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审查员 韩涛

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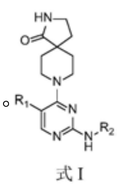
(54) 发明名称

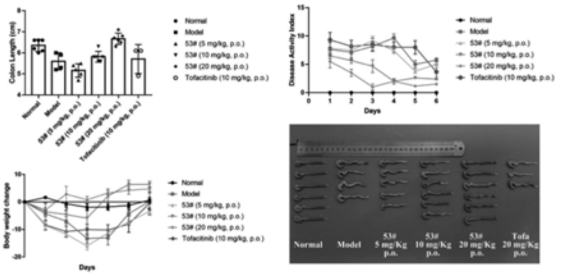
2,8-氮杂-[4,5]十螺环酮衍生物及其制备方法和用途

(57) 摘要

本发明提供了一种2,8-氮杂-[4,5]十螺环酮衍生物及其药学上可接受的盐,所述衍生物具有式I所示结构。本发明的衍生物具有抑制JAKs激酶活性的作用,但并非为一种JAKs激酶的泛抑制剂,而是对JAKs激酶的不同亚型存在选择作用,降低了副作用风险,在溃疡性结肠炎、斑秃等自身免疫疾病或免疫介导的疾病的治疗方面具有潜在应用价值。



式I



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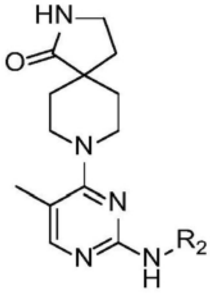
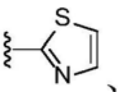
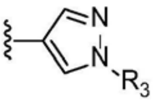
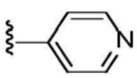
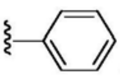
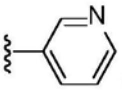
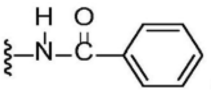
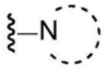
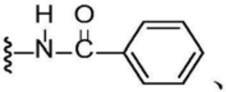
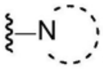
1.一种2,8-氮杂-[4,5]十螺环酮衍生物或其药学上可接受的盐或其氘代化合物，其特征在于，所述衍生物具有式II所示结构：



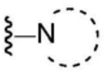
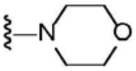
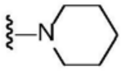
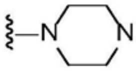
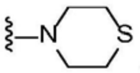
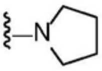
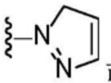
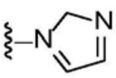
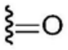
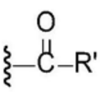
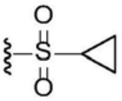
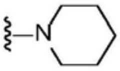
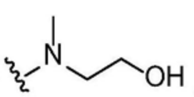
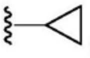
式II　　　　　　　　。

其中，R_2为、、或R_3、R_4、R_5取代或未取代的或；

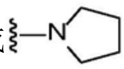
R_3为F、Cl、硝基、氨基、、甲氧基，R_6、R_7、R_8取代或未取代的甲基、、-OR_9或C$R_{10}R_{11}$；

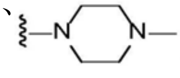
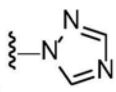
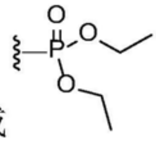
R_4、R_5分别独立选自H、F、Cl、硝基、氨基、、甲氧基，R_6、R_7、R_8取代或未取代的甲基、、-OR_9或C$R_{10}R_{11}$；

R_6、R_7、R_8分别独立选自H、D、F、甲基；

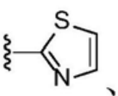
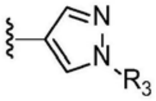
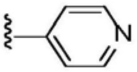
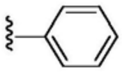
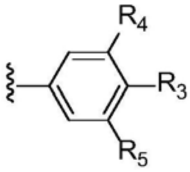
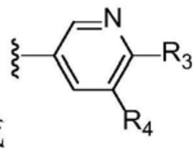
为R_a、R_b取代或未取代的、、、、、或；所述R_a、R_b分别独立选自甲基、乙基、、、、或，或R_a、R_b连接成环；其中，R’为甲基、乙基、丙基、叔丁基、$CH_3CH=CH$-、$(CH_3)_2C=CH$-或；

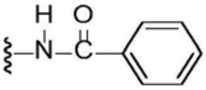
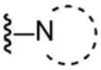
R_9为取代或未取代的乙基、丁基、己基、庚基、苄基、苯基或取代的吡啶基；

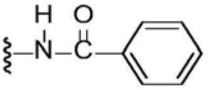
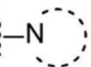
所述取代的取代基为硝基、F、Cl、-CONH-CH_3或；

R_{10}、R_{11}分别独立选自H、丙基、丁基、-COOR_c、苯基、苄基、、或，

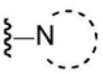
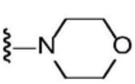
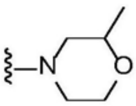
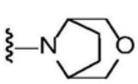
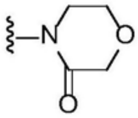
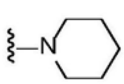
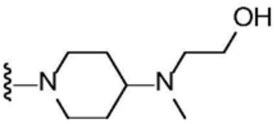
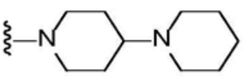
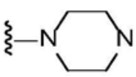
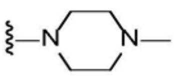
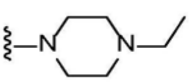
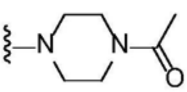
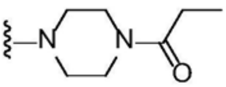
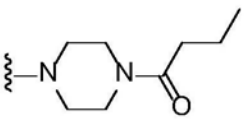
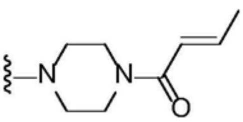
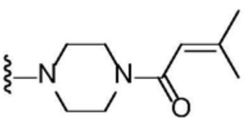
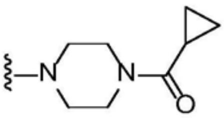
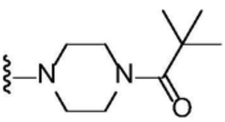
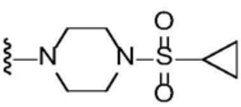
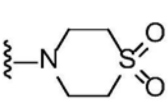
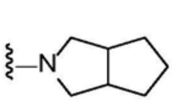
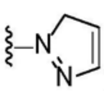
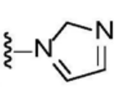
或R_{10}、R_{11}连接成饱和5～6元碳环；其中，R_c甲基、乙基或丁基。

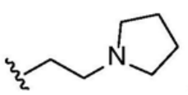
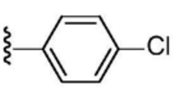
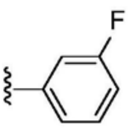
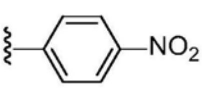
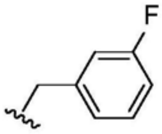
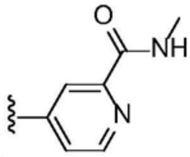
2.如权利要求1所述的衍生物或其药学上可接受的盐或其氘代化合物，其特征在于，所述R_2为、、、、或；

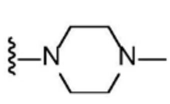
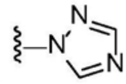
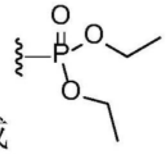
其中，R_3为F、Cl、硝基、氨基、、甲氧基，R_6、R_7、R_8取代或未取代的甲基、、-OR_9或$CR_{10}R_{11}$；

R_4、R_5分别独立选自H、F、Cl、硝基、氨基、、甲氧基，R_6、R_7、R_8取代或未取代的甲基、、-OR_9或$CR_{10}R_{11}$；

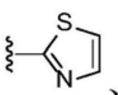
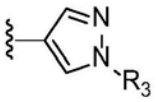
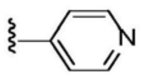
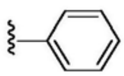
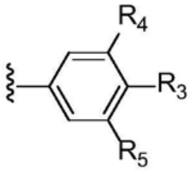
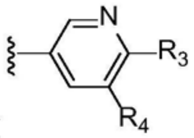
所述R_6、R_7、R_8分别独立选自H、D、F、甲基；

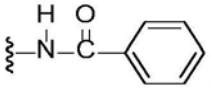
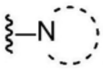
所述为、、、、、、、、、、、、、、、、、、、、、或；

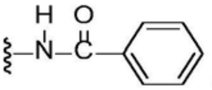
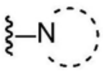
R_9为正丁基、正己基、正庚基、苄基、苯基、、、、、、或；

R_{10}为H,R_{11}为H、正丙基、正丁基、-COOR$_c$、苯基、苄基、、或;

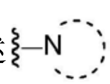
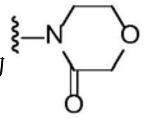
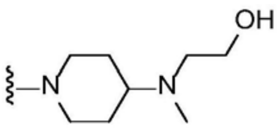
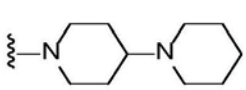
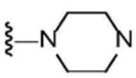
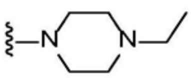
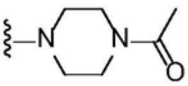
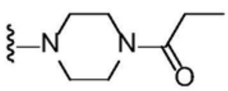
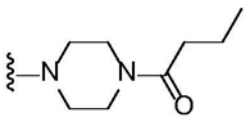
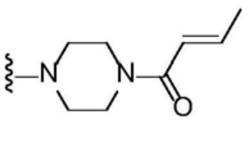
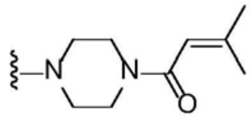
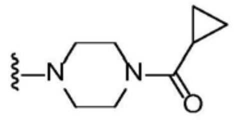
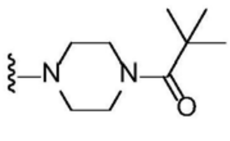
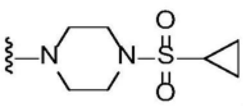
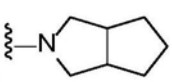
或R_{10}、R_{11}连接成环己烷基;其中,R_c甲基、乙基或正丁基。

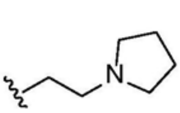
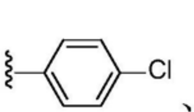
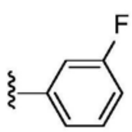
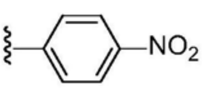
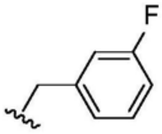
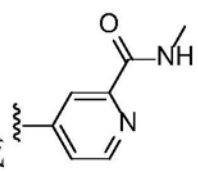
3.如权利要求2所述的衍生物或其药学上可接受的盐或其氘代化合物,其特征在于,所述R_2为、、、、或;

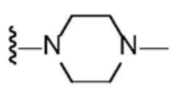
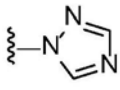
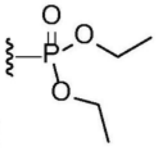
其中,R_3为F、Cl、硝基、氨基、、甲氧基,R_6、R_7、R_8取代或未取代的甲基、、-OR$_9$或CR$_{10}$R$_{11}$;

R_4、R_5分别独立选自H、F、Cl、、甲氧基,R_6、R_7、R_8取代或未取代的甲基、、-OR$_9$或CR$_{10}$R$_{11}$;

所述R_6、R_7、R_8分别独立选自H、D、F、甲基;

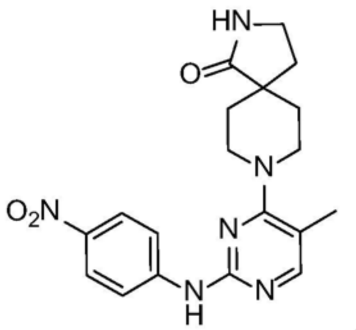
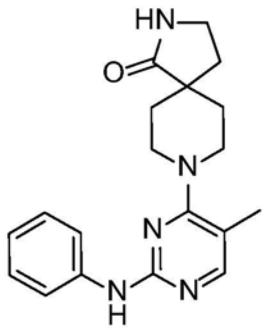
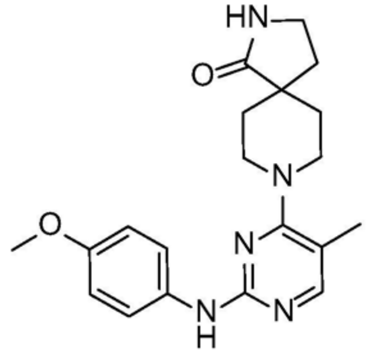
所述为、、、、、、、、、、、、或;

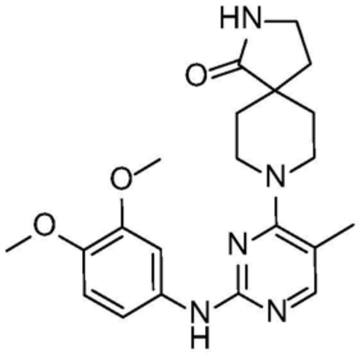
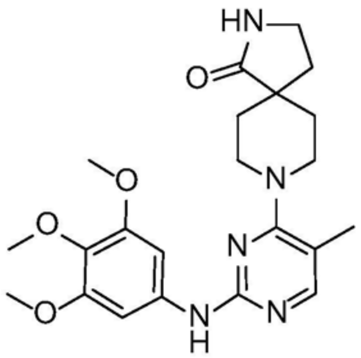
R_9为正丁基、正己基、正庚基、苄基、苯基、、、、、、或;

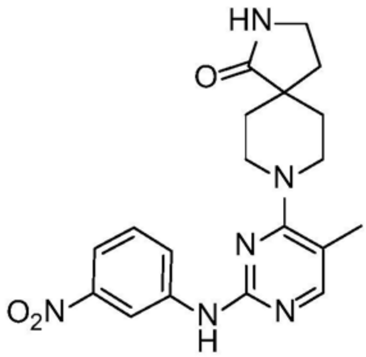
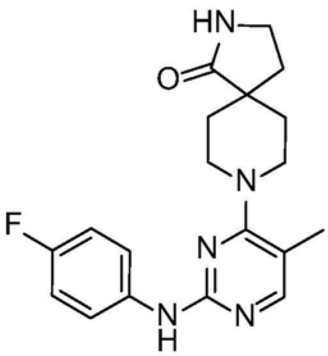
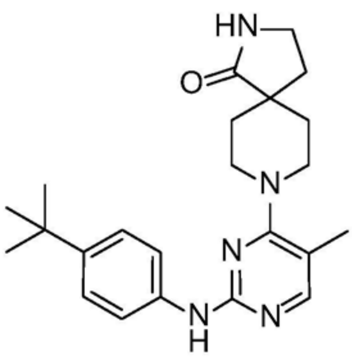
R_{10}为H，R_{11}为H、正丙基、正丁基、苯基、苄基、、或或；

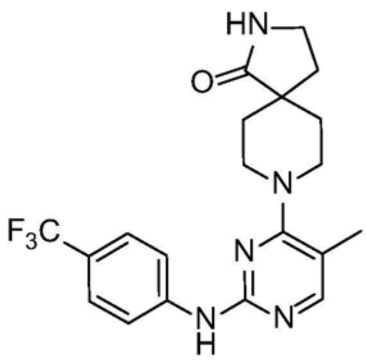
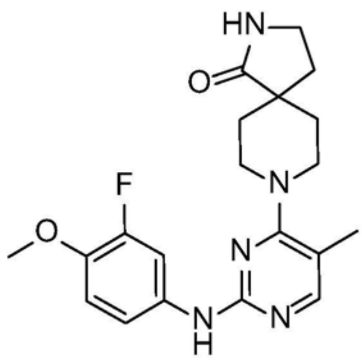
R_{10}、R_{11}连接成环己烷基。

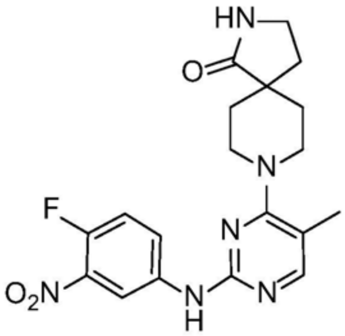
4.如权利要求1～3任一项所述的衍生物或其药学上可接受的盐或其氘代化合物，其特征在于，所述衍生物具有如下结构：

、、、

、、

、、、

、、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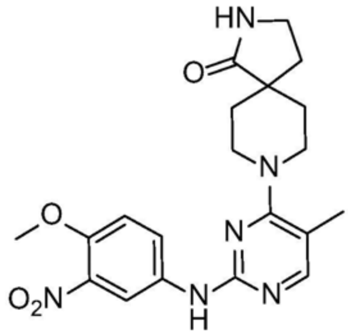
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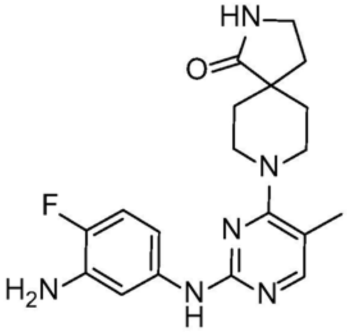
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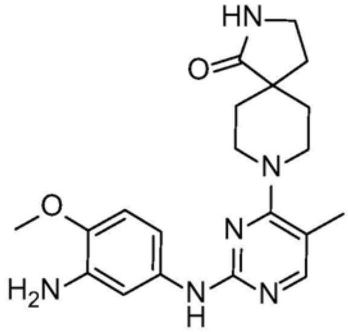
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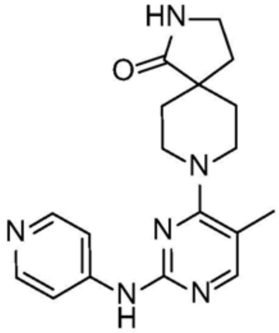
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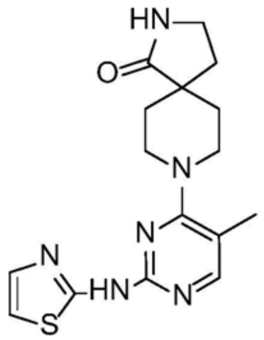
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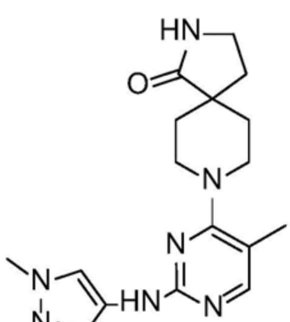
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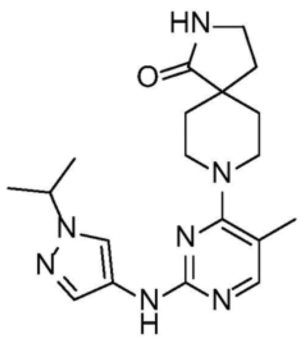
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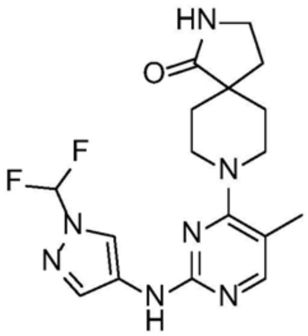
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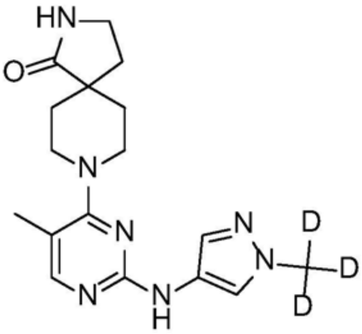
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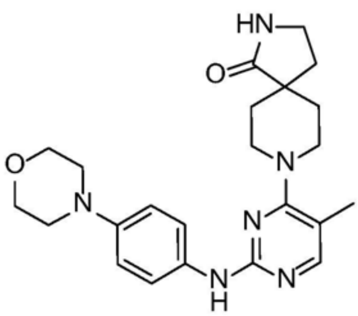
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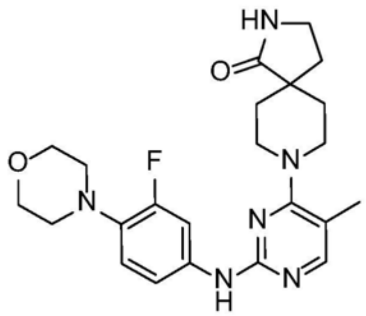
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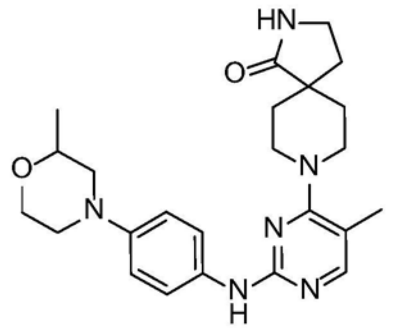

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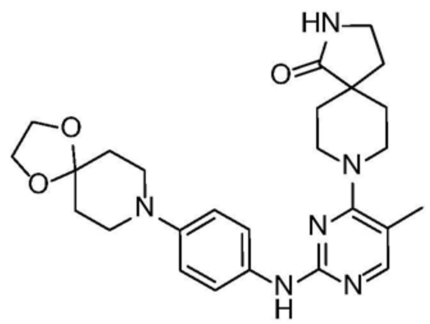

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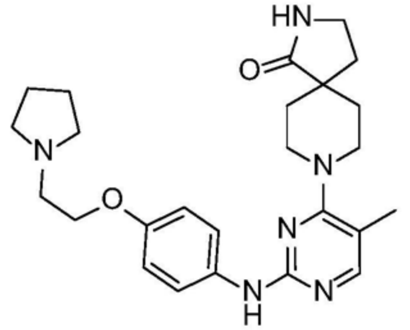

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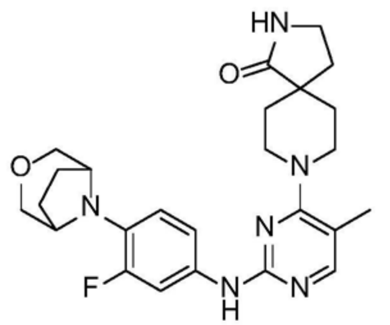

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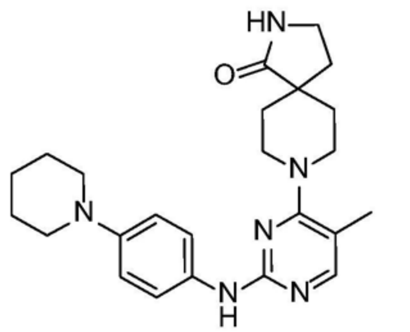

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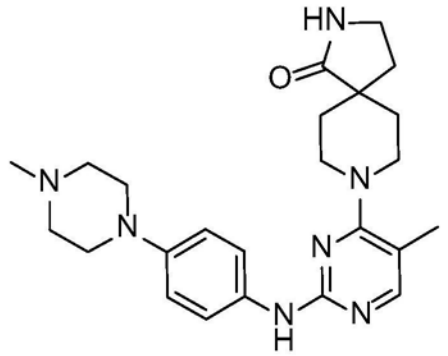

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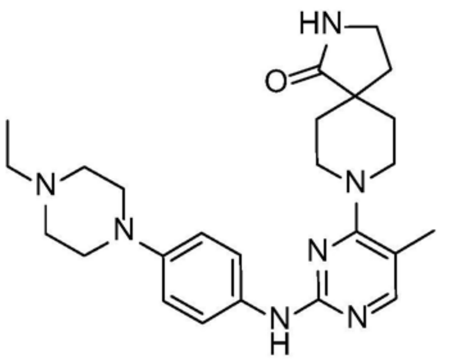

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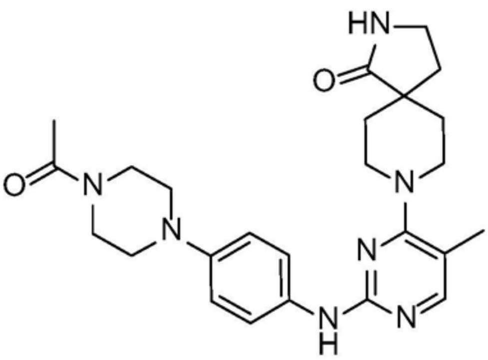

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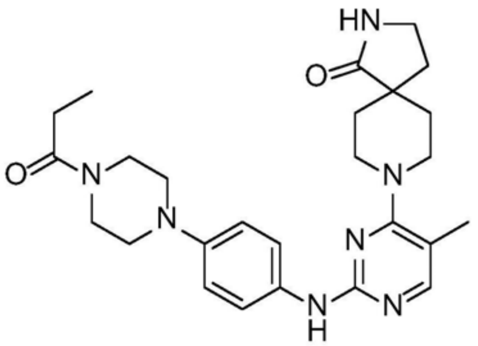

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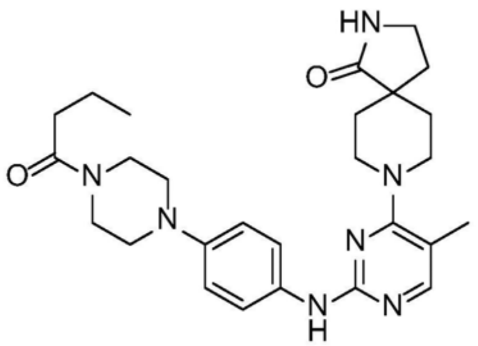

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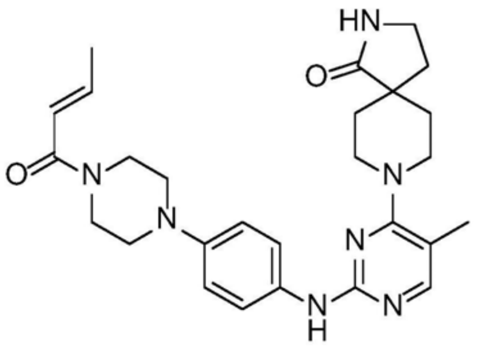

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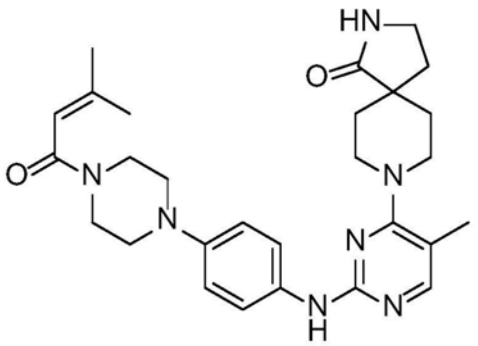

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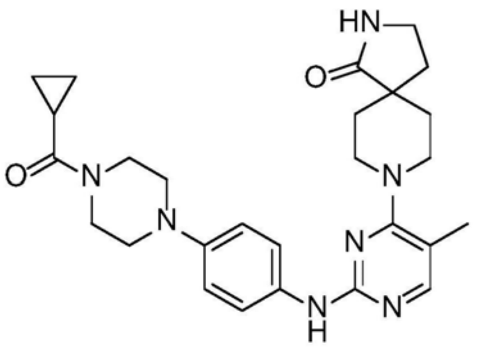

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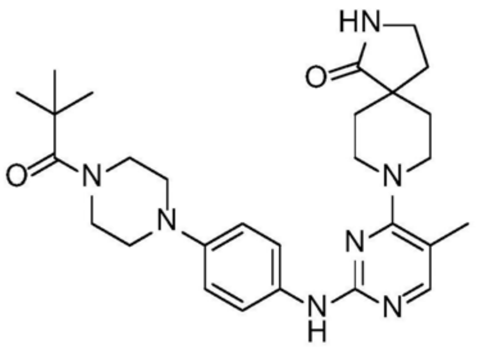

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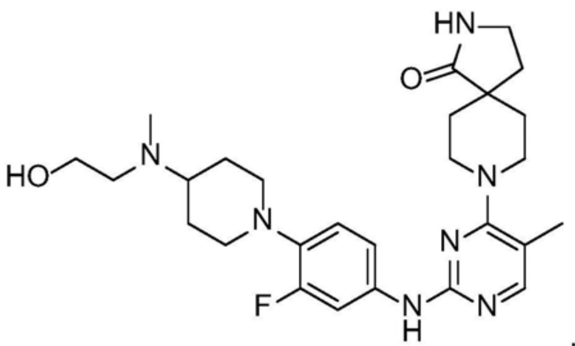

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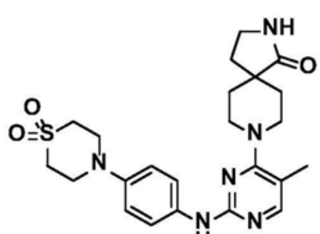

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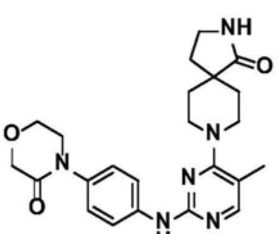

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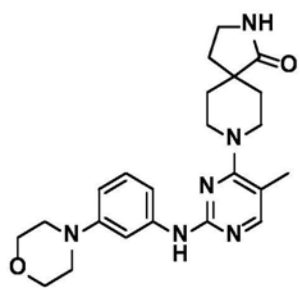

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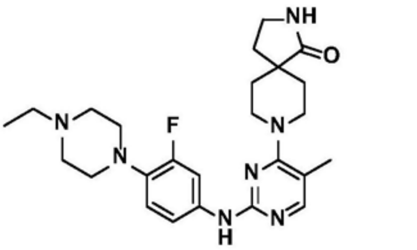
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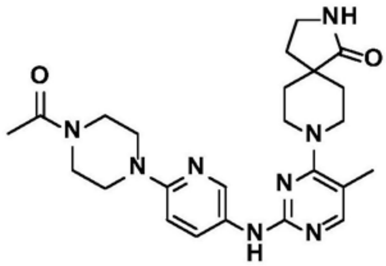
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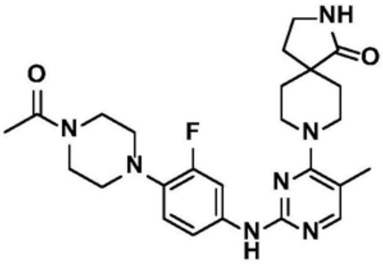
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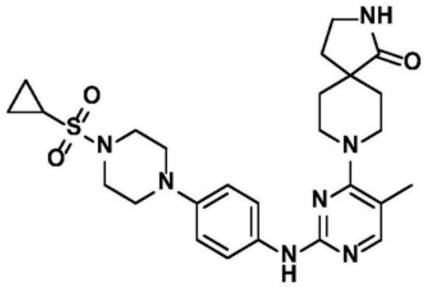
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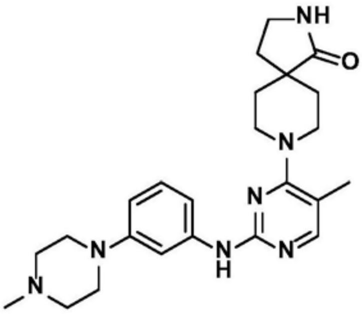
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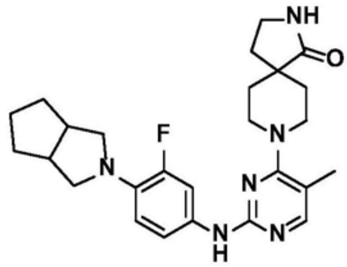
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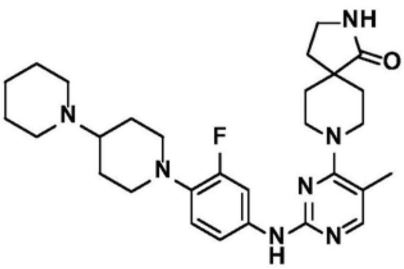
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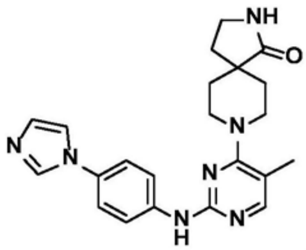
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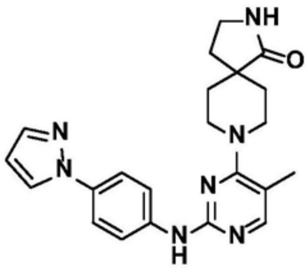
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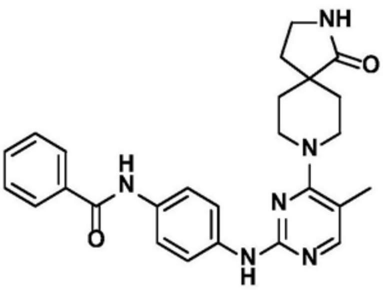
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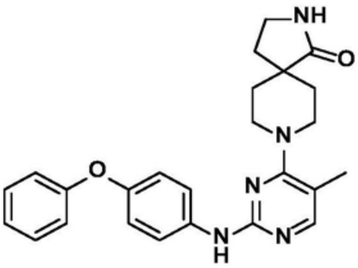
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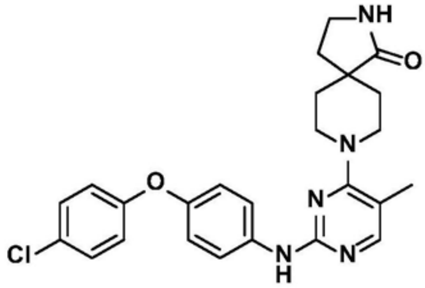
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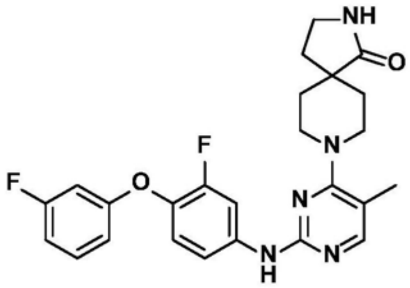
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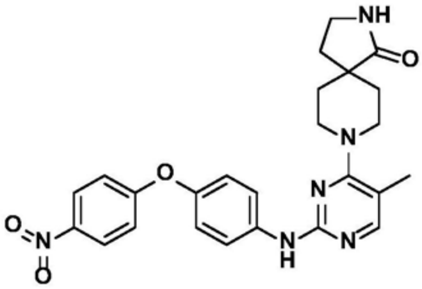
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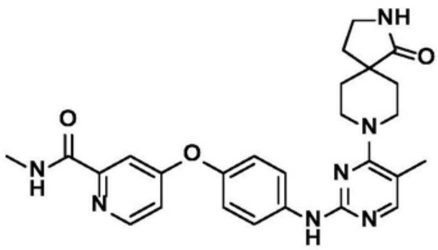
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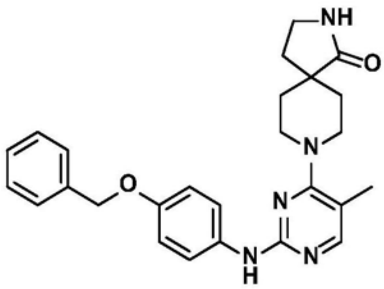
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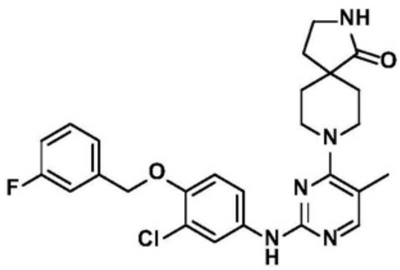
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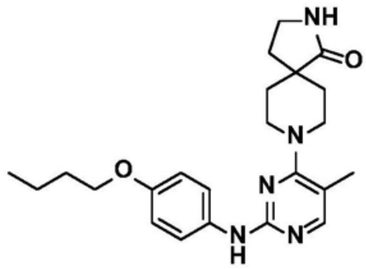
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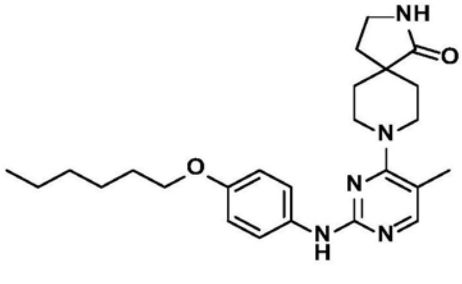
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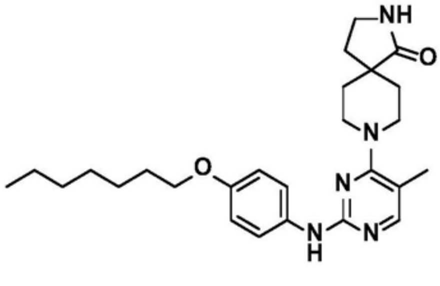
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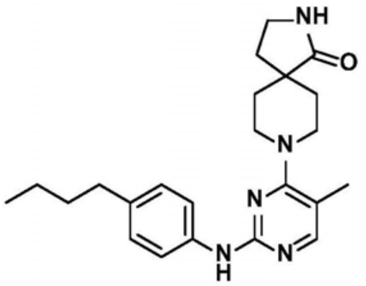
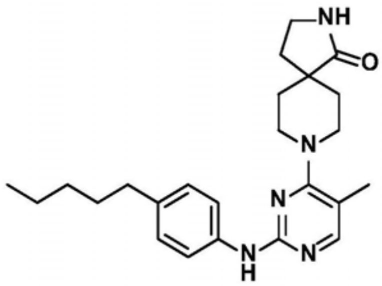
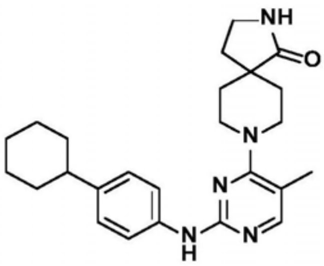
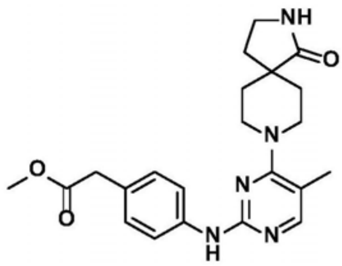
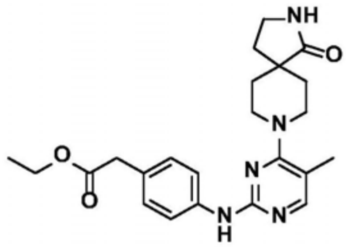
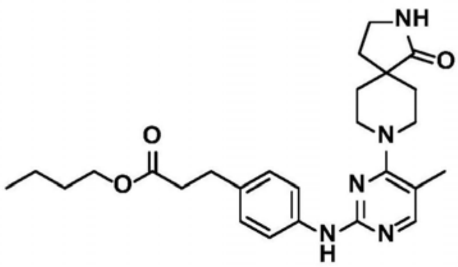
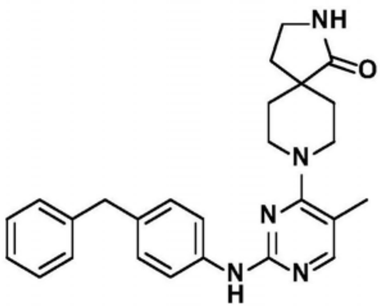
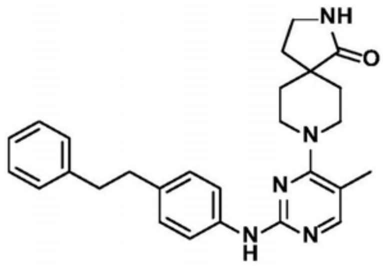
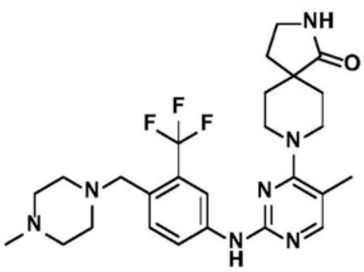
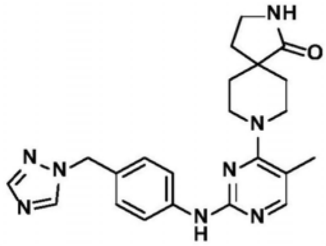
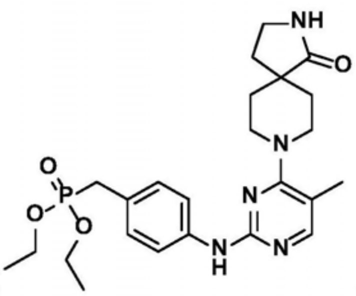
、、

、、、

、

、、

、或。

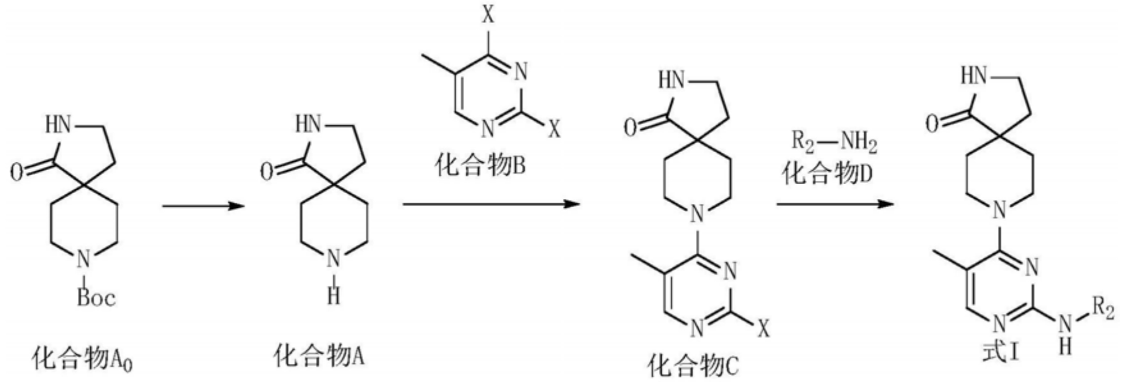
5.权利要求1～4任一项所述衍生物的制备方法，其特征在于，包括如下步骤：

(1)化合物A_0在三氟乙酸作用下反应脱去Boc保护基团得到化合物A；

(2)化合物A与化合物B在有机碱作用下反应得到化合物C；

(3)化合物C与化合物D在酸的作用下或在钯催化剂作用下反应得到式I化合物；

反应式如下：



其中,X为卤素。

6.如权利要求5所述的方法,其特征在于,步骤(1)所述反应为在有机溶剂中室温反应30～60min;

步骤(2)所述有机碱为三乙胺,所述反应为在醇溶剂中室温反应过夜;

步骤(3)所述反应为:在醇溶剂中,酸作用下110～115℃反应5～10小时;

或,在有机溶剂中,无机碱、配体和钯催化剂作用和惰性气体保护条件下,105～110℃反应8～10小时。

7.如权利要求6所述的方法,其特征在于,骤(1)所述反应为在二氯甲烷中20～30℃反应40min;

步骤(2)所述反应为在异丙醇中20～30℃反应10～20小时;

步骤(3)所述反应为:在醇溶剂中,浓盐酸作用下110～115℃反应5～10小时;

或,在二氧六环或N,N-二甲基甲酰胺中,碳酸铯、配体和三(二亚苄基丙酮)二钯作用和惰性气体保护条件下,105～110℃反应8～10小时,所述配体为1,1'-双(二苯基膦)二茂铁或者4,5-双二苯基膦-9,9-二甲基氧杂蒽。

8.权利要求1～4任一项所述衍生物或其药学上可接受的盐或其氘代化合物在JAKs激酶抑制剂中的用途,所述JAKs激酶抑制剂为JAK1激酶、JAK2激酶、JAK3激酶和/或TYK2激酶抑制剂。

9.权利要求1～4任一项所述衍生物或其药学上可接受的盐或其氘代化合物在制备防治自身免疫疾病、免疫介导的疾病和/或癌症的药物中的用途。

10.如权利要求9所述的用途,其特征在于,所述药物为防治类风湿性关节炎、成人强直性脊柱炎、真红细胞增多症、骨髓纤维化、系统性红斑狼疮、霍奇金病、炎症性肠病、银屑病、特应性皮炎、斑秃、镰状细胞性贫血、中条-西村综合征、慢性髓性白血病、急性髓性白血病、多发性骨髓瘤、乳腺癌、结肠癌、肺癌、前列腺癌、卵巢癌和/或肝癌的药物。

11.如权利要求10所述的用途,其特征在于,所述防治炎症性肠病的药物为防治克罗恩病、溃疡性结肠炎和/或未定型结肠炎的药物。

2,8-氮杂-[4,5]十螺环酮衍生物及其制备方法和用途

技术领域

[0001] 本发明属于药物化学领域,具体涉及2,8-氮杂-[4,5]十螺环酮衍生物及其 制备方法和用途。

背景技术

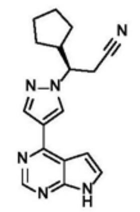
[0002] 蛋白酪氨酸激酶(Protein Tyrosine Kinase,PTK)是一种能够催化γ-磷酸 从ATP转移到酪氨酸残基的蛋白质,可分为非受体酪氨酸激酶(Non-receptor tyrosine kinase,NRTK)和受体酪氨酸激酶(Receptor tyrosine kinase,RPTK),其中JAKs激酶(Jauns Kinases,JAKs)是从免疫学角度研究最广泛的一种 NRTK,能够被各种细胞因子如干扰素(Interferons,IFNs)、白介素 (Interleukins,ILs)激活,激活后产生的信号通过相应机制传入细胞核诱导靶基 因转录。

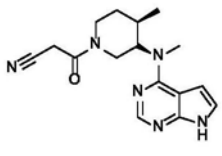
[0003] JAKs激酶家族包括JAK1、JAK2、JAK3以及TYK2四个亚型,在结构 上高度相关,功能相似,并在不同物种之间保守。JAKs激酶通过JAK-STAT 信号通路将特定的细胞因子传入的信号向胞内传递,其特定的信号诱导特定 的靶基因转录,产生相应的生物学功能,而胞外细胞因子种类多,JAKs激酶 以及STAT因子具有多亚型的特点,因此JAK-STAT信号通路具有多种组合,能够传递多种信号而产生多种生物效应。JAKs激酶能够被多种细胞因子调 控,其涉及的JAK-STAT信号通路介导人体重要的生物功能如免疫功能。症 因为JAKs激酶参与的信号通路与自身免疫疾病的发生密切相关,因此JAKs 激酶作为靶点被研究用于治疗各种自免疫疾病,从1989年Wilks发现JAK 激酶,1996年人们发现了JAKs的潜在价值,随后逐渐出现一系列靶向JAK 的抑制剂,并在后续的临床研究中发现了这些药物更多的作用。

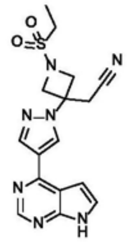
[0004] 2011年Ruxolitinib成为首个获美国食品药品监督管理局(Food and Drug Administration,FDA)批准的JAK1/2抑制剂,用于治疗中高危骨髓纤维化(Myelofibrosis,MF)。2019年Ruxolitinib在治疗霍奇金病(Hodgkin's disease, HD)中发挥良好的作用,最近Ruxolitinib在德国上市用于预防血管闭塞性危 象(Vaso-Occlusive Crisis,VOCs),其氘代物Deuruxolitinib被广泛用于开展斑 秃(Alopecia Areata,AA)的临床研究。Tofacitinib是一种JAK1/3抑制剂,于 2012年被FDA批准用于治疗类风湿性关节炎(Rheumatoid Arthritis,RA)。最 近开展治疗溃疡性结肠(Ulcerative Colitis,UC)的Phase III试验有效地改善患 者的健康。Tofacitinib进一步研究也证实了它对斑秃具有治疗效果。2021年, Tofacitinib被FDA批准用于成人强直性脊柱炎(Ankylosing Spondylitis,AS) 治疗。2018年FDA批准EliLilly公司开发的一种治疗RA的JAK1/2抑制剂Baricitinib,Baricitinib在治疗中重度特异性皮炎(Atopic Dermatitis,AD)的 PhaseII试验中显示出好的结果,并于2021年在日本作为孤儿药用于治疗中 条西村综合征(Nakajo-Nishimura syndrome,NNS)。2019年FDA分别批准了 JAK1/2的两种抑制剂Fedratinib和Upadacitinib,分别用于治疗患有中度II 型或高危原发性或继发性真性红细胞增多症(Polycythemia Vera,PV)后骨髓 纤维化的成人患者和中至重度的RA。Upadacitinib近期的PhaseII/III试验也 展示了在治疗活动性AS中较好的结果。

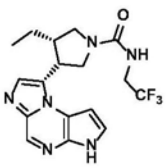
Peficitinib于2019年在日本上市用 于治疗对传统疗法反应不足的RA。Delgocitinib与Filgotinib作为目前最新上 市的两个药物,Delgocitinib由日本开发,最新的外用0.5% Delgocitinib软膏 在日本首次获得批准,用于治疗成人AD。Filgotinib于2021年经欧洲批准用 于治疗成人中至重度活动性UC,而患者对传统或生物制剂治疗方法响应不 佳。除了已上市的JAKs抑制剂以外,另外某些在研药物也具有治疗自身免 疫疾病的巨大潜力。如Brepocitinib正在开展银屑病(Psoriasis,PsO)、克罗恩 病(Crohn disease,CD)的PhaseII期临床研究,氘代Ruxolitinib(Deuruxolitinib) 其代谢稳定性优于Ruxolitinib,并且该药物正在评价用于AA的临床效果。

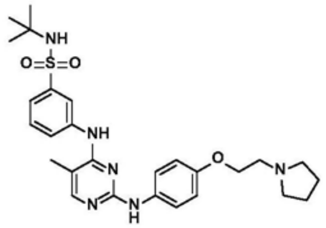
[0005] 除自身免疫疾病外,JAKs抑制剂在肿瘤治疗中也有应用价值,例如 JAK2-STAT3作为JAK-STAT通路中的重要信号轴,其持续性激活会通过影 响细胞生长、凋亡、周期等促进肿瘤发生发展。因而,JAK2抑制剂将有助 于削弱肿瘤细胞的恶性生物学行为,在血液系统肿瘤和乳腺癌、肺癌等实体 瘤中均具有一定的治疗价值。

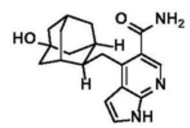

Ruxolitinib
Launched 2011


Tofacitinib
Launched 2012

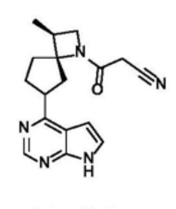

Baricitinib
Launched 2017

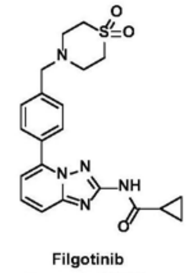

Upadacitinib(ABT-494)
Launched 2019

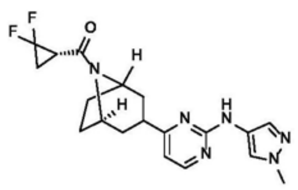

Fedratinib
Launched - 2019

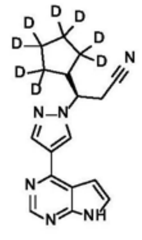

Peficitinib
Launched 2019

[0006]


Delgocitinib
Launched - 2020


Filgotinib
Launched 2020


Brepocitinib(JAK1/TYK2)
Phase II


Deuruxolitinib(CT-543,
Concert Pharmaceuticaals)
PhaseIII

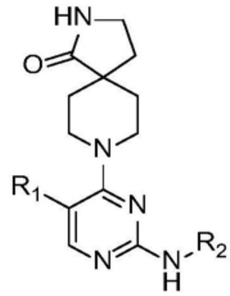
[0007] 不过，现有的JAKs激酶抑制剂仍存在抑制效果不佳的问题，此外，由 于JAK信号传导受多种细胞因子调控，因此其产生的功能是多样的，广泛涉 及人体各种生物功能，如免疫细胞的分化，抗感染，抗病毒等以及其他细胞 的正常功能的进行。因此对JAKs激酶的抑制可能会干扰机体的正常功能从 而产生副作用。虽然JAK抑制剂优先亲和特定的JAK，但由于脱靶效应，在 高剂量给药情况下可能作用于多个JAK亚型，进而可能导致血液、肝肾代谢或免疫方面出现不良反应。

[0008] 因此，研发新型、低毒、选择性的JAKs抑制剂应用于自身免疫疾病的 治疗仍是临床所亟需的。

发明内容

[0009] 本发明的目的在于提供一种新型、低毒、选择性的JAKs抑制剂。

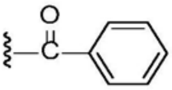
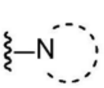
[0010] 本发明提供了一种2,8-氮杂-[4,5]十螺环酮衍生物或其药学上可接受的盐 或其氘代化合物，它具有式I所示结构：

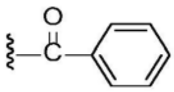
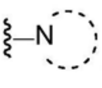
[0011] 

式I

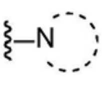
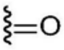
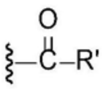
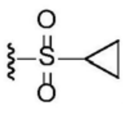
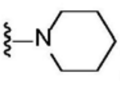
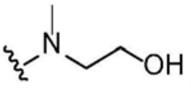
[0012] 其中，R_1为H或C1～C3烷基；

[0013] R_2为R_3、R_4、R_5取代或未取代的5～6元芳杂环，杂原子为N或S；

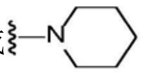
[0014] 所述R_3为卤素、硝基、氨基、取代的氨基、C1～C3烷氧基，R_6、R_7、R_8取代或未取代的C1～C3烷基、、-OR_9或$CR_{10}R_{11}$；

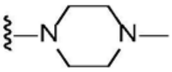
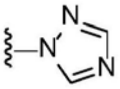
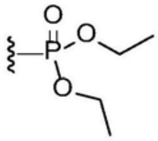
[0015] 所述R_4、R_5分别独立选自H、卤素、硝基、氨基、取代的氨 基、C1～C3烷氧基，R_6、R_7、R_8取代或未取代的C1～C3烷基、、-OR_9或$CR_{10}R_{11}$；

[0016] 所述R_6、R_7、R_8分别独立选自H、D、卤素或C1～C3烷基；

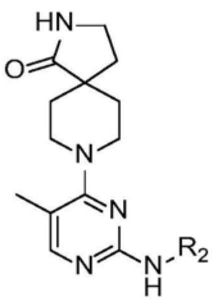
[0017] 所述为R_a、R_b取代或未取代的5～6元饱和或不饱和杂环，杂原子 为N、O或S；所述R_a、R_b分别独立选自C1～C3烷基、、、、或，或R_a、R_b连接成环；其中，R'为C1～C4烷基、C3～C4 烯基或；

[0018]　R_9为取代或未取代的C2～C7的烷基苄基、苯基或取代的吡啶基；

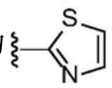
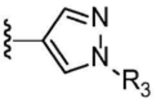
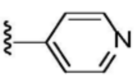
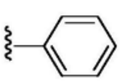
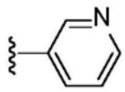
[0019]　所述取代的取代基为硝基、卤素、-CONH-CH_3或；

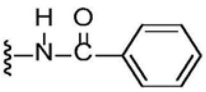
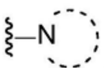
[0020]　R_{10}、R_{11}分别独立选自H、C3～C5烷基、-COOR$_c$、苯基、苄基、、或，或R_{10}、R_{11}连接成环；其中，R_c为C1～C4烷基。

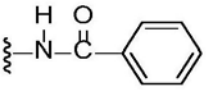
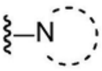
[0021]　进一步地，上述R_1为甲基，所述衍生物具有式II所示结构：

[0022]　

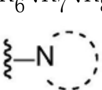
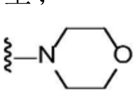
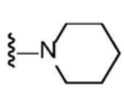
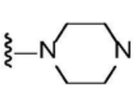
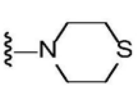
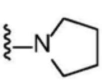
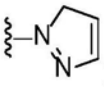
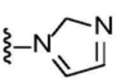
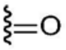
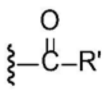
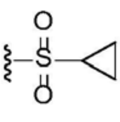
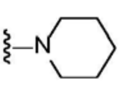
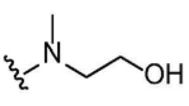
式II　。

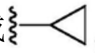
[0023]　更进一步地，上述R_2为、、或R_3、R_4、R_5取代或未取代的、；

[0024]　所述R_3为F、Cl、硝基、氨基、、甲氧基，R_6、R_7、R_8取代或未取代的甲基、、-OR$_9$或CR$_{10}$R$_{11}$；

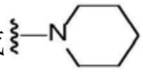
[0025]　R_4、R_5分别独立选自H、F、Cl、硝基、氨基、、甲氧基，R_6、R_7、R_8取代或未取代的甲基、、-OR$_9$或CR$_{10}$R$_{11}$；

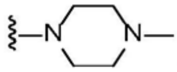
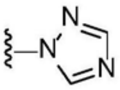
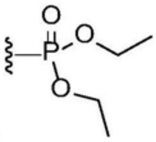
[0026]　所述R_6、R_7、R_8分别独立选自H、D、F、甲基；

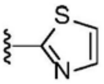
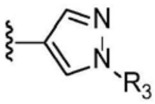
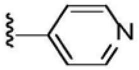
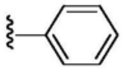
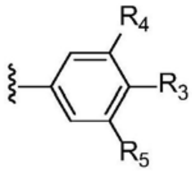
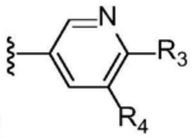
[0027]　所述为R_a、R_b取代或未取代的、、、、、或；所述R_a、R_b分别独立选自甲基、乙基、、、、或，或R_a、R_b连接成环；其中，R’为甲

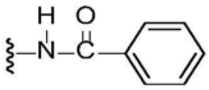
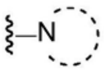
基、乙基、丙基、叔丁基、$CH_3CH=CH$-、$(CH_3)_2C=CH$-或;

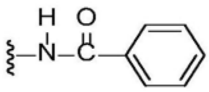
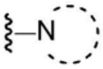
[0028] R_9为取代或未取代的乙基、丁基、己基、庚基、苄基、苯基或取代的吡 啶基;

[0029] 所述取代的取代基为硝基、F、Cl、-CONH-CH_3或;

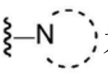
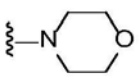
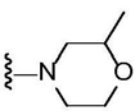
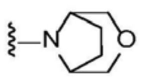
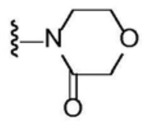
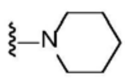
[0030] R_{10}、R_{11}分别独立选自H、丙基、丁基、-$COOR_c$、苯基、苄基、、或,或R_{10}、R_{11}连接成饱和5~6元碳环;其中,R_c甲基、乙基或丁基。

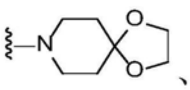
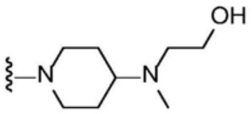
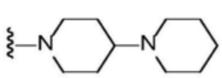
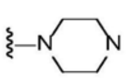
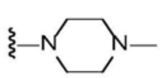
[0031] 更进一步地,上述R_2为、、、、或;

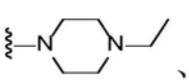
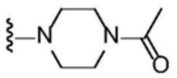
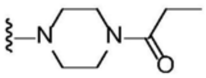
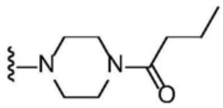
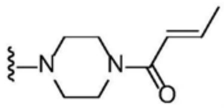
[0032] 其中,R_3为F、Cl、硝基、氨基、、甲氧基,R_6、R_7、R_8取代或未取代的甲基、、-OR_9或$CR_{10}R_{11}$;

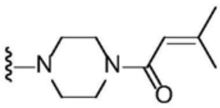
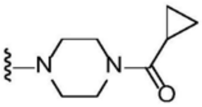
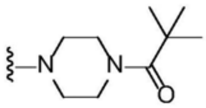
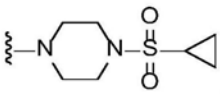
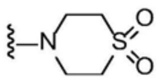
[0033] R_4、R_5分别独立选自H、F、Cl、硝基、氨基、、甲氧基, R_6、R_7、R_8取代或未取代的甲基、、-OR_9或$CR_{10}R_{11}$;

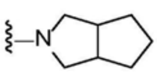
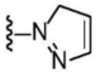
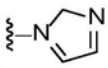
[0034] 所述R_6、R_7、R_8分别独立选自H、D、F、甲基;

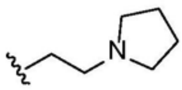
[0035] 所述为、、、、、

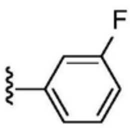
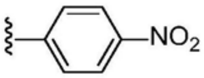
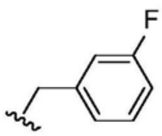
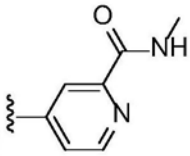
、、、、、

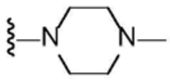
、、、、、

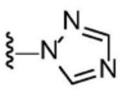
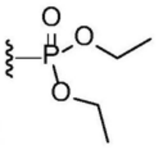
、、、、、

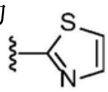
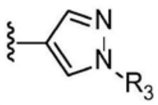
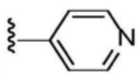
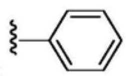
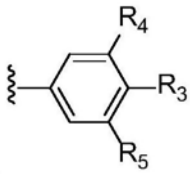
、或；

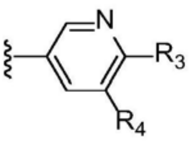
[0036] R_9为正丁基、正己基、正庚基、苄基、苯基、、、

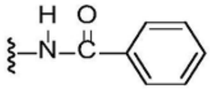
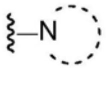
、、、或；

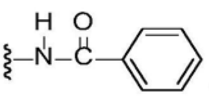
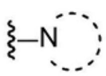
[0037] R_{10}为H，R_{11}为H、正丙基、正丁基、-COOR$_c$、苯基、苄基、、

或；或R_{10}、R_{11}连接成环己烷基；其中，R_c甲基、乙基或 正丁基。

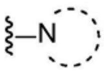
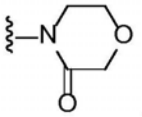
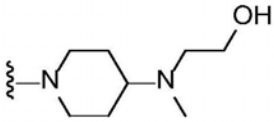
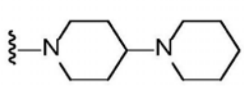
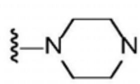
[0038] 更进一步地，上述R_2为、、、、

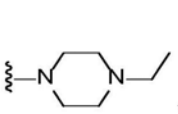
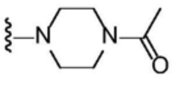
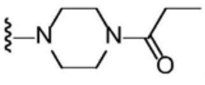
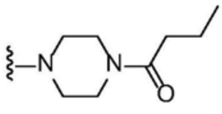
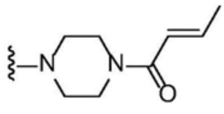
或；

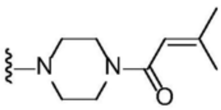
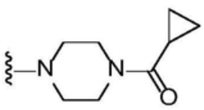
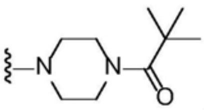
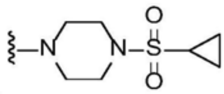
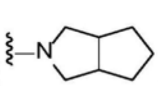
[0039] 其中，R_3为F、Cl、硝基、氨基、、甲氧基，R_6、R_7、R_8取代或未取代的甲基、、-OR$_9$或CR$_{10}$R$_{11}$；

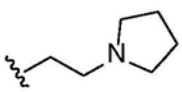
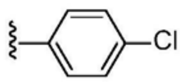
[0040] R_4、R_5分别独立选自H、F、Cl、、甲氧基，R_6、R_7、R_8取代或未取代的甲基、、-OR$_9$或CR$_{10}$R$_{11}$；

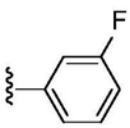
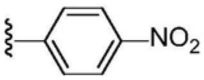
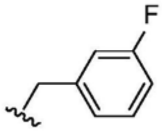
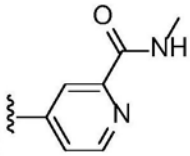
[0041]　所述R_6、R_7、R_8分别独立选自H、D、F、甲基；

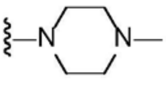
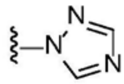
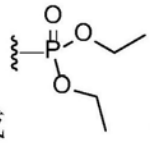
[0042]　所述为、、、、

、、、、、

、、、或；

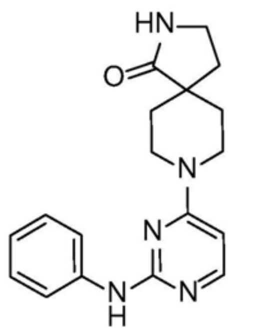
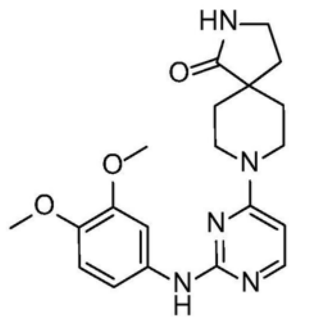
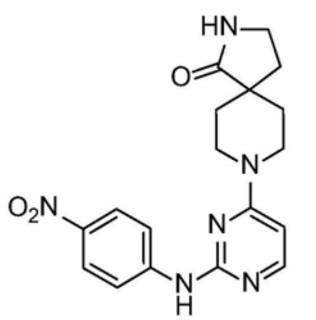
[0043]　R_9为正丁基、正己基、正庚基、苄基、苯基、、、

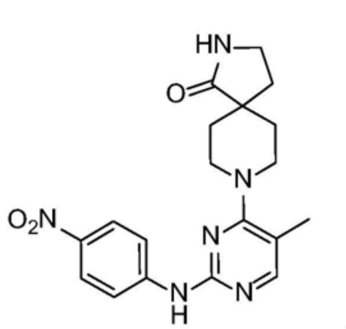
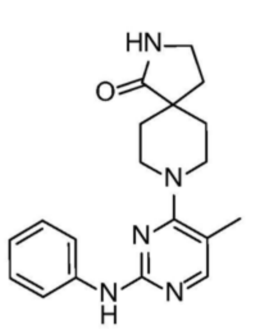
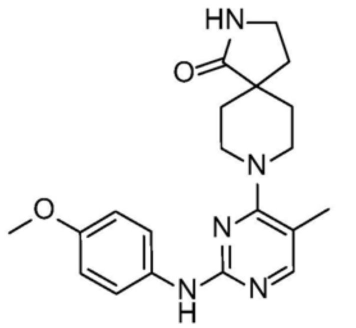
、、、或；

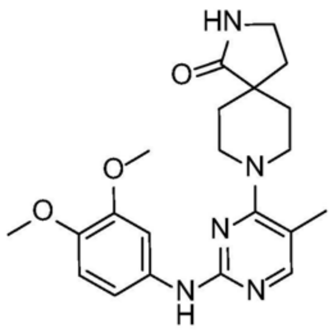
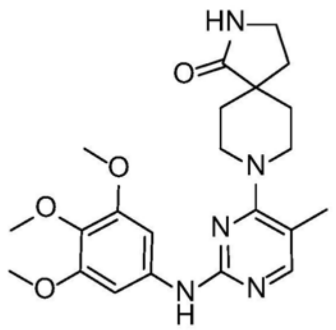
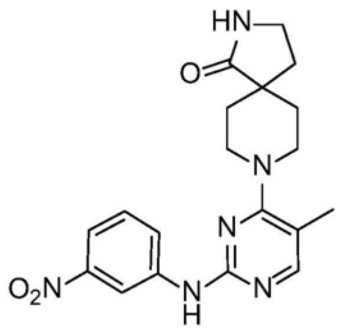
[0044]　R_{10}为H，R_{11}为H、正丙基、正丁基、苯基、苄基、、或；

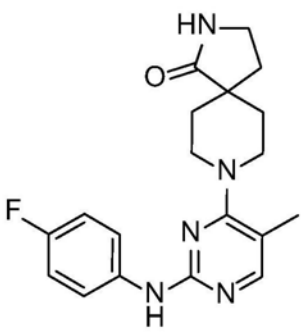
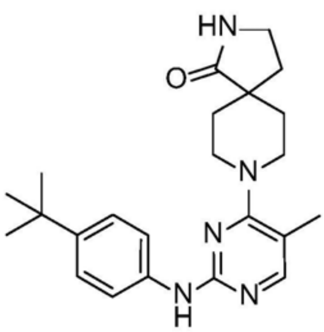
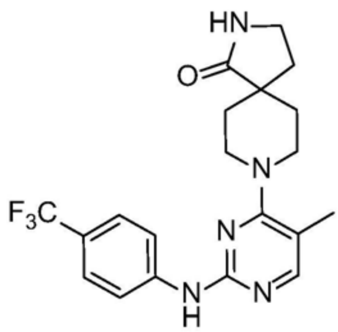
或R_{10}、R_{11}连接成环己烷基。

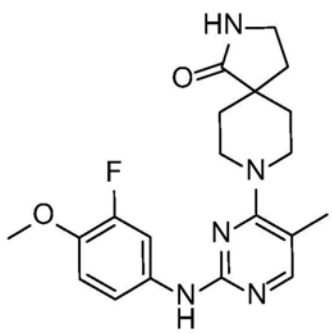
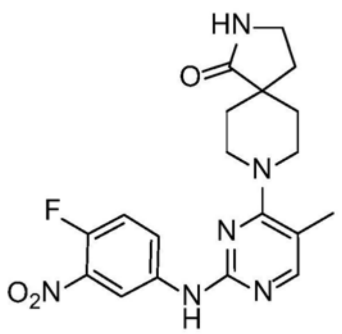
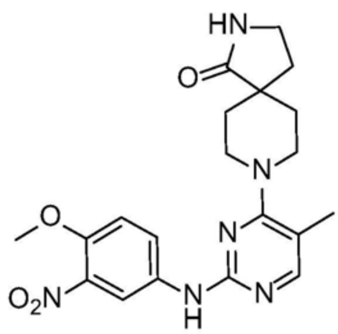
[0045]　更进一步地，上述衍生物具有如下结构：

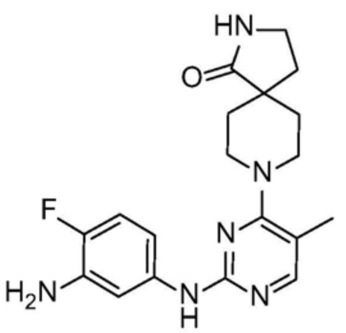
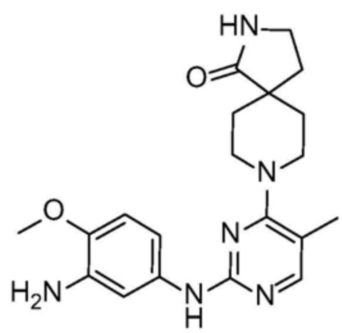
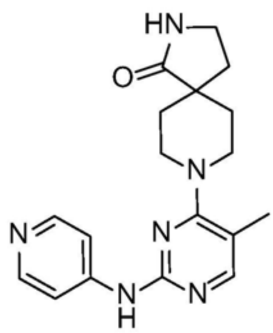
[0046]　、、、

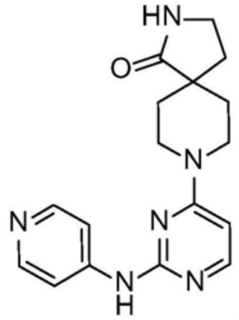
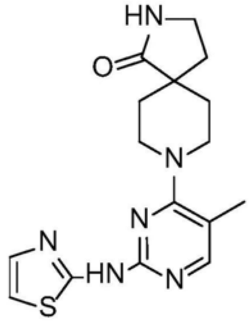
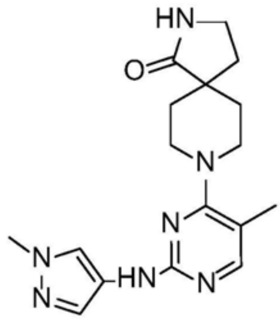
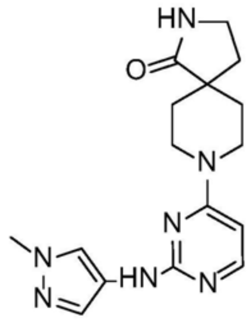
、、、

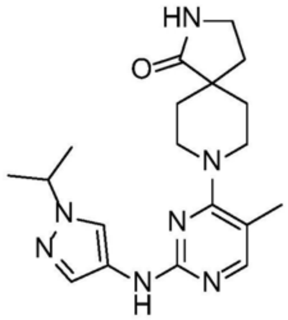
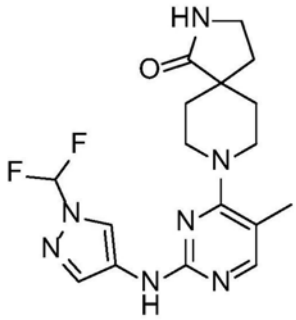
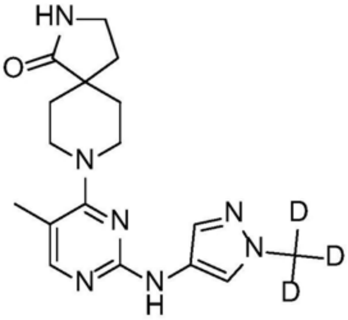
、、、

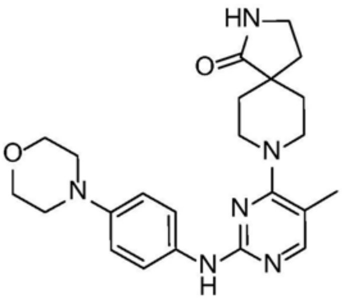
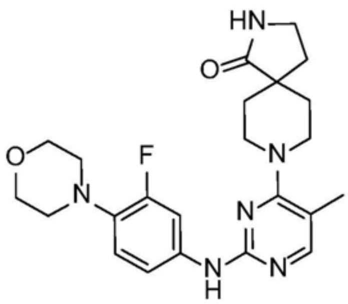
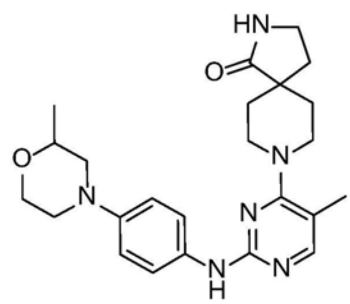
[0047] 、、、

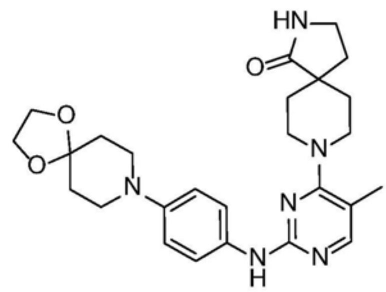
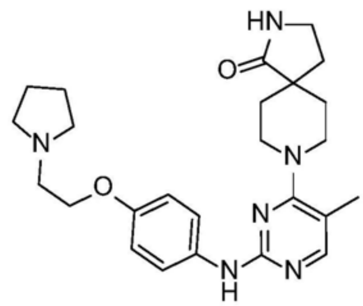
、、、

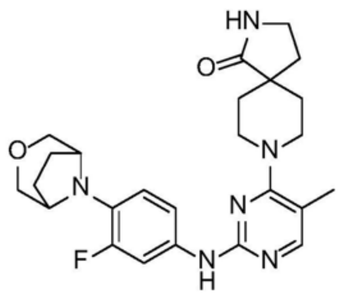
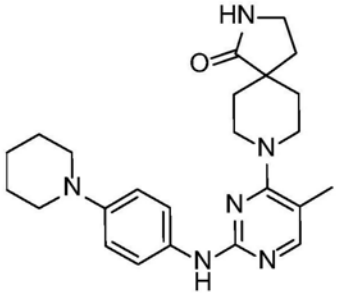
、、、

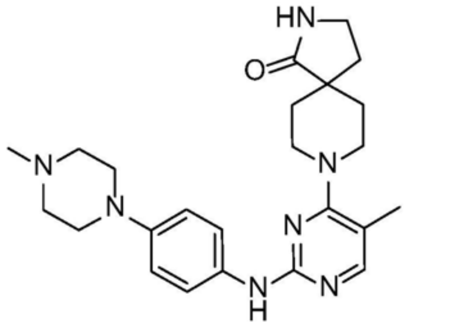
、、、、

、、、

[0048] 、、、

、、

、、



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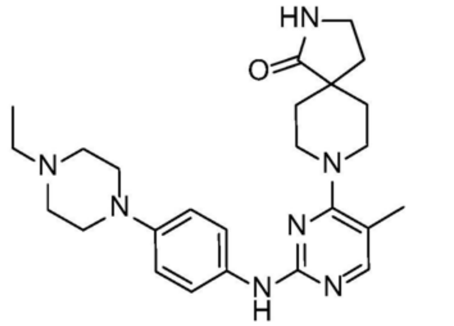

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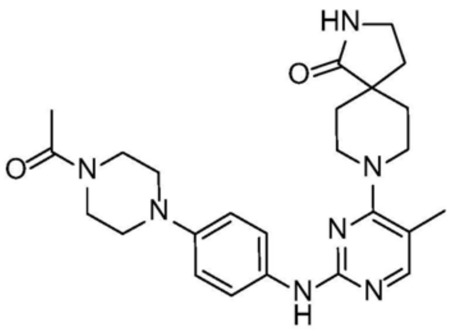

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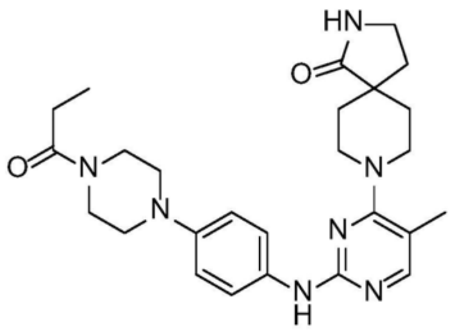

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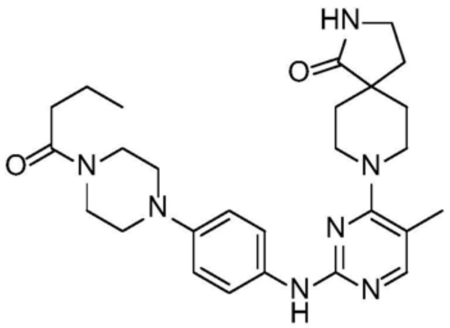
[0049]



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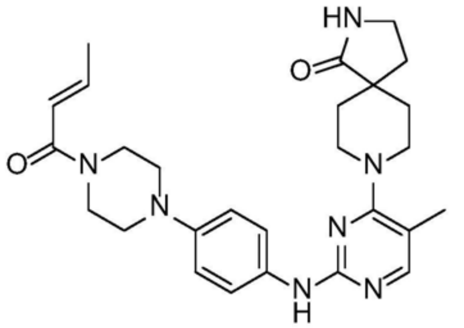

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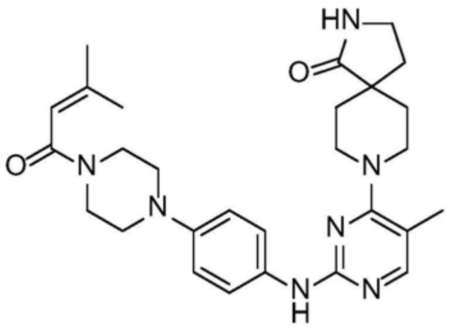

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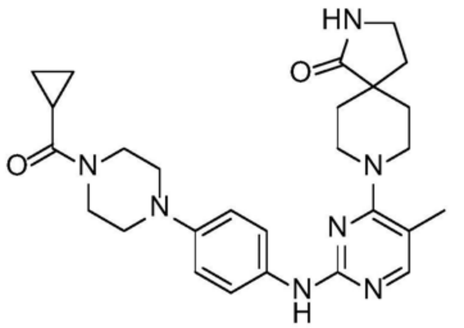

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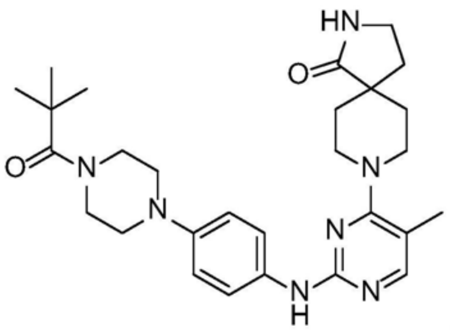

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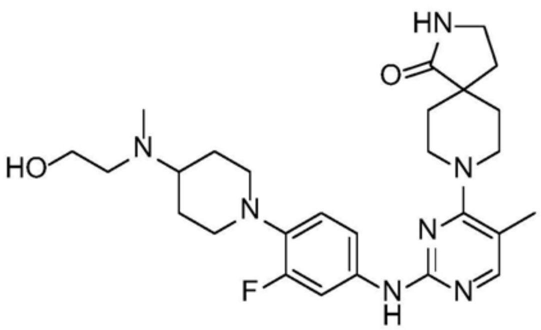

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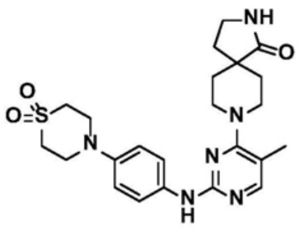
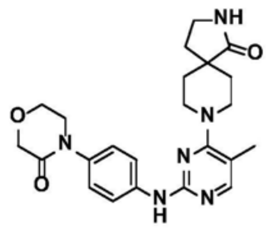
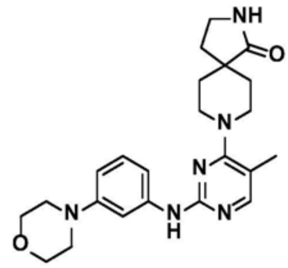
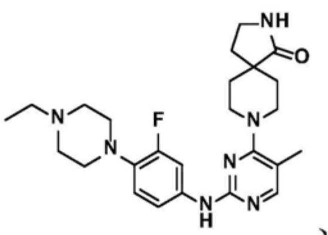
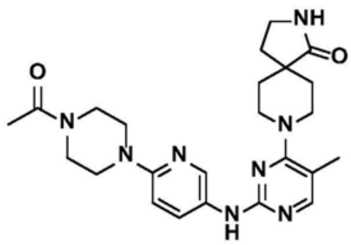
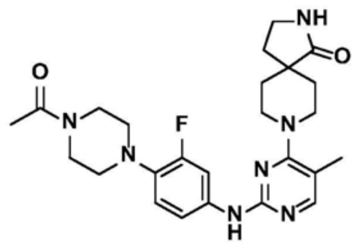
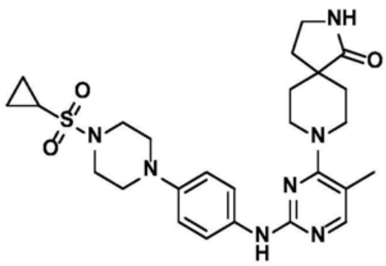
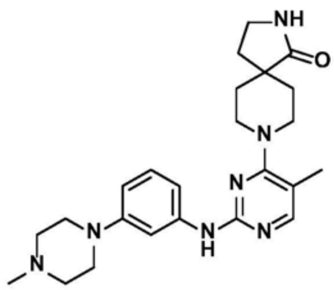
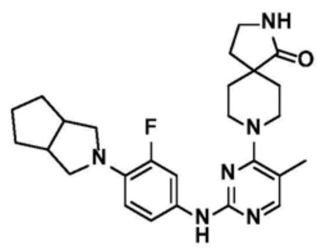
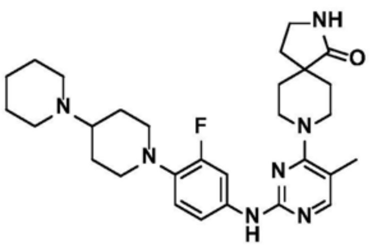
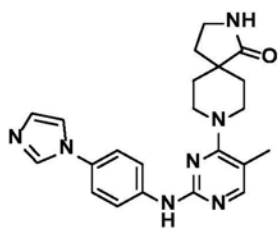
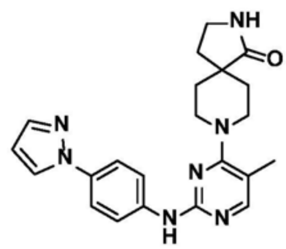
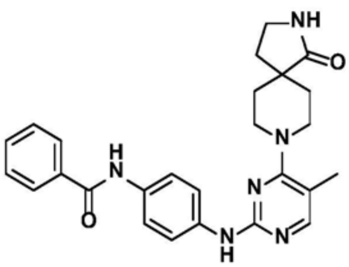
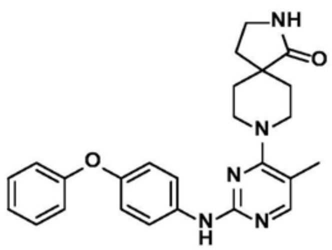
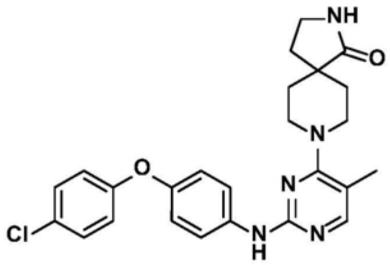
、、、

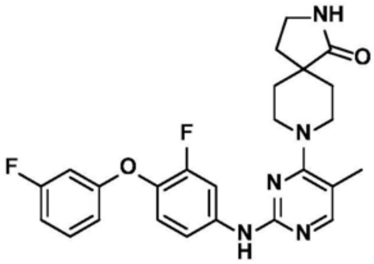
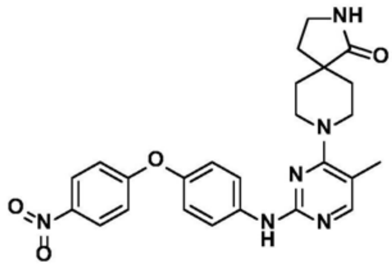
、、、

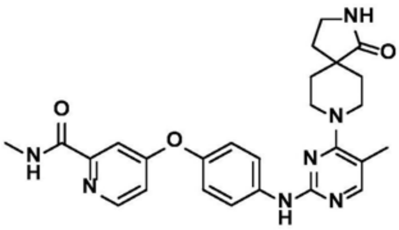
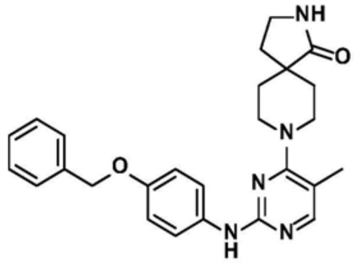
[0050] 、、、

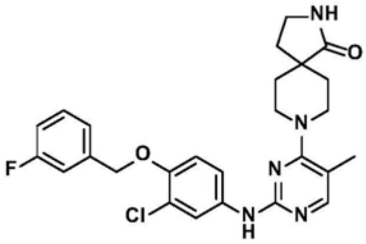
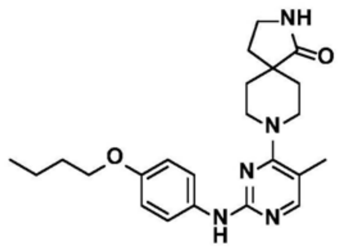
、、、

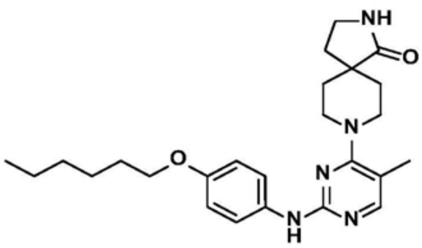
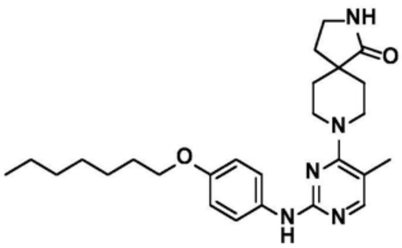
;

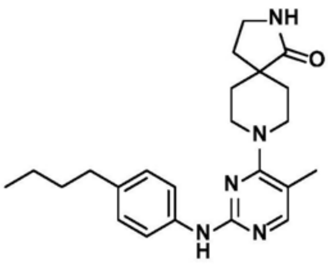
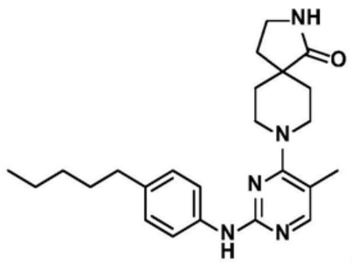
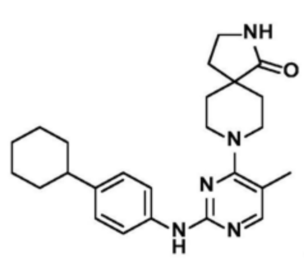
、、

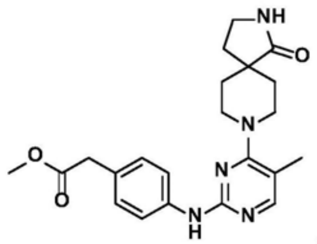
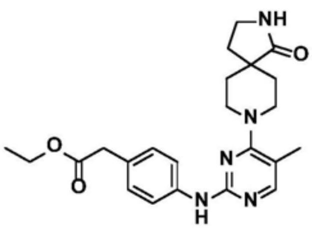
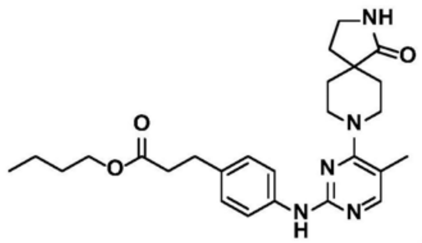
、、

[0051] 、、

、、

、；

、、、

、、、

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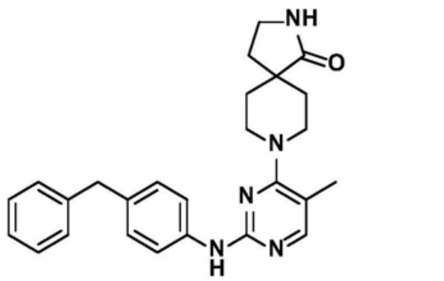
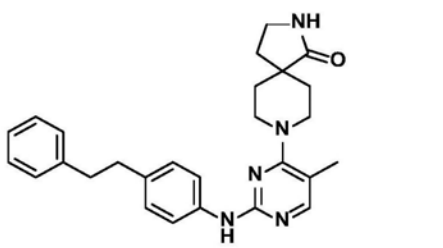
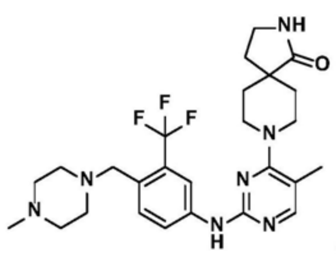
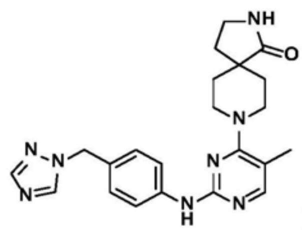
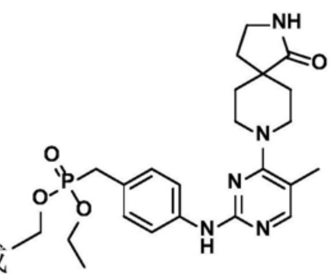
、、

、或。

[0053] 本发明还提供了上述化合物的制备方法，包括如下步骤：

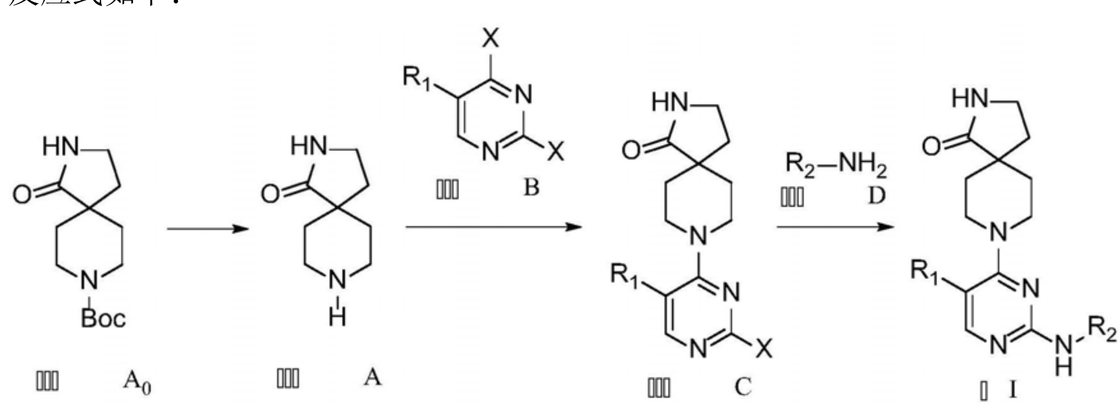
[0054] (1)化合物A_0在三氟乙酸作用下反应脱去Boc保护基团得到化合物A；

[0055] (2)化合物A与化合物B在有机碱作用下反应得到化合物C；

[0056] (3)化合物C与化合物D在酸的作用下或在钯催化剂作用下反应得到 式I化合物；

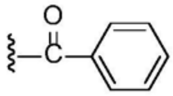
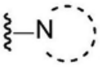
[0057] 反应式如下：

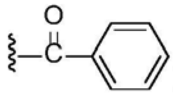
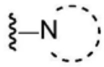
[0058]



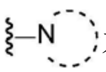
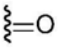
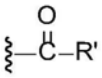
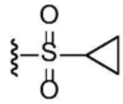
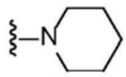
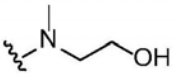
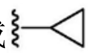
[0059] 其中，X为卤素；R_1为H或甲基；R_2为R_3、R_4、R_5取代或未取代的5～6 元芳杂环，杂原子

为N或S；

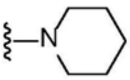
[0060] 所述R_3为卤素、硝基、氨基、取代的氨基、C1～C3烷氧基，R_6、R_7、R_8取代或未取代的C1～C3烷基、、-OR_9或$CR_{10}R_{11}$；

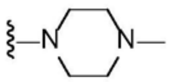
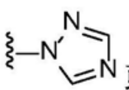
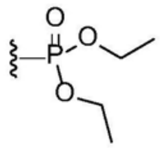
[0061] 所述R_4、R_5分别独立选自H、卤素、硝基、氨基、取代的氨 基、C1～C3烷氧基，R_6、R_7、R_8取代或未取代的C1～C3烷基、、-OR_9或$CR_{10}R_{11}$；

[0062] 所述R_6、R_7、R_8分别独立选自H、D、卤素或C1～C3烷基；

[0063] 所述为R_a、R_b取代或未取代的5～6元饱和或不饱和杂环，杂原子 为N、O或S；所述R_a、R_b分别独立选自C1～C3烷基、、、、或，或R_a、R_b连接成环；其中，R'为C1～C4烷基、C3～C4 烯基或；

[0064] R_9为取代或未取代的C2～C7的烷基苄基、苯基或取代的吡啶基；

[0065] 所述取代的取代基为硝基、卤素、-CONH-CH_3或；

[0066] R_{10}、R_{11}分别独立选自H、C3～C5烷基、-$COOR_c$、苯基、苄基、、或，或R_{10}、R_{11}连接成环；其中，R_c为C1～C4烷基。

[0067] 进一步地，上述步骤(1)所述反应为在有机溶剂中室温反应30～60min；优选为在二氯甲烷中20～30℃反应40min；

[0068] 步骤(2)所述有机碱为三乙胺，所述反应为在醇溶剂中室温反应过夜；优选为在异丙醇中20～30℃反应10～20小时；

[0069] 步骤(3)所述反应为：在醇溶剂中，酸作用下110～115℃反应5～10小 时，优选地，所述酸为浓盐酸；

[0070] 或，在有机溶剂中，无机碱、配体和钯催化剂作用和惰性气体保护条件 下，105～110℃反应8～10小时；优选地，所述有机溶剂为二氧六环或N,N- 二甲基甲酰胺，所述无机碱为碳酸铯，所述配体为1,1'-双(二苯基膦)二茂铁 或者4,5-双二苯基膦-9,9-二甲基氧杂蒽，所述钯催化剂为三(二亚苄基丙酮) 二钯。

[0071] 本发明还提供了上述衍生物或其药学上可接受的盐或其氘代化合物在 JAKs激酶抑制剂中的用途，所述JAKs激酶抑制剂为JAK1激酶、JAK2激 酶、JAK3激酶和/或TYK2激酶抑制剂。

[0072] 本发明还提供了上述衍生物或其药学上可接受的盐或其氘代化合物在制 备防治自身免疫疾病、免疫介导的疾病和/或癌症的药物中的用途。

[0073] 进一步地，上述药物为防治类风湿性关节炎、成人强直性脊柱炎、真红 细胞增多症、骨髓纤维化、系统性红斑狼疮、霍奇金病、炎症性肠病、银屑 病、特应性皮炎、斑秃、镰状细胞性贫血、中条-西村综合征、慢性髓性白血 病、急性髓性白血病、多发性骨髓瘤、乳腺癌、结肠癌、肺癌、前列腺癌、 卵巢癌和/或肝癌的药物；

[0074] 优选地，所述防治炎症性肠病的药物为防治克罗恩病、溃疡性结肠炎和/ 或未定型结肠炎的药物。

[0075] 本发明的衍生物具有抑制JAKs激酶活性的作用，但并非为一种JAKs 激酶的泛抑制剂，而是对JAKs激酶的不同亚型存在选择作用，降低了副作 用风险，在溃疡性结肠炎、斑秃等自身免疫疾病或免疫介导的疾病的治疗方 面具有潜在应用价值。

[0076] 关于本发明的使用术语的定义：除非另有说明，本文中基团或者术语提 供的初始定义适用于整篇说明书的该基团或者术语；对于本文没有具体定义 的术语，应该根据公开内容和上下文，给出本领域技术人员能够给予它们的 含义。

[0077] “取代”是指分子中的氢原子被其它不同的原子或分子所替换。

[0078] “卤素”为氟、氯、溴或碘。

[0079] “烷基”是烷烃分子中少掉一个氢原子而成的烃基，例如甲基$-CH_3$、乙 基$-CH_3CH_2$等。C1～C3烷基是指含有一个至三个碳原子的直链或支链的烃链，以此类推。

[0080] “C1～C3烷氧基”是指含有一至三个碳原子的烷氧基，以此类推。

[0081] “芳杂环”是指具有共轭的π电子体系的全碳单环或稠合多环(也就是共 享毗邻碳原子对的环)基团(例如苯基、萘基)中的部分碳原子被杂原子(N、O和/或S)替代的环状共轭体系。

[0082] “药学上可接受的盐”指本发明化合物与药学上可接受的无机酸和有机 酸所形成的盐，适合与对象(例如，人)的组织接触，而不会产生不适度的副 作用的盐。其中，优选的无机酸包括(但并不限于)：盐酸、氢溴酸、磷酸、 硝酸、硫酸；优选的有机酸包括(但并不限于)：甲酸、乙酸、丙酸、丁二酸、 萘二磺酸(1,5)、亚细亚酸、草酸、酒石酸、乳酸、水杨酸、苯甲酸、戊酸、 二乙基乙酸、丙二酸、琥珀酸、富马酸、庚二酸、己二酸、马来酸、苹果酸、 氨基磺酸、苯丙酸、葡糖酸、抗坏血酸、烟酸、异烟酸、甲磺酸、对甲苯磺 酸、柠檬酸，以及氨基酸。

[0083] “氘代化合物”是指化合物中的一个或多个氢原子被氘原子取代而成的 化合物。

[0084] 显然，根据本发明的上述内容，按照本领域的普通技术知识和惯用手段， 在不脱离本发明上述基本技术思想前提下，还可以做出其它多种形式的修改、替换或变更。

[0085] 以下通过实施例形式的具体实施方式，对本发明的上述内容再作进一步 的详细说明。但不应将此理解为本发明上述主题的范围仅限于以下的实例。凡基于本发明上述内容所实现的技术均属于本发明的范围。

附图说明

[0086] 图1为UC模型临床打分、体重改变率和结肠长度统计数据及照片(图 中53#表示实施例20的化合物)。

[0087] 图2为UC模型小鼠结肠病理切片(图中53#表示实施例20的化合物)。

[0088] 图3为小鼠背部毛发生长情况(图中化合物2表示实施例43的化合物，化合物4表示实施例45的化合物,化合物16表示实施例54的化合物)。

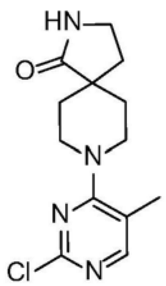
[0089] 图4为不同组小鼠毛发长度对比(图中化合物2表示实施例43的化合物，化合物4表示实施例45的化合物,化合物16表示实施例54的化合物)。

具体实施方式

[0090] 本发明所用原料与设备均为已知产品,通过购买市售产品所得。

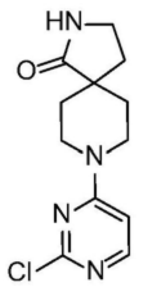
[0091] 中间体的合成：

[0092] 1、中间体a

[0093] 

[0094] 在500mL的圆底烧瓶中加入10g(39.27mmol)1-氧代-2,8-二氮杂螺 [4,5]癸烷-8-甲酸叔丁酯(1),再分别加入100mL的二氯甲烷与150mL三氟 乙酸,室温反应5h。待反应液完全澄清将反应液减压蒸馏除去所有溶剂,得 粗产品2。在2中直接加入异丙醇200mL作溶剂,加三乙胺20mL,加入 7.02g(47.12mmol)的2,4-二氯-5-甲基嘧啶,室温过夜。析出固体抽滤,无 水乙醚洗涤三次,白色固体即为粗产品a。产率约71％。^{1}H NMR(400MHz, DMSO-d_6)δ 8.01(d,J＝1.0Hz,1H),7.60(s,1H),3.98(dt,J＝13.8,4.1Hz,2H), 3.23-3.09(m,4H),2.19(s,3H),2.02(t,J＝6.8Hz,2H),1.78-1.66(m,2H), 1.45(dt,J＝13.7,3.3Hz,2H).

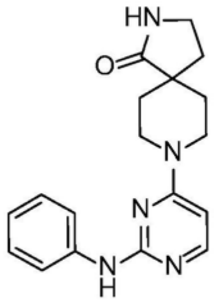
[0095] 2、中间体b

[0096] 

[0097] 同上操作得到中间体2,加入与上述等量异丙醇与三乙胺及7.02g(47.12 mmol)的2,4-二氯嘧啶,室温过夜。析出固体抽滤,无水乙醚洗涤三次,白 色固体即为粗产品b。产率约65％。^{1}H NMR(400MHz,DMSO-d_6)δ8.05(d,J ＝6.2Hz,1H),7.62(s,1H),6.86(d,J＝6.3Hz,1H),4.18(s,2H),3.27-3.15(m, 4H),2.03(t,J＝6.8Hz,2H),1.70-1.52(m,2H),1.51-1.37(m,2H).

[0098] 实施例1、本发明化合物的制备

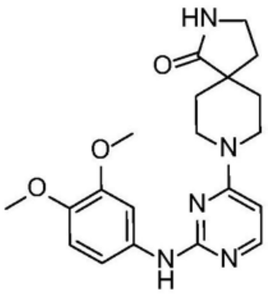
[0099] 8-(2-(phenylamino)pyrimidin-4-yl)-2,8-diazaspiro[4.5]decan-1-one

[0100] 

[0101] 210mg(0.75mmol)中间体b与85mg(0.9mmol)苯胺加到100ml原 底烧瓶中，在25mL正丁醇作溶剂以及两滴浓盐酸下100℃过夜。TLC监 测，反应结束后将溶剂旋干，Flash柱分离纯化得淡黄色固体产物。产率40％。^{1}H NMR(400MHz,DMSO-d_6)δ9.06(s,1H),7.95(d,J＝6.1Hz,1H), 7.77-7.65(m,2H),7.60(s,1H),7.28-7.19(m,2H),6.89(t,J＝7.3Hz,1H),6.31 (d,J＝6.2Hz,1H),4.23(d,J＝13.3Hz,2H),3.51-3.40(m,2H),3.26-3.09(m, 4H),1.70-1.58(m,2H),1.43(d,J＝13.2Hz,2H).^{13}C NMR(101MHz, DMSO-d_6)δ180.19,162.21,160.01,156.95,141.66,128.77,121.02,119.00, 95.70,42.43,41.13,38.42,31.60,31.57.HRMS-ESI:calcd for $C_{18}H_{21}N_5O$ $[M+H]^+$324.1818,found:324.1818.

[0102] 实施例2、本发明化合物的制备

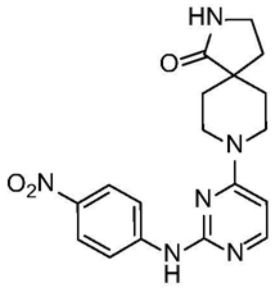
[0103] 8-(2-((3,4-dimethoxyphenyl)amino)pyrimidin-4-yl)-2,8-diazaspiro[4.5]decan -1-one

[0104] 

[0105] 合成方法同实施例1，仅需将实施例1的苯胺替换为本实施例化合物结 构对应的含氨基的化合物即可，后文的所有制备方法均同理。淡褐色固体产 物，产率30％。^{1}H NMR(400MHz,DMSO-d_6)δ8.88(s,1H),7.92(d,J＝6.1Hz, 1H),7.60(s,1H),7.49(d,J＝2.4Hz,1H),7.14-7.07(m,1H),6.84(d,J＝8.7Hz, 1H),6.26(d,J＝6.2Hz,1H),4.23(d,J＝13.3Hz,2H),3.71(d,J＝8.9Hz,6H), 3.25-3.09(m,4H),2.04(t,J＝6.7Hz,2H),1.63(td,J＝12.2,11.4,4.2Hz,3H), 1.42(d,J＝13.3Hz,2H).^{13}C NMR(101MHz,DMSO-d_6)δ180.21,162.18, 160.00,156.92,148.99,143.69,135.45,112.96,110.92,104.79,95.10,56.43,55.75,42.42,41.10,38.42,31.60,31.53.HRMS-ESI:calcd for $C_{20}H_{25}N_5O_3$ $[M+H]^+$384.2036,found:384.2032.

[0106] 实施例3、本发明化合物的制备

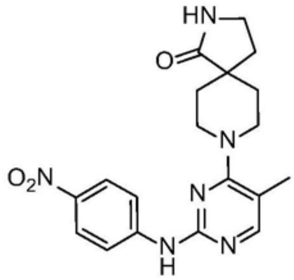
[0107] 8-(2-((4-nitrophenyl)amino)pyrimidin-4-yl)-2,8-diazaspiro[4.5]decan-1-one

[0108] 

[0109] 合成方法同实施例1。金黄色固体，产率44％。[1]H NMR(400MHz, DMSO-d_6)δ9.90(s,1H),8.16(d,J=9.3Hz,2H),8.05(d,J=6.1Hz,1H),7.97 (d,J=9.3Hz,2H),7.61(s,1H),6.47(d,J=6.2Hz,1H),4.25(s,2H),3.27-3.13 (m,4H),2.06(t,J=6.8Hz,2H),1.65(td,J=12.5,11.4,4.2Hz,2H),1.46(d,J= 13.6Hz,2H).[13]C NMR(101MHz,DMSO-d_6)δ180.16,162.12,159.20,156.73, 148.37,140.17,125.42,117.74,97.56,42.37,38.43,31.65.HRMS-ESI:calcd for $C_{18}H_{20}N_6O_3$[M+H]$^+$369.1676,found:369.1676.

[0110] 实施例4、本发明化合物的制备

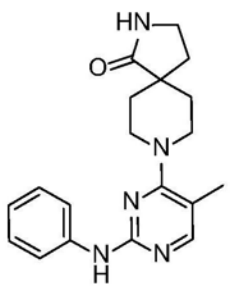
[0111] 8-(5-methyl-2-((4-nitrophenyl)amino)pyrimidin-4-yl)-2,8-diazaspiro[4.5]dec an-1-one

[0112] 

[0113] 210mg(0.75mmol)中间体a与140mg(0.9mmol)对硝基苯胺加到 100mL原底烧瓶中，在25mL正丁醇作溶剂以及两滴浓盐酸下100℃过夜。TLC监测，反应结束后将溶剂旋干，Flash柱分离纯化得金黄色固体。产率 45％。[1]H NMR(400MHz,DMSO-d_6)δ9.95(s,1H),8.16(d,J=9.2Hz,2H), 7.98(d,J=9.2Hz,3H),7.60(s,1H),3.96(dt,J=13.6,3.9Hz,2H),3.22(t,J= 6.8Hz,2H),3.18-3.06(m,2H),2.15(s,3H),2.05(t,J=6.8Hz,2H),1.79(td,J=12.6,11.8,3.9Hz,2H),1.48(d,J=13.1Hz,2H).[13]C NMR(101MHz, DMSO-d_6)δ180.37,164.80,158.87,157.55,148.44,140.00,125.47,117.41, 110.28,44.43,42.27,38.42,32.09,31.74,17.12.HRMS-ESI:calcd for $C_{19}H_{22}N_6O_3$[M+H]$^+$383.1832,found:383.1828.

[0114] 实施例5、本发明化合物的制备

[0115] 8-(5-methyl-2-(phenylamino)pyrimidin-4-yl)-2,8-diazaspiro[4.5]decan-1-one

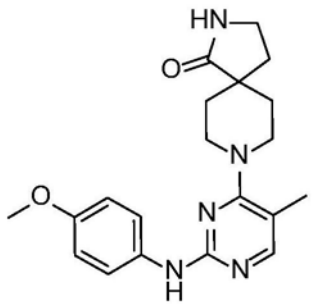
[0116] 

[0117] 合成方法同实施例4。淡黄色固体。产率40％。^{1}H NMR(400MHz，DMSO-d_6)δ9.04(s,1H),7.88(s,1H),7.72(d,J＝8.0Hz,2H),7.58(s,1H),7.22 (t,J＝7.8Hz,2H),6.86(t,J＝7.3Hz,1H),3.97-3.88(m,2H),3.21(t,J＝6.8Hz，2H),3.11-3.02(m,2H),2.11(s,3H),2.04(t,J＝6.8Hz,2H),1.78(td,J＝12.8，4.0Hz,2H),1.48-1.41(m,2H).^{13}C NMR(101MHz,DMSO-d_6)δ180.42，164.96,158.95,158.53,141.81,128.79,120.78,118.60,108.23,44.41,42.30，38.41,32.10,31.71,16.91.HRMS-ESI:calcd for $C_{19}H_{23}N_5O[M+H]^+$ 338.1982，found:338.1979.

[0118] 实施例6、本发明化合物的制备

[0119] 8-(2-((4-methoxyphenyl)amino)pyrimidin-4-yl)-2,8-diazaspiro[4.5]decan-1- one

[0120]

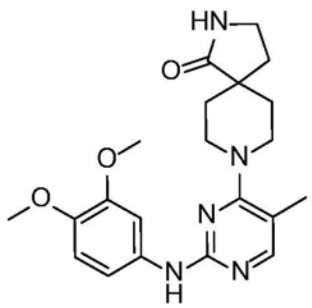


[0121] 合成方法同实施例4。淡褐色固体。产率37％。^{1}H NMR(400MHz，DMSO-d_6)δ8.81(s,1H),7.84(d,J＝0.9Hz,1H),7.67-7.53(m,3H),6.82(d,J ＝9.0Hz,2H),4.33(t,J＝5.1Hz,1H),3.93-3.83(m,2H),3.70(s,3H),3.20(t,J ＝6.8Hz,2H),3.09-2.97(m,2H),2.09(s,3H),2.03(t,J＝6.8Hz,2H),1.77(td，J＝12.9,4.0Hz,2H),1.43(d,J＝13.0Hz,2H).^{13}C NMR(101MHz,DMSO-d_6) δ180.45,165.01,158.92,158.68,153.97,135.05,120.22,114.08,107.64,56.51，55.61,44.40,42.31,38.41,32.09,31.70,19.01,16.85.HRMS-ESI:calcd for $C_{20}H_{25}N_5O_2[M+H]^+$368.2087,found:368.2082.

[0122] 实施例7、本发明化合物的制备

[0123] 8-(2-((3,4-dimethoxyphenyl)amino)-5-methylpyrimidin-4-yl)-2,8-diazaspiro[4.5]decan-1-one

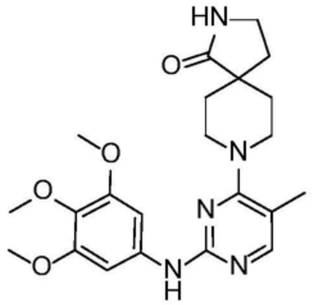
[0124]



[0125] 合成方法同实施例4。淡褐色固体。产率36％。^{1}H NMR(400MHz，DMSO-d_6)δ8.82(s,1H),7.87(s,1H),7.58(s,1H),7.48(d,J＝2.4Hz,1H),7.19 (dd,J＝8.7,2.4Hz,1H),6.83(d,J＝8.7Hz,1H),3.93-3.84(m,2H),3.73(s，3H),3.69(s,3H),3.20(t,J＝6.8Hz,2H),3.10-2.99(m,2H),2.09(s,3H),2.02(t，J＝6.8Hz,2H),1.77(td,J＝12.5,12.0,3.9Hz,2H),1.44(d,J＝13.1Hz,2H). ^{13}C NMR(101MHz,DMSO-d_6)δ180.43,165.11,158.97,158.59,149.08，143.54,135.68,113.02,110.47,107.78,104.48,56.44,55.81,44.48,42.24, 38.40, 32.15,31.69,16.81.HRMS-ESI:calcd for $C_{21}H_{27}N_5O_3[M+H]^+$398.2114,found: 398.2111.

[0126] 实施例8、本发明化合物的制备

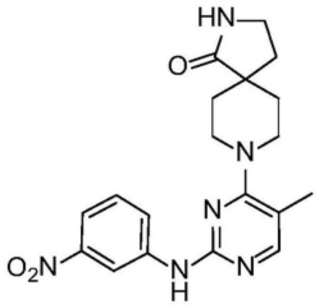
[0127] 8-(5-methyl-2-((3,4,5-trimethoxyphenyl)amino)pyrimidin-4-yl)-2,8-diazaspir o[4.5]decan-1-one

[0128] 

[0129] 合成方法同实施例4。淡褐色固体。产率35%。^{1}H NMR(400MHz, DMSO-d_6)δ8.90(s,1H),7.89(s,1H),7.59(s,1H),7.16(s,2H),3.94-3.85(m, 2H),3.74(s,6H),3.60(s,3H),3.20(t,J=6.8Hz,2H),3.11-2.99(m,2H),2.10 (s,3H),2.02(t,J=6.8Hz,2H),1.84-1.72(m,2H),1.44(d,J=13.3Hz,2H).^{13}C NMR(101MHz,DMSO-d_6)δ180.40,165.18,159.11,158.49,153.08,137.96, 132.00,108.20,96.44,60.59,56.09,44.55,42.17,38.38,32.20,31.69,16.80. HRMS-ESI:calcd for $C_{22}H_{29}N_5O_4[M+H]^+$428.2299,found:428.2293.

[0130] 实施例9、本发明化合物的制备

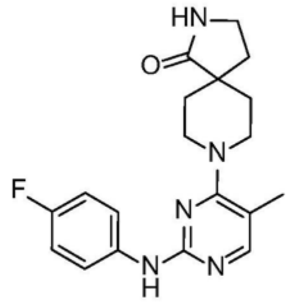
[0131] 8-(5-methyl-2-((3-nitrophenyl)amino)pyrimidin-4-yl)-2,8-diazaspiro[4.5]dec an-1-one

[0132] 

[0133] 171mg(0.5mmol)中间体a与84mg(0.55mmol)间硝基苯胺加到100 mL的三口圆底烧瓶中,最后加入50mg(0.05mmol)$Pd_2(dba)_3$,60mg(0.1 mmol)XantPhos,212mg(1mmol)K_3PO_4以及20mL二氧六环溶液中,98℃ 过夜。TLC监测,反应结束后将溶剂旋干,Flash柱分离纯化得金黄色固体。产率40%。^{1}H NMR(400MHz,DMSO-d_6)δ9.65(s,1H),9.03(t,J=2.3Hz,1H),8.01-7.88(m,2H),7.78-7.66(m,1H),7.59(s,1H),7.50(t,J=8.2Hz,1H), 4.05-3.93(m,2H),3.27-3.09(m,4H),2.14(s,3H),2.05(t,J=6.8Hz,2H), 1.87-1.73(m,2H),1.46(d,J=13.4Hz,2H).^{13}C NMR(101MHz,DMSO-d_6)δ 180.35,164.76,159.07,157.98,148.63,143.10,130.00,124.48,115.06,112.02, 109.19,44.45,42.25,38.41,32.15,31.77,17.09.HRMS-ESI:calcd for $C_{19}H_{22}N_6O_3[M+H]^+$383.1832,found:383.1829.

[0134] 实施例10、本发明化合物的制备

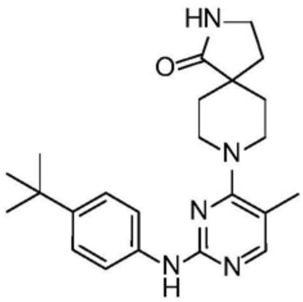
[0135] 8-(2-((4-fluorophenyl)amino)-5-methylpyrimidin-4-yl)-2,8-diazaspiro[4.5]de can-1-one

[0136] 

[0137] 合成方法同实施例4。白色固体。产率36％。^{1}H NMR(400MHz,DMSO-d_6) δ9.05(s,1H),7.88(s,1H),7.79-7.68(m,2H),7.58(s,1H),7.13-6.99(m,2H), 3.89(dt,J＝13.5,3.9Hz,2H),3.20(t,J＝6.8Hz,2H),3.12-2.98(m,2H),2.10 (s,3H),2.03(t,J＝6.8Hz,2H),1.77(td,J＝12.9,4.0Hz,2H),1.49-1.38(m, 2H).^{13}C NMR(101MHz,DMSO-d_6)δ180.40,164.97,158.93,158.45,138.24, 120.10,120.02,115.32,115.10,108.28,44.39,42.29,38.41,32.09,31.72,16.90. HRMS-ESI:calcd for $C_{19}H_{22}FN_5O$[M+H]$^+$356.1887,found:356.1882.

[0138] 实施例11、本发明化合物的制备

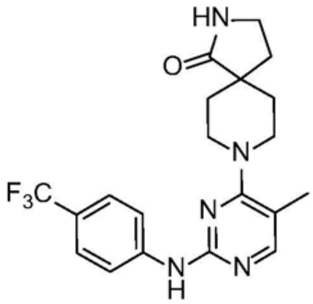
[0139] 8-(2-((4-(tert-butyl)phenyl)amino)-5-methylpyrimidin-4-yl)-2,8-diazaspiro[4 .5]decan-1-one

[0140] 

[0141] 合成方法同实施例4。白色固体。产率35％。^{1}H NMR(400MHz,DMSO-d_6) δ10.22(s,2H),9.73(s,1H),7.84(s,1H),7.63(s,1H),7.57-7.51(m,2H),7.36 -7.29(m,2H),4.12(d,J＝13.4Hz,2H),3.27(s,2H),3.21(t,J＝6.8Hz,2H), 2.17(s,3H),2.05(t,J＝6.8Hz,2H),1.83-1.71(m,2H),1.51(d,J＝13.3Hz, 2H),1.27(s,9H).^{13}C NMR(101MHz,DMSO-d_6)δ 180.13,163.95,145.18, 136.99,125.81,119.60,107.44,45.77,44.62,42.16,38.42,34.43,32.36,31.92, 31.72,17.70,8.87.HRMS-ESI:calcd for $C_{23}H_{31}N_5O$[M+H]$^+$394.2608,found: 394.2599.

[0142] 实施例12、本发明化合物的制备

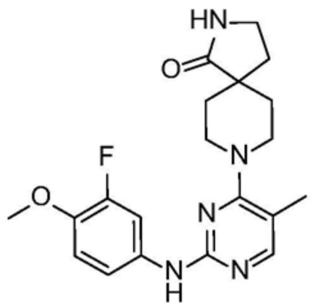
[0143] 8-(5-methyl-2-((4-(trifluoromethyl)phenyl)amino)pyrimidin-4-yl)-2,8-diazas piro[4.5]decan-1-one

[0144] 

[0145] 合成方法同实施例4。白色固体。产率37％。^{1}H NMR(400MHz,DMSO-d_6) δ10.43(s,1H),7.93(d,J＝1.0Hz,1H),7.85(d,J＝8.5Hz,2H),7.73-7.59(m, 3H),4.22-4.10(m,2H),3.39-3.28(m,2H),3.22(t,J＝6.8Hz,2H),2.20(s,3H), 2.05(t,J＝6.8Hz,2H),1.85-1.74(m,2H),1.54(d,J＝13.7Hz,2H).^{13}C NMR (101MHz,DMSO-d_6)δ180.07,163.70,143.19,126.49,126.45,119.54,108.50, 56.48,45.76,44.76,42.06,38.41,32.37,32.04,19.01,17.86,8.85.HRMS-ESI: calcd for $C_{20}H_{22}F_3N_5O$[M+H]$^+$406.1855,found:406.1851.

[0146] 实施例13、本发明化合物的制备

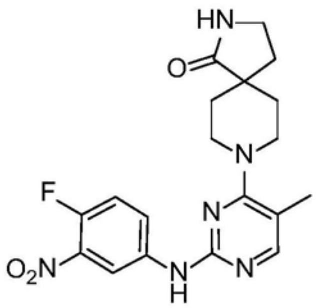
[0147] 8-(2-((3-fluoro-4-methoxyphenyl)amino)-5-methylpyrimidin-4-yl)-2,8-diaza spiro[4.5]decan-1-one

[0148] 

[0149] 合成方法同实施例4。白色固体。产率38％。^{1}H NMR(400MHz,DMSO-d_6) δ9.04(s,1H),7.88(s,1H),7.76(dd,J＝14.7,2.6Hz,1H),7.59(s,1H),7.39(dt, J＝9.1,1.9Hz,1H),7.04(t,J＝9.4Hz,1H),3.90(dt,J＝13.4,4.0Hz,2H),3.78 (s,3H),3.21(t,J＝6.8Hz,2H),3.15-2.95(m,2H),2.10(s,3H),2.04(t,J＝6.8 Hz,2H),1.78(td,J＝12.5,4.0Hz,2H),1.44(d,J＝13.1Hz,2H).^{13}C NMR(101 MHz,DMSO-d_6)δ180.39,164.91,158.95,158.35,141.17,135.82,135.72, 114.78,114.24,108.20,107.07,106.83,56.83,44.38,42.30,38.41,32.09,31.71, 16.91.HRMS-ESI:calcd for $C_{20}H_{24}FN_5O_2$[M+H]$^+$386.1993,found:386.1993.

[0150] 实施例14、本发明化合物的制备

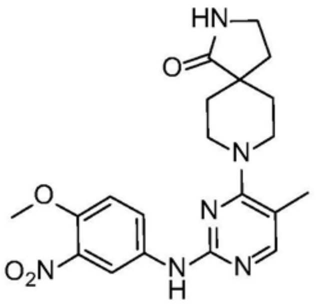
[0151] 8-(2-((4-fluoro-3-nitrophenyl)amino)-5-methylpyrimidin-4-yl)-2,8-diazaspir o[4.5]decan-1-one

[0152] 

[0153] 合成方法同实施例4。淡黄色固体。产率38％。^{1}H NMR(400MHz, DMSO-d_6)δ9.60(s,1H),8.91(dd,J＝7.0,2.8Hz,1H),7.95(s,1H),7.88(ddd,J ＝9.2,3.9,2.8Hz,1H),7.59(s,1H),7.47(dd,J＝11.2,9.2Hz,1H),3.96(dt,J＝ 13.5,4.0Hz,2H),3.21(t,J＝6.8Hz,2H),3.18-3.02(m,2H),2.13(s,3H),2.05 (t,J＝6.8Hz,2H),1.84-1.73(m,2H),1.45(d,J＝13.5Hz,2H).^{13}C NMR(101 MHz,DMSO-d_6)δ180.34,164.76,159.05,157.85,138.78,125.69,125.61, 118.91,118.69,113.80,109.19,44.42,42.23,38.41,32.15,31.77,17.07. HRMS-ESI:calcd for $C_{19}H_{21}FN_6O_3$[M+H]$^+$401.1738,found:401.1737.

[0154] 实施例15、本发明化合物的制备

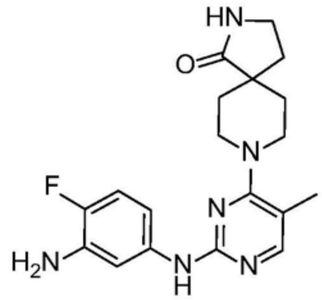
[0155] 8-(2-((3-fluoro-4-methoxyphenyl)amino)-5-methylpyrimidin-4-yl)-2,8-diaza spiro[4.5]decan-1-one

[0156] 

[0157] 合成方法同实施例4。淡黄色固体。产率36％。^{1}H NMR(400MHz, DMSO-d_6)δ9.31(s,1H),8.57(d,J＝2.8Hz,1H),7.90(s,1H),7.80(dd,J＝9.1, 2.8Hz,1H),7.58(s,1H),7.29(d,J＝9.2Hz,1H),3.94(d,J＝13.4Hz,2H),3.87 (s,3H),3.20(d,J＝6.8Hz,2H),3.10(t,J＝12.4Hz,2H),2.11(s,3H),2.04(t,J ＝6.8Hz,2H),1.77(td,J＝12.5,11.7,3.9Hz,2H),1.43(d,J＝13.2Hz,2H).^{13}C NMR(101MHz,DMSO-d_6)δ180.34,164.73,158.76,157.96,146.66,139.02, 135.06,124.74,115.30,114.30,108.49,57.22,44.40,42.24,38.40,32.13,31.76, 17.05.HRMS-ESI:calcd for $C_{20}H_{24}N_6O_4$[M+H]$^+$413.1938,found:413.1930

[0158] 实施例16、本发明化合物的制备

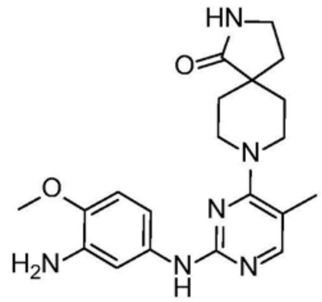
[0159] 8-(2-((3-amino-4-fluorophenyl)amino)-5-methylpyrimidin-4-yl)-2,8-diazaspi ro[4.5]decan-1-one

[0160] 

[0161] 由实施例14的化合物合成。实施例14的化合物(0.5mmol)置于10mL 原底烧瓶中,15mL甲醇作溶剂,2mL水合肼并Pd/C催化下加热回流。TLC 监测反应,反应完毕后硅藻土抽滤,浓缩滤液,Flash柱纯化得淡黄色固体。产率80%。^{1}H NMR(400MHz,DMSO-d_6)δ8.73(s,1H),7.84(s,1H),7.57(s, 1H),7.17(dd,J=8.5,2.3Hz,1H),6.89-6.76(m,2H),4.91(s,2H),3.87(d,J= 13.4Hz,2H),3.20(t,J=6.8Hz,2H),3.02(t,J=12.1Hz,2H),2.09(s,3H),2.03 (t,J=6.8Hz,2H),1.83-1.74(m,2H),1.43(d,J=13.2Hz,2H).^{13}C NMR(101 MHz,DMSO-d_6)δ180.49,165.02,158.78,158.61,138.14,136.21,136.08, 114.72,114.53,107.89,107.06,107.02,106.94,106.87,44.42,42.33,38.42, 32.08,31.68,16.85.HRMS-ESI:calcd for $C_{19}H_{23}FN_6O_3$[M+H]$^+$371.1996,found: 371.1990.

[0162] 实施例17、本发明化合物的制备

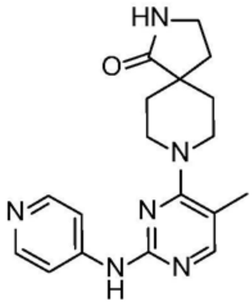
[0163] 8-(2-((3-amino-4-methoxyphenyl)amino)-5-methylpyrimidin-4-yl)-2,8-diaza spiro[4.5]decan-1-one

[0164] 

[0165] 合成方法实施例16,由实施例15的化合物合成而来。白色固体。产率 75%。^{1}H NMR(400MHz,DMSO-d_6)δ8.62(s,1H),7.80(s,1H),7.58(s,1H), 6.99(d,J=2.5Hz,1H),6.88(dd,J=8.6,2.5Hz,1H),6.66(d,J=8.7Hz,1H), 4.78(s,2H),3.90(d,J=13.7Hz,2H),3.70(s,3H),3.20(t,J=6.8Hz,2H), 3.09-2.98(m,2H),2.08(s,3H),2.03(t,J=6.8Hz,2H),1.77(td,J=12.6,4.0 Hz,2H),1.44(d,J=13.1Hz,2H).^{13}C NMR(101MHz,DMSO-d_6)δ 180.47, 164.93,158.32,157.91,141.93,137.68,135.10,111.31,107.47,107.33,106.31, 56.10,44.44,42.32,38.42,32.12,31.70,16.90.HRMS-ESI:calcd for $C_{20}H_{26}N_6O_2$[M+H]$^+$383.2196,found:383.2191.

[0166] 实施例18、本发明化合物的制备

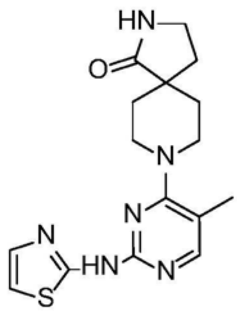
[0167] 8-(5-methyl-2-(pyridin-4-ylamino)pyrimidin-4-yl)-2,8-diazaspiro[4.5]decan- 1-one

[0168] 

[0169] 合成方法同实施例9。白色固体。产率36％。^{1}H NMR(400MHz,DMSO-d_6) δ9.61(s,1H),8.31(s,2H),7.97(s,1H),7.75(s,2H),7.60(s,1H),3.95(dd,J＝ 13.5,4.0Hz,2H),3.21(t,J＝6.8Hz,2H),3.16-3.06(m,2H),2.14(s,3H),2.05 (t,J＝6.8Hz,2H),1.86-1.72(m,2H),1.54-1.41(m,2H).^{13}C NMR(101MHz, DMSO-d_6)δ180.36,164.84,158.85,157.89,149.99,148.22,112.55,109.76, 44.41,42.26,38.42,32.11,31.74,17.03.HRMS-ESI:calcd for $C_{18}H_{22}N_6O$ $[M+H]^+$339.1934,found:339.1236.

[0170] 实施例19、本发明化合物的制备

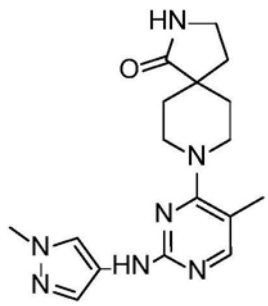
[0171] 8-(5-methyl-2-(thiazol-2-ylamino)pyrimidin-4-yl)-2,8-diazaspiro[4.5]decan- 1-one

[0172] 

[0173] 合成方法同实施例9。黄色固体。产率20％。^{1}H NMR(400MHz,DMSO-d_6) δ11.04(s,1H),7.97(s,1H),7.60(s,1H),7.35(d,J＝3.6Hz,1H),7.02(d,J＝ 3.6Hz,1H),4.11-3.98(m,2H),3.26-3.10(m,4H),2.14(s,3H),2.06(dd,J＝ 13.3,6.5Hz,2H),1.79(td,J＝12.6,4.0Hz,2H),1.48(d,J＝13.1Hz,2H).^{13}C NMR(101MHz,DMSO-d_6)δ180.37,164.66,155.63,138.24,111.95,109.31, 44.68,42.27,38.42,32.26,31.72,17.19.HRMS-ESI:calcd for $C_{16}H_{20}N_6OS$ $[M+H]^+$345.1498,found:345.1493.

[0174] 实施例20、本发明化合物的制备

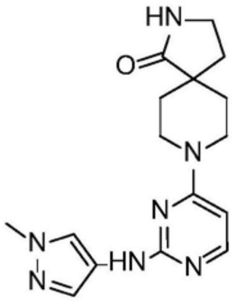
[0175] 8-(5-methyl-2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)-2,8-diazas piro[4.5]decan-1-one

[0176] 

[0177] 合成方法同实施例4。淡紫色固体。产率40％。^{1}H NMR(400MHz, DMSO-d_6)δ8.79(s, 1H),7.83(s,1H),7.73(s,1H),7.57(s,1H),7.45(s,1H), 3.85(dd,J=10.6,6.8Hz,2H),3.77(s,3H),3.21(t,J=6.8Hz,2H),3.02(t,J= 11.8Hz,2H),2.13-1.95(m,5H),1.77(td,J=12.5,4.0Hz,2H),1.44(d,J= 13.0Hz,2H).^{13}C NMR(101MHz,DMSO-d_6)δ180.26,159.72,157.06,130.15, 124.37,120.36,56.51,42.43,39.07,38.43,31.56,19.01.HRMS-ESI:calcd for $C_{17}H_{23}N_7O$[M+H]$^+$342.2043,found:342.2039.

[0178] 实施例21、本发明化合物的制备

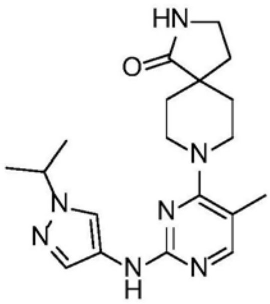
[0179] 8-(2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)-2,8-diazaspiro[4.5]d ecan-1-one

[0180]


[0181] 合成方法同实施例4。淡褐色固体。产率36％。^{1}H NMR(400MHz, DMSO-d_6)δ8.78(s,1H),7.89(d,J=6.0Hz,1H),7.72(s,1H),7.59(s,1H),7.42 (s,1H),6.17(d,J=6.1Hz,1H),4.19(d,J=13.3Hz,2H),3.77(s,3H),3.21(t,J =6.8Hz,2H),3.17-3.06(m,2H),2.04(t,J=6.8Hz,2H),1.69-1.56(m,2H), 1.41(d,J=13.1Hz,2H).^{13}C NMR(101MHz,DMSO-d_6)δ180.24,159.72, 157.06,130.14,124.38,120.34,42.43,39.08,38.42,31.57.HRMS-ESI:calcd for $C_{16}H_{21}N_7O$[M+H]$^+$328.1887,found:328.1882.

[0182] 实施例22、本发明化合物的制备

[0183] 8-(2-((1-isopropyl-1H-pyrazol-4-yl)amino)-5-methylpyrimidin-4-yl)-2,8-dia zaspiro[4.5]decan-1-one

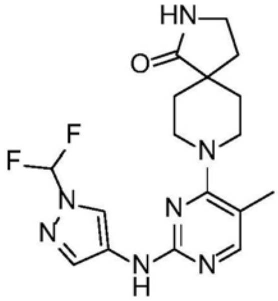
[0184]


[0185] 合成方法同实施例4。淡褐色固体。产率40％。^{1}H NMR(400MHz, DMSO-d_6)δ9.01(s,1H),7.81(s,2H),7.60(s,1H),7.48(s,1H),4.41(p,J=6.7 Hz,1H),3.94(dt,J=13.7,4.2Hz,2H),3.21(t,J=6.8Hz,2H),3.11(t,J=12.5 Hz,2H),2.09(s,3H),2.04(t,J=6.8Hz,2H),1.78(td,J=12.6,3.9Hz,2H), 1.46(d,J=13.6Hz,2H),1.39(s,3H),1.37(s,3H).^{13}C NMR(101MHz, DMSO-d_6)δ180.28,164.94,130.20,122.87,117.82,56.49,53.32,44.52,42.21, 38.40,32.24,31.79,23.12,19.02,17.10.HRMS-ESI:calcd for $C_{19}H_{27}N_7O$[M+H]$^+$370.2356,found:370.2355.

[0186] 实施例23、本发明化合物的制备

[0187] 8-(2-((1-(difluoromethyl)-1H-pyrazol-4-yl)amino)-5-methylpyrimidin-4-

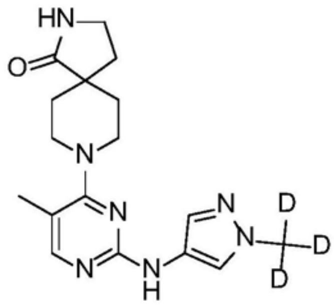
yl)- 2,8-diazaspiro[4.5]decan-1-one

[0188] 

[0189] 合成方法同实施例4。白色固体。产率40％。^{1}H NMR(400MHz,DMSO-d_6) δ9.14(s,1H),8.20(s,1H),7.89(s,1H),7.80(s,1H),7.59(s,1H),3.88(dt,J＝ 13.3,3.9Hz,2H),3.21(t,J＝6.8Hz,2H),3.13-3.00(m,2H),2.09(s,3H),2.04 (t,J＝6.8Hz,2H),1.78(td,J＝12.5,4.0Hz,2H),1.44(d,J＝13.0Hz,2H).^{13}C NMR(101MHz,DMSO-d_6)δ180.38,165.35,159.12,157.95,134.97,126.80, 115.50,111.34,44.42,42.27,38.40,32.11,31.71,16.82.HRMS-ESI:calcd for $C_{17}H_{21}F_2N_7O$[M+H]$^+$378.1855,found:378.1851.

[0190] 实施例24、本发明化合物的制备

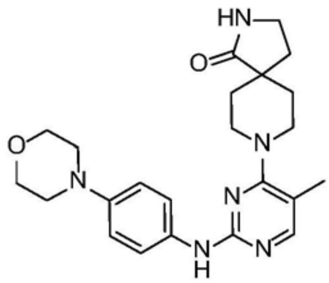
[0191] 8-(5-methyl-2-((1-(methyl-d_3)-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)-2,8-di azaspiro[4.5]decan-1-one

[0192] 

[0193] 合成方法同实施例4。白色固体。产率38％。^{1}H NMR(400MHz,DMSO-d_6) δ8.79(s,1H),7.82(s,1H),7.73(s,1H),7.57(s,1H),7.45(s,1H),3.85(d,J＝ 13.3Hz,2H),3.21(t,J＝6.8Hz,2H),3.02(t,J＝11.5Hz,2H),2.10-2.00(m, 5H),1.77(td,J＝12.9,3.8Hz,2H),1.44(d,J＝13.2Hz,2H).^{13}C NMR(101 MHz,DMSO-d_6)δ180.47,165.47,159.10,158.32,129.96,124.56,120.02,44.46, 42.32,38.42,32.10,31.66,16.72.HRMS-ESI:calcd for $C_{17}H_{20}D_3N_7O$[M+H]$^+$ 345.2231,found:345.2226.

[0194] 实施例25、本发明化合物的制备

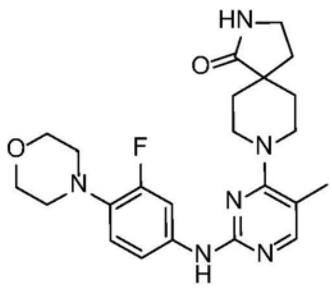
[0195] 8-(5-methyl-2-((4-morpholinophenyl)amino)pyrimidin-4-yl)-2,8-diazaspiro[4.5]decan-1-one

[0196] 

[0197] 合成方法同实施例4。白色固体。产率40％。^{1}H NMR(400MHz,DMSO-d_6) δ8.76(s,1H),7.84(s,1H),7.58(d,J＝9.0Hz,3H),6.84(d,J＝9.0Hz,2H), 3.88(d,J＝13.8Hz,2H),3.72(t,4H),3.20(t,J＝6.8Hz,2H),3.12-2.90(m,6H), 2.08(s,3H),2.03(t,J＝6.8Hz,2H),1.77(td,J＝12.5,12.1,3.9Hz,2H),1.43(d, J＝13.1Hz,2H).^{13}C NMR(101MHz,DMSO-d_6)δ180.45,165.02,158.98, 158.73,145.84,134.49,119.80,118.06,116.19,107.51,66.68,49.97,44.40, 42.32,38.42,32.09,31.70,16.85.HRMS-ESI:calcd for $C_{23}H_{30}N_6O_2$ $[M+H]^+$ 423.2509,found:423.2508.

[0198] 实施例26、本发明化合物的制备

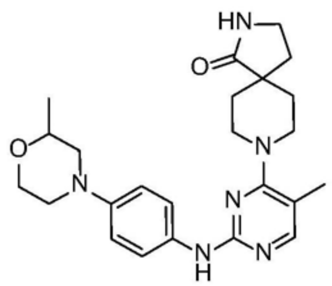
[0199] 8-(2-((3-fluoro-4-morpholinophenyl)amino)-5-methylpyrimidin-4-yl)-2,8-dia zaspiro[4.5]decan-1-one

[0200] 

[0201] 合成方法同实施例4。黄色固体。产率40％。^{1}H NMR(400MHz,DMSO-d_6) δ9.07(s,1H),7.88(s,1H),7.72(dd,J＝15.9,2.4Hz,1H),7.58(s,1H),7.39(dd, J＝8.8,2.4Hz,1H),6.93(t,J＝10.1,8.8Hz,1H),3.91(dt,J＝13.3,4.0Hz,2H), 3.77-3.65(m,4H),3.21(t,J＝6.8Hz,2H),3.14-3.00(m,2H),2.99-2.84(m, 4H),2.10(s,3H),2.04(t,J＝6.8Hz,2H),1.78(td,J＝12.5,3.9Hz,2H),1.44(d, J＝13.1Hz,2H).^{13}C NMR(101MHz,DMSO-d_6)δ 180.38,164.89,158.92, 158.30,137.58,137.47,133.22,119.61,119.56,114.37,114.34,108.27,106.82, 106.56,66.77,51.57,51.54,44.39,42.29,38.41,32.10,31.71,16.92.HRMS-ESI: calcd for $C_{23}H_{29}FN_6O_2$$[M+H]^+$441.2415,found:441.2414.

[0202] 实施例27、本发明化合物的制备

[0203] 8-(5-methyl-2-((4-(2-methylmorpholino)phenyl)amino)pyrimidin-4-yl)-2,8-d iazaspiro[4.5]decan-1-one

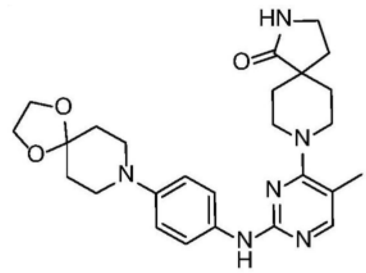
[0204] 

[0205] 合成方法同实施例4。白色固体。产率40％。^{1}H NMR(400MHz,DMSO-d_6) δ8.76(s,1H),7.84(s,1H),7.66-7.52(m,3H),6.84(d,J＝9.1Hz,2H), 3.95-3.81(m,3H),3.69-3.56(m,2H),3.45(dd,J＝11.7,2.5Hz,1H),3.40-3.32 (m,1H),3.20(t,J＝6.8Hz,2H),3.09-2.97(m,2H),2.58(dd,J＝11.7,3.4Hz, 1H),2.25(t,J＝11.7,10.0Hz,1H),2.08(s,3H),2.03(t,J＝6.8Hz,2H),1.77(td, J＝12.5,3.9Hz,2H),1.44(d,J＝13.1Hz,2H),1.14(d,J

=6.2Hz,3H).^{13}C NMR(101MHz,DMSO-d_6)δ180.43,165.02,159.00,158.73,145.67,134.41,119.79,116.21,107.47,71.65,66.39,56.13,49.21,44.41,42.32,38.41,32.10, 31.70,19.36,16.85.HRMS-ESI:calcd for $C_{24}H_{32}N_6O_2$[M+H]$^+$437.2666,found: 437.2663.

[0206] 实施例28、本发明化合物的制备

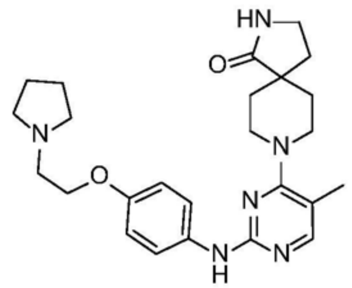
[0207] 8-(2-((4-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)phenyl)amino)-5-methylpyrim idin-4-yl)-2,8-diazaspiro[4.5]decan-1-one

[0208] 

[0209] 合成方法同实施例4,由4a与对应的5合成。淡黄色固体。产率35%。^{1}H NMR(400MHz,DMSO-d_6)δ8.74(s,1H),7.83(s,1H),7.62-7.51(m,3H), 6.84(dt,J=9.1,3.2Hz,2H),3.94-3.81(m,3H),3.40-3.34(m,2H),3.20(t,J= 6.8Hz,2H),3.16-3.11(m,2H),3.09-2.95(m,5H),2.08(s,3H),2.03(t,J=6.8 Hz,2H),1.84-1.66(m,6H),1.44(d,J=14.8Hz,2H).^{13}C NMR(101MHz, DMSO-d_6)δ180.45,165.03,158.97,158.75,145.60,119.84,116.92,98.09, 59.15,47.35,44.40,42.32,38.41,33.18,32.13,32.10,31.70,19.61,16.84,14.29. HRMS-ESI:calcd for $C_{26}H_{34}N_6O_3$[M+H]$^+$479.2771,found:479.2764.

[0210] 实施例29、本发明化合物的制备

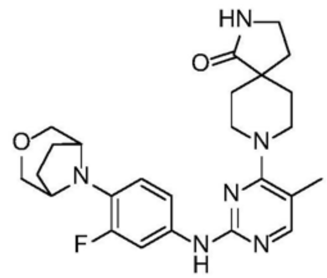
[0211] 8-(5-methyl-2-((4-(2-(pyrrolidin-1-yl)ethoxy)phenyl)amino)pyrimidin-4-yl)- 2,8-diazaspiro[4.5]decan-1-one

[0212] 

[0213] 合成方法同实施例4。褐色固体。产率25%。^{1}H NMR(400MHz,DMSO-d_6) δ10.85(s,1H),9.47(s,1H),7.83(s,1H),7.70-7.49(m,3H),7.06-6.91(m,2H), 4.31(t,J=5.0Hz,2H),4.12-3.98(m,2H),3.64-3.47(m,4H),3.25-3.00(m, 6H),2.14(s,3H),2.04(t,J=6.8Hz,2H),2.01-1.84(m,4H),1.82-1.70(m,2H), 1.47(d,J=13.2Hz,2H).^{13}C NMR(101MHz,DMSO-d_6)δ180.43,165.00, 158.96,158.67,152.73,135.44,120.14,114.94,107.72,56.49,54.32,54.20, 44.39,42.32,38.42,32.08,31.70,23.37,19.01,16.87.HRMS-ESI:calcd for $C_{25}H_{34}N_6O_2$[M+H]$^+$451.2822,found:451.2816.

[0214] 实施例30、本发明化合物的制备

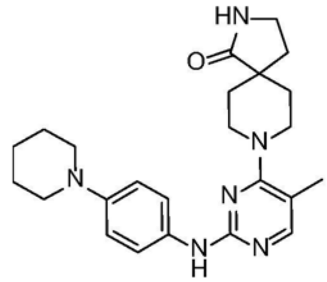
[0215] 8-(2-((4-(3-oxa-8-azabicyclo[3.2.1]octan-8-yl)-3-fluorophenyl)amino)-5-met hylpyrimidin-4-yl)-2,8-diazaspiro[4.5]decan-1-one

[0216] 

[0217] 合成方法同实施例4。淡黄色固体。产率29％。^{1}H NMR(400MHz，DMSO-d_6)δ8.99(s,1H),7.91-7.85(m,1H),7.72(dd,J＝16.3,2.5Hz,1H)，7.58(s,1H),7.28(dd,J＝9.0,2.5Hz,1H),6.90-6.83(m,1H),3.90(d,J＝13.3 Hz,2H),3.84(s,2H),3.73(d,J＝10.6Hz,2H),3.55-3.46(m,2H),3.21(t,J＝ 6.8Hz,2H),3.06(t,J＝12.4Hz,2H),2.09(s,3H),2.04(t,J＝6.8Hz,2H)，1.89-1.82(m,3H),1.82-1.72(m,2H),1.44(d,J＝13.3Hz,2H).^{13}C NMR(101 MHz,DMSO-d_6)δ180.39,164.93,158.94,158.39,130.53,118.13,114.59，108.04,107.28,107.03,71.54,59.19,59.16,44.39,42.30,38.41,32.11,31.72，26.50,16.91.HRMS-ESI:calcd for $C_{25}H_{31}FN_6O_2$[M+H]$^+$467.2572,found: 467.2567.

[0218] 实施例31、本发明化合物的制备

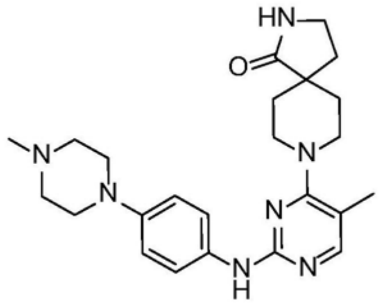
[0219] 8-(5-methyl-2-((4-(piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)-2,8-diazaspi ro[4.5]decan-1-one

[0220] 

[0221] 合成方法同实施例4。淡褐色固体。产率30％。^{1}H NMR(400MHz，DMSO-d_6)δ8.72(s,1H),7.83(s,1H),7.64-7.47(m,3H),6.82(d,J＝9.1Hz，2H),3.87(dt,J＝13.3,4.0Hz,2H),3.20(t,J＝6.8Hz,2H),3.0-2.90(m,6H)，2.08(s,3H),2.03(t,J＝6.8Hz,2H),1.77(td,J＝12.3,11.7,3.9Hz,2H)，1.68-1.55(m,4H),1.54-1.47(m,2H),1.43(d,J＝13.2Hz,2H).^{13}C NMR(101 MHz,DMSO-d_6)δ180.46,165.02,158.96,158.76,146.80,134.02,119.83,117.11,107.43,51.24,44.40,42.32,38.42,32.09,31.69,26.00,24.35,16.84. HRMS-ESI:calcd for $C_{24}H_{32}N_6O$[M+H]$^+$421.2717,found:421.2714.

[0222] 实施例32、本发明化合物的制备

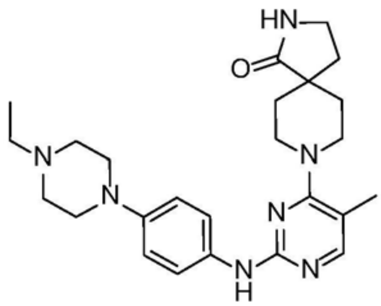
[0223] 8-(5-methyl-2-((4-(4-methylpiperazin-1-yl)phenyl)amino)pyrimidin-4-yl)-2，8-diazaspiro[4.5]decan-1-one

[0224] 

[0225] 合成方法同实施例4。淡褐色固体。产率30％。^{1}H NMR(400MHz, DMSO-d_6)δ8.74(s,1H),7.83(s,1H),7.56(d,J＝9.1Hz,3H),6.86-6.80(m, 2H),3.88(d,J＝13.3Hz,2H),3.20(t,J＝6.8Hz,2H),3.03(t,J＝4.9Hz,6H), 2.46(d,J＝4.7Hz,4H),2.22(s,3H),2.08(d,J＝1.8Hz,3H),2.03(t,J＝6.8Hz, 2H),1.82-1.71(m,3H),1.43(d,J＝13.2Hz,2H).^{13}C NMR(101MHz, DMSO-d_6)δ180.47,165.01,158.96,158.71,145.66,134.29,119.80,116.51,107.48,54.97,54.88,49.26,45.83,44.40,42.33,38.42,32.08,31.68,16.85. HRMS-ESI: calcd for $C_{24}H_{33}N_7O$[M+H]$^+$436.2826,found:436.2819.

[0226] 实施例33、本发明化合物的制备

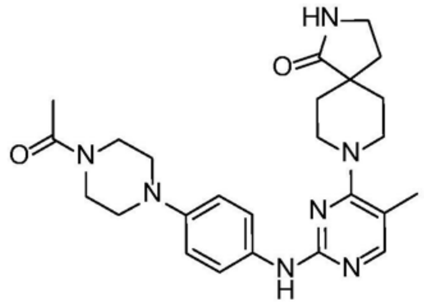
[0227] 8-(2-((4-(4-ethylpiperazin-1-yl)phenyl)amino)-5-methylpyrimidin-4-yl)-2,8- diazaspiro[4.5]decan-1-one

[0228] 

[0229] 合成方法同实施例4。淡黄色固体。产率32％。^{1}H NMR(400MHz, DMSO-d_6)δ8.76(s,1H),7.89-7.80(m,1H),7.67-7.51(m,3H),6.84(d,J＝9.1 Hz,2H),3.93-3.84(m,3H),3.68-3.58(m,2H),3.21(t,J＝6.8Hz,2H),3.02(t,J ＝12.0Hz,2H),2.08(s,3H),2.03(t,J＝6.8Hz,2H),1.77(td,J＝12.6,3.9Hz, 2H),1.44(d,J＝13.3Hz,2H),1.25(d,J＝9.3Hz,2H),1.14(d,J＝6.2Hz,3H). ^{13}C NMR(101MHz,DMSO-d_6)δ180.44,165.01,158.96,158.71,145.68, 134.39,119.81,116.21,107.47,71.65,66.39,56.13,49.21,44.41,42.32,38.42, 32.10,31.71,19.35,16.85.HRMS-ESI:calcd for $C_{25}H_{35}N_7O$[M+H]$^+$450.2982,found:450.2988.

[0230] 实施例34、本发明化合物的制备

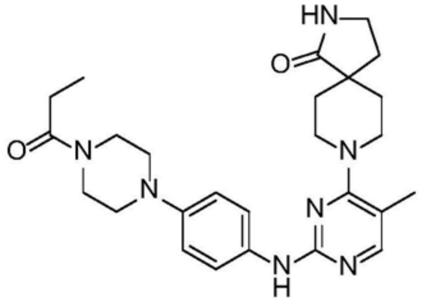
[0231] 8-(2-((4-(4-acetylpiperazin-1-yl)phenyl)amino)-5-methylpyrimidin-4-yl)-2,8 -diazaspiro[4.5]decan-1-one

[0232] 

[0233] 合成方法同实施例4。淡黄色固体。产率30％。^{1}H NMR(400MHz, DMSO-d_6)δ8.79(s,1H),7.84(s,1H),7.66-7.52(m,3H),6.87(d,J＝9.1Hz, 2H),3.88(d,J＝13.3Hz,2H),3.56(q,J＝5.0Hz,4H),3.20(t,J＝6.7Hz,2H), 3.11-2.99(m,4H),2.97(t,J＝5.3Hz,2H),2.08(s,3H),2.06-1.96(m,5H),1.77 (td,J＝12.5,4.0Hz,2H),1.44(d,J＝13.2Hz,2H).^{13}C NMR(101MHz, DMSO-d_6)δ180.42,168.67,164.99,158.80,158.61,145.62,134.72,119.81,117.14,107.56,50.34,49.90,46.12,44.41,42.31,41.29,38.41,32.10,31.71, 21.66,16.87.HRMS-ESI:calcd for $C_{25}H_{33}N_7O$[M+H]$^+$464.2775,found: 464.2769.

[0234] 实施例35、本发明化合物的制备

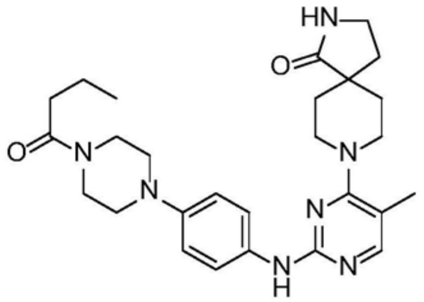
[0235] 8-(5-methyl-2-((4-(4-propionylpiperazin-1-yl)phenyl)amino)pyrimidin-4-yl)- 2,8-diazaspiro[4.5]decan-1-one

[0236] 

[0237] 合成方法同实施例4。淡黄色固体。产率30％。^{1}H NMR(400MHz, DMSO-d_6)δ8.78(s,1H),7.84(s,1H),7.59(d,J＝9.3Hz,3H),6.87(d,J＝9.0 Hz,2H),3.89(d,J＝13.2Hz,2H),3.58(s,4H),3.21(t,J＝6.8Hz,2H), 3.07-2.95(m,6H),2.38-2.31(m,2H),2.11-2.07(m,3H),2.04(t,J＝6.8Hz, 2H),1.77(td,J＝12.2,11.6,3.9Hz,2H),1.44(d,J＝13.2Hz,2H),1.01(t,J＝ 7.4Hz,3H).^{13}C NMR(101MHz,DMSO-d_6)δ180.47,171.83,165.01,158.94,158.69,145.60,134.76,119.77,117.13,107.57,44.40,42.32,38.42,32.09,31.69,25.99,19.00,16.85,9.86.HRMS-ESI:calcd for $C_{26}H_{35}N_7O_2$[M+H]$^+$478.2941, found: 478.2928.

[0238] 实施例36、本发明化合物的制备

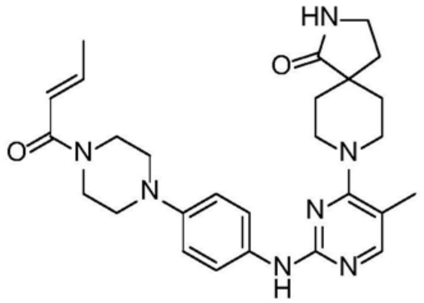
[0239] 8-(2-((4-(4-butyrylpiperazin-1-yl)phenyl)amino)-5-methylpyrimidin-4-yl)-2, 8-diazaspiro[4.5]decan-1-one

[0240] 

[0241] 合成方法同实施例4。淡黄色固体。产率30％。^{1}H NMR(400MHz, DMSO-d_6)δ8.78(s,1H),7.84(s,1H),7.59(d,J＝9.0Hz,3H),6.87(d,J＝8.8 Hz,2H),3.89(dd,J＝13.3,3.8Hz,2H),3.58(q,J＝4.8Hz,4H),3.21(t,J＝6.8 Hz,2H),3.10-2.93(m,6H),2.32(t,J＝7.4Hz,2H),2.09(s,3H),2.04(t,J＝6.8 Hz,2H),1.78(td,J＝12.4,11.7,4.0Hz,2H),1.60-1.39(m,4H),0.90(t,J＝7.4 Hz,3H).^{13}C NMR(101MHz,DMSO-d_6)δ180.46,171.00,165.01,158.96, 158.70,145.59,134.79,119.77,117.14,107.57,44.40,42.32,38.42,34.64,32.10, 31.70,18.69,16.85,15.62,14.27.HRMS-ESI:calcd for $C_{27}H_{37}N_7O_2$[M+H]$^+$ 492.3088,found:492.3089.

[0242] 实施例37、本发明化合物的制备

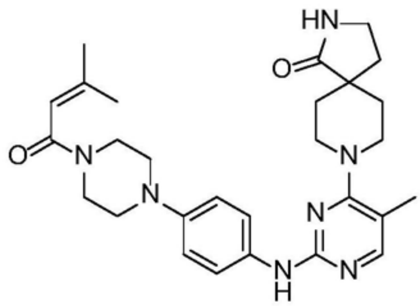
[0243] (E)-8-(2-((4-(4-(but-2-enoyl)piperazin-1-yl)phenyl)amino)-5-methylpyrimidi n-4-yl)-2,8-diazaspiro[4.5]decan-1-one

[0244] 

[0245] 合成方法同实施例4。淡黄色固体。产率30％。^{1}H NMR(400MHz, DMSO-d_6)δ8.77(s,1H),7.84(s,1H),7.59(d,J＝9.0Hz,3H),6.88(d,J＝8.9 Hz,2H),6.77-6.65(m,1H),6.54(dd,J＝15.0,1.8Hz,1H),3.93-3.84(m,2H), 3.66(s,4H),3.21(t,J＝6.8Hz,2H),3.14-2.83(m,6H),2.09(s,3H),2.04(t,J＝ 6.8Hz,2H),1.85(dd,J＝6.7,1.5Hz,3H),1.77(td,J＝12.6,11.6,4.1Hz,2H), 1.44(d,J＝13.1Hz,2H).^{13}C NMR(101MHz,DMSO-d_6)δ180.48,165.01, 164.80,158.94,158.69,145.54,141.27,134.79,122.31,119.79,117.15,107.58, 44.40,42.32,38.43,32.09,31.69,18.23,16.85.HRMS-ESI:calcd for $C_{27}H_{35}N_7O_2$[M+H]$^+$490.2931,found:490.2921.

[0246] 实施例38、本发明化合物的制备

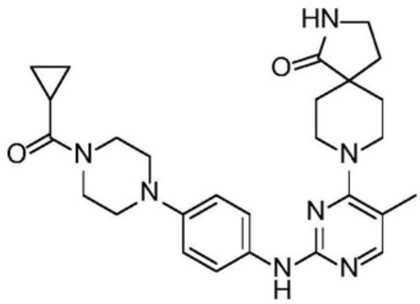
[0247] 8-(5-methyl-2-((4-(4-(3-methylbut-2-enoyl)piperazin-1-yl)phenyl)amino)pyr imidin-4-yl)-2,8-diazaspiro[4.5]decan-1-one

[0248] 

[0249] 合成方法同实施例4。淡黄色固体。产率32％。^{1}H NMR(400MHz, DMSO-d_6)δ8.78(s,1H),7.84(s,1H),7.59(d,J＝9.1Hz,3H),6.86(d,J＝9.0 Hz,2H),5.94(p,J＝1.3Hz,1H),3.88(d,J＝13.3Hz,2H),3.59(s,4H),3.20(t, J＝6.8Hz,2H),3.12-2.88(m,6H),2.08(s,3H),2.03(t,J＝6.8Hz,2H), 1.90-1.67(m,8H),1.43(d,J＝13.0Hz,2H).HRMS-ESI:calcd for $C_{28}H_{37}N_7O_2$ $[M+H]^+$504.3088,found:504.3085.

[0250] 实施例39、本发明化合物的制备

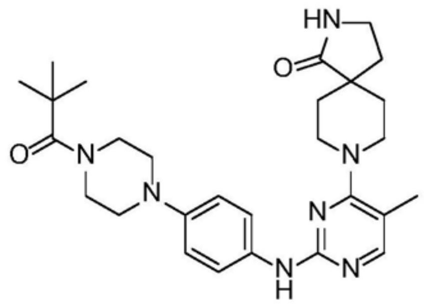
[0251] 8-(2-((4-(4-(cyclopropanecarbonyl)piperazin-1-yl)phenyl)amino)-5-methylp yrimidin-4-yl)-2,8-diazaspiro[4.5]decan-1-one

[0252] 

[0253] 合成方法同实施例4。淡黄色固体。产率31％。^{1}H NMR(400MHz, DMSO-d_6)δ8.78(s,1H),7.84(s,1H),7.67-7.53(m,3H),6.88(d,J＝9.0Hz, 2H),3.93-3.84(m,2H),3.80(s,2H),3.60(s,2H),3.21(t,J＝6.8Hz,2H), 3.15-2.91(m,6H),2.15-1.95(m,6H),1.77(td,J＝12.3,11.7,3.9Hz,2H),1.44 (d,J＝13.1Hz,2H),0.84-0.65(m,4H).^{13}C NMR(101MHz,DMSO-d_6)δ 180.44,171.51,165.02,158.96,158.71,145.59,134.80,119.76,117.13,107.57, 44.41,42.31,38.42,32.11,31.72,16.85,10.76,7.47.HRMS-ESI:calcd for $C_{27}H_{35}N_7O_2$$[M+H]^+$490.2931,found:490.2928.

[0254] 实施例40、本发明化合物的制备

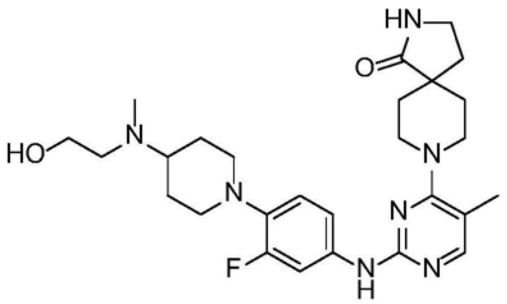
[0255] 8-(5-methyl-2-((4-(4-pivaloylpiperazin-1-yl)phenyl)amino)pyrimidin-4-yl)-2 ,8-diazaspiro[4.5]decan-1-one

[0256] 

[0257] 合成方法同实施例4。淡黄色固体。产率30％。^{1}H NMR(400MHz, DMSO-d_6)δ8.79(s, 1H),7.84(s,1H),7.59(d,J=9.1Hz,3H),6.86(d,J=9.1 Hz,2H),3.88(d,J=13.2Hz,2H),3.68(t,J=4.9Hz,4H),3.20(t,J=6.8Hz, 2H),3.13-2.88(m,6H),2.08(s,3H),2.03(t,J=6.8Hz,2H),1.77(td,J=12.3, 11.6,4.0Hz,2H),1.44(d,J=13.1Hz,2H),1.22(s,9H).HRMS-ESI:calcd for $C_{28}H_{39}N_7O_2$[M+H]$^+$506.3244,found:506.3237.

[0258] 实施例41、本发明化合物的制备

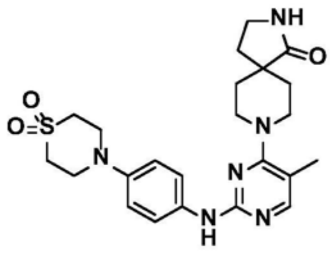
[0259] 8-(2-((3-fluoro-4-(4-((2-hydroxyethyl)(methyl)amino)piperidin-1-yl)phenyl) amino)-5-methylpyrimidin-4-yl)-2,8-diazaspiro[4.5]decan-1-one

[0260] 

[0261] 合成方法同实施例4。淡黄色固体。产率25%。^{1}H NMR(400MHz, DMSO-d_6)δ9.04(s,1H),7.88(s,1H),7.69(dd,J=15.7,2.4Hz,1H),7.59(s, 1H),7.35(dd,J=8.7,2.4Hz,1H),6.92(t,1H),4.27(s,1H),3.90(d,J=13.5Hz, 2H),3.44(s,2H),3.26(s,2H),3.21(t,J=6.8Hz,2H),3.06(t,J=12.4Hz,2H), 2.58(t,J=11.5Hz,2H),2.41(t,J=11.4Hz,1H),2.22(s,3H),2.09(d,J=4.7 Hz,3H),2.04(t,J=6.8Hz,2H),1.84-1.69(m,4H),1.61-1.53(m,2H),1.44(d, J=13.2Hz,2H).^{13}C NMR(101MHz,DMSO-d_6)δ180.39,164.89,158.92,158.33,119.95,119.91,114.30,114.27,108.18,106.78,106.52,61.12,59.62, 55.98,51.26,51.23,44.38,42.30,38.41,38.34,32.10,31.70,28.26,16.91. HRMS-ESI:calcd for $C_{27}H_{38}FN_7O_2$[M+H]$^+$512.3150,found:512.3149.

[0262] 实施例42、本发明化合物的制备

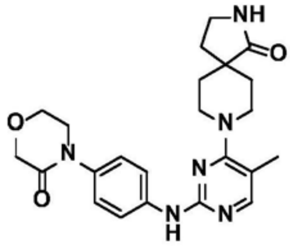
[0263] 8-(2-((4-(1,1-dioxidothiomorpholino)phenyl)amino)-5-methylpyrimidin-4-yl)-2,8-diazaspiro[4.5]decan-1-one

[0264] 

[0265] 称取中间体a(260mg,0.93mmol)与相应的胺(226mg,1mmol)于50ml 的圆底烧瓶中,加入20mL正丁醇溶解,常温下加入2-3滴浓HCl,将反应 体系置于115℃油浴锅中反应,反应6-8小时。通过TLC检测,反应结束后, 利用减压蒸馏将溶剂旋干,加入100目粗硅胶拌样,利用Flash柱分离纯化 得类白色固体产物。产率9%。^{1}H NMR(400MHz,DMSO-d_6)δ8.85(s,1H), 7.84(s,1H),7.66-7.57(m,3H),6.98-6.89(m,2H),3.89(dt,J=13.4,3.8Hz, 2H),3.69-3.59(m,4H),3.21(t,J=6.8Hz,2H),3.16-3.09(m,4H),3.08- 2.7(m,2H),2.09(s,3H),2.03(t,J=6.8Hz,2H),1.77(td,J=12.6,3.9Hz,2H), 1.44(d,J=13.0Hz,2H).^{13}C NMR(101MHz,DMSO-d_6)δ180.42,164.99, 158.91,158.62,142.56,134.90,119.90,119.90, 117.33,117.33,107.64,50.45, 48.40,48.40,44.40,44.40,42.31,42.31,38.42,32.09, 32.09,31.69, 16.87.HRMS-ESI:calculated for $C_{23}H_{30}N_6O_3S[M+H]^+$471.2178,found: 471.2176.

[0266] 实施例43、本发明化合物的制备

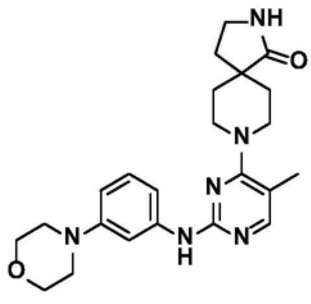
[0267] 4-(4-((5-methyl-4-(1-oxo-2,8-diazaspiro[4.5]decan-8-yl)pyrimidin-2-yl)amin o)phenyl)morpholin-3-one

[0268] 

[0269] 合成方法与实施例42相同。灰白色固体产物，产率10％。^{1}H NMR(400 MHz,DMSO-d_6) δ9.26(s,1H),7.89(s,1H),7.80-7.69(m,2H),7.61(s,1H), 7.28-7.19(m,2H),4.17(s,2H),4.00-3.90(m,4H),3.21(t,J＝6.8Hz,2H), 3.12-3.04(m,4H),2.12(s,3H),2.04(t,J＝6.8Hz,2H),1.78(td,J＝12.6,12.2, 3.9Hz,2H),1.51-1.41(m,2H).^{13}C NMR(101MHz,DMSO-d_6)δ180.37, 166.33,164.81,157.77,139.86,134.91,134.91,126.11,118.84,118.84,118.84,108.36, 68.20,64.00,49.71,44.43,42.29,38.42,38.42,32.11,31.69,31.69,17.02, 9.03.HRMS-ESI:calculated for $C_{23}H_{28}N_6O_3[M+H]^+$437.2301,found:437.2297.

[0270] 实施例44、本发明化合物的制备

[0271] 8-(5-methyl-2-((3-morpholinophenyl)amino)pyrimidin-4-yl)-2,8-diazaspiro[4.5]decan-1-one

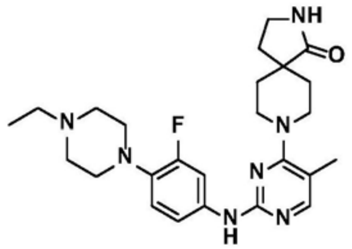
[0272] 

[0273] 合成方法与实施例42相同。得到褐白色固体产物，产率8％。^{1}H NMR(400 MHz,DMSO-d_6)δ8.90(s,1H),7.89(s,1H),7.61(s,1H),7.50(t,J＝2.2Hz, 1H),7.15(dd,J＝7.9,1.8Hz,1H),7.06(t,J＝8.0Hz,1H),6.47(dd,J＝8.0,2.3 Hz,1H),3.88(dt,J＝13.4,3.9Hz,2H),3.73(t,J＝4.7Hz,4H),3.21(t,J＝6.8 Hz,2H),3.06(dd,J＝5.8,3.6Hz,4H),3.02(d,J＝11.1Hz,2H),2.10(s,3H), 2.03(t,J＝6.8Hz,2H),1.78(td,J＝12.6,4.0Hz,2H),1.43(d,J＝13.2Hz,2H). ^{13}C NMR(101MHz,DMSO-d_6)δ180.46,165.14,159.01,158.56,151.96, 142.46,129.20,110.31,108.36,108.24,105.77,66.63,66.63,49.35,49.35,44.52, 42.25,42.25,38.42,32.14,32.14,31.68,16.76.HRMS-ESI:calculated for $C_{23}H_{30}N_6O_2[M+H]^+$423.2508,found:423.2503.

[0274] 实施例45、本发明化合物的制备

[0275] 8-(2-((4-(4-ethylpiperazin-1-yl)-3-fluorophenyl)amino)-5-

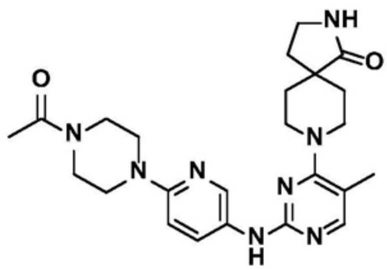
methylpyrimidin-4 -yl)-2,8-diazaspiro[4.5]decan-1-one

[0276] 

[0277] 称取中间体a(260mg,0.93mmol)与相应的胺(223mg,1mmol)于50ml 的圆底烧瓶中,加入$CsCO_3$(650mg,2mmol),加入110mg 1,1'-双(二苯基膦) 二茂铁(dppf)作配体(110mg,0.2mmol),加入一小匙$Pd(dba)_3$作为催化剂, 加入20ml二氧六环作溶剂,N_2保护,将反应体系放置115℃油浴锅中反应, 反应6-8小时。通过TLC检测,反应结束后,利用减压蒸馏将溶剂旋干,加 入100目粗硅胶拌样,利用Flash柱分离纯化得褐黄色固体产物。产率8%。^1H NMR(400MHz,DMSO-d_6)δ9.06(s,1H),7.88(s,1H),7.71(dd,J=15.8, 2.4Hz,1H),7.60(s,1H),7.36(dd,J=8.7,2.4Hz,1H),6.98-6.86(m,1H),3.90 (dt,J=13.4,3.9Hz,2H),3.42(s,4H),3.21(t,J=6.8Hz,2H),3.12-3.00(m, 2H),2.93(t,J=4.8Hz,4H),2.37(q,J=7.2Hz,2H),2.10(s,3H),2.04(t,J= 6.8Hz,2H),1.77(td,J=12.6,3.9Hz,2H),1.44(d,J=13.3Hz,2H),1.02(t,J= 7.2Hz,3H).^{13}C NMR(101MHz,Chloroform-d)δ181.81,165.44,158.47, 157.99,156.90,154.47,136.13,136.03,134.14,134.05,119.11,119.07,114.28, 114.25,108.66,107.72,107.46,52.94,52.36,50.99,50.96,44.32,42.34,38.81, 32.18,32.02,16.74,11.93.HRMS-ESI:calculated for $C_{25}H_{34}FN_7O[M+H]^+$ 468.2887,found:468.2881.

[0278] 实施例46、本发明化合物的制备

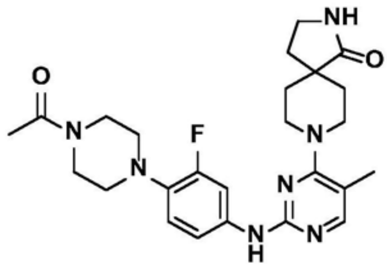
[0279] 8-(2-((6-(4-acetylpiperazin-1-yl)pyridin-3-yl)amino)-5-methylpyrimidin-4-yl)-2,8-diazaspiro[4.5]decan-1-one

[0280] 

[0281] 合成方法与实施例45相同。褐白色固体产物,产率3%。^1H NMR(400 MHz,DMSO-d_6)δ 8.82(s,1H),8.46(d,J=2.6Hz,1H),7.92(dd,J=9.1,2.7Hz, 1H),7.84(s,1H),7.60(s,1H),6.82(d,J=9.1Hz,1H),3.91-3.83(m,2H),3.56 -3.42(m,8H),3.21(t,J=6.8Hz,2H),3.01(t,J=12.1Hz,2H),2.09(s,3H), 2.04(d,J=3.5Hz,5H),1.76(td,J=12.7,3.9Hz,2H),1.43(d,J=13.2Hz,2H). HRMS-ESI:calculated for $C_{24}H_{32}N_8O_2[M+H]^+$465.2726,found:465.2728.

[0282] 实施例47、本发明化合物的制备

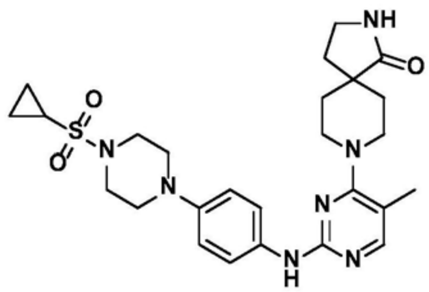
[0283] 8-(2-((4-(4-acetylpiperazin-1-yl)-3-fluorophenyl)amino)-5-methylpyrimidin- 4-yl)-2,8-diazaspiro[4.5]decan-1-one

[0284] 

[0285] 合成方法与实施例45相同，得到褐白色固体产物。产率3％。^{1}H NMR(400 MHz, DMSO-d_6) δ9.11(s,1H),7.89(s,1H),7.82-7.68(m,1H),7.60(s,1H), 7.43-7.33(m,1H), 6.95(q,J＝9.2Hz,1H),3.91(d,J＝13.2Hz,2H),3.57(q,J ＝4.9Hz,4H),3.21(t,J＝6.7Hz,2H),3.07(t,J＝12.1Hz,2H),2.89(dt,J＝ 25.9,5.1Hz,4H),2.10(s,3H),2.05(d,J＝7.2Hz,2H),2.03(s,3H),1.84-1.70 (m,2H),1.44(d,J＝13.2Hz,2H).HRMS-ESI: calculated for $C_{25}H_{32}FN_7O_2$ $[M+H]^+$482.2680,found:482.2672.

[0286] 实施例48、本发明化合物的制备

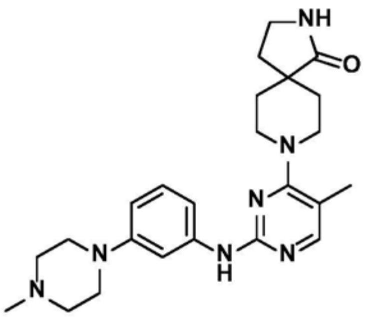
[0287] 8-(2-((4-(4-(cyclopropylsulfonyl)piperazin-1-yl)phenyl)amino)-5-methylpyri midin-4-yl)-2,8-diazaspiro[4.5]decan-1-one

[0288] 

[0289] 合成方法与实施例45相同，得到灰白色固体产物，产率2％。^{1}H NMR(400 MHz, DMSO-d_6) δ8.82(s,1H),7.84(s,1H),7.61(d,J＝9.0Hz,3H),6.92- 6.83(m,2H),3.92-3.83 (m,2H),3.33(s,2H),3.31(s,2H),3.21(t,J＝6.8Hz, 2H),3.12(dd,J＝6.3,3.7Hz,4H), 3.08-2.98(m,2H),2.69-2.60(m,1H),2.08 (s,3H),2.04(t,J＝6.8Hz,2H),1.82-1.71(m, 2H),1.44(d,J＝13.3Hz,2H), 1.01(dt,J＝8.0,3.1Hz,2H),0.95(dt,J＝5.2,3.0Hz,2H) .^{13}C NMR(101MHz, Chloroform-d)δ181.44,165.21,156.99,155.90,146.06,133.73, 120.64,120.64, 117.87,117.87,107.90,50.30,50.30,46.22,44.31,44.31,42.08, 42.08,38.74, 38.74,32.32,32.32,25.44,17.05,4.37,4.37.HRMS-ESI:calculated for $C_{26}H_{35}N_7O_3S$$[M+H]^+$526.2600,found:526.2592.

[0290] 实施例49、本发明化合物的制备

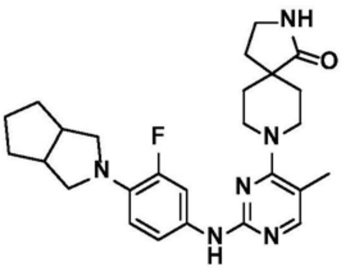
[0291] 8-(5-methyl-2-((3-(4-methylpiperazin-1-yl)phenyl)amino)pyrimidin-4-yl)-2, 8-diazaspiro[4.5]decan-1-one

[0292] 

[0293] 称取中间体a(260mg,0.93mmol)与相应的胺(191mg,1mmol)于50ml 圆底烧瓶中,加入$CsCO_3$(650mg,2mmol),加入4,5-双二苯基膦-9,9-二甲基 氧杂蒽(XantPhos)作配体(116mg,0.2mmol),加入一小匙Pd(dba)$_3$作为催化 剂,加入20ml二氧六环作溶剂,N_2保护,将反应体系放置115℃油浴锅中 反应,反应6-8小时。通过TLC检测,反应结束后,利用减压蒸馏将溶剂旋 干,加入100目粗硅胶拌样,利用Flash柱分离纯化得浅褐色固体产物。产 率3%。^{1}H NMR(400MHz,DMSO-d_6)δ8.87(s,1H),7.89(s,1H),7.61(s,1H), 7.50(t,J=2.2Hz,1H),7.11(d,J=7.9Hz,1H),7.04(t,J=8.1Hz,1H),6.45 (dd,J=8.0,2.3Hz,1H),3.88(dt,J=13.2,4.0Hz,2H),3.21(t,J=6.8Hz,2H), 3.09(t,J=5.0Hz,4H),3.01(d,J=11.2Hz,2H),2.44(t,J=5.0Hz,4H),2.22(s, 3H),2.10(s,3H),2.03(t,J=6.8Hz,2H),1.78(td,J=12.6,4.0Hz,2H),1.43(d, J=13.3Hz,2H).HRMS-ESI:calculated for $C_{24}H_{33}N_7O$[M+H]$^+$436.2825,found: 436.2826.

[0294] 实施例50、本发明化合物的制备

[0295] 8-(2-((3-fluoro-4-(hexahydrocyclopenta[c]pyrrol-2(1H)-yl)phenyl)amino)-5- methylpyrimidin-4-yl)-2,8-diazaspiro[4.5]decan-1-one

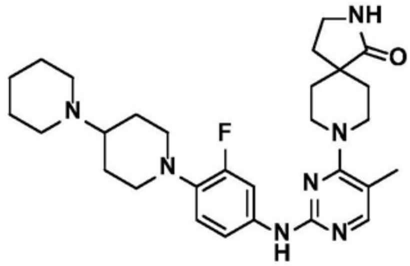
[0296] 

[0297] 合成方法与实施例42相同。灰褐色固体产物。产率10%。^{1}H NMR(400 MHz,DMSO-d_6) δ8.96(s,1H),7.91-7.82(m,1H),7.67(dd,J=16.5,2.4Hz, 1H),7.60(s,1H),7.30(dd,J=8.7,2.4Hz,1H),6.73(dd,J=10.2,8.8Hz,1H), 3.90(d,J=13.3Hz,2H),3.26-3.17(m,4H),3.05(t,J=12.0Hz,2H),2.85(dd, J=9.3,3.3Hz,2H),2.70-2.60(m,2H),2.09(s,3H),2.04(t,J=6.8Hz,2H), 1.77(td,J=14.2,3.4Hz,4H),1.65(dt,J=12.2,5.8Hz,1H),1.53-1.47(m, 1H),1.44(d,J=12.6Hz,4H).^{13}C NMR(101MHz,DMSO-d_6)δ180.39,164.89,158.94,158.38,154.56,152.18,135.16,135.05,131.30,131.20,117.99,117.93,114.52,107.90,106.96,106.70,57.81,57.77,44.38,42.32,42.01,38.41,33.35, 32.07,31.66,26.23,16.90.HRMS-ESI:calculated for $C_{26}H_{33}FN_6O$[M+H]$^+$ 465.2778,found: 465.2776.

[0298] 实施例51、本发明化合物的制备

[0299] 8-(2-((4-([1,4’-bipiperidin]-1’-yl)-3-fluorophenyl)amino)-5-

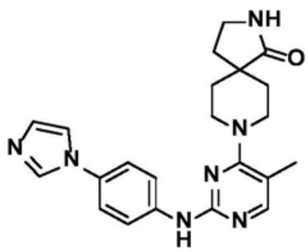
methylpyrimidin- 4-yl)-2,8-diazaspiro[4.5]decan-1-one

[0300] 

[0301] 合成方法与实施例42相同。灰白色固体产物。产率1％。^{1}H NMR(400 MHz,)δ7.83(s,1H),7.63(dd,J＝14.8,2.5Hz,1H),7.06(dd,J＝8.6,2.4Hz, 1H),6.85(t,J＝9.1Hz,1H),6.49-6.31(m,1H),6.10(s,1H),3.94(dt,J＝13.8, 4.5Hz,2H),3.51-3.43(m,2H),3.39(d,J＝6.9Hz,2H),3.11(ddd,J＝13.6, 11.1,2.8Hz,2H),2.72-2.66(m,2H),2.27-2.17(m,4H),2.13(d,J＝3.6Hz, 4H),2.07-1.91(m,10H),1.66-1.50(m,6H)..HRMS-ESI:calculated for $C_{29}H_{40}FN_{7}O$[M+H]$^{+}$522.3356,found:522.3356.

[0302] 实施例52、本发明化合物的制备

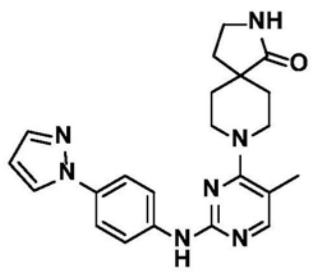
[0303] 8-(2-((4-(1H-imidazol-1-yl)phenyl)amino)-5-methylpyrimidin-4-yl)-2,8-diaz aspiro[4.5]decan-1-one

[0304] 

[0305] 合成方法与实施例45相同。灰白色固体产物。产率11％。^{1}H NMR(400 MHz,DMSO-d_6)δ9.25(s,1H),8.13(s,1H),7.92(s,1H),7.88(d,J＝9.0Hz, 2H),7.66-7.58(m,2H),7.50(d,J＝8.9Hz,2H),7.07(s,1H),3.93(dt,J＝13.3, 4.0Hz,2H),3.22(t,J＝6.8Hz,2H),3.14-3.01(m,2H),2.12(s,3H),2.05(t,J ＝6.8Hz,2H),1.79(td,J＝12.6,3.9Hz,2H),1.46(d,J＝13.2Hz,2H).^{13}C NMR (101MHz,DMSO-d_6)δ180.46,164.92,158.93,158.29,140.74,135.77,130.28, 129.86,121.23,121.23 119.21,119.21,118.59,108.58,44.41,42.33,42.33,38.44, 32.07,32.07,31.69,16.95.HRMS-ESI:calculated for $C_{22}H_{25}N_{7}O$[M+H]$^{+}$ 404.2199,found:404.2196.

[0306] 实施例53、本发明化合物的制备

[0307] 8-(2-((4-(1H-pyrazol-1-yl)phenyl)amino)-5-methylpyrimidin-4-yl)-2,8-diaza spiro[4.5]decan-1-one

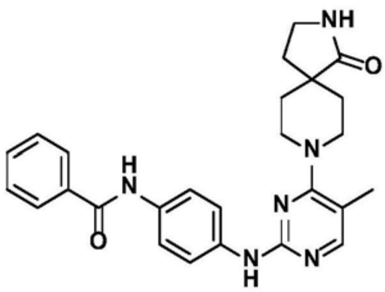
[0308] 

[0309] 合成方法与实施例45相同。灰白色固体产物。产率12％。^{1}H NMR(400 MHz,DMSO-d_6)

δ9.22(s,1H),8.36(d,J=2.5Hz,1H),7.92(s,1H),7.89- 7.82(m,2H),7.71-7.65(m,3H),7.60(s,1H),6.49(t,J=2.1Hz,1H),3.92(dt, J=13.3,4.0Hz,2H),3.21(t,J=6.8Hz,2H),3.13-3.02(m,2H),2.12(s,3H), 2.05(t,J=6.8Hz,2H),1.79(td,J=12.4,11.9,3.9Hz,2H),1.46(d,J=13.1Hz, 2H).^{13}C NMR(101MHz,DMSO-d_6)δ180.43,164.95,158.95,158.35,140.60, 140.15,133.53,127.62,119.25,119.25,119.02,119.02,108.45,107.67,44.42, 42.32,42.32,38.42,32.07,32.07,31.68,16.93.HRMS-ESI:calculated for $C_{22}H_{25}N_7O$[M+H]$^+$404.2199,found:404.2199.

[0310] 实施例54、本发明化合物的制备

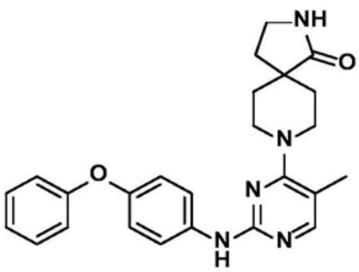
[0311] N-(4-((5-methyl-4-(1-oxo-2,8-diazaspiro[4.5]decan-8-yl)pyrimidin-2-yl)ami no)phenyl)benzamide

[0312] 

[0313] 合成方法与实施例45相同,得到白色固体产物。产率10%。^{1}H NMR(400 MHz,DMSO-d_6)δ10.09(s,1H),9.03(s,1H),7.95(dt,J=6.9,1.5Hz,2H),7.89 (s,1H),7.74-7.68(m,2H),7.66-7.48(m,6H),3.91(dt,J=13.3,3.9Hz,2H), 3.21(t,J=6.8Hz,2H),3.08-2.98(m,2H),2.11(s,3H),2.05(t,J=6.8Hz,2H), 1.79(td,J=12.7,3.9Hz,2H),1.45(d,J=13.3Hz,2H).^{13}C NMR(101MHz, DMSO-d_6)δ180.44,172.50,165.46,164.98,158.92,158.48,137.83,135.57, 132.59,131.78,131.78,128.79,127.97,127.97,121.31,121.31,118.71,118.71, 108.06,44.42,42.35,42.35,38.42,32.06,32.06,31.62,21.52,16.89.HRMS-ESI: calculated for $C_{26}H_{28}N_6O_2$[M+H]$^+$457.2352,found:457.2347.

[0314] 实施例55、本发明化合物的制备

[0315] 8-(5-methyl-2-((4-phenoxyphenyl)amino)pyrimidin-4-yl)-2,8-diazaspiro[4.5] decan-1-one

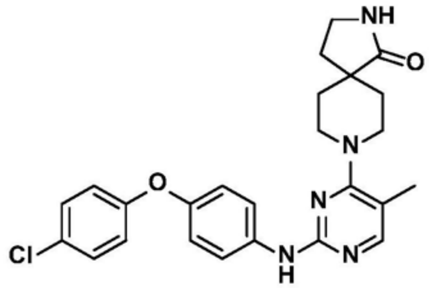
[0316] 

[0317] 合成方法与实施例42相同,得到灰白色固体产物。产率12%。^{1}H NMR (400MHz,DMSO-d_6)δ9.07(s,1H),7.90-7.86(m,1H),7.79-7.73(m,2H), 7.59(s,1H),7.37-7.31(m,2H),7.06(tt,J=7.2,1.1Hz,1H),6.97-6.91(m, 4H),3.93-3.85(m,2H),3.20(t,J=6.8Hz,2H),3.09-2.99(m,2H),2.10(s, 3H),2.03(t,J=6.8Hz,2H),1.77(td,J=12.6,12.2,3.9Hz,2H),1.44(d,J= 13.0Hz,2H).^{13}C NMR(101MHz,DMSO-d_6)δ180.44,164.98,158.92,158.47, 149.79,138.06,130.31,130.01,122.92,120.05,120.05,120.05, 120.05,117.78, 117.78,108.17,44.40,42.32,42.32,38.41,32.05,32.05,31.64, 16.90.HRMS-ESI: calculated for $C_{25}H_{27}N_5O_2[M+H]^+$430.2243,found:430.2243.

[0318] 实施例56、本发明化合物的制备

[0319] 8-(2-((4-(4-chlorophenoxy)phenyl)amino)-5-methylpyrimidin-4-yl)-2,8-diaz aspiro[4.5]decan-1-one

[0320]

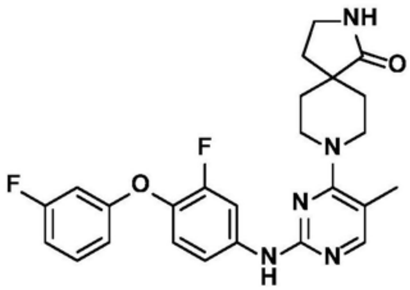


[0321] 合成方法与实施例42相同,得到白色固体产物。产率10%。^{1}H NMR(400 MHz,DMSO-d_6)δ9.12(s,1H),7.88(s,1H),7.83-7.73(m,2H),7.59(s,1H), 7.46-7.30(m,2H),7.04-6.90(m,4H),3.90(dt,J=13.6,4.0Hz,2H),3.20(t,J =6.8Hz,2H),3.11-2.99(m,2H),2.11(s,3H),2.03(t,J=6.8Hz,2H),1.77(td, J=12.6,4.0Hz,2H),1.44(d,J=13.2Hz,2H).^{13}C NMR(101MHz,DMSO-d_6) δ180.41,164.93,158.66,158.31,157.46,149.42,138.35,130.13,130.13,126.59, 120.22,120.22,120.11,120.11,119.38,119.38,108.23,44.41,42.31,42.31, 38.41,32.07,32.07,31.66,16.93.HRMS-ESI:calculated for $C_{25}H_{26}ClN_5O_2[M+H]^+$464.1853,found:464.1846.

[0322] 实施例57、本发明化合物的制备

[0323] 8-(2-((3-fluoro-4-(3-fluorophenoxy)phenyl)amino)-5-methylpyrimidin-4-yl)- 2,8-diazaspiro[4.5]decan-1-one

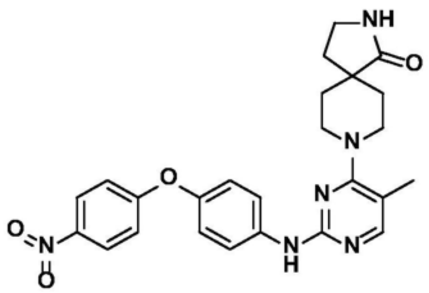
[0324]



[0325] 合成方法与实施例42相同,得到灰白色固体产物。产率11%。^{1}H NMR (400MHz,DMSO-d_6)δ9.38(s,1H),8.02(dd,J=14.3,2.5Hz,1H),7.93(s,1H), 7.60(s,1H),7.49(dt,J=9.1,1.7Hz,1H),7.37(td,J=8.3,6.8Hz,1H),7.18(t, J=9.2Hz,1H),6.90(td,J=8.5,2.4Hz,1H),6.83-6.70(m,2H),3.93(dt,J= 13.6,3.8Hz,2H),3.20(t,J=6.8Hz,2H),3.14-3.02(m,2H),2.12(s,3H),2.04 (t,J=6.8Hz,2H),1.78(dt,J=12.2,6.4Hz,2H),1.45(d,J=13.2Hz,2H).^{13}C NMR(101MHz,DMSO-d_6)δ180.37,164.85,162.11,159.96,159.85,158.89, 158.09,155.19,140.50,140.40,134.49,134.36,131.71,131.62,123.59,114.90, 112.00,109.79,109.58,108.89,106.75,106.52,103.96,103.71,44.38,42.29, 38.40,32.07,31.68,16.98.HRMS-ESI:calculated for $C_{25}H_{25}F_2N_5O_2[M+H]^+$466.2054,found:466.2048.

[0326] 实施例58、本发明化合物的制备

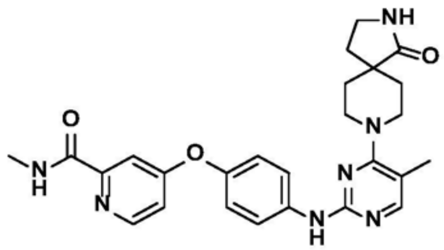
[0327] 8-(5-methyl-2-((4-(4-nitrophenoxy)phenyl)amino)pyrimidin-4-yl)-2,8-diazas piro[4.5]decan-1-one

[0328] 

[0329] 合成方法与实施例42相同,得到淡黄色固体产物。产率6%。^{1}H NMR(400 MHz, DMSO-d_6)δ9.21(s,1H),8.29-8.19(m,2H),7.91(s,1H),7.89-7.83(m, 2H),7.60(s,1H),7.09(d,J=8.8Hz,4H),3.92(dt,J=13.5,3.9Hz,2H),3.20(t, J=6.8Hz,2H),3.11-2.99(m,2H),2.12(s,3H),2.04(t,J=6.8Hz,2H),1.78 (td,J=12.6,3.9Hz,2H),1.45(d,J=13.3Hz,2H).^{13}C NMR(101MHz, DMSO-d_6)δ180.37,164.95,164.32,158.88,158.37,147.57,142.24,139.55, 126.62,126.62,121.25,121.25,120.06,120.06,117.09,117.09,108.45,44.41, 42.29,42.29,38.40,32.09,32.09,31.70,16.94.HRMS-ESI:calculated for $C_{25}H_{26}N_6O_4$[M+H]$^+$475.2094,found:475.2092.

[0330] 实施例59、本发明化合物的制备

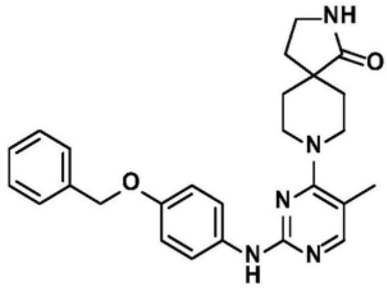
[0331] N-methyl-4-(4-((5-methyl-4-(1-oxo-2,8-diazaspiro[4.5]decan-8-yl)pyrimidin -2-yl)amino)phenoxy)picolinamide

[0332] 

[0333] 合成方法与实施例42相同,得到灰白色固体产物。产率7%。^{1}H NMR(400 MHz, DMSO-d_6)δ9.29(s,1H),8.76(q,J=4.8Hz,1H),8.49(d,J=5.6Hz,1H), 7.90(s,1H),7.88-7.83(m,2H),7.59(s,1H),7.39(d,J=2.6Hz,1H),7.12(dq, J=10.0,3.5,3.0Hz,3H),3.94(dt,J=13.3,3.9Hz,2H),3.20(t,J=6.8Hz,2H), 3.14-3.02(m,2H),2.78(d,J=4.8Hz,3H),2.13(s,3H),2.04(t,J=6.8Hz, 2H),1.78(td,J=12.3,11.8,3.9Hz,2H),1.46(d,J=13.3Hz,2H).^{13}C NMR (101MHz,DMSO-d_6)δ180.40,166.66,164.88,164.31,157.95,157.95,152.83, 150.79,146.91,139.52,121.50,121.50,120.31,120.31,114.38,109.11,108.47, 44.43,42.29,42.29,38.41,32.11,32.11,31.69,26.46,17.00.HRMS-ESI:calculated for $C_{26}H_{29}N_7O_3$[M+H]$^+$488.2410,found:488.2409.

[0334] 实施例60、本发明化合物的制备

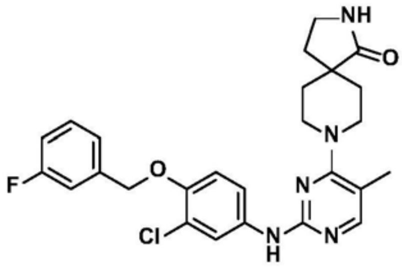
[0335] 8-(2-((4-(benzyloxy)phenyl)amino)-5-methylpyrimidin-4-yl)-2,8-diazaspiro[4.5]decan-1-one

[0336] 

[0337] 合成方法与实施例42相同，得到白色固体产物，产率4％。^{1}H NMR(400 MHz,DMSO-d_6)δ8.84(s,1H),7.85(s,1H),7.62(d,J＝2.3Hz,1H),7.60(d,J ＝4.2Hz,2H),7.46-7.41(m,2H),7.41-7.36(m,2H),7.35-7.28(m,1H), 6.94-6.87(m,2H),5.04(s,2H),3.88(dt,J＝13.4,3.9Hz,2H),3.20(t,J＝6.8 Hz,2H),3.08-2.97(m,2H),2.08(s,3H),2.03(t,J＝6.8Hz,2H),1.76(td,J＝ 12.5,4.0Hz,2H),1.43(d,J＝13.0Hz,2H).HRMS-ESI:calculated for $C_{26}H_{29}N_5O_2$[M+H]$^+$444.2399,found:444.2393.

[0338] 实施例61、本发明化合物的制备

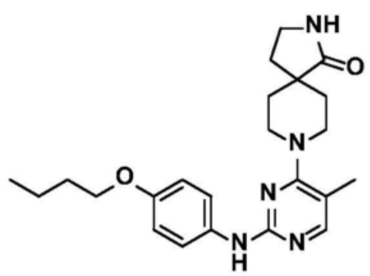
[0339] 8-(2-((3-chloro-4-((3-fluorobenzyl)oxy)phenyl)amino)-5-methylpyrimidin-4- yl)-2,8-diazaspiro[4.5]decan-1-one

[0340] 

[0341] 合成方法与实施例42相同，得到白色固体产物，产率7％。^{1}H NMR(400 MHz,DMSO-d_6)δ9.08(s,1H),8.02(d,J＝2.6Hz,1H),7.88(s,1H),7.60(s, 1H),7.53(dd,J＝9.0,2.6Hz,1H),7.45(td,J＝8.0,5.9Hz,1H),7.33-7.25(m, 2H),7.20-7.08(m,2H),5.16(s,2H),3.92(dt,J＝13.8,3.9Hz,2H),3.21(t,J＝ 6.8Hz,2H),3.14-3.03(m,2H),2.10(s,3H),2.04(t,J＝6.8Hz,2H),1.77(td,J ＝12.4,11.7,3.9Hz,2H),1.44(d,J＝13.4Hz,2H).^{13}C NMR(101MHz, DMSO-d_6)δ180.37,164.73,161.42,158.89,158.22,147.67,140.43,140.36, 136.36,130.98,130.90,123.78,123.76,121.75,120.00,118.13,115.37,115.14, 114.94,114.56,114.35,108.16,70.02,44.35,42.30,38.41,32.08,31.72,16.99.HRMS-ESI:calculated for $C_{26}H_{27}ClFN_5O_2$[M+H]$^+$496.1915,found: 496.1913.

[0342] 实施例62、本发明化合物的制备

[0343] 8-(2-((4-butoxyphenyl)amino)-5-methylpyrimidin-4-yl)-2,8-diazaspiro[4.5]d ecan-1-one

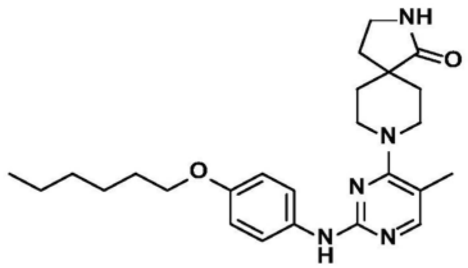
[0344] 

[0345] 合成方法与实施例42相同，得到白色固体产物，产率7％。^{1}H NMR(400 MHz,DMSO-d_6)δ8.81(s,1H),7.84(s,1H),7.63-7.56(m,3H),6.85-6.77(m, 2H),3.90(d,J＝6.6Hz,2H),3.87(d,J＝8.5Hz,2H),3.20(t,J＝6.8Hz,2H), 3.08-2.97(m,2H),2.08(s,3H),2.03(t,J＝6.8Hz,2H),1.76(td,J＝12.5,3.9 Hz,2H),1.66(dq,J＝8.4,6.5Hz,2H),1.44(dd,J＝6.6,2.5Hz,2H),1.41(d,J＝ 6.8Hz,2H),0.93(t,J＝7.4Hz,3H).^{13}C NMR(101MHz,DMSO-d_6)δ180.45, 164.98,158.95,158.68,153.35,134.94,120.19,120.19,114.69,114.69,107.63, 67.71,44.38,42.33,38.42,38.42,32.05,31.66,31.66,31.38,19.24,16.86,14.20.HRMS-ESI:calculated for$C_{22}H_{29}N_5O_2$[M+H]$^+$410.2556,found:410.2556.

[0346] 实施例63、本发明化合物的制备

[0347] 8-(2-((4-(hexyloxy)phenyl)amino)-5-methylpyrimidin-4-yl)-2,8-diazaspiro[4 .5]decan-1-one

[0348]

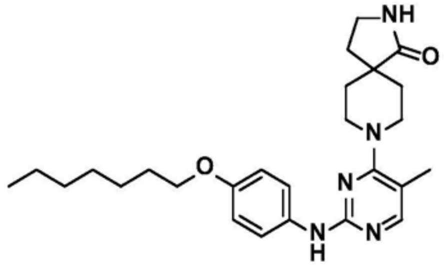


[0349] 合成方法与实施例42相同，得到灰白色固体产物，产率7％。^{1}H NMR(400 MHz,DMSO-d_6)δ8.83(s,1H),7.84(s,1H),7.64-7.55(m,3H),6.87-6.77(m, 2H),3.97-3.83(m,4H),3.21(t,J＝6.8Hz,2H),3.09-2.98(m,2H),2.09(s, 3H),2.04(t,J＝6.8Hz,2H),1.77(td,J＝12.7,3.9Hz,2H),1.72-1.62(m,2H), 1.49-1.36(m,4H),1.31(h,J＝4.0,3.5Hz,4H),0.91-0.85(m,3H).^{13}C NMR (101MHz,DMSO-d_6)δ180.41,164.95,158.65,158.52,153.41,134.84,120.26, 120.26,114.69,114.69,107.60,68.02,44.39,42.31,42.31,38.41,32.08,32.08, 31.68,31.51,29.27,25.71,22.56,16.88,14.38.HRMS-ESI:calculated for $C_{25}H_{35}N_5O_2$[M+H]$^+$438.2869,found:438.2865.

[0350] 实施例64、本发明化合物的制备

[0351] 8-(2-((4-(heptyloxy)phenyl)amino)-5-methylpyrimidin-4-yl)-2,8-diazaspiro[4.5]decan-1-one

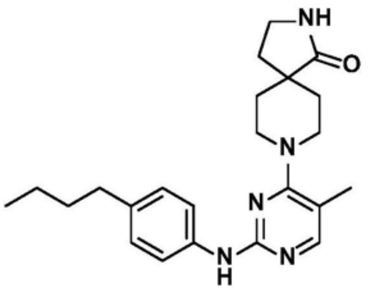
[0352]



[0353] 合成方法与实施例42相同，得到灰白色固体产物，产率8％。^{1}H NMR(400 MHz,DMSO-d_6)δ8.81(s,1H),7.84(s,1H),7.63-7.56(m,3H),6.87-6.75(m, 2H),3.88(td,J＝7.6,7.0,3.6Hz,4H),3.21(t,J＝6.8Hz,2H),3.09-2.97(m, 2H),2.09(s,3H),2.03(t,J＝6.8Hz,2H),1.77(td,J＝12.6,3.9Hz,2H),1.68(p, J＝6.7Hz,2H),1.45(s,2H),1.37-1.21(m,8H),0.89-0.85(m,3H).^{13}C NMR (101MHz,DMSO-d_6)δ180.44,164.98,158.94,158.68, 153.34,134.94,120.17, 120.17,114.68,114.68,107.61,68.01,44.38,42.32,42.32, 38.41,32.06,32.06, 31.73,31.66,29.31,28.95,26.00,22.53,16.86,14.42.HRMS-ESI: calculated for $C_{26}H_{37}N_5O_2$[M+H]$^+$452.3025,found:452.3022.

[0354] 实施例65、本发明化合物的制备

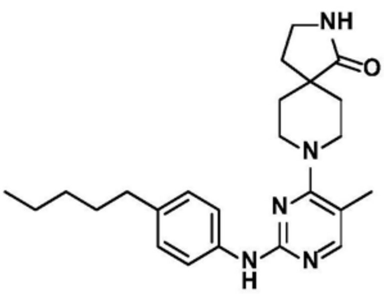
[0355] 8-(2-((4-butylphenyl)amino)-5-methylpyrimidin-4-yl)-2,8-diazaspiro[4.5]dec an-1-one

[0356] 

[0357] 合成方法与实施例42相同,得到白色固体产物,产率7%。^{1}H NMR(400 MHz,DMSO-d_6)δ8.97(s,1H),7.86(s,1H),7.61(d,J=8.7Hz,3H),7.04(d,J =8.4Hz,2H),3.90(dd,J=10.6,7.0Hz,2H),3.21(t,J=6.8Hz,2H),3.12- 2.99(m,2H),2.47(s,2H),2.10(s,3H),2.04(t,J=6.8Hz,2H),1.77(td,J=12.3, 11.8,3.9Hz,2H),1.52(ddd,J=9.3,6.7,2.1Hz,2H),1.44(d,J=13.2Hz,2H), 1.33-1.27(m,2H),0.89(t,J=7.3Hz,3H).^{13}C NMR(101MHz,DMSO-d_6)δ 180.40,164.88,158.24,158.20,139.22,134.80,128.57,128.57,118.79,118.79, 107.88,44.41,42.31,42.31,38.41,34.64,33.82,33.82,32.09,31.68,22.20,16.94, 14.28.HRMS-ESI:calculated for $C_{23}H_{31}N_5O$[M+H]$^+$394.2607,found:394.2606.

[0358] 实施例66、本发明化合物的制备

[0359] 8-(5-methyl-2-((4-pentylphenyl)amino)pyrimidin-4-yl)-2,8-diazaspiro[4.5]de can-1-one

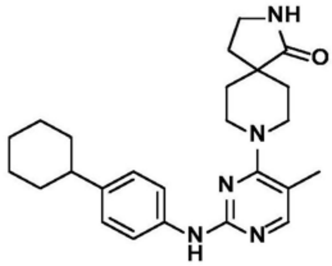
[0360] 

[0361] 合成方法与实施例42相同,得到灰白色固体产物,产率7%。^{1}H NMR(400 MHz,DMSO-d_6)δ8.93(s,1H),7.86(s,1H),7.65-7.56(m,3H),7.03(d,J=8.3 Hz,2H),3.90(dt,J=13.0,4.0Hz,2H),3.21(t,J=6.7Hz,2H),3.08-3.00(m, 2H),2.47(d,J=7.7Hz,2H),2.09(s,3H),2.04(t,J=6.9Hz,2H),1.77(td,J= 12.7,4.1Hz,2H),1.53(p,J=7.4Hz,2H),1.47-1.41(m,2H),1.31-1.25(m, 4H),0.87(d,J=6.7Hz,3H).HRMS-ESI:calculated for $C_{24}H_{33}N_5O$[M+H]$^+$ 408.2763found:408.2760.

[0362] 实施例67、本发明化合物的制备

[0363] 8-(2-((4-cyclohexylphenyl)amino)-5-methylpyrimidin-4-yl)-2,8-

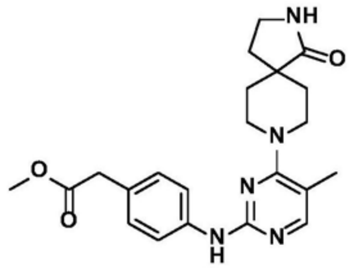
diazaspiro[4 .5]decan-1-one

[0364] 

[0365] 合成方法与实施例42相同,得到白色固体产物,产率9%。[1]H NMR(400 MHz,DMSO-d_6)δ8.92(s,1H),7.86(s,1H),7.65-7.61(m,2H),7.60(s,1H), 7.06(d,J=8.5Hz,2H),3.89(dt,J=13.5,3.9Hz,2H),3.21(t,J=6.8Hz,2H), 3.10-2.97(m,2H),2.41(d,J=10.2Hz,1H),2.09(s,3H),2.04(t,J=6.8Hz, 2H),1.85-1.64(m,8H),1.48-1.41(m,2H),1.40-1.30(m,4H).[13]C NMR (101MHz,DMSO-d_6)δ180.48,164.96,158.87,158.54,140.12,139.49,126.86, 126.86,118.67,118.67,107.92,44.39,43.57,42.35,42.35,38.43,34.67,34.67, 32.06,32.06,31.63,26.91,26.91,26.12,16.88.HRMS-ESI:calculated for $C_{25}H_{33}N_5O$[M+H]$^+$420.2763,found:420.2761.

[0366] 实施例68、本发明化合物的制备

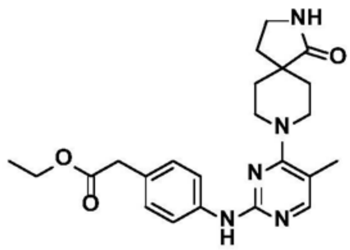
[0367] methyl-2-(4-((5-methyl-4-(1-oxo-2,8-diazaspiro[4.5]decan-8-yl)pyrimidin-2- yl)amino)phenyl)acetate

[0368] 

[0369] 合成方法与实施例42相同,得到灰白色固体产物,产率10%。[1]H NMR (400MHz,DMSO-d_6)δ9.02(s,1H),7.88(s,1H),7.72-7.64(m,2H),7.59(s, 1H),7.15-7.06(m,2H),3.90(dt,J=13.3,3.8Hz,2H),3.60(s,3H),3.57(s, 2H),3.21(t,J=6.8Hz,2H),3.09-2.99(m,2H),2.10(s,3H),2.04(t,J=6.8Hz, 2H),1.78(td,J=12.7,3.9Hz,2H),1.45(d,J=13.3Hz,2H).[13]C NMR(101 MHz,DMSO-d_6)δ180.44,172.43,164.96,158.94,158.47,140.56,129.69, 129.69,126.43,118.54,118.54,108.21,52.08,52.05,44.40,42.33,42.33,38.42, 32.06,32.06,31.64,16.89.HRMS-ESI:calculated for $C_{22}H_{27}N_5O_3$[M+H]$^+$410.2192,found:410.2190.

[0370] 实施例69、本发明化合物的制备

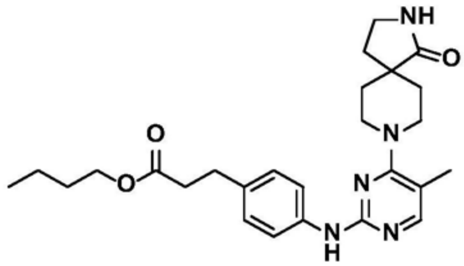
[0371] ethyl2-(4-((5-methyl-4-(1-oxo-2,8-diazaspiro[4.5]decan-8-yl)pyrimidin-2-yl) amino)phenyl)acetate

[0372] 

[0373] 合成方法与实施例42相同，得到灰白色固体产物，产率10％。^1H NMR (400MHz, DMSO-d_6) δ9.02(s,1H),7.88(s,1H),7.72-7.62(m,2H),7.59(s, 1H),7.17-7.07(m,2H),4.06(q,J＝7.1Hz,2H),3.90(dt,J＝13.5,4.0Hz,2H), 3.54(s,2H),3.21(t,J＝6.8Hz,2H),3.10-2.98(m,2H),2.10(s,3H),2.04(t,J ＝6.8Hz,2H),1.77(td,J＝12.4,11.9,3.9Hz,2H),1.44(d,J＝13.2Hz,2H), 1.18(t,J＝7.1Hz,3H).^{13}C NMR(101MHz,DMSO-d_6) δ 180.42,171.94, 164.96,158.95,158.48,140.53,129.65,129.65,126.52,118.54,118.54,108.20, 60.60,44.41,42.32,42.32,38.41,32.06,32.06,31.64,16.89,14.56.HRMS-ESI: calculated for $C_{23}H_{29}N_5O_3$[M+H]$^+$424.2348,found:424.2343.

[0374] 实施例70、本发明化合物的制备

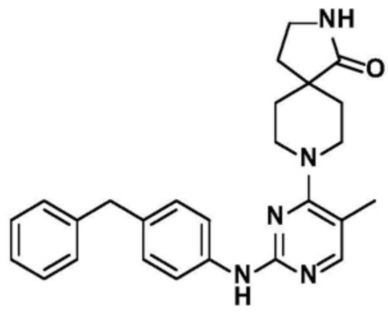
[0375] butyl3-(4-((5-methyl-4-(1-oxo-2,8-diazaspiro[4.5]decan-8-yl) pyrimidin-2-yl) amino)phenyl)propanoate

[0376] 

[0377] 取中间体a(260mg,0.93mmol)和3-(4-氨基苯基)丙酸(165mg,1mmol) 于50ml圆底烧瓶中，加入20mL正丁醇作溶剂，常温下加入4-6滴浓HCl，将反应体系放置115℃油浴锅中反应，反应6-8小时。通过TLC检测，反应 结束后，利用减压蒸馏将溶剂旋干，利用Flash柱分离纯化得白色固体产物。产率13％。^1H NMR(400MHz,DMSO-d_6) δ8.97(s,1H),7.87(s,1H),7.67- 7.56(m,3H),7.07(d,J＝8.5Hz,2H),3.99(t,J＝6.6Hz,2H),3.90(dt,J＝13.5,4.0Hz,2H),3.21(t,J＝6.8Hz,2H),3.11-2.98(m,2H),2.77(t,J＝7.5Hz,2H), 2.57(t,J＝7.5Hz,2H),2.10(s,3H),2.04(t,J＝6.8Hz,2H),1.77(td,J＝12.6, 3.9Hz,2H),1.55-1.48(m,2H),1.48-1.40(m,2H),1.32-1.25(m,2H),0.86 (t,J＝7.4Hz,3H).^{13}C NMR(101MHz,DMSO-d_6) δ180.37,172.80,164.93, 158.70,158.41,139.82,132.72,128.55,128.55,118.63,118.63,107.99,63.92, 44.41,42.30,42.30,38.41,35.84,35.84,32.10,31.69,30.66,30.21,19.06,16.90, 14.01.HRMS-ESI:calculated for $C_{26}H_{35}N_5O_3$[M+H]$^+$466.2818,found:466.2813.

[0378] 实施例71、本发明化合物的制备

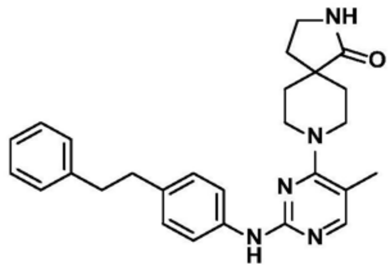
[0379] 8-(2-((4-benzylphenyl)amino)-5-methylpyrimidin-4-yl)-2,8-diazaspiro[4.5]d ecan-1-one

[0380] 

[0381] 合成方法与实施例42相同，得到白色固体产物。产率7%。^{1}H NMR(400 MHz,DMSO-d_6)δ8.96(s,1H),7.86(s,1H),7.68-7.62(m,2H),7.59(s,1H), 7.27(t,J=7.5Hz,2H), 7.23-7.13(m,3H),7.08(d,J=8.4Hz,2H),3.89(dd,J =10.7,6.7Hz,2H),3.85(s,2H), 3.20(t,J=6.8Hz,2H),3.09-2.98(m,2H), 2.09(s,3H),2.03(t,J=6.8Hz,2H),1.76(td,J =12.6,3.9Hz,2H),1.43(d,J= 13.1Hz,2H).^{13}C NMR(101MHz,DMSO-d_6)δ180.41,164.98, 158.95,158.53, 142.33,139.81,133.52,129.06,129.06,129.04,129.04,128.80, 128.80,126.24, 118.68,118.68,108.03,44.40,42.32,40.99,40.99,38.41,32.07, 32.07,31.63, 16.87.HRMS-ESI:calculated for $C_{26}H_{29}N_5O[M+H]^+$428.2450,found: 428.2448.

[0382] 实施例72、本发明化合物的制备

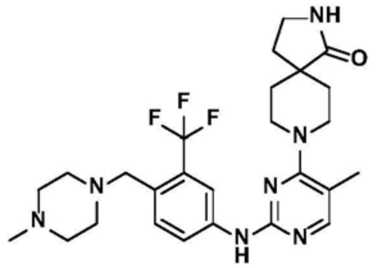
[0383] 8-(5-methyl-2-((4-phenethylphenyl)amino)pyrimidin-4-yl)-2,8-diazaspiro[4. 5]decan-1-one

[0384] 

[0385] 合成方法与实施例42相同，得到灰白色固体产物。产率8%。^{1}H NMR(400 MHz, DMSO-d_6)δ8.94(s,1H),7.87(s,1H),7.66-7.58(m,3H),7.26(t,J=7.4 Hz,2H),7.24-7.19 (m,2H),7.19-7.13(m,1H),7.07(d,J=8.2Hz,2H),3.90 (dq,J=13.5,3.8Hz,2H),3.21(t, J=6.7Hz,2H),3.09-2.99(m,2H),2.89- 2.75(m,4H),2.09(s,3H),2.04(t,J=7.0Hz,2H), 1.78(td,J=12.6,3.9Hz,2H), 1.44(d,J=13.1Hz,2H).^{13}C NMR(101MHz,DMSO-d_6)δ 180.41,164.96, 158.96,158.57,142.17,139.64,133.75,128.83,128.83,128.66, 128.66,128.64, 128.64,126.18,118.56,118.56,107.94,44.41,44.41,42.32,42.32, 38.42,37.79, 37.01,32.08,32.08,31.68,16.88.HRMS-ESI:calculated for $C_{27}H_{31}N_5O[M+H]^+$ 442.2607,found:442.2602.

[0386] 实施例73、本发明化合物的制备

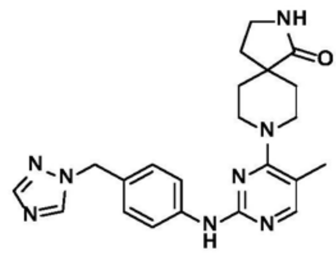
[0387] 8-(5-methyl-2-((4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phen yl)amino)pyrimidin-4-yl)-2,8-diazaspiro[4.5]decan-1-one

[0388] 

[0389] 合成方法与实施例45相同，得到灰白色固体产物。产率6%。^{1}H NMR(400 MHz, DMSO-d_6) δ9.40(s,1H),8.34(d,J=2.2Hz,1H),7.92(s,1H),7.82(dd,J =8.6,2.2Hz,1H),7.60(s,1H),7.53(d,J=8.6Hz,1H),3.92(dt,J=13.5,4.0 Hz,2H),3.50(s,2H),3.21(t,J=6.8Hz,2H),3.15-3.03(m,2H),2.34(s,8H), 2.15(s,3H),2.12(s,3H),2.04(t,J=6.8Hz,2H),1.77(td,J=12.7,12.2,4.0Hz, 2H),1.48-1.38(m,2H).^{13}C NMR(101MHz,DMSO-d_6) δ180.36,164.84, 159.07,158.18,140.89,131.49,128.52,127.61,121.57,115.13,108.70,57.96, 55.15,55.15,53.05,53.05,46.08,44.37,44.37,42.23,38.40,32.10,32.10,31.69, 16.98.HRMS-ESI:calculated for $C_{26}H_{34}F_3N_7O$[M+H]$^+$518.2855,found:518.2853.

[0390] 实施例74、本发明化合物的制备

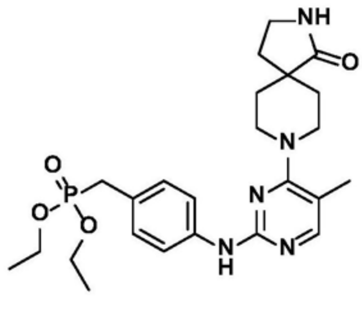
[0391] 8-(2-((4-((1H-1,2,4-triazol-1-yl)methyl)phenyl)amino)-5-methylpyrimidin-4- yl)-2,8-diazaspiro[4.5]decan-1-one

[0392] 

[0393] 合成方法与实施例42相同，得到浅黄色固体产物。产率2%。^{1}H NMR(400 MHz, DMSO-d_6) δ9.11(s,1H),8.60(s,1H),7.95(s,1H),7.89(s,1H),7.78- 7.67(m,2H),7.60(s,1H),7.18(d,J=8.6Hz,2H),5.30(s,2H),3.89(d,J=13.2 Hz,2H),3.21(t,J=6.8Hz,2H),3.04(t,J=11.9Hz,2H),2.10(s,3H),2.04(t,J =6.8Hz,2H),1.77(td,J=12.6,3.9Hz,2H),1.44(d,J=13.1Hz,2H). HRMS-ESI:calculated for $C_{22}H_{26}N_8O$[M+H]$^+$419.2308,found:419.2306.

[0394] 实施例75、本发明化合物的制备

[0395] diethyl(4-((5-methyl-4-(1-oxo-2,8-diazaspiro[4.5]decan-8-yl)pyrimidin-2-yl) amino)benzyl)phosphonate

[0396] 

[0397] 合成方法与实施例42相同，得到浅黄色固体产物。产率5％。^{1}H NMR(400 MHz，DMSO-d_6)δ9.01(s,1H),7.88(s,1H),7.66(d,J＝8.3Hz,2H),7.59(s, 1H),7.12(dd,J＝8.7,2.5Hz,2H),3.97-3.86(m,6H),3.20(t,J＝6.8Hz,2H), 3.16-3.00(m,4H),2.10(s,3H),2.04(t,J＝6.8Hz,2H),1.77(td,J＝12.6,3.9 Hz,2H),1.44(d,J＝13.2Hz,2H),1.17(t,J＝7.0Hz,6H).^{13}C NMR(101MHz, DMSO-d_6)δ180.38,164.97,158.97,158.49,140.28,130.13,130.06,124.06, 123.97,118.50,118.50,108.17,61.76,61.70,44.41,42.31,38.40,32.07,31.67, 16.89,16.72,16.67.HRMS-ESI:calculated for $C_{22}H_{27}N_5O_3$[M+H]$^+$ 488.2426, found:488.2419.

[0398] 以下通过实验例证明本发明的有益效果。

[0399] 实验例1、本发明化合物对JAKs激酶的抑制活性

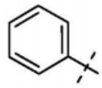
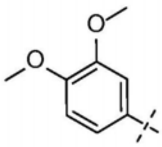
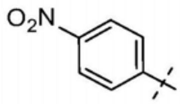
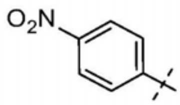
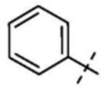
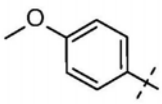
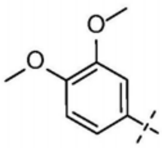
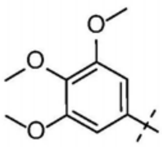
[0400] 1、实验方法

[0401] 体外抑制JAKs各亚型酶活性的实验由Eurofins合作完成。Eurofins测定 化合物设定浓度(1μM)下体外抑制JAKs各亚型后，JAKs的酶活率，并拟 合IC50值。

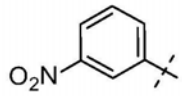
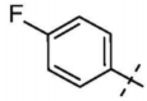
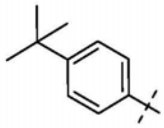
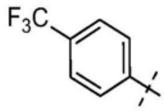
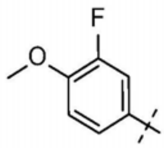
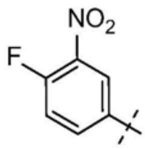
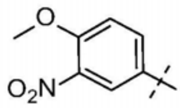
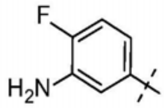
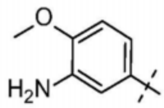
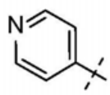
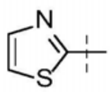
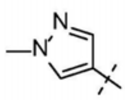
[0402] 2、实验结果

[0403] 表1 JAKs各亚型的酶活率

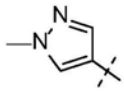
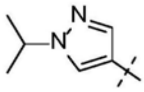
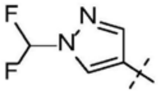
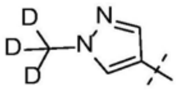
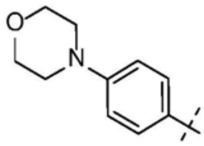
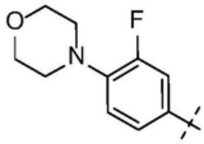
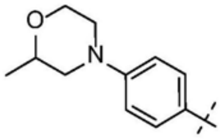
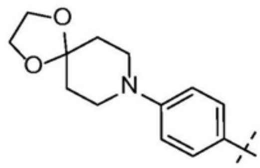
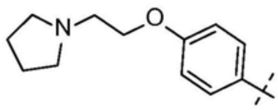
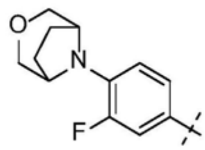
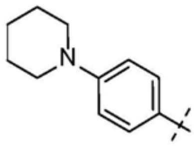
[0404]

实施例	R_1	Ar	酶活率 (1 μM[a], %)			
			JAK1	JAK2	JAK3	TYK2
1	H		79	94	87	66
2	H		78	61	69	72
3	H		68	76	70	41
4	Me		3	16	23	4
5	Me		23	32	33	9
6	Me		17	18	27	3
7	Me		16	16	34	10
8	Me		28	8	35	11

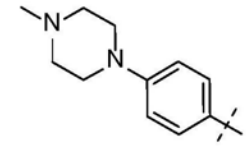
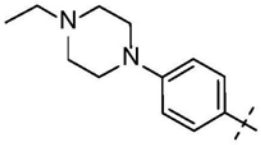
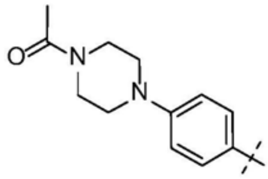
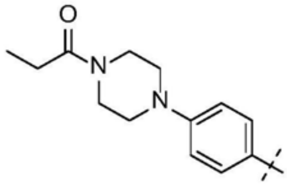
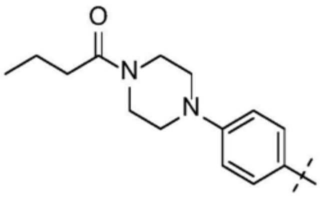
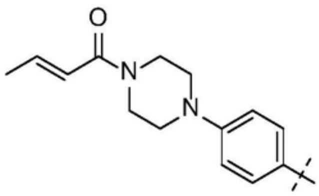
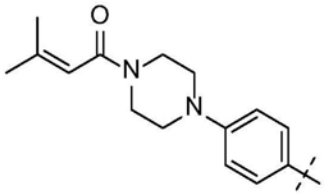
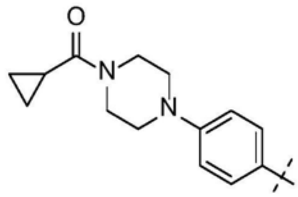
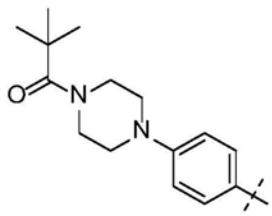
[0405]

9	Me		57	9	9	3
10	Me		21	32	28	15
11	Me		18	36	44	8
12	Me		14	22	22	5
13	Me		4	18	13	5
14	Me		87	14	17	5
15	Me		0	8	7	2
16	Me		0	12	13	4
17	Me		0	11	14	4
18	Me		22	31	63	12
19	Me		38	51	35	17
20	Me		5	25	25	4

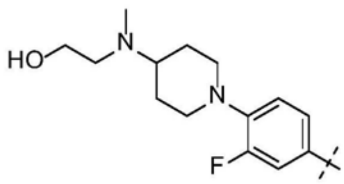
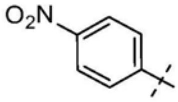
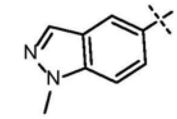
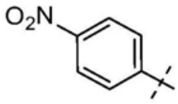
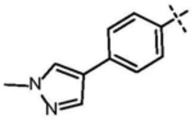
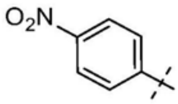
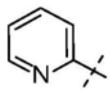
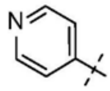
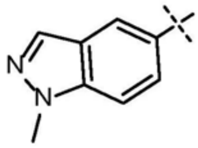
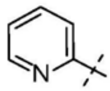
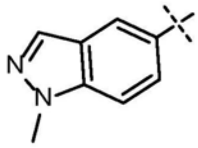
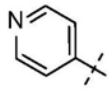
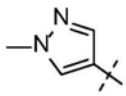
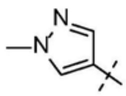
[0406]

21	H		76	85	84	63
22	Me		0	8	29	2
23	Me		4	16	24	0
24	Me		3	15	15	1
25	Me		7	0	11	3
26	Me		2	5	12	2
27	Me		7	0	12	2
28	Me		6	1	16	3
29	Me		42	17	30	11
30	Me		2	0	4	2
31	Me		4	2	13	4

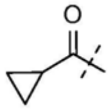
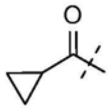
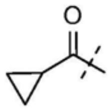
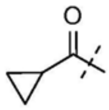
[0407]

32	Me		5	6	18	5
33	Me		5	0	10	3
34	Me		5	0	12	1
35	Me		1	3	7	2
36	Me		1	4	17	5
37	Me		0	6	3	3
38	Me		4	8	5	1
39	Me		4	7	2	0
40	Me		4	7	7	0

[0408]

41	Me		6	0	9	2
对比例1	Ph		94	100	85	89
对比例2			85	91	91	99
对比例3			93	92	100	100
对比例4	Ph		0	-4	7	-13
对比例5	Ph		22	6	-9	-1
对比例6			14	0	16	-10
对比例7			13	-4	-7	13
对比例8	-COOMe		7	20	-12	22
对比例9	-COOEt		3	31	-2	16
对比例10	H	H	-2	6	13	8
对比例11	Br	H	28	8	3	21

[0409]

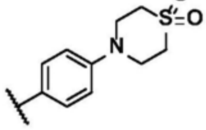
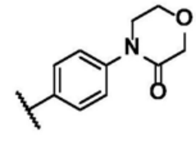
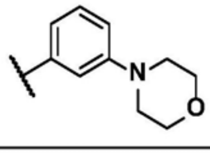
对比例12	Cl	H	-11	4	16	11
对比例13	F	H	-17	1	-4	-2
对比例14	H		0	0	0	0
对比例15	Br		15	14	17	42
对比例16	Cl		-6	9	20	35
对比例17	F		-22	4	9	2

[0410] 从表中可以看出，本发明化合物都是有效的JAKs激酶抑制剂，其中，说明R_1为甲基或H时具有较高的抑制活性，且R1为甲基时显著更优。

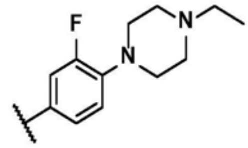
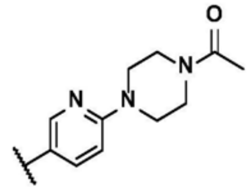
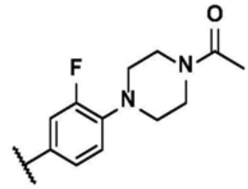
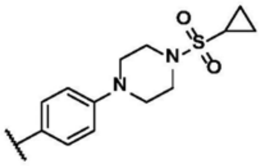
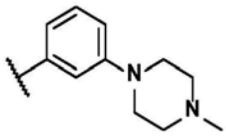
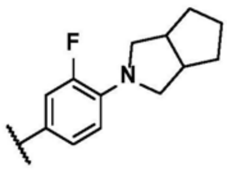
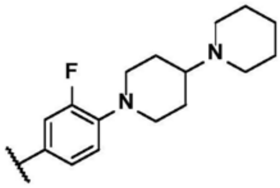
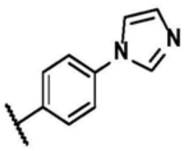
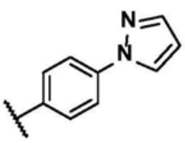
[0411] 因此，固定R_1基团为甲基，探究R_2基团的变化对JAKs酶活率的影响，得到的酶活率结果如表2所示：

[0412] 表2化合物的JAKs酶活率数据

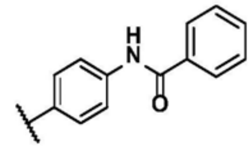
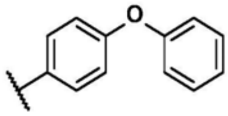
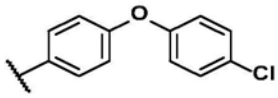
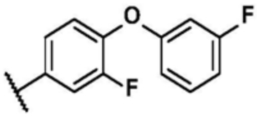
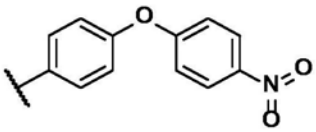
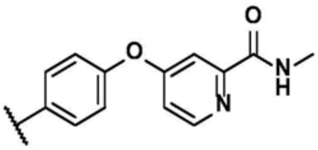
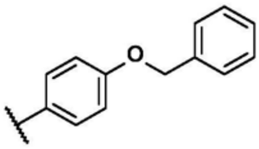
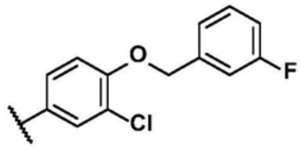
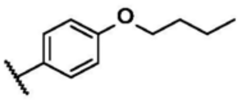
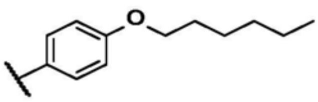
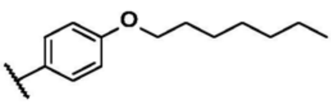
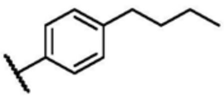
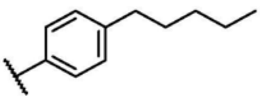
[0413]

实施例	R_2	酶活率 (1 μM$^{\alpha}$,%) JAK1	JAK2	JAK3	TYK2
42		5	5	4	2
43		8	11	15	3
44		26	12	24	10

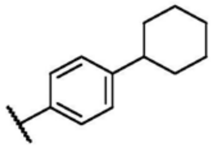
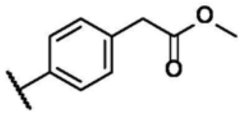
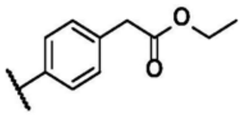
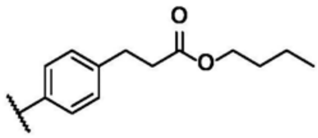
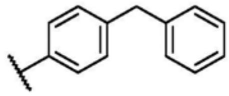
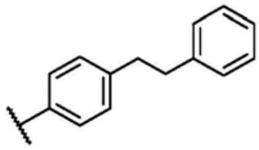
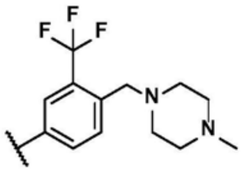
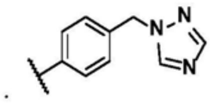
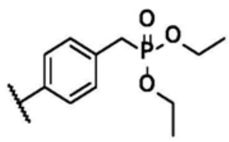
[0414]

45		5	6	7	3
46		8	5	9	1
47		3	3	4	0
48		3	4	7	1
49		15	18	33	12
50		9	11	8	1
51		35	18	26	5
52		1	10	9	1
53		2	11	9	1

[0415]

54		4	11	26	1
55		16	23	15	4
56		34	47	36	9
57		46	31	40	13
58		15	23	16	3
59		11	18	18	6
60		11	20	19	2
61		21	39	31	2
62		5	19	15	3
63		18	93	29	8
64		50	37	41	19
65		15	32	27	7
66		36	48	37	25

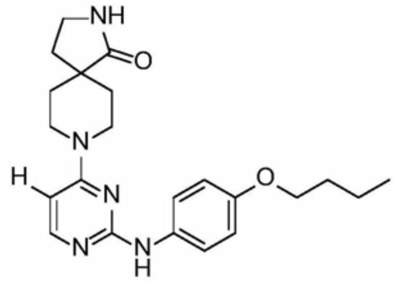
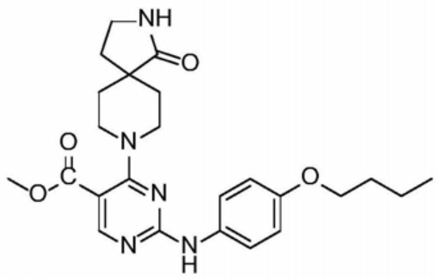
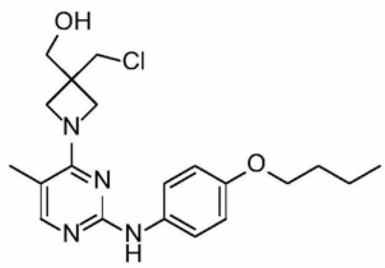
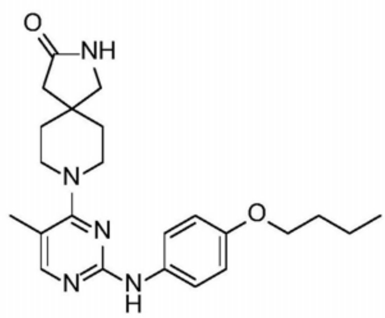
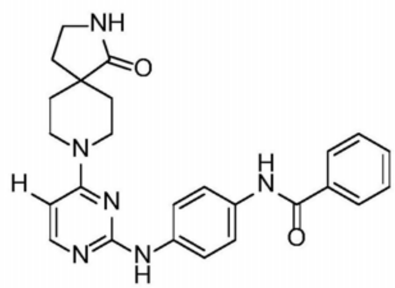
[0416]

67		21	49	26	5
68		4	-6	11	2
69		4	12	13	2
70		7	23	20	7
71		20	38	26	5
72		29	41	53	12
73		12	26	10	4
74		5	14	8	2
75		7	8	25	4
对比例18	H	100	92	96	89

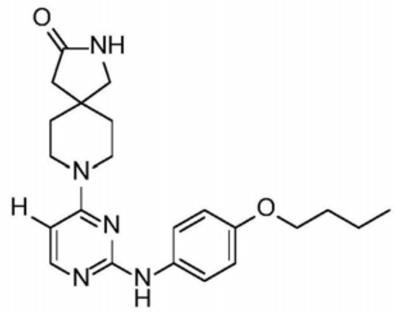
[0417]　根据表1、表2的内容可知，本发明化合物都是有效的JAKs激酶抑制剂，其中，R_1为甲基或H时，R_2为取代或未取代的C5～C6杂环结构时具有较高 的抑制活性，而对于C5～C6杂环结构上的杂原子和取代基而言，杂原子和/ 或取代基在间位或对位的抑制效果优于在邻位的抑制效果。

[0418]　进一步地，发明人进一步制备了母环与本发明不同，具有其它螺环结构 的对比例，并测试了其对JAKS激酶的抑制酶活效果，结果如表3所示：

[0419]

编号	结构	酶活率 (1 μM[a],%)			
		JAK1	JAK2	JAK3	TYK2
对比例 19		74	99	79	56
对比例 20		92	93	90	79
对比例 21		16	80	28	12
对比例 22		89	74	106	97
对比例 23		83	83	113	90

[0420]

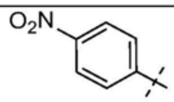
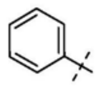
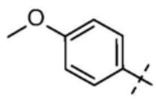
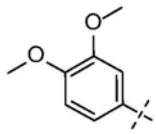
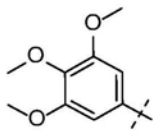
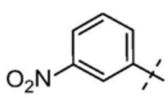
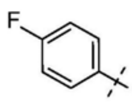
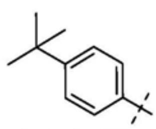
对比例 24		70	108	98	95

[0421] 可见,本发明的螺环结构的化合物与其他结构相比,具有显著更好的 JAKs酶抑制活性。

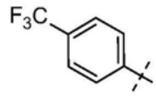
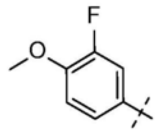
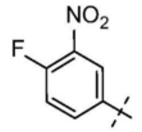
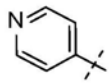
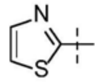
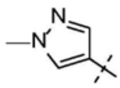
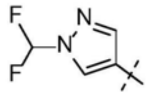
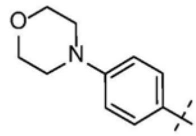
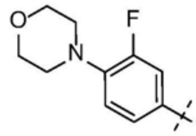
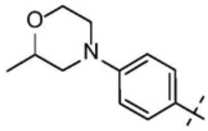
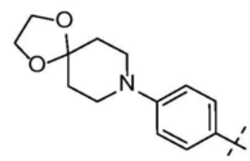
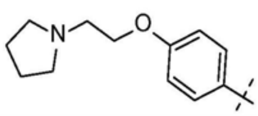
[0422] 对上述表1、表2中部分抑制效果较为优异的化合物进行对JAKs酶的 IC50值测试,结果如表3:

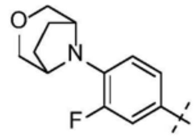
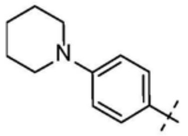
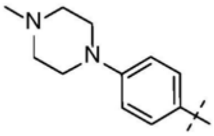
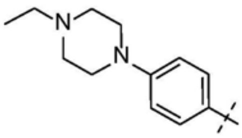
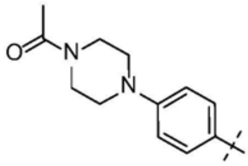
[0423] 表3

[0424]

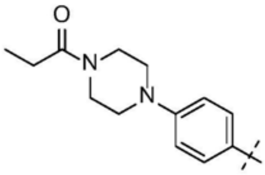
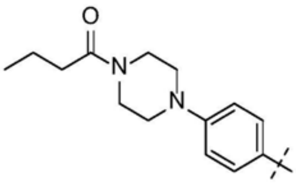
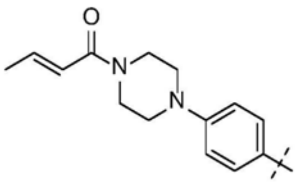
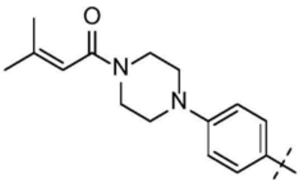
实施例	Ar	IC_{50} (nM)[a]			
		JAK1	JAK2	JAK3	TYK2
4		A	A	F	B
5		D	F	E	B
6		C	D	E	B
7		D	D	D	B
8		B	A	B	A
9		A	A	A	A
10		C	D	D	B
11		C	F	F	C

[0425]

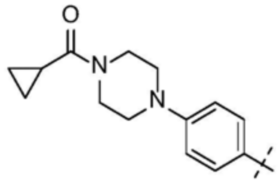
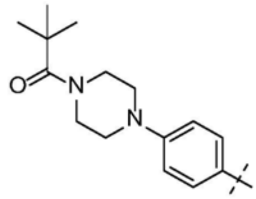
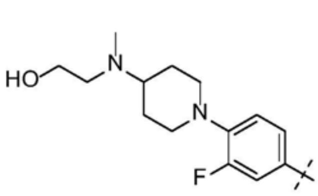
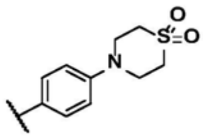
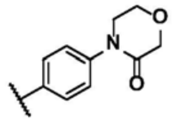
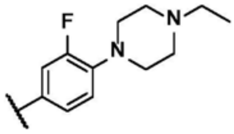
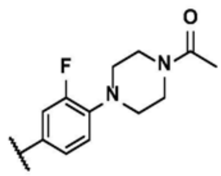
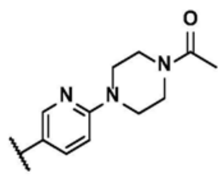
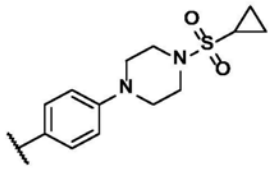
12		C	D	D	B
13		B	C	D	B
14		B	B	C	A
18		D	F	F	C
19		F	F	F	D
20		B	D	D	B
23		B	C	D	A
25		B	C	B	B
26		B	B	B	B
27		B	B	B	B
28		B	B	B	B
29		B	B	B	B

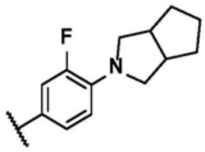
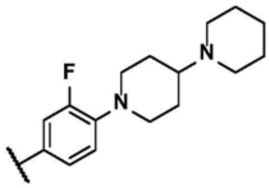
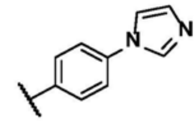
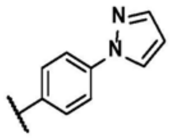
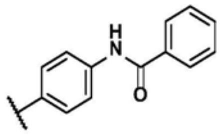
30		B	C	B	B
31		B	B	B	B
32		B	B	B	B
33		B	C	B	B
34		B	C	B	B

[0426]

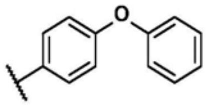
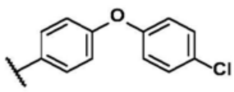
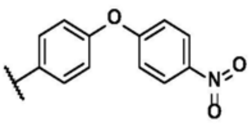
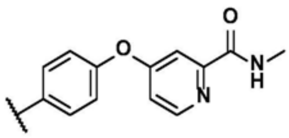
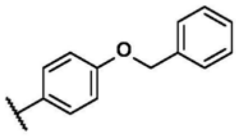
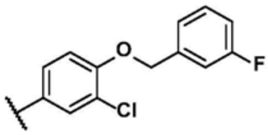
35		B	B	B	B
36		B	B	B	B
37		B	B	B	B
38		B	B	B	B

[0427]

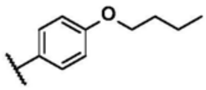
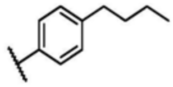
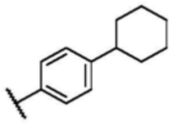
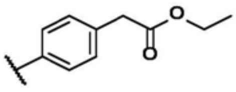
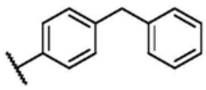
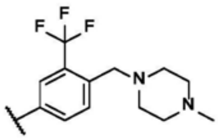
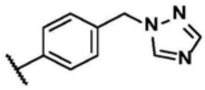
39		B	B	B	C
40		B	B	B	B
41		B	C	B	B
42		B	B	B	B
43		B	B	C	A
45		B	B	B	A
47		B	B	B	B
46		B	B	C	B
48		A	B	B	A

50		C	D	E	B
51		F	D	E	C
52		B	C	C	A
53		B	B	D	D
54		B	C	C	A

[0428]

55		C	B	C	B
56		E	F	E	D
58		C	D	D	B
59		C	D	C	E
60		B	B	B	B
61		D	E	D	F

[0429]

62		B	B	B	A
65		C	F	E	C
67		E	E	E	B
69		B	C	D	C
71		D	F	E	F
73		C	B	C	E
74		B	B	C	B
Brepocitinib		B	B	F	B

[0430] 注:表3中A指IC50≤10nM,B指10nM＜IC50≤100nM,C指100nM ＜IC50≤200nM,D指200nM＜IC50≤500nM,E指500nM＜IC50≤1000nM, F指IC50＞1000nM。

[0431] 以上结果说明,本发明化合物对JAKs激酶具有很好的抑制作用,且具 有独特的构效关系,对JAKs激酶的不同亚型具有一定的选择性,可降低毒 副作用风险,其抑制活性相比于市售产品Brepocitinib相当或更优,说明本发 明的化合物作为JAKs激酶抑制剂有很好的应用前景。

[0432] 实验例2、本发明化合物对炎性肠病的治疗

[0433] 1、DSS诱导的急性UC模型建立和疾病活动指数(DAI)评分标准:

[0434] C57BL/6小鼠按照体重随机分为正常组,DSS诱导组,Tofacitinib(10 mg/kg),实施例20化合物(5mg/kg,10mg/kg,20mg/kg)。实验开始当天, 除正常组外,所有组给予自由饮用2.5%DSS水溶液(此时标记为第一天), 正常对照组给予相同的不含DSS的灭菌水。给药体积为0.1mL/10g,每天一 次,连续给药6天。

[0435] 表4疾病活动指数(DAI)评分标准

[0436]

一般性状		体重下降（%）		粪便性状		直肠出血	
正常	0	0	0	正常	0	无血	0
毛耸起	1	1-5	1				
毛耸起及全是无力	2	6-10	2	松散	2	轻微出血	2
		11-15	3				
静止不动或无力	4	>15	4	稀便，或5min内观察不到排便	4	便血	4

[0437] 从建模之日起，每日观察小鼠进食、活动、毛发情况，称量动物体重，观察小鼠粪便性状及粪便隐血，出血状况，评估结肠炎严重程度。疾病活动 情况按进行评分，疾病活动指数(disease activity index,DAI)评分＝体重下 降评分+大便性状评分+大便隐血评分+毛色性状评分，计算得出每只小鼠的 疾病活动指数，总分为16分。

[0438] 2、给药：

[0439] 为了验证本发明化合物是否能用于治疗IBD，我们按照上述方法建立了 DSS诱导的UC动物模型。2.5％DSS饮水诱导6天后，小鼠均表现出明显的 UC相关症状。疾病鼠随机分组并给药治疗：模型组(Model)，阳性对照组 (Tofacitinib 10mg/kg)，治疗组分为低剂量(实施例20化合物5mg/kg)、中剂量(实施例20化合物10mg/kg)和高剂量(实施例20化合物20mg/kg)，并每天对各组小鼠进行评分及记录体重。在治疗终点时，采血并处死小鼠，取出肛门直盲肠末端的整个结肠和直肠段，并观察、测量结肠和直肠的长度，组织固定于福尔马林溶液中，制作组织切片，进行H&E染色。眼球取血对 血样使用ELISA试剂盒检测炎症因子表达。

[0440] 3、结果：

[0441] 结果如图1所示，治疗组的炎症反应都得到了一定的抑制，实施例20 化合物的治疗效果也呈现了剂量依存关系，其中、高剂量最终的治疗打分结 果均优于阳性Tofacitinib组，且中、高剂量组的小鼠体重在治疗结束时均得 到了恢复，明显优于Tofacitinib。经7天给药治疗，所有模型小鼠被处死， 分析结肠组织的病理状态，结果显示实施例20化合物的治疗效果明显，尤其 是高剂量20mg/kg组，小鼠的结肠长度已恢复正常长度。而Tofacitinib同等 剂量下仍有部分肠组织呈现炎症浸润的情况。病理切片也显示(图2)，中剂 量与高剂量治疗组的小鼠结肠已无炎性反应现象，实现了治愈效果。

[0442] 在初步确认了实施例20化合物于动物模型上的治疗效果后，我们进一步 进行ELISA试剂盒检测在不同给药剂量下，小鼠血清中炎症相关因子的表 达。根据第一次动物实验重新设置了给药剂量后，使用相同方式建立动物模 型及给药时间。实验结果可以看到中高剂量给药组的IL-6的表达相较于模型 组有明显降低，而IL-10相较于模型组有明显升

高。该结果证实了实施例20 化合物对于炎症的调控作用且存在剂量依赖关系。

[0443] 上述结果说明，本发明化合物可以有效降低炎症因子表达，治疗溃疡性 结肠炎效果优异。

[0444] 实验例3、本发明化合物对斑秃的治疗

[0445] 参考文献的方法(Paus R B,Handjiski B,Eichmüller S,et al. Chemotherapy-induced alopecia in mice.Induction by cyclophosphamide, inhibition by cyclosporine A,and modulation by dexamethasone[J].American Journal of Pathology,1994,144(4):719-34)，在诱导小鼠背部毛发处在静止期 的第二天，开始对每组小鼠口服给药(实施例43的化合物(图3、图4中的 化合物2)、实施例45的化合物(图3、图4中的化合物4)、实施例54的化 合物(图3、图4中的化合物16)以及阳性对照Ruxolitinib)，按照30mg/kg 的给药剂量持续给药。在给药的第8天，每只小鼠按照150mg/kg(0.1ml/10g)剂量腹腔注射环磷酰胺，环磷酰胺能够破环毛囊组织处快速分裂的细胞，破 环其毛发生长，从而诱导小鼠AA疾病的产生。给药一直持续39天，并对每 天小鼠背部毛发生长状况进行拍照，观察小鼠背部毛发的生长情况，选取每 一个阶段具有代表性的照片进行观察对比，如图3所示。

[0446] 从第一天为小鼠给药后，当小鼠的毛发长到能够测量的时候，通过游标 卡尺对数对不同组每只小鼠的头部、背部、尾部各测量五根毛发长度，其具 体数据如表，得到相应的数据，整理统计后如图4所示。可见，本发明化合 物能够对斑秃起到明显的改善作用，且效果与阳性对照药物芦可替尼 (ruxolitinib)相当。

[0447] 综上，本发明提供了一种2,8-氮杂-[4,5]十螺环酮衍生物，可作为一种新 型的JAKs激酶抑制剂，对JAKs激酶的不同亚型存在选择作用，降低了副作 用风险，在溃疡性结肠炎、斑秃等自身免疫疾病或免疫介导的疾病的治疗方 面具有潜在应用价值。

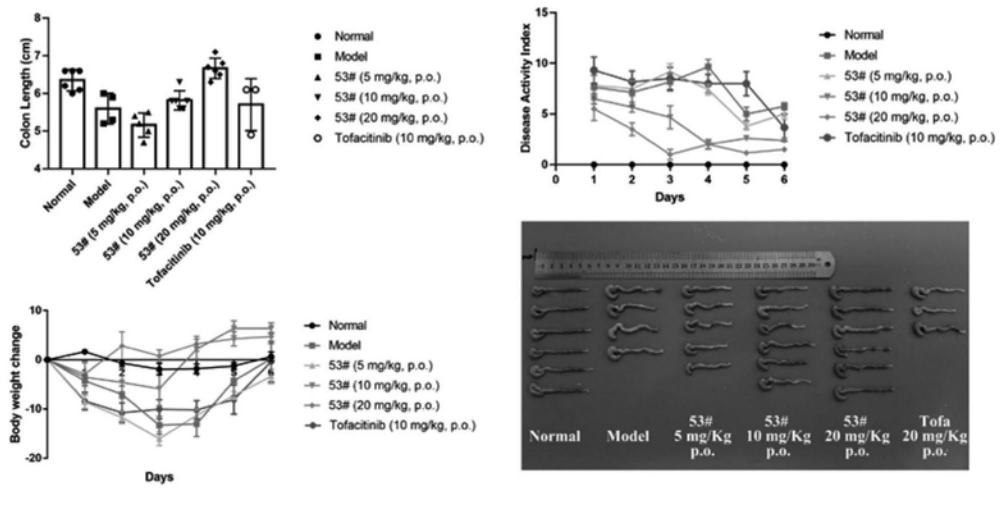

Colon Length (cm)
Normal
Model
53# (5 mg/kg, p.o.)
53# (10 mg/kg, p.o.)
53# (20 mg/kg, p.o.)
Tofacitinib (10 mg/kg, p.o.)
Disease Activity Index
Days
Body weight change
Normal
Model
53#
5 mg/Kg
p.o.
53#
10 mg/Kg
p.o.
53#
20 mg/Kg
p.o.
Tofa
20 mg/Kg
p.o.

图1

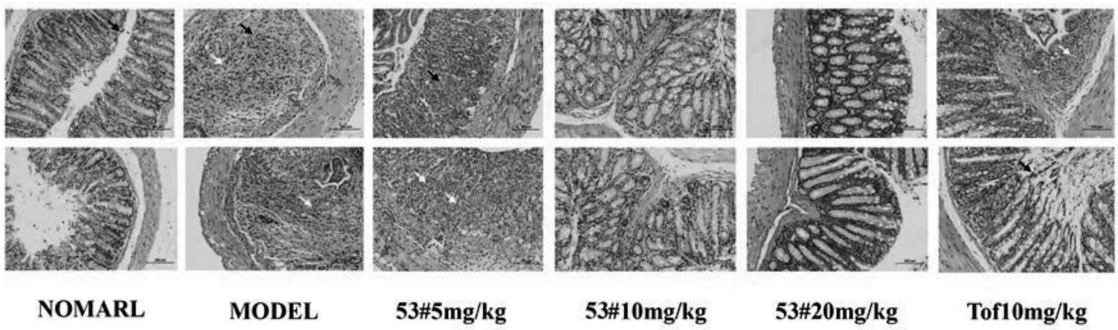

NOMARL
MODEL
53#5mg/kg
53#10mg/kg
53#20mg/kg
Tof10mg/kg

图2

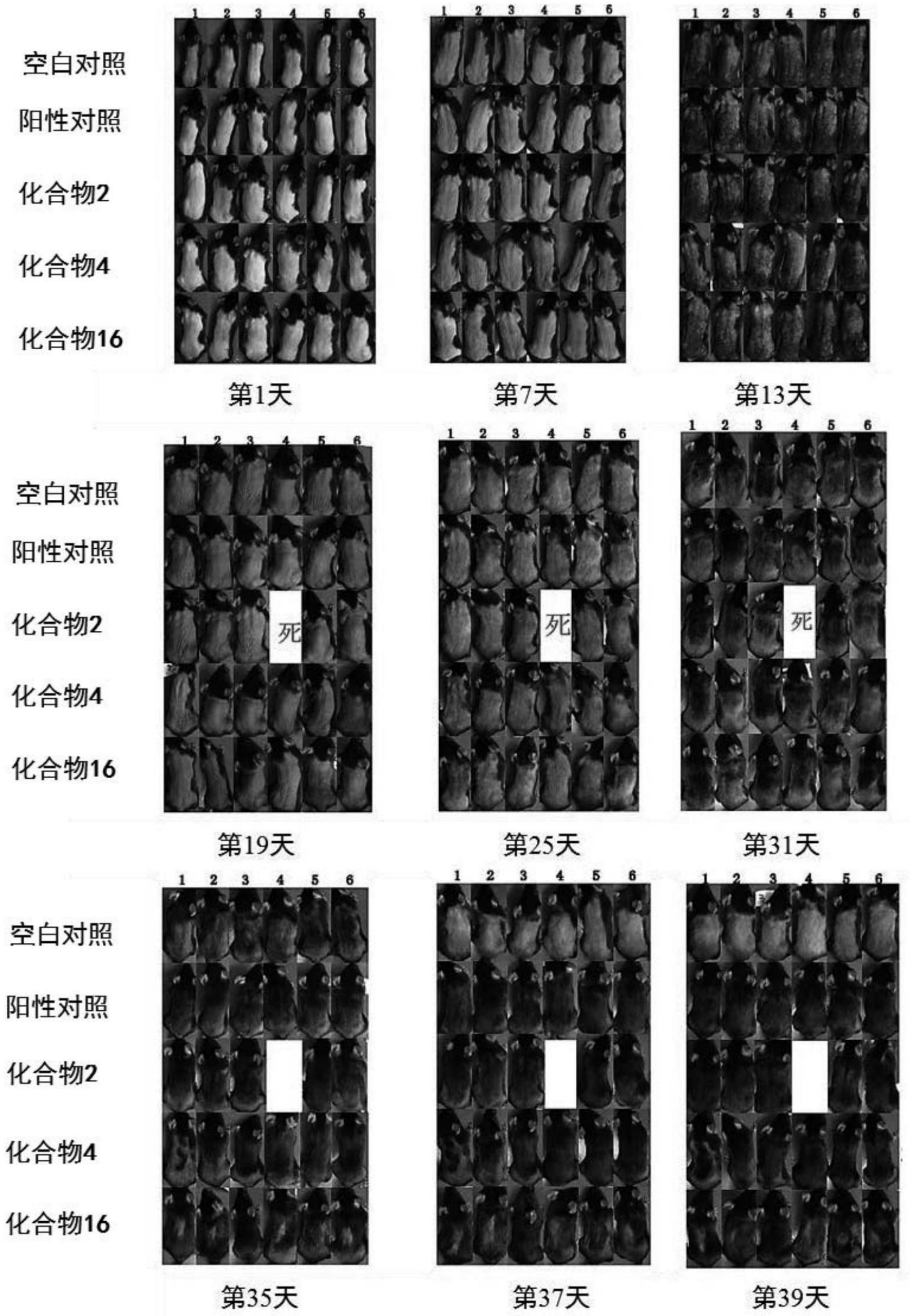

1 2 3 4 5 6
空白对照
阳性对照
化合物2
化合物4
化合物16
第1天
第7天
第13天
死
第19天
第25天
第31天
第35天
第37天
第39天

图3

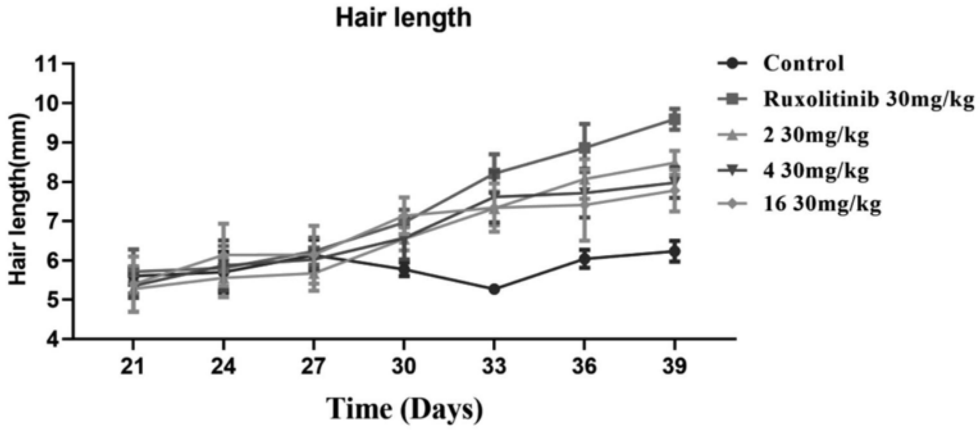

Hair length
Hair length(mm)
11
10
9
8
7
6
5
4
21
24
27
30
33
36
39
Time (Days)
Control
Ruxolitinib 30mg/kg
2 30mg/kg
4 30mg/kg
16 30mg/kg

图4