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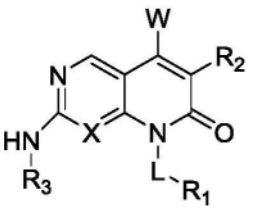
(54)发明名称

嘧啶并吡啶酮或者吡啶并吡啶酮类化合物及其应用

(57)摘要

一种具有式(I)结构的吡啶并嘧啶酮或者吡啶并吡啶酮类化合物或者其药学上可接受的盐或者其立体异构体或者其前药分子。该类化合物可以抑制EGFR的797位半胱氨酸突变成丝氨酸($EGFR^{C797S}$)突变体的活性,但对野生型EGFR活性较弱,可以有效抑制非小细胞肺癌肿瘤细胞的生长,可用于制备抗肿瘤药物,主要用于现有第三代EGFR小分子抑制剂类抗非小细胞肺癌药物Osimertinib(AZD9291),Olmutinib(HM6171),Rociletinib(9,CO-1686)等诱发的第797位半胱氨酸突变成丝氨酸(C797S)的临床耐药,其对野生型非小细胞肺癌具有选择性。



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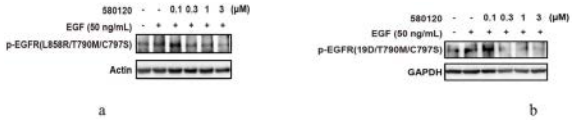
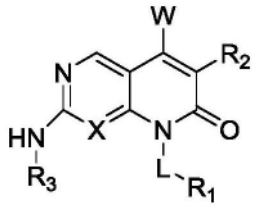


CN 110914267 B

1.具有式(I)结构的嘧啶并吡啶酮类化合物或者其药学上可接受的盐或者其立体异构体：

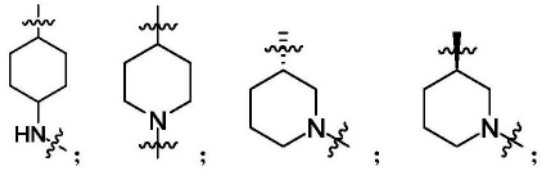


（Ⅰ）

其中，X任选自：N；

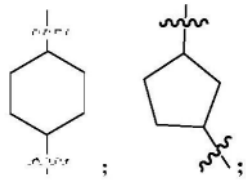
W任选自：H，CH_3，C_2-C_5烷基；

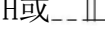
L任选自：

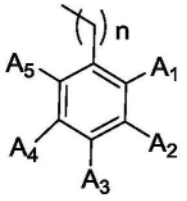


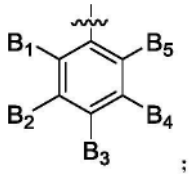
且R_1任选自：，其中，R_4任选自环丙基，环丁基，环戊基，环己基；

L任选自：



且R_1任选自：H或  ，其中，R_4任选自甲基，乙基，正丙基，异丙基，环丙基，正丁基，异丁基，叔丁基，环丁基，新戊基，环戊基，环己基；

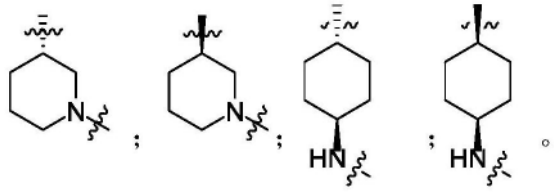
R_2任选自：  ，其中，n为0；A_1，A_2，A_3，A_4，A_5分别独立任选自：氢，氯，氟；

R_3任选自：  ，其中，

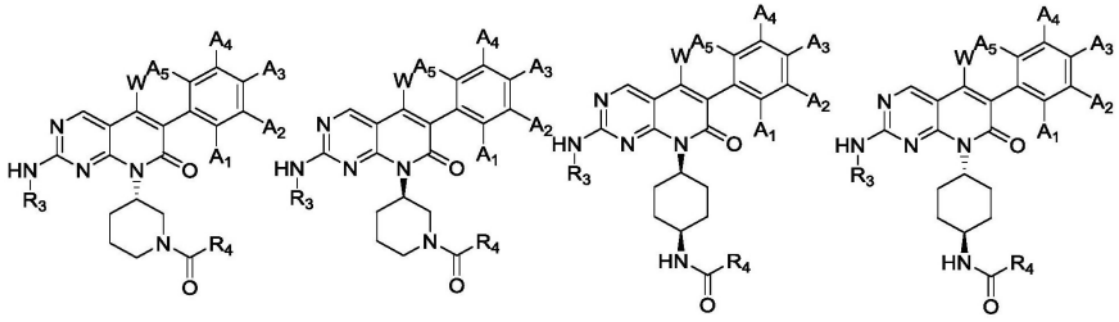
B_1，B_2，B_4，B_5分别独立任选自：H，氯，C_1～C_3烷基，

B_3选自：4-甲基哌嗪-1-基，N-乙基哌嗪基，4-异丙基哌嗪-1-基，哌啶基，9-甲基-3,9-二氮杂螺[5.5]十一烷-3-基，3-甲基-1,3-二氮杂环庚烷-1-基，(1S,4S)-5-甲基-2,5-二氮杂双环[2.2.1]庚-2-基，(2-(二甲基氨基)乙基)(甲基)氨基，4-(二甲基氨基)哌啶-1-基，7-甲基-2,7-二氮杂螺[3.5]壬烷-2-基，(R)-3,4-二甲基哌嗪-1-基，(S)-3,4-二甲基哌嗪-1-基，(3S,5R)-3,4,5-三甲基哌嗪-1-基，(R)-3-甲基哌嗪-1-基，4-(4-甲基哌嗪-1-基)哌啶-1-基。

2.根据权利要求1所述的嘧啶并吡啶酮类化合物或者其药学上可接受的盐或者其立体异构体，其特征在于，L选自：



3.根据权利要求1-2任一项所述的嘧啶并吡啶酮类化合物或者其药学上可接受的盐或者其立体异构体,其特征在于,所述化合物具有式III、式IV、式V或VI所示的结构:



III IV V VI。

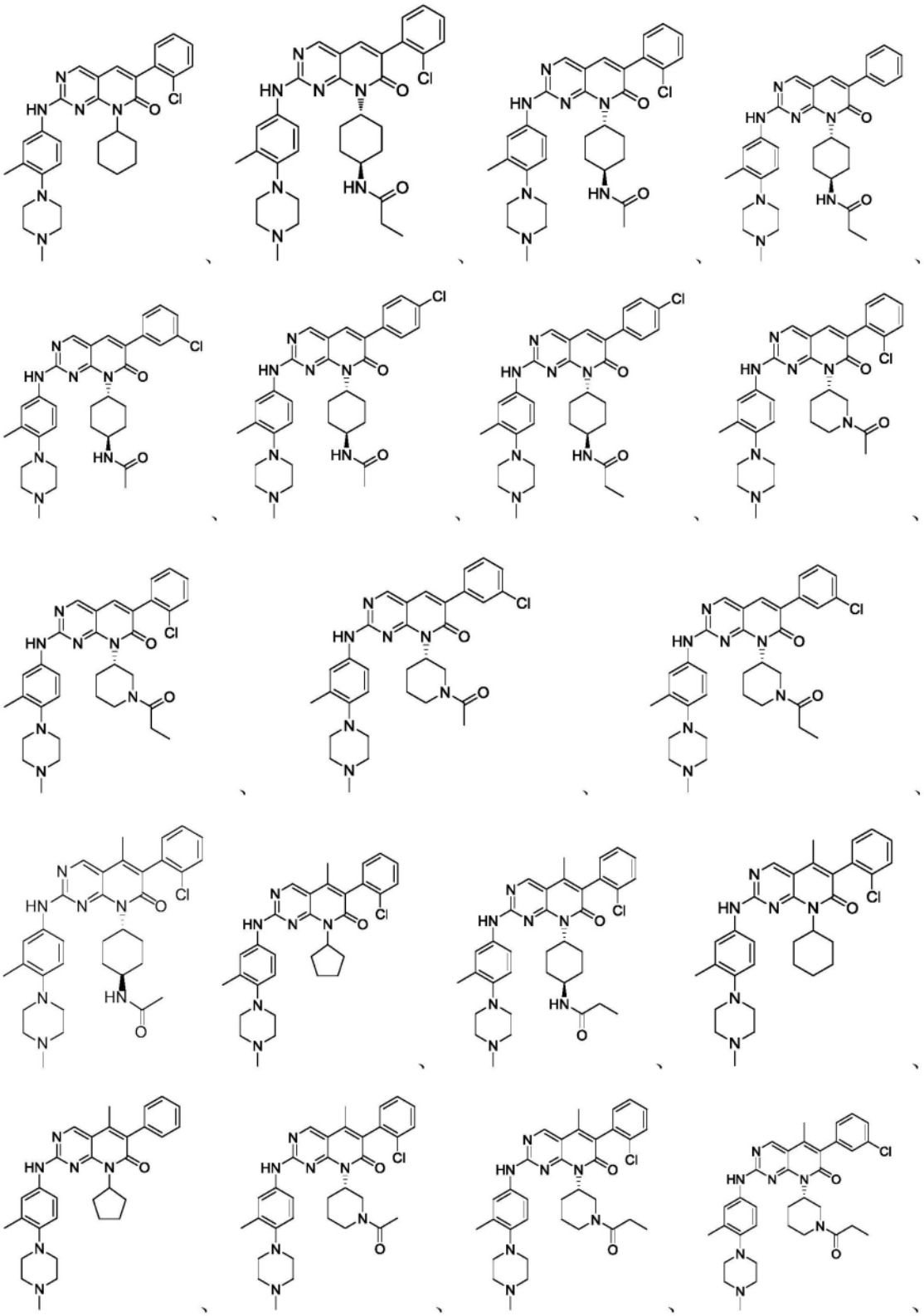
4.根据权利要求1-2任一项所述的嘧啶并吡啶酮类化合物或者其药学上可接受的盐或者其立体异构体,其特征在于,B_3选自:4-甲基哌嗪-1-基。

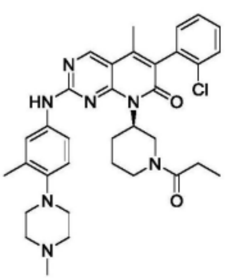
5.根据权利要求1-2任一项所述的嘧啶并吡啶酮类化合物或者其药学上可接受的盐或者其立体异构体,其特征在于,W选自:H,甲基,

B_1,B_2,B_4,B_5分别独立任选自:H,甲基,

B_3分别独立任选自:4-甲基哌嗪-1-基,哌啶基,9-甲基-3,9-二氮杂螺[5.5]十一烷-3-基,3-甲基-1,3-二氮杂环庚烷-1-基,(1S,4S)-5-甲基-2,5-二氮杂双环[2.2.1]庚-2-基,(2-(二甲基氨基)乙基)(甲基)氨基,4-(二甲基氨基)哌啶-1-基,7-甲基-2,7-二氮杂螺[3.5]壬烷-2-基,(R)-3,4-二甲基哌嗪-1-基,(3S,5R)-3,4,5-三甲基哌嗪-1-基,(R)-3-甲基哌嗪-1-基,4-(4-甲基哌嗪-1-基)哌啶-1-基。

6.嘧啶并吡啶酮类化合物或者其药学上可接受的盐或者其立体异构体,其特征在于,所述化合物选自:

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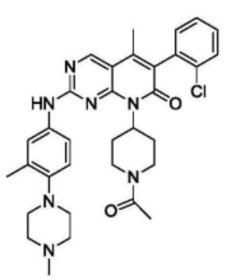
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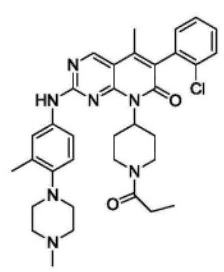
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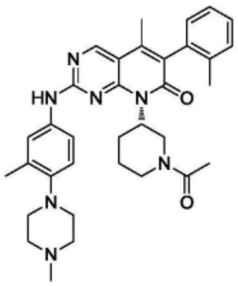
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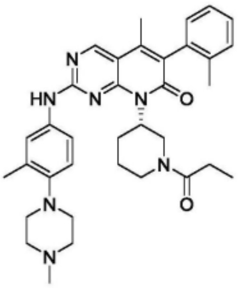
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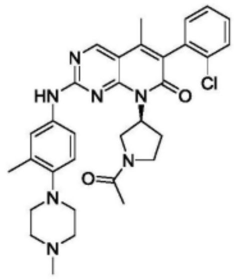
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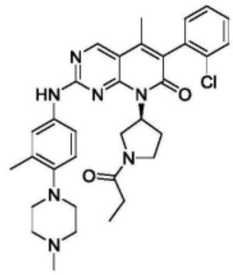
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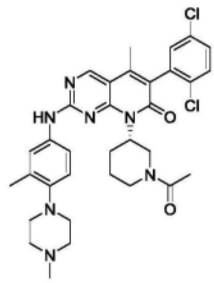
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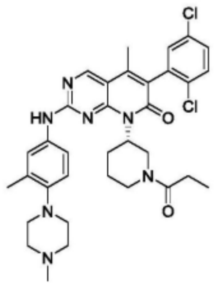
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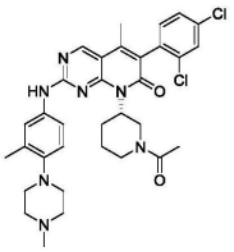
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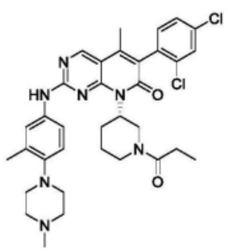
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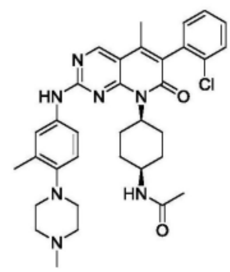
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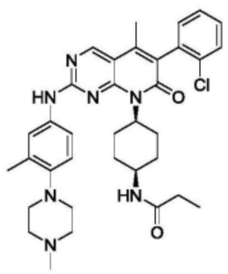
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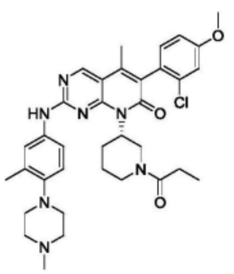
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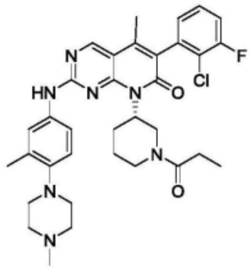
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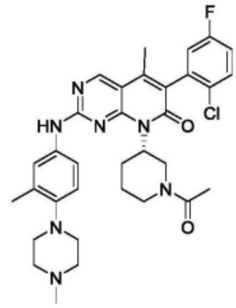
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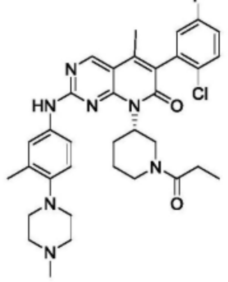
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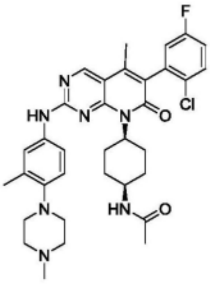
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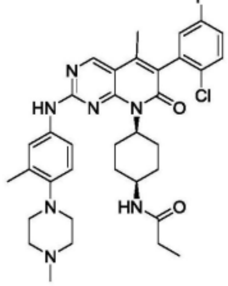
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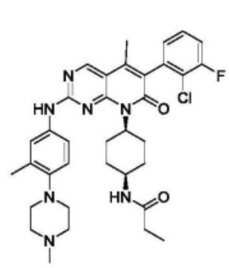
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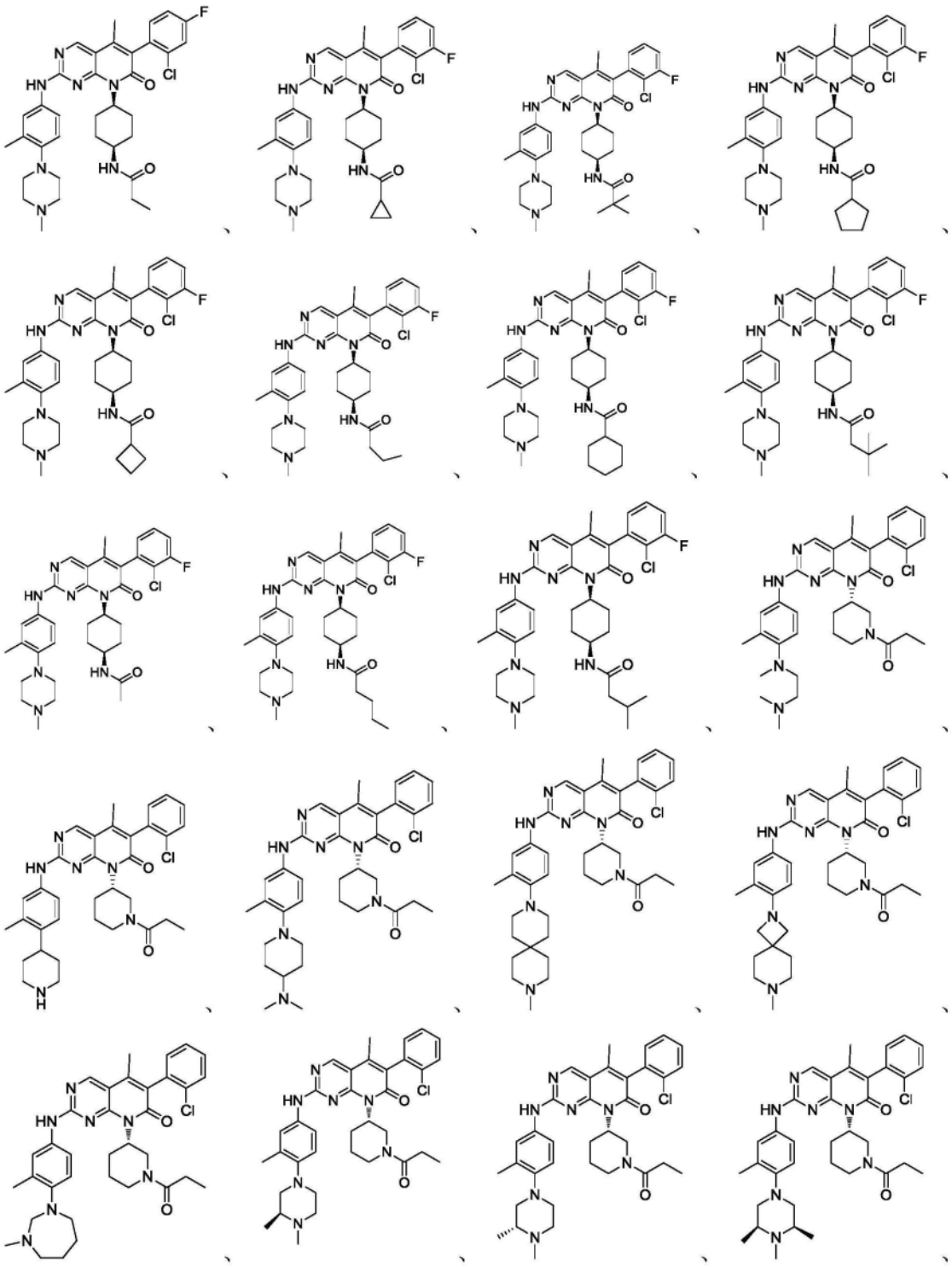
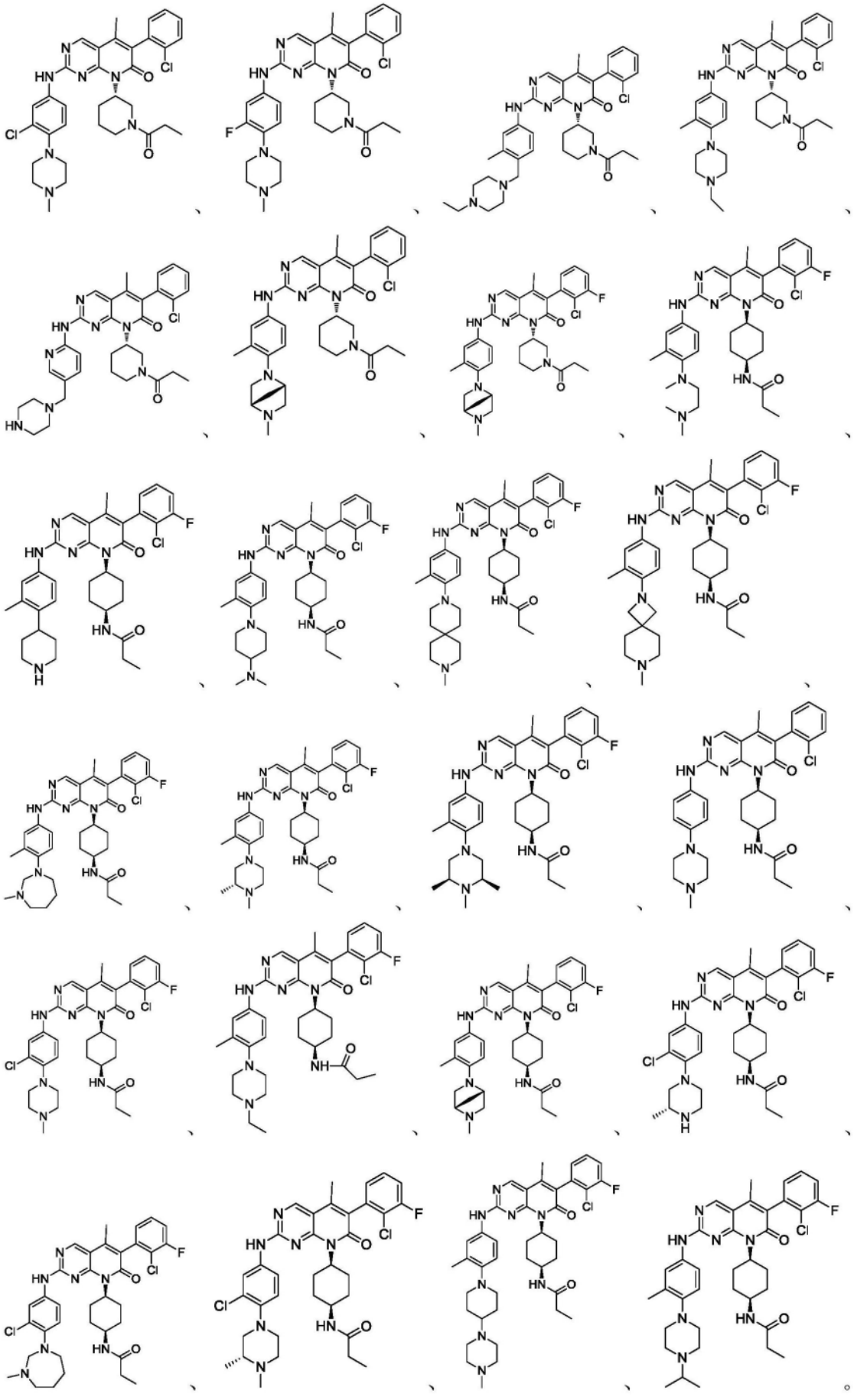




7.权利要求1－6任一项所述的嘧啶并吡啶酮类化合物或者其药学上可接受的盐或者其立体异构体在制备突变型EGFR抑制剂中的应用，所述突变型EGFR为$EGFR^{L858R/T790M}$或$EGFR^{L858R/T790M/C797S}$。

8.权利要求1－6任一项所述的嘧啶并吡啶酮类化合物或者其药学上可接受的盐或者其立体异构体在制备预防和治疗肿瘤的药物中的应用。

9.根据权利要求8所述的应用，其特征在于，所述肿瘤为EGFR基因突变的恶性肿瘤。

10.根据权利要求8所述的应用，其特征在于，所述肿瘤选自：非小细胞肺癌、恶性黑色素瘤、前列腺癌、肾癌、膀胱癌、卵巢癌、结肠癌、直肠癌、乳腺癌、宫颈癌、肺癌、喉癌、鼻咽癌、胰腺癌、多发性骨髓瘤、B淋巴瘤、白血病。

11.根据权利要求10所述的应用，其特征在于，所述肿瘤为$EGFR^{L858R/T790MC797S}$突变的非小细胞肺癌。

12.一种防治肿瘤的药物组合物，其特征在于，其活性成分包括有权利要求1—6任一项所述的嘧啶并吡啶酮类化合物或者其药学上可接受的盐或者其立体异构体。

嘧啶并吡啶酮或者吡啶并吡啶酮类化合物及其应用

技术领域

[0001] 本发明涉及化学医药领域,特别是涉及一种嘧啶并吡啶酮或者吡啶并吡啶酮类化合物及其应用。

背景技术

[0002] 肿瘤分子靶向治疗是基于对肿瘤生长密切相关的关键分子通过化学或生物学手段选择性杀伤肿瘤细胞的一种治疗方法。靶向治疗的特点为:特异性高,选择性强,毒副作用较轻;联合应用时,它可加强传统化疗、放疗的疗效,减少术后复发。以伊马替尼甲磺酸盐(STI571)(Novartis,2001),吉非替尼(ZD1839)(AstraZeneca,2003),厄罗替尼(OSI774)(Genentech and OSIP,2004),索拉菲尼对甲苯磺酸盐(Bay 43-9006)(Bayer and Onyx,2005),舒尼替尼苹果酸盐(SU11248)(Pfizer,2006)以及达沙替尼(BMS-354825)(Bristol-Myers Squibb,2006)为代表的靶向药物为肿瘤化疗开创了一个新时代。肿瘤靶向治疗在短短几年内得到了迅速发展。肿瘤靶向治疗的出现已对传统给药观念和模式构成冲击,例如,因毒副作用小靶向药物在I期临床试验中往往无法达到剂量限制性毒性和最大耐受剂量;用靶向治疗药物时无需用最大耐受剂量即可达到满意疗效。肿瘤靶向治疗是肿瘤治疗的热点和发展趋势。

[0003] 表皮生长因子受体(EGFR),一种受体酪氨酸蛋白激酶,调控了细胞的增殖,存活,粘连,迁移与分化。EGFR在多种肿瘤细胞中过度活化或持续活化,比如肺癌,乳腺癌,前列腺癌等。大约62%的非小细胞肺癌患者存在EGFR过量表达,对EGFR的抑制能显著提高部分患者的生存期。并且,2003～2004年上市的EGFR小分子抑制剂药物Gefitinib和Erlotinib,已经被用于晚期非小细胞肺癌的治疗,进一步明确了EGFR是治疗非小细胞肺癌的有效靶点。

[0004] 第一代EGFR小分子抑制剂在携带EGFR敏感突变的患者中获得了显著的临床疗效,延长了他们的生存期。但获益患者在使用药物10～12个月后,大部分患者会产生耐药。其中,超过50%的耐药患者(携带EGFR敏感突变)是由于EGFR发生了T790M二次突变产生耐药。相比L858R敏感突变的EGFR,L858R/T790M二次突变的EGFR对ATP的亲和力更强,而第一代药物均是ATP竞争性抑制剂,因此导致药物耐药。

[0005] 第二代EGFR不可逆抑制剂虽然在临床前研究获得较好的结果,但对野生型EGFR(EGFRWT)缺乏选择性,具有较大毒性。2013年FDA批准的EGFR不可逆抑制剂Gilotrif虽然对携带激活性EGFR突变(L858R,del E746-A750)的晚期NSCLC病人有效,但在临床最大耐受剂量(MTD)下,仍无法解决EGFRT790M突变引起的临床耐药。

[0006] 第三代克服EGFRT790M耐药的不可逆抑制剂Osimertinib(AZD9291),于2015年11月,获得美国FDA加速批准上市(Cancer discovery 2014,4(9),1046-1061),其在临床上能够有效治疗表皮生长因子受体(EGFR)T790M突变或对其它EGFR抑制剂耐药的晚期非小细胞肺癌患者。尽管Osimertinib在临床上治疗EGFRT790M突变的非小细胞肺癌取得了较大的成功,但是部分受益患者在经过9～14个月治疗后又出现了耐药的现象(Nature Medicine 2015,21(6),560-2)。经研究发现,高达40%的耐药患者由于(EGFR)C797S点突变导致了

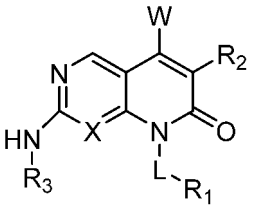
Osimertinib耐药。进一步的机制研究表明，(EGFR)C797S的点突变使797位的半胱氨酸转变为丝氨酸，导致Osimertinib无法与靶蛋白形成共价结合，最终引起耐药。目前临床尚缺乏针对新突变(C797S)单独用药有效的EGFR抑制剂。因此，迫切需要新类型，高选择性的EGFR抑制剂来解决(EGFR)C797S点突变导致的药物耐药性等问题。

发明内容

[0007] 基于此，本发明提供了一类新的嘧啶并吡啶酮或者吡啶并吡啶酮类化合物，该类化合物能够选择性抑制突变型EGFR的活性，可以克服现有EGFR酪氨酸激酶抑制剂的耐药性问题。

[0008] 具体技术方案如下：

[0009] 具有式(I)结构的嘧啶并吡啶酮或者吡啶并吡啶酮类化合物或者其药学上可接受的盐或者其立体异构体或者其前药分子：

[0010] 

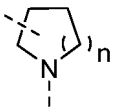
（Ⅰ）

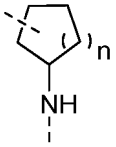
[0011] 其中，X任选自：CH或N；

[0012] W任选自：H，D，CH_3，CD_3，CF_3，CH_2F，CHF_2，F，Cl，Br，C_2-C_5烷基，C_3-C_6环烷基，取代的C_3-C_6环烷基；

[0013] L任选自：

[0014] (1)-$(CH_2)_n$NH-，其中n选自1-8之间的整数；

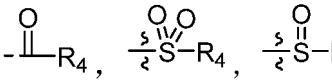
[0015] (2)  其中n任选自0，1，2，3；

[0016] (3)  其中n任选自0，1，2，3；

[0017] (4)C_5-C_{10}的单环烷基、桥环烷基或并环烷基；

[0018] R_1任选自：

[0019] (1)H，C_1～C_4烷氧基；

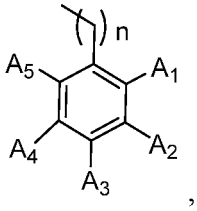
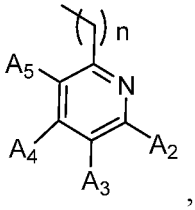
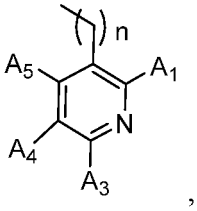
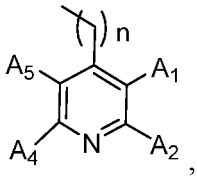
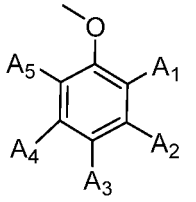
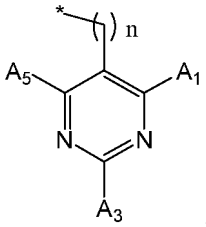
[0020] (2)  其中R_4任选自C_1-C_6烷基，C_3-C_6环烷基；

[0021] (3)$(CH_2)_n$Y，n＝0～6，Y选自卤素，羟基，氨基，(N-甲基)氨基，(N，N-二甲基)氨基；

[0022] R_2任选自：

[0023] (1)H，C_1-C_3烷基，C_3-C_6环烷基，取代的C_3-C_6环烷基；

[0024] (2)

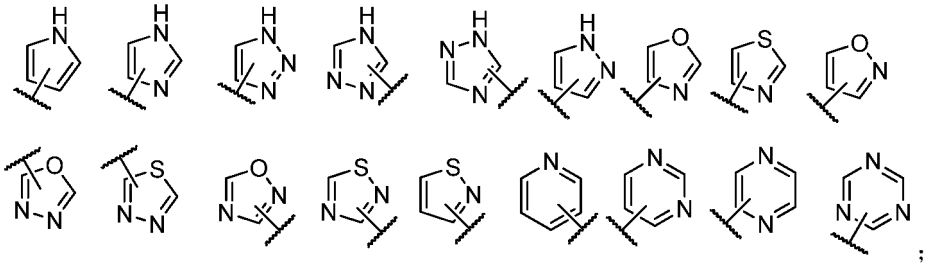







其中，n任选自0，1，2；A_1，A_2，A_3，A_4，A_5分别独立任选自：

[0025] (a)氢，卤素，C_1～C_4烷基，C_3～C_6环烷基，取代的C_3～C_6环烷基，C_1～C_4烷氧基，C_1～C_6含氟烷基，C_1～C_6含杂原子烷基，NO_2，CN，COOH，$CONH_2$；

[0026] (b)  其中，R_5，R_6分别独立选自C_1～C_5烷基，C_3～C_6环烷基，取代的C_3～C_6环烷基，R_5与R_6环合形成的含有1-3个杂原子的4-8元饱和杂环，R_5与R_6环合形成的含有1-3个杂原子的4-8元芳香杂环；

[0027] (c)含一个或多个氮原子并带有0-3个取代基的5元或6元芳香基，所述芳香基选自：

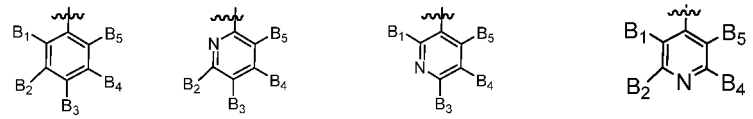
[0028]  ；

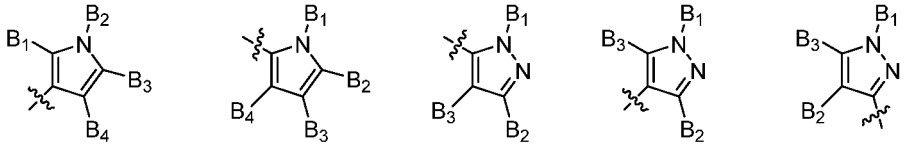
[0029] (d)A_1，A_2，A_3，A_4，A_5中任两个相邻取代基之间形成含有0-3个杂原子的5-12元饱和碳环或杂环；

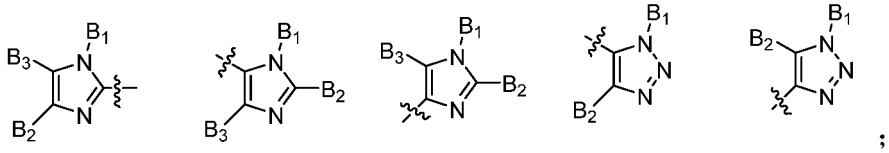
[0030] R_3任选自：

[0031] (1)C_1-C_6烷基，C_3-C_6环烷基；

[0032] (2)



[0033] 

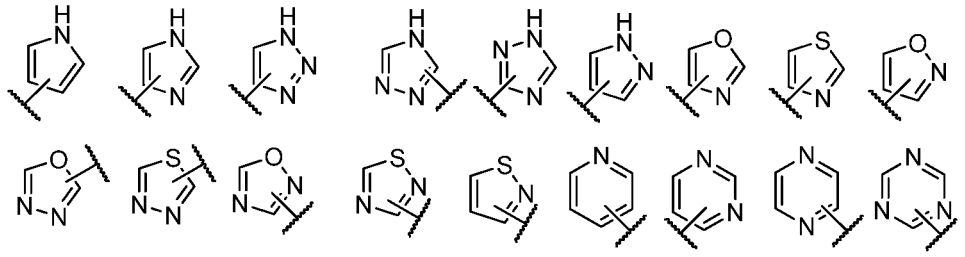

;

[0034] 其中B_1,B_2,B_3,B_4,B_5分别独立任选自:

[0035] (a)H,卤素,取代或未取代的C_1～C_6烷基,取代的乙氧基,C_1～C_4烷氧基,C_1～C_3含氟烷基,取代或未取代的C_4～C_6含杂原子烷基,C_4～C_9杂环基或者所述杂环基形成的酰胺,硝基,氰基;

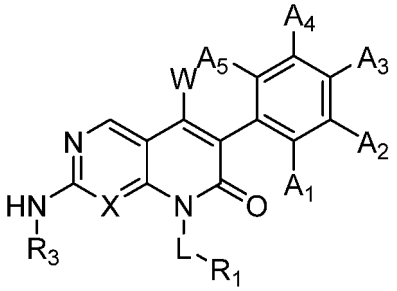
[0036] (b)  ,其中,R_5,R_6分别独立选自取代或未取代的C_1～C_5烷基,C_3～C_6环烷基,取代的C_3～C_6环烷基,R_5与R_6环合形成的含有1-3个杂原子的取代或未取代的4-8元饱和杂环,R_5与R_6环合形成的含有1-3个杂原子的取代或未取代的4-8元芳香杂环,R_5与R_6环合形成的含有1-3个杂原子的取代或未取代的8-12元饱和螺环,R_5与R_6环合形成的含有1-3个杂原子的取代或未取代的8-12元饱和稠环,R_5与R_6环合形成的含有1-3个杂原子的取代或未取代的8-12元饱和桥环;

[0037] (c)含一个或多个氮原子并带有0-3个取代基的5元或6元芳香基,所述芳香基选自:

[0038] 
;

[0039] (d)B_1,B_2,B_3,B_4,B_5中任两个相邻取代基之间形成含有0-3个杂原子的5-12元饱和碳环或杂环。

[0040] 在其中一些实施例中,所述化合物具有式(II)所示结构:

[0041] 
(Ⅱ)。

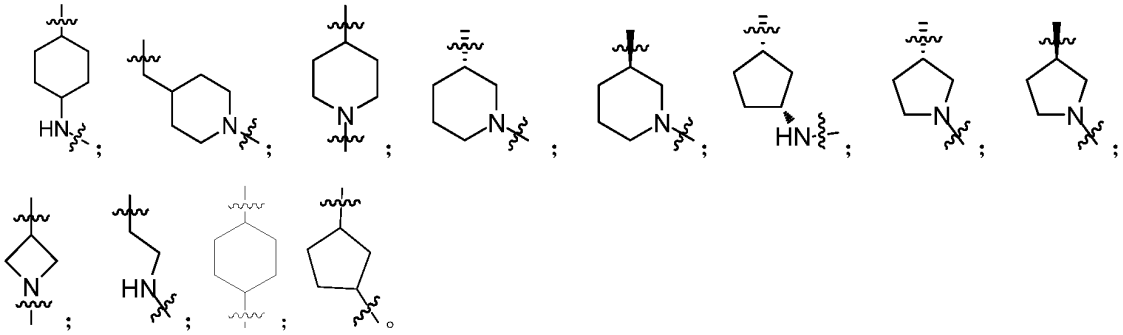
[0042] 在其中一些实施例中，A_1，A_2，A_3，A_4，A_5分别独立任选自：A_1，A_2，A_3，A_4，A_5分别独立任选自：氢，卤素，C_1～C_4烷基，C_3～C_6环烷基，C_1～C_4烷氧基，N，N-二甲基氨基乙氧基，N，N-二甲基氨基丙氧基，2-(N-甲基哌嗪基)乙氧基，2-(N-乙酰基哌嗪基)乙氧基，2-吗啡啉基乙氧基，2-硫啡啉基乙氧基，2-哌啶基乙氧基，2-四氢吡咯基乙氧基，N-甲基哌嗪基，吗啡啉基，硫啡啉，哌啶，四氢吡咯，咪唑，3-N，N-二甲基四氢吡咯，4-N，N-二甲基哌啶，4-乙酰基哌嗪，1-甲基-4-(哌嗪-4-取代)哌啶，4-(4-甲基哌嗪-1-取代)甲基，1-甲基哌啶-4-氨基，4-哌嗪-2-酮，1-甲基-4-哌嗪-2-酮，以及上述基团形成的酯，酰胺，砜，亚砜，脲。

[0043] 在其中一些实施例中，A_1，A_2，A_3，A_4，A_5分别独立任选自：氢，卤素，C_1～C_4烷基，C_3～C_6环烷基，C_1～C_4烷氧基。

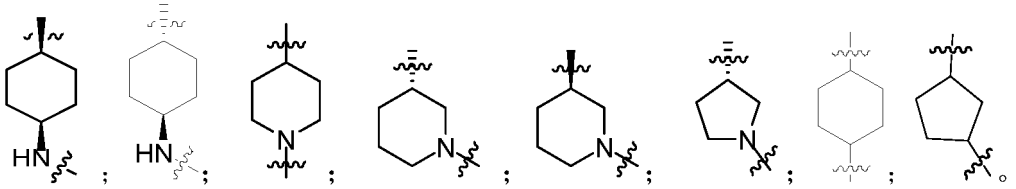
[0044] 在其中一些实施例中，A_1，A_2，A_3，A_4，A_5分别独立任选自：氢，氯，氟，甲基，甲氧基。

[0045] 在其中一些实施例中，W选自H，C_1-C_5烷基。

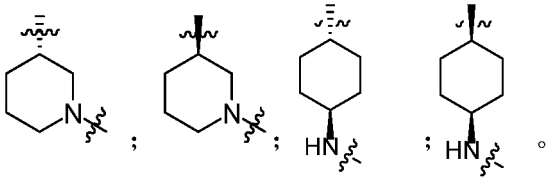
[0046] 在其中一些实施例中，L选自：

[0047] 

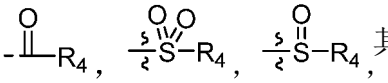
[0048] 在其中一些实施例中，L选自：

[0049] 

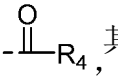
[0050] 在其中一些实施例中，L选自：

[0051] 

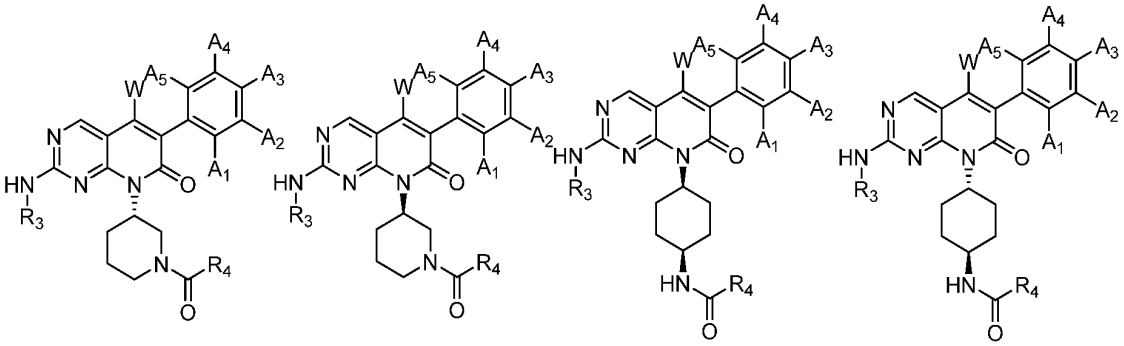
[0052] 在其中一些实施例中，R_1任选自：

[0053]  其中R_4任选自甲基，乙基，正丙基，异丙基，环丙基，正丁基，异丁基，叔丁基，环丁基，新戊基，环戊基，环己基。

[0054] 在其中一些实施例中，R_1任选自：

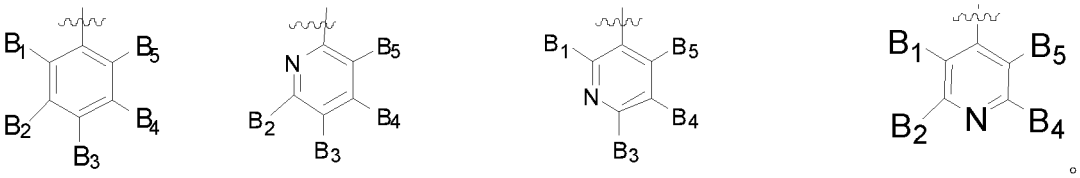
[0055]  其中R_4任选自甲基，乙基，正丙基，异丙基，环丙基，正丁基，异丁基，叔丁基，环丁基，新戊基，环戊基，环己基。

[0056] 在其中一些实施例中，所述化合物具有式III、式IV、式V或VI所示的结构：

[0057] 

III IV V VI。

[0058] 在其中一些实施例中，R_3任选自：

[0059] 

。

[0060] 在其中一些实施例中，B_1，B_2，B_3，B_4，B_5分别独立任选自：H，取代或未取代的C_1～C_6烷基，卤素，C_1-C_4烷氧基，C_1～C_3含氟烷基，取代的乙氧基，取代或未取代的C_4～C_9杂环基，  以及上述基团形成的酯，酰胺，砜，亚砜，脲；

[0061] 其中，R_5，R_6分别独立选自取代或未取代的C_1～C_5烷基，R_5与R_6环合形成的含有1-3个杂原子的取代或未取代的4-8元饱和杂环，R_5与R_6环合形成的含有1-3个杂原子的取代或未取代的4-8元芳香杂环，R_5与R_6环合形成的含有1-3个杂原子的取代或未取代的8-12元饱和螺环，R_5与R_6环合形成的含有1-3个杂原子的取代或未取代的8-12元饱和稠环，R_5与R_6环合形成的含有1-3个杂原子的取代或未取代的8-12元饱和桥环。

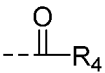
[0062] 在其中一些实施例中，B_1，B_2，B_3，B_4，B_5分别独立任选自：H，C_1～C_6烷基，卤素，C_1-C_4烷氧基，C_1～C_3含氟烷基，N，N-二甲基氨基乙氧基，N，N-二甲基氨基丙氧基，2-(N-甲基哌嗪基)乙氧基，2-(N-乙酰基哌嗪基)乙氧基，2-吗啡啉基乙氧基，2-硫啡啉基乙氧基，2-哌啶基乙氧基，2-四氢吡咯基乙氧基，N-甲基哌嗪基，N-乙基哌嗪基，哌嗪基，(R)-3，4-二甲基哌嗪基，(S)-3，4-二甲基哌嗪基，4-异丙基哌嗪-1-基，(3S，5R)-3，4，5-三甲基哌嗪-1-基，吗啡啉基，硫啡啉，哌啶基，4-(二甲基氨基)哌啶基，四氢吡咯基，咪唑基，3-N，N-二甲基四氢吡咯基，4-N，N-二甲基哌啶基，4-乙酰基哌嗪，1-甲基-4-(哌嗪-4-取代)哌啶基，4-(4-甲基哌嗪-1-基)哌啶基，4-(4-甲基哌嗪-1-取代)甲基，1-甲基哌啶-4-氨基，4-哌嗪-2-酮，1-甲基-4-哌嗪-2-酮，7-甲基-2，7-二氮杂螺[3.5]壬烷-2-基，9-甲基-3，9-二氮杂螺[5.5]十一烷-3-基，3-甲基-1，3-二氮杂环庚-1-基，(1S，4S)-5-甲基-2，5-二氮杂双环[2.2.1]庚-2-基，(2-(二甲基氨基)乙基)(甲基)氨基，(3AR，6AS)-5-甲基六氢吡咯并[3，4-c]吡咯-2(1H)-基，4-(氧杂环丁烷-3-基)哌嗪，4-乙基哌嗪-1-基)甲基，哌嗪-1-基甲基，以及上述基团形成的酯，酰胺，砜，亚砜，脲。

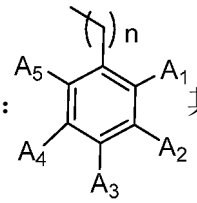
[0063] 在其中一些实施例中，B_1，B_2，B_3，B_4，B_5分别独立任选自：H，C_1～C_3烷基，卤素，4-甲基哌嗪-1-基，4-异丙基哌嗪-1-基，哌啶基，9-甲基-3，9-二氮杂螺[5.5]十一烷-3-基，3-甲基-1，3-二氮杂环庚烷-1-基，(1S，4S)-5-甲基-2，5-二氮杂双环[2.2.1]庚-2-基，(2-(二甲

基氨基)乙基)(甲基)氨基,4-(二甲基氨基)哌啶-1-基,7-甲基-2,7-二氮杂螺[3.5]壬烷-2-基,(R)-3,4-二甲基哌嗪-1-基,(3S,5R)-3,4,5-三甲基哌嗪-1-基,(R)-3-甲基哌嗪-1-基,4-(4-甲基哌嗪-1-基)哌啶-1-基。

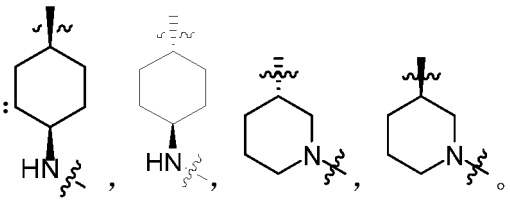
[0064] 在其中一些实施例中,B_1,B_2,B_4,B_5分别独立任选自:H,C_1～C_3烷基,卤素;B_3选自:4-甲基哌嗪-1-基,4-异丙基哌嗪-1-基,哌啶基,9-甲基-3,9-二氮杂螺[5.5]十一烷-3-基,3-甲基-1,3-二氮杂环庚烷-1-基,(1S,4S)-5-甲基-2,5-二氮杂双环[2.2.1]庚-2-基,(2-(二甲基氨基)乙基)(甲基)氨基,4-(二甲基氨基)哌啶-1-基,7-甲基-2,7-二氮杂螺[3.5]壬烷-2-基,(R)-3,4-二甲基哌嗪-1-基,(3S,5R)-3,4,5-三甲基哌嗪-1-基,(R)-3-甲基哌嗪-1-基,4-(4-甲基哌嗪-1-基)哌啶-1-基。

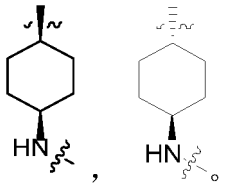
[0065] 在其中一些实施例中,W选自:H,甲基;X选自N;

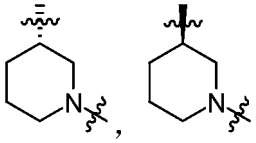
[0066] R_1选自:  ,其中,R_4选自:甲基,乙基,正丙基,异丙基,环丙基,正丁基,异丁基,叔丁基,环丁基,新戊基,环戊基,环己基;

[0067] R_2选自:  其中,n为0;A_1,A_2,A_3,A_4,A_5分别独立任选自:氢,氯,氟;

[0068] B_1,B_2,B_3,B_4,B_5分别独立任选自:H,甲基,卤素,4-甲基哌嗪-1-基,哌啶基,9-甲基-3,9-二氮杂螺[5.5]十一烷-3-基,3-甲基-1,3-二氮杂环庚烷-1-基,(1S,4S)-5-甲基-2,5-二氮杂双环[2.2.1]庚-2-基,(2-(二甲基氨基)乙基)(甲基)氨基,4-(二甲基氨基)哌啶-1-基,7-甲基-2,7-二氮杂螺[3.5]壬烷-2-基,(R)-3,4-二甲基哌嗪-1-基,(3S,5R)-3,4,5-三甲基哌嗪-1-基,(R)-3-甲基哌嗪-1-基,4-(4-甲基哌嗪-1-基)哌啶-1-基;

[0069] L选自:  。

[0070] 在其中一些实施例中,W为H;R_4选自:甲基,乙基,正丙基,异丙基,环丙基;A_1为氯,A_2,A_3,A_4,A_5均为氢;B_2为甲基,B_3为4-甲基哌嗪-1-基,B_1,B_4,B_5均为H;L选自:  。

[0071] 在其中一些实施例中,W为甲基;R_4选自:甲基,乙基,正丙基,异丙基,环丙基;A_1为氯,A_2,A_3,A_4,A_5均为氢;B_2为甲基,B_3为4-甲基哌嗪-1-基,B_1,B_4,B_5均为H;L选自:  。

[0072] 在其中一些实施例中,所述化合物选自:

[0073] 6-(2-氯苯基)-8-环己基-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)吡啶并

[2,3-d]嘧啶-7(8H)-酮、

[0074] 6-(2-氯苯基)-8-环戊基-5-甲基-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)吡啶并[2,3-d]嘧啶-7-(8H)-酮、

[0075] N-((1R,4R)-4-(6-(2-氯苯基)-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)-7-氧代吡啶并[2,13-d]嘧啶-8(7H)-基)环己基)丙酰胺、

[0076] N-((1R,4R)-4-(6-(2-氯苯基)-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)-7-氧代吡啶并[2,3-d]嘧啶-8(7H)-基)环己基)乙酰胺、

[0077] N-((1R,4R)-4-(6-(2-氯苯基)-5-甲基-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)-7-氧代吡啶并[2,3-d]嘧啶-8(7H)-基)环己基)丙酰胺、

[0078] N-((1R,4R)-4-(6-(2-氯苯基)-5-甲基-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)-7-氧代吡啶并[2,3-d]嘧啶-8(7H)-基)环己基)乙酰胺、

[0079] N-((1R,4R)-4-(2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)-7-氧代-6-苯基吡啶并[2,3-d]嘧啶-8(7H)-基)环己基)乙酰胺、

[0080] N-((1R,4R)-4-(2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)-7-氧代-6-苯基吡啶并[2,3-d]嘧啶-8(7H)-基)环己基)丙酰胺、

[0081] N-((1R,4R)-4-(6-(3-氯苯基)-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)-7-氧代吡啶并[2,3-d]嘧啶-8(7H)-基)环己基)乙酰胺、

[0082] N-((1R,4R)-4-(6-(3-氯苯基)-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)-7-氧代吡啶并[2,13-d]嘧啶-8(7H)-基)环己基)丙酰胺、

[0083] 6-(2-氯苯基)-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)-8-(1-乙酰基哌啶-4-基)吡啶并[2,3-d]嘧啶-7(8H)-酮、

[0084] S)-8-(1-乙酰基吡咯-3-基)-6-(2-氯苯基)-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)吡啶并[2,3-d]嘧啶-7(8H)-酮

[0085] 6-(2-氯苯基)-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)-8-(1-丙酰基哌啶-4-基)吡啶并[2,3-d]嘧啶-7(8H)-酮、

[0086] (S)-6-(2-氯苯基)-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)-8-(1-丙酰基吡咯烷-3-基)吡啶并[2,3-d]嘧啶-7(8H)-酮、

[0087] 6-(2-氯苯基)-8-环己基-5-甲基-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)吡啶并[2,3-d]嘧啶-7-(8H)-酮、

[0088] 6-(3-氯苯基)-8-环己基-5-甲基-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)吡啶并[2,3-d]嘧啶-7-(8H)-酮、

[0089] 8-环己基-5-甲基-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)-6-苯基吡啶并[2,3-d]嘧啶-7(8H)-酮、

[0090] 8-环己基-6-(2-氟苯基)-5-甲基-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)吡啶并[2,3-d]嘧啶-7-(8H)-酮、

[0091] 8-环己基-5-甲基-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)-6-(邻甲苯基)吡啶并[2,3-d]嘧啶-7-(8H)-酮、

[0092] 8-环己基-6-(2-甲氧基苯基)-5-甲基-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)吡啶并[2,3-d]嘧啶-7-(8H)-酮、

[0093] 6-(4-氯苯基)-8-环己基-5-甲基-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)吡啶并[2,3-d]嘧啶-7-(8H)-酮、

[0094] 8-((3S,5S,7S)-金刚烷-1-基)-6-(2-氯苯基)-5-甲基-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基基)氨基)吡啶并[2,3-d]嘧啶-7(8H)-酮、

[0095] 8-环己基-5-甲基-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)吡啶并[2,3-d]嘧啶-7(8H)-酮、

[0096] 8-环戊基-5-甲基-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)-6-苯基吡啶并[2,3-d]嘧啶-7(8H)-酮、

[0097] 6-(3-氯苯基)-8-环戊基-5-甲基-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)吡啶并[2,3-d]嘧啶-7-(8H)-酮、

[0098] N-((1R,4R)-4-(6-(4-氯苯基)-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)-7-氧代吡啶并[2,3-d]嘧啶-8(7H)-基)环己基)乙酰胺、

[0099] N-((1R,4R)-4-(6-(4-氯苯基)-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)-7-氧代吡啶并[2,3-d]嘧啶-8(7H)-基)环己基)丙酰胺、

[0100] (S)-8-(1-乙酰基-3-基)-6-(2-氯苯基)-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)吡啶并[2,3-d]嘧啶-7(8H)-酮、

[0101] (S)-6-(2-氯苯基)-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)-8-(1-丙酰基哌啶-3-基)吡啶并[2,3-d]嘧啶-7(8H)-酮、

[0102] (S)-8-(1-乙酰基-3-基)-6-(2-氯苯基)-5-甲基-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)吡啶并[2,3-d]嘧啶-7(8H)-酮、

[0103] (S)-6-(2-氯苯基)-5-甲基-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)-8-(1-丙酰基哌啶-3-基)吡啶并[2,3-d]嘧啶-7(8H)-酮、

[0104] (S)-8-(1-乙酰基-3-基)-6-(3-氯苯基)-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)吡啶并[2,3-d]嘧啶-7(8H)-酮、

[0105] (S)-6-(3-氯苯基)-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)-8-(1-丙酰基哌啶-3-基)吡啶并[2,3-d]嘧啶-7(8H)-酮、

[0106] (S)-8-(1-乙酰基-3-基)-6-(3-氯苯基)-5-甲基-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)吡啶并[2,3-d]嘧啶-7(8H)-酮、

[0107] (S)-6-(3-氯苯基)-5-甲基-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)-8-(1-丙酰基哌啶-3-基)吡啶并[2,3-d]嘧啶-7(8H)-酮、

[0108] (S)-8-(1-丙酰基-3-基)-6-(2-氯苯基)-5-甲基-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)吡啶并[2,3-d]嘧啶-7(8H)-酮、

[0109] 8-(1-乙酰基哌啶-4-基)-6-(2-氯苯基)-5-甲基-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)吡啶并[2,3-d]嘧啶-7(8H)-酮、

[0110] 6-(2-氯苯基)-5-甲基-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)-8-(1-丙哌啶-4-基)吡啶并[2,3-d]嘧啶-7(8H)-酮、

[0111] (S)-8-(1-乙酰基-3-基)-5-甲基-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)-6-(邻甲苯基)吡啶并[2,3-d]嘧啶-7(8H)-酮、

[0112] (S)-8-(1-丙酰基-3-基)-5-甲基-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨

基)-6-(邻甲苯基)吡啶并[2,3-d]嘧啶-7(8H)-酮、

[0113] (R)-8-(1-乙酰吡咯烷-3-基)-6-(2-氯苯基)-5-甲基-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)吡啶并[2,3-d]嘧啶-7(8H)-酮、

[0114] (R)-8-(1-丙酰吡咯烷-3-基)-6-(2-氯苯基)-5-甲基-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)吡啶并[2,3-d]嘧啶-7(8H)-酮、

[0115] (S)-8-(1-乙酰基-3-基)-6-(2,5-二氯苯基)-5-甲基-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)吡啶并[2,3-d]嘧啶-7(8H)-酮、

[0116] (S)-8-(1-丙酰基-3-基)-6-(2,5-二氯苯基)-5-甲基-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)吡啶并[2,3-d]嘧啶-7(8H)-酮、

[0117] (S)-8-(1-乙酰基-3-基)-6-(4-氯苯基)-5-甲基-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)吡啶并[2,3-d]嘧啶-7(8H)-酮、

[0118] (S)-8-(1-丙酰基-3-基)-6-(4-氯苯基)-5-甲基-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)吡啶并[2,3-d]嘧啶-7(8H)-酮、

[0119] (S)-8-(1-乙酰基-3-基)-6-(2,4-二氯苯基)-5-甲基-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)吡啶并[2,3-d]嘧啶-7(8H)-酮、

[0120] (S)-8-(1-丙酰基-3-基)-6-(2,4-二氯苯基)-5-甲基-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)吡啶并[2,3-d]嘧啶-7(8H)-酮、

[0121] (S)-6-(2-甲氧基苯基)-5-甲基-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)-8-(1-丙哌啶-3-基)吡啶并[2,3-d]嘧啶-7(8H)-酮、

[0122] (S)-8-(1-乙酰基-3-基)-6-(2-氟苯基)-5-甲基-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)吡啶并[2,3-d]嘧啶-7(8H)-酮、

[0123] (S)-8-(1-丙酰基-3-基)-6-(2-氟苯基)-5-甲基-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)吡啶并[2,3-d]嘧啶-7(8H)-酮、

[0124] (S)-8-(1-乙酰基-3-基)-5-甲基-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)-6-苯基吡啶并[2,3-d]嘧啶-7(8H)-酮、

[0125] (S)-8-(1-丙酰基-3-基)-5-甲基-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)-6-苯基吡啶并[2,3-d]嘧啶-7(8H)-酮、

[0126] (S)-8-(1-乙酰基-3-基)-6-(3,5-二氯苯基)-5-甲基-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)吡啶并[2,3-d]嘧啶-7(8H)-酮、

[0127] (S)-8-(1-丙酰基-3-基)-6-(3,5-二氯苯基)-5-甲基-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)吡啶并[2,3-d]嘧啶-7(8H)-酮、

[0128] N-((1S,4S)-4-(6-(2-氯苯基)-5-甲基-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)-7-氧代吡啶并[2,3-d]嘧啶-8(7H)-基)环己基)乙酰胺、

[0129] N-((1S,4S)-4-(6-(2-氯苯基)-5-甲基-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)-7-氧代吡啶并[2,3-d]嘧啶-8(7H)-基)环己基)丙酰胺、

[0130] (S)-8-(1-乙酰基-3-基)-6-(2-甲氧基嘧啶-5-基)-5-甲基-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)吡啶并[2,3-d]嘧啶-7(8H)-酮、

[0131] (S)-6-(2-甲氧基嘧啶-5-基)-5-甲基-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)-8-(1-丙哌啶-3-基)吡啶并[2,3-d]嘧啶-7(8H)-酮、

[0132] (S)-8-(1-乙酰基-3-基)-6-(2-氯-4-氟苯基)-5-甲基-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)吡啶并[2,3-d]嘧啶-7(8H)-酮、

[0133] (S)-8-(1-丙酰基-3-基)-6-(2-氯-4-氟苯基)-5-甲基-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)吡啶并[2,3-d]嘧啶-7(8H)-酮、

[0134] (S)-8-(1-乙酰基-3-基)-5-甲基-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)-6-(吡啶-4-基)吡啶并[2,3-d]嘧啶-7(8H)-酮、

[0135] (S)-8-(1-丙酰基-3-基)-5-甲基-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)-6-(吡啶-4-基)吡啶并[2,3-d]嘧啶-7(8H)-酮、

[0136] (S)-8-(1-乙酰基-3-基)-6-(2-氟吡啶-4-基)-5-甲基-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)吡啶并[2,3-d]嘧啶-7(8H)-酮、

[0137] (S)-8-(1-丙酰基-3-基)-6-(2-氟吡啶-4-基)-5-甲基-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)吡啶并[2,3-d]嘧啶-7(8H)-酮、

[0138] (S)-8-(1-丙酰基-3-基)-6-(2-氯-4-甲氧基苯基)-5-甲基-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)吡啶并[2,3-d]嘧啶-7(8H)-酮、

[0139] (S)-8-(1-乙酰基-3-基)-6-(3-氯吡啶-4-基)-5-甲基-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)吡啶并[2,3-d]嘧啶-7(8H)-酮、

[0140] (S)-8-(1-丙酰基-3-基)-6-(3-氯吡啶-4-基)-5-甲基-2-((3-甲基-4-(4-甲基哌嗪-1-基基)苯基)氨基)吡啶并[2,3-d]嘧啶-7(8H)-酮、

[0141] (S)-8-(1-乙酰基-3-基)-6-(呋喃-3-基)-5-甲基-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)吡啶并[2,3-d]嘧啶-7(8H)-酮、

[0142] (S)-8-(1-丙酰基-3-基)-6-(呋喃-3-基)-5-甲基-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)吡啶并[2,3-d]嘧啶-7(8H)-酮、

[0143] (S)-6-(2-氯-3-氟苯基)-5-甲基-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)-8-(1-丙哌啶-3-基)吡啶并[2,3-d]嘧啶-7(8H)-酮、

[0144] (S)-8-(1-乙酰基-3-基)-6-(2-氯-4-氟苯基)-5-甲基-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)吡啶并[2,3-d]嘧啶-7(8H)-酮、

[0145] (S)-6-(2-氯-4-氟苯基)-5-甲基-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)-8-(1-丙哌啶-3-基)吡啶并[2,3-d]嘧啶-7(8H)-酮、

[0146] N-((1S,4S)-4-(6-(2-氯-5-氟苯基)-5-甲基-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)-7-氧代吡啶并[2,3-d]嘧啶-8(7H)-基)环己基)乙酰胺、

[0147] N-((1S,4S)-4-(6-(2-氯-5-氟苯基)-5-甲基-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)-7-氧代吡啶并[2,3-d]嘧啶-8(7H)-基)环己基)丙酰胺、

[0148] N-((1S,4S)-4-(6-(2-氯-3-氟苯基)-5-甲基-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)-7-氧代吡啶并[2,3-d]嘧啶-8(7H)-基)环己基)丙酰胺、

[0149] N-((1S,4S)-4-(6-(2-氯-4-氟苯基)-5-甲基-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)-7-氧代吡啶并[2,3-d]嘧啶-8(7H)-基)环己基)丙酰胺、

[0150] N-((1S,4S)-4-(6-(2-氯-3-氟苯基)-5-甲基-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)-7-氧代吡啶并[2,3-d]嘧啶-8(7H)-基)环己基)环丙烷甲酰胺、

[0151] N-((1S,4S)-4-(6-(2-氯-3-氟苯基)-5-甲基-2-((3-甲基-4-(4-甲基哌嗪-1-基)

苯基)氨基)-7-氧代吡啶并[2,3-d]嘧啶-8(7H)-基)环己基)新戊酰胺、

[0152] N-((1S,4S)-4-(6-(2-氯-3-氟苯基)-5-甲基-2-((4-(4-甲基哌嗪-1-基)苯基)氨基)-7-氧代吡啶并[2,3-d]嘧啶-8(7H)-基)环己基)环戊烷甲酰胺、

[0153] N-((1S,4S)-4-(6-(2-氯-3-氟苯基)-5-甲基-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)-7-氧代吡啶并[2,3-d]嘧啶-8(7H)-基)环己基)环丁烷、

[0154] N-((1R,4R)-4-(6-(2-氯-3-氟苯基)-5-甲基-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)-7-氧代吡啶并[2,3-d]嘧啶-8(7H)-基)环己基)丁酰胺、

[0155] N-((1S,4S)-4-(6-(2-氯-3-氟苯基)-5-甲基-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)-7-氧代吡啶并[2,3-d]嘧啶-8(7H)-基)环己基)环己烷甲酰胺、

[0156] N-((1S,4S)-4-(6-(2-氯-3-氟苯基)-5-甲基-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)-7-氧代吡啶并[2,3-d]嘧啶-8(7H)-基)环己基)-3,3-二甲基丁酰胺、

[0157] N-((1S,4S)-4-(6-(2-氯-3-氟苯基)-5-甲基-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)-7-氧代吡啶并[2,3-d]嘧啶-8(7H)-基)环己基)乙酰胺、

[0158] N-((1S,4S)-4-(6-(2-氯-3-氟苯基)-5-甲基-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)-7-氧代吡啶并[2,3-d]嘧啶-8(7H)-基)环己基)戊酰胺、

[0159] N-((1S,4S)-4-(6-(2-氯-3-氟苯基)-5-甲基-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)-7-氧代吡啶并[2,3-d]嘧啶-8(7H)-基)环己基)-3-甲基丁酰胺、

[0160] (S)-6-(2-氯苯基)-5-甲基-2-((6-甲基-5-(4-甲基哌嗪-1-基)吡啶-2-基)氨基)-8-(1-丙哌啶-3-基)吡啶并[2,3-d]嘧啶-7(8H)-酮、

[0161] (S)-6-(2-氯苯基)-5-甲基-2-((5-(4-甲基哌嗪-1-基)吡啶-2-基)氨基)-8-(1-丙酰基哌啶-3-基)基)吡啶并[2,3-d]嘧啶-7(8H)-酮、

[0162] (S)-6-(2-氯苯基)-5-甲基-2-((5-(哌嗪-1-基)吡啶-2-基)氨基)-8-(1-丙哌啶-3-基)吡啶并[2,3-d]嘧啶-7(8H)-酮、

[0163] (S)-6-(2-氯苯基)-2-((4-((2-(二甲基氨基)乙基)(甲基)氨基)-3-甲基苯基)氨基)-5-甲基-8-(1-丙哌啶-3-基)吡啶并[2,3-d]嘧啶-7(8H)-酮、

[0164] (S)-6-(2-氯苯基)-2-((5-((4-乙基哌嗪-1-基)甲基)吡啶-2-基)氨基)-5-甲基-8-(1-丙酰基哌啶)吡啶-3-基)吡啶并[2,3-d]嘧啶-7(8H)-酮、

[0165] (S)-6-(2-氯苯基)-5-甲基-2-((3-甲基-4-(哌啶-4-基)苯基)氨基)-8-(1-丙酰基哌啶-3-基)吡啶并[2,3-d]嘧啶-7(8H)-酮、

[0166] (S)-6-(2-氯苯基)-2-((2-异丙氧基-5-甲基-4-(哌啶-4-基)苯基)氨基)-5-甲基-8-(1-丙哌啶-3-基)吡啶并[2,3-d]嘧啶-7(8H)-酮、

[0167] (S)-6-(2-氯苯基)-2-((4-(4-(二甲基氨基)哌啶-1-基)-3-甲基苯基)氨基)-5-甲基-8-(1-丙哌啶-3-基)吡啶并[2,3-d]嘧啶-7(8H)-酮、

[0168] (S)-6-(2-氯苯基)-5-甲基-2-((3-甲基-4-(9-甲基-3,9-二氮杂螺[5.5]十一烷-3-基)苯基)氨基)-8-(1-丙哌啶-3-基)吡啶并[2,3-d]嘧啶-7(8H)-酮、

[0169] (S)-6-(2-氯苯基)-5-甲基-2-((3-甲基-4-(7-甲基-2,7-二氮杂螺[3.5]壬-2-基)苯基)氨基)-8-(1-丙哌啶-3-基)吡啶并[2,3-d]嘧啶-7(8H)-酮、

[0170] 6-(2-氯苯基)-5-甲基-2-((3-甲基-4-((3AR,6AS)-5-甲基六氢吡咯并[3,4-c]吡咯-2(1H)-基)苯基)氨基)-8-((S)-1-丙哌啶-3-基)吡啶并[2,3-d]嘧啶-7(8H)-酮、

[0171] (S)-6-(2-氯苯基)-5-甲基-2-((3-甲基-4-(3-甲基-1,3-二氮杂环庚烷-1-基)苯基)氨基)-8-(1-丙酰哌啶-3-基)吡啶并[2,3-d]嘧啶-7(8H)-酮、

[0172] 6-(2-氯苯基)-2-((4-((S)-3,4-二甲基哌嗪-1-基)-3-甲基苯基)氨基)-5-甲基-8-((S)-1-丙哌啶-3-基)吡啶并[2,3-d]嘧啶-7(8H)-酮、

[0173] 6-(2-氯苯基)-2-((4-((R)-3,4-二甲基哌嗪-1-基)-3-甲基苯基)氨基)-5-甲基-8-((S)-1-丙哌啶-3-基)吡啶并[2,3-d]嘧啶-7(8H)-酮、

[0174] 6-(2-氯苯基)-5-甲基-2-((3-甲基-4-((3S,5R)-3,4,5-三甲基哌嗪-1-基)苯基)氨基)-8-((S)-1-丙酰基哌啶-3-基)吡啶并[2,3-d]嘧啶-7(8H)-酮、

[0175] (S)-6-(2-氯苯基)-5-甲基-2-((3-甲基-4-(4-(氧杂环丁烷-3-基)哌嗪-1-基)苯基)氨基)-8-(1-丙哌啶-3-基)吡啶并[2,3-d]嘧啶-7(8H)-酮、

[0176] (S)-8-(1-丙酰基-3-基)-6-(2-氯苯基)-5-甲基-2-((4-(4-甲基哌嗪-1-基)苯基)氨基)吡啶并[2,3-d]嘧啶-7(8H)-酮、

[0177] (S)-6-(2-氯苯基)-5-甲基-2-((2-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)-8-(1-丙哌啶-3-基)吡啶并[2,3-d]嘧啶-7(8H)-酮、

[0178] (S)-2-((3-氯-4-(4-甲基哌嗪-1-基)苯基)氨基)-6-(2-氯苯基)-5-甲基-8-(1-丙哌啶-3-基)吡啶并[2,3-d]嘧啶-7(8H)-酮、

[0179] (S)-6-(2-氯苯基)-5-甲基-2-((4-(4-甲基哌嗪-1-基)-3-(三氟甲基)苯基)氨基)-8-(1-丙哌啶-3-基)吡啶并[2,3-d]嘧啶-7(8H)-酮、

[0180] (S)-6-(2-氯苯基)-2-((3-氟-4-(4-甲基哌嗪-1-基)苯基)氨基)-5-甲基-8-(1-丙哌啶-3-基)吡啶并[2,3-d]嘧啶-7(8H)-酮、

[0181] (S)-6-(2-氯苯基)-2-((3-甲氧基-4-(4-甲基哌嗪-1-基)苯基)氨基)-5-甲基-8-(1-丙哌啶-3-基)吡啶并[2,3-d]嘧啶-7(8H)-酮、

[0182] (S)-6-(2-氯苯基)-2-((1-(2-(二甲基氨基)乙基)-1H-吡唑-4-基)氨基)-5-甲基-8-(1-丙哌啶-3-基)吡啶并[2,3-d]嘧啶-7(8H)-酮、

[0183] (S)-6-(2-氯苯基)-2-((1-(2-(二乙氨基)乙基)-1H-吡唑-4-基)氨基)-5-甲基-8-(1-丙哌啶-3-基)吡啶并[2,3-d]嘧啶-7(8H)-酮、

[0184] (S)-6-(2-氯苯基)-5-甲基-2-((5-((4-甲基哌嗪-1-基)甲基)吡啶-2-基)氨基)-8-(1-丙酰基哌啶)吡啶-3-基)吡啶并[2,3-d]嘧啶-7(8H)-酮、

[0185] (S)-6-(2-氯苯基)-2-((4-((4-乙基哌嗪-1-基)甲基)-3-甲基苯基)氨基)-5-甲基-8-(1-丙哌啶-3-基)吡啶并[2,3-d]嘧啶-7(8H)-酮、

[0186] (S)-6-(2-氯苯基)-2-((4-(4-乙基哌嗪-1-基)-3-甲基苯基)氨基)-5-甲基-8-(1-丙哌啶-3-基)吡啶并[2,3-d]嘧啶-7(8H)-酮、

[0187] (S)-6-(2-氯苯基)-5-甲基-2-((3-甲基-4-(哌嗪-1-基)苯基)氨基)-8-(1-丙哌啶-3-基)吡啶并[2,3-d]嘧啶-7(8H)-酮、

[0188] (S)-6-(2-氯苯基)-5-甲基-2-((5-(哌嗪-1-基甲基)吡啶-2-基)氨基)-8-(1-丙哌啶-3-基)吡啶并[2,3-d]嘧啶-7(8H)-酮、

[0189] 6-(2-氯苯基)-5-甲基-2-((3-甲基-4-((1S,4S)-5-甲基-2,5-二氮杂双环[2.2.1]庚-2-基)苯基)氨基)-8-((S)-1-丙酰基哌啶-3-基)吡啶并[2,3-d]嘧啶-7(8H)-酮、

[0190] 6-(2-氯-3-氟苯基)-5-甲基-2-((3-甲基-4-((1S,4S)-5-甲基-2,5-二氮杂双环[2.2.1]庚-2-基)苯基)氨基)-8-((S)-1-丙酰基哌啶-3-基)吡啶并[2,3-d]嘧啶-7(8H)-酮、

[0191] N-((1S,4S)-4-(6-(2-氯-3-氟苯基)-2-((4-((2-(二甲基氨基)乙基)(甲基)氨基)-3-甲基苯基)氨基基)-5-甲基-7-氧代吡啶并[2,3-d]嘧啶-8(7H-基)环己基)丙酰胺、

[0192] N-((1S,4S)-4-(6-(2-氯-3-氟苯基)-5-甲基-2-((3-甲基-4-(哌啶-4-基)苯基)氨基)-7-氧代吡啶并[2,3-d]嘧啶-8(7H)-基)环己基)丙酰胺、

[0193] N-((1S,4S)-4-(6-(2-氯-3-氟苯基)-2-((4-(4-(二甲基氨基)哌啶-1-基)-3-甲基苯基)氨基)-5-甲基-7-氧代吡啶并[2,3-d]嘧啶-8(7H)-基)环己基)丙酰胺、

[0194] N-((1S,4S)-4-(6-(2-氯-3-氟苯基)-5-甲基-2-((3-甲基-4-(9-甲基-3,9-二氮杂螺[5.5]十一烷-3-基)苯基)氨基)-7-氧代吡啶并[2,3-d]嘧啶-8(7H)-基)环己基)丙酰胺、

[0195] N-((1S,4S)-4-(6-(2-氯-3-氟苯基)-5-甲基-2-((3-甲基-4-(7-甲基-2,7-二氮杂螺[3.5]壬烷-2-基)苯基)氨基)-7-氧代吡啶并[2,3-d]嘧啶-8(7H)-基)环己基)丙酰胺、

[0196] N-((1S,4S)-4-(6-(2-氯-3-氟苯基)-5-甲基-2-((3-甲基-4-(3-甲基-1,3-二氮杂环庚-1-基)苯基)氨基)-7-氧代吡啶并[2,3-d]嘧啶-8(7H)-基)环己基)丙酰胺、

[0197] N-((1S,4S)-4-(6-(2-氯-3-氟苯基)-2-((4-((R)-3,4-二甲基哌嗪-1-基)-3-甲基苯基)氨基)-5-甲基-7-氧代吡啶并[2,3-d]嘧啶-8(7H)-基)环己基)丙酰胺、

[0198] N-((1S,4S)-4-(6-(2-氯-3-氟苯基)-5-甲基-2-((3-甲基-4-((3S,5R)-3,4,5-三甲基哌嗪-1-基)苯基)氨基)-7-氧代吡啶并[2,3-d]嘧啶-8(7H)-基)环己基)丙酰胺、

[0199] N-((1S,4S)-4-(6-(2-氯苯基)-5-甲基-2-((4-(4-甲基哌嗪-1-基)苯基)氨基)-7-氧代吡啶并[2,13-d]嘧啶-8(7H)-基)环己基)丙酰胺、

[0200] N-((1S,4S)-4-(6-(2-氯-3-氟苯基)-2-((3-氯-4-(4-甲基哌嗪-1-基)苯基)氨基)-5-甲基-7-氧代吡啶并[2,3-d]嘧啶-8(7H)-基)环己基)丙酰胺、

[0201] N-((1S,4S)-4-(6-(2-氯-3-氟苯基)-2-((4-(4-乙基哌嗪-1-基)-3-甲基苯基)氨基)-5-甲基-7-氧代吡啶并[2,3-d]嘧啶-8(7H)-基)环己基)丙酰胺、

[0202] N-((1S,4S)-4-(6-(2-氯-3-氟苯基)-5-甲基-2-((3-甲基-4-((1S,4S)-5-甲基-2,5-二氮杂双环[2.2.1]庚-2-基)苯基)氨基)-7-氧代吡啶并[2,3-d]嘧啶-8(7H)-基)环己基)丙酰胺、

[0203] N-((1S,4S)-4-(6-(2-氯-3-氟苯基)-2-((3-氯-4-((R)-3-甲基哌嗪-1-基)苯基)氨基)-5-甲基-7-氧代吡啶并[2,3-d]嘧啶-8(7H)-基)环己基)丙酰胺、

[0204] N-((1S,4S)-4-(6-(2-氯-3-氟苯基)-2-((3-氯-4-(3-甲基-1,3-二氮杂环庚-1-基)苯基)氨基)-5-甲基-7-氧代吡啶并[2,3-d]嘧啶-8(7H)-基)环己基)丙酰胺、

[0205] N-((1S,4S)-4-(6-(2-氯-3-氟苯基)-2-((3-氯-4-((R)-3,4-二甲基哌嗪-1-基)苯基)氨基)-5-甲基-7-氧代吡啶并[2,3-d]嘧啶-8(7H)-基)环己基)丙酰胺、

[0206] N-((1S,4S)-4-(6-(2-氯-3-氟苯基)-5-甲基-2-((3-甲基-4-(4-(4-甲基哌嗪-1-基)哌啶-1-基)苯基)氨基)-7-氧代吡啶并[2,3-d]嘧啶-8(7H)-基)环己基)丙酰胺、

[0207] N-((1S,4S)-4-(6-(2-氯-3-氟苯基)-2-((4-(4-异丙基哌嗪-1-基)-3-甲基苯基)氨基)-5-甲基-7-氧代吡啶并[2,3-d]嘧啶-8(7H)-基)环己基)丙酰胺。

[0208] 本发明还提供了上述吡啶并嘧啶酮或者吡啶并吡啶酮类化合物或者其药学上可接受的盐或者其立体异构体或者其前药分子的应用。

[0209] 具体技术方案如下：

[0210] 上述的吡啶并嘧啶酮或者吡啶并吡啶酮类化合物或者其药学上可接受的盐或者其立体异构体或者其前药分子在制备突变型EGFR抑制剂中的应用。

[0211] 上述的吡啶并嘧啶酮或者吡啶并吡啶酮类化合物或者其药学上可接受的盐或者其立体异构体或者其前药分子在制备预防和治疗肿瘤的药物中的应用。

[0212] 在其中一些实施例中，所述肿瘤为EGFR基因突变的恶性肿瘤。

[0213] 在其中一些实施例中，所述肿瘤包括：非小细胞肺癌、恶性黑色素瘤、前列腺癌、肾癌、膀胱癌、卵巢癌、结肠癌、直肠癌、乳腺癌、宫颈癌、肺癌、喉癌、鼻咽癌、胰腺癌、多发性骨髓瘤、B淋巴瘤、白血病。

[0214] 在其中一些实施例中，所述肿瘤为$EGFR^{L858R/T790MC797S}$突变的非小细胞肺癌。

[0215] 本发明还提供了一种防治肿瘤的药物组合物。

[0216] 具技术方案如下：

[0217] 一种防治肿瘤的药物组合物，其活性成分包括有上述的吡啶并嘧啶酮或者吡啶并吡啶酮类化合物或者其药学上可接受的盐或者其立体异构体或者其前药分子。

[0218] 在其中一些实施例中，所述肿瘤为EGFR基因突变的恶性肿瘤。

[0219] 在其中一些实施例中，所述肿瘤包括：非小细胞肺癌、恶性黑色素瘤、前列腺癌、肾癌、膀胱癌、卵巢癌、结肠癌、直肠癌、乳腺癌、宫颈癌、肺癌、喉癌、鼻咽癌、胰腺癌、多发性骨髓瘤、B淋巴瘤、白血病。

[0220] 在其中一些实施例中，所述肿瘤为$EGFR^{L858R/T790MC797S}$突变的非小细胞肺癌。

[0221] 本发明的吡啶并嘧啶酮或者吡啶并吡啶酮类化合物或者其药学上可接受的盐具有以优点和有益效果：

[0222] 本发明的化合物可以选择性抑制突变型EGFR的活性，并对EGFR，Her家族其他蛋白酶产生抑制作用，是一类新颖的能够克服现有EGFR酪氨酸激酶抑制剂耐药的并具有选择性和良好药代性质的蛋白激酶抑制剂。本发明的化合物可以有效抑制多种肿瘤细胞的生长，尤其能够选择性抑制$EGFR^{L858R/T790MC797S}$肺癌细胞，对比野生型癌细胞，部分优选化合物的选择性大于50倍。本发明的化合物可用于制备抗肿瘤药物，并可以克服现有药物(如吉非替尼，厄洛替尼，尤其是奥希替尼(AZD9291))诱发的耐药问题，主要用于现有第三代EGFR小分子抑制剂类抗非小细胞肺癌药物Osimertinib(AZD9291)，Olmutinib(HM6171)，Rociletinib(9,CO-1686)等诱发的第797位半胱氨酸突变成丝氨酸(C797S)耐药。本发明的化合物可用于防止各种肿瘤的术后复发，以及进一步的巩固治疗，达到延长肿瘤患者的生存期、提高其生活质量和抑制肿瘤恶化的目的。

附图说明

[0223] 图1为本发明的化合物560082对工具细胞中$EGFR^{L858R/T790M/C797S}$和$EGFR^{19D/T790M/C797S}$的磷酸化影响的测试结果图；

[0224] 图2为本发明的化合物580120对工具细胞中$EGFR^{L858R/T790M/C797S}$和$EGFR^{19D/T790M/C797S}$的磷酸化影响的测试结果图。

具体实施方式

[0225] 本发明所述化合物中，当任何变量(例如R_1、R等)在任何组分中出现超过一次，则其每次出现的定义独立于其它每次出现的定义。同样，允许取代基及变量的组合，只要这种组合使化合物稳定。自取代基划入环系统的线表示所指的键可连接到任何能取代的环原子上。如果环系统为多环，其意味着这种键仅连接到邻近环的任何适当的碳原子上。要理解本领域普通技术人员可选择本发明化合物的取代基及取代型式而提供化学上稳定的并可通过本领域技术和下列提出的方法自可容易获得的原料容易的合成的化合物。如果取代基自身被超过一个基团取代，应理解这些基团可在相同碳原子上或不同碳原子上，只要使结构稳定。短语“任选被一个或多个取代基取代”被认为与短语“任选被至少一个取代基取代”相当且在此情况下优选的实施方案将具有0-3个取代基。

[0226] 本文所用术语“烷基”和“亚烷基”意指包括具有特定碳原子数目的支链的和直链的饱和脂肪烃基。例如，“C_1-C_5烷基“中”C_1-C_5“的定义包括以直链或支链排列的具有1、2、3、4、或5个碳原子的基团。例如，”C_1-C_5烷基“具体包括甲基、乙基、正丙基、异丙基、正丁基、叔丁基、异丁基、戊基。术语“环烷基”指具有特定碳原子数目的单环饱和脂肪烃基。例如“环烷基”包括环丙基、甲基-环丙基、2,2-二甲基-环丁基、2-乙基-环戊基、环己基等。

[0227] 本文所用术语“杂芳基”代表环中多达6个原子的稳定的单环或每个环中多达6个原子的双环碳环，其中至少一个环为芳香环且含有1-4个选自O、N和S的杂原子。本定义范围内的杂芳基包括但不限于：咪唑基、三唑基、吡唑基、呋喃基、噻吩基、噁唑基、异噁唑基、吡嗪基、哒嗪基、吡啶基、嘧啶基、吡咯基。对于下列杂芳基的定义，“杂芳基”也理解为包括任何含有氮的杂芳基的N-氧化物衍生物。在杂芳基取代基是双环的且含有一个环为非芳香性或不含有杂原子的例子中，应理解各自经芳香环或经含杂原子环连接。

[0228] 本文中所用术语“杂环”或“杂环基”是指含有1-4个选自O、N和S的杂原子的5元-6元芳香性或非芳香性杂环，且包括双环基团。“杂环基”因此包括上面提及的杂芳基，也包括其二氢化及四氢化类似物。“杂环基”进一步的实施例包括但不限于：咪唑基、吲哚基、异噻唑基、异噁唑基、噁二唑基、噁唑基、氧杂环丁烷基(oxetanyl)、吡喃基、吡嗪基、吡唑基、哒嗪基、吡啶基、嘧啶基、吡咯基、喹噁啉基、四唑基、噻二唑基、噻唑基、噻吩基、三唑基、1,4-二噁烷基、吡咯烷基、二氢咪唑基、二氢异噁唑基、二氢异噻唑基、二氢噁二唑基、二氢噁唑基、二氢吡嗪基、二氢吡唑基、二氢吡啶基、二氢嘧啶基、二氢吡咯基、二氢四唑基、二氢噻二唑基、二氢噻唑基、二氢噻吩基、二氢三唑基、二氢氮杂环丁烷基、四氢呋喃基和四氢噻吩基，及其N-氧化物。杂环取代基的连接可通过碳原子或通过杂原子实现。在一个实施方案中，杂环选自咪唑基、吡啶基、1-吡咯烷酮、2-哌啶酮、2-嘧啶酮、2-吡咯烷酮、噻吩基、噁唑基、三氮唑基、异噁唑基。

[0229] 正如本领域技术人员所理解的，本文中所用“卤素”(“halo”)或“卤素”意指包括氯、氟、溴和碘。

[0230] 除非另有定义，烷基、环烷基、芳基、杂芳基和杂环基取代基可为未被取代的或取代的。例如，(C_1-C_6)烷基可被一个、两个或三个选自OH、卤素、烷氧基、二烷基氨基或杂环基例如吗啉基、哌啶基等的取代基取代。

[0231] 本发明包括式I-VI化合物的游离形式，也包括其药学上可接受的盐及立体异构体。本文中一些特定的示例性化合物为胺类化合物的质子化了的盐。术语“游离形式”指以

非盐形式的胺类化合物。包括在内的药学上可接受盐不仅包括本文所述特定化合物的示例性盐，也包括所有式I-VI化合物游离形式的典型的药学上可接受的盐。可使用本领域已知技术分离所述化合物特定盐的游离形式。例如，可通过用适当的碱稀水溶液例如NaOH稀水溶液、碳酸钾稀水溶液、稀氨水及碳酸氢钠稀水溶液处理该盐使游离形式再生。游离形式在某些物理性质例如在极性溶剂中溶解度上与其各自盐形式多少有些区别，但是为发明的目的这种酸盐及碱盐在其它药学方面与其各自游离形式相当。

[0232] 可通过常规化学方法自含有碱性部分或酸性部分的本发明化合物合成本发明的药学上可接受的盐。通常，通过离子交换色谱或通过游离碱和化学计算量或过量的所需盐形式的无机或有机酸在适当溶剂或多种溶剂的组合中反应制备碱性化合物的盐。类似的，通过和适当的无机或有机碱反应形成酸性化合物的盐。

[0233] 因此，本发明化合物的药学上可接受的盐包括通过碱性本发明化合物和无机或有机酸反应形成的本发明化合物的常规无毒盐。例如，常规的无毒盐包括得自无机酸例如盐酸、氢溴酸、硫酸、氨基磺酸、磷酸、硝酸等的盐，也包括自有机酸例如乙酸、丙酸、琥珀酸、乙醇酸、硬脂酸、乳酸、苹果酸、酒石酸、柠檬酸、抗坏血酸、扑酸、马来酸、羟基马来酸、苯乙酸、谷氨酸、苯甲酸、水杨酸、对氨基苯磺酸、2一乙酰氧基一苯甲酸、富马酸、甲苯磺酸、甲磺酸、乙烷二磺酸、草酸、羟乙基磺酸、三氟乙酸等制备的盐。

[0234] 如果本发明化合物为酸性的，则适当的“药学上可接受的盐”指通过药学上可接受的无毒碱包括无机碱及有机碱制备的盐。得自无机碱的盐包括铝盐、铵盐、钙盐、铜盐、铁盐、亚铁盐、锂盐、镁盐、锰盐、亚锰盐、钾盐、钠盐、锌盐等。特别优选铵盐、钙盐、镁盐、钾盐和钠盐。得自药学上可接受的有机无毒碱的盐，所述碱包括伯胺、仲胺和叔胺的盐，取代的胺包括天然存在的取代胺、环状胺及碱性离子交换树脂例如精氨酸、甜菜碱、咖啡因、胆碱、N,N′-二苄基乙二胺、二乙胺、2一二乙基氨基乙醇、2一二甲基氨基乙醇、氨基乙醇、乙醇胺、乙二胺、N一乙基吗啉、N一乙基哌啶、葡萄糖胺、氨基葡萄糖、组氨酸、羟钴胺、异丙基胺、赖氨酸、甲基葡萄糖胺、吗啉、哌嗪、哌啶、呱咤、多胺树脂、普鲁卡因、嘌呤、可可碱、三乙胺、三甲胺、三丙胺、氨基丁三醇等。

[0235] Berg等，“Pharmaceutical Salts，”J.Pharm.Sci.’1977:66:1-19更详细描述了上文所述药学上可接受的盐及其它典型的药学上可接受的盐的制备。

[0236] 由于在生理条件下化合物中脱质子化的酸性部分例如羧基可为阴离子的，而这种带有的电荷然后可被内部带有阳离子的质子化了的或烷基化的碱性部分例如四价氮原子平衡抵消，所以应注意本发明化合物是潜在的内盐或两性离子。

[0237] 除在文献中已知的或在实验程序中例证的标准方法外，可采用如下列方案中显示的反应制备本发明化合物。因此，下列说明性方案是为说明的目的而不是局限于所列化合物或任何特定的取代基。方案中显示的取代基数目并不必需符合权利要求中所用的数目，且为清楚起见，显示单取代基连接到在上文中式I的定义下允许有多取代基的化合物上。

[0238] 如发明所述式I-VI化合物，本领域的技术人员可以根据现有技术和所具备的常识，可以由4-氯-2-甲巯基嘧啶-5-碳酸乙酯或者2,4-二氯-5-溴嘧啶为起始原料通过几步反应合成。(具体合成步骤见实施例1,9,32等)

[0239] 本申请提供的具有式I-VI的化合物及其药学上可接受的盐可用于治疗人或其它哺乳动物肿瘤等过渡增殖性疾病或症状。

[0240] 在一个实施方案中，本申请所设计的化合物及其药学可接受的盐可以用于治疗或控制非小细胞肺癌、小细胞肺癌、肺腺癌、肺鳞癌、胰腺癌、乳腺癌、前列腺癌、肝癌、皮肤癌、上皮细胞癌、胃肠间质瘤、白血病、组织细胞性淋巴癌、鼻咽癌等过渡增殖性疾病。

[0241] 药物代谢物及前药

[0242] 本申请所涉及的化合物及其药学可接受的盐的代谢产物，以及可以在体内转变为本申请所涉及的化合物及其药学可接受的盐的结构的前药，也包含在本申请的权利要求中。

[0243] 联合用药

[0244] 式I-VI化合物可以与已知的治疗或改进相似病状的其它药物联用。联合给药时，原来药物的给药方式&剂量保持不变，而同时或随后服用式I-IV化合物。当式I-IV化合物与其它一种或几种药物同时服用时，优选使用同时含有一种或几种已知药物和式I-IV化合物的药用组合物。药物联用也包括在重叠的时间段服用式I-IV化合物与其它一种或几种已知药物。当式I-VI化合物与其它一种或几种药物进行药物联用时，式I-IV化合物或已知药物的剂量可能比它们单独用药时的剂量较低。

[0245] 可以与式I-VI化合物进行药物联用的药物或活性成分包括但不局限为：

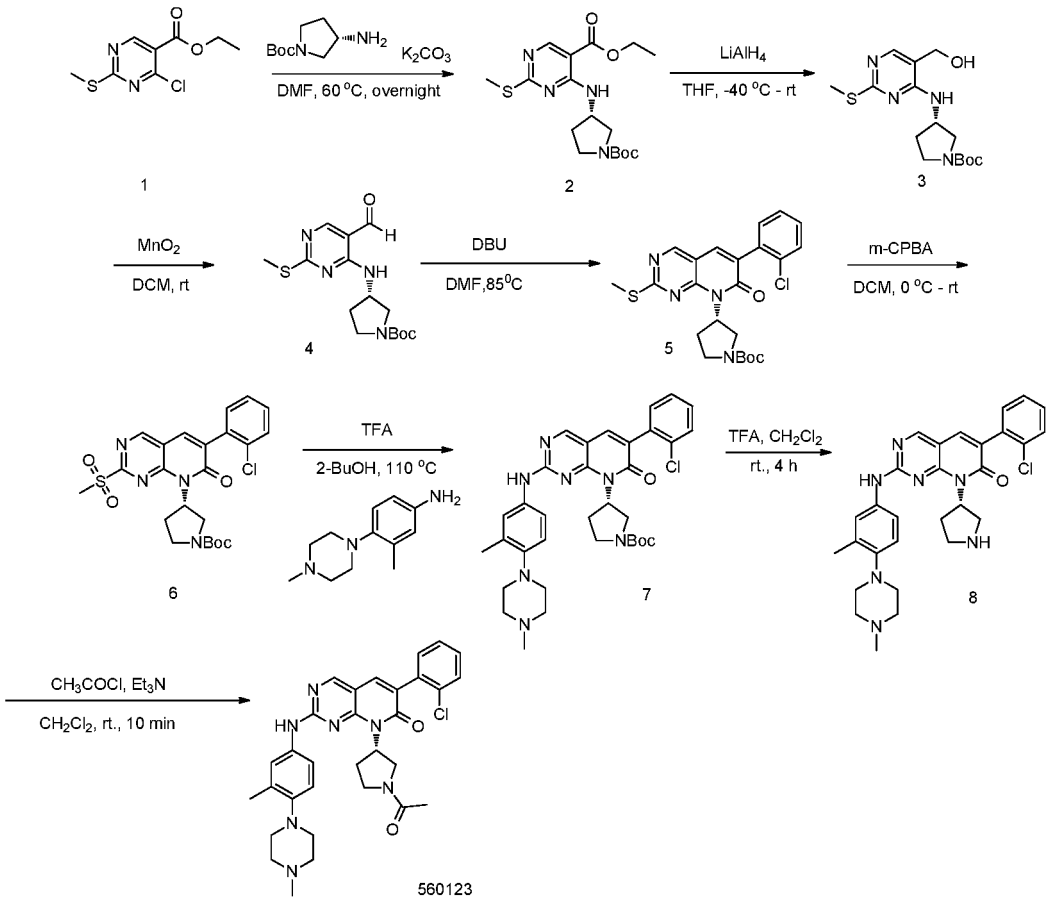
[0246] 雌激素受体调节剂、雄激素受体调节剂、视网膜样受体调节剂、细胞毒素/细胞抑制剂、抗增殖剂、蛋白转移酶抑制剂、HMG-CoA还原酶抑制剂、HIV蛋白激酶抑制剂、逆转录酶抑制剂、血管生成抑制剂、细胞增殖及生存信号抑制剂、干扰细胞周期关卡的药物和细胞凋亡诱导剂，细胞毒类药物、酪氨酸蛋白抑制剂、EGFR抑制剂、VEGFR抑制剂、丝氨酸/苏氨酸蛋白抑制剂、Bcr-Abl抑制剂，c-Kit抑制剂，Met抑制剂，Raf抑制剂，MEK抑制剂，MMP抑制剂，拓扑异构酶抑制剂、组氨酸去乙酰化酶抑制剂、蛋白酶体抑制剂、CDK抑制剂，Bcl-2家族蛋白抑制剂，MDM2家族蛋白抑制剂、IAP家族蛋白抑制剂、STAT家族蛋白抑制剂、PI3K抑制剂、AKT抑制剂、整联蛋白阻滞剂、干扰素-α、白介素-12、COX-2抑制剂、p53、p53激活剂、VEGF抗体、EGF抗体等。

[0247] 在一个实施方案中，可以与式I-VI化合物进行药物联用的药物或活性成分包括但不局限为：阿地白介素、阿仑膦酸、干扰素、阿曲诺英、别嘌醇、别嘌醇钠、帕洛诺司琼盐酸盐、六甲蜜胺、氨基格鲁米特、氨磷汀、氨柔比星、安丫啶、阿纳托唑、多拉司琼、aranesp、arglabin、三氧化二砷、阿诺新、5-氮胞苷、硫唑嘌呤、卡介苗或tice卡介苗、贝他定、醋酸倍他米松、倍他米松磷酸钠制剂、贝沙罗汀、硫酸博来霉素、溴尿甘、bortezomib、白消安、降钙素、阿来佐单抗注射剂、卡培他滨、卡铂、康士得、cefesone、西莫白介素、柔红霉素、苯丁酸氮芥、顺铂、克拉屈滨、克拉屈滨、氯屈磷酸、环磷酰胺、阿糖胞苷、达卡巴嗪、放线菌素D、柔红霉素脂质体、地塞米松、磷酸地塞米松、戊酸雌二醇、地尼白介素2、狄波美、地洛瑞林、地拉佐生、己烯雌酚、大扶康、多西他奇、去氧氟尿苷、阿霉素、屈大麻酚、钬-166-壳聚糖复合物、eligard、拉布立酶、盐酸表柔比星、阿瑞吡坦、表阿霉素、阿法依伯汀、红细胞生成素、依铂、左旋咪唑片、雌二醇制剂、17-β-雌二醇、雌莫司汀磷酸钠、炔雌醇、氨磷汀、羟磷酸、凡毕复、依托泊甙、法倔唑、他莫昔芬制剂、非格司亭、非那司提、非雷司替、氟尿苷、氟康唑、氟达拉滨、5-氟脱氧尿嘧啶核苷一磷酸盐、5-氟尿嘧啶、氟甲睾酮、氟他胺、福麦斯坦、1-β-D-阿糖呋喃糖胞噻啶-5’-硬脂酰磷酸酯、福莫司汀、氟维司群、丙种球蛋白、吉西他滨、吉妥单抗、甲磺酸伊马替尼、卡氮芥糯米纸胶囊剂、戈舍瑞林、盐酸格拉尼西隆、组氨瑞林、和美新、

氢化可的松、赤型-羟基壬基腺嘌呤、羟基脲、替坦异贝莫单抗、伊达比星、异环磷酰胺、干扰素α、干扰素-α2、干扰素α-2A、干扰素α-2B、干扰素α-n1、干扰素α-n3、干扰素β、干扰素γ-1a、白细胞介素-2、内含子A、易瑞沙、依立替康、凯特瑞、硫酸香菇多糖、来曲唑、甲酰四氢叶酸、亮丙瑞林、亮丙瑞林醋酸盐、左旋四咪唑、左旋亚叶酸钙盐、左甲状腺素钠、左甲状腺素钠制剂、洛莫司汀、氯尼达明、屈大麻酚、氮芥、甲钴胺、甲羟孕酮醋酸酯、醋酸甲地孕酮、美法仑、酯化雌激素、6-琉基嘌呤、美司钠、氨甲蝶呤、氨基乙酰丙酸甲酯、米替福新、美满霉素、丝裂霉素C、米托坦、米托蒽醌、曲洛司坦、柠檬酸阿霉素脂质体、奈达铂、聚乙二醇化非格司亭、奥普瑞白介素、neupogen、尼鲁米特、三苯氧胺、NSC-631570、重组人白细胞介素1-β、奥曲肽、盐酸奥丹西隆、去氢氢化可的松口服溶液剂、奥沙利铂、紫杉醇、泼尼松磷酸钠制剂、培门冬酶、派罗欣、喷司他丁、溶链菌制剂、盐酸匹鲁卡品、毗柔比星、普卡霉素、叶吩姆钠、泼尼莫司汀、司替泼尼松龙、泼尼松、倍美力、丙卡巴肼、重组人类红细胞生成素、雷替曲塞、利比、依替膦酸铼-186、美罗华、力度伸-A、罗莫肽、盐酸毛果芸香碱片剂、奥曲肽、沙莫司亭、司莫司汀、西佐喃、索布佐生、唬钠甲强龙、帕福斯酸、干细胞治疗、链佐星、氯化锶-89、左旋甲状腺素钠、他莫昔芬、坦舒洛辛、他索那明、tastolactone、泰索帝、替西硫津、替莫唑胺、替尼泊苷、丙酸睾酮、甲睾酮、硫鸟嘌呤、噻替哌、促甲状腺激素、替鲁膦酸、拓扑替康、托瑞米芬、托西莫单抗、曲妥珠单抗、曲奥舒凡、维A酸、甲氨喋呤片剂、三甲基密胺、三甲曲沙、乙酸曲普瑞林、双羟萘酸曲普瑞林、优福定、尿苷、戊柔比星、维司力农、长春碱、长春新碱、长春酰胺、长春瑞滨、维鲁利秦、右旋丙亚胺、净司他丁斯酯、枢复宁、紫杉醇蛋白质稳定制剂、acolbifene、干扰素r-1b、affinitak、氨基喋呤、阿佐昔芬、asoprisnil、阿他美坦、阿曲生坦、BAY43-9006、阿瓦斯丁、CCI-779、CDC-501、西乐葆、西妥昔单抗、克立那托、环丙孕酮醋酸酯、地西他滨、DN-101、阿霉素-MTC、dSLIM、度他雄胺、edotecarin、依氟鸟氨酸、依喜替康、芬维A胺、组胺二盐酸盐、组氨瑞林水凝胶植入物、钬-166DOTMP、伊班膦酸、干扰素γ、内含子-PEG、ixabepilone、匙孔形血蓝蛋白、L-651582、兰乐肽、拉索昔芬、libra、lonafamib、米泼昔芬、米诺屈酸酯、MS-209、脂质体MTP-PE、MX-6、那法瑞林、奈莫柔比星、新伐司他、诺拉曲特、奥利默森、onco-TCS、osidem、紫杉醇聚谷氨酸酯、帛米酸钠、PN-401、QS-21、夸西洋、R-1549、雷洛昔芬、豹蛙酶、13-顺维A酸、沙铂、西奥骨化醇、T-138067、tarceva、二十二碳六烯酸紫杉醇、胸腺素α1、嘎唑呋林、tipifarnib、替拉扎明、TLK-286、托瑞米芬、反式MID-1o7R、伐司朴达、伐普肽、vatalanib、维替泊芬、长春氟宁、Z-100和唑来麟酸或它们的组合。

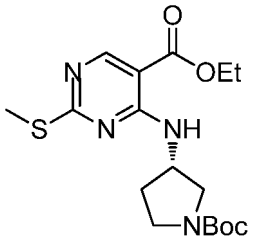
[0248] 以下实施例对本发明做进一步的描述，但该实施例并非用于限制本发明的保护范围。

[0249] 实施例1

[0250] 

[0251] 步骤1.(S)-4-(1-叔丁氧羰基吡咯基-3-氨基)-2-甲巯基嘧啶-5-碳酸乙酯(2)

[0252] (S)-ethyl-4-((1-(tert-butoxycarbonyl)pyrrolidin-3-yl)amino)-2-(methylthio)pyrimidine-5-carboxylate

[0253] 

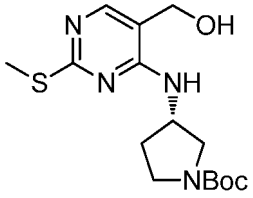
[0254] 4-氯-2-甲巯基嘧啶-5-碳酸乙酯(24.98g,107.4mmol),(S)-1-叔丁氧羰基-3-氨基吡咯烷(22.0g,118.2mmol),K_2CO_3(29.64g,214.8mmol)溶于50mL无水DMF中,氩气保护下,加热至60℃,搅拌过夜。冷却至室温,搅拌下加入500mL冰水,大量固体析出。减压过滤,真空干燥得白色固体6.0g(产率74%)。

[0255] ^1H NMR(400MHz,$CDCl_3$)δ8.63(s,1H),8.34(s,1H),4.72(s,J=2.4Hz,1H),4.31(q,J=7.2Hz,2H),3.77-3.73(m,1H),3.49-3.48(m,2H),3.36-3.34(m,0.5H),3.23-3.22(m,0.5H),2.52(s,3H),2.30-2.21(m,1H),1.94-1.93(m,1H),1.45(s,9H),1.36(t,J=7.2Hz,3H).

[0256] MS(ESI)m/z 383.2$[M+H]^+$.

[0257] 步骤2.(S)-叔丁基-3-(5-(羟甲基)-2-甲巯基嘧啶-4-氨基)吡咯-1-碳酸酯(3)

[0258] (S)-tert-butyl-3-((5-(hydroxymethyl)-2-(methylthio)pyrimidin-4-yl)amino)pyrrolidine-1-carboxylate

[0259] 

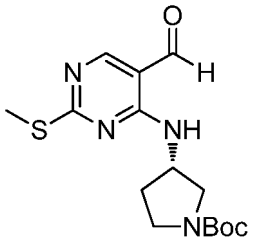
[0260] (S)-4-(1-叔丁氧羰基吡咯基-3-氨基)-2-甲巯基嘧啶-5-碳酸乙酯(2)(26.0g,79.15mmol)溶于200mL四氢呋喃中,冷却至-40℃,缓慢滴加四氢锂铝(6.02g,158.3mmol)的四氢呋喃悬浊液,搅拌并缓慢升至0℃,点板监测反应。原料反应完后,降温至-40℃,先后缓慢滴加6mL的水,6mL的10%氢氧化钠溶液和18mL的水淬灭反应,随后加入干燥的$MgSO_4$粉末,抽滤,浓缩。再用二氯甲烷和水萃取,取有机相,用无水Na_2SO_4干燥,然后过滤旋干,柱层析分离(SiO_2,CH_2Cl_2/MeOH梯度洗脱,40:1 to 20:1)得白色油状物13g(产率48%)。

[0261] ^1H NMR(400MHz,$CDCl_3$)δ7.74(s,1H),6,02(s,1H),4.68(d,J=5.6Hz,1H),4.52(s,2H),3.72-3.71(m,1H),3.46-3.45(m,2H),3.27-3.21(m,1H),2.50(s,3H),2.25-2.23(m,1H),1.92-1.91(m,1H),1.46(s,9H).

[0262] MS(ESI)m/z 341.2$[M+H]^+$.

[0263] 步骤3.(S)-叔丁基-3-(5-甲酰基-2-甲巯基嘧啶-4-氨基)吡咯-1-碳酸酯(4)

[0264] (S)-tert-butyl-3-((5-formyl-2-(methylthio)pyrimidin-4-yl)amino)pyrrolidine-1-carboxylate

[0265] 

[0266] (S)-叔丁基-3-(5-(羟甲基)-2-甲巯基嘧啶-4-氨基)吡咯-1-碳酸酯(3)(13g,11.53mmol)溶于100mL无水二氯甲烷中,分批加入3当量的活性二氧化锰(16.6g,191.10mmol),原料反应完后,用硅藻土抽滤,除去固体,旋干得油状物11.2g(产率87%)。

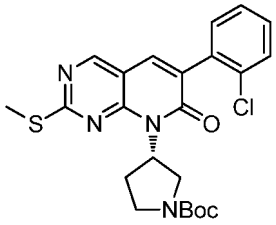
[0267] ^1H NMR(400MHz,$CDCl_3$)δ9.78(s,1H),8.64(s,1H),8.30(s,1H),4.72(s,1H),3.73-3.72(m,1H),3.47-3.46(m,2H),3.73-3.72(m,1H),3.34-3.21(m,1H),2.52(s,3H),2.26-2.23(m,1H),1.97-1.96(m,1H),1.44(s,9H).

[0268] MS(ESI)m/z 339.2$[M+H]^+$.

[0269] 步骤4:(S)-3-(6-(2-氯苯基)-2-(甲硫基)-7-氧代吡啶并[2,3-d]嘧啶-8(7H)-基)-吡咯烷-1-甲酸叔丁酯(5)

[0270] (S)-tert-butyl-3-(6-(2-chlorophenyl)-2-(methylthio)-7-oxopyrido[2,3-d]pyrimidin-8(7H)-yl)pyrrolidine-1-carboxylate

[0271] (S)-叔丁基-3-(5-甲酰基-2-甲巯基嘧啶-4-氨基)吡咯-1-碳酸酯(4)(2.0g,,5.9mmol)溶于2mL DMF中,加入邻氯苯乙酸乙酯(1.4g,7.0mmol),DBU(538.9mg,7.08mmol)缓慢升温至85℃,点板监测反应。原料反应完后,降温至室温,加入水淬灭反应,再用二氯甲烷和水萃取,取有机相,无水Na_2SO_4干燥,然后过滤旋干,柱层析分离(SiO_2,PE/EA梯度洗脱,10:1 to 5:1)得白色油状物1.0g(产率35%)

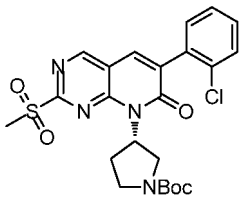
[0272] 

[0273] ^{1}H NMR(400MHz,$CDCl_3$)δ8.11(s,1H),7.50(d,J＝7.2Hz,1H),7.27(s,1H),7.36-7.31(m,3H),4.56-4.51(m,1H),3.88-3.83(m,1H),3.72-3.67(m,2H),3.44-3.39(m,1H),2.77-2.71(m,1H),2.54(s,3H),2.15-2.14(m,1H),1.45(s,9H).

[0274] MS(ESI)m/z 473.99$[M+H]^+$.

[0275] 步骤5.(S)-3-(6-(2-氯苯基)-2-(甲基磺酰基)-7-氧代吡啶并[2,3-d]嘧啶-8(7H)-基)-吡咯烷-1-甲酸叔丁酯(6)

[0276] (S)-tert-butyl-3-(6-(2-chlorophenyl)-2-(methylsulfonyl)-7-oxopyrido[2,3-d]pyrimidin-8(7H)-yl)pyrrolidine-1-carboxylate

[0277] 

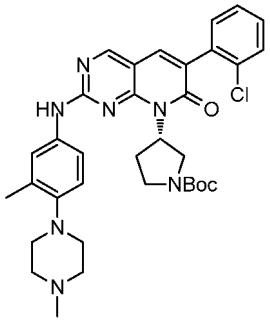
[0278] (S)-3-(6-(2-氯苯基)-2-(甲硫基)-7-氧代吡啶并[2,3-d]嘧啶-8(7H)-基)-吡咯烷-1-甲酸叔丁酯(5)(1.0g,2.0mmol)溶于5mL无水二氯甲烷中,0℃冰浴下,缓慢加入间氯过氧苯甲酸(1.2g,6.0mmol),回至室温,搅拌4小时。加入二氯甲烷稀释反应液,用50%$Na_2S_2O_3$/$NaHCO_3$水溶液淬灭反应。有机相用饱和食盐水洗涤两遍,无水Na_2SO_4干燥,过滤旋干,柱层析分离(SiO_2,PE/EA梯度洗脱,4:1 to 2:1)得产物0.6g(产率60%)

[0279] ^{1}H NMR(400MHz,$CDCl_3$)δ8.11(s,1H),7.50(d,J＝7.2Hz,1H),7.27(s,1H),7.36-7.31(m,3H),4.56-4.51(m,1H),3.88-3.83(m,1H),3.72-3.67(m,2H),3.44-3.39(m,1H),3.34(s,3H),2.77-2.71(m,1H),,2.15-2.14(m,1H),1.45(s,9H).

[0280] MS(ESI)m/z 505.12$[M+H]^+$.

[0281] 步骤6.(S)-3-(6-(2-氯苯基)-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)-7-氧代吡啶并[2,3-d]嘧啶-8(7H)-基)吡咯烷-1-羧酸叔丁酯(7)

[0282] (S)-tert-buty-3-(6-(2-chlorophenyl)-2-((3-methyl-4-(4-methylpiperazin-1-yl)phenyl)amino)-7-oxopyrido[2,3-d]pyrimidin-8(7H)-yl)pyrrolidine-1-carboxylate

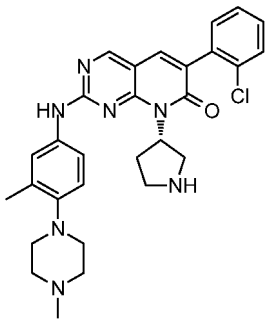
[0283] 

[0284] (S)-3-(6-(2-氯苯基)-2-(甲基磺酰基)-7-氧代吡啶并[2,3-d]嘧啶-8(7H)-基)-

吡咯烷-1-甲酸叔丁酯(6)(0.66g,1.3mmol)加入装有10mL仲丁醇的封瓶中,依次加入3-甲基-4-(4-甲基哌嗪-1-取代)苯胺(295mg,1.44mmol)和TFA(110μL,1.44mmol)。加热到110℃,搅拌18小时。冷却至室温,倒入10%$NaHCO_3$水溶液中,二氯甲烷萃取两遍,合并有机相,饱和食盐水洗涤两遍,无水Na_2SO_4干燥,过滤,旋干得化合物7,直接进行下一步反应。

[0285] 步骤7:(S)-6-(2-氯苯基)-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)-8-(吡咯烷-3-基)吡啶并[2,3-d]嘧啶-7(8H)-酮(8)

[0286] (S)-6-(2-chlorophenyl)-2-((3-methyl-4-(4-methylpiperazin-1-yl)phenyl)amino)-8-(pyrrolidin-3-yl)pyrido[2,3-d]pyrimidin-7(8H)-one

[0287] 

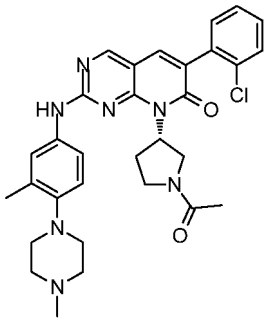
[0288] (S)-3-(6-(2-氯苯基)-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)-7-氧代吡啶并[2,3-d]嘧啶-8(7H)-基)吡咯烷-1-羧酸叔丁酯(7)溶于5mL二氯甲烷中,加入TFA(0.5mL),室温搅拌4h。反应液用二氯甲烷稀释,用饱和$NaHCO_3$溶液调节pH至9,二氯甲烷萃取两遍,合并有机相,10%$NaHCO_3$水溶液洗涤两遍,饱和食盐水洗涤两遍,无水Na_2SO_4干燥,过滤旋干,柱层析分离(SiO_2,CH_2Cl_2/MeOH/NH_4OH,40:1:to20:.1)得固体300mg(两步产率43%)。

[0289] ^1H NMR(400MHz,$CDCl_3$)δ7.98(s,1H),7.51(d,J=7.2Hz,1H),7.42(s,1H),7.37-7.31(m,4H),7.10(s,1H),7.04-7.02(m,1H),5.49-5.47(m,1H),4.73-4.66(m,1H),4.50-4.45(m,1H),3.30-3.47(m,2H),3.09-3.04(m,1H),2.94-2.92(m,4H),2.74-2.69(m,1H),2.67-2.65(m,4H),2.36(s,3H),2.32(s,3H),1.89-1.88(m,2H).

[0290] MS(ESI)m/z 531.06$[M+H]^+$.

[0291] 步骤8:(S)-8-(1-乙酰基吡咯-3-基)-6-(2-氯苯基)-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)吡啶并[2,3-d]嘧啶-7(8H)-酮(560123)

[0292] (S)-8-(1-acetylpyrrolidin-3-yl)-6-(2-chlorophenyl)-2-((3-methyl-4-(4-methylpiperazin-1-yl)ph enyl)amino)pyrido[2,3-d]pyrimidin-7(8H)-one

[0293] 

[0294] (S)-6-(2-氯苯基)-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)-8-(吡咯烷-3-基)吡啶并[2,3-d]嘧啶-7(8H)-酮(8)(150mg,0.28mmol)溶于10mL无水二氯甲烷中,0℃

冰浴下加入Et_3N(1.1mL,0.84mmol),缓慢加入乙酰氯(25μL,0.31mmol)。回至室温搅拌4小时。反应完后,加入10%$NaHCO_3$水溶液,二氯甲烷萃取两遍,合并有机相,用饱和食盐水洗涤一遍,无水Na_2SO_4干燥,过滤旋干,柱层析分离(SiO_2,CH_2Cl_2/MeOH/NH_4OH,40∶1∶0.4),并用高效液相色谱仪进一步纯化得固体130mg(产率92%)。

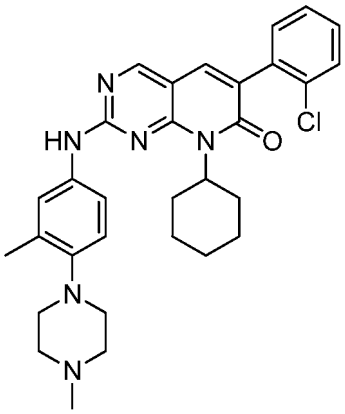
[0295] ^1H NMR(400MHz,DMSO)δ10.01(s,1H),8.80(s,1H),7.86(s,1H),7.73-7.30(m,5H),7.10(d,J=84.0Hz,1H),6.18(s,1H),3.77(dd,J=123.0,102.3Hz,4H),2.81(s,4H),2.23(s,5H),1.98(t,J=35.0Hz,3H),1.59-0.86(m,3H).

[0296] MS(ESI)m/z 573.06$[M+H]^+$

[0297] 实施例2

[0298] 6-(2-氯苯基)-8-环己基-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)吡啶并[2,3-d]嘧啶-7(8H)-酮(560069)

[0299] 6-(2-chlorophenyl)-8-cyclohexyl-2-((3-methyl-4-(4-methylpiperazin-1-yl)phenyl)amino)pyrid o[2,3-d]pyrimidin-7(8H)-one

[0300] 

[0301] 合成方法参见实施例1,产率57%。

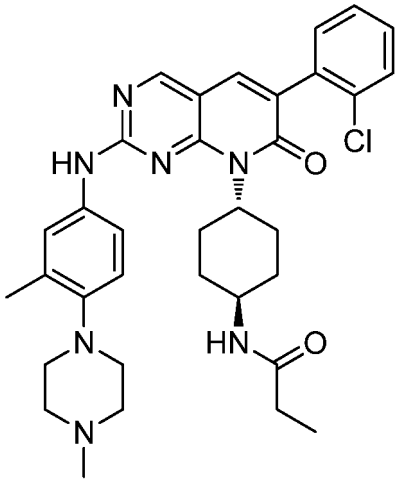
[0302] ^1H NMR(300MHz,DMSO)δ9.90(s,1H),8.74(s,1H),7.77(s,1H),7.65-7.19(m,6H),7.01(d,J=8.5Hz,1H),5.38(s,1H),2.82(s,4H),2.28(s,3H),2.23(s,3H),1.82(s,2H),1.60(d,J=12.6Hz,3H),1.29(t,J=18.5Hz,3H),1.17-0.82(m,2H),0.82(t,J=7.4Hz,1H).

[0303] MS(ESI)m/z 543.3$[M+H]^+$。

[0304] 实施例3

[0305] N-((1R,4R)-4-(6-(2-氯苯基)-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)-7-氧代吡啶并[2,13-d]嘧啶-8(7H)-基)环己基)丙酰胺(560080)

[0306] N-((1r,4r)-4-(6-(2-chlorophenyl)-2-((3-methyl-4-(4-methylpiperazin-1-yl)phenyl)amino)-7-oxopyrido[2,3-d]pyrimidin-8(7H)-yl)cyclohexyl)propionamide

[0307] 

[0308] 合成方法参见实施例1,产率79.6%。

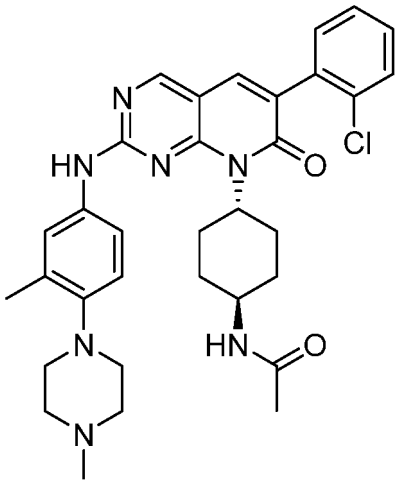
[0309] ^{1}H NMR(400MHz,DMSO)δ9.93(s,1H),8.76(s,1H),8.02(s,1H),7.83(s,1H),7.73(d,J=1.8Hz,1H),7.66-7.57(m,1H),7.57-7.50(m,1H),7.42(dd,J=4.7,3.5Hz,2H),7.09(s,1H),5.56-5.11(m,2H),2.86(d,J=4.2Hz,4H),2.57(s,2H),2.30(s,3H),2.28(s,3H),2.02-1.89(m,2H),1.79(d,J=19.3Hz,2H),1.71-1.52(m,2H),1.39(s,1H),1.35-1.25(m,1H),1.16(t,J=7.1Hz,1H).

[0310] MS(ESI)m/z 614.4[M+H]$^+$。

[0311] 实施例4

[0312] N-((1R,4R)-4-(6-(2-氯苯基)-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)-7-氧代吡啶并[2,3-d]嘧啶-8(7H)-基)环己基)乙酰胺(560081)

[0313] N-((1R,4R)-4-(6-(2-chlorophenyl)-2-((3-methyl-4-(4-methylpiperazin-1-yl)phenyl)amino)-7-oxopyrido[2,3-d]pyrimidin-8(7H)-yl)cyclohexyl)acetamide

[0314] 

[0315] 合成方法参见实施例1,产率73.3%。

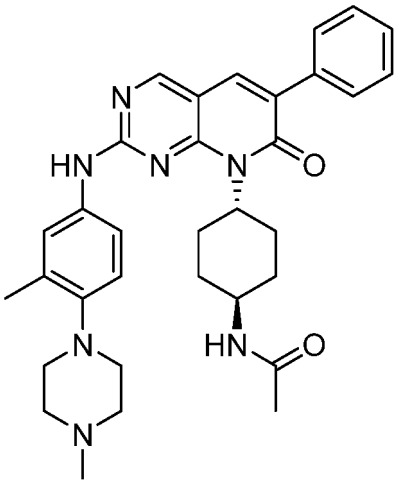
[0316] ^{1}H NMR(400MHz,DMSO)δ9.93(s,1H),8.76(s,1H),8.02(s,1H),7.83(s,1H),7.73(d,J=1.8Hz,1H),7.66-7.57(m,1H),7.57-7.50(m,1H),7.42(dd,J=4.7,3.5Hz,2H),7.09(s,1H),5.56-5.11(m,2H),2.86(d,J=4.2Hz,4H),2.57(s,2H),2.30(s,3H),2.28(s,3H),2.02-1.89(m,2H),1.79(d,J=19.3Hz,2H),1.71-1.52(m,2H),1.39(s,1H),1.35-1.25(m,1H),1.16(t,J=7.1Hz,1H).

[0317] MS(ESI)m/z 600.4[M+H]$^+$。

[0318] 实施例5

[0319] N-((1R,4R)-4-(2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)-7-氧代-6-苯基吡啶并[2,3-d]嘧啶-8(7H)-基)环己基)乙酰胺(560105)

[0320] N-((1r,4r)-4-(2-((3-methyl-4-(4-methylpiperazin-1-yl)phenyl)amino)-7-oxo-6-phenylpyrido[2,3-d]pyrimidin-8(7H)-yl)cyclohexyl)acetamide

[0321] 

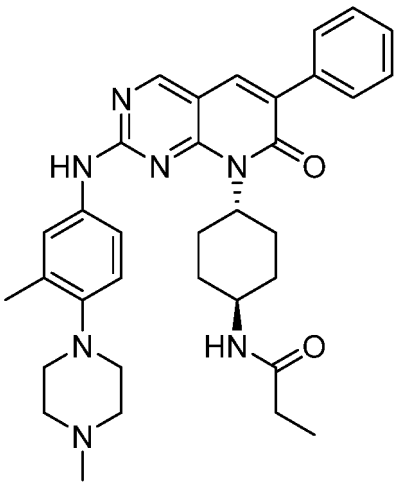
[0322] 合成方法参见实施例1,产率59.6%

[0323] ^{1}H NMR(400MHz,DMSO)δ9.81(d,J=56.6Hz,1H),8.76(s,1H),7.90(d,J=18.4Hz,1H),7.66(dd,J=20.1,18.6Hz,3H),7.54(d,J=8.0Hz,1H),7.47-7.28(m,3H),7.10(s,1H),5.34(d,J=43.0Hz,2H),2.96-2.73(m,5H),2.29(d,J=9.5Hz,2H),2.26(s,3H),2.07(q,J=7.6Hz,2H),,1.62(s,2H),1.43-1.13(m,3H),1.00(q,J=7.5Hz,3H).

[0324] 实施例6

[0325] N-((1R,4R)-4-(2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)-7-氧代-6-苯基吡啶并[2,3-d]嘧啶-8(7H)-基)环己基)丙酰胺(560107)

[0326] N-((1R,4R)-4-(2-((3-methyl-4-(4-methylpiperazin-1-yl)phenyl)amino)-7-oxo-6-phenylpyrido[2,3-d]pyrimidin-8(7H)-yl)cyclohexyl)propionamide

[0327] 

[0328] 合成方法参见实施例1,产率80.35%。

[0329] ^{1}H NMR(400MHz,DMSO)δ9.81(d,J=56.6Hz,1H),8.76(s,1H),7.90(d,J=18.4Hz,

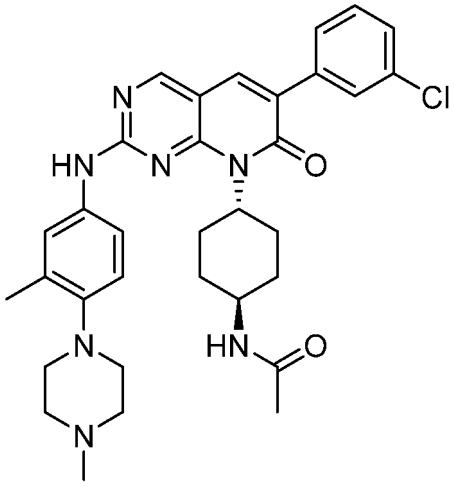
1H),7.66(dd,J＝20.1,18.6Hz,3H),7.54(d,J＝8.0Hz,1H),7.47-7.28(m,3H),7.10(s,1H),5.34(d,J＝43.0Hz,2H),2.96-2.73(m,5H),2.29(d,J＝9.5Hz,2H),2.26(s,3H),2.07(q,J＝7.6Hz,2H),1.94(dd,J＝21.1,10.0Hz,2H),1.62(s,2H),1.43-1.13(m,3H),1.00(q,J＝7.5Hz,3H).

[0330] MS(ESI)m/z 580.3$[M+H]^+$。

[0331] 实施例7

[0332] N-((1R,4R)-4-(6-(3-氯苯基)-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)-7-氧代吡啶并[2,3-d]嘧啶-8(7H)-基)环己基)乙酰胺(560109)

[0333] N-((1r,4r)-4-(6-(3-chlorophenyl)-2-((3-methyl-4-(4-methylpiperazin-1-yl)phenyl)amino)-7-oxopyrido[2,3-d]pyrimidin-8(7H)-yl)cyclohexyl)acetamide

[0334] 

[0335] 合成方法参见实施例1,产率81.3%。

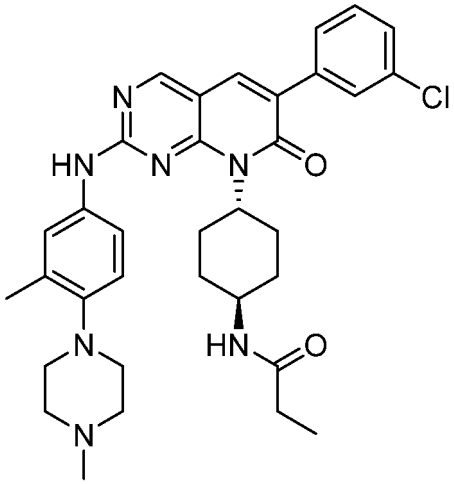
[0336] ^{1}H NMR(400MHz,DMSO)δ9.93(s,1H),8.76(s,1H),8.02(s,1H),7.83(s,1H),7.73(d,J＝1.8Hz,1H),7.66-7.57(m,1H),7.57-7.50(m,1H),7.42(dd,J＝4.7,3.5Hz,2H),7.09(s,1H),5.56-5.11(m,2H),2.86(d,J＝4.2Hz,4H),2.57(s,2H),2.30(s,3H),2.28(s,3H),2.02-1.89(m,2H),1.79(d,J＝19.3Hz,2H),1.71-1.52(m,2H),1.39(s,1H),1.35-1.25(m,1H),1.22(t,J＝7.2Hz,3H),1.16(t,J＝7.1Hz,1H).

[0337] MS(ESI)m/z 600.4$[M+H]^+$。

[0338] 实施例8

[0339] N-((1R,4R)-4-(6-(3-氯苯基)-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)-7-氧代吡啶并[2,13-d]嘧啶-8(7H)-基)环己基)丙酰胺(560110)

[0340] N-((1r,4r)-4-(6-(3-chlorophenyl)-2-((3-methyl-4-(4-methylpiperazin-1-yl)phenyl)amino)-7-oxopyrido[2,3-d]pyrimidin-8(7H)-yl)cyclohexyl)propionamide

[0341] 

[0342] 合成方法参见实施例1,产率78.9%。

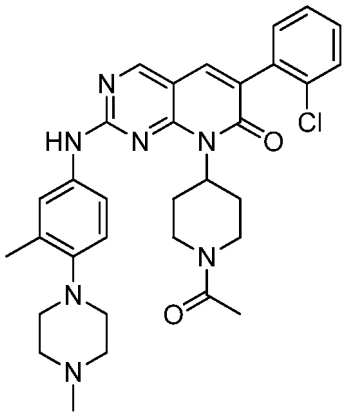
[0343] ^{1}H NMR(400MHz,DMSO)δ9.93(s,1H),8.76(s,1H),8.02(s,1H),7.83(s,1H),7.73(d,J=1.8Hz,1H),7.66-7.57(m,1H),7.57-7.50(m,1H),7.42(dd,J=4.7,3.5Hz,2H),7.09(s,1H),5.56-5.11(m,2H),2.86(d,J=4.2Hz,4H),2.57(s,2H),2.30(s,3H),2.28(s,3H),2.02-1.89(m,2H),1.79(t,J=19.3Hz,2H),1.71-1.52(m,2H),1.39(s,1H),1.35-1.25(m,1H),1.22(t,J=7.2Hz,3H),1.16(t,J=7.1Hz,1H).

[0344] MS(ESI)m/z 614.4[M+H]$^+$。

[0345] 实施例9

[0346] 6-(2-氯苯基)-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)-8-(1-乙酰基哌啶-4-基)吡啶并[2,3-d]嘧啶-7(8H)-酮(560121)

[0347] 8-(1-acetylpiperidin-4-yl)-6-(2-chlorophenyl)-2-((3-methyl-4-(4-methylpiperazin-1-yl)phenyl)amino)pyrido[2,3-d]pyrimidin-7(8H)-one

[0348] 

[0349] 合成方法参见实施例1,产率74.5%。

[0350] ^{1}H NMR(400MHz,DMSO)δ9.95(s,1H),8.76(s,1H),7.80(s,1H),7.60-7.47(m,3H),7.46-7.27(m,3H),7.00(d,J=8.6Hz,1H),5.60(s,1H),4.58(d,J=8.8Hz,1H),3.99(d,J=13.5Hz,2H),3.17-2.93(m,2H),2.79(d,J=31.6Hz,4H),2.55(s,4H),2.28(s,3H),2.27-2.15(m,3H),2.10-1.96(m,3H),1.73-1.58(m,2H).

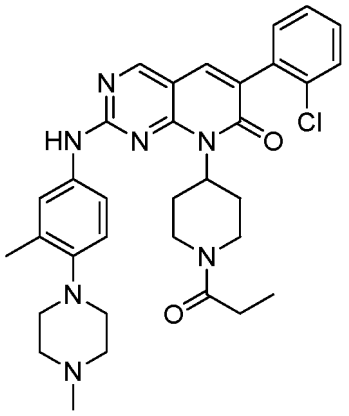
[0351] MS(ESI)m/z 586.2[M+H]+。

[0352] 实施例10

[0353] 6-(2-氯苯基)-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)-8-(1-丙酰基哌

啶-4-基)吡啶并[2,3-d]嘧啶-7(8H)-酮(560122)

[0354] 6-(2-chlorophenyl)-2-((3-methyl-4-(4-methylpiperazin-1-yl)phenyl)amino)-8-(1-propionylpiperidin-4-yl)pyrido[2,3-d]pyrimidin-7(8H)-one

[0355] 

[0356] 合成方法参见实施例1,产率72.7%。

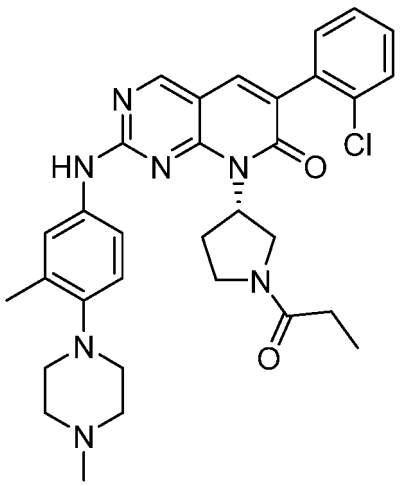
[0357] ^{1}H NMR(400MHz,DMSO)δ9.99(s,1H),8.77(s,1H),7.81(s,1H),7.52(d,J=4.1Hz,3H),7.41(d,J=10.1Hz,3H),7.01(d,J=8.3Hz,1H),5.63(s,1H),4.62(d,J=8.2Hz,1H),4.18-3.76(m,1H),3.05(t,J=11.7Hz,1H),2.82(s,4H),2.40-2.30(m,2H),2.26(s,3H),2.24(s,3H),1.97(d,J=11.0Hz,1H),1.67(s,2H),1.19(dd,J=18.3,11.2Hz,2H),1.00(t,J=7.2Hz,3H).

[0358] MS(ESI)m/z 600.4[M+H]$^+$。

[0359] 实施例11

[0360] (S)-6-(2-氯苯基)-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)-8-(1-丙酰基吡咯烷-3-基)吡啶并[2,3-d]嘧啶-7(8H)-酮(560124)

[0361] (S)-6-(2-chlorophenyl)-2-((3-methyl-4-(4-methylpiperazin-1-yl)phenyl)amino)-8-(1-propionylpyrrolidin-3-yl)pyrido[2,3-d]pyrimidin-7(8H)-one

[0362] 

[0363] 合成方法参见实施例1,产率76.8%。

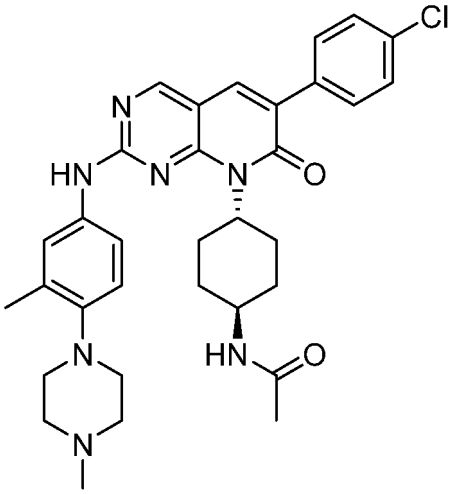
[0364] ^{1}H NMR(400MHz,DMSO)δ10.00(s,1H),8.80(d,J=2.5Hz,1H),7.85(d,J=5.6Hz,1H),7.61-7.27(m,6H),6.97(t,J=7.8Hz,1H),6.47-5.98(m,1H),2.81(s,5H),2.24(s,3H),2.22(s,3H),1.99(s,1H),1.17(t,J=7.1Hz,1H),0.98(ddd,J=14.8,12.4,7.4Hz,4H).

[0365] MS(ESI)m/z 586.2[M+H]$^+$。

[0366] 实施例12

[0367] N-((1R,4R)-4-(6-(4-氯苯基)-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)-7-氧代吡啶并[2,3-d]嘧啶-8(7H)-基)环己基)乙酰胺(570026)

[0368] N-((1R,4R)-4-(6-(4-chlorophenyl)-2-((3-methyl-4-(4-methylpiperazin-1-yl)phenyl)amino)-7-oxopyrido[2,3-d]pyrimidin-8(7H)-yl)cyclohexyl)acetamide

[0369] 

[0370] 合成方法参见实施例1,产率78.7%。

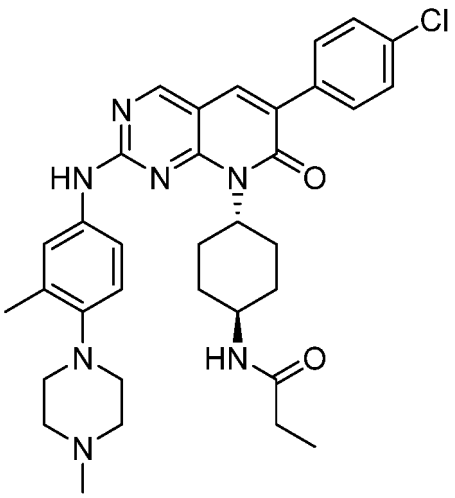
[0371] ^{1}H NMR(400MHz,DMSO)δ9.92(s,1H),8.77(s,1H),7.98(s,1H),7.91-7.75(m,1H),7.68(d,J=8.5Hz,2H),7.53(d,J=7.4Hz,1H),7.46(t,J=8.4Hz,2H),7.09(s,1H),5.32(s,2H),2.86(s,4H),2.28(d,J=2.3Hz,6H),1.94(d,J=11.3Hz,2H),1.81(t,J=5.9Hz,3H),1.63(s,2H),1.33(t,J=17.8Hz,4H).

[0372] MS(ESI)m/z 600.4[M+H]$^+$。

[0373] 实施例13

[0374] N-((1R,4R)-4-(6-(4-氯苯基)-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)-7-氧代吡啶并[2,3-d]嘧啶-8(7H)-基)环己基)丙酰胺(570027)

[0375] N-((1R,4R)-4-(6-(4-chlorophenyl)-2-((3-methyl-4-(4-methylpiperazin-1-yl)phenyl)amino)-7-oxopyrido[2,3-d]pyrimidin-8(7H)-yl)cyclohexyl)propionamide

[0376] 

[0377] 合成方法参见实施例1,产率75.9%。

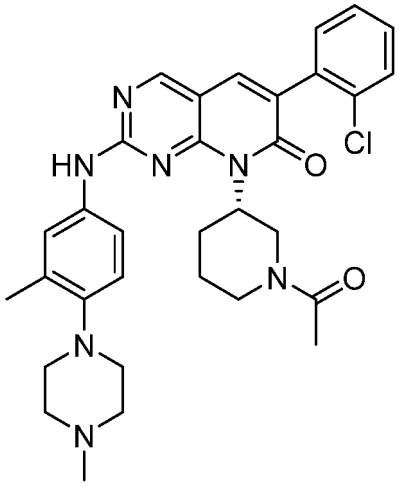
[0378] ^{1}H NMR(400MHz,DMSO)δ9.92(s,1H),8.77(s,1H),7.98(s,1H),7.91-7.75(m,1H),7.68(d,J＝8.5Hz,2H),7.53(d,J＝7.4Hz,1H),7.46(t,J＝8.4Hz,2H),7.09(s,1H),5.32(s,2H),2.86(s,4H),2.28(d,J＝2.3Hz,6H),1.94(d,J＝11.3Hz,2H),1.81(t,J＝5.9Hz,3H),1.33(t,J＝17.8Hz,4H).

[0379] MS(ESI)m/z 614.4$[M+H]^{+}$。

[0380] 实施例14

[0381] (S)-8-(1-乙酰基-3-基)-6-(2-氯苯基)-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)吡啶并[2,3-d]嘧啶-7(8H)-酮(570051)

[0382] (S)-8-(1-acetylpiperidin-3-yl)-6-(2-chlorophenyl)-2-((3-methyl-4-(4-methylpiperazin-1-yl)phenyl)amino)pyrido[2,3-d]pyrimidin-7(8H)-one

[0383] 

[0384] 合成方法参见实施例1,产率88.8%。

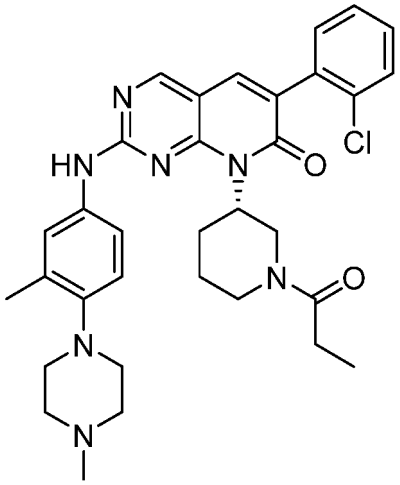
[0385] ^{1}H NMR(400MHz,DMSO)δ10.01(s,1H),8.79(s,1H),7.84(d,J＝4.7Hz,1H),7.47(d,J＝46.2Hz,5H),7.00(s,1H),5.36(d,J＝35.9Hz,1H),4.42(s,1H),3.85(dd,J＝94.2,53.4Hz,2H),2.83(s,5H),2.26(s,3H),2.24(s,3H),2.08(s,1H),1.80(s,3H),1.46(d,J＝13.6Hz,1H),1.24(s,1H).

[0386] MS(ESI)m/z 586.2$[M+H]^{+}$。

[0387] 实施例15

[0388] (S)-6-(2-氯苯基)-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)-8-(1-丙酰基哌啶-3-基)吡啶并[2,3-d]嘧啶-7(8H)-酮(570052)

[0389] (S)-6-(2-chlorophenyl)-2-((3-methyl-4-(4-methylpiperazin-1-yl)phenyl)amino)-8-(1-propionylpiperidin-3-yl)pyrido[2,3-d]pyrimidin-7(8H)-one

[0390] 

[0391] 合成方法参见实施例1,产率86%。

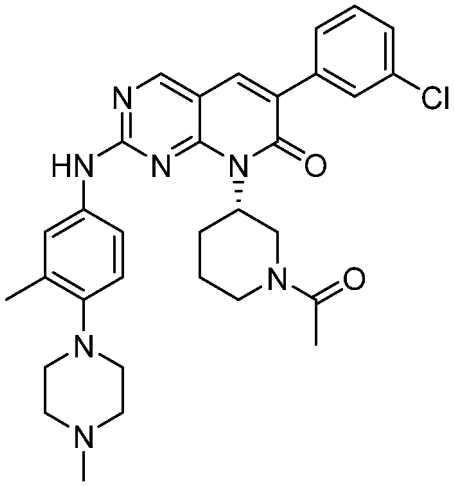
[0392] ^{1}H NMR(400MHz,DMSO)δ10.02(s,1H),8.78(s,1H),7.85(t,J=11.0Hz,1H),7.53(d,J=5.1Hz,2H),7.41(s,4H),6.97(s,1H),5.34(d,J=34.1Hz,1H),4.44(s,1H),4.17-3.86(m,1H),3.75(d,J=50.4Hz,1H),2.81(s,4H),2.25(s,3H),2.21(d,J=2.6Hz,3H),2.05-1.55(m,3H),1.46(s,1H),1.20-0.85(m,2H),0.80(s,1H).

[0393] MS(ESI)m/z 600.4[M+H]$^+$。

[0394] 实施例16

[0395] (S)-8-(1-乙酰基-3-基)-6-(3-氯苯基)-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)吡啶并[2,3-d]嘧啶-7(8H)-酮(570060)

[0396] (S)-8-(1-acetylpiperidin-3-yl)-6-(3-chlorophenyl)-2-((3-methyl-4-(4-methylpiperazin-1-yl)phenyl)amino)pyrido[2,3-d]pyrimidin-7(8H)-one

[0397] 

[0398] 合成方法参见实施例1,。

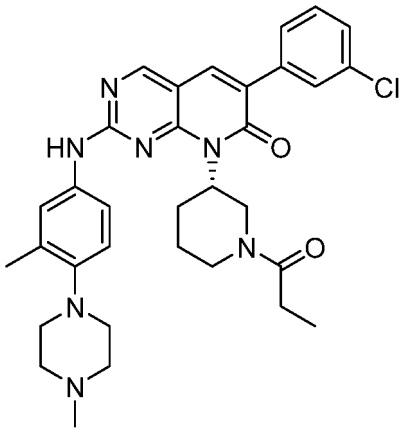
[0399] ^{1}H NMR(400MHz,DMSO)δ10.01(s,1H),8.79(s,1H),7.84(d,J=4.7Hz,1H),7.47(d,J=46.2Hz,5H),7.00(s,1H),5.36(d,J=35.9Hz,1H),4.42(s,1H),3.85(dd,J=94.2,53.4Hz,2H),2.83(s,5H),2.26(s,3H),2.24(s,3H),2.08(s,1H),1.80(s,3H),1.46(d,J=13.6Hz,1H),1.24(s,1H).

[0400] MS(ESI)m/z 586.2[M+H]$^+$。

[0401] 实施例17

[0402] (S)-6-(3-氯苯基)-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)-8-(1-丙酰基哌啶-3-基)吡啶并[2,3-d]嘧啶-7(8H)-酮(570061)

[0403] (S)-6-(3-chlorophenyl)-2-((3-methyl-4-(4-methylpiperazin-1-yl)phenyl)amino)-8-(1-propionylpiperidin-3-yl)pyrido[2,3-d]pyrimidin-7(8H)-one

[0404] 

[0405] 合成方法参见实施例1,产率85.7%。

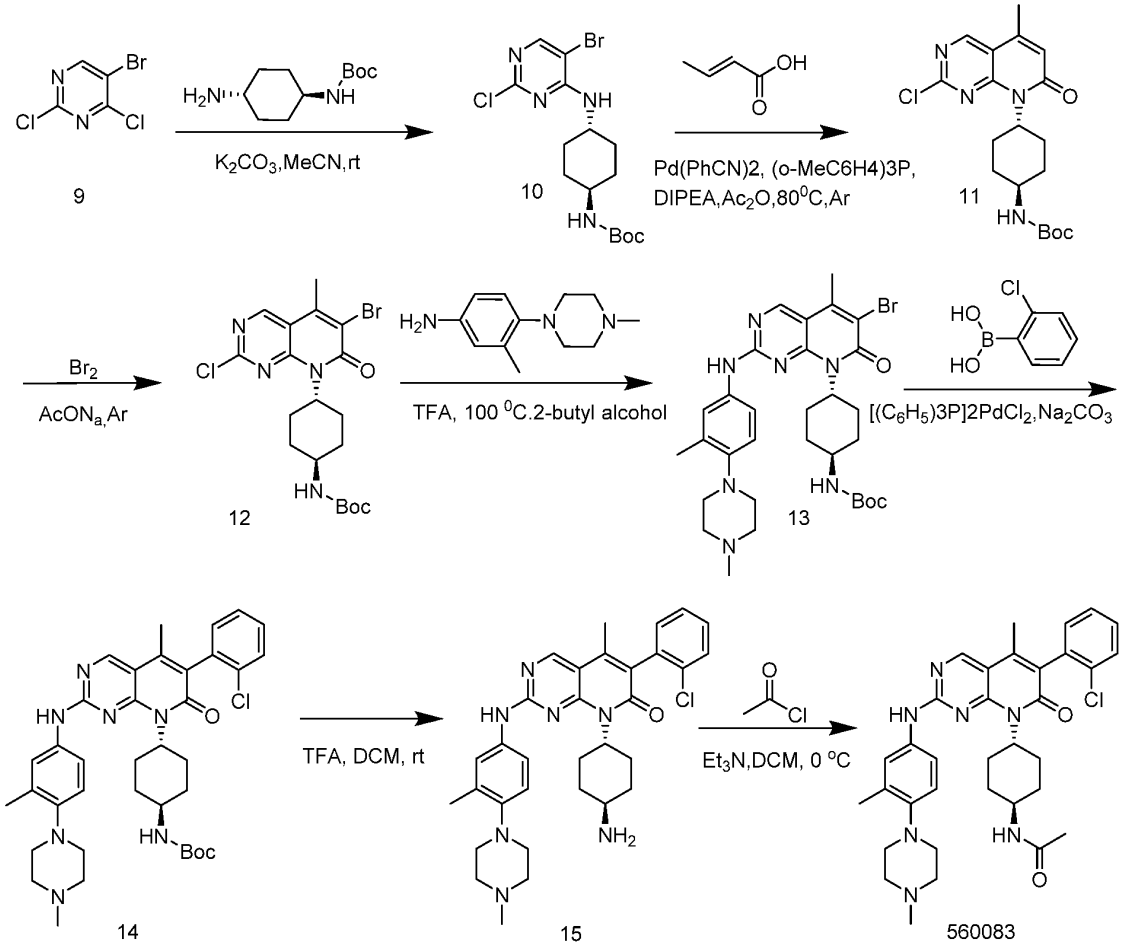
[0406] ^{1}H NMR(400MHz,DMSO)δ10.02(s,1H),8.78(s,1H),7.85(t,J=11.0Hz,1H),7.53(d,J=5.1Hz,2H),7.41(s,4H),6.97(s,1H),5.34(d,J=34.1Hz,1H),4.44(s,1H),4.17-3.86(m,1H),3.75(d,J=50.4Hz,1H),2.81(s,4H),2.25(s,3H),2.21(d,J=2.6Hz,3H),2.05-1.55(m,3H),1.46(s,1H),1.20-0.85(m,2H),0.80(s,1H).

[0407] MS(ESI)m/z 600.4$[M+H]^{+}$。

[0408] 实施例18

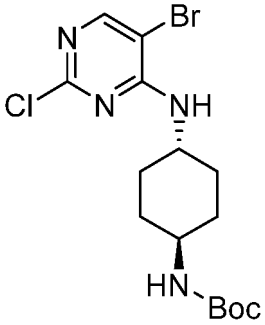
[0409] N-((1R,4R)-4-(6-(2-氯苯基)-5-甲基-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)-7-氧代吡啶并[2,3-d]嘧啶-8(7H)-基)环己基)乙酰胺(560083)

[0410] N-((1R,4R)-4-(6-(2-chlorophenyl)-5-methyl-2-((3-methyl-4-(4-methylpiperazin-1-yl)phenyl)amino)-7-oxopyrido[2,3-d]pyrimidin-8(7H)-yl)cyclohexyl)propionamide

[0411] 

[0412] 步骤9:((1R,4R)-4-((5-溴-2-氯嘧啶-4-基)氨基)环己基)氨基甲酸叔丁酯(10)

[0413] tert-butyl((1R,4R)-4-((5-bromo-2-chloropyrimidin-4-yl)amino)cyclohexyl)carbamate

[0414] 

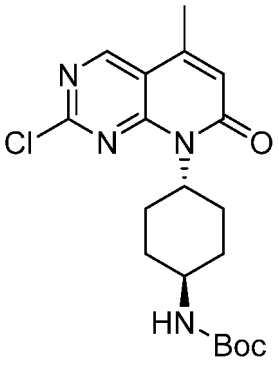
[0415] 室温下将5-溴-2,4-二氯嘧啶(9)(5.8g,25.45mmol)、反式-(4-氨基环己基)氨基甲酸叔丁酯(5.0g,23.23mmol)与K_2CO_3(6.4g,46.66mmol)加入到70mL MeCN中。混合体系继续室温搅拌,点板监测反应。原料反应完后,用二氯甲烷和水萃取,取有机相,无水Na_2SO_4干燥,然后过滤旋干,柱层析分离(SiO_2,PE/EA梯度洗脱,15:1to10:1)得白色油状物4.6g(产率48%)。

[0416] ^1H NMR(400MHz,DMSO)δ8.88(s,1H),5.34(s,1H),2.84(s,5H),2.30(d,J=18.1Hz,3H),2.11(s,3H),2.06(q,J=7.5Hz,2H),1.92(d,J=10.6Hz,2H),1.59(t,2H),1.38(s,9H)1.42-1.10(m,3H),1.05(s,1H),0.99(t,J=7.5Hz,3H).

[0417] MS(ESI)m/z 406.4$[M+H]^+$。

[0418] 步骤10:((1R,4R)-4-(2-氯-5-甲基-7-氧代吡啶并[2,3-d]嘧啶-8(7H)-基)环己基)氨基甲酸叔丁酯(11)

[0419] tert-butyl((1R,4R)-4-(2-chloro-5-methyl-7-oxopyrido[2,3-d]pyrimidin-8(7H)-yl)cyclohexyl)carbamate

[0420] 

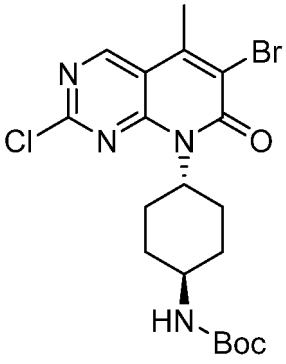
[0421] 室温下将化合物((1R,4R)-4-((5-溴-2-氯嘧啶-4-基)氨基)环己基)氨基甲酸叔丁酯(10)(3.25g,8.00mmol)和反式巴豆酸(6.75.g,80.0mmol)加入到THF(30mL)中,再将DIPEA(13mL)缓慢加入体系中,体系用Ar置换三次,然后再将二苯乙腈二氯化钯(0.16g,0.4mmol)和三(邻甲基苯基)膦(125mg,0.4mmol)加入到混合体系中,再次用Ar置换三次,体系加热至80℃搅拌反应24h,然后将Ac2O(1.9mL)加入到体系中,继续加热搅拌反应24h。停止加热,待体系温度降至室温,减压旋蒸除去部分溶剂,然后往体系中加入DCM(50mL),并用HCl(1M,100mL)洗涤有机相,然后用饱和食盐水(100mL)洗涤一次,收集有机相,用无水Na_2SO_4干燥30min,过滤,减压浓缩,柱层析得淡黄色固体即产物0.71g,产率30.0%。

[0422] ^1H NMR(400MHz,DMSO)δ8.88(s,1H),6.41(s=1H),7.27,5.75(s,1H),2.84(s,3H),2.24(s,3H),2.11(s,3H),2.06(q,J=7.5Hz,2H),1.92(d,J=10.6Hz,2H),1.59(s,9H)。

[0423] MS(ESI)m/z 393.6$[M+H]^+$。

[0424] 步骤11:((1R,4R)-4-(6-溴-2-氯-5-甲基-7-氧代吡啶并[2,3-d]嘧啶-8(7H)-基)环己基)氨基甲酸叔丁酯(12)

[0425] tert-butyl((1R,4R)-4-(6-bromo-2-chloro-5-methyl-7-oxopyrido[2,3-d]pyrimidin-8(7H)-yl)cyclohexyl)carbamate

[0426] 

[0427] 室温下将化合物((1R,4R)-4-(2-氯-5-甲基-7-氧代吡啶并[2,3-d]嘧啶-8(7H)-基)环己基)氨基甲酸叔丁酯(11)(383mg,0.97mmol)溶于AcOH(1.6mL)中,加入醋酸钠(320mg 3.88mmol),缓慢滴加液溴(0.013mL,2.7mmol),升温至55℃,搅拌过夜,加入饱和$Na_2S_2O_3$溶液,搅拌至体系红色消失,萃取分离的有机相,用水(5mL)和饱和食盐水(5mL)依次

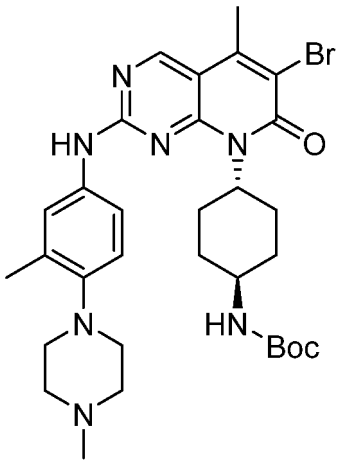
洗涤一次，收集有机相，用无水Na_2SO_4干燥30min，过滤，减压浓缩，柱层析得白色固体282mg，产率58.9％。

[0428] ^1H NMR(400MHz,DMSO)δ8.88(s,1H),,5.75(s,1H),2.84(s,3H),2.24(s,3H),2.11(s,3H),2.06(q,J＝7.5Hz,2H),1.92(d,J＝10.6Hz,2H),1.59(s,9H)。

[0429] MS(ESI)m/z 472.6$[M+H]^+$。

[0430] 步骤12：((1R,4R)-4-(6-溴-5-甲基-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)-7-氧代吡啶并[2,3-d]嘧啶-8(7H)-基)环己基)氨基甲酸叔丁酯(13)

[0431] tert-butyl((1R,4R)-4-(6-bromo-5-methyl-2-((3-methyl-4-(4-methylpiperazin-1-yl)phenyl)amino)-7-oxopyrido[2,3-d]pyrimidin-8(7H)-yl)cyclohexyl)carbamate

[0432] 

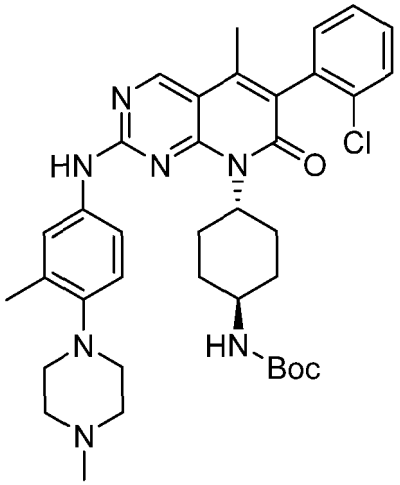
[0433] ((1R,4R)-4-(6-溴-2-氯-5-甲基-7-氧代吡啶并[2,3-d]嘧啶-8(7H)-基)环己基)氨基甲酸叔丁酯(12)(4.55mg,0.71mmol)加入装有7mL仲丁醇的封瓶中，依次加入3-甲基-4-(4-甲基哌嗪-1-取代)苯胺(160mg,0.78mmol)和TFA(50μL,0.71mmol)。加热到110℃，搅拌18小时。冷却至室温，倒入10％$NaHCO_3$水溶液中，二氯甲烷萃取两遍，合并有机相，饱和食盐水洗涤两遍，无水Na_2SO_4干燥，柱层析得黄色固体300mg，产率:66％。

[0434] ^1H NMR(400MHz,DMSO)δ9.86(s,1H),8.88(s,1H),7.41(dd,J＝5.1,2.6Hz,2H),7.27(d,J＝4.5Hz,1H),5.75(s,1H),5.34(s,1H),2.84(s,4H),2.30(d,J＝18.1Hz,3H),2.24(s,3H),2.11(s,3H),2.06(q,J＝7.5Hz,2H),1.92(d,J＝10.6Hz,2H),1.59(s,9H),1.42-110(m,3H),1.05(s,1H),0.99(t,J＝7.5Hz,3H).

[0435] MS(ESI)m/z 641.2$[M+H]^+$。

[0436] 步骤13：((1R,4R)-4-(6-(2-氯苯基)-5-甲基-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)-7-氧代吡啶并[2,3-d]嘧啶-8(7H)-基)环己基)氨基甲酸叔丁酯(14)

[0437] tert-butyl((1R,4R)-4-(6-(2-chlorophenyl)-5-methyl-2-((3-methyl-4-(4-methylpiperazin-1-yl)phenyl)amino)-7-oxopyrido[2,3-d]pyrimidin-8(7H)-yl)cyclohexyl)carbamate

[0438] 

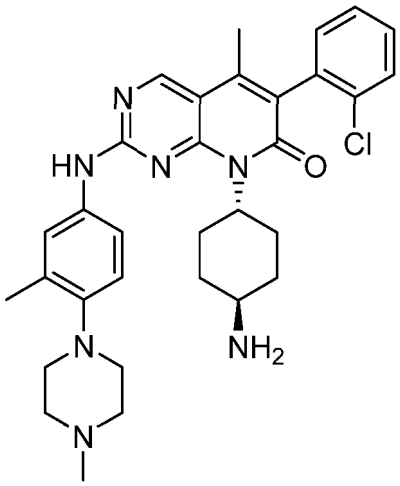
[0439] 室温下将化合物((1R,4R)-4-(6-溴-5-甲基-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)-7-氧代吡啶并[2,3-d]嘧啶-8(7H)-基)环己基)氨基甲酸叔丁酯(13)(336mg,0.5mmol),2-氯苯硼酸(410mg,2.6mmol),双三苯基磷二氯化钯(18.4mg,0.026mmol),Na_2CO_3(167mg,1.56mmol)加入到1,4-二氧六环(6mL)和H_2O(2mL)的混合溶剂中,体系用Ar置换空气,加热至110℃搅拌反应24h,停止加热,待体系降至室温,加入DCM(10mL)和饱和$NaHCO_3$(5mL)溶液,萃取分离,得有机相,用饱和食盐水(5mL)洗涤一次,收集有机相,用无水Na_2SO_4干燥30min,过滤,减压浓缩,柱层析得黄色固体280.mg,产率83.0%。

[0440] ^1H NMR(400MHz,DMSO)δ9.86(s,1H),8.88(s,1H),7.68(s,1H),7.54(t,J=7.9Hz,3H),7.41(dd,J=5.1,2.6Hz,2H),7.27(d,J=4.5Hz,1H),7.09(s,1H),5.75(s,1H),5.34(s,1H),2.84(s,4H),2.30(d,J=18.1Hz,3H),2.24(s,3H),2.11(s,3H),2.06(q,J=7.5Hz,2H),1.92(d,J=10.6Hz,2H),1.59(s,9H),1.42-110(m,3H),1.05(s,1H),0.99(t,J=7.5Hz,3H).

[0441] MS(ESI)m/z 673.2$[M+H]^+$。

[0442] 步骤14:8-((1R,4R)-4-氨基环己基)-6-(2-氯苯基)-5-甲基-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)吡啶并并[2,3-d]嘧啶-7(8H)-酮(15)

[0443] 8-((1R,4R)-4-aminocyclohexyl)-6-(2-chlorophenyl)-5-methyl-2-((3-methyl-4-(4-methylpiperazin-1-yl)phenyl)amino)pyrido[2,3-d]pyrimidin-7(8H)-one

[0444] 

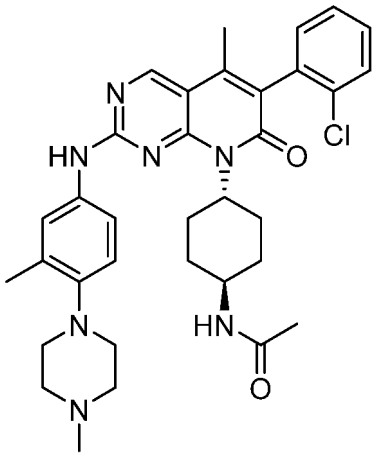
[0445] ((1R,4R)-4-(6-(2-氯苯基)-5-甲基-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)-7-氧代吡啶[2,3-d]嘧啶-8(7H)-基)环己基)氨基甲酸叔丁酯(14)280mg溶于5mL二氯甲烷中,加入TFA(0.5mL),室温搅拌4h。反应用二氯甲烷稀释,用饱和$NaHCO_3$溶液调节pH至9,二氯甲烷萃取两遍,合并有机相,10%$NaHCO_3$水溶液洗涤两遍,饱和食盐水洗涤两遍,无水Na_2SO_4干燥,过滤旋干,柱层析分离得到黄色固体200mg(产率84%)。

[0446] ^1H NMR(400MHz,DMSO)δ9.86(s,1H),8.88(s,1H),7.68(s,1H),7.54(t,J=7.9Hz,3H),7.41(dd,J=5.1,2.6Hz,2H),7.27(d,J=4.5Hz,1H),7.09(s,1H),5.75(s,1H),5.34(s,1H),2.84(s,5H),2.30(d,J=18.1Hz,3H),2.24(s,3H),2.11(s,3H),2.06(q,J=7.5Hz,2H),1.92(d,J=10.6Hz,2H),1.42-1.10(m,2H),1.05(s,1H),0.99(t,J=7.5Hz,3H).

[0447] MS(ESI)m/z 573.2$[M+H]^+$。

[0448] 步骤15:N-((1R,4R)-4-(6-(2-氯苯基)-5-甲基-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)-7-氧代吡啶并[2,3-d]嘧啶-8(7H)-基)环己基)乙酰胺(560083)

[0449] N-((1R,4R)-4-(6-(2-chlorophenyl)-5-methyl-2-((3-methyl-4-(4-methylpiperazin-1-yl)phenyl)amino)-7-oxopyrido[2,3-d]pyrimidin-8(7H)-yl)cyclohexyl)acetamide

[0450] 

[0451] 8-((1R,4R)-4-氨基环己基)-6-(2-氯苯基)-5-甲基-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)吡啶并并[2,3-d]嘧啶-7(8H)-酮(15)(150mg,0.28mmol)溶于10mL无水二氯甲烷中,0℃冰浴下加入Et_3N(1.1mL,0.84mmol),缓慢加入乙酰氯(25μL,0.31mmol)。回至室温搅拌4小时。反应完后,加入10%$NaHCO_3$水溶液,二氯甲烷萃取两遍,合并有机相,用饱和食盐水洗涤一遍,无水Na_2SO_4干燥,过滤旋干,柱层析分离(SiO_2,CH_2Cl_2/MeOH/NH_4OH,40:1:0.4),并用高效液相色谱仪进一步纯化得固体130mg(产率92%)。

[0452] ^1H NMR(400MHz,DMSO)δ9.86(s,1H),8.88(s,1H),7.68(s,1H),7.54(t,J=7.9Hz,3H),7.41(dd,J=5.1,2.6Hz,2H),7.27(d,J=4.5Hz,1H),7.09(s,1H),5.75(s,1H),5.34(s,1H),2.84(s,5H),2.30(d,J=18.1Hz,3H),2.24(s,3H),2.11(s,3H),2.06(q,J=7.5Hz,2H),1.92(d,J=10.6Hz,2H),1.59(t,2H),1.42-1.10(m,3H),1.05(s,1H),0.99(t,J=7.5Hz,3H)。

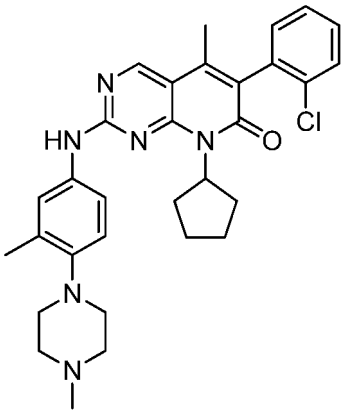
[0453] MS(ESI)m/z 600.4$[M+H]^+$。

[0454] 实施例19

[0455] 6-(2-氯苯基)-8-环戊基-5-甲基-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)

吡啶并[2,3-d]嘧啶-7-(8H)-酮(560070)

[0456] 6-(2-chlorophenyl)-8-cyclopentyl-5-methyl-2-((3-methyl-4-(4-methylpiperazin-1-yl)phenyl)amino)pyrido[2,3-d]pyrimidin-7(8H)-one

[0457] 

[0458] 合成方法参见实施例18,产率47.4%。

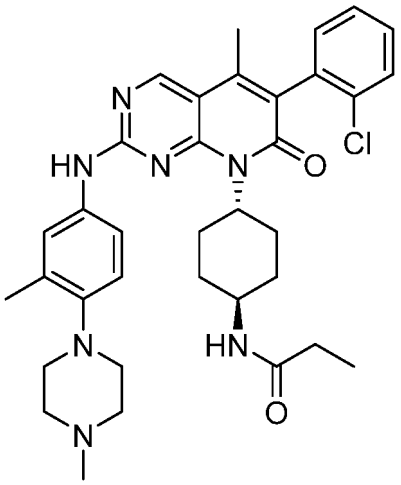
[0459] ^{1}H NMR(400MHz,$CDCl_3$)δ8.71(s,1H),7.57(s,1H),7.48(d,J=7.2Hz,1H),7.33(t,J=9.0Hz,3H),7.27-7.20(m,3H),7.05(d,J=8.5Hz,1H),6.12-5.85(m,1H),2.96(d,J=3.9Hz,4H),2.63(s,4H),2.39(s,4H),2.37-2.26(m,5H),2.16(s,3H),2.01(dd,J=37.8,11.7Hz,4H),1.89(d,J=5.9Hz,3H),1.63(t,J=15.7Hz,3H),1.38-1.14(m,3H),0.86(d,J=9.3Hz,1H).

[0460] MS(ESI)m/z 543.3$[M+H]^+$。

[0461] 实施例20

[0462] N-((1R,4R)-4-(6-(2-氯苯基)-5-甲基-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)-7-氧代吡啶并[2,3-d]嘧啶-8(7H)-基)环己基)丙酰胺(560082)

[0463] N-((1R,4R)-4-(6-(2-chlorophenyl)-5-methyl-2-((3-methyl-4-(4-methylpiperazin-1-yl)phenyl)amino)-7-oxopyrido[2,3-d]pyrimidin-8(7H)-yl)cyclohexyl)propionamide

[0464] 

[0465] 合成方法参见实施例18,产率92%。

[0466] ^{1}H NMR(400MHz,DMSO)δ9.86(s,1H),8.88(s,1H),7.68(s,1H),7.54(t,J=7.9Hz,3H),7.41(dd,J=5.1,2.6Hz,2H),7.27(d,J=4.5Hz,1H),7.09(s,1H),5.75(s,1H),5.34(s,1H),2.84(s,5H),2.30(d,J=18.1Hz,3H),2.24(s,3H),2.11(s,3H),2.06(q,J=7.5Hz,

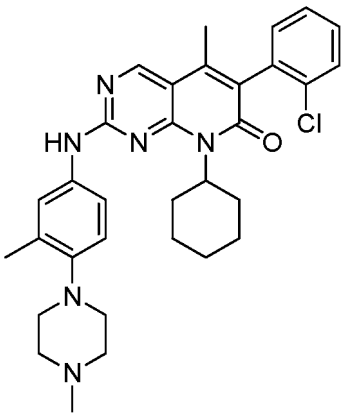
2H),1.92(d,J＝10.6Hz,2H),1.59(t,2H),1.42-1.10(m,3H),1.05(s,1H),0.99(t,J＝7.5Hz,3H).

[0467] MS(ESI)m/z 629.3[M+H]$^+$。

[0468] 实施例21

[0469] 6-(2-氯苯基)-8-环己基-5-甲基-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)吡啶并[2,3-d]嘧啶-7-(8H)-酮(560132)

[0470] 6-(2-chlorophenyl)-8-cyclohexyl-5-methyl-2-((3-methyl-4-(4-methylpiperazin-1-yl)phenyl)amino)pyrido[2,3-d]pyrimidin-7(8H)-one

[0471] 

[0472] 合成方法参见实施例18,产率47.6%。

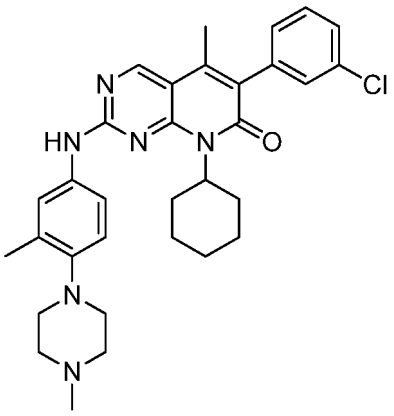
[0473] ^{1}H NMR(400MHz,$CDCl_3$)δ8.71(s,1H),7.57(s,1H),7.48(d,J＝7.2Hz,1H),7.33(t,J＝9.0Hz,3H),7.27-7.20(m,3H),7.05(d,J＝8.5Hz,1H),6.12-5.85(m,1H),2.96(d,J＝3.9Hz,4H),2.63(s,4H),2.39(s,4H),2.37-2.26(m,5H),2.16(s,3H),2.01(dd,J＝37.8,11.7Hz,4H),1.89(d,J＝5.9Hz,3H),1.63(t,J＝15.7Hz,3H),1.38-1.14(m,3H),0.86(d,J＝9.3Hz,2H).

[0474] MS(ESI)m/z 557.3[M+H]$^+$。

[0475] 实施例22

[0476] 6-(3-氯苯基)-8-环己基-5-甲基-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)吡啶并[2,3-d]嘧啶-7-(8H)-酮(560133)

[0477] 6-(3-chlorophenyl)-8-cyclohexyl-5-methyl-2-((3-methyl-4-(4-methylpiperazin-1-yl)phenyl)amino)pyrido[2,3-d]pyrimidin-7(8H)-one

[0478] 

[0479] 合成方法参见实施例18,产率78.3%。

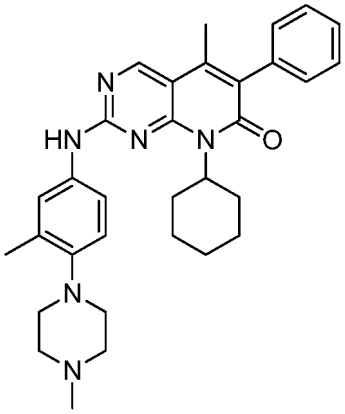
[0480] ^{1}H NMR(400MHz,DMSO)δ9.86(s,1H),8.86(s,1H),7.43(d,J＝5.7Hz,4H),7.23(d,J＝39.4Hz,2H),7.00(d,J＝8.0Hz,1H),5.36(d,J＝47.1Hz,1H),3.17-2.91(m,1H),2.81(s,4H),2.27(s,3H),2.23(s,3H),2.20(s,3H),1.84(d,J＝54.6Hz,3H),1.57(s,3H),1.26(d,J＝36.6Hz,3H),1.13-0.91(m,2H).

[0481] MS(ESI)m/z 557.3[M+H]$^+$。

[0482] 实施例23

[0483] 8-环己基-5-甲基-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)-6-苯基吡啶并[2,3-d]嘧啶-7(8H)-酮(560134)

[0484] 8-cyclohexyl-5-methyl-2-((3-methyl-4-(4-methylpiperazin-1-yl)phenyl)amino)-6-phenylpyrido[2,3-d]pyrimidin-7(8H)-one

[0485] 

[0486] 合成方法参见实施例18,产率89%。

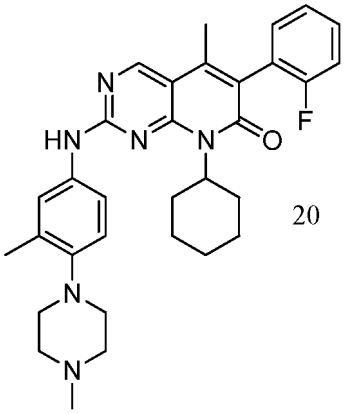
[0487] ^{1}H NMR(400MHz,DMSO)δ9.81(s,1H),8.85(s,1H),7.41(t,J＝19.3Hz,5H),7.11(d,J＝76.4Hz,2H),5.36(d,J＝40.5Hz,1H),2.81(s,4H),2.27(s,3H),2.23(s,3H),2.19(s,3H),1.79(d,J＝11.8Hz,2H),1.58(s,3H),1.27(d,J＝36.7Hz,3H).

[0488] MS(ESI)m/z 523.3[M+H]$^+$。

[0489] 实施例24

[0490] 8-环己基-6-(2-氟苯基)-5-甲基-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)吡啶并[2,3-d]嘧啶-7-(8H)-酮(560135)

[0491] 8-cyclohexyl-6-(2-fluorophenyl)-5-methyl-2-((3-methyl-4-(4-methylpiperazin-1-yl)phenyl)amino)pyrido[2,3-d]pyrimidin-7(8H)-one

[0492] 

[0493] 合成方法参见实施例18,产率47.3%。

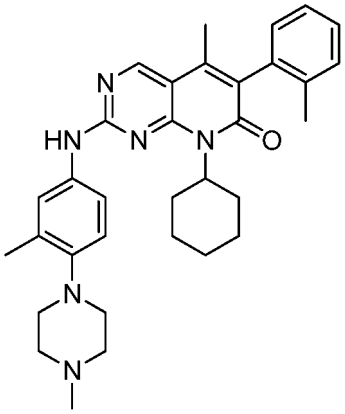
[0494] ^{1}H NMR(400MHz,DMSO)δ9.85(s,1H),8.87(s,1H),7.68-7.36(m,3H),7.25(td,J＝8.5,4.9Hz,3H),7.01(d,J＝8.6Hz,1H),5.33(dd,J＝23.8,19.1Hz,1H),4.37(s,1H),2.82(t,J＝4.4Hz,4H),2.27(s,3H),2.24(s,3H),2.19(s,3H),1.86-1.66(m,3H),1.58(s,3H),1.44-1.10(m,5H).

[0495] MS(ESI)m/z 541.3[M+H]$^+$。

[0496] 实施例25

[0497] 8-环己基-5-甲基-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)-6-(邻甲苯基)吡啶并[2,3-d]嘧啶-7-(8H)-酮(560136)

[0498] 8-cyclohexyl-5-methyl-2-((3-methyl-4-(4-methylpiperazin-1-yl)phenyl)amino)-6-(o-tolyl)pyrido[2,3-d]pyrimidin-7(8H)-one

[0499] 

[0500] 合成方法参见实施例18,产率49.2%。

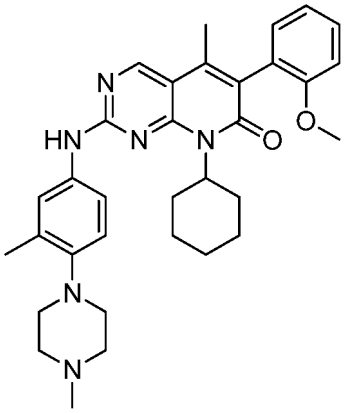
[0501] ^{1}H NMR(400MHz,DMSO)δ9.85(s,1H),8.87(s,1H),7.68-7.36(m,3H),7.25(td,J＝8.5,4.9Hz,3H),7.01(d,J＝8.6Hz,1H),5.33(dd,J＝23.8,19.1Hz,1H),4.37(s,1H),2.82(t,J＝4.4Hz,4H),2.47(s,3H)2.27(s,3H),2.24(s,3H),2.19(s,3H),1.86-1.66(m,3H),1.58(s,3H),1.44-1.10(m,5H).

[0502] MS(ESI)m/z 537.4[M+H]$^+$。

[0503] 实施例26

[0504] 8-环己基-6-(2-甲氧基苯基)-5-甲基-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)吡啶并[2,3-d]嘧啶-7-(8H)-酮(560138)

[0505] 8-cyclohexyl-6-(2-methoxyphenyl)-5-methyl-2-((3-methyl-4-(4-methylpiperazin-1-yl)phenyl)amino)pyrido[2,3-d]pyrimidin-7(8H)-one

[0506] 

[0507] 合成方法参见实施例18,产率42%。

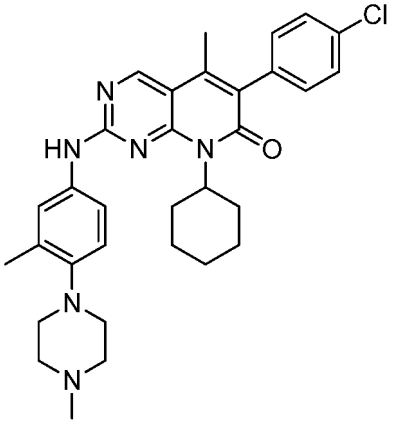
[0508] ^{1}H NMR(400MHz,DMSO)δ9.76(s,1H),8.79(d,J=24.7Hz,1H),7.79(s,1H),7.71-7.40(m,2H),7.35(t,J=7.2Hz,1H),7.20-6.91(m,3H),5.37(s,1H),3.85-3.58(m,3H),3.03(dt,J=13.9,7.1Hz,1H),2.82(s,3H),2.31(d,J=27.8Hz,3H),2.25(s,3H),2.09(s,2H),1.89-1.70(m,3H),1.60(d,J=24.8Hz,3H),1.27(dd,J=47.3,13.7Hz,3H),1.18-1.00(m,1H),0.98(d,J=7.2Hz,1H).

[0509] MS(ESI)m/z 553.4[M+H]$^{+}$。

[0510] 实施例27

[0511] 6-(4-氯苯基)-8-环己基-5-甲基-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)吡啶并[2,3-d]嘧啶-7-(8H)-酮(560140)

[0512] 6-(4-chlorophenyl)-8-cyclohexyl-5-methyl-2-((3-methyl-4-(4-methylpiperazin-1-yl)phenyl)amino)pyrido[2,3-d]pyrimidin-7(8H)-one

[0513] 

[0514] 合成方法参见实施例18,产率86%。

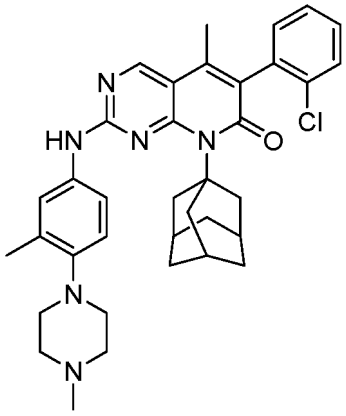
[0515] 1H NMR(400MHz,DMSO)δ9.76(s,1H),8.79(d,J=24.7Hz,1H),7.79(s,1H),7.71-7.40(m,2H),7.35(t,J=7.2Hz,1H),7.20-6.91(m,3H),5.37(s,1H),3.85-3.58(m,3H),3.03(dt,J=13.9,7.1Hz,1H),2.82(s,3H),2.31(d,J=27.8Hz,3H),2.09(s,2H),1.89-1.70(m,3H),1.60(d,J=24.8Hz,3H),1.27(dd,J=47.3,13.7Hz,3H),1.18-1.00(m,1H),0.98(d,J=7.2Hz,1H).

[0516] MS(ESI)m/z 557.3[M+H]$^{+}$。

[0517] 实施例28

[0518] 8-((3S,5S,7S)-金刚烷-1-基)-6-(2-氯苯基)-5-甲基-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基基)氨基)吡啶并[2,3-d]嘧啶-7(8H)-酮(560145)

[0519] 8-((3S,5S,7S)-adamantan-1-yl)-6-(2-chlorophenyl)-5-methyl-2-((3-methyl-4-(4-methylpiperazin-1-yl)phenyl)amino)pyrido[2,3-d]pyrimidin-7(8H)-one

[0520] 

[0521] 合成方法参见实施例18,产率47.9%。

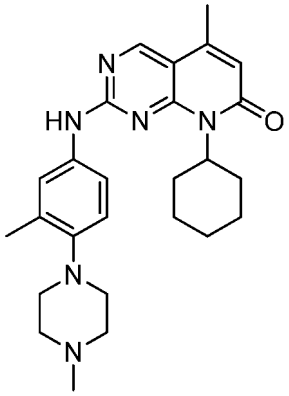
[0522] ^{1}H NMR(400MHz,DMSO)δ9.56(s,1H),8.75(s,1H),7.56-7.46(m,1H),7.46-7.27(m,4H),7.27-7.18(m,1H),7.00(d,J=8.0Hz,1H),3.03(td,J=12.8,7.2Hz,1H),2.80(d,J=3.6Hz,5H),2.56(s,6H),2.31-2.17(m,7H),2.07(d,J=11.2Hz,3H),1.97(d,J=10.7Hz,5H),1.77(s,1H),1.54(s,7H),1.21(d,J=29.3,7.2Hz,4H),1.05-0.93(m,2H).

[0523] MS(ESI)m/z 610.1[M+H]$^+$。

[0524] 实施例29

[0525] 8-环己基-5-甲基-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)吡啶并[2,3-d]嘧啶-7(8H)-酮(560150)

[0526] 8-cyclohexyl-5-methyl-2-((3-methyl-4-(4-methylpiperazin-1-yl)phenyl)amino)pyrido[2,3-d]pyrimidin-7(8H)-one

[0527] 

[0528] 合成方法参见实施例18,产率59.2%。

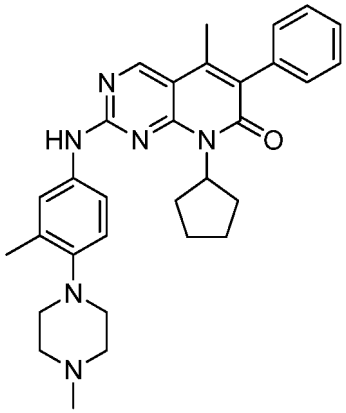
[0529] ^{1}H NMR(400MHz,DMSO)δ9.81(s,1H),8.76(s,1H),7.82-7.30(m,2H),7.01(d,J=8.6Hz,1H),6.15(s,1H),5.33(dd,J=12.4,7.7Hz,1H),2.82(d,J=4.2Hz,4H),2.40(d,J=35.7Hz,3H),2.27(s,3H),2.24(d,J=15.9Hz,3H),2.04-1.93(m,1H),1.80(d,J=20.0Hz,2H),1.65(s,1H),1.60-1.42(m,2H),1.41-1.28(m,2H).

[0530] MS(ESI)m/z 447.3[M+H]$^+$。

[0531] 实施例30

[0532] 8-环戊基-5-甲基-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)-6-苯基吡啶并[2,3-d]嘧啶-7(8H)-酮(570008)

[0533] 8-cyclopentyl-5-methyl-2-((3-methyl-4-(4-methylpiperazin-1-yl)phenyl)amino)-6-phenylpyrido[2,3-d]pyrimidin-7(8H)-one

[0534] 

[0535] 合成方法参见实施例18,产率42%。

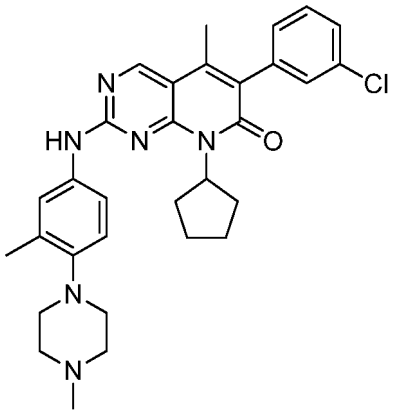
[0536] ^{1}H NMR(400MHz,DMSO)δ9.83(s,1H),8.88(s,1H),7.68(s,1H),7.53-7.29(m,3H),7.29-7.12(m,2H),7.00(d,J=8.6Hz,1H),6.20-5.51(m,1H),2.82(t,J=4.3Hz,3H),2.25(s,4H),2.20(s,3H),1.85(d,J=16.1Hz,2H),1.84-1.72(m,2H),1.64-1.48(m,2H).

[0537] MS(ESI)m/z 509.4[M+H]$^+$。

[0538] 实施例31

[0539] 6-(3-氯苯基)-8-环戊基-5-甲基-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)吡啶并[2,3-d]嘧啶-7-(8H)-酮(570012)

[0540] 6-(3-chlorophenyl)-8-cyclopentyl-5-methyl-2-((3-methyl-4-(4-methylpiperazin-1-yl)phenyl)amino)pyrido[2,3-d]pyrimidin-7(8H)-one

[0541] 

[0542] 合成方法参见实施例18,产率79.8%。

[0543] ^{1}H NMR(400MHz,DMSO)δ9.88(s,1H),8.89(s,1H),7.77-7.60(m,1H),7.56-7.35(m,3H),7.30(d,J=1.8Hz,1H),7.19(dt,J=6.8,1.7Hz,1H),7.00(d,J=8.6Hz,1H),6.06-5.77(m,1H),2.81(t,J=4.4Hz,4H),2.48(d,J=12.4Hz,4H),2.25(s,3H),2.23(s,3H),2.21(s,3H),1.87(s,2H),1.80(dd,J=12.3,7.1Hz,2H),1.57(dd,J=11.3,5.1Hz,3H).

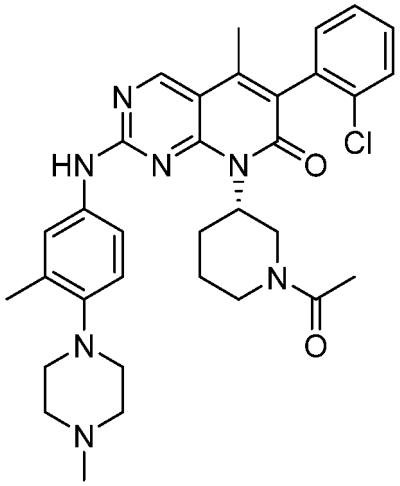
[0544] MS(ESI)m/z 543.3[M+H]$^+$。

[0545] 实施例32

[0546] (S)-8-(1-乙酰基-3-基)-6-(2-氯苯基)-5-甲基-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)吡啶并[2,3-d]嘧啶-7(8H)-酮(570056)

[0547] (S)-8-(1-acetylpiperidin-3-yl)-6-(2-chlorophenyl)-5-methyl-2-((3-methyl-4-(4-methylpiperazin-1-yl)phenyl)amino)pyrido[2,3-d]pyrimidin-7(8H)-

one

[0548] 

[0549] 合成方法参见实施例18,产率78.9%。

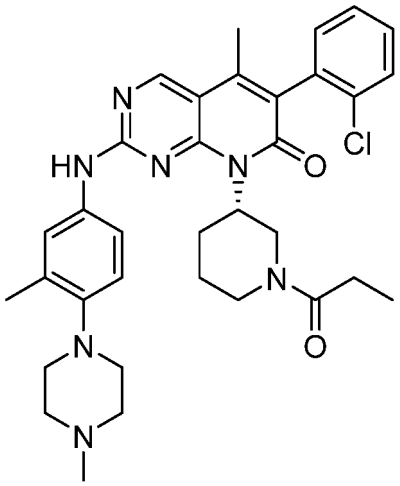
[0550] ^{1}H NMR(400MHz,DMSO)δ9.95(s,1H),8.91(d,J=3.8Hz,1H),7.72-7.48(m,2H),7.41(dd,J=4.8,2.7Hz,3H),7.36-7.20(m,1H),6.98(d,J=6.5Hz,1H),5.34(dd,J=21.8,17.0Hz,1H),4.40(s,1H),3.90(dd,J=97.8,35.0Hz,3H),2.81(s,5H),2.14(d,J=2.9Hz,3H),2.04(d,J=16.1Hz,1H),1.76(s,3H),1.45(s,1H),1.23(s,2H).

[0551] MS(ESI)m/z 600.3[M+H]$^+$。

[0552] 实施例33

[0553] (S)-6-(2-氯苯基)-5-甲基-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)-8-(1-丙酰基哌啶-3-基)吡啶并[2,3-d]嘧啶-7(8H)-酮(560057)

[0554] (S)-6-(2-chlorophenyl)-5-methyl-2-((3-methyl-4-(4-methylpiperazin-1-yl)phenyl)amino)-8-(1-propionylpiperidin-3-yl)pyrido[2,3-d]pyrimidin-7(8H)-one

[0555] 

[0556] 合成方法参见实施例18,产率82.6%。

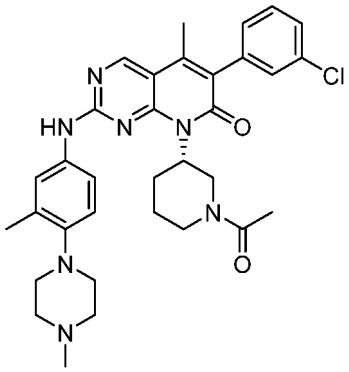
[0557] ^{1}H NMR(400MHz,DMSO)δ9.98(s,1H),8.91(s,1H),7.67-7.49(m,2H),7.49-7.33(m,3H),7.28(dd,J=7.9,4.0Hz,1H),6.96(s,1H),5.91-5.01(m,1H),4.43(s,1H),4.25-3.79(m,1H),3.79-3.46(m,1H),2.80(s,4H),2.23(s,3H),2.21(d,J=2.9Hz,3H),2.13(s,3H),1.77(s,3H),1.44(s,2H),0.98(d,J=21.7Hz,2H),0.81(s,2H).

[0558] MS(ESI)m/z 614.3[M+H]$^+$。

[0559] 实施例34

[0560] (S)-8-(1-乙酰基-3-基)-6-(3-氯苯基)-5-甲基-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)吡啶并[2,3-d]嘧啶-7(8H)-酮(570063)

[0561] (S)-8-(1-acetylpiperidin-3-yl)-6-(3-chlorophenyl)-5-methyl-2-((3-methyl-4-(4-methylpiperazin-1-yl)phenyl)amino)pyrido[2,3-d]pyrimidin-7(8H)-one

[0562] 

[0563] 合成方法参见实施例18,产率77.16%。

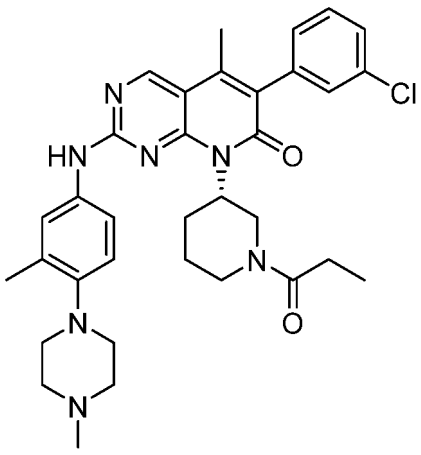
[0564] ^{1}H NMR(400MHz,DMSO)δ9.95(s,1H),8.91(d,J=3.8Hz,1H),7.72-7.48(m,2H),7.41(dd,J=4.8,2.7Hz,3H),7.36-7.20(m,1H),7.05(s,1H),6.98(d,J=6.5Hz,1H),5.34(dd,J=21.8,17.0Hz,1H),4.40(s,1H),3.90(dd,J=97.8,35.0Hz,3H),2.81(s,5H),2.14(d,J=2.9Hz,3H),2.04(d,J=16.1Hz,1H),1.76(s,3H),1.45(s,1H),1.23(s,2H).

[0565] MS(ESI)m/z 600.4[M+H]$^+$。

[0566] 实施例35

[0567] (S)-6-(3-氯苯基)-5-甲基-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)-8-(1-丙酰基哌啶-3-基)吡啶并[2,3-d]嘧啶-7(8H)-酮(570064)

[0568] (S)-6-(3-chlorophenyl)-5-methyl-2-((3-methyl-4-(4-methylpiperazin-1-yl)phenyl)amino)-8-(1-propionylpiperidin-3-yl)pyrido[2,3-d]pyrimidin-7(8H)-one

[0569] 

[0570] 合成方法参见实施例18,产率81.8%。

[0571] ^{1}H NMR(400MHz,DMSO)δ9.98(s,1H),8.91(s,1H),7.67-7.49(m,2H),7.49-7.33

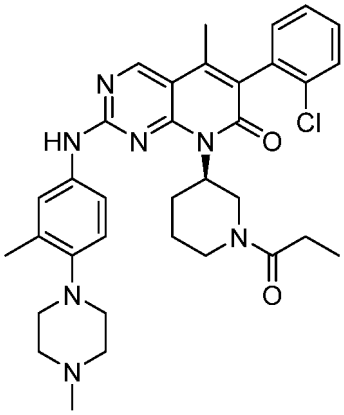
(m,3H),7.28(dd,J＝7.9,4.0Hz,1H),7.05(s,1H),6.96(s,1H),5.91-5.01(m,1H),4.43(s,1H),4.25-3.79(m,1H),3.79-3.46(m,1H),2.80(s,4H),2.23(s,3H),2.21(d,J＝2.9Hz,3H),2.13(s,3H),1.77(s,3H),1.44(s,2H),0.98(d,J＝21.7Hz,2H),0.81(s,2H).

[0572] MS(ESI)m/z 614.4[M+H]$^+$。

[0573] 实施例36

[0574] (S)-8-(1-丙酰基-3-基)-6-(2-氯苯基)-5-甲基-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)吡啶并[2,3-d]嘧啶-7(8H)-酮(570089)

[0575] (S)-6-(2-chlorophenyl)-5-methyl-2-((3-methyl-4-(4-methylpiperazin-1-yl)phenyl)amino)-8-(1-propionylpiperidin-3-yl)pyrido[2,3-d]pyrimidin-7(8H)-one

[0576] 

[0577] 合成方法如实施例18,产率76.9%。

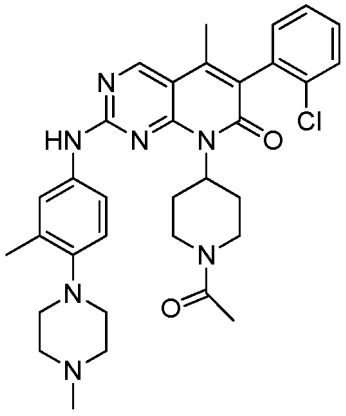
[0578] ^{1}H NMR(400MHz,DMSO)δ9.99(s,1H),8.77(s,1H),7.81(s,1H),7.52(d,J＝4.1Hz,3H),7.41(d,J＝10.1Hz,3H),7.01(d,J＝8.3Hz,1H)5.63(s,1H),4.62(d,J＝8.2Hz,1H),4.25-3.81(m,1H),3.05(t,J＝11.7Hz,1H),2.92-2.67(m,4H),2.57(d,J＝9.0Hz,2H),2.51(s,3H),2.41-2.35(m,2H),2.26(s,3H),2.24(s,3H),1.72(q,J＝37.9Hz,2H),1.00(t,J＝7.2Hz,3H).

[0579] MS(ESI)m/z 614.3[M+H]$^+$。

[0580] 实施例37

[0581] 8-(1-乙酰基哌啶-4-基)-6-(2-氯苯基)-5-甲基-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)吡啶并[2,3-d]嘧啶-7(8H)-酮(570104)

[0582] 8-(1-acetylpiperidin-4-yl)-6-(2-chlorophenyl)-5-methyl-2-((3-methyl-4-(4-methylpiperazin-1-yl)phenyl)amino)pyrido[2,3-d]pyrimidin-7(8H)-one

[0583] 

[0584] 合成方法如实施例18,产率86.8%。

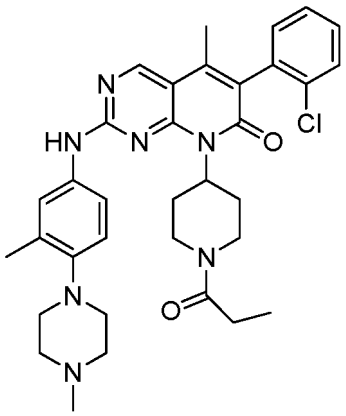
[0585] ^{1}H NMR(400MHz,DMSO)δ9.95(s,1H),8.91(s,1H),7.72-7.48(m,2H),7.41(dd,J=2.7Hz,3H),7.36-7.20(m,1H),6.98(s,1H),5.34(dd,J=21.8Hz,1H),4.40(s,1H),3.90(dd,J=35.0,11.2Hz,3H),3.6(t,J=8.7Hz,1H),2.92-2.67(m,4H),2.14(s,3H),2.04(d,J=16.1Hz,2H),1.85(s,3H)1.76(s,3H),1.45(s,1H),1.23(s,3H).

[0586] MS(ESI)m/z 600.3[M+H]$^+$。

[0587] 实施例38

[0588] 6-(2-氯苯基)-5-甲基-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)-8-(1-丙哌啶-4-基)吡啶并[2,3-d]嘧啶-7(8H)-酮(570105)

[0589] 6-(2-chlorophenyl)-5-methyl-2-((3-methyl-4-(4-methylpiperazin-1-yl)phenyl)amino)-8-(1-propionylpiperidin-4-yl)pyrido[2,3-d]pyrimidin-7(8H)-one

[0590] 

[0591] 合成方法如实施例18,产率75.2%。

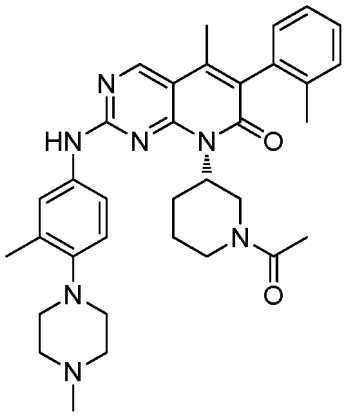
[0592] ^{1}H NMR(400MHz,DMSO)δ9.98(s,1H),8.91(s,1H),7.67-7.49(m,2H),7.49-7.33(m,3H),7.28(dd,J=7.9,4.0Hz,1H),6.96(s,1H),5.91-5.01(m,1H),4.62(d,J=8.2Hz,1H),4.25-3.81(m,1H),3.05(t,J=11.7Hz,1H),2.92-2.67(m,4H),2.57(d,J=9.0Hz,2H),2.51(s,3H),2.41-2.35(m,2H),2.26(s,3H),2.24(s,3H),1.72(q,J=37.9Hz,2H),1.00(t,J=7.2Hz,3H).

[0593] MS(ESI)m/z 614.3[M+H]$^+$。

[0594] 实施例39

[0595] (S)-8-(1-乙酰基-3-基)-5-甲基-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)-6-(邻甲苯基)吡啶并[2,3-d]嘧啶-7(8H)-酮(570111)

[0596] (S)-8-(1-acetylpiperidin-3-yl)-5-methyl-2-((3-methyl-4-(4-methylpiperazin-1-yl)phenyl)amino)-6-(o-tolyl)pyrido[2,3-d]pyrimidin-7(8H)-one

[0597] 

[0598] 合成方法如实施例18,产率79.5%。

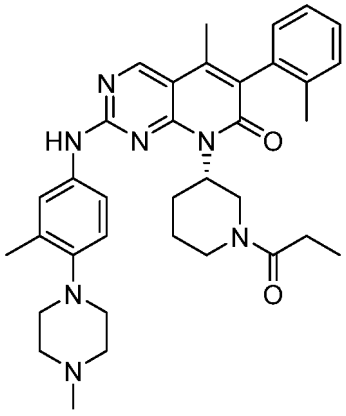
[0599] ^{1}H NMR(400MHz,DMSO)δ9.68(s,1H),8.94(s,1H),8.41(s,2H),7.85-7.20(m,3H),6.87(m,2H),5.68-5.00(m,1H),4.28(d,J=105.3Hz,1H),3.96(s,3H),2.81(s,4H),2.38(s,3H),2.30(d,J=5.0Hz,1H),2.32-2.27(m,2H),2.23(d,J=4.6Hz,2H),2.24-2.17(m,1H),2.19-1.85(m,2H),1.80(s,3H),1.62-1.29(m,2H),1.28(s,3H).

[0600] MS(ESI)m/z 580.2[M+H]$^+$

[0601] 实施例40

[0602] (S)-8-(1-丙酰基-3-基)-5-甲基-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)-6-(邻甲苯基)吡啶并[2,3-d]嘧啶-7(8H)-酮(570112)

[0603] (S)-5-methyl-2-((3-methyl-4-(4-methylpiperazin-1-yl)phenyl)amino)-8-(1-propionylpiperidin-3-yl)-6-(o-tolyl)pyrido[2,3-d]pyrimidin-7(8H)-one

[0604] 

[0605] 合成方法如实施例18,产率68%。

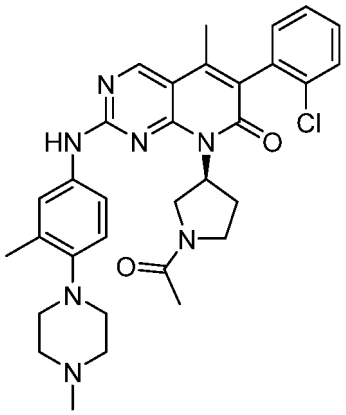
[0606] ^{1}H NMR(400MHz,DMSO)δ9.99(s,1H),8.77(s,1H),7.81(s,1H),7.52(d,J=4.1Hz,2H),7.41(d,J=10.1Hz,3H),7.01(d,J=8.3Hz,1H),5.63(s,1H),4.62(d,J=8.2Hz,1H),4.18-3.76(m,2H),3.05(t,J=11.7Hz,1H),2.82(s,4H),2.40-2.30(m,2H),2.26(s,3H),2.24(s,3H),1.97(d,J=11.0Hz,1H),1.67(s,3H),1.19(dd,J=18.3,11.2Hz,2H),1.00(t,J=7.2Hz,3H).

[0607] MS(ESI)m/z 594.4[M+H]$^+$。

[0608] 实施例41

[0609] (R)-8-(1-乙酰吡咯烷-3-基)-6-(2-氯苯基)-5-甲基-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)吡啶并[2,3-d]嘧啶-7(8H)-酮(570118)

[0610] (R)-8-(1-acetylpyrrolidin-3-yl)-6-(2-chlorophenyl)-5-methyl-2-((3-methyl-4-(4-methylpiperazin-1-yl)phenyl)amino)pyrido[2,3-d]pyrimidin-7(8H)-one

[0611] 

[0612] 合成方法如实施例18,产率67.7%。

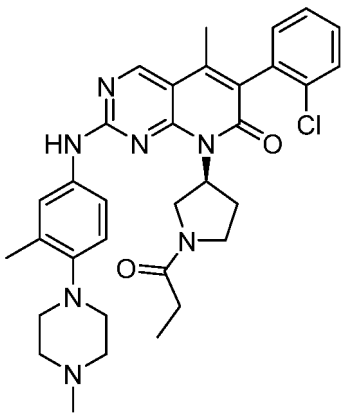
[0613] ^{1}H NMR(400MHz,DMSO)δ9.95(s,1H),8.91(s,1H),7.72-7.48(m,2H),7.41(dd,J=2.7Hz,3H),7.36-7.20(m,1H),6.98(s,1H),5.34(dd,J=21.8Hz,1H),4.40(s,1H),3.90(dd,J=35.0,11.2Hz,3H),3.6(t,J=8.7Hz,1H),2.92-2.67(m,4H),2.14(s,3H),1.85(s,3H)1.76(s,3H),1.45(s,1H),1.23(s,3H).

[0614] MS(ESI)m/z 587.0[M+H]+。

[0615] 实施例42

[0616] (R)-8-(1-丙酰吡咯烷-3-基)-6-(2-氯苯基)-5-甲基-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)吡啶并[2,3-d]嘧啶-7(8H)-酮(570119)

[0617] (R)-6-(2-chlorophenyl)-5-methyl-2-((3-methyl-4-(4-methylpiperazin-1-yl)phenyl)amino)-8-(1-propionylpyrrolidin-3-yl)pyrido[2,3-d]pyrimidin-7(8H)-one

[0618] 

[0619] 合成方法如实施例18,产率66.5%,

[0620] ^{1}H NMR(400MHz,DMSO)δ9.98(s,1H),8.91(s,1H),7.67-7.49(m,2H),7.49-7.33(m,3H),7.28(dd,J=7.9,4.0Hz,1H),6.96(s,1H),5.91-5.01(m,1H),4.62(d,J=8.2Hz,

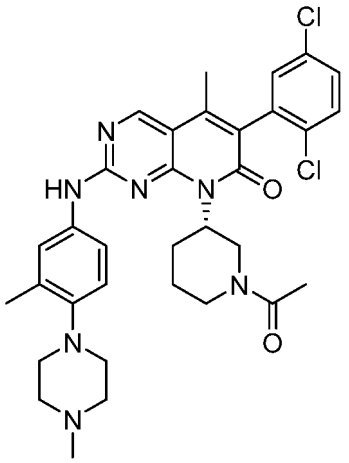
1H),4.25-3.81(m,1H),3.05(t,J＝11.7Hz,1H),2.92-2.67(m,4H),2.57(d,J＝9.0Hz,2H),2.51(s,3H),2.26(s,3H),2.24(s,3H),1.72(q,J＝37.9Hz,2H),1.00(t,J＝7.2Hz,3H).

[0621] MS(ESI)m/z 600.1$[M+H]^+$。

[0622] 实施例43

[0623] (S)-8-(1-乙酰基-3-基)-6-(2,5-二氯苯基)-5-甲基-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)吡啶并[2,3-d]嘧啶-7(8H)-酮(570144)

[0624] (S)-8-(1-acetylpiperidin-3-yl)-6-(2,5-dichlorophenyl)-5-methyl-2-((3-methyl-4-(4-methylpiperazin-1-yl)phenyl)amino)pyrido[2,3-d]pyrimidin-7(8H)-one

[0625] 

[0626] 合成方法如实施例18,产率75%。

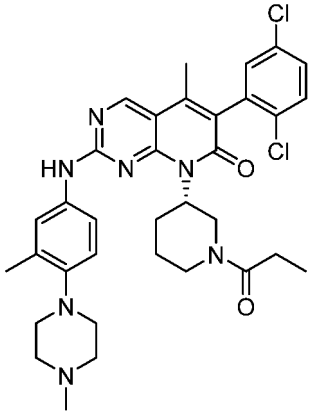
[0627] ^{1}H NMR(400MHz,DMSO)δ9.94(s,1H),8.90(s,1H),7.48(dd,J＝8.4,2.8Hz,2H),7.43(d,J＝29.2Hz,2H),7.25(s,1H),6.93(s,1H),4.40(s,1H),4.26-3.49(m,2H),2.75(s,4H),2.23(s,3H),2.22(d,J＝2.9Hz,2H),2.21(s,3H),2.13-1.94(m,2H),1.82(t,J＝29.3Hz,4H),1.60-1.30(m,2H),1.32(s,3H).

[0628] MS(ESI)m/z 634.3$[M+H]^+$。

[0629] 实施例44

[0630] (S)-8-(1-丙酰基-3-基)-6-(2,5-二氯苯基)-5-甲基-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)吡啶并[2,3-d]嘧啶-7(8H)-酮(570145)

[0631] (S)-6-(2,5-dichlorophenyl)-5-methyl-2-((3-methyl-4-(4-methylpiperazin-1-yl)phenyl)amino)-8-(1-propionylpiperidin-3-yl)pyrido[2,3-d]pyrimidin-7(8H)-one

[0632] 

[0633] 合成方法如实施例18,产率60.8%。

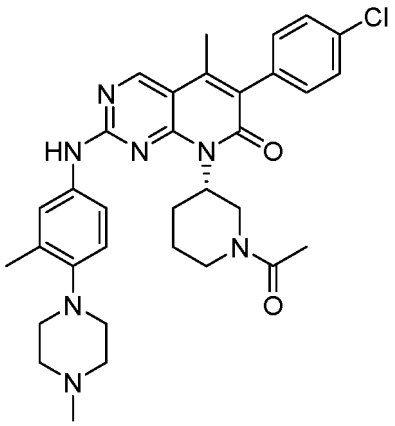
[0634] ^{1}H NMR(400MHz,DMSO)δ9.94(s,1H),8.90(s,1H),7.48(dd,J=8.4,2.8Hz,3H),7.43(d,J=29.2Hz,1H),7.25(s,1H),6.97(s,1H),4.40(s,1H),4.26-3.49(m,2H),2.75(s,4H),2.23(s,3H),2.22(d,J=2.9Hz,2H),2.21(q,2H),2.13-1.94(m,1H),1.82(t,J=29.3Hz,2H),1.60-1.30(m,2H),1.10(t,J=20.8,3H).

[0635] MS(ESI)m/z 648.1[M+H]$^+$。

[0636] 实施例45

[0637] (S)-8-(1-乙酰基-3-基)-6-(4-氯苯基)-5-甲基-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)吡啶并[2,3-d]嘧啶-7(8H)-酮(570149)

[0638] (S)-8-(1-acetylpiperidin-3-yl)-6-(4-chlorophenyl)-5-methyl-2-((3-methyl-4-(4-methylpiperazin-1-yl)phenyl)amino)pyrido[2,3-d]pyrimidin-7(8H)-one

[0639] 

[0640] 合成方法如实施例18,产率85.4%。

[0641] ^{1}H NMR(400MHz,DMSO)δ9.96(s,1H),8.90(s,1H),7.48(d,J=2.3Hz,1H),7.46(d,J=2.4Hz,1H),7.38(t,J=15.4Hz,1H),7.26(t,J=3.5Hz,1H),7.23(d,J=9.4Hz,1H),6.95(s,1H),5.82-5.03(m,1H),4.40(s,1H),4.26-3.49(m,2H),2.75(s,4H),2.23(s,3H),2.22(d,J=2.9Hz,2H),2.21(s,3H),2.13-1.94(m,2H),1.82(t,J=29.3Hz,4H),1.60-1.30(m,2H),1.32(s,3H).

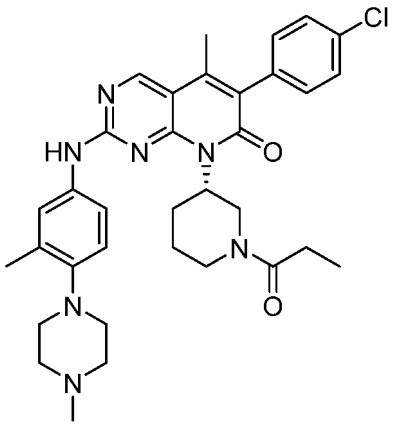
[0642] MS(ESI)m/z 600.2[M+H]$^+$。

[0643] 实施例46

[0644] (S)-8-(1-丙酰基-3-基)-6-(4-氯苯基)-5-甲基-2-((3-甲基-4-(4-甲基哌嗪-1-

基)苯基)氨基)吡啶并[2,3-d]嘧啶-7(8H)-酮(570150)

[0645] (S)-6-(4-chlorophenyl)-5-methyl-2-((3-methyl-4-(4-methylpiperazin-1-yl)phenyl)amino)-8-(1-propionylpiperidin-3-yl)pyrido[2,3-d]pyrimidin-7(8H)-one

[0646] 

[0647] 合成方法如实施例18,产率79.6%。

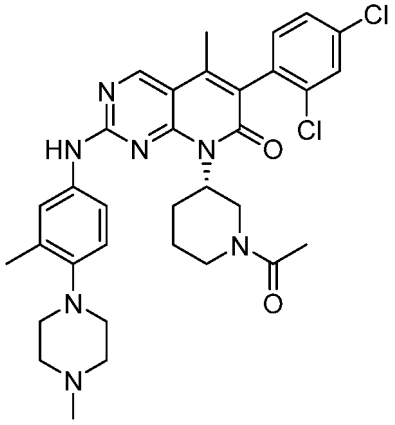
[0648] ^{1}H NMR(400MHz,DMSO)δ9.96(s,1H),8.90(s,1H),7.48(d,J=2.3Hz,1H),7.46(d,J=2.4Hz,1H),7.38(t,J=15.4Hz,1H),7.26(t,J=3.5Hz,1H),7.23(d,J=9.4Hz,1H),6.95(s,1H),5.82-5.03(m,1H),4.43(s,1H),4.22-3.54(m,2H),2.80(s,3H),2.23(d,J=3.1Hz,3H),2.22(d,J=4.2Hz,3H),2.21(s,3H),2.00-1.60(m,2H),1.40(t,J=48.0,Hz,2H),1.37-1.12(m,3H),1.01(s,1H),0.84(t,J=8.8Hz,3H).

[0649] MS(ESI)m/z 614.4[M+H]$^+$。

[0650] 实施例47

[0651] (S)-8-(1-乙酰基-3-基)-6-(2,4-二氯苯基)-5-甲基-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)吡啶并[2,3-d]嘧啶-7(8H)-酮(570157)

[0652] (S)-8-(1-acetylpiperidin-3-yl)-6-(2,4-dichlorophenyl)-5-methyl-2-((3-methyl-4-(4-methylpiper azin-1-yl)phenyl)amino)pyrido[2,3-d]pyrimidin-7(8H)-one

[0653] 

[0654] 合成方法如实施例18,产率69.4%。

[0655] ^{1}H NMR(400MHz,DMSO)δ9.99(s,1H),9.32(s,1H),7.71(s,1H),7.49(d,J=10.8Hz,2H),7.47-7.23(m,2H),6.88(s,1H),5.54-5.14(m,1H),4.43(t,J=83.0Hz,1H),3.72(dd,J=66.7Hz,2H),2.87(s,3H),2.22(s,3H),2.23-2.18(m,4H),2.15(s,3H),1.82

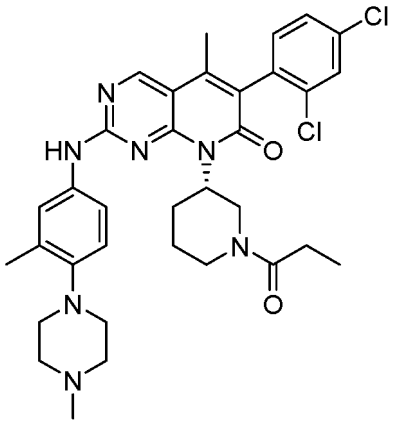
(t,J＝29.3Hz,2H),1.60-1.30(m,2H),1.32(s,3H)

[0656] MS(ESI)m/z 634.3[M+H]$^+$。

[0657] 实施例48

[0658] (S)-8-(1-丙酰基-3-基)-6-(2,4-二氯苯基)-5-甲基-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)吡啶并[2,3-d]嘧啶-7(8H)-酮(570158)

[0659] (S)-6-(2,4-dichlorophenyl)-5-methyl-2-((3-methyl-4-(4-methylpiperazin-1-yl)phenyl)amino)-8-(1-propionylpiperidin-3-yl)pyrido[2,3-d]pyrimidin-7(8H)-one

[0660] 

[0661] 合成方法如实施例18,产率55%。

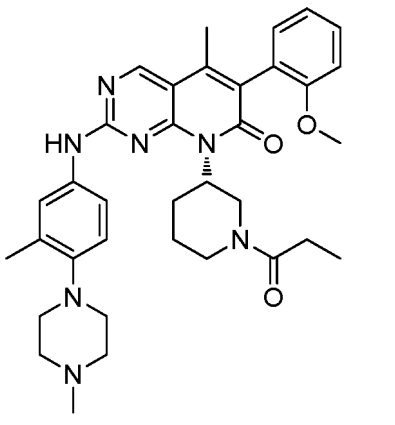
[0662] ^{1}H NMR(400MHz,DMSO)δ9.99(s,1H),9.32(s,1H),7.71(s,1H),7.49(d,J＝10.8Hz,2H),7.47-7.23(m,2H),6.88(s,1H),5.54-5.14(m,1H),4.43(t,J＝83.0Hz,1H),3.72(dd,J＝118.4,66.7Hz,2H),2.87(d,J＝53.7Hz,2H),2.22(s,3H),2.23-2.18(m,3H),2.15(s,3H),1.74(t,J＝52.9Hz,2H),1.55-1.30(m,2H),,1.13(q,J＝53.7,2H),0.93(t,J＝20.8,3H).

[0663] MS(ESI)m/z 649.3[M+H]$^+$。

[0664] 实施例49

[0665] (S)-6-(2-甲氧基苯基)-5-甲基-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)-8-(1-丙哌啶-3-基)吡啶并[2,3-d]嘧啶-7(8H)-酮(580011)

[0666] (S)-6-(2-methoxyphenyl)-5-methyl-2-((3-methyl-4-(4-methylpiperazin-1-yl)phenyl)amino)-8-(1-propionylpiperidin-3-yl)pyrido[2,3-d]pyrimidin-7(8H)-one

[0667] 

[0668] 合成方法如实施例18,产率.79.5%。

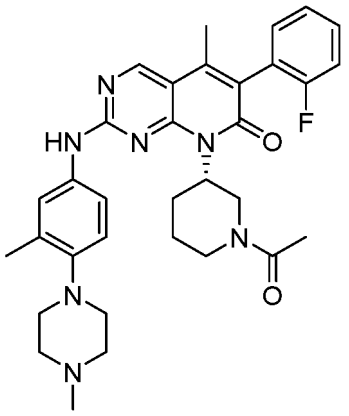
[0669] ^{1}H NMR(400MHz,DMSO)δ9.69(s,1H),8.94(s,1H),8.51(d,J=2.8Hz,3H),7.65-7.23(m,3H),6.86(d,J=68.6Hz,1H),5.82-5.08(m,1H),4.76-4.09(m,1H),3.96(s,3H),2.80(s,3H),2.49-2.37(m,4H),2.30(d,J=5.1Hz,3H),2.32-2.26(m,2H),2.22(d,J=9.6Hz,2H),2.18(q,J=19.8Hz,2H),1.76(s,3H),1.59-1.33(m,2H),1.36-1.13(m,2H),0.86(t,3H).

[0670] MS(ESI)m/z 610.2[M+H]$^+$。

[0671] 实施例50

[0672] (S)-8-(1-乙酰基-3-基)-6-(2-氟苯基)-5-甲基-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)吡啶并[2,3-d]嘧啶-7(8H)-酮(580013)

[0673] (S)-8-(1-acetylpiperidin-3-yl)-6-(2-fluorophenyl)-5-methyl-2-((3-methyl-4-(4-methylpiperazin-1-yl)phenyl)amino)pyrido[2,3-d]pyrimidin-7(8H)-one

[0674] 

[0675] 合成方法如实施例18,产率62%。

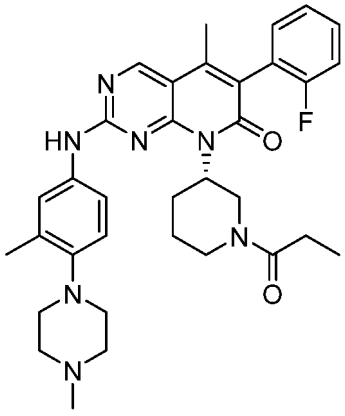
[0676] ^{1}H NMR(400MHz,DMSO)δ9.95(s,1H),8.91(s,1H),7.72-7.48(m,2H),7.41(dd,J=2.7Hz,3H),7.36-7.20(m,1H),6.98(s,1H),5.34(dd,J=21.8Hz,1H),4.40(s,1H),3.90(dd,J=35.0,11.2Hz,3H),3.6(t,J=8.7Hz,1H),2.92-2.67(m,4H),2.14(s,3H),2.04(d,J=16.1Hz,2H),1.85(s,3H)1.76(s,3H),1.45(s,1H),1.23(s,3H).

[0677] MS(ESI)m/z 584.1[M+H]$^+$。

[0678] 实施例51

[0679] (S)-8-(1-丙酰基-3-基)-6-(2-氟苯基)-5-甲基-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)吡啶并[2,3-d]嘧啶-7(8H)-酮(580014)

[0680] (S)-6-(2-fluorophenyl)-5-methyl-2-((3-methyl-4-(4-methylpiperazin-1-yl)phenyl)amino)-8-(1-propionylpiperidin-3-yl)pyrido[2,3-d]pyrimidin-7(8H)-one

[0681] 

[0682] 合成方法如实施例18,产率60.6%。

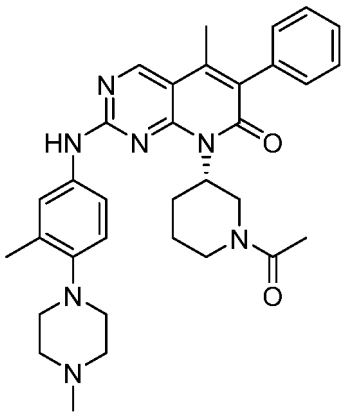
[0683] ^{1}H NMR(400MHz,DMSO)δ9.98(s,1H),8.91(s,1H),7.67-7.49(m,2H),7.49-7.33(m,3H),7.28(dd,J=7.9,4.0Hz,1H),6.96(s,1H),5.91-5.01(m,1H),4.62(d,J=8.2Hz,1H),4.25-3.81(m,1H),3.05(t,J=11.7Hz,1H),2.92-2.67(m,4H),2.57(d,J=9.0Hz,2H),2.51(s,3H),2.41-2.35(m,2H),2.26(s,3H),2.24(s,3H),1.72(q,J=37.9Hz,2H),1.00(t,J=7.2Hz,3H).

[0684] MS(ESI)m/z 598.1[M+H]$^+$。

[0685] 实施例52

[0686] (S)-8-(1-乙酰基-3-基)-5-甲基-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)-6-苯基吡啶并[2,3-d]嘧啶-7(8H)-酮(580018)

[0687] (S)-8-(1-acetylpiperidin-3-yl)-5-methyl-2-((3-methyl-4-(4-methylpiperazin-1-yl)phenyl)amino)-6-phenylpyrido[2,3-d]pyrimidin-7(8H)-one

[0688] 

[0689] 合成方法如实施例18,产率80.8%。

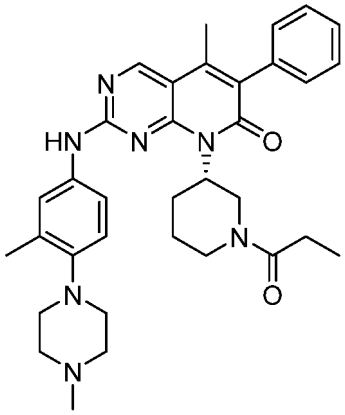
[0690] ^{1}H NMR(400MHz,DMSO)δ9.95(s,1H),8.91(s,1H),7.72-7.48(m,2H),7.41(dd,J=2.7Hz,3H),7.36-7.20(m,2H),6.98(s,1H),5.34(dd,J=21.8Hz,1H),4.40(s,1H),3.90(dd,J=35.0,11.2Hz,3H),3.6(t,J=8.7Hz,1H),2.92-2.67(m,4H),2.14(s,3H),2.04(d,J=16.1Hz,2H),1.85(s,3H)1.76(s,3H),1.45(s,1H),1.23(s,3H).

[0691] MS(ESI)m/z 588.1[M+Na]$^+$。

[0692] 实施例53

[0693] (S)-8-(1-丙酰基-3-基)-5-甲基-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)-6-苯基吡啶并[2,3-d]嘧啶-7(8H)-酮(580019)

[0694] (S)-5-methyl-2-((3-methyl-4-(4-methylpiperazin-1-yl)phenyl)amino)-6-phenyl-8-(1-propionylpiperidin-3-yl)pyrido[2,3-d]pyrimidin-7(8H)-one

[0695] 

[0696] 合成方法如实施例18,产率72.44%。

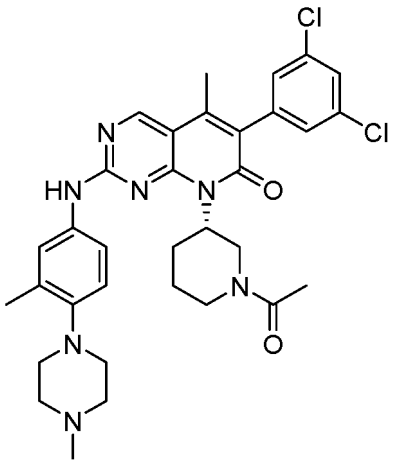
[0697] ^{1}H NMR(400MHz,DMSO)δ9.98(s,1H),8.91(s,1H),7.67-7.49(m,2H),7.49-7.33(m,3H),7.28(dd,J=7.9,4.0Hz,2H),6.96(s,1H),5.91-5.01(m,1H),4.62(d,J=8.2Hz,1H),4.25-3.81(m,1H),3.05(t,J=11.7Hz,1H),2.92-2.67(m,4H),2.57(d,J=9.0Hz,2H),2.51(s,3H),2.41-2.35(m,2H),2.26(s,3H),2.24(s,3H),1.72(q,J=37.9Hz,2H),1.00(t,J=7.2Hz,3H).

[0698] MS(ESI)m/z 580.2$[M+H]^+$。

[0699] 实施例54

[0700] (S)-8-(1-乙酰基-3-基)-6-(3,5-二氯苯基)-5-甲基-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)吡啶并[2,3-d]嘧啶-7(8H)-酮(580023)

[0701] (S)-8-(1-acetylpiperidin-3-yl)-6-(3,5-dichlorophenyl)-5-methyl-2-((3-methyl-4-(4-methylpiperazin-1-yl)phenyl)amino)pyrido[2,3-d]pyrimidin-7(8H)-one

[0702] 

[0703] 合成方法如实施例18,产率75.9%。

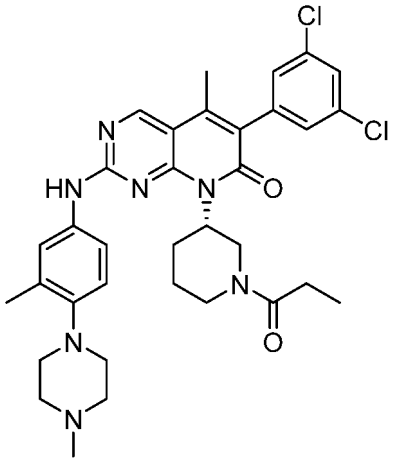
[0704] ^{1}H NMR(400MHz,DMSO)δ9.99(s,1H),9.32(s,1H),7.71(s,1H),7.49(s,2H),7.47-7.23(m,2H),6.88(s,1H),5.54-5.14(m,1H),4.43(t,J=83.0Hz,1H),3.72(dd,J=66.7Hz,2H),2.87(s,3H),2.22(s,3H),2.23-2.18(m,4H),2.15(s,3H),1.82(t,J=29.3Hz,2H),1.60-1.30(m,2H),1.06(s,3H).

[0705] MS(ESI)m/z 634.0[M+H]$^+$。

[0706] 实施例55

[0707] (S)-8-(1-丙酰基-3-基)-6-(3,5-二氯苯基)-5-甲基-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)吡啶并[2,3-d]嘧啶-7(8H)-酮(580024)

[0708] (S)-6-(3,5-dichlorophenyl)-5-methyl-2-((3-methyl-4-(4-methylpiperazin-1-yl)phenyl)amino)-8-(1-propionylpiperidin-3-yl)pyrido[2,3-d]pyrimidin-7(8H)-one

[0709] 

[0710] 合成方法如实施例18,产率85.4%。

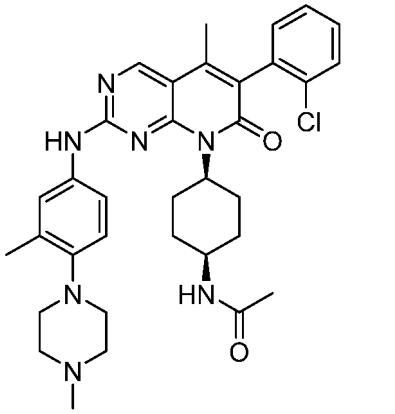
[0711] ^{1}H NMR(400MHz,DMSO)δ9.99(s,1H),9.32(s,1H),7.71(s,1H),7.49(s,2H),7.47-7.23(m,2H),6.88(s,1H),5.54-5.14(m,1H),4.43(t,J=83.0Hz,1H),3.72(dd,J=118.4,66.7Hz,2H),2.87(d,J=53.7Hz,2H),2.22(s,3H),2.23-2.18(m,3H),2.15(s,3H),1.74(t,J=52.9Hz,2H),1.55-1.30(m,2H),,1.13(q,J=53.7,2H),0.93(t,J=20.8,3H).

[0712] MS(ESI)m/z 648.1[M+H]$^+$。

[0713] 实施例56

[0714] N-((1S,4S)-4-(6-(2-氯苯基)-5-甲基-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)-7-氧代吡啶并[2,3-d]嘧啶-8(7H)-基)环己基)乙酰胺(580043)

[0715] N-((1s,4s)-4-(6-(2-chlorophenyl)-5-methyl-2-((3-methyl-4-(4-methylpiperazin-1-yl)phenyl)amino)-7-oxopyrido[2,3-d]pyrimidin-8(7H)-yl)cyclohexyl)acetamide

[0716] 

[0717] 合成方法如实施例18,产率81.96%。

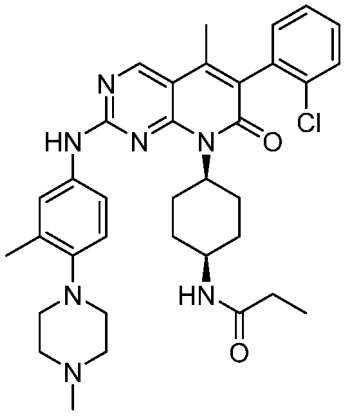
[0718] ^{1}H NMR(400MHz,DMSO)δ9.86(s,1H),8.88(s,1H),7.68(s,1H),7.54(t,J＝7.9Hz,2H),7.41(dd,J＝5.1,2.6Hz,2H),7.27(d,J＝4.5Hz,1H),7.09(s,1H),5.75(s,1H),5.34(s,1H),2.84(s,5H),2.30(d,J＝18.1Hz,3H),2.24(s,3H),2.11(s,3H),2.06(q,J＝7.5Hz,2H),1.92(d,J＝10.6Hz,2H),.159(t,2H),1.42-1.10(m,3H),1.05(s,1H),0.99(t,J＝7.5Hz,3H).

[0719] MS(ESI)m/z 614.0[M+H]$^+$。

[0720] 实施例57

[0721] N-((1S,4S)-4-(6-(2-氯苯基)-5-甲基-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)-7-氧代吡啶并[2,3-d]嘧啶-8(7H)-基)环己基)丙酰胺(580044)

[0722] N-((1s,4s)-4-(6-(2-chlorophenyl)-5-methyl-2-((3-methyl-4-(4-methylpiperazin-1-yl)phenyl)amino)-7-oxopyrido[2,3-d]pyrimidin-8(7H)-yl)cyclohexyl)propionamide

[0723] 

[0724] 合成方法如实施例18,产率81.6%。

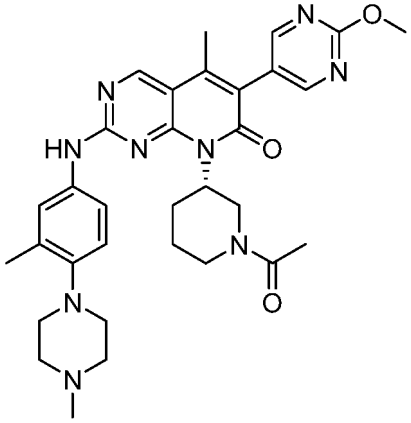
[0725] ^{1}H NMR(400MHz,DMSO)δ9.86(s,1H),8.88(s,1H),7.68(s,1H),7.54(t,J＝7.9Hz,3H),7.41(dd,J＝5.1,2.6Hz,2H),7.27(d,J＝4.5Hz,1H),7.09(s,1H),5.75(s,1H),5.34(s,1H),2.84(s,5H),2.30(d,J＝18.1Hz,3H),2.24(s,3H),2.11(s,3H),2.06(q,J＝7.5Hz,2H),1.92(d,J＝10.6Hz,2H),1.59(t,2H),1.42-1.10(m,3H),1.05(s,1H),0.99(t,J＝7.5Hz,3H).

[0726] MS(ESI)m/z 628.1[M+H]$^+$。

[0727] 实施例58

[0728] (S)-8-(1-乙酰基-3-基)-6-(2-甲氧基嘧啶-5-基)-5-甲基-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)吡啶并[2,3-d]嘧啶-7(8H)-酮(580053)

[0729] (S)-8-(1-acetylpiperidin-3-yl)-6-(2-methoxypyrimidin-5-yl)-5-methyl-2-((3-methyl-4-(4-methylpiperazin-1-yl)phenyl)amino)pyrido[2,3-d]pyrimidin-7(8H)-one

[0730] 

[0731] 合成方法如实施例18,产率77.5%。

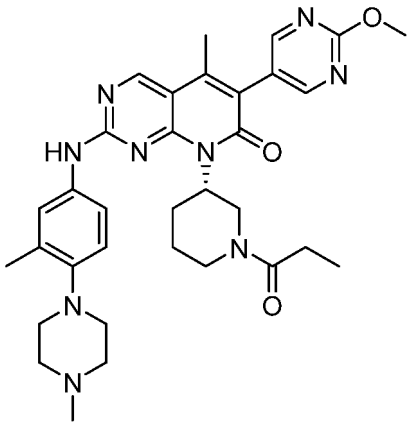
[0732] ^{1}H NMR(400MHz,DMSO)δ9.68(s,1H),8.94(s,1H),8.41(s,2H),7.85-7.20(m,2H),6.87(s,1H),5.68-5.00(m,1H),4.28(d,J=105.3Hz,1H),3.96(s,3H),2.81(s,4H),2.38(s,3H),2.30(d,J=5.0Hz,1H),2.32-2.27(m,2H),2.23(d,J=4.6Hz,2H),2.24-2.17(m,1H),2.19-1.85(m,2H),1.80(s,3H),1.62-1.29(m,2H),1.28(s,3H).

[0733] MS(ESI)m/z 598.2[M+H]$^+$。

[0734] 实施例59

[0735] (S)-6-(2-甲氧基嘧啶-5-基)-5-甲基-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)-8-(1-丙哌啶-3-基)吡啶并[2,3-d]嘧啶-7(8H)-酮(580054)

[0736] (S)-6-(2-methoxypyrimidin-5-yl)-5-methyl-2-((3-methyl-4-(4-methylpiperazin-1-yl)phenyl)amino)-8-(1-propionylpiperidin-3-yl)pyrido[2,3-d]pyrimidin-7(8H)-one

[0737] 

[0738] 合成方法如实施例18,产率.79.5%。

[0739] ^{1}H NMR(400MHz,DMSO)δ9.69(s,1H),8.94(s,1H),8.51(d,J=2.8Hz,2H),7.65-7.23(m,2H),6.86(d,J=68.6Hz,1H),5.82-5.08(m,1H),4.76-4.09(m,1H),3.96(s,3H),2.80(s,3H),2.49-2.37(m,4H),2.30(d,J=5.1Hz,3H),2.32-2.26(m,2H),2.22(d,J=9.6Hz,2H),2.18(q,J=19.8Hz,2H),1.76(s,3H),1.59-1.33(m,2H),1.36-1.13(m,2H),0.86(t,3H).

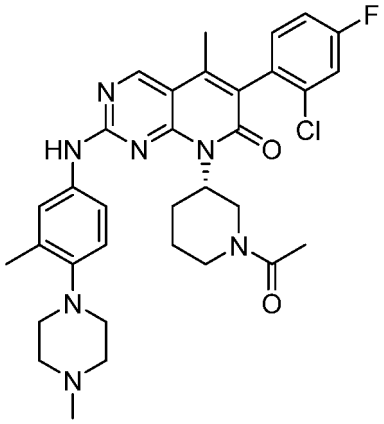
[0740] MS(ESI)m/z 612.2[M+H]$^+$。

[0741] 实施例60

[0742] (S)-8-(1-乙酰基-3-基)-6-(2-氯-4-氟苯基)-5-甲基-2-((3-甲基-4-(4-甲基哌

嗪-1-基)苯基)氨基)吡啶并[2,3-d]嘧啶-7(8H)-酮(580058)

[0743] (S)-8-(1-acetylpiperidin-3-yl)-6-(2-chloro-4-fluorophenyl)-5-methyl-2-((3-methyl-4-(4-methylpiperazin-1-yl)phenyl)amino)pyrido[2,3-d]pyrimidin-7(8H)-one

[0744] 

[0745] 合成方法如实施例18,产率80.9%。

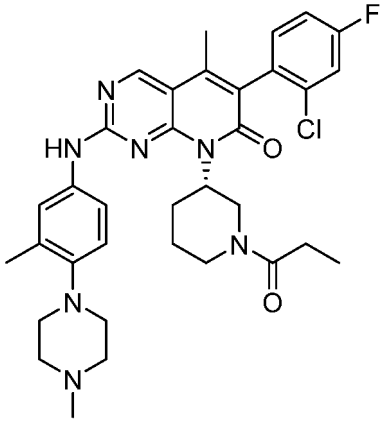
[0746] ^{1}H NMR(400MHz,DMSO)δ9.99(s,1H),9.32(s,1H),7.71(s,1H),7.49(d,J=10.8Hz,2H),7.47-7.23(m,2H),6.88(s,1H),5.54-5.14(m,1H),4.43(t,J=83.0Hz,1H),3.72(dd,J=66.7Hz,2H),2.87(s,3H),2.22(s,3H),2.23-2.18(m,4H),2.15(s,3H),1.82(t,J=29.3Hz,2H),1.60-1.30(m,2H),1.32(s,3H).

[0747] MS(ESI)m/z 618.1[M+H]$^+$。

[0748] 实施例61

[0749] (S)-8-(1-丙酰基-3-基)-6-(2-氯-4-氟苯基)-5-甲基-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)吡啶并[2,3-d]嘧啶-7(8H)-酮(580061)

[0750] (S)-6-(2-chloro-4-fluorophenyl)-5-methyl-2-((3-methyl-4-(4-methylpiperazin-1-yl)phenyl)amino)-8-(1-propionylpiperidin-3-yl)pyrido[2,3-d]pyrimidin-7(8H)-one

[0751] 

[0752] 合成方法如实施例18,产率87.5%。

[0753] ^{1}H NMR(400MHz,DMSO)δ9.99(s,1H),9.32(s,1H),7.71(s,1H),7.49(d,J=10.8Hz,2H),7.47-7.23(m,2H),6.88(s,1H),5.54-5.14(m,1H),4.43(t,J=83.0Hz,1H),3.72(dd,J=118.4,66.7Hz,2H),2.87(d,J=53.7Hz,2H),2.22(s,3H),2.23-2.18(m,3H),2.15(s,3H),1.74(t,J=52.9Hz,2H),1.55-1.30(m,2H),,1.13(q,J=53.7,2H),0.93(t,J

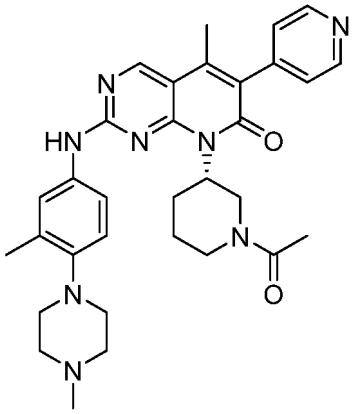
＝20.8,3H).

[0754] MS(ESI)m/z 632.0[M+H]$^+$。

[0755] 实施例62

[0756] (S)-8-(1-乙酰基-3-基)-5-甲基-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)-6-(吡啶-4-基)吡啶并[2,3-d]嘧啶-7(8H)-酮(580067)

[0757] (S)-8-(1-acetylpiperidin-3-yl)-5-methyl-2-((3-methyl-4-(4-methylpiperazin-1-yl)phenyl)amino)-6-(pyridin-4-yl)pyrido[2,3-d]pyrimidin-7(8H)-one

[0758] 

[0759] 合成方法如实施例18,产率79.4%。

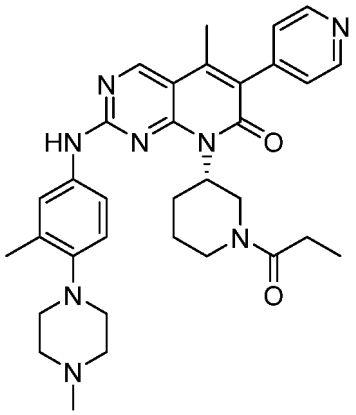
[0760] ^{1}H NMR(400MHz,DMSO)δ9.96(s,1H),8.90(s,1H),7.48(d,J＝2.3Hz,1H),7.46(d,J＝2.4Hz,1H),7.38(t,J＝15.4Hz,1H),7.26(t,J＝3.5Hz,1H),7.23(d,J＝9.4Hz,1H),6.95(s,1H),5.82-5.03(m,1H),4.40(s,1H),4.26-3.49(m,2H),2.75(s,4H),2.23(s,3H),2.22(d,J＝2.9Hz,2H),2.21(s,3H),2.13-1.94(m,2H),1.82(t,J＝29.3Hz,4H),1.60-1.30(m,2H),1.32(s,3H).

[0761] MS(ESI)m/z 567.2[M+H]$^+$

[0762] 实施例63

[0763] (S)-8-(1-丙酰基-3-基)-5-甲基-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)-6-(吡啶-4-基)吡啶并[2,3-d]嘧啶-7(8H)-酮(580068)

[0764] (S)-5-methyl-2-((3-methyl-4-(4-methylpiperazin-1-yl)phenyl)amino)-8-(1-propionylpiperidin-3-yl)-6-(pyridin-4-yl)pyrido[2,3-d]pyrimidin-7(8H)-one

[0765] 

[0766] 合成方法如实施例18

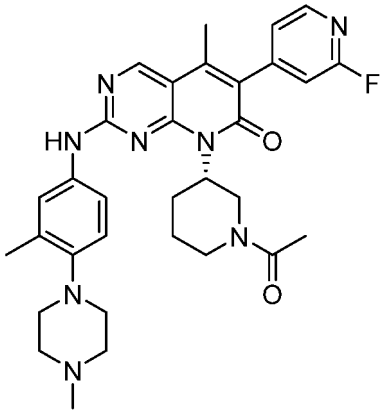
[0767] ^{1}H NMR(400MHz,DMSO)δ9.99(s,1H),9.32(s,1H),7.71(s,1H),7.49(d,J＝10.8Hz,2H),7.47-7.23(m,2H),6.88(s,1H),5.54-5.14(m,1H),4.43(t,J＝83.0Hz,1H),3.72(dd,J＝66.7Hz,2H),2.87(s,3H),2.22(s,3H),2.23-2.18(m,4H),2.15(s,3H),1.82(t,J＝29.3Hz,2H),1.60-1.30(m,2H),1.32(s,3H).(产率79.6％)

[0768] MS(ESI)m/z 581.2[M+H]$^+$。

[0769] 实施例64

[0770] (S)-8-(1-乙酰基-3-基)-6-(2-氟吡啶-4-基)-5-甲基-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)吡啶并[2,3-d]嘧啶-7(8H)-酮(580073)

[0771] (S)-8-(1-acetylpiperidin-3-yl)-6-(2-fluoropyridin-4-yl)-5-methyl-2-((3-methyl-4-(4-methylpiperazin-1-yl)phenyl)amino)pyrido[2,3-d]pyrimidin-7(8H)-one

[0772] 

[0773] 合成方法如实施例18,产率76.9％。

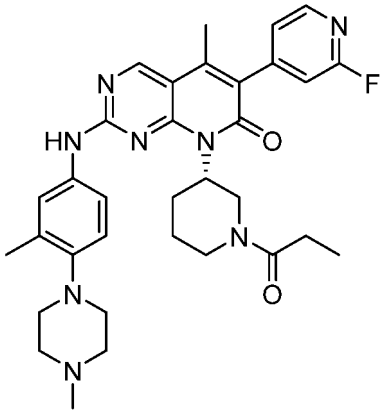
[0774] ^{1}H NMR(400MHz,DMSO)δ9.99(s,1H),9.32(s,1H),7.71(s,1H),7.49(d,J＝10.8Hz,2H),7.47-7.23(m,2H),6.88(s,1H),5.54-5.14(m,1H),4.43(t,J＝83.0Hz,1H),3.72(dd,J＝66.7Hz,2H),2.87(s,3H),2.22(s,3H),2.23-2.18(m,4H),2.15(s,3H),1.82(t,J＝29.3Hz,2H),1.60-1.30(m,2H),1.32(s,3H).

[0775] MS(ESI)m/z 585.2[M+H]$^+$。

[0776] 实施例65

[0777] (S)-8-(1-丙酰基-3-基)-6-(2-氟吡啶-4-基)-5-甲基-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)吡啶并[2,3-d]嘧啶-7(8H)-酮(580074)

[0778] (S)-6-(2-fluoropyridin-4-yl)-5-methyl-2-((3-methyl-4-(4-methylpiperazin-1-yl)phenyl)amino)-8-(1-propionylpiperidin-3-yl)pyrido[2,3-d]pyrimidin-7(8H)-one

[0779] 

[0780] 合成方法如实施例18,产率79.85%。

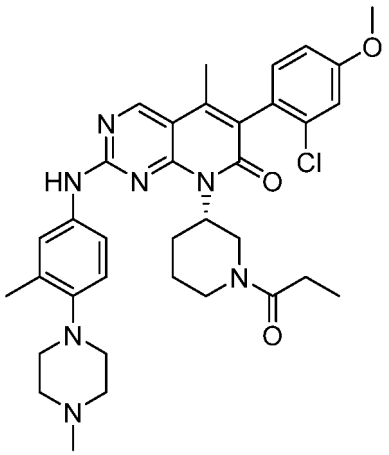
[0781] ^{1}H NMR(400MHz,DMSO)δ10.05(s,1H),8.96(s,1H),8.29(dd,J=4.9,2.7Hz,1H),7.78-7.30(m,2H),7.38-7.19(m,1H),7.19-7.00(m,1H),7.05-6.59(m,1H),5.34(d,J=150.9,142.3Hz,1H),4.97-4.11(m,1H),4.27-3.46(m,2H),3.00-2.68(m,4H),2.26(s,1H),2.23(d,J=5.7Hz,3H),2.21(d,J=2.8Hz,3H),1.94-1.59(m,2H),1.52-1.32(m,2H),1.36-1.18(m,3H),1.09-0.90(m,2H),0.91-0.78(m,2H).

[0782] MS(ESI)m/z 599.2[M+H]$^+$。

[0783] 实施例66

[0784] (S)-8-(1-丙酰基-3-基)-6-(2-氯-4-甲氧基苯基)-5-甲基-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)吡啶并[2,3-d]嘧啶-7(8H)-酮(580082)

[0785] (S)-6-(2-chloro-4-methoxyphenyl)-5-methyl-2-((3-methyl-4-(4-methylpiperazin-1-yl)phenyl)amino)-8-(1-propionylpiperidin-3-yl)pyrido[2,3-d]pyrimidin-7(8H)-one

[0786] 

[0787] 合成方法如实施例18,产率76.4%。

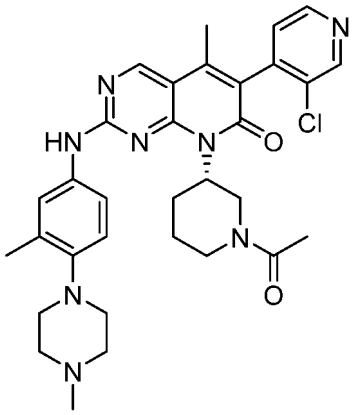
[0788] ^{1}H NMR(400MHz,DMSO)δ9.99(s,1H),8.77(s,1H),7.81(s,1H),7.52(d,J=4.1Hz,2H),7.41(d,J=10.1Hz,1H),7.01(d,J=8.3Hz,1H),5.82-5.08(m,1H),4.76-4.09(m,1H),3.96(s,3H),2.80(s,3H),2.49-2.37(m,4H),2.30(d,J=5.1Hz,3H),2.32-2.26(m,2H),2.22(d,J=9.6Hz,2H),2.18(q,J=19.8Hz,2H),1.76(s,3H),1.59-1.33(m,2H),1.36-1.13(m,2H),0.86(t,3H).

[0789] MS(ESI)m/z 644.2[M+H]$^+$。

[0790] 实施例67

[0791] (S)-8-(1-乙酰基-3-基)-6-(3-氯吡啶-4-基)-5-甲基-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)吡啶并[2,3-d]嘧啶-7(8H)-酮(580097)

[0792] (S)-8-(1-acetylpiperidin-3-yl)-6-(3-chloropyridin-4-yl)-5-methyl-2-((3-methyl-4-(4-methylpiperazin-1-yl)phenyl)amino)pyrido[2,3-d]pyrimidin-7(8H)-one

[0793] 

[0794] 合成方法如实施例18,产率74.1%。

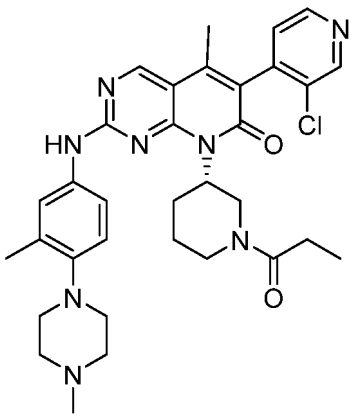
[0795] ^{1}H NMR(400MHz,DMSO)δ9.99(s,1H),9.32(s,1H),7.71(s,1H),7.49(d,J=10.8Hz,2H),7.47-7.23(m,2H),6.88(s,1H),5.54-5.14(m,1H),4.43(t,J=83.0Hz,1H),3.72(dd,J=66.7Hz,2H),2.87(s,3H),2.22(s,3H),2.23-2.18(m,4H),2.15(s,3H),1.82(t,J=29.3Hz,2H),1.60-1.30(m,2H),1.32(s,3H).

[0796] MS(ESI)m/z 601.0$[M+H]^+$。

[0797] 实施例68

[0798] (S)-8-(1-丙酰基-3-基)-6-(3-氯吡啶-4-基)-5-甲基-2-((3-甲基-4-(4-甲基哌嗪-1-基基)苯基)氨基)吡啶并[2,3-d]嘧啶-7(8H)-酮(580098)

[0799] (S)-6-(3-chloropyridin-4-yl)-5-methyl-2-((3-methyl-4-(4-methylpiperazin-1-yl)phenyl)amino)-8-(1-propionylpiperidin-3-yl)pyrido[2,3-d]pyrimidin-7(8H)-one

[0800] 

[0801] 合成方法如实施例18,产率73%。

[0802] ^{1}H NMR(400MHz,DMSO)δ10.05(s,1H),8.96(s,1H),8.29(dd,J=4.9,2.7Hz,1H),7.78-7.30(m,2H),7.38-7.19(m,1H),7.19-7.00(m,1H),7.05-6.59(m,1H),5.34(d,J=

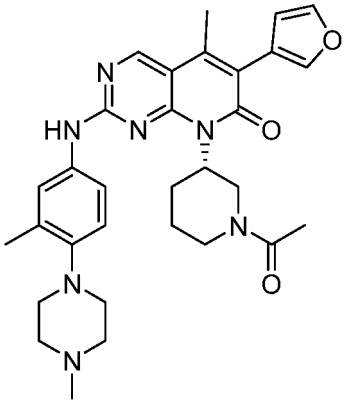
150.9,142.3Hz,1H),4.97-4.11(m,1H),4.27-3.46(m,2H),3.00-2.68(m,4H),2.26(s,1H),2.23(d,J=5.7Hz,3H),2.21(d,J=2.8Hz,3H),1.94-1.59(m,2H),1.52-1.32(m,2H),1.36-1.18(m,3H),1.09-0.90(m,2H),0.91-0.78(m,2H).

[0803] MS(ESI)m/z 614.9$[M+H]^+$。

[0804] 实施例69

[0805] (S)-8-(1-乙酰基-3-基)-6-(呋喃-3-基)-5-甲基-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)吡啶并[2,3-d]嘧啶-7(8H)-酮(580112)

[0806] (S)-8-(1-acetylpiperidin-3-yl)-6-(furan-3-yl)-5-methyl-2-((3-methyl-4-(4-methylpiperazin-1-yl)phenyl)amino)pyrido[2,3-d]pyrimidin-7(8H)-one

[0807] 

[0808] 合成方法如实施例18,产率68.9%。

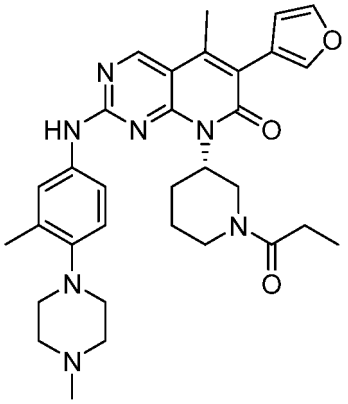
[0809] ^{1}H NMR(400MHz,DMSO)δ9.99(s,1H),9.32(s,1H),8.25(s,1H),7.71(s,1H),7.49(d,J=10.8Hz,2H),7.23(d,J=13.7Hz,1H),6.88(d,J=14.0Hz,1H),5.54-5.14(m,1H),4.43(t,J=83.0Hz,1H),3.72(dd,J=66.7Hz,2H),2.87(s,3H),2.22(s,3H),2.23-2.18(m,4H),2.15(s,3H),1.82(t,J=29.3Hz,2H),1.60-1.30(m,2H),1.32(s,3H).

[0810] MS(ESI)m/z 556.0$[M+H]^+$。

[0811] 实施例70

[0812] (S)-8-(1-丙酰基-3-基)-6-(呋喃-3-基)-5-甲基-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)吡啶并[2,3-d]嘧啶-7(8H)-酮(580113)

[0813] (S)-6-(furan-3-yl)-5-methyl-2-((3-methyl-4-(4-methylpiperazin-1-yl)phenyl)amino)-8-(1-propionylpiperidin-3-yl)pyrido[2,3-d]pyrimidin-7(8H)-one

[0814] 

[0815] 合成方法如实施例18,产率58.5%。

[0816] ^{1}H NMR(400MHz,DMSO)δ9.99(s,1H),9.32(s,1H),8.25(s,1H),7.71(s,1H),7.49

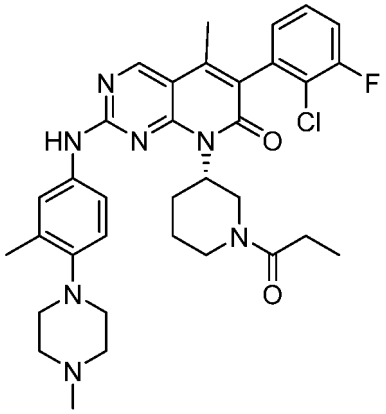
(d,J＝10.8Hz,2H),7.23(d,J＝13.7Hz,1H),6.88(d,J＝14.0Hz,1H),5.34(d,J＝150.9,142.3Hz,1H),4.97-4.11(m,1H),4.27-3.46(m,2H),3.00-2.68(m,4H),2.26(s,1H),2.23(d,J＝5.7Hz,3H),2.21(d,J＝2.8Hz,3H),1.94-1.59(m,2H),1.52-1.32(m,2H),1.36-1.18(m,3H),1.09-0.90(m,2H),0.91-0.78(m,2H).

[0817] MS(ESI)m/z 570.4$[M+H]^+$。

[0818] 实施例71

[0819] (S)-6-(2-氯-3-氟苯基)-5-甲基-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)-8-(1-丙哌啶-3-基)吡啶并[2,3-d]嘧啶-7(8H)-酮(580120)

[0820] (S)-6-(2-chloro-3-fluorophenyl)-5-methyl-2-((3-methyl-4-(4-methylpiperazin-1-yl)phenyl)amino)-8-(1-propionylpiperidin-3-yl)pyrido[2,3-d]pyrimidin-7(8H)-one

[0821] 

[0822] 合成方法如实施例18,产率63.7%。

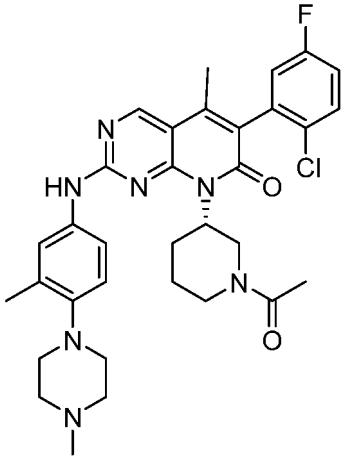
[0823] ^{1}H NMR(400MHz,DMSO)δ9.99(s,1H),9.32(s,1H),7.71(s,1H),7.49(d,J＝10.8Hz,2H),7.47-7.23(m,2H),6.88(s,1H),5.54-5.14(m,1H),4.43(t,J＝83.0Hz,1H),3.72(dd,J＝118.4,66.7Hz,2H),2.87(d,J＝53.7Hz,2H),2.22(s,3H),2.23-2.18(m,3H),2.15(s,3H),1.74(t,J＝52.9Hz,2H),1.55-1.30(m,2H),,1.13(q,J＝53.7,2H),0.93(t,J＝20.8,3H).

[0824] MS(ESI)m/z 632.4$[M+H]^+$。

[0825] 实施例72

[0826] (S)-8-(1-乙酰基-3-基)-6-(2-氯-4-氟苯基)-5-甲基-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)吡啶并[2,3-d]嘧啶-7(8H)-酮(580123)

[0827] (S)-8-(1-acetylpiperidin-3-yl)-6-(2-chloro-4-fluorophenyl)-5-methyl-2-((3-methyl-4-(4-methylpiperazin-1-yl)phenyl)amino)pyrido[2,3-d]pyrimidin-7(8H)-one

[0828] 

[0829] 合成方法如实施例18,产率63.3%。

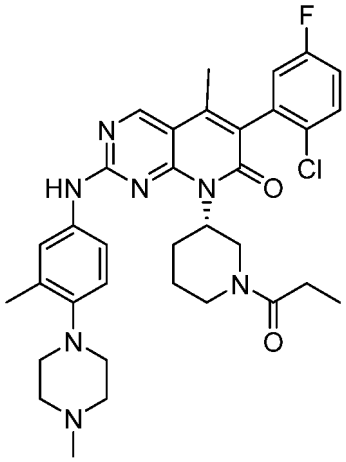
[0830] ^{1}H NMR(400MHz,DMSO)δ9.99(s,1H),9.32(s,1H),7.71(s,1H),7.49(d,J=10.8Hz,2H),7.47-7.23(m,2H),6.88(s,1H),5.54-5.14(m,1H),4.43(t,J=83.0Hz,1H),3.72(dd,J=66.7Hz,2H),2.87(s,3H),2.22(s,3H),2.23-2.18(m,4H),2.15(s,3H),1.82(t,J=29.3Hz,2H),1.60-1.30(m,2H),1.32(s,3H).

[0831] MS(ESI)m/z 618.4[M+H]$^+$。

[0832] 实施例73

[0833] (S)-6-(2-氯-4-氟苯基)-5-甲基-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)-8-(1-丙哌啶-3-基)吡啶并[2,3-d]嘧啶-7(8H)-酮(580124)

[0834] (S)-6-(2-chloro-4-fluorophenyl)-5-methyl-2-((3-methyl-4-(4-methylpiperazin-1-yl)phenyl)amino)-8-(1-propionylpiperidin-3-yl)pyrido[2,3-d]pyrimidin-7(8H)-one

[0835] 

[0836] 合成方法如实施例18,产率61.8%。

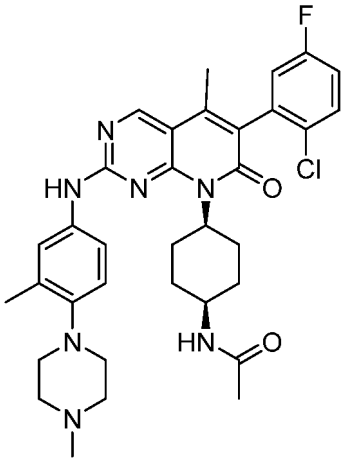
[0837] ^{1}H NMR(400MHz,DMSO)δ9.99(s,1H),9.32(s,1H),7.71(s,1H),7.49(d,J=10.8Hz,2H),7.47-7.23(m,2H),6.88(s,1H),5.54-5.14(m,1H),4.43(t,J=83.0Hz,1H),3.72(dd,J=118.4,66.7Hz,2H),2.87(d,J=53.7Hz,2H),2.22(s,3H),2.23-2.18(m,3H),2.15(s,3H),1.74(t,J=52.9Hz,2H),1.55-1.30(m,2H),,1.13(q,J=53.7,2H),0.93(t,J=20.8,3H).

[0838] MS(ESI)m/z 632.3[M+H]$^+$。

[0839] 实施例74

[0840] N-((1S,4S)-4-(6-(2-氯-5-氟苯基)-5-甲基-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)-7-氧代吡啶并[2,3-d]嘧啶-8(7H)-基)环己基)乙酰胺(580145)

[0841] N-((1s,4s)-4-(6-(2-chloro-5-fluorophenyl)-5-methyl-2-((3-methyl-4-(4-methylpiperazin-1-yl)phenyl)amino)-7-oxopyrido[2,3-d]pyrimidin-8(7H)-yl)cyclohexyl)acetamide

[0842] 

[0843] 合成方法如实施例18,产率72.9%。

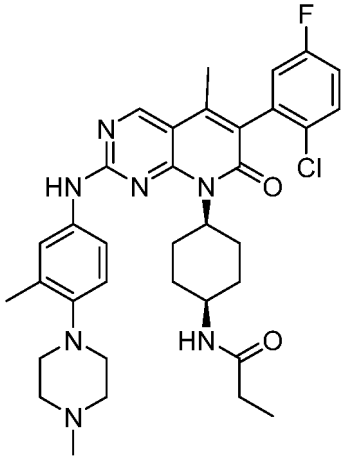
[0844] ^{1}H NMR(400MHz,DMSO)δ9.94(s,1H),8.85(s,1H),7.79-7.56(m,2H),7.51(s,1H),7.43(dd,J=17.3,10.5,6.7Hz,2H),7.22-7.05(m,1H),7.02(t,J=7.3Hz,1H),5.37(d,J=39.8Hz,1H),4.35(t,J=5.0Hz,1H),4.30-4.12(m,1H),4.01(dt,J=12.1,6.9Hz,1H),3.88(s,4H),3.55-3.35(m,2H),2.93-2.71(m,2H),2.37(s,3H),2.28(s,3H),2.21(d,J=24.3Hz,2H),2.12(d,J=12.2Hz,3H),2.03-1.73(m,2H),1.93(s,3H),1.70-1.34(m,2H),0.86(s,3H).

[0845] MS(ESI)m/z 632.3$[M+H]^+$。

[0846] 实施例75

[0847] N-((1S,4S)-4-(6-(2-氯-5-氟苯基)-5-甲基-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)-7-氧代吡啶并[2,3-d]嘧啶-8(7H)-基)环己基)丙酰胺(580146)

[0848] N-((1s,4s)-4-(6-(2-chloro-5-fluorophenyl)-5-methyl-2-((3-methyl-4-(4-methylpiperazin-1-yl)phenyl)amino)-7-oxopyrido[2,3-d]pyrimidin-8(7H)-yl)cyclohexyl)propionamide

[0849] 

[0850] 合成方法如实施例18,产率73.4%。

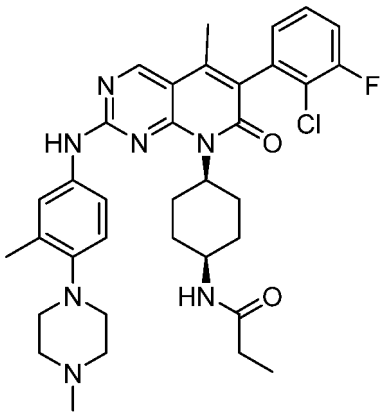
[0851] ^{1}H NMR(400MHz,DMSO)δ9.94(s,1H),8.85(s,1H),7.79-7.56(m,2H),7.51(s,1H),7.43(dd,J=17.3,10.5,6.7Hz,2H),7.22-7.05(m,1H),7.02(t,J=7.3Hz,1H),5.37(d,J=39.8Hz,1H),4.35(t,J=5.0Hz,1H),4.30-4.12(m,1H),4.01(dt,J=12.1,6.9Hz,1H),3.88(s,4H),3.55-3.35(m,2H),2.93-2.71(m,2H),2.37(s,3H),2.28(s,3H),2.21(d,J=24.3Hz,2H),2.12(d,J=12.2Hz,3H),2.03-1.73(t,2H),1.93(s,3H),1.70-1.34(m,2H),0.86(q,J=5.3Hz,3H).

[0852] MS(ESI)m/z 646.8[M+H]$^+$。

[0853] 实施例76

[0854] N-((1S,4S)-4-(6-(2-氯-3-氟苯基)-5-甲基-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)-7-氧代吡啶并[2,3-d]嘧啶-8(7H)-基)环己基)丙酰胺(580152)

[0855] N-((1s,4s)-4-(6-(2-chloro-3-fluorophenyl)-5-methyl-2-((3-methyl-4-(4-methylpiperazin-1-yl)phenyl)amino)-7-oxopyrido[2,3-d]pyrimidin-8(7H)-yl)cyclohexyl)propionamide

[0856] 

[0857] 合成方法如实施例18,产率70.3%。

[0858] ^{1}H NMR(400MHz,DMSO)δ9.94(s,1H),8.85(s,1H),7.79-7.56(m,2H),7.51(s,1H),7.43(dd,J=17.3,10.5,6.7Hz,2H),7.22-7.05(m,1H),7.02(t,J=7.3Hz,1H),5.37(d,J=39.8Hz,1H),4.35(t,J=5.0Hz,1H),4.30-4.12(m,1H),4.01(dt,J=12.1,6.9Hz,1H),3.88(s,4H),3.55-3.35(m,2H),2.93-2.71(m,2H),2.37(s,3H),2.28(s,3H),2.21(d,J=24.3Hz,2H),2.12(d,J=12.2Hz,3H),2.03-1.73(t,2H),1.93(s,3H),1.70-1.34(m,2H),

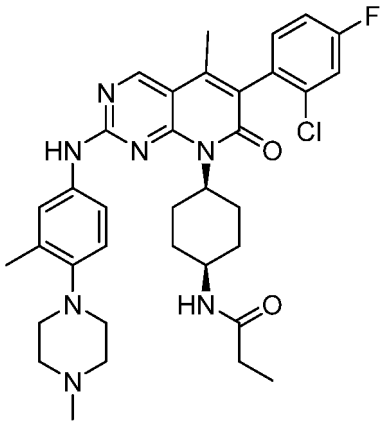
0.86(q,J＝5.3Hz,3H).

[0859] MS(ESI)m/z 646.2[M+H]$^+$。

[0860] 实施例77

[0861] N-((1S,4S)-4-(6-(2-氯-4-氟苯基)-5-甲基-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)-7-氧代吡啶并[2,3-d]嘧啶-8(7H)-基)环己基)丙酰胺(590011)

[0862] N-((1s,4s)-4-(6-(2-chloro-4-fluorophenyl)-5-methyl-2-((3-methyl-4-(4-methylpiperazin-1-yl)phenyl)amino)-7-oxopyrido[2,3-d]pyrimidin-8(7H)-yl)cyclohexyl)propionamide

[0863] 

[0864] 合成方法如实施例18,产率70％。

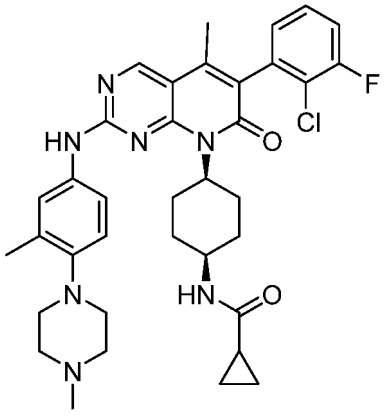
[0865] ^{1}H NMR(400MHz,DMSO)δ9.94(s,1H),8.85(s,1H),7.79-7.56(m,2H),7.51(s,1H),7.43(dd,J＝17.3,10.5,6.7Hz,2H),7.22-7.05(m,1H),7.02(t,J＝7.3Hz,1H),5.37(d,J＝39.8Hz,1H),4.35(t,J＝5.0Hz,1H),4.30-4.12(m,1H),4.01(dt,J＝12.1,6.9Hz,1H),3.88(s,4H),3.55-3.35(m,2H),2.93-2.71(m,2H),2.37(s,3H),2.28(s,3H),2.21(d,J＝24.3Hz,2H),2.12(d,J＝12.2Hz,3H),2.03-1.73(t,2H),1.93(s,3H),1.70-1.34(m,2H),0.86(q,J＝5.3Hz,3H).

[0866] MS(ESI)m/z 646.3[M+H]$^+$。

[0867] 实施例78

[0868] N-((1S,4S)-4-(6-(2-氯-3-氟苯基)-5-甲基-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)-7-氧代吡啶并[2,3-d]嘧啶-8(7H)-基)环己基)环丙烷甲酰胺(590024)

[0869] N-((1s,4s)-4-(6-(2-chloro-3-fluorophenyl)-5-methyl-2-((3-methyl-4-(4-methylpiperazin-1-yl)phenyl)amino)-7-oxopyrido[2,3-d]pyrimidin-8(7H)-yl)cyclohexyl)cyclopropanecarboxamide

[0870] 

[0871] 合成方法如实施例18,产率67.4%。

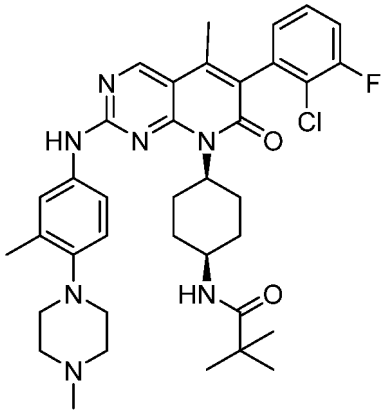
[0872] ^{1}H NMR(400MHz,DMSO)δ9.94(s,1H),8.85(s,1H),7.79-7.56(m,2H),7.51(s,1H),7.43(dd,J=17.3,10.5,6.7Hz,2H),7.22-7.05(m,1H),7.02(t,J=7.3Hz,1H),5.37(d,J=39.8Hz,1H),4.35(t,J=5.0Hz,1H),4.30-4.12(m,1H),4.01(dt,J=12.1,6.9Hz,1H),3.88(s,4H),3.55-3.35(m,2H),2.93-2.71(m,2H),2.37(s,3H),2.28(s,3H),2.21(d,J=24.3Hz,2H),2.12(d,J=12.2Hz,3H),2.03-1.73(m,2H),1.93(s,3H),1.70-1.34(m,2H),1.18-0.91(m,2H),1.13-0.93(m,2H),0.86(t,J=14.7Hz,3H)。

[0873] MS(ESI)m/z 658.3[M+H]$^+$。

[0874] 实施例79

[0875] N-((1S,4S)-4-(6-(2-氯-3-氟苯基)-5-甲基-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)-7-氧代吡啶并[2,3-d]嘧啶-8(7H)-基)环己基)新戊酰胺(590030)

[0876] N-((1s,4s)-4-(6-(2-chloro-3-fluorophenyl)-5-methyl-2-((3-methyl-4-(4-methylpiperazin-1-yl)phenyl)amino)-7-oxopyrido[2,3-d]pyrimidin-8(7H)-yl)cyclohexyl)pivalamide

[0877] 

[0878] 合成方法如实施例18,产率69.8%。

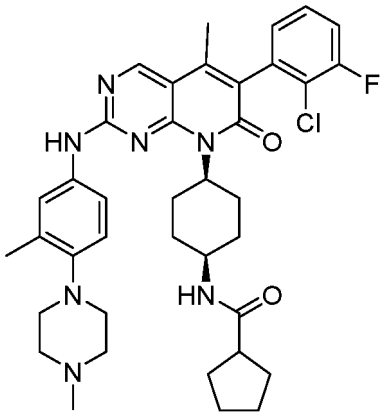
[0879] ^{1}H NMR(400MHz,DMSO)δ9.94(s,1H),8.85(s,1H),7.79-7.56(m,2H),7.51(s,1H),7.43(dd,J=17.3,10.5,6.7Hz,2H),7.22-7.05(m,1H),7.02(t,J=7.3Hz,1H),5.37(d,J=39.8Hz,1H),4.35(t,J=5.0Hz,1H),4.30-4.12(m,1H),4.01(dt,J=12.1,6.9Hz,1H),3.88(s,4H),3.55-3.35(m,2H),2.93-2.71(m,2H),2.37(s,3H),2.28(s,3H),2.21(d,J=24.3Hz,2H),2.12(d,J=12.2Hz,3H),2.03-1.73(m,2H),1.93(s,3H),1.34(s,9H).

[0880] MS(ESI)m/z 674.4[M+H]$^+$。

[0881] 实施例80

[0882] N-((1S,4S)-4-(6-(2-氯-3-氟苯基)-5-甲基-2-((4-(4-甲基哌嗪-1-基)苯基)氨基)-7-氧代吡啶并[2,3-d]嘧啶-8(7H)-基)环己基)环戊烷甲酰胺(590031)

[0883] N-((1s,4s)-4-(6-(2-chloro-3-fluorophenyl)-5-methyl-2-((4-(4-methylpiperazin-1-yl)phenyl)amino)-7-oxopyrido[2,3-d]pyrimidin-8(7H)-yl)cyclohexyl)cyclopentanecarboxamide

[0884] 

[0885] 合成方法如实施例18,产率73.3%。

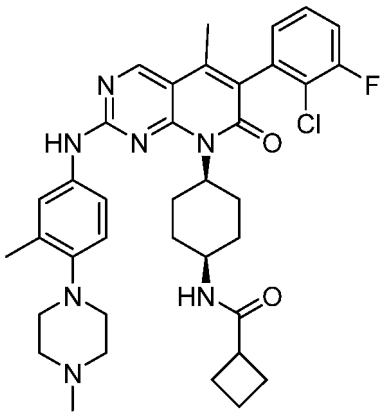
[0886] ^{1}H NMR(400MHz,DMSO)δ9.95(s,1H),9.13-8.70(m,1H),7.66-7.48(m,2H),7.49-7.40(m,2H),7.22-7.12(m,1H),7.00(dd,J=16.3,10.3Hz,1H),5.76(s,1H),5.42(s,1H),3.52-3.36(m,2H),2.82(s,4H),2.32(s,3H),2.26(d,J=10.1Hz,3H),2.21(d,J=18.7Hz,3H),2.14(s,3H),2.00(m,2H),1.93(s,3H)1.64(t,J=13.7Hz,4H),1.62-1.47(m,3H),1.40(t,J=14.0Hz,2H),1.23(dd,J=13.3,6.7Hz,3H),1.19-1.10(m,2H),1.04(dd,J=15.5,8.5Hz,2H).

[0887] MS(ESI)m/z 686.5[M+H]$^+$

[0888] 实施例81

[0889] N-((1S,4S)-4-(6-(2-氯-3-氟苯基)-5-甲基-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)-7-氧代吡啶并[2,3-d]嘧啶-8(7H)-基)环己基)环丁烷(590034)

[0890] N-((1s,4s)-4-(6-(2-chloro-3-fluorophenyl)-5-methyl-2-((3-methyl-4-(4-methylpiperazin-1-yl)phenyl)amino)-7-oxopyrido[2,3-d]pyrimidin-8(7H)-yl)cyclohexyl)cyclobutanecarboxamide

[0891] 

[0892] 合成方法如实施例18,产率70%。

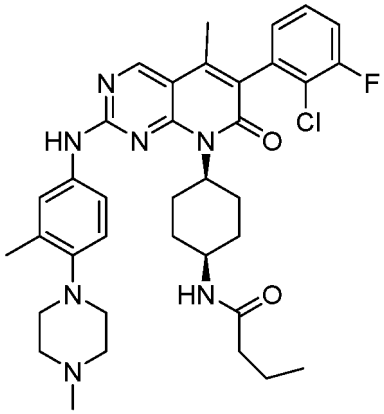
[0893] ^{1}H NMR(400MHz,DMSO)δ9.95(s,1H),9.13-8.70(m,1H),7.66-7.48(m,2H),7.49-7.40(m,2H),7.22-7.12(m,1H),7.00(dd,J＝16.3,10.3Hz,1H),5.76(s,1H),5.42(s,1H),3.52-3.36(m,2H),2.82(s,4H),2.32(s,3H),2.26(d,J＝10.1Hz,3H),2.21(d,J＝18.7Hz,3H),2.14(s,3H),2.00(m,2H),1.93(s,3H)1.64(t,J＝13.7Hz,4H),1.62-1.47(m,3H),1.40(t,J＝14.0Hz,2H),1.23(dd,J＝13.3,6.7Hz,3H),1.04(dd,J＝15.5,8.5Hz,2H).

[0894] MS(ESI)m/z 672.4[M+H]$^+$。

[0895] 实施例82

[0896] N-((1S,4S)-4-(6-(2-氯-3-氟苯基)-5-甲基-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)-7-氧代吡啶并[2,3-d]嘧啶-8(7H)-基)环己基)丁酰胺(590037)

[0897] N-((1s,4s)-4-(6-(2-chloro-3-fluorophenyl)-5-methyl-2-((3-methyl-4-(4-methylpiperazin-1-yl)phenyl)amino)-7-oxopyrido[2,3-d]pyrimidin-8(7H)-yl)cyclohexyl)butyramide

[0898] 

[0899] 合成方法如实施例18,产率64.1%。

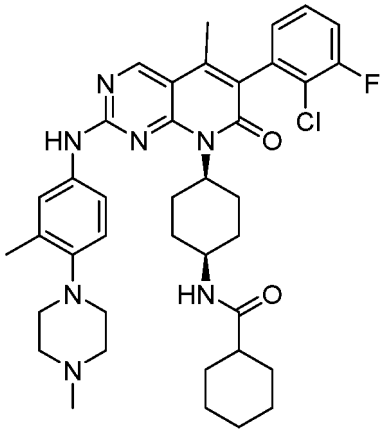
[0900] ^{1}H NMR(400MHz,DMSO)δ9.94(s,1H),8.85(s,1H),7.79-7.56(m,2H),7.51(s,1H),7.43(dd,J＝17.3,10.5,6.7Hz,2H),7.22-7.05(m,1H),7.02(t,J＝7.3Hz,1H),5.37(d,J＝39.8Hz,1H),4.35(t,J＝5.0Hz,1H),4.30-4.12(m,1H),4.01(dt,J＝12.1,6.9Hz,1H),3.88(s,4H),3.55-3.35(m,2H),2.93-2.71(m,2H),2.37(s,3H),2.28(s,3H),2.21(d,J＝24.3Hz,2H),2.12(d,J＝12.2Hz,3H),2.03-1.73(m,2H),1.93(s,3H),1.70-1.34(m,2H),1.18-0.91(m,2H),1.13-0.93(m,2H),0.86(t,J＝14.7Hz,3H).

[0901] MS(ESI)m/z 660.4[M+H]$^+$。

[0902] 实施例83

[0903] N-((1S,4S)-4-(6-(2-氯-3-氟苯基)-5-甲基-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)-7-氧代吡啶并[2,3-d]嘧啶-8(7H)-基)环己基)环己烷甲酰胺(590039)

[0904] N-((1s,4s)-4-(6-(2-chloro-3-fluorophenyl)-5-methyl-2-((3-methyl-4-(4-methylpiperazin-1-yl)phenyl)amino)-7-oxopyrido[2,3-d]pyrimidin-8(7H)-yl)cyclohexyl)cyclohexanecarboxamide

[0905] 

[0906] 合成方法如实施例18,产率71.4%。

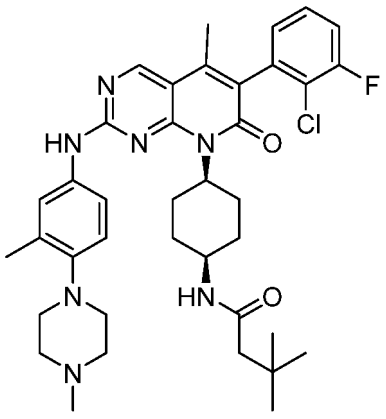
[0907] ^{1}H NMR(400MHz,DMSO)δ9.95(s,1H),9.13-8.70(m,1H),7.66-7.48(m,2H),7.49-7.40(m,2H),7.22-7.12(m,1H),7.00(dd,J=16.3,10.3Hz,1H),5.76(s,1H),5.42(s,1H),3.52-3.36(m,2H),2.82(s,4H),2.32(s,3H),2.26(d,J=10.1Hz,3H),2.21(d,J=18.7Hz,3H),2.14(s,3H),2.00(m,2H),1.93(s,3H)1.64(t,J=13.7Hz,4H),1.62-1.47(m,3H),1.40(t,J=14.0Hz,2H),1.36-1.27(m,2H),1.23(dd,J=13.3,6.7Hz,3H),1.19-1.10(m,2H),1.04(dd,J=15.5,8.5Hz,2H).

[0908] MS(ESI)m/z 700.5[M+H]$^+$。

[0909] 实施例84

[0910] N-((1S,4S)-4-(6-(2-氯-3-氟苯基)-5-甲基-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)-7-氧代吡啶并[2,3-d]嘧啶-8(7H)-基)环己基)-3,3-二甲基丁酰胺(590040)

[0911] N-((1s,4s)-4-(6-(2-chloro-3-fluorophenyl)-5-methyl-2-((3-methyl-4-(4-methylpiperazin-1-yl)phenyl)amino)-7-oxopyrido[2,3-d]pyrimidin-8(7H)-yl)cyclohexyl)-3,3-dimethylbutanamide

[0912] 

[0913] 合成方法如实施例18,产率67.5%。

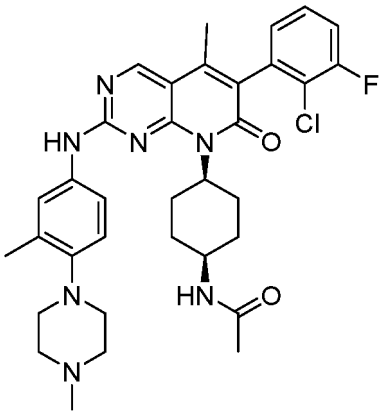
[0914] ^{1}H NMR(400MHz,DMSO)δ9.99(s,1H),9.32(s,1H),7.71(s,1H),7.49(d,J=10.8Hz,2H),7.47-7.23(m,2H),6.88(s,1H),5.54-5.14(m,1H),4.43(t,J=83.0Hz,1H),3.72(dd,J=66.7Hz,2H),3.69-3.37(m,2H)2.87(s,3H),2.22(s,3H),2.23-2.18(m,4H),2.15(s,3H),1.82(t,J=29.3Hz,2H),1.60-1.30(m,2H),1.32(s,9H).

[0915] MS(ESI)m/z 688.4[M+H]$^+$。

[0916] 实施例85

[0917] N-((1S,4S)-4-(6-(2-氯-3-氟苯基)-5-甲基-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)-7-氧代吡啶并[2,3-d]嘧啶-8(7H)-基)环己基)乙酰胺(590041)

[0918] N-((1s,4s)-4-(6-(2-chloro-3-fluorophenyl)-5-methyl-2-((3-methyl-4-(4-methylpiperazin-1-yl)phenyl)amino)-7-oxopyrido[2,3-d]pyrimidin-8(7H)-yl)cyclohexyl)acetamide

[0919] 

[0920] 合成方法如实施例18,产率65.2%。

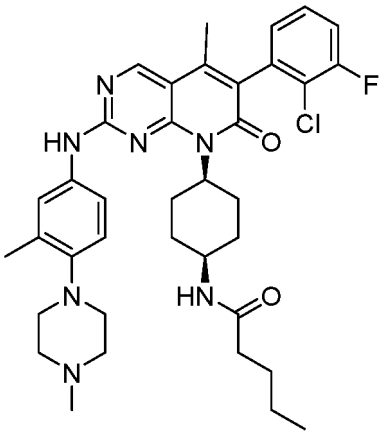
[0921] ^{1}H NMR(400MHz,DMSO)δ9.99(s,1H),9.32(s,1H),7.71(s,1H),7.49(d,J=10.8Hz,2H),7.47-7.23(m,2H),6.88(s,1H),5.54-5.14(m,1H),4.43(t,J=83.0Hz,1H),3.72(dd,J=66.7Hz,2H),3.69-3.37(m,2H)2.87(s,3H),2.22(s,3H),2.23-2.18(m,4H),2.15(s,3H),1.82(t,J=29.3Hz,2H),1.60-1.30(m,2H),1.32(s,3H).

[0922] MS(ESI)m/z 632.3[M+H]$^+$。

[0923] 实施例86

[0924] N-((1S,4S)-4-(6-(2-氯-3-氟苯基)-5-甲基-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)-7-氧代吡啶并[2,3-d]嘧啶-8(7H)-基)环己基)戊酰胺(590047)

[0925] N-((1s,4s)-4-(6-(2-chloro-3-fluorophenyl)-5-methyl-2-((3-methyl-4-(4-methylpiperazin-1-yl)phenyl)amino)-7-oxopyrido[2,3-d]pyrimidin-8(7H)-yl)cyclohexyl)pentanamide

[0926] 

[0927] 合成方法如实施例18,产率67%。

[0928] ^{1}H NMR(400MHz,DMSO)δ9.94(s,1H),8.85(s,1H),7.79-7.56(m,2H),7.51(s,1H),7.43(dd,J=17.3,10.5,6.7Hz,2H),7.22-7.05(m,1H),7.02(t,J=7.3Hz,1H),5.41(s,1H),4.28(dt,J=13.2,5.8Hz,1H),4.18-3.71(m,2H),3.69-3.37(m,2H),2.79(s,4H),

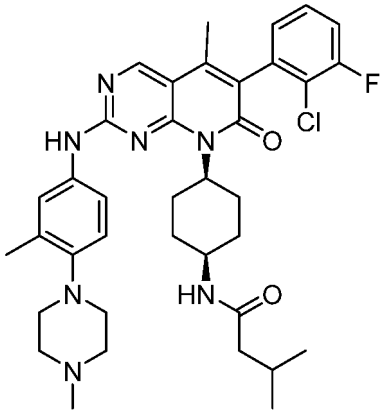
2.39-2.26(m,3H),2.32(s,3H),2.24(s,3H),2.19-2.07(t,J＝7.0Hz,1H),1.93(s,3H),1.99-1.81(m,1H),1.68-1.50(m,2H),1.50-1.35(m,3H),1.37-1.14(m,2H),1.14-0.95(m,2H),0.87(t,J＝17.0,3H).

[0929] MS(ESI)m/z 674.4[M+H]$^+$。

[0930] 实施例87

[0931] N-((1S,4S)-4-(6-(2-氯-3-氟苯基)-5-甲基-2-((3-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)-7-氧代吡啶并[2,3-d]嘧啶-8(7H)-基)环己基)-3-甲基丁酰胺(590048)

[0932] N-((1s,4s)-4-(6-(2-chloro-3-fluorophenyl)-5-methyl-2-((3-methyl-4-(4-methylpiperazin-1-yl)phenyl)amino)-7-oxopyrido[2,3-d]pyrimidin-8(7H)-yl)cyclohexyl)-3-methylbutanamide

[0933] 

[0934] 合成方法如实施例18,产率66.48%。

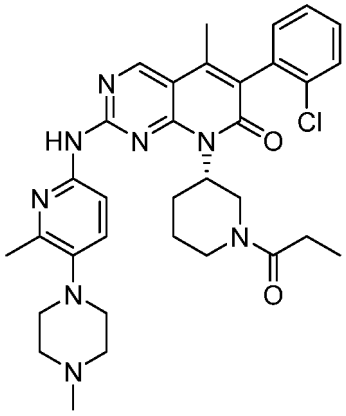
[0935] ^{1}H NMR(400MHz,DMSO)δ9.94(s,1H),8.85(s,1H),7.79-7.56(m,2H),7.51(s,1H),7.43(dd,J＝17.3,10.5,6.7Hz,2H),7.22-7.05(m,1H),7.02(t,J＝7.3Hz,1H),5.41(s,1H),4.28(dt,J＝13.2,5.8Hz,1H),4.18-3.71(m,1H),3.69-3.37(m,1H),2.79(s,4H),2.39-2.26(m,3H),2.32(s,3H),2.24(s,3H),2.19-2.07(t,J＝7.0Hz,1H),1.93(s,3H),1.99-1.81(m,1H),1.68-1.50(m,2H),1.50-1.35(m,3H),1.37-1.14(m,2H),1.14-0.95(m,2H),0.87(dd,J＝17.0,4.9Hz,2H),0.85-0.77(m,6H).

[0936] MS(ESI)m/z 674.4[M+H]$^+$。

[0937] 实施例88

[0938] (S)-6-(2-氯苯基)-5-甲基-2-((6-甲基-5-(4-甲基哌嗪-1-基)吡啶-2-基)氨基)-8-(1-丙哌啶-3-基)吡啶并[2,3-d]嘧啶-7(8H)-酮(10201B)

[0939] (S)-6-(2-chlorophenyl)-5-methyl-2-((6-methyl-5-(4-methylpiperazin-1-yl)pyridin-2-yl)amino)-8-(1-propionyl piperidin-3-yl)pyrido[2,3-d]pyrimidin-7(8H)-one

[0940] 

[0941] 合成方法如实施例18,产率85.4%。

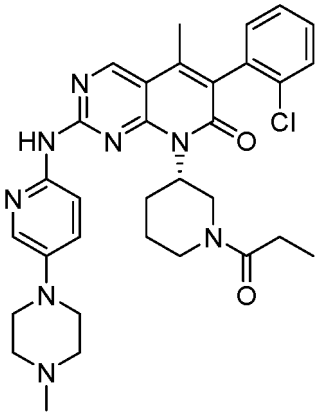
[0942] ^{1}H NMR(400MHz,Chloroform-d)δ8.83(d,J=11.0Hz,1H),8.04(dd,J=20.7,10.7Hz,2H),7.55-7.46(m,1H),7.46-7.32(m,3H),7.25-7.19(m,1H),5.50(s,1H),4.70(d,J=12.6Hz,1H),4.00-3.71(m,2H),3.06(d,J=13.4Hz,1H),2.97(d,J=6.2Hz,3H),2.88(d,J=11.4Hz,1H),2.63(d,J=25.4Hz,3H),2.49(d,J=3.7Hz,2H),2.43(dd,J=12.3,6.1Hz,3H),2.30(p,J=7.3Hz,1H),2.25-2.17(m,3H),1.91(d,J=23.1Hz,3H),1.61(d,J=10.0Hz,2H),1.07(td,J=7.4,3.6Hz,2H),0.87(dd,J=15.5,8.4Hz,2H).

[0943] MS(ESI)m/z 615.3[M+H]$^+$。

[0944] 实施例89

[0945] (S)-6-(2-氯苯基)-5-甲基-2-((5-(4-甲基哌嗪-1-基)吡啶-2-基)氨基)-8-(1-丙酰基哌啶-3-基)基)吡啶并[2,3-d]嘧啶-7(8H)-酮(10301B)

[0946] (S)-6-(2-chlorophenyl)-5-methyl-2-((5-(4-methylpiperazin-1-yl)pyridin-2-yl)amino)-8-(1-propionyl piperidin-3-yl)pyrido[2,3-d]pyrimidin-7(8H)-one

[0947] 

[0948] 合成方法如实施例18,产率67%。

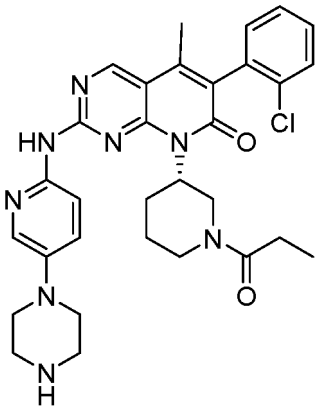
[0949] ^{1}H NMR(400MHz,DMSO-d6)δ10.22(d,J=18.0Hz,1H),8.95(s,1H),8.07(s,1H),7.88(s,1H),7.60-7.52(m,1H),7.45-7.40(m,2H),7.37-7.26(m,2H),4.49-3.67(m,1H),3.30(s,2H),3.16(s,3H),2.31(d,J=15.9Hz,7H),2.15(d,J=2.9Hz,4H),2.04-1.96(m,1H),1.76(d,J=39.0Hz,3H),1.45(s,2H),1.02(t,J=7.3Hz,2H),0.93-0.78(m,3H).

[0950] MS(ESI)m/z 601.2[M+H]$^+$。

[0951] 实施例90

[0952] (S)-6-(2-氯苯基)-5-甲基-2-((5-(哌嗪-1-基)吡啶-2-基)氨基)-8-(1-丙哌啶-3-基)吡啶并[2,3-d]嘧啶-7(8H)-酮(10401B)

[0953] (S)-6-(2-chlorophenyl)-5-methyl-2-((5-(piperazin-1-yl)pyridin-2-yl)amino)-8-(1-propionylpiperidin-3-yl)pyrido[2,3-d]pyrimidin-7(8H)-one

[0954] 

[0955] 合成方法如实施例18,产率87.2%。

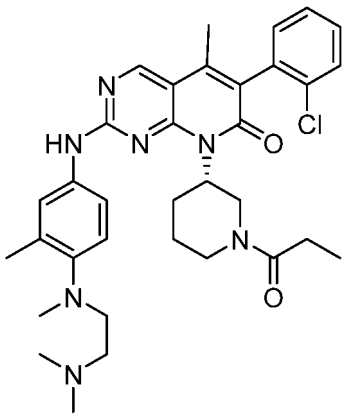
[0956] ^{1}H NMR(400MHz,DMSO-d6)δ10.21(d,J=18.1Hz,1H),8.94(d,J=2.9Hz,1H),8.04(d,J=2.9Hz,1H),7.87(s,1H),7.68-7.51(m,1H),7.36(ddt,J=49.1,9.1,5.4Hz,4H),5.33(s,1H),4.58-3.60(m,2H),3.06(t,J=3.5Hz,5H),2.87(dt,J=6.7,3.4Hz,4H),2.64(s,1H),2.40(s,1H),2.33-2.22(m,1H),2.15(d,J=2.9Hz,3H),2.02-1.34(m,4H),1.09-0.78(m,4H).

[0957] MS(ESI)m/z 588.2$[M+H]^+$。

[0958] 实施例91

[0959] (S)-6-(2-氯苯基)-2-((4-((2-(二甲基氨基)乙基)(甲基)氨基)-3-甲基苯基)氨基)-5-甲基-8-(1-丙哌啶-3-基)吡啶并[2,3-d]嘧啶-7(8H)-酮(10501B)

[0960] (S)-6-(2-chlorophenyl)-2-((4-((2-(dimethylamino)ethyl)(methyl)amino)-3-methylphenyl)amino)-5-methyl-8-(1-propionylpiperidin-3-yl)pyrido[2,3-d]pyrimidin-7(8H)-one

[0961] 

[0962] 合成方法如实施例18,产率77.3%。

[0963] ^{1}H NMR(400MHz,DMSO-d6)δ9.96(s,1H),8.91(d,J=3.6Hz,1H),7.63-7.25(m,6H),7.01(d,J=8.6Hz,1H),5.41(d,J=8.9Hz,1H),4.43(s,1H),4.12-3.55(m,2H),3.26-3.07(m,1H),2.92(td,J=7.0,2.4Hz,3H),2.50(p,J=1.8Hz,1H),2.38(q,J=6.8Hz,3H),

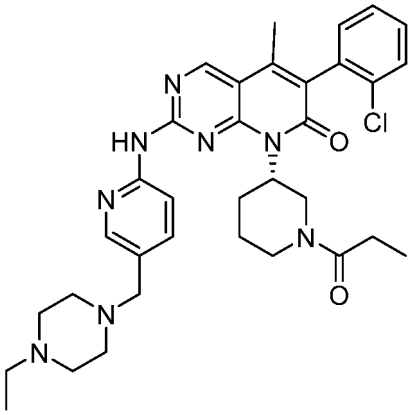
2.21(d,J＝2.8Hz,4H),2.18-2.10(m,9H),1.76(s,2H),1.46(d,J＝14.3Hz,1H),1.02(t,J＝7.3Hz,2H),0.83(d,J＝9.4Hz,2H).

[0964] MS(ESI)m/z 616.9$[M+H]^+$。

[0965] 实施例92

[0966] (S)-6-(2-氯苯基)-2-((5-((4-乙基哌嗪-1-基)甲基)吡啶-2-基)氨基)-5-甲基-8-(1-丙酰基哌啶)吡啶-3-基)吡啶并[2,3-d]嘧啶-7(8H)-酮(10801B)

[0967] (S)-6-(2-chlorophenyl)-2-((5-((4-ethylpiperazin-1-yl)methyl)pyridin-2-yl)amino)-5-methyl-8-(1-propionyl piperidin-3-yl)pyrido[2,3-d]pyrimidin-7(8H)-one(10801B)

[0968] 

[0969] 合成方法如实施例18,产率56.7%。

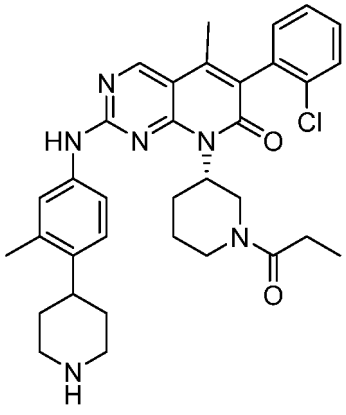
[0970] ^1H NMR(400MHz,DMSO-d6)δ10.50(d,J＝21.6Hz,1H),9.00(d,J＝3.9Hz,1H),8.23(d,J＝2.8Hz,1H),8.13-7.93(m,1H),7.88-7.53(m,2H),7.47-7.14(m,3H),5.62-4.94(m,1H),4.14(dd,J＝245.0,24.4Hz,2H),3.45(d,J＝2.8Hz,3H),2.82(d,J＝125.1Hz,1H),2.46-2.21(m,10H),2.16(d,J＝3.5Hz,3H),2.10-1.94(m,1H),1.92-1.32(m,4H),1.11-1.01(m,2H),0.98(t,J＝7.2Hz,3H),0.87(dq,J＝14.1,6.7Hz,2H).

[0971] MS(ESI)m/z 629.30$[M+H]^+$。

[0972] 实施例93

[0973] (S)-6-(2-氯苯基)-5-甲基-2-((3-甲基-4-(哌啶-4-基)苯基)氨基)-8-(1-丙酰基哌啶-3-基)吡啶并[2,3-d]嘧啶-7(8H)-酮(10901B)

[0974] (S)-6-(2-chlorophenyl)-5-methyl-2-((3-methyl-4-(piperidin-4-yl)phenyl)amino)-8-(1-propionyl piperidin-3-yl)pyrido[2,3-d]pyrimidin-7(8H)-one

[0975] 

[0976] 合成方法如实施例18,产率81.2%。

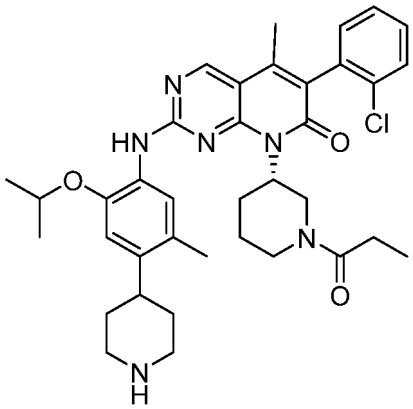
[0977] ^{1}H NMR(400MHz,DMSO-d6)δ10.03(s,1H),8.93(d,J=4.1Hz,1H),7.70-7.37(m,5H),7.36-7.24(m,1H),7.10(s,1H),5.47(d,J=46.2Hz,1H),4.44(s,1H),3.85(dd,J=95.6,42.7Hz,2H),3.13(t,J=10.8Hz,2H),3.01-2.59(m,4H),2.27(d,J=3.0Hz,5H),2.14(t,J=2.7Hz,4H),1.71(d,J=48.4Hz,4H),1.61-1.36(m,3H),1.01(s,2H),0.82(d,J=20.5Hz,2H).

[0978] MS(ESI)m/z 599.6[M+H]$^+$。

[0979] 实施例94

[0980] (S)-6-(2-氯苯基)-2-((2-异丙氧基-5-甲基-4-(哌啶-4-基)苯基)氨基)-5-甲基-8-(1-丙哌啶-3-基)吡啶并[2,3-d]嘧啶-7(8H)-酮(11001B)

[0981] (S)-6-(2-chlorophenyl)-2-((2-isopropoxy-5-methyl-4-(piperidin-4-yl)phenyl)amino)-5-methyl-8-(1-propionylpiperidin-3-yl)pyrido[2,3-d]pyrimidin-7(8H)-one

[0982] 

[0983] 合成方法如实施例18,产率74.3%。

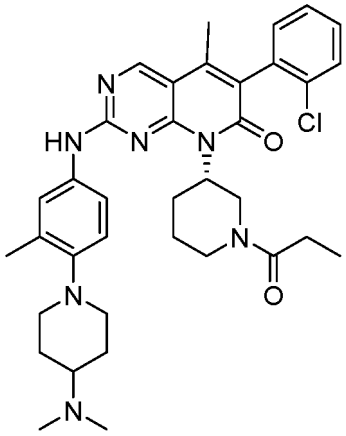
[0984] ^{1}H NMR(400MHz,DMSO-d6)δ8.89(d,J=5.8Hz,1H),7.62-7.50(m,1H),7.47-7.15(m,4H),6.87(d,J=21.1Hz,1H),5.63-4.69(m,1H),4.62-3.85(m,3H),3.62(s,2H),3.31-2.62(m,6H),2.22(d,J=4.2Hz,3H),2.16-2.10(m,3H),2.02(dd,J=30.1,16.3Hz,2H),1.71(d,J=25.3Hz,6H),1.18(s,6H),0.96(t,J=7.4Hz,2H),0.88-0.77(m,3H).

[0985] MS(ESI)m/z 658.3[M+H]$^+$。

[0986] 实施例95

[0987] (S)-6-(2-氯苯基)-2-((4-(4-(二甲基氨基)哌啶-1-基)-3-甲基苯基)氨基)-5-甲基-8-(1-丙哌啶-3-基)吡啶并[2,3-d]嘧啶-7(8H)-酮(11101B)

[0988] (S)-6-(2-chlorophenyl)-2-((4-(4-(dimethylamino)piperidin-1-yl)-3-methylphenyl)amino)-5-methyl-8-(1-propionylpiperidin-3-yl)pyrido[2,3-d]pyrimidin-7(8H)-one

[0989] 

[0990] 合成方法如实施例18,产率79.7%。

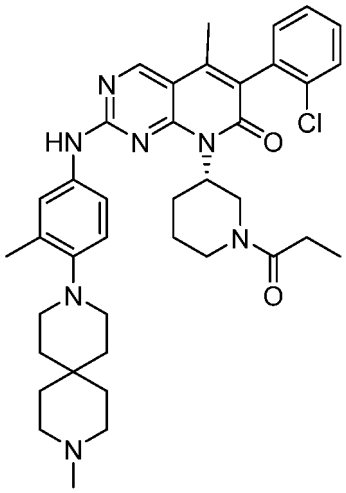
[0991] ^{1}H NMR(400MHz,DMSO-d6)δ9.97(s,1H),8.91(d,J=3.6Hz,1H),7.67-7.19(m,6H),6.94(d,J=8.3Hz,1H),5.59-5.28(m,1H),4.58-3.58(m,2H),3.11(d,J=35.6Hz,2H),2.78-2.53(m,3H),2.42-2.25(m,8H),2.21(d,J=3.4Hz,3H),2.14(t,J=2.6Hz,4H),1.93-1.70(m,4H),1.67-1.36(m,4H),1.01(s,2H),0.82(d,J=21.3Hz,2H).

[0992] MS(ESI)m/z 642.4[M+H]$^+$。

[0993] 实施例96

[0994] (S)-6-(2-氯苯基)-5-甲基-2-((3-甲基-4-(9-甲基-3,9-二氮杂螺[5.5]十一烷-3-基)苯基)氨基)-8-(1-丙哌啶-3-基)吡啶并[2,3-d]嘧啶-7(8H)-酮(11201B)

[0995] (S)-6-(2-chlorophenyl)-5-methyl-2-((3-methyl-4-(9-methyl-3,9-diazaspiro[5.5]undecan-3-yl)phenyl)amino)-8-(1-propionylpiperidin-3-yl)pyrido[2,3-d]pyrimidin-7(8H)-one

[0996] 

[0997] 合成方法如实施例18,产率76.7%。

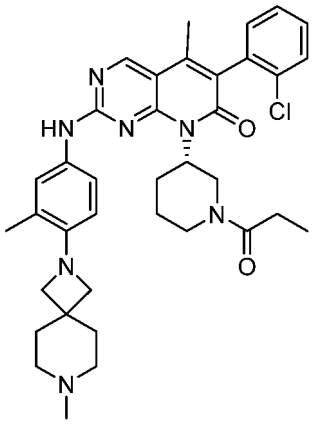
[0998] ^{1}H NMR(400MHz,DMSO-d6)δ9.98(s,1H),8.91(d,J=4.1Hz,1H),7.75-7.21(m,6H),6.98(s,1H),5.45(d,J=32.9Hz,1H),4.43(s,1H),3.84(dd,J=101.7,37.8Hz,2H),2.75(q,J=7.0,5.7Hz,4H),2.31(s,5H),2.23-1.97(m,9H),1.93-1.66(m,2H),1.53(dt,J=21.3,5.2Hz,9H),1.09-0.64(m,4H).

[0999] MS(ESI)m/z 683.2[M+H]$^+$。

[1000] 实施例97

[1001] (S)-6-(2-氯苯基)-5-甲基-2-((3-甲基-4-(7-甲基-2,7-二氮杂螺[3.5]壬-2-基)苯基)氨基)-8-(1-丙哌啶-3-基)吡啶并[2,3-d]嘧啶-7(8H)-酮(11301B)

[1002] (S)-6-(2-chlorophenyl)-5-methyl-2-((3-methyl-4-(7-methyl-2,7-diazaspiro[3.5]nonan-2-yl)phenyl)amino)-8-(1-propionylpiperidin-3-yl)pyrido[2,3-d]pyrimidin-7(8H)-one

[1003] 

[1004] 合成方法如实施例18,产率66.9%。

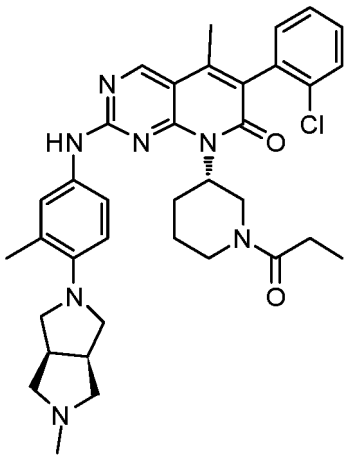
[1005] ^{1}H NMR(400MHz,DMSO-d6)δ9.76(s,1H),8.85(d,J=3.2Hz,1H),7.62-7.51(m,1H),7.47-7.18(m,5H),6.52(s,1H),5.58-4.88(m,2H),4.23(d,J=155.3Hz,1H),3.62(s,2H),3.55-3.38(m,4H),3.30(d,J=4.2Hz,2H),3.14(d,J=2.7Hz,3H),2.80-2.56(m,1H),2.35-2.20(m,1H),2.16-2.05(m,9H),1.76(d,J=47.2Hz,5H),1.42(d,J=23.7Hz,1H),1.01(t,J=7.3Hz,2H),0.84(d,J=6.9Hz,2H).

[1006] MS(ESI)m/z 654.3[M+H]$^+$。

[1007] 实施例98

[1008] 6-(2-氯苯基)-5-甲基-2-((3-甲基-4-((3AR,6AS)-5-甲基六氢吡咯并[3,4-c]吡咯-2(1H)-基)苯基)氨基)-8-((S)-1-丙哌啶-3-基)吡啶并[2,3-d]嘧啶-7(8H)-酮(11401B)

[1009] 6-(2-chlorophenyl)-5-methyl-2-((3-methyl-4-((3aR,6aS)-5-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)phenyl)amino)-8-((S)-1-propionylpiperidin-3-yl)pyrido[2,3-d]pyrimidin-7(8H)-one

[1010] 

[1011] 合成方法如实施例18,产率76.2%

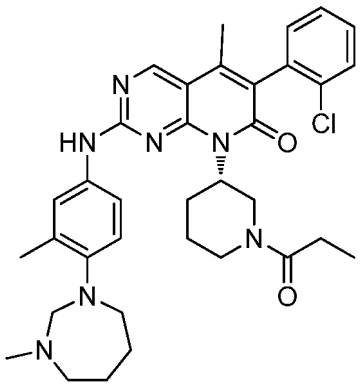
[1012] ^{1}H NMR(400MHz,DMSO-d6)δ10.05(d,J＝60.4Hz,1H),8.90(d,J＝3.7Hz,1H),7.60-7.24(m,6H),7.00-6.84(m,1H),5.38(s,1H),4.60-3.54(m,1H),3.27-2.57(m,8H),2.33(d,J＝9.4Hz,6H),2.23(d,J＝2.5Hz,3H),2.13(t,J＝2.7Hz,4H),2.06-1.26(m,6H),0.93(d,J＝62.9Hz,4H).

[1013] MS(ESI)m/z 640.7[M+H]$^+$。

[1014] 实施例99

[1015] (S)-6-(2-氯苯基)-5-甲基-2-((3-甲基-4-(3-甲基-1,3-二氮杂环庚烷-1-基)苯基)氨基)-8-(1-丙酰哌啶-3-基)吡啶并[2,3-d]嘧啶-7(8H)-酮(11501B)

[1016] (S)-6-(2-chlorophenyl)-5-methyl-2-((3-methyl-4-(3-methyl-1,3-diazepan-1-yl)phenyl)amino)-8-(1-propionylpiperidin-3-yl)pyrido[2,3-d]pyrimidin-7(8H)-one

[1017] 

[1018] 合成方法如实施例18,产率57.8%。

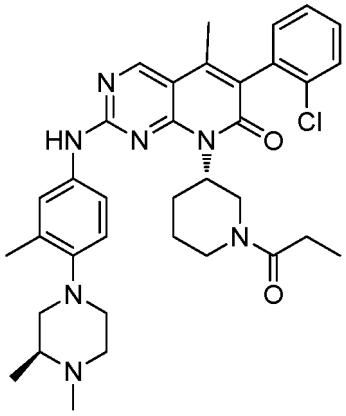
[1019] ^{1}H NMR(400MHz,DMSO-d6)δ9.95(s,1H),8.90(d,J＝4.8Hz,1H),7.59-7.24(m,6H),7.04-6.93(m,1H),5.45(d,J＝42.1Hz,1H),4.58-3.57(m,2H),3.16-2.88(m,4H),2.69(q,J＝8.9,7.4Hz,4H),2.34(d,J＝5.4Hz,4H),2.22(d,J＝2.9Hz,3H),2.13(t,J＝3.0Hz,3H),2.00(dd,J＝14.6,7.1Hz,1H),1.94-1.61(m,5H),1.42(d,J＝22.0Hz,2H),1.08-0.65(m,4H).

[1020] MS(ESI)m/z 628.7[M+H]$^+$。

[1021] 实施例100

[1022] 6-(2-氯苯基)-2-((4-((S)-3,4-二甲基哌嗪-1-基)-3-甲基苯基)氨基)-5-甲基-8-((S)-1-丙哌啶-3-基)吡啶并[2,3-d]嘧啶-7(8H)-酮(11601B)

[1023] 6-(2-chlorophenyl)-2-((4-((S)-3,4-dimethylpiperazin-1-yl)-3-methylphenyl)amino)-5-methyl-8-((S)-1-propionylpiperidin-3-yl)pyrido[2,3-d]pyrimidin-7(8H)-one

[1024] 

[1025] 合成方法如实施例18,产率53.9%。

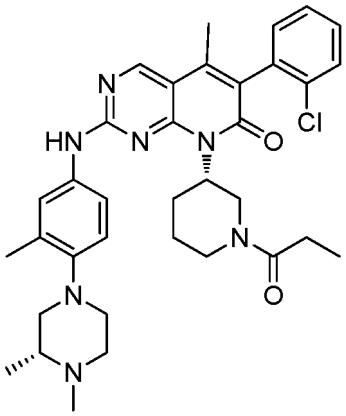
[1026] ^{1}H NMR(400MHz,DMSO-d6)δ10.05(d,J=60.9Hz,1H),8.90(d,J=5.1Hz,1H),7.66-7.21(m,6H),7.06-6.83(m,1H),5.41(s,1H),4.44(s,1H),3.84(dd,J=101.7,39.7Hz,2H),3.10-2.57(m,5H),2.47-2.27(m,4H),2.26-2.17(m,7H),2.13(t,J=2.9Hz,3H),1.76(s,3H),1.45(d,J=14.2Hz,1H),1.07-0.98(m,4H),0.82(d,J=18.0Hz,2H).

[1027] MS(ESI)m/z 628.3$[M+H]^+$。

[1028] 实施例101

[1029] 6-(2-氯苯基)-2-((4-((R)-3,4-二甲基哌嗪-1-基)-3-甲基苯基)氨基)-5-甲基-8-((S)-1-丙哌啶-3-基)吡啶并[2,3-d]嘧啶-7(8H)-酮(11701B)

[1030] 6-(2-chlorophenyl)-2-((4-((R)-3,4-dimethylpiperazin-1-yl)-3-methylphenyl)amino)-5-methyl-8-((S)-1-propionylpiperidin-3-yl)pyrido[2,3-d]pyrimidin-7(8H)-one

[1031] 

[1032] 合成方法如实施例18,产率66.7%。

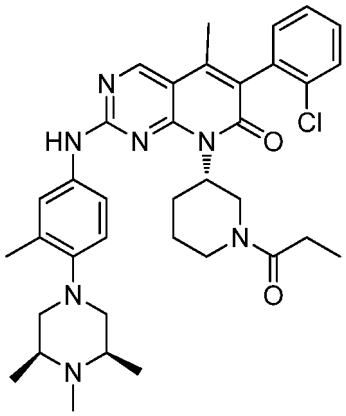
[1033] ^{1}H NMR(400MHz,DMSO-d6)δ9.96(s,1H),8.90(d,J=6.7Hz,1H),7.62-7.22(m,6H),6.93(d,J=9.9Hz,1H),5.41(s,1H),4.57-4.25(m,1H),3.84(dd,J=103.1,40.2Hz,2H),2.94-2.66(m,5H),2.38(dt,J=29.3,12.5Hz,4H),2.22(d,J=5.6Hz,7H),2.13(d,J=4.5Hz,3H),1.76(s,2H),1.44(t,J=13.9Hz,1H),1.10-0.95(m,5H),0.89-0.71(m,2H).

[1034] MS(ESI)m/z 628.3$[M+H]^+$。

[1035] 实施例102

[1036] 6-(2-氯苯基)-5-甲基-2-((3-甲基-4-((3S,5R)-3,4,5-三甲基哌嗪-1-基)苯基)氨基)-8-((S)-1-丙酰基哌啶-3-基)吡啶并[2,3-d]嘧啶-7(8H)-酮(11801B)

[1037] 6-(2-chlorophenyl)-5-methyl-2-((3-methyl-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)phenyl)amino)-8-((S)-1-propionylpiperidin-3-yl)pyrido[2,3-d]pyrimidin-7(8H)-one

[1038] 

[1039] 合成方法如实施例18,产率86.7%。

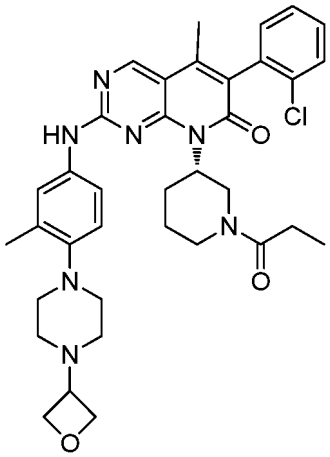
[1040] ^{1}H NMR(400MHz,DMSO-d6)δ9.99(s,1H),8.91(d,J=3.0Hz,1H),7.66-7.51(m,2H),7.48-7.34(m,3H),7.34-7.24(m,1H),6.91(s,1H),5.66-5.28(m,1H),4.42(d,J=28.0Hz,1H),3.84(dd,J=106.4,39.1Hz,2H),3.06-2.59(m,3H),2.46-2.28(m,5H),2.22(d,J=4.5Hz,6H),2.14(d,J=3.0Hz,3H),2.04-1.63(m,3H),1.61-1.31(m,2H),1.11-0.99(m,7H),0.85(td,J=15.5,13.1,7.9Hz,2H).

[1041] MS(ESI)m/z 642.3[M+H]$^+$。

[1042] 实施例103

[1043] (S)-6-(2-氯苯基)-5-甲基-2-((3-甲基-4-(4-(氧杂环丁烷-3-基)哌嗪-1-基)苯基)氨基)-8-(1-丙哌啶-3-基)吡啶并[2,3-d]嘧啶-7(8H)-酮(12102B)

[1044] (S)-6-(2-chlorophenyl)-5-methyl-2-((3-methyl-4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)amino)-8-(1-propionylpiperidin-3-yl)pyrido[2,3-d]pyrimidin-7(8H)-one

[1045] 

[1046] 合成方法如实施例18,产率68.9%。

[1047] ^{1}H NMR(400MHz,DMSO-d6)δ10.05(d,J=48.1Hz,1H),8.91(d,J=4.6Hz,1H),7.67-7.35(m,5H),7.37-7.18(m,1H),7.07-6.90(m,1H),5.47(d,J=43.9Hz,1H),4.82-4.20(m,5H),4.15-3.40(m,2H),3.10-2.56(m,5H),2.41(s,5H),2.21(d,J=2.7Hz,3H),

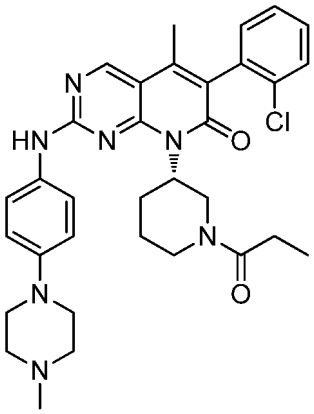
2.18-2.09(m,3H),2.08-1.93(m,1H),1.91-1.32(m,4H),1.06-0.66(m,4H).

[1048] MS(ESI)m/z 656.3[M+H]$^+$。

[1049] 实施例104

[1050] (S)-8-(1-丙酰基-3-基)-6-(2-氯苯基)-5-甲基-2-((4-(4-甲基哌嗪-1-基)苯基)氨基)吡啶并[2,3-d]嘧啶-7(8H)-酮

[1051] (S)-6-(2-chlorophenyl)-5-methyl-2-((4-(4-methylpiperazin-1-yl)phenyl)amino)-8-(1-propionylpiperidin-3-yl)pyrido[2,3-d]pyrimidin-7(8H)-one(12201B)

[1052] 

[1053] 合成方法如实施例18,产率87%。

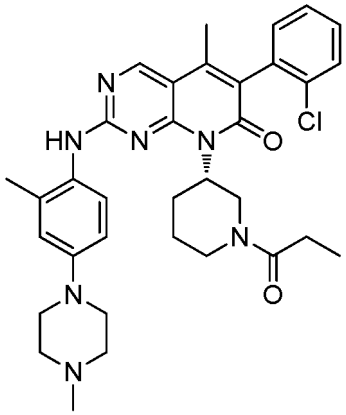
[1054] ^{1}H NMR(400MHz,DMSO-d6)δ10.04(d,J=59.8Hz,1H),8.89(d,J=3.0Hz,1H),7.69-7.47(m,3H),7.47-7.37(m,2H),7.37-7.25(m,1H),7.00-6.76(m,2H),5.46(d,J=56.8Hz,1H),4.64-3.49(m,3H),3.08(d,J=5.6Hz,4H),2.67(d,J=2.6Hz,2H),2.34(d,J=88.4Hz,7H),2.13(d,J=2.7Hz,4H),1.95-1.31(m,4H),0.93(d,J=67.2Hz,3H).

[1055] MS(ESI)m/z 600.3[M+H]$^+$。

[1056] 实施例105

[1057] (S)-6-(2-氯苯基)-5-甲基-2-((2-甲基-4-(4-甲基哌嗪-1-基)苯基)氨基)-8-(1-丙哌啶-3-基)吡啶并[2,3-d]嘧啶-7(8H)-酮(12301B)

[1058] (S)-6-(2-chlorophenyl)-5-methyl-2-((2-methyl-4-(4-methylpiperazin-1-yl)phenyl)amino)-8-(1-propionylpiperidin-3-yl)pyrido[2,3-d]pyrimidin-7(8H)-one

[1059] 

[1060] 合成方法如实施例18,产率73.4%。

[1061] ^{1}H NMR(400MHz,DMSO-d6)δ10.11(s,1H),9.28(d,J=12.4Hz,1H),8.83(s,1H),

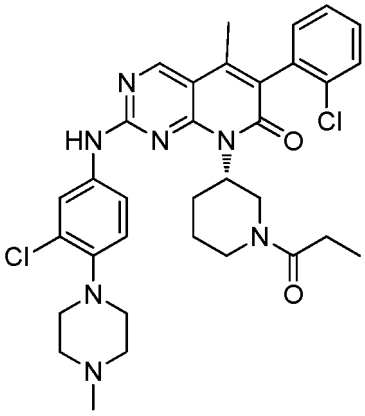
7.62-7.49(m,1H),7.40(dq,J＝7.1,3.9,3.1Hz,2H),7.35-7.21(m,2H),7.13(td,J＝7.8,1.7Hz,1H),7.02-6.72(m,3H),5.03-3.44(m,2H),3.12(s,4H),2.33(s,2H),2.26(d,J＝4.8Hz,4H),2.15(d,J＝3.4Hz,3H),2.12-2.05(m,4H),2.04-1.87(m,1H),1.86-1.28(m,4H),1.05-0.77(m,4H).

[1062] MS(ESI)m/z 614.4$[M+H]^+$。

[1063] 实施例106

[1064] (S)-2-((3-氯-4-(4-甲基哌嗪-1-基)苯基)氨基)-6-(2-氯苯基)-5-甲基-8-(1-丙哌啶-3-基)吡啶并[2,3-d]嘧啶-7(8H)-酮(12401B)

[1065] (S)-2-((3-chloro-4-(4-methylpiperazin-1-yl)phenyl)amino)-6-(2-chlorophenyl)-5-methyl-8-(1-propionylpiperidin-3-yl)pyrido[2,3-d]pyrimidin-7(8H)-one(12401B)

[1066] 

[1067] 合成方法如实施例18,产率76.7%。

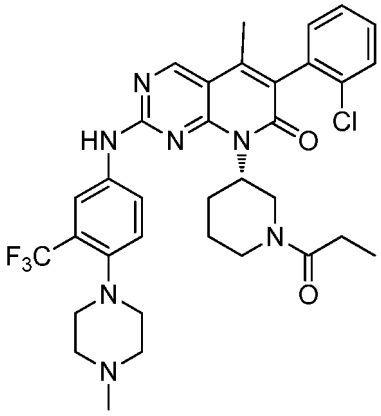
[1068] ^{1}H NMR(400MHz,DMSO-d6)δ10.15(d,J＝28.8Hz,1H),8.96(d,J＝3.4Hz,1H),7.90(d,J＝36.5Hz,1H),7.68-7.38(m,4H),7.38-7.26(m,1H),7.11(s,1H),5.44(d,J＝96.5Hz,1H),4.61-3.56(m,2H),3.30(t,J＝7.0Hz,4H),2.94(s,4H),2.69(s,3H),2.35(d,J＝20.5Hz,2H),2.26(d,J＝3.0Hz,3H),2.21-2.09(m,5H),2.01-1.43(m,7H),0.92(dt,J＝61.2,7.8Hz,4H).

[1069] MS(ESI)m/z 634.4$[M+H]^+$。

[1070] 实施例107

[1071] (S)-6-(2-氯苯基)-5-甲基-2-((4-(4-甲基哌嗪-1-基)-3-(三氟甲基)苯基)氨基)-8-(1-丙哌啶-3-基)吡啶并[2,3-d]嘧啶-7(8H)-酮(12601B)

[1072] (S)-6-(2-chlorophenyl)-5-methyl-2-((4-(4-methylpiperazin-1-yl)-3-(trifluoromethyl)phenyl)amino)-8-(1-propionylpiperidin-3-yl)pyrido[2,3-d]pyrimidin-7(8H)-one

[1073] 

[1074] 合成方法如实施例18,产率86.7%。

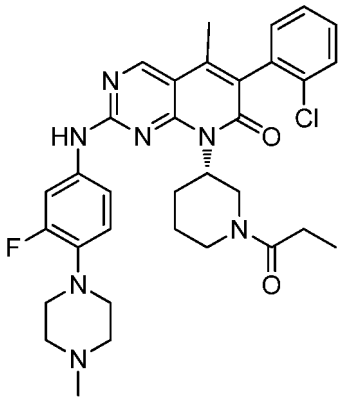
[1075] ^{1}H NMR(400MHz,DMSO-d6)δ10.26(s,1H),8.97(d,J=6.7Hz,1H),8.02-7.91(m,1H),7.67-7.58(m,3H),7.54(ddd,J=8.7,4.9,2.2Hz,3H),7.46-7.37(m,2H),7.33-7.25(m,1H),5.35(s,1H),4.44(d,J=13.0Hz,1H),4.21-3.51(m,2H),2.83(q,J=4.7Hz,4H),2.42(d,J=27.8Hz,4H),2.23(d,J=2.1Hz,3H),2.15(t,J=2.8Hz,3H),1.78(d,J=24.5Hz,2H),1.56-1.39(m,1H),1.02(t,J=7.4Hz,2H),0.90-0.72(m,2H).

[1076] MS(ESI)m/z 668.3[M+H]$^+$。

[1077] 实施例108

[1078] (S)-6-(2-氯苯基)-2-((3-氟-4-(4-甲基哌嗪-1-基)苯基)氨基)-5-甲基-8-(1-丙哌啶-3-基)吡啶并[2,3-d]嘧啶-7(8H)-酮(12701B)

[1079] (S)-6-(2-chlorophenyl)-2-((3-fluoro-4-(4-methylpiperazin-1-yl)phenyl)amino)-5-methyl-8-(1-propionylpiperidin-3-yl)pyrido[2,3-d]pyrimidin-7(8H)-one

[1080] 

[1081] 合成方法如实施例18,产率63.7%。

[1082] ^{1}H NMR(400MHz,DMSO-d6)δ10.12(s,1H),8.94(d,J=5.2Hz,1H),7.77-7.51(m,2H),7.50-7.20(m,4H),7.09-6.87(m,1H),5.35(s,1H),4.58-4.29(m,1H),4.14-3.59(m,2H),3.10-2.88(m,4H),2.78-2.59(m,1H),2.47(s,3H),2.42-2.28(m,2H),2.22(s,3H),2.14(d,J=2.8Hz,3H),2.09-1.32(m,4H),0.92(dt,J=63.4,7.8Hz,4H).

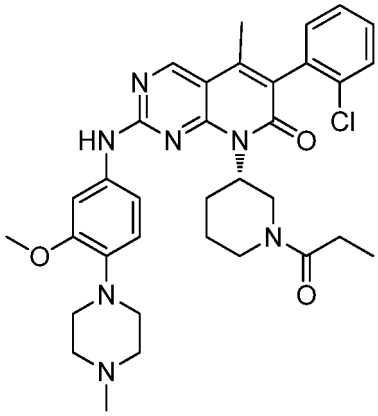
[1083] MS(ESI)m/z 618.3[M+H]$^+$。

[1084] 实施例109

[1085] (S)-6-(2-氯苯基)-2-((3-甲氧基-4-(4-甲基哌嗪-1-基)苯基)氨基)-5-甲基-8-(1-丙哌啶-3-基)吡啶并[2,3-d]嘧啶-7(8H)-酮(12801B)

[1086] (S)-6-(2-chlorophenyl)-2-((3-methoxy-4-(4-methylpiperazin-1-yl)

phenyl)amino)-5-methyl-8-(1-propionylpiperidin-3-yl)pyrido[2,3-d]pyrimidin-7(8H)-one

[1087] 

[1088] 合成方法如实施例18,产率84%。

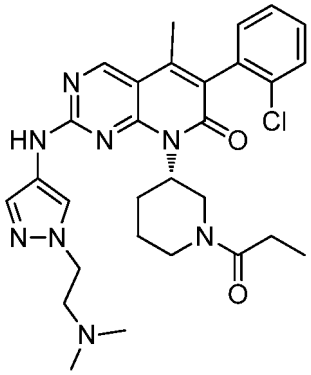
[1089] 1H NMR(400MHz,DMSO-d6)δ9.92(s,1H),8.91(s,1H),7.55(d,J=6.3Hz,1H),7.41(d,J=6.8Hz,3H),7.36-6.67(m,4H),5.39(s,1H),4.16(d,J=210.3Hz,2H),3.58(s,1H),3.36(s,3H),2.93(s,4H),2.80-2.58(m,1H),2.38(s,2H),2.23(s,3H),2.13(s,3H),1.59(d,J=116.5Hz,5H),1.10-0.67(m,4H).

[1090] MS(ESI)m/z 630.3$[M+H]^+$。

[1091] 实施例110

[1092] (S)-6-(2-氯苯基)-2-((1-(2-(二甲基氨基)乙基)-1H-吡唑-4-基)氨基)-5-甲基-8-(1-丙哌啶-3-基)吡啶并[2,3-d]嘧啶-7(8H)-酮(12901B)

[1093] (S)-6-(2-chlorophenyl)-2-((1-(2-(dimethylamino)ethyl)-1H-pyrazol-4-yl)amino)-5-methyl-8-(1-propionylpiperidin-3-yl)pyrido[2,3-d]pyrimidin-7(8H)-one

[1094] 

[1095] 合成方法如实施例18,产率68%。

[1096] ^{1}H NMR(400MHz,DMSO-d6)δ10.15(s,1H),8.90(d,J=5.8Hz,1H),8.15-7.98(m,1H),7.86(q,J=15.6,11.6Hz,2H),7.77-7.50(m,3H),5.41(s,1H),4.34(d,J=26.9Hz,3H),3.80(s,2H),3.15(s,2H),2.56(s,3H),2.39(s,3H),2.19-2.09(m,3H),1.79(d,J=46.8Hz,3H),1.48(s,2H),1.02(d,J=10.0Hz,3H),0.83(s,2H).

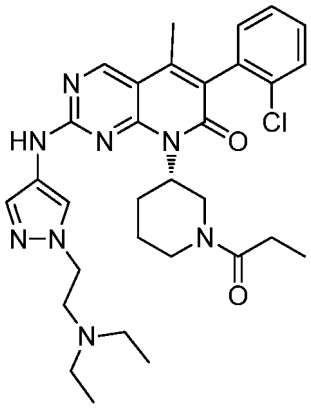
[1097] MS(ESI)m/z 563.1$[M+H]^+$。

[1098] 实施例111

[1099] (S)-6-(2-氯苯基)-2-((1-(2-(二乙氨基)乙基)-1H-吡唑-4-基)氨基)-5-甲基-

8-(1-丙哌啶-3-基)吡啶并[2,3-d]嘧啶-7(8H)-酮(13001B)

[1100] (S)-6-(2-chlorophenyl)-2-((1-(2-(diethylamino)ethyl)-1H-pyrazol-4-yl)amino)-5-methyl-8-(1-propionylpiperidin-3-yl)pyrido[2,3-d]pyrimidin-7(8H)-one

[1101] 

[1102] 合成方法如实施例18,产率56.7%。

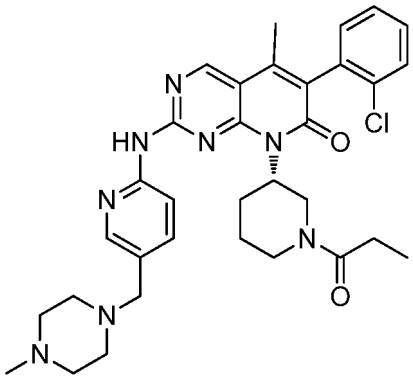
[1103] ^{1}H NMR(400MHz,DMSO-d6)δ9.97(d,J=104.5Hz,1H),8.89(t,J=7.5Hz,1H),8.31(s,1H),7.68-7.50(m,2H),7.29(dp,J=28.8,8.5,7.3Hz,4H),5.39(s,1H),4.60-4.29(m,1H),4.26-3.99(m,3H),3.99-3.61(m,2H),2.77(d,J=45.7Hz,3H),2.33(d,J=40.3Hz,2H),2.13(s,4H),1.92-1.41(m,4H),0.99(d,J=34.2Hz,10H).

[1104] MS(ESI)m/z 590.2[M+H]$^+$。

[1105] 实施例112

[1106] (S)-6-(2-氯苯基)-5-甲基-2-((5-((4-甲基哌嗪-1-基)甲基)吡啶-2-基)氨基)-8-(1-丙酰基哌啶)吡啶-3-基)吡啶并[2,3-d]嘧啶-7(8H)-酮(13201B)

[1107] (S)-6-(2-chlorophenyl)-5-methyl-2-((5-((4-methylpiperazin-1-yl)methyl)pyridin-2-yl)amino)-8-(1-propionylpiperidin-3-yl)pyrido[2,3-d]pyrimidin-7(8H)-one

[1108] 

[1109] 合成方法如实施例18,产率69%。

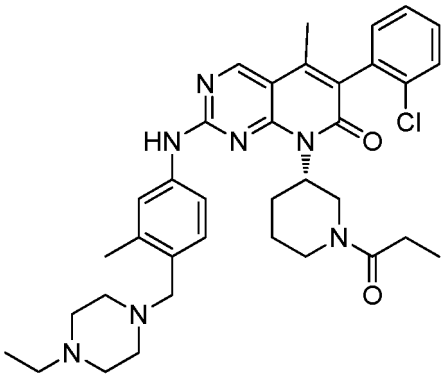
[1110] ^{1}H NMR(400MHz,DMSO-d6)δ10.51(s,1H),9.08-8.94(m,1H),8.23(s,1H),8.05(t,J=9.8Hz,1H),7.73-7.53(m,2H),7.43(dt,J=6.6,1.8Hz,2H),7.29(q,J=5.2,4.0Hz,1H),5.33(d,J=4.9Hz,1H),4.54-4.35(m,1H),3.84(d,J=39.7Hz,1H),3.45(s,2H),2.77-2.61(m,1H),2.47-2.25(m,7H),2.25-2.10(m,6H),2.04-1.66(m,4H),1.55-1.31(m,2H),1.05(s,2H),0.86(q,J=7.1,6.3Hz,3H).

[1111] MS(ESI)m/z 615.7[M+H]$^+$。

[1112] 实施例113

[1113] (S)-6-(2-氯苯基)-2-((4-((4-乙基哌嗪-1-基)甲基)-3-甲基苯基)氨基)-5-甲基-8-(1-丙哌啶-3-基)吡啶并[2,3-d]嘧啶-7(8H)-酮(13301B)

[1114] (S)-6-(2-chlorophenyl)-2-((4-((4-ethylpiperazin-1-yl)methyl)-3-methylphenyl)amino)-5-methyl-8-(1-propionylpiperidin-3-yl)pyrido[2,3-d]pyrimidin-7(8H)-one

[1115] 

[1116] 合成方法如实施例18,产率58%。

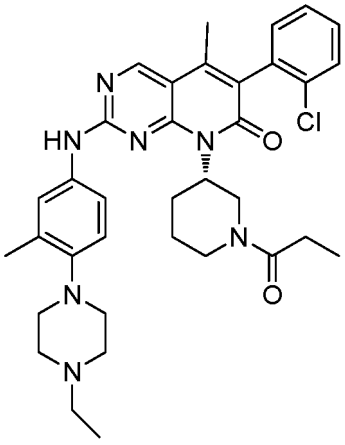
[1117] ^{1}H NMR(400MHz,DMSO-d6)δ10.06(s,1H),8.93(d,J=4.7Hz,1H),7.59-7.52(m,1H),7.46-7.37(m,3H),7.37-7.22(m,2H),7.17-7.02(m,1H),5.41(s,1H),4.40(d,J=32.8Hz,1H),4.18-3.43(m,3H),3.09-2.56(m,2H),2.47-2.21(m,13H),2.14(t,J=2.9Hz,4H),1.94-1.34(m,4H),1.01(dt,J=24.8,7.0Hz,5H),0.82(s,2H).

[1118] MS(ESI)m/z 642.4[M+H]$^+$。

[1119] 实施例114

[1120] (S)-6-(2-氯苯基)-2-((4-(4-乙基哌嗪-1-基)-3-甲基苯基)氨基)-5-甲基-8-(1-丙哌啶-3-基)吡啶并[2,3-d]嘧啶-7(8H)-酮(14101B)

[1121] (S)-6-(2-chlorophenyl)-2-((4-(4-ethylpiperazin-1-yl)-3-methylphenyl)amino)-5-methyl-8-(1-propionylpiperidin-3-yl)pyrido[2,3-d]pyrimidin-7(8H)-one

[1122] 

[1123] 合成方法如实施例18,产率64%。

[1124] ^{1}H NMR(400MHz,DMSO-d6)δ9.98(s,1H),8.91(d,J=4.2Hz,1H),7.61-7.37(m,5H),7.29(dtd,J=12.6,7.2,6.2,3.5Hz,1H),7.03-6.90(m,1H),5.47(d,J=48.1Hz,1H),4.51-3.60(m,2H),2.81(t,J=5.0Hz,5H),2.54(s,3H),2.41(s,4H),2.21(d,J=2.9Hz,

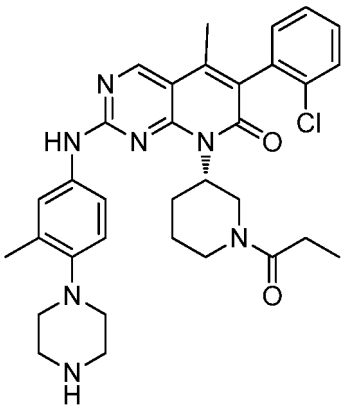
4H),2.13(t,J=2.7Hz,3H),1.92-1.32(m,4H),1.04(td,J=7.2,2.6Hz,5H),0.90-0.70(m,2H).

[1125] MS(ESI)m/z 628.3[M+H]$^+$。

[1126] 实施例115

[1127] (S)-6-(2-氯苯基)-5-甲基-2-((3-甲基-4-(哌嗪-1-基)苯基)氨基)-8-(1-丙哌啶-3-基)吡啶并[2,3-d]嘧啶-7(8H)-酮(14201B)

[1128] (S)-6-(2-chlorophenyl)-5-methyl-2-((3-methyl-4-(piperazin-1-yl)phenyl)amino)-8-(1-propionylpiperidin-3-yl)pyrido[2,3-d]pyrimidin-7(8H)-one

[1129] 

[1130] 合成方法如实施例18,产率86%。

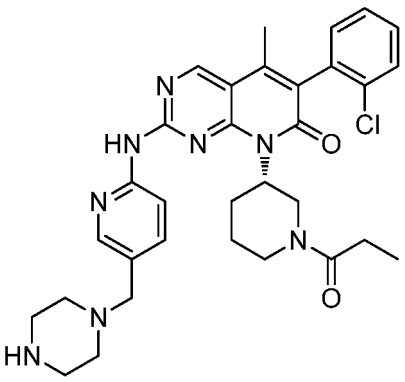
[1131] ^{1}H NMR(400MHz,Chloroform-d)δ8.69(d,J=11.3Hz,1H),7.54-7.46(m,1H),7.34(dq,J=8.5,5.1,3.2Hz,2H),7.22(q,J=5.4Hz,1H),6.87(dd,J=14.3,8.3Hz,1H),6.60(d,J=2.9Hz,1H),6.52(dd,J=8.5,2.6Hz,1H),5.43(d,J=34.5Hz,1H),4.65(dd,J=23.9,12.6Hz,1H),4.33(s,1H),4.02(s,3H),3.80(dd,J=34.7,13.4Hz,2H),3.50(s,2H),2.90(t,J=5.0Hz,5H),2.53(t,J=12.8Hz,1H),2.37(t,J=7.2Hz,2H),2.31(s,3H),2.16(d,J=7.4Hz,3H),1.84(d,J=12.3Hz,2H),1.14(t,J=7.5Hz,3H).

[1132] MS(ESI)m/z 600.3[M+H]$^+$。

[1133] 实施例116

[1134] (S)-6-(2-氯苯基)-5-甲基-2-((5-(哌嗪-1-基甲基)吡啶-2-基)氨基)-8-(1-丙哌啶-3-基)吡啶并[2,3-d]嘧啶-7(8H)-酮(14401B)

[1135] (S)-6-(2-chlorophenyl)-5-methyl-2-((5-(piperazin-1-ylmethyl)pyridin-2-yl)amino)-8-(1-propionylpiperidin-3-yl)pyrido[2,3-d]pyrimidin-7(8H)-one

[1136] 

[1137] 合成方法如实施例18,产率87%。

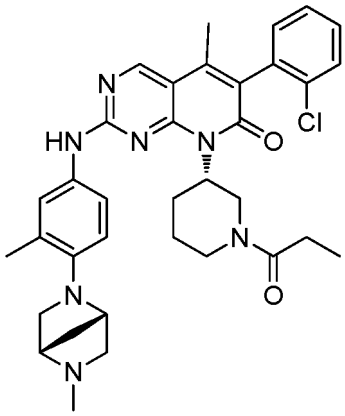
[1138] ^{1}H NMR(400MHz,DMSO-d6)δ10.52(s,1H),9.00(d,J＝3.6Hz,1H),8.24(d,J＝2.7Hz,1H),8.05(dt,J＝9.0,4.6Hz,1H),7.72-7.52(m,2H),7.42(td,J＝7.0,5.9,4.0Hz,2H),7.35-7.21(m,1H),5.32(d,J＝5.0Hz,1H),4.14(dd,J＝243.6,25.0Hz,4H),3.01(s,1H),2.88-2.75(m,4H),2.49-2.32(m,6H),2.31-2.19(m,1H),2.18-2.12(m,3H),2.07-1.65(m,3H),1.50-1.38(m,1H),1.12-0.97(m,2H),0.95-0.77(m,2H).

[1139] MS(ESI)m/z 601.2[M+H]$^+$。

[1140] 实施例117

[1141] 6-(2-氯苯基)-5-甲基-2-((3-甲基-4-((1S,4S)-5-甲基-2,5-二氮杂双环[2.2.1]庚-2-基)苯基)氨基)-8-((S)-1-丙酰基哌啶-3-基)吡啶并[2,3-d]嘧啶-7(8H)-酮(14601B)

[1142] 6-(2-chlorophenyl)-5-methyl-2-((3-methyl-4-((1S,4S)-5-methyl-2,5-diazabicyclo[2.2.1]heptan-2-yl)phenyl)amino)-8-((S)-1-propionylpiperidin-3-yl)pyrido[2,3-d]pyrimidin-7(8H)-one

[1143] 

[1144] 合成方法如实施例18,产率84.3%。

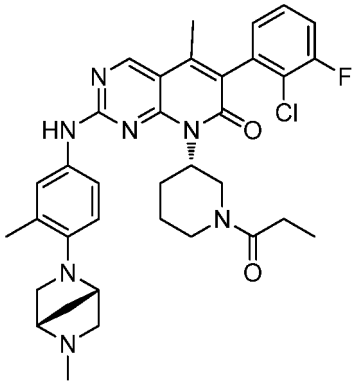
[1145] ^{1}H NMR(400MHz,DMSO-d6)δ9.72(d,J＝110.7Hz,1H),8.88(d,J＝4.3Hz,1H),7.59-7.51(m,1H),7.48-7.21(m,5H),6.73(d,J＝8.9Hz,1H),5.61-5.22(m,1H),4.42(s,1H),3.85(d,J＝72.6Hz,3H),3.38(d,J＝7.0Hz,2H),3.27-3.15(m,2H),2.75(h,J＝9.6,8.4Hz,3H),2.31(d,J＝5.3Hz,4H),2.18(d,J＝2.3Hz,3H),2.13(t,J＝2.7Hz,3H),1.89-1.64(m,4H),1.43(q,J＝17.4,13.6Hz,1H),1.00(t,J＝7.4Hz,2H),0.85(t,J＝5.7Hz,2H).

[1146] MS(ESI)m/z 626.6[M+H]$^+$。

[1147] 实施例118

[1148] 6-(2-氯-3-氟苯基)-5-甲基-2-((3-甲基-4-((1S,4S)-5-甲基-2,5-二氮杂双环[2.2.1]庚-2-基)苯基)氨基)-8-((S)-1-丙酰基哌啶-3-基)吡啶并[2,3-d]嘧啶-7(8H)-酮(14602B)

[1149] 6-(2-chloro-3-fluorophenyl)-5-methyl-2-((3-methyl-4-((1S,4S)-5-methyl-2,5-diazabicyclo[2.2.1]heptan-2-yl)phenyl)amino)-8-((S)-1-propionylpiperidin-3-yl)pyrido[2,3-d]pyrimidin-7(8H)-one

[1150] 

[1151] 合成方法如实施例18,产率76%。

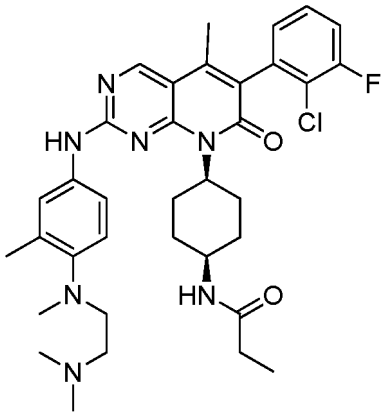
[1152] ^{1}H NMR(400MHz,DMSO-d6)δ9.91(s,1H),8.90(d,J=3.6Hz,1H),7.51-7.24(m,4H),7.20-7.12(m,1H),6.73(d,J=9.1Hz,1H),5.58-5.32(m,1H),4.42(s,1H),3.85(d,J=72.4Hz,4H),3.37(s,1H),3.21(d,J=15.1Hz,2H),2.83-2.65(m,3H),2.30(d,J=5.6Hz,3H),2.18(d,J=2.6Hz,3H),2.14(t,J=2.7Hz,3H),2.04-1.95(m,1H),1.87-1.68(m,4H),1.45(s,1H),1.00(s,2H),0.88-0.80(m,2H).

[1153] MS(ESI)m/z 644.6[M+H]$^+$。

[1154] 实施例119

[1155] N-((1S,4S)-4-(6-(2-氯-3-氟苯基)-2-((4-((2-(二甲基氨基)乙基)(甲基)氨基)-3-甲基苯基)氨基基)-5-甲基-7-氧代吡啶并[2,3-d]嘧啶-8(7H-基)环己基)丙酰胺(20502B)

[1156] N-((1s,4s)-4-(6-(2-chloro-3-fluorophenyl)-2-((4-((2-(dimethylamino)ethyl)(methyl)amino)-3-methylphenyl)amino)-5-methyl-7-oxopyrido[2,3-d]pyrimidin-8(7H)-yl)cyclohexyl)propionamide

[1157] 

[1158] 合成方法如实施例18,产率77%。

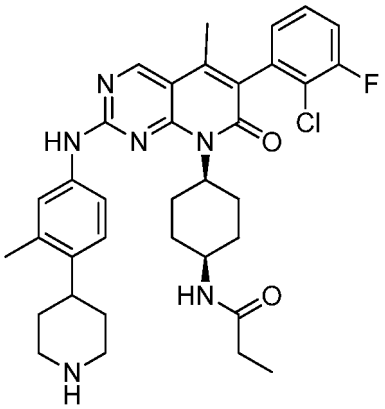
[1159] ^{1}H NMR(400MHz,DMSO-d6)δ9.93(s,1H),8.91(s,1H),7.64-7.54(m,2H),7.52-7.43(m,3H),7.15(dd,J=5.8,3.3Hz,1H),7.08(d,J=8.7Hz,1H),5.42(s,1H),3.85(s,1H),3.04-2.90(m,2H),2.88-2.70(m,2H),2.63(s,3H),2.36(q,J=7.7Hz,2H),2.28(s,3H),2.14(s,9H),2.07-1.84(m,3H),1.48(dd,J=43.5,12.4Hz,4H),0.97(t,J=7.6Hz,3H),0.90-0.75(m,1H).

[1160] MS(ESI)m/z 648.2[M+H]$^+$。

[1161] 实施例120

[1162] N-((1S,4S)-4-(6-(2-氯-3-氟苯基)-5-甲基-2-((3-甲基-4-(哌啶-4-基)苯基)氨基)-7-氧代吡啶并[2,3-d]嘧啶-8(7H)-基)环己基)丙酰胺(20902B)

[1163] N-((1s,4s)-4-(6-(2-chloro-3-fluorophenyl)-5-methyl-2-((3-methyl-4-(piperidin-4-yl)phenyl)amino)-7-oxopyrido[2,3-d]pyrimidin-8(7H)-yl)cyclohexyl)propionamide

[1164] 

[1165] 合成方法如实施例18,产率69%。

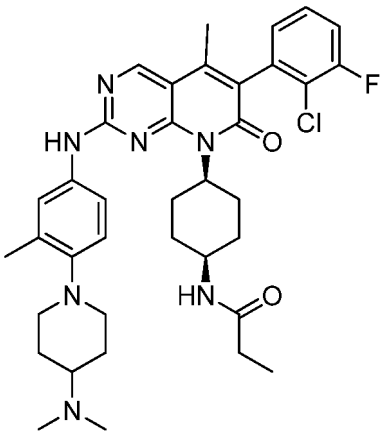
[1166] ^{1}H NMR(400MHz,DMSO-d6)δ10.02(s,1H),8.93(s,1H),8.65(d,J=11.2Hz,1H),8.37(d,J=11.7Hz,1H),7.64(dd,J=8.5,2.5Hz,2H),7.52(d,J=2.3Hz,1H),7.48-7.42(m,2H),7.19-7.10(m,2H),5.43(s,1H),3.86(d,J=4.9Hz,1H),3.39(d,J=12.2Hz,2H),3.14-2.98(m,3H),2.91-2.65(m,2H),2.36(s,3H),2.15(s,3H),2.12(d,J=7.6Hz,1H),1.99-1.75(m,6H),1.49(dd,J=39.1,12.8Hz,4H),0.97(t,J=7.6Hz,3H).

[1167] MS(ESI)m/z 631.2[M+H]$^+$。

[1168] 实施例121

[1169] N-((1S,4S)-4-(6-(2-氯-3-氟苯基)-2-((4-(4-(二甲基氨基)哌啶-1-基)-3-甲基苯基)氨基)-5-甲基-7-氧代吡啶并[2,3-d]嘧啶-8(7H)-基)环己基)丙酰胺(21102B)

[1170] N-((1s,4s)-4-(6-(2-chloro-3-fluorophenyl)-2-((4-(4-(dimethylamino)piperidin-1-yl)-3-methylphenyl)amino)-5-methyl-7-oxopyrido[2,3-d]pyrimidin-8(7H)-yl)cyclohexyl)propionamide

[1171] 

[1172] 合成方法如实施例18,产率71%。

[1173] ^{1}H NMR(400MHz,DMSO-d6)δ9.92(s,1H),8.90(s,1H),7.69-7.55(m,2H),7.52-7.38(m,3H),7.14(dd,J=5.8,3.4Hz,1H),7.00(d,J=8.7Hz,1H),5.43(d,J=8.3Hz,1H),

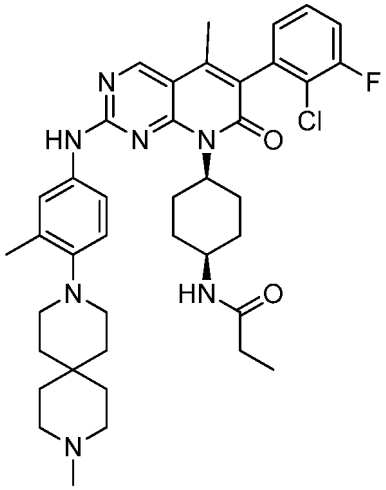
3.87(dt,J＝6.1,3.2Hz,1H),3.05(d,J＝11.0Hz,2H),2.79(dd,J＝28.6,13.4Hz,2H),2.64-2.53(m,2H),2.27(s,3H),2.23(s,6H),2.19(dd,J＝4.4,3.0Hz,1H),2.14(d,J＝3.2Hz,5H),1.97-1.88(m,2H),1.87-1.80(m,2H),1.54(qd,J＝11.7,3.7Hz,4H),1.47-1.38(m,2H),0.97(t,J＝7.6Hz,3H).

[1174] MS(ESI)m/z 675.2$[M+H]^+$。

[1175] 实施例122

[1176] N-((1S,4S)-4-(6-(2-氯-3-氟苯基)-5-甲基-2-((3-甲基-4-(9-甲基-3,9-二氮杂螺[5.5]十一烷-3-基)苯基)氨基)-7-氧代吡啶并[2,3-d]嘧啶-8(7H)-基)环己基)丙酰胺(21202B)

[1177] N-((1s,4s)-4-(6-(2-chloro-3-fluorophenyl)-5-methyl-2-((3-methyl-4-(9-methyl-3,9-diazaspiro[5.5]undecan-3-yl)phenyl)amino)-7-oxopyrido[2,3-d]pyrimidin-8(7H)-yl)cyclohexyl)propionamide

[1178] 

[1179] 合成方法如实施例18,产率65%。

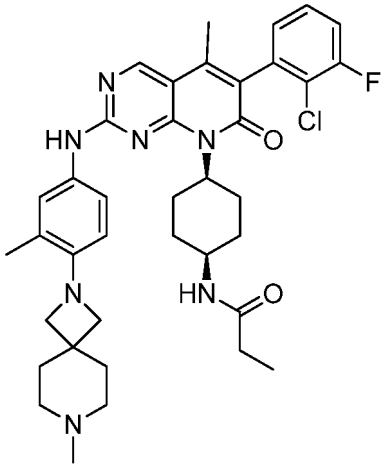
[1180] 1H NMR(400MHz,DMSO-d6)δ10.13(s,1H),8.94(s,1H),8.06(d,J＝2.5Hz,1H),7.64-7.55(m,1H),7.51-7.41(m,3H),7.19(d,J＝8.8Hz,1H),7.17-7.12(m,1H),5.42(t,J＝10.0Hz,1H),3.86(dt,J＝6.2,3.1Hz,1H),3.21(dq,J＝6.0,3.9,2.8Hz,4H),2.84-2.63(m,6H),2.32(s,3H),2.14(d,J＝9.3Hz,5H),1.95-1.85(m,4H),1.76-1.57(m,2H),1.49-1.37(m,2H),0.97(t,J＝7.6Hz,3H).

[1181] MS(ESI)m/z 714.5$[M+H]^+$。

[1182] 实施例123

[1183] N-((1S,4S)-4-(6-(2-氯-3-氟苯基)-5-甲基-2-((3-甲基-4-(7-甲基-2,7-二氮杂螺[3.5]壬烷-2-基)苯基)氨基)-7-氧代吡啶并[2,3-d]嘧啶-8(7H)-基)环己基)丙酰胺(21302B)

[1184] N-((1s,4s)-4-(6-(2-chloro-3-fluorophenyl)-5-methyl-2-((3-methyl-4-(7-methyl-2,7-diazaspiro[3.5]nonan-2-yl)phenyl)amino)-7-oxopyrido[2,3-d]pyrimidin-8(7H)-yl)cyclohexyl)propionamide

[1185] 

[1186] 合成方法如实施例18,产率85%。

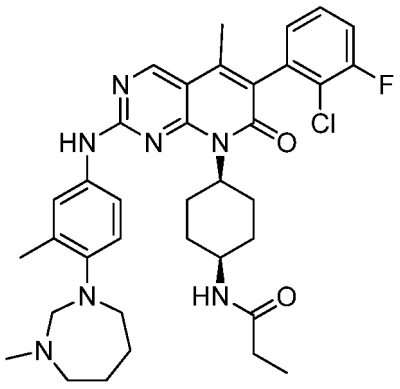
[1187] ^{1}H NMR(400MHz,DMSO-d6)δ9.77(s,1H),8.85(s,1H),7.62(s,1H),7.49-7.41(m,2H),7.41-7.34(m,2H),7.14(dd,J=5.8,3.3Hz,1H),6.60(d,J=9.3Hz,1H),5.42(s,1H),5.04(t,J=6.5Hz,1H),3.85(s,1H),3.61(q,J=9.3,8.5Hz,2H),3.47(dd,J=14.7,8.8Hz,4H),3.30(s,2H),3.14(s,3H),2.90-2.64(m,2H),2.14(d,J=12.9Hz,9H),1.90(s,2H),1.82(s,2H),1.52(d,J=14.9Hz,2H),1.41(d,J=12.2Hz,2H),0.97(t,J=7.6Hz,3H).

[1188] MS(ESI)m/z 686.3[M+H]$^+$。

[1189] 实施例124

[1190] N-((1S,4S)-4-(6-(2-氯-3-氟苯基)-5-甲基-2-((3-甲基-4-(3-甲基-1,3-二氮杂环庚-1-基)苯基)氨基)-7-氧代吡啶并[2,3-d]嘧啶-8(7H)-基)环己基)丙酰胺(21502B)

[1191] N-((1s,4s)-4-(6-(2-chloro-3-fluorophenyl)-5-methyl-2-((3-methyl-4-(3-methyl-1,3-diazepan-1-yl)phenyl)amino)-7-oxopyrido[2,3-d]pyrimidin-8(7H)-yl)cyclohexyl)propionamide

[1192] 

[1193] 合成方法如实施例18,产率83%。

[1194] ^{1}H NMR(400MHz,DMSO-d6)δ9.91(s,1H),8.91(s,1H),7.65-7.55(m,2H),7.51-7.41(m,3H),7.15(dd,J=5.8,3.3Hz,1H),7.06(d,J=8.7Hz,1H),5.42(s,1H),3.86(s,1H),3.16-3.04(m,4H),2.71(q,J=7.6,6.5Hz,6H),2.35(s,3H),2.29(s,3H),2.14(s,5H),1.87(p,J=5.9Hz,4H),1.61-1.49(m,2H),1.42(d,J=12.3Hz,2H),0.97(t,J=7.6Hz,3H).

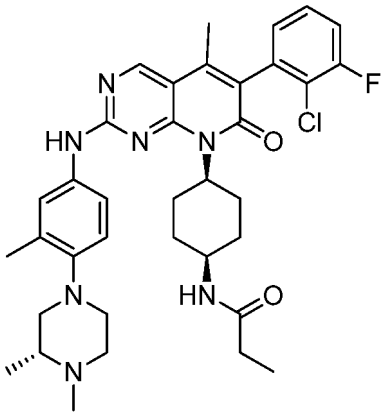
[1195] MS(ESI)m/z 660.3[M+H]$^+$。

[1196] 实施例125

[1197] N-((1S,4S)-4-(6-(2-氯-3-氟苯基)-2-((4-((R)-3,4-二甲基哌嗪-1-基)-3-甲

基苯基)氨基)-5-甲基-7-氧代吡啶并[2,3-d]嘧啶-8(7H)-基)环己基)丙酰胺(21702B)

[1198] N-((1s,4s)-4-(6-(2-chloro-3-fluorophenyl)-2-((4-((R)-3,4-dimethylpiperazin-1-yl)-3-methylphenyl)amino)-5-methyl-7-oxopyrido[2,3-d]pyrimidin-8(7H)-yl)cyclohexyl)propionamide

[1199] 

[1200] 合成方法如实施例18,产率82%。

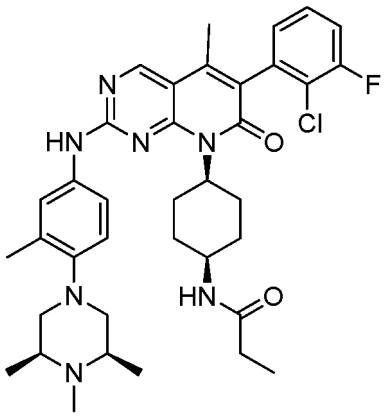
[1201] ^{1}H NMR(400MHz,DMSO-d6)δ9.93(s,1H),8.91(s,1H),7.60(d,J=2.8Hz,2H),7.53-7.42(m,3H),7.15(dd,J=5.8,3.4Hz,1H),7.01(d,J=8.7Hz,1H),5.42(s,1H),3.86(s,1H),2.94-2.69(m,6H),2.41(t,J=10.3Hz,1H),2.35-2.31(m,1H),2.28(s,3H),2.22(s,3H),2.14(s,5H),1.91(s,2H),1.42(d,J=12.1Hz,5H),1.02(d,J=6.1Hz,3H),0.97(t,J=7.6Hz,3H).

[1202] MS(ESI)m/z 660.3[M+H]$^+$。

[1203] 实施例126

[1204] N-((1S,4S)-4-(6-(2-氯-3-氟苯基)-5-甲基-2-((3-甲基-4-((3S,5R)-3,4,5-三甲基哌嗪-1-基)苯基)氨基)-7-氧代吡啶并[2,3-d]嘧啶-8(7H)-基)环己基)丙酰胺(21802B)

[1205] N-((1s,4s)-4-(6-(2-chloro-3-fluorophenyl)-5-methyl-2-((3-methyl-4-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)phenyl)amino)-7-oxopyrido[2,3-d]pyrimidin-8(7H)-yl)cyclohexyl)propionamide

[1206] 

[1207] 合成方法如实施例18,产率73%。

[1208] ^{1}H NMR(400MHz,DMSO-d6)δ9.91(s,1H),8.91(s,1H),7.60(d,J=2.6Hz,2H),7.47(ddd,J=15.8,7.9,2.8Hz,3H),7.15(t,J=4.6Hz,1H),6.98(d,J=8.6Hz,1H),5.42(s,

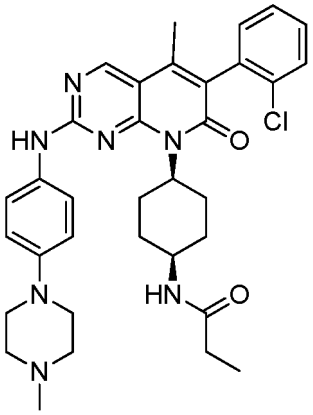
1H),3.87(s,1H),2.87(d,J＝10.8Hz,4H),2.43(t,J＝10.7Hz,2H),2.36-2.29(m,2H),2.28(s,3H),2.21(s,3H),2.14(s,5H),1.91(d,J＝9.5Hz,2H),1.63-1.49(m,2H),1.42(d,J＝12.2Hz,2H),1.04(d,J＝6.0Hz,6H),0.97(t,J＝7.6Hz,3H).

[1209] MS(ESI)m/z 674.3$[M+H]^+$。

[1210] 实施例127

[1211] N-((1S,4S)-4-(6-(2-氯苯基)-5-甲基-2-((4-(4-甲基哌嗪-1-基)苯基)氨基)-7-氧代吡啶并[2,13-d]嘧啶-8(7H)-基)环己基)丙酰胺(22201B)

[1212] N-((1s,4s)-4-(6-(2-chlorophenyl)-5-methyl-2-((4-(4-methylpiperazin-1-yl)phenyl)amino)-7-oxopyrido[2,3-d]pyrimidin-8(7H)-yl)cyclohexyl)propionamide

[1213] 

[1214] 合成方法如实施例18,产率81%。

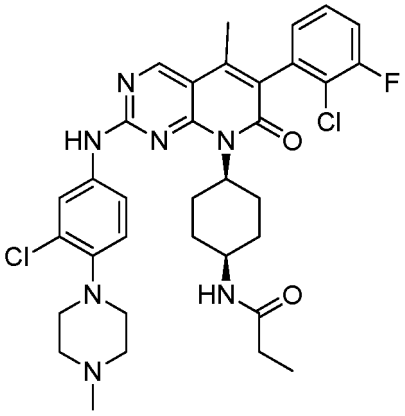
[1215] ^1H NMR(400MHz,DMSO-d6)δ9.87(s,1H),8.87(s,1H),7.68-7.51(m,4H),7.48-7.37(m,2H),7.32-7.24(m,1H),6.99-6.89(m,2H),5.36(d,J＝36.2Hz,1H),3.89(p,J＝3.0Hz,1H),3.10(t,J＝4.9Hz,4H),2.93-2.66(m,2H),2.47(t,J＝4.9Hz,4H),2.23(s,3H),2.18-2.13(m,2H),2.12(s,3H),1.96-1.85(m,2H),1.62-1.48(m,2H),1.43(d,J＝11.2Hz,2H),0.98(t,J＝7.6Hz,3H).

[1216] MS(ESI)m/z 614.2$[M+H]^+$。

[1217] 实施例128

[1218] N-((1S,4S)-4-(6-(2-氯-3-氟苯基)-2-((3-氯-4-(4-甲基哌嗪-1-基)苯基)氨基)-5-甲基-7-氧代吡啶并[2,3-d]嘧啶-8(7H)-基)环己基)丙酰胺(22402B)

[1219] N-((1s,4s)-4-(6-(2-chloro-3-fluorophenyl)-2-((3-chloro-4-(4-methylpiperazin-1-yl)phenyl)amino)-5-methyl-7-oxopyrido[2,3-d]pyrimidin-8(7H)-yl)cyclohexyl)propionamid

[1220] 

[1221] 合成方法如实施例18,产率79%。

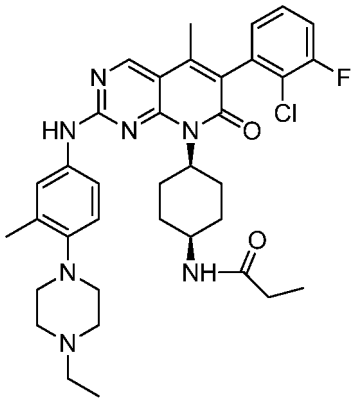
[1222] ^{1}H NMR(400MHz,DMSO-d6)δ10.18(s,1H),8.96(s,1H),8.10(d,J=2.5Hz,1H),7.60(d,J=5.1Hz,1H),7.55-7.40(m,3H),7.24-7.10(m,2H),5.54-5.29(m,1H),2.96(s,4H),2.80(s,3H),2.25(s,3H),2.16(s,3H),2.12(t,J=7.6Hz,2H),1.94(d,J=25.0Hz,3H),1.65(s,3H),1.45(s,3H),0.97(t,J=7.5Hz,3H),0.85(t,J=6.6Hz,1H).

[1223] MS(ESI)m/z 666.8[M+H]$^+$。

[1224] 实施例129

[1225] N-((1S,4S)-4-(6-(2-氯-3-氟苯基)-2-((4-(4-乙基哌嗪-1-基)-3-甲基苯基)氨基)-5-甲基-7-氧代吡啶并[2,3-d]嘧啶-8(7H)-基)环己基)丙酰胺(24102B)

[1226] N-((1s,4s)-4-(6-(2-chloro-3-fluorophenyl)-2-((4-(4-ethylpiperazin-1-yl)-3-methylphenyl)amino)-5-methyl-7-oxopyrido[2,3-d]pyrimidin-8(7H)-yl)cyclohexyl)propionamide

[1227] 

[1228] 合成方法如实施例18,产率77%。

[1229] ^{1}H NMR(400MHz,DMSO-d6)δ9.92(s,1H),8.91(s,1H),7.59(d,J=2.6Hz,2H),7.50(dd,J=8.6,2.6Hz,1H),7.48-7.42(m,2H),7.20-7.12(m,1H),7.03(d,J=8.7Hz,1H),5.42(s,1H),3.86(s,1H),2.83(t,J=4.8Hz,6H),2.53(s,3H),2.40(d,J=7.6Hz,2H),2.28(s,3H),2.14(s,5H),1.91(s,2H),1.48(dd,J=49.7,11.7Hz,5H),1.04(t,J=7.2Hz,3H),0.97(t,J=7.6Hz,3H).

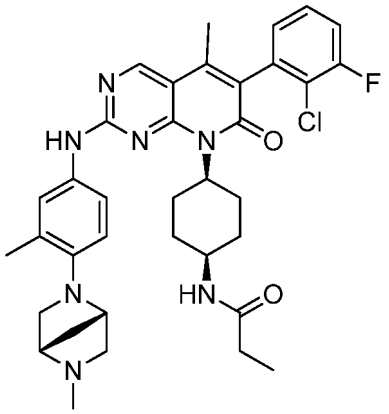
[1230] MS(ESI)m/z 660.3[M+H]$^+$。

[1231] 实施例130

[1232] N-((1S,4S)-4-(6-(2-氯-3-氟苯基)-5-甲基-2-((3-甲基-4-((1S,4S)-5-甲基-

2,5-二氮杂双环[2.2.1]庚-2-基)苯基)氨基)-7-氧代吡啶并[2,3-d]嘧啶-8(7H)-基)环己基)丙酰胺(24602B)

[1233] N-((1s,4s)-4-(6-(2-chloro-3-fluorophenyl)-5-methyl-2-((3-methyl-4-((1S,4S)-5-methyl-2,5-diazabicyclo[2.2.1]heptan-2-yl)phenyl)amino)-7-oxopyrido[2,3-d]pyrimidin-8(7H)-yl)cyclohexyl)propionamide

[1234] 

[1235] 合成方法如实施例18,产率82%。

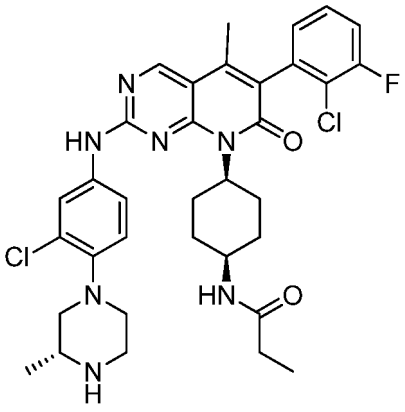
[1236] ^{1}H NMR(400MHz,DMSO-d6)δ9.85(s,1H),8.88(s,1H),7.59(s,1H),7.49-7.41(m,3H),7.37(dt,J=8.7,2.5Hz,1H),7.19-7.11(m,1H),6.76(d,J=8.8Hz,1H),5.42(s,1H),3.90(d,J=43.2Hz,2H),3.29-3.19(m,2H),2.91-2.61(m,4H),2.29(s,3H),2.24(s,3H),2.13(s,5H),1.89(s,2H),1.84-1.66(m,2H),1.53(d,J=14.7Hz,2H),1.41(d,J=12.4Hz,2H),0.97(t,J=7.6Hz,3H).

[1237] MS(ESI)m/z 658.4[M+H]$^+$。

[1238] 实施例131

[1239] N-((1S,4S)-4-(6-(2-氯-3-氟苯基)-2-((3-氯-4-((R)-3-甲基哌嗪-1-基)苯基)氨基)-5-甲基-7-氧代吡啶并[2,3-d]嘧啶-8(7H)-基)环己基)丙酰胺(24802B)

[1240] N-((1s,4s)-4-(6-(2-chloro-3-fluorophenyl)-2-((3-chloro-4-((R)-3-methylpiperazin-1-yl)phenyl)amino)-5-methyl-7-oxopyrido[2,3-d]pyrimidin-8(7H)-yl)cyclohexyl)propionamide

[1241] 

[1242] 合成方法如实施例18,产率75%。

[1243] ^{1}H NMR(400MHz,DMSO-d6)δ10.15(s,1H),8.96(s,1H),8.09(d,J=2.4Hz,1H),7.59(d,J=5.8Hz,1H),7.54-7.39(m,3H),7.26-7.09(m,2H),5.42(s,1H),3.97-3.76(m,

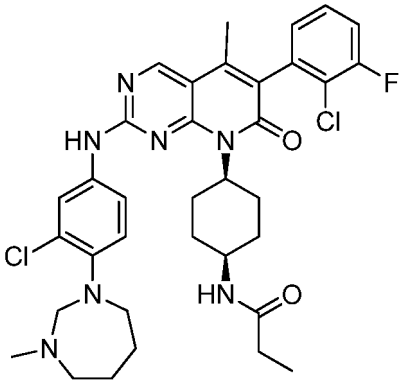
1H),3.13-3.02(m,2H),2.99-2.65(m,5H),2.59(td,J＝10.8,3.1Hz,1H),2.28(t,J＝10.3Hz,1H),2.15(s,3H),2.12(t,J＝7.6Hz,2H),1.91(s,2H),1.74-1.58(m,2H),1.49-1.38(m,2H),1.02-0.94(m,6H).

[1244] MS(ESI)m/z 666.8[M+H]$^+$。

[1245] 实施例132

[1246] N-((1S,4S)-4-(6-(2-氯-3-氟苯基)-2-((3-氯-4-(3-甲基-1,3-二氮杂环庚-1-基)苯基)氨基)-5-甲基-7-氧代吡啶并[2,3-d]嘧啶-8(7H)-基)环己基)丙酰胺(24902B)

[1247] N-((1s,4s)-4-(6-(2-chloro-3-fluorophenyl)-2-((3-chloro-4-(3-methyl-1,3-diazepan-1-yl)phenyl)amino)-5-methyl-7-oxopyrido[2,3-d]pyrimidin-8(7H)-yl)cyclohexyl)propionamide

[1248] 

[1249] 合成方法如实施例18,产率67%

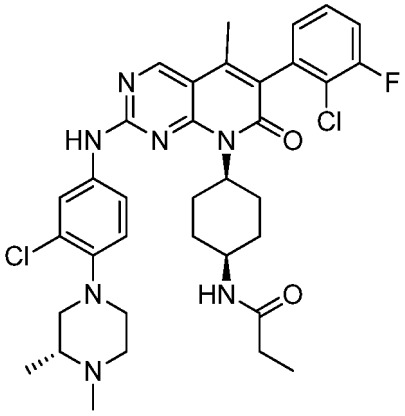
[1250] ^{1}H NMR(400MHz,DMSO-d6)δ10.13(s,1H),8.94(s,1H),8.06(d,J＝2.5Hz,1H),7.64-7.55(m,1H),7.51-7.41(m,3H),7.19(d,J＝8.8Hz,1H),7.17-7.12(m,1H),5.42(t,J＝10.0Hz,1H),3.86(dt,J＝6.2,3.1Hz,1H),3.21(dq,J＝6.0,3.9,2.8Hz,4H),2.84-2.63(m,6H),2.32(s,3H),2.14(d,J＝9.3Hz,5H),1.95-1.85(m,4H),1.76-1.57(m,2H),1.49-1.37(m,2H),0.97(t,J＝7.6Hz,3H).

[1251] MS(ESI)m/z 680.6[M+H]$^+$。

[1252] 实施例133

[1253] N-((1S,4S)-4-(6-(2-氯-3-氟苯基)-2-((3-氯-4-((R)-3,4-二甲基哌嗪-1-基)苯基)氨基)-5-甲基-7-氧代吡啶并[2,3-d]嘧啶-8(7H)-基)环己基)丙酰胺(25002B)

[1254] N-((1s,4s)-4-(6-(2-chloro-3-fluorophenyl)-2-((3-chloro-4-((R)-3,4-dimethylpiperazin-1-yl)phenyl)amino)-5-methyl-7-oxopyrido[2,3-d]pyrimidin-8(7H)-yl)cyclohexyl)propionamide

[1255] 

[1256] 合成方法如实施例18,产率74%。

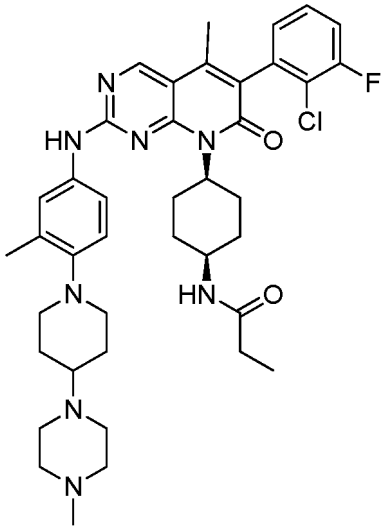
[1257] ^{1}H NMR(400MHz,DMSO-d6)δ10.10(d,J=32.1Hz,0H),8.95(s,1H),8.15-8.01(m,1H),7.60(d,J=5.8Hz,1H),7.52-7.41(m,3H),7.19-7.10(m,2H),5.42(s,1H),3.86(s,1H),3.09(ddt,J=21.3,11.0,2.6Hz,3H),2.87-2.73(m,4H),2.45(t,J=10.2Hz,1H),2.33(td,J=11.6,2.9Hz,1H),2.22(s,4H),2.15(s,3H),2.12(t,J=7.5Hz,2H),1.89(s,2H),1.65(s,2H),1.43(d,J=12.4Hz,2H),1.02(d,J=6.2Hz,3H),0.97(t,J=7.6Hz,3H).

[1258] MS(ESI)m/z 680.6[M+H]$^+$。

[1259] 实施例134

[1260] N-((1S,4S)-4-(6-(2-氯-3-氟苯基)-5-甲基-2-((3-甲基-4-(4-(4-甲基哌嗪-1-基)哌啶-1-基)苯基)氨基)-7-氧代吡啶并[2,3-d]嘧啶-8(7H)-基)环己基)丙酰胺(25102B)

[1261] N-((1s,4s)-4-(6-(2-chloro-3-fluorophenyl)-5-methyl-2-((3-methyl-4-(4-(4-methylpiperazin-1-yl)piperidin-1-yl)phenyl)amino)-7-oxopyrido[2,3-d]pyrimidin-8(7H)-yl)cyclohexyl)propionamide

[1262] 

[1263] 合成方法如实施例18,产率86%。

[1264] ^{1}H NMR(400MHz,DMSO-d6)δ9.92(s,1H),8.91(s,1H),7.59(t,J=3.9Hz,2H),7.52-7.41(m,3H),7.18-7.12(m,1H),7.01(d,J=8.7Hz,1H),5.42(s,1H),3.86(s,1H),3.06(d,J=11.3Hz,2H),2.78(d,J=27.5Hz,2H),2.59(t,J=11.5Hz,5H),2.37(d,J=37.3Hz,4H),2.27(s,3H),2.22(s,3H),2.14(s,5H),1.98-1.79(m,5H),1.62-1.51(m,4H),

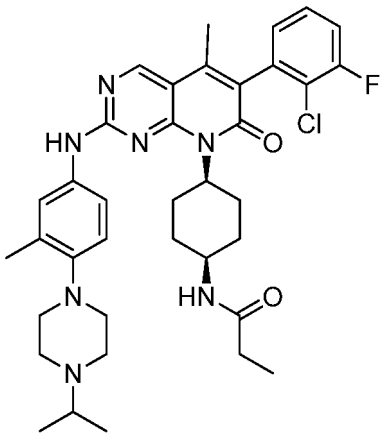
1.42(d,J＝12.3Hz,3H),0.97(t,J＝7.6Hz,3H).

[1265] MS(ESI)m/z 729.6[M+H]$^+$。

[1266] 实施例135

[1267] N-((1S,4S)-4-(6-(2-氯-3-氟苯基)-2-((4-(4-异丙基哌嗪-1-基)-3-甲基苯基)氨基)-5-甲基-7-氧代吡啶并[2,3-d]嘧啶-8(7H)-基)环己基)丙酰胺(25202B)

[1268] N-((1s,4s)-4-(6-(2-chloro-3-fluorophenyl)-2-((4-(4-isopropylpiperazin-1-yl)-3-methylphenyl)amino)-5-methyl-7-oxopyrido[2,3-d]pyrimidin-8(7H)-yl)cyclohexyl)propionamide

[1269] 

[1270] 合成方法如实施例18,产率67%。

[1271] ^{1}H NMR(400MHz,DMSO-d6)δ9.92(s,1H),8.90(s,1H),7.66-7.52(m,2H),7.50(dd,J＝8.6,2.6Hz,1H),7.49-7.39(m,2H),7.19-7.09(m,1H),7.02(d,J＝8.7Hz,1H),5.42(s,1H),3.87(dt,J＝6.5,3.1Hz,1H),2.90-2.55(m,11H),2.28(s,3H),2.14(s,5H),1.91(t,J＝10.6Hz,2H),1.55(h,J＝10.6,10.0Hz,2H),1.47-1.38(m,2H),1.01(d,J＝6.5Hz,6H),0.97(t,J＝7.6Hz,3H).

[1272] MS(ESI)m/z 674.3[M+H]$^+$。

[1273] 实施例136

[1274] 化合物对EGFR野生型,EGFR-L858R/T790M,EGFR-L858R/T790M/C797S突变的激酶EC_{50}测试

[1275] EGFR(WT)为野生型表皮生长因子受体,EGFR(T790M)为带有第790位氨基酸由苏氨酸突变成甲硫氨酸的表皮生长因子受体,EGFR(L858R)为带有第858位氨基酸由亮氨酸突变成精氨酸的表皮生长因子受体,EGFR(L861Q)为带有第861位氨基酸由亮氨酸突变成谷氨酰胺的表皮生长因子受体,EGFR(L858R/T790M)为带有第858位氨基酸由亮氨酸突变成谷氨酰胺,第790位氨基酸由苏氨酸突变成甲硫氨酸双突变的表皮生长因子受体。EGFR(L858R/T790M/C797S)为带有第858位氨基酸由亮氨酸突变成谷氨酰胺,第790位氨基酸由苏氨酸突变成甲硫氨酸,第797位由半胱氨酸突变为丝氨酸的三突变的表皮生长因子受体。

[1276] 激酶活性检测:应用Z′-LYTE^{TM}技术(采用荧光进行检测、酶偶联形式,以磷酸化和非磷酸化多肽对蛋白水解切割的敏感性差异为基础),采用荧光共振能量转移(FRET)原理,使用Z′LYTE^{T}M FRET肽类底物,二级反应检测化合物的激酶活性。(invitrogen,Z′-LYTE^{TM} KINASE ASSAY KIT-TYR 2 PEPTIDE,PV3191)将EGFR-T790M激酶(invitrogen,PV4803)逐级稀释后加入FRET肽,ATP,再加入不同浓度的化合物,反应1h后,加入位点特异性蛋白酶,识

别并切割非磷酸化的FRET肽，反应1h，使用400nm激发波长，检测445nm及520nm吸收。

[1277] 化合物的抑制率% = $\frac{\text{阴性对照组 OD 值平均值-加化合物组 OD 值平均值}}{\text{阴性对照组 OD 值平均值}} \times 100\%$

[1278] IC_{50}值通过抑制曲线以四参数拟合计算。

[1279] 得出抑制率与药物浓度成正相关，做出激酶活性与浓度关系曲线，计算IC_{50}值。

[1280] 表1中所列为化合物编号以及对应激酶活性结果。

[1281] 表1化合物激酶抑制活性

Compd	IC_{50} (nM)		
	$EGFR^{WT}$	$EGFR^{L858R/T790M}$	$EGFR^{L858R/T790M/C797S}$
560123	12.3	2305	
560069	36.8±12.7	98.5±1.5	315.3±84.3
560080	3.8±2.1	9.3±1.1	38.1±10.1
560081	6.9±2.2	7.2±2.1	47.8±17.6
560105	27.7	4803	
560107	9.6	96.5	
560109	264.2±9.8	51.5±36.7	65.4±12.1
560110	29.1	1869	
560121	6.11	652.1	
560122	5.4	629.7	
560124	24.3	4282	
570026	41.8±9.1	217.2±85.4	215.7±87.8
570027	75.3±19.0	191.3±76.1	413.8±171.1
570051	36.9±16.7	274.2±41.9	87.0±16.4

[1282]

	570052	53.3±17.6	328.0±96.6	61.5±21.8
	570060	190.8±55.2	164.3±13.2	295.0±86.5
	570061	248.1±78.4	372.2±165.7	650.5±231.3
	560083	146.5±9.8	197.8±28.9	218.0±60.1
	560070	366.9±120.6	80.0±4.9	313.1±7.9
	560082	180.9±80.8	64.8±22.6	519.9±83.4
	560132	483.5±138.7	504.9±46.9	215.2±38.8
	560133	1343	＞10μM	
	560134	708.2	8459	
	560135	434.6	5397	
	560136	764.2	＞10μM	
	560138	1115	＞10μM	
	560140	10500	＞10μM	
	560145	4127	＞10μM	
	560150	＞10μM	7939	
	570008	542.5±184.3	538.0±178.4	108.2±31.9
[1283]	**570012**	>1000	588.6±98.4	>1000
	570056	>1000	186.2±74.1	68.7±11.7
	570057	>1000	112.8±13.2	57.4±24.3
	570063	>1000	>1000	>1000
	570064	>1000	418.8±37.6	>1000
	570089	322.6±159.5	55.1±13.9	1150.3±32.6
	570104	705.4±277.3	281.8±83.2	274.5±33.3
	570105	280.5±39.5	119.7±28.4	866.9±146.4
	570111	965.8±47.9	1345.6±43.5	2426.4±17.3
	570112	872.8±426.0	3021.0±1010.5	2900.8±561.4
	570118	1082.1±118.7	1555.8±22.1	2048.2±120.8
	570119	867.1±175.0	1196.1±196.2	1621.5±378.1
	570144	>1000	499.1±122.6	695.4±63.1
	570145	>1000	334.8±59.0	688.9±176.1
	570149	>1000	>1000	>1000
	570150	>1000	>1000	>1000
	570157	>1000	631.4±185.3	195.7±81.6
	570158	>1000	306.8±37.5	481.2±91.9

	580011	>1000	>1000	>1000
	580013	>1000	>1000	>1000
	580014	>1000	>1000	>1000
	580018	>1000	>1000	>1000
	580019	>1000	>1000	>1000
	580023	>1000	>1000	>1000
	580024	>1000	>1000	>1000
	580043	>1000	53.0±32.2	50.5±19.0
	580044	>1000	83.2±2.5	18.2±4.7
	580053	>1000	>1000	>1000
	580054	>1000	>1000	>1000
	580058	>1000	>1000	>1000
	580061	>1000	>1000	>1000
	580067	>1000	>1000	>1000
	580068	>1000	>1000	>1000
	580073	>1000	>1000	>1000
	580074	>1000	>1000	>1000
[1284]	**580082**	>1000	>1000	487.1±246.5
	580097	>1000	>1000	>1000
	580098	>1000	>1000	>1000
	580112	>1000	>1000	>1000
	580113	>1000	>1000	>1000
	580120	>1000	155.6±21.5	27.5±11.6
	580123	>1000	>1000	200.9±64.7
	580124	>1000	>1000	64.0±23.8
	580145	509.5±181.4	19.4±2.5	23.9±5.9
	580146	381.4±142.5	21.9±1.1	14.6±5.5
	580152	149.7±25.3	4.8±0.7	3.5±2.5
	590011	133.4±21.4	62.8±9.6	57.8±31.7
	590024	65.1±28.0	9.8±3.3	22.9±8.2
	590030	186.9±50.0	20.8±12.0	40.6±8.4
	590031	261.7±61.4	38.1±5.1	58.0±27.8
	590034	262.8±96.3	24.2±5.0	46.8±22.7
	590037	179.8±24.4	6.8±2.6	16.1±6.4

	590039	286.1±55.2	7.7±2.0	39.7±19.3
	590040	174.8±51.5	8.0±0.9	35.2±10.3
	590041	317.2±124.6	8.7±0.7	29.7±8.4
	590047	214.5±92.4	4.4±1.3	15.3±5.3
	590048	203.4±80.2	3.2±1.1	8.9±2.2
	10201B	>1000	>1000	>1000
	10301B	>1000	>1000	>1000
	10401B	>1000	>1000	>1000
	10501B	>1000	>1000	246.2±111.3
	10801B	>1000	>1000	>1000
	10901B	>1000	255.0±89.6	235.2±124.1
	11001B	>1000	>1000	>1000
	11101B	>1000	338.7±115.6	>1000
	11201B	>1000	229.0±29.0	133.8±51.2
	11301B	>1000	>1000	110.4±23.6
	11401B	>1000	>1000	>1000
[1285]	**11501B**	>1000	79.5±9.5	89.4±34.2
	11601B	>1000	>1000	364.8±166.2
	11701B	>1000	>1000	68.7±22.4
	11801B	>1000	>1000	221.6±92.5
	12102B	>1000	>1000	>10>10000
	12201B	>1000	799.0±124.8	>1000
	12301B	>1000	>1000	>1000
	12401B	>1000	423.4±125.6	>1000
	12601B	>1000	>1000	>1000
	12701B	>1000	241.0±164.8	>1000
	12801B	>1000	>1000	>1000
	12901B	>1000	>1000	>1000
	13001B	>1000	>1000	>1000
	13201B	>1000	>1000	>1000
	13301B	>1000	696.2±286.1	539.2±302.2
	14101B	>1000	709.3±133.9	209.6±58.8
	14201B	>1000	>1000	>1000
	14401B	>1000	364.5±109.0	513.5±151.7

	14601B	>1000	116.1±25.5	146.5±60.5
	14602B	>1000	47.9±7.8	68.7±12.0
	20502B	180.7±71.9	6.6±2.2	23.5±10.4
	20902B	255.6±114.8	6.5±1.7	31.6±5.6
	21102B	133.5±43.8	6.5±1.7	12.6±5.0
	21202B	236.1±51.3	15.8±2.2	21.6±2.4
	21302B	182.7±88.4	5.6±0.7	24.5±8.2
	21502B	129.0±18.4	3.5±1.1	18.0±6.7
	21702B	240.3±85.2	22.0±11.3	20.9±8.6
[1286]	**21802B**	145.2±57.4	6.6±1.3	21.4±7.7
	22201B	88.4±25.1	39.5±16.9	28.4±9.8
	22402B	52.9±33.0	88.1±12.0	377.6±37.2
	24102B	97.8±4.6	16.2±2.7	38.6±21.0
	24602B	43.8±18.5	8.1±2.1	23.1±4.3
	24802B	234.1±69.9	40.3±6.9	60.5±13.6
	24902B	455.2±258.7	27.1±4.9	47.1±15.0
	25002B	305.6±29.0	30.3±10.6	77.7±14.2
	25102B	191.9±61.7	67.6±90.5	29.5±10.5
	25202B	149.1±27.8	12.9±2.3	43.2±11.3

[1287] 实施例137

[1288] 化合物对BaF3 EGFRL858R/T790M/C797S工具细胞细胞株的体外增殖抑制作用

[1289] 细胞株:BaF3 EGFRL858R/T790M/C797S工具细胞细胞株。

[1290] 方法:磺酰罗单明B(sulforhodamine B,SRB)法,具体如下:将一定数量处于对数生长期的不同肿瘤细胞接种于96孔培养板,培养24h细胞贴壁后,加入不同浓度的本发明的受试化合物,每个浓度设三复孔,并设定相应浓度的DMSO溶液对照及无细胞调零孔。用药物处理细胞72h后,倾去培养液,加入100μL冰预冷的10%的三氯乙酸溶液固定细胞,4℃放置1h后用蒸馏水洗涤5次,空气中自然干燥。然后加入100μL SRB(4mg/mL)(Sigma,St Louis,MO,USA)溶液,室温中染色15min,去染色液,用1%冰醋酸洗涤5次,空气干燥。最后加入150μL 10mM的Tris溶液(pH 10.5),可调波长式微孔板酶标仪(VERSAmax™,Molecular Device Corporation,Sunnyvale,CA,USA)在515nm波长下测定OD值。以下列公式计算药物对细胞生长的抑制率:抑制率(%)=(OD对照-OD加药)/OD对照×100%。

[1291] 根据化合物对这些细胞的生长抑制作用,我们计算出其半数抑制浓度(IC_{50})值如表2所描述。

[1292] 表2化合物细胞活性

[1293]

Compd	IC_{50} (μM)
	BaF3 EGFRL858R/T790M/C797S 工具细胞细胞株
560080	**<1 μM**
560081	**<1 μM**
570056	**<10μM**
570057	**<10μM**
580043	**<10μM**
580044	**<10μM**
580120	**<10μM**
580124	**<10μM**
11701B	**<10μM**

[1294] 结果发现(见表2),本发明的嘧啶并吡啶酮或者吡啶并嘧啶酮类化合物可显著抑制BaF3EGFRL858R/T790M/C797S细胞的增殖,抑制率与药物浓度成正相关。

[1295] 实施例138

[1296] 本发明的嘧啶并吡啶酮或者吡啶并吡啶酮类化合物对$EGFR^{L858R/T790M/C797S}$和$EGFR^{19D/T790M/C797S}$工具细胞中靶点的活化有显著抑制作用。

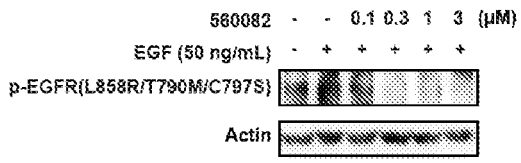
[1297] 使用常规Western Blot(免疫印迹法)进行检测,具体如下:分别将处于对数生长期的BaF3-$EGFR^{L858R/T790M/C797S}$细胞和BaF3-$EGFR^{19D/T790M/C797S}$细胞按一定数量种于6孔板,培养箱内贴壁培养过夜后,换无血清培养液饥饿24h,加入一定浓度的化合物作用2h,加入EGF刺激因子,50ng/mL作用10min,用裂解液裂解细胞收样。然后取适量样品进行SDS-PAGE电泳,电泳结束后用半干电转移系统将蛋白转移至硝酸纤维素膜,将硝酸纤维素膜置于封闭液(5%脱脂奶粉稀释于含0.1%Tween 20的TBS)中室温封闭2h,然后将膜分别置于一抗溶液(1:500稀释于含0.1%Tween 20的TBS)中4℃孵育过夜。用含0.1%Tween 20的TBS洗涤三次,每次15min。将膜置于二抗溶液(辣根过氧化物酶标记羊抗兔的IgG,1:2000稀释于含0.1%Tween 20的TBS)中室温反应1h。同上洗膜三次后,用ECL plus试剂发色,Image Quant LAS 4000拍照。结果如图1-图2所示。

[1298] 通过图1中的a图可以发现,化合物560082浓度依赖地抑制工具细胞中$EGFR^{L858R/T790M/C797S}$的磷酸化。通过图1中的b图可以发现,化合物560082浓度依赖地抑制工具细胞中$EGFR^{19D/T790M/C797S}$的磷酸化。

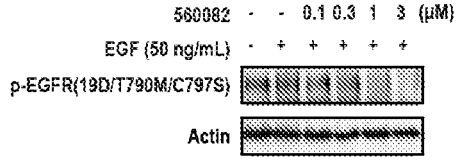
[1299] 通过图2中的a图可以发现,化合物580120浓度依赖地抑制工具细胞中$EGFR^{L858R/T790M/C797S}$的磷酸化通过图2中的b图可以发现,化合物580120浓度依赖地抑制工具细胞中$EGFR^{19D/T790M/C797S}$的磷酸化。

[1300] 以上所述实施例的各技术特征可以进行任意的组合,为使描述简洁,未对上述实施例中的各个技术特征所有可能的组合都进行描述,然而,只要这些技术特征的组合不存在矛盾,都应当认为是本说明书记载的范围。

[1301] 以上所述实施例仅表达了本发明的几种实施方式,其描述较为具体和详细,但并不能因此而理解为对发明专利范围的限制。应当指出的是,对于本领域的普通技术人员来说,在不脱离本发明构思的前提下,还可以做出若干变形和改进,这些都属于本发明的保护范围。因此,本发明专利的保护范围应以所附权利要求为准。

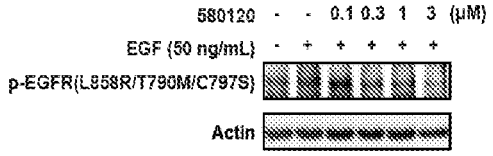

560082 - - 0.1 0.3 1 3 (μM)
EGF (50 ng/mL) - + + + + +
p-EGFR(L858R/T790M/C797S)
Actin

a

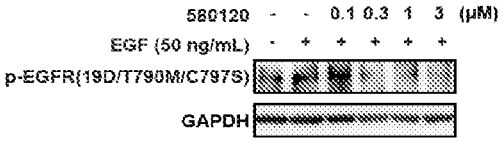

560082 - - 0.1 0.3 1 3 (μM)
EGF (50 ng/mL) - + + + + +
p-EGFR(19D/T790M/C797S)
Actin

b

图1


580120 - - 0.1 0.3 1 3 (μM)
EGF (50 ng/mL) - + + + + +
p-EGFR(L858R/T790M/C797S)
Actin

a


580120 - - 0.1 0.3 1 3 (μM)
EGF (50 ng/mL) - + + + + +
p-EGFR(19D/T790M/C797S)
GAPDH

b

图2