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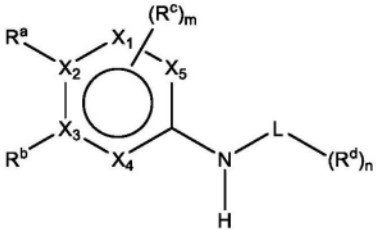
权利要求书7页 说明书406页

(54)发明名称

铁死亡调节剂、其制备和用途

(57)摘要

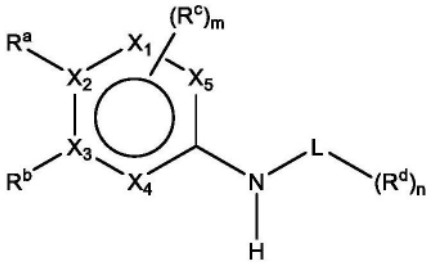
本公开提供式I的化合物、包含其的组合物和使用其的方法，包括在治疗各种疾病和病症，例如涉及铁死亡的那些中的用途。



式I

CN 118076581 A

1.以下结构式I的化合物：



式 I

其互变异构体，该化合物或该互变异构体的溶剂化物或立体异构体，或前述的药学上可接受的盐，其中：

L是环烷基，杂环基，或C；

X_1、X_2、X_3、X_4和X_5各自独立地是C或N；

R^a不存在或选自H，卤素，CN，任选被取代的杂原子，任选被取代的烷基，任选被取代的烯基，任选被取代的炔基，任选被取代的酰基，任选被取代的环烷基，任选被取代的杂环基，任选被取代的芳基，和任选被取代的杂芳基；

R^b不存在或选自H，卤素，CN，任选被取代的杂原子，任选被取代的烷基，任选被取代的环烷基，和任选被取代的杂环基；

R^a和R^b可以连在一起形成任选被取代的3-10元碳环、杂环、芳族、或杂芳族的环；

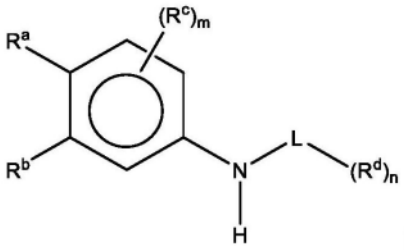
R^c，每次出现时，独立地选自卤素，任选被取代的杂原子，和任选被取代的烷基；

R^c中的一个与R^b可以连在一起形成任选被取代的3-10元碳环、杂环、芳族、或杂芳族的环；

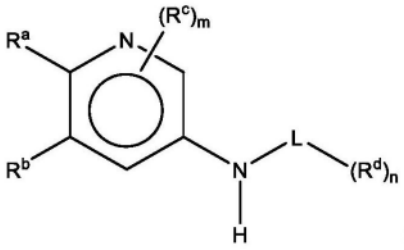
R^d，每次出现时，独立地选自卤素，CN，任选被取代的杂原子，任选被取代的烷基，任选被取代的烯基，任选被取代的炔基，任选被取代的酰基，任选被取代的环烷基，任选被取代的杂环基，任选被取代的芳基，和任选被取代的杂芳基；和

m和n各自是独立选自0、1、2和3的整数。

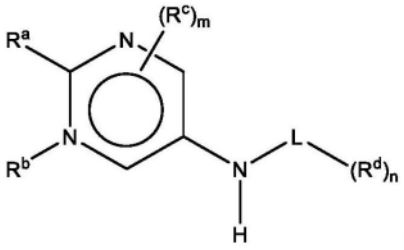
2.权利要求1的化合物，其中化合物具有以下结构式IIa至IIh之一：



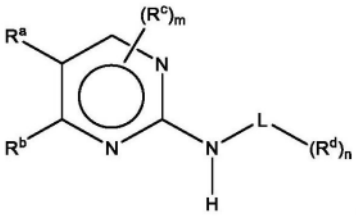
式 IIa



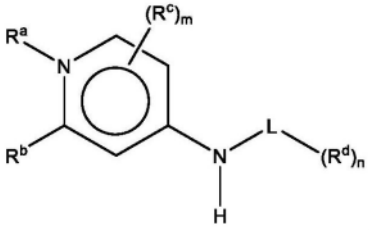
式 IIb



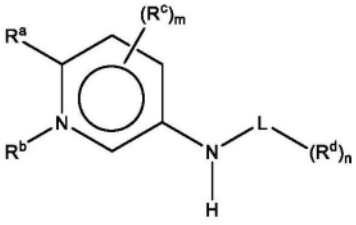
式 IIc



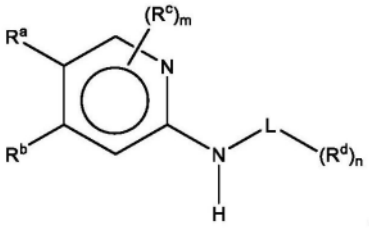
式 IId



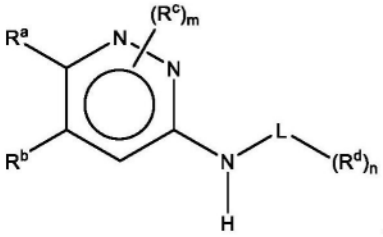
式 IIe



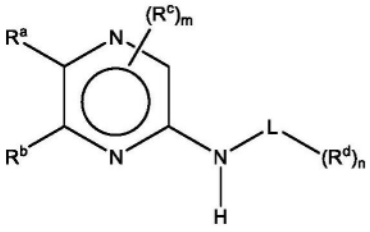
式 IIf



式 IIg



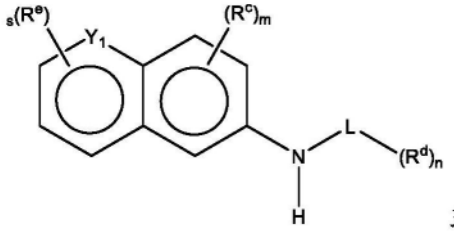
式 IIh



式 IIi

其互变异构体,该化合物或该互变异构体的溶剂化物或立体异构体,或前述的药学上可接受的盐。

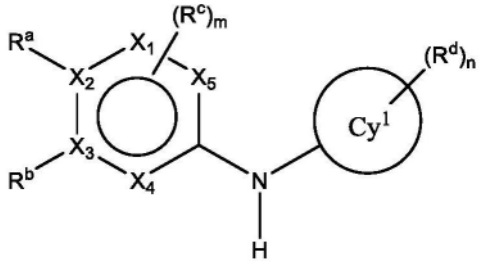
3.权利要求1的化合物,其中化合物具有以下结构式IIj之一:



式 IIj

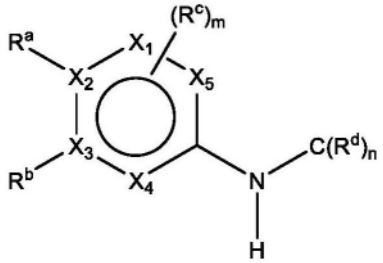
其互变异构体,该化合物或该互变异构体的溶剂化物或立体异构体,或前述的药学上可接受的盐,其中Y_1是N或C;R^e,每次出现时,独立地选自任选被取代的环烷基,任选被取代的杂环基,任选被取代的芳基,和任选被取代的杂芳基;和s是选自0、1、2和3的整数。

4.权利要求1的化合物,其中化合物具有以下结构式IIIa和IIIb之一:



式 IIIa

其中Cy^1是3-10元环烷基或3-10元杂环基;

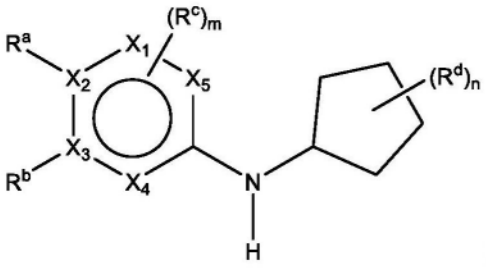


式 IIIb

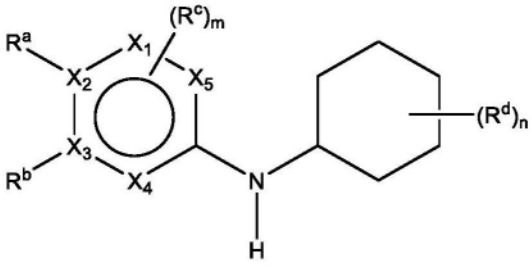
其互变异构体,该化合物或该互变异构体的溶剂化物或立体异构体,或前述的药学上

可接受的盐。

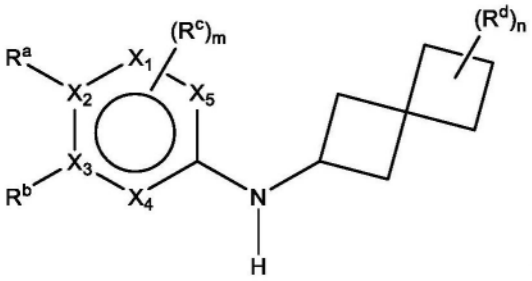
5.权利要求1-4中任一项的化合物,其中化合物具有以下结构式IVa至IVf之一:



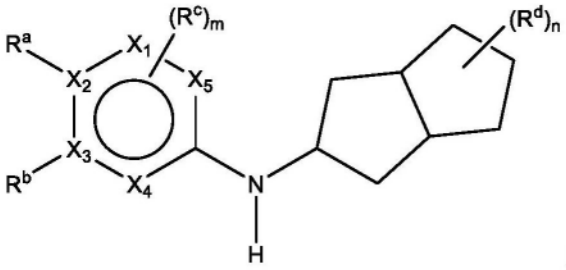
式 IVa



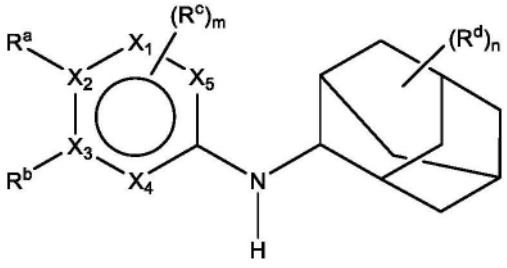
式 IVb



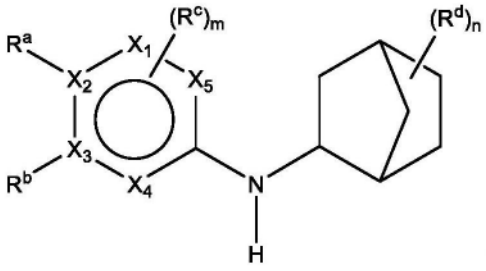
式 IVc



式 IVd



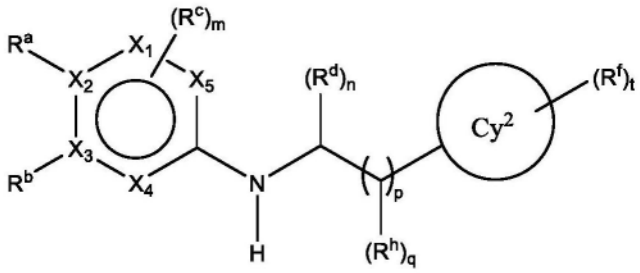
式 IVe



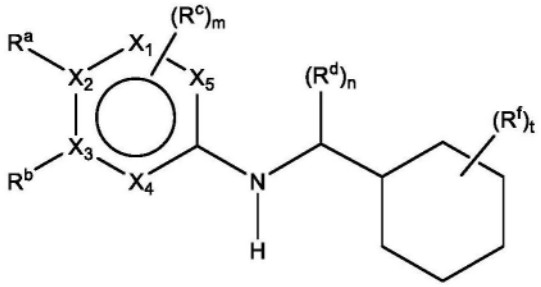
式 IVf

其互变异构体,该化合物或该互变异构体的溶剂化物或立体异构体,或前述的药学上可接受的盐。

6.权利要求1-4中任一项的化合物,其中化合物具有以下结构式Va和VIa之一:



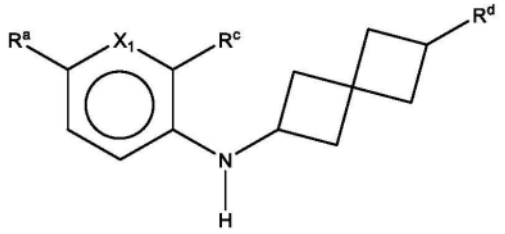
式 Va



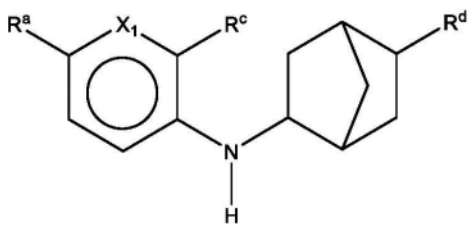
式 VIa

其互变异构体,该化合物或该互变异构体的溶剂化物或立体异构体,或前述的药学上可接受的盐,其中Cy^2是3-10元环烷基或3-10元杂环基;R^f,每次出现时,独立地选自卤素,CN,任选被取代的杂原子,任选被取代的烷基,任选被取代的烯基,任选被取代的炔基,任选被取代的酰基,任选被取代的环烷基,任选被取代的杂环基,任选被取代的芳基,和任选被取代的杂芳基;R^h,每次出现时,独立地选自卤素,CN,和任选被取代的C_1-C_6烷基;n是选自0、1和2的整数;p是选自0、1、2、3、4和5的整数;q是选自0、1和2的整数;并且t是独立选自0、1、2和3的整数;优选地n是0,q是0,并且p是0,1,2和3。

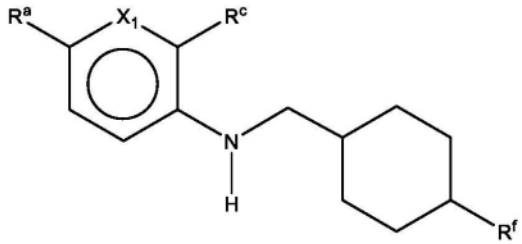
7.权利要求1的化合物,其中化合物具有以下结构式VIIa-VIIe之一:



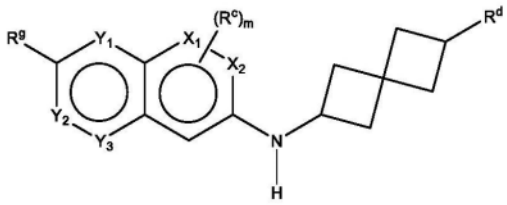
VIIa



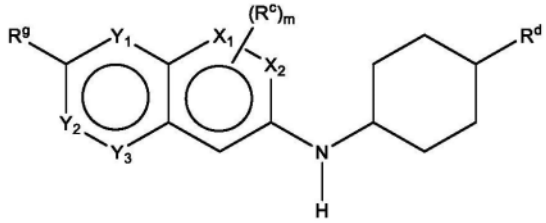
VIIb



VIIc



VIId

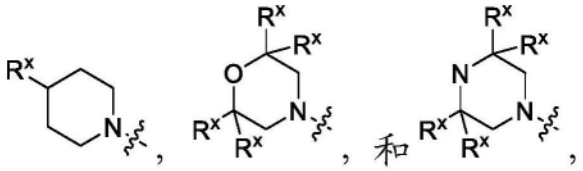


VIIe

其互变异构体,该化合物或该互变异构体的溶剂化物或立体异构体,或前述的药学上可接受的盐,其中:

X_1和X_2独立地是C或N;

Y_1,Y_2和Y_3独立地是C或N;

R^a选自  ,其中R^x,每次出现时,独立地选自H,CF_3,-CH_3,和-CH_2CH_3;

R^c选自卤素,C_1-C_2烷基,和C_1-C_2烷氧基;

R^d选自NH_2和-C(=O)NH_2;

R^f选自NH_2和-C(=O)NH_2;和

m是0或1。

8.一种化合物,其选自说明书中所公开的化合物1-661,其互变异构体,该化合物或该互变异构体的溶剂化物或立体异构体,或前述的药学上可接受的盐。

9.一种药物组合物,其包括根据权利要求1-8中任一项的化合物,其互变异构体,该化合物或该互变异构体的溶剂化物或立体异构体,或前述的药学上可接受的盐和至少一种药学上可接受的载体。

10.治疗疾病或病症(优选选自神经病,中风,神经退行性疾病,帕金森病,肌萎缩侧索硬化症(AML),多发性硬化症,亨廷顿病,路易体痴呆,弗里德赖希共济失调,毛囊形态发生,糖尿病,败血症,移植排斥,脑室周围白质软化,缺血再灌注损伤,凝血,心肌梗塞,和肾功能

障碍),治疗涉及铁死亡的疾病或病症,或调节铁死亡的方法,包括向需要其的受试者施用治疗有效量的根据权利要求1-8中任一项的化合物,其互变异构体,该化合物或该互变异构体的溶剂化物或立体异构体,或前述的药学上可接受的盐或根据权利要求9的药物组合物;或使需要其的受试者接触根据权利要求1-8中任一项的化合物,其互变异构体,该化合物或该互变异构体的溶剂化物或立体异构体,或前述的药学上可接受的盐或根据权利要求9的药物组合物。

铁死亡调节剂、其制备和用途

技术领域

[0001] 本公开涉及调节铁死亡的化合物、包含该化合物的组合物、制备该化合物的方法、以及使用该化合物治疗各种疾病或病症(例如涉及铁死亡的那些)的方法。

背景技术

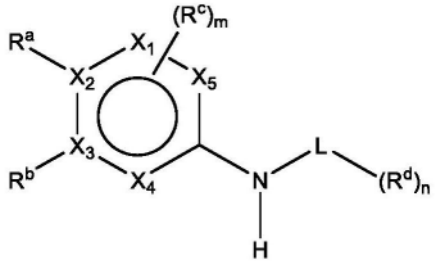
[0002] 铁死亡是一种依赖于铁的程序性细胞死亡,其特征是脂质过氧化物的积累,并且在遗传和生化上不同于其他形式的受调节细胞死亡,例如细胞凋亡、自噬和坏死。(Dixon等人,Cell 149,1060-1072(2012))。Conrad等人,Nature Chemical Biology,第15卷,2019年12月,1137-1147对铁死亡的某些机制和铁死亡细胞死亡的关键因素进行了回顾和说明。

[0003] 铁死亡与许多疾病或病症有关,包括神经病、中风、神经退行性疾病(例如阿尔茨海默病)、帕金森病、肌萎缩侧索硬化症(AML)、多发性硬化症、亨廷顿病、路易体痴呆、弗里德赖希共济失调、毛囊形态发生、糖尿病、败血症、移植排斥、脑室周围白质软化、缺血再灌注损伤、凝血、心肌梗塞和肾功能障碍例如急性肾衰竭。例如,铁死亡调节因子Gpx4的失活会引发小鼠急性肾衰竭。(Angeli等人,Nature Cell Biology,2014年11月17日在线公开;DOI:10.1038/ncb3064)。铁死亡被认为与多种病理生理学背景有关,例如肿瘤抑制、抗病毒免疫、神经变性和缺血/再灌注损伤(IRI)。(Angeli等人,Trends in Pharmacological Sciences,2017年5月,第38卷,第5期,489-498(2017)。)

[0004] Skouta等人,J.Am.Chem.Soc.,dx.doi.org/10.1021/ja411006a和$WO_2$013152039A1、$WO_2$015084749A1、$WO_2$019154795A1、$WO_2$016075137A1、$WO_2$020185738A1和PCT/CN2021/078601公开了调节铁死亡的某些化合物。

发明内容

[0005] 本公开的一个方面提供了一种化合物,该化合物选自在本文公开的式的化合物,其互变异构体,该化合物或该互变异构体的溶剂化物或立体异构体,或前述的药学上可接受的盐,其可用于治疗各种疾病或病症,例如涉及铁死亡的疾病或病症。例如,本文公开的是以下结构式I的化合物:

[0006] 

式(I)

[0007] 其互变异构体,该化合物或该互变异构体的溶剂化物或立体异构体,或前述的药学上可接受的盐,其中:

[0008] L是环烷基,杂环基,或C;

[0009] X_1、X_2、X_3、X_4和X_5各自独立地是C或N;

[0010] R^a不存在或选自H,卤素,CN,任选被取代的杂原子,任选被取代的烷基,任选被取代的烯基,任选被取代的炔基,任选被取代的酰基,任选被取代的环烷基,任选被取代的杂环基,任选被取代的芳基,和任选被取代的杂芳基;

[0011] R^b不存在或选自H,卤素,CN,任选被取代的杂原子,任选被取代的烷基,任选被取代的环烷基,和任选被取代的杂环基;

[0012] R^a和R^b可以连在一起形成任选被取代的3-10元碳环、杂环、芳族、或杂芳族的环;

[0013] R^c,每次出现时,独立地选自卤素,任选被取代的杂原子,和任选被取代的烷基;

[0014] R^c中的一个与R^b可以连在一起形成任选被取代的3-10元碳环、杂环、芳族、或杂芳族的环;

[0015] R^d,每次出现时,独立地选自卤素,CN,任选被取代的杂原子,任选被取代的烷基,任选被取代的烯基,任选被取代的炔基,任选被取代的酰基,任选被取代的环烷基,任选被取代的杂环基,任选被取代的芳基,和任选被取代的杂芳基;和

[0016] m和n各自是独立选自0、1、2和3的整数。

[0017] 在本公开的一个方面中,本文中公开的式的化合物选自以下所示的化合物1至573,其互变异构体,该化合物或该互变异构体的溶剂化物或立体异构体,或前述的药学上可接受的盐。

[0018] 在一些实施方案中,本公开提供了药物组合物,包括本文公开的式的化合物,其互变异构体,该化合物或该互变异构体的溶剂化物或立体异构体,或前述的药学上可接受的盐,和药学上可接受的载体。在一些实施方案中,药物组合物可以包括选自以下所示的化合物1至573的化合物,其互变异构体,该化合物或该互变异构体的溶剂化物或立体异构体,或前述的药学上可接受的盐,和药学上可接受的载体。这些组合物还可包含另外的活性药剂。

[0019] 在本公开的一个方面中,本文中公开的式的化合物选自以下所示的化合物574至661,其互变异构体,该化合物或该互变异构体的溶剂化物或立体异构体,或前述的药学上可接受的盐。

[0020] 在一些实施方案中,本公开提供了药物组合物,包括本文公开的式的化合物,其互变异构体,该化合物或该互变异构体的溶剂化物或立体异构体,或前述的药学上可接受的盐,和药学上可接受的载体。在一些实施方案中,药物组合物可以包括选自以下所示的化合物574至661的化合物,其互变异构体,该化合物或该互变异构体的溶剂化物或立体异构体,或前述的药学上可接受的盐,和药学上可接受的载体。这些组合物还可包含另外的活性药剂。

[0021] 本公开的另一方面提供了治疗疾病或病症的方法,包括向需要其的受试者施用治疗有效量的本文公开的式的化合物,其互变异构体,该化合物或该互变异构体的溶剂化物或立体异构体,或前述的药学上可接受的盐,或包含前述中任一种的药物组合物,其中所示疾病或病症选自神经病,中风,神经退行性疾病(例如阿尔茨海默病),帕金森病,肌萎缩侧索硬化症(AML),多发性硬化症,亨廷顿病,路易体痴呆,弗里德赖希共济失调,毛囊形态发生,糖尿病,败血症,移植排斥,脑室周围白质软化,缺血再灌注损伤,凝血,心肌梗塞,和肾功能障碍如急性肾衰竭。

[0022] 本公开的另一方面提供治疗涉及铁死亡的疾病或病症的方法,包括向需要其的受

试者施用治疗有效量的本文公开的式的化合物,其互变异构体,该化合物或该互变异构体的溶剂化物或立体异构体,或前述的药学上可接受的盐,或包含前述中任一种的药物组合物。

[0023] 在一些实施方案中,治疗方法包括向需要其的受试者施用选自以下所示的化合物1至573的化合物,其互变异构体,该化合物或该互变异构体的溶剂化物或立体异构体,或前述的药学上可接受的盐,或包含前述中任一种的药物组合物。

[0024] 在一些实施方案中,治疗方法包括向有其需要的受试者施用另外的活性药剂,或者在与本文公开的式的化合物,其互变异构体,该化合物或该互变异构体的溶剂化物或立体异构体,或前述的药学上可接受的盐相同的药物组合物中,或在单独的组合物中。在一些实施方案中,治疗方法包括施用选自以下所示的化合物1至573的化合物,其互变异构体,该化合物或该互变异构体的溶剂化物或立体异构体,或前述的药学上可接受的盐与在相同的药物组合物中或者在单独的组合物中的另外的活性药剂.当作为单独的组合物施用时,另外的治疗剂可以在施用本文公开的化合物、互变异构体、溶剂化物、立体异构体或药学上可接受的盐之前、同时或之后施用。

[0025] 本文还公开了在有其需要的受试者中调节(例如抑制)铁死亡的方法,包括使受试者接触本文公开的式的化合物,其互变异构体,该化合物或该互变异构体的溶剂化物或立体异构体,或前述的药学上可接受的盐,或包含前述中任一种的药物组合物。在一些实施方案中,在有其需要的受试者中调节(例如抑制)铁死亡的方法包括使受试者接触选自以下所示的化合物1至573的化合物,其互变异构体,该化合物或该互变异构体的溶剂化物或立体异构体,或前述的药学上可接受的盐,或包含前述中任一种的药物组合物。

[0026] 在一些实施方案中,治疗方法包括向需要其的受试者施用选自以下所示的化合物574至661的化合物,其互变异构体,该化合物或该互变异构体的溶剂化物或立体异构体,或前述的药学上可接受的盐,或包含前述中任一种的药物组合物。

[0027] 在一些实施方案中,治疗方法包括向有其需要的受试者施用另外的活性药剂,或者在与本文公开的式的化合物,其互变异构体,该化合物或该互变异构体的溶剂化物或立体异构体,或前述的药学上可接受的盐相同的药物组合物中,或在单独的组合物中。在一些实施方案中,治疗方法包括施用选自以下所示的化合物574至661的化合物,其互变异构体,该化合物或该互变异构体的溶剂化物或立体异构体,或前述的药学上可接受的盐与在相同的药物组合物中或者在单独的组合物中的另外的活性药剂。当作为单独的组合物施用时,另外的治疗剂可以在施用本文公开的化合物、互变异构体、溶剂化物、立体异构体或药学上可接受的盐之前、同时或之后施用。

[0028] 本文还公开了在有其需要的受试者中调节(例如抑制)铁死亡的方法,包括使受试者接触本文公开的式的化合物,其互变异构体,该化合物或该互变异构体的溶剂化物或立体异构体,或前述的药学上可接受的盐,或包含前述中任一种的药物组合物。在一些实施方案中,在有其需要的受试者中调节(例如抑制)铁死亡的方法包括使受试者接触选自以下所示的化合物574至661的化合物,其互变异构体,该化合物或该互变异构体的溶剂化物或立体异构体,或前述的药学上可接受的盐,或包含前述中任一种的药物组合物。

具体实施方式

[0029] I.定义

[0030] 术语“一种”或“一个”当涉及本文使用的名词时涵盖表述“至少一个”,因此涵盖名词的单数和复数单元。例如,“另外的药剂”是指单一或两种或更多种另外的药剂。

[0031] 术语“烷基”是指含有1-20,例如1-18、1-12、1-10、1-8、1-6、1-4或1-3个碳原子的选自直链和支链饱和烃基的烃基。烷基的实例包括甲基、乙基、1-丙基或正丙基(″n-Pr″)、2-丙基或异丙基(″i-Pr″)、1-丁基或正丁基(″n-Bu″)、2-甲基-1-丙基或异丁基(″i-Bu″)、1-甲基丙基或仲丁基(″s-Bu″)和1,1-二甲基乙基或叔丁基(″t-Bu″)。烷基的其他实例包括1-戊基、2-戊基、3-戊基、2-甲基-2-丁基、3-甲基-2-丁基、3-甲基-1-丁基、2-甲基-1-丁基、1-己基、2-己基、3-己基、2-甲基-2-戊基、3-甲基-2-戊基、4-甲基-2-戊基、3-甲基-3-戊基、2-甲基-3-戊基、2,3-二甲基-2-丁基和3,3-二甲基-2-丁基。低级烷基含有1-8个,优选1-6个,更优选1-4个碳原子,和更优选1-3个碳原子。

[0032] 术语“烯基”是指包含至少一个C=C双键和2-20个,例如2-18、2-12、2-10、2-8、2-6或2-4个碳原子的选自直链和支链烃基的烃基。烯基的实例可以选自乙烯基(ethenyl or vinyl)、丙-1-烯基、丙-2-烯基、2-甲基丙-1-烯基、丁-1-烯基、丁-2-烯基、丁-3-烯基、丁-1,3-二烯基、2-甲基丁-1,3-二烯、己-1-烯基、己-2-烯基、己-3-烯基、己-4-烯基和己-1,3-二烯基。低级烯基含有2-8个、优选2-6个、和更优选2-4个碳原子。

[0033] 术语“炔基”是指包含至少一个C≡C三键和2-20个,例如2-18、2-12、2-10、2-8、2-6或2-4个碳原子的选自直链和支链烃基的烃基。炔基的实例包括乙炔基、1-丙炔基、2-丙炔基(炔丙基)、1-丁炔基、2-丁炔基和3-丁炔基。低级炔基含有2-8个、优选2-6个、和更优选2-4个碳原子。

[0034] 术语“杂烷基”是指如本文所定义的烷基,其中一个或多个组成碳原子已被杂原子例如氮、氧或硫替代,例如CH_3CH_2OH、$CH_3CH_2OC_2H_5$、CH_3CH_2SH、$CH_3CH_2SC_2H_5$、$CH_3CH_2NH_2$、$CH_3CH_2NHC_2H_5$等。在一些实施方案中,除了用氮、氧或硫替代一个或多个组成碳原子之外,杂烷基还任选地如本文所定义地被取代。

[0035] 术语“环烷基”是指选自饱和和部分不饱和环状烃基的烃基,例如单环和多环(例如双环和三环)基团。例如,环烷基可以具有3-12、3-10、或3-8、或3-6、或3-4、或5-6个碳原子。甚至进一步例如,环烷基可以是具有3-12、或3-8、或3-6、或3-4、或5-6个碳原子的单环基团。单环环烷基的实例包括环丙基、环丁基、环戊基、1-环戊-1-烯基、1-环戊-2-烯基、1-环戊-3-烯基、环己基、1-环己-1-烯基、1-环己-2-烯基、1-环己-3-烯基、环己二烯基、环庚基、环辛基、环壬基、环癸基、环十一烷基和环十二烷基。双环环烷基的实例包括作为选自[4,4]、[4,5]、[5,5]、[5,6]和[6,6]环系的双环,或作为选自双环[2.2.1]庚烷、双环[2.2.2]辛烷和双环[3.2.2]壬烷的桥联双环排列的具有7-12个环原子的那些。该环可以是饱和的或具有至少一个双键(即部分不饱和),但不是完全共轭的,并且不是芳族的,芳族在本文中定义。

[0036] 术语“杂环”或“杂环基”(″heterocyclic″or″heterocycle″or″杂环基″)是指选自4-至12-元,例如3-至6-元、3-至5-元、4-至5-元,或5-6元单环、双环和三环的饱和和部分不饱和环的环,其除了1、2、3或4个选自例如氧、硫、氮和硅的杂原子之外,还包含至少一个碳原子。“杂环”还指与5-、6-和/或7-元环烷基、碳环芳族或杂芳族环稠合的包含至少一个选

自N、O和S的杂原子的5-至7-元杂环,条件是当杂环与碳环芳族或杂芳族环稠合时,连接点位于杂环处,并且当杂环与环烷基稠合时,连接点可以位于环烷基或杂环处。

[0037] “杂环”还指包含至少一个选自N、O和S的杂原子的脂族螺环,条件是连接点位于杂环处。所述环可以是饱和的或具有至少一个双键(即部分不饱和)。杂环可以被氧代取代。连接点可以是杂环中的碳或杂原子。杂环不是本文定义的杂芳基。

[0038] 杂环的实例包括但不限于(从指定优先的连接位置1开始编号)1-吡咯烷基、2-吡咯烷基、2,4-咪唑烷基、2,3-吡唑烷基、1-哌啶基、2-哌啶基、3-哌啶基、4-哌啶基、2,5-哌嗪基、吡喃基、2-吗啉基、3-吗啉基、环氧乙烷基、氮杂环丙烷基、硫杂环丙烷基、氮杂环丁烷基、氧杂环丁烷基、硫杂环丁烷基、1,2-二硫杂环丁烷基、1,3-二硫杂环丁烷基、二氢吡啶基、四氢吡啶基、硫代吗啉基、硫氧杂环己烷基、哌嗪基、高哌嗪基、高哌啶基、氮杂环庚烷基、氧杂环庚烷基、硫杂环庚烷基、1,4-氧硫杂环己烷基、1,4-二氧杂环庚烷基、1,4-氧硫杂环庚烷基、1,4-氧氮杂环庚烷基、1,4-二硫杂环庚烷基、1,4-硫氮杂环庚烷基、1,4-二氮杂环庚烷基、1,4-二噻烷基、1,4-氧硫杂环己烷、氧氮杂环庚三烯基、二氮杂环庚三烯基、硫氮杂环庚三烯基、二氢噻吩基、二氢吡喃基、二氢呋喃基、四氢呋喃基、四氢噻吩基、四氢吡喃基、四氢噻喃基、1-吡咯啉基、2-吡咯啉基、3-吡咯啉基、二氢吲哚基、2H-吡喃基、4H-吡喃基、1,4-二氧杂环己烷基、1,3-二氧杂环戊烷基、吡唑啉基、吡唑烷基、二噻烷基、二硫杂环戊烷基、吡唑烷基、咪唑啉基、嘧啶酮基、1,1-二氧代-硫代吗啉基、3-氮杂双环[3.1.0]己基、3-氮杂双环[4.1.0]庚基和氮杂双环[2.2.2]己基。取代的杂环还包括被一个或多个氧代基团取代的环系,例如哌啶基N-氧化物、吗啉基-N-氧化物、1-氧代-1-硫代吗啉基和1,1-二氧代-1-硫代吗啉基。

[0039] 本文中的术语“稠合环”是指多环体系,例如二环或三环体系,其中两个环仅共同分享两个环原子和一个键。稠合环的实例可包括稠合双环环烷基环,例如作为选自如上所述的[4,4]、[4,5]、[5,5]、[5,6]和[6,6]环系的双环排列的具有7至12个环原子的那些;稠合双环芳环,例如如上所述的7至12元双环芳环体系,稠合三环芳环,例如如上所述的10至15元三环芳环体系;稠合双环杂芳环,例如如上所述的8至12元双环杂芳环,稠合三环杂芳环,例如如上所述的11至14元三环杂芳环;和如上所述的稠合双环或三环杂环。

[0040] 术语“杂原子”是指氧、硫、氮、磷和硅中的一种或多种,包括氮或硫的任何氧化形式;杂环的任何碱性氮或可取代氮的季铵化形式,例如N(如在3,4-二氢-2H-吡咯基中)、NH(如在吡咯烷基中)或NR^+(其中R是例如任选取代的烷基)(如在N-取代的吡咯烷基中)。

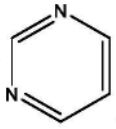
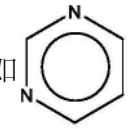
[0041] 本文所用的术语“不饱和”是指基团具有一个或多个不饱和单元或不饱和度。不饱和是一种状态,其中化合物中并非所有可用的价键都被取代基满足,因此该化合物含有一个或多个双键或三键。

[0042] 本文所用的术语“烷氧基”是指其中烷基的一个碳被氧原子替代的如上所定义的烷基,条件是该氧原子连接在两个碳原子之间。

[0043] 术语“卤素”包括F、Cl、Br和I,即分别为氟、氯、溴和碘。

[0044] 如本文所用,“CN”、“氰基”或“腈”基团是指-C≡N。

[0045] 本文所用的“芳环”是指含有具有由[4n+2]p轨道电子组成的离域π电子轨道的共轭平面环系的碳环或杂环,其中n是0至6的整数。“非芳族”环是指不满足上文对芳环提出的要求的碳环或杂环,并且可以是完全或部分饱和的。芳环的非限制性实例包括芳环和杂芳

环,其进一步定义如下。“芳环”可以被描述为具有共轭双键的环,例如  ,或描述为具有内环的环,例如  。

[0046] 本文中的术语“芳基”是指选自以下的基团:单环碳环芳环,例如苯基;双环体系,例如7-12元双环环系,其中至少一个环是碳环和芳族,选自例如萘、茚满和1,2,3,4-四氢喹啉;和三环环系,例如10-15元三环环系,其中至少一个环是碳环和芳族的,例如芴。

[0047] 例如,芳基可以是与任选地包含至少一个选自N、O和S的杂原子的5-7元环烷基或杂环稠合的6元碳环芳环,条件是当碳环芳环与杂环稠合时,连接点在碳环芳环处,并且当碳环芳环与环烷基稠合时,连接点可以在碳环芳环处或在环烷基处。由取代苯衍生物形成并在环原子上具有自由价的二价基团称为取代亚苯基。衍生自单价多环烃基(其名称通过从具有自由价的碳原子上除去一个氢原子而以“-基”结尾)的二价基团,通过在相应的单价基团的名称中添加“-亚基”来命名,例如,具有两个连接点的萘基称为亚萘基。

[0048] 术语“杂芳基”是指选自以下的基团:包含1、2、3或4个选自N、O和S的杂原子的5-至7-元,例如5-至6-元芳族单环,其余环原子为碳;包含1、2、3或4个选自N、O和S的杂原子的8至12元双环,其余环原子为碳,且其中至少一个环为芳族且至少一个杂原子存在于芳环中;和包含1、2、3或4个选自N、O和S的杂原子的11-至14-元三环,其余环原子为碳,并且其中至少一个环为芳族的且至少一个杂原子存在于芳环中。

[0049] 例如,杂芳基可以是与5元至7元环烷基环稠合的5元至7元杂环芳环。对于其中仅一个环包含至少一个杂原子的此类稠合双环杂芳环体系,连接点可以在杂芳环处或在环烷基环处。

[0050] 当杂芳基中的S和O原子的总数超过1时,这些杂原子彼此不相邻。在一些实施方案中,杂芳基中的S和O原子的总数不超过2。在一些实施方案中,芳族杂环中的S和O原子的总数不超过1。

[0051] 杂芳基的实例包括但不限于(从指定优先的连接位置1开始编号)吡啶基(例如2-吡啶基、3-吡啶基或4-吡啶基)、噌啉基、吡嗪基、2,4-嘧啶基、3,5-嘧啶基、2,4-咪唑基、咪唑并吡啶基、异噁唑基、噁唑基、噻唑基、异噻唑基、噻二唑基、四唑基、噻吩基、三嗪基、苯并噻吩基、呋喃基、苯并呋喃基、苯并咪唑基、吲哚基、异吲哚基、吲哚啉基、酞嗪基、吡嗪基、哒嗪基、吡咯基、三唑基、喹啉基、异喹啉基、吡唑基、吡咯并吡啶基(例如1H-吡咯并[2,3-b]吡啶-5-基)、吡唑并吡啶基(例如1H-吡唑并[3,4-b]吡啶-5-基)、苯并噁唑基(例如苯并[d]噁唑-6-基)、蝶啶基、噁呤基、1-氧杂-2,3-二唑基、1-氧杂-2,4-二唑基、1-氧杂-2,5-二唑基、1-氧杂-3,4-二唑基、1-硫杂-2,3-二唑基、1-硫杂-2,4-二唑基、1-硫杂-2,5-二唑基、1-硫杂-3,4-二唑基、呋咱基、苯并呋咱基、苯并噻吩基、苯并噻唑基、苯并噁唑基、喹唑啉基、喹喔啉基、萘啶基、呋喃并吡啶基、苯并噻唑基(例如苯并[d]噻唑-6-基)、吲唑基(例如1H-吲唑-5-基)和5,6,7,8-四氢异喹啉基。

[0052] 术语“酰基”是指这样的取代基,其中取代基中的连接点是羰基。示例性酰基包括但不限于-C(=O)R’、-C(=O)NR’R”或-C(=O)OR’,其中R’和R”独立地选自氢、烷基、烯基、

炔基、杂烷基、杂烯基、杂炔基、环烷基、芳基、杂环基或杂芳基，其任何一个都可进一步被一个或多个取代基取代。

[0053] 有些化合物可能以不同的氢连接点存在，称为“互变异构体”。例如，包含羰基-$CH_2C(O)$-基团(酮形式)的化合物可发生互变异构以形成羟基-CH＝C(OH)-基团(烯醇形式)。如果适用的话，酮和烯醇形式，单独的和以它们的混合物的形式，也旨在包括在内。

[0054] 本公开的化合物、互变异构体、溶剂化物或药学上可接受的盐可以含有不对称中心并且因此可以作为对映异构体存在。例如，当化合物具有两个或更多个不对称中心时，它们还可以作为非对映异构体存在。对映异构体和非对映异构体属于更广泛的立体异构体类别。所有这些可能的立体异构体，如基本上纯的拆分的对映异构体、其外消旋混合物、以及非对映异构体的混合物都旨在包括在本公开内容中。旨在包括化合物、互变异构体、溶剂化物和其药学上可接受的盐的所有立体异构体。除非另外具体提及，否则提及一种异构体适用于任何可能的异构体。当异构体组成未明确时，所有可能的异构体都包括在内。

[0055] 非对映异构体混合物可以通过本领域技术人员熟知的方法，例如通过层析法和/或分级结晶，基于其物理化学差异而分离成其单独的非对映异构体。对映异构体可以通过以下方式分离：通过与适当的光学活性化合物(例如，手性助剂，如手性醇或Mosher氏酰氯)反应将对映异构混合物转化为非对映异构混合物，分离非对映异构体并将各个非对映异构体转化(例如，水解)为相应的纯对映异构体。对映异构体也可以通过使用手性HPLC柱进行分离。

[0056] 单一立体异构体，例如基本上纯的对映异构体，可以通过使用诸如使用光学活性拆分剂形成非对映异构体的方法拆分外消旋混合物来获得。本公开的手性化合物的外消旋混合物可以通过任何合适的方法分离和离析，包括：(1)采用手性化合物形成离子非对映异构盐并通过分级结晶或其他方法分离，(2)采用手性衍生剂形成非对映异构化合物，分离非对映异构体，和转化成纯的立体异构体，(3)直接在手性条件下分离基本上纯的或富集的立体异构体。

[0057] 在立体异构体的上下文中，术语“基本上纯的”是指目标立体异构体含有按重量计不超过35％，例如不超过30％，进一步例如不超过25％，甚至进一步例如不超过20％的任何其他立体异构体。在一些实施方案中，术语“基本上纯的”是指目标立体异构体含有按重量计不超过10％、例如不超过5％、例如不超过1％的任何其他立体异构体。

[0058] 除非另有说明，本文描述的结构意在包括该结构的所有异构形式，例如外消旋混合物、顺式/反式异构体、几何(或构象)异构体，例如(Z)和(E)双键异构体，和(Z)和(E)构象异构体。因此，本文公开的化合物的几何和构象混合物在本公开的范围内。除非另有说明，本公开化合物的所有互变异构形式均在本公开的范围内。

[0059] 本公开提供了所公开的化合物、互变异构体、溶剂化物和立体异构体的药学上可接受的盐。化合物的盐在酸和化合物的碱性基团(例如氨基官能团)之间形成，或者在碱和化合物的酸性基团(例如羧基官能团)之间形成。

[0060] 本文所用的术语“药学上可接受的”是指在合理的医学判断范围内适合与人类和其他哺乳动物的组织接触而没有过度毒性、刺激、过敏反应等的组分，并与合理的收益/风险比相称。“药学上可接受的盐”是指在给予接受者后能够直接或间接提供本公开的化合物的任何无毒盐。

[0061] “药学上可接受的盐”包括但不限于与无机酸形成的盐,选自例如盐酸盐、磷酸盐、二磷酸盐、氢溴酸盐、硫酸盐、亚硫酸盐/亚磺酸盐(sulfinates)和硝酸盐;以及与有机酸形成的盐,选自例如苹果酸盐、马来酸盐、富马酸盐、酒石酸盐、琥珀酸盐、柠檬酸盐、乳酸盐、甲磺酸盐、对甲苯磺酸盐、2-羟乙基磺酸盐、苯甲酸盐、水杨酸盐、硬脂酸盐、烷酸盐如乙酸盐,和与HOOC-(CH_2)n-COOH形成的盐,其中n选自0至4。类似地,药学上可接受的阳离子的实例包括但不限于钠、钾、钙、镁、铝、锂和铵。合适的药学上可接受的盐是例如S.M.Berge等人.J.Pharmaceutical Sciences,1977,66,第1至19页中公开的那些。

[0062] 通常用于形成药学上可接受的盐的酸包括无机酸,例如氢硫酸(氢bisulfide)、盐酸、氢溴酸、氢碘酸、硫酸和磷酸,以及有机酸,例如对甲苯磺酸、水杨酸、酒石酸、酒石酸(bitartaric acid)、抗坏血酸、马来酸、苯磺酸、富马酸、葡萄糖酸、葡萄糖醛酸、甲酸、谷氨酸、甲磺酸、乙磺酸、苯磺酸、乳酸、草酸、对溴苯磺酸、碳酸、琥珀酸、柠檬酸、苯甲酸和乙酸。因此,此类药学上可接受的盐包括硫酸盐、焦硫酸盐、硫酸氢盐、亚硫酸盐、亚硫酸氢盐、磷酸盐、磷酸一氢盐、磷酸二氢盐、偏磷酸盐、焦磷酸盐、氯化物、溴化物、碘化物、乙酸盐、丙酸盐、癸酸盐(decanoate(即caprate))、辛酸盐、丙烯酸盐、甲酸盐、异丁酸盐、庚酸盐、丙炔酸盐、草酸盐、丙二酸盐、琥珀酸盐、辛二酸盐、癸二酸盐、富马酸盐、马来酸盐、丁炔-1,4-二酸盐、己炔-1,6-二酸盐、苯甲酸盐、氯苯甲酸盐、甲基苯甲酸盐、二硝基苯甲酸盐、羟基苯甲酸盐、甲氧基苯甲酸盐、邻苯二甲酸盐、对苯二甲酸盐、磺酸盐、二甲苯磺酸盐、苯乙酸盐、苯丙酸盐、苯丁酸盐、柠檬酸盐、乳酸盐、β-羟基丁酸盐、乙醇酸盐、酒石酸盐、甲磺酸盐、丙磺酸盐、萘-1-磺酸盐、萘-2-磺酸盐、扁桃酸盐等盐类。在一些实施方案中,药学上可接受的酸加成盐包括与无机酸例如盐酸和氢溴酸形成的那些,以及与有机酸例如马来酸形成的那些。

[0063] 衍生自适当碱的药学上可接受的盐包括碱金属盐、碱土金属盐、铵盐和$N^+(C_{1-4}$烷基$)_4$盐。本公开还设想了本文公开的化合物的任何碱性含氮基团的季铵化。碱金属盐和碱土金属盐的合适的非限制性实例包括钠盐、锂盐、钾盐、钙盐和镁盐。药学上可接受的盐的其他非限制性实例包括使用抗衡离子例如卤离子、氢氧根、羧酸根、硫酸根、磷酸根、硝酸根、低级烷基磺酸根和芳基磺酸根形成的铵、季铵和胺阳离子的盐。药学上可接受的盐的其他合适的非限制性实例包括苯磺酸盐和葡糖胺盐。

[0064] 如果以酸加成盐形式获得化合物,则可以通过碱化酸加成盐的溶液来获得游离碱。相反,如果产物是游离碱,加成盐,例如药学上可接受的加成盐,可以通过将游离碱溶解在合适的有机溶剂中并用酸处理该溶液来制备,按照由碱化合物制备酸加成盐的常规方法进行。本领域技术人员将认识到无需过度实验即可使用的各种合成方法来制备无毒的药学上可接受的加成盐。

[0065] 本公开的化合物、互变异构体、溶剂化物、立体异构体和药学上可接受的盐还可以在构成此类化合物的一个或多个原子处含有非天然比例的原子同位素。例如,$-CD_3$、$-CD_2H$或$-CDH_2$含有一个或多个氘来代替氢。例如,化合物可用放射性同位素例如氚(^3H)、碘-125(^{125}I)或碳14(^{14}C)进行放射性标记。本公开化合物的所有同位素变体,无论是否具有放射性,都旨在涵盖在本公开的范围内。

[0066] 如本文所用的“任选取代的”可与短语“取代或未取代的”互换。一般而言,术语“取代的”是指给定结构中的氢基团被特定取代基的基团取代。除非另有说明,“任选取代的”基团可以在该基团的每个可取代位置具有取代基,并且当任何给定结构中的多于一个位置可

以被多于一个选自特定基团的取代基取代时,该取代基可以是每个位置都相同或不同。本公开内容设想的取代基的组合是导致形成稳定的或化学上可行的化合物的那些。

[0067] 在一些实施方案中,取代基独立地选自任选取代的杂原子和任选取代的、任选杂化的、任选环状的C_1-C_{18}烃基,特别是其中任选取代的、任选杂化的、任选环状的C_1-C_{18}烃基是任选取代的、任选杂化的、任选环状的烷基、烯基或炔基,或任选取代的、任选杂化的-芳基;和/或任选取代的杂原子是卤素、任选取代的羟基(例如烷氧基、芳氧基)、任选取代的酰基(例如甲酰基、烷酰基、氨基甲酰基、羧基、酰胺基)、任选取代的氨基(例如氨基、烷基氨基、二烷基氨基、酰胺基、磺酰胺基)、任选取代的硫醇(例如巯基、烷基硫醇、芳基硫醇)、任选取代的亚磺酰基或磺酰基(例如烷基亚磺酰基、芳基亚磺酰基、烷基磺酰基、芳基磺酰基)、硝基或氰基。

[0068] 在一些实施方案中,取代基独立地选自:卤素、-R'、-OR'、=O、=NR'、=N-OR'、-NR'R″、-SR'、-SiR'R″R'″、-OC(=O)R'、-C(=O)R'、-CO_2R'、-C(=O)NR'R″、-OC(=O)NR'R″、-NR″C(=O)R'、-NR'-C(=O)NR″R'″、-NR'-SO_2NR″R'″、-NR″CO_2R'、-NH-C(NH_2)=NH、-NR'C(NH_2)=NH、-NH-C(NH_2)=NR'、-S(O)R'、-SO_2R'、-SO_2NR'R″、-NR″SO_2R、-CN、-NO_2、-N_3、-CH(Ph)$_2$、全氟(C_1-C_4)烷氧基和全氟(C_1-C_4)烷基,数量为0至3个,其中特别优选具有0、1或2个取代基的那些基团。R'、R″和R'″各自独立地表示氢、未取代的C_1-C_8烷基和杂烷基、被1-3个卤素取代的C_1-C_8烷基和杂烷基、未取代的芳基、被1-3个卤素取代的芳基、未取代的烷基、烷氧基、或硫代烷氧基、或芳基-(C_1-C_4)烷基。当R'和R″连接至同一氮原子时,它们可以与该氮原子结合形成5-、6-或7-元环。因此,-NR'R″包括例如1-吡咯烷基和4-吗啉基。当芳基为1,2,3,4-四氢萘基时,其可以被取代或未取代的C_3-C_7螺环烷基取代。C_3-C_7螺环烷基可以以与本文对"环烷基"定义相同的方式被取代。

[0069] 在一些实施方案中,取代基选自:卤素、-R'、-OR'、=O、-NR'R″、-SR'、-SiR'R″R'″、-OC(=O)R'、-C(=O)R'、-CO_2R'、-C(=O)NR'R″、-OC(=O)NR'R″、-NR″C(=O)R'、-NR″CO_2R'、-NR'-SO_2NR″R'″、-S(=O)R'、-SO_2R'、-SO_2NR'R″、-NR″SO_2R、-CN、-NO_2、全氟C_1-C_4烷氧基和全氟C_1-C_4烷基,其中R'和R″如上文定义。

[0070] 在一些实施方案中,取代基独立地选自取代的或未取代的杂原子、取代的或未取代的含有0-3个杂原子的C_1-C_6烷基(例如,C_1-C_3烷基或C_1-C_2烷基)、取代的或未取代的含0-3个杂原子的C_2-C_6烯基(例如,C_2-C_4烯基)、取代或未取代的含0-3个杂原子的C_2-C_6炔基(例如,C_2-C_4炔基)、或取代或未取代的,含0-3个杂原子的C_6-C_{14}芳基(例如,C_5-C_6芳基),其中每个杂原子独立地是氧、磷、硫或氮。

[0071] 在一些实施方案中,取代基独立地选自醛、醛亚胺、烷酰氧基、烷氧基、烷氧基羰基、烷氧基、烷基、烯基、炔基、胺、偶氮、卤素、氨基甲酰基、羰基、甲酰胺基、羧基、氰基、酯、卤代甲酰基、氢过氧基、羟基、亚胺、异氰化物、异氰酸酯、N-叔丁氧基羰基、硝酸酯、腈、亚硝酸酯、硝基、亚硝基、磷酸酯、膦酰基、硫化物、磺酰基、磺基、巯基、硫醇、硫氰基、三氟甲基和三氟甲基醚(OCF_3)基团。

[0072] 优选的取代基在本文中公开并在表、结构、实施例和权利要求中举例说明,并且可以应用于本公开的不同化合物。例如,给定化合物的取代基可以与其他化合物组合使用。

[0073] 将反应产物彼此分离和/或与起始材料分离可能是有利的。通过本领域常见的技术将每个步骤或一系列步骤的所需产物分离和/或纯化(下文中分离)至所需的均质度。通

常,此类分离涉及多相萃取、从溶剂或溶剂混合物中结晶、蒸馏、升华或层析法。层析法可以涉及多种方法,包括例如反相和正相;尺寸排阻;离子交换;高、中、低压液相层析(色谱)方法和装置;小规模分析;模拟移动床("SMB")和制备型薄层或厚层层析,以及小规模薄层和快速层析技术。本领域技术人员可以应用此类技术来实现期望的分离。

[0074] 可用于本公开内容的合适的碱的非限制性实例包括水、甲醇(MeOH)、乙醇(EtOH)、二氯甲烷或亚甲基氯化物(CH_2Cl_2)、甲苯、乙腈(MeCN)、二甲基甲酰胺(DMF)、二甲亚砜(DMSO)、乙酸甲酯(MeOAc)、乙酸乙酯(EtOAc)、庚烷、乙酸异丙酯(IPAc)、乙酸叔丁酯(t-BuOAc)、异丙醇(IPA)、四氢呋喃(THF)、2-甲基四氢呋喃(2-Me THF)、甲基乙基酮(MEK)、叔丁醇、二乙醚(Et_2O)、甲基叔丁基醚(MTBE)、1,4-二氧杂环己烷和N-甲基吡咯烷酮(NMP)。

[0075] 可用于本公开内容的合适溶剂的非限制性实例包括1,8-二氮杂双环[5.4.0]十一碳-7-烯(DBU)、叔丁醇钾(KOtBu)、碳酸钾(K_2CO_3)、N-甲基吗啉(NMM)、三乙胺(Et_3N;TEA)、二异丙基乙胺(i-Pr_2EtN;DIPEA)、吡啶、氢氧化钾(KOH)、氢氧化钠(NaOH)、氢氧化锂(LiOH)和甲醇钠(NaOMe;$NaOCH_3$)。

[0076] 术语"受试者"是指包括人类在内的动物。

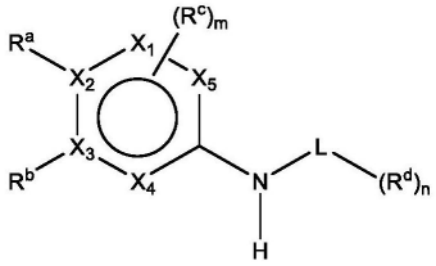
[0077] 术语"治疗有效量"是指产生所施用的期望效果(例如,改善疾病或病症、减轻疾病或病症的严重性、和/或减缓疾病或病症进展,例如选自神经病、中风、神经退行性疾病(例如阿尔茨海默病)、帕金森病、肌萎缩侧索硬化症(AML)、多发性硬化症、亨廷顿病、路易体痴呆、弗里德赖希共济失调、毛囊形态发生、糖尿病、败血症、移植排斥、脑室周围白质软化、缺血再灌注损伤、凝血、心肌梗塞和肾功能障碍如急性肾衰竭的疾病或病症)的化合物的量。该疾病或病症可能涉及失调的,例如异常的,铁死亡。治疗有效量的精确量将取决于治疗的目的并且可以由本领域技术人员使用已知技术确定(参见,例如,Lloyd(1999),The Art,Science和Technology of Pharmaceutical Compounding)。

[0078] 如本文所用的术语"治疗"及其同源词是指减缓或停止疾病进展。本文使用的"治疗"及其同源词包括但不限于以下内容:完全或部分缓解、治愈疾病或病症或其症状、降低疾病或病症的风险,例如神经病、中风、神经退行性疾病(例如,阿尔茨海默病)、帕金森病、肌萎缩侧索硬化症(AML)、多发性硬化症、亨廷顿病、路易体痴呆、弗里德赖希共济失调、毛囊形态发生、糖尿病、败血症、移植排斥、脑室周围白质软化、缺血再灌注损伤、凝血、心肌梗塞和肾功能障碍,如急性肾衰竭。该疾病或病症可能涉及失调的,例如异常的,铁死亡。可以根据本领域已知的方法和技术评估任何这些症状的改善或减轻其严重性。

[0079] 当与诸如百分比的数字结合使用时,术语"约"和"大约"包括指定的数字和数字的范围(例如,百分比范围,例如相对于特定点值±10%的范围),这是本领域普通技术人员所认可的。

[0080] II.化合物和组合物

[0081] 在第一实施方案中,本公开的化合物是以下结构式I的化合物:

[0082] 

式(I)

[0083] 其互变异构体,该化合物或该互变异构体的溶剂化物或立体异构体,或前述的药学上可接受的盐,其中:

[0084] L是环烷基,杂环基,或C;

[0085] X_1、X_2、X_3、X_4和X_5各自独立地是C或N;

[0086] R^a不存在或选自H,卤素,CN,任选被取代的杂原子,任选被取代的烷基,任选被取代的烯基,任选被取代的炔基,任选被取代的酰基,任选被取代的环烷基,任选被取代的杂环基,任选被取代的芳基,和任选被取代的杂芳基;

[0087] R^b不存在或选自H,卤素,CN,任选被取代的杂原子,任选被取代的烷基,任选被取代的环烷基,和任选被取代的杂环基;

[0088] R^a和R^b可以连在一起形成任选被取代的3-10元碳环、杂环、芳族、或杂芳族的环;

[0089] R^c,每次出现时,独立地选自卤素,任选被取代的杂原子,和任选被取代的烷基;

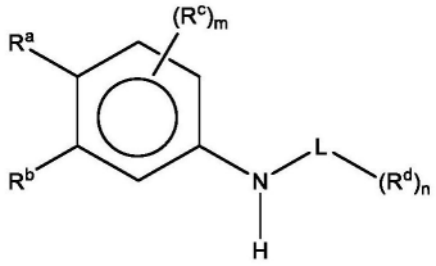
[0090] R^c中的一个与R^b可以连在一起形成任选被取代的3-10元碳环、杂环、芳族、或杂芳族的环;

[0091] R^d,每次出现时,独立地选自卤素,CN,任选被取代的杂原子,任选被取代的烷基,任选被取代的烯基,任选被取代的炔基,任选被取代的酰基,任选被取代的环烷基,任选被取代的杂环基,任选被取代的芳基,和任选被取代的杂芳基;和

[0092] m和n各自是独立地选自0、1、2和3的整数。

[0093] 本文公开的取代基的组合是导致形成稳定的或化学上可行的化合物的那些。为了缩写或根据惯例,连接到某些原子(例如碳原子C或氮原子N)的某些氢原子没有在化学结构、式、或符号中具体说明;氢原子被认为存在到某些原子(例如,C或N)的化合价完整的程度。

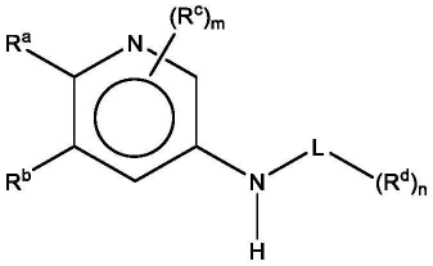
[0094] 在第二实施方案中,本公开的化合物是以下结构式IIa的化合物:

[0095] 

式 IIa

[0096] 其互变异构体,该化合物或该互变异构体的溶剂化物或立体异构体,或前述的药学上可接受的盐;且此处未具体定义的所有其他变量如前述实施方案中任一个中所定义。

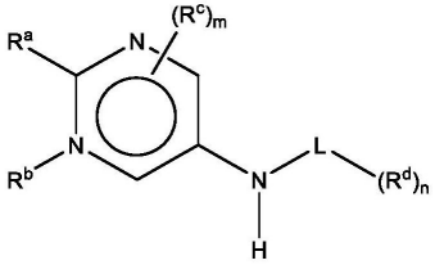
[0097] 在第三实施方案中,本公开的化合物是以下结构式IIb的化合物:

[0098] 

[0099] 式IIb

[0100] 其互变异构体,该化合物或该互变异构体的溶剂化物或立体异构体,或前述的药学上可接受的盐;且此处未具体定义的所有其他变量如前述实施方案中任一个中所定义。

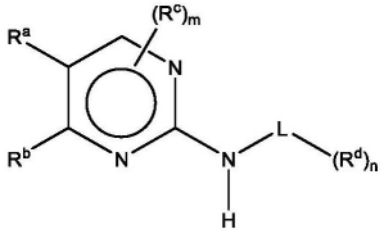
[0101] 在第四实施方案中,本公开的化合物是以下结构式IIc的化合物:

[0102] 

式 IIc

[0103] 其互变异构体,该化合物或该互变异构体的溶剂化物或立体异构体,或前述的药学上可接受的盐;且此处未具体定义的所有其他变量如前述实施方案中任一个中所定义。

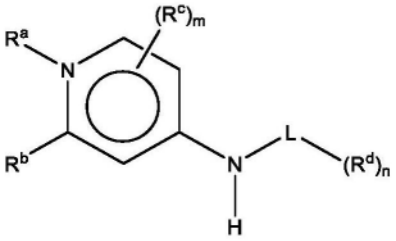
[0104] 在第五实施方案中,本公开的化合物是以下结构式IId的化合物:

[0105] 

式 IId

[0106] 其互变异构体,该化合物或该互变异构体的溶剂化物或立体异构体,或前述的药学上可接受的盐;且此处未具体定义的所有其他变量如前述实施方案中任一个中所定义。

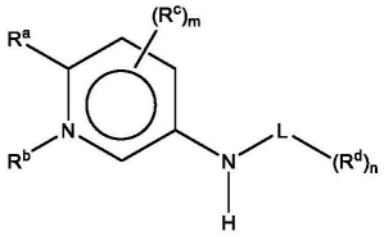
[0107] 在第六实施方案中,本公开的化合物是以下结构式IIe的化合物:

[0108] 

式 IIe

[0109] 其互变异构体,该化合物或该互变异构体的溶剂化物或立体异构体,或前述的药学上可接受的盐;且此处未具体定义的所有其他变量如前述实施方案中任一个中所定义。

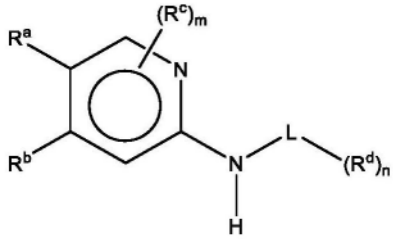
[0110] 在第七实施方案中,本公开的化合物是以下结构式IIf的化合物:

[0111] 

式 IIf

[0112] 其互变异构体,该化合物或该互变异构体的溶剂化物或立体异构体,或前述的药学上可接受的盐;且此处未具体定义的所有其他变量如前述实施方案中任一个中所定义。

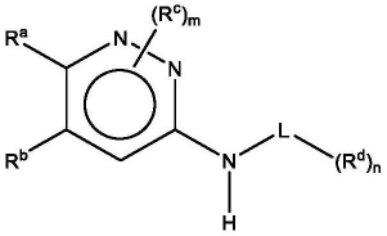
[0113] 在第八实施方案中,本公开的化合物是以下结构式IIg的化合物:

[0114] 

式 IIg

[0115] 其互变异构体,该化合物或该互变异构体的溶剂化物或立体异构体,或前述的药学上可接受的盐;且此处未具体定义的所有其他变量如前述实施方案中任一个中所定义。

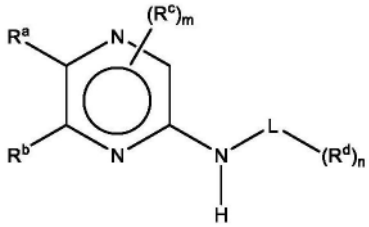
[0116] 在第九实施方案中,本公开的化合物是以下结构式IIh的化合物:

[0117] 

式 IIh

[0118] 其互变异构体,该化合物或该互变异构体的溶剂化物或立体异构体,或前述的药学上可接受的盐;且此处未具体定义的所有其他变量如前述实施方案中任一个中所定义。

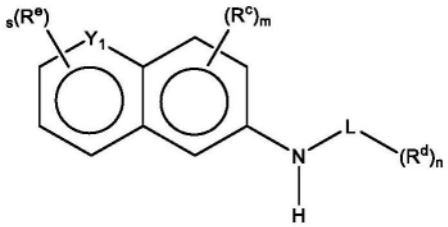
[0119] 在第十实施方案中,本公开的化合物是以下结构式IIi的化合物:

[0120] 

式 IIi

[0121] 其互变异构体,该化合物或该互变异构体的溶剂化物或立体异构体,或前述的药学上可接受的盐;且此处未具体定义的所有其他变量如前述实施方案中任一个中所定义。

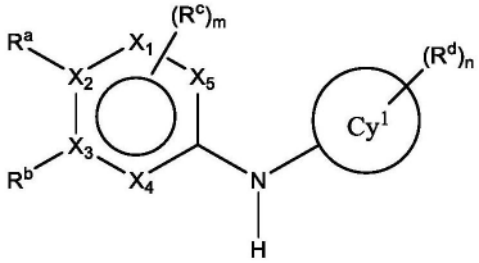
[0122] 在第十一实施方案中,本公开的化合物是以下结构式IIj的化合物:

[0123] 

式 IIj

[0124] 其互变异构体,该化合物或该互变异构体的溶剂化物或立体异构体,或前述的药学上可接受的盐;且此处未具体定义的所有其他变量如前述实施方案中任一个中所定义。

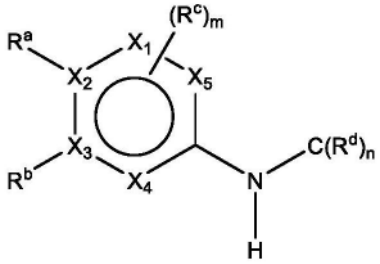
[0125] 在第十二实施方案中,本公开的化合物是以下结构式IIIa的化合物:

[0126] 

式 IIIa

[0127] 其互变异构体,该化合物或该互变异构体的溶剂化物或立体异构体,或前述的药学上可接受的盐;其中Cy^1是3-10元环烷基或3-10元杂环基;且此处未具体定义的所有其他变量如前述实施方案中任一个中所定义。

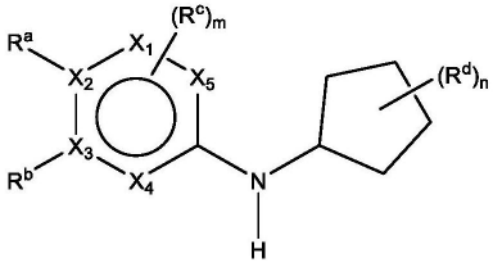
[0128] 在第十三实施方案中,本公开的化合物是以下结构式IIIb的化合物:

[0129] 

式 IIIb

[0130] 其互变异构体,该化合物或该互变异构体的溶剂化物或立体异构体,或前述的药学上可接受的盐;且此处未具体定义的所有其他变量如前述实施方案中任一个中所定义。

[0131] 在第十四实施方案中,本公开的化合物是以下结构式IVa的化合物:

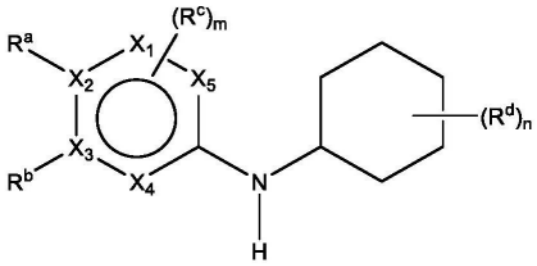
[0132] 

式 IVa

[0133] 其互变异构体,该化合物或该互变异构体的溶剂化物或立体异构体,或前述的药

学上可接受的盐;且此处未具体定义的所有其他变量如前述实施方案中任一个中所定义。

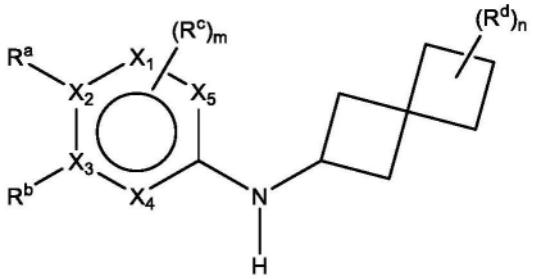
[0134] 在第十五实施方案中,本公开的化合物是以下结构式IVb的化合物:

[0135] 

式 IVb

[0136] 其互变异构体,该化合物或该互变异构体的溶剂化物或立体异构体,或前述的药学上可接受的盐;且此处未具体定义的所有其他变量如前述实施方案中任一个中所定义。

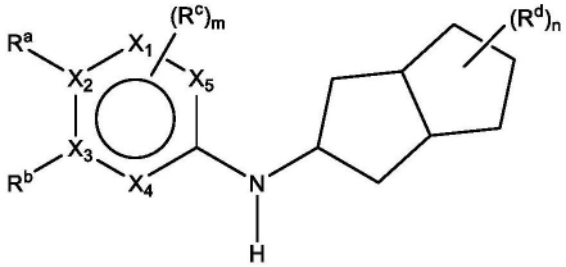
[0137] 在第十六实施方案中,本公开的化合物是以下结构式IVc的化合物:

[0138] 

式 IVc

[0139] 其互变异构体,该化合物或该互变异构体的溶剂化物或立体异构体,或前述的药学上可接受的盐;且此处未具体定义的所有其他变量如前述实施方案中任一个中所定义。

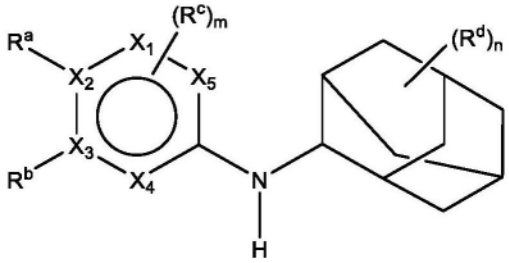
[0140] 在第十七实施方案中,本公开的化合物是以下结构式IVd的化合物:

[0141] 

式 IVd

[0142] 其互变异构体,该化合物或该互变异构体的溶剂化物或立体异构体,或前述的药学上可接受的盐;且此处未具体定义的所有其他变量如前述实施方案中任一个中所定义。

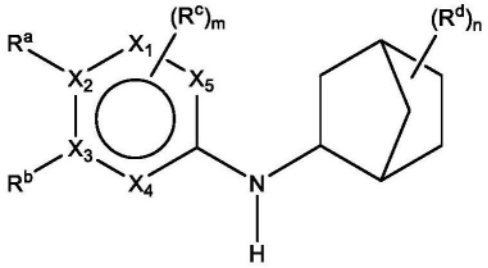
[0143] 在第十八实施方案中,本公开的化合物是以下结构式IVe的化合物:

[0144] 

式 IVe

[0145] 其互变异构体,该化合物或该互变异构体的溶剂化物或立体异构体,或前述的药学上可接受的盐;且此处未具体定义的所有其他变量如前述实施方案中任一个中所定义。

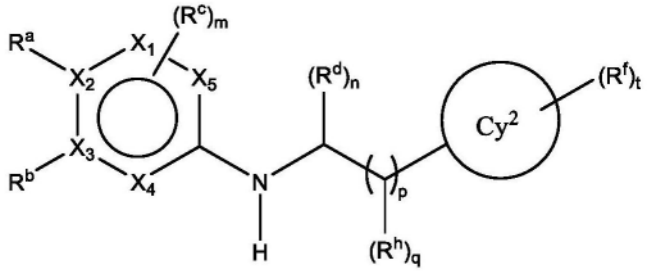
[0146] 在第十九实施方案中,本公开的化合物是以下结构式IVf的化合物:

[0147] 

式 IVf

[0148] 其互变异构体,该化合物或该互变异构体的溶剂化物或立体异构体,或前述的药学上可接受的盐;且此处未具体定义的所有其他变量如前述实施方案中任一个中所定义。

[0149] 在第二十实施方案中,本公开的化合物是以下结构式Va的化合物:

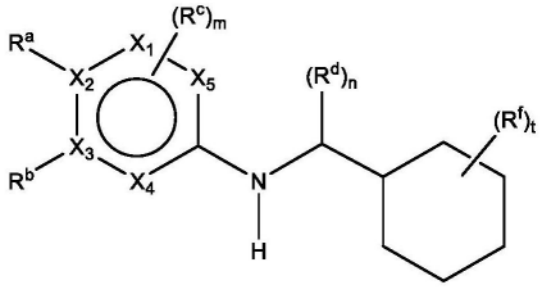
[0150] 

式 Va

[0151] 其互变异构体,该化合物或该互变异构体的溶剂化物或立体异构体,或前述的药学上可接受的盐,其中Cy^2是3-10元环烷基或3-10元杂环基;R^f,每次出现时,独立地选自卤素,CN,任选被取代的杂原子,任选被取代的烷基,任选被取代的烯基,任选被取代的炔基,任选被取代的酰基,任选被取代的环烷基,任选被取代的杂环基,任选被取代的芳基,和任选被取代的杂芳基;R^h,每次出现时,独立地选自卤素,CN,和任选被取代的C_1-C_6烷基;n是选自0、1和2的整数;p是选自0、1、2、3、4和5的整数;q是选自0、1和2的整数;t独立选自0、1、2和3的整数;且此处未具体定义的所有其他变量如前述实施方案中任一个中所定义。

[0152] 在第二十一实施方案中,在本公开内容的化合物,互变异构体,该化合物或该互变异构体的溶剂化物或立体异构体,或药学上可接受的盐中,每次出现时,n是0,q是0,并且p是0,1,2和3;且此处未具体定义的所有其他变量如前述实施方案中任一个中所定义。

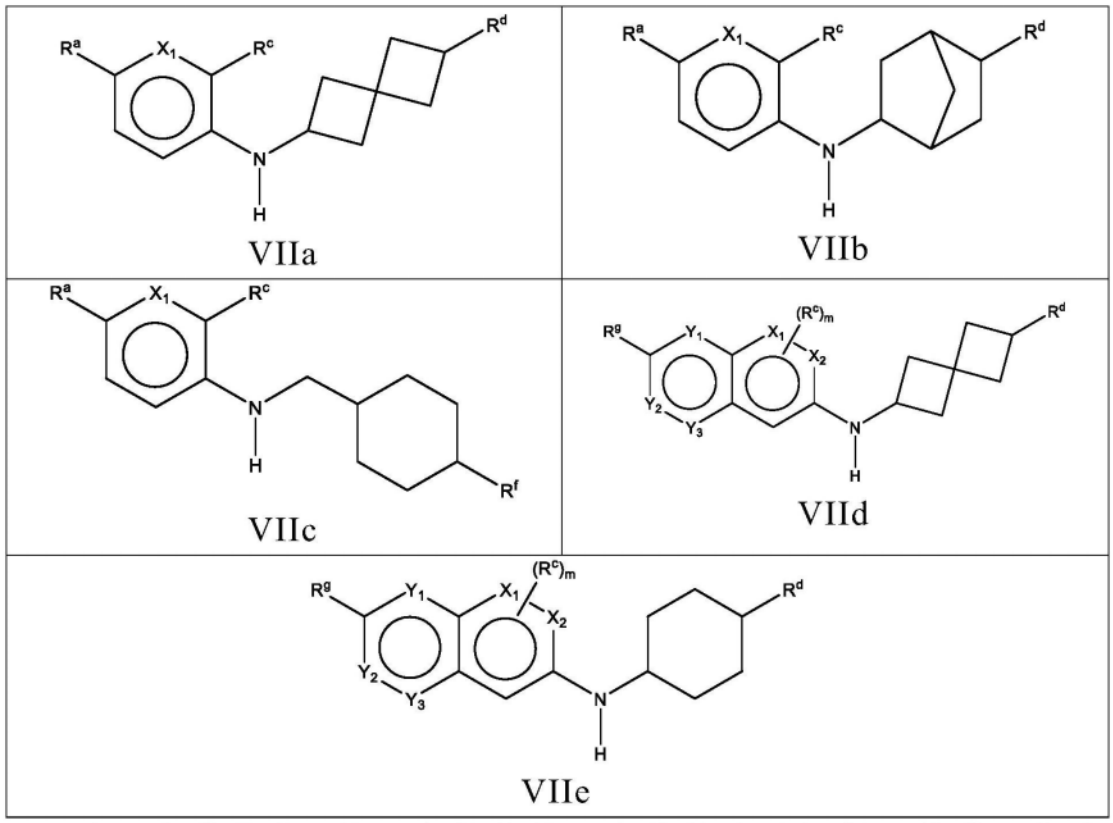
[0153] 在第二十二实施方案中,本公开的化合物是以下结构式VIa的化合物:

[0154] 

式 VIa

[0155] 其互变异构体,该化合物或该互变异构体的溶剂化物或立体异构体,或前述的药学上可接受的盐;且此处未具体定义的所有其他变量如前述实施方案中任一个中所定义。

[0156] 中在第二十三实施方案,本公开的化合物是以下结构式VIIa-VIIe的化合物:

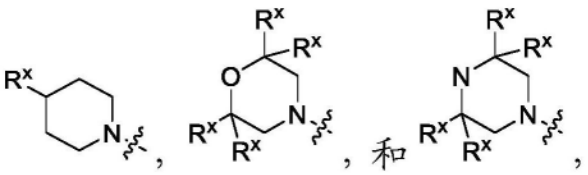
[0157] 

VIIa VIIb VIIc VIId VIIe

[0158] 其互变异构体,该化合物或该互变异构体的溶剂化物或立体异构体,或前述的药学上可接受的盐,其中:

[0159] X_1和X_2独立地是C或N;

[0160] Y_1,Y_2和Y_3独立地是C或N;

[0161] R^a选自  其中R^x,每次出现时,独立地选自H,CF_3,$-CH_3$,和$-CH_2CH_3$;

[0162] R^c选自卤素,C_1-C_2烷基,和C_1-C_2烷氧基;

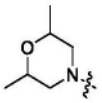
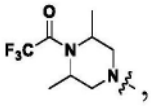
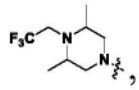
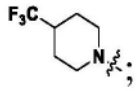
[0163] R^d选自NH_2和-C(=O)NH_2;

[0164] R^f选自NH_2和-C(=O)NH_2;和

[0165] m是0或1;

[0166] 且此处未具体定义的所有其他变量如前述实施方案中任一个中所定义。

[0167] 在第二十四实施方案中,在本公开内容的化合物,互变异构体,该化合物或该互变异构体的溶剂化物或立体异构体,或药学上可接受的盐中,R^e,每次出现时,独立地选自5-6元环烷基和5-6元杂环基;此处未具体定义的所有其他变量如前述实施方案中任一个中所定义。

[0168] 在第二十五实施方案中,在本公开内容的化合物,互变异构体,该化合物或该互变异构体的溶剂化物或立体异构体,或药学上可接受的盐中,R^e选自  ,  ,  ,和  ;此处未具体定义的所有其他变量如前述实施方案中任一个中所定义。

[0169] 在第二十六实施方案中,在本公开内容的化合物,互变异构体,该化合物或该互变异构体的溶剂化物或立体异构体,或药学上可接受的盐中,R^f,每次出现时,独立地选自卤素,氰基,C_1-C_{10}烷基,苯基,5-7元杂芳基,苯基,3-10元杂环基,C_3-C_{10}环烷基,-C(=O)R^s,C_2-C_{10}烯基,=O,=NR^p;-C(=O)OR^s,-C(=O)NR^pR^q,-NR^pR^q,和-NR^pC(=O)R^s,其中

[0170] R^f的C_1-C_{10}烷基和C_2-C_{10}烯基各自任选被1-3个选自以下的基团取代:5-7元杂芳基,C_3-C_{10}环烷基,3-10元杂环基,-OR^s,-C(=O)NR^pR^q,-NR^pC(=O)NR^qR^r,和-NR^pR^q;

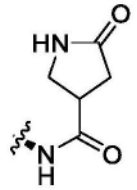
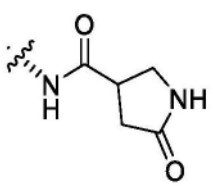
[0171] R^f的3-10元杂环基和C_3-C_{10}环烷基以及R^f的C_1-C_{10}烷基和C_2-C_{10}烯基的3-10元杂环基和C_3-C_6环烷基,各自任选被1-3个选自以下的基团取代:=O和任选被1-3个选自卤素和-OR^s的基团取代的C_1-C_6烷基;

[0172] R^f的苯基和5-7元杂芳基以及R^f的C_1-C_{10}烷基和C_2-C_{10}烯基的5-7元杂芳基各自任选被1-3个选自以下的基团取代:任选被1-3个选自卤素和-OR^s的基团取代的C_1-C_6烷基;

[0173] R^p,R^q,和R^r,对于每次出现,独立地选自氢,C_3-C_{10}环烷基,和C_1-C_{10}烷基,其中R^p,R^q,和R^r的C_3-C_{10}环烷基和C_1-C_{10}烷基各自任选被1-3个选自以下的基团取代:卤素,-OR^s和-C(=O)OR^s;

[0174] R^s,每次出现时,独立地选自H,C_3-C_{10}环烷基,3-10元杂环基,和任选被1-3个选自以下的基团取代的C_1-C_{10}烷基:卤素,C_3-C_{10}环烷基,3-10元杂环基,和C_1-C_6烷氧基,其中

[0175] R^s的C_3-C_{10}环烷基和3-10元杂环基以及R^s的C_1-C_{10}烷基的C_3-C_{10}环烷基和3-10元杂环基各自任选被1-3个任选被卤素取代的C_1-C_6烷基的基团取代,和R^s的C_1-C_{10}烷基的C_1-C_6烷氧基任选被1-3个卤素的基团取代;此处未具体定义的所有其他变量如前述实施方案中任一个中所定义。

[0176] 在第二十七实施方案中,在本公开内容的化合物,互变异构体,该化合物或该互变异构体的溶剂化物或立体异构体,或药学上可接受的盐中,R^f,对于每次出现,选自H,甲基,NH_2,-$NH(CH_2)_2OH$,-CH_2NH_2,  ,  ,-NHC(=O)NH_2,-$NHCH_3$,-C(=O)NH_2,

和-NHBoc。

[0177] 在第二十八实施方案中,在本公开内容的化合物,互变异构体,该化合物或该互变异构体的溶剂化物或立体异构体,或药学上可接受的盐中,R^a不存在或选自氢,卤素,氰基,C_1-C_{10}烷基,C_2-C_{10}烯基,C_2-C_{10}炔基,C_3-C_{10}环烷基,3-10元杂环基,苯基,5-7元杂芳基,-C(=O)R^s,-C(=O)OR^s,-NR^pR^q,-OR^s,其中

[0178] R^a的C_3-C_{10}环烷基,3-10元杂环基,苯基,和5-7元杂芳基各自任选被1-3个选自以下的基团取代:卤素,OR^s,和任选被1-3个卤素的基团取代的C_1-C_{10}烷基;

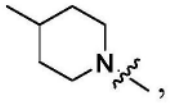
[0179] R^a的C_1-C_{10}烷基,C_2-C_{10}烯基,和C_2-C_{10}炔基各自任选被1-3个选自以下的基团取代:卤素,3-10元杂环基,和-OR^s;

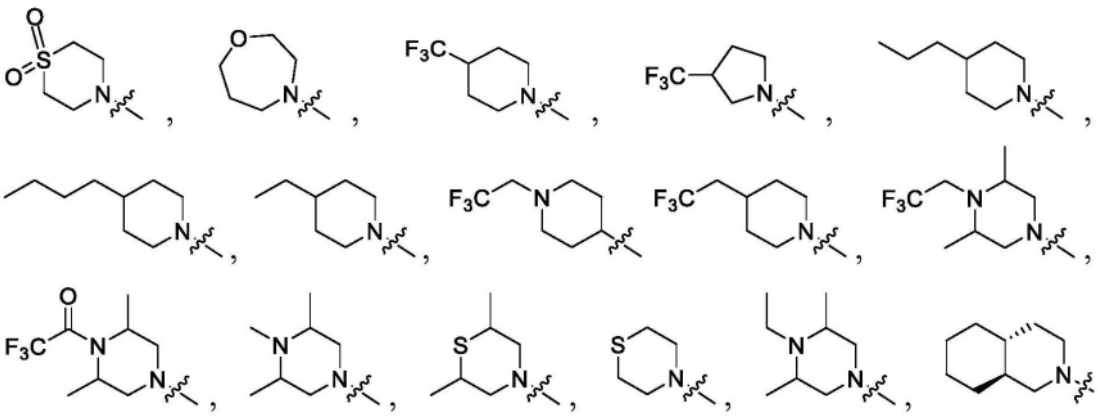
[0180] R^p和R^q,对于每次出现,独立地选自氢,C_3-C_{10}环烷基,和C_1-C_{10}烷基,其中R^p和R^q的C_3-C_{10}环烷基和C_1-C_{10}烷基各自任选被1-3个选自以下的基团取代:卤素,-OR^s和-C(=O)OR^s;

[0181] R^s,对于每次出现,选自H,C_3-C_{10}环烷基,3-10元杂环基,5-6元芳基,和C_1-C_{10}烷基,其任选被1-3个选自以下的基团取代:卤素,C_3-C_{10}环烷基,3-10元杂环基,和C_1-C_6烷氧基,其中R^s的C_3-C_{10}环烷基和3-10元杂环基以及R^s的C_1-C_{10}烷基的C_3-C_{10}环烷基和3-10元杂环基各自任选被1-3个任选被卤素取代的C_1-C_6烷基的基团取代,和R^s的C_1-C_{10}烷基的C_1-C_6烷氧基任选被1-3个卤素的基团取代;和

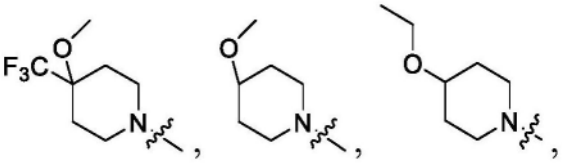
[0182] 此处未具体定义的所有其他变量如前述实施方案中任一个中所定义。

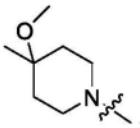
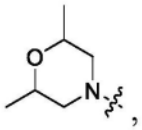
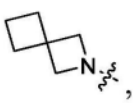
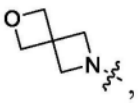
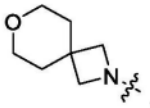
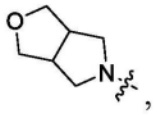
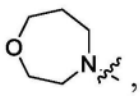
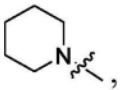
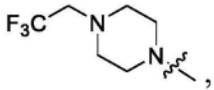
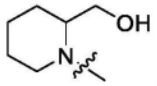
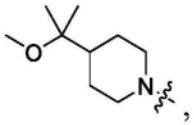
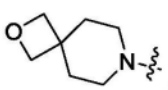
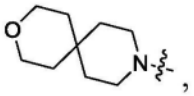
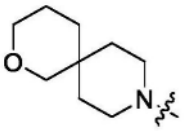
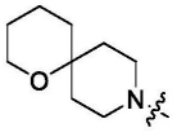
[0183] 在第二十九实施方案中,在本公开内容的化合物,互变异构体,该化合物或该互变异构体的溶剂化物或立体异构体,或药学上可接受的盐中,R^a不存在或选自H,F,Cl,Br,甲基,





-$CH(CH_2CH_3)_2$,-$CH(CH_3)_2$,-$OCH(CH_3)_2$,-CH_2CH_3,-$CH_2CH_2CH_3$,-$NHCH_2CF_3$,-$N(CH_3)CH_2CF_3$,-$O(CH_2)_3CH_3$,-$O(CH_2)_2CH_3$,-$(CH_2)_2CH_3$,-$(CH_2)_4CH_3$,-$(CH_2)_3CH_3$,

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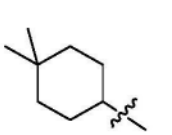
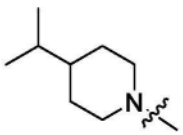
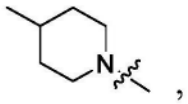
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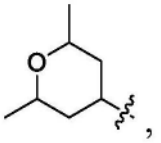
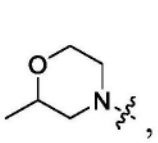
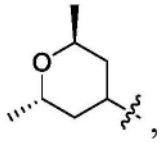
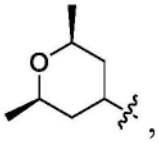
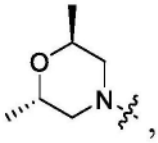
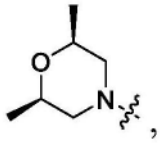
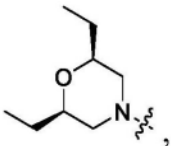
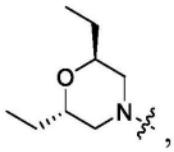
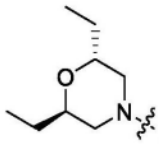
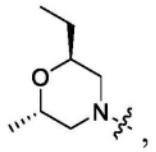
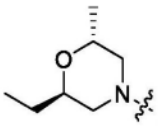
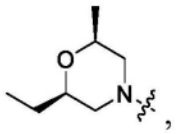
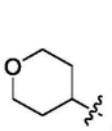
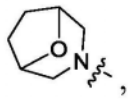
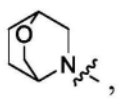
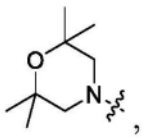
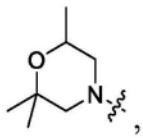
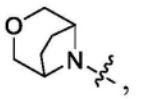
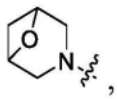
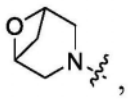
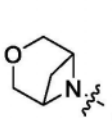
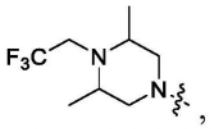
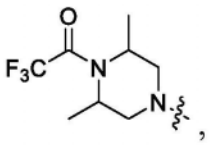
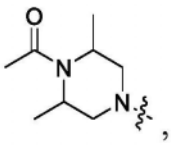
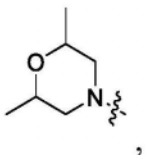
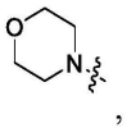
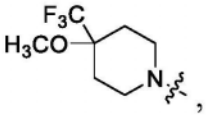
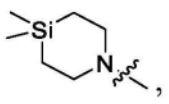
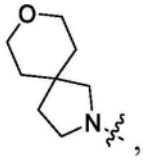
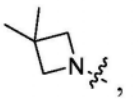
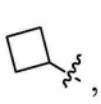

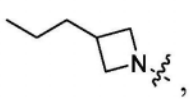
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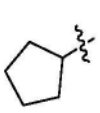
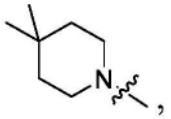
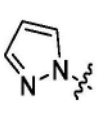
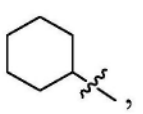
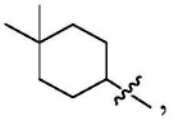
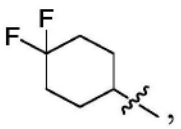
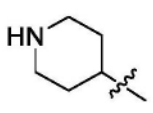
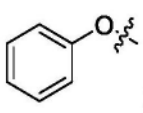
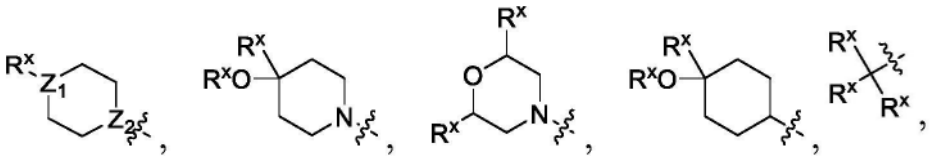
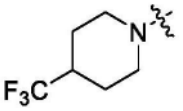


-CF$_3$,-CH$_2$CF$_3$,-N(CH$_2$CH$_3$)$_2$,





和  ；此处未具体定义的所有其他变量如前述实施方案中任一个中所定义。

[0184] 在第三十实施方案中,在本公开内容的化合物,互变异构体,该化合物或该互变异构体的溶剂化物或立体异构体,或药学上可接受的盐中,R^a选自



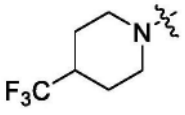
$-OR^x$,和$-CH_2R^x$,其中Z_1和Z_2独立地选自C和N,R^x,每次出现时,独立地选自任选被1-3个卤素的基团取代的C_1-C_4烷基;此处未具体定义的所有其他变量如前述实施方案中任一个中所定义。

[0185] 在第三十一实施方案中,在本公开内容的化合物,互变异构体,该化合物或该互变异构体的溶剂化物或立体异构体,或药学上可接受的盐中,R^b不存在或选自H,卤素,C_1-C_6烷基,$-NR^pR^q$,CN,C_1-C_6烷氧基,和任选被任选被1-3个选自卤素的基团取代的C_1-C_3烷基取代的5-6元的杂环基,其中R^p和R^q各自选自C_1-C_6烷基,和其中R^b的C_1-C_6烷基和C_1-C_6烷氧基以及R^p和R^q的C_1-C_6烷基各自任选被1-3个选自卤素的基团取代;此处未具体定义的所有其他变量如前述实施方案中任一个中所定义。

[0186] 在第三十二实施方案中,在本公开内容的化合物,互变异构体,该化合物或该互变异构体的溶剂化物或立体异构体,或药学上可接受的盐中,R^b不存在或者是H,甲基,乙基,$-O(CH_2)_4OCH_3$,$-O(CH_2)_3OCH_3$,$-O(CH_2)_2OCH_3$,$-O(CH_2)_2NH_2$,$-(CH_2)_5CH_3$,$-O(CH_2)_5CH_3$,$-(CH_2)_2OCH_3$,$-O(CH_2)_2OH$,F,$-OCH_3$,$-CF_3$,Cl,CN,$-C(CH_3)_3$,和  ;此处未具体定义的所有其他变量如前述实施方案中任一个中所定义。

[0187] 在第三十三实施方案中,在本公开内容的化合物,互变异构体,该化合物或该互变异构体的溶剂化物或立体异构体,或药学上可接受的盐中,R^b不存在或选自卤素,C_1-C_2烷基,和C_1-C_2烷氧基;此处未具体定义的所有其他变量如前述实施方案中任一个中所定义。

[0188] 在第三十四实施方案中,在本公开内容的化合物,互变异构体,该化合物或该互变异构体的溶剂化物或立体异构体,或药学上可接受的盐中,R^c,每次出现时,独立地选自卤素,C_1-C_6烷基,$-NR^pR^q$,CN,和C_1-C_6烷氧基,其中R^p和R^q各自选自C_1-C_6烷基,和其中R^b的C_1-C_6烷基和C_1-C_6烷氧基以及R^p和R^q的C_1-C_6烷基各自任选被1-3个选自卤素的基团取代;此处未具体定义的所有其他变量如前述实施方案中任一个中所定义。

[0189] 在第三十五实施方案中,在本公开内容的化合物,互变异构体,该化合物或该互变异构体的溶剂化物或立体异构体,或药学上可接受的盐中,R^c选自甲基,乙基,$-O(CH_2)_4OCH_3$,$-O(CH_2)_3OCH_3$,$-O(CH_2)_2OCH_3$,$-O(CH_2)_2NH_2$,$-(CH_2)_5CH_3$,$-O(CH_2)_5CH_3$,$-(CH_2)_2OCH_3$,$-O(CH_2)_2OH$,F,$-OCH_3$,$-CF_3$,Cl,CN,  和$-C(CH_3)_3$;此处未具体定义的所有其他变量如前述实施方案中任一个中所定义。

[0190] 在第三十六实施方案中,在本公开内容的化合物,互变异构体,该化合物或该互变异构体的溶剂化物或立体异构体,或药学上可接受的盐中,R^c选自卤素,C_1-C_2烷基,和C_1-C_2烷氧基;此处未具体定义的所有其他变量如前述实施方案中任一个中所定义。

[0191] 在第三十七实施方案中,在本公开内容的化合物,互变异构体,该化合物或该互变

异构体的溶剂化物或立体异构体,或药学上可接受的盐中,R^d,对于每次出现,是不存在或独立地选自卤素,氰基,C_1-C_{10}烷基,苯基,5-7元杂芳基,苯基,3-10元杂环基,C_3-C_{10}环烷基,-C(=O)R^s,C_2-C_{10}烯基,=O,=NR^p;-C(=O)OR^s,-C(=O)NR^pR^q,-NR^pR^q,和-NR^pC(=O)R^s,其中

[0192] R^d的C_1-C_{10}烷基和C_2-C_{10}烯基各自任选被1-3个选自以下的基团取代:5-7元杂芳基,C_3-C_{10}环烷基,3-10元杂环基,-OR^s,-C(=O)NR^pR^q,-NR^pC(=O)NR^qR^r,和-NR^pR^q;

[0193] R^d的3-10元杂环基和C_3-C_{10}环烷基以及R^d的C_1-C_{10}烷基和C_2-C_{10}烯基的3-10元杂环基和C_3-C_6环烷基,各自任选被1-3个选自以下的基团取代:=O和任选被1-3个选自卤素和-OR^s的基团取代的C_1-C_6烷基;

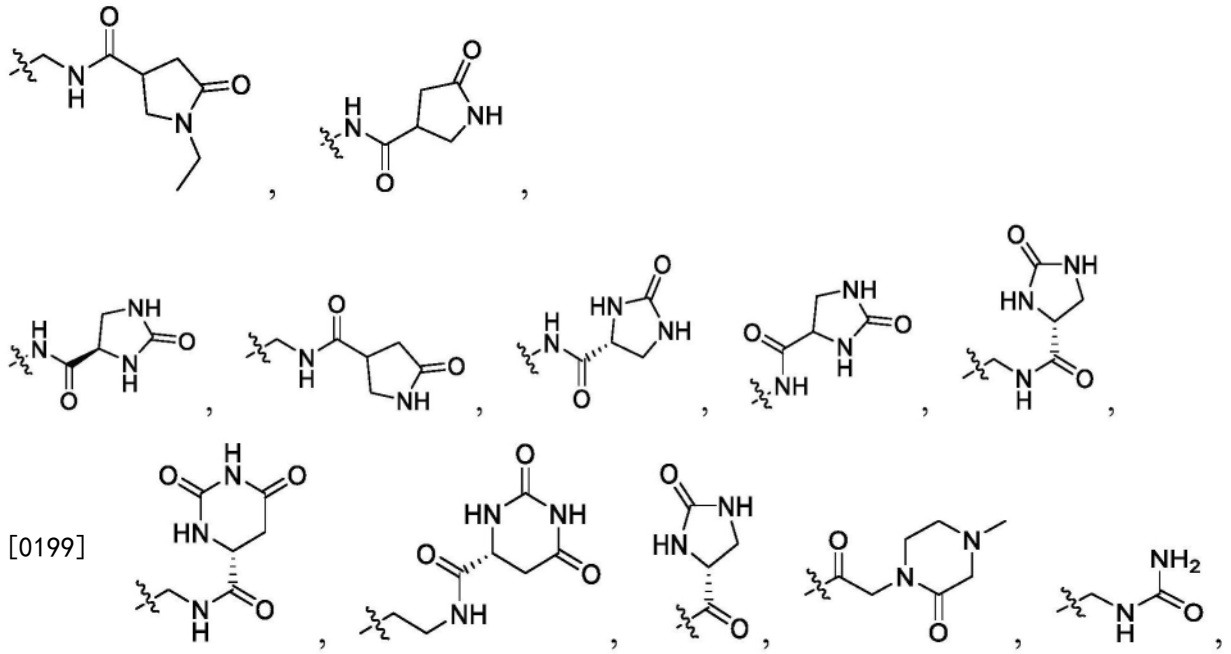
[0194] R^d的苯基和5-7元杂芳基以及R^d的C_1-C_{10}烷基和C_2-C_{10}烯基的5-7元杂芳基各自任选被1-3个选自以下的基团取代:任选被1-3个选自卤素和-OR^s的基团取代的C_1-C_6烷基;

[0195] R^p,R^q,和R^r,对于每次出现,独立地选自氢,C_3-C_{10}环烷基,和C_1-C_{10}烷基,其中R^p,R^q,和R^r的C_3-C_{10}环烷基和C_1-C_{10}烷基各自任选被1-3个选自以下的基团取代:卤素,-OR^s和-C(=O)OR^s;

[0196] R^s,每次出现时,独立地选自H,C_3-C_{10}环烷基,3-10元杂环基,和任选被1-3个选自以下的基团取代的C_1-C_{10}烷基:卤素,C_3-C_{10}环烷基,3-10元杂环基,和C_1-C_6烷氧基,其中

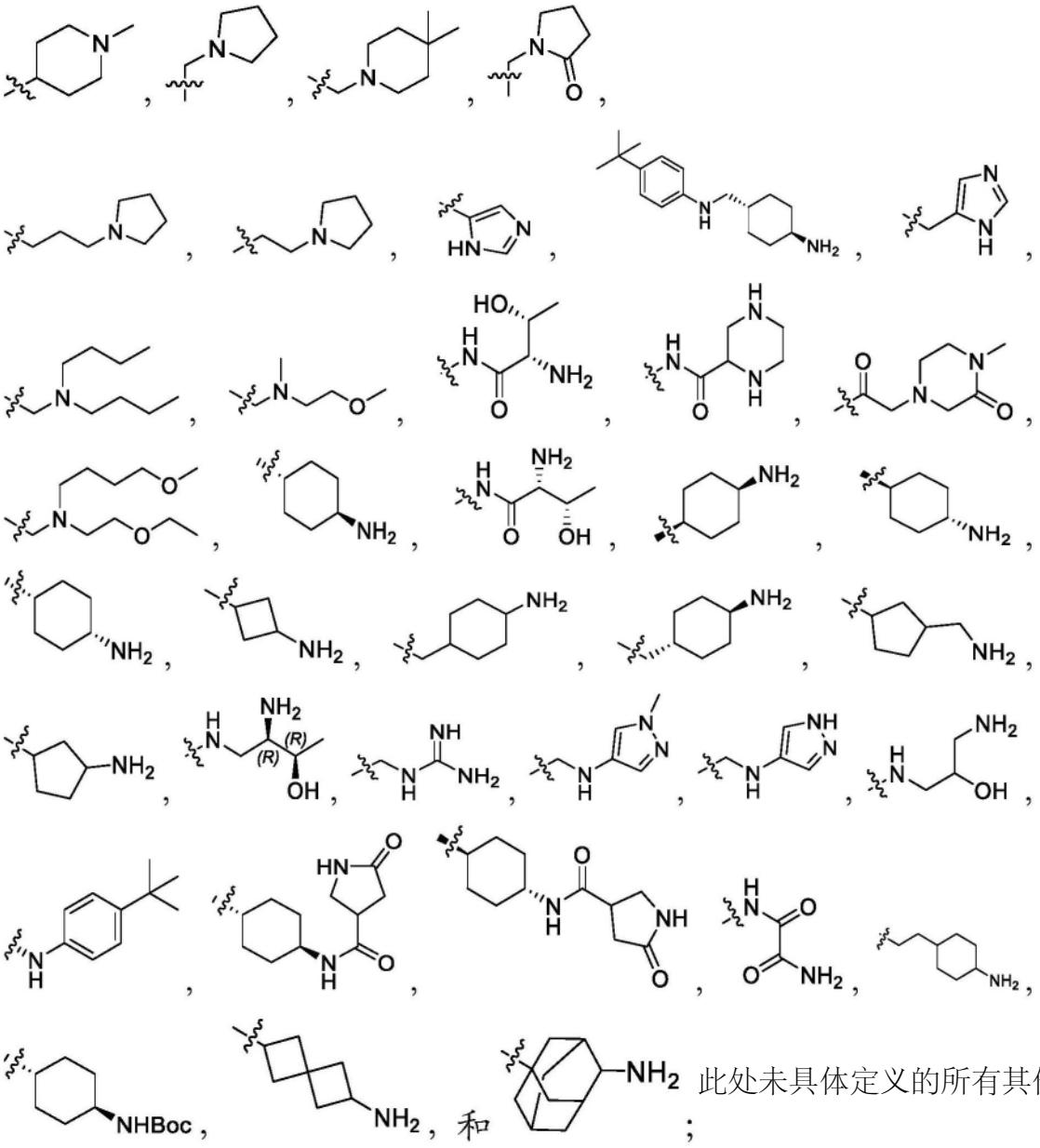
[0197] R^s的C_3-C_{10}环烷基和3-10元杂环基以及R^s的C_1-C_{10}烷基的C_3-C_{10}环烷基和3-10元杂环基各自任选被1-3个任选被卤素取代的C_1-C_6烷基的基团取代,和R^s的C_1-C_{10}烷基的C_1-C_6烷氧基任选被1-3个卤素的基团取代;此处未具体定义的所有其他变量如前述实施方案中任一个中所定义。

[0198] 在第三十八实施方案中,在本公开内容的化合物,互变异构体,该化合物或该互变异构体的溶剂化物或立体异构体,或药学上可接受的盐中,R^d不存在或选自

[0199] 

F,甲基,乙基,丙基,丁基,-$(CH_2)_3NCH_3$,-$CH_2N(CH_3)_2$,-$CH_2N^+(CH_3)_3$,-$(CH_2)_3N(CH_3)_2$,-$(CH_2)_3NH_2$,-$(CH_2)_5NH_2$,-$(CH_2)_4NH_2$,-$CH_2CH_2NH_2$,-CH_2NH_2,-CH_2NHCH_3,-$CHCH_3NH_2$,-$C(CH_3)_2NH_2$,-$CH_2NH(CH_2)_2OH$,-$(CH_2)_2NHC(=O)NH_2$,-$CH_2OCH_2CH_2NH_2$,-CH_2CH_2OH,-CH_2OH,-CH_2OCH_3,-

$CH_2CH_2CH_2OCH_3$，$-CH_2OCH_2CH_2OCH_3$，$-CH_2OCH_2CH_2OH$，$-C(=O)N(CH_3)_2$，$-C(=O)NHCH_3$，$-C(=O)NHNH_2$，$-C(=O)NHOH$，$-CH_2OH$，OH，$-O(CH_2)_2N(CH_3)_2$，=O，$-C(=O)OCH_3$，$-C(=O)OH$，$-C(=O)NH_2$，$-NH_2$，$-NHC(=O)CH_3$，$-NHC(=O)NH_2$，$-NH(CH_2)_2OH$，$-NH(CH_2)_3OH$，$-NH(CH_2)_4OH$，$-NH(CH_2)_3NH_2$，$-NH(CH_2)_2NH_2$，$-NHCH_2CH_2N(CH_3)_2$，$-NHCH_2CF_3$，$-NHCH_2CH_2F$，$-NHCH_2CHF_2$，$-NHCH_2CH_3$，$-NHCH_2CH_2OCH_3$，$-N(CH_3)_2$，$-NHCH_3$，$-NHOH$，$-NHSO_2NH_2$，$-SO_2NH_2$，

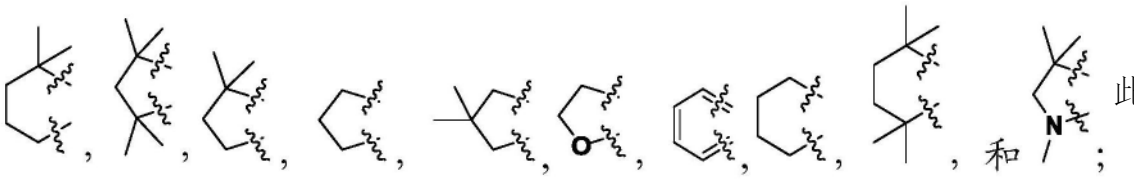


此处未具体定义的所有其他变量如前述实施方案中任一个中所定义。

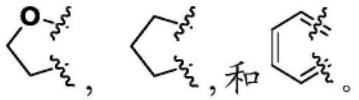
[0200] 在第三十九实施方案中，在本公开内容的化合物，互变异构体，该化合物或该互变异构体的溶剂化物或立体异构体，或药学上可接受的盐中，R^d选自$-C(=O)NR^pR^q$，和C_1-C_6烷基，其中C_1-C_6烷基任选被1-3个选自以下的基团取代：C_1-C_3烷氧基，$-C(=O)NR^pR^q$，和$-NR^pR^q$，其中R^p和R^q各自选自H和C_1-C_3烷基；此处未具体定义的所有其他变量如前述实施方案中任一个中所定义。

[0201] 在第四十实施方案中，在本公开内容的化合物，互变异构体，该化合物或该互变异构体的溶剂化物或立体异构体，或药学上可接受的盐中，R^a和R^b连在一起形成5-6元碳环、杂

环、芳族、或杂芳族的环，其任选被1-4个选自任选被取代的C_1-C_6烷基的基团取代；此处未具体定义的所有其他变量如前述实施方案中任一个中所定义。

[0202] 在第四十一实施方案中，在本公开内容的化合物，互变异构体，该化合物或该互变异构体的溶剂化物或立体异构体，或药学上可接受的盐中，R^a和R^b连在一起形成选自以下的结构：  ，此处未具体定义的所有其他变量如前述实施方案中任一个中所定义。

[0203] 在第四十二实施方案中，在本公开内容的化合物，互变异构体，该化合物或该互变异构体的溶剂化物或立体异构体，或药学上可接受的盐中，R^b和R^c连在一起形成5-6元碳环、杂环、芳族、或杂芳族的环，其任选被1-4个选自任选被取代的C_1-C_6烷基的基团取代；此处未具体定义的所有其他变量如前述实施方案中任一个中所定义。

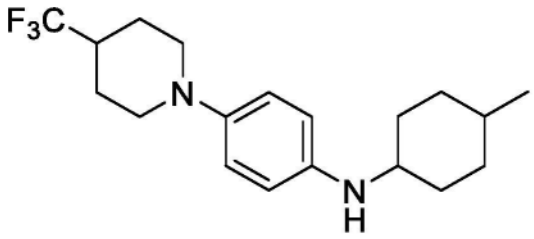
[0204] 在第四十三实施方案中，在本公开内容的化合物，互变异构体，该化合物或该互变异构体的溶剂化物或立体异构体，或药学上可接受的盐中，R^b和R^c连在一起形成选自以下的结构：  。

[0205] 在某些实施方案中，本公开的至少一个化合物选自表1中所述的化合物1至573，其互变异构体，表1中所述的化合物或互变异构体的溶剂化物或立体异构体，或前述的药学上可接受的盐。

[0206] 在某些实施方案中，本公开的至少一个化合物选自表1中所述的化合物574至661，其互变异构体，表1中所述的化合物或互变异构体的溶剂化物或立体异构体，或前述的药学上可接受的盐。

[0207] 本公开中的某些化合物以立体异构体的混合物的形式制备和获得。例如，化合物124以该化合物的两种立体异构体以1:0.3比例的混合物(在下段中描述为“1:0.3混合物”)的形式制备和获得，其中立体异构体的比例通过NMR测定。

[0208] 在本公开中，当化合物用带后缀的化合物编号表示时，例如“A/B”或“A/B/C/D”，其表示制备、分离和测试该化合物的立体异构体，例如两种或四种立体异构体，分别表示为A和B，或表示为A、B、C和D。例如，

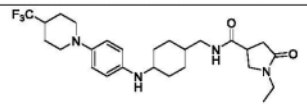
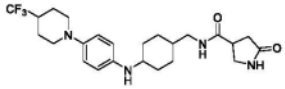
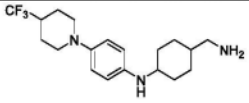
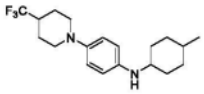
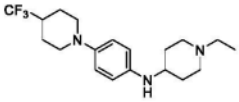
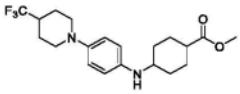
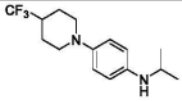
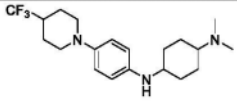
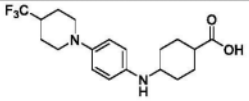
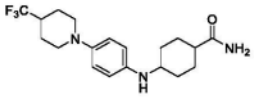
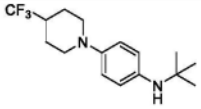
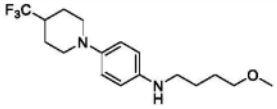
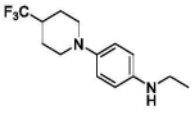
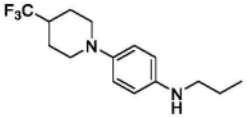
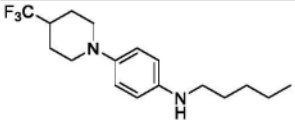
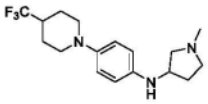
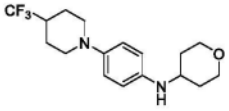
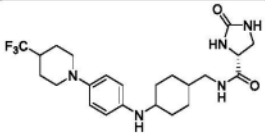
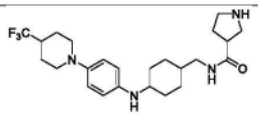
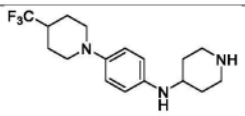
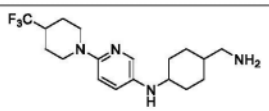
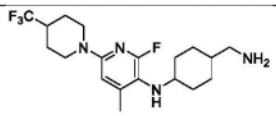
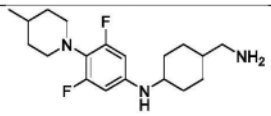
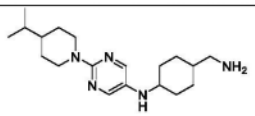
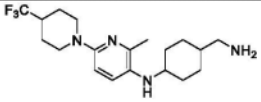
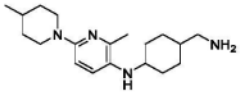
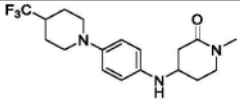
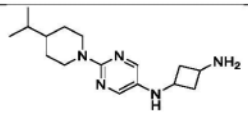
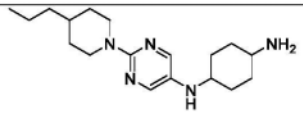
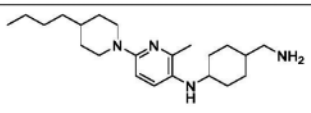
[0209] 

[0210] 4A/B

[0211] 意指制备并分离(参见实施例1中的段落)并测试(参见实施例2中的段落)化合物4的两种立体异构体(4A和4B)。

[0212] 表1：化合物1至573和化合物574-661

[0213]

 1	 2	 3
 4A/B	 5	 6A/B
 7	 8	 9
 10	 11	 12
 13	 14	 15
 16	 17	 18
 19	 20	 21
 22	 23A/B	 24A/B
 25	 26	 27
 28	 29	 30

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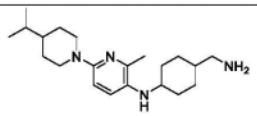
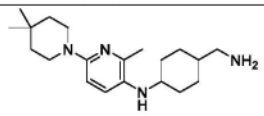
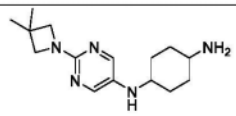
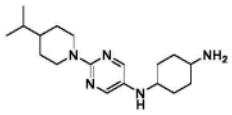
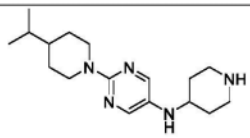
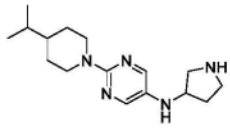
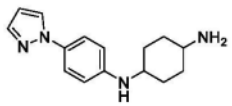
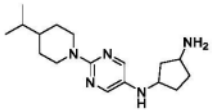
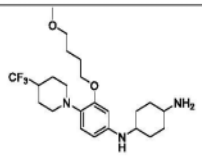
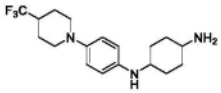
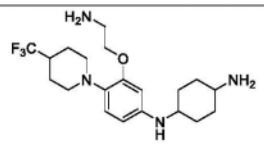
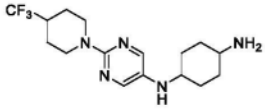
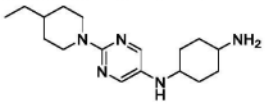
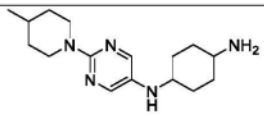
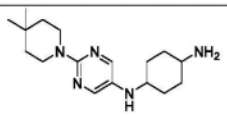
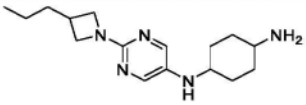
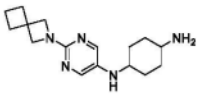
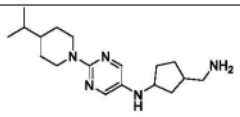
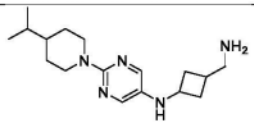
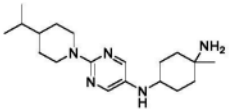
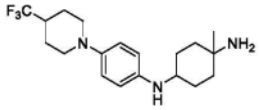
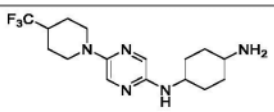
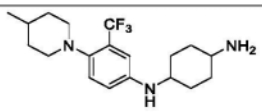
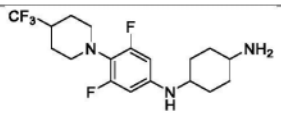
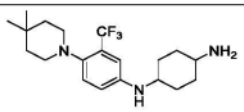
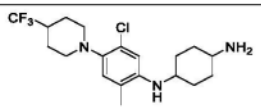
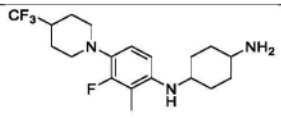
 31	 32A/B	 33A/B
 34A/B	 35	 36
 37A/B	 38	 39
 40	 41A/B	 42
 43	 44	 45
 46	 47	 48
 49	 50	 51
 52	 53A/B	 54A/B
 55	 56	 57

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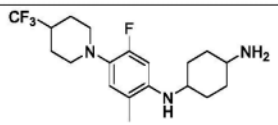
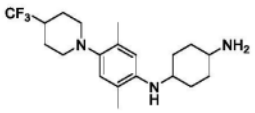
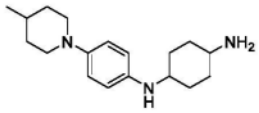
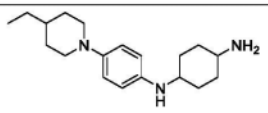
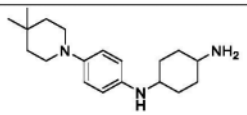
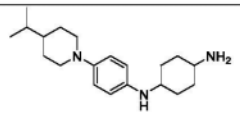
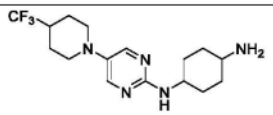
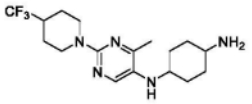
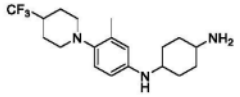
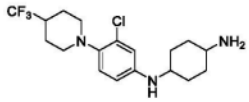
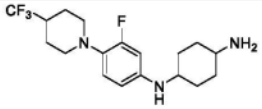
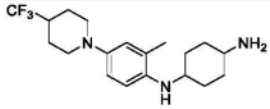
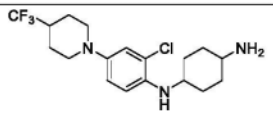
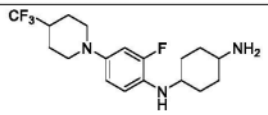
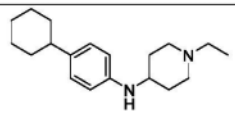
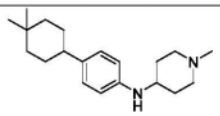
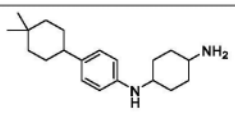
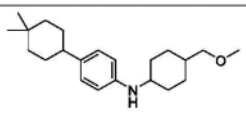
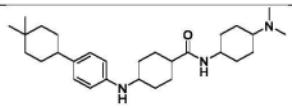
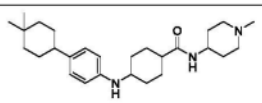
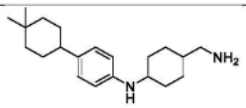
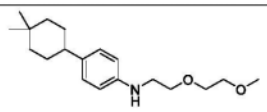
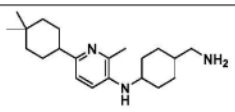
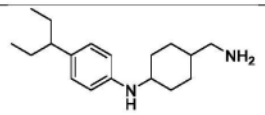
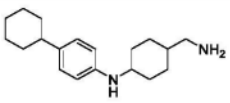
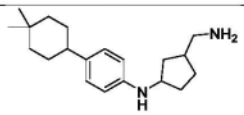
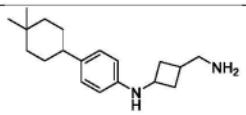
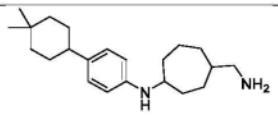
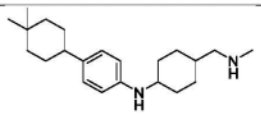
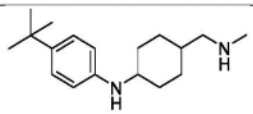
 58	 59	 60
 61	 62	 63
 64A/B	 65A/B	 66
 67	 68	 69
 70	 71	 72
 73	 74	 75
 76A/B	 77	 78
 79	 80	 81A/B
 82A/B	 83	 84
 85	 86	 87

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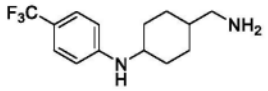
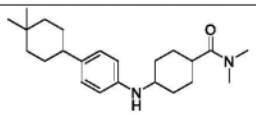
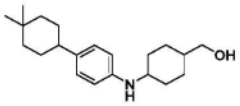
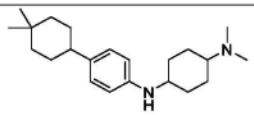
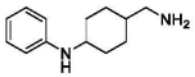
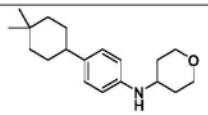
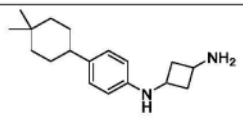
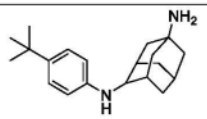
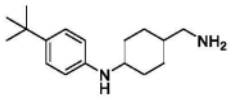
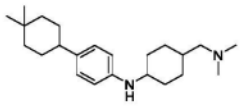
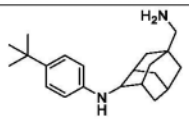
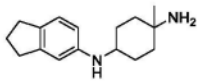
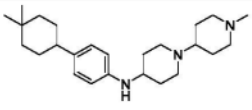
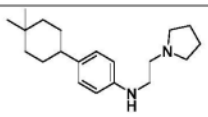
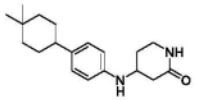
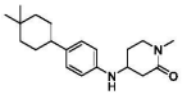
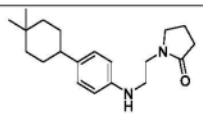
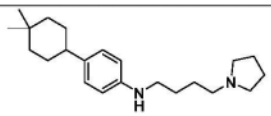
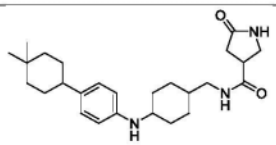
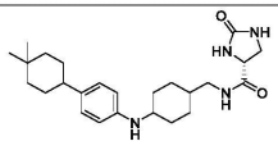
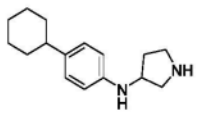
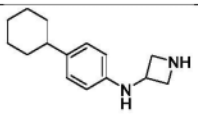
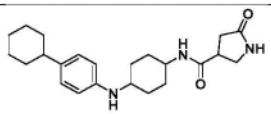
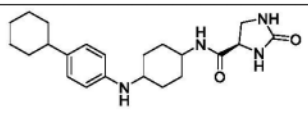
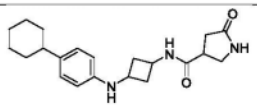
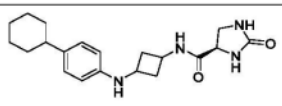
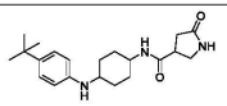
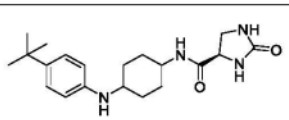
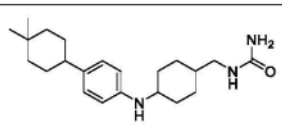
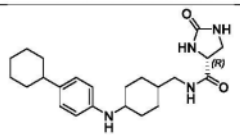
 88	 89	 90
 91A/B	 92	 93
 94	 95	 96
 97A/B	 98	 99
 100	 101	 102
 103	 104	 105
 106A/B	 107A/B	 108
 109	 110	 111
 112	 113	 114A/B
 115A/B	 116	 117A/B

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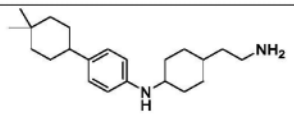
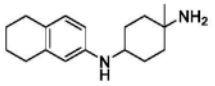
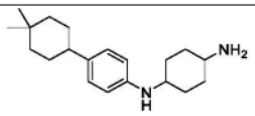
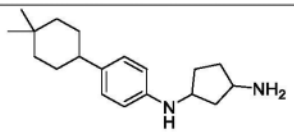
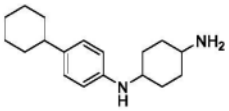
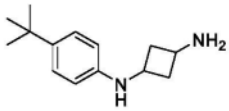
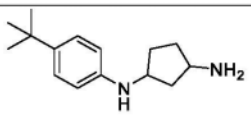
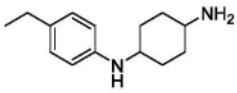
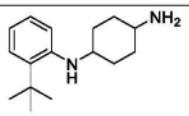
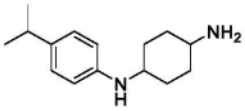
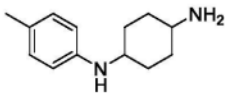
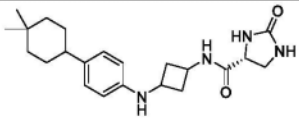
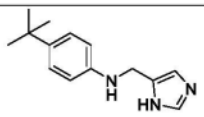
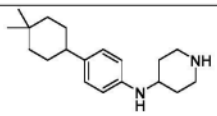
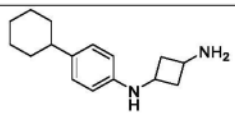
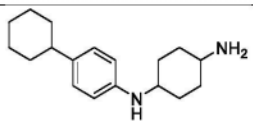
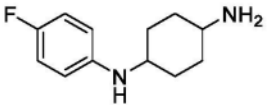
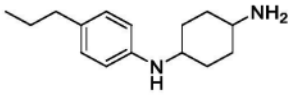
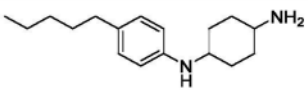
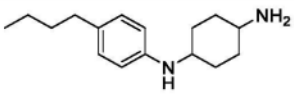
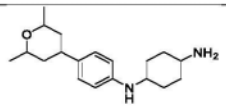
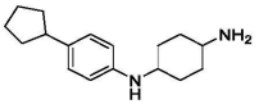
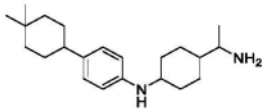
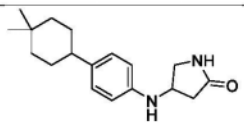
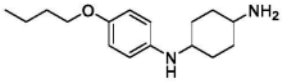
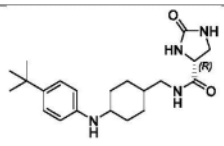
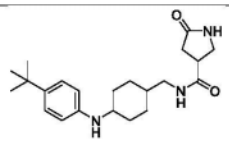
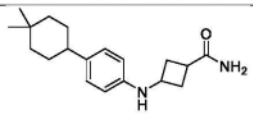
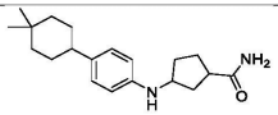
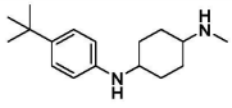
 118	 119	 120A/B
 121A/B	 122	 123
 124	 125	 126
 127	 128	 129
 130	 131	 132
 133	 134	 135A/B
 136	 137	 138
 139A/B	 140	 141
 142A/B	 143A/B	 144A/B
 145	 146A/B	 147

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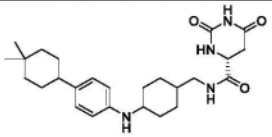
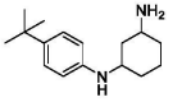
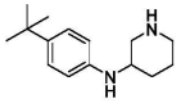
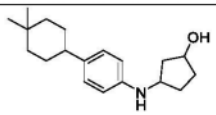
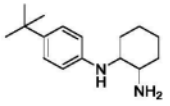
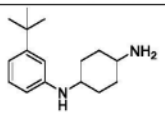
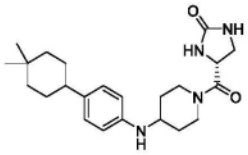
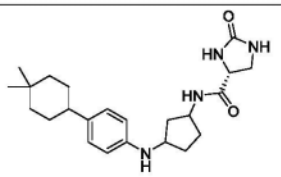
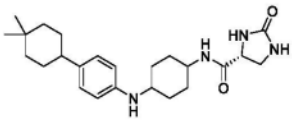
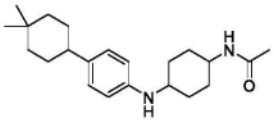
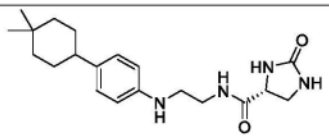
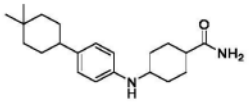
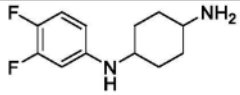
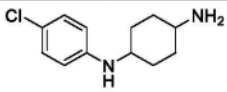
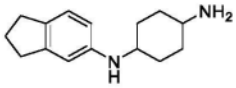
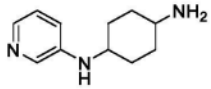
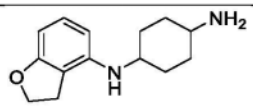
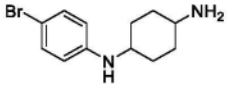
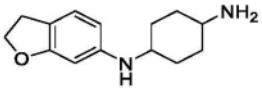
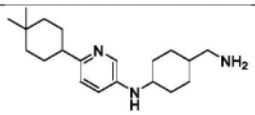
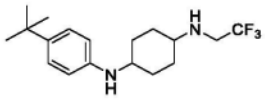
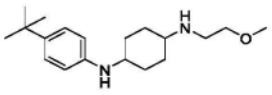
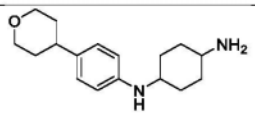
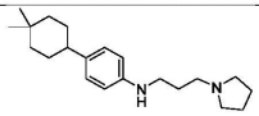
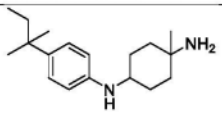
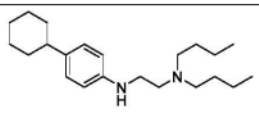
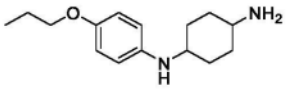
 148A/B	 149A/B	 150
 151	 152	 153A/B
 154	 155	 156A/B/C
 157A/B	 158	 159A/B
 160	 161	 162
 163	 164	 165
 166	 167	 168A/B
 169	 170	 171
 172	 173	 174

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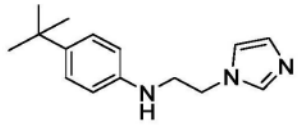
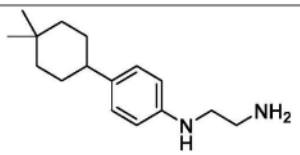
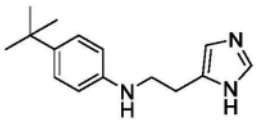
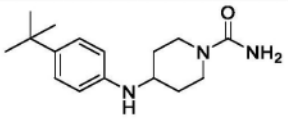
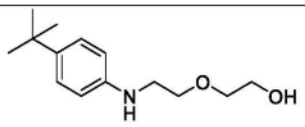
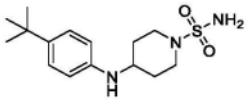
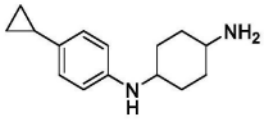
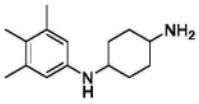
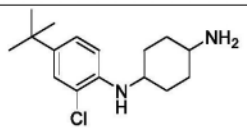
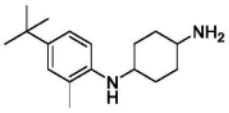
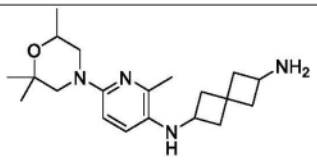
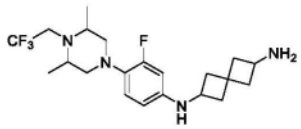
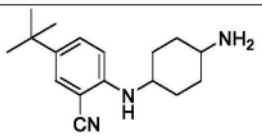
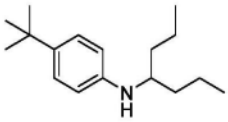
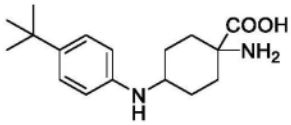
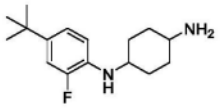
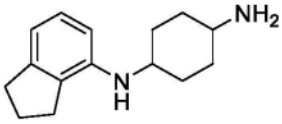
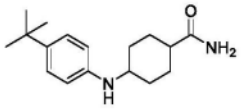
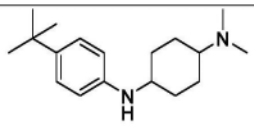
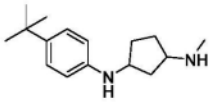
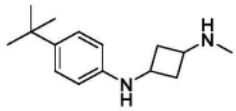
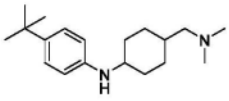
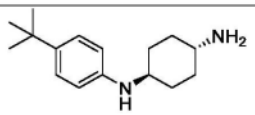
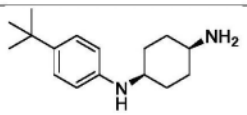
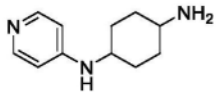
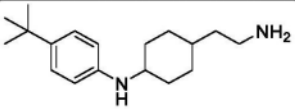
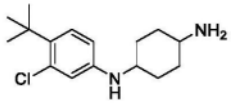
 175	 176	 177
 178	 179	 180
 181	 182A/B	 183A/B
 184	 185	 186
 187	 188	 189
 190	 191A/B	 192
 193A/B	 194	 195
 196	 197	 198
 199	 200A/B	 201

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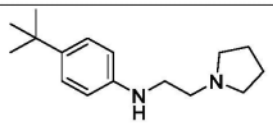
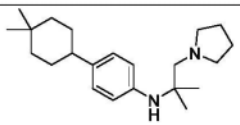
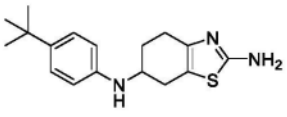
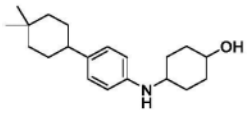
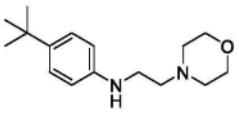
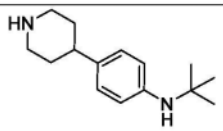
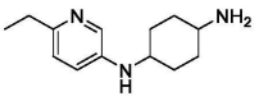
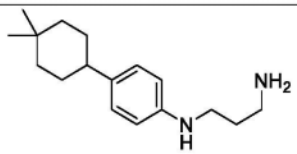
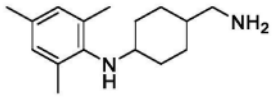
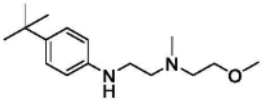
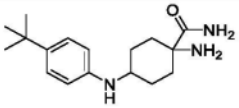
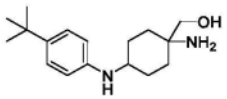
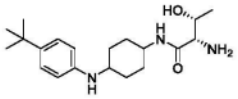
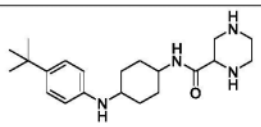
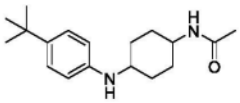
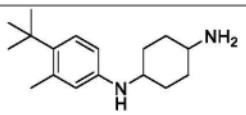
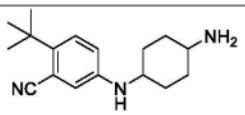
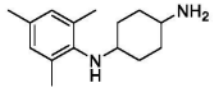
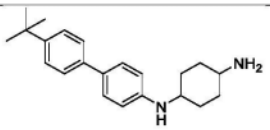
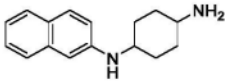
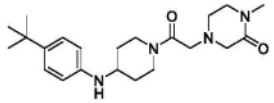
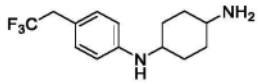
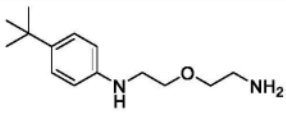
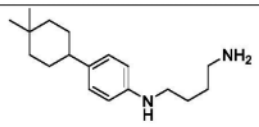
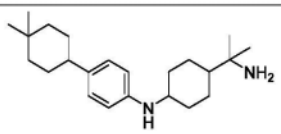
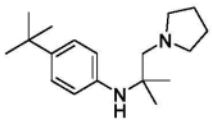
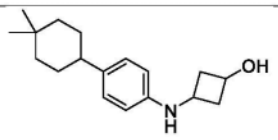
 202	 203	 204
 205A/B	 206	 207
 208	 209	 210
 211	 212	 213A/B
 214	 215	 216A/B
 217	 218	 219
 220	 221	 222
 223	 224	 225
 226	 227	 228A/B

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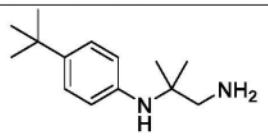
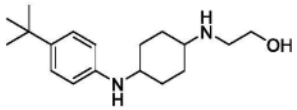
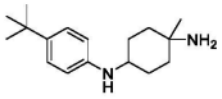
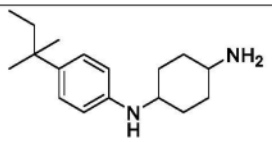
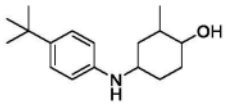
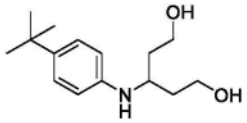
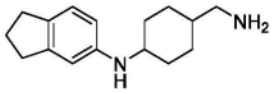
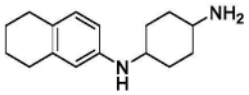
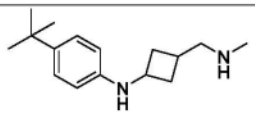
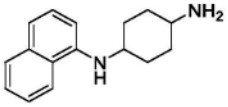
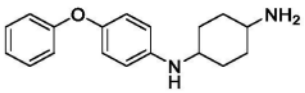
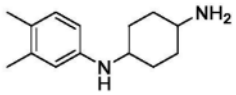
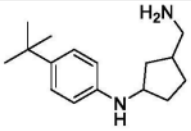
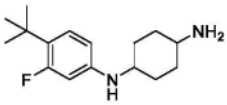
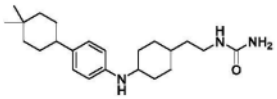
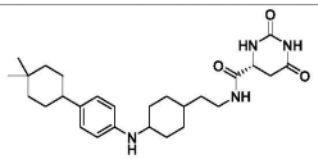
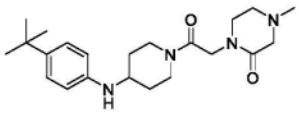
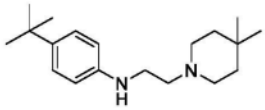
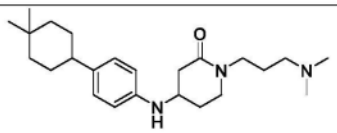
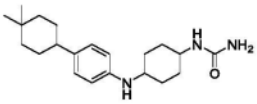
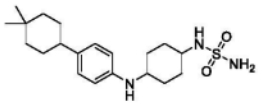
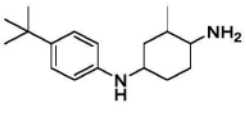
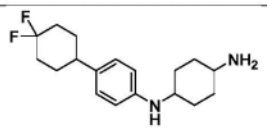
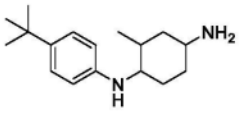
 229	 230	 231A/B
 232A/B	 233A/B	 234
 235	 236	 237
 238	 239	 240
 241	 242A/B	 243
 244A/B	 245	 246
 247	 248	 249
 250A/B	 251A/B	 252A/B/C/D

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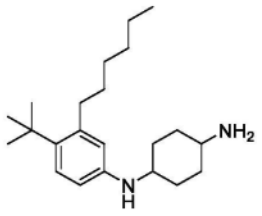
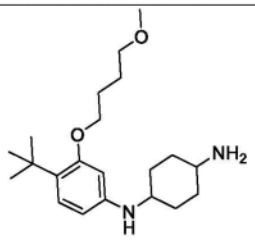
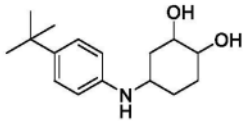
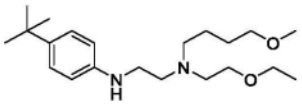
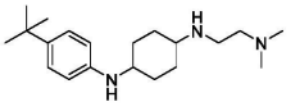
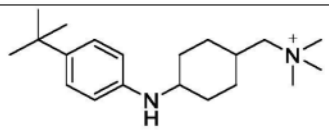
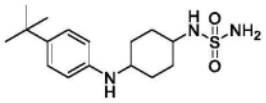
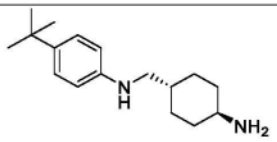
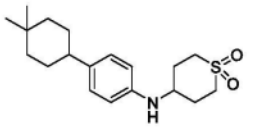
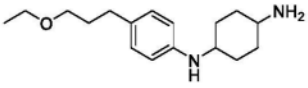
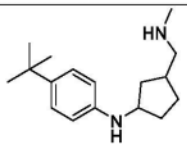
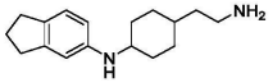
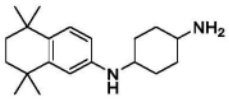
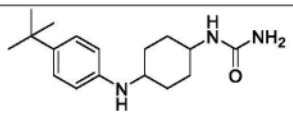
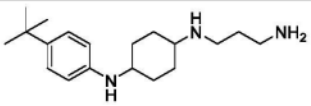
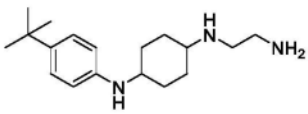
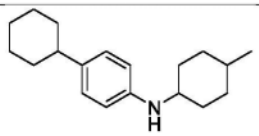
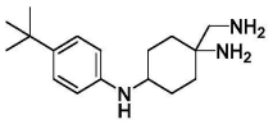
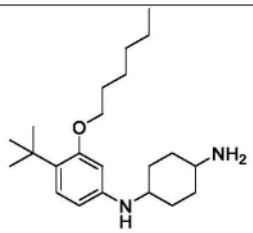
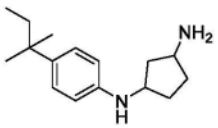
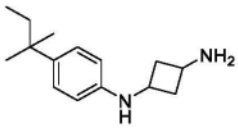
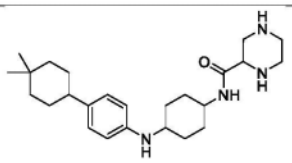
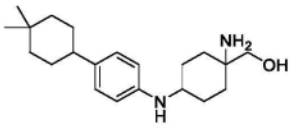
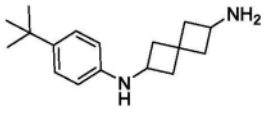
 253A/B	 254	 255
 256	 257	 258
 259A/B	 260	 261
 262	 263	 264
 265	 266A/B	 267
 268	 269	 270
 271	 272	 273
 274	 275A/B	 276

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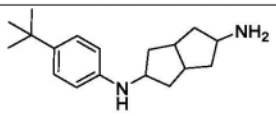
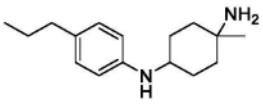
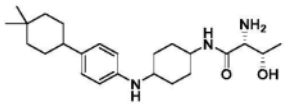
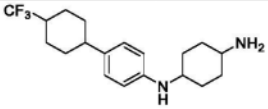
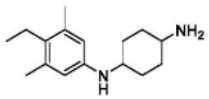
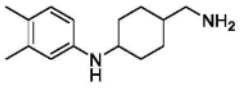
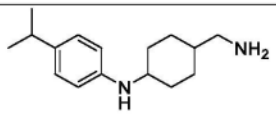
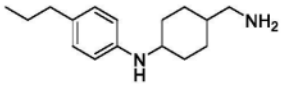
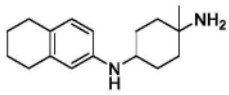
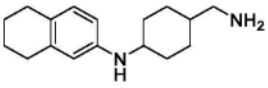
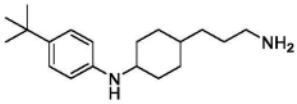
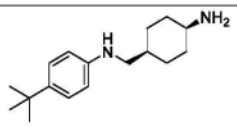
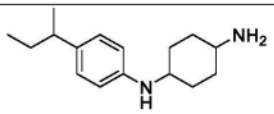
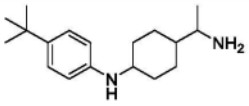
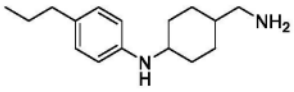
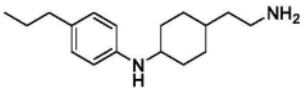
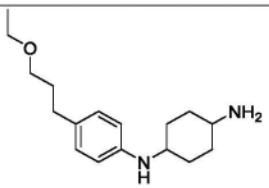
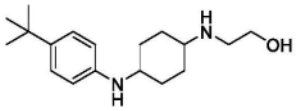
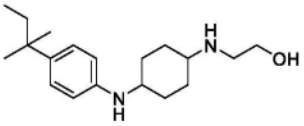
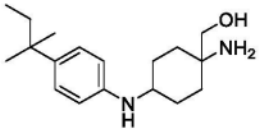
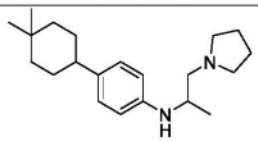
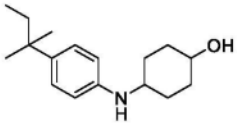
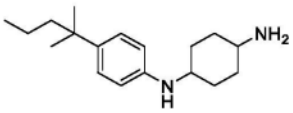
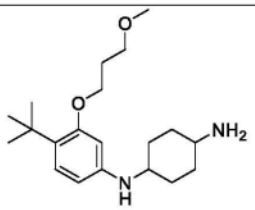
 277	 278	 279
 280	 281	 282
 283	 284	 285
 286	 287	 288
 289A/B	 290	 291
 292	 293	 294A/B
 295A/B	 296A/B	 297
 298	 299A/B	 300A/B

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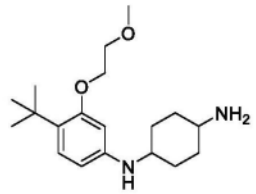
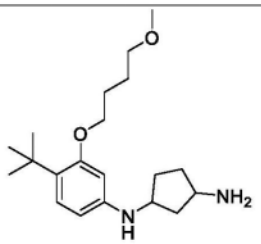
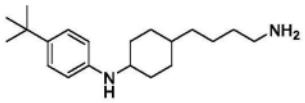
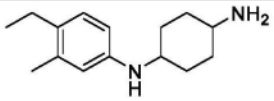
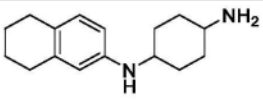
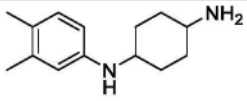
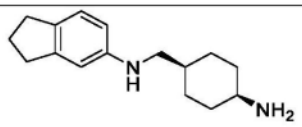
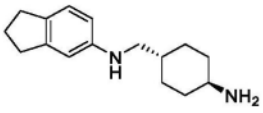
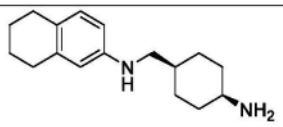
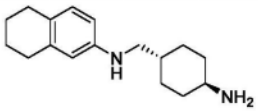
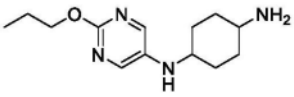
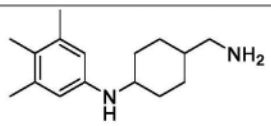
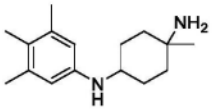
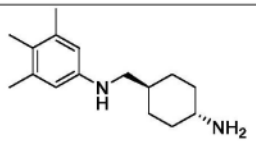
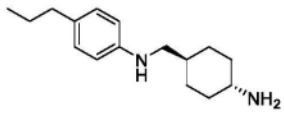
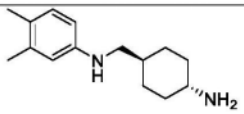
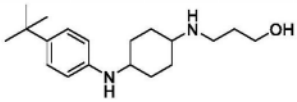
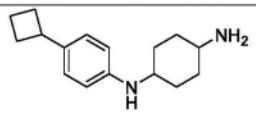
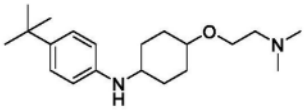
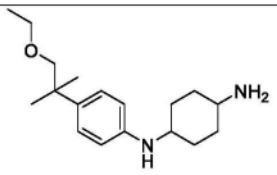
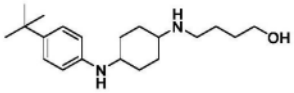
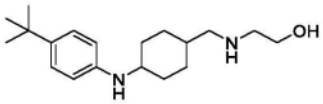
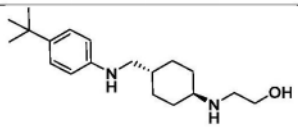
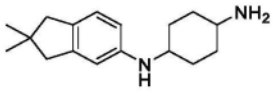
 301A/B	 302	 303
 304	 305A/B	 306A/B
 307	 308	 309
 310	 311	 312
 313A/B	 314	 315
 316	 317	 318A/B
 319A/B	 320A/B	 321
 322	 323	 324

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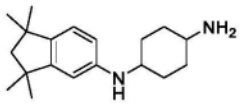
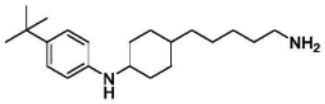
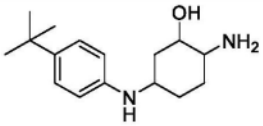
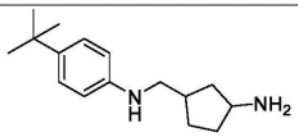
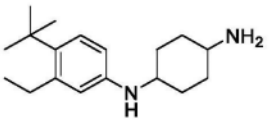
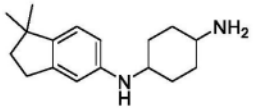
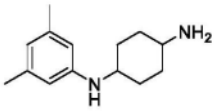
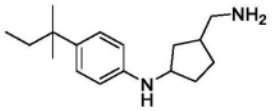
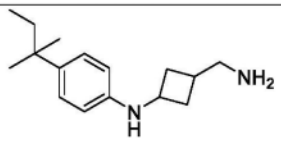
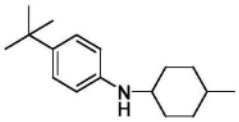
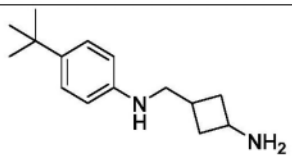
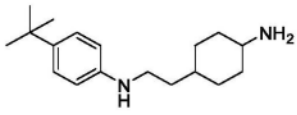
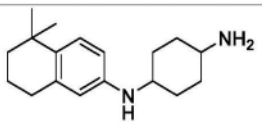
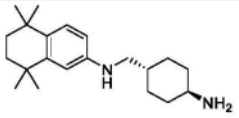
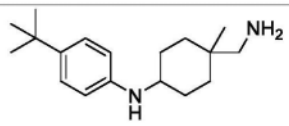
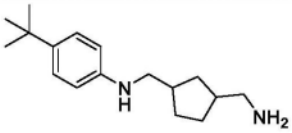
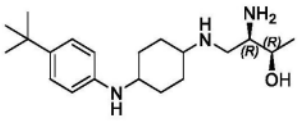
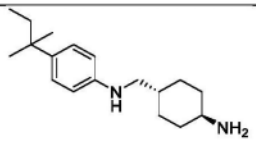
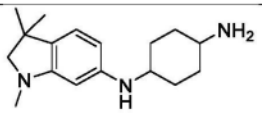
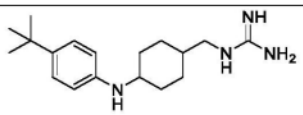
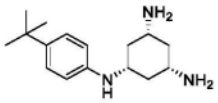
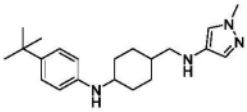
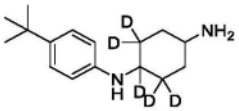
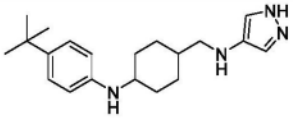
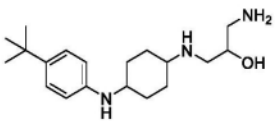
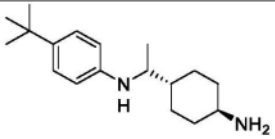
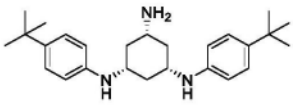
 325A/B	 326	 327
 328	 329	 330A/B
 331	 332	 333
 334	 335A/B	 336A/B
 337A/B	 338	 339
 340	 341	 342
 343	 344	 345
 346	 347	 348
 349A/B	 350	 351

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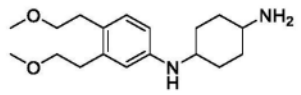
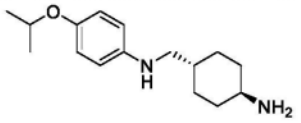
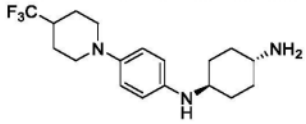
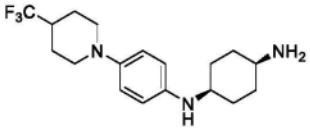
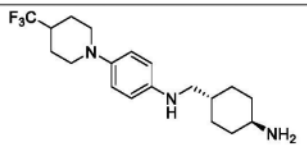
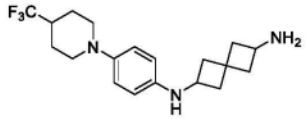
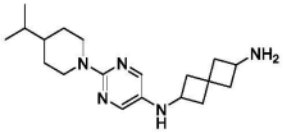
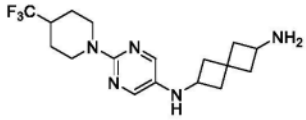
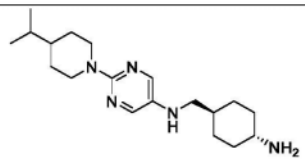
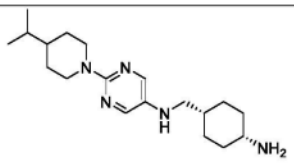
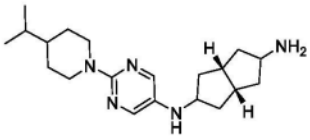
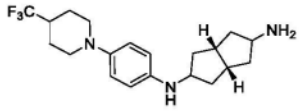
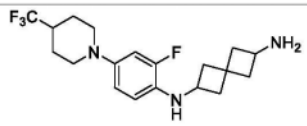
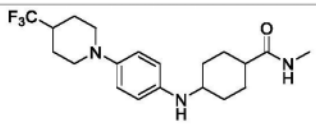
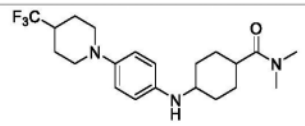
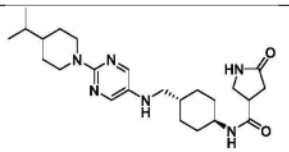
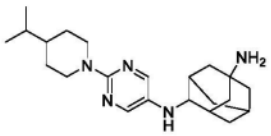
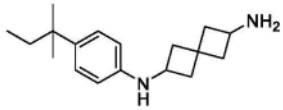
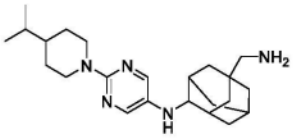
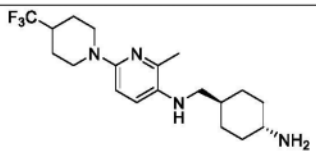
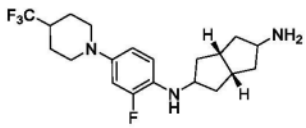
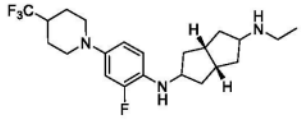
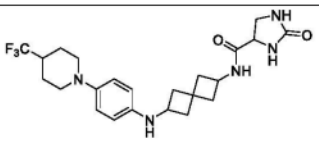
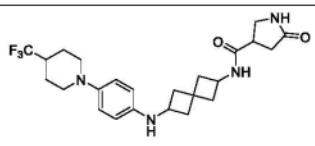
 352	 353	 354
 355	 356	 357
 358	 359	 360
 361	 362	 363
 364	 365	 366
 367	 368	 369
 370	 371	 372
 373	 374	 375

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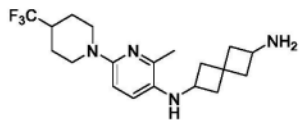
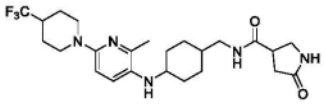
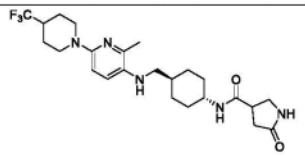
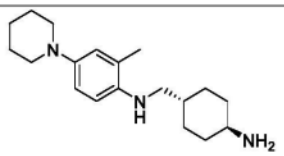
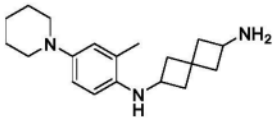
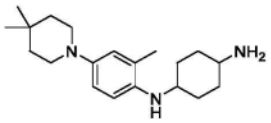
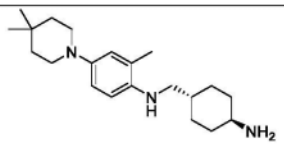
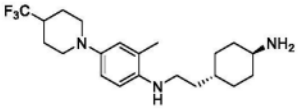
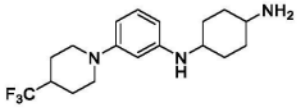
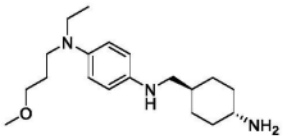
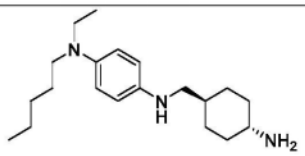
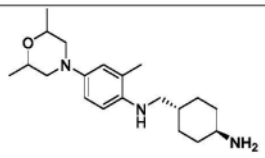
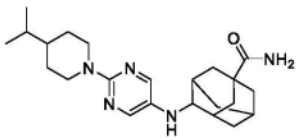
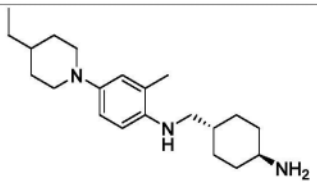
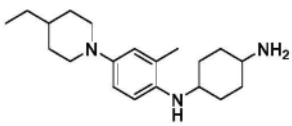
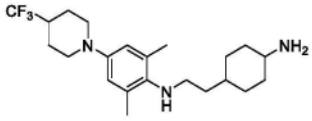
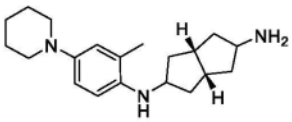
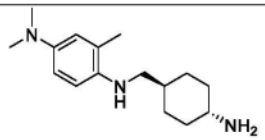
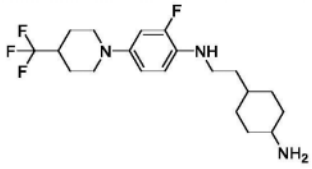
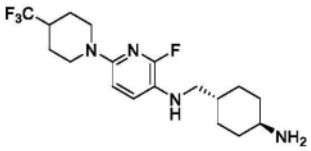
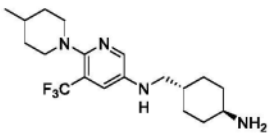
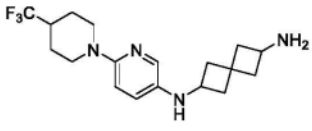
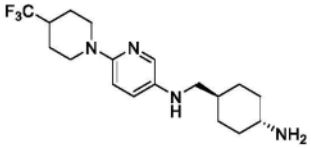
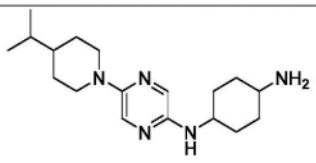
 376	 377	 378
 379	 380	 381
 382	 383	 384
 385	 386	 387
 388	 389	 390
 391	 392	 393
 394	 395	 396
 397	 398	 399

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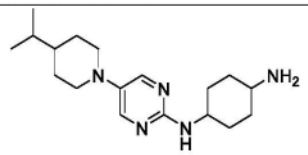
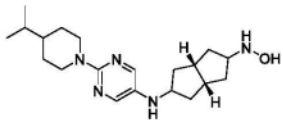
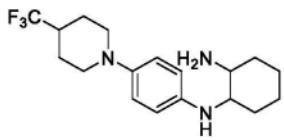
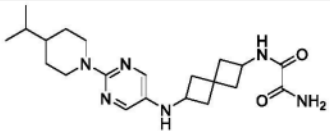
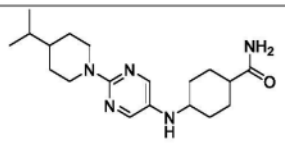
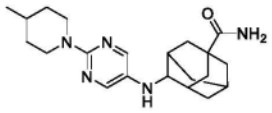
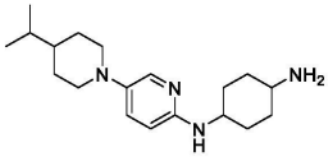
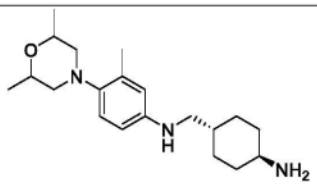
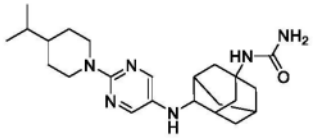
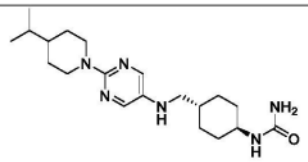
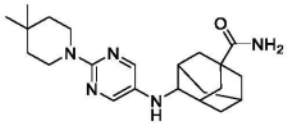
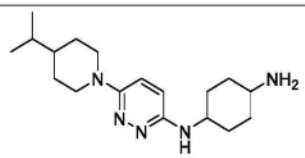
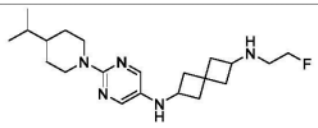
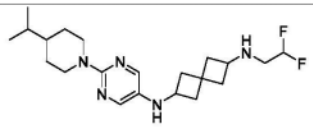
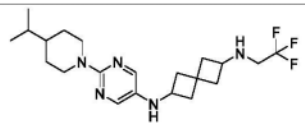
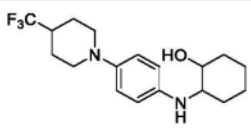
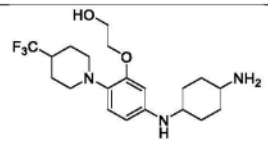
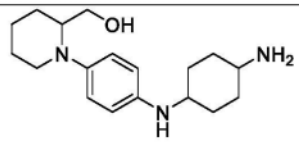
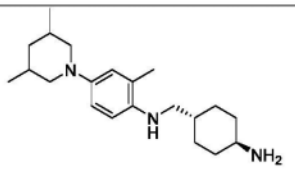
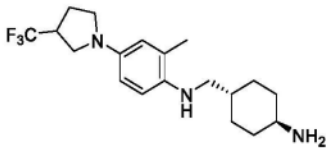
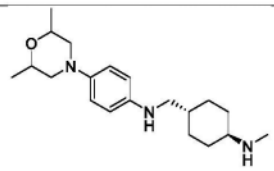
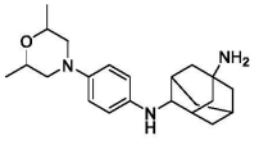
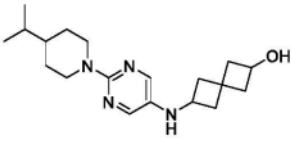
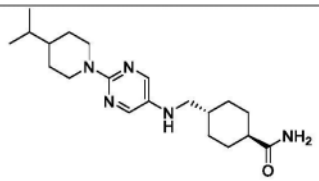
 400	 401	 402
 403	 404	 405
 406	 407	 408
 409	 410	 411
 412	 413	 414
 415	 416	 417A/B
 418	 419	 420
 421A/B	 422	 423

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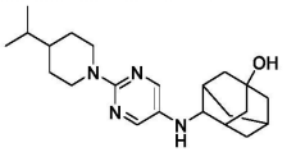
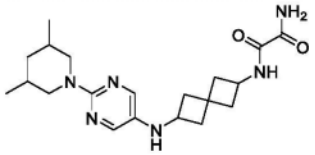
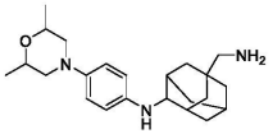
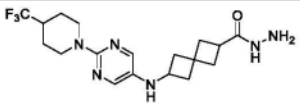
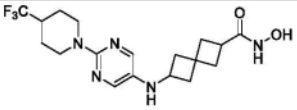
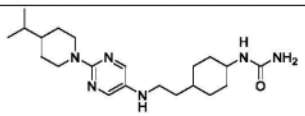
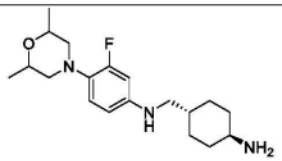
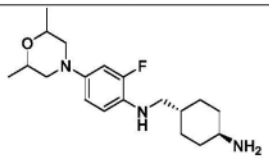
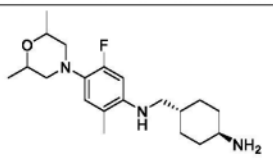
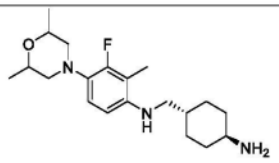
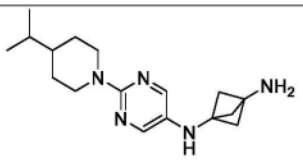
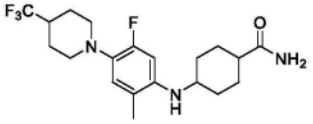
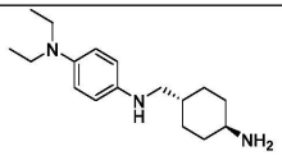
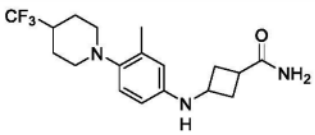
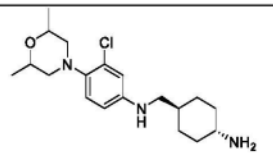
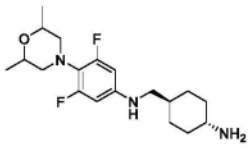
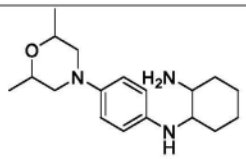
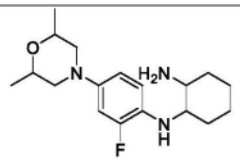
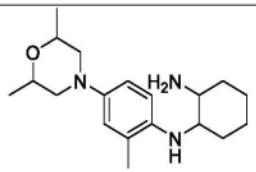
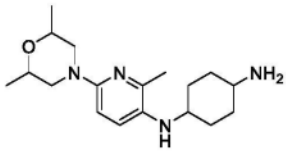
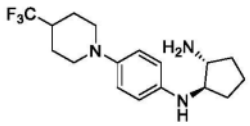
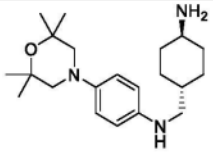
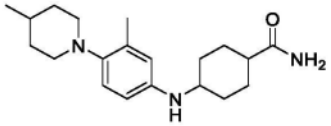
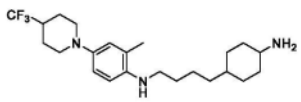
 424	 425	 426
 427	 428	 429
 430	 431	 432
 433	 434	 435
 436	 437	 438
 439	 440	 441
 442	 443	 444
 445	 446A/B	 447

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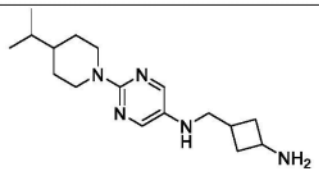
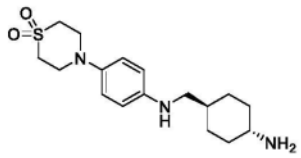
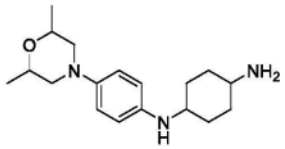
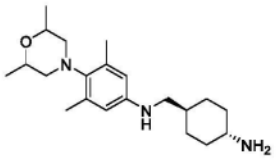
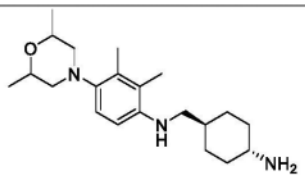
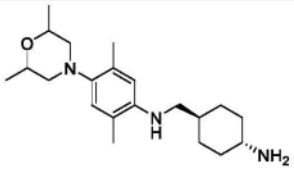
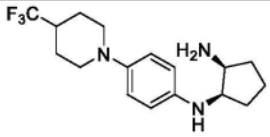
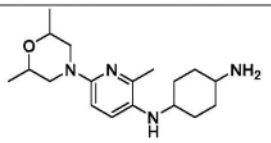
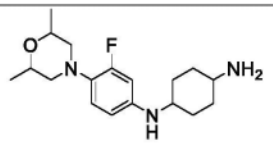
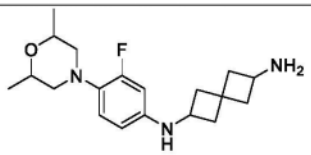
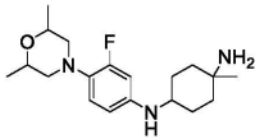
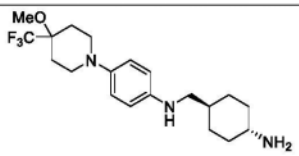
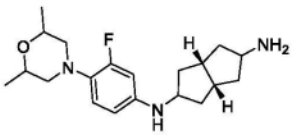
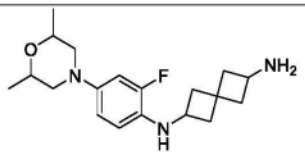
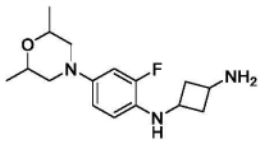
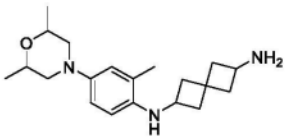
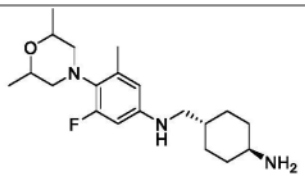
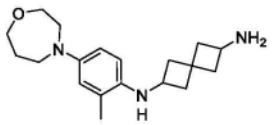
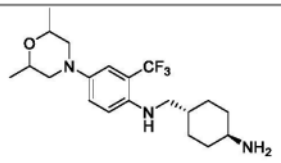
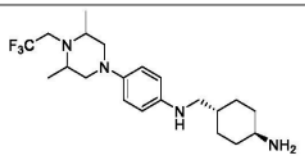
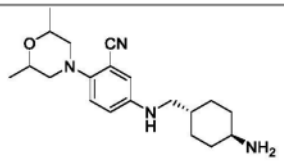
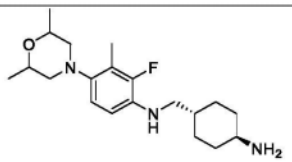
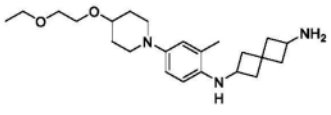
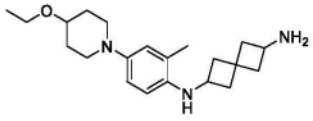
 448	 449	 450
 451	 452	 453
 454	 455	 456
 457	 458	 459
 460	 461	 462
 463	 464	 465
 466	 467	 468
 469	 470	 471

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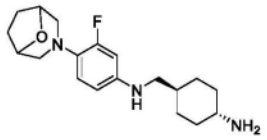
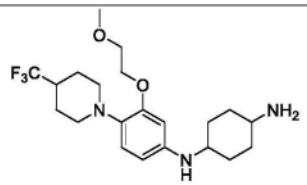
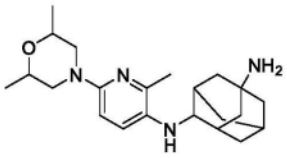
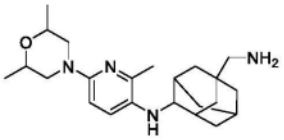
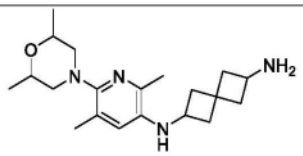
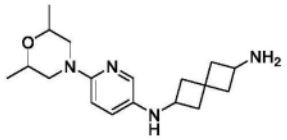
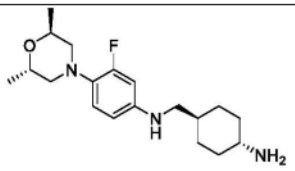
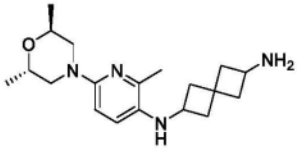
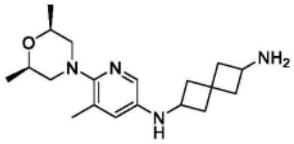
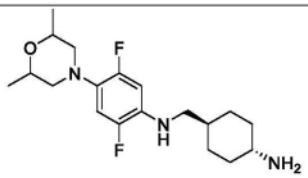
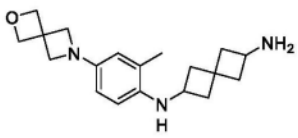
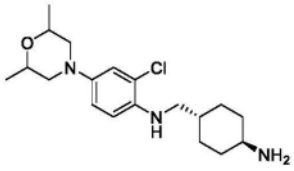
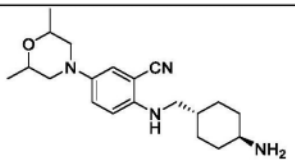
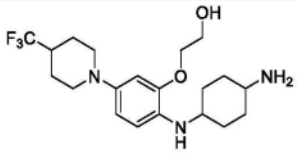
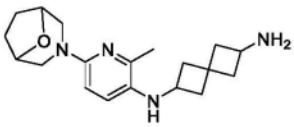
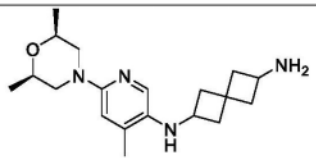
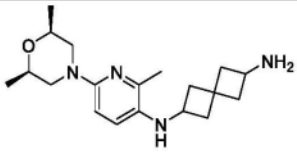
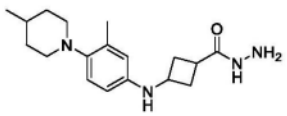
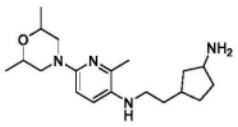
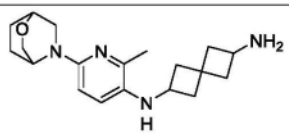
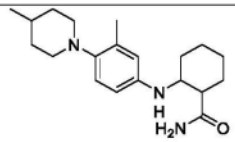
 472	 473	 474
 475A/B	 476	 477
 478	 479	 480
 481	 482	 483
 484	 485	 486
 487	 488A/B	 489
 490	 491	 492

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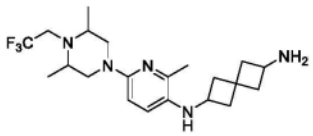
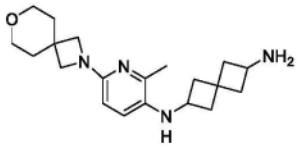
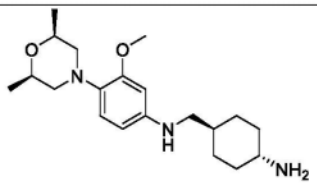
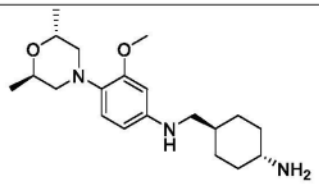
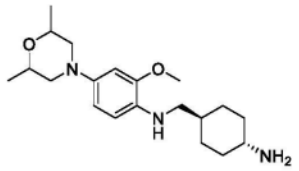
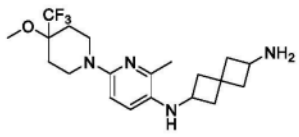
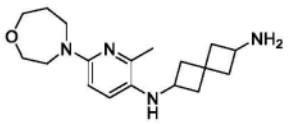
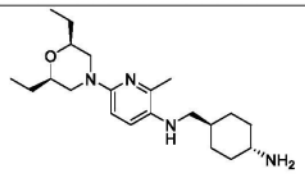
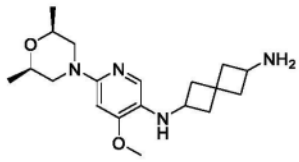
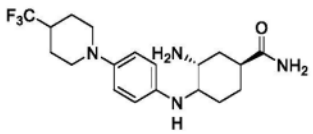
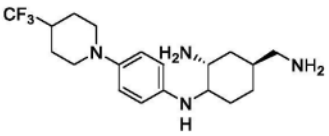
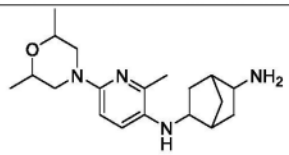
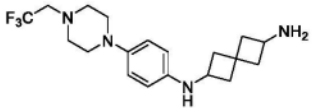
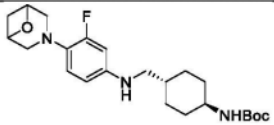
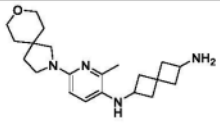
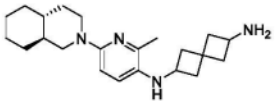
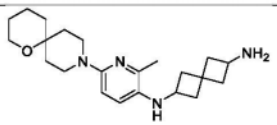
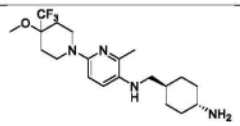
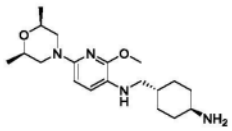
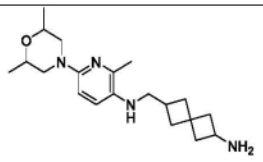
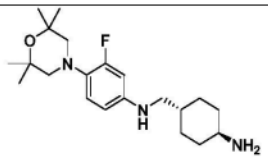
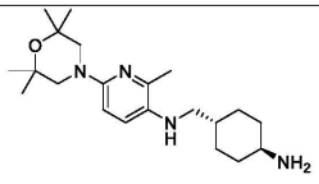
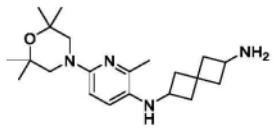
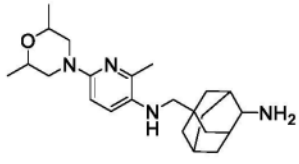
 493	 494	 495
 496	 497	 498
 499	 500	 501
 502	 503	 504
 505	 506	 507
 508	 509	 510
 511	 512	 513
 514	 515	 516A/B

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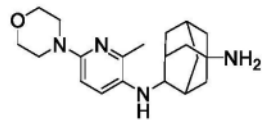
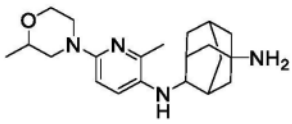
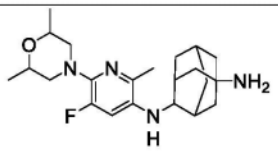
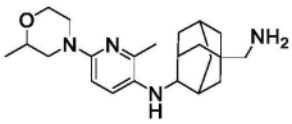
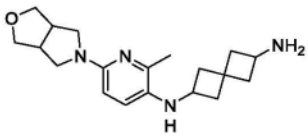
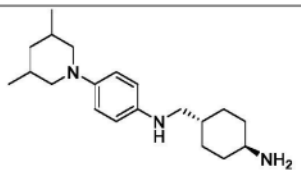
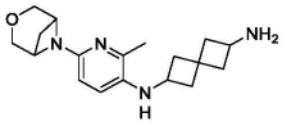
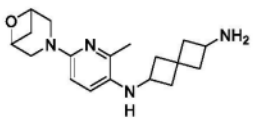
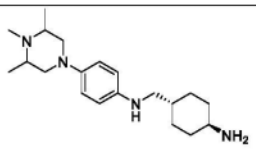
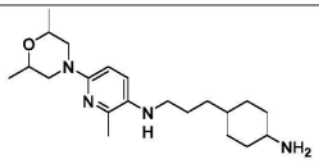
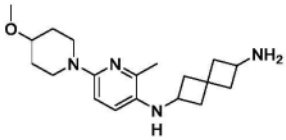
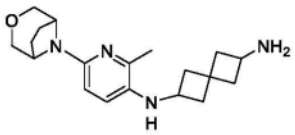
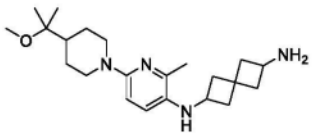
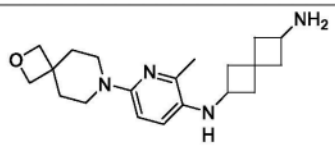
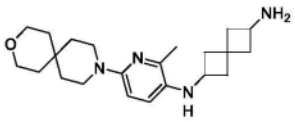
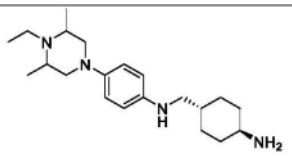
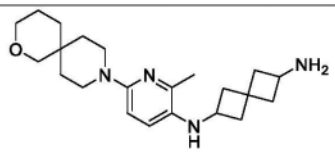
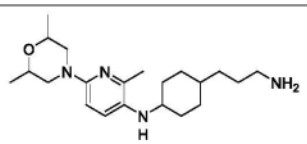
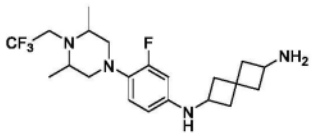
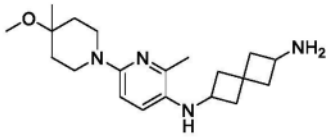
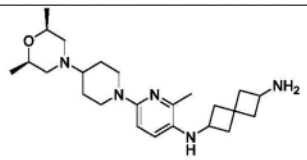
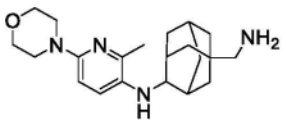
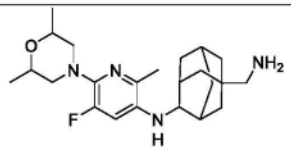
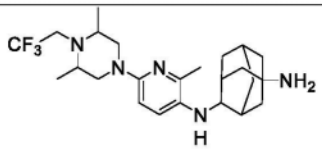
 517	 518	 519
 520	 521	 522
 523	 524	 525
 526	 527	 528
 529	 530	 531
 532	 533	 534
 535	 536	 537
 538A/B	 539A/B	 540

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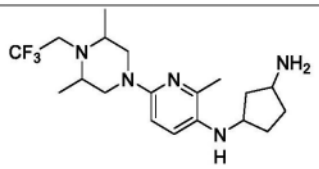
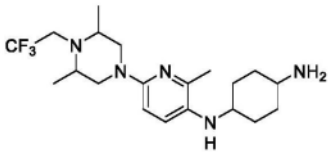
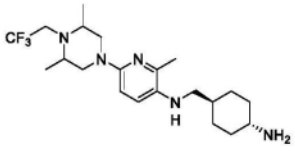
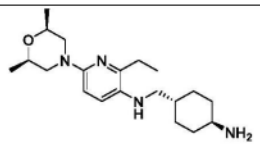
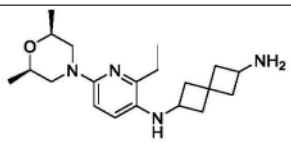
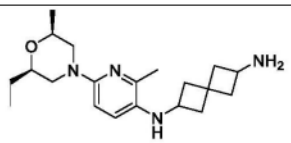
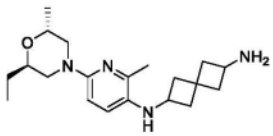
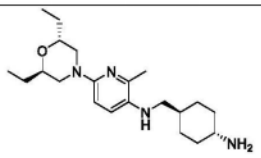
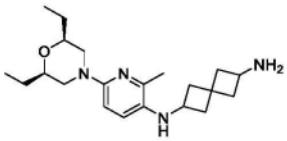
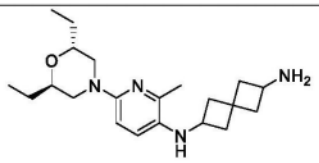
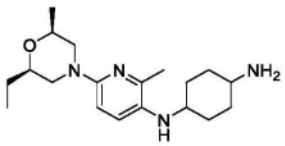
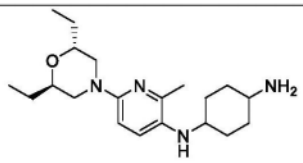
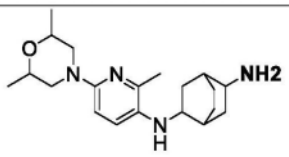
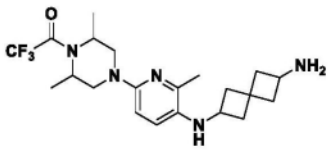
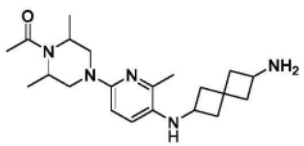
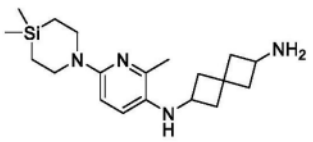
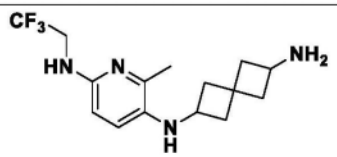
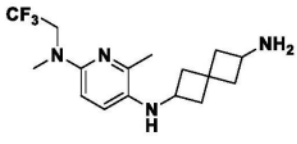
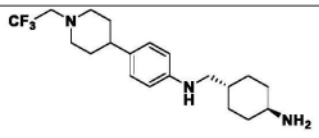
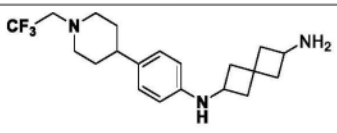
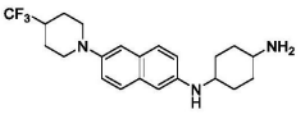
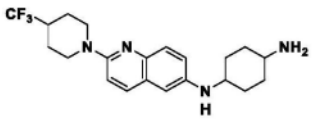
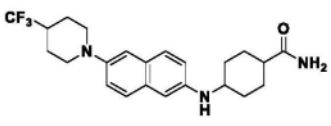
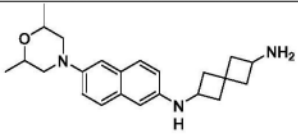
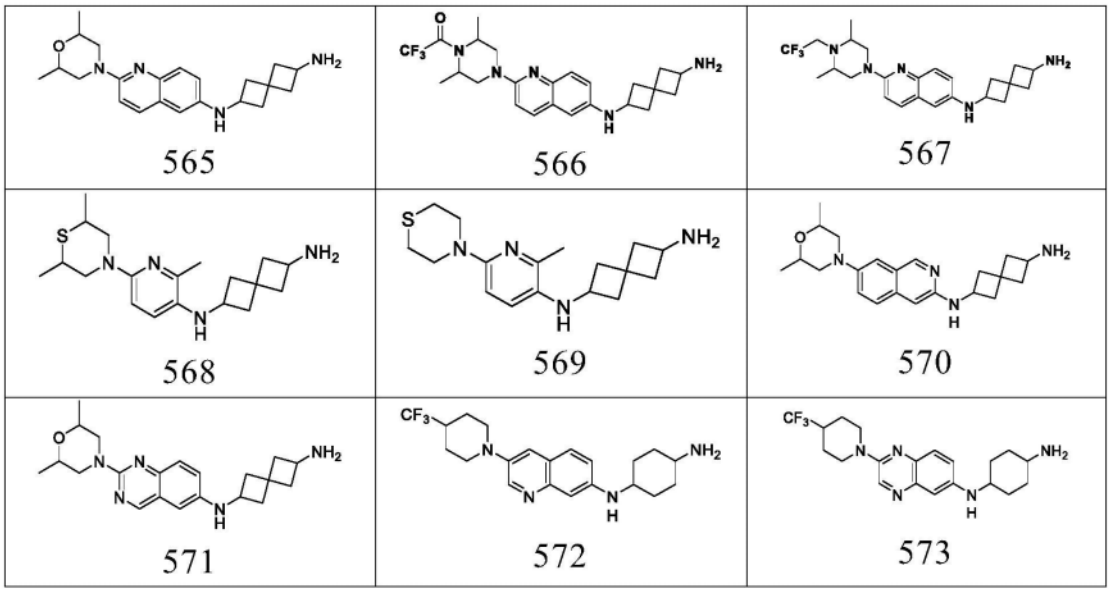
 541	 542	 543
 544	 545	 546
 547	 548	 549
 550	 551	 552
 553	 554	 555
 556	 557	 558
 559	 560	 561
 562	 563	 564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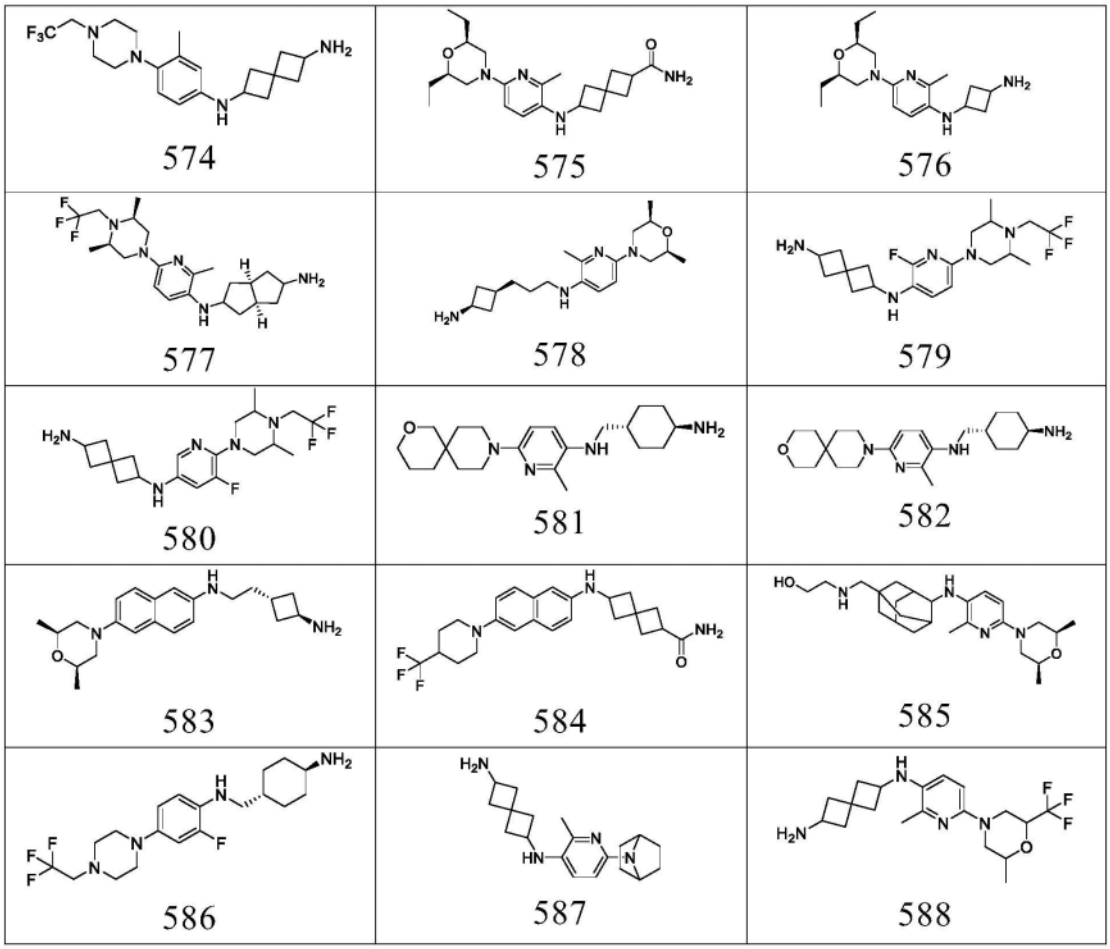
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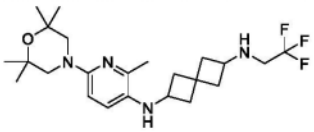
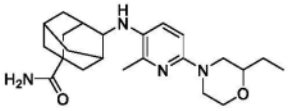
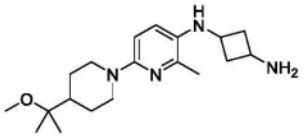
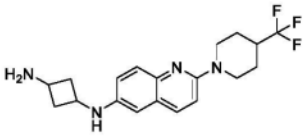
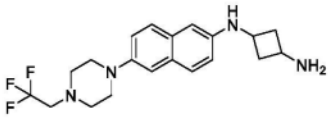
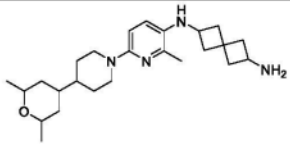
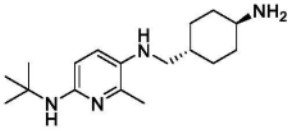
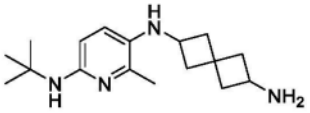
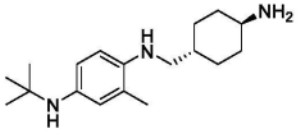
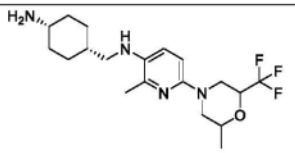
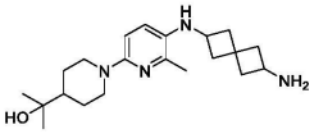
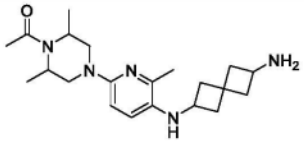
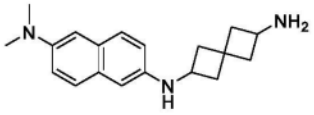
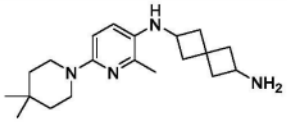
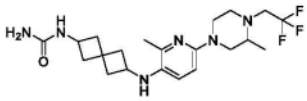
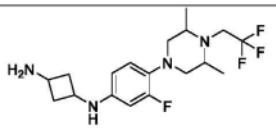
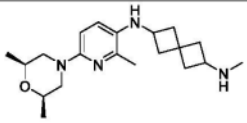
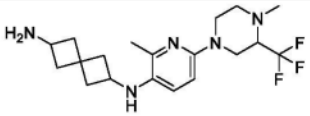
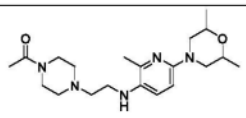
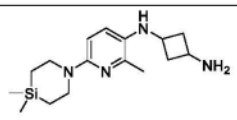
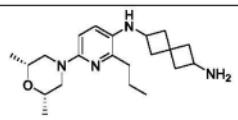
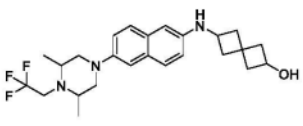
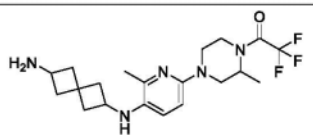
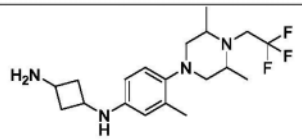
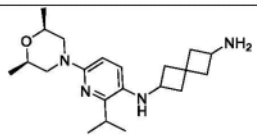
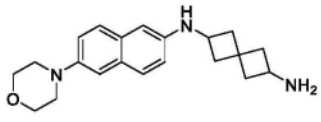
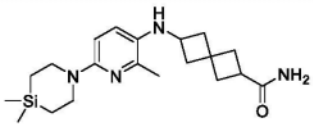
 589	 590	 591
 592	 593	 594
 595	 596	 597
 598	 599	 600
 601	 602	 603
 604	 605	 606
 607	 608	 609
 610	 611	 612
 613	 614	 615

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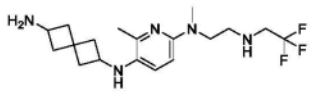
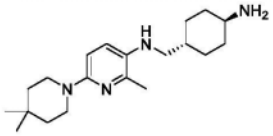
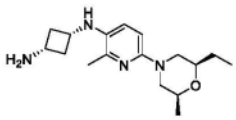
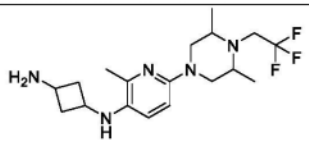
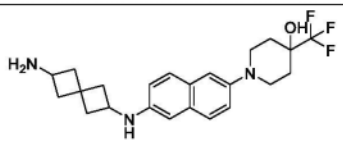
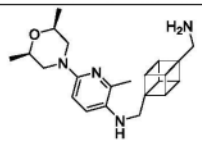
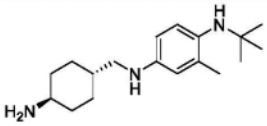
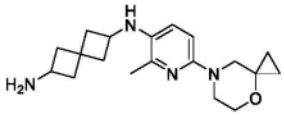
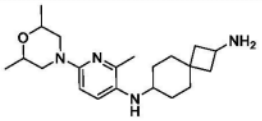
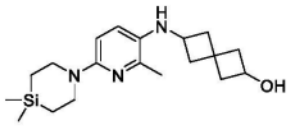
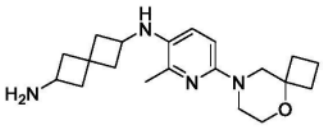
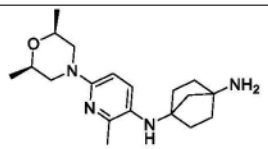
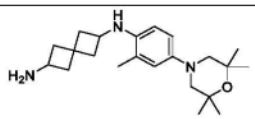
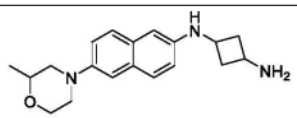
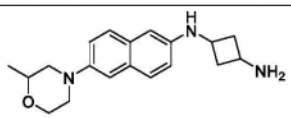
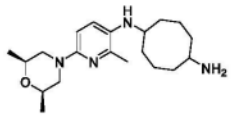
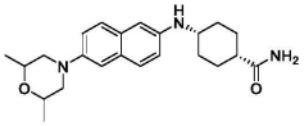
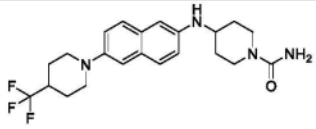
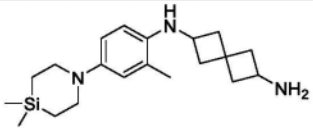
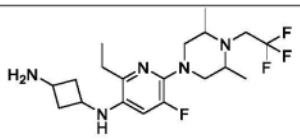
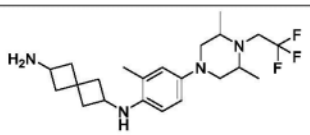
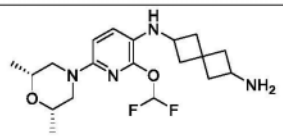
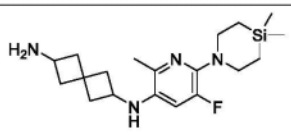
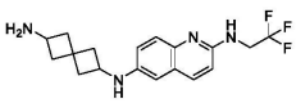
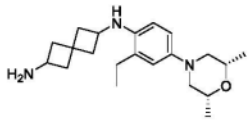
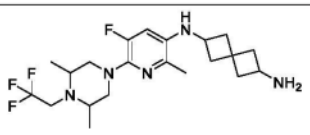
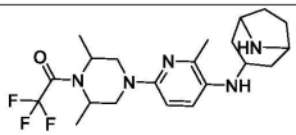
 616	 617	 618
 619	 620	 621
 622	 623	 624
 625	 626	 627
 628	 629	 630
 631	 632	 633
 634	 635	 636
 637	 638	 639
 640	 641	 642

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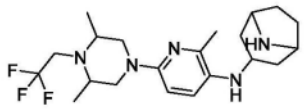
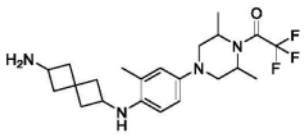
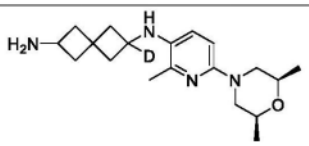
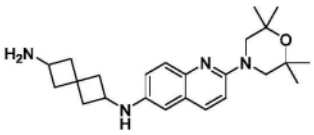
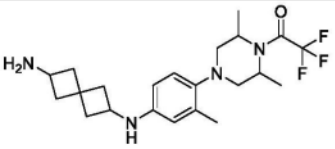
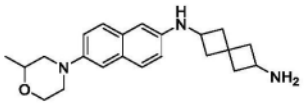
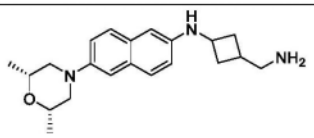
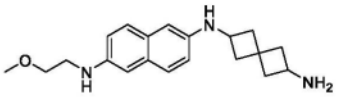
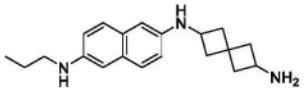
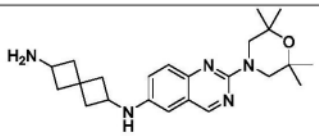
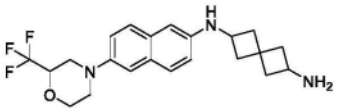
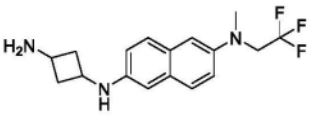
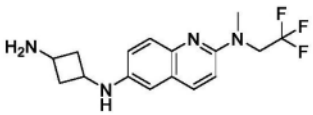
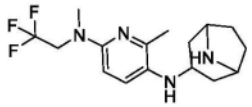
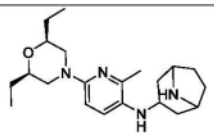
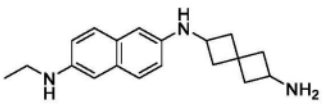
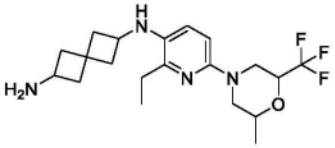
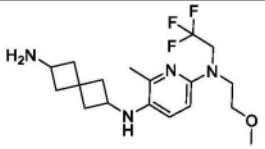
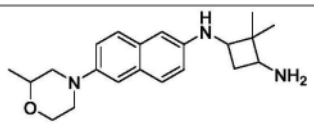
 643	 644	 645
 646	 647	 648
 649	 650	 651
 652	 653	 654
 655	 656	 657
 658	 659	 660
 661		

[0239] 本公开的另一方面提供了药物组合物,其包含至少一种选自本文公开的式的化合物、化合物1至573、其互变异构体,该化合物或该互变异构体的溶剂化物或立体异构体,或前述的药学上可接受的盐,和至少一种药学上可接受的载体。

[0240] 本公开的另一方面提供了药物组合物,其包含至少一种选自本文公开的式的化合物、化合物574至661、其互变异构体,该化合物或该互变异构体的溶剂化物或立体异构体,或前述的药学上可接受的盐,和至少一种药学上可接受的载体。

[0241] 在一些实施方案中,药学上可接受的载体选自药学上可接受的赋形剂和药学上可接受的佐剂。在一些实施方案中,药学上可接受的载体选自药学上可接受的填料、崩解剂、表面活性剂、粘合剂和润滑剂。

[0242] 还应当理解,本公开的药物组合物可以用于联合疗法;也就是说,本文所述的药物组合物还可包含另外的活性药剂。或者,包含选自本文公开的式的化合物、化合物1至573、

其互变异构体,该化合物或该互变异构体的溶剂化物或立体异构体,或前述的药学上可接受的盐的药物组合物可以作为单独的组合物与包含另外的活性药剂的组合物同时、在其之前或在其之后施用。

[0243] 还应当理解,本公开的药物组合物可以用于联合疗法;也就是说,本文所述的药物组合物还可包含另外的活性药剂。或者,包含选自本文公开的式的化合物、化合物574至661、其互变异构体,该化合物或该互变异构体的溶剂化物或立体异构体,或前述的药学上可接受的盐的药物组合物可以作为单独的组合物与包含另外的活性药剂的组合物同时、在其之前或在其之后施用。

[0244] 在一些实施方案中,药学上可接受的载体可以选自佐剂和赋形剂。本文所用的药学上可接受的载体可以选自例如适合所需的特定剂型的任何和所有溶剂、稀释剂、其他液体赋形剂、分散助剂、悬浮助剂、表面活性剂、等渗剂、增稠剂、乳化剂、防腐剂、固体粘合剂和润滑剂。Remington:The Science和Practice of Pharmacy,第21版,2005,编著D.B.Troy,Lippincott Williams&Wilkins,Philadelphia,和Encyclopedia of Pharmaceutical Technology,编著J.Swarbrick和J.C.Boylan,1988to 1999,Marcel Dekker,New York公开了用于配制药物组合物的各种载体及其制备的已知技术。除非任何常规载体与本公开的化合物不相容,例如通过产生任何不期望的生物效应或以有害方式与药物组合物的任何其他组分相互作用,否则其使用涵盖在本公开的范围内。合适的药学上可接受的载体的非限制性实例包括离子交换剂、氧化铝、硬脂酸铝、卵磷脂、血清蛋白(例如人血清白蛋白)、缓冲物质(例如磷酸盐、甘氨酸、山梨酸和山梨酸钾)、饱和植物脂肪酸、水、盐和电解质的偏甘油酯混合物(如硫酸鱼精蛋白、磷酸氢二钠、磷酸氢钾、氯化钠和锌盐)、胶体二氧化硅、三硅酸镁、聚乙烯吡咯烷酮、聚丙烯酸酯、蜡、聚乙烯-聚氧丙烯-嵌段聚合物、羊毛脂、糖类(如乳糖、葡萄糖和蔗糖)、淀粉(如玉米淀粉和马铃薯淀粉)、纤维素及其衍生物(如羧甲基纤维素钠、乙基纤维素和醋酸纤维素)、粉状黄芪胶、麦芽、明胶、滑石、赋形剂(如可可脂和栓剂蜡)、油类(如花生油、棉籽油、红花油、芝麻油、橄榄油、玉米油和大豆油)、二醇类(如丙二醇和聚乙二醇)、酯类(如油酸乙酯和月桂酸乙酯)、琼脂、缓冲剂(如氢氧化镁和氢氧化铝)、海藻酸、无热原水、等渗盐水、林格氏溶液、乙醇、磷酸盐缓冲溶液、无毒相容润滑剂(如月桂基硫酸钠和硬脂酸镁)、着色剂、脱模剂、包衣剂、甜味剂、调味剂、芳香剂、防腐剂和抗氧化剂。

[0245] 可以以固体剂型口服,例如胶囊、片剂、锭剂、糖衣丸、颗粒剂和粉末,或以液体剂型口服,例如酏剂、糖浆、乳剂、分散剂和混悬剂施用选自本文公开的式的化合物、化合物1至573、其互变异构体,该化合物或该互变异构体的溶剂化物或立体异构体,或前述的药学上可接受的盐,或本文公开的药物组合物。本文所述的化合物、互变异构体、溶剂化物、立体异构体或药学上可接受的盐还可以以无菌液体剂型例如分散体、混悬剂或溶液剂肠胃外施用。也可用于施用本文所述的化合物、互变异构体、溶剂化物、立体异构体或药学上可接受的盐的其他剂型,作为软膏剂、乳膏剂、滴剂、透皮贴剂或粉末用于局部施用、作为眼用溶液剂或混悬剂剂型,例如滴眼剂用于经眼施用,作为气溶胶喷雾剂或粉末组合物用于吸入或鼻内施用,或作为乳膏剂、软膏剂、喷雾剂或栓剂用于直肠或阴道施用。

[0246] 可以以固体剂型口服,例如胶囊、片剂、锭剂、糖衣丸、颗粒剂和粉末,或以液体剂型口服,例如酏剂、糖浆、乳剂、分散剂和混悬剂施用选自本文公开的式的化合物、化合物

574至661、其互变异构体,该化合物或该互变异构体的溶剂化物或立体异构体,或前述的药学上可接受的盐,或本文公开的药物组合物。本文所述的化合物、互变异构体、溶剂化物、立体异构体或药学上可接受的盐还可以以无菌液体剂型例如分散体、混悬剂或溶液剂肠胃外施用。也可用于施用本文所述的化合物、互变异构体、溶剂化物、立体异构体或药学上可接受的盐的其他剂型,作为软膏剂、乳膏剂、滴剂、透皮贴剂或粉末用于局部施用、作为眼用溶液剂或混悬剂剂型,例如滴眼剂用于经眼施用,作为气溶胶喷雾剂或粉末组合物用于吸入或鼻内施用,或作为乳膏剂、软膏剂、喷雾剂或栓剂用于直肠或阴道施用。

[0247] 也可以使用含有本文公开的化合物,其互变异构体,该化合物或该互变异构体的溶剂化物或立体异构体,和/或前述的药学上可接受的盐和粉末状载体,例如乳糖、淀粉、纤维素衍生物、硬脂酸镁、硬脂酸等的明胶胶囊。类似的稀释剂可用于制造压缩片剂。片剂和胶囊都可以制造为缓释产品,以在一段时间内持续释放药物。压缩片剂可以包糖衣或包薄膜衣,以掩盖任何不愉快的味道并保护片剂免受大气影响,也可以包肠溶衣,以便在胃肠道中选择性崩解。

[0248] 用于口服施用的液体剂型还可包含至少一种选自着色剂和调味剂的试剂以增加患者接受度。

[0249] 一般而言,水、合适的油、盐水、水性右旋糖(葡萄糖)和相关的糖溶液和二醇例如丙二醇或聚乙二醇可以是用于肠胃外溶液的合适载体的实例。用于肠胃外施用的溶液可以包含至少一种本文描述的化合物的水溶性盐、至少一种合适的稳定剂和如果需要的话至少一种缓冲物质。抗氧化剂例如亚硫酸氢钠、亚硫酸钠或抗坏血酸,单独或组合,可以是合适的稳定剂的实例。柠檬酸及其盐和EDTA钠也可以用作合适的稳定剂的实例。此外,肠胃外溶液还可以包含至少一种防腐剂,其选自例如苯扎氯铵、对羟基苯甲酸甲酯和对羟基苯甲酸丙酯以及氯丁醇。

[0250] 药学上可接受的载体例如选自与组合物的活性成分相容(并且在一些实施方案中,能够稳定活性成分)并且对待治疗的受试者无害的载体。例如,增溶剂例如环糊精(其可以与本文公开的至少一种化合物和/或至少一种药学上可接受的盐形成特定的、更可溶的复合物)可以用作用于递送活性成分的药物赋形剂。其他载体的实例包括胶体二氧化硅、硬脂酸镁、纤维素、月桂基硫酸钠和颜料例如D&C黄#10。合适的药学上可接受的载体描述于Remington's Pharmaceutical Sciences,A.Osol中。

[0251] 对于通过吸入给药,本文所述的化合物、互变异构体、溶剂化物、立体异构体或药学上可接受的盐可以方便地以来自加压包或喷雾器的气溶胶喷雾呈现的形式递送。本文所述的化合物、互变异构体、溶剂化物、立体异构体或药学上可接受的盐还可以以粉末形式递送,其可以被配制,并且粉末组合物可以借助吹入粉末吸入器装置被吸入。用于吸入的一种示例性递送系统可以是定量吸入(MDI)气溶胶,其可以配制为本文所述的化合物、互变异构体、溶剂化物、立体异构体或药学上可接受的盐在至少一种合适的推进剂中的悬浮液或溶液,所述推进剂例如选自碳氟化合物和碳氢化合物。

[0252] 对于眼部施用,眼用制剂可以用适当重量百分比的本文所述的化合物、互变异构体、溶剂化物、立体异构体或药学上可接受的盐在适当的眼用赋形剂中的溶液或悬浮液配制,使得本文所述的化合物、互变异构体、溶剂化物、立体异构体或药学上可接受的盐与眼表面保持接触足够的时间段以允许化合物渗透眼睛的角膜和内部区域。

[0253] 用于施用本文所述的化合物、互变异构体、溶剂化物、立体异构体或药学上可接受的盐的有用的药物剂型包括但不限于硬明胶胶囊和软明胶胶囊、片剂、肠胃外注射剂和口服混悬剂。在一些实施方案中,本文公开的药物组合物可以是本领域已知的可控释放或持续释放组合物的形式。

[0254] 术语“单位剂型”是指适合作为人类受试者和其他哺乳动物的单位剂量的物理离散单位,每个单位含有经计算产生所需治疗效果的预定量的活性材料以及合适的药物赋形剂。典型的单位剂型包括液体组合物的预填充、预先计量的安瓿或注射器,或者在固体组合物的情况下的丸剂、片剂、胶囊、锭剂等。在此类组合物中,活性材料通常为约0.1至约50重量%或优选约1至约40重量%的组分,其余为有助于形成所需剂型的各种赋形剂或载体和加工助剂。单位剂量制剂优选为每单位约5、10、25、50、100、250、500或1,000mg。在一个具体的实施方案中,单位剂型被包装在适合顺序使用的合装(multipack)中,例如包含至少6、9或12个单位剂型的片材的泡罩包装。

[0255] 在一些实施方案中,单位胶囊可通过各自用例如100毫克本文所述的粉末状化合物、互变异构体、溶剂化物、立体异构体或药学上可接受的盐、150毫克乳糖、50毫克纤维素和6毫克硬脂酸镁填充标准两片式硬明胶胶囊来制备。

[0256] 在一些实施方案中,可以制备本文所述的化合物、互变异构体、溶剂化物、立体异构体或药学上可接受的盐和可消化油例如大豆油、棉籽油或橄榄油的混合物,并通过正排量泵注射到明胶中以形成含有100毫克活性成分的软明胶胶囊。将胶囊洗涤并干燥。

[0257] 在一些实施方案中,片剂可通过常规程序制备,使得剂量单位包含例如100毫克化合物、其立体异构体或其药学上可接受的盐、0.2毫克胶体二氧化硅、5毫克硬脂酸镁、275毫克微晶纤维素、11毫克淀粉和98.8毫克乳糖。可以应用适当的包衣来增加适口性或延迟吸收。

[0258] 在一些实施方案中,适合通过注射施用的肠胃外组合物可以通过将按重量计1.5%的本文公开的化合物和/或至少一种对映异构体、非对映异构体或其药学上可接受的盐在按体积计10%的丙二醇中搅拌来制备。将溶液用注射用水配制成预期体积并灭菌。

[0259] 在一些实施方案中,可以制备用于口服施用的水悬浮液。例如,可以使用这样的水悬浮液:每5毫升水悬浮液包含100毫克细碎化合物、其立体异构体或其药学上可接受的盐、100毫克羧甲基纤维素钠、5毫克苯甲酸钠、1.0克山梨糖醇溶液,U.S.P.和0.025毫升香草醛。

[0260] 当本文所述的化合物、互变异构体、溶剂化物、立体异构体或药学上可接受的盐逐步施用或与至少一种其他治疗剂联合施用时,通常可以使用相同的剂型。药物物理联合给药时,应根据联合药物的相容性选择剂型和给药途径。因此,术语共同施用应理解为包括同时或依次施用至少两种药剂,或者作为至少两种活性成分的固定剂量组合施用。

[0261] 本文公开的化合物、互变异构体、溶剂化物、立体异构体或药学上可接受的盐可以作为唯一活性成分施用或与至少一种第二活性成分组合施用。

[0262] 本文所述的化合物、互变异构体、溶剂化物或立体异构体可以其本身或以其药学上可接受的盐的形式使用,例如盐酸盐、氢溴酸盐、乙酸盐、硫酸盐、柠檬酸盐、碳酸盐、三氟乙酸盐等。当本文所述的化合物、互变异构体、溶剂化物、立体异构体或药学上可接受的盐含有相对酸性的官能团时,可以通过添加纯的或在合适的惰性溶剂中的所需碱来获得盐。

药学上可接受的碱加成盐的实例包括钠盐、钾盐、钙盐、铵盐、有机胺盐或镁盐等。当本文所述的化合物、互变异构体、溶剂化物或立体异构体含有相对碱性的官能团时，可以通过添加纯的或在合适的惰性溶剂中的所需的酸来获得盐。药学上可接受的酸加成盐的实例包括衍生自无机酸如盐酸、氢溴酸、硝酸、碳酸、一氢碳酸、磷酸、一氢磷酸、二氢磷酸、硫酸、一氢硫酸、氢碘酸或亚磷酸等的那些，以及衍生自相对无毒的有机酸，如乙酸、丙酸、异丁酸、马来酸、丙二酸、苯甲酸、琥珀酸、辛二酸、富马酸、乳酸、扁桃酸、邻苯二甲酸、苯磺酸、对甲苯磺酸、柠檬酸、酒石酸、甲磺酸等的盐。还包括氨基酸盐例如精氨酸盐等，以及有机酸例如葡萄糖醛酸或半乳糖醛酸等的盐(参见，例如，Berge等人，“Pharmaceutical Salts，”Journal of Pharmaceutical Science，1977，66，1-19)。

[0263] 本文所述的药学上可接受的盐的中性形式可以通过使盐与碱或酸接触并以常规方式分离母体化合物来再生。

[0264] 本公开提供了前药。本文所述的化合物、互变异构体、溶剂化物、立体异构体或药学上可接受的盐的前药在生理条件下容易发生化学变化，以提供本公开的化合物、互变异构体、溶剂化物、立体异构体或药学上可接受的盐。另外，前药可以在离体环境中通过化学或生物化学方法转化为本公开的化合物、互变异构体、溶剂化物、立体异构体或药学上可接受的盐。例如，当与合适的酶或化学试剂一起放置在透皮贴剂储库中时，前药可以缓慢转化为本公开的化合物、互变异构体、溶剂化物、立体异构体或药学上可接受的盐。前药通常很有用，因为在某些情况下，它们可能比母体药物更容易施用。例如，它们通过口服给药可能比母体药物具有更高的生物利用度。与母体药物相比，前药还可以在药理学组合物中具有改善的溶解度。多种前药衍生物是本领域已知的，例如依赖于前药的水解裂解或氧化活化的那些。前药的不受限实例为这样的本公开的化合物，其作为酯(“前药”)施用，但随后代谢水解成羧酸，即活性实体。

[0265] 本公开的某些化合物、互变异构体、立体异构体或药学上可接受的盐可以以非溶剂化形式以及溶剂化形式存在，包括水合物形式。本公开的某些化合物、互变异构体、溶剂化物、立体异构体或药学上可接受的盐可以多种结晶或非晶形式存在。

[0266] 本公开中的某些化合物、互变异构体、溶剂化物或药学上可接受的盐具有不对称碳原子(光学中心)或双键；外消旋体、对映异构体、非对映异构体、几何异构体和各种异构体都旨在涵盖在本公开的范围内。

[0267] III.治疗方法和用途

[0268] 本公开的另一方面提供了治疗疾病或病症的方法，包括向需要其的受试者施用治疗有效量的本文公开的式的化合物、其互变异构体，该化合物或该互变异构体的溶剂化物或立体异构体，或前述的药学上可接受的盐，或包含任何前述项目的药物组合物，其中所述疾病或病症选自神经病、中风、神经退行性疾病(例如阿尔茨海默病)、帕金森病、肌萎缩侧索硬化症(AML)、多发性硬化症、亨廷顿病、路易体痴呆、弗里德赖希共济失调、毛囊形态发生、糖尿病、败血症、移植排斥、脑室周围白质软化、缺血再灌注损伤、凝血、心肌梗塞和肾功能障碍例如急性肾衰竭。在一些实施方案中，疾病或病症涉及失调的铁死亡，例如异常的铁死亡。

[0269] 另一方面，本文公开的是本文所述的化合物、互变异构体、溶剂化物、立体异构体或药学上可接受的盐，包括本文公开的式的化合物、化合物1至573、其互变异构体，该化合

物或该互变异构体的溶剂化物或立体异构体,或前述的药学上可接受的盐、或其药物组合物,用作药物。

[0270] 另一方面,本文公开的是本文所述的化合物、互变异构体、溶剂化物、立体异构体或药学上可接受的盐,包括本文公开的式的化合物、化合物574至661、其互变异构体,该化合物或该互变异构体的溶剂化物或立体异构体,或前述的药学上可接受的盐、或其药物组合物,用作药物。

[0271] 另一方面,本文公开了本文所述的化合物、互变异构体、溶剂化物、立体异构体或药学上可接受的盐,包括本文公开的式的化合物、化合物1至573、其互变异构体,该化合物或该互变异构体的溶剂化物或立体异构体,或前述的药学上可接受的盐、或其药物组合物,用于制备用于治疗选自神经病、中风、神经退行性疾病(例如,阿尔茨海默病)、帕金森病、肌萎缩侧索硬化症(AML)、多发性硬化症、亨廷顿病、路易体痴呆、弗里德赖希共济失调、毛囊形态发生、糖尿病、败血症、移植排斥、脑室周围白质软化、缺血再灌注损伤、凝血、心肌梗塞和肾功能障碍例如急性肾衰竭的疾病或病症的药物的用途。在一些实施方案中,所述疾病或病症涉及失调的铁死亡,例如异常的铁死亡。

[0272] 另一方面,本文公开了本文所述的化合物、互变异构体、溶剂化物、立体异构体或药学上可接受的盐,包括本文公开的式的化合物、化合物574至661、其互变异构体,该化合物或该互变异构体的溶剂化物或立体异构体,或前述的药学上可接受的盐、或其药物组合物,用于制备用于治疗选自神经病、中风、神经退行性疾病(例如,阿尔茨海默病)、帕金森病、肌萎缩侧索硬化症(AML)、多发性硬化症、亨廷顿病、路易体痴呆、弗里德赖希共济失调、毛囊形态发生、糖尿病、败血症、移植排斥、脑室周围白质软化、缺血再灌注损伤、凝血、心肌梗塞和肾功能障碍例如急性肾衰竭的疾病或病症的药物的用途。在一些实施方案中,所述疾病或病症涉及失调的铁死亡,例如异常的铁死亡。

[0273] 在本公开的另一方面,本文所述的化合物、互变异构体、溶剂化物、立体异构体或药学上可接受的盐,包括本文公开的式的化合物、化合物1至573、其互变异构体,该化合物或该互变异构体的溶剂化物或立体异构体,或前述的药学上可接受的盐、或其药物组合物,用于治疗选自神经病、中风、神经退行性疾病(例如阿尔茨海默病)、帕金森病、肌萎缩侧索硬化症(AML)、多发性硬化症、亨廷顿病、路易体痴呆、弗里德赖希共济失调、毛囊形态发生、糖尿病、败血症、移植排斥、脑室周围白质软化、缺血再灌注损伤、凝血、心肌梗塞和肾功能障碍例如急性肾衰竭的疾病或病症。在一些实施方案中,所述疾病或病症涉及失调的铁死亡,例如异常的铁死亡。

[0274] 在本公开的另一方面,本文所述的化合物、互变异构体、溶剂化物、立体异构体或药学上可接受的盐,包括本文公开的式的化合物、化合物574至661、其互变异构体,该化合物或该互变异构体的溶剂化物或立体异构体,或前述的药学上可接受的盐、或其药物组合物,用于治疗选自神经病、中风、神经退行性疾病(例如阿尔茨海默病)、帕金森病、肌萎缩侧索硬化症(AML)、多发性硬化症、亨廷顿病、路易体痴呆、弗里德赖希共济失调、毛囊形态发生、糖尿病、败血症、移植排斥、脑室周围白质软化、缺血再灌注损伤、凝血、心肌梗塞和肾功能障碍例如急性肾衰竭的疾病或病症。在一些实施方案中,所述疾病或病症涉及失调的铁死亡,例如异常的铁死亡。

[0275] 本公开的另一方面提供了在需要其的受试者中调节(例如抑制)铁死亡的方法,包

括向受试者施用治疗有效量的本文公开的式的化合物、其互变异构体,该化合物或该互变异构体的溶剂化物或立体异构体,或前述物质的药学上可接受的盐,或包含前述项目中任一种的药物组合物。

[0276] 另一方面,本文公开了本文所述的化合物、互变异构体、溶剂化物、立体异构体或药学上可接受的盐,包括本文公开的式的化合物、化合物1至573、其互变异构体,该化合物或该互变异构体的溶剂化物或立体异构体,或前述的药学上可接受的盐、或其药物组合物用于在需要其的受试者中调节(例如抑制)铁死亡的用途。

[0277] 另一方面,本文公开了本文所述的化合物、互变异构体、溶剂化物、立体异构体或药学上可接受的盐,包括本文公开的式的化合物、化合物574至661、其互变异构体,该化合物或该互变异构体的溶剂化物或立体异构体,或前述的药学上可接受的盐、或其药物组合物用于在需要其的受试者中调节(例如抑制)铁死亡的用途。

[0278] 在本公开的另一方面,本文所述的化合物、互变异构体、所述化合物或所述互变异构体的溶剂化物或立体异构体、或药学上可接受的盐,包括本文公开的式的化合物、化合物1至573、其互变异构体,该化合物或该互变异构体的溶剂化物或立体异构体,或前述的药学上可接受的盐、或其药物组合物,用于在需要其的受试者中通过使所述受试者接触所述化合物、互变异构体、所述化合物或所述互变异构体的溶剂化物或立体异构体、药学上可接受的盐、或药物组合物来调节(例如抑制)铁死亡。

[0279] 在本公开的另一方面,本文所述的化合物、互变异构体、所述化合物或所述互变异构体的溶剂化物或立体异构体、或药学上可接受的盐,包括本文公开的式的化合物、化合物574至661、其互变异构体,该化合物或该互变异构体的溶剂化物或立体异构体,或前述的药学上可接受的盐、或其药物组合物,用于在需要其的受试者中通过使所述受试者接触所述化合物、互变异构体、所述化合物或所述互变异构体的溶剂化物或立体异构体、药学上可接受的盐、或药物组合物来调节(例如抑制)铁死亡。

[0280] 本文公开的式的化合物、化合物1至573、其互变异构体,该化合物或该互变异构体的溶剂化物或立体异构体,或前述的药学上可接受的盐、或其药物组合物可以每日一次、每日两次或每天三次施用,例如用于治疗选自神经病、中风、神经退行性疾病(例如阿尔茨海默病)、帕金森病、肌萎缩侧索硬化症(AML)、多发性硬化症、亨廷顿病、路易体痴呆、弗里德赖希共济失调、毛囊形态发生、糖尿病、败血症、移植排斥、脑室周围白质软化、缺血再灌注损伤、凝血、心肌梗塞和肾功能障碍例如急性肾衰竭的疾病或病症。在一些实施方案中,所述疾病或病症涉及失调的铁死亡,例如异常的铁死亡。

[0281] 本文公开的式的化合物、化合物574至661、其互变异构体,该化合物或该互变异构体的溶剂化物或立体异构体,或前述的药学上可接受的盐、或其药物组合物可以每日一次、每日两次或每天三次施用,例如用于治疗选自神经病、中风、神经退行性疾病(例如阿尔茨海默病)、帕金森病、肌萎缩侧索硬化症(AML)、多发性硬化症、亨廷顿病、路易体痴呆、弗里德赖希共济失调、毛囊形态发生、糖尿病、败血症、移植排斥、脑室周围白质软化、缺血再灌注损伤、凝血、心肌梗塞和肾功能障碍例如急性肾衰竭的疾病或病症。在一些实施方案中,所述疾病或病症涉及失调的铁死亡,例如异常的铁死亡。

[0282] 本文公开的式的化合物、化合物1至573、其互变异构体,该化合物或该互变异构体的溶剂化物或立体异构体,或前述的药学上可接受的盐、或其药物组合物可以例如以各种

形式施用,例如口服、局部、直肠、肠胃外、通过吸入喷雾或通过植入型药盒(implanted reservoir),尽管在任何给定情况下最合适的途径将取决于特定宿主以及施用活性成分所为的病症的性质和严重程度。本文使用的术语“肠胃外”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。本文公开的组合物可以方便地以单位剂型存在并通过本领域熟知的任何方法制备。肠胃外给药可以通过在选定的时间段内连续输注来进行。本公开中设想的其他施用形式如国际专利申请号WO2013/075083、WO 2013/075084、WO 2013/078320、WO 2013/120104、WO 2014/124418、WO 2014/151142和WO 2015/023915中所述。

[0283] 本文公开的式的化合物、化合物574至661、其互变异构体,该化合物或该互变异构体的溶剂化物或立体异构体,或前述的药学上可接受的盐、或其药物组合物可以例如以各种形式施用,例如口服、局部、直肠、肠胃外、通过吸入喷雾或通过植入型药盒(implanted reservoir),尽管在任何给定情况下最合适的途径将取决于特定宿主以及施用活性成分所为的病症的性质和严重程度。本文使用的术语“肠胃外”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。本文公开的组合物可以方便地以单位剂型存在并通过本领域熟知的任何方法制备。肠胃外给药可以通过在选定的时间段内连续输注来进行。本公开中设想的其他施用形式如国际专利申请号WO 2013/075083、WO 2013/075084、WO 2013/078320、WO 2013/120104、WO 2014/124418、WO 2014/151142和WO 2015/023915中所述。

[0284] 该接触通常通过向受试者施用有效量的一种或多种本文公开的化合物、互变异构体、溶剂化物、立体异构体和药学上可接受的盐来实现。一般而言,调整施用以实现约0.1至50、优选0.5至10、更优选1至10mg/kg的治疗剂量,但最佳剂量是化合物特异性的,并且通常针对每种化合物凭经验确定。

[0285] 施用的剂量将取决于多种因素,例如接受者的年龄、健康状况和体重、疾病的程度、同时治疗的类型(如果有的话)、治疗的频率以及所需效果的性质。一般而言,活性成分的每日剂量可以变化,例如每天0.1至2000毫克。例如,每天一次或多次10-500毫克可能有效获得所需的结果。

[0286] 在一些实施方案中,2mg至1500mg或5mg至1000mg的本文公开的式的化合物、化合物1至573、其互变异构体,该化合物或该互变异构体的溶剂化物或立体异构体,或前述的药学上可接受的盐或其药物组合物每日一次、每日两次或每日三次施用。本文所述的化合物、互变异构体、溶剂化物、立体异构体或药学上可接受的盐以早晨/白天给药方式施用,夜间为停药期。

[0287] 在一些实施方案中,2mg至1500mg或5mg至1000mg的本文公开的式的化合物、化合物574至661、其互变异构体,该化合物或该互变异构体的溶剂化物或立体异构体,或前述的药学上可接受的盐或其药物组合物每日一次、每日两次或每日三次施用。本文所述的化合物、互变异构体、溶剂化物、立体异构体或药学上可接受的盐以早晨/白天给药方式施用,夜间为停药期。

[0288] 实施例

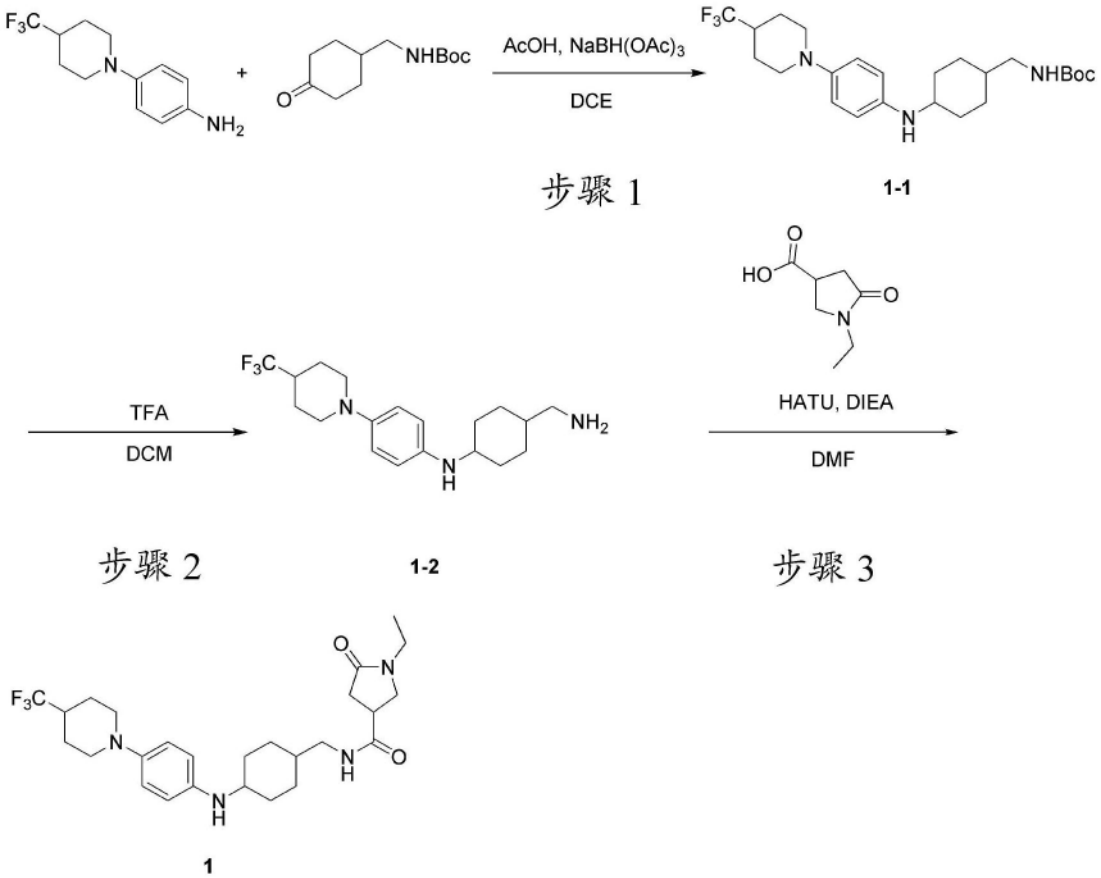
[0289] 为了可以更全面地理解本文描述的公开内容,本文公开了以下实施例。应当理解,这些实施例仅用于说明性目的并且不应被解释为以任何方式限制本公开内容。

[0290] 实施例1:示例性化合物的合成

[0291] 本公开内容的化合物,其选自本文所述的化学式的化合物、其互变异构体、该化合物或该互变异构体的溶剂化物或立体异构体、或前述的药学上可接受的盐,可以根据标准化学实践或如本文中所举例说明的,包括作为式I的代表性实例的化合物1至661的以下合成方案,进行制备。

[0292] 化合物1

[0293] 1-乙基-5-氧代-N-((4-((4-(4-(三氟甲基)哌啶-1-基)苯基)氨基)环己基)甲基)吡咯烷-3-甲酰胺

[0294] 

[0295] 步骤1:制备((4-((4-(4-(三氟甲基)哌啶-1-基)苯基)氨基)环己基)甲基)氨基甲酸叔丁酯(1-1)

[0296] 在室温搅拌4-(4-(三氟甲基)哌啶-1-基)苯胺(100mg,0.41mmol),((4-氧代环己基)甲基)氨基甲酸叔丁酯(140mg,0.62mmol)和AcOH(0.1mL)/DCE(10mL)的溶液30分钟。添加$NaBH(OAc)_3$(174mg,0.82mmol),在室温搅拌混合物2小时。用DCM(25mL×3)萃取混合物。将合并的有机层用盐水洗涤(15mL×3),用Na_2SO_4干燥,以及浓缩而得到粗产物,将其通过TLC提纯(MeOH/DCM=1/20)而得到期望的产物(130mg,69.9%)(紫色固体)。质谱(m/z):456.3$[M+H]^+$。

[0297] 步骤2:制备N-(4-(氨基甲基)环己基)-4-(4-(三氟甲基)哌啶-1-基)苯胺(1-2)

[0298] 向1-1(130mg,0.29mmol)/DCM(10mL)的溶液中添加TFA(1mL)。在室温搅拌溶液1小时。将混合物用1MNaOH碱化至pH=9,浓缩,然后用DCM(25mL×3)萃取。将合并的有机层用盐水洗涤(15mL×3),用Na_2SO_4干燥,以及浓缩,将其通过TLC提纯(MeOH/DCM=1/5)而得到期望

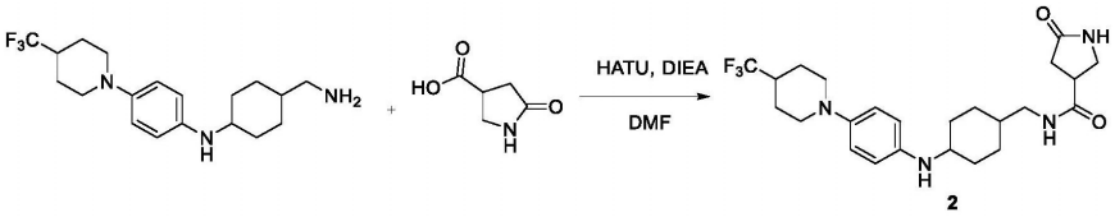
的产物(79.2mg,78.2%)(紫色固体)。质谱(m/z):356.3[M+H]$^+$。

[0299] 步骤3:制备1-乙基-5-氧代-N-((4-((4-(4-(三氟甲基)哌啶-1-基)苯基)氨基)环己基)甲基)吡咯烷-3-甲酰胺(1)

[0300] 在室温搅拌1-2(50mg,0.141mmol),1-乙基-5-氧代吡咯烷-3-甲酸(28mg,0.183mmol),HATU(33mg,0.183mmol)和DIEA(23mg,0183mmol)/DMF(5mL)的溶液2小时。用EA(25mL×3)萃取混合物。将合并的有机层用盐水洗涤(15mL×3),用Na_2SO_4干燥,以及浓缩而得到粗产物,将其通过TLC提纯(MeOH/DCM=1/10)而得到期望的产物(23.7mg,34.0%)(紫色固体)。^{1}H NMR(400MHz,DMSO-d_6)δ8.05(t,J=5.6Hz,1H),6.74(d,J=8.4Hz,2H),6.47(d,J=8.4Hz,2H),4.87(s,1H),3.50(t,J=9.2Hz,1H),3.41(d,J=14.4Hz,2H),3.33-3.30(m,1H),3.22-3.15(m,2H),3.13-3.06(m,1H),3.04(d,J=12.0Hz,1H),2.94(t,J=6.4Hz,2H),2.55(s,1H),2.38(dd,J=8.8,3.0Hz,3H),1.96(d,J=10.4Hz,2H),1.85(d,J=12.4Hz,2H),1.71(d,J=10.8Hz,2H),1.57(tt,J=12.8,6.4Hz,2H),1.37(s,1H),1.06-0.93(m,7H)。质谱(m/z):495.3[M+H]$^+$。

[0301] 化合物2

[0302] 5-氧代-N-((4-((4-(4-(三氟甲基)哌啶-1-基)苯基)氨基)环己基)甲基)吡咯烷-3-甲酰胺

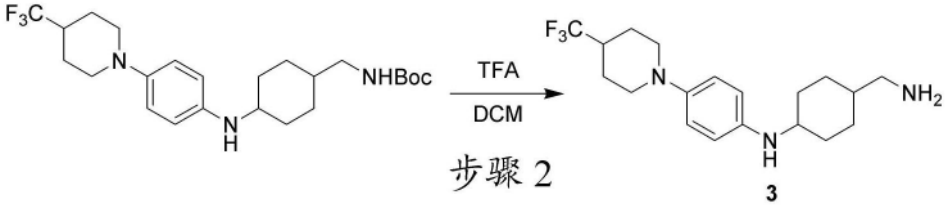
[0303] 

2

[0304] 根据为1的程序,由4-(4-(三氟甲基)哌啶-1-基)苯胺(50mg,0.141mmol),5-氧代吡咯烷-3-甲酸(24mg,0.183mmol),HATU(33mg,0.183mmol)和DIEA(23mg,0183mmol)/DMF(5mL)制备标题化合物2(23.7mg),总收率为34.0%(紫色固体)。^{1}H NMR(400MHz,DMSO-d_6)δ7.95(s,1H),7.50(s,1H),6.86-6.38(m,4H),3.34(s,2H),3.16-2.94(m,4H),2.85(t,J=6.4Hz,2H),2.33(s,1H),2.20(dd,J=8.4,1.6Hz,2H),1.88(d,J=11.4Hz,2H),1.79(d,J=12.4Hz,2H),1.64(d,J=12.0Hz,2H),1.49(s,2H),1.30(d,J=7.6Hz,1H),1.24-1.13(m,2H),1.02(s,1H),0.91(t,J=12.0Hz,2H)。质谱(m/z):466.55[M+H]$^+$。

[0305] 化合物3

[0306] N-(4-(氨基甲基)环己基)-4-(4-(三氟甲基)哌啶-1-基)苯胺

[0307] 

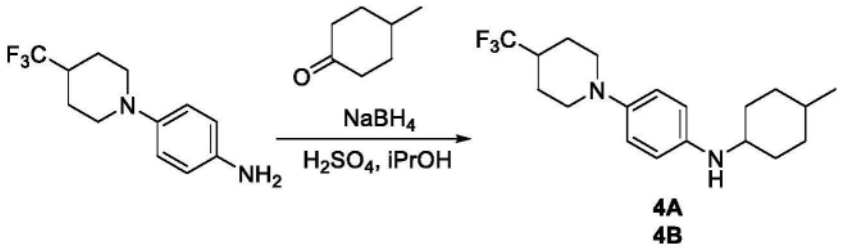
步骤2
3

[0308] 向((4-((4-(4-(三氟甲基)哌啶-1-基)苯基)氨基)环己基)甲基)氨基甲酸叔丁酯(1-1;130mg,0.29mmol)/DCM(10mL)的溶液中添加TFA(1mL)。在室温搅拌溶液1小时。将混合物用1M NaOH碱化至pH=9并浓缩,然后用DCM(25mL×3)萃取。将合并的有机层用盐水洗涤(15mL×3),用Na_2SO_4干燥,以及浓缩,将其通过TLC提纯(MeOH/DCM=1/5)而得到期望的产物

(紫色固体)(79.2mg,78.2%),由^{1}H NMR证明为1:2的混合物。^{1}H NMR(400MHz,DMSO-d_6)δ 7.91(s,2H),6.75(dd,J=9.2,2.4Hz,2H),6.57-6.51(m,1.4H),6.50-6.45(m,0.7H),4.95(d,J=29.2Hz,1H),3.44(t,J=3.2Hz,4H),2.68(d,J=6.8Hz,1.4H),2.63(d,J=6.8Hz,0.7H),2.55(d,J=2.4Hz,2H),2.42-2.30(m,1H),1.98(d,J=8.8Hz,1H),1.89-1.81(m,2H),1.71-1.36(m,9H)。质谱(m/z):356.3[M+H]$^+$。

[0309] 化合物4

[0310] N-(4-甲基环己基)-4-(4-(三氟甲基)哌啶-1-基)苯胺

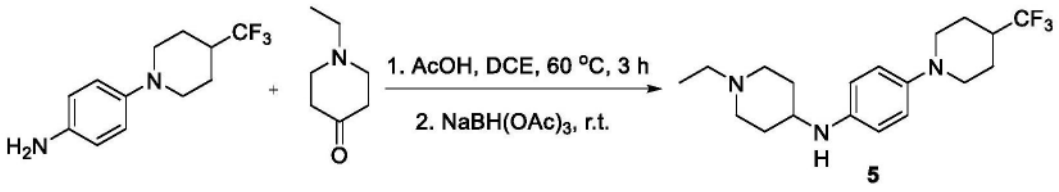
[0311] 

4A
4B

[0312] 在0℃向4-(4-(三氟甲基)哌啶-1-基)苯胺(100mg,0.4mmol)和4-甲基环己烷-1-酮(55mg,0.49mmol)/异丙醇(5mL)的溶液中滴加3滴的硫酸。在室温搅拌混合物30分钟,然后在0℃缓慢添加$NaBH_4$(31mg,0.8mmol)。搅拌所得的混合物过夜。将反应用饱和$NaHCO_3$水溶液淬灭并用二氯甲烷(5mL)萃取3次。合并有机层并分别用水、饱和$NaHCO_3$和盐水洗涤,用$MgSO_4$干燥,过滤,并在减压下浓缩。残余物的提纯方法为:硅胶柱色谱(石油醚/AcOEt,4/1)并然后用Prep-HPLC提纯(柱:X Select-CSH-Prep 5μm OBD,19*150mm;ACN/水(0.5%TFA)=5%-5%-95%-95%-5%,0min-1min-10min-11min-15.0min)而得到33.4mg的4A(Rt=6.05min)(白色粉末),收率为23.9%和20.4mg的4B(Rt=6.16min)(白色粉末),收率为14.6%。4A:^{1}H NMR(400MHz,DMSO-d_6)δ6.73(d,J=8.9Hz,2H),6.52(d,J=8.9Hz,2H),4.94(s,1H),3.41(d,J=12.0Hz,2H),2.54(d,J=2.6Hz,2H),2.35(m,1H),1.89-1.79(m,2H),1.54(m,7H),1.42(m,2H),1.38-1.26(m,2H),1.23(s,1H),0.89(d,J=6.6Hz,3H)。质谱(m/z):341.3[M+H]$^+$。4B:^{1}H NMR(400MHz,DMSO-d_6)δ6.73(d,J=8.4Hz,2H),6.47(d,J=8.4Hz,2H),4.85(s,1H),3.41(d,J=11.9Hz,2H),3.00(s,1H),2.43-2.22(m,1H),1.89(dd,J=31.5,12.0Hz,4H),1.67(d,J=12.0Hz,2H),1.56(qd,J=12.4,3.9Hz,2H),1.40-1.25(m,1H),1.14-0.93(m,4H),0.87(d,J=6.5Hz,3H)。质谱(m/z):341.3[M+H]$^+$。

[0313] 化合物5

[0314] 1-乙基-N-(4-(4-(三氟甲基)哌啶-1-基)苯基)哌啶-4-胺

[0315] 

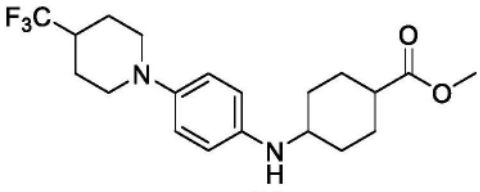
5

[0316] 向4-(4-(三氟甲基)哌啶-1-基)苯胺(150mg,0.61mmol)/DCE(5mL)的溶液中添加1-乙基哌啶-4-酮(94mg,0.73mmol)和乙酸(3.7mg,0.061mmol)。在60℃搅拌所得的混合物3小时,并然后冷却至室温。添加三乙酰氧基硼氢化钠(388mg,1.83mmol)并在室温搅拌反应3小时。将反应用水(10mL)淬灭,并用EA(10mL)萃取3次。将合并的有机相用硫酸钠干燥,并在真空下除去。残余物的提纯方法为:prep-HPLC(柱-Xbridge-C18 150x 21.2mm,5um;移动

相:ACN-H_2O(0.1%FA),40%-60%)而得到期望的产物(35mg,16.2%)(白色固体)。^{1}H NMR(300MHz,$CDCl_3$)δ6.84(d,J=9.0Hz,2H),6.59(d,J=9.0Hz,2H),3.52(d,J=12.1Hz,2H),3.35(s,2H),2.93(d,J=9.0Hz,2H),2.70(d,J=10.8Hz,2H),2.59(t,J=11.8Hz,2H),2.26(s,2H),2.06-1.89(m,5H),1.86-1.68(m,3H),1.40(t,J=9.0Hz,3H)。质谱(m/z):356.2[M+H]$^+$。

[0317] 化合物6

[0318] 4-((4-(4-(三氟甲基)哌啶-1-基)苯基)氨基)环己烷-1-甲酸甲酯

[0319] 

6A

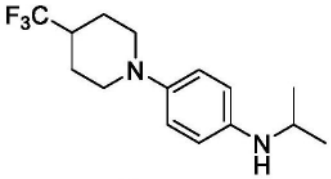
6B

[0320] 根据为4的程序,由4-(4-(三氟甲基)哌啶-1-基)苯胺(200mg,0.82mmol),4-氧代环己烷-1-甲酸甲酯(192mg,1.23mmol)和$NaBH(OAc)_3$(347mg,1.64mmol)制备标题化合物6A(Rt=5.37min;89.3mg,28.4%)(玫瑰棕色固体)和6B(Rt=5.31min;93.6mg,29.7%)(玫瑰棕色固体),其提纯方法为:Prep-HPLC(柱:X Select-CSH-Prep 5μm OBD,19*150mm;ACN/水(0.5%TFA)=5%-5%-95%-95%-5%,0min-1min-10min-11min-15.0min)。

[0321] 6A:^{1}H NMR(400MHz,DMSO-d_6)δ6.74(d,J=8.9Hz,2H),6.51(d,J=8.9Hz,2H),5.01(d,J=7.8Hz,1H),3.60(s,3H),3.41(d,J=12.1Hz,2H),3.29(d,J=8.1Hz,1H),2.56-2.51(m,2H),2.42-2.28(m,1H),1.93-1.81(m,4H),1.53-1.72(m,6H),1.52-1.39(m,3H)。质谱(m/z):385.4[M+H]$^+$。6B:^{1}H NMR(400MHz,DMSO-d_6)δ6.74(d,J=8.5Hz,2H),6.49(d,J=8.8Hz,2H),4.90(s,1H),3.59(s,3H),3.42(dd,J=14.7,5.8Hz,2H),3.07(s,1H),2.55(s,2H),2.46-2.35(m,3H),2.31-2.19(m,4H),2.19-2.06(m,3H),1.56(qd,J=12.3,3.9Hz,2H),1.45(qd,J=13.1,3.1Hz,2H)。质谱(m/z):385.4[M+H]$^+$。

[0322] 化合物7

[0323] N-异丙基-4-(4-(三氟甲基)哌啶-1-基)苯胺

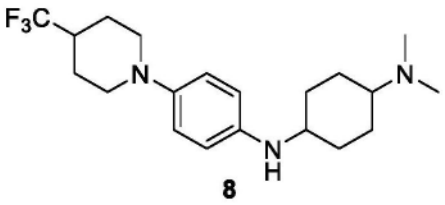
[0324] 

7

[0325] 根据为5的程序,由4-(4-(三氟甲基)哌啶-1-基)苯胺(81mg,0.3mmol),丙酮(0.2mL),1滴浓H_2SO_4,$NaBH(AcO)_3$(76mg,0.36mmol)和THF(10mL)制备标题化合物7(12.0mg),总收率为12.6%(黄色固体)。^{1}H NMR(400MHz,DMSO-d_6)δ6.78(d,J=8.2Hz,2H),6.54(d,J=7.6Hz,2H),3.52-3.41(m,3H),2.62-2.52(m,2H),2.43-2.35(m,1H),1.86(d,J=12.5Hz,2H),1.61-1.50(m,2H),1.09(d,J=6.2Hz,6H)。质谱(m/z):287.2[M+H]$^+$。

[0326] 化合物8

[0327] N^1,N^1-二甲基-N^4-(4-(4-(三氟甲基)哌啶-1-基)苯基)环己烷-1,4-二胺

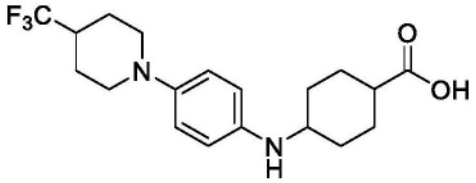
[0328] 

8

[0329] 根据为5的程序,由4-(4-(三氟甲基)哌啶-1-基)苯胺(180mg,0.74mmol),4-(二甲基氨基)环己烷-1-酮(125mg,0.89mmol),乙酸(3.7mg,0.061mmol),三乙酰氧基硼氢化钠(469mg,2.22mmol)和DCE(5mL)制备标题化合物8(53mg),总收率为19.4%(棕色油)。^{1}H NMR(300MHz,$CDCl_3$)δ=6.84(d,J=8.7Hz,2H),6.64-6.50(m,2H),3.51(d,J=10.8Hz,2H),3.13(t,J=11.0Hz,1H),2.58(t,J=12.0Hz,2H),2.30(d,J=4.2Hz,6H),2.24-2.14(m,2H),1.95(m,4H),1.89-1.73(m,4H),1.62(m,3H),1.45-1.28(m,1H)。质谱(m/z):185.7[M+2H]$^{2+}$/2。

[0330] 化合物9

[0331] 4-((4-(4-(三氟甲基)哌啶-1-基)苯基)氨基)环己烷-1-甲酸

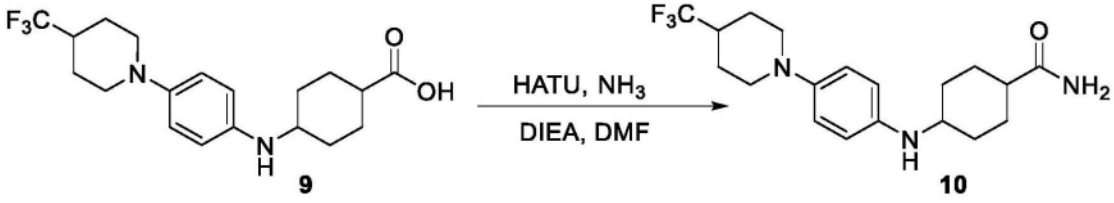
[0332] 

9

[0333] 根据为4的程序,由4-(4-(三氟甲基)哌啶-1-基)苯胺(200mg,0.82mmol),4-氧代环己烷-1-甲酸(140mg,0.98mmol)和$NaBH(OAc)_3$(347mg,1.64mmol)制备标题化合物9(127mg),收率为41.8%(玫瑰棕色固体),经^{1}H NMR证明为1:1的混合物。^{1}H NMR(400MHz,DMSO-d_6)δ6.74(d,J=8.1Hz,2H),6.50(s,2H),3.41(d,J=11.7Hz,2H),3.25(s,1H),3.05(s,1H),2.42-2.27(m,2H),2.15(tt,J=11.9,3.5Hz,1H),1.91(dt,J=35.0,14.3Hz,5H),1.69-1.49(m,4H),1.41(qd,J=13.2,3.2Hz,2H),1.09(q,J=12.0Hz,1H)。质谱(m/z):371.5[M+H]$^+$。

[0334] 化合物10

[0335] 4-((4-(4-(三氟甲基)哌啶-1-基)苯基)氨基)环己烷-1-甲酰胺

[0336] 

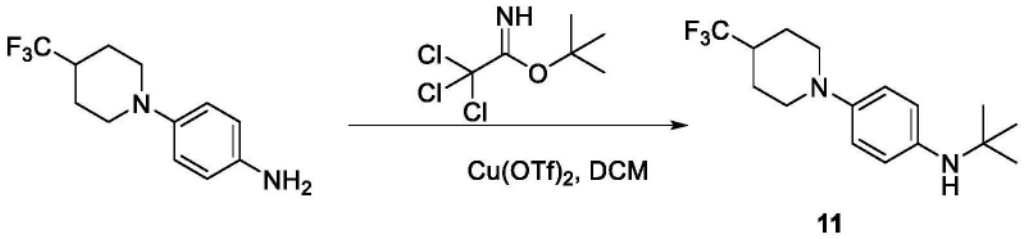
9 10

[0337] 向4-((4-(4-(三氟甲基)哌啶-1-基)苯基)氨基)环己烷-1-甲酸(70mg,0.19mmol)和HATU(86mg,0.23mmol)/超干N,N-二甲基甲酰胺(5mL)的溶液中添加N-乙基-N-异丙基丙-2-胺(94mL,0.57mmol)。搅拌混合物30分钟并在0℃缓慢滴加氢氧化铵(0.5mL)。在室温搅拌所得溶液过夜。在搅拌下将混合物一滴滴加入水(15mL)。将沉淀物过滤,并且将滤饼用水洗涤三次并在真空中干燥。残余物的提纯方法为:prep-TLC而得到期望的产物10(28.3mg)(淡桃色粉末),经^{1}H NMR证实为1:1混合物,收率为40.5%。^{1}H NMR(400MHz,DMSO-d_6)δ7.19(s,1H),6.74(d,J=8.3Hz,2H),6.67(s,1H),6.49(d,J=8.2Hz,2H),4.89(s,1H),3.42(d,J=

11.8Hz,2H),3.04(s,1H),2.54(d,J＝11.2Hz,2H),2.41-2.28(m,1H),2.10-1.92(m,3H),1.85(d,J＝12.7Hz,2H),1.76(d,J＝13.1Hz,2H),1.56(td,J＝13.9,10.1Hz,2H),1.50-1.36(m,2H),1.06(q,J＝12.3Hz,2H)。质谱(m/z):370.3[M+H]$^+$。

[0338] 化合物11

[0339] N-(叔丁基)-4-(4-(三氟甲基)哌啶-1-基)苯胺

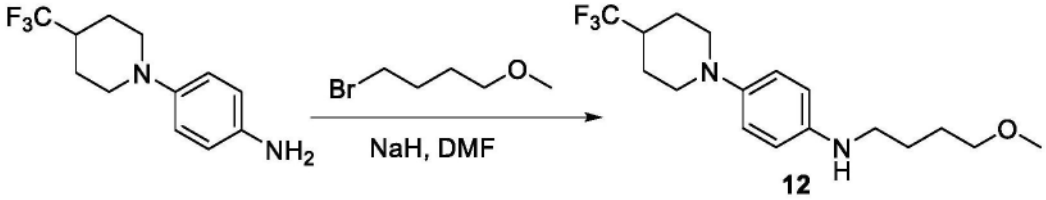
[0340] 

11

[0341] 向4-(4-(三氟甲基)哌啶-1-基)苯胺(122mg,0.5mmol)/无水DCM(20mL)的溶液中添加Cu(OTf)$_2$(9.0mg,25umol)和2,2,2-三氯乙酰亚胺酸叔丁酯(272.5mg,1.25mmol)。然后在氩气下在室温搅拌反应2小时。将反应用水(20mL×3)洗涤,用Na_2SO_4干燥,以及浓缩。残余物的提纯方法为:prep-TLC(EA/PE＝1/2)而得到期望的产物11(8.6mg,5.7%)(黄色固体)。^{1}H NMR(400MHz,DMSO-d_6)δ10.23(s,2H),7.25-7.17(m,2H),7.11-7.03(m,2H),3.88(d,J＝12.6Hz,2H),2.79(t,J＝11.6Hz,2H),2.59-2.53(m,1H),1.89(d,J＝12.0Hz,2H),1.57-1.44(m,2H),1.27(s,9H)。质谱(m/z):301.2[M+H]$^+$。

[0342] 化合物12

[0343] N-(4-甲氧基丁基)-4-(4-(三氟甲基)哌啶-1-基)苯胺

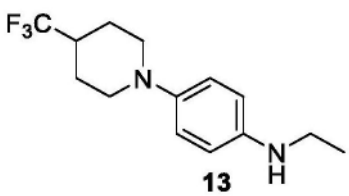
[0344] 

12

[0345] 在0℃向4-(4-(三氟甲基)哌啶-1-基)苯胺(100mg,0.4mmol)/超干N,N-二甲基甲酰胺(5mL)的溶液中添加NaH(19.7mg,0.5mmol)。搅拌混合物30分钟并添加1-溴-4-甲氧基丁烷(68mg,0.4mmol)。在100℃搅拌所得的溶液过夜。在0℃将反应用水(20mL)稀释并用乙酸乙酯(5mL)萃取三次。合并有机层并分别用水、饱和NH_4Cl(水溶液)、盐水洗涤,用$MgSO_4$干燥,过滤,并在减压下浓缩。残余物的提纯方法为:prep-HPLC而得到28mg的期望的产物12(淡玫瑰棕色油),收率为20.7%。^{1}H NMR(400MHz,DMSO-d_6)δ6.75(d,J＝8.8Hz,2H),6.47(d,J＝8.8Hz,2H),5.09(s,1H),3.41(d,J＝12.0Hz,2H),3.31(d,J＝6.0Hz,2H),3.21(s,3H),2.92(s,2H),2.53(dd,J＝11.0,2.0Hz,2H),2.43-2.28(m,1H),1.91-1.77(m,2H),1.46-1.65(m,6H)。质谱(m/z):331.3[M+H]$^+$。

[0346] 化合物13

[0347] N-乙基-4-(4-(三氟甲基)哌啶-1-基)苯胺

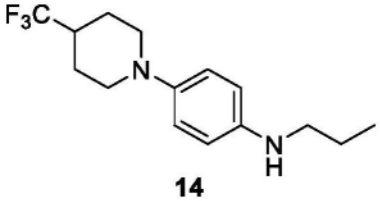
[0348] 

13

[0349] 由4-(4-(三氟甲基)哌啶-1-基)苯胺(100mg,0.4mmol),碘乙烷(32mg,0.4mmol)和碳酸钾(57mg,0.4mmol),根据为12的程序制备标题化合物13(32mg),收率为28.7%(土色粉末)。^{1}H NMR(400MHz,DMSO-d_6)δ6.75(d,J=8.4Hz,2H),6.47(d,J=8.3Hz,2H),5.05(s,1H),3.41(d,J=11.9Hz,2H),2.94(q,J=7.1Hz,2H),2.54(s,2H),2.40-2.26(m,1H),1.84(d,J=12.4Hz,2H),1.55(qd,J=12.3,4.1Hz,2H),1.12(t,J=7.1Hz,3H)。质谱(m/z):273.5[M+H]$^+$。

[0350] 化合物14

[0351] N-丙基-4-(4-(三氟甲基)哌啶-1-基)苯胺

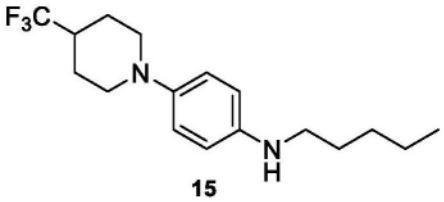
[0352] 

14

[0353] 由4-(4-(三氟甲基)哌啶-1-基)苯胺(50mg,0.2mmol),1-碘丙烷(35mg,0.2mmol)和碳酸钾(42mg,0.3mmol),根据为12的程序,制备标题化合物14(34.4mg),收率为58.7%(灰白色粉末)。^{1}H NMR(400MHz,DMSO-d_6)δ6.75(d,J=8.8Hz,2H),6.48(d,J=8.8Hz,2H),5.12(s,1H),3.42(d,J=12.1Hz,2H),2.89(t,J=7.1Hz,2H),2.55(s,2H),2.29-2.42(m,1H),1.85(d,J=12.1Hz,2H),1.64-1.45(m,4H),0.92(t,J=7.4Hz,3H)。质谱(m/z):287.3[M+H]$^+$。

[0354] 化合物15

[0355] N-戊基-4-(4-(三氟甲基)哌啶-1-基)苯胺

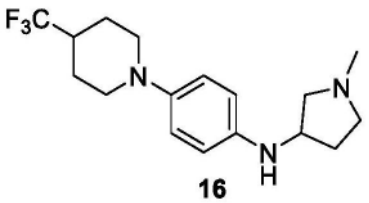
[0356] 

15

[0357] 由4-(4-(三氟甲基)哌啶-1-基)苯胺(50mg,0.2mmol),1-碘戊烷(40mg,0.2mmol)和碳酸钾(42mg,0.3mmol),根据为12的程序制备标题化合物15(34.4mg),收率为51.4%(灰白色粉末)。^{1}H NMR(400MHz,DMSO-d_6)δ6.75(d,J=8.8Hz,2H),6.47(d,J=8.8Hz,2H),5.08(s,1H),3.49-3.38(m,2H),2.91(t,J=7.1Hz,2H),2.56-2.52(m,2H),2.36(dt,J=8.8,4.4Hz,1H),1.85(d,J=12.2Hz,2H),1.64-1.43(m,4H),1.32(tq,J=6.0,2.8Hz,4H),0.94-0.82(m,3H)。质谱(m/z):315.3[M+H]$^+$。

[0358] 化合物16

[0359] 1-甲基-N-(4-(4-(三氟甲基)哌啶-1-基)苯基)吡咯烷-3-胺

[0360] 

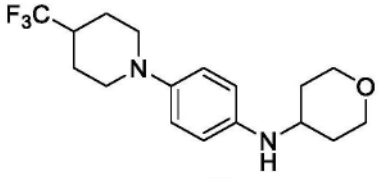
16

[0361] 由4-(4-(三氟甲基)哌啶-1-基)苯胺(100mg,0.4mmol),1-甲基吡咯烷-3-酮

(48mg,0.49mmol)和$NaBH(OAc)_3$(173mg,0.82mmol),根据为4的程序制备标题化合物16(31.1mg),收率为23.2%(灰白色粉末),经^1H NMR证明为1:1的混合物。^1H NMR(400MHz,DMSO-d_6)δ6.80(d,J=8.9Hz,2H),6.51(d,J=8.9Hz,2H),5.50(s,1H),4.04(s,1H),3.46(d,J=12.2Hz,3H),3.07(d,J=46.4Hz,2H),2.74(s,3H),2.53(d,J=2.4Hz,2H),2.45-2.25(m,2H),1.84(d,J=3.7Hz,3H),1.46-1.61(m,2H),1.23(d,J=3.3Hz,2H)。质谱(m/z):328.2$[M+H]^+$。

[0362] 化合物17

[0363] N-(4-(4-(三氟甲基)哌啶-1-基)苯基)四氢-2H-吡喃-4-胺

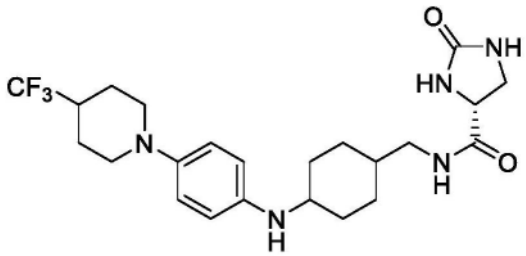
[0364] 

17

[0365] 由4-(4-(三氟甲基)环己基)苯胺(50mg,0.205mmol),四氢-4H-吡喃-4-酮(25mg,0.246mmol),AcOH(0.1mL),$NaBH(OAc)_3$(87mg,0.41mmol)和DCE(10mL),根据为1-1的程序制备标题化合物17(23.9mg),总收率为35.8%(紫色固体),经^1H NMR证明为1:2的混合物。^1H NMR(400MHz,DMSO-d_6)δ7.29-6.83(m,4H),3.94-3.83(m,2H),3.79-3.66(m,2H),3.53(s,1H),3.30(s,2H),3.06(s,1H),2.62(s,1H),1.96(s,2H),1.80(d,J=12.4Hz,2H),1.74-1.38(d,m,4H)。质谱(m/z):329.3$[M+H]^+$。

[0366] 化合物18

[0367] (R)-2-氧代-N-((4-((4-(4-(三氟甲基)哌啶-1-基)苯基)氨基)环己基)甲基)咪唑烷-4-甲酰胺

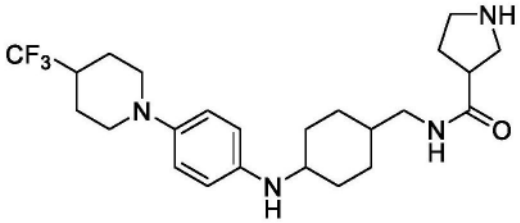
[0368] 

18

[0369] 由N-(4-(氨基甲基)环己基)-4-(4-(三氟甲基)哌啶-1-基)苯胺(17mg,0.05mmol),根据为化合物1的程序制备标题化合物18(6.1mg),总收率为27%(玫瑰棕色固体)。^1H NMR(400MHz,DMSO-d_6)δ9.14(s,1H),7.90(s,1H),6.79(d,J=8.4Hz,2H),6.53(d,J=8.4Hz,2H),6.30(s,1H),5.32(s,1H),3.68-3.46(m,3H),3.25-2.99(m,3H),2.95-2.87(m,2H),2.64-2.55(m,2H),2.21(m,1H),2.05-1.87(m,4H),1.75-1.50(m,4H),1.45-1.31(m,3H),1.15-0.95(m,2H)。质谱(m/z):468.3$[M+H]^+$。

[0370] 化合物19

[0371] N-((4-((4-(4-(三氟甲基)哌啶-1-基)苯基)氨基)环己基)甲基)吡咯烷-3-甲酰胺

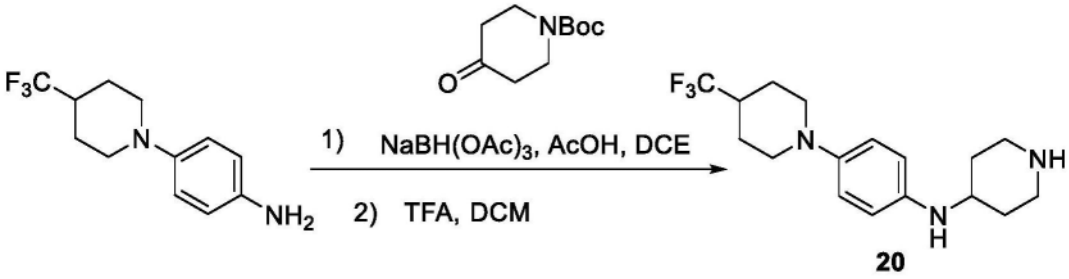
[0372] 

19

[0373] 由N-(4-(氨基甲基)环己基)-4-(4-(三氟甲基)哌啶-1-基)苯胺(17mg,0.05mmol),根据为化合物1的程序制备标题化合物19(9.2mg),总收率为42%(玫瑰棕色固体)。^{1}H NMR(400MHz,DMSO-d_6)δ9.63(s,1H),8.33(s,1H),6.73(d,J=8.4Hz,2H),6.46(d,J=8.4Hz,2H),5.29(s,1H),3.34-3.23(m,3H),3.17-3.01(m,5H),2.95-2.85(m,2H),2.28-2.13(m,2H),2.11(m,1H),2.00-1.81(m,6H),1.75-1.65(m,2H),1.62-1.37(m,3H),1.36-1.17(m,2H),1.08-0.94(m,2H)。质谱(m/z):453.2[M+H]$^+$。

[0374] 化合物20

[0375] N-(4-(4-(三氟甲基)哌啶-1-基)苯基)哌啶-4-胺

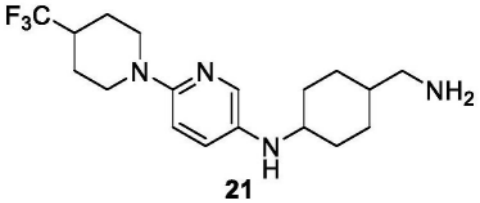
[0376] 

20

[0377] 向4-(4-(三氟甲基)哌啶-1-基)苯胺(100mg,0.4mmol)和4-氧代哌啶-1-甲酸叔丁酯(122.4mg,0.61mmol)/1,2-二氯乙烷(5mL)的溶液中添加乙酸(49mg,0.82mmol)。在室温搅拌混合物30分钟,然后在0℃缓慢添加NaBH(OAc)$_3$(173mg,0.8mmol)。搅拌所得的混合物过夜。添加二氯甲烷(5mL)并且添加2,2,2-三氟乙酸(1mL)。搅拌所得的混合物另外的2小时。将反应用饱和$NaHCO_3$水溶液淬灭并用二氯甲烷(5mL)萃取3次。合并有机层并分别用水、饱和$NaHCO_3$、盐水洗涤,用$MgSO_4$干燥,过滤,并在减压下浓缩。残余物的提纯方法为:硅胶柱色谱(石油醚/AcOEt,1/1)而得到37.2mg的期望的产物20(淡玫瑰棕色粉末),收率为28.3%。^{1}H NMR(400MHz,DMSO-d_6)δ9.08(d,J=52.9Hz,2H),7.59(s,1H),6.75(d,J=59.6Hz,3H),3.46(d,J=23.1Hz,3H),3.27(d,J=13.1Hz,2H),2.95(d,J=11.0Hz,2H),2.01(d,J=13.6Hz,3H),1.88(s,2H),1.60(s,4H),1.24(s,2H)。质谱(m/z):328.6[M+H]$^+$。

[0378] 化合物21

[0379] N-(4-(氨基甲基)环己基)-6-(4-(三氟甲基)哌啶-1-基)吡啶-3-胺

[0380] 

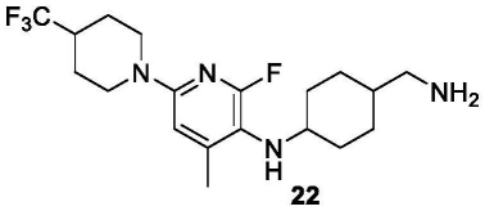
21

[0381] 由6-(4-(三氟甲基)哌啶-1-基)吡啶-3-胺(100mg,0.4mmol),((4-氧代环己基)甲基)氨基甲酸叔丁酯(111mg,0.49mmol)和NaBH(OAc)$_3$(173mg,0.8mmol),根据为20的程序制

备标题化合物21(46.3mg),收率为32.87%(淡黄色粉末),经^{1}H NMR证明为1:1的混合物。^{1}H NMR(400MHz,DMSO-d_6)δ8.25(s,3H),7.67(s,1H),7.09(s,1H),6.77(d,J=9.0Hz,1H),4.12(d,J=12.7Hz,2H),3.06(s,1H),2.78-2.58(m,4H),2.05-1.91(m,1H),1.83(d,J=12.5Hz,3H),1.74(s,1H),1.62(s,1H),1.57-1.37(m,5H),1.05(td,J=25.1,23.5,10.3Hz,2H)。质谱(m/z):357.5[M+H]$^+$。

[0382] 化合物22

[0383] N-(4-(氨基甲基)环己基)-2-氟-4-甲基-6-(4-(三氟甲基)哌啶-1-基)吡啶-3-胺

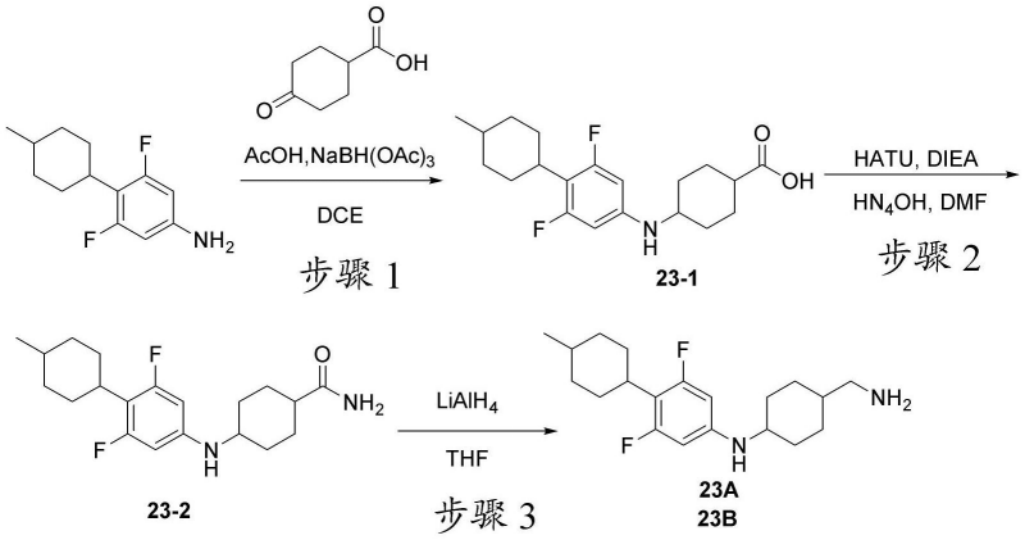
[0384] 

22

[0385] 由2-氟-4-甲基-6-(4-(三氟甲基)哌啶-1-基)吡啶-3-胺(50mg,0.18mmol),((4-氧代环己基)甲基)氨基甲酸叔丁酯(61mg,0.27mmol)和NaBH(OAc)$_3$(76mg,0.36mmol),根据为20的程序制备标题化合物22(30.2mg),收率为42.56%(淡玫瑰棕色粉末),经^{1}H NMR证明为1:1的混合物。^{1}H NMR(400MHz,DMSO-d_6)δ8.05(s,3H),6.61(s,1H),4.31-4.03(m,2H),3.09(s,1H),2.76(d,J=12.9Hz,2H),2.61(s,1H),2.29(s,3H),2.07-1.94(m,1H),1.82(t,J=16.8Hz,4H),1.52(s,4H),1.39(qd,J=12.5,4.0Hz,2H),0.95(q,J=10.3,8.0Hz,1H)。质谱(m/z):389.4[M+H]$^+$。

[0386] 化合物23

[0387] N-(4-(氨基甲基)环己基)-3,5-二氟-4-(4-甲基环己基)苯胺

[0388] 

[0389] 步骤1:制备4-((3,5-二氟-4-(4-甲基环己基)苯基)氨基)环己烷-1-甲酸(23-1)

[0390] 由3,5-二氟-4-(4-甲基环己基)苯胺(500mg,2.212mmol),4-氧代环己烷-1-甲酸(377mg,2.655mmol),AcOH(0.1mL),NaBH(OAc)$_3$(938mg,4.424mmol)和DCE(15mL),根据为1-1的程序制备标题化合物23-1(605mg),总收率为77.7%(棕色固体)。质谱(m/z):353.3[M+H]$^+$。

[0391] 步骤2:制备4-((3,5-二氟-4-(4-甲基环己基)苯基)氨基)环己烷-1-甲酰胺(23-2)

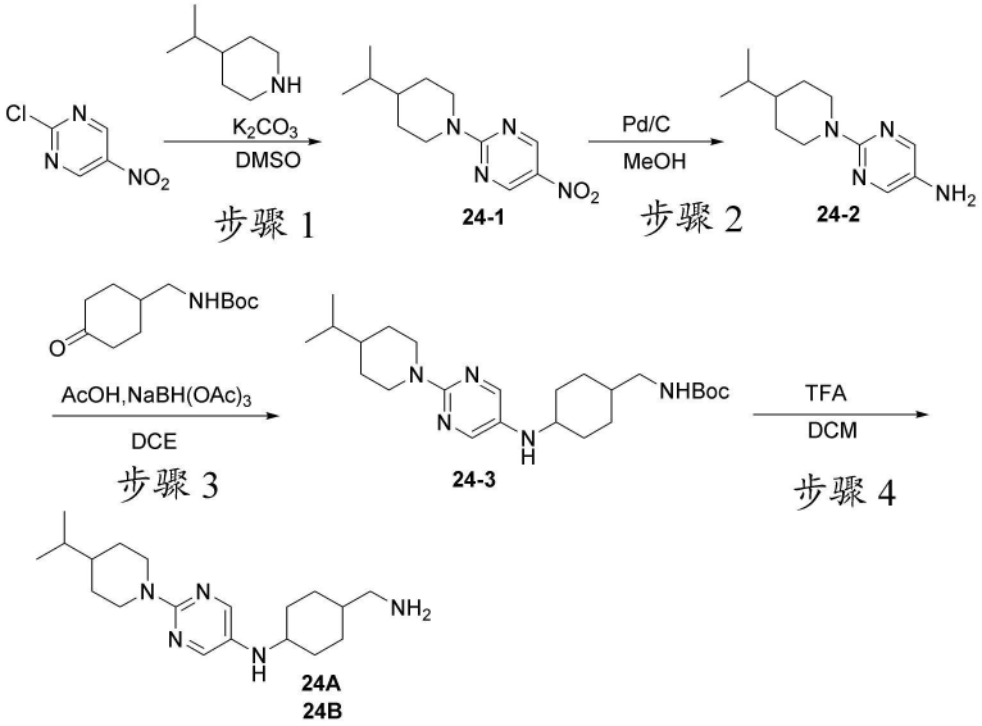
[0392] 由4-((3,5-二氟-4-(4-甲基环己基)苯基)氨基)环己烷-1-甲酸(605mg,1.72mmol),NH_4OH(3mL),HATU(770mg,2.23mmol),DIEA(660mg,5.16mmol)和DCE(15mL),根据为1的程序制备标题化合物23-2(453mg),总收率为75.1%(黄色固体)。质谱(m/z):352.3$[M+H]^+$。

[0393] 步骤3:制备N-(4-(氨基甲基)环己基)-3,5-二氟-4-(4-甲基环己基)苯胺(23)

[0394] 在0℃向4-((3,5-二氟-4-(4-甲基环己基)苯基)氨基)环己烷-1-甲酰胺(50mg,0.142mmol)/THF(5mL)的溶液中添加$LiAlH_4$(21mg,0.57mmol)。在室温搅拌混合物16小时。用EA(25mL×3)萃取混合物。将合并的有机层用盐水洗涤(15mL×3),用Na_2SO_4干燥,以及浓缩而得到粗产物,其提纯方法为:prep HPLC(XSelect-CSH-Prep 5μm OBD,19*150mm柱;ACN/水(0.5%TFA)=15%-25%-95%-95%-10%,0min-10min-10.5min-11.5min-13min)而得到期望的产物23A(Rt=8.9min)(棕色固体)(2.4mg,5.0%)和23B(Rt=9.8min)(棕色固体)(2.5mg,5.0%)。23A:^{1}H NMR(400MHz,DMSO-d_6)δ6.15(d,J=12.4Hz,2H),3.08(s,1H),2.93-2.87(m,3H),2.72-2.63(m,2H),1.97(q,J=6.0,4.0Hz,2H),1.78(d,J=7.2Hz,2H),1.64-1.56(m,2H),1.50(s,1H),1.45-1.35(m,1H),1.23(q,J=7.2,6.4Hz,3H),1.12-0.99(m,4H),0.93(d,J=6.4Hz,3H)。质谱(m/z):338.3$[M+H]^+$。23B:^{1}H NMR(400MHz,DMSO-d_6)δ6.16(d,J=12.4Hz,2H),3.36(d,J=4.8Hz,1H),2.93-2.80(m,4H),2.68(q,J=6.0Hz,2H),1.65-1.46(m,9H),1.41-1.28(m,3H),1.19(q,J=7.2,5.6Hz,4H),0.89(d,J=6.4Hz,3H)。质谱(m/z):338.3$[M+H]^+$。

[0395] 化合物24

[0396] N-(4-(氨基甲基)环己基)-2-(4-异丙基哌啶-1-基)嘧啶-5-胺

[0397] 

[0398] 步骤1:制备2-(4-异丙基哌啶-1-基)-5-硝基嘧啶(24-1)

[0399] 将4-异丙基哌啶(500mg,3.94mmol),2-氯-5-硝基嘧啶(688mg,4.33mmol),K_2CO_3(815mg,5.91mmol)/DMSO(20mL)的溶液在100℃搅拌16小时。用EA(25mL×3)萃取混合物。将

合并的有机层用盐水洗涤(15mL×3),用Na_2SO_4干燥,以及浓缩而得到粗产物,将其通过TLC提纯(EA:PE=1:5)而得到期望的产物(黄色固体)(752mg,76.3%)。质谱(m/z):251.3[M+H]$^+$。

[0400] 步骤2:制备2-(4-异丙基哌啶-1-基)嘧啶-5-胺(24-2)

[0401] 2-(4-异丙基哌啶-1-基)-5-硝基嘧啶(752mg,3.42mmol)和Pd/C(70mg)/MeOH(20mL)的溶液在室温在氢气气氛下搅拌2小时。将反应过滤并将滤液浓缩而得到期望的产物(黑色固体)(587mg,88%)。质谱(m/z):221.3[M+H]$^+$。

[0402] 步骤3:制备((4-((2-(4-异丙基哌啶-1-基)嘧啶-5-基)氨基)环己基)甲基)氨基甲酸叔丁酯(24-3)

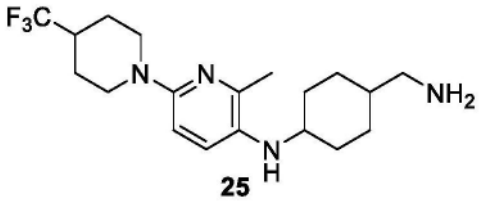
[0403] 由2-(4-异丙基哌啶-1-基)嘧啶-5-胺(50mg,0.241mmol),((4-氧代环己基)甲基)氨基甲酸叔丁酯(66mg,0.289mmol),AcOH(0.1mL),$NaBH(OAc)_3$(102mg,0.428mmol)和DCE(10mL),根据为1-1的程序制备标题化合物24-3(32mg),总收率为31%(黄色油)。质谱(m/z):432.3[M+H]$^+$。

[0404] 步骤4:制备N-(4-(氨基甲基)环己基)-2-(4-异丙基哌啶-1-基)嘧啶-5-胺(24)

[0405] 向24-3(32mg,0.074mmol)/DCM(10mL)的溶液中添加TFA(1mL)。在室温搅拌溶液1小时。将混合物用1M NaOH碱化至pH=9并浓缩,然后用DCM(25mL×3)萃取。将合并的有机层用盐水洗涤(15mL×3),用Na_2SO_4干燥,以及浓缩,其提纯方法为:Prep-HPLC(XSelect-CSH-Prep 5μm OBD,19*150mm柱;溶剂体系(ACN/水(0.5%TFA)=15%-24%-95%-95%-15%,0-12min-12.5min-13.5min-15min)而得到期望的产物24A(Rt=9.6min)(黄色固体)(3.1mg,12.6%)和24B(Rt=11.4min)(黄色油)(5.1mg,6.3%)。24A:^{1}H NMR(400MHz,DMSO-d_6)δ7.65(s,2H),4.48(d,J=13.2Hz,1H),2.63(td,J=10.4,8.4,6.0Hz,3H),1.96(dd,J=14.4,7.2Hz,3H),1.69(dd,J=50.8,12.4Hz,3H),1.51-1.32(m,2H),1.20(d,J=3.2Hz,9H),1.10-0.95(m,4H),0.84-0.80(m,6H)。质谱(m/z):332.3[M+H]$^+$。24B:^{1}H NMR(400MHz,DMSO-d_6)δ7.69(s,2H),4.48(d,J=12.8Hz,1H),3.36(s,4H),2.75-2.58(m,4H),1.69-1.33(m,11H),1.20(d,J=3.6Hz,4H),1.10-0.98(m,2H),0.83(dd,J=6.8,2.8Hz,6H)。质谱(m/z):332.3[M+H]$^+$。

[0406] 化合物25

[0407] N-(4-(氨基甲基)环己基)-2-甲基-6-(4-(三氟甲基)哌啶-1-基)吡啶-3-胺

[0408] 

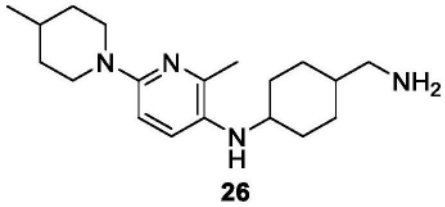
25

[0409] 由2-甲基-6-(4-(三氟甲基)哌啶-1-基)吡啶-3-胺(50mg,0.19mmol),((4-氧代环己基)甲基)氨基甲酸叔丁酯(63mg,0.27mmol)和$NaBH(OAc)_3$(79mg,0.36mmol),根据为20的程序制备标题化合物25(7.9mg),收率为11.8%(黄色固体),经^{1}H NMR证明为1:1的混合物。^{1}H NMR(400MHz,DMSO-d_6)δ8.09(s,3H),6.91(d,J=7.8Hz,1H),6.56(d,J=8.9Hz,1H),4.12(d,J=12.8Hz,2H),3.04(s,1H),2.75(s,1H),2.70-2.55(m,3H),2.25(s,1H),2.21(s,2H),2.05-1.91(m,2H),1.83(d,J=12.5Hz,3H),1.55(d,J=17.8Hz,3H),1.44(td,J=12.8,

12.4,8.1Hz,3H),1.05(t,J=12.6Hz,2H),0.88-0.81(m,1H)。质谱(m/z):371.5[M+H]$^+$。

[0410] 化合物26

[0411] N-(4-(氨基甲基)环己基)-2-甲基-6-(4-甲基哌啶-1-基)吡啶-3-胺

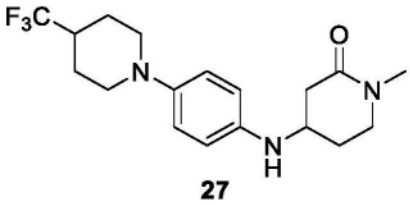
[0412] 

26

[0413] 由2-甲基-6-(4-甲基哌啶-1-基)吡啶-3-胺(50mg,0.24mmol),((4-氧代环己基)甲基)氨基甲酸叔丁酯(83mg,0.37mmol)和$NaBH(OAc)_3$(103mg,0.48mmol),根据为20的程序制备标题化合物26(19.1mg),收率为24.8%(淡黄色粉末),经^{1}H NMR证明为1:1的混合物。^{1}H NMR(400MHz,DMSO-d_6)δ11.07(s,1H),8.16(s,3H),6.68(s,1H),4.21(t,J=6.5Hz,1H),2.68(d,J=60.5Hz,4H),2.37(s,3H),2.04-1.91(m,1H),1.82(s,2H),1.73-1.42(m,9H),1.06(d,J=6.6Hz,3H),0.91(d,J=6.4Hz,4H)。质谱(m/z):317.4[M+H]$^+$。

[0414] 化合物27

[0415] 1-甲基-4-((4-(4-(三氟甲基)哌啶-1-基)苯基)氨基)哌啶-2-酮

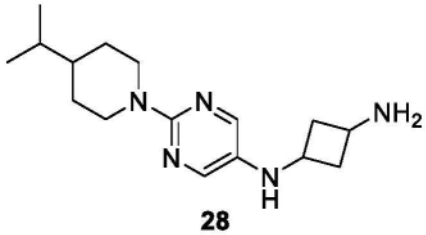
[0416] 

27

[0417] 由1-甲基哌啶-2,4-二酮(50mg,0.39mmol),MeOH(5mL)添加4-(4-(三氟甲基)哌啶-1-基)苯胺(115mg,0.47mmol),乙酸(2.34mg,0.039mmol)和氰基硼氢化钠(73mg,1.17mmol),根据为5的程序制备标题化合物27(89mg),收率为64.2%(白色固体)。^{1}H NMR(300MHz,$CDCl_3$)δ6.86(d,J=8.7Hz,2H),6.59(d,J=8.7Hz,2H),3.75-3.72(m,1H),3.53(d,J=11.7Hz,2H),3.39-3.32(m,2H),2.97(s,3H),2.85(dd,J=18.0,5.1,1H),2.59(t,J=8.7Hz,2H),2.32-2.23(m,1H),2.21-2.14(m,1H),2.12-2.08(m,1H),1.96(d,J=12.6Hz,2H),1.86-1.71(m,3H)。质谱(m/z):356.2[M+H]$^+$。

[0418] 化合物28

[0419] N^1-(2-(4-异丙基哌啶-1-基)嘧啶-5-基)环丁烷-1,3-二胺

[0420] 

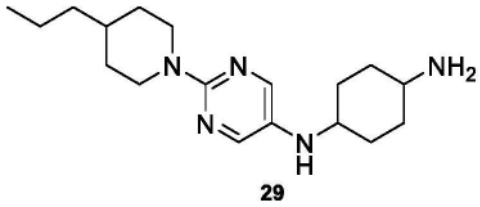
28

[0421] 由(3-((2-(4-异丙基哌啶-1-基)嘧啶-5-基)氨基)环丁基)氨基甲酸叔丁酯(53mg,0.14mmol),DCM(1mL)和TFA(1mL)根据为24的程序,制备标题化合物28(22.3mg),收率为57.1%(白色固体),经^{1}H NMR证明为1:4的混合物。^{1}H NMR(400MHz,DMSO-d_6)δ7.77(s,0.4H),7.72(s,1.6H),5.33(d,J=6.4Hz,0.8H),5.19(d,J=7.2Hz,0.2H),4.45(dt,J=

12.6,2.6Hz,2H),3.80-3.70(m,1H),3.56-3.49(m,1H),3.32-3.20(m,2H),2.62-2.55(m,2H),2.50-2.48(m,0.8H),2.08-1.95(m,3.2H),1.66-1.56(m,2H),1.52-1.42(m,0.2H),1.39-1.30(m,0.8H),1.21-1.12(m,1H),1.08-0.96(m,2H),0.82(d,J=6.8Hz,6H)。质谱(m/z):290.3$[M+H]^+$。

[0422] 化合物29

[0423] N^1-(2-(4-丙基哌啶-1-基)嘧啶-5-基)环己烷-1,4-二胺

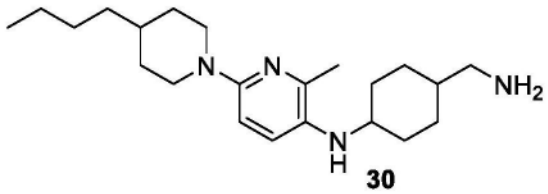
[0424] 

29

[0425] 由((4-((4-(4-(三氟甲基)哌啶-1-基)苯基)氨基)环己基)甲基)氨基甲酸叔丁酯(130mg,0.312mmol),TFA(1mL)和DCM(10mL),根据为24的程序制备标题化合物29(32.2mg),总收率为32.3%(黄色固体),经^{1}H NMR证明为1:2的混合物。^{1}H NMR(400MHz,DMSO-d_6)δ8.24(s,2H),7.89(d,J=14.4Hz,2H),4.86(dd,J=20.4,7.2Hz,1H),4.38(dd,J=13.6,3.2Hz,2H),3.08-2.95(m,1H),2.64(tt,J=12.8,2.4Hz,2H),1.95(tt,J=8.6,3.2Hz,2H),1.78-1.51(m,5H),1.40(ddd,J=15.2,12.0,6.8Hz,2H),1.31-1.23(m,2H),1.19-1.07(m,3H),0.97(qd,J=12.4,4.0Hz,2H),0.83(t,J=7.2Hz,3H)。质谱(m/z):318.3$[M+H]^+$。

[0426] 化合物30

[0427] N-(4-(氨基甲基)环己基)-6-(4-丁基哌啶-1-基)-2-甲基吡啶-3-胺

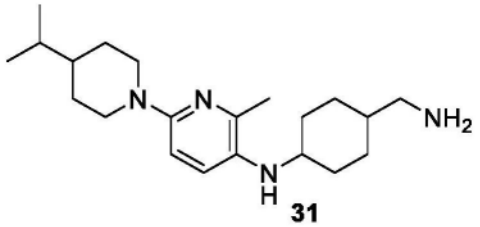
[0428] 

30

[0429] 由6-(4-丁基哌啶-1-基)-2-甲基吡啶-3-胺(50mg,0.20mmol),((4-氧代环己基)甲基)氨基甲酸叔丁酯(73mg,0.32mmol)和根据为20的程序制备标题化合物30(7.2mg),收率为10.1%(淡黄色粉末),经^{1}H NMR证明为1:1的混合物。^{1}H NMR(400MHz,DMSO-d_6)δ7.73(s,3H),7.43(s,1H),2.79(t,J=6.5Hz,2H),2.67(d,J=12.5Hz,1H),2.39(d,J=9.0Hz,3H),1.98(td,J=18.0,16.5,9.6Hz,2H),1.85-1.73(m,4H),1.66-1.40(m,8H),1.28(dd,J=7.8,3.3Hz,6H),0.86(dt,J=10.8,6.8Hz,4H)。质谱(m/z):331.3$[M+H]^+$。

[0430] 化合物31

[0431] N-(4-(氨基甲基)环己基)-6-(4-异丙基哌啶-1-基)-2-甲基吡啶-3-胺

[0432] 

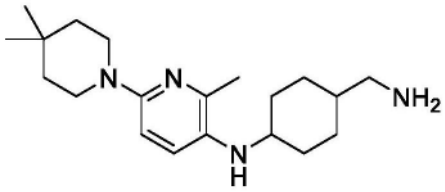
31

[0433] 由6-(4-异丙基哌啶-1-基)-2-甲基吡啶-3-胺(50mg,0.21mmol),((4-氧代环己基)甲基)氨基甲酸叔丁酯(73mg,0.32mmol)和根据为20的程序制备标题化合物31

(16.0mg),收率为20.6%(淡黄色粉末),经^{1}H NMR证明为1:1的混合物。^{1}H NMR(400MHz,DMSO-d_6)δ8.26(s,3H),6.96(s,1H),6.59(s,1H),4.07(s,2H),2.75(s,1H),2.61(s,2H),2.28(s,3H),1.96(s,1H),1.83(s,2H),1.77-1.35(m,9H),1.20(d,J=26.6Hz,4H),1.02(d,J=11.7Hz,1H),0.88(s,3H),0.86(s,3H)。质谱(m/z):345.6[M+H]$^+$。

[0434] 化合物32

[0435] N-(4-(氨基甲基)环己基)-6-(4,4-二甲基哌啶-1-基)-2-甲基吡啶-3-胺

[0436] 

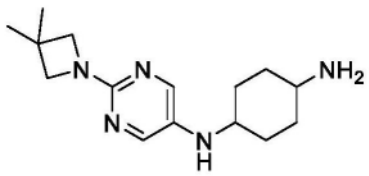
32A

32B

[0437] 由6-(4,4-二甲基哌啶-1-基)-2-甲基吡啶-3-胺(50mg,0.23mmol),((4-氧代环己基)甲基)氨基甲酸叔丁酯(77mg,0.34mmol)和根据为20的程序制备标题化合物32。混合物的提纯方法:制备HPLC(柱:X Select-CSH-Prep 5μm OBD,19*150mm;ACN/水(0.5%TFA)=5%-5%-95%-95%-5%,0min-1min-10.0min-11.0min-15.0min)得到化合物32A(Rt=3.69min)(黄色固体)和化合物32B(Rt=3.79min)(黄色固体)。32A(18.2mg,23.9%):^{1}H NMR(400MHz,DMSO-d_6)δ8.15(s,3H),6.99(s,1H),6.68(s,1H),3.37-3.41(m,3H),2.75(s,1H),2.61(s,1H),2.32(s,3H),1.82(s,2H),1.55(d,J=25.7Hz,6H),1.35(s,4H),1.22(s,1H),1.00(d,J=11.0Hz,1H),0.94(s,6H)。质谱(m/z):331.5[M+H]$^+$。32B(8.8mg,11.6%):^{1}H NMR(400MHz,DMSO-d_6)δ8.04(s,3H),7.22(s,1H),6.66(s,1H),3.52(d,J=17.5Hz,2H),2.75(s,1H),2.63(s,1H),2.27(s,2H),1.99(q,J=7.0Hz,3H),1.80(s,2H),1.48(d,J=31.8Hz,7H),1.35(s,4H),0.94(s,6H),0.88-0.81(m,1H)。质谱(m/z):331.5[M+H]$^+$。

[0438] 化合物33

[0439] N^1-(2-(3,3-二甲基氮杂环丁烷-1-基)嘧啶-5-基)环己烷-1,4-二胺

[0440] 

33A

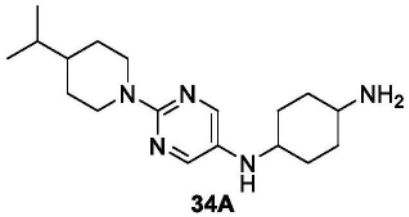
33B

[0441] 根据为24的程序,由(4-((2-(3,3-二甲基氮杂环丁烷-1-基)嘧啶-5-基)氨基)环己基)氨基甲酸叔丁酯(110mg,0.293mmol),DCM(10mL)和TFA(1mL)制备标题产物33A(Rt=6.8min;13.5mg,16.8%)(黄色固体)和33B(Rt=8.0min;8.3mg,10.3%)(黄色固体),其提纯方法为:Prep-HPLC(XSelect-CSH-Prep 5μm OBD,19*150mm柱;溶剂体系(ACN/水(0.5%TFA)=15%-25%-95%-95%-15%,0-13min-13.5min-14.5min-16min)。33A:^{1}H NMR(400MHz,DMSO-d_6)δ7.92-7.89(m,2H),3.67-3.63(m,2H),3.59(d,J=7.6Hz,3H),2.94(dd,J=8.4,2.4Hz,2H),1.97-1.89(m,4H),1.32(td,J=8.4,3.2Hz,3H),1.25-1.21(m,6H),1.19(dd,J=9.2,2.4Hz,3H)。质谱(m/z):276.3[M+H]$^+$。33B:^{1}H NMR(400MHz,DMSO-d_6)δ7.92(s,2H),3.64(d,J=5.2Hz,3H),3.22(d,J=7.6Hz,2H),1.73(t,J=3.6Hz,8H),1.26(d,J=

6.0Hz,6H),1.22(d,J＝10.4Hz,3H)。质谱(m/z):276.3[M+H]$^+$。

[0442] 化合物34

[0443] N^1-(2-(4-异丙基哌啶-1-基)嘧啶-5-基)环己烷-1,4-二胺

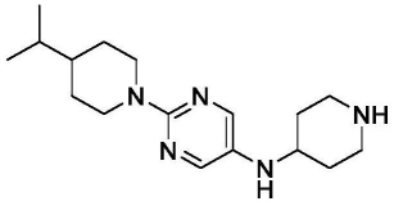
[0444] 

34A
34B

[0445] 根据为24的程序,由(4-((2-(4-异丙基哌啶-1-基)嘧啶-5-基)氨基)环己基)氨基甲酸叔丁酯(130mg,0.312mmol),DCM(10mL)和TFA(1mL)制备标题产物34A(Rt＝5.8min)(白色固体)(18.8mg,19.2%)和34B(Rt＝6.6min)(黄色固体)(16.8mg,17.2%),其提纯方法为:Prep-HPLC(溶剂体系(ACN/水(0.5%TFA)＝10%-45%-95%-95%-10%,0-7min-7.5min-8.5min-10min)。34A:^{1}H NMR(400MHz,DMSO-d_6)δ8.02(s,1H),7.87(s,1H),7.80(d,J＝4.8Hz,2H),4.50(d,J＝12.8Hz,2H),3.07(d,J＝11.2Hz,1H),2.95(s,1H),2.71-2.61(m,2H),1.99-1.86(m,4H),1.64(d,J＝12.4Hz,2H),1.35(dp,J＝22.0,7.6,7.2Hz,3H),1.20(q,J＝12.8,10.0Hz,3H),1.04(qd,J＝12.4,4.0Hz,2H),0.82(d,J＝6.8Hz,6H)。质谱(m/z):318.3[M+H]$^+$。34B:^{1}H NMR(400MHz,DMSO-d_6)δ7.94(s,1H),7.89(s,1H),7.78(s,2H),4.49-4.44(m,2H),3.15(d,J＝39.6Hz,1H),2.64(td,J＝12.8,2.8Hz,2H),1.74-1.54(m,10H),1.37(dq,J＝13.2,6.8Hz,1H),1.23-1.17(m,2H),1.04(qd,J＝12.4,4.0Hz,2H),0.85-0.80(m,6H)。质谱(m/z):318.3[M+H]$^+$。

[0446] 化合物35

[0447] 2-(4-异丙基哌啶-1-基)-N-(哌啶-4-基)嘧啶-5-胺

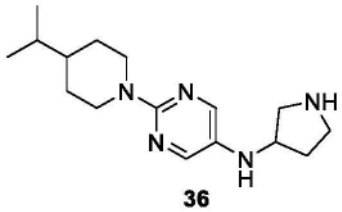
[0448] 

35

[0449] 由4-((2-(4-异丙基哌啶-1-基)嘧啶-5-基)氨基)哌啶-1-甲酸叔丁酯(140mg,0.347mmol),TFA(1mL),和DCM(10mL),根据为24的程序制备标题化合物35(39.8mg),总收率为38.1%(黄色油),经^{1}H NMR证明为1:2的混合物。^{1}H NMR(400MHz,DMSO-d_6)δ7.96(s,2H),4.47(dq,J＝12.4,2.8Hz,2H),3.44-3.36(m,1H),3.28(t,J＝15.2Hz,3H),2.90(p,J＝15.2,13.2Hz,3H),2.64(td,J＝12.8,2.8Hz,2H),2.01-1.94(m,2H),1.67-1.59(m,3H),1.47(dt,J＝11.2,3.2Hz,1H),1.35(dd,J＝13.2,6.4Hz,1H),1.20(d,J＝4.0Hz,1H),1.05(tt,J＝12.4,6.4Hz,2H),0.82(d,J＝6.8Hz,6H)。质谱(m/z):304.3[M+H]$^+$。

[0450] 化合物36

[0451] 2-(4-异丙基哌啶-1-基)-N-(吡咯烷-3-基)嘧啶-5-胺

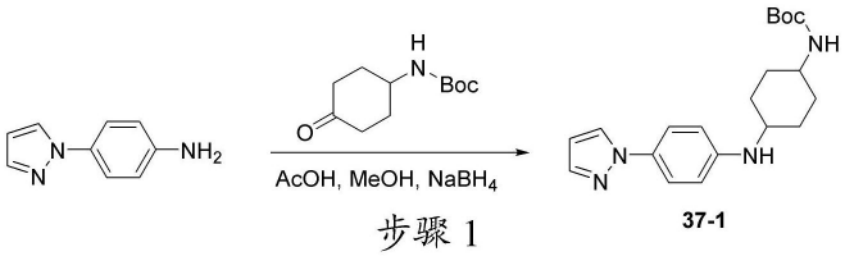
[0452] 

36

[0453] 由4-((2-(4-异丙基哌啶-1-基)嘧啶-5-基)氨基)哌啶-1-甲酸叔丁酯(130mg,0.334mmol),TFA(1mL),和DCM(10mL),根据为24的程序制备标题化合物36(35.0mg),总收率为36.5%(黄色油)。^{1}H NMR(400MHz,DMSO-d_6)δ7.91(s,2H),4.47(dt,J=14.0,3.2Hz,2H),3.97(td,J=6.4,3.2Hz,1H),3.87(s,1H),3.35(dd,J=12.0,6.0Hz,1H),3.25-3.15(m,2H),3.00(dq,J=9.6,4.8Hz,1H),2.64(td,J=12.8,2.8Hz,2H),2.23-2.14(m,1H),1.66-1.58(m,3H),1.37(dq,J=13.2,6.4Hz,2H),1.04(qd,J=12.4,4.0Hz,3H),0.83(s,3H),0.81(s,3H)。质谱(m/z):290.3[M+H]$^+$。

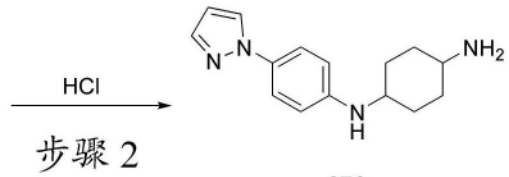
[0454] 化合物37

[0455] N^1-(4-(1H-吡唑-1-基)苯基)环己烷-1,4-二胺

[0456] 

步骤 1

37-1



步骤 2

37A

37B

[0457] 步骤1:制备(4-((4-(1H-吡唑-1-基)苯基)氨基)环己基)氨基甲酸叔丁酯(37-1)

[0458] 向4-(1H-吡唑-1-基)苯胺(150mg,0.94mmol)/MeOH(10mL)的溶液中添加一滴AcOH和(4-氧代环己基)氨基甲酸叔丁酯(201.9mg,0.94mmol),并在50℃搅拌混合物1小时。然后在冷却到25℃后添加$NaBH_4$(71.24mg,1.88mmol)。然后在25℃搅拌混合物16小时。LCMS显示反应完成。将反应用水(10mL)淬灭,用EA(10mL*3)萃取。将合并的有机层用盐水(20mL)洗涤,用硫酸钠干燥,过滤和浓缩。残余物的提纯方法为:使用EA/PE(1:3)的combi-flash(闪式色谱)而得到37-1(0.2g,59.3%,收率)(黄色固体)。MS(m/z)356.8[M+H]$^+$。

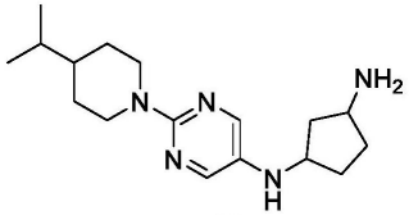
[0459] 步骤2:制备N-(4-(叔丁基)苯基)-N-(2,2,2-三氟乙基)环己烷-1,4-二胺(37)

[0460] 化合物37-1(200mg,0.56mmol)和HCl/1,4-二氧杂环己烷(10mL,4N)被置于烧瓶中在25℃搅拌16小时。在减压蒸馏过量的1,4-二氧杂环己烷并且残余物的提纯方法为:prep-HPLC(柱-Xbridge-C18 150x 19mm,5um;移动相:ACN-H_2O(0.1%FA),2%-20%)而得到37A(31.2mg)(白色固体)和37B(21.9mg)(白色固体)。37A:^{1}H NMR(400MHz,DMSO-d_6)δ8.42(s,1H),8.20(d,J=2.3Hz,1H),7.61(d,J=1.5Hz,1H),7.47(d,J=8.9Hz,2H),6.64(d,J=8.9Hz,2H),6.45-6.42(m,1H),5.61(d,J=7.8Hz,1H),3.17(s,1H),2.89(s,1H),1.97(dd,J

＝34.9,11.9Hz,4H),1.39(d,J＝13.0Hz,2H),1.23-1.14(m,2H).MS(m/z)257.2[M+H]$^+$。HPLC:Rt:2.643min(柱:XBRIDGE 2.1*50mm,3.5um;移动相:H_2O(0.05％TFA)/ACN(0.05％TFA),ACN由0％至60％7分钟内,7-8min,ACN由60％至100％;0.8mL/min)。37B:^{1}H NMR(400MHz,CD_3OD)δ8.55(s,1H),7.96(d,J＝2.2Hz,1H),7.63(d,J＝1.6Hz,1H),7.40(d,J＝8.9Hz,2H),6.73(d,J＝8.9Hz,2H),6.45(t,J＝2.1Hz,1H),3.60(s,1H),3.23(s,1H),1.97-1.74(m,8H).MS(m/z)257.2[M+H]$^+$。HPLC:Rt:3.112min(柱:XBRIDGE 2.1*50mm,3.5um;移动相:H_2O(0.05％TFA)ACN(0.05％TFA),ACN由0％至60％7分钟内,7-8min,ACN由60％至100％;0.8mL/min)。

[0461] 化合物38

[0462] N^1-(2-(4-异丙基哌啶-1-基)嘧啶-5-基)环戊烷-1,3-二胺

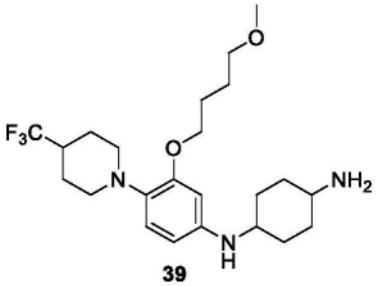
[0463] 

38

[0464] 由(3-((2-(4-异丙基哌啶-1-基)嘧啶-5-基)氨基)环戊基)氨基甲酸叔丁酯(120mg,0.298mmol),TFA(1mL),和DCM(10mL),根据为24的程序制备标题化合物38(5.9mg),总收率为6.7％(黄色固体)。^{1}H NMR(400MHz,DMSO-d_6)δ7.86(d,J＝6.0Hz,2H),4.46(d,J＝12.8Hz,1H),3.81(d,J＝20.4Hz,2H),3.61(t,J＝6.8Hz,2H),2.62-2.60(m,1H),2.11-2.02(m,1H),1.99-1.88(m,3H),1.62(d,J＝15.2Hz,3H),1.57-1.48(m,1H),1.36(dt,J＝11.6,5.8Hz,2H),1.04(qd,J＝12.4,4.4Hz,2H),0.83(s,3H),0.81(d,J＝2.0Hz,3H)。质谱(m/z):304.3[M+H]$^+$。

[0465] 化合物39

[0466] N^1-(3-(4-甲氧基丁氧基)-4-(4-(三氟甲基)哌啶-1-基)苯基)环己烷-1,4-二胺

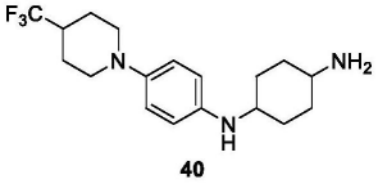
[0467] 

39

[0468] 由(4-((3-(4-甲氧基丁氧基)-4-(4-(三氟甲基)哌啶-1-基)苯基)氨基)环己基)氨基甲酸叔丁酯(120mg,0.221mmol),TFA(1mL),和DCM(10mL),根据为24的程序制备标题化合物39(69.1mg),总收率为70.4％(紫色固体),经^{1}H NMR证明为1:2的混合物。^{1}H NMR(400MHz,DMSO-d_6)δ8.26(s,2H),8.17(s,1H),6.62(d,J＝8.4Hz,1H),6.23(d,J＝24.8Hz,1H),6.04(s,1H),3.83(d,J＝7.6Hz,2H),3.37-3.34(m,2H),3.19(s,5H),2.96(d,J＝51.2Hz,2H),2.31(s,1H),1.95(d,J＝11.6Hz,3H),1.84-1.60(m,10H),1.57-1.40(m,4H),1.11(d,J＝12.0Hz,1H)。质谱(m/z):444.3[M+H]$^+$。

[0469] 化合物40

[0470] N^1-(4-(4-(三氟甲基)哌啶-1-基)苯基)环己烷-1,4-二胺

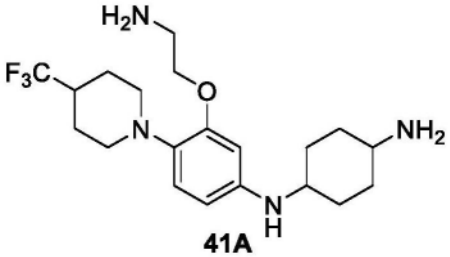
[0471] 

40

[0472] 由N^1-(4-(4-(三氟甲基)哌啶-1-基)苯基)环己烷-1,4-二胺(150mg,0.34mmol),TFA(1mL),和DCM(10mL),根据为24的程序制备标题化合物40(56.2mg),总收率为48.9%(紫色固体),经^{1}H NMR证明为1:2的混合物。^{1}H NMR(400MHz,DMSO-d_6)δ8.07(s,3H),6.75-6.68(m,2H),6.52-6.43(m,2H),4.92(d,J=7.2Hz,1H),3.41-3.29(m,4H),3.01(s,1H),2.94-2.82(m,1H),2.32(d,J=9.2Hz,1H),1.94(d,J=12.0Hz,2H),1.81(d,J=12.0Hz,2H),1.75-1.65(m,2H),1.52(qd,J=12.4,4.1Hz,3H),1.45-1.36(m,1H),1.15-1.06(m,1H)。质谱(m/z):342.3[M+H]$^+$。

[0473] 化合物41

[0474] N^1-(3-(2-氨基乙氧基)-4-(4-(三氟甲基)哌啶-1-基)苯基)环己烷-1,4-二胺

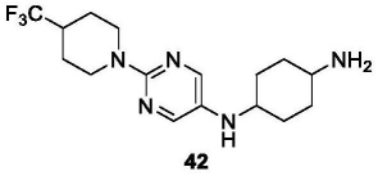
[0475] 

41A
41B

[0476] 由(2-(5-氨基-2-(4-(三氟甲基)哌啶-1-基)苯氧基)乙基)氨基甲酸叔丁酯(100mg,0.25mmol),(4-氧代环己基)氨基甲酸叔丁酯(79mg,0.37mmol),根据为化合物20的程序制备标题化合物41A,41B。残余物的提纯方法为:制备HPLC((柱:X Select-CSH-Prep 5μm OBD,19*150mm;ACN/水(0.5%TFA)=0%-30%-95%-95%-10%,0min-7min-7.5min-8.5min-10.0min)而得到化合物41A(Rt=4.39min),收率为5.6%(白色固体)和41B(Rt=4.82min),收率为6.24%(白色固体)。41A:^{1}H NMR(400MHz,DMSO-d_6)δ8.01(s,3H),7.86(s,3H),6.56(s,1H),6.17(d,J=8.8Hz,1H),3.13(s,2H),2.01-1.85(m,8H),1.87-1.46(m,9H),1.45(s,2H),0.85(t,J=6.5Hz,2H)。质谱(m/z):401.4[M+H]$^+$。41B:^{1}H NMR(400MHz,DMSO-d_6)δ8.05(s,3H),7.80(s,3H),6.37(s,1H),6.28(d,J=8.8Hz,1H),4.17(s,1H),3.13(s,2H),2.07-1.88(m,6H),1.79-1.56(m,11H),1.45(s,1H),0.85(t,J=6.5Hz,2H)。质谱(m/z):401.4[M+H]$^+$。

[0477] 化合物42

[0478] N^1-(2-(4-(三氟甲基)哌啶-1-基)嘧啶-5-基)环己烷-1,4-二胺

[0479] 

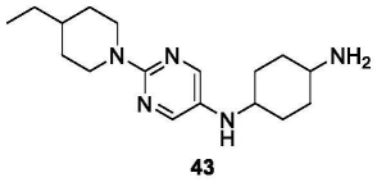
42

[0480] 由(4-((2-(4-(三氟甲基)哌啶-1-基)嘧啶-5-基)氨基)环己基)氨基甲酸叔丁酯

(150mg,0.39mmol),TFA(1mL),和DCM(10mL),根据为24的程序制备标题化合物42(102.7mg),总收率为87.9%(黄色固体),经^{1}H NMR证明为2:3的混合物。^{1}H NMR(400MHz,DMSO-d_6)δ8.27(s,2H),7.92(d,J=13.6Hz,2H),5.04(d,J=6.0Hz,0.4H),4.98(d,J=8.4Hz,0.6H),4.49(d,J=13.2Hz,2H),3.02(dt,J=9.6,4.8Hz,1H),2.89(tt,J=12.0,3.6Hz,1H),2.72(td,J=12.8,2.4Hz,2H),1.95(dt,J=12.4,4.9Hz,2H),1.80-1.74(m,2H),1.70(q,J=6.4,5.2Hz,2H),1.59-1.49(m,1H),1.41(dd,J=12.8,3.2Hz,1H),1.29(tt,J=12.4,6.4Hz,2H),1.09(qd,J=12.8,11.6,4.8Hz,1H)。质谱(m/z):344.3[M+H]$^+$。

[0481] 化合物43

[0482] N^1-(2-(4-乙基哌啶-1-基)嘧啶-5-基)环己烷-1,4-二胺

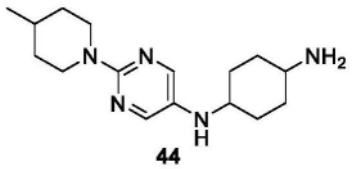
[0483] 

43

[0484] 由(4-((2-(4-(三氟甲基)哌啶-1-基)嘧啶-5-基)氨基)环己基)氨基甲酸叔丁酯(150mg,0.39mmol),TFA(1mL),和DCM(10mL),根据为24的程序制备标题化合物43(67.5mg),总收率为71.8%(黄色固体),经^{1}H NMR证明为1:1的混合物。^{1}H NMR(400MHz,DMSO-d_6)δ8.29(s,2H),7.89(d,J=14.4Hz,2H),4.91(d,J=6.0Hz,0.5H),4.86(d,J=8.4Hz,0.5H),4.45-4.31(m,2H),3.32(d,J=21.6Hz,2H),3.07-2.95(m,1H),2.88(dq,J=11.6,6.0,4.0Hz,1H),2.63(tt,J=12.4,2.4Hz,2H),1.94(tt,J=9.6,3.6Hz,2H),1.73-1.59(m,4H),1.57-1.48(m,1H),1.46-1.36(m,1H),1.28(dp,J=11.2,4.0Hz,1H),1.18(dd,J=8.4,5.6Hz,2H),0.96(qd,J=12.4,4.0Hz,2H),0.82(t,J=7.6Hz,3H)。质谱(m/z):304.3[M+H]$^+$。

[0485] 化合物44

[0486] N^1-(2-(4-甲基哌啶-1-基)嘧啶-5-基)环己烷-1,4-二胺

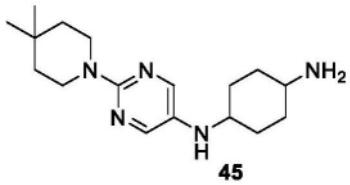
[0487] 

44

[0488] 由(4-((2-(4-(三氟甲基)哌啶-1-基)嘧啶-5-基)氨基)环己基)氨基甲酸叔丁酯(87mg,0.224mmol),TFA(1mL),和DCM(10mL),根据为24的程序制备标题化合物44(17.0mg),总收率为26.2%(黄色固体),经^{1}H NMR证明为2:3的混合物。^{1}H NMR(400MHz,DMSO-d_6)δ7.88(d,J=14.0Hz,2H),5.04(d,J=6.0Hz,0.4H),4.98(d,J=8.4Hz,0.6H),4.41-4.28(m,2H),3.01(dd,J=10.4,5.6Hz,1H),2.86(t,J=12.0Hz,1H),2.65(td,J=12.4,2.4Hz,2H),1.93(d,J=11.2Hz,2H),1.69(d,J=11.2Hz,2H),1.55(td,J=13.2,3.6Hz,3H),1.41-1.34(m,1H),1.10(t,J=11.6Hz,1H),1.03-0.93(m,2H),0.86(d,J=6.4Hz,3H)。质谱(m/z):290.3[M+H]$^+$。

[0489] 化合物45

[0490] N^1-(2-(4,4-二甲基哌啶-1-基)嘧啶-5-基)环己烷-1,4-二胺

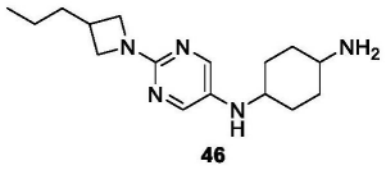
[0491] 

45

[0492] 由(4-((2-(4,4-二甲基哌啶-1-基)嘧啶-5-基)氨基)环己基)氨基甲酸叔丁酯(109mg,0.270mmol),TFA(1mL),和DCM(10mL),根据为24的程序制备标题化合物45(54.7mg),总收率为66.7%(黄色固体),经^{1}H NMR证明为1:1的混合物。^{1}H NMR(400MHz,DMSO-d_6)δ7.94(d,J=15.2Hz,2H),4.92(dd,J=19.2,6.8Hz,1H),3.55(td,J=5.6,2.0Hz,4H),3.06(d,J=8.8Hz,2H),2.92(td,J=11.6,6.0Hz,1H),2.03-1.96(m,2H),1.83-1.65(m,3H),1.58(d,J=13.6Hz,1H),1.49-1.42(m,1H),1.32-1.26(m,4H),1.19-1.08(m,1H),0.94(s,6H)。质谱(m/z):304.3[M+H]$^+$。

[0493] 化合物46

[0494] N^1-(2-(3-丙基氮杂环丁烷-1-基)嘧啶-5-基)环己烷-1,4-二胺

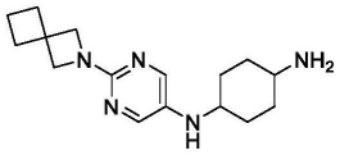
[0495] 

46

[0496] 由(4-((2-(3-丙基氮杂环丁烷-1-基)嘧啶-5-基)氨基)环己基)氨基甲酸叔丁酯(52mg,0.134mmol),TFA(1mL),和DCM(10mL),根据为24的程序制备标题化合物46(4.3mg),总收率为11.1%(黄色固体),经^{1}H NMR证明为1:2的混合物。^{1}H NMR(400MHz,DMSO-d_6)δ7.91(d,J=12.4Hz,2H),4.97(d,J=22.4Hz,1H),3.96(t,J=8.0Hz,2H),3.49(dd,J=8.0,5.6Hz,2H),3.04(s,1H),2.93(s,1H),1.99(s,2H),1.73(d,J=9.6Hz,2H),1.57-1.52(m,2H),1.47-1.40(m,2H),1.32-1.19(m,5H),1.16-1.10(m,1H),0.88(t,J=7.2Hz,3H)。质谱(m/z):290.3[M+H]$^+$。

[0497] 化合物47

[0498] N^1-(2-(2-氮杂螺[3.3]庚烷-2-基)嘧啶-5-基)环己烷-1,4-二胺

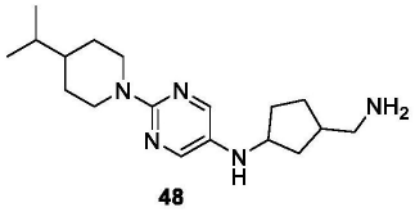
[0499] 

47

[0500] 由(4-((2-(2-氮杂螺[3.3]庚烷-2-基)嘧啶-5-基)氨基)环己基)氨基甲酸叔丁酯(98mg,0.253mmol),TFA(1mL),和DCM(10mL),根据为24的程序制备标题化合物47(26.1mg),总收率为35.6%(黄色固体),经^{1}H NMR证明为1:2的混合物。^{1}H NMR(400MHz,DMSO-d_6)δ7.91(d,J=13.2Hz,2H),5.04(d,J=6.0Hz,0.3H),4.98(d,J=8.4Hz,0.7H),3.84(s,3H),2.96(dd,J=33.6,21.6Hz,2H),2.13(t,J=7.6Hz,4H),2.03-1.93(m,3H),1.84-1.71(m,4H),1.57-1.38(m,2H),1.16-1.10(m,1H)。质谱(m/z):288.3[M+H]$^+$。

[0501] 化合物48

[0502] N-(3-(氨基甲基)环戊基)-2-(4-异丙基哌啶-1-基)嘧啶-5-胺

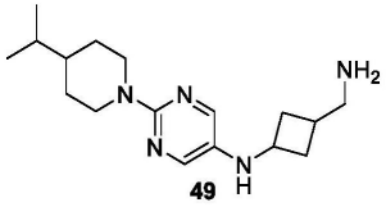
[0503] 

48

[0504] 由2-(4-异丙基哌啶-1-基)嘧啶-5-胺(50mg,0.23mmol),((3-氧代环戊基)甲基)氨基甲酸叔丁酯(73mg,0.34mmol)和根据为20的程序制备标题化合物48(6.1mg),收率为8.4%(白色粉末),经^{1}H NMR证明为1:1的混合物。^{1}H NMR(400MHz,DMSO-d_6)δ7.99(s,3H),7.86(d,J=2.8Hz,2H),4.51(q,J=16.0,14.9Hz,2H),2.66(d,J=23.1Hz,2H),1.64(d,J=12.9Hz,4H),1.40(q,J=6.6Hz,3H),1.34-1.15(m,5H),1.09(td,J=12.5,4.0Hz,3H),0.86(d,J=2.8Hz,4H),0.84(s,3H)。质谱(m/z):317.3[M+H]$^+$。

[0505] 化合物49

[0506] N-(3-(氨基甲基)环丁基)-2-(4-异丙基哌啶-1-基)嘧啶-5-胺

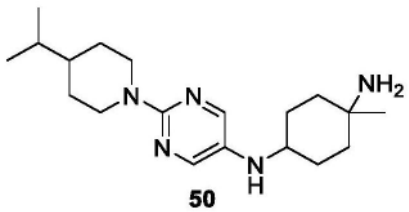
[0507] 

49

[0508] 由2-(4-异丙基哌啶-1-基)嘧啶-5-胺(200mg,0.91mmol),3-氧代环丁烷-1-甲酸(155mg,1.36mmol),根据为23的程序以三步制备标题化合物49(26.6mg),总收率为9.6%(白色粉末),经^{1}H NMR证明为1:1的混合物。^{1}H NMR(400MHz,DMSO-d_6)δ11.07(s,1H),8.16(s,3H),6.68(s,1H),4.21(t,J=6.5Hz,2H),2.68(d,J=60.5Hz,3H),2.37(s,3H),2.03-1.89(m,1H),1.82(s,2H),1.73-1.39(m,7H),1.22(d,J=3.1Hz,3H),1.06(d,J=6.6Hz,2H),0.91(d,J=6.4Hz,3H)。质谱(m/z):304.6[M+H]$^+$。

[0509] 化合物50

[0510] N^1-(2-(4-异丙基哌啶-1-基)嘧啶-5-基)-4-甲基环已烷-1,4-二胺

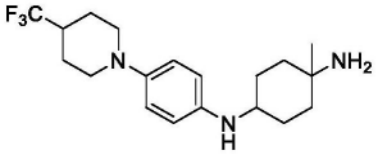
[0511] 

50

[0512] 由2-(4-异丙基哌啶-1-基)嘧啶-5-胺(70mg,0.34mmol),(1-甲基-4-氧代环已基)氨基甲酸叔丁酯(110mg,0.52mmol)和根据为20的程序制备标题化合物50(56.3mg),收率为53.4%(淡黄色粉末),经^{1}H NMR证明为1:1的混合物。^{1}H NMR(400MHz,DMSO-d_6)δ8.10(d,J=18.4Hz,3H),7.92(d,J=11.0Hz,2H),4.82(dd,J=36.7,7.5Hz,1H),4.56-4.42(m,2H),3.13(d,J=43.4Hz,1H),2.62(td,J=12.8,2.5Hz,2H),1.97-1.81(m,2H),1.74(d,J=13.4Hz,2H),1.69-1.57(m,4H),1.53(h,J=7.5,6.3Hz,1H),1.40(h,J=6.7Hz,1H),1.27(d,J=7.0Hz,4H),1.07(qd,J=12.3,4.2Hz,2H),0.85(d,J=6.7Hz,6H)。质谱(m/z):332.4[M+H]$^+$。

[0513] 化合物50

[0514] 1-甲基-N^4-(4-(4-(三氟甲基)哌啶-1-基)苯基)环己烷-1,4-二胺

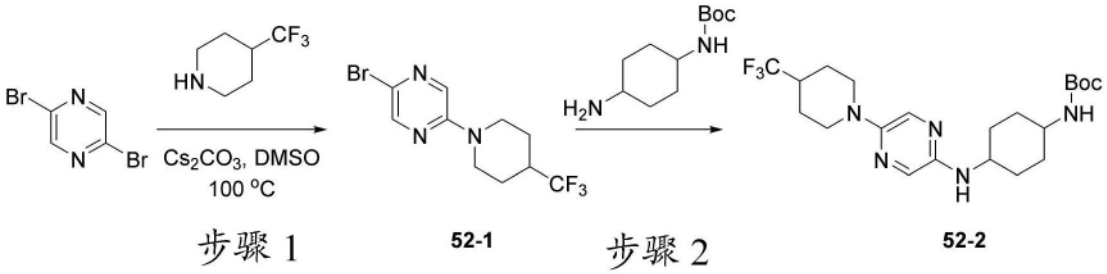
[0515] 

51

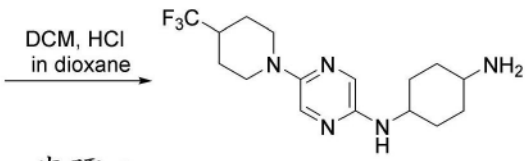
[0516] 由(1-甲基-4-((4-(4-(三氟甲基)哌啶-1-基)苯基)氨基)环己基)氨基甲酸叔丁酯(79mg,0.174mmol),TFA(1mL),和DCM(10mL),根据为24的程序制备标题化合物51(47.2mg),总收率为75.8%(紫色固体)。^{1}H NMR(400MHz,DMSO-d_6)δ8.33(d,J=36.4Hz,3H),6.78(s,2H),6.68-6.39(m,2H),3.16(d,J=55.2Hz,1H),2.38(s,1H),2.05-1.43(m,11H),1.30(d,J=7.5Hz,3H)。质谱(m/z):356.3[M+H]$^+$。

[0517] 化合物52

[0518] N^1-(5-(4-(三氟甲基)哌啶-1-基)吡嗪-2-基)环己烷-1,4-二胺

[0519] 

步骤1 52-1 步骤2 52-2



步骤3 52

[0520] in dioxane:在二氧杂环己烷中

[0521] 步骤1:制备2-溴-5-(4-(三氟甲基)哌啶-1-基)吡嗪(52-1)

[0522] 向2,5-二溴吡嗪(3g,12.6mmol)/DMSO(30mL)的溶液中添加4-(三氟甲基)哌啶(1.93g,12.6mmol)和Cs_2CO_3(6.16g,18.9mmol)。然后在100℃搅拌混合物2小时。LCMS显示反应完成。将混合物添加到H_2O中并且过滤而得到化合物52-1(3.5g,89.7%,收率)(黄色固体)。MS(m/z):310.0[M+H]$^+$。

[0523] 步骤2:制备(4-((5-(4-(三氟甲基)哌啶-1-基)吡嗪-2-基)氨基)环己基)氨基甲酸叔丁酯(52-2)

[0524] 在25℃在氮气气氛下向2-溴-5-(4-(三氟甲基)哌啶-1-基)吡嗪(0.2g,0.64mmol),(4-氨基环己基)氨基甲酸叔丁酯(139mg,0.64mmol),Cs_2CO_3(420mg,1.29mmol)和Ruphos(60mg,0.13mmol)/二氧杂环己烷(10mL)的溶液中添加$Pd_2(dba)_3$(59mg,0.064mmol)。然后在90℃搅拌混合物过夜。LCMS显示反应完成。将反应过滤并浓缩。残余物的提纯方法为:使用EA/PE(1:2)的combi-flash(闪式色谱)而得到52-2(0.1g,34.8%,收率)(黄色固体)。MS(m/z)443.7[M+H]$^+$。

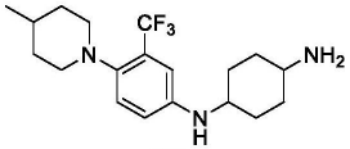
[0525] 步骤3:制备N^1-(5-(4-(三氟甲基)哌啶-1-基)吡嗪-2-基)环己烷-1,4-二胺(52)

[0526] 向化合物3(100mg,0.22mmol)/THF(2mL)的溶液中添加HCl/二氧杂环己烷(2mL)。

然后在25℃搅拌混合物1小时。LCMS显示反应完成。将反应浓缩。残余物的提纯方法为:prep-HPLC而得到52(6mg,7.7%,收率)(黄色固体)。^{1}H NMR(300MHz,CD_3OD)δ7.64(d,J=1.3Hz,1H),7.62(s,1H),3.96(d,J=12.6Hz,2H),3.80(s,1H),3.22-3.15(m,1H),2.67(t,J=12.6Hz,2H),2.36-2.21(m,1H),1.94-1.54(m,12H).MS(m/z)344.2$[M+H]^+$。

[0527] 化合物53

[0528] N^1-(4-(4-甲基哌啶-1-基)-3-(三氟甲基)苯基)环己烷-1,4-二胺

[0529] 

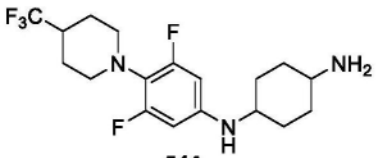
53A

53B

[0530] 根据为24的程序,由(4-((4-(4-甲基哌啶-1-基)-3-(三氟甲基)苯基)氨基)环己基)氨基甲酸叔丁酯(121mg,0.266mmol),DCM(10mL)和TFA(1mL)制备期望的产物53A(Rt=10.9min)(黄色固体)(15.1mg,16.1%)和53B(Rt=14.4min)(黄色油)(14.3mg,15.5%),其提纯方法为:Prep-HPLC(柱:X Select-CSH-Prep 5μm OBD,19*150mm;溶剂体系(ACN/水(0.5%TFA)=10%-90%-95%-95%-10%,0-12min-12.5min-13.5min-15min)。53A:^{1}H NMR(400MHz,DMSO-d_6)δ7.20(d,J=8.4Hz,1H),6.70(d,J=10.0Hz,2H),5.63(d,J=8.0Hz,1H),3.10-3.00(m,1H),2.71(dt,J=11.6,3.3Hz,2H),2.58(td,J=11.6,2.4Hz,2H),1.91-1.81(m,2H),1.77-1.66(m,2H),1.58(dd,J=12.8,3.5Hz,2H),1.43-1.34(m,1H),1.23-1.13(m,3H),1.08(t,J=9.2Hz,3H),0.89(d,J=6.4Hz,3H)。质谱(m/z):356.3$[M+H]^+$。53B:^{1}H NMR(400MHz,DMSO-d_6)δ7.20(d,J=8.4Hz,1H),6.70(d,J=10.0Hz,2H),5.63(d,J=8.0Hz,1H),3.10-3.00(m,1H),2.71(dt,J=11.6,3.3Hz,2H),2.58(td,J=11.6,2.4Hz,2H),1.91-1.81(m,2H),1.77-1.66(m,2H),1.58(dd,J=12.8,3.5Hz,2H),1.43-1.34(m,1H),1.23-1.13(m,3H),1.08(t,J=9.2Hz,3H),0.89(d,J=6.4Hz,3H)。质谱(m/z):356.3$[M+H]^+$。

[0531] 化合物54

[0532] N^1-(3,5-二氟-4-(4-(三氟甲基)哌啶-1-基)苯基)环己烷-1,4-二胺

[0533] 

54A

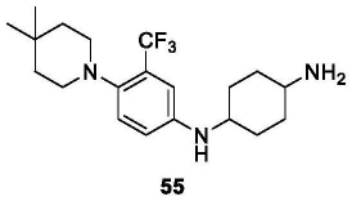
54B

[0534] 由(4-((3,5-二氟-4-(4-(三氟甲基)哌啶-1-基)苯基)氨基)环己基)氨基甲酸叔丁酯(150mg,0.314mmol),DCM(10mL),和TFA(1mL),根据为24的程序制备期望的产物54A(Rt=12.2min)(白色固体)(44.4mg,37.0%)和54B(Rt=12.9min)(黄色固体)(42.0mg,34.8%),其提纯方法为:Prep-HPLC(柱:X Select-CSH-Prep 5μm OBD,19*150mm;溶剂体系(ACN/水(0.5%TFA)=10%-85%-95%-95%-10%,0-14min-14.5min-15.5min-17min)。54A:^{1}H NMR(400MHz,DMSO-d_6)δ7.80(d,J=5.2Hz,3H),6.17(d,J=12.0Hz,2H),3.05(dq,J=11.2,6.0,3.6Hz,1H),3.00-2.89(m,5H),2.33(dq,J=8.8,5.2,4.4Hz,1H),1.99-1.84(m,4H),1.82-1.73(m,2H),1.54-1.33(m,4H),1.11(dt,J=13.2,10.4Hz,2H)。质谱(m/z):

378.3[M+H]$^+$。54B:^{1}H NMR(400MHz,DMSO-d_6)δ7.80(d,J=5.2Hz,3H),6.17(d,J=12.0Hz,2H),3.05(dq,J=11.2,6.0,3.6Hz,1H),3.00-2.89(m,5H),2.33(dq,J=8.8,5.2,4.4Hz,1H),1.99-1.84(m,4H),1.82-1.73(m,2H),1.54-1.33(m,4H),1.11(dt,J=13.2,10.4Hz,2H)。质谱(m/z):378.3[M+H]$^+$。

[0535] 化合物55

[0536] N^1-(4-(4,4-二甲基哌啶-1-基)-3-(三氟甲基)苯基)环己烷-1,4-二胺

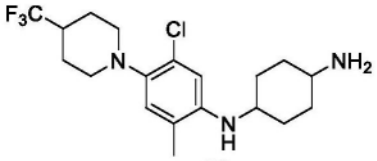
[0537] 

55

[0538] 由(4-((4-(4,4-二甲基哌啶-1-基)-3-(三氟甲基)苯基)氨基)环己基)氨基甲酸叔丁酯(93mg,0.198mmol),TFA(1mL),和DCM(10mL),根据为24的程序制备标题化合物55(38.9mg),总收率为53.4%(棕色固体),经^{1}H NMR证明为1:2的混合物。^{1}H NMR(400MHz,DMSO-d6)δ7.30(dd,J=9.2,6.8Hz,1H),6.85-6.69(m,2H),5.79(dd,J=12.8,6.8Hz,1H),3.40-3.32(m,2H),3.06(ddd,J=19.6,9.6,4.4Hz,1H),2.91(tt,J=11.6,3.6Hz,1H),2.68-2.57(m,4H),1.99-1.91(m,2H),1.71(dd,J=8.0,4.0Hz,2H),1.60-1.51(m,1H),1.49-1.41(m,1H),1.34(t,J=5.6Hz,4H),1.16-1.10(m,1H),0.92(s,6H)。质谱(m/z):370.3[M+H]$^+$。

[0539] 化合物56

[0540] N^1-(5-氯-2-甲基-4-(4-(三氟甲基)哌啶-1-基)苯基)环己烷-1,4-二胺

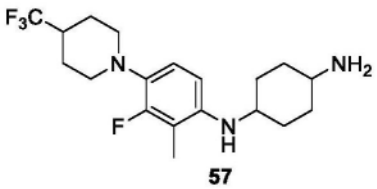
[0541] 

56

[0542] 由(4-((4-(4,4-二甲基哌啶-1-基)-3-(三氟甲基)苯基)氨基)环己基)氨基甲酸叔丁酯(88mg,0.18mmol),TFA(1mL),和DCM(10mL),根据为24的程序制备标题化合物56(13.9mg),总收率为20%(棕色固体),经^{1}H NMR证明为1:2的混合物。^{1}H NMR(400MHz,DMSO-d6)δ6.82(d,J=14.8Hz,1H),6.53(d,J=4.0Hz,1H),4.34(d,J=8.0Hz,1H),3.08(d,J=12.0Hz,3H),2.61-2.52(m,3H),2.09(s,1H),2.00(s,2H),1.98-1.91(m,3H),1.87-1.76(m,3H),1.69(d,J=6.0Hz,1H),1.56(td,J=12.4,4.0Hz,3H),1.47-1.33(m,2H),1.24(d,J=13.2Hz,1H)。质谱(m/z):390.3[M+H]$^+$。

[0543] 化合物57

[0544] N^1-(3-氟-2-甲基-4-(4-(三氟甲基)哌啶-1-基)苯基)环己烷-1,4-二胺

[0545] 

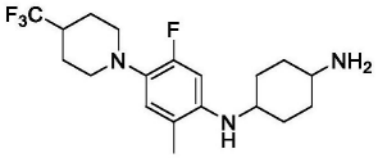
57

[0546] 由(4-((3-氟-2-甲基-4-(4-(三氟甲基)哌啶-1-基)苯基)氨基)环己基)氨基甲酸

叔丁酯(117mg,0.247mmol),TFA(1mL),和DCM(10mL),根据为24的程序制备标题化合物57(48.7mg),总收率为52.8%(紫色固体),经^{1}H NMR证明为1:2的混合物。^{1}H NMR(400MHz,DMSO-d6)δ6.70(td,J=9.2,5.6Hz,1H),6.29(dd,J=8.8,3.6Hz,1H),4.21(dd,J=108.4,7.2Hz,1H),3.21-2.79(m,4H),2.59-2.51(m,2H),2.34(d,J=11.2Hz,1H),2.01(d,J=2.0Hz,1H),1.97-1.95(m,1H),1.92(d,J=2.0Hz,2H),1.82(d,J=14.4Hz,3H),1.71(dq,J=12.8,8.8,8.0Hz,2H),1.55(ddt,J=15.2,12.4,6.4Hz,3H),1.49-1.41(m,1H),1.30-1.16(m,2H)。Mass(m/z):3 74.3[M+H]$^+$。

[0547] 化合物58

[0548] N^1-(5-氟-2-甲基-4-(4-(三氟甲基)哌啶-1-基)苯基)环己烷-1,4-二胺

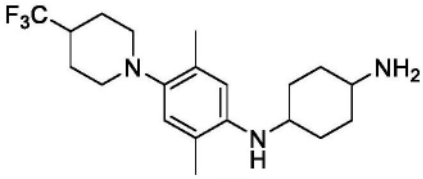
[0549] 

58

[0550] 由(4-((5-氟-2-甲基-4-(4-(三氟甲基)哌啶-1-基)苯基)氨基)环己基)氨基甲酸叔丁酯(92mg,0.194mmol),TFA(1mL),和DCM(10mL),根据为24的程序制备标题化合物58(44.1mg),总收率为60.7%(棕色固体),经^{1}H NMR证明为1:2的混合物。^{1}H NMR(400MHz,DMSO-d6)δ6.70(dd,J=14.8,9.6Hz,1H),6.34(dd,J=15.2,6.4Hz,1H),4.15(dd,J=104.4,7.4Hz,1H),3.48-3.30(m,2H),3.20-3.03(m,3H),2.87(tt,J=11.6,3.6Hz,1H),2.57(tt,J=12.0,3.2Hz,2H),2.37-2.26(m,1H),2.06(s,1H),1.96(d,J=8.0Hz,4H),1.85-1.68(m,4H),1.61-1.42(m,4H),1.32-1.15(m,2H)。质谱(m/z):374.3[M+H]$^+$。

[0551] 化合物59

[0552] N^1-(2,5-二甲基-4-(4-(三氟甲基)哌啶-1-基)苯基)环己烷-1,4-二胺

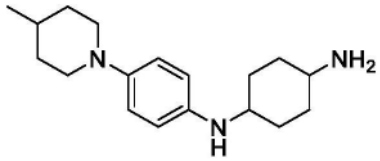
[0553] 

59

[0554] 由(4-((2,5-二甲基-4-(4-(三氟甲基)哌啶-1-基)苯基)氨基)环己基)氨基甲酸叔丁酯(137mg,0.292mmol),TFA(1mL),和DCM(10mL),根据为24的程序制备标题化合物59(57.4mg),总收率为53.2%(黄色固体),经^{1}H NMR证明为1:2的混合物。^{1}H NMR(400MHz,DMSO-d6)δ6.67(d,J=11.6Hz,1H),6.36(s,1H),3.87(d,J=75.6Hz,1H),3.07(d,J=17.6Hz,1H),2.89(d,J=10.4Hz,3H),2.58-2.50(m,2H),2.34-2.26(m,1H),2.10(d,J=3.2Hz,4H),2.06(s,2H),1.96(d,J=7.2Hz,4H),1.84-1.77(m,3H),1.71(dd,J=7.6,4.0Hz,2H),1.52(qd,J=12.5,10.4,3.6Hz,4H),1.23(d,J=12.0Hz,1H)。质谱(m/z):370.3[M+H]$^+$。

[0555] 化合物60

[0556] N^1-(4-(4-甲基哌啶-1-基)苯基)环己烷-1,4-二胺

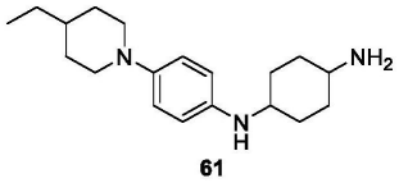
[0557] 

60

[0558] 由4-(4-甲基哌啶-1-基)苯胺(63.9mg,0.31mmol),(4-氧代环己基)氨基甲酸叔丁酯(100mg,0.47mmol)和根据为20的程序制备标题化合物60(51.9mg),收率为53.7%(棕色固体),经^{1}H NMR证明为1:1的混合物。^{1}H NMR(400MHz,DMSO-d6)δ8.29(d,J=33.4Hz,3H),7.82-7.23(m,1H),6.64(s,2H),3.38(s,3H),3.16(d,J=4.7Hz,1H),3.08(s,1H),2.94(s,1H),2.00(s,2H),1.75(s,7H),1.47(d,J=12.3Hz,2H),1.23(s,1H),0.95(d,J=4.6Hz,3H)。质谱(m/z):288.5[M+H]$^+$。

[0559] 化合物61

[0560] N^1-(4-(4-乙基哌啶-1-基)苯基)环己烷-1,4-二胺

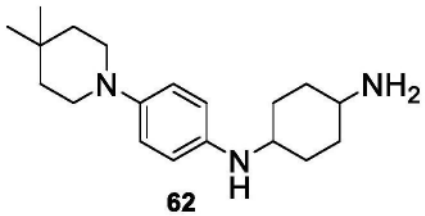
[0561] 

61

[0562] 由4-(4-乙基哌啶-1-基)苯胺(63.9mg,0.31mmol),(4-氧代环己基)氨基甲酸叔丁酯(100mg,0.47mmol)和根据为20的程序制备标题化合物61(38.5mg),收率为40.8%(棕色固体),经^{1}H NMR证明为1:1的混合物。^{1}H NMR(400MHz,DMSO-d6)δ8.19(d,J=31.7Hz,3H),7.35(d,J=94.4Hz,1H),6.56(s,3H),3.33(s,4H),3.12(d,J=5.0Hz,1H),3.04(s,1H),2.90(s,1H),1.95(s,2H),1.71(s,5H),1.55(s,1H),1.49-1.35(m,2H),1.31-1.02(m,4H),0.85(t,J=7.2Hz,3H).MS(m/z):302.5[M+H]$^+$。

[0563] 化合物62

[0564] N^1-(4-(4,4-二甲基哌啶-1-基)苯基)环己烷-1,4-二胺

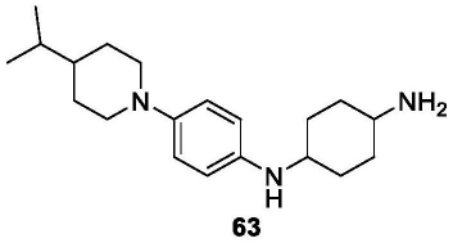
[0565] 

62

[0566] 由4-(4,4-二甲基哌啶-1-基)苯胺(59mg,0.31mmol),(4-氧代环己基)氨基甲酸叔丁酯(100mg,0.47mmol)和根据为20的程序制备标题化合物62(31.5mg),收率为35.8%(棕色固体),经^{1}H NMR证明为1:1的混合物。^{1}H NMR(400MHz,DMSO-d6)δ8.20(d,J=30.2Hz,3H),6.78(s,1H),6.56(s,2H),3.17(d,J=5.1Hz,1H),2.95(s,4H),1.99(s,2H),1.74(s,3H),1.65-1.33(m,6H),1.24(s,2H),0.96(s,6H)。质谱(m/z):302.6[M+H]$^+$。

[0567] 化合物63

[0568] N^1-(4-(4-异丙基哌啶-1-基)苯基)环己烷-1,4-二胺

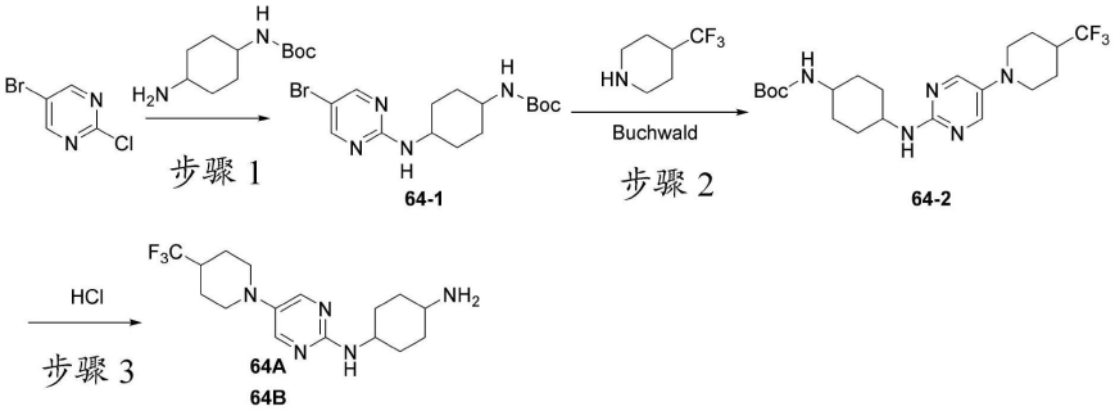
[0569] 

63

[0570] 由4-(4-异丙基哌啶-1-基)苯胺(68mg,0.31mmol),(4-氧代环己基)氨基甲酸叔丁酯(100mg,0.47mmol)和根据为20的程序制备标题化合物63(40.5mg),收率为40.4%(棕色固体),经^{1}H NMR证明为1:1的混合物。^{1}H NMR(400MHz,DMSO-d6)δ8.17-7.95(m,3H),7.28(s,2H),6.68(s,2H),3.14(s,1H),2.99(s,1H),2.23-2.13(m,1H),1.98(s,2H),1.78(dd,J=27.0,10.1Hz,7H),1.62(s,1H),1.46(s,3H),1.23(s,2H),0.89(d,J=6.5Hz,6H)。质谱(m/z):316.6[M+H]$^+$。

[0571] 化合物64

[0572] (4-((2R,6S)-2,6-二甲基四氢-2H-吡喃-4-基)苯基)氨基甲酸叔丁酯

[0573] 

[0574] 步骤1:制备(4-((5-溴嘧啶-2-基)氨基)环己基)氨基甲酸叔丁酯(64-1)

[0575] 向5-溴-2-氯嘧啶(0.5g,2.62mmol)/DMF(10mL)的溶液中添加(4-氨基环己基)氨基甲酸叔丁酯(0.67g,3.14mmol)和Cs_2CO_3(2.56g,7.86mmol),在90℃搅拌混合物过夜。用水(30mL)稀释,反应用EA(20mL)萃取三次。有机相用NaCl水溶液(20mL)洗涤三次,用硫酸钠干燥,减压浓缩并且残余物的提纯方法为:快速色谱而得到期望的产物(0.4g,41.2%)(黄色油)。质谱(m/z):371.2[M+H]$^+$。

[0576] 步骤2:制备(4-((5-(4-(三氟甲基)哌啶-1-基)嘧啶-2-基)氨基)环己基)氨基甲酸叔丁酯(64-2)

[0577] 向(4-((5-溴嘧啶-2-基)氨基)环己基)氨基甲酸叔丁酯(0.2g,0.5mmol)/二氧杂环己烷(5mL)的溶液中添加4-(三氟甲基)哌啶(320mg,2mmol),Cs_2CO_3(0.5g,1.53mmol),Ruphos(70mg,0.1mmol)和$Pd_2(dba)_3$(265mg,0.23mmol)。然后在100℃搅拌混合物12小时。用水(10mL)淬灭,反应用EA(10mL)萃取三次,用硫酸钠干燥,减压浓缩并且残余物的提纯方法为:快速色谱而得到期望的产物(0.16g,50.2%)(无色油)。质谱(m/z):248.2[M+H]$^+$。

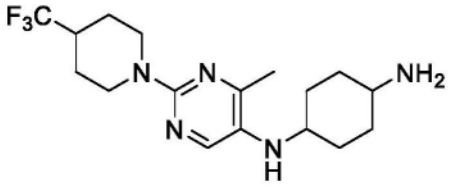
[0578] 步骤3:制备(4-((2R,6S)-2,6-二甲基四氢-2H-吡喃-4-基)苯基)氨基甲酸叔丁酯(64)

[0579] 向(4-((2R,6S)-2,6-二甲基-3,6-二氢-2H-吡喃-4-基)苯基)氨基甲酸叔丁酯(0.16g,0.36mmol)/THF(5mL)的溶液中添加HCl/二氧杂环己烷(5mL)并搅拌混合物2小时。

用$NaHCO_3$(10mL)淬灭,反应用EA(10mL)萃取三次,用硫酸钠干燥,减压浓缩并且残余物的提纯方法为:prep-HPLC(柱-Xbridge-C18 150x 21.2mm,5um;移动相:ACN-H_2O(0.1%FA),40%-60%)而得到期望的产物64A(14.5mg)(白色固体)和64B(20.2mg)(白色固体)。64A:^1H NMR(400MHz,CD_3OD)δ8.54(s,1H),8.10(s,2H),3.70-3.66(m,1H),3.44(d,J=12.0Hz,2H),3.18-3.03(m,1H),2.68(m,2H),2.34-2.18(m,1H),2.19-2.02(m,4H),1.97(d,J=12.8Hz,2H),1.71(m,2H),1.52(m,2H),1.44-1.29(m,2H)。质谱(m/z):344.2$[M+H]^+$。HPLC:Rt:4.333min(柱:XBRIDGE 2.1*50mm,3.5um;移动相:H_2O(0.05%TFA)ACN(0.05%TFA),ACN由0%至60%在7分钟内,7-8min,ACN由60%至100%;0.8mL/min).64B:^1H NMR(400MHz,CD_3OD)δ=8.53(s,1H),8.13(s,2H),3.95(s,1H),3.46(d,J=12.0Hz,2H),3.27-3.19(m,1H),2.74-2.63(m,2H),2.34-2.21(m,1H),1.99-1.86(m,6H),1.81-1.66(m,6H)。质谱(m/z):344.2$[M+H]^+$。HPLC:Rt:4.488min(柱:XBRIDGE 2.1*50mm,3.5um;移动相:H_2O(0.05%TFA)ACN(0.05%TFA),ACN由0%至60%在7分钟内,7-8min,ACN由60%至100%;0.8mL/min)。

[0580] 化合物65

[0581] N^1-(4-甲基-2-(4-(三氟甲基)哌啶-1-基)嘧啶-5-基)环己烷-1,4-二胺

[0582] 

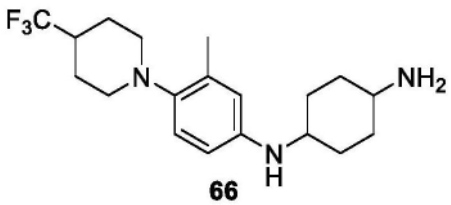
65A

65B

[0583] 根据为64的程序,由向(4-((4-甲基-2-(4-(三氟甲基)哌啶-1-基)嘧啶-5-基)氨基)环己基)氨基甲酸叔丁酯(53mg,0.12mmol),HCl/二氧杂环己烷(4N;3mL)和CH_2Cl_2(3mL)的溶液中制备标题化合物65A(6.2mg,13%)(白色固体)和65B(11.5mg,28%)(白色固体)。65A:^1H NMR(400MHz,CD_3OD)δ7.77(s,1H),4.67(d,J=13.3Hz,2H),2.94-2.88(m,1H),2.80(td,J=13.1,2.4Hz,2H),2.51-2.34(m,1H),2.34(s,3H),1.87(d,J=1.4Hz,2H),1.79-1.68(m,6H),1.65-1.56(m,2H),1.53-1.46(m,3H)。质谱(m/z):358.2$[M+H]^+$。HPLC:Rt:3.792min(柱:XBRIDGE 2.1*50mm,3.5um;移动相:H_2O(0.05%TFA)/ACN(0.05%TFA),ACN由0%至60%在7分钟内,7-8min,ACN由60%至100%;0.8mL/min)。65B:^1H NMR(400MHz,CD_3OD)δ7.78(s,1H),4.73-4.61(m,2H),3.12-3.00(m,1H),2.86-2.77(m,2H),2.76-2.67(m,1H),2.48-2.34(m,1H),2.29(s,3H),2.12-1.99(m,2H),1.99-1.83(m,4H),1.53-1.46(m,2H),1.36-1.25(m,4H)。质谱(m/z):358.2$[M+H]^+$。HPLC:Rt:3.855min(柱:XBRIDGE 2.1*50mm,3.5um;移动相:H_2O(0.05%TFA)/ACN(0.05%TFA),ACN由0%至60%在7分钟内,7-8min,ACN由60%至100%;0.8mL/min)。

[0584] 化合物66

[0585] N^1-(3-甲基-4-(4-(三氟甲基)哌啶-1-基)苯基)环己烷-1,4-二胺

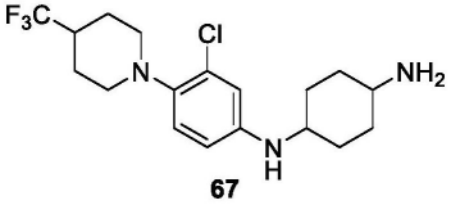
[0586] 

66

[0587] 由(4-((3-甲基-4-(4-(三氟甲基)哌啶-1-基)苯基)氨基)环己基)氨基甲酸叔丁酯(128mg,0.281mmol),TFA(1mL),和DCM(10mL),根据为24的程序制备标题化合物66(53.1mg),总收率为53.2%(紫色固体),经^{1}H NMR证明为1:2的混合物。^{1}H NMR(400MHz,DMSO-d6)δ6.77(t,J=7.6Hz,1H),6.54-6.28(m,2H),3.08-2.97(m,1H),2.93-2.86(m,2H),2.56-2.48(m,2H),2.34-2.25(m,1H),2.08(dd,J=8.4,2.3Hz,3H),1.96(dt,J=13.2,7.2Hz,3H),1.85-1.65(m,6H),1.61-1.35(m,5H)。质谱(m/z):356.3[M+H]$^+$。

[0588] 化合物67

[0589] N^1-(3-氯-4-(4-(三氟甲基)哌啶-1-基)苯基)环己烷-1,4-二胺

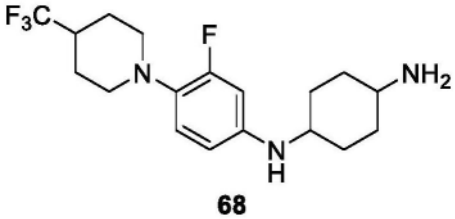
[0590] 

67

[0591] 由(4-((3-氯-4-(4-(三氟甲基)哌啶-1-基)苯基)氨基)环己基)氨基甲酸叔丁酯(80mg,0.168mmol),TFA(1mL),和DCM(10mL),根据为24的程序制备标题化合物67(33.1mg),总收率为52.4%(紫色固体),经^{1}H NMR证明为1:2的混合物。^{1}H NMR(400MHz,DMSO-d6)δ6.88(dd,J=8.8,6.4Hz,1H),6.62(dd,J=21.2,2.4Hz,1H),6.48(ddd,J=14.8,8.7,2.7Hz,1H),5.50(d,J=6.4Hz,1H),3.32(t,J=4.4Hz,1H),3.12-2.98(m,3H),2.96-2.81(m,1H),2.53(tt,J=11.6,2.4Hz,2H),2.38-2.27(m,1H),1.92(dt,J=17.2,13.6Hz,3H),1.84-1.65(m,5H),1.59-1.40(m,4H)。质谱(m/z):376.3[M+H]$^+$。

[0592] 化合物68

[0593] N^1-(3-氟-4-(4-(三氟甲基)哌啶-1-基)苯基)环己烷-1,4-二胺

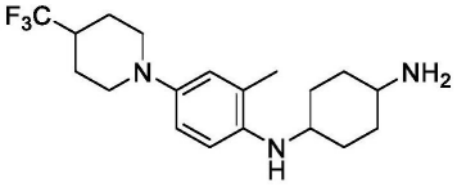
[0594] 

68

[0595] 由(4-((3-氟-4-(4-(三氟甲基)哌啶-1-基)苯基)氨基)环己基)氨基甲酸叔丁酯(137mg,0.299mmol),TFA(1mL),和DCM(10mL),根据为24的程序制备标题化合物68(84.4mg),总收率为78.8%(紫色固体),经^{1}H NMR证明为1:2的混合物。^{1}H NMR(400MHz,DMSO-d6)δ6.85-6.72(m,1H),6.44-6.23(m,2H),5.46(s,1H),3.35-3.27(m,1H),3.12(d,J=11.4Hz,2H),3.02(s,1H),2.90(s,1H),2.61-2.51(m,2H),2.39-2.26(m,1H),2.02-1.89(m,3H),1.85-1.65(m,5H),1.63-1.50(m,3H),1.50-1.33(m,2H)。质谱(m/z):360.3[M+H]$^+$。

[0596] 化合物69

[0597] N^1-(2-甲基-4-(4-(三氟甲基)哌啶-1-基)苯基)环己烷-1,4-二胺

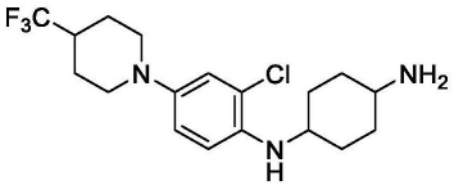
[0598] 

69

[0599] 由(4-((2-甲基-4-(4-(三氟甲基)哌啶-1-基)苯基)氨基)环己基)氨基甲酸叔丁酯(132mg,0.290mmol),TFA(1mL),和DCM(10mL),根据为24的程序制备标题化合物69(84.4mg),总收率为81.9%(紫色固体),经^{1}H NMR证明为1:2的混合物。^{1}H NMR(400MHz,DMSO-d6)δ6.83-6.56(m,2H),6.46(s,1H),3.99-3.67(m,1H),3.45(d,J=29.6Hz,3H),3.05(s,1H),2.89(s,1H),2.34(s,1H),2.15-1.89(m,6H),1.88-1.65(m,6H),1.63-1.35(m,5H)。质谱(m/z):356.3[M+H]$^+$。

[0600] 化合物70

[0601] N^1-(2-氯-4-(4-(三氟甲基)哌啶-1-基)苯基)环己烷-1,4-二胺

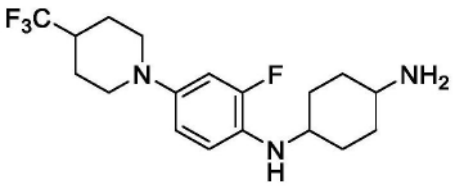
[0602] 

70

[0603] 由(4-((3-氯-4-(4-(三氟甲基)哌啶-1-基)苯基)氨基)环己基)氨基甲酸叔丁酯(153mg,0.322mmol),TFA(1mL),和DCM(10mL),根据为24的程序制备标题化合物70(101.0mg),总收率为83.5%(紫色固体),经^{1}H NMR证明为1:2的混合物。^{1}H NMR(400MHz,DMSO-d6)δ6.88(dd,J=13.2,2.7Hz,1H),6.79(ddd,J=9.6,6.8,2.8Hz,1H),6.68(dd,J=9.2,4.8Hz,1H),4.17(dd,J=40.4,8.0Hz,1H),3.49-3.43(m,2H),3.18-3.05(m,1H),2.88(s,1H),2.53(ddd,J=12.8,3.6,2.0Hz,2H),2.39-2.30(m,1H),2.04-1.88(m,3H),1.85-1.60(m,6H),1.59-1.38(m,4H)。质谱(m/z):376.3[M+H]$^+$。

[0604] 化合物71

[0605] N^1-(2-氟-4-(4-(三氟甲基)哌啶-1-基)苯基)环己烷-1,4-二胺

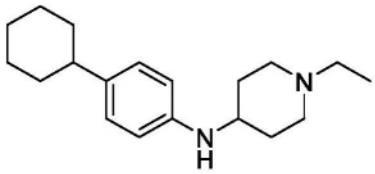
[0606] 

71

[0607] 由(4-((3-氟-4-(4-(三氟甲基)哌啶-1-基)苯基)氨基)环己基)氨基甲酸叔丁酯(107mg,0.233mmol),TFA(1mL),和DCM(10mL),根据为24的程序制备标题化合物71(64.2mg),总收率为76.2%(紫色固体),经^{1}H NMR证明为1:2的混合物。^{1}H NMR(400MHz,DMSO-d6)δ6.67(td,J=28.8,16.4Hz,3H),4.57-4.11(m,1H),3.48(t,J=9.6Hz,2H),3.07(s,1H),2.87(s,1H),2.59-2.48(m,2H),2.37(dt,J=22.4,7.6Hz,1H),2.02-1.86(m,3H),1.85-1.65(m,4H),1.60-1.36(m,4H),1.20(q,J=12.4Hz,2H)。质谱(m/z):360.3[M+H]$^+$。

[0608] 化合物72

[0609] N-(4-环己基苯基)-1-乙基哌啶-4-胺

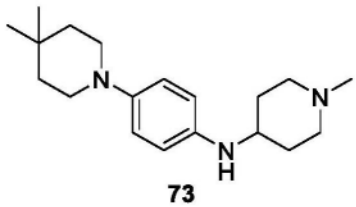
[0610] 

72

[0611] 由4-环己基苯胺(100mg,0.57mmol),DCE(5mL),1-乙基哌啶-4-酮(87mg,0.69mmol),乙酸(3.42mg,0.057mmol),和三乙酰氧基硼氢化钠(363mg,1.71mmol),根据为5的程序获得标题化合物72(115mg,70.5%)(棕色油)。^{1}H NMR(300MHz,DMSO-d6)δ=6.87(d,J=8.4Hz,2H),6.46(d,J=8.4Hz,2H),5.15(s,1H),2.80(d,J=11.4Hz,2H),2.52-2.47(m,2H),2.33-2.23(m,2H),1.97(t,J=11.4Hz,2H),1.83(s,1H),1.70(d,J=11.4Hz,5H),1.27(m,7H),0.97(t,J=7.2Hz,3H)。质谱(m/z):287.3[M+H]$^+$。

[0612] 化合物73

[0613] N-(4-(4,4-二甲基哌啶-1-基)苯基)-1-甲基哌啶-4-胺

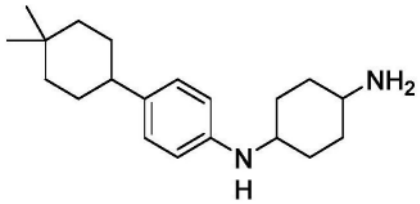
[0614] 

73

[0615] 由4-(4,4-二甲基环己基)苯胺(50mg,0.246mmol),1-甲基哌啶-4-酮(33mg,0.295mmol),AcOH(0.1mL),NaBH(OAc)$_3$(104mg,0.493mmol)和DCE(10mL),根据为5的程序制备标题化合物73(6.1mg),总收率为8.1%(粉色固体),经^{1}H NMR证明为1:2的混合物。^{1}H NMR(400MHz,氯仿-d)δ6.96-6.90(m,2H),6.54-6.47(m,2H),5.44-5.27(m,1H),3.12(d,J=11.6Hz,3H),2.68(s,2H),2.22(tt,J=10.0,5.2Hz,1H),1.98(dt,J=14.4,4.0Hz,2H),1.64-1.37(m,9H),1.31-1.21(m,3H),0.93(d,J=8.4Hz,6H)。质谱(m/z):301.3[M+H]$^+$。

[0616] 化合物74

[0617] N^1-(4-(4,4-二甲基环己基)苯基)环己烷-1,4-二胺

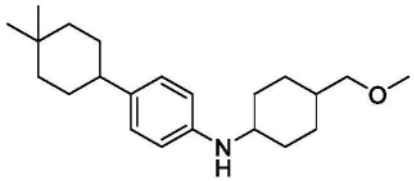
[0618] 

74

[0619] 由(4-((4-(4,4-二甲基环己基)苯基)氨基)环己基)氨基甲酸叔丁酯(180mg,0.45mmol)和HCl/1,4-二氧杂环己烷(10mL,4N),根据为37的程序制备标题化合物74(130mg,62.8%)(白色固体)。^{1}H NMR(400MHz,DMSO-d6)δ8.10(brs,2H),7.36(brs,3H),3.80-3.57(m,3H),3.49-3.25(m,1H),2.96(br,1H),2.44-2.37(m,1H),2.04-1.63(m,4H),1.61-1.46(m,4H),1.31(m,6H),0.91(d,J=12.0Hz,6H).MS(m/z)301.3。

[0620] 化合物75

[0621] N-(4-环己基苯基)-1-乙基哌啶-4-胺

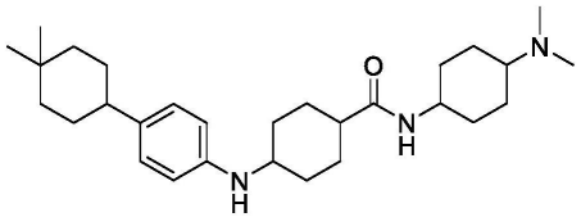
[0622] 

75

[0623] 由4-(甲氧基甲基)环己烷-1-酮(84mg,0.59mmol),DCE(5mL),4-(4,4-二甲基环己基)苯胺(100mg,0.49mmol)和乙酸(2.9mg,0.059mmol),根据为5的程序制备标题化合物75(23mg,14.2%)(黄色油)。^{1}H NMR(300MHz,CDCl3)δ7.07-6.98(m,2H),6.59-6.50(m,2H),3.35(d,J=2.0Hz,3H),3.24(dd,J=12.3Hz,9.9Hz,2H),2.33-2.25(m,1H),1.87-1.84(d,J=6.9Hz,1H),1.74-1.54(m,8H),1.47(d,J=14.4Hz,2H),1.38-1.24(m,4H),1.09(d,J=9.9Hz,2H),0.96-0.94(m,6H)。质谱(m/z):330.3[M+H]$^+$。

[0624] 化合物76

[0625] (4-(二甲基氨基)环己基)-4-((4-(4,4-二甲基环己基)苯基)氨基)环己烷-1-甲酰胺

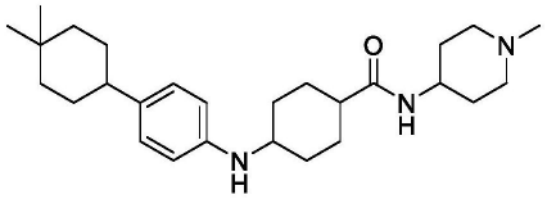
[0626] 

76A
76B

[0627] 由4-((4-(4,4-二甲基环己基)苯基)氨基)环己烷-1-甲酸(15mg,0.046mmol),N^1,N^1-二甲基环己烷-1,4-二胺(7.1mg,0.05mmol),DIEA(16.5mg,0.05mmol)/DMF(1mL)和DMT-MM(14.8mg,0.05mmol),根据为1的程序制备期望的产物76A(Rt=4.89min;4.2mg,20%)(白色固体)和76B(Rt=4.78min;4.0mg,19%)(白色固体),其提纯方法为:制备HPLC(柱:X Select-CSH-Prep 5μm OBD,19*150mm;ACN/水(5‰TFA)=10%-30%-95%-95%-10%,0-7min-7.5min-8.5min-10.0min).76A:^{1}H NMR(400MHz,DMSO-d6)δ8.06(d,J=7.6Hz,1H),7.77(d,J=7.6Hz,1H),6.93(m,2H),6.49(m,2H),3.93-3.76(m,1H),3.63-3.54(m,1H),3.18-3.04(m,2H),2.68(d,J=4.8Hz,6H),2.23(m,1H),2.03-1.63(m,10H),1.58-1.36(m,8H),1.35-1.18(m,4H),1.08(m,2H),0.93(d,J=8.4Hz,6H)。质谱(m/z):454.3[M+H]$^+$。76B:^{1}H NMR(400MHz,DMSO-d6)δ8.05(d,J=7.6Hz,1H),7.70(d,J=7.6Hz,1H),6.93(m,2H),6.48(m,2H),3.82(m,1H),3.71(s,1H),3.55-3.42(m,1H),3.13(m,1H),2.67(d,J=4.8Hz,6H),2.22(m,1H),2.05-1.65(m,10H),1.91-1.63(m,8H),1.59-1.01(m,6H),0.93(d,J=8.4Hz,6H)。质谱(m/z):454.3[M+H]$^+$。

[0628] 化合物77

[0629] 4-((4-(4,4-二甲基环己基)苯基)氨基)-N-(1-甲基哌啶-4-基)环己烷-1-甲酰胺

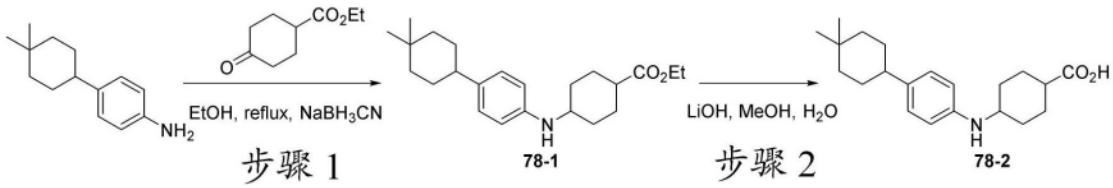
[0630] 

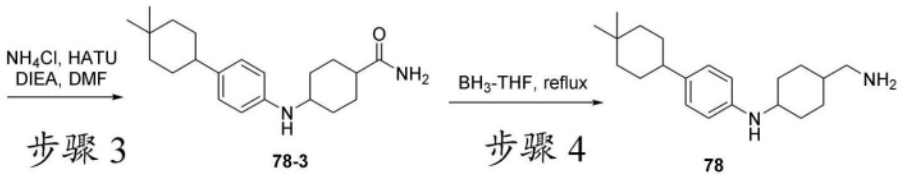
77

[0631] 由4-((4-(4,4-二甲基环己基)苯基)氨基)环己烷-1-甲酸(15mg,0.046mmol),1-甲基哌啶-4-胺(5.7mg,0.05mmol),DIEA(16.5mg,0.05mmol)和DMT-MM(14.8mg,0.05mmol),根据为1的程序制备标题化合物77(7.2mg),总收率为37%(黄色固体),经^{1}H NMR证明为1:2的混合物。^{1}H NMR(400MHz,DMSO-d6)δ8.11(d,J=8.0Hz,1H),7.96(d,J=8.0Hz,1H),6.93(m,2H),6.51(m,2H),3.93(m,1H),3.82(m,1H),3.72(m,1H),3.65-3.55(m,1H),3.31-2.91(m,3H),2.69(s,1H),2.69(s,2H),2.28-2.13(m,1H),2.13-1.63(m,8H),1.62-1.37(m,6H),1.36-1.17(m,4H),1.14-1.05(m,2H),0.94(s,3H),0.92(s,3H)。质谱(m/z):426.2[M+H]$^+$。

[0632] 化合物78

[0633] N-(4-(氨基甲基)环己基)-4-(4,4-二甲基环己基)苯胺

[0634] 



[0635] reflux:回流

[0636] 步骤1:制备4-((4-(4,4-二甲基环己基)苯基)氨基)环己烷-1-甲酸乙酯(78-1)

[0637] 在90℃搅拌4-(4,4-二甲基环己基)苯胺(0.4g,1.97mmol)和4-氧代环己烷-1-甲酸乙酯(0.335g,1.97mmol)/EtOH的混合物1小时。然后向混合物中添加$NaBH_3CN$(0.37g,5.91mmol)。在25℃搅拌混合物4小时。将混合物用H_2O淬灭并用EA萃取。浓缩有机相并且通过硅胶柱色谱提纯,洗脱用PE/EA=2:1而得到78-1(黄色油)(0.36g,51%)。质谱(m/z):358.3[M+H]$^+$。

[0638] 步骤2:制备4-((4-(4,4-二甲基环己基)苯基)氨基)环己烷-1-甲酸(78-2)

[0639] 在25℃向78-1(0.36g,1mmol)/MeOH(10mL)的溶液中添加$LiOH.H_2O$(0.13g,3mmol)。在25℃搅拌反应6小时。用1N HCl将混合物的pH调节到3,用EA萃取。浓缩有机相而得到78-2(黄色油)(0.28g,85.1%)。质谱(m/z):329.9[M+H]$^+$。

[0640] 步骤3:制备4-((4-(4,4-二甲基环己基)苯基)氨基)环己烷-1-甲酰胺(78-3)

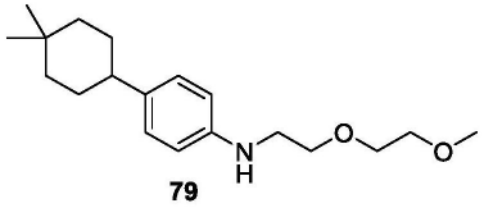
[0641] 在25℃向78-2(0.18g,0.55mmol)和HATU(0.21g,0.55mmol)/DMF(5mL)的溶液中添加NH_4Cl(87mg,1.65mmol)和DIEA(0.21g,1.65mmol)。在25℃搅拌反应16小时。将混合物用EA稀释并且用水洗涤。浓缩有机相并且通过硅胶柱色谱提纯,洗脱用PE/EA=1:1而得到78-3(黄色固体)(0.11g,61%)。质谱(m/z):328.9[M+H]$^+$。

[0642] 步骤4:制备N-(4-(氨基甲基)环己基)-4-(4,4-二甲基环己基)苯胺(78)

[0643] 向78-3(0.15g,0.46mmol)/THF(1mL)的溶液中添加BH_3-THF(10mL)。在70℃搅拌反应16小时。将混合物用MeOH和水淬灭,浓缩并用EA萃取。浓缩有机相并通过prep-TLC提纯,洗脱用DCM:MeOH=9:1(0.5%$NH_3.H_2O$)而得到78(82mg,57.3%)(黄色固体)。^{1}H NMR(300MHz,CD_3OD)δ6.99(d,J=8.4Hz,2H),6.69-6.53(m,2H),3.56(d,J=5.7Hz,2H),2.90-2.87(m,1H),2.29-2.11(m,1H),1.77-1.13(m,17H),0.95(d,J=12Hz,6H)。质谱(m/z):315.0$[M+H]^+$。

[0644] 化合物79

[0645] 4-(4,4-二甲基环己基)-N-(2-(2-甲氧基乙氧基)乙基)苯胺

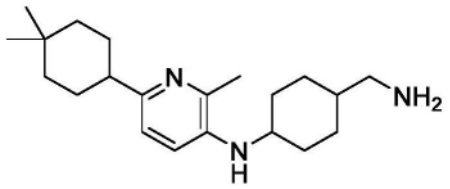
[0646] 

79

[0647] 由4-(4,4-二甲基环己基)苯胺(50mg,0.25mmol),1-碘-2-(2-甲氧基乙氧基)乙烷(56mg,0.25mmol)和碳酸钾(41mg,0.3mmol),根据为12的程序制备标题化合物79(34.4mg),收率为41.9%(淡黄色粉末)。^{1}H NMR(400MHz,DMSO-d6)δ7.19(s,2H),7.00(s,2H),3.65-3.39(m,5H),3.24(s,3H),2.35(s,1H),1.98(dt,J=13.0,7.0Hz,1H),1.60-1.50(m,4H),1.43(d,J=12.9Hz,2H),1.30(t,J=8.8Hz,2H),1.23(s,2H),0.95(s,3H),0.92(s,3H)。质谱(m/z):306.4$[M+H]^+$。

[0648] 化合物80

[0649] N-(4-(氨基甲基)环己基)-6-(4,4-二甲基环己基)-2-甲基吡啶-3-胺

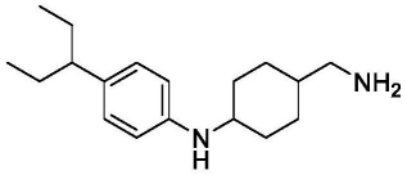
[0650] 

80

[0651] 由((4-((6-(4,4-二甲基环己基)-2-甲基吡啶-3-基)氨基)环己基)甲基)氨基甲酸叔丁酯(16.0mg,37.2umol)和TFA(3mL),根据为24的程序制备标题化合物80(3.0mg),总收率为3.0%(黄色固体),经^{1}H NMR证实为1:1混合物。^{1}H NMR(400MHz,DMSO-d6)δ7.91(s,3H),7.20(s,2H),2.81-2.76(m,1H),2.52(s,3H),2.46-2.38(m,2H),1.99-1.92(m,1H),1.86-1.73(m,2H),1.67-1.51(m,9H),1.47-1.41(m,1H),1.33-1.25(m,3H),1.13-1.05(m,1H),0.95(d,J=9.4Hz,6H)。质谱(m/z):330.4$[M+H]^+$。

[0652] 化合物81

[0653] N-(4-(氨基甲基)环己基)-4-(戊烷-3-基)苯胺

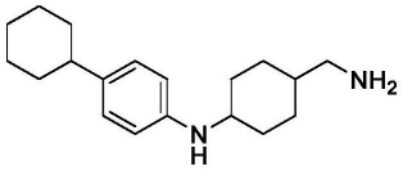
[0654] 

81A
81B

[0655] 由((4-((4-(戊烷-3-基)苯基)氨基)环己基)甲基)氨基甲酸叔丁酯(96mg,0.277mmol),DCM(10mL)和TFA(1mL),根据为24的程序制备期望的产物81A(Rt=9.0min)(白色固体)(8.2mg,11.4%)和81B(Rt=10.4min)(白色固体)(34.1mg,48.8%),其提纯方法为:prep HPLC(溶剂体系(柱:X Select-CSH-Prep 5μm OBD,19*150mm;ACN/水(0.5%TFA)=15%-25%-95%-95%-15%,0-10min-10.5min-11.5min-13min)。81A:^{1}H NMR(400MHz,DMSO-d6)δ7.81(s,2H),7.21-6.93(m,4H),2.69-2.58(m,2H),2.25(s,1H),1.90(d,J=12.4Hz,2H),1.79(d,J=12.8Hz,2H),1.67-1.36(m,5H),1.26(s,2H),0.98(q,J=12.4Hz,2H),0.66(t,J=7.2Hz,6H)。质谱(m/z):275.3[M+H]$^+$。81B:^{1}H NMR(400MHz,DMSO-d6)δ7.86(s,2H),7.21-6.93(m,4H),3.44(td,J=7.2,3.6Hz,1H),2.75(p,J=6.0Hz,2H),2.25(dp,J=9.2,5.2Hz,1H),1.75(s,1H),1.66-1.36(m,12H),0.66(t,J=7.2Hz,6H)。质谱(m/z):275.3[M+H]$^+$。

[0656] 化合物82

[0657] N-(4-(氨基甲基)环己基)-4-环己基苯胺

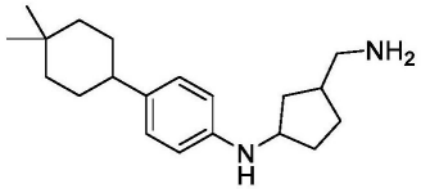
[0658] 

82A
82B

[0659] 由((4-((4-环己基苯基)氨基)环己基)甲基)氨基甲酸叔丁酯(169mg,0.438mmol),DCM(10mL)和TFA(1mL),根据为24的程序,制备期望的产物82A(Rt=8.3min)(黄色油)(13.4mg,10.7%)和82B(Rt=10.7min)(白色固体)(57.6mg,46.0%),其提纯方法为:prep HPLC(溶剂体系(ACN/水(0.5%TFA)=15%-25%-95%-95%-15%,0-13min-13.5min-14.5min-16min)。82A:^{1}H NMR(400MHz,DMSO-d6)δ7.90-7.67(m,3H),7.16(s,2H),6.99(s,2H),3.19(s,1H),2.63(p,J=6.0Hz,2H),2.41(s,1H),1.91(dd,J=13.2,4.0Hz,2H),1.80-1.69(m,6H),1.69-1.62(m,1H),1.49(ddh,J=12.0,7.9,4.4Hz,1H),1.32(dd,J=12.0,9.2Hz,4H),1.27-1.18(m,3H),0.97(qd,J=13.2,3.2Hz,2H)。质谱(m/z):287.3[M+H]$^+$。82B:^{1}H NMR(400MHz,DMSO-d6)δ7.81(s,3H),7.14(s,2H),6.96(s,2H),3.42(dq,J=7.2,4.0Hz,1H),2.74(q,J=5.6,5.2Hz,2H),2.41(d,J=11.6Hz,1H),1.79-1.44(m,15H),1.31(t,J=10.4Hz,4H)。质谱(m/z):287.3[M+H]$^+$。

[0660] 化合物83

[0661] N-(3-(氨基甲基)环戊基)-4-(4,4-二甲基环己基)苯胺

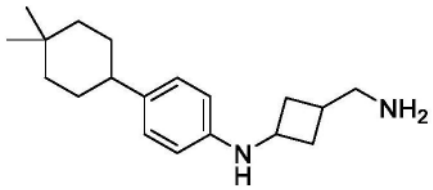
[0662] 

83

[0663] 由4-(4,4-二甲基环己基)苯胺(50mg,0.25mmol),((3-氧代环戊基)甲基)氨基甲酸叔丁酯(79mg,0.37mmol)和$NaBH(OAc)_3$(104mg,0.49mmol),根据为20的程序制备标题化合物83(18.1mg),收率为24.5%(淡黄色粉末),经^1H NMR证明为1:1的混合物。^1H NMR(400MHz,DMSO-d6)δ7.91(s,2H),6.95(d,J=7.9Hz,2H),6.49(s,2H),5.54-5.27(m,1H),3.78-3.64(m,1H),2.77(dd,J=12.5,6.3Hz,2H),2.25(dq,J=12.7,7.1Hz,2H),2.08-1.96(m,1H),1.89(ddd,J=14.4,9.2,5.6Hz,1H),1.83-1.72(m,1H),1.53(dd,J=10.4,3.4Hz,4H),1.50-1.38(m,4H),1.30(dd,J=12.1,5.2Hz,2H),1.11(q,J=8.5Hz,1H),0.95(s,3H),0.93(s,3H)。质谱(m/z):301.6$[M+H]^+$。

[0664] 化合物84

[0665] N-(3-(氨基甲基)环丁基)-4-(4,4-二甲基环己基)苯胺

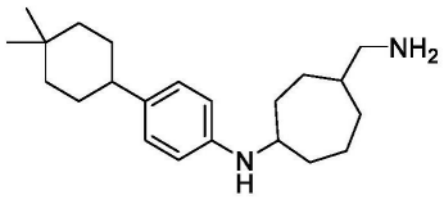
[0666] 

84

[0667] 由3-((4-(4,4-二甲基环己基)苯基)氨基)环丁烷-1-甲酰胺,THF,和AlLiH4,根据为23的程序制备标题化合物84(94mg,78.2%)(灰白色固体),经^1H NMR证明为1:0.43的混合物。^1H NMR(400MHz,DMSO-d6)δ7.89(s,4H),6.94(d,J=8.3Hz,3H),6.45-6.36(m,3H),5.68(dd,J=6.6,0.0Hz,1H),5.59(d,J=7.1Hz,0.43H),3.89(h,J=7.0Hz,1H),3.67(q,J=7.4Hz,0.43H),2.96(d,J=7.9Hz,2H),2.82(d,J=7.3Hz,1H),2.49-2.38(m,3H),2.21(td,J=11.9,5.5Hz,4H),2.09-1.85(m,3H),1.58-1.46(m,7H),1.42(d,J=13.8Hz,4H),1.33-1.20(m,6H),0.93(d,J=8.3Hz,9H)。质谱(m/z):287.3$[M+H]^+$。

[0668] 化合物85

[0669] 4-(氨基甲基)-N-(4-(4,4-二甲基环己基)苯基)环庚烷-1-胺

[0670] 

85

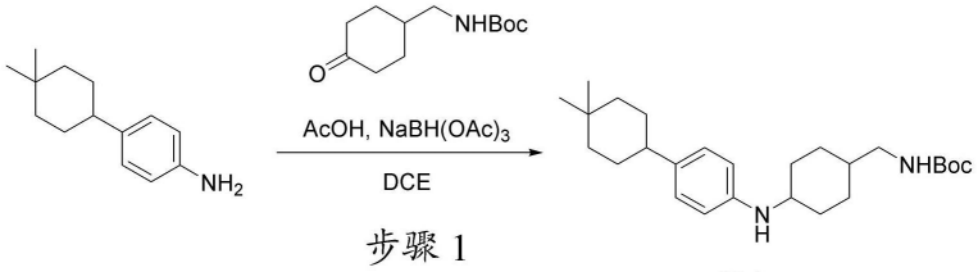
[0671] 由4-(4,4-二甲基环己基)苯胺(100mg,0.49mmol),4-氧代环庚烷-1-甲酸(92mg,0.59mmol),根据为23的程序以三步制备标题化合物85(15.8mg),总收率为9.78%(白色粉末),经^1H NMR证明为1:1的混合物。^1H NMR(400MHz,DMSO-d6)δ7.73(s,3H),7.20(s,2H),6.94(s,1H),2.70-2.58(m,2H),2.35(s,1H),2.02-1.90(m,1H),1.83(s,1H),1.74(d,J=

14.5Hz,3H),1.63-1.48(m,7H),1.47-1.37(m,3H),1.29(td,J＝12.6,6.3Hz,3H),1.10(t,J＝13.6Hz,1H),0.95(s,3H),0.93(s,3H)。质谱(m/z):329.6[M+H]$^+$。

[0672] 化合物86

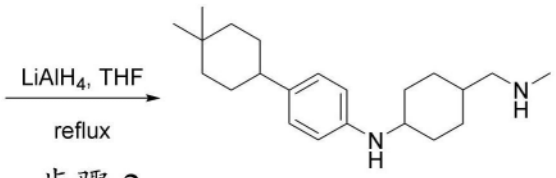
[0673] 4-(4,4-二甲基环己基)-N-(4-((甲基氨基)甲基)环己基)苯胺

[0674]



步骤 1

86-1



步骤 2

86

[0675] reflux:回流

[0676] 步骤1:制备((4-((4-(4,4-二甲基环己基)苯基)氨基)环己基)甲基)氨基甲酸叔丁酯(86-1)

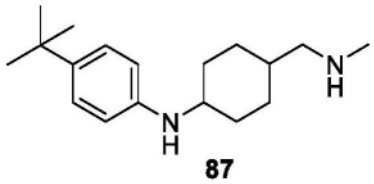
[0677] 在室温将4-(4,4-二甲基环己基)苯胺(101.5mg,0.5mmol),((4-氧代环己基)甲基)氨基甲酸叔丁酯(136mg,0.6mmol)和乙酸(0.029mL,0.5mmol)/DCE(5mL)的混合物搅拌1小时。其后添加211mg(1mmol)的三乙酰氧基硼氢化钠并搅拌混合物过夜。向混合物中,添加饱和$NaHCO_3$水溶液并且用乙酸乙酯萃取混合物。将合并的有机层用$MgSO_4$干燥并蒸发。混合物的提纯方法:prep-TLC而得到中间体(176mg,85%)(白色固体)。质谱(m/z):415.2[M+H]$^+$。

[0678] 步骤2:制备4-(4,4-二甲基环己基)-N-(4-((甲基氨基)甲基)环己基)苯胺(86)

[0679] 将((4-((4-(4,4-二甲基环己基)苯基)氨基)环己基)甲基)氨基甲酸叔丁酯(41mg,0.1mmol)/THF(1mL)缓慢滴加到$LiAlH_4$(14.8mg,0.4mmol)/THF(1mL)的悬浮液。将混合物加热至回流并且搅拌过夜。向混合物中,添加饱和$NaHCO_3$水溶液并且用乙酸乙酯萃取混合物。将合并的有机层用$MgSO_4$干燥并蒸发。混合物的提纯方法:prep-TLC而得到标题化合物(16.2mg,49%)(玫瑰棕色固体),由^{1}H NMR证明为1:2的混合物。^{1}H NMR(400MHz,DMSO-d6)δ8.92(s,2H),6.94(d,J＝8.8Hz,2H),6.54(d,J＝8.8Hz,2H),3.41(s,1H),3.36(s,3H),2.78(m,1.3H),2.72(m,0.6H),2.20(m,1H),1.97(m,0.6H),1.81(m,1.3H),1.68-1.35(m,12H),1.26(m,2H),1.07(m,1H),0.93(s,3H),0.91(s,3H)。质谱(m/z):329.3[M+H]$^+$。

[0680] 化合物87

[0681] 4-(叔丁基)-N-(4-((甲基氨基)甲基)环己基)苯胺

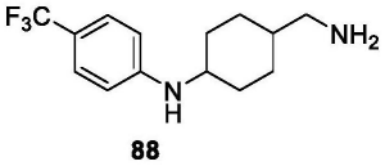
[0682] 

87

[0683] 由((4-((4-(叔丁基)苯基)氨基)环己基)甲基)氨基甲酸叔丁酯(36mg,0.1mmol),和$LiAlH_4$(14.8mg,0.4mmol),根据为86的程序制备标题化合物87(16.4mg),总收率为60%(黄色固体),经^{1}H NMR证明为1:3的混合物。^{1}H NMR(400MHz,甲醇-d4)δ7.35-7.15(m,2H),6.87-6.66(m,2H),3.55(m,0.7H),3.22(m,0.3H),2.96(d,J=6.8Hz,1.5H),2.89(d,J=6.4Hz,0.5H),2.71(s,3H),2.16-1.45(m,8H),1.25(s,9H)。质谱(m/z):275.4$[M+H]^+$。

[0684] 化合物88

[0685] N-(4-(氨基甲基)环己基)-4-(三氟甲基)苯胺

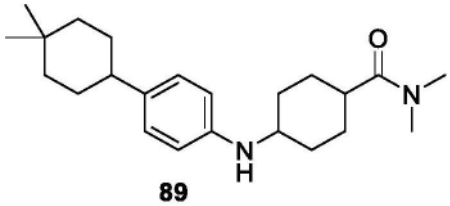
[0686] 

88

[0687] 由((4-((4-(三氟甲基)苯基)氨基)环己基)甲基)氨基甲酸叔丁酯(74mg,0.2mmol)和TFA(0.15mL,2mmol),根据为24的程序制备期望的产物(白色固体)(35mg,65%),经^{1}H NMR证明为1:2的混合物。^{1}H NMR(400MHz,DMSO-d6)δ7.82(s,3H),7.34-7.29(m,2H),6.69-6.58(m,2H),3.50(m,0.7H),3.16(m,0.3H),2.68(d,J=6.0Hz,1.4H),2.64(d,J=6.8Hz,0.7H),1.96(m,1H),1.83-1.07(m,8H)。质谱(m/z):273.3$[M+H]^+$。

[0688] 化合物89

[0689] 4-((4-(4,4-二甲基环己基)苯基)氨基)-N,N-二甲基环己烷-1-甲酰胺

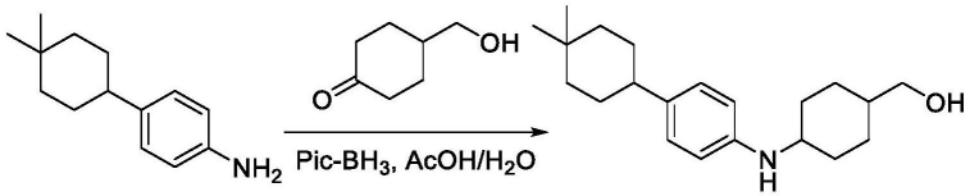
[0690] 

89

[0691] 由4-((4-(4,4-二甲基环己基)苯基)氨基)环己烷-1-甲酸(33mg,0.1mmol),二甲胺(0.45mg,0.15mmol),DIEA(0.045mL,0.26mmol)和DMT-MM(76mg,0.26mmol),根据为1的程序制备标题化合物89(5.4mg),总收率为14%(白色固体),经^{1}H NMR证明为1:3的混合物。^{1}H NMR(400MHz,DMSO-d6)δ6.92(d,J=8.8Hz,2H),6.52(d,J=8.8Hz,0.7H),6.48(d,J=8.8Hz,1.3H),3.44(m,1H),3.09(m,1H),3.01(s,3H),2.80(s,3H),1.99(m,1H),1.72-1.36(m,12H),1.33-1.12(m,4H),0.94(s,3H),0.92(s,3H)。质谱(m/z):357.2$[M+H]^+$。

[0692] 化合物90

[0693] N-羟基-2-(4-甲基哌嗪-1-基)-N-(4-((4-(1-甲基哌啶-4-基)苯基)氨基)苄基)乙酰胺

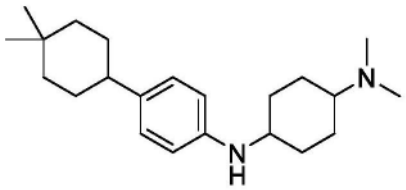
[0694] 

90A
90B

[0695] 在25℃搅拌4-(4,4-二甲基环己基)苯胺(100mg,0.49mmol),4-(羟基甲基)环己烷-1-酮(94.55mg,0.7377mmol)和Pic-BH_3(52-皮考啉-硼烷;3mg,0.49mmol)/AcOH/H_2O(10/1)(22mL)的溶液2小时。在过滤后,减压除去溶剂并且残余物的提纯方法为:prep-HPLC(柱-Xbridge-C18 150x 21.2mm,5um;移动相:ACN-H_2O(0.1%FA),40%-60%)而得到90A(94mg)(白色固体)和90B(86mg)(白色固体)。90A:^{1}H NMR(300MHz,DMSO-d6)δ6.92(d,J=8.4Hz,2H),6.47(d,J=8.4Hz,2H),5.11(s,1H),4.42(s,1H),3.23(d,J=5.3Hz,2H),3.06(s,1H),2.21(s,2H),1.98(d,J=10.6Hz,1H),1.76(d,J=11.6Hz,2H),1.54-1.31(m,9H),1.11-0.95(m,4H),0.93(d,J=8.4Hz,6H)。质谱(m/z):316.3[M+H]$^+$。HPLC:Rt=5.824min(柱-Xbridge 5u C18 150x19mm;流速:20mL/min.移动相:ACN-H_2O(0.1%FA),35%-60%)。90B:MS(m/z):316.3[M+H]$^+$。^{1}H NMR(400MHz,DMSO-d6)δ6.87(d,J=8.4Hz,2H),6.46(d,J=8.4Hz,2H),5.16-5.04(m,1H),4.38-4.30(m,1H),3.42-3.34(m,1H),3.23(d,J=5.2Hz,2H),2.22-2.07(m,1H),1.60-1.17(m,18H),0.89(d,J=8.4Hz,6H)。MS(m/z):316.3[M+H]$^+$。HPLC Rt=7.933min(柱-Xbridge 5u C18 150x 19mm;流速:20mL/min.移动相:ACN-H_2O(0.1%FA),35%-60%)。

[0696] 化合物91

[0697] N^1-(4-(4,4-二甲基环己基)苯基)-N4,N4-二甲基环己烷-1,4-二胺

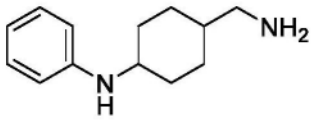
[0698] 

91A
91B

[0699] 根据为化合物1-1的程序制备标题化合物91A,91B。粗制残余物的提纯方法为:制备TLC(H_2O/MeOH/DCM=0.1/1/5)而得到化合物91A(Rf值=0.36),收率为19.2%(白色固体)和91B(Rf值=0.30),收率为14.8%(白色固体)。91A:^{1}H NMR(400MHz,DMSO-d6)δ10.10(s,1H),6.94-6.87(m,2H91),6.51(d,J=8.6Hz,2H),3.55-3.46(m,1H),3.17-3.06(m,1H),2.65(s,6H),2.23-2.14(m,1H),1.88-1.81(m,2H),1.77-1.66(m,4H),1.57-1.46(m,6H),1.41-1.35(m,2H),1.27-1.19(m,2H),0.89(d,J=8.6Hz,6H)。Mass(m/z):329.3[M+H]$^+$。91B:^{1}H NMR(400MHz,DMSO-d6)δ6.90(d,J=8.0Hz,2H),6.44(d,J=8.0Hz,2H),5.19(s,1H),3.10(t,J=11.2Hz,2H),2.65(t,J=4.8Hz,6H),2.22-2.12(m,1H),2.04-1.97(m,4H),1.57-1.36(m,8H),1.26-1.08(m,4H),0.89(d,J=8.4Hz,6H)。质谱(m/z):329.3[M+H]$^+$。

[0700] 化合物92

[0701] N-(4-(氨基甲基)环己基)苯胺

[0702] 

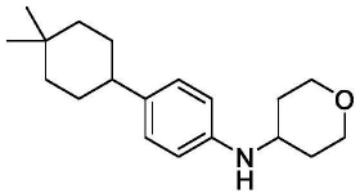
92A

92B

[0703] 由((4-(苯基氨基)环己基)甲基)氨基甲酸叔丁酯(270mg,0.888mmol),DCM(10mL)和TFA(1mL),根据为24的程序制备期望的产物92A(Rt＝7.1min)(黄色油)(122.2mg,67.4%)和92B(Rt＝7.9min)(白色固体)(45.5mg,25.1%),其提纯方法为:Prep-HPLC(柱:X Select-CSH-Prep 5μm OBD,19*150mm;溶剂体系(ACN/水(0.5%TFA)＝0-90%-50%-50%-100%,0-10min-10.5min-11.5min-13min)。92A:^{1}H NMR(400MHz,DMSO-d6)δ7.91(s,3H),7.21(t,J＝7.6Hz,2H),6.91(d,J＝8.0Hz,2H),6.84(t,J＝7.6Hz,1H),3.45(tt,J＝6.8,3.7Hz,1H),2.74(p,J＝6.0Hz,2H),1.73(h,J＝6.0Hz,1H),1.67-1.43(m,8H)。质谱(m/z):205.3$[M+H]^+$。92B:^{1}H NMR(400MHz,DMSO-d6)δ7.82(s,3H),7.21(t,J＝7.7Hz,2H),6.96-6.79(m,3H),3.21(tt,J＝11.3,3.8Hz,1H),2.64(p,J＝5.8Hz,2H),1.99-1.88(m,2H),1.84-1.72(m,2H),1.50(ttt,J＝10.5,6.9,3.4Hz,1H),1.28-1.12(m,2H),1.00(qd,J＝13.2,3.2Hz,2H)。质谱(m/z):205.3$[M+H]^+$。

[0704] 化合物93

[0705] N-(4-(4,4-二甲基环己基)苯基)四氢-2H-吡喃-4-胺

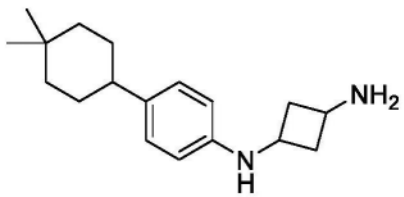
[0706] 

93

[0707] 由4-(4,4-二甲基环己基)苯胺(30mg,0.14mmol),四氢-4H-吡喃-4-酮(29mg,0.29mmol)和根据为4的程序制备标题化合物93(28.5mg),收率为67.2%(白色粉末)。^{1}H NMR(400MHz,DMSO-d6)δ6.92(d,J＝8.3Hz,2H),6.51(d,J＝8.1Hz,2H),5.23(d,J＝8.2Hz,1H),3.95-3.75(m,2H),3.41-3.37(m,2H),2.20(td,J＝10.3,5.3Hz,1H),1.93-1.78(m,2H),1.52(dd,J＝9.4,4.4Hz,3H),1.48-1.36(m,3H),1.35-1.21(m,5H),0.94(s,3H),0.92(s,3H)。质谱(m/z):289.6$[M+H]^+$。

[0708] 化合物94

[0709] N^1-(4-(4,4-二甲基环己基)苯基)环丁烷-1,3-二胺

[0710] 

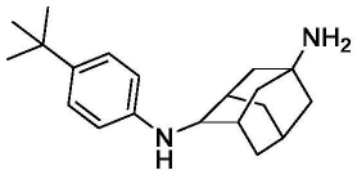
94

[0711] 由4-(4,4-二甲基环己基)苯胺(39mg,0.19mmol),和(3-氧代环丁基)氨基甲酸叔丁酯(53mg,0.29mmol),根据为20的程序制备标题化合物94(46.3mg),收率为88.6%(淡黄

色粉末)经^{1}H NMR证明为1:0.1的混合物。^{1}H NMR(400MHz,DMSO-d6)δ8.36(s,3H),7.00-6.88(m,2H),6.45-6.41(m,0.2H),6.41-6.34(m,2H),5.81(d,J=6.2Hz,1H),5.73(d,J=6.4Hz,0.1H),4.05(q,J=7.0Hz,1H),3.72(tt,J=8.1,5.2Hz,1H),2.44(tt,J=7.7,5.2Hz,2H),2.29-2.09(m,3H),1.51(dp,J=11.7,3.8Hz,4H),1.41(dt,J=14.5,3.1Hz,2H),1.34-1.18(m,3H),0.93(s,3H),0.91(s,3H)。质谱(m/z):273.4[M+H]$^+$。

[0712] 化合物95

[0713] N^4-(4-(叔丁基)苯基)金刚烷-1,4-二胺

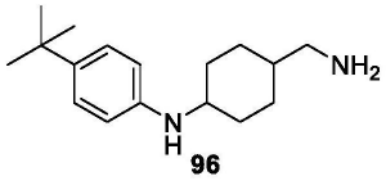
[0714] 

95

[0715] 根据为20的程序,制备标题化合物95(25.6mg),总收率为36.6%(白色固体)。^{1}H NMR(400MHz,DMSO-d6)δ8.02(s,2H),7.94(s,1H),7.12-7.04(m,2H),6.55(dd,J=20.0,8.4Hz,2H),5.40-5.27(m,1H),2.23-2.06(m,2H),2.05-1.75(m,7H),1.72-1.63(m,1H),1.63-1.51(m,1H),1.39-1.29(m,2H),1.20(s,9H)。质谱(m/z):299.3[M+H]$^+$。

[0716] 化合物96

[0717] N-(4-(氨基甲基)环己基)-4-(叔丁基)苯胺

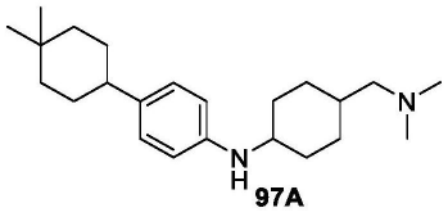
[0718] 

96

[0719] 由((4-((4-(叔丁基)苯基)氨基)环己基)甲基)氨基甲酸叔丁酯(36mg,0.1mmol),和TFA(0.075mL,1mmol),根据为24的程序制备标题化合物96(4.8mg),总收率为19%(白色固体),经^{1}H NMR证明为1:2的混合物。^{1}H NMR(400MHz,DMSO-d6)δ7.93(s,3H),7.07(d,J=8.0Hz,2H),6.47(d,J=8.0Hz,2H),3.40(m,0.7H),3.06(m,0.3H),2.63(m,2H),1.95(m,0.6H),1.77(m,0.3H),1.68-1.32(m,8H),1.17(s,9H)。质谱(m/z):261.2[M+H]$^+$。

[0720] 化合物97

[0721] N-(4-((二甲基氨基)甲基)环己基)-4-(4,4-二甲基环己基)苯胺

[0722] 

97A

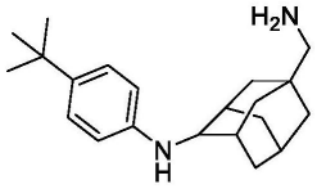
97B

[0723] 由4-((4-(4,4-二甲基环己基)苯基)氨基)-N,N-二甲基环己烷-1-甲酰胺(36mg,0.1mmol),和$LiAlH_4$(14.8mg,0.4mmol),根据为23的程序制备标题化合物97A(Rt=5.48min;4.8mg,28%)和97B(Rt=6.22min;2.0mg,12%),其提纯方法为:制备HPLC(柱:X Select-CSH-Prep5μm OBD,19*150mm;ACN/水(5‰TFA=20%-65%-95%-95%-10%,0-

13min-13.5min-14.5min-16.0min)。97A:^{1}H NMR(400MHz,DMSO-d6)δ6.92(d,J=8.4Hz,2H),6.46(d,J=8.4Hz,2H),3.06(m,1H),2.88(m,2H),2.69(s,6H),2.20(m,1H),1.98-1.82(m,5H),1.54-1.38(m,8H),1.14-1.02(m,4H),0.90(s,3H),0.88(s,3H)。质谱(m/z):343.4[M+H]$^+$。97B:^{1}H NMR(400MHz,DMSO-d6)δ6.92(d,J=8.4Hz,2H),6.50(d,J=8.4Hz,2H),2.73(m,1H),2.67(m,2H),2.51(s,6H),2.20(m,1H),1.94-1.03(m,4H),1.65-1.35(m,13H),0.94(s,3H),0.92(s,3H)。质谱(m/z):343.4[M+H]$^+$。

[0724] 化合物98

[0725] 5-(氨基甲基)-N-(4-(叔丁基)苯基)金刚烷-2-胺

[0726] 

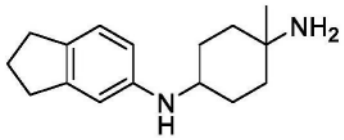
98A

98B

[0727] 根据为化合物20的程序,制备标题化合物98A和98B。产物提纯的方法:制备HPLC(柱:X Select-CSH-Prep 5μm OBD,19*150mm;ACN/水(0.5%TFA)=0%-0%-30%-95%-95%-0%,0min-2min-9min-9.5min-10.5min-12.0)而得到化合物98A(Rt=9.03min),收率为35.6%(白色固体)和98B(Rt=7.56min),收率为31.2%(白色固体)。98A^{1}H NMR(400MHz,甲醇-d4)δ7.17-7.11(m,2H),6.66-6.60(m,2H),3.49-3.42(m,1H),2.33(s,2H),2.08-2.01(m,4H),1.97-1.90(m,1H),1.64-1.60(m,4H),1.55-1.51(m,2H),1.51-1.44(m,1H),1.25(s,9H)。质谱(m/z):313.3[M+H]$^+$。98B ^{1}H NMR(400MHz,甲醇-d4)δ7.17-7.11(m,2H),6.67-6.60(m,2H),3.51-3.46(m,1H),2.42(s,2H),2.13-2.07(m,2H),2.03-1.97(m,1H),1.88-1.78(m,5H),1.54-1.47(m,2H),1.35-1.27(m,2H),1.25(s,9H)。质谱(m/z):313.3[M+H]$^+$。

[0728] 化合物99

[0729] N^1-(2,3-二氢-1H-茚-5-基)-4-甲基环己烷-1,4-二胺

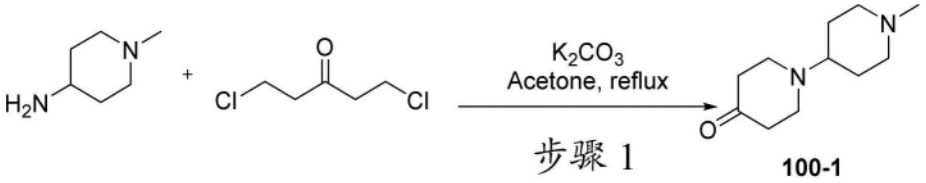
[0730] 

99

[0731] 由(4-((2,3-二氢-1H-茚-5-基)氨基)-1-甲基环己基)氨基甲酸叔丁酯(168mg,0.488mmol),TFA(1mL),和DCM(10mL),根据为24的程序制备标题化合物99(102.5mg),总收率为93.8%(白色固体)。^{1}H NMR(400MHz,DMSO-d6)δ8.29(d,J=36.0Hz,3H),6.90(d,J=8.0Hz,1H),6.53-6.45(m,1H),6.44-6.34(m,1H),5.34-4.83(m,1H),3.30-3.08(m,1H),2.70(dt,J=15.2,7.2Hz,4H),1.99-1.87(m,4H),1.80-1.48(m,6H),1.30(d,J=8.0Hz,3H)。质谱(m/z):245.3[M+H]$^+$。

[0732] 化合物100

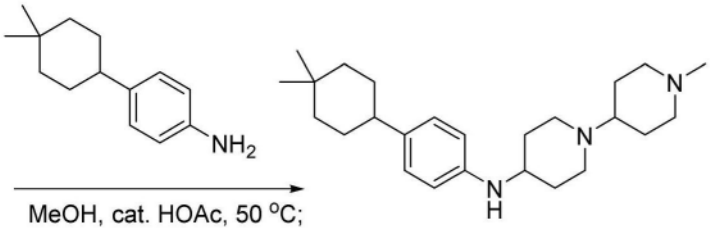
[0733] N-(4-(4,4-二甲基环己基)苯基)-1'-甲基-[1,4'-联哌啶]-4-胺



步骤 1

100-1

[0734]



步骤 2

100

[0735] Acetone:丙酮reflux:回流

[0736] 步骤1:制备1'-甲基-[1,4'-bi哌啶]-4-酮(100-1)

[0737] 在25℃向1-甲基哌啶-4-胺(1g,8.8mmol)/丙酮(20mL)的溶液中添加K_2CO_3(2.7g,19.3mmol)和1,5-二氯戊烷-3-酮(1.5g,9.7mmol)。然后在70℃搅拌混合物3小时。LCMS显示反应完成。将混合物过滤并浓缩而得到化合物2(0.5g,27%,收率)(黄色油)。MS(m/z):197.1$[M+H]^+$。

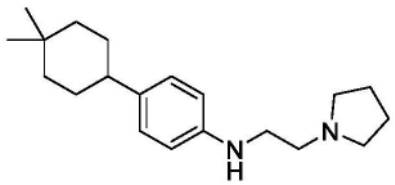
[0738] 步骤2:制备N-(4-(4,4-二甲基环己基)苯基)-1'-甲基-[1,4'-联哌啶]-4-胺(100)

[0739] 在25℃向化合物100-1(0.5g,2.55mmol)/MeOH(20mL)和一滴AcOH的溶液中添加4-(4,4-二甲基环己基)苯胺(570mg,2.8mmol)。然后在50℃搅拌混合物1小时。然后在冷却到25℃后向混合物中添加$NaBH_3CN$(480mg,7.6mmol)。然后在25℃搅拌混合物2小时。LCMS显示反应完成。将反应用水(10mL)淬灭,用EA(10mL*3)萃取。将合并的有机层用盐水(20mL)洗涤,用硫酸钠干燥,过滤和浓缩。残余物的提纯方法为:使用EA/PE(1:0)的combi-flash(闪式色谱)而得到化合物5(10mg,10.2%,收率)(黄色固体)。^1H NMR(300MHz,CD_3OD)δ6.88(d,J=8.1Hz,2H),6.52(d,J=8.1Hz,2H),3.25(s,3H),2.97-2.85(m,4H),2.33(t,J=11.5Hz,3H),2.06-1.81(m,7H),1.55-1.45(m,7H),1.44-1.30(m,6H),0.86(d,J=12.1Hz,6H)。MS(m/z)384.0$[M+H]^+$。

[0740] 化合物101

[0741] 4-(4,4-二甲基环己基)-N-(2-(吡咯烷-1-基)乙基)苯胺

[0742]



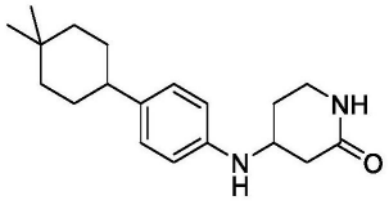
101

[0743] 由2-(吡咯烷-1-基)乙醛(40mg,0.35mmol),4-(4,4-二甲基环己基)苯胺(60mg,0.30mmol),MeOH(10mL),一滴AcOH,和$NaBH_3CN$(14.2mg,0.89mmol),根据为5的程序制备标题化合物101(8mg,9.0%)。^1H NMR(400MHz,CDC13)δ8.56(s,1H),7.05(d,J=8.4Hz,2H),6.57(d,J=8.4Hz,2H),3.52(t,J=5.6Hz,2H),3.19(t,J=5.6Hz,6H),2.32-2.26(m,1H),

2.02(t,J＝6.6Hz,4H),1.69-1.42(m,6H),1.30(td,J＝13.1,4.1Hz,2H),0.96(t,J＝7.9Hz,6H)。质谱(m/z):301.0[M+H]$^+$。

[0744] 化合物102

[0745] 4-((4-(4,4-二甲基环己基)苯基)氨基)哌啶-2-酮

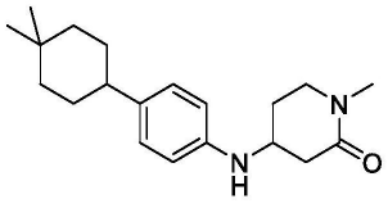
[0746] 

102

[0747] 由4-(4,4-二甲基环己基)苯胺(50mg,0.25mmol),MeOH(5mL),哌啶-2,4-二酮(30mg,0.27mmol),乙酸(1.5mg,0.025mmol)和氰基硼氢化钠(46mg,0.75mmol),根据为5的程序制备标题产物102(42mg,56％)(黄色固体)。^{1}H NMR(300MHz,CDCl3)δ7.08(d,J＝8.4Hz,2H),6.62(d,J＝8.4Hz,2H),6.05(s,1H),3.85-3.76(m,1H),3.49-3.31(m,2H),2.83(dd,J＝17.4Hz,4.5Hz,1H),2.36-2.27(m,2H),2.20-2.16(m,1H),1.85-1.73(m,2H),1.67-1.63(m,1H),1.58-1.54(m,1H),1.50-1.45(m,2H),1.36-1.25(m,2H),0.95(d,J＝5.1Hz,6H)。质谱(m/z):301.2[M+H]$^+$。

[0748] 化合物103

[0749] 4-((4-(4,4-二甲基环己基)苯基)氨基)-1-甲基哌啶-2-酮

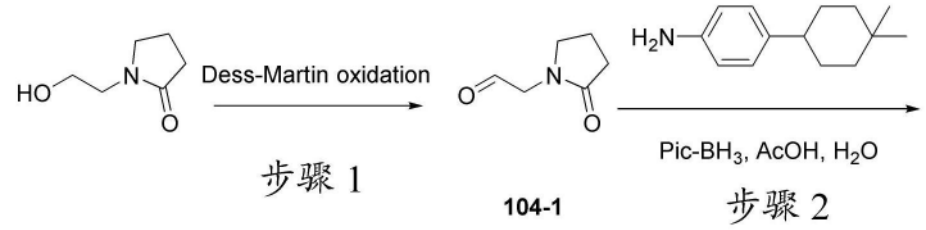
[0750] 

103

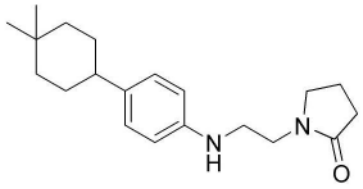
[0751] 由4-(4,4-二甲基环己基)苯胺(50mg,0.25mmol),MeOH(5mL),1-甲基哌啶-2,4-二酮(35mg,0.27mmol),乙酸(1.5mg,0.025mmol)和氰基硼氢化钠(46mg,0.75mmol),根据为5的程序获得期望的产物(50mg,63.7％)(白色固体)。^{1}H NMR(400MHz,CDCl3)δ7.06(d,J＝8.4Hz,2H),6.58(d,J＝8.4Hz,2H),3.79-3.75(m,1H),3.40-3.33(m,2H),2.97(s,3H),2.84(dd,J＝17.2Hz,4.4Hz,1H),2.33-2.27(m,2H),2.22-2.19(m,1H),1.84-1.80(m,2H),1.66-1.60(m,1H),1.57-1.54(m,1H),1.49-1.44(m,2H),1.31(td,J＝8.8Hz,4.0Hz,2H),0.95(d,J＝7.2Hz,6H)。质谱(m/z):315.2[M+H]$^+$。

[0752] 化合物104

[0753] N-羟基-2-(4-甲基哌嗪-1-基)-N-(4-((4-(1-甲基哌啶-4-基)苯基)氨基)苄基)乙酰胺



[0754]



104

[0755] oxidation:氧化

[0756] 步骤1:制备2-(2-氧代吡咯烷-1-基)乙醛(104-1)

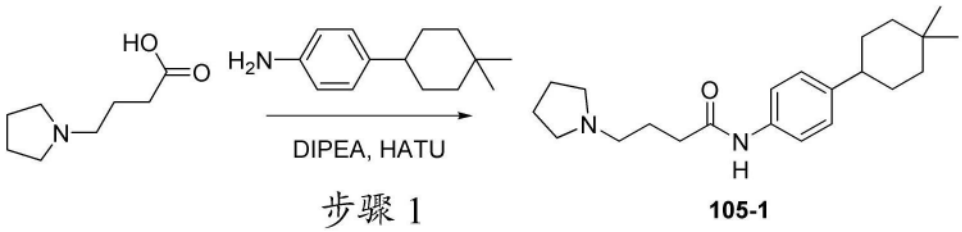
[0757] 在室温搅拌1-(2-羟基乙基)吡咯烷-2-酮(2g,15.4mmol)和Dess-Martin试剂(13.06g,30.8mmol)/DCM(50mL)的混合物10分钟。将反应混合物过滤并蒸发,残余物的提纯方法为:硅胶柱(PE/EA=1:1)而得到产物(黄色油)(1.54g,78.2%)。

[0758] 步骤2:制备1-(2-((4-(4,4-二甲基环己基)苯基)氨基)乙基)吡咯烷-2-酮(104)

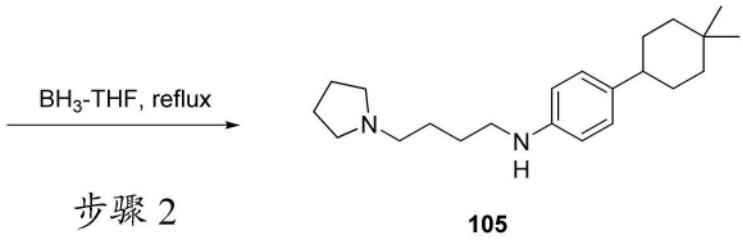
[0759] 在室温搅拌2-(2-氧代吡咯烷-1-基)乙醛(50mg,0.35mmol),4-(4,4-二甲基环己基)苯胺(60mg,0.3mmol)和Pic-BH_3(56mg,0.88mmol)/AcOH/H_2O=1/9(5mL)的混合物溶液3小时。用饱和$NaHCO_3$水溶液将反应混合物调节到pH8,用EA(10mL)萃取,用Na_2SO_4干燥,过滤和减压浓缩。残余物的提纯方法为:prep-HPLC而得到期望的产物(10mg,6.7%)(白色固体))。^{1}H NMR(400MHz,CDCl3)δ7.07(d,J=8.4Hz,2H),6.68(d,J=8.4Hz,2H),3.58(t,J=5.7Hz,2H),3.44(t,J=7.1Hz,2H),3.35-3.27(m,2H),2.39(t,J=8.1Hz,2H),2.36-2.26(m,1H),2.01(dt,J=15.5,7.6Hz,2H),1.69-1.43(m,7H),1.36-1.23(m,3H),0.95(d,J=7.1Hz,6H)。质谱(m/z):314.7[M+H]$^+$。

[0760] 化合物105

[0761] 4-(4,4-二甲基环己基)-N-(4-(吡咯烷-1-基)丁基)苯胺



[0762]



105

[0763] reflux:回流

[0764] 步骤1:制备N-(4-(4,4-二甲基环己基)苯基)-4-(吡咯烷-1-基)丁酰胺(105-1)

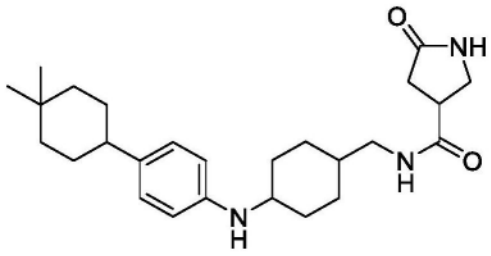
[0765] 向4-(吡咯烷-1-基)丁酸(46mg,0.29mmol)/DCM(5mL)的溶液中添加4-(4,4-二甲基环己基)苯胺(50mg,0.25mmol),DIEA(95mg,0.75mmol)和HATU(140mg,0.375mmol)。然后在室温搅拌混合物3小时。将反应用EA(10mL)萃取3次。将合并的有机层用硫酸钠干燥并且减压浓缩。残余物的提纯方法为:快速色谱而得到期望的产物(35mg,40.9%)(黄色油)。质谱(m/z):330.3[M+H]$^+$。

[0766] 步骤2:制备4-(4,4-二甲基环己基)-N-(4-(吡咯烷-1-基)丁基)苯胺(105)

[0767] 向N-(4-(4,4-二甲基环己基)苯基)-4-(吡咯烷-1-基)丁酰胺(35mg,0.10mmol)/THF(2mL)的溶液中添加BH_3-THF(15mL)并在70℃搅拌混合物2小时。将反应用水(10mL)淬灭,并用EA(10mL)萃取3次。将合并的有机相层用硫酸钠干燥并且减压浓缩。残余物的提纯方法为:prep-HPLC(柱-Xbridge-C18 150x 21.2mm,5um;移动相:ACN-H_2O(0.1%FA),40%-60%)而得到期望的产物(13mg,41.2%)(黑色固体)。^{1}H NMR(400MHz,CDC13)δ7.04(d,J=8.4Hz,2H),6.57(d,J=8.4Hz,2H),3.69(t,J=5.6Hz,1H),3.15(t,J=6.8Hz,2H),2.91-2.82(m,2H),2.30(m,1H),2.05-1.96(m,4H),1.91-1.83(m,1H),1.73-1.66(m,2H),1.56(dd,J=12.4Hz,3.2Hz,3H),1.46(d,J=12.6,2H),1.32(dd,J=13.1Hz,4.0Hz,3H),0.95(d,J=7.4Hz,6H)。质谱(m/z):329.3[M+H]$^+$。

[0768] 化合物106

[0769] N-((4-((4-(4,4-二甲基环己基)苯基)氨基)环己基)甲基)-5-氧代吡咯烷-3-甲酰胺

[0770] 

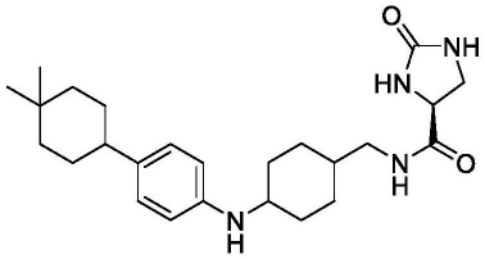
106A
106B

[0771] 由N-(4-(氨基甲基)环己基)-4-(4,4-二甲基环己基)苯胺(19mg,0.06mmol),根据为1的程序制备标题化合物106A(Rt=5.28min;6.8mg),总收率为27%(白色固体)和106B(Rt=6.21min;5.4mg),总收率为21%(白色固体),其提纯方法为:制备HPLC(柱:X Select-CSH-Prep 5μm OBD,19*150mm;ACN/水(5‰TFA)=30%-45%-75%-95%-10%,0-7min-7.5min-8.5min-10.0min)。106A:^{1}H NMR(400MHz,DMSO-d6)δ7.97(t,J=5.6Hz,1H),7.57(s,1H),6.92(d,J=8.4Hz,2H),6.47(d,J=8.4Hz,2H),5.14(m,1H),3.38(m,2H),3.23-3.08(m,2H),3.00(t,J=6.4Hz,2H),2.31-2.17(m,3H),1.96(m,1H),1.70(m,1H),1.65-1.26(m,15H),0.94(s,3H),0.92(s,3H)。质谱(m/z):426.3[M+H]$^+$。106B:^{1}H NMR(400MHz,DMSO-d6)δ7.97(t,J=5.6Hz,1H),7.57(s,1H),6.92(d,J=8.4Hz,2H),6.51(d,J=8.4Hz,2H),5.17(m,1H),3.41(m,2H),3.21-3.06(m,2H),2.93(t,J=6.4Hz,2H),2.33-2.17(m,3H),2.06-1.31(m,17H),0.94(s,3H),0.92(s,3H)。质谱(m/z):426.3[M+H]$^+$。

[0772] 化合物107

[0773] (S)-N-((4-((4-(4,4-二甲基环己基)苯基)氨基)环己基)甲基)-2-氧代咪唑烷-

4-甲酰胺

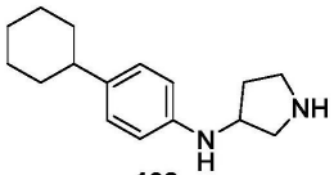
[0774] 

107A
107B

[0775] 由N-(4-(氨基甲基)环己基)-4-(4,4-二甲基环己基)苯胺(19mg,0.06mmol),根据为1的程序制备标题化合物107A(Rt＝4.98min;3.7mg),总收率为15％(白色固体)和化合物107B(Rt＝5.76min;5.4mg),总收率为22％(白色固体),其提纯方法为:制备HPLC(柱:X Select-CSH-Prep 5μm OBD,19*150mm;ACN/水(5‰TFA)＝30％-45％-95％-95％-10％,0-7min-7.5min-8.5min-10.0min)。107A:^{1}H NMR(400MHz,DMSO-d6)δ7.86(t,J＝5.6Hz,1H),6.91(d,J＝8.0Hz,2H),6.46(d,J＝8.0Hz,2H),6.30(s,1H),5.10(m,1H),4.05(m,1H),3.52(m,1H),3.18(m,1H),3.07-2.91(m,2H),2.21(m,1H),1.70(m,1H),1.64-1.24(m,16H),0.94(s,3H),0.91(s,3H)。质谱(m/z):427.2[M+H]$^+$。107B:^{1}H NMR(400MHz,DMSO-d6)δ7.88(t,J＝5.6Hz,1H),6.91(d,J＝8.0Hz,2H),6.51(d,J＝8.0Hz,2H),6.29(s,1H),5.20(m,1H),4.06(m,1H),3.51(m,1H),3.14(m,1H),3.09-2.93(m,2H),2.21(m,1H),1.70(m,1H),1.67-1.23(m,16H),0.94(s,3H),0.91(s,3H)。质谱(m/z):427.2[M+H]$^+$。

[0776] 化合物108

[0777] N-(4-环己基苯基)吡咯烷-3-胺

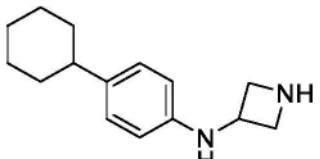
[0778] 

108

[0779] 由3-((4-环己基苯基)氨基)吡咯烷-1-甲酸叔丁酯(34.1mg,0.1mmol),根据为24的程序制备标题化合物SIR2-1443(20mg),总收率为83％(白色固体)。^{1}H NMR(400MHz,DMSO-d6)δ6.96(d,J＝8.4Hz,2H),6.52(d,J＝8.4Hz,2H),5.74(s,1H),4.03(m,1H),3.30-3.13(m,4H),3.00(m,1H),2.32(m,1H),2.22-2.05(m,1H),1.94-1.57(m,6H),1.31(m,4H)。质谱(m/z):245.2[M+H]$^+$。

[0780] 化合物109

[0781] N-(4-环己基苯基)氮杂环丁烷-3-胺

[0782] 

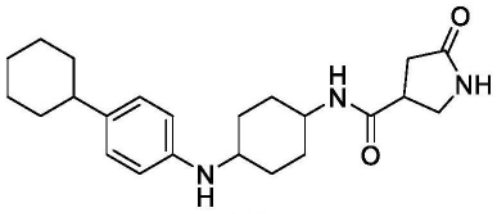
109

[0783] 由3-((4-环己基苯基)氨基)氮杂环丁烷-1-甲酸叔丁酯(33.0mg,0.1mmol),根据为24的程序制备标题化合物109(18mg),总收率为78％(白色固体)。^{1}H NMR(400MHz,DMSO-

d6)δ9.04(s,1H),6.96(d,J=8.4Hz,2H),6.44(d,J=8.4Hz,2H),6.21(s,1H),4.28(m,1H),4.20(m,2H),3.77(m,2H),2.32(m,1H),1.80-1,63(m,4H),1.36-1.17(m,6H)。质谱(m/z):231.3[M+H]$^+$。

[0784] 化合物110

[0785] N-(4-((4-环己基苯基)氨基)环己基)-5-氧代吡咯烷-3-甲酰胺

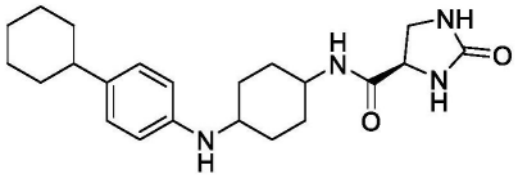
[0786] 

110

[0787] 由N^1-(4-环己基苯基)环己烷-1,4-二胺(27.2mg,0.1mmol),根据为1的程序制备标题化合物110(12.0mg),总收率为31%(白色固体),经^{1}H NMR证明为2:3的混合物。^{1}H NMR(400MHz,DMSO-d6)δ7.91(s,0.6H),7.84(s,0.4H),7.56(d,J=8.4Hz,1.2H),6.90(d,J=8.4Hz,0.8H),6.50(d,J=8.4Hz,1.2H),6.50(d,J=8.4Hz,0.8H),5.16(s,0.6H),5.10(s,0.4H),3.66(m,1H),3.55-3.37(m,2H),3.22-3.06(m,2H),2.34-2.21(m,3H),1.95-1.66(m,10H),1.37-1.05(m,8H)。质谱(m/z):384.3[M+H]$^+$。

[0788] 化合物111

[0789] (R)-N-(4-((4-环己基苯基)氨基)环己基)-2-氧代咪唑烷-4-甲酰胺

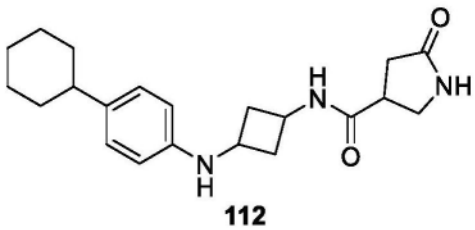
[0790] 

111

[0791] 由N^1-(4-环己基苯基)环己烷-1,4-二胺(27.2mg,0.1mmol),根据为1的程序制备标题化合物111(13.0mg),总收率为34%(白色固体),经^{1}H NMR证明为1:1的混合物。^{1}H NMR(400MHz,DMSO-d6)δ7.72(s,0.5H),7.72(s,0.5H),6.91(d,J=8.4Hz,1H),6.88(d,J=8.4Hz,1H),6.51(m,2H),6.29(s,1H),5.16(s,0.5H),5.11(s,0.5H),4.15-3.97(m,1H),3.75-3.45(m,2H),3.22-3.04(m,2H),2.29(m,1H),2.04-1.50(m,10H),1.43-1.04(m,8H)。质谱(m/z):385.2[M+H]$^+$。

[0792] 化合物112

[0793] N-(3-((4-环己基苯基)氨基)环丁基)-5-氧代吡咯烷-3-甲酰胺

[0794] 

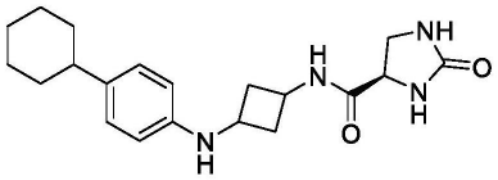
112

[0795] 由N^1-(4-环己基苯基)环丁烷-1,3-二胺(24.4mg,0.1mmol),根据为1的程序制备标题化合物112(11.6mg),总收率为33%(白色固体),经^{1}H NMR证明为1:4的混合物。^{1}H NMR

(400MHz,DMSO-d6)δ8.37(s,0.8H),8.25(s,0.2H),7.58(s,1H),6.92(d,J=8.4Hz,1.6H),6.89(d,J=8.4Hz,0.4H),6.42(d,J=8.4Hz,0.4H),6.38(d,J=8.4Hz,1.6H),5.76(s,1H),4.29(m,1H),3.92(m,0.2H),3.82(m,0.8H),3.41(m,1H),3.26-3.04(m,2H),2.35-2.17(m,5H),2.11(m,2H),1.78-1.64(m,4H),1.37-1.11(m,6H)。质谱(m/z):356.2[M+H]$^+$。

[0796] 化合物113

[0797] (R)-N-(3-((4-环己基苯基)氨基)环丁基)-2-氧代咪唑烷-4-甲酰胺

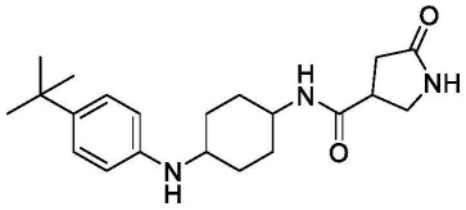
[0798] 

113

[0799] 由N^1-(4-环己基苯基)环丁烷-1,3-二胺(24.4mg,0.1mmol),根据为1的程序制备标题化合物113(7.2mg),总收率为21%(白色固体),经^{1}H NMR证明为1:4的混合物。^{1}H NMR(400MHz,DMSO-d6)δ8.28(s,1H),8.28(s,0.8H),8.14(s,0.2H),6.95(d,J=8.4Hz,1.6H),6.89(d,J=8.4Hz,0.4H),6.49(s,1H),6.45(d,J=8.4Hz,0.4H),6.38(d,J=8.4Hz,1.6H),6.33(s,1H),5.75(m,0.8H),5.58(m,0.2H),4.32(m,1H),4.06(m,0.8H),3.96(m,0.2H),3.82(m,1H),3.52(m,1H),3.27-3.09(m,1H),2.36-2.22(m,3H),2.15-2.08(m,2H),1.87-1.58(m,4H),1.45-1.05(m,6H)。质谱(m/z):357.4[M+H]$^+$。

[0800] 化合物114

[0801] N-(4-((4-(叔丁基)苯基)氨基)环己基)-5-氧代吡咯烷-3-甲酰胺

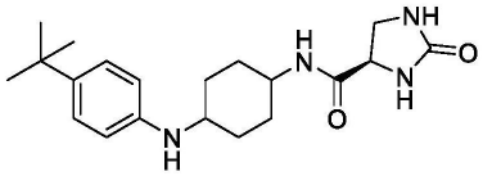
[0802] 

114A
114B

[0803] 由N^1-(4-(叔丁基)苯基)环己烷-1,4-二胺(49.2mg,0.2mmol),根据为1的程序制备标题化合物114A(Rt=6.00min;10.2mg),总收率为29%(白色固体)和114B(Rt=8.03min;10.8mg)制备,总收率为30%(白色固体),其提纯方法为:制备HPLC(柱:X Select-CSH-Prep 5μm OBD,19*150mm;ACN/水(5‰TFA)=20%-23%-95%-95%-0%,0-11min-11.5min-12.5min-14.0min)。114A:^{1}H NMR(400MHz,DMSO-d6)δ7.87(d,J=7.2Hz,1H),7.56(s,1H),7.07(d,J=8.8Hz,2H),6.51(d,J=8.8Hz,2H),5.18(s,1H),3.66(s,1H),3.38(m,1H),3.29(m,1H),3.18(m,2H),2.26(m,2H),1.67-1.53(m,8H),1.20(s,9H)。质谱(m/z):358.3[M+H]$^+$。114B:^{1}H NMR(400MHz,DMSO-d6)δ7.93(d,J=7.6Hz,1H),7.57(s,1H),7.06(d,J=8.4Hz,2H),6.48(d,J=8.4Hz,2H),5.12(s,1H),3.51(m,1H),3.37(m,1H),3.24-3.14(m,1H),3.14-3.04(m,2H),2.26(m,2H),2.04-1.89(m,2H),1.85-1.73(m,2H),1.35-1.22(m,4H),1.20(s,9H)。质谱(m/z):358.3[M+H]$^+$。

[0804] 化合物115

[0805] (R)-N-(4-((4-(叔丁基)苯基)氨基)环己基)-2-氧代咪唑烷-4-甲酰胺

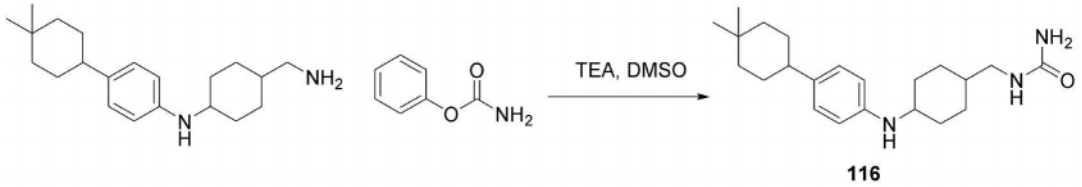
[0806] 

115A
115B

[0807] 由N^1-(4-(叔丁基)苯基)环己烷-1,4-二胺(49.2mg,0.2mmol),根据为1的程序制备标题化合物115A(Rt=5.88min;7.0mg),总收率为20%(白色固体)和115B(Rt=7.52min;10.8mg),总收率为30%(白色固体),其提纯方法为:制备HPLC(柱:X Select-CSH-Prep 5μm OBD,19*150mm;ACN/水(5‰TFA)=18%-18%-95%-95%-10%,0-11min-11.5min-12.5min-10.0min)。115A:^{1}H NMR(400MHz,DMSO-d6)δ7.76(d,J=7.6Hz,1H),7.07(d,J=8.4Hz,1H),6.54-6.45(m,3H),6.29(s,1H),5.16(s,1H),4.03(m,1H),3.51(m,2H),3.19(m,1H),3.15-3.03(m,1H),2.04-1.89(m,2H),1.84-1.75(m,2H),1.43-1.26(m,4H),1.20(s,9H)。质谱(m/z):359.2$[M+H]^+$。115A:^{1}H NMR(400MHz,DMSO-d6)δ7.61(d,J=7.2Hz,1H),7.08(d,J=8.4Hz,2H),6.59-6.51(m,3H),6.30(s,1H),5.22(s,1H),4.08(m,1H),3.69(m,1H),3.51(m,1H),3.32(m,1H),3.20(m,1H),1.75-1.47(m,8H),1.20(s,9H)。质谱(m/z):359.2$[M+H]^+$。

[0808] 化合物116

[0809] 1-((4-((4-(4,4-二甲基环己基)苯基)氨基)环己基)甲基)脲

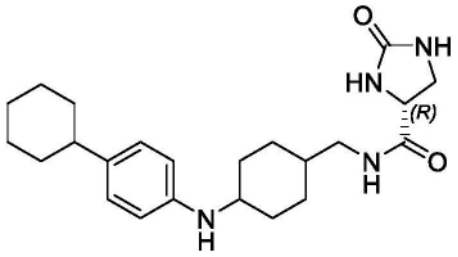
[0810] 

116

[0811] N-(4-(氨基甲基)环己基)-4-(4,4-二甲基环己基)苯胺(31.4mg,0.1mmol)和三乙胺(0.028mL,0.2mmol)都被溶于2mL的DMSO中。然后添加氨基甲酸苯酯(16.4mg,0.12mmol)。搅拌所得的溶液过夜。将水添加到反应混合物并且用乙酸乙酯萃取混合物。将合并的有机层用$MgSO_4$干燥并蒸发。混合物的提纯方法:prep-TLC而得到期望的产物(白色固体)(16.8mg,48%),经^{1}H NMR证明为1:4的混合物。^{1}H NMR(400MHz,DMSO-d6)6.95-6.86(m,2H),6.50(d,J=8.4Hz,1.2H),6.46(d,J=8.4Hz,0.8H),5.96(m,1H),5.34(s,2H),5.16(m,0.6H),5.09(m,0.4H),3.12-2.98(m,1H),2.88(m,1.6H),2.82(m,0.8H),2.20(m,1H),1.98(m,1H),1.75-1.25(m,16H),0.94(s,3H),0.92(s,3H)。质谱(m/z):358.4$[M+H]^+$。

[0812] 化合物117

[0813] (R)-N-((4-((4-环己基苯基)氨基)环己基)甲基)-2-氧代咪唑烷-4-甲酰胺

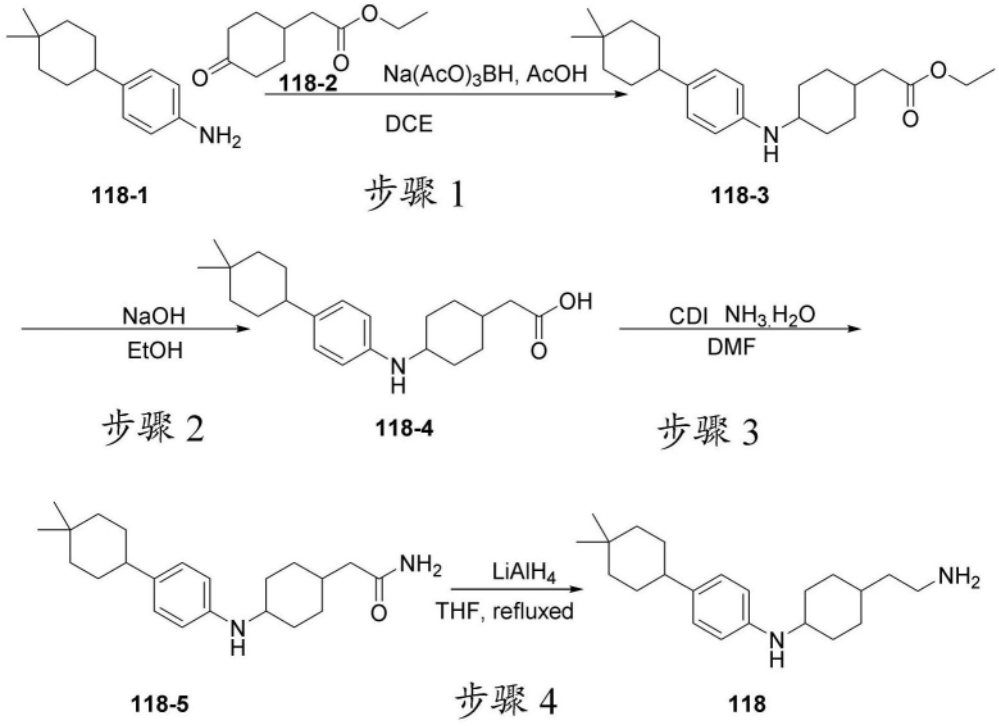
[0814] 

117A
117B

[0815] 由N-(4-(氨基甲基)环己基)-4-环己基苯胺(57.2mg,0.2mmol),(R)-2-氧代咪唑烷-4-甲酸(33.8mg,0.26mmol),DMF(2.0mL),DIEA(77.4mg,0.6mmol)和HATU(83.6mg,0.22mmol),根据为1的程序制备标题产物117A(白色固体)(10.9mg,18.6%)和117B(白色固体)(10.9mg,13.7%)。^{1}H NMR(400MHz,DMSO-d6)δ10.10(s,1H),6.94-6.87(m,2H),6.51(d,J=8.6Hz,2H),3.55-3.46(m,1H),3.17-3.06(m,1H),2.65(s,6H),2.23-2.14(m,1H),1.88-1.81(m,2H),1.77-1.66(m,4H),1.57-1.46(m,6H),1.41-1.35(m,2H),1.27-1.19(m,2H),0.89(d,J=8.6Hz,6H)。质谱(m/z):329.3[M+H]$^+$。Rt=4.778mins(Agilent,poroshell 120,SB-C18 2.7μm,4.6x50mm,ACN/水(0.1%FA)=5%-5%-95%-95%-95%-5%,0-0.5min-10min-10.5min-12.0min)。^{1}H NMR(400MHz,DMSO-d6)δ6.90(d,J=8.0Hz,2H),6.44(d,J=8.0Hz,2H),5.19(s,1H),3.10(t,J=11.2Hz,2H),2.65(t,J=4.8Hz,6H),2.22-2.12(m,1H),2.04-1.97(m,4H),1.57-1.36(m,8H),1.26-1.08(m,4H),0.89(d,J=8.4Hz,6H)。质谱(m/z):329.3[M+H]$^+$。Rt=4.456mins(Agilent,poroshell 120,SB-C18 2.7μm,4.6x50mm,ACN/水(0.1%FA)=5%-5%-95%-95%-95%-5%,0-0.5min-10min-10.5min-12.0min)。

[0816] 化合物118

[0817] N-(4-(2-氨基乙基)环己基)-4-(4,4-二甲基环己基)苯胺

[0818] 

[0819] refluxed:回流

[0820] 步骤1:制备2-(4-((4-(4,4-二甲基环己基)苯基)氨基)环己基乙酸乙酯(118-3)

[0821] 由4-(4,4-二甲基环己基)苯胺(203mg,1.0mmol),乙基2-(4-((4-(4,4-二甲基环己基)苯基)氨基)环己基乙酸乙酯(368mg,2.0mmol)和$NaBH(OAc)_3$(424mg,2.0mmol),根据为1-1的程序制备标题化合物118-3(231mg),总收率为62.3%(黄色固体)。质谱(m/z):372.3$[M+H]^+$。

[0822] 步骤2:制备2-(4-((4-(4,4-二甲基环己基)苯基)氨基)环己基)乙酸(118-4)

[0823] 向2-(4-((4-(4,4-二甲基环己基)苯基)氨基)环己基乙酸乙酯(170mg,0.5mmol)/EtOH(10mL)的溶液中添加NaOH(100mg,2.5mmol)。在65℃搅拌混合物3小时,冷却到室温,并用2N HCl水溶液酸化而调节pH至3。将混合物用(3x50 mL)萃取DCM。将合并的有机层用水洗涤,用Na_2SO_4干燥,过滤,和浓缩而得到期望的产物黄色固体(157mg,100%)。质谱(m/z):342.3$[M-H]^+$。

[0824] 步骤3:制备2-(4-((4-(4,4-二甲基环己基)苯基)氨基)环己基)乙酰胺(118-5)

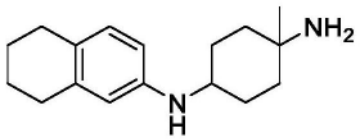
[0825] 向2-(4-((4-(4,4-二甲基环己基)苯基)氨基)环己基)乙酸(150mg,0.44mmol)/DMF(2.0mL)的溶液中添加CDI(78mg,0.48mmol)。在100℃搅拌混合物3小时,冷却到0℃,添加$NH_3.H_2O$(0.1mmol)。在室温搅拌混合物30分钟。添加5mL的水。将混合物用DCM(3x5mL)萃取。将合并的有机层用水洗涤,用Na_2SO_4干燥,过滤,和浓缩。残余物的提纯方法为:prep-TLC(EA/PE=1/2)而得到期望的产物黄色固体(60mg,40%)。质谱(m/z):343.3$[M+H]^+$。

[0826] 步骤4:制备N-(4-(2-氨基乙基)环己基)-4-(4,4-二甲基环己基)苯胺(118)

[0827] 在0℃向2-(4-((4-(4,4-二甲基环己基)苯基)氨基)环己基)乙酰胺(50mg,0.15mol)/THF(10mL)的溶液中添加$LiAlH_4$(24g,0.6mol),并使混合物回流2小时。在冷却到0℃后,添加水(24uL)、10%NaOH(48uL)和水(972mL),并在室温搅拌混合物3分钟。将固体过滤并且用THF(10mL*2)洗涤滤饼;然后将合并的滤液用Na_2SO_4干燥并浓缩。残余物的提纯方法为:prep-TLC(MeOH/DCM=1/5)而得到期望的产物(16.2mg,34.0%)(白色固体),经^1H NMR证明为7:3的混合物。^1H NMR(400MHz,DMSO-d6)δ7.84(s,3H),6.89(d,J=7.8Hz,2H),6.49(s,2H),3.40-3.35(m,0.7H),3.09-3.00(m,0.3H)2.81-2.70(m,2H),2.23-2.15(m,1H),1.97-1.88(m,1H),1.73-1.65(m,1H),1.57-1.27(m,16H),0.89(d,J=8.5Hz,6H)。质谱(m/z):329.3$[M+H]^+$。

[0828] 化合物119

[0829] 1-甲基-N^4-(5,6,7,8-四氢萘-2-基)环己烷-1,4-二胺

[0830] 

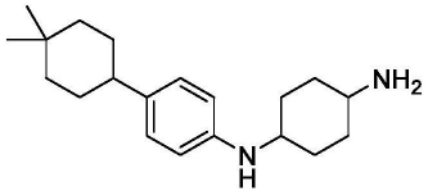
119

[0831] 由(1-甲基-4-((5,6,7,8-四氢萘-2-基)氨基)环己基)氨基甲酸叔丁酯(123mg,0.344mmol),TFA(1mL),和DCM(10mL),根据为24的程序制备标题化合物119(86.3mg),总收率为97.4%(白色固体)。^1H NMR(400MHz,DMSO-d6)δ8.29(d,J=40.0Hz,3H),6.77(dd,J=14.8,7.2Hz,1H),6.55-6.26(m,2H),4.98(s,1H),3.25(dt,J=8.0,4.0Hz,1H),2.58(dd,J=16.0,5.6Hz,4H),2.01-1.84(m,2H),1.80-1.71(m,2H),1.70-1.64(m,5H),1.52(ddd,J=

13.6,10.0,4.0Hz,2H),1.29(d,J＝8.8Hz,3H)。质谱(m/z):259.3[M+H]$^+$。

[0832] 化合物120

[0833] N^1-(4-(4,4-二甲基环己基)苯基)环己烷-1,4-二胺

[0834] 

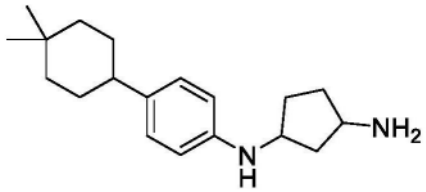
120A

120B

[0835] 由4-(4,4-二甲基环己基)苯胺(50mg,0.24mmol),(3-氧代环丁基)氨基甲酸叔丁酯(79mg,0.37mmol)和根据为20的程序,制备标题化合物120A(Rt＝5.22min;18.3mg),收率为24.7%(淡黄色粉末),和制备化合物120B(Rt＝5.87min;5.4mg),收率为7.31%(淡黄色粉末),提纯方法为:Prep-HPLC(柱:X Select-CSH-Prep 5μm OBD,19*150mm;ACN/水(0.5%TFA)＝5%-5%-95%-95%-5%,0min-1min-10min-11min-15.0min)。120A:^{1}H NMR(400MHz,DMSO-d6)δ7.85(s,3H),7.12(s,1H),6.84(s,2H),6.65(s,1H),3.21(s,1H),2.07-1.89(m,4H),1.38(qd,J＝12.0,11.3,6.1Hz,2H),1.31-1.16(m,11H)。质谱(m/z):301.5[M+H]$^+$。120B:^{1}H NMR(400MHz,DMSO-d6)δ7.83(s,2H),7.13-6.93(m,1H),6.60(d,J＝84.7Hz,3H),3.47(s,1H),3.14(s,1H),1.88-1.56(m,7H),1.24(d,J＝1.2Hz,9H)。质谱(m/z):301.5[M+H]$^+$。

[0836] 化合物121

[0837] N^1-(4-(4,4-二甲基环己基)苯基)环戊烷-1,3-二胺

[0838] 

121A

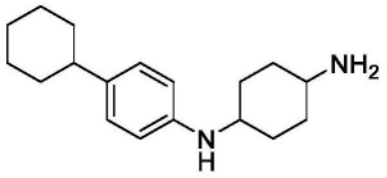
121B

[0839] 由4-(4,4-二甲基环己基)苯胺(100mg,0.49mmol),(3-氧代环戊基)氨基甲酸叔丁酯(146mg,0.74mmol)和根据为20的程序制备标题化合物121A(Rt＝5.76min;11.0mg),收率为7.8%(白色粉末)和制备化合物121B(Rt＝5.91min;6.8mg),收率为4.8%(白色粉末),提纯方法为:Prep-HPLC(柱:X Select-CSH-Prep 5μm OBD,19*150mm;ACN/水(0.5%TFA)＝5%-5%-95%-95%-5%,0min-1min-10min-11min-15.0min)。121A:^{1}H NMR(400MHz,DMSO-d6)δ7.81(s,3H),7.01(d,J＝8.2Hz,2H),6.63(d,J＝40.9Hz,2H),3.91-3.75(m,1H),3.64(s,1H),2.26(q,J＝5.7Hz,1H),2.16-2.05(m,2H),1.99(p,J＝6.9,6.5Hz,1H),1.87(q,J＝6.0,5.2Hz,2H),1.57-1.48(m,5H),1.43(d,J＝13.1Hz,2H),1.30(d,J＝13.8Hz,2H),0.95(s,3H),0.93(s,3H)。质谱(m/z):287.3[M+H]$^+$。121B:^{1}H NMR(400MHz,DMSO-d6)δ7.84(s,3H),7.00(d,J＝9.2Hz,2H),6.56(s,2H),3.71(d,J＝7.1Hz,1H),3.54(s,1H),2.20-2.32(m,1H),1.98(dt,J＝15.4,7.8Hz,3H),1.75-1.59(m,2H),1.54(d,J＝8.4Hz,4H),1.43(d,J

=13.1Hz,3H),1.34-1.28(m,2H),0.95(s,3H),0.93(s,3H)。质谱(m/z):287.3[M+H]$^+$。

[0840] 化合物122

[0841] N^1-(4-环己基苯基)环己烷-1,4-二胺

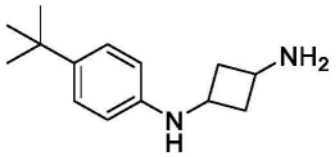
[0842] 

122

[0843] 由4-环己基苯胺(50mg,0.27mmol),(3-氧代环丁基)氨基甲酸叔丁酯(91mg,0.43mmol)和根据为20的程序制备标题化合物122(2.2mg),收率为2.8%(玫瑰棕色固体)。^{1}H NMR(400MHz,甲醇-d4)δ7.20(d,J=8.3Hz,2H),6.99(d,J=8.1Hz,2H),3.58(s,1H),2.48(s,1H),2.02(q,J=6.6Hz,1H),1.95-1.77(m,12H),1.74(d,J=13.0Hz,1H),1.51-1.36(m,4H),1.31(s,1H)。质谱(m/z):273.3[M+H]$^+$。

[0844] 化合物123

[0845] N^1-(4-(叔丁基)苯基)环丁烷-1,3-二胺

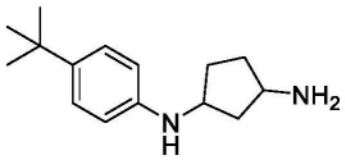
[0846] 

123

[0847] 由4-(叔丁基)苯胺(100mg,0.67mmol),(3-氧代环丁基)氨基甲酸叔丁酯(186mg,1.1mmol)和根据为20的程序制备标题化合物123(48.7mg),收率为33.2%(白色粉末),经^{1}H NMR证明为4:1的混合物。^{1}H NMR(400MHz,DMSO-d6)δ8.43(s,3H),7.12-7.08(m,2H),6.43-6.37(m,2H),5.83(d,J=6.3Hz,1H),4.07(h,J=6.6Hz,1H),3.72(td,J=8.2,4.2Hz,1H),2.45(td,J=7.7,3.8Hz,2H),2.15(ddd,J=13.2,8.1,5.0Hz,2H),1.20(d,J=0.9Hz,9H)。质谱(m/z):219.2[M+H]$^+$。

[0848] 化合物124

[0849] N^1-(4-(叔丁基)苯基)环戊烷-1,3-二胺

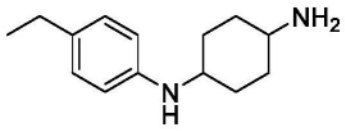
[0850] 

124

[0851] 由4-(叔丁基)苯胺(100mg,0.67mmol),(3-氧代环戊基)氨基甲酸叔丁酯(200mg,1.01mmol)和根据为20的程序制备标题化合物124(40.0mg),收率为25.6%(白色粉末)经^{1}H NMR证明为1:0.3的混合物。^{1}H NMR(400MHz,DMSO-d6)δ8.15(s,4H),7.11-7.03(m,3H),6.49(dd,J=8.7,6.8Hz,3H),5.65(s,0.3H),5.45(d,J=7.0Hz,1H),3.88(h,J=6.2Hz,1H),3.71(s,0.3H),3.62-3.54(m,1H),3.48(p,J=7.1Hz,0.3H),2.38(dt,J=14.2,7.3Hz,0.3H),2.09(tdd,J=13.0,10.0,6.1Hz,2H),2.01-1.87(m,2H),1.86-1.70(m,2H),1.68-1.54(m,1H),1.52-1.41(m,2H),1.26-1.21(m,2H),1.20(s,12H)。质谱(m/z):233.3[M+H]$^+$。

[0852] 化合物125

[0853] N^1-(4-乙基苯基)环己烷-1,4-二胺

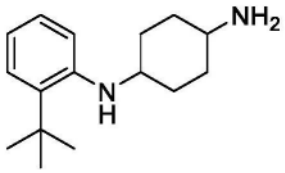
[0854] 

125

[0855] 由4-乙基苯胺(100mg,0.82mmol),(4-氧代环己基)氨基甲酸叔丁酯(263mg,1.24mmol)和根据为20的程序制备标题化合物125(36.0mg),收率为19.9%(白色粉末),经^{1}H NMR证明为2:1的混合物。^{1}H NMR(400MHz,DMSO-d6)δ8.01(s,3H),6.90(dd,J=8.4,6.3Hz,2H),6.56-6.45(m,2H),5.21-5.11(m,1H),3.09(s,1H),2.97(s,0.46H),2.43(qd,J=7.6,2.6Hz,2H),1.99(t,J=13.8Hz,2H),1.84-1.66(m,3H),1.61(d,J=11.3Hz,1H),1.44(q,J=12.8,12.2Hz,1H),1.22-1.12(m,1H),1.12-1.07(m,3H)。质谱(m/z):219.4[M+H]$^+$。

[0856] 化合物126

[0857] N^1-(2-(叔丁基)苯基)环己烷-1,4-二胺(126)

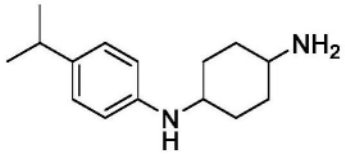
[0858] 

126

[0859] 由2-(叔丁基)苯胺(93mg,0.63mmol),(4-氧代环己基)氨基甲酸叔丁酯(200mg,0.94mmol)和根据为20的程序制备标题化合物126(54.8mg),收率为33.1%(白色粉末),经^{1}H NMR证明为8:1的混合物。^{1}H NMR(400MHz,DMSO-d6)δ8.20(s,3H),7.11(dd,J=7.8,1.6Hz,1H),7.02(ddd,J=8.4,7.2,1.5Hz,1H),6.71-6.65(m,1H),6.55(tt,J=7.6,1.7Hz,1H),3.82(d,J=8.0Hz,1H),3.33-3.21(m,1H),3.05-2.92(m,1H),2.13-1.96(m,4H),1.82(d,J=9.2Hz,1H),1.50(qd,J=12.7,3.2Hz,2H),1.39(s,1H),1.34(s,8H)。质谱(m/z):247.3[M+H]$^+$。

[0860] 化合物127

[0861] N^1-(4-异丙基苯基)环己烷-1,4-二胺

[0862] 

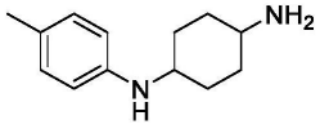
127

[0863] 由4-异丙基苯胺(85mg,0.63mmol),(4-氧代环己基)氨基甲酸叔丁酯(200mg,0.94mmol)和根据为20的程序制备标题化合物127(56.4mg),收率为39.0%(白色粉末),经^{1}H NMR证明为2:1的混合物。^{1}H NMR(400MHz,DMSO-d6)δ8.21(d,J=32.0Hz,3H),6.97-6.89(m,2H),6.52(dd,J=13.3,8.3Hz,2H),5.19(s,1H),3.08(s,1H),2.95(s,1H),2.72(ddd,J=13.8,6.9,2.1Hz,1H),2.05-1.93(m,2H),1.75(tt,J=10.4,5.2Hz,3H),1.66-1.55(m,1H),1.53-1.39(m,1H),1.18(t,J=10.9Hz,1H),1.14(d,J=1.3Hz,3H),1.12(d,J=1.3Hz,

3H)。质谱(m/z):233.3[M+H]$^+$。

[0864] 化合物128

[0865] N^1-(对甲苯基)环己烷-1,4-二胺

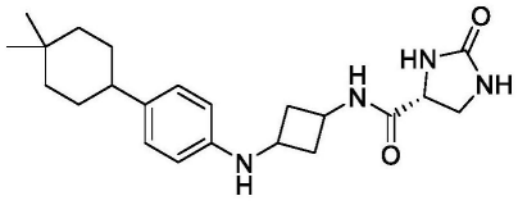
[0866] 

128

[0867] 由对甲苯胺(63mg,0.59mmol),(4-氧代环己基)氨基甲酸叔丁酯(188mg,0.89mmol)和根据为20的程序制备标题化合物128(27.7mg),收率为23.0%(白色粉末),经^{1}H NMR证明为3:2的混合物。^{1}H NMR(400MHz,DMSO-d6)δ8.31-8.21(m,2H),8.17(s,1H),6.87(dd,J=8.1,4.8Hz,2H),6.56-6.43(m,2H),5.15(s,1H),3.08(s,1H),2.95(s,1H),2.13(d,J=2.1Hz,3H),2.00(dd,J=13.0,4.1Hz,3H),1.75(tt,J=12.3,10.0,4.3Hz,2H),1.60(d,J=12.8Hz,1H),1.54-1.39(m,1H),1.15(q,J=12.0Hz,1H)。质谱(m/z):205.2[M+H]$^+$。

[0868] 化合物129

[0869] (R)-N-(3-((4-(4,4-二甲基环己基)苯基)氨基)环丁基)-2-氧代咪唑烷-4-甲酰胺

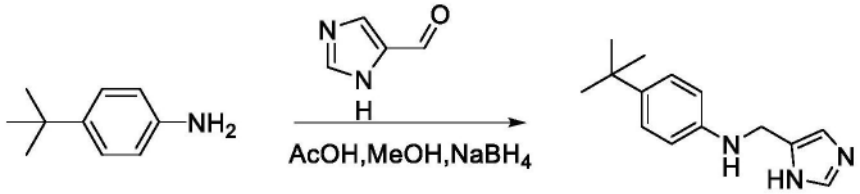
[0870] 

129

[0871] 由N^1-(4-(4,4-二甲基环己基)苯基)环丁烷-1,3-二胺(30mg,0.11mmol),(R)-2-氧代咪唑烷-4-甲酸(19mg,0.14mmol)和根据为10的程序制备标题化合物129(7.1mg),收率为16.77%(白色粉末),经^{1}H NMR证明为1:0.3的混合物。^{1}H NMR(400MHz,DMSO-d6)δ8.32(d,J=7.1Hz,1H),6.99-6.90(m,2H),6.51(s,1H),6.43-6.37(m,2H),6.30(s,1H),5.77(d,J=5.9Hz,1H),4.33(q,J=7.0Hz,1H),4.05(ddd,J=9.7,6.1,1.6Hz,1H),3.84(s,1H),2.25(ddd,J=20.3,11.4,5.3Hz,2H),2.12(td,J=8.2,4.1Hz,2H),2.00(p,J=6.9,6.5Hz,2H),1.59-1.50(m,4H),1.50-1.38(m,4H),1.13(dd,J=6.9,1.4Hz,1H),0.95(s,3H),0.93(s,3H)。质谱(m/z):385.3[M+H]$^+$。

[0872] 化合物130

[0873] N-((1H-咪唑5-基)甲基)-4-(叔丁基)苯胺

[0874] 

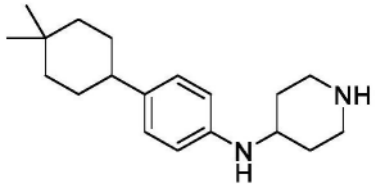
130

[0875] 向4-(叔丁基)苯胺(150mg,1.0mmol)/MeOH(10mL)和一滴AcOH的溶液中添加1H-咪唑-5-甲醛(201.9mg,1.0mmol)和在50℃搅拌混合物1小时。然后在冷却到25℃后向混合物

中添加$NaBH_4$(76mg,2mmol)。然后在25℃搅拌混合物16小时。LCMS显示反应完成。将反应用水(10mL)淬灭,用EA(10mL*3)萃取。将合并的有机层用盐水(20mL)洗涤,用硫酸钠干燥,过滤和浓缩。残余物的提纯方法为:使用EA/PE(1:3)的combi-flash(闪式色谱)而得到130(0.12g,52.0%,收率)(黄色固体)。^{1}H NMR(400MHz,DMSO-d6)δ7.52(d,J=1.2Hz,1H),7.05-7.02(m,2H),6.87(d,J=0.7Hz,1H),6.54-6.51(m,2H),5.54(d,J=1.2Hz,1H),4.05(s,2H),1.16(s,9H).MS(m/z)230.2$[M+H]^+$。

[0876] 化合物131

[0877] N-(4-(4,4-二甲基环己基)苯基)哌啶-4-胺

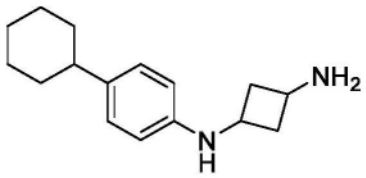
[0878] 

131

[0879] 由4-(4,4-二甲基环己基)苯胺(50mg,0.25mmol),4-氧代哌啶-1-甲酸叔丁酯(74mg,0.37mmol)和根据为20的程序制备标题化合物131(14.7mg),收率为15.4%(白色粉末)。^{1}H NMR(400MHz,DMSO-d6)δ8.57(s,1H),8.39(s,1H),7.00(d,J=8.1Hz,2H),6.62(d,J=8.0Hz,2H),3.49(p,J=5.8Hz,1H),3.30(s,2H),2.97(q,J=11.2Hz,2H),2.25(tt,J=10.5,5.2Hz,1H),2.07-1.94(m,2H),1.53(dt,J=10.8,3.4Hz,5H),1.48-1.38(m,3H),1.31-1.23(m,2H),0.93(s,3H),0.91(s,3H)。质谱(m/z):287.5$[M+H]^+$。

[0880] 化合物132

[0881] N^1-(4-环己基苯基)环丁烷-1,3-二胺

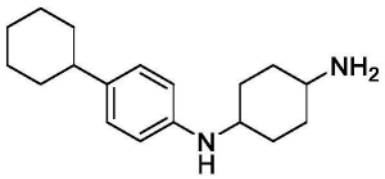
[0882] 

132

[0883] 由4-环己基苯胺(100mg,0.57mmol),(3-氧代环丁基)氨基甲酸叔丁酯(158mg,0.86mmol)和根据为20的程序制备标题化合物132(20.3mg),收率为14.5%(白色粉末),经^{1}H NMR证明为9:1的混合物。^{1}H NMR(400MHz,DMSO-d6)δ8.38(s,2H),6.97-6.87(m,2H),6.41-6.36(m,2H),5.81(d,J=6.2Hz,1H),4.05(q,J=5.9Hz,1H),3.72(ddd,J=13.3,8.2,5.2Hz,1H),2.44(tt,J=7.7,5.1Hz,2H),2.30(s,1H),2.14(ddd,J=13.0,8.0,4.9Hz,2H),1.80-1.63(m,5H),1.29(d,J=11.7Hz,4H),1.26-1.10(m,1H)。质谱(m/z):245.3$[M+H]^+$。

[0884] 化合物133

[0885] N^1-(4-环己基苯基)环己烷-1,4-二胺

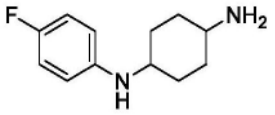
[0886] 

133

[0887] 由4-环己基苯胺(50mg,0.27mmol),(3-氧代环丁基)氨基甲酸叔丁酯(91mg,0.43mmol)和根据为20的程序制备标题化合物133(5.0mg),收率为6.1%(白色粉末)。^{1}H NMR(400MHz,DMSO-d6)δ7.78(s,3H),7.02(s,2H),6.67(s,1H),3.15(s,1H),2.99(s,1H),2.35(s,1H),2.07-1.86(m,6H),1.83-1.62(m,6H),1.39-1.28(m,6H)。质谱(m/z):273.3[M+H]$^+$。

[0888] 化合物134

[0889] N^1-(4-氟苯基)环己烷-1,4-二胺

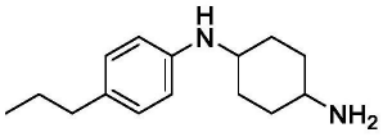
[0890] 

134

[0891] 由(4-((4-氟苯基)氨基)环己基)氨基甲酸叔丁酯(207mg,0.672mmol),TFA(1mL),和DCM(10mL),根据为24的程序制备标题化合物134(56.2mg),总收率为40.1%(紫色固体),经^{1}H NMR证明为1:2的混合物。^{1}H NMR(400MHz,DMSO-d6)δ7.93(s,3H),6.98(t,J=8.9Hz,2H),6.75(dd,J=8.8,4.6Hz,2H),3.44-3.36(m,1H),3.13(dp,J=11.5,6.1,5.5Hz,1H),1.78-1.55(m,8H)。质谱(m/z):209.3[M+H]$^+$。

[0892] 化合物135

[0893] N^1-(4-丙基苯基)环己烷-1,4-二胺

[0894] 

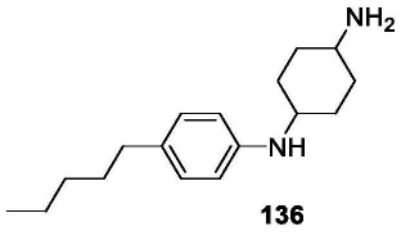
135A

135B

[0895] 由(4-((4-环戊基苯基)氨基)环己基)氨基甲酸叔丁酯(170mg,5.12mmol)和HCl/1,4-二氧杂环己烷(10mL,4N),根据为24的程序制备标题化合物135A(35.5mg)(白色固体)和135B(42.8mg)(白色固体)。135A:^{1}H NMR(400MHz,CD_3OD)δ7.41-7.10(m,4H),3.47(brs,1H),3.14(brs,1H),2.65-2.55(m,2H),2.13(d,J=9.8Hz,4H),1.70-1.45(m,6H),0.94(t,J=7.2Hz,3H)。MS(m/z):233[M+H]$^+$。HPLC:Rt=3.384min(柱:XBRIDGE 3.5um 2.1*50mm,移动相:H_2O(0.05%TFA)-ACN(0.05%TFA),ACN从0至60%在7分钟内,流速:0.8mL/min)。135B:^{1}H NMR(400MHz,CD_3OD)δ7.44-7.30(m,4H),3.66(br,^{1}H),3.46(br,^{1}H),2.64(dd,J=15.5,8.2Hz,3H),2.14-1.81(m,6H),1.76-1.55(m,3H),0.94(td,J=7.3,5.2Hz,4H)。MS(m/z):233[M+H]$^+$。HPLC:Rt=3.580min(柱:XBRIDGE 3.5um 2.1*50mm,移动相:H_2O(0.05%TFA)-ACN(0.05%TFA),ACN从0至60%在7分钟内,流速:0.8mL/min)。

[0896] 化合物136

[0897] N^1-(4-戊基苯基)环己烷-1,4-二胺

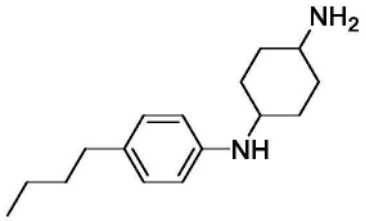
[0898] 

136

[0899] 由(4-((4-戊基苯基)氨基)环己基)氨基甲酸叔丁酯(79mg,0.22mmol)和HCl/1,4-二氧杂环己烷(10mL,4N),根据为24的程序制备标题化合物136(55mg,95.4%)(白色固体)。^{1}H NMR(400MHz,CD_3OD)δ7.44-7.12(m,4H),3.69-3.37(m,2H),3.20-3.08(m,1H),2.70-2.57(m,2H),2.15(br,2H),1.91(brs,4H),1.57(br,4H),1.41-1.24(br,4H),0.90(t,J=6.9Hz,3H).MS(m/z)261.3$[M+H]^+$。

[0900] 化合物137

[0901] N^1-(4-丁基苯基)环己烷-1,4-二胺

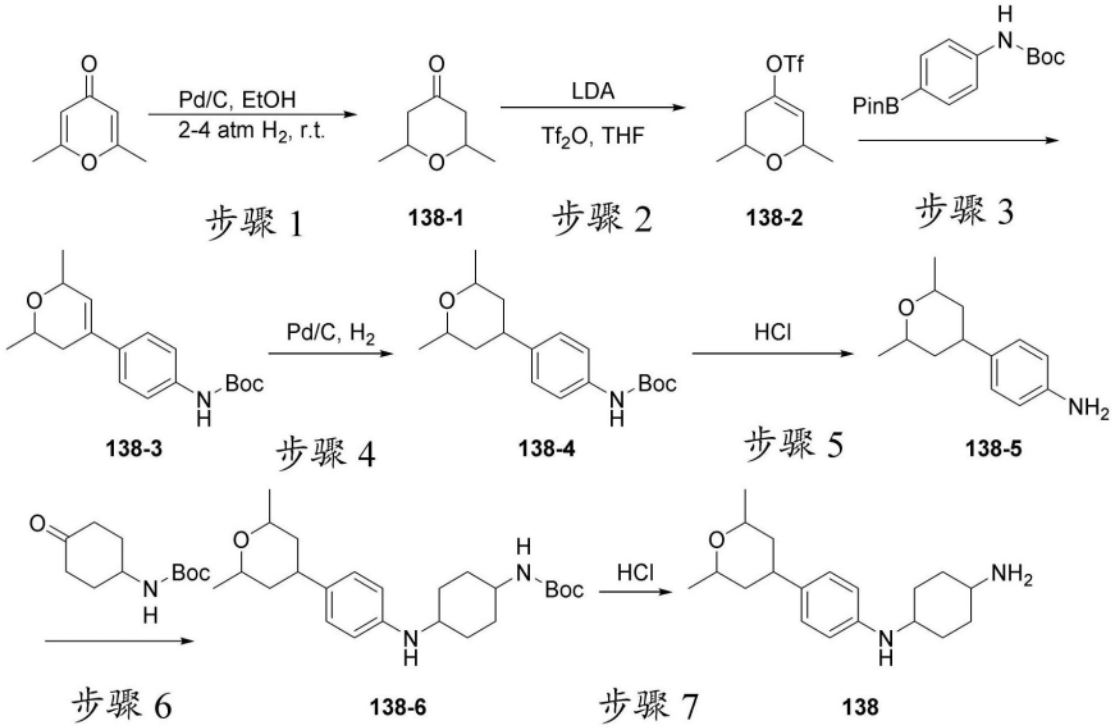
[0902] 

137

[0903] 由(4-((4-丁基苯基)氨基)环己基)氨基甲酸叔丁酯(90mg,0.26mmol)和HCl/1,4-二氧杂环己烷(10mL,4N),根据为37的程序制备标题化合物137(78mg,79.2%)(白色固体)。^{1}H NMR(400MHz,CDCl3)δ6.98(d,J=8.4Hz,2H),6.55(d,J=8.4Hz,2H),3.26(br,1H),3.08(br,1H),2.55-2.40(m,2H),2.30-2.08(m,4H),1.65-1.50(m,4H),1.35-1.30(m,2H),1.29-1.24(m,2H),1.24-1.08(m,2H),0.91(t,J=7.2Hz,3H).MS(m/z):247$[M+H]^+$。

[0904] 化合物138

[0905] N^1-(4-(2,6-二甲基四氢-2H-吡喃-4-基)苯基)环己烷-1,4-二胺

[0906] 

[0907] 步骤1:制备2,6-二甲基四氢-4H-吡喃-4-酮(138-1)

[0908] 向2,6-二甲基-4H-吡喃-4-酮(5g,40.3mmol)/EtOH(200mL)的溶液中添加钯(1g)。然后在氢气气氛下在3巴在25℃搅拌混合物8小时。在过滤钯后,真空除去有机相并且残余物的提纯方法为:快速色谱而得到期望的产物(1.4g,63.7%)(无色油)。^{1}H NMR(400MHz,DMSO-d6)δ3.76-3.64(m,2H),2.22-2.18(m,4H),1.20(d,J=8Hz,6H)。

[0909] 步骤2:制备三氟甲磺酸2,6-二甲基-3,6-二氢-2H-吡喃-4-基酯(138-2)

[0910] 向2,6-二甲基四氢-4H-吡喃-4-酮(0.7g,5.47mmol)/THF(20mL)的溶液中添加LDA(10mL,6.56mmol)并且在-78℃在氮气气氛下搅拌混合物30分钟。然后将三氟乙酸酐(5.2g,6.56mmol)滴加到混合物中并且在25℃搅拌过夜。将反应用水淬灭(30mL),并用EA(10mL)萃取3次。将合并的有机相用NaOH水溶液(10mL)洗涤3次和用硫酸钠干燥,真空除去而得到粗产物(0.6g,42.1%)(黄色油)。^{1}H NMR(400MHz,DMSO-d6)δ6.81-6.76(m,1H),3.81-3.71(m,2H),3.34(s,2H),2.50(s,6H)。

[0911] 步骤3:制备(4-(2,6-二甲基-3,6-二氢-2H-吡喃-4-基)苯基)氨基甲酸叔丁酯(138-2)

[0912] 向三氟甲磺酸2,6-二甲基-3,6-二氢-2H-吡喃-4-基酯(0.6g,2.3mmol)/二氧杂环己烷:H_2O=4:1(20mL)的溶液中添加4-(N-Boc-氨基)苯基硼酸频哪醇酯(733mg,2.3mmol),碳酸钾(952mg,6.9mmol)和四(三苯基膦)钯(265mg,0.23mmol)。然后在90℃搅拌混合物12小时。将反应用水淬灭(30mL),并用EA(10mL)萃取3次。将合并的有机相用硫酸钠干燥,减压浓缩并且残余物的提纯方法为:快速色谱而得到期望的产物(0.35g,50.2%)(黄色油)。质谱(m/z):248.2$[M+H]^+$。

[0913] 步骤4:制备(4-(2,6-二甲基四氢-2H-吡喃-4-基)苯基)氨基甲酸叔丁酯(138-3)

[0914] 向(4-((2R,6S)-2,6-二甲基-3,6-二氢-2H-吡喃-4-基)苯基)氨基甲酸叔丁酯(0.35g,1.16mmol)/MeOH(10mL)的溶液中添加钯(80mg)。然后在25℃在氮气气氛下搅拌混

合物3小时。在过滤钯后,真空除去有机相并且残余物的提纯方法为:快速色谱而得到期望的产物(黄色油)(0.33g,98.3%)。质谱(m/z):250.2[M+H]$^+$。

[0915] 步骤5:制备4-(2,6-二甲基四氢-2H-吡喃-4-基)苯胺(138-4)

[0916] 向(4-(2,6-二甲基四氢-2H-吡喃-4-基)苯基)氨基甲酸叔丁酯(0.33g,1.08mmol)/THF(5mL)的溶液中添加HCl/二氧杂环己烷(5mL)并搅拌混合物2小时。将反应用$NaHCO_3$(10mL)淬灭,用EA(10mL)萃取三次并且用硫酸钠干燥。在过滤后,真空除去有机相并且残余物的提纯方法为:快速色谱而得到期望的产物(0.16g,72.3%)(白色固体)。^{1}H NMR(400MHz,CDCl3)δ7.00(d,J=8Hz,2H),6.65(d,J=8Hz,2H),3.58(m,3H),2.69(m,1H),1.78-1.74(m,2H),1.35-1.26(m,2H),1.24(d,J=4Hz,6H).Mass m/z):220.2[M+H]$^+$。

[0917] 步骤6:制备(4-((4-(2,6-二甲基四氢-2H-吡喃-4-基)苯基)氨基)环己基)氨基甲酸叔丁酯(138-5)

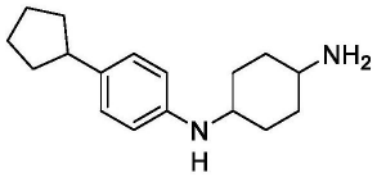
[0918] 向4-(2,6-二甲基四氢-2H-吡喃-4-基)苯胺(60mg,0.29mmol)/MeOH(5mL)的溶液中添加(4-氧代环己基)氨基甲酸叔丁酯(62.3mg,0.29mmol)和乙酸(1.74mg,0.029mmol)。然后在60℃搅拌混合物3小时。在将反应冷却到室温后,添加氰基硼氢化钠(54.8mg,0.87mmol)。在室温搅拌反应3小时。将反应用水(10mL)淬灭,用EA(10mL)萃取三次并且用硫酸钠干燥。在过滤后,真空除去有机相并且残余物的提纯方法为:快速色谱而得到期望的产物(70mg,58.6%)(白色固体)。质谱(m/z):402.8[M+H]$^+$。

[0919] 步骤7:制备N^1-(4-(2,6-二甲基四氢-2H-吡喃-4-基)苯基)环己烷-1,4-二胺(138)

[0920] 向4-(2,6-二甲基四氢-2H-吡喃-4-基)苯胺(70mg,0.17mmol)/THF(5mL)的溶液中添加HCl/二氧杂环己烷(4N;5mL)并搅拌混合物2小时。将反应用$NaHCO_3$(10mL)淬灭,用EA(10mL)萃取三次并且用硫酸钠干燥。在过滤后,真空除去有机相并且残余物的提纯方法为:prep-HPLC(柱-Xbridge-C18 150x 21.2mm,5um;移动相:ACN-H_2O(0.1%FA),40%-60%)而得到期望的产物(32mg,62.3%)(白色固体)。^{1}H NMR(400MHz,CDCl3)δ7.00(d,J=8.4Hz,2H),6.57(d,J=8.4Hz,2H),3.57(m,3H),3.19(s,1H),2.66(m,1H),1.95-1.58(m,10H),1.37-1.13(m,9H)。质谱(m/z):303.3[M+H]$^+$。

[0921] 化合物139

[0922] N^1-(4-环戊基苯基)环己烷-1,4-二胺

[0923] 

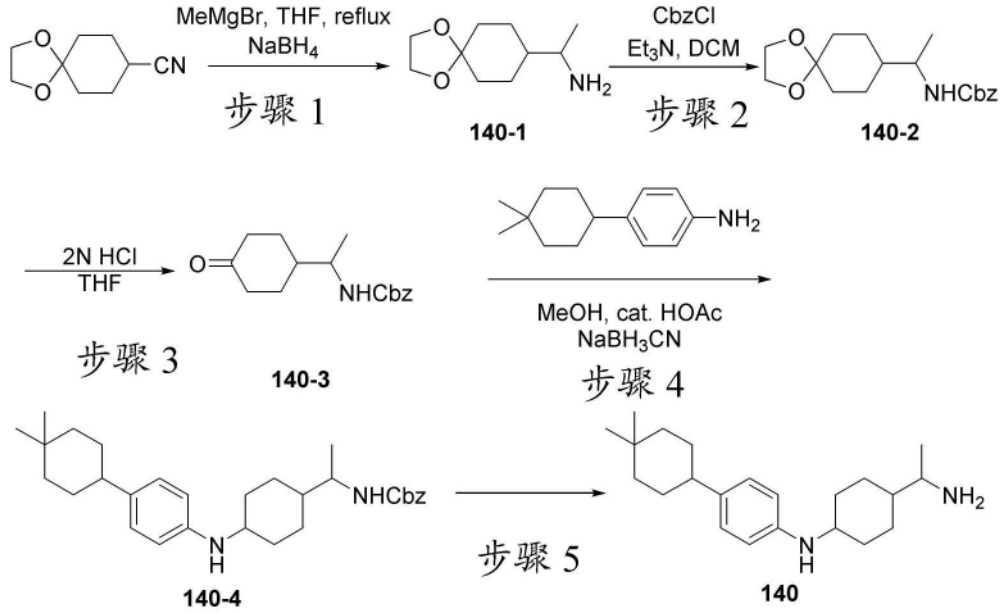
139A
139B

[0924] 根据为24的程序,由(4-((4-环戊基苯基)氨基)环己基)氨基甲酸叔丁酯(120mg,0.33mmol)和HCl/1,4-二氧杂环己烷(10mL,4N)制备标题化合物139A(46.5mg)(白色固体)和139B(32.9mg)(白色固体)。139A:^{1}H NMR(400MHz,CD_3OD)δ7.37(br,2H),7.20(br,2H),3.58(br,1H),3.39(br,1H),3.19-2.97(m,1H),2.13(br,2H),2.00-1.34(m,14H).MS(m/z)259[M+H]$^+$。HPLC:Rt=3.787min(柱:XBRIDGE 3.5um 2.1*50mm,移动相:H_2O(0.05%TFA)-

ACN(0.05％TFA),ACN从0至60％在7分钟内,流速:0.8mL/min)。139B:^{1}H NMR(400MHz,CD_3OD)δ7.37(br,2H),7.20(br,2H),3.58(br,1H),3.39(br,1H),3.19-2.97(m,1H),2.13(br,2H),2.00-1.34(m,14H).MS(m/z)259[M+H]$^+$。HPLC:Rt＝3.991min(柱:XBRIDGE 3.5um 2.1*50mm,移动相:H_2O(0.05％TFA)-ACN(0.05％TFA),ACN从0至60％在7分钟内,流速:0.8mL/min)。

[0925] 化合物140

[0926] N-(4-(1-氨基乙基)环己基)-4-(4,4-二甲基环己基)苯胺

[0927] 

[0928] reflux:回流

[0929] 步骤1:制备1-(1,4-二氧杂螺[4.5]癸烷-8-基)乙-1-胺(140-1)

[0930] 在0℃在氮气气氛下向1,4-二氧杂螺[4.5]癸烷-8-甲腈(1g,6mmol)/THF(10mL)的溶液中添加MeMgBr(2mL,6mmol)。然后在70℃搅拌混合物2小时。然后在冷却到25℃后向混合物中添加$NaBH_4$(0.68g,18mmol)。然后在25℃搅拌混合物2小时。LCMS显示反应完成。将反应用水(20mL)淬灭,用EA(20mL*3)萃取。将合并的有机层用盐水(40mL)洗涤,用硫酸钠干燥,过滤和浓缩。残余物的提纯方法为:使用EA/PE(1:0)的combi-flash(闪式色谱)而得到化合物140-1(0.2g,18.2％,收率)(黄色固体)。MS(m/z)186.2[M+H]$^+$。

[0931] 步骤2:制备(1-(1,4-二氧杂螺[4.5]癸烷-8-基)乙基)氨基甲酸苄基酯(140-2)

[0932] 向化合物140-1(0.2g,1.1mmol)/DCM(10mL)的溶液中添加TEA(218.5mg,2.2mmol)和CbzCl(202.6mg,1.2mmol)。然后在25℃搅拌混合物2小时。LCMS显示反应完成。将混合物添加到H_2O,用EA(20mL*3)萃取。将合并的有机层用盐水(40mL)洗涤,用硫酸钠干燥,过滤和浓缩。残余物的提纯方法为:使用EA/PE(1:3)的combi-flash(闪式色谱)而得到化合物140-2(0.2g,58％,收率)(黄色油)。MS(m/z)342.2[M+Na]$^+$。

[0933] 步骤3:制备(1-(4-氧代环己基)乙基)氨基甲酸苄基酯(140-3)

[0934] 在25℃向140-2(0.2g,0.62mmol)/THF(2mL)的溶液中添加2NHCl(2mL)。然后在25℃搅拌混合物10小时。LCMS显示反应完成。将反应浓缩。残余物的提纯方法为:使用EA/PE(1:2)的combi-flash(闪式色谱)而得到化合物4(0.105g,61％,收率)(黄色油)。MS(m/z)275.8[M+H]$^+$。

[0935] 步骤4:制备(1-(4-((4-(4,4-二甲基环己基)苯基)氨基)环己基)乙基)氨基甲酸苄基酯(140-4)

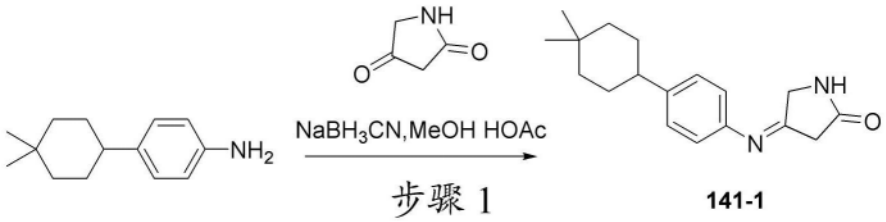
[0936] 向140-3(105mg,0.36mmol)/MeOH(5mL)和一滴AcOH的溶液中添加4-(4,4-二甲基环己基)苯胺(74mg,0.36mmol)和在50℃搅拌混合物1小时。然后在冷却到25℃后向混合物中添加$NaBH_3CN$(68.5mg,1.1mmol)。然后在25℃搅拌混合物2小时。LCMS显示反应完成。将反应用水(10mL)淬灭,用EA(10mL*3)萃取。将合并的有机层用盐水(20mL)洗涤,用硫酸钠干燥,过滤和浓缩。残余物的提纯方法为:使用EA/PE(1:3)的combi-flash(闪式色谱)而得到化合物5(0.1g,59.5%,收率)(黄色固体)。MS(m/z)462.8$[M+H]^+$。

[0937] 步骤5:制备N-(4-(1-氨基乙基)环己基)-4-(4,4-二甲基环己基)苯胺(140)

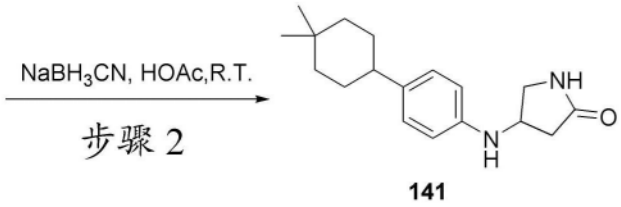
[0938] 在氮气气氛下在25℃向化合物140-4(0.1g,0.21mmol)/DCM(5mL)的溶液中添加Et3SiH(75.4mg,0.65mmol),TEA(44mg,0.43mmol)和Pd(OAc)2(5mg,0.021mmol)。然后在25℃搅拌混合物2小时。LCMS显示反应完成。反应用水(20mL)慢慢地淬灭,用EA(20mL*3)萃取。将合并的有机层用盐水(40mL)洗涤,用硫酸钠干燥,过滤和浓缩。残余物的提纯方法为:使用DCM/MeOH(10:1)的combi-flash(闪式色谱)而得到化合物140(10mg,13%,收率)(黄色固体)。^1H NMR(300MHz,CD_3OD)δ6.96-6.88(m,2H),6.61-6.54(m,2H),3.58-3.50(m,1H),3.15-3.01(m,1H),2.29-1.87(m,2H),1.66-1.39(m,16H),1.20(m,3H),0.91(d,J=12Hz,6H).MS(m/z)329.3$[M+H]^+$。

[0939] 化合物141

[0940] 4-((4-(4,4-二甲基环己基)苯基)氨基)吡咯烷-2-酮(141)



[0941]



[0942] 步骤1:制备(Z)-4-((4-(4,4-二甲基环己基)苯基)亚氨基)吡咯烷-2-酮(141-1)

[0943] 在50℃搅拌4-(4,4-二甲基环己基)苯胺(100mg,0.49mmol),吡咯烷-2,4-二酮(63.4mg,0.64mmol)和$NaBH_3CN$(61.8mg,0.98mmol)/MeOH(10mL)和HOAc(1滴)的混合物过夜。在冷却后,真空除去过量的MeOH,残余的油用乙酸乙酯(20mL)and水(10mL)萃取三次。合并有机相,真空除去溶剂并且通过硅胶色谱(PE:EA=10:1)提纯粗产物而得到亚胺中间体(98mg,55.7%)(油)。质谱(m/z):285.2$[M+H]^+$。

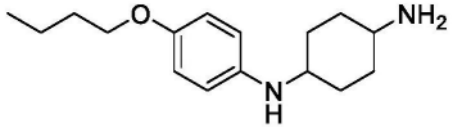
[0944] 步骤2:制备4-((4-(4,4-二甲基环己基)苯基)氨基)吡咯烷-2-酮(141)

[0945] 向(Z)-4-((4-(4,4-二甲基环己基)苯基)亚氨基)吡咯烷-2-酮(70mg,0.25mmol)/HOAc(10mL)的溶液中添加$NaBH_3CN$(15.5mg,0.25mmol)。在25℃搅拌混合物过夜。在反应完

成后,将反应溶液用水洗涤,真空除去溶剂并且残余物的提纯方法为:prep-HPLC(柱-Xbridge-C18 150x 21.2mm,5um;移动相:ACN-H_2O(0.1%FA),40%-70%)而得到期望的产物141(8mg)(白色固体)。^1H NMR(400MHz,DMSO-d6)δ8.19(s,1H),7.13(t,4H),7.03(t,4H),3.94(s,2H),3.81(s,2H),3.55(s,2H),2.88(s,3H),2.37-2.30(m,1H),1.63-1.51(m,4H),1.45(d,2H),1.35-1.26(m,2H),0.95(d,6H)。质谱(m/z):287.3$[M+H]^+$。

[0946] 化合物142

[0947] N^1-(4-丁氧基苯基)环己烷-1,4-二胺

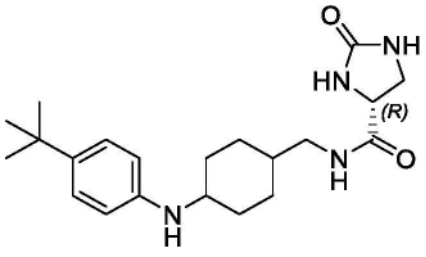
[0948] 

142A
142B

[0949] 由(4-((4-丁氧基苯基)氨基)环己基)氨基甲酸叔丁酯(200mg,0.55mmol)和HCl/1,4-二氧杂环己烷(10mL,4N),根据为24的程序制备标题化合物142A(17.1mg)(白色固体)和142B(20.7mg)(白色固体)。142A:^1H NMR(400MHz,DMSO-d6)δ8.42(s,1H),6.68(d,J=8.9Hz,2H),6.50(d,J=8.9Hz,2H),3.81(t,J=6.5Hz,2H),3.01(d,J=11.2Hz,1H),2.87(d,J=11.1Hz,1H),1.94(dd,J=23.9,11.9Hz,4H),1.66-1.58(m,2H),1.48-1.31(m,4H),1.12(d,J=12.7Hz,2H),0.91(t,J=7.4Hz,3H)。MS(m/z)263.2$[M+H]^+$。HPLC:Rt:3.789min(柱:XBRIDGE 2.1*50mm,3.5um;移动相:H_2O(0.05%TFA)/ACN(0.05%TFA),ACN由0%至60%在7分钟内,7-8min,ACN由60%至100%;0.8mL/min)。142B:^1H NMR(400MHz,DMSO-d6))δ8.42(s,1H),6.69(d,J=8.9Hz,2H),6.54(d,J=8.7Hz,2H),3.81(t,J=6.5Hz,2H),3.34(s,1H),3.00(s,1H),1.74-1.53(m,11H),1.40(dd,J=15.0,7.4Hz,2H),0.91(t,J=7.4Hz,3H)。MS(m/z)263.2$[M+H]^+$。HPLC:Rt:3.887min(柱:XBRIDGE 2.1*50mm,3.5um;移动相:H_2O(0.05%TFA)/ACN(0.05%TFA),ACN由0%至60%在7分钟内,7-8min,ACN由60%至100%;0.8mL/min)。

[0950] 化合物143

[0951] (R)-N-((4-((4-(叔丁基)苯基)氨基)环己基)甲基)-2-氧代咪唑烷-4-甲酰胺

[0952] 

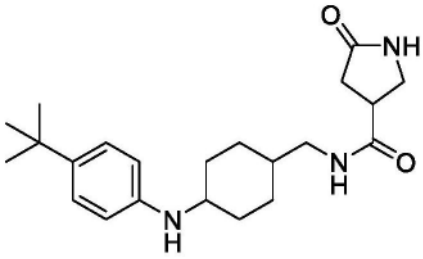
143A
143B

[0953] 根据为化合物1的程序,制备标题化合物143A和143B。粗制残余物的提纯方法为:制备TLC(MeOH:二氯甲烷=1:10)而得到10.4mg的化合物143A,收率为18.6%(淡黄色固体)和5.1mg的143B,收率为5.0%(淡黄色固体)。143A:^1H NMR(301MHz,DMSO-d6)δ7.94(t,J=5.6Hz,1H),7.46-6.94(m,5H),6.53(s,1H),6.34(s,1H),4.08-4.03(m,1H),3.54(t,J=9.3Hz,1H),3.47-3.40(m,1H),3.22-3.03(m,3H),1.72-1.39(m,8H),1.26(s,6H)。质谱(m/

z):373.3[M+H]$^+$。HPLC:Rt＝0.334mins(Agilent,poroshell 120,SB-C18 2.7μm,4.6x50mm,ACN/水(0.1%FA)＝5%-5%-95%-95%-95%-5%,0-0.5min-10min-10.5min-12.0min)。143B:^{1}H NMR(301MHz,DMSO-d6)δ7.89(t,J＝5.9Hz,1H),7.45-6.94(m,5H),6.51(s,1H),6.33(s,1H),4.04(dd,J＝9.7,6.3Hz,1H),3.53(t,J＝9.3Hz,1H),3.30-3.14(m,2H),2.94(t,J＝6.3Hz,2H),1.92(d,J＝12.0Hz,2H),1.73(d,J＝12.7Hz,2H),1.50-1.32(m,2H),1.26(s,6H),0.95(q,J＝12.7Hz,2H)。质谱(m/z):373.3[M+H]$^+$。HPLC:Rt＝0.238mins(Agilent,poroshell 120,SB-C18 2.7μm,4.6x50mm,ACN/水(0.1%FA)＝5%-5%-95%-95%-95%-5%,0-0.5min-10min-10.5min-12.0min)。

[0954] 化合物144

[0955] N-((4-((4-(叔丁基)苯基)氨基)环己基)甲基)-5-氧代吡咯烷-3-甲酰胺

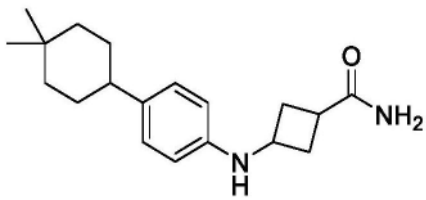
[0956] 

144A
144B

[0957] 根据为化合物1的程序制备标题化合物144A和144B。粗制残余物的提纯方法为:制备TLC(MeOH:二氯甲烷＝1:10)而得到3.7mg的化合物144A,收率为6.6%(淡黄色固体)和4.6mg的144B,收率为8.3%(淡黄色固体)。144A:^{1}H NMR(301MHz,DMSO-d6)δ8.01(t,J＝5.7Hz,1H),7.59(s,1H),7.35(s,2H),7.14-6.86(m,3H),3.50-3.33(m,3H),3.23-3.03(m,4H),2.28(d,J＝8.3Hz,2H),1.66-1.54(m,4H),1.50-1.39(m,4H),1.25(s,9H)。质谱(m/z):373.3[M+H]$^+$。HPLC:Rt＝0.372mins(Agilent,poroshell 120,SB-C18 2.7μm,4.6x50mm,ACN/水(0.1%FA)＝5%-5%-95%-95%-95%-5%,0-0.5min-10min-10.5min-12.0min)。144B:^{1}H NMR(301MHz,DMSO-d6)δ7.98(t,J＝5.7Hz,1H),7.58(s,1H),7.44-7.30(m,2H),7.12-6.83(m,3H),3.38(t,J＝8.8Hz,1H),3.27-3.08(m,4H),2.92(t,J＝6.3Hz,2H),2.26(d,J＝8.4Hz,2H),1.92(d,J＝12.0Hz,2H),1.73(d,J＝12.7Hz,2H),1.40-1.15(m,11H),1.00-0.90(m,2H)。质谱(m/z):373.3[M+H]$^+$。HPLC:Rt＝0.173mins(Agilent,poroshell 120,SB-C18 2.7μm,4.6x50mm,ACN/水(0.1%FA)＝5%-5%-95%-95%-95%-5%,0-0.5min-10min-10.5min-12.0min)。

[0958] 化合物145

[0959] 3-((4-(4,4-二甲基环己基)苯基)氨基)环丁烷-1-甲酰胺

[0960] 

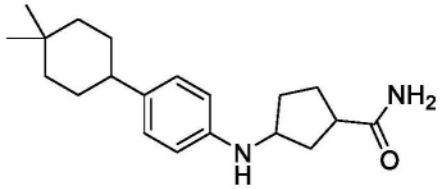
145

[0961] 由3-((4-(4,4-二甲基环己基)苯基)氨基)环丁烷-1-甲酸(55mg,0.18mmol),CDI

(59mg,0.36mmol)和$NH_3.H_2O$(0.5mL),根据为118-5的程序制备标题化合物145(8.7mg),总收率为15.8%(白色固体),经^1H NMR证明为7:3的混合物。^1H NMR(301MHz,DMSO-d6)δ7.24-7.19(m,1H),6.97-6.90(m,2H),6.78-6.72(m,1H),6.43(d,J=8.4Hz,0.8H),6.38(d,J=8.4Hz,1.2H),5.66(d,J=6.4Hz,0.6H),5.63(d,J=6.4Hz,0.4H),3.89-3.82(m,0.6H),3.69-3.63(m,0.4H),2.97-2.84(m,1H),2.48-2.34(m,4H),2.03-1.89(m,3H),1.56-1.37(m,6H),0.93(d,J=6.4Hz,6H)。质谱(m/z):301.3$[M+H]^+$。

[0962] 化合物146

[0963] 3-((4-(4,4-二甲基环己基)苯基)氨基)环戊烷-1-甲酰胺

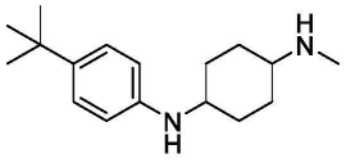
[0964] 

146A
146B

[0965] 根据为化合物118-5的程序制备标题化合物146A和146B。粗制残余物的提纯方法为:制备TLC(MeOH:二氯甲烷=1:10)而得到化合物146A,收率为61.4%(淡黄色固体)和146B,收率为47.3%(淡黄色固体)。146A:^1H NMR(400MHz,DMSO-d6)δ7.21(s,1H),6.90(d,J=8.4Hz,2H),6.67(s,1H),6.43(d,J=7.6Hz,2H),5.30(s,1H),3.73-3.62(m,1H),2.69(p,J=8.1Hz,1H),2.21-2.13(m,1H),1.96-1.82(m,3H),1.65-1.57(m,2H),1.52-1.35(m,8H),1.28-1.21(m,2H),0.90(d,J=8.8Hz,6H)。质谱(m/z):315.3$[M+H]^+$。HPLC:Rt=1.198mins(Agilent,poroshell 120,SB-C18 2.7μm,4.6x50mm,ACN/水(0.1%FA)=5%-5%-95%-95%-95%-5%,0-0.5min-10min-10.5min-12.0min)。146B:^1H NMR(400MHz,DMSO-d6)δ7.21(s,1H),6.90(d,J=8.0Hz,2H),6.67(s,1H),6.43(d,J=8.0Hz,2H),5.30(s,1H),3.72-3.65(m,1H),2.69(p,J=8.0Hz,1H),2.10-2.20(m,2H),2.01-1.82(m,3H),1.66-1.57(m,2H),1.49-1.35(m,7H),1.27-1.20(m,2H),0.90(d,J=8.8Hz,6H)。质谱(m/z):315.3$[M+H]^+$。HPLC:Rt=1.807mins(Agilent,poroshell 120,SB-C18 2.7μm,4.6x50mm,ACN/水(0.1%FA)=5%-5%-95%-95%-95%-5%,0-0.5min-10min-10.5min-12.0min)。

[0966] 化合物147

[0967] N^1-(4-(叔丁基)苯基)-N4-甲基环己烷-1,4-二胺

[0968] 

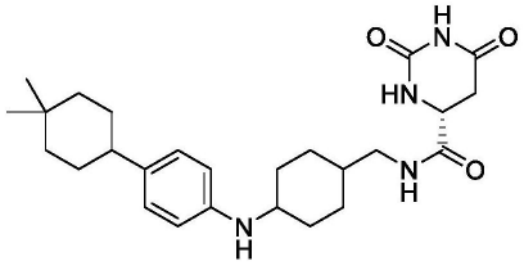
147A
147B

[0969] 根据为化合物118的程序制备标题化合物147A和147B。粗制残余物的提纯方法为:制备TLC(MeOH:二氯甲烷=1:5)而得到化合物147A,收率为27.5%(淡黄色固体)和147B,收率为7.7%(淡黄色固体)。147A:^1H NMR(400MHz,DMSO-d6)δ8.70(s,2H),7.05(d,J=8.6Hz,3H),6.50(d,J=8.4Hz,2H),5.19(d,J=5.6Hz,1H),3.45-3.36(m,1H),3.00-2.93(m,1H),

2.46(s,3H),1.82-1.70(m,6H),1.59-1.49(m,2H),1.17(s,9H)。质谱(m/z):261.3[M+H]$^+$。HPLC:Rt＝0.423mins(Agilent,poroshell 120,SB-C18 2.7μm,4.6x50mm,ACN/水(0.1%FA)＝5%-5%-95%-95%-95%-5%,0-0.5min-10min-10.5min-12.0min)。147B:^{1}H NMR(400MHz,DMSO-d6)δ7.11-7.00(m,2H),6.50-6.41(m,2H),5.10(d,J＝8.2Hz,1H),3.44-3.27(m,2H),3.12-3.03(m,2H),6.50-6.41(m,2H),2.30-2.18(m,4H),1.97-1.84(m,4H),1.20(s,9H),1.13-0.98(m,4H)。质谱(m/z):261.3[M+H]$^+$。HPLC:Rt＝0.318mins(Agilent,poroshell 120,SB-C18 2.7μm,4.6x50mm,ACN/水(0.1%FA)＝5%-5%-95%-95%-95%-5%,0-0.5min-10min-10.5min-12.0min)。

[0970] 化合物148

[0971] (R)-N-((4-((4-(4,4-二甲基环己基)苯基)氨基)环己基)甲基)-2,6-二氧代六氢嘧啶-4-甲酰胺

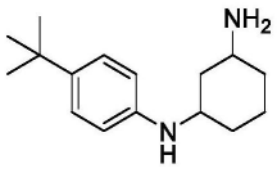
[0972] 

148 A/B

[0973] 由N^1-(4-(叔丁基)苯基)环己烷-1,4-二胺(18.6mg,0.06mmol),根据为化合物1的程序制备标题化合物148。混合物的提纯方法:制备HPLC(柱:X Select-CSH-Prep 5μm OBD,19*150mm;ACN/水(0.5%TFA)＝20%-45%-95%-95%-10%,0min-12min-12.5min-13.5min-15min)而得到化合物148A(Rt＝9.79min)(沙褐色固体)和化合物148B(Rt＝10.42min)(沙褐色固体)。148A(7.0mg,26%):^{1}H NMR(400MHz,DMSO-d6)δ9.98(s,1H),8.00(s,1H),7.54(s,1H),7.29-7.03(m,4H),6.95(s,1H),3.92(m,1H),3.17(m,1H),2.88(m,2H),2.66-2.54(m,2H),2.29(m,1H),1.97-1.85(m,3H),1.68(m,2H),1.56-1.22(m,12H),0.92(s,3H),0.89(s,3H)。质谱(m/z):455.2[M+H]$^+$。148B(14.1mg,53%):^{1}H NMR(400MHz,DMSO-d6)δ9.97(s,1H),8.01(s,1H),7.55(s,1H),7.29-6.84(m,5H),3.93(m,1H),3.01(m,2H),2.80(m,1H),2.54(m,1H),2.42(m,1H),2.29(m,1H),1.63-1.46(m,8H),1.44-1.33(m,6H),1.31-1.23(m,3H),0.92(s,3H),0.89(s,3H)。质谱(m/z):455.2[M+H]$^+$。

[0974] 化合物149

[0975] N^1-(4-(叔丁基)苯基)环己烷-1,3-二胺

[0976] 

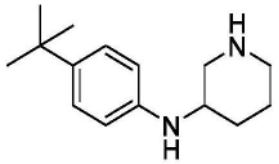
149 A
149 B

[0977] 由(3-((4-(叔丁基)苯基)氨基)环己基)氨基甲酸叔丁酯(520mg,1.5mmol),根据为化合物88的程序制备标题化合物149。混合物的提纯方法:制备HPLC(柱:X Select-CSH-

Prep 5μm OBD,19*150mm;ACN/水(0.5%TFA)＝10%-32%-95%-95%-10%,0min-10min-10.5min-11.5min-13min)而得到化合物149A(Rt＝6.88min)(白色固体)和化合物149B(Rt＝9.25min)(白色固体)。149A(79.8mg,21%):^{1}H NMR(400MHz,DMSO-d6)δ7.33(d,J＝8.4Hz,2H),6.94(d,J＝8.4Hz,2H),3.39(m,1H),3.09(m,1H),2.25-1.75(m,4H),1.44-1.28(m,4H),1.24(s,9H)。质谱(m/z):247.2[M+H]$^+$。149B(188.5mg,51%):^{1}H NMR(400MHz,DMSO-d6)δ7.28(d,J＝8.4Hz,2H),6.89(d,J＝8.4Hz,2H),3.77(m,1H),3.46(m,1H),2.13-1.32(m,8H),1.23(s,9H)。质谱(m/z):247.2[M+H]$^+$。

[0978] 化合物150

[0979] N-(4-(叔丁基)苯基)哌啶-3-胺

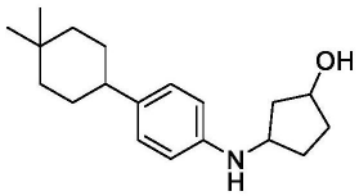
[0980] 

150

[0981] 由3-((4-(叔丁基)苯基)氨基)哌啶-1-甲酸叔丁酯(498mg,1.5mmol),根据为化合物88的程序制备标题化合物150(151.2mg)。^{1}H NMR(400MHz,DMSO-d6)δ7.09(d,J＝8.4Hz,2H),6.95(s,1H),6.58(d,J＝8.4Hz,2H),5.52(s,1H),3.59(s,1H),3.29-3.06(m,2H),2.74-2.56(m,2H),1.98-1.38(m,4H),1.20(s,9H)。质谱(m/z):233.4[M+H]$^+$。

[0982] 化合物151

[0983] 3-((4-(4,4-二甲基环己基)苯基)氨基)环戊烷-1-醇

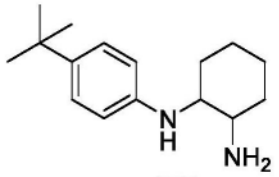
[0984] 

151

[0985] 由4-(4,4-二甲基环己基)苯胺(31mg,0.15mmol)和3-羟基环戊烷-1-酮(20mg,0.2mmol),根据为化合物4的程序制备标题化合物151(32.1mg),总收率为76%(巧克力色固体)。^{1}H NMR(400MHz,DMSO-d6)δ6.93(d,J＝8.4Hz,2H),6.47(d,J＝8.4Hz,2H),5.40(s,1H),4.49(s,1H),4.19(m,1H),3.79(m,1H),2.20(m,1H),2.12-1.83(m,3H),1.55-1.27(m,11H),0.93(s,3H),0.91(s,3H)。质谱(m/z):288.4[M+H]$^+$。

[0986] 化合物152

[0987] N^1-(4-(叔丁基)苯基)环己烷-1,2-二胺

[0988] 

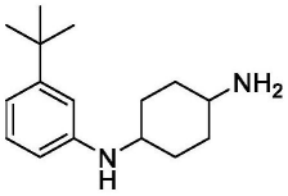
152

[0989] 由4-(叔丁基)苯胺(223mg,1.5mmol)和(2-氧代环己基)氨基甲酸叔丁酯(426mg,2.0mmol),根据为化合物24的程序制备标题化合物152(271.5mg),总收率为67%(黄色固

体)。^{1}H NMR(400MHz,DMSO-d6)δ7.11(d,J=8.4Hz,2H),6.67(d,J=8.4Hz,2H),3.32(m,1H),2.95(m,1H),2.26-1.92(m,2H),1.83-1.31(m,4H),1.21(s,9H),1.18-1.07(m,2H)。质谱(m/z):247.3[M+H]$^+$。

[0990] 化合物153

[0991] N^1-(3-(叔丁基)苯基)环己烷-1,4-二胺

[0992] 

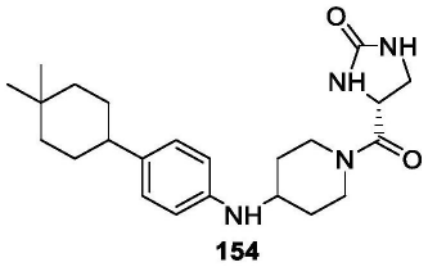
153A

153B

[0993] 由3-(叔丁基)苯胺(100mg,0.67mmol),(4-氧代环己基)氨基甲酸叔丁酯(214mg,1.01mmol)和根据为20的程序制备标题化合物153A(Rt=3.65min;45.3mg),收率为27.4%(白色粉末)和制备化合物153B(Rt=4.28min;36.7mg),收率为22.2%(白色粉末),提纯方法为:Prep-HPLC(柱:X Select-CSH-Prep 5μm OBD,19*150mm;ACN/水(0.5%TFA)=5%-5%-95%-95%-5%,0min-1min-10min-11min-15.0min)。153A:^{1}H NMR(400MHz,DMSO-d6)δ7.85(s,3H),7.12(s,1H),6.84(s,2H),6.65(s,1H),3.21(s,1H),3.06-2.93(m,1H),2.07-1.89(m,4H),1.38(qd,J=12.0,11.3,6.1Hz,2H),1.25(d,J=6.3Hz,2H),1.24-1.20(m,9H).153:^{1}H NMR(400MHz,DMSO-d6)δ7.83(s,2H),7.13-6.93(m,1H),6.60(d,J=84.7Hz,3H),3.47(s,1H),3.14(s,1H),1.88-1.56(m,8H),1.24(d,J=1.2Hz,9H)。质谱(m/z):247.6[M+H]$^+$。

[0994] 化合物154

[0995] (R)-4-(4-((4-(4,4-二甲基环己基)苯基)氨基)哌啶-1-羰基)咪唑烷-2-酮

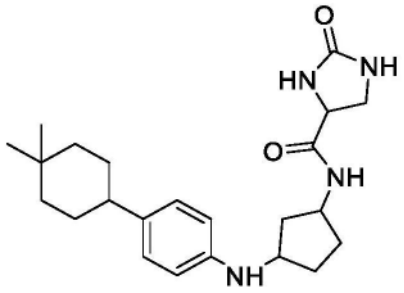
[0996] 

154

[0997] 由N-(4-(4,4-二甲基环己基)苯基)哌啶-4-胺(21.4mg,0.07mmol),(R)-2-氧代咪唑烷-4-甲酸(11mg,0.08mmol)和根据为1的程序制备标题化合物154(21.2mg),收率为71.2%(白色粉末)。^{1}H NMR(400MHz,DMSO-d6)δ7.22(s,1H),6.94(d,J=8.1Hz,2H),6.67(s,1H),6.52(d,J=8.0Hz,2H),6.26(d,J=6.6Hz,1H),4.55-4.60(m,1H),4.18(s,1H),2.40-2.45(m,2H),1.90(s,2H),1.52(s,4H),1.49-1.37(m,9H),1.08-1.13(m,1H),0.94(s,3H),0.92(s,3H)。质谱(m/z):399.3[M+H]$^+$。

[0998] 化合物155

[0999] N^1-(4-(4,4-二甲基环己基)苯基)环戊烷-1,3-二胺

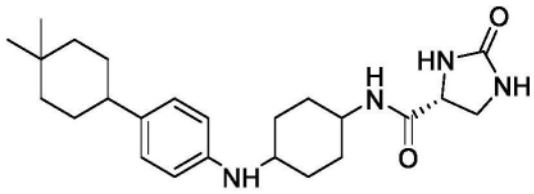
[1000] 

155

[1001] 由N^1-(4-(4,4-二甲基环己基)苯基)环戊烷-1,3-二胺(166mg,0.58mmol),(R)-2-氧代咪唑烷-4-甲酸(83mg,0.64mmol)和根据为1的程序制备标题化合物155(76.4mg),收率为33.0%(白色粉末),经^{1}H NMR证明为2:1的混合物。^{1}H NMR(400MHz,DMSO-d6)δ7.93(s,1H),7.20(d,J=63.2Hz,4H),6.37(d,J=61.1Hz,2H),4.28-4.21(m,1H),4.00(dd,J=9.8,6.2Hz,2H),3.50(td,J=9.0,6.7Hz,1H),3.24-3.11(m,1H),2.38(s,1H),2.09-1.97(m,2H),1.87(d,J=8.7Hz,1H),1.76(dt,J=13.8,7.3Hz,1H),1.57(d,J=11.0Hz,5H),1.43(d,J=12.5Hz,3H),1.31(d,J=14.5Hz,1H),0.95(s,3H),0.92(s,3H)。质谱(m/z):399.4[M+H]$^+$。

[1002] 化合物156

[1003] (R)-N-(4-((4-(4,4-二甲基环己基)苯基)氨基)环己基)-2-氧代咪唑烷-4-甲酰胺

[1004] 

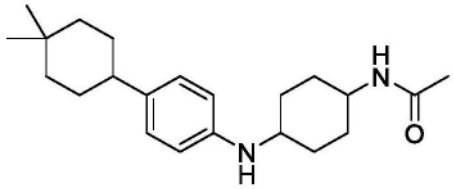
156A

156B

[1005] 由N^1-(4-(4,4-二甲基环己基)苯基)环己烷-1,4-二胺(57mg,0.19mmol),(R)-2-氧代咪唑烷-4-甲酸(27mg,0.21mmol),根据为1的程序制备标题化合物156A(Rt=6.19min;4.5mg),收率为5.7%(白色粉末)和制备化合物156B(Rt=7.19min;10mg),收率为12.6%(白色粉末),提纯方法为:Prep-HPLC(柱:X Select-CSH-Prep 5μm OBD,19*150mm;ACN/水(0.5%TFA)=25%-43%-95%-95%-10%,0min-10.0min-10.5min-11.5min-13.0min)。156A:^{1}H NMR(400MHz,DMSO-d6)δ7.77(d,J=7.8Hz,1H),7.23(s,2H),7.14-6.91(s,1H),6.48(s,1H),6.30(s,1H),4.03(dd,J=9.7,6.0Hz,2H),3.55-3.48(m,2H),3.17(dd,J=8.9,6.1Hz,1H),2.00(q,J=6.8,6.2Hz,1H),1.93(d,J=10.8Hz,2H),1.82(d,J=10.8Hz,2H),1.64-1.51(m,4H),1.45(d,J=12.3Hz,3H),1.32(t,J=9.0Hz,4H),0.97(s,3H),0.94(s,3H)。质谱(m/z):413.4[M+H]$^+$。156B:^{1}H NMR(400MHz,DMSO-d6)δ7.64-7.50(m,1H),7.21(s,2H),7.00(s,1H),6.51(s,1H),6.31(s,1H),4.09(dd,J=9.7,5.9Hz,1H),3.72(s,1H),3.52(t,J=9.3Hz,1H),3.39(d,J=8.5Hz,1H),3.20(dd,J=8.9,5.9Hz,1H),1.98(p,J=7.0,6.5Hz,1H),1.74(s,2H),1.69-1.60(m,4H),1.60-1.48(m,6H),1.43(d,J=12.8Hz,2H),1.31(d,J=13.7Hz,2H),0.95(s,3H),0.92(s,3H).质谱(m/z):413.4[M+H]$^+$。

[1006] 化合物157

[1007] N-(4-((4-(4,4-二甲基环己基)苯基)氨基)环己基)乙酰胺

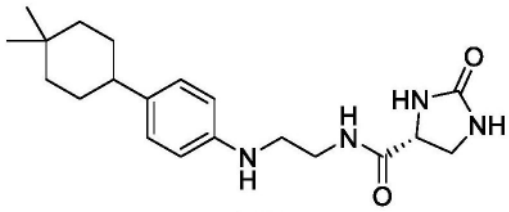
[1008] 

157A
157B

[1009] 由N^1-(4-(4,4-二甲基环己基)苯基)环己烷-1,4-二胺(100mg,0.33mmol),乙酸(30mg,0.50mmol)和根据为1的程序制备标题化合物157A(Rt=6.02min;18.7mg),收率为16.4%(白色粉末)和制备化合物157B(Rt=6.34min;25.4mg),收率为22.8%(白色粉末),提纯方法为:Prep-HPLC(柱:X Select-CSH-Prep 5μm OBD,19*150mm;ACN/水(0.5%TFA)=5%-5%-95%-95%-5%,0min-1min-10min-11min-15.0min)。175A:^{1}H NMR(400MHz,DMSO-d6)δ7.77(d,J=7.6Hz,1H),7.29(s,2H),7.13(s,2H),3.53-3.39(m,1H),2.40(s,1H),1.99(q,J=6.9,6.4Hz,1H),1.95-1.77(m,4H),1.75(s,3H),1.66-1.52(m,4H),1.49-1.40(m,3H),1.39-1.26(m,4H),1.17(d,J=12.7Hz,1H),0.95(s,3H),0.92(s,3H)。质谱(m/z):343.5[M+H]$^+$。175B:^{1}H NMR(400MHz,DMSO-d6)δ7.74(d,J=5.9Hz,1H),7.31(s,2H),7.14(s,2H),3.69(q,J=4.7Hz,1H),3.40(d,J=6.8Hz,1H),2.41(s,1H),1.83(s,3H),1.76(q,J=7.3,5.8Hz,2H),1.67(q,J=5.7Hz,4H),1.63-1.56(m,4H),1.56-1.41(m,4H),1.37-1.27(m,2H),0.97(s,3H),0.94(s,3H)。质谱(m/z):343.5[M+H]$^+$。

[1010] 化合物158

[1011] (R)-N-(2-((4-(4,4-二甲基环己基)苯基)氨基)乙基)-2-氧代咪唑烷-4-甲酰胺

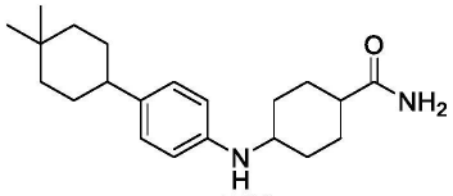
[1012] 

158

[1013] 由N^1-(4-(4,4-二甲基环己基)苯基)乙烷-1,2-二胺(41mg,0.17mmol),(R)-2-氧代咪唑烷-4-甲酸(32mg,0.25mmol),根据为1的程序制备标题化合物158(7.6mg),收率为12.7%(白色粉末)。^{1}H NMR(400MHz,DMSO-d6)δ8.04(t,J=5.8Hz,1H),6.98-6.93(m,2H),6.55-6.48(m,3H),6.37-6.30(m,1H),4.06(ddd,J=9.8,6.4,1.9Hz,1H),3.55(ddd,J=9.9,8.9,1.1Hz,1H),3.28-3.23(m,2H),3.19(ddd,J=8.9,6.4,1.3Hz,1H),3.06(q,J=6.5Hz,2H),2.23(tt,J=10.3,5.1Hz,1H),1.52(td,J=12.0,11.1,3.3Hz,4H),1.43(d,J=13.1Hz,3H),1.30(dd,J=12.2,5.3Hz,1H),0.95(s,3H),0.93(s,3H)。质谱(m/z):359.3[M+H]$^+$。

[1014] 化合物159

[1015] 4-((4-(4,4-二甲基环己基)苯基)氨基)环己烷-1-甲酰胺

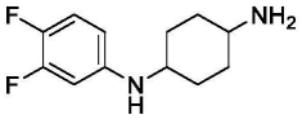
[1016] 

159A
159B

[1017] 由4-(4,4-二甲基环己基)苯胺(100mg,0.493mmol),4-氧代环己烷-1-甲酰胺(104mg,0.739mmol),AcOH(0.1mL),$NaBH(OAc)_3$(209mg,0.986mmol)和DCE(10mL),根据为1-1的程序制备标题化合物159,其提纯方法为:prep HPLC(柱:X Select-CSH-Prep 5μm OBD,19*150mm;ACN/水(0.5%TFA)=25%-50%-95%-95%-10%,0min-10min-10.5min-11.5min-13min)而得到期望的产物159A(Rt=7.1min)(白色固体)(20.5mg,12.7%)和159B(Rt=8.8min)(白色固体)(32.4mg,20.0%)。159A:^{1}H NMR(400MHz,DMSO-d6)δ7.23(s,1H),6.90(d,J=8.0Hz,2H),6.55(s,1H),6.23(d,J=7.2Hz,2H),5.22(s,1H),3.72-3.62(m,1H),2.71(p,J=8.0Hz,1H),2.26-2.13(m,1H),1.96-1.82(m,3H),1.65-1.57(m,2H),1.51-1.33(m,10H),1.25-1.21(m,2H),0.93(d,J=8.0Hz,6H)。质谱(m/z):328.3$[M+H]^+$。159B:^{1}H NMR(400MHz,DMSO-d6)δ7.21(s,1H),6.90(d,J=8.0Hz,2H),6.67(s,1H),6.43(d,J=8.0Hz,2H),5.28(s,1H),3.72-3.65(m,1H),2.67(p,J=8.0Hz,1H),1.65-1.56(m,2H),2.01-1.82(m,3H),1.66-1.57(m,2H),1.48-1.34(m,9H),1.27-1.20(m,2H),0.90(d,J=8.8Hz,6H)。质谱(m/z):328.3$[M+H]^+$。

[1018] 化合物160

[1019] N^1-(3,4-二氟苯基)环己烷-1,4-二胺

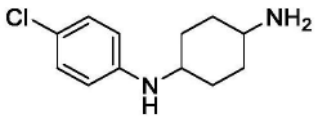
[1020] 

160

[1021] 由(4-((3,4-二氟苯基)氨基)环己基)氨基甲酸叔丁酯(73mg,0.215mmol),TFA(1mL),和DCM(10mL),根据为24的程序制备标题化合物160(22.9mg),总收率为47.2%(白色固体),经^{1}H NMR证明为1:2的混合物。^{1}H NMR(400MHz,DMSO-d6)δ7.19-6.97(m,1H),6.56(dddd,J=13.6,10.0,6.8,2.8Hz,1H),6.45-6.26(m,1H),5.75(dd,J=14.8,6.8Hz,1H),3.15-2.89(m,2H),1.99(dt,J=12.8,4.8Hz,2H),1.75(tt,J=8.4,4.0Hz,3H),1.60(dq,J=15.2,6.4,5.6Hz,1H),1.48(qd,J=13.6,12.8,3.6Hz,1H),1.25-1.11(m,2H)。质谱(m/z):227.3$[M+H]^+$。

[1022] 化合物161

[1023] N^1-(4-氯苯基)环己烷-1,4-二胺

[1024] 

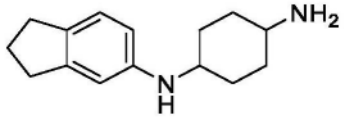
161

[1025] 由(4-((4-氯苯基)氨基)环己基)氨基甲酸叔丁酯(85mg,0.262mmol),TFA(1mL),和DCM(10mL),根据为24的程序制备标题化合物161(28.6mg),总收率为48.5%(白色固体),

经^{1}H NMR证明为1:2的混合物。^{1}H NMR(400MHz,DMSO-d6)δ7.19-7.00(m,2H),6.62(dd,J=9.5,3.0Hz,2H),3.38(t,J=4.0Hz,3H),3.17-3.00(m,3H),2.01(q,J=9.9,9.3Hz,2H),1.76(q,J=5.2,3.9Hz,3H),1.65-1.55(m,1H),1.53-1.41(m,1H)。质谱(m/z):225.3[M+H]$^+$。

[1026] 化合物162

[1027] N^1-(2,3-二氢-1H-茚-5-基)环己烷-1,4-二胺

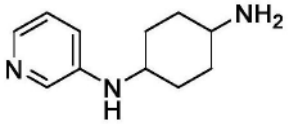
[1028] 

162

[1029] 由(4-((2,3-二氢-1H-茚-5-基)氨基)环己基)氨基甲酸叔丁酯(89mg,0.27mmol),TFA(1mL),和DCM(10mL),根据为24的程序制备标题化合物162(32.7mg),总收率为53.2%(白色固体),经^{1}H NMR证明为1:2的混合物。^{1}H NMR(400MHz,DMSO-d6)δ8.25(d,J=34.0Hz,3H),6.91(d,J=8.0Hz,1H),6.50(s,1H),6.41(d,J=8.4Hz,1H),5.11(s,1H),3.15-2.86(m,2H),2.71(dt,J=15.2,7.2Hz,4H),2.00(dd,J=13.2,4.0Hz,2H),1.92(q,J=7.2Hz,2H),1.76(tt,J=14.0,8.0Hz,3H),1.59(td,J=10.0,4.8Hz,1H),1.52-1.39(m,1H)。质谱(m/z):231.3[M+H]$^+$。

[1030] 化合物163

[1031] N^1-(吡啶-3-基)环己烷-1,4-二胺

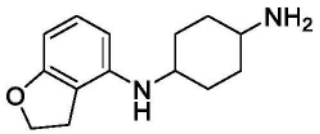
[1032] 

163

[1033] 由(4-(吡啶-3-基氨基)环己基)氨基甲酸叔丁酯(55mg,0.189mmol),TFA(1mL),和DCM(10mL),根据为24的程序制备标题化合物163(13.6mg),总收率为37.8%(黄色固体),经^{1}H NMR证明为1:2的混合物。^{1}H NMR(400MHz,DMSO-d6)δ7.96(dd,J=24.4,2.8Hz,1H),7.69(ddd,J=8.0,4.4,1.2Hz,1H),7.05(dt,J=8.4,4.8Hz,1H),6.94(dddd,J=8.4,6.0,2.8,1.2Hz,1H),5.84(t,J=6.4Hz,1H),3.17-3.02(m,1H),2.90(d,J=13.2Hz,1H),1.97(ddd,J=12.4,7.2,3.2Hz,2H),1.73(dq,J=10.0,5.2Hz,3H),1.60(ddd,J=13.6,8.0,4.0Hz,1H),1.50-1.37(m,1H),1.24-1.09(m,2H)。质谱(m/z):192.3[M+H]$^+$。

[1034] 化合物164

[1035] N^1-(2,3-二氢苯并呋喃-4-基)环己烷-1,4-二胺

[1036] 

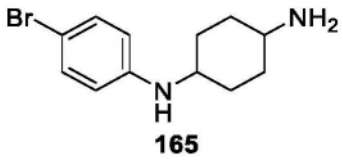
164

[1037] 由(4-((2,3-二氢苯并呋喃-4-基)氨基)环己基)氨基甲酸叔丁酯(105mg,0.316mmol),TFA(1mL),和DCM(10mL),根据为24的程序制备标题化合物164(64.8mg),总收率为89%(白色固体),经^{1}H NMR证明为1:2的混合物。^{1}H NMR(400MHz,DMSO-d6)δ6.81(q,J=7.6Hz,1H),6.07(d,J=8.4Hz,1H),5.98(dd,J=16.4,7.6Hz,1H),4.84-4.37(m,3H),3.18-

3.05(m,1H),2.93(dt,J=41.2,8.8Hz,3H),2.02-1.90(m,2H),1.84-1.74(m,2H),1.73-1.65(m,1H),1.63-1.54(m,1H),1.50-1.37(m,1H),1.25(td,J=12.8,11.2,4.0Hz,1H)。质谱(m/z):233.3[M+H]$^+$。

[1038] 化合物165

[1039] N^1-(4-溴苯基)环己烷-1,4-二胺

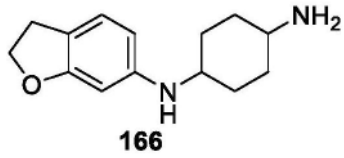
[1040] 

165

[1041] 由(4-((4-溴苯基)氨基)环己基)氨基甲酸叔丁酯(176mg,0.477mmol),TFA(1mL),和DCM(10mL),根据为24的程序制备标题化合物165(106.7mg),总收率为83.1%(白色固体),经^{1}H NMR证明为1:2的混合物。^{1}H NMR(400MHz,DMSO-d6)δ7.13(t,J=8.4Hz,2H),6.56-6.46(m,2H),5.76-5.64(m,1H),3.09-2.85(m,2H),2.00-1.92(m,2H),1.81-1.64(m,3H),1.62-1.51(m,1H),1.50-1.38(m,1H),1.18-1.13(m,1H)。质谱(m/z):270.3[M+H]$^+$。

[1042] 化合物166

[1043] N^1-(2,3-二氢苯并呋喃-6-基)环己烷-1,4-二胺

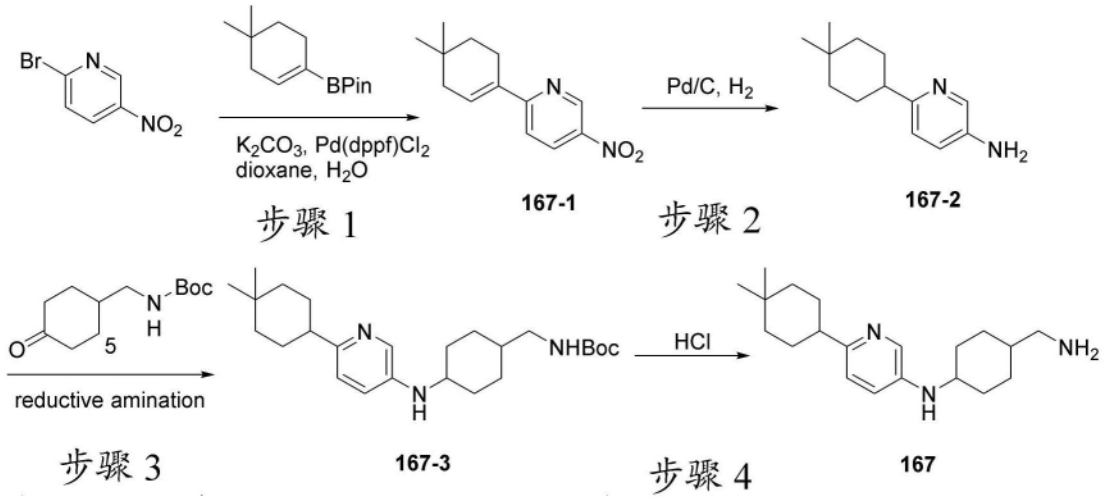
[1044] 

166

[1045] 由(4-((2,3-二氢苯并呋喃-6-基)氨基)环己基)氨基甲酸叔丁酯(160mg,0.482mmol),TFA(1mL),和DCM(10mL),根据为24的程序制备标题化合物166(78.2mg),总收率为69.8%(黄色固体),经^{1}H NMR证明为1:2的混合物。^{1}H NMR(400MHz,DMSO-d6)δ6.83(dd,J=8.0,5.6Hz,1H),6.12-5.91(m,2H),5.23(d,J=7.6Hz,1H),4.37(td,J=8.4,1.2Hz,2H),3.06-2.85(m,4H),1.98-1.92(m,2H),1.75-1.67(m,3H),1.58-1.50(m,1H),1.48-1.37(m,1H),1.15-1.03(m,1H)。质谱(m/z):233.3[M+H]$^+$。

[1046] 化合物167

[1047] N-(4-(氨基甲基)环己基)-6-(4,4-二甲基环己基)吡啶-3-胺

[1048] 

[1049] dioxane:二氧杂环己烷reductive amination:还原胺化

[1050] 步骤1:制备2-(4,4-二甲基环己-1-烯-1-基)-5-硝基吡啶(167-1)

[1051] 向2-溴-5-硝基吡啶(500mg,2.46mmol),2-(4,4-二甲基环己-1-烯-1-基)-4,4,5,5-四甲基-1,3,2-二氧杂硼杂环戊烷(459mg,3.69mmol),K_2CO_3(1019mg,7.39mmol)/1,4-二氧杂环己烷(10mL)和水(1mL)的溶液中添加Pd(dppf)Cl2(285mg,0.25mmol)。在氮气气氛下搅拌混合物,回流过夜。在冷却到环境温度后,将混合物减压浓缩。残余物的提纯方法为:硅胶柱而得到化合物167-1(500mg,87.3%,收率)(黄色固体)。MS(m/z)233.2$[M+H]^+$。

[1052] 步骤2:制备6-(4,4-二甲基环己基)吡啶-3-胺(167-2)

[1053] 向2-(4,4-二甲基环己-1-烯-1-基)-5-硝基吡啶(500mg,2.15mmol)/MeOH(10mL)2-(4,4-二甲基环己-1-烯-1-基)-5-硝基吡啶(500mg,2.15mmol)/MeOH(10mL)的溶液中添加Pd/C(200mg,10%),在氢气气氛下使混合物反应16小时。然后将其过滤并且真空除去溶剂而得到化合物167-2(390mg,88.6%,收率)(黄色固体)。MS(m/z)205.1$[M+H]^+$。

[1054] 步骤3:制备((4-((6-(4,4-二甲基环己基)吡啶-3-基)氨基)环己基)甲基)氨基甲酸叔丁酯(167-3)

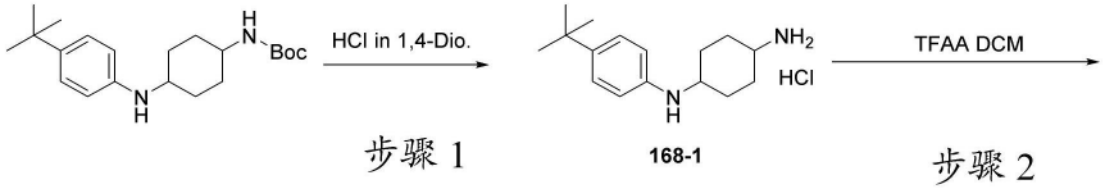
[1055] 向化合物4(200mg,0.98mmol)/MeOH(10mL)和一滴AcOH的溶液中添加化合物167-2(223mg,0.98mmol)。添加氰基硼氢化钠(123mg,1.96mmol)并在50℃搅拌混合物16小时。LCMS显示反应完成。将反应用水(10mL)淬灭,并用EA(10mL*3)萃取。将合并的有机层用盐水(20mL)洗涤,用硫酸钠干燥,过滤和浓缩。残余物的提纯方法为:使用EA/PE(1:3)的combi-flash(闪式色谱)而得到化合物167-3(0.4g,98.3%,收率)(黄色固体)。MS(m/z)415.9$[M+H]^+$。

[1056] 步骤4:制备N-(4-(氨基甲基)环己基)-6-(4,4-二甲基环己基)吡啶-3-胺(167)

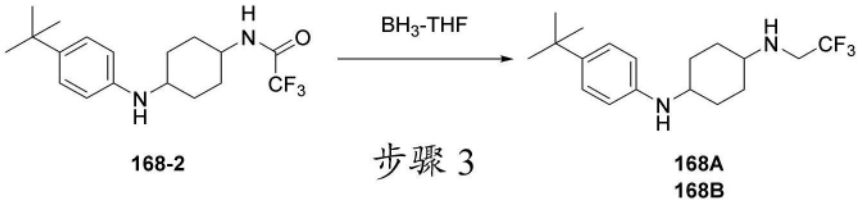
[1057] 化合物167-3(200mg,0.48mmol)和HCl/1,4-二氧杂环己烷(10mL,4N)被置于烧瓶中在25℃搅拌16小时。过量的1,4-二氧杂环己烷被真空蒸馏掉并且残余物的提纯方法为:prep-HPLC(柱-Xbridge-C18150x 19mm,5um;移动相:ACN-H_2O(0.1%FA),2%-20%)而得到167(45mg 29.6%)(白色固体)。^1H NMR(400MHz,CD_3OD)δ7.86-7.60(m,3H),3.35(s,1H),2.85(dd,J=15.4,7.2Hz,2H),2.78-2.66(m,1H),2.16-2.11(m,1H),1.94-1.90(m,1H),1.83-1.65(m,7H),1.59-1.20(m,8H),1.01(d,J=16.8Hz,6H).MS(m/z)316.3$[M+H]^+$。

[1058] 化合物168

[1059] N-(4-(叔丁基)苯基)-N-(2,2,2-三氟乙基)环己烷-1,4-二胺



[1060]



[1061] 1,4-Dio.:1,4-二氧杂环己烷

[1062] 步骤1:制备N-(4-(叔丁基)苯基)环己烷-1,4-二胺盐酸盐(168-1)

[1063] (4-((4-(叔丁基)苯基)氨基)环己基)氨基甲酸叔丁酯(1.2g,3.5mmol)和HCl/1,4-二氧杂环己烷(20mL,4N)被置于烧瓶中并且在25℃搅拌18小时。将溶液真空浓缩而得到1g的N-(4-(叔丁基)苯基)环己烷-1,4-二胺盐酸盐(收率:90%)。质谱(m/z):247.3[M+H]$^+$。

[1064] 步骤2:制备N-(4-((4-(叔丁基)苯基)氨基)环己基)-2,2,2-三氟乙酰胺(168-2)

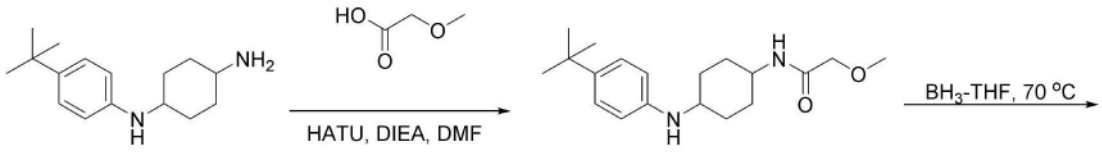
[1065] 向100mL的圆底烧瓶中装入168-1(400mg,1.62mmol),TFAA(680mg,3.2mg)和DCM(20mL)。在25℃搅拌反应2小时。将固体过滤并且将滤液真空除去。残余物通过快速柱色谱法提纯而得到200mg的168-2(收率:36.1%)(灰白色固体)。质谱(m/z):342.8[M+H]$^+$。

[1066] 步骤2:制备N-(4-(叔丁基)苯基)-N-(2,2,2-三氟乙基)环己烷-1,4-二胺(168)

[1067] 在70℃搅拌168-2(200mg,0.58mmol),BH_3-THF(10mL)/THF(5mL)的溶液18小时。将固体过滤并且将溶剂真空除去。残余物的提纯方法为:prep-HPLC(柱-Xbridge-C18 150x19mm,5um;移动相:ACN-H_2O(0.1%FA),25%-40%)而得到168A(15.4mg)(白色固体)和168B(8.3mg)(白色固体)。168A:^{1}H NMR(400MHz,CD_3OD)δ7.15-7.11(m,2H),6.62-6.58(m,2H),3.45-3.37(m,1H),3.20(q,J=9.8Hz,2H),2.69(td,J=7.4,3.6Hz,1H),1.76-1.68(m,2H),1.68-1.60(m,4H),1.59-1.50(m,2H),1.23(s,9H)。质谱(m/z):329.3[M+H]$^+$。HPLC:Rt=4.699min(柱:XBRIDGE 3.5um 2.1*50mm,移动相:H_2O(0.05%TFA)-ACN(0.05%TFA),ACN从0至60%在7分钟内,流速:0.8mL/min)。168B:^{1}H NMR(400MHz,CD_3OD)δ7.13(d,J=8.6Hz,2H),6.59(d,J=8.6Hz,2H),3.23-3.18(m,2H),3.17(d,J=3.8Hz,1H),2.52(dt,J=9.6,4.8Hz,1H),2.10-1.93(m,4H),1.23(s,9H),1.21-1.10(m,4H)。质谱(m/z):329.3[M+H]$^+$。HPLC:Rt=5.096min(柱:XBRIDGE 3.5um 2.1*50mm,移动相:H_2O(0.05%TFA)-ACN(0.05%TFA),ACN从0至60%在7分钟内,流速:0.8mL/min)。

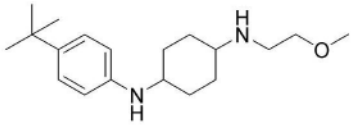
[1068] 化合物169

[1069] 1-N-(4-(叔丁基)苯基)-N^4-(2-甲氧基乙基)环己烷-1,4-二胺(169)



步骤 1 169-1 步骤 2

[1070]



169

[1071] 步骤1:制备1-N-(4-((4-(叔丁基)苯基)氨基)环己基)-2-甲氧基乙酰胺(169-1)

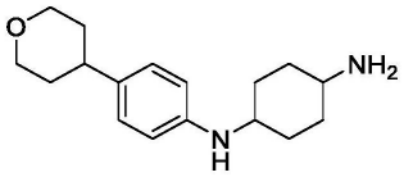
[1072] 在25℃搅拌1-N-(4-(叔丁基)苯基)环己烷-1,4-二胺(300mg,1.06mmol),2-甲氧基乙酸(114mg,1.27mmol),HATU(605mg,1.6mmol),DIEA(685mg,5.3mmol)/DMF(10mL)的混合物过夜。将其用H_2O(30mL)淬灭并用DCM(3x30 mL)萃取。将有机层合并,用盐水NaCl(2x30mL)洗涤并且用$MgSO_4$干燥,过滤并且浓缩。将粗产物施加到硅胶柱(4g),用PE:EA(5:1)洗脱而得到产物(100mg,收率:90%)(黄色固体)。质谱(m/z):318.9[M+H]$^+$。

[1073] 步骤2:制备1-N-(4-(叔丁基)苯基)-N^4-(2-甲氧基乙基)环己烷-1,4-二胺(169)

[1074] 向169-1(100mg,0.31mmol)/THF(5mL)的溶液中添加BH_3-THF(15mL)。然后在70℃搅拌混合物16小时。将反应真空浓缩。残余物的提纯方法为:prep-TLC而得到期望的产物(10.8mg)(白色固体)。^{1}H NMR(400MHz,DMSO-d6)δ7.04(d,J=8.4Hz,2H),6.49(d,J=8,4Hz,2H),3.49(t,J=5.2Hz,2H),3.32(d,J=6.6Hz,2H),3.25(s,3H),2.93-2.86(m,2H),1.75-1.45(m,8H),1.16(d,J=6.8Hz,9H)。质谱(m/z):452.3$[M+H]^+$。

[1075] 化合物170

[1076] 1-N-(4-(四氢-2H-吡喃-4-基)苯基)环己烷-1,4-二胺

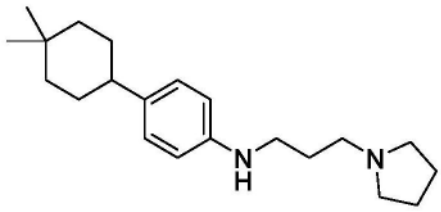
[1077] 

170

[1078] 由(4-((4-(四氢-2H-吡喃-4-基)苯基)氨基)环己基)氨基甲酸叔丁酯(300mg,0.8mmol),1,4-二氧杂环己烷(5mL)和HCl/1,4-二氧杂环己烷(5mL;4N),根据为37的程序制备期望的产物(52.8mg)(白色固体)。^{1}H NMR(400MHz,DMSO-d6)δ6.94(d,J=8.5Hz,2H),6.55(d,J=8.4Hz,2H),5.32(br,1H),3.91(dd,J=10.4,3.1Hz,2H),3.38(d,J=3.1Hz,2H),3.00(br,1H),2.52(br,1H),1.76-1.52(m,12H)。质谱(m/z):275.3$[M+H]^+$。

[1079] 化合物171

[1080] 4-(4,4-二甲基环己基)-N-(3-(吡咯烷-1-基)丙基)苯胺

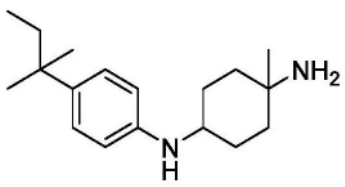
[1081] 

171

[1082] 由N-(4-(4,4-二甲基环己基)苯基)-3-(吡咯烷-1-基)丙酰胺(80mg,0.24mmol),THF(1mL)和BH_3-THF(30mL),根据为169的程序制备期望的产物171(45mg)(白色固体)。^{1}H NMR(400MHz,DMSO-d6)δ7.03(d,2H),6.61(d,2H),3.52(br,2H),3.19(t,2H),3.10(t,2H),3.00(br,2H),2.29-2.24(m,1H),2.05-1.85(m,6H),1.55-1.23(m,8H),0.95(d,6H)。质谱(m/z):315.3$[M+H]^+$。

[1083] 化合物172

[1084] 1-甲基-N^4-(4-(叔戊基)苯基)环己烷-1,4-二胺

[1085] 

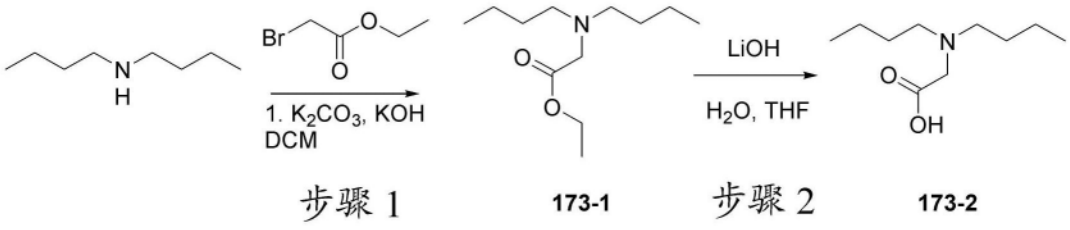
172

[1086] 由(1-甲基-4-((4-(叔戊基)苯基)氨基)环己基)氨基甲酸叔丁酯(144mg,0.385mmol),TFA(1mL),和DCM(10mL),根据为24的程序制备标题化合物172(96.9mg),总收

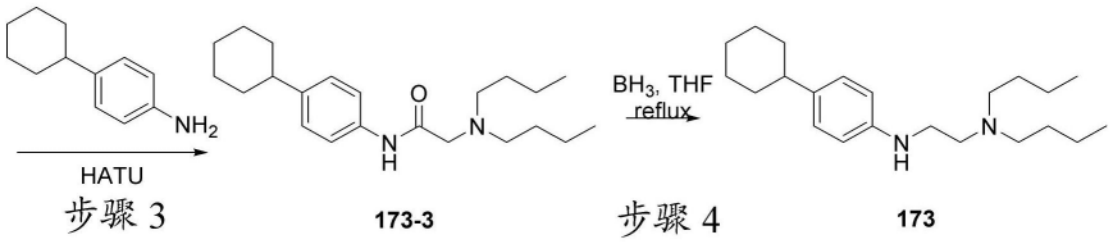
率为91.8%(白色固体)。^{1}H NMR(400MHz,DMSO-d6)δ8.30(d,J=36.0Hz,3H),7.02(d,J=8.4Hz,2H),6.56(d,J=8.4Hz,2H),5.08(s,1H),3.14(s,1H),1.96(d,J=14.8Hz,2H),1.81-1.61(m,4H),1.52(q,J=7.6Hz,3H),1.30(d,J=8.0Hz,3H),1.16(d,J=1.2Hz,6H),0.61(t,J=7.2Hz,3H)。质谱(m/z):275.3[M+H]$^+$。

[1087] 化合物173

[1088] N^1,N^1-二丁基-N^2-(4-环已基苯基)乙烷-1,2-二胺



[1089]



[1090] reflux:回流

[1091] 步骤1:制备二丁基甘氨酸乙酯(173-1)

[1092] 在40℃搅拌二丁胺(1g,7.74mmol),2-溴乙酸乙酯(1.55g,9.28mmol),KOH(434mg,7.74mmol),K_2CO_3(1.07g,7.74mmol)/DCM(40mL)的混合物过夜。在冷却到室温后,添加40mL的水。将固体通过硅胶色谱提纯。获得目标产物(1.58g,95%)(无色油)。质谱(m/z):216.2[M+H]$^+$。

[1093] 步骤2:制备二丁基甘氨酸(173-2)

[1094] 在室温搅拌二丁基甘氨酸乙酯(1g,4.64mmol),LiOH(334mg,14mmol)/H_2O(10mL)和THF(10mL)的混合物过夜。将反应减压浓缩。固体(840mg,97%)被直接用于下一步中。质谱(m/z):188.2[M+H]$^+$。

[1095] 步骤3:制备N-(4-环已基苯基)-2-(二丁基氨基)乙酰胺(173-3)

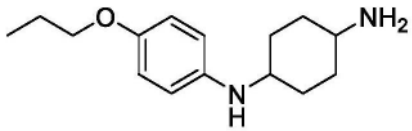
[1096] 在室温搅拌二丁基甘氨酸(840mg,4.49mmol),4-环已基苯胺(943mg,5.38mmol),HATU(2.05g,5.38mmol),DIPEA(870mg,6.37mmol)/DMF(20mL)的混合物过夜。然后添加40mL的水。将固体通过硅胶色谱提纯。获得目标产物(1.6g,75%)(黄色固体)。质谱(m/z):345.2[M+H]$^+$。

[1097] 步骤4:制备N^1,N^1-二丁基-N^2-(4-环已基苯基)乙烷-1,2-二胺(173)

[1098] 将N-(4-环已基苯基)-2-(二丁基氨基)乙酰胺(200mg,0.58mmol)添加到BH_3-THF(20mL)并在70℃搅拌混合物过夜。将反应真空浓缩。残余物的提纯方法为:prep-TLC而得到期望的产物(白色固体)。(20mg,10%)。^{1}H NMR(400MHz,CD_3OD)δ7.03(d,J=8.5Hz,2H),6.65(d,J=8.6Hz,2H),3.48(d,J=6.0Hz,2H),3.35(d,J=5.9Hz,2H),3.22-3.13(m,4H),2.44-2.33(m,1H),1.86-1.72(m,4H),1.72-1.61(m,4H),1.49-1.33(m,8H),1.33-1.26(m,2H),0.98(t,J=7.3Hz,6H)。质谱(m/z):331.2[M+H]$^+$。

[1099] 化合物174

[1100] N^1-(4-丙氧基苯基)环己烷-1,4-二胺

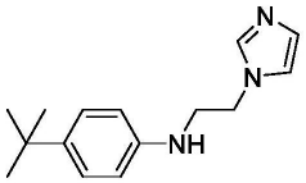
[1101] 

174

[1102] 由(4-((4-丙氧基苯基)氨基)环己基)氨基甲酸叔丁酯(600mg,11.73mmol),1,4-二氧杂环己烷(10mL)和1,4-二氧杂环己烷/HCl(10mL),根据为37的程序制备期望的产物174(白色固体)(82.2mg,18.8%)。^{1}H NMR(400MHz,DMSO-d6)δ8.49(s,1H),6.69(d,2H),6.57(d,2H),3.77(t,2H),3.37(br,1H),3.02(br,1H),1.83-1.54(m,8H),0.94(t,3H)。质谱(m/z):249.3[M+H]$^+$。

[1103] 化合物175

[1104] N-(2-(1H-咪唑1-基)乙基)-4-(叔丁基)苯胺

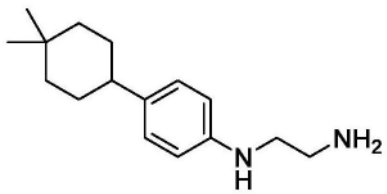
[1105] 

175

[1106] 由N-(4-(叔丁基)苯基)-2-(1H-咪唑1-基)乙酰胺(312mg,1.21mmol),THF(1mL)和BH_3-THF(30mL),根据为169的程序制备期望的产物175(白色固体)(34.8mg,11.7%)。^{1}H NMR(400MHz,DMSO-d6)δ9.06(s,1H),7.78(s,1H),7.68(s,1H),7.11(d,2H),6.54(d,2H),4.33(br,2H),3.48(br,2H),1.21(s,9H)。质谱(m/z):244.3[M+H]$^+$。

[1107] 化合物176

[1108] N^1-(4-(4,4-二甲基环己基)苯基)乙烷-1,2-二胺

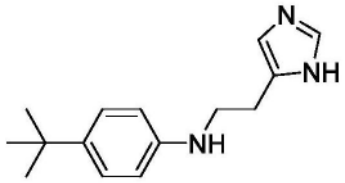
[1109] 

176

[1110] 由(2-((4-(4,4-二甲基环己基)苯基)氨基)乙基)氨基甲酸叔丁酯(55mg,0.16mmol),1,4-二氧杂环己烷(10mL)和1,4-二氧杂环己烷/HCl(10mL),根据为37的程序制备期望的产物176(白色固体)(37.4mg,95.3%)。^{1}H NMR(400MHz,DMSO-d6)δ6.96(d,2H),6.51(d,2H),3.19(br,2H),2.88(br,2H),2.28-2.20(m,1H),1.54-1.24(m,8H),0.93(d,6H)。质谱(m/z):247.3[M+H]$^+$。

[1111] 化合物177

[1112] N-(2-(1H-咪唑5-基)乙基)-4-(叔丁基)苯胺

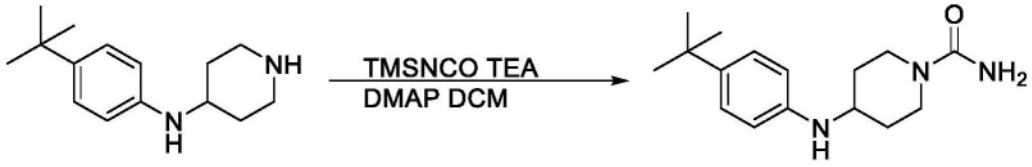
[1113] 

177

[1114] 由N-(4-(叔丁基)苯基)-2-(1H-咪唑5-基)乙酰胺(300mg,1.17mmol),THF(1mL)和BH_3-THF(30mL),根据为169的程序制备期望的产物(65.1mg,22.9%)(棕色油)。^{1}H NMR(400MHz,DMSO-d6)δ9.06(s,1H),7.78(s,1H),7.68(s,1H),7.11(d,J=8.6Hz,2H),6.53(d,J=8.6Hz,2H),4.32(t,J=5.7Hz,2H),3.47(t,J=5.7Hz,2H),1.21(s,9H)。质谱(m/z):244.3$[M+H]^+$。

[1115] 化合物178

[1116] 4-((4-(叔丁基)苯基)氨基)哌啶-1-甲酰胺

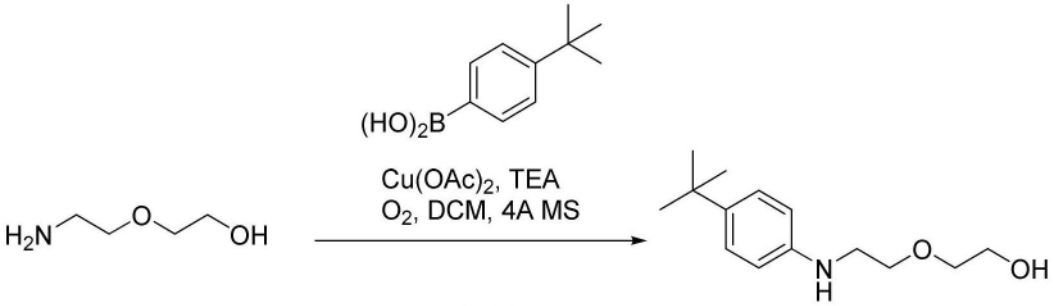
[1117] 

178

[1118] 在室温搅拌N-(4-(叔丁基)苯基)哌啶-4-胺(100mg,0.43mmol),TMSNCO(50mg,0.43mmol),TEA(87mg,0.86mmol)和DMAP(11mg,0.086mmol)/DCM(5mL)的混合物溶液18小时。将固体过滤并且将溶剂真空除去。残余物的提纯方法为:prep-HPLC(柱-Xbridge-C18 150x 19mm,5um;移动相:ACN-H_2O(0.1%FA),25%-40%)而得到178(38.2mg)(白色固体)。^{1}H NMR(400MHz,CD_3OD)δ7.19-7.13(m,2H),6.68-6.61(m,2H),3.95(s,2H),3.45(tt,J=10.2,4.0Hz,1H),2.97(d,J=2.2Hz,2H),2.04-1.94(m,2H),1.42-1.29(m,2H),1.25(s,9H)。质谱(m/z):276.2$[M+H]^+$。

[1119] 化合物179

[1120] 2-(2-((4-(叔丁基)苯基)氨基)乙氧基)乙-1-醇

[1121] 

步骤 1

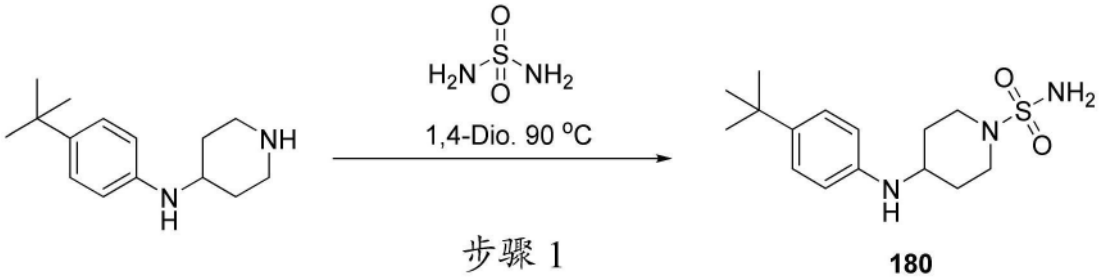
179

[1122] 向100mL的圆底烧瓶中装入2-(2-氨基乙氧基)乙-1-醇(400mg,3.8mmol,1.00eq),(4-(叔丁基)苯基)硼酸(677mg,3.8mmol,1.00eq),Cu(OAc)2(1382mg,7.6mmol,2.00eq)和TEA(1924mg,19mmol,5.00eq)和4Å MS(1g)。在室温在氧气气氛下搅拌反应18小时。将固体过滤并且将溶剂真空除去。残余物的提纯方法为:prep-HPLC(柱-Xbridge-C18 150x 19mm,5um;移动相:ACN-H_2O(0.1%FA),25%-40%)而得到179(40.1mg)(白色固体)。^{1}H NMR

(400MHz,CD_3OD)δ7.64-7.59(m,2H),7.44-7.39(m,2H),3.76(dd,3.9Hz,2H),3.71-3.67(m,2H),3.64-3.60(m,2H),3.58(d,2H),1.34(d,9H)。质谱(m/z):238.2$[M+H]^+$。

[1123] 化合物180

[1124] 4-((4-(叔丁基)苯基)氨基)哌啶-1-磺酰胺

[1125] 

步骤 1

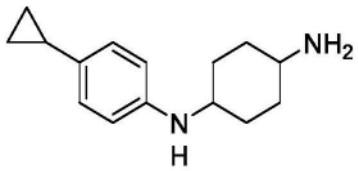
180

[1126] 1,4-Dio.:1,4-二氧杂环己烷

[1127] 向10mL的圆底烧瓶中装入N-(4-(叔丁基)苯基)哌啶-4-胺(100mg,0.43mmol),1,4-二氧杂环己烷(5mL)和硫酸二酰胺(50mg,0.52mmol)。在90℃搅拌反应18小时。将反应混合物过滤并且将滤液浓缩。残余物的提纯方法为:prep-HPLC(柱-Xbridge-C18 150x 19mm,5um;移动相:ACN-H_2O(0.1%FA),25%-40%)而得到180(21.5mg)(白色固体)。^1H NMR(400MHz,CD_3OD)δ7.19-7.14(m,2H),6.63(d,2H),3.60(d,2H),3.37-3.32(m,1H),2.78(td,2H),2.08(d,2H),1.55-1.45(m,2H),1.25(s,9H)。质谱(m/z):311.9$[M+H]^+$。

[1128] 化合物181

[1129] N^1-(4-环丙基苯基)环己烷-1,4-二胺

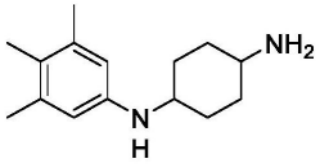
[1130] 

181

[1131] 由(4-((4-环丙基苯基)氨基)环己基)氨基甲酸叔丁酯(130mg)andHCl/1,4-二氧杂环己烷(10mL,4N),根据为37的程序制备标题化合物181(47mg,55.8%)(白色固体)。^1H NMR(400MHz,CD_3OD)δ7.24-6.98(m,4H),3.15-3.07(m,2H),2.20-2.00(m,4H),1.97-1.81(m,1H),1.58-1.35(m,4H),1.02-0.88(m,2H),0.71-0.56(m,2H).MS(m/z):231.2$[M+H]^+$。

[1132] 化合物182

[1133] N^1-(3,4,5-三甲基苯基)环己烷-1,4-二胺

[1134] 

182

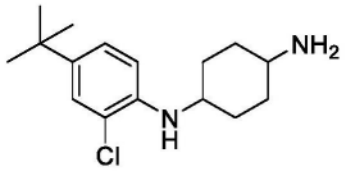
[1135] 步骤2:制备N^1-(3,4,5-三甲基苯基)环己烷-1,4-二胺(182)

[1136] 由(4-((3,4,5-三甲基苯基)氨基)环己基)氨基甲酸叔丁酯(110mg,0.33mmol)和HCl/1,4-二氧杂环己烷(10mL,4N),根据为37的程序制备标题化合物182A(47.4mg)(白色固体)和182B(40.3mg)(白色固体)。182A:^1H NMR(400MHz,CD_3OD)δ6.87(s,2H),3.57(br,^1H),

3.35(br,^{1}H)2.29(s,6H),2.16(s,3H),1.86(br,8H)。质谱(m/z):233.3[M+H]$^+$。HPLC:Rt:3.206min(柱:XBRIDGE 2.1*50mm,3.5um;移动相:H_2O(0.05%TFA)/ACN(0.05%TFA),ACN由0%至60%在7分钟内,7-8min,ACN由60%至100%;0.8mL/min)。182B:^{1}H NMR(400MHz,CD_3OD)δ6.93(s,2H),3.56(s,1H),3.28(s,1H),2.20(s,6H),2.11(s,3H),1.49(br,8H)。质谱(m/z):233.3[M+H]$^+$。HPLC:Rt:3.685min(柱:XBRIDGE 2.1*50mm,3.5um;移动相:H_2O(0.05%TFA)/ACN(0.05%TFA),ACN由0%至60%在7分钟内,7-8min,ACN由60%至100%;0.8mL/min)。

[1137] 化合物183

[1138] N^1-(4-(叔丁基)-2-氯苯基)环己烷-1,4-二胺

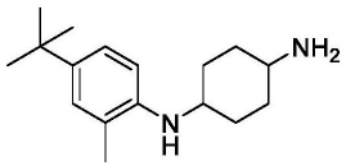
[1139] 

183A
183B

[1140] 由市售的4-(叔丁基)-2-氯苯胺(18.3mg,0.1mmol),根据为化合物24的程序制备标题化合物183。混合物的提纯方法:制备HPLC(柱:X Select-CSH-Prep 5μm OBD,19*150mm;ACN/水(0.5%TFA)=5%-305%-95%-95%-10%,0min-10min-10.5min-11.5min-13min)而得到化合物183A(Rt=7.49min)(黄色固体)和化合物184B(Rt=7.26min)(黄色固体)。183A(5.4mg,19%):^{1}H NMR(400MHz,DMSO-d6)8.05(s,2H),7.26-7.09(m,2H),6.72(d,J=8.8Hz,1H),4.40(d,J=7.6Hz,1H),3.59(s,1H),3.25(s,1H),1.82-1.62(m,8H),1.21(s,9H)。质谱(m/z):281.4[M+H]$^+$。183B(18.4mg,66%):^{1}H NMR(400MHz,DMSO-d6)8.06(s,2H),7.28-7.11(m,2H),6.74(d,J=8.8Hz,1H),4.55(d,J=7.6Hz,1H),3.42(s,1H),2.98(s,1H),2.05-1.94(m,4H),1.53-1.31(m,4H),1.21(s,9H)。质谱(m/z):281.4[M+H]$^+$。

[1141] 化合物184

[1142] N^1-(4-(叔丁基)-2-甲基苯基)环己烷-1,4-二胺

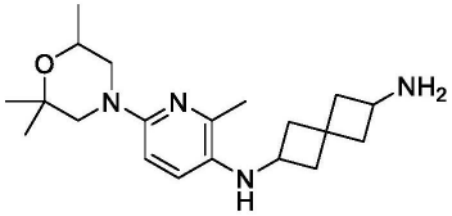
[1143] 

184

[1144] 由4-(叔丁基)-2-甲基苯胺(16mg,0.1mmol),根据为化合物24的程序制备标题化合物184(15.6mg),总收率为43%(黄色固体),经^{1}H NMR证明为1:2的混合物。^{1}H NMR(400MHz,DMSO-d6)δ8.20(s,3H),7.01(s,1H),6.99-6.96(m,1H),6.52-6.45(m,1H),3.53(s,1H),3.20-3.05(m,0.6H),3.02-2.84(m,0.3H),2.14(s,2H),2.05(s,1H),2.00(m,2H),1.87-1.41(m,6H),1.20(s,9H)。质谱(m/z):261.4[M+H]$^+$。

[1145] 化合物185

[1146] N^2-(2-甲基-6-(2,2,6-三甲基吗啉代)吡啶-3-基)螺[3.3]庚烷-2,6-二胺

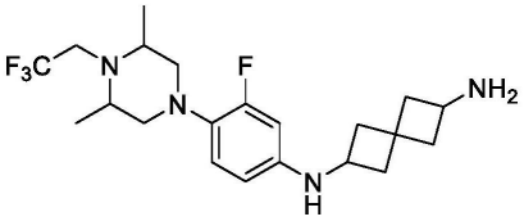
[1147] 

185

[1148] 根据为化合物24的程序,制备标题化合物185(23.3mg),总收率为67.5%(黄色固体)。^{1}H NMR(400MHz,DMSO-d6)δ6.78(d,J=8.8Hz,1H),6.53(d,J=8.8Hz,1H),4.02-3.80(m,2H),3.77-3.63(m,2H),3.53(m,1H),2.43-2.31(m,2H),2.27-2.14(m,5H),2.10(m,1H),2.01-1.87(m,2H),1.22(s,3H),1.16(s,3H),1.07(d,J=6.0Hz,3H)。质谱(m/z):345.2[M+H]$^+$。

[1149] 化合物186

[1150] N^2-(4-(3,5-二甲基-4-(2,2,2-三氟乙基)哌嗪-1-基)-3-氟苯基)螺-[3.3]庚烷-2,6-二胺

[1151] 

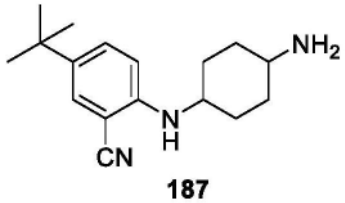
186A

186B

[1152] 根据为24的程序,制备标题化合物186A(5.4mg)(白色固体)和186B(5.8mg)(白色固体)。186A:^{1}H NMR(400MHz,DMSO-d6)δ6.81(t,J=8.8Hz,1H),6.31-6.26(m,2H),3.76-3.59(m,2H),3.34(q,J=9.8Hz,2H),3.03(dd,J=8.6,2.2Hz,2H),2.93(d,J=6.2Hz,2H),2.54-2.30(m,6H),2.20-2.09(m,2H),1.94-1.86(m,2H),1.11(d,J=6.2Hz,6H)。质谱(m/z):415.3[M+H]$^+$。HPLC:Rt:3.919min(柱:XBRIDGE 2.1*50mm,3.5um;移动相:H_2O(0.05%TFA),ACN(0.05%TFA),ACN由0%至60%在7分钟内,7-8min,ACN由60%至100%;0.8mL/min)。186B:^{1}H NMR(400MHz,DMSO-d6)δ6.82(d,J=8.6Hz,1H),6.32-6.21(m,2H),3.68(d,J=32.8Hz,2H),3.34(d,J=10.0Hz,2H),3.09-2.94(m,4H),2.61-2.48(m,2H),2.40(t,J=10.8Hz,4H),2.14(s,2H),1.96-1.78(m,2H),1.11(d,J=6.2Hz,6H)。质谱(m/z):415.3[M+H]$^+$。HPLC:Rt:3.921min(柱:XBRIDGE 2.1*50mm,3.5um;移动相:H_2O(0.05%TFA),ACN(0.05%TFA),ACN由0%至60%在7分钟内,7-8min,ACN由60%至100%;0.8mL/min)。

[1153] 化合物187

[1154] 2-((4-氨基环己基)氨基)-5-(叔丁基)苯腈

[1155] 

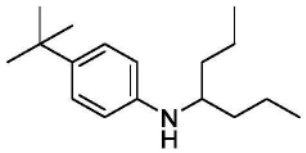
187

[1156] 由2-氨基-5-(叔丁基)苯腈(17.4mg,0.1mmol),根据为化合物88的程序制备标题

化合物187(21.9mg),总收率为78％(黄色固体),经^{1}H NMR证明为1:2的混合物。^{1}H NMR(400MHz,DMSO-d6)δ8.16(s,3H),7.28-7.11(m,2H),6.74(m,1H),3.42(s,1H),3.21-3.04(m,0.6H),3.00-2.88(m,0.3H),2.98(m,1H),2.10-1.93(m,4H),1.56-1.33(m,4H),1.22(s,9H)。质谱(m/z):272.3[M+H]$^+$。

[1157] 化合物188

[1158] 4-(叔丁基)-N-(庚烷-4-基)苯胺

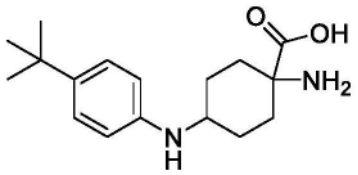
[1159] 

188

[1160] 由4-(叔丁基)苯胺(14.9mg,0.1mmol),根据为化合物4的程序制备标题化合物188(16.9mg),总收率为68％(黄色油)。^{1}H NMR(400MHz,DMSO-d6)δ7.11(d,J＝8.4Hz,2H),6.97(s,1H),6.54(d,J＝8.4Hz,2H),3.11(m,1H),1.54-1.31(m,8H),1.21(s,9H),0.88(m,6H)。质谱(m/z):248.3[M+H]$^+$。

[1161] 化合物189

[1162] 1-氨基-4-((4-(叔丁基)苯基)氨基)环己烷-1-甲酸

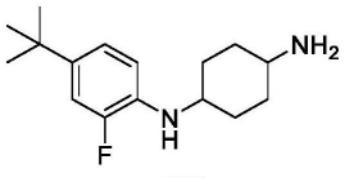
[1163] 

189

[1164] 由4-(叔丁基)苯胺(14.9mg,0.1mmol),根据为化合物24的程序制备标题化合物189(9.1mg),总收率为31％(白色固体),经^{1}H NMR证明为1:1的混合物。^{1}H NMR(400MHz,DMSO-d6)δ7.56(s,3H),7.07(d,J＝8.8Hz,1H),7.04(d,J＝8.8Hz,1H),6.51(d,J＝8.8Hz,2H),3.14(m,1H),2.14-1.81(m,3H),1.80-1.60(m,3H),1.47-1.29(m,2H),1.20(s,9H)。质谱(m/z):291.3[M+H]$^+$。

[1165] 化合物190

[1166] N^1-(4-(叔丁基)-2-氟苯基)环己烷-1,4-二胺

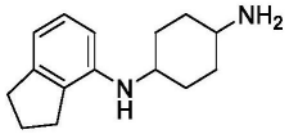
[1167] 

190

[1168] 由4-(叔丁基)-2-氟苯胺(25.1mg,0.15mmol),根据为化合物88的程序制备标题化合物190(26.4mg),总收率为67％(白色固体),经^{1}H NMR证明为1:2的混合物。^{1}H NMR(400MHz,DMSO-d6)δ8.28(s,2H),7.06-6.96(m,2H),6.68(m,1H),4.81(s,0.6H),4.53(s,0.3H),3.13(m,1.3H),2.97-2.85(m,0.7H),1.98(m,3H),1.87-1.56(m,3H),1.47-1.23(m,2H),1.19(s,9H)。质谱(m/z):265.2[M+H]$^+$。

[1169] 化合物191

[1170] N^1-(2,3-二氢-1H-茚-4-基)环己烷-1,4-二胺

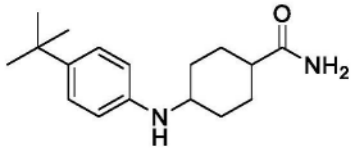
[1171] 

191A
191B

[1172] 由(4-((2,3-二氢-1H-茚-4-基)氨基)环己基)氨基甲酸叔丁酯(217mg,0.658mmol),TFA(1mL),和DCM(10mL),根据为24的程序制备标题化合物191,其提纯方法为:prep HPLC(溶剂体系(柱:X Select-CSH-Prep 5μm OBD,19*150mm;ACN/水(0.5%TFA)=15%-25%-95%-95%-10%,0min-10min-10.5min-11.5min-13min)而得到期望的产物191A(Rt=8.0min)(白色固体)(47.4mg,31.4%)和191B(Rt=9.2min)(白色固体)(38.2mg,25.3%)。191A:^{1}H NMR(400MHz,DMSO-d6)δ6.96(s,1H),6.56(d,J=44.0Hz,2H),3.19(s,1H),2.95(s,1H),2.77(t,J=7.6Hz,2H),2.66(s,2H),1.95(td,J=15.2,13.2,5.6Hz,6H),1.45-1.18(m,5H)。质谱(m/z):231.3$[M+H]^+$。191B:^{1}H NMR(400MHz,DMSO-d6)δ6.94(t,J=8.8Hz,1H),6.54(d,J=57.2Hz,2H),3.50(d,J=8.8Hz,1H),3.13(s,1H),2.88-2.62(m,4H),1.96(p,J=7.2Hz,2H),1.83-1.72(m,2H),1.65(q,J=14.4,11.6Hz,6H)。质谱(m/z):231.3$[M+H]^+$。

[1173] 化合物192

[1174] 4-((4-(叔丁基)苯基)氨基)环己烷-1-甲酰胺

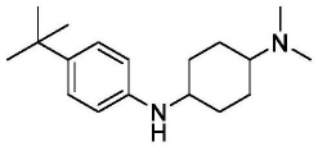
[1175] 

192

[1176] 由4-(叔丁基)苯胺(100mg,0.671mmol),4-氧代环己烷-1-甲酰胺(142mg,1.006mmol),AcOH(0.1mL),$NaBH(OAc)_3$(286mg,1.344mmol)和DCE(10mL),根据为1-1的程序制备标题化合物192(100.3mg),总收率为54.5%(白色固体),由^{1}H NMR证明为1:2的混合物。^{1}H NMR(400MHz,DMSO-d6)δ7.18(d,J=12.0Hz,1H),7.03(dd,J=8.8,2.8Hz,2H),6.66(d,J=8.4Hz,1H),6.49(t,J=9.6Hz,2H),3.36(s,1H),2.17-1.99(m,1H),1.94(dd,J=12.0,4.0Hz,1H),1.75(ddd,J=14.8,11.6,5.2Hz,2H),1.63(d,J=13.2Hz,1H),1.56-1.36(m,3H),1.23(s,3H),1.16(s,9H),1.07(t,J=12.0Hz,1H)。质谱(m/z):275.3$[M+H]^+$。

[1177] 化合物193

[1178] N^1-(4-(叔丁基)苯基)-N4,N4-二甲基环己烷-1,4-二胺

[1179] 

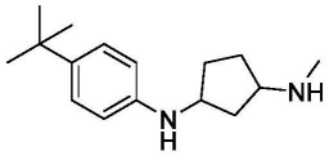
193A
193B

[1180] 由4-(叔丁基)苯胺(50mg,0.336mmol),4-(二甲基氨基)环己烷-1-酮(71mg,0.503mmol),AcOH(0.1mL),$NaBH(OAc)_3$(143mg,0.672mmol)和DCE(10mL),根据为1-1的程序

制备标题化合物193,其提纯方法为:prep HPLC(柱:X Select-CSH-Prep 5μm OBD,19*150mm;ACN/水(0.5%TFA)=15%-25%-75%-85%-11%,0min-10min-10.5min-11.5min-13min),而得到期望的产物193A(Rt=7.5min)(白色固体)(28.7mg,31.5%)和193B(Rt=8.8min)(白色固体)(20.2mg,21.7%)。193A:^{1}H NMR(400MHz,DMSO-d6)δ7.28(d,J=8.0Hz,2H),6.85(s,2H),3.33-3.08(m,2H),2.73(d,J=4.8Hz,6H),2.04(q,J=10.8,8.8Hz,4H),1.51(dd,J=13.6,10.4Hz,2H),1.31(dd,J=18.8,7.6Hz,2H),1.24(s,9H)。质谱(m/z):275.3[M+H]$^+$。193B:^{1}H NMR(400MHz,DMSO-d6)δ7.36(d,J=8.0Hz,2H),7.01(s,2H),3.31(d,J=22.8Hz,1H),3.24-3.12(m,1H),2.73(d,J=4.8Hz,6H),2.04(d,J=11.2Hz,4H),1.61-1.46(m,2H),1.42-1.31(m,2H),1.26(s,9H)。质谱(m/z):275.3[M+H]$^+$。

[1181] 化合物194

[1182] N^1-(4-(叔丁基)苯基)-N3-甲基环戊烷-1,3-二胺

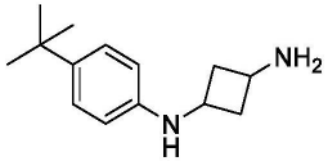
[1183] 

194

[1184] 由(3-((4-(叔丁基)苯基)氨基)环戊基)氨基甲酸叔丁酯(83mg,0.25mmol),$LiAlH_4$(37mg,1.00mmol),和THF(5mL),根据为23的程序制备标题化合物194(8.0mg),总收率为13.0%(棕色固体)。^{1}H NMR(400MHz,DMSO-d6)δ7.07-7.04(m,2H),6.51-6.46(m,2H),3.90(s,1H),3.46(q,J=7.2Hz,1H),2.43(s,3H),2.15-2.03(m,3H),1.88-1.66(m,2H),1.52-1.42(m,1H),1.19(s,9H)。质谱(m/z):247.3[M+H]$^+$。

[1185] 化合物195

[1186] N^1-(4-(叔丁基)苯基)环丁烷-1,3-二胺

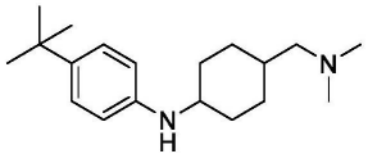
[1187] 

195

[1188] 由(3-((4-(叔丁基)苯基)氨基)环丁基)氨基甲酸叔丁酯(110mg,0.346mmol),$LiAlH_4$(51mg,1.384mmol)和THF(5mL),根据为23的程序制备标题化合物195(12.3mg),总收率为15.3%(黄色油)。^{1}H NMR(400MHz,DMSO-d6)δ6.20(dd,J=8.8,2.8Hz,2H),5.60-5.50(m,2H),3.21(q,J=7.2Hz,1H),2.81-2.67(m,1H),1.78(dtd,J=9.6,7.2,2.8Hz,1H),1.67(dq,J=6.8,2.4Hz,1H),1.63(h,J=2.0Hz,2H),1.53(d,J=7.8Hz,3H),1.33-1.12(m,2H),0.31(s,9H)。质谱(m/z):233.3[M+H]$^+$。

[1189] 化合物196

[1190] 4-(叔丁基)-N-(4-((二甲基氨基)甲基)环己基)苯胺

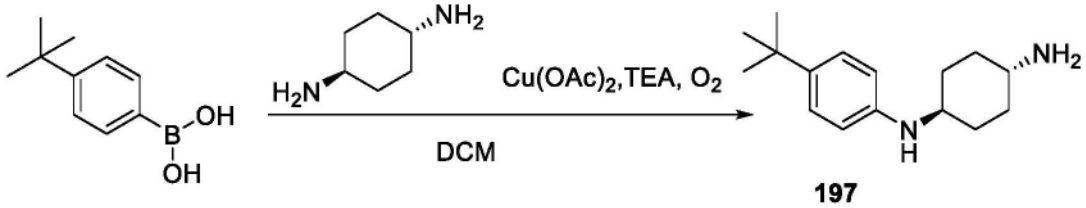
[1191] 

196

[1192] 由4-((4-(叔丁基)苯基)氨基)-N,N-二甲基环己烷-1-甲酰胺(150mg,0.497mmol),$LiAlH_4$(74mg,1.987mmol)和THF(10mL),根据为23的程序制备标题化合物196(62.2mg),总收率为43.5%(棕色油)。^{1}H NMR(400MHz,DMSO-d6)δ7.07-7.01(m,2H),6.55-6.44(m,2H),5.19(s,1H),3.45-3.33(m,2H),3.05(s,1H),2.61(d,J=27.2Hz,2H),2.48(s,6H),1.96(dd,J=13.2,3.6Hz,1H),1.89-1.82(m,1H),1.64-1.49(m,3H),1.19(s,9H)。质谱(m/z):289.3[M+H]$^+$。

[1193] 化合物197

[1194] (1r,4r)-N^1-(4-(叔丁基)苯基)环己烷-1,4-二胺

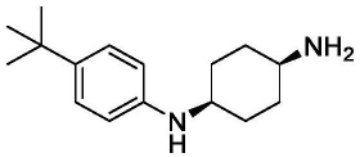
[1195] 

197

[1196] 在室温搅拌4-(叔丁基)苯胺(178.1mg,1.0mmol),Cu(OAc)2(185.4mg,1.5mmol),TEA(0.28mL,2.0mmol)和粉末化的4 ÅMS(0.75g)/CH_2Cl_2(10.0mL)的悬浮液5分钟。向此混合物中添加(1r,4r)-环己烷-1,4-二胺(22.2mg,0.2mmol)。在室温在氧气气氛下搅拌反应混合物24小时。然后将反应混合物通过硅藻土的塞子过滤,所得的溶液用3x10mL的乙酸乙酯萃取。合并有机相,用水(30mL)洗涤,干燥并且减压浓缩。残余物的提纯方法为:prep-TLC(MeOH/DCM=1:5)而得到期望的产物(白色固体)。(70.4mg,28.5%)。^{1}H NMR(400MHz,DMSO-d6)δ7.28(d,J=8.4Hz,2H),6.88(d,J=8.4Hz,2H),3.22(m,1H),2.99(m,1H),2.04-1.92(m,4H),1.45-1.27(m,4H),1.23(s,9H)。质谱(m/z):247.2[M+H]$^+$。

[1197] 化合物198

[1198] (1s,4s)-N^1-(4-(叔丁基)苯基)环己烷-1,4-二胺

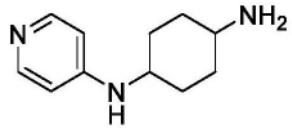
[1199] 

198

[1200] 由4-(叔丁基)苯胺(178.1mg,1.0mmol),(1s,4s)-环己烷-1,4-二胺(171mg,1.5mmol),根据为化合物197的程序制备标题化合物198(76.1mg),总收率为30.8%(白色固体)。^{1}H NMR(400MHz,DMSO-d6)δ7.19(d,J=8.4Hz,2H),6.71(d,J=8.4Hz,2H),3.43(m,1H),3.15(m,1H),1.86-1.54(m,8H),1.22(s,9H)。质谱(m/z):247.2[M+H]$^+$。

[1201] 化合物199

[1202] N^1-(吡啶-4-基)环己烷-1,4-二胺

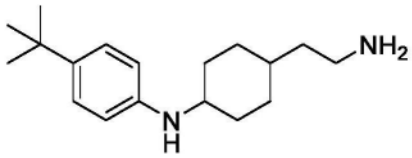
[1203] 

199

[1204] 由吡啶-4-胺(100mg,1.06mmol),(4-氧代环己基)氨基甲酸叔丁酯(339mg,1.59mmol)和根据为20的程序制备标题化合物199(6.1mg),收率为1.97%(白色粉末),经^{1}H NMR证明为1:1的混合物。^{1}H NMR(400MHz,DMSO-d6)δ8.15-8.08(m,2H),8.03(s,3H),6.83-6.71(m,2H),3.76(s,1H),2.97(s,1H),2.26(q,J=2.6,2.0Hz,1H),2.23(t,J=2.7Hz,1H),2.14(dh,J=12.9,3.3Hz,2H),1.74(ddd,J=12.7,11.0,4.5Hz,2H),1.50-1.37(m,2H)。质谱(m/z):192.4[M+H]$^+$。

[1205] 化合物200

[1206] N-(4-(2-氨基乙基)环己基)-4-(叔丁基)苯胺

[1207] 

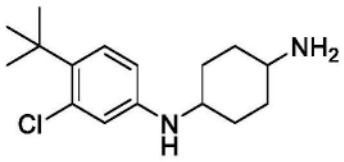
200A

200B

[1208] 由4-(叔丁基)苯胺(300mg,2.01mmol),乙基2-(4-氧代环己基乙酸乙酯(555mg,3.02mmol),根据为84的程序,以三步制备标题化合物200A(Rt=7.31min;53.2mg),总收率为9.8%(白色粉末)和以三步制备化合物200B(Rt=8.47min;50.2mg),总收率为9.1%(白色粉末),提纯方法为:Prep-HPLC(柱:X Select-CSH-Prep 5μm OBD,19*150mm;ACN/水(0.5%TFA)=5%-33%-95%-95%-5%,0min-10.0min-10.5min-11.5min-13.0min)。200A:^{1}H NMR(400MHz,DMSO-d6)δ7.63(s,3H),7.01-7.32(br,2H),6.41-6.82(br,2H),3.46(s,1H),2.82(s,2H),1.61(s,4H),1.49(d,J=10.8Hz,7H),1.23(s,9H)。质谱(m/z):275.6[M+H]$^+$。200B:^{1}H NMR(400MHz,DMSO-d6)δ7.59(s,3H),6.94-7.38(br,2H),6.43-6.72(br,2H),2.78(s,2H),1.88-1.97(m,2H),1.73(d,J=12.4Hz,2H),1.46-1.36(m,2H),1.36-1.23(br,2H),1.22(s,9H),0.98(d,J=12.8Hz,2H)。质谱(m/z):275.6[M+H]$^+$。

[1209] 化合物201

[1210] N^1-(4-(叔丁基)-3-氯苯基)环己烷-1,4-二胺

[1211] 

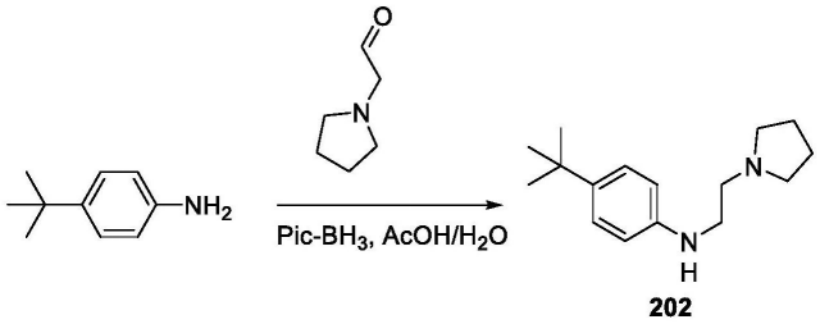
201

[1212] 由4-(叔丁基)-3-氯苯胺(100mg,0.54mmol),(4-氧代环己基)氨基甲酸叔丁酯(174mg,0.82mmol)和根据为20的程序制备标题化合物201(68.1mg),收率为44.54%(白色粉末),经^{1}H NMR证明为5:4的混合物。^{1}H NMR(400MHz,DMSO-d6)δ8.18(s,2H),7.13(dd,J=8.7,5.7Hz,1H),6.61(dd,J=20.6,2.5Hz,1H),6.48(ddd,J=11.5,8.7,2.6Hz,1H),5.64

(dd,J＝15.8,6.9Hz,1H),3.08(q,J＝6.9Hz,1H),3.01-2.89(m,1H),2.04-1.93(m,2H),1.80-1.69(m,3H),1.61(d,J＝8.6Hz,1H),1.54-1.41(m,1H),1.36(d,J＝1.5Hz,9H),1.21-1.10(m,1H)。质谱(m/z):281.5[M+H]$^+$。

[1213] 化合物202

[1214] 2-(吡咯烷-1-基)乙醛--4-(叔丁基)-N-(2-(吡咯烷-1-基)乙基)苯胺--4-(叔丁基)苯胺

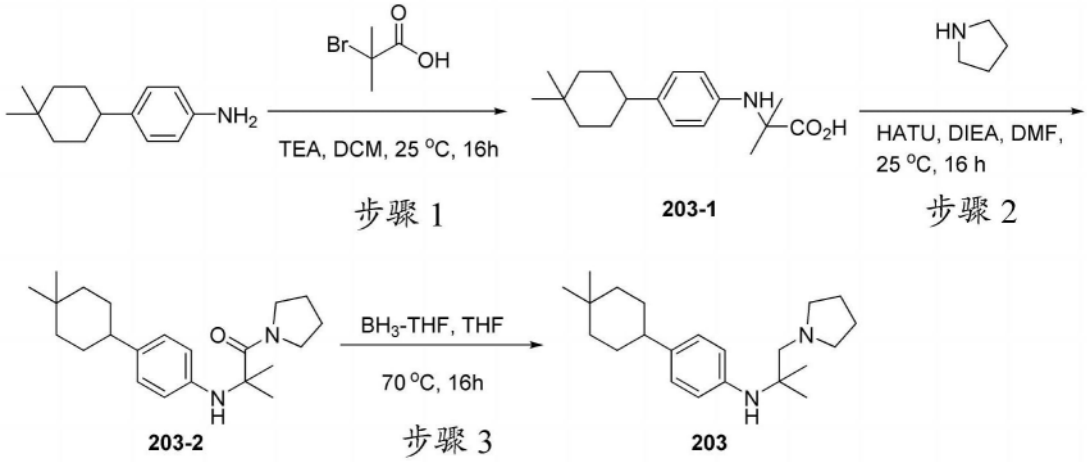
[1215] 

202

[1216] 由4-(叔丁基)苯胺(100mg,0.67mmol),AcOH/H_2O(10:1;11mL),2-(吡咯烷-1-基)乙醛(76mg,0.67mmol)和Pic-BH_3(108mg,1.0mmol),根据为90的程序制备化合物202(32mg,19%)(黄色固体)。^{1}H NMR(400MHz,CD_3OD)δ7.20(d,J＝8.4Hz,2H),6.64(d,J＝8.4Hz,2H),3.47(t,J＝6.0Hz,2H),3.37(t,J＝6.0Hz,2H),3.32(s,2H),3.28(dt,J＝3.2,1.6Hz,2H),2.06(br,4H),1.26-1.21(m,10H)。质谱(m/z):274.2[M+H]$^+$。

[1217] 化合物203

[1218] 1-N-(4-(叔丁基)苯基)-N^4-(2-甲氧基乙基)环已烷-1,4-二胺

[1219] 

[1220] 步骤1:2-((4-(4,4-二甲基环已基)苯基)氨基)-2-甲基丙酸(203-1)

[1221] 在25℃搅拌4-(4,4-二甲基环已基)苯胺(100mg,0.49mmol),2-甲氧基-乙酸(123mg,0.73mmol),TEA(100mg,0.98mmol)/DCM(5mL)的混合物过夜。将其用H_2O(30mL)淬灭并用DCM(3x30 mL)萃取。将有机层合并,用盐水NaCl(2x30 mL)洗涤并且用$MgSO_4$干燥,过滤并且浓缩而得到目标产物(黄色油)(200mg,收率:80%)。质谱(m/z):289.9[M+H]$^+$。

[1222] 步骤2:2-((4-(4,4-二甲基环已基)苯基)氨基)-2-甲基-1-(吡咯烷-1-基)丙-1-酮(203-2)

[1223] 向203-1(100mg,0.34mmol),吡咯烷(29.49mg,0.41mmol)/DMF(5mL)的溶液中添加HATU(197mg,0.52mmol)和DIEA(134mg,1.03mmol)。然后在25℃搅拌混合物过夜。将其用H_2O

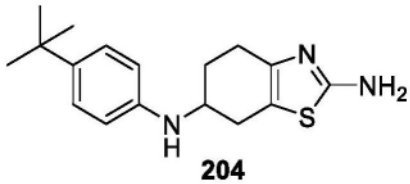
(30mL)淬灭并用EA(3x30 mL)萃取。将有机层合并,用盐水NaCl(2x30 mL)洗涤并且用$MgSO_4$干燥,过滤并且浓缩。将粗产物施加到硅胶柱(4g),用PE:EA(10:1)洗脱而得到产物(40mg,收率:27%)。质谱(m/z):342.9$[M+H]^+$。

[1224] 步骤3:制备4-(4,4-二甲基环己基)-N-(2-甲基-1-(吡咯烷-1-基)丙-2-基)苯胺(203)

[1225] 向203-2(50mg,0.15mmol),2-(4-甲基哌嗪-1-基)乙酸(66mg,0.42mmol)/THF(5mL)的溶液中添加BH_3-THF(10mL)。然后在室温搅拌混合物过夜。将反应真空浓缩。残余物的提纯方法为:prep-TLC而得到期望的产物(15.5mg)(白色固体)。^1H NMR(400MHz,CD_3OD)δ 7.09(d,J=8.4Hz,2H),6.83(d,J=8.4Hz,2H),3.67(br,2H),3.49(br,2H),3.30(br,2H),2.38-2.30(m,1H),2.07(br,4H),1.65-1.57(m,4H),1.49(d,J=11.2Hz,2H),1.39-1.31(m,8H),0.97(d,J=15.8Hz,6H)。质谱(m/z):329.0$[M+H]^+$。

[1226] 化合物204

[1227] 4-N-(4-(叔丁基)苯基)-4,5,6,7-四氢苯并[d]噻唑-2,6-二胺

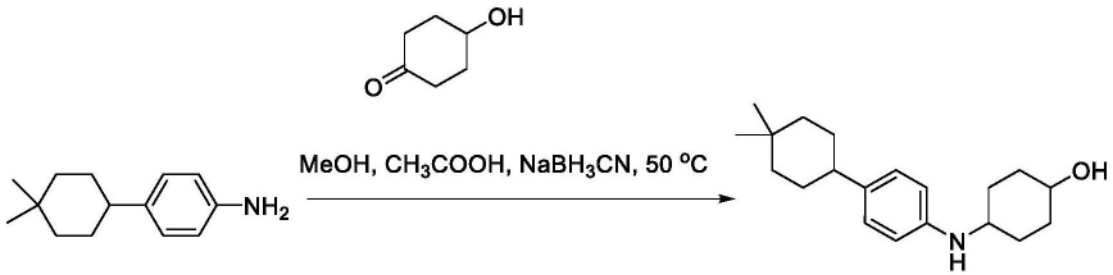
[1228] 

204

[1229] 由4-(叔丁基)苯胺(90mg,0.6mmol),2-氨基-4,7-二氢苯并[d]噻唑-6(5H)-酮(101mg,0.6mmol),Pic-BH_3(98mg,0.9mmol),H_2O(9mL)和HOAc(1mL),根据为90的程序制备标题化合物204(31.6mg)(白色固体)。^1H NMR(400MHz,CD_3OD)δ7.20-7.14(m,2H),6.69-6.64(m,2H),3.77(dddd,J=10.6,8.0,5.0,2.8Hz,1H),2.92(dd,J=15.8,4.4Hz,1H),2.65-2.55(m,2H),2.46-2.39(m,1H),2.18-2.10(m,1H),1.82-1.72(m,1H),1.26(s,9H)。质谱(m/z):302.2$[M+H]^+$。

[1230] 化合物205

[1231] 4-((4-(4,4-二甲基环己基)苯基)氨基)环己烷-1-醇

[1232] 

205A

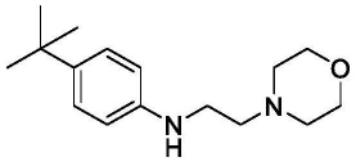
205B

[1233] 在50℃搅拌4-(4,4-二甲基环己基)苯胺(80mg,0.39mmol),4-羟基环己烷-1-酮(53.9mg,0.47mmol)和$NaBH_3CN$(49.5mg,0.79mmol)/MeOH(10mL)和CH3COOH(1滴)的混合物过夜。在冷却后,过量的MeOH被真空蒸馏掉并且残余的油被真空蒸馏掉。然后反应溶液用乙酸乙酯(20mL)和水(20mL)萃取三次。然后真空除去溶剂并且残余物的提纯方法为:prep-HPLC(柱-Xbridge-C18 150x 21.2mm,5um;移动相:ACN-H_2O(0.1%FA),32%-37%)而得到期望的产物205A:(30.3mg,24.6%)(白色固体)和205B(38.1mg,30.9%)(白色固体)。205A

:^{1}H NMR(400MHz,DMSO-d6)δ6.93(d,2H),6.50(d,2H),4.54(br,^{1}H),3.39(br,^{1}H),3.08(br,^{1}H),2.26-2.16(m,1H),1.86(dd,4H),1.56-1.46(m,4H),1.42(d,2H),1.31-1.20(m,4H),1.18-1.07(m,2H),0.93(d,6H)。质谱(m/z):301.9[M+H]$^+$。HPLC:Rt:5.674min(柱:XBRIDGE 2.1*50mm,3.5um;移动相:H_2O(0.05%TFA)/ACN(0.05%TFA),ACN由0%至60%在7分钟内,7-8min,ACN由60%至100%;0.8mL/min)。205B:^{1}H NMR(400MHz,DMSO-d6)δ6.90(d,2H),6.49(d,2H),5.16(br,1H),4.37(br,1H),3.68(br,1H),3.18(br,1H),2.20(br,1H),1.58-1.10(m,14H),0.93(d,6H)。质谱(m/z):301.9[M+H]$^+$。HPLC:Rt:5.919min(柱:XBRIDGE 2.1*50mm,3.5um;移动相:H_2O(0.05%TFA)/ACN(0.05%TFA),ACN由0%至60%7分钟内,7-8min,ACN由60%至100%;0.8mL/min)。

[1234] 化合物206

[1235] U4-(叔丁基)-N-(2-吗啉代乙基)苯胺

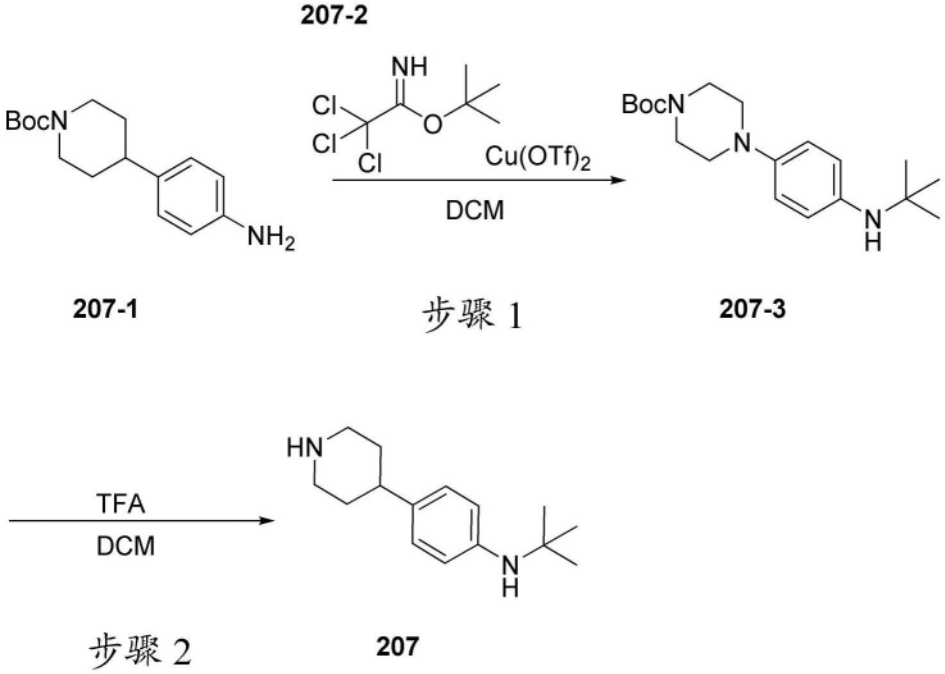
[1236] 

206

[1237] 由4-叔丁基苯胺(80mg,0.54mmol),2-吗啉代乙醛(83.1mg,0.64mmol),硼烷-2-皮考啉复合物(86.0mg,0.80mmol),CH3COOH(1mL)和H_2O(9mL),根据为90的程序制备期望的产物206(10.1mg,7.1%)(白色油)。^{1}H NMR(400MHz,CD_3OD)δ7.19-7.14(m,2H),6.64-6.57(m,2H),3.73-3.67(m,4H),3.21(t,J=6.6Hz,2H),2.59(t,J=6.6Hz,2H),2.50(m,4H),1.25(s,9H)。质谱(m/z):263.0[M+H]$^+$。

[1238] 化合物207

[1239] N-(叔丁基)-4-(哌啶-4-基)苯胺

[1240] 

[1241] 步骤1:制备4-(4-(叔丁基氨基)苯基)哌嗪-1-甲酸叔丁酯(207-3)

[1242] 由4-(4-氨基苯基)哌啶-1-甲酸叔丁酯(276mg,1.0mmol),2,2,2-三氯乙酰亚胺酸

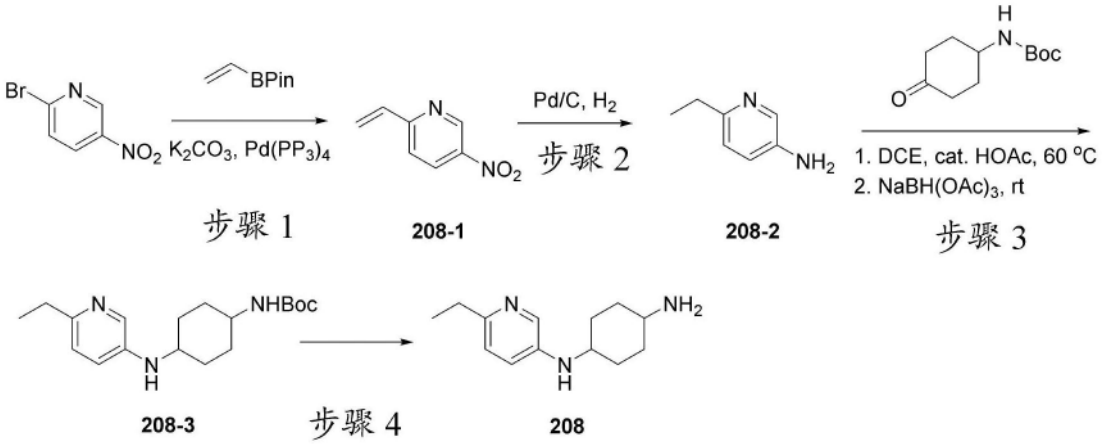
叔丁酯(545mg,2.5mmol)和Cu(OTf)2(18.1mg,50umol),根据为11的程序制备标题化合物207-3(33.0mg),总收率为10.0%(白色固体)。质谱(m/z):333.3[M+H]+。

[1243] 步骤2:制备N-(叔丁基)-4-(哌啶-4-基)苯胺(207)

[1244] 由4-(4-(叔丁基氨基)苯基)哌嗪-1-甲酸叔丁酯(33mg,0.1mmol)和TFA(1.0mL),根据为24的程序制备标题化合物207(6.8mg),总收率为30.6%(黄色固体)。1H NMR(400MHz,DMSO-d6)δ10.54(s,1H),8.48(d,J=83.7Hz,1H),7.35(s,4H),3.36(d,J=12.5Hz,2H),3.04-2.79(m,3H),1.92(d,J=13.7Hz,2H),1.73(qd,J=13.0,4.0Hz,2H),1.25(s,9H)。质谱(m/z):233.3[M+H]+。

[1245] 化合物208

[1246] N1-(6-乙基吡啶-3-基)环己烷-1,4-二胺

[1247] 

[1248] 步骤1:制备5-硝基-2-乙烯基吡啶(208-1)

[1249] 向2-溴-5-硝基吡啶(500mg,2.46mmol),4,4,5,5-四甲基-2-乙烯基-1,3,2-二氧杂硼杂环戊烷(569mg,3.69mmol),K_2CO_3(1019mg,7.39mmol)/1,4-二氧杂环己烷(20mL)和水(2mL)的溶液中添加$Pd(PPh_3)_4$(285mg,0.24mmol)。在氮气气氛下搅拌混合物,回流过夜。在冷却到环境温度后,减压浓缩。残余物的提纯方法为:硅胶柱而得到化合物208-1(370mg,100%,收率)(黄色固体)。MS(m/z):150.9[M+H]+。

[1250] 步骤2:制备6-乙基吡啶-3-胺(208-2)

[1251] 向2-(4,4-二甲基环己-1-烯-1-基)-5-硝基吡啶(350mg,2.33mmol)/MeOH(10mL)的溶液中添加Pd/C(35mg,10%),并且在氢气气氛下使混合物反应16小时。然后将反应过滤并且真空除去溶剂而得到化合物208-2(260mg,91.2%,收率)(黄色固体)。MS(m/z):123.0[M+H]+。

[1252] 步骤3:制备(4-((6-乙基吡啶-3-基)氨基)环己基)氨基甲酸叔丁酯(208-3)

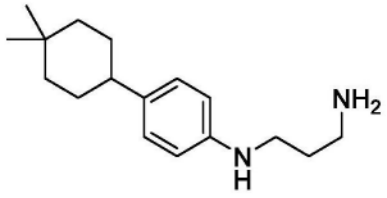
[1253] 向化合物208-2(260mg,2.13mmol)/MeOH(10mL)和一滴AcOH的溶液中添加(4-氧代环己基)氨基甲酸叔丁酯(501mg,2.34mmol)。然后向混合物中添加$NaBH_4$(160mg,4.26mmol)并在25℃搅拌混合物16小时。LCMS显示反应完成。将反应用水(10mL)淬灭,用EA(10mL*3)萃取。将合并的有机层用盐水(20mL)洗涤,用硫酸钠干燥,过滤和浓缩。残余物的提纯方法为:使用EA/PE(1:3)的combi-flash(闪式色谱)而得到化合物208-3(0.4g,58.8%,收率)(黄色固体)。MS(m/z):319.9[M+H]+。

[1254] 步骤4:制备N1-(6-乙基吡啶-3-基)环己烷-1,4-二胺(208)

[1255] 化合物208-3(200mg,0.63mmol)和HCl/1,4-二氧杂环己烷(10mL,4N)被置于烧瓶中,在25℃搅拌16小时。过量的1,4-二氧杂环己烷被真空蒸馏掉并且残余物的提纯方法为:prep-HPLC(柱-Xbridge-C18150x 19mm,5um;移动相:ACN-H_2O(0.1%FA),20%-40%)而得到208(7.7mg 5.61%)(白色固体)。^{1}H NMR(400MHz,DMSO-d6)δ7.92(d,J=2.5Hz,1H),7.83(s,2H),7.53(s,2H),6.58(s,1H),3.30-3.26(m,1H),3.04(s,1H),2.77(dd,J=15.2,7.3Hz,2H),2.52(d,J=1.9Hz,2H),2.10-1.86(m,4H),1.44(d,J=11.8Hz,2H),1.21(t,J=7.6Hz,3H).MS(m/z)220.2$[M+H]^+$。

[1256] 化合物209

[1257] 1-N-(4-(4,4-二甲基环己基)苯基)丙烷-1,3-二胺

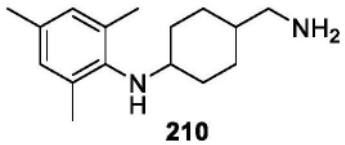
[1258] 

209

[1259] 由(3-((4-(4,4-二甲基环己基)苯基)氨基)丙基)氨基甲酸叔丁酯(50mg,0.14mmol),1,4-二氧杂环己烷(5mL)和HCl/1,4-二氧杂环己烷(5mL),根据为24的程序制备标题化合物209(19.8mg)(白色固体)。^{1}H NMR(400MHz,CD_3OD)δ7.17(d,J=8.2Hz,2H),6.89(d,J=8.4Hz,2H),3.06-3.02(m,2H),2.41-2.34(m,1H),2.01-1.96(m,2H),1.65-1.35(m,10H),0.99(s,3H),0.95(s,3H)。质谱(m/z):260.9$[M+H]^+$。

[1260] 化合物210

[1261] N-[4-(氨基甲基)环己基]-2,4,6-三甲基苯胺

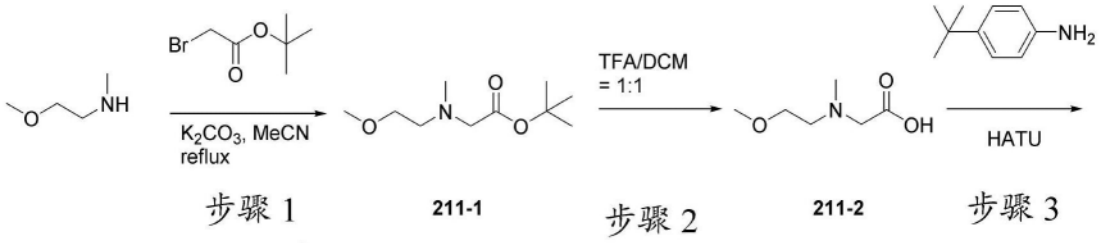
[1262] 

210

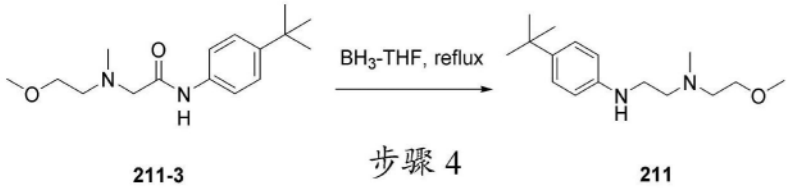
[1263] 由N-({4-[(2,4,6-三甲基苯基)氨基]环己基}甲基)氨基甲酸叔丁酯(160mg,0.46mmol)和HCl/MeOH(10mL,4N),根据为37的程序制备标题化合物210(16.2mg)(黄色油)。^{1}H NMR(300MHz,CD_3OD)δ6.72(s,2H),3.11(br,1H),2.64(br,2H),2.13(s,6H),2.12(br,3H),1.55(br,9H).MS(m/z)247.0$[M+H]^+$。

[1264] 化合物211

[1265] N^1-(4-(叔丁基)苯基)-N^2-(2-甲氧基乙基)-N^2-甲基乙烷-1,2-二胺



[1266]



[1267] reflux:回流

[1268] 步骤1:制备N-(2-甲氧基乙基)-N-甲基甘氨酸叔丁酯(211-1)

[1269] 在80℃搅拌2-甲氧基-N-甲基乙-1-胺(800mg,9.00mmol),2-溴乙酸叔丁酯(2.45mg,12.6mmol),K_2CO_3(2.48g,18mmol)/MeCN(50mL)的混合物过夜。在冷却到室温后,添加40mL的水。将固体通过硅胶色谱提纯。获得目标产物(无色油)。质谱(m/z):204.0$[M+H]^+$。

[1270] 步骤2:制备N-(2-甲氧基乙基)-N-甲基甘氨酸(211-2)

[1271] 在室温搅拌N-(2-甲氧基乙基)-N-甲基甘氨酸叔丁酯(572mg,2.81mmol)/TFA(20mL)和DCM(2mL)的混合物过夜。将反应减压浓缩。固体被直接用于下一步中。质谱(m/z):148.2$[M+H]^+$。

[1272] 步骤3:制备N-(4-(叔丁基)苯基)-2-((2-甲氧基乙基)(甲基)氨基)乙酰胺(211-3)

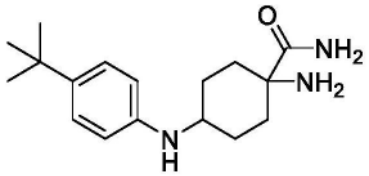
[1273] 在室温搅拌N-(2-甲氧基乙基)-N-甲基甘氨酸(402mg,273mmol),4-(叔丁基)苯胺(489mg,3.28mmol),HATU(1.25g,3.28mmol),DIPEA(530mg,4.1mmol)/DMF(20mL)的混合物过夜。然后添加40mL的水。将固体通过硅胶色谱提纯。获得目标产物(543mg,71%)(黄色固体)。质谱(m/z):279.2$[M+H]^+$。

[1274] 步骤4:制备N^1-(4-(叔丁基)苯基)-N^2-(2-甲氧基乙基)-N^2-甲基乙烷-1,2-二胺(211)

[1275] 将N-(4-(叔丁基)苯基)-2-((2-甲氧基乙基)(甲基)氨基)乙酰胺(200mg,0.72mmol)添加到BH_3-THF(20mL)并在70℃搅拌混合物过夜。将反应真空浓缩。残余物的提纯方法为:prep-TLC而得到期望的产物(11mg,6%)(白色固体)。^1H NMR(400MHz,CD_3OD)δ 7.21(d,J=8.8Hz,2H),6.66(d,J=8.7Hz,2H),3.71-3.63(m,2H),3.47(t,J=6.1Hz,2H),3.33(s,3H),3.28(d,J=4.9Hz,4H),2.85(s,3H),1.26(s,9H)。质谱(m/z):365.2$[M+H]^+$。

[1276] 化合物212

[1277] 1-氨基-4-((4-(叔丁基)苯基)氨基)环己烷-1-甲酰胺

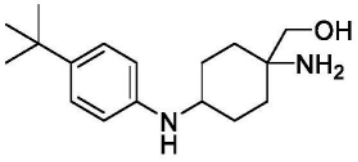
[1278] 

212

[1279] 由1-氨基-4-((4-(叔丁基)苯基)氨基)环己烷-1-甲酸(14.5mg,0.05mmol),根据为化合物24的程序制备标题化合物212(8.0mg),总收率为57%(白色固体),经^{1}H NMR证明为1:1的混合物。^{1}H NMR(400MHz,DMSO-d6)δ8.20(s,3H),7.95(s,1H),7.67(s,1H),7.11(d,J=8.4Hz,2H),6.52(d,J=8.4Hz,2H),3.28(m,0.5H),2.67(m,0.5H),2.23-2.15(m,2H),2.03-1.86(m,4H),1.63-1.45(m,2H),1.21(s,9H)。质谱(m/z):290.1[M+H]$^+$。

[1280] 化合物213

[1281] (1-氨基-4-((4-(叔丁基)苯基)氨基)环己基)甲醇

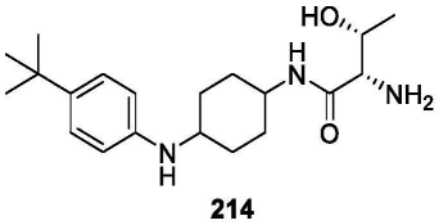
[1282] 

213A
213B

[1283] 由1-氨基-4-((4-(叔丁基)苯基)氨基)环己烷-1-甲酸(14.5mg,0.05mmol),根据为化合物86的程序制备标题化合物213。混合物的提纯方法:制备HPLC(柱:X Select-CSH-Prep 5μm OBD,19*150mm;ACN/水(0.5%TFA)=5%-30%-95%-95%-5%,0min-10min-10.5min-11.5min-13min)而得到化合物213A(Rt=3.16min)(白色固体)和化合物213B(Rt=3.57min)(白色固体)。213A(4.6mg,17%):^{1}H NMR(400MHz,DMSO-d6)δ7.85(s,2H),7.36(s,1H),7.17(d,J=8.4Hz,2H),6.61(d,J=8.4Hz,2H),3.43(s,2H),2.64(m,1H),1.95-1.51(m,4H),1.22(s,9H)。质谱(m/z):277.3[M+H]$^+$。213B(6.8mg,25%):^{1}H NMR(400MHz,DMSO-d6)δ7.83(s,2H),7.34(s,1H),7.08(d,J=8.4Hz,2H),6.50(d,J=8.4Hz,2H),3.55(s,2H),2.66(m,1H),2.05-1.87(m,4H),1.63-1.41(m,4H),1.22(s,9H)。质谱(m/z):277.3[M+H]$^+$。

[1284] 化合物214

[1285] (2S,3R)-2-氨基-N-(4-((4-(叔丁基)苯基)氨基)环己基)-3-羟基丁酰胺

[1286] 

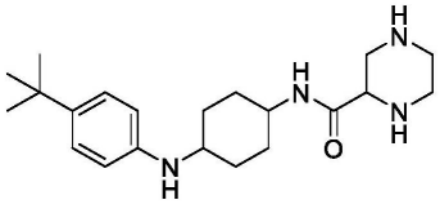
214

[1287] 由((2S,3R)-1-((4-((4-(叔丁基)苯基)氨基)环己基)氨基)-3-羟基-1-氧代丁烷-2-基)氨基甲酸叔丁酯(22.4mg,0.05mmol),根据为化合物1的程序制备标题化合物214(11.6mg),总收率为68%(白色固体),经^{1}H NMR证明为1:1的混合物。^{1}H NMR(400MHz,DMSO-d6)δ8.18(s,1H),7.05(d,J=8.4Hz,1H),7.02(d,J=8.4Hz,1H),6.65(s,3H),6.49(d,J=8.4Hz,1H),6.45(d,J=8.4Hz,1H),5.19(s,2H),4.06-3.43(m,2H),3.37(s,1H),3.27(s,

1H),1.94(m,1H),1.78(m,1H),1.58(m,4H),1.31(m,2H),1.16(s,9H),1.08(d,J＝3.2Hz,1.5H),1.06(d,J＝3.2Hz,1.5H)。质谱(m/z):348.2[M+H]$^+$。

[1288] 化合物215

[1289] N-(4-((4-(叔丁基)苯基)氨基)环己基)哌嗪-2-甲酰胺

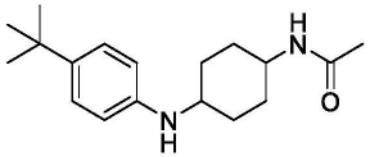
[1290] 

215

[1291] 由2-((4-((4-(叔丁基)苯基)氨基)环己基)氨基甲酰基)哌嗪-1,4-二甲酸二叔丁酯(27.9mg,0.05mmol),根据为化合物1的程序制备标题化合物215(7.8mg),总收率为43%(白色固体),经^{1}H NMR证明为1:1的混合物。^{1}H NMR(400MHz,DMSO-d6)δ7.55(s,1H),7.06(d,J＝8.4Hz,1H),7.04(d,J＝8.4Hz,1H),6.51(d,J＝8.4Hz,1H),6.47(d,J＝8.4Hz,1H),5.16(s,1H),3.68(m,0.5H),3.50(m,0.5H),3.31(s,1H),3.10(m,2H),2.92-2.53(m,4H),2.46(s,1H),1.95(m,1H),1.76(m,1H),1.65-1.50(m,4H),1.27(m,2H),1.19(s,9H)。质谱(m/z):359.3[M+H]$^+$。

[1292] 化合物216

[1293] N-(4-((4-(叔丁基)苯基)氨基)环己基)乙酰胺

[1294] 

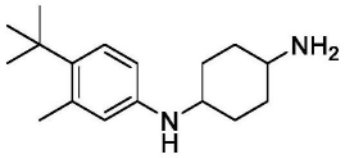
216A

216B

[1295] 由N^1-(4-(叔丁基)苯基)环己烷-1,4-二胺(100mg,0.41mmol),乙酸(49mg,0.81mmol),根据为1的程序制备标题化合物216A(Rt＝4.57min;3mg),收率为7.0%(白色粉末)和制备化合物216B(Rt＝4.72min;18.2mg),收率为18.2%(白色粉末),提纯方法为:Prep-HPLC(柱:X Select-CSH-Prep 5μm OBD,19*150mm;ACN/水(0.5%TFA)＝5%-5%-95%-95%-5%,0min-1min-10min-11min-15.0min)。216A:^{1}H NMR(400MHz,DMSO-d6)δ7.80(d,J＝7.6Hz,1H),7.40(s,2H),7.08(s,2H),3.56-3.42(m,1H),3.31(s,1H),1.95-1.80(m,4H),1.77(s,3H),1.40-1.32(m,2H),1.27(s,9H),1.22-1.16(m,2H)。质谱(m/z):289.2[M+H]$^+$。216B:^{1}H NMR(400MHz,DMSO-d6)δ7.73(d,J＝6.1Hz,1H),7.39(s,2H),7.07(s,2H),3.67(d,J＝5.4Hz,1H),3.38(dd,J＝9.2,3.7Hz,1H),1.81(s,3H),1.73(t,J＝9.6Hz,2H),1.65(q,J＝6.4,5.5Hz,4H),1.54-1.42(m,2H),1.25(s,9H)。质谱(m/z):289.2[M+H]$^+$。

[1296] 化合物217

[1297] N^1-(4-(叔丁基)-3-甲基苯基)环己烷-1,4-二胺

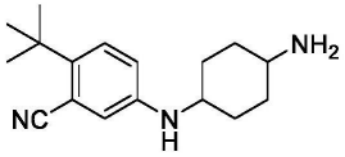
[1298] 

217

[1299] 由4-(叔丁基)-3-甲基苯胺(110mg,0.67mmol),(4-氧代环己基)氨基甲酸叔丁酯(215mg,1.01mmol)和根据为20的程序制备标题化合物217(47.9mg),收率为30.0%(白色粉末),经^{1}H NMR证明为1:1的混合物。^{1}H NMR(400MHz,DMSO-d6)δ7.79(s,3H),7.08(d,J=8.5Hz,1H),6.50(s,2H),3.41(s,1H),3.13(s,1H),2.38(s,3H),1.82-1.65(m,6H),1.62(d,J=10.1Hz,2H),1.29(s,9H)。质谱(m/z):261.3[M+H]$^+$。

[1300] 化合物218

[1301] 5-((4-氨基环己基)氨基)-2-(叔丁基)苯腈

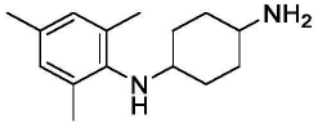
[1302] 

218

[1303] 由5-氨基-2-(叔丁基)苯腈(100mg,0.57mmol),(4-氧代环己基)氨基甲酸叔丁酯(183mg,0.86mmol)和根据为20的程序制备标题化合物218(96.2mg),收率为61.7%(白色粉末)经^{1}H NMR证明为1:0.7的混合物。^{1}H NMR(400MHz,DMSO-d6)δ8.23(s,5H),7.21(t,J=8.5Hz,2H),6.94(d,J=2.7Hz,1H),6.91(d,J=2.6Hz,1H),6.83(dd,J=8.9,2.7Hz,1H),6.79(dd,J=8.8,2.7Hz,1H),5.92(d,J=5.9Hz,1H),5.87(d,J=8.0Hz,1H),3.42(s,1H),3.20-3.01(m,2H),2.94(ddt,J=11.7,7.5,3.6Hz,1H),2.03-1.92(m,4H),1.74(dq,J=8.8,5.7Hz,5H),1.67-1.56(m,2H),1.54-1.42(m,2H),1.37(d,J=1.6Hz,16H),1.27-1.08(m,4H)。质谱(m/z):272.7[M+H]$^+$。

[1304] 化合物219

[1305] N^1-均三甲苯基环己烷-1,4-二胺

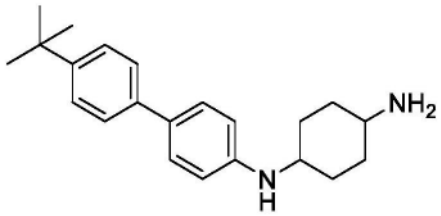
[1306] 

219

[1307] 由(4-(均三甲苯基氨基)环己基)氨基甲酸叔丁酯(95mg,0.286mmol),TFA(1mL),和DCM(10mL),根据为24的程序制备标题化合物219(23.7mg),总收率为35.7%(白色固体),经^{1}H NMR证明为1:2的混合物。^{1}H NMR(400MHz,DMSO-d6)δ6.69(s,2H),3.04(d,J=39.6Hz,1H),2.91-2.59(m,1H),2.16-2.08(m,9H),1.95-1.89(m,1H),1.77(d,J=9.2Hz,2H),1.64(dt,J=10.0,6.4Hz,2H),1.49(td,J=9.6,4.4Hz,1H),1.25(dt,J=23.2,11.2Hz,2H)。质谱(m/z):233.3[M+H]$^+$。

[1308] 化合物220

[1309] N^1-(4'-(叔丁基)-[1,1'-联苯]-4-基)环己烷-1,4-二胺

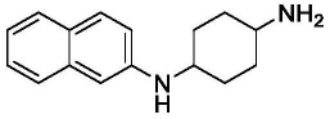
[1310] 

220

[1311] 由(4-(均三甲苯基氨基)环己基)氨基甲酸叔丁酯(149mg,0.353mmol),TFA(1mL),和DCM(10mL),根据为24的程序制备标题化合物220(72.6mg),总收率为35.7%(白色固体),经^{1}H NMR证明为1:2的混合物。^{1}H NMR(400MHz,DMSO-d6)δ7.40(dq,J=8.8,2.4Hz,2H),7.35-7.31(m,4H),6.68-6.57(m,2H),5.60(s,1H),3.46-2.84(m,3H),2.06-1.68(m,5H),1.64-1.40(m,2H),1.24(s,9H)。质谱(m/z):323.3[M+H]$^+$。

[1312] 化合物221

[1313] N^1-(萘-2-基)环己烷-1,4-二胺

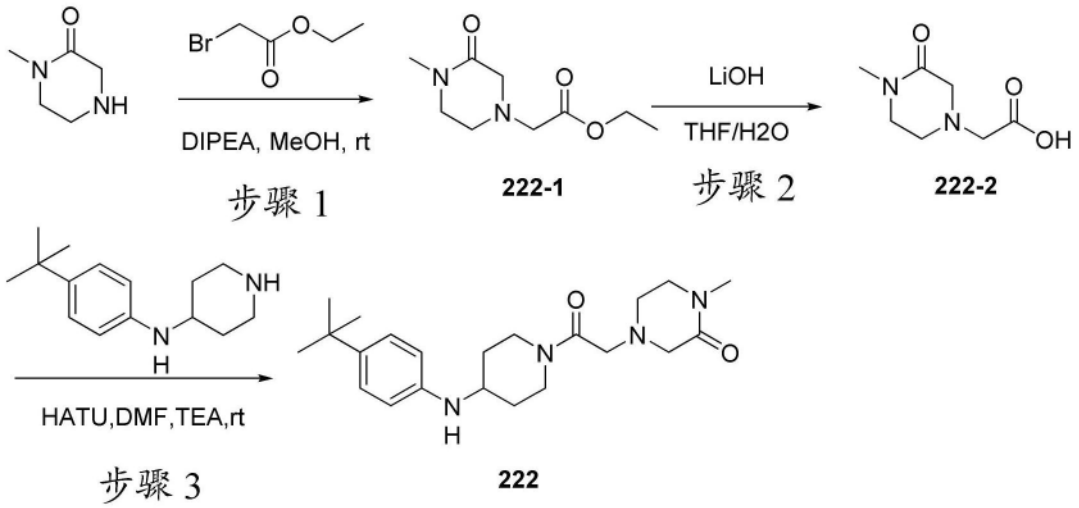
[1314] 

221

[1315] 由(4-(萘-2-基氨基)环己基)氨基甲酸叔丁酯(174mg,0.512mmol),TFA(1mL),和DCM(10mL),根据为24的程序制备标题化合物221(87.2mg),总收率为70.7%(白色固体),经^{1}H NMR证明为1:2的混合物。^{1}H NMR(400MHz,DMSO-d6)δ7.61-7.47(m,3H),7.24(dddd,J=8.0,6.8,3.2,1.2Hz,1H),7.09-6.86(m,2H),6.68(dd,J=12.4,2.4Hz,1H),5.80-5.74(m,1H),3.56-3.17(m,3H),3.12-2.92(m,1H),2.12-2.03(m,1H),2.03-1.95(m,1H),1.85(dd,J=12.4,4.0Hz,1H),1.74(q,J=5.6Hz,2H),1.69-1.59(m,1H),1.56-1.43(m,1H)。质谱(m/z):241.3[M+H]$^+$。

[1316] 化合物222

[1317] 4-(2-{4-[(4-叔丁基苯基)氨基]哌啶-1-基}-2-氧代乙基)-1-甲基哌嗪-2-酮

[1318] 

[1319] 步骤1:制备2-(4-甲基-3-氧代哌嗪-1-基乙酸乙酯(222-1)

[1320] 在25℃搅拌1-甲基哌嗪-2-酮(400mg,3.50mmol),2-溴乙酸乙酯(878mg,

5.25mmol)和N,N-二异丙基乙胺(906mg,7.00mmol)/MeOH(30mL)的溶液过夜。LCMS显示反应完成。将反应用水(50mL)淬灭,用EA(50mL*3)萃取。将合并的有机层用盐水(20mL)洗涤,用硫酸钠干燥,过滤和浓缩。残余物的提纯方法为:使用EA/PE(1:3)的combi-flash(闪式色谱)而得到化合物222-1(550mg,76.8%,收率)(黄色固体)。MS(m/z):200.9[M+H]$^+$。

[1321] 步骤2:制备(4-甲基-3-氧代哌嗪-1-基)乙酸(222-2)

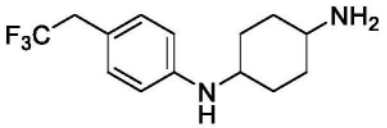
[1322] 在25℃搅拌产物222-1(200mg,0.99mmol)和LiOH(101mg,19.9mmol)/THF/H_2O(1:1)(30mL)的溶液过夜。LCMS显示反应完成。将反应浓缩并冻干而得到化合物222-2(50mg,85.47%,收率)(黄色油)。质谱(m/z):173.2[M+H]$^+$。

[1323] 步骤3:制备4-(2-{4-[(4-叔丁基苯基)氨基]哌啶-1-基}-2-氧代乙基)-1-甲基哌嗪-2-酮(222)

[1324] 在25℃搅拌化合物222-2(100mg,0.58mmol),N-(4-叔丁基苯基)哌啶-4-胺(135mg,0.58mmol),HATU(331mg,0.87mmol)和三乙胺(117mg,1.16mmol)/DMF(30mL)的溶液过夜。LCMS显示反应完成。将反应用水(50mL)淬灭,用EA(50mL*3)萃取。将合并的有机层用盐水(40mL)洗涤,用硫酸钠干燥,过滤和浓缩。残余物的提纯方法为:使用EA/PE(2:3)的combi-flash(闪式色谱)而得到化合物222(50mg,21.1%)(白色固体)。^{1}H NMR(400MHz,CD_3OD)δ7.58(d,J=8.4Hz,2H),7.30(d,J=8.4Hz,2H),4.59(br,1h),4.12(br,1H),3.84(s,3H),3.78-3.62(m,2H),3.49(s,3H),3.31-3.13(m,2H),3.02(s,3H),2.06(d,J=11.6Hz,2H),1.86-1.47(m,3H),1.31(s,12H)。质谱(m/z):386.9[M+H]$^+$。

[1325] 化合物223

[1326] N^1-(4-(2,2,2-三氟乙基)苯基)环己烷-1,4-二胺

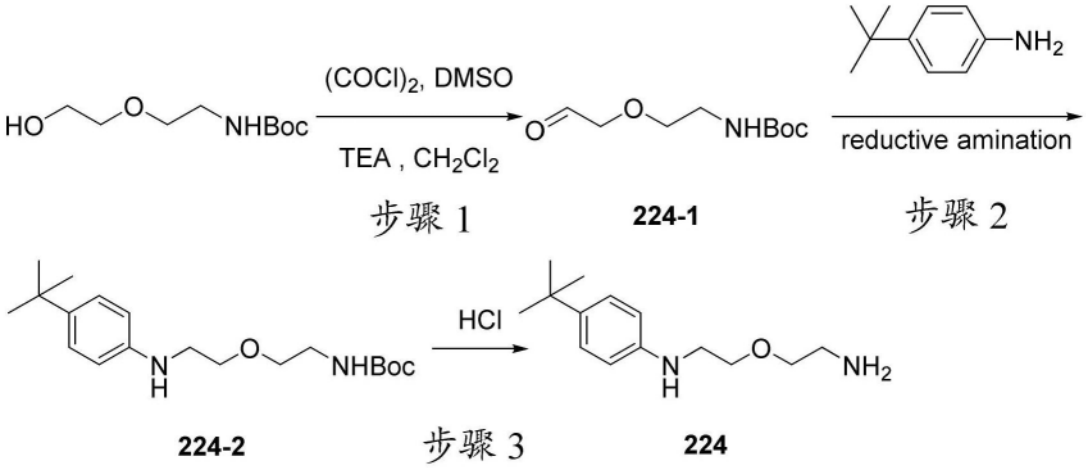
[1327] 

223

[1328] 由(4-((4-(2,2,2-三氟乙基)苯基)氨基)环己基)氨基甲酸叔丁酯(278mg,0.74mmol),1,4-二氧杂环己烷(10mL)和1,4-二氧杂环己烷/HCl(10mL),根据为37的程序制备期望的产物223(50.8mg,24.5%)(白色固体)。^{1}H NMR(400MHz,DMSO-d6)δ7.92(s,3H),7.05(d,2H),6.62(d,2H),3.44-3.36(m,3H),3.13(br,1H),1.89-1.39(m,8H)。质谱(m/z):273.1[M+H]$^+$。

[1329] 化合物224

[1330] N-(2-(2-氨基乙氧基)乙基)-4-(叔丁基)苯胺

[1331] 

[1332] reductive amination:还原胺化

[1333] 步骤1:制备(2-(2-氧代乙氧基)乙基)氨基甲酸叔丁酯(224-1)

[1334] 在-78℃在氮气气氛下向(COCl)2(2.13g,16.8mmol)/CH_2Cl_2(15mL)的混合物滴加DMSO(2.85g,36.5mmol)/CH_2Cl_2(15mL)。在添加后,搅拌溶液30分钟并且然后添加(2-(2-羟基乙氧基)乙基)氨基甲酸叔丁酯(1.5g,7.31mmol)/CH_2Cl_2(15mL)的溶液。在添加TEA(6.66g,65.8mmol)后,在-78℃搅拌反应30分钟并且然后在室温搅拌过夜。添加100mL的水。将有机相合并,用Na_2SO_4干燥,过滤并且浓缩而得到产物。获得目标产物(1.3g,88%)(黄色固体)。质谱(m/z):225.9$[M+H]^+$。

[1335] 步骤2:制备(2-(2-((4-(叔丁基)苯基)氨基)乙氧基)乙基)氨基甲酸叔丁酯(224-2)

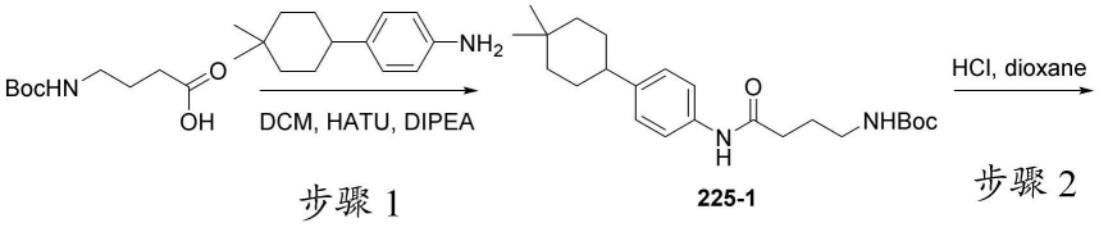
[1336] 在室温搅拌(2-(2-氧代乙氧基)乙基)氨基甲酸叔丁酯(100mg,0.49mmol),4-(叔丁基)苯胺(73mg,0.49mmol),Pic-BH_3(63mg,0.59mmol)/H_2O(9mL)和CH3COOH(1mL)的混合物5小时。然后将反应用$NaHCO_3$水溶液淬灭。将有机相合并,用Na_2SO_4干燥,过滤并且浓缩。通过硅胶色谱获得目标产物(122mg,74%)。质谱(m/z):336.9$[M+H]^+$。

[1337] 步骤3:制备N-(2-(2-氨基乙氧基)乙基)-4-(叔丁基)苯胺(224)

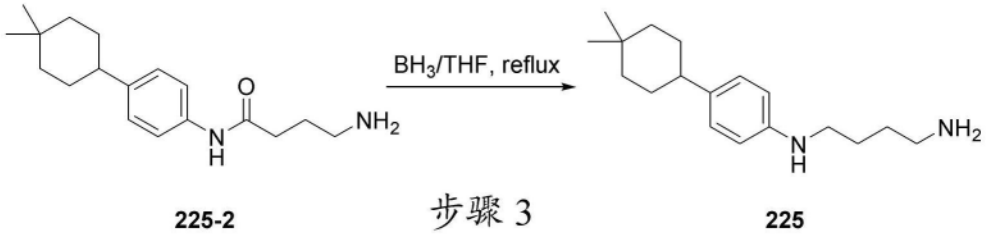
[1338] 向(2-(2-((4-(叔丁基)苯基)氨基)乙氧基)乙基)氨基甲酸叔丁酯(122mg,0.36mmol)/HCl的溶液中添加二氧杂环己烷(3mL)和CH_2Cl_2(3mL)。然后在室温搅拌混合物过夜。将反应真空浓缩。残余物的提纯方法为:prep-TLC而得到期望的产物(23mg,27%)(白色固体)。^1H NMR(400MHz,CD_3OD)δ7.19(d,J=8.7Hz,2H),6.68(d,J=8.7Hz,2H),3.69(dt,J=12.8,5.2Hz,4H),3.30-3.27(m,2H),3.14-3.04(m,2H),1.26(s,9H)。质谱(m/z):236.9$[M+H]^+$。

[1339] 化合物225

[1340] N^1-(4-(4,4-二甲基环己基)苯基)丙烷-1,3-二胺



[1341]



[1342] dioxane:二氧杂环己烷reflux:回流

[1343] 步骤1:制备(3-((4-(4,4-二甲基环己基)苯基)氨基)-3-氧代丙基)氨基甲酸叔丁酯(225-1)

[1344] 在室温搅拌4-((叔丁氧基羰基)氨基)丁酸(600mg,2.95mmol),4-(4,4-二甲基环己基)苯胺(500mg,2.45mmol),HATU(1.12g,2.95mmol),和DIPEA(955mg,7.4mmol)/DCM(20mL)的混合物2小时。将反应用水洗涤,用Na_2SO_4干燥,以及真空浓缩。残余物的提纯方法为:prep-TLC而得到产物(淡黄色固体)(500mg,44.7%)。质谱(m/z):288.7[M-Boc+H]$^+$。

[1345] 步骤2:制备3-氨基-N-(4-(4,4-二甲基环己基)苯基)丙酰胺(225-2)

[1346] 向(3-((4-(4,4-二甲基环己基)苯基)氨基)-3-氧代丙基)氨基甲酸叔丁酯(300mg,0.772mmol)/二氧杂环己烷的溶液中添加HCl(20mL,4M),在室温搅拌2小时。将反应减压浓缩。用Na2CO3饱和水溶液将残余物调节到pH=8,用EA(20mL)萃取,用Na_2SO_4干燥,过滤并通过prep-TLC提纯而得到产物(黄色固体)(80mg,34.1%)。质谱(m/z):288.7[M+H]$^+$。

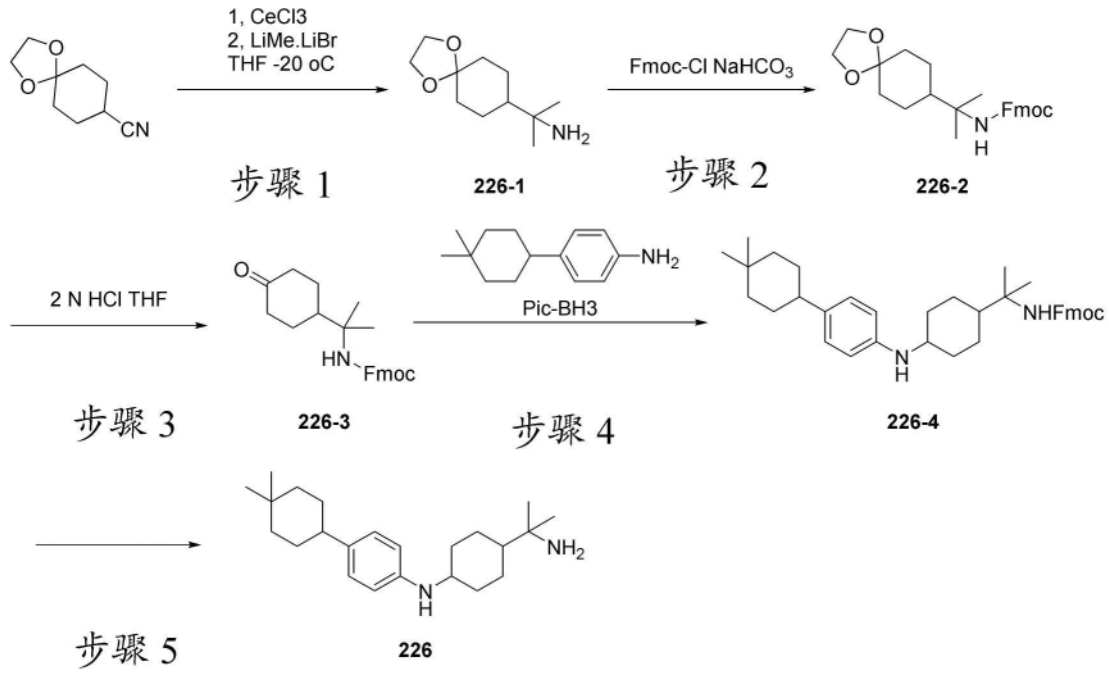
[1347] 步骤3:制备N^1-(4-(4,4-二甲基环己基)苯基)丁烷-1,4-二胺(225)

[1348] 向3-氨基-N-(4-(4,4-二甲基环己基)苯基)丙酰胺(80mg,0.28mmol)/BH_3-THF(20mL,1M)的溶液中添加,在80℃搅拌16小时。将反应减压浓缩,用水洗涤,用EA萃取,用Na_2SO_4干燥。残余物的提纯方法为:prep-HPLC而得到期望的产物(白色固体)。(17.8mg,23.3%)。^{1}H NMR(400MHz,CDCl3)δ7.04(d,J=8.3Hz,2H),6.56(d,J=8.3Hz,2H),3.11(t,J=6.6Hz,2H),2.77(t,J=6.7Hz,2H),2.35-2.25(m,1H),1.70-1.46(m,11H),1.38-1.19(m,3H),0.95(d,J=7.3Hz,6H)。质谱(m/z):274.7[M+H]$^+$。

[1349] 化合物226

[1350] N-(4-(2-氨基丙-2-基)环己基)-4-(4,4-二甲基环己基)苯胺

[1351]



[1352] 步骤1:制备2-(1,4-二氧杂螺[4.5]癸烷-8-基)丙-2-胺(226-1)

[1353] 向1,4-二氧杂螺[4.5]癸烷-8-甲腈(500mg,2.87mmol),$CeCl_3$(1474mg,5.74mmol)和LiMe-LiBr(3mL,3N/THF)/THF(10mL)的溶液中。在氮气气氛下在-20℃搅拌反应18小时。将乙酸乙酯添加到反应混合物并且通过Celite过滤,并且用水和饱和盐水洗涤滤液。有机层用硫酸镁干燥并且减压浓缩。残余物的提纯方法为:硅胶柱而得到215mg(收率:37.5%)的226-1(黄色油)。质谱(m/z):200.2$[M+H]^+$。

[1354] 步骤2:制备(2-(1,4-二氧杂螺[4.5]癸烷-8-基)丙-2-基)氨基甲酸(9H-芴-9-基)甲基酯(226-2)

[1355] 向226-1(100mg,0.5mmol)和$NaHCO_3$(84mg,1mmol)/H_2O(10mL)的溶液中添加Fmoc-Cl(143mg,0.55mmol)。在25℃搅拌混合物过夜。将乙酸乙酯添加到反应混合物并且将混合物通过Celite过滤。用水和饱和盐水洗涤滤液。有机层用硫酸镁干燥并且减压浓缩。残余物的提纯方法为:硅胶柱而得到230mg的226-3(收率:90%)(黄色固体)。质谱(m/z):444.2$[M+Na]^+$。

[1356] 步骤3:制备(2-(4-氧代环己基)丙-2-基)氨基甲酸(9H-芴-9-基)甲基酯(226-3)

[1357] 226-2(700mg,1.67mmol)和HCl/THF(10mL,2N)被置于烧瓶中,在25℃搅拌18小时。过量的THF被真空蒸馏掉并且残余物的提纯方法为:硅胶柱而得到400mg的226-4(收率:63.4%)(黄色固体)。质谱(m/z):378.0$[M+H]^+$。

[1358] 步骤4:制备(2-(4-((4-(4,4-二甲基环己基)苯基)氨基)环己基)丙-2-基)氨基甲酸(9H-芴-9-基)甲基酯(226-4)

[1359] 向226-3(212mg,0.6mmol),4-(4,4-二甲基环己基)苯胺(113mg,0.6mmol)和Pic-BH_3(98mg,0.9mmol)/H_2O(9mL)和HOAc(1mL)的溶液中。在室温搅拌反应18小时。将固体过滤并且将溶剂真空除去。残余物的提纯方法为:硅胶柱而得到250mg的226(收率:74.0%)(黄色固体)。质谱(m/z):565.3$[M+H]^+$。

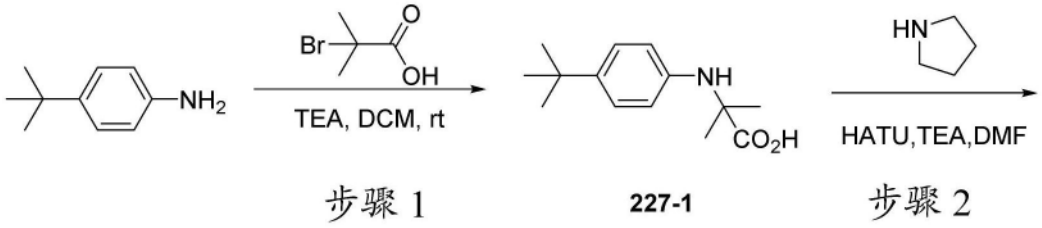
[1360] 步骤5:制备N-(4-(2-氨基丙-2-基)环己基)-4-(4,4-二甲基环己基)苯胺(226)

[1361] 向226-4(190mg,0.34mmol)和哌啶(1mL)/MeOH(5mL)的溶液中。在室温搅拌反应18

小时。将固体过滤并且将溶剂真空除去。残余物的提纯方法为:prep-HPLC(柱-Xbridge-C18 150x 19mm,5um;移动相:ACN-H_2O(0.1%FA),40%-60%)而得到226(15.4mg)(白色固体)。质谱(m/z):343.3[M+H]$^+$。^{1}H NMR(400MHz,CD_3OD)δ6.98(d,J=8.4Hz,2H),6.62(d,J=8.4Hz,2H),3.64(s,1H),2.31-2.23(m,1H),2.04(d,J=12.8Hz,2H),1.66-1.42(m,13H),1.39-1.33(m,2H),1.31(s,6H),0.96(d,J=16.0Hz,6H)。

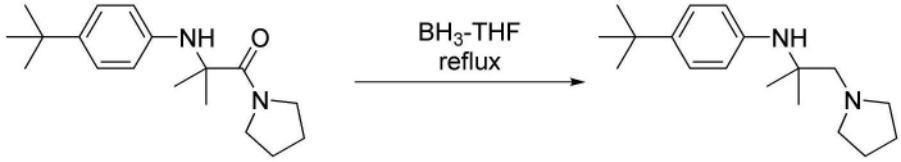
[1362] 化合物227

[1363] 4-(叔丁基)-N-(2-甲基-1-(吡咯烷-1-基)丙-2-基)苯胺



步骤 1 227-1 步骤 2

[1364]



227-2 步骤 3 227

[1365] reflux:回流

[1366] 步骤1:制备2-((4-(叔丁基)苯基)氨基)-2-甲基丙酸(227-1)

[1367] 在25℃搅拌过夜4-(叔丁基)苯胺(500mg,3.35mmol),2-溴-2-甲基丙酸(671mg,4.02mmol)和TEA(677mg,6.7mmol)/DCM(30mL)的溶液。LCMS显示反应完成。将反应用水淬灭(30mL),用DCM(30mL*3)萃取。将合并的有机层用盐水洗涤(50mL),用硫酸钠干燥,过滤和浓缩。残余物的提纯方法为:使用EA/PE(1:1)的combi-flash(闪式色谱)而得到化合物3(700mg,79.9%,收率)(黄色固体)。质谱(m/z):235.9[M+H]$^+$。

[1368] 步骤2:制备2-((4-(叔丁基)苯基)氨基)-2-甲基-1-(吡咯烷-1-基)丙-1-酮(227-2)

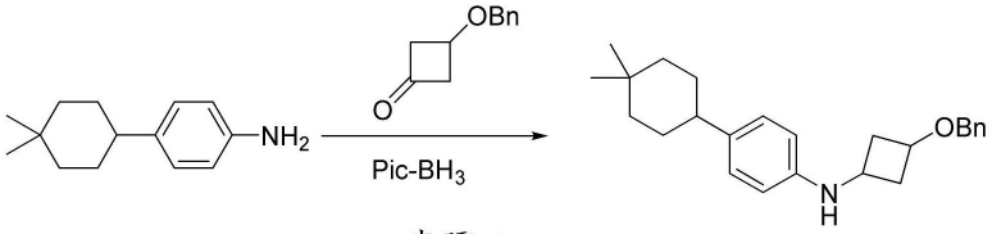
[1369] 在25℃搅拌227-1(700mg,2.97mmol),吡咯烷(211mg,2.97mmol),HATU(262mg,5.95mmol)和TEA(600mg,5.95mmol)/DMF(30mL)的溶液过夜。LCMS显示反应完成。将反应用水(50mL)淬灭,用EA(50mL*3)萃取。将合并的有机层用盐水洗涤(50mL),用硫酸钠干燥,过滤和浓缩。残余物的提纯方法为:使用EA/PE(4:1)的combi-flash(闪式色谱)而得到化合物5(800mg,81.6%,收率)(黄色油)。质谱(m/z):289.3[M+H]$^+$。

[1370] 步骤3:制备4-(叔丁基)-N-(2-甲基-1-(吡咯烷-1-基)丙-2-基)苯胺(227)

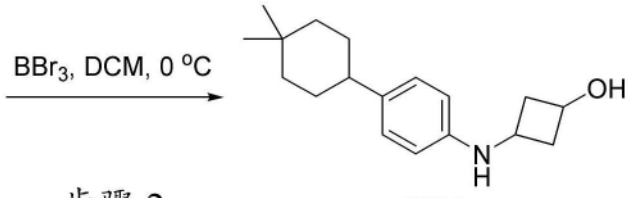
[1371] 在回流下搅拌227-2(100mg)/BH_3-THF(20mL)的溶液2小时,用MeOH淬灭,减压浓缩并且残余物的提纯方法为:prep-HPLC(柱-Xbridge-C18 150x 19mm,5um;移动相:ACN-H_2O(0.1%FA),20%-40%)而得到227-2(42mg)(白色固体)。^{1}H NMR(400MHz,CD_3OD)δ7.30(br,2H),6.83(br,2H),3.94-3.44(m,4H),3.30(br,2H),2.08(br,4H),1.40(br,6H),1.28(s,9H).MS(m/z)275[M+H]$^+$。

[1372] 化合物228

[1373] 3-((4-(4,4-二甲基环己基)苯基)氨基)环丁烷-1-醇

[1374] 

步骤 1 228-1



步骤 2 228A 228B

[1375] 步骤1:制备N-(3-(苄基氧基)环丁基)-4-(4,4-二甲基环己基)苯胺(228-1)

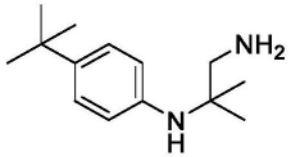
[1376] 向4-(4,4-二甲基环己基)苯胺(200mg,1mmol),3-(苄基氧基)环丁烷-1-酮(176mg,1mmol),Pic-BH_3(87mg,0.86mmol)/H_2O(9mL)和HOAc(1mL)的溶液中。在室温搅拌反应18小时。将反应混合物过滤并且滤液通过硅胶柱提纯而得到300mg的228-1(收率:82.4%)(黄色固体)。质谱(m/z):364.3$[M+H]^+$。

[1377] 步骤2:制备3-((4-(4,4-二甲基环己基)苯基)氨基)环丁烷-1-醇(228)

[1378] 在-10℃向228-1(300mg,0.83mmol)/DCM(10mL)的溶液中添加BBr3(1mL)并且在-10℃搅拌18小时。将反应混合物浓缩并且残余物的提纯方法为:prep-HPLC(柱-Xbridge-C18 150x 19mm,5um;移动相:ACN-H_2O(0.1%FA),25%-40%)而得到228A(32.8mg)(白色固体)&228B(31.7mg)(白色固体)。228A:^1H NMR(400MHz,CD_3OD)δ6.97(d,J=8.4Hz,2H),6.50(d,J=8.4Hz,2H),4.42(d,J=5.4Hz,1H),3.93(t,J=4.2Hz,1H),2.32-2.28(m,1H),2.27-2.21(m,2H),2.23-2.14(m,2H),1.69-1.54(m,4H),1.47(d,J=11.4Hz,2H),1.39-1.26(m,2H),0.96(d,J=16.4Hz,6H)。质谱(m/z):274.3$[M+H]^+$。HPLC:Rt=5.555min(柱:XBRIDGE 3.5um,2.1*50mm,移动相:H_2O(0.05%TFA)-ACN(0.05%TFA),ACN从0至60%在7分钟内,7-8min,ACN由60%至100%,流速:0.8mL/min)。228B:^1H NMR(400MHz,CD_3OD)δ6.97(d,J=8.4Hz,2H),6.50(d,J=8.4Hz,2H),4.43(t,J=5.4Hz,1H),3.93(t,J=4.2Hz,1H),2.34-2.13(m,5H),1.66-1.55(m,4H),1.47(d,J=11.8Hz,2H),1.36-1.23(m,2H),0.96(d,J=16.4Hz,6H).HPLC:Rt=5.570min(柱:XBRIDGE 3.5um,2.1*50mm,移动相:H_2O(0.05%TFA)-ACN(0.05%TFA),ACN从0至60%在7分钟内,7-8min,ACN由60%至100%,流速:0.8mL/min)。

[1379] 化合物229

[1380] N-(4-(叔丁基)苯基)-2-甲基丙烷-1,2-二胺

[1381] 

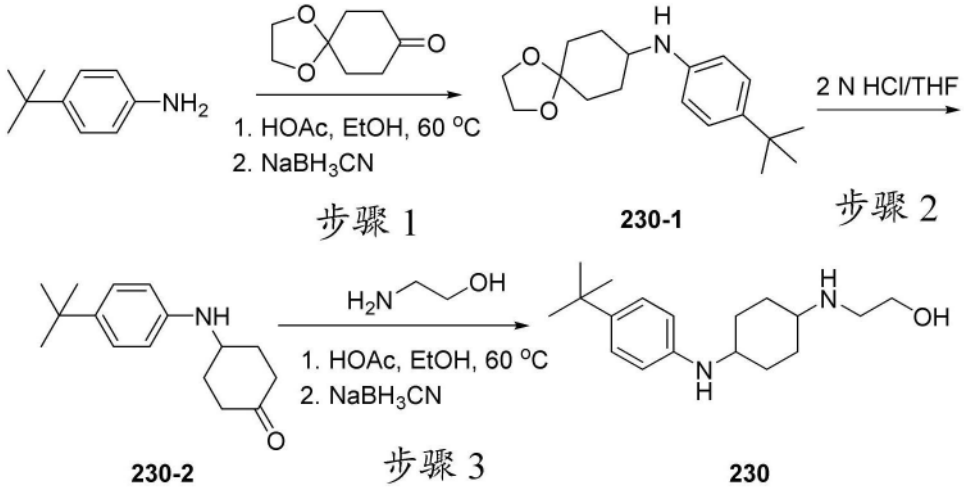
229

[1382] 由2-((4-(叔丁基)苯基)氨基)-2-甲基丙酰胺(150mg,0.64mmol),BH_3-THF(10mL)

和THF(5mL),根据为105的程序制备标题化合物229(34.7mg)(白色固体)。^{1}H NMR(400MHz,CD_3OD)δ7.23(d,2H),6.80(d,2H),3.07(s,2H),1.28(d,15H)。质谱(m/z):221.0$[M+H]^+$。

[1383] 化合物230

[1384] 2-((4-((4-(叔丁基)苯基)氨基)环己基)氨基)乙-1-醇

[1385] 

[1386] 步骤1:制备N-(4-(叔丁基)苯基)-1,4-二氧杂螺[4.5]癸烷-8-胺(230-1)

[1387] 向4-(叔丁基)苯胺(1g,6.71mmol)/MeOH(10mL)的溶液中添加1,4-二氧杂螺[4.5]癸烷-8-酮(1.04g,6.71mmol)并且在60℃搅拌混合物1小时。然后氰基硼氢化钠(1.27g,20.13mmol)被添加到混合物。在室温搅拌反应3小时。用水(50mL)淬灭,反应用EA(10mL)萃取3次。将合并的有机层用硫酸钠干燥,减压浓缩并且残余物的提纯方法为:快速色谱而得到期望的产物(1.6g,82.6%)(白色固体)。质谱(m/z):289.9$[M+H]^+$。

[1388] 步骤2:制备4-((4-(叔丁基)苯基)氨基)环己烷-1-酮(230-2)

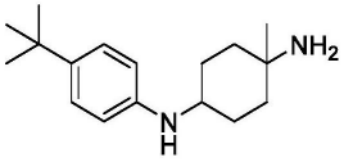
[1389] 向N-(4-(叔丁基)苯基)-1,4-二氧杂螺[4.5]癸烷-8-胺(1.6g,5.54mmol)/THF(5mL)的溶液中添加HCl/THF(2N,5mL)并搅拌混合物2小时。用$NaHCO_3$(10mL)淬灭,反应用EA(10mL)萃取3次。将合并的有机层用硫酸钠干燥,真空浓缩而得到产物(0.9g,66.2%)(白色固体)。质谱(m/z):246.2$[M+H]^+$。

[1390] 步骤3:制备2-((4-((4-(叔丁基)苯基)氨基)环己基)氨基)乙-1-醇(230)

[1391] 由4-((4-(叔丁基)苯基)氨基)环己烷-1-酮(100mg,0.41mmol),MeOH(5mL),2-氨基乙-1-醇(25mg,0.41mmol),乙酸(2.46mg,0.041mmol)和氰基硼氢化钠(77.49mg,12.3mmol),根据为5的程序制备期望的产物230(113mg,95%)(黄色固体)。^{1}H NMR(400MHz,DMSO-d6)δ7.06(d,J=8.8Hz,2H),6.49(dd,J=13.6Hz,8.4Hz,2H),5.13(s,1H),3.49(s,3H),3.20(m,1H),2.67(m,2H),2.51(s,1H),1.95(t,J=14.0Hz,2H),1.69-1.49(m,3H),1.20(s,12H)。质谱(m/z):290.9$[M+H]^+$。

[1392] 化合物231

[1393] N^1-(4-(叔丁基)苯基)-4-甲基环己烷-1,4-二胺

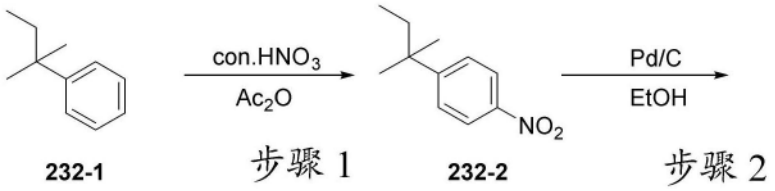
[1394] 

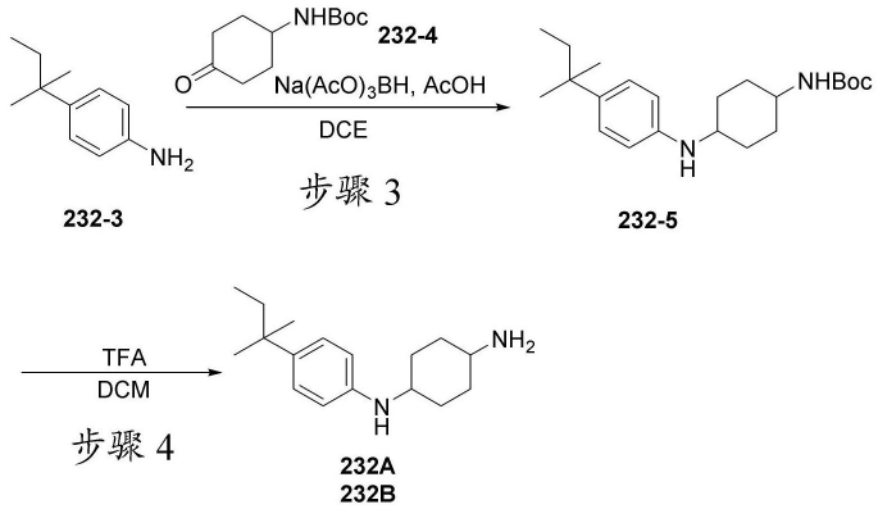
231A
231B

[1395] 根据为化合物24的程序,制备标题化合物231A和231B。粗制残余物的提纯方法为:制备HPLC(柱:X Select-CSH-Prep 5μm OBD,19*150mm;ACN/水(0.5%TFA)=10%-30%-95%-95%-0,0min-7min-7.5min-8.5min-10min)而得到化合物231A(Rt=6.49min),收率为5.7%(白色固体)和231B(Rt=5.60min),收率为8.7%(白色固体)。231A:^{1}H NMR(400MHz,DMSO-d6)δ7.90(s,2H),7.06(d,J=7.4Hz,2H),6.61-6.36(m,2H),5.06(s,1H),3.26-3.18(m,1H),1.86-1.71(m,4H),1.57-1.49(m,4H),1.23(s,3H),1.17(s,9H)。质谱(m/z):261.3[M+H]$^+$。231B:^{1}H NMR(400MHz,DMSO-d6)δ7.95-7.72(m,3H),7.28-7.03(m,2H),6.90-6.61(m,2H),3.26-3.11(m,1H),1.87-1.78(m,2H),1.75-1.66(m,2H),1.60-1.50(m,2H),1.45-1.33(m,2H),1.24(s,3H),1.20(s,9H)。质谱(m/z):261.3[M+H]$^+$。

[1396] 化合物232

[1397] N^1-(4-(叔戊基)苯基)环已烷-1,4-二胺



[1398] 

[1399] 步骤1:制备1-硝基-4-(叔戊基)苯(232-2)

[1400] 在-5℃向叔戊基苯(388mg,2.0mol)/乙酸酐(5.0mL)的搅拌溶液中慢慢地添加浓HNO_3(0.3mL)。在0℃保持反应1小时并且然后在室温保持18小时。添加水(10mL)。反应用EtOAc(3x10 mL)萃取,用Na_2SO_4干燥,以及真空浓缩。残余物的提纯方法为:prep-TLC(DCM/PE=1/10)而得到标题化合物(230mg,60%)。

[1401] 步骤2:制备4-(叔戊基)苯胺(232-3)

[1402] 向1-硝基-4-(叔戊基)苯(230mg,1.2mmol)/EtOH(10mL)的溶液中添加10%Pd/C(12.6mg,12umol)。然后在室温(RT)在氢气气氛下搅拌反应过夜。Pd/C被滤掉。将滤液真空浓缩。残余物的提纯方法为:prep-TLC(EA/PE=1/3)而得到期望的产物(黄色固体)(1.8g,81.8%)。质谱(m/z):164.3$[M+H]^+$。

[1403] 步骤3:制备(4-((4-(叔戊基)苯基)氨基)环已基)氨基甲酸叔丁酯(232-5)

[1404] 由4-(叔戊基)苯胺(110mg,0.67mmol),(4-氧代环已基)氨基甲酸叔丁酯(285mg,1.34mmol)和$Na(AcO)_3BH$(283mg,1.34mmol),根据为24-1的程序制备标题化合物232-5(120mg),总收率为50.0%(粗制黄色固体)。质谱(m/z):361.3$[M+H]^+$。

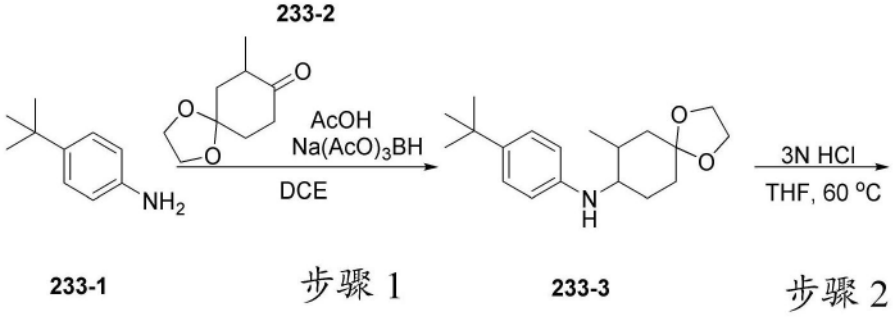
[1405] 步骤4:N^1-(4-(叔戊基)苯基)环已烷-1,4-二胺(232)

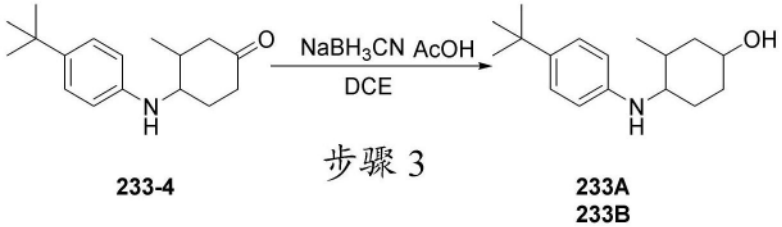
[1406] 根据为化合物28的程序,制备标题化合物232A和232B。粗制残余物的提纯方法为:制备HPLC(柱:X Select-CSH-Prep 5μm OBD,19*150mm;ACN/水(0.5%TFA)=10%-33%-95%-95%-10%,0min-7min-7.5min-8.5min-10min)而得到化合物232A(Rt=6.23min),收率为14.9%(白色固体)和232B(Rt=5.05min),收率为34.7%(白色固体)。231A:^1H NMR(400MHz,DMSO-d6)δ7.74(s,3H),7.04(d,J=8.0Hz,2H),6.59(s,2H),3.41-3.32(m,1H),3.16-3.03(m,1H),1.78-1.57(m,8H),1.50(q,J=7.4Hz,2H),1.13(s,6H),0.57(t,J=7.4Hz,3H)。质谱(m/z):261.3$[M+H]^+$。231B:^1H NMR(400MHz,DMSO-d6)δ7.79(s,3H),7.32-7.04(m,2H),6.92-6.50(m,2H),3.28-3.09(m,1H),3.03-2.90(m,1H),1.93(t,J=10.8Hz,4H),1.52(q,J=7.6Hz,2H),1.40-1.12(m,10H),0.57(t,J=7.4Hz,3H)。质谱(m/z):261.3$[M+H]^+$。

[1407] 化合物233

[1408] 4-((4-(叔丁基)苯基)氨基)-3-甲基环已烷-1-醇

[1409]





[1410] 步骤1:制备N-(4-(叔丁基)苯基)-7-甲基-1,4-二氧杂螺[4.5]癸烷-8-胺(233-3)

[1411] 由4-(叔戊基)苯胺(1.86mg,1.25mmol),7-甲基-1,4-二氧杂螺[4.5]癸烷-8-酮(319mg,1.88mmol)和$Na(AcO)_3BH$(399mg,1.88mmol),根据为1-1的程序制备标题化合物233-3(350mg),总收率为92.3%(黄色固体)。质谱(m/z):304.3$[M+H]^+$。

[1412] 步骤2:制备4-((4-(叔丁基)苯基)氨基)-3-甲基环已烷-1-酮(233-4)

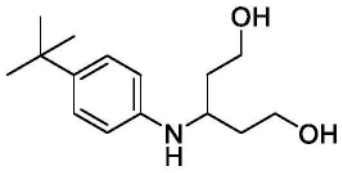
[1413] 将N-(4-(叔丁基)苯基)-7-甲基-1,4-二氧杂螺[4.5]癸烷-8-胺(350mg,1.16mmol)/10mL四氢呋喃和10mL的1M盐酸的溶液加热到60℃30分钟。在冷却到0℃后,用碳酸钠溶液将溶液的pH调节到8-9。然后用DCM(20mL×3)萃取混合物。将合并的有机层用水(20mL)洗涤,用Na_2SO_4干燥,以及浓缩而得到期望的产物(黄色固体)(280mg,93.6%)。质谱(m/z):260.3$[M+H]^+$。

[1414] 步骤3:制备4-((4-(叔丁基)苯基)氨基)-3-甲基环己烷-1-醇(233)

[1415] 向4-((4-(叔丁基)苯基)氨基)-3-甲基环己烷-1-酮(130mg,0.6mmol)/DCE(10mL)的溶液中添加$NaBH_3CN$(62g,1mmol)和5滴的AcOH。在室温搅拌混合物3小时。然后将反应用水(10mL)洗涤,用Na_2SO_4干燥,过滤并且真空浓缩。残余物的提纯方法为:prep-TLC(MeOH/DCM=1/10)而得到化合物233A,收率为15.9%(淡黄色固体)和233B,收率为11.4%(淡黄色固体)。233A:^1H NMR(400MHz,DMSO-d6)δ7.23-7.03(m,2H),6.96-6.61(m,2H),5.31(s,2H),3.50-3.36(m,2H),1.81-1.68(m,2H),1.56-1.28(m,5H),1.19(s,10H),0.93(d,J=6.9Hz,3H)。质谱(m/z):262.3$[M+H]^+$。HPLC:Rt=6.485mins(Agilent,poroshell 120,SB-C18 2.7μm,4.6x50mm,ACN/水(0.1%FA)=5%-5%-95%-95%-95%-5%,0-0.5min-10min-10.5min-12.0min)。233B:^1H NMR(400MHz,DMSO-d6)δ7.87-6.30(m,5H),3.41-3.32(m,1H),2.90(qd,J=13.4,12.2,6.8Hz,1H),2.03-1.43(m,5H),1.20(s,9H),1.15-0.93(m,7H)。质谱(m/z):262.3$[M+H]^+$。HPLC:Rt=5.229mins(Agilent,poroshell 120,SB-C18 2.7μm,4.6x50mm,ACN/水(0.1%FA)=5%-5%-95%-95%-95%-5%,0-0.5min-10min-10.5min-12.0min)。

[1416] 化合物234

[1417] 3-((4-(叔丁基)苯基)氨基)戊烷-1,5-二醇

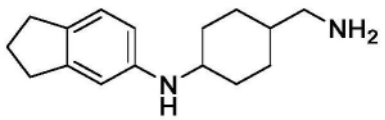
[1418] 

234

[1419] 由4-(叔丁基)苯胺(75mg,0.5mmol),根据为化合物4的程序制备标题化合物234(72.7mg),总收率为58%(白色固体)。^1H NMR(400MHz,DMSO-d6)δ7.05(d,J=8.4Hz,2H),6.51(d,J=8.4Hz,2H),5.07(s,1H),4.39(s,2H),3.46(t,J=68.4Hz,4H),3.35(m,1H),1.59(m,4H),1.20(s,9H)。质谱(m/z):252.3$[M+H]^+$。

[1420] 化合物235

[1421] N-(4-(氨基甲基)环己基)-2,3-二氢-1H-茚-5-胺

[1422] 

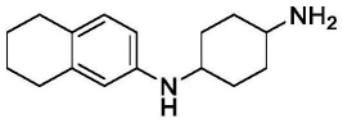
235

[1423] 由(4-((2,3-二氢-1H-茚-5-基)氨基)环己基)氨基甲酸叔丁酯(205mg,0.596mmol),TFA(1mL),和DCM(10mL),根据为24的程序制备标题化合物235(131.4mg),总收率为90.3%(白色固体),经1HNMR证实为1:2的混合物。^1H NMR(400MHz,DMSO-d6)δ6.84(dd,

J＝8.0,3.2Hz,1H),6.47-6.25(m,2H),5.06(d,J＝24.0Hz,1H),3.35(d,J＝27.2Hz,1H),2.73-2.53(m,6H),1.98-1.73(m,3H),1.61-1.35(m,6H),1.01(q,J＝9.6Hz,1H)。质谱(m/z):245.3[M+H]$^+$。

[1424] 化合物236

[1425] N^1-(5,6,7,8-四氢萘-2-基)环已烷-1,4-二胺

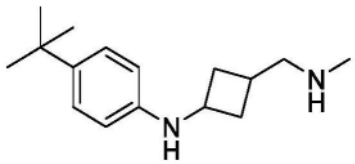
[1426] 

236

[1427] 由(4-((5,6,7,8-四氢萘-2-基)氨基)环已基)氨基甲酸叔丁酯(180mg,0.523mmol),TFA(1mL),和DCM(10mL),根据为24的程序制备标题化合物236(93.7mg),总收率为73.4%(白色固体),经1HNMR证实为1:2的混合物。^{1}H NMR(400MHz,DMSO-d6)δ6.74(d,J＝8.0Hz,1H),6.46-6.20(m,2H),5.03(s,1H),3.00(d,J＝54.4Hz,2H),2.57(d,J＝18.4Hz,4H),1.99(d,J＝11.6Hz,2H),1.75(d,J＝15.2Hz,3H),1.66(p,J＝3.2Hz,4H),1.59(d,J＝12.4Hz,1H),1.46(q,J＝12.4Hz,1H),1.18(t,J＝18.8Hz,1H)。质谱(m/z):245.3[M+H]$^+$。

[1428] 化合物237

[1429] 4-(叔丁基)-N-(3-((甲基氨基)甲基)环丁基)苯胺

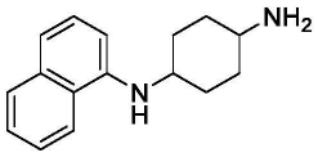
[1430] 

237

[1431] 由3-((4-(叔丁基)苯基)氨基)-N-甲基环丁烷-1-甲酰胺(75mg,0.288mmol),$LiAlH_4$(43mg,1.152mmol)和THF(10mL),根据为23的程序制备标题化合物237(17.9mg),总收率为25.3%(橙色固体)。^{1}H NMR(400MHz,DMSO-d6)δ7.73(s,1H),7.09-6.96(m,2H),6.46-6.30(m,2H),5.65(dd,J＝13.6,7.2Hz,1H),3.74(dq,J＝84.4,8.0,7.6Hz,1H),2.69-2.56(m,1H),2.53(dd,J＝10.8,4.4Hz,3H),2.42-2.32(m,2H),1.98-1.83(m,2H),1.16(s,9H)。质谱(m/z):247.3[M+H]$^+$。

[1432] 化合物238

[1433] N^1-(萘-1-基)环已烷-1,4-二胺

[1434] 

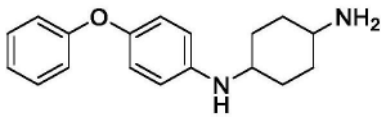
238

[1435] 由(4-(萘-1-基氨基)环已基)氨基甲酸叔丁酯(198mg,0.582mmol),TFA(1mL),和DCM(10mL),根据为24的程序制备标题化合物238(119.1mg),总收率为85%(粉色固体),经1HNMR证实为1:2的混合物。^{1}H NMR(400MHz,DMSO-d6)δ8.38(s,1H),8.32-8.24(m,1H),8.19(dd,J＝20.8,8.0Hz,1H),7.70(td,J＝8.4,1.6Hz,1H),7.42-7.30(m,2H),7.23(td,J＝8.0,5.6Hz,1H),7.06(dd,J＝17.2,8.0Hz,1H),6.52(t,J＝7.2Hz,1H),5.89-5.39(m,1H),

3.17-2.88(m,1H),2.13-2.01(m,2H),1.95(dq,J=8.8,4.4Hz,1H),1.84(t,J=10.0Hz,1H),1.78-1.72(m,1H),1.70-1.61(m,1H),1.59-1.46(m,1H),1.44-1.31(m,1H)。质谱(m/z):241.3[M+H]$^+$。

[1436] 化合物239

[1437] N^1-(4-苯氧基苯基)环已烷-1,4-二胺

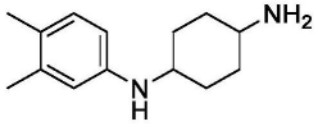
[1438] 

239

[1439] 由(4-((4-苯氧基苯基)氨基)环已基)氨基甲酸叔丁酯(179mg,0.469mmol),TFA(1mL),和DCM(10mL),根据为24的程序制备标题化合物239(93.2mg),总收率为70.6%(白色固体),经1HNMR证实为1:2的混合物。^{1}H NMR(400MHz,DMSO-d6)δ7.29(tt,J=7.2,2.0Hz,2H),7.04-6.94(m,1H),6.89-6.77(m,4H),6.71-6.55(m,2H),5.32(d,J=5.0Hz,1H),3.09(s,1H),2.95(s,1H),2.01(d,J=11.2Hz,3H),1.78(qd,J=12.0,10.8,7.2Hz,3H),1.61(dt,J=13.6,7.2Hz,1H),1.54-1.40(m,1H)。质谱(m/z):283.3[M+H]$^+$。

[1440] 化合物240

[1441] N^1-(3,4-二甲基苯基)环已烷-1,4-二胺

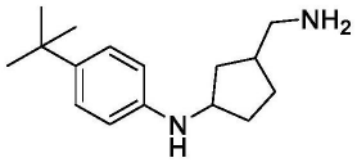
[1442] 

240

[1443] 由(4-((3,4-二甲基苯基)氨基)环已基)氨基甲酸叔丁酯(178mg,0.560mmol),TFA(1mL),和DCM(10mL),根据为24的程序制备标题化合物240(80.2mg),总收率为65.6%(白色固体),经1HNMR证实为1:2的混合物。^{1}H NMR(400MHz,DMSO-d6)δ6.76(dd,J=8.0,5.2Hz,1H),6.36(dd,J=18.0,2.4Hz,1H),6.27(ddd,J=15.6,8.0,2.4Hz,1H),4.98(d,J=7.6Hz,1H),3.37-2.75(m,2H),2.05(d,J=2.0Hz,3H),2.00(d,J=2.4Hz,3H),1.97-1.86(m,2H),1.73-1.47(m,4H),1.36(qd,J=13.6,12.4,3.6Hz,1H),1.15-1.02(m,1H)。质谱(m/z):219.3[M+H]$^+$。

[1444] 化合物241

[1445] N-(3-(氨基甲基)环戊基)-4-(叔丁基)苯胺

[1446] 

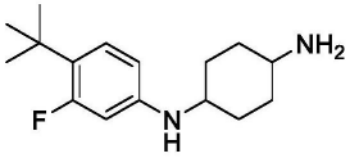
241

[1447] 由3-((4-(叔丁基)苯基)氨基)环戊烷-1-甲酰胺(83mg,0.319mmol),$LiAlH_4$(47mg,1.276mmol)和THF(10mL),根据为23的程序制备标题化合物241(4.2mg),总收率为5.4%(粉色固体)。^{1}H NMR(400MHz,DMSO-d6)δ7.06(d,J=8.0Hz,2H),6.50(s,2H),3.67(dt,J=12.8,6.3Hz,1H),2.71(d,J=16.8Hz,2H),2.29-1.91(m,3H),1.84(ddd,J=14.0 9.2,5.6Hz,1H),1.77-1.66(m,1H),1.46-1.35(m,2H),1.17(s,9H)。质谱(m/z):247.3[M+H

]+。

[1448] 化合物242

[1449] N1-(4-(叔丁基)-3-氟苯基)环己烷-1,4-二胺2,2,2-三氟乙酸乙酯

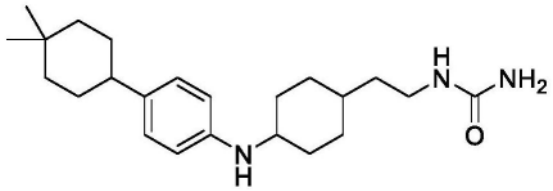
[1450] 

242A
242B

[1451] 根据为化合物20的程序制备标题化合物242A和242B。残余物的提纯方法为:制备HPLC(柱:X Select-CSH-Prep 5μm OBD,19*150mm;ACN/水(0.5%TFA)=25%-30%-95%-95%-10%,0min-10min-10.5min-11.5min-13min)而得到化合物242A(Rt=8.13min),收率为19.0%(白色固体)和242B(Rt=8.63min),收率为18.1%(白色固体)。242A:1H NMR(400MHz,DMSO-d6)δ7.80(s,3H),6.97(dd,J=10.2,8.2Hz,1H),6.37-6.21(m,2H),3.09(d,J=22.1Hz,1H),2.99(d,J=5.1Hz,1H),2.06-1.87(m,4H),1.51-1.33(m,2H),1.24(d,J=0.8Hz,9H),1.15(q,J=11.4Hz,2H)。质谱(m/z):265.3[M+H]+。242B:1H NMR(400MHz,DMSO-d6)δ7.80(s,3H),7.09(dt,J=8.7,1.1Hz,1H),6.56(q,J=2.5Hz,1H),6.44(dt,J=8.7,2.2Hz,1H),3.07(dd,J=14.5,7.3Hz,1H),2.97(d,J=4.8Hz,1H),2.00-1.84(m,4H),1.44-1.34(m,2H),1.32(s,9H),1.13(q,J=11.6Hz,2H)。质谱(m/z):265.3[M+H]+。

[1452] 化合物243

[1453] 1-(2-(4-((4-(4,4-二甲基环己基)苯基)氨基)环己基)乙基)脲

[1454] 

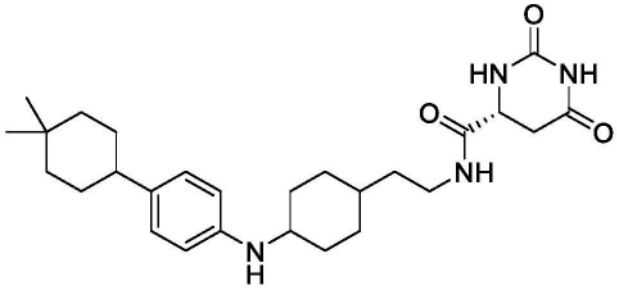
243

[1455] 由N-(4-(2-氨基乙基)环己基)-4-(4,4-二甲基环己基)苯胺(36mg,0.11mmol),DMSO(5mL),氨基甲酸苯酯(18mg,0.13mmol),根据为116的程序制备期望的产物243(10.1mg)(白色粉末),经1HNMR证实为1:1混合物,收率为24.8%。1H NMR(400MHz,DMSO-d6)δ6.91(d,J=8.0Hz,2H),6.49(dd,J=19.6,7.9Hz,2H),5.86(s,1H),5.34(s,2H),5.13(d,J=27.3Hz,1H),2.97(d,J=6.7Hz,2H),2.20(d,J=6.4Hz,1H),1.97(t,J=14.1Hz,2H),1.73(d,J=12.5Hz,1H),1.60-1.49(m,6H),1.49-1.36(m,6H),1.30(dd,J=14.1,8.1Hz,5H),1.03(dt,J=21.9,11.7Hz,2H),0.94(s,3H),0.92(s,3H)。质谱(m/z):372.6[M+H]+。

[1456] 化合物244

[1457] (R)-N-(2-(4-((4-(4,4-二甲基环己基)苯基)氨基)环己基)乙基)-2,6-二氧代六氢嘧啶-4-甲酰胺

[1458]



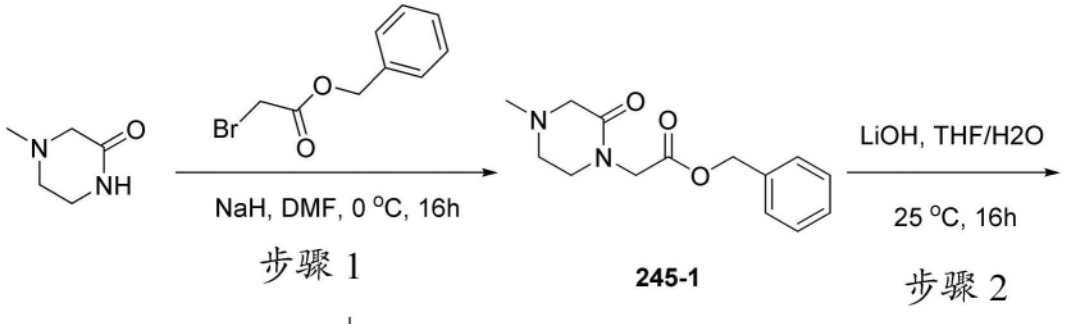
244A
244B

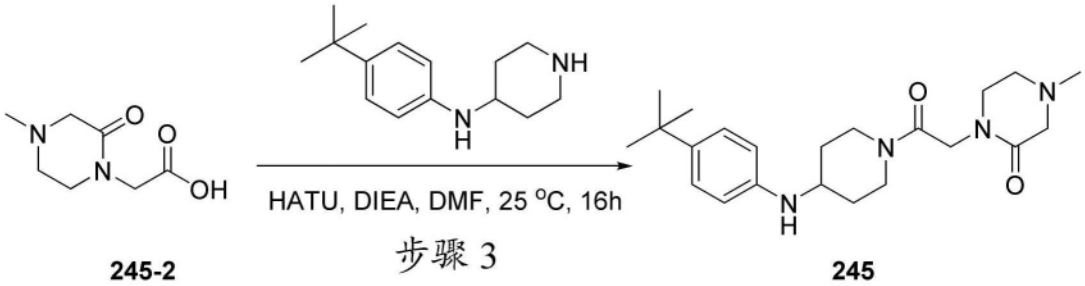
[1459] 由N-(4-(2-氨基乙基)环己基)-4-(4,4-二甲基环己基)苯胺(50mg,0.15mmol),(R)-2,6-二氧代六氢嘧啶-4-甲酸(29mg,0.18mmol),根据为1的程序制备标题化合物244(244A和244B),收率为18.6%(白色粉末)。混合物的提纯方法:制备HPLC(柱:X Select-CSH-Prep 5μm OBD,19*150mm;ACN/水(0.5%TFA)=5%-5%-95%-95%-5%,0min-1min-10min-11min-15.0min)得到化合物244A(Rt=6.11min)(白色固体)和化合物244B(Rt=5.90min)(白色固体)。^{1}H NMR(400MHz,DMSO-d6)δ10.02(d,J=1.9Hz,1H),8.02(t,J=5.6Hz,1H),7.64-7.51(m,1H),6.93(d,J=8.0Hz,2H),6.52(d,J=8.1Hz,2H),5.18(s,1H),3.93(dt,J=7.1,3.5Hz,1H),3.39(s,1H),3.15-3.03(m,2H),2.83(dd,J=16.6,7.2Hz,1H),2.43(dd,J=16.2,3.2Hz,1H),2.21(dq,J=10.5,5.8,5.4Hz,1H),1.53(dt,J=8.0,3.3Hz,7H),1.49-1.42(m,4H),1.42-1.34(m,5H),1.29(dd,J=12.3,5.2Hz,3H),0.95(s,3H),0.93(s,3H)。质谱(m/z):469.3$[M+H]^+$。

[1460] 化合物245

[1461] 1-(2-(4-((4-(叔丁基)苯基)氨基)哌啶-1-基)-2-氧代乙基)-4-甲基哌嗪-2-酮

[1462]





245-2 245

[1463] 步骤1:2-(4-甲基-2-氧代哌嗪-1-基乙酸苄酯(245-1)

[1464] 在0℃将4-甲基哌嗪-2-酮(500mg,4.38mmol),NaH(210.26mg,5.25mmol)/THF(5mL)的混合物搅拌1小时。然后将其添加到2-溴乙酸苄酯(1.1g,4.81mmol)。将其用H_2O(30mL)淬灭并用DCM(3x30mL)萃取。将有机层合并,用盐水NaCl(2x30 mL)洗涤并且用$MgSO_4$干燥,过滤并且浓缩而得到产物(800mg,收率:55.7%)(黄色油)。质谱(m/z):262.9$[M+H]^+$。

[1465] 步骤2:2-(4-甲基-2-氧代哌嗪-1-基)乙酸(245-2)

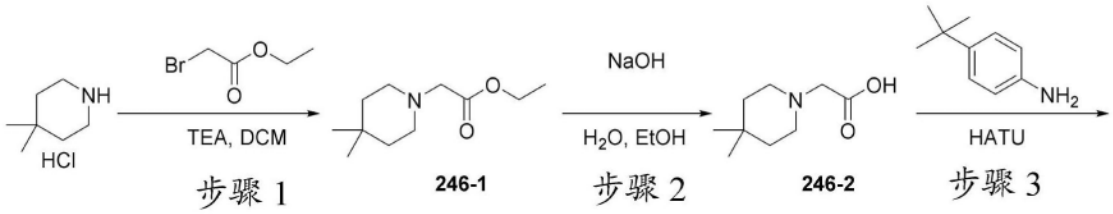
[1466] 向245-1(300mg,1.14mmol),LiOH(273.89mg,11.43mmol)/THF/H_2O=1:1(5mL)的溶液中。然后在25℃搅拌混合物过夜。将其用H_2O(300mL)淬灭并用EA(3x300 mL)萃取。将有机层合并,用盐水NaCl(2x300 mL)洗涤并且用$MgSO_4$干燥,过滤并且浓缩而得到目标产物(100mg,收率:40.6%)(黄色油)。

[1467] 步骤3:制备1-(2-(4-((4-(叔丁基)苯基)氨基)哌啶-1-基)-2-氧代乙基)-4-甲基哌嗪-2-酮(245)

[1468] 向245-2(80mg,0.46mmol),N-(4-(叔丁基)苯基)哌啶-4-胺(107.96mg,0.46mmol)/DMF(5mL)的溶液中添加HATU(88.33mg,0.23mmol),和DIEA(600.45mg,4.64mmol)。然后在室温搅拌混合物过夜。将反应真空浓缩。残余物的提纯方法为:prep-TLC而得到期望的产物245(19.8mg)(白色固体)。^1H NMR(400MHz,CD_3OD)δ7.16(d,J=9.2Hz,2H),6.63(dd,J=9.2Hz,2H),4.34(d,J=16.0Hz,2H),4.20(d,J=16.4Hz,1H),3.85(d,J=14.0Hz,1H),3.59-3.47(m,1H),3.41(t,J=5.4Hz,2H),3.18(s,2H),2.90(t,J=12.4Hz,1H),2.79(s,2H),2.38(d,J=1.6Hz,3H),2.03(dd,J=19.4,14.8Hz,2H),1.45-1.26(m,2H),1.23(s,9H)。质谱(m/z):315.2$[M+H]^+$。

[1469] 化合物246

[1470] 4-(叔丁基)-N-(2-(4,4-二甲基哌啶-1-基)乙基)苯胺



[1471]

[1472] 步骤1:2-(4,4-二甲基哌啶-1-基乙酸乙酯(246-1)

[1473] 在25℃将4,4-二甲基哌啶(500mg,4.41mmol)和TEA(1.78g,17.66mmol)/DCM(10mL)的混合物搅拌过夜。然后将其添加到2-溴乙酸乙酯(811.39mg,4.85mmol)。将其用H_2O(300mL)淬灭并用DCM(3x300 mL)萃取。将有机层合并,用盐水NaCl(2x300 mL)洗涤并且用$MgSO_4$干燥,过滤并且浓缩而得到目标产物(600mg,61.3%)(黄色油)。

[1474] 步骤2:2-(4,4-二甲基哌啶-1-基)乙酸(246-2)

[1475] 向246-1(600mg,3.01mmol),NaOH(361.26mg,9.03mmol)/H_2O/EtOH=2:1(15mL)的溶液中。然后在50℃搅拌混合物过夜。将其用H_2O(300mL)淬灭并用EA(3x300 mL)萃取。将有机层合并,用盐水NaCl(2x300 mL)洗涤并且用$MgSO_4$干燥,过滤并且浓缩而得到目标产物(300mg,52.3%)(黄色油)。

[1476] 步骤3:N-(4-(叔丁基)苯基)-2-(4,4-二甲基哌啶-1-基)乙酰胺(246-3)

[1477] 向246-2(150mg,0.87mmol),和4-(叔丁基)苯胺(130.73mg,0.87mmol)/DMF(5mL)

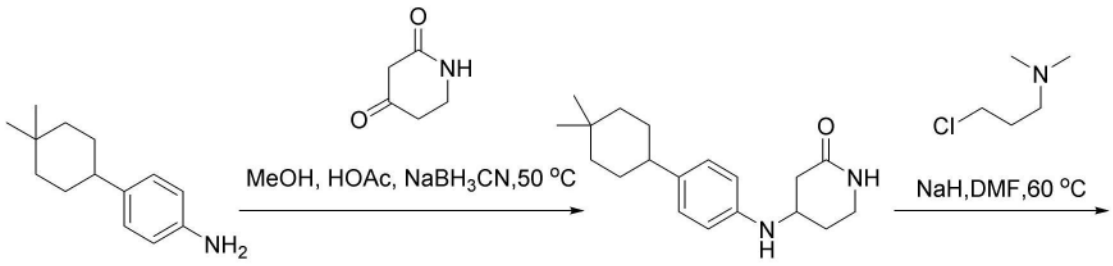
的溶液中添加HATU(499.62mg,1.31mmol),TEA(433.21mg,4.38mmol)。然后在室温搅拌混合物过夜。将其用H_2O(100mL)淬灭并用EA(3x100mL)萃取。将有机层合并,用盐水洗涤NaCl(2x100mL)并且用$MgSO_4$干燥,过滤并且浓缩。将粗产物施加到硅胶柱(12g),用PE:EA(5:1)洗脱而得到产物(300mg,90.5%)(黄色固体)。质谱(m/z):302.9$[M+H]^+$。

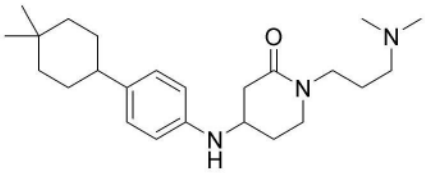
[1478] 步骤4:制备4-(叔丁基)-N-(2-(4,4-二甲基哌啶-1-基)乙基)苯胺(246)

[1479] 向246-3(160mg,0.53mmol)/THF(5mL)的溶液中添加BH_3-THF(5mL)。然后在25℃搅拌混合物过夜。将反应真空浓缩。残余物的提纯方法为:prep-TLC而得到期望的产物246(39.5mg)(白色固体)。^1H NMR(400MHz,CD_3OD)δ8.40(s,1H),7.17(t,J=5.8Hz,2H),6.62(d,J=8.8Hz,2H),3.49(t,J=5.6Hz,2H),3.29(dd,J=4.8,3.2Hz,4H),3.28(s,2H),1.64(d,J=5.0Hz,4H),1.27-1.18(m,9H),1.03(d,J=7.0Hz,6H)。质谱(m/z):289.0$[M+H]^+$。

[1480] 化合物247

[1481] 1-(3-(二甲基氨基)丙基)-4-((4-(4,4-二甲基环己基)苯基)氨基)哌啶-2-酮

[1482] 



247

[1483] 步骤1:制备4-((4-(4,4-二甲基环己基)苯基)氨基)哌啶-2-酮(247-1)

[1484] 在50℃将4-(4,4-二甲基环己基)苯胺(200mg,0.98mmol),1λ2-哌啶-2,4-二酮(133.5mg,1.18mmol)和$NaBH_3CN$(123.6mg,1.97mmol)/MeOH(10mL)和AcOH(1滴)的混合物搅拌过夜。在冷却后,将反应溶液用水洗涤,并且过量的MeOH被真空蒸馏掉并且残余的油被真空蒸馏掉。然后反应溶液用乙酸乙酯(30mL)和水(30mL)萃取三次。合并有机相,真空除去溶剂并且通过硅胶色谱(PE:EA=5:1)提纯粗产物而得到期望的产物(油)(220mg,44.7%)。质谱(m/z):300.9$[M+H]^+$。

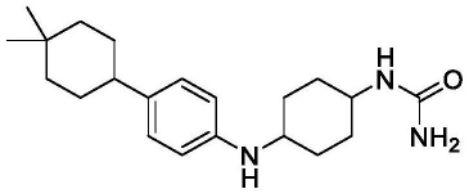
[1485] 步骤2:制备1-(3-(二甲基氨基)丙基)-4-((4-(4,4-二甲基环己基)苯基)氨基)哌啶-2-酮(247)

[1486] 在60℃将4-((4-(4,4-二甲基环己基)苯基)氨基)哌啶-2-酮(132mg,0.44mmol),3-氯-N,N-二甲基丙-1-胺(80.2mg,0.66mmol)和NaH(21.1mg,0.88mmol)/DMF(3mL)的混合物搅拌16小时。在反应完成后,用水淬灭溶液并且真空除去并且残余物的提纯方法为:prep-HPLC(柱-Xbridge-C18 150x 21.2mm,5um;移动相:ACN-H_2O(0.1%FA),40%-60%)而得到期望的产物247(22.2mg,12.7%)(棕色油)。^1H NMR(400MHz,DMSO-d6)δ6.95(d,J=

8.4Hz,2H),6.52(d,J=8.4Hz,2H),5.39(br,1H),3.65(br,1H),3.34-3.24(m,4H),2.58-2.54(m,1H),2.36-2.24(m,3H),2.20(s,6H),2.15-2.03(m,2H),1.67-1.23(m,11H),0.93(d,J=8.6Hz,6H)。质谱(m/z):386.3$[M+H]^+$。

[1487] 化合物248

[1488] 1-(4-((4-(4,4-二甲基环己基)苯基)氨基)环己基)脲

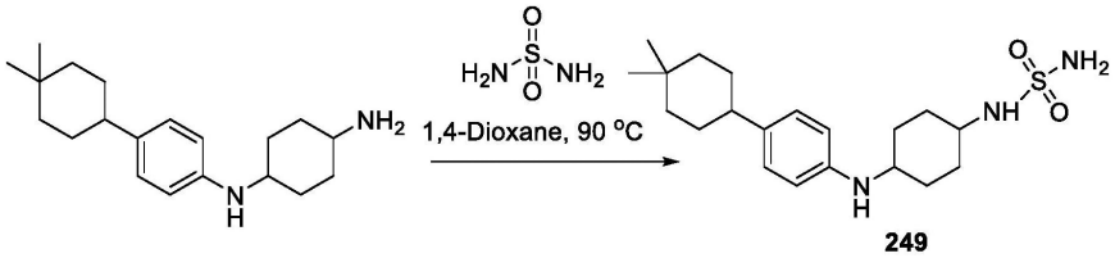
[1489] 

248

[1490] 由N^1-(4-(4,4-二甲基环己基)苯基)环己烷-1,4-二胺(105mg,0.34mmol),TMSNCO(40.25mg,0.35mmol),TEA(70.7mg,0.70mmol),DMAP(8.5mg,0.07mmol)和DCM(10mL),根据为178的程序制备期望的产物248(15.7mg,12.0%)(白色固体)。^{1}H NMR(400MHz,DMSO-d6)δ6.92(d,J=8.3Hz,2H),6.50(d,J=8.3Hz,2H),5.96(br,1H),5.37(br,2H),5.16(br,1H),3.25(br,1H),2.20(br,1H),1.64-1.23(m,17H),0.93(d,J=8.4Hz,6H)。质谱(m/z):343.9$[M+H]^+$。

[1491] 化合物249

[1492] N-(4-{[4-(4,4-二甲基环己基)苯基]氨基}环己基)氨基磺酰胺

[1493] 

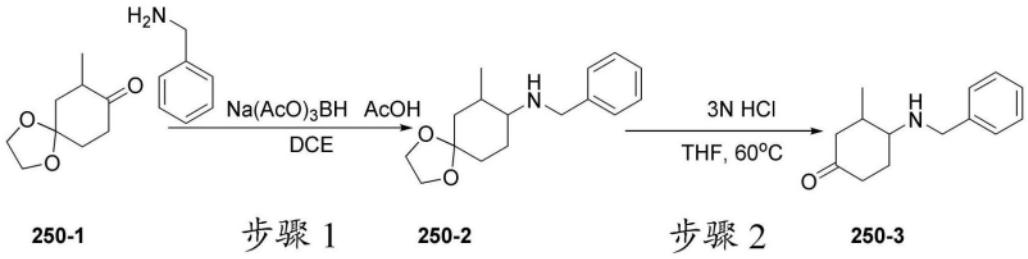
249

[1494] 1,4-dioxane:1,4-二氧杂环己烷

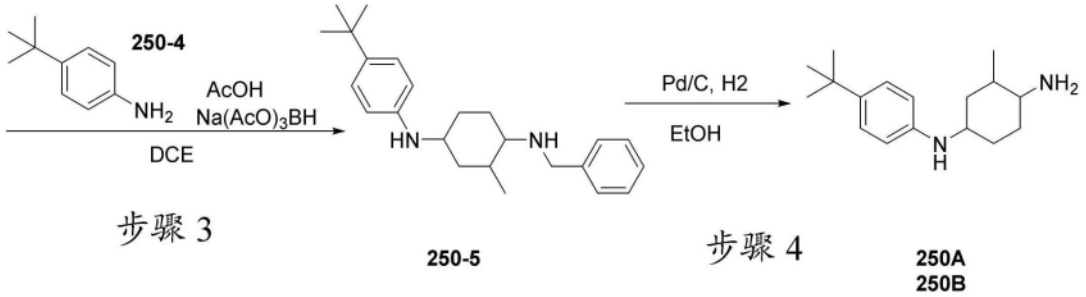
[1495] 在90℃在氮气气氛下将1-N-[4-(4,4-二甲基环己基)苯基]环己烷-1,4-二胺(95mg,0.32mmol)和氨磺酰胺(36.5mg,0.38mmol)/1,4-二氧杂环己烷(10mL)的溶液搅拌过夜。在冷却到室温后,将反应真空浓缩并且残余物的提纯方法为:prep-HPLC(柱-Xbridge-C18 150x 21.2mm,5um;移动相:ACN-H_2O(0.1%FA),30%-50%)而得到期望的产物249(13.2mg,10.5%)(白色固体)。^{1}H NMR(400MHz,DMSO-d6)δ6.92(d,J=8.3Hz,2H),6.49(d,J=8.4Hz,2H),6.45(s,2H),6.39(d,J=5.7Hz,1H),5.09(br,1H),3.25(br,2H),2.28-2.16(m,1H),1.67-1.24(m,16H),0.93(d,J=8.6Hz,6H)。质谱(m/z):380.3$[M+H]^+$。

[1496] 化合物250

[1497] N^1-(4-(叔丁基)苯基)-3-甲基环己烷-1,4-二胺



[1498]



[1499] 步骤1:制备N-苄基-7-甲基-1,4-二氧杂螺[4.5]癸烷-8-胺(250-2)

[1500] 由7-甲基-1,4-二氧杂螺[4.5]癸烷-8-酮(510mg,3.0mmol)苯基甲胺(321mg,3.0mmol)和$Na(AcO)_3BH$(954mg,4.5mmol),根据为24-1的程序制备标题化合物250-2(420mg),总收率为53.6%(浅黄色油)。质谱(m/z):262.2$[M+H]^+$。

[1501] 步骤2:制备4-(苄基氨基)-3-甲基环己烷-1-酮(250-3)

[1502] 由7-甲基-1,4-二氧杂螺[4.5]癸烷-8-酮(300mg,1.15mmol)和3NHCl(1.0mL),根据为233-4的程序制备标题化合物250-3(185mg),总收率为74.0%(浅黄色油)。质谱(m/z):217.3$[M+H]^+$。

[1503] 步骤3:制备N^1-苄基-N^4-(4-(叔丁基)苯基)-2-甲基环己烷-1,4-二胺(250-5)

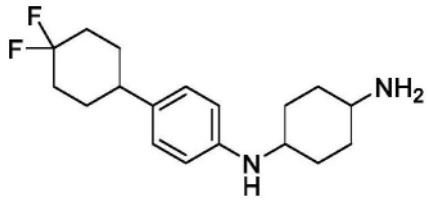
[1504] 由4-(苄基氨基)-3-甲基环己烷-1-酮(150mg,0.69mmol),4-(叔丁基)苯胺(103mg,0.69mmol)和$Na(AcO)_3BH$(293mg,1.38mmol),根据为24-1的程序制备标题化合物250-5(120mg),总收率为50.0%(浅黄色油)。质谱(m/z):351.3$[M+H]^+$。

[1505] 步骤4:制备N^1-(4-(叔丁基)苯基)-3-甲基环己烷-1,4-二胺(250)

[1506] 根据为化合物232-3的程序制备标题化合物250A和250B。粗制残余物的提纯方法为:制备HPLC(柱:X Select-CSH-Prep 5μm OBD,19*150mm;ACN/水(0.5%TFA)=10%-27%-95%-95%-10%,0min-12min-12.5min-13.5min-15min)而得到化合物250A(Rt=10.17min),收率为4.0%(白色固体)和250B(Rt=5.05min),收率为15.3%(白色固体)。250A:^1H NMR(400MHz,甲醇-d4)δ7.15-7.10(m,2H),6.61-6.57(m,2H),3.62-3.58(m,H),2.47(td,J=10.0,4.0Hz,1H),1.92-1.81(m,2H),1.73-1.55(m,3H),1.37-1.29(m,2H),1.23(s,9H),0.98(d,J=6.4Hz,3H)。质谱(m/z):261.3$[M+H]^+$。250B:^1H NMR(400MHz,甲醇-d4)δ7.16-7.10(m,2H),6.61-6.57(m,2H),3.25-3.18(m,1H),2.95-2.89(m,1H),1.86-1.62(m,5H),1.32-1.20(m,11H),0.94(d,J=6.8Hz,3H)。质谱(m/z):261.3$[M+H]^+$。

[1507] 化合物251

[1508] N^1-(4-(4,4-二氟环己基)苯基)环己烷-1,4-二胺

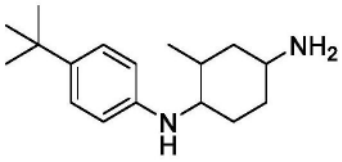
[1509] 

251A
251B

[1510] 根据为化合物24的程序制备标题化合物251A和251B。粗制残余物的提纯方法为:制备HPLC(柱:X Select-CSH-Prep 5μm OBD,19*150mm;ACN/水(0.5%TFA)=10%-30%-95%-95%-10%,0min-10min-10.5min-11.5min-13min)而得到化合物251A(Rt=8.29min),收率为17.7%(白色固体)和251B(Rt=6.36min),收率为8.8%(白色固体)。251A:^{1}H NMR(400MHz,DMSO-d6)δ6.87(d,J=8.6Hz,2H),6.47(d,J=8.6Hz,2H),5.16(d,J=7.6Hz,1H),3.26-3.16(m,1H),2.80-2.71(m,1H),2.04-1.72(m,7H),1.62-1.42(m,10H)。质谱(m/z):309.3[M+H]$^+$。251B:^{1}H NMR(400MHz,DMSO-d6)δ6.87(d,J=8.5Hz,2H),6.43(d,J=8.6Hz,2H),5.11(d,J=8.2Hz,1H),3.07-2.94(m,1H),2.48-2.49(m,1H),2.07-1.67(m,11H),1.57-1.48(m,3H),1.11-0.99(m,4H)。质谱(m/z):309.3[M+H]$^+$。

[1511] 化合物252

[1512] N^1-(4-(叔丁基)苯基)-2-甲基环己烷-1,4-二胺

[1513] 

252A
252B
252C
252D

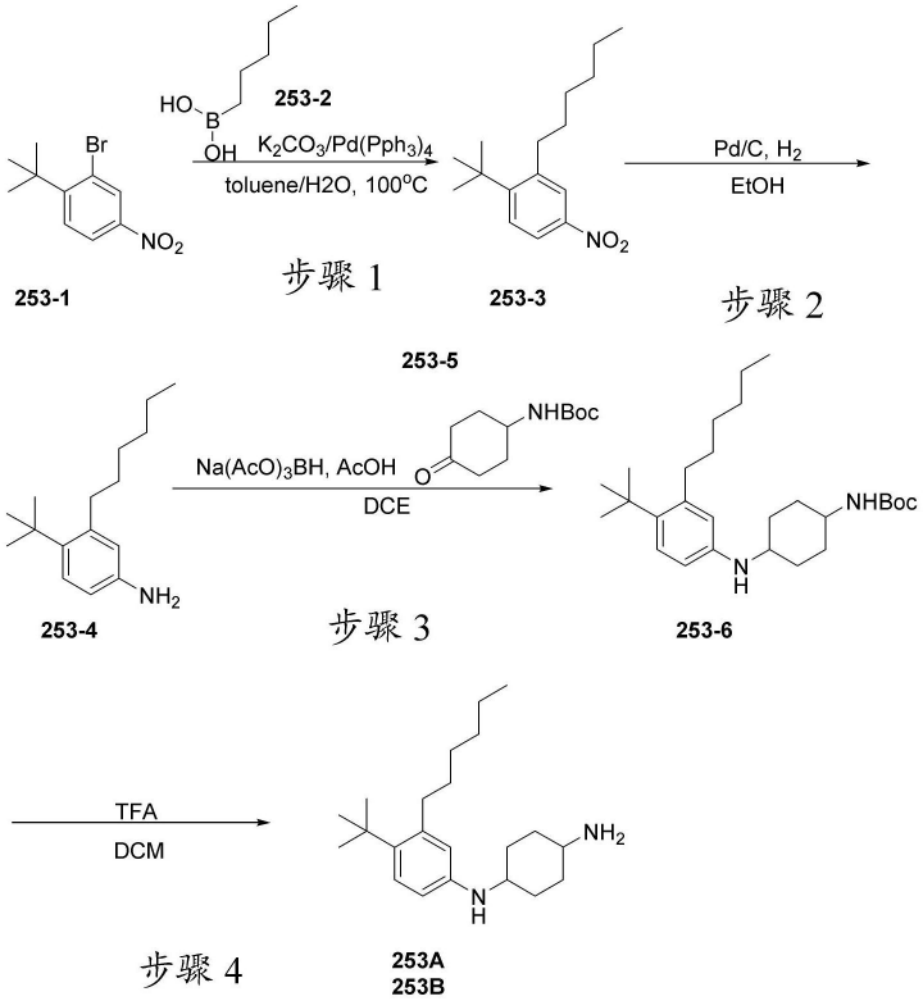
[1514] 根据为化合物250的程序制备标题化合物252A,252B,252C,252D。粗制残余物的提纯方法为:制备HPLC(柱:X Select-CSH-Prep5μm OBD,19*150mm;ACN/水(0.5%TFA)=10%-43%-95%-95%-10%,0min-10min-10.5min-11.5min-13min)而得到化合物252A(Rt=9.55min),收率为1.1%(白色固体),252B(Rt=7.47min),收率为2.8%(白色固体),252C(Rt=6.45min),收率为2.7%(白色固体)和252D(Rt=5.88min),收率为7.3%(白色固体)。252A:^{1}H NMR(400MHz,甲醇-d4)δ7.12-7.07(m,2H),6.61-6.54(m,2H),3.51-3.45(m,1H),2.77-2.63(m,1H),1.98-1.91(m,1H),1.86-1.74(m,1H),1.67-1.56(m,2H),1.47-1.36(m,1H),1.33-1.26(m,2H),1.23(s,9H),0.97(d,J=7.0Hz,3H)。质谱(m/z):261.3[M+H]$^+$。252B:^{1}H NMR(400MHz,甲醇-d4)δ7.16-7.05(m,2H),6.57-6.46(m,2H),3.14-2.92(m,2H),1.89-1.77(m,2H),1.75-1.54(m,3H),1.52-1.39(m,3H),1.23(s,9H),1.01(d,J=6.8Hz,3H)。质谱(m/z):261.3[M+H]$^+$。252C:^{1}H NMR(400MHz,甲醇-d4)δ7.10-7.06(m,2H),6.53-6.48(m,2H),2.81-2.67(m,2H),2.11-1.81(m,4H),1.51-1.41(m,1H),1.22(s,9H),1.14-1.02(m,2H),1.00(d,J=6.4Hz,3H)。质谱(m/z):261.3[M+H]$^+$。252D:^{1}H NMR(400MHz,甲醇-d4)δ7.14-7.09(m,2H),6.62-6.55(m,2H),3.44-3.37(m,1H),2.94-2.84(m,1H),2.32-2.24

(m,1H),1.91-1.84(m,1H),1.79-1.66(m,2H),1.59-1.51(m,1H),1.45-1.35(m,1H),1.30-1.19(m,10H),0.88(d,J＝7.2Hz,3H)。质谱(m/z):261.3[M+H]$^+$。

[1515] 化合物253

[1516] N^1-(4-(叔丁基)-3-己基苯基)环己烷-1,4-二胺

[1517]



[1518] toluene:甲苯

[1519] 步骤1:制备1-(叔丁基)-2-己基-4-硝基苯(253-3)

[1520] 由2-溴-1-(叔丁基)-4-硝基苯(193mg,0.74mmol),戊基硼酸(593mg,4.5mmol),K_2CO_3(153mg,1.11mmol)和Pd$(PPh_3)_4$(177mg,0.15mmol),根据为208-1的程序制备标题化合物253-3(150mg),总收率为46.2%(浅黄色油)。

[1521] 步骤2:制备4-(叔丁基)-3-己基苯胺(253-4)

[1522] 由1-(叔丁基)-2-己基-4-硝基苯(150mg,0.57mmol)和10%Pd/C(3.6mg,3.4umol),根据为208-2的程序制备标题化合物253-4(50mg),总收率为63.1%(黄色固体)。质谱(m/z):234.3[M+H]$^+$。

[1523] 步骤3:制备(4-((4-(叔丁基)-3-己基苯基)氨基)环己基)氨基甲酸叔丁酯(253-6)

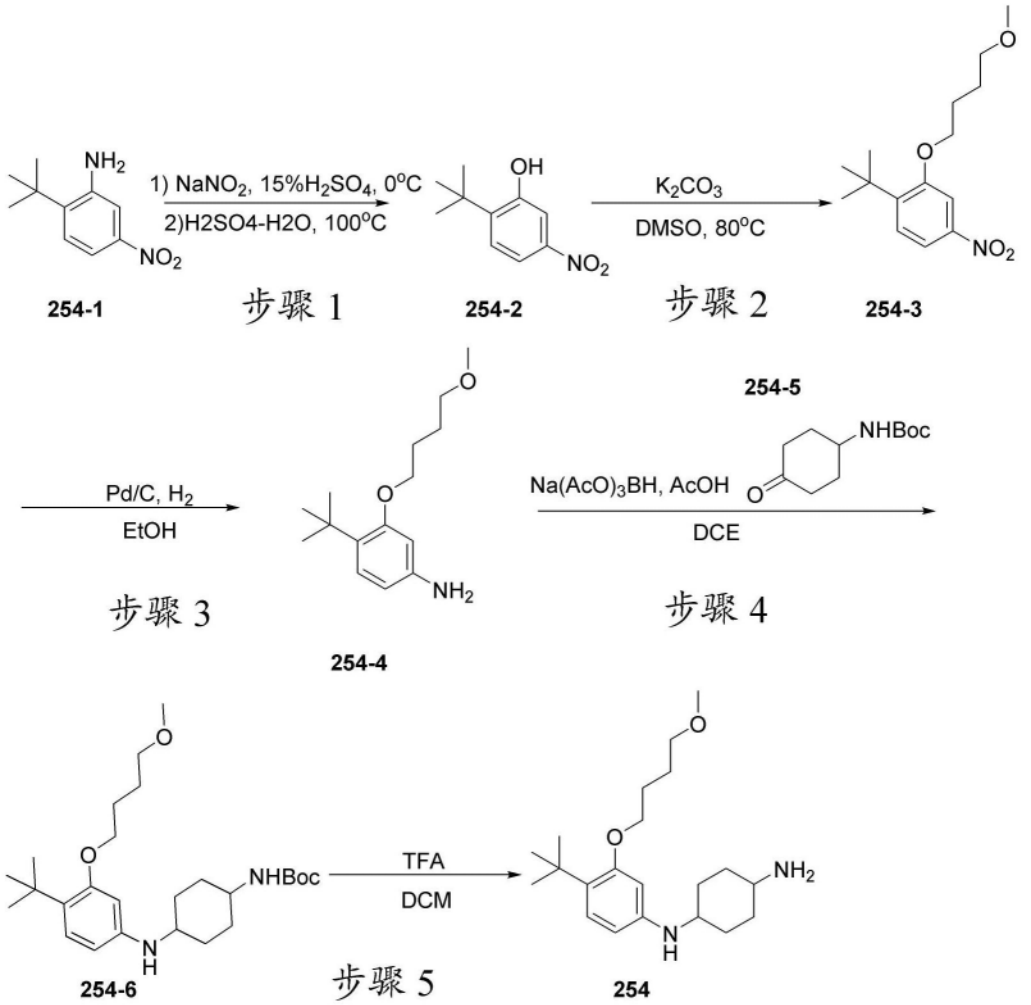
[1524] 由4-(叔丁基)-3-己基苯胺(50mg,0.21mmol),(4-氧代环己基)氨基甲酸叔丁酯(89mg,0.42mmol)和Na$(AcO)_3$BH(89mg,0.42mmol),根据为24-1的程序制备标题化合物253-6(35mg),总收率为38.8%(黄色固体)。质谱(m/z):431.4[M+H]$^+$。

[1525] 步骤4:制备N^1-(4-(叔丁基)-3-己基苯基)环己烷-1,4-二胺(253)

[1526] 根据为化合物24的程序制备标题化合物253A和253B。粗制残余物的提纯方法为:制备TLC(H_2O/MeOH/DCM=0.1/1/5)而得到化合物253A(Rf值=0.40),收率为57.4%(白色固体)和253B(Rf值=0.36),收率为15.3%(白色固体)。253A:^{1}H NMR(400MHz,甲醇-d4)δ7.08(d,J=8.8Hz,1H),6.49(d,J=2.8Hz,1H),6.39(dd,J=8.6,2.8Hz,1H),3.56-3.49(m,1H),3.24-3.15(m,1H),2.74-2.67(m,2H),1.88-1.71(m,8H),1.61-1.52(m,2H),1.46-1.36(m,2H),1.36-1.31(m,13H),0.94-0.86(m,3H)。质谱(m/z):331.3$[M+H]^+$。253B:^{1}H NMR(400MHz,甲醇-d4)δ7.08(d,J=8.6Hz,1H),6.49(d,J=2.8Hz,1H),6.40(dd,J=8.6,2.7Hz,1H),3.24-3.17(m,1H),3.11-3.04(m,1H),2.74-2.67(m,2H),2.17-2.10(m,2H),2.09-1.99(m,2H),1.57-1.26(m,21H),0.93-0.85(m,3H)。质谱(m/z):331.3$[M+H]^+$。

[1527] 化合物254

[1528] N^1-(4-(叔丁基)-3-(4-甲氧基丁氧基)苯基)环己烷-1,4-二胺

[1529] 

[1530] 步骤1:制备2-(叔丁基)-5-硝基苯酚(254-2)

[1531] 在0℃向2-叔丁基-5-硝基苯胺(582g,3.0mmol)/10mL的15%$H2SO_4$的混合物中滴加NaNO2(217mg,3.15mmol)/水(3mL)的溶液。在0-5℃搅拌所得的混合物20分钟。然后将溶液滴加到5mL的$H2SO_4$-H_2O(V/V=1/2)(在100℃搅拌)的溶液中。在100℃搅拌所得的混合物20分钟。在冷却到室温并且用DCM(20mL×3)萃取后,将合并的有机层用水(20mL)洗涤,用

Na_2SO_4干燥,以及浓缩。残余物的提纯方法为:prep-TLC(DCM/PE=1/3)而得到标题化合物(黄色油)(300mg,51.5%)。质谱(m/z):194.0$[M-H]^-$。

[1532] 步骤2:制备1-(叔丁基)-2-(4-甲氧基丁氧基)-4-硝基苯(254-3)

[1533] 向2-(叔丁基)-5-硝基苯酚(150mg,0.77mmol),KI(12.8mg,77ummol)和K_2CO_3(212mg,1.54mmol)/DMSO(2.0mL)的混合物中添加1-溴-4-甲氧基丁烷(190mg,1.15mmol)。然后在80℃搅拌混合物过夜。在冷却到室温后,添加5mL,并且用DCM(10mL×3)萃取。将合并的有机层用水(10mL×3)洗涤,用Na_2SO_4干燥,以及浓缩而得到标题化合物(粗产物黄色油)(216mg,100%)。

[1534] 步骤3:制备4-(叔丁基)-3-(4-甲氧基丁氧基)苯胺(254-4)

[1535] 由1-(叔丁基)-2-(4-甲氧基丁氧基)-4-硝基苯(216mg,0.77mmol)和10%Pd/C(81.6mg,77umol),根据为208-2的程序制备标题化合物254-4(193mg),总收率为100%(黄色固体)。质谱(m/z):252.4$[M+H]^+$。

[1536] 步骤4:制备N^1-(4-(叔丁基)-3-(4-甲氧基丁氧基)苯基)环己烷-1,4-二胺(254-6)

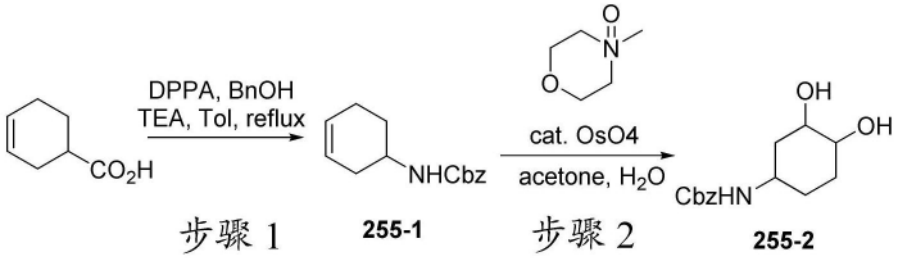
[1537] 由4-(叔丁基)-3-(4-甲氧基丁氧基)苯胺(193mg,0.77mmol),(4-氧代环己基)氨基甲酸叔丁酯(328mg,1.54mmol)和$Na(AcO)_3BH$(326mg,1.54mmol),根据为24-1的程序制备标题化合物254-6(62mg),总收率为18.0%(黄色固体)。质谱(m/z):449.4$[M+H]^+$。

[1538] 步骤5:制备N^1-(4-(叔丁基)-3-(4-甲氧基丁氧基)苯基)环己烷-1,4-二胺(254)

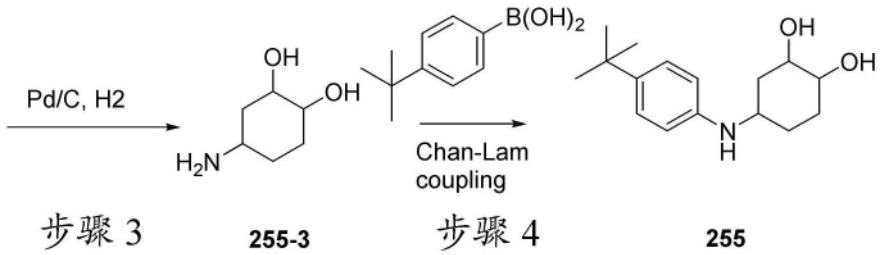
[1539] 由N^1-(4-(叔丁基)-3-(4-甲氧基丁氧基)苯基)环己烷-1,4-二胺(62mg,0.14mmol)和TFA(2.0mL),根据为24的程序制备标题化合物254(32.2mg),总收率为66.1%(白色固体),经^{1}HNMR证明为1:1的混合物。^{1}H NMR(400MHz,甲醇-d_4)δ6.99(dd,J=10.4,8.4Hz,1H),6.30(t,J=2.6Hz,1H),6.20(dd,J=8.4,2.3Hz,0.5H),6.15(dd,J=8.4,2.3Hz,0.5H),3.93(t,J=6.0Hz,2H),3.56-3.49(m,0.5H),3.46(t,J=6.2Hz,2H),3.33(s,3H),3.26-3.19(m,1H),3.12-3.04(m,0.5H),2.19-2.11(m,1H),2.10-2.04(m,0.5H),1.95-1.65(m,8H),1.56-1.45(m,1H),1.37-1.12(m,11H)。质谱(m/z):349.3$[M+H]^+$。

[1540] 化合物255

[1541] 4-((4-(叔丁基)苯基)氨基)环己烷-1,2-二醇



[1542]



[1543] reflux:回流acetone:丙酮coupling:耦合

[1544] 步骤1:制备环己-3-烯-1-基氨基甲酸苄酯(255-1)

[1545] 使环己-3-烯-1-甲酸(1g,7.93mmol),TEA(882mg,8.72mmol)和DPPA(2.18g,7.93mmol)/甲苯(40mL)的混合物回流2小时。在添加BnOH(857mg,7.93mmol)后,使混合物回流10小时。将混合物真空蒸发并且所得的残余物用乙酸乙酯稀释。将有机层顺序用1N盐酸,饱和碳酸氢钠水溶液和盐水洗涤。将有机相合并,用Na_2SO_4干燥,过滤并且浓缩而得到产物(1.56g,85%)(黄色固体)。质谱(m/z):232.1$[M+H]^+$。

[1546] 步骤2:制备(3,4-二羟基环己基)氨基甲酸苄酯(255-2)

[1547] 向(3,4-二羟基环己基)氨基甲酸苄酯(1.56g,6.74mmol)/四氢呋喃(40mL)和水(5mL)的混合物的溶液中添加4-甲基吗啉4-氧化物(1.19g,10.1mmol)和OSO_4(500mg,1.97mmol)。在环境温度搅拌混合物30分钟。所得的混合物用$Na_2S_2O_3$水溶液淬灭并且所得的残余物用乙酸乙酯稀释。将有机相合并,用Na_2SO_4干燥,过滤并且浓缩而得到产物(1.1g,62%)(白色固体)。质谱(m/z):266.1$[M+H]^+$。

[1548] 步骤3:制备4-氨基环己烷-1,2-二醇(255-3)

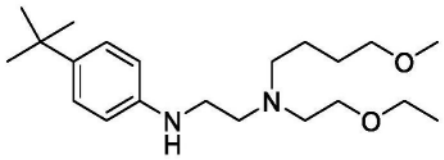
[1549] 在环境温度在氢气气氛下将(3,4-二羟基环己基)氨基甲酸苄酯(700mg,2.64mmol)和Pd/C(281mg,0.26mmol)/乙醇(10mL)的混合物搅拌过夜。通过过滤除去催化剂,并且将滤液真空蒸发。获得目标产物(288mg,83%)(白色固体)。质谱(m/z):132.1$[M+H]^+$。

[1550] 步骤4:制备4-((4-(叔丁基)苯基)氨基)环己烷-1,2-二醇(255)

[1551] 向4-氨基环己烷-1,2-二醇(288mg,2.20mmol),(4-(叔丁基)苯基)硼酸(391mg,2.20mmol)和TEA(1.11g,11mmol)/CH_2Cl_2(20mL)的溶液中添加Cu(OAc)2(877mg,4.39mmol)。然后在室温搅拌混合物过夜。将反应通过celite过滤并且将滤液真空蒸发。残余物的提纯方法为:prep-TLC而得到期望的产物255(11.4mg,4%)(黄色固体)。^1H NMR(400MHz,CD_3OD)δ 7.15(d,J=8.8Hz,2H),7.15(d,J=8.8Hz,2H),4.01-3.94(m,1H),3.70-3.56(m,2H),2.21-2.12(m,1H),2.06-1.97(m,1H),1.86-1.75(m,1H),1.75-1.65(m,1H),1.44-1.35(m,1H),1.26(s,9H)。质谱(m/z):263.9$[M+H]^+$。

[1552] 化合物256

[1553] N^1-(4-(叔丁基)苯基)-N^2-(2-乙氧基乙基)-N^2-(4-甲氧基丁基)乙烷-1,2-二胺

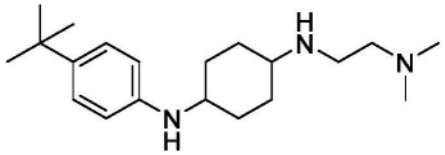
[1554] 

256

[1555] 由N-(4-(叔丁基)苯基)-2-((2-乙氧基乙基)(4-甲氧基丁基)氨基)乙酰胺(139mg,0.38mmol),和BH_3-THF(20mL),根据为105的程序制备标题化合物256(44mg,33%)(白色固体)。^1H NMR(400MHz,CD_3OD)δ7.22(d,J=8.7Hz,2H),6.67(dd,J=8.6,2.0Hz,2H),3.70(s,2H),3.48(q,J=7.0Hz,4H),3.39(dt,J=4.3,3.7Hz,6H),3.32(s,3H),3.27-3.18(m,2H),1.85-1.74(m,2H),1.64-1.56(m,3H),1.28-1.25(m,9H),1.15(t,J=7.0Hz,3H)。质谱(m/z):350.9$[M+H]^+$。

[1556] 化合物257

[1557] N-(4-环己基苯基)-1-乙基哌啶-4-胺

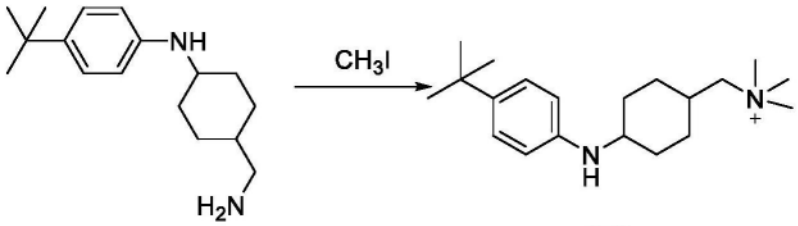
[1558] 

257

[1559] 由4-((4-(叔丁基)苯基)氨基)环己烷-1-酮(100mg,0.41mmol),MeOH(5mL),N^1,N^1-二甲基乙烷-1,2-二胺(36mg,0.41mmol)和乙酸(2.46mg,0.041mmol),根据为5的程序制备标题化合物257(17.2mg,13.2%)(黄色固体)。^{1}H NMR(400MHz,CDCl3)δ8.49(s,1H),7.17(d,J=8.0Hz,2H),6.52(d,J=8.0Hz,2H),3.26-2.95(m,5H),2.52(s,6H),2.22(m,4H),1.62(s,2H),1.25(s,9H),1.21-1.04(m,2H)。质谱(m/z):318.3$[M+H]^+$。

[1560] 化合物258

[1561] 1-(4-((4-(叔丁基)苯基)氨基)环己基)-N,N,N-三甲基甲铵

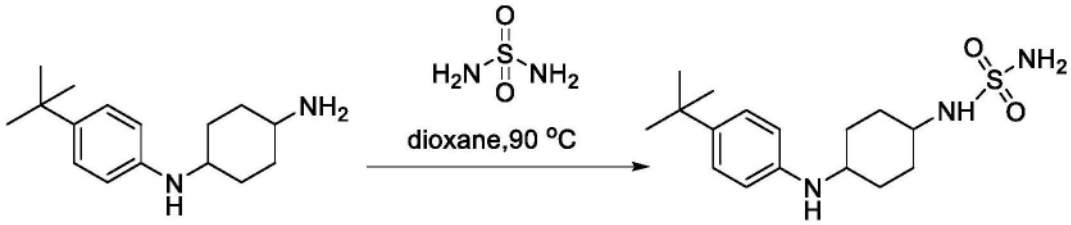
[1562] 

258

[1563] 向N-(4-(氨基甲基)环己基)-4-(叔丁基)苯胺(120mg,0.46mmol)/MeOH(5mL)的溶液中添加K_2CO_3(180mg,1.30mmol)和碘甲烷(327mg,2.3mmol)。然后在25℃搅拌混合物12小时。用水(20mL)淬灭,将反应用EA(10mL)萃取三次。将合并的有机层用硫酸钠干燥,真空浓缩并且残余物的提纯方法为:prep-HPLC(柱-Xbridge-C18 150x 21.2mm,5um;移动相:ACN-H_2O(0.1%FA),40%-60%)而得到期望的产物258(10.1mg,7.2%)(白色固体)。^{1}H NMR(400MHz,DMSO-d6)δ8.38(s,1H),7.07(d,J=8.4Hz,2H),6.53(d,J=8.4Hz,2H),3.37(s,1H),3.24(s,2H),3.07(s,9H),2.07(s,1H),1.67(d,J=12Hz,2H),1.55(s,6H),1.20(s,9H)。质谱(m/z):303.3$[M+H]^+$。

[1564] 化合物259

[1565] N-(4-{[4-(4,4-二甲基环己基)苯基]氨基}环己基)氨基磺酰胺

[1566] 

259A

259B

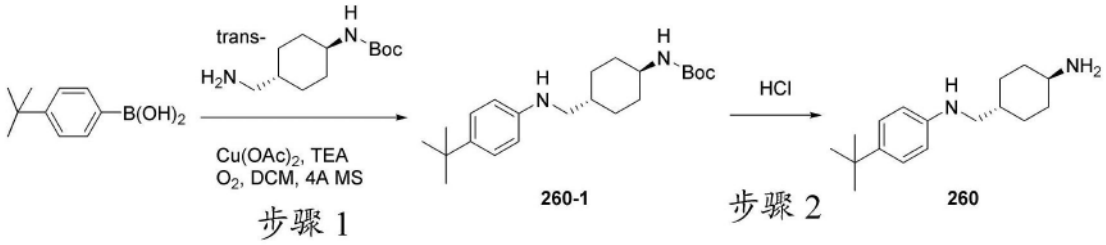
[1567] dioxane:二氧杂环己烷

[1568] 在90℃在氮气气氛下将N^1-(4-(叔丁基)苯基)环己烷-1,4-二胺(70mg,0.28mmol),和氨磺酰胺(32.8mg,0.34mmol)/1,4-二氧杂环己烷(10mL)的溶液搅拌过夜。在

冷却到室温后,将反应真空浓缩并且残余物的提纯方法为:prep-HPLC(柱-Xbridge-C18 150x 21.2mm,5um;移动相:ACN-H_2O(0.1%FA),20%-40%)而得到期望的产物295A(19.3mg,20.6%)(白色固体)和295B(11.0mg,11.7%)(白色固体)。259A:^{1}H NMR(400MHz,DMSO-d6)δ7.06(d,J=8.6Hz,2H),6.51(d,J=8.6Hz,2H),6.45(s,2H),6.38(d,J=5.8Hz,1H),5.11(br,1H),3.57(br,1H),2.54(br,1H),1.76-1.56(m,8H),1.20(s,9H)。质谱(m/z):326.2$[M+H]^+$。HPLC:Rt=3.384min(柱:XBRIDGE 3.5um,2.1*50mm,移动相:H_2O(0.05%TFA)-ACN(0.05%TFA),ACN从0至60%在7分钟内,7-8min,ACN由60%至100%,流速:0.8mL/min)。259B:^{1}H NMR(400MHz,DMSO-d6)δ7.40(br,2H),7.17(br,2H),6.57(d,J=6.7Hz,1H),6.50(br,2H),3.25(br,1H),3.03(br,1H),1.96(t,J=15.2Hz,4H),1.42(br,2H),1.26(s,9H),1.21-1.18(m,2H)。质谱(m/z):326.2$[M+H]^+$。HPLC:Rt=3.273min(柱:XBRIDGE 3.5um,2.1*50mm,移动相:H_2O(0.05%TFA)-ACN(0.05%TFA),ACN从0至60%在7分钟内,7-8min,ACN由60%至100%,流速:0.8mL/min)。

[1569] 化合物260

[1570] N-(((1r,4r)-4-氨基环已基)甲基)-4-(叔丁基)苯胺

[1571] 

[1572] 步骤1:制备((1r,4r)-4-(((4-(叔丁基)苯基)氨基)甲基)环已基)氨基甲酸叔丁酯(260-1)

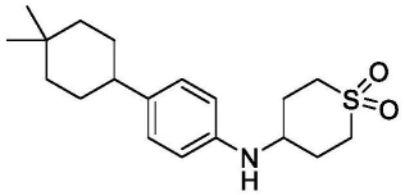
[1573] 向100mL的圆底烧瓶中装入((1r,4r)-4-(氨基甲基)环已基)氨基甲酸叔丁酯(232mg,1.01mmol,1.1eq),(4-(叔丁基)苯基)硼酸(150mg,0.84mmol,1.00eq),Cu(OAc)2(306mg,1.7mmol,和2.00eq)和TEA(426mg,4.2mmol,5.00eq)和4 Å MS(1g)。在室温在氧气气氛下搅拌反应18小时。将固体过滤并且将溶剂真空除去。残余物的提纯方法为:快速色谱而得到260-1(0.2g,65.6%收率)(黄色固体)。MS(m/z)361.3$[M+H]^+$。

[1574] 步骤2:制备N-(((1r,4r)-4-氨基环已基)甲基)-4-(叔丁基)苯胺(260)

[1575] 260-1(200mg,0.28mmol)和HCl/1,4-二氧杂环已烷(10mL,4N)被置于烧杯中,在25℃搅拌16小时。过量的1,4-二氧杂环已烷被真空蒸馏掉并且残余物的提纯方法为:快速色谱而得到260(68.2mg47.3%)(白色固体)。^{1}H NMR(400MHz,DMSO-d6)δ7.06(d,J=8.6Hz,2H),6.46(d,J=8.6Hz,2H),5.36(t,J=5.5Hz,1H),2.79(t,J=6.2Hz,2H),1.76(s,4H),1.42(s,1H),1.20(s,9H),0.94(d,J=8.4Hz,4H)。MS(m/z)261.3$[M+H]^+$。

[1576] 化合物261

[1577] 4-((4-(4,4-二甲基环已基)苯基)氨基)四氢-2H-噻喃1,1-二氧化物

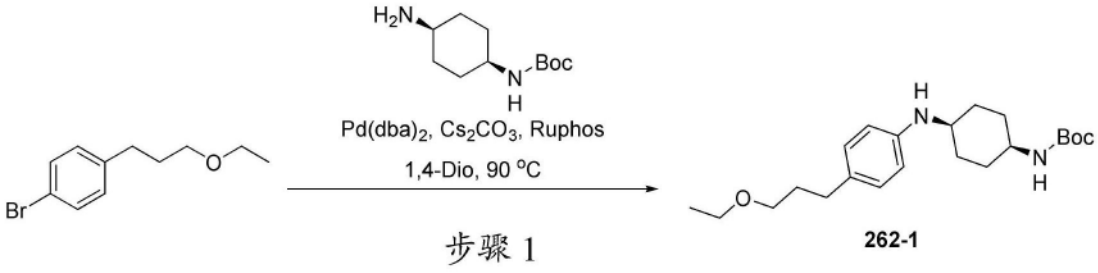
[1578] 

261

[1579] 由4-(4,4-二甲基环己基)苯胺(70mg,0.34mmol),四氢-4H-噻喃-4-酮1,1-二氧化物(61.2mg,0.41mmol),硼烷-2-皮考啉复合物(55.2mg,0.52mmol),CH3COOH(1mL)和H_2O(9mL),根据为90的程序制备期望的产物261(5.4mg,4.5%)(白色固体)。^{1}H NMR(400MHz,DMSO-d6)δ6.96(d,J=8.3Hz,2H),6.53(d,J=8.4Hz,2H),5.46(d,J=8.7Hz,1H),3.60(d,J=8.7Hz,1H),3.23-3.10(m,4H),2.23-2.13(m,3H),1.92-1.83(m,2H),1.59-1.37(m,6H),1.31-1.23(m,2H),0.93(d,J=8.8Hz,6H)。质谱(m/z):336.3$[M+H]^+$。

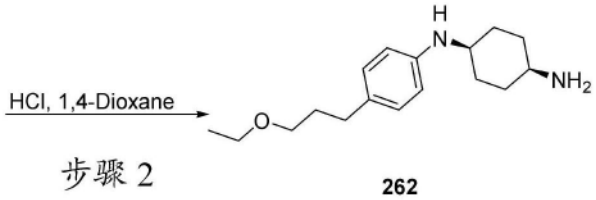
[1580] 化合物262

[1581] (1s,4s)-N^1-(4-(3-乙氧基丙基)苯基)环己烷-1,4-二胺

[1582] 

步骤 1

262-1



步骤 2

262

[1583] 1,4-Dio.=1,4-dioxane:1,4-二氧杂环己烷

[1584] 步骤1:制备((1s,4s)-4-((4-(3-乙氧基丙基)苯基)氨基)环己基)氨基甲酸叔丁酯(262-1)

[1585] 在90℃在氮气气氛下将1-溴-4-(3-乙氧基丙基)苯(200mg,0.82mmol),((1s,4s)-4-氨基环己基)氨基甲酸叔丁酯(352.6mg,1.65mmol),$Pd_2(dba)_3$(75.3mg,0.08mmol),Ruphos(76.8mg,0.16mmol),Cs_2CO_3(536.0mg,1.65mmol)/1,4-二氧杂环己烷(10mL)的混合物搅拌过夜。在冷却到室温后,将反应溶液用水洗涤,并且将反应溶液用乙酸乙酯(20mL)和水(20mL)萃取三次。合并有机相,真空除去溶剂并且通过硅胶色谱(PE:EA=5:1)提纯粗产物而得到期望的产物(300mg,58.1%)(油)。质谱(m/z):377.3$[M+H]^+$。

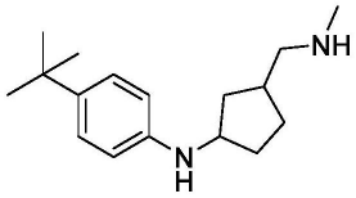
[1586] 步骤2:制备(1s,4s)-N^1-(4-(3-乙氧基丙基)苯基)环己烷-1,4-二胺(262)

[1587] 在25℃搅拌((1s,4s)-4-((4-(3-乙氧基丙基)苯基)氨基)环己基)氨基甲酸叔丁酯(300mg,0.79mmol)/1,4-二氧杂环己烷(10mL)和1,4-二氧杂环己烷/HCl(10mL)的混合物16小时。在反应完成后,真空除去溶剂并且残余物的提纯方法为:prep-HPLC(柱-Xbridge-C18 150x 21.2mm,5um;移动相:ACN-H_2O(0.1%FA),5%-20%)而得到期望的产物262(白色固体)(23.6mg,10.7%)。^{1}H NMR(400MHz,DMSO-d6)δ6.88(d,J=8.3Hz,2H),6.54(d,J=

8.3Hz,2H),5.36(br,1H),3.41-3.35(m,3H),3.31(t,J=6.5Hz,2H),3.02(br,1H),2.43(t,J=7.6Hz,2H),1.93-1.53(m,10H),1.10(t,J=7.0Hz,3H)。质谱(m/z):277.3[M+H]$^+$。

[1588] 化合物263

[1589] 4-(叔丁基)-N-(3-((甲基氨基)甲基)环戊基)苯胺

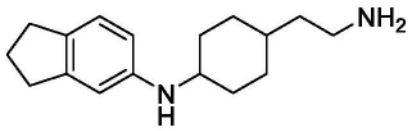
[1590] 

263

[1591] 由3-((4-(叔丁基)苯基)氨基)-N-甲基环戊烷-1-甲酰胺(90mg,0.328mmol),$LiAlH_4$(49mg,1.314mmol)和THF(10mL),根据为23的程序制备标题化合物263(18.8mg),总收率为22.0%(黄色固体)。^{1}H NMR(400MHz,DMSO-d6)δ7.09-6.96(m,2H),6.45(d,J=8.2Hz,2H),5.63-5.22(m,1H),3.64(s,1H),2.82(s,2H),2.43(s,3H),2.26-2.19(m,2H),1.89-1.69(m,3H),1.47-1.43(m,1H),1.16(s,9H)。质谱(m/z):261.3[M+H]$^+$。

[1592] 化合物264

[1593] N-(4-(2-氨基乙基)环己基)-2,3-二氢-1H-茚-5-胺

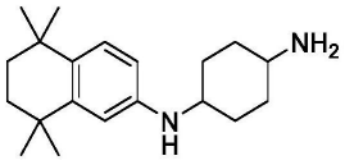
[1594] 

264

[1595] 由2-(4-((2,3-二氢-1H-茚-5-基)氨基)环己基)乙酰胺(145mg,0.533mmol),$LiAlH_4$(79mg,2.132mmol)和THF(10mL),根据为23的程序制备标题化合物264(47.1mg),总收率为34.2%(棕色固体)。^{1}H NMR(400MHz,DMSO-d6)δ6.90(dd,J=8.0,4.2Hz,1H),6.55-6.38(m,2H),5.65-4.98(m,1H),2.71(dq,J=14.8,8.8,7.2Hz,6H),1.93(p,J=7.2Hz,3H),1.76-1.33(m,11H)。质谱(m/z):259.3[M+H]$^+$。

[1596] 化合物265

[1597] N^1-(5,5,8,8-四甲基-5,6,7,8-四氢萘-2-基)环己烷-1,4-二胺

[1598] 

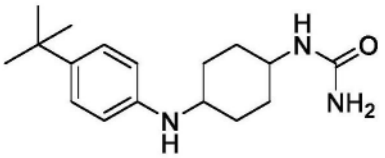
265

[1599] 由5,5,8,8-四甲基-5,6,7,8-四氢萘-2-胺(50mg,0.25mmol),(4-氧代环己基)氨基甲酸叔丁酯(78mg,0.37mmol)和根据为20的程序制备标题化合物265(21.8mg),收率为29.5%(白色粉末),经^{1}H NMR证实为1:0.41的混合物。^{1}H NMR(400MHz,DMSO-d6)δ8.01(s,4H),7.00(dd,J=8.5,4.7Hz,1H),6.51(d,J=2.5Hz,0.40H),6.45(d,J=2.5Hz,1H),6.37(td,J=8.6,8.0,2.4Hz,1H),5.14(d,J=5.4Hz,0.41H),5.08(d,J=8.0Hz,1H),3.40(s,0.41H),3.17(d,J=4.9Hz,1H),3.08(d,J=8.3Hz,1H),2.98(tt,J=11.5,3.7Hz,1H),1.99(td,J=10.4,5.3Hz,4H),1.85-1.67(m,2H),1.58(s,6H),1.44(qd,J=13.5,12.4,3.8Hz,

2H),1.21-1.13(m,18H)。质谱(m/z):301.6[M+H]$^+$。

[1600] 化合物266

[1601] 1-(4-((4-(叔丁基)苯基)氨基)环己基)脲

[1602] 

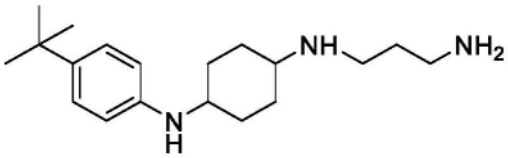
266A

266B

[1603] 由1-N-(4-(叔丁基)苯基)环己烷-1,4-二胺(100mg,0.4mmol),DCM(7mL),TMSNCO(46.76mg,0.4mmol),TEA(104.92mg,0.81mmol)和DMAP(9.92mg,0.08mmol),根据为178的程序制备标题化合物266A(26.94mg)(白色固体)和266B(25.46mg)(白色固体)。266A:^{1}H NMR(400MHz,CD_3OD)δ7.15-7.12(m,2H),6.62-6.59(m,2H),3.50-3.37(m,1H),3.19-3.13(m,1H),2.05(dd,J=7.0,3.6Hz,2H),1.98-1.92(m,2H),1.25-1.21(m,13H)。质谱(m/z):289.9[M+H]$^+$。HPLC:Rt=4.262min(柱:XBRIDGE 3.5um,2.1*50mm,移动相:H_2O(0.05%TFA)-ACN(0.05%TFA),ACN从0至60%在7分钟内,7-8min,ACN由60%至100%,流速:0.8mL/min)。266B:^{1}H NMR(400MHz,CD_3OD)δ7.15-7.12(m,2H),6.62-6.58(m,2H),3.64(s,1H),3.36(tt,J=7.0,3.6Hz,1H),1.80-1.72(m,2H),1.65(dd,J=10.8,5.4Hz,4H),1.61-1.53(m,2H),1.23(s,9H)。质谱(m/z):289.9[M+H]$^+$。HPLC:Rt=4.328min(柱:XBRIDGE 3.5um,2.1*50mm,移动相:H_2O(0.05%TFA)-ACN(0.05%TFA),ACN从0至60%在7分钟内,7-8min,ACN由60%至100%,流速:0.8mL/min)。

[1604] 化合物267

[1605] 1-N-(3-氨基丙基)-4-N-(4-(叔丁基)苯基)环己烷-1,4-二胺

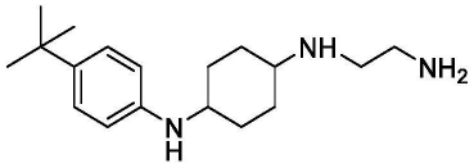
[1606] 

267

[1607] 由(3-((4-((4-(叔丁基)苯基)氨基)环己基)氨基)丙基)氨基甲酸叔丁酯(100mg,0.25mmol),1,4-二氧杂环己烷(5mL)和HCl/1,4-二氧杂环己烷(10mL),根据为224的程序制备期望的产物267(24.8mg)(白色固体)。^{1}H NMR(400MHz,CD_3OD)δ7.24-7.17(m,2H),6.76(t,J=9.2Hz,2H),3.46-3.38(m,1H),3.24-3.19(m,01H),3.17-3.13(m,1H),3.03(t,J=3.6Hz,0.5H),2.68-2.62(m,2H),2.59(dd,J=9.6,5.6Hz,0.5H),1.94-1.88(m,1H),1.82-1.70(m,3H),1.67-1.59(m,3H),1.59-1.26(m,3H),1.25(s,9H)。质谱(m/z):304.0[M+H]$^+$。

[1608] 化合物268

[1609] 1-N-(2-氨基乙基)-N^4-(4-(叔丁基)苯基)环己烷-1,4-二胺

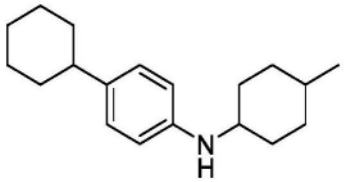
[1610] 

268

[1611] 由(2-((4-((4-(叔丁基)苯基)氨基)环己基)氨基)乙基)氨基甲酸叔丁酯(100mg,0.25mmol),1,4-二氧杂环己烷(5mL)和HCl/1,4-二氧杂环己烷(10mL),根据为224的程序制备标题化合物268(6mg)(白色固体)。^{1}H NMR(400MHz,CD_3OD)δ7.15(d,J=8.8Hz,2H),6.62(d,J=8.8Hz,2H),3.23(dd,J=6.2,2.4Hz,4H),3.07(m,1H),2.17(d,J=11.0Hz,4H),1.56-1.45(m,2H),1.40-1.18(m,12H)。质谱(m/z):290.0$[M+H]^+$。

[1612] 化合物269

[1613] 4-环己基-N-(4-甲基环己基)苯胺

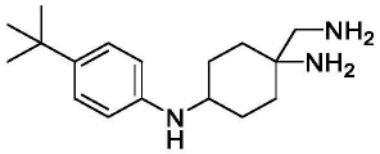
[1614] 

269

[1615] 由4-环己基苯胺(9mg,0.05mmol),根据为化合物4的程序制备标题化合物269(10.2mg),总收率为74%(白色固体),经^{1}H NMR证实为1:4的混合物。^{1}H NMR(400MHz,DMSO-d6)δ6.89(d,J=8.4Hz,2H),6.51(d,J=8.4Hz,1.6H),6.46(d,J=8.4Hz,0.4H),5.26(br s,1H),3.17(m,0.8H),3.04(m,0.2H),2.28(m,1H),1.80-1.11(m,19H),0.89(m,3H)。质谱(m/z):272.1$[M+H]^+$。

[1616] 化合物270

[1617] 1-(氨基甲基)-N^4-(4-(叔丁基)苯基)环己烷-1,4-二胺

[1618] 

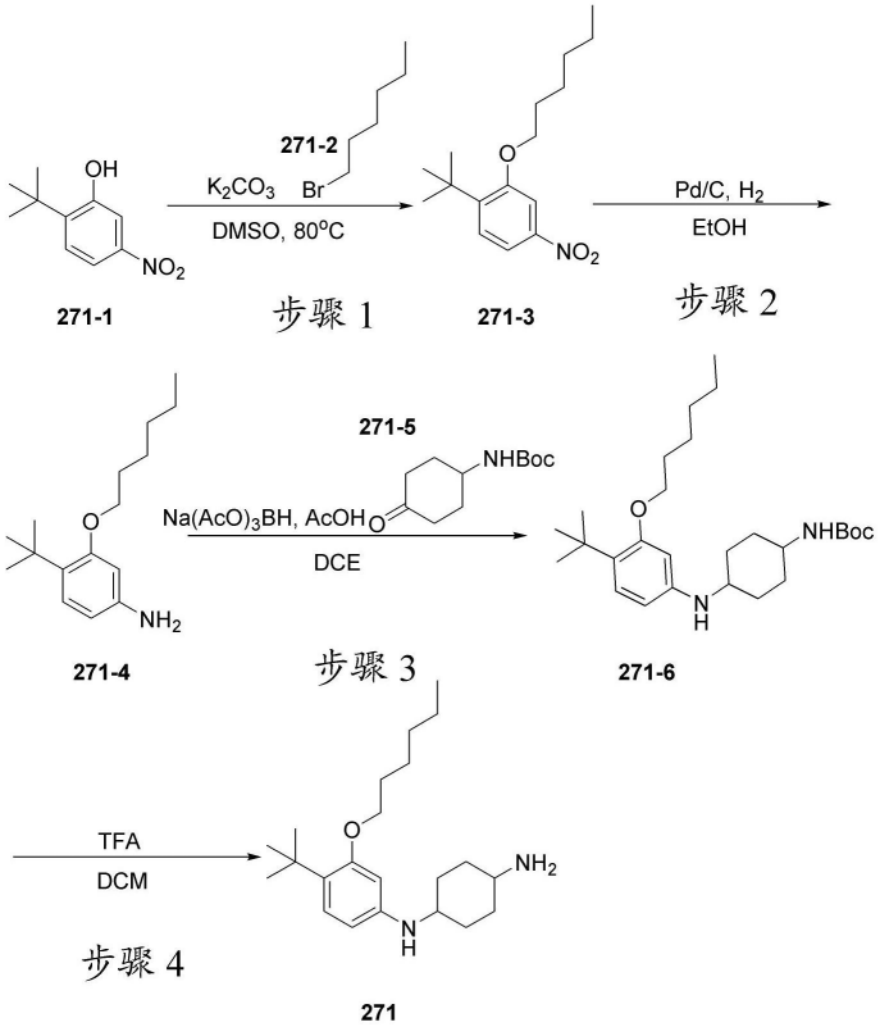
270

[1619] 由1-氨基-4-((4-(叔丁基)苯基)氨基)环己烷-1-甲酰胺(15mg,0.05mmol),根据为化合物86的程序制备标题化合物270(6.4mg),总收率为46%(淡黄色固体),经^{1}HNMR证明为1:1的混合物。^{1}H NMR(400MHz,DMSO-d6)δ8.91(br s,4H),7.12(d,J=8.4Hz,2H),6.64(d,J=8.4Hz,2H),5.31(br s,1H),3.27(s,2H),3.20(m,0.5H),3.04(m,0.5H),2.11-1.38(m,8H),1.21(s,9H)。质谱(m/z):276.1$[M+H]^+$。

[1620] 化合物271

[1621] N^1-(4-(叔丁基)-3-(己基氧基)苯基)环己烷-1,4-二胺

[1622]



[1623] 步骤1:制备1-(叔丁基)-2-(己基氧基)-4-硝基苯(271-3)

[1624] 由2-(叔丁基)-5-硝基苯酚(150mg,0.77mmol),1-溴己烷(165mg,1.14mmol)和K_2CO_3(212mg,1.54mmol),根据为254-3的程序制备标题化合物271-3(215mg),总收率为100%(黄色固体)。

[1625] 步骤2:制备4-(叔丁基)-3-(己基氧基)苯胺(271-4)

[1626] 由1-(叔丁基)-2-(己基氧基)-4-硝基苯(215mg,0.77mmol)和10%Pd/C(81.6mg,77umol),根据为208-2的程序制备标题化合物271-4(60mg),总收率为31.3%(黄色固体)。质谱(m/z):250.4$[M+H]^+$。

[1627] 步骤3:(4-((4-(叔丁基)-3-(己基氧基)苯基)氨基)环己基)氨基甲酸叔丁酯(271-6)

[1628] 由4-(叔丁基)-3-(己基氧基)苯胺(60mg,0.24mmol),(4-氧代环己基)氨基甲酸叔丁酯(102mg,0.48mmol)和$Na(AcO)_3BH$(102mg,0.48mmol),根据为24-1的程序制备标题化合物271-6(43mg),总收率为40.2%(黄色固体)。质谱(m/z):447.4$[M+H]^+$。

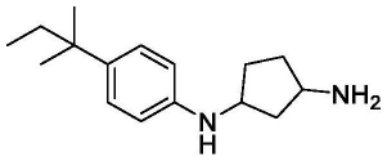
[1629] 步骤4:N^1-(4-(叔丁基)-3-(己基氧基)苯基)环己烷-1,4-二胺(271)

[1630] 由(4-((4-(叔丁基)-3-(己基氧基)苯基)氨基)环己基)氨基甲酸叔丁酯(43mg,96umol)和TFA(2.0mL),根据为24的程序制备标题化合物271(18.0mg),总收率为54.2%(白色固体),经^1H NMR证实为1:1的混合物。^1H NMR(400MHz,甲醇-d4)δ7.12-7.01(m,0.5H),

6.98(d,J＝8.4Hz,0.5H),6.40-6.10(m,2H),4.06-3.84(m,4H),3.61-3.50(m,0.5H),3.25-3.17(m,1H),3.12-3.02(m,0.5H),2.15(d,J＝12.8Hz,1H),2.06(d,J＝12.6Hz,1H),1.91-1.70(m,6H),1.58-1.44(m,4H),1.38-1.34(m,4H),1.30(d,J＝3.6Hz,9H),0.96-0.85(m,3H)。质谱(m/z):347.4[M+H]$^+$。

[1631] 化合物272

[1632] N^1-(4-(叔戊基)苯基)环戊烷-1,3-二胺

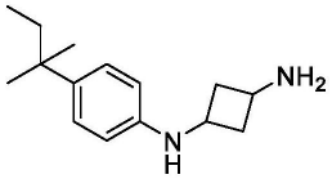
[1633] 

272

[1634] 由(3-((4-(叔戊基)苯基)氨基)环戊基)氨基甲酸叔丁酯(25mg,70umol)和TFA(2.0mL),根据为24的程序制备标题化合物272(10.3mg),总收率为57.8%(白色固体),经^{1}H NMR证实为1:1的混合物。^{1}H NMR(400MHz,甲醇-d4)δ8.53-8.39(m,2H),8.06-7.95(m,2H),5.38(p,J＝6.0Hz,0.5H),5.24(p,J＝6.5Hz,0.5H),5.11(p,J＝7.2Hz,0.5H),5.05-4.96(m,0.5H),3.98-3.31(m,4H),3.26-2.88(m,4H),2.58(s,6H),2.02(td,J＝7.4,1.0Hz,3H).质谱(m/z):247.3[M+H]$^+$。

[1635] 化合物273

[1636] N^1-(4-(叔戊基)苯基)环丁烷-1,3-二胺

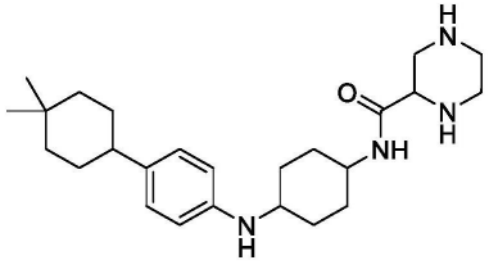
[1637] 

273

[1638] 由(3-((4-(叔戊基)苯基)氨基)环丁基)氨基甲酸叔丁酯(25mg,80umol)和TFA(2.0mL),根据为24的程序制备标题化合物273(5.0mg),总收率为28.4%(白色固体),经^{1}H NMR证实为3:2的混合物,。^{1}H NMR(400MHz,甲醇-d4)δ7.13-7.02(m,2H),6.57-6.48(m,2H),4.16-4.04(m,0.6H),3.93-3.83(m,0.6H),3.78-3.67(m,0.4H),3.60-3.49(m,0.4H),2.95-2.78(m,0.4H),2.57-2.39(m,1.6H),2.39-2.27(m,1.6H),2.03-1.85(m,0.4H),1.67-1.45(m,2H),0.62(t,J＝7.4Hz,3H)。质谱(m/z):233.3[M+H]$^+$。

[1639] 化合物274

[1640] N-(4-((4-(4,4-二甲基环己基)苯基)氨基)环己基)哌嗪-2-甲酰胺

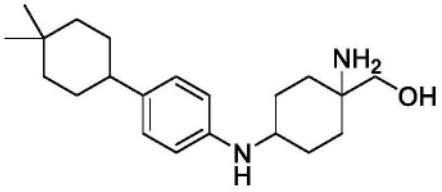
[1641] 

274

[1642] 由N^1-(4-(4,4-二甲基环己基)苯基)环己烷-1,4-二胺(50mg,0.17mmol),1,4-双(叔丁氧基羰基)哌嗪-2-甲酸(82mg,0.25mmol),根据为1的程序制备标题化合物274(28.1mg),收率为40.93%(白色粉末),经^{1}HNMR证明为1:1的混合物,。^{1}H NMR(400MHz,DMSO-d6)δ7.47(dd,J=24.8,7.9Hz,1H),6.92(dd,J=8.4,3.7Hz,2H),6.48(dd,J=16.2,8.1Hz,2H),5.14(dd,J=25.0,7.8Hz,1H),3.69(s,1H),3.51(s,1H),3.15-3.00(m,2H),2.87(d,J=11.9Hz,1H),2.79-2.62(m,2H),2.20(s,1H),1.95(d,J=12.8Hz,1H),1.82-1.71(m,1H),1.57(d,J=37.1Hz,8H),1.41(d,J=13.3Hz,3H),1.28(q,J=12.8,11.7Hz,4H),1.15(d,J=12.4Hz,1H),0.94(s,3H),0.92(s,3H)。质谱(m/z):413.5[M+H]$^+$。

[1643] 化合物275

[1644] 1-氨基-4-((4-(4,4-二甲基环己基)苯基)氨基)环己基)甲醇

[1645] 

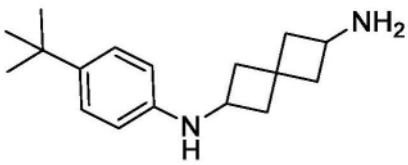
275A

275B

[1646] 根据为化合物20的程序制备标题化合物275A和275B。残余物的提纯方法为:制备HPLC(柱:X Select-CSH-Prep 5μm OBD,19*150mm;ACN/水(0.5%TFA)=0%-40%-95%-95%-10%,0min-10min-10.5min-11.5min-13.0min)而得到化合物275A(Rt=5.25min),收率为3.34%(白色固体)和275B(Rt=5.53min),收率为13.5%(白色固体)。275A:^{1}H NMR(400MHz,DMSO-d6)δ6.91(d,J=8.2Hz,2H),6.47(d,J=8.4Hz,2H),5.12(d,J=8.0Hz,1H),4.67(s,1H),3.19(s,1H),2.21(dt,J=11.0,5.4Hz,1H),2.00(q,J=7.0,6.3Hz,1H),1.79(s,2H),1.63(d,J=10.6Hz,2H),1.50(dd,J=12.9,9.3Hz,4H),1.42(d,J=14.0Hz,3H),1.33-1.26(m,5H),0.94(s,3H),0.92(s,3H),0.85(t,J=6.7Hz,1H)。质谱(m/z):331.5[M+H]$^+$。275B:^{1}H NMR(400MHz,DMSO-d6)δ6.91(d,J=7.9Hz,2H),6.46(d,J=8.1Hz,2H),5.07(s,1H),4.58(s,1H),3.11(s,2H),3.03(s,1H),2.20(s,1H),2.01(s,2H),1.69(s,3H),1.51(s,6H),1.35(s,3H),0.94(s,3H),0.92(s,3H),0.85(s,1H)。质谱(m/z):331.5[M+H]$^+$。

[1647] 化合物276

[1648] N^2-(4-(叔丁基)苯基)螺[3.3]庚烷-2,6-二胺

[1649] 

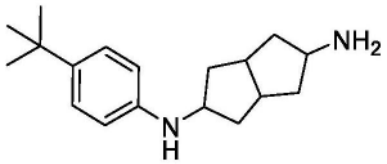
276

[1650] 由4-(叔丁基)苯胺(75mg,0.50mmol),(6-氧代螺[3.3]庚烷-2-基)氨基甲酸叔丁酯(170mg,0.75mmol)和根据为20的程序制备标题化合物276(45.2mg),收率为34.8%(白色粉末),经^{1}HNMR证明为1:1的混合物。^{1}H NMR(400MHz,DMSO-d6)δ8.11(s,2H),7.11-7.00(m,2H),6.45-6.35(m,2H),5.59(s,1H),3.66(t,J=7.6Hz,1H),3.54(s,1H),2.43-2.29(m,

2H),2.22-2.06(m,3H),1.82(td,J=11.1,7.7Hz,2H),1.23(s,1H),1.19(s,9H)。质谱(m/z):259.2[M+H]$^+$。

[1651] 化合物277

[1652] N^2-(4-(叔丁基)苯基)八氢戊搭烯-2,5-二胺

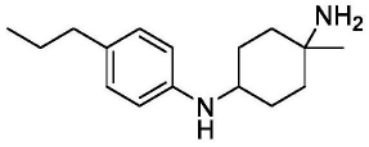
[1653] 

277

[1654] 由4-(叔丁基)苯胺(100mg,0.67mmol),(3as,6as)-四氢戊搭烯-2,5(1H,3H)-二酮(278mg,2.0mmol)和$NaBH(OAc)_3$(284mg,1.34mmol),根据为20的程序制备标题化合物277(24.0mg),四步总收率为13.1%(白色固体),经^{1}HNMR证明为1:1的混合物,。^{1}H NMR(400MHz,DMSO-d6)δ8.06(d,J=18.4Hz,3H),7.07(d,J=8.1Hz,2H),6.53(s,2H),5.42(s,1H),3.66(d,J=6.6Hz,1H),3.51(s,1H),2.36(q,J=8.2,7.5Hz,1H),2.29-2.14(m,3H),1.74(dd,J=12.8,7.1Hz,1H),1.46-1.33(m,2H),1.19(s,9H)。质谱(m/z):273.1[M+H]$^+$。

[1655] 化合物278

[1656] 1-甲基-N^4-(4-丙基苯基)环己烷-1,4-二胺

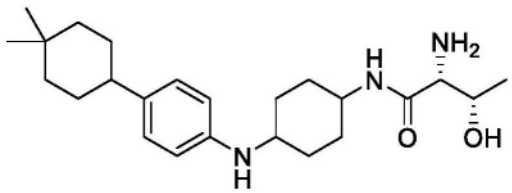
[1657] 

278

[1658] 由4-丙基苯胺(50mg,0.37mmol),(1-甲基-4-氧代环己基)氨基甲酸叔丁酯(100mg,0.44mmol)和根据为20的程序制备标题化合物278(60.6mg),收率为66.5%(白色粉末),经^{1}HNMR证明为1:1的混合物,。^{1}H NMR(400MHz,DMSO-d6)δ8.06(d,J=26.1Hz,3H),6.87(d,J=7.9Hz,2H),6.51(d,J=8.3Hz,2H),5.12(d,J=50.3Hz,1H),3.12(s,1H),2.37(t,J=7.5Hz,2H),1.88(td,J=11.0,9.5,5.7Hz,2H),1.82-1.70(m,2H),1.65(td,J=12.6,3.5Hz,1H),1.55(d,J=9.9Hz,2H),1.49(q,J=7.4Hz,2H),1.27(d,J=7.5Hz,4H),0.85(t,J=7.3Hz,3H)。质谱(m/z):247.3[M+H]$^+$。

[1659] 化合物279

[1660] (2R,3S)-2-氨基-N-(4-((4-(4,4-二甲基环己基)苯基)氨基)环己基)-3-羟基丁酰胺

[1661] 

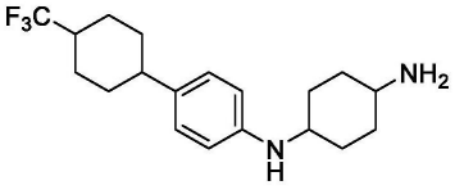
279

[1662] 由N^1-(4-(4,4-二甲基环己基)苯基)环己烷-1,4-二胺(100mg,0.33mmol),(叔丁氧基羰基)-D-苏氨酸(109mg,0.50mmol),根据为1的程序制备标题化合物279(9.1mg),收率

为36.37％(白色粉末),经^{1}HNMR证明为1:1的混合物。^{1}H NMR(400MHz,DMSO-d6)δ8.26(s,3H),6.94(s,2H),6.60(s,2H),4.07(s,2H),2.75(s,1H),2.61(s,2H),2.28(s,3H),1.96(s,1H),1.83(s,2H),1.77-1.35(m,8H),1.20(d,J＝26.6Hz,4H),1.02(d,J＝11.7Hz,1H),0.88(s,3H),0.86(s,3H)。质谱(m/z):402.3[M+H]$^+$。

[1663] 化合物280

[1664] N^1-(4-(4-(三氟甲基)环己基)苯基)环己烷-1,4-二胺

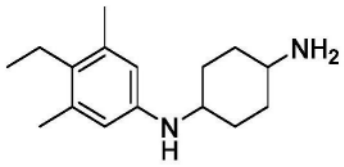
[1665] 

280

[1666] 由(4-((4-(4-(三氟甲基)环己基)苯基)氨基)环己基)氨基甲酸叔丁酯(75mg,0.17mmol),TFA(1mL),和DCM(10mL),根据为24的程序制备标题化合物280(53.4mg),总收率为91.4％(白色固体),经^{1}H NMR证实为1:2的混合物。^{1}H NMR(400MHz,DMSO-d6)δ7.00-6.87(m,2H),6.63-6.43(m,2H),5.29(d,J＝26.8Hz,1H),3.00(d,J＝55.2Hz,2H),2.59(s,1H),2.44(t,J＝6.8Hz,1H),2.06-1.90(m,3H),1.73(dq,J＝23.2,13.6,9.6Hz,10H),1.51-1.35(m,2H),1.20-1.10(m,1H)。质谱(m/z):341.3[M+H]$^+$。

[1667] 化合物281

[1668] N^1-(4-乙基-3,5-二甲基苯基)环己烷-1,4-二胺

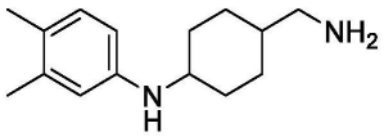
[1669] 

281

[1670] 由(4-((4-乙基-3,5-二甲基苯基)氨基)环己基)氨基甲酸叔丁酯(103mg,0.298mmol),TFA(1mL),和DCM(10mL),根据为24的程序制备标题化合物281(66.8mg),总收率为91.2％(黄色固体),经^{1}H NMR证实为1:2的混合物。^{1}H NMR(400MHz,DMSO-d6)δ6.24(d,J＝16.8Hz,2H),3.13-2.88(m,2H),2.44(q,J＝7.6Hz,2H),2.15(s,6H),2.12(d,J＝1.8Hz,1H),1.98(d,J＝11.2Hz,2H),1.76(d,J＝14.8Hz,3H),1.63-1.53(m,1H),1.49(dd,J＝12.8,9.2Hz,1H),0.98(t,J＝7.2Hz,3H)。质谱(m/z):247.3[M+H]$^+$。

[1671] 化合物282

[1672] N-(4-(氨基甲基)环己基)-3,4-二甲基苯胺

[1673] 

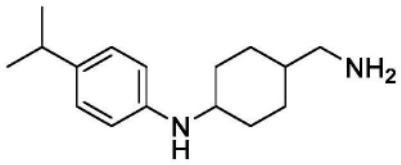
282

[1674] 由((4-((3,4-二甲基苯基)氨基)环己基)甲基)氨基甲酸叔丁酯(98mg,0.295mmol),TFA(1mL),和DCM(10mL),根据为24的程序制备标题化合物282(64.1mg),总收率为93.4％(黄色固体),经^{1}H NMR证实为1:2的混合物。^{1}H NMR(400MHz,DMSO-d6)δ6.79(dd,

J＝8.4,2.8Hz,1H),6.50-6.24(m,2H),5.05(dd,J＝30.4,8.0Hz,1H),3.48-2.99(m,1H),2.64(dd,J＝23.6,6.8Hz,2H),2.09(d,J＝2.0Hz,3H),2.04(s,3H),2.00-1.92(m,1H),1.83(dd,J＝8.8,4.8Hz,1H),1.70(d,J＝9.6Hz,1H),1.64-1.58(m,1H),1.49(pd,J＝14.0,10.8,4.0Hz,4H)。质谱(m/z):233.3[M+H]$^+$。

[1675] 化合物283

[1676] N-(4-(氨基甲基)环己基)-4-异丙基苯胺

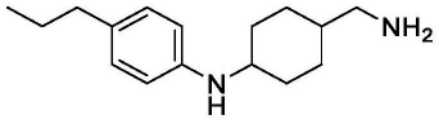
[1677] 

283

[1678] 由((4-((4-异丙基苯基)氨基)环己基)甲基)氨基甲酸叔丁酯(105mg,0.303mmol),TFA(1mL),和DCM(10mL),根据为24的程序制备标题化合物283(52.7mg),总收率为70.2％(黄色固体),经^{1}H NMR证实为1:2的混合物。^{1}H NMR(400MHz,DMSO-d6)δ7.02-6.88(m,2H),6.60(d,J＝9.7Hz,2H),3.51-3.04(m,2H),2.75-2.59(m,3H),2.03-1.42(m,8H),1.13(d,J＝6.8Hz,6H)。质谱(m/z):247.3[M+H]$^+$。

[1679] 化合物284

[1680] N-(4-(氨基甲基)环己基)-4-异丙基苯胺

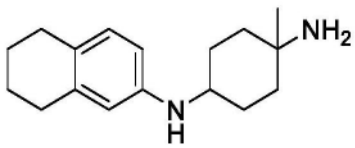
[1681] 

284

[1682] 由((4-((4-丙基苯基)氨基)环己基)甲基)氨基甲酸叔丁酯(85mg,0.246mmol),TFA(1mL),和DCM(10mL),根据为24的程序制备标题化合物284(20.7mg),总收率为40.9％(黄色固体),经^{1}H NMR证实为1:2的混合物。^{1}H NMR(400MHz,DMSO-d6)δ6.86(dd,J＝8.4,2.8Hz,2H),6.50(dd,J＝27.6,8.0Hz,2H),5.19(dd,J＝26.4,8.0Hz,1H),3.43(s,1H),3.07(s,1H),2.66(dd,J＝22.0,6.8Hz,2H),2.36(t,J＝7.6Hz,2H),2.02-1.77(m,2H),1.53(tdt,J＝25.2,15.6,8.8Hz,8H),0.86(t,J＝7.2Hz,3H)。质谱(m/z):247.3[M+H]$^+$。

[1683] 化合物285

[1684] 1-甲基-N^4-(5,6,7,8-四氢萘-2-基)环己烷-1,4-二胺

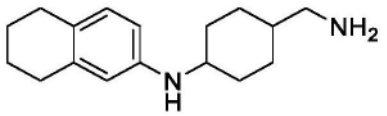
[1685] 

285

[1686] 由(1-甲基-4-((5,6,7,8-四氢萘-2-基)氨基)环己基)氨基甲酸叔丁酯(101mg,0.282mmol),TFA(1mL),和DCM(10mL),根据为24的程序制备标题化合物285(66.8mg),总收率为91％(白色固体),经^{1}H NMR证实为1:2的混合物。^{1}H NMR(400MHz,DMSO-d6)δ6.74(dd,J＝8.4,3.2Hz,1H),6.47-6.22(m,2H),3.31-3.04(m,1H),2.62-2.53(m,4H),2.00-1.83(m,2H),1.81-1.46(m,10H),1.30(d,J＝7.2Hz,3H)。质谱(m/z):259.3[M+H]$^+$。

[1687] 化合物286

[1688] N-(4-(氨基甲基)环己基)-5,6,7,8-四氢萘-2-胺

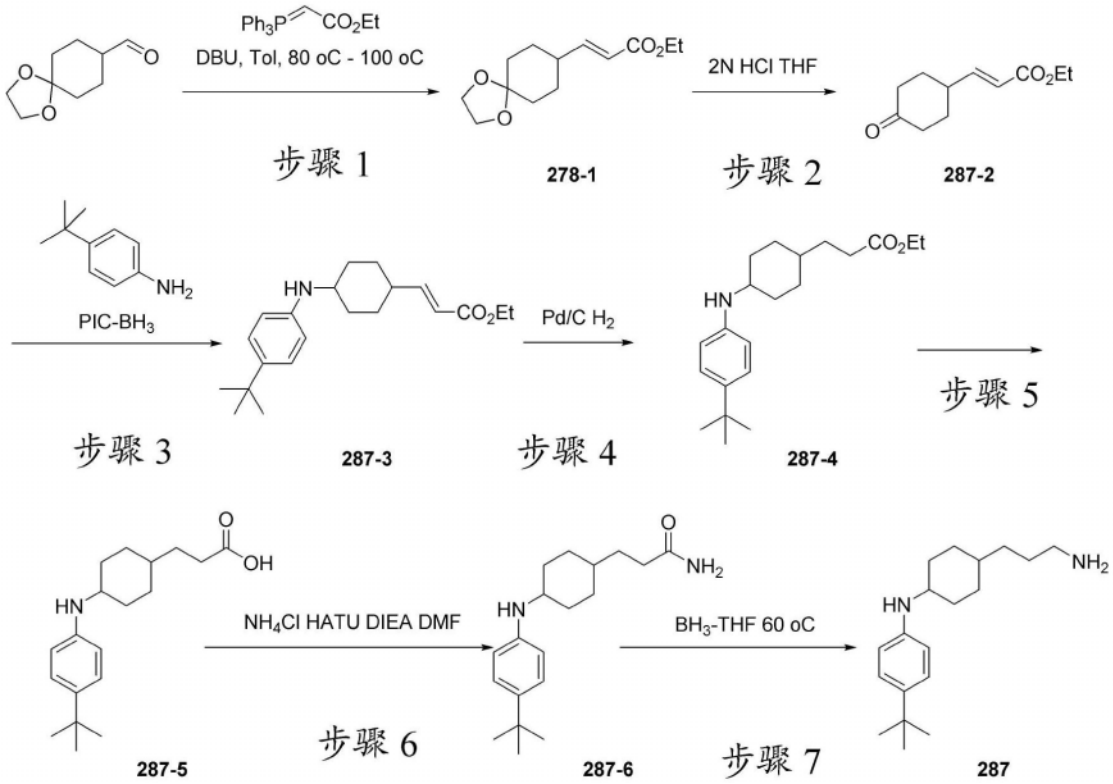
[1689] 

286

[1690] 由((4-((5,6,7,8-四氢萘-2-基)氨基)环己基)甲基)氨基甲酸叔丁酯(93mg,0.26mmol),TFA(1mL),和DCM(10mL),根据为24的程序制备标题化合物286(33.5mg),总收率为50%(黄色固体),经^{1}H NMR证实为1:2的混合物。^{1}H NMR(400MHz,DMSO-d6)δ6.72(dd,J=8.4,3.2Hz,1H),6.45-6.14(m,2H),5.03(dd,J=27.2,8.4Hz,1H),3.51-2.98(m,1H),2.64(d,J=6.8Hz,1H),2.61-2.51(m,5H),1.97(d,J=9.6Hz,1H),1.80(dd,J=13.2,8.0Hz,1H),1.66(p,J=2.8Hz,5H),1.56-1.35(m,4H),1.04(q,J=11.2Hz,1H)。质谱(m/z):259.3[M+H]$^+$。

[1691] 化合物287

[1692] N-(4-(3-氨基丙基)环己基)-4-(叔丁基)苯胺

[1693] 

[1694] 步骤1:制备(E)-3-(1,4-二氧杂螺[4.5]癸烷-8-基)丙烯酸乙酯(287-1)

[1695] 在100℃在氮气气氛下将1,4-二氧杂螺[4.5]癸烷-8-甲醛(1g,5.8mmol),DBU(1.07g,7.1mmol)和2-(三苯基-15-亚膦基(phosphaneylidene)乙酸乙酯(3g,8.8mmol)/甲苯(20mL)的溶液搅拌18小时。将固体过滤并且将溶剂真空除去。残余物的提纯方法为:硅胶柱而得到1g的287-1(收率:71.5%)(黄色固体)。质谱(m/z):241.2[M+H]$^+$。

[1696] 步骤2:制备(E)-3-(4-氧代环己基)丙烯酸乙酯(287-2)

[1697] 287-1(1g,4.1mmol)和HCl/THF(20mL,2N)被置于烧杯中,并且在25℃搅拌18小时。将过量的THF真空除去并且残余物的提纯方法为:硅胶柱而得到500mg的287-2(收率:

61.9%)(黄色油)。质谱(m/z):197.2[M+H]$^+$。

[1698] 步骤3:制备(E)-3-(4-((4-(叔丁基)苯基)氨基)环己基)丙烯酸乙酯(287-3)

[1699] 向287-2(200mg,1mmol),4-(叔丁基)苯胺(150mg,1mmol)和$NaBH_3CN$(120mg,2mmol)/MeOH(10mL)的溶液中。在室温搅拌反应18小时。将固体过滤并且将溶剂真空除去。残余物的提纯方法为:硅胶柱而得到220mg的287-3(收率:66.7%)(黄色固体)。质谱(m/z):330.3[M+H]$^+$。

[1700] 步骤4:制备3-(4-((4-(叔丁基)苯基)氨基)环己基)丙酸乙酯(287-4)

[1701] 在25℃在氢气气氛下将287-3(220mg,0.67mmol),Pd/C(20mg)/MeOH(10mL)的溶液搅拌18小时。将固体过滤并且将溶剂真空除去。残余物的提纯方法为:硅胶柱而得到150mg的287-4(收率:67.4%)(黄色固体)。质谱(m/z):332.3[M+H]$^+$。

[1702] 步骤5:制备3-(4-((4-(叔丁基)苯基)氨基)环己基)丙酸(287-5)

[1703] 向287-4(150mg,0.45mmol)/H_2O(5mL)和THF(5mL)的溶液中添加NaOH(90mg,2.25mmol)。在25℃搅拌混合物过夜。将乙酸乙酯添加到反应混合物并且将混合物通过Celite过滤。用水和饱和盐水洗涤滤液。有机层用硫酸镁干燥并且减压浓缩。残余物的提纯方法为:硅胶柱而得到100mg的287-5(收率:73.1%)(黄色油)。质谱(m/z):304.2[M+H]$^+$。

[1704] 步骤6:制备3-(4-((4-(叔丁基)苯基)氨基)环己基)丙烯酰胺(287-6)

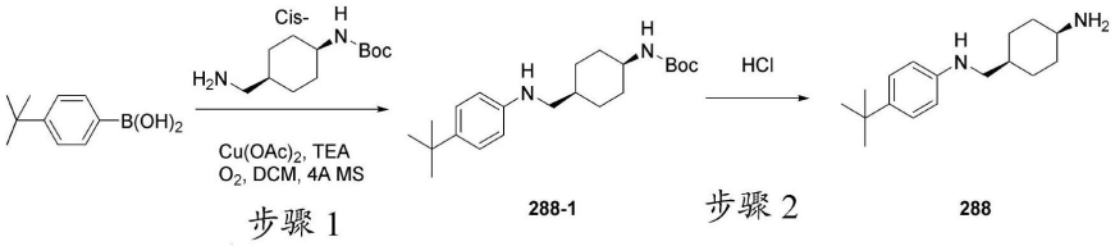
[1705] 在室温将287-5(150mg,0.5mmol),NH_4Cl(80mg,1.5mmol),HATU(281mg,0.75mmol)和DIEA(191mg,1.5mmol)/DMF(10mL)的溶液搅拌18小时。将固体过滤并且将溶剂真空除去。残余物的提纯方法为:硅胶柱而得到200mg的287-6(收率:90.1%)(黄色固体)。质谱(m/z):302.9[M+H]$^+$。

[1706] 步骤7:制备N-(4-(3-氨基丙基)环己基)-4-(叔丁基)苯胺(287)

[1707] 在70℃将287-6(60mg,0.2mmol),BH_3-THF(10mL)/THF(5mL)的溶液搅拌18小时。将固体过滤并且将溶剂真空除去。残余物的提纯方法为:prep-HPLC(柱-Xbridge-C18 150x19mm,5um;移动相:ACN-H_2O(0.1%FA),25%-40%)而得到287(7.0mg)(白色固体)。^{1}H NMR(400MHz,CD_3OD)δ7.14(d,J=8.6Hz,2H),6.62(d,J=8.6Hz,2H),3.49-3.43(m,1H),2.64(t,J=7.4Hz,2H),1.79-1.61(m,4H),1.58-1.47(m,4H),1.40(s,3H),1.31(m,2H),1.25(s,9H)。质谱(m/z):289.0[M+H]$^+$。

[1708] 化合物288

[1709] N-(((1s,4s)-4-氨基环己基)甲基)-4-(叔丁基)苯胺

[1710] 

[1711] 步骤1:制备((1s,4s)-4-(((4-(叔丁基)苯基)氨基)甲基)环己基)氨基甲酸叔丁酯(288-1)

[1712] 向100mL的圆底烧瓶中装入((1s,4s)-4-(氨基甲基)环己基)氨基甲酸叔丁酯(155mg,0.67mmol,1.1eq),(4-(叔丁基)苯基)硼酸(100mg,0.56mmol,1.00eq),Cu(OAc)2

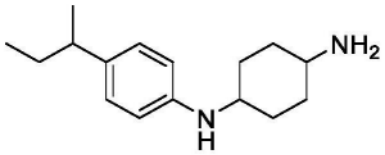
(204mg,1.1mmol,and2.00 eq)和TEA(284mg,2.8mmol,5.00eq)和4 Å MS(1g),。在室温在氧气气氛下搅拌反应18小时。将固体过滤并且将溶剂真空除去。残余物的提纯方法为:快速色谱而得到288-1(0.1g,49.2%收率)(黄色固体)。MS(m/z)361.3[M+H]$^+$。

[1713] 步骤2:制备N-(((1s,4s)-4-氨基环已基)甲基)-4-(叔丁基)苯胺(288)

[1714] 288-1(100mg,0.28mmol)和HCl/1,4-二氧杂环已烷(10mL,4N)被置于烧杯中,在25℃搅拌16小时。过量的1,4-二氧杂环已烷被真空蒸馏掉并且残余物的提纯方法为:快速色谱而得到288(59.1mg82.0%)(白色固体)。^{1}H NMR(400MHz,CD_3OD)δ7.55-7.52(m,2H),7.30-7.26(m,2H),3.35-3.30(m,3H),1.97(dd,J=7.1,3.6Hz,1H),1.85-1.71(m,6H),1.65-1.57(m,2H),1.31(s,9H)。MS(m/z)261.2[M+H]$^+$。

[1715] 化合物289

[1716] 1-N-(4-(仲丁基)苯基)环已烷-1,4-二胺

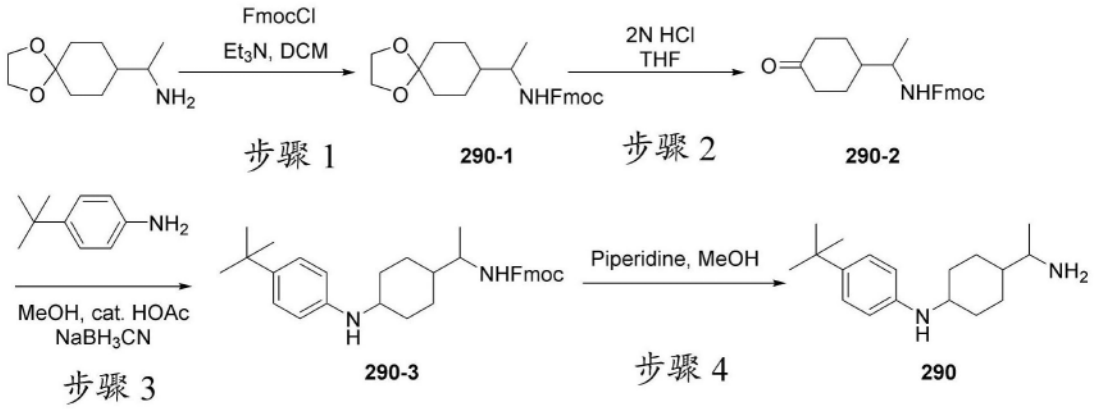
[1717] 

289A
289B

[1718] 由(4-((4-(仲丁基)苯基)氨基)环已基)氨基甲酸叔丁酯(100mg,0.28mmol),1,4-二氧杂环已烷(5mL)和HCl/1,4-二氧杂环已烷(10mL),根据为37的程序制备标题化合物289A(64.1mg)(白色固体)和289B(51.4mg)(白色固体)。289A:^{1}H NMR(400MHz,CD_3OD)δ6.93(d,J=8.4Hz,2H),6.61(d,J=8.6Hz,2H),3.22-3.11(m,1H),2.70-2.60(m,1H),2.43(dd,J=14.2,7.0Hz,1H),2.06(d,J=11.8Hz,2H),1.91(d,J=11.8Hz,2H),1.59-1.47(m,2H),1.31-1.21(m,3H),1.16(d,J=7.0Hz,4H),0.78(t,J=7.4Hz,3H)。质谱(m/z):247.2[M+H]$^+$。HPLC:Rt=3.770min(柱:XBRIDGE 3.5um,2.1*50mm,移动相:H_2O(0.05%TFA)-ACN(0.05%TFA),ACN从0至60%在7分钟内,7-8min,ACN由60%至100%,流速:0.8mL/min)。289B:^{1}H NMR(400MHz,CD_3OD)δ6.93(d,J=8.4Hz,2H),6.63(d,J=8.6Hz,2H),3.44(s,1H),2.83(d,J=8.2Hz,1H),2.46-2.41(m,1H),1.77-1.49(m,10H),1.17(d,J=6.8Hz,3H),0.79(t,J=7.4Hz,3H)。质谱(m/z):247.2[M+H]$^+$。HPLC:Rt=3.962min(柱:XBRIDGE 3.5um,2.1*50mm,移动相:H_2O(0.05%TFA)-ACN(0.05%TFA),ACN从0至60%在7分钟内,7-8min,ACN由60%至100%,流速:0.8mL/min)。

[1719] 化合物290

[1720] N-(4-(1-氨基乙基)环已基)-4-(叔丁基)苯胺

[1721] 

[1722] piperidine:哌啶

[1723] 步骤1:制备(9H-芴-9-基)甲基(1-(1,4-二氧杂螺[4.5]癸烷-8-基)乙基)氨基甲酸叔丁酯(290-1)

[1724] 向1-(1,4-二氧杂螺[4.5]癸烷-8-基)乙-1-胺(0.5g,2.7mmol)/DCM(10mL)的溶液中添加DIEA(697mg,5.4mmol)和FmocCl(600mg,2.7mmol)。然后在25℃搅拌混合物2小时。LCMS显示反应完成。将混合物添加到H_2O,用EA(20mL*3)萃取。将合并的有机层用盐水(40mL)洗涤,用硫酸钠干燥,过滤并浓缩。残余物的提纯方法为:使用EA/PE(1:1)的combi-flash(闪式色谱)而得到290-1(0.5g,45.4%收率)(黄色油)。MS(m/z)407.8$[M+H]^+$。

[1725] 步骤2:制备(9H-芴-9-基)甲基(1-(4-氧代环己基)乙基)氨基甲酸叔丁酯(290-2)

[1726] 在25℃向290-1(0.25g,0.61mmol)/THF(4mL)的溶液中添加2NHCl(4mL)。然后在25℃搅拌混合物10小时。LCMS显示反应完成。将反应浓缩。残余物的提纯方法为:使用EA/PE(1:2)的combi-flash(闪式色谱)而得到290-2(0.17g,76.2%收率)(黄色油)。MS(m/z)364.2$[M+H]^+$。

[1727] 步骤3:制备(9H-芴-9-基)甲基(1-(4-((4-(叔丁基)苯基)氨基)环己基)乙基)氨基甲酸叔丁酯(290-3)

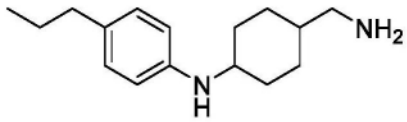
[1728] 向290-2(100mg,0.27mmol)/MeOH(5mL)和一滴AcOH的溶液中添加4-(叔丁基)苯胺(41mg,0.27mmol)并且在50℃搅拌混合物1小时。然后在冷却到25℃后将混合物加到$NaBH_3CN$(51mg,0.81mmol)。然后在25℃搅拌混合物2小时。LCMS显示反应完成。将反应用水(10mL)淬灭,用EA(10mL*3)萃取。将合并的有机层用盐水(20mL)洗涤,用硫酸钠干燥,过滤并浓缩。残余物的提纯方法为:使用EA/PE(1:2)的combi-flash(闪式色谱)而得到290-3(0.1g,73.5%收率)(黄色固体)。MS(m/z)496.8$[M+H]^+$。

[1729] 步骤4:制备N-(4-(1-氨基乙基)环己基)-4-(叔丁基)苯胺(290)

[1730] 在25℃向290-3(0.1g,0.20mmol)/MeOH(2mL)的溶液中添加哌啶(2mL)。然后在25℃搅拌混合物4小时。LCMS显示反应完成。将反应浓缩。残余物的提纯方法为:prep-HPLC而得到290(10mg,13%收率)(黄色固体)。^1H NMR(300MHz,CD_3OD)δ7.63(d,J=7.2Hz,2H),7.46-7.36(m,2H),3.53-3.38(m,1H),3.20-3.10(m,1H),2.10(d,J=11.2Hz,1H),2.00-1.42(m,8H),1.35(s,9H),1.27-1.22(m,3H).MS(m/z)275.3$[M+H]^+$。

[1731] 化合物291

[1732] N-(4-(氨基甲基)环己基)-4-丙基苯胺

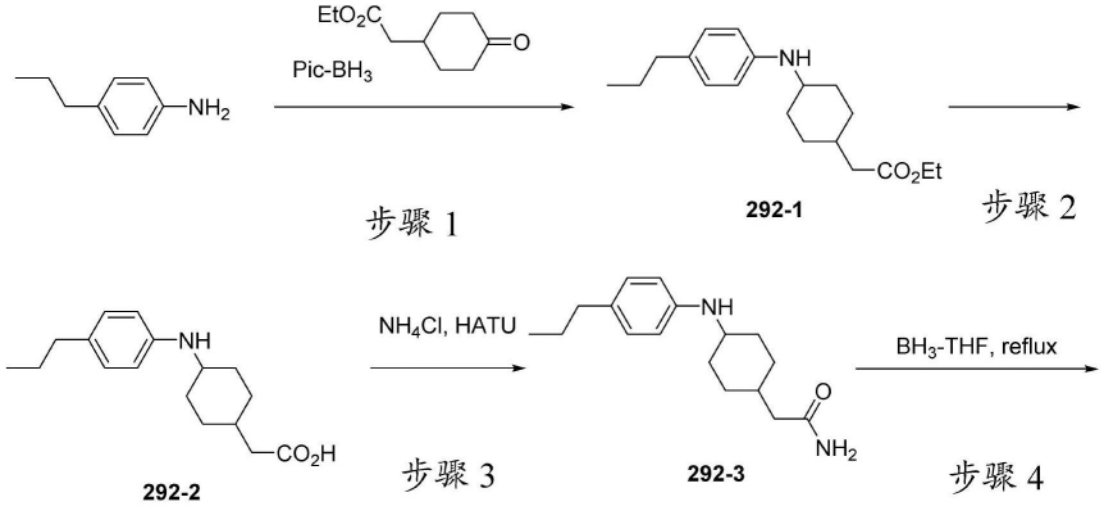
[1733] 

291

[1734] 由((4-((4-丙基苯基)氨基)环己基)甲基)氨基甲酸叔丁酯(150mg,0.43mmol),1,4-二氧杂环己烷(10mL)和1,4-二氧杂环己烷/HCl(10mL),根据为224的程序制备标题化合物291(30.6mg,28.8%)(白色固体)。^{1}H NMR(400MHz,DMSO-d6)δ6.86(d,J=7.6Hz,2H),6.46(d,J=7.7Hz,2H),5.13(br,1H),3.07(br,1H),2.63(br,2H),2.36(t,J=7.2Hz,2H),1.97(br,2H),1.81(br,2H),1.50-1.45(m,3H),1.10-0.95(m,4H),0.85(t,J=7.0Hz,3H)。质谱(m/z):247.3[M+H]$^+$。

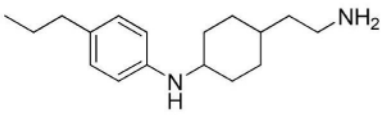
[1735] 化合物292

[1736] N-(4-(2-氨基乙基)环己基)-4-丙基苯胺

[1737] 

292-1 292-2 292-3

步骤 1 步骤 2 步骤 3 步骤 4



292

[1738] reflux:回流

[1739] 步骤1:制备2-(4-((4-丙基苯基)氨基)环己基乙酸乙酯(292-1)

[1740] 在室温搅拌4-丙基苯胺(500mg,3.7mmol),2-(4-氧代环己基乙酸乙酯(681mg,3.7mmol)和Pic-BH_3(474mg,4.44mmol)/H_2O(9mL)和HOAc(1mL)的溶液18小时。将固体过滤并且将溶剂真空除去。残余物的提纯方法为:硅胶柱而得到600mg的292-1(收率:53.3%)(黄色固体)。质谱(m/z):304.3[M+H]$^+$。

[1741] 步骤2:制备2-(4-((4-丙基苯基)氨基)环己基)乙酸(292-2)

[1742] 向292-1(600mg,2mmol)/H_2O(5mL)和THF(5mL)的溶液中添加LiOH(780mg,20mmol)。在25℃搅拌混合物过夜。将乙酸乙酯添加到反应混合物并且将混合物通过Celite过滤。用水和饱和盐水洗涤滤液。有机层用硫酸镁干燥并且减压浓缩。残余物的提纯方法

为:硅胶柱而得到200mg的292-2(收率:36.2%)(黄色油)。质谱(m/z):276.2[M+H]$^+$。

[1743] 步骤3:制备2-(4-((4-丙基苯基)氨基)环己基)乙酰胺(292-3)

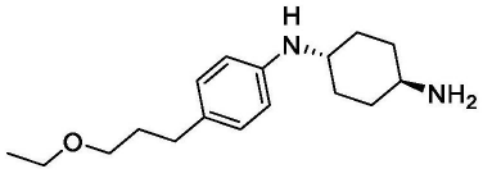
[1744] 在室温搅拌292-2(300mg,1.1mmol),NH_4Cl(70mg,1.3mmol),HATU(621mg,1.6mmol)和DIEA(281mg,2.2mmol)/DMF(10mL)的溶液18小时。将固体过滤并且将溶剂真空除去。残余物的提纯方法为:硅胶柱而得到200mg的292-3(收率:66.1%)(黄色固体)。质谱(m/z):275.2[M+H]$^+$。

[1745] 步骤4:制备N-(4-(2-氨基乙基)环己基)-4-丙基苯胺(292)

[1746] 在70℃搅拌292-3(200mg,0.73mmol),BH_3-THF(10mL)/THF(5mL)的溶液18小时。将固体过滤并且将溶剂真空除去。残余物的提纯方法为:prep-HPLC(柱-Xbridge-C18 150x 19mm,5um;移动相:ACN-H_2O(0.1%FA),25%-40%)而得到292(13.4mg)(白色固体)。质谱(m/z):261.3[M+H]$^+$。^{1}H NMR(400MHz,DMSO-d6)δ6.81(d,J=8.4Hz,2H),6.42(d,J=8.4Hz,2H),3.09-2.97(m,1H),2.80-2.68(m,2H),2.36-2.28(m,2H),1.92(d,J=11.6Hz,2H),1.68(d,J=12.0Hz,2H),1.51-1.36(m,4H),1.34-1.20(m,1H),1.11-0.89(m,4H),0.81(t,J=7.4Hz,3H)。

[1747] 化合物293

[1748] (1r,4r)-N^1-(4-(3-乙氧基丙基)苯基)环己烷-1,4-二胺

[1749] 

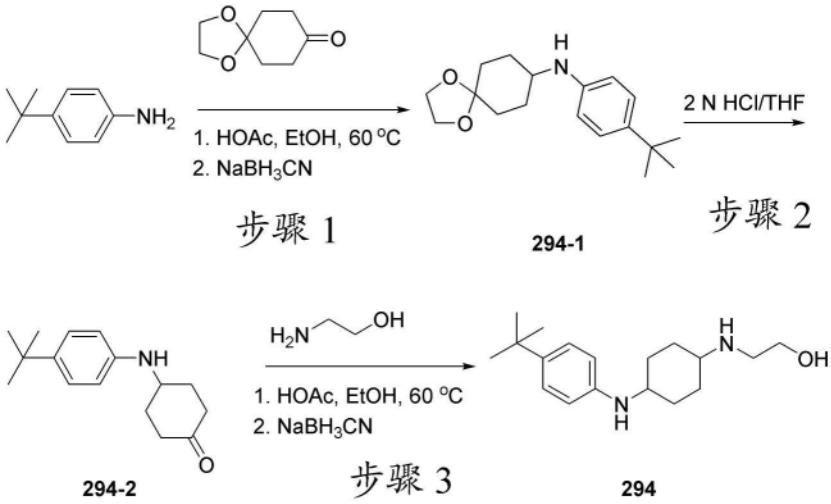
293

[1750] 在25℃搅拌((1r,4r)-4-((4-(3-乙氧基丙基)苯基)氨基)环己基)氨基甲酸叔丁酯(300mg,0.79mmol)/1,4-二氧杂环己烷(10mL)和1,4-二氧杂环己烷/HCl(10mL)的混合物16小时。在反应完成后,真空除去溶剂,并且残余物的提纯方法为:prep-HPLC(柱-Xbridge-C18 150x 21.2mm,5um;移动相:ACN-H_2O(0.1%FA),2%-10%)而得到期望的产物(白色固体)。(30.5mg,13.7%)。^{1}H NMR(400MHz,DMSO-d6)δ6.87(d,J=8.2Hz,2H),6.48(d,J=8.3Hz,2H),3.41-3.35(m,2H),3.31(t,J=6.5Hz,2H),3.08(br,1H),2.90(br,1H),2.45-2.41(m,2H),2.02-1.91(m,4H),1.73-1.64(m,2H),1.42-1.36(m,2H),1.24-1.12(m,2H),1.09(d,J=7.0Hz,3H)。质谱(m/z):277.3[M+H]$^+$。

[1751] 化合物294

[1752] 2-((4-((4-(叔丁基)苯基)氨基)环己基)氨基)乙-1-醇

[1753]



[1754] 步骤1:制备N-(4-(叔丁基)苯基)-1,4-二氧杂螺[4.5]癸烷-8-胺(294-1)

[1755] 向4-(叔丁基)苯胺(1g,6.71mmol)/MeOH(10mL)的溶液中添加1,4-二氧杂螺[4.5]癸烷-8-酮(1.04g,6.71mmol)并且在60℃搅拌混合物1小时。然后氰基硼氢化钠(1.27g,20.13mmol)被添加到混合物。在室温搅拌反应3小时。用水(50mL)淬灭,将反应用EA(10mL)萃取三次。有机相用硫酸钠干燥,真空除去并且残余物的提纯方法为:快速色谱而得到期望的产物(1.6g,82.6%)(白色固体)。质谱(m/z):289.9$[M+H]^+$。

[1756] 步骤2:制备4-((4-(叔丁基)苯基)氨基)环己烷-1-酮(294-2)

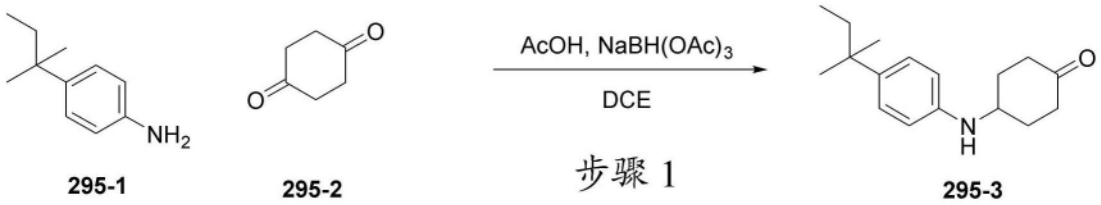
[1757] 向N-(4-(叔丁基)苯基)-1,4-二氧杂螺[4.5]癸烷-8-胺(1.6g,5.54mmol)/THF(5mL)的溶液中添加HCl/THF(2N,5mL)和搅拌混合物2小时。用$NaHCO_3$(10mL)淬灭,将反应用EA(10mL)萃取三次。有机相用硫酸钠干燥,真空除去,获得产物(0.9g,66.2%)(白色固体)。质谱(m/z):246.2$[M+H]^+$。

[1758] 步骤3:制备2-((4-((4-(叔丁基)苯基)氨基)环己基)氨基)乙-1-醇(294)

[1759] 向4-((4-(叔丁基)苯基)氨基)环己烷-1-酮(100mg,0.41mmol)/MeOH(5mL)的溶液中添加2-氨基乙-1-醇(25mg,0.41mmol)和乙酸(2.46mg,0.041mmol)。然后在60℃搅拌混合物1小时。在将反应冷却到室温后,添加氰基硼氢化钠(77.49mg,12.3mmol)。在室温搅拌反应3小时。用水(10mL)淬灭,将反应用EA(10mL)萃取三次。有机相用硫酸钠干燥,真空除去并且残余物的提纯方法为:prep-HPLC(柱-Xbridge-C18 150x 21.2mm,5um;移动相:ACN-H_2O(0.1%FA),40%-60%)而得到期望的产物(混合物;113mg,95%)(黄色固体)。^1H NMR(400MHz,DMSO-d6)δ7.06(d,J=8.8Hz,2H),6.49(dd,J=13.6Hz,8.4Hz,2H),5.13(s,1H),3.49(s,3H),3.20(m,1H),2.67(m,2H),2.51(s,1H),1.95(t,J=14.0Hz,2H),1.69-1.49(m,3H),1.20(s,12H)。质谱(m/z):290.9$[M+H]^+$。HPLC:Rt:3.505min,3.849min(柱:XBRIDGE 2.1*50mm,3.5um;移动相:H_2O(0.05%TFA)/ACN(0.05%TFA),ACN由0%至60%7分钟内,7-8min,ACN由60%至100%;0.8mL/min)。

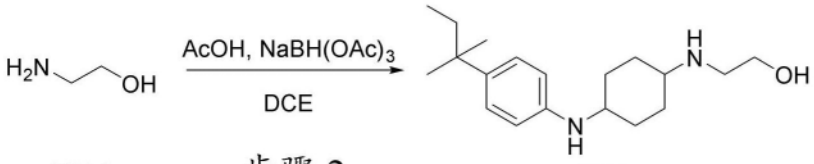
[1760] 化合物295

[1761] 2-((4-((4-(叔戊基)苯基)氨基)环己基)氨基)乙-1-醇



295-1 295-2 295-3

[1762]



295-4 295A 295B

[1763] 步骤1:制备4-((4-(叔戊基)苯基)氨基)环己烷-1-酮(295-3)

[1764] 由4-(叔戊基)苯胺(26mg,0.1mmol)和环己烷-1,4-二酮(66mg,0.6mmol),根据为化合物4的程序制备化合物295-3(99mg),总收率为77%(白色固体)。质谱(m/z):260.2[M+H]$^+$。

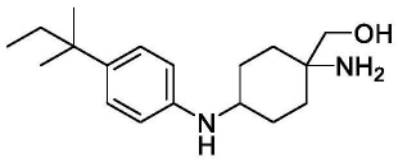
[1765] 步骤2:制备2-((4-((4-(叔戊基)苯基)氨基)环己基)氨基)乙-1-醇(295)

[1766] 在室温将4-((4-(叔戊基)苯基)氨基)环己烷-1-酮(26mg,0.1mmol),2-氨基乙-1-醇(4.4mg,0.12mmol)和乙酸(0.06mL,0.1mmol)/DCE(5mL)的混合物搅拌1小时。其后添加三乙酰氧基硼氢化钠(42mg,0.2mmol)并且搅拌混合物过夜。向该混合物中添加饱和$NaHCO_3$水溶液并且将混合物用乙酸乙酯萃取。将合并的有机层用硫酸镁干燥并蒸发。混合物的提纯方法:制备HPLC(柱:X Select-CSH-Prep 5μm OBD,19*150mm;ACN/水(0.5%TFA)=5%-40%-95%-95%-5%,0min-10min-10.5min-11.5min-13min)而得到化合物295A(Rt=6.58min)(白色固体)和化合物295B(Rt=7.83min)(白色固体)。295A(7.1mg,24%):^{1}H NMR(400MHz,DMSO-d6)δ8.79(s,1H),7.03(d,J=8.4Hz,2H),6.55(d,J=8.4Hz,2H),5.29(s,1H),5.18(s,1H),3.68(m,2H),3.45(m,1H),3.09(m,1H),2.99(m,2H),1.90-1.75(m,6H),1.63-1.48(m,4H),1.16(s,6H),0.60(t,J=7.2Hz,3H)。质谱(m/z):305.1[M+H]$^+$。295B(10.2mg,34%):^{1}H NMR(400MHz,DMSO-d6)δ8.96(s,1H),7.03(d,J=8.4Hz,2H),6.61(d,J=8.4Hz,2H),5.28(s,1H),5.18(s,1H),3.68(m,2H),3.44(m,1H),3.09(m,1H),2.97(m,2H),2.17-1.73(m,4H),1.58-1.41(m,4H),1.22(m,2H),1.15(s,6H),0.59(t,J=7.2Hz,3H)。质谱(m/z):305.1[M+H]$^+$。

[1767] 化合物296

[1768] (1-氨基-4-((4-(叔戊基)苯基)氨基)环己基)甲醇

[1769]



296A 296B

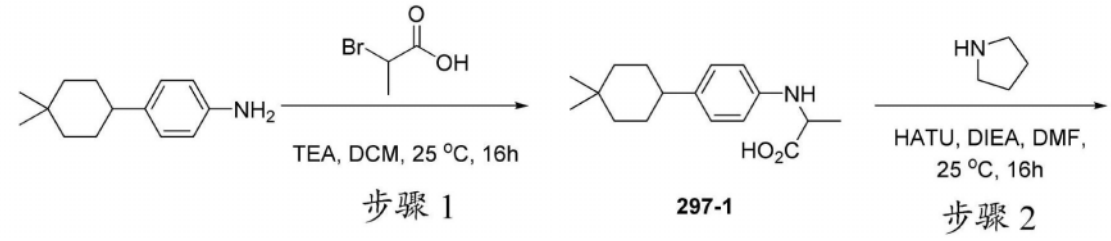
[1770] 由1-氨基-4-((4-(叔戊基)苯基)氨基)环己烷-1-甲酸(31mg,0.1mmol),根据为化

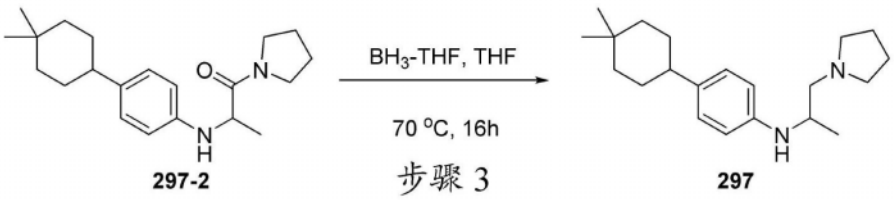
合物4的程序制备标题化合物296。混合物的提纯方法:制备HPLC(ACN/水(5‰TFA=5-30-95-95-5,0-10-10.5-11.5-13.0min)而得到化合物296A(Rt=4.33min)(玫瑰棕色固体)和化合物296B(Rt=3.95min)(玫瑰棕色固体)。296A(15.6mg,54%):^{1}H NMR(400MHz,DMSO-d6)δ7.93(s,2H),7.02(d,J=8.4Hz,2H),6.51(d,J=8.4Hz,2H),5.47(s,1H),5.07(s,1H),3.46(s,2H),3.23(m,1H),1.95-1.68(m,4H),1.65-1.40(m,6H),1.16(s,6H),0.61(t,J=7.2Hz,3H)。质谱(m/z):291.2[M+H]$^+$。296B(10.2mg,35%):^{1}H NMR(400MHz,DMSO-d6)δ7.94(s,2H),7.01(d,J=8.4Hz,2H),6.51(d,J=8.4Hz,2H),5.48(s,1H),5.27(s,1H),3.46(s,2H),3.15(m,1H),1.95-1.80(m,4H),1.65-1.48(m,4H),1.35-1.23(m,3H),1.15(s,6H),0.60(t,J=7.2Hz,3H)。质谱(m/z):291.2[M+H]$^+$。

[1771] 化合物297

[1772] 4-(4,4-二甲基环已基)-N-(1-(吡咯烷-1-基)丙-2-基)苯胺

[1773]





[1774] 步骤1:(4-(4,4-二甲基环已基)苯基)丙氨酸(297-1)

[1775] 在25℃将4-(4,4-二甲基环已基)苯胺(100mg,0.49mmol),2-溴丙酸(112.85mg,0.74mmol),TEA(99.53mg,0.98mmol)/DCM(5mL)的混合物搅拌过夜。将其用H_2O(30mL)淬灭并用DCM(3x30 mL)萃取。将有机层合并,用盐水NaCl(2x30 mL)洗涤并且用$MgSO_4$干燥,过滤并且浓缩而得到目标产物(100mg,59%)(黄色油)。质谱(m/z):276.0[M+H]$^+$。

[1776] 步骤2:2-((4-(4,4-二甲基环已基)苯基)氨基)-1-(吡咯烷-1-基)丙-1-酮(297-2)

[1777] 向297-1(100mg,0.36mmol),吡咯烷(51.65mg,0.72mmol)/DMF(7mL)的溶液中添加HATU(207.1mg,0.54mmol)和DIEA(93.86mg,0.72mmol)。然后在25℃搅拌混合物过夜。将其用H_2O(30mL)淬灭并用EA(3x30 mL)萃取。将有机层合并,用盐水NaCl(2x30 mL)洗涤并且用$MgSO_4$干燥,过滤并且浓缩。将粗产物施加到硅胶柱(4g),用PE:EA(10:1)洗脱而得到产物(50mg,13.4%)。质谱(m/z):329.3[M+H]$^+$。

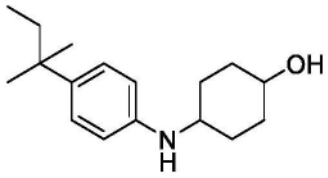
[1778] 步骤3:制备4-(4,4-二甲基环已基)-N-(1-(吡咯烷-1-基)丙-2-基)苯胺(297)

[1779] 向297-2(50mg,0.15mmol),2-(4-甲基哌嗪-1-基)乙酸(66mg,0.42mmol)/THF(5mL)的溶液中添加BH_3-THF(10mL)。然后在室温搅拌混合物过夜。将反应真空浓缩。残余物的提纯方法为:prep-TLC而得到期望的产物297(19.8mg)(白色固体)。^{1}H NMR(400MHz,CD_3OD)δ7.06-6.96(m,2H),6.72-6.59(m,2H),3.90-3.79(m,1H),3.27-3.17(m,3H),3.10(d,J=6.6Hz,2H),2.34-2.21(m,1H),2.01(d,J=6.6Hz,4H),1.67-1.30(m,9H),1.15(d,J

=6.4Hz,3H),0.96(s,3H),0.92(s,3H)。质谱(m/z):315.2[M+H]$^+$。

[1780] 化合物298

[1781] 4-((4-(叔戊基)苯基)氨基)环己烷-1-醇

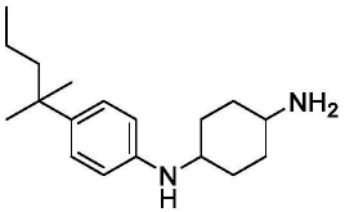
[1782] 

298

[1783] 由4-(叔戊基)苯胺(49.2mg,0.3mmol),4-羟基环己烷-1-酮(68.4mg,0.6mmol)和Na(AcO)$_3$BH(127mg,0.6mmol),根据为4的程序制备标题化合物298(47.8mg),总收率为61.0%(淡黄色固体)。^{1}H NMR(400MHz,DMSO-d6)δ7.06-6.80(m,2H),6.59-6.27(m,2H),5.12(d,J=8.0Hz,0.5H),5.04(d,J=8..0Hz,0.5H),4.50(d,J=4.4Hz,0.5H),4.34(d,J=3.0Hz,0.5H),3.71-3.59(m,0.5H),3.36(s,0.5H),3.21-3.10(m,0.5H),3.02(s,0.5H),1.87(d,J=12.8Hz,0.5H),1.78(d,J=12.4Hz,0.5H),1.62-1.41(m,10H),1.12(s,6H),0.57(td,J=7.4,2.0Hz,3H)。质谱(m/z):262.3[M+H]$^+$。

[1784] 化合物299

[1785] N^1-(4-(叔戊基)苯基)环己烷-1,4-二胺

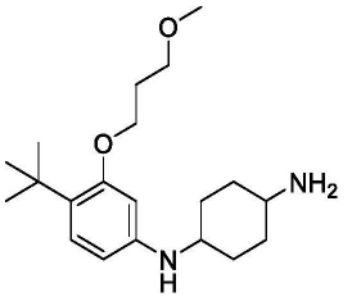
[1786] 

299A
299B

[1787] 根据为化合物232的程序制备标题化合物299A和299B。粗制残余物的提纯方法为:制备TLC(H$_2$O/MeOH/DCM=0.1/1/5)而得到化合物299A,收率为30.9%(白色固体)和299B,收率为25.3%(白色固体)。299A:^{1}H NMR(400MHz,DMSO-d6)δ7.61(s,2H),7.05-6.98(m,2H),6.56-6.48(m,2H),5.20(d,J=5.6Hz,1H),3.43-3.36(m,1H),3.07(p,J=6.4Hz,1H),1.85-1.56(m,6H),1.51-1.36(m,2H),1.17(s,6H),1.07-0.95(m,2H),0.77(t,J=7.3Hz,3H)。质谱(m/z):275.3[M+H]$^+$。HPLC:Rt=1.816mins(Agilent,poroshell 120,SB-C18 2.7μm,4.6x50mm,ACN/水(0.1%FA)=5%-5%-95%-95%-95%-5%,0-0.5min-10min-10.5min-12.0min)。299B:^{1}H NMR(400MHz,DMSO-d6)δ7.04-6.96(m,2H),6.67-6.45(m,4H),5.15(d,J=8.0Hz,1H),3.13-3.01(m,1H),2.90-2.79(m,1H),2.07-1.84(m,4H),1.51-1.41(m,2H),1.38-1.28(m,2H),1.21-1.11(m,7H),1.02-0.96(m,1H),0.77(t,J=7.2Hz,3H)。质谱(m/z):275.3[M+H]$^+$。HPLC:Rt=1.561mins(Agilent,poroshell 120,SB-C18 2.7μm,4.6x50mm,ACN/水(0.1%FA)=5%-5%-95%-95%-95%-5%,0-0.5min-10min-10.5min-12.0min)。

[1788] 化合物300

[1789] N^1-(4-(叔丁基)-3-(3-甲氧基丙氧基)苯基)环己烷-1,4-二胺

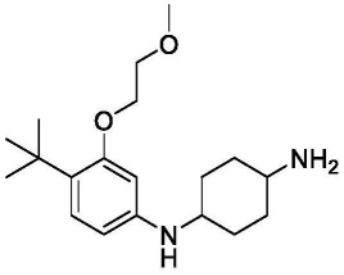
[1790] 

300A
300B

[1791] 根据为化合物254的程序制备标题化合物300A和300B。粗制残余物的提纯方法为：制备TLC(H_2O/MeOH/DCM＝0.1/1/5)而得到化合物300A,收率为33.4％(白色固体)和300B,收率为25.3％(白色固体)。300A:^{1}H NMR(400MHz,甲醇-d4)δ6.98(d,J＝8.4Hz,1H),6.30(d,J＝2.3Hz,1H),6.16(dd,J＝8.4,2.3Hz,1H),3.99(t,J＝6.2Hz,2H),3.60(t,J＝6.2Hz,2H),3.55-3.50(m,1H),3.33(s,3H),3.23-3.17(m,1H),2.04(q,J＝6.2Hz,2H),1.88-1.73(m,8H),1.30-1.29(m,9H)。Mass(m/z):335.3[M+H]$^+$。HPLC:Rt＝4.800mins(Agilent,poroshell 120,SB-C18 2.7μm,4.6x50mm,ACN/水(0.1％FA)＝5％-5％-95％-95％-95％-5％,0-0.5min-10min-10.5min-12.0min)。300B:^{1}H NMR(400MHz,甲醇-d4)δ6.99(d,J＝8.4Hz,1H),6.30(d,J＝2.3Hz,1H),6.18(dd,J＝8.4,2.3Hz,1H),3.99(t,J＝6.2Hz,2H),3.60(t,J＝6.2Hz,2H),3.33(s,3H),3.28-3.17(m,4H),3.16-3.02(m,1H),2.18-2.12(m,2H),2.10-2.02(m,4H),1.49(td,J＝12.5,3.3Hz,2H),1.30(s,9H),1.28-1.21(m,2H)。质谱(m/z):335.3[M+H]$^+$。HPLC:Rt＝4.284mins(Agilent,poroshell 120,SB-C18 2.7μm,4.6x50mm,ACN/水(0.1％FA)＝5％-5％-95％-95％-95％-5％,0-0.5min-10min-10.5min-12.0min)。

[1792] 化合物301

[1793] N^1-(4-(叔丁基)-3-(2-甲氧基乙氧基)苯基)环己烷-1,4-二胺

[1794] 

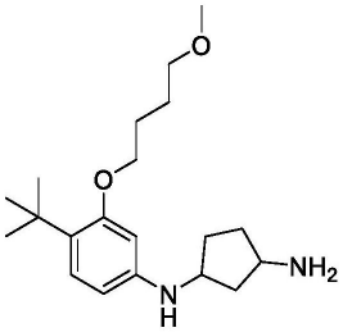
301A
301B

[1795] 根据为化合物254的程序制备标题化合物301A和301B。粗制残余物的提纯方法为：制备TLC(H_2O/MeOH/DCM＝0.1/1/5)而得到化合物301A,收率为31.2％(白色固体)和301B,收率为21.3％(白色固体)。301A:^{1}H NMR(400MHz,甲醇-d4)δ8.07(d,J＝8.4Hz,1H),7.38(s,1H),7.25(d,J＝8.4Hz,1H),5.15-5.08(m,2H),4.88-4.81(m,2H),4.70-4.54(m,1H),4.49(s,3H),4.34-4.25(m,1H),2.97-2.77(m,8H),2.38(s,9H)。质谱(m/z):321.3[M+H]$^+$。HPLC:Rt＝4.678mins(Agilent,poroshell 120,SB-C18 2.7μm,4.6x50mm,ACN/水(0.1％FA)＝5％-5％-95％-95％-95％-5％,0-0.5min-10min-10.5min-12.0min)。301B:^{1}H NMR

(400MHz,甲醇-d4)δ6.98(d,J＝8.4Hz,1H),6.27(d,J＝2.3Hz,1H),6.17(dd,J＝8.4,2.3Hz,1H),4.06-3.99(m,2H),3.79-3.71(m,2H),3.40(s,3H),3.23-3.10(m,1H),3.10-2.98(m,1H),2.19-2.01(m,4H),1.56-1.44(m,2H),1.30(s,9H),1.28-1.19(m,2H)。Mass(m/z):321.3[M+H]$^+$。HPLC:Rt＝4.231mins(Agilent,poroshell 120,SB-C18 2.7μm,4.6x50mm,ACN/水(0.1%FA)＝5%-5%-95%-95%-95%-5%,0-0.5min-10min-10.5min-12.0min)。

[1796] 化合物302

[1797] N^1-(4-(叔丁基)-3-(4-甲氧基丁氧基)苯基)环戊烷-1,3-二胺

[1798] 

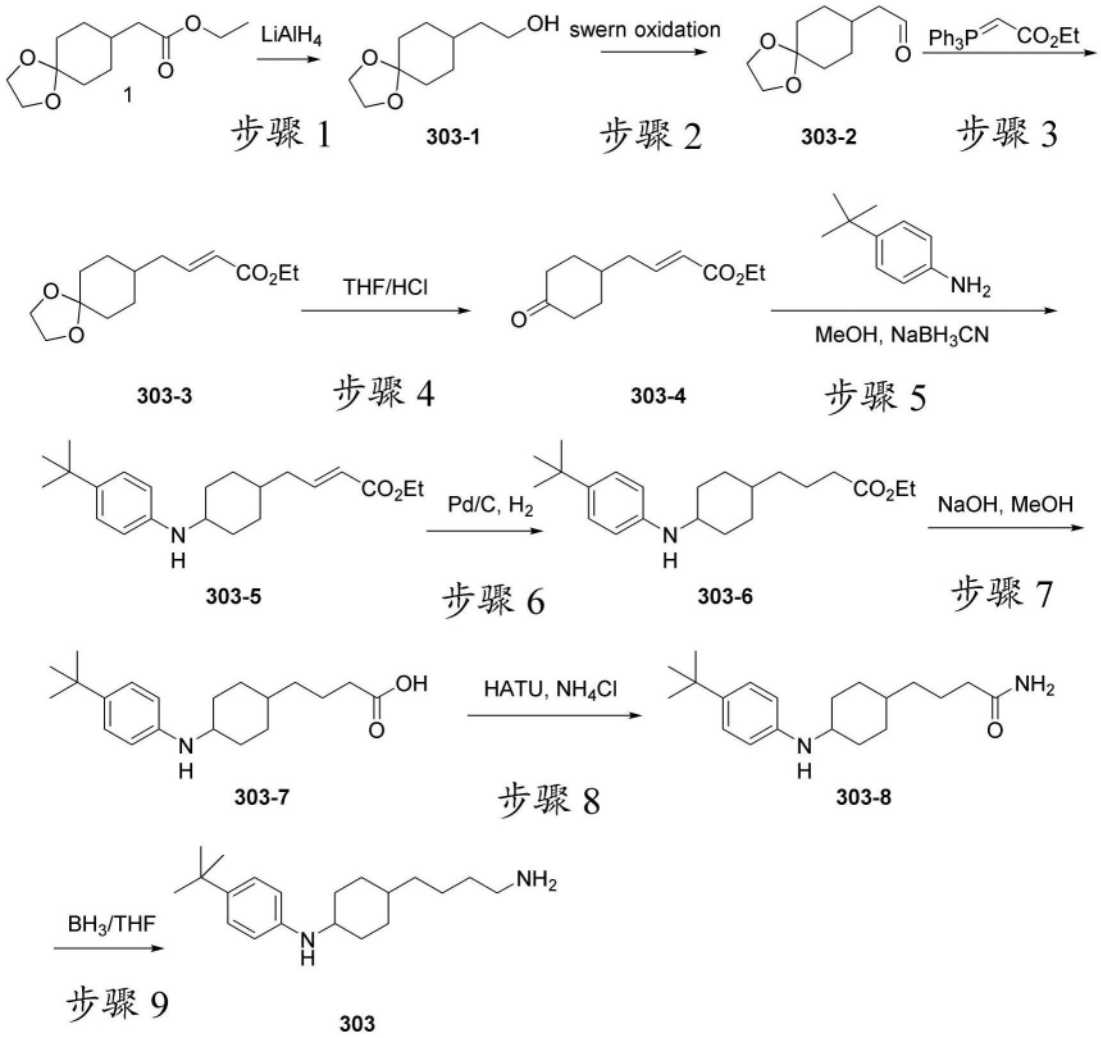
302

[1799] 由(3-((4-(叔丁基)-3-(4-甲氧基丁氧基)苯基)氨基)环戊基)氨基甲酸叔丁酯(58mg,0.13mmol)和TFA(2.0mL),根据为254的程序制备标题化合物302(12.5mg),总收率为28.2%(黄色固体),经^{1}H NMR证实为7:3的混合物。^{1}H NMR(400MHz,甲醇-d4)δ7.00(dd,J＝8.4,4.1Hz,1H),6.29(d,J＝11.8Hz,1H),6.18(t,J＝10.5Hz,1H),4.02-3.97(m,0.7H),3.97-3.92(m,2H),3.87-3.83(m,2H),3.76-3.68(m,0.7H),3.64-3.59(m,0.3H),3.46(t,J＝6.2Hz,2H),3.33(s,3H),2.55-1.77(m,10H),1.69-1.57(m,2H),1.30(s,9H)。质谱(m/z):335.3[M+H]$^+$。

[1800] 化合物303

[1801] N-(4-(4-氨基丁基)环己基)-4-(叔丁基)苯胺

[1802]



[1803] oxidation:氧化

[1804] 步骤1:制备2-(1,4-二氧杂螺[4.5]癸烷-8-基)乙-1-醇(303-1)

[1805] 在3分钟内向在0℃搅拌的2-(1,4-二氧杂螺[4.5]癸烷-8-基乙酸乙酯(2g,8.76mmol)/THF(30mL)的溶液中添加$LiAlH_4$(998mg,26.28mmol)。在25℃搅拌16小时后,将1mL的H_2O添加到混合物。将混合物过滤,用H_2O稀释,用EA萃取,用Na_2SO_4干燥,过滤并蒸发而得到产物(1.5g,92%)。^1H NMR(400MHz,CDCl3)δ3.94(s,4H),3.70(t,J=6.6Hz,2H),1.75(d,J=9.8Hz,4H),1.62-1.40(m,7H),1.27(dd,J=22.2,11.3Hz,2H)。

[1806] 步骤2:制备2-(1,4-二氧杂螺[4.5]癸烷-8-基)乙醛(303-2)

[1807] 向冷却到-78℃的草酰氯(1.23g,9.66mmol)/THF(20mL)的溶液中添加DMSO(1.05g,13.42mmol)并且在-78℃搅拌30分钟。然后2-(1,4-二氧杂螺[4.5]癸烷-8-基)乙-1-醇(1.5g,8.05mmol)的溶液被滴加到混合物中。在搅拌1.5小时后,滴加三乙胺(6.52g,64.43mmol)。然后将反应升温至室温并且搅拌12小时。将混合物过滤,蒸发并且将残余物施加到使用EA/PE(0:1-1:5)的硅胶柱而得到产物(930mg,94%)。^1H NMR(301MHz,CDCl3)δ9.77(s,1H),3.94(s,4H),2.36(d,J=6.6Hz,2H),1.94(s,1H),1.75(d,J=11.1Hz,4H),1.58(t,J=12.2Hz,2H),1.43-1.18(m,2H)。

[1808] 步骤3:制备(E)-4-(1,4-二氧杂螺[4.5]癸烷-8-基)丁-2-烯酸乙酯(303-3)

[1809] 向在80℃搅拌的2-(1,4-二氧杂螺[4.5]癸烷-8-基)乙醛(800mg,4.34mmol)/Tol

(20mL)的溶液中添加DBU(4.54g,13.03mmol)和2-(三苯基-15-亚膦基(phosphanylidene)乙酸乙酯(1.98g,13.03mmol)。在80℃搅拌反应混合物16小时。将残余物施加到使用EA:PE(0:1-1:5)的硅胶柱而得到产物(黄色油)(800mg,72.4%)。质谱(m/z):254.7[M+H]$^+$。

[1810] 步骤4:制备(E)-4-(4-氧代环己基)丁-2-烯酸乙酯(303-4)

[1811] 向(E)-4-(1,4-二氧杂螺[4.5]癸烷-8-基)丁-2-烯酸乙酯(800mg,3.15mmol)/THF(20mL)的溶液中添加2NHCl(10mL)。然后在室温搅拌混合物16小时。将反应减压浓缩。将残余物施加到使用EA:PE(0:1-1:5)的硅胶柱而得到期望的产物(无色油)。(615mg,92.98%)。^{1}H NMR(300MHz,CDCl3)δ7.03-6.87(m,1H),5.85(d,J=15.5Hz,1H),4.14(dq,J=21.0,6.9Hz,2H),2.49-2.29(m,4H),2.23(t,J=7.0Hz,2H),2.14-2.00(m,2H),2.00-1.81(m,1H),1.53-1.36(m,2H),1.29(t,J=7.1Hz,3H)。

[1812] 步骤5:制备(E)-4-(4-((4-(叔丁基)苯基)氨基)环己基)丁-2-烯酸乙酯(303-5)

[1813] 在50℃搅拌(E)-4-(4-氧代环己基)丁-2-烯酸乙酯(615mg,2.92mmol)和4-(叔丁基)苯胺(524mg,3.51mmol)/THF(20mL)的溶液2小时。然后将混合物冷却到室温并且添加$NaBH_3CN$(551mg,8.77mmol)。在室温搅拌混合物16小时。将反应减压浓缩。将残余物施加到使用EA:PE(0:1-1:5)的硅胶柱而得到期望的产物(无色油)(530mg,52.7%)。质谱(m/z):343.7[M+H]$^+$。

[1814] 步骤6:制备4-(4-((4-(叔丁基)苯基)氨基)环己基)丁酸乙酯(303-6)

[1815] 向(E)-4-(4-((4-(叔丁基)苯基)氨基)环己基)丁-2-烯酸乙酯(530mg,1.54mmol)/THF(20mL)的溶液中添加Pd/C(50mg)。然后在室温在氢气气氛下搅拌混合物16小时。过滤粗产物混合物,真空浓缩而得到期望的产物(无色油)。(520mg,97.5%)。质谱(m/z):345.7[M+H]$^+$。

[1816] 步骤7:制备4-(4-((4-(叔丁基)苯基)氨基)环己基)丁酸(303-7)

[1817] 向4-(4-((4-(叔丁基)苯基)氨基)环己基)丁酸乙酯(520mg,1.50mmol)/MeOH(15mL)的溶液中添加4N NaOH(1.1mL)。然后在50℃搅拌混合物16小时。将反应用2N HCl调节到pH=4,用EA(30mL×3)萃取,用Na_2SO_4干燥,过滤,真空浓缩。直接使用残余物(无色油)(455mg,95.2%)。

[1818] 步骤8:制备4-(4-((4-(叔丁基)苯基)氨基)环己基)丁酰胺(303-8)

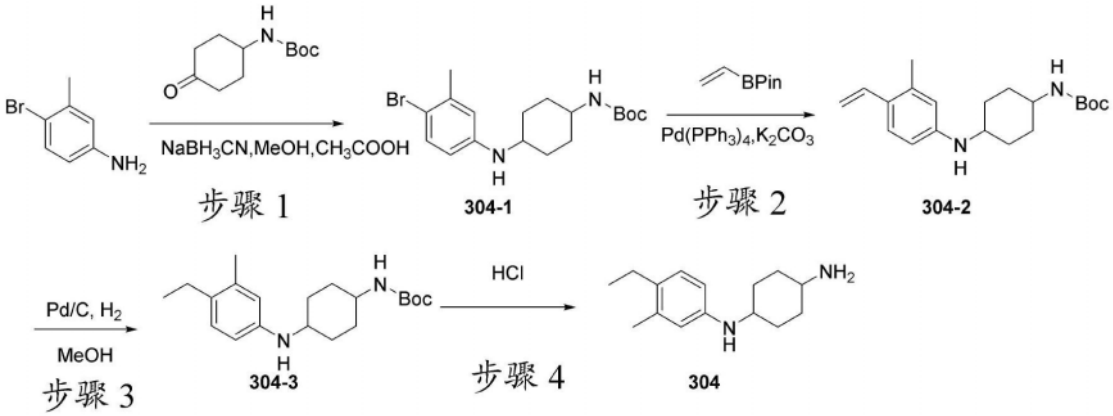
[1819] 在室温将4-(4-((4-(叔丁基)苯基)氨基)环己基)丁酸(120mg,0.378mmol),NH_4Cl(61mg,1.134mmol),HATU(287mg,0.756mmol)和TEA(115mg,1.134mmol)/DCM(10mL)的溶液搅拌2小时。将反应用水洗涤,用EA(20mL×3)萃取,用Na_2SO_4干燥,过滤并且真空浓缩。将残余物施加到使用EA:PE(0:1-2:1)的硅胶柱而得到期望的产物(100mg,83.5%)(白色固体)。质谱(m/z):316.7[M+H]$^+$。

[1820] 步骤9:制备乙基N-(4-(4-氨基丁基)环己基)-4-(叔丁基)苯胺(303)

[1821] 在50℃将4-(4-((4-(叔丁基)苯基)氨基)环己基)丁酰胺(100mg,0.32mmol)/BH_3-THF(30mL)搅拌16小时。将混合物用甲醇淬灭,蒸发并且通过prep-HPLC提纯而得到产物(29.2mg,30.2%)(白色固体)。^{1}H NMR(400MHz,甲醇-d4)δ7.16-7.11(m,2H),6.63-6.58(m,2H),3.17-3.07(m,1H),2.93-2.84(m,2H),1.71-1.51(m,6H),1.44-1.32(m,6H),1.23(s,9H),1.16-0.99(m,3H)。质谱(m/z):303.2[M+H]$^+$。

[1822] 化合物304

[1823] N^1-(4-乙基-3-甲基苯基)环己烷-1,4-二胺

[1824] 

[1825] 步骤1:制备(4-((6-乙基吡啶-3-基)氨基)环己基)氨基甲酸叔丁酯(304-1)

[1826] 向4-溴-3-甲基苯胺(1g,5.4mmol)/MeOH(10mL)和一滴AcOH的溶液中添加(4-氧代环己基)氨基甲酸叔丁酯(1.4g,6.5mmol)。然后将混合物加到$NaBH_3CN$(680mg,10.8mmol)并且在25℃搅拌混合物16小时。LCMS显示反应完成。将反应用水(10mL)淬灭,用EA(10mL*3)萃取。将合并的有机层用盐水(20mL)洗涤,用硫酸钠干燥,过滤并浓缩。残余物的提纯方法为:使用EA/PE(1:3)的combi-flash(闪式色谱)而得到而得到304-1(1.5g,72.2%收率)(黄色固体)。MS(m/z)383.1$[M+H]^+$。

[1827] 步骤2:制备(4-((3-甲基-4-乙烯基苯基)氨基)环己基)氨基甲酸叔丁酯(304-2)

[1828] 向304-1(400mg,1.04mmol),4,4,5,5-四甲基-2-乙烯基-1,3,2-二氧杂硼杂环戊烷(240mg,1.56mmol),K_2CO_3(430mg,3.12mmol)/1,4-二氧杂环己烷(20mL)和水(2mL)的溶液中添加$Pd(PPh_3)_4$(120mg,0.10mmol)。在氮气气氛下搅拌混合物,回流过夜。在冷却到环境温度后,减压浓缩。残余物的提纯方法为:硅胶柱而得到304-2(240mg,69.5%收率)(黄色固体)。MS(m/z)330.9$[M+H]^+$。

[1829] 步骤3:制备(4-((4-乙基-3-甲基苯基)氨基)环己基)氨基甲酸叔丁酯(304-3)

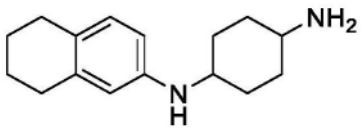
[1830] 向2-(4,4-二甲基环己-1-烯-1-基)-5-硝基吡啶(240mg,0.72mmol)/MeOH(10mL)的溶液中添加Pd/C(50mg,10%),使混合物在氢气气氛下反应16小时,然后过滤并且真空除去溶剂而得到304-3(140mg,57.9%收率)(黄色固体)。MS(m/z)332.9$[M+H]^+$。

[1831] 步骤4:制备N^1-(4-乙基-3-甲基苯基)环己烷-1,4-二胺(304)

[1832] 304-3(140mg,0.42mmol)和HCl/1,4-二氧杂环己烷(10mL,4N)被置于烧杯中,在25℃搅拌16小时。过量的1,4-二氧杂环己烷被真空蒸馏掉并且残余物的提纯方法为:prep-HPLC(柱-Xbridge-C18 150x19mm,5um;移动相:ACN-H_2O(0.1%FA),20%-40%)而得到304(36mg 36.9%)(白色固体)。^1H NMR(400MHz,CD_3OD)δ7.28(dd,J=23.3,8.0Hz,1H),7.14(d,J=9.3Hz,1H),7.07(d,J=9.2Hz,1H),3.65-3.37(m,1H),3.24-3.06(m,1H),2.65(dd,J=9.6,7.6Hz,2H),2.34(d,J=9.4Hz,3H),2.14-2.07(m,2H),1.89(dd,J=10.6,6.6Hz,4H),1.58-1.44(m,2H),1.18(td,J=7.6,3.7Hz,3H)。MS(m/z)233.2$[M+H]^+$。

[1833] 化合物305

[1834] N^1-(5,6,7,8-四氢萘-2-基)环己烷-1,4-二胺

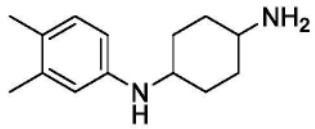
[1835] 

305A
305B

[1836] 由(4-((5,6,7,8-四氢萘-2-基)氨基)环己基)氨基甲酸叔丁酯(88mg,0.256mmol),TFA(1mL),和DCM(10mL),根据为24的程序制备标题化合物305,其提纯方法:prep HPLC(柱:X Select-CSH-Prep 5μm OBD,19*150mm;ACN/水(0.5%TFA)=10%-25%-85%-95%-15%,0min-10min-10.5min-11.5min-13min)而得到期望的产物305A(Rt=5.9min)(白色固体)(2.7mg,4.3%)和305B(Rt=7.0min)(黄色油)(8.9mg,14.2%)。305A:^{1}H NMR(400MHz,DMSO-d6)δ6.74(d,J=8.0Hz,1H),6.46-6.20(m,2H),5.03(s,1H),3.00(d,J=54.8Hz,2H),2.57(d,J=18.8Hz,4H),1.99(d,J=11.6Hz,2H),1.75(d,J=15.2Hz,3H),1.66(p,J=3.2Hz,4H),1.59(d,J=12.4Hz,1H),1.46(q,J=12.0Hz,1H),1.18(t,J=20.0Hz,1H)。质谱(m/z):245.3[M+H]$^+$。305B:^{1}H NMR(400MHz,DMSO-d6)δ6.74(d,J=8.0Hz,1H),6.46-6.20(m,2H),5.03(s,1H),3.00(d,J=54.8Hz,2H),2.57(d,J=18.8Hz,4H),1.99(d,J=11.6Hz,2H),1.75(d,J=15.2Hz,3H),1.66(p,J=3.2Hz,4H),1.59(d,J=12.4Hz,1H),1.46(q,J=12.0Hz,1H),1.18(t,J=20.0Hz,1H)。质谱(m/z):245.3[M+H]$^+$。

[1837] 化合物306

[1838] N^1-(3,4-二甲基苯基)环己烷-1,4-二胺

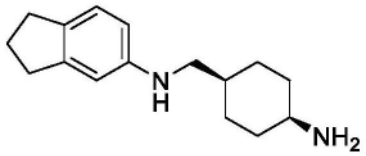
[1839] 

306A
306B

[1840] 由(4-((3,4-二甲基苯基)氨基)环己基)氨基甲酸叔丁酯(128mg,0.402mmol),TFA(1mL),和DCM(10mL),根据为24的程序制备标题化合物306,其提纯方法:prep HPLC(溶剂体系(柱:X Select-CSH-Prep 5μm OBD,19*150mm;ACN/水(0.5%TFA)=15%-25%-95%-95%-15%,0min-9min-9.5min-10.5min-13min)而得到期望的产物306A(Rt=6.6min)(白色固体)(4.8mg,5.4%)和306B(Rt=7.5min)(白色固体)(5.5mg,6.3%)。306A:^{1}H NMR(400MHz,DMSO-d6)δ6.76(dd,J=8.0,5.2Hz,1H),6.36(dd,J=18.4,2.4Hz,1H),6.27(ddd,J=15.6,8.0,2.4Hz,1H),4.98(d,J=7.6Hz,1H),3.37-2.75(m,2H),2.05(d,J=2.4Hz,3H),2.00(d,J=2.4Hz,3H),1.97-1.86(m,2H),1.73-1.47(m,4H),1.36(qd,J=13.6,12.4,3.6Hz,1H),1.15-1.02(m,1H)。质谱(m/z):219.3[M+H]$^+$。306B:^{1}H NMR(400MHz,DMSO-d6)δ6.76(dd,J=8.0,5.2Hz,1H),6.36(dd,J=18.4,2.4Hz,1H),6.27(ddd,J=15.6,8.0,2.4Hz,1H),4.98(d,J=7.6Hz,1H),3.37-2.75(m,2H),2.05(d,J=2.4Hz,3H),2.00(d,J=2.4Hz,3H),1.97-1.86(m,2H),1.73-1.47(m,4H),1.36(qd,J=13.6,12.4,3.6Hz,1H),1.15-1.02(m,1H)。质谱(m/z):219.3[M+H]$^+$。

[1841] 化合物307

[1842] N-(((1s,4s)-4-氨基环己基)甲基)-2,3-二氢-1H-茚-5-胺

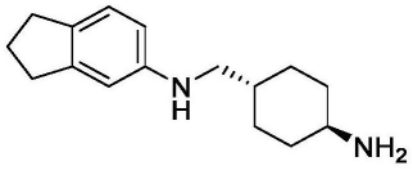
[1843] 

307

[1844] 由((1s,4s)-4-((E)-((2,3-二氢-1H-茚-5-基)亚氨基)甲基)环己基)氨基甲酸叔丁酯(91mg,0.264mmol),TFA(1mL),和DCM(10mL),根据为24的程序制备标题化合物307(48.2mg),总收率为74.7%(黄色固体)。^{1}H NMR(400MHz,DMSO-d6)δ6.88(d,J=8.0Hz,1H),6.49-6.29(m,2H),5.43(dt,J=21.6,5.6Hz,1H),3.15(tt,J=7.2,3.2Hz,1H),2.86(dt,J=46.0,5.6Hz,2H),2.70(dt,J=14.8,7.2Hz,4H),2.03-1.84(m,3H),1.78-1.44(m,7H),1.41-1.26(m,1H)。质谱(m/z):245.3[M+H]$^+$。

[1845] 化合物308

[1846] N-(((1r,4r)-4-氨基环己基)甲基)-2,3-二氢-1H-茚-5-胺(308)

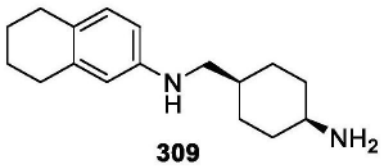
[1847] 

308

[1848] 由((1r,4r)-4-((E)-((2,3-二氢-1H-茚-5-基)亚氨基)甲基)环己基)氨基甲酸叔丁酯(113mg,0.328mmol),TFA(1mL),和DCM(10mL),根据为24的程序制备标题化合物308(43.9mg),总收率为54.9%(黄色固体)。^{1}H NMR(400MHz,DMSO-d6)δ6.89(d,J=8.0Hz,1H),6.42(d,J=2.4Hz,1H),6.33(dd,J=8.0,2.0Hz,1H),5.39(q,J=6.0Hz,1H),2.91(td,J=12.0,10.0,6.0Hz,1H),2.81(t,J=5.6Hz,2H),2.70(dt,J=14.8,7.4Hz,4H),2.02-1.90(m,4H),1.90-1.81(m,2H),1.72-1.40(m,2H),1.36-1.19(m,2H),0.98(qd,J=13.2,3.1Hz,2H)。质谱(m/z):245.3[M+H]$^+$。

[1849] 化合物309

[1850] N-(((1r,4r)-4-氨基环己基)甲基)-5,6,7,8-四氢萘-2-胺

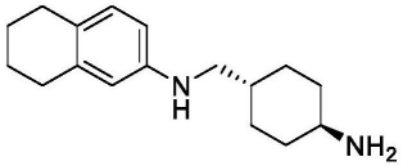
[1851] 

309

[1852] 由((1s,4s)-4-((E)-((5,6,7,8-四氢萘-2-基)亚氨基)甲基)环己基)氨基甲酸叔丁酯(75mg,0.209mmol),TFA(1mL),和DCM(10mL),根据为24的程序制备标题化合物309(15.1mg),总收率为27.8%(黄色固体)。^{1}H NMR(400MHz,DMSO-d6)δ6.72(d,J=8.2Hz,1H),6.38-6.27(m,1H),6.22(dd,J=8.2,2.4Hz,1H),5.32(dt,J=17.5,5.8Hz,1H),3.14(tt,J=7.2,3.3Hz,1H),2.84(dt,J=44.0,6.1Hz,2H),2.57(d,J=5.1Hz,4H),1.96(td,J=12.3,11.4,5.7Hz,1H),1.84(d,J=13.4Hz,1H),1.75-1.54(m,9H),1.51(q,J=4.4,4.0Hz,1H),1.30(tt,J=12.7,6.7Hz,1H),1.10-0.89(m,1H)。质谱(m/z):259.3[M+H]$^+$。

[1853] 化合物310

[1854] N-(((1r,4r)-4-氨基环己基)甲基)-5,6,7,8-四氢萘-2-胺

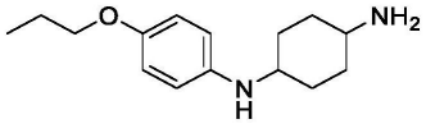
[1855] 

310

[1856] 由((1s,4s)-4-((E)-((5,6,7,8-四氢萘-2-基)亚氨基)甲基)环己基)氨基甲酸叔丁酯(82mg,0.229mmol),TFA(1mL),和DCM(10mL),根据为24的程序制备标题化合物310(37mg),总收率为27.8%(黄色固体)。^{1}H NMR(400MHz,DMSO-d6)δ6.70(d,J=8.4Hz,1H),6.31(dd,J=8.4,2.4Hz,1H),6.20(d,J=2.4Hz,1H),5.30(s,1H),2.87(ddt,J=12.0,7.6,4.0Hz,1H),2.77(d,J=6.4Hz,2H),2.56(dd,J=14.0,8.8Hz,4H),1.98(dd,J=12.8,4.0Hz,2H),1.89-1.77(m,2H),1.64(h,J=4.0,3.6Hz,4H),1.52-1.40(m,1H),1.32(qd,J=12.4,3.2Hz,2H),0.96(qd,J=13.2,3.1Hz,2H)。质谱(m/z):259.3[M+H]$^+$。

[1857] 化合物311

[1858] N^1-(4-丙氧基苯基)环己烷-1,4-二胺

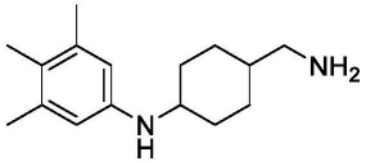
[1859] 

311

[1860] 由(4-((4-丙氧基苯基)氨基)环己基)氨基甲酸叔丁酯(193mg,0.554mmol),TFA(1mL),和DCM(10mL),根据为24的程序制备标题化合物311(89.7mg),总收率为65.2%(黄色油),经^{1}H NMR证实为1:2的混合物。^{1}H NMR(400MHz,DMSO-d6)δ7.96(d,J=12.4Hz,2H),5.43(dd,J=48.0,7.6Hz,1H),4.05(td,J=6.8,1.6Hz,2H),2.43(d,J=5.6Hz,2H),2.20(d,J=3.6Hz,2H),1.72(dd,J=12.8,4.3Hz,4H),1.63(d,J=6.4Hz,4H),0.89(t,J=7.6Hz,3H)。Mass(m/z):249.3[M+H]$^+$。

[1861] 化合物312

[1862] N-(4-(氨基甲基)环己基)-3,4,5-三甲基苯胺

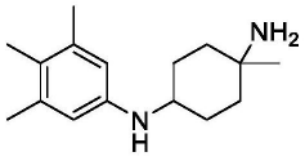
[1863] 

312

[1864] 由((4-((3,4,5-三甲基苯基)氨基)环己基)甲基)氨基甲酸叔丁酯(137mg,0.369mmol),TFA(1mL),和DCM(10mL),根据为24的程序制备标题化合物312(59.6mg),总收率为61.2%(黄色固体),经^{1}H NMR证实为1:2的混合物。^{1}H NMR(400MHz,DMSO-d6)δ6.21(d,J=28.0Hz,2H),4.86(d,J=30.8Hz,1H),3.16-2.67(m,1H),2.54(dd,J=26.4,6.8Hz,2H),2.06(d,J=2.0Hz,6H),1.91(d,J=1.2Hz,3H),1.83-1.66(m,1H),1.56(dq,J=9.2,4.2Hz,2H),1.51-1.31(m,4H)。质谱(m/z):247.3[M+H]$^+$。

[1865] 化合物313

[1866] 1-甲基-N^4-(3,4,5-三甲基苯基)环己烷-1,4-二胺

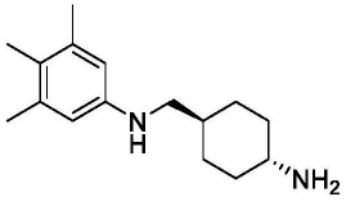
[1867] 

313

[1868] 由3,4,5-三甲基苯胺(50mg,0.37mmol)和(1-甲基-4-氧代环己基)氨基甲酸叔丁酯(50mg,0.22mmol),根据为20的程序制备标题化合物313A(13.6mg),收率为14.9%(棕色固体)和制备化合物313B(14.9mg),收率为16.35%(棕色固体)。313A:^{1}H NMR(400MHz,DMSO-d6)δ8.05(d,J=31.5Hz,2H),6.26(d,J=11.9Hz,2H),4.84(d,J=69.4Hz,1H),3.19(d,J=42.5Hz,1H),2.11(s,6H),1.96(s,3H),1.92-1.83(m,2H),1.80-1.70(m,2H),1.70-1.61(m,1H),1.55(t,J=8.4Hz,2H),1.31(s,1H),1.28(d,J=6.6Hz,3H)。质谱(m/z):247.5[M+H]$^+$。313B:^{1}H NMR(400MHz,DMSO-d6)δ8.08(s,2H),6.25(s,1H),6.22(s,1H),5.02-4.61(m,1H),3.17(d,J=45.2Hz,1H),2.09(s,6H),1.94(d,J=2.1Hz,3H),1.89-1.81(m,2H),1.71(s,2H),1.64(s,1H),1.53(d,J=9.7Hz,1H),1.31-1.20(m,5H)。质谱(m/z):247.5[M+H]$^+$。

[1869] 化合物314

[1870] N-(((1r,4r)-4-氨基环己基)甲基)-3,4,5-三甲基苯胺

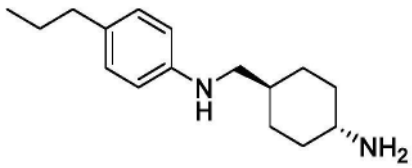
[1871] 

314

[1872] 由3,4,5-三甲基苯胺(40mg,0.29mmol)和((1r,4r)-4-甲酰基环己基)氨基甲酸叔丁酯(80mg,0.35mmol),根据为20的程序制备标题化合物314(34.2mg),收率为47.3%(白色粉末)。^{1}H NMR(400MHz,DMSO-d6)δ8.23-7.95(m,2H),6.22(d,J=8.3Hz,2H),5.18(s,1H),2.90(d,J=7.4Hz,1H),2.83-2.74(m,2H),2.10(s,6H),1.95(s,3H),1.84(dd,J=13.9,3.6Hz,2H),1.64(d,J=6.9Hz,1H),1.57-1.38(m,2H),1.39-1.19(m,2H),1.06-0.91(m,2H)。质谱(m/z):247.2[M+H]$^+$。

[1873] 化合物315

[1874] N-(((1r,4r)-4-氨基环己基)甲基)-4-丙基苯胺

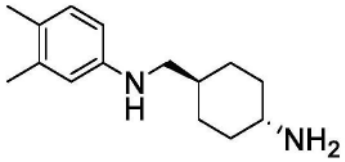
[1875] 

[1876] 由4-丙基苯胺(40mg,0.29mmol)和((1r,4r)-4-甲酰基环己基)氨基甲酸叔丁酯(80mg,0.35mmol),根据为20的程序制备标题化合物315(12.3mg),收率为17.02%(白色粉末)。^{1}H NMR(400MHz,DMSO-d6)δ8.01(d,J=19.6Hz,2H),6.87(dd,J=8.5,2.1Hz,2H),6.47(dd,J=8.9,7.2Hz,2H),5.43(s,1H),2.93(q,J=7.8,6.7Hz,1H),2.81(t,J=6.2Hz,1H),2.37(t,J=7.5Hz,2H),2.00-1.81(m,3H),1.66(s,1H),1.61-1.37(m,4H),1.29(dd,J=

26.4,13.7Hz,2H),1.09-0.95(m,2H),0.86(t,J＝7.3Hz,3H)。质谱(m/z):247.6[M+H]$^+$。

[1877] 化合物316

[1878] N-(((1r,4r)-4-氨基环己基)甲基)-3,4-二甲基苯胺

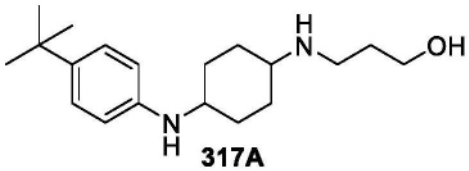
[1879] 

316

[1880] 由3,4-二甲基苯胺(35mg,0.29mmol)和((1r,4r)-4-甲酰基环己基)氨基甲酸叔丁酯(80mg,0.35mmol),根据为20的程序制备标题化合物316(34.9mg),收率为52.0%(白色粉末)。^{1}H NMR(400MHz,DMSO-d6)δ7.91(s,2H),6.81(d,J＝8.2Hz,1H),6.38(s,1H),6.29(d,J＝8.1Hz,1H),5.29(s,1H),2.81(d,J＝6.6Hz,2H),2.10(s,3H),2.05(s,3H),2.00-1.90(m,2H),1.90-1.81(m,2H),1.64(t,J＝6.2Hz,1H),1.54(q,J＝5.7Hz,1H),1.33-1.23(m,2H),1.06-0.93(m,2H)。质谱(m/z):233.2[M+H]$^+$。

[1881] 化合物317

[1882] 3-((4-((4-(叔丁基)苯基)氨基)环己基)氨基)丙-1-醇

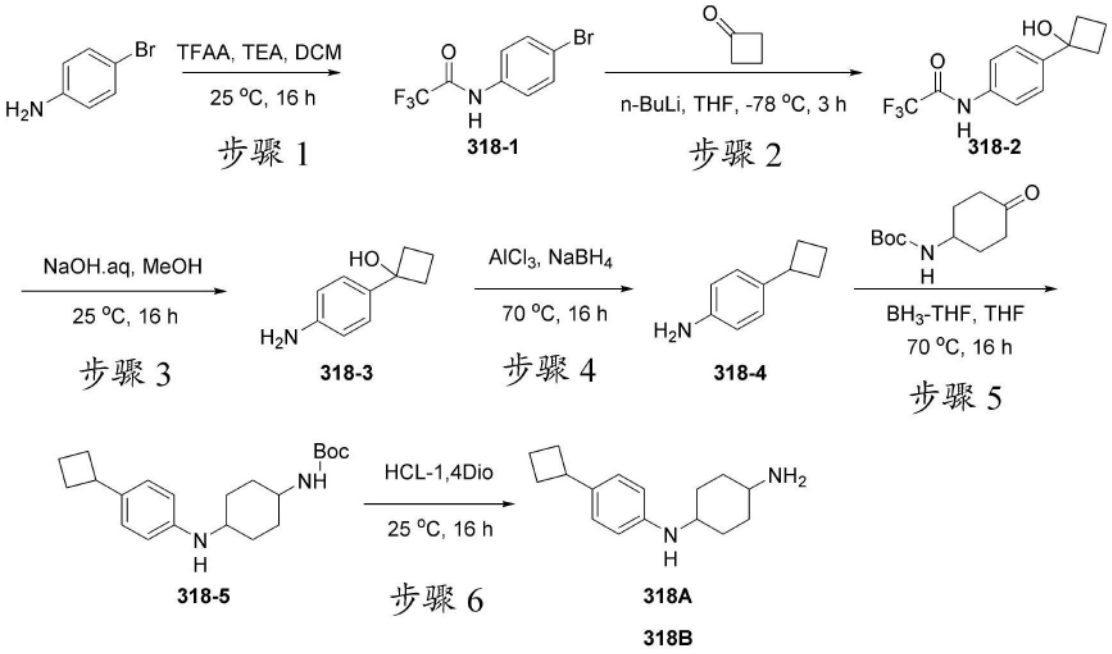
[1883] 

317A
317B

[1884] 由4-((4-(叔丁基)苯基)氨基)环己烷-1-酮(50mg,0.20mmol),甲基3-氨基丙-1-醇(46mg,0.61mmol)和NaBH(OAc)$_3$(86mg,0.40mmol),根据为20的程序制备标题化合物317A(21.1mg),收率为34.0%(白色粉末)和制备化合物317B(22.3mg),收率为35.9%(白色粉末)。317A:^{1}H NMR(400MHz,DMSO-d6)δ8.61(s,1H),7.13-6.99(m,2H),6.59-6.46(m,2H),5.22(d,J＝5.6Hz,1H),4.76(s,1H),3.48(t,J＝6.0Hz,2H),3.46-3.41(m,1H),3.07(s,1H),2.95(s,2H),1.88-1.67(m,8H),1.57(ddd,J＝13.9,9.5,3.6Hz,2H),1.20(s,9H)。质谱(m/z):305.6[M+H]$^+$。HPLC:Rt＝2.070mins(Agilent,poroshell 120,SB-C18 2.7μm,4.6x50mm,ACN/水(0.1%)＝5%-5%-95%-95%-95%-5%,0-0.5min-10min-10.5min-12.0min)。317B:^{1}H NMR(400MHz,DMSO-d6)δ7.12-7.02(m,2H),6.55-6.46(m,2H),5.20(d,J＝8.1Hz,1H),3.49(t,J＝6.0Hz,2H),3.16-3.05(m,1H),2.96(q,J＝7.9Hz,3H),2.15-1.98(m,4H),1.85-1.74(m,2H),1.48(q,J＝12.2,11.7Hz,2H),1.21(s,9H),1.19-1.12(m,2H)。质谱(m/z):305.6[M+H]$^+$。HPLC:Rt＝1.944mins(Agilent,poroshell 120,SB-C18 2.7μm,4.6x50mm,ACN/水(0.1%)＝5%-5%-95%-95%-95%-5%,0-0.5min-10min-10.5min-12.0min)。

[1885] 化合物318

[1886] 1-N-(4-环丁基苯基)环己烷-1,4-二胺

[1887] 

[1888] 步骤1:N-(4-溴苯基)-2,2,2-三氟乙酰胺(318-1)

[1889] 在25℃将4-溴苯胺(1g,5.8mmol),TFAA(2.35mL),TEA(1.23mL)/DCM(10mL)的混合物搅拌过夜。用1N NaOH将水相的pH调整到8。将其用H_2O(300mL)淬灭并用EA(3x300 mL)萃取,用Na_2SO_4干燥,浓缩而得到目标产物(600mg,收率:30.7%)(黄色固体)。

[1890] 步骤2:2,2,2-三氟-N-(4-(1-羟基环丁基)苯基)乙酰胺(318-2)

[1891] 在-78℃向318-1(600mg,2.23mmol),环丁酮(156.3mg,2.23mmol)/THF(10mL)的溶液中添加n-BuLi(5.3mL)。然后在室温搅拌混合物过夜。反应通过添加NH_4Cl水溶液淬灭。将其用H_2O(100mL)淬灭并用DCM(3x100 mL)萃取。将有机层合并,用盐水NaCl(2x100 mL)洗涤并且用$MgSO_4$干燥,过滤并且浓缩。将粗产物施加到硅胶柱(12g),用PE:EA(5:1)洗脱而得到产物(400mg,收率:90%)(黄色固体)。质谱(m/z):241.9/262.9$[M+H]^+$。

[1892] 步骤3:1-(4-氨基苯基)环丁烷-1-醇(318-3)

[1893] 在25℃向318-2(400mg,1.53mmol)/MeOH(5mL)的溶液中添加1N NaOH(10mL)。然后在室温搅拌混合物过夜。将反应真空浓缩。将其用H_2O(100mL)淬灭并用DCM(3x100 mL)萃取,用$MgSO_4$干燥,过滤并且浓缩而得到目标产物(200mg,收率:63.8%)(黄色固体)。质谱(m/z):164.2$[M+H]^+$。

[1894] 步骤4:4-环丁基苯胺(318-4)

[1895] 在0℃向318-3(200mg,1.22mmol)/THF(5mL)的溶液中添加$NaBH_4$(254.96mg,6.74mmol)。然后分批添加$AlCl_3$(490.18mg,3.67mmol)。然后在室温搅拌混合物过夜。将反应真空浓缩。将其用H_2O(100mL)淬灭并用EA(3x100 mL)萃取。将粗产物施加到硅胶柱(12g),用PE:EA(5:1)洗脱而得到产物(200mg,收率:63.8%)(黄色固体)。质谱(m/z):148.2$[M+H]^+$。

[1896] 步骤5:(4-((4-环丁基苯基)氨基)环己基)氨基甲酸叔丁酯(318-5)

[1897] 在25℃搅拌318-4(80mg,0.31mmol),Pic-BH_3(87.22mg,0.81mmol)/AcOH/H_2O=1:10(5.5mL)的溶液过夜。用$NaHCO_3$水溶液将水相的pH调整到8。将其用H_2O(30mL)淬灭并用EA(3x30 mL)萃取,用$MgSO_4$干燥,过滤并且浓缩而得到目标产物(100mg,收率:17.2%)(黄色

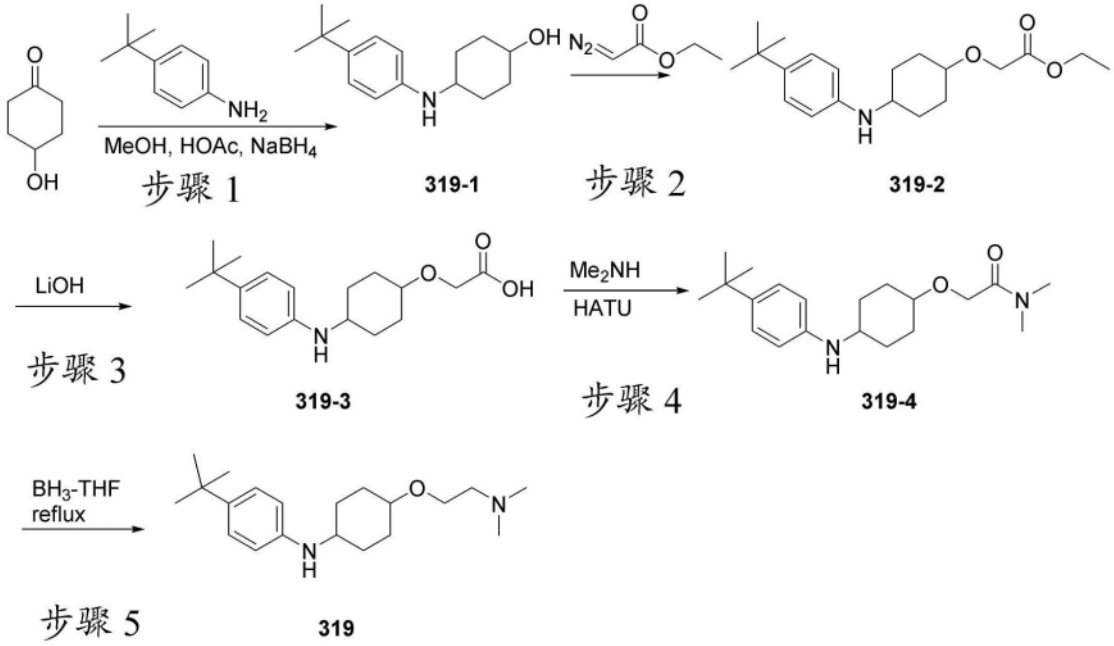
固体)。质谱(m/z):345.3[M+H]$^+$。

[1898] 步骤6:制备N^1-(4-环丁基苯基)环己烷-1,4-二胺(318)

[1899] 向318-5(200mg,0.57mmol)/1,4-二氧杂环己烷(5mL)的溶液中添加HCl/1,4-二氧杂环己烷(10mL)。然后在25℃搅拌混合物过夜。将反应真空浓缩。残余物的提纯方法为:prep-TLC而得到期望的产物318A(5.4mg)(白色固体)和318B(17.8mg)(白色固体)。318A:^{1}H NMR(400MHz,CD_3OD)δ7.01-6.94(m,2H),6.64-6.52(m,2H),3.47-3.31(m,2H),3.27-3.15(m,0.5H),3.10-3.02(m,0.5H),2.29-2.20(m,2H),2.17-2.10(m,2H),2.09-1.96(m,5H),1.83-1.75(m,1H),1.49(qd,J=13.0,3.6Hz,2H),1.34-1.17(m,2H)。质谱(m/z):452.3[M+H]$^+$。HPLC:Rt=3.582min(柱:XBRIDGE 3.5um,2.1*50mm,移动相:H_2O(0.05%TFA)-ACN(0.05%TFA),ACN从0至60%在7分钟内,7-8min,ACN由60%至100%,流速:0.8mL/min)。318B:^{1}H NMR(400MHz,CD_3OD)δ7.06-6.91(m,2H),6.67-6.52(m,2H),3.52(s,1H),3.44-3.32(m,1H),3.25-3.09(m,1H),2.29-2.16(m,2H),2.10-1.91(m,3H),1.90-1.58(m,9H)。质谱(m/z):452.3[M+H]$^+$。HPLC:Rt=3.757min(柱:XBRIDGE 3.5um,2.1*50mm,移动相:H_2O(0.05%TFA)-ACN(0.05%TFA),ACN从0至60%在7分钟内,7-8min,ACN由60%至100%,流速:0.8mL/min)。

[1900] 化合物319

[1901] 4-(叔丁基)-N-(4-(2-(二甲基氨基)乙氧基)环己基)苯胺

[1902] 

[1903] reflux:回流

[1904] 步骤1:制备4-((4-(叔丁基)苯基)氨基)环己烷-1-醇(319-1)

[1905] 向4-羟基环己烷-1-酮(2000mg,17.52mmol)/MeOH(50mL)和一滴AcOH的溶液中添加4-(叔丁基)苯胺(3138mg,21.03mmol)并且在50℃搅拌混合物1小时。然后在冷却到25℃后,将混合物加到$NaBH_4$(1325mg,35.04mmol)。然后在25℃搅拌混合物16小时。LCMS显示反应完成。将反应用水(10mL)淬灭,用EA(10mL*3)萃取。将合并的有机层用盐水(20mL)洗涤,用硫酸钠干燥,过滤并浓缩。残余物的提纯方法为:使用EA/PE(1:3)的combi-flash(闪式色谱)而得到而得到319-1(1500mg,34.6%收率)(黄色固体)。MS(m/z)247.9[M+H]$^+$。

[1906] 步骤2:2-((4-((4-(叔丁基)苯基)氨基)环己基)氧基乙酸乙酯(319-2)

[1907] 向4-[(4-叔丁基苯基)氨基]环己烷-1-醇(500mg,2.02mmol)/DCM(10mL)的溶液中添加2-重氮乙酸乙酯(276.7mg,2.43mmol),铑(II)乙酸乙酯二聚物(89.34mg,0.20mmol),将混合物真空除去。残余物通过快速柱色谱法提纯而得到319-2(400mg,59.3%收率)(黄色固体)。MS(m/z):333.8[M+H]$^+$。

[1908] 步骤3:制备2-((4-((4-(叔丁基)苯基)氨基)环己基)氧基)乙酸(319-3)

[1909] 向319-2(400mg,1.20mmol)/THF(4mL)和水(4mL)的溶液中添加LiOH(172.3mg,7.2mmol)并且在25℃搅拌混合物2小时。将溶剂真空除去。溶于水(20mL)并且用1NHCl调整pH=2,用EA(20mL*3)萃取。将合并的有机层用盐水(20mL)洗涤,用硫酸钠干燥,过滤并且浓缩而得到319-3(200mg,54.6%收率)(黄色固体)。MS(m/z)306.2[M+H]$^+$。

[1910] 步骤4:制备2-((4-((4-(叔丁基)苯基)氨基)环己基)氧基)-N,N-二甲基乙酰胺(319-4)

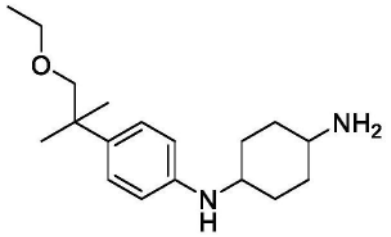
[1911] 向2-((4-((4-(叔丁基)苯基)氨基)环己基)氧基)乙酸(200mg,0.66mmol)/DMF(5mL)的溶液中添加2N Me_2NH(0.7mL,1.31mmol),三乙胺(9198.8mg,1.96mmol)和HATU(373.5mg,0.98mmol)。然后在室温搅拌混合物2小时。将反应用EA(10mL)萃取三次。有机层用硫酸钠干燥,真空浓缩并且残余物的提纯方法为:快速色谱而得到期望的产物(100mg,45.9%)(黄色油)。MS(m/z)332.9[M+H]$^+$。

[1912] 步骤5:制备4-(叔丁基)-N-(4-(2-(二甲基氨基)乙氧基)环己基)苯胺(319)

[1913] 向2-((4-((4-(叔丁基)苯基)氨基)环己基)氧基)-N,N-二甲基乙酰胺(70mg,0.21mmol)/THF(2mL)的溶液中添加$LiAlH_4$(16.8mg,0.42mmol)并且在50℃搅拌混合物16小时。将反应用水淬灭(1mL),1N NaOH(1mL)和水(3mL)。残余物被过滤并且将滤液真空除去并且残余物的提纯方法为:prep-HPLC(柱-Xbridge-C18 150x 21.2mm,5um;移动相:ACN-H_2O(0.1%FA),40%-60%)而得到319A(10.4mg)(白色固体)和319B(15.5mg)(白色固体)。319A:^{1}H NMR(400MHz,CD_3OD)δ7.61(d,J=8.4Hz,2H),7.35(d,J=8.5Hz,2H),3.83-3.79(m,2H),3.46(d,J=3.8Hz,1H),2.91(s,6H),2.68(s,4H),2.20(d,J=10.2Hz,2H),2.09(s,1H),1.55(d,J=12.5Hz,2H),1.36(s,9H)。MS(m/z)319.3[M+H]$^+$。HPLC:Rt:3.843min(柱:XBRIDGE 2.1*50mm,3.5um;移动相:H_2O(0.05%TFA)/ACN(0.05%TFA),ACN由0%至60%7分钟内,7-8min,ACN由60%至100%;0.8mL/min)。319B:^{1}H NMR(400MHz,CD_3OD)δ7.51(d,J=8.6Hz,2H),7.27(d,J=8.6Hz,2H),3.68-3.64(m,2H),3.58(s,1H),3.43-3.36(m,1H),3.30-3.26(m,2H),2.85(s,6H),1.99(d,J=15.0Hz,2H),1.78-1.66(m,4H),1.46(d,J=16.7Hz,2H),1.25(s,9H)。MS(m/z)319.3[M+H]$^+$。HPLC:Rt:3.977min(柱:XBRIDGE 2.1*50mm,3.5um;移动相:H_2O(0.05%TFA)/ACN(0.05%TFA),ACN由0%至60%7分钟内,7-8min,ACN由60%至100%;0.8mL/min)。

[1914] 化合物320

[1915] N^1-(4-(1-乙氧基-2-甲基丙-2-基)苯基)环己烷-1,4-二胺

[1916] 

320A
320B

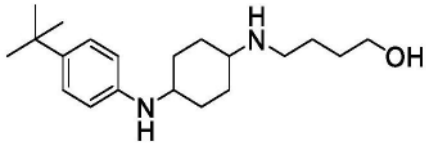
[1917] 由(4-((4-(1-乙氧基-2-甲基丙-2-基)苯基)氨基)环己基)氨基甲酸叔丁酯(120mg,0.3mmol),根据为化合物24的程序制备标题化合物320。混合物的提纯方法:制备HPLC(柱:X Select-CSH-Prep 5μm OBD,19*150mm;ACN/水(0.5%TFA)=15%-33%-95%-95%-10%,0min-10min-10.5min-11.5min-13.0min)而得到化合物320A(Rt=7.46min)(白色固体)和化合物320B(Rt=9.14min)(白色固体)。320A(33.1mg,38%):

[1918] ^{1}H NMR(400MHz,DMSO-d6)δ8.20(s,2H),7.06(d,J=8.4Hz,2H),6.53(d,J=8.4Hz,2H),5.25(s,1H),3.33(m,2H),3.27(s,2H),3.07(m,2H),1.84-1.68(m,6H),1.65-1.50(m,2H),1.17(s,6H),1.06(t,J=7.2Hz,3H)。质谱(m/z):291.3[M+H]$^+$。320B(34.1mg,39%):

[1919] ^{1}H NMR(400MHz,DMSO-d6)δ8.34(s,2H),7.05(d,J=8.4Hz,2H),6.52(d,J=8.4Hz,2H),5.29(s,1H),3.34(m,2H),3.27(s,2H),3.07(m,1H),2.93(m,1H),2.10-1.88(m,4H),1.55-1.39(m,2H),1.21(m,2H),1.16(s,6H),1.05(t,J=7.2Hz,3H)。质谱(m/z):291.3[M+H]$^+$。

[1920] 化合物321

[1921] 4-((4-((4-(叔丁基)苯基)氨基)环己基)氨基)丁烷-1-醇

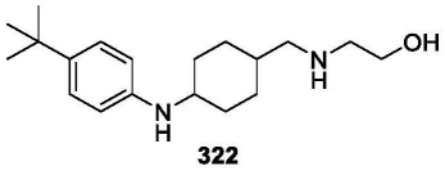
[1922] 

321

[1923] 由4-((4-(叔丁基)苯基)氨基)环己烷-1-酮(50mg,0.20mmol),甲基4-氨基丁烷-1-醇(54mg,0.61mmol)和NaBH(OAc)$_3$(86mg,0.41mmol),根据为20的程序制备标题化合物321(60.9mg),收率为93.8%(白色粉末),经^{1}HNMR证明为1:1的混合物。^{1}H NMR(400MHz,DMSO-d6)δ8.81(s,1H),8.67(s,1H),7.08(dd,J=8.5,5.9Hz,2H),6.52(dd,J=15.8,8.5Hz,2H),5.21(s,1H),4.60(q,J=5.2,3.9Hz,1H),3.42(q,J=5.8Hz,2H),2.98(s,2H),2.90(s,2H),2.15-1.97(m,3H),1.87-1.73(m,2H),1.68(dq,J=15.5,7.9,7.5Hz,2H),1.56(t,J=13.6Hz,1H),1.51-1.39(m,3H),1.21(d,J=1.5Hz,11H)。质谱(m/z):319.2[M+H]$^+$。

[1924] 化合物322

[1925] 2-(((4-((4-(叔丁基)苯基)氨基)环己基)甲基)氨基)乙-1-醇

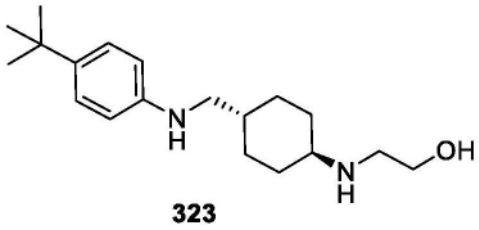
[1926] 

322

[1927] 制备由N-(4-(氨基甲基)环己基)-4-(叔丁基)苯胺(50mg,0.19mmol),2-溴乙-1-醇(24mg,0.19mmol)和碳酸钾(40mg,0.29mmol),根据为12的程序标题化合物322(18mg),收率为30.79%(白色粉末),经^{1}HNMR证明为1:1的混合物。^{1}H NMR(400MHz,DMSO-d6)δ8.73(s,1H),8.00(s,2H),7.41(s,3H),3.68(dt,J=11.4,5.4Hz,1H),3.45(s,1H),3.27(s,1H),2.91(s,1H),2.77(s,1H),2.63(t,J=6.3Hz,1H),1.97(d,J=11.9Hz,1H),1.83(d,J=14.4Hz,1H),1.77-1.45(m,6H),1.26(d,J=3.6Hz,9H),0.98(d,J=12.5Hz,1H)。质谱(m/z):305.2[M+H]$^+$。

[1928] 化合物323

[1929] 2-(((1r,4r)-4-(((4-(叔丁基)苯基)氨基)甲基)环己基)氨基)乙-1-醇

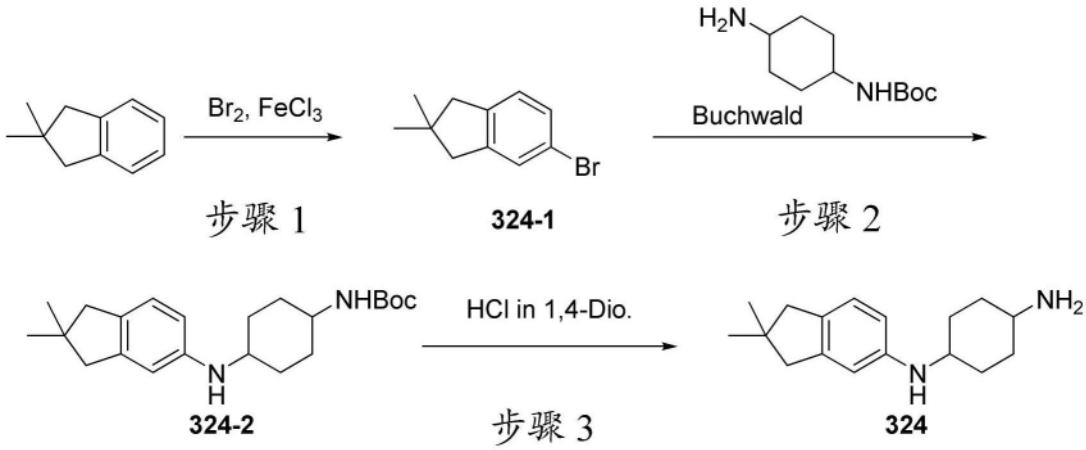
[1930] 

323

[1931] 由N-(((1r,4r)-4-氨基环己基)甲基)-4-(叔丁基)苯胺(50mg,0.19mmol),2-溴乙-1-醇(24mg,0.19mmol)和碳酸钾(40mg,0.29mmol),根据为12的程序制备标题化合物323(25.9mg),收率为44.31%(白色粉末)。^{1}H NMR(400MHz,DMSO-d6)δ8.74(s,1H),8.01(s,1H),7.08(d,J=8.2Hz,2H),6.49(s,2H),5.52-5.15(m,2H),3.67(s,1H),2.98(s,2H),2.82(d,J=6.4Hz,2H),2.09(d,J=12.0Hz,1H),2.01-1.83(m,3H),1.47(s,1H),1.40-1.22(m,4H),1.20(s,9H),1.00(q,J=12.4Hz,2H)。质谱(m/z):305.2[M+H]$^+$。

[1932] 化合物324

[1933] N-(2,2-二甲基-2,3-二氢-1H-茚-5-基)环己烷-1,4-二胺

[1934] 

[1935] 步骤1:制备5-溴-2,2-二甲基-2,3-二氢-1H-茚(324-1)

[1936] 在0℃搅拌2,2-二甲基-2,3-二氢-1H-茚(500mg,2.87mmol),FeCl3(3.4mg,0.021mmol)和Br2(460mg,2.87mmol)/DCM(10mL)的溶液18小时。将混合物真空浓缩而得到

300mg(粗产物)的324-1(收率:46.7%)(黄色油)。

[1937] 步骤2:制备(4-((2,2-二甲基-2,3-二氢-1H-茚-5-基)氨基)环己基)氨基甲酸叔丁酯(324-2)

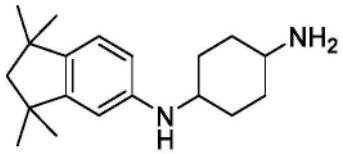
[1938] 向324-1(300mg,1.33mmol),(4-氨基环己基)氨基甲酸叔丁酯(314mg,1.33mmol),Cs_2CO_3(868mg,2.66mmol)和Ruphos(124mg,0.26mmol)/1,4-二氧杂环己烷(15mL)的溶液中添加$Pd_2(dba)_3$(122mg,0.13mmol)。在氮气气氛下搅拌混合物,回流过夜。在冷却到环境温度后,将乙酸乙酯添加到反应混合物并且将混合物通过Celite过滤。用水和饱和盐水洗涤滤液。有机层用硫酸镁干燥并且减压浓缩。残余物的提纯方法为:硅胶柱而得到100mg的324-2(收率:20.7%)(黄色固体)。质谱(m/z):364.3$[M+H]^+$。

[1939] 步骤3:制备N-(2,2-二甲基-2,3-二氢-1H-茚-5-基)环己烷-1,4-二胺(324)

[1940] 324-2(100mg,0.28mmol)和HCl/1,4-二氧杂环己烷(10mL,4N)被置于烧杯中,并且在25℃搅拌18小时。将过量的1,4-二氧杂环己烷(Dio.)真空除去并且残余物的提纯方法为:prep-HPLC(柱-Xbridge-C18 150x 19mm,5um;移动相:ACN-H_2O(0.1%FA),25%-40%)而得到324(11.4mg)(白色固体)。^1H NMR(400MHz,DMSO-d6)δ6.83(d,J=8.0Hz,1H),6.38(s,1H),6.31(d,J=8.0Hz,1H),5.06(s,1H),3.06(s,1H),2.87(s,1H),2.53(s,4H),1.95(dd,J=22.8,12.8Hz,4H),1.36(dd,J=22.0,12.2Hz,2H),1.22-1.09(m,2H),1.07(s,6H)。质谱(m/z):259.3$[M+H]^+$。

[1941] 化合物325

[1942] N^1-(1,1,3,3-四甲基-2,3-二氢-1H-茚-5-基)环己烷-1,4-二胺

[1943] 

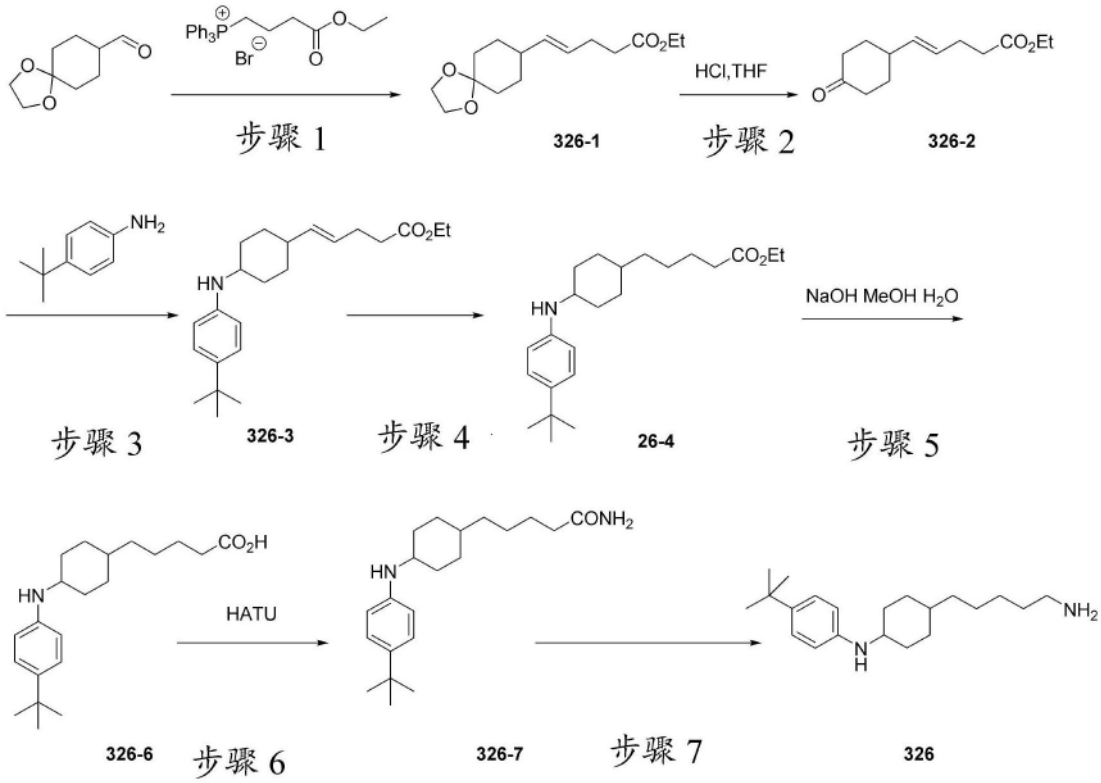
325A
325B

[1944] 由(4-((1,1,3,3-四甲基-2,3-二氢-1H-茚-5-基)氨基)环己基)氨基甲酸叔丁酯(400mg,0.25mmol),1,4-二氧杂环己烷(5mL)和HCl/1,4-二氧杂环己烷(10mL),根据为324的程序制备标题化合物325A(45.7mg)(白色固体)和325B(54.8mg)(白色固体)。325A:^1H NMR(400MHz,CD_3OD)δ6.85(d,J=8.0Hz,1H),6.50(dd,J=8.2,2.2Hz,1H),6.40(d,J=2.2Hz,1H),3.53(s,1H),3.24-3.14(m,1H),1.88-1.66(m,10H),1.22(d,J=7.4Hz,12H)。质谱(m/z):452.3$[M+H]^+$。HPLC:Rt=4.180min(柱:XBRIDGE 3.5um,2.1*50mm,移动相:H_2O(0.05%TFA)-ACN(0.05%TFA),ACN从0至60%在7分钟内,7-8min,ACN由60%至100%,流速:0.8mL/min)。325B:^1H NMR(400MHz,CD_3OD)δ6.85(d,J=8.0Hz,1H),6.50(dd,J=8.2,2.2Hz,1H),6.40(d,J=2.2Hz,1H),3.53(s,1H),3.24-3.14(m,1H),1.88-1.66(m,10H),1.22(d,J=7.4Hz,12H)。质谱(m/z):452.3$[M+H]^+$。HPLC:Rt=4.480min(柱:XBRIDGE 3.5um,2.1*50mm,移动相:H_2O(0.05%TFA)-ACN(0.05%TFA),ACN从0至60%在7分钟内,7-8min,ACN由60%至100%,流速:0.8mL/min)。

[1945] 化合物326

[1946] N-(4-(5-氨基戊基)环己基)-4-(叔丁基)苯胺

[1947]



[1948] 步骤1:制备(E)-5-(1,4-二氧杂螺[4.5]癸烷-8-基)戊-4-烯酸乙酯(326-1)

[1949] 在0℃在氮气气氛下搅拌1,4-二氧杂螺[4.5]癸烷-8-甲醛(1000mg,5.9mmol),NaH(940mg,23.6mmol)和(4-乙氧基-4-氧代丁基)三苯基溴化鏻(5380mg,11.8mmol)/THF(10mL)的溶液18小时。将固体过滤并且将溶剂真空除去。残余物的提纯方法为:硅胶柱而得到1g的326-1(收率:63.4%)(黄色固体)。

[1950] 步骤2:制备(E)-5-(4-氧代环己基)戊-4-烯酸乙酯(326-2)

[1951] 326-1(370mg,1.4mmol)和HCl/THF(20mL,2N)被置于烧杯中,并且在25℃搅拌18小时。将过量的THF真空除去并且残余物的提纯方法为:硅胶柱而得到320mg的326-2(收率:86.4%)(黄色油)。

[1952] 步骤3:制备(E)-5-(4-((4-(叔丁基)苯基)氨基)环己基)戊-4-烯酸乙酯(326-3)

[1953] 在室温搅拌326-2(320mg,1.42mmol),4-(叔丁基)苯胺(214mg,1.42mmol)和$NaBH_3CN$(179mg,2.84mmol)/MeOH(10mL)的溶液18小时。将固体过滤并且将溶剂真空除去。残余物的提纯方法为:硅胶柱而得到225mg的326-3(收率:44.3%)(黄色固体)。质谱(m/z):358.2$[M+H]^+$。

[1954] 步骤4:制备5-(4-((4-(叔丁基)苯基)氨基)环己基)戊烯酸乙酯(326-4)

[1955] 在25℃在氢气气氛下搅拌326-3(225mg,0.63mmol),Pd/C(20mg)/MeOH(10mL)的溶液18小时。将固体过滤并且将溶剂真空除去。残余物的提纯方法为:硅胶柱而得到120mg的326-4(收率:52.9%)(黄色固体)。质谱(m/z):360.3$[M+H]^+$。

[1956] 步骤5:制备5-(4-((4-(叔丁基)苯基)氨基)环己基)戊烯酸(326-5)

[1957] 向326-4(120mg,0.33mmol)/H_2O(5mL)和THF(5mL)的溶液中添加NaOH(66mg,1.65mmol)。在25℃搅拌混合物过夜。将乙酸乙酯添加到反应混合物并且将混合物通过Celite过滤。用水和饱和盐水洗涤滤液。有机层用硫酸镁干燥并且减压浓缩。残余物的提纯

方法为:硅胶柱而得到60mg的326-5(收率:56.3%)(黄色油)。质谱(m/z):332.3[M+1]+。

[1958] 步骤6:制备5-(4-((4-(叔丁基)苯基)氨基)环己基)戊酰胺(326-6)

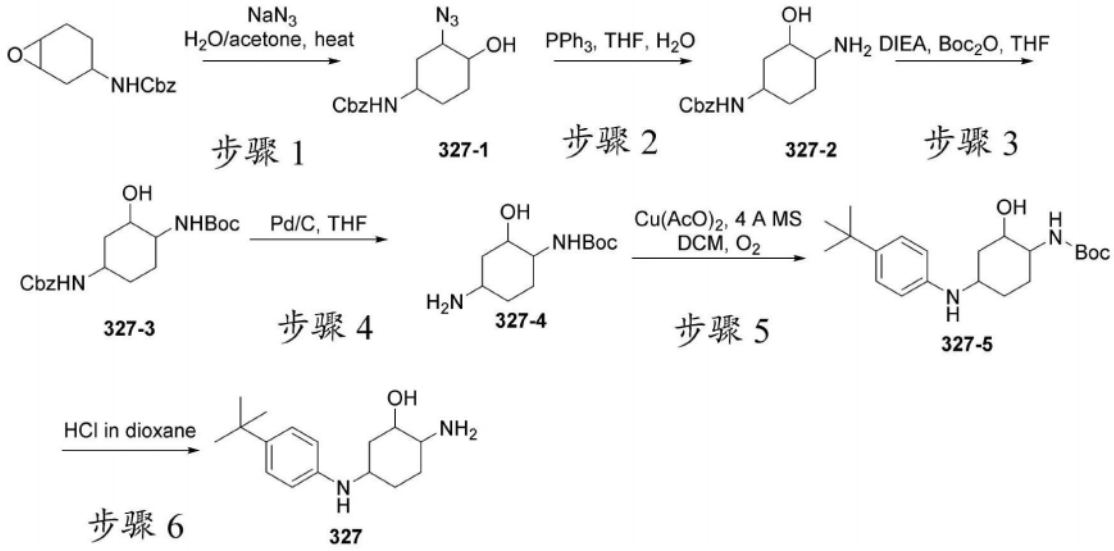
[1959] 在室温搅拌326-5(87mg,0.26mmol),NH_4Cl(56mg,1mmol),HATU(149mg,0.39mmol)和DIEA(169mg,1.3mmol)/DMF(10mL)的溶液18小时。将固体过滤并且将溶剂真空除去。残余物的提纯方法为:硅胶柱而得到40mg的326-6(收率:46.4%)(黄色固体)。质谱(m/z):331.3$[M+H]^+$。

[1960] 步骤7:制备N-(4-(5-氨基戊基)环己基)-4-(叔丁基)苯胺(326)

[1961] 在70℃搅拌326-6(40mg,0.12mmol),BH_3-THF(10mL)/THF(5mL)的溶液18小时。将固体过滤并且将溶剂真空除去。残余物的提纯方法为:prep-HPLC(柱-Xbridge-C18 150x19mm,5um;移动相:ACN-H_2O(0.1%FA),25%-40%)而得到326(5.3mg)(白色固体)。^1H NMR(400MHz,DMSO-d6)δ7.05(d,J=8.8Hz,2H),6.46(d,J=8.8Hz,2H),5.09(s,1H),3.05(s,2H),2.70(t,J=7.2Hz,2H),1.96(d,J=12.0Hz,2H),1.73(d,J=12.0Hz,2H),1.49(s,2H),1.25(d,J=15.6Hz,6H),1.16(d,J=30.8Hz,9H),1.01(dd,J=24.8,11.9Hz,5H)。质谱(m/z):317.3$[M+H]^+$。

[1962] 化合物327

[1963] 2-氨基-5-((4-(叔丁基)苯基)氨基)环己烷-1-醇

[1964] 

[1965] acetone:丙酮heat:加热HCl in dioxane:HCl/二氧杂环己烷

[1966] 步骤1:制备(3-叠氮-4-羟基环己基)氨基甲酸苄酯(327-1)

[1967] 在25℃向(7-氧杂双环[4.1.0]庚烷-3-基)氨基甲酸苄酯(0.9g,3.6mmol)/丙酮(10mL)和H_2O(1mL)的溶液中添加NaN3(0.26g,4mmol)。然后在70℃搅拌混合物4小时。LCMS显示反应完成。将反应用水(20mL)淬灭,用EA(20mL*3)萃取。将合并的有机层用盐水(40mL)洗涤,用硫酸钠干燥,过滤并且浓缩而得到327-1(0.7g,66.3%收率)(黄色油)。MS(m/z):313.1$[M+Na]^+$。

[1968] 步骤2:制备(4-氨基-3-羟基环己基)氨基甲酸苄酯(327-2)

[1969] 在氮气气氛下在25℃向327-1(0.7g,2.4mmol)/THF(10mL)和H_2O(2mL)的溶液中添加PPh3(500mg,1.90mmol)。然后在25℃搅拌混合物过夜。LCMS显示反应完成。将混合物添加到H_2O并用EA洗涤。将水相浓缩而得到327-2(700mg,100%收率)(黄色固体)。MS(m/z):

265.2[M+H]$^+$。

[1970] 步骤3:制备苄基叔丁基(2-羟基环己烷-1,4-二基)二氨基甲酸酯(327-3)

[1971] 在25℃向327-2(0.7g,2.6mmol)/THF(10mL)添加Boc2O(630mg,2.9mmol)和DIEA(513mg,4mmol)的溶液中。然后在25℃搅拌混合物4小时。LCMS显示反应完成。反应用水(20mL)慢慢地淬灭,用EA(20mL*3)萃取。将合并的有机层用盐水(40mL)洗涤,用硫酸钠干燥,过滤并浓缩。残余物的提纯方法为:使用EA/PE(1:2)的combi-flash(闪式色谱)而得到327-3(0.5g,60%收率)(白色固体)。MS(m/z):387.2[M+Na]$^+$。

[1972] 步骤4:制备(4-氨基-2-羟基环己基)氨基甲酸叔丁酯(327-4)

[1973] 向327-3(550mg,1.51mmol)/THF(10mL)的溶液中添加湿Pd/C(80mg)并且在25℃搅拌混合物8小时。LCMS显示反应完成。将反应过滤并且浓缩而得到327-4(120mg,34.6%收率)(黄色固体)。MS(m/z):230.2[M+H]$^+$。

[1974] 步骤5:制备(4-((4-(叔丁基)苯基)氨基)-2-羟基环己基)氨基甲酸叔丁酯(327-5)

[1975] 在氧气气氛下在25℃向327-4(0.12g,0.52mmol)/DCM(10mL)的溶液中添加(4-(叔丁基)苯基)硼酸(92.8mg,0.52mmol),Cu(AcO)2(10mg,0.052mmol)和4A MS(100mg)。然后在25℃搅拌混合物过夜。LCMS显示反应完成。反应用水(20mL)慢慢地淬灭,用EA(20mL*3)萃取。将合并的有机层用盐水(40mL)洗涤,用硫酸钠干燥,过滤并浓缩。残余物的提纯方法为:使用EA/PE(1:1)的combi-flash(闪式色谱)而得到327-5(0.11g,58.5%收率)(黄色固体)。MS(m/z):362.9[M+H]$^+$。

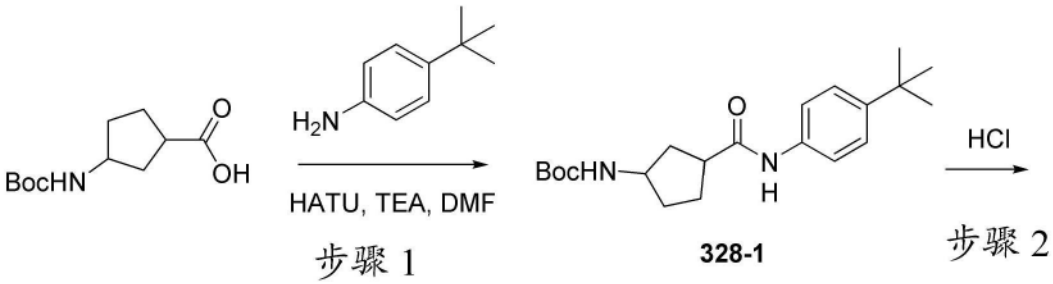
[1976] 步骤6:制备2-氨基-5-((4-(叔丁基)苯基)氨基)环己烷-1-醇(327)

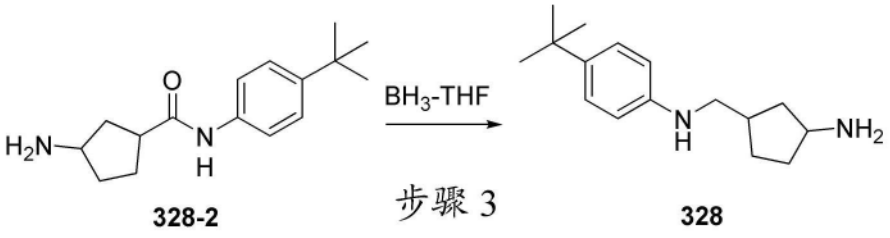
[1977] 向327-5(110mg,0.30mmol)/DCM(4mL)的溶液中添加HCl/二氧杂环己烷(4mL),并且在25℃搅拌混合物2小时。LCMS显示反应完成。将残余物浓缩。残余物的提纯方法为:Prep-HPLC而得到327(15mg,18.8%收率)(黄色固体)。^{1}H NMR(400MHz,CD_3OD)δ7.60(d,J=7.6Hz,2H),7.43(d,J=7.6Hz,2H),3.97-3.85(m,1H),3.75-3.65(m,1H),3.52-3.42(m,1H),2.42-2.25(m,1H),2.09-1.75(m,5H),1.32(s,9H)。MS(m/z):263.0[M+H]$^+$。

[1978] 化合物328

[1979] N-((3-氨基环戊基)甲基)-4-(叔丁基)苯胺

[1980]





[1981] 步骤1:制备(3-((4-(叔丁基)苯基)氨基甲酰基)环戊基)氨基甲酸叔丁酯(328-1)

[1982] 在室温搅拌3-((叔丁氧基羰基)氨基)环戊烷-1-甲酸(300mg,1.31mmol),4-(叔丁基)苯胺(234mg,1.57mmol),HATU(597mg,1.57mmol),DIPEA(254mg,1.96mmol)/DMF(5mL)的混合物过夜。然后添加40mL的水。将固体通过硅胶色谱提纯。获得目标产物(430mg,91%)(黄色固体)。质谱(m/z):383.3[M+H]$^+$。

[1983] 步骤2:制备3-氨基-N-(4-(叔丁基)苯基)环戊烷-1-甲酰胺(328-2)

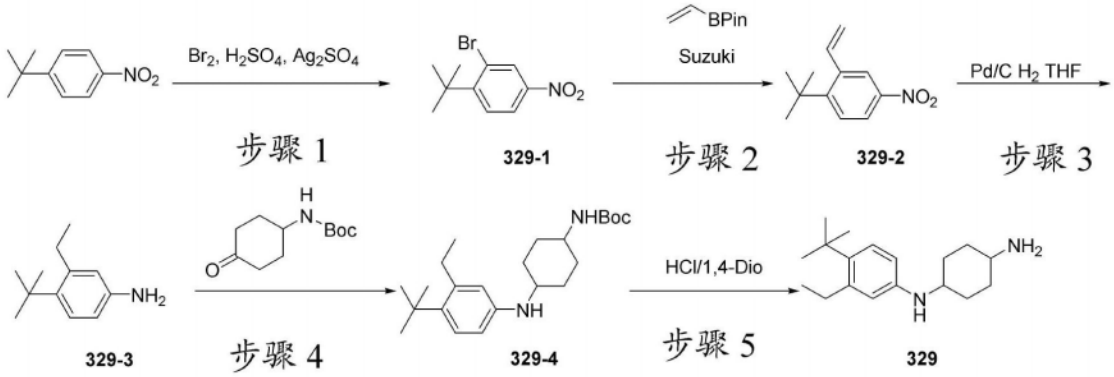
[1984] 向(3-((4-(叔丁基)苯基)氨基甲酰基)环戊基)氨基甲酸叔丁酯(430mg,1.92mmol)/HCl/二氧杂环己烷(5mL)和CH_2Cl_2(5mL)的溶液中。然后在室温搅拌混合物过夜。将反应真空浓缩。残余物的提纯方法为:prep-TLC而得到期望的产物(305mg,97%)(白色固体)。质谱(m/z):261.3[M+H]$^+$。

[1985] 步骤3:制备N-((3-氨基环戊基)甲基)-4-(叔丁基)苯胺(328)

[1986] 向3-氨基-N-(4-(叔丁基)苯基)环戊烷-1-甲酰胺(305mg,1.17mmol)/BH_3-THF(20mL)的溶液中。然后在70℃搅拌混合物过夜。将反应真空浓缩。残余物的提纯方法为:prep-HPLC而得到期望的产物(45.2mg,16%)(白色固体)。^{1}H NMR(400MHz,CD_3OD)δ7.15(d,J=8.8Hz,2H),6.60(d,J=8.7Hz,2H),3.49-3.36(m,1H),3.07(d,J=6.6Hz,1H),2.34-2.16(m,2H),2.08-1.80(m,2H),1.61-1.46(m,2H),1.34-1.29(m,1H),1.25(s,9H)。质谱(m/z):247.3[M+H]$^+$。

[1987] 化合物329

[1988] 1-N-(4-(叔丁基)-3-乙基苯基)环己烷-1,4-二胺

[1989] 

[1990] 步骤1:制备2-溴-1-(叔丁基)-4-硝基苯(329-1)

[1991] 将1-(叔丁基)-4-硝基苯(1g,5.6mmol),Ag2SO_4(2.97g,9.5mmol)/H2SO_4(10mL)的混合物添加Br2(0.89g,5.6mmol)并且在室温搅拌16小时。将混合物倒入稀NaHSO3溶液并且用乙酸乙酯(3x100mL)萃取。将其用H_2O(300mL)淬灭并用EA(3x300 mL)萃取,用MgSO_4干燥,过滤并且浓缩而得到目标产物(600mg,收率:33.3%)(黑色固体)。

[1992] 步骤2:制备1-(叔丁基)-4-硝基-2-乙烯基苯(329-2)

[1993] 向329-1(600mg,2.32mmol)/1,4-二氧杂环己烷(10mL)的溶液中添加Pd(PPh_3)$_4$(268.62mg,0.23mmol),K_2CO_3(962.38mg,6.97mmol)和4,4,5,5-四甲基-2-乙烯基-1,3,2-二氧杂硼杂环戊烷(999.75mg,5.814mmol)。然后在90℃搅拌混合物过夜。将其用H_2O(100mL)淬灭并用EA(3x100 mL)萃取。将粗产物施加到硅胶柱(12g),用PE:EA(10:1)洗脱而得到产物(300mg,收率:50.3%)(黄色固体)。

[1994] 步骤3:制备4-(叔丁基)-3-乙基苯胺(329-3)

[1995] 向329-2(300mg,1.46mmol)/THF(10mL)的溶液中添加Pd/C(15.55mg,0.14mmol)。然后在室温搅拌混合物过夜。将其用H_2O(100mL)淬灭并用EA(3x100 mL)萃取。将有机层合并,用盐水洗涤NaCl(2x100 mL)并且用$MgSO_4$干燥,过滤并且浓缩而得到目标产物(150mg,收率:46.3%)(黄色固体)。质谱(m/z):178.2$[M+H]^+$。

[1996] 步骤4:制备4-环丁基苯胺(329-4)

[1997] 在25℃搅拌1-N-(4-(叔丁基)苯基)环己烷-1,4-二胺(150mg,0.84mmol),(3-氧代丙基)氨基甲酸叔丁酯(181.3mg,0.84mmol),Pic-BH_3(135.75mg,1.27mmol)/AcOH/H_2O=1:10(5.5mL)的混合物过夜。用$NaHCO_3$水溶液将水相的pH调整到8。将其用H_2O(30mL)淬灭并用EA(3x30 mL)萃取,用$MgSO_4$干燥,过滤并且浓缩而得到目标产物(200mg,收率:37.8%)(黄色固体)。质谱(m/z):375.3$[M+H]^+$。

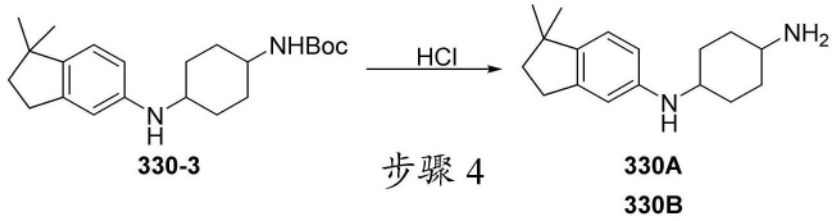
[1998] 步骤5:制备1-N-(4-(叔丁基)-3-乙基苯基)环己烷-1,4-二胺(329)

[1999] 向329-4(200mg,0.53mmol)/1,4-二氧杂环己烷(5mL)的溶液中添加4N HCl/1,4-二氧杂环己烷(10mL)。然后在25℃搅拌混合物过夜。将反应真空浓缩。残余物的提纯方法为:prep-TLC而得到期望的产物329(22.8mg)(白色固体)。^{1}H NMR(400MHz,CD_3OD)δ7.07(d,J=8.6Hz,1H),6.50(d,J=2.8Hz,1H),6.38(dd,J=8.6,2.8Hz,1H),3.52(s,1H),3.25-3.12(m,1H),2.77(q,J=7.6Hz,2H),1.91-1.70(m,8H),1.32(s,9H),1.20(t,J=7.4Hz,3H)。质谱(m/z):275.0$[M+H]^+$。

[2000] 化合物330

[2001] N^1-(1,1-二甲基-2,3-二氢-1H-茚-5-基)环己烷-1,4-二胺

[2002]



[2003] 步骤1:制备3,3-二甲基-6-硝基-2,3-二氢-1H-茚-1-酮(330-1)

[2004] 在0℃向3,3-二甲基-2,3-二氢-1H-茚-1-酮(2g,12.5mmol)/$H2SO_4$(10mL)的溶液中添加KNO3(1.39g,13.7mmol)。然后在0℃搅拌混合物2小时。LCMS显示反应完成。将反应用冰水(20mL)淬灭。将混合物过滤而得到330-1(1.6g,62.5%收率)(黄色固体)。MS(m/z):206.1$[M+H]^+$。

[2005] 步骤2:制备1,1-二甲基-2,3-二氢-1H-茚-5-胺(330-2)

[2006] 在氢气气氛下在25℃向3,3-二甲基-6-硝基-2,3-二氢-1H-茚-1-酮(0.2g,0.97mmol)/MeOH(10mL)的溶液中添加MeSO3H(93mg,0.97mmol)和Pd(OH)2/C(50mg)。然后在25℃和2atm搅拌混合物过夜。LCMS显示反应完成。将混合物过滤并且浓缩而得到330-2(0.15g,95.5%收率)(棕色油)。MS(m/z)162.2$[M+H]^+$。

[2007] 步骤3:制备(4-((1,1-二甲基-2,3-二氢-1H-茚-5-基)氨基)环己基)氨基甲酸叔丁酯(330-3)

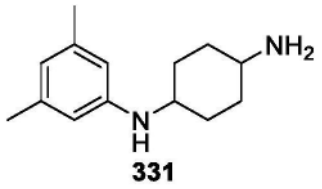
[2008] 在25℃向1,1-二甲基-2,3-二氢-1H-茚-5-胺(0.15g,0.93mmol)/MeOH(10mL)和AcOH(0.1mL)的溶液中添加(4-氧代环己基)氨基甲酸叔丁酯(218mg,1.02mmol)。然后在50℃搅拌混合物2小时。然后在冷却到25℃后将混合物加到$NaBH_3CN$(175mg,2.79mmol)。在25℃搅拌混合物6小时。LCMS显示反应完成。反应用冰水(20mL)慢慢地淬灭,用EA(20mL*3)萃取。将合并的有机层用盐水(40mL)洗涤,用硫酸钠干燥,过滤并浓缩。残余物的提纯方法为:使用EA/PE(1:1)的combi-flash(闪式色谱)而得到330-3(0.14g,42%收率)(黄色固体)。MS(m/z)359.2$[M+H]^+$。

[2009] 步骤4:制备N^1-(1,1-二甲基-2,3-二氢-1H-茚-5-基)环己烷-1,4-二胺(330)

[2010] 向(4-((1,1-二甲基-2,3-二氢-1H-茚-5-基)氨基)环己基)氨基甲酸叔丁酯(140mg,0.39mmol)/DCM(5mL)的溶液中添加HCl/二氧杂环己烷(5mL),并且在25℃搅拌混合物2小时。LCMS显示反应完成。将残余物浓缩。残余物的提纯方法为:Prep-HPLC而得到330A(16mg,15.8%收率)(白色固体)和330B(21.2mg,21%收率)(白色固体)。330A:^1H NMR(300MHz,CD_3OD)δ7.30(d,J=8.0Hz,1H),7.27-7.16(m,2H),3.55-3.40(m,1H),3.20-3.05(m,1H),2.92(t,J=7.2Hz,2H),2.20-2.05(m,4H),1.95(t,J=7.2Hz,2H),1.65-1.37(m,4H),1.23(s,6H)。MS(m/z):259.3$[M+H]^+$。HPLC:Rt:3.807min(柱:XBRIDGE 2.1*50mm,3.5um;移动相:H_2O(0.05%TFA)/ACN(0.05%TFA),ACN由0%至60%7分钟内,7-8min,ACN由60%至100%;0.8mL/min)。330B:^1H NMR(300MHz,CD_3OD)δ7.39-7.25(m,3H),3.70-3.50(m,1H),3.45-3.35(m,1H),2.92(t,J=7.2Hz,2H),2.10-1.80(m,10H),1.23(s,6H)。MS(m/z):259.3$[M+H]^+$。HPLC:Rt:3.915min(柱:XBRIDGE 2.1*50mm,3.5um;移动相:H_2O(0.05%TFA)/ACN(0.05%TFA),ACN由0%至60%7分钟内,7-8min,ACN由60%至100%;0.8mL/min)。

[2011] 化合物331

[2012] N^1-(3,5-二甲基苯基)环己烷-1,4-二胺

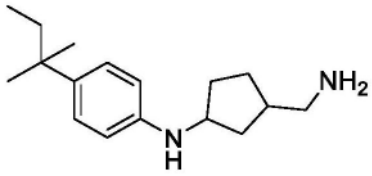
[2013] 

331

[2014] 由3,5-二甲基苯胺(50mg,0.41mmol),(4-氧代环己基)氨基甲酸叔丁酯(132mg,0.61mmol),根据为20的程序制备标题化合物331(81.1mg),收率为90.0%(白色粉末)。^1H NMR(400MHz,DMSO-d6)δ7.96(d,J=22.4Hz,2H),6.20(s,1H),6.19-6.11(m,2H),5.18(s,1H),3.40(s,1H),3.08(d,J=11.5Hz,1H),2.97(s,1H),2.12(d,J=2.0Hz,6H),2.05-1.91(m,2H),1.81-1.65(m,2H),1.51-1.35(m,1H),1.21-1.08(m,1H)。质谱(m/z):219.4$[M+H]^+$。

[2015] 化合物332

[2016] 3-((4-(叔戊基)苯基)氨基)环戊烷-1-甲酰胺

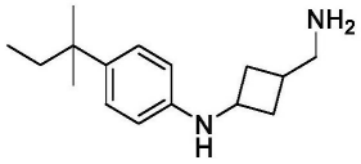
[2017] 

332

[2018] 由3-((4-(叔戊基)苯基)氨基)环戊烷-1-甲酰胺(82mg,0.3mmol)和$LiAlH_4$(34mg,0.9mmol),根据为118的程序制备标题化合物332(15.6mg),总收率为20.0%(白色固体),经^1H NMR证实为3:2的混合物。^1H NMR(400MHz,甲醇-d4)δ7.10-7.03(m,2H),6.62-6.56(m,2H),3.88-3.76(m,1H),2.76(dd,J=12.7,7.3Hz,2H),2.34-1.75(m,4H),1.65-1.33(m,4H),1.19(s,6H),0.63(t,J=7.4Hz,3H)。质谱(m/z):276.3$[M+H]^+$。

[2019] 化合物333

[2020] N-(3-(氨基甲基)环丁基)-4-(叔戊基)苯胺

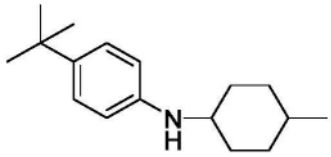
[2021] 

333

[2022] 由3-((4-(叔戊基)苯基)氨基)环丁烷-1-甲酰胺(83mg,0.32mmol)和$LiAlH_4$(36mg,0.96mmol),根据为118的程序制备标题化合物333(30.5mg),总收率为38.8%(白色固体),经^1H NMR证实为3:2的混合物。^1H NMR(301MHz,甲醇-d4)δ7.07-7.00(m,2H),6.46-6.58(m,2H),4.00-3.86(m,0.4H),3.84-3.68(m,0.6H),95(d,J=7.2Hz,0.8H),2.84(d,J=7.2Hz,1.2H),2.60-2.47(m,2H),2.28-2.13(m,1.2H),2.09-1.97(m,0.8H),1.60-1.47(m,2H),0.59(t,J=7.4Hz,3H)。质谱(m/z):247.3$[M+H]^+$。

[2023] 化合物334

[2024] 4-(叔丁基)-N-(4-甲基环己基)苯胺

[2025] 

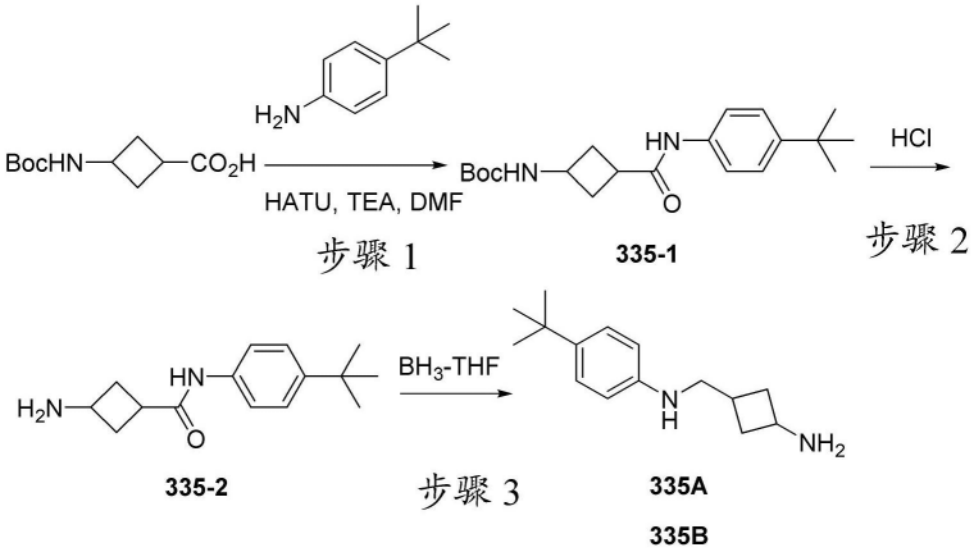
334

[2026] 由4-(叔丁基)苯胺(400mg,2.68mmol),4-甲基环己烷-1-酮(361mg,3.22mmol),DCM(5mL),和三乙酰氧基硼氢化钠(1.14g,5.36mmol),根据为1-1的程序制备标题化合物334(565mg,86.1%)(黄色油)。^1H NMR(400MHz,DMSO-d6)δ7.10-7.00(m,2H),6.54-6.44(m,2H),5.12(dd,J=35.9,8.0Hz,1H),3.37(s,1H),1.93(d,J=11.6Hz,1H),1.69-1.28(m,7H),1.20(d,J=1.3Hz,9H),1.05(t,J=9.2Hz,1H),0.89(dd,J=8.2,6.5Hz,3H)。质谱(m/z):246.2$[M+H]^+$。

[2027] 化合物335

[2028] N-((3-氨基环丁基)甲基)-4-(叔丁基)苯胺

[2029]



[2030] 步骤1:制备(3-((4-(叔丁基)苯基)氨基甲酰基)环丁基)氨基甲酸叔丁酯(335-1)

[2031] 在室温搅拌3-((叔丁氧基羰基)氨基)环戊烷-1-甲酸(300mg,1.31mmol),4-(叔丁基)苯胺(250mg,1.67mmol),HATU(636mg,1.67mmol),DIPEA(270mg,2.09mmol)/DMF(5mL)的混合物过夜。然后添加40mL的水。将固体通过硅胶色谱提纯。获得目标产物(451mg,93%)(黄色固体)。质谱(m/z):346.9$[M+H]^+$。

[2032] 步骤2:制备3-氨基-N-(4-(叔丁基)苯基)环丁烷-1-甲酰胺(335-2)

[2033] 向(3-((4-(叔丁基)苯基)氨基甲酰基)环丁基)氨基甲酸叔丁酯(451mg,1.30mmol)/CH_2Cl_2(5mL)的溶液中添加HCl/二氧杂环己烷(4N;5mL)。然后在室温搅拌混合物过夜。将反应真空浓缩。残余物的提纯方法为:prep-TLC而得到期望的产物(303mg,92%)(白色固体)。质谱(m/z):247.2$[M+H]^+$。

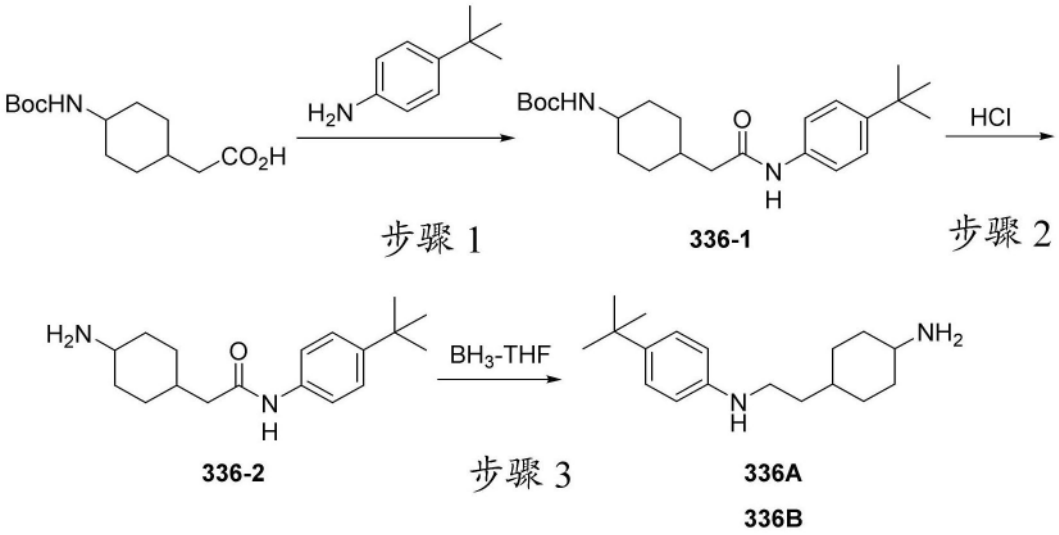
[2034] 步骤3:制备N-((3-氨基环丁基)甲基)-4-(叔丁基)苯胺(335)

[2035] 向3-氨基-N-(4-(叔丁基)苯基)环丁烷-1-甲酰胺(303mg,1.23mmol)/BH_3-THF(20mL)的溶液中。然后在70℃搅拌混合物过夜。将反应真空浓缩。残余物的提纯方法为:prep-HPLC而得到期望的产物335A(27.2mg,7%)(白色固体)和335B(9.8mg,4%)(白色固体)。335A:^{1}H NMR(400MHz,CD_3OD)δ7.15(d,J=8.7Hz,2H),6.59(d,J=8.7Hz,2H),3.43-3.37(m,1H),3.09(d,J=6.5Hz,2H),2.47-2.40(m,2H),2.30-2.21(m,1H),1.69-1.60(m,2H),1.25(s,9H)。质谱(m/z):233.3$[M+H]^+$。HPLC:Rt:3.621min(柱:XBRIDGE 2.1*50mm,3.5um;移动相:H_2O(0.05%TFA)/ACN(0.05%TFA),ACN由0%至60%7分钟内,7-8min,ACN由60%至100%;0.8mL/min)。335B:^{1}H NMR(400MHz,CD_3OD)δ7.15(d,J=8.7Hz,2H),6.60(d,J=8.7Hz,2H),3.81-3.66(m,1H),3.17(d,J=7.6Hz,2H),2.67-2.60(m,1H),2.27-2.03(m,4H),1.25(s,9H)。质谱(m/z):233.3$[M+H]^+$。HPLC:Rt:3.714min(柱:XBRIDGE 2.1*50mm,3.5um;移动相:H_2O(0.05%TFA)/ACN(0.05%TFA),ACN由0%至60%7分钟内,7-8min,ACN由60%至100%;0.8mL/min)。

[2036] 化合物336

[2037] N-(2-(4-氨基环己基)乙基)-4-(叔丁基)苯胺

[2038]



[2039] 步骤1:制备(4-(2-((4-(叔丁基)苯基)氨基)-2-氧代乙基)环己基)氨基甲酸叔丁酯(336-1)

[2040] 向2-(4-((叔丁氧基羰基)氨基)环己基)乙酸(0.2g,0.78mmol)/DMF(10mL)的溶液中添加4-(叔丁基)苯胺(0.14g,0.94mmol),HATU(0.44mg,1.17mmol),DIEA(0.3g,2.34mmol),在25℃搅拌混合物2小时。用水(30mL)稀释,将反应用EA(20mL)萃取三次。有机相用NaCl水溶液(20mL)洗涤三次,用硫酸钠干燥,真空浓缩并且残余物的提纯方法为:快速色谱而得到期望的产物(0.15g,49.5%)(无色油)。质谱(m/z):333.2$[M+H]^+$。

[2041] 步骤2:制备2-(4-氨基环己基)-N-(4-(叔丁基)苯基)乙酰胺(336-2)

[2042] 向(4-(2-((4-(叔丁基)苯基)氨基)-2-氧代乙基)环己基)氨基甲酸叔丁酯(0.15g,0.39mmol)/THF(5mL)的溶液中添加HCl/二氧杂环己烷(5mL)和搅拌混合物2小时。用$NaHCO_3$(10mL)淬灭,将反应用EA(10mL)萃取三次。将合并的有机层用硫酸钠干燥,真空浓缩并且残余物的提纯方法为:快速色谱而得到期望的产物(0.1g,88.9%)(无色油)。质谱(m/z):289.2$[M+H]^+$。

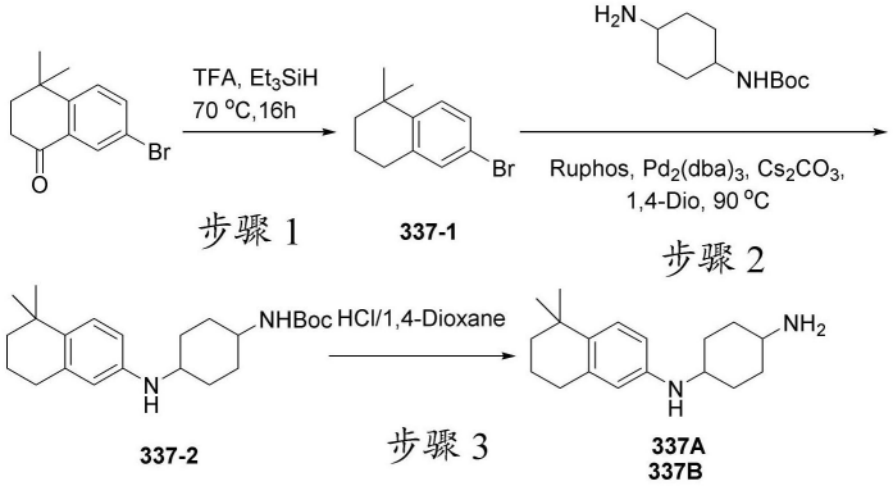
[2043] 步骤3:制备N-(2-(4-氨基环己基)乙基)-4-(叔丁基)苯胺(336)

[2044] 向2-(4-氨基环己基)-N-(4-(叔丁基)苯基)乙酰胺(0.2g,0.5mmol)/THF(2mL)的溶液中添加BH_3-THF(15mL)和在70℃搅拌混合物2小时。用水(10mL)淬灭,将反应用EA(10mL)萃取三次。将合并的有机层用硫酸钠干燥,真空浓缩并且残余物的提纯方法为:prep-HPLC(柱-Xbridge-C18 150x 21.2mm,5um;移动相:ACN-H_2O(0.1%FA),40%-60%)而得到期望的产物336A(11.1mg)(黑色固体)和336B(3.4mg)(黑色固体)。336A:^1H NMR(400MHz,CDCl3)δ7.19(d,J=8.4,2H),6.54(d,J=8.4,2H),3.09(t,J=6.8,2H),2.98(s,1H),2.08(s,2H),1.86(d,J=11.6,2H),1.51-1.42(m,5H),1.27(s,9H),1.01(d,J=12.0,2H)。质谱(m/z):274.9$[M+H]^+$。HPLC:Rt=3.801min(柱:XBRIDGE 3.5um,2.1*50mm,移动相:H_2O(0.05%TFA)-ACN(0.05%TFA),ACN从0至60%在7分钟内,7-8min,ACN由60%至100%,流速:0.8mL/min)。336B:^1H NMR(400MHz,CDCl3)δ7.23(d,J=8.4,2H),6.72(d,J=8.4,2H),3.42(s,1H),3.12(s,2H),1.92(s,2H),1.72(s,4H),1.60(s,5H),1.27(s,9H)。质谱(m/z):274.9$[M+H]^+$。HPLC:Rt=4.110min(柱:XBRIDGE 3.5um,2.1*50mm,移动相:H_2O(0.05%TFA)-ACN(0.05%TFA),ACN从0至60%在7分钟内,7-8min,ACN由60%至100%,流速:0.8mL/

min)。

[2045] 化合物337

[2046] 1-N-(5,5-二甲基-5,6,7,8-四氢萘-2-基)环己烷-1,4-二胺

[2047] 

[2048] 步骤1:6-溴-1,1-二甲基-1,2,3,4-四氢萘(337-1)

[2049] 向7-溴-4,4-二甲基-3,4-二氢萘-1(2H)-酮(500mg,1.97mmol)/TFA(7mL)的混合物添加Et3SiH(2.3g,19.8mmol)。将其用H_2O(30mL)淬灭并用DCM(3x30 mL)萃取。将有机层合并,用盐水NaCl(2x30 mL)洗涤并且用$MgSO_4$干燥,过滤并且浓缩而得到目标产物(500mg,收率:95.2%)(黄色油)。

[2050] 步骤2:(4-((5,5-二甲基-5,6,7,8-四氢萘-2-基)氨基)环-己基)氨基甲酸叔丁酯(337-2)

[2051] 向337-1(300mg,1.25mmol)/1,4-二氧杂环己烷(15mL)的溶液中添加(4-氨基环己基)氨基甲酸叔丁酯(268.82mg,1.25mmol),$Pd_2(dba)_3$(144.87mg,0.13mmol),Ruphos(117mg,0.25mmol)和Cs_2CO_3(817.42mg,2.5mmol)。然后在90℃搅拌混合物16小时。将其用H_2O(300mL)淬灭并用EA(3x300 mL)萃取。将有机层合并,用盐水NaCl(2x300 mL)洗涤并且用$MgSO_4$干燥,过滤并且浓缩。将粗产物施加到硅胶柱(24g),用PE:EA(10:1)洗脱而得到产物(200mg,收率:38.5%)(白色固体)。质谱(m/z):373.3$[M+H]^+$。

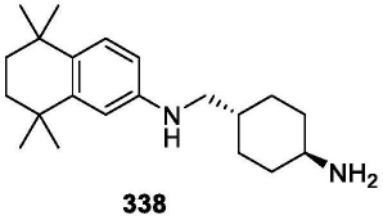
[2052] 步骤3:制备1-N-(5,5-二甲基-5,6,7,8-四氢萘-2-基)环己烷-1,4-二胺(337)

[2053] 向337-2(200mg,0.54mmol)/1,4-二氧杂环己烷(5mL)的溶液中添加4N HCl/1,4-二氧杂环己烷(10mL)。然后在25℃搅拌混合物过夜。将反应真空浓缩。残余物的提纯方法为:prep-TLC而得到期望的产物337A(56.1mg)(白色固体)和337B(24.7mg)(白色固体)。337A:^1H NMR(400MHz,CD_3OD)δ7.47(dd,J=8.4,5.2Hz,1H),7.07(d,J=8.4Hz,1H),6.97(d,J=9.8Hz,1H),3.44(m,1H),3.11(m,1H),2.92-2.70(m,2H),2.11(d,J=10.0Hz,4H),1.87-1.76(m,2H),1.71-1.64(m,2H),1.58-1.41(m,4H),1.27-1.24(m,6H)。质谱(m/z):373.0$[M+H]^+$。HPLC:Rt=4.141min(柱:XBRIDGE 3.5um,2.1*50mm,移动相:H_2O(0.05%TFA)-ACN(0.05%TFA),ACN从0至60%在7分钟内,7-8min,ACN由60%至100%,流速:0.8mL/min)。337B:^1H NMR(400MHz,CD_3OD)δ7.47(d,J=8.4Hz,1H),7.17-7.08(m,1H),7.02(s,1H),3.59(s,1H),3.39(s,1H),2.77(t,J=6.2Hz,2H),2.03-1.77(m,10H),1.72-1.59(m,2H),1.25(d,J=14.8Hz,6H)。质谱(m/z):373.0$[M+H]^+$。HPLC:Rt=4.266min(柱:XBRIDGE 3.5um,

2.1*50mm,移动相:H_2O(0.05％TFA)-ACN(0.05％TFA),ACN从0至60％在7分钟内,7-8min,ACN由60％至100％,流速:0.8mL/min)。

[2054] 化合物338

[2055] N-(((1r,4r)-4-氨基环己基)甲基)-5,5,8,8-四甲基-5,6,7,8-四氢萘-2-胺

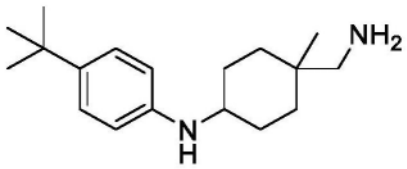
[2056] 

338

[2057] 由((1r,4r)-4-(((5,5,8,8-四甲基-5,6,7,8-四氢萘-2-基)氨基)甲基)环己基)氨基甲酸叔丁酯,DCM(6mL)和2,2,2-三氟乙酸(3mL),根据为24的程序制备标题化合物338(25.7mg,21.1％)(黄色油)。^{1}H NMR(400MHz,DMSO-d6)δ7.79-7.59(m,3H),6.96(d,J＝8.5Hz,1H),6.46-6.26(m,2H),2.91(d,J＝5.0Hz,1H),2.78(d,J＝6.5Hz,2H),1.97-1.77(m,4H),1.54(d,J＝2.1Hz,4H),1.42(s,1H),1.30-1.17(m,2H),1.15(s,6H),1.12(s,6H),1.04-0.90(m,2H)。质谱(m/z):315.3$[M+H]^+$。

[2058] 化合物339

[2059] N-(4-(氨基甲基)-4-甲基环己基)-4-(叔丁基)苯胺

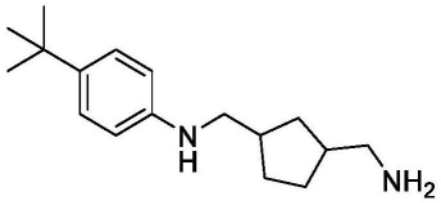
[2060] 

339

[2061] 由4-(叔丁基)苯胺(70mg,0.47mmol)和1-甲基-4-氧代环己烷-1-甲腈(77mg,0.56mmol),根据为84的程序制备标题化合物339(57.1mg),两步总收率为44.9％(白色粉末)。^{1}H NMR(300MHz,DMSO-d6)δ7.81(s,3H),7.06(d,J＝8.0Hz,2H),6.49(s,2H),3.17(d,J＝12.1Hz,1H),2.75(d,J＝5.7Hz,2H),1.84-1.53(m,5H),1.43(s,1H),1.27(s,2H),1.19(s,9H),0.96(d,J＝5.1Hz,3H)。质谱(m/z):275.3$[M+H]^+$。

[2062] 化合物340

[2063] N-((3-(氨基甲基)环戊基)甲基)-4-(叔丁基)苯胺

[2064] 

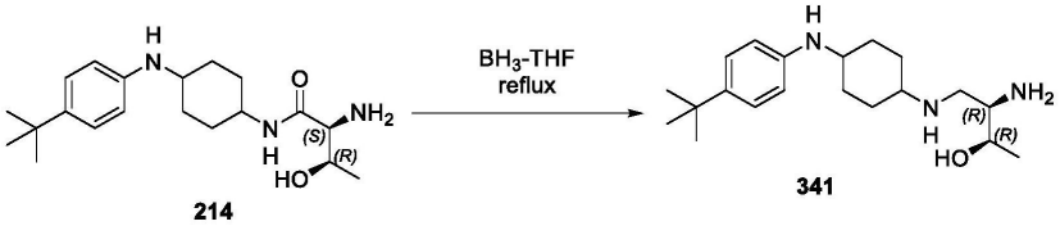
340

[2065] 由4-(叔丁基)苯胺(100mg,0.67mmol)和环戊烷-1,3-二甲酸(318mg,2.01mmol),根据为84的程序制备标题化合物340(57.1mg),两步总收率为44.9％(白色粉末)。^{1}H NMR(400MHz,DMSO-d6)δ7.98(s,2H),7.13-7.00(m,2H),6.54-6.41(m,2H),5.36(s,1H),2.89(dd,J＝7.0,4.6Hz,2H),2.74(d,J＝7.2Hz,2H),2.24-2.04(m,2H),2.00(dt,J＝13.8,7.0Hz,1H),1.82-1.63(m,2H),1.41-1.27(m,2H),1.19(s,9H),0.89(dt,J＝12.5,9.6Hz,

1H)。质谱(m/z):261.4[M+H]$^+$。

[2066] 化合物341

[2067] (2R,3R)-3-氨基-4-((4-((4-(叔丁基)苯基)氨基)环己基)氨基)丁烷-2-醇

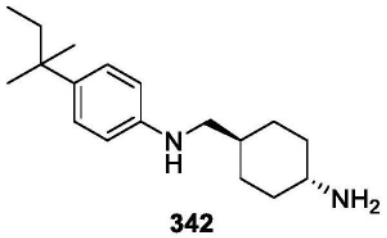
[2068] 

214 341

[2069] 向(2S,3R)-2-氨基-N-(4-((4-(叔丁基)苯基)氨基)环己基)-3-羟基丁酰胺(230mg,0.66mmol)/THF(5mL)的溶液中添加BH_3-THF(10mL)。在70℃搅拌反应18小时。将固体过滤并且将溶剂真空除去。残余物的提纯方法为:prep-HPLC(柱-Xbridge-C18 150x19mm,5um;移动相:ACN-H_2O(0.1%FA),25%-40%)而得到341(80.2mg)(白色固体)。^{1}H NMR(400MHz,DMSO-d6)δ8.29(s,2H),7.06(d,J=8.6Hz,2H),6.48(d,J=8.6Hz,2H),3.73-3.63(m,1H),3.09(t,J=10.4Hz,1H),2.83(t,J=9.6Hz,2H),2.63(m,1H),1.96(s,4H),1.28(d,J=9.4Hz,1H),1.20(s,9H),1.14(dd,J=18.6,6.8Hz,6H)。质谱(m/z):334.3[M+H]$^+$。

[2070] 化合物342

[2071] N-(((1r,4r)-4-氨基环己基)甲基)-4-(叔戊基)苯胺

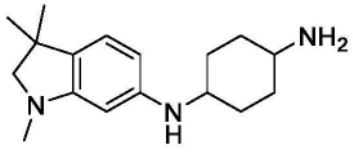
[2072] 

342

[2073] 由((1r,4r)-4-(((4-(叔戊基)苯基)氨基)甲基)环己基)氨基甲酸叔丁酯(72mg,0.193mmol),TFA(1mL)和DCM(10mL),根据为24的程序制备标题化合物342(7.5mg),总收率为14.2%(白色固体)。^{1}H NMR(400MHz,DMSO-d6)δ7.84(s,3H),7.00(d,J=8.4Hz,2H),6.48(d,J=8.4Hz,2H),5.44(q,J=8.8,5.6Hz,1H),2.94-2.74(m,3H),2.02-1.79(m,4H),1.52(q,J=7.2Hz,3H),1.30(qd,J=12.8,3.6Hz,2H),1.16(s,5H),1.07-0.91(m,2H),0.60(t,J=7.2Hz,3H)。质谱(m/z):275.3[M+H]$^+$。

[2074] 化合物343

[2075] N^1-(1,3,3-三甲基吲哚啉-6-基)环己烷-1,4-二胺

[2076] 

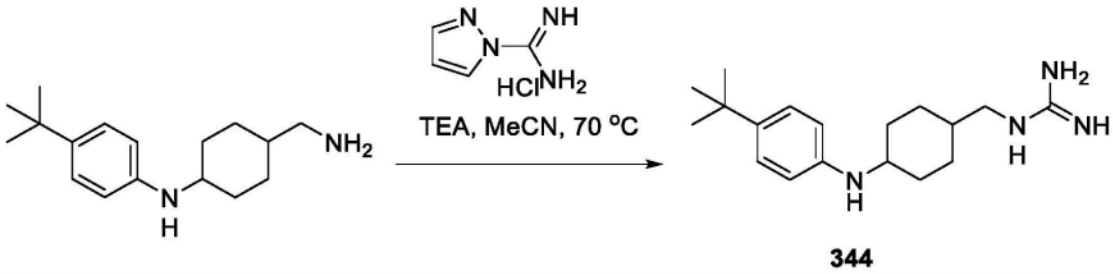
343

[2077] 由(4-((1,3,3-三甲基吲哚啉-6-基)氨基)环己基)氨基甲酸叔丁酯(200mg,0.53mmol),1,4-二氧杂环己烷(5mL)和HCl/1,4-二氧杂环己烷(5mL),根据为37的程序制备标题化合物343(21.7mg)(黄色固体)。^{1}H NMR(400MHz,CD_3OD)δ6.68-6.62(m,1H),6.02-5.93(m,1H),5.85(dd,J=13.8,1.8Hz,1H),3.34(s,1H),3.21(dt,J=3.2,1.6Hz,2H),2.75-

2.66(m,1H),2.62-2.52(m,3H),1.59(tdd,J=11.6,10.4,4.8Hz,6H),1.42(dt,J=10.8,7.0Hz,2H),1.12(s,6H)。质谱(m/z):274.3[M+H]$^+$。

[2078] 化合物344

[2079] 1-((4-((4-(叔丁基)苯基)氨基)环己基)甲基)胍

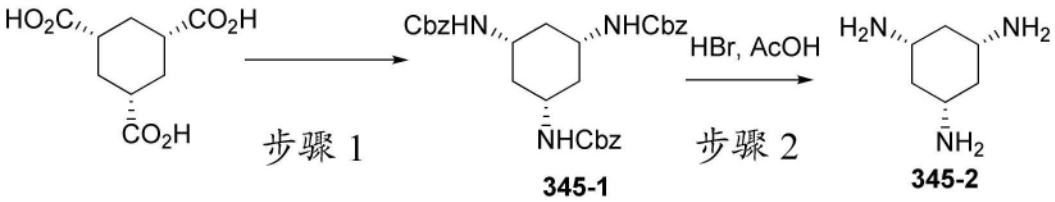
[2080] 

344

[2081] 向10mL的圆底烧瓶中装入N-(4-(氨基甲基)环己基)-4-(叔丁基)苯胺(120mg,0.46mmol),1H-吡唑-1-羧酰胺(carboximidamide)盐酸盐(76mg,0.69mmol),TEA(93mg,0.92mmol)和1,4-二氧杂环己烷(5mL)。在70℃搅拌反应18小时。将反应混合物过滤并且将滤液浓缩。残余物的提纯方法为:prep-HPLC(柱-Xbridge-C18 150x 19mm,5um;移动相:ACN-H_2O(0.1%FA),25%-40%)而得到344(18.3mg)(白色固体)。^{1}H NMR(400MHz,DMSO-d6)δ 8.76(s,1H),8.40(s,1H),7.73(s,2H),7.07(d,J=8.8Hz,2H),6.53(d,J=8.8Hz,2H),3.45(s,1H),2.98(t,J=5.8Hz,2H),1.68-1.39(m,9H),1.20(s,9H)。质谱(m/z):303.3[M+H]$^+$。

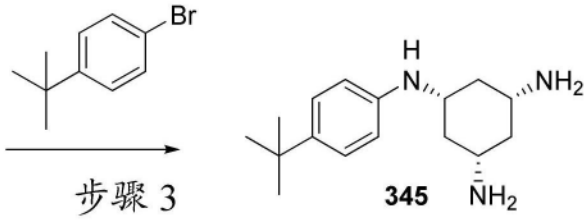
[2082] 化合物345

[2083] (1s,3R,5S)-N^1-(4-(叔丁基)苯基)环己烷-1,3,5-三胺



345-1 345-2

[2084]



345

[2085] 步骤1:制备(1s,3s,5s)-环己烷-1,3,5-三胺(345-1)

[2086] 添加cis-1,3,5-环己烷三羧酸(1.0g,4.6mmol),三乙胺(1.4g,13.8mmol),和二苯基磷酰叠氮化物(3.8g,13.8mmol)/甲苯(30mL),然后在室温搅拌30分钟。在80℃搅拌混合物90分钟,然后向该混合物中添加苄基醇(1.99g,18.4mmol),使溶液回流24小时。将溶液冷却到环境温度。通过过滤收集白色沉淀,用冷甲苯洗涤沉淀而得到产物(1.7g,69.5%)。质谱(m/z):532.3[M+H]$^+$。

[2087] 步骤2:制备(1s,3s,5s)-环己烷-1,3,5-三胺(345-2)

[2088] 将三氨基甲酸苄酯(1.4g,2.63mmol)溶解于33%HBr/冰醋酸(5mL)。在搅拌下使混合物搁置90分钟。向该混合物中添加二乙醚(100mL),滤出产物,用二乙醚洗涤产物而得到

产物(300mg,88.2%)。质谱(m/z):130.1[M+H]$^+$。

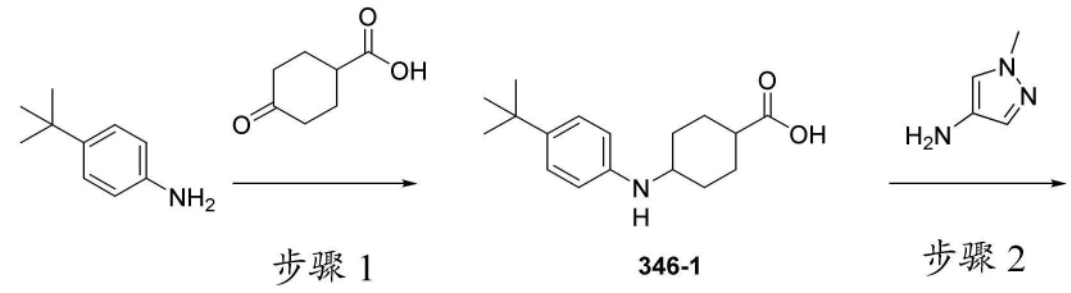
[2089] 步骤3:制备(1s,3R,5S)-N^1-(4-(叔丁基)苯基)环己烷-1,3,5-三胺(345)

[2090] 向环己烷-1,3,5-三胺三氢溴酸盐(174mg,0.47mmol),1-溴-4-叔丁基苯(50mg,0.23mmol)/甲苯(10mL)的溶液中添加$Pd_2(dba)_3$(43mg,0.047mmol),Cs_2CO_3(611mg,1.88mmol),和RuPhos(22mg,0.047mmol),并且将混合物加热到110℃16小时,然后冷却到室温,真空除去溶剂。残余物的提纯方法为:prep-HPLC(柱-Gemini-C18 150x21.2mm,5um;移动相:ACN-H_2O(0.1%FA),5%-20%)而得到期望的产物345(黄色固体)(12.2mg,19.9%)。^{1}H NMR(400MHz,DMSO-d6)δ7.16(d,J=8.5Hz,2H),6.63(d,J=8.3Hz,2H),3.47(s,1H),3.17(s,1H),2.54(s,2H),2.22(d,J=10.8Hz,3H),1.45-1.37(m,1H),1.22(s,9H),1.19(s,1H)。质谱(m/z):262.3[M+H]$^+$。

[2091] 化合物346

[2092] N-((4-((4-(叔丁基)苯基)氨基)环己基)甲基)-1-甲基-1H-吡唑-4-胺

[2093]



[2094] 步骤1:制备4-((4-(叔丁基)苯基)氨基)环己烷-1-甲酸(346-1)

[2095] 在50℃搅拌4-(叔丁基)苯胺(1g,0.0067mmol),4-氧代环己烷-1-甲酸(1.14g,0.0080mmol)和$NaBH_3CN$(0.84g,0.0134mmol)/MeOH(10mL)和HOAc(1滴)的混合物过夜。在冷却后,将过量的MeOH真空除去并且将残余物用水稀释(20mL),用乙酸乙酯(20mL)萃取三次。合并有机相,真空除去溶剂并且通过硅胶色谱(PE:EA=3:1)提纯粗产物而得到期望的产物(油)(1.5g,49.2%)。质谱(m/z):276.3[M+H]$^+$。

[2096] 步骤2:制备4-((4-(叔丁基)苯基)氨基)-N-(1-甲基-1H-吡唑-4-基)环己烷-1-甲酰胺(346-2)

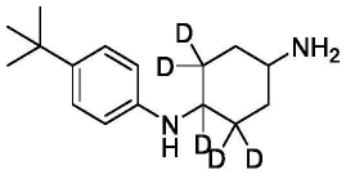
[2097] 在室温将4-((4-(叔丁基)苯基)氨基)环己烷-1-甲酸(100mg,0.3631mmol),1-甲基-1H-吡唑-4-胺(42.3mg,0.4357mmol),HATU(207.1mg,0.5447mmol)和DIEA(140.8mg,1.0893mmol)/DMF(10mL)的混合物搅拌过夜。然后反应溶液用水(30mL)稀释,用乙酸乙酯(20mL)萃取三次。合并有机相,真空除去溶剂并且通过硅胶色谱(PE/EA=2:1)提纯粗产物而得到期望的产物(油)(200mg,77.7%)。质谱(m/z):355.5[M+H]$^+$。

[2098] 步骤3:制备N-((4-((4-(叔丁基)苯基)氨基)环己基)甲基)-1-甲基-1H-吡唑-4-胺(346)

[2099] 向N-((4-((4-(叔丁基)苯基)氨基)环己基)甲基)-1-甲基-1H-吡唑-4-胺(200mg,0.5642mmol)/THF(1mL)的溶液中添加BH_3-THF(30mL)。然后在70℃搅拌混合物过夜。在反应完成后,真空除去溶剂并且残余物的提纯方法为:prep-HPLC(柱-Xbridge-C18 150x21.2mm,5um;移动相:ACN-H_2O(0.1%FA),2%-20%)而得到期望的产物346(6mg,3%)(白色固体)。^{1}H NMR(400MHz,CD_3OD)δ7.15(dd,J=11.9,9.2Hz,4H),6.65(d,J=8.6Hz,2H),3.79(s,3H),3.53(s,1H),2.89(d,J=6.8Hz,2H),1.74-1.44(m,9H),1.28(s,9H)。质谱(m/z):341.2$[M+H]^+$。

[2100] 化合物347

[2101] N^1-(4-(叔丁基)苯基)环己烷-1,2,2,6,6-d5-1,4-二胺

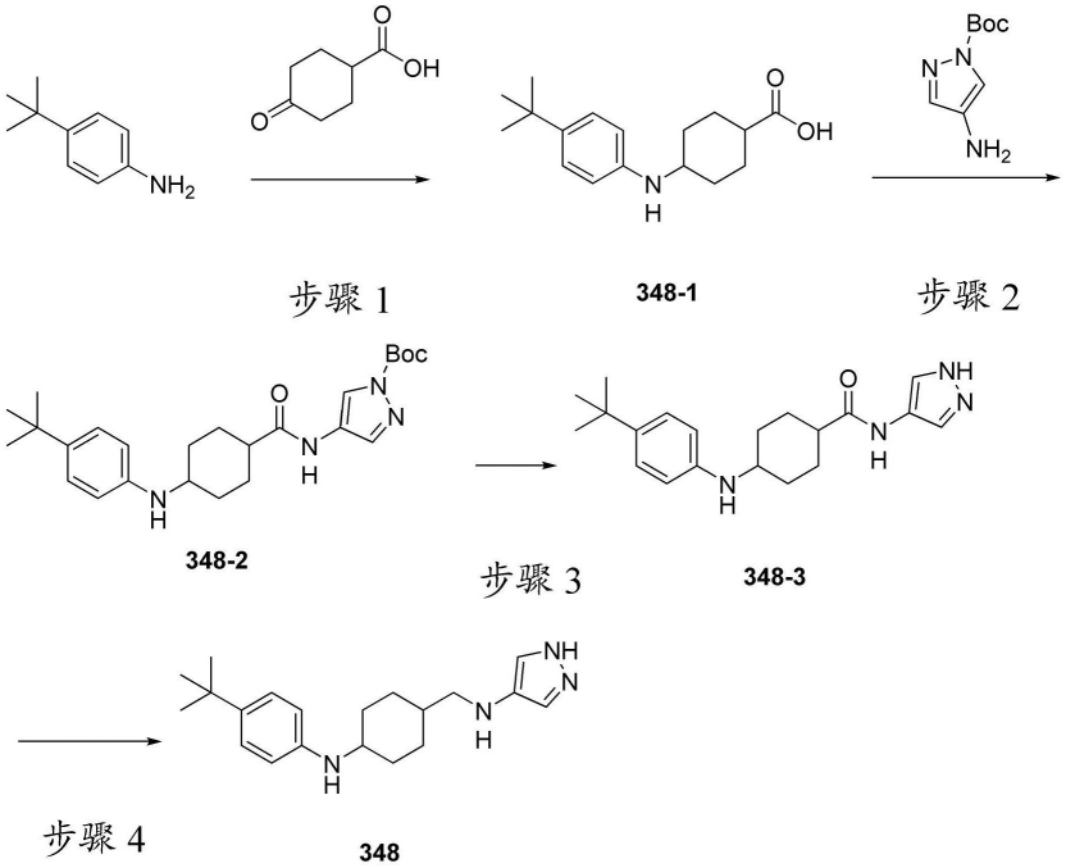
[2102] 

347

[2103] 由(4-((4-(叔丁基)苯基)氨基)环己基-3,3,4,5,5-d5)氨基甲酸叔丁酯(176mg,0.5mmol),和TFA,根据为化合物24的程序制备标题化合物347(105.7mg),总收率为83.9%(白色固体)。^{1}H NMR(400MHz,甲醇-d4)δ7.16(d,J=8.4Hz,2H),6.61(d,J=8.4Hz,2H),3.19-2.95(m,1H),2.07-1.98(m,1H),1.85-1.67(m,2H),1.52-1.40(m,1H),1.25(s,9H)。质谱(m/z):252.3$[M+H]^+$。

[2104] 化合物348

[2105] N-((4-((4-(叔丁基)苯基)氨基)环己基)甲基)-1H-吡唑-4-胺

[2106] 

[2107] 步骤1:制备4-((4-(叔丁基)苯基)氨基)环己烷-1-甲酸(348-1)

[2108] 在50℃将4-(叔丁基)苯胺(1g,0.0067mmol),4-氧代环己烷-1-甲酸(1.14g,0.0080mmol)和$NaBH_3CN$(0.84g,0.0134mmol)/MeOH(10mL)和HOAc(1滴)的混合物搅拌过夜。在冷却后,将过量的MeOH真空除去并且残余物用水(20mL)稀释,用乙酸乙酯(20mL)萃取三次。合并有机相,真空除去溶剂并且通过硅胶色谱(PE:EA=3:1)提纯粗产物而得到期望的产物(油)(1.5g,49.2%)。质谱(m/z):276.3$[M+H]^+$。

[2109] 步骤2:4-(4-((4-(叔丁基)苯基)氨基)环己烷-1-甲酰胺基(carboxamido))-1H-吡唑-1-甲酸叔丁酯(348-2)

[2110] 在室温将4-((4-(叔丁基)苯基)氨基)环己烷-1-甲酸(300mg,1.0894mmol),4-氨基-1H-吡唑-1-甲酸叔丁酯(301.03mg,1.6341mmol),EDCI(313.26mg,1.6341mmol),DIEA(281.59mg,2.1788mmol)和HOBT(220.80mg,1.6341mmol)/DMF(10mL)的混合物搅拌过夜。然后反应溶液用水(30mL)稀释,用乙酸乙酯(20mL)萃取三次。合并有机相,真空除去溶剂并且通过硅胶色谱(PE/EA=5:1)提纯粗产物而得到期望的产物(油)(376mg,46.4%)。质谱(m/z):441.5$[M+H]^+$。

[2111] 步骤3:制备4-((4-(叔丁基)苯基)氨基)-N-(1H-吡唑-4-基)环己烷-1-甲酰胺(348-3)

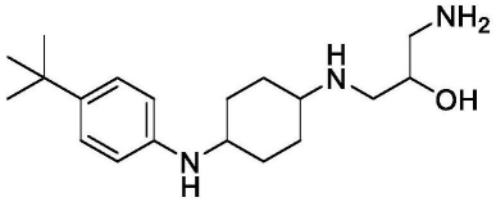
[2112] 在25℃搅拌4-(4-((4-(叔丁基)苯基)氨基)环己烷-1-甲酰胺基(carboxamido))-1H-吡唑-1-甲酸甲酯(376mg,0.8515mmol)/1,4-二氧杂环己烷(10mL)和1,4-二氧杂环己烷/HCl(10mL)的混合物16小时。在反应完成后,真空除去溶剂而得到期望的产物(油)(200mg,38.6%)。质谱(m/z):340.9$[M+H]^+$。

[2113] 步骤4:制备N-((4-((4-(叔丁基)苯基)氨基)环己基)甲基)-1H-吡唑-4-胺(348)

[2114] 向N-((4-((4-(叔丁基)苯基)氨基)环己基)甲基)-1-甲基-1H-吡唑-4-胺(200mg,0.5874mmol)/THF(1mL)的溶液中添加BH_3-THF(30mL)。然后在25℃搅拌混合物过夜。在反应完成后,真空除去溶剂并且残余物的提纯方法为:prep-HPLC(柱-Xbridge-C18 150x 19mm,5um;移动相:ACN-H_2O(0.05%NH_3),55%-60%)而得到期望的产物348(9.7mg,5.0%)(紫色固体)。^{1}H NMR(400MHz,DMSO-d6)δ12.00(s,1H),7.06(d,J=8.6Hz,2H),7.01(s,2H),6.47(d,J=8.6Hz,2H),5.10(d,J=7.8Hz,1H),4.26(brs,1H),3.08(brs,1H),2.69(d,J=6.5Hz,2H),1.98(m,2H),1.84(m,2H),1.47(brs,1H),1.20(s,9H),1.05(q,J=10.9Hz,4H)。质谱(m/z):327.5$[M+H]^+$。

[2115] 化合物349

[2116] 1-氨基-3-((4-((4-(叔丁基)苯基)氨基)环己基)氨基)丙-2-醇

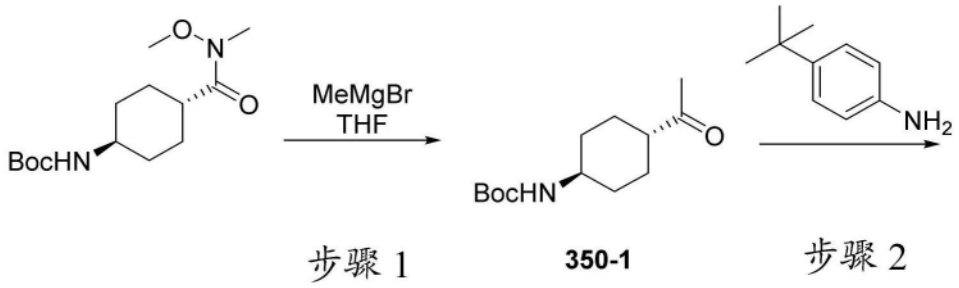
[2117] 

349A
349B

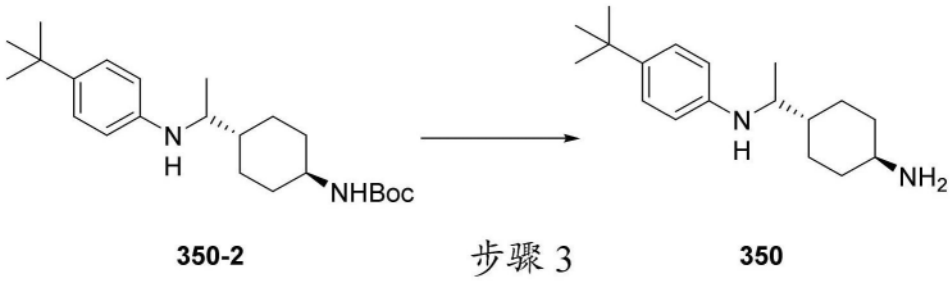
[2118] 由(3-((4-((4-(叔丁基)苯基)氨基)环己基)氨基)-2-羟基丙基)氨基甲酸叔丁酯(300mg,0.68mmol),和4MHCl/二氧杂环己烷(20mL),根据为37的程序制备标题化合物349A(68.7mg,29.8%)(黄色固体)和化合物349B(62mg,27.4%)(黄色固体)。349A:^{1}H NMR(400MHz,CD_3OD)δ7.37(d,J=8.7Hz,2H),6.96(d,J=8.6Hz,2H),4.14(tt,J=9.3,3.3Hz,0H),3.41-3.32(m,0H),3.23-3.00(m,2H),2.94(d,J=8.6Hz,1H),2.18(s,2H),1.65-1.34(m,2H),1.28(s,5H)。质谱(m/z):320.8$[M+H]^+$。HPLC:Rt:2.996min(柱:XBRIDGE 2.1*50mm,3.5um;移动相:H_2O(0.05%TFA),ACN(0.05%TFA),ACN由0%至60%7分钟内,7-8min,ACN由60%至100%;0.8mL/min)。349B:^{1}H NMR(400MHz,CD_3OD)δ7.14(d,J=8.7Hz,2H),6.60(d,J=8.7Hz,2H),4.19-4.11(m,1H),3.63-3.56(m,0H),3.23-2.99(m,2H),2.92(dd,J=13.0,8.6Hz,1H),2.02-1.67(m,8H),1.23(d,J=1.7Hz,9H)。质谱(m/z):320.8$[M+H]^+$。HPLC:Rt:3.380min(柱:XBRIDGE 2.1*50mm,3.5um;移动相:H_2O(0.05%TFA)ACN(0.05%TFA),ACN由0%至60%7分钟内,7-8min,ACN由60%至100%;0.8mL/min)。

[2119] 化合物350

[2120] N-((S)-1-((1r,4S)-4-氨基环己基)乙基)-4-(叔丁基)苯胺



[2121]



[2122] 步骤1:制备((1r,4r)-4-乙酰基环已基)氨基甲酸叔丁酯(350-1)

[2123] 在0℃在氮气气氛下将((1r,4r)-4-(甲氧基(甲基)氨基甲酰基)环已基)氨基甲酸叔丁酯(500mg,1.746mmol),和CH3MgBr(1.46mL,4.365mmol)/THF(10mL)的混合物搅拌过夜。在冷却后,稀释,用乙酸乙酯(20mL)萃取三次。合并有机相,真空除去溶剂并且通过硅胶色谱(PE:EA=2:1)提纯粗产物而得到期望的产物(白色固体)(350mg,46.5%)。质谱(m/z):242.17[M+H]$^+$。

[2124] 步骤2:制备((1S,4r)-4-((S)-1-((4-(叔丁基)苯基)氨基)乙基)环已基)氨基甲酸叔丁酯(350-2)

[2125] 在25℃将4-(叔丁基)苯胺(200mg,1.3402mmol),叔丁基((1r,4r)-4-乙酰基环已基)氨基甲酸叔丁酯(485.4mg,2.0103mmol)和$NaBH(OAc)_3$(852.13mg,4.0206mmol)/DCM(20mL)的混合物搅拌过夜。在冷却后,将过量的DCM真空除去并且残余物用DCM(20mL)和水(20mL)萃取三次。合并有机层,真空除去溶剂并且通过硅胶色谱(PE:EA=7:1)提纯粗产物而得到期望的产物(150mg,14.9%)(油)。质谱(m/z):375.3[M+H]$^+$。

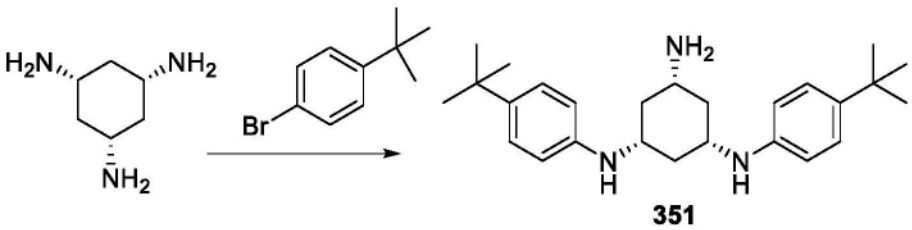
[2126] 步骤3:制备N-((S)-1-((1r,4S)-4-氨基环已基)乙基)-4-(叔丁基)苯胺(350)

[2127] 粗产物通过下述方法被提纯:prep-HPLC(柱-Gemini-C18 150x21.2mm,5um;移动相:ACN-H_2O(0.1%FA),10%-30%)而得到期望的产物350(30.1mg,26.2%)(白色固体)。^{1}H NMR(400MHz,DMSO-d6)δ7.05(d,J=8.7Hz,2H),6.46(d,J=8.7Hz,2H),5.10(s,1H),3.18(m,1H),2.81(m,1H),2.00-1.69(m,4H),1.39-1.22(m,2H),1.20(s,10H),1.13-1.03(m,2H),1.01(d,J=6.5Hz,3H)。质谱(m/z):275.3[M+H]$^+$。

[2128] 化合物351

[2129] (1R,3S,5r)-N1,N3-双(4-(叔丁基)苯基)环已烷-1,3,5-三胺

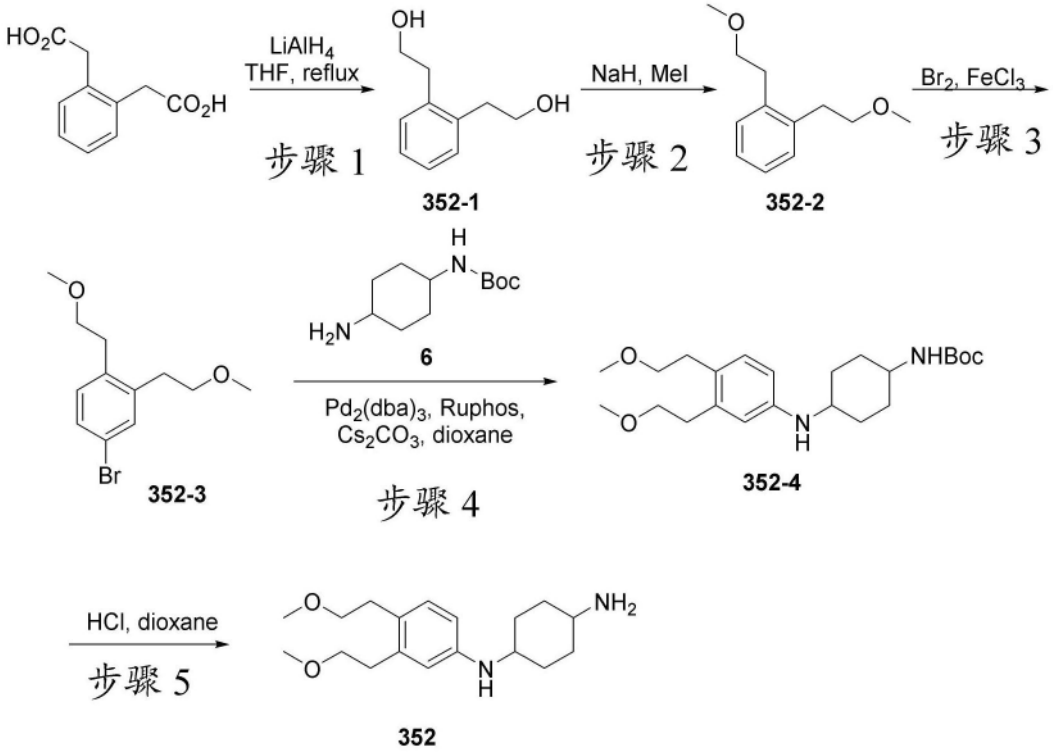
[2130]



[2131] 向环己烷-1,3,5-三胺三氢溴酸盐,和1-溴-4-叔丁基苯(100mg,0.27mmol)/甲苯(10mL)的溶液中添加$Pd_2(dba)_3$(49mg,0.054mmol),Cs_2CO_3(701mg,2.15mmol),和RuPhos(25mg,0.054mmol),和将混合物加热到110℃16小时,然后冷却到室温,真空除去溶剂,残余物的提纯方法为:prep-HPLC(柱-Gemini-C18 150x 21.2mm,5um;移动相:ACN-H_2O(0.1%FA),5%-20%)而得到期望的产物(黄色固体)(8mg,7.5%)。^1H NMR(400MHz,CD_3OD)δ7.23(d,J=8.4Hz,4H),6.73(d,J=7.6Hz,4H),3.58(brs,2H),3.37(brs,2H),2.68(s,1H),2.45(d,J=11.5Hz,4H),1.28(s,16H)。质谱(m/z):394.4$[M+H]^+$。

[2132] 化合物352

[2133] N-(4-(4-氨基环己基)苯基)-3,4-双(2-甲氧基乙基)苯胺

[2134] 

[2135] 步骤1:制备2,2'-(1,2-亚苯基)双(乙-1-醇)(352-1)

[2136] 在25℃向2,2'-(1,2-亚苯基)二乙酸(5g,25.7mmol)/THF(80mL)的混合物添加$LiAlH_4$(3.9g,10.28mmol)。在70℃搅拌反应16小时。将反应用水淬灭。将混合物用EA(20mL)稀释和用水(20mL×3)洗涤。有机相浓缩而得到352-1(灰白色固体)(4g,84%)。质谱(m/z):167.2$[M+H]^+$。

[2137] 步骤2:制备1,2-双(2-甲氧基乙基)苯(352-2)

[2138] 在0℃向352-1(4g,24.1mmol)/THF(100mL)的溶液中添加NaH(1.21g,50.6mmol)。在0℃搅拌反应0.5小时。然后向反应中添加MeI(6.84g,48.2mmol)。在25℃搅拌反应2小时。将反应用水淬灭。将混合物用EA(20mL)稀释和用水(20mL×3)洗涤。有机相浓缩并且通过硅胶柱色谱(PE:EA=4:1)提纯而得到352-2(灰白色固体)(3g,58%)。质谱(m/z):195.2$[M+H]^+$。

[2139] 步骤3:制备4-溴-1,2-双(2-甲氧基乙基)苯(352-3)

[2140] 在25℃向353-2(2g,10.3mmol)/DCE(20mL)的溶液中添加FeCl3(5.01g,30.9mmol)和Br2(3.29g,20.6mmol)。在70℃搅拌反应16小时。将反应用水淬灭。将混合物用EA(20mL)

稀释,用水(20mL×3)洗涤并且用Na2S2SO3水溶液洗涤。有机相浓缩并且通过硅胶柱色谱(PE:EA=10:1)提纯而得到353-3(白色固体)(0.5g,15.5%)。质谱(m/z):273.1[M+H]$^+$。

[2141] 步骤4:制备(4-((3,4-双(2-甲氧基乙基)苯基)氨基)环己基)氨基甲酸叔丁酯(352-4)

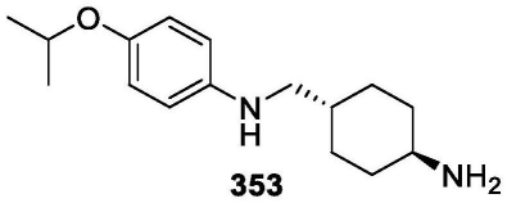
[2142] 在氮气气氛下在90℃将353-3(0.1g,0.4mmol),(4-氨基环己基)氨基甲酸叔丁酯(85.6mg,0.4mmol),Ruphos(0.04g,0.08mmol),Cs_2CO_3(260mg,0.8mmol)和$Pd_2(dba)_3$(36.6mg,0.04mmol)/二氧杂环己烷(2mL)的混合物搅拌16小时。将混合物过滤,浓缩并且通过Prep-TLC(PE:EA=1:1)提纯而得到352-4(黄色固体)(0.01g,5.6%)。质谱(m/z):406.8[M+H]$^+$。

[2143] 步骤5:制备N^1-(3,4-双(2-甲氧基乙基)苯基)环己烷-1,4-二胺(352)

[2144] 向352-4(0.01g,0.0245mmol)/DCM(5mL)的溶液中添加HCl/二氧杂环己烷(1mL)。在25℃搅拌反应2小时。将混合物浓缩并且通过Prep-TLC(DCM:MeOH=10:1)提纯而得到352(5mg,60%)(黄色固体)。^{1}H NMR(300MHz,CD_3OD)δ7.25(d,J=9Hz,1H),7.12-6.98(m,1H),6.96-6.76(m,1H),3.75-3.30(m,8H),3.29-2.66(m,6H),2.12(s,2H),1.85-1.49(m,8H)。质谱(m/z):307.3[M+H]$^+$。

[2145] 化合物353

[2146] N-(((1r,4r)-4-氨基环己基)甲基)-4-异丙氧基苯胺

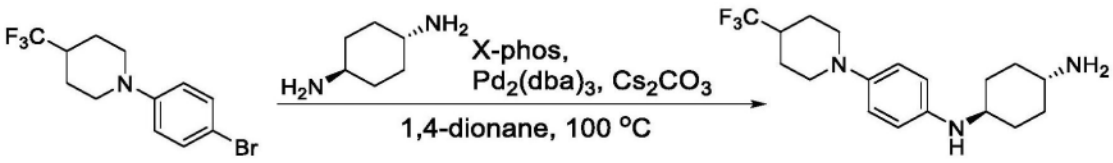
[2147] 

353

[2148] 由((1r,4r)-4-(((4-异丙氧基苯基)氨基)甲基)环己基)氨基甲酸叔丁酯(201mg,0.5777mmol),DCM(10mL)和TFA(1mL),根据为24的程序制备标题化合物353(26.1mg,17.0%)(白色固体)。^{1}H NMR(400MHz,CD_3OD)δ6.76-6.70(m,2H),6.62-6.56(m,2H),4.35(dt,J=12.1,6.1Hz,1H),2.87(d,J=6.7Hz,2H),2.56(tt,J=10.9,3.5Hz,1H),1.88(d,J=10.1Hz,4H),1.58-1.47(m,1H),1.24(d,J=6.1Hz,6H),1.15-0.98(m,4H)。质谱(m/z):263.20[M+H]$^+$。

[2149] 化合物354

[2150] (1r,4r)-N^1-(4-(4-(三氟甲基)哌啶-1-基)苯基)环己烷-1,4-二胺

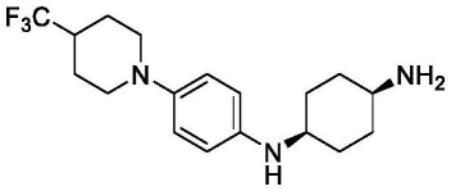
[2151] 

[2152] 在100℃在氮气气氛下将1-(4-溴苯基)-4-(三氟甲基)哌啶(46.1mg,0.15mmol),(1r,4r)-环己烷-1,4-二胺(22.2mg,0.2mmol),$Pd_2(dba)_3$(4.6mg,5umol),X-phos(12mg,25umol),andCs_2CO_3(65.6mg,0.2mmol)/1,4-二氧杂环己烷(3.0mL)的混合物搅拌过夜。在冷却到室温后,添加5mL的水。所得的溶液用3x10mL的乙酸乙酯萃取。合并有机相,用水(30mL)洗涤,干燥并且真空浓缩。残余物的提纯方法为:prep-TLC(MeOH/DCM=1:5)而得到期望的产物(16.1mg,31.4%)(玫瑰棕色固体)。^{1}H NMR(400MHz,DMSO-d6)δ6.81(d,J=8.4Hz,2H),

6.61(d,J＝8.4Hz,2H),3.55-3.42(m,2H),3.07(m,1H),2.94(m,1H),2.68-2.55(m,2H),2.16-1.96(m,4H),1.93-1.77(m,4H),1.58(m,1H),1.54-1.36(m,2H),1.27-1.11(m,s 2H)。质谱(m/z):342.3[M+H]$^+$。

[2153] 化合物355

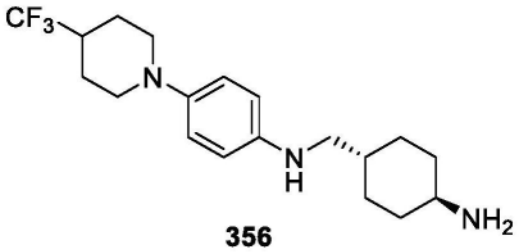
[2154] (1s,4s)-N^1-(4-(4-(三氟甲基)哌啶-1-基)苯基)环己烷-1,4-二胺

[2155] 

[2156] 由1-(4-溴苯基)-4-(三氟甲基)哌啶(46.1mg,0.15mmol),(1s,4s)-环己烷-1,4-二胺(22.2mg,0.2mmol),根据为化合物354的程序制备标题化合物355(26.1mg),总收率为50.8%(玫瑰棕色固体)。^{1}H NMR(400MHz,DMSO-d6)δ6.76(d,J＝8.4Hz,2H),6.55(d,J＝8.4Hz,2H),3.50-3.37(m,2H),3.33(m,1H),3.06(m,1H),2.62-2.53(m,2H),1.92-1.83(m,2H),1.80-1.67(m,6H),1.64-1.48(m,5H)。质谱(m/z):342.3[M+H]$^+$。

[2157] 化合物356

[2158] N-(((1r,4r)-4-氨基环己基)甲基)-4-(4-(三氟甲基)哌啶-1-基)苯胺

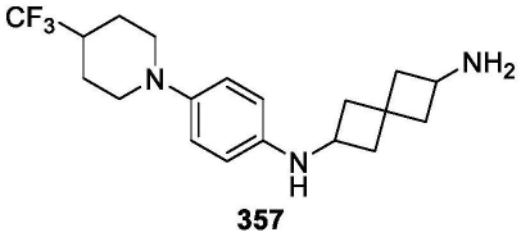
[2159] 

356

[2160] 由((1r,4r)-4-(((4-(4-(三氟甲基)哌啶-1-基)苯基)氨基)甲基)环己基)氨基甲酸叔丁酯(79mg,0.174mmol),DCM(10mL)和TFA(1mL),根据为24的程序制备期望的产物(29.4mg,47.7%)(紫色固体)。^{1}H NMR(400MHz,DMSO-d6)δ8.26(s,3H),6.79(s,2H),6.53(s,2H),3.42(s,2H),2.84(d,J＝33.6Hz,3H),2.05-1.79(m,7H),1.51(d,J＝38.4Hz,4H),1.32(d,J＝13.6Hz,2H),0.99(s,3H)。质谱(m/z):356.3[M+H]$^+$。

[2161] 化合物357

[2162] N^2-(4-(4-(三氟甲基)哌啶-1-基)苯基)螺[3.3]庚烷-2,6-二胺

[2163] 

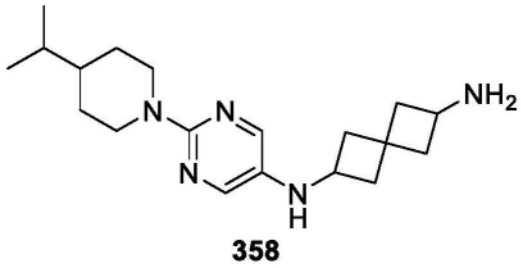
357

[2164] 由4-(4-(三氟甲基)哌啶-1-基)苯胺(54.2mg,0.22mmol)和(6-氧代螺[3.3]庚烷-2-基)氨基甲酸叔丁酯(60mg,0.27mmol),根据为20的程序制备标题化合物357(47.0mg),收率为55.9%(白色粉末),经^{1}H NMR证实为1:0.2的混合物。^{1}H NMR(400MHz,DMSO-d6)δ8.21(s,2H),6.74(d,J＝8.7Hz,2H),6.49-6.32(m,2H),5.37(d,J＝6.8Hz,1H),3.63(q,J＝7.2Hz,1H),3.54(p,J＝8.1Hz,1H),3.42(d,J＝11.9Hz,2H),2.55(d,J＝2.5Hz,3H),2.42-

2.27(m,3H),2.25-2.09(m,3H),1.91-1.70(m,4H),1.56(qd,J＝12.5,4.0Hz,2H)。质谱(m/z):354.3[M+H]$^+$。

[2165] 化合物358

[2166] N^2-(2-(4-异丙基哌啶-1-基)嘧啶-5-基)螺[3.3]庚烷-2,6-二胺

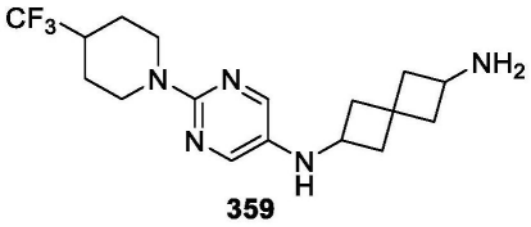
[2167] 

358

[2168] 由2-(4-异丙基哌啶-1-基)嘧啶-5-胺(49.3mg,0.22mmol)和(6-氧代螺[3.3]庚烷-2-基)氨基甲酸叔丁酯(60mg,0.27mmol),根据为20的程序制备标题化合物358(55.2mg),收率为75.4%(白色粉末),经^{1}H NMR证实为1:0.2的混合物。^{1}H NMR(400MHz,DMSO-d6)δ8.11(s,3H),7.79(s,2H),5.29(d,J＝7.4Hz,1H),4.47(dt,J＝12.7,2.8Hz,2H),3.63(p,J＝7.4Hz,1H),3.52(p,J＝8.1Hz,1H),2.61(td,J＝12.6,2.5Hz,2H),2.41-2.28(m,2H),2.15(ddt,J＝11.5,8.4,4.5Hz,3H),1.79(dt,J＝11.3,8.2Hz,2H),1.63(dd,J＝12.9,3.2Hz,2H),1.38(hept,J＝6.6Hz,1H),1.26-1.14(m,1H),1.06(qd,J＝12.4,4.2Hz,2H),0.84(d,J＝6.8Hz,6H)。质谱(m/z):330.3[M+H]$^+$。

[2169] 化合物359

[2170] N^2-(2-(4-(三氟甲基)哌啶-1-基)嘧啶-5-基)螺[3.3]庚烷-2,6-二胺

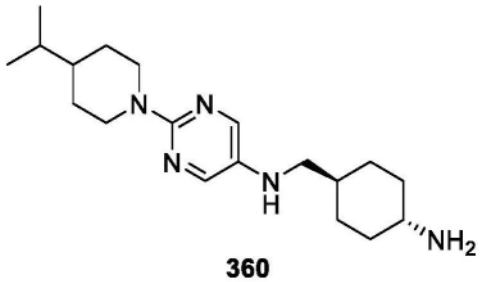
[2171] 

359

[2172] 由2-(4-(三氟甲基)哌啶-1-基)嘧啶-5-胺(55.1mg,0.22mmol)和(6-氧代螺[3.3]庚烷-2-基)氨基甲酸叔丁酯(60mg,0.27mmol),根据为20的程序制备标题化合物359(17.2mg),收率为21.8%(白色粉末),经^{1}H NMR证实为1:0.2的混合物。^{1}H NMR(400MHz,DMSO-d6)δ8.24(s,3H),7.82(s,2H),5.41(d,J＝7.2Hz,1H),4.65-4.44(m,2H),3.64(h,J＝7.4Hz,1H),3.53(p,J＝8.1Hz,1H),2.76(td,J＝12.9,2.5Hz,2H),2.56(td,J＝8.7,3.8Hz,1H),2.42-2.28(m,2H),2.26-2.12(m,3H),1.81(td,J＝11.5,9.6,5.9Hz,4H),1.34(qd,J＝12.6,4.2Hz,2H)。质谱(m/z):356.2[M+H]$^+$。

[2173] 化合物360

[2174] N-(((1r,4r)-4-氨基环己基)甲基)-2-(4-异丙基哌啶-1-基)嘧啶-5-胺

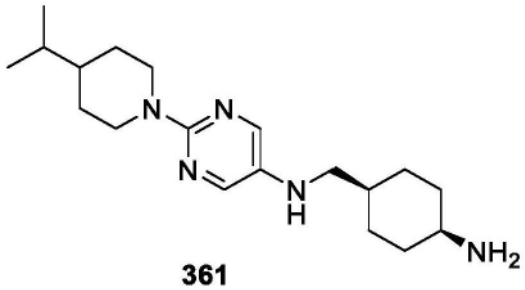
[2175] 

360

[2176] 由((1r,4r)-4-(((2-(4-异丙基哌啶-1-基)嘧啶-5-基)氨基)甲基)环己基)氨基甲酸叔丁酯(粗),DCM(6mL)和2,2,2-三氟乙酸(3mL),根据为24的程序制备期望的产物360(白色固体)(38.8mg,42.3%)。^{1}H NMR(400MHz,DMSO-d6)δ7.86(s,2H),5.05(t,J=6.0Hz,1H),4.47(d,J=12.9Hz,2H),2.78(t,J=6.4Hz,2H),2.70-2.54(m,4H),1.77(d,J=9.8Hz,4H),1.64(d,J=12.8Hz,2H),1.40(dd,J=13.0,6.6Hz,2H),1.26-0.91(m,7H),0.85(d,J=6.8Hz,6H)。质谱(m/z):332.3[M+H]$^+$。

[2177] 化合物361

[2178] N-(((1s,4s)-4-氨基环己基)甲基)-2-(4-异丙基哌啶-1-基)嘧啶-5-胺

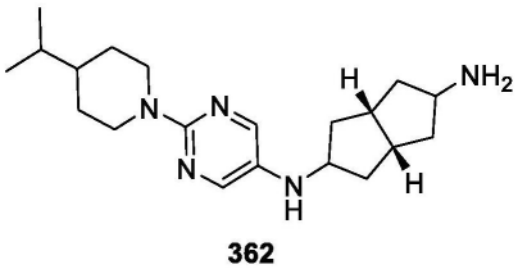
[2179] 

361

[2180] 由((1s,4s)-4-(((2-(4-异丙基哌啶-1-基)嘧啶-5-基)氨基)甲基)环己基)氨基甲酸叔丁酯,根据为24的程序制备期望的产物361(10.8mg,11.9%)(黄色固体)。^{1}H NMR(400MHz,DMSO-d6)δ7.99(s,1H),7.87(d,J=4.9Hz,1H),5.07(t,J=5.9Hz,1H),4.57-4.41(m,2H),2.97-2.79(m,2H),2.70-2.56(m,2H),2.41-2.34(m,1H),1.82-1.56(m,3H),1.43(dt,J=13.2,10.2Hz,6H),1.17(d,J=32.5Hz,2H),1.16-0.97(m,2H),0.85(d,J=6.8Hz,6H)。质谱(m/z):332.3[M+H]$^+$。

[2181] 化合物362

[2182] (3aR,6aS)-N^2-(2-(4-异丙基哌啶-1-基)嘧啶-5-基)八氢戊搭烯-2,5-二胺

[2183] 

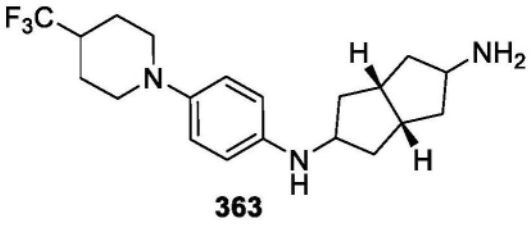
362

[2184] 由2-(4-异丙基哌啶-1-基)嘧啶-5-胺(106mg,0.48mmol)和(3as,6as)-四氢戊搭烯-2,5(1H,3H)-二酮(200mg,1.45mmol),根据为20的程序制备标题化合物362(16.7mg),三步总收率为21.8%(白色粉末),经^{1}H NMR证实为1:0.8的混合物。^{1}H NMR(400MHz,DMSO-d6)δ8.10(s,3H),7.91(s,2H),5.12(d,J=5.9Hz,1H),4.48(d,J=12.8Hz,2H),2.62(t,J=

12.2Hz,1H),2.38(s,4H),2.21(td,J=15.6,14.1,6.9Hz,5H),1.64(d,J=12.7Hz,2H),1.40(dq,J=13.7,8.2,6.6Hz,4H),1.09(td,J=12.2,4.0Hz,2H),0.85(d,J=6.7Hz,6H)。质谱(m/z):344.4[M+H]$^+$。

[2185] 化合物363

[2186] (3aR,6aS)-N^2-(4-(4-(三氟甲基)哌啶-1-基)苯基)八氢戊搭烯-2,5-二胺

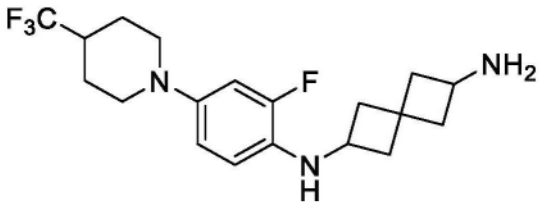
[2187] 

363

[2188] 由4-(4-(三氟甲基)哌啶-1-基)苯胺(118mg,0.48mmol)和(3as,6as)-四氢戊搭烯-2,5(1H,3H)-二酮(200mg,1.45mmol),根据为20的程序制备标题化合物363(30.8mg),三步总收率为17.5%(白色粉末),经^{1}H NMR证实为1:0.8的混合物。^{1}H NMR(400MHz,DMSO-d6)δ8.08(s,3H),6.76(dd,J=8.7,6.5Hz,2H),6.50(dd,J=8.6,6.2Hz,2H),5.17(d,J=40.9Hz,1H),3.84-3.50(m,1H),3.42(d,J=12.3Hz,2H),2.38(s,2H),2.22(td,J=13.8,12.2,6.4Hz,3H),1.86(d,J=11.9Hz,2H),1.74(tt,J=16.3,7.1Hz,1H),1.63-1.50(m,2H),1.50-1.34(m,2H),1.35-1.14(m,3H)。质谱(m/z):368.7[M+H]$^+$。

[2189] 化合物364

[2190] N^2-(2-氟-4-(4-(三氟甲基)哌啶-1-基)苯基)螺[3.3]庚烷-2,6-二胺

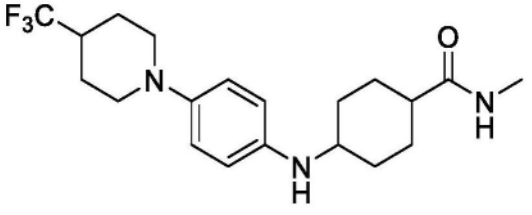
[2191] 

364

[2192] 由2-氟-4-(4-(三氟甲基)哌啶-1-基)苯胺(70mg,0.27mmol)和(6-氧代螺[3.3]庚烷-2-基)氨基甲酸叔丁酯(90mg,0.40mmol),根据为20的程序制备标题化合物364(14.5mg),收率为11.5%(白色粉末),经^{1}H NMR证实为1:0.2的混合物。^{1}H NMR(400MHz,DMSO-d6)δ8.15(s,3H),6.73(dd,J=14.5,2.6Hz,1H),6.58(dd,J=8.6,2.6Hz,1H),6.54-6.42(m,1H),5.01(d,J=7.1Hz,1H),3.67(h,J=7.3Hz,1H),3.50(d,J=12.3Hz,3H),2.56(dd,J=12.2,2.5Hz,3H),2.42-2.26(m,3H),2.24-2.07(m,3H),1.96-1.79(m,4H),1.53(qd,J=12.5,4.0Hz,2H)。质谱(m/z):472.4[M+H]$^+$。

[2193] 化合物365

[2194] N-甲基-4-((4-(4-(三氟甲基)哌啶-1-基)苯基)氨基)环己烷-1-甲酰胺

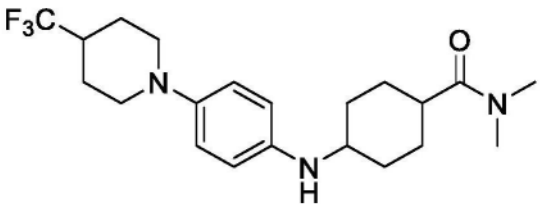
[2195] 

365

[2196] 由4-((4-(4-(三氟甲基)哌啶-1-基)苯基)氨基)环己烷-1-甲酸(100mg,0.27mmol)和甲胺盐酸盐(73mg,1.08mmol),根据为10的程序制备标题化合物365(10.1mg),收率为9.7%(白色粉末)。^{1}H NMR(400MHz,DMSO-d6)δ7.66(d,J=4.7Hz,1H),6.79-6.69(m,2H),6.50-6.44(m,2H),4.87(d,J=8.5Hz,1H),3.41(d,J=12.0Hz,2H),3.04(d,J=7.8Hz,1H),2.55(t,J=4.3Hz,5H),2.42-2.34(m,1H),2.09-1.93(m,3H),1.85(d,J=12.5Hz,2H),1.78-1.67(m,2H),1.57(td,J=12.5,4.0Hz,2H),1.45(qd,J=13.5,3.7Hz,3H),1.11-0.97(m,2H)。质谱(m/z):384.3[M+H]$^+$。

[2197] 化合物366

[2198] N,N-二甲基-4-((4-(4-(三氟甲基)哌啶-1-基)苯基)氨基)环己烷-1-甲酰胺

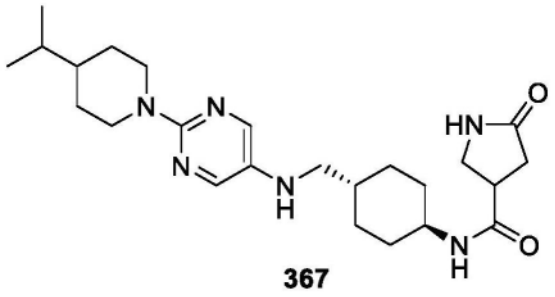
[2199] 

366

[2200] 由4-((4-(4-(三氟甲基)哌啶-1-基)苯基)氨基)环己烷-1-甲酸(100mg,0.27mmol)和二甲胺(36mg,0.80mmol),根据为10的程序制备标题化合物366(31.9mg),收率为29.8%(白色粉末)。^{1}H NMR(400MHz,DMSO-d6)δ6.74(d,J=8.2Hz,2H),6.51(s,2H),4.89(s,1H),3.42(d,J=11.6Hz,2H),3.06(s,1H),3.00(s,3H),2.79(s,3H),2.04-1.92(m,3H),1.85(d,J=12.5Hz,2H),1.68(d,J=13.1Hz,2H),1.56(d,J=12.4Hz,3H),1.44(q,J=13.3Hz,3H),1.13(q,J=12.4Hz,3H)。质谱(m/z):398.4[M+H]$^+$。

[2201] 化合物367

[2202] N-((1r,4r)-4-(((2-(4-异丙基哌啶-1-基)嘧啶-5-基)氨基)甲基)环己基)-5-氧代吡咯烷-3-甲酰胺

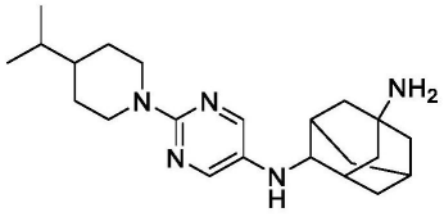
[2203] 

367

[2204] 由N-(((1r,4r)-4-氨基环己基)甲基)-2-(4-异丙基哌啶-1-基)嘧啶-5-胺(50mg,0.151mmol),5-氧代吡咯烷-3-甲酸(25mg,0.196mmol),HATU(75mg,0.196mmol),DIEA(58mg,0.453mmol)和DMF(5mL),根据为1的程序制备期望的产物367(32.7mg,49.0%)(黄色固体)。^{1}H NMR(400MHz,DMSO-d6)δ8.18(dt,J=12.8,5.6Hz,1H),7.94(s,1H),7.88(s,1H),7.59(s,1H),4.91(dd,J=71.2,8.4Hz,1H),4.58-4.41(m,2H),3.44-3.38(m,2H),3.25-3.16(m,2H),2.96(dt,J=30.0,6.4Hz,3H),2.61(td,J=12.5,2.4Hz,2H),2.27(dd,J=8.4,4.0Hz,2H),1.94(d,J=11.2Hz,1H),1.74-1.55(m,4H),1.54-1.45(m,2H),1.44-1.36(m,3H),1.14-0.96(m,4H),0.85(d,J=6.8Hz,6H)。质谱(m/z):443.3[M+H]$^+$。

[2205] 化合物368

[2206] N^4-(2-(4-异丙基哌啶-1-基)嘧啶-5-基)金刚烷-1,4-二胺

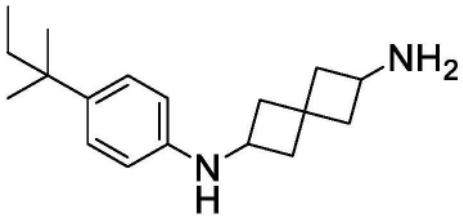
[2207] 

368

[2208] 由2-(4-异丙基哌啶-1-基)嘧啶-5-胺(100mg,0.45mmol)和(4-氧代金刚烷-1-基)氨基甲酸叔丁酯(180mg,0.34mmol),根据为20的程序制备标题化合物368(4.6mg),收率为2.16%(白色粉末),经^{1}H NMR证实为1:0.3的混合物。^{1}H NMR(301MHz,甲醇-d4)δ7.97(s,1H),7.95(s,1H),6.80(s,3H),4.99(d,J=6.9Hz,2H),2.73(s,2H),2.60(s,3H),2.28-2.10(m,5H),1.98(d,J=28.3Hz,5H),1.73(d,J=12.5Hz,4H),1.60(s,3H),0.90(d,J=3.0Hz,6H)。质谱(m/z):470.4$[M+H]^+$。

[2209] 化合物369

[2210] N^2-(4-(叔戊基)苯基)螺[3.3]庚烷-2,6-二胺

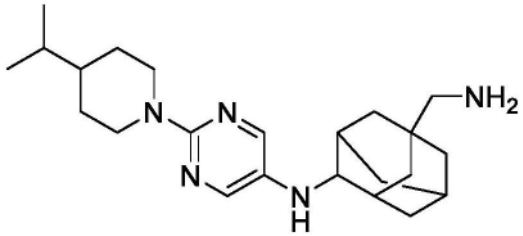
[2211] 

369

[2212] 由4-(叔戊基)苯胺(100mg,0.43mmol)和(6-氧代螺[3.3]庚烷-2-基)氨基甲酸叔丁酯(116mg,0.50mmol),根据为20的程序制备标题化合物369(44.3mg),收率为38.5%(白色粉末)。^{1}H NMR(400MHz,DMSO-d6)δ7.03-6.95(m,2H),6.44-6.33(m,2H),5.50(d,J=6.7Hz,1H),3.63(h,J=7.3Hz,1H),3.22-3.10(m,1H),2.39(ddd,J=11.3,7.1,4.7Hz,1H),2.35-2.21(m,2H),2.11(ddd,J=11.8,7.1,5.2Hz,1H),1.75(td,J=11.0,7.8Hz,2H),1.65(ddd,J=18.9,10.8,8.4Hz,2H),1.51(q,J=7.4Hz,2H),1.14(s,6H),0.59(t,J=7.3Hz,3H)。质谱(m/z):273.1$[M+H]^+$。

[2213] 化合物370

[2214] N-(5-(氨基甲基)金刚烷-2-基)-2-(4-异丙基哌啶-1-基)嘧啶-5-胺

[2215] 

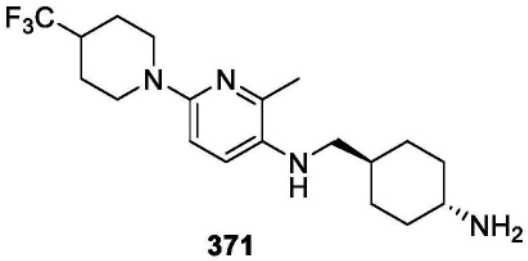
370

[2216] 由2-(4-异丙基哌啶-1-基)嘧啶-5-胺(200mg,0.90mmol)和4-氧代金刚烷-1-甲酸(260mg,1.36mmol),根据为84的程序制备标题化合物370(8.6mg),两步总收率为6.8%(白

色粉末)。^{1}H NMR(400MHz,DMSO-d6)δ7.93(d,J=2.3Hz,1H),7.19(s,1H),6.65(s,1H),5.31(t,J=4.8Hz,1H),4.46(d,J=12.2Hz,1H),1.99(q,J=6.8,6.2Hz,7H),1.66(s,5H),1.42(d,J=18.3Hz,6H),1.06-1.01(m,3H),0.84(dd,J=6.9,3.8Hz,8H)。质谱(m/z):399.8[M+H]$^+$。

[2217] 化合物371

[2218] N-(((1r,4r)-4-氨基环己基)甲基)-2-甲基-6-(4-(三氟甲基)哌啶-1-基)吡啶-3-胺

[2219] 

371

[2220] 由2-甲基-6-(4-(三氟甲基)哌啶-1-基)吡啶-3-胺(70mg,0.27mmol)和((1r,4r)-4-甲酰基环己基)氨基甲酸叔丁酯(114mg,0.54mmol),根据为20的程序制备标题化合物371(23.6mg),收率为23.6%(白色粉末)。^{1}H NMR(400MHz,DMSO-d6)δ7.46(s,1H),7.33(s,1H),7.20(s,1H),6.90(s,1H),6.61(s,1H),4.10(d,J=12.7Hz,2H),3.03-2.77(m,3H),2.64(s,2H),2.25(s,3H),2.05-1.92(m,2H),1.86(d,J=15.5Hz,4H),1.48(s,3H),1.36-1.26(m,2H),1.10-0.91(m,2H)。质谱(m/z):371.3[M+H]$^+$。

[2221] 化合物372

[2222] (3aR,6aS)-N^2-(2-氟-4-(4-(三氟甲基)哌啶-1-基)苯基)八氢戊搭烯-2,5-二胺

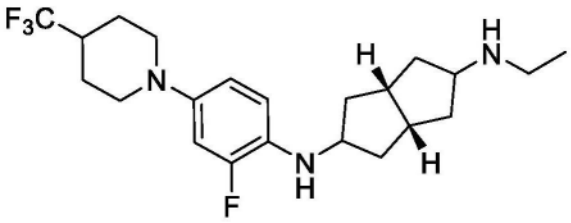
[2223]

372

[2224] 由2-氟-4-(4-(三氟甲基)哌啶-1-基)苯胺(150mg,0.57mmol)和(3as,6as)-四氢戊搭烯-2,5(1H,3H)-二酮(237mg,1.72mmol),根据为20的程序制备标题化合物372(11.2mg),三步总收率为8.1%(白色粉末),经^{1}H NMR证实为1:0.8的混合物。^{1}H NMR(400MHz,甲醇-d4)δ6.87-6.63(m,3H),3.81(d,J=11.7Hz,1H),3.52(ddt,J=15.2,6.6,3.6Hz,2H),2.75-2.50(m,4H),2.46-2.32(m,3H),2.25(dtt,J=17.2,8.7,4.5Hz,1H),2.03-1.87(m,3H),1.70(qd,J=12.6,4.1Hz,3H),1.48(td,J=11.8,7.9Hz,1H),1.39-1.26(m,2H)。质谱(m/z):386.2[M+H]$^+$。

[2225] 化合物373

[2226] (3aR,6aS)-N^2-乙基-N5-(2-氟-4-(4-(三氟甲基)哌啶-1-基)苯基)八氢戊搭烯-2,5-二胺

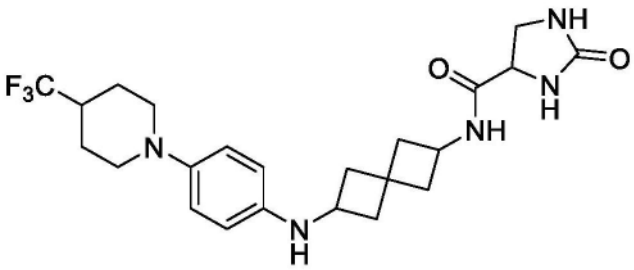
[2227] 

373

[2228] 由2-氟-4-(4-(三氟甲基)哌啶-1-基)苯胺(150mg,0.57mmol)和(3as,6as)-四氢戊搭烯-2,5(1H,3H)-二酮(237mg,1.72mmol),根据为20的程序制备标题化合物373(7.8mg),三步总收率为6.5%(白色粉末),经^{1}H NMR证实为1:0.8的混合物。^{1}H NMR(400MHz,DMSO-d6)δ7.90(s,1H),6.84-6.49(m,3H),3.76(d,J=12.5Hz,1H),3.50(t,J=9.9Hz,2H),2.90(d,J=7.3Hz,1H),2.70-2.62(m,3H),2.26(d,J=8.5Hz,2H),1.99(q,J=6.9,6.4Hz,2H),1.88(d,J=17.5Hz,2H),1.64-1.38(m,4H),1.23-1.13(m,4H),0.95(s,1H),0.87-0.80(m,1H)。质谱(m/z):414.5[M+H]$^+$。

[2229] 化合物374

[2230] 2-氧代-N-(6-((4-(4-(三氟甲基)哌啶-1-基)苯基)氨基)螺[3.3]庚烷-2-基)咪唑烷-4-甲酰胺

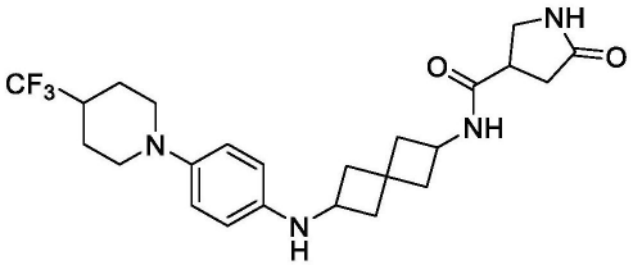
[2231] 

374

[2232] 由N^2-(4-(4-(三氟甲基)哌啶-1-基)苯基)螺[3.3]庚烷-2,6-二胺(50mg,0.14mmol)和2-氧代咪唑烷-4-甲酸(22mg,0.17mmol),根据为1的程序制备标题化合物374(33.4mg),收率为50.7%(白色粉末)。^{1}H NMR(400MHz,DMSO-d6)δ8.05(d,J=7.7Hz,1H),6.78-6.70(m,2H),6.41(dd,J=8.8,6.7Hz,3H),6.27(s,1H),5.31(d,J=6.8Hz,1H),4.10(h,J=8.0Hz,1H),3.98(ddd,J=9.7,6.1,1.6Hz,1H),3.62(h,J=7.4Hz,1H),3.49(t,J=9.3Hz,1H),3.41(d,J=12.1Hz,2H),3.16(ddd,J=9.0,6.1,1.3Hz,1H),2.40-2.25(m,4H),2.16(q,J=5.5Hz,1H),1.96(ddd,J=19.9,12.8,9.1Hz,3H),1.90-1.71(m,5H),1.55(qd,J=12.4,4.1Hz,2H)。质谱(m/z):466.5[M+H]$^+$。

[2233] 化合物375

[2234] 5-氧代-N-(6-((4-(4-(三氟甲基)哌啶-1-基)苯基)氨基)螺[3.3]庚烷-2-基)吡咯烷-3-甲酰胺

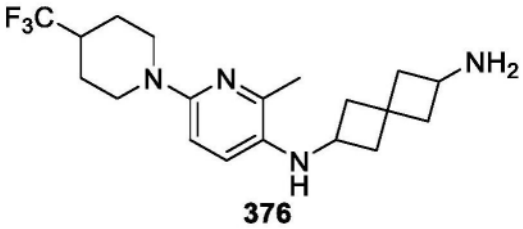
[2235] 

375

[2236] 由N^2-(4-(4-(三氟甲基)哌啶-1-基)苯基)螺[3.3]庚烷-2,6-二胺(50mg,0.14mmol)和5-氧代吡咯烷-3-甲酸(22mg,0.17mmol),根据为1的程序制备标题化合物375(45.1mg),收率为68.6%(白色粉末)。^{1}H NMR(400MHz,DMSO-d6)δ8.15(d,J=7.5Hz,1H),7.54(s,1H),6.80-6.69(m,2H),6.46-6.34(m,2H),5.31(d,J=6.8Hz,1H),4.06(h,J=8.0Hz,1H),3.62(h,J=7.4Hz,1H),3.40(d,J=12.4Hz,2H),3.36(dd,J=8.9,1.9Hz,1H),3.16(ddd,J=9.6,6.5,3.5Hz,1H),3.04(qd,J=8.6,6.5Hz,1H),2.54(d,J=2.5Hz,2H),2.39-2.27(m,3H),2.27-2.20(m,2H),2.16(dt,J=11.9,6.2Hz,1H),2.03-1.69(m,7H),1.55(qd,J=12.5,4.1Hz,2H)。质谱(m/z):465.7[M+H]$^+$。

[2237] 化合物376

[2238] N^2-(2-甲基-6-(4-(三氟甲基)哌啶-1-基)吡啶-3-基)螺[3.3]庚烷-2,6-二胺

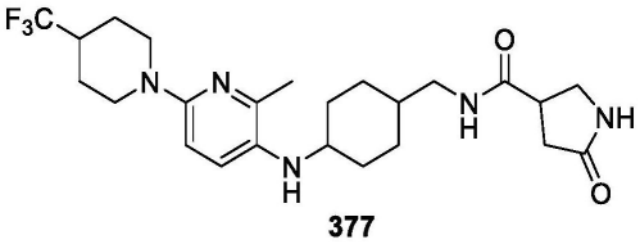


376

[2239] 由2-甲基-6-(4-(三氟甲基)哌啶-1-基)吡啶-3-胺(70mg,0.27mmol)和(6-氧代螺[3.3]庚烷-2-基)氨基甲酸叔丁酯(79mg,0.35mmol),根据为20的程序制备标题化合物376(19.3mg),收率为19.4%(白色粉末)。^{1}H NMR(400MHz,甲醇-d4)δ6.91(d,J=9.5Hz,1H),6.62(s,1H),4.04(s,2H),3.69(p,J=8.1Hz,2H),2.83-2.52(m,4H),2.47(dt,J=11.7,6.0Hz,1H),2.41-2.10(m,7H),2.10-1.79(m,4H),1.72-1.55(m,2H)。质谱(m/z):369.7[M+H]$^+$。

[2240] 化合物377

[2241] N-((4-((2-甲基-6-(4-(三氟甲基)哌啶-1-基)吡啶-3-基)氨基)环己基)甲基)-5-氧代吡咯烷-3-甲酰胺

[2242] 

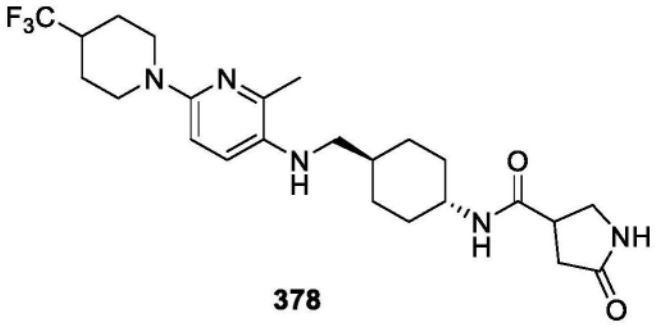
377

[2243] 由N-(4-(氨基甲基)环己基)-2-甲基-6-(4-(三氟甲基)哌啶-1-基)吡啶-3-胺(50mg,0.13mmol)和5-氧代吡咯烷-3-甲酸(21mg,0.16mmol),根据为10的程序制备标题化合物377(10.6mg),收率为16.3%(白色粉末)。^{1}H NMR(400MHz,甲醇-d4)δ7.05(s,1H),4.06

(s,2H),3.58(dd,J＝9.9,8.8Hz,2H),3.46(dd,J＝9.9,6.4Hz,2H),3.35(s,1H),3.18(d,J＝7.1Hz,2H),3.08(dd,J＝6.8,1.2Hz,1H),2.60-2.43(m,4H),1.93(s,3H),1.80-1.51(m,6H),1.45-1.35(m,2H),1.16-1.01(m,1H)。质谱(m/z):482.4[M+H]$^+$。

[2244] 化合物378

[2245] N-((1r,4r)-4-(((2-甲基-6-(4-(三氟甲基)哌啶-1-基)吡啶-3-基)氨基)甲基)环己基)-5-氧代吡咯烷-3-甲酰胺

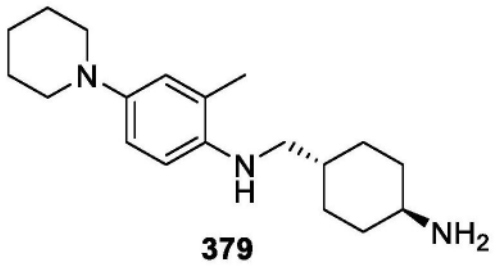
[2246] 

378

[2247] 由N-(((1r,4r)-4-氨基环己基)甲基)-2-甲基-6-(4-(三氟甲基)哌啶-1-基)吡啶-3-胺(40mg,0.11mmol)和5-氧代吡咯烷-3-甲酸(17mg,0.13mmol),根据为10的程序制备标题化合物378(12.0mg),收率为16.3%(白色粉末)。^{1}H NMR(400MHz,DMSO-d6)δ7.86(d,J＝7.9Hz,1H),7.56(s,1H),6.83(d,J＝8.8Hz,1H),6.55(d,J＝8.7Hz,1H),4.41(t,J＝6.0Hz,1H),4.11(d,J＝12.7Hz,2H),3.50(tt,J＝7.4,3.8Hz,1H),3.41-3.34(m,1H),3.19(dd,J＝9.3,6.4Hz,1H),3.12-3.00(m,1H),2.84(t,J＝6.3Hz,2H),2.60(td,J＝12.5,2.5Hz,3H),2.38-2.23(m,3H),2.22(s,3H),1.88-1.74(m,6H),1.46(qd,J＝12.5,4.4Hz,3H),1.20-1.05(m,2H),1.05-0.92(m,2H)。质谱(m/z):482.2[M+H]$^+$。

[2248] 化合物379

[2249] N-(((1r,4r)-4-氨基环己基)甲基)-2-甲基-4-(哌啶-1-基)苯胺

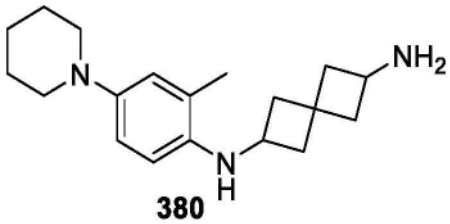
[2250] 

379

[2251] 由2-甲基-4-(哌啶-1-基)苯胺(40mg,0.23mmol)和((1r,4r)-4-甲酰基环己基)氨基甲酸叔丁酯(54mg,0.33mmol),根据为20的程序制备标题化合物379(21mg),收率为49.5%(白色粉末)。^{1}H NMR(400MHz,DMSO-d6)δ8.01(s,3H),6.67(s,2H),6.38(s,1H),4.37(s,1H),2.88(d,J＝25.2Hz,5H),2.04(s,3H),1.96(t,J＝8.3Hz,2H),1.85(d,J＝12.8Hz,2H),1.54(d,J＝58.9Hz,7H),1.35-1.20(m,3H),0.98(q,J＝12.7Hz,2H)。质谱(m/z):302.6[M+H]$^+$。

[2252] 化合物380

[2253] N^2-(2-甲基-4-(哌啶-1-基)苯基)螺[3.3]庚烷-2,6-二胺

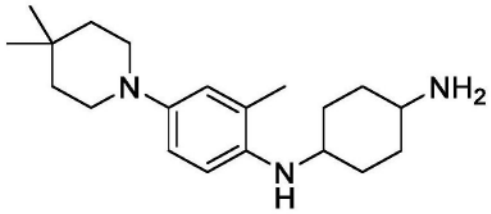
[2254] 

380

[2255] 由2-甲基-4-(哌啶-1-基)苯胺(40mg,0.2mmol)和(6-氧代螺[3.3]庚烷-2-基)氨基甲酸叔丁酯(51mg,0.32mmol),根据为20的程序制备标题化合物380(26mg),收率为59.2%(白色粉末)。^{1}H NMR(400MHz,DMSO-d6)δ8.30-8.05(m,3H),7.51-7.07(m,1H),6.38(s,1H),3.71(s,1H),3.55(s,1H),3.24-2.93(m,2H),2.39(dd,J=12.4,6.7Hz,2H),2.17(q,J=10.4,9.6Hz,3H),2.06(s,3H),2.02-1.87(m,3H),1.74(s,3H),1.48(d,J=30.5Hz,2H),1.32-1.17(m,3H)。质谱(m/z):300.6[M+H]$^+$。

[2256] 化合物381

[2257] N^1-(4-(4,4-二甲基哌啶-1-基)-2-甲基苯基)环己烷-1,4-二胺

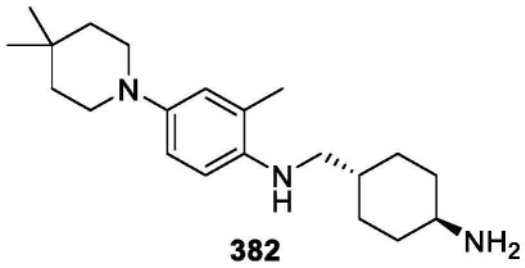
[2258] 

381

[2259] 由4-(4,4-二甲基哌啶-1-基)-2-甲基苯胺(40mg,0.18mmol)和(4-氧代环己基)氨基甲酸叔丁酯(45mg,0.24mmol),根据为20的程序制备标题化合物381(22mg),收率为43.2%(白色粉末)。^{1}H NMR(400MHz,DMSO-d6)δ7.96(s,3H),6.55(s,2H),3.04(d,J=63.1Hz,5H),2.23-1.88(m,6H),1.75(d,J=41.8Hz,4H),1.45(s,5H),0.96(d,J=4.2Hz,6H)。质谱(m/z):316.4[M+H]$^+$。

[2260] 化合物382

[2261] N-(((1r,4r)-4-氨基环己基)甲基)-4-(4,4-二甲基哌啶-1-基)-2-甲基苯胺

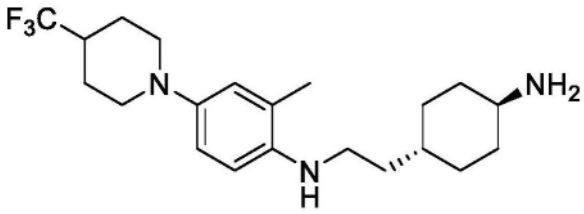
[2262] 

382

[2263] 由4-(4,4-二甲基哌啶-1-基)-2-甲基苯胺(55mg,0.23mmol)和((1r,4r)-4-甲酰基环己基)氨基甲酸叔丁酯(64mg,0.31mmol),根据为20的程序制备标题化合物382(38mg),收率为64.2%(白色粉末)。^{1}H NMR(400MHz,DMSO-d6)δ7.96(s,3H),7.38-7.02(m,1H),6.61(d,J=48.8Hz,2H),3.04(d,J=63.1Hz,5H),2.04(dd,J=43.5,19.9Hz,6H),1.75(d,J=41.8Hz,4H),1.56-1.35(m,5H),1.28(s,1H),0.96(d,J=4.2Hz,6H)。质谱(m/z):330.5[M+H]$^+$。

[2264] 化合物383

[2265] N-(2-((1r,4r)-4-氨基环己基)乙基)-2-甲基-4-(4-(三氟甲基)哌啶-1-基)苯胺

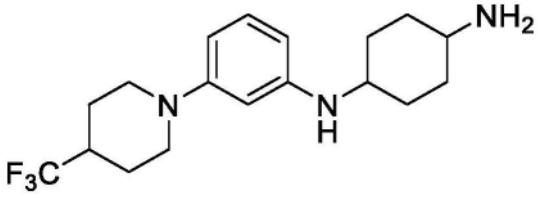
[2266] 

383

[2267] 由2-甲基-4-(4-(三氟甲基)哌啶-1-基)苯胺(70mg,0.32mmol)和((1r,4r)-4-(2-氧代乙基)环己基)氨基甲酸叔丁酯(95mg,0.46mmol),根据为20的程序制备标题化合物383(18mg),收率为23.5%(白色粉末)。^{1}H NMR(400MHz,DMSO-d6)δ7.88(s,3H),6.70(s,1H),6.65(d,J=8.8Hz,1H),6.42(d,J=8.6Hz,1H),4.27(s,1H),3.46(t,J=12.0Hz,2H),3.01(s,2H),2.93(s,1H),2.37(d,J=10.7Hz,1H),2.04(s,3H),1.93(d,J=12.3Hz,3H),1.83(t,J=16.9Hz,4H),1.56(d,J=12.1Hz,2H),1.47(d,J=7.0Hz,2H),1.36-1.25(m,3H),1.07-0.92(m,2H)。质谱(m/z):384.3[M+H]$^+$。

[2268] 化合物384

[2269] N^1-(3-(4-(三氟甲基)哌啶-1-基)苯基)环己烷-1,4-二胺

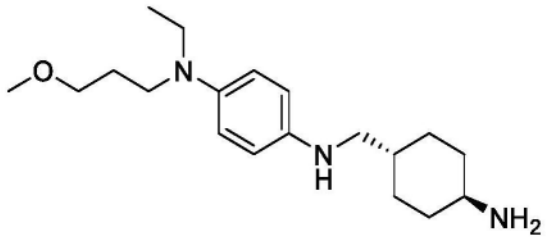
[2270] 

384

[2271] 由(4-((3-(4-(三氟甲基)哌啶-1-基)苯基)氨基)环己基)氨基甲酸叔丁酯,根据为24的程序制备标题化合物384(64mg,55.8%)(黄色固体)。^{1}H NMR(400MHz,DMSO-d6)δ7.90(d,J=12.0,1H),7.13-7.02(m,1H),6.59-6.32(m,2H),3.81-3.62(m,2H),3.46(s,1H),3.25(s,1H),3.19-3.08(m,1H),2.95(d,J=4.0,2H),2.63-2.54(m,2H),2.05-1.85(m,4H),1.85-1.51(m,6H),1.33(m,2H)。质谱(m/z):341.9[M+H]$^+$。

[2272] 化合物385

[2273] N^1-(((1r,4r)-4-氨基环己基)甲基)-N4-乙基-N^4-(3-甲氧基丙基)苯-1,4-二胺

[2274] 

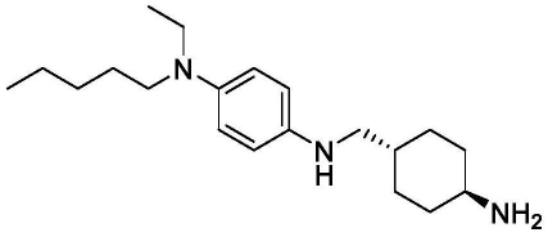
385

[2275] 由((1r,4r)-4-(((4-(乙基(3-甲氧基丙基)氨基)苯基)氨基)甲基)环己基)氨基甲酸叔丁酯(68mg,0.162mmol),TFA(1mL)和DCM(10mL),根据为24的程序制备标题化合物385(24.8mg),总收率为47.9%(紫色固体)。^{1}H NMR(400MHz,DMSO-d6)δ6.88-6.39(m,4H),3.23-3.20(m,3H),3.18(d,J=2.4Hz,2H),2.82(q,J=7.2Hz,3H),2.00-1.90(m,3H),1.86-

1.77(m,3H),1.69-1.59(m,4H),1.30(t,J＝12.0Hz,2H),1.16(t,J＝7.2Hz,2H),1.08-0.93(m,7H)。质谱(m/z):320.3[M+H]$^+$。

[2276] 化合物386

[2277] N^1-(((1r,4r)-4-氨基环己基)甲基)-N4-乙基-N4-戊基苯-1,4-二胺

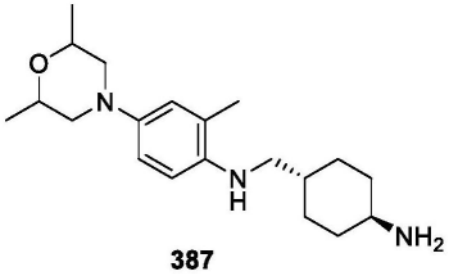
[2278] 

386

[2279] 由((1r,4r)-4-(((4-(乙基(戊基)氨基)苯基)氨基)甲基)环己基)氨基甲酸叔丁酯(77mg,0.185mmol),TFA(1mL),和DCM(10mL),根据为1-2的程序制备标题化合物386(41.8mg),总收率为71.5%(紫色固体)。^{1}H NMR(400MHz,DMSO-d6)δ6.70-6.47(m,4H),3.25-3.17(m,3H),2.92-2.73(m,4H),1.94(d,J＝12.4Hz,3H),1.83(d,J＝12.8Hz,2H),1.49-1.38(m,4H),1.28-1.25(m,3H),0.97-0.91(m,4H),0.86-0.75(m,8H)。质谱(m/z):318.3[M+H]$^+$。

[2280] 化合物387

[2281] N-(((1r,4r)-4-氨基环己基)甲基)-4-(2,6-二甲基吗啉代)-2-甲基苯胺

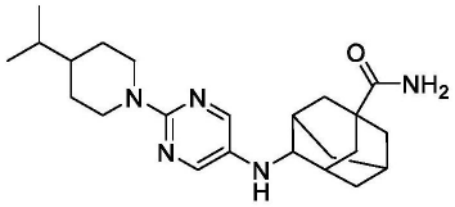
[2282] 

387

[2283] 由((1r,4r)-4-(((4-(2,6-二甲基吗啉代)-2-甲基苯基)氨基)甲基)环己基)氨基甲酸叔丁酯(88mg,0.204mmol),TFA(1mL),和DCM(10mL),根据为24的程序制备标题化合物387(38.5mg),总收率为57.0%(紫色固体)。^{1}H NMR(400MHz,DMSO-d6)δ8.23(s,3H),6.63(d,J＝2.8Hz,1H),6.57(dd,J＝8.8,2.8Hz,1H),6.35(d,J＝8.8Hz,1H),4.33(s,1H),3.62(dqd,J＝12.4,6.0,2.0Hz,2H),3.23(dt,J＝10.8,2.0Hz,2H),2.85(s,1H),2.83-2.77(m,2H),2.09-2.04(m,2H),2.01(s,3H),1.96(dt,J＝13.2,3.2Hz,2H),1.82(dd,J＝13.6,3.6Hz,2H),1.55-1.43(m,1H),1.30(qd,J＝12.4,3.2Hz,2H),1.07(d,J＝6.0Hz,6H),1.00-0.88(m,2H)。质谱(m/z):332.3[M+H]$^+$。

[2284] 化合物388

[2285] 4-((2-(4-异丙基哌啶-1-基)嘧啶-5-基)氨基)金刚烷-1-甲酰胺

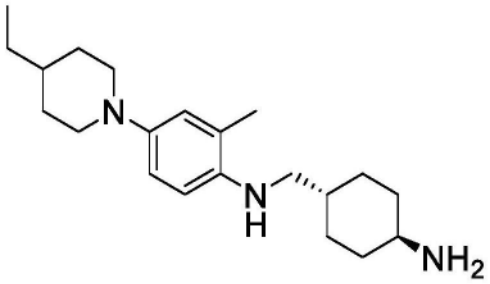
[2286] 

388

[2287] 由2-(4-异丙基哌啶-1-基)嘧啶-5-胺(70mg,0.27mmol)和4-氧代金刚烷-1-甲酰胺(73mg,0.34mmol),根据为20的程序制备标题化合物388(34mg),收率为47.8%(白色粉末)。^{1}H NMR(400MHz,DMSO-d6)δ7.94(d,J=4.0Hz,2H),6.97(s,1H),6.72(s,1H),5.00(dd,J=8.2,4.6Hz,1H),4.47(dt,J=12.9,2.8Hz,2H),2.61(td,J=12.8,2.4Hz,2H),2.03-1.89(m,4H),1.89-1.79(m,4H),1.72(dd,J=12.1,4.0Hz,3H),1.67-1.60(m,2H),1.43-1.33(m,3H),1.18(ddd,J=12.1,6.0,3.0Hz,1H),1.07(qd,J=12.3,4.0Hz,2H),0.85(d,J=6.7Hz,6H)。质谱(m/z):398.4[M+H]$^+$。

[2288] 化合物389

[2289] N-(((1r,4r)-4-氨基环已基)甲基)-4-(4-乙基哌啶-1-基)-2-甲基苯胺

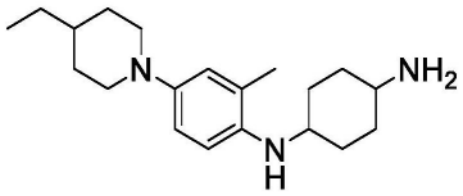
[2290] 

389

[2291] 由4-(4-乙基哌啶-1-基)-2-甲基苯胺(70mg,0.23mmol)和((1r,4r)-4-甲酰基环已基)氨基甲酸叔丁酯(83mg,0.32mmol),根据为20的程序制备标题化合物389(18mg),收率为28.4%(淡玫瑰色的粉末)。^{1}H NMR(400MHz,DMSO-d6)δ7.98(s,3H),6.47(s,1H),2.92(s,4H),2.08(s,3H),1.99(d,J=22.8Hz,3H),1.85(s,4H),1.55(s,2H),1.29(q,J=14.1,13.6Hz,5H),1.00(d,J=13.2Hz,2H),0.90(t,J=7.3Hz,4H)。质谱(m/z):330.3[M+H]$^+$。

[2292] 化合物390

[2293] N^1-(4-(4-乙基哌啶-1-基)-2-甲基苯基)环已烷-1,4-二胺

[2294] 

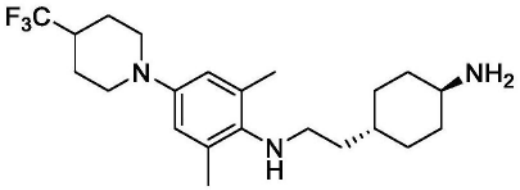
390

[2295] 由4-(4-乙基哌啶-1-基)-2-甲基苯胺(70mg,0.23mmol)和(4-氧代环已基)氨基甲酸叔丁酯(75mg,0.32mmol),根据为20的程序制备标题化合物390(29mg),收率为54.6%(淡玫瑰色的粉末)。^{1}H NMR(400MHz,DMSO-d6)δ8.04(s,3H),6.65(s,2H),6.48(s,1H),3.70(s,1H),3.48(s,1H),3.36(d,J=11.3Hz,2H),3.13(d,J=22.8Hz,1H),2.95(s,1H),2.11(s,

1H),2.01(d,J＝19.5Hz,3H),1.75(d,J＝32.9Hz,6H),1.44(q,J＝12.1Hz,1H),1.25(dd,J＝12.3,5.4Hz,6H),0.88(t,J＝7.2Hz,3H)。质谱(m/z):316.4[M+H]$^+$。

[2296] 化合物391

[2297] N-(2-((1r,4r)-4-氨基环已基)乙基)-2,6-二甲基-4-(4-(三氟甲基)哌啶-1-基)苯胺

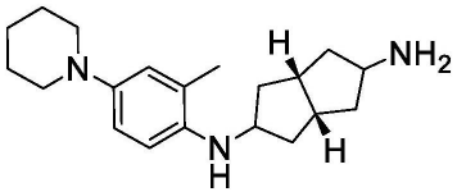
[2298] 

391

[2299] 由2,6-二甲基-4-(4-(三氟甲基)哌啶-1-基)苯胺(100mg,0.35mmol)和((1r,4r)-4-(2-氧代乙基)环已基)氨基甲酸叔丁酯(83mg,0.43mmol),根据为20的程序制备标题化合物391(11mg),收率为17.5％(浅黄色粉末)。^{1}H NMR(400MHz,DMSO-d6)δ7.74(s,3H),6.56(s,2H),4.09(d,J＝5.2Hz,1H),3.58(d,J＝12.4Hz,2H),3.16(d,J＝5.2Hz,2H),2.75(d,J＝6.5Hz,2H),2.16(s,6H),1.95-1.80(m,5H),1.75(d,J＝12.9Hz,2H),1.52(d,J＝9.1Hz,3H),1.37(s,2H),0.96(d,J＝12.6Hz,2H)。质谱(m/z):398.5[M+H]$^+$。

[2300] 化合物392

[2301] (3aR,6aS)-N^2-(2-甲基-4-(哌啶-1-基)苯基)八氢戊搭烯-2,5-二胺

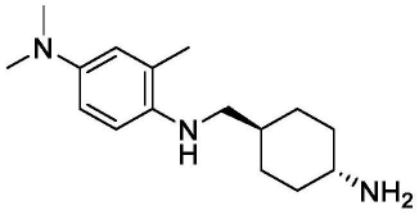
[2302] 

392

[2303] 由2-甲基-4-(哌啶-1-基)苯胺(100mg,0.63mmol)和(3as,6as)-四氢戊搭烯-2,5(1H,3H)-二酮(278mg,2.0mmol),根据为20的程序制备标题化合物392(32mg),三步总收率为15.3％(白色固体),经^{1}HNMR证明为1:1的混合物。^{1}H NMR(400MHz,DMSO-d6)δ8.39(s,3H),7.65-7.21(m,3H),6.62(s,1H),3.83(d,J＝68.0Hz,2H),2.39(s,2H),2.31-2.16(m,3H),2.11(s,4H),1.77(s,4H),1.58(s,2H),1.46(q,J＝11.9,11.1Hz,3H),1.36(s,2H)。质谱(m/z):314.6[M+H]$^+$。

[2304] 化合物393

[2305] N^1-(((1r,4r)-4-氨基环已基)甲基)-N4,N4,2-三甲基苯-1,4-二胺

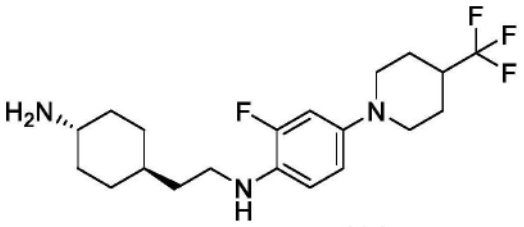
[2306] 

[2307] 根据为化合物24的程序制备标题化合物393(15.2mg),总收率为50.2％(紫色固体)。^{1}H NMR(400MHz,DMSO-d6)δ7.78(s,3H),7.27-7.12(m,2H),6.64-6.48(m,1H),3.60-

3.50(m,2H),3.38(s,6H),2.96-2.93(m,1H),2.12(s,3H),1.99-1.85(m,4H),1.63-1.51(m,1H),1.32-1.19(m,4H)。质谱(m/z):262.2[M+H]$^+$。

[2308] 化合物394

[2309] N-(2-((1r,4r)-4-氨基环已基)乙基)-2-氟-4-(4-(三氟甲基)哌啶-1-基)苯胺

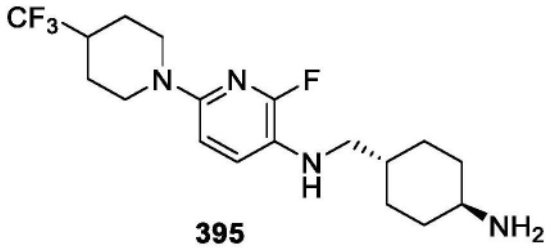
[2310] 

394

[2311] 由((1r,4r)-4-(2-((2-氟-4-(4-(三氟甲基)哌啶-1-基)苯基)氨基)乙基)环已基)氨基甲酸叔丁酯,根据为24的程序制备期望的产物394(白色固体)(19.7mg,26.6%)。^{1}H NMR(400MHz,DMSO-d6)δ7.81(s,3H),6.75-6.66(m,1H),6.61-6.50(m,2H),4.73(s,1H),3.54-3.42(m,2H),2.98(q,J=6.8Hz,2H),2.94-2.79(m,1H),2.41-2.32(m,1H),1.94-1.71(m,6H),1.51(qd,J=12.5,4.1Hz,2H),1.40(q,J=7.0Hz,2H),1.24(q,J=13.0,11.9Hz,4H),1.01-0.86(m,2H)。质谱(m/z):388.2[M+H]$^+$。

[2312] 化合物395

[2313] N-(((1r,4r)-4-氨基环已基)甲基)-2-氟-6-(4-(三氟甲基)哌啶-1-基)吡啶-3-胺

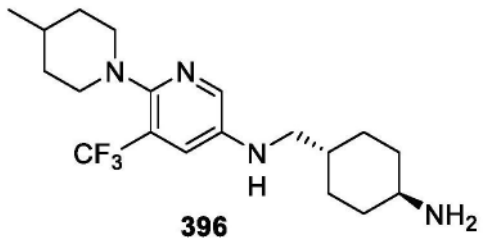
[2314] 

395

[2315] 由((1r,4r)-4-(((2-氟-6-(4-(三氟甲基)哌啶-1-基)吡啶-3-基)氨基)甲基)环已基)氨基甲酸叔丁酯(140mg,0.3mmol),DCM(5mL)和TFA(1mL),根据为24的程序制备标题化合物395(9.5mg,8.5%)(黄色固体)。^{1}H NMR(400MHz,CD_3OD)δ7.17-7.01(m,1H),6.50(d,J=7.6,1H),4.04-4.01(m,2H),2.99-2.89(m,3H),2.68-2.61(m,1H),2.29-2.63(m,1H),1.98-1.81(m,6H),1.52-1.44(m,3H),1.34-1.19(m,2H),1.09-0.99(m,2H)。质谱(m/z):375.2[M+H]$^+$。

[2316] 化合物396

[2317] N-(((1r,4r)-4-氨基环已基)甲基)-6-(4-甲基哌啶-1-基)-5-(三氟甲基)吡啶-3-胺

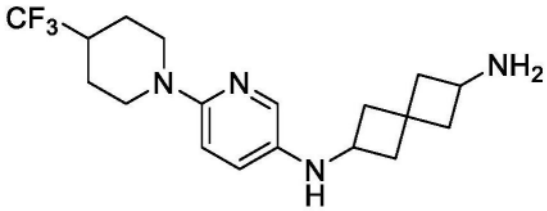
[2318] 

396

[2319] 向((1r,4r)-4-(((6-(4-甲基哌啶-1-基)-5-(三氟甲基)吡啶-3-基)氨基)甲基)环己基)氨基甲酸叔丁酯(200mg,0.52mmol),1,4-二氧杂环己烷(2mL)和HCl/1,4-二氧杂环己烷(5mL)的溶液中,根据为37的程序制备标题化合物396(28.1mg,17.8%)。^{1}H NMR(400MHz,DMSO-d6)δ7.95(d,J=2.8Hz,1H),7.14(d,J=2.8Hz,1H),6.09(t,J=5.6Hz,1H),2.91-2.86(m,4H),2.75(m,3H),1.86(br,4H),1.64(d,J=10.4Hz,2H),1.49-1.41(m,2H),1.26-1.16(m,4H),1.06-0.98(m,2H),0.94(d,J=6.4Hz,3H)。质谱(m/z):371.3[M+H]$^+$。

[2320] 化合物397

[2321] N^2-(6-(4-(三氟甲基)哌啶-1-基)吡啶-3-基)螺[3.3]庚烷-2,6-二胺

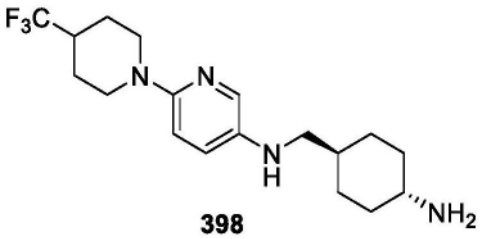
[2322] 

397

[2323] 由6-(4-(三氟甲基)哌啶-1-基)吡啶-3-胺(70mg,0.22mmol)和(6-氧代螺[3.3]庚烷-2-基)氨基甲酸叔丁酯(77mg,0.31mmol),根据为20的程序制备标题化合物397(42.9mg),收率为47.4%(白色粉末)。^{1}H NMR(400MHz,DMSO-d6)δ8.30-8.14(m,3H),7.46(d,J=2.9Hz,1H),6.97(d,J=9.6Hz,1H),6.79(d,J=9.0Hz,1H),4.11(d,J=12.8Hz,2H),3.66(p,J=7.4Hz,1H),3.54(s,1H),3.34(s,1H),2.79-2.65(m,2H),2.47(dd,J=5.5,3.2Hz,1H),2.42-2.29(m,2H),2.24-2.13(m,3H),1.83(q,J=8.2,7.8Hz,4H),1.45(qd,J=12.5,4.1Hz,2H)。质谱(m/z):355.2[M+H]$^+$。

[2324] 化合物398

[2325] N-(((1r,4r)-4-氨基环己基)甲基)-6-(4-(三氟甲基)哌啶-1-基)吡啶-3-胺

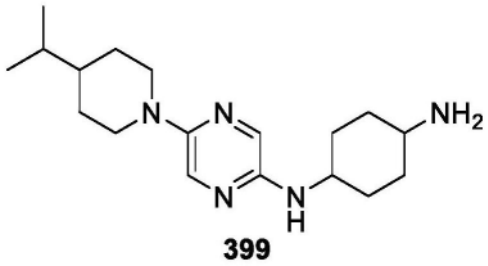
[2326] 

398

[2327] 由6-(4-(三氟甲基)哌啶-1-基)吡啶-3-胺(80mg,0.29mmol)和((1r,4r)-4-甲酰基环己基)氨基甲酸叔丁酯(85mg,0.37mmol),根据为20的程序制备标题化合物398(50mg),收率为56.8%(白色粉末)。^{1}H NMR(400MHz,DMSO-d6)δ7.98-7.84(m,3H),7.52(s,1H),7.02(s,1H),6.79(d,J=9.0Hz,1H),5.31(s,1H),4.08(d,J=12.8Hz,2H),2.92(d,J=4.9Hz,1H),2.80(d,J=6.6Hz,2H),2.69(t,J=12.1Hz,2H),1.99-1.89(m,2H),1.89-1.76(m,4H),1.44(qd,J=12.6,4.2Hz,3H),1.27(dt,J=14.9,11.2Hz,2H),1.09-0.90(m,2H)。质谱(m/z):357.5[M+H]$^+$。

[2328] 化合物399

[2329] N^1-(5-(4-异丙基哌啶-1-基)吡嗪-2-基)环己烷-1,4-二胺

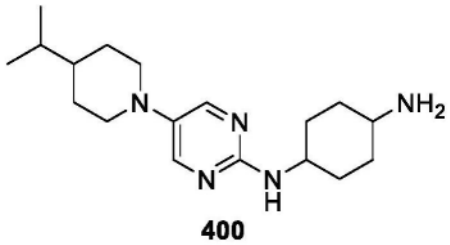
[2330] 

399

[2331] 由(4-((5-(4-异丙基哌啶-1-基)吡嗪-2-基)氨基)环己基)氨基甲酸叔丁酯(130mg,0.312mmol),TFA(1mL),和DCM(10mL),根据为1-2的程序制备标题化合物399(29.0mg),总收率为29.3%(黄色固体)。^{1}H NMR(400MHz,DMSO-d6)δ7.70-7.54(m,2H),6.11(dd,J=6.8,3.2Hz,1H),3.89(d,J=12.0Hz,2H),2.89(2,J=13.0Hz,1H),2.50(d,J=1.6Hz,2H),1.95(t,J=12.0Hz,4H),1.70(d,J=6.4Hz,2H),1.64(d,J=12.0Hz,3H),1.55(s,1H),1.46-1.35(m,4H),1.16-1.11(m,3H),0.83(s,3H),0.82(s,3H)。质谱(m/z):318.3[M+H]$^+$。

[2332] 化合物400

[2333] N^1-(5-(4-异丙基哌啶-1-基)嘧啶-2-基)环己烷-1,4-二胺

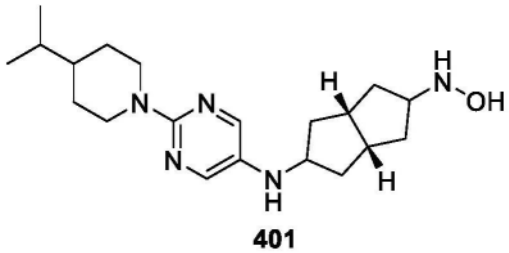
[2334] 

400

[2335] 由(4-((5-(4-异丙基哌啶-1-基)嘧啶-2-基)氨基)环己基)氨基甲酸叔丁酯(48mg,0.115mmol),TFA(1mL),和DCM(10mL),根据为24的程序制备标题化合物400(11.2mg),总收率为30.7%(白色固体)。^{1}H NMR(400MHz,DMSO-d6)δ8.18(s,2H),8.04(d,J=8.4Hz,2H),3.36(d,J=9.6Hz,2H),2.50(s,2H),2.41(s,2H),1.90(d,J=18.0Hz,3H),1.71-1.49(m,4H),1.40(dd,J=13.2,7.2Hz,3H),1.26(td,J=12.4,3.6Hz,4H),1.03(s,1H),0.84(d,J=6.8Hz,6H)。质谱(m/z):318.3[M+H]$^+$。

[2336] 化合物401

[2337] N-((3aR,6aS)-5-(羟基氨基)八氢戊搭烯-2-基)-2-(4-异丙基哌啶-1-基)嘧啶-5-胺

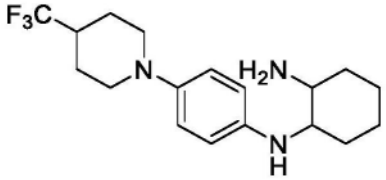
[2338] 

401

[2339] 根据为化合物1的程序制备标题化合物401(6.9mg),总收率为38.3%(黄色固体)。^{1}H NMR(400MHz,甲醇-d4)δ7.93(s,2H),4.55-4.46(m,2H),2.78-2.67(m,2H),2.62(m,1H),2.52(m,1H),2.36-2.13(m,3H),1.85(m,1H),1.77-1.68(m,3H),1.61(m,1H),1.48-1.31(m,4H),1.27-1.13(m,4H),0.91(d,J=6.4Hz,6H)。质谱(m/z):360.3[M+H]$^+$。

[2340] 化合物402

[2341] N^1-(4-(4-(三氟甲基)哌啶-1-基)苯基)环己烷-1,2-二胺

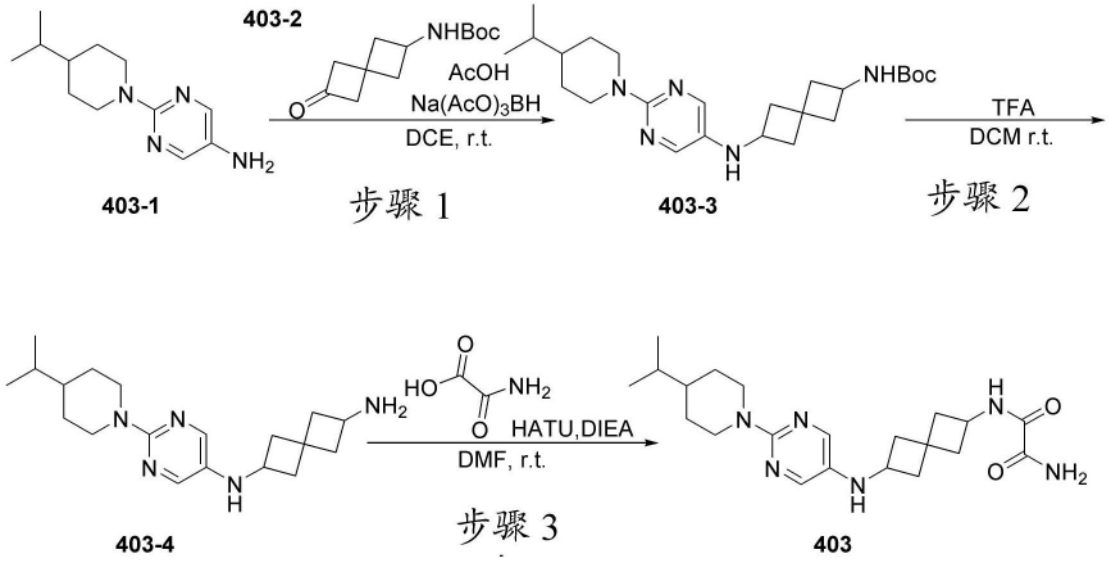
[2342] 

402

[2343] 根据为化合物24的程序制备标题化合物402(24.2mg),总收率为70.7%(玫瑰棕色固体)。^{1}H NMR(400MHz,甲醇-d4)δ6.91(d,J=8.8Hz,2H),6.74(d,J=8.4Hz,2H),3.57-3.46(m,2H),3.21(m,1H),2.95(m,1H),2.68-2.57(m,2H),2.25(m,1H),2.17-2.06(m,2H),1.98-1.91(m,2H),1.87-1.63(m,4H),1.56-1.24(m,4H)。质谱(m/z):342.2$[M+H]^+$。

[2344] 化合物403

[2345] N^1-(6-((2-(4-异丙基哌啶-1-基)嘧啶-5-基)氨基)螺[3.3]庚烷-2-基)草酰胺

[2346] 

403-1 步骤1 403-3 步骤2 403-4 步骤3 403

[2347] 步骤1:制备(6-((2-(4-异丙基哌啶-1-基)嘧啶-5-基)氨基)螺[3.3]庚烷-2-基)氨基甲酸叔丁酯(403-3)

[2348] 向2-(4-异丙基哌啶-1-基)嘧啶-5-胺(220mg,1.0mmol),(6-氧代螺[3.3]庚烷-2-基)氨基甲酸叔丁酯(225mg,1.0mmol)/DCE(15mL)添加的溶液中一滴AcOH。然后在室温搅拌混合物30分钟。添加$Na(AcO)_3BH$(424mg,2.0mmol)。在室温搅拌反应过夜。将反应混合物用水洗涤(20mL×3),用Na_2SO_4干燥,以及浓缩。残余物的提纯方法为:prep-TLC(EA/PE=1/2)而得到期望的产物(235mg,54.8%)(黄色固体)。质谱(m/z):430.3$[M+H]^+$。

[2349] 步骤2:制备N^2-(2-(4-异丙基哌啶-1-基)嘧啶-5-基)螺[3.3]庚烷-2,6-二胺(403-4)

[2350] 向(6-((2-(4-异丙基哌啶-1-基)嘧啶-5-基)氨基)螺[3.3]庚烷-2-基)氨基甲酸叔丁酯(235mg,0.58mmol)/DCM(3.0mL)的溶液中添加TFA(3.0mL)。然后在室温搅拌溶液30分钟并浓缩。添加5mL的水。用碳酸钠溶液将滤液的pH调整到8-9。然后用DCM(5mL×3)萃取混合物。将合并的有机层用水洗涤(10mL),用Na_2SO_4干燥,以及浓缩。残余物的提纯方法为:prep-TLC(MeOH/DCM=1/5)而得到期望的产物(176mg,92.2%)(黄色固体)。质谱(m/z):

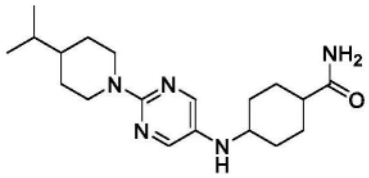
330.2[M+H]$^+$。

[2351] 步骤3:制备N^1-(6-((2-(4-异丙基哌啶-1-基)嘧啶-5-基)氨基)螺[3.3]庚烷-2-基)草酰胺(403)

[2352] 向2-氨基-2-氧代乙酸(8.9mg,0.1mmol)和HATU(38.0mg,0.1mmol)/DMF(1.0mL)的溶液中添加DIEA(38.7mg,0.3mmol)。随后添加N^2-(2-(4-异丙基哌啶-1-基)嘧啶-5-基)螺[3.3]庚烷-2,6-二胺(33.0mg,0.1mmol),然后在室温搅拌反应混合物10小时。添加5.0mL的水。然后用DCM(5.0mL×3)萃取混合物。将合并的有机层用水(5.0mL×3)洗涤,用Na_2SO_4干燥,以及真空浓缩。残余物的提纯方法为:prep-TLC(MeOH/DCM=1/10)而得到期望的产物403(10.9mg,18.6%)(黄色固体)。^{1}H NMR(400MHz,DMSO-d6)δ8.86(d,J=8.3Hz,1H),8.01(s,1H),7.79(s,2H),7.74(s,1H),5.24(d,J=7.4Hz,1H),4.51-4.45(m,2H),4.16-4.05(m,1H),3.66-3.59(m,1H),2.66-2.59(m,2H),2.35-2.10(m,6H),1.84-1.72(m,2H),1.67-1.60(m,2H),1.46-1.36(m,1H),1.22-1.17(m,1H),1.12-1.01(m,2H),0.85(d,J=6.8Hz,6H)。质谱(m/z):401.2[M+H]$^+$。

[2353] 化合物404

[2354] 4-((2-(4-异丙基哌啶-1-基)嘧啶-5-基)氨基)环己烷-1-甲酰胺

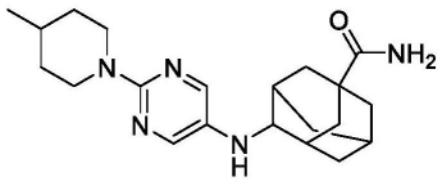
[2355] 

404

[2356] 由2-(4-异丙基哌啶-1-基)嘧啶-5-胺(70mg,0.23mmol)和4-氧代环己烷-1-甲酰胺(73mg,0.35mmol),根据为20的程序制备标题化合物404(32.1mg),收率为34.7%(白色粉末)。^{1}H NMR(400MHz,DMSO-d6)δ7.92(s,1H),7.89(s,1H),7.17(d,J=13.3Hz,1H),6.68(d,J=11.6Hz,1H),4.93(d,J=8.0Hz,1H),4.53-4.42(m,2H),2.62(td,J=12.5,2.4Hz,2H),2.17(dq,J=9.3,5.2,4.5Hz,1H),2.00-1.94(m,1H),1.77(dd,J=12.5,9.3Hz,2H),1.64(d,J=12.6Hz,3H),1.59-1.44(m,3H),1.40(dt,J=13.3,6.6Hz,1H),1.25-1.17(m,1H),1.15-1.02(m,3H),0.86(d,J=6.8Hz,6H)。质谱(m/z):346.5[M+H]$^+$。

[2357] 化合物405

[2358] 4-((2-(4-甲基哌啶-1-基)嘧啶-5-基)氨基)金刚烷-1-甲酰胺

[2359] 

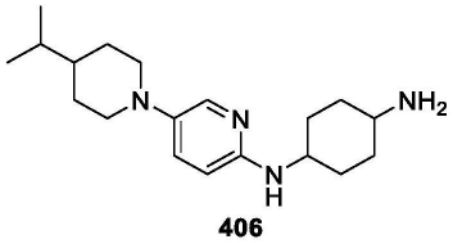
405

[2360] 由2-(4-甲基哌啶-1-基)嘧啶-5-胺(40mg,0.17mmol)和4-氧代金刚烷-1-甲酰胺(46mg,0.24mmol),根据为20的程序制备标题化合物405(6.5mg),收率为13.5%(白色粉末)。^{1}H NMR(400MHz,DMSO-d6)δ7.91(d,J=4.0Hz,2H),6.93(s,1H),6.68(s,1H),4.97(d,J=8.0Hz,1H),4.36(d,J=12.9Hz,2H),2.73-2.61(m,3H),1.94(dd,J=26.9,14.2Hz,5H),1.82(d,J=13.7Hz,4H),1.71(s,2H),1.57(d,J=13.2Hz,2H),1.34(d,J=12.3Hz,2H),

1.04-0.93(m,2H),0.87(d,J＝6.4Hz,3H)。质谱(m/z):370.3[M+H]$^+$。

[2361] 化合物406

[2362] N^1-(5-(4-异丙基哌啶-1-基)吡啶-2-基)环己烷-1,4-二胺

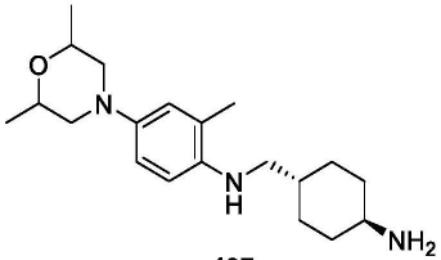
[2363] 

406

[2364] 由(4-((5-(4-异丙基哌啶-1-基)吡啶-2-基)氨基)环己基)氨基甲酸叔丁酯(150mg,0.36mmol),DCM(2mL)和TFA(1mL),根据为24的程序制备标题化合物406(21.1mg,18.5%)(淡棕色固体)。^{1}H NMR(400MHz,DMSO-d6)δ7.59(t,J＝2.8Hz,1H),7.10(dt,J＝9.0,3.0Hz,1H),6.44-6.29(m,1H),5.73(dd,J＝17.8,7.6Hz,1H),3.74-3.30(m,1H),2.43-2.35(m,2H),1.91-1.56(m,7H),1.54-1.34(m,3H),1.32-1.17(m,3H),1.17-0.97(m,4H),0.84(d,J＝6.8Hz,6H)。MS(m/z):317.3[M+H]$^+$。

[2365] 化合物407

[2366] N-(((1r,4r)-4-氨基环己基)甲基)-4-(2,6-二甲基吗啉代)-2-甲基苯胺

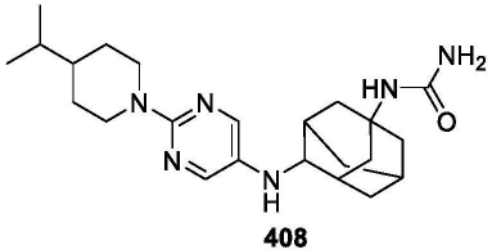
[2367] 

407

[2368] 由((1r,4r)-4-(((4-(2,6-二甲基吗啉代)-2-甲基苯基)氨基)甲基)环己基)氨基甲酸叔丁酯(122mg,0.283mmol),TFA(1mL),和DCM(10mL),根据为24的程序制备标题化合物407(61.2mg),总收率为65.3%(白色固体)。^{1}H NMR(400MHz,DMSO-d6)δ8.30-8.15(m,3H),6.74(d,J＝8.4Hz,1H),6.36(s,2H),3.70-3.59(m,2H),2.85(s,1H),2.72(dd,J＝22.0,8.8Hz,4H),2.19(t,J＝10.8Hz,2H),2.11(s,3H),1.98-1.90(m,2H),1.81(d,J＝12.8Hz,2H),1.41(s,1H),1.35-1.23(m,2H),1.04(d,J＝6.4Hz,6H),1.00-0.88(m,2H)。质谱(m/z):332.3[M+H]$^+$。

[2369] 化合物408

[2370] 1-(4-((2-(4-异丙基哌啶-1-基)嘧啶-5-基)氨基)金刚烷-1-基)脲

[2371] 

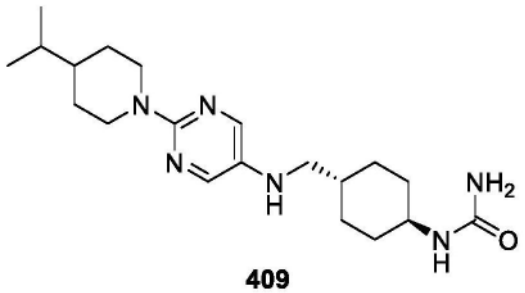
408

[2372] 由N^4-(2-(4-异丙基哌啶-1-基)嘧啶-5-基)金刚烷-1,4-二胺(46mg,0.18mmol)和氨基甲酸苯酯(24mg,0.17mmol),根据为243的程序制备标题化合物408(6.5mg),收率为

13.5%(白色粉末)。^{1}H NMR(400MHz,DMSO-d6)δ7.94(d,J=4.3Hz,2H),5.89(s,1H),5.72(s,1H),4.48(d,J=12.9Hz,2H),2.62(td,J=12.8,2.2Hz,2H),2.40(d,J=3.8Hz,3H),2.20-2.09(m,6H),2.11-2.04(m,4H),1.68-1.59(m,3H),1.47-1.31(m,2H),1.08(qd,J=12.2,4.1Hz,2H),0.86(d,J=6.7Hz,6H)。质谱(m/z):413.5[M+H]$^+$。

[2373] 化合物409

[2374] 1-((1r,4r)-4-(((2-(4-异丙基哌啶-1-基)嘧啶-5-基)氨基)甲基)环己基)脲

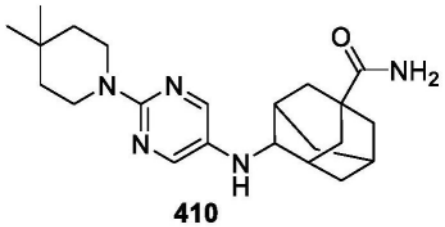
[2375] 

409

[2376] 由N-(((1r,4r)-4-氨基环己基)甲基)-2-(4-异丙基哌啶-1-基)嘧啶-5-胺(51mg,0.19mmol)和氨基甲酸苯酯(25mg,0.17mmol),根据为243的程序制备标题化合物409(6.9mg),收率为14.2%(白色粉末)。^{1}H NMR(400MHz,DMSO-d6)δ7.86(s,2H),5.76(d,J=8.0Hz,1H),5.06(t,J=6.1Hz,1H),4.46(d,J=13.2Hz,2H),3.23(s,1H),2.78(t,J=6.3Hz,2H),2.61(t,J=12.1Hz,2H),1.78(d,J=11.6Hz,4H),1.63(d,J=11.9Hz,2H),1.39(dd,J=13.0,6.7Hz,2H),1.16(s,1H),1.08(td,J=12.3,4.0Hz,2H),0.99(q,J=11.8,11.0Hz,4H),0.84(d,J=6.8Hz,6H)。质谱(m/z):375.4[M+H]$^+$。

[2377] 化合物410

[2378] 4-((2-(4,4-二甲基哌啶-1-基)嘧啶-5-基)氨基)金刚烷-1-甲酰胺

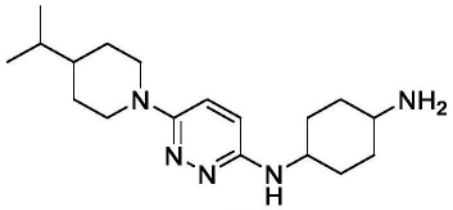
[2379] 

410

[2380] 由2-(4,4-二甲基哌啶-1-基)嘧啶-5-胺(68mg,0.18mmol)和4-氧代金刚烷-1-甲酰胺(41mg,0.25mmol),根据为20的程序制备标题化合物410(8.2mg),收率为12.09%(白色粉末)。^{1}H NMR(400MHz,DMSO-d6)δ7.95(d,J=4.1Hz,2H),6.98(s,1H),6.73(s,1H),5.01(d,J=7.8Hz,1H),3.60-3.50(m,4H),2.89(s,2H),2.73(s,1H),2.03-1.91(m,2H),1.89-1.79(m,3H),1.75(d,J=2.9Hz,3H),1.38(d,J=12.4Hz,2H),1.33-1.25(m,4H),0.94(s,6H)。质谱(m/z):384.2[M+H]$^+$。

[2381] 化合物411

[2382] N^1-(6-(4-异丙基哌啶-1-基)哒嗪-3-基)环己烷-1,4-二胺

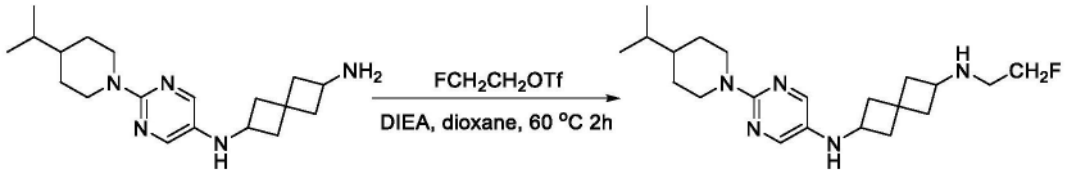
[2383] 

411

[2384] 由(4-((6-(4-异丙基哌啶-1-基)哒嗪-3-基)氨基)环己基)氨基甲酸叔丁酯(60mg,0.14mmol),DCM(2mL)和TFA(1mL),根据为24的程序制备标题化合物411(8.4mg,17.5%)(灰白色固体)。^{1}H NMR(400MHz,DMSO-d6)δ7.08(dd,J=9.7,2.3Hz,1H),6.72(dd,J=39.5,9.6Hz,1H),5.93(dd,J=12.3,7.2Hz,1H),4.00(d,J=12.3Hz,2H),3.90-3.51(m,1H),3.04-2.72(m,1H),2.64-2.57(m,2H),2.00-1.96(m,1H),1.80-1.76(m,1H),1.75-1.61(m,3H),1.61-1.48(m,1H),1.46-1.37(m,2H),1.28-1.05(m,6H),0.87(d,J=6.8Hz,6H)。MS(m/z):318.3[M+H]$^+$。

[2385] 化合物412

[2386] N^2-(2-氟乙基)-N6-(2-(4-异丙基哌啶-1-基)嘧啶-5-基)螺[3.3]庚烷-2,6-二胺

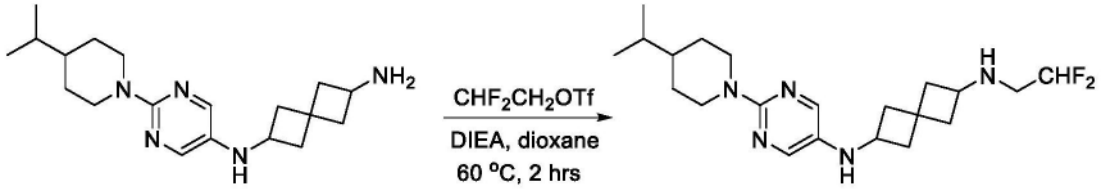
[2387] 

412

[2388] 向2-N-[2-(4-异丙基哌啶-1-基)嘧啶-5-基]螺[3.3]庚烷-2,6-二胺盐酸盐(100mg,0.31mmol)/二氧杂环己烷(20mL)的溶液中添加TEA(92mg,0.91mmol),三氟甲磺酸2-氟乙酯(119mg,0.61mmol),将混合物加热到60℃2小时,然后将混合物真空除去。残余物的提纯方法为:prep-HPLC(柱-Gemini-C18 150x 21.2mm,5um;移动相:ACN-H_2O(0.1%FA),5%-20%)而得到期望的产物412(6.7mg,5.8%)(黄色固体)。^{1}H NMR(400MHz,CD_3OD)δ7.81(s,2H),4.73-4.70(m,1H),4.62-4.57(m,1H),4.47(d,J=13.2Hz,2H),3.69(dt,J=11.8,7.8Hz,2H),3.22(s,1H),3.18-3.14(m,1H),2.71(dd,J=18.0,7.2Hz,2H),2.60-2.51(m,2H),2.45-2.33(m,2H),2.23-2.14(m,2H),1.97-1.89(m,2H),1.70(d,J=11.9Hz,2H),1.45-1.37(m,1H),1.26-1.11(m,3H),0.88(d,J=6.8Hz,6H)。MS(m/z):376.3[M+H]$^+$。

[2389] 化合物413

[2390] N^2-(2,2-二氟乙基)-N6-(2-(4-异丙基哌啶-1-基)嘧啶-5-基)螺[3.3]庚烷-2,6-二胺

[2391] 

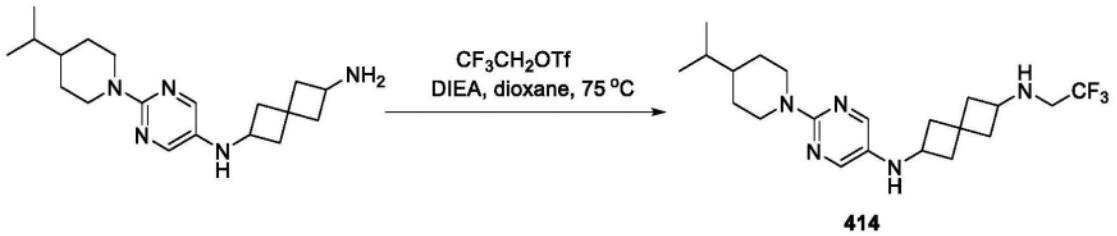
413

[2392] 向2-N-[2-(4-异丙基哌啶-1-基)嘧啶-5-基]螺[3.3]庚烷-2,6-二胺盐酸盐(100mg,0.31mmol)/MeOH(20mL)的溶液中添加DIEA(118mg,0.91mmol),三氟甲磺酸2,2-二氟乙酯(130mg,0.61mmol),在室温搅拌混合物2小时,然后将混合物真空除去。残余物的提

纯方法为:prep-HPLC(柱-Gemini-C18 150x 21.2mm,5um;移动相:ACN-H_2O(0.1%FA),5%-20%)而得到期望的产物(黄色固体)(8.7mg,7.2%)。^1H NMR(400MHz,CD_3OD)δ7.81(s,2H),6.13(dd,J=55.6,52.9Hz,1H),4.47(d,J=13.2Hz,2H),3.73-3.55(m,2H),3.28-3.19(m,2H),2.71(dd,J=18.0,7.2Hz,2H),2.57-2.47(m,2H),2.43-2.30(m,2H),2.17-2.08(m,2H),1.91(dt,J=11.2,8.3Hz,2H),1.70(d,J=11.8Hz,2H),1.44-1.37(m,1H),1.18(m,3H),0.88(d,J=6.8Hz,6H)。MS(m/z):394.2$[M+H]^+$。

[2393] 化合物414

[2394] N^2-(2-(4-异丙基哌啶-1-基)嘧啶-5-基)-N6-(2,2,2-三氟乙基)螺[3.3]庚烷-2,6-二胺

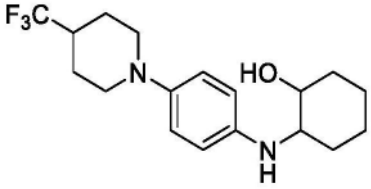
[2395] 

414

[2396] 向2-N-[2-(4-异丙基哌啶-1-基)嘧啶-5-基]螺[3.3]庚烷-2,6-二胺盐酸盐(100mg,0.27mmol)/二氧杂环己烷(20mL)的溶液中添加DIEA(106mg,0.82mmol),三氟甲磺酸2,2,2-三氟乙酯(127mg,0.55mmol),并且在室温搅拌混合物2小时,然后将混合物真空除去。残余物的提纯方法为:prep-HPLC(柱-Gemini-C18 150x 21.2mm,5um;移动相:ACN-H_2O(0.1%FA),5%-20%)而得到期望的产物(3.3mg,2.9%)(黄色固体)。^1H NMR(400MHz,CD_3OD)δ7.81(d,J=0.7Hz,2H),4.49-4.44(m,2H),3.66(t,J=7.5Hz,1H),3.21(d,J=7.5Hz,1H),3.09(d,J=9.9Hz,2H),2.74-2.67(m,2H),2.48(ddd,J=11.3,6.3,2.8Hz,1H),2.41-2.29(m,2H),2.22-2.16(m,1H),1.87-1.78(m,4H),1.73-1.68(m,2H),1.45-1.38(m,1H),1.19(m,3H),0.88(d,J=6.8Hz,6H)。MS(m/z):412.3$[M+H]^+$。

[2397] 化合物415

[2398] 2-((4-(4-(三氟甲基)哌啶-1-基)苯基)氨基)环己烷-1-醇

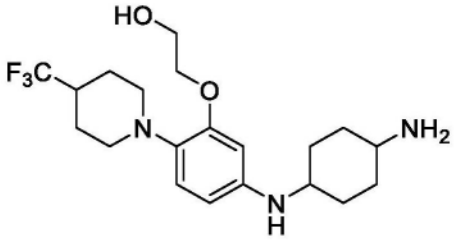
[2399] 

415

[2400] 根据为化合物4的程序制备标题化合物415(20.6mg),总收率为60.1%(白色固体)。^1H NMR(400MHz,DMSO-d6)δ6.74(d,J=8.8Hz,2H),6.52(d,J=8.0Hz,2H),4.48(m,1H),3.47-3.36(m,2H),3.23(m,1H),2.42-2.30(m,2H),1.96(m,1H),1.90-1.81(m,2H),1.75-1.43(m,6H),1.35-1.23(m,4H)。质谱(m/z):343.2$[M+H]^+$。

[2401] 化合物416

[2402] (5-((4-氨基环己基)氨基)-2-(4-(三氟甲基)哌啶-1-基)苯氧基)乙-1-醇

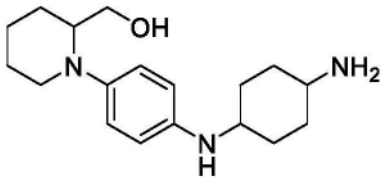
[2403] 

416

[2404] 根据为化合物24的程序制备标题化合物416(43.7mg),总收率为72.5%(白色固体)。^{1}H NMR(400MHz,DMSO-d6)δ6.66(s,1H),6.23(d,J=8.8Hz,1H),6.09(d,J=8.4Hz,1H),3.90(m,2H),3.67(m,2H),3.30-3.21(m,2H),3.06(m,1H),2.96(m,1H),2.42-2.31(m,2H),2.05-1.90(m,2H),1.87-1.34(m,10H),1.26-1.09(m,1H)。质谱(m/z):402.2[M+H]$^+$。

[2405] 化合物417

[2406] (1-(4-((4-氨基环己基)氨基)苯基)哌啶-2-基)甲醇

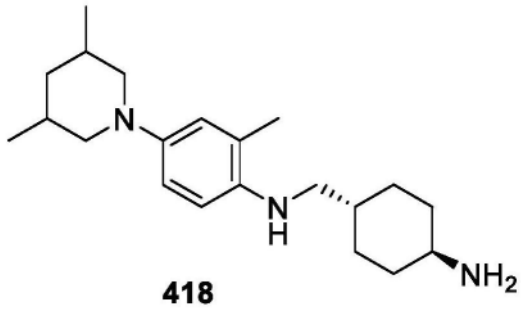
[2407] 

417A
417B

[2408] 根据为化合物24的程序制备标题化合物417。混合物的提纯方法:prep HPLC(XSelect-CSH-Prep 5μm OBD,19*150mm柱;ACN/水(0.5%TFA)=10%-35%-95%-95%-0%,0min-10min-10.5min-11.5min-13min)而得到化合物417A(Rt=8.52min),收率为37.8%(灰色固体)and 417B(Rt=9.64min),收率为12.2%(灰色固体)。417A:^{1}H NMR(400MHz,甲醇-d4)δ7.01(d,J=8.8Hz,2H),6.74(d,J=8.8Hz,2H),3.61-3.40(m,2H),3.22-2.93(m,3H),2.85(m,1H),2.76(m,1H),2.05-1.80(m,4H),1.63-1.54(m,2H),1.50-1.20(m,6H),1.18-1.03(m,2H)。质谱(m/z):304.2[M+H]$^+$。417B:^{1}H NMR(400MHz,甲醇-d4)δ7.02(d,J=8.8Hz,2H),6.74(d,J=8.8Hz,2H),3.50-3.35(m,2H),3.21-2.95(m,3H),2.84(m,1H),2.76(m,1H),2.05-1.91(m,3H),1.85-1.63(m,4H),1.60-1.53(m,3H),1.23-1.05(m,4H)。质谱(m/z):304.2[M+H]$^+$。

[2409] 化合物418

[2410] N-(((1r,4r)-4-氨基环己基)甲基)-2-氟-6-(4-(三氟甲基)哌啶-1-基)吡啶-3-胺

[2411] 

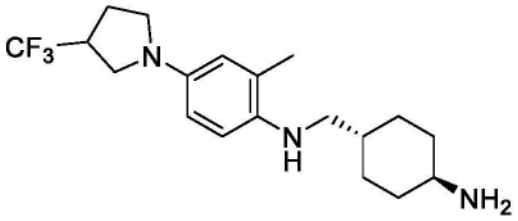
418

[2412] 由((1r,4r)-4-(((4-(3,5-二甲基哌啶-1-基)-2-甲基苯基)氨基)甲基)环己基)

氨基甲酸叔丁酯(100mg,0.23mmol),DCM(5mL)和TFA(1mL),根据为24的程序制备标题化合物418(14.1mg,22%)(黄色固体)。^{1}H NMR(400MHz,DMSO-d6)δ=6.65(s,2H),6.38(s,1H),4.25(s,1H),3.30(s,9H),2.83(s,2H),2.04-1.97(m,3H),1.80-1.71(m,4H),1.48(s,1H),1.24(s,2H),1.08(s,1H),0.87(s,6H)。质谱(m/z):329.9[M+H]$^+$。

[2413] 化合物419

[2414] N-(((1r,4r)-4-氨基环己基)甲基)-2-甲基-4-(3-(三氟甲基)吡咯烷-1-基)苯胺

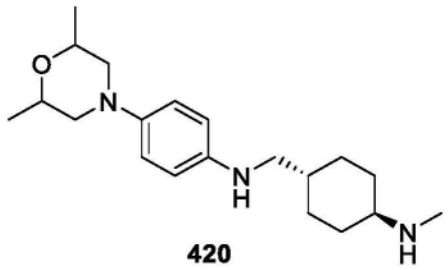
[2415] 

419

[2416] 由((1r,4r)-4-(((2-甲基-4-(3-(三氟甲基)吡咯烷-1-基)苯基)氨基)甲基)环己基)氨基甲酸叔丁酯(160mg,0.35mmol),DCM(10mL)和TFA(1mL),根据为24的程序制备标题化合物419(45.1mg,35.8%)(紫色固体)。^{1}H NMR(400MHz,DMSO-d6)δ6.40(m,3H),3.43-3.28(m,2H),3.23-3.11(m,3H),2.91(m,1H),2.83(d,J=6.6Hz,2H),2.25-2.18(m,1H),2.06(s,3H),2.02-1.84(m,5H),1.52(s,1H),1.30-1.20(m,2H),1.00(m,2H)。质谱(m/z):356.22[M+H]$^+$。

[2417] 化合物420

[2418] 4-(2,6-二甲基吗啉代)-N-(((1r,4r)-4-(甲基氨基)环己基)甲基)苯胺

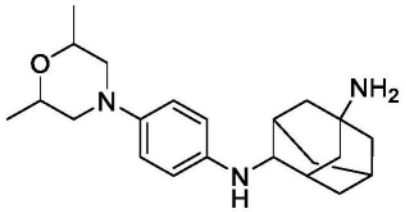
[2419] 

420

[2420] 由((1r,4r)-4-(((4-(2,6-二甲基吗啉代)苯基)氨基)甲基)环己基)氨基甲酸叔丁酯(100mg,0.24mmol),THF(3mL)和LAH(0.3mL,0.71mmol),根据为23的程序制备标题化合物420(4.2mg,5%)(白色固体)。^{1}H NMR(400MHz,DMSO-d6)δ6.73-6.64(m,2H),6.48-6.39(m,2H),5.06(s,1H),3.69-3.57(m,2H),3.25-3.17(m,2H),2.74(t,J=5.4Hz,2H),2.27(s,3H),2.12-2.02(m,2H),1.91-1.83(m,2H),1.82-1.75(m,2H),1.43-1.39(m,1H),1.22-1.18(m,1H),1.08(d,J=6.3Hz,6H),1.01-0.78(m,4H)。MS(m/z):332.3[M+H]$^+$。

[2421] 化合物421

[2422] N^4-(4-(2,6-二甲基吗啉代)苯基)金刚烷-1,4-二胺

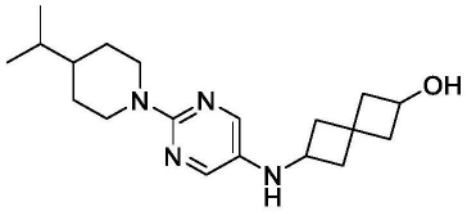
[2423] 

421A
421B

[2424] 由(4-((4-(2,6-二甲基吗啉代)苯基)氨基)金刚烷-1-基)氨基甲酸叔丁酯(100mg,0.22mmol),DCM(3mL),和TFA(1mL),根据为24的程序制备标题化合物421A(Rt＝7.5min)(17mg,21.7%)(白色固体)和化合物421B(Rt＝8.76min)(11.4mg,14.6%)(白色固体),其提纯方法为:Prep-HPLC(XSelect-CSH-Prep 5μm OBD,19*150mm柱;ACN/水(0.5%TFA)＝0%-30%-95%-95%-0%,0min-10min-10.5min-11.5min-13min)。421A:^{1}H NMR(400MHz,DMSO-d6)δ6.72-6.64(m,2H),6.55-6.47(m,2H),4.94(d,J＝7.5Hz,1H),3.69-3.57(m,2H),3.27-3.19(m,3H),2.12-2.02(m,2H),1.93-1.85(m,5H),1.74-1.45(m,7H),1.27-1.18(m,3H),1.08(d,J＝6.2Hz,6H)。MS(m/z):356.3[M+H]$^+$。421B:^{1}H NMR(400MHz,DMSO-d6)δ6.72-6.64(m,2H),6.56-6.47(m,2H),4.88(d,J＝7.3Hz,1H),3.69-3.57(m,2H),3.25-3.15(m,3H),2.12-2.02(m,2H),2.00-1.89(m,3H),1.77(d,J＝12.2Hz,2H),1.68-1.51(m,5H),1.46-1.40(m,2H),1.23-1.16(m,3H),1.08(d,J＝6.3Hz,6H)。MS(m/z):356.3[M+H]$^+$。

[2425] 化合物422

[2426] 6-((2-(4-异丙基哌啶-1-基)嘧啶-5-基)氨基)螺[3.3]庚烷-2-醇

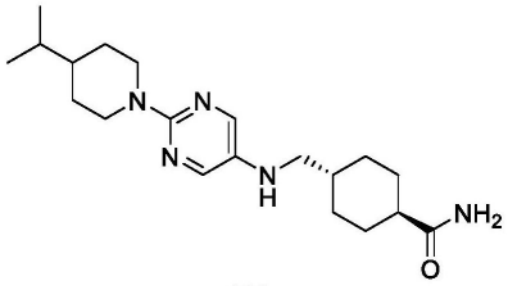
[2427] 

422

[2428] 由2-(4-异丙基哌啶-1-基)嘧啶-5-胺(50mg,0.23mmol)和6-羟基螺[3.3]庚烷-2-酮(34mg,0.27mmol),根据为20的程序制备标题化合物422(32.3mg),收率为43.07%(白色粉末)。^{1}H NMR(400MHz,DMSO-d6)δ7.77(s,2H),5.22(d,J＝7.5Hz,1H),4.88(d,J＝6.4Hz,1H),4.47(dt,J＝12.4,3.0Hz,2H),3.99-3.90(m,1H),3.61(q,J＝7.5Hz,1H),2.61(td,J＝12.6,2.5Hz,2H),2.53(dd,J＝7.7,1.9Hz,1H),2.40-2.31(m,2H),2.27(ddd,J＝11.5,7.1,4.7Hz,1H),2.15(dt,J＝11.7,6.2Hz,1H),1.85-1.78(m,2H),1.74(ddd,J＝11.2,7.9,3.3Hz,2H),1.67-1.60(m,2H),1.44-1.33(m,1H),1.20(ddt,J＝14.7,6.1,3.0Hz,1H),1.06(qd,J＝12.3,4.2Hz,2H),0.85(d,J＝6.8Hz,6H)。质谱(m/z):331.4[M+H]$^+$。

[2429] 化合物423

[2430] (1r,4r)-4-(((2-(4-异丙基哌啶-1-基)嘧啶-5-基)氨基)甲基)环己烷-1-甲酰胺

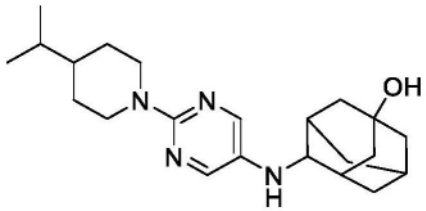
[2431] 

423

[2432] 由(1r,4r)-4-(((2-(4-异丙基哌啶-1-基)嘧啶-5-基)氨基)甲基)环己烷-1-甲酸(50mg,0.14mmol)和氨(0.500mL),根据为10的程序制备标题化合物423(8.5mg),收率为17.0%(白色粉末)。^{1}H NMR(400MHz,DMSO-d6)δ7.87(s,1H),7.16(s,1H),6.64(s,1H),4.54(dd,J=53.1,13.4Hz,2H),2.79(t,J=6.4Hz,1H),2.66-2.57(m,2H),2.01(t,J=6.1Hz,1H),1.74(ddd,J=46.9,30.3,12.6Hz,8H),1.41(dt,J=13.4,6.6Hz,3H),1.24(s,7H),1.16-1.00(m,1H),0.96-0.81(m,6H)。质谱(m/z):360.5[M+H]$^+$。

[2433] 化合物424

[2434] 4-((2-(4-异丙基哌啶-1-基)嘧啶-5-基)氨基)金刚烷-1-醇

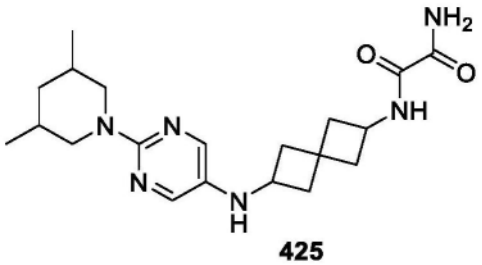
[2435] 

424

[2436] 由2-(4-异丙基哌啶-1-基)嘧啶-5-胺(50mg,0.23mmol)和5-羟基金刚烷-2-酮(45mg,0.27mmol),根据为20的程序制备标题化合物424(28.6mg),收率为34.01%(白色粉末)。^{1}H NMR(400MHz,DMSO-d6)δ7.90(d,J=1.9Hz,2H),4.92(dd,J=12.4,7.7Hz,1H),4.44(dt,J=12.7,2.7Hz,2H),4.33(d,J=18.2Hz,1H),2.58(td,J=12.6,2.5Hz,2H),1.98(d,J=30.4Hz,3H),1.86(d,J=12.7Hz,2H),1.69(d,J=11.6Hz,1H),1.65-1.49(m,7H),1.40-1.33(m,1H),1.33-1.13(m,2H),1.04(qd,J=12.2,4.1Hz,2H),0.82(d,J=6.8Hz,6H)。质谱(m/z):371.4[M+H]$^+$。

[2437] 化合物425

[2438] N^1-(6-((2-(3,5-二甲基哌啶-1-基)嘧啶-5-基)氨基)螺[3.3]庚烷-2-基)草酰胺

[2439] 

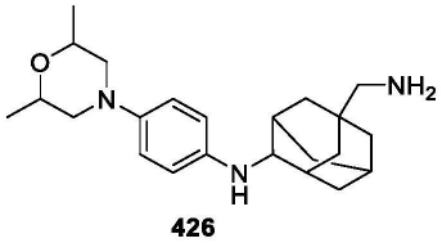
425

[2440] 由N^2-(2-(3,5-二甲基哌啶-1-基)嘧啶-5-基)螺[3.3]庚烷-2,6-二胺(18mg,0.057mmol)和2-氨基-2-氧代乙酸(6mg,0.068mmol),根据为10的程序制备标题化合物425(4.8mg),收率为21.7%(白色粉末)。^{1}H NMR(400MHz,DMSO-d6)δ8.85(d,J=8.3Hz,1H),8.01(s,1H),7.78(s,1H),7.73(s,1H),4.42(d,J=13.8Hz,2H),3.68-3.54(m,3H),3.17-

3.08(m,3H),2.25-2.09(m,2H),1.73(d,J＝10.5Hz,2H),1.19(d,J＝6.7Hz,6H),0.85(dd,J＝6.7,3.5Hz,6H)。质谱(m/z):387.4[M+H]$^+$。

[2441] 化合物426

[2442] 5-(氨基甲基)-N-(4-(2,6-二甲基吗啉代)苯基)金刚烷-2-胺

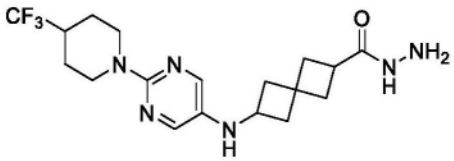
[2443] 

426

[2444] 由4-(2,6-二甲基吗啉代)苯胺(70mg,0.34mmol)和4-氧代金刚烷-1-甲酸(99mg,0.51mmol),根据为84的程序制备标题化合物426(28.2mg),两步总收率为26.7％(白色粉末)。^{1}H NMR(400MHz,DMSO-d6)δ7.91(s,2H),6.75(s,2H),6.58(s,2H),5.08(s,1H),3.68(s,2H),2.12(s,2H),1.98(s,4H),1.91(d,J＝6.6Hz,2H),1.72(d,J＝17.9Hz,2H),1.63(s,3H),1.53(s,2H),1.49(s,1H),1.35(d,J＝12.2Hz,1H),1.25(d,J＝7.8Hz,1H),1.12(d,J＝6.0Hz,6H)。质谱(m/z):389.3[M+H]$^+$。

[2445] 化合物427

[2446] 6-((2-(4-(三氟甲基)哌啶-1-基)嘧啶-5-基)氨基)螺[3.3]庚烷-2-碳酰肼

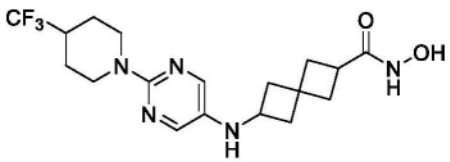
[2447] 

427

[2448] 由6-((2-(4-(三氟甲基)哌啶-1-基)嘧啶-5-基)氨基)螺[3.3]庚烷-2-甲酸(30mg,0.078mmol),氢氧化肼溶液(23mg,0.468mmol),HATU(45mg,0.117mmol)和DIEA(30mg,0.234mmol)和DMF(5mL),根据为1的程序制备标题化合物427(5.1mg),总收率为16.4％(黄色固体)。^{1}H NMR(400MHz,DMSO-d6)δ9.01(s,1H),8.92(s,1H),7.78(s,2H),4.54-4.11(m,7H),3.63-3.51(m,2H),2.80(t,J＝8.4Hz,1H),2.72(td,J＝12.8,2.5Hz,2H),2.25(td,J＝6.8,3.4Hz,1H),2.18-2.03(m,3H),1.93-1.87(m,1H),1.77(dd,J＝12.4,3.8Hz,3H),1.71(s,3H),1.67(dd,J＝11.2,7.8Hz,1H),1.28(tt,J＝12.0,5.2Hz,8H),0.86-0.78(m,1H)。质谱(m/z):399.3[M+H]$^+$。

[2449] 化合物428

[2450] N-羟基-6-((2-(4-(三氟甲基)哌啶-1-基)嘧啶-5-基)氨基)螺[3.3]庚烷-2-甲酰胺

[2451] 

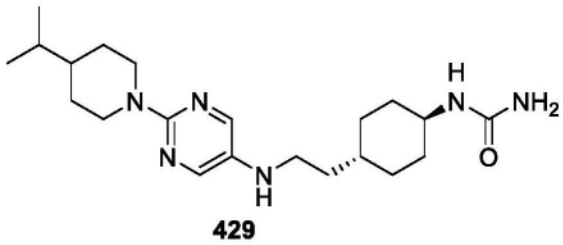
428

[2452] 由6-((2-(4-(三氟甲基)哌啶-1-基)嘧啶-5-基)氨基)螺[3.3]庚烷-2-甲酸

(30mg,0.078mmol),羟基胺盐酸盐(11mg,0.156mmol),HATU(45mg,0.117mmol)和DIEA(30mg,0.234mmol)和DMF(5mL),根据为1的程序制备标题化合物428(7.0mg),总收率为22.4%(黄色固体)。^{1}H NMR(400MHz,DMSO-d6)δ10.37(s,1H),8.65(d,J=1.6Hz,1H),7.78(s,2H),5.36(d,J=7.2Hz,1H),4.49(d,J=13.2Hz,2H),3.57(q,J=7.2Hz,1H),2.78-2.68(m,3H),2.26(q,J=5.6,5.2Hz,1H),2.11(ddd,J=22.0,11.2,8.4Hz,3H),1.89(ddd,J=12.0,8.0,4.0Hz,1H),1.77(dd,J=12.0,4.0Hz,3H),1.67(dd,J=11.2,8.0Hz,1H),1.30(qd,J=12.4,4.0Hz,4H)。质谱(m/z):400.3[M+H]$^+$。

[2453] 化合物429

[2454] 1-((1r,4r)-4-(2-((2-(4-异丙基哌啶-1-基)嘧啶-5-基)氨基)乙基)环己基)脲

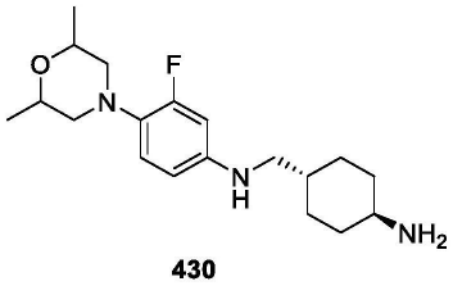
[2455] 

429

[2456] 由N-(2-((1r,4r)-4-氨基环己基)乙基)-2-(4-异丙基哌啶-1-基)嘧啶-5-胺(100mg,0.2894mmol),DCM(10mL),TMSNCO(33.34mg,0.2894mmol),TEA(87.85mg,0.8682mmol)和DMAP(7.07mg,0.0579mmol),根据为178的程序制备标题化合物429(4.4mg,3.7%)。^{1}H NMR(400MHz,DMSO-d6)δ7.86(s,2H),5.78(d,J=8.0Hz,1H),5.28(s,2H),4.94(s,1H),4.48(d,J=13.0Hz,2H),3.25-3.19(m,1H),2.94(t,J=6.9Hz,2H),2.67-2.58(m,2H),1.83-1.61(m,6H),1.46-1.36(m,3H),1.13(m,8H),0.85(d,J=6.8Hz,6H)。质谱(m/z):389.30[M+H]$^+$。

[2457] 化合物430

[2458] N-(((1r,4r)-4-氨基环己基)甲基)-4-(2,6-二甲基吗啉代)-3-氟苯胺

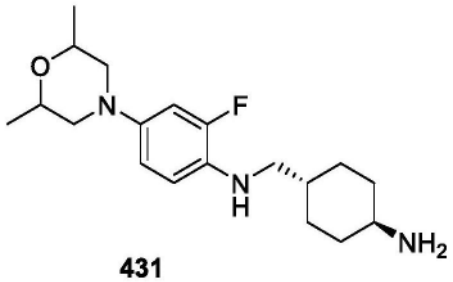
[2459] 

430

[2460] 由((1r,4r)-4-(((4-(2,6-二甲基吗啉代)-3-氟苯基)氨基)甲基)环己基)氨基甲酸叔丁酯(100mg,0.23mmol),DCM(3mL)和TFA(1mL),根据为24的程序制备标题化合物430(10mg,12.9%)(白色固体)。^{1}H NMR(400MHz,DMSO-d6)δ6.79(dd,J=10.0,8.6Hz,1H),6.33(dd,J=15.0,2.5Hz,1H),6.28(dd,J=8.6,2.7Hz,1H),5.56(t,J=5.8Hz,1H),3.75-3.63(m,2H),3.00-2.92(m,2H),2.77(t,J=6.2Hz,2H),2.53-2.52(m,1H),2.29-2.20(m,2H),1.80-1.73(m,4H),1.42-1.37(m,1H),1.08(d,J=6.2Hz,6H),1.03-0.86(m,4H)。MS(m/z):336.3[M+H]$^+$。

[2461] 化合物431

[2462] N-(((1r,4r)-4-氨基环己基)甲基)-4-(2,6-二甲基吗啉代)-2-氟苯胺

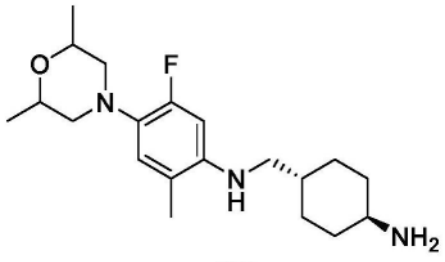
[2463] 

431

[2464] 由((1r,4r)-4-(((4-(2,6-二甲基吗啉代)-2-氟苯基)氨基)甲基)环己基)氨基甲酸叔丁酯(100mg,0.23mmol),DCM(3mL)和TFA(1mL),根据为24的程序制备标题化合物431(20.9mg,27.1%)(白色固体)。^{1}H NMR(400MHz,DMSO-d6)δ6.77-6.68(m,1H),6.63-6.52(m,2H),4.82-4.75(m,1H),3.72-3.60(m,2H),3.37-3.29(m,2H),2.83(t,J=6.4Hz,2H),2.29-2.25(m,1H),2.16-2.06(m,2H),1.79-1.72(m,4H),1.53-1.37(m,1H),1.12(d,J=6.3Hz,6H),1.04-0.84(m,4H)。MS(m/z):336.3[M+H]$^+$。

[2465] 化合物432

[2466] N-(((1r,4r)-4-氨基环己基)甲基)-4-(2,6-二甲基吗啉代)-5-氟-2-甲基苯胺

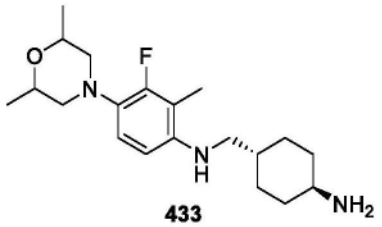
[2467] 

433

[2468] 由((1r,4r)-4-(((4-(2,6-二甲基吗啉代)-5-氟-2-甲基苯基)氨基)甲基)环己基)氨基甲酸叔丁酯(80mg,0.178mmol),TFA(1mL),和DCM(10mL),根据为24的程序制备标题化合物432(41.2mg),总收率为66.1%(粉色固体)。^{1}H NMR(400MHz,DMSO-d6)δ8.40-8.22(m,3H),6.71(d,J=10.0Hz,1H),6.28(d,J=15.2Hz,1H),4.83(s,1H),3.76-3.63(m,2H),2.98(d,J=11.2Hz,2H),2.87(t,J=12.0Hz,3H),2.27(t,J=10.8Hz,2H),2.06-1.93(m,5H),1.89-1.80(m,2H),1.52(s,1H),1.34(qd,J=12.4,3.2Hz,2H),1.09(d,J=6.4Hz,6H),1.03-0.92(m,2H)。质谱(m/z):350.3[M+H]$^+$。

[2469] 化合物433

[2470] N-(((1r,4r)-4-氨基环己基)甲基)-4-(2,6-二甲基吗啉代)-3-氟-2-甲基苯胺

[2471] 

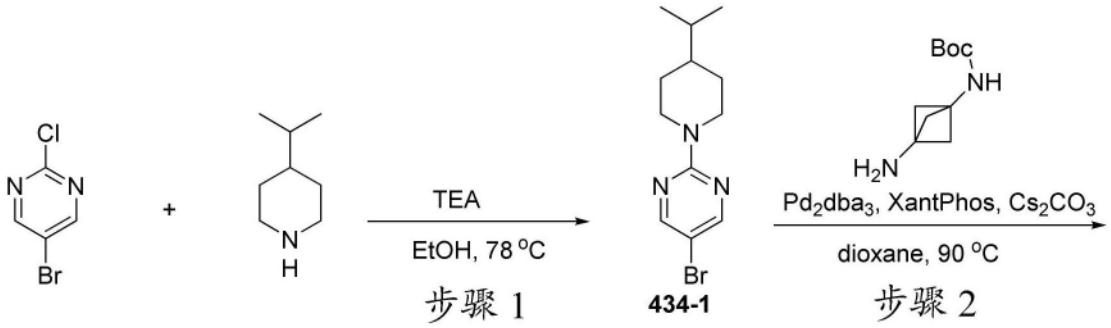
433

[2472] 由((1r,4r)-4-(((4-(2,6-二甲基吗啉代)-3-氟-2-甲基苯基)氨基)甲基)环己基)氨基甲酸叔丁酯(70mg,0.156mmol),TFA(1mL),和DCM(10mL),根据为24的程序制备标题化合物433(23.5mg),总收率为43.1%(绿色固体)。^{1}H NMR(400MHz,DMSO-d6)δ8.32(s,3H),6.70(t,J=9.2Hz,1H),6.23(d,J=8.8Hz,1H),4.84(d,J=5.6Hz,1H),3.77-3.64(m,2H),

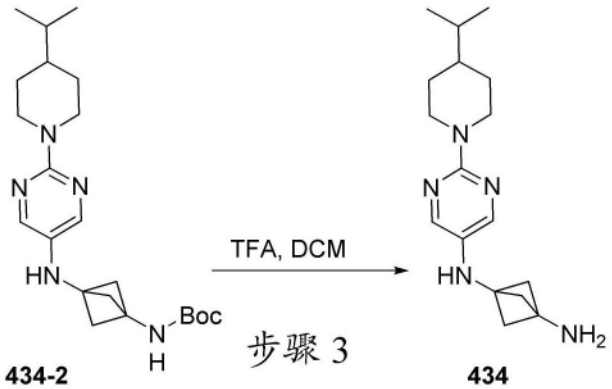
3.03-2.95(m,2H),2.86(t,J＝5.6Hz,3H),2.23(t,J＝10.8Hz,2H),2.05-1.93(m,5H),1.90-1.80(m,2H),1.53(d,J＝9.2Hz,1H),1.35(qd,J＝12.4,3.6Hz,2H),1.09(d,J＝6.4Hz,6H),1.04-0.91(m,2H)。质谱(m/z):350.3[M+H]$^+$。

[2473] 化合物434

[2474] N^1-(2-(4-异丙基哌啶-1-基)嘧啶-5-基)双环[1.1.1]戊烷-1,3-二胺



[2475]



[2476] 步骤1:制备5-溴-2-(4-异丙基哌啶-1-基)嘧啶(434-1)

[2477] 在氮气气氛下在78℃将5-溴-2-氯嘧啶(200mg,1.04mmol),三甲基胺(202mg,2.00mmol)和4-异丙基哌啶(127mg,1.00mmol)/乙醇(2mL)的混合物搅拌过夜。所得的混合物真空浓缩并且通过快速硅胶柱色谱(石油醚/乙酸乙酯5/1)提纯而得到期望的产物5-溴-2-(4-异丙基哌啶-1-基)嘧啶(125mg,44.2%)(白色固体)。MS(m/z):284,286[M+H]$^+$。

[2478] 步骤2:制备(3-((2-(4-异丙基哌啶-1-基)嘧啶-5-基)氨基)双环[1.1.1]戊烷-1-基)氨基甲酸叔丁酯(434-2)

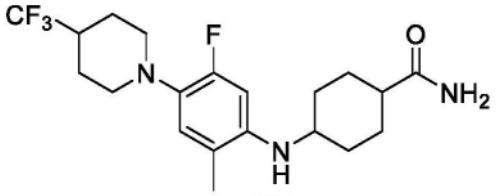
[2479] 向5-溴-2-(4-异丙基哌啶-1-基)嘧啶(110mg,0.41mmol),(3-氨基双环[1.1.1]戊烷-1-基)氨基甲酸叔丁酯(100mg,0.51mmol),Cs_2CO_3(200mg,0.62mmol),Pd2dba3(18mg,0.02mmol)和XantPhos(40mg,0.07mmol)/二氧杂环己烷(3mL)的混合物鼓入氮气3分钟,然后在90℃搅拌过夜。添加另外的(3-氨基双环[1.1.1]戊烷-1-基)氨基甲酸叔丁酯(30mg),Cs_2CO_3(50mg),Pd2dba3(9mg)和XantPhos(20mg)并且搅拌混合物16小时。原料仍然保留一些并且将反应冷却并且用水稀释。所得的混合物用乙酸乙酯萃取两次并且将合并的有机层用盐水洗涤,用硫酸钠干燥并且真空浓缩。残余物的提纯方法为:Prep-TLC(DCM/MeOH 20/1)而得到(3-((2-(4-异丙基哌啶-1-基)嘧啶-5-基)氨基)双环[1.1.1]戊烷-1-基)氨基甲酸叔丁酯(46mg,28%)(黄色固体)。MS(m/z):402[M+H]$^+$。

[2480] 步骤3:制备N^1-(2-(4-异丙基哌啶-1-基)嘧啶-5-基)双环[1.1.1]戊烷-1,3-二胺(434)

[2481] 向(3-((2-(4-异丙基哌啶-1-基)嘧啶-5-基)氨基)双环[1.1.1]戊烷-1-基)氨基甲酸叔丁酯(45mg,0.11mmol)/二氯甲烷(1mL)的溶液中添加三氟乙酸(0.2mL)和在室温搅拌过夜。所得的混合物用乙酸乙酯稀释并且用碳酸氢钠溶液和盐水洗涤。有机层用硫酸钠干燥并且真空浓缩。残余物的提纯方法为:Prep-TLC(二氯甲烷/甲醇15/1)而得到标题化合物N^1-(2-(4-异丙基哌啶-1-基)嘧啶-5-基)双环[1.1.1]戊烷-1,3-二胺434(1.5mg,4.5%)(无色油)。^{1}H NMR(400MHz,氯仿-d)δ8.12(s,2H),4.69(d,J=13.1Hz,2H),2.82-2.68(m,2H),2.59(s,2H),2.42(s,2H),1.76-1.65(m,2H),1.39(dt,J=13.3,6.7Hz,1H),1.29-1.05(m,9H),0.83(d,J=6.7Hz,6H)。MS(m/z):302$[M+H]^+$。

[2482] 化合物435

[2483] 4-((5-氟-2-甲基-4-(4-(三氟甲基)哌啶-1-基)苯基)氨基)环己烷-1-甲酰胺

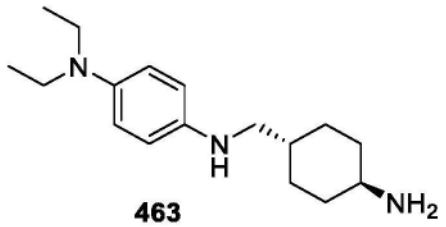
[2484] 

435

[2485] 由5-氟-2-甲基-4-(4-(三氟甲基)哌啶-1-基)苯胺(100mg,0.36mmol),4-氧代环己烷-1-甲酰胺(50mg,0.36mmol),$NaBH(OAc)_3$(76.3mg,0.36mmol),和DCE(10mL),根据为4的程序制备标题化合物435(37.9mg,26.1%)。^{1}H NMR(400MHz,DMSO-d6)δ7.15(s,1H),6.71(d,J=10.0Hz,2H),6.30(d,J=15.0Hz,1H),4.11(d,J=6.4Hz,1H),3.33(d,J=3.0Hz,1H),3.13(d,J=11.6Hz,2H),2.58(dd,J=11.8,10.2Hz,2H),2.39-2.28(m,1H),2.18(tt,J=7.8,4.0Hz,1H),2.00(s,3H),1.82(d,J=12.0Hz,2H),1.74-1.54(m,10H)。质谱(m/z):401.8$[M+H]^+$。

[2486] 化合物436

[2487] N-(((1r,4r)-4-氨基环己基)甲基)-2-氟-6-(4-(三氟甲基)哌啶-1-基)吡啶-3-胺

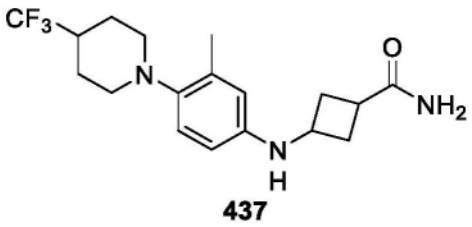
[2488] 

463

[2489] 由((1r,4r)-4-(((4-(二乙基氨基)苯基)氨基)甲基)环己基)氨基甲酸叔丁酯(190mg,0.5mmol),DCM(5mL)和TFA(1mL),根据为24的程序制备标题化合物463(14.1mg,22%)(黄色固体)。^{1}H NMR(400MHz,DMSO-d6)δ=6.59(d,J=8.8,2H),6.46(d,J=8.8,2H),4.90(s,1H),3.08(q,J=7.2,4H),2.75(d,J=4.4,2H),2.47-2.43(m,1H),1.86-1.66(m,4H),1.49-1.34(m,2H),1.00-0.88(m,9H)。质谱(m/z):276.3$[M+H]^+$。

[2490] 化合物437

[2491] 3-((3-甲基-4-(4-(三氟甲基)哌啶-1-基)苯基)氨基)环丁烷-1-甲酰胺

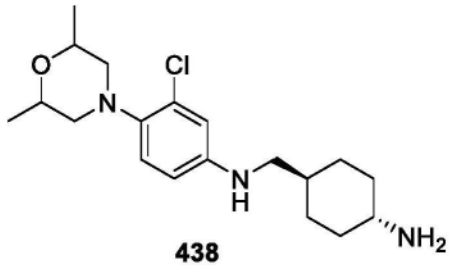
[2492] 

437

[2493] 由3-({3-甲基-4-[4-(三氟甲基)哌啶-1-基]苯基}氨基)环丁烷-1-甲酸(100mg,0.28mmol),氯化铵(30mg,0.56mmol),三乙胺(85mg,0.84mmol),和HATU(160mg,0.42mmol),根据为1的程序制备标题化合物437(27.5mg,27.5%)(黄色固体)。^{1}H NMR(400MHz,DMSO-d6)δ7.17(s,1H),6.77(d,J=8.5Hz,1H),6.71(s,1H),6.27(d,J=2.6Hz,1H),6.21(dd,J=8.5,2.7Hz,1H),5.48(d,J=6.7Hz,1H),3.81(dd,J=13.9,6.8Hz,1H),2.89(m,3H),2.51(t,J=3.3Hz,1H),2.42-2.36(m,3H),2.31-2.28(m,1H),2.10(s,3H),1.95-1.89(m,2H),1.82(d,J=12.3Hz,2H),1.54(dd,J=12.3,3.7Hz,2H)。质谱(m/z):356.3[M+H]$^+$。

[2494] 化合物438

[2495] N-(((1r,4r)-4-氨基环已基)甲基)-3-氯-4-(2,6-二甲基吗啉代)苯胺

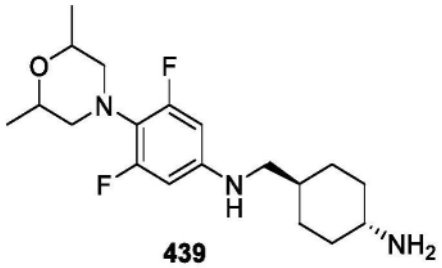
[2496] 

438

[2497] 由3-氯-4-(2,6-二甲基吗啉代)苯胺(70mg,0.29mmol)和((1r,4r)-4-甲酰基环已基)氨基甲酸叔丁酯(99mg,0.44mmol),根据为20的程序制备标题化合物438(41.0mg),收率为40.07%(白色粉末)。^{1}H NMR(400MHz,DMSO-d6)δ8.04-7.84(m,3H),6.92(d,J=8.7Hz,1H),6.60(d,J=2.6Hz,1H),6.48(dd,J=8.7,2.6Hz,1H),5.70(s,1H),3.69(dqd,J=12.6,6.2,2.0Hz,2H),3.00-2.88(m,3H),2.81(d,J=6.5Hz,2H),2.26(dd,J=11.4,9.9Hz,2H),1.98-1.80(m,4H),1.44(s,1H),1.31-1.20(m,2H),1.09(d,J=6.3Hz,6H),1.00(q,J=11.8Hz,2H)。质谱(m/z):352.5[M+H]$^+$。

[2498] 化合物439

[2499] N-(((1r,4r)-4-氨基环已基)甲基)-4-(2,6-二甲基吗啉代)-3,5-二氟苯胺

[2500] 

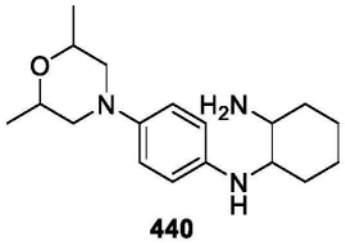
439

[2501] 由4-(2,6-二甲基吗啉代)-3,5-二氟苯胺(100mg,0.41mmol)和((1r,4r)-4-甲酰基环已基)氨基甲酸叔丁酯(175mg,0.83mmol),根据为20的程序制备标题化合物439(46.2mg),收率为31.67%(白色粉末)。^{1}H NMR(400MHz,DMSO-d6)δ7.31(s,2H),6.22-5.98(m,3H),3.61(dtd,J=8.6,6.1,2.3Hz,2H),2.96-2.86(m,1H),2.84-2.72(m,4H),2.68-

2.61(m,2H),2.01-1.77(m,4H),1.42(d,J＝3.5Hz,1H),1.36-1.22(m,2H),1.04(d,J＝6.2Hz,6H),1.01-0.91(m,2H)。质谱(m/z):354.5[M+H]$^+$。

[2502] 化合物440

[2503] N^1-(4-(2,6-二甲基吗啉代)苯基)环己烷-1,2-二胺

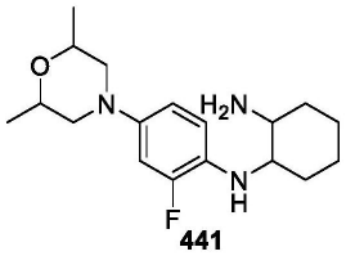
[2504] 

440

[2505] 由4-(2,6-二甲基吗啉代)苯胺(64mg,0.31mmol)和(2-氧代环己基)氨基甲酸叔丁酯(100mg,0.47mmol),根据为20的程序制备标题化合物440(20.9mg),收率为20.9%(白色粉末)。^{1}H NMR(400MHz,DMSO-d6)δ7.92(s,2H),6.82-6.75(m,2H),6.67-6.57(m,2H),4.90(s,1H),3.67(ddt,J＝13.2,6.9,3.4Hz,2H),3.33-3.28(m,2H),3.15(s,1H),2.88(d,J＝9.4Hz,1H),2.12(ddd,J＝11.9,10.3,1.7Hz,2H),2.00(dd,J＝34.1,12.8Hz,2H),1.68(d,J＝23.8Hz,2H),1.41(q,J＝12.3,11.8Hz,1H),1.25(q,J＝11.1,10.7Hz,2H),1.12(d,J＝6.2Hz,6H),1.10-1.00(m,1H)。质谱(m/z):304.5[M+H]$^+$。

[2506] 化合物441

[2507] N^1-(4-(2,6-二甲基吗啉代)-2-氟苯基)环己烷-1,2-二胺

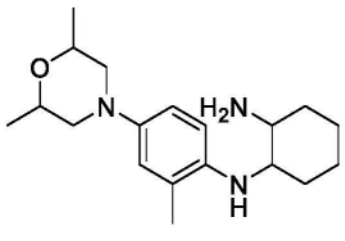
[2508] 

441

[2509] 由4-(2,6-二甲基吗啉代)-2-氟苯胺(71mg,0.31mmol)和(2-氧代环己基)氨基甲酸叔丁酯(100mg,0.47mmol),根据为20的程序制备标题化合物441(10.1mg),收率为10.6%(白色粉末)。^{1}H NMR(400MHz,DMSO-d6)δ7.89(s,2H),6.84-6.71(m,2H),6.63(d,J＝9.2Hz,1H),4.67(d,J＝10.4Hz,1H),3.72-3.59(m,2H),3.39(d,J＝11.4Hz,2H),3.18(s,1H),3.05(s,1H),2.13(t,J＝10.8Hz,2H),2.04(d,J＝12.6Hz,1H),1.90(d,J＝7.0Hz,1H),1.68(d,J＝29.5Hz,2H),1.40(d,J＝12.5Hz,1H),1.28-1.17(m,2H),1.13(d,J＝6.3Hz,6H)。质谱(m/z):322.3[M+H]$^+$。

[2510] 化合物442

[2511] N^1-(4-(2,6-二甲基吗啉代)-2-甲基苯基)环己烷-1,2-二胺

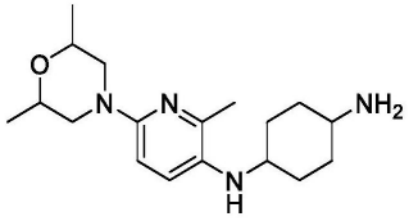
[2512] 

442

[2513] 由4-(2,6-二甲基吗啉代)-2-甲基苯胺(69mg,0.31mmol)和(2-氧代环己基)氨基甲酸叔丁酯(100mg,0.47mmol),根据为20的程序制备标题化合物442(33.3mg),收率为34.5%(白色粉末)。^{1}H NMR(400MHz,DMSO-d6)δ7.88(s,2H),6.79-6.50(m,3H),4.14(s,1H),3.67(s,2H),3.15(d,J=37.6Hz,2H),2.17(s,1H),2.12(s,6H),1.96(d,J=12.6Hz,1H),1.80-1.59(m,2H),1.55-1.32(m,2H),1.23(s,2H),1.12(d,J=6.2Hz,6H)。质谱(m/z):318.4[M+H]$^+$。

[2514] 化合物443

[2515] N^1-(6-(2,6-二甲基吗啉代)-2-甲基吡啶-3-基)环己烷-1,4-二胺

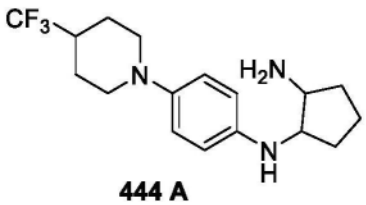
[2516] 

443

[2517] 由6-(2,6-二甲基吗啉代)-2-甲基吡啶-3-胺(50mg,0.22mmol)和(4-氧代环己基)氨基甲酸叔丁酯(72mg,0.34mmol),根据为20的程序制备标题化合物443(17.7mg),收率为24.6%(白色粉末)。^{1}H NMR(400MHz,DMSO-d6)δ8.16(d,J=21.0Hz,3H),6.99(s,1H),6.59(s,1H),3.88(d,J=11.7Hz,2H),3.60(d,J=8.6Hz,2H),3.45(s,1H),3.10(s,1H),2.94(s,1H),2.38-2.12(m,5H),2.05-1.91(m,2H),1.85-1.67(m,3H),1.60(s,1H),1.43(d,J=12.2Hz,1H),1.14(d,J=6.2Hz,6H)。质谱(m/z):319.3[M+H]$^+$。

[2518] 化合物444

[2519] (1R,2R)-N^1-(4-(4-(三氟甲基)哌啶-1-基)苯基)环戊烷-1,2-二胺

[2520] 

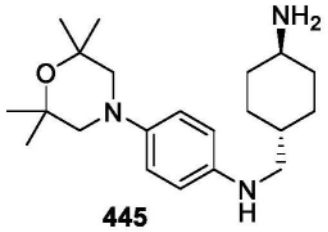
444 A

444 B

[2521] 由4-(4-(三氟甲基)哌啶-1-基)苯胺(50mg,0.20mmol)和叔丁基(2-氧代环戊基)氨基甲酸叔丁酯(61mg,0.30mmol),根据为20的程序制备标题化合物444A(12mg),收率为17.9%(白色粉末)和化合物444B(23mg)制备,收率为36%(白色粉末)。444A:^{1}H NMR(400MHz,DMSO-d6)δ6.14(d,J=8.3Hz,2H),5.91(d,J=8.1Hz,2H),2.98(dq,J=11.1,6.3,5.6Hz,2H),2.69(d,J=12.1Hz,2H),1.85(t,J=12.1Hz,2H),1.52-1.37(m,2H),1.37-1.28(m,1H),1.22-1.12(m,2H),1.05(q,J=8.1Hz,2H),0.99-0.82(m,4H)。质谱(m/z):328.3[M+H]$^+$。444B:^{1}H NMR(400MHz,DMSO-d6)δ6.12(d,J=8.4Hz,2H),5.86(d,J=8.2Hz,2H),2.93(t,J=7.1Hz,1H),2.68(d,J=11.9Hz,2H),2.58(d,J=7.2Hz,1H),1.85(t,J=12.1Hz,2H),1.41(tt,J=13.9,7.1Hz,3H),1.16(d,J=13.0Hz,2H),1.04(q,J=7.4Hz,2H),0.91(dp,J=21.7,8.2Hz,3H),0.69(dd,J=13.7,7.3Hz,1H)。质谱(m/z):328.3[M+H]$^+$。

[2522] 化合物445

[2523] N-(((1r,4r)-4-氨基环己基)甲基)-4-(2,2,6,6-四甲基吗啉代)苯胺

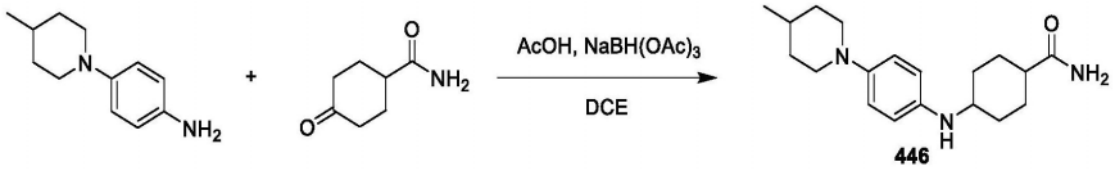
[2524] 

445

[2525] 根据为化合物354的程序制备标题化合物445(31.5mg),总收率为60.9%(深蓝色固体)。^{1}H NMR(400MHz,Pyridine-d5)δ7.04-6.96(m,2H),6.92-6.84(m,2H),5.19(s,3H),3.44-3.35(m,1H),2.99-2.95(m,2H),2.52-2.42(m,2H),1.95-1.88(m,2H),1.85-1.74(m,2H),1.66-1.57(m,1H),1.43-1.15(m,16H),1.07-0.95(m,2H)。质谱(m/z):346.3[M+H]$^+$。

[2526] 化合物446

[2527] 4-((4-(4-甲基哌啶-1-基)苯基)氨基)环己烷-1-甲酰胺

[2528] 

446

[2529] 在室温搅拌4-(4-甲基哌啶-1-基)苯胺(50mg,0.240mmol),4-氧代环己烷-1-甲酰胺(51mg,0.360mmol)和AcOH(0.1mL)/DCE(10mL)的溶液30分钟,然后添加NaBH(OAc)$_3$(130mg,0.614mmol)。在室温搅拌混合物2小时。用DCM(25mL×3)萃取混合物。将合并的有机层用盐水洗涤(15mL×3),用Na_2SO_4干燥,以及浓缩而得到粗产物,其提纯方法:prep HPLC(XSelect-CSH-Prep 5μm OBD,19*150mm柱;ACN/水(0.5%NH_3H_2O)=50%-77%-95%-95%-0%,0min-8min-8.5min-9.5min-11min),而得到期望的产物446A(Rt=6.1min)(白色固体)(24.6mg,31.1%)和446B(Rt=7.1min)(白色固体)(27.1mg,33.3%)。

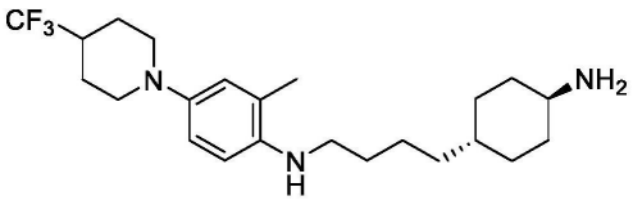
[2530] 446A

[2531] ^{1}H NMR(400MHz,DMSO-d6)δ7.23-7.17(m,1H),6.77(d,J=8.4Hz,1H),6.69-6.63(m,1H),6.38(d,J=2.8Hz,1H),6.32(dd,J=8.4,2.8Hz,1H),4.89(d,J=8.4Hz,1H),3.04(tdt,J=11.2,7.2,3.6Hz,1H),2.83(dt,J=12.0,3.2Hz,2H),2.46(dd,J=11.6,2.4Hz,2H),2.11(s,3H),2.01(ddq,J=27.2,12.0,3.6Hz,3H),1.76(dt,J=14.4,3.6Hz,2H),1.69-1.60(m,2H),1.43(qd,J=13.0,3.6Hz,3H),1.25(qd,J=12.0,3.6Hz,2H),1.13-0.99(m,2H),0.94(d,J=6.4Hz,3H)。446B

[2532] ^{1}H NMR(400MHz,DMSO-d6)δ7.16(s,1H),6.78(d,J=8.4Hz,1H),6.69(s,1H),6.43(d,J=2.8Hz,1H),6.36(dd,J=8.4,2.8Hz,1H),5.00(d,J=7.6Hz,1H),2.83(dt,J=12.0,3.6Hz,2H),2.46(dd,J=11.6,2.4Hz,2H),2.12(s,4H),1.83-1.71(m,2H),1.70-1.60(m,4H),1.59-1.35(m,5H),1.25(qd,J=11.6,3.6Hz,2H),0.94(d,J=6.4Hz,3H)。质谱(m/z):330.3[M+H]$^+$。

[2533] 化合物447

[2534] N-(4-((1r,4s)-4-氨基环己基)丁基)-2-甲基-4-(4-(三氟甲基)哌啶-1-基)苯胺

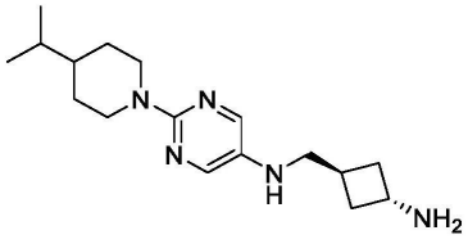
[2535] 

447

[2536] 由4-((1r,4s)-4-氨基环己基)-N-(2-甲基-4-(4-(三氟甲基)哌啶-1-基)苯基)丁酰胺(100mg,0.18mmol)/BH_3-THF(20mL),根据为105的程序制备标题化合物447(17.4mg,23.2%)(白色固体)。^{1}H NMR(400MHz,CD_3OD)δ6.80(s,2H),6.58(d,J=8.7Hz,1H),3.47(d,J=11.8Hz,2H),3.10(dd,J=14.9,7.8Hz,2H),2.86-2.77(m,1H),2.60(t,J=11.2Hz,2H),2.31-2.22(m,1H),2.12(s,3H),1.95(d,J=11.9Hz,4H),1.84(d,J=12.1Hz,2H),1.78-1.68(m,2H),1.61(dt,J=15.0,7.5Hz,2H),1.41(d,J=15.5Hz,2H),1.32-1.19(m,6H),1.07-0.95(m,2H)。质谱(m/z):412.3$[M+H]^+$。

[2537] 化合物448

[2538] N-(((1r,3r)-3-氨基环丁基)甲基)-2-(4-异丙基哌啶-1-基)嘧啶-5-胺

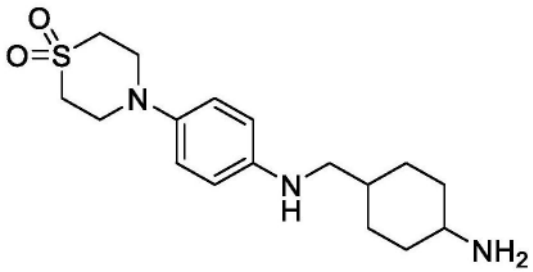
[2539] 

448

[2540] 由((1r,3r)-3-(((2-(4-异丙基哌啶-1-基)嘧啶-5-基)氨基)甲基)环丁基)氨基甲酸叔丁酯(100mg,0.24mmol),1,4-二氧杂环己烷(3mL)和HCl/1,4-二氧杂环己烷(1mL),根据为37的程序制备标题化合物448(28.2mg)(黄色固体)。^{1}H NMR(400MHz,CD_3OD)δ7.89(s,2H),4.47(d,J=13.2Hz,2H),3.83(d,J=7.4Hz,1H),3.12(d,J=7.4Hz,2H),2.70(s,2H),2.25(d,J=5.6Hz,4H),1.70(d,J=11.6Hz,2H),1.41(qd,J=13.2,6.6Hz,1H),1.22-1.13(m,4H),0.88(d,J=6.8Hz,6H)。质谱(m/z):304.3$[M+H]^+$。

[2541] 化合物449

[2542] 4-(4-(((4-氨基环己基)甲基)氨基)苯基)硫代吗啉1,1-二氧化物

[2543] 

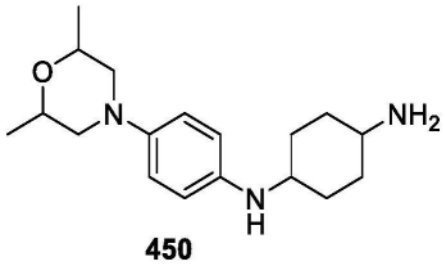
449

[2544] 由(4-(((4-(1,1-dioxido硫代吗啉代苯基)氨基)甲基)环己基)氨基甲酸叔丁酯(200mg,0.46mmol),DCM(5mL)和TFA(1mL),根据为24的程序制备标题化合物449(122mg,66.7%)(黄色固体)。^{1}H NMR(400MHz,CDC13)δ6.83(d,J=8.4,2H),6.55(d,J=8.4,2H),

3.58(s,4H),3.11(s,4H),2.92(d,J＝6.4,2H),2.62(s,1H),1.90-1.83(m,4H),1.51(s,1H),1.38(s,1H),1.20-0.94(m,4H)。质谱(m/z):337.9[M+H]$^+$。

[2545] 化合物450

[2546] N^1-(4-(2,6-二甲基吗啉代)苯基)环己烷-1,4-二胺

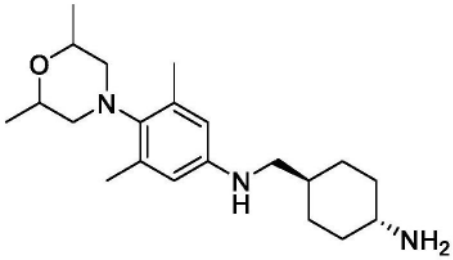
[2547] 

450

[2548] 由(4-((4-(2,6-二甲基吗啉代)苯基)氨基)环己基)氨基甲酸叔丁酯,根据为24的程序制备期望的产物450(黄色固体)(21.5mg,24.4%)。^{1}H NMR(400MHz,DMSO-d6)δ7.93(s,1H),7.07(d,J＝8.5Hz,2H),6.94(t,J＝10.7Hz,2H),3.5-3.2(m,6H),1.6-1.5(m,2H),1.20(d,J＝4.9Hz,6H),0.71-0.64(m,2H)。质谱(m/z):304.2[M+H]$^+$。

[2549] 化合物451

[2550] (((1r,4r)-4-氨基环己基)甲基)-4-(2,6-二甲基吗啉代)-3,5-二甲基苯胺

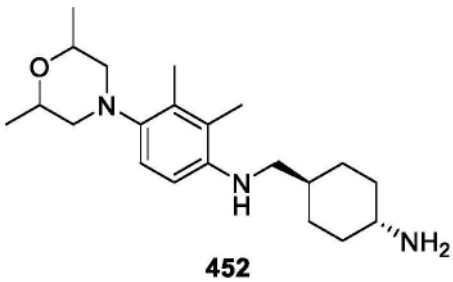
[2551] 

451

[2552] 根据为化合物24的程序制备标题化合物451(14.2mg),总收率为41.0%(白色固体)。^{1}H NMR(400MHz,DMSO-d6)δ6.20(d,J＝2.8Hz,1H),6.08(d,J＝2.8Hz,1H),3.73-3.58(m,2H),2.90-2.72(m,5H),2.65-2.57(m,2H),2.14(s,3H),2.12(s,3H),2.02-1.75(m,4H),1.64-1.42(m,2H),1.36-1.23(m,3H),1.05(d,J＝6.4Hz,6H),1.00-0.87(m,2H)。质谱(m/z):346.3[M+H]$^+$。

[2553] 化合物452

[2554] N-(((1r,4r)-4-氨基环己基)甲基)-4-(2,6-二甲基吗啉代)-2,3-二甲基苯胺

[2555] 

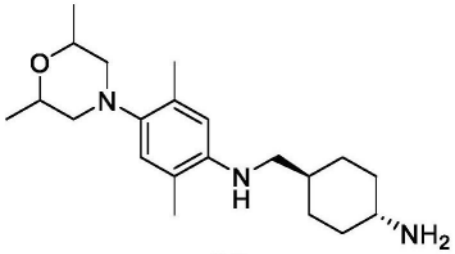
452

[2556] 根据为化合物24的程序制备标题化合物452(22.5mg),总收率为65.2%(白色固体)。^{1}H NMR(400MHz,DMSO-d6)δ6.21(d,J＝2.8Hz,1H),6.09(d,J＝2.8Hz,1H),3.72-3.61(m,2H),2.95-2.74(m,5H),2.63-2.56(m,2H),2.14(s,3H),2.13(s,3H),2.02-1.92(m,2H),

1.88-1.80(m,2H),1.36-1.22(m,3H),1.06(d,J＝6.4Hz,6H),1.02-0.88(m,2H)。质谱(m/z):346.3[M+H]$^+$。

[2557] 化合物453

[2558] N-(((1r,4r)-4-氨基环已基)甲基)-4-(2,6-二甲基吗啉代)-2,5-二甲基苯胺

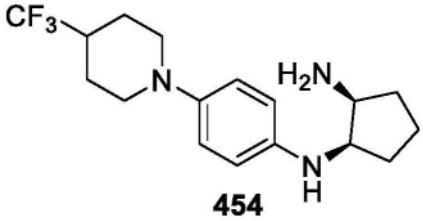
[2559] 

453

[2560] 根据为化合物24的程序制备标题化合物453(18.1mg),总收率为52.7％(白色固体)。^{1}H NMR(400MHz,DMSO-d6)δ6.69(s,1H),6.30(s,1H),3.76-3.62(m,2H),3.01-2.83(m,3H),2.78-2.67(m,2H),2.35-2.21(m,2H),2.17(s,3H),2.02(s,3H),2.00-1.91(m,2H),1.91-1.82(m,2H),1.39-1.17(m,3H),1.08(d,J＝6.4Hz,6H),1.01-0.89(m,2H)。质谱(m/z):346.3[M+H]$^+$。

[2561] 化合物454

[2562] (1R,2S)-N^1-(4-(4-(三氟甲基)哌啶-1-基)苯基)环戊烷-1,2-二胺

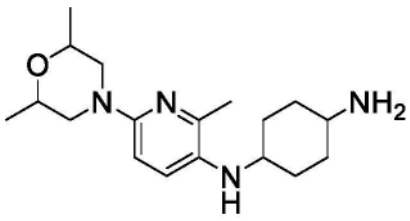
[2563] 

454

[2564] 由4-(4-(三氟甲基)哌啶-1-基)苯胺(50mg,0.20mmol)和(2-氧代环戊基)氨基甲酸叔丁酯(61mg,0.30mmol),根据为24的程序制备标题化合物454(23mg),收率为36％(白色粉末)。^{1}H NMR(400MHz,DMSO-d6)δ6.12(d,J＝8.4Hz,2H),5.86(d,J＝8.2Hz,2H),2.93(t,J＝7.1Hz,1H),2.68(d,J＝11.9Hz,2H),2.58(d,J＝7.2Hz,1H),1.85(t,J＝12.1Hz,2H),1.41(tt,J＝13.9,7.1Hz,3H),1.16(d,J＝13.0Hz,2H),1.04(q,J＝7.4Hz,2H),0.91(dp,J＝21.7,8.2Hz,3H),0.69(dd,J＝13.7,7.3Hz,1H)。质谱(m/z):328.3[M+H]$^+$。

[2565] 化合物455

[2566] (1s,4s)-N^1-(6-(2,6-二甲基吗啉代)-2-甲基吡啶-3-基)环已烷-1,4-二胺

[2567] 

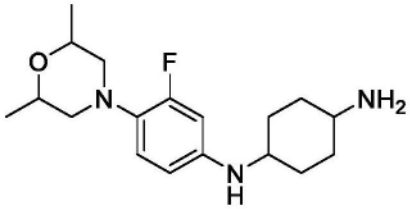
455A
455B

[2568] 由6-(2,6-二甲基吗啉代)-2-甲基吡啶-3-胺(Rt＝7.62min;50mg,0.22mmol)和(4-氧代环已基)氨基甲酸叔丁酯(Rt＝8.07;72mg,0.34mmol),根据为20的程序制备标题化

合物455A(4.6mg),收率为6.5%(白色粉末)和化合物455B(1.4mg)制备,收率为1.7%(白色粉末),其提纯方法为:Prep-HPLC(柱:X Select-CSH-Prep 5μm OBD,19*150mm;ACN/水(0.5%TFA)=0%-20%-95%-95%-10%,0min-10min-10.5min-11.5min-13.0min)。455A:^{1}H NMR(400MHz,DMSO-d6)δ6.89(d,J=8.9Hz,1H),6.50(d,J=8.7Hz,1H),3.88(d,J=8.3Hz,1H),3.85-3.79(m,2H),3.60(ddd,J=10.4,6.2,2.4Hz,2H),2.98(s,1H),2.18(s,2H),2.14(dd,J=12.3,10.4Hz,2H),1.82(dd,J=46.2,11.3Hz,4H),1.25-1.15(m,4H),1.13(d,J=6.2Hz,6H)。质谱(m/z):319.3[M+H]$^+$。455B:^{1}H NMR(400MHz,DMSO-d6)δ6.85(d,J=8.9Hz,1H),6.57(d,J=8.7Hz,1H),3.85(d,J=8.3Hz,1H),3.85-3.75(m,2H),3.61(ddd,J=10.4,6.3,2.2Hz,2H),2.96(s,1H),2.18(s,2H),2.14(dd,J=12.3,10.4Hz,2H),1.82(dd,J=46.2,11.3Hz,4H),1.23-1.11(m,4H),0.94(d,J=6.5Hz,6H)。质谱(m/z):319.3[M+H]$^+$。

[2569] 化合物456

[2570] N^1-(4-(2,6-二甲基吗啉代)-3-氟苯基)环己烷-1,4-二胺

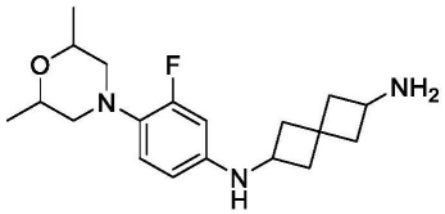
[2571] 

456

[2572] 由4-(2,6-二甲基吗啉代)-3-氟苯胺(50mg,0.22mmol)和(4-氧代环己基)氨基甲酸叔丁酯(71mg,0.33mmol),根据为20的程序制备标题化合物456(24.3mg),收率为33.9%(白色粉末)。^{1}H NMR(400MHz,DMSO-d6)δ8.18(s,2H),6.80(s,1H),6.48-6.27(m,2H),5.43(s,1H),3.69(ddd,J=8.6,6.4,2.1Hz,2H),3.07(s,1H),2.97(d,J=11.1Hz,3H),2.25(t,J=10.7Hz,2H),1.98(d,J=11.4Hz,4H),1.73(s,1H),1.59(s,1H),1.45(q,J=12.0Hz,2H),1.09(d,J=6.2Hz,6H)。质谱(m/z):322.5[M+H]$^+$。

[2573] 化合物457

[2574] N^2-(4-(2,6-二甲基吗啉代)-3-氟苯基)螺[3.3]庚烷-2,6-二胺

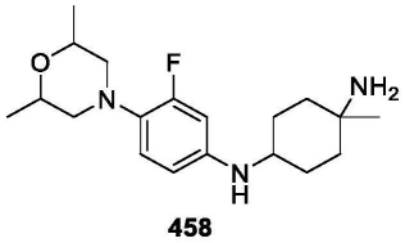
[2575] 

457

[2576] 由4-(2,6-二甲基吗啉代)-3-氟苯胺(50mg,0.22mmol)和(6-氧代螺[3.3]庚烷-2-基)氨基甲酸叔丁酯(75mg,0.34mmol),根据为20的程序制备标题化合物457(22.8mg),收率为30.7%(白色粉末)。^{1}H NMR(400MHz,DMSO-d6)δ8.19(s,2H),6.80(t,J=9.2Hz,1H),6.33-6.17(m,2H),5.83(s,1H),3.67(ddd,J=20.7,11.2,6.1Hz,3H),3.54(d,J=7.0Hz,1H),2.97(d,J=11.1Hz,2H),2.43-2.29(m,3H),2.25(t,J=10.7Hz,2H),2.21-2.10(m,3H),1.86-1.73(m,2H),1.08(d,J=6.2Hz,6H)。质谱(m/z):334.6[M+H]$^+$。

[2577] 化合物458

[2578] N^1-(4-(2,6-二甲基吗啉代)-3-氟苯基)-4-甲基环己烷-1,4-二胺

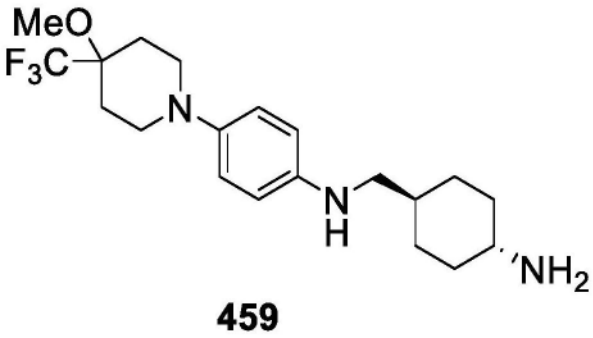
[2579] 

458

[2580] 由4-(2,6-二甲基吗啉代)-3-氟苯胺(50mg,0.22mmol)和(1-甲基-4-氧代环己基)氨基甲酸叔丁酯(61mg,0.27mmol),根据为20的程序制备标题化合物458(51.7mg),收率为69.1%(白色粉末)。^{1}H NMR(400MHz,DMSO-d6)δ8.25(d,J=32.3Hz,2H),6.80(t,J=9.3Hz,1H),6.50-6.25(m,2H),5.39(d,J=50.6Hz,1H),3.69(ddt,J=13.9,7.5,3.8Hz,2H),3.15(d,J=42.1Hz,1H),2.97(d,J=11.0Hz,2H),2.25(t,J=10.7Hz,2H),1.98-1.83(m,2H),1.71(p,J=12.0,11.1Hz,3H),1.63-1.47(m,2H),1.28(d,J=6.8Hz,4H),1.08(d,J=6.2Hz,6H)。质谱(m/z):336.3$[M+H]^+$。

[2581] 化合物459

[2582] N-(((1r,4r)-4-氨基环己基)甲基)-4-(4-甲氧基-4-(三氟甲基)哌啶-1-基)苯胺

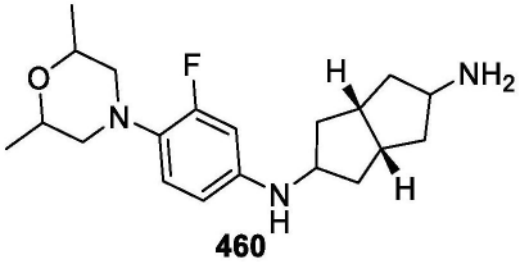
[2583] 

459

[2584] 由4-(4-甲氧基-4-(三氟甲基)哌啶-1-基)苯胺(50mg,0.18mmol)和((1r,4r)-4-甲酰基环己基)氨基甲酸叔丁酯(62mg,0.27mmol),根据为20的程序制备标题化合物459(42.3mg),收率为60.2%(白色粉末)。^{1}H NMR(400MHz,DMSO-d6)δ7.99(s,2H),6.77(d,J=8.4Hz,2H),6.47(d,J=8.4Hz,2H),5.21(s,1H),3.37(d,J=1.5Hz,3H),3.25(d,J=12.0Hz,2H),2.91(s,1H),2.78(s,2H),2.71-2.63(m,2H),1.96(d,J=12.7Hz,4H),1.82(q,J=12.0,10.9Hz,4H),1.44(s,1H),1.27(q,J=13.2,12.8Hz,2H),0.98(q,J=12.5Hz,2H)。质谱(m/z):386.8$[M+H]^+$。

[2585] 化合物460

[2586] (3aR,6aS)-N^2-(4-(2,6-二甲基吗啉代)-3-氟苯基)八氢戊搭烯-2,5-二胺

[2587] 

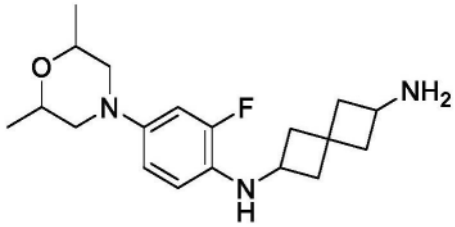
460

[2588] 由4-(2,6-二甲基吗啉代)-3-氟苯胺(100mg,0.45mmol)和(3as,6as)-四氢戊搭

烯-2,5(1H,3H)-二酮(198mg,0.86mmol),根据为20的程序制备标题化合物460(19.7mg),三步总收率为24.5%(白色固体),经^{1}H NMR证实为1:0.1的混合物。^{1}H NMR(400MHz,甲醇-d4)δ7.53-7.38(m,2H),6.85(t,J=9.2Hz,1H),6.41(d,J=15.0Hz,2H),4.11(s,1H),3.81(p,J=6.9,5.5Hz,2H),3.70(dt,J=16.0,6.4Hz,1H),3.49(tt,J=11.2,6.5Hz,1H),3.06(d,J=11.3Hz,2H),2.67(d,J=10.3Hz,1H),2.61-2.50(m,2H),2.43-2.28(m,5H),1.98-1.73(m,2H),1.46(td,J=11.9,8.2Hz,1H),1.17(d,J=6.3Hz,6H)。质谱(m/z):347.3[M+H]$^+$。

[2589] 化合物461

[2590] N^2-(4-(2,6-二甲基吗啉代)-2-氟苯基)螺[3.3]庚烷-2,6-二胺

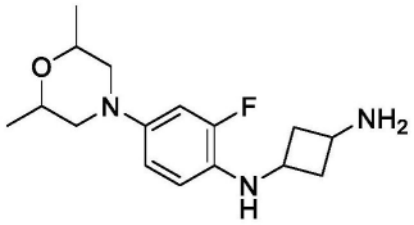
[2591] 

461

[2592] 由(6-((4-(2,6-二甲基吗啉代)-2-氟苯基)氨基)螺[3.3]庚烷-2-基)氨基甲酸叔丁酯(49mg,0.113mmol),TFA(1mL),和DCM(10mL),根据为24的程序制备标题化合物461(7.2mg),总收率为19.1%(紫色固体)。^{1}H NMR(400MHz,DMSO-d6)δ8.38(s,2H),6.72(dd,J=14.8,2.4Hz,1H),6.59-6.45(m,2H),4.98(d,J=7.2Hz,1H),3.73-3.60(m,3H),3.51(q,J=8.0Hz,1H),3.34(dt,J=10.8,2.0Hz,2H),2.46(td,J=6.8,3.2Hz,1H),2.34(dddd,J=22.8,11.6,7.2,3.6Hz,2H),2.26-2.15(m,3H),2.11(dd,J=11.6,10.0Hz,2H),1.91(dt,J=11.2,7.2Hz,2H),1.12(d,J=6.4Hz,6H)。质谱(m/z):334.3[M+H]$^+$。

[2593] 化合物462

[2594] N^1-(4-(2,6-二甲基吗啉代)-2-氟苯基)环丁烷-1,3-二胺

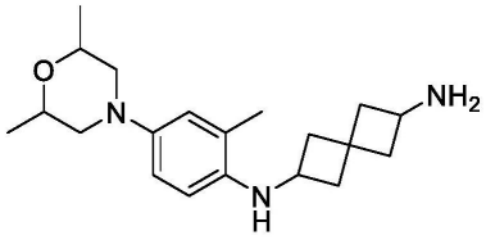
[2595] 

462

[2596] 由(3-((4-(2,6-二甲基吗啉代)-2-氟苯基)氨基)环丁基)氨基甲酸叔丁酯(50mg,0.127mmol),TFA(1mL),和DCM(10mL),根据为24的程序制备标题化合物462(7.8mg),总收率为20.9%(绿色固体)。^{1}H NMR(400MHz,DMSO-d6)δ10.96(s,1H),9.31-9.15(m,2H),8.19-8.01(m,1H),7.15(t,J=9.2Hz,1H),7.01-6.91(m,1H),6.86(dd,J=8.8,2.8Hz,1H),5.23(dd,J=12.0,1.6Hz,1H),3.73-3.60(m,4H),2.46(s,3H),2.31(dd,J=12.0,10.0Hz,2H),1.16(d,J=6.0Hz,6H)。质谱(m/z):294.3[M+H]$^+$。

[2597] 化合物463

[2598] N^2-(4-(2,6-二甲基吗啉代)-2-甲基苯基)螺[3.3]庚烷-2,6-二胺

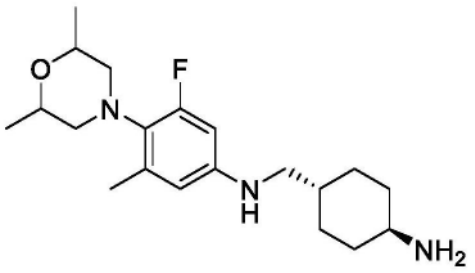
[2599] 

463

[2600] 由(6-((4-(2,6-二甲基吗啉代)-2-甲基苯基)氨基)螺[3.3]庚烷-2-基)氨基甲酸叔丁酯(88mg,0.205mmol),TFA(1mL)和DCM(10mL),根据为24的程序制备标题化合物463(33.8mg),总收率为50.0%(紫色固体)。^{1}H NMR(400MHz,DMSO-d6)δ8.36(s,3H),6.62(d,J=2.8Hz,1H),6.54(dd,J=8.8,2.8Hz,1H),6.26(d,J=8.8Hz,1H),4.41(d,J=6.8Hz,1H),3.62(dqd,J=10.4,6.0,2.4Hz,3H),3.51-3.44(m,1H),3.23(dt,J=10.4,2.0Hz,2H),2.32(dtd,J=16.8,7.2,4.0Hz,2H),2.19(dd,J=11.2,8.4Hz,1H),2.13(dd,J=8.0,4.0Hz,2H),2.09-2.02(m,2H),2.00(s,3H),1.86(ddd,J=11.2,8.0,5.6Hz,2H),1.07(d,J=6.0Hz,6H)。质谱(m/z):330.3[M+H]$^+$。

[2601] 化合物464

[2602] N-(((1r,4r)-4-氨基环己基)甲基)-4-(2,6-二甲基吗啉代)-3-氟-5-甲基苯胺

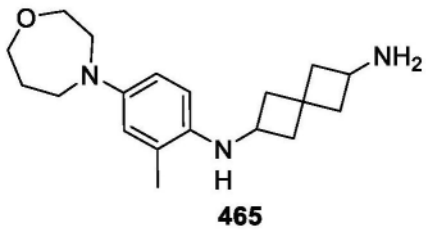
[2603] 

464

[2604] 根据为化合物354的程序制备标题化合物464(15.2mg),总收率为7.1%(淡黄色固体)。^{1}H NMR(400MHz,甲醇-d4)δ6.26-6.21(m,1H),6.15-6.07(m,1H),3.79-3.71(m,2H),3.08-3.00(m,1H),2.93-2.87(m,2H),2.82-2.75(m,2H),2.69-2.64(m,2H),2.21(s,3H),2.10-1.94(m,4H),1.65-1.57(m,1H),1.43-1.33(m,2H),1.18-1.02(m,8H)。质谱(m/z):350.2[M+H]$^+$。

[2605] 化合物465

[2606] N^2-(2-甲基-4-(1,4-氧杂氮杂环庚烷-4-基)苯基)螺[3.3]庚烷-2,6-二胺

[2607] 

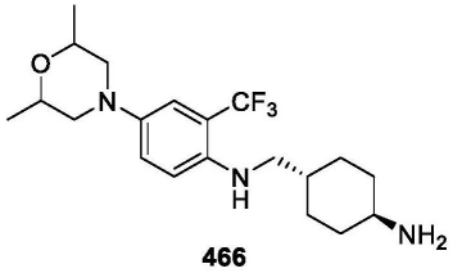
465

[2608] 由(6-((2-甲基-4-(1,4-氧杂氮杂环庚烷-4-基)苯基)氨基)螺[3.3]庚烷-2-基)氨基甲酸叔丁酯(180mg,0.4321mmol),1,4-二氧杂环己烷(10mL)和HCl/1,4-二氧杂环己烷(10mL),根据为37的程序制备期望的产物465(45mg,31.4%)(油)。^{1}H NMR(400MHz,DMSO-d6)δ6.49(s,1H),6.42(d,J=8.4Hz,1H),6.28(d,J=8.6Hz,1H),4.14(brs,1H),3.72-3.65

(m,2H),3.59(s,1H),3.54(t,J＝5.5Hz,2H),3.38-3.24(m,2H),3.19-3.13(m,1H),2.43-2.37(m,1H),2.33-2.23(m,2H),2.14-2.09(m,1H),2.03(s,3H),1.83(m,5H),1.69-1.59(m,2H)。质谱(m/z):316.23[M+H]$^+$。

[2609] 化合物466

[2610] N-(((1r,4r)-4-氨基环已基)甲基)-4-(2,6-二甲基吗啉代)-2-(三氟甲基)苯胺

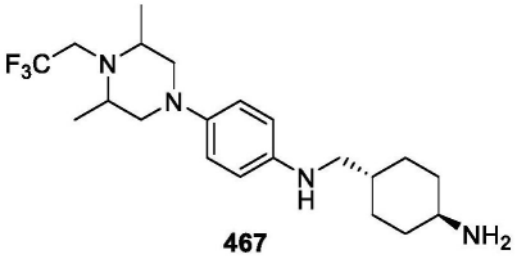
[2611] 

466

[2612] 由((1r,4r)-4-(((4-(2,6-二甲基吗啉代)-2-(三氟甲基)苯基)氨基)甲基)环已基)氨基甲酸叔丁酯(120mg,0.2461mmol),DCM(10mL)和TFA(1mL),根据为24的程序制备标题化合物466(16.2mg,16.7%)(黄色固体)。^{1}H NMR(400MHz,DMSO-d6)δ7.09(d,J＝9.1Hz,1H),6.95(d,J＝2.5Hz,1H),6.75(d,J＝9.0Hz,1H),3.73-3.62(m,3H),3.36(brs,7H),2.96(d,J＝6.2Hz,2H),2.85(s,1H),2.14(s,1H),1.89(s,2H),1.78(d,J＝11.0Hz,2H),1.13(d,J＝6.2Hz,6H)。质谱(m/z):386.23[M+H]$^+$。

[2613] 化合物467

[2614] N-(((1r,4r)-4-氨基环已基)甲基)-4-(3,5-二甲基-4-(2,2,2-三氟乙基)哌嗪-1-基)苯胺

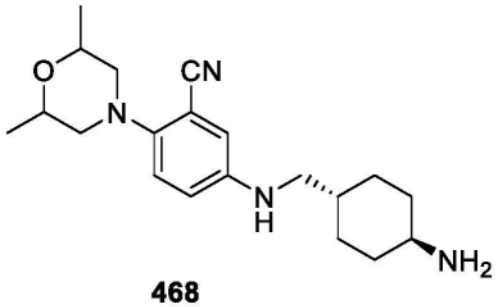
[2615] 

467

[2616] 由((1r,4r)-4-(((4-(3,5-二甲基-4-(2,2,2-三氟乙基)哌嗪-1-基)苯基)氨基)甲基)环已基)氨基甲酸叔丁酯(0.06g,0.3mmol),DCM(5mL)和TFA(1mL),根据为24的程序制备标题化合物467(黄色固体)(10mg,20%)。^{1}H NMR(400MHz,CD_3OD)δ7.28(d,J＝9.0Hz,2H),6.96(d,J＝9.0Hz,2H),3.54-3.52(m,4H),3.26(s,2H),3.16-2.91(m,5H),2.04-2.02(m,4H),1.69(s,1H),1.40-1.38(m,2H),1.32-1.04(m,8H)。质谱(m/z):398.8[M+H]+。

[2617] 化合物468

[2618] 5-((((1r,4r)-4-氨基环已基)甲基)氨基)-2-(2,6-二甲基吗啉代)-苯腈

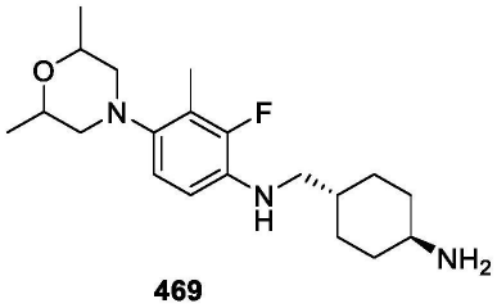
[2619] 

468

[2620] 由((1r,4r)-4-(((3-cyano-4-(2,6-二甲基吗啉代)苯基)氨基)-甲基)环己基)氨基甲酸叔丁酯(200mg,0.45mmol),DCM(10mL)和TFA(1mL),根据为24的程序制备标题化合物468(84mg)(白色固体)。^{1}H NMR(400MHz,CD_3OD)δ6.99(d,J=8.8Hz,1H),6.84(dd,J=8.8,2.8Hz,1H),6.79(d,J=2.8Hz,1H),3.89-3.77(m,2H),3.11(d,J=10.8Hz,2H),3.05(td,J=8.0,4.0Hz,1H),2.94(d,J=6.6Hz,2H),2.46-2.37(m,2H),2.02(dd,J=31.0,11.8Hz,4H),1.65-1.53(m,1H),1.40(m,2H),1.18(d,J=6.2Hz,6H),1.10(dd,J=19.2,8.8Hz,2H)。质谱(m/z):343.3$[M+H]^+$。

[2621] 化合物469

[2622] N-(((1r,4r)-4-氨基环己基)甲基)-4-(2,6-二甲基吗啉代)-2-氟-3-甲基苯胺

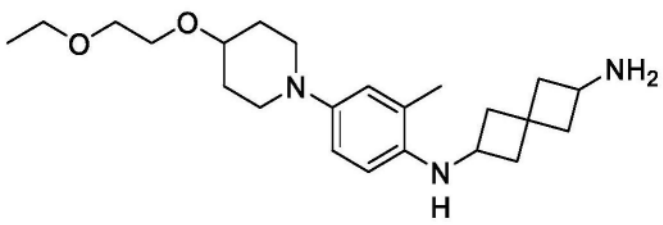
[2623] 

469

[2624] 由((1r,4r)-4-(((4-(2,6-二甲基吗啉代)-2-氟-3-甲基苯基)-氨基)甲基)环己基)氨基甲酸叔丁酯(200mg,0.44mmol),DCM(10mL),和TFA(1mL),根据为24的程序制备标题化合物469(141mg)(白色固体)。^{1}H NMR(400MHz,CD_3OD)δ6.70(dd,J=8.6,1.2Hz,1H),6.52(t,J=9.2Hz,1H),3.81(brs,2H),3.05(ddd,J=15.8,7.8,3.8Hz,1H),3.00(t,J=6.6Hz,2H),2.81(d,J=10.8Hz,2H),2.39-2.26(m,2H),2.17(d,J=2.8Hz,3H),2.01(dd,J=31.0,11.6Hz,4H),1.67-1.53(m,1H),1.37(qd,J=12.6,3.0Hz,2H),1.16(d,J=6.2Hz,6H),1.14-1.03(m,2H)。质谱(m/z):350.3$[M+H]^+$。

[2625] 化合物470

[2626] N^2-(4-(4-(2-乙氧基乙氧基)哌啶-1-基)-2-甲基苯基)螺[3.3]庚烷-2,6-二胺

[2627] 

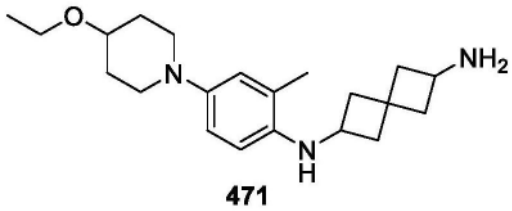
470

[2628] 由(6-((4-(4-(2-乙氧基乙氧基)哌啶-1-基)-2-甲基苯基)氨基)螺[3.3]庚烷-2-

基)氨基甲酸叔丁酯(150mg,0.24mmol),1,4-二氧杂环己烷(3mL)和HCl/1,4-二氧杂环己烷(1mL),根据为24的程序制备标题化合物470(40mg)(黄色固体)(40mg,33.5%)。^{1}H NMR(400MHz,DMSO-d6)δ6.66(d,J=2.5Hz,1H),6.59(dd,J=8.5,2.6Hz,1H),6.27(d,J=8.6Hz,1H),4.36(d,J=6.0Hz,1H),3.66-3.59(m,1H),3.55-3.51(m,2H),3.47(dd,J=4.4,2.3Hz,2H),3.44-3.41(m,2H),3.20(s,3H),2.65-2.57(m,2H),2.45-2.38(m,1H),2.30(dt,J=11.5,4.5Hz,2H),2.15-2.09(m,1H),2.02(s,3H),1.93-1.81(m,4H),1.68(dd,J=14.3,6.0Hz,2H),1.55-1.47(m,2H),1.10(t,J=7.0Hz,3H)。质谱(m/z):388.3[M+H]$^+$。

[2629] 化合物471

[2630] N^2-(4-(4-乙氧基哌啶-1-基)-2-甲基苯基)螺[3.3]庚烷-2,6-二胺

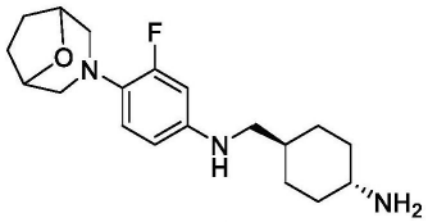
[2631] 

471

[2632] 由(6-((4-(4-乙氧基哌啶-1-基)-2-甲基苯基)氨基)螺[3.3]庚烷-2-基)氨基甲酸叔丁酯(319mg,0.72mmol),HCl/二氧杂环己烷(5mL)和DCM(5mL),根据为37的程序制备标题化合物471(47.7mg,19%)(白色固体)。^{1}H NMR(400MHz,CD_3OD)δ6.83-6.73(m,2H),6.47(d,J=8.5Hz,1H),3.81-3.73(m,1H),3.56(q,J=7.0Hz,2H),3.49-3.40(m,1H),3.29-3.22(m,2H),2.78-2.69(m,2H),2.57-2.50(m,1H),2.48-2.41(m,1H),2.40-2.32(m,1H),2.28-2.21(m,1H),2.11(s,3H),2.06-1.96(m,2H),1.94-1.76(m,4H),1.74-1.62(m,2H),1.19(t,J=7.0Hz,3H)。质谱(m/z):344.3[M+H]$^+$。

[2633] 化合物472

[2634] N-(((1r,4r)-4-氨基环己基)甲基)-4-(8-氧杂-3-氮杂双环[3.2.1]辛烷-3-基)-3-氟苯胺

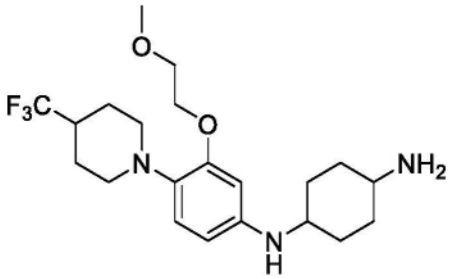
[2635] 

472

[2636] 根据为化合物24的程序制备标题化合物472(19.5mg),总收率为58.4%(灰色固体)。^{1}H NMR(400MHz,DMSO-d6)δ6.75(m,1H),6.45-6.20(m,2H),4.32-4.26(m,2H),2.91(m,1H),2.85-2.71(m,6H),2.05-1.93(m,4H),1.89-1.70(m,4H),1.44-1.24(m,3H),1.05-0.92(m,2H)。质谱(m/z):334.2[M+H]$^+$。

[2637] 化合物473

[2638] N^1-(3-(2-甲氧基乙氧基)-4-(4-(三氟甲基)哌啶-1-基)苯基)环己烷-1,4-二胺

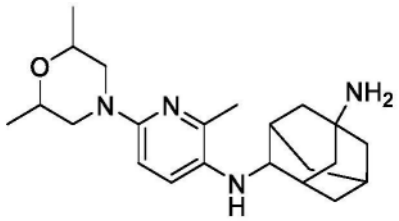
[2639] 

473

[2640] 根据为化合物24的程序制备标题化合物473(18.1mg),总收率为43.5％(白色固体)。^{1}H NMR(400MHz,DMSO-d6)δ6.66(s,1H),6.35-6.05(m,2H),4.10-3.95(m,2H),3.72-3.57(m,2H),3.28(s,3H),3.30-3.22(m,2H),3.07(m,1H),2.95(m,1H),2.47-2.38(m,2H),2.33(m,1H),2.06-1.93(m,2H),1.89-1.65(m,5H),1.62-1.36(m,4H),1.14(m,1H)。质谱(m/z):416.3[M+H]$^+$。

[2641] 化合物474

[2642] N^4-(6-(2,6-二甲基吗啉代)-2-甲基吡啶-3-基)金刚烷-1,4-二胺

[2643] 

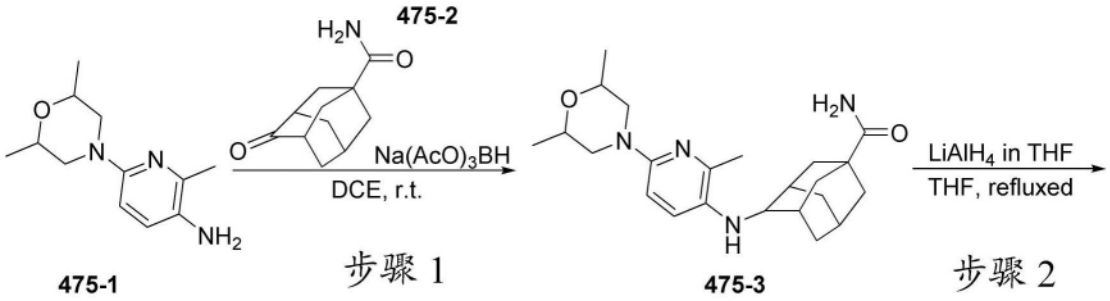
474A

474B

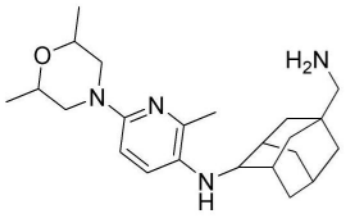
[2644] 根据为化合物24的程序制备标题化合物474A和474B。残余物的提纯方法为:制备HPLC(XSelect-CSH-Prep 5μm OBD,19*150mm柱;ACN/水(0.5％TFA)＝0％-0％-30％-95％-95％-0％,0min-2min-9min-9.5min-10.5min-12.0min)而得到化合物474A(Rt＝7.35min)收率:22.6％(白色固体)和474B(Rt＝7.86min)收率:14.0.％(白色固体)。474A:^{1}H NMR(400MHz,DMSO-d6)δ6.84(d,J＝8.9Hz,1H),6.48(d,J＝8.8Hz,1H),3.83-3.78(m,3H),3.61-3.54(m,2H),3.41(br,3H),3.31-3.28(m,1H),2.24(s,3H),2.12(dd,J＝12.4,10.4Hz,2H),1.97-1.85(m,5H),1.69-1.62(m,2H),1.61-1.53(m,4H),1.31-1.25(m,2H),1.10(d,J＝6.3Hz,6H)。质谱(m/z):374.2[M+H]$^+$。474B:^{1}H NMR(400MHz,DMSO-d6)δ7.51(br,3H),6.90(d,J＝8.8Hz,1H),6.52(d,J＝8.8Hz,1H),3.91-3.81(m,3H),3.65-3.57(m,2H),3.30(d,J＝3.1Hz,1H),2.31(s,3H),2.21-2.12(m,4H),2.11-2.04(m,3H),1.80-1.63(m,6H),1.54-1.46(m,2H),1.14(d,J＝6.2Hz,6H)。质谱(m/z):374.2[M+H]$^+$。

[2645] 化合物475

[2646] N-(5-(氨基甲基)金刚烷-2-基)-6-(2,6-二甲基吗啉代)-2-甲基吡啶-3-胺



[2647]



475A
475B

[2648] 步骤1:制备4-((6-(2,6-二甲基吗啉代)-2-甲基吡啶-3-基)氨基)金刚烷-1-甲酰胺(475-3)

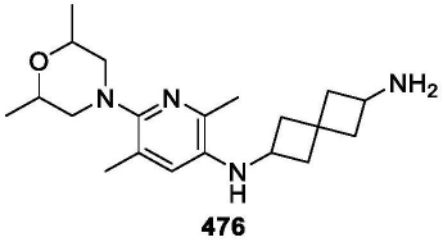
[2649] 由6-(2,6-二甲基吗啉代)-2-甲基吡啶-3-胺(150mg,0.68mmol),4-氧代金刚烷-1-甲酰胺(131mg,0.68mmol)和$Na(AcO)_3BH$(288mg,1.36mmol)inDCE(5.0mL),根据为403-3的程序制备标题化合物475-3(16.0mg),总收率为68.7%(黄色固体)。质谱(m/z):399.2$[M+H]^+$。

[2650] 步骤2:制备N-(5-(氨基甲基)金刚烷-2-基)-6-(2,6-二甲基吗啉代)-2-甲基吡啶-3-胺(475)

[2651] 在0℃向4-((6-(2,6-二甲基吗啉代)-2-甲基吡啶-3-基)氨基)金刚烷-1-甲酰胺(186mg,0.47mol)/THF(10mL)的溶液添加0.39mL的$LiAlH_4$(35.7mg,0.6mol)/THF的溶液,并使混合物回流2小时。在冷却到0℃后,添加水(35.7uL),10%NaOH(71.4uL)和水(107.1uL),在室温搅拌混合物3分钟。将固体过滤并且用THF(10mL*2)洗涤灰色滤饼;然后将合并的滤液用Na_2SO_4干燥并浓缩。残余物的提纯方法为:制备HPLC(XSelect-CSH-Prep 5μm OBD,19*150mm柱;ACN/水(0.5%TFA)=0%-0%-40%-95%-95%-0%,0min-2min-9min-9.5min-10.5min-12min)而得到化合物475A(Rt=7.89min),收率为14.5%(白色固体)和475B(Rt=8.56min),收率为6.3%(白色固体)。475A:^1H NMR(400MHz,DMSO-d6)δ7.84(s,3H),6.87(d,J=8.6Hz,1H),6.54(d,J=8.8Hz,1H),3.98-3.79(m,3H),3.67-3.55(m,2H),3.35-3.30(m,2H),2.30(s,3H),2.22-2.13(m,2H),2.04-1.90(m,5H),1.64-1.58(m,2H),1.55-1.50(m,2H),1.40-1.33(m,2H),1.14(d,J=6.2Hz,6H)。质谱(m/z):385.2$[M+H]^+$。475B:^1H NMR(400MHz,DMSO-d6)δ7.43(s,3H),6.91(d,J=8.8Hz,1H),6.52(d,J=8.7Hz,1H),3.88-3.82(m,2H),3.81-3.76(m,1H),3.66-3.57(m,2H),3.40-3.35(m,2H),2.29(s,3H),2.20-2.13(m,2H),2.02-1.95(m,3H),1.81-1.73(m,4H),1.71-1.66(m,2H),1.51-1.47(m,2H),1.29-1.22(m,2H),1.14(d,J=6.2Hz,6H)。质谱(m/z):385.2$[M+H]^+$。

[2652] 化合物476

[2653] N^2-(6-(2,6-二甲基吗啉代)-2,5-二甲基吡啶-3-基)螺[3.3]庚烷-2,6-二胺

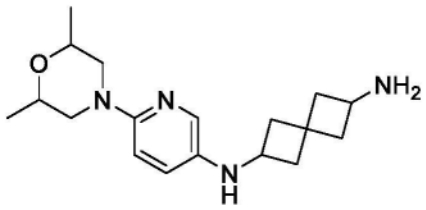
[2654] 

476

[2655] 根据为化合物24的程序制备标题化合物476(18.0mg),总收率为60.9%(深蓝色固体)。^{1}H NMR(400MHz,Deuterium Oxide)δ6.87(s,1H),3.83-3.73(m,2H),3.69-3.59(m,2H),2.98(d,J=12.2Hz,2H),2.51-2.39(m,4H),2.37-2.30(m,1H),2.26-2.18(m,1H),2.14-2.03(m,8H),1.88-1.79(m,2H),1.06(d,J=6.3Hz,6H)。质谱(m/z):345.2[M+H]$^+$。

[2656] 化合物477

[2657] N^2-(6-(2,6-二甲基吗啉代)吡啶-3-基)螺[3.3]庚烷-2,6-二胺

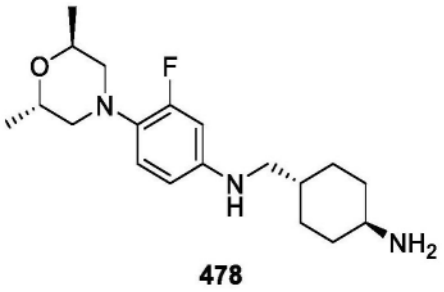
[2658] 

477

[2659] 由(6-((6-(2,6-二甲基吗啉代)吡啶-3-基)氨基)螺[3.3]庚烷-2-基)氨基甲酸叔丁酯(125mg,0.300mmol),TFA(1mL),和DCM(10mL),根据为24的程序制备标题化合物477(55.2mg),总收率为53.1%(绿色固体)。^{1}H NMR(400MHz,DMSO-d6)δ8.43(s,3H),7.49(d,J=2.8Hz,1H),6.92(dd,J=8.8,2.8Hz,1H),6.71(d,J=9.2Hz,1H),3.89-3.80(m,2H),3.70-3.57(m,3H),3.51(d,J=8.4Hz,2H),2.47(td,J=6.8,3.6Hz,1H),2.35(tdt,J=11.6,6.8,4.0Hz,2H),2.27-2.15(m,5H),1.82(dt,J=11.2,8.0Hz,2H),1.13(d,J=6.0Hz,6H)。质谱(m/z):317.3[M+H]$^+$。

[2660] 化合物478

[2661] N-(((1r,4S)-4-氨基环已基)甲基)-4-((2S,6S)-2,6-二甲基吗啉代)-3-氟苯胺

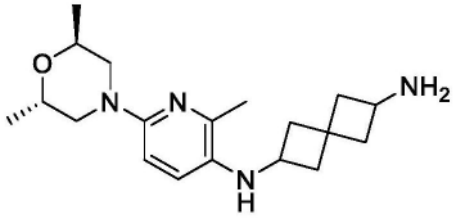
[2662] 

478

[2663] 由((1S,4r)-4-(((4-((2S,6S)-2,6-二甲基吗啉代)-3-氟苯基)氨基)甲基)环已基)氨基甲酸叔丁酯(138mg,0.317mmol),TFA(1mL),和DCM(10mL),根据为24的程序制备标题化合物478(41.9mg),总收率为39.6%(白色固体)。^{1}H NMR(400MHz,DMSO-d6)δ8.31(s,3H),6.77(dd,J=10.0,8.8Hz,1H),6.39-6.26(m,2H),5.68(t,J=6.0Hz,1H),3.99(pd,J=6.4,3.2Hz,2H),2.93-2.75(m,5H),2.58-2.52(m,2H),2.05-1.94(m,2H),1.90-1.78(m,2H),1.51-1.27(m,3H),1.20(d,J=6.4Hz,6H),0.98(tdd,J=15.2,11.2,4.8Hz,2H)。质谱(m/z):336.3[M+H]$^+$。

[2664] 化合物479

[2665] N^2-(6-((2S,6S)-2,6-二甲基吗啉代)-2-甲基吡啶-3-基)螺[3.3]庚烷-2,6-二胺

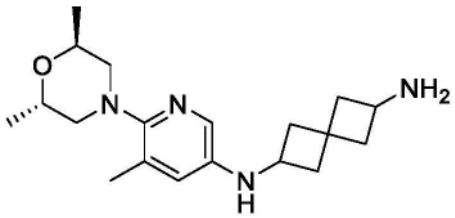
[2666] 

479

[2667] 由(6-((6-((2S,6S)-2,6-二甲基吗啉代)-2-甲基吡啶-3-基)氨基)螺[3.3]庚烷-2-基)氨基甲酸叔丁酯(109mg,0.253mmol),TFA(1mL),和DCM(10mL),根据为24的程序制备标题化合物479(51.5mg),总收率为61.6%(黄色固体)。^{1}H NMR(400MHz,DMSO-d6)δ8.41(s,3H),6.76(s,1H),6.50(d,J=8.4Hz,1H),4.60(s,1H),3.99(tt,J=10.0,4.8Hz,2H),3.71-3.59(m,1H),3.53(s,1H),3.30(dd,J=12.4,3.2Hz,2H),2.92(dd,J=12.0,6.0Hz,2H),2.47(t,J=5.6Hz,1H),2.36(dddd,J=20.0,11.6,7.2,4.0Hz,2H),2.26-2.15(m,6H),1.92(p,J=6.4Hz,2H),1.17(d,J=6.4Hz,6H)。质谱(m/z):331.3[M+H]$^+$。

[2668] 化合物480

[2669] N^2-(6-((2S,6S)-2,6-二甲基吗啉代)-5-甲基吡啶-3-基)螺[3.3]庚烷-2,6-二胺

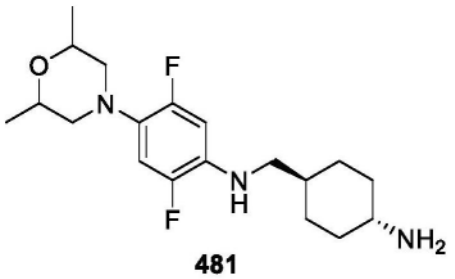
[2670] 

480

[2671] 由(6-((6-((2S,6S)-2,6-二甲基吗啉代)-5-甲基吡啶-3-基)氨基)螺[3.3]庚烷-2-基)氨基甲酸叔丁酯(111mg,0.258mmol),TFA(1mL),和DCM(10mL),根据为24的程序制备标题化合物480(47.4mg),总收率为55.6%(黄色固体)。^{1}H NMR(400MHz,DMSO-d6)δ8.35(s,3H),7.42(d,J=2.8Hz,1H),6.75(d,J=2.8Hz,1H),5.71(s,1H),3.73-3.64(m,3H),3.00-2.89(m,2H),2.51-2.46(m,1H),2.37(qd,J=11.6,6.4Hz,4H),2.24-2.16(m,3H),2.15(s,3H),1.82(dt,J=11.2,8.4Hz,2H),1.08(d,J=6.0Hz,6H)。质谱(m/z):331.3[M+H]$^+$。

[2672] 化合物481

[2673] N-(((1r,4r)-4-氨基环己基)甲基)-4-(2,6-二甲基吗啉代)-2,5-二氟苯胺

[2674] 

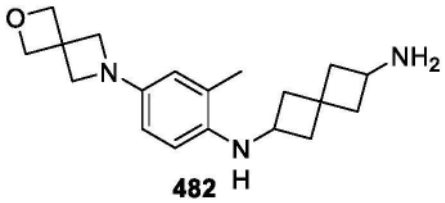
481

[2675] 根据为24的程序制备标题化合物481(4mg)(白色固体)。^{1}H NMR(400MHz,DMSO-d6)δ6.79(dd,J=13.3,8.0Hz,1H),6.51(dd,J=14.2,8.0Hz,1H),5.35-5.24(m,1H),3.69

(ddt,J＝12.7,6.5,3.2Hz,2H),3.05-2.95(m,2H),2.84(t,J＝6.4Hz,2H),2.25(t,J＝10.8Hz,2H),1.99(p,J＝7.0,6.5Hz,1H),1.76(dd,J＝22.6,10.2Hz,4H),1.45(d,J＝12.5Hz,1H),1.31-1.18(m,4H),1.09(d,J＝6.2Hz,6H)。质谱(m/z):354.2[M+H]$^+$。

[2676] 化合物482

[2677] N^2-(2-甲基-4-(2-氧杂-6-氮杂螺[3.3]庚烷-6-基)苯基)螺[3.3]庚烷-2,6-二胺

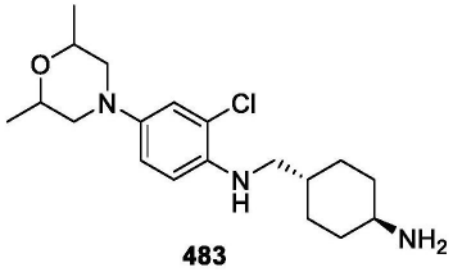
[2678] 

482

[2679] 由(6-((2-甲基-4-(2-氧杂-6-氮杂螺[3.3]庚烷-6-基)苯基)氨基)螺[3.3]庚烷-2-基)氨基甲酸叔丁酯(160mg,0.39mmol),DCM(10mL)和TFA(1mL),根据为24的程序制备标题化合物482(24.1mg,16.8%)(油状物)。^{1}H NMR(400MHz,CD_3OD)δ6.46(m,1H),6.33(m,2H),4.79(s,4H),3.88(brs,4H),3.74(brs,1H),3.42(t,J＝7.6Hz,1H),2.57-2.50(m,1H),2.51-2.44(m,1H),2.38(m,1H),2.30-2.22(m,1H),2.10(s,3H),1.92(m,4H)。质谱(m/z):314.22[M+H]$^+$。

[2680] 化合物483

[2681] N-(((1r,4r)-4-氨基环己基)甲基)-2-氯-4-(2,6-二甲基吗啉代)苯胺

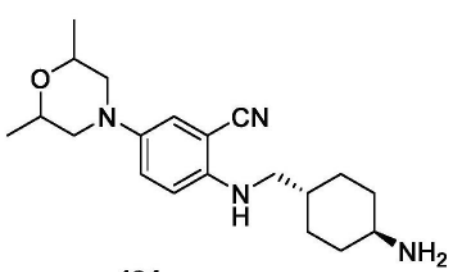
[2682] 

483

[2683] 由((1r,4r)-4-(((2-氯-4-(2,6-二甲基吗啉代)苯基)氨基)甲基)环己基)氨基甲酸叔丁酯(90mg,0.2mmol),DCM(20mL)和TFA(4mL),根据为24的程序制备标题化合物483(29.8mg,收率:75.9%)(黑色油)。^{1}H NMR(400MHz,CD_3OD)δ7.18(dd,J＝9.2,2.9Hz,1H),6.96(d,J＝2.8Hz,1H),6.73(d,J＝9.2Hz,1H),3.77(ddd,J＝10.2,6.3,2.2Hz,2H),3.30-3.24(m,2H),3.04(d,J＝6.8Hz,2H),2.64(s,1H),2.28-2.19(m,2H),1.96-1.83(m,4H),1.64-1.50(m,1H),1.24-0.99(m,10H)。质谱(m/z):351.8[M+H]$^+$。

[2684] 化合物484

[2685] 2-((((1r,4r)-4-氨基环己基)甲基)氨基)-5-(2,6-二甲基吗啉代)苯腈

[2686] 

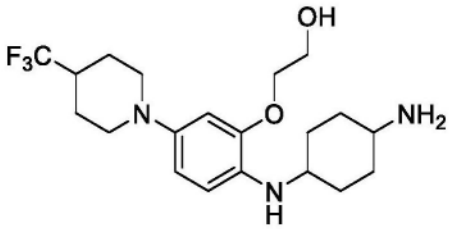
484

[2687] 由((1r,4r)-4-(((2-cyano-4-(2,6-二甲基吗啉代)苯基)氨基)甲基)环己基)氨

基甲酸叔丁酯(100mg,0.21mmol),DCM(20mL)和TFA(4mL),根据为24的程序制备标题化合物484(29mg,收率:37.2%)(蓝色固体)。^{1}H NMR(400MHz,CD_3OD)δ6.92(d,J=2.7Hz,1H),6.84(dd,J=8.9,2.7Hz,1H),6.67(d,J=8.9Hz,1H),3.77(ddd,J=10.2,6.3,2.2Hz,2H),3.27(d,J=10.6Hz,2H),3.00(d,J=6.8Hz,2H),2.67(tt,J=11.2,3.8Hz,1H),2.29-2.19(m,2H),1.99-1.83(m,4H),1.56(ddd,J=11.1,7.7,4.0Hz,1H),1.16(dd,J=32.3,17.3Hz,10H)。质谱(m/z):342.9[M+H]$^+$。

[2688] 化合物485

[2689] 2-(2-((4-氨基环己基)氨基)-5-(4-(三氟甲基)哌啶-1-基)苯氧基)乙-1-醇

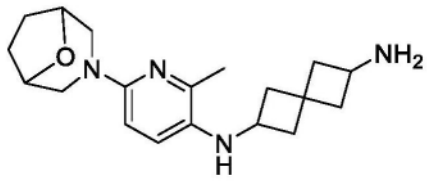
[2690] 

485

[2691] 由(4-((2-(2-羟基乙氧基)-4-(4-(三氟甲基)哌啶-1-基)苯基)氨基)环己基)氨基甲酸叔丁酯(100mg,0.20mmol),1,4-二氧杂环己烷(3mL)和HCl/1,4-二氧杂环己烷(1mL),根据为37的程序制备期望的产物(黄色固体)(4.7mg,5.8%)。^{1}H NMR(400MHz,CD_3OD)δ8.54(s,2H),6.64(d,J=8.3Hz,2H),6.57(s,1H),4.06(s,2H),3.92-3.88(m,2H),3.50(dd,J=13.8,6.7Hz,3H),3.34(s,1H),2.97(s,1H),2.65(s,3H),2.24(s,1H),1.96(d,J=11.9Hz,2H),1.72(m,10H)。质谱(m/z):402.2[M+H]$^+$。

[2692] 化合物486

[2693] N^2-(6-(8-氧杂-3-氮杂双环[3.2.1]辛烷-3-基)-2-甲基吡啶-3-基)螺[3.3]庚烷-2,6-二胺

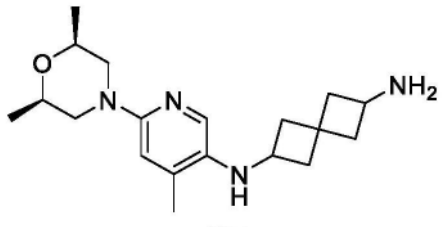
[2694] 

486

[2695] 根据为化合物24的程序制备标题化合物486(50.2mg),总收率为76.3%(紫色固体)。^{1}H NMR(400MHz,DMSO-d6)δ6.72(d,J=8.8Hz,1H),6.37(d,J=8.8Hz,1H),4.41-4.30(m,2H),3.69-3.46(m,3H),3.16(m,1H),2.78-2.67(m,2H),2.43-2.30(m,2H),2.25-2.06(m,7H),1.96-1.84(m,2H),1.80-1.68(m,4H)。质谱(m/z):329.2[M+H]$^+$。

[2696] 化合物487

[2697] N^2-(6-((2S,6R)-2,6-二甲基吗啉代)-4-甲基吡啶-3-基)螺[3.3]庚烷-2,6-二胺

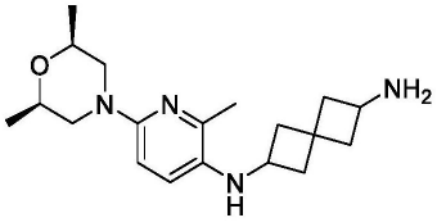
[2698] 

487

[2699] 根据为化合物24的程序制备标题化合物487(52.1mg),总收率为52.4%(白色固体)。^{1}H NMR(400MHz,DMSO-d6)δ7.26(s,1H),6.69(s,1H),3.95-3.82(m,2H),3.76-3.47(m,5H),3.16(m,1H),2.44-2.30(m,2H),2.27-2.12(m,4H),2.09(s,3H),1.97-1.86(m,2H),1.12(d,J=6.4Hz,6H)。质谱(m/z):331.2[M+H]$^+$。

[2700] 化合物488

[2701] N^2-(6-(2,6-二甲基吗啉代)-2-甲基吡啶-3-基)螺[3.3]庚烷-2,6-二胺

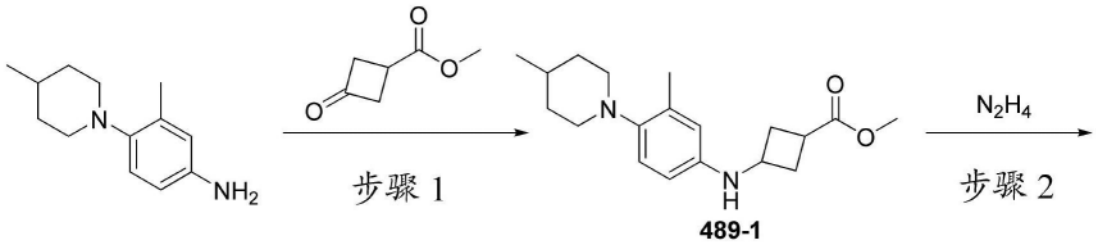
[2702] 

488A
488B

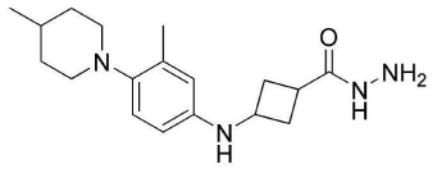
[2703] 根据为化合物24的程序制备标题化合物488。混合物的提纯方法:CHIRALPAK IG-3,4.6*50mm,3μm(溶剂体系(MTBE(3‰异丙胺):EtOH=80:20)而得到化合物488A(Rt=1.614min)收率13.6%(淡黄色固体)和488B(Rt=2.177min),收率14.5%(淡黄色固体)。488A:^{1}H NMR(400MHz,甲醇-d4)δ6.86(d,J=8.4Hz,1H),6.52(d,J=8.4Hz,1H),3.85-3.64(m,5H),3.27(m,1H),2.56-2.39(m,2H),2.35(m,1H),2.31-2.22(m,6H),1.96-1.75(m,4H),1.21(d,J=6.0Hz,6H)。质谱(m/z):331.2[M+H]$^+$。488B:^{1}H NMR(400MHz,甲醇-d4)δ6.87(d,J=8.8Hz,1H),6.53(d,J=8.8Hz,1H),3.85-3.64(m,5H),3.27(m,1H),2.62-2.40(m,2H),2.38-2.32(m,2H),2.28(s,3H),2.26-2.19(m,2H),1.97-1.72(m,4H),1.21(d,J=6.0Hz,6H)。质谱(m/z):331.2[M+H]$^+$。

[2704] 化合物489

[2705] 3-((3-甲基-4-(4-甲基哌啶-1-基)苯基)氨基)环丁烷-1-碳酰肼

[2706] 

489-1



489

[2707] 步骤1:制备3-((3-甲基-4-(4-甲基哌啶-1-基)苯基)氨基)环丁烷-1-甲酸甲酯(489-1)

[2708] 向3-甲基-4-(4-甲基哌啶-1-基)苯胺(0.2g,0.98mmol)/DCE(5mL)的溶液中添加3-氧代环丁烷-1-甲酸甲酯(125mg,0.98mmol)和$NaBH(OAc)_3$(623mg,2.94mmol)。在室温搅拌反应3小时。用水(10mL)淬灭,反应用EA(10mL)萃取3次。将合并的有机层用硫酸钠干燥,

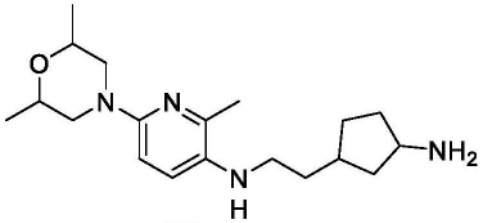
浓缩并且通过快速色谱纯化,洗脱用PE/EA＝10:1至1:1而得到期望的产物(黄色油)(0.22g,60%)。质谱(m/z):316.9[M+H]$^+$。

[2709] 步骤2:制备3-((3-甲基-4-(4-甲基哌啶-1-基)苯基)氨基)环丁烷-1-碳酰肼(489)

[2710] 向3-((3-甲基-4-(4-甲基哌啶-1-基)苯基)氨基)环丁烷-1-甲酸甲酯(220mg,0.7mmol)/EtOH(10mL)的溶液中添加N2H4(50mg)并在80℃搅拌混合物2小时。用水淬灭(30mL),反应用EA(10mL)萃取3次。将合并的有机层用硫酸钠干燥,真空除去并且残余物的提纯方法为:制备HPLC(column-Gemini-C18 150x 21.2mm,5um;移动相:ACN-H_2O(0.1%FA),10%-40%)而得到化合物489(83mg,42.9%)(黄色固体)。质谱(m/z):316.8[M+H]$^+$。^{1}H NMR(400MHz,DMSO-d6)δ6.79(dd,J＝8.4,3.6,1H),6.35-6.22(m,2H),5.55-5.50(m,1H),3.91-3.68(m,1H),3.64(s,1H),3.59(s,2H),2.84-2.81(m,2H),2.55-2.52(m,1H),2.47-2.44(m,1H),2.12-2.04(m,4H),1.98-1.91(m,1H),1.65-1.63(m,2H),1.42-1.37(m,1H),1.29-1.20(m,2H),0.94(d,J＝6.4,3H)。质谱(m/z):317.3[M+H]$^+$。

[2711] 化合物490

[2712] N-(2-(3-氨基环戊基)乙基)-6-(2,6-二甲基吗啉代)-2-甲基吡啶-3-胺

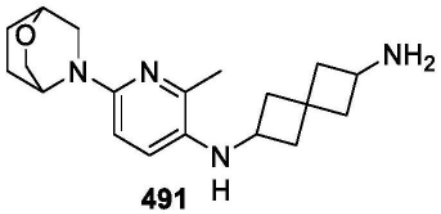
[2713] 

490

[2714] 由N-(4-氨基苯基)-2,2,2-三氟-N-甲基乙酰胺(0.45g,1.3mmol),BH_3-THF(10mL)和THF(5mL),根据为150的程序制备标题化合物490(40.4mg,9.4%,收率)(黄色固体)。^{1}H NMR(400MHz,DMSO-d6)δ＝6.83(d,J＝8.8,1H),6.51(d,J＝8.8,1H),4.30(s,1H),3.83(d,J＝11.2,2H),3.63-3.60(m,2H),3.29-3.14(m,1H),2.94(t,J＝7.2,2H),2.21(s,3H),2.09-1.94(m,1H),1.89-1.79(m,2H),1.78-1.65(m,1H),1.65-1.40(m,3H),1.39-1.17(m,2H),1.14(d,J＝6.4,7H)。质谱(m/z):332.9[M+H]$^+$。

[2715] 化合物491

[2716] N^2-(6-(2-氧杂-5-氮杂双环[2.2.2]辛烷-5-基)-2-甲基吡啶-3-基)螺[3.3]-庚烷-2,6-二胺

[2717] 

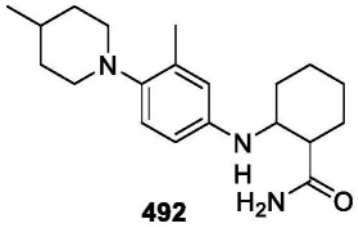
491

[2718] 由(6-((6-(2-氧杂-5-氮杂双环[2.2.2]辛烷-5-基)-2-甲基吡啶-3-基)氨基)螺[3.3]庚烷-2-基)氨基甲酸叔丁酯(400mg,0.84mmol),DCM(10mL)和TFA(1mL),根据为24的程序制备标题化合物(35mg)(白色固体)。^{1}H NMR(400MHz,DMSO-d6)δ6.71(d,J＝8.8Hz,1H),6.18(d,J＝8.8Hz,1H),4.37(s,1H),3.90-3.88(m,1H),3.86(t,J＝5.6Hz,2H),3.79-3.75(m,0.4H),3.53(br,2H),3.31(d,J＝10.4Hz,1H),3.15(m,1H),2.44-2.32(m,1H),

2.31-2.25(m,1H),2.24-2.17(m,1H),2.16-2.12(m,3H),2.12-2.05(m,1H),2.00-1.91(m,1H),1.89-1.70(m,5H),1.68-1.57(m,2H)。质谱(m/z):329.3[M+H]$^+$。

[2719] 化合物492

[2720] 2-((3-甲基-4-(4-甲基哌啶-1-基)苯基)氨基)环己烷-1-甲酰胺

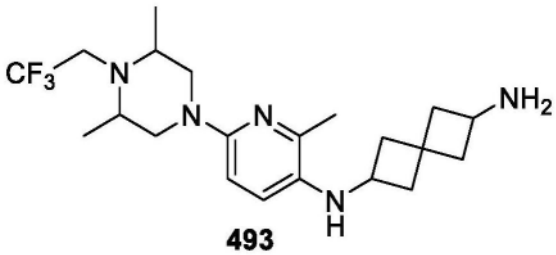
[2721] 

492

[2722] 由2-((3-甲基-4-(4-甲基哌啶-1-基)苯基)氨基)环己烷-1-羧酸(100mg,0.3mmol),DMF(15mL),NH_4Cl(19.42mg,0.36mmol),HATU(172.59mg,0.45mmol)和DIEA(117.32mg,0.9mmol),根据为1的程序制备标题化合物(141mg)(白色固体)。^{1}H NMR(400MHz,DMSO-d6)δ7.18(s,1H),6.74(d,J=8.6Hz,1H),6.71(s,1H),6.41(d,J=2.6Hz,1H),6.35(dd,J=8.4,2.7Hz,1H),3.63(d,J=3.2Hz,1H),2.79(d,J=11.6Hz,2H),2.46-2.39(m,3H),2.08(s,3H),1.79(br,2H),1.64-1.21(m,12H),0.90(d,J=6.6Hz,3H)。质谱(m/z):330.3[M+H]$^+$。

[2723] 化合物493

[2724] N^2-(6-(3,5-二甲基-4-(2,2,2-三氟乙基)哌嗪-1-基)-2-甲基吡啶-3-基)螺[3.3]庚烷-2,6-二胺

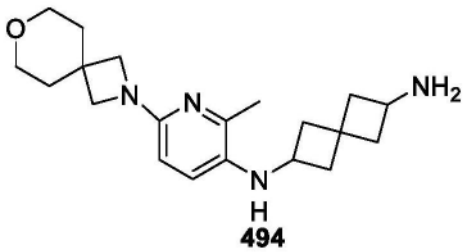
[2725] 

493

[2726] 由(6-((6-(3,5-二甲基-4-(2,2,2-三氟乙基)哌嗪-1-基)-2-甲基吡啶-3-基)氨基)螺[3.3]庚烷-2-基)氨基甲酸叔丁酯(0.2g,0.4mmol),DCM(5mL)和TFA(1mL),根据为24的程序制备标题化合物493(40mg,25%)(黄色油)。^{1}H NMR(400MHz,CD_3OD)δ6.84(d,J=8.6Hz,1H),6.52(d,J=8.6Hz,1H),3.74-3.68(m,3H),3.41-3.30(m,3H),2.87-2.83(m,2H),2.57-2.32(m,5H),2.28-2.22(m,4H),1.94-1.83(m,4H),1.14(d,J=6.2Hz,6H)。质谱(m/z):411.8[M+H]$^+$。

[2727] 化合物494

[2728] N^2-(2-甲基-6-(7-氧杂-2-氮杂螺[3.5]壬烷-2-基)吡啶-3-基)螺[3.3]庚烷-2,6-二胺

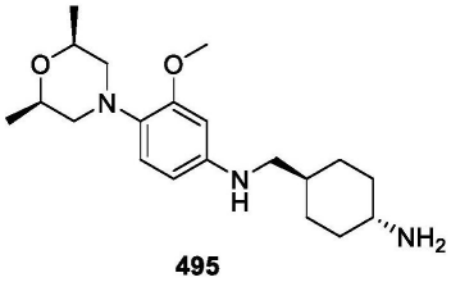
[2729] 

494

[2730] 由(4-((2-(2-羟基乙氧基)-4-(4-(三氟甲基)哌啶-1-基)苯基)氨基)环己基)氨基甲酸叔丁酯(170mg,0.38mmol),1,4-二氧杂环己烷(3mL)和HCl/1,4-二氧杂环己烷(1mL),根据为37的程序制备标题化合物494(4.1mg,3.1%)(黄色固体)。^{1}H NMR(400MHz,CD_3OD)δ7.15(d,J=8.4Hz,1H),6.41(d,J=8.3Hz,1H),3.69(m,5H),2.64 2.00(m,7H),1.86-1.79(m,4H),1.70-1.60(m,4H)。质谱(m/z):342.8[M+H]$^+$。

[2731] 化合物495

[2732] N-(((1r,4R)-4-氨基环己基)甲基)-4-((2S,6R)-2,6-二甲基吗啉代)-3-甲氧基苯胺

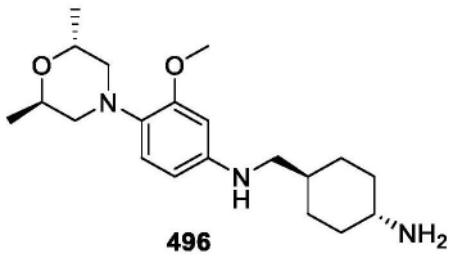
[2733] 

495

[2734] 由4-(2,6-二甲基吗啉代)-3-甲氧基苯胺(70mg,0.30mmol)和((1r,4r)-4-甲酰基环己基)氨基甲酸叔丁酯(101mg,0.44mmol),根据为20的程序制备标题化合物495(57.2mg),收率为55.6%(白色粉末)。^{1}H NMR(400MHz,DMSO-d6)δ8.13(s,2H),6.65(s,1H),6.25(s,1H),6.05(s,1H),5.34(s,1H),3.71(s,3H),2.96(d,J=39.4Hz,3H),2.81(s,2H),2.17(s,2H),2.02-1.93(m,2H),1.86(d,J=13.0Hz,2H),1.46(s,1H),1.31(td,J=13.4,10.1Hz,3H),1.08(d,J=6.3Hz,6H),1.01(d,J=12.8Hz,2H)。质谱(m/z):348.3[M+H]$^+$。

[2735] 化合物496

[2736] N-(((1r,4R)-4-氨基环己基)甲基)-4-((2S,6R)-2,6-二甲基吗啉代)-3-甲氧基苯胺

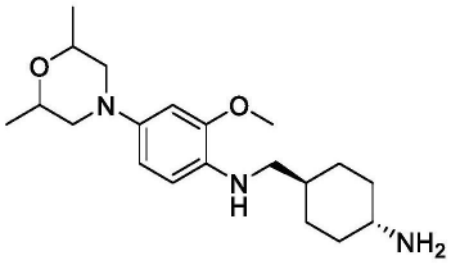
[2737] 

496

[2738] 由4-(2,6-二甲基吗啉代)-3-甲氧基苯胺(70mg,0.30mmol)和((1r,4r)-4-甲酰基环己基)氨基甲酸叔丁酯(101mg,0.44mmol),根据为20的程序制备标题化合物496(13.7mg),收率为14.1%(白色粉末)。^{1}H NMR(400MHz,DMSO-d6)δ8.05(s,2H),6.64(s,1H),6.24(s,1H),6.04(s,1H),3.70(s,5H),2.95(d,J=39.1Hz,3H),2.81(s,2H),2.16(s,1H),1.95(d,J=12.0Hz,2H),1.85(d,J=12.9Hz,2H),1.45(s,1H),1.35-1.21(m,3H),1.07(d,J=6.3Hz,6H),1.03-0.93(m,2H)。质谱(m/z):348.3[M+H]$^+$。

[2739] 化合物497

[2740] N-(((1r,4r)-4-氨基环己基)甲基)-4-(2,6-二甲基吗啉代)-2-甲氧基苯胺

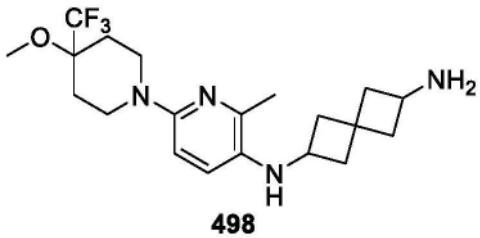
[2741] 

497

[2742] 由4-(2,6-二甲基吗啉代)-2-甲氧基苯胺(70mg,0.30mmol)和((1r,4r)-4-甲酰基环己基)氨基甲酸叔丁酯(101mg,0.44mmol),根据为20的程序制备标题化合物497(46.7mg),收率为45.4%(白色粉末)。^{1}H NMR(400MHz,DMSO-d6)δ8.04(s,3H),6.55(s,1H),6.37(d,J=22.1Hz,2H),4.36(s,1H),3.78(d,J=6.0Hz,3H),3.68(s,2H),2.88(d,J=24.0Hz,3H),2.14(s,2H),1.95(s,2H),1.82(d,J=12.7Hz,2H),1.50(s,1H),1.28(q,J=13.3,12.7Hz,3H),1.19-1.08(m,6H),0.99(s,2H)。质谱(m/z):348.7[M+H]$^+$。

[2743] 化合物498

[2744] N^2-(6-(4-甲氧基-4-(三氟甲基)哌啶-1-基)-2-甲基吡啶-3-基)螺[3.3]庚烷-2,6-二胺

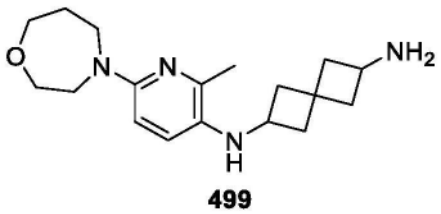
[2745] 

498

[2746] 由(6-((6-(4-甲氧基-4-(三氟甲基)哌啶-1-基)-2-甲基吡啶-3-基)氨基)螺[3.3]庚烷-2-基)氨基甲酸叔丁酯(68mg,0.137mmol),TFA(1mL),和DCM(10mL),根据为24的程序制备标题化合物498(6.0mg),总收率为11.0%(白色固体)。^{1}H NMR(400MHz,DMSO-d6)δ6.72(dd,J=8.8,4.0Hz,1H),6.55(d,J=8.8Hz,1H),4.52(d,J=7.2Hz,1H),3.94(d,J=12.8Hz,2H),3.84(q,J=8.0Hz,1H),3.61(q,J=7.4Hz,1H),3.38(s,3H),2.74(td,J=12.8,2.4Hz,2H),2.46-2.40(m,1H),2.27(td,J=10.4,6.0Hz,2H),2.20(s,3H),2.10(dd,J=11.2,6.0Hz,1H),1.97-1.64(m,8H)。质谱(m/z):399.3[M+H]$^+$。

[2747] 化合物499

[2748] N^2-(2-甲基-6-(1,4-氧杂氮杂环庚烷-4-基)吡啶-3-基)螺[3.3]庚烷-2,6-二胺

[2749] 

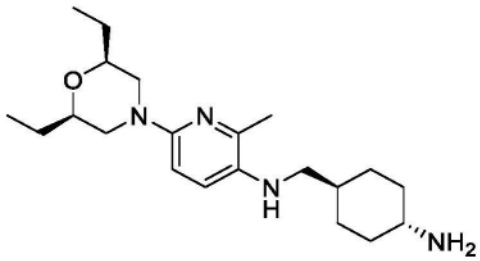
499

[2750] 由(6-((2-甲基-6-(1,4-氧杂氮杂环庚烷-4-基)吡啶-3-基)氨基)螺[3.3]庚烷-2-基)氨基甲酸叔丁酯(158mg,0.380mmol),TFA(1mL),和DCM(10mL),根据为24的程序制备标题化合物499(41.1mg),总收率为31.2%(黄色固体)。^{1}H NMR(400MHz,DMSO-d6)δ8.44(s,3H),6.86(s,1H),6.40(d,J=8.4Hz,1H),3.70-3.58(m,8H),3.55(t,J=5.6Hz,3H),2.49-

2.42(m,1H),2.35(dddd,J＝19.6,11.2,7.2,2.8Hz,3H),2.25(d,J＝8.0Hz,4H),2.21-2.14(m,3H),1.96(s,2H),1.84(p,J＝5.6Hz,2H)。质谱(m/z):317.3[M+H]$^+$。

[2751] 化合物500

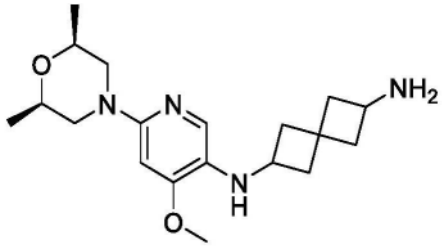
[2752] N-(((1r,4R)-4-氨基环己基)甲基)-6-((2R,6S)-2,6-二乙基吗啉代)-2-甲基吡啶-3-胺

[2753] 

[2754] 根据为化合物24的程序制备标题化合物500(30.8mg),总收率为53.1%(淡黄色固体)。^{1}H NMR(400MHz,DMSO-d6)δ7.75(s,2H),6.83(d,J＝8.7Hz,1H),6.52(d,J＝8.7Hz,1H),4.44(s,1H),3.84(d,J＝11.9Hz,2H),3.41-3.36(m,2H),2.98-2.91(m,1H),2.88-2.79(m,2H),2.22(s,3H),2.21-2.14(m,2H),1.97-1.84(m,4H),1.51-1.45(m,4H),1.30-1.25(m,2H),1.06-0.90(m,8H)。质谱(m/z):361.3[M+H]$^+$。

[2755] 化合物501

[2756] N^2-(6-((2R,6S)-2,6-二甲基吗啉代)-4-甲氧基吡啶-3-基)螺[3.3]庚烷-2,6-二胺

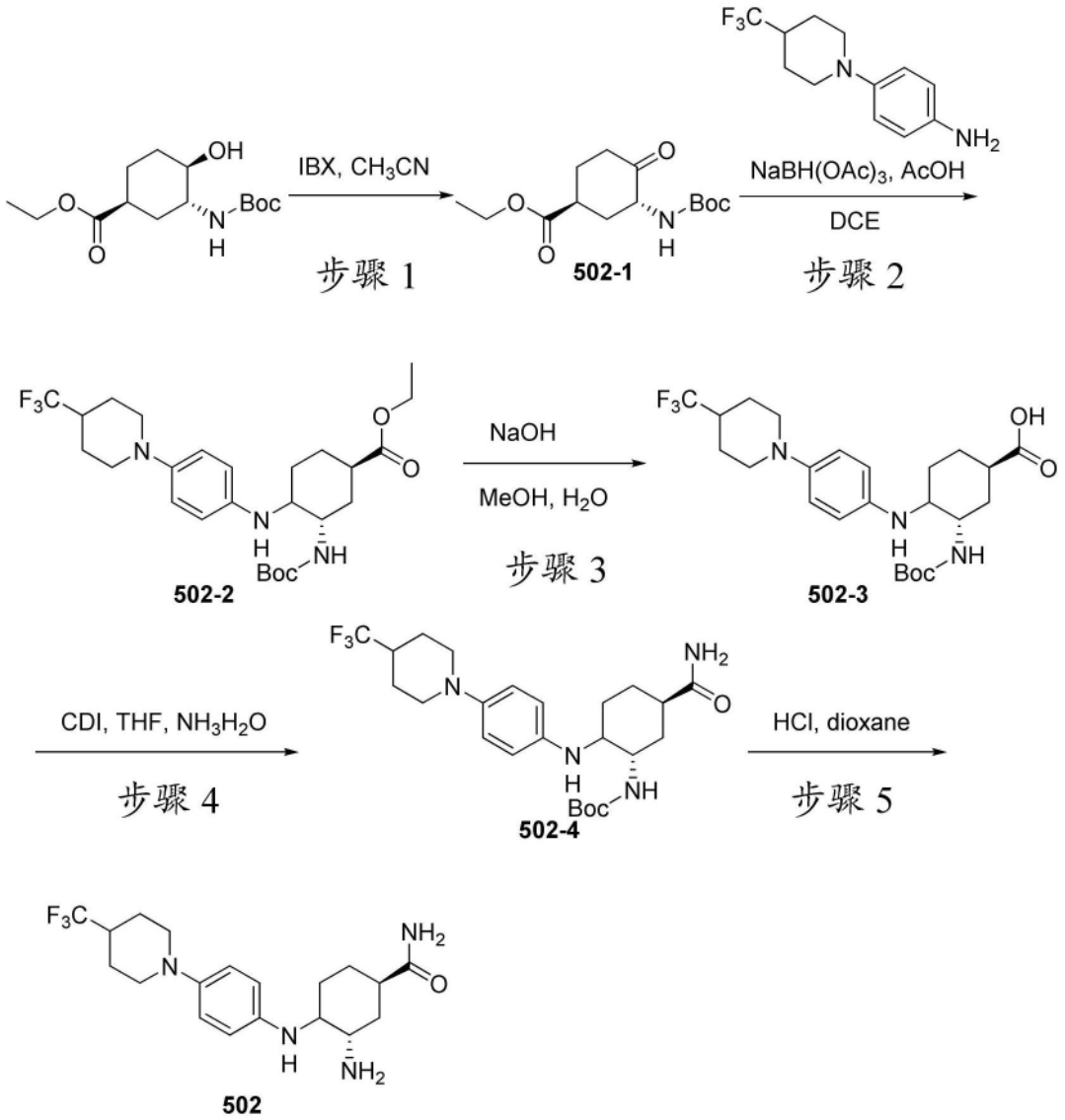
[2757] 

[2758] 根据为化合物34的程序制备标题化合物501(28.8mg),总收率为16.6%(淡黄色固体)。^{1}H NMR(400MHz,DMSO-d6)δ8.26(s,3H),7.06(s,1H),6.51(s,1H),4.04-3.97(m,2H),3.90(s,3H),3.69-3.58(m,3H),3.56-3.50(m,1H),3.41-3.29(m,2H),2.50-2.45(m,2H),2.42-2.30(m,4H),2.23-2.13(m,3H),1.96-1.86(m,2H)。质谱(m/z):347.2[M+H]$^+$。

[2759] 化合物502

[2760] (1R,3S)-3-氨基-4-((4-(4-(三氟甲基)哌啶-1-基)苯基)氨基)环己烷-1-甲酰胺

[2761]



[2762] 步骤1:制备(1S,3R)-3-((叔丁氧基羰基)氨基)-4-氧代环己烷-1-甲酸甲酯(502-1)

[2763] 使(1S,3R,4R)-3-((叔丁氧基羰基)氨基)-4-羟基环己烷-1-甲酸甲酯(3g,10.5mmol)和IBX(6g,21.4mmol)/乙腈(80mL)的混合物回流过夜。添加另外的IBX(3g,10.7mmol)并且搅拌另外的5小时。将反应冷却并且过滤。将滤液浓缩而得到(1S,3R)-3-((叔丁氧基羰基)氨基)-4-氧代环己烷-1-甲酸甲酯(3.2g粗产物,定量)(白色固体)。未经进一步纯化直接使用粗产物。

[2764] 步骤2:制备(1R,3S)-3-((叔丁氧基羰基)氨基)-4-((4-(4-(三氟甲基)哌啶-1-基)苯基)氨基)环己烷-1-甲酸甲酯(502-2)

[2765] 搅拌4-(4-(三氟甲基)哌啶-1-基)苯胺(500mg,2.05mmol),(1S,3R)-3-((叔丁氧基羰基)氨基)-4-氧代环己烷-1-甲酸甲酯(800mg,2.81mmol),和一滴AcOH/DCE(10mL)的溶液10分钟,然后添加$NaBH(OAc)_3$(600mg,2.84mmol)并且在室温搅拌过夜。将反应用碳酸氢钠水溶液淬灭并用DCM萃取。将合并的有机层用盐水洗涤,用硫酸钠干燥并且减压浓缩。残余物的提纯方法为:硅胶快速色谱(PE/EA=90/10至70/30)而得到500mg(47.5%)的标题化合物(灰色固体)。质谱(m/z):514.5$[M+H]^+$。

[2766] 步骤3:制备(1R,3S)-3-((叔丁氧基羰基)氨基)-4-((4-(4-(三氟甲基)哌啶-1-基)苯基)氨基)环己烷-1-甲酸(502-3)

[2767] 搅拌(1R,3S)-3-((叔丁氧基羰基)氨基)-4-((4-(4-(三氟甲基)哌啶-1-基)苯基)氨基)环己烷-1-甲酸甲酯(300mg,0.584mmol)和氢氧化钠(300mg,7.5mmol)/THF(1mL),MeOH(1mL)和水(0.5mL)的混合物2小时。将反应减压浓缩,用2N HCl调整pH到5-6并用乙酸乙酯萃取。有机层用硫酸钠干燥并且真空浓缩而得到粗产物(280mg,98.8%)(黑色浆液)。质谱(m/z):486.5$[M+H]^+$。

[2768] 步骤4:制备((1S,5R)-5-氨基甲酰基-2-((4-(4-(三氟甲基)哌啶-1-基)苯基)氨基)环己基)氨基甲酸叔丁酯(502-4)

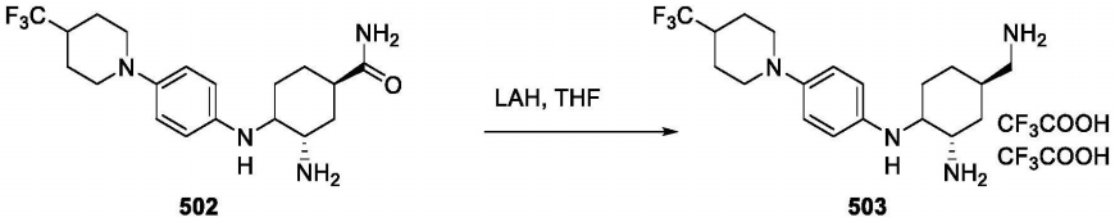
[2769] 使(1R,3S)-3-((叔丁氧基羰基)氨基)-4-((4-(4-(三氟甲基)哌啶-1-基)苯基)氨基)环己烷-1-甲酸(200mg,0.412mmol)和CDI(150mg,2.42mmol)/THF(2mL)的混合物回流过夜并且缓慢添加到NH_3H_2O(5mL)。搅拌所得的混合物10分钟,然后用EtOAc萃取两次。将合并的有机层用硫酸钠干燥并且减压浓缩。残余物的提纯方法为:Prep-TLC(EtOAc)而得到180mg(90.2%)的产物(灰色固体)。质谱(m/z):485.5$[M+H]^+$。

[2770] 步骤5:制备(1R,3S)-3-氨基-4-((4-(4-(三氟甲基)哌啶-1-基)苯基)氨基)环己烷-1-甲酰胺(502)

[2771] 在室温搅拌((1S,5R)-5-氨基甲酰基-2-((4-(4-(三氟甲基)哌啶-1-基)苯基)氨基)环己基)氨基甲酸叔丁酯(89mg,0.18mmol)/4N HCl/二氧杂环己烷(1.5mL)的溶液0.5小时。将反应浓缩,用碳酸氢钠碱化并用EA/EtOH(10/1)萃取3次。将合并的有机层用硫酸钠干燥并且减压浓缩。残余物的提纯方法为:Prep-TLC(DCM/MeOH/NH_4OH 100/20/1,Rf=0.1)而得到标题化合物502(50.7mg,73.1%)(白色固体)。^1H NMR(400MHz,DMSO-d6)δ7.30-7.14(m,1H),6.83-6.67(m,3H),6.66-6.48(m,2H),5.04-4.79(m,1H),3.50-3.38(m,2H),2.95-2.83(m,1H),2.76-2.65(m,1H),2.39-2.30(m,1H),2.21-2.12(m,1H),2.03-1.76(m,5H),1.76-1.50(m,3H),1.45-1.21(m,2H),1.09-0.90(m,1H)。质谱(m/z):385.4$[M+H]^+$。

[2772] 化合物503

[2773] (2S,4R)-4-(氨基甲基)-N^1-(4-(4-(三氟甲基)哌啶-1-基)苯基)环己烷-1,2-二胺双(2,2,2-三氟乙酸盐)

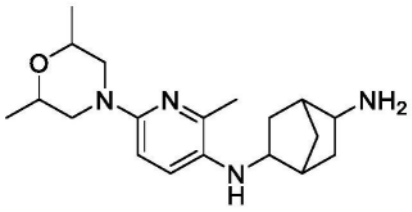
[2774] 

502 503

[2775] 使(1R,3S)-3-氨基-4-((4-(4-(三氟甲基)哌啶-1-基)苯基)氨基)环己烷-1-甲酰胺(30mg,0.08mmol)和$LiAlH_4$(1N/THF,0.2mL)/THF(2mL)的溶液回流2小时。将反应冷却并且用$Na_2SO_4 10H_2O$淬灭,过滤并且将滤液浓缩和通过Prep-HPLC纯化而得到(2S,4R)-4-(氨基甲基)-N^1-(4-(4-(三氟甲基)哌啶-1-基)苯基)环己烷-1,2-二胺双(2,2,2-三氟乙酸盐)502(5.2mg,10.8%)(灰色固体)。^1H NMR(400MHz,DMSO-d6)δ8.03-7.70(m,6H),7.15-6.93(m,2H),6.67(d,J=8.5Hz,2H),3.65-3.47(m,6H),3.03-2.85(m,1H),2.85-2.65(m,2H),2.15-1.89(m,4H),1.84-1.50(m,4H),1.30-0.93(m,2H)。质谱(m/z):371.3$[M+H]^+$。

[2776] 化合物504

[2777] N^2-(6-(2,6-二甲基吗啉代)-2-甲基吡啶-3-基)双环[2.2.1]庚烷-2,5-二胺

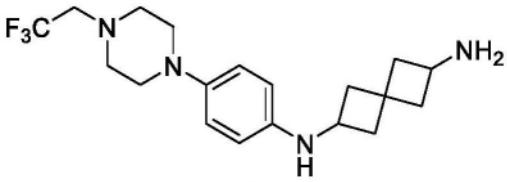
[2778] 

504

[2779] 根据为化合物24的程序制备标题化合物504(14.8mg),总收率为44.8%(白色固体)。^{1}H NMR(400MHz,DMSO-d6)δ6.94(d,J=8.8Hz,1H),6.55(d,J=8.8Hz,1H),3.95-3.50(m,5H),3.17(m,1H),2.46-2.10(m,7H),2.02-1.76(m,3H),1.67-1.45(m,2H),1.36(m,1H),1.12(d,J=6.0Hz,6H)。质谱(m/z):331.2$[M+H]^+$。

[2780] 化合物505

[2781] N^2-(4-(4-(2,2,2-三氟乙基)哌嗪-1-基)苯基)螺[3.3]庚烷-2,6-二胺

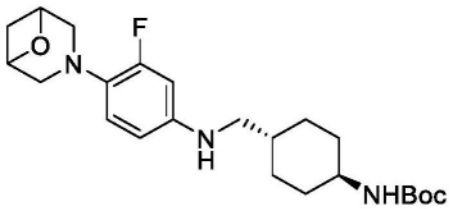
[2782] 

505

[2783] 根据为化合物24的程序制备标题化合物505(25.1mg),总收率为68.0%(灰色固体)。^{1}H NMR(400MHz,DMSO-d6)δ6.85-6.68(m,2H),6.57-6.44(m,2H),3.37(s,2H),3.27-3.15(m,2H),2.83-2.67(m,6H),2.05-1.98(m,2H),1.89-1.77(m,2H),1.52-1.24(m,4H),1.05-0.93(m,2H)。质谱(m/z):369.2$[M+H]^+$。

[2784] 化合物506

[2785] ((1r,4r)-4-(((4-(6-氧杂-3-氮杂双环[3.1.1]庚烷-3-基)-3-氟苯基)氨基)甲基)环己基)氨基甲酸叔丁酯

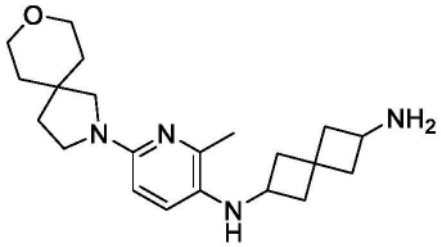
[2786] 

506

[2787] 由4-(6-氧杂-3-氮杂双环[3.1.1]庚烷-3-基)-3-氟苯胺(50mg,0.240mmol),((1r,4r)-4-甲酰基环己基)氨基甲酸叔丁酯(82mg,0.360mmol),AcOH(0.1mL),$NaBH(OAc)_3$(102mg,0.480mmol)和DCE(10mL),根据为24-1的程序制备标题化合物506(14.8mg),总收率为14.7%(白色固体)。^{1}H NMR(400MHz,DMSO-d6)δ6.87(dd,J=10.4,8.8Hz,1H),6.69(d,J=8.0Hz,1H),6.41-6.25(m,2H),5.46(t,J=5.6Hz,1H),4.53(d,J=6.0Hz,2H),3.38(d,J=11.2Hz,2H),3.31(s,2H),3.17(d,J=8.0Hz,1H),2.99(dt,J=8.0,6.4Hz,1H),2.78(t,J=6.0Hz,2H),2.23(d,J=8.0Hz,1H),1.80(d,J=11.6Hz,4H),1.37(s,9H),1.16-1.05(m,2H),1.01-0.89(m,2H)。质谱(m/z):420.3$[M+H]^+$。

[2788] 化合物507

[2789] N^2-(2-甲基-6-(8-氧杂-2-氮杂螺[4.5]癸烷-2-基)吡啶-3-基)螺[3.3]庚烷-2,6-二胺

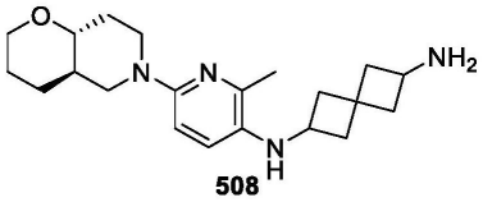
[2790] 

507

[2791] 由(6-((2-甲基-6-(8-氧杂-2-氮杂螺[4.5]癸烷-2-基)吡啶-3-基)氨基)螺[3.3]庚烷-2-基)氨基甲酸叔丁酯(55mg,0.121mmol),TFA(1mL),和DCM(10mL),根据为24的程序制备标题化合物507(12.7mg),总收率为29.5%(黄色固体)。^{1}H NMR(400MHz,DMSO-d6)δ8.52(s,1H),8.42(s,1H),3.71-3.49(m,4H),3.43(s,1H),3.32(s,2H),3.21-3.14(m,1H),3.12-3.07(m,1H),2.45(d,J=8.0Hz,2H),2.42-2.30(m,2H),2.19(d,J=8.5Hz,1H),1.94(d,J=20.0Hz,1H),1.86(t,J=7.2Hz,1H),1.53(d,J=5.2Hz,2H)。质谱(m/z):357.3[M+H]$^+$。

[2792] 化合物508

[2793] N^2-(6-((4aR,8aR)-六氢-2H-吡喃并[3,2-c]吡啶-6(5H)-基)-2-甲基吡啶-3-基)螺[3.3]庚烷-2,6-二胺

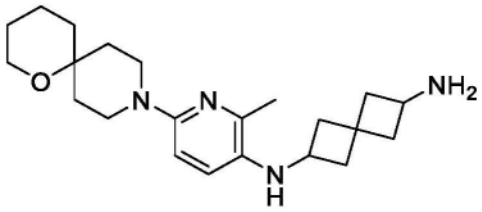
[2794] 

508

[2795] 由(6-((6-((4aR,8aR)-六氢-2H-吡喃并[3,2-c]吡啶-6(5H)-基)-2-甲基吡啶-3-基)氨基)螺[3.3]庚烷-2-基)氨基甲酸叔丁酯(72mg,0.158mmol),TFA(1mL),和DCM(10mL),根据为24的程序制备标题化合物508(48.8mg),总收率为86.7%(黄色固体)。^{1}H NMR(400MHz,DMSO-d6)δ8.44(s,3H),6.82-6.68(m,1H),6.54(d,J=8.8Hz,1H),4.60(s,1H),4.07(d,J=12.8Hz,1H),3.88(dd,J=16.8,11.4Hz,2H),3.71-3.46(m,3H),3.00(td,J=10.4,4.2Hz,1H),2.61(t,J=13.2Hz,2H),2.41-2.30(m,2H),2.22(td,J=15.6,13.2,8.0Hz,7H),1.93(d,J=11.2Hz,2H),1.73(dd,J=32.0,12.0Hz,2H),1.57(qd,J=7.6,5.2,3.2Hz,2H),1.50-1.28(m,2H),1.26-1.11(m,1H)。质谱(m/z):357.3[M+H]$^+$。

[2796] 化合物509

[2797] N^2-(2-甲基-6-(1-氧杂-9-氮杂螺[5.5]十一烷-9-基)吡啶-3-基)螺[3.3]庚烷-2,6-二胺

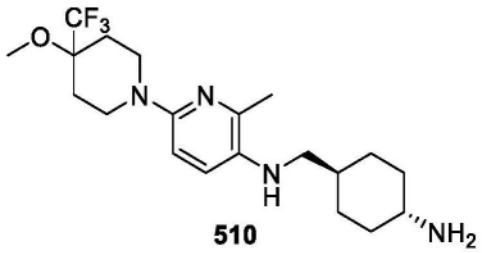
[2798] 

509

[2799] 由(6-((2-甲基-6-(1-氧杂-9-氮杂螺[5.5]十一烷-9-基)吡啶-3-基)氨基)螺[3.3]庚烷-2-基)氨基甲酸叔丁酯(69mg,0.147mmol),TFA(1mL),和DCM(10mL),根据为24的程序制备标题化合物509(48.4mg),总收率为89.0%(黄色固体)。^{1}H NMR(400MHz,DMSO-d6)δ8.47(d,J=39.6Hz,6H),7.11(s,1H),6.43(s,1H),3.71-3.50(m,8H),3.43(s,2H),3.32(s,1H),3.19-3.14(m,2H),3.11-3.06(m,2H),2.45(d,J=8.0Hz,5H),2.40-2.30(m,4H),2.22(dd,J=21.6,8.4Hz,3H),1.96(s,1H),1.86(t,J=7.2Hz,2H),1.53(d,J=5.2Hz,4H)。质谱(m/z):371.3[M+H]$^+$。

[2800] 化合物510

[2801] N-(((1r,4r)-4-氨基环己基)甲基)-6-(4-甲氧基-4-(三氟甲基)哌啶-1-基)-2-甲基吡啶-3-胺

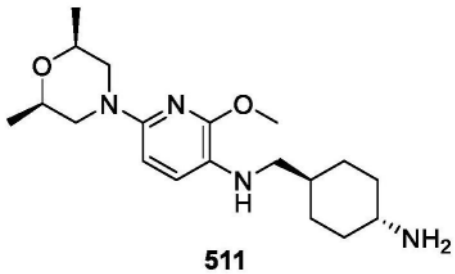
[2802] 

510

[2803] 由((1r,4r)-4-(((6-(4-甲氧基-4-(三氟甲基)哌啶-1-基)-2-甲基吡啶-3-基)氨基)甲基)环己基)氨基甲酸叔丁酯(88mg,0.176mmol),TFA(1mL)和DCM(10mL),根据为24的程序制备标题化合物510(24.8mg),总收率为35.2%(白色固体)。^{1}H NMR(400MHz,DMSO-d6)δ8.45-8.18(m,3H),7.20-6.71(m,2H),4.83(s,1H),3.52(s,2H),3.12(s,3H),2.88(d,J=6.8Hz,3H),2.32(s,3H),2.05-1.95(m,2H),1.87(d,J=12.8Hz,2H),1.74(d,J=13.2Hz,2H),1.53(s,2H),1.42-1.27(m,2H),1.00(dd,J=13.6,10.4Hz,2H)。质谱(m/z):401.3[M+H]$^+$。

[2804] 化合物511

[2805] N-(((1r,4R)-4-氨基环己基)甲基)-6-((2S,6R)-2,6-二甲基吗啉代)-2-甲氧基吡啶-3-胺

[2806] 

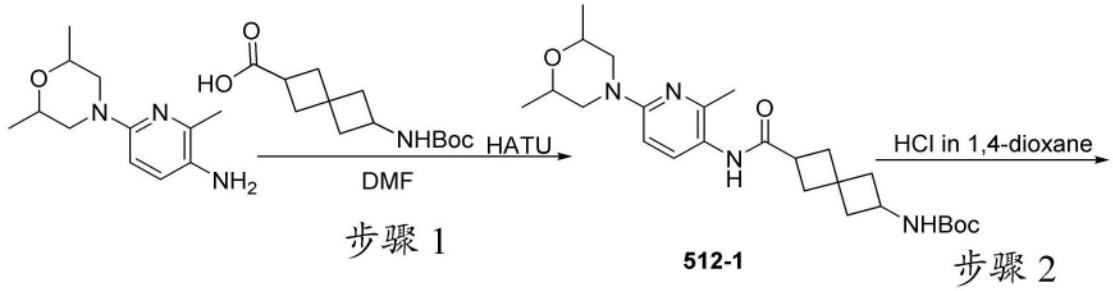
511

[2807] 由((1R,4r)-4-(((6-((2S,6R)-2,6-二甲基吗啉代)-2-甲氧基吡啶-3-基)氨基)甲基)环己基)氨基甲酸叔丁酯(66mg,0.147mmol),TFA(1mL),和DCM(10mL),根据为24的程

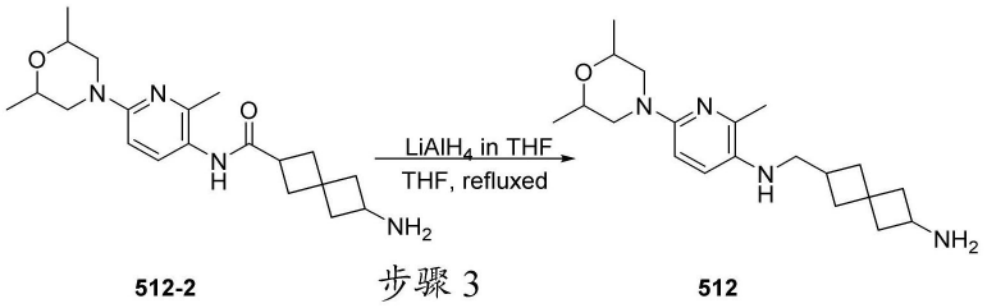
序制备标题化合物511(14.5mg),总收率为28.3%(紫色固体)。^{1}H NMR(400MHz,DMSO-d6)δ 8.13(s,2H),6.75(d,J=8.0Hz,1H),6.16(d,J=8.0Hz,1H),4.33(s,1H),3.99(td,J=6.4,3.2Hz,1H),3.79(d,J=2.4Hz,1H),3.63(ddd,J=10.4,6.4,2.4Hz,2H),3.27(dd,J=12.0,3.2Hz,1H),2.96-2.79(m,4H),2.23-2.12(m,3H),1.96(d,J=12.0Hz,2H),1.81(d,J=12.8Hz,2H),1.47(s,1H),1.29(d,J=13.6Hz,2H),1.17(s,1H),1.17-1.12(m,6H),0.97(q,J=12.8,12.4Hz,2H)。质谱(m/z):349.3[M+H]$^+$。

[2808] 化合物512

[2809] N-((6-氨基螺[3.3]庚烷-2-基)甲基)-6-(2,6-二甲基吗啉代)-2-甲基吡啶-3-胺



[2810]



[2811] 步骤1:制备(6-((6-(2,6-二甲基吗啉代)-2-甲基吡啶-3-基)氨基甲酰基)螺[3.3]庚烷-2-基)氨基甲酸叔丁酯(512-1)

[2812] 由6-((叔丁氧基羰基)氨基)螺[3.3]庚烷-2-甲酸(338mg,1.5mmol),6-(2,6-二甲基吗啉代)-2-甲基吡啶-3-胺(219mg,1.0mmol),DIEA(387mg,mmol)和HATU(456mg,1.2mmol),根据为403的程序制备标题化合物512-1(360mg),总收率为78.6%(黄色固体)。质谱(m/z):381.3[M+H]$^+$。

[2813] 步骤2:制备6-氨基-N-(6-(2,6-二甲基吗啉代)-2-甲基吡啶-3-基)螺[3.3]庚烷-2-甲酰胺(512-2)

[2814] 由(6-((6-(2,6-二甲基吗啉代)-2-甲基吡啶-3-基)氨基甲酰基)螺[3.3]庚烷-2-基)氨基甲酸叔丁酯(360mg,0.79mmol)和5.0mL的HCl/1,4-二氧杂环己烷,根据为化合物37的程序制备标题化合物512-2(260mg),总收率为92.5%(淡黄色固体)。质谱(m/z):359.2[M+H]$^+$。

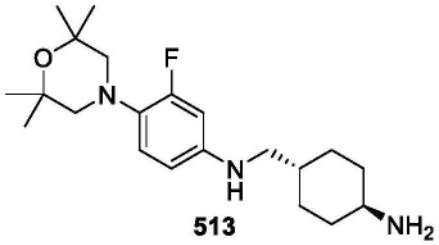
[2815] 步骤3:制备N-((6-氨基螺[3.3]庚烷-2-基)甲基)-6-(2,6-二甲基吗啉代)-2-甲基吡啶-3-胺(512)

[2816] 由6-氨基-N-(6-(2,6-二甲基吗啉代)-2-甲基吡啶-3-基)螺[3.3]庚烷-2-甲酰胺(200mg,0.56mmol)和1.16mL的$LiAlH_4$/THF(2.4M,2.78mmol),根据为化合物23的程序制备标题化合物512(9.4mg),总收率为4.9%(紫色固体)。^{1}H NMR(400MHz,DMSO-d6)δ7.87(s,

3H),6.82(d,J＝8.8Hz,1H),6.50(d,J＝8.7Hz,1H),4.28(t,J＝5.8Hz,1H),3.87-3.79(m,2H),3.67-3.47(m,4H),2.97(t,J＝6.4Hz,2H),2.39(s,1H),2.22-2.01(m,9H),1.81-1.68(m,2H),1.14(d,J＝6.2Hz,6H)。质谱(m/z):345.2[M+H]$^+$。

[2817] 化合物513

[2818] N-(((1r,4r)-4-氨基环己基)甲基)-3-氟-4-(2,2,6,6-四甲基吗啉代)苯胺

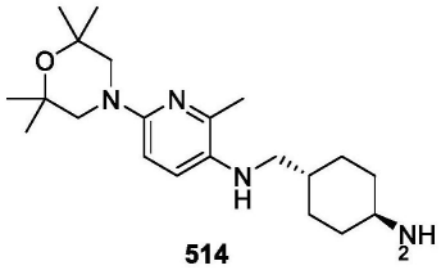
[2819] 

513

[2820] 根据为化合物24的程序制备标题化合物513(22.0mg),总收率为40.2%(白色固体)。^{1}H NMR(400MHz,DMSO-d6)δ8.04(s,3H),6.79(dd,J＝10.0,8.6Hz,1H),6.35(dd,J＝14.7,2.5Hz,1H),6.29(dd,J＝8.6,2.6Hz,1H),2.96-2.85(m,1H),2.80(t,J＝6.1Hz,2H),2.01-1.93(m,2H),1.88-1.78(m,2H),1.49-1.39(m,1H),1.34-1.24(m,2H),1.21(s,12H),1.04-0.91(m,2H)。质谱(m/z):364.2[M+H]$^+$。

[2821] 化合物514

[2822] N-(((1r,4r)-4-氨基环己基)甲基)-2-甲基-6-(2,2,6,6-四甲基吗啉代)吡啶-3-胺

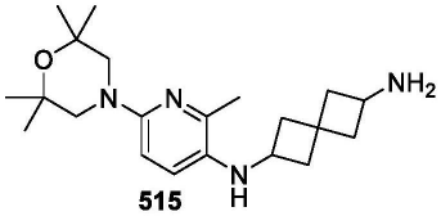
[2823] 

514

[2824] 根据为化合物24的程序制备标题化合物514(13.0mg),总收率为24.1%(黄色固体)。^{1}H NMR(400MHz,DMSO-d6)δ8.15(s,3H),7.10-6.76(m,1H),6.69-6.37(m,1H),4.63-4.32(m,1H),3.23-3.07(m,3H),2.97-2.72(m,3H),2.27(s,3H),2.03-1.80(m,4H),1.63-1.44(m,1H),1.36-1.27(m,2H),1.18(s,12H),1.06-0.93(m,2H)。质谱(m/z):361.3[M+H]$^+$。

[2825] 化合物515

[2826] N^2-(2-甲基-6-(2,2,6,6-四甲基吗啉代)吡啶-3-基)螺[3.3]庚烷-2,6-二胺

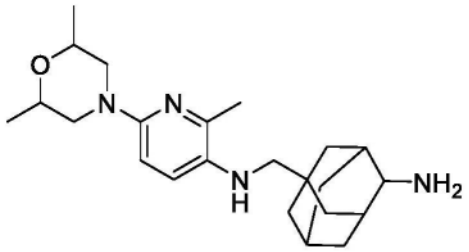
[2827] 

515

[2828] 根据为化合物24的程序制备标题化合物515(15.2mg),总收率为28.3%(白色固体)。^{1}H NMR(400MHz,DMSO-d6)δ8.13(s,3H),6.76(s,1H),6.53(d,J＝8.1Hz,1H),4.61-4.45(m,1H),3.61(d,J＝35.7Hz,2H),3.14-3.06(m,4H),2.45-2.34(m,2H),2.27-2.05(m,7H),1.98-1.87(m,7H),1.18(s,12H)。质谱(m/z):359.2[M+H]$^+$。

[2829] 化合物516

[2830] N-(((1s,4r)-4-氨基金刚烷-1-基)甲基)-6-(2,6-二甲基吗啉代)-2-甲基吡啶-3-胺

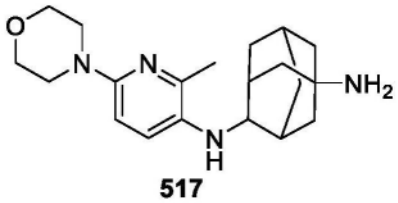
[2831] 

516A
516B

[2832] 由6-(2,6-二甲基吗啉代)-2-甲基吡啶-3-胺(300mg,1.36mmol)和4-氧代金刚烷-1-甲酸(316mg,1.63mmol),根据为20的程序制备标题化合物516A(Rt=8.59min;5.4mg),三步总收率为7.2%(白色固体)和制备化合物516B(Rt=9.96min;1.4mg),三步总收率为2.5%(白色固体)。目标产物的提纯方法:Prep-HPLC(柱:X Select-CSH-Prep 5μm OBD,19*150mm;ACN/水(0.5%TFA)=0%-25%-95%-95%-10%,0min-13min-13.5min-14.5min-16.0min)。516A:^{1}H NMR(400MHz,DMSO-d6)δ6.93(d,J=8.8Hz,1H),6.50(d,J=8.7Hz,1H),3.97(t,J=6.5Hz,1H),3.88-3.79(m,2H),3.62(ddd,J=10.3,6.3,2.4Hz,2H),2.84(s,1H),2.71(d,J=6.0Hz,2H),2.15(dd,J=12.3,10.3Hz,3H),2.03(d,J=12.6Hz,2H),1.83(d,J=10.4Hz,1H),1.67(s,2H),1.54(dd,J=24.3,11.6Hz,6H),1.32-1.23(m,3H),1.14(d,J=6.2Hz,6H)。质谱(m/z):385.6[M+H]$^+$。516B:^{1}H NMR(400MHz,DMSO-d6)δ6.93(d,J=8.8Hz,1H),6.50(d,J=8.5Hz,1H),3.97(t,J=6.5Hz,1H),3.89-3.79(m,2H),3.68(ddd,J=10.3,6.3,2.4Hz,2H),2.86(s,1H),2.71(d,J=6.0Hz,2H),2.15(dd,J=12.3,10.3Hz,3H),2.03(d,J=12.7Hz,2H),1.83(d,J=10.9Hz,1H),1.67(s,2H),1.52(dd,J=24.3,11.6Hz,6H),1.38-1.26(m,2H),1.18(d,J=6.2Hz,6H)。质谱(m/z):385.6[M+H]$^+$。

[2833] 化合物517

[2834] N^4-(2-甲基-6-吗啉代吡啶-3-基)金刚烷-1,4-二胺

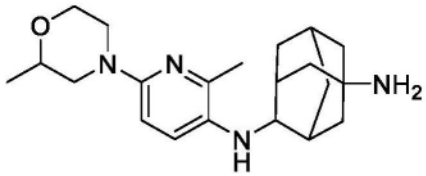
[2835] 

517

[2836] 由2-甲基-6-吗啉代吡啶-3-胺(70mg,0.36mmol)和(4-氧代金刚烷-1-基)氨基甲酸叔丁酯(114mg,0.44mmol),根据为20的程序制备标题化合物517(38.4mg),收率为30.5%(白色粉末)。^{1}H NMR(400MHz,DMSO-d6)δ8.26(s,2H),8.18(s,1H),6.99(s,1H),6.59(s,1H),4.00(s,1H),3.69(t,J=4.7Hz,5H),3.23(s,2H),2.34(dt,J=4.0,2.1Hz,2H),2.22-2.00(m,5H),1.99-1.86(m,4H),1.86-1.73(m,3H),1.62(dd,J=43.0,12.0Hz,1H),1.36(d,J=12.5Hz,2H)。质谱(m/z):343.4[M+H]$^+$。

[2837] 化合物518

[2838] N^4-(2-甲基-6-(2-甲基吗啉代)吡啶-3-基)金刚烷-1,4-二胺

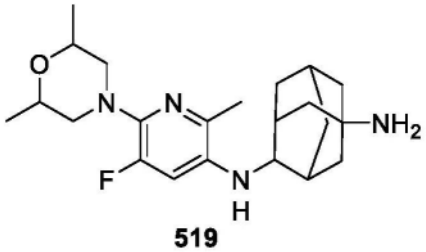
[2839] 

518

[2840] 由2-甲基-6-(2-甲基吗啉代)吡啶-3-胺(70mg,0.34mmol)和(4-氧代金刚烷-1-基)氨基甲酸叔丁酯(108mg,0.41mmol),根据为20的程序制备标题化合物518(31.0mg),收率为27.7%(白色粉末)。^{1}H NMR(400MHz,DMSO-d6)δ8.27(s,2H),8.18(s,1H),7.03(s,1H),6.61(s,1H),3.95-3.83(m,2H),3.76(d,J=12.4Hz,1H),3.54(t,J=11.3Hz,2H),3.36(s,3H),2.35(s,2H),2.22-1.70(m,11H),1.60(dd,J=41.7,12.1Hz,1H),1.34(d,J=12.4Hz,1H),1.13(d,J=6.2Hz,3H)。质谱(m/z):357.4[M+H]$^+$。

[2841] 化合物519

[2842] N^4-(6-(2,6-二甲基吗啉代)-5-氟-2-甲基吡啶-3-基)金刚烷-1,4-二胺

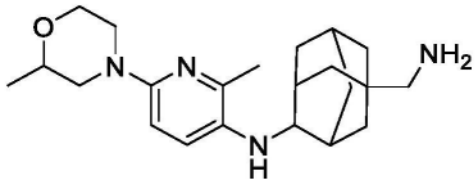


519

[2843] 由6-(2,6-二甲基吗啉代)-5-氟-2-甲基吡啶-3-胺(50mg,0.21mmol)和(4-氧代金刚烷-1-基)氨基甲酸叔丁酯(67mg,0.25mmol),根据为20的程序制备标题化合物519(15.0mg),收率为18.5%(白色粉末)。^{1}H NMR(400MHz,DMSO-d6)δ8.13(s,3H),6.87(dd,J=14.6,8.5Hz,1H),4.31-4.19(m,1H),3.68(ddd,J=10.4,6.2,2.1Hz,2H),3.38(t,J=13.2Hz,3H),2.26(d,J=1.1Hz,2H),2.19-2.05(m,3H),2.04-1.92(m,3H),1.87(d,J=11.6Hz,1H),1.79(d,J=18.7Hz,3H),1.65(d,J=12.6Hz,1H),1.56(d,J=11.2Hz,1H),1.35(d,J=12.8Hz,1H),1.09(d,J=6.2Hz,6H)。质谱(m/z):389.5[M+H]$^+$。

[2844] 化合物520

[2845] N-(5-(氨基甲基)金刚烷-2-基)-2-甲基-6-(2-甲基吗啉代)吡啶-3-胺

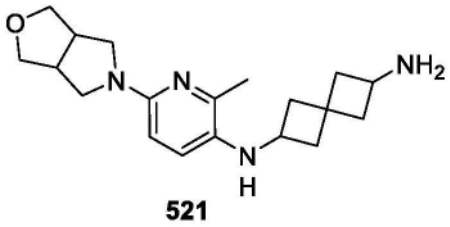
[2846] 

520

[2847] 由2-甲基-6-(2-甲基吗啉代)吡啶-3-胺(200mg,1.03mmol)和4-氧代金刚烷-1-甲酸(301mg,1.51mmol),根据为84的程序制备标题化合物520(50.3mg),两步的总收率为43.2%(白色粉末)。^{1}H NMR(400MHz,DMSO-d6)δ8.09(s,3H),6.90(s,1H),6.57(s,1H),3.88(d,J=11.5Hz,3H),3.76(d,J=12.3Hz,1H),3.64-3.46(m,3H),2.61(d,J=13.9Hz,2H),2.33(d,J=10.8Hz,4H),1.95(d,J=29.9Hz,5H),1.80-1.67(m,2H),1.64(d,J=2.9Hz,3H),1.58-1.47(m,3H),1.34(dd,J=26.2,12.2Hz,3H),1.14(d,J=6.2Hz,3H)。质谱(m/z):371.5[M+H]$^+$。

[2848] 化合物521

[2849] 叔丁基(6-((2-甲基-6-(四氢-1H-呋喃并[3,4-c]吡咯-5(3H)-基)吡啶-3-基)氨基)螺[3.3]庚烷-2-基)氨基甲酸叔丁酯

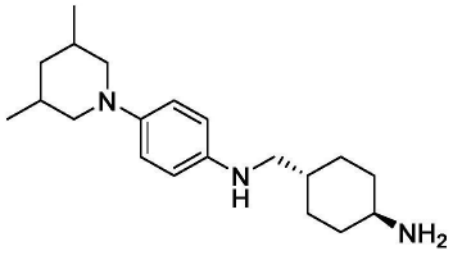
[2850] 

521

[2851] 由(6-((2-甲基-6-(四氢-1H-呋喃并[3,4-c]吡咯-5(3H)-基)吡啶-3-基)氨基)螺[3.3]庚烷-2-基)氨基甲酸叔丁酯(70mg,0.163mmol),DCM(3mL)和TFA(1mL)并且通过prep-HPLC(CH3CN/0.05%FA/水)提纯,根据为24的程序制备标题化合物521(6.8mg,11.6%,收率)(淡棕色固体)。^{1}H NMR(400MHz,DMSO-d6)δ6.87(d,J=8.7Hz,1H),6.32(d,J=8.7Hz,1H),3.96-3.91(m,2H),3.74-3.63(m,1H),3.60(dd,J=8.8,3.9Hz,2H),3.49-3.33(m,3H),3.28-3.24(m,2H),3.02-2.95(m,2H),2.57-2.41(m,2H),2.40-2.36(m 1H),2.31-2.23(m,4H),2.02-1.86(m,4H).MS(m/z):329.2[M+H]$^+$。

[2852] 化合物522

[2853] N-(((1r,4r)-4-氨基环已基)甲基)-4-(3,5-二甲基哌啶-1-基)苯胺

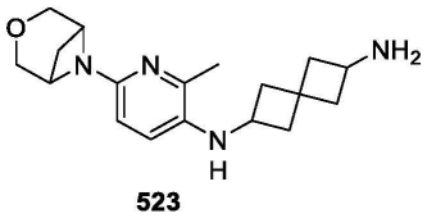
[2854] 

522

[2855] 由((1r,4r)-4-(((4-(3,5-二甲基哌啶-1-基)苯基)氨基)甲基)环已基)氨基甲酸叔丁酯(350mg,0.8401mmol),DCM(10mL)和TFA(1mL),根据为24的程序制备标题化合物522(25.3mg,9.4%)(白色固体)。^{1}H NMR(400MHz,CD_3OD)δ6.91-6.84(m,2H),6.62-6.58(m,2H),3.29-3.26(m,1H),2.88(d,J=6.7Hz,2H),2.55(ddd,J=14.4,7.3,3.5Hz,1H),2.06(t,J=11.3Hz,2H),1.90-1.76(m,7H),1.52(brs,1H),1.16-0.94(m,5H),0.93(d,J=6.4Hz,6H),0.67-0.57(m,1H)。质谱(m/z):316.3[M+H]$^+$。

[2856] 化合物523

[2857] N^2-(6-(3-氧杂-6-氮杂双环[3.1.1]庚烷-6-基)-2-甲基吡啶-3-基)螺[3.3]庚烷-2,6-二胺

[2858] 

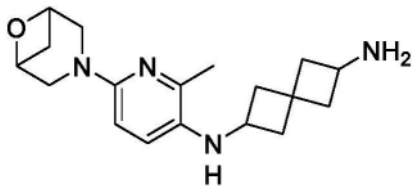
523

[2859] 由(6-((6-(3-氧杂-6-氮杂双环[3.1.1]庚烷-6-基)-2-甲基吡啶-3-基)氨基)螺[3.3]庚烷-2-基)氨基甲酸叔丁酯(170mg,0.4091mmol),DCM(10mL)和TFA(1mL),根据为24

的程序制备标题化合物523(1.5mg,1.12%,收率)(白色固体)。^{1}H NMR(400MHz,CD_3OD)δ6.91(d,J=8.5Hz,1H),6.34(d,J=8.5Hz,1H),4.28(m,4H),3.70(m,4H),2.71(d,J=6.7Hz,1H),2.52-2.34(m,3H),2.26(s,3H),2.03-1.59(m,6H)。质谱(m/z):315.2$[M+H]^+$。

[2860] 化合物524

[2861] N^2-(6-(6-氧杂-3-氮杂双环[3.1.1]庚烷-3-基)-2-甲基吡啶-3-基)螺[3.3]庚烷-2,6-二胺

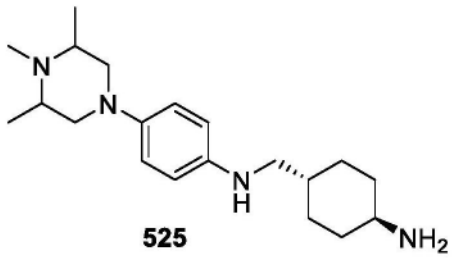
[2862] 

524

[2863] 由(6-((6-(6-氧杂-3-氮杂双环[3.1.1]庚烷-3-基)-2-甲基吡啶-3-基)氨基)螺[3.3]庚烷-2-基)氨基甲酸叔丁酯(0.1g,0.24mmol),DCM(5mL)和TFA(1mL),根据为24的程序制备标题化合物524(6.9mg,9.1%,收率)(黄色油)。^{1}H NMR(400MHz,CD_3OD)δ6.93(d,J=8.8Hz,1H),6.39(d,J=8.8Hz,1H),4.72(d,J=6Hz,2H),3.75-3.63(m,3H),3.50(d,J=12Hz,2H),3.33(t,J=7.4Hz,1H),3.18-3.20(m,1H),2.55-2.15(m,7H),2.01-1.81(m,5H)。质谱(m/z):314.9$[M+H]^+$。

[2864] 化合物525

[2865] N-(((1r,4r)-4-氨基环己基)甲基)-4-(3,4,5-三甲基哌嗪-1-基)苯胺

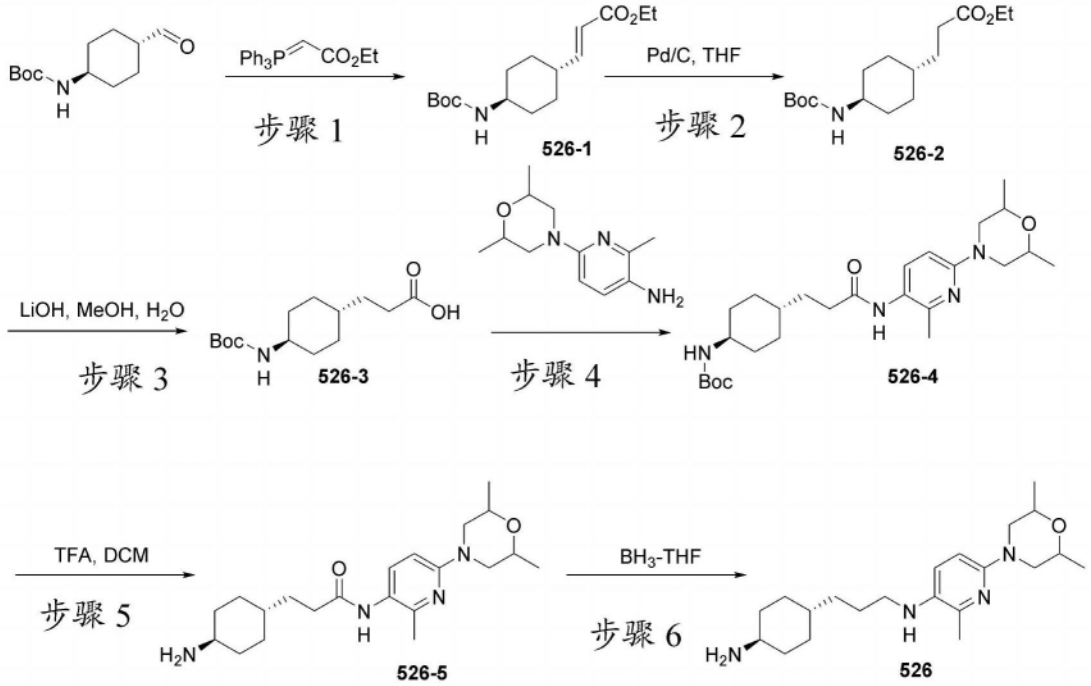
[2866] 

525

[2867] 由((1r,4r)-4-(((4-(3,4,5-三甲基哌嗪-1-基)苯基)氨基)甲基)环己基)氨基甲酸叔丁酯(0.12g,0.28mmol),DCM(5mL)和TFA(1mL),根据为24的程序制备标题化合物525(40.8mg,44.3%,收率)(黄色固体)。^{1}H NMR(400MHz,CD_3OD)δ6.86-6.76(m,2H),6.62-6.50(m,2H),3.29-3.22(m,2H),2.86(d,J=6.6Hz,2H),2.58-2.56(m,1H),2.45-2.37(m,4H),2.31(s,3H),1.94-1.82(m,4H),1.51(s,1H),1.20-0.97(m,10H)。质谱(m/z):330.9$[M+H]^+$。

[2868] 化合物526

[2869] N-(3-((1r,4s)-4-氨基环己基)丙基)-6-(2,6-二甲基吗啉代)-2-甲基吡啶-3-胺

[2870] 

[2871] 步骤1:制备(E)-3-((1r,4r)-4-((叔丁氧基羰基)氨基)环己基)丙烯酸乙酯(526-1)

[2872] 在25℃搅拌((1r,4r)-4-甲酰基环己基)氨基甲酸叔丁酯(3g,13.1mmol),2-(三苯基-15-亚膦基(phosphaneylidene)乙酸乙酯(4.56g,13.1mmol),NaH(0.38g,15.7mmol)和THF(20mL)的混合物2小时。将混合物用EA(20mL)稀释和用水(20mL×3)洗涤。浓缩有机相而得到526-1(黄色固体)(4g,72%)。质谱(m/z):319.8[M+Na]$^+$。

[2873] 步骤2:制备3-((1r,4r)-4-((叔丁氧基羰基)氨基)环己基)丙酸乙酯(526-2)

[2874] 在氢气气氛下在25℃向526-1(4g,13.4mmol)/THF(30mL)的溶液中添加湿Pd/C(1g)。在25℃搅拌反应3小时。将混合物过滤并浓缩而得到526-2(灰色油)(2g,45%)。质谱(m/z):199.9[M+H]$^+$。

[2875] 步骤3:制备3-((1r,4r)-4-((叔丁氧基羰基)氨基)环己基)丙酸(526-3)

[2876] 在25℃向526-2(2g,6.7mmol)/MeOH(20mL)的溶液中添加LiOH(0.84g,20.1mmol)。在25℃搅拌反应2小时。TLC显示SM被消耗。将混合物倒入水中并且过滤而得到526-3(白色固体)(2g,100%)。

[2877] 步骤4:制备((1r,4r)-4-(3-((6-(2,6-二甲基吗啉代)-2-甲基吡啶-3-基)氨基)-3-氧代丙基)环己基)氨基甲酸叔丁酯(526-4)

[2878] 向526-3(0.2g,0.7mmol),6-(2,6-二甲基吗啉代)-2-甲基吡啶-3-胺(0.15g,0.7mmol)和HATU(0.27g,0.7mmol)/DMF(5mL)的溶液中添加DIEA(0.27g,2.1mmol)。在25℃搅拌反应16小时。将混合物倒入水中并且过滤而得到526-4(白色固体)(0.3g,86%)。质谱(m/z):474.8[M+H]$^+$。

[2879] 步骤5:制备3-((1r,4r)-4-氨基环己基)-N-(6-(2,6-二甲基吗啉代)-2-甲基吡啶-3-基)丙酰胺(526-5)

[2880] 向526-4(0.3g,0.6mmol)/DCM(5mL)的溶液中添加TFA(1mL)。在25℃搅拌反应2小时。用Na2CO3水溶液将混合物的pH调节到8并用DCM萃取。浓缩有机相而得到526-5(棕色固

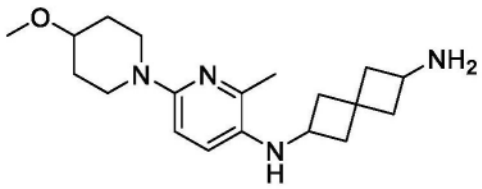
体)(0.2g,89.3%)。质谱(m/z):374.8[M+H]$^+$。

[2881] 步骤6:N-(3-((1r,4s)-4-氨基环己基)丙基)-6-(2,6-二甲基吗啉代)-2-甲基吡啶-3-胺(526)

[2882] 在25℃向526-5(0.2g,0.5mmol)/THF(1mL)的溶液中添加BH_3-THF(5mL)。在70℃搅拌反应16小时。将混合物用EA(200mL)稀释和用水(200mL×3)洗涤。浓缩有机相并且通过Prep-TLC(DCM:MeOH=10:1)提纯而得到526(12.5mg,6.5%)(白色固体)。^{1}H NMR(400MHz,CD_3OD)δ6.96(d,J=8.6Hz,1H),6.54(d,J=8.6Hz,1H),3.78-3.67(m,4H),3.02(t,J=7.2Hz,2H),2.56-2.54(m,1H),2.32-2.22(m,5H),1.80-1.78(m,4H),1.60-1.68(m,2H),1.37-0.91(m,13H)。质谱(m/z):360.9[M+H]$^+$。

[2883] 化合物527

[2884] 6-(4-甲氧基哌啶-1-基)-2-甲基-3-硝基吡啶

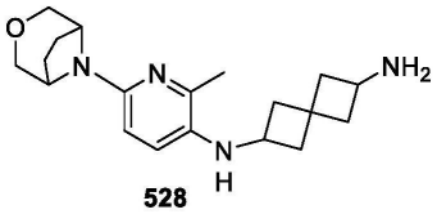
[2885] 

527

[2886] 由(6-((6-(4-甲氧基哌啶-1-基)-2-甲基吡啶-3-基)氨基)螺[3.3]庚烷-2-基)氨基甲酸叔丁酯(200mg,0.43mmol),DCM(20mL)和TFA(4mL),根据为24的程序制备标题化合物527(43mg,27.8)(白色固体)。^{1}H NMR(400MHz,CD_3OD)δ6.83(d,J=8.7Hz,1H),6.54(d,J=8.7Hz,1H),3.68(d,J=7.8Hz,3H),3.34(m,4H),2.90(t,2H),2.53-2.29(m,3H),2.24(m,4H),1.99-1.91(m,2H),1.91-1.74(m,4H),1.57(s,2H),1.28(t,J=7.9Hz,1H)。质谱(m/z):330.8[M+H]$^+$。

[2887] 化合物528

[2888] N^2-(6-(3-氧杂-8-氮杂双环[3.2.1]辛烷-8-基)-2-甲基吡啶-3-基)螺[3.3]庚烷-2,6-二胺

[2889] 

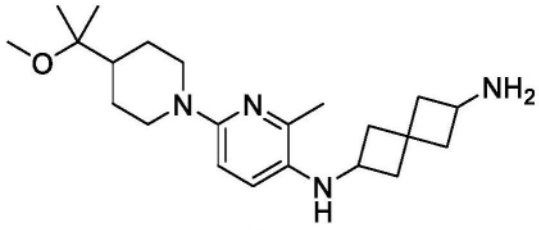
528

[2890] 由(6-((6-(3-氧杂-8-氮杂双环[3.2.1]辛烷-8-基)-2-甲基吡啶-3-基)氨基)螺[3.3]庚烷-2-基)氨基甲酸叔丁酯(150mg,0.38mmol),1,4-二氧杂环己烷(3mL)和HCl/1,4-二氧杂环己烷(1mL),根据为37的程序制备期望的产物(黄色固体)(23.2mg,16.1%,收率)。^{1}H NMR(400MHz,DMSO-d6)δ6.71(dd,J=8.7,4.0Hz,1H),6.49(d,J=8.6Hz,1H),4.45(d,J=7.3Hz,1H),4.25(s,2H),3.91-3.74(m,1H),3.63(m,3H),3.47(d,J=9.8Hz,2H),3.23-3.13(m,1H),2.42-2.22(m,3H),2.18(s,3H),2.15-2.09(m,1H),1.84(m,4H),1.74-1.63(m,3H)。质谱(m/z):328.8[M+H]$^+$。

[2891] 化合物529

[2892] N^2-(6-(4-(2-甲氧基丙-2-基)哌啶-1-基)-2-甲基吡啶-3-基)螺[3.3]-庚烷-2,

6-二胺

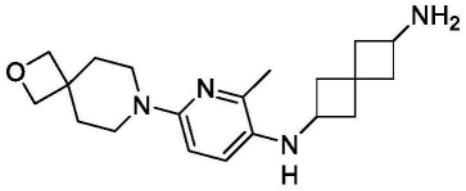
[2893] 

529

[2894] 由(6-((6-(4-(2-甲氧基丙-2-基)哌啶-1-基)-2-甲基吡啶-3-基)氨基)螺[3.3]庚烷-2-基)氨基甲酸叔丁酯(40mg,0.08mmol),DCM(10mL)和TFA(1mL),根据为24的程序制备标题化合物529(2.8mg)(黄色油)。^{1}H NMR(400MHz,CD_3OD)δ7.94(d,J=9.4Hz,1H),7.56(d,J=8.8Hz,1H),7.20(d,J=9.6Hz,1H),7.15(dd,J=8.8,2.4Hz,1H),6.93(d,J=2.4Hz,1H),4.00(d,J=13.4Hz,2H),3.52-3.40(m,2H),3.37-3.27(m,3H),1.93(d,J=13.2Hz,2H),1.72-1.59(m,2H),1.22(s,3H)。质谱(m/z):373.3[M+H]$^+$。

[2895] 化合物530

[2896] 2-N-(2-甲基-6-{2-氧杂-7-氮杂螺[3.5]壬烷-7-基}吡啶-3-基)螺[3.3]庚烷-2,6-二胺

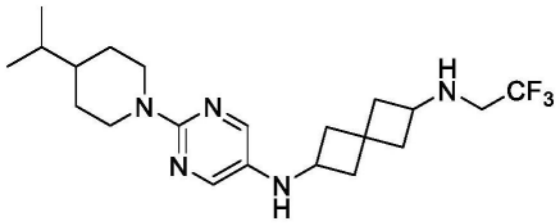
[2897] 

530

[2898] 由{6-[(2-甲基-6-{2-氧杂-7-氮杂螺[3.5]壬烷-7-基}吡啶-3-基)氨基]螺[3.3]庚烷-2-基}氨基甲酸叔丁酯(70mg,0.16mmol),DCM(5mL)和TFA(1mL),根据为24的程序制备标题化合物530(6.5mg,4.2%)(淡黄色固体)。^{1}H NMR(400MHz,DMSO-d6)δ8.30(s,1H),7.44(d,J=8.6Hz,1H),6.93(d,J=8.7Hz,1H),5.83(d,J=6.0Hz,1H),5.24(d,J=66.0Hz,1H),4.12(s,2H),3.87-3.72(m,4H),3.67(s,1H),3.50(d,J=7.6Hz,2H),3.34(s,6H),2.40(d,J=4.3Hz,1H),2.33(s,2H),2.19(d,J=3.9Hz,2H),2.12-1.93(m,3H),1.83(s,1H),1.23(s,1H)。质谱(m/z):343.1[M+H]$^+$。

[2899] 化合物531

[2900] N^2-(2-(4-异丙基哌啶-1-基)嘧啶-5-基)-N6-(2,2,2-三氟乙基)螺[3.3]庚烷-2,6-二胺

[2901] 

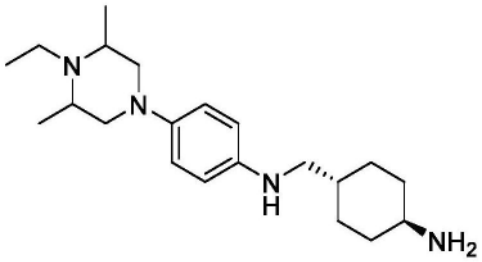
531

[2902] 由DIEA(106mg,0.82mmol),三氟甲磺酸2,2,2-三氟乙酯(127mg,0.55mmol),2-N-[2-(4-异丙基哌啶-1-基)嘧啶-5-基]螺[3.3]庚烷-2,6-二胺盐酸盐(100mg,0.27mmol)和

二氧杂环己烷(20mL),根据为414的程序制备期望的产物(3.3mg,2.9%,收率)(黄色固体)。^{1}H NMR(400MHz,CD_3OD)δ7.81(d,J=0.7Hz,2H),4.49-4.44(m,2H),3.66(t,J=7.5Hz,1H),3.21(d,J=7.5Hz,1H),3.09(d,J=9.9Hz,2H),2.74-2.67(m,2H),2.48(ddd,J=11.3,6.3,2.8Hz,1H),2.41-2.29(m,2H),2.22-2.16(m,1H),1.87-1.78(m,4H),1.73-1.68(m,2H),1.45-1.38(m,1H),1.19(m,3H),0.88(d,J=6.8Hz,6H)。质谱(m/z):412.3[M+H]$^+$。

[2903] 化合物532

[2904] N-(((1r,4r)-4-氨基环己基)甲基)-4-(4-乙基-3,5-二甲基哌嗪-1-基)苯胺

[2905] 

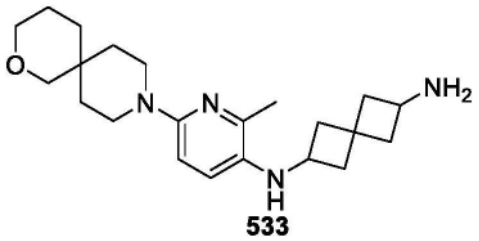
532

[2906] 由((1r,4r)-4-(((4-(4-乙基-3,5-二甲基哌嗪-1-基)苯基)氨基)甲基)环己基)氨基甲酸叔丁酯(0.12g,0.3mmol),DCM(5mL)和TFA(1mL),根据为24的程序制备标题化合物532(20mg,20%)(黄色固体)(21.1mg,18.5%)。^{1}H NMR(400MHz,CD_3OD)δ6.83(d,J=8.8Hz,2H),6.59(d,J=8.8Hz,2H),3.24(d,J=11.0Hz,2H),2.98(q,J=7.2Hz,2H),2.84-2.83(m,4H),2.78-2.66(m,1H),2.38(t,J=11.0Hz,2H),1.8

[2907] 9-1.91(m,4H),1.51-1.49(m,1H),1.25-0.91(m,13H)。质谱(m/z):345.1[M+H]$^+$。

[2908] 化合物533

[2909] N^2-(2-甲基-6-(2-氧杂-9-氮杂螺[5.5]十一烷-9-基)吡啶-3-基)螺[3.3]庚烷-2,6-二胺

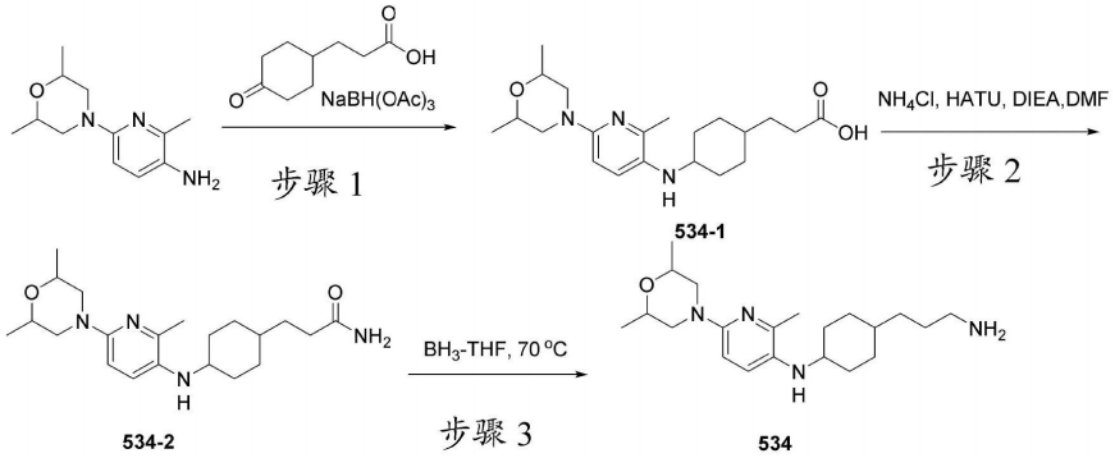
[2910] 

533

[2911] 由(6-((2-甲基-6-(2-氧杂-9-氮杂螺[5.5]十一烷-9-基)吡啶-3-基)氨基)螺[3.3]庚烷-2-基)氨基甲酸叔丁酯(200mg,0.424mmol),DCM(10mL)和TFA(1mL),根据为24的程序制备标题化合物533(51.9mg,58.3%,收率)(黄色固体)。^{1}H NMR(400MHz,CD_3OD)δ6.88(d,J=8.7Hz,1H),6.58(d,J=8.7Hz,1H),3.78-3.70(m,1H),3.67(dd,J=10.5,5.7Hz,2H),3.49(s,2H),3.30(d,J=1.1Hz,1H),3.29-3.20(m,4H),2.56-2.35(m,3H),2.29(s,3H),2.25(m,1H),1.87-1.75(m,4H),1.68-1.57(m,8H)。质谱(m/z):371.27[M+H]$^+$。

[2912] 化合物534

[2913] N-(4-(3-氨基丙基)环己基)-6-(2,6-二甲基吗啉代)-2-甲基吡啶-3-胺

[2914] 

[2915] 步骤1:制备3-(4-((6-(2,6-二甲基吗啉代)-2-甲基吡啶-3-基)氨基)环己基)丙酸(534-1)

[2916] 在25℃搅拌6-(2,6-二甲基吗啉代)-2-甲基吡啶-3-胺(500mg,2.26mmol),3-(4-氧代环己基)丙酸(384mg,2.26mmol),和$NaBH(OAc)_3$(479mg,2.26mmol)/DCE(10mL)的混合物过夜。在反应完成后,真空除去溶剂并且通过硅胶色谱提纯粗产物而得到3-(4-((6-(2,6-二甲基吗啉代)-2-甲基吡啶-3-基)氨基)环己基)丙酸(300mg,35.3%)(黄色固体)。质谱(m/z):376.1$[M+H]^+$。

[2917] 步骤2:制备3-(4-((6-(2,6-二甲基吗啉代)-2-甲基吡啶-3-基)氨基)环己基)丙酰胺(534-2)

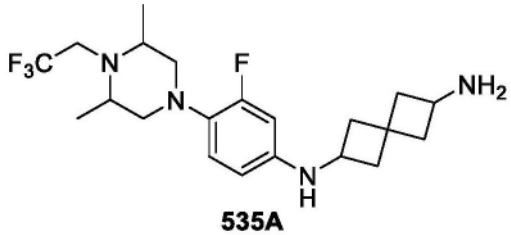
[2918] 向3-(4-((6-(2,6-二甲基吗啉代)-2-甲基吡啶-3-基)氨基)环己基)丙酸(300mg,1.1mmol),NH_4Cl(70mg,1.3mmol),HATU(621mg,1.6mmol)和DIEA(281mg,2.2mmol)/DMF(10mL)的溶液中。在室温搅拌反应18小时。将固体过滤并且将溶剂真空除去。残余物的提纯方法为:硅胶柱而得到200mg的3-(4-((6-(2,6-二甲基吗啉代)-2-甲基吡啶-3-基)氨基)环己基)丙酰胺(黄色固体)。质谱(m/z):375.1$[M+H]^+$。

[2919] 步骤3:制备N-(4-(3-氨基丙基)环己基)-6-(2,6-二甲基吗啉代)-2-甲基吡啶-3-胺(534)

[2920] 向3-(4-((6-(2,6-二甲基吗啉代)-2-甲基吡啶-3-基)氨基)环己基)丙酰胺(200mg,0.53mmol),BH_3-THF(10mL)/THF(5mL)的溶液中。在70℃搅拌反应18小时。将固体过滤并且将溶剂真空除去。残余物的提纯方法为:prep-HPLC(柱-Xbridge-C18 150x 19mm,5um;移动相:ACN-H_2O(0.1%FA),25%-40%)而得到534(8.0mg)(白色固体)。^1H NMR(400MHz,DMSO-d6)δ6.86(d,J=8.8Hz,1H),6.50-6.46(m,1H),3.83-3.78(m,3H),3.61-3.54(m,2H),2.85(d,J=5.8Hz,1H),2.61(dd,J=3.8,1.8Hz,1H),2.51-2.48(m,1H),2.20(s,3H),2.17-2.13(m,1H),2.12(d,J=1.6Hz,1H),2.09(d,J=3.2Hz,0H),1.56-1.28(m,10H),1.25-1.18(m,3H),1.10(d,J=6.2Hz,6H)。质谱(m/z):361.3$[M+H]^+$。

[2921] 化合物535

[2922] N^2-(4-(3,5-二甲基-4-(2,2,2-三氟乙基)哌嗪-1-基)-3-氟苯基)螺-[3.3]庚烷-2,6-二胺

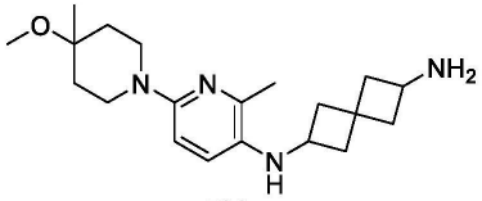
[2923] 

535A
535B

[2924] 由(6-((4-(3,5-二甲基-4-(2,2,2-三氟乙基)哌嗪-1-基)-3-氟-苯基)氨基)螺[3.3]庚烷-2-基)氨基甲酸叔丁酯(150mg,0.29mmol),DCM(10mL)和TFA(1mL),根据为24的程序制备标题化合物535A(5.4mg)(白色固体)和化合物535B(5.8mg)(白色固体)。535A:^{1}H NMR(400MHz,DMSO-d6)δ6.81(t,J=8.8Hz,1H),6.31-6.26(m,2H),3.76-3.59(m,2H),3.34(q,J=9.8Hz,2H),3.03(dd,J=8.6,2.2Hz,2H),2.93(d,J=6.2Hz,2H),2.54-2.30(m,6H),2.20-2.09(m,2H),1.94-1.86(m,2H),1.11(d,J=6.2Hz,6H)。质谱(m/z):415.3[M+H]$^+$。HPLC:Rt:3.919min(柱:XBRIDGE 2.1*50mm,3.5um;移动相:H_2O(0.05%TFA)ACN(0.05%TFA)/ACN由0%至60%在7分钟内,7-8min,ACN由60%至100%;0.8mL/min)。535B:^{1}H NMR(400MHz,DMSO-d6)δ6.82(d,J=8.6Hz,1H),6.32-6.21(m,2H),3.68(d,J=32.8Hz,2H),3.34(d,J=10.0Hz,2H),3.09-3.00(m,2H),2.94(dd,J=14.2,13.6Hz,2H),2.61-2.48(m,2H),2.40(t,J=10.8Hz,4H),2.14(s,2H),1.96-1.78(m,2H),1.11(d,J=6.2Hz,6H)。HPLC:Rt:3.921min(柱:XBRIDGE 2.1*50mm,3.5um;移动相:H_2O(0.05%TFA)/ACN(0.05%TFA),ACN由0%至60%在7分钟内,7-8min,ACN由60%至100%;0.8mL/min)。

[2925] 化合物536

[2926] N^2-(6-(4-甲氧基-4-甲基哌啶-1-基)-2-甲基吡啶-3-基)螺[3.3]庚烷-2,6-二胺

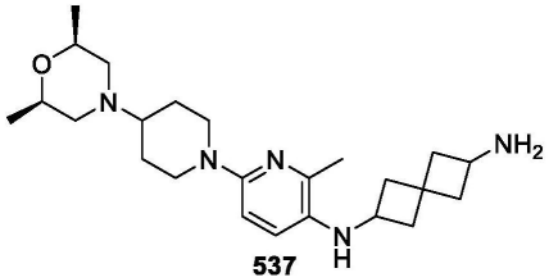
[2927] 

536

[2928] 由(6-((6-(4-甲氧基-4-甲基哌啶-1-基)-2-甲基吡啶-3-基)氨基)螺[3.3]庚烷-2-基)氨基甲酸叔丁酯(68mg,0.153mmol),TFA(1mL)和DCM(10mL),根据为24的程序制备标题化合物536(25.0mg),总收率为47.3%(黄色固体)。^{1}H NMR(400MHz,DMSO-d6)δ8.41(s,3H),7.20-6.71(m,2H),4.86(s,1H),3.75-3.42(m,5H),3.12(s,5H),2.43-2.15(m,8H),1.97(s,2H),1.73(d,J=13.6Hz,2H),1.53(s,2H),1.12(s,3H)。质谱(m/z):345.3[M+H]$^+$。

[2929] 化合物537

[2930] N^2-(6-(4-((2S,6R)-2,6-二甲基吗啉代)哌啶-1-基)-2-甲基吡啶-3-基)螺[3.3]庚烷-2,6-二胺

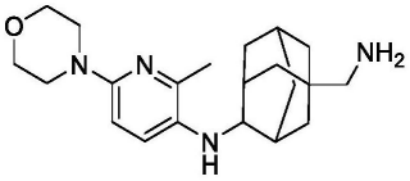
[2931] 

537

[2932] 由(6-((6-(4-((2S,6R)-2,6-二甲基吗啉代)哌啶-1-基)-2-甲基吡啶-3-基)氨基)螺[3.3]庚烷-2-基)氨基甲酸叔丁酯(50mg,0.097mmol),TFA(1mL),和DCM(10mL),根据为24的程序制备标题化合物537(17.6mg),总收率为43.7%(黄色固体)。^{1}H NMR(400MHz,DMSO-d6)δ8.74-8.35(m,5H),6.73(d,J=8.8Hz,1H),6.56(d,J=8.8Hz,1H),4.59(s,1H),4.27-3.94(m,4H),3.68-3.46(m,3H),3.19-3.07(m,3H),2.56(d,J=12.0Hz,2H),2.45(ddt,J=9.2,5.2,1.6Hz,4H),2.39-2.31(m,2H),2.28-2.10(m,8H),1.91(td,J=11.2,10.4,5.2Hz,2H),1.70(s,2H),1.12(d,J=6.4Hz,6H)。质谱(m/z):434.3[M+H]$^+$。

[2933] 化合物538

[2934] N-((2r,5s)-5-(氨基甲基)金刚烷-2-基)-2-甲基-6-吗啉代吡啶-3-胺

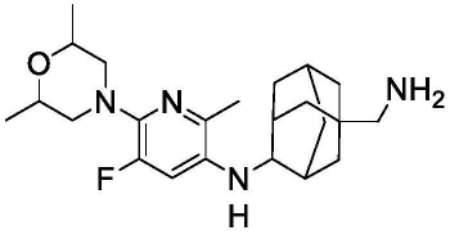
[2935] 

538 A
538 B

[2936] 由2-甲基-6-吗啉代吡啶-3-胺(200mg,1.03mmol)和4-氧代金刚烷-1-甲酸(301mg,1.55mmol),根据为84的程序制备标题化合物538A(Rt=9.41min;7.8mg),两步的总收率为6.5%(白色粉末)和制备化合物538B(Rt=10.48min;3.1mg),两步的总收率为2.5%(白色粉末),其提纯方法为:Prep-HPLC(柱:X Select-CSH-Prep 5μm OBD,19*150mm;ACN/水(0.5%TFA)=0%-0%-30%-95%-95%-0%,0min-2min-12min-12.5min-13.5min-15.0min)。538A:^{1}H NMR(400MHz,DMSO-d6)δ6.86(d,J=8.8Hz,1H),6.52(d,J=8.7Hz,1H),3.86(d,J=6.3Hz,1H),3.68(t,J=4.8Hz,4H),3.18(t,J=4.8Hz,4H),2.28(s,3H),2.22(s,2H),1.96(d,J=13.4Hz,4H),1.87(s,1H),1.51(s,4H),1.42(d,J=3.1Hz,2H),1.35(d,J=12.1Hz,2H)。质谱(m/z):357.3[M+H]$^+$。538B:^{1}H NMR(400MHz,DMSO-d6)δ6.91(dd,J=8.8,3.6Hz,1H),6.53(d,J=8.7Hz,1H),3.76(d,J=6.9Hz,1H),3.72-3.63(m,4H),3.19(t,J=4.8Hz,4H),2.27(d,J=2.3Hz,3H),2.20(s,2H),1.95(d,J=21.2Hz,3H),1.72(q,J=14.8,13.7Hz,6H),1.48-1.37(m,2H),1.28-1.13(m,3H)。质谱(m/z):357.3[M+H]$^+$。

[2937] 化合物539

[2938] N-((2r,5s)-5-(氨基甲基)金刚烷-2-基)-6-(2,6-二甲基吗啉代)-5-氟-2-甲基吡啶-3-胺

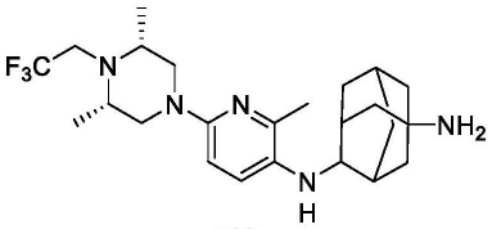
[2939] 

539A
539B

[2940] 由6-(2,6-二甲基吗啉代)-5-氟-2-甲基吡啶-3-胺(70mg,0.29mmol)和4-氧代金刚烷-1-甲酸(85mg,0.44mmol),根据为84的程序制备标题化合物539A(Rt＝6.04min;2.1mg),两步的总收率为2.7％(白色粉末)和制备化合物539B(Rt＝6.82min;1.1mg),两步的总收率为1.4％(白色粉末)。目标产物的提纯方法:Prep-HPLC(柱:X Select-CSH-Prep 5μm OBD,19*150mm;ACN/水(0.5％TFA)＝15％-45％-95％-95％-10％,0min-7min-7.5min-8.5min-10.0min)。539A:^{1}H NMR(400MHz,DMSO-d6)δ6.79(d,J＝14.6Hz,1H),4.21(d,J＝6.0Hz,1H),3.74-3.63(m,2H),2.36(d,J＝2.0Hz,2H),2.29-2.24(m,5H),2.02-1.85(m,5H),1.55(q,J＝12.2Hz,4H),1.45(d,J＝2.8Hz,2H),1.38(d,J＝12.2Hz,2H),1.11(d,J＝6.2Hz,6H)。质谱(m/z):403.5[M+H]$^+$。539B:^{1}H NMR(400MHz,DMSO-d6)δ6.82(dd,J＝14.6,6.4Hz,1H),6.66(s,1H),4.06(d,J＝6.4Hz,1H),3.73-3.61(m,2H),3.37(s,3H),2.38-2.33(m,2H),2.25(d,J＝1.1Hz,3H),2.18(s,1H),2.02-1.94(m,5H),1.91(s,1H),1.78(d,J＝13.2Hz,2H),1.71-1.61(m,4H),1.44(t,J＝6.8Hz,2H),1.39(s,2H),1.17(s,1H),1.09(d,J＝6.3Hz,6H),0.86-0.80(m,2H)。质谱(m/z):403.5[M+H]$^+$。

[2941] 化合物540

[2942] N^4-(6-((3R,5S)-3,5-二甲基-4-(2,2,2-三氟乙基)哌嗪-1-基)-2-甲基吡啶-3-基)金刚烷-1,4-二胺

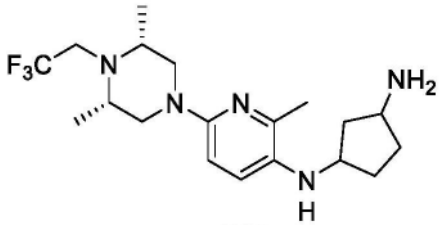
[2943] 

540

[2944] 由6-((3R,5S)-3,5-二甲基-4-(2,2,2-三氟乙基)哌嗪-1-基)-2-甲基吡啶-3-胺(42mg,0.14mmol)和(4-氧代金刚烷-1-基)氨基甲酸叔丁酯(44mg,0.17mmol),根据为20的程序制备标题化合物540(33.0mg),收率为52.6％(白色粉末)。^{1}H NMR(400MHz,DMSO-d6)δ8.08(d,J＝34.9Hz,3H),6.98(s,1H),6.62(s,1H),3.86(d,J＝12.1Hz,2H),3.39(d,J＝10.8Hz,3H),2.76(s,2H),2.36(s,4H),2.12(d,J＝22.3Hz,3H),2.01(d,J＝22.0Hz,2H),1.96-1.84(m,3H),1.79(d,J＝16.9Hz,3H),1.68(d,J＝12.7Hz,1H),1.55(d,J＝11.3Hz,1H),1.36(d,J＝12.5Hz,1H),1.10(d,J＝6.2Hz,6H)。质谱(m/z):451.7[M+H]$^+$。

[2945] 化合物541

[2946] N^1-(6-((3R,5S)-3,5-二甲基-4-(2,2,2-三氟乙基)哌嗪-1-基)-2-甲基吡啶-3-基)环戊烷-1,3-二胺

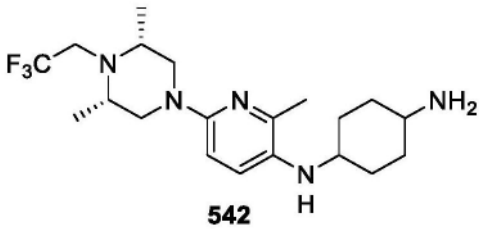
[2947] 

541

[2948] 由6-((3R,5S)-3,5-二甲基-4-(2,2,2-三氟乙基)哌嗪-1-基)-2-甲基吡啶-3-胺(42mg,0.14mmol)和(3-氧代环戊基)氨基甲酸叔丁酯(42mg,0.21mmol),根据为20的程序制备标题化合物541(31.4mg),收率为57.89%(白色粉末)。^{1}H NMR(400MHz,DMSO-d6)δ8.20(d,J=29.6Hz,3H),7.01(s,1H),6.67(s,1H),4.47(s,1H),3.88(s,3H),3.64(t,J=53.5Hz,4H),2.76(s,2H),2.43-2.23(m,4H),2.10(d,J=15.5Hz,1H),2.02-1.71(m,3H),1.69-1.45(m,1H),1.10(d,J=6.2Hz,6H)。质谱(m/z):386.3[M+H]$^+$。

[2949] 化合物542

[2950] N^1-(6-((3R,5S)-3,5-二甲基-4-(2,2,2-三氟乙基)哌嗪-1-基)-2-甲基吡啶-3-基)环己烷-1,4-二胺

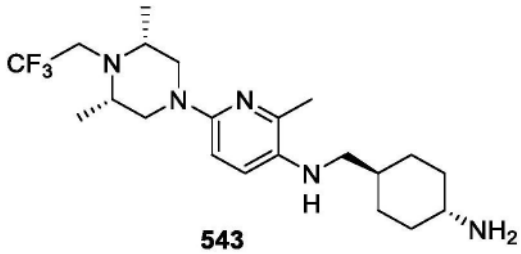
[2951] 

542

[2952] 由6-((3R,5S)-3,5-二甲基-4-(2,2,2-三氟乙基)哌嗪-1-基)-2-甲基吡啶-3-胺(44mg,0.21mmol)和(4-氧代环己基)氨基甲酸叔丁酯(42mg,0.21mmol),根据为20的程序制备标题化合物542(38.4mg),收率为69.19%(白色粉末)。^{1}H NMR(400MHz,DMSO-d6)δ8.41-8.21(m,3H),7.04(s,1H),6.65(s,1H),3.88(d,J=12.9Hz,2H),3.43(d,J=24.3Hz,1H),3.11(s,1H),2.92(s,1H),2.75(s,2H),2.35(s,5H),1.99(s,2H),1.75(d,J=26.4Hz,3H),1.60(s,1H),1.44(d,J=11.9Hz,1H),1.09(d,J=6.2Hz,6H)。质谱(m/z):400.4[M+H]$^+$。

[2953] 化合物543

[2954] N-(((1r,4R)-4-氨基环己基)甲基)-6-((3R,5S)-3,5-二甲基-4-(2,2,2-三氟乙基)哌嗪-1-基)-2-甲基吡啶-3-胺

[2955] 

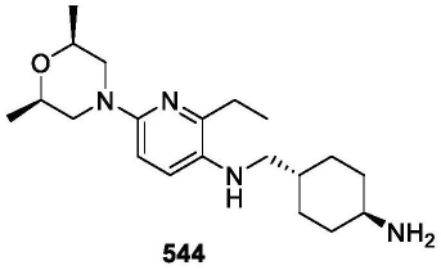
543

[2956] 由6-((3R,5S)-3,5-二甲基-4-(2,2,2-三氟乙基)哌嗪-1-基)-2-甲基吡啶-3-胺(44mg,0.21mmol)和((1r,4r)-4-甲酰基环己基)氨基甲酸叔丁酯(47mg,0.21mmol),根据为24的程序制备标题化合物543(32.3mg),收率为56.2%(白色粉末)。^{1}H NMR(400MHz,DMSO-d6)δ8.03(s,3H),6.94(s,1H),6.63(s,1H),4.57(s,1H),3.82(s,2H),2.99-2.69(m,6H),2.42-2.19(m,5H),1.89(dd,J=27.9,15.3Hz,4H),1.49(s,1H),1.35-1.21(m,2H),1.08(d,

J＝6.0Hz,6H),0.98(d,J＝12.9Hz,2H)。质谱(m/z):414.7[M+H]$^+$。

[2957] 化合物544

[2958] N-(((1r,4R)-4-氨基环已基)甲基)-6-((2S,6R)-2,6-二甲基吗啉代)-2-乙基吡啶-3-胺

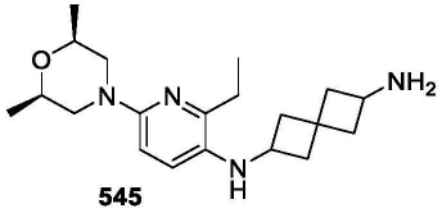
[2959] 

544

[2960] 根据为化合物24的程序制备标题化合物544(30.9mg),总收率为28.3%(紫色固体)。^{1}H NMR(400MHz,DMSO-d6)δ8.10(s,3H),6.88(br,1H),6.53(br,1H),4.66-4.29(m,1H),3.98-3.72(m,2H),3.71-3.55(m,2H),2.96-2.82(m,2H),2.26-2.10(m,2H),2.03-1.91(m,2H),1.89-1.80(m,2H),1.57-1.43(m,1H),1.35-1.25(m,2H),1.18-1.10(m,9H),1.05-0.92(m,2H)。质谱(m/z):347.2[M+H]$^+$。

[2961] 化合物545

[2962] N^2-(6-((2S,6R)-2,6-二甲基吗啉代)-2-乙基吡啶-3-基)螺[3.3]庚烷-2,6-二胺

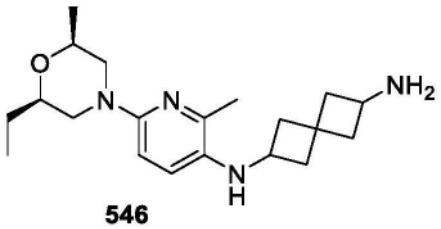
[2963] 

545

[2964] 根据为化合物24的程序制备标题化合物545(16.4mg),总收率为31.8%(黄色固体)。^{1}H NMR(400MHz,DMSO-d6)δ8.14(d,J＝5.2Hz,3H),6.76(br,1H),6.51(br,1H),4.72-4.43(m,1H),3.94-3.78(m,2H),3.70-3.48(m,5H),2.62-2.53(m,2H),2.43-2.33(m,2H),2.22-2.13(m,4H),1.97-1.85(m,2H),1.17-1.12(m,9H)。质谱(m/z):345.2[M+H]$^+$。

[2965] 化合物546

[2966] N^2-(6-((2R,6S)-2-乙基-6-甲基吗啉代)-2-甲基吡啶-3-基)螺[3.3]庚烷-2,6-二胺

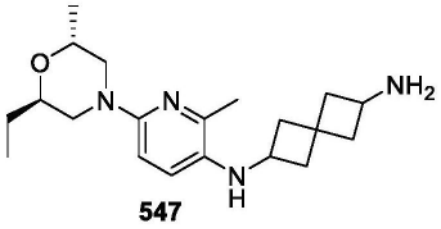
[2967] 

546

[2968] 根据为化合物24的程序制备标题化合物546(12.3mg),总收率为52.8%(淡黄色固体)。^{1}H NMR(400MHz,DMSO-d6)δ7.98(s,3H),6.80-6.66(m,1H),6.56-6.46(m,1H),4.61-4.49(m,1H),4.41-4.31(m,1H),3.88-3.78(m,2H),3.67-3.52(m,4H),2.29-2.07(m,8H),2.01-1.83(m,2H),1.53-1.43(m,2H),1.14(d,J＝6.1Hz,3H),0.94(d,J＝7.4Hz,3H)。质谱(m/z):345.3[M+H]$^+$。

[2969] 化合物547

[2970] N^2-(6-((2R,6R)-2-乙基-6-甲基吗啉代)-2-甲基吡啶-3-基)螺[3.3]庚烷-2,6-二胺

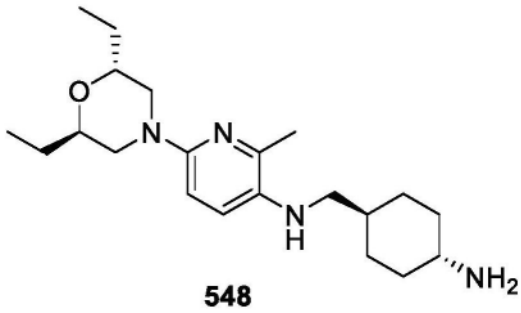
[2971] 

547

[2972] 根据为化合物24的程序制备标题化合物547(13.9mg),总收率为63.5%(淡黄色固体)。^{1}H NMR(400MHz,DMSO-d6)δ7.86(s,3H),6.72(d,J=8.7Hz,1H),6.48(d,J=8.7Hz,1H),3.97-3.87(m,1H),3.72-3.67(m,1H),3.66-3.60(m,1H),3.58-3.52(m,1H),3.40-3.37(m,1H),3.21(dd,J=12.2,3.5Hz,1H),3.05(dd,J=12.2,5.5Hz,1H),2.82(dd,J=12.1,6.6Hz,1H),2.45-2.34(m,2H),2.26-2.04(m,7H),1.94-1.85(m,2H),1.69-1.59(m,2H),1.53-1.43(m,1H),1.16(d,J=6.4Hz,3H),0.88(t,J=7.4Hz,3H)。质谱(m/z):345.3[M+H]$^+$。

[2973] 化合物548

[2974] N-(((1r,4R)-4-氨基环己基)甲基)-6-((2R,6R)-2,6-二乙基吗啉代)-2-甲基吡啶-3-胺

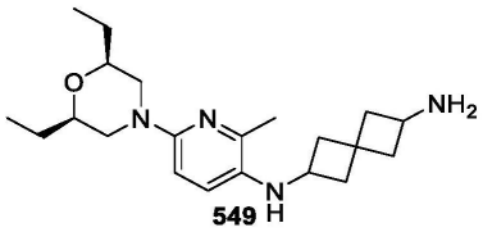
[2975] 

548

[2976] 根据为化合物24的程序制备标题化合物548(13.6mg),总收率为37.8%(淡黄色固体)。^{1}H NMR(400MHz,DMSO-d6)δ7.92(s,3H),6.82(d,J=8.8Hz,1H),6.50(d,J=8.7Hz,1H),4.48-4.37(m,1H),3.67-3.61(m,1H),3.28(dd,J=12.0,3.3Hz,2H),2.96(dd,J=12.2,6.0Hz,2H),2.87-2.79(m,2H),2.21(s,3H),1.98-1.92(m,2H),1.89-1.81(m,2H),1.68-1.60(m,2H),1.51-1.44(m,2H),1.28-1.22(m,2H),1.04-0.96(m,2H),0.90(t,J=7.4Hz,6H)。质谱(m/z):361.3[M+H]$^+$。

[2977] 化合物549

[2978] N^2-(6-((2S,6R)-2,6-二乙基吗啉代)-2-甲基吡啶-3-基)螺[3.3]庚烷-2,6-二胺

[2979] 

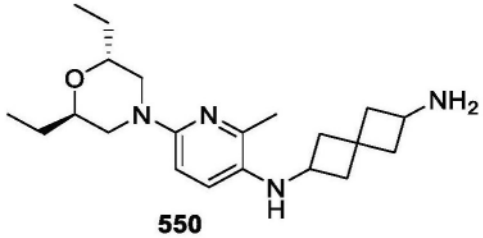
549

[2980] 根据为化合物24的程序制备标题化合物549(13.6mg),总收率为66.3%(淡黄色固

体)。^{1}H NMR(400MHz,甲醇-d4)δ6.90(d,J=8.8Hz,1H),6.56(d,J=8.5Hz,1H),3.81-3.75(m,2H),3.51-3.43(m,2H),2.65-2.45(m,4H),2.43-2.25(m,7H),2.21-2.14(m,2H),2.05-1.97(m,2H),1.62-1.52(m,4H),1.02(t,J=7.4Hz,6H)。质谱(m/z):359.2[M+H]$^+$。

[2981] 化合物550

[2982] N^2-(6-((2R,6R)-2,6-二乙基吗啉代)-2-甲基吡啶-3-基)螺[3.3]庚烷-2,6-二胺

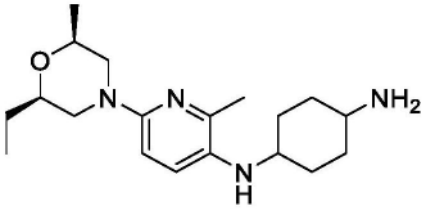
[2983] 

550

[2984] 根据为化合物24的程序制备标题化合物550(13.8mg),总收率为38.5%(淡黄色固体)。^{1}H NMR(400MHz,甲醇-d4)δ6.92(d,J=6.8Hz,1H),6.55(d,J=14.7Hz,1H),3.83-3.72(m,2H),3.41-3.33(m,2H),3.07-2.96(m,2H),2.68-2.52(m,2H),2.50-2.13(m,9H),2.05-1.95(m,2H),1.83-1.69(m,2H),1.58-1.48(m,2H),0.98(t,J=7.5Hz,6H)。质谱(m/z):359.2[M+H]$^+$。

[2985] 化合物551

[2986] N^1-(6-((2R,6S)-2-乙基-6-甲基吗啉代)-2-甲基吡啶-3-基)环己烷-1,4-二胺

[2987] 

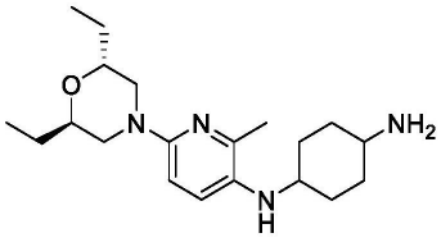
551A

551B

[2988] 根据为化合物24的程序制备标题化合物551A和551B。粗制残余物的提纯方法为:制备TLC(H_2O:MeOH:二氯甲烷=0.1:1:5)而得到化合物551A,收率为26.1%(淡黄色固体)和551B,收率为37.0%(淡黄色固体)。551A:^{1}H NMR(400MHz,甲醇-d4)δ7.04(d,J=8.7Hz,1H),6.57(d,J=8.8Hz,1H),3.83-3.78(m,2H),3.73-3.69(m,2H),3.57-3.53(m,2H),2.34(s,3H),2.31-2.27(m,2H),2.06-1.98(m,4H),1.81-1.75(m,4H),1.61-1.58(m,2H),1.22(d,J=6.2Hz,3H),1.01(t,J=7.4Hz,3H)。质谱(m/z):333.3[M+H]$^+$。HPLC:Rt=2.846mins(Agilent,poroshell 120,SB-C18 2.7μm,4.6x50mm,ACN/水(0.1%FA)=5%-5%-95%-95%-95%-5%,0min-0.5min-10min-10.5min-12.0min)551B:^{1}H NMR(400MHz,甲醇-d4)δ7.06(d,J=10.3Hz,1H),6.59(d,J=9.3Hz,2H),3.86-3.67(m,3H),3.64-3.56(m,1H),3.53-3.48(m,1H),3.24-3.07(m,3H),2.29(s,3H),2.17-2.01(m,4H),1.62-1.49(m,4H),1.37-1.31(m,2H),1.22(d,J=3.6Hz,3H),1.07-0.95(m,3H)。质谱(m/z):333.3[M+H]$^+$。HPLC:Rt=2.607mins(Agilent,poroshell 120,SB-C18 2.7μm,4.6x50mm,ACN/水(0.1%FA)=5%-5%-95%-95%-95%-5%,0min-0.5min-10min-10.5min-12.0min)。

[2989] 化合物552

[2990] N^1-(6-((2R,6R)-2,6-二乙基吗啉代)-2-甲基吡啶-3-基)环己烷-1,4-二胺

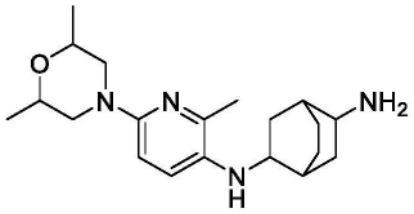
[2991] 

552A
552B

[2992] 根据为化合物24的程序制备标题化合物552A和552B。粗制残余物的提纯方法为：制备TLC(H_2O:MeOH:二氯甲烷＝0.1:1:5)而得到化合物552A,收率14.4％(淡黄色固体)和552B,收率23.3％(淡黄色固体)。552A:^{1}H NMR(400MHz,甲醇-d4)δ7.04(d,J＝8.7Hz,1H),6.57(d,J＝8.6Hz,1H),4.22-4.11(m,1H),3.84-3.77(m,2H),3.57-3.52(m,1H),3.51-3.44(m,2H),3.27-3.19(m,2H),2.34(s,3H),1.90-1.71(m,8H),1.61-1.51(m,4H),1.06-0.98(m,6H)。质谱(m/z):333.3[M+H]$^+$。HPLC:Rt＝3.329mins(Agilent,poroshell 120,SB-C18 2.7μm,4.6x50mm,ACN/水(0.1％FA)＝5％-5％-95％-95％-95％-5％,0min-0.5min-10min-10.5min-12.0min)。552B:^{1}H NMR(400MHz,甲醇-d4)δ7.03(br,^{1}H),6.56(br,^{1}H),4.26-4.10(m,1H),3.90-3.72(m,2H),3.53-3.41(m,2H),3.24-3.07(m,3H),2.29(s,3H),2.18-2.02(m,4H),1.64-1.47(m,6H),1.41-1.30(m,2H),1.09-0.94(m,6H)。质谱(m/z):333.3[M+H]$^+$。HPLC:Rt＝3.195mins(Agilent,poroshell 120,SB-C18 2.7μm,4.6x50mm,ACN/水(0.1％FA)＝5％-5％-95％-95％-95％-5％,0min-0.5min-10min-10.5min-12.0min)。

[2993] 化合物553

[2994] N^2-(6-(2,6-二甲基吗啉代)-2-甲基吡啶-3-基)双环[2.2.2]辛烷-2,5-二胺

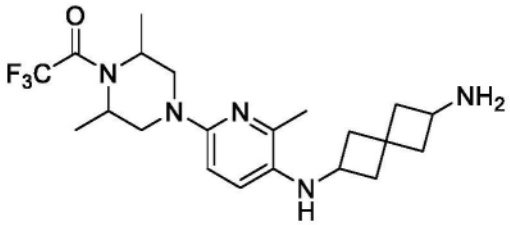
[2995] 

553

[2996] 根据为化合物24的程序制备标题化合物553(44.0mg),总收率为51.2％(白色固体)。^{1}H NMR(400MHz,DMSO-d6)δ6.84(d,J＝8.8Hz,1H),6.51(d,J＝8.8Hz,1H),4.16(m,1H),3.95-3.77(m,2H),3.67-3.54(m,2H),3.25(m,1H),2.40-2.30(m,2H),2.25(s,3H),2.21-2.13(m,2H),2.08-1.95(m,2H),1.86-1.63(m,3H),1.52-1.27(m,3H),1.12(d,J＝6.0Hz,6H)。质谱(m/z):345.3[M+H]$^+$。

[2997] 化合物554

[2998] 1-(4-(5-((6-氨基螺[3.3]庚烷-2-基)氨基)-6-甲基吡啶-2-基)-2,6-二甲基哌嗪-1-基)-2,2,2-三氟乙-1-酮

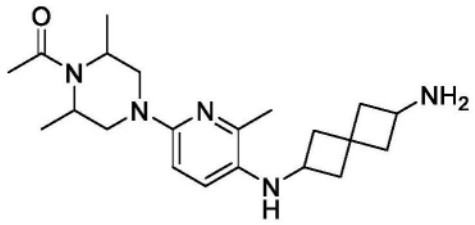
[2999] 

554

[3000] 由(6-((6-(3,5-二甲基-4-(2,2,2-三氟乙酰基)哌嗪-1-基)-2-甲基吡啶-3-基)氨基)螺[3.3]庚烷-2-基)氨基甲酸叔丁酯(0.1g,0.2mmol),DCM(5mL)和TFA(1mL),根据为24的程序制备标题化合物554(黄色固体)(23mg,28.5%,收率)。^{1}H NMR(400MHz,CD_3OD)δ6.86(d,J=8.6Hz,1H),6.60(d,J=8.6Hz,1H),4.59(s,1H),4.27(s,1H),3.92(d,J=11.6Hz,2H),3.71-3.73(m,1H),3.47-3.49(m,1H),2.82-2.84(m,2H),2.59-2.35(m,3H),2.33-2.25(m,4H),1.97-1.99(m,4H),1.43(d,J=22.2Hz,6H)。质谱(m/z):425.7[M+H]+。

[3001] 化合物555

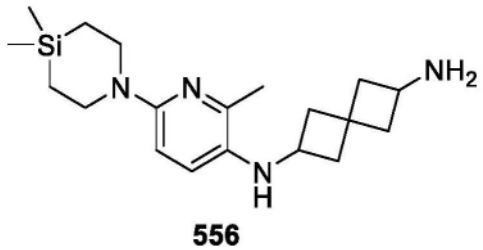
[3002] 1-(4-(5-((6-氨基螺[3.3]庚烷-2-基)氨基)-6-甲基吡啶-2-基)-2,6-二甲基哌嗪-1-基)乙-1-酮

[3003] 

[3004] 由(6-((6-(4-乙酰基-3,5-二甲基哌嗪-1-基)-2-甲基吡啶-3-基)氨基)螺[3.3]庚烷-2-基)氨基甲酸叔丁酯(56.6mg,0.12mmol),TFA,根据为化合物24的程序制备标题化合物555(34.8mg),总收率为77.9%(黄色固体)。^{1}H NMR(400MHz,DMSO-d6)δ6.77(d,J=8.4Hz,1H),6.60(d,J=8.4Hz,1H),4.78-4.26(m,2H),3.95-3.81(m,2H),3.65(m,1H),3.54(m,1H),2.75-2.60(m,2H),2.44-2.28(m,2H),2.22(s,3H),2.20-2.13(m,4H),2.04(s,3H),1.97-1.85(m,2H),1.22(d,J=6.4Hz,6H).Mass(m/z):372.2$[M+H]^+$。

[3005] 化合物556

[3006] N^2-(6-(4,4-二甲基-1,4-氮杂硅杂环己烷-1-基)-2-甲基吡啶-3-基)螺[3.3]庚烷-2,6-二胺

[3007] 

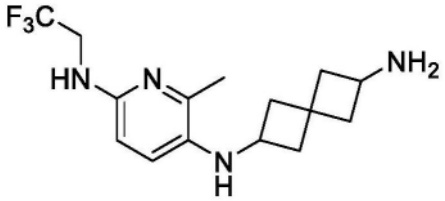
556

[3008] 由(6-((6-(4,4-二甲基-1,4-氮杂硅杂环己烷-1-基)-2-甲基吡啶-3-基)氨基)螺[3.3]庚烷-2-基)氨基甲酸叔丁酯(95mg,0.21mmol),HCl/二氧杂环己烷(5mL)和DCM(5mL),根据为37的程序制备标题化合物556(17.4mg,24%)(黄色固体)。^{1}H NMR(400MHz,CD_3OD)δ6.88(d,J=8.8Hz,1H),6.53(d,J=8.7Hz,1H),3.82-3.64(m,5H),3.55-3.45(m,1H),2.60-

2.46(m,2H),2.43-2.37(m,1H),2.33-2.22(m,4H),2.07-1.91(m,4H),0.79-0.71(m,4H),0.07(s,6H)。质谱(m/z):345.3[M+H]$^+$。

[3009] 化合物557

[3010] N5-(6-氨基螺[3.3]庚烷-2-基)-6-甲基-N^2-(2,2,2-三氟乙基)吡啶-2,5-二胺

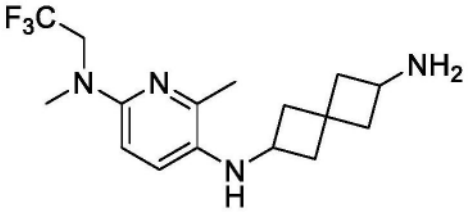
[3011] 

557

[3012] 由(5-((6-((叔丁氧基羰基)氨基)螺[3.3]庚烷-2-基)氨基)-6-甲基吡啶-2-基)(2,2,2-三氟乙基)氨基甲酸叔丁酯(129mg,0.2502mmol),DCM(10mL)和TFA(1mL),根据为24的程序制备标题化合物557(22.2mg,28.2%)(白色固体)。^{1}H NMR(400MHz,CD_3OD)δ6.88(d,J=8.7Hz,1H),6.41(d,J=8.5Hz,1H),3.99(q,J=9.5Hz,2H),3.70(t,J=7.6Hz,1H),3.29(d,J=8.4Hz,1H),2.56-2.42(m,2H),2.36(ddd,J=11.6,6.8,5.1Hz,1H),2.27(s,3H),2.27-2.23(m,1H),1.96-1.78(m,4H)。质谱(m/z):315.1[M+H]$^+$。

[3013] 化合物558

[3014] N5-(6-氨基螺[3.3]庚烷-2-基)-N2,6-二甲基-N^2-(2,2,2-三氟乙基)吡啶-2,5-二胺

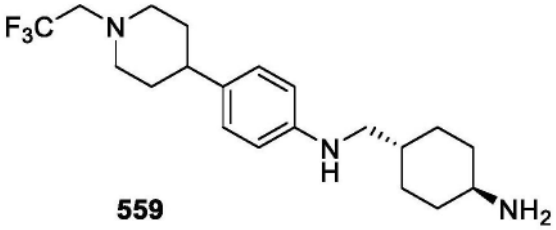
[3015] 

558

[3016] 由(6-((2-甲基-6-(甲基(2,2,2-三氟乙基)氨基)吡啶-3-基)氨基)螺[3.3]庚烷-2-基)氨基甲酸叔丁酯(165mg,0.3851mmol),DCM(10mL)和TFA(1mL),根据为24的程序制备标题化合物558(13.1mg,9.8%)(黄色固体)。^{1}H NMR(400MHz,CD_3OD)δ6.92(d,J=8.7Hz,1H),6.47(d,J=8.7Hz,1H),4.29(q,J=9.5Hz,2H),3.72(p,J=7.6Hz,1H),3.32-3.28(m,1H),3.03(s,3H),2.58-2.42(m,2H),2.37(ddd,J=11.7,6.9,5.0Hz,1H),2.29(s,3H),2.28-2.23(m,1H),1.97-1.78(m,4H)。质谱(m/z):329.3[M+H]$^+$。

[3017] 化合物559

[3018] N-(((1r,4r)-4-氨基环己基)甲基)-4-(1-(2,2,2-三氟乙基)哌啶-4-基)苯胺

[3019] 

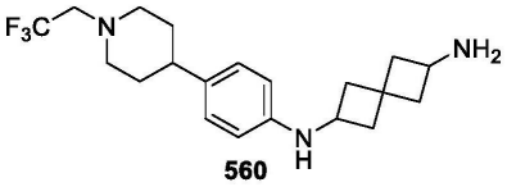
559

[3020] 由((1r,4r)-4-(((4-(1-(2,2,2-三氟乙基)哌啶-4-基)苯基)氨基)甲基)环己基)氨基甲酸叔丁酯(127mg,0.27mmol)和HCl/二氧杂环己烷(5mL)和DCM(5mL),根据为37的程

序制备标题化合物559(75.1mg,75%)(白色固体)。^{1}H NMR(400MHz,CD_3OD)δ6.98(d,J=8.5Hz,2H),6.57(d,J=8.6Hz,2H),3.13-3.01(m,4H),2.93(d,J=6.7Hz,2H),2.90-2.81(m,1H),2.50-2.40(m,2H),2.40-2.31(m,1H),2.06-1.87(m,4H),1.78-1.68(m,4H),1.63-1.53(m,1H),1.32-1.22(m,2H),1.15-1.02(m,2H)。质谱(m/z):370.2$[M+H]^+$。

[3021] 化合物560

[3022] N^2-(4-(1-(2,2,2-三氟乙基)哌啶-4-基)苯基)螺[3.3]庚烷-2,6-二胺

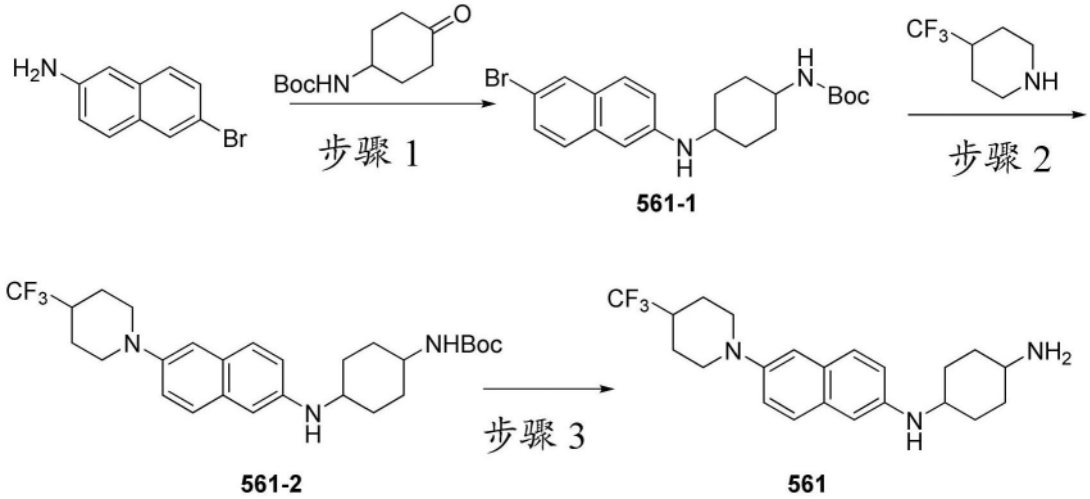
[3023] 

560

[3024] 由(6-((4-(1-(2,2,2-三氟乙基)哌啶-4-基)苯基)氨基)螺[3.3]庚烷-2-基)氨基甲酸叔丁酯(122mg,0.26mmol),HCl/二氧杂环己烷(5mL)和DCM(5mL),根据为37的程序制备标题化合物560(103.3mg,98%)(黄色固体)。^{1}H NMR(400MHz,CD_3OD)δ6.98(d,J=8.5Hz,2H),6.53(d,J=8.5Hz,2H),3.82-3.71(m,1H),3.55-3.41(m,1H),3.13-3.00(m,4H),2.58-2.24(m,7H),2.08-1.82(m,4H),1.77-1.65(m,4H)。质谱(m/z):368.2$[M+H]^+$。

[3025] 化合物561

[3026] N^1-(6-(4-(三氟甲基)哌啶-1-基)萘-2-基)环己烷-1,4-二胺

[3027] 

[3028] 步骤1:制备(4-((6-溴萘-2-基)氨基)环己基)氨基甲酸叔丁酯(561-1)

[3029] 在50℃搅拌6-溴萘-2-胺(300mg,1.35mmol),(4-氧代环己基)氨基甲酸叔丁酯(345mg,1.62mmol),$NaBH_3CN$(169mg,2.7mmol)/MeOH(20mL),CH3COOH(0.1mL)的混合物2小时。将其用H_2O(30mL)淬灭并用EA(3x30 mL)萃取,将有机层浓缩而得到产物(0.4g,收率:70.4%)(黄色固体)。质谱(m/z):419.2$[M+H]^+$。

[3030] 步骤2:制备(4-((6-(4-(三氟甲基)哌啶-1-基)萘-2-基)氨基)环己基)氨基甲酸叔丁酯(561-2)

[3031] 在110℃搅拌(4-((6-溴萘-2-基)氨基)环己基)氨基甲酸叔丁酯(200mg,0.47mmol),4-(三氟甲基)哌啶(88mg,0.57mmol),RuPhos(44mg,0.09mmol),$Pd_2(dba)_3$(87mg,0.095mmol),和Cs_2CO_3(465mg,1.42mmol)/甲苯(20mL)的混合物3小时。将其用H_2O(30mL)淬灭并用EA(3x30 mL)萃取,将有机层浓缩而得到产物(0.2g,85%)(黄色固体)。质

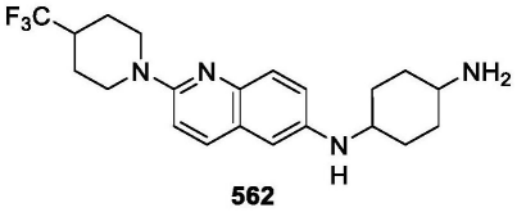
谱(m/z):491.7[M+H]$^+$。

[3032] 步骤3:制备N^1-(6-(4-(三氟甲基)哌啶-1-基)萘-2-基)环己烷-1,4-二胺(561)

[3033] 向8(200mg,0.21mmol)/1,4-二氧杂环己烷(3mL)的溶液中添加HCl/1,4-二氧杂环己烷(1mL)。然后在25℃搅拌混合物过夜。真空除去溶剂并且残余物的提纯方法为:prep-HPLC(柱-Gemini-C18 150x21.2mm,5um;移动相:ACN-H_2O(0.1%FA),5%-20%)而得到期望的产物(33.5mg,21.0%)(黄色固体)。^{1}H NMR(400MHz,CD_3OD)δ7.87-7.67(m,3H),7.46(m,1H),7.41-7.10(m,2H),3.86(t,J=14.7Hz,10H),3.86(m,2H),3.70s(m,1H),3.1(m,1H),2.37-1.75(m,12H),2.04(m,2H)。质谱(m/z):491.7[M-H]-。

[3034] 化合物562

[3035] N^1-(2-(4-(三氟甲基)哌啶-1-基)喹啉-6-基)环己烷-1,4-二胺

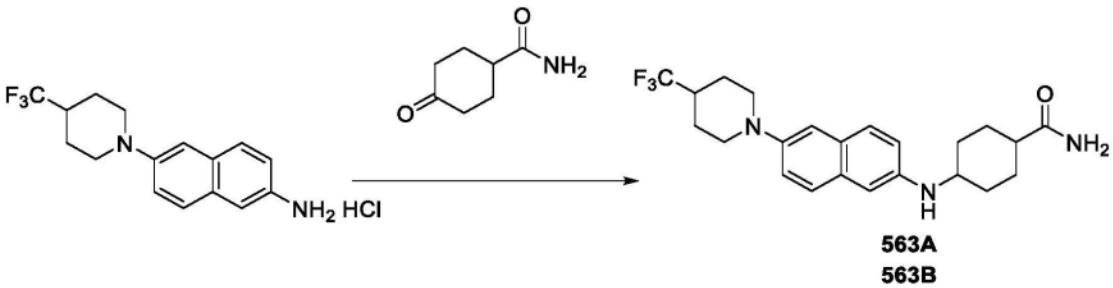
[3036] 

562

[3037] 由(4-((2-(4-(三氟甲基)哌啶-1-基)喹啉-6-基)氨基)环己基)氨基甲酸叔丁酯(305mg,0.6179mmol),1.4-二氧杂环己烷(10mL)和HCl/1,4-二氧杂环己烷(10mL),根据为24的程序制备标题化合物562A(41.9mg,32.5%)(黄色固体)和562B(黄色固体)(36.4mg,28.2%)。562A:^{1}H NMR(400MHz,DMSO-d6)δ7.82(d,J=9.1Hz,1H),7.36(d,J=9.0Hz,1H),7.10(d,J=9.2Hz,1H),7.01(dd,J=9.0,2.5Hz,1H),6.66(d,J=2.4Hz,1H),4.47(d,J=13.2Hz,2H),3.19(dd,J=15.1,6.5Hz,1H),2.98(t,J=11.2Hz,1H),2.84(t,J=11.9Hz,2H),2.66-2.54(m,1H),2.15-1.82(m,6H),1.54-1.38(m,4H),1.31-1.13(m,2H)。质谱(m/z):392.8[M+H]$^+$。HPLC:Rt:3.067min(柱:XBRIDGE 2.1*50mm,3.5um;移动相:H_2O(0.05%TFA)/ACN(0.05%TFA),ACN由0%至60%在7分钟内,7-8min,ACN由60%至100%;0.8mL/min)。562B:^{1}H NMR(400MHz,DMSO-d6)δ7.80(d,J=9.1Hz,1H),7.37(d,J=9.0Hz,1H),7.25-6.96(m,2H),6.64(d,J=2.2Hz,1H),5.65(s,1H),4.47(d,J=13.0Hz,2H),3.51(s,1H),3.05(s,1H),2.84(t,J=11.9Hz,2H),1.83(dd,J=34.8,16.2Hz,6H),1.75-1.54(m,4H),1.45(qd,J=12.5,3.9Hz,2H)。质谱(m/z):392.8[M+H]$^+$。HPLC:Rt:3.391min(柱:XBRIDGE 2.1*50mm,3.5um;移动相:H_2O(0.05%TFA)/ACN(0.05%TFA),ACN由0%至60%在7分钟内,7-8min,ACN由60%至100%;0.8mL/min)。

[3038] 化合物563

[3039] 4-((6-(4-(三氟甲基)哌啶-1-基)萘-2-基)氨基)环己烷-1-甲酰胺

[3040] 

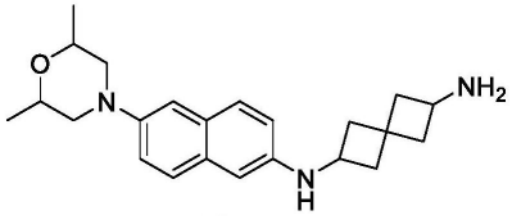
563A
563B

[3041] 在25℃搅拌6-(4-(三氟甲基)哌啶-1-基)萘-2-胺盐酸盐(100mg,0.3014mmol),4-

氧代环己烷-1-甲酰胺(42.55mg,0.3014mmol)和三乙酰氧基硼氢化钠(191.64mg,0.9042mmol)/DCE(20mL)的混合物过夜。在冷却后,将过量的DCE真空除去并且残余物用DCM(30mL)和水(30mL)萃取三次。合并有机层,真空除去溶剂并且粗产物的提纯方法:prep-HPLC(柱-Gemini-C18 150x 21.2mm,5um;移动相:ACN-H_2O(0.1%FA),20%-50%)而得到期望的产物563A(灰色固体)(9.5mg,7.1%)和563B(紫色固体)(9.9mg,7.4%)。563A:^{1}H NMR(400MHz,CD_3OD)δ7.39(dd,J=8.9,2.5Hz,2H),7.07(dd,J=9.0,2.4Hz,1H),7.00(d,J=2.3Hz,1H),6.81(dd,J=8.8,2.3Hz,1H),6.70(d,J=2.1Hz,1H),3.63(d,J=12.3Hz,2H),3.28-3.22(m,1H),2.59(td,J=12.2,2.0Hz,2H),2.26-2.07(m,4H),1.94-1.79(m,4H),1.66(tt,J=12.5,6.4Hz,2H),1.59-1.47(m,2H),1.14(dt,J=13.1,10.5Hz,2H)。HPLC:Rt:4.428min(柱:XBRIDGE 2.1*50mm,3.5um;移动相:H_2O(0.05%TFA)ACN(0.05%TFA),ACN由0%至60%在7分钟内,7-8min,ACN由60%至100%;0.8mL/min)。563B:^{1}H NMR(400MHz,CD_3OD)δ7.39(dd,J=8.8,2.1Hz,2H),7.08(dd,J=9.0,2.4Hz,1H),7.01(d,J=2.3Hz,1H),6.88(dd,J=8.8,2.3Hz,1H),6.69(d,J=2.1Hz,1H),3.64(d,J=11.7Hz,2H),3.59(s,1H),2.61(dd,J=12.3,10.0Hz,2H),2.32-2.17(m,2H),1.91(d,J=11.7Hz,2H),1.85-1.75(m,4H),1.73-1.54(m,6H)。质谱(m/z):419.7$[M+H]^+$。HPLC:Rt:4.598min(柱:XBRIDGE 2.1*50mm,3.5um;移动相:H_2O(0.05%TFA)ACN(0.05%TFA),ACN由0%至60%在7分钟内,7-8min,ACN由60%至100%;0.8mL/min)。

[3042] 化合物564

[3043] N^2-(6-(2,6-二甲基吗啉代)萘-2-基)螺[3.3]庚烷-2,6-二胺

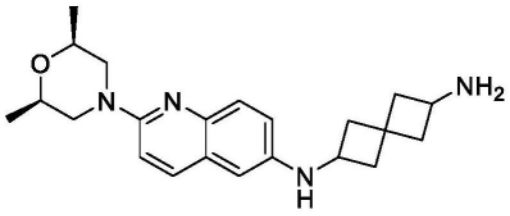
[3044] 

564

[3045] 由(6-((6-(2,6-二甲基吗啉代)萘-2-基)氨基)螺[3.3]庚烷-2-基)氨基甲酸叔丁酯(100mg,0.21mmol),DCM(3mL)和TFA(1mL),根据为24的程序制备标题化合物N^2-(6-(2,6-二甲基吗啉代)萘-2-基)螺[3.3]庚烷-2,6-二胺564(41.8mg,53%)(灰白色固体)。^{1}H NMR(400MHz,DMSO-d6)δ7.41(t,J=8.3Hz,2H),7.14(dd,J=9.0,2.5Hz,1H),6.93(d,J=2.4Hz,1H),6.79(dd,J=8.8,2.3Hz,1H),6.47(d,J=2.3Hz,1H),5.76(d,J=6.6Hz,1H),3.77-3.64(m,3H),3.55-3.47(m,2H),3.22-3.09(m,1H),2.50-2.49(m,1H),2.43-2.41(m,1H),2.37-2.27(m,2H),2.24-2.16(m,2H),2.14-2.05(m,1H),2.03-1.88(m,1H),1.85-1.72(m,2H),1.71-1.57(m,2H),1.13(d,J=6.3Hz,6H).MS(m/z):366.3$[M+H]^+$。

[3046] 化合物565

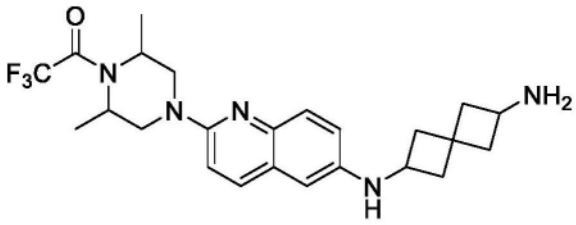
[3047] N^2-(2-((2S,6R)-2,6-二甲基吗啉代)喹啉-6-基)螺[3.3]庚烷-2,6-二胺

[3048] 

[3049] 由(6-((2-((2S,6R)-2,6-二甲基吗啉代)喹啉-6-基)氨基)螺[3.3]庚烷-2-基)氨基甲酸叔丁酯(30.0mg,0.065mmol),TFA,根据为化合物24的程序制备标题化合物565(20.2mg),总收率为84.6%(淡黄色固体)。^{1}H NMR(400MHz,DMSO-d6)δ7.81(d,J=9.2Hz,1H),7.36(d,J=8.8Hz,1H),7.09(d,J=9.2Hz,1H),6.95(dd,J=9.2,2.4Hz,1H),6.49(d,J=2.4Hz,1H),4.27-4.11(m,2H),3.73(m,1H),3.67-3.56(m,2H),3.24(m,1H),2.42-2.31(m,5H),2.17(m,1H),1.92-1.75(m,4H),1.17(d,J=6.4Hz,6H)。质谱(m/z):367.2[M+H]$^+$。

[3050] 化合物566

[3051] 1-(4-(5-((6-氨基螺[3.3]庚烷-2-基)氨基)-6-甲基吡啶-2-基)-2,6-二甲基哌嗪-1-基)-2,2,2-三氟乙-1-酮

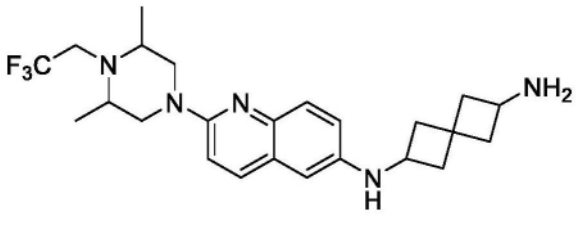
[3052] 

566

[3053] 由(6-((2-(3,5-二甲基-4-(2,2,2-三氟乙酰基)哌嗪-1-基)喹啉-6-基)氨基)螺[3.3]庚烷-2-基)氨基甲酸叔丁酯(0.1g,0.2mmol),DCM(5mL)和TFA(1mL),根据为24的程序制备标题化合物566(15mg,18.3%)(黄色固体)。^{1}H NMR(400MHz,CD_3OD)δ7.82(d,J=9Hz,1H),7.45(d,J=9.0Hz,1H),7.08(d,J=9.0Hz,1H),7.00(dd,J=9.0,2.5Hz,1H),6.60(d,J=2.4Hz,1H),4.63(s,1H),4.32-4.31(m,3H),3.83-3.81(m,1H),3.46-3.45(m,1H),3.11(d,J=11.8Hz,2H),2.64-2.41(m,3H),2.36-2.24(m,1H),2.07-1.87(m,4H),1.42(d,J=19.8Hz,6H)。质谱(m/z):461.7[M+H]+。

[3054] 化合物567

[3055] N^2-(2-(3,5-二甲基-4-(2,2,2-三氟乙基)哌嗪-1-基)喹啉-6-基)螺-[3.3]庚烷-2,6-二胺

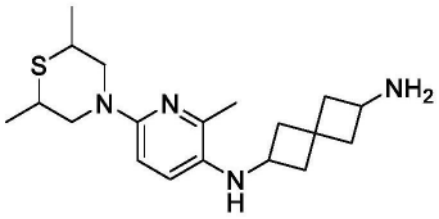
[3056] 

567

[3057] 由(6-((2-(3,5-二甲基-4-(2,2,2-三氟乙基)哌嗪-1-基)喹啉-6-基)氨基)螺[3.3]庚烷-2-基)氨基甲酸叔丁酯(100mg,0.18mmol),DCM(10mL)和TFA(1mL),根据为24的程序制备标题化合物567(31.6mg)(白色固体)。^{1}H NMR(400MHz,DMSO-d6)δ7.76(d,J=9.2Hz,1H),7.31(d,J=9.0Hz,1H),7.07(d,J=9.2Hz,1H),6.91(dd,J=9.0,2.6Hz,1H),6.45(d,J=2.6Hz,1H),5.79(d,J=6.4Hz,1H),4.13(d,J=12.0Hz,2H),3.69(d,J=7.0Hz,1H),3.33(t,J=8.0Hz,3H),3.27-3.22(m,1H),2.76-2.69(m,2H),2.56-2.48(m,3H),2.37-2.29(m,2H),2.16-2.07(m,1H),1.76(ddd,J=14.2,10.8,2.6Hz,3H),1.09(d,J=6.2Hz,6H)。质谱(m/z):448.2[M+H]$^+$。

[3058] 化合物568

[3059] N^2-(6-(2,6-二甲基硫代吗啉代)-2-甲基吡啶-3-基)螺[3.3]庚烷-2,6-二胺

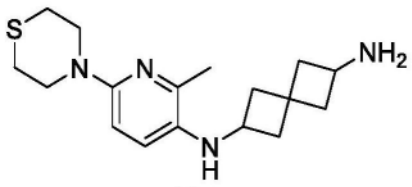
[3060] 

568

[3061] 由(6-((6-(2,6-二甲基硫代吗啉代)-2-甲基吡啶-3-基)氨基)-螺[3.3]庚烷-2-基)氨基甲酸叔丁酯(100mg,0.22mmol),DCM(10mL)和TFA(1mL),根据为24的程序制备标题化合物568(8.1mg,98.4%)(白色固体)。^{1}H NMR(400MHz,CD_3OD)δ6.89(d,J=8.8Hz,1H),6.55(d,J=8.8Hz,1H),4.24(dd,J=13.0,2.6Hz,2H),3.77-3.69(m,1H),3.29(dd,J=8.6,7.4Hz,1H),3.06(ddd,J=10.6,6.8,2.8Hz,2H),2.60-2.50(m,3H),2.48-2.34(m,2H),2.29(s,3H),2.28-2.18(m,1H),1.97-1.78(m,4H),1.16(d,J=6.8Hz,6H)。质谱(m/z):347.2[M+H]$^+$。

[3062] 化合物569

[3063] N^2-(2-甲基-6-硫代吗啉代吡啶-3-基)螺[3.3]庚烷-2,6-二胺

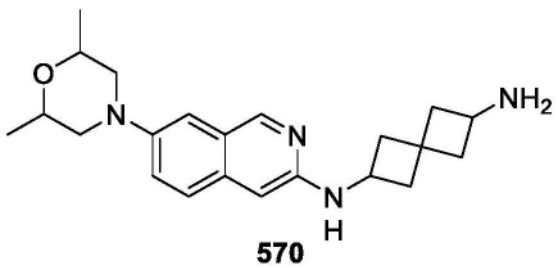
[3064] 

569

[3065] 由(6-((2-甲基-6-硫代吗啉代吡啶-3-基)氨基)螺[3.3]庚烷-2-基)氨基甲酸叔丁酯(100mg,0.2389mmol),DCM(10mL),和TFA(1mL),根据为568的程序制备期望的产物569(10.3mg,12.85%)(油)。^{1}H NMR(400MHz,CD_3OD)δ6.77(d,J=8.7Hz,1H),6.44(d,J=8.7Hz,1H),3.61(p,J=7.6Hz,1H),3.55-3.47(m,4H),3.26-3.15(m,1H),2.60-2.53(m,4H),2.46-2.23(m,3H),2.17(s,3H),2.14(dd,J=6.7,5.4Hz,1H),1.86-1.67(m,4H)。质谱(m/z):318.9[M+H]$^+$。

[3066] 化合物570

[3067] N^2-(7-(2,6-二甲基吗啉代)异喹啉-3-基)螺[3.3]庚烷-2,6-二胺

[3068] 

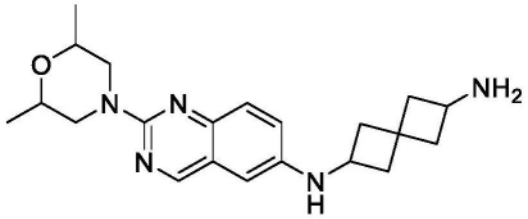
570

[3069] 由(6-((7-(2,6-二甲基吗啉代)异喹啉-3-基)氨基)螺[3.3]庚烷-2-基)氨基甲酸叔丁酯(150mg,0.21mmol),TFA(2mL)和DCM(10mL),根据为24的程序制备标题化合物570(9.3mg)(白色固体)。^{1}H NMR(400MHz,DMSO-d6)δ8.67(s,1H),7.48(d,J=9.2Hz,1H),7.41(dd,J=9.2,2.2Hz,1H),7.06(s,1H),6.95(d,J=7.6Hz,1H),6.39(d,J=4.4Hz,1H),6.27

(t,J＝8.4Hz,1H),3.96(dd,J＝14.8,7.2Hz,1H),3.83(dd,J＝16.0,8.0Hz,1H),3.76-3.70(m,2H),3.58(d,J＝10.8Hz,2H),3.24-3.13(m,1H),2.38-2.30(m,2H),2.28-2.22(m,2H),2.14(s,1H),1.97-1.92(m,1H),1.90-1.85(m,2H),1.74-1.61(m,1H),1.17(d,J＝6.2Hz,6H)。质谱(m/z):367.3[M+H]$^+$。

[3070] 化合物571

[3071] N^2-(2-(2,6-二甲基吗啉代)喹唑啉-6-基)螺[3.3]庚烷-2,6-二胺

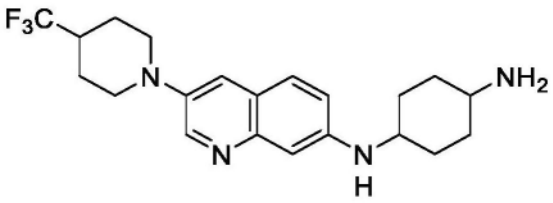
[3072] 

571

[3073] 由(6-((2-(2,6-二甲基吗啉代)喹唑啉-6-基)氨基)螺[3.3]庚烷-2-基)氨基甲酸叔丁酯(72mg,0.15mmol),5mL的HCl/1,4-二氧杂环己烷的溶液,根据为37的程序制备标题化合物571(47.3mg,83.6%)。^{1}H NMR(400MHz,DMSO-d6)δ8.97(s,1H),8.10(s,2H),7.41-7.31(m,2H),7.26-7.15(m,1H),6.57(s,1H),6.17(s,1H),4.53(dd,J＝13.3,2.4Hz,2H),3.76(t,J＝7.6Hz,1H),3.63-3.52(m,3H),2.62-2.56(m,1H),2.53-2.52(m,2H),2.48-2.40(m,2H),2.29-2.10(m,3H),1.94-1.83(m,2H),1.17(d,J＝6.2Hz,6H)。质谱(m/z):368.2[M+H]$^+$。

[3074] 化合物572

[3075] N^1-(3-(4-(三氟甲基)哌啶-1-基)喹啉-7-基)环己烷-1,4-二胺

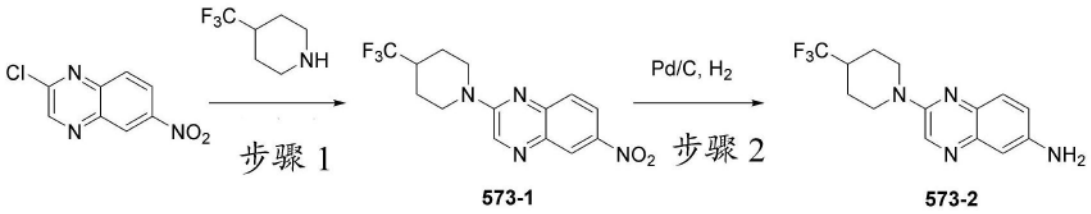
[3076] 

572

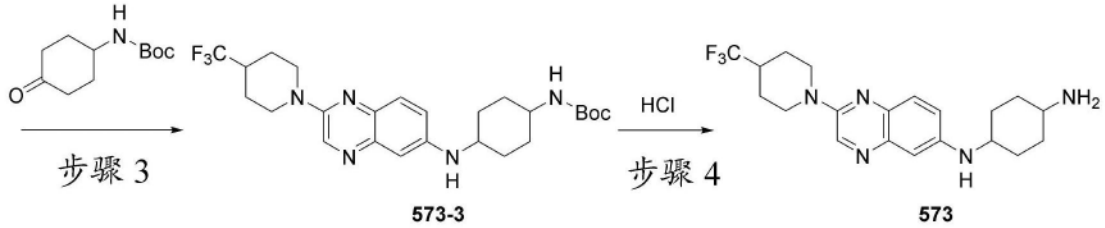
[3077] 由(4-((3-(4-(三氟甲基)哌啶-1-基)喹啉-7-基)氨基)环己基)氨基甲酸叔丁酯(100mg,0.21mmol)和HCl/1,4-Dio.(10mL,4N),根据为37的程序制备标题化合物572(10.1mg)(白色固体)。^{1}H NMR(400MHz,DMSO-d6)δ8.58(d,J＝2.8Hz,1H),7.51(d,J＝8.8Hz,1H),7.42(d,J＝2.8Hz,1H),7.08(d,J＝8.8Hz,1H),6.76(s,1H),5.96(s,1H),3.76(d,J＝12.2Hz,2H),3.56(s,1H),3.10(s,1H),2.72(t,J＝11.4Hz,2H),2.54(s,1H),1.99-1.55(m,13H)。质谱(m/z):393.2[M+H]$^+$。

[3078] 化合物573

[3079] N^1-(2-(4-(三氟甲基)哌啶-1-基)喹喔啉-6-基)环己烷-1,4-二胺



[3080]



[3081] 步骤1:制备1-(3-硝基苯基)-4-(三氟甲基)哌啶(573-1)

[3082] 在100℃搅拌2-氯-6-硝基喹喔啉(0.2g,0.95mmol),4-(三氟甲基)哌啶(0.15g,0.95mmol),Cs_2CO_3(617mg,1.9mmol)和DMF(10mL)的混合物3小时。将混合物用EA(400mL)稀释和用水(300mL×3)洗涤。浓缩有机相并且通过快速色谱提纯,洗脱用PE:EA=10:1至1:1而得到期望的产物(0.33g,92.0%)(黄色固体)。质谱(m/z):326.8$[M+H]^+$。

[3083] 步骤2:制备2-(4-(三氟甲基)哌啶-1-基)喹喔啉-6-胺(573-2)

[3084] 在氢气气氛下在25℃搅拌1-(3-硝基苯基)-4-(三氟甲基)哌啶(0.33g,1mmol)和Pd/C(80mg)/THF(10mL)的溶液中3小时。浓缩有机相并且通过快速色谱提纯,洗脱用DCM:MeOH=10:1至5:1而得到期望的产物(黄色油)(0.3g,99%)。质谱(m/z):297.2$[M+H]^+$。

[3085] 步骤3:制备(4-((3-(4-(三氟甲基)哌啶-1-基)苯基)氨基)环己基)氨基甲酸叔丁酯(573-3)

[3086] 2-(4-(三氟甲基)哌啶-1-基)喹喔啉-6-胺(0.3g,1mmol),(4-氧代环己基)氨基甲酸叔丁酯(0.2g,1mmol),$NaBH(OAc)_3$(0.63g,3mmol)和DCE(10mL)的混合物。在室温搅拌反应3小时。用水(10mL)淬灭,反应用EA(10mL)萃取3次。将合并的有机层用硫酸钠干燥,浓缩并且通过快速色谱纯化,洗脱用PE/EA=10:1至1:1而得到期望的产物(黄色油)(0.3g,60.8%)。质谱(m/z):493.7[M-tBu+H]+。

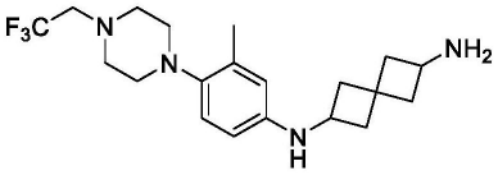
[3087] 步骤4:制备N^1-(2-(4-(三氟甲基)哌啶-1-基)喹喔啉-6-基)环己烷-1,4-二胺(573):

[3088] 向(4-((3-(4-(三氟甲基)哌啶-1-基)苯基)氨基)环己基)氨基甲酸叔丁酯(300mg,0.61mmol)/DCM(5mL)的溶液中添加TFA(1mL)并搅拌混合物2小时。用$NaHCO_3$(10mL)淬灭,反应用EA(10mL)萃取3次。将合并的有机层用硫酸钠干燥,真空除去并且残余物的提纯方法为:制备(柱-Gemini-C18 150x 21.2mm,5um;移动相:ACN-H_2O(0.1%FA),10%-30%)而得到573A(102.9mg)(黄色固体)和573B(107.6mg)(黄色固体)。573A:^1H NMR(400MHz,CD_3OD)δ8.75(s,1H),7.71(d,J=9.2,1H),7.50-7.40(m,1H),7.25(d,J=2.4,1H),4.66(d,J=13.6,2H),3.60-3.44(m,1H),3.25-3.09(m,3H),2.65-2.55(m,1H),2.29-2.14(m,4H),2.07(d,J=10.9,2H),1.77-1.41(m,6H)。质谱(m/z):394.2$[M+H]^+$。HPLC:Rt=3.886min(柱:XBRIDGE 3.5um,2.1*50mm;移动相:H_2O(0.05%TFA)-ACN(0.05%TFA),ACN从0至60%在7分钟内,流速:0.8mL/min)。573B:^1H NMR(400MHz,CD_3OD)δ8.72(s,1H),7.68(d,J=9.2,1H),7.44(dd,J=9.2,2.4,1H),7.02(d,J=2.4,1H),4.62(d,J=13.6,2H),3.73(s,

1H),3.21-3.15(m,2H),2.65-2.55(m,1H),2.12-1.82(m,11H),1.76-1.65(m,2H)。质谱(m/z):394.2[M+H]$^+$。HPLC:Rt＝4.058min(柱:XBRIDGE 3.5um,2.1*50mm;移动相:H_2O(0.05%TFA)-ACN(0.05%TFA),ACN从0至60%在7分钟内,流速:0.8mL/min)。

[3089] 化合物574

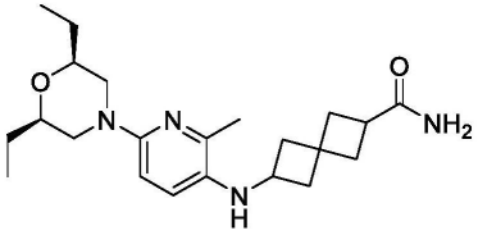
[3090] N^2-(3-甲基-4-(4-(2,2,2-三氟乙基)哌嗪-1-基)苯基)螺[3.3]庚烷-2,6-二胺

[3091] 

[3092] 根据为化合物24所述的程序制备标题化合物574(26.1mg,51.3%)(白色固体)。^{1}H NMR(400MHz,DMSO-d6)δ8.38(s,3H),6.81(d,J＝8.4Hz,1H),6.33(d,J＝2.8Hz,1H),6.27(d,J＝8.4Hz,1H),5.68-5.26(m,1H),3.64(d,J＝7.2Hz,1H),3.57-3.47(m,1H),3.21(q,J＝10.3Hz,2H),2.71(s,7H),2.39-2.30(m,2H),2.23-2.15(m,3H),2.13(s,3H),1.86-1.76(m,2H)。质谱(m/z):383.2[M+H]$^+$。

[3093] 化合物575

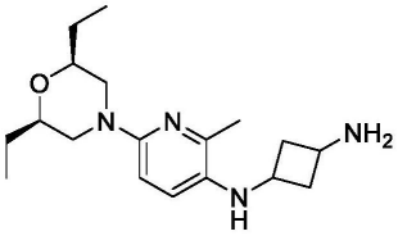
[3094] 6-((6-((2S,6R)-2,6-二乙基吗啉代)-2-甲基吡啶-3-基)氨基)螺[3.3]庚烷-2-甲酰胺

[3095] 

[3096] 根据为化合物5所述的程序制备标题化合物575(9.3mg,23.5%)(淡黄色固体)。^{1}H NMR(400MHz,DMSO-d6)δ7.10(s,2H),6.73(d,J＝8.7Hz,1H),6.64(s,1H),6.50(d,J＝8.7Hz,1H),4.58-4.41(m,1H),3.84(d,J＝11.9Hz,2H),3.65-3.56(m,1H),3.44-3.37(m,3H),2.91-2.81(m,1H),2.35-2.07(m,9H),2.01-1.95(m,1H),1.94-1.86(m,1H),1.83-1.75(m,1H),1.54-1.43(m,4H),0.94(t,J＝7.4Hz,6H)。质谱(m/z):387.3[M+H]$^+$。

[3097] 化合物576

[3098] N^1-(6-((2S,6R)-2,6-二乙基吗啉代)-2-甲基吡啶-3-基)环丁烷-1,3-二胺

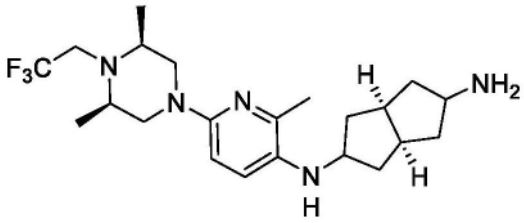
[3099] 

[3100] 根据为化合物24所述的程序制备标题化合物576(4.2mg,15.5%)(淡黄色固体)。^{1}H NMR(400MHz,甲醇-d4)δ6.79(d,J＝8.7Hz,1H),6.55(d,J＝8.9Hz,1H),4.16-4.03(m,1H),3.98-3.90(m,1H),3.85-3.75(m,2H),3.54-3.44(m,2H),2.61-2.49(m,2H),2.33(s,3H),1.67-1.50(m,4H),1.39-1.26(m,4H),1.02(t,J＝7.5Hz,6H)。质谱(m/z):319.2[M+H

]+。

[3101] 化合物577

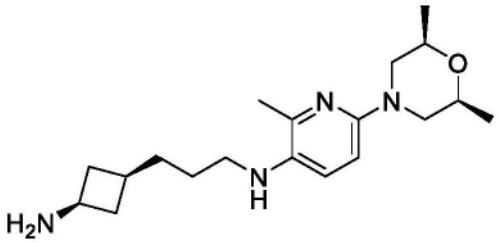
[3102] (3aR,6aS)-N2-(6-((3R,5S)-3,5-二甲基-4-(2,2,2-三氟乙基)哌嗪-1-基)-2-甲基吡啶-3-基)八氢戊搭烯-2,5-二胺

[3103] 

[3104] 由6-((3R,5S)-3,5-二甲基-4-(2,2,2-三氟乙基)哌嗪-1-基)-2-甲基吡啶-3-胺和(3as,6as)-四氢戊搭烯-2,5(1H,3H)-二酮,根据为24的程序制备标题化合物577(13.5mg),两步总收率为17.5%(白色固体),经1H NMR证明为1:0.1的混合物。1H NMR(400MHz,DMSO-d6)δ8.06(s,3H),7.92(s,1H),6.58(s,1H),4.02(s,1H),3.84(s,3H),2.74(s,5H),2.23(s,4H),1.73(d,J=24.9Hz,4H),1.39(s,3H),1.10(d,J=6.3Hz,9H)。质谱(m/z):426.4[M+H]+。

[3105] 化合物578

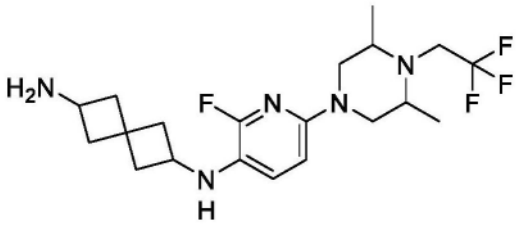
[3106] N-(3-((1s,3R)-3-氨基环丁基)丙基)-6-((2S,6R)-2,6-二甲基吗啉代)-2-甲基吡啶-3-胺

[3107] 

[3108] 根据为化合物23所述的程序制备标题化合物578(61.9mg,63.7%)(白色固体)。1H NMR(400MHz,DMSO-d6)δ6.82(d,J=8.8Hz,1H),6.51(d,J=8.8Hz,1H),4.32(s,1H),3.83(d,J=11.2Hz,2H),3.64-3.57(m,2H),2.92(s,2H),2.26(d,J=7.6Hz,1H),2.20(s,3H),2.18-2.11(m,2H),1.82-1.66(m,1H),1.46-1.37(m,4H),1.23(d,J=6.4Hz,2H),1.14(d,J=6.4Hz,6H)。质谱(m/z):332.9[M+H]+。

[3109] 化合物579

[3110] N2-(6-(3,5-二甲基-4-(2,2,2-三氟乙基)哌嗪-1-基)-2-氟吡啶-3-基)螺[3.3]庚烷-2,6-二胺

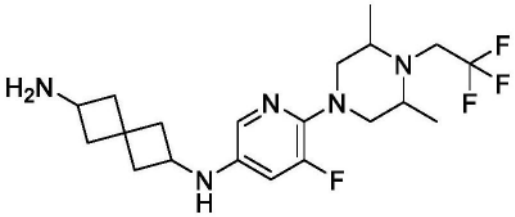
[3111] 

[3112] 根据为化合物24所述的程序制备标题化合物579(37.6mg,50%)(棕色油)。1H NMR(400MHz,DMSO-d6)δ6.99-6.94(m,1H),6.53(d,J=8.4,1H),4.96(d,J=6.0,1H),3.74(d,J

＝11.2,2H),3.66-3.61(m,1H),3.38-3.30(m,2H),3.20-3.13(m,1H),2.74-2.72(m,2H),2.39-2.28(m,5H),2.26-2.17(m,2H),2.16-2.04(m,1H),1.87-1.80(m,2H),1.69-1.57(m,2H),1.09(d,J＝6.4,6H)。质谱(m/z):416.2[M+H]$^+$。

[3113] 化合物580

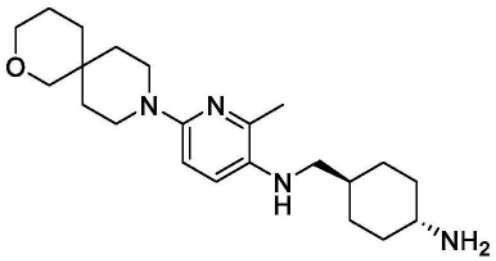
[3114] N^2-(6-(3,5-二甲基-4-(2,2,2-三氟乙基)哌嗪-1-基)-5-氟吡啶-3-基)螺[3.3]庚烷-2,6-二胺

[3115] 

[3116] 根据为化合物24所述的程序制备标题化合物580(105.6mg,43.68%)(黄色固体)。^{1}H NMR(400MHz,CD_3OD)δ7.37(d,J＝2.0Hz,1H),6.76(dd,J＝14.0,2.4Hz,1H),3.73(dt,J＝15.6,7.6Hz,1H),3.50-3.30(m,4H),2.95(br,2H),2.63-2.32(m,7H),1.94-1.80(m,4H),1.16(d,J＝6.4Hz,6H)。质谱(m/z):415.8[M+H]$^+$。

[3117] 化合物581

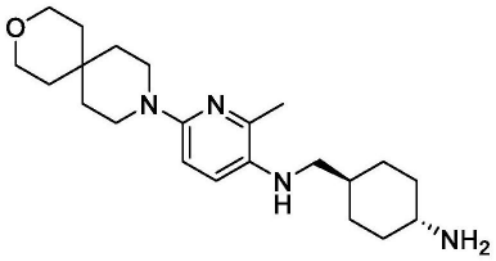
[3118] N-(((1r,4r)-4-氨基环己基)甲基)-2-甲基-6-(2-氧杂-9-氮杂螺[5.5]十一烷-9-基)吡啶-3-胺

[3119] 

[3120] 根据为化合物24所述的程序制备标题化合物581(39.1mg,12.7%)(白色固体)。^{1}H NMR(400MHz,DMSO-d6)δ6.79(d,J＝8.8Hz,1H),6.49(d,J＝8.8Hz,1H),4.30(s,1H),3.53(t,J＝4.8Hz,2H),3.34(s,2H),3.22(t,J＝5.2Hz,4H),2.81(s,2H),2.46(d,J＝3.2Hz,1H),2.20(s,3H),1.79-1.73(m,4H),1.51-1.37(m,9H),1.01-0.85(m,4H)。质谱(m/z):373.3[M+H]$^+$。

[3121] 化合物582

[3122] N-(((1r,4r)-4-氨基环己基)甲基)-2-甲基-6-(3-氧杂-9-氮杂螺[5.5]十一烷-9-基)吡啶-3-胺

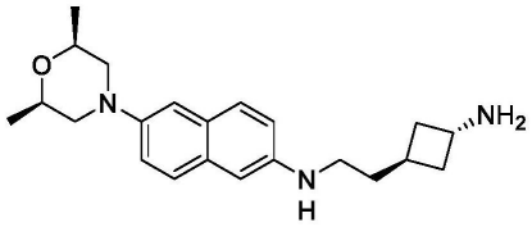
[3123] 

[3124] 根据为化合物24所述的程序制备标题化合物582(33.60mg,28.42%)(白色固体)

。^{1}H NMR(400MHz,CD_3OD)δ6.84(d,J=8.8Hz,1H),6.49(d,J=8.8Hz,1H),3.61-3.57(m,4H),3.18-3.11(m,4H),2.83(d,J=6.8Hz,2H),2.53-2.44(m,1H),2.19(s,3H),1.84-1.75(m,4H),1.59-1.54(m,4H),1.48-1.41(m,5H),1.12-1.04(m,4H)。质谱(m/z):372.9[M+H]$^+$。

[3125] 化合物583

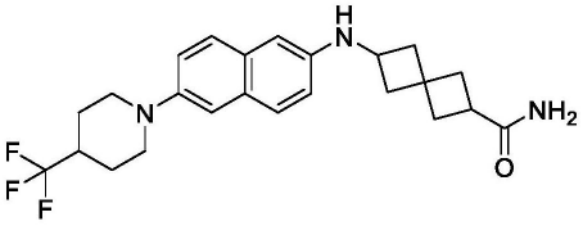
[3126] N-(2-((1r,3S)-3-氨基环丁基)乙基)-6-((2S,6R)-2,6-二甲基吗啉代)萘-2-胺

[3127] 

[3128] 根据为化合物78所述的程序制备标题化合物583(黄色固体)。^{1}H NMR(400MHz,CD_3OD)δ7.50(dd,J=8.8,5.6Hz,2H),7.18(dd,J=9.0,2.4Hz,1H),7.05(d,J=2.3Hz,1H),6.91(dd,J=8.8,2.3Hz,1H),6.74(d,J=2.2Hz,1H),3.89-2.79(m,2H),3.60-3.55(m,2H),3.51(d,J=10.8Hz,2H),3.14-3.04(m,2H),2.47-2.28(m,3H),2.12-1.96(m,4H),1.83(dd,J=14.6,7.6Hz,2H),1.62-1.57(m,1H),1.24(d,J=6.3Hz,6H)。质谱(m/z):353.8[M+H]$^+$。

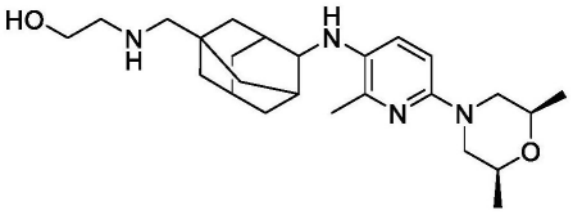
[3129] 化合物584

[3130] 6-((6-(4-(三氟甲基)哌啶-1-基)萘-2-基)氨基)螺[3.3]庚烷-2-甲酰胺

[3131] 

[3132] 根据为化合物10所述的程序制备标题化合物584(白色固体)(27.4mg,20%)。^{1}H NMR(400MHz,CD_3OD)δ7.49(dd,J=8.8,4.7Hz,2H),7.17(dd,J=9.0,2.4Hz,1H),7.09(d,J=2.2Hz,1H),6.88(dd,J=8.8,2.3Hz,1H),6.66(d,J=2.0Hz,1H),3.90-3.79(m,1H),3.72(d,J=12.3Hz,2H),3.08-2.97(m,1H),2.71-2.60(m,3H),2.51-2.41(m,1H),2.33(d,J=8.6Hz,2H),2.31-2.19(m,2H),2.17-2.09(m,1H),2.03-1.94(m,3H),1.86(dd,J=11.4,8.0Hz,1H),1.80-1.66(m,2H)。质谱(m/z):432.2[M+H]$^+$。

[3133] 化合物585

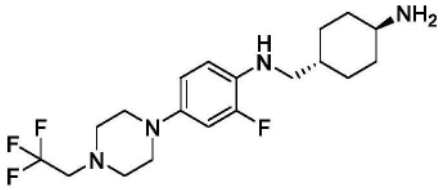
[3134] 

[3135] 根据为化合物24所述的程序制备标题化合物585(51.2mg,55.6%)(淡黄色固体)。^{1}H NMR(400MHz,DMSO-d6)δ9.42(s,1H),8.51(s,2H),7.01-6.74(m,1H),6.67-6.34(m,1H),5.35-5.20(m,1H),4.42-4.28(m,1H),3.91-3.82(m,3H),3.76-3.68(m,2H),3.64-3.55(m,2H),3.47-3.37(m,2H),3.15(d,J=12.5Hz,1H),3.04-2.94(m,2H),2.69(d,J=13.4Hz,2H),2.37-2.28(m,3H),2.24-2.14(m,2H),2.06-1.90(m,4H),1.77-1.66(m,3H),1.62-1.53

(m,2H),1.44-1.34(m,3H),1.16-1.06(m,9H)。质谱(m/z):429.3[M+H]$^+$。

[3136] 化合物586

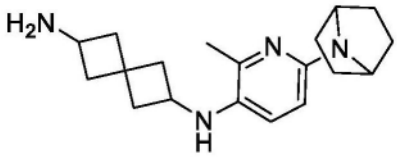
[3137] N-(((1r,4r)-4-氨基环已基)甲基)-2-氟-4-(4-(2,2,2-三氟乙基)哌嗪-1-基)苯胺

[3138] 

[3139] 根据为化合物24所述的程序制备标题化合物586(5.2mg,19.8%)(白色固体)。^{1}H NMR(400MHz,DMSO-d6)δ6.71(d,J=14.4Hz,1H),6.57(d,J=5.2Hz,2H),4.77(d,J=6.4Hz,1H),3.25-3.17(m,2H),2.95(t,J=4.8Hz,4H),2.83(t,J=6.8Hz,2H),2.72(t,J=4.8Hz,4H),1.74(d,J=9.2Hz,4H),1.52-1.39(m,2H),1.00-0.87(m,4H)。质谱(m/z):389.2[M+H]$^+$。

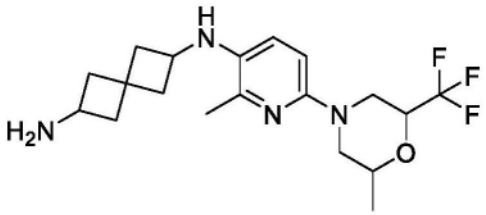
[3140] 化合物587

[3141] N^2-(6-(7-氮杂双环[2.2.1]庚烷-7-基)-2-甲基吡啶-3-基)螺[3.3]庚烷-2,6-二胺

[3142] 

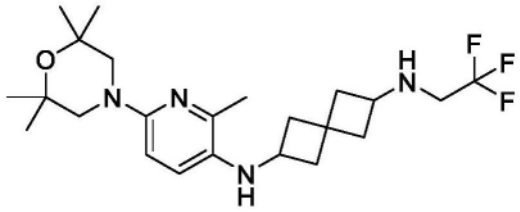
[3143] 根据为化合物24所述的程序制备标题化合物587(28.5mg,54.4%)(黄色固体)。^{1}H NMR(400MHz,DMSO-d6)δ8.38(s,3H),6.80(d,J=8.4Hz,2H),4.89(s,1H),4.45(s,2H),3.72-3.46(m,2H),2.43-2.28(m,4H),2.26-2.14(m,3H),1.96(d,J=10.4Hz,2H),1.68-1.60(m,3H),1.40(d,J=7.6Hz,3H)。质谱(m/z):313.3[M+H]$^+$。

[3144] 化合物588

[3145] 

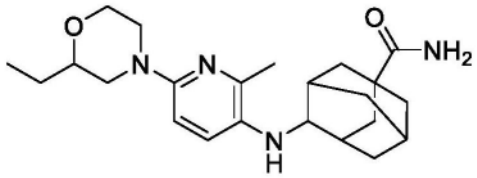
[3146] 根据为化合物24所述的程序制备标题化合物588(16.2mg,52.3%)(淡黄色固体)。^{1}H NMR(400MHz,DMSO-d6)δ8.07(br s,2H),6.76(d,J=8.4Hz,1H),6.56(d,J=8.4Hz,1H),4.61(br s,1H),4.53-4.41(m,1H),4.21-4.10(m,1H),3.72-3.62(m,1H),3.60-3.47(m,2H),3.45-3.37(m,2H),3.00-2.89(m,1H),2.44-2.30(m,2H),2.22(s,3H),2.20-2.07(m,4H),1.98-1.86(m,2H),1.22(d,J=6.4Hz,3H)。质谱(m/z):385.2[M+H]$^+$。

[3147] 化合物589

[3148] 

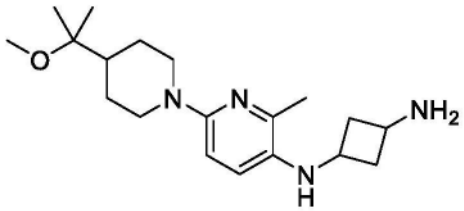
[3149] 根据为化合物23所述的程序制备标题化合物589(17.6mg,34.1%)(淡黄色固体)。^{1}H NMR(400MHz,氯仿-d)δ6.76(d,J=8.4Hz,1H),6.42(d,J=8.4Hz,1H),3.74(p,J=7.6Hz,1H),3.29(p,J=7.6Hz,1H),3.19(s,4H),3.10(q,J=9.6Hz,2H),2.59-2.49(m,1H),2.47-2.38(m,2H),2.29(s,3H),2.28-2.22(m,1H),1.89-1.73(m,4H),1.29(s,12H)。质谱(m/z):441.3[M+H]$^+$。

[3150] 化合物590

[3151] 

[3152] 根据为化合物10所述的程序制备标题化合物590(10.0mg,31.2%)(白色固体)。^{1}H NMR(400MHz,DMSO-d6)δ6.99(s,1H),6.88(d,J=8.7Hz,1H),6.73(s,1H),6.54(d,J=8.7Hz,1H),3.94-3.83(m,3H),3.75(d,J=12.3Hz,1H),3.54(t,J=11.4Hz,1H),3.44-3.35(m,2H),2.36-2.21(m,5H),2.01-1.93(m,4H),1.91-1.80(m,5H),1.78-1.71(m,2H),1.53-1.36(m,4H),0.93(t,J=7.5Hz,3H)。质谱(m/z):399.3[M+H]$^+$。

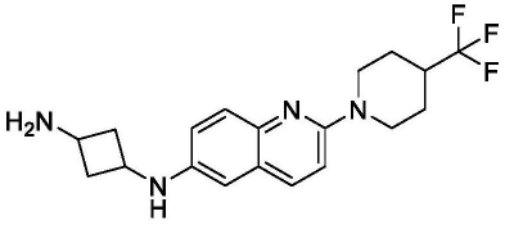
[3153] 化合物591

[3154] 

[3155] 根据为化合物24所述的程序制备标题化合物591(20.8mg,46.2%)(白色固体)。^{1}H NMR(400MHz,)δ6.83-6.74(m,1H),6.64-6.56(m,1H),4.18-3.84(m,4H),3.21(s,3H),2.67-2.48(m,4H),2.47-2.26(m,5H),1.82-1.71(m,2H),1.68-1.56(m,1H),1.51-1.37(m,2H),1.15(s,6H)。质谱(m/z):333.4[M+H]$^+$。

[3156] 化合物592

[3157] N^1-(2-(4-(三氟甲基)哌啶-1-基)喹啉-6-基)环丁烷-1,3-二胺

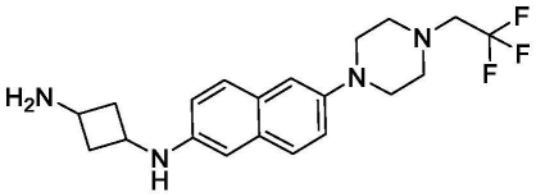
[3158] 

[3159] 根据为化合物24所述的程序制备标题化合物592(15.9mg,36.1%)(黄色固体)。^{1}H NMR(400MHz,DMSO-d6)δ7.80(d,J=9.2Hz,1H),7.37(d,J=8.4Hz,1H),7.10(d,J=9.2Hz,

1H),6.98(d,J=9.2Hz,1H),6.41(s,1H),5.98-5.74(m,1H),4.47(d,J=13.2Hz,2H),3.94-3.73(m,1H),3.60-3.46(m,1H),2.84(t,J=12.8Hz,2H),2.73-2.52(m,3H),2.06(q,J=8.4Hz,3H),1.93-1.73(m,3H),1.47(t,J=12.8Hz,2H)。质谱(m/z):365.2[M+H]$^+$。

[3160] 化合物593

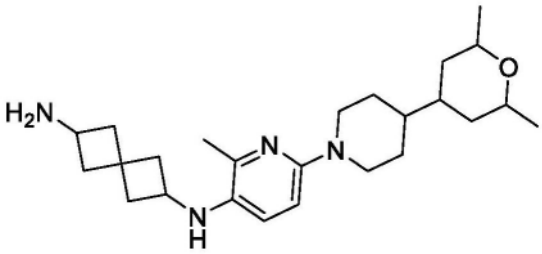
[3161] N^1-(6-(4-(2,2,2-三氟乙基)哌嗪-1-基)萘-2-基)环丁烷-1,3-二胺

[3162] 

[3163] 根据为化合物24所述的程序制备标题化合物593(6.5mg,15.9%)(白色固体)。^{1}H NMR(400MHz,DMSO-d6)δ8.50(s,3H),7.67-7.52(m,1H),7.47(d,J=8.0Hz,1H),7.15(d,J=8.8Hz,1H),7.00(s,1H),6.88(d,J=8.8Hz,1H),6.51(s,1H),6.18-6.02(m,1H),4.17(s,1H),3.77(s,1H),3.24(t,J=10.4Hz,2H),3.13(s,2H),2.79(s,3H),2.23(s,2H),2.12-1.97(m,1H)。质谱(m/z):379.3[M+H]$^+$。

[3164] 化合物594

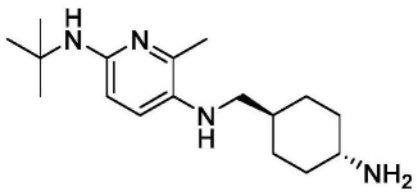
[3165] N^2-(6-(4-(2,6-二甲基四氢-2H-吡喃-4-基)哌啶-1-基)-2-甲基吡啶-3-基)螺[3.3]庚烷-2,6-二胺

[3166] 

[3167] 根据为化合物24所述的程序制备标题化合物594(3.1mg,19.25%)(白色固体)。^{1}H NMR(400MHz,CD_3OD)δ6.88(d,J=8.8Hz,1H),6.58(d,J=8.8Hz,1H),3.97(d,J=12.4Hz,2H),3.80-3.67(m,2H),3.50(dd,J=9.6,6.4Hz,2H),2.65-2.56(m,4H),2.50-2.44(m,1H),2.44-2.35(m,1H),2.29(s,3H),2.23-2.17(m,3H),2.02(d,J=10.8Hz,2H),1.83(d,J=12.6Hz,2H),1.75-1.71(m,2H),1.32(s,3H),1.19(d,J=6.2Hz,6H),0.90-0.86(m,3H)。质谱(m/z):413.4[M+H]$^+$。

[3168] 化合物595

[3169] N5-(((1r,4r)-4-氨基环己基)甲基)-N^2-(叔丁基)-6-甲基吡啶-2,5-二胺

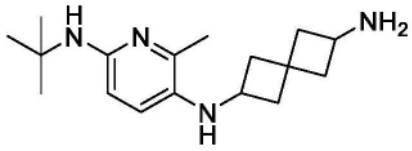
[3170] 

[3171] 根据为化合物24所述的程序制备标题化合物595(65.2mg,33.3%)(黑色固体)。^{1}H NMR(400MHz,DMSO-d6)δ6.71(d,J=8.8,1H),6.27(d,J=8.8,1H),4.95(s,1H),3.98(s,1H),2.76(d,J=6.4,2H),2.49-2.40(m,1H),2.17(s,3H),1.79-1.75(m,4H),1.43-1.31(m,

1H),1.31(s,9H),1.04-0.83(m,4H)。质谱(m/z):290.9[M+H]$^+$。

[3172] 化合物596

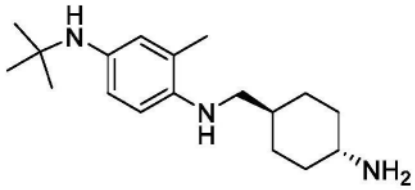
[3173] N5-(6-氨基螺[3.3]庚烷-2-基)-N^2-(叔丁基)-6-甲基吡啶-2,5-二胺

[3174] 

[3175] 根据为化合物24所述的程序制备标题化合物596(101.7mg,58%)(黑色固体)。^{1}H NMR(400MHz,DMSO-d6)δ6.60(d,J=8.8,1H),6.23(d,J=8.4,1H),5.00(s,1H),4.12(s,1H),3.56-3.52(m,1H),3.19-3.12(m,1H),2.39-2.35(m,1H),2.33-2.27(m,1H),2.26-2.19(m,1H),2.15(s,3H),2.12-2.08(m,1H),1.83-1.77(m,2H),1.67-1.59(m,2H),1.30(s,9H)。质谱(m/z):288.9[M+H]$^+$。

[3176] 化合物597

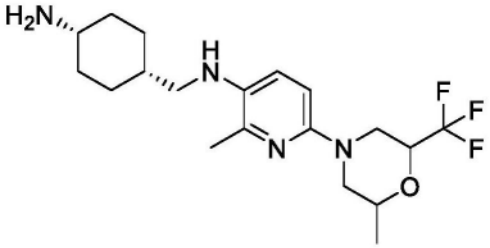
[3177] N^1-(((1r,4r)-4-氨基环己基)甲基)-N^4-(叔丁基)-2-甲基苯-1,4-二胺

[3178] 

[3179] 根据为化合物24所述的程序制备标题化合物597(92.3mg,82.82%)(白色固体)。^{1}H NMR(400MHz,DMSO-d6)δ6.55(dd,J=6.4,2.4Hz,2H),6.33-6.28(m,1H),4.15(s,1H),2.81(d,J=6.4Hz,2H),2.46(dd,J=8.8,5.2Hz,1H),2.01(s,3H),1.83-1.73(m,4H),1.48(dd,J=6.8,3.6Hz,1H),1.10(s,9H),0.95(q,J=10.4Hz,4H)。质谱(m/z):289.3[M+H]$^+$。

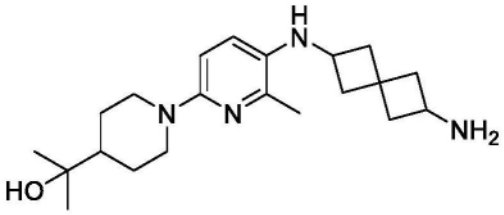
[3180] 化合物598

[3181] N-(((1s,4s)-4-氨基环己基)甲基)-2-甲基-6-(2-甲基-6-(三氟甲基)吗啉代)吡啶-3-胺

[3182] 

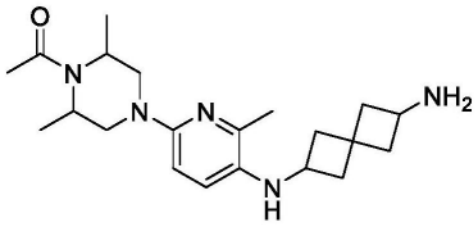
[3183] 根据为化合物24所述的程序制备标题化合物598(15.3mg,42.5%)(淡黄色固体)。^{1}H NMR(400MHz,DMSO-d6)δ7.92(br s,2H),6.86(d,J=8.4Hz,1H),6.58(d,J=8.4Hz,1H),4.62-4.42(m,2H),4.23-4.10(m,1H),3.56-3.46(m,1H),3.46-3.37(m,2H),3.17(br s,1H),2.97-2.86(m,3H),2.23(d,J=3.5Hz,3H),1.78-1.58(m,5H),1.57-1.46(m,4H),1.23(d,J=6.4Hz,4H)。质谱(m/z):387.2[M+H]$^+$。

[3184] 化合物599

[3185] 

[3186] 根据为化合物24所述的程序制备标题化合物599(13.1mg,22.5%)(淡黄色固体)。^{1}H NMR(400MHz,DMSO-d6)δ8.15(br s,3H),6.85(d,J=8.4Hz,1H),6.63(d,J=8.4Hz,1H),4.71(br s,1H),4.26-3.88(m,3H),3.74-3.48(m,2H),2.44-2.31(m,3H),2.25(s,3H),2.21-2.09(m,3H),2.03-1.86(m,2H),1.83-1.66(m,2H),1.40-1.15(m,4H),1.04(s,6H)。质谱(m/z):359.3[M+H]$^+$。

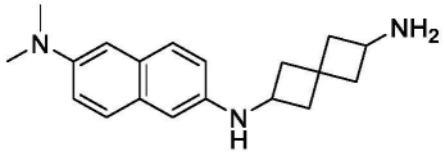
[3187] 化合物600

[3188] 

[3189] 根据为化合物24所述的程序制备标题化合物600(25.7mg,42.5%)(淡黄色固体)。^{1}H NMR(400MHz,DMSO-d6)δ8.28(br s,3H),6.77(d,J=8.4Hz,1H),6.60(d,J=8.4Hz,1H),4.75-4.33(m,1H),4.26-3.99(m,1H),3.88(d,J=12.3Hz,2H),3.72-3.59(m,1H),3.57-3.46(m,1H),2.78-2.54(m,2H),2.40-2.28(m,2H),2.28-2.10(m,6H),2.04(s,3H),2.00-1.74(m,3H),1.22(d,J=6.4Hz,4H)。质谱(m/z):372.3[M+H]$^+$。

[3190] 化合物601

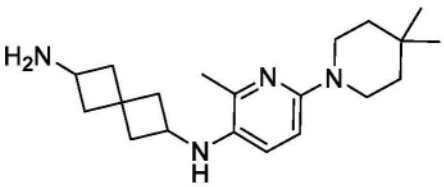
[3191] N^2-(6-氨基螺[3.3]庚烷-2-基)-N^6,N^6-二甲基萘-2,6-二胺

[3192] 

[3193] 根据为化合物24所述的程序制备标题化合物601(38.7mg,43.5%)(黄色油)。^{1}H NMR(400MHz,DMSO-d6)δ7.42(dd,J=14.8,9.2Hz,2H),7.07(dd,J=9.2,2.4Hz,1H),6.82-6.78(m,2H),6.48(d,J=2.0Hz,1H),5.68(d,J=6.8Hz,1H),3.73(dd,J=14.4,7.2Hz,1H),3.19(dd,J=15.2,7.6Hz,1H),2.88(s,6H),2.50-2.45(m,1H),2.34(dt,J=11.6,6.0Hz,2H),2.15-2.11(m,1H),1.83-1.77(m,2H),1.69-1.63(m,2H)。质谱(m/z):296.2[M+H]$^+$。

[3194] 化合物602

[3195] N^2-(6-(4,4-二甲基哌啶-1-基)-2-甲基吡啶-3-基)螺[3.3]庚烷-2,6-二胺

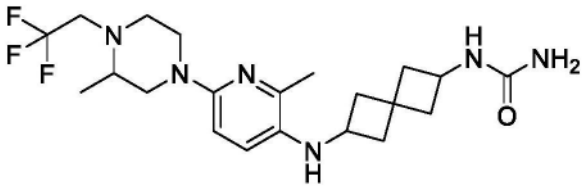
[3196] 

[3197] 根据为化合物24所述的程序制备标题化合物602(33.1mg,58.3%)(黄色固体)。^{1}H

NMR(400MHz,DMSO-d6)δ8.46(s,3H),6.99(s,1H),6.75(s,1H),4.96(s,1H),3.70(s,1H),3.52(s,1H),3.38-3.23(m,5H),2.43-2.13(m,8H),2.00(s,2H),1.41(s,4H),0.95(s,6H)。质谱(m/z):329.3[M+H]$^+$。

[3198] 化合物603

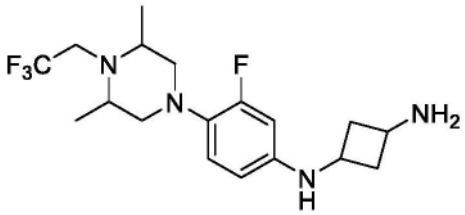
[3199] 1-(6-((2-甲基-6-(3-甲基-4-(2,2,2-三氟乙基)哌嗪-1-基)吡啶-3-基)氨基)螺[3.3]庚烷-2-基)脲

[3200] 

[3201] 根据为化合物24所述的程序制备标题化合物603(15.1mg,33.6%)(白色固体)。^{1}H NMR(400MHz,DMSO-d6)δ6.82-6.66(m,1H),6.57-6.43(m,1H),6.15(d,J=8.2Hz,1H),5.34(s,2H),4.64-4.40(m,1H),3.96-3.84(m,1H),3.71-3.53(m,3H),3.51-3.35(m,2H),3.14-2.94(m,2H),2.86-2.79(m,1H),2.70-2.62(m,3H),2.44-2.09(m,7H),2.00-1.70(m,4H),1.07(d,J=6.2Hz,3H)。质谱(m/z):441.2[M+H]$^+$。

[3202] 化合物604

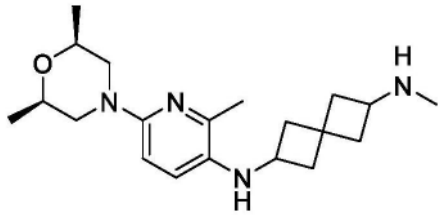
[3203] N^1-(4-(3,5-二甲基-4-(2,2,2-三氟乙基)哌嗪-1-基)-3-氟苯基)环丁烷-1,3-二胺

[3204] 

[3205] 根据为化合物24所述的程序制备标题化合物604(214.9mg,83.3%)(白色固体)。^{1}H NMR(400MHz,DMSO-d6)δ6.81-6.77(m,1H),6.25-6.18(m,2H),5.85-5.76(m,1H),3.79(d,J=5.6,1H),3.53-3.50(m,1H),3.39-3.31(m,2H),3.19-3.18(m,1H),2.96(d,J=10.8,2H),2.84(s,2H),2.62-2.58(m,1H),2.35(t,J=10.8,2H),2.03(t,J=6.0,3H),1.52-1.44(m,1H),1.05(d,J=6.0,6H)。质谱(m/z):374.8[M+H]$^+$。

[3206] 化合物605

[3207] N^2-(6-((2R,6S)-2,6-二甲基吗啉代)-2-甲基吡啶-3-基)-N6-甲基螺[3.3]庚烷-2,6-二胺

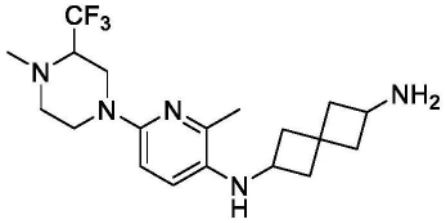
[3208] 

[3209] 根据为化合物23所述的程序制备标题化合物605(20mg,29%)。^{1}H NMR(400MHz,CD_3OD)δ7.47(d,J=9.6Hz,1H),7.10(d,J=9.6Hz,1H),3.93-3.58(m,6H),2.71-2.45(m,11H),2.39-2.37(m,1H),2.23-2.21(m,2H),2.13-2.03(m,2H),1.23(d,J=6.4Hz,6H)。质谱

(m/z):344.9[M+H]$^+$。

[3210] 化合物606

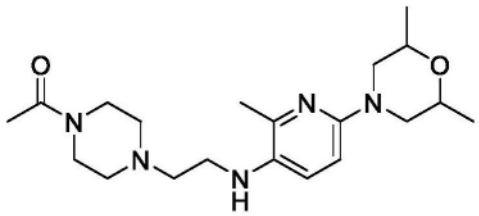
[3211] N^2-(2-甲基-6-(4-甲基-3-(三氟甲基)哌嗪-1-基)吡啶-3-基)螺[3.3]庚烷-2,6-二胺

[3212] 

[3213] 根据为化合物24所述的程序制备标题化合物606(20mg,26.1%)(白色固体)。^{1}H NMR(400MHz,CD_3OD)δ6.77(d,J=8.8Hz,1H),6.46(d,J=8.8Hz,1H),3.89(d,J=10.0Hz,1H),3.64-3.61(m,1H),3.52-3.35(m,2H),2.95-2.81(m,4H),2.50-2.17(m,11H),2.00-1.78(m,4H)。质谱(m/z):383.8[M+H]$^+$。

[3214] 化合物607

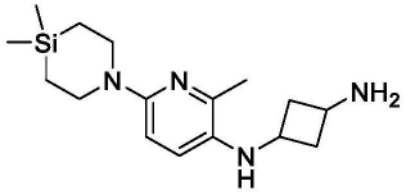
[3215] 1-(4-(2-((6-(2,6-二甲基吗啉代)-2-甲基吡啶-3-基)氨基)乙基)哌嗪-1-基)乙-1-酮

[3216] 

[3217] 根据为化合物24所述的程序制备标题化合物607(20.1mg,17.85%,收率)(黄色固体)。^{1}H NMR(400MHz,CD_3OD)δ7.05(d,J=8.8Hz,1H),6.60(d,J=8.8Hz,1H),3.82-3.72(m,4H),3.67-3.54(m,4H),3.23(t,J=6.4Hz,2H),2.68(t,J=6.4Hz,2H),2.59-2.54(m,2H),2.54-2.47(m,2H),2.33(s,3H),2.32-2.25(m,2H),2.12(s,3H),1.24(d,J=6.4Hz,6H)。质谱(m/z):375.8[M+H]$^+$。

[3218] 化合物608

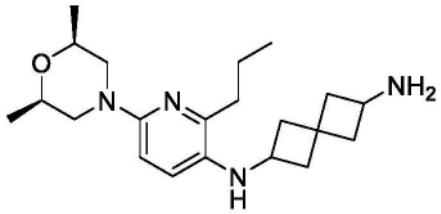
[3219] N^1-(6-(4,4-二甲基-1,4-氮杂硅杂环己烷-1-基)-2-甲基吡啶-3-基)环丁烷-1,3-二胺

[3220] 

[3221] 根据为化合物24所述的程序制备标题化合物608(50.8mg,70%)(黄色固体)。^{1}H NMR(400MHz,CD_3OD)δ6.92(d,J=8.8Hz,0.16H),6.81(d,J=8.8Hz,0.79H),6.53(d,J=8.7Hz,1H),4.01-3.89(m,0.78H),3.79-3.61(m,5H),3.25-3.15(m,0.28H),2.84-2.73(m,0.32H),2.30(s,3H),2.26-2.16(m,3.27H),1.69-1.60(m,0.38H),0.78-0.72(m,4.24H),0.07(s,6H)。质谱(m/z):304.9[M+H]$^+$。

[3222] 化合物609

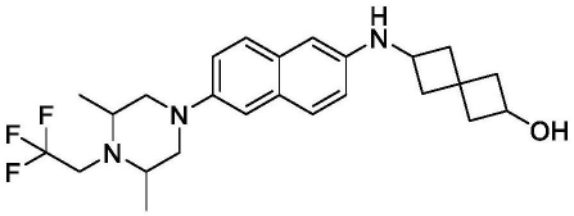
[3223] N^2-(6-((2S,6R)-2,6-二甲基吗啉代)-2-丙基吡啶-3-基)螺[3.3]庚烷-2,6-二胺

[3224] 

[3225] 根据为化合物24所述的程序制备标题化合物609(106mg,59.1%)(白色固体)。^{1}H NMR(400MHz,CD_3OD)δ6.83(d,J=8.8Hz,1H),6.49(t,J=7.6Hz,1H),3.79(d,J=11.6Hz,2H),3.73-3.64(m,3H),3.29-3.25(m,1H),2.59-2.51(m,2H),2.46-2.40(m,2H),2.32-2.21(m,4H),1.82-1.73(m,6H),1.18(t,J=5.2Hz,6H),0.96(t,J=7.6Hz,3H)。质谱(m/z):359.3$[M+H]^+$。

[3226] 化合物610

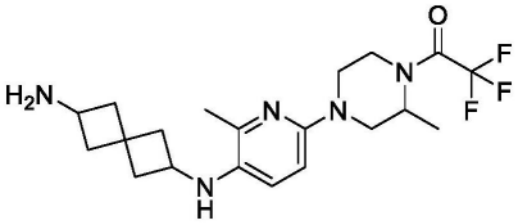
[3227] 6-((6-(3,5-二甲基-4-(2,2,2-三氟乙基)哌嗪-1-基)萘-2-基)氨基)螺[3.3]庚烷-2-醇

[3228] 

[3229] 根据为化合物5所述的程序制备标题化合物610(22.5mg,31.2%)(淡黄色固体)。^{1}H NMR(400MHz,DMSO-d6)δ7.44(dd,J=8.8,5.2Hz,2H),7.17(dd,J=8.8,2.4Hz,1H),6.96(d,J=2.4Hz,1H),6.82(dd,J=8.8,2.4Hz,1H),6.50(d,J=2.4Hz,1H),5.79(d,J=6.4Hz,1H),4.89(d,J=6.4Hz,1H),4.06-3.92(m,1H),3.81-3.67(m,1H),3.52(d,J=11.5Hz,2H),3.39(q,J=10.4Hz,2H),2.96-2.78(m,2H),2.48-2.29(m,5H),2.26-2.12(m,1H),1.92-1.75(m,4H),1.12(d,J=6.2Hz,6H)。质谱(m/z):448.3$[M+H]^+$。

[3230] 化合物611

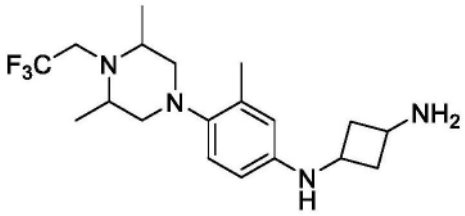
[3231] 1-(4-(5-((6-氨基螺[3.3]庚烷-2-基)氨基)-6-甲基吡啶-2-基)-2-甲基哌嗪-1-基)-2,2,2-三氟乙-1-酮

[3232] 

[3233] 根据为化合物24所述的程序制备标题化合物611(25.1mg,34.1%)(淡黄色固体)。^{1}H NMR(400MHz,DMSO-d6)δ8.09(s,3H),6.74(d,J=8.7Hz,1H),6.59-6.48(m,1H),4.66-4.55(m,1H),4.31-4.18(m,1H),4.16-3.73(m,3H),3.70-3.45(m,3H),3.28-3.16(m,1H),2.88-2.72(m,1H),2.71-2.60(m,1H),2.45-2.29(m,2H),2.21(s,3H),2.19-2.08(m,2H),1.96-1.85(m,2H),1.34(d,J=6.5Hz,1H),1.24(d,J=6.5Hz,2H).质谱(m/z):412.2$[M+H]^+$。

[3234] 化合物612

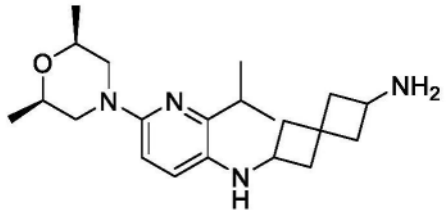
[3235] N^1-(4-(3,5-二甲基-4-(2,2,2-三氟乙基)哌嗪-1-基)-3-甲基苯基)环丁烷-1,3-二胺

[3236] 

[3237] 根据为化合物24所述的程序制备标题化合物612(23.1mg,14.3%)(白色固体)。^{1}H NMR(400MHz,DMSO-d6)δ=6.77(d,J=8.4,1H),6.29(d,J=2.0,1H),6.23-6.21(m,1H),5.50-5.42(m,1H),3.77(d,J=5.2,1H),3.48-3.45(m,1H),3.40-3.33(m,3H),2.82(s,2H),2.74(d,J=11.2,2H),2.32(t,J=10.8,2H),2.14(s,4H),2.02-1.94(m,4H),1.04(d,J=6.0,6H)。质谱(m/z):370.8$[M+H]^+$。

[3238] 化合物613

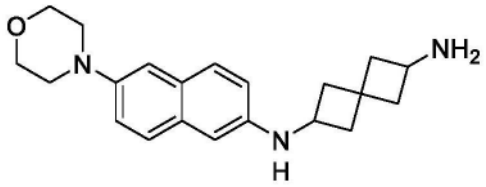
[3239] N^2-(6-((2S,6R)-2,6-二甲基吗啉代)-2-异丙基吡啶-3-基)螺[3.3]庚烷-2,6-二胺

[3240] 

[3241] 根据为化合物24所述的程序制备标题化合物613(1.5mg,2.36%)(白色固体)。^{1}H NMR(400MHz,CD_3OD)6.85(d,J=8.8Hz,1H),6.48(d,J=8.8Hz,1H),3.91-3.86(m,2H),3.75-3.63(m,3H),3.12-3.04(m,1H),2.52-2.35(m,2H),2.34-2.13(m,5H),2.02-1.98(m,1H),1.91-1.72(m,4H),1.57(dd,J=6.8,0.8Hz,1H),1.18(dd,J=12.4,6.4Hz,12H)。质谱(m/z):358.9$[M+H]^+$。

[3242] 化合物614

[3243] N^2-(6-吗啉代萘-2-基)螺[3.3]庚烷-2,6-二胺

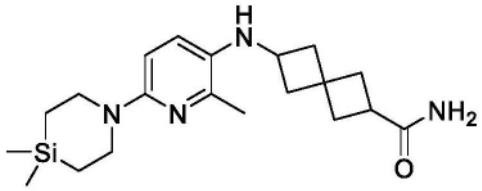
[3244] 

[3245] 根据为化合物24所述的程序制备标题化合物614(8.6mg,5.75%)(白色固体)。^{1}H NMR(400MHz,CD_3OD)δ7.47(dd,J=8.8,6.4Hz,2H),7.15(dd,J=9.2,2.8Hz,1H),7.04(d,J=2.4Hz,1H),6.85(dd,J=8.8,2.4Hz,1H),6.64(d,J=2.4Hz,1H),3.86-3.82(m,5H),3.32(dd,J=11.6,4.4Hz,1H),3.14-3.11(m,4H),2.60-2.54(m,1H),2.49-2.38(m,2H),2.28-2.21(m,1H),1.86(m,4H)。质谱(m/z):337.9$[M+H]^+$。

[3246] 化合物615

[3247] 6-((6-(4,4-二甲基-1,4-氮杂硅杂环己烷-1-基)-2-甲基吡啶-3-基)氨基)螺

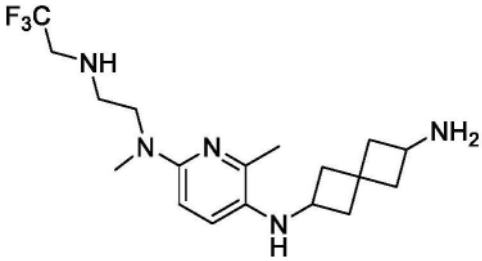
[3.3]庚烷-2-甲酰胺

[3248] 

[3249] 根据为化合物10所述的程序制备标题化合物615(29.1mg,19%)(黄色固体)。^{1}H NMR(400MHz,CD_3OD)δ6.99(s,1H),6.65(s,1H),3.84-3.61(m,3H),3.27-3.18(m,0.60H),3.08-2.96(m,1H),2.64-2.55(m,1H),2.45-2.36(m,1.51H),2.31(d,J=8.6Hz,2.51H),2.28-2.21(m,1.54H),2.17-2.08(m,1.40H),2.01-1.93(m,1H),1.91-1.82(m,1H),1.37(d,J=6.6Hz,3.50H),0.83-0.74(m,4H),0.09(s,6H)。质谱(m/z):373.3$[M+H]^+$。

[3250] 化合物616

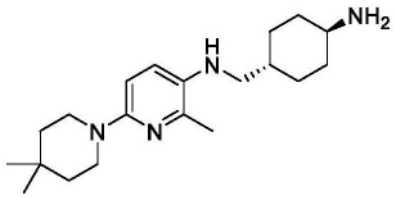
[3251] N5-(6-氨基螺[3.3]庚烷-2-基)-N2,6-二甲基-N^2-(2-((2,2,2-三氟乙基)氨基)乙基)吡啶-2,5-二胺

[3252] 

[3253] 根据为化合物24所述的程序制备标题化合物616(12.7mg,15.9%)(白色固体)。^{1}H NMR(400MHz,CDCl3)δ6.75(d,J=8.8Hz,1H),6.31(d,J=8.8Hz,1H),3.75-3.68(m,1H),3.59(t,J=6.0Hz,2H),3.45-3.37(m,1H),3.24(q,J=9.6Hz,2H),2.95-2.90(m,5H),2.56-2.37(m,4H),2.27(s,3H),1.88-1.77(m,4H)。质谱(m/z):371.9$[M+H]^+$。

[3254] 化合物617

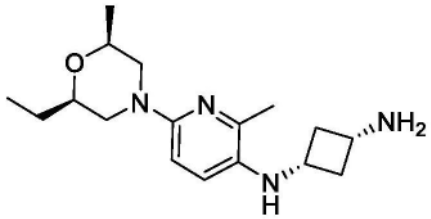
[3255] N-(((1r,4r)-4-氨基环己基)甲基)-6-(4,4-二甲基哌啶-1-基)-2-甲基吡啶-3-胺

[3256] 

[3257] 根据为化合物24所述的程序制备标题化合物617(28.0mg,29.4%)(黄色固体)。^{1}H NMR(400MHz,DMSO-d6)δ8.33(s,3H),7.08(s,1H),6.77(s,1H),4.89(s,1H),3.35-3.26(m,2H),2.89(s,3H),2.34(s,3H),2.00(s,2H),1.86(d,J=12.8Hz,2H),1.54-1.26(m,7H),1.02(d,J=16.4Hz,2H),0.95(s,6H)。质谱(m/z):331.3$[M+H]^+$。

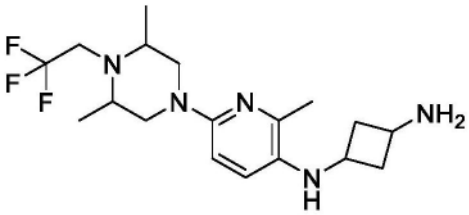
[3258] 化合物618

[3259] (1s,3S)-N^1-(6-((2R,6S)-2-乙基-6-甲基吗啉代)-2-甲基吡啶-3-基)环丁烷-1,3-二胺

[3260] 

[3261] 根据为化合物24所述的程序制备标题化合物618(1.7mg,4.2%)(黄色固体)。^{1}H NMR(400MHz,DMSO-d6)δ6.62(d,J=8.8Hz,1H),6.50(d,J=8.8Hz,1H),3.82(t,J=12.8Hz,3H),3.59(d,J=10.0Hz,1H),3.44(d,J=7.6Hz,2H),2.26-2.20(m,3H),2.16(t,J=11.2Hz,2H),2.10-2.02(m,2H),2.01-1.90(m,2H),1.47(q,J=7.6Hz,2H),1.14(d,J=6.0Hz,3H),0.98-0.90(m,3H)。质谱(m/z):305.3[M+H]$^+$。

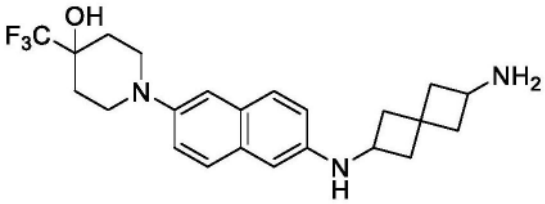
[3262] 化合物619

[3263] 

[3264] 根据为化合物24所述的程序制备标题化合物619(35.6mg,56.2%)(淡黄色固体)。^{1}H NMR(400MHz,DMSO-d6)δ8.48-8.15(m,3H),6.73-6.49(m,2H),4.96-4.65(m,1H),4.12-3.99(m,1H),3.89-3.67(m,3H),2.82-2.70(m,2H),2.46-2.40(m,2H),2.37-2.17(m,7H),1.09(d,J=6.2Hz,6H)。质谱(m/z):372.2[M+H]$^+$。

[3265] 化合物620

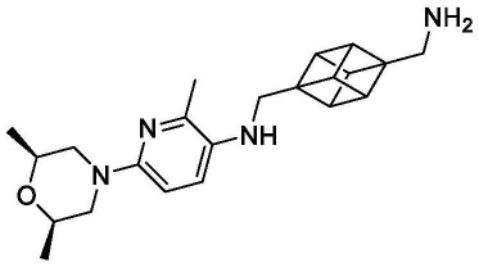
[3266] 1-(6-((6-氨基螺[3.3]庚烷-2-基)氨基)萘-2-基)-4-(三氟甲基)哌啶-4-醇

[3267] 

[3268] 根据为化合物24所述的程序制备标题化合物620(3mg,4.03%)(白色固体)。^{1}H NMR(400MHz,CD_3OD)δ7.47(dd,J=8.8,5.6Hz,2H),7.17(dd,J=9.2,2.4Hz,1H),7.11(d,J=1.6Hz,1H),6.85(dd,J=8.8,2.4Hz,1H),6.64(d,J=1.6Hz,1H),3.84(p,J=7.6Hz,1H),3.53(d,J=12.0Hz,2H),2.99(dd,J=12.0,10.4Hz,2H),2.59-2.52(m,1H),2.48-2.37(m,2H),2.26-2.19(m,1H),2.03-1.75(m,9H)。质谱(m/z):420.2[M+H]$^+$。

[3269] 化合物621

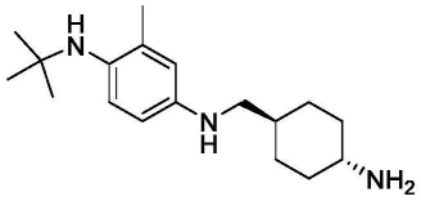
[3270] N-((4-(氨基甲基)立方烷-1-基)甲基)-6-((2S,6R)-2,6-二甲基吗啉代)-2-甲基吡啶-3-胺

[3271] 

[3272] 根据为化合物24所述的程序制备标题化合物621(11mg,12.5%)(白色固体)。^{1}H NMR(400MHz,DMSO-d6)δ8.49(s,1H),6.97(d,J=8.8,1H),6.51(d,J=8.8,1H),3.85(d,J=10.8,2H),3.63-3.59(m,8H),3.20(s,2H),3.12(s,2H),2.22(s,2H),2.20-2.11(m,2H),1.64(s,1H),1.13(d,J=6.4,6H)。质谱(m/z):367.3[M+H]$^+$。

[3273] 化合物622

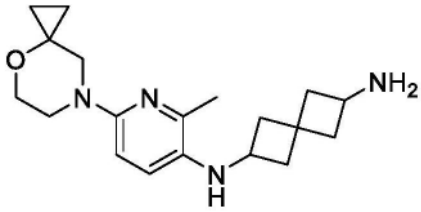
[3274] N^4-(((1r,4r)-4-氨基环己基)甲基)-N^1-(叔丁基)-2-甲基苯-1,4-二胺

[3275] 

[3276] 根据为化合物24所述的程序制备标题化合物622(43mg,32.15%)(白色固体)。^{1}H NMR(400MHz,CD_3OD)δ6.86(d,J=8.4Hz,1H),6.52-6.44(m,2H),2.90(d,J=6.8Hz,2H),2.59(m,J=10.8,3.6Hz,1H),2.21(s,3H),1.91(d,J=9.6Hz,4H),1.59-1.51(m,1H),1.21(s,9H),1.17-1.01(m,4H)。质谱(m/z):290.0[M+H]$^+$。

[3277] 化合物623

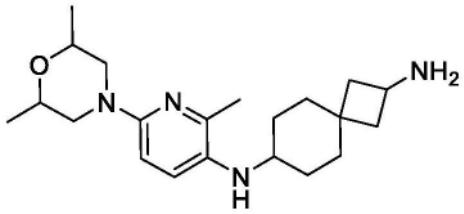
[3278] N^2-(2-甲基-6-(4-氧杂-7-氮杂螺[2.5]辛烷-7-基)吡啶-3-基)螺[3.3]庚烷-2,6-二胺

[3279] 

[3280] 根据为化合物24所述的程序制备标题化合物623(15.3mg,12.10%)(白色固体)。^{1}H NMR(400MHz,CD_3OD)δ6.89(d,J=8.8Hz,1H),6.55(d,J=8.8Hz,1H),3.90-3.85(m,2H),3.73(t,J=7.6Hz,1H),3.37(s,1H),3.31(dd,J=3.2,1.6Hz,2H),3.23(s,2H),2.56-2.35(m,3H),2.29(s,3H),2.28-2.23(m,1H),1.96-1.77(m,4H),0.79(d,J=5.2Hz,2H),0.72-0.64(m,2H)。质谱(m/z):328.9[M+H]$^+$。

[3281] 化合物624

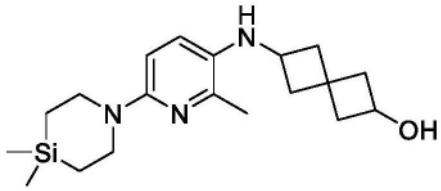
[3282] N7-(6-(2,6-二甲基吗啉代)-2-甲基吡啶-3-基)螺[3.5]壬烷-2,7-二胺

[3283] 

[3284] 根据为化合物24所述的程序制备标题化合物624(57.4mg,50.8%)(黄色固体)。^{1}H NMR(400MHz,DMSO-d6)δ8.48(s,3H),7.02(s,1H),6.56(s,1H),4.03-3.81(m,2H),3.60(t,J=8.4Hz,3H),3.06(s,1H),2.39-2.08(m,6H),1.98(d,J=8.0Hz,2H),1.89(t,J=10.0Hz,1H),1.74(t,J=14.4Hz,4H),1.46-1.26(m,3H),1.14(d,J=6.4Hz,6H)。质谱(m/z):359.2[M+H]$^+$。

[3285] 化合物625

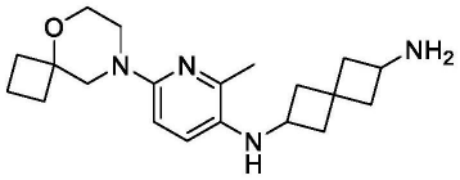
[3286] 6-((6-(4,4-二甲基-1,4-氮杂硅杂环己烷-1-基)-2-甲基吡啶-3-基)氨基)螺[3.3]庚烷-2-醇

[3287] 

[3288] 根据为化合物5所述的程序制备标题化合物625(24.7mg,27%)(黄色油)。^{1}H NMR(400MHz,CD_3OD)δ6.88(d,J=8.8Hz,1H),6.52(d,J=8.8Hz,1H),4.16-4.05(m,1H),3.78-3.65(m,5H),2.51-2.42(m,2H),2.40-2.33(m,1H),2.31-2.24(m,4H),2.00-1.88(m,4H),0.78-0.73(m,4H),0.07(s,6H)。质谱(m/z):346.2[M+H]$^+$。

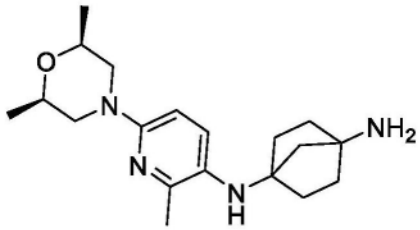
[3289] 化合物626

[3290] N^2-(2-甲基-6-(5-氧杂-8-氮杂螺[3.5]壬烷-8-基)吡啶-3-基)螺[3.3]庚烷-2,6-二胺

[3291] 

[3292] 根据为化合物24所述的程序制备标题化合物626(4.0mg,6.2%)(白色固体)。^{1}H NMR(400MHz,CD_3OD)δ6.78(d,J=8.8Hz,1H),6.46(d,J=8.8Hz,1H),3.64-3.60(m,3H),3.22-3.19(m,1H),3.07-3.04(m,2H),2.44-2.39(m,1H),2.35(dd,J=11.2,5.2Hz,1H),2.29-2.24(m,1H),2.19(s,3H),2.15(dd,J=8.8,3.6Hz,1H),2.04-1.88(m,5H),1.85-1.61(m,7H)。质谱(m/z):343.3[M+H]$^+$。

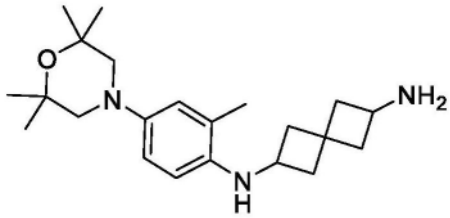
[3293] 化合物627

[3294] 

[3295] 根据为化合物24所述的程序制备标题化合物627(21.1mg,32.2%)(淡黄色固体)。^{1}H NMR(400MHz,DMSO-d6)δ8.38(br s,3H),6.74(d,J=8.4Hz,1H),6.49(d,J=8.4Hz,1H),4.75-4.42(m,1H),3.83(d,J=12.0Hz,2H),3.72-3.41(m,5H),2.49-2.43(m,1H),2.42-2.28(m,2H),2.23(s,3H),2.20-2.06(m,5H),1.98-1.84(m,2H),1.12(d,J=6.2Hz,6H)。质谱(m/z):331.3[M+H]$^+$。

[3296] 化合物628

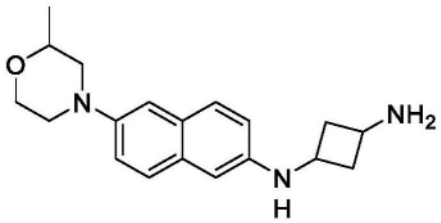
[3297] N^2-(2-甲基-4-(2,2,6,6-四甲基吗啉代)苯基)螺[3.3]庚烷-2,6-二胺

[3298] 

[3299] 根据为化合物24所述的程序制备标题化合物628(24.6mg,36.5%)(黄色固体)。^{1}H NMR(400MHz,DMSO-d6)δ8.39(s,3H),6.73-6.52(m,2H),6.34(s,1H),4.59(s,1H),3.68(s,1H),3.58-3.47(m,1H),2.75-2.62(m,3H),2.42-2.31(m,2H),2.28-2.15(m,3H),2.13-2.01(m,3H),1.99-1.86(m,2H),1.20(s,12H)。质谱(m/z):358.3[M+H]$^+$。

[3300] 化合物629

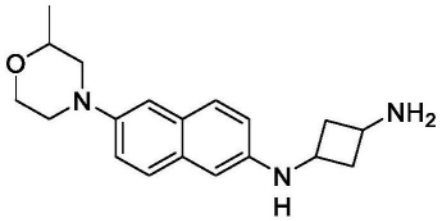
[3301] N^1-(6-(2-甲基吗啉代)萘-2-基)环丁烷-1,3-二胺

[3302] 

[3303] 根据为化合物24所述的程序制备标题化合物629(1.2mg,1.09%)(白色固体)。^{1}H NMR(400MHz,DMSO-d6)δ7.46(d,J=8.8Hz,2H),7.17(dd,J=9.2,2.4Hz,1H),6.98(d,J=2.4Hz,1H),6.86(dd,J=8.8,2.4Hz,1H),6.43(d,J=2.0Hz,1H),5.87(d,J=5.6Hz,1H),3.91(dd,J=11.2,1.6Hz,2H),3.71-3.63(m,2H),3.57-3.44(m,3H),2.65-2.60(m,1H),2.31(dd,J=11.6,10.4Hz,1H),2.11-2.01(m,4H),1.16(d,J=6.4Hz,3H)。质谱(m/z):311.9[M+H]$^+$。

[3304] 化合物630

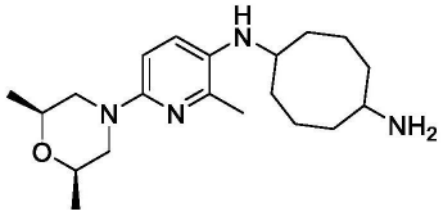
[3305] N^1-(6-(2-甲基吗啉代)萘-2-基)环丁烷-1,3-二胺

[3306] 

[3307] 根据为化合物24所述的程序制备标题化合物630(20.3mg,18.37%)(白色固体)。^{1}H NMR(400MHz,DMSO-d6)δ7.45(dd,J=8.8,4.4Hz,2H),7.17(dd,J=8.8,2.4Hz,1H),6.98(d,J=2.4Hz,1H),6.85(dd,J=8.8,2.2Hz,1H),6.53(d,J=2.0Hz,1H),5.77(d,J=6.4Hz,1H),3.91(dd,J=11.2,2.0Hz,1H),3.71-3.63(m,2H),3.55(d,J=11.6Hz,1H),3.46(d,J=11.6Hz,1H),3.39(d,J=6.8Hz,1H),3.11-3.03(m,1H),2.74-2.66(m,2H),2.62(td,J=11.6,3.2Hz,1H),2.31(dd,J=11.6,10.0Hz,1H),1.49(J=8.8,2.8Hz,2H),1.16(d,J=6.2Hz,3H)。质谱(m/z):311.9[M+H]$^+$。

[3308] 化合物631

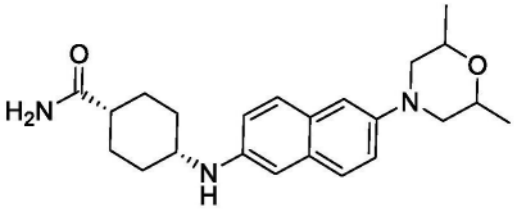
[3309] N^1-(6-((2R,6S)-2,6-二甲基吗啉代)-2-甲基吡啶-3-基)环辛烷-1,5-二胺

[3310] 

[3311] 根据为化合物24所述的程序制备标题化合物631(8.1mg,13%)(黄色油)。^{1}H NMR(400MHz,CD_3OD)δ7.57(d,J=9.4Hz,1H),7.07(d,J=9.5Hz,1H),3.75(d,J=10.8Hz,4H),3.59(d,J=2.8Hz,1H),3.38(t,J=9.2Hz,1H),2.64(dd,J=16.2,7.2Hz,2H),2.47(s,3H),1.81(m,12H),1.21(d,J=6.2Hz,6H)。质谱(m/z):346.9[M+H]$^+$。

[3312] 化合物632

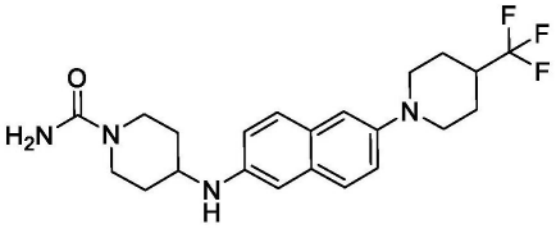
[3313] (1s,4s)-4-((6-(2,6-二甲基吗啉代)萘-2-基)氨基)环己烷-1-甲酰胺

[3314] 

[3315] 根据为化合物24所述的程序制备标题化合物632(12.7mg,19.0%)(紫色固体)。^{1}H NMR(400MHz,DMSO-d6)δ7.44(d,J=8.8Hz,2H),7.20-7.14(m,2H),7.00-6.94(m,2H),6.71(s,1H),6.63(d,J=2.0Hz,1H),5.49(d,J=7.2Hz,1H),3.78-3.68(m,2H),3.58-3.49(m,3H),2.27-2.15(m,3H),1.89-1.69(m,4H),1.67-1.48(m,4H),1.16(d,J=6.0Hz,6H)。质谱(m/z):382.3[M+H]$^+$。

[3316] 化合物633

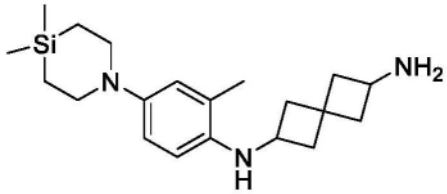
[3317] 4-((6-(4-(三氟甲基)哌啶-1-基)萘-2-基)氨基)哌啶-1-甲酰胺

[3318] 

[3319] 根据为化合物24所述的程序制备标题化合物633(2.8mg,4.9%)(橙色固体)。^{1}H NMR(400MHz,DMSO-d6)δ7.46(d,J=8.8Hz,2H),7.17(dd,J=8.8,2.4Hz,1H),7.02(d,J=2.4Hz,1H),6.89(dd,J=8.8,2.4Hz,1H),6.71(d,J=2.4Hz,1H),5.92(s,2H),5.51(d,J=8.0Hz,1H),3.88(d,J=13.6Hz,2H),3.74(d,J=12.0Hz,2H),3.54-3.42(m,1H),2.96-2.83(m,2H),2.75-2.62(m,3H),1.97-1.84(m,4H),1.67-1.53(m,2H),1.32-1.24(m,2H)。质谱(m/z):421.2[M+H]$^+$。

[3320] 化合物634

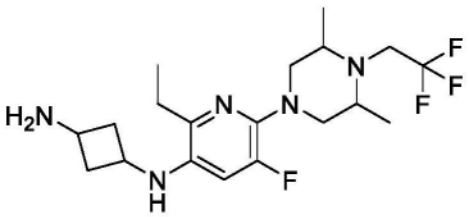
[3321] N^2-(4-(4,4-二甲基-1,4-氮杂硅杂环己烷-1-基)-2-甲基苯基)螺[3.3]庚烷-2,6-二胺

[3322] 

[3323] 根据为化合物24所述的程序制备标题化合物634(32.4mg,38.9%)(白色固体)。^{1}H NMR(400MHz,CDCl3)δ6.63(d,J=8.8Hz,2H),6.36(d,J=8.1Hz,1H),3.74-3.68(m,1H),3.41(d,J=5.6Hz,4H),2.49-2.22(m,7H),2.04(s,3H),1.74(ddd,J=22.2,10.8,5.3Hz,5H),0.77-0.68(m,6H)。质谱(m/z):344.2[M+H]$^+$。

[3324] 化合物635

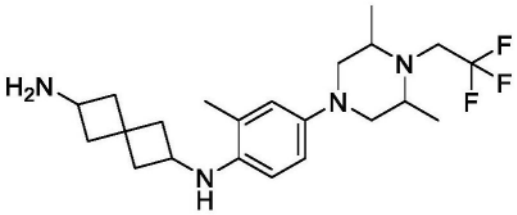
[3325] N^1-(6-(3,5-二甲基-4-(2,2,2-三氟乙基)哌嗪-1-基)-2-乙基-5-氟吡啶-3-基)环丁烷-1,3-二胺

[3326] 

[3327] 根据为化合物24所述的程序制备标题化合物635(26.2,50%)(油)。^{1}H NMR(400MHz,CD_3OD)δ6.60(dd,J=47.5,14.1Hz,1H),3.97-3.87(m,0.5H),3.65(dd,J=13.8,6.3Hz,0.5H),3.50(d,J=12.2Hz,2H),3.37(s,2H),3.19(dd,J=15.3,7.9Hz,1H),2.95(s,2H),2.84-2.72(m,1H),2.59(s,4H),2.30-2.14(m,2H),1.65(ddd,J=17.4,8.7,2.8Hz,1H),1.23(td,J=7.5,2.0Hz,3H),1.14(d,J=6.3Hz,6H).质谱(m/z):404.3[M+H]$^+$。

[3328] 化合物636

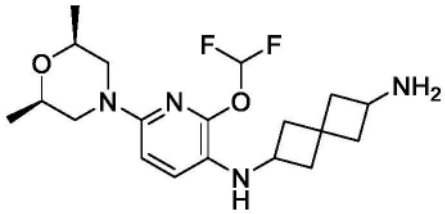
[3329] N^2-(4-(3,5-二甲基-4-(2,2,2-三氟乙基)哌嗪-1-基)-2-甲基苯基)螺[3.3]庚烷-2,6-二胺

[3330] 

[3331] 根据为化合物24所述的程序制备标题化合物636(8mg,10%)(油)。^{1}H NMR(400MHz,CD_3OD)δ6.73(m,2H),6.64(m,3H),6.47(m,1H),3.77(m,1H),3.37(m,3H),3.25(d,J=11.4Hz,2H),2.93(m,2H),2.55(td,J=11.4,5.8Hz,1H),2.47(m,1H),2.37(dt,J=11.4,9.2Hz,3H),2.27(m,1H),2.12(s,3H),1.89(m,4H),1.16(d,J=6.3Hz,7H)。质谱(m/z):411.3$[M+H]^+$。

[3332] 化合物637

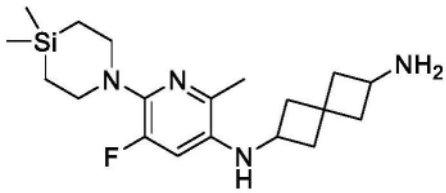
[3333] N^2-(2-(二氟甲氧基)-6-((2S,6R)-2,6-二甲基吗啉代)吡啶-3-基)螺[3.3]庚烷-2,6-二胺

[3334] 

[3335] 根据为化合物24所述的程序制备标题化合物637(18.6mg,48.9%)(紫色固体)。^{1}H NMR(400MHz,DMSO-d6)δ8.18(s,2H),7.70(t,J=73.5Hz,2H),7.00-6.88(m,1H),6.47(d,J=8.4Hz,1H),4.68(s,1H),3.89-3.77(m,2H),3.73-3.52(m,4H),2.49-2.43(m,2H),2.40-2.28(m,2H),2.24-2.13(m,4H),2.00-1.86(m,2H)。质谱(m/z):383.2$[M+H]^+$。

[3336] 化合物638

[3337] N^2-(6-(4,4-二甲基-1,4-氮杂硅杂环己烷-1-基)-5-氟-2-甲基吡啶-3-基)螺[3.3]庚烷-2,6-二胺

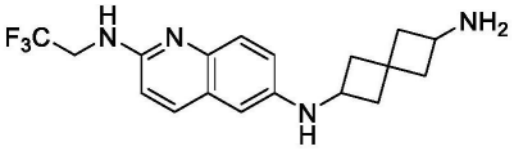
[3338] 

[3339] 根据为化合物24所述的程序制备标题化合物638(59.1mg,75.42%)(白色固体)。

[3340] ^{1}H NMR(400MHz,CD_3OD)δ6.61(d,J=14.0Hz,1H),3.74-3.66(m,1H),3.51-3.44(m,4H),3.28(dd,J=8.8,7.2Hz,1H),2.57-2.36(m,3H),2.31-2.24(m,1H),2.24(d,J=1.2Hz,3H),1.97-1.77(m,4H),0.90-0.84(m,4H),0.13-0.08(m,6H)。质谱(m/z):363.3$[M+H]^+$。

[3341] 化合物639

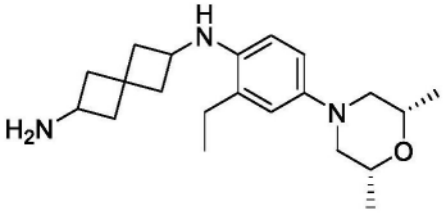
[3342] N6-(6-氨基螺[3.3]庚烷-2-基)-N^2-(2,2,2-三氟乙基)喹啉-2,6-二胺

[3343] 

[3344] 根据为化合物24所述的程序制备标题化合物639(10.3mg,13.24%)(白色固体)。^{1}H NMR(400MHz,CD_3OD)δ7.75(d,J=8.8Hz,1H),7.47(d,J=9.2Hz,1H),7.01(dd,J=9.2,2.4Hz,1H),6.74(d,J=8.8Hz,1H),6.64(d,J=2.4Hz,1H),4.23(q,J=9.6Hz,2H),3.90-3.82(m,1H),3.36(dd,J=14.4,7.2Hz,1H),2.63-2.56(m,1H),2.53-2.41(m,2H),2.32-2.24(m,1H),1.99-1.79(m,4H)。质谱(m/z):351.2$[M+H]^+$。

[3345] 化合物640

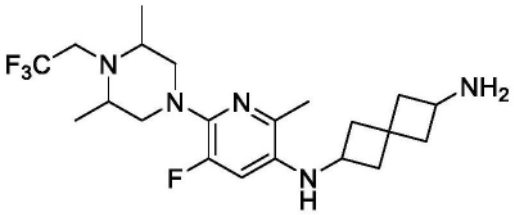
[3346] N^2-(4-((2S,6R)-2,6-二甲基吗啉代)-2-乙基苯基)螺[3.3]庚烷-2,6-二胺

[3347] 

[3348] 根据为化合物24所述的程序制备标题化合物640(41.6mg,73%)(黄色固体)。^{1}H NMR(400MHz,CD_3OD SPE)δ6.76(d,J=2.4Hz,1H),6.72(d,J=8.6Hz,1H),6.50(d,J=8.6Hz,1H),3.85-3.73(m,3H),3.42-3.33(m,1H),3.27(d,J=10.9Hz,2H),2.59-2.43(m,4H),2.42-2.36(m,1H),2.31-2.22(m,3H),1.99-1.82(m,4H),1.22-1.16(m,9H)。质谱(m/z):344.2$[M+H]^+$。

[3349] 化合物641

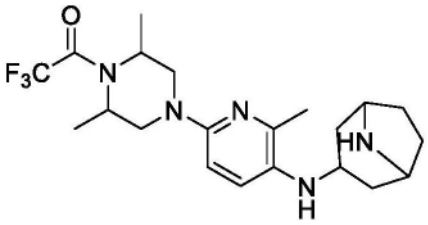
[3350] N^2-(6-(3,5-二甲基-4-(2,2,2-三氟乙基)哌嗪-1-基)-5-氟-2-甲基吡啶-3-基)螺[3.3]庚烷-2,6-二胺

[3351] 

[3352] 根据为化合物24所述的程序制备标题化合物641(5mg,31.2%)(白色固体)。^{1}H NMR(400MHz,CD_3OD)δ6.59(d,J=13.6Hz,1H),3.74-3.63(m,1H),3.47-3.30(m,5H),2.90(d,J=6.4Hz,2H),2.60-2.35(m,5H),2.32-2.18(m,4H),1.93-1.90(m,4H),1.11(d,J=6.4Hz,6H)。质谱(m/z):430.1$[M+H]^+$。

[3353] 化合物642

[3354] 1-(4-(5-((8-氮杂双环[3.2.1]辛烷-3-基)氨基)-6-甲基吡啶-2-基)-2,6-二甲基哌嗪-1-基)-2,2,2-三氟乙-1-酮

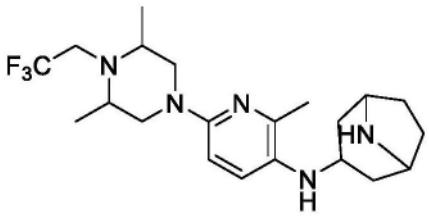
[3355] 

[3356] 根据为化合物24所述的程序制备标题化合物642(27.9mg,28.76%)(白色固体)。^{1}H NMR(400MHz,CDCl3)δ6.78(d,J=8.8Hz,1H),6.51(d,J=8.8Hz,1H),4.67(s,1H),4.26

(s,1H),3.97(s,2H),3.68(d,J=4.4Hz,3H),3.28(s,1H),2.90(s,2H),2.33(s,3H),2.29-2.23(m,2H),2.11(s,1H),2.01-1.95(m,2H),1.81(d,J=14.4Hz,2H),1.46(d,J=17.2Hz,6H)。质谱(m/z):426.2[M+H]$^+$。

[3357] 化合物643

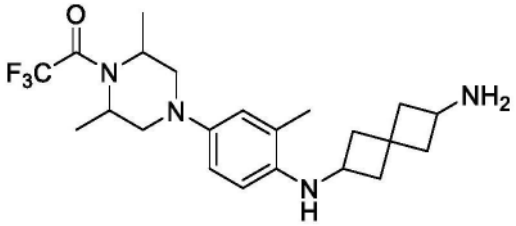
[3358] N-(6-(3,5-二甲基-4-(2,2,2-三氟乙基)哌嗪-1-基)-2-甲基吡啶-3-基)-8-氮杂双环[3.2.1]辛烷-3-胺

[3359] 

[3360] 根据为化合物24所述的程序制备标题化合物643(4.5mg,4.65%)(白色固体)。^{1}H NMR(400MHz,CDCl3)δ6.75(d,J=8.8Hz,1H),6.44(d,J=8.8Hz,1H),3.85(d,J=11.2Hz,2H),3.65(s,3H),3.33-3.26(m,2H),2.97(s,2H),2.48-2.42(m,2H),2.32(s,3H),2.21(d,J=11.2Hz,2H),2.09(d,J=7.6Hz,2H),1.95(s,2H),1.79(d,J=14.4Hz,2H),1.19(d,J=6.4Hz,6H)。质谱(m/z):412.1[M+H]$^+$。

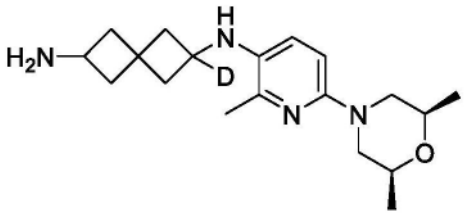
[3361] 化合物644

[3362] 1-(4-(4-((6-氨基螺[3.3]庚烷-2-基)氨基)-3-甲基苯基)-2,6-二甲基哌嗪-1-基)-2,2,2-三氟乙-1-酮

[3363] 

[3364] 根据为化合物24所述的程序制备标题化合物644(12.5mg,10.30%)(白色固体)。^{1}H NMR(400MHz,CDCl3)δ6.75-6.70(m,2H),6.43(d,J=8.4Hz,1H),4.63(s,1H),4.21(s,1H),3.84-3.76(m,1H),3.42(s,1H),3.21(d,J=11.2Hz,2H),2.84(d,J=12.0Hz,2H),2.58-2.43(m,3H),2.30(dd,J=11.2,5.6Hz,1H),2.12(s,3H),1.89-1.81(m,4H),1.51(d,J=24.4Hz,6H)。质谱(m/z):425.1[M+H]$^+$。

[3365] 化合物645

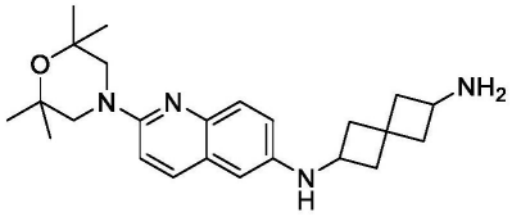
[3366] 

[3367] 根据为化合物24所述的程序制备标题化合物645(15.2mg,21.1%)(淡黄色固体)。^{1}H NMR(400MHz,DMSO-d6)δ8.11(br s,2H),6.81-6.67(m,1H),6.50(d,J=8.4Hz,1H),4.54(br s,1H),3.83(d,J=12.0Hz,2H),3.68-3.52(m,3H),2.48-2.27(m,4H),2.21(s,3H),2.19-2.07(m,4H),1.96-1.82(m,2H),1.13(d,J=6.2Hz,6H)。质谱(m/z):332.3[M+H

]+。

[3368] 化合物646

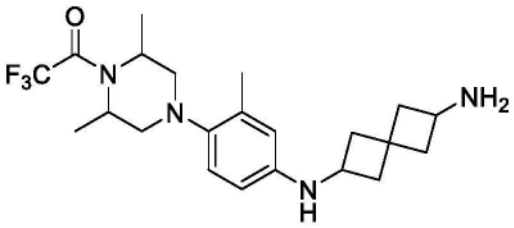
[3369] N^2-(2-(2,2,6,6-四甲基吗啉代)喹啉-6-基)螺[3.3]庚烷-2,6-二胺

[3370] 

[3371] 根据为化合物24所述的程序制备标题化合物646(10mg,41.6%)(白色固体)。^{1}H NMR(400MHz,CD_3OD)δ7.79(d,J=9.2Hz,1H),7.44(d,J=9.2Hz,1H),6.99(dd,J=9.2,2.4Hz,2H),6.59(d,J=2.4Hz,1H),3.89-3.75(m,1H),3.47(s,4H),2.61-2.35(m,3H),2.25-2.23(m,1H),1.95-1.74(m,4H),1.26(s,12H)。质谱(m/z):395.1[M+H]+。

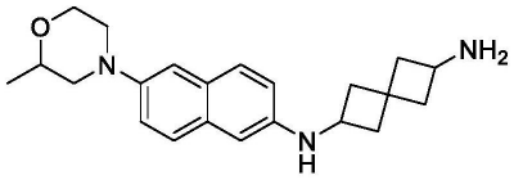
[3372] 化合物647

[3373] 1-(4-(4-((6-氨基螺[3.3]庚烷-2-基)氨基)-2-甲基苯基)-2,6-二甲基哌嗪-1-基)-2,2,2-三氟乙-1-酮

[3374] 

[3375] 根据为化合物24所述的程序制备标题化合物647(15.4mg,23.79%)(白色固体)。^{1}H NMR(400MHz,CDCl3)δ6.86(d,J=8.4Hz,1H),6.39(d,J=2.4Hz,1H),6.35(dd,J=8.4,2.8Hz,1H),4.62(s,1H),4.20(s,1H),3.80-3.73(m,1H),3.46-3.39(m,1H),2.87(s,4H),2.55-2.41(m,3H),2.32(d,J=12.0Hz,4H),1.85(m,J=11.6,8.8Hz,4H),1.60-1.51(m,6H)。质谱(m/z):429.2[M+H]+。

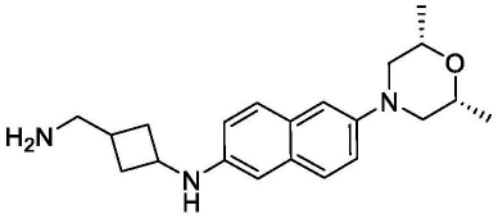
[3376] 化合物648

[3377] 

[3378] 根据为化合物24所述的程序制备标题化合物648(48.8mg,83.1%)(白色固体)。^{1}H NMR(400MHz,DMSO-d6)δ7.97(s,2H),7.46(dd,J=9.0,2.2Hz,2H),7.18(dd,J=9.0,2.5Hz,1H),6.98(d,J=2.5Hz,1H),6.83(dd,J=8.8,2.3Hz,1H),6.52(d,J=2.3Hz,1H),5.85(d,J=6.4Hz,1H),3.95-3.89(m,1H),3.82-3.74(m,1H),3.71-3.63(m,2H),3.61-3.52(m,2H),3.50-3.43(m,1H),2.70-2.55(m,2H),2.47-2.40(m,2H),2.37-2.28(m,1H),2.26-2.10(m,3H),1.95-1.82(m,2H),1.16(d,J=6.2Hz,3H)。质谱(m/z):352.4[M+H]+。

[3379] 化合物649

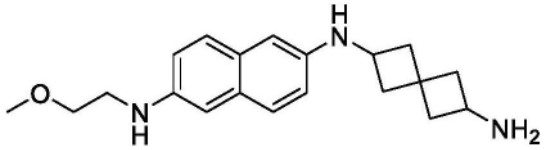
[3380] N-(3-(氨基甲基)环丁基)-6-((2S,6R)-2,6-二甲基吗啉代)萘-2-胺

[3381] 

[3382] 根据为化合物24所述的程序制备标题化合物649(7.6mg,10.2%)(黄色固体)。^{1}H NMR(400MHz,DMSO-d6)δ7.45(d,J=8.8Hz,2H),7.18(dd,J=9.2,2.4Hz,1H),6.97(d,J=2.4Hz,1H),6.88-6.82(m,1H),6.56-6.44(m,1H),5.82(d,J=6.4Hz,1H),3.91(h,J=6.8Hz,1H),3.78-3.66(m,2H),3.59-3.51(m,2H),3.30(s,1H),2.24(t,J=10.4Hz,2H),2.11-2.19(m,2H),1.96-1.85(m,1H),1.29(s,1H),1.16(d,J=6.0Hz,6H)。质谱(m/z):340.2[M+H]$^+$。

[3383] 化合物650

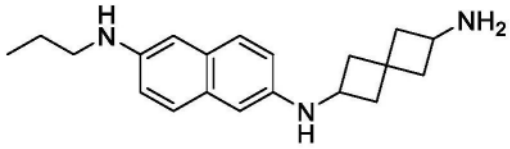
[3384] N^2-(6-氨基螺[3.3]庚烷-2-基)-N6-(2-甲氧基乙基)萘-2,6-二胺

[3385] 

[3386] 根据为化合物24所述的程序制备标题化合物650(18.4mg,24.6%)(淡黄色固体)。^{1}H NMR(400MHz,DMSO-d6)δ8.18(br s,2H),7.49-7.12(m,3H),6.88(d,J=8.8Hz,1H),6.79(d,J=8.8Hz,1H),6.63(s,1H),6.51(s,1H),5.69(br s,1H),3.76(s,1H),3.66-3.48(m,3H),3.29(s,3H),3.26-3.16(m,2H),2.63-2.53(m,1H),2.46-2.34(m,2H),2.27-2.10(m,3H),1.98-1.79(m,2H)。质谱(m/z):326.3[M+H]$^+$。

[3387] 化合物651

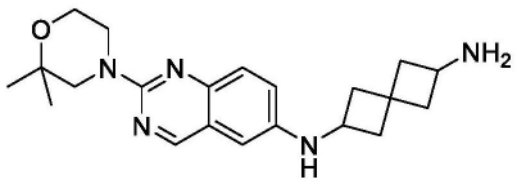
[3388] N^2-(6-氨基螺[3.3]庚烷-2-基)-N^6-丙基萘-2,6-二胺

[3389] 

[3390] 根据为化合物24所述的程序制备标题化合物651(13.5mg,8.81%)(黄色固体)。^{1}H NMR(400MHz,CD_3OD)δ7.41(d,J=7.6Hz,2H),6.90(dd,J=8.8,2.4Hz,1H),6.85(dd,J=8.8,2.4Hz,1H),6.77(d,J=1.6Hz,1H),6.69(d,J=1.6Hz,1H),3.90-3.82(m,1H),3.34(d,J=4.4Hz,1H),3.11(t,J=7.2Hz,2H),2.62-2.55(m,1H),2.52-2.40(m,2H),2.31-2.24(m,1H),1.96-1.81(m,4H),1.70(dd,J=14.4,7.2Hz,2H),1.05(t,J=7.2Hz,3H)。质谱(m/z):310.1[M+H]$^+$。

[3391] 化合物652

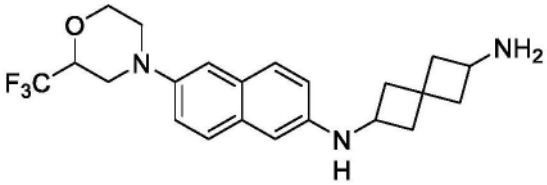
[3392] N^2-(2-(2,2-二甲基吗啉代)喹唑啉-6-基)螺[3.3]庚烷-2,6-二胺

[3393] 

[3394] 根据为化合物24所述的程序制备标题化合物652(4.9mg,4.10%)(黄色固体)。^{1}H NMR(400MHz,DMSO-d_6)δ8.96(s,1H),7.31(d,J=9.2Hz,1H),7.17(dd,J=9.2,2.4Hz,1H),6.53(d,J=2.4Hz,1H),6.05(d,J=6.4Hz,1H),3.72(dd,J=14.4,7.2Hz,1H),3.63(s,4H),3.20(d,J=7.6Hz,2H),2.39-2.33(m,2H),2.13(dd,J=10.4,5.6Hz,1H),2.04-1.87(m,1H),1.81(d,J=8.0Hz,3H),1.70(s,2H),1.18(s,12H)。质谱(m/z):396.1[M+H]$^+$。

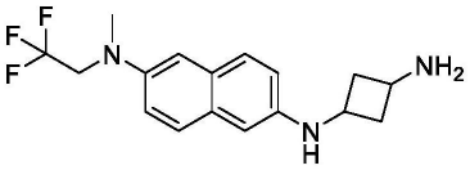
[3395] 化合物653

[3396] N^2-(6-(2-(三氟甲基)吗啉代)萘-2-基)螺[3.3]庚烷-2,6-二胺

[3397] 

[3398] 根据为化合物24所述的程序制备标题化合物653(10.6mg,14.58%)(白色固体)。^{1}H NMR(400MHz,DMSO-d_6)δ7.49(dd,J=8.8,5.2Hz,2H),7.22(dd,J=9.2,2.4Hz,1H),7.09(s,1H),6.85(dd,J=8.8,2.4Hz,1H),6.52(s,1H),5.87(d,J=6.4Hz,1H),4.37(s,1H),4.09(d,J=9.2Hz,1H),3.86-3.64(m,4H),3.55(d,J=12.0Hz,1H),3.24-3.18(m,1H),2.79-2.66(m,3H),2.49-2.46(m,2H),2.40-2.32(m,2H),2.13(dd,J=11.2,5.2Hz,1H),1.88-1.63(m,4H)。质谱(m/z):406.2[M+H]$^+$。

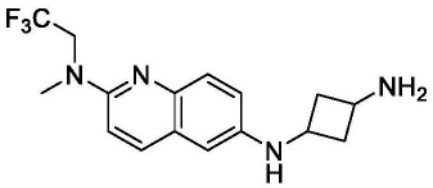
[3399] 化合物654

[3400] 

[3401] 根据为化合物24所述的程序制备标题化合物654(49.6mg,78.3%)(白色固体)。^{1}H NMR(400MHz,DMSO-d_6)δ8.25(s,2H),7.48(d,J=8.8Hz,2H),7.17(dd,J=9.0,2.6Hz,1H),6.95(d,J=2.7Hz,1H),6.90-6.81(m,1H),6.58-6.43(m,1H),6.06-5.89(m,1H),4.34-4.19(m,2H),4.15-4.05(m,1H),3.88-3.75(m,1H),3.03(s,3H),2.57-2.51(m,1H),2.31-2.17(m,2H)。质谱(m/z):324.2[M+H]$^+$。

[3402] 化合物655

[3403] N^6-(3-氨基环丁基)-N^2-甲基-N^2-(2,2,2-三氟乙基)喹啉-2,6-二胺

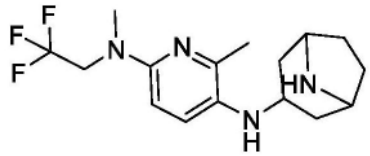
[3404] 

[3405] 根据为化合物24所述的程序制备标题化合物655(6.6mg,5.96%)(黄色固体)。^{1}H NMR(400MHz,CD_3OD)δ7.75(d,J=9.2Hz,1H),7.39(d,J=9.2Hz,1H),6.95-6.88(m,2H),6.56(d,J=2.8Hz,1H),4.34(q,J=9.2Hz,2H),3.47(dd,J=11.2,4.0Hz,1H),3.14-3.08(m,4H),2.76-2.70(m,2H),1.58-1.45(m,2H)。质谱(m/z):325.0[M+H]$^+$。

[3406] 化合物656

[3407] N^5-(8-氮杂双环[3.2.1]辛烷-3-基)-N^2,6-二甲基-N^2-(2,2,2-三氟乙基)吡啶-2,

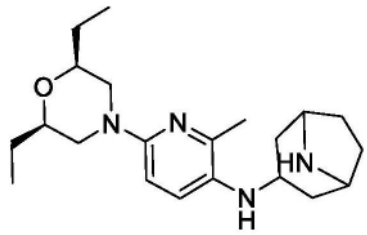
5-二胺

[3408] 

[3409] 根据为化合物24所述的程序制备标题化合物656(37.2mg,50.6%)(白色固体)。^{1}H NMR(400MHz,DMSO-d_6)δ9.40(s,2H),6.88(d,J=8.8Hz,1H),6.48(d,J=8.8Hz,1H),4.45-4.27(m,3H),3.87(q,J=3.2Hz,2H),3.58(t,J=5.6Hz,1H),2.98(s,3H),2.27(d,J=12.0Hz,7H),2.01-1.89(m,4H)。质谱(m/z):329.2[M+H]$^+$。

[3410] 化合物657

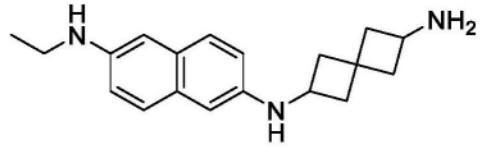
[3411] N-(6-((2S,6R)-2,6-二乙基吗啉代)-2-甲基吡啶-3-基)-8-氮杂双环[3.2.1]辛烷-3-胺

[3412] 

[3413] 根据为化合物24所述的程序制备标题化合物657(25.9mg,35.7%)(黄色固体)。^{1}H NMR(400MHz,DMSO-d_6)δ9.43(s,1H),9.31(s,1H),6.86(d,J=8.8Hz,1H),6.57(d,J=8.4Hz,1H),4.43(s,1H),3.96-3.83(m,4H),3.59(t,J=5.6Hz,1H),3.96-3.83(m,1H),2.33-2.16(m,9H),2.00-1.88(m,4H),1.56-1.40(m,4H),0.95(t,J=7.6Hz,6H)。质谱(m/z):359.3[M+H]$^+$。

[3414] 化合物658

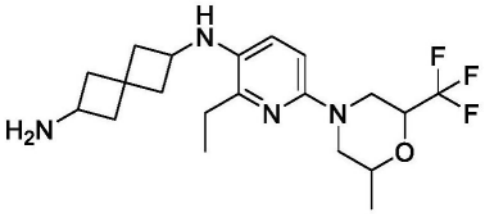
[3415] N^2-(6-氨基螺[3.3]庚烷-2-基)-N^6-乙基萘-2,6-二胺

[3416] 

[3417] 根据为化合物24所述的程序制备标题化合物658(17.1mg,18.66%)(紫色固体)。^{1}H NMR(400MHz,CD_3OD)δ7.29(d,J=8.8Hz,2H),6.82-6.73(,2H),6.66(d,J=2.0Hz,1H),6.56(d,J=2.0Hz,1H),3.73(p,J=7.6Hz,1H),3.16(dd,J=8.4,7.6Hz,1H),3.05(q,J=7.2Hz,2H),2.48-2.40(m,1H),2.38-2.25(m,2H),2.16-2.09(m,1H),1.82-1.64(m,4H),1.16(t,J=7.2Hz,3H)。质谱(m/z):296.1[M+H]$^+$。

[3418] 化合物659

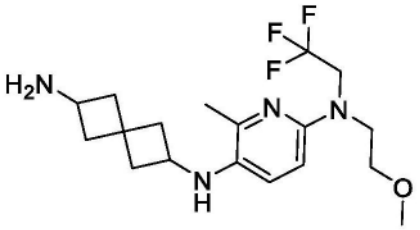
[3419] N^2-(2-乙基-6-(2-甲基-6-(三氟甲基)吗啉代)吡啶-3-基)螺[3.3]庚烷-2,6-二胺

[3420] 

[3421] 根据为化合物24所述的程序制备标题化合物659(4mg,15.5%)(黄色固体)。^{1}H NMR(400MHz,CD_3OD)δ6.86(d,J=8.6Hz,1H),6.54(d,J=8.6Hz,1H),4.16-4.08(m,2H),3.88-3.66(m,3H),3.49-3.36(m,1H),2.66-2.21(m,8H),1.95-1.83(m,4H),1.24-1.09(m,6H).MS(ESI)m/z 399.1$[M+H]^+$。

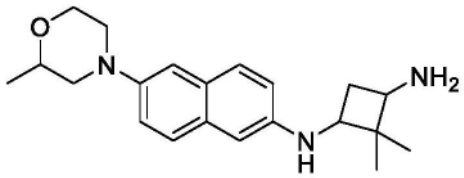
[3422] 化合物660

[3423] N^5-(6-氨基螺[3.3]庚烷-2-基)-N^2-(2-甲氧基乙基)-6-甲基-N^2-(2,2,2-三氟乙基)吡啶-2,5-二胺

[3424] 

[3425] 根据为化合物24所述的程序制备标题化合物660(21.2mg,26.0%)(黄色固体)。^{1}H NMR(400MHz,DMSO-d_6)δ6.73(d,J=8.8,1H),6.50(d,J=8.8Hz,1H),4.33(q,J=9.6Hz,2H),3.64-3.54(m,3H),3.46(t,J=6.0Hz,2H),3.23(s,3H),3.14(q,J=7.6Hz,1H),2.43-2.35(m,1H),2.35-2.29(m,1H),2.27-2.21(m,1H),2.19(s,3H),2.15-2.07(m,1H),1.88-1.78(m,2H),1.70-1.58(m,2H)。质谱(m/z):346.3$[M+H]^+$。

[3426] 化合物661

[3427] 

[3428] 根据为化合物24所述的程序制备标题化合物661(51.7mg,77.8%)(白色固体)。^{1}H NMR(400MHz,DMSO-d_6)δ7.64-7.28(m,4H),7.22-7.13(m,1H),7.02-6.88(m,2H),6.64-6.49(m,1H),5.98-5.79(m,1H),3.96-3.80(m,2H),3.74-3.62(m,2H),3.59-3.43(m,3H),3.26-3.17(m,1H),2.68-2.54(m,1H),2.39-2.27(m,2H),2.26-2.16(m,1H),1.28(d,J=7.7Hz,3H),1.17(d,J=6.2Hz,3H),0.97(d,J=10.2Hz,3H)。质谱(m/z):340.2$[M+H]^+$。

[3429] 实施例2.在HT-1080细胞活力测定中确定EC_{50}值

[3430] 将HT-1080(ATCC,CCL-121)细胞(100μl中6000个)接种于96孔板(Corning)中,并在37℃、5%CO_2湿润气氛的孵育箱中培养过夜。然后用铁死亡诱导剂RSL3(TargetMol)和3倍、10点连续稀释系列化合物(最高浓度为1.1μM)处理细胞20小时。使用Cell Titer-Glo Kit(Promega)评估细胞活力。使用酶标仪(Envision,PerkinElmer)测量发光强度,并通过将数据相对于未处理的对照归一化来计算细胞活力。化合物(例如化合物1-573和574-661)的EC_{50}值在GraphPad Prism(GraphPad Software,Inc.,San Diego,CA,USA)中计算。使用具

有S形剂量响应的非线性回归模型对曲线进行拟合。

[3431] 化合物1-573的铁死亡抑制活性总结于表2中。在表2中,如下提供活性:+++=0.1nM≤EC_{50}<100nM;++=100nM≤EC_{50}<1000nM;+=1000nM≤EC_{50}<10000nM。

[3432] 表2.化合物1至573的EC_{50}值

[3433]

化合物编号	EC_{50} (nM)	化合物编号	EC_{50} (nM)	化合物编号	EC_{50} (nM)
1	+++	192	++	383	+++
2	+++	193A/B	++/++	384	++
3	+++	194	++	385	++
4A/B	+++/+++	195	++	386	+++
5	+++	196	+++	387	+++
6A/B	+++/+++	197	+++	388	+++
7	+++	198	++	389	+++
8	+++	199	+	390	+++
9	+	200A/B	+++/+++	391	+++
10	+++	201	++	392	+++

[3434]

11	++	202	+	393	+++
12	+++	203	++	394	+++
13	+++	204	++	395	+++
14	+++	205A/B	+++/+++	396	+++
15	+++	206	+	397	+++
16	+++	207	+	398	+++
17	+++	208	+	399	+++
18	+++	209	+++	400	+
19	+++	210	+	401	+++
20	+++	211	+	402	+++
21	+++	212	+	403	+++
22	++	213A/B	++/++	404	+++
23A/B	+++/++ +	214	+++	405	+++
24A/B	+++/++ +	215	+++	406	+++
25	+++	216A/B	++/++	407	+++
26	+++	217	+++	408	+++
27	++	218	++	409	+++
28	+++	219	+	410	+++
29	+++	220	+++	411	+++
30	+++	221	+++	412	+++
31	+++	222	+	413	+++
32A/B	+++/++ +	223	+	414	+++
33A/B	+/+	224	++	415	+++
34A/B	+++/++ +	225	+++	416	+++
35	+++	226	+++	417A/B	+++/++
36	+++	227	+	418	+++
37A/B	+/+	228A/B	+++/+++	419	+++
38	+++	229	+	420	+++
39	+++	230	+++	421A/B	+++/++ +
40	+++	231A/B	+++/+++	422	+++
41A/B	++/++	232A/B	+++/+++	423	+++

[3435]

42	+++	233A/B	++/++	424	+++
43	+++	234	+	425	+++
44	+++	235	+++	426	+++
45	+++	236	+++	427	+++
46	++	237	+	428	+++
47	++	238	+++	429	+++
48	+++	239	+++	430	+++
49	+++	240	++	431	+++
50	+++	241	+++	432	+++
51	+++	242A/B	+++/+++	433	+++
52	+++	243	+++	434	+
53A/B	+++/+++	244A/B	+++/+++	435	+++
54A/B	+++/+++	245	+	436	+++
55	+++	246	++	437	+++
56	+++	247	+++	438	+++
57	+++	248	++	439	++
58	+++	249	+++	440	++
59	+++	250A/B	+++/+++	441	++
60	+++	251A/B	+++/+++	442	++
61	+++	252A/B/C/D	++/+++/+++/+++	443	++
62	+++	253A/B	+++/+++	444	+++
63	+++	254	+++	445	+++
64A/B	+/+	255	+	446A/B	+++/+++
65A/B	+++/+++	256	+	447	+++
66	+++	257	+++	448	+++
67	+++	258	+	449	+
68	+++	259A/B	++/++	450	++
69	+++	260	+++	451	+++
70	+++	261	++	452	+++
71	+++	262	++	453	+++
72	+++	263	++	454	+++

[3436]

73	+++	264	+++	455A/B	++/++
74	+++	265	+++	456	++
75	++	266A/B	++/++	457	++
76A/B	+++/++ +	267	+	458	++
77	+++	268	+++	459	+++
78	+++	269	++	460	+++
79	++	270	++	461	+++
80	++	271	+++	462	+
81A/B	++/++	272	+++	463	+++
82A/B	+++/++ +	273	+++	464	+++
83	+++	274	+++	465	+++
84	+++	275A/B	+++/+++	466	++
85	+++	276	+++	467	+++
86	+++	277	+++	468	+++
87	+++	278	+++	469	++
88	+	279	+++	470	+++
89	+++	280	+++	471	+++
90	+++	281	+++	472	+++
91A/B	+++/++ +	282	++	473	+++
92A/B	+/++	283	+++	474A/B	+++/++ +
93	+++	284	+++	475A/B	+++/++ +
94	+++	285	+++	476	+++
95	+++	286	+++	477	++
96	+++	287	+++	478	+++
97A/B	+++/++ +	288	+++	479	+++
98	+++	289A/B	+++/+++	480	++
99	+++	290	+++	481	++
100	++	291	+++	482	+++
101	+++	292	+++	483	+++
102	+++	293	++	484	+

[3437]

103	++	294A/B	+++/+++	485	+++
104	++	295A/B	++/+++	486	+++
105	+++	296A/B	+++/+++	487	++
106A/B	+++/++	297	+++	488A/B	+++/++
107A/B	+++/++	298	++	489	+++
108	++	299A/B	+++/+++	490	+++
109	++	300A/B	+++/+++	491	+++
110	++	301A/B	+++/+++	492	+++
111	++	302	+++	493	+++
112	++	303	+++	494	++
113	++	304	++	495	++
114A/B	++/++	305A/B	+++/+++	496	++
115A/B	++/++	306A/B	++/++	497	+++
116	+++	307	+++	498	+++
117A/B	+++/++	308	+++	499	++
118	+++	309	+++	500	+++
119	+++	310	+++	501	+
120A/B	+++/++	311	+	502	+++
121A/B	+++/++	312	+++	503	+++
122	+++	313A/B	+++/+++	504	+++
123	++	314	+++	505	+++
124	++	315	+++	506	+++
125	++	316	+++	507	++
126	+	317	+++	508	+++
127	++	318A/B	+++/+++	509	+++
128	++	319A/B	++/++	510	+++
129	++	320A/B	++/++	511	+++
130	++	321	++	512	+++
131	+++	322	+++	513	+++
132	+++	323	+++	514	+++
133	+++	324	+++	515	+++

[3438]

134	+	325A/B	+++/+++	516A/B	+++/+++
135A/B	++/++	326	+++	517	++
136	+++	327	++	518	+++
137	+++	328	+++	519	+++
138	++	329	+++	520	+++
139A/B	+++/+++	330A/B	+++/+++	521	+++
140	+++	331	++	522	+++
141	++	332	+++	523	+
142A/B	+++/+++	333	+++	524	++
143A/B	++/++	334	++	525	++
144A/B	++/++	335A/B	++/+++	526	+++
145	+++	336A/B	+++/+++	527	+++
146A/B	+++/+++	337A/B	+++/+++	528	++
147	+++	338	+++	529	+++
148A/B	+++/+++	339	+++	530	+
149A/B	++/++	340	+++	531	+++
150	++	341	+++	532	++
151	+++	342	+++	533	+++
152	++	343	+++	534	+++
153A/B	++/++	344	+++	535	+++
154	++	345	++	536	+++
155	+++	346	+++	537	++
156A/B/C	+++	347	+++	538A/B	+++/+++
157A/B	+++/+++	348	+++	539A/B	+++/++
158	++	349A/B	+++/+++	540	+++
159A/B	+++/++	350	+++	541	+++
160	+	351	+++	542	+++
161	+	352	+	543	+++
162	++	353	+++	544	+++

[3439]

163	+	354	+++	545	+++
164	+	355	+++	546	+++
165	+	356	+++	547	+++
166	+	357	+++	548	+++
167	++	358	+++	549	+++
168A/B	+/+	359	+++	550	+++
169	++	360	+++	551	++
170	+	361	+++	552	+++
171	+++	362	+++	553	++
172	+++	363	+++	554	+++
173	++	364	+++	555	+++
174	+++	365	+++	556	+++
175	+	366	+++	557	+++
176	++	367	+++	558	+++
177	+	368	+++	559	+++
178	+	369	+++	560	+++
179	+	370	+++	561	+++
180	++	371	+++	562	+++
181	++	372	+++	563	+++
182A/B	++/++	373	+++	564	+++
183A/B	+/+	374	+++	565	+++
184	++	375	+++	566	+++
185	+	376	+++	567	+++
186	++	377	+++	568	+++
187	+	378	+++	569	+++
188	++	379	+++	570	+++
189	+	380	+++	571	+++
190	++	381	+++	572	+++
191A/B	+/+	382	+++	573	+++

[3440] 化合物574-661的铁死亡抑制活性总结于表3中。在表3中,如下提供活性:+++=0.1nM≤EC_{50}<100nM;++=100nM≤EC_{50}<1000nM;+=1000nM≤EC_{50}<10000nM。

[3441] 表3.化合物574至661的EC_{50}值

[3442]

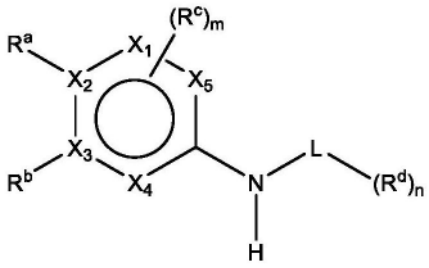
化合物编号	EC_{50} (nM)	化合物编号	EC_{50} (nM)	化合物编号	EC_{50} (nM)

[3443]

574	+++	604	+++	634	+++
575	+++	605	+++	635	+++
576	+++	606	+++	636	+++
577	+++	607	++	637	+++
578	+++	608	+++	638	+++
579	+++	609	+++	639	+++
580	+++	610	+++	640	+++
581	+++	611	+++	641	+++
582	+++	612	+++	642	+++
583	+++	613	+++	643	+++
584	+++	614	+++	644	+++
585	+++	615	+++	645	+++
586	+++	616	+++	646	+++
587	++	617	+++	647	+++
588	+++	618	++	648	+++
589	+++	619	+++	649	+++
590	++	620	+++	650	+++
591	++	621	+++	651	+++
592	+++	622	+++	652	+++
593	+++	623	+++	653	+++
594	+++	624	+++	654	+++
595	+++	625	+++	655	+++
596	+++	626	+++	656	+++
597	+++	627	++	657	+++
598	+++	628	+++	658	+++
599	++	629	+++	659	+++
600	++	630	+++	660	+++
601	+++	631	+++	661	+++
602	+++	632	+++		
603	+++	633	+++		

[3444] 本公开内容涉及以下技术方案:1.以下结构式I的化合物:

[3445]



式 I

[3446] 其互变异构体,该化合物或该互变异构体的溶剂化物或立体异构体,或前述的药学上可接受的盐,其中:

[3447] L是环烷基,杂环基,或C;

[3448] X_1、X_2、X_3、X_4和X_5各自独立地是C或N;

[3449] R^a不存在或选自H,卤素,CN,任选被取代的杂原子,任选被取代的烷基,任选被取代的烯基,任选被取代的炔基,任选被取代的酰基,任选被取代的环烷基,任选被取代的杂环基,任选被取代的芳基,和任选被取代的杂芳基;

[3450] R^b不存在或选自H,卤素,CN,任选被取代的杂原子,任选被取代的烷基,任选被取代的环烷基,和任选被取代的杂环基;

[3451] R^a和R^b可以连在一起形成任选被取代的3-10元碳环、杂环、芳族、或杂芳族的环;

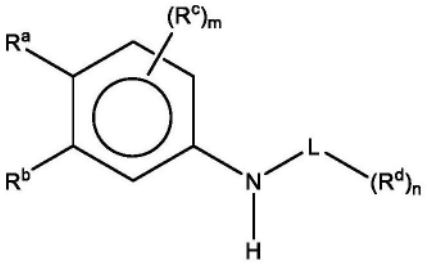
[3452] R^c,每次出现时,独立地选自卤素,任选被取代的杂原子,和任选被取代的烷基;

[3453] R^c中的一个与R^b可以连在一起形成任选被取代的3-10元碳环、杂环、芳族、或杂芳族的环;

[3454] R^d,每次出现时,独立地选自卤素,CN,任选被取代的杂原子,任选被取代的烷基,任选被取代的烯基,任选被取代的炔基,任选被取代的酰基,任选被取代的环烷基,任选被取代的杂环基,任选被取代的芳基,和任选被取代的杂芳基;和

[3455] m和n各自是独立选自0、1、2和3的整数。

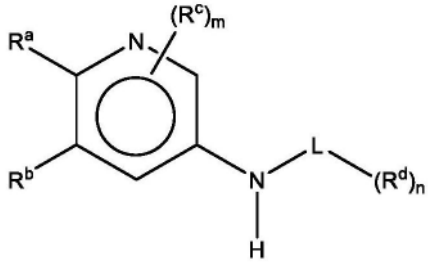
[3456] 2.技术方案1的化合物,其中化合物具有以下结构式IIa:

[3457] 

[3458] 式 IIa

[3459] 其互变异构体,该化合物或该互变异构体的溶剂化物或立体异构体,或前述的药学上可接受的盐。

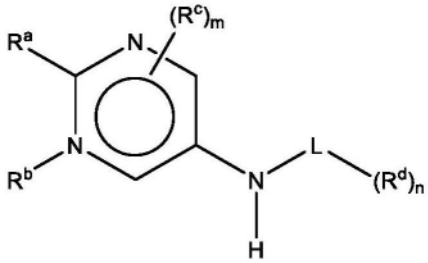
[3460] 3.技术方案1的化合物,其中化合物具有以下结构式IIb:

[3461] 

式 IIb

[3462] 其互变异构体,该化合物或该互变异构体的溶剂化物或立体异构体,或前述的药学上可接受的盐。

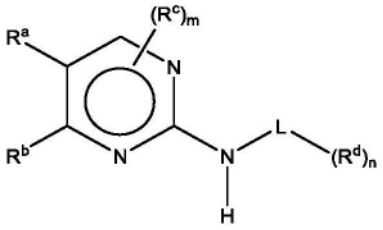
[3463] 4.技术方案1的化合物,其中化合物具有以下结构式IIc:

[3464] 

式 IIc

[3465] 其互变异构体,该化合物或该互变异构体的溶剂化物或立体异构体,或前述的药学上可接受的盐。

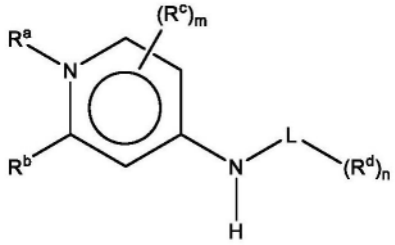
[3466] 5.技术方案1的化合物,其中化合物具有以下结构式IId之一:

[3467] 

式 IId

[3468] 其互变异构体,该化合物或该互变异构体的溶剂化物或立体异构体,或前述的药学上可接受的盐。

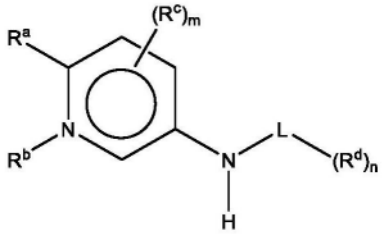
[3469] 6.技术方案1的化合物,其中化合物具有以下结构式IIe之一:

[3470] 

式 IIe

[3471] 其互变异构体,该化合物或该互变异构体的溶剂化物或立体异构体,或前述的药学上可接受的盐。

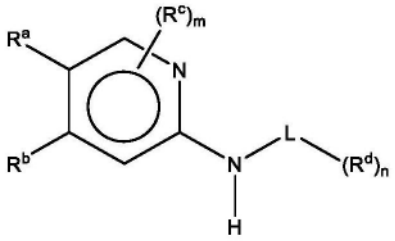
[3472] 7.技术方案1的化合物,其中化合物具有以下结构式IIf之一:

[3473] 

式 IIf

[3474] 其互变异构体,该化合物或该互变异构体的溶剂化物或立体异构体,或前述的药学上可接受的盐。

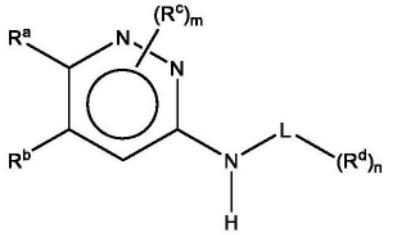
[3475] 8.技术方案1的化合物,其中化合物具有以下结构式IIg之一:

[3476] 

式 IIg

[3477] 其互变异构体,该化合物或该互变异构体的溶剂化物或立体异构体,或前述的药学上可接受的盐。

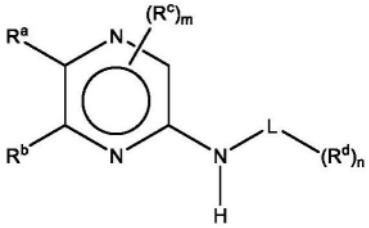
[3478] 9.技术方案1的化合物,其中化合物具有以下结构式IIh之一:

[3479] 

式 IIh

[3480] 其互变异构体,该化合物或该互变异构体的溶剂化物或立体异构体,或前述的药学上可接受的盐。

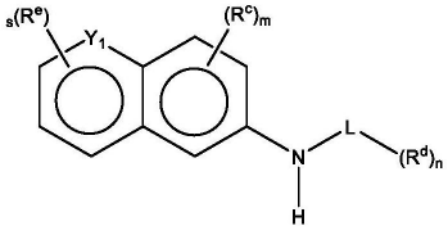
[3481] 10.技术方案1的化合物,其中化合物具有以下结构式IIi之一:

[3482] 

式 IIi

[3483] 其互变异构体,该化合物或该互变异构体的溶剂化物或立体异构体,或前述的药学上可接受的盐。

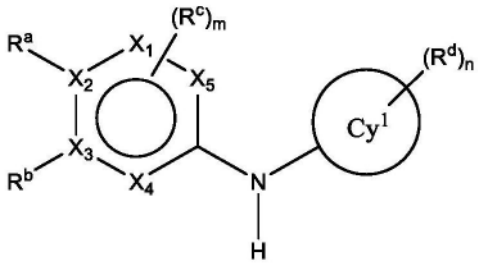
[3484] 11.技术方案1的化合物,其中化合物具有以下结构式IIj之一:

[3485] 

式 IIj

[3486] 其互变异构体,该化合物或该互变异构体的溶剂化物或立体异构体,或前述的药学上可接受的盐,其中Y_1是N或C;R^e,每次出现时,独立地选自任选被取代的环烷基,任选被取代的杂环基,任选被取代的芳基,和任选被取代的杂芳基;和s是选自0、1、2和3的整数。

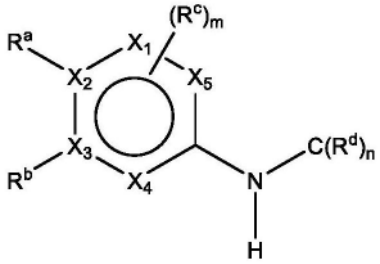
[3487] 12.技术方案1的化合物,其中化合物具有以下结构式IIIa:

[3488] 

式 IIIa

[3489] 其互变异构体,该化合物或该互变异构体的溶剂化物或立体异构体,或前述的药学上可接受的盐,其中Cy^1是3-10元环烷基或3-10元杂环基。

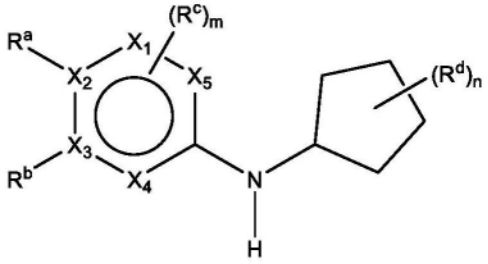
[3490] 13.技术方案1的化合物,其中化合物具有以下结构式IIIb:

[3491] 

式 IIIb

[3492] 其互变异构体,该化合物或该互变异构体的溶剂化物或立体异构体,或前述的药学上可接受的盐。

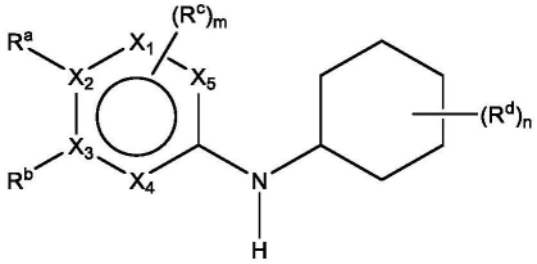
[3493] 14.技术方案1和12中任一项的化合物,其中化合物具有以下结构式IVa:

[3494] 

式 IVa

[3495] 其互变异构体,该化合物或该互变异构体的溶剂化物或立体异构体,或前述的药学上可接受的盐。

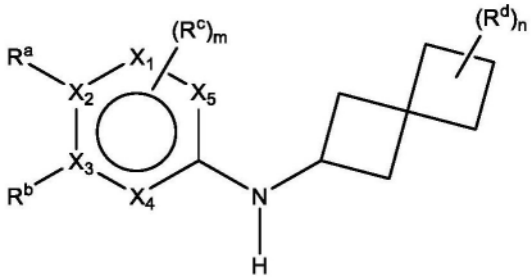
[3496] 15.技术方案1和12中任一项的化合物,其中化合物具有以下结构式IVb之一:

[3497] 

式 IVb

[3498] 其互变异构体,该化合物或该互变异构体的溶剂化物或立体异构体,或前述的药学上可接受的盐。

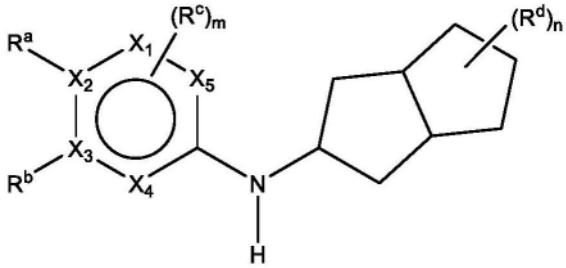
[3499] 16.技术方案1和12中任一项的化合物,其中化合物具有以下结构式IVc之一:

[3500] 

式 IVc

[3501] 其互变异构体,该化合物或该互变异构体的溶剂化物或立体异构体,或前述的药学上可接受的盐。

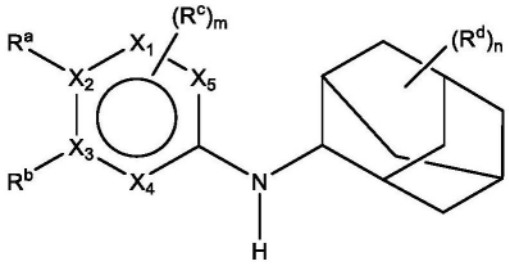
[3502] 17.技术方案1和12中任一项的化合物,其中化合物具有以下结构式IVd之一:

[3503] 

式 IVd

[3504] 其互变异构体,该化合物或该互变异构体的溶剂化物或立体异构体,或前述的药学上可接受的盐。

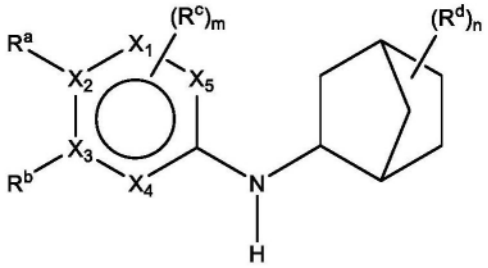
[3505] 18.技术方案1和12中任一项的化合物,其中化合物具有以下结构式IVe之一:

[3506] 

式 IVe

[3507] 其互变异构体,该化合物或该互变异构体的溶剂化物或立体异构体,或前述的药学上可接受的盐。

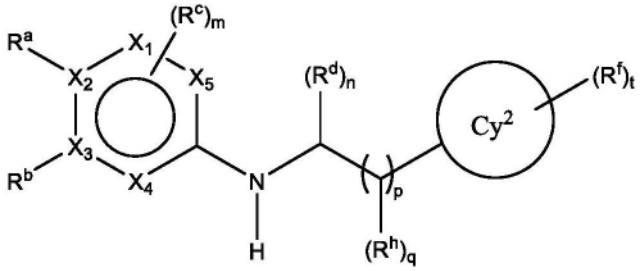
[3508] 19.技术方案1和12中任一项的化合物,其中化合物具有以下结构式IVf之一:

[3509] 

式 IVf

[3510] 其互变异构体,该化合物或该互变异构体的溶剂化物或立体异构体,或前述的药学上可接受的盐。

[3511] 20.技术方案1和13中任一项的化合物,其中化合物具有以下结构式Va之一:

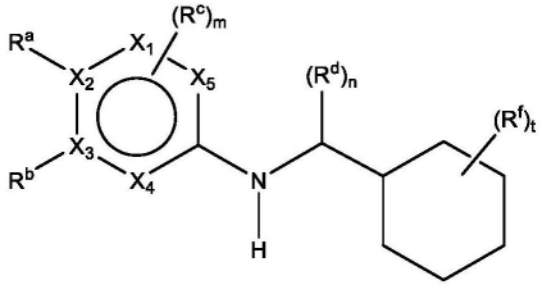
[3512] 

式 Va

[3513] 其互变异构体,该化合物或该互变异构体的溶剂化物或立体异构体,或前述的药学上可接受的盐,其中Cy^2是3-10元环烷基或3-10元杂环基;R^f,每次出现时,独立地选自卤素,CN,任选被取代的杂原子,任选被取代的烷基,任选被取代的烯基,任选被取代的炔基,任选被取代的酰基,任选被取代的环烷基,任选被取代的杂环基,任选被取代的芳基,和任选被取代的杂芳基;R^h,每次出现时,独立地选自卤素,CN,和任选被取代的C_1-C_6烷基;n是选自0、1和2的整数;p是选自0、1、2、3、4和5的整数;q是选自0、1和2的整数;并且t是独立选自0、1、2和3的整数。

[3514] 21.技术方案20的化合物,互变异构体,溶剂化物,立体异构体,或药学上可接受的盐,其中n是0,q是0,并且p是0,1,2和3。

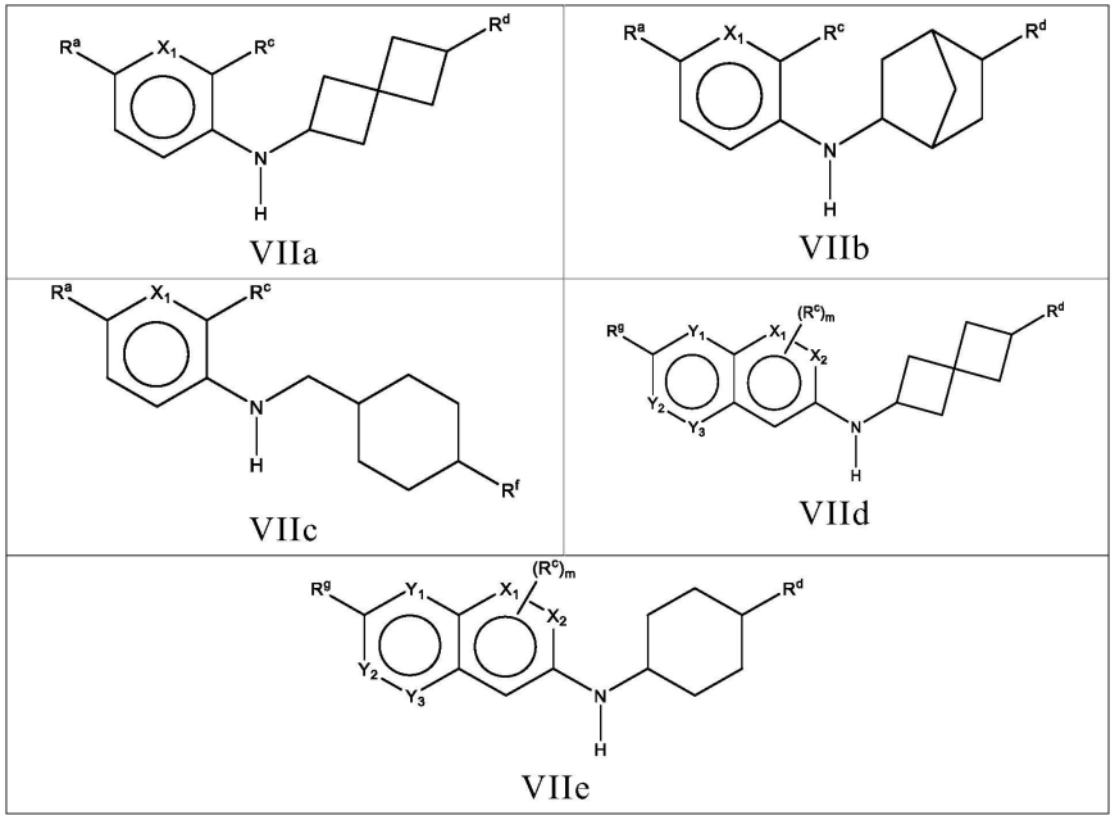
[3515] 22.技术方案1,13,和20中任一项的化合物,其中化合物具有以下结构式VIa之一:

[3516] 

式 VIa

[3517] 其互变异构体,该化合物或该互变异构体的溶剂化物或立体异构体,或前述的药学上可接受的盐。

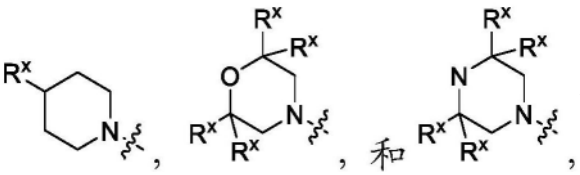
[3518] 23.技术方案1的化合物,其中化合物具有以下结构式VIIa-VIIe之一:

[3519] 

[3520] 其互变异构体,该化合物或该互变异构体的溶剂化物或立体异构体,或前述的药学上可接受的盐,其中:

[3521] X_1和X_2独立地是C或N;

[3522] Y_1,Y_2和Y_3独立地是C或N;

[3523] R^a选自  其中R^x,每次出现时,独立地选自H,CF_3,-CH_3,和-CH_2CH_3;

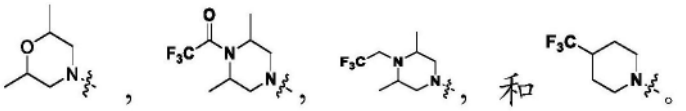
[3524] R^c选自卤素,C_1-C_2烷基,和C_1-C_2烷氧基;

[3525] R^d选自NH_2和-C(=O)NH_2;

[3526] R^f选自NH_2和-C(=O)NH_2;和

[3527] m是0或1。

[3528] 24.技术方案11的化合物,互变异构体,溶剂化物,立体异构体,或药学上可接受的盐,其中R^e,对于每次出现,独立地选自5-6元环烷基和5-6元杂环基,各自独立地被0、1、2或3个选自任选被1-4个选自=O和卤素的基团取代的C_1-C_6烷基的基团取代。

[3529] 25.技术方案11和24中任一项的化合物,互变异构体,溶剂化物,立体异构体,或药学上可接受的盐,其中R^e,每次出现时,独立地选自  。

[3530] 26.技术方案20-22中任一项的化合物,互变异构体,溶剂化物,立体异构体,或药

学上可接受的盐,其中R^f,每次出现时,独立地选自H,卤素,氰基,C_1-C_{10}烷基,苯基,5-7元杂芳基,苯基,3-10元杂环基,C_3-C_{10}环烷基,-C(=O)R^s,C_2-C_{10}烯基,=O,=NR^p;-C(=O)OR^s,-C(=O)NR^pR^q,-NR^pR^q,和-NR^pC(=O)R^s,其中

[3531] R^f的C_1-C_{10}烷基和C_2-C_{10}烯基各自任选被1-3个选自以下的基团取代:5-7元杂芳基,C_3-C_{10}环烷基,3-10元杂环基,-OR^s,-C(=O)NR^pR^q,-NR^pC(=O)NR^qR^r,和-NR^pR^q;

[3532] R^f的3-10元杂环基和C_3-C_{10}环烷基以及R^f的C_1-C_{10}烷基和C_2-C_{10}烯基的3-10元杂环基和C_3-C_6环烷基,各自任选被1-3个选自以下的基团取代:=O和任选被1-3个选自卤素和-OR^s的基团取代的C_1-C_6烷基;

[3533] R^f的苯基和5-7元杂芳基以及R^f的C_1-C_{10}烷基和C_2-C_{10}烯基的5-7元杂芳基各自任选被1-3个选自以下的基团取代:任选被1-3个选自卤素和-OR^s的基团取代的C_1-C_6烷基;

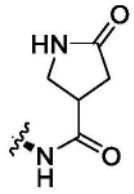
[3534] R^p,R^q,和R^r,对于每次出现,独立地选自氢,C_3-C_{10}环烷基,和C_1-C_{10}烷基,其中R^p,R^q,和R^r的C_3-C_{10}环烷基和C_1-C_{10}烷基各自任选被1-3个选自以下的基团取代:卤素,-OR^s和-C(=O)OR^s;

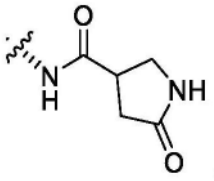
[3535] R^s,每次出现时,独立地选自H,NH_2,C_3-C_{10}环烷基,3-10元杂环基,和C_1-C_{10}烷基,其任选被1-3个选自以下的基团取代:卤素,C_3-C_{10}环烷基,3-10元杂环基,和C_1-C_6烷氧基,其中

[3536] R^s的C_3-C_{10}环烷基和3-10元杂环基以及R^s的C_1-C_{10}烷基的C_3-C_{10}环烷基和3-10元杂环基各自任选被1-3个任选被=O和卤素取代的C_1-C_6烷基的基团取代,和R^s的C_1-C_{10}烷基的C_1-C_6烷氧基任选被1-3个卤素的基团取代。

[3537] 27.技术方案20-22和26中任一项的化合物,互变异构体,溶剂化物,立体异构体,或药学上可接受的盐

[3538] 其中R^f,对于每次出现,选自H,甲基,NH_2,-$NH(CH_2)_2OH$,-CH_2NH_2,



,


,-NHC(=O)NH_2,-$NHCH_3$,-C(=O)NH_2,和-NHBoc。

[3539] 28.技术方案1-10,12-22,和26-27中任一项的化合物,互变异构体,溶剂化物,立体异构体,或药学上可接受的盐,其中R^a不存在或选自氢,卤素,氰基,C_1-C_{10}烷基,C_2-C_{10}烯基,C_2-C_{10}炔基,C_3-C_{10}环烷基,3-10元杂环基,苯基,5-7元杂芳基,-C(=O)R^s,-C(=O)OR^s,-NR^pR^q,-OR^s,其中

[3540] R^a的C_3-C_{10}环烷基,3-10元杂环基,苯基,和5-7元杂芳基各自任选被1-3个选自以下的基团取代:卤素,=O,OR^s,和C_1-C_{10}烷基,其任选被1-3个选自以下的基团取代:=O,OH,-OR^s,和卤素;

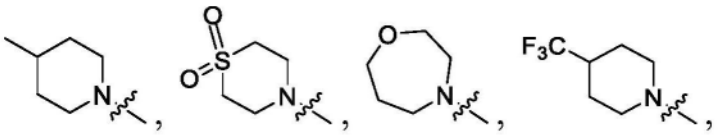
[3541] R^a的C_1-C_{10}烷基,C_2-C_{10}烯基,和C_2-C_{10}炔基各自任选被1-3个选自以下的基团取代:卤素,3-10元杂环基,和-OR^s;

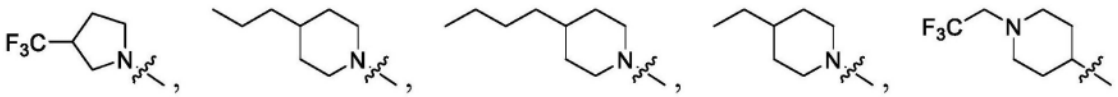
[3542] R^p和R^q,对于每次出现,独立地选自氢,C_3-C_{10}环烷基,和C_1-C_{10}烷基,其中R^p和R^q的C_3-C_{10}环烷基和C_1-C_{10}烷基各自任选被1-3个选自以下的基团取代:卤素,-OR^s和-C(=O)OR^s;

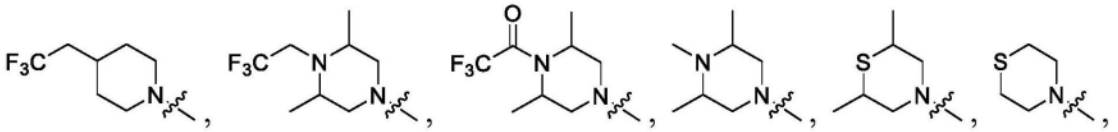
[3543] R^s,对于每次出现,选自H,NH_2,C_3-C_{10}环烷基,3-10元杂环基,5-6元芳基,和C_1-C_{10}烷基,其任选被1-3个选自以下的基团取代:卤素,C_3-C_{10}环烷基,3-10元杂环基,和C_1-C_6烷氧基,其中R^s的C_3-C_{10}环烷基和3-10元杂环基以及R^s的C_1-C_{10}烷基的C_3-C_{10}环烷基和3-10元杂环

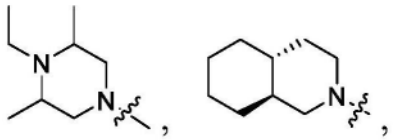
基各自任选被1-3个任选被=O和卤素取代的C_1-C_6烷基的基团取代,和R^s的C_1-C_{10}烷基的C_1-C_6烷氧基任选被1-3个卤素的基团取代。

[3544] 29.技术方案1-10,12-22,和26-28中任一项的化合物,互变异构体,溶剂化物,立体异构体,或药学上可接受的盐,其中R^a不存在或选自H,F,Cl,Br,甲基,

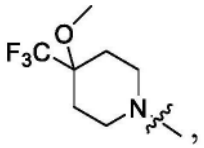


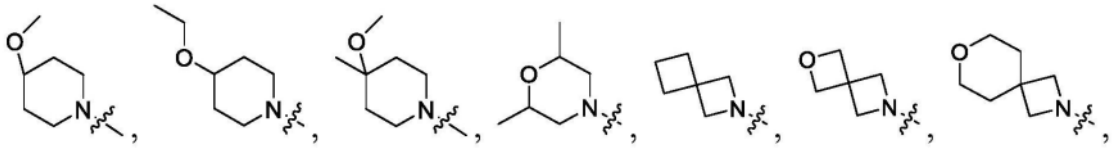


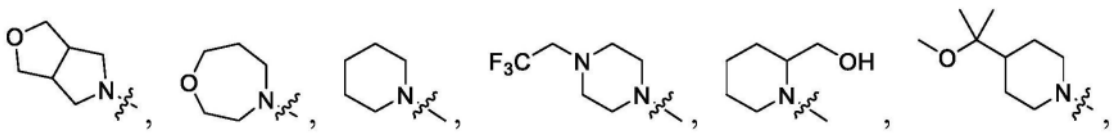


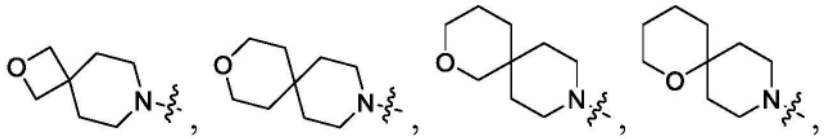


-CH(CH$_2$CH$_3$)$_2$,-CH(CH$_3$)$_2$,-OCH(CH$_3$)$_2$,-CH$_2$CH$_3$,-CH$_2$CH$_2$CH$_3$,-NHCH$_2$CF$_3$,-N(CH$_3$)CH$_2$CF$_3$,-O(CH$_2$)$_3$CH$_3$,-O(CH$_2$)$_2$CH$_3$,-(CH$_2$)$_2$CH$_3$,-(CH$_2$)$_4$CH$_3$,-(CH$_2$)$_3$CH$_3$,

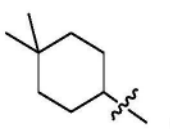


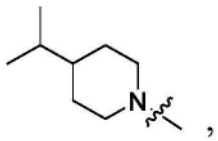


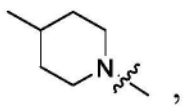




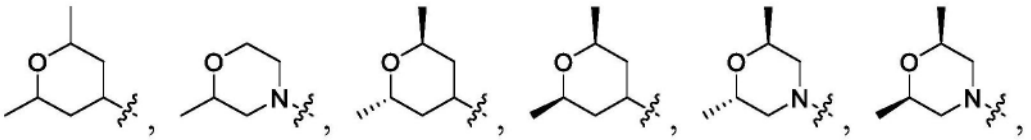
-N(CH$_2$CH$_3$)(CH$_2$)$_4$CH$_3$,-N(CH$_2$CH$_3$)(CH$_2$)$_3$OCH$_3$,

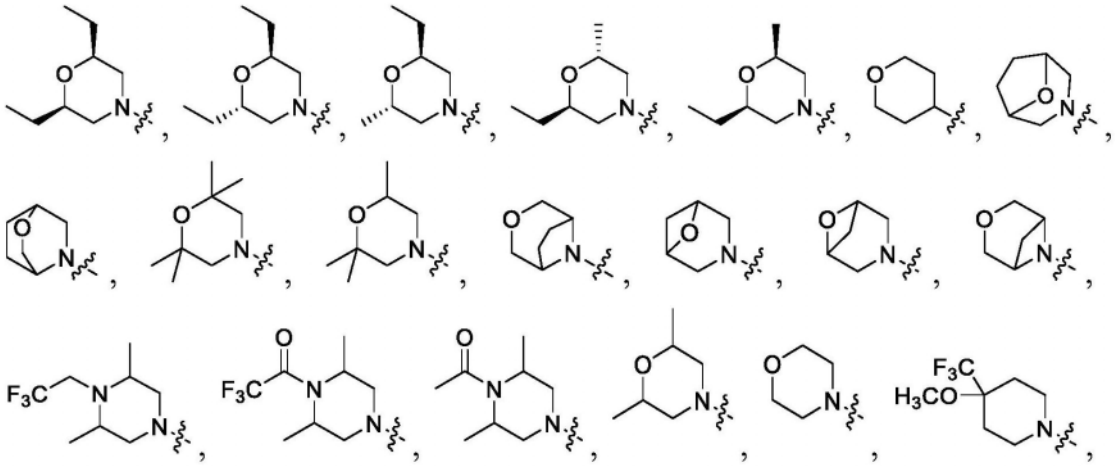


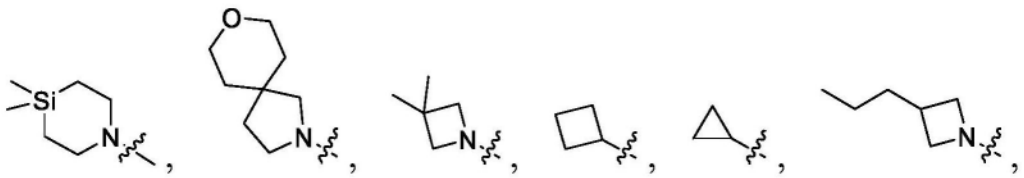
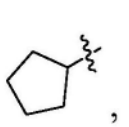
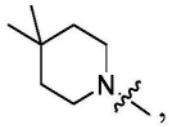
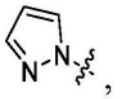
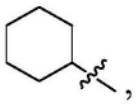


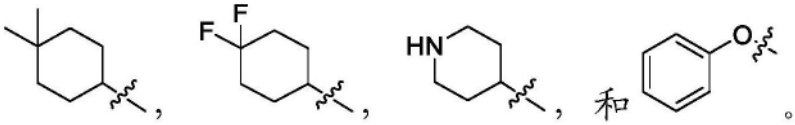


-C(CH$_3$)$_2$CH$_2$CH$_3$,-C(CH$_3$)$_2$CH$_2$CH$_2$CH$_3$,-C(CH$_3$)$_2$CH$_2$OCH$_2$CH$_3$,-C(CH$_3$)$_3$,

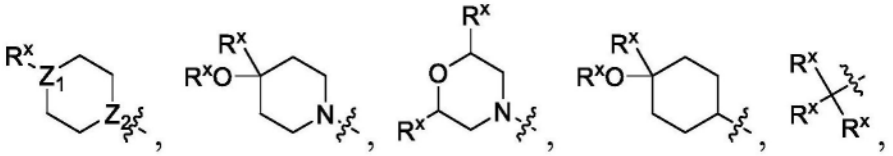




[3545]  -N$(CH_3)_2$,-O$(CH_2)_2OCH_2CH_3$,-OCH_2CH_3,-$(CH_2)_2OCH_3$,-$(CH_2)_3OCH_2CH_3$,   -CF_3,-CH_2CF_3,-$N(CH_2CH_3)_2$,  

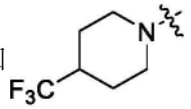
 和 。

[3546] 30.技术方案1-10,12-22,和26-28中任一项的化合物,互变异构体,溶剂化物,立体异构体,或药学上可接受的盐,其中R^a选自

 -OR^x,和-CH_2R^x,其中Z_1和Z_2独立地选自C和N,R^x,每次出现时,独立地选自任选被1-3个卤素的基团取代的C_1-C_4烷基。

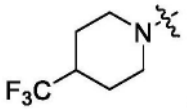
[3547] 31.技术方案1-10,12-22,和26-30中任一项的化合物,互变异构体,溶剂化物,立体异构体,或药学上可接受的盐,其中R^b不存在或选自H,卤素,C_1-C_6烷基,-NR^pR^q,CN,C_1-C_6烷氧基,和任选被任选被1-3个选自卤素的基团取代的C_1-C_3烷基取代的5-6元的杂环基,其中R^p和R^q各自选自C_1-C_6烷基,和其中R^b的C_1-C_6烷基和C_1-C_6烷氧基以及R^p和R^q的C_1-C_6烷基各自任选被1-3个选自卤素,-OR^s,和-NH_2的基团取代。

[3548] 32.技术方案1-10,12-22,和26-31中任一项的化合物,互变异构体,溶剂化物,立体异构体,或药学上可接受的盐,其中R^b不存在或者是H,甲基,乙基,-O$(CH_2)_4OCH_3$,-O$(CH_2)_3OCH_3$,-O$(CH_2)_2OCH_3$,-O$(CH_2)_2NH_2$,-$(CH_2)_5CH_3$,-O$(CH_2)_5CH_3$,-$(CH_2)_2OCH_3$,-O$(CH_2)_2OH$,F,-

OCH_3,$-CF_3$,Cl,CN,$-C(CH_3)_3$,和  。

[3549] 33.技术方案1-10,12-22,和26-31中任一项的化合物,互变异构体,溶剂化物,立体异构体,或药学上可接受的盐,其中R^b不存在或选自卤素,C_1-C_2烷基,和C_1-C_2烷氧基。

[3550] 34.技术方案1-22和24-33中任一项的化合物,互变异构体,溶剂化物,立体异构体,或药学上可接受的盐,其中R^c,每次出现时,独立地选自卤素,C_1-C_6烷基,$-NR^pR^q$,CN,和C_1-C_6烷氧基,其中R^p和R^q各自选自C_1-C_6烷基,和其中R^b的C_1-C_6烷基和C_1-C_6烷氧基以及R^p和R^q的C_1-C_6烷基各自任选被1-3个选自以下的基团取代:卤素,$-OR^s$,和$-NH_2$。

[3551] 35.技术方案1-22和24-34中任一项的化合物,互变异构体,溶剂化物,立体异构体,或药学上可接受的盐,其中R^c选自甲基,乙基,$-O(CH_2)_4OCH_3$,$-O(CH_2)_3OCH_3$,$-O(CH_2)_2OCH_3$,$-O(CH_2)_2NH_2$,$-(CH_2)_5CH_3$,$-O(CH_2)_5CH_3$,$-(CH_2)_2OCH_3$,$-O(CH_2)_2OH$,F,$-OCH_3$,$-CF_3$,Cl,CN,  ,和$-C(CH_3)_3$。

[3552] 36.技术方案1-22和24-34中任一项的化合物,互变异构体,溶剂化物,立体异构体,或药学上可接受的盐,其中R^c选自卤素,C_1-C_2烷基,和C_1-C_2烷氧基。

[3553] 37.技术方案1-22和24-36中任一项的化合物,互变异构体,溶剂化物,立体异构体,或药学上可接受的盐,其中R^d,对于每次出现,是不存在或独立地选自卤素,-OH,氰基,C_1-C_{10}烷基,苯基,5-7元杂芳基,苯基,3-10元杂环基,C_3-C_{10}环烷基,$-C(=O)R^s$,$-SO_2R^s$,C_2-C_{10}烯基,=O,$=NR^p$;$-C(=O)OR^s$,$-C(=O)NR^pR^q$,$-NR^pR^q$,$-NR^pC(=O)R^s$,和$-NR^pSO_2R^s$,其中

[3554] R^d的C_1-C_{10}烷基和C_2-C_{10}烯基各自任选被1-3个选自以下的基团取代:5-7元杂芳基,C_3-C_{10}环烷基,3-10元杂环基,$-OR^s$,$-C(=O)NR^pR^q$,$NR^pC(=O)R^s$,$-NR^pC(=NH)R^s$,$-NR^pC(=O)NR^qR^r$,和$-NR^pR^q$;

[3555] R^d的3-10元杂环基和C_3-C_{10}环烷基以及R^d的C_1-C_{10}烷基和C_2-C_{10}烯基的3-10元杂环基和C_3-C_6环烷基,各自任选被1-3个选自以下的基团取代:=O,$-NR^pR^q$,$NR^pC(=O)R^s$,和任选被1-3个选自卤素和$-OR^s$的基团取代的C_1-C_6烷基;

[3556] R^d的苯基和5-7元杂芳基以及R^d的C_1-C_{10}烷基和C_2-C_{10}烯基的5-7元杂芳基各自任选被1-3个选自以下的基团取代:任选被1-3个选自卤素和$-OR^s$的基团取代的C_1-C_6烷基;

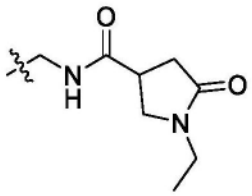
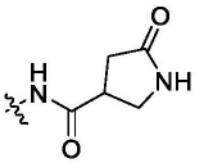
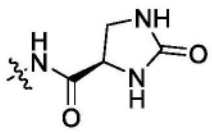
[3557] R^p,R^q,和R^r,对于每次出现,独立地选自氢,-OH,C_3-C_{10}环烷基,5-7元杂芳基,5-6元芳基,和C_1-C_{10}烷基,其中R^p,R^q,和R^r的C_3-C_{10}环烷基,5-7元杂芳基,5-6元芳基,和C_1-C_{10}烷基各自任选被1-3个选自以下的基团取代:卤素,C_1-C_6烷基,$-OR^s$和$-C(=O)OR^s$;

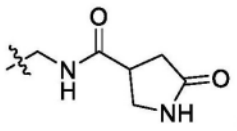
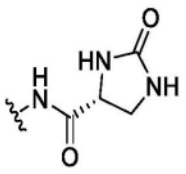
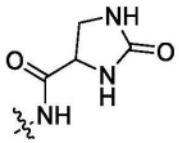
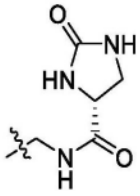
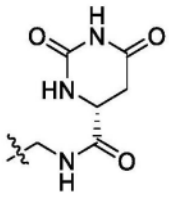
[3558] R^s,每次出现时,独立地选自H,$-NH_2$,C_3-C_{10}环烷基,3-10元杂环基,和C_1-C_{10}烷基,其任选被1-3个选自以下的基团取代:卤素,=O,NH_2,C_3-C_{10}环烷基,3-10元杂环基,和C_1-C_6烷氧基,其中

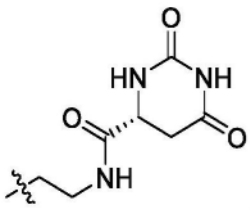
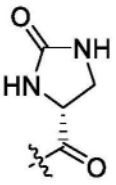
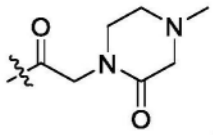
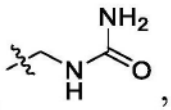
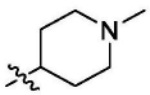
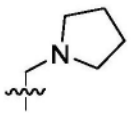
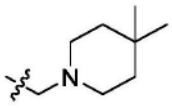
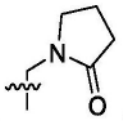
[3559] R^s的C_3-C_{10}环烷基和3-10元杂环基以及R^s的C_1-C_{10}烷基的C_3-C_{10}环烷基和3-10元杂环基各自任选被1-3个选自以下的基团取代:=O和任选被卤素取代的C_1-C_6烷基,和R^s的C_1-C_{10}烷基的C_1-C_6烷氧基任选被1-3个卤素的基团取代。

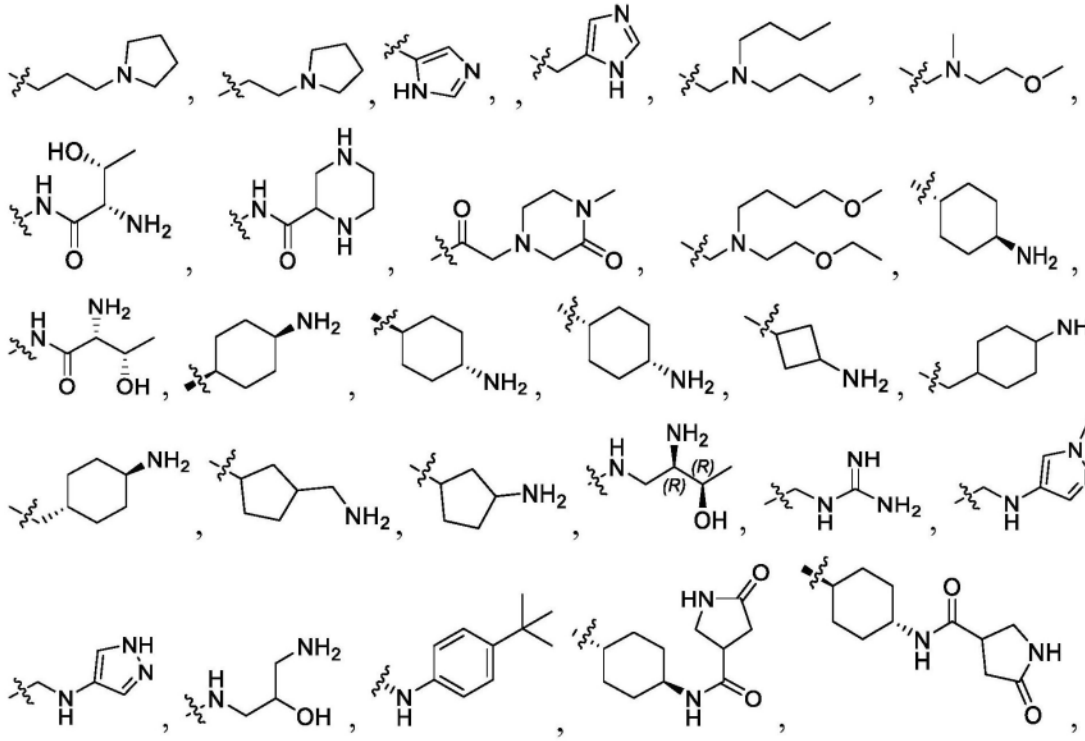
[3560] 38.技术方案1-22和24-37中任一项的化合物,互变异构体,溶剂化物,立体异构

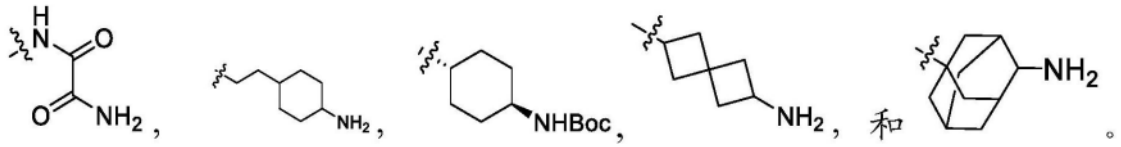
体，或药学上可接受的盐，其中R^d，对于每次出现，不存在或选自

 ，  ，  ，

 ，  ，  ，  ，  ，

[3561]  ，  ，  ，  ，F，甲基，乙基，丙基，丁基，$-(CH_2)_3NHCH_3$，$-CH_2N(CH_3)_2$，$-CH_2N^+(CH_3)_3$，$-(CH_2)_3N(CH_3)_2$，$-(CH_2)_3NH_2$，$-(CH_2)_5NH_2$，$-(CH_2)_4NH_2$，$-CH_2CH_2NH_2$，$-CH_2NH_2$，$-CH_2NHCH_3$，$-CHCH_3NH_2$，$-C(CH_3)_2NH_2$，$-CH_2NH(CH_2)_2OH$，$-(CH_2)_2NHC(=O)NH_2$，$-CH_2OCH_2CH_2NH_2$，$-CH_2CH_2OH$，$-CH_2OH$，$-CH_2OCH_3$，$-CH_2CH_2CH_2OCH_3$，$-CH_2OCH_2CH_2OCH_3$，$-CH_2OCH_2CH_2OH$，$-C(=O)N(CH_3)_2$，$-C(=O)NHCH_3$，$-C(=O)NHNH_2$，$-C(=O)NHOH$，$-CH_2OH$，OH，$-O(CH_2)_2N(CH_3)_2$，=O，$-C(=O)OCH_3$，$-C(=O)OH$，$-C(=O)NH_2$，$-NH_2$，$-NHC(=O)CH_3$，$-NHC(=O)NH_2$，$-NH(CH_2)_2OH$，$-NH(CH_2)_3OH$，$-NH(CH_2)_4OH$，$-NH(CH_2)_3NH_2$，$-NH(CH_2)_2NH_2$，$-NHCH_2CH_2N(CH_3)_2$，$-NHCH_2CF_3$，$-NHCH_2CH_2F$，$-NHCH_2CHF_2$，$-NHCH_2CH_3$，$-NHCH_2CH_2OCH_3$，$-N(CH_3)_2$，$-NHCH_3$，$-NHOH$，$-NHSO_2NH_2$，$-SO_2NH_2$，  ，  ，  ，  ，

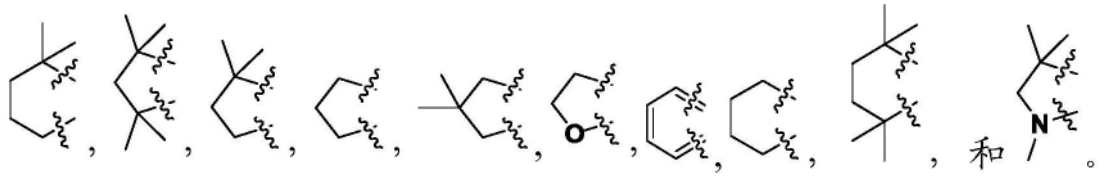


[3562] 

[3563] 39.技术方案1-22和24-37中任一项的化合物,互变异构体,溶剂化物,立体异构体,或药学上可接受的盐,其中R^d选自-C(=O)NR^pR^q,和C_1-C_6烷基,其中C_1-C_6烷基任选被1-3个选自以下的基团取代:C_1-C_3烷氧基,-C(=O)NR^pR^q,和-NR^pR^q,其中R^p和R^q各自选自H和C_1-C_3烷基。

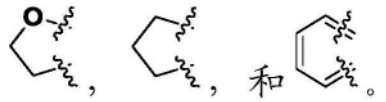
[3564] 40.技术方案1-10和12-22中任一项的化合物,互变异构体,溶剂化物,立体异构体,或药学上可接受的盐,其中R^a和R^b连在一起形成5-6元碳环、杂环、芳族、或杂芳族的环,其任选被1-4个选自任选被取代的C_1-C_6烷基的基团取代。

[3565] 41.技术方案1-10,12-22,和40中任一项的化合物,互变异构体,溶剂化物,立体异构体,或药学上可接受的盐,其中R^a和R^b连在一起形成选自以下的结构:



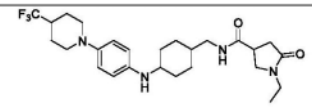
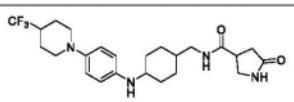
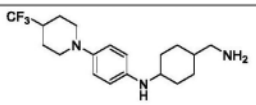
[3566] 42.技术方案1-10和12-22中任一项的化合物,互变异构体,溶剂化物,立体异构体,或药学上可接受的盐,其中R^b和R^c连在一起形成5-6元碳环、杂环、芳族、或杂芳族的环,其任选被1-4个选自任选被取代的C_1-C_6烷基的基团取代。

[3567] 43.技术方案1-10,12-22,和42中任一项的化合物,互变异构体,溶剂化物,立体异构体,或药学上可接受的盐,其中R^b和R^c连在一起形成选自以下的结构:

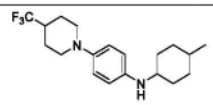
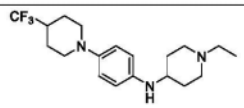
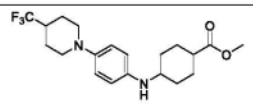
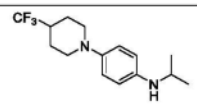
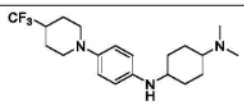
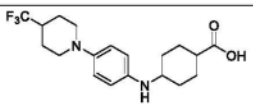
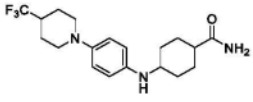
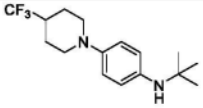
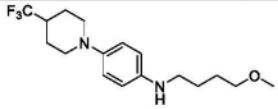
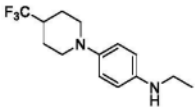
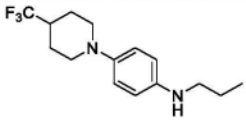
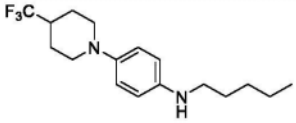
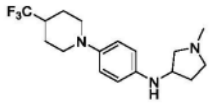
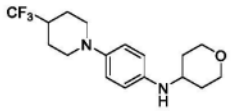
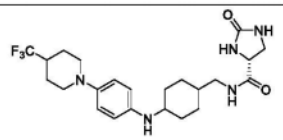
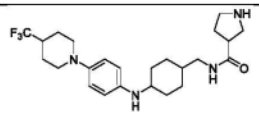
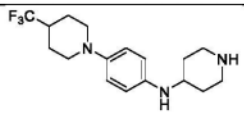
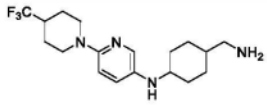
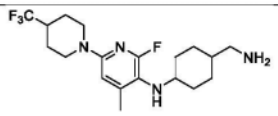
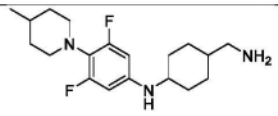
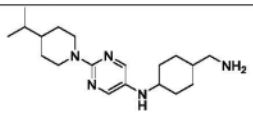
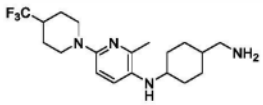
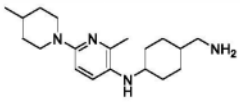
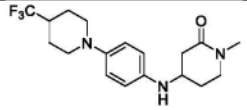
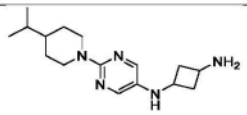
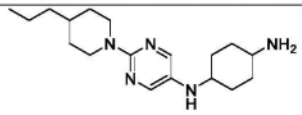
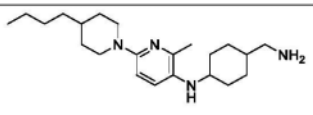
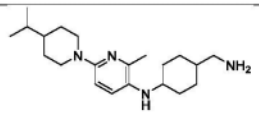
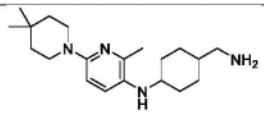
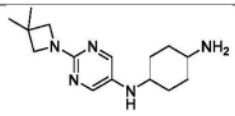


[3568] 44.一种化合物,其选自:

[3569]

 1	 2	 3

[3570]

 4A/B	 5	 6A/B
 7	 8	 9
 10	 11	 12
 13	 14	 15
 16	 17	 18
 19	 20	 21
 22	 23A/B	 24A/B
 25	 26	 27
 28	 29	 30
 31	 32A/B	 33A/B

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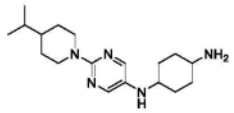
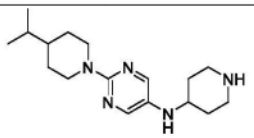
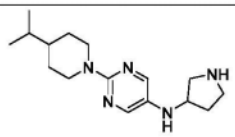
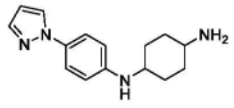
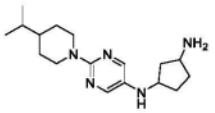
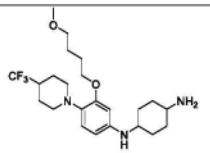
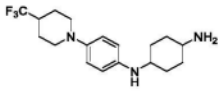
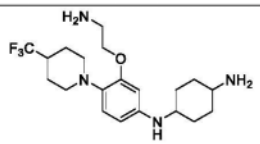
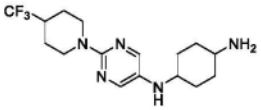
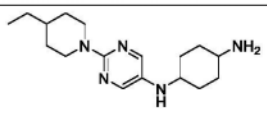
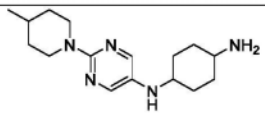
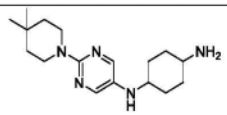
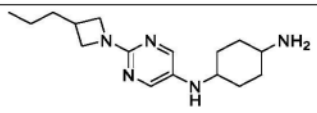
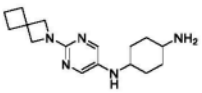
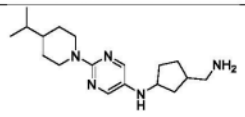
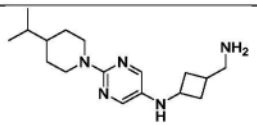
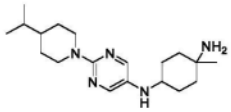
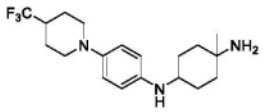
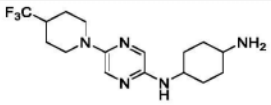
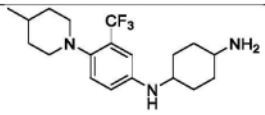
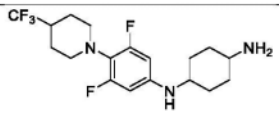
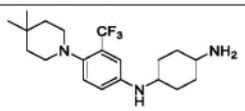
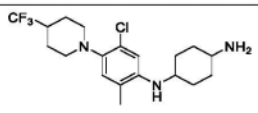
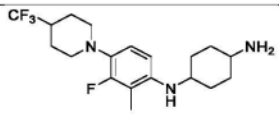
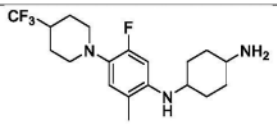
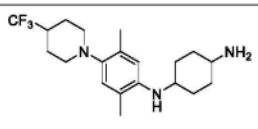
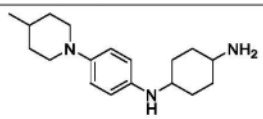
 34A/B	 35	 36
 37A/B	 38	 39
 40	 41A/B	 42
 43	 44	 45
 46	 47	 48
 49	 50	 51
 52	 53A/B	 54A/B
 55	 56	 57
 58	 59	 60

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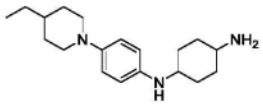
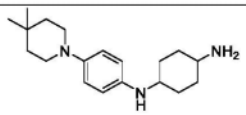
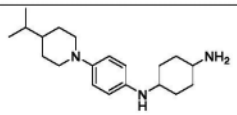
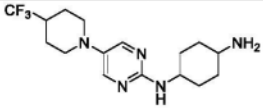
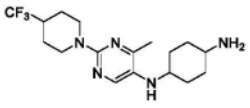
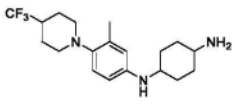
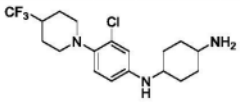
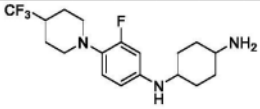
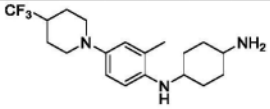
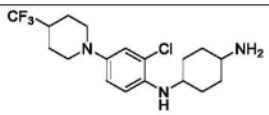
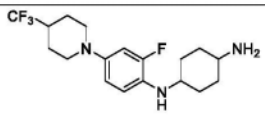
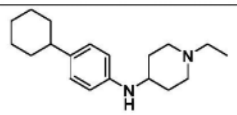
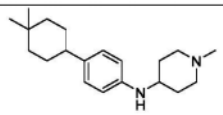
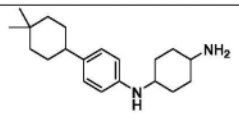
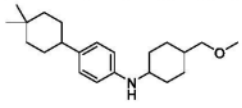
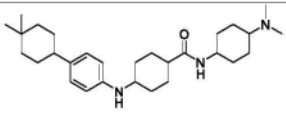
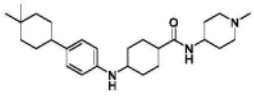
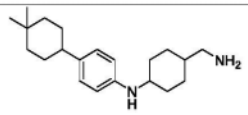
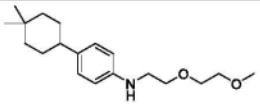
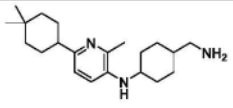
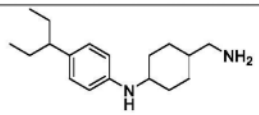
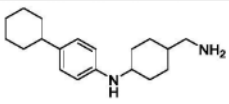
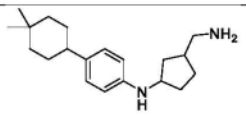
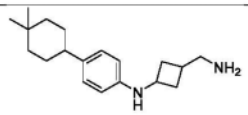
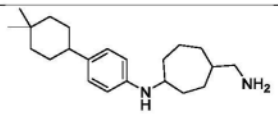
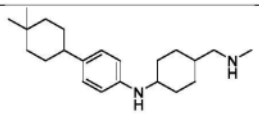
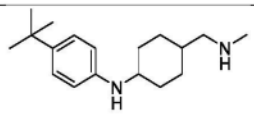
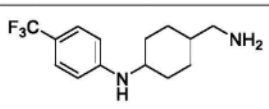
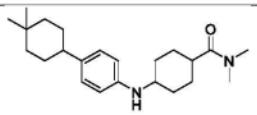
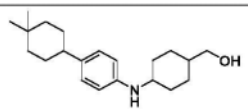
 61	 62	 63
 64A/B	 65A/B	 66
 67	 68	 69
 70	 71	 72
 73	 74	 75
 76A/B	 77	 78
 79	 80	 81A/B
 82A/B	 83	 84
 85	 86	 87
 88	 89	 90

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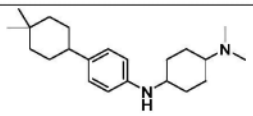
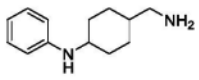
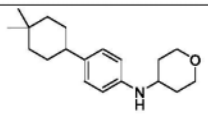
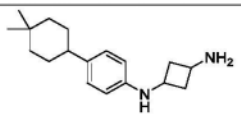
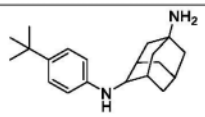
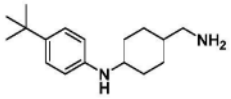
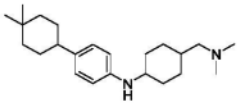
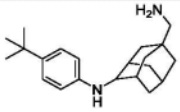
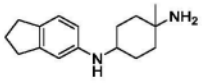
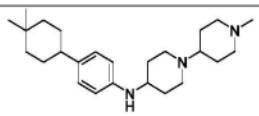
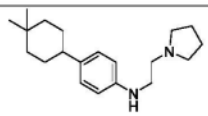
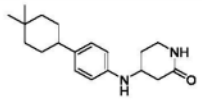
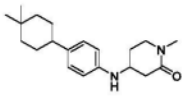
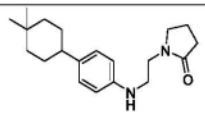
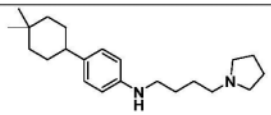
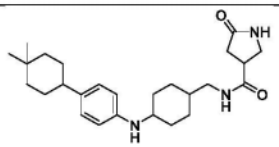
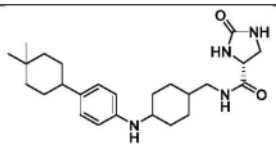
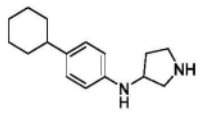
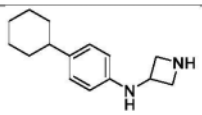
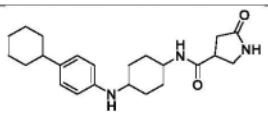
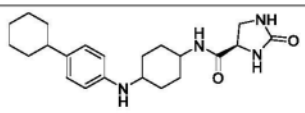
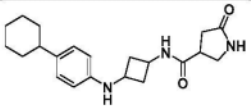
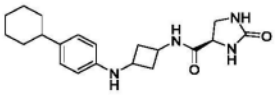
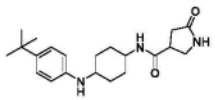
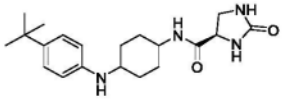
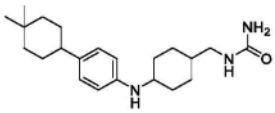
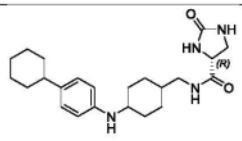
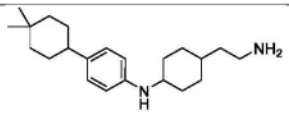
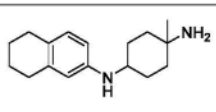
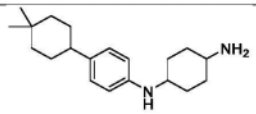
 91A/B	 92	 93
 94	 95	 96
 97A/B	 98	 99
 100	 101	 102
 103	 104	 105
 106A/B	 107A/B	 108
 109	 110	 111
 112	 113	 114A/B
 115A/B	 116	 117A/B
 118	 119	 120A/B

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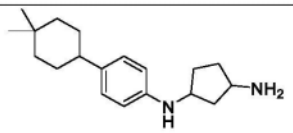
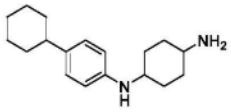
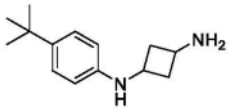
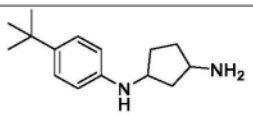
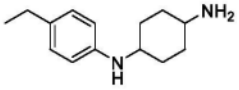
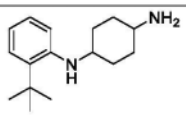
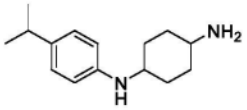
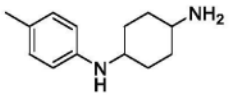
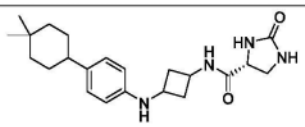
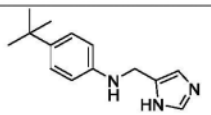
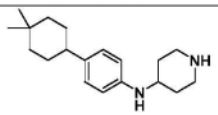
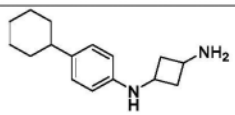
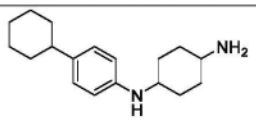
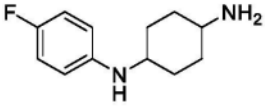
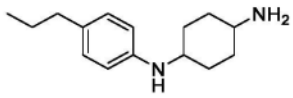
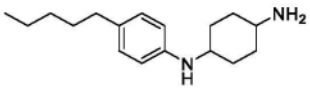
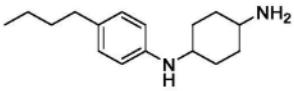
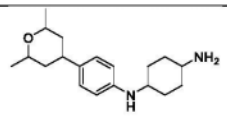
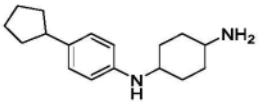
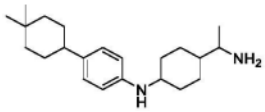
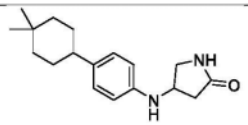
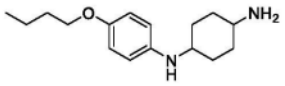
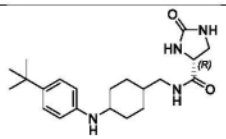
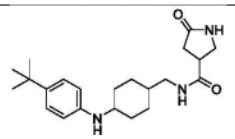
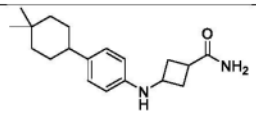
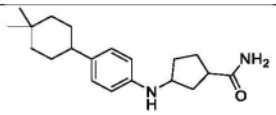
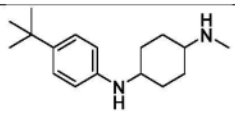
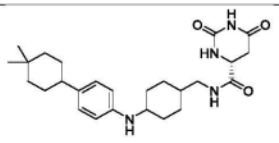
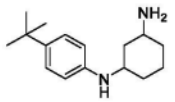
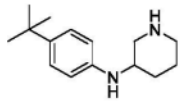
 121A/B	 122	 123
 124	 125	 126
 127	 128	 129
 130	 131	 132
 133	 134	 135A/B
 136	 137	 138
 139A/B	 140	 141
 142A/B	 143A/B	 144A/B
 145	 146A/B	 147
 148A/B	 149A/B	 150

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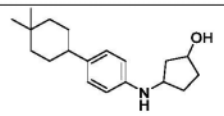
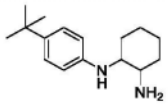
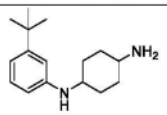
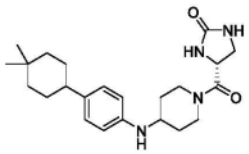
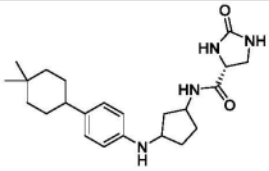
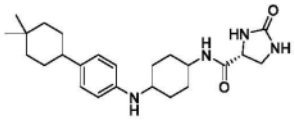
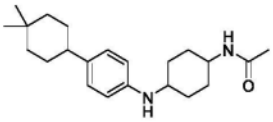
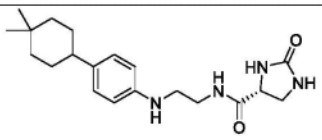
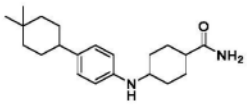
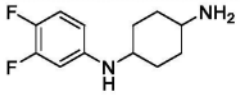
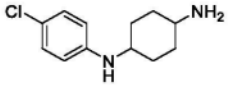
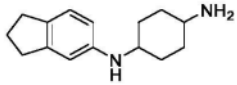
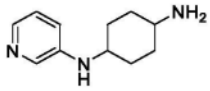
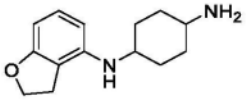
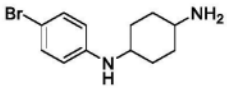
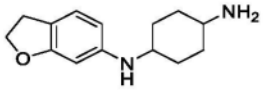
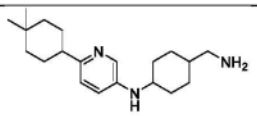
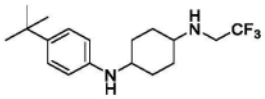
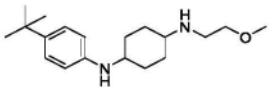
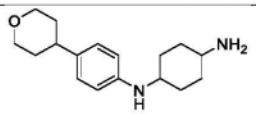
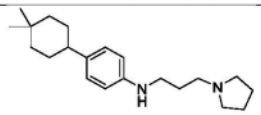
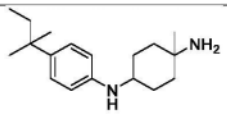
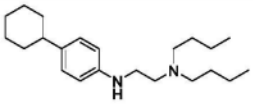
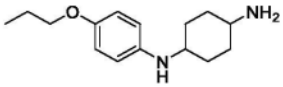
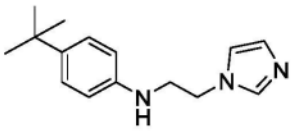
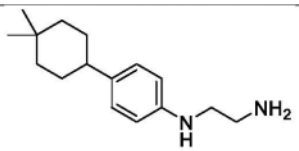
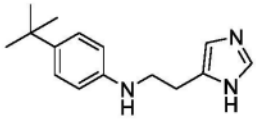
 151	 152	 153A/B
 154	 155	 156A/B/C
 157A/B	 158	 159A/B
 160	 161	 162
 163	 164	 165
 166	 167	 168A/B
 169	 170	 171
 172	 173	 174
 175	 176	 177

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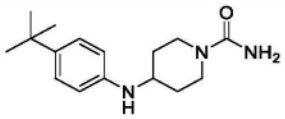
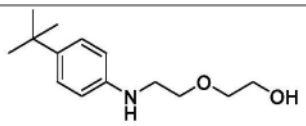
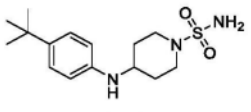
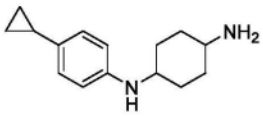
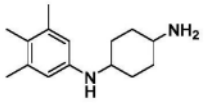
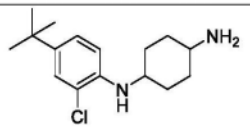
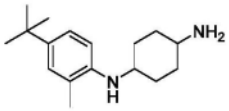
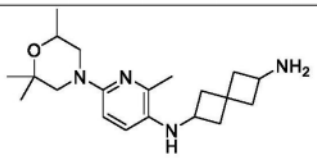
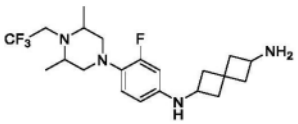
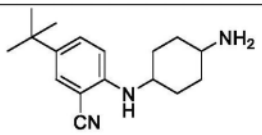
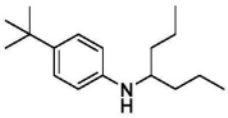
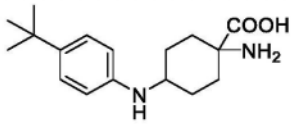
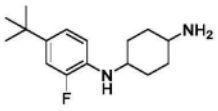
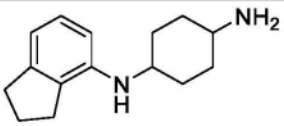
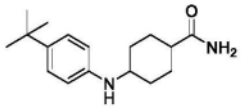
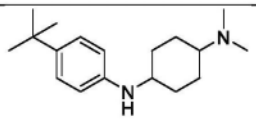
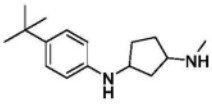
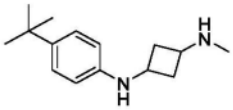
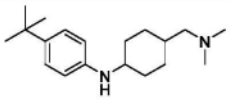
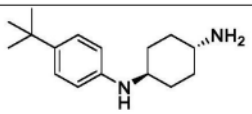
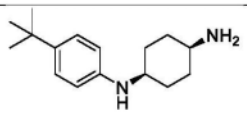
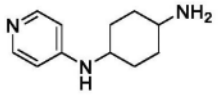
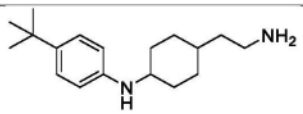
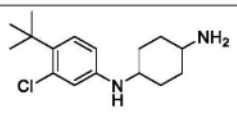
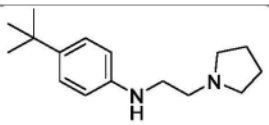
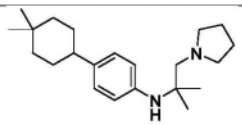
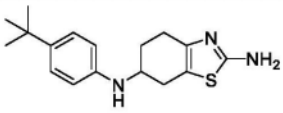
 178	 179	 180
 181	 182A/B	 183A/B
 184	 185	 186
 187	 188	 189
 190	 191A/B	 192
 193A/B	 194	 195
 196	 197	 198
 199	 200A/B	 201
 202	 203	 204

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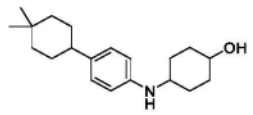
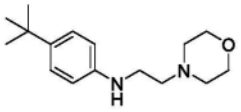
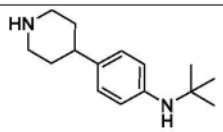
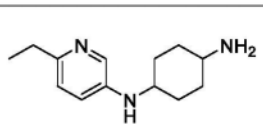
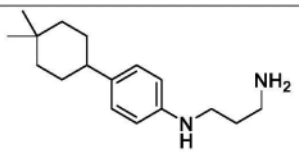
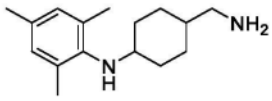
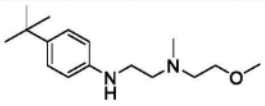
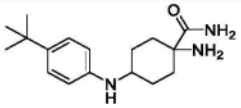
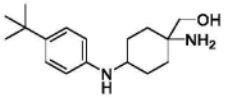
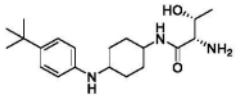
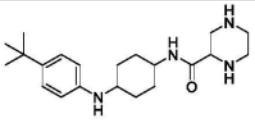
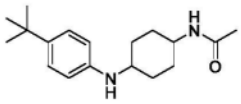
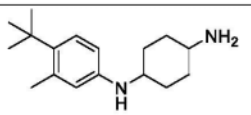
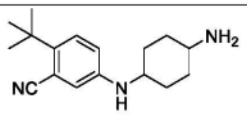
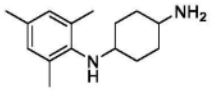
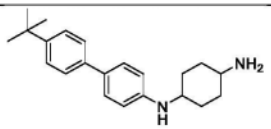
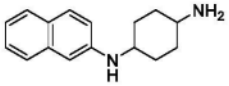
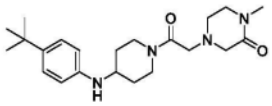
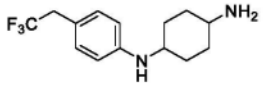
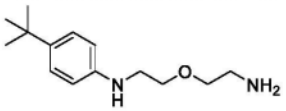
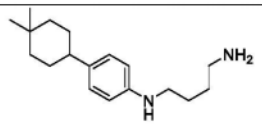
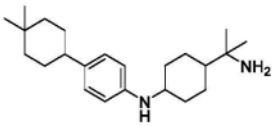
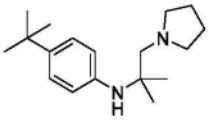
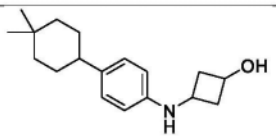
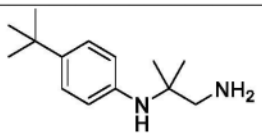
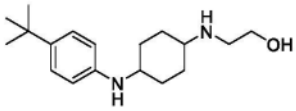
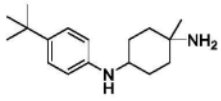
 205A/B	 206	 207
 208	 209	 210
 211	 212	 213A/B
 214	 215	 216A/B
 217	 218	 219
 220	 221	 222
 223	 224	 225
 226	 227	 228A/B
 229	 230	 231A/B

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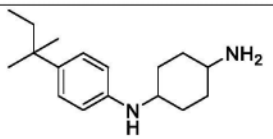
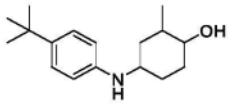
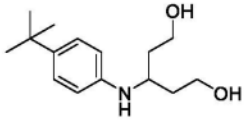
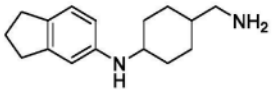
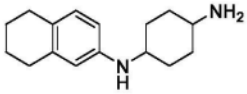
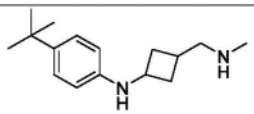
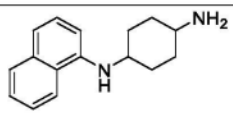
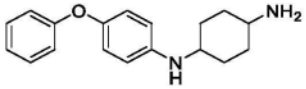
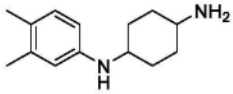
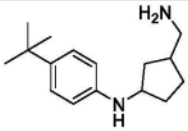
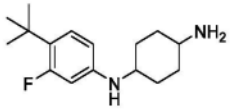
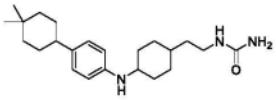
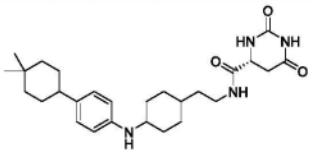
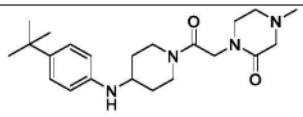
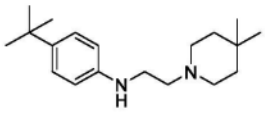
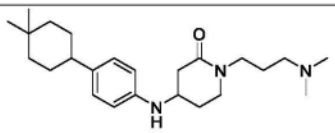
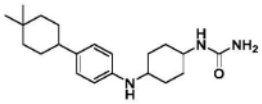
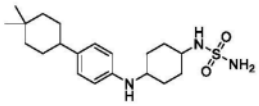
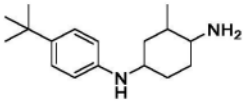
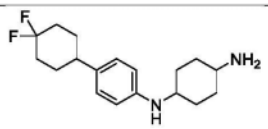
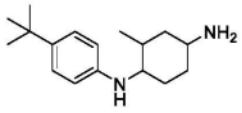
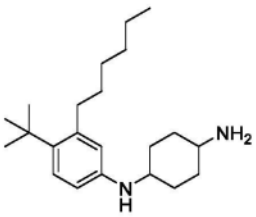
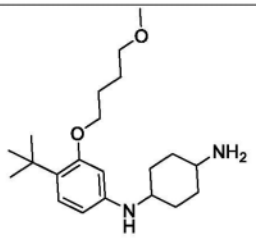
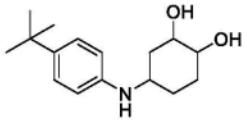
 232A/B	 233A/B	 234
 235	 236	 237
 238	 239	 240
 241	 242A/B	 243
 244A/B	 245	 246
 247	 248	 249
 250A/B	 251A/B	 252A/B/C/D
 253A/B	 254	 255

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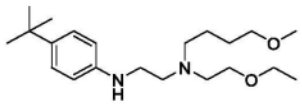
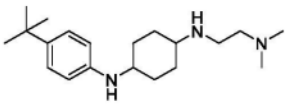
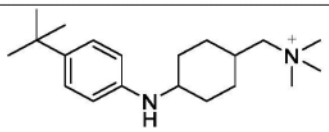
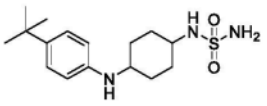
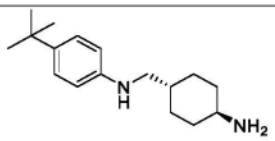
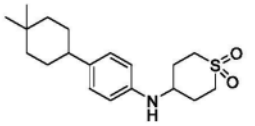
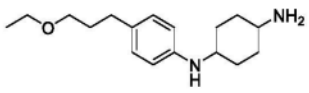
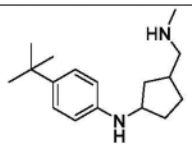
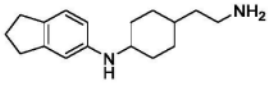
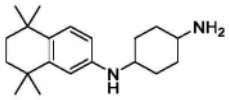
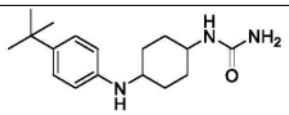
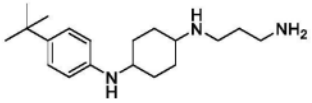
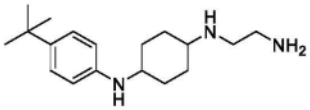
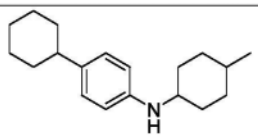
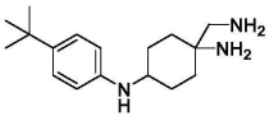
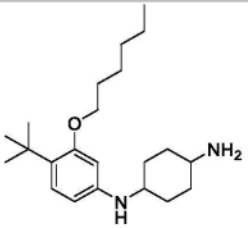
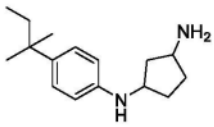
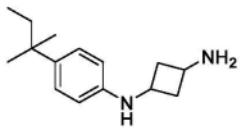
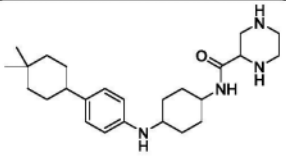
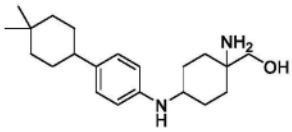
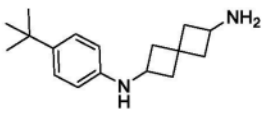
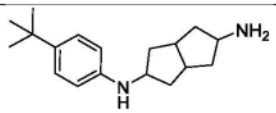
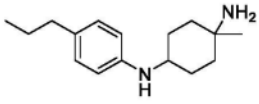
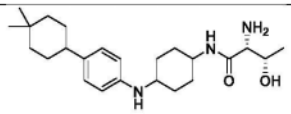
 256	 257	 258
 259A/B	 260	 261
 262	 263	 264
 265	 266A/B	 267
 268	 269	 270
 271	 272	 273
 274	 275A/B	 276
 277	 278	 279

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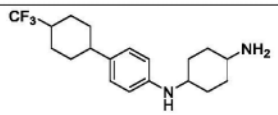
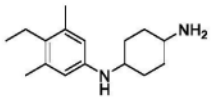
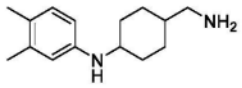
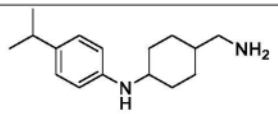
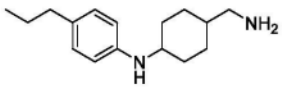
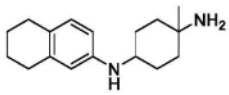
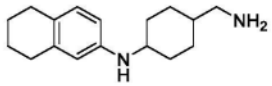
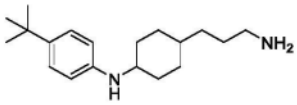
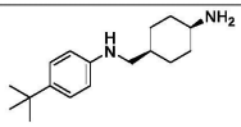
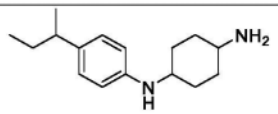
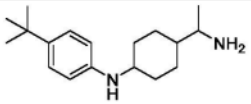
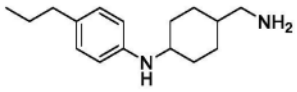
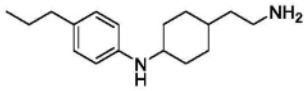
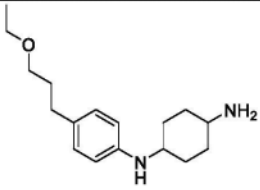
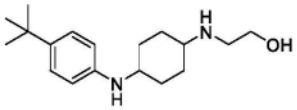
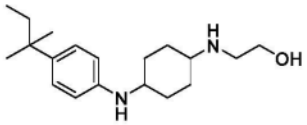
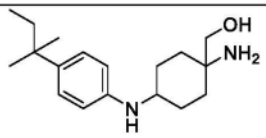
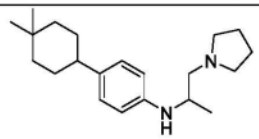
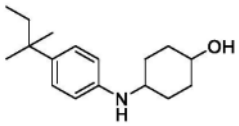
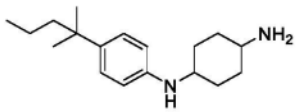
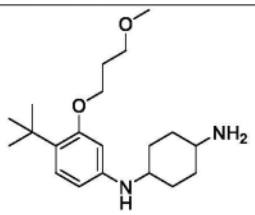
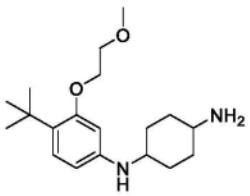
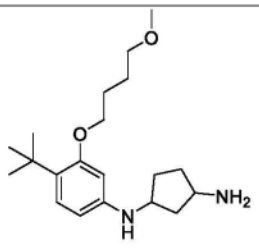
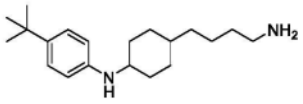
 280	 281	 282
 283	 284	 285
 286	 287	 288
 289A/B	 290	 291
 292	 293	 294A/B
 295A/B	 296A/B	 297
 298	 299A/B	 300A/B
 301A/B	 302	 303

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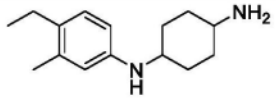
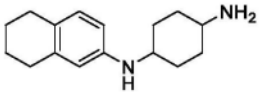
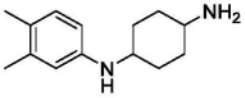
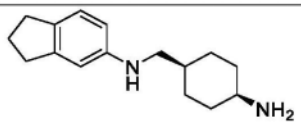
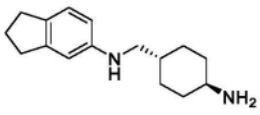
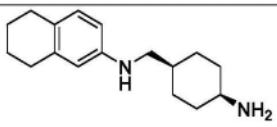
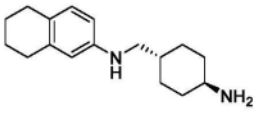
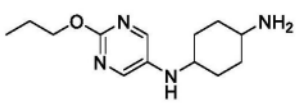
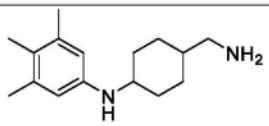
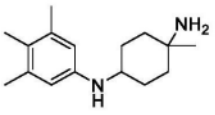
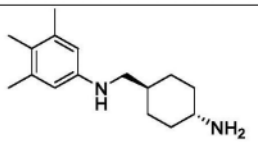
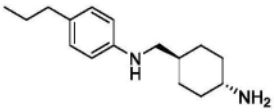
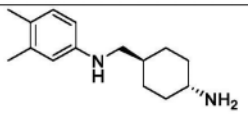
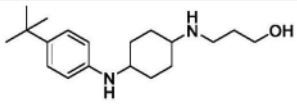
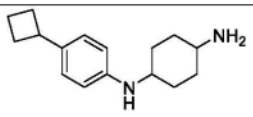
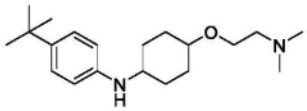
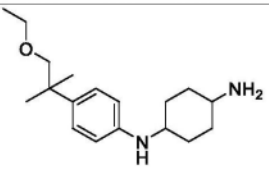
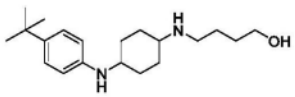
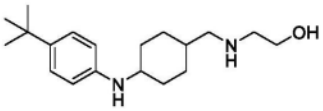
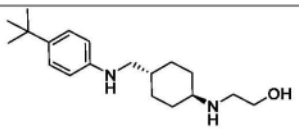
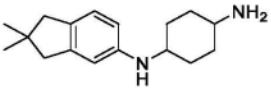
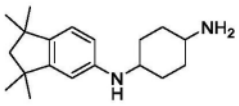
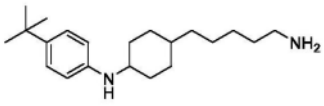
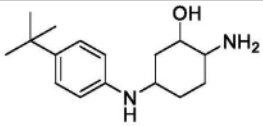
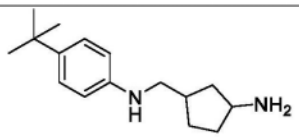
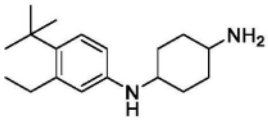
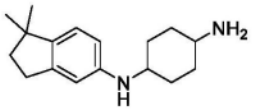
 304	 305A/B	 306A/B
 307	 308	 309
 310	 311	 312
 313A/B	 314	 315
 316	 317	 318A/B
 319A/B	 320A/B	 321
 322	 323	 324
 325A/B	 326	 327
 328	 329	 330A/B

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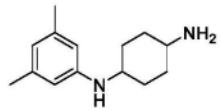
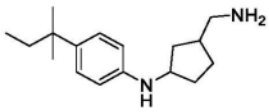
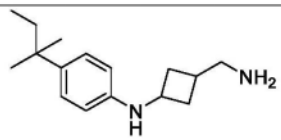
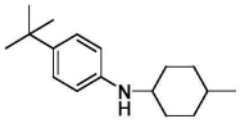
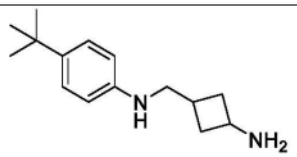
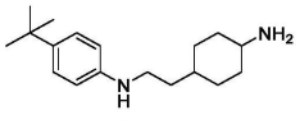
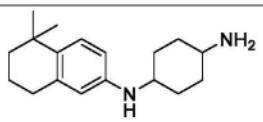
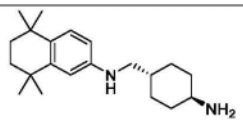
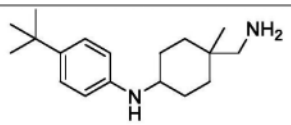
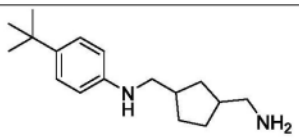
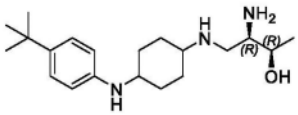
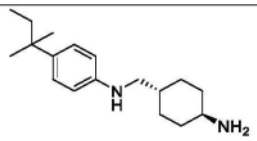
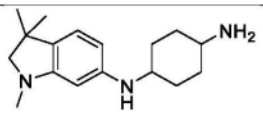
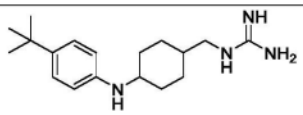
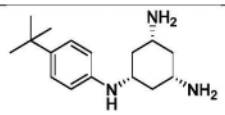
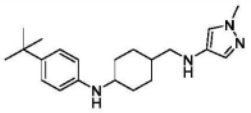
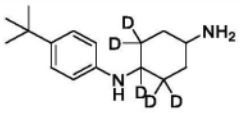
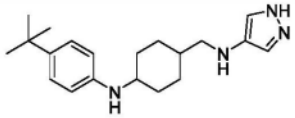
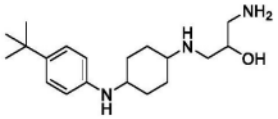
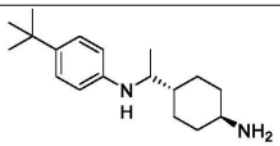
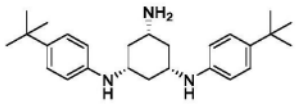
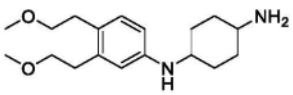
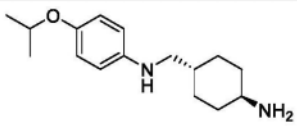
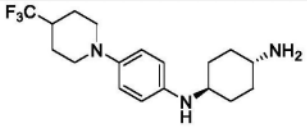
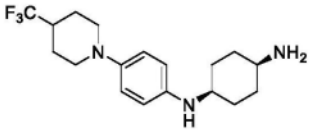
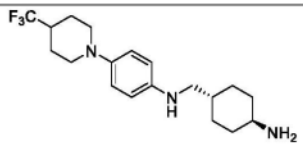
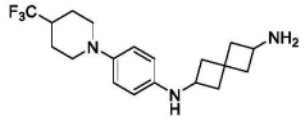
 331	 332	 333
 334	 335A/B	 336A/B
 337A/B	 338	 339
 340	 341	 342
 343	 344	 345
 346	 347	 348
 349A/B	 350	 351
 352	 353	 354
 355	 356	 357

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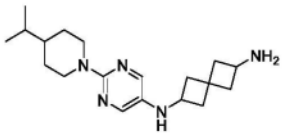
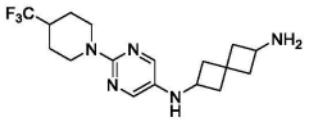
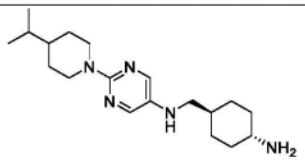
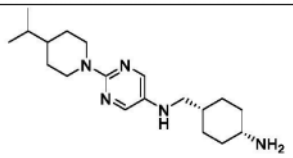
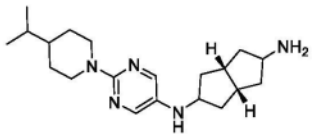
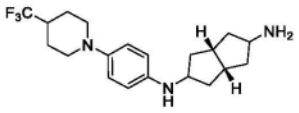
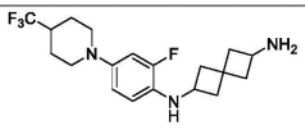
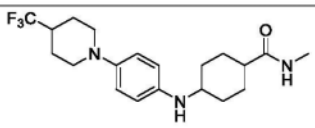
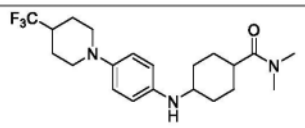
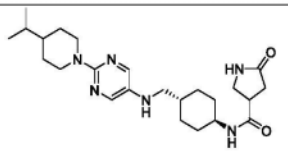
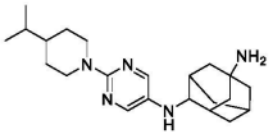
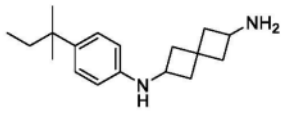
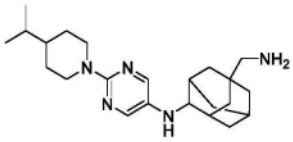
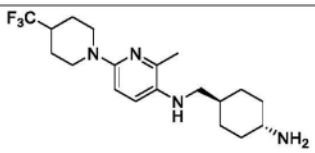
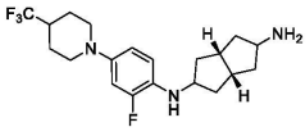
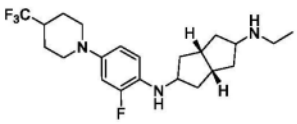
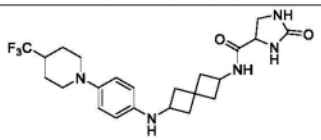
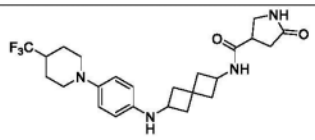
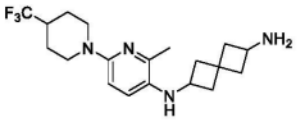
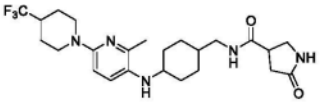
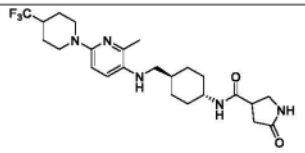
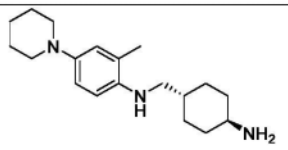
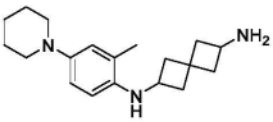
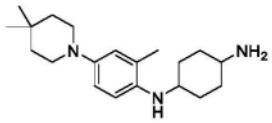
 358	 359	 360
 361	 362	 363
 364	 365	 366
 367	 368	 369
 370	 371	 372
 373	 374	 375
 376	 377	 378
 379	 380	 381

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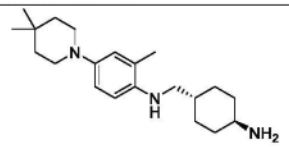
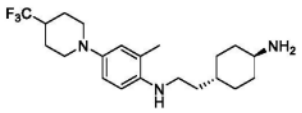
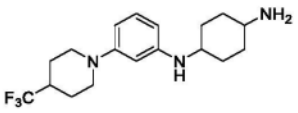
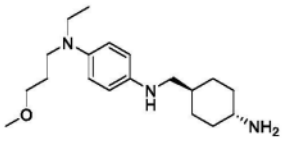
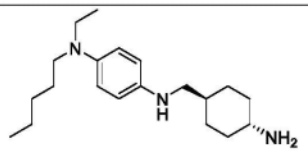
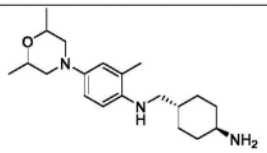
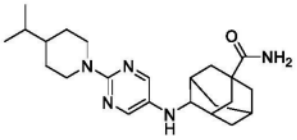
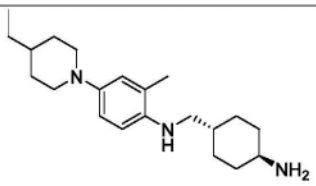
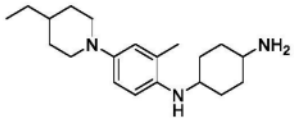
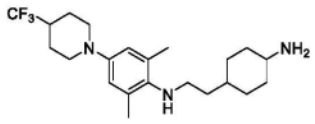
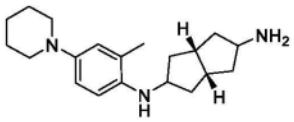
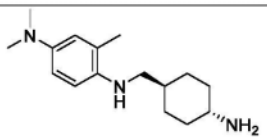
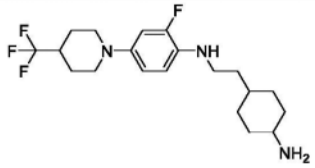
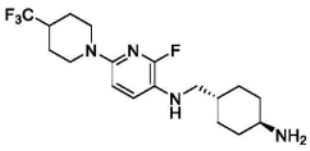
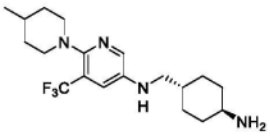
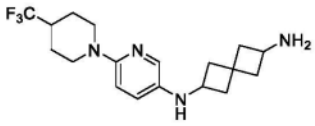
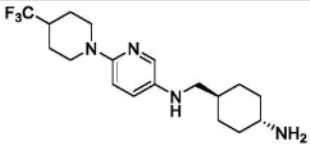
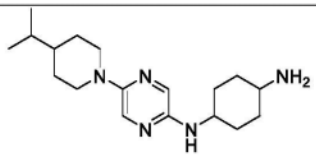
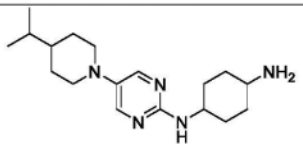
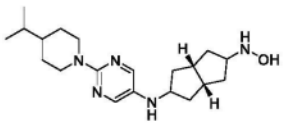
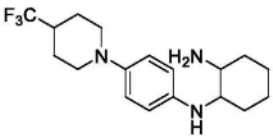
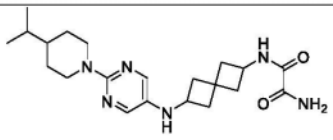
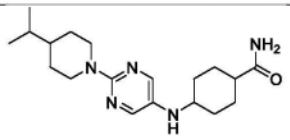
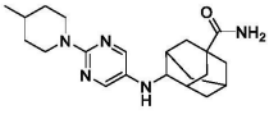
 382	 383	 384
 385	 386	 387
 388	 389	 390
 391	 392	 393
 394	 395	 396
 397	 398	 399
 400	 401	 402
 403	 404	 405

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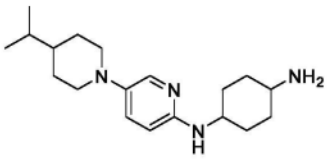
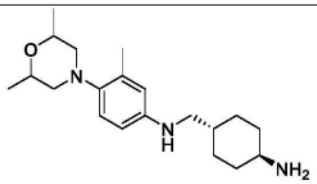
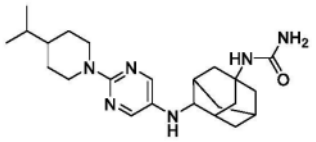
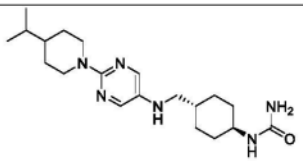
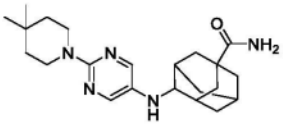
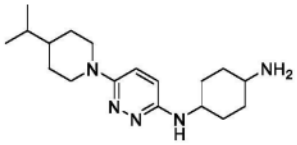
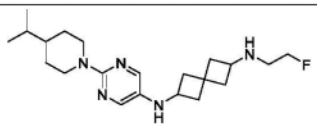
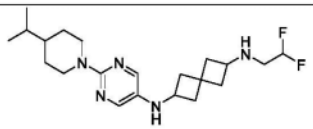
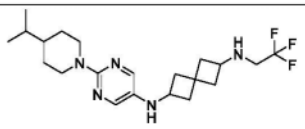
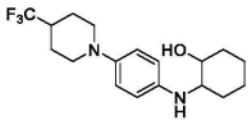
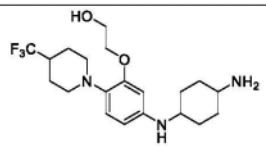
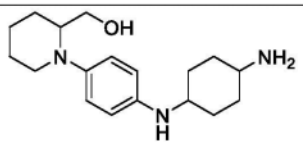
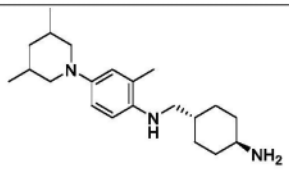
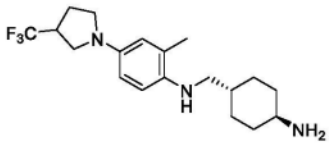
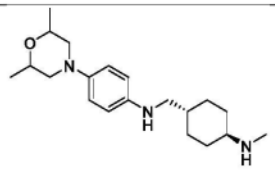
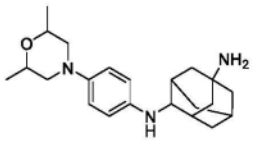
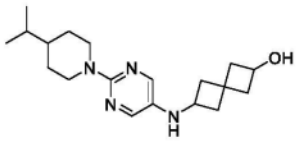
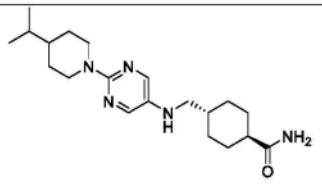
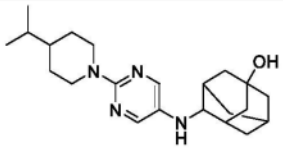
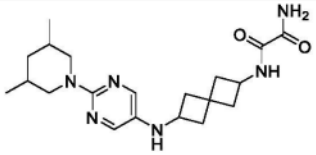
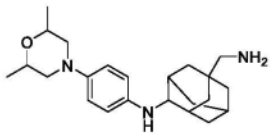
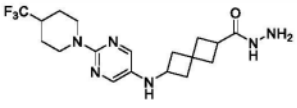
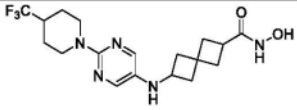
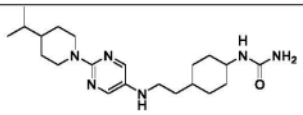
 406	 407	 408
 409	 410	 411
 412	 413	 414
 415	 416	 417A/B
 418	 419	 420
 421A/B	 422	 423
 424	 425	 426
 427	 428	 429

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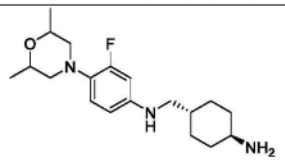
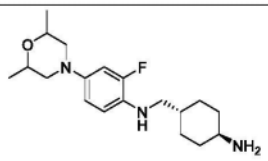
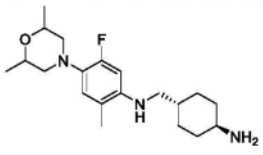
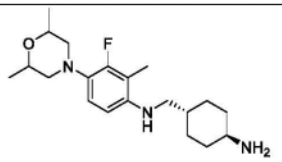
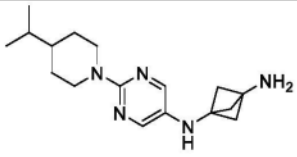
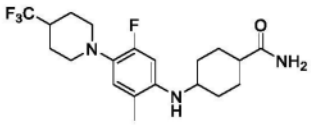
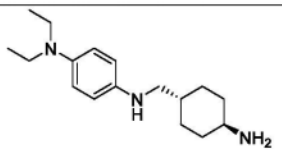
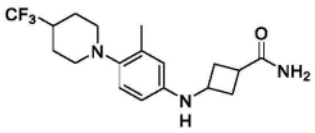
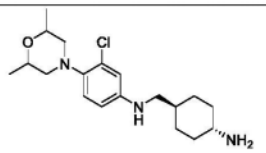
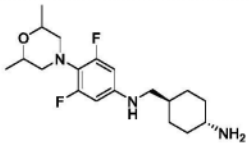
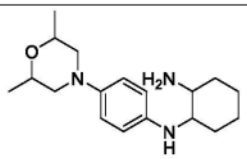
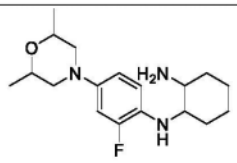
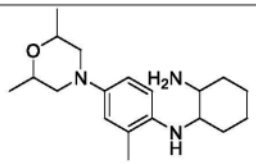
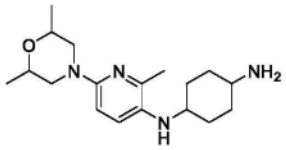
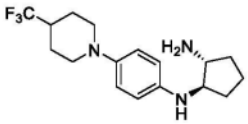
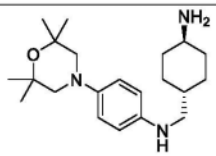
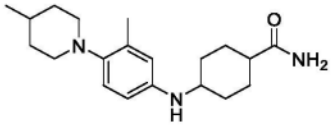
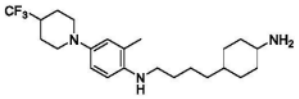
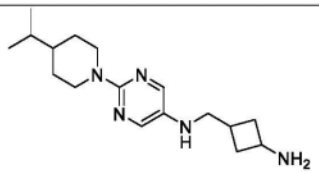
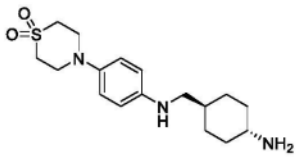
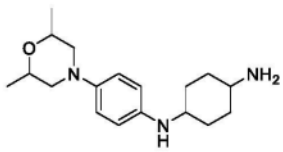
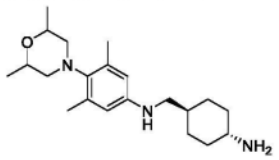
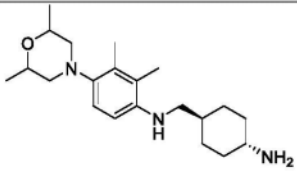
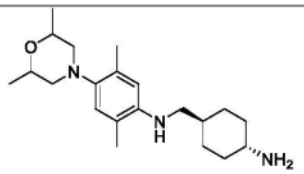
 430	 431	 432
 433	 434	 435
 436	 437	 438
 439	 440	 441
 442	 443	 444
 445	 446A/B	 447
 448	 449	 450
 451	 452	 453

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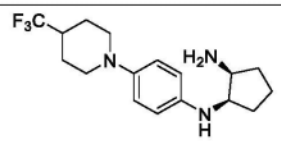
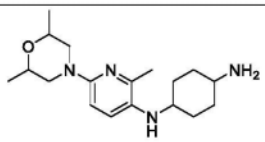
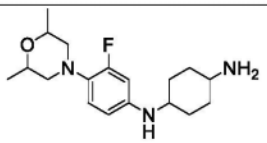
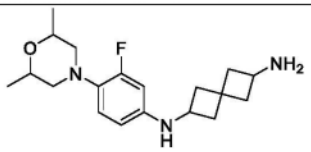
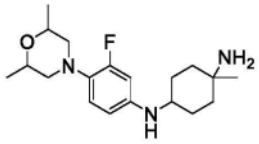
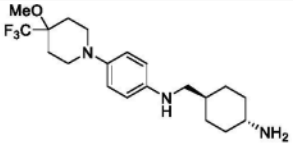
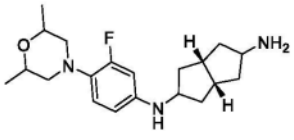
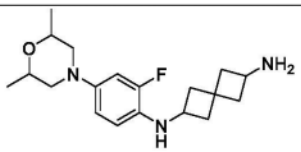
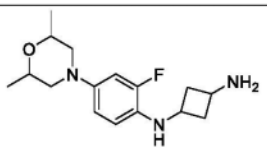
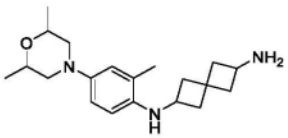
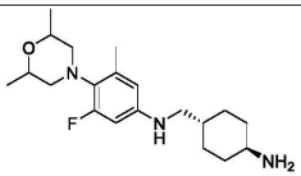
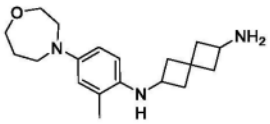
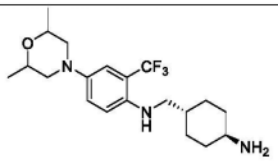
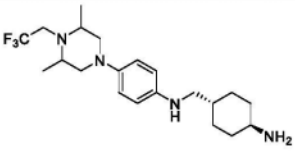
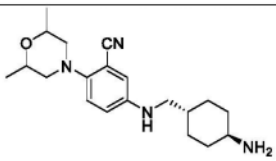
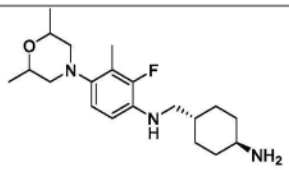
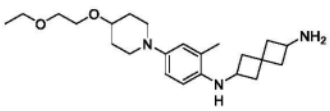
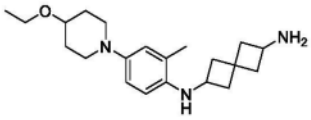
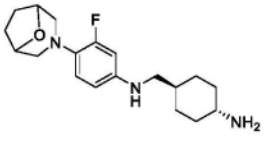
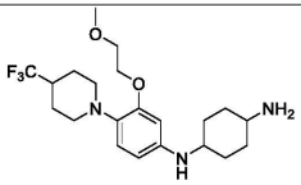
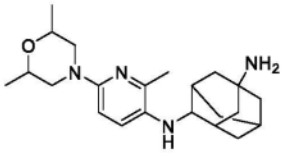
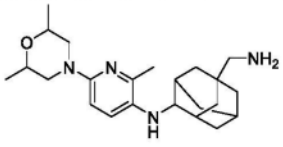
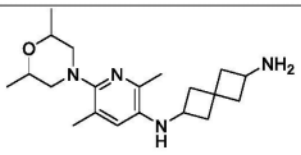
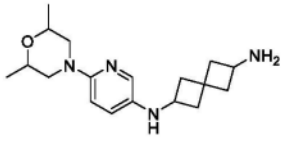
 454	 455	 456
 457	 458	 459
 460	 461	 462
 463	 464	 465
 466	 467	 468
 469	 470	 471
 472	 473	 474
 475A/B	 476	 477

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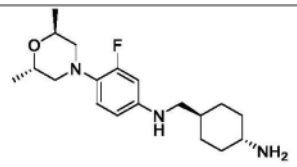
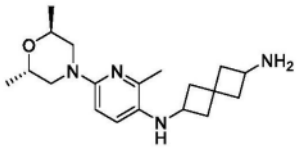
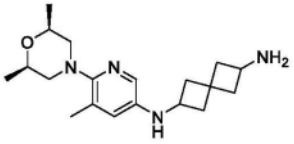
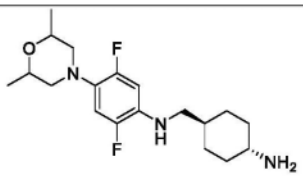
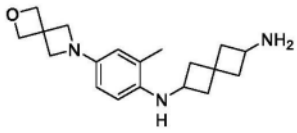
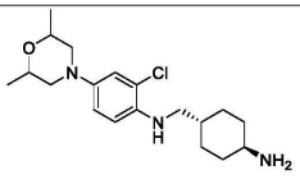
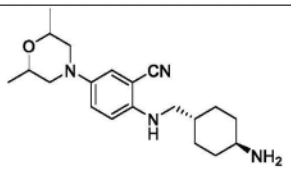
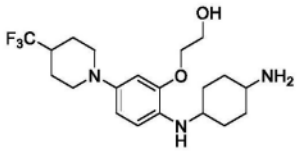
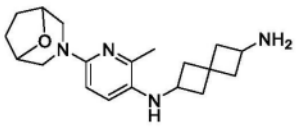
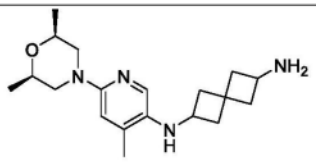
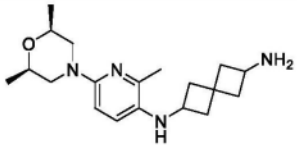
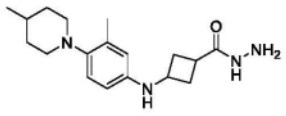
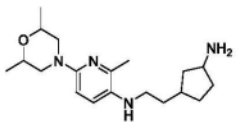
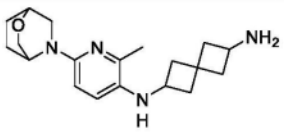
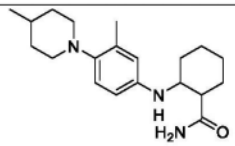
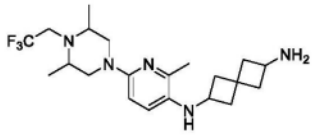
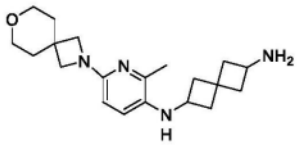
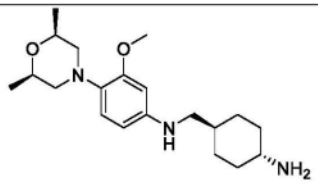
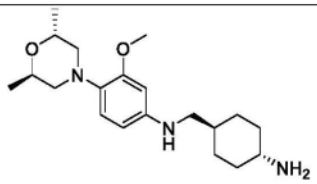
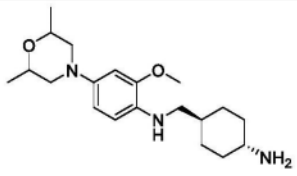
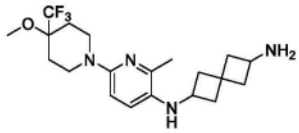
 478	 479	 480
 481	 482	 483
 484	 485	 486
 487	 488A/B	 489
 490	 491	 492
 493	 494	 495
 496	 497	 498

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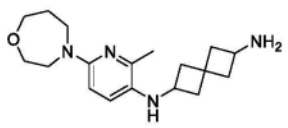
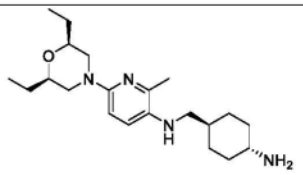
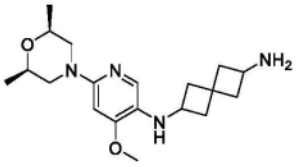
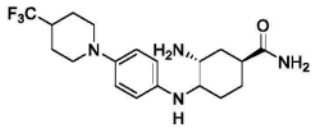
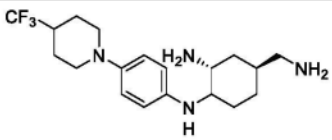
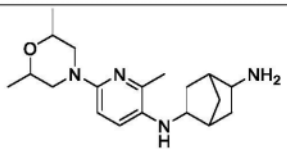
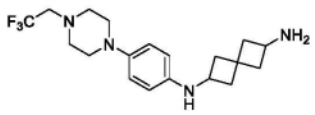
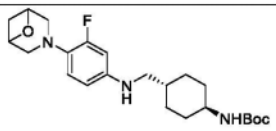
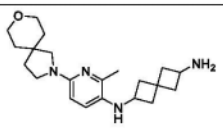
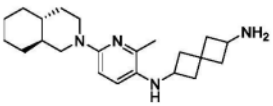
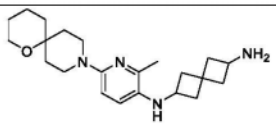
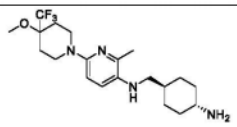
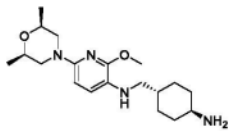
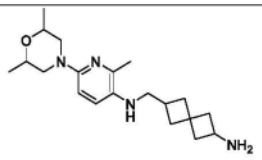
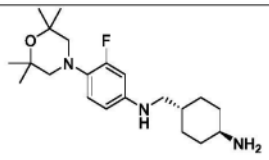
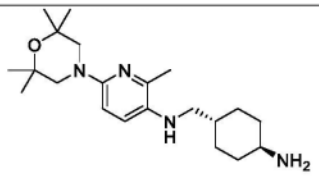
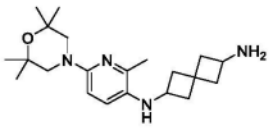
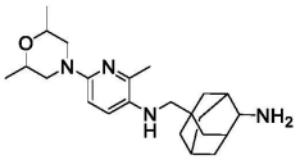
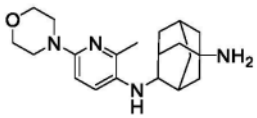
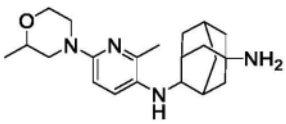
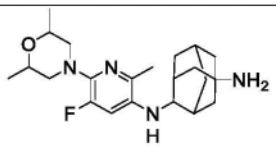
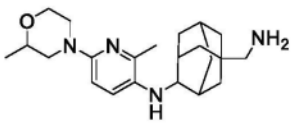
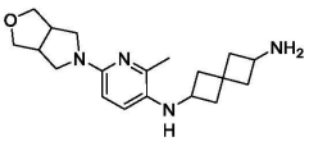
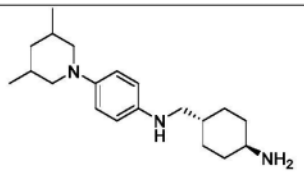
 499	 500	 501
 502	 503	 504
 505	 506	 507
 508	 509	 510
 511	 512	 513
 514	 515	 516A/B
 517	 518	 519
 520	 521	 522

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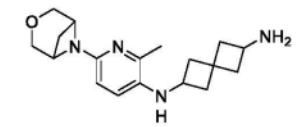
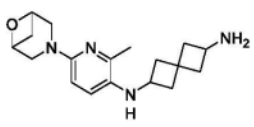
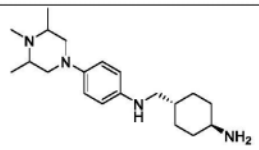
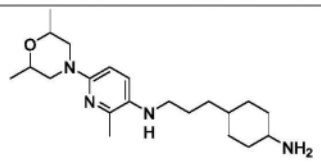
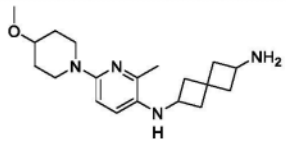
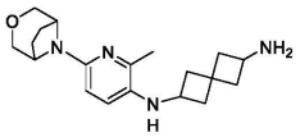
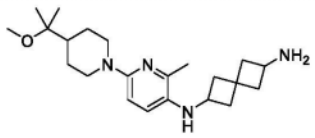
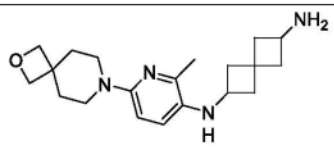
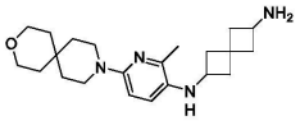
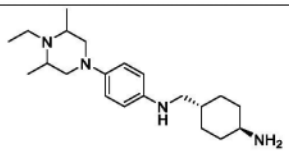
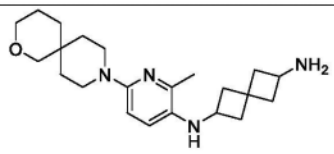
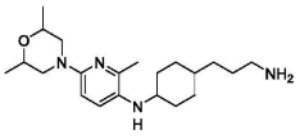
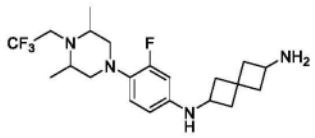
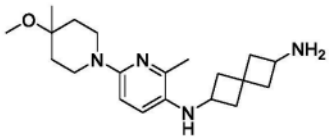
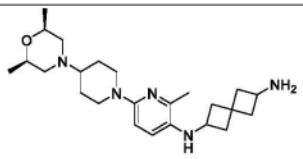
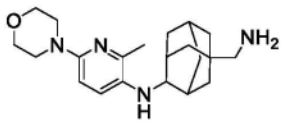
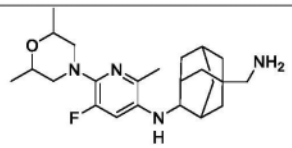
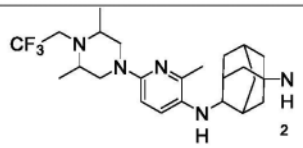
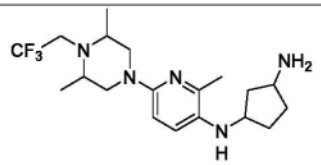
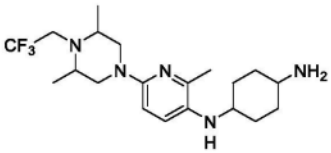
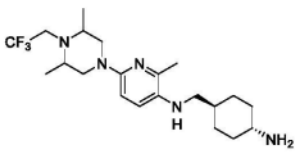
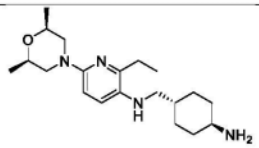
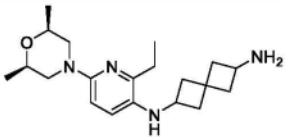
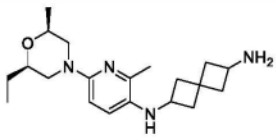
 523	 524	 525
 526	 527	 528
 529	 530	 531
 532	 533	 534
 535	 536	 537
 538A/B	 539A/B	 540
 541	 542	 543
 544	 545	 546

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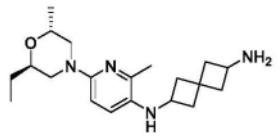
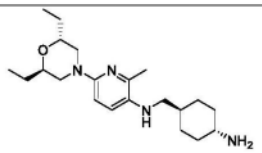
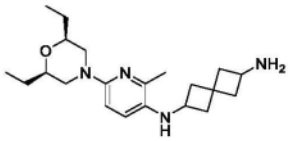
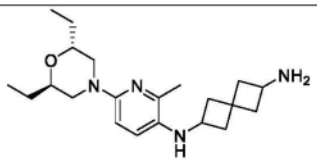
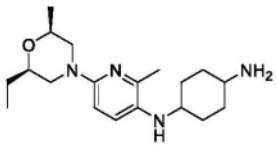
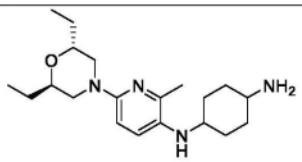
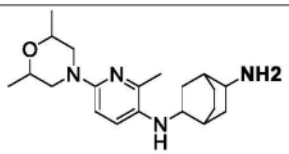
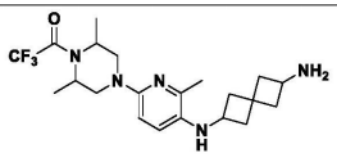
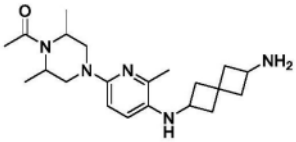
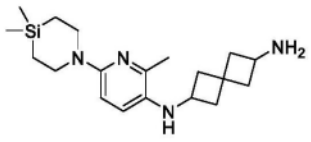
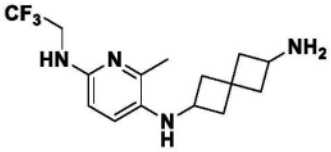
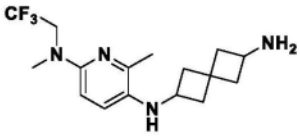
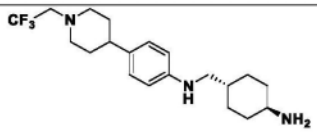
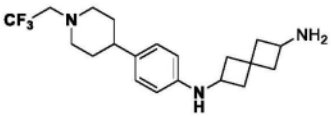
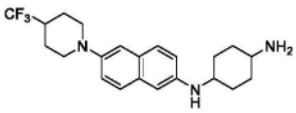
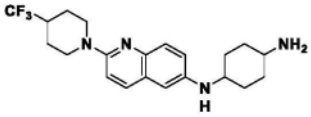
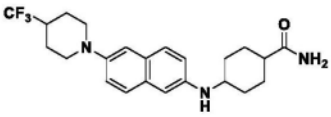
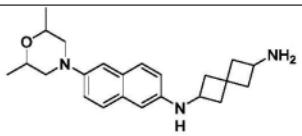
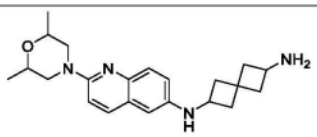
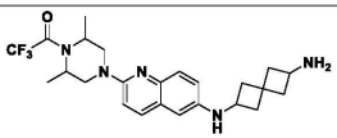
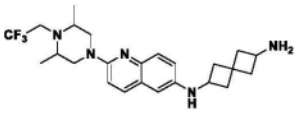
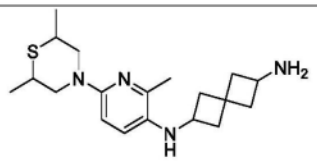
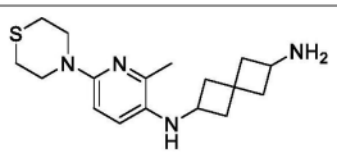
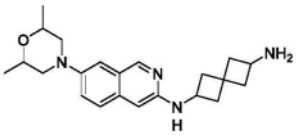
 547	 548	 549
 550	 551	 552
 553	 554	 555
 556	 557	 558
 559	 560	 561
 562	 563	 564
 565	 566	 567
 568	 569	 570

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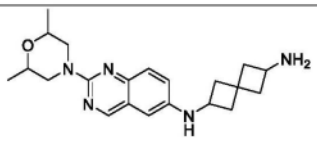
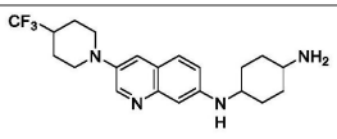
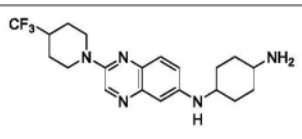
 571	 572	 573

[3593] 其互变异构体,该化合物或该互变异构体的溶剂化物或立体异构体,或前述的药

学上可接受的盐。

[3594] 45.一种药物组合物,其包括根据技术方案1至44中任一项的化合物,其互变异构体,该化合物或该互变异构体的溶剂化物或立体异构体,或前述的药学上可接受的盐和至少一种药学上可接受的载体。

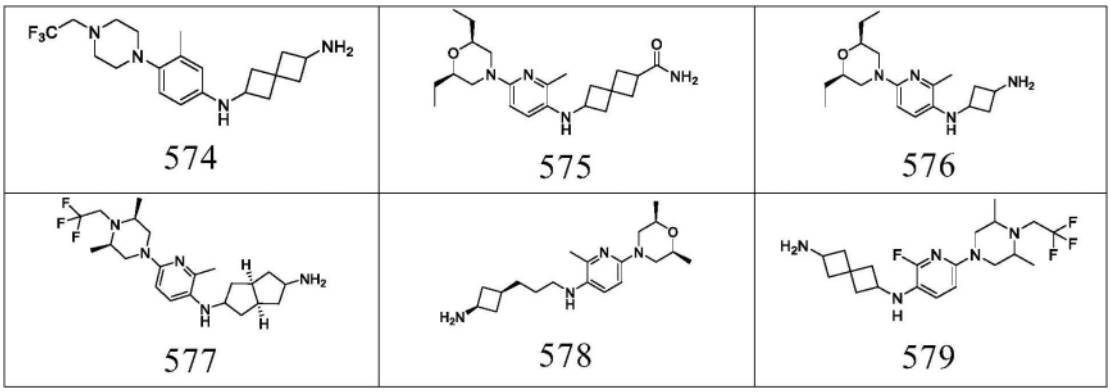
[3595] 46.治疗疾病或病症的方法,包括向需要其的受试者施用治疗有效量的根据技术方案1至44中任一项的化合物,其互变异构体,该化合物或该互变异构体的溶剂化物或立体异构体,或前述的药学上可接受的盐或根据技术方案45的药物组合物;其中疾病或病症选自神经病,中风,神经退行性疾病,帕金森病,肌萎缩侧索硬化症(AML),多发性硬化症,亨廷顿病,路易体痴呆,弗里德赖希共济失调,毛囊形态发生,糖尿病,败血症,移植排斥,脑室周围白质软化,缺血再灌注损伤,凝血,心肌梗塞,和肾功能障碍。

[3596] 47.治疗涉及铁死亡的疾病或病症的方法,包括向需要其的受试者施用治疗有效量的根据技术方案1至44中任一项的化合物,其互变异构体,该化合物或该互变异构体的溶剂化物或立体异构体,或前述的药学上可接受的盐或根据技术方案45的药物组合物。

[3597] 48.调节铁死亡的方法,包括使需要其的受试者接触根据技术方案1至44中任一项的化合物,其互变异构体,该化合物或该互变异构体的溶剂化物或立体异构体,或前述的药学上可接受的盐或根据技术方案45的药物组合物。

[3598] 49.一种化合物,其选自:

[3599]



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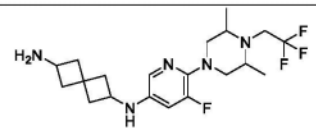
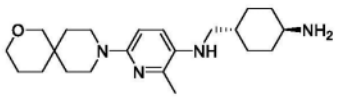
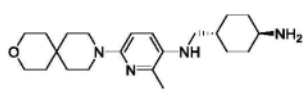
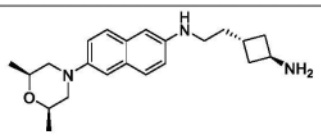
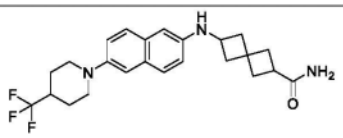
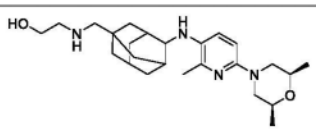
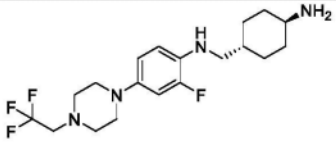
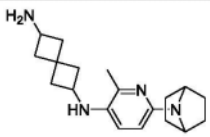
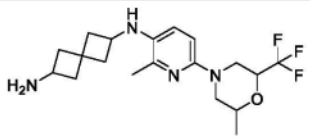
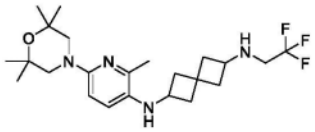
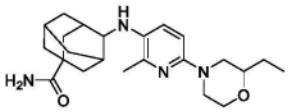
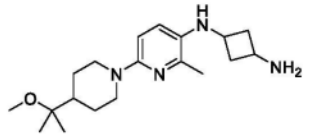
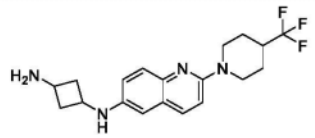
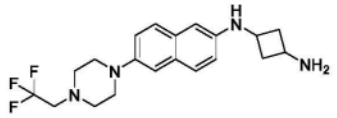
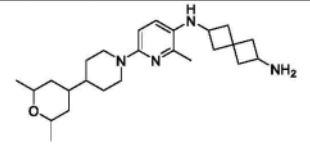
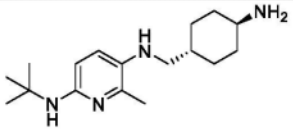
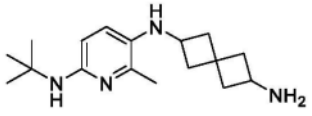
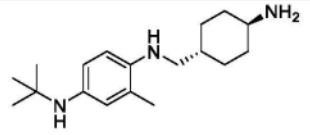
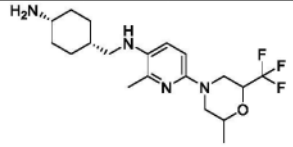
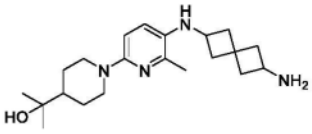
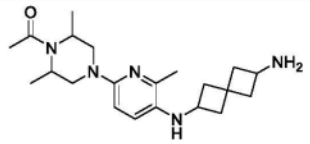
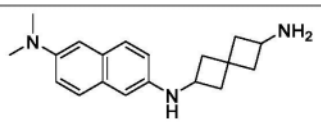
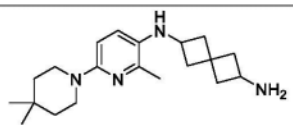
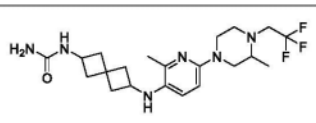
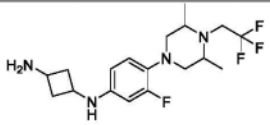
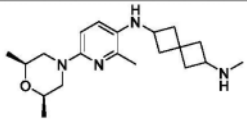
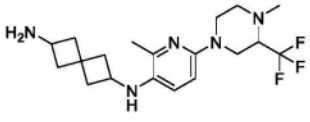
 580	 581	 582
 583	 584	 585
 586	 587	 588
 589	 590	 591
 592	 593	 594
 595	 596	 597
 598	 599	 600
 601	 602	 603
 604	 605	 606

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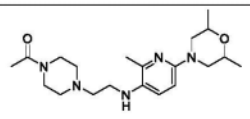
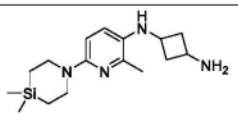
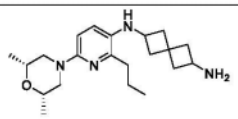
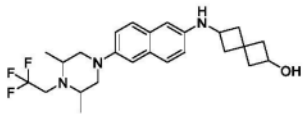
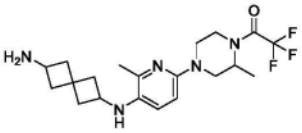
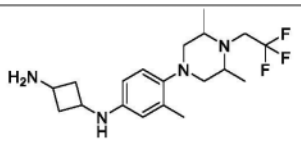
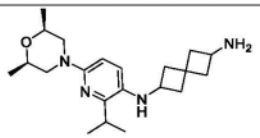
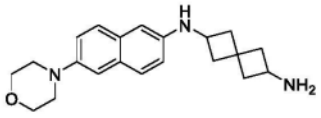
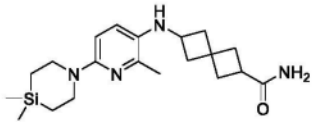
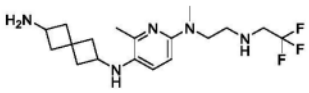
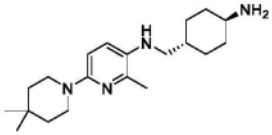
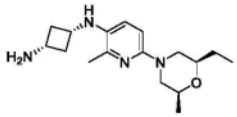
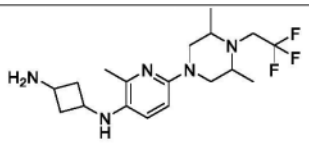
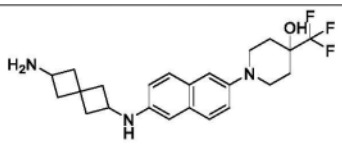
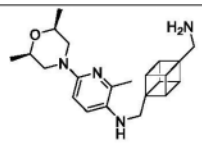
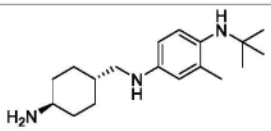
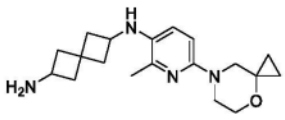
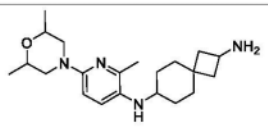
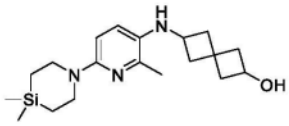
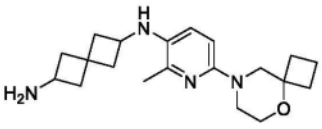
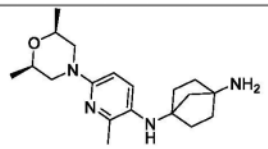
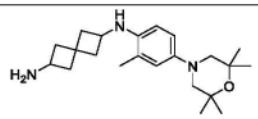
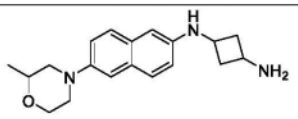
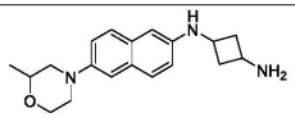
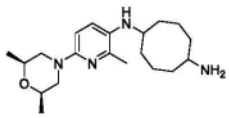
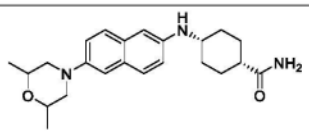
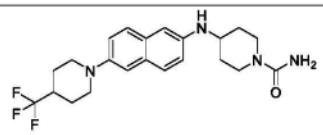
 607	 608	 609
 610	 611	 612
 613	 614	 615
 616	 617	 618
 619	 620	 621
 622	 623	 624
 625	 626	 627
 628	 629	 630
 631	 632	 633

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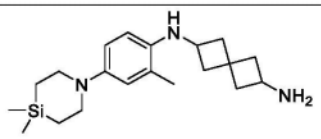
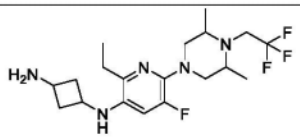
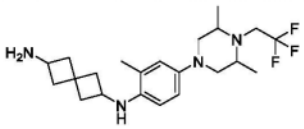
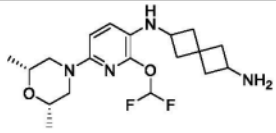
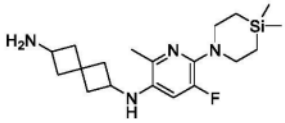
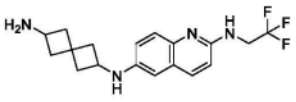
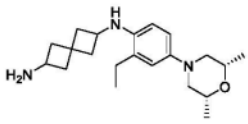
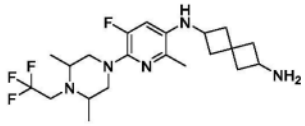
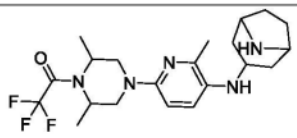
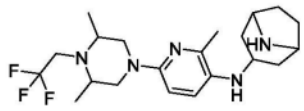
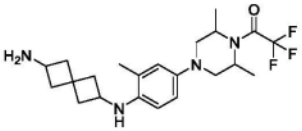
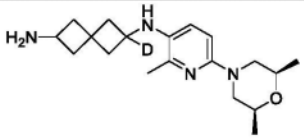
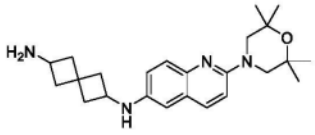
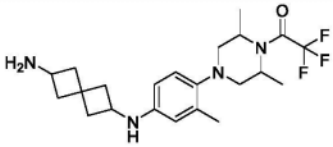
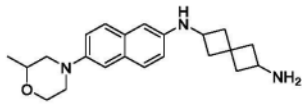
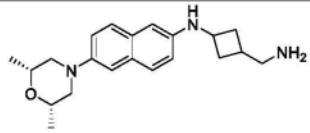
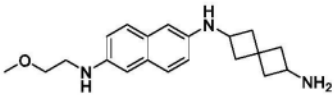
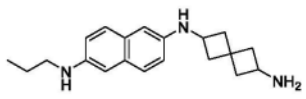
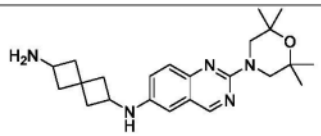
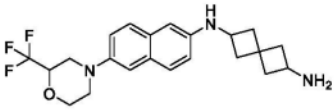
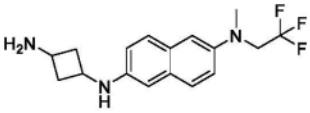
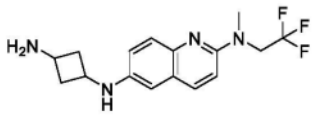
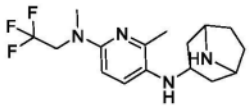
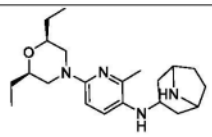
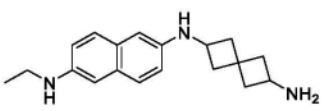
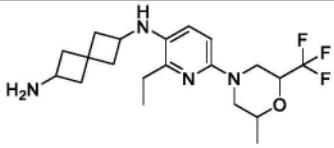
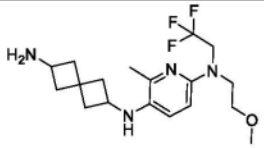
 634	 635	 636
 637	 638	 639
 640	 641	 642
 643	 644	 645
 646	 647	 648
 649	 650	 651
 652	 653	 654
 655	 656	 657
 658	 659	 660

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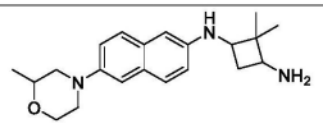 661		

[3604] 其互变异构体,该化合物或该互变异构体的溶剂化物或立体异构体,或前述的药学上可接受的盐。

[3605] 50.一种药物组合物,其包括根据技术方案49的化合物,其互变异构体,该化合物或该互变异构体的溶剂化物或立体异构体,或前述的药学上可接受的盐和至少一种药学上可接受的载体。

[3606] 51.治疗疾病或病症的方法,包括向需要其的受试者施用治疗有效量的根据技术方案49的化合物,其互变异构体,该化合物或该互变异构体的溶剂化物或立体异构体,或前述的药学上可接受的盐或根据技术方案50的药物组合物;其中疾病或病症选自神经病,中风,神经退行性疾病,帕金森病,肌萎缩侧索硬化症(AML),多发性硬化症,亨廷顿病,路易体痴呆,弗里德赖希共济失调,毛囊形态发生,糖尿病,败血症,移植排斥,脑室周围白质软化,缺血再灌注损伤,凝血,心肌梗塞,和肾功能障碍。

[3607] 52.治疗涉及铁死亡的疾病或病症的方法,包括向需要其的受试者施用治疗有效量的根据技术方案49的化合物,其互变异构体,该化合物或该互变异构体的溶剂化物或立体异构体,或前述的药学上可接受的盐或根据技术方案50的药物组合物。

[3608] 53.调节铁死亡的方法,包括使需要其的受试者接触根据技术方案49的化合物,其互变异构体,该化合物或该互变异构体的溶剂化物或立体异构体,或前述的药学上可接受的盐或根据技术方案50的药物组合物。

[3609] 本说明书中引用的所有出版物,包括但不限于公开文本和公开申请,均如同完整阐述一样通过引用并入本文。如果本文引用的出版物的某些内容与本公开内容矛盾或不一致,则以本公开内容为准。

[3610] 本领域技术人员将容易地从本公开内容和权利要求中认识到,在不脱离如以下权利要求所限定的公开内容的精神和范围的情况下,可以在其中做出各种改变、修改和变型。