7.78 (m, 4H), 8.07 (d, 1H), 8.36 (d, 1H), 8.40 (d, 1H), 9.18 (s, 1H); HPLC纯度: 96.72%; LCMS: 555 (M^+ +1)。

[1512] N-(4-(4-(吡啶-4-基甲基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (VIII-33):

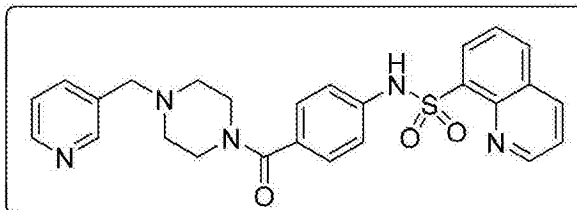
[1513]



[1514] ^1H NMR (400MHz, CDCl_3) δ : 2.40 (br s, 4H), 3.33 (br s, 2H), 3.41 (s, 2H), 3.64 (br s, 2H), 7.06 (d, 2H), 7.18 (d, 2H), 7.26 (d, 3H), 7.58–7.63 (m, 2H), 8.01 (d, 1H), 8.28 (d, 1H), 8.38 (d, 1H), 8.79 (br s, 2H), 9.18 (s, 1H); HPLC纯度: 97.4%; LCMS: 488.3 ($\text{M}^+ + 1$).

[1515] N-(4-(4-(吡啶-3-基甲基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (VIII-34):

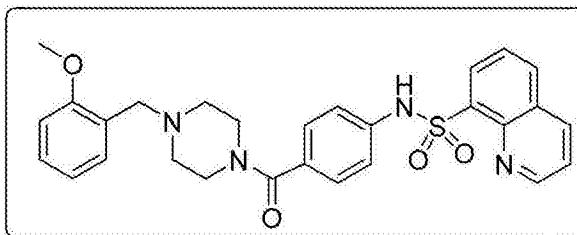
[1516]



[1517] ^1H NMR (400MHz, CDCl_3) δ : 2.40 (br s, 4H), 3.33 (br s, 2H), 3.41 (s, 2H), 3.64 (br s, 2H), 7.06 (d, 2H), 7.18 (d, 2H), 7.26 (d, 3H), 7.58–7.63 (m, 2H), 8.01 (d, 1H), 8.28 (d, 1H), 8.38 (d, 1H), 8.51–8.59 (m, 2H), 9.18 (s, 1H); HPLC纯度: 98.50%; LCMS: 488.0 ($\text{M}^+ + 1$).

[1518] N-(4-(4-(2-甲氧基苄基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (VIII-35):

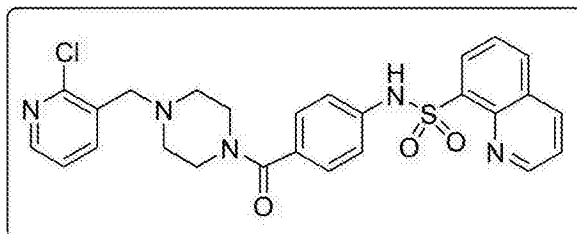
[1519]



[1520] ^1H NMR (400MHz, CDCl_3) δ : 2.42 (br d, 4H), 3.38 (br s, 2H), 3.58 (s, 2H), 3.70 (br s, 2H), 3.80 (s, 3H), 6.83–6.93 (m, 2H), 7.06 (d, 2H), 7.18 (d, 2H), 7.20–7.26 (m, 2H), 7.58–7.63 (m, 2H), 8.01 (d, 1H), 8.28 (d, 1H), 8.38 (d, 1H), 8.51–8.59 (m, 2H), 9.18 (s, 1H); HPLC纯度: 98.9%; LCMS: 517.1 ($\text{M}^+ + 1$).

[1521] N-(4-(4-((2-氯吡啶-3-基)甲基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (VIII-36):

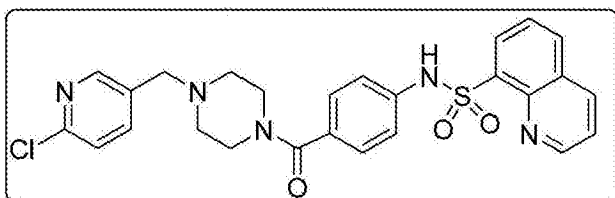
[1522]



[1523] ^1H NMR (400MHz, CDCl_3) δ : 2.44 (br s, 4H), 3.41 (br s, 2H), 3.60 (s, 2H), 3.74 (br s, 2H), 7.06 (d, 2H), 7.20 (d, 2H), 7.22–7.28 (m, 2H), 7.59–7.66 (m, 2H), 7.81 (d, 1H), 8.01 (d, 1H), 8.35 (d, 2H), 8.39 (d, 1H), 8.59 (s, 1H), 9.18 (s, 1H); HPLC纯度: 98.6%; LCMS: 522 (M^+).

[1524] N-(4-(4-((6-氯吡啶-3-基)甲基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (VIII-37):

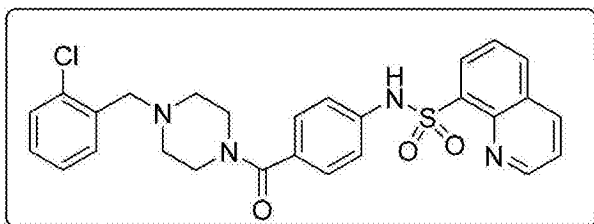
[1525]



[1526] ^1H NMR (400MHz, CDCl_3) δ : 2.44 (br s, 4H), 3.41 (br s, 2H), 3.54 (s, 2H), 3.74 (br s, 2H), 7.06 (d, 2H), 7.20 (d, 2H), 7.22–7.28 (m, 2H), 7.59–7.66 (m, 3H), 8.01 (d, 1H), 8.35 (d, 2H), 8.39 (d, 1H), 8.59 (s, 1H), 9.18 (s, 1H); HPLC纯度: 99.22%; LCMS: 522 (M^+)。

[1527] N-(4-(4-(2-氯苄基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (VIII-38):

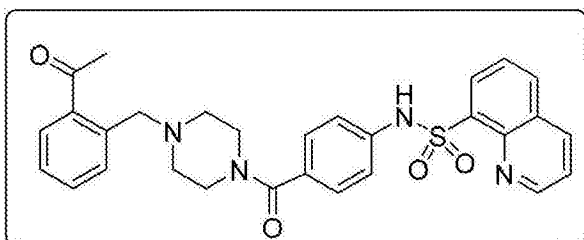
[1528]



[1529] ^1H NMR (400MHz, CDCl_3) δ : 2.44 (br d, 4H), 3.41 (br s, 2H), 3.61 (s, 2H), 3.74 (br s, 2H), 7.06 (d, 2H), 7.08–7.24 (m, 4H), 7.32 (d, 1H), 7.39 (d, 1H), 7.59–7.7.65 (m, 2H), 8.01 (d, 1H), 8.35 (d, 1H), 8.39 (d, 1H), 8.58 (s, 1H), 9.18 (s, 1H); HPLC纯度: 94.42%; LCMS: 521 (M^+)。

[1530] N-(4-(4-(2-乙酰基苄基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (VIII-39):

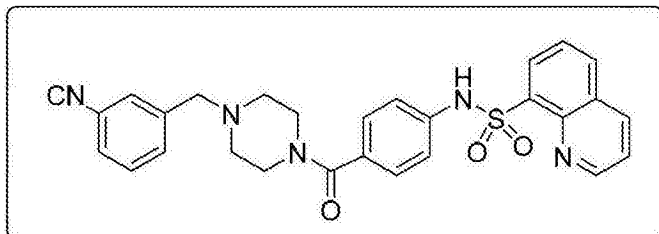
[1531]



[1532] ^1H NMR (400MHz, CDCl_3) δ : 2.38 (br d, 4H), 2.58 (s, 3H), 3.31 (br s, 2H), 3.60 (s, 2H), 3.64 (br s, 2H), 7.03 (d, 2H), 7.15 (d, 2H), 7.30–7.41 (m, 3H), 7.43 (d, 1H), 7.59–7.64 (m, 2H), 8.01 (d, 1H), 8.30 (d, 1H), 8.38 (d, 1H), 8.56 (s, 1H), 9.18 (s, 1H); HPLC纯度: 96.32%; LCMS: 529 ($\text{M}^+ + 1$)。

[1533] N-(4-(4-(3-氰基苄基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (VIII-40):

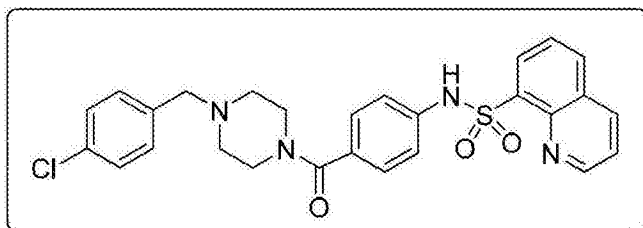
[1534]



[1535] ^1H NMR (400MHz, CDCl_3) δ : 2.43 (br d, 4H), 3.38 (br s, 2H), 3.68 (s, 4H), 7.08 (d, 2H), 7.18 (d, 2H), 7.40 (t, 1H), 7.45–7.70 (m, 5H), 8.01 (d, 1H), 8.28 (d, 1H), 8.38 (d, 1H), 8.56 (s, 1H), 9.18 (s, 1H); HPLC: 98.2%; LCMS: 512 ($\text{M}^+ + 1$)。

[1536] N-(4-(4-(4-氯苄基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (VIII-41):

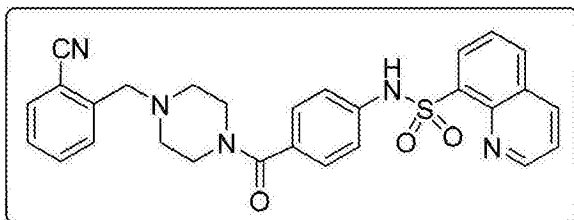
[1537]



[1538] ^1H NMR (400MHz, CDCl_3) δ : 2.39 (br d, 4H), 3.39 (br s, 2H), 3.50 (s, 2H), 3.64 (br s, 2H), 7.06 (d, 2H), 7.17 (d, 2H), 7.40 (d, 2H), 7.44 (d, 1H), 7.56–7.63 (m, 4H), 8.01 (d, 1H), 8.28 (d, 1H), 8.38 (d, 1H), 8.56 (s, 1H), 9.18 (s, 1H); HPLC纯度: 96.9%; LCMS: 521 (M^+ +1)。

[1539] N-(4-(4-(2-氰基苄基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (VIII-42):

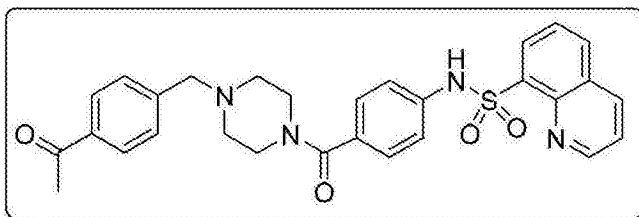
[1540]



[1541] ^1H NMR (400MHz, CDCl_3) δ : 2.39 (br s, 4H), 3.38 (br s, 2H), 3.50 (s, 2H), 3.68 (br s, 2H), 7.03 (d, 2H), 7.18 (d, 2H), 7.40 (t, 1H), 7.51–7.64 (m, 4H), 8.01 (d, 1H), 8.28 (d, 1H), 8.38 (d, 1H), 8.56 (s, 1H), 9.18 (s, 1H); HPLC纯度: 97.70%; ESMS: 512 (M^+ +1)。

[1542] N-(4-(4-(4-乙酰基苄基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (VIII-43):

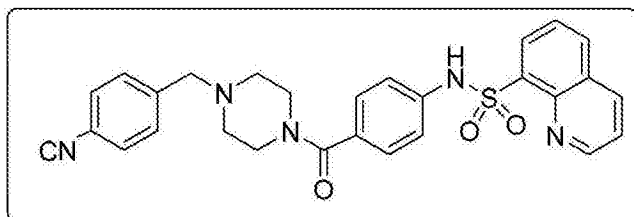
[1543]



[1544] ^1H NMR (400MHz, CDCl_3) δ : 2.38 (br d, 4H), 2.58 (s, 3H), 3.34 (br s, 2H), 3.58 (s, 2H), 3.68 (br s, 2H), 7.03 (d, 2H), 7.15 (d, 2H), 7.40 (d, 2H), 7.43 (d, 1H), 7.59–7.64 (m, 2H), 7.91 (d, 2H), 8.01 (d, 1H), 8.30 (d, 1H), 8.38 (d, 1H), 8.56 (s, 1H), 9.18 (s, 1H); HPLC纯度: 92.23%; ESMS: 529 (M^+ +1)。

[1545] N-(4-(4-(4-氰基苄基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (VIII-44):

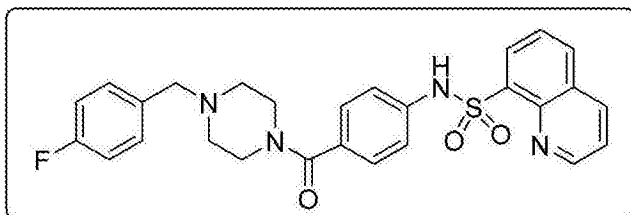
[1546]



[1547] ^1H NMR (400MHz, CDCl_3) δ : 2.39 (br s, 4H), 3.38 (br s, 2H), 3.52 (s, 2H), 3.68 (br s, 2H), 7.03 (d, 2H), 7.18 (d, 2H), 7.40 (d, 1H), 7.59–7.64 (m, 4H), 8.01 (d, 1H), 8.28 (d, 1H), 8.38 (d, 1H), 8.56 (s, 1H), 9.18 (s, 1H); HPLC纯度: 98.71%; LCMS: 512 (M^+ +1)。

[1548] N-(4-(4-(4-氟苄基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (VIII-45):

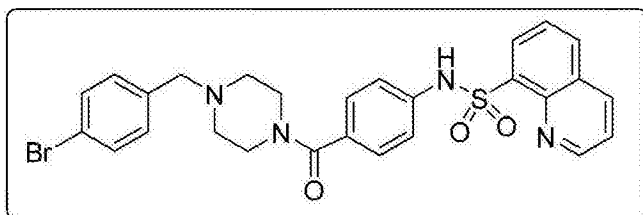
[1549]



[1550] ^1H NMR (400MHz, CDCl_3) δ : 2.38 (br d, 4H), 3.35 (br s, 2H), 3.46 (s, 2H), 3.64 (br s, 2H), 6.94 (t, 2H), 7.06 (t, 2H), 7.18 (d, 2H), 7.24–7.28 (m, 2H), 7.56–7.63 (m, 2H), 8.01 (d, 1H), 8.28 (d, 1H), 8.38 (d, 1H), 8.56 (s, 1H), 9.18 (s, 1H); HPLC纯度: 94.7%; LCMS: 505 ($\text{M}^+ + 1$).

[1551] N-(4-(4-(4-溴苄基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (VIII-46):

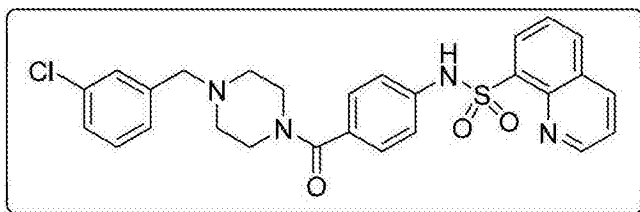
[1552]



[1553] ^1H NMR (400MHz, CDCl_3) δ : 2.38 (br d, 4H), 3.31 (br s, 2H), 3.41 (s, 2H), 3.64 (br s, 2H), 7.06 (d, 2H), 7.18 (t, 3H), 7.40 (d, 2H), 7.56–7.63 (m, 2H), 8.01 (d, 1H), 8.28 (d, 1H), 8.38 (d, 1H), 8.56 (s, 1H), 9.18 (s, 1H); HPLC纯度: 99.7%; LCMS: 567 ($\text{M}^+ + 2$).

[1554] N-(4-(4-(3-氯苄基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (VIII-47):

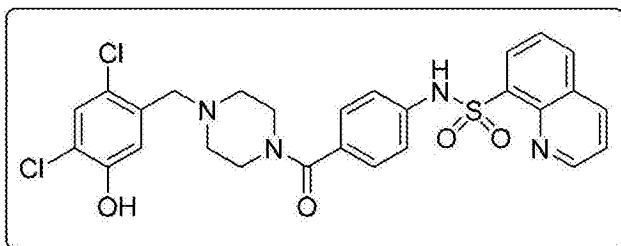
[1555]



[1556] ^1H NMR (400MHz, CDCl_3) δ : 2.39 (br d, 4H), 3.39 (br s, 2H), 3.48 (s, 2H), 3.64 (br s, 2H), 7.06 (d, 2H), 7.17 (d, 2H), 7.40 (d, 2H), 7.44 (d, 1H), 7.58–7.63 (m, 2H), 8.01 (d, 1H), 8.28 (d, 1H), 8.38 (d, 1H), 8.56 (s, 1H), 9.18 (s, 1H); HPLC纯度: 98.98%; ESMS: 521 ($\text{M}^+ + 1$).

[1557] N-(4-(4-(2,4-二氯-5-羟基苄基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (VIII-49):

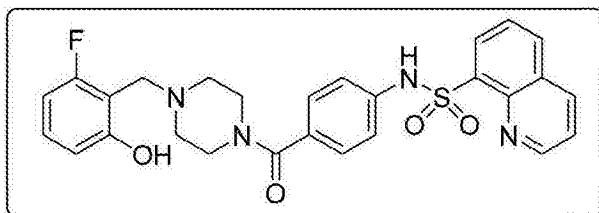
[1558]



[1559] ^1H NMR (400MHz, $\text{DMSO}-d_6$) δ : 2.39 (br s, 4H), 3.48 (br s, 4H), 3.70 (s, 2H), 6.98 (s, 1H), 7.01 (s, 1H), 7.10–7.20 (m, 4H), 7.70–7.79 (m, 2H), 8.28 (d, 1H), 8.43 (d, 1H), 8.55 (d, 1H), 9.18 (s, 1H), 10.41 (s, 1H); HPLC纯度: 95.42%; LCMS: 571 (M^+).

[1560] N-(4-(4-(2-氟-6-羟基苄基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (VIII-50):

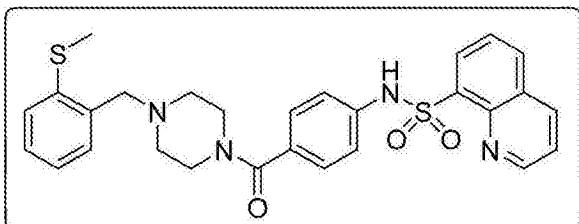
[1561]



[1562] ^1H NMR (400MHz, DMSO- d_6) δ : 2.39 (s, 4H), 3.42 (br s, 4H), 3.63 (s, 3H), 6.56–6.62 (m, 2H), 7.10–7.19 (m, 4H), 7.70–7.79 (m, 2H), 8.28 (d, 1H), 8.43 (d, 1H), 8.55 (d, 1H), 9.18 (s, 1H), 10.41 (s, 1H); HPLC纯度: 99.89%; LCMS: 521 (M^+ +1)。

[1563] N-(4-(4-(2-(甲硫基)苄基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (VIII-51):

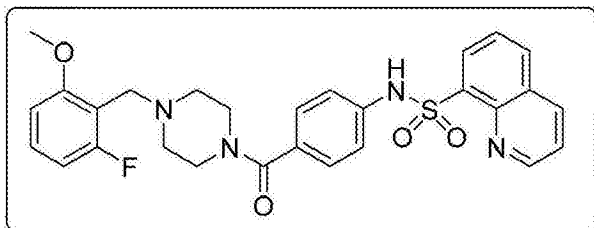
[1564]



[1565] ^1H NMR (400MHz, DMSO- d_6) δ : 2.35 (br s, 4H), 2.39 (s, 3H), 3.43 (s, 4H), 3.61 (s, 2H), 7.10–7.19 (m, 4H), 7.26 (s, 3H), 7.30 (q, 1H), 7.70–7.79 (m, 2H), 8.28 (d, 1H), 8.43 (d, 1H), 8.55 (d, 1H), 9.18 (s, 1H), 10.41 (s, 1H); HPLC纯度: 91.14%; LCMS: 533 (M^+ +1)。

[1566] N-(4-(4-(2-氟-6-甲氧基苄基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (VIII-52):

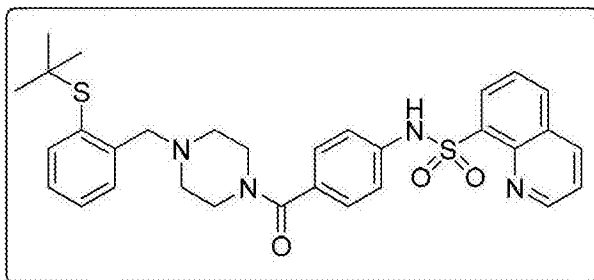
[1567]



[1568] ^1H NMR (400MHz, DMSO- d_6) δ : 2.32 (br s, 4H), 3.55 (s, 3H), 3.62 (br s, 4H), 3.80 (s, 2H), 6.78 (t, 1H), 6.84 (d, 1H), 7.13 (s, 4H), 7.30 (q, 1H), 7.70–7.79 (m, 2H), 8.28 (d, 1H), 8.43 (d, 1H), 8.55 (d, 1H), 9.18 (s, 1H), 10.41 (s, 1H); HPLC纯度: 98.18%; LCMS: 535 (M^+ +1)。

[1569] N-(4-(4-(2-(叔丁基硫基)苄基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (VIII-53):

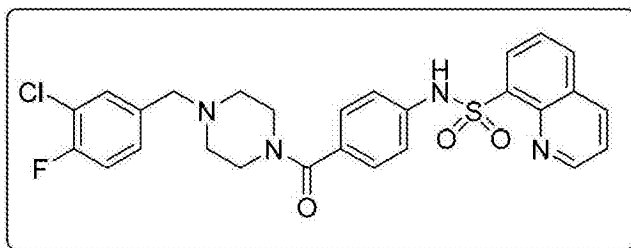
[1570]



[1571] ^1H NMR (400MHz, DMSO- d_6) δ : 1.24 (s, 9H), 2.37 (br s, 4H), 3.30 (br s, 4H), 3.78 (s, 2H), 7.08–7.18 (m, 4H), 7.25 (t, 1H), 7.41 (t, 1H), 7.50–7.59 (m, 2H), 7.70–7.79 (m, 2H), 8.29 (d, 1H), 8.43 (d, 1H), 8.48 (d, 1H), 9.18 (s, 1H), 10.41 (s, 1H); HPLC纯度: 97.92%; LCMS: 575 (M^+ +1)。

[1572] N-(4-(4-(3-氯-4-氟苄基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (VIII-54):

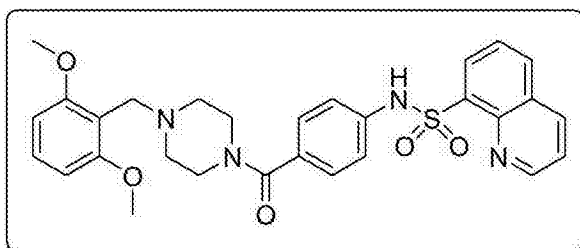
[1573]



[1574] ^1H NMR (400MHz, DMSO- d_6) δ : 2.29 (br s, 4H), 3.43 (s, 4H), 3.62 (s, 2H), 7.06–7.18 (m, 4H), 7.25–7.39 (m, 2H), 7.46 (d, 1H), 7.70–7.79 (m, 2H), 8.29 (d, 1H), 8.43 (d, 1H), 8.48 (d, 1H), 9.18 (s, 1H), 10.41 (s, 1H); HPLC纯度: 96.47%; LCMS: 539 (M^+).

[1575] N-(4-(4-(2,6-二甲氧基苄基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (VIII-55):

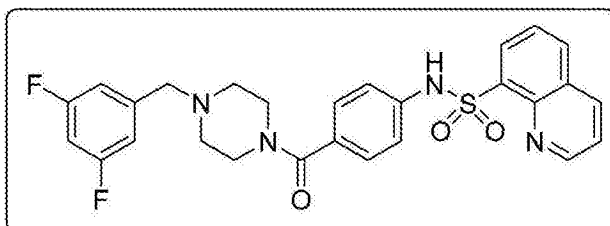
[1576]



[1577] ^1H NMR (400MHz, DMSO- d_6) δ : 2.32 (br s, 4H), 3.50 (br s, 4H), 3.76 (s, 6H), 3.81 (s, 2H), 6.60 (d, 2H), 7.10 (s, 3H), 7.22 (t, 1H), 7.70–7.79 (m, 2H), 8.28 (d, 1H), 8.43 (d, 1H), 8.54 (d, 1H), 9.18 (s, 1H), 10.41 (br s, 1H); HPLC纯度: 94.09%; LCMS: 547 ($M^+ + 1$).

[1578] N-(4-(4-(3,5-二氟苄基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (VIII-56):

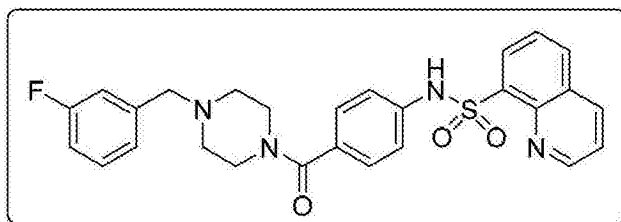
[1579]



[1580] ^1H NMR (400MHz, DMSO- d_6) δ : 2.30 (br s, 4H), 3.45 (s, 3H), 7.01 (d, 2H), 7.10–7.21 (m, 4H), 7.70–7.79 (m, 2H), 8.29 (d, 1H), 8.43 (d, 1H), 8.48 (d, 1H), 9.18 (s, 1H), 10.41 (s, 1H); HPLC纯度: 96.47%; LCMS: 523 ($M^+ + 1$).

[1581] N-(4-(4-(3-氟苄基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (VIII-57):

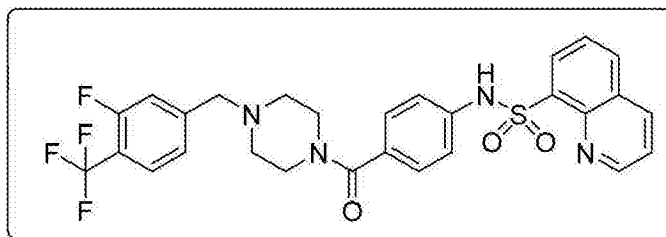
[1582]



[1583] ^1H NMR (400MHz, DMSO- d_6) δ : 2.36 (br s, 4H), 3.41 (br s, 2H), 3.59 (s, 2H), 7.10–7.21 (m, 6H), 7.37–7.40 (m, 1H), 7.70–7.79 (m, 2H), 8.31 (d, 1H), 8.43 (d, 1H), 8.48 (d, 1H), 9.18 (s, 1H), 10.41 (s, 1H); HPLC纯度: 94.31%; LCMS: 505 ($M^+ + 1$).

[1584] N-(4-(4-(3-氟-4-(三氟甲基)苄基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (VIII-58):

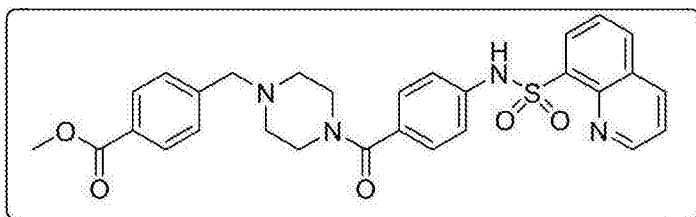
[1585]



[1586] ^1H NMR (400MHz, DMSO- d_6) δ : 2.36 (br s, 4H), 3.42 (br s, 4H), 3.59 (s, 3H), 7.10–7.21 (m, 4H), 7.39 (d, 1H), 7.42 (d, 1H), 7.70–7.79 (m, 2H), 8.32 (d, 1H), 8.43 (d, 1H), 8.48 (d, 1H), 9.18 (s, 1H), 10.41 (s, 1H); HPLC纯度: 96.69%; LCMS: 595 (M^+ +23)。

[1587] 4-((4-(4-(喹啉-8-亚磺酰氨基)苯甲酰基)哌嗪-1-基)甲基)苯甲酸甲酯(VIII-59):

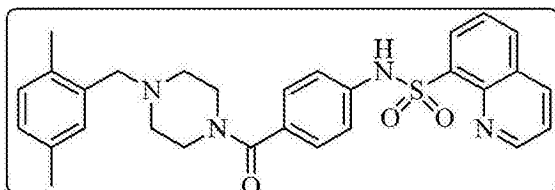
[1588]



[1589] ^1H NMR (400MHz, DMSO- d_6) δ : 2.36 (br s, 4H), 3.43 (br s, 4H), 3.59 (s, 2H), 3.83 (s, 3H), 7.10–7.21 (m, 4H), 7.46 (d, 2H), 7.70–7.79 (m, 2H), 7.95 (d, 2H), 8.32 (d, 1H), 8.43 (d, 1H), 8.48 (d, 1H), 9.18 (s, 1H), 10.41 (s, 1H); HPLC纯度: 97.92%; LCMS: 545 (M^+ +1)

[1590] N-(4-(4-(2,5-二甲基苄基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺(VIII-60):

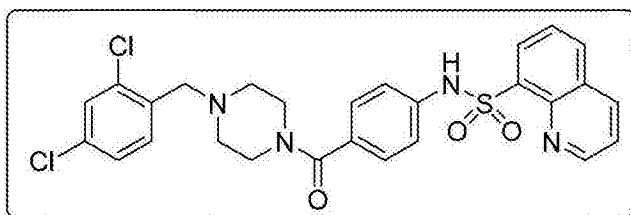
[1591]



[1592] ^1H NMR (400MHz, DMSO- d_6) δ : 2.38 (s, 6H), 2.41 (br s, 4H), 3.41 (br s, 4H), 6.97–7.02 (m, 2H), 7.10–7.21 (m, 3H), 7.31 (s, 1H), 7.70–7.79 (m, 2H), 8.29 (d, 1H), 8.43 (d, 1H), 8.56 (d, 1H), 9.18 (s, 1H), 10.41 (br s, 1H); HPLC纯度: 99.73%; LCMS: 515 (M^+ +1)。

[1593] N-(4-(4-(2,4-二氯苄基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺(VIII-61):

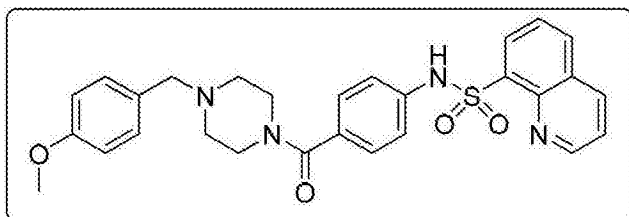
[1594]



[1595] ^1H NMR (400MHz, DMSO- d_6) δ : 2.38 (br s, 4H), 3.41 (br s, 4H), 3.59 (s, 2H), 7.10 (q, 4H), 7.39 (d, 1H), 7.43 (d, 1H), 7.59 (s, 1H), 7.70–7.79 (m, 2H), 8.29 (d, 1H), 8.43 (d, 1H), 8.56 (d, 1H), 9.18 (s, 1H), 10.41 (br s, 1H); HPLC纯度: 99.34%; LCMS: 555 (M^+)。

[1596] N-(4-(4-(4-甲氧基苄基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺(VIII-62):

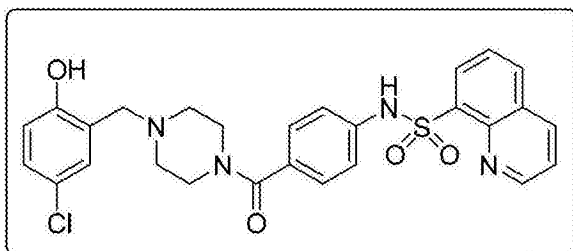
[1597]



[1598] ^1H NMR (400MHz, DMSO- d_6) δ : 2.32 (br s, 4H), 3.52 (br s, 4H), 3.79 (s, 2H), 6.81 (d, 2H), 7.10–7.21 (m, 5H), 7.31 (s, 1H), 7.70–7.79 (m, 2H), 8.28 (d, 1H), 8.43 (d, 1H), 8.56 (d, 1H), 9.18 (s, 1H), 10.41 (br s, 1H); HPLC纯度: 96.49%; LCMS: 539 (M^+ +23)。

[1599] N-(4-(4-(5-氯-2-羟基苄基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (VIII-63):

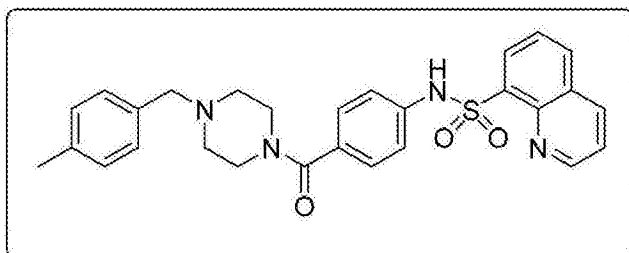
[1600]



[1601] ^1H NMR (400MHz, DMSO- d_6) δ : 2.38 (br s, 4H), 3.59 (s, 4H), 3.62 (s, 2H), 6.79 (d, 2H), 7.06–7.21 (m, 6H), 7.70–7.81 (m, 2H), 8.31 (d, 1H), 8.28 (d, 1H), 8.38 (d, 1H), 8.56 (s, 1H), 9.18 (s, 1H), 10.41 (s, 1H); HPLC纯度: 97.02%; LCMS: 537 (M^+)。

[1602] N-(4-(4-(4-甲基苄基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (VIII-64):

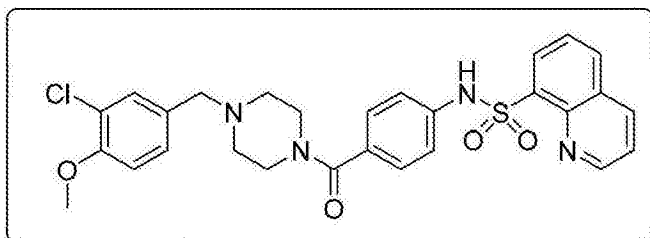
[1603]



[1604] ^1H NMR (400MHz, DMSO- d_6) δ : 2.30 (s, 4H), 3.42 (s, 4H), 3.46 (s, 2H), 7.06–7.20 (m, 8H), 7.70–7.79 (m, 2H), 8.28 (d, 1H), 8.43 (d, 1H), 8.56 (d, 1H), 9.18 (s, 1H), 10.41 (br s, 1H); HPLC纯度: 98.59%; LCMS: 501 (M^+ +1)。

[1605] N-(4-(4-(3-氯-4-甲氧基苄基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (VIII-65):

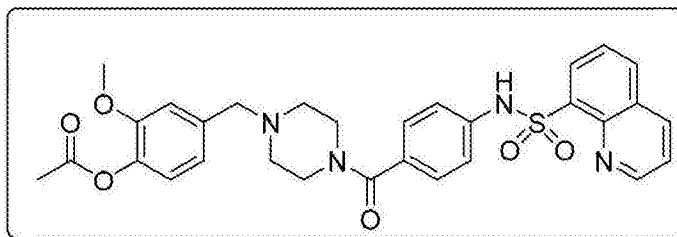
[1606]



[1607] ^1H NMR (400MHz, DMSO- d_6) δ : 2.30 (br s, 4H), 3.45 (br s, 6H), 3.81 (s, 3H), 7.04–7.21 (m, 6H), 7.31 (s, 1H), 7.70–7.79 (m, 2H), 8.28 (d, 1H), 8.43 (d, 1H), 8.56 (d, 1H), 9.18 (s, 1H), 10.41 (br s, 1H); HPLC纯度: 99.70%; LCMS: 551 (M^+)。

[1608] 乙酸2-甲氧基-4-((4-(4-(喹啉-8-亚磺酰氨基)苯甲酰基)哌嗪-1-基)甲基)苯酯 (VIII-66):

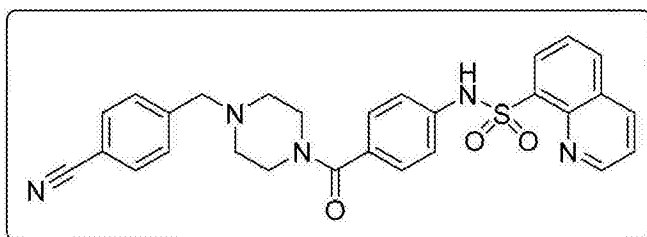
[1609]



[1610] ^1H NMR (400MHz, DMSO- d_6) δ : 2.22 (s, 3H), 2.38 (br s, 4H), 3.31 (br s, 2H), 3.51 (s, 4H), 3.80 (s, 3H), 6.89 (d, 1H), 7.04 (d, 2H), 7.10–7.23 (m, 4H), 7.71–7.79 (m, 2H), 8.31 (d, 1H), 8.45 (d, 1H), 8.56 (d, 1H), 9.18 (d, 1H), 10.42 (s, 1H); HPLC纯度: 91.90%; LCMS: 575 (M^+ + 1)。

[1611] N-(4-(4-(4-氰基苄基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (VIII-67):

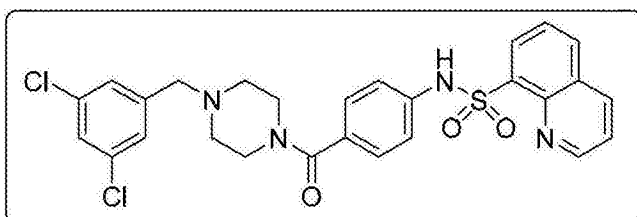
[1612]



[1613] ^1H NMR (400MHz, DMSO- d_6) δ : 2.23 (br s, 4H), 3.41 (br s, 2H), 3.54 (s, 2H), 7.06 (q, 4H), 7.22 (s, 2H), 7.62–7.76 (m, 4H), 8.22 (d, 1H), 8.38 (d, 1H), 8.44 (d, 1H), 9.08 (s, 1H), 10.40 (s, 1H); HPLC纯度: 99.87%; MS: 512 (M^+ + 1)。

[1614] N-(4-(4-(3,5-二氯苄基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (VIII-68):

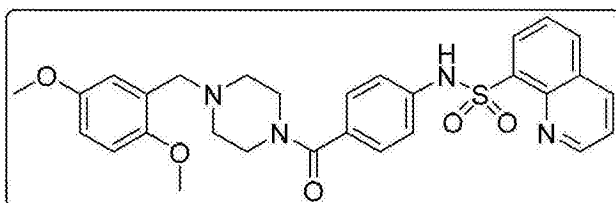
[1615]



[1616] ^1H NMR (400MHz, DMSO- d_6) δ : 2.24 (br s, 4H), 3.41 (br s, 4H), 3.44 (s, 2H), 7.08 (q, 3H), 7.30 (2H), 7.41 (s, 1H), 7.60–7.66 (m, 2H), 8.21 (d, 1H), 8.38 (d, 1H), 8.44 (d, 1H), 9.08 (s, 1H), 10.38 (s, 1H); HPLC纯度: 99.83%; LCMS: 555 (M^+)。

[1617] N-(4-(4-(2,5-二甲氧基苄基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (VIII-69):

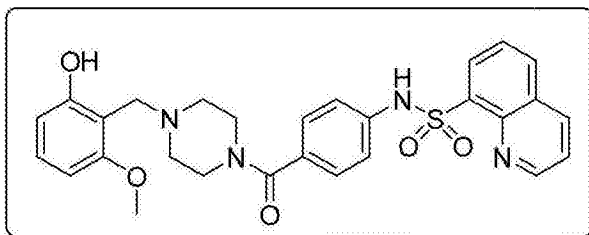
[1618]



[1619] ^1H NMR (400MHz, DMSO- d_6) δ : 2.23 (br s, 4H), 3.40 (s, 4H), 3.61 (d, 6H), 3.72 (s, 2H), 6.82 (d, 3H), 7.02–7.10 (m, 4H), 7.60–7.68 (m, 2H), 8.22 (d, 1H), 8.38 (d, 1H), 8.44 (d, 1H), 9.08 (s, 1H), 10.40 (s, 1H); HPLC纯度: 98.63%; LCMS: 547 (M^+ + 1)。

[1620] N-(4-(4-(2-羟基-6-甲氧基苄基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (VIII-70):

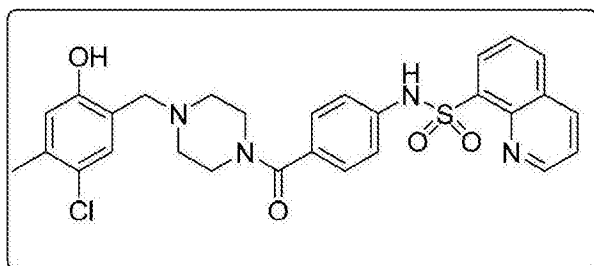
[1621]



[1622] ^1H NMR (400MHz, DMSO- d_6) δ : 2.36 (br s, 4H), 3.54 (s, 4H), 3.61 (s, 2H), 3.64 (s, 3H), 6.36 (d, 1H), 7.00–7.10 (m, 5H), 7.60–7.68 (m, 2H), 8.20 (d, 1H), 8.38 (d, 1H), 8.44 (d, 1H), 9.08 (s, 1H), 10.40 (s, 1H); HPLC纯度: 98.03%; LCMS: 533 (M^+ + 1)。

[1623] N-(4-(4-(5-氯-2-羟基-4-甲基苄基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (VIII-71):

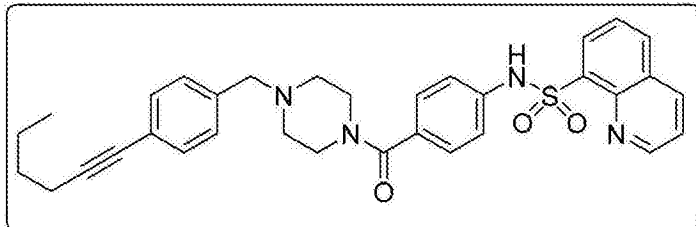
[1624]



[1625] ^1H NMR (400MHz, DMSO- d_6) δ : 2.18 (s, 3H), 2.30 (br s, 4H), 3.41 (s, 4H), 3.46 (s, 2H), 6.68 (s, 1H), 7.10–7.19 (m, 4H), 7.65–7.78 (m, 2H), 8.24 (d, 1H), 8.41 (d, 1H), 8.51 (d, 1H), 9.12 (s, 1H), 10.40 (s, 1H); HPLC纯度: 96.25%; LCMS: 551 (M^+)。

[1626] N-(4-(4-(4-(己-1-炔基)苄基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (VIII-72):

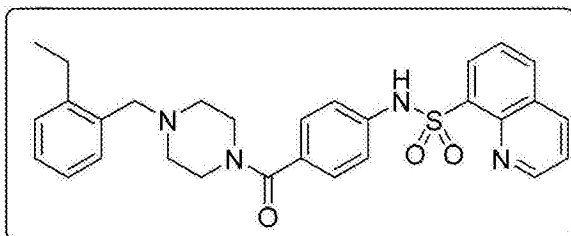
[1627]



[1628] ^1H NMR (400MHz, DMSO- d_6) δ : 0.93 (t, 3H), 1.38–1.41 (m, 4H), 2.22 (br s, 6H), 2.38 (t, 2H), 2.80 (s, 3H), 3.44 (s, 2H), 6.22 (d, 1H), 7.00–7.12 (m, 4H), 7.22 (dd, 2H), 7.62–7.70 (m, 2H), 8.24 (d, 1H), 8.38 (d, 1H), 8.44 (d, 1H), 9.08 (s, 1H), 9.60 (br s, 1H), 10.36 (s, 1H); HPLC纯度: 99.84%; LCMS: 567 (M^+ + 1)。

[1629] N-(4-(4-(2-乙基苄基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (VIII-73):

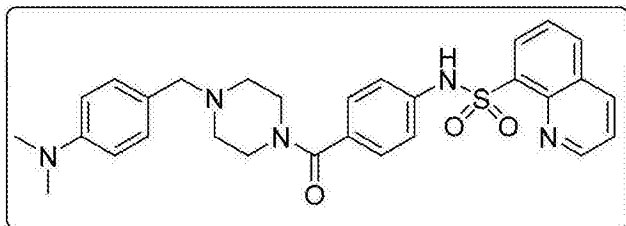
[1630]



[1631] ^1H NMR (400MHz, DMSO- d_6) δ : 1.12 (t, 3H), 2.23 (br s, 4H), 2.62 (q, 2H), 3.40 (s, 2H), 3.43 (br s, 4H), 7.04–7.20 (m, 5H), 7.65–7.70 (m, 2H), 8.25 (d, 1H), 8.41 (d, 1H), 8.50 (d, 1H), 9.10 (s, 1H), 10.40 (s, 1H); HPLC纯度: 98.83%; LCMS: 515 (M^+ + 1)。

[1632] N-(4-(4-(4-(二甲基氨基)苄基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺(VIII-74):

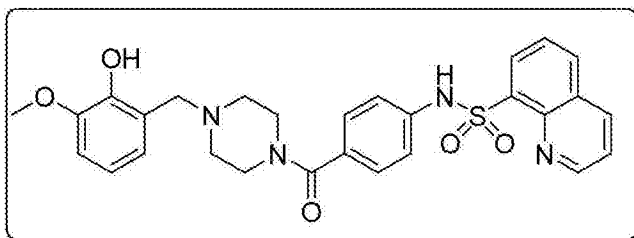
[1633]



[1634] ^1H NMR (400MHz, DMSO- d_6) δ : 2.21 (br s, 4H), 2.81 (s, 6H), 3.41 (br s, 6H), 6.61 (d, 2H), 7.01–7.11 (m, 6H), 7.48 (d, 2H), 7.63–7.70 (m, 2H), 8.22 (d, 1H), 8.38 (d, 1H), 8.45 (d, 1H), 9.08 (s, 1H), 10.40 (br s, 1H); HPLC纯度: 96.86%; LCMS: 552 (M^+ +23)。

[1635] N-(4-(4-(2-羟基-3-甲氧基苄基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺(VIII-75):

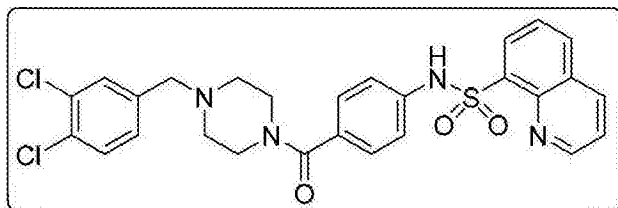
[1636]



[1637] ^1H NMR (400MHz, DMSO- d_6) δ : 2.30 (br s, 4H), 3.41 (br s, 4H), 3.54 (s, 2H), 3.75 (s, 3H), 6.66 (s, 2H), 6.80 (d, 1H), 7.20 (q, 4H), 7.48 (d, 2H), 7.62–7.70 (m, 2H), 8.24 (d, 1H), 8.38 (d, 1H), 8.48 (d, 1H), 9.10 (s, 1H), 10.40 (s, 1H); HPLC纯度: 99.76%; LCMS: 555 (M^+ +23)。

[1638] N-(4-(4-(3,4-二氯苄基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺(VIII-76):

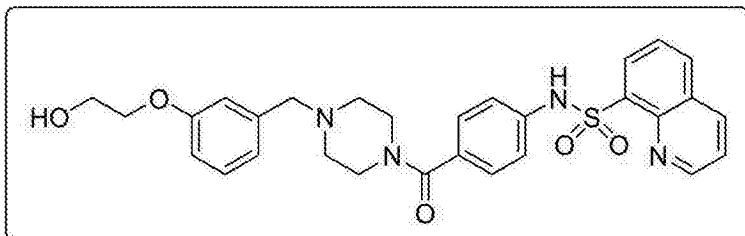
[1639]



[1640] ^1H NMR (400MHz, DMSO- d_6) δ : 2.24 (br s, 4H), 3.41 (s, 4H), 3.45 (s, 2H), 7.05 (q, 4H), 7.24 (d, 1H), 7.52–7.58 (m, 2H), 7.66–7.74 (m, 4H), 8.24 (d, 1H), 8.38 (d, 1H), 8.48 (d, 1H), 9.10 (s, 1H), 10.40 (br s, 1H); HPLC纯度: 97.35%; LCMS: 555 (M^+)。

[1641] N-(4-(4-(3-(2-羟基乙氧基)苄基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺(VIII-77):

[1642]

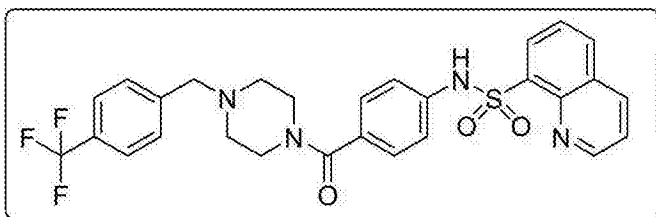


[1643] ^1H NMR (400MHz, DMSO- d_6) δ : 2.23 (br s, 4H), 3.40 (s, 4H), 3.69 (q, 2H), 3.98 (t, 2H), 4.78 (s, 2H), 6.79–7.01 (m, 3H), 7.12 (q, 4H), 7.18 (t, 1H), 7.62–7.70 (m, 2H), 8.26 (d, 1H), 8.38 (d, 1H), 8.46 (s, 1H), 9.10 (s, 1H), 10.38 (s, 1H); HPLC纯度: 97.11%; LCMS: 547 (M^+)。

+1)。

[1644] N-(4-(4-(4-(三氟甲基)苄基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺(VIII-78):

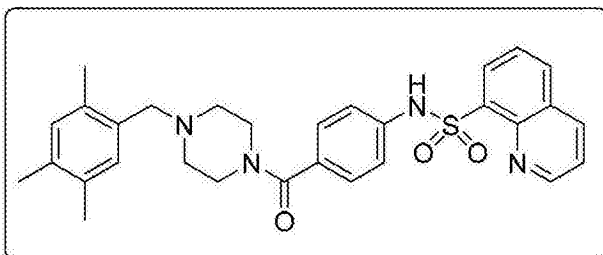
[1645]



[1646] ^1H NMR (400MHz, DMSO- d_6) δ : 2.24 (br s, 4H), 3.46 (br s, 4H), 3.55 (s, 2H), 7.08 (q, 4H), 7.48 (d, 2H), 7.60-7.70 (m, 4H), 8.24 (d, 1H), 8.38 (d, 1H), 8.48 (d, 1H), 9.10 (s, 1H), 10.40 (s, 1H); HPLC纯度: 99.28%; LCMS: 555 (M^+ +1)。

[1647] N-(4-(4-(2,4,5-三甲基苄基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺(VIII-79):

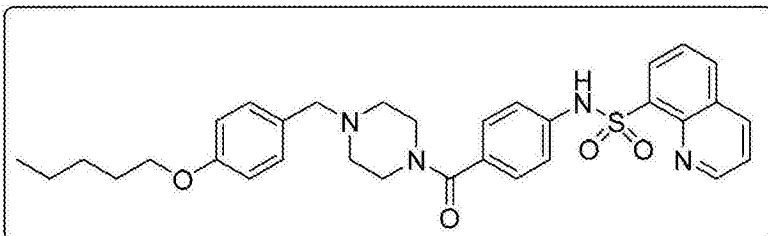
[1648]



[1649] ^1H NMR (400MHz, DMSO- d_6) δ : 2.12 (s, 6H), 2.20 (s, 3H), 2.23 (br s, 4H), 3.41 (br s, 4H), 3.46 (s, 2H), 6.88 (d, 2H), 7.08 (q, 4H), 7.62-7.70 (m, 2H), 8.28 (d, 1H), 8.40 (d, 1H), 8.48 (d, 1H), 9.10 (s, 1H), 10.40 (s, 1H); HPLC纯度: 99.58%; LCMS: 529 (M^+ +1)。

[1650] N-(4-(4-(4-(戊氧基)苄基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺(VIII-80):

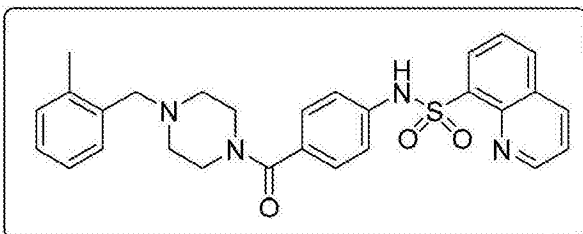
[1651]



[1652] ^1H NMR (400MHz, DMSO- d_6) δ : 0.85 (t, 3H), 1.25-1.39 (m, 4H), 1.65 (五重峰, 2H), 2.22 (br s, 4H), 3.38 (s, 4H), 3.41 (s, 2H), 3.90 (t, 2H), 6.80 (d, 2H), 7.08-7.14 (m, 6H), 7.68-7.75 (m, 2H), 8.28 (d, 1H), 8.40 (d, 1H), 8.50 (s, 1H), 9.10 (s, 1H), 10.40 (s, 1H); HPLC纯度: 99.80%; LCMS: 573 (M^+ +1)。

[1653] N-(4-(4-(2-甲基苄基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺(VIII-81):

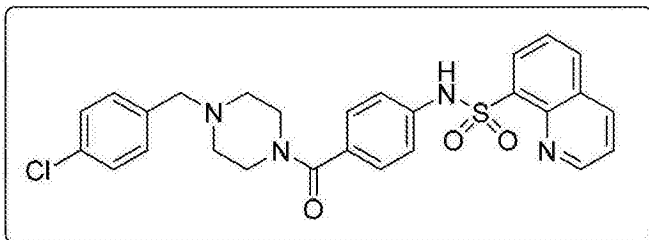
[1654]



[1655] ^1H NMR (400MHz, DMSO- d_6) δ : 2.24 (s, 3H), 2.36 (br s, 4H), 3.38 (s, 4H), 3.40 (s, 2H), 7.05-7.20 (m, 6H), 7.65-7.74 (m, 2H), 8.26 (d, 1H), 8.39 (d, 1H), 8.46 (s, 1H), 9.10 (s, 1H), 10.40 (s, 1H); HPLC纯度: 98.75%; LCMS: 501 (M^+ +1)。

[1656] N-(4-(4-(4-氯苄基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺(VIII-82):

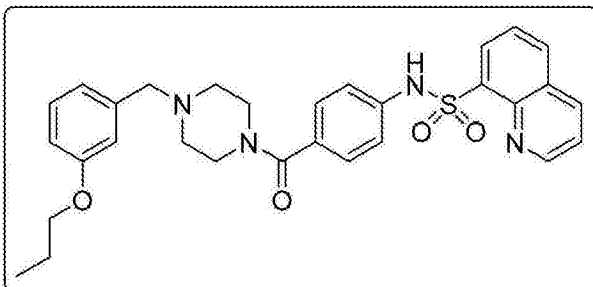
[1657]



[1658] ^1H NMR (400MHz, CDCl_3) δ : 2.38 (br d, 4H), 3.31 (br s, 2H), 3.41 (s, 2H), 3.64 (br s, 2H), 6.94 (d, 2H), 7.06 (t, 4H), 7.40 (d, 2H), 7.56–7.63 (m, 2H), 8.01 (d, 1H), 8.28 (m, 2H), 9.18 (s, 1H); HPLC纯度: 97.61%; LCMS: 522.0 (M^+).

[1659] N-(4-(4-(3-丙氧基苄基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺(VIII-83):

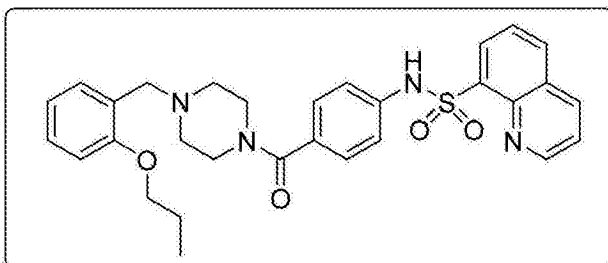
[1660]



[1661] ^1H NMR (400MHz, $\text{DMSO}-d_6$) δ : 0.97 (t, 3H), 1.70 (q, 2H), 2.32 (s, 4H), 3.41 (br s, 4H), 3.90 (t, 2H), 4.22 (br s, 2H), 6.99 (d, 2H), 7.17 (dd, 4H), 7.36 (t, 1H), 7.68–7.74 (m, 2H), 8.28 (d, 1H), 8.39 (d, 1H), 8.50 (d, 1H), 9.16 (s, 1H), 10.50 (s, 1H); HPLC纯度: 99.57%; LCMS: 545 ($\text{M}^+ + 1$).

[1662] N-(4-(4-(2-丙氧基苄基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺(VIII-84):

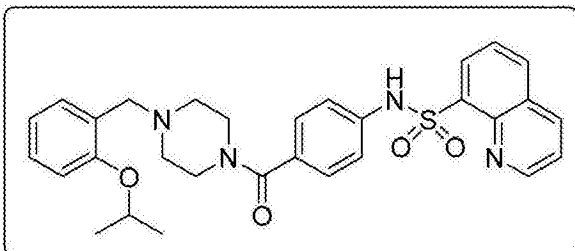
[1663]



[1664] ^1H NMR (400MHz, $\text{DMSO}-d_6$) δ : 0.97 (t, 3H), 1.70 (q, 2H), 2.36 (br s, 4H), 3.42 (br s, 4H), 3.90 (t, 2H), 4.22 (br s, 2H), 6.99 (d, 2H), 7.17 (dd, 4H), 7.40 (br s, 1H), 7.68–7.74 (m, 2H), 8.28 (d, 1H), 8.39 (d, 1H), 8.50 (d, 1H), 9.16 (s, 1H), 10.50 (s, 1H); HPLC纯度: 99.12%; LCMS: 545 ($\text{M}^+ + 1$).

[1665] N-(4-(4-(2-异丙氧基苄基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺(VIII-85):

[1666]

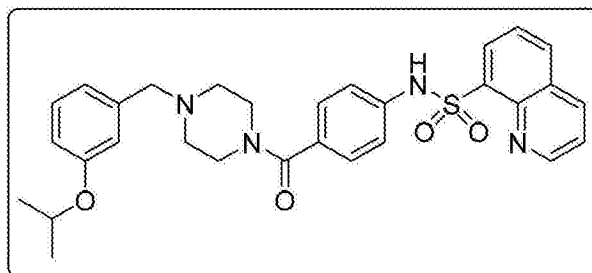


[1667] ^1H NMR (400MHz, $\text{DMSO}-d_6$) δ : 1.37 (d, 6H), 3.12 (br s, 3H), 4.25 (br s, 2H), 4.71–

4.75 (m, 1H), 7.01 (t, 2H), 7.17 (d, 2H), 7.22 (d, 2H), 7.42 (br s, 2H), 7.70–7.79 (m, 2H), 8.30 (d, 1H), 8.42 (d, 1H), 8.51 (d, 1H), 9.14 (s, 1H), 9.50 (br s, 1H), 10.55 (s, 1H); HPLC纯度: 99.17%; LCMS: 545 ($M^+ + 1$)。

[1668] N-(4-(4-(3-异丙氧基苄基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (VIII-86):

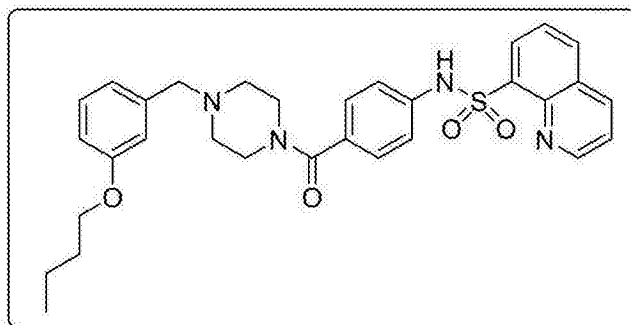
[1669]



[1670] ^1H NMR (400MHz, DMSO- d_6) δ : 1.29 (d, 6H), 2.36 (br s, 4H), 3.02 (br s, 4H), 4.25 (s, 2H), 4.62 (六重峰, 1H), 6.99–7.09 (m, 3H), 7.20 (dd, 4H), 7.39 (t, 1H), 7.70–7.79 (m, 2H), 8.30 (d, 1H), 8.42 (d, 1H), 8.51 (d, 1H), 9.14 (s, 1H), 9.79 (br s, 1H), 10.57 (s, 1H); HPLC纯度: 99.11%; LCMS: 545 ($M^+ + 1$)。

[1671] N-(4-(4-(3-丁氧基苄基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (VIII-87):

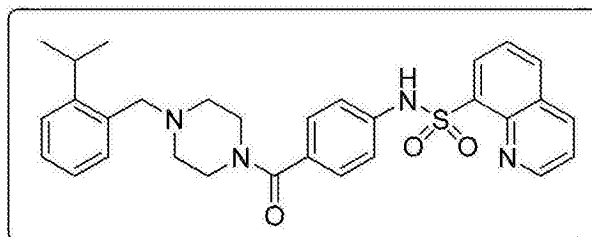
[1672]



[1673] ^1H NMR (400MHz, DMSO- d_6) δ : 0.90 (t, 3H), 1.21 (六重峰, 2H), 1.64 (五重峰, 2H), 2.31 (br s, 4H), 3.36 (br s, 4H), 3.92 (t, 2H), 4.23 (s, 2H), 6.93–7.01 (m, 2H), 7.17 (q, 4H), 7.31 (s, 2H), 7.63–7.74 (m, 2H), 8.28 (d, 1H), 8.40 (d, 1H), 8.51 (d, 1H), 9.10 (s, 1H), 9.50 (br s, 1H), 10.55 (s, 1H); HPLC纯度: 99.06%; LCMS: 559 ($M^+ + 1$)。

[1674] N-(4-(4-(2-异丙基苄基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (VIII-88):

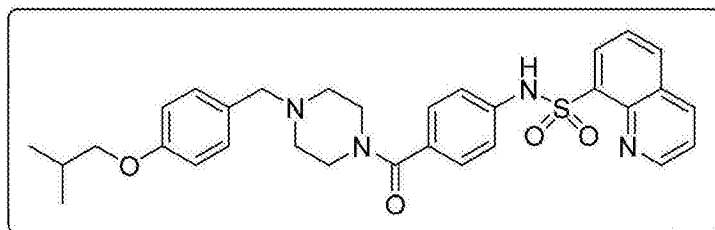
[1675]



[1676] ^1H NMR (400MHz, DMSO- d_6) δ : 1.17 (d, 6H), 3.10 (br s, 4H), 3.21 (br s, 4H), 4.35 (s, 2H), 4.62 (sextate, 1H), 7.18 (dd, 4H), 7.17 (d, 2H), 7.21 (br s, 1H), 7.20 (s, 2H), 7.68–7.74 (m, 2H), 8.28 (d, 1H), 8.40 (d, 1H), 8.51 (d, 1H), 9.14 (s, 1H), 9.50 (br s, 1H), 10.55 (s, 1H); HPLC纯度: 99.16%; LCMS: 529 ($M^+ + 1$)。

[1677] N-(4-(4-(4-异丁氧基苄基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (VIII-89):

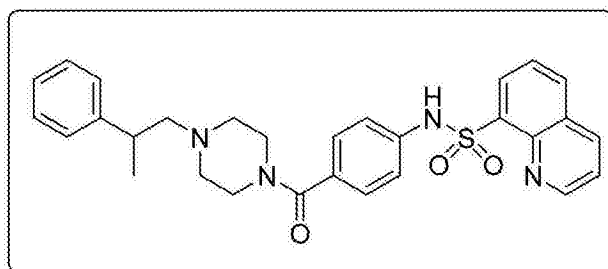
[1678]



[1679] ^1H NMR (400MHz, DMSO- d_6) δ : 0.96 (d, 6H), 2.00 (七重峰, 1H), 2.99 (br s, 2H), 3.18 (br s, 2H), 3.22 (br s, 2H), 3.70 (d, 2H), 4.20 (s, 2H), 6.99 (d, 2H), 7.18 (dd, 4H), 7.35 (d, 2H), 7.65–7.73 (m, 2H), 8.28 (d, 1H), 8.40 (d, 1H), 8.51 (d, 1H), 9.10 (s, 1H), 9.50 (br s, 1H), 10.55 (s, 1H); HPLC纯度: 99.06%; LCMS: 559 (M^+ +1)。

[1680] N-(4-(4-(2-苯基丙基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (VIII-90):

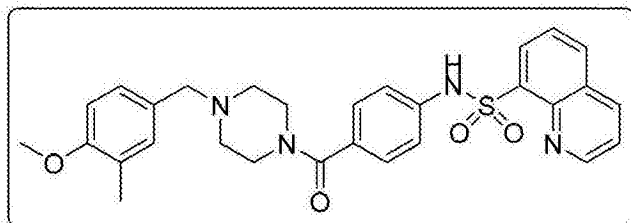
[1681]



[1682] ^1H NMR (400MHz, DMSO- d_6) δ : 1.21 (d, 3H), 2.99 (br s, 3H), 3.21 (br s, 2H), 7.17 (d, 4H), 7.21–7.35 (m, 4H), 7.63–7.74 (m, 2H), 8.28 (d, 1H), 8.40 (d, 1H), 8.51 (d, 1H), 9.10 (s, 1H), 9.24 (br s, 1H), 10.55 (s, 1H); HPLC纯度: 99.88%; LCMS: 515 (M^+ +1)。

[1683] N-(4-(4-(4-甲氧基-3-甲基苄基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (VIII-91):

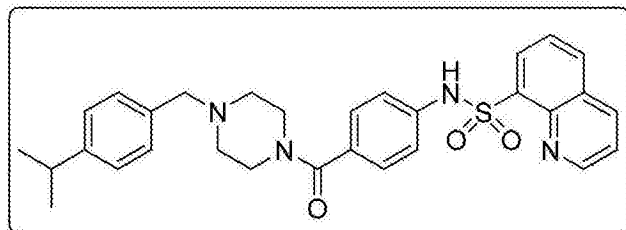
[1684]



[1685] ^1H NMR (400MHz, DMSO- d_6) δ : 2.19 (s, 3H), 3.02 (br s, 2H), 3.20 (br s, 2H), 3.30 (br s, 4H), 3.80 (s, 3H), 4.21 (s, 2H), 7.01 (d, 1H), 7.16–7.29 (m, 4H), 7.70–7.79 (m, 2H), 8.28 (d, 1H), 8.44 (d, 1H), 8.57 (d, 1H), 9.14 (s, 1H), 9.78 (br s, 1H), 10.55 (s, 1H); HPLC纯度: 99.86%; LCMS: 531 (M^+ +1)。

[1686] N-(4-(4-(4-异丙基苄基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (VIII-92):

[1687]

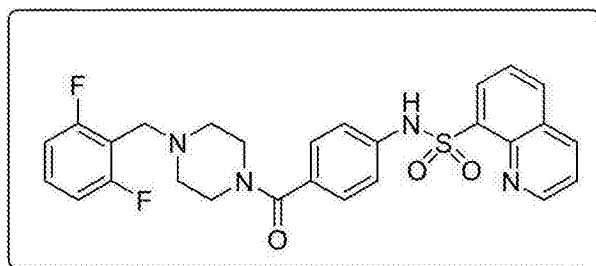


[1688] ^1H NMR (400MHz, DMSO- d_6) δ : 1.20 (d, 6H), 2.31 (br s, 4H), 2.95 (五重峰, 1H), 3.42 (br s, 4H), 4.22 (br s, 2H), 7.20 (dd, 4H), 7.39 (q, 4H), 7.70–7.78 (m, 2H), 8.28 (d, 1H), 8.46 (d, 1H), 8.53 (d, 1H), 9.14 (s, 1H), 9.60 (br s, 1H), 10.58 (s, 1H); HPLC纯度: 97.92%;

LCMS: 529 ($M^+ + 1$)。

[1689] N-(4-(4-(2,6-二氟苄基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺化合物(VIII-93):

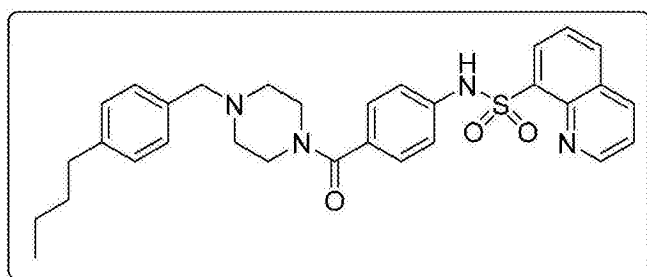
[1690]



[1691] ^1H NMR (400MHz, DMSO- d_6) δ : 2.31 (br s, 4H), 3.44 (br s, 4H), 3.61 (s, 2H), 7.02–7.26 (m, 5H), 7.56 (br s, 1H), 7.70–7.78 (m, 2H), 8.28 (d, 1H), 8.43 (d, 1H), 8.50 (d, 1H), 9.14 (s, 1H), 10.42 (s, 1H); HPLC纯度: 99.64%; LCMS: 523 ($M^+ + 1$)。

[1692] N-(4-(4-(4-丁基苄基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺(VIII-94):

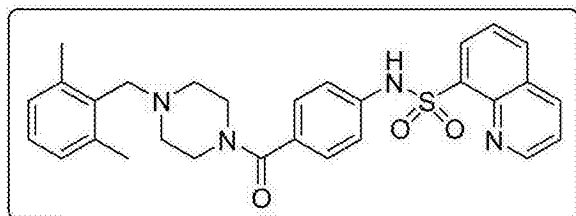
[1693]



[1694] ^1H NMR (400MHz, DMSO- d_6) δ : 0.85 (t, 3H), 1.25 (六重峰, 2H), 1.32 (五重峰, 2H), 2.59 (t, 2H), 3.01 (br s, 4H), 3.12 (br s, 2H), 3.22 (br s, 2H), 4.21 (s, (2H), 7.11 (d, 2H), 7.21 (d, 2H), 7.25 (d, 2H), 7.30 (d, 2H), 7.63–7.71 (m, 2H), 8.28 (d, 1H), 8.40 (d, 1H), 8.51 (d, 1H), 9.10 (s, 1H), 9.78 (br s, 1H), 10.50 (s, 1H); HPLC纯度: 99.98%; LCMS: 543 ($M^+ + 1$)。

[1695] N-(4-(4-(2,6-二甲基苄基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺(VIII-95):

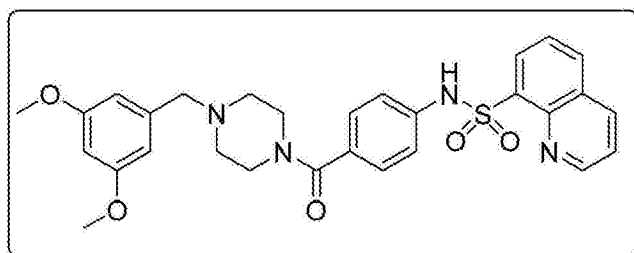
[1696]



[1697] ^1H NMR (400MHz, DMSO- d_6) δ : 2.25 (s, 6H), 2.41 (br s, 4H), 3.02 (br s, 2H), 3.20 (br s, 2H), 4.21 (br s, 2H), 7.05 (d, 3H), 7.17 (d, 2H), 7.24 (d, 2H), 7.70–7.79 (m, 2H), 8.28 (d, 1H), 8.44 (d, 1H), 8.57 (d, 1H), 9.14 (s, 1H), 9.78 (br s, 1H), 10.55 (s, 1H); HPLC纯度: 98.76%; LCMS: 515 ($M^+ + 1$)。

[1698] N-(4-(4-(3,5-二甲氧基苄基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺(VIII-96):

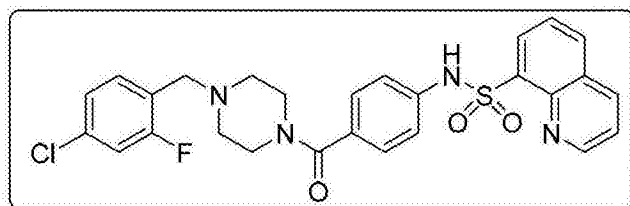
[1699]



[1700] ^1H NMR (400MHz, DMSO- d_6) δ : 2.32 (br s, 4H), 3.44 (br s, 4H), 3.72 (d, 6H), 4.19 (s, 2H), 6.59 (d, 1H), 7.18 (dd, 4H), 7.69–7.75 (m, 2H), 8.28 (d, 1H), 8.42 (d, 1H), 8.50 (d, 1H), 9.14 (s, 1H), 9.78 (br s, 1H), 10.51 (s, 1H); HPLC纯度: 93.00%; LCMS: 547 (M^+ +1)。

[1701] N-(4-(4-(4-氯-2-氟苄基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (VIII-97):

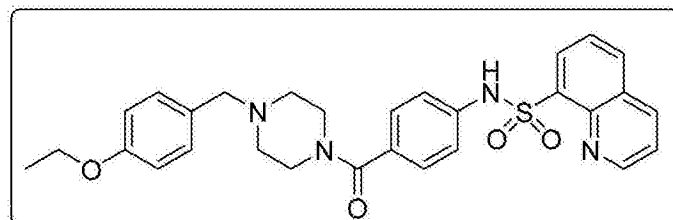
[1702]



[1703] ^1H NMR (400MHz, DMSO- d_6) δ : 2.38 (br s, 4H), 3.46 (br s, 4H), 3.77 (s, 3H), 4.40 (s, 2H), 7.22 (q, 4H), 7.34–7.44 (m, 2H), 7.55 (t, 1H), 7.63–7.70 (m, 2H), 8.20 (d, 1H), 8.42 (d, 2H), 9.14 (s, 1H); HPLC纯度: 98.85%; LCMS: 539 (M^+)。

[1704] N-(4-(4-(4-乙氧基苄基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (VIII-98):

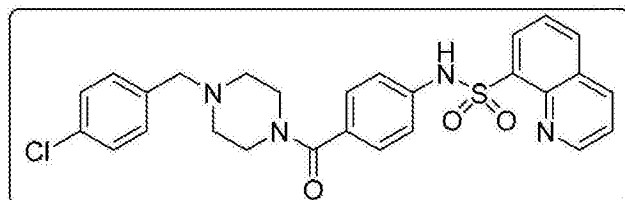
[1705]



[1706] ^1H NMR (400MHz, DMSO- d_6) δ : 1.23 (t, 2H), 4.00 (q, 2H), 4.20 (s, 2H), 6.97 (d, 2H), 7.17 (dd, 4H), 7.36 (d, 1H), 7.69–7.75 (m, 2H), 8.28 (d, 1H), 8.41 (d, 1H), 8.51 (d, 1H), 9.10 (s, 1H), 9.50 (br s, 1H), 10.50 (s, 1H); HPLC纯度: 96.83%; LCMS: 531 (M^+ +1)。

[1707] N-(4-(4-(4-氯苄基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (VIII-99):

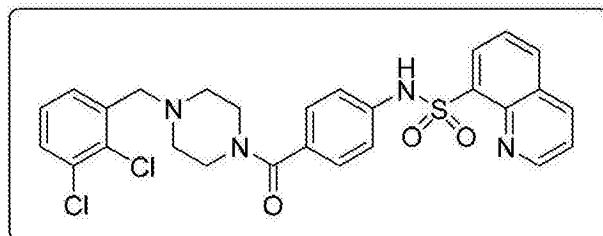
[1708]



[1709] ^1H NMR (400MHz, CD_3OD) δ : 2.34 (br s, 4H), 3.23 (br s, 2H), 3.62 (br s, 2H), 4.30 (s, 2H), 7.16–7.20 (m, 4H), 7.37–7.57 (m, 4H), 7.79–7.84 (m, 2H), 8.15 (d, 1H), 8.40 (d, 1H), 9.10 (s, 1H), 9.50 (br s, 1H); HPLC纯度: 99.75%; LCMS: 521 (M^+)。

[1710] N-(4-(4-(2,3-二氯苄基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (VIII-100):

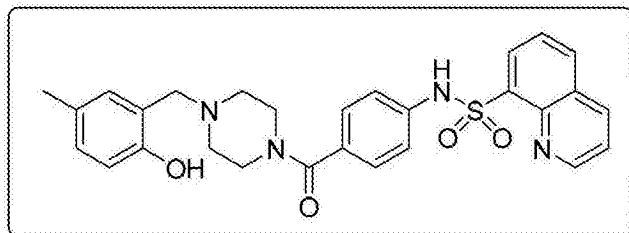
[1711]



[1712] ^1H NMR (400MHz, CD_3OD) δ : 2.32 (br s, 4H), 3.62 (br s, 4H), 3.81 (s, 2H), 7.21 (q, 4H), 7.42 (t, 2H), 7.58 (d, 2H), 7.61–7.72 (m, 2H), 8.18 (d, 1H), 8.41 (d, 1H), 9.18 (s, 1H); HPLC纯度: 99.15%; LCMS: 555 (M^+ +1)。

[1713] N-(4-(4-(2-羟基-5-甲基苄基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺(VIII-101):

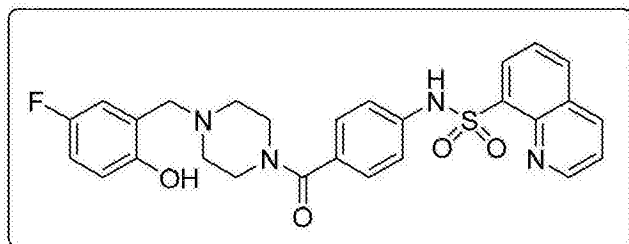
[1714]



[1715] ^1H NMR (400MHz, $\text{CD}_3\text{OD}-d_6$) δ : 2.08 (s, 3H), 2.22 (s, 4H), 3.32 (s, 4H), 3.72 (s, 2H), 4.21 (s, 1H), 6.80 (d, 1H), 7.10 (s, 2H), 7.18-7.25 (m, 3H), 7.61-7.68 (m, 2H), 8.18 (d, 1H), 8.40 (d, 2H), 9.14 (s, 1H); HPLC纯度: 98.02%; LCMS: 517 ($\text{M}^+ + 1$).

[1716] N-(4-(4-(5-氟-2-羟基苄基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺(VIII-102):

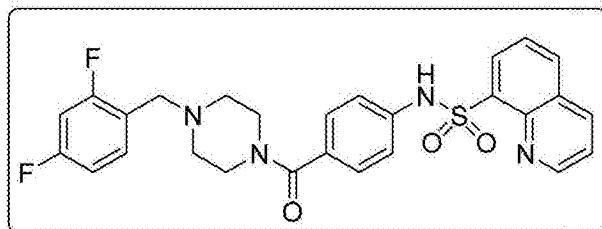
[1717]



[1718] ^1H NMR (400MHz, $\text{DMSO}-d_6$) δ : 2.30 (br s, 4H), 3.31 (br s, 4H), 3.72 (s, 2H), 6.90-6.95 (m, 3H), 7.04-7.18 (m, 2H), 7.20-7.25 (m, 3H), 7.60-7.65 (m, 2H), 8.41 (d, 2H), 9.10 (s, 1H); HPLC纯度: 98.95%; LCMS: 521 ($\text{M}^+ + 1$).

[1719] N-(4-(4-(2,4-二氟苄基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺(103):

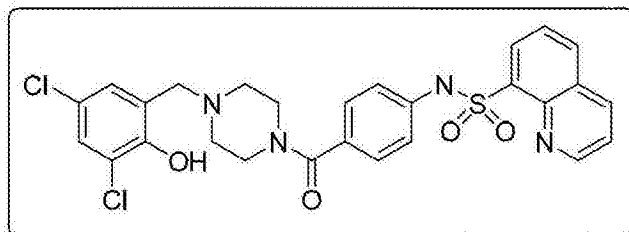
[1720]



[1721] ^1H NMR (400MHz, $\text{DMSO}-d_6$) δ : 2.36 (br s, 4H), 3.3 (br s, 4H), 3.7 (s, 2H), 7.05-7.22 (m, 5H), 7.55 (d, 2H), 7.60-7.65 (m, 2H), 8.18 (d, 1H), 8.40 (d, 2H), 9.10 (s, 1H); HPLC纯度: 99.24%; LCMS: 523.1 ($\text{M}^+ + 1$).

[1722] N-(4-(4-(3,5-二氯-2-羟基苄基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺(VIII-104):

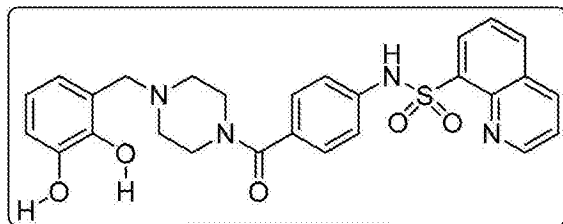
[1723]



[1724] ^1H NMR (400MHz, $\text{DMSO}-d_6$) δ : 2.37 (br s, 4H), 3.32 (br s, 4H), 3.71 (s, 2H), 4.2 (s, 1H), 7.19-7.23 (m, 4H), 7.39 (s, 1H), 7.56 (s, 1H), 7.62-7.68 (m, 2H), 8.18 (d, 2H), 8.40 (d, 1H), 9.13 (s, 1H); HPLC纯度: 99.95%; LCMS: 572.3 ($\text{M}^+ + 1$).

[1725] N-(4-(4-(2,3-二羟基苄基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺(VIII-105):

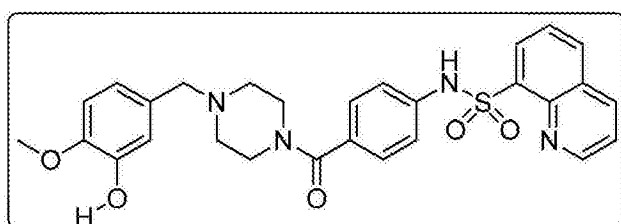
[1726]



[1727] ^1H NMR (400MHz, DMSO-d_6) δ : 2.30 (br s, 4H), 3.32 (br s, 4H), 3.76 (s, 2H), 4.2 (br s, 2H), 7.19-7.23 (m, 4H), 7.39 (s, 1H), 7.56 (s, 1H), 7.62-7.68 (m, 3H), 8.18 (d, 2H), 8.40 (d, 1H), 9.13 (s, 1H); HPLC纯度: 91.9%; LCMS: 519.1 (M^+ +1)。

[1728] N-(4-(4-(3-羟基-4-甲氧基苄基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺(VIII-106):

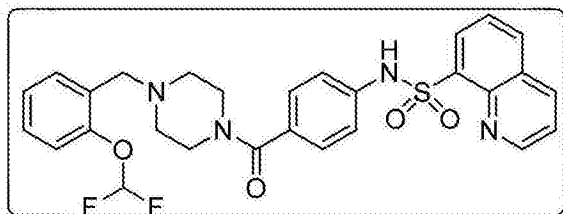
[1729]



[1730] ^1H NMR (400MHz, DMSO-d_6) δ : 3.19 (br s, 4H), 3.3-3.6 (m, 4H), 3.7 (s, 2H), 3.81 (s, 3H), 6.85 (d, 2H), 6.97 (d, 1H), 7.18-7.24 (m, 5H), 7.60-7.66 (m, 2H), 8.18 (d, 1H), 8.41 (d, 1H), 9.13 (s, 1H); HPLC纯度: 97.5%; LCMS: 533.1 (M^+ +1)。

[1731] N-(4-(4-(2-(二氟甲氧基)苄基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺(VIII-107):

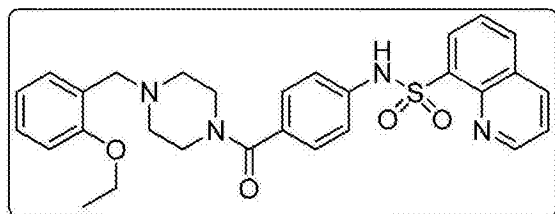
[1732]



[1733] ^1H NMR (400MHz, DMSO-d_6) δ : 2.7 (s, 1H), 3.19 (br s, 4H), 3.3-3.6 (m, 4H), 3.7 (s, 2H), 6.97-7.0 (m, 4H), 7.18-7.24 (m, 5H), 7.60-7.66 (m, 2H), 8.18 (d, 1H), 8.41 (d, 1H), 9.13 (s, 1H); HPLC纯度: 99.4%; LCMS: 553.1 (M^+ +1)。

[1734] N-(4-(4-(2-乙氧基苄基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺(VIII-108):

[1735]

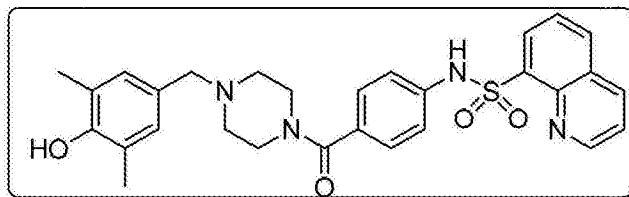


[1736] ^1H NMR (400MHz, DMSO-d_6) δ : 1.89 (t, 3H), 3.19 (br s, 4H), 3.3-3.6 (m, 4H), 3.7 (s, 2H), 3.91 (q, 2H), 6.97-7.0 (m, 4H), 7.18-7.24 (m, 5H), 7.60-7.66 (m, 2H), 8.18 (d, 1H), 8.41 (d, 1H), 9.13 (s, 1H); HPLC纯度: 96.2%; LCMS: 553.1 (M^+ +1)。

[1737] N-(4-(4-(4-羟基-3,5-二甲基苄基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺(VIII-

109) :

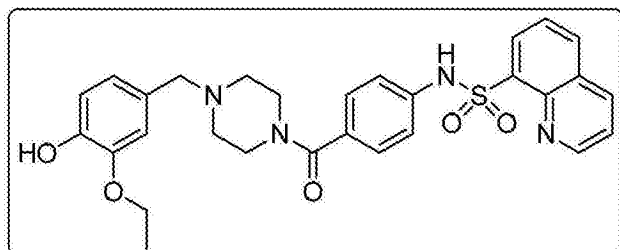
[1738]



[1739] ^1H NMR (400MHz, DMSO-d_6) δ : 2.2 (s, 6H), 3.19 (br s, 4H), 3.3–3.6 (m, 4H), 3.7 (s, 2H), 6.97–7.0 (m, 4H), 7.18–7.24 (m, 3H), 7.60–7.66 (m, 2H), 8.18 (d, 1H), 8.41 (d, 1H), 9.13 (s, 1H); HPLC纯度: 98.4%; LCMS: 531.1 (M^+ +1)。

[1740] N-(4-(4-(3-乙氧基-4-羟基苄基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (VIII-110) :

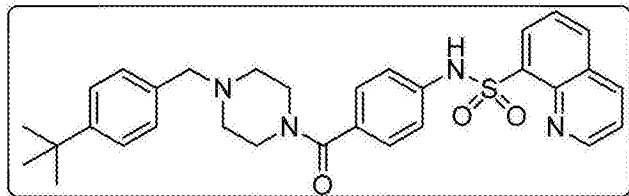
[1741]



[1742] ^1H NMR (400MHz, CDCl_3) δ : 1.41 (t, 3H), 2.42 (br s, 4H), 3.25–3.95 (m, 4H), 3.42 (q, 2H), 3.60 (br s, 2H), 4.21 (s, 1H), 6.75 (s, 2H), 6.90 (s, 1H), 7.19 (s, 4H), 7.62–7.67 (m, 2H), 8.18 (d, 1H), 8.40 (d, 2H), 9.18 (s, 1H); HPLC纯度: 99.29%; LCMS: 546.1 (M^+ +1)。

[1743] N-(4-(4-(4-(叔丁基)苄基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (VIII-111) :

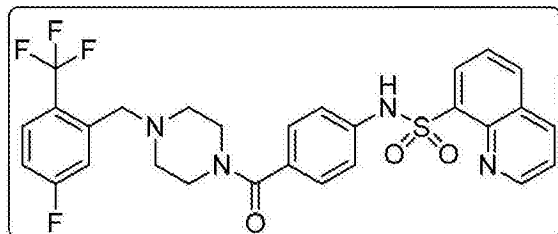
[1744]



[1745] ^1H NMR (400MHz, CD_3OD) δ : 1.30 (s, 9H), 2.56 (br s, 4H), 3.30 (br s, 4H), 3.68 (s, 2H), 7.20 (dd, 4H), 7.45 (dd, 4H), 7.70–7.80 (m, 2H), 8.45 (d, 2H), 8.55 (d, 1H), 9.18 (s, 1H), 10.54 (s, 1H); HPLC纯度: 98.47%; LCMS: 543.0 (M^+ +1)。

[1746] N-(4-(4-(5-氟-2-(三氟甲基)苄基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (VIII-112) :

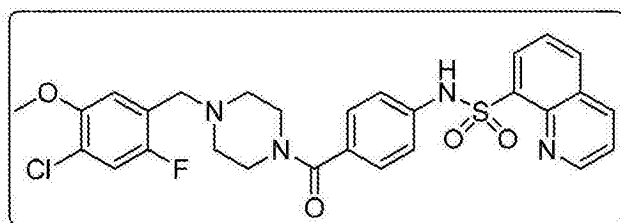
[1747]



[1748] ^1H NMR (400MHz, CDCl_3) δ : 2.45 (br s, 4H), 3.2–3.6 (m, 4H), 3.70 (s, 2H), 7.20 (s, 4H), 7.59–7.74 (m, 4H), 8.18 (d, 2H), 8.40 (m, 2H), 9.16 (s, 1H); HPLC纯度: 99.35%; LCMS: 573.1 (M^+ +1)。

[1749] N-(4-(4-(4-氯-2-氟-5-甲氧基苄基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺(VIII-113):

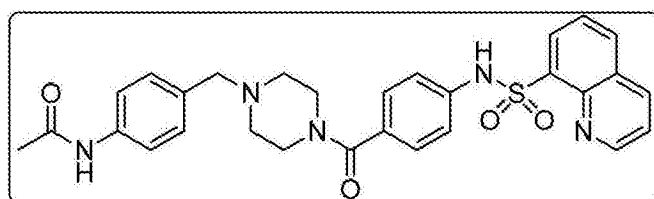
[1750]



[1751] ^1H NMR (400MHz, CD_3OD) δ : 2.91 (br s, 4H), 3.77 (br s, 4H), 3.92 (s, 2H), 4.01 (s, 3H), 7.20-7.25 (m, 4H), 7.40 (d, 1H), 7.62-7.68 (m, 3H), 8.18 (d, 1H), 8.41 (d, 2H), 9.13 (s, 1H); HPLC纯度: 99.42%; LCMS: 569 (M^+ +1)。

[1752] N-(4-((4-(4-(喹啉-8-亚磺酰氨基)苯甲酰基)哌嗪-1-基)甲基)苯基)乙酰胺(VIII-114):

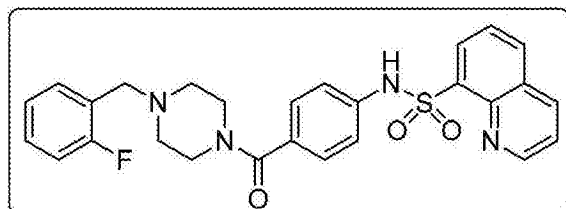
[1753]



[1754] ^1H NMR (400MHz, $\text{DMSO}-d_6$) δ : 2.01 (s, 3H), 3.01 (br s, 4H), 3.20 (br s, 2H), 3.30 (br s, 2H), 4.24 (s, 2H), 7.20 (dd, 4H), 7.40 (d, 2H), 7.65 (d, 2H), 7.70-7.80 (m, 2H), 8.30 (d, 1H), 8.45 (d, 1H), 8.52 (d, 1H), 9.18 (s, 1H), 10.60 (s, 1H); HPLC纯度: 95.84%; LCMS: 544.1 (M^+ +1)。

[1755] N-(4-(4-(2-氟苄基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺(VIII-115):

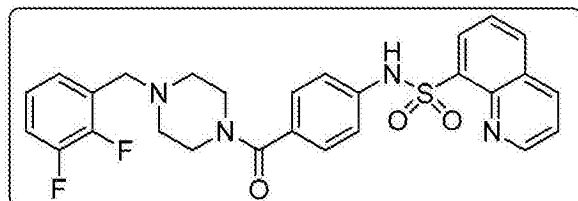
[1756]



[1757] ^1H NMR (400MHz, $\text{CD}_3\text{OD}-d_6$) δ : 3.01 (br s, 4H), 3.20 (br s, 2H), 3.30 (br s, 2H), 3.82 (s, 2H), 7.02-7.20 (m, 5H), 7.24-7.41 (m, 2H), 7.61-7.67 (m, 2H), 8.18 (d, 1H), 8.41 (t, 2H), 9.12 (s, 1H); HPLC纯度: 99.03%; LCMS: 505 (M^+ +1)。

[1758] N-(4-(4-(2,3-二氟苄基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺(VIII-116):

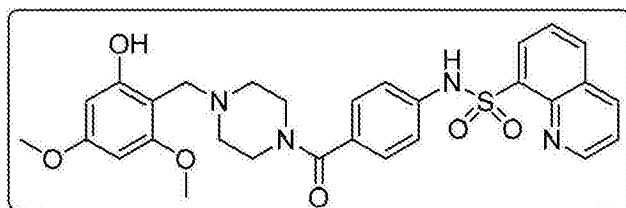
[1759]



[1760] ^1H NMR (400MHz, $\text{CD}_3\text{OD}-d_6$) δ : 3.01 (br s, 4H), 3.20 (br s, 2H), 3.30 (br s, 2H), 4.24 (s, 2H), 7.16-7.34 (m, 6H), 7.39-7.47 (m, 2H), 7.61-7.67 (m, 2H), 8.18 (d, 1H), 8.41 (d, 1H), 9.12 (s, 1H); HPLC纯度: 97.11%; LCMS: 523.2 (M^+ +1)。

[1761] N-(4-(4-(2-羟基-4,6-二甲氧基苄基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺(VIII-117):

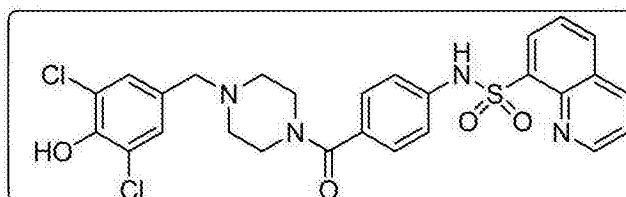
[1762]



[1763] ^1H NMR (400MHz, CDCl_3) δ : 3.15 (br s, 2H), 3.2-3.6 (br s, 6H), 3.39 (br s, 2H), 3.78 (s, 3H), 3.81 (s, 3H), 6.17 (d, 2H), 7.22 (q, 4H), 7.62-7.68 (m, 2H), 8.18 (d, 1H), 8.41 (d, 1H), 9.17 (s, 1H); HPLC纯度: 97.92%; LCMS: 563 (M^+).

[1764] N-(4-(4-(3,5-二氯-4-羟基苄基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺(VIII-118):

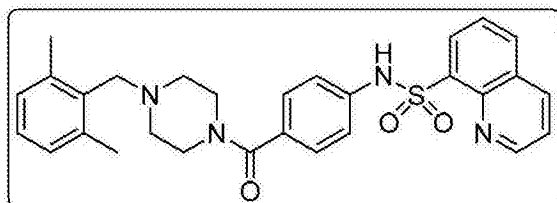
[1765]



[1766] ^1H NMR (400MHz, DMSO-d_6) δ : 3.04 (br s, 2H), 3.30 (br s, 4H), 4.12 (s, 4H), 4.2 (s, 1H), 7.21 (dd, 4H), 7.27 (s, 1H), 7.50 (s, 2H), 7.69-7.78 (m, 2H), 8.30 (d, 1H), 8.50 (d, 2H), 10.59 (s, 1H); HPLC纯度: 93.26%; LCMS: 571.3 (M^+).

[1767] N-(4-(4-(2,6-二甲基苄基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺(VIII-119):

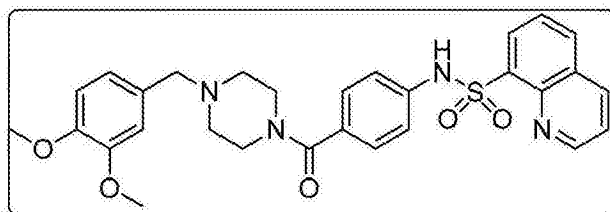
[1768]



[1769] ^1H NMR (400MHz, DMSO-d_6) δ : 2.44 (s, 6H), 3.34 (s, 6H), 3.39 (br s, 2H), 4.45 (s, 2H), 7.19-7.30 (m, 6H), 7.63-7.70 (m, 3H), 8.20 (d, 1H), 8.42 (d, 2H), 9.18 (s, 1H); HPLC纯度: 98.10%; LCMS: 515 ($\text{M}^+ + 1$).

[1770] N-(4-(4-(3,4-二甲氧基苄基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺(VIII-120):

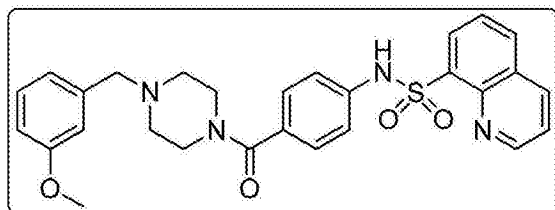
[1771]



[1772] ^1H NMR (400MHz, CD_3OD) δ : 3.4-3.6 (br s, 2H), 3.85 (d, 6H), 4.1 (s, 6H), 4.29 (s, 2H), 7.02 (d, 3H), 7.21-7.27 (m, 4H), 7.63-7.72 (m, 2H), 8.20 (d, 1H), 8.42 (d, 1H), 9.14 (s, 1H); HPLC纯度: 99.44%; LCMS: 547 ($\text{M}^+ + 1$).

[1773] N-(4-(4-(3-甲氧基苄基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺(VIII-121):

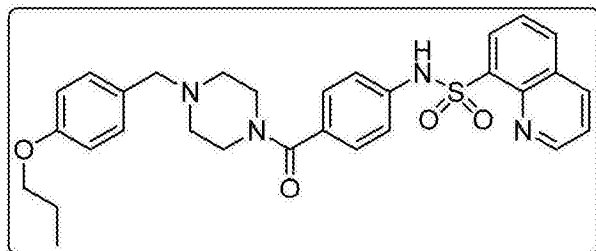
[1774]



[1775] ^1H NMR (400MHz, CD_3OD) δ : 2.81 (br s, 4H), 3.20 (br s, 4H), 3.78 (s, 3H), 4.25 (s, 2H), 7.01 (t, 2H), 7.20 (t, 3H), 7.39 (t, 1H), 7.61–7.67 (m, 2H), 8.18 (d, 1H), 8.41 (d, 2H), 9.14 (s, 1H); HPLC纯度: 97.82%; LCMS: 517 (M^+ +1)。

[1776] N-(4-(4-(4-丙氧基苄基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (VIII-122):

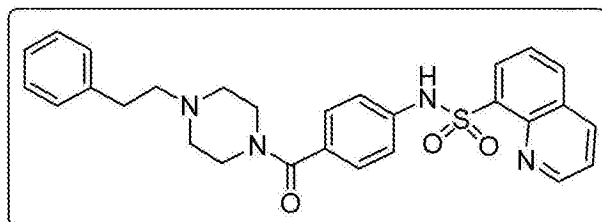
[1777]



[1778] ^1H NMR (400MHz, CD_3OD) δ : 1.01 (t, 3H), 1.78 (六重峰, 2H), 3.2–3.85 (br s, 4H), 3.9–4.0 (br s, 4H), 3.92 (t, 2H), 4.22 (s, 2H), 6.97 (d, 2H), 7.21 (q, 4H), 7.38 (d, 2H), 7.61–7.67 (m, 2H), 8.18 (d, 1H), 8.40 (d, 2H), 9.10 (s, 1H); HPLC纯度: 98.67%; LCMS: 545 (M^+ +1)。

[1779] N-(4-(4-苄基哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (VIII-123):

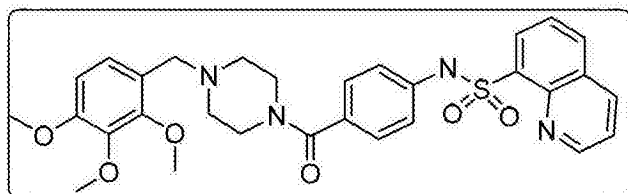
[1780]



[1781] ^1H NMR (400MHz, $\text{DMSO}-d_6$) δ : 2.01 (t, 2H), 2.20 (t, 2H), 2.8 (br s, 2H), 3.2–3.89 (m, 6H), 7.04–7.32 (m, 4H), 7.59–7.63 (m, 6H), 8.01 (d, 1H), 8.25 (dd, 2H), 8.41 (d, 1H), 9.18 (s, 1H); HPLC纯度: 99.43%; LCMS: 501 (M^+ +1)。

[1782] N-(4-(4-(2,3,4-三甲氧基苄基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (VIII-124):

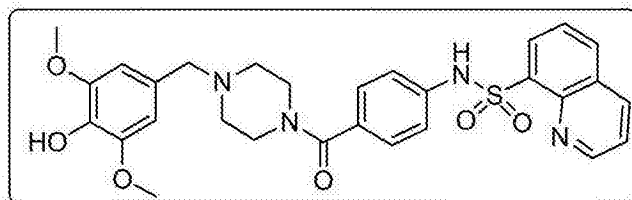
[1783]



[1784] ^1H NMR (400MHz, $\text{DMSO}-d_6$) δ : 3.01 (br s, 2H), 3.32–3.71 (m, 6H), 3.78 (s, 3H), 3.84 (s, 3H), 3.86 (s, 3H), 4.22 (br s, 2H), 6.89 (d, 1H), 7.18 (d, 3H), 7.25 (d, 2H), 7.72–7.80 (m, 2H), 8.30 (d, 1H), 8.45 (d, 1H), 8.55 (d, 1H), 9.18 (d, 1H), 10.59 (s, 1H); HPLC纯度: 99.84%; LCMS: 577 (M^+ +1)。

[1785] N-(4-(4-(4-羟基-3,5-二甲氧基苄基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (VIII-125):

[1786]

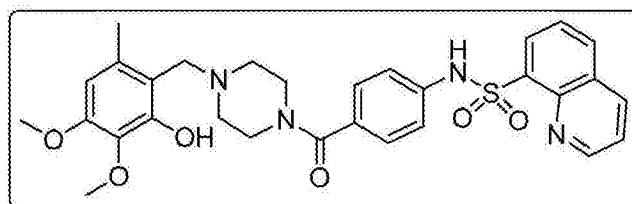


[1787] ^1H NMR (400MHz, DMSO- d_6) δ : 3.01 (br s, 2H), 3.21 (br s, 2H), 3.3-3.7 (m, 6H), 3.79 (s, 6H), 6.75 (s, 2H), 7.20 (dd, 4H), 7.70-7.80 (m, 2H), 8.31 (d, 1H), 8.46 (d, 2H), 8.55 (d, 1H), 10.59 (s, 1H); HPLC纯度:

[1788] 99.21%; LCMS: 563 ($M^+ + 1$).

[1789] N-(4-(4-(2-羟基-3,4-二甲氧基-6-甲基苄基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (VIII-126):

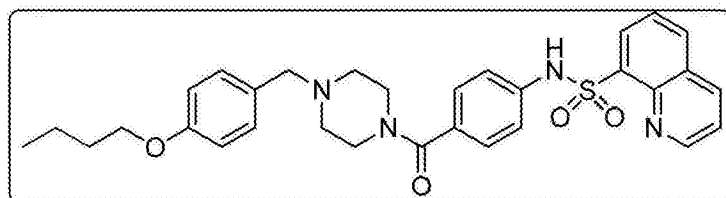
[1790]



[1791] ^1H NMR (400MHz, DMSO- d_6) δ : 2.11 (s, 3H), 3.18 (br s, 4H), 3.30 (br s, 4H), 3.66 (s, 3H), 3.75 (s, 3H), 4.18 (s, 2H), 6.48 (s, 1H), 7.20 (dd, 4H), 7.70-7.80 (m, 2H), 8.31 (d, 1H), 8.44 (d, 2H), 8.52 (d, 1H), 8.78 (br s, 1H), 9.10 (br s, 1H), 9.19 (s, 1H), 9.60 (br s, 1H), 10.53 (s, 1H); HPLC纯度: 97.01%; LCMS: 577 ($M^+ + 1$).

[1792] N-(4-(4-(4-丁氧基苄基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (VIII-127):

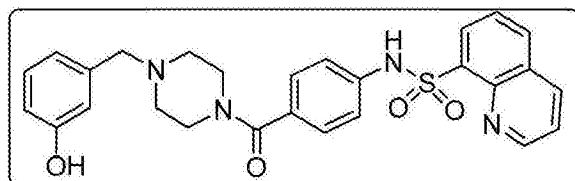
[1793]



[1794] ^1H NMR (400MHz, DMSO- d_6) δ : 0.92 (t, 3H), 1.41 (六重峰, 2H), 1.68 (五重峰, 2H), 3.00 (br s, 2H), 3.15 (br s, 2H), 3.25 (br s, 4H), 3.92 (t, 2H), 4.22 (s, 2H), 6.97 (d, 2H), 7.20 (dd, 4H), 7.38 (d, 2H), 7.70-7.79 (m, 2H), 8.44 (d, 1H), 8.50 (d, 1H), 9.12 (s, 1H), 9.64 (br s, 1H), 10.50 (s, 1H); HPLC纯度: 98.86%; LCMS: 559 ($M^+ + 1$).

[1795] N-(4-(4-(3-羟基苄基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (VIII-128):

[1796]

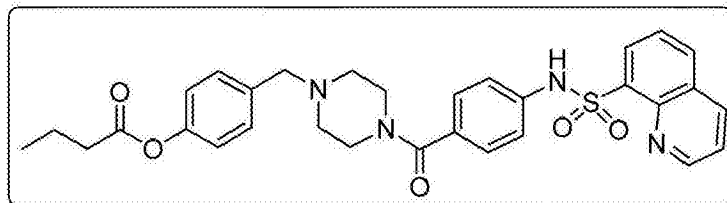


[1797] ^1H NMR (400MHz, DMSO- d_6) δ : 2.81 (br s, 2H), 3.00 (br s, 6H), 4.20 (br s, 2H), 6.80 (s, 2H), 7.20 (dd, 4H), 7.70-7.80 (m, 2H), 8.31 (d, 1H), 8.46 (d, 2H), 8.55 (d, 1H), 9.17 (s, 1H), 9.70 (br s, 1H), 10.56 (s, 1H); HPLC纯度: 99.28%; LCMS: 503 ($M^+ + 1$).

[1798] 丁酸4-((4-(4-(喹啉-8-亚磺酰氨基)苯甲酰基)哌嗪-1-基)甲基)苯酯 (VIII-

129) :

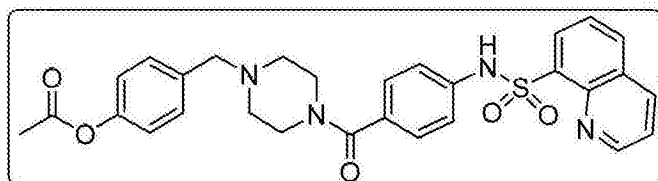
[1799]



[1800] ^1H NMR (400MHz, DMSO- d_6) δ : 0.99 (t, 3H), 1.61 (六重峰, 2H), 2.56 (t, 2H), 3.03 (br s, 4H), 3.61 (br s, 4H), 4.24 (br s, 2H), 7.10–7.20 (m, 5H), 7.45 (d, 2H), 7.65–7.72 (m, 2H), 8.23 (d, 1H), 8.41 (d, 2H), 8.51 (d, 1H), 9.10 (s, 1H), 9.78 (br s, 1H), 10.50 (s, 1H); HPLC纯度: 99.17%; LCMS: 573 (M^+ +1)。

[1801] 乙酸4-((4-(4-(喹啉-8-亚磺酰氨基)苯甲酰基)哌嗪-1-基)甲基)苯酯(VIII-130) :

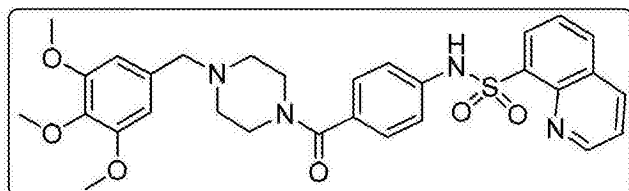
[1802]



[1803] ^1H NMR (400MHz, DMSO- d_6) δ : 2.24 (s, 3H), 2.38 (br s, 4H), 3.42 (br s, 4H), 3.78 (s, 2H), 7.10 (d, 2H), 7.20 (d, 2H), 7.44 (d, 2H), 7.63–7.71 (m, 2H), 8.25 (d, 1H), 8.41 (d, 2H), 8.45 (d, 1H), 9.10 (s, 1H), 9.70 (br s, 1H), 10.50 (s, 1H); HPLC纯度: 95.24%; LCMS: 545 (M^+ +1)。

[1804] N-(4-(4-(3,4,5-三甲氧基苄基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺(VIII-131) :

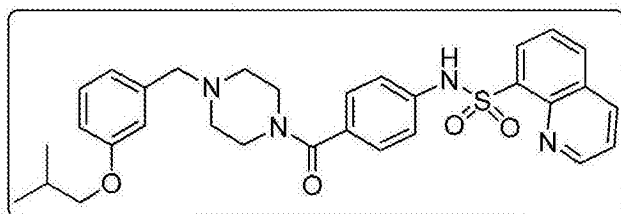
[1805]



[1806] ^1H NMR (400MHz, DMSO- d_6) δ : 3.75 (s, 3H), 3.81 (s, 6H), 4.22 (s, 2H), 6.78 (s, 2H), 7.21 (q, 4H), 7.63–7.68 (m, 2H), 8.16 (d, 1H), 8.40 (d, 2H), 9.10 (s, 1H); HPLC纯度: 98.81%; LCMS: 577 (M^+ +1)。

[1807] N-(4-(4-(3-异丁氧基苄基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺(VIII-132) :

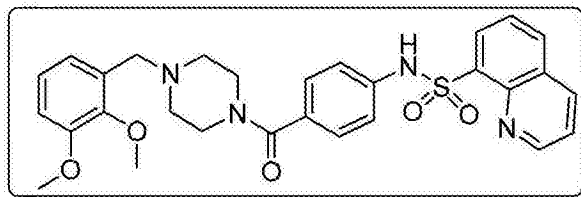
[1808]



[1809] ^1H NMR (400MHz, DMSO- d_6) δ : 1.00 (d, 6H), 2.02 (七重峰, 1H), 3.05 (br s, 4H), 3.30 (br s, 4H), 3.80 (d, 2H), 3.91 (d, 2H), 7.00–7.08 (m, 2H), 7.20 (dd, 4H), 7.39 (t, 1H), 7.71–7.80 (m, 2H), 8.30 (d, 1H), 8.45 (d, 1H), 8.58 (d, 1H), 9.15 (s, 1H), 9.90 (br s, 1H), 10.58 (s, 1H); HPLC纯度: 99.17%; LCMS: 559 (M^+ +1)。

[1810] N-(4-(4-(2,3-二甲氧基苄基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (VIII-133) :

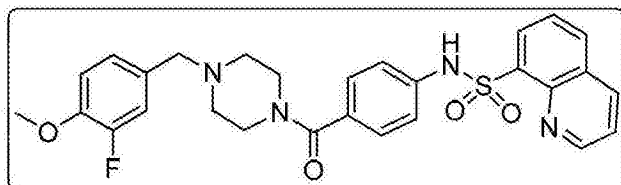
[1811]



[1812] ^1H NMR (400MHz, DMSO- d_6) δ : 2.25 (br s, 4H), 3.41 (br s, 4H), 3.64 (s, 3H), 3.72 (s, 2H), 3.78 (s, 3H), 6.80–7.05 (m, 6H), 7.21 (q, 1H), 7.59–7.70 (m, 2H), 8.14 (d, 1H), 8.38–8.42 (m, 2H), 9.01 (s, 1H); HPLC纯度: 98.50%; LCMS: 547 (M^+ +1)。

[1813] N-(4-(4-(3-氟-4-甲氧基苄基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (VIII-134) :

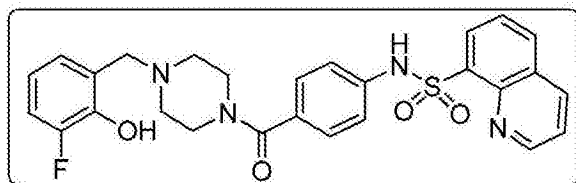
[1814]



[1815] ^1H NMR (400MHz, DMSO- d_6) δ : 2.81 (br s, 2H), 3.01 (br s, 2H), 3.25 (br s, 4H), 3.82 (s, 2H), 3.90 (s, 3H), 7.17 (d, 2H), 7.21 (d, 3H), 7.35 (1H), 7.70–7.78 (m, 2H), 8.30 (d, 1H), 8.43 (d, 2H), 8.55 (d, 1H), 9.12 (br s, 1H), 10.58 (s, 1H); HPLC纯度: 95.38%; LCMS: 535 (M^+ +1)。

[1816] N-(4-(4-(3-氟-2-羟基苄基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (VIII-135) :

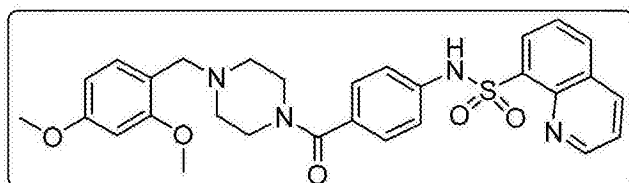
[1817]



[1818] ^1H NMR (400MHz, DMSO- d_6) δ : 2.38 (br s, 4H), 3.43 (br s, 4H), 3.62 (s, 2H), 4.38 (s, 1H), 6.90 (q, 1H), 7.10–7.28 (m, 6H), 7.62 (d, 2H), 8.18 (d, 1H), 8.40 (d, 2H), 9.10 (s, 1H); HPLC纯度: 98.81%; LCMS: 521 (M^+ +1)。

[1819] N-(4-(4-(2,4-二甲氧基苄基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (VIII-136) :

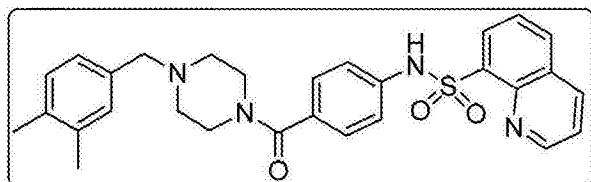
[1820]



[1821] ^1H NMR (400MHz, DMSO- d_6) δ : 2.52 (br s, 4H), 3.30 (br s, 4H), 3.70–3.98 (m, 8H), 6.58–6.64 (m, 2H), 7.16 (d, 2H), 7.22 (d, 2H), 7.33 (d, 1H), 7.70–7.79 (m, 2H), 8.28 (d, 1H), 8.44 (d, 2H), 8.55 (d, 1H), 9.10 (s, 1H), 9.50 (br s, 1H), 10.51 (s, 1H); HPLC纯度: 92.62%; LCMS: 547 (M^+ +1)。

[1822] N-(4-(4-(3,4-二甲基苄基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (VIII-137) :

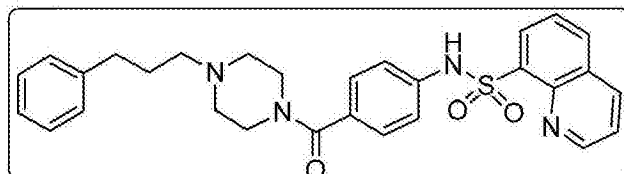
[1823]



[1824] ^1H NMR (400MHz, DMSO- d_6) δ : 2.20 (s, 3H), 2.25 (br s, 4H), 2.50 (s, 3H), 3.42 (br s, 4H), 3.81 (s, 2H), 6.96–7.20 (m, 7H), 7.68–7.76 (m, 2H), 8.26 (d, 1H), 8.40 (d, 2H), 8.54 (d, 1H), 9.13 (s, 1H), 10.40 (br s, 1H); HPLC纯度: 96.74%; LCMS: 515 (M^+ +1)。

[1825] N-(4-(4-(3-苯基丙基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (VIII-138):

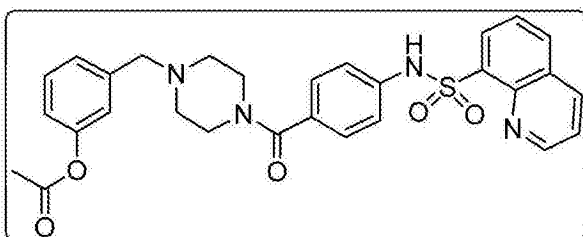
[1826]



[1827] ^1H NMR (400MHz, DMSO- d_6) δ : 1.70 (t, 2H), 2.24 (br s, 4H), 2.48–2.60 (m, 4H), 3.44 (br s, 4H), 7.18–7.24 (m, 8H), 7.70–7.79 (m, 2H), 8.30 (d, 1H), 8.42 (d, 1H), 8.58 (d, 1H), 9.16 (s, 1H), 10.41 (s, 1H); HPLC纯度: 93.22%; LCMS: 515 (M^+ +1)。

[1828] 乙酸3-((4-(4-(喹啉-8-亚磺酰氨基)苯甲酰基)哌嗪-1-基)甲基)苯酯 (VIII-139):

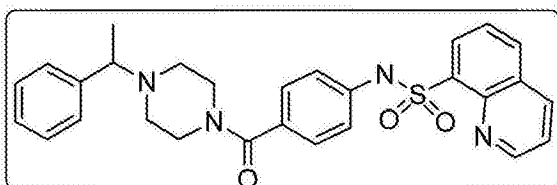
[1829]



[1830] ^1H NMR (400MHz, DMSO- d_6) δ : 2.24 (s, 4H), 2.30 (br s, 2H), 3.40 (br s, 4H), 3.52 (s, 2H), 7.01–7.21 (m, 6H), 7.38 (t, 1H), 7.70–7.79 (m, 2H), 8.29 (d, 1H), 8.42 (d, 1H), 8.58 (d, 1H), 9.15 (s, 1H), 10.41 (s, 1H); HPLC纯度: 93.39%; LCMS: 545 (M^+ +1)。

[1831] N-(4-(4-(1-苯基乙基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (VIII-140):

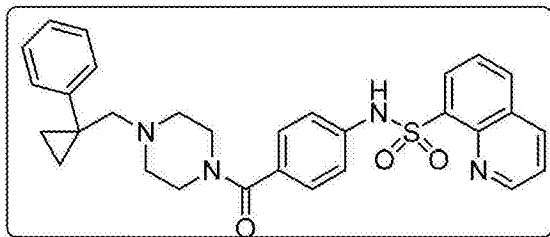
[1832]



[1833] ^1H NMR (400MHz, DMSO- d_6) δ : 1.22 (d, 3H), 2.20 (br s, 2H), 2.24 (br s, 2H), 3.42 (br s, 4H), 3.68 (s, 2H), 7.04 (s, 3H), 7.17–7.26 (m, 4H), 7.66–7.74 (m, 2H), 8.24 (d, 1H), 8.39 (d, 1H), 8.50 (d, 1H), 9.16 (s, 1H), 10.40 (s, 1H); HPLC纯度: 99.27%; LCMS: 501 (M^+ +1)。

[1834] N-(4-(4-((1-苯基环丙基)甲基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (VIII-141):

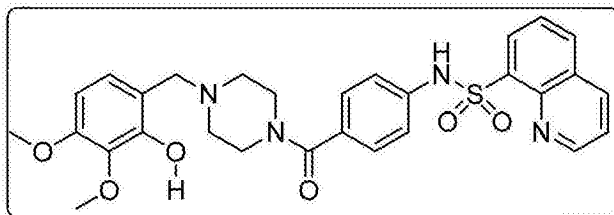
[1835]



[1836] ^1H NMR (400MHz, DMSO- d_6) δ : 1.03 (d, 4H), 2.38 (br s, 2H), 2.61 (s, 2H), 3.50 (br s, 4H), 7.19 (s, 4H), 7.25 (t, 1H), 7.36 (t, 2H), 7.42 (d, 2H), 7.60–7.65 (m, 2H), 8.18 (d, 1H), 8.40 (d, 1H), 9.12 (s, 1H); HPLC纯度: 94.05%; LCMS: 527 (M^+ +1)。

[1837] N-(4-(4-(2-羟基-3,4-二甲氧基苄基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (VIII-142):

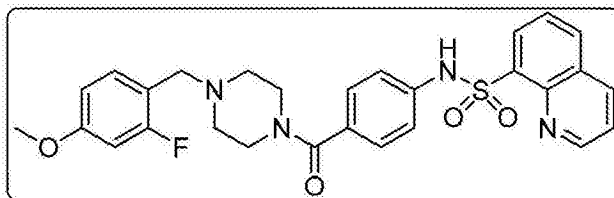
[1838]



[1839] ^1H NMR (400MHz, DMSO- d_6) δ : 2.38 (brs, 4H), 3.06 (br s, 4H), 3.65 (s, 2H), 3.70 (s, 3H), 3.80 (s, 3H), 4.18 (s, 1H), 6.59 (d, 1H), 7.00 (d, 1H), 7.18 (dd, 4H), 7.68–7.77 (m, 2H), 8.26 (d, 1H), 8.48 (d, 3H), 8.53 (d, 1H), 9.18 (s, 1H), 9.42 (br s, 1H), 9.61 (s, 1H), 10.51 (s, 1H); HPLC纯度: 93.10%; LCMS: 563 (M^+ +1)。

[1840] N-(4-(4-(2-氟-4-甲氧基苄基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (VIII-143):

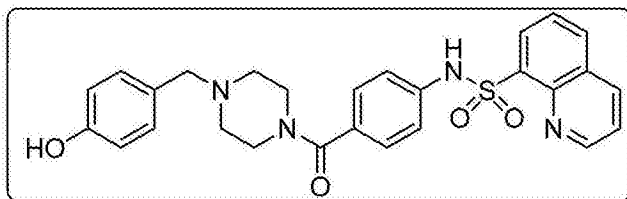
[1841]



[1842] ^1H NMR (400MHz, DMSO- d_6) δ : 2.39 (br s, 4H), 3.20 (br s, 4H), 3.72 (s, 2H), 3.80 (s, 3H), 6.79 (s, 1H), 6.90–7.01 (m, 2H), 7.18–7.24 (m, 2H), 7.44 (br s, 1H), 7.71–7.80 (m, 2H), 8.30 (d, 1H), 8.49 (d, 1H), 8.57 (d, 1H), 9.18 (s, 1H), 9.82 (br s, 1H), 10.48 (s, 1H); HPLC纯度: 96.28%; LCMS: 435 (M^+ +1)。

[1843] N-(4-(4-(4-羟基苄基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (VIII-144):

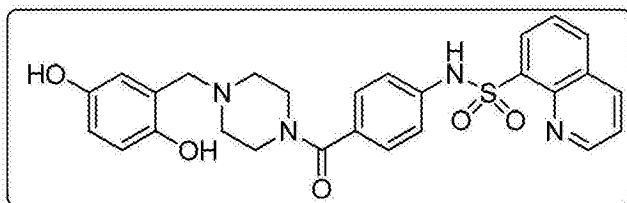
[1844]



[1845] ^1H NMR (400MHz, DMSO- d_6) δ : 2.42 (br s, 4H), 3.20 (br s, 4H), 3.71 (s, 2H), 6.77 (d, 1H), 6.84 (d, 2H), 7.18–7.24 (m, 5H), 7.61–7.67 (m, 2H), 8.17 (d, 1H), 8.40 (d, 2H), 9.10 (s, 1H); HPLC纯度: 92.29%; LCMS: 503 (M^+ +1)。

[1846] N-(4-(4-(2,5-二羟基苄基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (VIII-145):

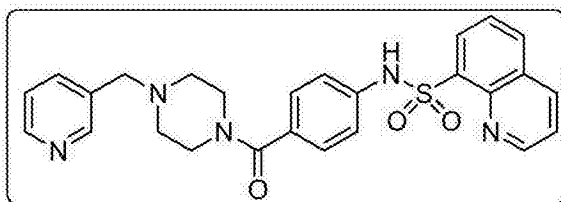
[1847]



[1848] ^1H NMR (400MHz, DMSO- d_6) δ : 2.38 (br s, 4H), 3.38 (br s, 4H), 3.50 (s, 2H), 6.45–6.59 (m, 3H), 7.04–7.18 (m, 4H), 7.65–7.77 (m, 2H), 8.24 (d, 1H), 8.40 (d, 1H), 8.50 (d, 1H), 8.61 (s, 1H), 9.18 (s, 1H), 10.41 (s, 1H); HPLC纯度: 98.19%; LCMS: 519 (M^+ +1)。

[1849] N-(4-(4-(吡啶-3-基甲基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (VIII-146):

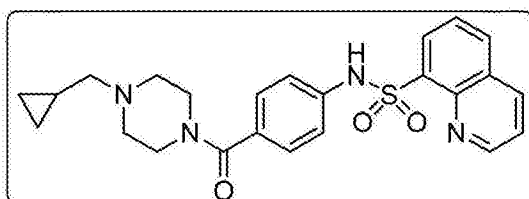
[1850]



[1851] ^1H NMR (400MHz, DMSO- d_6) δ : 2.25 (br s, 4H), 3.30 (br s, 4H), 3.59 (s, 2H), 7.06–7.18 (s, 3H), 7.35–7.40 (m, 1H), 7.65–7.77 (m, 2H), 8.26 (d, 1H), 8.40–8.56 (m, 3H), 9.18 (s, 1H), 10.41 (s, 1H); HPLC纯度: 99.48%; LCMS: 488 (M^+ +1)。

[1852] N-(4-(4-(环丙基甲基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (VIII-147):

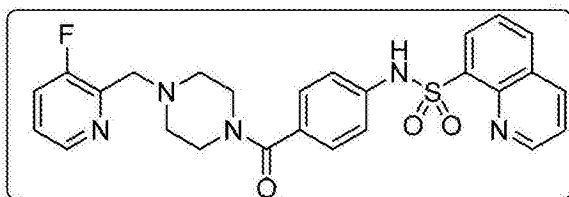
[1853]



[1854] ^1H NMR (400MHz, DMSO- d_6) δ : 0.03 (s, 2H), 0.43 (s, 2H), 0.78–0.84 (m, 1H), 2.18 (d, 2H), 2.39 (br s, 4H), 3.25 (br s, 2H), 3.46 (br s, 2H), 7.10–7.19 (m, 3H), 7.76–7.80 (m, 2H), 8.26 (d, 1H), 8.43 (d, 1H), 8.58 (d, 1H), 9.17 (s, 1H), 10.41 (s, 1H); HPLC纯度: 98.98%; LCMS: 451 (M^+ +1)。

[1855] N-(4-(4-((3-氟吡啶-2-基)甲基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (VIII-148):

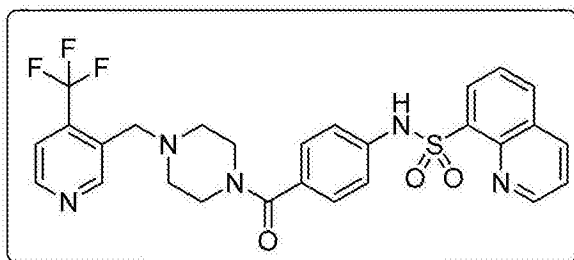
[1856]



[1857] ^1H NMR (400MHz, DMSO- d_6) δ : 2.37 (br s, 4H), 3.21 (br s, 2H), 3.46 (br s, 4H), 3.62 (s, 2H), 7.06–7.11 (m, 3H), 7.40 (t, 1H), 7.62–7.77 (m, 2H), 8.21 (d, 1H), 8.25 (dd, 2H), 8.50 (d, 1H), 9.18 (s, 1H), 10.41 (s, 1H); HPLC纯度: 98.83%; LCMS: 506 (M^+ +1)。

[1858] N-(4-(4-((4-(三氟甲基)吡啶-3-基)甲基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (VIII-149):

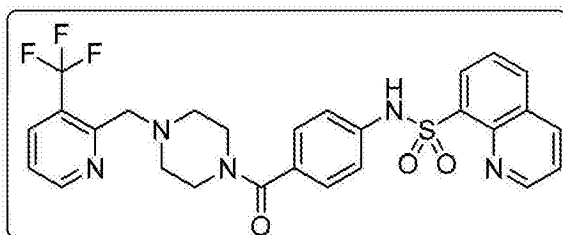
[1859]



[1860] ^1H NMR (400MHz, DMSO- d_6) δ : 2.37 (br s, 4H), 3.31 (br s, 4H), 3.62 (s, 2H), 7.06–7.17 (m, 3H), 7.62–7.77 (m, 2H), 8.21 (d, 1H), 8.38 (d, 1H), 8.50 (d, 1H), 8.72 (s, 1H), 8.90 (s, 1H), 9.10 (s, 1H), 10.40 (s, 1H); HPLC纯度: 99.86%; LCMS: 556 (M^+ +1)。

[1861] N-(4-(4-((3-(三氟甲基)吡啶-2-基)甲基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (VIII-150):

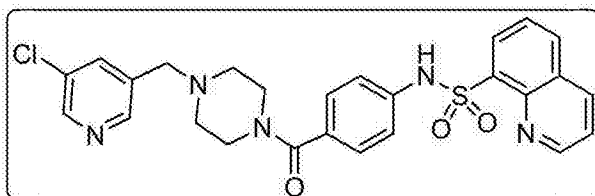
[1862]



[1863] ^1H NMR (400MHz, DMSO- d_6) δ : 2.37 (br s, 4H), 3.21 (br s, 2H), 3.46 (br s, 2H), 3.70 (s, 2H), 7.06–7.11 (m, 4H), 7.50 (t, 1H), 7.68–7.77 (m, 2H), 8.15 (d, 1H), 8.25 (d, 1H), 8.40 (d, 1H), 8.50 (d, 1H), 8.76 (s, 1H), 9.18 (s, 1H), 10.41 (s, 1H); HPLC纯度: 98.67%; LCMS: 556 (M^+ +1)。

[1864] N-(4-(4-((5-氯吡啶-3-基)甲基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (VIII-151):

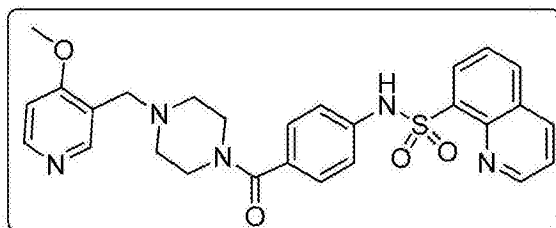
[1865]



[1866] ^1H NMR (400MHz, DMSO- d_6) δ : 2.31 (br s, 4H), 3.38 (br s, 4H), 3.72 (s, 2H), 6.91–7.06 (m, 4H), 7.40 (d, 2H), 7.56–7.63 (m, 2H), 8.0–8.3 (m, 4H), 9.18 (s, 1H); HPLC: 98.2%; LCMS: 523.2 (M^+ +1)。

[1867] N-(4-(4-((4-甲氧基吡啶-3-基)甲基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (VIII-152):

[1868]

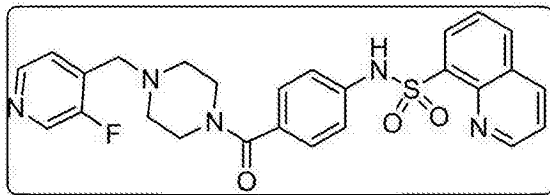


[1869] ^1H NMR (400MHz, DMSO- d_6) δ : 2.38 (br s, 4H), 3.51 (br s, 4H), 3.61 (s, 2H), 7.21–7.81 (m, 6H), 7.40 (m, 2H), 7.56–7.63 (m, 2H), 8.01 (m, 1H), 8.56 (m, 1H), 9.18 (s, 1H); HPLC纯

度:98.2%;LCMS:518.1 (M^+ +1)。

[1870] N-(4-(4-((3-氟吡啶-4-基)甲基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺(VIII-153):

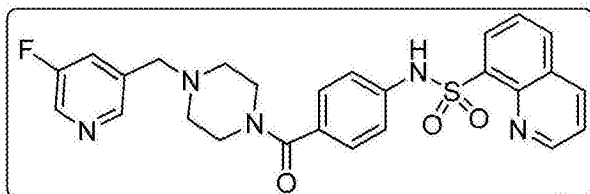
[1871]



[1872] ^1H NMR (400MHz, CDCl_3) δ : 2.38 (s, 4H), 3.31 (br s, 4H), 3.64 (m, 2H), 7.0-7.6 (m, 6H), 7.40 (m, 2H), 7.0-7.6 (m, 2H), 8.56 (m, 2H), 9.18 (s, 1H); HPLC纯度:96.5% LCMS:506.1 (M^+ +1)。

[1873] N-(4-(4-((5-氟吡啶-3-基)甲基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺(VIII-154):

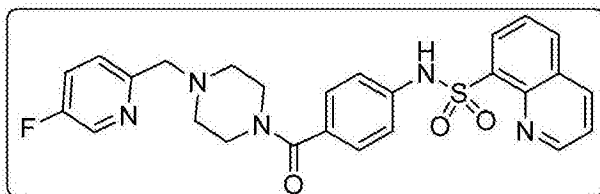
[1874]



[1875] ^1H NMR (400MHz, DMSO-d_6) δ : 2.38 (s, 2H), 3.31 (m, 2H), 3.41 (m, 2H), 3.64 (m, 2H), 7.0-7.6 (m, 6H), 7.40 (m, 2H), 7.0-7.6 (d, 2H), 8.56 (d, 2H), 9.18 (m, 1H), 10.3 (m, 1H); HPLC纯度:98.5%; LCMS:506.1 (M^+ +1)。

[1876] N-(4-(4-((5-氟吡啶-2-基)甲基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺(VIII-155):

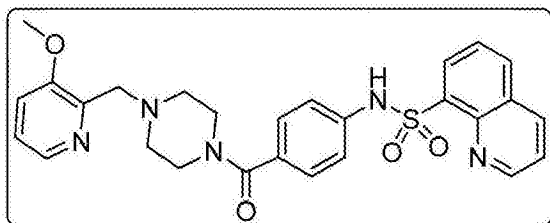
[1877]



[1878] ^1H NMR (400MHz, DMSO-d_6) δ : 2.38 (s, 4H), 3.32 (br s, 2H), 3.52 (brs, 2H), 3.8 (s, 2H), 7.0-7.6 (m, 6H), 7.40 (m, 2H), 7.0-7.6 (d, 2H), 8.56 (d, 2H), 9.18 (m, 1H); HPLC纯度:99.3%; LCMS:506.1 (M^+ +1)。

[1879] N-(4-(4-((3-甲氧基吡啶-2-基)甲基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺(VIII-156):

[1880]

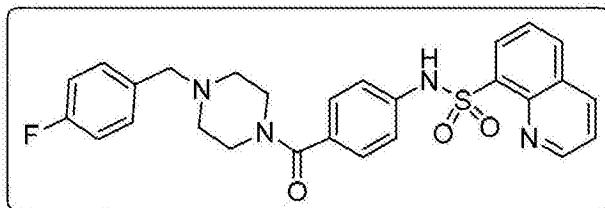


[1881] ^1H NMR (400MHz, DMSO-d_6) δ : 2.38 (s, 4H), 3.41 (m, 4H), 3.8 (m, 2H), 3.91 (s, 3H), 7.0-7.7 (m, 8H), 8.0-8.51 (m, 4H), 9.12 (m, 1H), 10.4 (s, 1H); HPLC纯度:97.3%; LCMS:518.3

($M^+ + 1$)。

[1882] N-(4-(4-(4-氟苄基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺(VIII-157)：

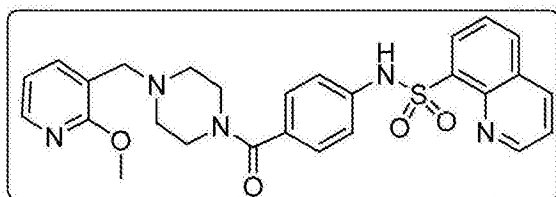
[1883]



[1884] ^1H NMR (400MHz, DMSO- d_6) δ : 2.41 (br s, 4H), 3.21 (m, 4H), 3.3-3.8 (m, 2H), 7.05-7.71 (m, 8H), 8.22-8.62 (m, 5H), 9.12 (m, 1H), 10.4 (s, 1H); HPLC纯度: 99.3%; LCMS: 505.2 ($M^+ + 1$)。

[1885] N-(4-(4-((2-甲氧基吡啶-3-基)甲基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺(VIII-158)：

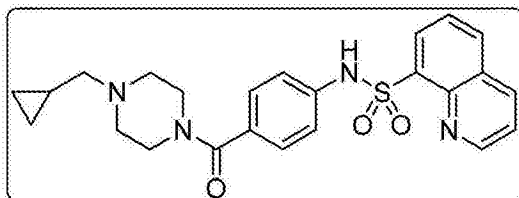
[1886]



[1887] ^1H NMR (400MHz, DMSO- d_6) δ : 2.41 (br s, 4H), 3.21 (s, 4H), 3.3-3.8 (br s, 2H), 7.05-7.72 (m, 10H), 8.22-8.61 (m, 3H), 9.12 (m, 1H), 10.41 (s, 1H); HPLC纯度: 98.6%; LCMS: 505.2 ($M^+ + 1$)。

[1888] N-(4-(4-(环丙基甲基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺(VIII-159)：

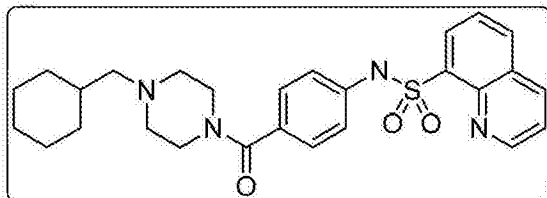
[1889]



[1890] ^1H NMR (400MHz, DMSO- d_6) δ : 0.04-0.45 (m, 2H), 0.61-0.66 (m, 2H), 1.4-1.6 (m, 1H), 2.21-2.38 (m, 4H), 2.61 (d, 2H), 3.31-3.61 (br s, 4H), 6.94-7.06 (m, 4H), 7.40 (d, 2H), 7.56-7.63 (m, 2H), 8.28 (d, 1H), 9.18 (s, 1H), 10.4 (s, 1H); HPLC纯度: 99.6%; LCMS: 451.3 ($M^+ + 1$)。

[1891] N-(4-(4-(环己基甲基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺(VIII-160)：

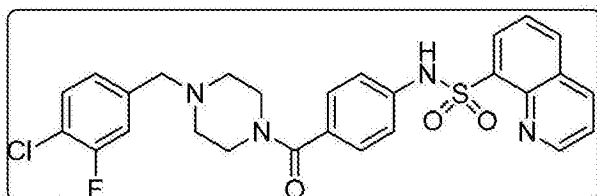
[1892]



[1893] ^1H NMR (400MHz, DMSO- d_6) δ : 0.8 (m, 2H), 1.2 (m, 4H), 1.4 (s, 1H), 1.7 (m, 4H), 2.32 (m, 4H), 2.62 (br s, 2H), 3.42 (br s, 4H), 7.0-7.4 (m, 4H), 7.5-7.7 (m, 2H), 8.3-8.6 (m, 3H), 9.1 (d, 1H), 10.4 (s, 1H); HPLC纯度: 99.3%; MS: 493.3 ($M^+ + 1$)。

[1894] N-(4-(4-(4-氯-3-氟苄基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺(VIII-161)：

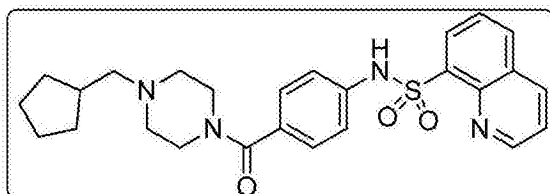
[1895]



[1896] ^1H NMR (400MHz, DMSO- d_6) δ : 2.22–2.41 (m, 4H), 3.21–3.81 (m, 6H), 7.02–7.51 (m, 7H), 7.61–7.72 (m, 2H), 8.31–8.62 (m, 3H), 9.12 (d, 1H), 10.4 (s, 1H); HPLC纯度: 96.8%; LCMS: 539.0 (M^+ 1)。

[1897] N-(4-(4-(环戊基甲基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (VIII-162):

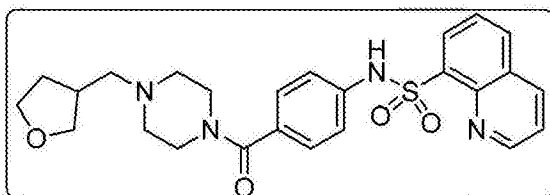
[1898]



[1899] ^1H NMR (400MHz, DMSO- d_6) δ : 1.10 (六重峰, 2H), 1.40–1.53 (m, 4H), 1.60 (br s, 2H), 1.99 (五重峰, 1H), 2.20 (d, 4H), 2.43 (br s, 2H), 3.32 (br s, 4H), 7.10 (t, 4H), 7.62–7.69 (m, 5H), 8.25 (d, 1H), 8.40 (d, 1H), 8.47 (d, 1H), 9.10 (d, 1H), 10.28 (s, 1H); HPLC纯度: 98.26%; LCMS: 479 (M^+ 1)。

[1900] N-(4-(4-((四氢呋喃-3-基)甲基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (VIII-163):

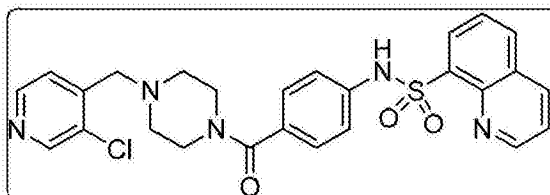
[1901]



[1902] ^1H NMR (400MHz, DMSO- d_6) δ : 1.42 (六重峰, 1H), 1.6–1.8 (m, 2H), 2.20–2.40 (m, 4H), 3.42–3.52 (m, 4H), 3.61–3.75 (m, 4H), 3.80–4.05 (m, 2H), 7.04–7.14 (m, 4H), 7.62–7.69 (m, 2H), 8.25 (d, 1H), 8.40 (d, 1H), 8.47 (d, 1H), 9.10 (d, 1H); HPLC纯度: 98.26%; LCMS: 479 (M^+ 1)。

[1903] N-(4-(4-((3-氯吡啶-4-基)甲基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (VIII-164):

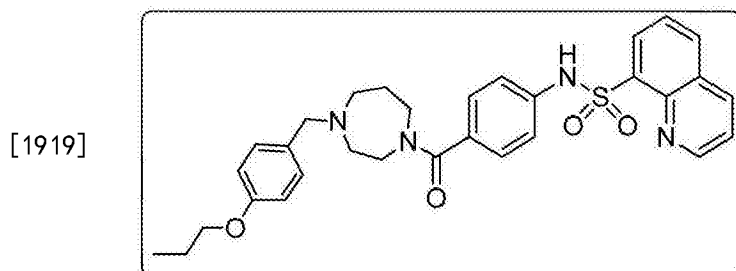
[1904]



[1905] ^1H NMR (400MHz, DMSO- d_6) δ : 2.37 (br s, 4H), 3.42 (br s, 4H), 3.59 (s, 2H), 7.10 (q, 4H), 7.50 (s, 1H), 7.62–7.69 (m, 2H), 8.25 (d, 1H), 8.42 (d, 1H), 8.46–8.52 (m, 2H), 8.58 (s, 1H), 9.10 (d, 1H), 10.30 (s, 1H); HPLC纯度: 96.59%; LCMS: 522 (M^+)。

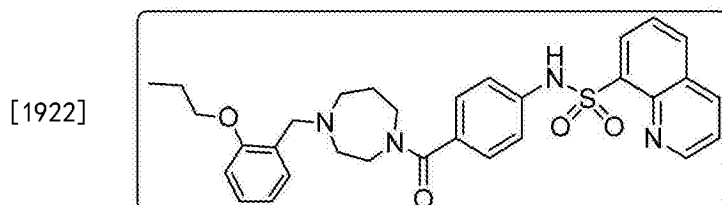
[1906] N-(4-(4-((四氢呋喃-3-基)甲基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (VIII-165):

[1918] N-(4-(4-(4-丙氧基苄基)-1,4-二氮杂环庚烷-1-羰基)苯基)喹啉-8-磺酰胺(VIII-169):



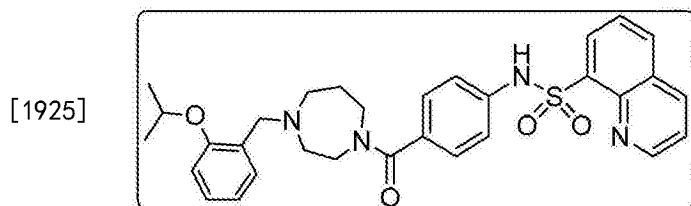
[1920] ^1H NMR (400MHz, CD_3OD) δ : 1.04 (t, 3H), 1.80 (q, 2H), 2.06 (br s, 2H), 3.55 (br s, 4H), 3.99 (t, 4H), 4.35 (s, 2H), 7.00–7.10 (m, 2H), 7.19–7.28 (m, 3H), 7.66–7.70 (m, 2H), 8.19 (d, 1H), 8.42 (d, 2H), 9.18 (d, 1H); HPLC纯度: 98.74%; LCMS: 559 (M^+ +1)。

[1921] N-(4-(4-(2-丙氧基苄基)-1,4-二氮杂环庚烷-1-羰基)苯基)喹啉-8-磺酰胺(VIII-170):



[1923] ^1H NMR (400MHz, CD_3OD) δ : 1.04 (t, 3H), 1.84 (br s, 2H), 2.16 (br s, 2H), 3.58 (br s, 4H), 4.08 (br s, 2H), 4.25 (br d, 1H), 4.40 (s, 2H), 7.04 (t, 1H), 7.19 (d, 1H), 7.20–7.28 (m, 4H), 7.44 (d, 1H), 7.53 (t, 1H), 7.68–7.72 (m, 2H), 8.21 (d, 1H), 8.42 (d, 2H), 9.18 (d, 1H); HPLC纯度: 97.74%; LCMS: 559 (M^+ +1)。

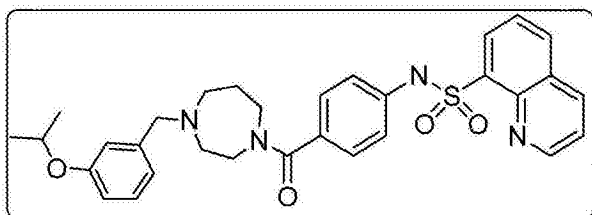
[1924] N-(4-(4-(2-异丙氧基苄基)-1,4-二氮杂环庚烷-1-羰基)苯基)喹啉-8-磺酰胺(VIII-171):



[1926] ^1H NMR (400MHz, CD_3OD) δ : 1.38 (s, 6H), 2.16 (br s, 2H), 3.55 (br s, 3H), 4.18 (br d, 1H), 4.38 (s, 2H), 4.79 (s, 1H), 7.04 (t, 1H), 7.19 (d, 1H), 7.21–7.34 (m, 4H), 7.40–7.52 (m, 2H), 7.53 (t, 1H), 7.67–7.72 (m, 2H), 8.21 (d, 1H), 8.44 (d, 2H), 9.18 (s, 1H); LCMS: 559 (M^+ +1); HPLC纯度: 98.99%。

[1927] N-(4-(4-(3-异丙氧基苄基)-1,4-二氮杂环庚烷-1-羰基)苯基)喹啉-8-磺酰胺(VIII-172):

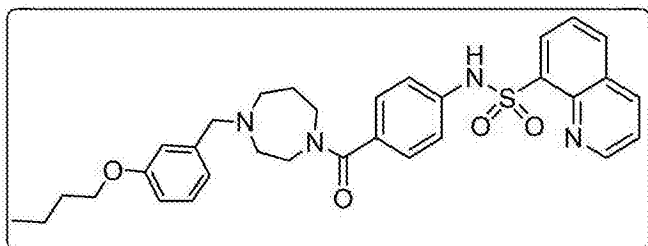
[1928]



[1929] ^1H NMR (400MHz, CD_3OD) δ : 1.38 (d, 6H), 1.4 (m, 1H), 2.08 (br s, 2H), 3.18 (br s, 2H), 3.56 (br s, 4H), 4.38 (s, 2H), 4.68 (m, 2H), 6.99–7.10 (m, 2H), 7.20–7.30 (m, 5H), 7.40 (t, 1H), 7.65–7.70 (m, 2H), 8.20 (d, 1H), 8.43 (d, 2H), 9.18 (d, 1H); HPLC纯度: 99.68%; LCMS: 559 (M^+ 1)。

[1930] N-(4-(4-(3-丁氧基苄基)-1,4-二氮杂环庚烷-1-羰基)苯基)喹啉-8-磺酰胺 (VIII-173):

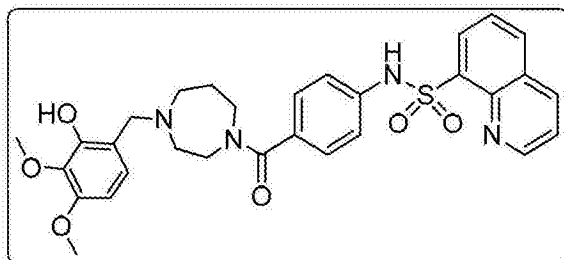
[1931]



[1932] ^1H NMR (400MHz, CD_3OD) δ : 1.01 (t, 3H), 1.50 (六重峰, 2H), 1.79 (五重峰, 2H), 2.06 (br s, 2H), 3.58 (br s, 4H), 3.6–3.9 (m, 4H), 4.03 (t, 2H), 4.38 (s, 2H), 7.00–7.08 (m, 3H), 7.19–7.26 (m, 4H), 7.41 (t, 1H), 7.63–7.69 (m, 2H), 8.19 (d, 1H), 8.42 (d, 2H), 9.18 (d, 1H); HPLC纯度: 99.75%; LCMS: 573 (M^+ 1)。

[1933] N-(4-(4-(2-羟基-3,4-二甲氧基苄基)-1,4-二氮杂环庚烷-1-羰基)苯基)喹啉-8-磺酰胺 (VIII-174):

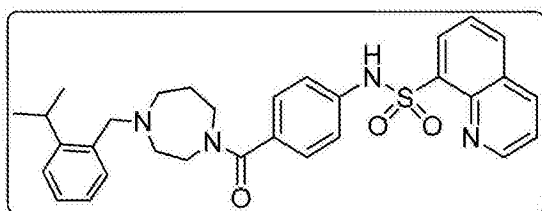
[1934]



[1935] ^1H NMR (400MHz, CD_3OD) δ : 2.18 (br s, 2H), 3.18 (br s, 2H), 3.56 (br s, 4H), 3.80 (s, 3H), 3.84 (s, 3H), 4.18 (br s, 2H), 4.30 (s, 2H), 6.61 (d, 2H), 7.03 (d, 2H), 7.19–7.27 (m, 2H), 7.61–7.66 (m, 2H), 8.19 (d, 1H), 8.42 (d, 2H), 9.18 (d, 1H); HPLC纯度: 97.61%; LCMS: 577 (M^+ 1)。

[1936] N-(4-(4-(2-异丙基苄基)-1,4-二氮杂环庚烷-1-羰基)苯基)喹啉-8-磺酰胺 (VIII-175):

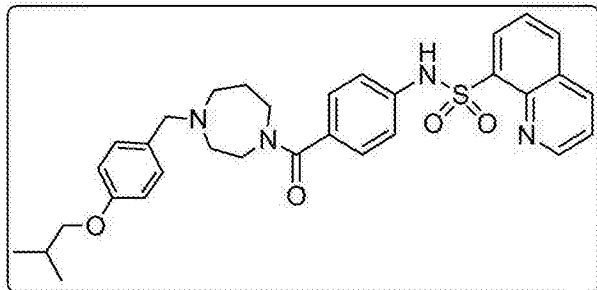
[1937]



[1938] ^1H NMR (400MHz, CD_3OD) δ : 1.22 (d, 6H), 2.05 (br s, 1H), 3.56 (brs, 8H), 4.50 (s, 4H), 7.20–7.39 (m, 5H), 7.40–7.56 (m, 3H), 7.64–7.69 (m, 2H), 8.20 (d, 1H), 8.42 (d, 2H), 9.18 (d, 1H); HPLC纯度: 98.73%; LCMS: 543 ($\text{M}^+ + 1$)。

[1939] N-(4-(4-(4-异丁氧基苄基)-1,4-二氮杂环庚烷-1-羰基)苯基)喹啉-8-磺酰胺 (VIII-176):

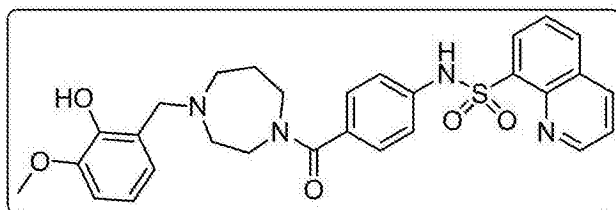
[1940]



[1941] ^1H NMR (400MHz, CD_3OD) δ : 1.04 (d, 6H), 2.02–2.17 (m, 3H), 3.15 (br d, 2H), 3.56 (br d, 4H), 3.79 (d, 2H), 4.20 (br d, 2H), 4.35 (s, 2H), 7.02 (d, 2H), 7.24 (t, 3H), 7.41 (d, 2H), 7.68–7.74 (m, 2H), 8.21 (d, 2H), 8.42 (d, 2H), 9.18 (d, 1H); HPLC纯度: 98.56%; LCMS: 573 ($\text{M}^+ + 1$)。

[1942] N-(4-(4-(2-羟基-3-甲氧基苄基)-1,4-二氮杂环庚烷-1-羰基)苯基)喹啉-8-磺酰胺 (VIII-177):

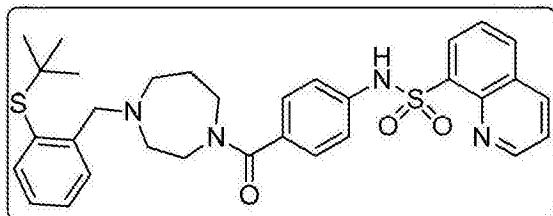
[1943]



[1944] ^1H NMR (400MHz, $\text{DMSO}-d_6$) δ : 1.61 (br s, 1H), 1.77 (br s, 1H), 2.60 (br s, 4H), 2.70 (br s, 2H), 3.58 (br s, 2H), 3.78 (s, 2H), 3.9 (s, 3H), 6.63 (d, 3H), 6.80 (br s, 1H), 7.12 (d, 2H), 7.77 (br s, 2H), 8.28 (s, 1H), 8.42 (d, 2H), 8.58 (s, 1H), 9.18 (s, 1H), 10.40 (s, 1H); HPLC纯度: 98.72%; LCMS: 547 ($\text{M}^+ + 1$)。

[1945] N-(4-(4-(2-(叔丁基硫基)苄基)-1,4-二氮杂环庚烷-1-羰基)苯基)喹啉-8-磺酰胺 (VIII-178):

[1946]

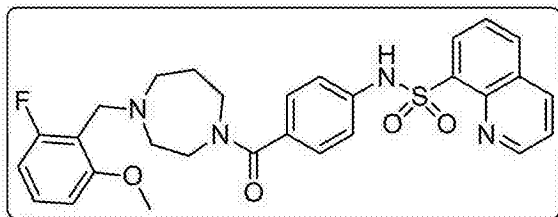


[1947] ^1H NMR (400MHz, $\text{DMSO}-d_6$) δ : 1.20 (d, 9H), 1.61 (br s, 1H), 1.77 (br s, 1H), 2.60 (br s, 1H), 2.70 (br s, 1H), 3.25 (br s, 2H), 3.58 (br s, 4H), 3.83 (d, 2H), 7.10 (d, 3H), 7.20 (br s, 2H), 7.49 (br s, 1H), 7.77 (br s, 4H), 8.28 (s, 1H), 8.42 (d, 1H), 8.58 (s, 1H), 9.18 (s, 1H), 10.40 (s, 1H); HPLC纯度: 91.52%; LCMS: 589 ($\text{M}^+ + 1$)。

[1948] N-(4-(4-(2-氟-6-甲氧基苄基)-1,4-二氮杂环庚烷-1-羰基)苯基)喹啉-8-磺酰胺

胺(VIII-179):

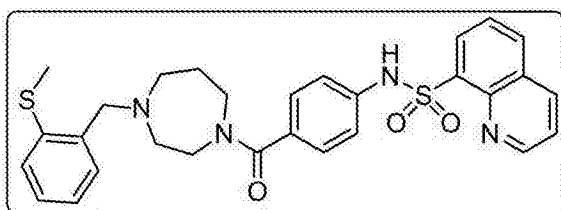
[1949]



[1950] ^1H NMR (400MHz, DMSO- d_6) δ : 1.61 (br s, 1H), 1.77 (br s, 1H), 2.60 (br s, 2H), 3.10 (br s, 2H), 3.45-3.55 (m, 4H), 3.64 (s, 3H), 3.81 (s, 2H), 6.77-6.87 (m, 2H), 7.08-7.20 (m, 4H), 7.30 (br s, 1H), 7.77-7.80 (m, 2H), 8.28 (d, 1H), 8.42 (d, 1H), 8.58 (d, 1H), 9.18 (s, 1H), 10.40 (s, 1H); HPLC纯度: 99.88%; LCMS: 549 (M^+ +1)。

[1951] N-(4-(4-(2-(甲硫基)苄基)-1,4-二氮杂环庚烷-1-羰基)苯基)喹啉-8-磺酰胺(VIII-180):

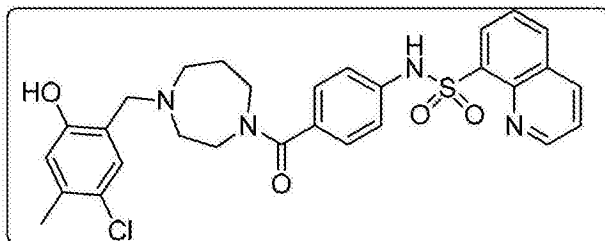
[1952]



[1953] ^1H NMR (400MHz, DMSO- d_6) δ : 1.61 (br s, 1H), 1.77 (br s, 1H), 2.38 (d, 4H), 2.60 (br s, 2H), 3.25 (br s, 2H), 3.58 (s, 2H), 3.6 (s, 3H), 7.00-7.18 (m, 5H), 7.24 (d, 2H), 7.77-7.80 (d, 2H), 8.28 (d, 1H), 8.42 (d, 2H), 8.58 (s, 1H), 9.18 (s, 1H), 10.40 (s, 1H); HPLC纯度: 99.77%; LCMS: 547 (M^+ +1)。

[1954] N-(4-(4-(5-氯-2-羟基-4-甲基苄基)-1,4-二氮杂环庚烷-1-羰基)苯基)喹啉-8-磺酰胺(VIII-181):

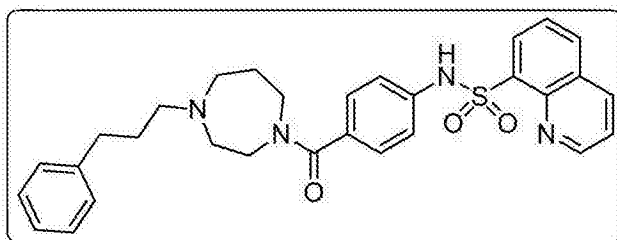
[1955]



[1956] ^1H NMR (400MHz, DMSO- d_6) δ : 1.61 (br s, 1H), 1.77 (br s, 1H), 2.25 (s, 4H), 2.78 (br s, 2H), 3.50-3.78 (m, 4H), 6.78 (d, 1H), 7.10-7.20 (m, 4H), 7.77-7.80 (m, 2H), 8.28 (s, 1H), 8.42 (d, 2H), 8.58 (s, 1H), 9.18 (s, 1H), 10.40 (s, 1H); HPLC纯度: 99.85%; LCMS: 565 (M^+ +1)。

[1957] N-(4-(4-(3-苯基丙基)-1,4-二氮杂环庚烷-1-羰基)苯基)喹啉-8-磺酰胺(VIII-182):

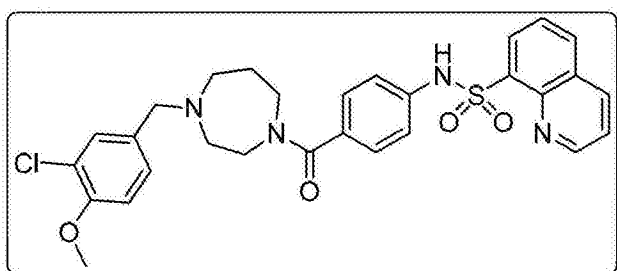
[1958]



[1959] ^1H NMR (400MHz, DMSO- d_6) δ : 1.32 (m, 2H), 1.61 (br s, 2H), 1.77 (br s, 2H), 2.1 (t, 2H), 2.38 (d, 2H), 2.60 (br s, 1H), 3.28 (br s, 3H), 3.58 (br s, 2H), 7.05–7.31 (m, 7H), 7.77–7.80 (m, 3H), 8.28 (d, 1H), 8.42 (d, 2H), 8.58 (d, 1H), 9.18 (s, 1H), 10.40 (s, 1H); HPLC 纯度: 99.73%; LCMS: 529 ($M^+ + 1$).

[1960] N-(4-(4-(3-氯-4-甲氧基苄基)-1,4-二氮杂环庚烷-1-羰基)苯基)喹啉-8-磺酰胺 (VIII-183):

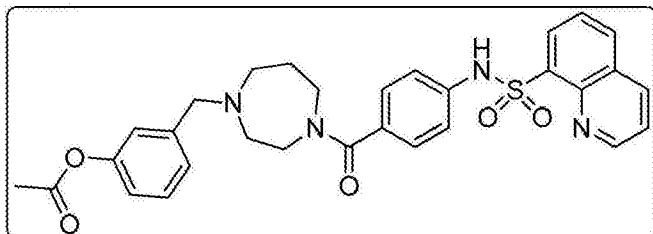
[1961]



[1962] ^1H NMR (400MHz, DMSO- d_6) δ : 1.61 (br s, 1H), 1.77 (br s, 1H), 2.60 (br s, 2H), 3.22 (br s, 2H), 3.57 (s, 4H), 3.82 (s, 2H), 7.01–7.38 (m, 6H), 7.77 (br s, 2H), 8.28 (s, 1H), 8.42 (d, 1H), 8.58 (s, 1H), 9.18 (s, 1H), 10.40 (s, 1H); HPLC 纯度: 99.50%; LCMS: 565 ($M^+ + 1$).

[1963] 乙酸3-((4-(4-(喹啉-8-亚磺酰氨基)苯甲酰基)-1,4-二氮杂环庚烷-1-基)甲基)苯酯 (VIII-184):

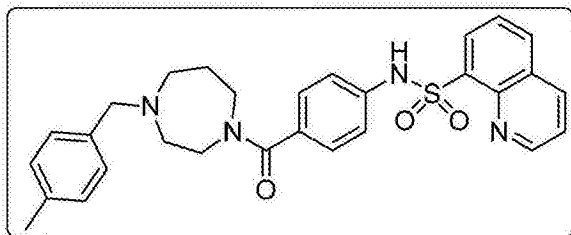
[1964]



[1965] ^1H NMR (400MHz, DMSO- d_6) δ : 1.61 (br s, 1H), 1.77 (br s, 1H), 2.60 (br s, 4H), 2.70 (br s, 2H), 3.58 (br s, 2H), 3.78 (s, 2H), 6.63 (d, 2H), 6.80 (br s, 2H), 7.12 (d, 2H), 7.77 (br s, 2H), 8.28 (s, 1H), 8.42 (d, 2H), 8.58 (s, 1H), 9.18 (s, 1H), 10.40 (s, 1H); HPLC 纯度: 98.72%; LCMS: 547 ($M^+ + 1$).

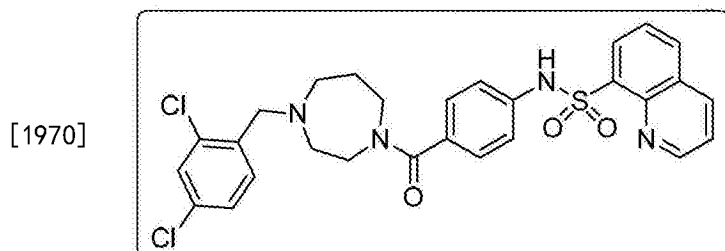
[1966] N-(4-(4-(4-甲基苄基)-1,4-二氮杂环庚烷-1-羰基)苯基)喹啉-8-磺酰胺 (VIII-185):

[1967]



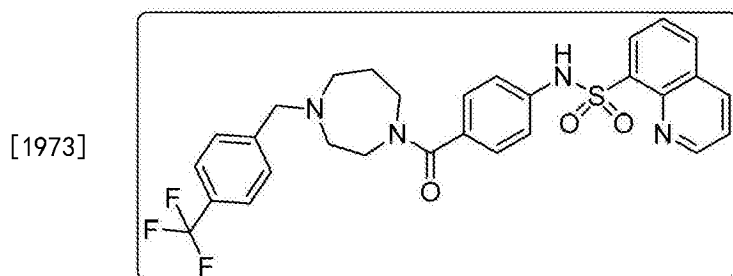
[1968] ^1H NMR (400MHz, DMSO- d_6) δ : 1.61 (br s, 1H), 1.77 (br s, 1H), 2.26 (s, 3H), 2.39–2.62 (m, 4H), 3.10 (br s, 2H), 3.50 (br s, 4H), 7.01–7.20 (m, 7H), 7.77–7.80 (m, 2H), 8.28 (br s, 1H), 8.42 (d, 1H), 8.58 (d, 2H), 9.18 (s, 1H), 10.41 (s, 1H); HPLC纯度: 97.70%; LCMS: 515 (M^+ +1)。

[1969] N-(4-(4-(2,4-二氯苄基)-1,4-二氮杂环庚烷-1-羰基)苯基)喹啉-8-磺酰胺 (VIII-186):



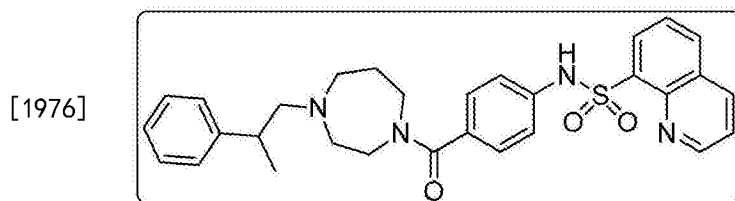
[1971] ^1H NMR (400MHz, DMSO- d_6) δ : 1.61 (br s, 1H), 1.77 (br s, 1H), 2.50–2.76 (m, 2H), 3.45–3.70 (m, 4H), 3.7–3.9 (m, 4H), 7.05–7.20 (m, 2H), 7.36–7.60 (m, 4H), 7.77–7.80 (m, 2H), 8.28 (d, 1H), 8.42 (d, 1H), 8.58 (d, 2H), 9.18 (s, 1H), 10.41 (s, 1H); HPLC纯度: 99.76%; LCMS: 569 (M^+ +1)。

[1972] N-(4-(4-(4-(三氟甲基)苄基)-1,4-二氮杂环庚烷-1-羰基)苯基)喹啉-8-磺酰胺 (VIII-187):



[1974] ^1H NMR (400MHz, DMSO- d_6) δ : 1.61 (br s, 1H), 1.77 (br s, 1H), 2.50–2.60 (m, 2H), 3.10 (br s, 2H), 3.50 (br s, 4H), 3.55–3.9 (m, 2H), 7.10 (s, 4H), 7.20–7.38 (m, 3H), 7.77–7.80 (m, 2H), 8.28 (br s, 1H), 8.42 (d, 1H), 8.58 (d, 2H), 9.18 (s, 1H), 10.41 (s, 1H); MS: 569 (M^+ +1); HPLC纯度: 99.47%; LCMS: 569 (M^+ +1)。

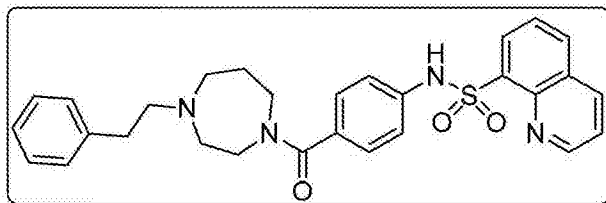
[1975] N-(4-(4-(2-苯基丙基)-1,4-二氮杂环庚烷-1-羰基)苯基)喹啉-8-磺酰胺 (VIII-188):



[1977] ^1H NMR (400MHz, CD_3OD) δ : 1.0 (q, 1H), 1.36 (d, 3H), 2.04 (br s, 2H), 3.10 (br s, 2H), 3.44 (br s, 4H), 3.56 (br s, 2H), 4.09 (br s, 2H), 7.10 (s, 4H), 7.24–7.40 (m, 4H), 7.62–7.68 (m, 3H), 8.18 (d, 1H), 8.42 (d, 2H), 9.18 (s, 1H); HPLC纯度: 99.86%; LCMS: 529 (M^+ +1)。

[1978] N-(4-(4-苄基-1,4-二氮杂环庚烷-1-羰基)苯基)喹啉-8-磺酰胺 (VIII-189) :

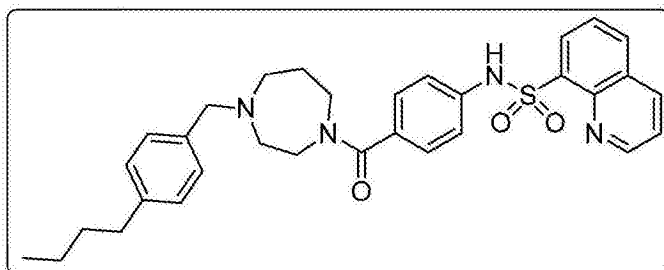
[1979]



[1980] ^1H NMR (400MHz, CD_3OD) δ : 2.10 (br s, 2H), 3.06 (br s, 2H), 3.40 (br s, 4H), 3.62 (br s, 2H), 3.79 (t, 2H), 4.09 (br s, 2H), 7.20-7.39 (m, 8H), 7.62-7.68 (m, 2H), 8.18 (d, 1H), 8.42 (d, 2H), 9.18 (s, 1H); HPLC纯度: 97.56%; LCMS: 515 (M^+ +1)。

[1981] N-(4-(4-(4-丁基苄基)-1,4-二氮杂环庚烷-1-羰基)苯基)喹啉-8-磺酰胺 (VIII-190) :

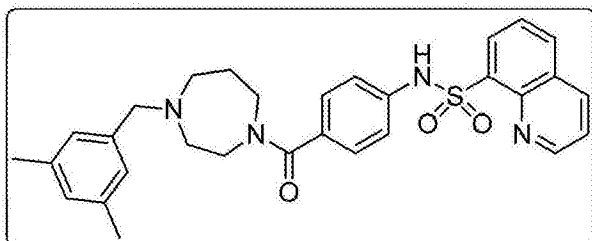
[1982]



[1983] ^1H NMR (400MHz, CD_3OD) δ : 0.92 (t, 3H), 1.37 (六重峰, 2H), 1.58 (六重峰, 2H), 2.03 (br s, 2H), 2.62 (t, 2H), 3.16 (br s, 2H), 3.50 (br s, 4H), 4.19 (br s, 2H), 4.24 (s, 2H), 7.17-7.23 (m, 4H), 7.25-7.38 (m, 4H), 7.61-7.65 (m, 2H), 8.18 (d, 1H), 8.41 (d, 2H), 9.16 (s, 1H); HPLC纯度: 99.72%; LCMS: 557 (M^+ +1)。

[1984] N-(4-(4-(3,5-二甲基苄基)-1,4-二氮杂环庚烷-1-羰基)苯基)喹啉-8-磺酰胺 (VIII-191) :

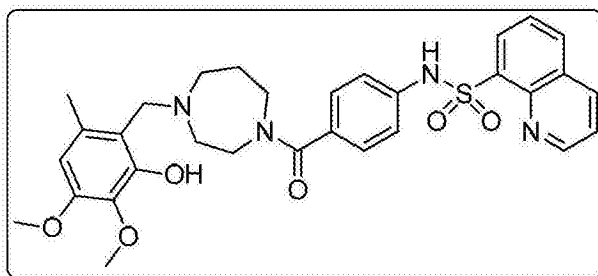
[1985]



[1986] ^1H NMR (400MHz, CD_3OD) δ : 2.01 (br s, 2H), 2.28 (s, 6H), 3.10 (br s, 2H), 3.44 (br s, 4H), 3.18 (br s, 1H), 4.12 (s, 2H), 7.02 (s, 2H), 7.10 (s, 1H), 7.14-7.22 (m, 4H), 7.60-7.65 (m, 2H), 8.18 (d, 1H), 8.42 (d, 2H), 9.18 (s, 1H); HPLC纯度: 99.81%; LCMS: 529 (M^+ +1)。

[1987] N-(4-(4-(2-羟基-3,4-二甲氧基-6-甲基苄基)-1,4-二氮杂环庚烷-1-羰基)苯基)喹啉-8-磺酰胺 (VIII-192) :

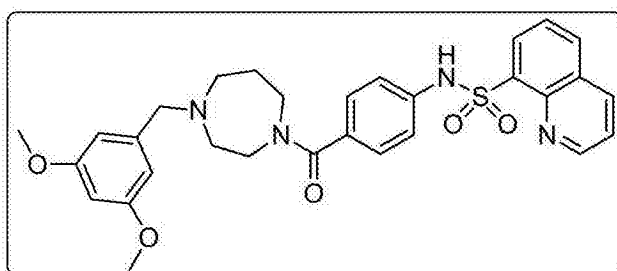
[1988]



[1989] ^1H NMR (400MHz, CD_3OD) δ : 2.12 (br s, 2H), 2.38 (s, 3H), 3.58 (br s, 5H), 3.79 (s, 3H), 3.83 (s, 3H), 3.85–3.9 (m, 2H), 4.21 (br s, 1H), 4.38 (s, 2H), 6.50 (s, 1H), 7.20–7.30 (m, 4H), 7.62–7.68 (m, 2H), 8.18 (d, 1H), 8.42 (d, 2H), 9.18 (s, 1H); HPLC纯度: 98.77%; LCMS: 591 (M^+ +1)。

[1990] N-(4-(4-(3,5-二甲氧基苄基)-1,4-二氮杂环庚烷-1-羰基)苯基)喹啉-8-磺酰胺 (VIII-193):

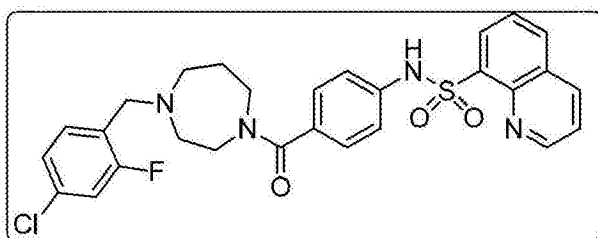
[1991]



[1992] ^1H NMR (400MHz, CD_3OD) δ : 2.02 (br s, 2H), 3.51 (br s, 3H), 3.2–3.7 (m, 3H), 3.79 (s, 2H), 3.81 (s, 6H), 4.28 (s, 2H), 6.63 (d, 2H), 7.20–7.27 (m, 5H), 7.62–7.68 (m, 2H), 8.18 (d, 1H), 8.42 (d, 2H), 9.18 (s, 1H); HPLC纯度: 94.85%; LCMS: 561 (M^+ +1)。

[1993] N-(4-(4-(4-氯-2-氟苄基)-1,4-二氮杂环庚烷-1-羰基)苯基)喹啉-8-磺酰胺 (VIII-193):

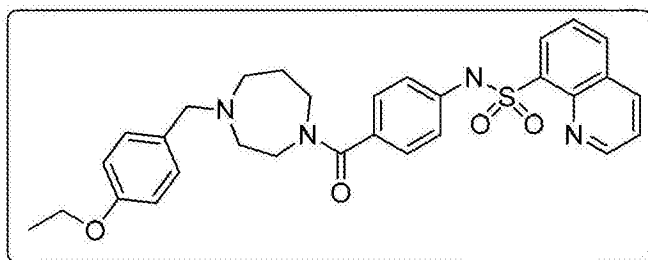
[1994]



[1995] ^1H NMR (400MHz, CD_3OD) δ : 2.03 (br s, 2H), 3.40 (br s, 4H), 3.61 (br s, 2H), 4.38 (s, 2H), 6.63 (d, 2H), 7.15–7.27 (m, 4H), 7.32–7.38 (m, 2H), 7.52 (t, 1H), 7.60–7.65 (m, 2H), 8.18 (d, 1H), 8.41 (d, 2H), 9.18 (s, 1H); HPLC纯度: 99.99%; LCMS: 553 (M^+)。

[1996] N-(4-(4-(4-乙氧基苄基)-1,4-二氮杂环庚烷-1-羰基)苯基)喹啉-8-磺酰胺 (VIII-194):

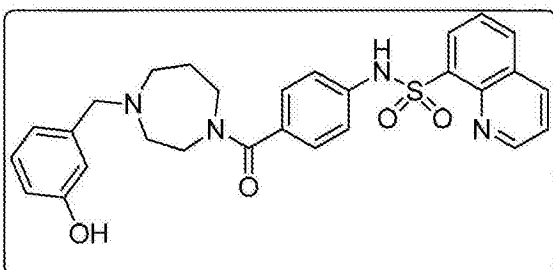
[1997]



[1998] ^1H NMR (400MHz, CD_3OD) δ : 1.39 (t, 3H), 2.03 (br s, 2H), 3.10 (br s, 1H), 3.57 (br s, 5H), 3.71 (br s, 2H), 4.06 (q, 2H), 4.19 (br s, 1H), 4.30 (s, 1H), 6.63 (d, 2H), 7.00 (d, 2H), 7.18–7.27 (m, 2H), 7.38 (d, 2H), 7.62–7.68 (m, 2H), 8.18 (d, 1H), 8.42 (d, 2H), 9.18 (s, 1H); HPLC纯度: 98.87%; LCMS: 545.0 (M^+ +1)。

[1999] N-(4-(4-(3-羟基苄基)-1,4-二氮杂环庚烷-1-羰基)苯基)喹啉-8-磺酰胺 (VIII-195):

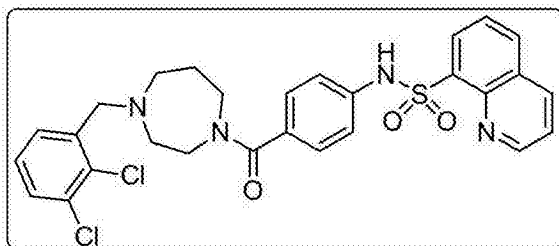
[2000]



[2001] ^1H NMR (400MHz, CD_3OD) δ : 2.02 (br s, 2H), 3.18 (br s, 2H), 3.59 (s, 4H), 4.20 (br s, 2H), 4.31 (s, 2H), 6.90 (d, 3H), 7.19–7.32 (m, 5H), 7.62–7.68 (m, 2H), 8.18 (d, 1H), 8.42 (d, 2H), 9.18 (s, 1H); HPLC纯度: 96.26%; LCMS: 517.2 (M^+ +1)。

[2002] N-(4-(4-(2,3-二氯苄基)-1,4-二氮杂环庚烷-1-羰基)苯基)喹啉-8-磺酰胺 (VIII-196):

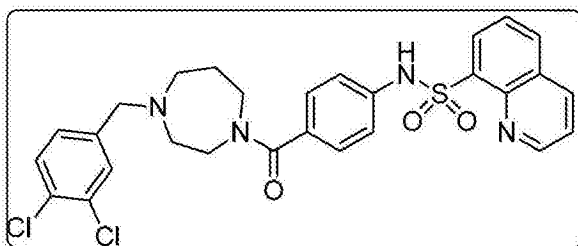
[2003]



[2004] ^1H NMR (400MHz, CD_3OD) δ : 2.12 (br s, 2H), 3.53 (br s, 6H), 3.73 (br s, 2H), 4.59 (s, 2H), 6.63 (d, 2H), 7.20–7.30 (m, 3H), 7.44 (t, 1H), 7.59 (s, 1H), 7.63–7.68 (m, 2H), 7.78 (d, 1H), 8.18 (d, 1H), 8.42 (d, 1H), 9.18 (s, 1H); HPLC纯度: 99.29%; LCMS: 569 (M^+ +1)。

[2005] N-(4-(4-(3,4-二氯苄基)-1,4-二氮杂环庚烷-1-羰基)苯基)喹啉-8-磺酰胺 (VIII-197):

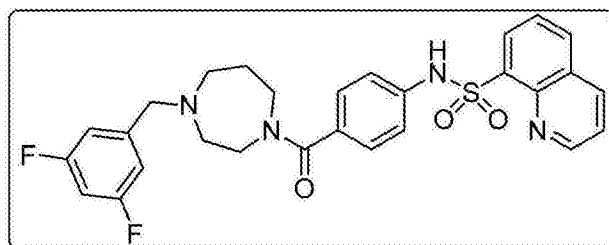
[2006]



[2007] ^1H NMR (400MHz, DMSO-d₆) δ : 1.60 (br s, 1H), 1.78 (br s, 1H), 2.60 (br s, 2H), 2.62 (br s, 2H), 3.23 (br s, 2H), 3.58 (br s, 2H), 3.50–3.62 (m, 2H), 7.07–7.18 (m, 3H), 7.24 (dd, 1H), 7.43–7.60 (m, 2H), 7.70–7.79 (m, 2H), 8.24 (d, 1H), 8.42 (d, 2H), 8.55 (d, 1H), 9.18 (s, 1H), 10.42 (s, 1H); HPLC纯度: 99.76%; LCMS: 569.1 (M^+ +1)。

[2008] N-(4-(4-(3,5-二氟苄基)-1,4-二氮杂环庚烷-1-羰基)苯基)喹啉-8-磺酰胺 (VIII-198):

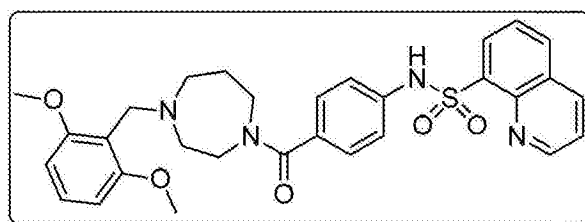
[2009]



[2010] ^1H NMR (400MHz, DMSO-d₆) δ : 1.60 (br s, 1H), 1.78 (br s, 1H), 2.60 (br s, 2H), 2.62 (br s, 2H), 3.23 (br s, 4H), 3.50–3.62 (m, 2H), 6.95–7.20 (m, 6H), 7.74 (s, 2H), 8.24 (d, 1H), 8.42 (d, 2H), 8.55 (d, 1H), 9.18 (s, 1H), 10.42 (s, 1H); HPLC纯度: 98.49%; LCMS: 559.1 (M^+ +23)。

[2011] N-(4-(4-(2,6-二甲氧基苄基)-1,4-二氮杂环庚烷-1-羰基)苯基)喹啉-8-磺酰胺 (VIII-199):

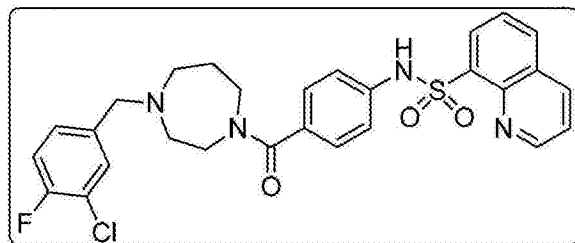
[2012]



[2013] ^1H NMR (400MHz, DMSO-d₆) δ : 1.60 (br s, 1H), 1.71 (br s, 1H), 2.62 (br s, 3H), 3.21 (br s, 2H), 3.50 (s, 3H), 3.59 (s, 3H), 3.79 (s, 2H), 6.58 (d, 1H), 6.61 (d, 2H), 7.02–7.21 (m, 4H), 7.62–7.68 (m, 2H), 8.18 (d, 1H), 8.42 (d, 2H), 9.18 (s, 1H), 10.39 (s, 1H); HPLC纯度: 99.26%; LCMS: 561 (M^+ +1)。

[2014] N-(4-(4-(3-氯-4-氟苄基)-1,4-二氮杂环庚烷-1-羰基)苯基)喹啉-8-磺酰胺 (VIII-200):

[2015]

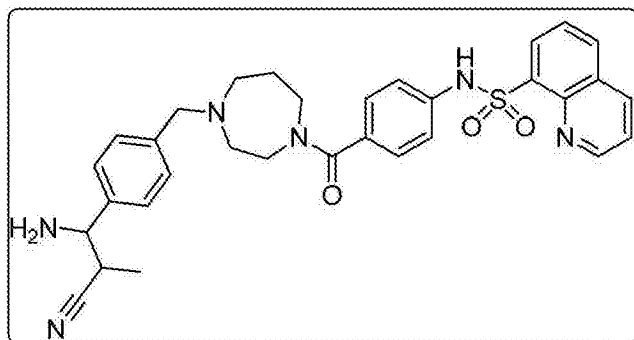


[2016] ^1H NMR (400MHz, DMSO-d₆) δ : 1.61 (br s, 1H), 1.80 (br s, 1H), 3.42 (dd, 6H), 7.08–7.18 (m, 3H), 7.20–7.55 (m, 3H), 7.70–7.80 (m, 2H), 8.28 (d, 1H), 8.42 (d, 2H), 8.58 (d, 1H), 9.18 (s, 1H), 10.40 (s, 1H); HPLC纯度: 99.54%; LCMS: 561 (M^+)。

[2017] N-(4-(4-(4-(1-氨基-2-氰基丙基)苄基)-1,4-二氮杂环庚烷-1-羰基)苯基)喹

啉-8-磺酰胺 (VIII-201) :

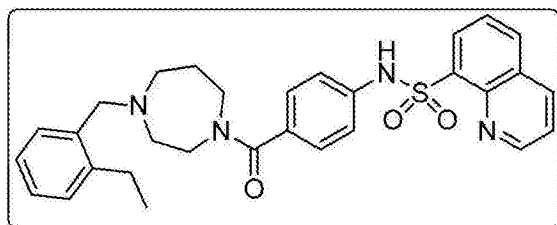
[2018]



[2019] ^1H NMR (400MHz, DMSO- d_6) δ : 1.61 (br s, 1H), 1.7 (s, 1H), 1.80 (br s, 1H), 2.70 (t, 2H), 2.93 (s, 3H), 3.23 (br s, 2H), 3.40-3.59 (m, 4H), 3.64 (t, 1H), 6.68 (t, 2H), 7.01-7.18 (m, 5H), 7.70 (br s, 2H), 8.28 (t, 1H), 8.42 (d, 2H), 8.58 (t, 1H), 9.18 (s, 1H), 10.40 (s, 1H); HPLC纯度: 96.64%; LCMS: 605 (M^+ +23)。

[2020] N-(4-(4-(2-乙基苄基)-1,4-二氮杂环庚烷-1-羰基)苯基)喹啉-8-磺酰胺 (VIII-202) :

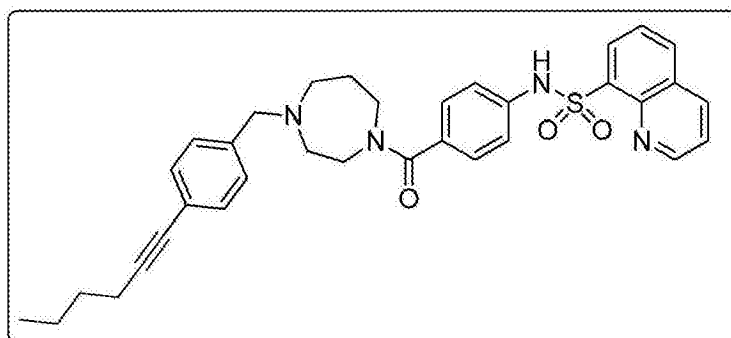
[2021]



[2022] ^1H NMR (400MHz, DMSO- d_6) δ : 1.0-1.17 (m, 2H), 1.2 (t, 3H), 1.59 (br s, 1H), 1.74 (br s, 1H), 2.1 (m, 2H), 2.42-2.75 (m, 5H), 3.2-3.6 (m, 3H), 7.01-7.22 (m, 7H), 7.75 (s, 2H), 8.28 (d, 1H), 8.42 (d, 2H), 8.58 (d, 1H), 9.18 (s, 1H), 10.40 (s, 1H); HPLC纯度: 99.16%; LCMS: 529 (M^+ +1)。

[2023] N-(4-(4-(4-(己-1-炔-1-基)苄基)-1,4-二氮杂环庚烷-1-羰基)苯基)喹啉-8-磺酰胺 (VIII-203) :

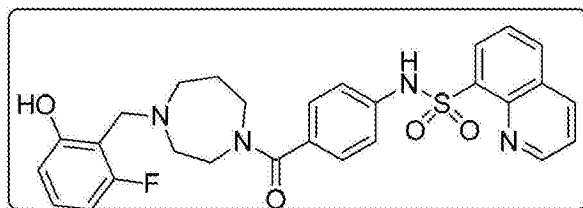
[2024]



[2025] ^1H NMR (400MHz, DMSO- d_6) δ : 0.92 (t, 3H), 1.40-1.60 (m, 5H), 1.77 (br s, 2H), 3.20 (br s, 4H), 3.50 (br s, 6H), 7.03-7.38 (m, 7H), 7.78 (br s, 2H), 8.28 (br s, 1H), 8.42 (d, 2H), 8.58 (d, 1H), 9.18 (s, 1H), 10.40 (s, 1H); HPLC纯度: 99.77%; LCMS: 581 (M^+ +1)。

[2026] N-(4-(4-(2-氟-6-羟基苄基)-1,4-二氮杂环庚烷-1-羰基)苯基)喹啉-8-磺酰胺 (VIII-204) :

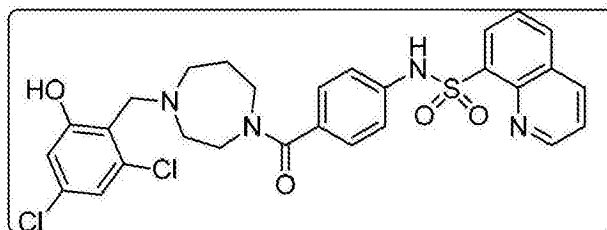
[2027]



[2028] ^1H NMR (400MHz, DMSO- d_6) δ : 1.61 (br s, 1H), 1.77 (br s, 1H), 2.60 (br s, 2H), 2.78 (br s, 1H), 3.20-3.42 (m, 3H), 3.58 (d, 2H), 3.79 (d, 2H), 4.1 (s, 1H), 6.59 (br s, 2H), 7.10-7.20 (m, 4H), 7.71-7.80 (m, 2H), 8.28 (d, 1H), 8.42 (d, 1H), 8.58 (d, 1H), 9.18 (s, 1H), 10.40 (s, 1H); HPLC纯度: 99.78%; LCMS: 535 (M^+ +1)。

[2029] N-(4-(4-(2,4-二氯-6-羟基苄基)-1,4-二氮杂环庚烷-1-羰基)苯基)喹啉-8-磺酰胺 (VIII-205):

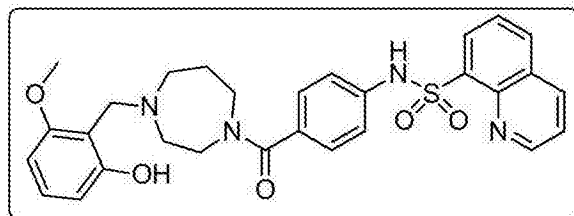
[2030]



[2031] ^1H NMR (400MHz, DMSO- d_6) δ : 1.61 (br s, 1H), 1.77 (br s, 1H), 2.58-2.80 (m, 3H), 3.20-3.68 (m, 5H), 3.79 (d, 2H), 6.78 (d, 1H), 6.99 (d, 1H), 7.09-7.20 (m, 4H), 7.71-7.80 (m, 2H), 8.28 (d, 1H), 8.42 (d, 1H), 8.58 (d, 1H), 9.18 (s, 1H), 10.40 (s, 1H); HPLC纯度: 99.58%; LCMS: 585 (M^+ +1)。

[2032] N-(4-(4-(2-羟基-6-甲氧基苄基)-1,4-二氮杂环庚烷-1-羰基)苯基)喹啉-8-磺酰胺 (VIII-206):

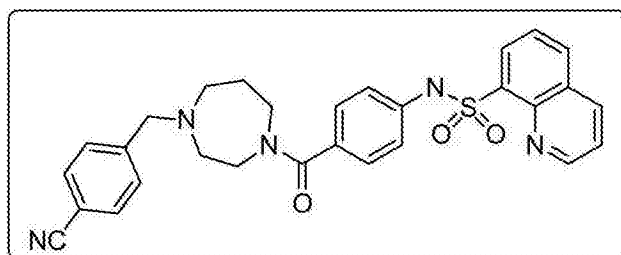
[2033]



[2034] ^1H NMR (400MHz, DMSO- d_6) δ : 1.61 (br s, 1H), 1.77 (br s, 1H), 2.60 (br s, 2H), 3.21 (br s, 2H), 3.42-3.58 (m, 2H), 3.53 (s, 2H), 3.68 (d, 2H), 6.26-6.45 (m, 2H), 7.03-7.20 (m, 3H), 7.71-7.80 (m, 2H), 8.28 (s, 2H), 8.42 (d, 2H), 8.58 (s, 1H), 9.18 (s, 1H), 10.41 (s, 1H); HPLC纯度: 99.89%; LCMS: 547 (M^+ +1)。

[2035] N-(4-(4-(4-氰基苄基)-1,4-二氮杂环庚烷-1-羰基)苯基)喹啉-8-磺酰胺 (VIII-207):

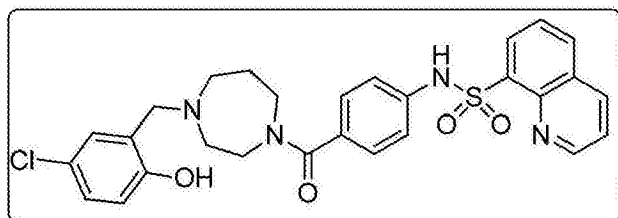
[2036]



[2037] ^1H NMR (400MHz, DMSO- d_6) δ : 1.61 (br s, 1H), 1.77 (br s, 1H), 2.60 (br s, 2H), 3.21 (br s, 2H), 3.42–3.58 (m, 2H), 3.53 (s, 2H), 3.68 (d, 2H), 7.10–7.20 (m, 3H), 7.41–7.58 (m, 2H), 7.71–7.81 (m, 3H), 8.28 (d, 1H), 8.42 (d, 2H), 8.58 (d, 1H), 9.18 (s, 1H), 10.40 (s, 1H); HPLC纯度: 97.75%; LCMS: 526.2 (M^+ +1)。

[2038] N-(4-(4-(5-氯-2-羟基苄基)-1,4-二氮杂环庚烷-1-羰基)苯基)喹啉-8-磺酰胺 (VIII-208):

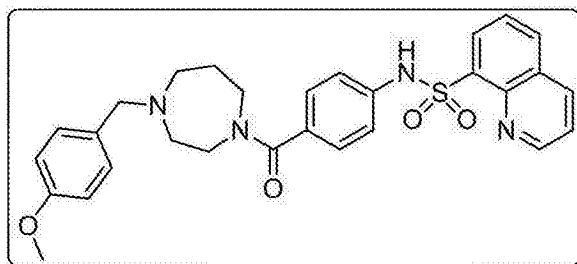
[2039]



[2040] ^1H NMR (400MHz, DMSO- d_6) δ : 1.61 (br s, 1H), 1.77 (br s, 1H), 2.60–2.78 (m, 2H), 3.21 (br s, 2H), 3.42–3.58 (m, 2H), 3.50–3.71 (m, 4H), 6.74–6.80 (m, 1H), 7.08–7.20 (m, 5H), 7.71–7.80 (m, 2H), 8.28 (br s, 1H), 8.42 (d, 2H), 8.58 (br s, 1H), 9.18 (s, 1H), 10.40 (s, 1H); HPLC纯度: 99.40%; LCMS: 551.1 (M^+)。

[2041] N-(4-(4-(4-methoxybenzyl)-1,4-二氮杂环庚烷-1-羰基)苯基)喹啉-8-磺酰胺 (VIII-208):

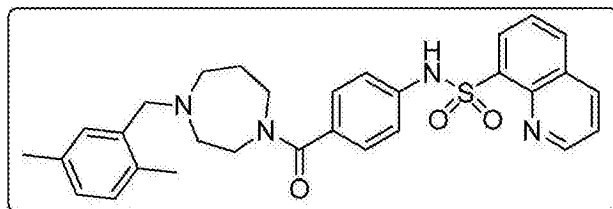
[2042]



[2043] ^1H NMR (400MHz, DMSO- d_6) δ : 1.61 (br s, 1H), 1.77 (br s, 1H), 2.40 (br s, 1H), 2.60 (br s, 1H), 3.21 (br s, 2H), 3.42–3.58 (m, 4H), 3.77 (s, 2H), 6.80–6.91 (m, 2H), 7.06–7.20 (m, 4H), 7.71–7.79 (m, 2H), 8.28 (br s, 1H), 8.42 (d, 2H), 8.58 (br s, 1H), 9.18 (s, 1H), 10.40 (s, 1H); HPLC纯度: 99.04%; LCMS: 531 (M^+ +1)。

[2044] N-(4-(4-(2,5-二甲基苄基)-1,4-二氮杂环庚烷-1-羰基)苯基)喹啉-8-磺酰胺 (VIII-209):

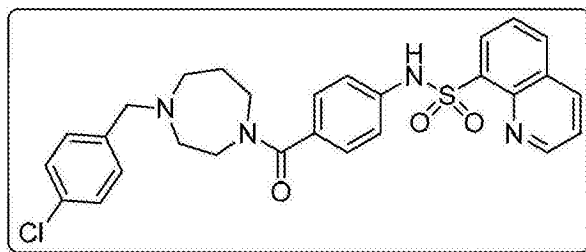
[2045]



[2046] ^1H NMR (400MHz, DMSO- d_6) δ : 1.61 (br s, 1H), 1.77 (br s, 1H), 2.10–2.25 (m, 2H), 2.24 (s, 2H), 2.60–2.67 (m, 2H), 2.60 (br s, 2H), 3.20–3.60 (m, 2H), 6.90–7.20 (m, 5H), 7.71–7.80 (m, 2H), 8.28 (d, 1H), 8.42 (d, 2H), 8.58 (d, 1H), 9.18 (s, 1H), 10.40 (s, 1H); HPLC纯度: 98.86%; LCMS: 529 (M^+ +1)。

[2047] N-(4-(4-(3,5-二氯苄基)-1,4-二氮杂环庚烷-1-羰基)苯基)喹啉-8-磺酰胺

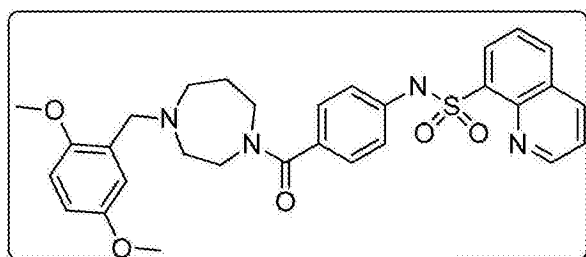
[2057]



[2058] ^1H NMR (400MHz, DMSO- d_6) δ : 1.59 (s, 1H), 1.78 (s, 1H), 2.41 (s, 1H), 2.52–2.64 (m, 2H), 3.25 (br s, 2H), 3.55 (s, 2H), 3.59 (s, 2H), 7.08–7.17 (m, 3H), 7.20–7.40 (m, 4H), 7.68–7.75 (m, 2H), 8.28 (d, 1H), 8.42 (d, 1H), 8.53 (d, 1H), 9.18 (s, 1H), 10.39 (s, 1H); HPLC纯度: 97.45%; LCMS: 535.1 (M^+).

[2059] N-(4-(4-(2,5-二甲氧基苄基)-1,4-二氮杂环庚烷-1-羰基)苯基)喹啉-8-磺酰胺 (VIII-214):

[2060]



[2061] ^1H NMR (400MHz, DMSO- d_6) δ : 1.63 (br s, 1H), 1.78 (br s, 1H), 2.2 (br s, 2H), 2.62 (br s, 2H), 3.24 (br s, 2H), 3.48–3.66 (m, 4H), 3.7–3.86 (s, 6H), 6.71–6.81 (m, 1H), 6.82–6.99 (m, 2H), 7.05–7.17 (m, 3H), 7.70–7.79 (m, 2H), 8.28 (d, 1H), 8.42 (d, 1H), 8.56 (d, 1H), 9.18 (s, 1H), 10.39 (s, 1H); HPLC纯度: 98.43%; LCMS: 561 ($M^+ + 1$).

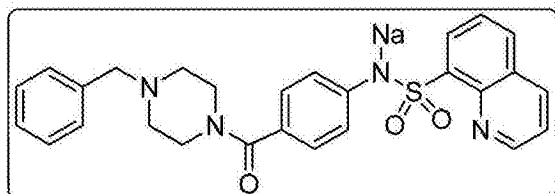
[2062] 相应盐的合成:

[2063] 用于制备盐的一般程序:

[2064] 将N-(4-(4-苄基哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (0.25mmol) 在甲醇 (5ml) 中的溶液加入氢氧化钠/甲磺酸 (0.25mmol, 1.0eq), 将反应混合物在室温搅拌3h。将在减压下除去溶剂, 与戊烷共沸, 得到为淡黄色固体状的盐。

[2065] (4-(4-苄基哌嗪-1-羰基)苯基)(喹啉-8-基磺酰基)酰胺钠 (VIII-215):

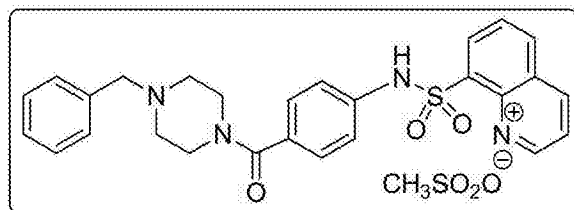
[2066]



[2067] ^1H NMR (400MHz, CDCl_3) δ : 2.38 (br d, 4H), 3.31 (br s, 2H), 3.41 (s, 2H), 3.64 (br s, 2H), 6.94 (d, 2H), 7.06 (t, 4H), 7.40 (d, 2H), 7.56–7.63 (m, 2H), 8.01 (d, 1H), 8.28 (d, 1H), 8.38 (d, 1H), 8.56 (s, 1H), 9.18 (s, 1H); LCMS: 508.5 ($M^+ + 23$).

[2068] 8-(N-(4-(4-苄基哌嗪-1-羰基)苯基)氨磺酰基)喹啉-1-甲磺酸盐 (VIII-216):

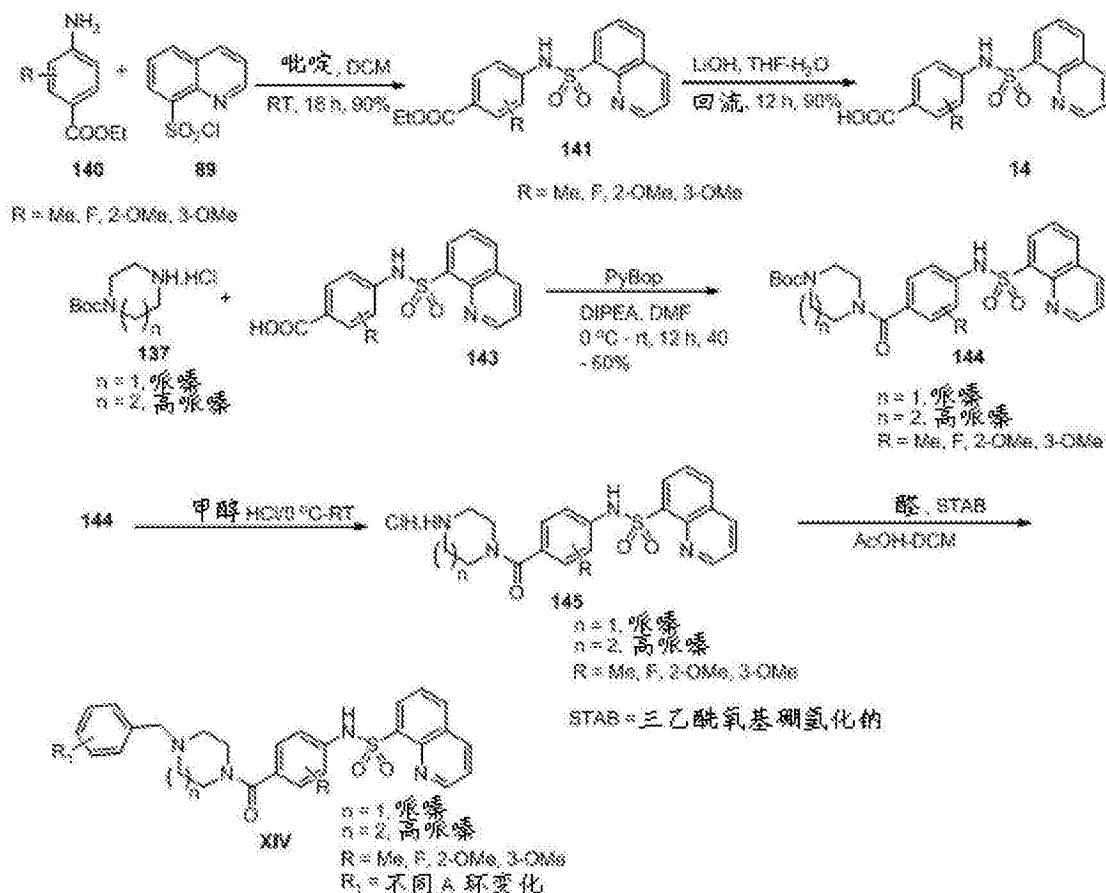
[2069]



[2070] ¹H NMR (400MHz, CDCl₃) δ: 2.38 (br d, 4H), 3.31 (br s, 2H), 3.41 (s, 2H), 3.64 (br s, 2H), 6.94 (d, 2H), 7.06 (t, 4H), 7.40 (d, 2H), 7.56–7.63 (m, 2H), 8.01 (d, 1H), 8.28 (d, 1H), 8.38 (d, 1H), 8.56 (s, 1H), 9.18 (s, 1H); LCMS: 487.0 (M⁺+1)。

[2071] 具有3-甲基、2-甲基、3-氟、3-氯、3-甲氧基和2-甲氧基取代的苯基环的基于哌嗪的苄基衍生物的合成

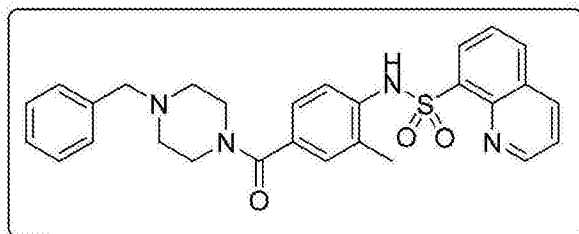
[2072] 流程22



[2074] 通过按照流程21中对于式(VIII)化合物所提及的类似程序(具有相应关键步骤例如磺酰胺形成、酯水解、酰胺键形成和还原胺化),由苯胺140(0.25mmol)开始进行化合物140-145和式(XIV)化合物的合成。

[2075] N-(4-(4-苄基哌嗪-1-羰基)-2-甲基苯基)喹啉-8-磺酰胺(XIV-1):

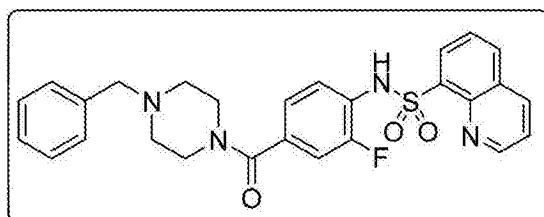
[2076]



[2077] ^1H NMR (400MHz, CDCl_3) δ : 2.22 (s, 3H), 2.65 (br s, 4H), 3.50 (br s, 4H), 4.20 (s, 2H), 7.01 (d, 1H), 7.12 (s, 1H), 7.39 (t, 2H), 7.48 (q, 2H), 7.60–7.68 (m, 2H), 8.18 (d, 1H), 8.28 (d, 1H), 8.43 (d, 1H), 9.18 (d, 1H); HPLC纯度: 98.75%; LCMS: 501 (M^+ +1)。

[2078] N-(4-(4-苄基哌嗪-1-羰基)-2-氟苯基)喹啉-8-磺酰胺 (XIV-2):

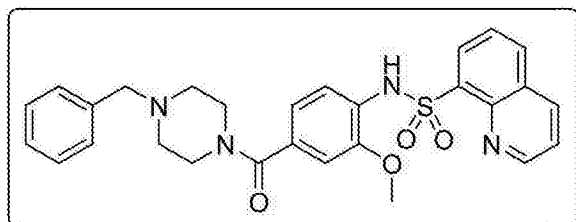
[2079]



[2080] ^1H NMR (400MHz, CDCl_3) δ : 2.62 (br s, 4H), 3.80 (br s, 4H), 4.20 (s, 2H), 6.99 (d, 1H), 7.03 (d, 1H), 7.39 (d, 2H), 7.40–7.48 (m, 3H), 7.60–7.68 (m, 2H), 7.80 (t, 1H), 8.18 (d, 1H), 8.26 (d, 1H), 8.43 (d, 1H), 9.18 (d, 1H); HPLC纯度: 97.86%; LCMS: 505 (M^+ +1)。

[2081] N-(4-(4-苄基哌嗪-1-羰基)-2-甲氧基苯基)喹啉-8-磺酰胺 (XIV-3):

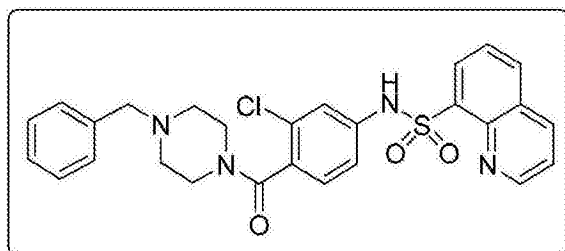
[2082]



[2083] ^1H NMR (400MHz, CDCl_3) δ : 2.46 (br s, 4H), 3.50 (br s, 4H), 3.66 (s, 3H), 4.20 (br s, 2H), 6.40 (br s, 1H), 6.94 (br s, 1H), 7.39 (d, 2H), 7.42–7.48 (m, 3H), 7.61–7.66 (m, 2H), 8.18 (d, 1H), 8.36 (d, 1H), 8.41 (d, 1H), 9.18 (d, 1H); HPLC纯度: 99.99%; LCMS: 517 (M^+ +1)。

[2084] N-(4-(4-苄基哌嗪-1-羰基)-3-氯苯基)喹啉-8-磺酰胺 (XIV-4):

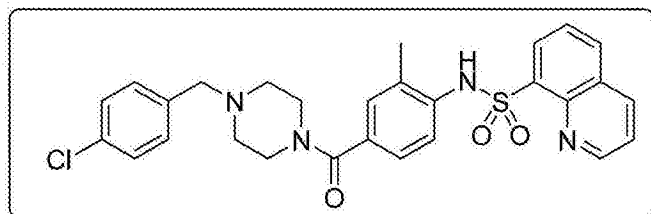
[2085]



[2086] ^1H NMR (400MHz, CDCl_3) δ : 2.32 (br s, 4H), 3.42 (br s, 4H), 4.38 (s, 2H), 7.16 (q, 2H), 7.30 (s, 1H), 7.49 (s, 4H), 7.64–7.73 (m, 2H), 8.21 (d, 1H), 8.42 (t, 2H), 9.18 (d, 1H); HPLC纯度: 96.62% LCMS: 521 (M^+)。

[2087] N-(4-(4-(4-氯苄基)哌嗪-1-羰基)-2-甲基苯基)喹啉-8-磺酰胺 (XIV-5):

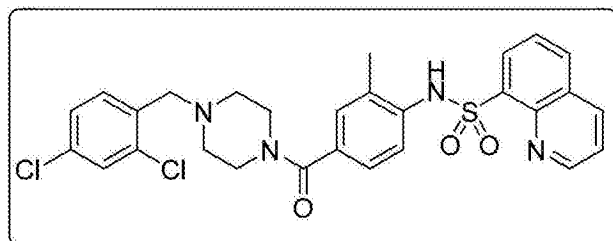
[2088]



[2089] ^1H NMR (400MHz, DMSO- d_6) δ : 2.01 (s, 3H), 2.37 (br s, 4H), 3.41 (br s, 4H), 3.50 (s, 2H), 6.97 (s, 2H), 7.06 (s, 1H), 7.39 (dd, 2H), 7.54 (s, 1H), 7.62-7.77 (m, 2H), 8.21-8.30 (m, 3H), 8.52 (d, 1H), 9.18 (s, 1H), 9.34 (s, 1H); HPLC纯度: 97.97%; LCMS: 535 (M^+).

[2090] N-(4-(4-(2,4-二氯苄基)哌嗪-1-羰基)-2-甲基苯基)喹啉-8-磺酰胺 (XIV-6):

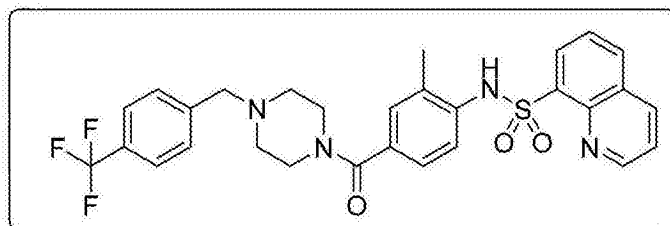
[2091]



[2092] ^1H NMR (400MHz, DMSO- d_6) δ : 2.01 (s, 3H), 2.37 (br s, 4H), 3.42 (br s, 4H), 3.50 (s, 2H), 6.97 (s, 2H), 7.06 (s, 1H), 7.39 (dd, 2H), 7.54 (s, 1H), 7.62-7.77 (m, 2H), 8.21-8.30 (m, 2H), 8.52 (d, 1H), 9.18 (s, 1H); HPLC纯度: 97.97%; LCMS: 569 (M^+).

[2093] N-(2-甲基-4-(4-(4-(三氟甲基)苄基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (XIV-7):

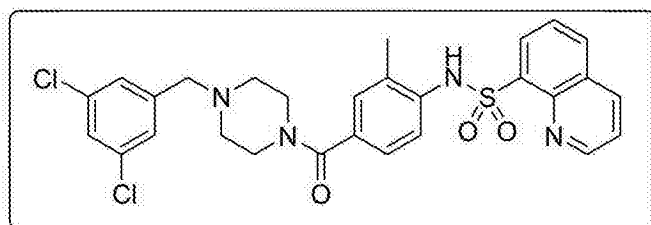
[2094]



[2095] ^1H NMR (400MHz, DMSO- d_6) δ : 2.01 (s, 3H), 2.37 (br s, 4H), 3.41 (br s, 4H), 3.53 (s, 2H), 6.97 (s, 2H), 7.06 (s, 1H), 7.46 (d, 2H), 7.62-7.77 (m, 4H), 8.21-8.30 (m, 2H), 8.57 (d, 1H), 9.18 (s, 1H), 9.21 (br s, 1H); HPLC纯度: 96.00%; LCMS: 569 ($M^+ + 1$).

[2096] N-(4-(4-(3,5-二氯苄基)哌嗪-1-羰基)-2-甲基苯基)喹啉-8-磺酰胺 (XIV-8):

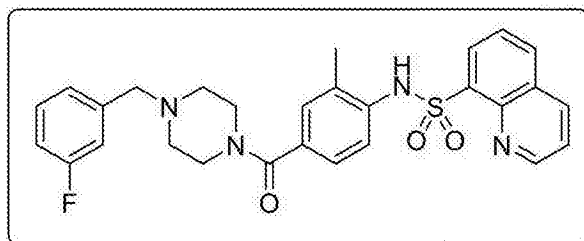
[2097]



[2098] ^1H NMR (400MHz, DMSO- d_6) δ : 2.01 (s, 3H), 2.37 (br s, 4H), 3.46 (s, 4H), 6.97 (s, 2H), 7.06 (s, 1H), 7.31 (s, 2H), 7.46 (s, 1H), 7.62-7.77 (m, 3H), 8.21-8.30 (m, 2H), 8.57 (d, 1H), 9.18 (s, 1H), 9.39 (s, 1H); HPLC纯度: 99.45%; LCMS: 569 (M^+).

[2099] N-(4-(4-(3-氟苄基)哌嗪-1-羰基)-2-甲基苯基)喹啉-8-磺酰胺 (XIV-9):

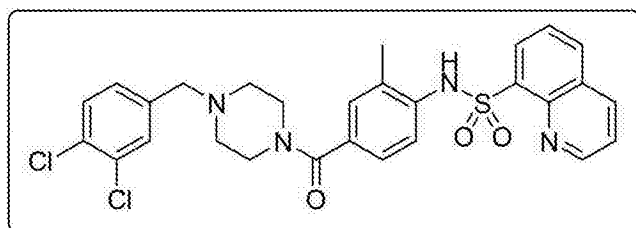
[2100]



[2101] ^1H NMR (400MHz, DMSO- d_6) δ : 2.01 (s, 3H), 2.30 (br s, 4H), 3.41 (br s, 4H), 3.47 (s, 2H), 6.97 (s, 2H), 6.99–7.16 (m, 4H), 7.25–7.34 (m, 1H), 7.62–7.77 (m, 2H), 8.21–8.30 (m, 2H), 8.57 (d, 1H), 9.18 (s, 1H), 9.21 (s, 1H); HPLC纯度: 97.71%; LCMS: 519 (M^+ +1)。

[2102] N-(4-(4-(3,4-二氯苄基)哌嗪-1-羰基)-2-甲基苯基)喹啉-8-磺酰胺 (XIV-10) :

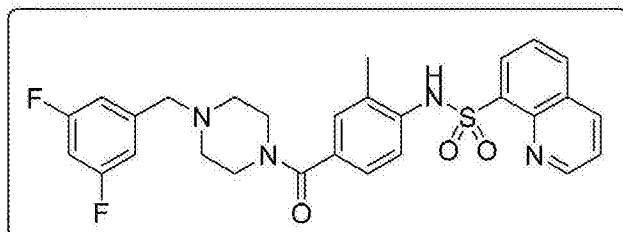
[2103]



[2104] ^1H NMR (400MHz, DMSO- d_6) δ : 2.01 (s, 3H), 2.25 (br s, 4H), 3.45 (s, 4H), 6.97 (s, 2H), 7.06 (m, 1H), 7.25 (d, 1H), 7.58 (t, 2H), 7.62–7.77 (m, 2H), 8.21–8.30 (m, 2H), 8.57 (d, 1H), 9.18 (s, 1H), 9.21 (s, 1H); HPLC纯度: 94.90%; LCMS: 569 (M^+)。

[2105] N-(4-(4-(3,5-二氟苄基)哌嗪-1-羰基)-2-甲基苯基)喹啉-8-磺酰胺 (XIV-11) :

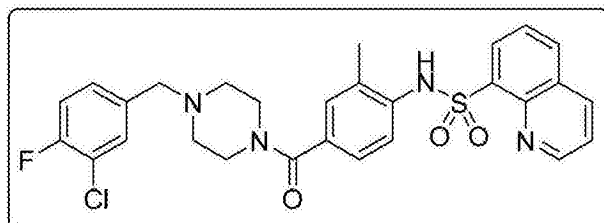
[2106]



[2107] ^1H NMR (400MHz, DMSO- d_6) δ : 2.01 (s, 3H), 2.25 (br s, 4H), 3.45 (s, 4H), 3.52 (s, 2H), 6.97–7.10 (m, 5H), 7.62–7.77 (m, 3H), 8.21–8.30 (m, 2H), 8.57 (d, 1H), 9.18 (s, 1H), 9.21 (s, 1H); HPLC纯度: 97.84%; LCMS: 536 (M^+ +23)。

[2108] N-(4-(4-(3-氯-4-氟苄基)哌嗪-1-羰基)-2-甲基苯基)喹啉-8-磺酰胺 (XIV-12) :

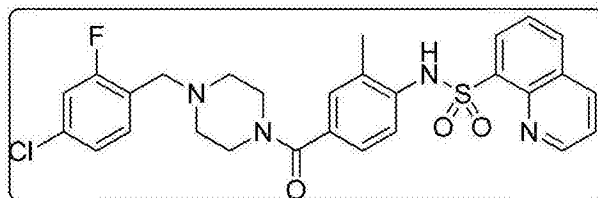
[2109]



[2110] ^1H NMR (400MHz, DMSO- d_6) δ : 2.01 (s, 3H), 2.25 (br s, 4H), 3.43 (s, 4H), 3.46 (s, 2H), 6.97 (s, 2H), 7.06 (s, 1H), 7.21–7.35 (m, 2H), 7.42 (d, 1H), 7.62–7.77 (m, 2H), 8.21–8.30 (m, 2H), 8.53 (d, 1H), 9.18 (s, 1H), 9.21 (s, 1H); HPLC纯度: 94.61%; LCMS: 553 (M^+)。

[2111] N-(4-(4-(4-氯-2-氟苄基)哌嗪-1-羰基)-2-甲基苯基)喹啉-8-磺酰胺 (XIV-13) :

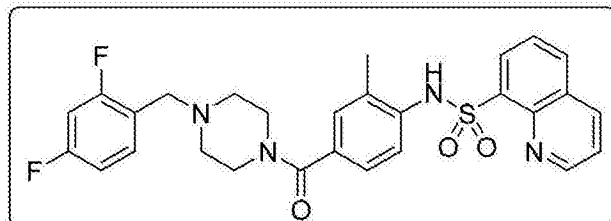
[2112]



[2113] ^1H NMR (400MHz, DMSO- d_6) δ : 2.01 (s, 3H), 2.25 (br s, 4H), 3.20 (br s, 2H), 3.45 (s, 4H), 6.97 (s, 2H), 7.06 (s, 1H), 7.21 (d, 1H), 7.31–7.39 (m, 2H), 7.62–7.77 (m, 2H), 8.21–8.30 (m, 2H), 8.57 (d, 1H), 9.18 (s, 1H), 9.21 (s, 1H); HPLC纯度: 96.23%; LCMS: 553 (M^+).

[2114] N-(4-(4-(2,4-二氟苄基)哌嗪-1-羰基)-2-甲基苯基)喹啉-8-磺酰胺 (XIV-14):

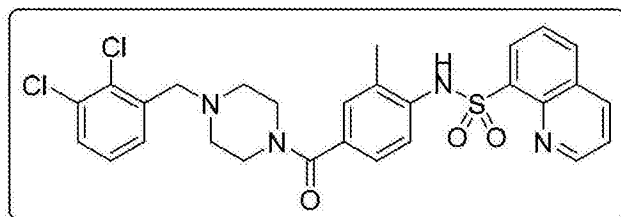
[2115]



[2116] ^1H NMR (400MHz, DMSO- d_6) δ : 2.01 (s, 3H), 2.25 (br s, 4H), 3.20 (br s, 2H), 3.45 (s, 4H), 6.97–7.06 (m, 4H), 7.20 (t, 1H), 7.31–7.39 (m, 1H), 7.62–7.77 (m, 2H), 8.21–8.30 (m, 2H), 8.57 (d, 1H), 9.18 (s, 1H), 9.21 (s, 1H); HPLC纯度: 99.12%; LCMS: 537 ($M^+ + 1$).

[2117] N-(4-(4-(2,3-二氯苄基)哌嗪-1-羰基)-2-甲基苯基)喹啉-8-磺酰胺 (XIV-15):

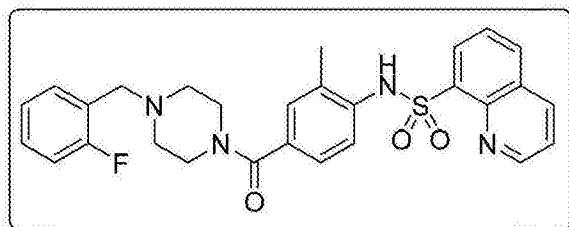
[2118]



[2119] ^1H NMR (400MHz, DMSO- d_6) δ : 2.01 (s, 3H), 2.25 (br s, 4H), 3.37 (s, 4H), 3.45 (s, 2H), 6.97 (s, 2H), 7.06 (s, 1H), 7.25 (t, 1H), 7.42 (d, 1H), 7.50 (d, 1H), 7.62–7.77 (m, 2H), 8.21–8.30 (m, 2H), 8.57 (d, 1H), 9.18 (s, 1H), 9.21 (s, 1H); HPLC纯度: 98.43%; LCMS: 569 (M^+).

[2120] N-(4-(4-(2-氟苄基)哌嗪-1-羰基)-2-甲基苯基)喹啉-8-磺酰胺 (XIV-16):

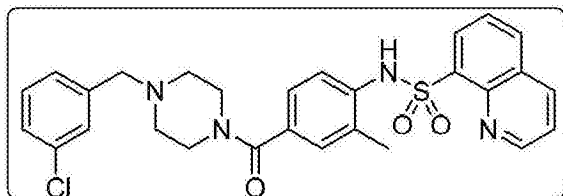
[2121]



[2122] ^1H NMR (400MHz, DMSO- d_6) δ : 2.01 (s, 3H), 2.30 (br s, 4H), 3.25 (s, 4H), 3.47 (s, 2H), 6.97 (s, 2H), 7.06 (s, 1H), 7.10–7.20 (m, 2H), 7.24–7.38 (m, 2H), 7.62–7.77 (m, 2H), 8.21–8.30 (m, 2H), 8.57 (d, 1H), 9.18 (s, 1H), 9.21 (s, 1H); HPLC纯度: 98.71%; LCMS: 519 ($M^+ + 1$).

[2123] N-(4-(4-(3-氯苄基)哌嗪-1-羰基)-2-甲基苯基)喹啉-8-磺酰胺 (XIV-17):

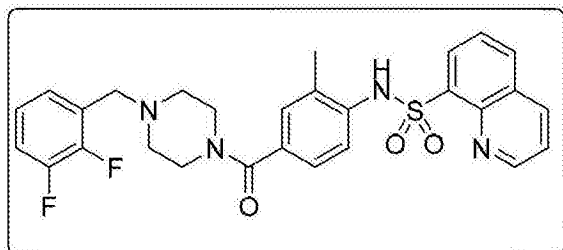
[2124]



[2125] ^1H NMR (400MHz, DMSO- d_6) δ 2.01 (s, 3H), 2.37 (br s, 4H), 3.37 (br s, 4H), 3.44 (s, 2H), 6.97 (s, 2H), 7.06 (s, 1H), 7.20–7.29 (m, 4H), 7.62–7.77 (m, 2H), 8.21–8.30 (m, 2H), 8.56 (d, 1H), 9.18 (s, 1H), 9.34 (s, 1H); HPLC纯度: 99.25%; LCMS: 535 (M^+).

[2126] N-(4-(4-(2,3-二氟苄基)哌嗪-1-羰基)-2-甲基苯基)喹啉-8-磺酰胺 (XIV-18):

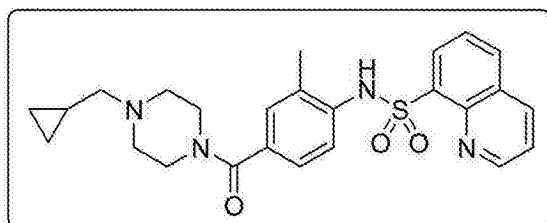
[2127]



[2128] ^1H NMR (400MHz, DMSO- d_6) δ 2.01 (s, 3H), 2.25 (br s, 4H), 3.46 (br s, 4H), 3.59 (s, 2H), 6.97 (s, 2H), 7.06 (s, 1H), 7.25–7.36 (m, 2H), 7.63–7.77 (m, 2H), 8.21–8.30 (m, 2H), 8.57 (d, 1H), 9.18 (s, 1H), 9.21 (s, 1H); HPLC纯度: 96.79%; LCMS: 537 (M^+).

[2129] N-(4-(4-(环丙基甲基)哌嗪-1-羰基)-2-甲基苯基)喹啉-8-磺酰胺 (XIV-19):

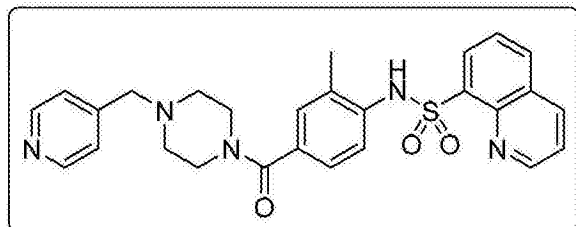
[2130]



[2131] ^1H NMR (400MHz, DMSO- d_6) δ : 0.03–0.05 (m, 2H), 0.30–0.31 (m, 2H), 0.45–0.47 (m, 1H), 2.01 (s, 3H), 2.17 (d, 2H), 2.25 (br s, 4H), 3.22 (br s, 4H), 3.59 (s, 2H), 6.97 (s, 2H), 7.06 (s, 1H), 7.63–7.77 (m, 2H), 8.21–8.30 (m, 2H), 8.57 (d, 1H), 9.18 (s, 1H), 9.21 (s, 1H); HPLC纯度: 98.31%; LCMS: 465 (M^+).

[2132] N-(2-甲基-4-(4-(吡啶-4-基甲基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (XIV-20):

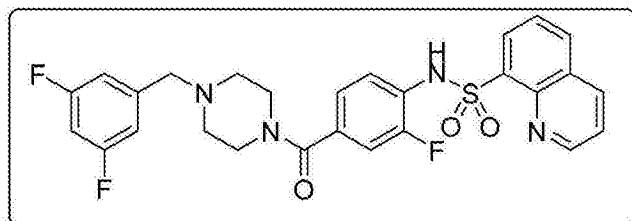
[2133]



[2134] ^1H NMR (400MHz, DMSO- d_6) δ : 2.01 (s, 3H), 2.25 (br s, 4H), 3.46 (br s, 4H), 3.50 (s, 2H), 6.97 (s, 2H), 7.06 (s, 1H), 7.31 (m, 2H), 7.63–7.77 (m, 3H), 8.21–8.30 (m, 2H), 8.54 (d, 1H), 8.58 (d, 1H), 9.18 (s, 1H), 9.21 (br s, 1H); HPLC纯度: 94.88%; LCMS: 502 (M^+).

[2135] N-(4-(4-(3,5-二氟苄基)哌嗪-1-羰基)-2-氟苯基)喹啉-8-磺酰胺 (XIV-21):

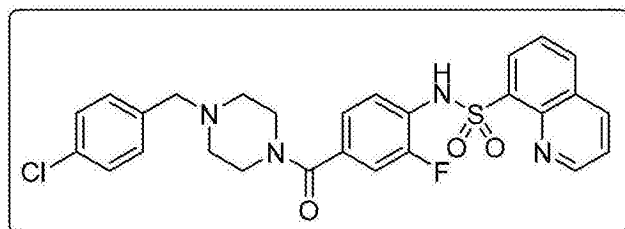
[2136]



[2137] ^1H NMR (400MHz, DMSO- d_6) δ : 2.38 (br s, 4H), 3.52 (br s, 4H), 3.58 (s, 2H), 7.01–7.18 (m, 4H), 7.38 (t, 1H), 7.71–7.82 (m, 3H), 8.32 (t, 2H), 8.60 (d, 1H), 9.12 (s, 1H), 9.98 (s, 1H); HPLC纯度: 98.93%; LCMS: 541 (M^+).

[2138] N-(4-(4-(4-氯苄基)哌嗪-1-羰基)-2-氟苄基)喹啉-8-磺酰胺 (XIV-22):

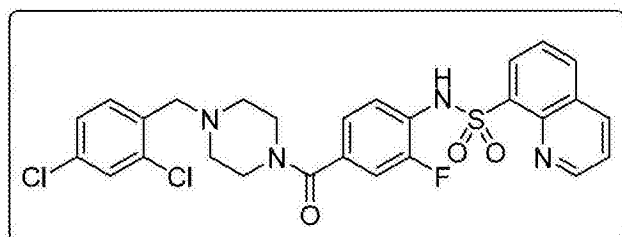
[2139]



[2140] ^1H NMR (400MHz, DMSO- d_6) δ : 2.38 (br s, 4H), 3.28 (br s, 4H), 3.55 (br s, 2H), 7.08 (t, 2H), 7.35–7.40 (m, 4H), 7.71–7.80 (m, 3H), 8.32 (t, 2H), 8.60 (d, 1H), 9.18 (s, 1H), 9.98 (s, 1H); HPLC纯度: 98.58%; LCMS: 539 (M^+).

[2141] N-(4-(4-(2,4-二氯苄基)哌嗪-1-羰基)-2-氟苄基)喹啉-8-磺酰胺 (XIV-23):

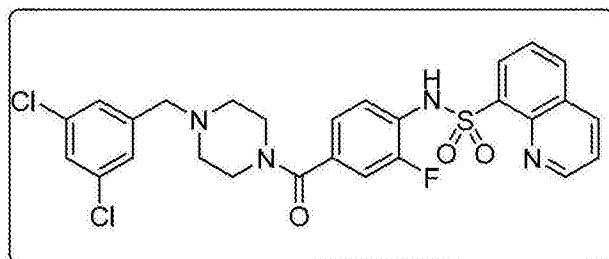
[2142]



[2143] ^1H NMR (400MHz, DMSO- d_6) δ : 2.38 (br s, 3H), 3.46 (br s, 4H), 3.58 (s, 2H), 7.08 (t, 2H), 7.35 (t, 1H), 7.40 (d, 1H), 7.50 (d, 1H), 7.60 (s, 1H), 7.71–7.79 (m, 2H), 8.32 (t, 2H), 8.60 (d, 1H), 9.18 (s, 1H), 9.98 (s, 1H); HPLC纯度: 98.58%; LCMS: 573 (M^+).

[2144] N-(4-(4-(3,5-二氯苄基)哌嗪-1-羰基)-2-氟苄基)喹啉-8-磺酰胺 (XIV-24):

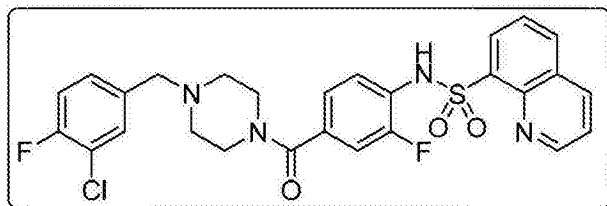
[2145]



[2146] ^1H NMR (400MHz, DMSO- d_6) δ : 2.38 (br s, 4H), 3.28 (br s, 4H), 3.55 (br s, 2H), 7.10 (t, 2H), 7.30–7.38 (m, 3H), 7.50 (s, 1H), 7.71–7.80 (m, 2H), 8.32 (t, 2H), 8.58 (d, 1H), 9.18 (s, 1H), 9.98 (s, 1H); HPLC纯度: 97.63%; LCMS: 573 (M^+).

[2147] N-(4-(4-(3-氯-4-氟苄基)哌嗪-1-羰基)-2-氟苄基)喹啉-8-磺酰胺 (XIV-25):

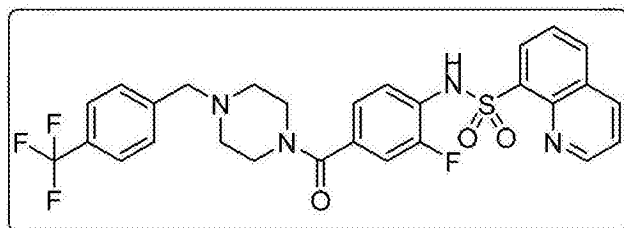
[2148]



[2149] ^1H NMR (400MHz, DMSO- d_6) δ : 2.38 (br s, 3H), 3.28 (br s, 4H), 3.55 (s, 2H), 7.10 (t, 2H), 7.29–7.40 (m, 3H), 7.50 (d, 1H), 7.71–7.80 (m, 2H), 8.30 (t, 2H), 8.60 (d, 1H), 9.18 (s, 1H), 9.98 (s, 1H); HPLC纯度: 96.66%; LCMS: 557 (M^+).

[2150] N-(2-氟-4-(4-(4-(三氟甲基)苄基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (XIV-26):

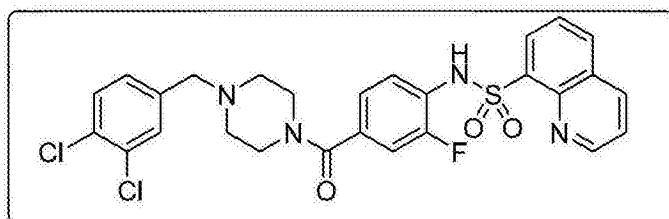
[2151]



[2152] ^1H NMR (400MHz, DMSO- d_6) δ : 2.38 (br s, 4H), 3.46 (br s, 4H), 3.60 (s, 2H), 7.10 (t, 2H), 7.35 (t, 1H), 7.59 (d, 2H), 7.63–7.78 (m, 4H), 8.32 (t, 2H), 8.60 (d, 1H), 9.18 (s, 1H), 9.98 (s, 1H); HPLC纯度: 99.96%; LCMS: 573 (M^+).

[2153] N-(4-(4-(3,4-二氯苄基)哌嗪-1-羰基)-2-氟苄基)喹啉-8-磺酰胺 (XIV-27):

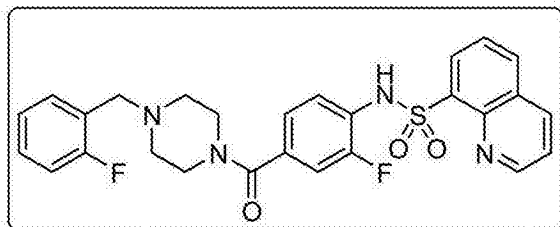
[2154]



[2155] ^1H NMR (400MHz, DMSO- d_6) δ : 2.38 (br s, 3H), 3.28 (br s, 4H), 3.55 (s, 2H), 7.10 (t, 2H), 7.28–7.40 (m, 2H), 7.58 (t, 2H), 7.70–7.79 (m, 2H), 8.32 (t, 2H), 8.60 (d, 1H), 9.18 (s, 1H), 9.98 (s, 1H); HPLC纯度: 98.23%; LCMS: 573 (M^+).

[2156] N-(2-氟-4-(4-(2-氟苄基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (XIV-28):

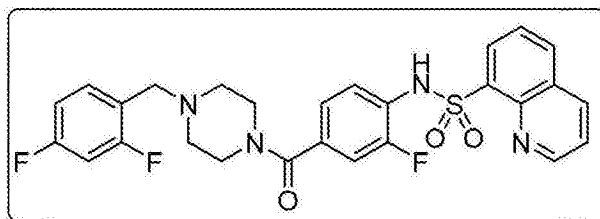
[2157]



[2158] ^1H NMR (400MHz, DMSO- d_6) δ : 2.38 (br s, 4H), 3.48 (br s, 4H), 3.58 (s, 2H), 7.05–7.20 (m, 3H), 7.28–7.40 (m, 2H), 7.70–7.79 (m, 2H), 8.32 (t, 2H), 8.60 (d, 1H), 9.18 (s, 1H), 9.98 (s, 1H); HPLC纯度: 96.54%; LCMS: 523 (M^+).

[2159] N-(4-(4-(2,4-二氟苄基)哌嗪-1-羰基)-2-氟苄基)喹啉-8-磺酰胺 (XIV-29):

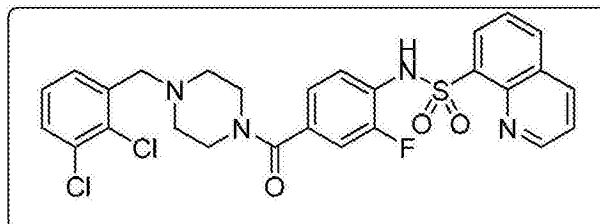
[2160]



[2161] ^1H NMR (400MHz, DMSO- d_6) δ : 2.38 (br s, 4H), 3.22 (br s, 4H), 3.58 (s, 2H), 7.03–7.20 (m, 3H), 7.20 (t, 1H), 7.38 (t, 1H), 7.44 (q, 1H), 7.70–7.79 (m, 2H), 8.32 (t, 2H), 8.60 (d, 1H), 9.18 (s, 1H), 9.98 (s, 1H); HPLC纯度: 99.52%; LCMS: 541 (M^+ + 1)。

[2162] N-(4-(4-(2,3-二氯苄基)哌嗪-1-羰基)-2-氟苯基)喹啉-8-磺酰胺 (XIV-30) :

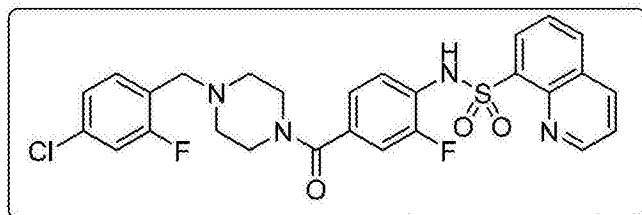
[2163]



[2164] ^1H NMR (400MHz, DMSO- d_6) δ : 2.38 (br s, 4H), 3.22 (br s, 4H), 3.58 (s, 2H), 7.12 (m, 3H), 7.31–7.40 (m, 1H), 7.44 (d, 1H), 7.60 (d, 1H), 7.70–7.79 (m, 2H), 8.32 (t, 2H), 8.60 (d, 1H), 9.12 (s, 1H), 9.98 (s, 1H); HPLC纯度: 97.43%; LCMS: 573 (M^+)。

[2165] N-(4-(4-(4-氯-2-氟苄基)哌嗪-1-羰基)-2-氟苯基)喹啉-8-磺酰胺 (XIV-31) :

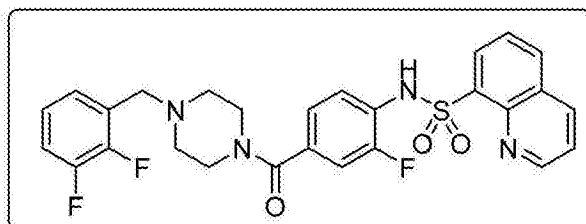
[2166]



[2167] ^1H NMR (400MHz, DMSO- d_6) δ : 2.38 (br s, 3H), 3.22 (br s, 4H), 3.58 (s, 2H), 7.10 (t, 2H), 7.23–7.46 (m, 4H), 7.70–7.79 (m, 2H), 8.32 (t, 2H), 8.60 (d, 1H), 9.18 (s, 1H), 9.98 (s, 1H); HPLC纯度: 99.89%; LCMS: 557 (M^+)。

[2168] N-(4-(4-(2,3-二氟苄基)哌嗪-1-羰基)-2-氟苯基)喹啉-8-磺酰胺 (XIV-32) :

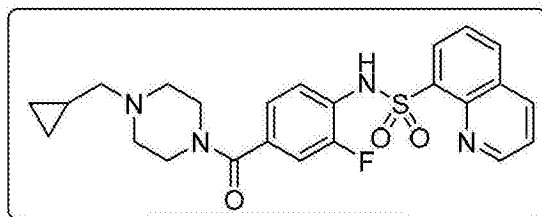
[2169]



[2170] ^1H NMR (400MHz, DMSO- d_6) δ : 2.38 (br s, 3H), 3.26 (br s, 4H), 3.58 (s, 2H), 7.03–7.25 (m, 4H), 7.38 (t, 2H), 7.70–7.79 (m, 2H), 8.32 (t, 2H), 8.60 (d, 1H), 9.12 (s, 1H), 9.98 (s, 1H); HPLC纯度: 99.04%; LCMS: 541 (M^+ + 1)。

[2171] N-(4-(4-(环丙基甲基)哌嗪-1-羰基)-2-氟苯基)喹啉-8-磺酰胺 (XIV-33) :

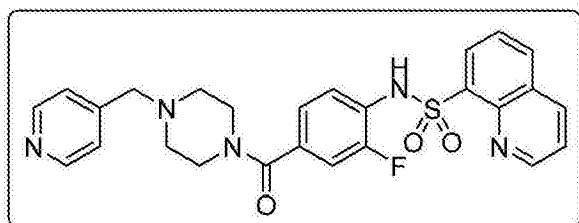
[2172]



[2173] ^1H NMR (400MHz, DMSO- d_6) δ : 0.03–0.035 (m, 2H), 0.64–0.66 (m, 2H), 0.81–0.83 (m, 1H), 2.20 (s, 2H), 2.38 (br s, 4H), 3.52 (br s, 4H), 7.10 (m, 2H), 7.38 (t, 1H), 7.70–7.79 (m, 2H), 8.32 (t, 2H), 8.60 (d, 1H), 9.12 (s, 1H), 9.98 (s, 1H); HPLC纯度: 97.67%; LCMS: 469 (M^+ + 1)。

[2174] N-(2-氟-4-(4-(吡啶-4-基甲基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (XIV-34) :

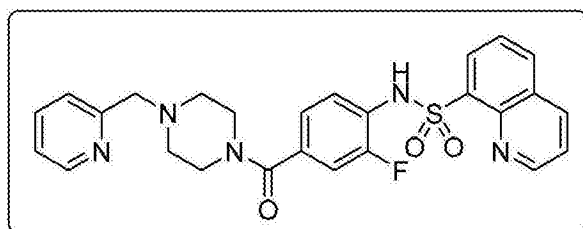
[2175]



[2176] ^1H NMR (400MHz, DMSO- d_6) δ : 2.38 (br s, 4H), 3.48 (br s, 4H), 3.59 (s, 2H), 7.12 (t, 2H), 7.38 (s, 3H), 7.70–7.79 (m, 2H), 8.32 (t, 2H), 8.57 (d, 2H), 8.60 (d, 1H), 9.10 (s, 1H), 9.98 (s, 1H); HPLC纯度: 97.70%; LCMS: 506 (M^+ + 1)。

[2177] N-(2-氟-4-(4-(吡啶-2-基甲基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (XIV-35) :

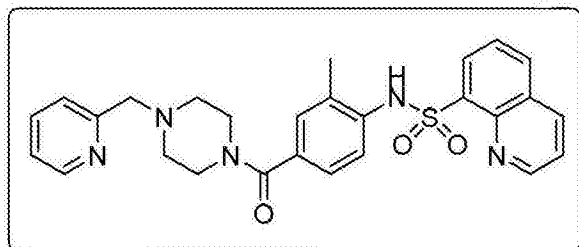
[2178]



[2179] ^1H NMR (400MHz, DMSO- d_6) δ : 2.38 (br s, 4H), 3.22 (br s, 4H), 3.62 (s, 2H), 7.13 (t, 2H), 7.22–7.38 (m, 2H), 7.42 (d, 1H), 7.70–7.79 (m, 3H), 8.32 (t, 2H), 8.50 (s, 1H), 8.60 (d, 1H), 9.18 (s, 1H), 9.98 (s, 1H); HPLC纯度: 99.74%; LCMS: 506 (M^+ + 1)。

[2180] N-(2-甲基-4-(4-(吡啶-2-基甲基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (XIV-36) :

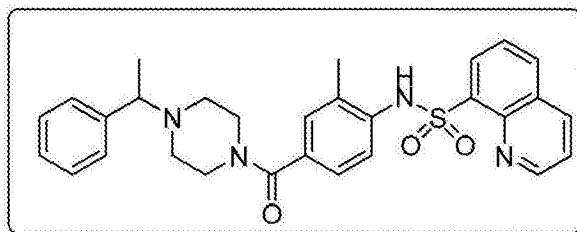
[2181]



[2182] ^1H NMR (400MHz, DMSO- d_6) δ : 2.01 (s, 3H), 2.38 (br s, 4H), 3.52 (br s, 4H), 3.60 (s, 2H), 6.97 (s, 2H), 7.03 (s, 1H), 7.23 (t, 1H), 7.40 (d, 1H), 7.64–7.78 (m, 4H), 8.25 (dd, 2H), 8.46 (d, 1H), 8.58 (d, 1H), 9.08 (s, 1H); HPLC纯度: 98.36%; LCMS: 502 (M^+ + 1)。

[2183] N-(2-甲基-4-(4-(1-苯基乙基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (XIV-37) :

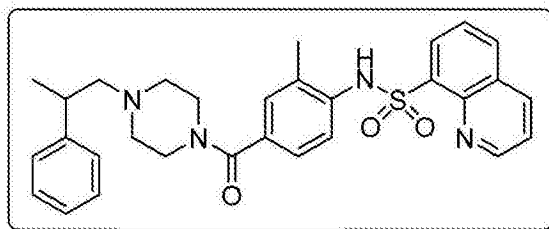
[2184]



[2185] ^1H NMR (400MHz, DMSO- d_6) δ : 1.21 (d, 3H), 2.01 (s, 3H), 2.18–2.40 (m, 4H), 3.42 (br s, 4H), 3.46 (q, 1H), 6.90 (s, 2H), 7.01 (s, 1H), 7.18–7.34 (m, 5H), 7.64–7.78 (m, 2H), 8.25 (dd, 2H), 8.38 (d, 1H), 9.18 (s, 1H), 9.31 (s, 1H); HPLC纯度: 99.85%; LCMS: 515 (M^+ +1)。

[2186] N-(2-甲基-4-(4-(2-苯基丙基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (XIV-38):

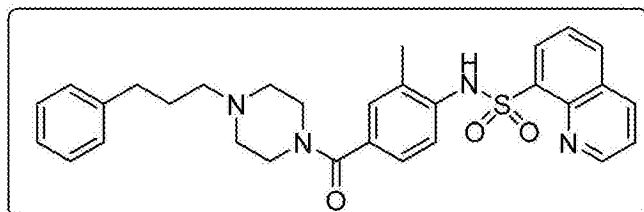
[2187]



[2188] ^1H NMR (400MHz, DMSO- d_6) δ : 1.15 (d, 3H), 2.01 (s, 3H), 2.20–2.38 (m, 6H), 3.48 (br s, 4H), 3.85 (q, 1H), 6.97 (s, 2H), 7.01 (s, 1H), 7.05–7.30 (m, 5H), 7.62–7.76 (m, 2H), 8.25 (dd, 2H), 8.58 (d, 1H), 9.18 (s, 1H), 9.31 (br s, 1H); HPLC纯度: 95.95%; LCMS: 529 (M^+ +1)。

[2189] N-(2-甲基-4-(4-(3-苯基丙基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (XIV-39):

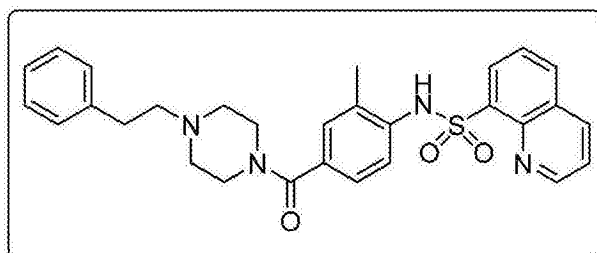
[2190]



[2191] ^1H NMR (400MHz, DMSO- d_6) δ : 1.62 (m, 2H), 2.01 (s, 3H), 2.18–2.40 (m, 6H), 2.56 (br s, 2H), 3.43–3.56 (m, 4H), 6.97 (s, 2H), 7.01 (s, 1H), 7.13–7.28 (m, 5H), 7.64–7.78 (m, 2H), 8.25 (dd, 2H), 8.56 (d, 1H), 9.10 (s, 1H), 9.31 (s, 1H); HPLC纯度: 98.98%; LCMS: 529 (M^+ +1)。

[2192] N-(2-甲基-4-(4-苯乙基哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (XIV-40):

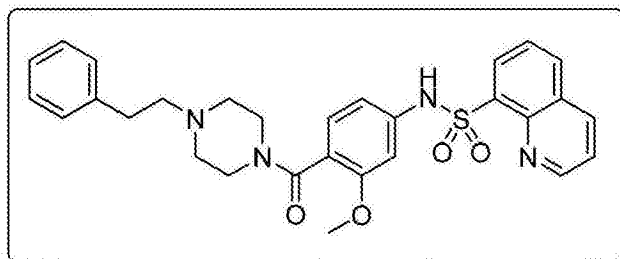
[2193]



[2194] ^1H NMR (400MHz, CDCl_3) δ : 2.01 (s, 3H), 2.38 (br s, 4H), 2.58 (t, 2H), 2.65 (t, 2H), 3.50 (br s, 4H), 6.97 (s, 2H), 7.01 (s, 1H), 7.15–7.28 (m, 5H), 7.62–7.78 (m, 2H), 8.25 (dd, 2H), 8.38 (d, 1H), 9.18 (s, 1H), 9.31 (br s, 1H); LCMS: 515 (M^+ +1); HPLC纯度: 97.07%。

[2195] N-(3-甲氧基-4-(4-苯乙基哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (XIV-41):

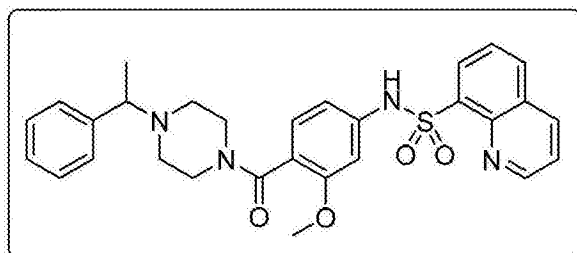
[2196]



[2197] ^1H NMR (400MHz, DMSO- d_6) δ : 2.21–2.58 (m, 6H), 2.73–2.79 (m, 2H), 3.18 (d, 2H), 3.66 (s, 3H), 6.38 (d, 1H), 6.87 (d, 2H), 7.19–7.30 (m, 4H), 7.59–7.62 (m, 2H), 8.02 (d, 1H), 8.25 (d, 2H), 8.35 (d, 1H), 8.42 (s, 2H), 9.18 (d, 1H); HPLC纯度: 99.42%; LCMS: 531 (M^+ +1)。

[2198] N-(3-甲氧基-4-(4-(1-苯基乙基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (XIV-42):

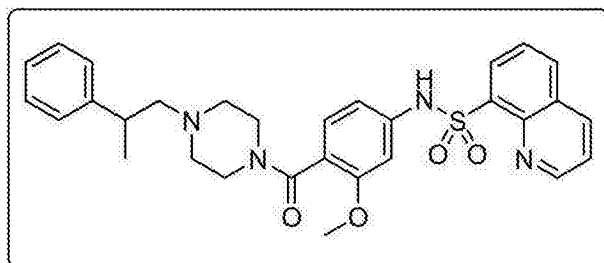
[2199]



[2200] ^1H NMR (400MHz, CDCl_3) δ : 1.34 (d, 3H), 2.15–2.40 (m, 4H), 3.20 (br s, 4H), 3.35 (q, 1H), 3.62 (s, 3H), 6.35 (d, 1H), 6.82 (d, 2H), 7.18–7.28 (m, 3H), 7.58–7.62 (m, 2H), 8.02 (d, 1H), 8.28 (d, 1H), 8.35 (d, 1H), 8.41 (s, 1H), 9.18 (d, 1H); HPLC纯度: 97.00%; LCMS: 531 (M^+ +1)。

[2201] N-(3-甲氧基-4-(4-(2-苯基丙基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (XIV-43):

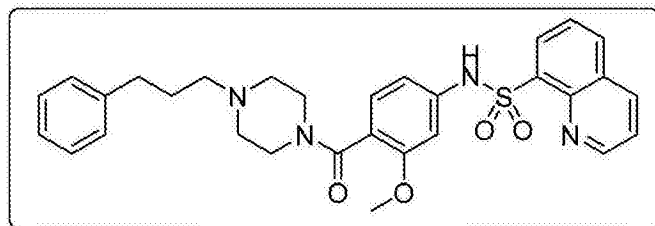
[2202]



[2203] ^1H NMR (400MHz, CDCl_3) δ : 1.21 (d, 3H), 2.12–2.45 (m, 6H), 2.84–2.93 (m, 1H), 3.10 (br s, 4H), 3.62 (s, 3H), 6.37 (d, 1H), 6.82 (d, 2H), 7.18 (d, 2H), 7.28 (d, 2H), 7.58–7.62 (m, 2H), 8.02 (d, 1H), 8.28 (d, 1H), 8.35 (d, 1H), 8.41 (s, 1H), 9.18 (d, 1H); HPLC纯度: 99.00%; LCMS: 545 (M^+ +1)。

[2204] N-(3-甲氧基-4-(4-(3-苯基丙基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (XIV-44):

[2205]

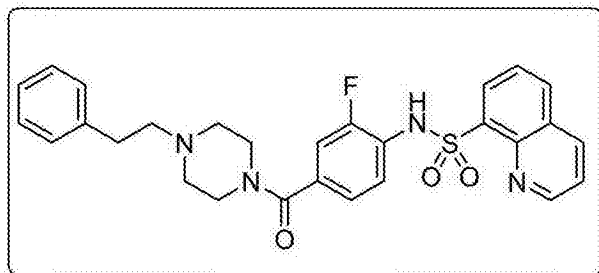


[2206] ^1H NMR (400MHz, CDCl_3) δ : 1.78 (五重峰, 2H), 2.20 (br s, 2H), 2.35 (t, 4H), 2.60 (t, 2H), 3.15 (m, 4H), 3.62 (s, 3H), 6.35 (d, 1H), 6.84 (d, 2H), 7.10–7.28 (m, 4H), 7.58–7.62 (m,

2H), 8.02 (d, 1H), 8.28 (d, 1H), 8.35 (d, 1H), 8.41 (s, 1H), 9.18 (d, 1H); HPLC纯度: 99.00%; LCMS: 545 ($M^+ + 1$)。

[2207] N-(2-氟-4-(4-苄基哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (XIV-45):

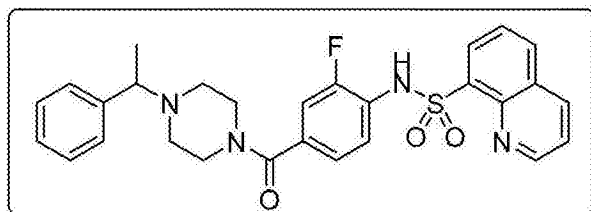
[2208]



[2209] ^1H NMR (400MHz, CDCl_3) δ : 2.44 (m, 4H), 2.59 (br s, 2H), 2.76 (d, 2H), 3.40 (br s, 2H), 3.62 (br s, 2H), 6.90 (d, 1H), 7.01 (d, 1H), 7.12–7.30 (m, 4H), 7.58–7.62 (m, 2H), 7.70 (t, 1H), 8.02 (d, 1H), 8.28 (d, 1H), 8.37 (d, 1H), 8.81 (br s, 1H), 9.18 (d, 1H); HPLC纯度: 96.00%; LCMS: 519 ($M^+ + 1$)。

[2210] N-(2-氟-4-(4-(1-苄基乙基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (XIV-46):

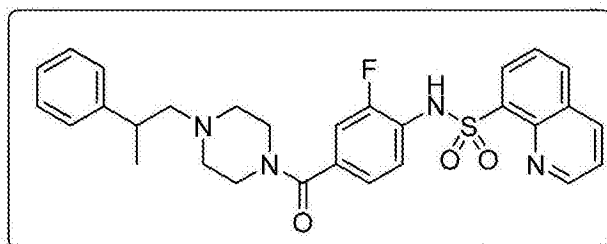
[2211]



[2212] ^1H NMR (400MHz, CDCl_3) δ : 1.31 (d, 3H), 2.38 (br s, 4H), 3.36 (q, 3H), 3.58 (br s, 2H), 6.82 (d, 1H), 7.00 (d, 1H), 7.18–7.30 (d, 5H), 7.58–7.62 (m, 2H), 7.70 (t, 1H), 8.02 (d, 1H), 8.28 (d, 1H), 8.35 (d, 1H), 8.41 (s, 1H), 8.80 (br s, 1H), 9.18 (d, 1H); HPLC纯度: 99.00%; LCMS: 519 (M^+)。

[2213] N-(2-氟-4-(4-(2-苄基丙基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (XIV-47):

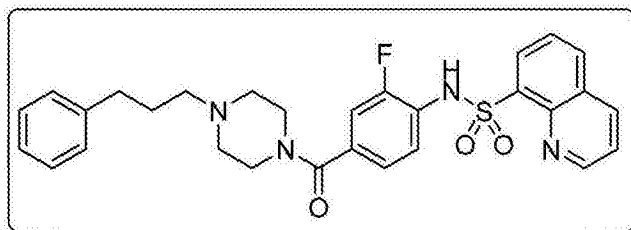
[2214]



[2215] ^1H NMR (400MHz, CDCl_3) δ : 1.21 (d, 3H), 2.20–2.55 (m, 6H), 2.84 (m, 1H), 3.35 (br s, 2H), 3.58 (br s, 2H), 6.82 (d, 1H), 7.01 (d, 1H), 7.12–7.28 (m, 4H), 7.58–7.62 (m, 3H), 7.70 (t, 1H), 8.02 (d, 1H), 8.28 (d, 1H), 8.35 (d, 1H), 8.80 (br s, 1H), 9.18 (d, 1H); HPLC纯度: 97.00%; LCMS: 533 ($M^+ + 1$)。

[2216] N-(2-氟-4-(4-(3-苄基丙基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (XIV-48):

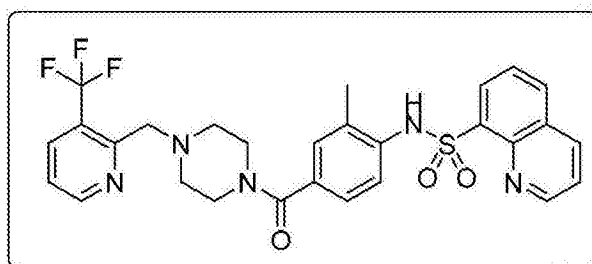
[2217]



[2218] ^1H NMR (400MHz, CDCl_3) δ : 1.77 (五重峰, 2H), 2.20–2.42 (m, 6H), 2.62 (t, 2H), 3.40 (br s, 2H), 3.60 (br s, 2H), 6.90 (d, 1H), 7.01 (d, 1H), 7.12–7.30 (m, 4H), 7.58–7.62 (m, 2H), 7.70 (t, 1H), 8.02 (d, 1H), 8.28 (d, 1H), 8.37 (d, 1H), 8.81 (br s, 1H), 9.18 (d, 1H); HPLC 纯度: 98.00%; LCMS: 533 (M^+ +1)。

[2219] N-(2-甲基-4-(4-(3-(三氟甲基)吡啶-2-基)甲基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (XIV-49):

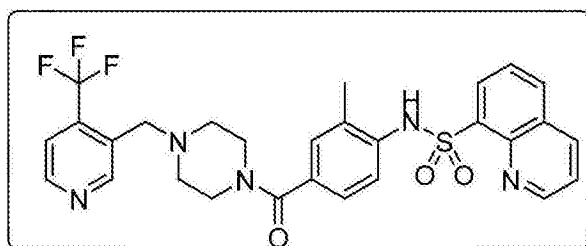
[2220]



[2221] ^1H NMR (400MHz, $\text{DMSO}-d_6$) δ : 2.01 (s, 3H), 2.37 (br s, 4H), 3.14 (br s, 2H), 3.46 (s, 2H), 6.97 (s, 2H), 7.06 (s, 1H), 7.51 (t, 1H), 7.62–7.77 (m, 2H), 8.17 (d, 1H), 8.25 (dd, 2H), 8.58 (d, 1H), 8.78 (s, 1H), 9.18 (s, 1H), 9.39 (s, 1H); HPLC 纯度: 97.97%; LCMS: 592 (M^+ +23)。

[2222] N-(2-甲基-4-(4-(4-(三氟甲基)吡啶-3-基)甲基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (XIV-50):

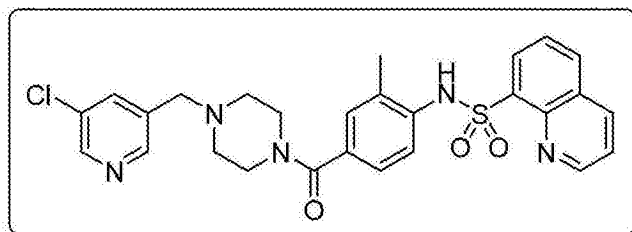
[2223]



[2224] ^1H NMR (400MHz, $\text{DMSO}-d_6$) δ : 2.01 (s, 3H), 2.37 (br s, 4H), 3.46 (br s, 4H), 3.64 (s, 2H), 6.97 (s, 2H), 7.06 (s, 1H), 7.62–7.77 (m, 3H), 8.20–8.30 (m, 2H), 8.56 (d, 1H), 8.78 (s, 1H), 8.90 (s, 1H), 9.18 (s, 1H), 9.39 (br s, 1H); HPLC 纯度: 98.71%; LCMS: 570 (M^+ +1)。

[2225] N-(4-(4-(5-氯吡啶-3-基)甲基)哌嗪-1-羰基)-2-甲基苯基)喹啉-8-磺酰胺 (XIV-51):

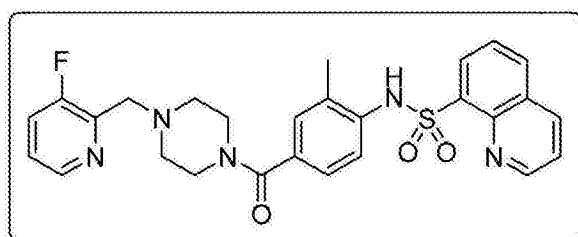
[2226]



[2227] ^1H NMR (400MHz, DMSO- d_6) δ : 2.01 (s, 3H), 2.37 (br s, 4H), 3.26 (br s, 4H), 3.51 (s, 2H), 6.98 (s, 2H), 7.06 (s, 1H), 7.62-7.77 (m, 2H), 7.81 (s, 1H), 8.25 (dd, 2H), 8.41 (s, 1H), 8.50 (s, 1H), 8.58 (d, 1H), 9.11 (s, 1H), 9.39 (s, 1H); HPLC纯度: 99.11%; LCMS: 536 (M^+).

[2228] N-(4-(4-((3-氟吡啶-2-基)甲基)哌嗪-1-羰基)-2-甲基苯基)喹啉-8-磺酰胺 (XIV-52):

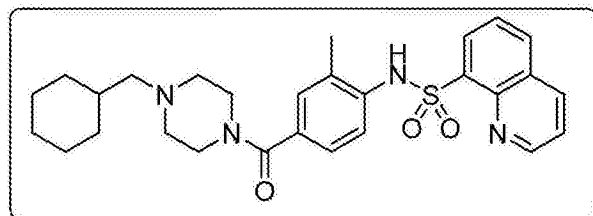
[2229]



[2230] ^1H NMR (400MHz, DMSO- d_6) δ : 2.01 (s, 3H), 2.37 (br s, 4H), 3.21 (br s, 2H), 3.46 (br s, 2H), 3.64 (s, 2H), 6.97 (s, 2H), 7.06 (s, 1H), 7.37-7.41 (m, 1H), 7.62-7.77 (m, 3H), 8.22 (d, 1H), 8.27 (d, 1H), 8.36 (s, 1H), 8.58 (d, 1H), 9.10 (s, 1H), 9.38 (s, 1H); HPLC纯度: 99.15%; LCMS: 520 (M^+).

[2231] N-(4-(4-(环己基甲基)哌嗪-1-羰基)-2-甲基苯基)喹啉-8-磺酰胺 (XIV-53):

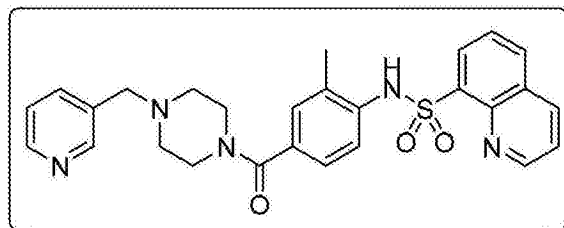
[2232]



[2233] ^1H NMR (400MHz, DMSO- d_6) δ : 0.72-0.90 (m, 2H), 1.05-1.21 (m, 4H), 1.41 (br s, 1H), 1.56-1.74 (m, 4H), 2.01 (s, 3H), 2.25 (br s, 5H), 3.20 (br s, 2H), 3.46 (br s, 2H), 6.97 (s, 2H), 7.06 (s, 1H), 7.62-7.77 (m, 2H), 8.25 (dd, 2H), 8.58 (d, 1H), 9.18 (s, 1H), 9.39 (br s, 1H); HPLC纯度: 94.98%; LCMS: 507 (M^+).

[2234] N-(2-甲基-4-(4-(吡啶-3-基甲基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (XIV-54):

[2235]

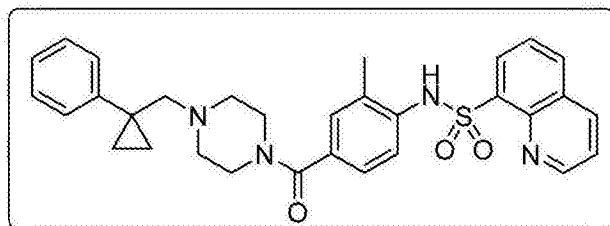


[2236] ^1H NMR (400MHz, DMSO- d_6) δ : 2.01 (s, 3H), 2.30 (br s, 4H), 3.41 (br s, 4H), 3.46 (s, 2H), 6.97 (s, 2H), 7.06 (s, 1H), 7.31 (t, 1H), 7.62-7.77 (m, 2H), 8.25 (dd, 2H), 8.42 (s,

2H), 8.58 (d, 1H), 9.18 (s, 1H), 9.39 (s, 1H); HPLC纯度: 96.73%; LCMS: 502 (M^+ +1)。

[2237] N-(2-甲基-4-(4-((1-苯基环丙基)甲基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (XIV-55):

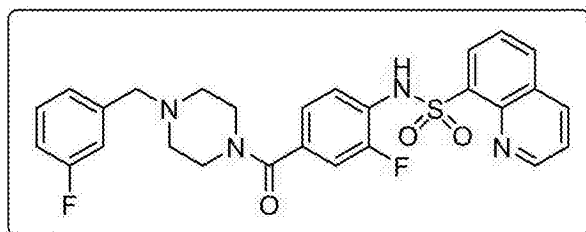
[2238]



[2239] ^1H NMR (400MHz, DMSO- d_6) δ : 0.65 (s, 2H), 0.78 (s, 2H), 2.01 (s, 3H), 2.36 (br s, 4H), 2.63 (br s, 2H), 3.41 (br s, 4H), 6.97 (s, 2H), 7.06 (s, 1H), 7.12 (t, 1H), 7.20-7.28 (m, 4H), 7.62-7.77 (m, 2H), 8.25 (dd, 2H), 8.58 (d, 1H), 9.18 (s, 1H), 9.39 (s, 1H); HPLC纯度: 96.19%; LCMS: 541 (M^+ +1)。

[2240] N-(2-氟-4-(4-(3-氟苄基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (XIV-56):

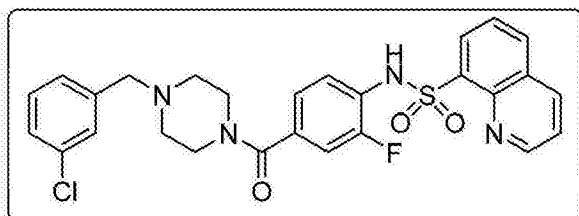
[2241]



[2242] ^1H NMR (400MHz, DMSO- d_6) δ : 2.45 (s, 4H), 3.56 (br s, 4H), 3.66 (s, 2H), 7.06-7.26 (m, 4H), 7.28-7.39 (m, 2H), 7.62-7.79 (m, 3H), 8.21-8.36 (m, 2H), 8.57 (d, 1H), 9.18 (s, 1H), 9.85 (s, 1H); HPLC纯度: 93.25%; LCMS: 522.57 (M^+)。

[2243] N-(4-(4-(3-氯苄基)哌嗪-1-羰基)-2-氟苯基)喹啉-8-磺酰胺 (XIV-57):

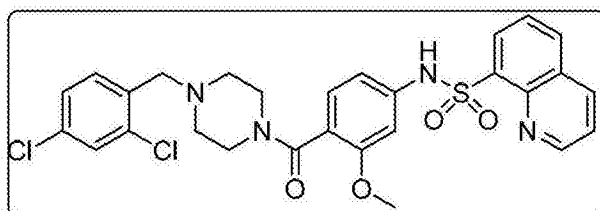
[2244]



[2245] ^1H NMR (400MHz, DMSO- d_6) δ : 2.25 (s, 4H), 3.41 (br s, 4H), 3.47 (s, 2H), 7.01-7.09 (m, 2H), 7.22-7.36 (m, 5H), 7.61-7.78 (m, 2H), 8.21-8.38 (m, 2H), 8.55-8.60 (m, 1H), 9.01 (s, 1H), 9.9 (s, 1H); HPLC纯度: 97.30%; LCMS: 539 (M^+)。

[2246] N-(4-(4-(2,4-二氯苄基)哌嗪-1-羰基)-3-甲氧基苯基)喹啉-8-磺酰胺 (XIV-58):

[2247]

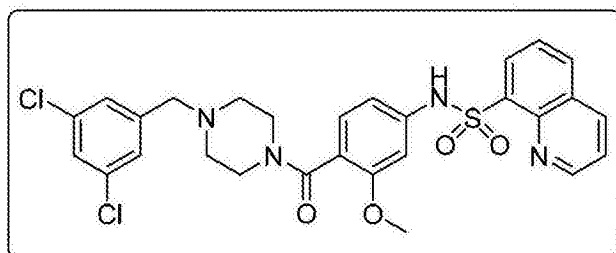


[2248] ^1H NMR (400MHz, DMSO- d_6) δ : 2.20-2.39 (m, 4H), 3.41 (br s, 4H), 3.46 (s, 2H), 3.56

(s, 3H), 6.61–6.81 (m, 3H), 7.36–7.60 (m, 3H), 7.62–7.67 (m, 2H), 8.25 (d, 1H), 8.41–8.58 (m, 2H), 9.18 (s, 1H), 10.25 (s, 1H); HPLC纯度: 98.16%; LCMS: 585.50 (M^+)。

[2249] N-(4-(4-(3,5-二氯苄基)哌嗪-1-羰基)-3-甲氧基苯基)喹啉-8-磺酰胺 (XIV-59):

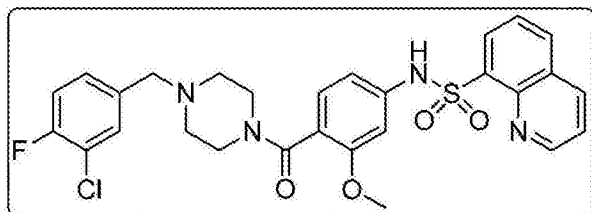
[2250]



[2251] ^1H NMR (400MHz, DMSO- d_6) δ : 2.20–2.39 (m, 4H), 3.26 (br s, 4H), 3.46 (s, 2H), 3.56 (s, 3H), 6.61–6.85 (m, 3H), 7.26 (s, 2H), 7.45 (s, 1H), 7.63–7.78 (m, 2H), 8.20–8.60 (m, 3H), 9.18 (s, 1H), 10.25 (s, 1H); HPLC纯度: 97.92%; LCMS: 584.1 (M^+)。

[2252] N-(4-(4-(3-氯-4-氟苄基)哌嗪-1-羰基)-3-甲氧基苯基)喹啉-8-磺酰胺 (XIV-60):

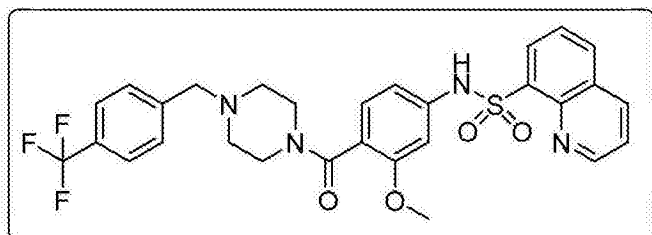
[2253]



[2254] ^1H NMR (400MHz, DMSO- d_6) δ : 2.20–2.39 (m, 4H), 3.26 (br s, 4H), 3.46 (s, 2H), 3.56 (s, 3H), 6.61–6.85 (m, 3H), 7.21–7.55 (m, 3H), 7.62–7.75 (m, 2H), 8.21–8.60 (m, 3H), 9.18 (s, 1H), 10.25 (s, 1H); HPLC纯度: 98.4%; LCMS: 569 (M^+)。

[2255] N-(3-甲氧基-4-(4-(4-(三氟甲基)苄基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (XIV-61):

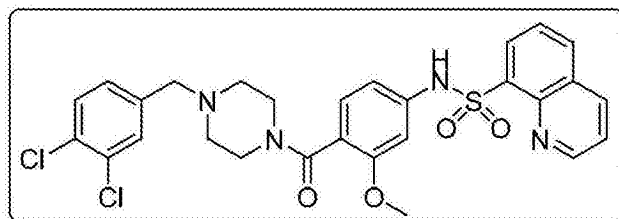
[2256]



[2257] ^1H NMR (400MHz, DMSO- d_6) δ : 2.20–2.39 (m, 4H), 2.97 (br s, 4H), 3.46 (s, 2H), 3.56 (s, 3H), 6.61–6.85 (m, 3H), 7.42–7.58 (m, 2H), 7.61–7.78 (m, 4H), 8.21–8.60 (m, 3H), 9.18 (s, 1H), 10.25 (s, 1H); HPLC纯度: 99.24%; LCMS: 584.6 (M^+)。

[2258] N-(4-(4-(3,4-二氯苄基)哌嗪-1-羰基)-3-甲氧基苯基)喹啉-8-磺酰胺 (XIV-62):

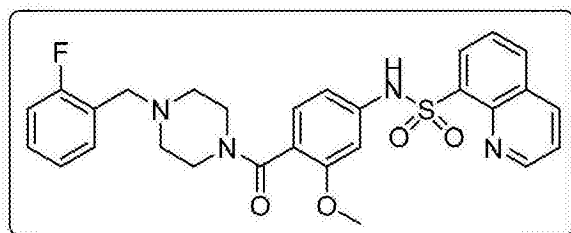
[2259]



[2260] ^1H NMR (400MHz, DMSO- d_6) δ : 2.08–2.39 (m, 4H), 2.97 (br s, 4H), 3.46 (s, 2H), 3.56 (s, 3H), 6.61–6.85 (m, 3H), 7.25 (d, 1H), 7.45–7.60 (m, 2H), 7.63–7.80 (m, 2H), 7.62–7.77 (m, 3H), 8.21–8.60 (m, 3H), 9.18 (s, 1H), 10.25 (s, 1H), HPLC纯度: 98.45%; LCMS: 585.50 (M^+).

[2261] N-(4-(4-(2-氟苄基)哌嗪-1-羰基)-3-甲氧基苯基)喹啉-8-磺酰胺 (XIV-63):

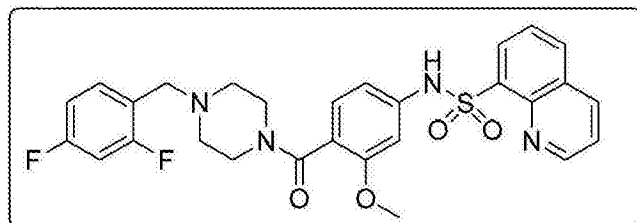
[2262]



[2263] ^1H NMR (400MHz, DMSO- d_6) δ : 2.08–2.39 (m, 4H), 2.97 (br s, 4H), 3.46 (s, 2H), 3.56 (s, 3H), 6.61–6.85 (m, 3H), 7.06–7.45 (m, 4H), 7.71 (s, 2H), 8.21–8.60 (m, 3H), 9.18 (s, 1H), 10.25 (s, 1H) HPLC纯度: 98.29%; LCMS: 534.8 (M^+).

[2264] N-(4-(4-(2,4-二氟苄基)哌嗪-1-羰基)-3-甲氧基苯基)喹啉-8-磺酰胺 (XIV-64):

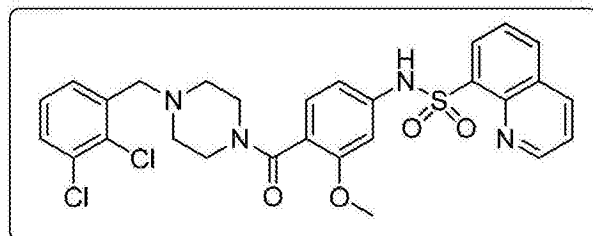
[2265]



[2266] ^1H NMR (400MHz, DMSO- d_6) δ : 2.08–2.39 (m, 4H), 2.97 (br s, 4H), 3.46 (s, 2H), 3.56 (s, 3H), 6.61–6.85 (m, 3H), 7.01–7.21 (m, 2H), 7.35–7.42 (m, 1H), 7.62–7.78 (m, 2H), 8.21–8.60 (m, 3H), 9.18 (s, 1H), 10.25 (s, 1H) HPLC纯度: 99.00%; LCMS: 552.59 (M^+).

[2267] N-(4-(4-(2,3-二氯苄基)哌嗪-1-羰基)-3-甲氧基苯基)喹啉-8-磺酰胺 (XIV-65):

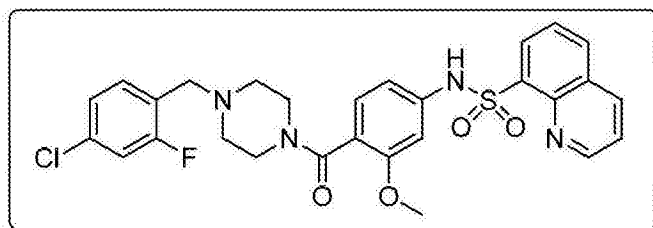
[2268]



[2269] ^1H NMR (400MHz, DMSO- d_6) δ : 2.08–2.39 (m, 4H), 3.21 (br s, 4H), 3.46 (s, 2H), 3.61 (s, 3H), 6.61–6.85 (m, 3H), 7.35–7.59 (m, 3H), 7.63–7.75 (m, 2H), 8.21–8.60 (m, 3H), 9.18 (s, 1H), 10.25 (s, 1H); HPLC纯度: 99.17%; LCMS: 585.50 (M^+).

[2270] N-(4-(4-(4-氯-2-氟苄基)哌嗪-1-羰基)-3-甲氧基苯基)喹啉-8-磺酰胺 (XIV-66):

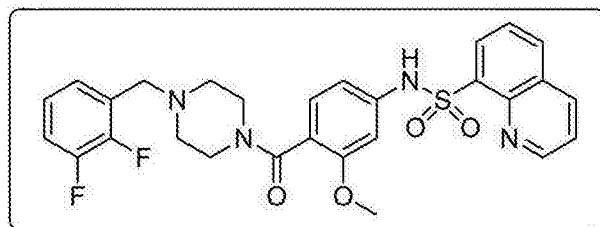
[2271]



[2272] ^1H NMR (400MHz, DMSO- d_6) δ : 2.08-2.39 (m, 4H), 3.25 (br s, 4H), 3.46 (s, 2H), 3.61 (s, 3H), 6.61-6.85 (m, 3H), 7.22-7.42 (m, 3H), 7.65-7.75 (m, 2H), 8.21-8.60 (m, 3H), 9.18 (s, 1H), 10.25 (s, 1H); HPLC纯度: 91.3%; LCMS: 569 (M^+).

[2273] N-(4-(4-(2,3-二氟苄基)哌嗪-1-羰基)-3-甲氧基苯基)喹啉-8-磺酰胺 (XIV-67):

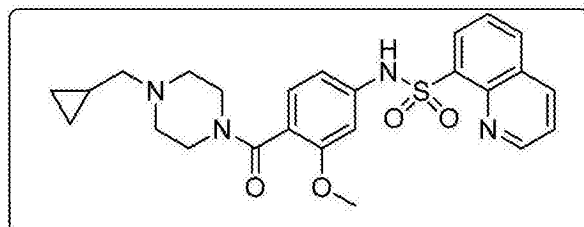
[2274]



[2275] ^1H NMR (400MHz, DMSO- d_6) δ : 2.08-2.39 (m, 4H), 3.21 (br s, 4H), 3.46 (s, 2H), 3.61 (s, 3H), 6.61-6.85 (m, 3H), 7.12-7.40 (m, 3H), 7.65-7.75 (m, 2H), 8.21-8.62 (m, 3H), 9.18 (s, 1H), 10.25 (s, 1H); HPLC纯度: 98.39%; LCMS: 552.5 (M^+).

[2276] N-(4-(4-(环丙基甲基)哌嗪-1-羰基)-3-甲氧基苯基)喹啉-8-磺酰胺 (XIV-68):

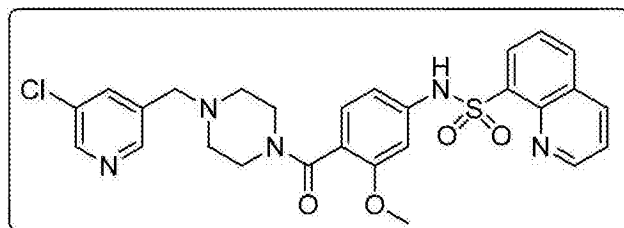
[2277]



[2278] ^1H NMR (400MHz, DMSO- d_6) δ : 0.10-0.15 (m, 2H), 0.70-0.82 (m, 1H), 1.20-1.30 (m, 2H), 2.02-2.42 (m, 6H), 2.90-3.05 (m, 4H), 3.63 (s, 3H), 6.61-6.85 (m, 3H), 7.65-7.75 (m, 2H), 8.21-8.60 (m, 3H), 9.18 (s, 1H), 10.25 (s, 1H), HPLC纯度: 98%; LCMS: 480.5 (M^+).

[2279] N-(4-(4-((5-氯吡啶-3-基)甲基)哌嗪-1-羰基)-3-甲氧基苯基)喹啉-8-磺酰胺 (XIV-69):

[2280]

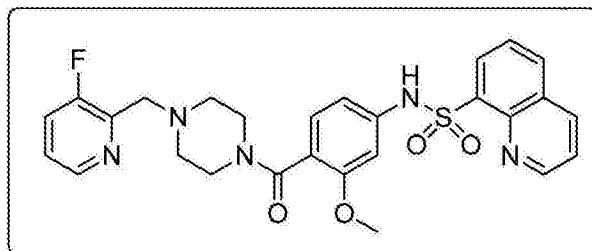


[2281] ^1H NMR (400MHz, DMSO- d_6) δ : 2.08-2.39 (m, 4H), 3.21 (br s, 4H), 3.46 (s, 2H), 3.61 (s, 3H), 6.61-6.85 (m, 3H), 7.62-7.83 (m, 3H), 8.21-8.60 (m, 5H), 9.18 (s, 1H), 10.25 (s,

1H); HPLC纯度:96.1%; LCMS:551 (M^+)。

[2282] N-(4-(4-((3-氟吡啶-2-基)甲基)哌嗪-1-羰基)-3-甲氧基苯基)喹啉-8-磺酰胺 (XIV-70):

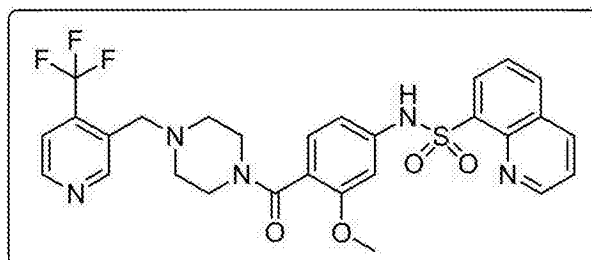
[2283]



[2284] ^1H NMR (400MHz, DMSO- d_6) δ : 2.08-2.39 (m, 4H), 3.21 (br s, 4H), 3.46 (s, 2H), 3.61 (s, 3H), 6.61-6.85 (m, 3H), 7.38-4.42 (m, 1H), 7.61-7.78 (m, 3H), 8.21-8.60 (m, 4H), 9.18 (s, 1H), 10.25 (s, 1H); HPLC纯度:99.54%; LCMS:535.5 (M^+)。

[2285] N-(3-甲氧基-4-(4-((4-(三氟甲基)吡啶-3-基)甲基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (XIV-71):

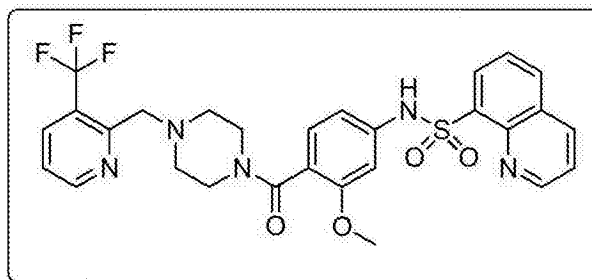
[2286]



[2287] ^1H NMR (400MHz, DMSO- d_6) δ : 2.08-2.39 (m, 4H), 3.15 (br s, 4H), 3.46 (s, 2H), 3.61 (s, 3H), 6.61-6.85 (m, 3H), 7.62-7.77 (m, 3H), 8.21-8.60 (m, 3H), 8.70-8.90 (m, 2H), 9.18 (s, 1H), 10.25 (s, 1H); HPLC纯度:98.48%; LCMS:585.6 (M^+)。

[2288] N-(3-甲氧基-4-(4-((3-(三氟甲基)吡啶-2-基)甲基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (XIV-72):

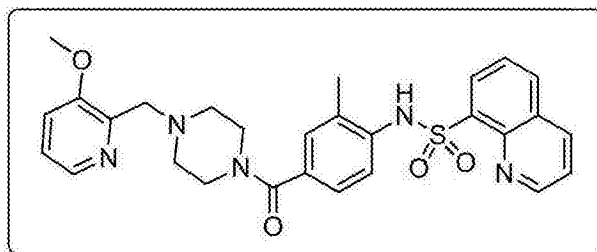
[2289]



[2290] ^1H NMR (400MHz, DMSO- d_6) δ : 2.25 (br s, 4H), 2.85 (br s, 2H), 3.42 (br s, 2H), 3.58 (s, 3H), 3.76 (br s, 2H), 6.60 (d, 1H), 6.78 (s, 1H), 6.92 (d, 1H), 7.46 (t, 1H), 7.63-7.70 (m, 2H), 8.18 (d, 1H), 8.22 (d, 1H), 8.37-8.45 (dd, 2H), 8.78 (d, 1H), 9.18 (s, 1H), 10.29 (s, 1H); HPLC纯度:95.85%; LCMS:586.1 (M^+ +1)。

[2291] N-(4-(4-((3-甲氧基吡啶-2-基)甲基)哌嗪-1-羰基)-2-甲基苯基)喹啉-8-磺酰胺 (XIV-73):

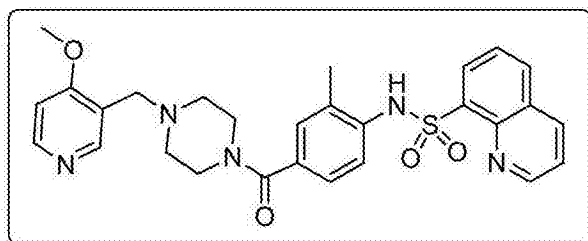
[2292]



[2293] ^1H NMR (400MHz, DMSO- d_6) δ : 2.01 (s, 3H), 2.39 (br s, 4H), 3.46 (s, 4H), 3.61 (s, 2H), 3.79 (s, 3H), 6.97 (s, 2H), 7.06 (s, 1H), 7.22-7.32 (s, 1H), 7.39 (d, 1H), 7.64-7.81 (m, 2H), 8.12 (d, 1H), 8.21-8.36 (m, 2H), 8.57 (d, 1H), 9.18 (s, 1H), 9.39 (s, 1H); HPLC纯度: 99.29%; LCMS: 532 (M^+).

[2294] N-(4-(4-((4-甲氧基吡啶-3-基)甲基)哌嗪-1-羰基)-2-甲基苯基)喹啉-8-磺酰胺 (XIV-74):

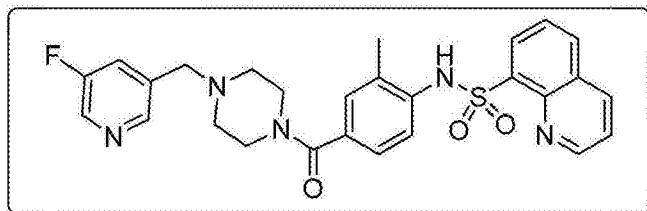
[2295]



[2296] ^1H NMR (400MHz, DMSO- d_6) δ : 2.01 (s, 3H), 2.37 (br s, 4H), 3.46 (br s, 6H), 3.79 (s, 3H), 6.97-7.06 (m, 3H), 7.10 (s, 1H), 7.66-7.79 (m, 2H), 8.21-8.38 (m, 4H), 8.57 (d, 1H), 9.16 (s, 1H), 9.39 (s, 1H); HPLC纯度: 98.22%; LCMS: 532 (M^+).

[2297] N-(4-(4-((5-氟吡啶-3-基)甲基)哌嗪-1-羰基)-2-甲基苯基)喹啉-8-磺酰胺 (XIV-75):

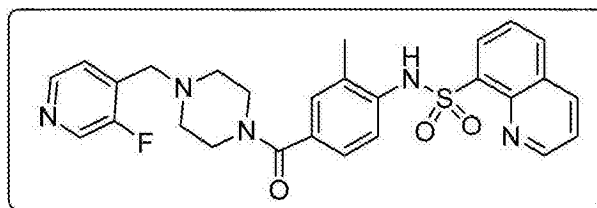
[2298]



[2299] ^1H NMR (400MHz, DMSO- d_6) δ : 2.01 (s, 3H), 2.37 (br s, 4H), 3.25 (s, 4H), 3.58 (s, 2H), 6.96 (s, 2H), 7.06 (s, 1H), 7.60-7.79 (m, 3H), 8.21-8.30 (m, 3H), 8.43 (s, 1H), 8.57 (d, 1H), 9.16 (s, 1H), 9.39 (s, 1H); HPLC纯度: 94.48%; LCMS: 520.3 (M^+).

[2300] N-(4-(4-((5-氟吡啶-3-基)甲基)哌嗪-1-羰基)-2-甲基苯基)喹啉-8-磺酰胺 (XIV-76):

[2301]

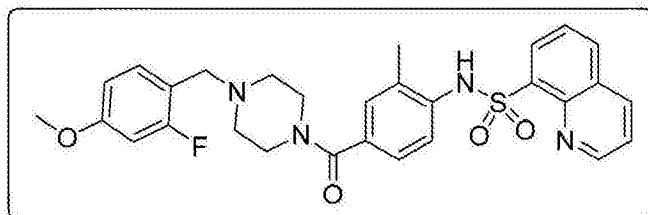


[2302] ^1H NMR (400MHz, DMSO- d_6) δ : 2.01 (s, 3H), 2.37 (br s, 4H), 3.25 (s, 4H), 3.58 (s, 2H), 6.96 (s, 2H), 7.06 (s, 1H), 7.42 (t, 1H), 7.60-7.79 (m, 2H), 8.21-8.30 (m, 3H), 8.46 (s,

1H), 8.57 (d, 1H), 9.16 (s, 1H), 9.39 (s, 1H); HPLC纯度: 99.87%; LCMS: 520.3 ($M^+ + 1$)。

[2303] N-(4-(4-(2-氟-4-甲氧基苄基)哌嗪-1-羰基)-2-甲基苯基)喹啉-8-磺酰胺 (XIV-77):

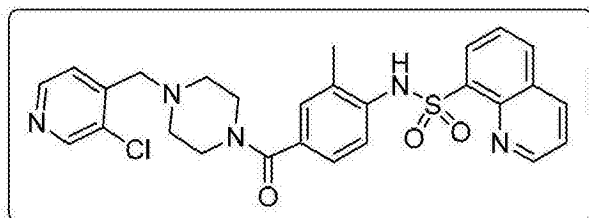
[2304]



[2305] ^1H NMR (400MHz, DMSO- d_6) δ : 2.01 (s, 3H), 2.37 (br s, 4H), 3.25 (br s, 4H), 3.58 (s, 2H), 3.76 (s, 3H), 6.65-6.78 (m, 2H), 6.96 (s, 2H), 7.06 (s, 1H), 7.21 (t, 1H), 7.61-7.79 (m, 2H), 8.21-8.30 (m, 2H), 8.57 (d, 1H), 9.16 (s, 1H), 9.39 (s, 1H); HPLC纯度: 99.37%; LCMS: 549.3 ($M^+ + 1$)。

[2306] N-(4-(4-((3-氯吡啶-4-基)甲基)哌嗪-1-羰基)-2-甲基苯基)喹啉-8-磺酰胺 (XIV-78):

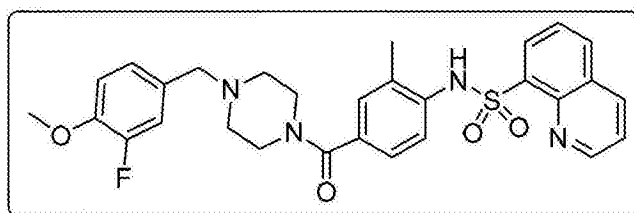
[2307]



[2308] ^1H NMR (400MHz, DMSO- d_6) δ : 2.01 (s, 3H), 2.37 (br s, 4H), 3.24 (br s, 4H), 3.59 (br s, 2H), 6.97 (s, 2H), 7.06 (s, 1H), 7.46 (d, 1H), 7.62-7.77 (m, 2H), 8.21-8.30 (m, 2H), 8.44 (d, 1H), 8.52-8.60 (m, 2H), 9.16 (s, 1H), 9.39 (s, 1H); HPLC纯度: 99.46%; LCMS: 536 (M^+)。

[2309] N-(4-(4-(3-氟-4-甲氧基苄基)哌嗪-1-羰基)-2-甲基苯基)喹啉-8-磺酰胺 (XIV-79):

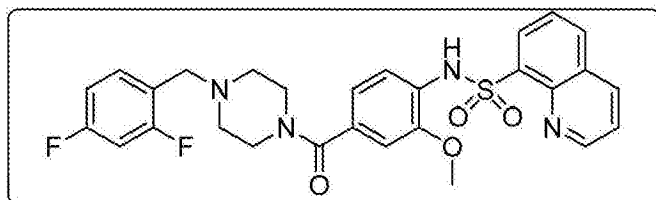
[2310]



[2311] ^1H NMR (400MHz, DMSO- d_6) δ : 2.01 (s, 3H), 2.37 (br s, 4H), 3.25 (s, 4H), 3.58 (s, 2H), 3.79 (s, 3H), 6.96-7.18 (m, 6H), 7.60-7.78 (m, 2H), 8.21-8.36 (m, 2H), 8.57 (d, 1H), 9.16 (s, 1H), 9.39 (s, 1H); HPLC纯度: 99.01%; LCMS: 549.3 ($M^+ + 1$)。

[2312] N-(4-(4-(2,4-二氟苄基)哌嗪-1-羰基)-2-甲氧基苯基)喹啉-8-磺酰胺 (XIV-80):

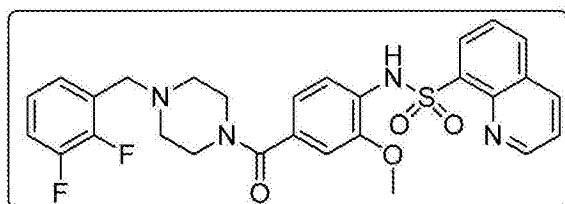
[2313]



[2314] ^1H NMR (400MHz, DMSO- d_6) δ : 2.37 (br s, 4H), 3.31 (s, 6H), 3.56 (s, 3H), 6.75 (s, 1H), 6.81 (d, 1H), 7.05 (t, 1H), 7.20 (t, 1H), 7.37-7.42 (m, 2H), 7.66-7.79 (m, 2H), 8.25 (d, 2H), 8.57 (d, 1H), 9.13 (s, 1H), 9.21 (s, 1H); HPLC纯度: 99.51%; LCMS: 553 (M^+).

[2315] N-(4-(4-(2,3-二氟苄基)哌嗪-1-羰基)-2-甲氧基苯基)喹啉-8-磺酰胺 (XIV-81):

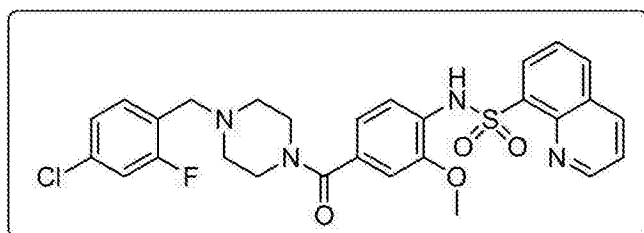
[2316]



[2317] ^1H NMR (400MHz, DMSO- d_6) δ : 2.37 (br s, 4H), 3.31 (br s, 6H), 3.58 (s, 3H), 6.75 (s, 1H), 6.81 (d, 1H), 7.05-7.12 (m, 1H), 7.22-7.38 (m, 1H), 7.41 (d, 1H), 7.66-7.79 (m, 2H), 8.25 (d, 2H), 8.57 (d, 1H), 9.13 (s, 1H), 9.21 (s, 1H); HPLC纯度: 96.99%; LCMS: 553 (M^+).

[2318] N-(4-(4-(4-氯-2-氟苄基)哌嗪-1-羰基)-2-甲氧基苯基)喹啉-8-磺酰胺 (XIV-82):

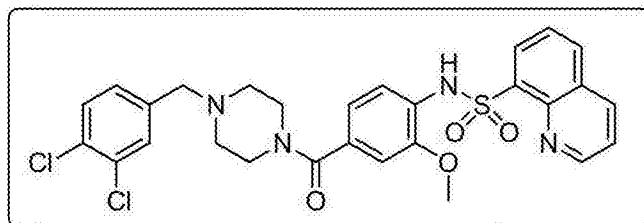
[2319]



[2320] ^1H NMR (400MHz, DMSO- d_6) δ : 2.37 (br s, 4H), 3.31 (s, 6H), 3.58 (s, 3H), 6.75 (s, 1H), 6.81 (d, 1H), 7.21 (d, 1H), 7.33-7.44 (m, 3H), 7.66-7.79 (m, 2H), 8.25 (d, 2H), 8.57 (d, 1H), 9.13 (s, 1H), 9.21 (s, 1H); HPLC纯度: 97.45%; LCMS: 553 (M^+).

[2321] N-(4-(4-(3,4-二氯苄基)哌嗪-1-羰基)-2-甲氧基苯基)喹啉-8-磺酰胺 (XIV-83):

[2322]

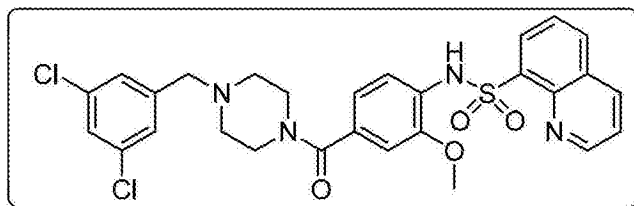


[2323] ^1H NMR (400MHz, DMSO- d_6) δ : 2.37 (br s, 4H), 3.31 (br s, 6H), 3.55 (s, 3H), 6.75 (s, 1H), 6.81 (d, 1H), 7.23 (d, 1H), 7.42 (d, 1H), 7.55-7.61 (m, 2H), 7.66-7.79 (m, 2H), 8.25 (d, 2H), 8.57 (d, 1H), 9.13 (s, 1H), 9.21 (s, 1H); HPLC纯度: 99.49%; LCMS: 585 (M^+).

[2324] N-(4-(4-(3,5-二氯苄基)哌嗪-1-羰基)-2-甲氧基苯基)喹啉-8-磺酰胺 (XIV-

84) :

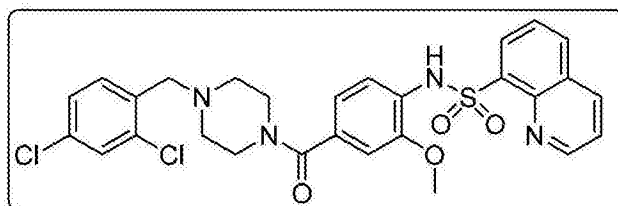
[2325]



[2326] ^1H NMR (400MHz, DMSO- d_6) δ 2.37 (br s, 4H), 3.31 (br s, 6H), 3.55 (s, 3H), 6.75 (s, 1H), 6.81 (d, 1H), 7.38 (s, 1H), 7.42–7.50 (m, 3H), 7.66–7.79 (m, 2H), 8.25 (d, 2H), 8.59 (d, 1H), 9.13 (s, 1H), 9.21 (s, 1H); HPLC纯度: 99.43%; LCMS: 585 (M^+).

[2327] N-(4-(4-(2,4-二氯苄基)哌嗪-1-羰基)-2-甲氧基苄基)喹啉-8-磺酰胺 (XIV-85) :

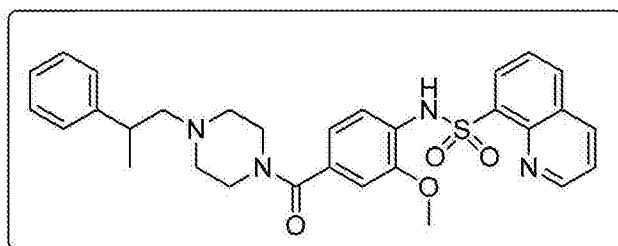
[2328]



[2329] ^1H NMR (400MHz, DMSO- d_6) δ 2.37 (br s, 4H), 3.31 (br s, 4H), 3.41 (s, 2H), 3.57 (s, 3H), 6.75 (s, 1H), 6.81 (d, 1H), 7.38–7.59 (m, 4H), 7.64–7.79 (m, 2H), 8.25 (d, 2H), 8.59 (d, 1H), 9.13 (s, 1H), 9.21 (s, 1H); HPLC纯度: 99.87%; LCMS: 585 (M^+).

[2330] N-(2-甲氧基-4-(4-(2-苯基丙基)哌嗪-1-羰基)苄基)喹啉-8-磺酰胺 (XIV-86) :

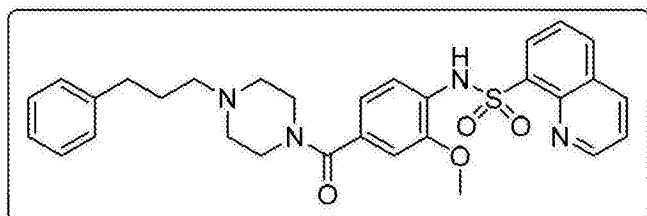
[2331]



[2332] ^1H NMR (400MHz, DMSO- d_6) δ : 1.18 (d, 3H), 2.37 (br s, 4H), 2.41 (m, 1H), 2.46 (br s, 4H), 3.36 (br s, 2H), 3.41 (s, 3H), 6.75 (s, 1H), 6.81 (d, 1H), 7.16–7.36 (m, 5H), 7.41 (d, 1H), 7.62–7.77 (m, 2H), 8.24 (d, 2H), 8.57 (d, 1H), 9.18 (s, 1H), 9.39 (s, 1H); HPLC纯度: 99.41%; LCMS: 545 (M^+).

[2333] N-(2-甲氧基-4-(4-(3-苯基丙基)哌嗪-1-羰基)苄基)喹啉-8-磺酰胺 (XIV-87) :

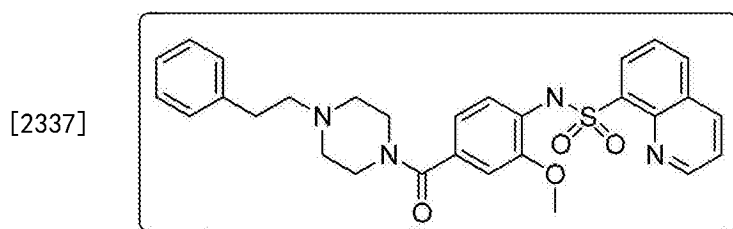
[2334]



[2335] ^1H NMR (400MHz, DMSO- d_6) δ : 1.65 (t, 2H), 2.27–2.38 (m, 6H), 2.52–2.58 (m, 2H), 3.36 (br s, 6H), 3.41 (br s, 5H), 6.75 (s, 1H), 6.81 (d, 1H), 7.16–7.32 (m, 5H), 7.41 (d, 1H), 7.62–7.77 (m, 2H), 8.24 (d, 2H), 8.57 (d, 1H), 9.18 (s, 1H), 9.39 (s, 1H); HPLC纯度: 99.69%;

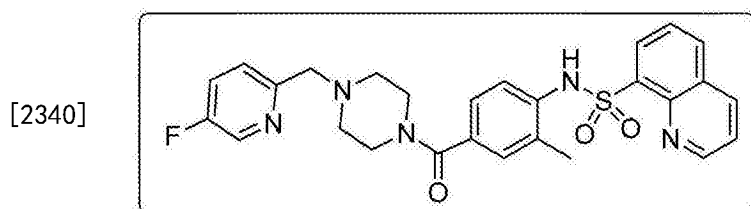
LCMS:545 (M^+)。

[2336] N-(2-甲氧基-4-(4-苄基哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (XIV-88) :



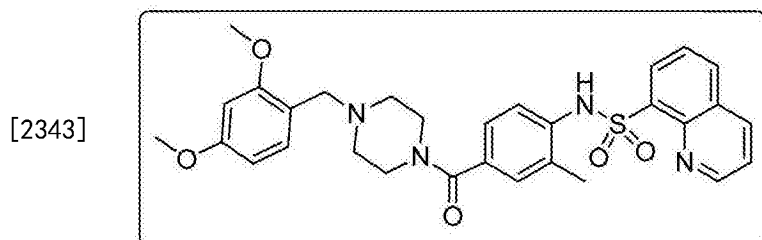
[2338] 1H NMR (400MHz, DMSO- d_6) δ : 2.39 (s, 4H), 2.61-2.72 (m, 2H), 3.36 (br s, 6H), 3.41 (s, 3H), 6.75 (s, 1H), 6.81 (d, 1H), 7.16-7.32 (m, 5H), 7.41 (d, 1H), 7.62-7.77 (m, 2H), 8.24 (d, 2H), 8.57 (d, 1H), 9.18 (s, 1H), 9.39 (s, 1H); HPLC纯度: 99.41%; LCMS: 545 (M^+ +1)。

[2339] N-(4-(4-((5-氟吡啶-2-基)甲基)哌嗪-1-羰基)-2-甲基苯基)喹啉-8-磺酰胺 (XIV-89) :



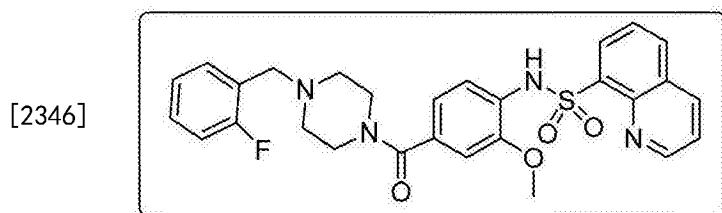
[2341] 1H NMR (400MHz, DMSO- d_6) δ : 2.01 (s, 3H), 2.39 (br s, 4H), 3.31 (br s, 4H), 3.61 (s, 2H), 6.98-7.08 (m, 3H), 7.44-7.56 (m, 2H), 7.62-7.79 (m, 3H), 8.21-8.32 (m, 2H), 8.41 (s, 1H), 8.56-8.60 (m, 1H), 9.16 (s, 1H), 9.38 (s, 1H); HPLC纯度: 99.82%; LCMS: 520 (M^+ +1)。

[2342] N-(4-(4-(2,4-二甲氧基苄基)哌嗪-1-羰基)-2-甲基苯基)喹啉-8-磺酰胺 (XIV-90) :



[2344] 1H NMR (400MHz, DMSO- d_6) δ : 2.01 (s, 3H), 2.37 (br s, 4H), 3.31 (br s, 4H), 3.42 (s, 2H), 3.76 (s, 6H), 6.42 (d, 1H), 6.52 (s, 1H), 6.97-7.18 (m, 4H), 7.64-7.79 (m, 2H), 8.21-8.36 (m, 2H), 8.59 (d, 1H), 9.16 (s, 1H), 9.39 (s, 1H); HPLC纯度: 94.33%; LCMS: 561 (M^+ +1)。

[2345] N-(4-(4-(2-氟苄基)哌嗪-1-羰基)-2-甲氧基苯基)喹啉-8-磺酰胺 (XIV-91) :

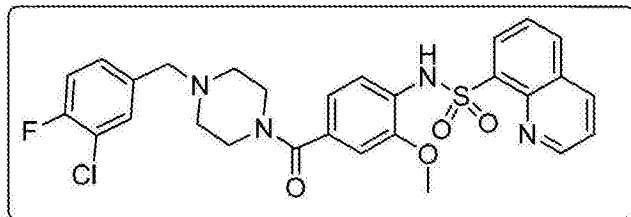


[2347] 1H NMR (400MHz, DMSO- d_6) δ : 2.37 (br s, 4H), 3.36 (s, 4H), 3.42 (s, 2H), 3.56 (s, 3H), 6.79 (s, 1H), 6.82 (d, 1H), 7.15-7.19 (m, 4H), 7.21-7.44 (m, 3H), 8.24 (m, 2H), 8.57 (d,

1H), 9.18 (s, 1H), 9.39 (s, 1H); HPLC纯度: 97.44%; LCMS: 535 (M^+)。

[2348] N-(4-(4-(3-氯-4-氟苄基)哌嗪-1-羰基)-2-甲氧基苯基)喹啉-8-磺酰胺 (XIV-92):

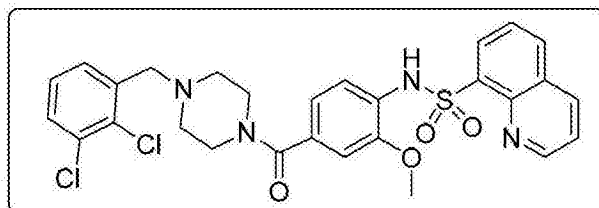
[2349]



[2350] 1H NMR (400MHz, DMSO- d_6) δ : 2.37 (br s, 4H), 3.36 (s, 4H), 3.42 (s, 2H), 3.56 (s, 3H), 6.79 (s, 1H), 6.82 (d, 1H), 7.21-7.45 (m, 4H), 7.62-7.78 (m, 2H), 8.24 (d, 2H), 8.57 (d, 1H), 9.16 (s, 1H), 9.19 (s, 1H); HPLC纯度: 99.19%; LCMS: 569 (M^+)。

[2351] N-(4-(4-(2,3-二氯苄基)哌嗪-1-羰基)-2-甲氧基苯基)喹啉-8-磺酰胺 (XIV-93):

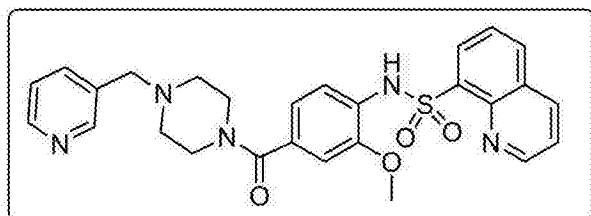
[2352]



[2353] 1H NMR (400MHz, DMSO- d_6) δ : 2.37 (br s, 4H), 3.36 (s, 4H), 3.42 (s, 2H), 3.59 (s, 3H), 6.79 (s, 1H), 6.82 (d, 1H), 7.24-7.58 (m, 4H), 7.62-7.78 (m, 2H), 8.24 (d, 2H), 8.57 (d, 1H), 9.16 (s, 1H), 9.19 (s, 1H); HPLC纯度: 99.80%; LCMS: 585 (M^+)。

[2354] N-(2-甲氧基-4-(4-(吡啶-3-基甲基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (XIV-94):

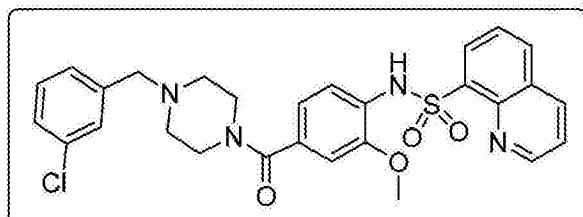
[2355]



[2356] 1H NMR (400MHz, DMSO- d_6) δ : 2.37 (br s, 4H), 3.32 (s, 4H), 3.42 (s, 3H), 3.56 (s, 2H), 6.79 (s, 1H), 6.82 (d, 1H), 7.30-7.46 (m, 2H), 7.62-7.79 (m, 3H), 8.24 (d, 2H), 8.40-8.59 (m, 2H), 9.10 (s, 1H), 9.19 (s, 1H); HPLC纯度: 98.45%; LCMS: 518 ($M^+ + 1$)。

[2357] N-(4-(4-(3-氯苄基)哌嗪-1-羰基)-2-甲氧基苯基)喹啉-8-磺酰胺 (XIV-95):

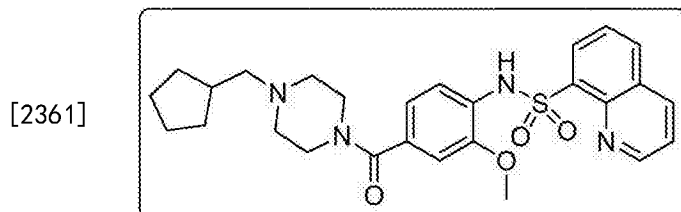
[2358]



[2359] 1H NMR (400MHz, DMSO- d_6) δ : 2.37 (br s, 4H), 3.36 (s, 4H), 3.42 (s, 3H), 3.59 (s,

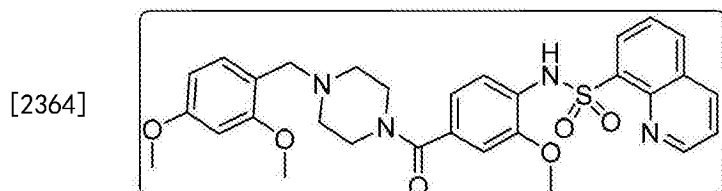
2H), 6.79 (s, 1H), 6.82 (d, 1H), 7.21–7.44 (m, 5H), 7.62–7.78 (m, 2H), 8.24 (d, 2H), 8.57 (d, 1H), 9.16 (s, 1H), 9.19 (s, 1H); HPLC纯度: 98.92%; LCMS: 551 (M^+)。

[2360] N-(4-(4-(环戊基甲基)哌嗪-1-羰基)-2-甲氧基苯基)喹啉-8-磺酰胺 (XIV-96):



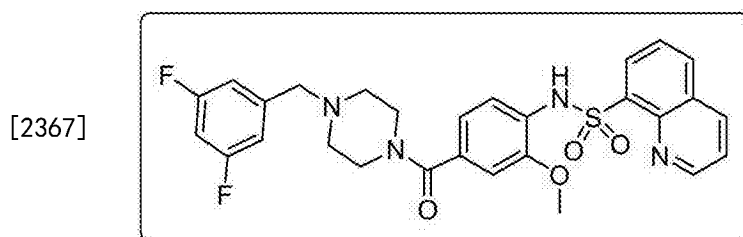
[2362] ^1H NMR (400MHz, DMSO- d_6) δ : 1.15–1.19 (m, 2H), 1.40–1.71 (m, 6H), 2.01–2.05 (m, 1H), 2.30–2.37 (br s, 6H), 3.36 (s, 4H), 3.42 (s, 3H), 6.79 (s, 1H), 6.82 (d, 1H), 7.41 (d, 1H), 7.62–7.78 (m, 2H), 8.24 (d, 2H), 8.57 (d, 1H), 9.12 (s, 1H), 9.19 (s, 1H); HPLC纯度: 99.58%; LCMS: 509 (M^+ +1)。

[2363] N-(4-(4-(2,4-二甲氧基苄基)哌嗪-1-羰基)-2-甲氧基苯基)喹啉-8-磺酰胺 (XIV-97):



[2365] ^1H NMR (400MHz, DMSO- d_6) δ : 2.37 (br s, 4H), 3.36 (br s, 6H), 3.42 (s, 3H), 3.78 (s, 6H), 6.42–6.51 (m, 2H), 6.79 (s, 1H), 6.82 (d, 1H), 7.41 (d, 1H), 7.62–7.78 (m, 2H), 8.24 (d, 2H), 8.57 (d, 1H), 9.12 (s, 1H), 9.19 (s, 1H); HPLC纯度: 96.10%; LCMS: 577 (M^+ +1)。

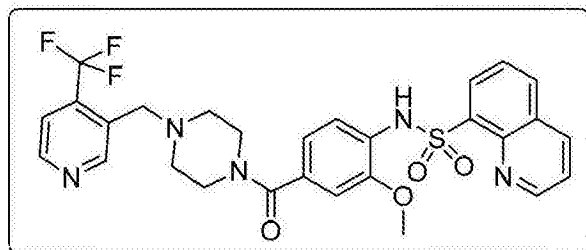
[2366] N-(4-(4-(3,5-二氟苄基)哌嗪-1-羰基)-2-甲氧基苯基)喹啉-8-磺酰胺 (XIV-98):



[2368] ^1H NMR (400MHz, DMSO- d_6) δ : 2.37 (br s, 4H), 3.36 (s, 4H), 3.41 (s, 3H), 3.52 (s, 2H), 6.78 (s, 1H), 6.81 (d, 1H), 6.97–7.16 (m, 3H), 7.41 (d, 1H), 7.62–7.80 (m, 2H), 8.21–8.30 (m, 2H), 8.57 (d, 1H), 9.08 (s, 1H), 9.18 (s, 1H); HPLC纯度: 99.30%; LCMS: 553 (M^+ +1)。

[2369] N-(2-甲氧基-4-(4-((4-(三氟甲基)吡啶-3-基)甲基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (XIV-99):

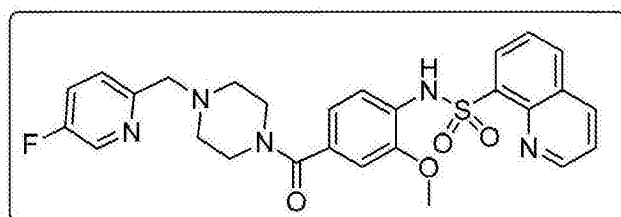
[2370]



[2371] ^1H NMR (400MHz, DMSO- d_6) δ : 2.37 (br s, 4H), 3.36 (s, 4H), 3.41 (s, 3H), 3.62 (s, 2H), 6.78 (s, 1H), 6.81 (d, 1H), 6.97–7.16 (m, 3H), 7.41 (d, 1H), 7.64–7.80 (m, 3H), 8.21–8.30 (m, 2H), 8.57 (d, 1H), 8.76 (d, 1H), 8.84 (s, 1H), 9.08 (s, 1H), 9.18 (s, 1H); HPLC纯度: 96.90%; LCMS: 586 (M^+ +1)。

[2372] N-(4-(4-(5-氟吡啶-2-基)甲基)哌嗪-1-羰基)-2-甲氧基苯基)喹啉-8-磺酰胺 (XIV-100):

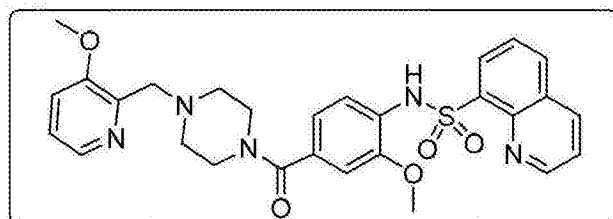
[2373]



[2374] ^1H NMR (400MHz, DMSO- d_6) δ : 2.37 (br s, 4H), 3.36 (s, 4H), 3.41 (s, 3H), 3.59 (s, 2H), 6.78 (s, 1H), 6.81 (d, 1H), 7.41–7.52 (m, 2H), 7.64–7.80 (m, 3H), 8.21–8.30 (m, 2H), 8.41 (s, 2H), 8.57 (d, 2H), 9.08 (s, 1H), 9.18 (s, 1H); HPLC纯度: 98.81%; LCMS: 536 (M^+ +1)。

[2375] N-(2-甲氧基-4-(4-(3-甲氧基吡啶-2-基)甲基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (XIV-101):

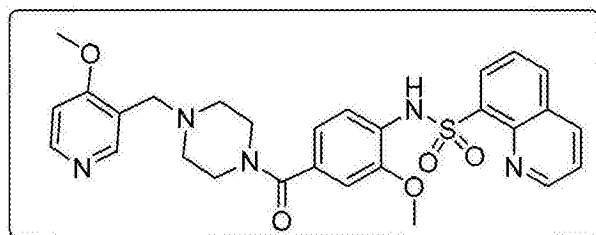
[2376]



[2377] ^1H NMR (400MHz, DMSO- d_6) δ : 2.39 (br s, 4H), 3.36 (s, 4H), 3.41 (s, 3H), 3.59 (s, 2H), 3.79 (s, 3H), 6.78 (s, 1H), 6.81 (d, 1H), 7.21–7.43 (m, 3H), 7.64–7.80 (m, 2H), 8.05 (s, 1H), 8.24–8.30 (m, 2H), 8.57 (d, 1H), 9.08 (s, 1H), 9.18 (s, 1H); HPLC纯度: 99.08%; LCMS: 548 (M^+ +1)。

[2378] N-(2-甲氧基-4-(4-(4-甲氧基吡啶-3-基)甲基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (XIV-102):

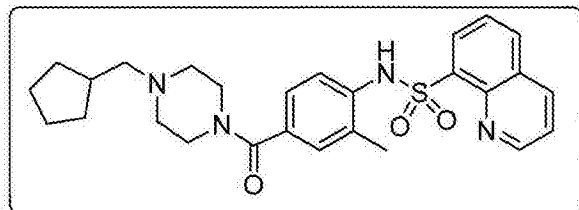
[2379]



[2380] ^1H NMR (400MHz, DMSO- d_6) δ : 2.39 (br s, 4H), 3.36 (s, 4H), 3.41 (s, 3H), 3.55 (s, 2H), 3.81 (s, 3H), 6.78 (s, 1H), 6.81 (d, 1H), 7.01 (s, 1H), 7.41 (s, 1H), 7.64–7.80 (m, 2H), 8.24–8.39 (m, 4H), 8.59 (d, 1H), 9.08 (s, 1H), 9.18 (s, 1H); HPLC纯度: 97.31%; LCMS: 548 (M^+ +1)。

[2381] N-(4-(4-(环戊基甲基)哌嗪-1-羰基)-2-甲基苯基)喹啉-8-磺酰胺 (XIV-103):

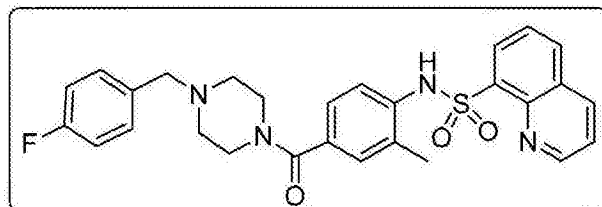
[2382]



[2383] ^1H NMR (400MHz, DMSO- d_6) δ : 0.81–0.84 (m, 1H), 1.1–1.32 (m, 3H), 1.4–1.75 (m, 5H), 2.1 (s, 3H), 2.12–2.4 (br s, 6H), 3.18–3.62 (br s, 4H), 6.9–7.14 (s, 3H), 7.62–7.77 (m, 2H), 8.21–8.35 (m, 2H), 8.57 (d, 1H), 9.18 (s, 1H), 9.39 (s, 1H); HPLC纯度: 99.55%; LCMS: 493.3 (M^+ +1)。

[2384] N-(4-(4-(4-氟苄基)哌嗪-1-羰基)-2-甲基苯基)喹啉-8-磺酰胺 (XIV-104):

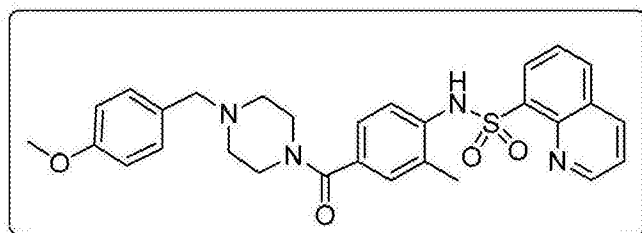
[2385]



[2386] ^1H NMR (400MHz, DMSO- d_6) δ : 2.01 (s, 3H), 2.2–2.37 (br s, 4H), 3.18–3.34 (br s, 2H), 3.42–3.59 (br s, 4H), 6.96 (s, 2H), 7.06–7.16 (m, 3H), 7.31 (t, 2H), 7.61–7.79 (m, 2H), 8.21–8.30 (m, 2H), 8.57 (d, 1H), 9.16 (s, 1H), 9.39 (s, 1H); HPLC纯度: 99.31%; LCMS: 519.3 (M^+ +1)。

[2387] N-(4-(4-(4-甲氧基苄基)哌嗪-1-羰基)-2-甲基苯基)喹啉-8-磺酰胺 (XIV-105):

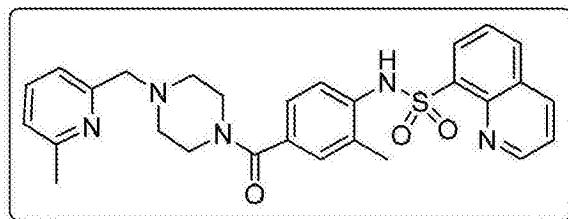
[2388]



[2389] ^1H NMR (400MHz, DMSO- d_6) δ : 2.01 (s, 3H), 2.37 (br s, 4H), 3.18–3.28 (br s, 4H), 3.46 (s, 2H), 3.71 (s, 3H), 6.82 (d, 2H), 6.96 (d, 2H), 7.06 (s, 1H), 7.19 (d, 2H), 7.62–7.77 (m, 2H), 8.21–8.30 (m, 2H), 8.57 (d, 1H), 9.18 (s, 1H), 9.39 (s, 1H); HPLC纯度: 94.41%。LCMS: 531.15 (M^+ +1)。

[2390] N-(2-甲基-4-(4-((6-甲基吡啶-2-基)甲基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (XIV-106):

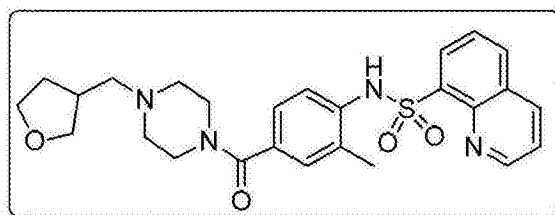
[2391]



[2392] ^1H NMR (400MHz, DMSO- d_6) δ : 2.01 (s, 3H), 2.34 (br s, 4H), 2.39 (s, 3H), 3.21 (br s, 4H), 3.58 (s, 2H), 6.97–7.16 (m, 4H), 7.21 (d, 2H), 7.62–7.77 (m, 3H), 8.21–8.34 (m, 2H), 8.57 (d, 1H), 9.18 (s, 1H); HPLC纯度: 95.18%; LCMS: 516.35 (M^+ +1)。

[2393] N-(2-甲基-4-(4-((四氢呋喃-3-基)甲基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (XIV-107):

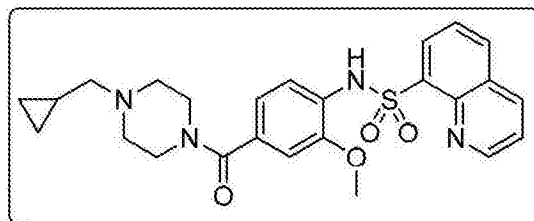
[2394]



[2395] ^1H NMR (400MHz, DMSO- d_6) δ : 0.82–0.84 (m, 1H), 1.22 (s, 2H), 1.42–1.58 (br s, 1H), 1.82–1.96 (m, 1H), 2.04 (s, 3H), 2.21–2.31 (m, 5H), 3.16–3.51 (br s, 5H), 3.72–3.85 (m, 2H), 6.97–7.04 (m, 3H), 7.62–7.77 (m, 2H), 8.21–8.30 (m, 2H), 8.57 (d, 1H), 9.18 (s, 1H), 9.39 (s, 1H); HPLC纯度: 98.714%; LCMS: 495.35 (M^+ +1)。

[2396] N-(4-(4-(环丙基甲基)哌嗪-1-羰基)-2-甲氧基苯基)喹啉-8-磺酰胺 (XIV-108):

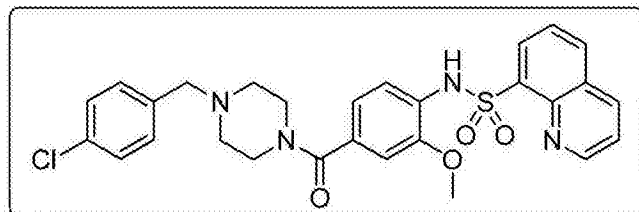
[2397]



[2398] ^1H NMR (400MHz, DMSO- d_6) δ : 0.21 (s, 2H), 0.41 (s, 2H), 0.91 (br s, 1H), 2.12 (s, 2H), 2.39 (br s, 4H), 3.36 (s, 4H), 3.41 (s, 3H), 6.78 (s, 1H), 6.81 (d, 1H), 7.41 (d, 1H), 7.62–7.82 (m, 2H), 8.21–8.30 (m, 2H), 8.57 (d, 1H), 9.08 (s, 1H), 9.19 (s, 1H); HPLC纯度: 99.74%; LCMS: 481 (M^+ +1)。

[2399] N-(4-(4-(4-氯苄基)哌嗪-1-羰基)-2-甲氧基苯基)喹啉-8-磺酰胺 (XIV-109):

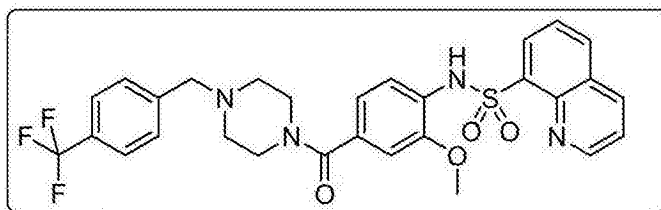
[2400]



[2401] ^1H NMR (400MHz, DMSO- d_6) δ : 2.31 (br s, 4H), 3.36 (s, 4H), 3.41 (s, 3H), 3.44 (s, 2H), 6.78 (s, 1H), 6.81 (d, 1H), 7.21–7.43 (m, 5H), 7.62–7.78 (m, 2H), 8.21–8.30 (m, 2H), 8.55 (d, 1H), 9.08 (s, 1H), 9.19 (s, 1H); HPLC纯度: 94.85%; LCMS: 551 (M^+)。

[2402] N-(2-甲氧基-4-(4-(4-(三氟甲基)苄基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (XIV-110):

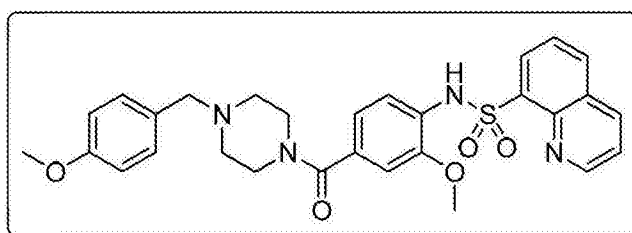
[2403]



[2404] ^1H NMR (400MHz, DMSO- d_6) δ : 2.37 (br s, 4H), 3.36 (s, 4H), 3.41 (s, 3H), 3.59 (s, 2H), 6.78 (s, 1H), 6.81 (d, 1H), 7.41–7.56 (m, 3H), 7.62–7.78 (m, 4H), 8.21–8.30 (m, 2H), 8.58 (d, 1H), 9.08 (s, 1H), 9.19 (s, 1H); HPLC纯度: 98.62%; LCMS: 585 (M^+ +1)。

[2405] N-(2-甲氧基-4-(4-(4-甲氧基苄基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (XIV-111):

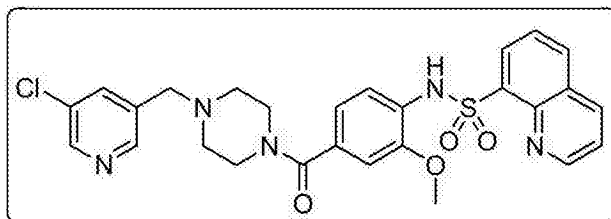
[2406]



[2407] ^1H NMR (400MHz, DMSO- d_6) δ : 2.35 (br s, 4H), 3.36 (s, 4H), 3.41 (s, 3H), 3.43 (s, 2H), 3.66 (s, 3H), 6.76–6.90 (m, 4H), 7.19 (d, 2H), 7.41 (s, 1H), 7.62–7.78 (m, 2H), 8.21–8.30 (m, 2H), 8.58 (d, 1H), 9.05 (s, 1H), 9.19 (s, 1H); HPLC纯度: 97.73%; LCMS: 547 (M^+ +1)。

[2408] N-(4-(4-((5-氯吡啶-3-基)甲基)哌嗪-1-羰基)-2-甲氧基苯基)喹啉-8-磺酰胺 (XIV-112):

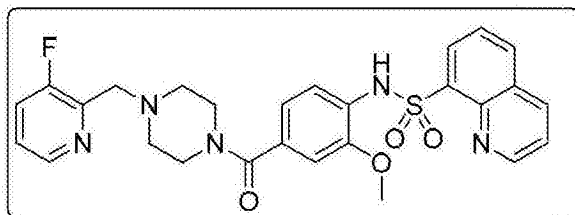
[2409]



[2410] ^1H NMR (400MHz, DMSO- d_6) δ : 2.31 (br s, 4H), 3.37 (s, 4H), 3.41 (s, 3H), 3.55 (s, 2H), 6.78 (s, 1H), 6.81 (d, 1H), 7.41 (d, 1H), 7.62–7.82 (m, 3H), 8.21–8.30 (m, 2H), 8.41–8.61 (m, 3H), 9.05 (s, 1H), 9.19 (s, 1H); HPLC纯度: 99.46%; LCMS: 553 (M^+ +1)。

[2411] N-(4-(4-((3-氟吡啶-2-基)甲基)哌嗪-1-羰基)-2-甲氧基苯基)喹啉-8-磺酰胺 (XIV-113):

[2412]

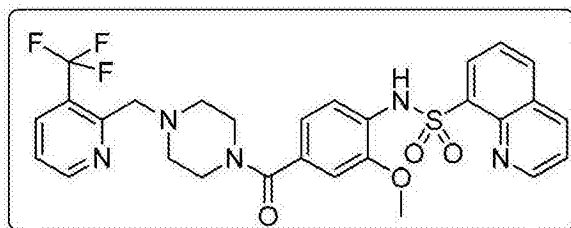


[2413] ^1H NMR (400MHz, DMSO- d_6) δ : 2.39 (br s, 4H), 3.37 (s, 4H), 3.41 (s, 3H), 3.61 (s,

2H), 6.78 (s, 1H), 6.81 (d, 1H), 7.41–7.45 (m, 2H), 7.62–7.80 (m, 4H), 8.21–8.39 (m, 3H), 8.59 (s, 1H), 9.18 (s, 1H); HPLC纯度: 96.15%; LCMS: 536 (M^+)。

[2414] N-(2-甲氧基-4-(4-((3-(三氟甲基)吡啶-2-基)甲基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (XIV-114):

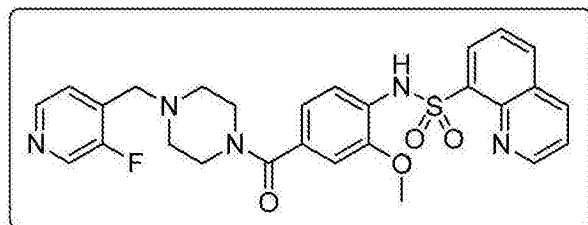
[2415]



[2416] ^1H NMR (400MHz, DMSO- d_6) δ : 2.39 (br s, 4H), 3.37 (s, 4H), 3.43 (s, 3H), 3.70 (s, 2H), 6.78 (s, 1H), 6.81 (d, 1H), 7.41–7.59 (m, 2H), 7.64–7.80 (m, 2H), 8.18 (d, 1H), 8.24–8.29 (m, 2H), 8.59 (d, 1H), 8.79 (d, 1H), 9.08 (s, 1H), 9.18 (s, 1H); HPLC纯度: 99.41%; LCMS: 586 (M^+ + 1)。

[2417] N-(4-(4-((3-氟吡啶-4-基)甲基)哌嗪-1-羰基)-2-甲氧基苯基)喹啉-8-磺酰胺 (XIV-115):

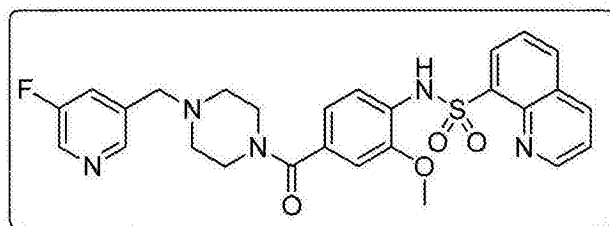
[2418]



[2419] ^1H NMR (400MHz, DMSO- d_6) δ : 2.45 (s, 4H), 3.47 (s, 4H), 3.56 (s, 3H), 3.61 (s, 2H), 6.72–6.85 (m, 2H), 7.38–7.42 (m, 2H), 7.62–7.81 (m, 2H), 8.21–8.40 (m, 3H), 8.57 (d, 2H), 9.08 (s, 1H), 9.21 (s, 1H); HPLC纯度: 99.2%; LCMS: 535 (M^+)。

[2420] N-(4-(4-((5-氟吡啶-3-基)甲基)哌嗪-1-羰基)-2-甲氧基苯基)喹啉-8-磺酰胺 (XIV-116):

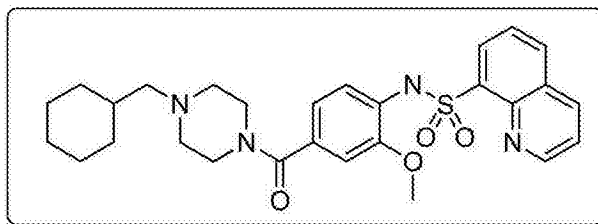
[2421]



[2422] ^1H NMR (400MHz, DMSO- d_6) δ : 2.45 (s, 4H), 3.47 (s, 4H), 3.56 (s, 3H), 3.61 (s, 2H), 6.72–6.85 (m, 2H), 7.42 (d, 1H), 7.58–7.81 (m, 3H), 8.21–8.40 (m, 3H), 8.57 (d, 2H), 9.08 (s, 1H), 9.21 (s, 1H); HPLC纯度: 99.8%; LCMS: 535 (M^+)。

[2423] N-(4-(4-(环己基甲基)哌嗪-1-羰基)-2-甲氧基苯基)喹啉-8-磺酰胺 (XIV-117):

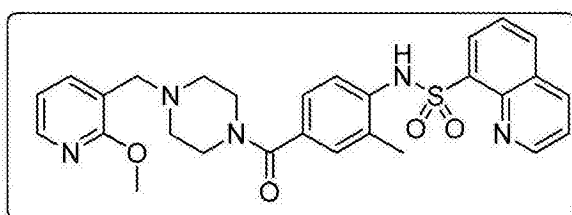
[2424]



[2425] ^1H NMR (400MHz, DMSO- d_6) δ : 0.70–0.84 (m, 2H), 1.01–1.21 (m, 3H), 1.35–1.42 (m, 1H), 1.61–1.74 (m, 5H), 2.02 (d, 2H), 2.25 (br s, 4H), 3.47 (s, 2H), 3.56 (s, 3H), 3.61 (s, 2H), 6.65–6.82 (m, 2H), 7.42 (d, 1H), 7.65–7.80 (m, 2H), 8.35 (d, 2H), 8.60 (d, 1H), 9.08 (s, 1H), 9.19 (d, 1H); HPLC纯度: 99.7%; LCMS: 522 (M^+).

[2426] N-(4-(4-(2-甲氧基吡啶-3-基)甲基)哌嗪-1-羰基)-2-甲基苯基)喹啉-8-磺酰胺 (XIV-118):

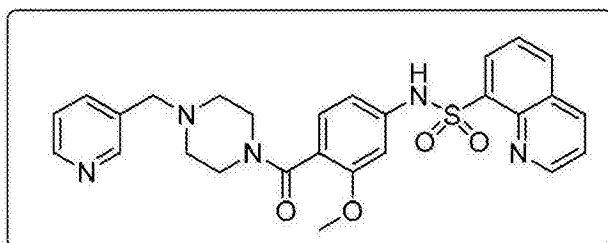
[2427]



[2428] ^1H NMR (400MHz, DMSO- d_6) δ : 2.01 (s, 3H), 2.37 (br s, 4H), 3.46 (s, 4H), 3.56 (s, 2H), 3.86 (s, 3H), 6.96–7.02 (m, 3H), 7.61–7.79 (m, 3H), 8.0 (d, 1H), 8.22–8.35 (m, 2H), 8.58 (d, 1H), 9.15 (s, 1H), 9.35 (s, 1H); HPLC纯度: 97.2%; LCMS: 531 (M^+).

[2429] N-(3-甲氧基-4-(4-(吡啶-3-基甲基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (XIV-119):

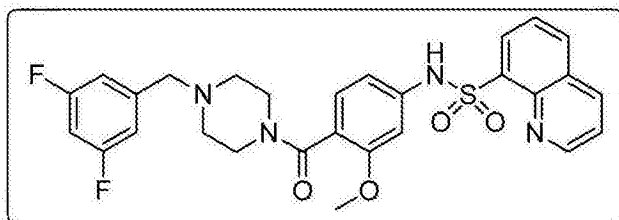
[2430]



[2431] ^1H NMR (400MHz, DMSO- d_6) δ : 2.01–2.38 (s, 4H), 2.97 (br s, 2H), 3.46 (s, 4H), 3.56 (s, 3H), 6.65–6.97 (m, 3H), 7.36 (m, 1H), 7.61–7.78 (m, 3H), 8.20–8.58 (m, 5H), 9.18 (s, 1H), 10.25 (s, 1H); HPLC纯度: 99.09%; LCMS: 517.6 (M^+).

[2432] N-(4-(4-(3,5-二氟苄基)哌嗪-1-羰基)-3-甲氧基苯基)喹啉-8-磺酰胺 (XIV-120):

[2433]

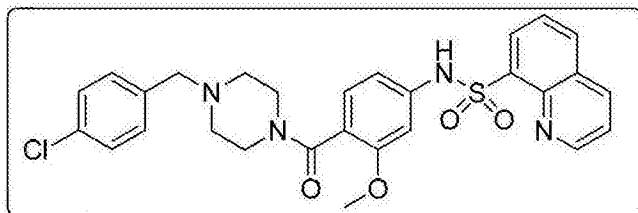


[2434] ^1H NMR (400MHz, DMSO- d_6) δ : 2.31 (br s, 4H), 3.02 (br s, 2H), 3.46 (br s, 4H), 3.59 (s, 3H), 6.81 (d, 1H), 6.78 (s, 1H), 6.85 (d, 1H), 7.06–7.18 (m, 3H), 7.71–7.76 (m, 2H),

8.24 (d, 1H), 8.42–8.58 (m, 2H), 9.18 (s, 1H), 10.28 (s, 1H); HPLC纯度: 99.20%; LCMS: 553 ($M^+ + 1$)。

[2435] N-(4-(4-(4-氯苄基)哌嗪-1-羰基)-3-甲氧基苯基)喹啉-8-磺酰胺 (XIV-121):

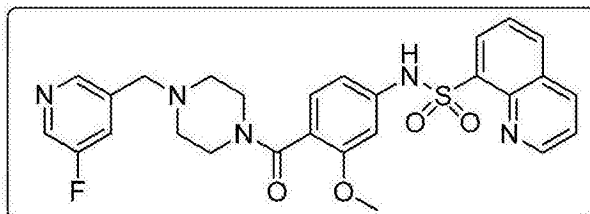
[2436]



[2437] ^1H NMR (400MHz, DMSO- d_6) δ : 2.36 (br s, 4H), 3.37 (s, 4H), 3.42 (s, 3H), 3.46 (s, 2H), 6.78 (s, 1H), 6.81 (d, 1H), 7.24–7.43 (m, 5H), 7.62–7.78 (m, 2H), 8.21–8.30 (m, 2H), 8.57 (d, 1H), 9.08 (s, 1H), 9.19 (s, 1H); HPLC纯度: 95.65%; LCMS: 551 (M^+)。

[2438] N-(4-(4-((5-氟吡啶-3-基)甲基)哌嗪-1-羰基)-3-甲氧基苯基)喹啉-8-磺酰胺 (XIV-122):

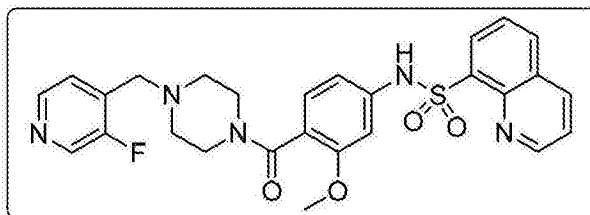
[2439]



[2440] ^1H NMR (400MHz, DMSO- d_6) δ : 2.19 (s, 2H), 2.25 (br s, 2H), 2.95 (br s, 2H), 3.52 (d, 5H), 6.61 (d, 1H), 6.78 (s, 1H), 6.83 (d, 1H), 7.60 (d, 1H), 7.70–7.79 (m, 2H), 8.28 (d, 1H), 8.34 (s, 1H), 8.39–8.48 (m, 3H), 9.16 (d, 1H), 10.30 (s, 1H); HPLC纯度: 99.58%; LCMS: 536 ($M^+ + 1$)。

[2441] N-(4-(4-((3-氟吡啶-4-基)甲基)哌嗪-1-羰基)-3-甲氧基苯基)喹啉-8-磺酰胺 (XIV-123):

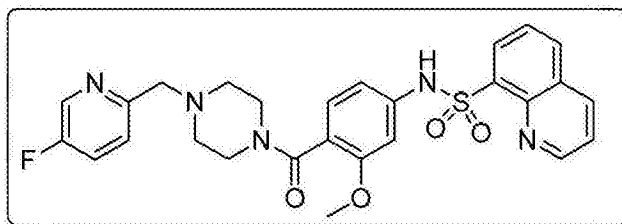
[2442]



[2443] ^1H NMR (400MHz, DMSO- d_6) δ : 2.21 (br s, 2H), 2.30 (br s, 2H), 3.00 (br s, 2H), 3.58 (d, 5H), 6.61 (d, 1H), 6.78 (s, 1H), 6.84 (d, 1H), 7.44 (t, 1H), 7.70–7.79 (m, 2H), 8.28 (d, 1H), 8.40 (d, 1H), 8.44 (d, 2H), 8.51 (s, 2H), 9.16 (d, 1H), 10.30 (s, 1H); HPLC纯度: 90.34%; LCMS: 536 ($M^+ + 1$)。

[2444] N-(4-(4-((5-氟吡啶-2-基)甲基)哌嗪-1-羰基)-3-甲氧基苯基)喹啉-8-磺酰胺 (XIV-124):

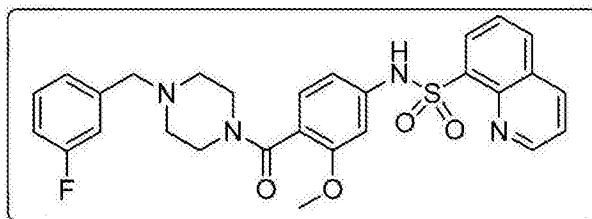
[2445]



[2446] ^1H NMR (400MHz, DMSO- d_6) δ : 2.19 (br s, 2H), 2.25 (br s, 2H), 2.95 (br s, 2H), 3.41 (br s, 2H), 3.58 (s, 3H), 6.61 (d, 1H), 6.78 (s, 1H), 6.83 (d, 1H), 7.47 (t, 1H), 7.60–7.78 (m, 2H), 8.24 (d, 1H), 8.39–8.48 (m, 3H), 9.16 (d, 1H), 10.30 (s, 1H); HPLC纯度: 99.57%; LCMS: 536 (M^+ + 1)。

[2447] N-(4-(4-(3-氟苄基)哌嗪-1-羰基)-3-甲氧基苯基)喹啉-8-磺酰胺 (XIV-125) :

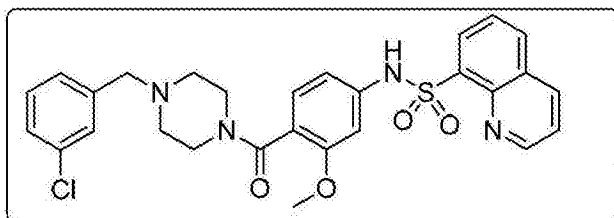
[2448]



[2449] ^1H NMR (400MHz, DMSO- d_6) δ : 2.19 (br s, 2H), 2.25 (br s, 2H), 2.95 (br s, 2H), 3.42 (s, 2H), 3.52 (s, 3H), 6.60 (d, 1H), 6.78 (s, 1H), 6.82 (d, 1H), 7.00–7.16 (m, 3H), 7.30 (q, 1H), 7.64–7.71 (m, 2H), 8.28 (d, 1H), 8.34 (s, 1H), 8.38 (d, 1H), 9.16 (d, 1H), 10.30 (s, 1H); HPLC纯度: 99.82%; LCMS: 535 (M^+ + 1)。

[2450] N-(4-(4-(3-氯苄基)哌嗪-1-羰基)-3-甲氧基苯基)喹啉-8-磺酰胺 (XIV-126) :

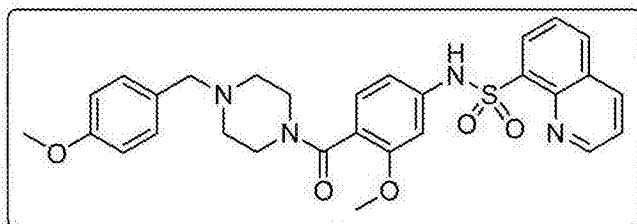
[2451]



[2452] ^1H NMR (400MHz, DMSO- d_6) δ : 2.19 (br s, 2H), 2.25 (br s, 2H), 2.97 (br s, 2H), 3.42 (s, 2H), 3.52 (s, 3H), 6.61 (d, 1H), 6.78 (s, 1H), 6.82 (d, 1H), 7.24 (d, 1H), 7.28–7.37 (m, 2H), 8.28 (d, 1H), 8.39 (s, 1H), 8.50 (d, 1H), 9.16 (d, 1H), 10.30 (s, 1H); HPLC纯度: 99.53%; LCMS: 551 (M^+)。

[2453] N-(3-甲氧基-4-(4-(4-甲氧基苄基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (XIV-127) :

[2454]

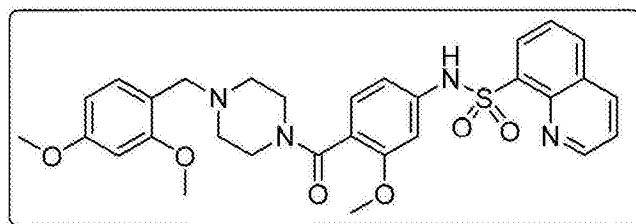


[2455] ^1H NMR (400MHz, DMSO- d_6) δ : 2.19 (br s, 2H), 2.25 (br s, 2H), 2.97 (br s, 2H), 3.31 (br s, 2H), 3.59 (s, 2H), 3.63 (s, 3H), 6.61 (d, 1H), 6.78 (s, 1H), 6.82 (d, 3H), 7.12–

7.21 (m, 2H), 7.62–7.70 (m, 2H), 8.28 (d, 1H), 8.39 (s, 1H), 8.50 (d, 1H), 9.16 (d, 1H), 10.26 (s, 1H); HPLC纯度: 90.80%; LCMS: 546 ($M^+ + 1$)。

[2456] N-(4-(4-(2,4-二甲氧基苄基)哌嗪-1-羰基)-3-甲氧基苯基)喹啉-8-磺酰胺 (XIV-128):

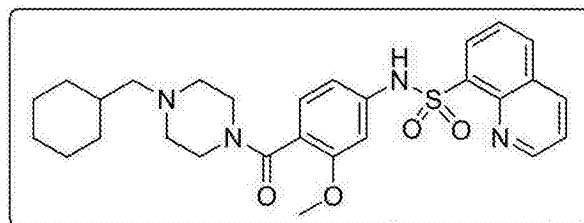
[2457]



[2458] ^1H NMR (400MHz, DMSO- d_6) δ : 2.25 (br s, 2H), 2.97 (br s, 2H), 3.42 (br s, 4H), 3.59 (s, 2H), 3.63 (s, 3H), 3.73 (s, 6H), 6.45 (d, 1H), 6.50 (s, 1H), 6.64 (d, 1H), 6.78 (s, 1H), 6.82 (d, 1H), 7.12 (d, 1H), 7.65–7.72 (m, 2H), 8.28 (d, 1H), 8.40 (s, 1H), 8.50 (d, 1H), 9.16 (d, 1H), 10.26 (s, 1H); HPLC纯度: 99.78%; LCMS: 577 ($M^+ + 1$)。

[2459] N-(4-(4-(环己基甲基)哌嗪-1-羰基)-3-甲氧基苯基)喹啉-8-磺酰胺 (XIV-129):

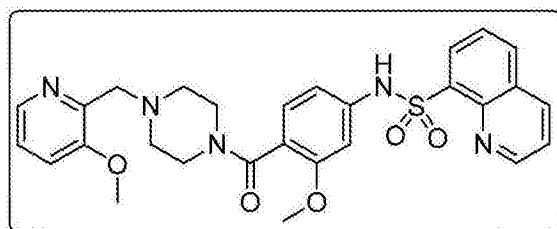
[2460]



[2461] ^1H NMR (400MHz, DMSO- d_6) δ : 0.78 (q, 2H), 1.11 (d, 2H), 1.40 (brs, 1H), 1.54–1.71 (m, 2H), 1.99–2.30 (m, 8H), 2.90 (br s, 4H), 3.45 (d, 1H), 3.59 (s, 3H), 3.70 (s, 1H), 6.61 (d, 1H), 6.76 (s, 1H), 6.82 (d, 3H), 7.62–7.70 (m, 2H), 8.28 (d, 1H), 8.40 (s, 1H), 8.47 (m, 1H), 9.10 (d, 1H), 10.26 (s, 1H); HPLC纯度: 98.50%; LCMS: 546 ($M^+ + 1$)。

[2462] N-(3-甲氧基-4-(4-((3-甲氧基吡啶-2-基)甲基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (XIV-130):

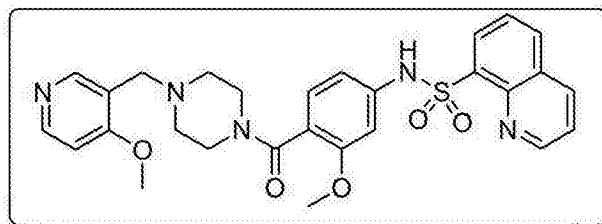
[2463]



[2464] ^1H NMR (400MHz, DMSO- d_6) δ : 2.22 (br s, 2H), 2.38 (br s, 2H), 2.87 (br s, 4H), 3.41 (s, 3H), 3.59 (br s, 5H), 3.73 (s, 2H), 6.76 (s, 1H), 6.82 (d, 1H), 7.21 (s, 1H), 7.40 (d, 1H), 7.62–7.69 (m, 2H), 8.03 (s, 1H), 8.27 (d, 1H), 8.39 (s, 1H), 8.50 (m, 1H), 9.10 (d, 1H), 10.23 (s, 1H); HPLC纯度: 99.86%; LCMS: 548 ($M^+ + 1$)。

[2465] N-(3-甲氧基-4-(4-((4-甲氧基吡啶-3-基)甲基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (XIV-131):

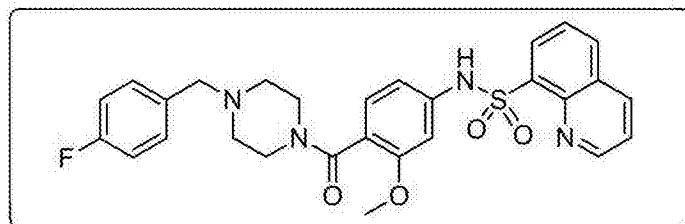
[2466]



[2467] ^1H NMR (400MHz, DMSO- d_6) δ : 2.22 (br s, 2H), 2.38 (br s, 2H), 2.90 (br s, 4H), 3.41 (s, 3H), 3.55 (s, 3H), 3.80 (s, 2H), 6.60 (d, 1H), 6.72 (s, 1H), 6.82 (d, 1H), 7.00 (d, 1H), 7.62–7.69 (m, 2H), 8.29 (s, 2H), 8.35 (d, 1H), 8.39 (s, 1H), 8.50 (m, 1H), 9.10 (d, 1H); HPLC纯度: 92.10%; LCMS: 548 (M^+ 1)。

[2468] N-(4-(4-(4-氟苄基)哌嗪-1-羰基)-3-甲氧基苯基)喹啉-8-磺酰胺 (XIV-132):

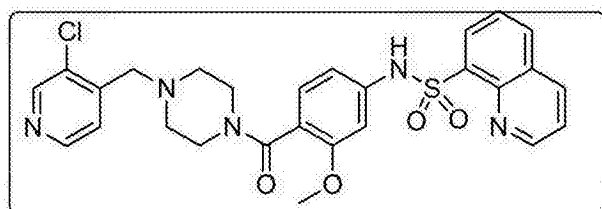
[2469]



[2470] ^1H NMR (400MHz, DMSO- d_6) δ : 2.19 (br s, 2H), 2.25 (br s, 2H), 2.95 (br s, 4H), 3.42 (s, 2H), 3.52 (s, 3H), 6.60 (d, 1H), 6.78 (s, 1H), 6.82 (d, 1H), 7.10 (t, 2H), 7.23 (t, 2H), 7.63–7.71 (m, 2H), 8.25 (d, 1H), 8.40 (d, 1H), 8.48 (d, 1H), 9.16 (d, 1H), 10.30 (s, 1H); HPLC纯度: 99.62%; LCMS: 535 (M^+ 1)。

[2471] N-(4-(4-((3-氯吡啶-4-基)甲基)哌嗪-1-羰基)-3-甲氧基苯基)喹啉-8-磺酰胺 (XIV-133):

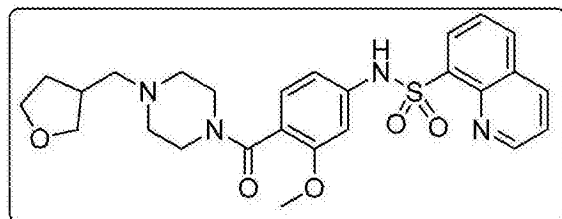
[2472]



[2473] ^1H NMR (400MHz, DMSO- d_6) δ : 2.24 (br s, 2H), 2.25 (br s, 2H), 2.95 (br s, 4H), 3.58 (s, 5H), 6.61 (d, 1H), 6.74 (s, 1H), 6.83 (d, 1H), 7.47 (d, 1H), 7.63–7.72 (m, 2H), 8.23 (d, 1H), 8.39–8.49 (m, 3H), 8.54 (s, 1H), 9.16 (d, 1H), 10.30 (s, 1H); HPLC纯度: 98.63%; LCMS: 552 (M^+)。

[2474] N-(3-甲氧基-4-(4-((四氢呋喃-3-基)甲基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (XIV-134):

[2475]

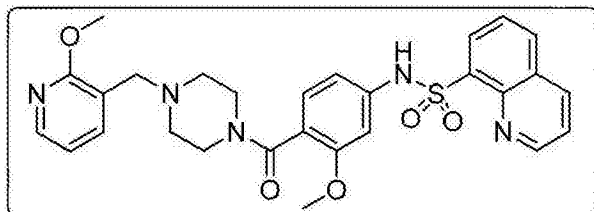


[2476] ^1H NMR (400MHz, DMSO- d_6) δ : 1.42 (m, 2H), 1.83 (m, 2H), 2.19 (d, 2H), 2.24–2.39 (m,

4H), 2.95 (br s, 4H), 3.48 (d, 1H), 3.56 (s, 3H), 3.63 (q, 2H), 6.60 (d, 1H), 6.76 (s, 1H), 6.81 (d, 1H), 7.63–7.70 (m, 2H), 8.24 (d, 1H), 8.40 (d, 1H), 8.50 (d, 1H), 9.10 (d, 1H), 10.26 (s, 1H); HPLC纯度: 98.40%; LCMS: 511 ($M^+ + 1$)。

[2477] N-(3-甲氧基-4-(4-((2-甲氧基吡啶-3-基)甲基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (XIV-135):

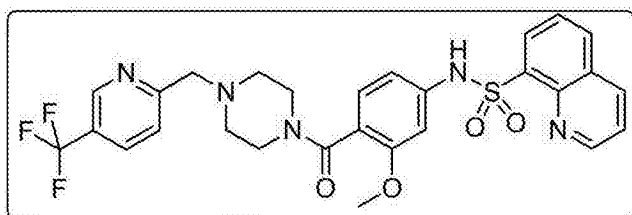
[2478]



[2479] ^1H NMR (400MHz, DMSO- d_6) δ : 2.22 (br s, 2H), 2.38 (br s, 4H), 2.90 (br s, 4H), 3.41 (s, 3H), 3.55 (s, 3H), 3.80 (s, 2H), 6.61 (d, 1H), 6.75 (s, 1H), 6.82 (d, 1H), 6.97 (t, 1H), 7.60–7.73 (m, 3H), 8.02 (s, 1H), 8.27 (d, 1H), 8.39 (s, 1H), 8.50 (m, 1H), 9.10 (d, 1H), 10.28 (s, 1H); HPLC纯度: 99.85%; LCMS: 548 ($M^+ + 1$)。

[2480] N-(3-甲氧基-4-(4-((5-(三氟甲基)吡啶-2-基)甲基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (XIV-136):

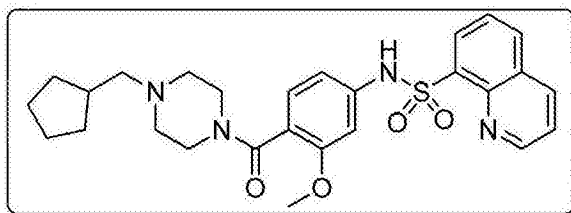
[2481]



[2482] ^1H NMR (400MHz, DMSO- d_6) δ : 2.22 (br s, 2H), 2.38 (br s, 2H), 2.99 (br s, 4H), 3.58 (s, 3H), 3.67 (s, 2H), 6.61 (d, 1H), 6.74 (s, 1H), 6.82 (d, 1H), 7.62–7.73 (m, 3H), 8.19 (d, 1H), 8.26 (d, 1H), 8.4 (d, 1H), 8.50 (m, 1H), 8.82 (s, 1H), 9.10 (d, 1H), 10.30 (s, 1H); HPLC纯度: 94.67%; LCMS: 586 ($M^+ + 1$)。

[2483] N-(4-(4-(环戊基甲基)哌嗪-1-羰基)-3-甲氧基苯基)喹啉-8-磺酰胺 (XIV-137):

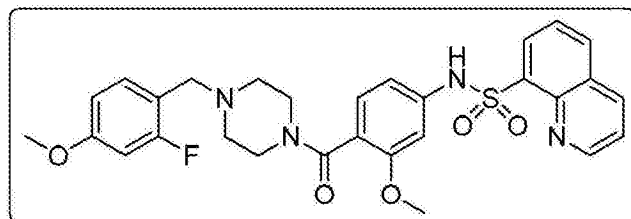
[2484]



[2485] ^1H NMR (400MHz, DMSO- d_6) δ : 1.10 (六重峰, 2H), 1.38–1.50 (m, 3H), 1.55–1.61 (m, 3H), 1.99 (五重峰, 1H), 2.07 (d, 2H), 2.30 (br s, 4H), 2.90 (br s, 4H), 3.59 (s, 3H), 6.60 (d, 1H), 6.72 (s, 1H), 6.82 (d, 1H), 7.62–7.69 (m, 2H), 8.25 (s, 1H), 8.40 (d, 1H), 8.47 (d, 1H), 9.10 (d, 1H), 10.24 (s, 1H); HPLC纯度: 99.86%; LCMS: 509 ($M^+ + 1$)。

[2486] N-(4-(4-(2-氟-4-甲氧基苄基)哌嗪-1-羰基)-3-甲氧基苯基)喹啉-8-磺酰胺 (XIV-138):

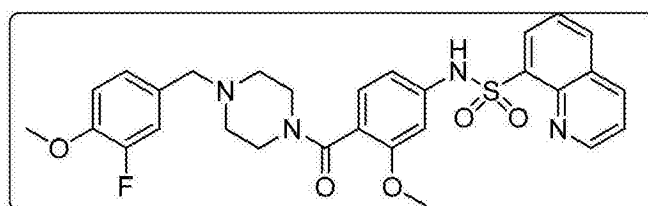
[2487]



[2488] ^1H NMR (400MHz, DMSO- d_6) δ : 2.20 (br s, 2H), 2.35 (br s, 2H), 2.90 (br s, 4H), 3.41 (s, 3H), 3.60 (s, 3H), 3.78 (s, 2H), 6.61 (d, 1H), 6.70–6.80 (m, 2H), 6.84 (d, 1H), 7.22 (t, 1H), 7.70–7.80 (m, 2H), 8.26 (d, 1H), 8.42 (d, 1H), 8.50 (d, 1H), 9.16 (s, 1H), 10.28 (s, 1H); HPLC纯度: 90.48%; LCMS: 565 (M^+ +1)。

[2489] N-(4-(4-(3-氟-4-甲氧基苄基)哌嗪-1-羰基)-3-甲氧基苄基)喹啉-8-磺酰胺 (XIV-139):

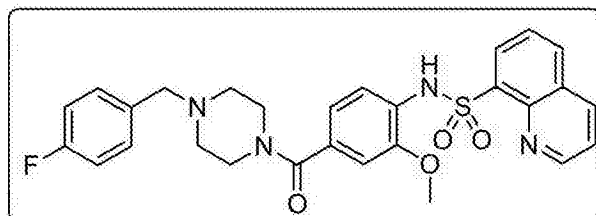
[2490]



[2491] ^1H NMR (400MHz, DMSO- d_6) δ : 2.20 (br s, 2H), 2.35 (br s, 2H), 2.97 (br s, 4H), 3.42 (s, 3H), 3.59 (s, 3H), 3.82 (s, 2H), 6.61 (d, 1H), 6.80 (s, 1H), 6.84 (d, 1H), 7.02–7.18 (m, 3H), 7.70–7.80 (m, 2H), 8.26 (d, 1H), 8.42 (d, 1H), 8.50 (d, 1H), 9.16 (s, 1H), 10.28 (s, 1H); HPLC纯度: 99.65%; LCMS: 565 (M^+ +1)。

[2492] N-(4-(4-(4-氟苄基)哌嗪-1-羰基)-2-甲氧基苄基)喹啉-8-磺酰胺 (XIV-140):

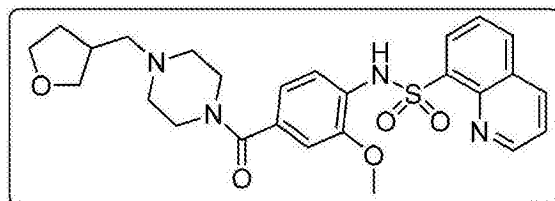
[2493]



[2494] ^1H NMR (400MHz, DMSO- d_6) δ : 2.24 (br s, 4H), 3.20–3.45 (m, 6H), 3.61 (s, 3H), 6.77 (s, 1H), 6.82 (d, 1H), 7.21 (t, 2H), 7.28 (t, 2H), 7.40 (d, 1H), 7.65–7.77 (m, 2H), 8.26 (d, 2H), 8.56 (d, 1H), 9.07 (s, 1H), 9.20 (s, 1H); HPLC纯度: 95.43%; LCMS: 535 (M^+ +1)。

[2495] N-(2-甲氧基-4-(4-((四氢呋喃-3-基)甲基)哌嗪-1-羰基)苄基)喹啉-8-磺酰胺 (XIV-141):

[2496]

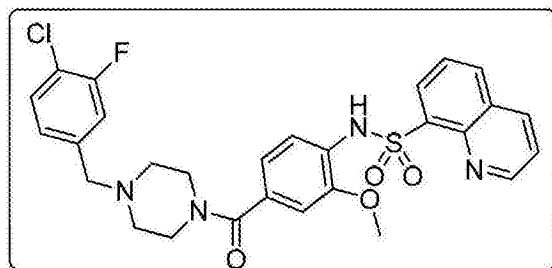


[2497] ^1H NMR (400MHz, DMSO- d_6) δ : 1.45 (m, 2H), 1.86 (m, 2H), 2.20 (d, 2H), 2.24–2.39 (m, 4H), 2.95 (br s, 4H), 3.48 (d, 1H), 3.56 (s, 3H), 3.63 (q, 2H), 6.79 (s, 1H), 6.83 (d, 1H), 7.42 (d, 1H), 7.70–7.80 (m, 2H), 8.42 (d, 2H), 8.59 (d, 1H), 9.04 (br s, 1H), 9.18 (s, 1H); HPLC纯

度:98.88%;LCMS:511 ($M^+ + 1$)。

[2498] N-(4-(4-(4-氯-3-氟苄基)哌嗪-1-羰基)-2-甲氧基苯基)喹啉-8-磺酰胺 (XIV-142):

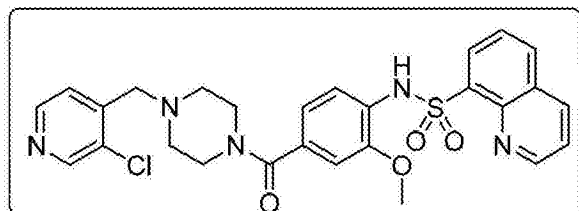
[2499]



[2500] ^1H NMR (400MHz, DMSO- d_6) δ : 2.37 (br s, 4H), 3.36 (s, 4H), 3.42 (s, 3H), 3.56 (s, 2H), 6.78 (s, 1H), 6.84 (d, 1H), 7.18 (s, 1H), 7.31-7.56 (m, 3H), 7.63-7.81 (m, 2H), 8.24-8.30 (m, 2H), 8.57 (d, 1H), 9.08 (s, 1H), 9.19 (d, 1H); HPLC纯度:97.47%;LCMS:569 (M^+)。

[2501] N-(4-(4-((3-氯吡啶-4-基)甲基)哌嗪-1-羰基)-2-甲氧基苯基)喹啉-8-磺酰胺 (XIV-143):

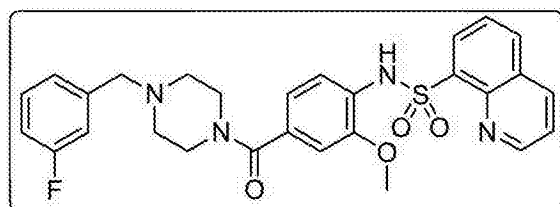
[2502]



[2503] ^1H NMR (400MHz, DMSO- d_6) δ : 2.41 (br s, 4H), 3.36 (s, 4H), 3.44 (s, 3H), 3.60 (s, 2H), 6.78 (s, 1H), 6.82 (d, 1H), 7.41-7.51 (m, 2H), 7.65-7.80 (m, 2H), 8.22-8.30 (m, 2H), 8.42-8.58 (m, 3H), 9.08 (s, 1H), 9.18 (d, 1H); HPLC纯度:99.17%;LCMS:552 (M^+)。

[2504] N-(4-(4-(3-氟苄基)哌嗪-1-羰基)-2-甲氧基苯基)喹啉-8-磺酰胺 (XIV-144):

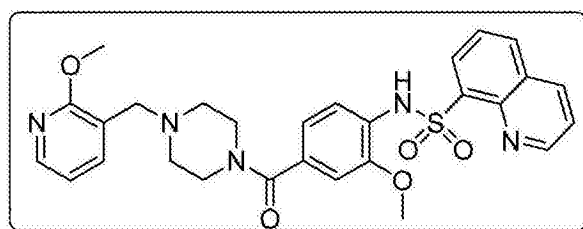
[2505]



[2506] ^1H NMR (400MHz, DMSO- d_6) δ : 2.37 (br s, 4H), 3.36 (s, 4H), 3.42 (s, 3H), 3.56 (s, 2H), 6.78 (s, 1H), 6.84 (d, 1H), 7.18 (s, 1H), 7.31-7.56 (m, 3H), 7.63-7.81 (m, 2H), 8.24-8.30 (m, 2H), 8.57 (d, 1H), 9.08 (s, 1H), 9.19 (d, 1H); HPLC纯度:97.47%;LCMS:535 (M^+)。

[2507] N-(2-甲氧基-4-(4-((2-甲氧基吡啶-3-基)甲基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (XIV-145):

[2508]

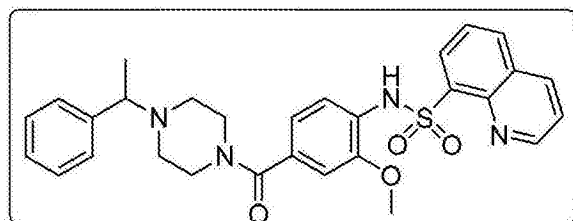


[2509] ^1H NMR (400MHz, DMSO- d_6) δ : 2.37 (br s, 4H), 3.36 (s, 4H), 3.41 (s, 3H), 3.46 (s,

2H), 3.81 (s, 3H), 6.78 (s, 1H), 6.81 (d, 1H), 6.97-7.01 (m, 1H), 7.41 (d, 1H), 7.62-7.78 (m, 3H), 8.01 (d, 1H), 8.21-8.30 (m, 2H), 8.57 (d, 1H), 9.08 (s, 1H), 9.19 (d, 1H); HPLC纯度: 99.95%; LCMS: 548 (M^+)。

[2510] N-(2-甲氧基-4-(4-(1-苯基乙基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (XIV-146):

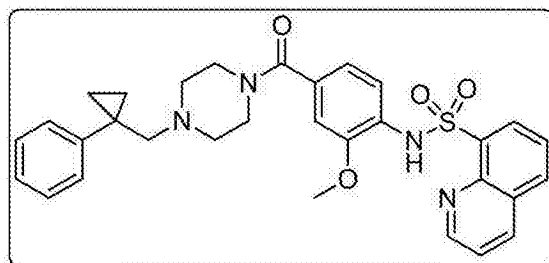
[2511]



[2512] ^1H NMR (400MHz, DMSO- d_6) δ : 1.21 (d, 3H), 2.37 (br s, 4H), 3.36-3.41 (m, 8H), 6.71 (s, 1H), 6.78 (d, 1H), 7.11-7.29 (m, 5H), 7.36 (d, 1H), 7.60-7.76 (m, 2H), 8.21-8.30 (m, 2H), 8.48 (d, 1H), 9.01 (s, 1H), 9.12 (s, 1H); HPLC纯度: 95.62%; LCMS: 531 (M^+ +1)。

[2513] N-(2-甲氧基-4-(4-((1-苯基环丙基)甲基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (XIV-147):

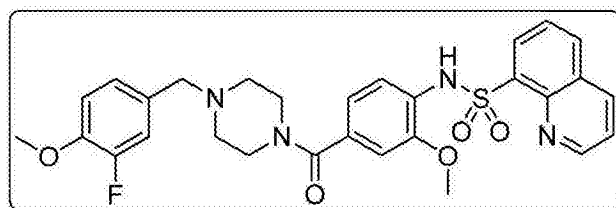
[2514]



[2515] ^1H NMR (400MHz, DMSO- d_6) δ : 0.06 (s, 2H), 0.08 (s, 2H), 2.37 (br s, 4H), 3.16 (s, 4H), 3.41 (br s, 5H), 6.78 (s, 1H), 6.81 (s, 1H), 7.12 (s, 2H), 7.19-7.26 (m, 4H), 7.42 (d, 1H), 7.65-7.80 (m, 2H), 8.25-8.31 (m, 2H), 8.58 (d, 1H), 9.10 (s, 1H), 9.19 (s, 1H); HPLC纯度: 99.97%; LCMS: 557 (M^+ +1)。

[2516] N-(4-(4-(3-氟-4-甲氧基苄基)哌嗪-1-羰基)-2-甲氧基苄基)喹啉-8-磺酰胺 (XIV-148):

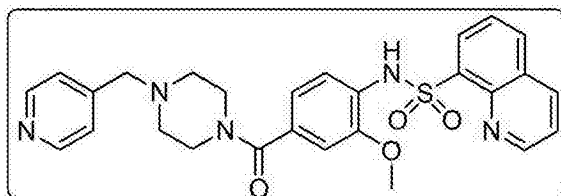
[2517]



[2518] ^1H NMR (400MHz, DMSO- d_6) δ : 2.31 (br s, 4H), 3.32 (s, 4H), 3.41 (s, 2H), 3.43 (s, 3H), 3.80 (s, 3H), 6.78 (s, 1H), 6.82 (d, 1H), 6.98-7.18 (m, 3H), 7.21 (d, 1H), 7.31 (s, 2H), 7.64-7.80 (m, 2H), 8.21-8.30 (m, 2H), 8.57 (d, 1H), 9.08 (s, 1H), 9.19 (s, 1H); HPLC纯度: 92.22%; LCMS: 565 (M^+ +1)。

[2519] N-(2-甲氧基-4-(4-(吡啶-4-基甲基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (XIV-149):

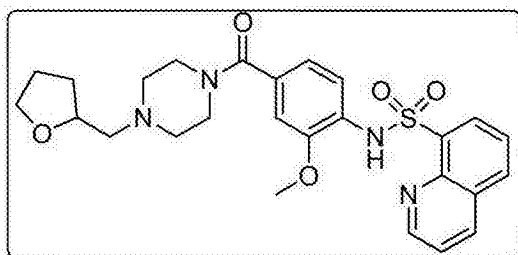
[2520]



[2521] ^1H NMR (400MHz, DMSO- d_6) δ : 2.32 (br s, 4H), 3.41 (s, 3H), 3.50 (s, 4H), 3.62 (s, 2H), 6.75 (s, 1H), 6.82 (d, 1H), 7.28 (d, 2H), 7.41 (d, 1H), 7.66–7.80 (d, 2H), 8.30 (s, 2H), 8.50 (d, 2H), 8.59 (d, 1H), 9.18 (s, 1H); HPLC纯度: 97.52%; LCMS: 518 (M^+ +1)。

[2522] N-(2-甲氧基-4-(4-((四氢呋喃-2-基)甲基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (XIV-150):

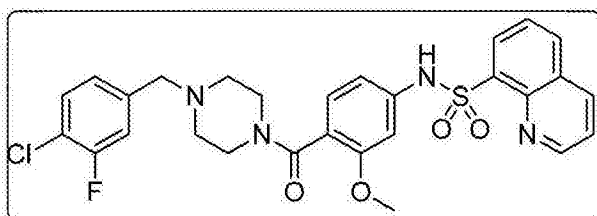
[2523]



[2524] ^1H NMR (400MHz, DMSO- d_6) δ : 1.45 (五重峰, 2H), 1.78 (五重峰, 2H), 1.90 (六重峰, 1H), 2.30–2.41 (m, 7H), 3.41 (s, 3H), 3.60 (q, 2H), 3.70 (q, 2H), 3.95 (五重峰, 1H), 6.78 (s, 1H), 6.82 (d, 1H), 7.42 (d, 1H), 7.70–7.81 (m, 2H), 8.30 (d, 1H), 8.60 (d, 1H), 9.10 (s, 1H), 9.20 (s, 1H); HPLC纯度: 99.24%; LCMS: 511 (M^+ +1)。

[2525] N-(4-(4-(4-氯-3-氟苄基)哌嗪-1-羰基)-3-甲氧基苯基)喹啉-8-磺酰胺 (XIV-151):

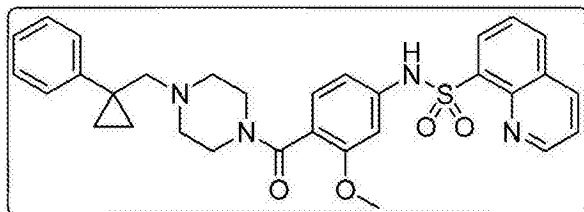
[2526]



[2527] ^1H NMR (400MHz, DMSO- d_6) δ : 2.19 (br s, 2H), 2.28 (br s, 2H), 2.97 (br s, 4H), 3.44 (s, 3H), 3.58 (s, 2H), 6.61 (d, 1H), 6.78 (s, 1H), 6.83 (d, 1H), 7.15 (1H), 7.30 (d, 1H), 7.49 (d, 1H), 7.70–7.78 (m, 2H), 8.24 (d, 1H), 8.42 (d, 1H), 8.50 (d, 1H), 9.10 (s, 1H), 10.30 (s, 1H); HPLC纯度: 98.63%; LCMS: 569 (M^+)。

[2528] N-(3-甲氧基-4-(4-((1-苯基环丙基)甲基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (XIV-152):

[2529]

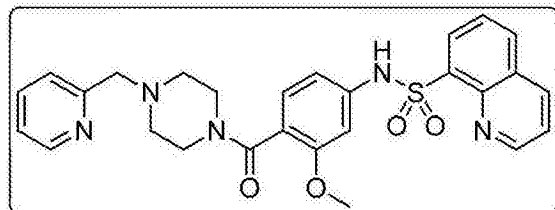


[2530] ^1H NMR (400MHz, DMSO- d_6) δ : 0.64 (s, 2H), 0.78 (s, 2H), 2.18 (br s, 4H), 2.39 (s,

2H), 2.81 (br s, 4H), 3.41 (s, 3H), 6.61 (d, 1H), 6.78 (s, 1H), 6.82 (d, 1H), 7.10 (q, 1H), 7.12 (t, 1H), 7.20–7.28 (m, 4H), 7.70–7.80 (m, 2H), 8.23 (d, 1H), 8.41 (d, 1H), 8.50 (d, 1H), 9.13 (s, 1H), 10.30 (s, 1H); HPLC纯度: 99.99%; LCMS: 557 (M^+ +1)。

[2531] N-(3-甲氧基-4-(4-(吡啶-2-基甲基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (XIV-153):

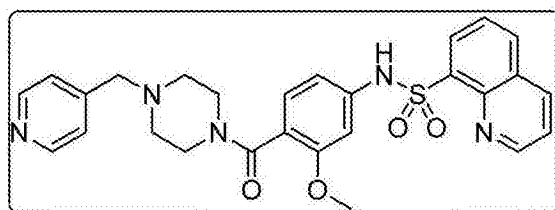
[2532]



[2533] ^1H NMR (400MHz, DMSO- d_6) δ : 2.22 (br s, 2H), 2.39 (br s, 2H), 2.98 (br s, 2H), 3.57 (br s, 2H), 3.60 (s, 5H), 6.62 (d, 1H), 6.78 (s, 1H), 6.82 (d, 1H), 7.20 (s, 1H), 7.40 (d, 1H), 7.66–7.79 (m, 3H), 8.21–8.30 (m, 2H), 8.40–8.50 (m, 2H), 9.16 (s, 1H), 10.30 (s, 1H); HPLC纯度: 98.14%; LCMS: 518 (M^+ +1)。

[2534] N-(3-甲氧基-4-(4-(吡啶-4-基甲基)哌嗪-1-羰基)苯基)喹啉-8-磺酰胺 (XIV-154):

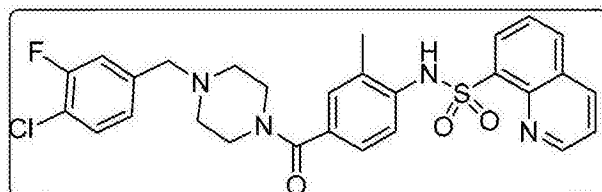
[2535]



[2536] ^1H NMR (400MHz, DMSO- d_6) δ : 2.20 (br s, 2H), 2.30 (br s, 2H), 2.98 (br s, 4H), 3.50 (s, 3H), 3.58 (s, 2H), 6.62 (d, 1H), 6.78 (s, 1H), 6.82 (d, 1H), 7.24 (s, 2H), 7.65–7.73 (m, 2H), 8.21–8.30 (m, 2H), 8.40 (d, 1H), 8.43–8.50 (m, 2H), 9.10 (s, 1H), 10.23 (br s, 1H); HPLC纯度: 99.69%; LCMS: 518 (M^+ +1)。

[2537] N-(4-(4-(4-氯-3-氟苄基)哌嗪-1-羰基)-2-甲基苯基)喹啉-8-磺酰胺 (XIV-155):

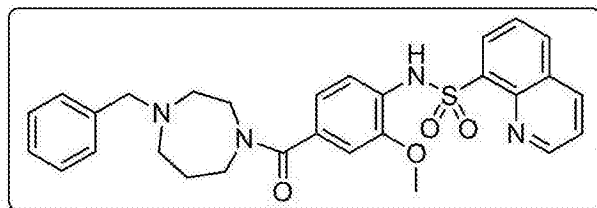
[2538]



[2539] ^1H NMR (400MHz, DMSO- d_6) δ : 2.01 (s, 3H), 2.38 (br s, 4H), 3.50 (s, 4H), 3.56 (s, 2H), 7.00 (s, 2H), 7.06 (s, 1H), 7.18 (d, 1H), 7.35 (d, 1H), 7.52 (t, 1H), 7.70–7.80 (m, 2H), 8.29 (q, 2H), 8.59 (d, 1H), 9.15 (s, 1H), 9.38 (s, 1H); HPLC纯度: 99.25%; LCMS: 553 (M^+)。

[2540] N-(4-(4-苄基-1,4-二氮杂环庚烷-1-羰基)-2-甲氧基苯基)喹啉-8-磺酰胺 (XIV-156):

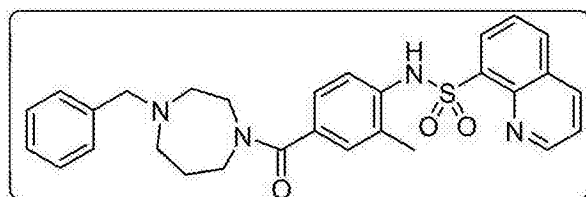
[2541]



[2542] ^1H NMR (400MHz, DMSO- d_6) δ : 2.22 (br s, 2H), 3.01 (br s, 2H), 3.52-3.58 (m, 9H), 4.39 (br s, 2H), 6.66 (d, 1H), 6.80 (s, 1H), 7.50 (br s, 4H), 7.74-7.79 (m, 2H), 8.30 (d, 1H), 8.47 (d, 2H), 8.59 (d, 1H), 9.18 (d, 1H), 10.40 (s, 1H); HPLC纯度: 99.00%; LCMS: 531 (M^+ +1)。

[2543] N-(4-(4-苄基-1,4-二氮杂环庚烷-1-羰基)-2-甲基苯基)喹啉-8-磺酰胺 (XIV-157):

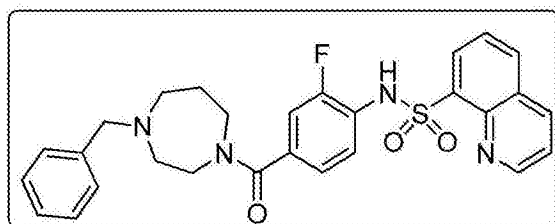
[2544]



[2545] ^1H NMR (400MHz, CD_3OD) δ : 2.06 (s, 3H), 2.14 (br s, 2H), 2.22 (s, 4H), 3.58 (br s, 4H), 4.40 (s, 2H), 7.10 (br s, 1H), 7.22 (d, 2H), 7.50 (s, 4H), 7.68-7.77 (m, 2H), 8.21 (d, 1H), 8.38 (d, 1H), 8.51 (d, 1H), 9.18 (d, 1H); HPLC纯度: 99.04%; LCMS: 515 (M^+ +1)。

[2546] N-(4-(4-苄基-1,4-二氮杂环庚烷-1-羰基)-2-氟苯基)喹啉-8-磺酰胺 (XIV-158):

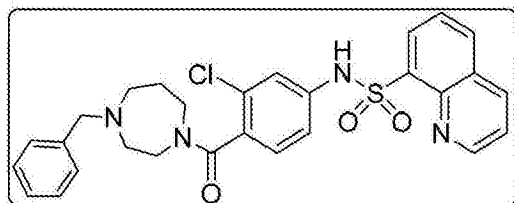
[2547]



[2548] ^1H NMR (400MHz, CDCl_3) δ : 2.21 (br s, 6H), 3.43 (br s, 4H), 4.21 (s, 2H), 6.97 (d, 1H), 7.08 (br s, 1H), 7.42 (t, 4H), 7.63-7.68 (m, 2H), 7.79 (t, 1H), 8.09 (d, 1H), 8.28 (d, 1H), 8.38 (d, 1H), 9.18 (d, 1H); HPLC纯度: 96.67%; LCMS: 519 (M^+ +1)。

[2549] N-(4-(4-苄基-1,4-二氮杂环庚烷-1-羰基)-3-氯苯基)喹啉-8-磺酰胺 (XIV-159):

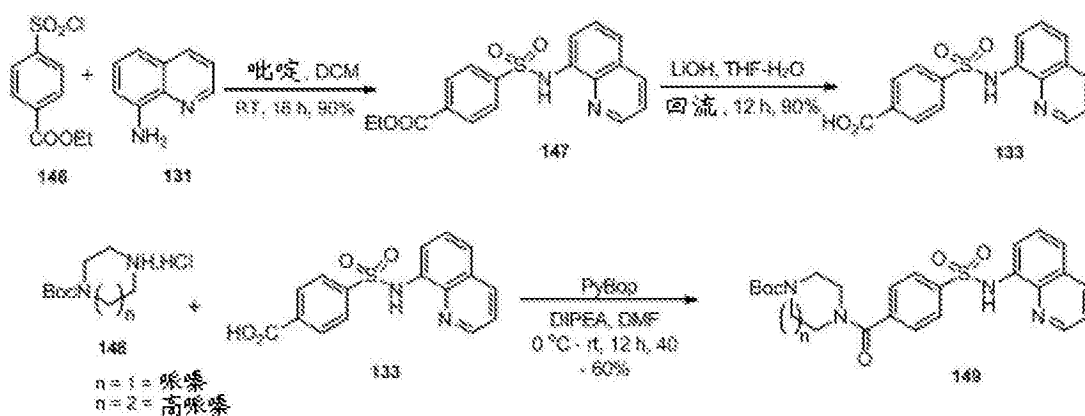
[2550]



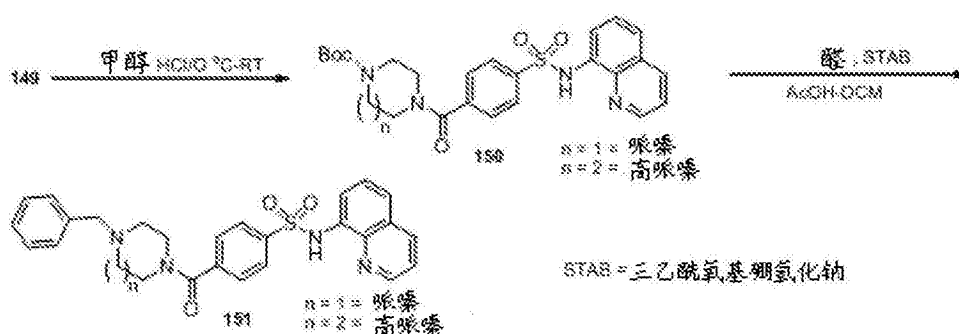
[2551] ^1H NMR (400MHz, CDCl_3) δ : 2.12 (br s, 1H), 2.50 (br s, 1H), 3.09 (br s, 2H), 3.29 (br s, 1H), 3.58 (br s, 2H), 3.67 (br s, 2H), 4.20 (s, 2H), 4.41 (br s, 1H), 6.99 (d, 2H), 7.28-7.39 (m, 4H), 7.66 (t, 2H), 8.21 (d, 1H), 8.38 (d, 1H), 8.42 (d, 1H), 9.18 (s, 1H); HPLC纯度: 95.33%; LCMS: 535 (M^+)。

[2552] 反磺酰胺苄基和烷基衍生物的合成

[2553] 流程23



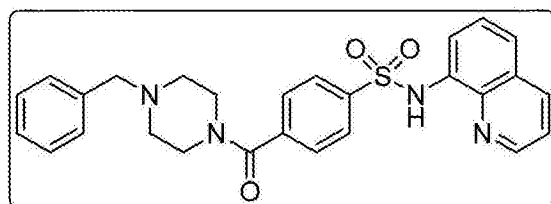
[2554]



[2555] 通过按照具有各自关键步骤与流程21中对于式(VIII)化合物提及的程序类似的程序(具有相应的关键步骤例如酯水解、在三乙酰氧基硼氢化钠的存在下还原胺化之后在PyBop的存在下酰胺键形成),由苯胺131(0.25mmol)进行化合物151的合成。

[2556] 4-(4-苄基哌嗪-1-羰基)-N-(喹啉-8-基)苯磺酰胺(151a):

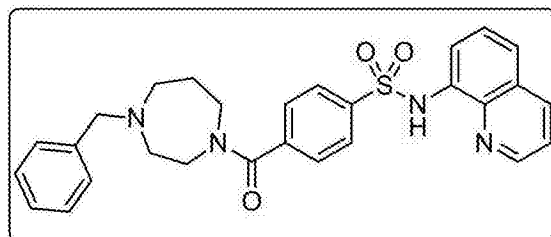
[2557]



[2558] ^1H NMR (400MHz, DMSO- d_6) δ : 2.24 (br s, 2H), 2.40 (br s, 2H), 3.10 (br s, 2H), 3.55 (s, 2H), 3.59 (s, 2H), 7.21-7.39 (m, 4H), 7.42 (d, 2H), 7.58 (d, 2H), 7.91 (d, 2H), 8.37 (d, 1H), 8.81 (s, 1H), 10.15 (br s, 1H); HPLC: 99.26%; LCMS: 487 (M^+ +1)。

[2559] 4-(4-苄基-1,4-二氮杂环庚烷-1-羰基)-N-(喹啉-8-基)苯磺酰胺(151b):

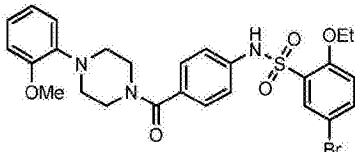
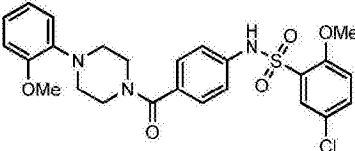
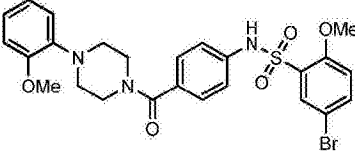
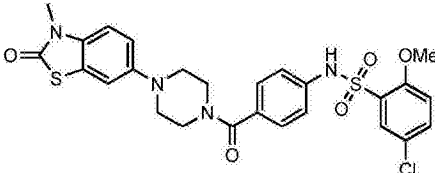
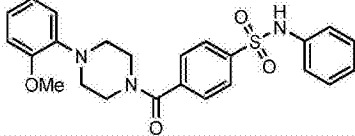
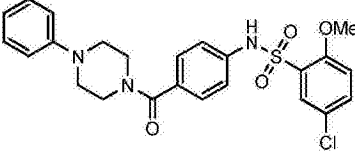
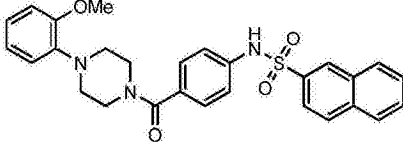
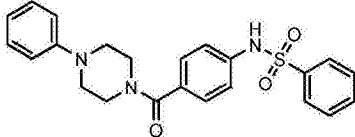
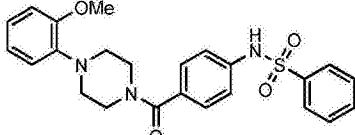
[2560]

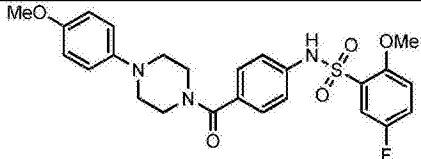
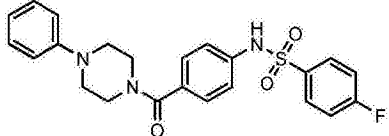
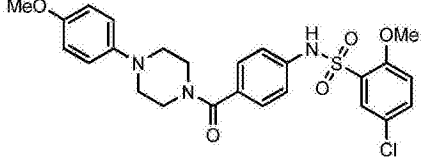
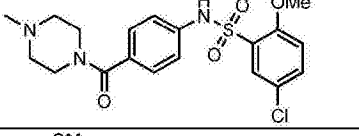
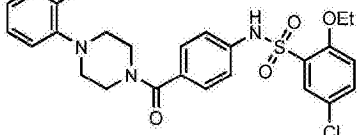
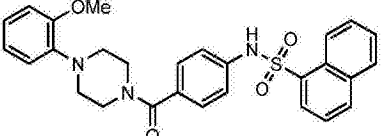
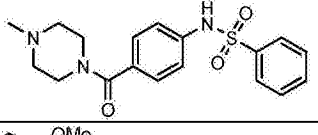
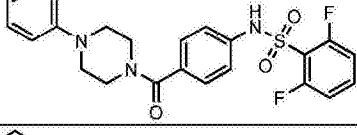
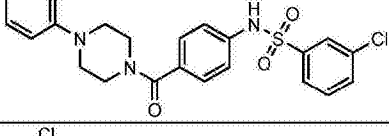
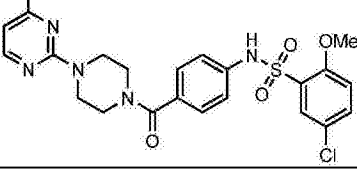


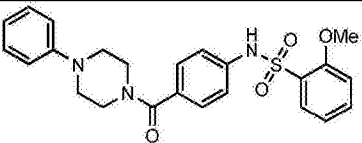
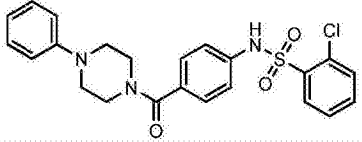
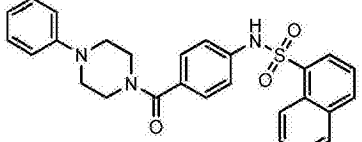
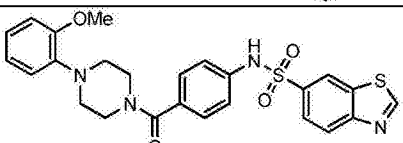
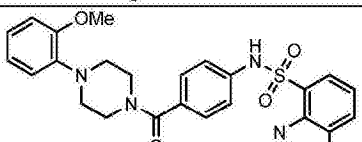
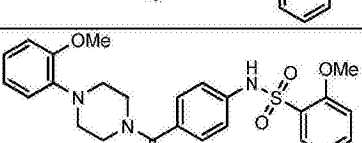
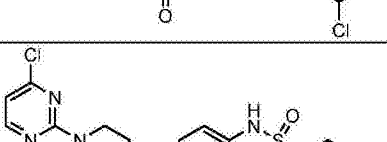
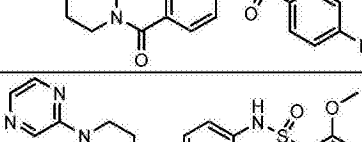
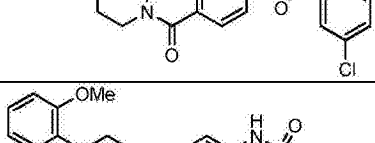
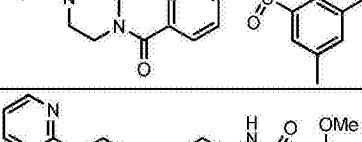
[2561] ^1H NMR (400MHz, DMSO- d_6) δ : 1.55 (s, 1H), 1.75 (s, 1H), 2.41 (s, 2H), 2.52-2.64 (m,

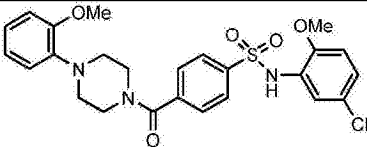
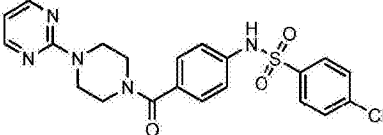
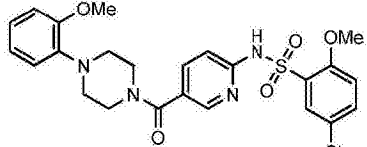
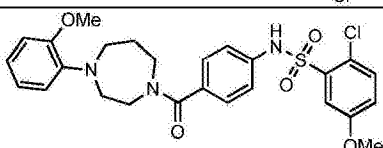
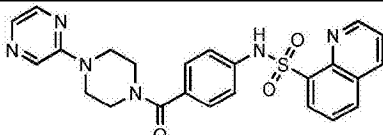
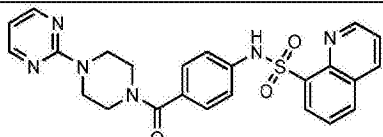
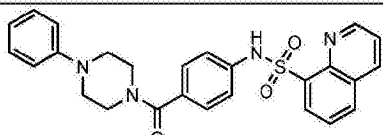
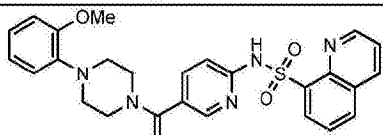
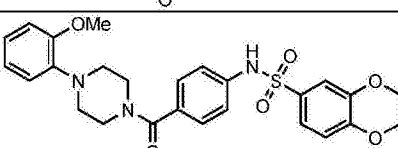
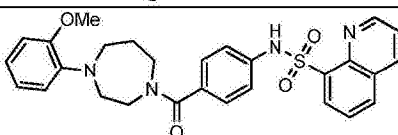
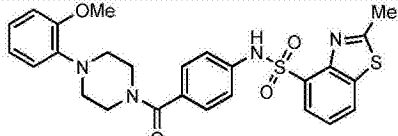
2H), 3.05 (d, 2H), 3.58-3.62 (m, 4H), 7.19-7.32 (m, 3H), 7.36-7.47 (m, 2H), 7.58 (d, 1H), 7.63-7.77 (m, 2H), 7.81-7.89 (m, 2H), 8.30 (dd, 1H), 8.78 (dd, 1H), 10.05 (s, 1H); HPLC纯度: 99.89%; LCMS: 501 (M^+1)。

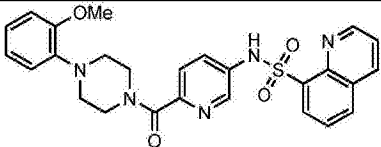
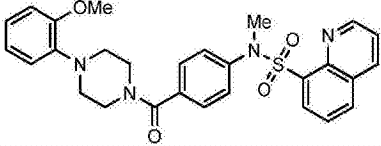
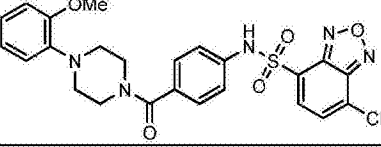
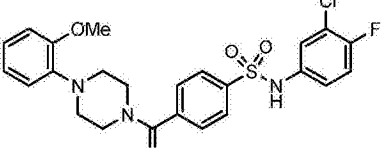
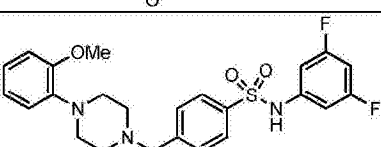
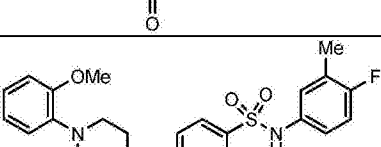
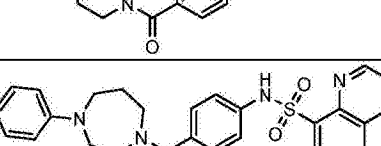
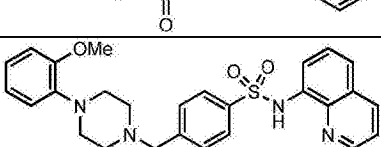
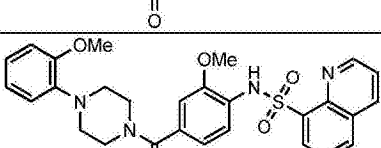
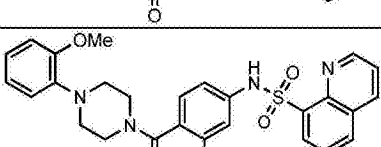
[2562] 尽管已经描述了本发明的一些实施方案的一些方面, 不过应理解, 本领域技术人员将容易想到各种变更、修饰和改进。此类变更、修饰和改进旨在为本公开内容的一部分, 并且旨在本发明的精神和范围之内。因此, 上文的描述和附图仅仅用于举例。

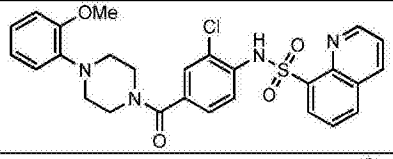
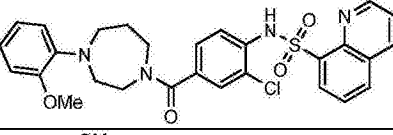
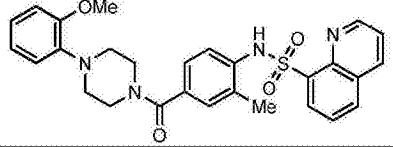
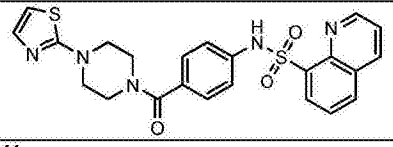
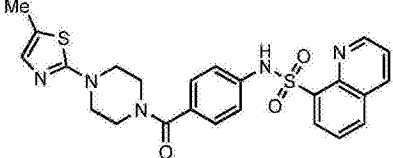
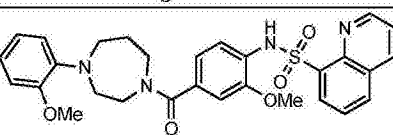
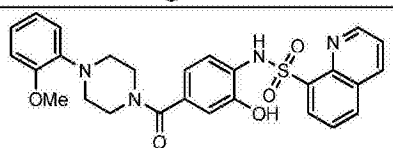
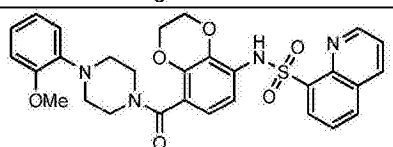
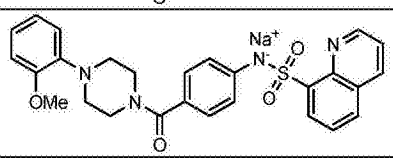
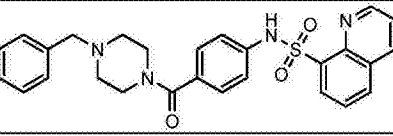
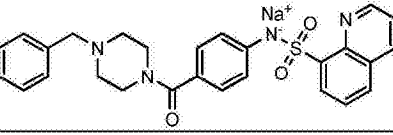
化合物	AC ₅₀
	C
	B
	B
	C
	C
	A
	C
	C
	B

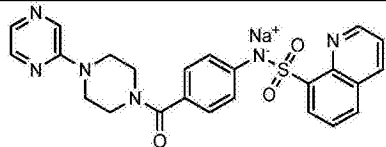
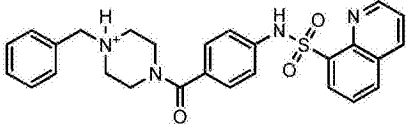
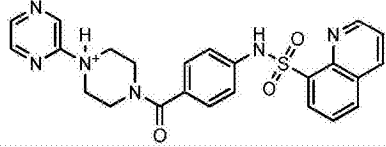
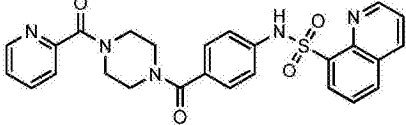
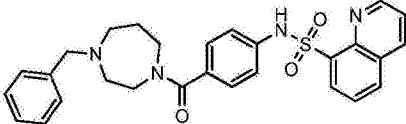
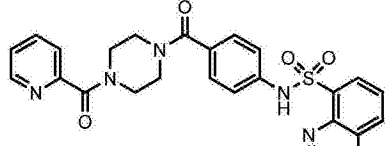
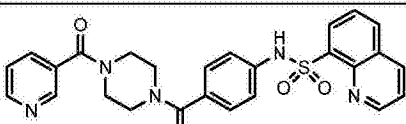
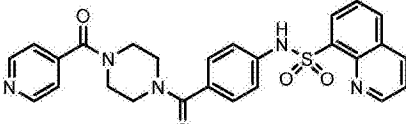
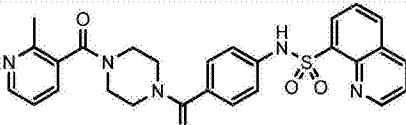
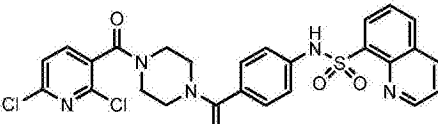
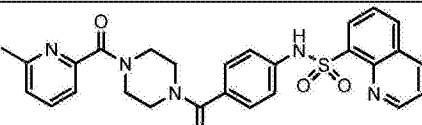
化合物	AC ₅₀
	B
	C
	B
	B
	B
	A
	C
	C
	C
	C

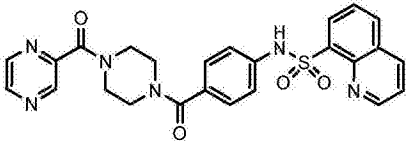
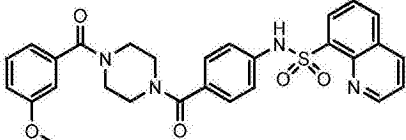
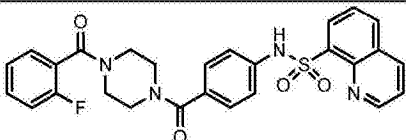
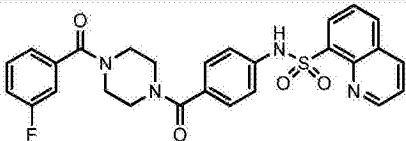
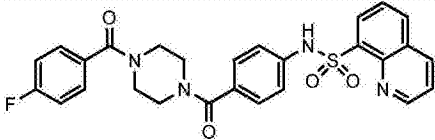
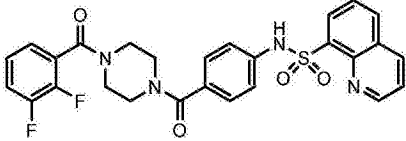
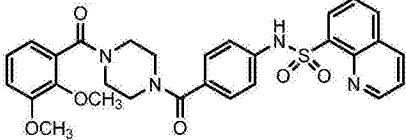
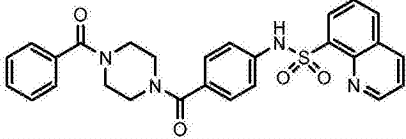
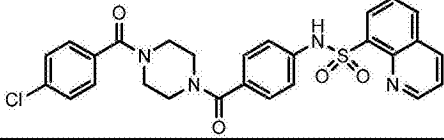
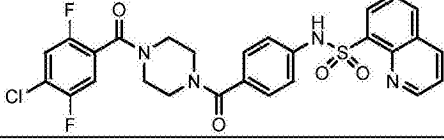
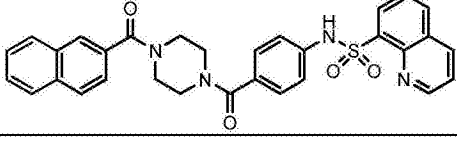
化合物	AC ₅₀
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	C
	B
	C
	A
	B
	C
	C
	A
	C

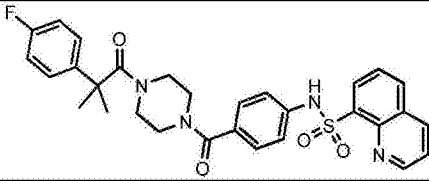
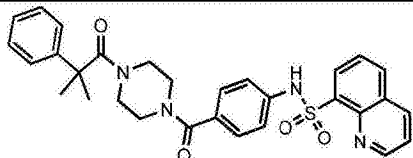
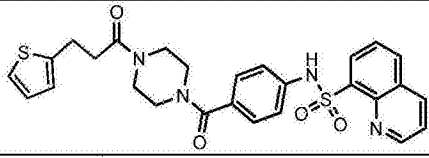
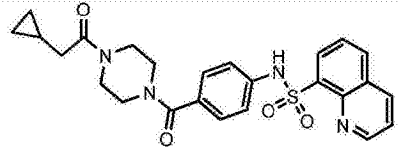
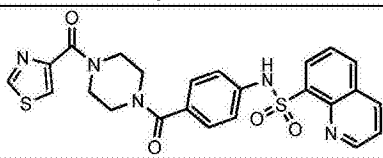
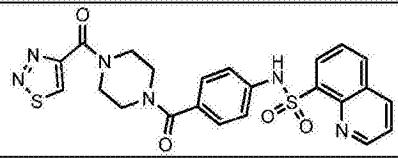
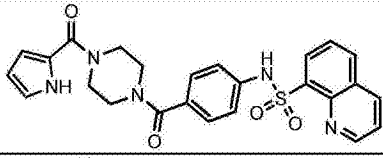
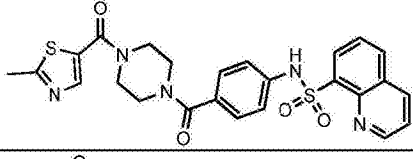
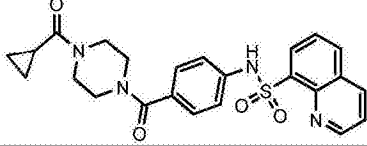
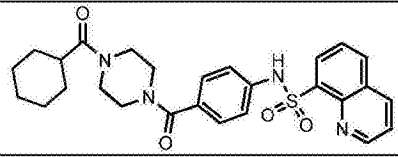
化合物	AC ₅₀
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	C
	C
	B
	B
	C
	A
	C
	C
	A
	C

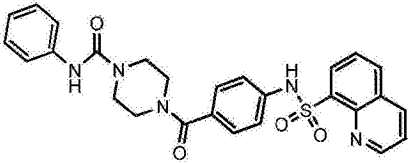
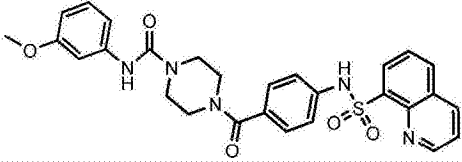
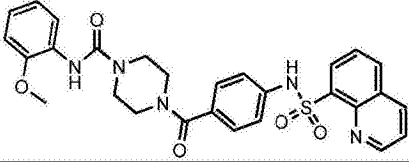
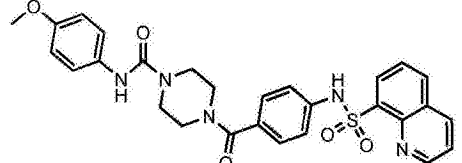
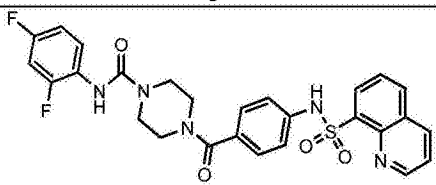
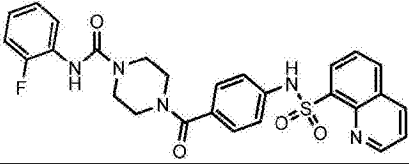
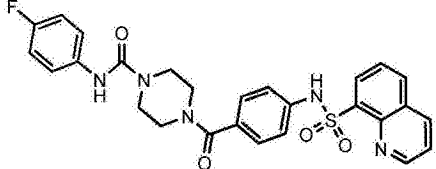
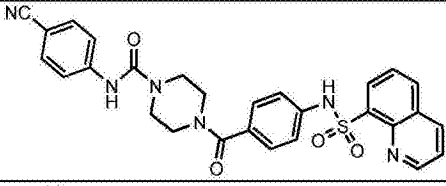
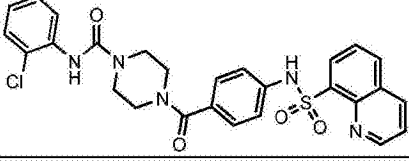
化合物	AC ₅₀
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	C
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	C
	C
	B
	C
	B
	B

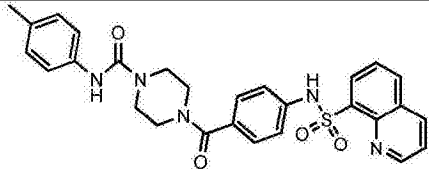
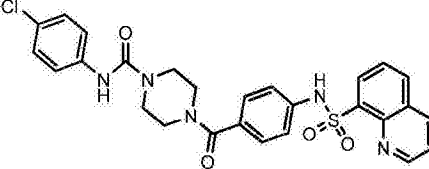
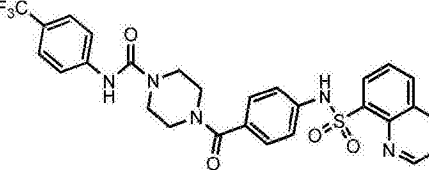
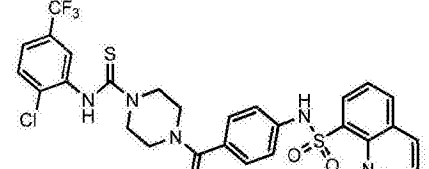
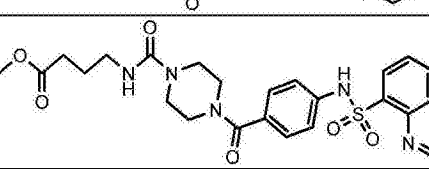
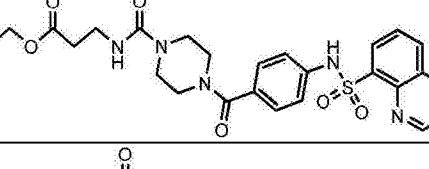
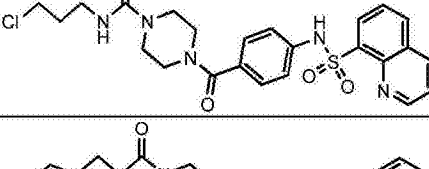
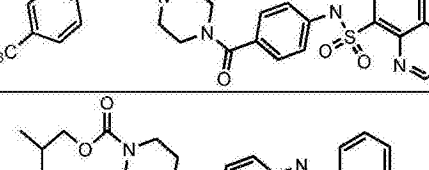
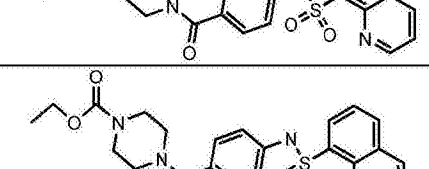
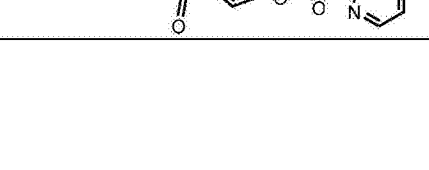
化合物	AC ₅₀
	B
	A
	A
	B
	B
	A
	A
	C
	A
	A
	A

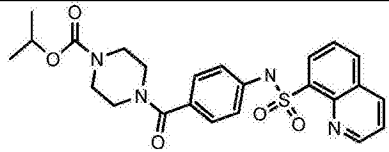
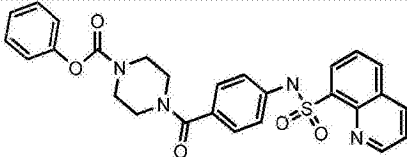
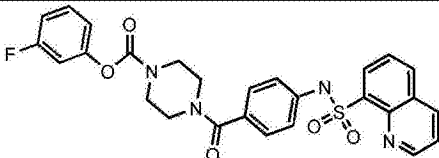
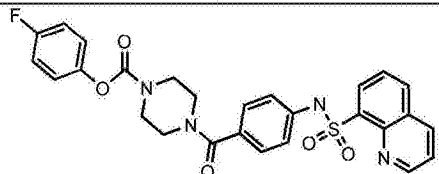
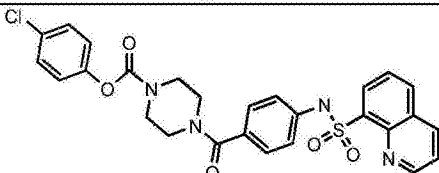
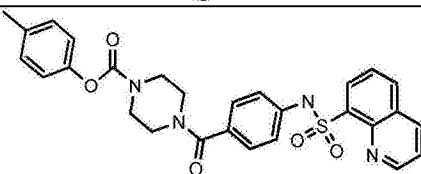
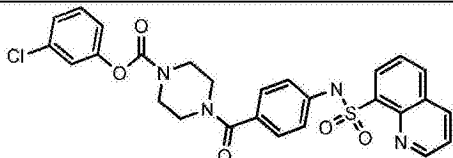
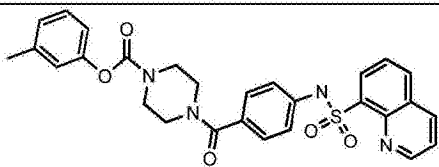
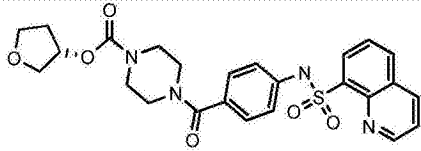
化合物	AC ₅₀
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	B
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	A
	A
	B
	B
	B

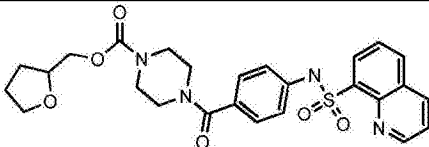
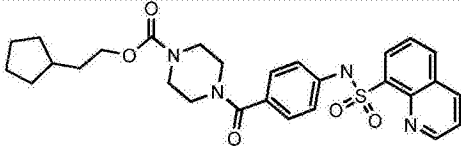
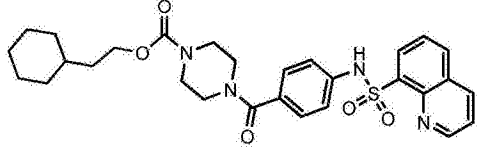
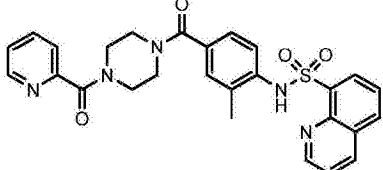
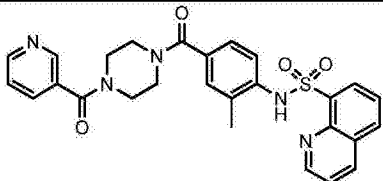
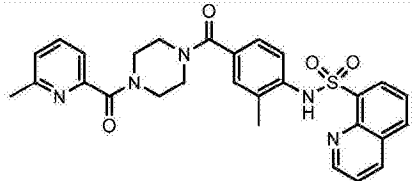
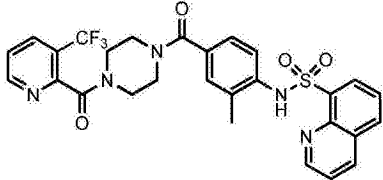
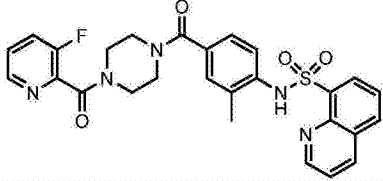
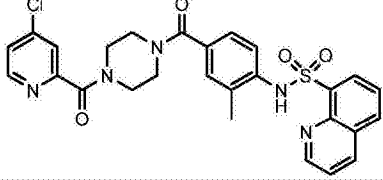
化合物	AC ₅₀
	B
	A
	A
	A
	A
	A
	A
	A
	B
	E
	B

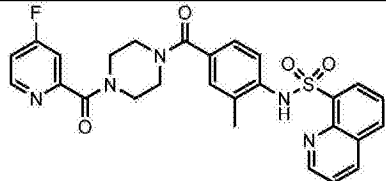
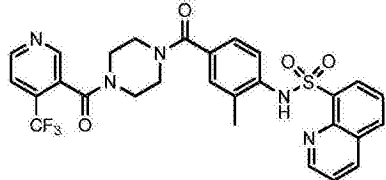
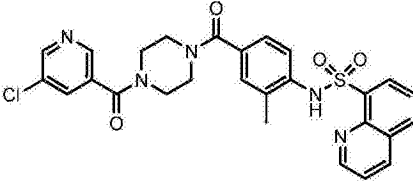
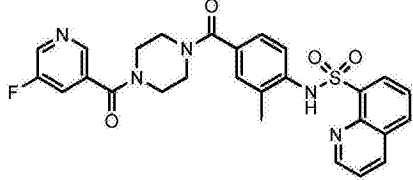
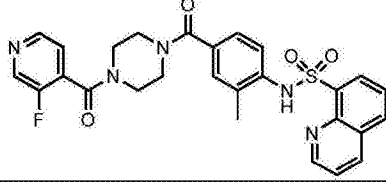
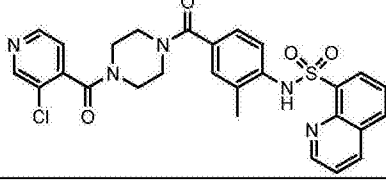
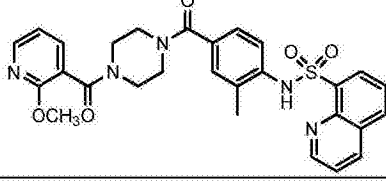
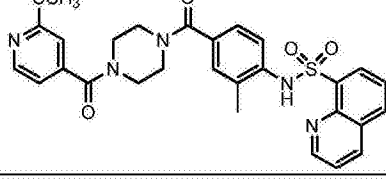
化合物	AC ₅₀
	A
	A
	A
	B
	A
	A
	A
	A
	B
	A

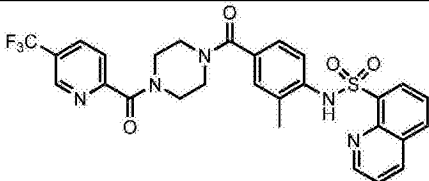
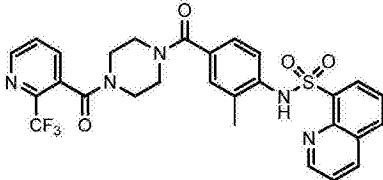
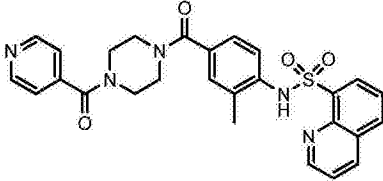
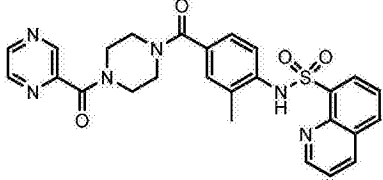
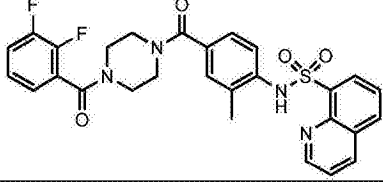
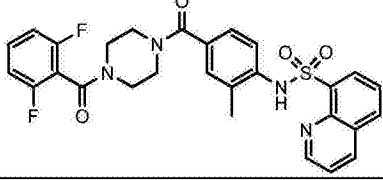
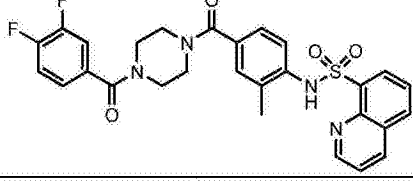
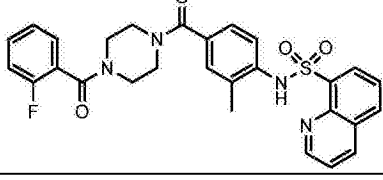
化合物	AC ₅₀
	E
	E
	D
	E
	D
	C
	E
	E
	D

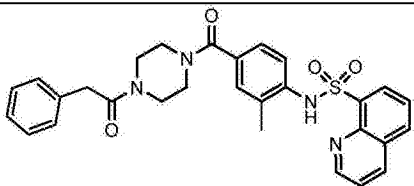
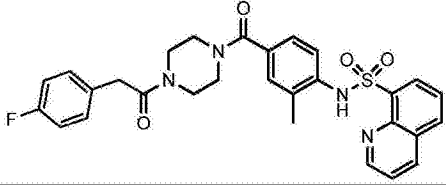
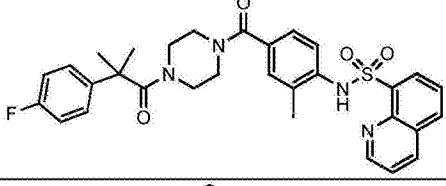
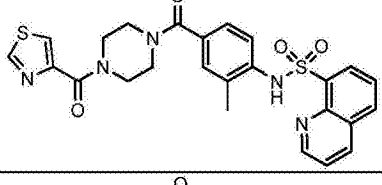
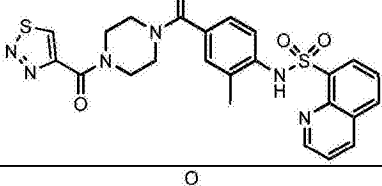
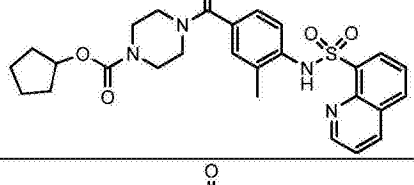
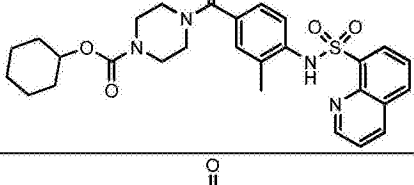
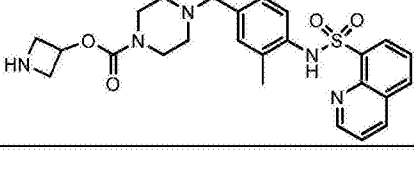
化合物	AC ₅₀
	E
	E
	E
	A
	D
	D
	B
	B
	A
	B

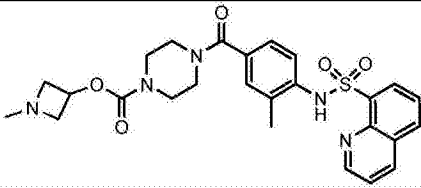
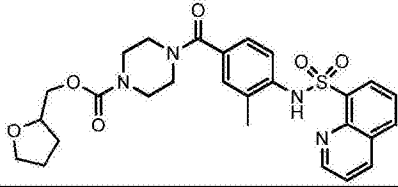
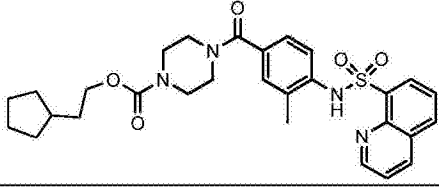
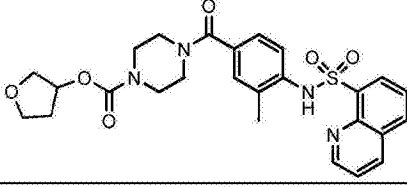
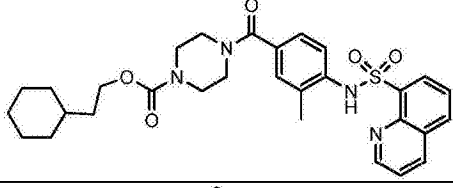
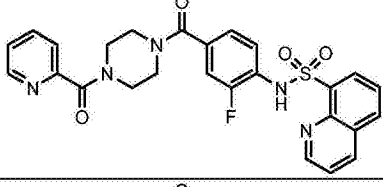
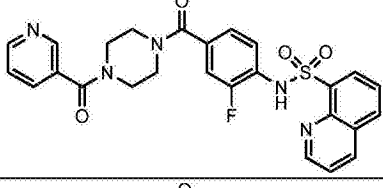
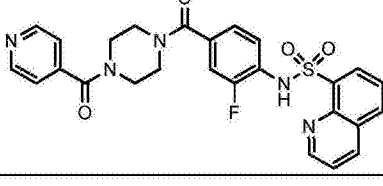
化合物	AC ₅₀
	A
	C
	C
	D
	B
	E
	E
	D
	C

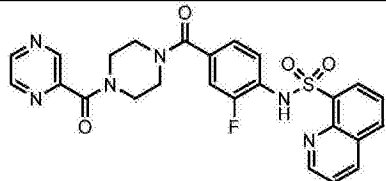
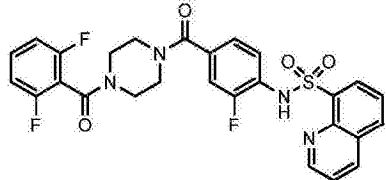
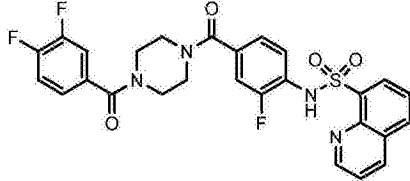
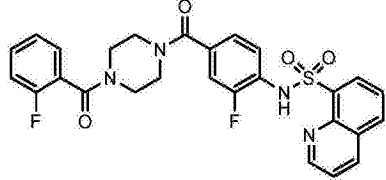
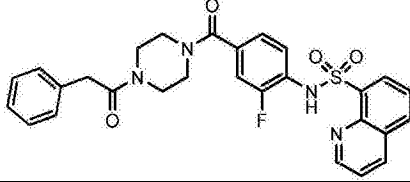
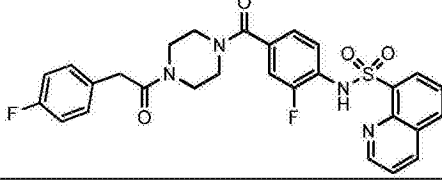
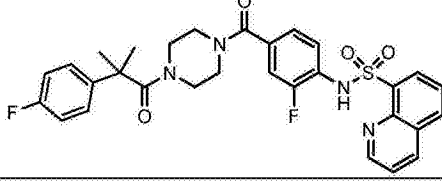
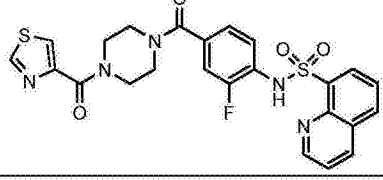
化合物	AC ₅₀
	B
	A
	B
	A
	A
	A
	A
	A
	E

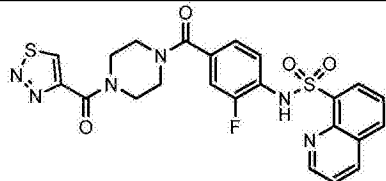
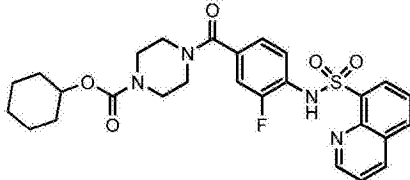
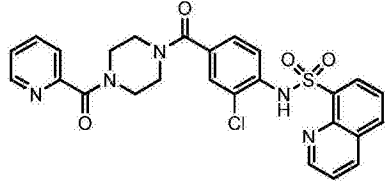
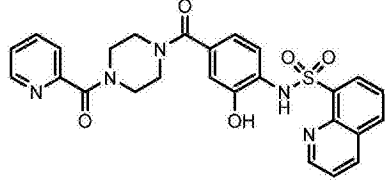
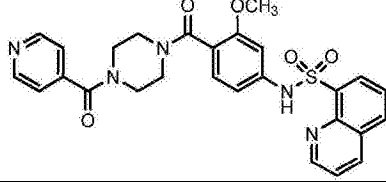
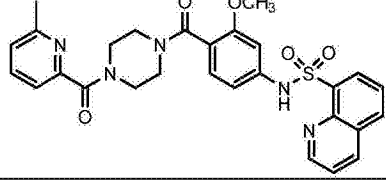
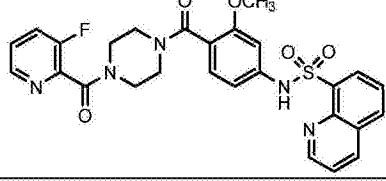
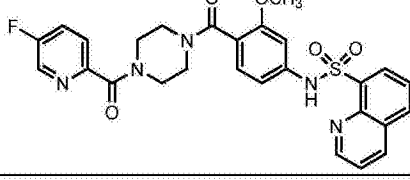
化合物	AC ₅₀
	E
	A
	A
	A
	A
	A
	A
	A

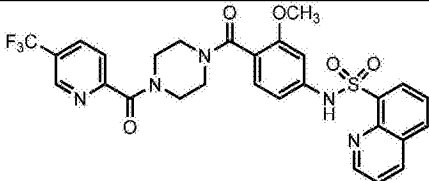
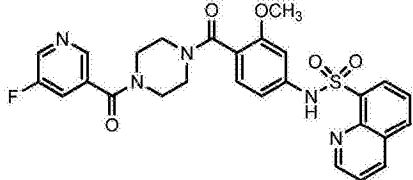
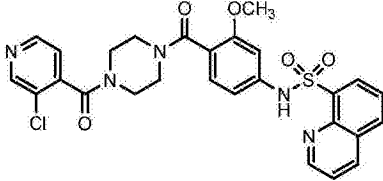
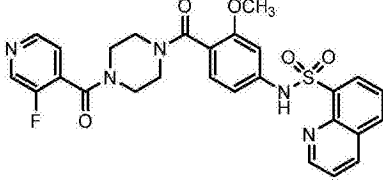
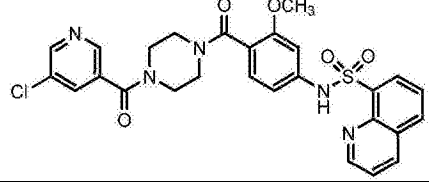
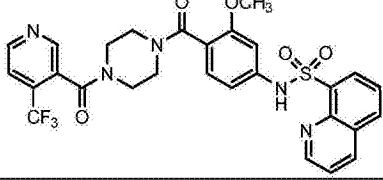
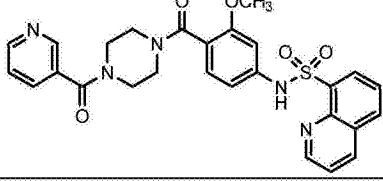
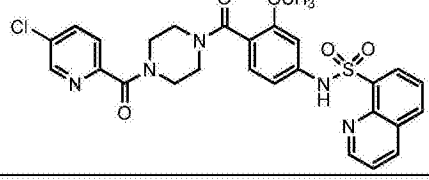
化合物	AC ₅₀
	B
	A
	B
	A
	A
	A
	A
	A

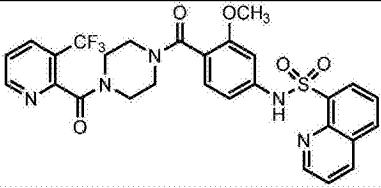
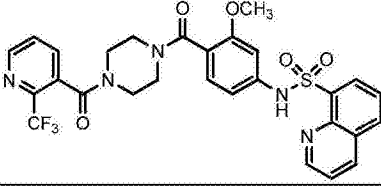
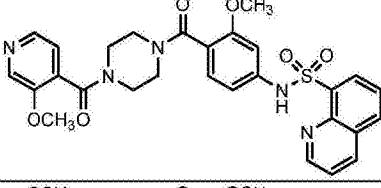
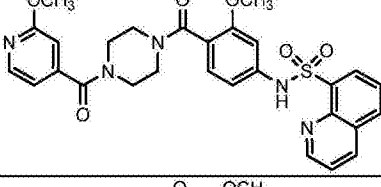
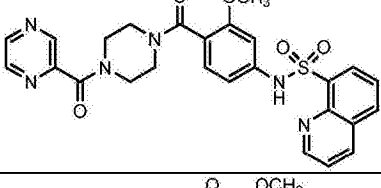
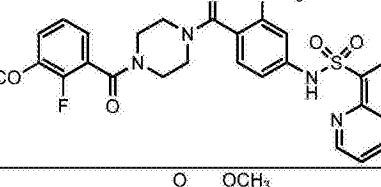
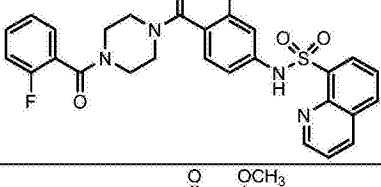
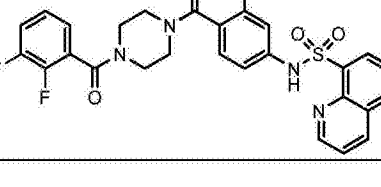
化合物	AC ₅₀
	A
	A
	A
	A
	A
	B
	C
	D

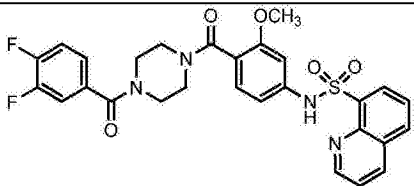
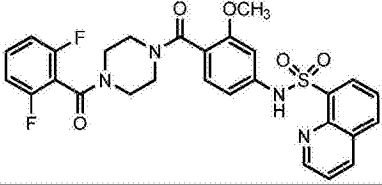
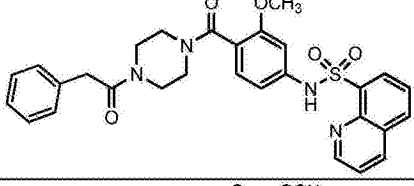
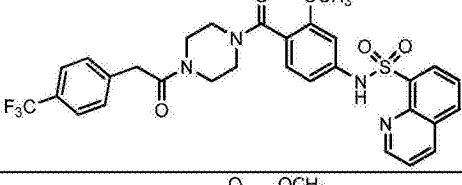
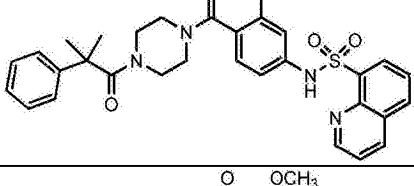
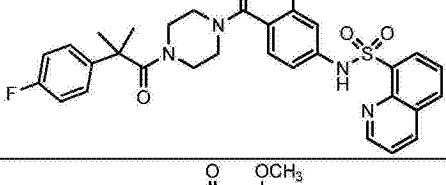
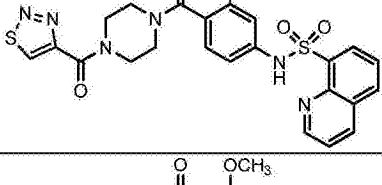
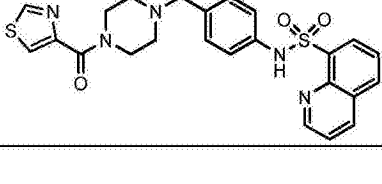
化合物	AC ₅₀
	D
	B
	B
	D
	C
	B
	C
	D

化合物	AC ₅₀
	C
	B
	B
	B
	D
	B
	B
	B

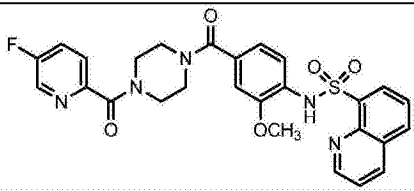
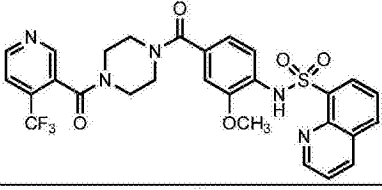
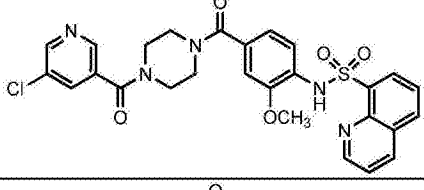
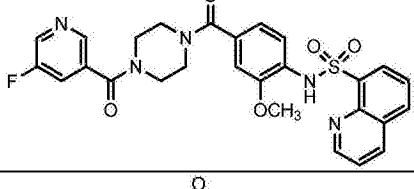
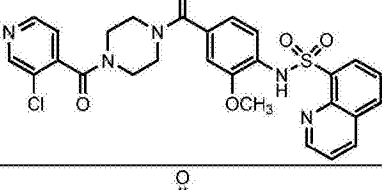
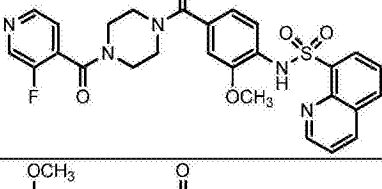
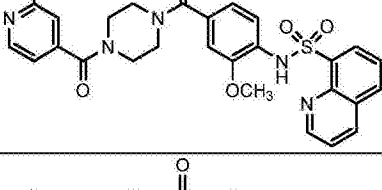
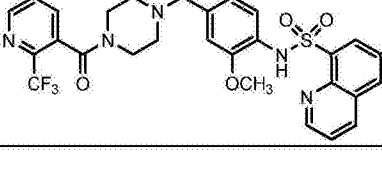
化合物	AC ₅₀
	B
	B
	C
	A
	B
	A
	B
	B

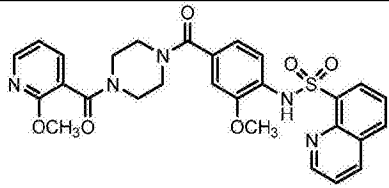
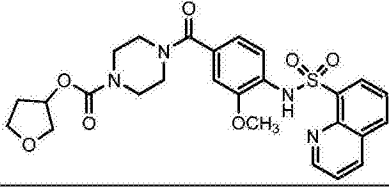
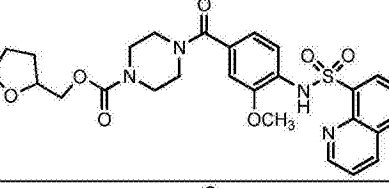
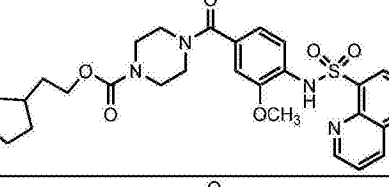
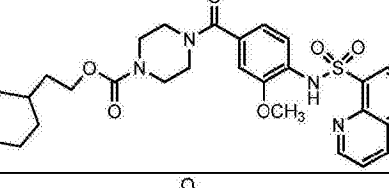
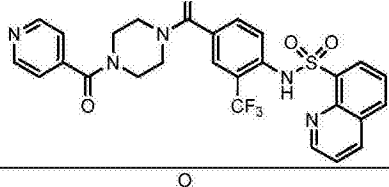
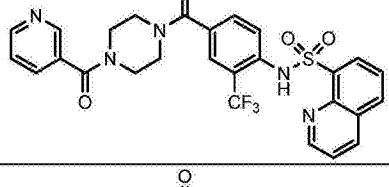
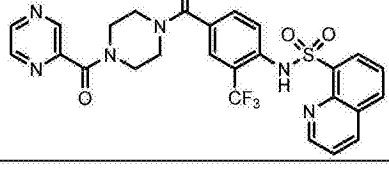
化合物	AC ₅₀
	B
	B
	B
	B
	A
	B
	B
	B

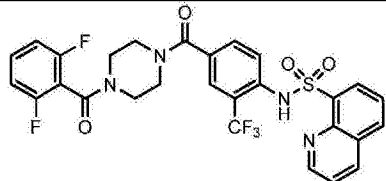
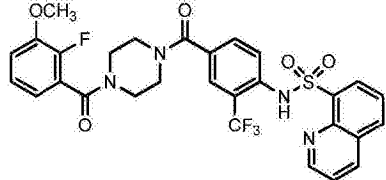
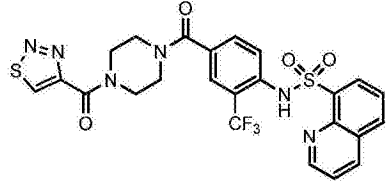
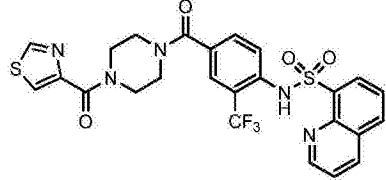
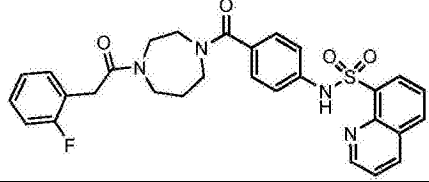
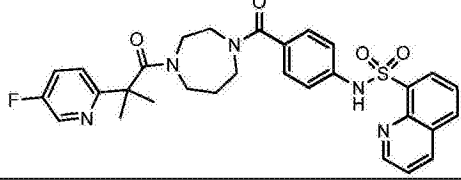
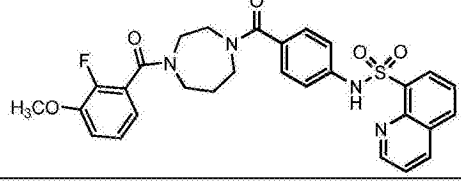
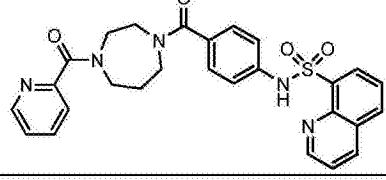
化合物	AC ₅₀
	B
	B
	A
	B
	B
	A
	B
	A

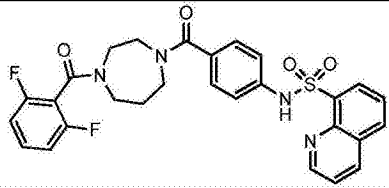
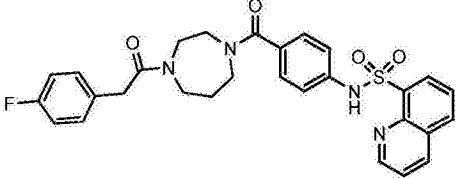
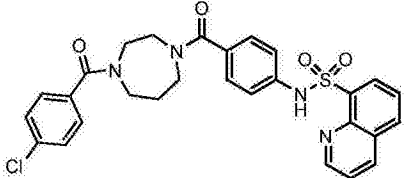
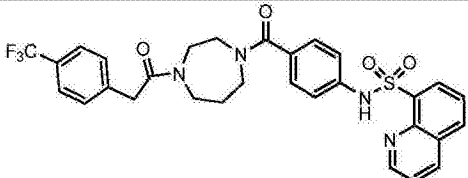
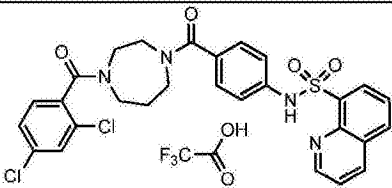
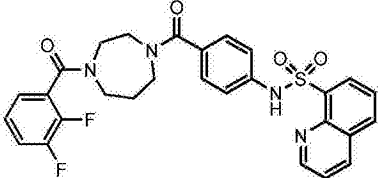
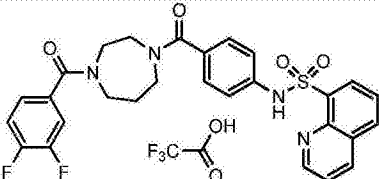
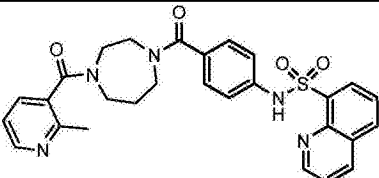
化合物	AC ₅₀
	B
	A
	A
	C
	B
	B
	A
	A

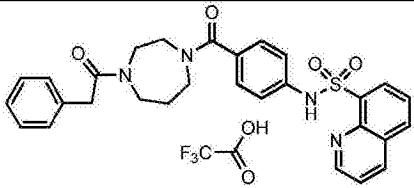
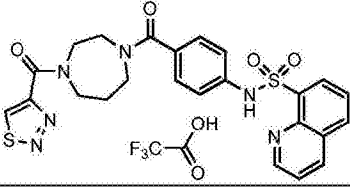
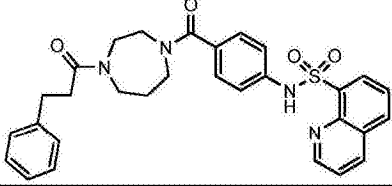
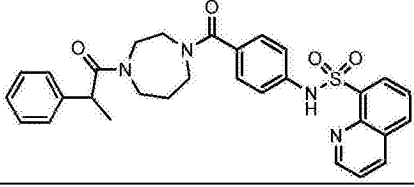
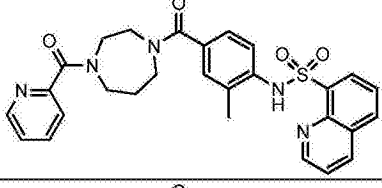
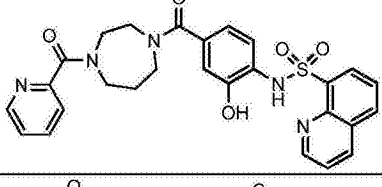
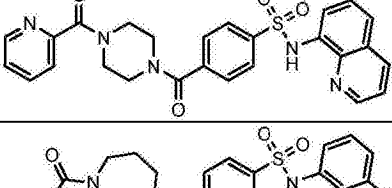
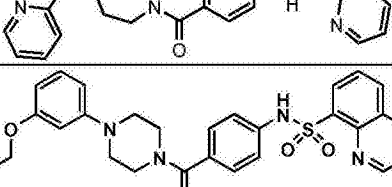
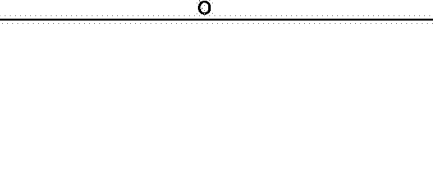
化合物	AC ₅₀
	A
	B
	B
	A
	B
	B
	B
	B

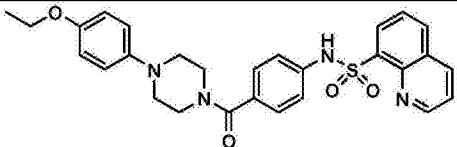
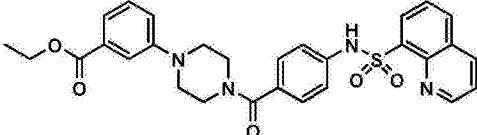
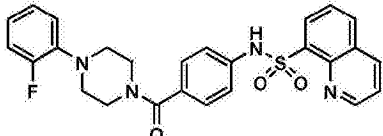
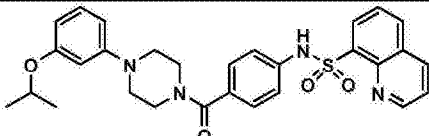
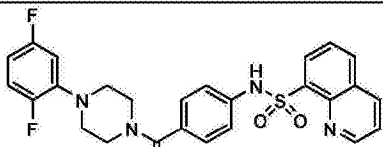
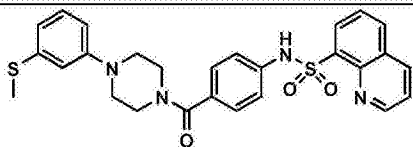
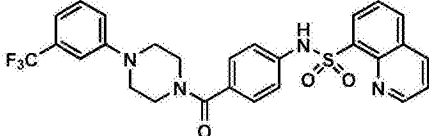
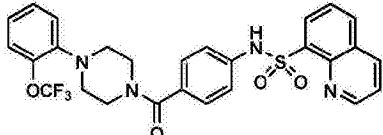
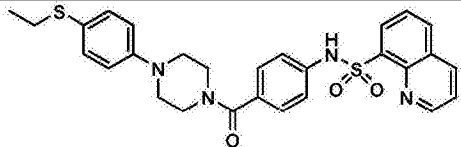
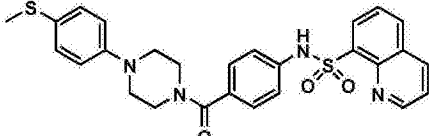
化合物	AC ₅₀
	B
	B
	B
	B
	B
	B
	B
	B

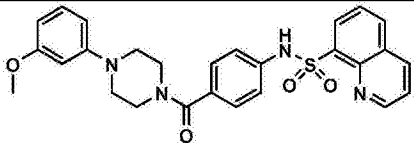
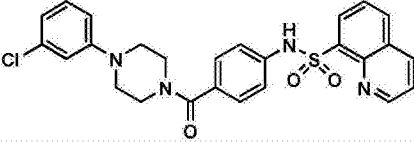
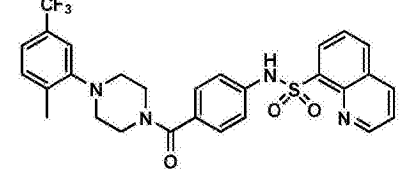
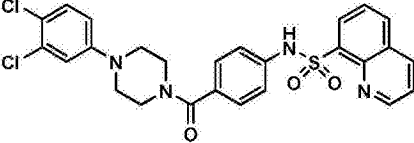
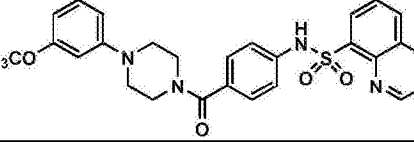
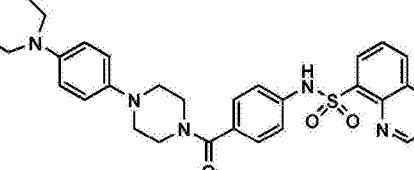
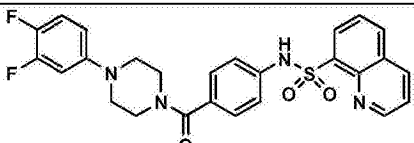
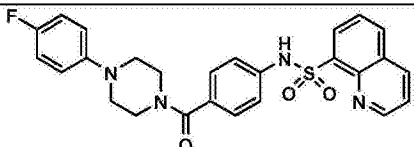
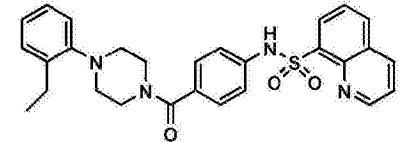
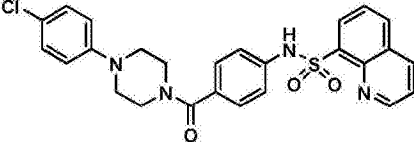
化合物	AC ₅₀
	B
	E
	B
	A
	B
	D
	D
	D

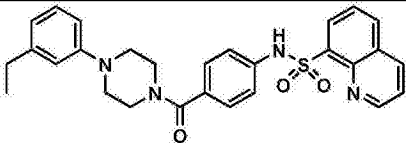
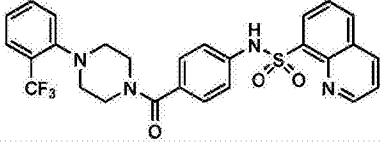
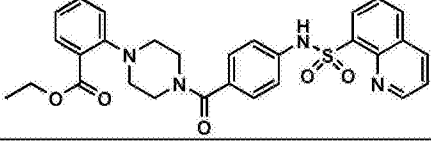
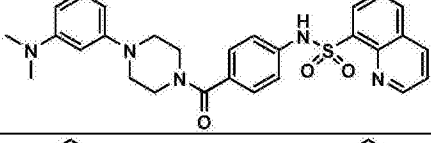
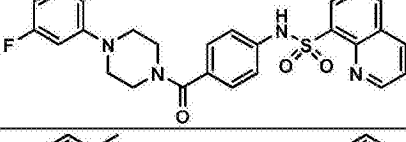
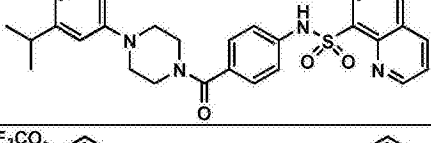
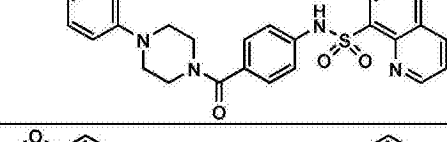
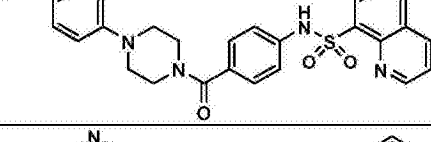
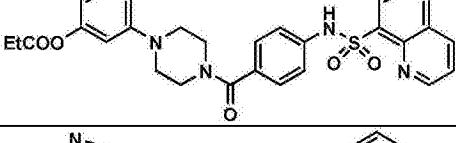
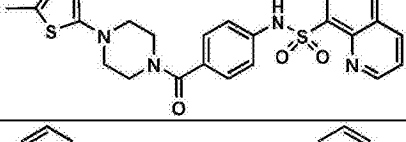
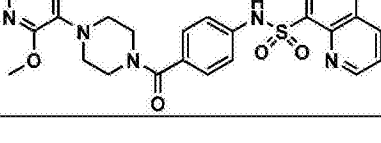
化合物	AC ₅₀
	B
	E
	D
	D
	D
	
	B
	C

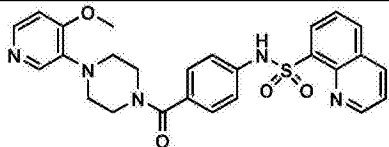
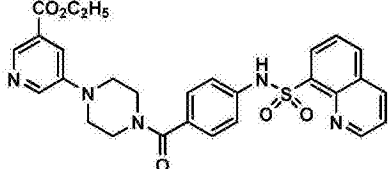
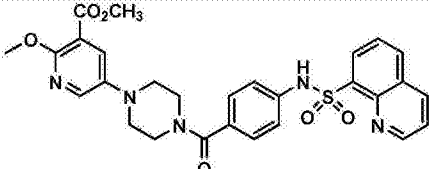
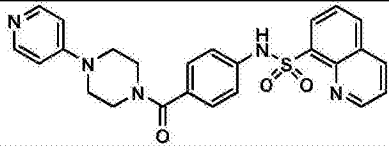
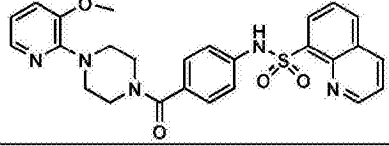
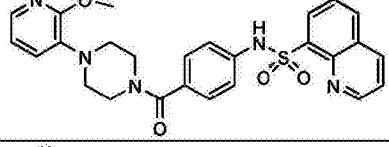
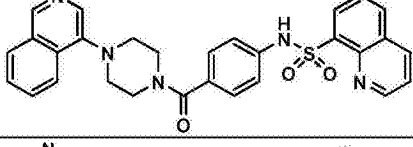
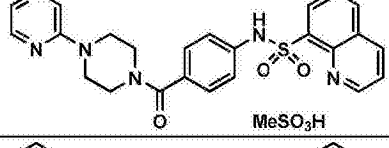
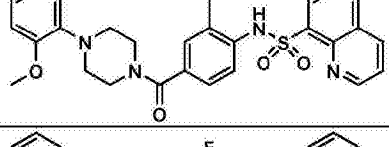
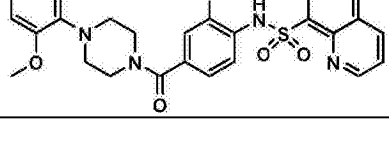
化合物	AC ₅₀
	A
	B
	B
	E
	B
	A
	B
	B

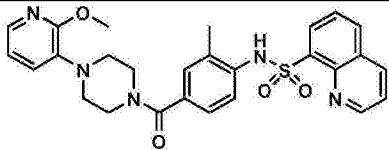
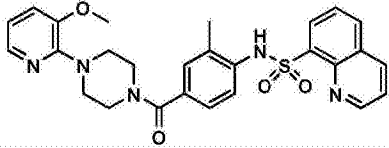
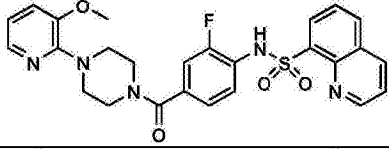
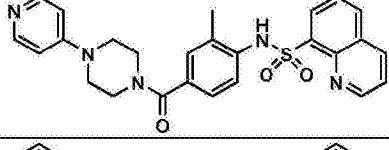
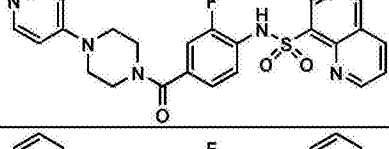
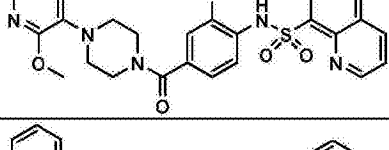
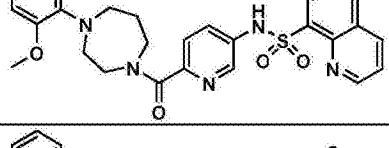
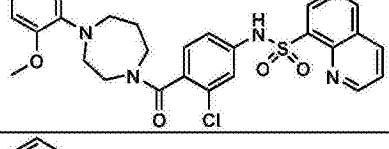
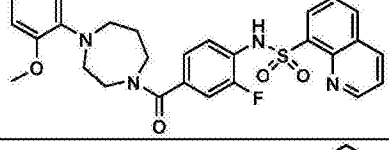
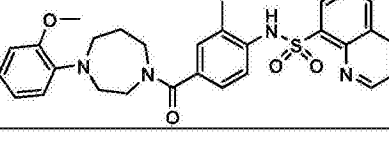
化合物	AC ₅₀
	B
	B
	B
	B
	B
	A
	A
	D
	A

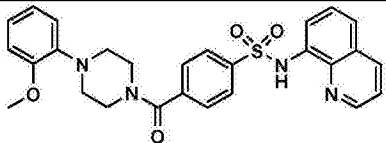
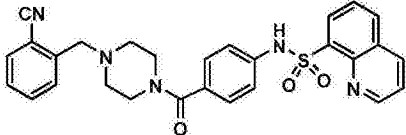
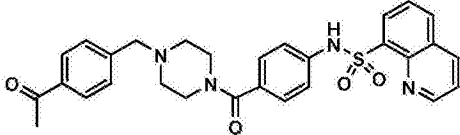
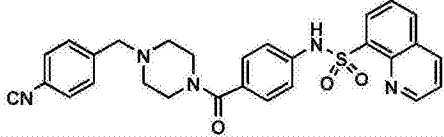
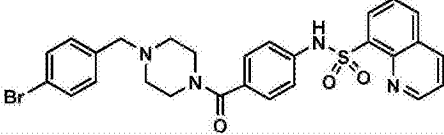
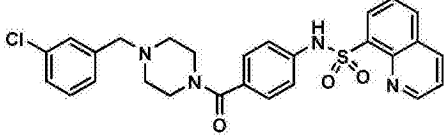
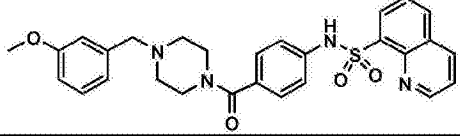
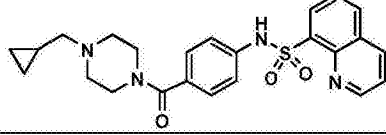
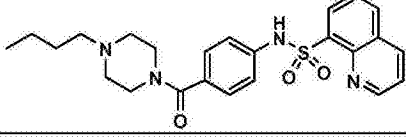
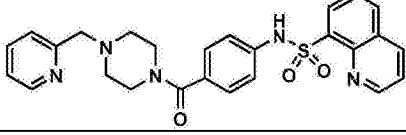
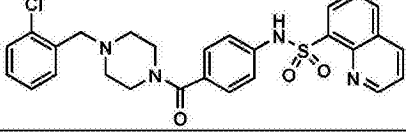
化合物	AC ₅₀
	B
	B
	A
	B
	A
	A
	B
	A
	B
	B

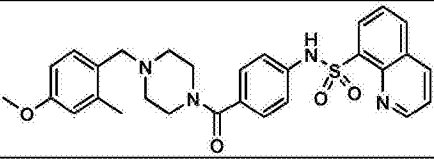
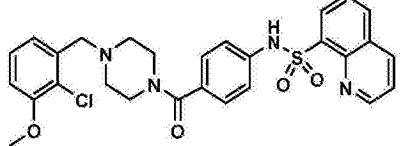
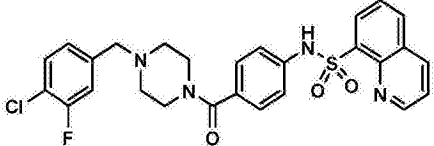
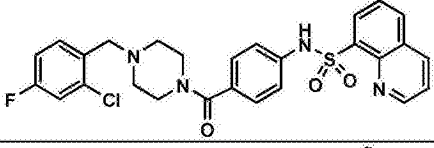
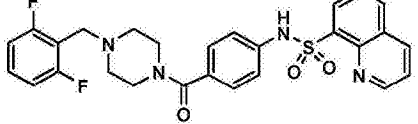
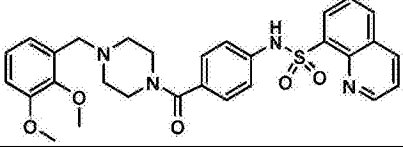
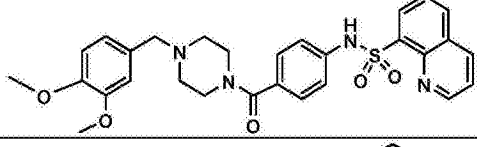
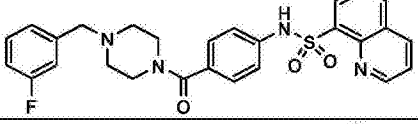
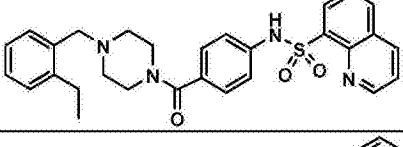
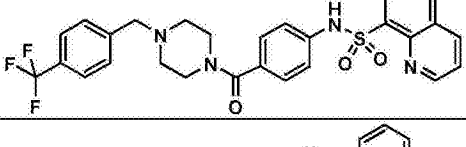
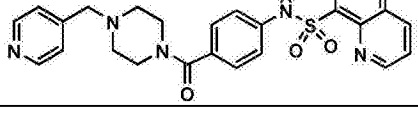
化合物	AC ₅₀
	A
	A
	B
	B
	B
	D
	A
	A
	A
	A

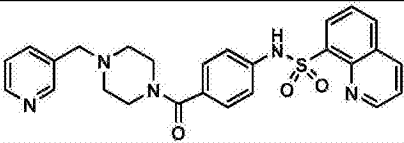
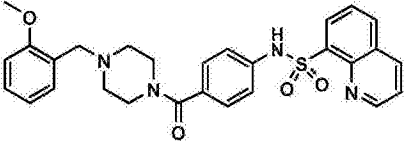
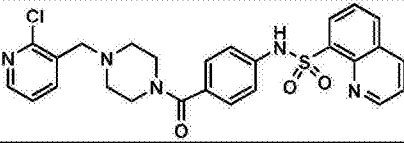
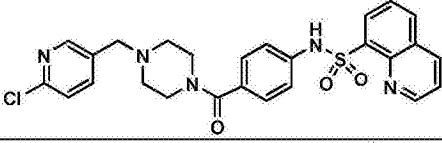
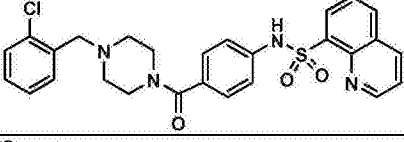
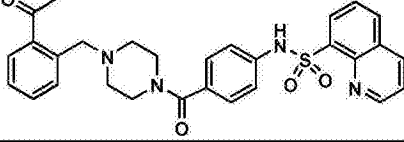
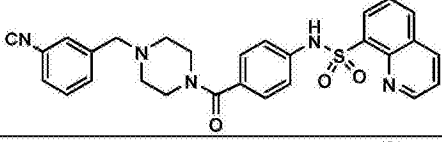
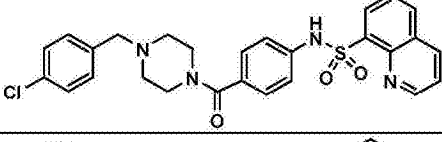
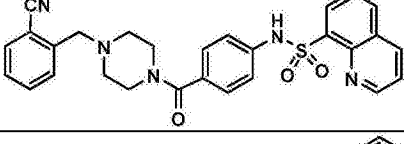
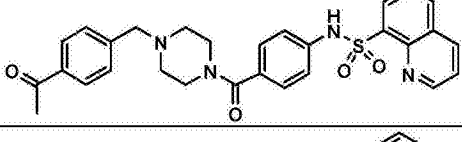
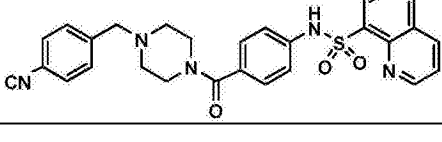
化合物	AC ₅₀
	A
	A
	A
	A
	A
	B
	B
	B
	E
	D
	A

化合物	AC ₅₀
	B
	D
	A
	E
	A
	A
	A
 MeSO ₃ H	A
	A
	B

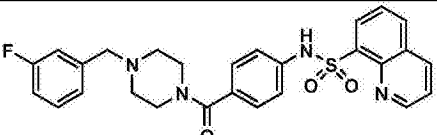
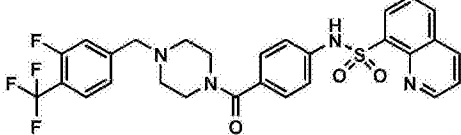
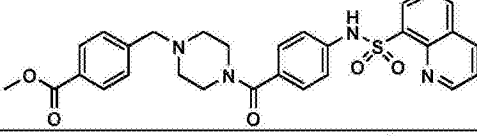
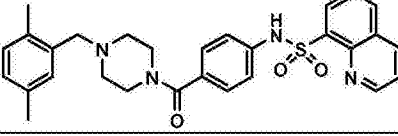
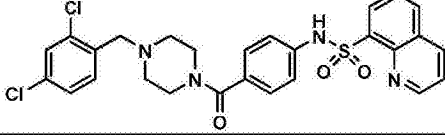
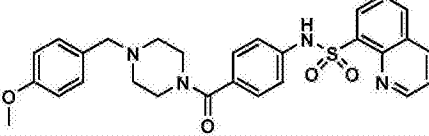
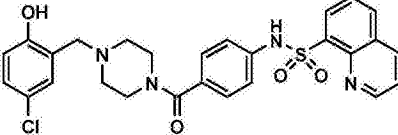
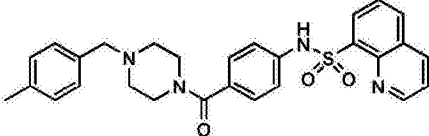
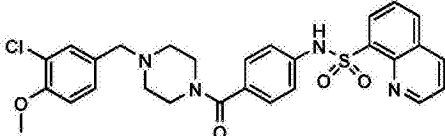
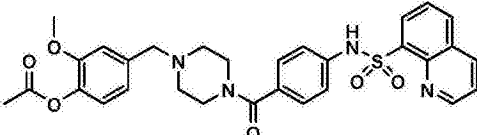
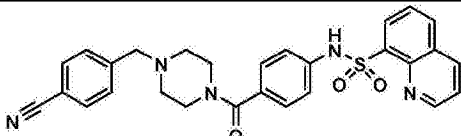
化合物	AC ₅₀
	A
	A
	E
	E
	D
	E
	C
	B
	B
	A

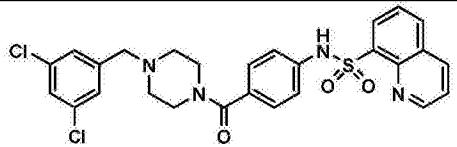
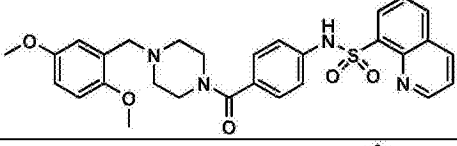
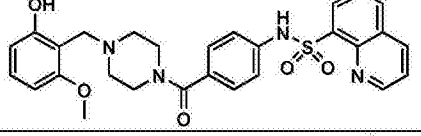
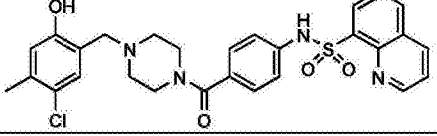
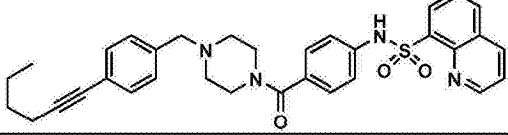
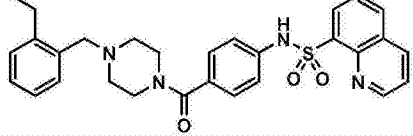
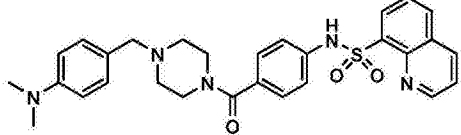
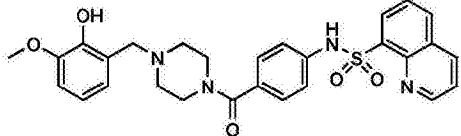
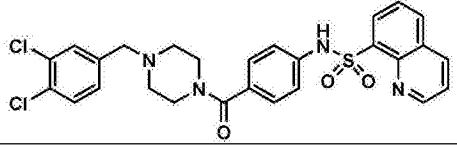
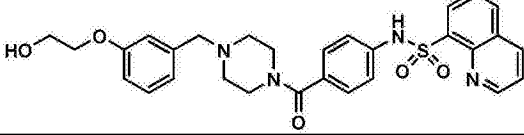
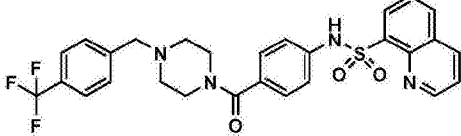
化合物	AC ₅₀
	A
	A
	B
	A
	A
	A
	A
	A
	A
	A
	A

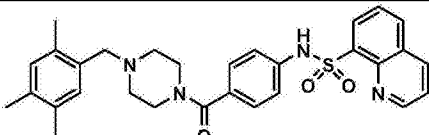
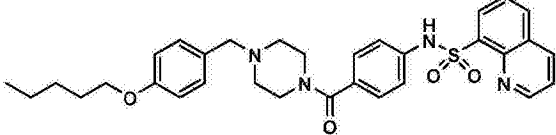
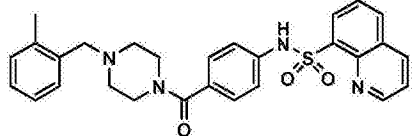
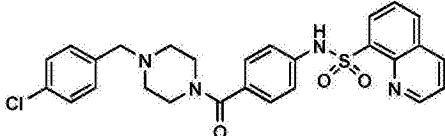
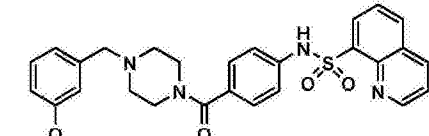
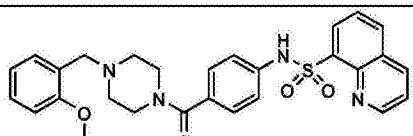
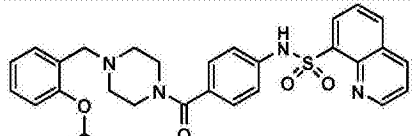
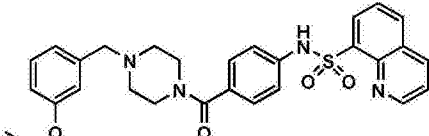
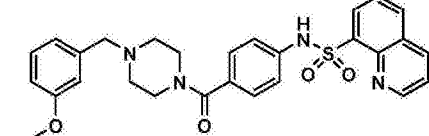
化合物	AC ₅₀
	B
	B
	A
	B
	A
	B
	B
	A
	B
	B
	A

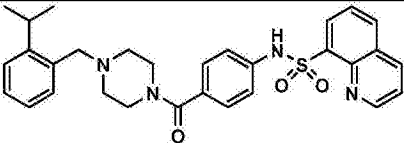
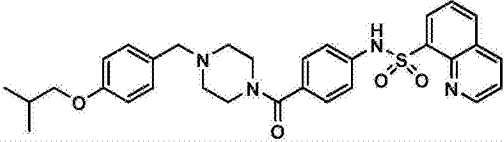
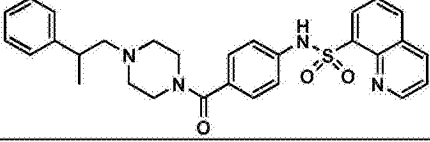
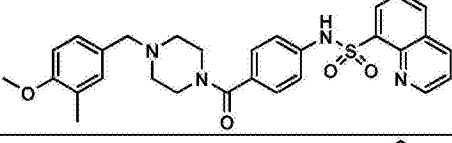
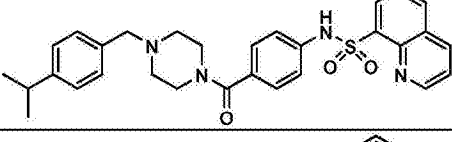
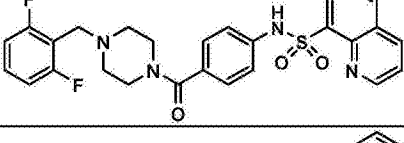
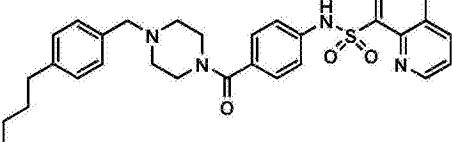
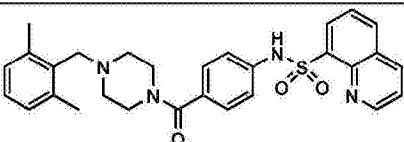
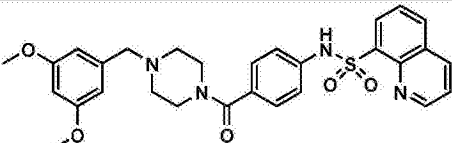
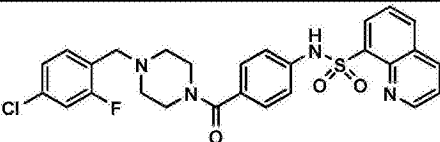
化合物	AC ₅₀
	A
	A
	A
	A
	A
	A
	A
	A
	A
	B
	A

化合物	AC ₅₀
	A
	A
	A
	A
	A
	A
	A
	B
	A
	A
	A

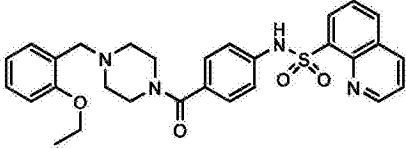
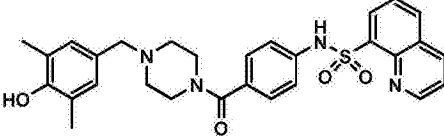
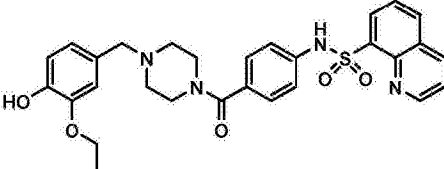
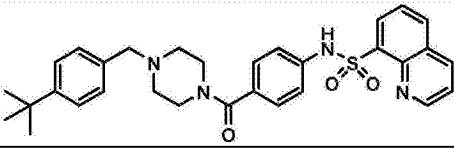
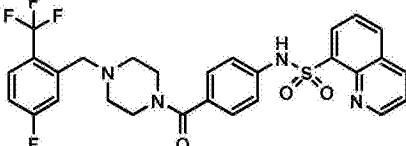
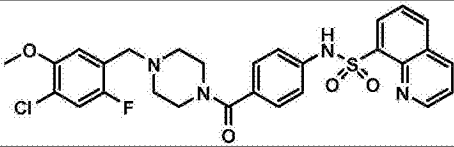
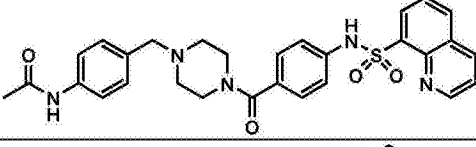
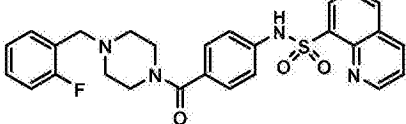
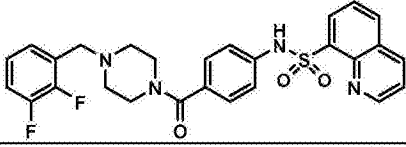
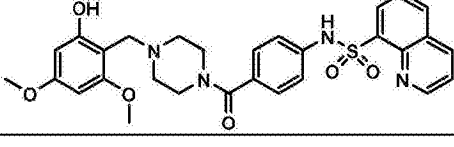
化合物	AC ₅₀
	A
	A
	B
	A
	A
	A
	A
	A
	A
	B
	A

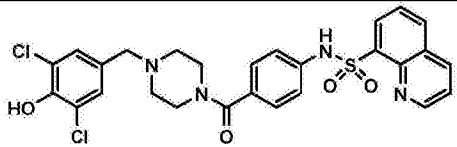
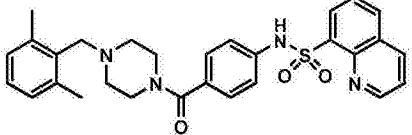
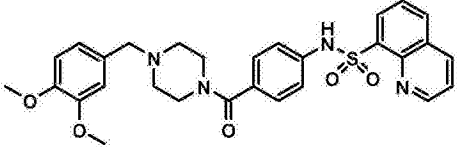
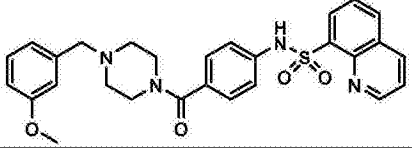
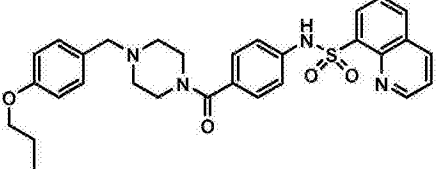
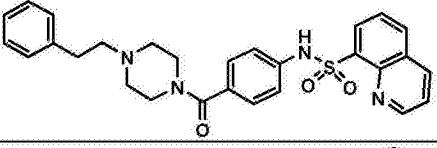
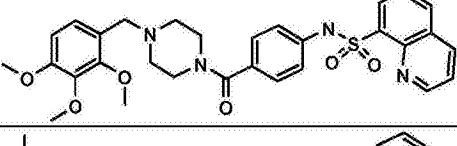
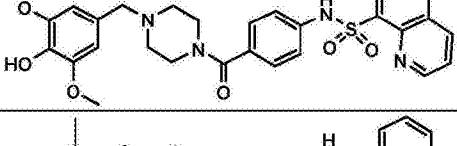
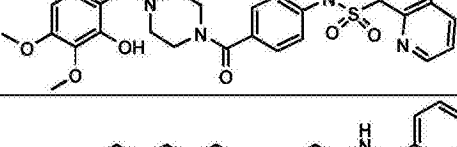
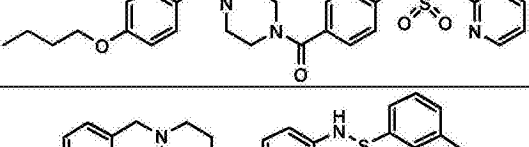
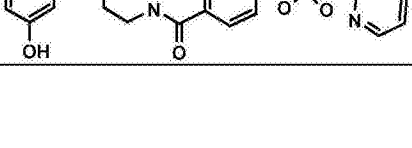
化合物	AC ₅₀
	A
	A
	A
	A
	B
	B
	B
	A
	A
	A
	B

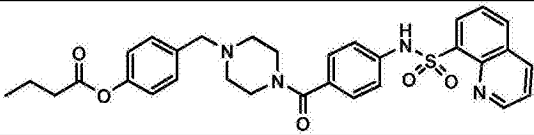
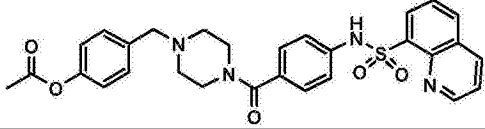
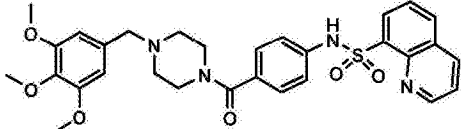
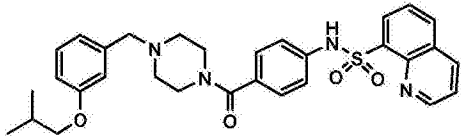
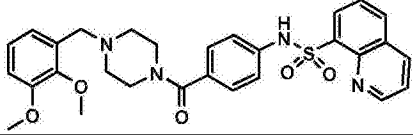
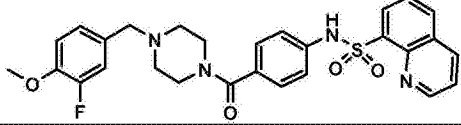
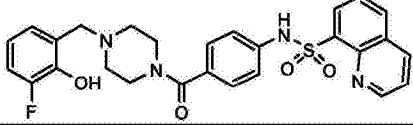
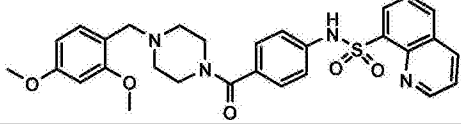
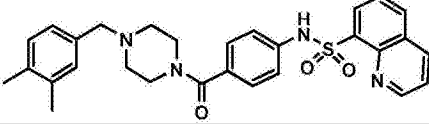
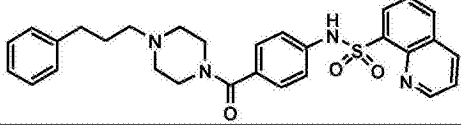
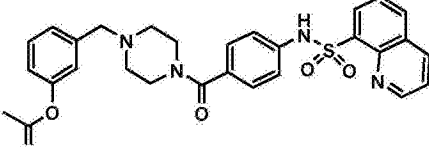
化合物	AC ₅₀
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	B
	A
	A
	B
	B
	B
	B
	B

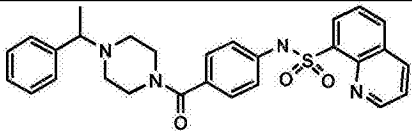
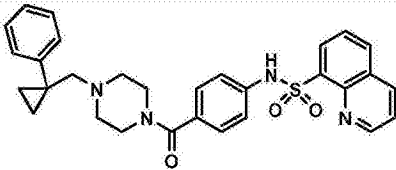
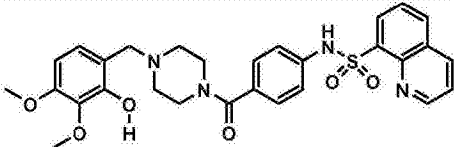
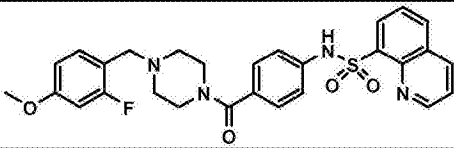
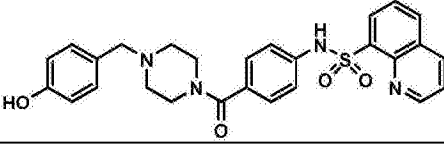
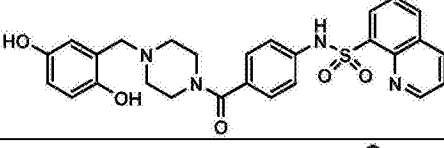
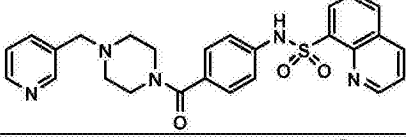
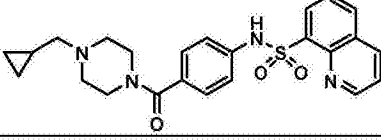
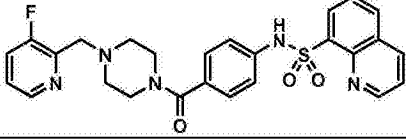
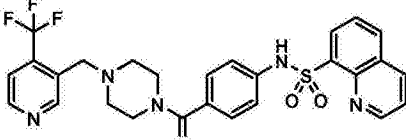
化合物	AC ₅₀
	B
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	A

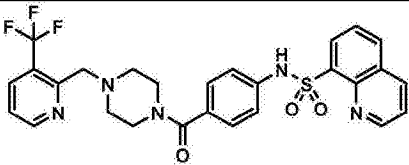
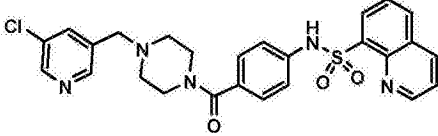
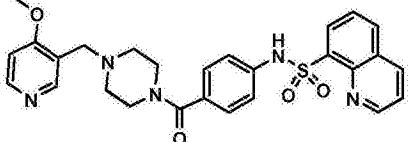
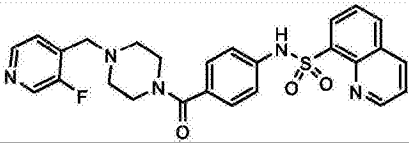
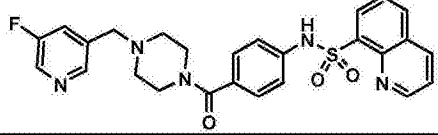
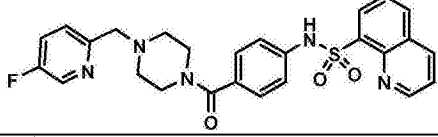
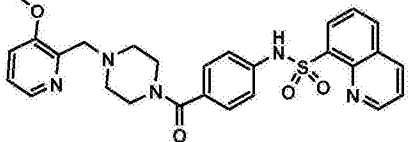
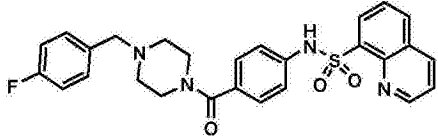
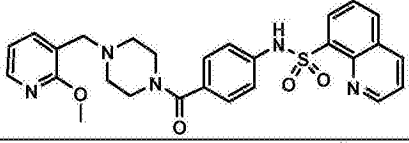
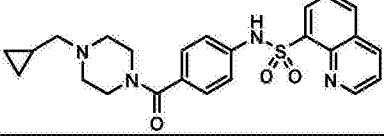
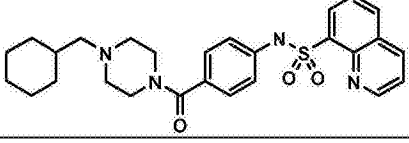
化合物	AC ₅₀
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	A

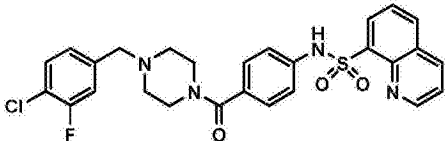
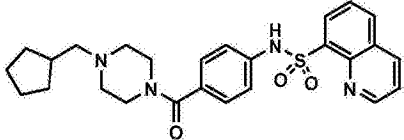
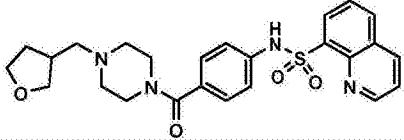
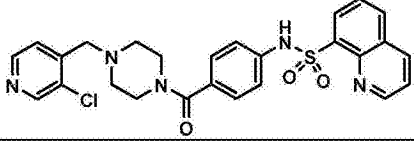
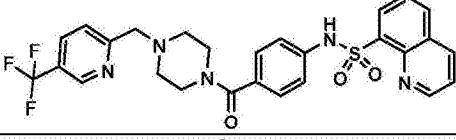
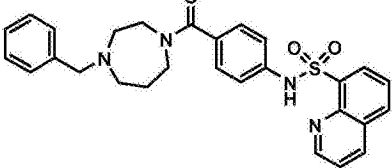
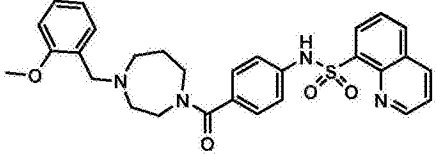
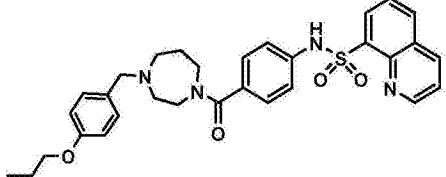
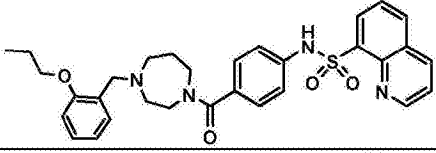
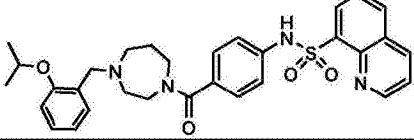
化合物	AC ₅₀
	A
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	A
	B
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	B
	A
	A
	B

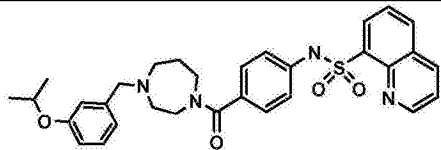
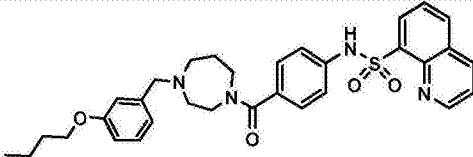
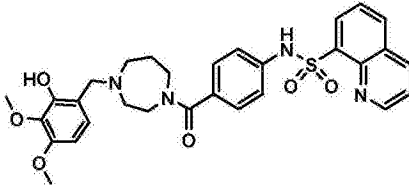
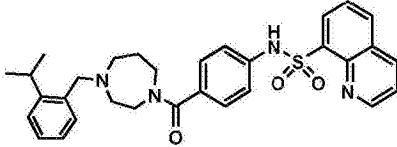
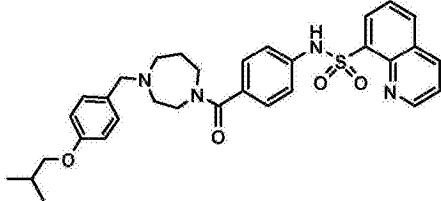
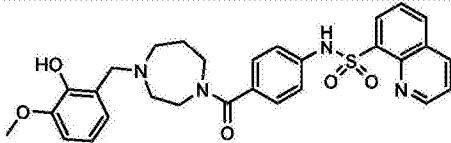
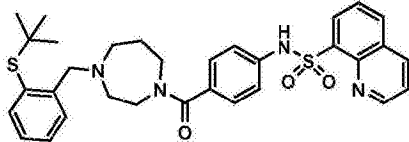
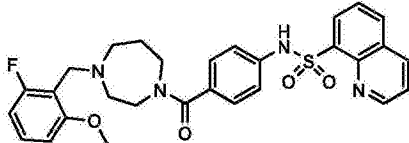
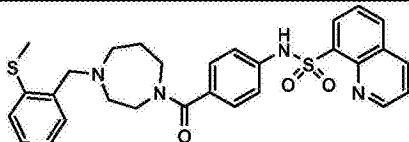
化合物	AC ₅₀
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	B
	A
	B
	A
	D
	B
	C
	B
	A

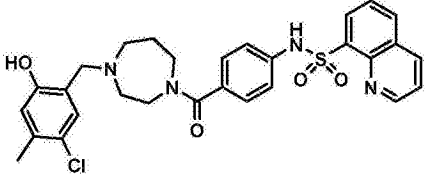
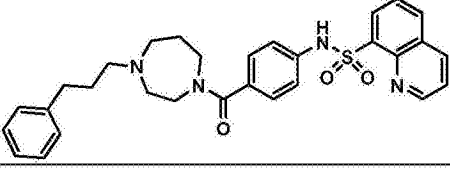
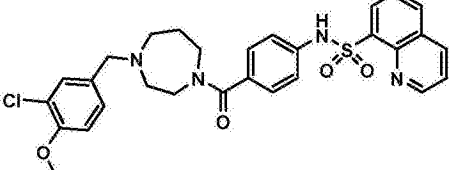
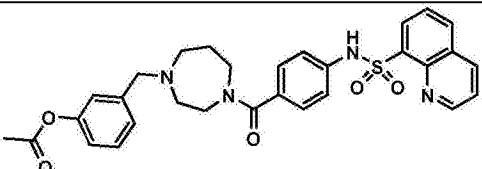
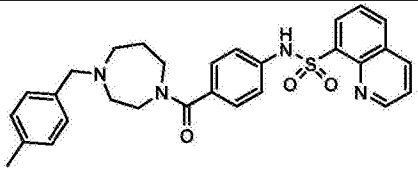
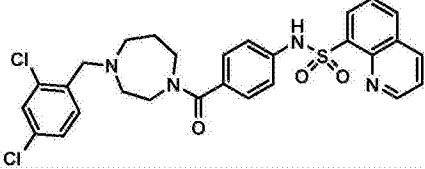
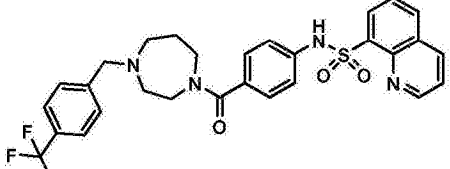
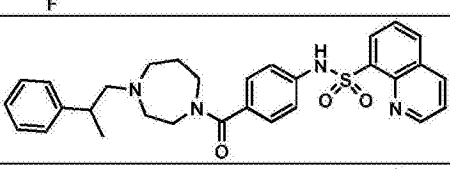
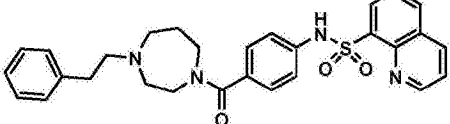
化合物	AC ₅₀
	A
	A
	D
	B
	B
	A
	A
	B
	A
	A
	A

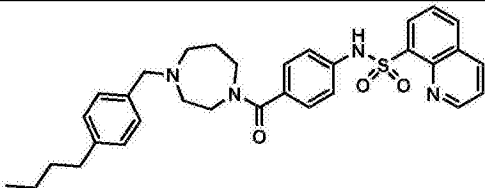
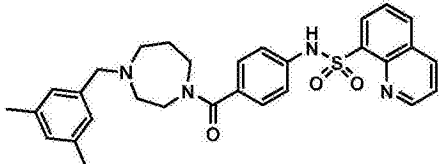
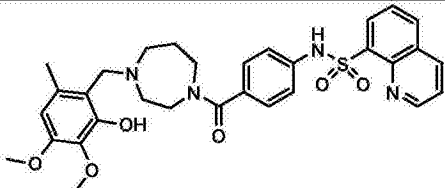
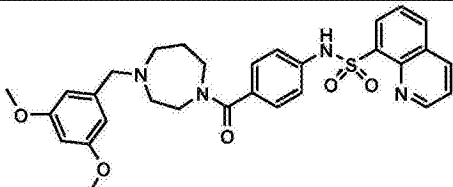
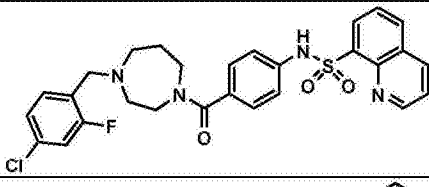
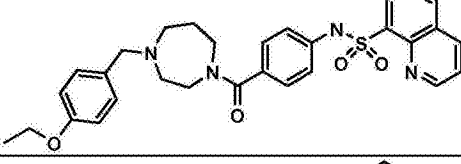
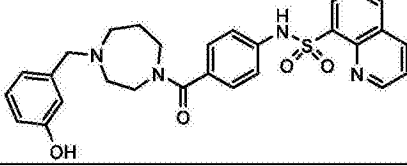
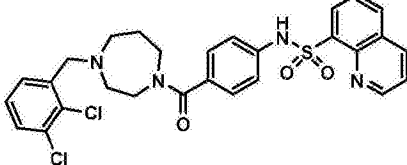
化合物	AC ₅₀
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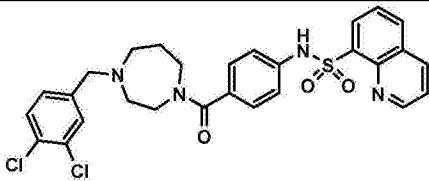
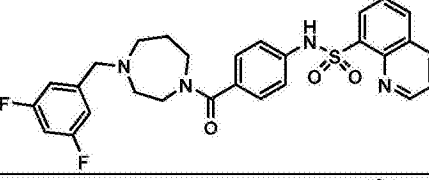
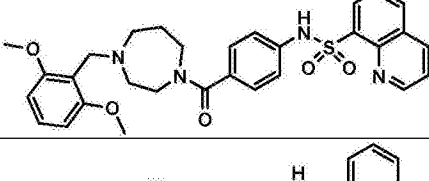
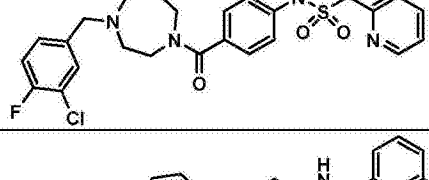
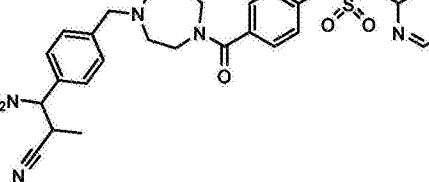
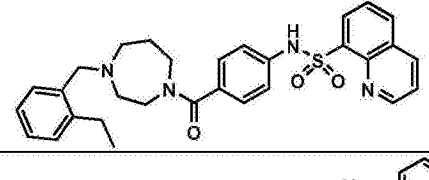
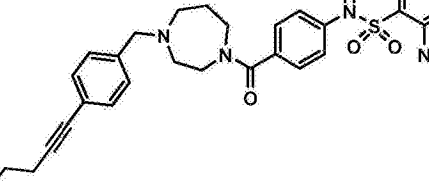
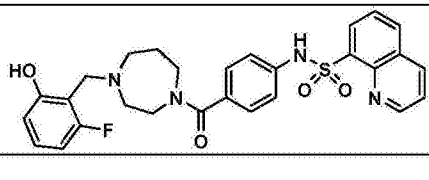
化合物	AC ₅₀
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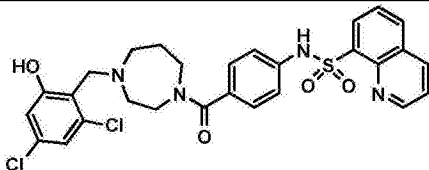
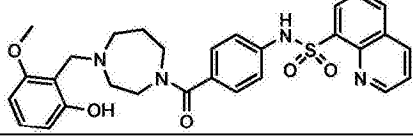
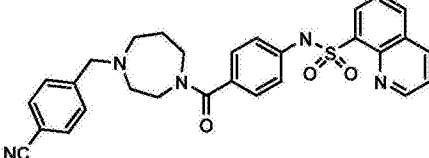
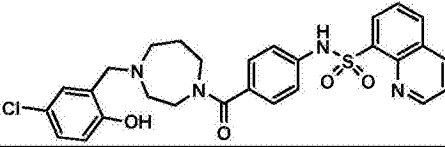
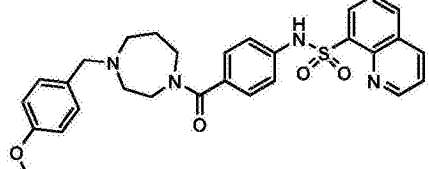
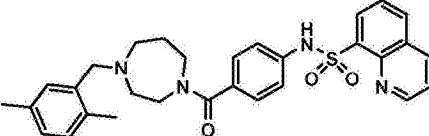
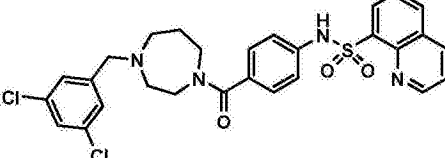
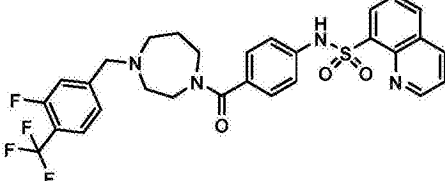
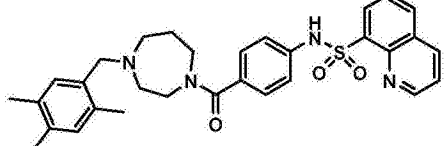
化合物	AC ₅₀
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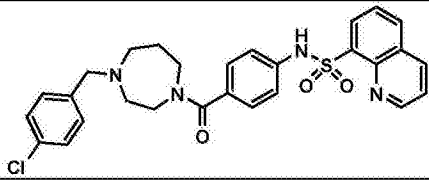
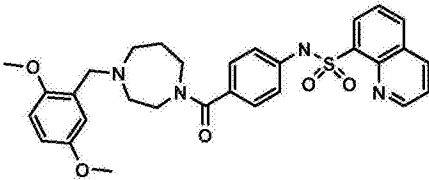
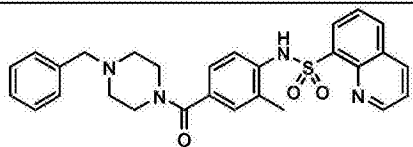
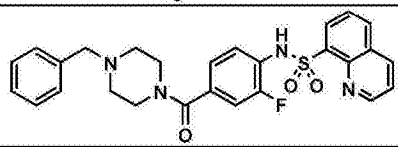
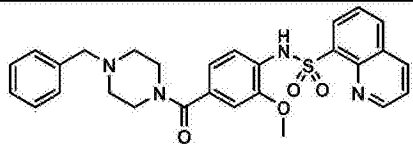
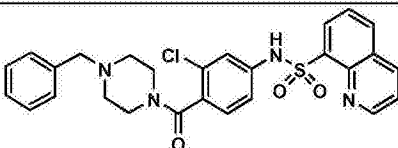
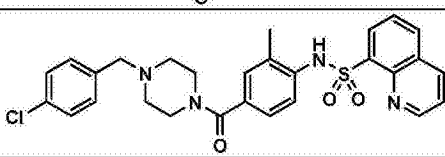
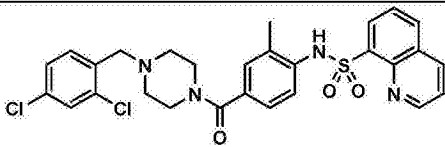
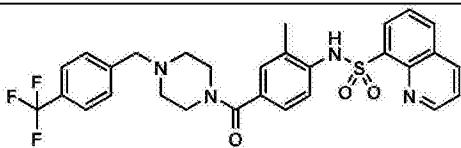
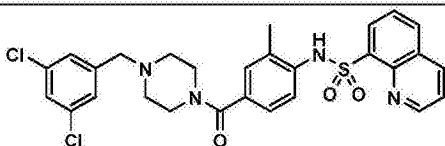
化合物	AC ₅₀
	D
	D
	D
	B
	D
	B
	A
	A
	B

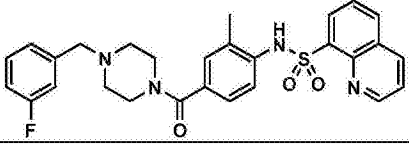
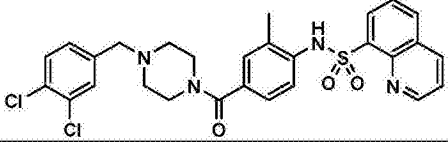
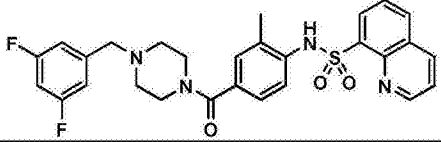
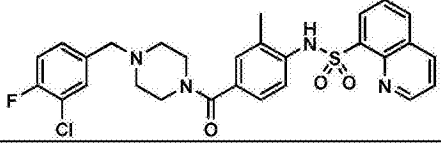
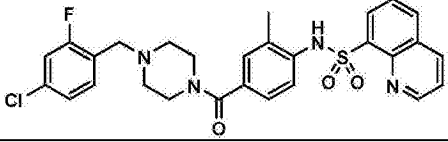
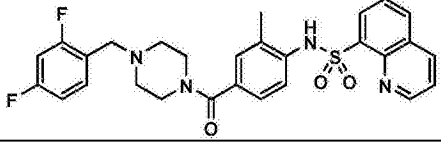
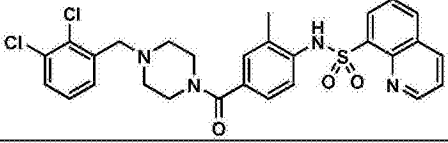
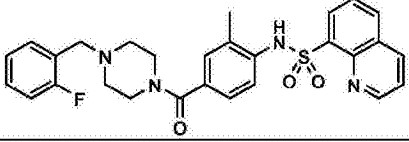
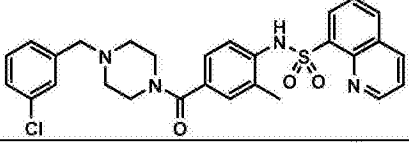
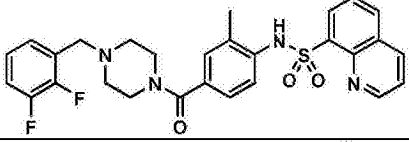
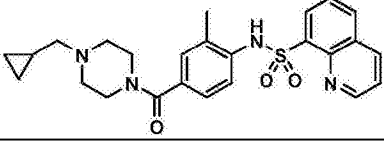
化合物	AC ₅₀
	C
	D
	D
	B
	D
	A
	B
	B
	A

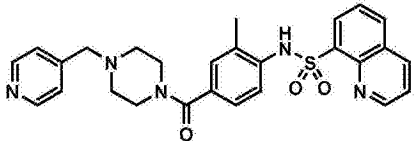
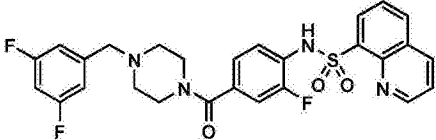
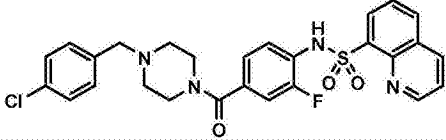
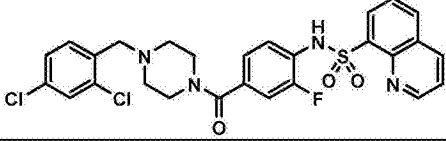
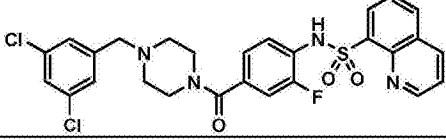
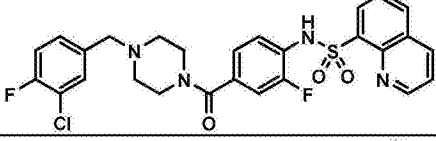
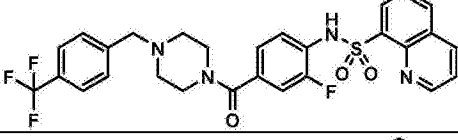
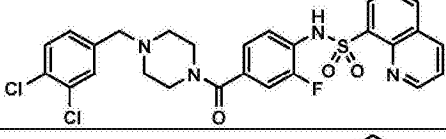
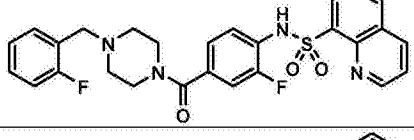
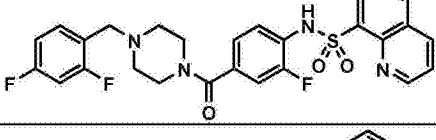
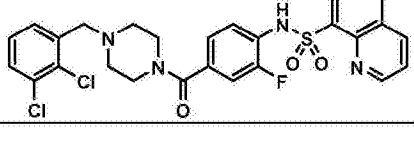
化合物	AC ₅₀
	D
	B
	D
	D
	B
	D
	A
	B

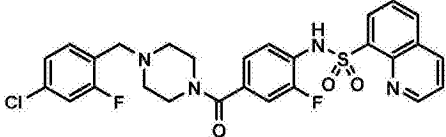
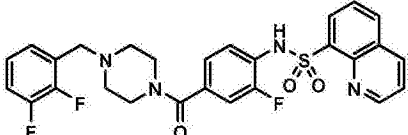
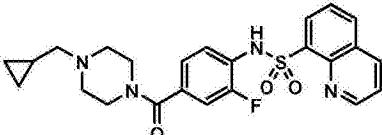
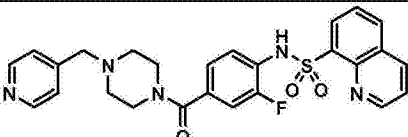
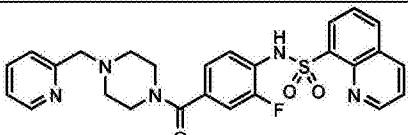
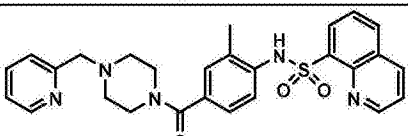
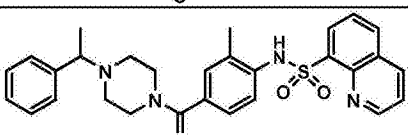
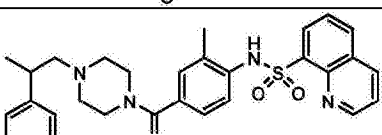
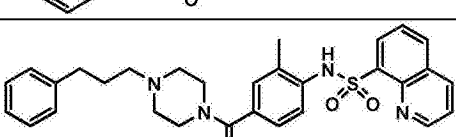
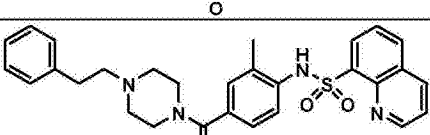
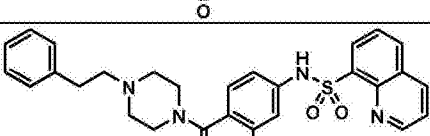
化合物	AC ₅₀
	B
	A
	E
	A
	D
	A
	B
	A

化合物	AC ₅₀
	B
	E
	B
	A
	B
	B
	D
	D
	D

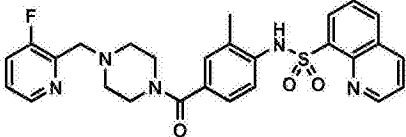
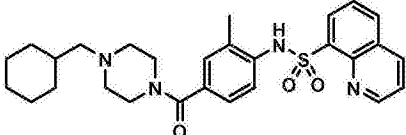
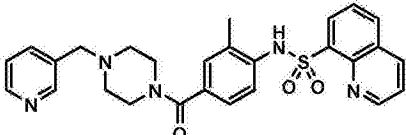
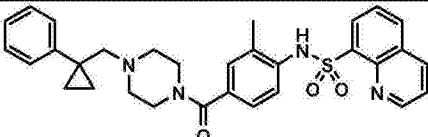
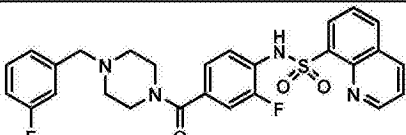
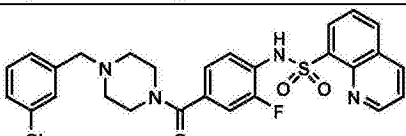
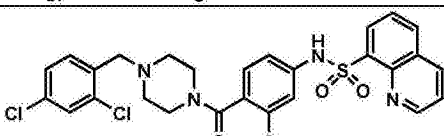
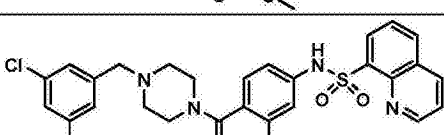
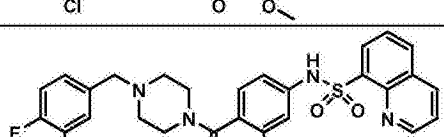
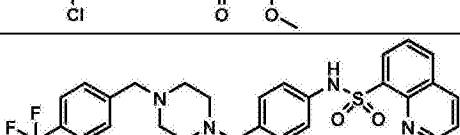
化合物	AC ₅₀
	B
	B
	A
	B
	A
	A
	A
	A
	A
	A

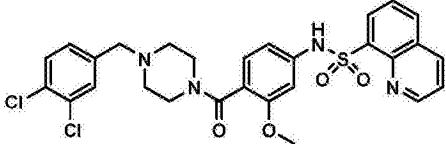
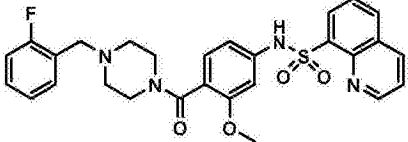
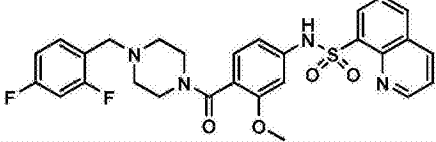
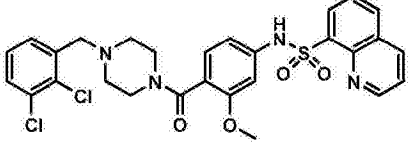
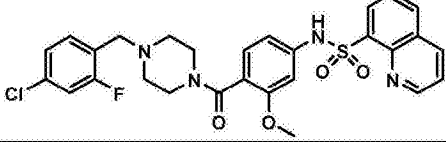
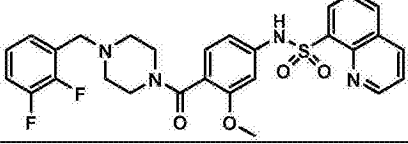
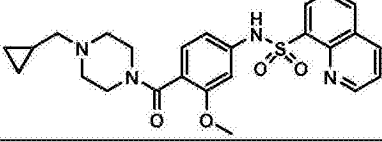
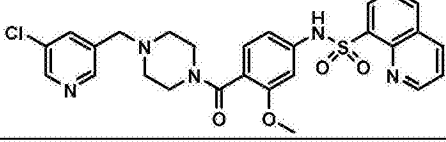
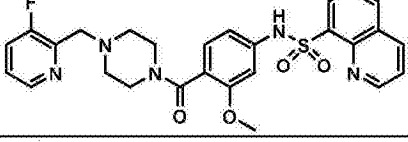
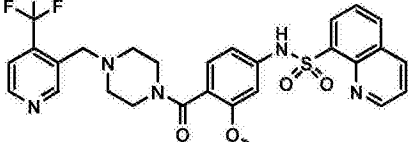
化合物	AC ₅₀
	A
	A
	A
	A
	A
	A
	A
	A
	A
	A
	A

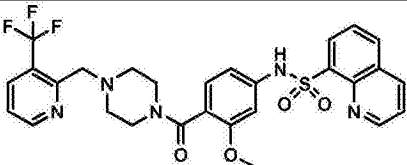
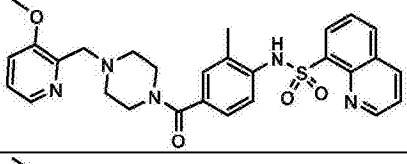
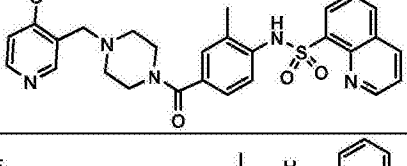
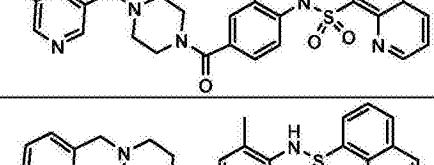
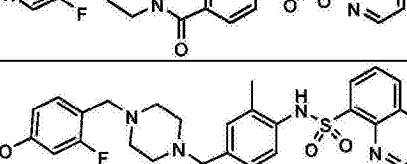
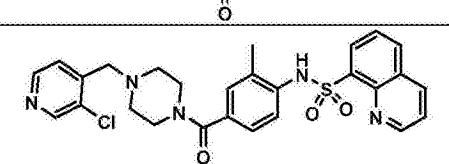
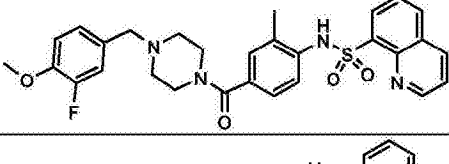
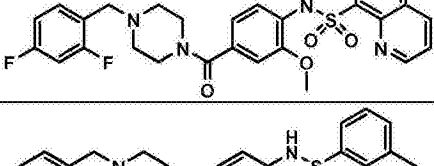
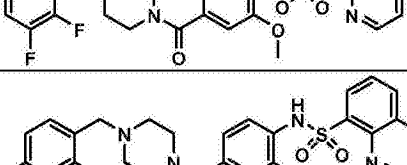
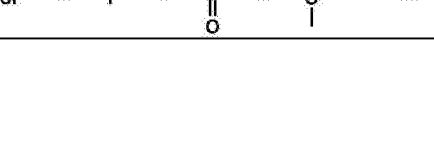
化合物	AC ₅₀
	A
	A
	B
	B
	B
	A
	B
	A
	B
	B
	A

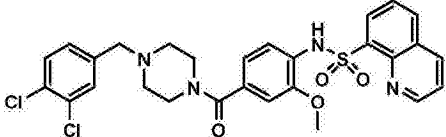
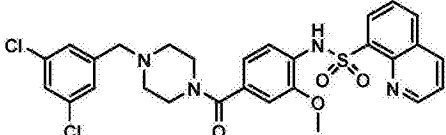
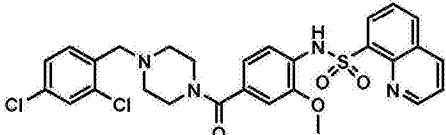
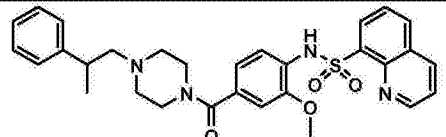
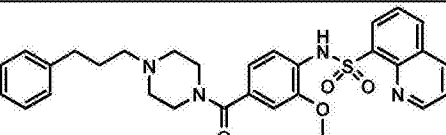
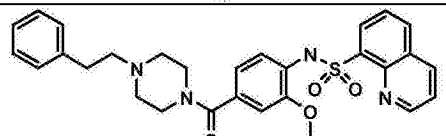
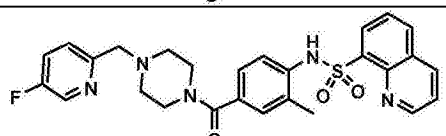
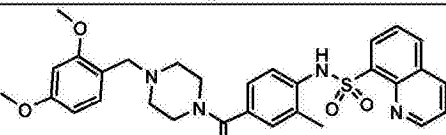
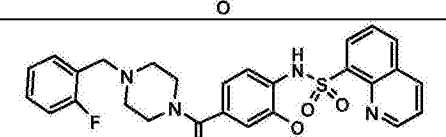
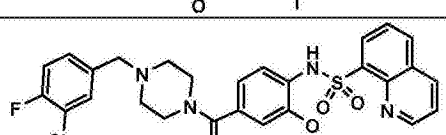
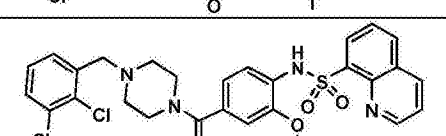
化合物	AC ₅₀
	B
	A
	B
	B
	B
	A
	A
	A
	A
	A
	A

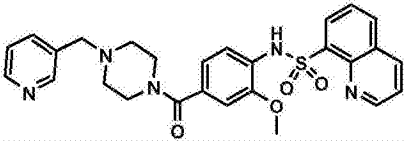
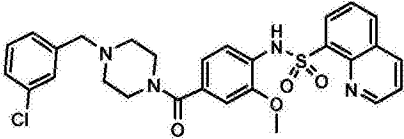
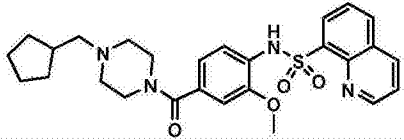
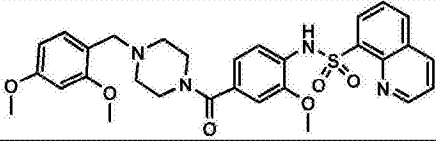
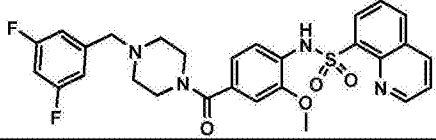
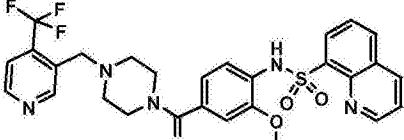
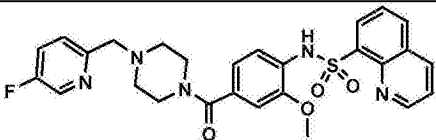
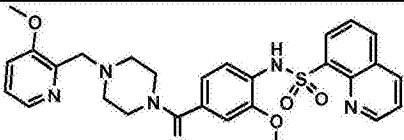
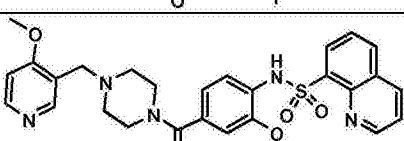
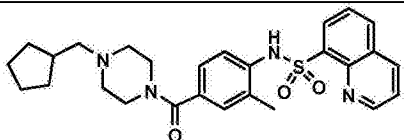
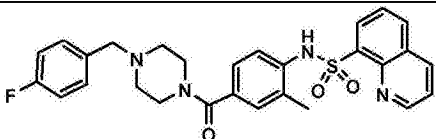
化合物	AC ₅₀
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	A
	A
	B
	B
	B
	B
	A
	A
	A

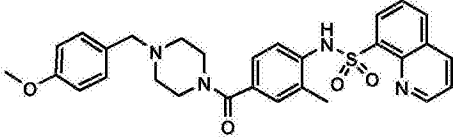
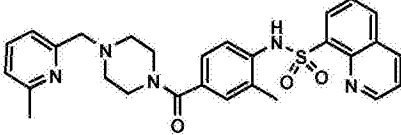
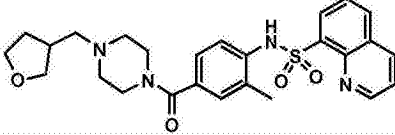
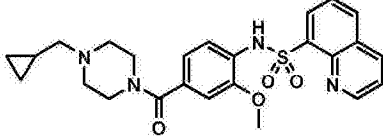
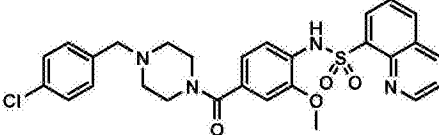
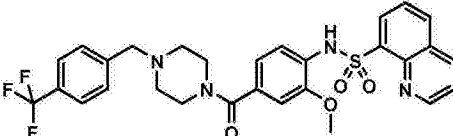
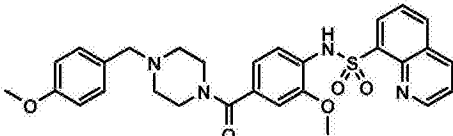
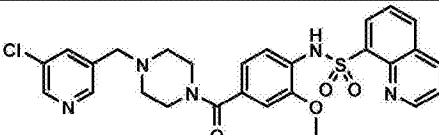
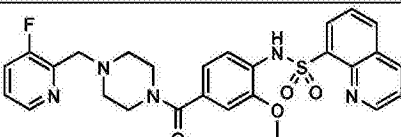
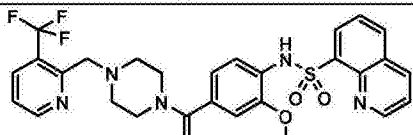
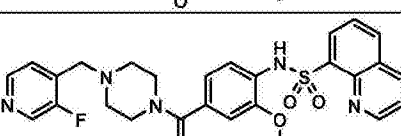
化合物	AC ₅₀
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	A
	A
	A
	A
	A
	B
	A
	A
	A

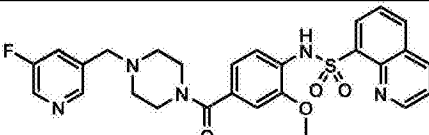
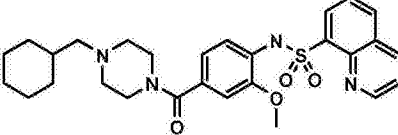
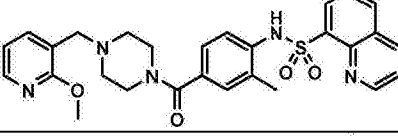
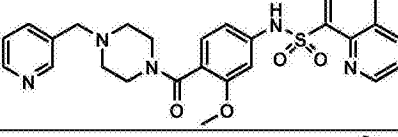
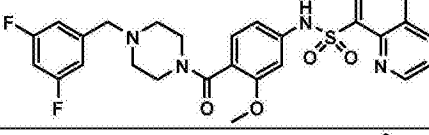
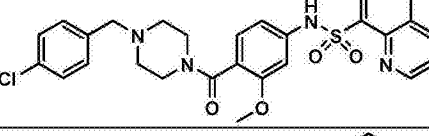
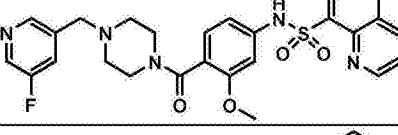
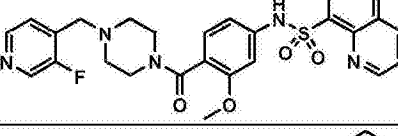
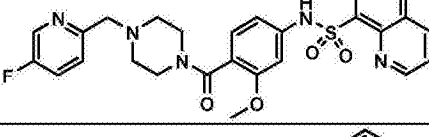
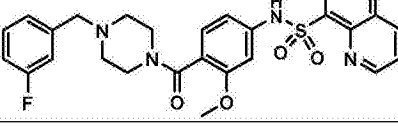
化合物	AC ₅₀
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	B
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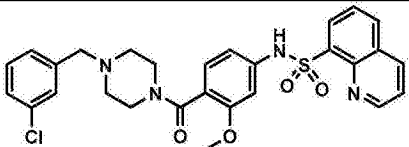
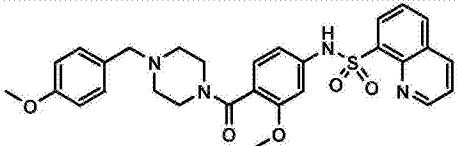
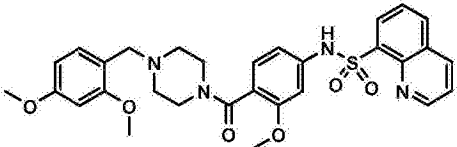
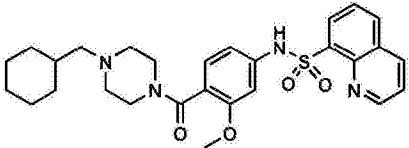
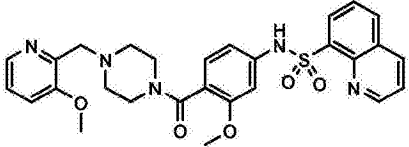
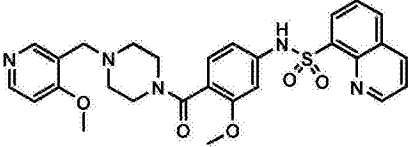
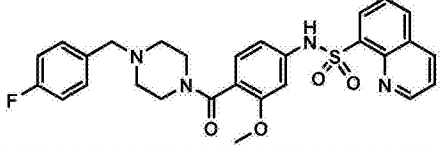
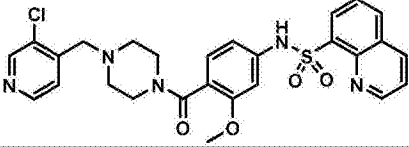
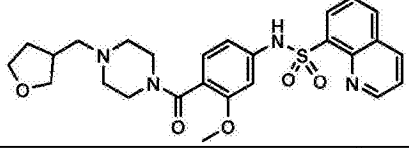
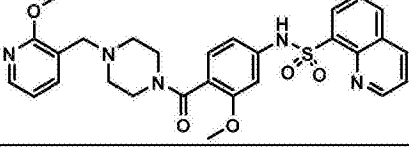
化合物	AC ₅₀
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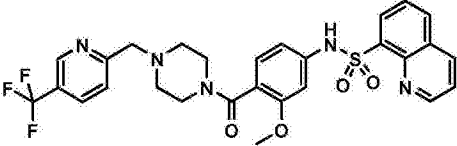
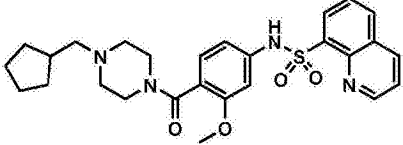
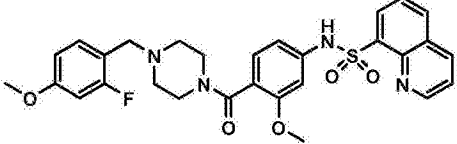
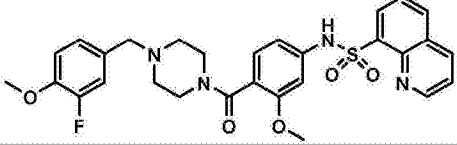
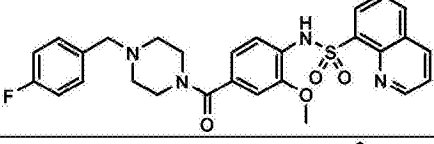
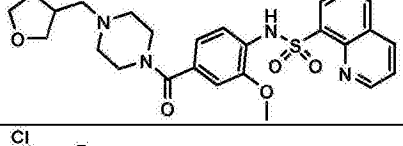
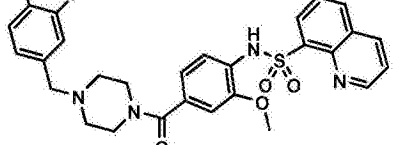
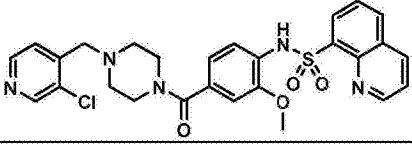
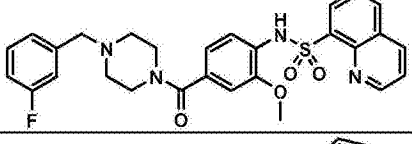
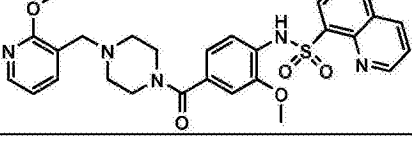
化合物	AC ₅₀
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	B
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	A

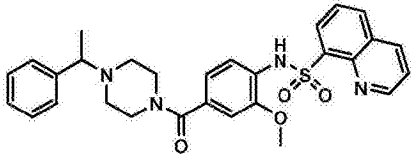
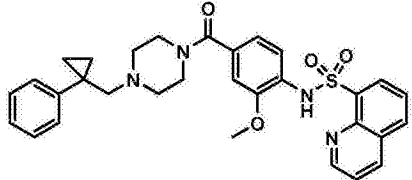
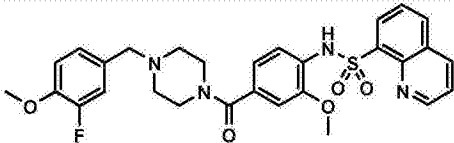
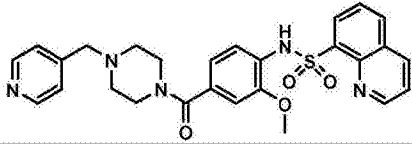
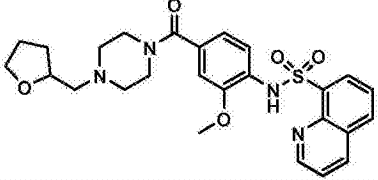
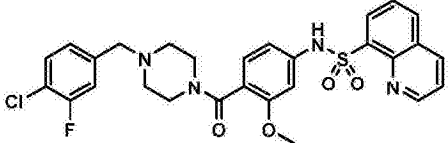
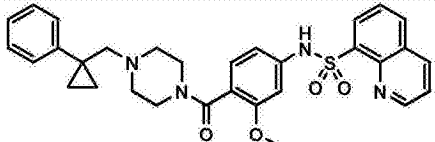
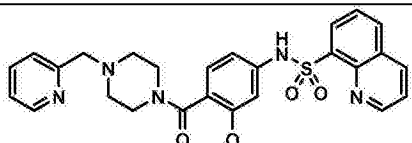
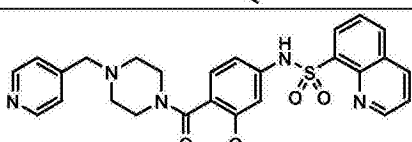
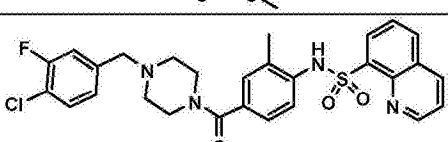
化合物	AC ₅₀
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	A
	A
	B
	A
	B
	A
	B
	B
	B
	B

化合物	AC ₅₀
	B
	D
	A
	A
	A
	A
	A
	A
	A
	A
	A

化合物	AC ₅₀
	A
	A
	A
	A
	A
	A
	A
	B
	B
	A

化合物	AC ₅₀
	A
	B
	A
	B
	B
	B
	A
	A
	B
	B

化合物	AC ₅₀
	B
	B
	A
	A
	A
	B
	A
	A
	A
	A

化合物	AC ₅₀
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	B
	A
	B
	A
	B
	A

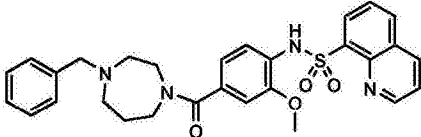
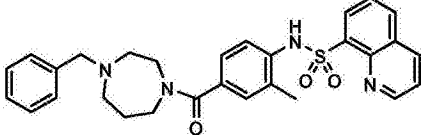
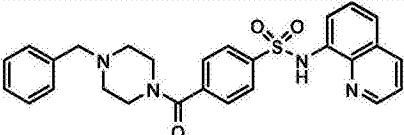
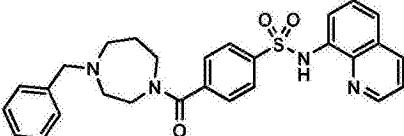
化合物	AC ₅₀
	B
	A
	C
	C
	A
	A

图1