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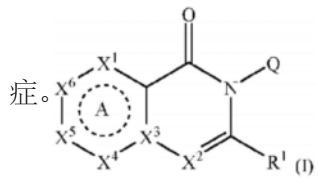
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审查员 祝智慧
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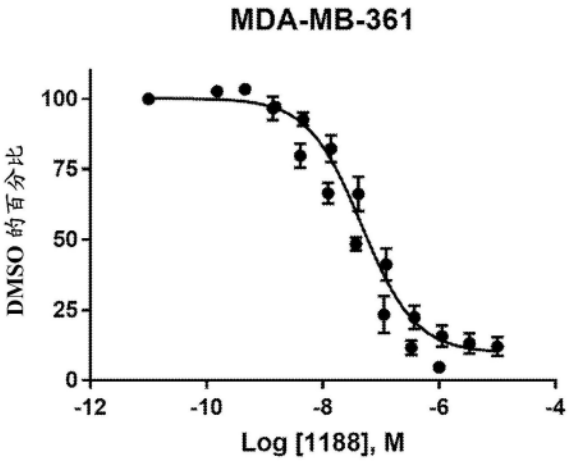
(54)发明名称

抑制EIF4E的4-氧代-3,4-二氢吡啶并[3,4-D]嘧啶化合物

(57)摘要

本发明提供了根据式I的化合物或其立体异构体,互变异构体或药学上可接受的盐的合成,药学上可接受的制剂和用途。对于式I化合物,X^1,X^2,X^3,X^4,X^5,X^6,Q,L^1,L^2,Y,R^1,R^2,R^3,R^4,R^5,R^6,R^7,R^8以及环A,B和C在说明书中定义。本发明的式I化合物是eIF4e的抑制剂并且可以用于许多治疗应用,包括但不限于治疗炎症和各种癌症。





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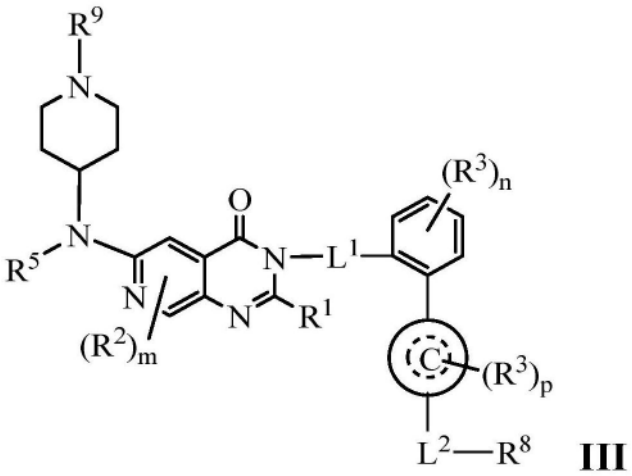
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Rajan S. Giri et al..Synthesis and evaluation of quinazolinone derivatives as inhibitors of NF-kB, AP-1 mediated transcription and eIF-4E mediated translational activation: Inhibitors of multi-pathways involve in cancer.《European Journal of Medicinal Chemistry》.2010,第45卷第3558-3563页.

Florian Ro¨rsch et al..Structure-Activity Relationship of Nonacidic Quinazolinone Inhibitors of Human Microsomal Prostaglandin Synthase 1 (mPGES 1).《J. Med. Chem.》.2012,第55卷第3792-3803页.

1.式III的化合物:



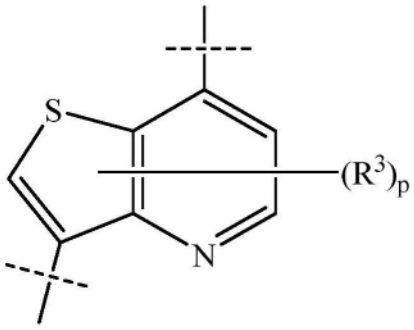
III

或其药学上可接受的盐,其中:

L^1为-(CH_2)-,-$(CH_2)_2$-,-$(CH_2)_3$-,-CH((C1-C8)烷基)(CH_2)-,-CH((C1-C8)烷基)$(CH_2)_2$-,-$(CH_2)_2$-O-,-CH_2CH=CH-,-CH_2C≡C-或-CH_2(环丙基)-;

L^2为-C$(R^6)$$(R^6)$-,-C$(R^6)$$(R^6)C(R^6)$$(R^6)$-,-C$(R^6)$=C$(R^6)$-,-N$(R^5)C(R^6)$$(R^6)$-,-OC$(R^6)$$(R^6)$-,-C(=O)-,-C(=O)N$(R^5)C(R^6)$$(R^6)$-或键;

环C为



;

R^1为H,OH,卤素,CN,$(C_1$-$C_8)$烷基,$(C_1$-$C_8)$卤代烷基,$(C_3$-$C_6)$环烷基或NR^5R^5;

R^2独立地为H,卤素,CN,$(C_1$-$C_8)$烷基,$(C_1$-$C_8)$卤代烷基或OR^5;

R^3独立地为OH,卤素,CN,NO_2,$(C_1$-$C_6)$烷基或$(C_1$-$C_6)$卤代烷基;

R^5独立地为H,$(C_1$-$C_3)$烷基,$(C_1$-$C_3)$卤代烷基或$(C_3$-$C_5)$环烷基;

R^6独立地为H,OH,卤素,CN,$(C_1$-$C_3)$烷基,$(C_1$-$C_3)$卤代烷基或$(C_1$-$C_3)$烷氧基;

R^7独立地为H,$(C_1$-$C_8)$烷基或$(C_1$-$C_8)$卤代烷基;

R^8为H,OH,CO_2H,CO_2R^7,CF_2C$(R^6)_2$OH,C$(R^6)_2$OH,C$(CF_3)_2$OH,SO_2H,SO_3H,CF_2SO_2C$(R^6)_3$,CF_2SO_2N(H)R^5,SO_2N(H)R^5,SO_2N(H)C(O)R^6,C(O)N(H)SO_2R^5,C(O)卤代烷基,C(O)N(H)OR^5,C(O)N(R^5)OH,C(O)N(H)R^5或C(O)NR^5C(O)N$(R^5)_2$;

R^9为H,$(C_1$-$C_8)$烷基,$(C_1$-$C_8)$卤代烷基或$(C_3$-$C_5)$环烷基;

m为0,1或2;

n为0,1,2或3;

p为0,1,2或3;

其中任何烷基,亚烷基或环烷基任选地被1,2或3个选自以下的基团取代:OH,CN,卤素,

(C_1-C_8)烷基,(C_1-C_8)卤代烷基,O(C_1-C_8)烷基,O(C_1-C_8)卤代烷基,亚烷基-C(O)NH_2或亚烷基-C(O)-NH(Me)。

2.权利要求1的化合物或盐,其中L^2为键。

3.权利要求1的化合物或盐,其中R^1为H,(C_1-C_8)烷基或(C_1-C_8)卤代烷基。

4.权利要求1的化合物或盐,其中R^2为卤素,CN,(C_1-C_8)烷基,(C_1-C_8)卤代烷基或OR^5。

5.权利要求1的化合物或盐,其中R^2为卤素,CN或(C_1-C_8)卤代烷基。

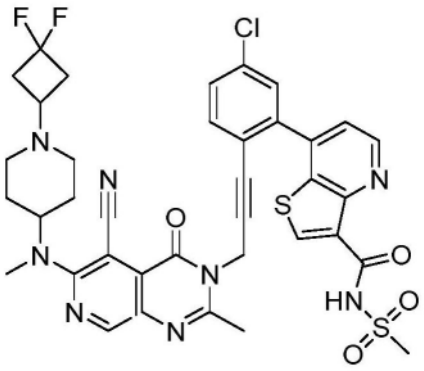
6.权利要求1的化合物或盐,其中R^5为H,(C_1-C_3)烷基或(C_1-C_3)卤代烷基。

7.权利要求1的化合物或盐,其中R^8为CO_2H或C(O)N(H)SO_2R^5。

8.权利要求1的化合物或盐,其中R^9为(C_3-C_5)环烷基。

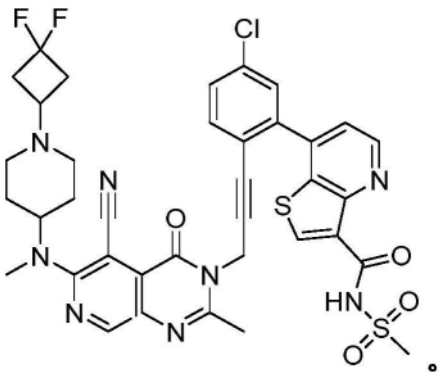
9.权利要求1的化合物或盐,其中p=0或1。

10.具有下式的化合物:



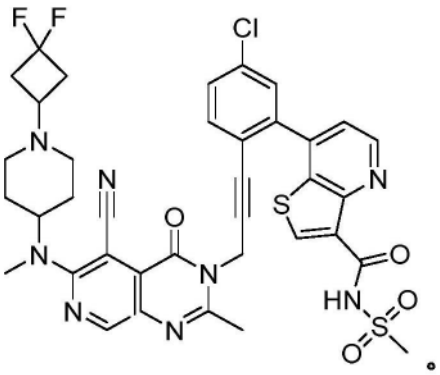
或其药学上可接受的盐。

11.具有下式的化合物:



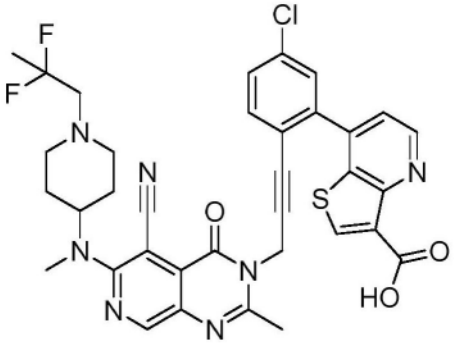
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12.具有下式的化合物的药学上可接受的盐:



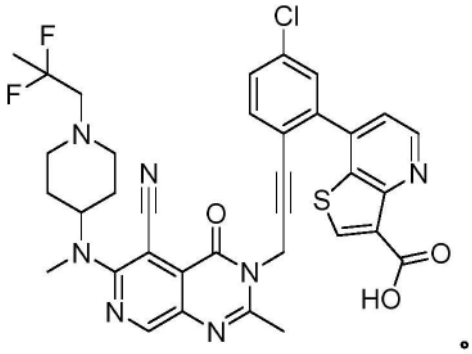
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13.具有下式的化合物：

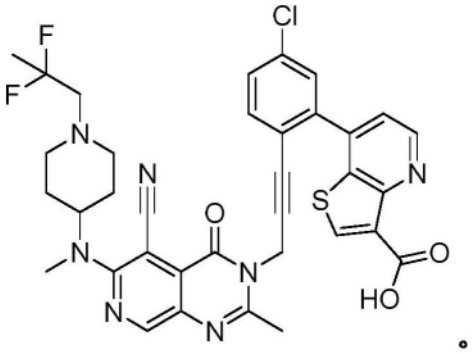


或其药学上可接受的盐。

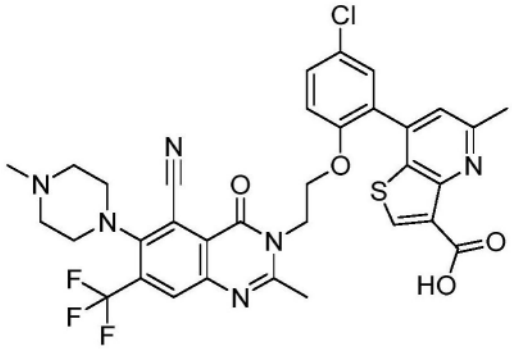
14.具有下式的化合物：



15.具有下式的化合物的药学上可接受的盐：

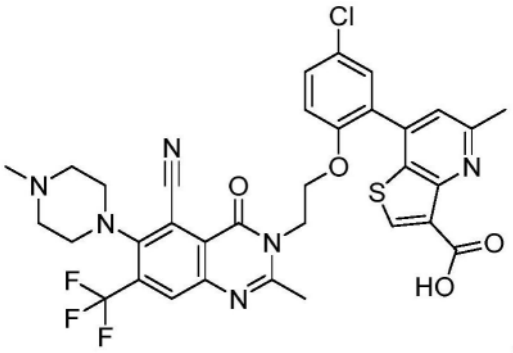


16.具有下式的化合物：

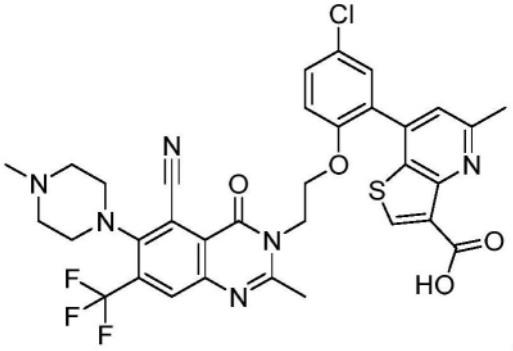


或其药学上可接受的盐。

17.具有下式的化合物：



18.具有下式的化合物的药学上可接受的盐：



19.药物组合物,包含：

(a)权利要求1-18中任一项的化合物或盐;和

(b)药学上可接受的载体,稀释剂或赋形剂。

20.权利要求1-18中任一项的化合物或盐在制备用于治疗癌症的药物中的用途。

21.权利要求20的用途,其中所述癌症是结肠癌,胃癌,甲状腺癌,肺癌,白血病,B细胞淋巴瘤,T细胞淋巴瘤,毛细胞淋巴瘤,霍奇金淋巴瘤,非霍奇金淋巴瘤,伯基特淋巴瘤,胰腺癌,黑色素瘤,脑癌,CNS癌,肾癌,前列腺癌,卵巢癌或乳腺癌。

22.权利要求21的用途,其中所述癌症是转移癌。

23.权利要求21的用途,其中所述癌症是乳腺癌,前列腺癌或肺癌。

24.权利要求23的用途,其中所述癌症是乳腺癌。

25.权利要求24的用途,其中所述乳腺癌是激素受体阳性乳腺癌。

抑制EIF4E的4-氧代-3,4-二氢吡啶并[3,4-D]嘧啶化合物

[0001] 领域

[0002] 本发明一般地涉及具有作为真核起始因子4e(eIF4e)的抑制剂的活性的化合物,以及利用本发明的化合物作为用于治疗eIF4e依赖性疾病(包括治疗癌症)的治疗剂的相关组合物和方法。

[0003] 背景

[0004] 真核起始因子4E(eIF4E)是一种通用翻译因子,但它具有优先增强信使RNA(mRNA)翻译的潜力,从而导致恶性肿瘤相关蛋白的产生。这种选择性可能与对eIF4E及其结合伴侣的需求增加有关,以翻译在其5'-非翻译区(5'-UTR)中包含大量二级结构的mRNA。这些mRNA包括那些编码控制细胞周期进程和肿瘤发生的特定蛋白质的mRNA。在正常细胞条件下,由于活性eIF4E的可用性受到限制,因此这些恶性肿瘤相关mRNA的翻译受到抑制;然而,当eIF4E过表达或过度激活时,其水平会增加。已经在许多类型的肿瘤和癌细胞系中发现了升高的eIF4E水平,包括结肠癌,乳腺癌,膀胱癌,肺癌,前列腺癌,胃肠道癌,头颈癌,霍奇金淋巴瘤和神经母细胞瘤。

[0005] 帽依赖性翻译的起始被认为依赖于eIF4F的组装,eIF4F是一种起始因子复合物,包括eIF4E,支架蛋白eIF4G和RNA解旋酶eIF4A。因为eIF4E是这些蛋白质中唯一一种直接与mRNA帽结构结合的蛋白质,所以它是eIF4F在5'帽处组装的关键因素。支架蛋白eIF4G还通过与eIF3的相互作用将40S核糖体亚基募集到mRNA并结合eIF4B(一种有助于eIF4A的RNA解旋酶功能的蛋白质),从而促进含有结构化5'-UTR的mRNA的翻译。作为eIF4F复合物的一部分的eIF4E的可用性是控制翻译速率的限制因素,因此eIF4E是mRNA翻译的重要调节剂。

[0006] eIF4E活性的调节形成了PI3K/Akt/mTOR和Ras/Raf/MAPK信号传导途径的汇聚节点。PI3K(磷酸肌醇3-激酶)/PTEN(10号染色体上缺失的磷酸酶和张力蛋白同源物)/Akt/mTOR(雷帕霉素的哺乳动物靶标)途径通常参与肿瘤发生以及对癌症治疗的敏感性和抗性。通过PI3K/PTEN/Akt/mTOR途径的信号传导失调通常是由于该途径关键组分的基因改变和/或上游生长因子受体或信号传导组分突变。当被例如细胞外生长因子,有丝分裂原,细胞因子和/或受体激活时,PI3K引发事件级联,PDK1激活Akt,其转而使包含TSC1和2的肿瘤抑制复合物(结节性硬化复合物1/2)磷酸化和失活,导致Rheb-GTP激活mTORC1(雷帕霉素复合物1的靶标)。PI3K对PDK1和Akt的激活受到PTEN的负调节。

[0007] PTEN是一种关键的肿瘤抑制基因,并且经常在人类癌症中发生突变或沉默。其缺失导致Akt激活并增加下游mTORC1信号传导。mTOR复合物1(mTORC1)参与肿瘤性转化似乎取决于其对eIF4F复合物的调节作用;eIF4E的过表达可以赋予对雷帕霉素的抗性。mTORC1调节eIF4F复合物组装,这对于与细胞生长,防止细胞凋亡和转化相关的mRNA的翻译至关重要。mTORC1通过4E-BP的磷酸化和失活以及随后4E-BP从eIF4E的解离来实现调节。然后,这使eIF4E能够与支架蛋白eIF4G相互作用,从而允许组装eIF4F复合物以翻译结构化mRNA。mTORC1还促进翻译激活剂S6K的激活,所述翻译激活剂S6K使核糖体蛋白S6和包括eIF4B在内的其他底物磷酸化。mTORC1信号传导被雷帕霉素及其类似物(rapalog)抑制,但这些化合物变构地起作用,而不是直接抑制mTOR激酶活性。

[0008] 鉴于PI3K/Akt/mTOR途径在高比例的癌症中调节编码原癌蛋白(pro-oncogenic protein)的基因的mRNA翻译和激活的mTORC1信号传导的重要性,已积极寻求这些激酶作为肿瘤药物靶标。已经确定了许多药理学抑制剂,其中一些已达到高级临床阶段。然而,最近才发现mTOR途径参与复杂的反馈回路,该回路会损害Akt的激活。已经表明,长期使用mTOR抑制剂治疗癌细胞或患者会引起PI3K活性升高,从而导致Akt和eIF4E的磷酸化,并促进癌细胞存活。在Akt和mTOR的下游作用的eIF4E重现Akt在肿瘤发生和耐药性中的作用,并且经由eIF4E的Akt信号传导是体内肿瘤发生和耐药性的重要机制。

[0009] 除了PI3K/Akt/mTOR途径以外,eIF4E也是Ras/Raf/MAP信号级联的靶标,所述Ras/Raf/MAP信号级联由生长因子激活且用于应激激活的p38MAP激酶途径。Erk1/2和p38然后使MAP激酶相互作用激酶1(Mnk1)和MAP激酶相互作用激酶2(Mnk2)磷酸化。Erk途径也在许多癌症中被激活,这反映了例如Ras中的激活突变(在大约20%的肿瘤中发现)或Ras GTP酶激活蛋白NF1功能丧失。Mnk1和Mnk2是苏氨酸/丝氨酸蛋白激酶,借助eIF4E和Mnk之间的相互作用,特异性磷酸化eIF4F复合物中eIF4E的丝氨酸209(Ser209),这有助于招募Mnk作用于eIF4E。具有其中Ser209被丙氨酸替代的突变eIF4E的小鼠没有显示出eIF4E磷酸化并且显示显著减弱的肿瘤生长。值得注意的是,虽然Mnk活性对于eIF4E介导的致癌性转化是必需的,但它对于正常发育是非必需的。因此,药理学抑制Mnk为癌症提供了一种有吸引力的治疗策略。

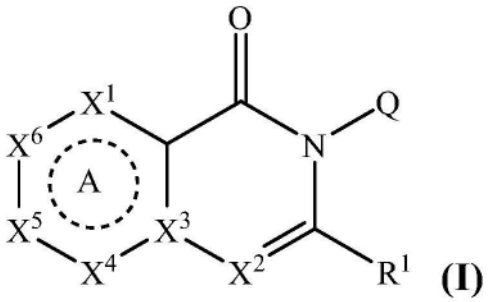
[0010] 尽管对Mnk结构和功能的了解有所增加,但在探索药理学Mnk抑制剂方面进展甚微,并且已报道相对较少的Mnk抑制剂:CGP052088(Tschopp等人,Mol Cell Biol Res Commun.3(4):205-211,2000);CGP57380(Rowlett等人,Am J Physiol Gastrointest Liver Physiol.294(2):G452-459,2008);和尾孢酰胺(Konicek等人,Cancer Res.71(5):1849-1857,2011)。然而,主要出于Mnk靶标验证的目的使用这些化合物。最近,研究人员已提出用于治疗受Mnk1和/或Mnk2的激酶活性的抑制影响的疾病的另外的化合物,包括例如国际专利申请公开案WO2014/044691和其中引用的各种专利文献中公开的化合物,Yu等人,European Journal of Med.Chem.,95:116-126,2015公开的4-(二氢吡啶酮-3-基)氨基-5-甲基噻吩并[2,3,-d]嘧啶,和国际专利申请公开案WO2015/200481中公开的6'-((6-氨基嘧啶-4-基)氨基)-8'-甲基-2'H-螺[环己烷-1,3'-咪唑并[1,5-a]吡啶]-1',5'-二酮和各种化合物。

[0011] 因此,尽管在该领域已经取得了进展,但本领域仍然非常需要特异性抑制eFI4E活性,特别是关于eIF4E在调节癌症途径中的作用的化合物,以及相关的组合物和方法。本发明满足了该需求并提供了另外的相关优点。

[0012] 概述

[0013] 本发明涉及抑制或调节eIF4E活性的化合物,以及这样的化合物的立体异构体,互变异构体和药学上可接受的盐。本发明还涉及包含这样的化合物的药学上可接受的组合物以及用于治疗将受益于eIF4E抑制的病症例如癌症的相关方法。

[0014] 在一个实施方案中,本发明涉及根据式I的化合物

[0015] 

(I)

[0016] 或其立体异构体,互变异构体或药学上可接受的盐,其中:

[0017] X^1为CR^2,-C-L^1-Y或N;

[0018] X^2,X^5和X^6独立地为CR^2或N,

[0019] 其中X^5和X^6与3或4个碳原子或氮原子一起组合形成5-或6-元环烷基或杂环基,

[0020] 或当X^2为CR^2时,R^1和R^2与它们所连接的原子一起形成6-元芳基或杂芳基;

[0021] X^3为C,或当X^4为键时,X^3为C或N;

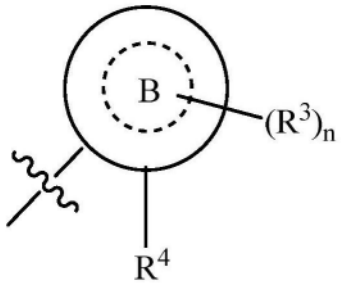
[0022] X^4为键,CR^2或N,

[0023] 其中X^4和X^5与3或4个碳原子或氮原子一起组合形成5-或6-元杂芳基;

[0024] Q为H或-L^1-Y;

[0025] L^1为-(CH_2)-,-$(CH_2)_2$-,-$(CH_2)_3$-,-CH((C_1-C_8)烷基)(CH_2)-,-CH((C_1-C_8)烷基)$(CH_2)_2$-,-$(CH_2)_2$-O-,-CH_2CH=CH-,-CH_2C≡C-或-CH_2(环丙基)-;

[0026] Y为

[0027]  其中

,

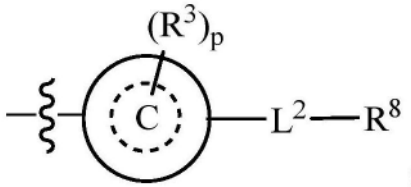
[0028] 环B为6-元芳基,杂芳基或杂环基;

[0029] R^1为H,OH,卤素,CN,(C_1-C_8)烷基,(C_1-C_8)卤代烷基,(C_3-C_6)环烷基或NR^5R^5;

[0030] R^2独立地为H,卤素,CN,NO,NO_2,C≡H,(C_1-C_8)烷基,(C_1-C_8)卤代烷基,CH_2SR^5,OR^5,NHR^5,NR^5R^5,[(C_1-C_8)亚烷基]杂环基,[(C_1-C_8)亚烷基]杂芳基,[(C_1-C_8)亚烷基]NHR^5,[(C_1-C_8)亚烷基]NR^5R^5,[(C_1-C_8)亚炔基(alkylyne)]NR^5R^5,C(O)R^5,C(O)OR^5,C(O)NHR^5,C(O)NR^5R^5,SR^5,S(O)R^5,SO_2R^5,SO_2NHR^5,$SO_2NR^5R^5$,NH(CO)R^6,NR^5(CO)R^6,芳基,杂芳基,环烷基或杂环基;

[0031] R^3独立地为OH,卤素,CN,NO_2,(C_1-C_6)烷基,(C_1-C_6)卤代烷基,(C_1-C_6)烷氧基,C≡H,NHR^7,NR^7R^7,CO_2H,CO_2R^7,[(C_1-C_3)亚烷基](C_1-C_3)烷氧基,[(C_1-C_3)亚烷基]CO_2H,(C_3-C_5)环烷基,=O,=S,SR^7,SO_2R^7,NH(CO)R^7或NR^7(CO)R^7;

[0032] R^4为H,OH,卤素,CN,(C_1-C_3)烷基,(C_1-C_3)卤代烷基,(C_1-C_3)烷氧基,SR^7或Z,其中Z为

[0033] 

[0034] 环C为环烷基,杂环基,芳基或杂芳基;

[0035] L^2为-C(R^6)(R^6)-,-C(R^6)(R^6)C(R^6)(R^6)-,-C(R^6)=C(R^6)-,-N(R^5)C(R^6)(R^6)-,-OC(R^6)(R^6)-,-C(=O)-,-C(=O)N(R^5)C(R^6)(R^6)-或键;

[0036] R^5独立地为H,(C_1-C_3)烷基,(C_1-C_3)卤代烷基,(C_3-C_5)环烷基,CO_2H,[(C_1-C_3)亚烷基]杂芳基,[(C_1-C_3)亚烷基]芳基,[(C_1-C_3)亚烷基]CO_2H,杂环基,芳基或杂芳基,

[0037] 或其中两个R^5取代基与氮原子一起形成4-,5-,6-或7-元杂环基;

[0038] R^6独立地为H,OH,卤素,CN,(C_1-C_3)烷基,(C_1-C_3)卤代烷基,(C_1-C_3)烷氧基,NHR^7,NR^7R^7,CO_2H,[(C_1-C_3)亚烷基]CO_2H,(C_3-C_5)环烷基,SR^7,NH(CO)R^7或NR^7(CO)R^7;

[0039] R^7独立地为H,(C_1-C_8)烷基,(C_1-C_8)卤代烷基,环烷基,杂环基,芳基或杂芳基;

[0040] R^8为H,OH,CO_2H,CO_2R^7,$CF_2C(R^6)_2OH$,$C(R^6)_2OH$,$C(CF_3)_2OH$,SO_2H,SO_3H,$CF_2SO_2C(R6)_3$,$CF_2SO_2N(H)R^5$,$SO_2N(H)R^5$,$SO_2N(H)C(O)R^6$,C(O)N(H)SO_2R^5,C(O)卤代烷基,C(O)N(H)OR^5,C(O)N(R^5)OH,C(O)N(H)R^5,C(O)NR^5C(O)N(R^5)$_2$,P(O)(OR^5)OH,P(O)(O)N(H)R^5,P(O)(C(R^6)$_3$)C(R^6)$_3$,B(OH)$_2$,杂环基或杂芳基;

[0041] n为0,1,2或3;

[0042] p为0,1,2或3;

[0043] 其中任何烷基,亚烷基,环烷基,杂环基,杂芳基或芳基任选地被1,2或3个选自以下的基团取代:OH,CN,SH,SCH_3,SO_2CH_3,SO_2NH_2,SO_2NH(C_1-C_4)烷基,卤素,NH_2,NH(C_1-C_4)烷基,N[(C_1-C_4)烷基]$_2$,NH(芳基),C(O)NH_2,C(O)NH(烷基),$CH_2C(O)NH$(烷基),COOH,COOMe,乙酰基,(C_1-C_8)烷基,(C_1-C_8)卤代烷基,O(C_1-C_8)烷基,O(C_1-C_8)卤代烷基,(C_2-C_8)烯基,(C_2-C_8)炔基,烷硫基(thioalkyl),氰基亚甲基,烷基氨基,亚烷基-C(O)NH_2,亚烷基-C(O)-NH(Me),NHC(O)烷基,CH_2-C(O)-(C_1-C_8)烷基,C(O)-(C_1-C_8)烷基和烷基羰基氨基,或任选地被OH,卤素,(C_1-C_8)烷基,(C_1-C_8)卤代烷基,O(C_1-C_8)烷基或O(C_1-C_8)卤代烷基取代的环烷基,杂环基,芳基或杂芳基,

[0044] 其中当X^4为键时,环A形成5-元杂芳基,其中X^1,X^5和X^6除了上文定义的取代基以外可以为NR^2,并且X^1可以另外为-N-L^1-Y;并且

[0045] 其中Q为-L^1-Y,或X^1为-C-L^1-Y或-N-L^1-Y。

[0046] 本发明还提供了药物组合物,其包含(i)治疗有效量的至少一种根据式I,式II,式III,式IV,式V或式VI的化合物或其立体异构体,互变异构体或药学上可接受的盐;(ii)与药学上可接受的载体,稀释剂或赋形剂组合。

[0047] 本发明还提供了用于减弱或抑制至少一种过表达eIF4E的细胞中的eIF4E活性的方法,所述方法包含使至少一种细胞与根据式I的化合物或其立体异构体,互变异构体或药学上可接受的盐接触。

[0048] 根据本发明的方法,至少一种细胞是结肠癌细胞,胃癌细胞,甲状腺癌细胞,肺癌细胞,白血病细胞,B细胞淋巴瘤,T细胞淋巴瘤,毛细胞淋巴瘤,霍奇金淋巴瘤细胞,非霍奇

金淋巴瘤细胞,伯基特淋巴瘤细胞,胰腺癌细胞,黑色素瘤细胞,多发性黑色素瘤细胞,脑癌细胞,CNS癌细胞,肾癌细胞,前列腺癌细胞,卵巢癌细胞或乳腺癌细胞。

[0049] 根据又一个实施方案,本发明提供了用于治疗有需要的哺乳动物的eIF4E依赖性病症的方法,所述方法包含给予所述哺乳动物(i)治疗有效量的至少一种根据式I,式II,式III,式IV,式V或式VI的化合物或其立体异构体,互变异构体或药学上可接受的盐,或(ii)根据本发明的药物组合物。

[0050] 根据本发明的化合物和药学上可接受的制剂用于治疗eIF4E依赖性病症,例如结肠癌,胃癌,甲状腺癌,肺癌,白血病,B细胞淋巴瘤,T细胞淋巴瘤,毛细胞淋巴瘤,霍奇金淋巴瘤,非霍奇金淋巴瘤,伯基特淋巴瘤,胰腺癌,黑色素瘤,多发性黑色素瘤,脑癌,CNS癌,肾癌,前列腺癌,卵巢癌或乳腺癌。

[0051] 本发明的以上实施方案和其他方面在下面的详细描述中是显而易见的。本文列出了各种参考文献,其更详细地描述了某些背景信息,程序,化合物和/或组合物,并且各自通过引用整体并入本文。

附图说明

[0052] 图1,显示使用化合物1188的细胞增殖测定结果的图表。

[0053] 图2,显示使用化合物634的细胞增殖测定结果的图表。

[0054] 图3,显示使用化合物1141的细胞增殖测定结果的图表。

具体实施方式

[0055] 在以下描述中,阐述了某些具体细节以便提供对本发明的各种实施方案的透彻理解。然而,本领域技术人员将理解,可以在没有这些细节的情况下实施本发明。除非上下文另有要求,否则在整个本说明书和权利要求书中,词语“包含(comprise)”及其变体,例如“包含(comprises)”和“包含(comprising)”,应以开放,包容的意义解释(即,“包括但不限于”)。

[0056] 在整个说明书中对“一个实施方案”或“实施方案”的引用意味着结合该实施方案描述的特定特征,结构或特性包括在本发明的至少一个实施方案中。因此,在整个说明书的各处出现的短语“在一个实施方案中”或“在实施方案中”不一定都指代相同的实施方案。此外,特定的特征,结构或特性可以在一个或多个实施方案中以任何合适的方式组合。

[0057] 定义

[0058] 如本文所使用,除非有相反说明,否则以下术语和短语具有下文注明的含义。

[0059] “氨基”是指-NH_2取代基。

[0060] “氨基羰基”是指-C(O)NH_2取代基。

[0061] “羧基”是指-CO_2H取代基。

[0062] “羰基”是指-C(O)-,-(CO)-或-C(=O)-基团。所有符号在本说明书中都可以互换使用。

[0063] “氰基”是指-C≡N取代基。

[0064] “氰基亚烷基”是指-(亚烷基)C≡N取代基。

[0065] “乙酰基”是指-C(O)CH_3取代基。

[0066] “羟基(hydroxy)”或“羟基(hydroxyl)”是指-OH取代基。

[0067] “羟基亚烷基”是指-(亚烷基)OH取代基。

[0068] “氧代”是指=O取代基。

[0069] “硫醇基(thio)”或“硫羟基(thiol)”是指-SH取代基。

[0070] “烷基”是指仅由碳和氢原子组成的饱和直链或支链烃链基团,其具有1至12个碳原子(C_1-C_{12}烷基),1至8个碳原子(C_1-C_8烷基)或1至6个碳原子(C_1-C_6烷基),并且其通过单键连接到分子的其余部分。示例性烷基包括甲基,乙基,正丙基,1-甲基乙基(异丙基),正丁基,正戊基,1,1-二甲基乙基(叔丁基),3-甲基己基,2-甲基己基等。

[0071] “低级烷基”具有与上文定义的烷基相同的含义,但具有1-4个碳原子(C_1-C_4烷基)。

[0072] “烯基”是指具有至少一个双键和2至12个碳原子(C_2-C_{12}烯基),2至8个碳原子(C_2-C_8烯基)或2至6个碳原子(C_2-C_6烯基)的不饱和烷基,并且其通过单键连接到分子的其余部分,例如乙烯基,丙烯基,丁烯基,戊烯基,己烯基等。

[0073] “炔基”是指具有至少一个三键和2至12个碳原子(C_2-C_{12}炔基),2至10个碳原子(C_2-C_{10}炔基),2至8个碳原子(C_2-C_8炔基)或2至6个碳原子(C_2-C_6炔基)的不饱和烷基,并且其通过单键连接到分子的其余部分,例如乙炔基,丙炔基,丁炔基,戊炔基,己炔基等。

[0074] “亚烷基”或“亚烷基链”分别是指仅由碳和氢组成的将分子的其余部分与基团连接的直链或支链二价烃(烷基)链。亚烷基可以具有1至12个碳原子,例如亚甲基,亚乙基,亚丙基,亚正丁基等。亚烷基链通过单键或双键连接到分子的其余部分。亚烷基链与分子其余部分的连接点可以通过链内的一个碳或任意两个碳。“任选地取代的亚烷基”是指亚烷基或取代的亚烷基。

[0075] “亚烯基”是指二价烯烃。亚烯基的实例包括但不限于亚乙烯基((-CH=CH-)及其所有立体异构形式和构象异构形式。“取代的亚烯基”是指二价取代的烯烃。“任选取代的亚烯基”是指亚烯基或取代的亚烯基。

[0076] “亚炔基(alkynylene)”是指二价炔烃。亚炔基的实例包括但不限于亚乙炔基,亚丙炔基。“取代的亚炔基”是指二价取代的炔烃。

[0077] “烷氧基”是指式-OR_a的基团,其中R_a是如上定义的具有指定数目的碳原子的烷基。烷氧基的实例包括但不限于-O-甲基(甲氧基),-O-乙基(乙氧基),-O-丙基(丙氧基),-O-异丙基(异丙氧基)等。

[0078] “烷基氨基”是指式-NHR_a或-NR_aR_a的基团,其中每个R_a独立地为如上定义的具有指定数目的碳原子的烷基。

[0079] “环烷基氨基”是指式-NHR_a或-NR_aR_a的基团,其中R_a为如本文所定义的环烷基。

[0080] “烷基羰基氨基”是指式-NHC(O)R_a或-NR_aC(O)R_a的基团,其中R_a为如本文所定义的具有指定数目的碳原子的烷基。

[0081] “环烷基羰基氨基”是指式-NHC(O)R_a或-NR_aC(O)R_a的基团,其中R_a为如本文定义的环烷基。

[0082] “烷基氨基羰基”是指式-C(O)NHR_a或-C(O)NR_aR_a的基团,其中每个R_a独立地为如本文所定义的具有指定数目的碳原子的烷基。

[0083] “环烷基氨基羰基”是指式-C(O)NHR_a的基团,其中R_a为如本文所定义的环烷基。

[0084] “芳基”是指包含氢,6至18个碳原子和至少一个芳环的烃环系统基团。示例性芳基

是包含氢和6至9个碳原子和至少一个芳环的烃环系统基团;包含氢和9至12个碳原子和至少一个芳环的烃环系统基团;包含氢和12至15个碳原子和至少一个芳环的烃环系统基团;或包含氢和15至18个碳原子和至少一个芳环的烃环系统基团。出于本发明的目的,芳基可以是单环,双环,三环或四环环系统,其可以包括稠环或桥环系统。芳基包括但不限于衍生自苊蒽(aceanthrylene),苊,苊菲(acephenanthrylene),蒽,蒽,苯,䓛,苯芴(fluoranthene),芴,as-二环戊熳并苯(as-indacene),s-二环戊熳并苯(s-indacene),茚满,茚,萘,苣(phenalene),菲,昔苯(pleiadene),芘和联三苯叉(triphenylene)。“任选地取代的芳基”是指芳基或取代的芳基。

[0085] “亚芳基”表示二价芳基,并且“取代的亚芳基”是指二价取代的芳基。

[0086] “芳烷基”或“芳亚烷基”可以互换使用并且指式-R_b-R_c的基团,其中R_b是如本文定义的亚烷基链并且R_c是如本文定义的一个或多个芳基,例如苄基,二苯基甲基等。

[0087] “环烷基”是指仅由碳和氢原子组成的稳定的非芳族单环或多环烃基,其可以包括具有3至15个碳原子,优选具有3至10个碳原子,3至9个碳原子,3至8个碳原子,3至7个碳原子,3至6个碳原子,3至5个碳原子的稠环或桥环系统,具有4个碳原子的环,或具有3个碳原子的环。环烷基环可以是饱和的或不饱和的并且通过单键连接到分子的其余部分。单环基团包括例如环丙基,环丁基,环戊基,环己基,环庚基和环辛基。多环基团包括例如金刚烷基,降冰片基(norbornyl),十氢化萘基,7,7-二甲基-二环[2.2.1]庚基等。

[0088] “环烷基亚烷基”或“环烷基烷基”可以互换使用并且指式-R_bR_e的基团,其中R_b是如本文所定义的亚烷基链并且R_e是如本文所定义的环烷基。在某些实施方案中,R_b进一步被环烷基取代,使得环烷基亚烷基包含两个环烷基部分。环丙基亚烷基和环丁基亚烷基是分别包含至少一个环丙基或至少一个环丁基的示例性的环烷基亚烷基。

[0089] “稠合的”是指与本发明的化合物中的现有环结构稠合的本文所述的任何环结构。当稠合的环为杂环基环或杂芳基环时,成为稠合杂环基环或稠合杂芳基环的一部分的现有环结构上的任何碳原子可以被氮原子替代。

[0090] “卤代”或“卤素”是指溴代(溴),氯代(氯),氟代(氟)或碘代(碘)。

[0091] “卤代烷基”是指如本文所定义的具有指定数目的碳原子的烷基,其中所述烷基的一个或多个氢原子被如上所定义的卤素(卤代基)取代。卤素原子可以相同或不同。示例性卤代烷基是三氟甲基,二氟甲基,三氯甲基,2,2,2-三氟乙基,1,2-二氟乙基,3-溴-2-氟丙基,1,2-二溴乙基等。

[0092] “杂环基”,“杂环”或“杂环环”是指稳定的3-至18-元饱和或不饱和基团,其由2至12个碳原子和1至6个杂原子,例如1至5个杂原子,1至4个杂原子,1至3个杂原子或1至2个杂原子组成,所述杂原子选自氮,氧和硫。示例性杂环包括但不限于稳定的3-15元饱和或不饱和基团,稳定的3-12元饱和或不饱和基团,稳定的3-9元饱和或不饱和基团,稳定的8-元饱和或不饱和基团,稳定的7-元饱和或不饱和基团,稳定的6-元饱和或不饱和基团或稳定的5-元饱和或不饱和基团。

[0093] 除非在说明书中另有具体说明,否则杂环基可以是单环,双环,三环或四环系统,其可以包括稠环,桥环或螺环系统;并且杂环基中的氮,碳或硫原子可以任选地被氧化;氮原子可以任选地被季铵化;杂环基可以是部分或完全饱和的。非芳族杂环基的实例包括但不限于,氧杂环丙烷,氧杂环丁烷,氮杂环丁烷基,二氧戊环基,噻吩基[1,3]二噻烷基,十氢

异喹啉,咪唑啉基,咪唑烷基,异噻唑烷基,异噁唑烷基,吗啉基,八氢吲哚基,八氢异吲哚基,2-氧代哌嗪基,2-氧代哌啶基,2-氧代吡咯烷基,噁唑烷基,哌啶基,哌嗪基,4-哌啶酮基,吡咯烷基,吡唑烷基,奎宁环基,噻唑烷基,四氢呋喃基,硫杂环丁烷基,三噻烷基,四氢吡喃基,硫代吗啉基,硫吗啉基(thiamorpholinyl),1-氧代-硫代吗啉基和1,1-二氧代-硫代吗啉基。杂环基包括如本文所定义的杂芳基,并且芳族杂环基的实例列于下文杂芳基的定义中。

[0094] “杂环基烷基”或“杂环基亚烷基”是指式-R_bR_f的基团,其中R_b是如本文定义的亚烷基链,并且R_f是如上定义的杂环基,并且如果杂环基是含氮杂环基,则所述杂环基可以与氮原子上的烷基连接。

[0095] “杂芳基”或“杂亚芳基”是指包含氢原子,1至13个碳原子,1至6个选自氮,氧和硫的杂原子,和至少一个芳环的5-至14-元环系统基团。出于本发明的目的,杂芳基可以是包含至少1个杂原子,至少2个杂原子,至少3个杂原子,至少4个杂原子,至少5个杂原子或至少6个杂原子的稳定的5-12元环,稳定的5-10元环,稳定的5-9元环,稳定的5-8元环,稳定的5-7元环或稳定的6元环。杂芳基可以是单环,双环,三环或四环环系统,其可以包括稠环或桥环系统;并且杂芳基中的氮,碳或硫原子可以任选地被氧化;氮原子可以任选地被季铵化。杂原子可以是芳环或非芳环的成员,条件是杂芳基中的至少一个环是芳环。实例包括但不限于,氮杂环庚三烯基,吖啶基,苯并咪唑基,苯并噻唑基,苯并吲哚基,苯并间二氧杂环戊烯基,苯并呋喃基,苯并噁唑基,苯并噻唑基,苯并噻二唑基,苯并[b][1,4]二氧杂环庚三烯基,1,4-苯并二氧杂环己基,苯并萘并呋喃基,苯并噁唑基,苯并间二氧杂环戊烯基,苯并二噁英基,苯并吡喃基,苯并吡喃酮基,苯并呋喃基,苯并呋喃酮基,苯并噻吩基(benzothienyl)(苯并噻吩基(benzothiophenyl)),苯并三唑基,苯并[4,6]咪唑并[1,2-a]吡啶基,咔唑基,噌啉基,二苯并呋喃基,二苯并噻吩基,呋喃基,呋喃酮基,异噻唑基,咪唑基,吲唑基,吲哚基,吲唑基,异吲哚基,二氢吲哚基,二氢异吲哚基,异喹啉基,中氮茚基(indolizinyl),异噁唑基,萘啶基,噁二唑基,2-氧代氮杂环庚三烯基,噁唑基,氧杂环丙烷基,1-氧吡啶基,1-氧嘧啶基,1-氧吡嗪基,1-氧哒嗪基,1-苯基-1H-吡咯基,吩嗪基,吩噻嗪基,吩噁嗪基,酞嗪基,蝶啶基,嘌呤基,吡咯基,吡唑基,吡啶基,吡嗪基,嘧啶基,哒嗪基,喹唑啉基,喹喔啉基,喹啉基,奎宁环基,异喹啉基,四氢喹啉基,噻唑基,噻二唑基,三唑基,四唑基,三嗪基和噻吩基(thiophenyl)(即噻吩基(thienyl))。

[0096] “杂芳基烷基”或“杂芳基亚烷基”是指式-R_bR_g的基团,其中R_b是如上定义的亚烷基链并且R_g是如上定义的杂芳基。

[0097] “烷硫基(thioalkyl)”是指式-SR_a的基团,其中R_a是包含1至12个碳原子,至少1-10个碳原子,至少1-8个碳原子,至少1-6个碳原子或至少1-4个碳原子的如上定义的烷基基团。

[0098] “杂环基氨基”是指式-NHR_f的基团,其中R_f是如上定义的杂环基。

[0099] “硫酮”是指连接到饱和或不饱和(C_3-C_8)环状部分或(C_1-C_8)非环状部分的碳原子上的=S基团。

[0100] “亚砜”是指-S(O)-基团,其中硫原子与两个碳原子共价连接。

[0101] “砜”是指-$S(O)_2$-或-(SO_2)-基团,其中六价硫通过双键连接到两个氧原子中的每一个,并且通过单一共价键进一步连接到两个碳原子。

[0102] 术语“肟”是指-C(R_a)=N-OR_a基团,其中R_a是如上定义的氢,低级烷基,亚烷基或亚芳基。

[0103] 本发明的化合物可以各种异构形式存在,以及以一种或多种互变异构形式存在,包括单一互变异构体和互变异构体的混合物。术语“异构体”旨在涵盖本发明的化合物的所有异构形式,包括该化合物的互变异构形式。

[0104] 本文描述的一些化合物可以具有不对称中心,因此以不同的对映异构体和非对映异构体形式存在。本发明的化合物可以是光学异构体或非对映异构体的形式。因此,本发明包括光学异构体,非对映异构体及其混合物(包括外消旋混合物)形式的如本文所述的本发明的化合物及其用途。本发明的化合物的光学异构体可以通过已知技术例如不对称合成,手性色谱或通过使用旋光拆分剂经由立体异构体的化学分离获得。

[0105] 除非另有说明,否则“立体异构体”是指化合物的一种立体异构体,其基本上不含该化合物的其他立体异构体。因此,具有一个手性中心的立体异构纯化合物将基本上不含该化合物的相反对映异构体。具有两个手性中心的立体异构纯化合物将基本上不含该化合物的其他非对映异构体。典型的立体异构纯化合物包含大于约80重量%的化合物的一种立体异构体和小于约20重量%的化合物的其他立体异构体,例如大于约90重量%的化合物的一种立体异构体和小于约10重量%的化合物的其他立体异构体,或大于约95重量%的化合物的一种立体异构体和小于约5重量%的化合物的其他立体异构体,或大于约97重量%的化合物的一种立体异构体和小于约3重量%的化合物的其他立体异构体。

[0106] 如果所描绘的结构与赋予该结构的名称之间存在差异,则以所描绘的结构为准。此外,如果结构或结构的部分的立体化学未用例如粗线或虚线表示,则结构或结构的部分将被解释为包含其所有立体异构体。然而,在一些情况下,如果存在一个以上的手性中心,则结构和名称可以表示为单一对映异构体,以帮助描述相关的立体化学。有机合成领域的技术人员将知道化合物是否由用于制备它们的方法制备为单一对映异构体。

[0107] 在本说明书中,“药学上可接受的盐”是本发明的化合物的药学上可接受的有机或无机酸或碱盐。代表性的药学上可接受的盐包括例如碱金属盐,碱土金属盐,铵盐,水溶性和水不溶性盐,例如乙酸盐,氨芘磺酸盐(amsonate)(4,4-二氨基芪-2,2-二磺酸盐),苯磺酸盐,苯甲酸盐,碳酸氢盐,硫酸氢盐,酒石酸氢盐,硼酸盐,溴化物,丁酸盐,钙盐,乙二胺四乙酸钙,樟脑磺酸盐,碳酸盐,氯化物,柠檬酸盐,克拉维酸盐(clavulariate),二盐酸盐,乙二胺四乙酸盐,乙二磺酸盐,丙酸酯十二烷基硫酸盐,乙磺酸盐,富马酸盐(fiunarate),葡庚糖酸盐,葡糖酸盐,谷氨酸盐,乙醇酰氨基苯胂酸盐(glycollylarsanilate),六氟磷酸盐,已基间苯二酚盐(resorcinate),海巴明(hydrabamine),氢溴酸盐,盐酸盐,羟基萘甲酸盐,碘化物,异硫代硫酸盐(isothionate),乳酸盐,乳糖酸盐,月桂酸盐,苹果酸盐,马来酸盐,扁桃酸盐,甲磺酸盐,甲基溴化物,甲基硝酸盐,甲基硫酸盐,粘酸盐,萘磺酸盐,硝酸盐,N-甲基葡萄糖胺铵盐,3-羟基-2-萘甲酸盐,油酸盐,草酸盐,棕榈酸盐,双羟萘酸盐(1,1-亚甲基-双-2-羟基-3-萘甲酸盐,依伯酸盐(einbonate)),泛酸盐,磷酸盐/磷酸氢盐,苦味酸盐,聚半乳糖醛酸盐,丙酸盐,对甲苯磺酸盐,水杨酸盐,硬脂酸盐,碱式乙酸盐,琥珀酸盐,硫酸盐,磺基水杨酸盐(sulfosaliculate),苏拉酸盐(suramate),单宁酸盐,酒石酸盐,茶氯酸盐,甲苯磺酸盐,三乙基碘和戊酸盐。药学上可接受的盐可以在其结构中具有多于一个的带电原子。在这种情况下,药学上可接受的盐可以具有多个抗衡离子。因此,药学上可接

受的盐可以具有一个或多个带电原子和/或一个或多个抗衡离子。

[0108] 术语“治疗(treat)”,“治疗(treating)”和“治疗(treatment)”是指疾病或与疾病相关的症状的改善或根除。在某些实施方案中,这样的术语是指使由于给予患有这样的疾病的患者一种或多种预防或治疗剂而导致的疾病的传播或恶化最小化。在本发明的上下文中,术语“治疗(treat)”,“治疗(treating)”和“治疗(treatment)”还指:

[0109] (i)预防在哺乳动物中发生疾病或病症,特别是当这样的哺乳动物易患该病症但尚未被诊断为患有该病症时;

[0110] (ii)抑制疾病或病症,即阻止其发展;

[0111] (iii)缓解疾病或病症,即导致疾病或病症消退;或

[0112] (iv)缓解由疾病或病症引起的症状,即在不解决潜在疾病或病症的情况下缓解疼痛。如本文所使用,术语“疾病”和“病症”可以互换使用或可以不同,因为特定的疾病或病症可能没有已知的病原体(因此病因尚未解决),因此它是尚未被认为是一种疾病,而只是一种不良病症或综合征,其中临床医生已经确定了或多或少的特定的一组症状。

[0113] 术语“有效量”是指足以在疾病的治疗或预防中提供治疗或预防益处或延迟或最小化与疾病相关的症状的本发明的化合物或其他活性成分的量。此外,关于本发明的化合物的治疗有效量是指在疾病的治疗或预防中提供治疗益处的单独或与其他疗法组合的治疗剂的量。与本发明的化合物结合使用时,该术语可以包括改善整体治疗,减少或避免疾病的症状或原因,或增强治疗功效或与另一种治疗剂的协同作用的量。

[0114] 术语“抑制”或“抑制剂”是指相对于(1)对照,内源或参考靶标或途径,或(2)在靶标或途径不存在的情况下,直接或间接地改变,干扰,减少,下调,阻断,抑制,消除或降解靶基因,靶蛋白或信号传导途径的表达,量或活性,其中改变,干扰,减少,下调,阻断,抑制,消除或降解是统计学,生物学或临床显著的。术语“抑制”或“抑制剂”包括基因“敲除”和基因“敲低”方法,例如通过染色体编辑。

[0115] 术语“调节(modulate)”,“调节(modulation)”等是指化合物增加或减少例如真核起始因子4E(eIF4E)的功能或活性的能力。各种形式的“调节”旨在涵盖与eIF4E相关的活性的抑制,拮抗,部分拮抗,激活,激动和/或部分激动。eIF4E抑制剂是结合,部分或完全阻断刺激,减少,阻止,延迟激活,使信号转导失活,不敏感或下调的化合物。化合物调节eIF4E活性的能力可以在酶法测定或基于细胞的测定中证明。

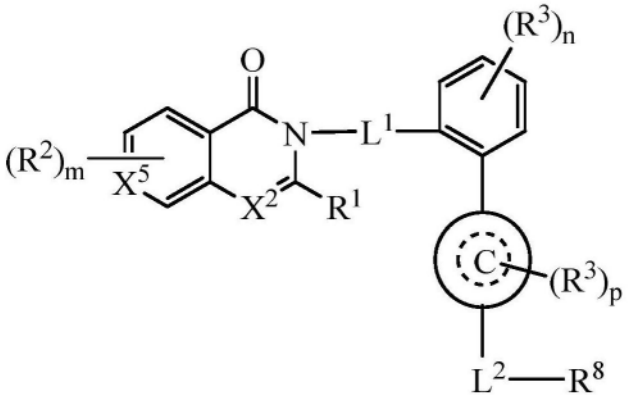
[0116] “患者”或受试者”包括动物,例如人,牛,马,绵羊,羊羔,猪,鸡,火鸡,鹌鹑,猫,狗,小鼠,大鼠,兔或豚鼠。动物可以是哺乳动物,例如非灵长类动物和灵长类动物(例如猴和人)。在一个实施方案中,患者是人类,例如人类婴儿,儿童,青少年或成人。

[0117] 术语“前药”是指药物的前体,一种在给予患者后必须通过代谢过程进行化学转化,然后才能成为活性药理学药剂的化合物。根据式I的化合物的示例性前药是酯,乙酰胺和酰胺。

[0118] 本发明的化合物

[0119] 本发明通常涉及式I的种类涵盖的化合物或其立体异构体,互变异构体或药学上可接受的盐。

[0120] 在一个实施方案中,本发明涉及根据式II的化合物

[0121] 

(II),

[0122] 或其立体异构体,互变异构体或药学上可接受的盐,其中:

[0123] X^2和X^5独立地为CR^2或N,

[0124] 或当X^2为CR^2时,R^1和R^2与它们所连接的原子一起形成6-元芳基或杂芳基;

[0125] L^1为-(CH_2)-,-$(CH_2)_2$-,-$(CH_2)_3$-,-CH((C_1-C_8)烷基)(CH_2)-,-CH((C_1-C_8)烷基)$(CH_2)_2$-,-$(CH_2)_2$-O-,-CH_2CH=CH-,-CH_2C≡C-或-CH_2(环丙基)-;

[0126] L^2为-C(R^6) (R^6)-,-C(R^6) (R^6)C(R^6) (R^6)-,-C(R^6)=C(R^6)-,-N(R^5)C(R^6) (R^6)-,-OC(R^6) (R^6)-,-C(=O)-,-C(=O)N(R^5)C(R^6) (R^6)-或键;

[0127] 环C为环烷基,杂环基,芳基或杂芳基;

[0128] R^1为H,OH,卤素,CN,(C_1-C_8)烷基,(C_1-C_8)卤代烷基,(C_3-C_6)环烷基或NR^5R^5;

[0129] R^2独立地为H,卤素,CN,NO,NO_2,C≡H,(C_1-C_8)烷基,(C_1-C_8)卤代烷基,CH_2SR^5,OR^5,NHR^5,NR^5R^5,[(C_1-C_8)亚烷基]杂环基,[(C_1-C_8)亚烷基]杂芳基,[(C_1-C_8)亚烷基]NHR^5,[(C_1-C_8)亚烷基]NR^5R^5,[(C_1-C_8)亚炔基]NR^5R^5,C(O)R^5,C(O)OR^5,C(O)NHR^5,C(O)NR^5R^5,SR^5,S(O)R^5,SO_2R^5,SO_2NHR^5,$SO_2NR^5R^5$,NH(CO)R^6,NR^5(CO)R^6,芳基,杂芳基,环烷基或杂环基;

[0130] R^3独立地为OH,卤素,CN,NO_2,(C_1-C_6)烷基,(C_1-C_6)卤代烷基,(C_1-C_6)烷氧基,C≡H,NHR^7,NR^7R^7,CO_2H,CO_2R^7,[(C_1-C_3)亚烷基](C_1-C_3)烷氧基,[(C_1-C_3)亚烷基]CO_2H,(C_3-C_5)环烷基,=O,=S,SR^7,SO_2R^7,NH(CO)R^7或NR^7(CO)R^7;

[0131] R^5独立地为H,(C_1-C_3)烷基,(C_1-C_3)卤代烷基,(C_3-C_5)环烷基,CO_2H,[(C_1-C_3)亚烷基]杂芳基,[(C_1-C_3)亚烷基]芳基,[(C_1-C_3)亚烷基]CO_2H,杂环基,芳基或杂芳基,

[0132] 或其中两个R^5取代基与氮原子一起形成4-,5-,6-或7-元杂环基;

[0133] R^6独立地为H,OH,卤素,CN,(C_1-C_3)烷基,(C_1-C_3)卤代烷基,(C_1-C_3)烷氧基,NHR^7,NR^7R^7,CO_2H,[(C_1-C_3)亚烷基]CO_2H,(C_3-C_5)环烷基,SR^7,NH(CO)R^7或NR^7(CO)R^7;

[0134] R^7独立地为H,(C_1-C_8)烷基,(C_1-C_8)卤代烷基,环烷基,杂环基,芳基或杂芳基;

[0135] R^8为H,OH,CO_2H,CO_2R^7,$CF_2C(R^6)_2OH$,$C(R^6)_2OH$,$C(CF_3)_2OH$,SO_2H,SO_3H,$CF_2SO_2C(R^6)_3$,$CF_2SO_2N(H)R^5$,$SO_2N(H)R^5$,$SO_2N(H)C(O)R^6$,C(O)N(H)SO_2R^5,C(O)卤代烷基,C(O)N(H)OR^5,C(O)$N(R^5)OH$,C(O)N(H)R^5,C(O)NR^5C(O)$N(R^5)_2$,P(O)$(OR^5)OH$,P(O)(O)N(H)R^5,P(O)$(C(R^6)_3)C(R^6)_3$,$B(OH)_2$,杂环基或杂芳基;

[0136] m为0,1,2或3;

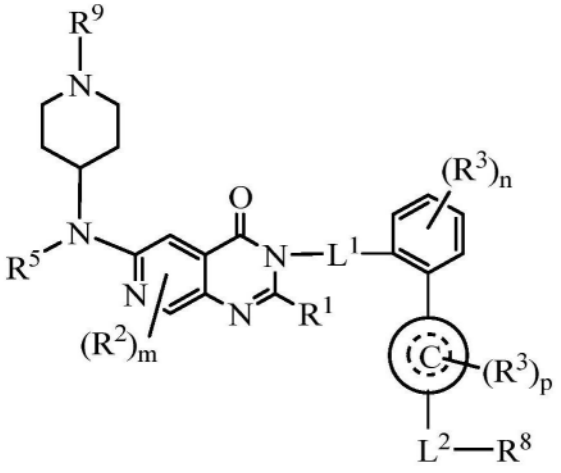
[0137] n为0,1,2或3;

[0138] p为0,1,2或3;

[0139] 其中任何烷基,亚烷基,环烷基,杂环基,杂芳基或芳基任选地被1,2或3个选自以

下的基团取代:OH,CN,SH,SCH_3,SO_2CH_3,SO_2NH_2,$SO_2NH(C_1-C_4)$烷基,卤素,NH_2,$NH(C_1-C_4)$烷基,$N[(C_1-C_4)$烷基$]_2$,NH(芳基),C(O)NH_2,C(O)NH(烷基),$CH_2C(O)NH$(烷基),COOH,COOMe,乙酰基,(C_1-C_8)烷基,(C_1-C_8)卤代烷基,$O(C_1-C_8)$烷基,$O(C_1-C_8)$卤代烷基,(C_2-C_8)烯基,(C_2-C_8)炔基,烷硫基,氰基亚甲基,烷基氨基,亚烷基-C(O)NH_2,亚烷基-C(O)-NH(Me),NHC(O)烷基,$CH_2-C(O)-(C_1-C_8)$烷基,$C(O)-(C_1-C_8)$烷基和烷基羰基氨基,或任选地被OH,卤素,(C_1-C_8)烷基,(C_1-C_8)卤代烷基,$O(C_1-C_8)$烷基或$O(C_1-C_8)$卤代烷基取代的环烷基,杂环基,芳基或杂芳基。

[0140] 在另一个实施方案中,本发明涉及式III的化合物

[0141] 

(III),

[0142] 或其立体异构体,互变异构体或药学上可接受的盐,其中:

[0143] L^1为$-(CH_2)-$,$-(CH_2)_2-$,$-(CH_2)_3-$,$-CH((C_1-C_8)$烷基$)(CH_2)-$,$-CH((C_1-C_8)$烷基$)(CH_2)_2-$,$-(CH_2)_2-O-$,$-CH_2CH=CH-$,$-CH_2C\equiv C-$或$-CH_2$(环丙基)-;

[0144] L^2为$-C(R^6)(R^6)-$,$-C(R^6)(R^6)C(R^6)(R^6)-$,$-C(R^6)=C(R^6)-$,$-N(R^5)C(R^6)(R^6)-$,$-OC(R^6)(R^6)-$,$-C(=O)-$,$-C(=O)N(R^5)C(R^6)(R^6)-$或键;

[0145] 环C为杂芳基;

[0146] R^1为H,OH,卤素,CN,(C_1-C_8)烷基,(C_1-C_8)卤代烷基,(C_3-C_6)环烷基或NR^5R^5;

[0147] R^2独立地为H,卤素,CN,NO,NO_2,C≡H,(C_1-C_8)烷基,(C_1-C_8)卤代烷基,CH_2SR^5,OR^5,NHR^5,NR^5R^5,$[(C_1-C_8)$亚烷基$]$杂环基,$[(C_1-C_8)$亚烷基$]$杂芳基,$[(C_1-C_8)$亚烷基$]NHR^5$,$[(C_1-C_8)$亚烷基$]NR^5R^5$,$[(C_1-C_8)$亚炔基$]NR^5R^5$,$C(O)R^5$,$C(O)OR^5$,$C(O)NHR^5$,$C(O)NR^5R^5$,SR^5,$S(O)R^5$,SO_2R^5,SO_2NHR^5,$SO_2NR^5R^5$,$NH(CO)R^6$,$NR^5(CO)R^6$,芳基,杂芳基,环烷基或杂环基;

[0148] R^3独立地为OH,卤素,CN,NO_2,(C_1-C_6)烷基,(C_1-C_6)卤代烷基,(C_1-C_6)烷氧基,C≡H,NHR^7,NR^7R^7,CO_2H,CO_2R^7,$[(C_1-C_3)$亚烷基$](C_1-C_3)$烷氧基,$[(C_1-C_3)$亚烷基$]CO_2H$,(C_3-C_5)环烷基,=O,=S,SR^7,SO_2R^7,$NH(CO)R^7$或$NR^7(CO)R^7$;

[0149] R^5独立地为H,(C_1-C_3)烷基,(C_1-C_3)卤代烷基,(C_3-C_5)环烷基或杂环基;

[0150] R^6独立地为H,OH,卤素,CN,(C_1-C_3)烷基,(C_1-C_3)卤代烷基,(C_1-C_3)烷氧基,NHR^7,NR^7R^7,CO_2H,$[(C_1-C_3)$亚烷基$]CO_2H$,(C_3-C_5)环烷基,SR^7,$NH(CO)R^7$或$NR^7(CO)R^7$;

[0151] R^7独立地为H,(C_1-C_8)烷基,(C_1-C_8)卤代烷基,环烷基,杂环基,芳基或杂芳基;

[0152] R^8为H,OH,CO_2H,CO_2R^7,$CF_2C(R^6)_2OH$,$C(R^6)_2OH$,$C(CF_3)_2OH$,SO_2H,SO_3H,$CF_2SO_2C(R^6)_3$,$CF_2SO_2N(H)R^5$,$SO_2N(H)R^5$,$SO_2N(H)C(O)R^6$,$C(O)N(H)SO_2R^5$,C(O)卤代烷基,$C(O)N(H)OR^5$,$C(O)N(R^5)OH$,$C(O)N(H)R^5$,$C(O)NR^5C(O)N(R^5)_2$,$P(O)(OR^5)OH$,$P(O)(O)N(H)R^5$,$P(O)(C(R^6)_3)C$

$(R^6)_3$,$B(OH)_2$,杂环基或杂芳基;

[0153] R^9为H,(C_1-C_8)烷基,(C_1-C_8)卤代烷基,环烷基或杂环基;

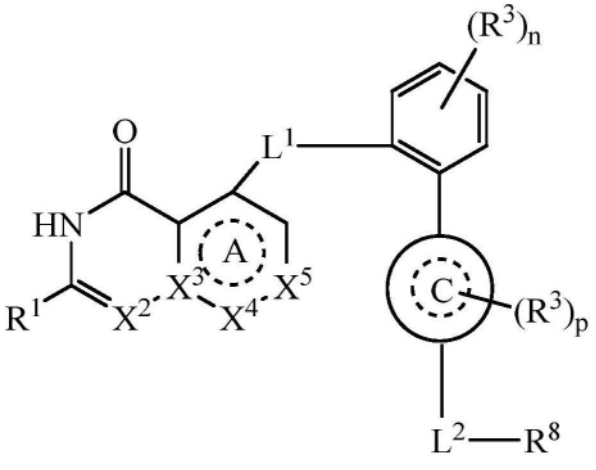
[0154] m为0,1或2;

[0155] n为0,1,2或3;

[0156] p为0,1,2或3;

[0157] 其中任何烷基,亚烷基,环烷基,杂环基,杂芳基或芳基任选地被1,2或3个选自以下的基团取代:OH,CN,SH,SCH_3,SO_2CH_3,SO_2NH_2,$SO_2NH(C_1-C_4)$烷基,卤素,NH_2,$NH(C_1-C_4)$烷基,$N[(C_1-C_4)$烷基$]_2$,NH(芳基),C(O)NH_2,C(O)NH(烷基),$CH_2C(O)NH$(烷基),COOH,COOMe,乙酰基,(C_1-C_8)烷基,(C_1-C_8)卤代烷基,$O(C_1-C_8)$烷基,$O(C_1-C_8)$卤代烷基,(C_2-C_8)烯基,(C_2-C_8)炔基,烷硫基,氰基亚甲基,烷基氨基,亚烷基-C(O)NH_2,亚烷基-C(O)-NH(Me),NHC(O)烷基,CH_2-C(O)-(C_1-C_8)烷基,C(O)-(C_1-C_8)烷基和烷基羰基氨基。

[0158] 在一个实施方案中,本发明涉及根据式IV的化合物

[0159] 

(IV),

[0160] 或其立体异构体,互变异构体或药学上可接受的盐,其中:

[0161] X^2和X^5独立地为CR^2或N,

[0162] 或当X^2为CR^2时,R^1和R^2与它们所连接的原子一起形成6-元芳基或杂芳基;

[0163] X^3为C,或当X^4为键时,X^3为C或N;

[0164] X^4为键,CR^2或N,

[0165] 其中X^4和X^5与3或4个碳原子或氮原子一起组合形成5-或6-元杂芳基;

[0166] L^1为-(CH_2)-,-$(CH_2)_2$-,-$(CH_2)_3$-,-CH((C_1-C_8)烷基)(CH_2)-,-CH((C_1-C_8)烷基)$(CH_2)_2$-,-$(CH_2)_2$-O-,-CH_2CH=CH-,-CH_2C≡C-或-CH_2(环丙基)-;

[0167] L^2为-C(R^6) (R^6)-,-C(R^6) (R^6)C(R^6) (R^6)-,-C(R^6)=C(R^6)-,-N(R^5)C(R^6) (R^6)-,-OC(R^6) (R^6)-,-C(=O)-,-C(=O)N(R^5)C(R^6) (R^6)-;

[0168] 环C为环烷基,杂环基,芳基或杂芳基;

[0169] R^1为H,OH,卤素,CN,(C_1-C_8)烷基,(C_1-C_8)卤代烷基,(C_3-C_6)环烷基或NR^5R^5;

[0170] R^2独立地为H,卤素,CN,NO,NO_2,C≡H,(C_1-C_8)烷基,(C_1-C_8)卤代烷基,CH_2SR^5,OR^5,NHR^5,NR^5R^5,[(C_1-C_8)亚烷基]杂环基,[(C_1-C_8)亚烷基]杂芳基,[(C_1-C_8)亚烷基]NHR^5,[(C_1-C_8)亚烷基]NR^5R^5,[(C_1-C_8)亚炔基]NR^5R^5,C(O)R^5,C(O)OR^5,C(O)NHR^5,C(O)NR^5R^5,SR^5,S(O)R^5,SO_2R^5,SO_2NHR^5,$SO_2NR^5R^5$,NH(CO)R^6,NR^5(CO)R^6,芳基,杂芳基,环烷基或杂环基;

[0171] R^3独立地为OH,卤素,CN,NO_2,(C_1-C_6)烷基,(C_1-C_6)卤代烷基,(C_1-C_6)烷氧基,C≡H,

NHR^7,NR^7R^7,CO_2H,CO_2R^7,[(C_1-C_3)亚烷基](C_1-C_3)烷氧基,[(C_1-C_3)亚烷基]CO_2H,(C_3-C_5)环烷基,=O,=S,SR^7,SO_2R^7,$NH(CO)R^7$或$NR^7(CO)R^7$;

[0172] R^5独立地为H,(C_1-C_3)烷基,(C_1-C_3)卤代烷基,(C_3-C_5)环烷基,CO_2H,[(C_1-C_3)亚烷基]杂芳基,[(C_1-C_3)亚烷基]芳基,[(C_1-C_3)亚烷基]CO_2H,杂环基,芳基或杂芳基,

[0173] 或其中两个R^5取代基与氮原子一起形成4-,5-,6-或7-元杂环基;

[0174] R^6独立地为H,OH,卤素,CN,(C_1-C_3)烷基,(C_1-C_3)卤代烷基,(C_1-C_3)烷氧基,NHR^7,NR^7R^7,CO_2H,[(C_1-C_3)亚烷基]CO_2H,(C_3-C_5)环烷基,SR^7,$NH(CO)R^7$或$NR^7(CO)R^7$;

[0175] R^7独立地为H,(C_1-C_8)烷基,(C_1-C_8)卤代烷基,环烷基,杂环基,芳基或杂芳基;

[0176] R^8为H,OH,CO_2H,CO_2R^7,$CF_2C(R^6)_2OH$,$C(R^6)_2OH$,$C(CF_3)_2OH$,SO_2H,SO_3H,$CF_2SO_2C(R^6)_3$,$CF_2SO_2N(H)R^5$,$SO_2N(H)R^5$,$SO_2N(H)C(O)R^6$,C(O)N(H)SO_2R^5,C(O)卤代烷基,C(O)N(H)OR^5,C(O)$N(R^5)OH$,C(O)N(H)R^5,C(O)$NR^5C(O)N(R^5)_2$,P(O)(OR^5)OH,P(O)(O)N(H)R^5,P(O)($C(R^6)_3$)$C(R^6)_3$,$B(OH)_2$,杂环基或杂芳基;

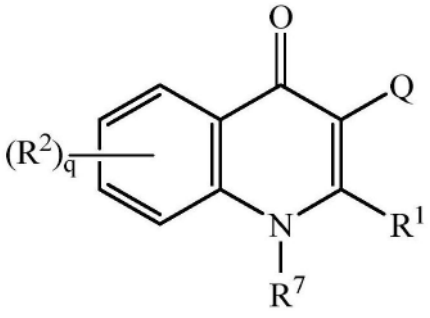
[0177] n为0,1,2或3;

[0178] p为0,1,2或3;

[0179] 其中任何烷基,亚烷基,环烷基,杂环基,杂芳基或芳基任选地被1,2或3个选自以下的基团取代:OH,CN,SH,SCH_3,SO_2CH_3,SO_2NH_2,$SO_2NH(C_1$-$C_4)$烷基,卤素,NH_2,$NH(C_1$-$C_4)$烷基,$N[(C_1$-$C_4)$烷基]$_2$,NH(芳基),C(O)NH_2,C(O)NH(烷基),$CH_2C(O)NH$(烷基),COOH,COOMe,乙酰基,(C_1-C_8)烷基,(C_1-C_8)卤代烷基,O(C_1-C_8)烷基,O(C_1-C_8)卤代烷基,(C_2-C_8)烯基,(C_2-C_8)炔基,烷硫基,氰基亚甲基,烷基氨基,亚烷基-C(O)NH_2,亚烷基-C(O)-NH(Me),NHC(O)烷基,CH_2-C(O)-(C_1-C_8)烷基,C(O)-(C_1-C_8)烷基和烷基羰基氨基,或任选地被OH,卤素,(C_1-C_8)烷基,(C_1-C_8)卤代烷基,O(C_1-C_8)烷基或O(C_1-C_8)卤代烷基取代的环烷基,杂环基,芳基或杂芳基,

[0180] 其中当X^4为键时,环A形成5-元杂芳基,其中X^1和X^5除了C以外可以为N。

[0181] 在另一个实施方案中,本发明涉及式V的化合物

[0182] 

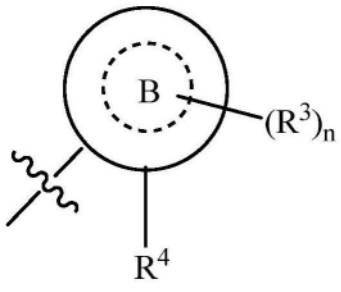
(V),

[0183] 或其立体异构体,互变异构体或药学上可接受的盐,其中:

[0184] Q为-L^1-Y;

[0185] L^1为-(CH_2)-,-(CH_2)$_2$-,-(CH_2)$_3$-,-CH((C_1-C_8)烷基)(CH_2)-,-CH((C_1-C_8)烷基)(CH_2)$_2$-,-(CH_2)$_2$-O-,-CH_2CH=CH-,-CH_2C≡C-或-CH_2(环丙基)-;

[0186] Y为

[0187] 

其中，

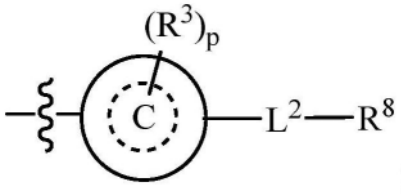
[0188] 环B为6-元芳基，杂芳基或杂环基；

[0189] R^1为H，OH，卤素，CN，(C_1-C_8)烷基，(C_1-C_8)卤代烷基，(C_3-C_6)环烷基或NR^5R^5；

[0190] R^2独立地为H，卤素，CN，NO，NO_2，C≡H，(C_1-C_8)烷基，(C_1-C_8)卤代烷基，CH_2SR^5，OR^5，NHR^5，NR^5R^5，[(C_1-C_8)亚烷基]杂环基，[(C_1-C_8)亚烷基]杂芳基，[(C_1-C_8)亚烷基]NHR^5，[(C_1-C_8)亚烷基]NR^5R^5，[(C_1-C_8)亚炔基]NR^5R^5，$C(O)R^5$，$C(O)OR^5$，$C(O)NHR^5$，$C(O)NR^5R^5$，SR^5，$S(O)R^5$，SO_2R^5，SO_2NHR^5，$SO_2NR^5R^5$，$NH(CO)R^6$，$NR^5(CO)R^6$，芳基，杂芳基，环烷基或杂环基；

[0191] R^3独立地为OH，卤素，CN，NO_2，(C_1-C_6)烷基，(C_1-C_6)卤代烷基，(C_1-C_6)烷氧基，C≡H，NHR^7，NR^7R^7，CO_2H，CO_2R^7，[(C_1-C_3)亚烷基](C_1-C_3)烷氧基，[(C_1-C_3)亚烷基]CO_2H，(C_3-C_5)环烷基，=O，=S，SR^7，SO_2R^7，$NH(CO)R^7$或$NR^7(CO)R^7$；

[0192] R^4为H，OH，卤素，CN，(C_1-C_3)烷基，(C_1-C_3)卤代烷基，(C_1-C_3)烷氧基，SR^7或Z，其中Z为

[0193] 

；

[0194] 环C为环烷基，杂环基，芳基或杂芳基；

[0195] L^2为$-C(R^6)(R^6)-$，$-C(R^6)(R^6)C(R^6)(R^6)-$，$-C(R^6)=C(R^6)-$，$-N(R^5)C(R^6)(R^6)-$，$-OC(R^6)(R^6)-$，$-C(=O)-$，$-C(=O)N(R^5)C(R^6)(R^6)-$或键；

[0196] R^5独立地为H，(C_1-C_3)烷基，(C_1-C_3)卤代烷基，(C_3-C_5)环烷基，CO_2H，[(C_1-C_3)亚烷基]杂芳基，[(C_1-C_3)亚烷基]芳基，[(C_1-C_3)亚烷基]CO_2H，杂环基，芳基或杂芳基，

[0197] 或其中两个R^5取代基与氮原子一起形成4-，5-或6-元杂环基；

[0198] R^6独立地为H，OH，卤素，CN，(C_1-C_3)烷基，(C_1-C_3)卤代烷基，(C_1-C_3)烷氧基，NHR^7，NR^7R^7，CO_2H，[(C_1-C_3)亚烷基]CO_2H，(C_3-C_5)环烷基，SR^7，$NH(CO)R^7$或$NR^7(CO)R^7$；

[0199] R^7独立地为H，(C_1-C_8)烷基，(C_1-C_8)卤代烷基，环烷基，杂环基，芳基或杂芳基；

[0200] R^8为H，OH，CO_2H，CO_2R^7，$CF_2C(R^6)_2OH$，$C(R^6)_2OH$，$C(CF_3)_2OH$，SO_2H，SO_3H，$CF_2SO_2C(R^6)_3$，$CF_2SO_2N(H)R^5$，$SO_2N(H)R^5$，$SO_2N(H)C(O)R^6$，$C(O)N(H)SO_2R^5$，C(O)卤代烷基，$C(O)N(H)OR^5$，$C(O)N(R^5)OH$，$C(O)N(H)R^5$，$P(O)(OR^5)OH$，$P(O)(O)N(H)R^5$，$P(O)(C(R^6)_3)C(R^6)_3$，$B(OH)_2$，杂环基或杂芳基；

[0201] n为0，1，2或3；

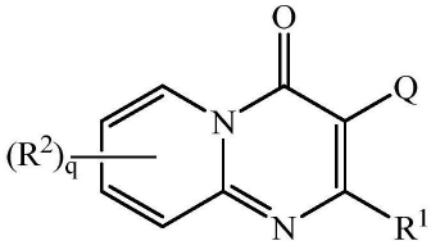
[0202] p为0，1，2或3；

[0203] q为0，1，2，3或4；

[0204] 其中任何烷基，亚烷基，环烷基，杂环基，杂芳基或芳基任选地被1，2或3个选自以

下的基团取代:OH,CN,SH,SCH_3,SO_2CH_3,SO_2NH_2,$SO_2NH(C_1-C_4)$烷基,卤素,NH_2,$NH(C_1-C_4)$烷基,$N[(C_1-C_4)烷基]_2$,NH(芳基),C(O)NH_2,C(O)NH(烷基),$CH_2C(O)NH$(烷基),COOH,COOMe,乙酰基,(C_1-C_8)烷基,(C_1-C_8)卤代烷基,$O(C_1-C_8)$烷基,$O(C_1-C_8)$卤代烷基,(C_2-C_8)烯基,(C_2-C_8)炔基,烷硫基,氰基亚甲基,烷基氨基,亚烷基-C(O)NH_2,亚烷基-C(O)-NH(Me),NHC(O)烷基,$CH_2-C(O)-(C_1-C_8)$烷基,C(O)-(C_1-C_8)烷基和烷基羰基氨基,或任选地被OH,卤素,(C_1-C_8)烷基,(C_1-C_8)卤代烷基,$O(C_1-C_8)$烷基或$O(C_1-C_8)$卤代烷基取代的环烷基,杂环基,芳基或杂芳基。

[0205] 在另一个实施方案中,本发明涉及式VI的化合物

[0206] 

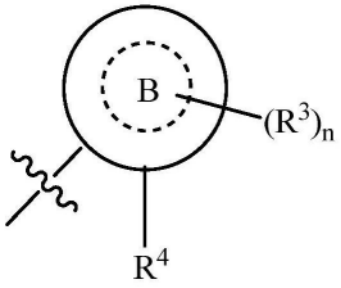
(VI),

[0207] 或其立体异构体,互变异构体或药学上可接受的盐,其中:

[0208] Q为$-L^1-Y$;

[0209] L^1为$-(CH_2)-$,$-(CH_2)_2-$,$-(CH_2)_3-$,-CH((C1-C8)烷基)$(CH_2)-$,-CH((C1-C8)烷基)$(CH_2)_2-$,$-(CH_2)_2-O-$,$-CH_2CH=CH-$,$-CH_2C\equiv C-$或$-CH_2$(环丙基)-;

[0210] Y为

[0211] 

其中

,

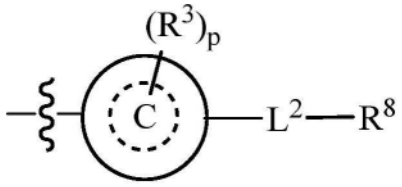
[0212] 环B为6-元芳基,杂芳基或杂环基;

[0213] R^1为H,OH,卤素,CN,(C_1-C_8)烷基,(C_1-C_8)卤代烷基,(C_3-C_6)环烷基或NR^5R^5;

[0214] R^2独立地为H,卤素,CN,NO,NO_2,C≡H,(C_1-C_8)烷基,(C_1-C_8)卤代烷基,CH_2SR^5,OR^5,NHR^5,NR^5R^5,[(C_1-C_8)亚烷基]杂环基,[(C_1-C_8)亚烷基]杂芳基,[(C_1-C_8)亚烷基]NHR^5,[(C_1-C_8)亚烷基]NR^5R^5,[(C_1-C_8)亚炔基]NR^5R^5,$C(O)R^5$,$C(O)OR^5$,$C(O)NHR^5$,$C(O)NR^5R^5$,SR^5,$S(O)R^5$,SO_2R^5,SO_2NHR^5,$SO_2NR^5R^5$,$NH(CO)R^6$,$NR^5(CO)R^6$,芳基,杂芳基,环烷基或杂环基;

[0215] R^3独立地为OH,卤素,CN,NO_2,(C_1-C_6)烷基,(C_1-C_6)卤代烷基,(C_1-C_6)烷氧基,C≡H,NHR^7,NR^7R^7,CO_2H,CO_2R^7,[(C_1-C_3)亚烷基](C_1-C_3)烷氧基,[(C_1-C_3)亚烷基]CO_2H,(C_3-C_5)环烷基,=O,=S,SR^7,SO_2R^7,$NH(CO)R^7$或$NR^7(CO)R^7$;

[0216] R^4为H,OH,卤素,CN,(C_1-C_3)烷基,(C_1-C_3)卤代烷基,(C_1-C_3)烷氧基,SR^7或Z,其中Z为

[0217] 

;

[0218] 环C为环烷基,杂环基,芳基或杂芳基;

[0219] L^2为-C(R^6)(R^6)-,-C(R^6)(R^6)C(R^6)(R^6)-,-C(R^6)=C(R^6)-,-N(R^5)C(R^6)(R^6)-,-OC(R^6)(R^6)-,-C(=O)-,-C(=O)N(R^5)C(R^6)(R^6)-或键;

[0220] R^5独立地为H,(C_1-C_3)烷基,(C_1-C_3)卤代烷基,(C_3-C_5)环烷基,CO_2H,[(C_1-C_3)亚烷基]杂芳基,[(C_1-C_3)亚烷基]芳基,[(C_1-C_3)亚烷基]CO_2H,杂环基,芳基或杂芳基,

[0221] 或其中两个R^5取代基与氮原子一起形成4-,5-或6-元杂环基;

[0222] R^6独立地为H,OH,卤素,CN,(C_1-C_3)烷基,(C_1-C_3)卤代烷基,(C_1-C_3)烷氧基,NHR^7,NR^7R^7,CO_2H,[(C_1-C_3)亚烷基]CO_2H,(C_3-C_5)环烷基,SR^7,NH(CO)R^7或NR^7(CO)R^7;

[0223] R^7独立地为H,(C_1-C_8)烷基,(C_1-C_8)卤代烷基,环烷基,杂环基,芳基或杂芳基;

[0224] R^8为H,OH,CO_2H,CO_2R^7,$CF_2C(R^6)_2OH$,$C(R^6)_2OH$,$C(CF_3)_2OH$,SO_2H,SO_3H,$CF_2SO_2C(R^6)_3$,$CF_2SO_2N(H)R^5$,$SO_2N(H)R^5$,$SO_2N(H)C(O)R^6$,C(O)N(H)SO_2R^5,C(O)卤代烷基,C(O)N(H)OR^5,C(O)N(R^5)OH,C(O)N(H)R^5,C(O)NR^5C(O)N(R^5)$_2$,P(O)(OR^5)OH,P(O)(O)N(H)R^5,P(O)($C(R^6)_3$)$C(R^6)_3$,$B(OH)_2$,杂环基或杂芳基;

[0225] n为0,1,2或3;

[0226] p为0,1,2或3;

[0227] q为0,1,2,3或4;

[0228] 其中任何烷基,亚烷基,环烷基,杂环基,杂芳基或芳基任选地被1,2或3个选自以下的基团取代:OH,CN,SH,SCH_3,SO_2CH_3,SO_2NH_2,SO_2NH(C_1-C_4)烷基,卤素,NH_2,NH(C_1-C_4)烷基,N[(C_1-C_4)烷基]$_2$,NH(芳基),C(O)NH_2,C(O)NH(烷基),CH_2C(O)NH(烷基),COOH,COOMe,乙酰基,(C_1-C_8)烷基,(C_1-C_8)卤代烷基,O(C_1-C_8)烷基,O(C_1-C_8)卤代烷基,(C_2-C_8)烯基,(C_2-C_8)炔基,烷硫基,氰基亚甲基,烷基氨基,亚烷基-C(O)NH_2,亚烷基-C(O)-NH(Me),NHC(O)烷基,CH_2-C(O)-(C_1-C_8)烷基,C(O)-(C_1-C_8)烷基和烷基羰基氨基,或任选地被OH,卤素,(C_1-C_8)烷基,(C_1-C_8)卤代烷基,O(C_1-C_8)烷基或O(C_1-C_8)卤代烷基取代的环烷基,杂环基,芳基或杂芳基。

[0229] 在一个实施方案中,式I,II和IV的X^2为N。

[0230] 在一个实施方案中,式I和IV的X^3为C。

[0231] 在一个实施方案中,式I和IV的X^4为CR^2或N。

[0232] 在一个实施方案中,式I和IV的X^5为CR^2。

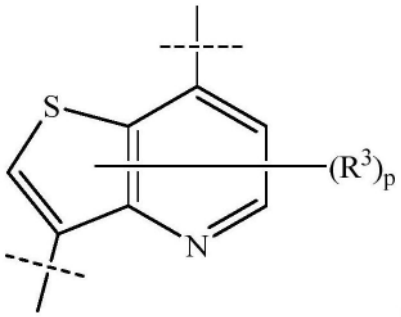
[0233] 在一个实施方案中,式I,II,III,IV,V和VI的L^1为-$(CH_2)_2$-O-,-CH_2CH=CH-或-CH_2C≡C-。在另一个实施方案中,L^1为-$(CH_2)_2$-O-。

[0234] 在一个实施方案中,式I,II,III,IV,V和VI的L^2为键。

[0235] 在一个实施方案中,式I,V和VI的环B为芳基。

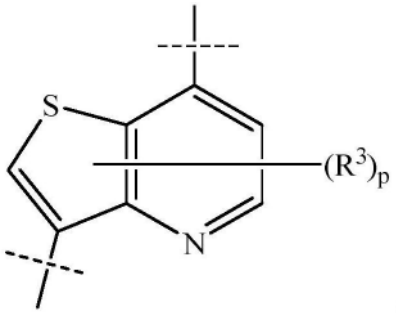
[0236] 在一个实施方案中,式I,II,III,IV,V和VI的环C为杂芳基。

[0237] 在一个实施方案中,式I,II,III,IV,V和VI的环C为

[0238] 

。

[0239] 在一个实施方案中,式III的环C为

[0240] 

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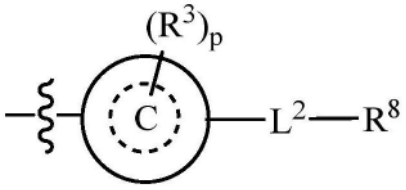
[0241] 在一个实施方案中,式I,II,III,IV,V和VI的R^1为H,(C_1-C_8)烷基或(C_1-C_8)卤代烷基。

[0242] 在一个实施方案中,式IV的R^1为NHR^5或$N[(C_1-C_3)烷基](R^5)$。

[0243] 在一个实施方案中,式I,II,III,IV,V和VI的R^2为卤素,CN,(C_1-C_8)烷基,(C_1-C_8)卤代烷基或OR^5。在另一个实施方案中,R^2为卤素,CN或(C_1-C_8)卤代烷基。

[0244] 在一个实施方案中,式I,II,III,IV,V和VI的R^3为卤素,CN,(C_1-C_3)烷基或(C_1-C_3)卤代烷基。

[0245] 在一个实施方案中,式I,V和VI的R^4为Z,其中Z为

[0246] 

;

[0247] 在一个实施方案中,式I,II,III,V和VI的R^5为H,(C_1-C_3)烷基或(C_1-C_3)卤代烷基。在另一个实施方案中,式IV的R^5为芳基。在另一个实施方案中,式I,II,III,IV,V和VI的R^5为H,(C_1-C_3)烷基或(C_1-C_3)卤代烷基。

[0248] 在一个实施方案中,式I,II,III,IV,V和VI的R^6为H,OH,卤素,CN,(C_1-C_3)烷基,(C_1-C_3)卤代烷基或(C_1-C_3)烷氧基。

[0249] 在一个实施方案中,式I,II,III,IV,V和VI的R^7为H,(C_1-C_8)烷基或(C_1-C_8)卤代烷基。

[0250] 在一个实施方案中,式I,II,III,IV,V和VI的R^8为CO_2H或$C(O)N(H)SO_2R^5$。

[0251] 在一个实施方案中,式III的R^9为(C_1-C_8)烷基或(C_1-C_8)卤代烷基。

[0252] 在一个实施方案中,式III的R^9为环烷基或杂环基。

[0253] 在一个实施方案中,式I和II的“m”=2或3。在另一个实施方案中,式I,II,IV,V和

VI的“n”＝1或2。在又一个实施方案中,式I,II,III,IV,V和VI的“p”＝0或1。

[0254] 在一个实施方案中,烷基,环烷基,杂环基,杂芳基或芳基的任选的取代基为OH,CN,卤素,(C_1-C_8)烷基,O(C_1-C_8)烷基,卤代烷基,亚烷基-C(O)NH_2或亚烷基-C(O)-NH(Me)。

[0255] 在一个实施方案中,烷基,环烷基,杂环基,杂芳基或芳基的任选的取代基为任选地被OH,卤素,(C_1-C_8)烷基,(C_1-C_8)卤代烷基,O(C_1-C_8)烷基或O(C_1-C_8)卤代烷基取代的环烷基,杂环基,芳基或杂芳基。

[0256] 在一个实施方案中,根据式I,II,III,IV,V和VI的化合物选自化合物1-1250。

[0257] 根据式I,II,III,IV,V和VI的本发明的化合物可以通过使一个或多个原子被具有不同原子质量或质量数的原子替代而进行同位素标记。可以掺入根据式I,II,III,IV,V和VI的化合物中的同位素的实例包括氢,碳,氮,氧,磷,氟,氯或碘的同位素。这样的同位素的示例分别为^{2}H,^{3}H,^{11}C,^{13}C,^{14}C,^{13}N,^{15}N,^{15}O,^{17}O,^{18}O,^{31}P,^{32}P,^{35}S,^{18}F,^{36}Cl,^{123}I和^{125}I。这些放射性标记的化合物可以用于测量来自生物组织,包括给予这样的标记的化合物的受试者的生物分布,组织浓度以及运输和排泄的动力学。标记的化合物也用于确定治疗效果,作用位点或作用方式以及候选治疗剂与药理学上重要的靶标的结合亲和力。因此,根据式I,II,III,IV,V和VI的某些放射性标记的化合物可以用于药物和/或组织分布研究。放射性同位素氚(即^{3}H)和碳14(即^{14}C)鉴于其易于掺入和现成的检测方式而特别地用于此目的。

[0258] 用较重的同位素例如氘(即^{2}H)进行替代提供了由于更高的代谢稳定性,例如含氘化合物的体内半衰期增加而产生的某些治疗优势。用氘替代氢可以减少治疗效果所需的剂量,因此在探索或临床环境中可以是优选的。

[0259] 用发射正电子的同位素,例如^{11}C,^{18}F,^{15}O和^{13}N进行替代提供了本发明的化合物的标记的类似物,其可用于正电子发射断层扫描(PET)研究,例如,用于检查底物受体占据。根据式I,II,III,IV,V和VI的同位素标记的化合物通常可以使用合适的同位素标记试剂,通过本领域技术人员已知的常规技术制备或通过与以下在制备和实施例部分中描述的那些类似的方法制备。

[0260] 本文公开的本发明的实施方案还意在包括根据式I,II,III,IV,V和VI的化合物的体内代谢产物。这样的产物可以由例如氧化,还原,水解,酰胺化,酯化和等过程产生,主要归因于给予本发明的化合物后的酶活性。因此,本发明包括在将这样的化合物给予哺乳动物足以产生代谢产物的一段时间之后,作为对本发明的化合物有酶活性或非酶活性的副产物产生的化合物。代谢产物,特别是药学活性代谢物,通常通过以下方式确定:将可检测剂量的本发明的放射性标记的化合物给予受试者,例如大鼠,小鼠,豚鼠,猴或人,持续在此期间发生代谢的足够长的时间段,以及从从接受放射性标记的化合物的受试者获得的尿液,血液或其他生物样品中分离代谢产物。

[0261] 本发明还提供式I,II,III,IV,V和VI的化合物的药学上可接受的盐形式。包括在本发明范围内的是酸和碱加成盐,它们是通过使药学上合适的酸或药学上合适的碱与本发明的化合物接触而形成的。

[0262] 为此,“药学上可接受的酸加成盐”是指保留游离碱的生物学有效性和性质的那些盐,其在生物学或其他方面不是不希望的,并且由无机酸和有机酸形成,所述无机酸例如但不限于盐酸,氢溴酸,硫酸,硝酸,磷酸等,所述有机酸例如但不限于乙酸,2,2-二氯乙酸,己二酸,海藻酸,抗坏血酸,天冬氨酸,苯磺酸,苯甲酸,4-乙酰氨基苯甲酸,樟脑酸,樟脑-10-

磺酸,癸酸,己酸,辛酸,碳酸,肉桂酸,柠檬酸,环拉酸,十二烷基硫酸,乙-1,2-二磺酸,乙磺酸,2-羟基乙磺酸,甲酸,富马酸,半乳糖二酸,龙胆酸,葡庚糖酸,葡萄糖酸,葡糖醛酸,谷氨酸,戊二酸,2-氧代戊二酸,甘油磷酸,乙醇酸,马尿酸,异丁酸,乳酸,乳糖酸,月桂酸,马来酸,苹果酸,丙二酸,扁桃酸,甲磺酸,粘酸,萘-1,5-二磺酸,萘-2-磺酸,1-羟基-2-萘甲酸,烟酸,油酸,乳清酸,草酸,棕榈酸,帕莫酸(pamoic acid),丙酸,焦谷氨酸,丙酮酸,水杨酸,4-氨基水杨酸,癸二酸,硬脂酸,琥珀酸,酒石酸,硫氰酸,对甲基苯磺酸,三氟乙酸,十一碳烯酸等。

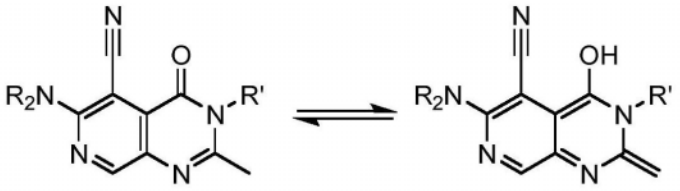
[0263] 类似地,“药学上可接受的碱加成盐”是指保留游离酸的生物学有效性和性质的那些盐,其在生物学或其他方面不是不希望的。这些盐是通过向游离酸中添加无机碱或有机碱来制备的。衍生自无机碱的盐包括但不限于钠盐,钾盐,锂盐,铵盐,钙盐,镁盐,铁盐,锌盐,铜盐,锰盐,铝盐等。优选的无机盐是铵盐,钠盐,钾盐,钙盐和镁盐。衍生自有机碱的盐包括但不限于伯胺,仲胺和叔胺,取代胺,包括天然存在的取代胺,环状胺和碱性离子交换树脂的盐,例如氨,异丙胺,三甲胺,二乙胺,三乙胺,三丙胺,二乙醇胺,乙醇胺,N,N-二甲基乙醇胺(deanol),2-二甲基氨基乙醇,2-二乙基氨基乙醇,二环己胺,赖氨酸,精氨酸,组氨酸,咖啡因,普鲁卡因,海巴明,胆碱,甜菜碱,苯乙苄胺,苄星,乙二胺,葡糖胺,甲基葡糖胺,可可碱,三乙醇胺,氨丁三醇,嘌呤,哌嗪,哌啶,N-乙基哌啶,聚胺树脂等。特别优选的有机碱是异丙胺,二乙胺,乙醇胺,三甲胺,二环己胺,胆碱和咖啡因。

[0264] 结晶通常产生本发明的化合物的溶剂合物。如本文所使用,术语“溶剂合物”是指包含本发明的化合物的一个或多个分子与溶剂的一个或多个分子的聚集体。溶剂可以是水,在这种情况下溶剂合物可以是水合物。可供选择地,溶剂可以是有机溶剂。因此,本发明的化合物可以作为水合物,包括一水合物,二水合物,半水合物,倍半水合物,三水合物,四水合物等,以及相应的溶剂化形式存在。本发明的化合物可以是真正的溶剂合物,而在其他情况下,本发明的化合物可以仅保留外来水或者是水与一些外来溶剂的混合物。

[0265] “立体异构体”是指由通过相同键键合的相同原子组成,但具有不可互换的不同三维结构的化合物。本发明涵盖各种立体异构体及其混合物,并且包括“对映异构体”,其是指其分子彼此为不可重叠的镜像的两种立体异构体。

[0266] 本发明的化合物或其药学上可接受的盐可以包含一个或多个不对称中心,因此可以产生对映异构体,非对映异构体和其他立体异构体形式,其可以在绝对立体化学方面定义为(R)-或(S)-或,如对于氨基酸定义为(D)-或(L)-。本发明旨在包括所有这些可能的异构体,以及它们的外消旋和光学纯形式。光学活性(+)和(-),(R)-和(S)-或(D)-和(L)-异构体可以使用手性合成子或手性试剂制备,或使用常规技术例如色谱和分级结晶进行拆分。用于制备/分离单个对映异构体的常规技术包括由合适的光学纯前体手性合成或使用例如手性高压液相色谱(HPLC)拆分外消旋体(或盐或衍生物的外消旋体)。当本文所述的化合物包含烯属双键或其他几何不对称中心时,除非另有说明,否则该化合物旨在包括E和Z几何异构体。同样,所有互变异构形式也应包括在内。

[0267] 术语“互变异构体”是指从分子的一个原子到同一分子的另一个原子的质子转移。例如:



[0268]





[0269] 本发明中提供的化合物可以描述为不同的互变异构体,并且当化合物具有互变异构形式时,所有的互变异构形式都意图在本发明的范围内,并且化合物的命名不排除该化合物的任何互变异构体。

[0270] 本发明的化合物是使用常规合成方法合成的,更具体地,是使用下面提到的通用方法合成的。

[0271] 药物制剂

[0272] 在一个实施方案中,根据式I,II,III,IV,V和VI的化合物被配制成药学上可接受的组合物,其包含在给予哺乳动物药物组合物后有效治疗特定疾病或病症的量的式I,II,III,IV,V和VI的化合物。根据本发明的药物组合物可以包含式I,II,III,IV,V和VI的化合物与药学上可接受的载体,稀释剂或赋形剂的组合。

[0273] 在这方面,“药学上可接受的载体,稀释剂或赋形剂”包括但不限于已被美国食品和药物管理局批准为可接受被用于人类或家养动物的任何辅助剂,载体,赋形剂,助流剂,甜味剂,稀释剂,防腐剂,染料/着色剂,增味剂,表面活性剂,润湿剂,分散剂,助悬剂,稳定剂,等渗剂,溶剂或乳化剂。

[0274] 此外,“哺乳动物”包括人类和诸如实验室动物和家庭宠物(例如,猫,狗,猪,牛,绵羊,山羊,马,兔子)的家养动物和诸如野生动物的非家养动物等。

[0275] 本发明的药物组合物可以通过将本发明的化合物与适宜的药学上可接受的载体,稀释剂或赋形剂组合来制备,并且可以配制成固体,半固体,液体或气体形式的制剂,例如片剂,胶囊剂,散剂,颗粒剂,软膏剂,溶液剂,栓剂,注射剂,吸入剂,凝胶剂,微球和气雾剂。这样的药物组合物的通常的给药途径包括但不限于口服,局部,透皮,吸入,肠胃外,舌下,口腔,直肠,阴道和鼻内。如本文所使用,术语肠胃外包括皮下注射,静脉内,肌肉内,胸骨内注射或输注技术。本发明的药物组合物被配制成使得其中包含的活性成分在将组合物给予患者时是生物可利用的。将给予受试者或患者的组合物采用一个或多个剂量单位的形式,其中例如片剂可以是单一剂量单位,并且气雾剂形式的本发明的化合物的容器可以容纳多个剂量单位。制备这样的剂型的实际方法对于本领域技术人员来说是已知的或将是显而易见的;例如,参见Remington:The Science and Practice of Pharmacy,第20版(Philadelphia College of Pharmacy and Science,2000)。在任何情况下,待给药的组合物将包含治疗有效量的本发明的化合物或其药学上可接受的盐,用于根据本发明的教导治

疗关注的疾病或病症。

[0276] 本发明的药物组合物可以是固体或液体的形式。一方面,(多种)载体是颗粒状的,因此组合物是例如片剂或粉末形式。(多种)载体可以是液体,其中组合物为例如口服糖浆,可注射的液体或气雾剂,其可用于例如吸入给药。当意图用于口服给药时,药物组合物优选为固体或液体形式,其中半固体,半液体,悬浮液和凝胶形式包括在本文被视为固体或液体的形式内。

[0277] 作为用于口服给药的固体组合物,药物组合物可以配制成粉末,颗粒,压缩片剂,丸剂,胶囊,口香糖,薄片等形式。这样的固体组合物通常将包含一种或多种惰性稀释剂或可食用载体。此外,可以存在以下一种或多种:粘合剂,例如羧甲基纤维素,乙基纤维素,微晶纤维素,黄蓍胶或明胶;赋形剂,如淀粉,乳糖或糊精;崩解剂,如海藻酸,海藻酸钠,Primogel,玉米淀粉等;润滑剂,如硬脂酸镁或Sterotex等;助流剂,例如胶体二氧化硅;甜味剂,例如蔗糖或糖精;调味剂,如薄荷,水杨酸甲酯或桔子香精;和着色剂。

[0278] 当药物组合物为胶囊形式,例如明胶胶囊时,除了上述类型的材料之外,其还可以包含液体载体,例如聚乙二醇或油。

[0279] 药物组合物可以是液体形式,例如酏剂,糖浆剂,溶液剂,乳剂或混悬剂。作为两个实例,该液体可以用于口服给药或通过注射递送。当意图用于口服给药时,优选的组合物除本发明的化合物外还含有甜味剂,防腐剂,染料/着色剂和增味剂中的一种或多种。在意图通过注射给药的组合物中,可以包含表面活性剂,防腐剂,润湿剂,分散剂,助悬剂,缓冲剂,稳定剂和等渗剂中的一种或多种。

[0280] 本发明的液体药物组合物无论是溶液剂,混悬剂还是其他类似形式,可以包含以下辅助剂中的一种或多种:无菌稀释剂,例如注射用水,盐水溶液,优选生理盐水,林格氏溶液,等渗氯化钠,不挥发性油,例如可充当溶剂或悬浮介质的合成甘油单酯或甘油二酯,聚乙二醇,甘油,丙二醇或其他溶剂;抗菌剂,例如苯甲醇或对羟基苯甲酸甲酯;抗氧化剂,例如抗坏血酸或亚硫酸氢钠;螯合剂,例如乙二胺四乙酸;缓冲剂,例如乙酸盐,柠檬酸盐或磷酸盐;以及用于调节张力的试剂,例如氯化钠或葡萄糖。肠胃外制剂可以封装在安瓿,一次性注射器或玻璃或塑料制成的多剂量小瓶中。生理盐水是优选的佐剂。可注射的药物组合物优选是无菌的。

[0281] 意图用于肠胃外或口服给药的本发明的液体药物组合物应含有一定量的本发明的化合物,以便获得合适的剂量。

[0282] 本发明的药物组合物可以意图用于局部给药,在这种情况下,载体可以适当地包括溶液,乳液,软膏或凝胶基质。例如,所述基质可以包含以下中的一种或多种:凡士林,羊毛脂,聚乙二醇,蜂蜡,矿物油,稀释剂如水和醇,以及乳化剂和稳定剂。增稠剂可以存在于用于局部给药的药物组合物中。如果意图用于透皮给药,则该组合物可以包括透皮贴剂或离子电渗装置。

[0283] 本发明的药物组合物可以意图用于以例如栓剂的形式直肠给药,其将在直肠中融化并释放药物。用于直肠给药的组合物可以含有油质基质作为合适的无刺激性赋形剂。这样的基质包括但不限于羊毛脂,可可脂和聚乙二醇。

[0284] 本发明的药物组合物可以包含改变固体或液体剂量单位的物理形式的各种材料。例如,组合物可以包含在活性成分周围形成包衣壳的材料。形成包衣壳的材料通常是惰性

的,并且可以选自例如糖,虫胶和其他肠溶包衣剂。可供选择地,可以将活性成分装入明胶胶囊中。

[0285] 固体或液体形式的本发明的药物组合物可以包含与本发明的化合物结合并因此有助于化合物的递送的试剂。可以以该能力起作用的合适的试剂包括单克隆或多克隆抗体,蛋白质或脂质体。

[0286] 本发明的药物组合物可以由可以作为气雾剂给药的剂量单位组成。术语气雾剂用于表示从具有胶体性质的系统到由加压包装组成的系统的各种系统。可以通过液化或压缩气体或通过分配活性成分的合适泵系统进行递送。本发明的化合物的气雾剂可以单相,双相或三相系统递送以递送(多种)活性成分。气雾剂的递送包括必要的容器,启动器,阀门,子容器等,它们一起可以形成套件。本领域技术人员无需过多实验即可确定优选的气雾剂。

[0287] 本发明的药物组合物可以通过制药领域众所周知的任何方法制备。例如,意图通过注射给药的药物组合物可以通过将本发明的化合物与无菌蒸馏水组合以形成溶液来制备。可以添加表面活性剂以促进均匀溶液或悬浮液的形成。表面活性剂是与本发明的化合物非共价相互作用以促进化合物在水性递送系统中溶解或均匀悬浮的化合物。

[0288] 在某些实施方案中,将包含式I,II,III,IV,V和VI的化合物的药物组合物以足以在给药后抑制eIF4E活性,并且优选对其具有可接受的毒性的量给予哺乳动物。式I,II,III,IV,V和VI的化合物的eIF4E活性可以由本领域技术人员确定,例如,在以下实施例中所述。本领域技术人员可以容易地确定合适的浓度和剂量。

[0289] 治疗用途

[0290] 本发明的化合物或其药学上可接受的盐以治疗有效量给药,该量将根据包括以下在内的多种因素而变化:所采用的特定化合物的活性;化合物的代谢稳定性和作用持续时间;患者的年龄,体重,一般健康状况,性别和饮食;给药方式和时间;排泄率;药物组合;特定障碍或病症的严重程度;和接受治疗的受试者。

[0291] “有效量”或“治疗有效量”是指本发明的化合物的量,其当给予哺乳动物,优选人时,足以实现如下定义的哺乳动物,优选人的eIF4E相关病症或疾病的治疗。构成“治疗有效量”的本发明的化合物的量将根据化合物,病症及其严重程度,给药方式和待治疗哺乳动物的年龄而变化,但本领域普通技术人员可以考虑到其自身的知识和本发明而常规地确定。

[0292] 本发明的化合物或其药学上可接受的盐也可以与一种或多种其他治疗剂同时,在其之前或之后给药。这样的联合治疗包括给予含有本发明的化合物和一种或多种另外的活性剂的单一药物剂量制剂,以及给予在其各自的单独药物剂量制剂中的本发明的化合物和每种活性剂。例如,本发明的化合物和其他活性剂可以在单一口服剂量组合物例如片剂或胶囊剂中一起给予患者,或者每种药剂在单独的口服剂量制剂中给予。当使用单独的剂量制剂时,本发明的化合物和一种或多种另外的活性剂可在基本上相同的时间给予,即同时给予,或在分开的交错时间给予,即依次给予;联合治疗被理解为包括所有这些方案。

[0293] 在某些实施方案中,公开的化合物可用于抑制eIF4E的活性和/或可用于分析模型系统中的eIF4E信号传导活性和/或用于预防,治疗或改善与涉及eIF4E的疾病,障碍或病理病症,优选困扰人类的疾病相关的症状。抑制eIF4E活性的化合物将可用于预防,治疗,改善或减少以下疾病的症状或进展:不受控制的细胞生长,增殖和/或存活,不适当的细胞免疫反应或不适当的细胞炎症反应的疾病,或伴随不受控制的细胞生长,增殖和/或存活,不适

当的细胞免疫反应或不适当的细胞炎症反应疾病的症状或进展的疾病,特别地,其中不受控制的细胞生长,增殖和/或存活,不适当的细胞免疫反应或不适当的细胞炎症反应由eIF4E介导,例如血液肿瘤,实体瘤和/或其转移瘤,包括白血病和骨髓增生异常综合征,恶性淋巴瘤,例如B细胞淋巴瘤,T细胞淋巴瘤,毛细胞淋巴瘤,霍奇金淋巴瘤,非霍奇金淋巴瘤和伯基特淋巴瘤,头颈部肿瘤,包括脑肿瘤和脑转移瘤,胸部肿瘤,包括非小细胞和小细胞肺肿瘤,胃肠道肿瘤,内分泌肿瘤,乳腺和其他妇科肿瘤,泌尿系统肿瘤,包括肾,膀胱和前列腺肿瘤,皮肤肿瘤和肉瘤,和/或其转移瘤。

[0294] 此外,本发明的化合物及其药物组合物是用于预防和/或治疗细胞因子相关疾病的候选治疗剂,所述疾病例如炎性疾病,过敏或与促炎细胞因子相关的其他病症。示例性炎性疾病包括但不限于慢性或急性炎症,关节炎症,例如慢性炎性关节炎,类风湿性关节炎,银屑病性关节炎,骨关节炎,幼年型类风湿性关节炎,赖特综合征,类风湿性创伤性关节炎,风疹性关节炎,急性滑膜炎和痛风性关节炎;炎性皮肤病,例如晒伤,银屑病,红皮病型银屑病,脓疱型银屑病,湿疹,皮炎,急性或慢性移植物形成,特应性皮炎,接触性皮炎,荨麻疹和硬皮病;胃肠道炎症,如炎性肠病,克罗恩病及相关病症,溃疡性结肠炎,结肠炎和憩室炎;肾炎,尿道炎,输卵管炎,卵巢炎,子宫肌内膜炎(endomyometritis),脊柱炎,系统性红斑狼疮及相关障碍,多发性硬化,哮喘,脑膜炎,脊髓炎,脑脊髓炎,脑炎,静脉炎,血栓性静脉炎;呼吸系统疾病,如哮喘,支气管炎,慢性阻塞性肺病(COPD),炎症性肺病和成人呼吸窘迫综合征和过敏性鼻炎;心内膜炎,骨髓炎,风湿热,风湿性心包炎,风湿性心内膜炎,风湿性心肌炎,风湿性二尖瓣疾病,风湿性主动脉瓣疾病,前列腺炎,前列腺膀胱炎,脊柱关节病(spondoarthropathy)强直性脊柱炎,滑膜炎,腱鞘炎,肌炎,咽炎,风湿性多肌痛,肩部肌腱炎或粘液囊炎,痛风,假性痛风,血管炎;甲状腺炎性疾病,其选自肉芽肿性甲状腺炎,淋巴细胞性甲状腺炎,侵袭性纤维性甲状腺炎,急性甲状腺炎;桥本甲状腺炎,川崎病,雷诺现象,干燥综合征,神经炎性疾病,败血症,结膜炎,角膜炎,虹膜睫状体炎,视神经炎,耳炎,淋巴腺炎,鼻咽炎(nasopaharingitis),鼻窦炎,咽炎,扁桃体炎,喉炎,会厌炎,支气管炎,肺炎,口腔炎,牙龈炎,食管炎,胃炎,腹膜炎,肝炎,胆石症,胆囊炎,肾小球肾炎,Goodpasture病,新月体性肾小球肾炎,胰腺炎,子宫肌内膜炎,子宫肌炎,子宫炎,宫颈炎,宫颈内膜炎,外宫颈炎,宫旁组织炎,结核,阴道炎,外阴炎,矽肺,结节病,尘肺病,热症(pyresis),炎性多关节病,银屑病性关节病,肠纤维化,支气管扩张和肠病性关节病。

[0295] 此外,本发明的化合物及其药物组合物是用于预防和/或治疗纤维化疾病的候选治疗剂,所述疾病例如各种形式的纤维化,纤维瘤或引起纤维化的任何疾病,无论是作为主要症状还是次要症状。示例性纤维化疾病包括但不限于病毒性肝炎,肝纤维化,血吸虫病,脂肪性肝炎(酒精性或非酒精性),肝硬化,特发性肺纤维化(IPF),系统性硬化症(硬皮病),肾源性系统性纤维化(NSF),糖尿病,未经治疗的高血压,心脏病发作,高血压,动脉粥样硬化,再狭窄,黄斑变性,视网膜和玻璃体视网膜病变,瘢痕瘤,肥厚性瘢痕,克罗恩病和阿尔茨海默病。

[0296] 尽管炎症是这些疾病的统一致病过程,但目前的疗法仅治疗疾病的症状而不是炎症的根本原因。本发明的组合物可用于治疗和/或预防炎性疾病和相关并发症和障碍。

[0297] 因此,某些实施方案涉及用于治疗有需要的哺乳动物的eIF4E依赖性病症的方法,所述方法包含给予哺乳动物有效量的如上所述的药物组合物(即,包含一种或多种式I,II,

III,IV,V和VI的化合物的药物组合物)。

[0298] 如上所述,蛋白质合成的失调是人类癌症中的常见事件。翻译控制的关键调节因子是eIF4E,其活性是致瘤性的关键决定因素。eIF4E的抑制剂是治疗细胞增殖性障碍如癌症的合适的候选治疗剂。多种癌症,包括实体瘤,淋巴瘤和白血病,都适合本文公开的组合物和方法。可以治疗的癌症类型包括但不限于:乳腺腺癌,前列腺腺癌和结肠腺癌;各种形式的肺支气管癌;骨髓;黑色素瘤;肝癌;成神经细胞瘤;乳头状瘤;胺前体摄取与脱羧细胞瘤;迷芽瘤;鳃原瘤;恶性类癌综合征;类癌心脏病;和癌(例如,沃克(Walker)癌,基底细胞癌,基底鳞状细胞癌,布-皮(Brown-Pearce)癌,导管癌,埃利希瘤,Krebs 2,麦克尔(Merkel)细胞癌,粘液癌,非小细胞肺癌,燕麦细胞癌,乳头状癌,硬癌,细支气管癌,支气管癌,鳞状细胞癌和移行细胞癌)。可以治疗的其他类型的癌症包括:组织细胞障碍;白血病;恶性组织细胞增多症;霍奇金病;免疫增生性小肠病;非霍奇金淋巴瘤;T细胞淋巴瘤,B细胞淋巴瘤,毛细胞淋巴瘤,伯基特淋巴瘤,浆细胞瘤;网状内皮增生症;黑色素瘤;软骨母细胞瘤;软骨瘤;软骨肉瘤;纤维瘤;纤维肉瘤;巨细胞瘤;组织细胞瘤;脂肪瘤;脂肪肉瘤;间皮瘤;粘液瘤;粘液肉瘤;骨瘤;骨肉瘤;脊索瘤;颅咽管瘤;无性细胞瘤;错构瘤;间质瘤;中肾瘤;肌肉瘤;釉母细胞瘤;牙骨质瘤;牙瘤;畸胎瘤;胸腺瘤;滋养细胞肿瘤。

[0299] 可以使用本发明的化合物治疗的其他癌症包括但不限于腺瘤;胆管瘤;胆脂瘤;圆柱瘤;囊腺癌;囊腺瘤;粒层细胞瘤;两性母细胞瘤;肝癌;汗腺瘤;胰岛细胞瘤;莱迪希细胞瘤;乳头状瘤;支持细胞瘤;泡膜细胞瘤;平滑肌瘤;平滑肌肉瘤;成肌细胞瘤;肌瘤;肌肉瘤;横纹肌瘤;横纹肌肉瘤;室管膜瘤;神经节细胞瘤;胶质瘤;髓母细胞瘤;脑膜瘤;神经鞘瘤;成神经细胞瘤;神经上皮瘤;神经纤维瘤;神经瘤;副神经节瘤;非嗜铬性副神经节瘤。

[0300] 在一个实施方案中,本发明的化合物是用于治疗癌症的候选治疗剂,所述癌症如血管角化瘤;血管淋巴样增生伴嗜酸性粒细胞增多;硬化性血管瘤;血管瘤病;血管球瘤;血管内皮瘤;血管瘤;血管外皮细胞瘤;血管肉瘤;淋巴管瘤;淋巴管肌瘤;淋巴管肉瘤;松果体瘤;癌肉瘤;软骨肉瘤;叶状囊肉瘤;纤维肉瘤;血管肉瘤;平滑肌肉瘤;白血病肉瘤;脂肪肉瘤;淋巴管肉瘤;肌肉瘤;粘液肉瘤;卵巢癌;横纹肌肉瘤;肉瘤;赘生物(neoplasm);神经纤维瘤病;和宫颈异型增生。

[0301] 在一个具体实施方案中,本发明提供了用于治疗以下的方法:实体瘤,结肠癌,直肠癌,结肠直肠癌,膀胱癌,胃癌,食道癌,头颈癌,骨髓增生异常综合征,脑癌,CNS癌,恶性胶质瘤,胶质母细胞瘤,肝细胞癌(hepatocellular cancer),肝细胞癌(hepatocellular carcinoma),甲状腺癌,肺癌,非小细胞肺癌,血液学癌症,急性和慢性白血病,B细胞淋巴瘤,华氏巨球蛋白血症,T细胞淋巴瘤,毛细胞淋巴瘤,弥漫性大B细胞淋巴瘤,霍奇金淋巴瘤,非霍奇金淋巴瘤,伯基特淋巴瘤,胰腺癌,黑色素瘤,骨髓瘤,多发性骨髓瘤,胰腺癌,肾细胞癌,肾癌,宫颈癌,尿路上皮癌,前列腺癌,去势抵抗性前列腺癌,卵巢癌,乳腺癌,三阴性乳腺癌,激素受体阳性乳腺癌或HER2+乳腺癌。根据这样的方法,可以将治疗有效量的至少一种根据式I,II,III,IV,V和VI的化合物或其立体异构体,互变异构体或药学上可接受的盐给予已被诊断患有细胞增殖性疾病,例如癌症的受试者。可供选择地,可以将包含至少一种根据式I,II,III,IV,V和VI的化合物或其立体异构体,互变异构体或药学上可接受的盐的药物组合物给予已被诊断患有癌症的受试者。

[0302] 在某些实施方案中,将根据本发明的化合物与其他常规癌症疗法如放射治疗或手

术共同给予患有癌症的受试者。放射疗法在本领域中是众所周知的并且包括X射线疗法,例如γ-辐射,和放射性药物疗法。

[0303] 在某些实施方案中,本发明的eIF4E抑制剂化合物与至少一种抗癌剂一起使用。抗癌剂包括化学治疗药物。化学治疗剂包括但不限于染色质功能抑制剂,拓扑异构酶抑制剂,微管抑制药物,DNA损伤剂,抗代谢物(例如叶酸拮抗剂,嘧啶类似物,嘌呤类似物和糖修饰类似物),DNA合成抑制剂,DNA相互作用剂(例如嵌入剂)和DNA修复抑制剂。

[0304] 示例性化学治疗剂包括但不限于以下群组:抗代谢物/抗癌剂,例如嘧啶类似物(5-氟尿嘧啶,氟尿苷,卡培他滨,吉西他滨和阿糖胞苷)和嘌呤类似物,叶酸拮抗剂和相关抑制剂(巯嘌呤,硫鸟嘌呤,喷司他丁和2-氯脱氧腺苷(克拉屈滨));抗增殖/抗有丝分裂剂,包括天然产物,如长春花生物碱(长春花碱,长春新碱和长春瑞滨),微管破坏剂,如紫杉烷(紫杉醇,多西他赛),长春新碱,长春花碱,诺考达唑,埃博霉素和诺维本,表鬼臼毒素(epidipodophyllotoxin)(依托泊苷,替尼泊苷),DNA损伤剂(放线菌素,安吖啶,蒽环类药物,博来霉素,白消安,喜树碱,卡铂,苯丁酸氮芥,顺铂,环磷酰胺,癌得星(Cytoxan),放线菌素,柔红霉素,多柔比星,表柔比星,六甲基密胺,奥沙利铂,异环磷酰胺,美法仑,二氯甲基二乙胺,丝裂霉素,米托蒽醌,亚硝基脲,普卡霉素,甲基苄肼,泰素,泰素帝,替莫唑胺,替尼泊苷,三亚乙基硫代磷酰胺和依托泊苷(VP 16));抗生素,例如放线菌素(放线菌素D),柔红霉素,多柔比星(阿霉素),伊达比星,蒽环霉素,米托蒽醌,博来霉素,普卡霉素(光神霉素)和丝裂霉素;酶(L-天冬酰胺酶,其全身性代谢L-天冬酰胺且剥夺不具有合成其自身的天冬酰胺的能力的细胞);抗血小板剂;抗增殖/抗有丝分裂烷化剂,例如氮芥(二氯甲基二乙胺,环磷酰胺和类似物,美法仑,苯丁酸氮芥),乙烯亚胺和甲基密胺(六甲基密胺和噻替派),烷基磺酸盐-白消安,亚硝基脲(卡莫司汀(BCNU)和类似物,链脲佐菌素),三氮烯-达卡巴嗪(dacarbazinine)(DTIC);抗增殖/抗有丝分裂抗代谢物,例如叶酸类似物(甲氨蝶呤);铂配位复合物(顺铂,卡铂),甲基苄肼,羟基脲,米托坦,氨鲁米特,激素类似物(雌激素,他莫昔芬,戈舍瑞林,比卡鲁胺,尼鲁米特)和芳香酶抑制剂(来曲唑,阿那曲唑);抗凝血剂(肝素,合成肝素盐和其他凝血酶抑制剂);纤维蛋白溶解剂(如组织纤溶酶原激活物,链激酶和尿激酶),阿司匹林,双嘧达莫,噻氯匹定,氯吡格雷,阿昔单抗;抗迁移剂(antimigratory agent);抗分泌剂(布雷菲德菌素(breveldin));免疫抑制剂(环孢菌素,他克莫司(FK-506),西罗莫司(雷帕霉素)),硫唑嘌呤,吗替麦考酚酯);抗血管生成化合物(TNP470,染料木黄酮)和生长因子抑制剂(血管内皮生长因子(VEGF)抑制剂,纤维母细胞生长因子(FGF)抑制剂);血管紧张素受体阻断剂;一氧化氮供体;反义寡核苷酸;抗体(曲妥珠单抗,利妥昔单抗);嵌合抗原受体;细胞周期抑制剂和分化诱导剂(维甲酸);mTOR抑制剂,拓扑异构酶抑制剂(多柔比星(阿霉素),安吖啶,喜树碱,柔红霉素,放线菌素,替尼泊苷(eniposide),表柔比星,依托泊苷,伊达比星,伊立替康(CPT-11)和米托蒽醌,拓扑替康,伊立替康),皮质类固醇(可的松,地塞米松,氢化可的松,甲基泼尼松龙,泼尼松和泼尼松龙);生长因子信号转导激酶抑制剂;线粒体功能障碍诱导剂,毒素,如霍乱毒素,蓖麻毒素,假单胞菌外毒素,百日咳博代氏杆菌腺苷酸环化酶毒素或白喉毒素,和半胱天冬酶活化剂;和染色质破坏剂。

[0305] 在某些实施方案中,可以与eIF4E抑制剂组合使用的另外的治疗剂是免疫抑制组分的抑制剂,其可以是免疫检查点分子或基因,代谢酶,免疫抑制细胞因子,T_{reg}细胞或其任何组合的抑制剂。如本文所使用,术语“免疫抑制组分”是指提供抑制信号以帮助控制或抑

制免疫反应的一种或多种细胞,蛋白质,分子,化合物或复合物。例如,免疫抑制组分包括部分或完全阻断免疫刺激;减少,防止或延迟免疫激活;或增加,激活或上调免疫抑制的那些分子。如本文所使用的“控制或抑制免疫反应”是指减少抗原呈递,T细胞活化,T细胞增殖,T细胞效应器功能,细胞因子分泌或产生以及靶细胞裂解中的任何一种或多种。这样的调节,控制或抑制可以促进或允许过度增殖性疾病或障碍(例如癌症,慢性感染)的持续存在。

[0306] 免疫检查点分子包括免疫检查点配体,例如,PD-L1,PD-L2,CD80,CD86,B7-H3,B7-H4,HVEM,腺苷,GAL9,VISTA,CEACAM-1,CEACAM-3,CEACAM-5,PVRL2,和免疫检查点受体,例如PD-1,CTLA-4,BTLA,KIR,LAG3,TIM3,A2aR,CD244/2B4,CD160,TIGIT,LAIR-1和PVRIG/CD112R。代谢酶包括精氨酸酶和吲哚胺2,3-双加氧酶(IDO)),免疫抑制细胞因子包括IL-10,IL-4,IL-1RA和IL-35。在某些实施方案中,免疫抑制组分的抑制剂是小分子,反义分子,核酶,RNAi分子(例如,siRNA),抗体或其抗原结合片段或融合多肽(例如,Fc融合蛋白)。

[0307] PD-1特异性抗体可以是匹地利珠单抗,纳武单抗,派姆单抗,MEDI0680(原名AMP-514),AMP-224或BMS-936558。

[0308] PD-L1特异性抗体可以是MDX-1105(BMS-936559),德瓦鲁单抗(原名MEDI4736),阿特珠单抗(原名MPDL3280A)或阿维鲁单抗(原名MSB0010718C)。对PD-L1具有特异性的化合物可以是BMS-1001或BMS-1166。

[0309] CTLA4抑制剂可以是CTLA4特异性抗体,例如替西木单抗或伊匹单抗,或CTLA4-Ig融合蛋白(例如,阿巴西普,贝拉西普)。

[0310] LAG3抑制剂可以是LAG525,IMP321,IMP701,9H12或BMS-986016。

[0311] IDO抑制剂可以是左旋-1-甲基色氨酸,艾卡哚司他(epacadostat)(INCB024360;Liu等人,Blood 115:3520-30,2010),依布硒啉(Terentis等人,Biochem.49:591-600,2010),吲哚莫德,NLG919(Mautino等人,美国癌症研究协会2013年第104届年会;2013年4月6-10日),1-甲基-色氨酸(1-MT)-替拉扎明或其任意组合。

[0312] 在某些实施方案中,根据本发明的eIF4E抑制剂在相同的制剂中或在分开的制剂中同时使用,或作为联合治疗方案的一部分与另外的(多种)药剂顺序使用。

[0313] 根据式I,II,III,IV,V和VI的eIF4E抑制剂,包括其相应的盐,以及式I,II,III,IV,V和VI化合物的药学上可接受的组合物,也可以有效地作为治疗剂用于治疗或预防患者,优选人的细胞因子介导的障碍,例如炎症。在一个实施方案中,根据本发明的化合物或组合物特别适用于治疗或预防选自以下的疾病:慢性或急性炎症,慢性炎性关节炎,类风湿性关节炎,银屑病,COPD,炎性肠病,感染性休克,克罗恩病,溃疡性结肠炎,多发性硬化和哮喘。

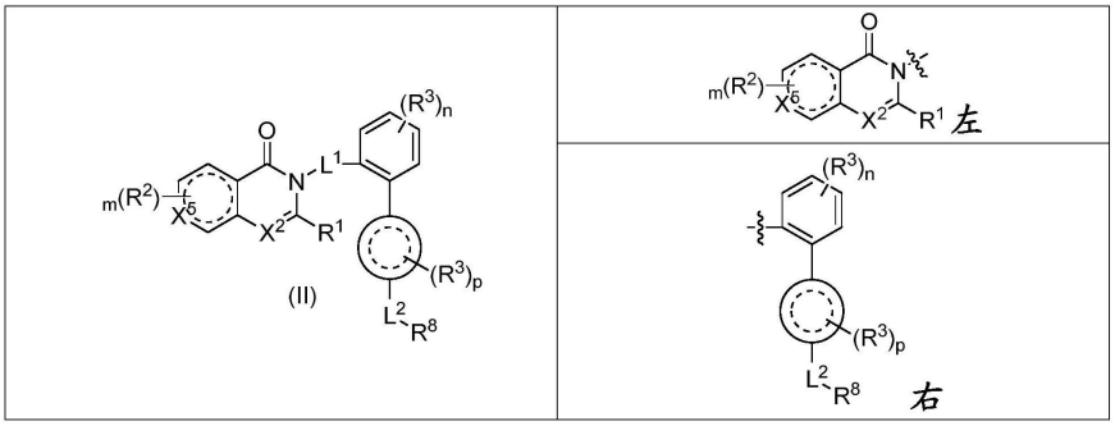
[0314] 本发明的化合物,其相应的盐和药学上可接受的组合物是用于治疗脑相关障碍的候选治疗剂,所述障碍包括但不限于自闭症,脆性X-综合征,帕金森病和阿尔茨海默病。通过给予需要治疗的受试者式I,II,III,IV,V和VI的化合物,其药学上可接受的盐形式或式I,II,III,IV,V和VI的化合物或其盐的药学上可接受的组合物来实现治疗。

[0315] 本发明还支持本发明的化合物或本发明的化合物的药学上可接受的制剂作为eIF4E活性的抑制剂的用途。这样的抑制是通过使表达eIF4E的细胞与化合物或药学上可接受的制剂接触以降低或抑制eIF4E活性来实现的,从而为有需要的哺乳动物的eIF4E依赖性病症提供治疗功效。

[0316] 根据式I,II,III,IV,V和VI的化合物或含有式I,II,III,IV,V和VI的化合物的组合物的治疗有效剂量通常为约1至2000mg/天,约10至约1000mg/天,约10至约500mg/天,约10至约250mg/天,约10至约100mg/天或约10至约50mg/天。治疗有效剂量可以一个或多个剂量给药。然而,应当理解,用于任何特定患者的本发明的化合物的具体剂量将取决于多种因素,例如年龄,性别,体重,一般健康状况,饮食,待治疗患者的个体反应,给药时间,待治疗疾病的严重程度,所施用的特定化合物的活性,剂型,施用方式和伴随用药。给定情况下的治疗有效量将容易地通过常规实验确定,并且在普通临床医生或医师的技能和判断范围内。在任何情况下,化合物或组合物将基于患者的独特病症以允许递送治疗有效量的剂量和方式给药。

[0317] 合成化合物的通用方法

[0318] 本发明所述的化合物具有左侧和右侧,如下式(II)所示:

[0319] 

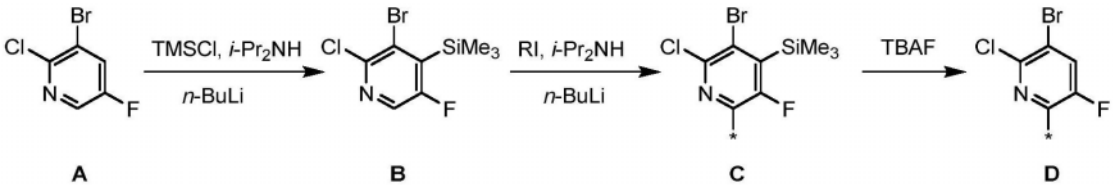
[0320] 通常,本发明中描述的化合物可以通过构建左侧和右侧并将两侧偶联在一起来合成,如下面的通用方法中所述。在偶联之前在左侧进行的许多反应,例如氰化,可以延迟直到偶联完成。类似地,一些作为偶联后方案列出的反应可以在偶联反应之前进行,以获得相同的结果。

[0321] 实施例1.合成7-氮杂-噻吩基吡啶和衍生化合物的通用方法

[0322] 表1中的7-氮杂-噻吩基吡啶化合物可以使用实施例1中描述的方法来合成。对于一些化合物,以下实施例2和/或实施例3中描述的一些反应可以用于制备化合物。

[0323] 实施例1A.合成左侧的方法

[0324] 实施例1A.1

[0325] 

[0326] 在0℃下向干燥的N-异丙基丙-2-胺(1.2当量)的THF溶液(0.3M)中缓慢加入正丁基锂(2.5M的己烷溶液)(1.2当量),并将混合物搅拌10min。直接使用该LDA的THF溶液。在-78℃下向3-溴-2-氯-5-氟-吡啶(A,1当量)的THF溶液(0.3M)中加入该LDA溶液,并将得到的深色混合物搅拌45min。加入氯(三甲基)硅烷(1.7当量),并将混合物在约15h内升温至室温。用水淬灭反应混合物,分离各层,水层用乙酸乙酯萃取。合并有机层,与硅胶一起蒸发,将自由流动的硅胶装载在柱上,并通过硅胶色谱纯化(3-溴-2-氯-5-氟-6-甲基-4-吡啶

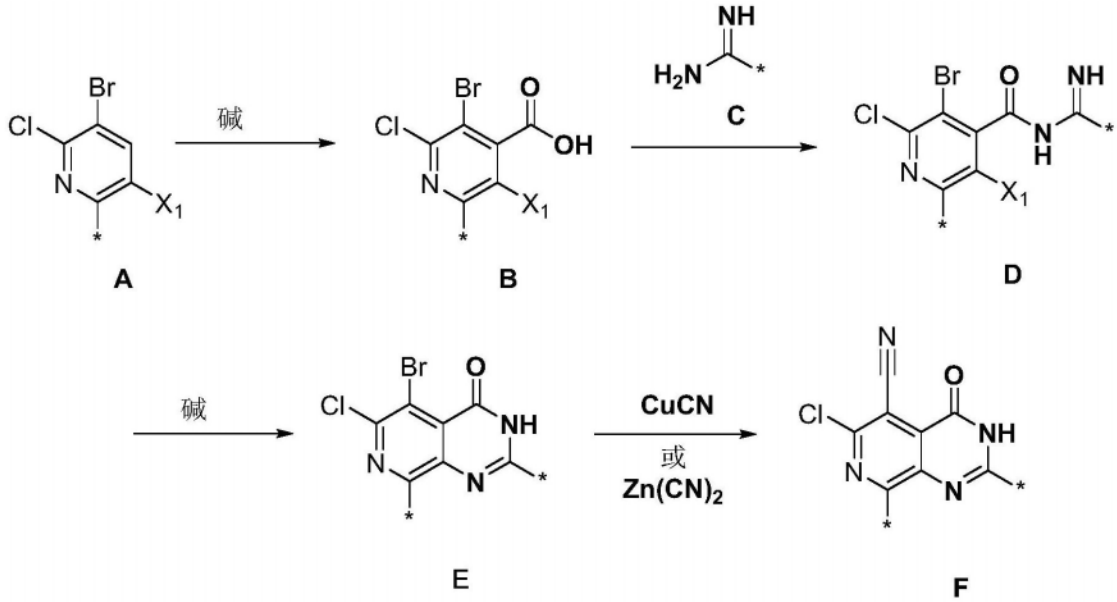
基)-三甲基-硅烷(B)。

[0327] 在-78℃下向(3-溴-2-氯-5-氟-4-吡啶基)-三甲基-硅烷(B,1当量)的THF溶液(0.25M)中加入如上制备的LDA溶液(1.2当量),将得到的深色混合物搅拌45min。加入碘甲烷(10当量),并将混合物在约15h内升温至室温。用水淬灭反应混合物,分离各层,水层再用乙酸乙酯萃取。合并有机层,与硅胶一起蒸发,将自由流动的硅胶装载到柱上,并通过硅胶色谱纯化(3-溴-2-氯-5-氟-6-甲基-4-吡啶基)-三甲基-硅烷(C)。

[0328] 将(3-溴-2-氯-5-氟-6-甲基-4-吡啶基)-三甲基-硅烷(C,1当量)溶于THF(0.67M)中,冷却至0℃,加入四丁基氟化铵(THF溶液)(1.2当量),将混合物在0℃下搅拌。10min后,用NH4Cl(水溶液)淬灭反应,并用EtOAc稀释。有机相用水洗涤两次,干燥,过滤,浓缩,装载到柱上,并通过硅胶色谱纯化3-溴-2-氯-5-氟-6-甲基吡啶(D)。

[0329] 实施例1A.2

[0330]



[0331] 在-96℃(内部温度)下向3-溴-2-氯-5-氟-6-甲基吡啶(A,1当量)的四氢呋喃溶液(0.40M)中在60min的时间段内加入二异丙基氨基锂溶液(1.2当量;2M的四氢呋喃溶液),维持内部温度在-96和-84℃之间,并将反应混合物在-96至-90℃下维持2h。将二氧化碳气体吹扫到反应混合物中35分钟,维持内部温度在-95至-78℃。通过TLC监测反应进展,并将反应混合物升温至-50至-45℃。用饱和氯化铵水溶液淬灭,并搅拌10min。将溶液用6N盐酸酸化至pH 2.0-1.5,用乙酸乙酯稀释,有机层用水洗涤。水层用乙酸乙酯萃取,减压浓缩合并的有机层,在二氯甲烷中搅拌,过滤固体沉淀,用二氯甲烷洗涤并真空干燥,得到3-溴-2-氯-5-氟-6-甲基异烟酸(B)。

[0332] 向3-溴-2-氯-5-氟-6-甲基异烟酸(B,1当量)的N,N-二甲基甲酰胺溶液(0.32M)中加入乙脒盐酸盐(C,1.4当量),并将反应混合物在0℃下冷却。加入N,N-二异丙基乙胺(5当量)和HATU(1.1当量),并将反应混合物在室温下搅拌1h。反应混合物用水稀释,用乙酸乙酯萃取,合并的有机层用无水硫酸钠干燥,过滤并浓缩,得到3-溴-2-氯-5-氟-N-(1-亚氨基乙基)-6-甲基异烟酰胺(D)。

[0333] 在0℃下向搅拌的3-溴-2-氯-5-氟-N-(1-亚氨基乙基)-6-甲基异烟酰胺(D,1当量)的四氢呋喃溶液(2M)中加入氢化钠(60%)(1当量),并在0℃下搅拌1h。将反应物质缓慢

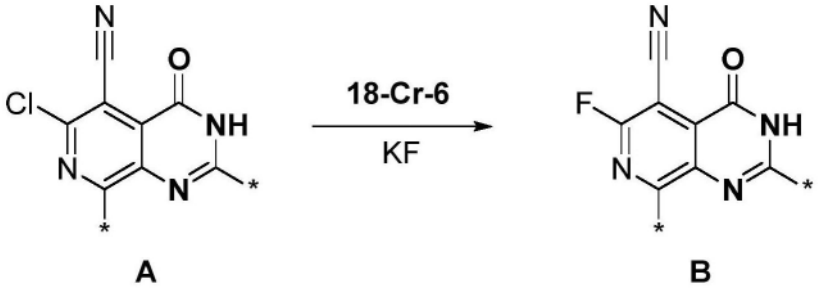
升温至室温并搅拌16h。将反应物质冷却至0℃,用2N盐酸酸化(pH约2),过滤得到的固体,用10%甲醇的乙醚溶液洗涤并干燥,得到5-溴-6-氯-2,8-二甲基吡啶并[3,4-d]嘧啶-4(3H)-酮(E)。

[0334] 在室温下向搅拌的5-溴-6-氯-2,8-二甲基吡啶并[3,4-d]嘧啶-4(3H)-酮(E,1当量)的N,N-二甲基甲酰胺溶液(0.056M)中,加入氰化亚铜(I)(1.2当量)。将反应加热至100℃并搅拌16h。用1N盐酸淬灭反应,过滤固体,用乙醚洗涤并通过色谱纯化,得到6-氯-2,8-二甲基-4-氧代-3,4-二氢吡啶并[3,4-d]嘧啶-5-甲腈(F)。

[0335] 将5-溴-6-氯-2,8-二甲基吡啶并[3,4-d]嘧啶-4(3H)-酮(E,1当量),氰化亚铜(I)(1.2当量)和NMP(0.072M)在具有搅拌棒的可密封容器中混合。将得到的混合物密封,搅拌,并在90℃下加热20h。冷却至室温后,将反应混合物用1%TFA的乙腈溶液稀释,过滤并通过色谱纯化,得到6-氯-2,8-二甲基-4-氧代-3,4-二氢吡啶并[3,4-d]嘧啶-5-甲腈(F)。

[0336] 在室温下向5-溴-6-氯-2,8-二甲基吡啶并[3,4-d]嘧啶-4(3H)-酮(E,1当量)的N,N-二甲基乙酰胺溶液(0.07M)中加入二氰基锌(1.4当量)和四(三苯基膦)钯(2.0当量)。将混合物用氩气脱气5min,并在130℃下搅拌5h。冷却至室温后,混合物用二甲基亚砜和乙腈稀释并通过色谱纯化,得到6-氯-2,8-二甲基-4-氧代-3,4-二氢吡啶并[3,4-d]嘧啶-5-甲腈(F)。

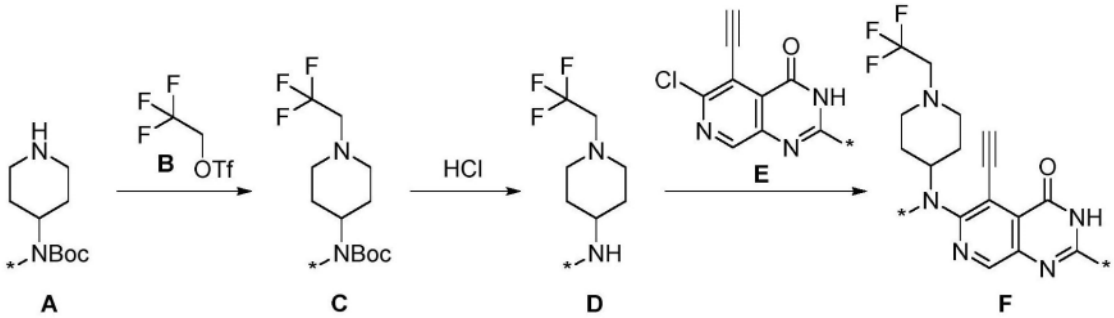
[0337] 实施例1A.3

[0338] 

A B

[0339] 将6-氯-2-甲基-4-氧代-3,4-二氢吡啶并[3,4-d]嘧啶-5-甲腈(A,1当量)的二甲基亚砜溶液(0.23M)用氩气吹扫10分钟。将18-冠-6醚(1.5当量)和氟化钾(5当量)加入反应混合物中,继续吹扫5分钟,在160℃下预热的油浴中搅拌2h。将反应混合物冷却,倒入冰冷的水中,用乙酸乙酯萃取,乙酸乙酯层用盐水溶液洗涤,用无水硫酸钠干燥,浓缩并与乙醚一起研磨,得到6-氟-2-甲基-4-氧代-3,4-二氢吡啶并[3,4-d]嘧啶-5-甲腈(B)。

[0340] 实施例1A.4

[0341] 

A C D F

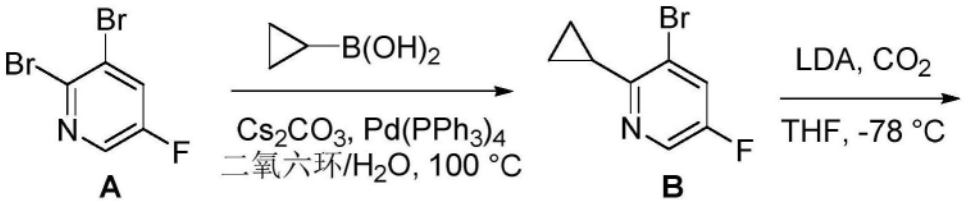
[0342] 向甲基(哌啶-4-基)氨基甲酸叔丁酯(A,1当量)和N,N-二异丙基乙胺(10当量)的乙腈溶液(0.35M)中滴加三氟甲磺酸2,2,2-三氟乙酯(2,1.25当量),将混合物在室温下搅拌16h。反应混合物用水稀释,用二氯甲烷萃取,有机层用无水硫酸钠干燥,过滤,浓缩并通

过快速柱色谱纯化,得到甲基(1-(2,2,2-三氟乙基)哌啶-4-基)氨基甲酸叔丁酯(C)。

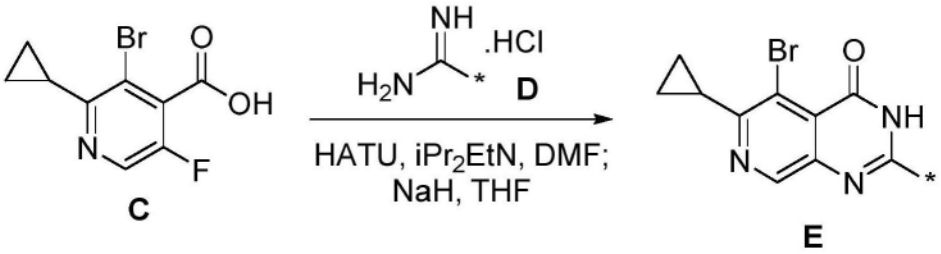
[0343] 将甲基(1-(2,2,2-三氟乙基)哌啶-4-基)氨基甲酸叔丁酯(C,1当量)的盐酸溶液(4M的1,4-二氧六环溶液,0.34M)在室温下搅拌4h。将反应混合物浓缩,得到N-甲基-1-(2,2,2-三氟乙基)哌啶-4-胺盐酸盐(D)。

[0344] 向6-氯-2-甲基-4-氧代-3,4-二氢吡啶并[3,4-d]嘧啶-5-甲腈(E,1当量)和N-甲基-1-(2,2,2-三氟乙基)哌啶-4-胺盐酸盐(D,3当量)的N,N-二甲基乙酰胺溶液(0.24M)中加入氟化钾(8当量)和18-冠-6(1当量),并将反应混合物在130℃下加热16h。将反应混合物冷却,用水稀释,用乙酸乙酯萃取,有机层用水洗涤,用无水硫酸钠干燥,过滤,浓缩并通过快速柱色谱纯化,得到2-甲基-6-(甲基(1-(2,2,2-三氟乙基)哌啶-4-基)氨基)-4-氧代-3,4-二氢吡啶并[3,4-d]嘧啶-5-甲腈(F)。

[0345] 实施例1A.5



[0346]



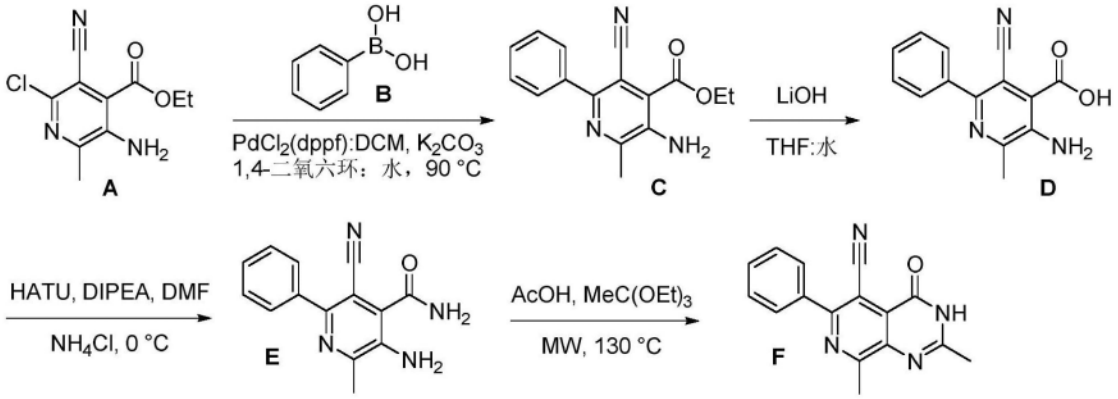
[0347] 将1,4-二氧六环(24mL)和水(8mL)加入2,3-二溴-5-氟吡啶(A,3000mg,11.8mmol),环丙基硼酸(1112mg,12.9mmol)和碳酸铯(8436mg,25.9mmol)的混合物中。将混合物用氩气鼓泡吹动5min。将四(三苯基膦)钯(680mg,0.590mmol)加入混合物中,将混合物抽真空并回充氩气三次。将得到的澄清黄色反应混合物在110℃下搅拌72h。混合物用乙酸乙酯稀释,用盐水洗涤,用无水硫酸镁干燥,并在过滤后真空浓缩。通过硅胶柱色谱纯化(0至5%乙酸乙酯的己烷溶液),得到3-溴-2-环丙基-5-氟吡啶(B)。

[0348] 在0℃下在氩气下将正丁基锂(2.5M的己烷溶液,2.1mL,5.30mmol)加入搅拌的二异丙胺(0.81mL,5.80mmol)的THF(5mL)溶液中。将得到的浅黄色溶液在0℃下搅拌10min,然后将其缓慢加入在-78℃下在氩气下的搅拌的3-溴-2-环丙基-5-氟吡啶(B,1000mg,4.60mmol)的四氢呋喃(20mL)溶液中。将得到的黄色反应混合物在-78℃下在氩气下搅拌30min,然后用二氧化碳气体鼓泡2min。将混合物在-78℃下搅拌10min,然后在5min内升温至室温。将反应用0.1N氢氧化钠稀释,并用乙醚萃取。水层用3M盐酸酸化,用乙酸乙酯萃取两次,用无水硫酸镁干燥,过滤后真空浓缩,得到3-溴-2-环丙基-5-氟异烟酸(C)。

[0349] 在0℃下向3-溴-2-环丙基-5-氟异烟酸(C,730.mg,2.81mmol)的N,N-二甲基甲酰胺(14mL)溶液中加入1-[双(二甲基氨基)亚甲基]-1H-1,2,3-三唑并[4,5-b]吡啶鎓3-氧化物六氟磷酸盐(1387mg,3.60mmol)和N,N-二异丙基乙胺(2.0mL,11.2mmol)。将混合物在室温下搅拌5min,将乙脒盐酸盐(D,345mg,3.60mmol)加入混合物中。在室温下搅拌混合物17h

后,将冰冷的水加入混合物,并用乙酸乙酯萃取两次。将合并的萃取液用氯化铵水溶液,碳酸氢钠水溶液和盐水洗涤,用无水硫酸镁干燥,并在过滤后真空浓缩。将残留物溶于四氢呋喃(18mL)中,在0℃下将氢化钠(60%在矿物油中,225mg,5.60mmol)加入混合物中。搅拌混合物18h后,将冰冷的水加入混合物中,用乙酸乙酯萃取三次,用无水硫酸镁干燥,并在过滤后真空浓缩。残留物与二氯甲烷一起研磨并过滤,得到5-溴-6-环丙基-2-甲基吡啶并[3,4-d]嘧啶-4(3H)-酮(E)。

[0350] 实施例1A.6

[0351] 

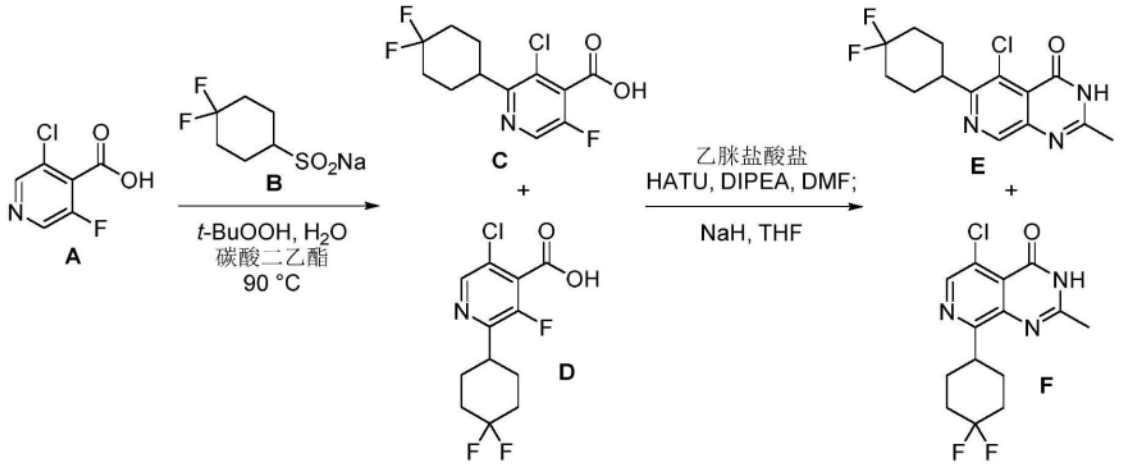
[0352] 向3-氨基-6-氯-5-氰基-2-甲基异烟酸乙酯(A,0.90g,3.75mmol)在1,4-二氧六环和水(4:1,10.0mL)中的溶液中加入苯基硼酸(B,0.68g,5.62mmol)和碳酸钾(1.53g,11.25mmol)。将反应混合物用氩气吹扫5min。然后加入[1,1-双(二苯基膦)二茂铁]二氯化钯(II)(与二氯甲烷的复合物,0.031g,0.037mmol),并将反应混合物在90℃下加热5h。在该时间后,将反应混合物冷却,用水稀释,并用乙酸乙酯萃取。将有机层用无水硫酸钠干燥,过滤并浓缩,得到粗产物。使用30-40%乙酸乙酯的己烷溶液,通过硅胶(100-200目)柱色谱将其纯化,得到3-氨基-5-氰基-2-甲基-6-苯基异烟酸乙酯(C)。

[0353] 在室温下向3-氨基-5-氰基-2-甲基-6-苯基异烟酸乙酯(C,0.6g,2.13mmol)在四氢呋喃和水(4:1,6mL)中的溶液中加入氢氧化锂(0.44g,10.67mmol)。将该反应混合物在室温下搅拌2h。在该时间后,将反应混合物用水稀释,用1N盐酸酸化,并用乙酸乙酯萃取。将有机层用无水硫酸钠干燥,过滤并浓缩,得到粗产物。将其用乙醚洗涤,得到3-氨基-5-氰基-2-甲基-6-苯基异烟酸(D)。

[0354] 向3-氨基-5-氰基-2-甲基-6-苯基异烟酸(D,0.5g,1.97mmol)的N,N-二甲基甲酰胺(5.0mL)溶液中加入氯化铵(0.31g,5.92mmol)和1-[双(二甲基氨基)亚甲基]-1H-1,2,3-三唑并[4,5-b]吡啶鎓3-氧化物六氟磷酸盐(0.840g,2.21mmol)。将该反应混合物冷却至0℃,加入N,N-二异丙基乙胺(2.7mL,14.70mmol),并将反应混合物在0℃下搅拌10min。然后将反应混合物用水稀释,并用乙酸乙酯萃取。将有机层用无水硫酸钠干燥,过滤并浓缩,得到粗产物。使用30-40%乙酸乙酯的己烷溶液,通过硅胶(100-200目)柱色谱将其纯化,得到3-氨基-5-氰基-2-甲基-6-苯基异烟酰胺(E)。

[0355] 将3-氨基-5-氰基-2-甲基-6-苯基异烟酰胺(E,0.4g,1.19mmol)在原乙酸三乙酯和乙酸(4:1,4mL)中的溶液在130℃下在微波下加热2h。在该时间后,将反应混合物冷却,用己烷稀释并过滤,得到2,8-二甲基-4-氧代-6-苯基-3,4-二氢吡啶并[3,4-d]嘧啶-5-甲腈(F)。

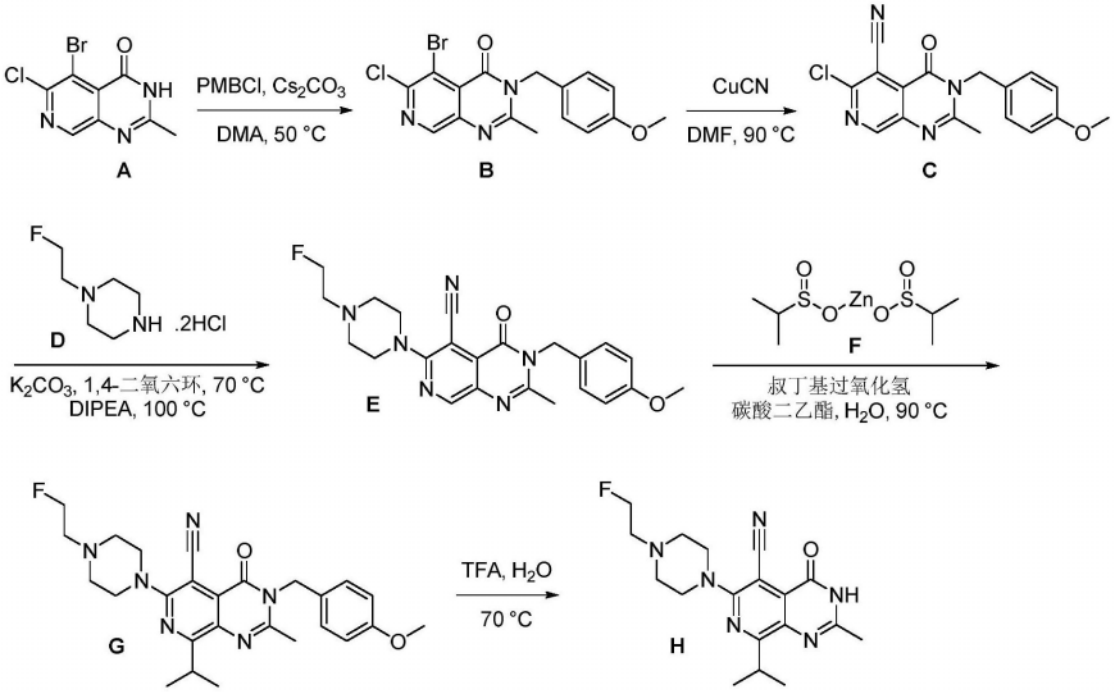
[0356] 实施例1A.7

[0357] 

[0358] 在氩气下向搅拌的3-氯-5-氟异烟酸(A,1当量)在碳酸二乙酯(0.29M)和水(0.44M)中的混合物中加入4,4-二氟环己烷-1-亚磺酸钠(B,3当量),并将混合物冷却至0℃。加入叔丁基过氧化氢(70重量%的水溶液)(10当量),将混合物搅拌5min,然后在90℃下在氩气下用油浴加热3h。在旋转蒸发仪上除去挥发物。将残留物溶于水,乙腈和TFA的混合物中,过滤并通过制备HPLC纯化,得到3-氯-2-(4,4-二氟环己基)-5-氟异烟酸(C)和5-氯-2-(4,4-二氟环己基)-3-氟异烟酸(D)的混合物。

[0359] 在室温下在氩气下将HATU(1.1当量)加入搅拌的3-氯-2-(4,4-二氟环己基)-5-氟异烟酸(C)和5-氯-2-(4,4-二氟环己基)-3-氟异烟酸(D,1当量)的DMF溶液(0.46M)中。2min后加入N,N-二异丙基乙胺(1.1当量)。在室温下搅拌35min后,加入乙脒盐酸盐(2当量)和N,N-二异丙基乙胺(2.2当量)的DMF溶液(5.6M)(将其用加热枪加热并超声处理使得乙脒全部溶解)。将得到的溶液在室温下在氩气下剧烈搅拌1.5h。反应混合物用乙酸乙酯稀释,并用盐水洗涤三次。将有机层用硫酸镁干燥,过滤,在旋转蒸发仪上浓缩,并在高真空下干燥,得到粘稠的黄褐色油状物。将油状物在氩气下在搅拌下溶于THF(0.046M)中。加入氢化钠(2.2当量),将反应混合物在室温下在氩气下剧烈搅拌21h。剧烈搅拌下加入氯化铵(5当量)的水溶液(0.14M)。将得到的混合物分配于乙酸乙酯和盐水之间。将有机层用硫酸镁干燥,过滤并在旋转蒸发仪上浓缩。将残留物溶于NMP,乙腈和TFA中,过滤并通过制备HPLC纯化,得到5-氯-6-(4,4-二氟环己基)-2-甲基吡啶并[3,4-d]嘧啶-4(3H)-酮(E)和5-氯-8-(4,4-二氟环己基)-2-甲基吡啶并[3,4-d]嘧啶-4(3H)-酮(F)

[0360] 实施例1A.8

[0361] 

[0362] 在室温下在氩气下将4-甲氧基苄基氯(1.27mL,9.38mmol)加入搅拌的5-溴-6-氯-2-甲基吡啶并[3,4-d]嘧啶-4(3H)-酮(A,1.98g,7.21mmol)和碳酸铯(3.29g,10.1mmol)在DMA(14mL)中的混合物中。将得到的混合物剧烈搅拌,并在50℃下在氩气下加热2h。反应混合物用乙酸乙酯(1.5L)稀释,用水洗涤一次,并用盐水洗涤两次。将有机层用硫酸镁干燥,过滤,在旋转蒸发仪上与硅胶一起浓缩并通过硅胶色谱纯化(0-40%乙酸乙酯的二氯甲烷溶液),得到5-溴-6-氯-3-(4-甲氧基苄基)-2-甲基吡啶并[3,4-d]嘧啶-4(3H)-酮(B)。

[0363] 在90℃下在氩气下将5-溴-6-氯-3-(4-甲氧基苄基)-2-甲基吡啶并[3,4-d]嘧啶-4(3H)-酮(B,1.24g,3.14mmol)在搅拌下溶于DMF(20mL)中。加入氰化亚铜(I)(338mg,3.77mmol),并将得到的澄清红色溶液在90℃下在氩气下加热搅拌1h 40min。趁热将反应混合物用乙酸乙酯稀释,并通过硅藻土(Celite)过滤到乙酸乙酯(600mL)中。滤饼用乙酸乙酯洗涤。将滤液与水一起振摇得到乳液,将其过滤。将滤液分配于乙酸乙酯和盐水之间。将有机层用盐水洗涤两次,用硫酸镁干燥,过滤,在旋转蒸发仪上与硅胶一起浓缩并通过硅胶色谱纯化(0-100%乙酸乙酯的二氯甲烷溶液),得到6-氯-3-(4-甲氧基苄基)-2-甲基-4-氧代-3,4-二氢吡啶并[3,4-d]嘧啶-5-甲腈(C)。

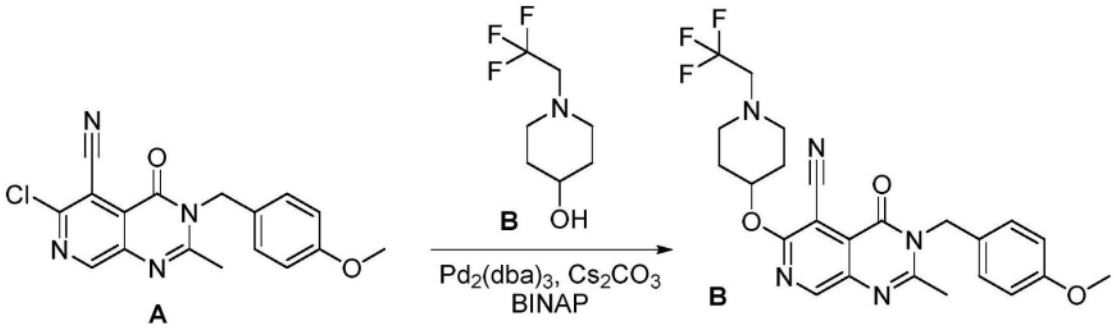
[0364] 在具有搅拌棒的可密封容器中将6-氯-3-(4-甲氧基苄基)-2-甲基-4-氧代-3,4-二氢吡啶并[3,4-d]嘧啶-5-甲腈(C,100mg,0.293mmol),1-(2-氟乙基)哌嗪二盐酸盐(D,120mg,0.587mmol),碳酸钾(183mg,1.32mmol)和NMP(1.5mL)混合。将得到的混合物密封,剧烈搅拌,并用油浴在70℃下加热40min。加入N,N-二异丙基乙胺(0.26mL,1.47mmol),并将得到的混合物密封,剧烈搅拌,并用油浴在100℃下加热1h。冷却至室温后,将反应混合物用甲醇和乙酸(0.34mL,5.87mmol)稀释。将得到的混合物过滤,并通过制备HPLC纯化(10-45%的乙腈在含0.1%TFA的水中的溶液)。将含有期望产物的级分合并,并在旋转蒸发仪上浓缩至约20mL,然后冻干至干,得到黄色油状物。将油状物溶于乙腈中,装载到来自Phenomenex的2克Strata X-C离子交换柱上。依次用水,乙腈,甲醇,然后用5%氢氧化铵的甲醇溶液洗脱柱子。将含有期望产物的洗脱液在旋转蒸发仪上浓缩,并在高真空下干燥,得到6-(4-(2-氟乙

基)哌嗪-1-基)-3-(4-甲氧基苄基)-2-甲基-4-氧代-3,4-二氢吡啶并[3,4-d]嘧啶-5-甲腈(E)。

[0365] 在氩气下向搅拌的6-(4-(2-氟乙基)哌嗪-1-基)-3-(4-甲氧基苄基)-2-甲基-4-氧代-3,4-二氢吡啶并[3,4-d]嘧啶-5-甲腈(E,28.2mg,0.065mmol)在碳酸二乙酯(0.4mL)和水(0.2mL)中的混合物中加入双((异丙基亚磺酰基)氧基)锌(F,54.2mg,0.194mmol),接着加入叔丁基过氧化氢(70重量%的水溶液)(0.092mL,0.666mmol)。将混合物搅拌,并在氩气下用油浴在90℃下加热10min。将反应混合物用NMP,乙酸和甲醇稀释,过滤,并通过制备HPLC纯化(15-65%的乙腈在含0.1%TFA的水中的溶液)。将含有期望产物的级分装载到来自Phenomenex的Strata X-C离子交换柱上。依次用水,乙腈,甲醇,然后用5%氢氧化铵的甲醇溶液洗脱柱。将含有期望产物的洗脱液在旋转蒸发仪上浓缩,并在高真空下干燥,得到6-(4-(2-氟乙基)哌嗪-1-基)-8-异丙基-3-(4-甲氧基苄基)-2-甲基-4-氧代-3,4-二氢吡啶并[3,4-d]嘧啶-5-甲腈(G)。

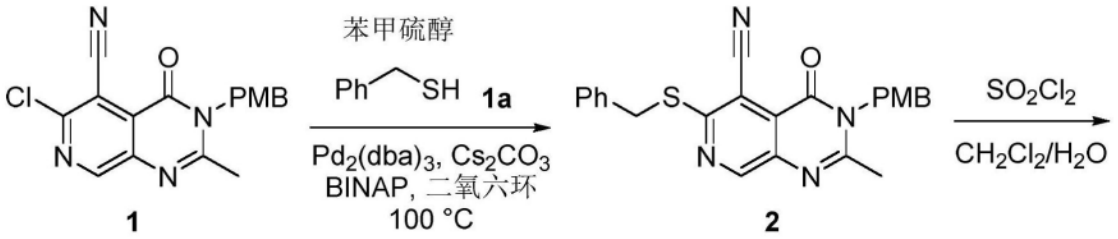
[0366] 在具有搅拌棒的可密封容器中将6-(4-(2-氟乙基)哌嗪-1-基)-8-异丙基-3-(4-甲氧基苄基)-2-甲基-4-氧代-3,4-二氢吡啶并[3,4-d]嘧啶-5-甲腈(G,23.8mg,0.050mmol),TFA(2mL)和水(0.1mL)混合,密封,搅拌,并在70℃下加热1h。在旋转蒸发仪上除去挥发物。将残留物溶于NMP和甲醇中,过滤,并通过制备HPLC纯化(10-40%的乙腈在含0.1%TFA的水中的溶液)。将含有期望产物的级分装载到来自Phenomenex的Strata X-C离子交换柱。依次用水,乙腈,甲醇,然后用5%氢氧化铵的甲醇溶液洗脱柱。将含有期望产物的洗脱液在旋转蒸发仪上浓缩,并在高真空下干燥,得到6-(4-(2-氟乙基)哌嗪-1-基)-8-异丙基-2-甲基-4-氧代-3,4-二氢吡啶并[3,4-d]嘧啶-5-甲腈(H)。

[0367] 实施例1A.9

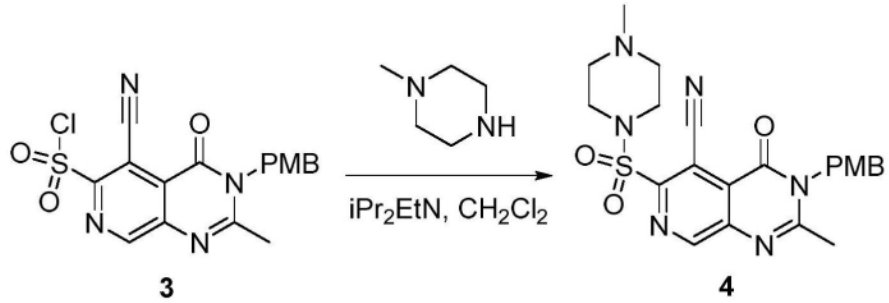
[0368] 

[0369] 在室温下向6-氯-3-(4-甲氧基苄基)-2-甲基-4-氧代-3,4-二氢吡啶并[3,4-d]嘧啶-5-甲腈(A,192mg,0.560mmol)的1,4-二氧六环(5.6mL)溶液中加入1-(2,2,2-三氟乙基)哌啶-4-醇(B,206mg,1.13mmol),碳酸铯(367mg,1.13mmol),2,2'-双(二苯基膦基)-1,1'-联萘(105mg,0.169mmol)和三(二亚苄基丙酮)二钯(103mg,0.113mmol)。将混合物用氩气鼓泡5min,并在100℃下搅拌2h。将混合物用乙酸乙酯稀释,并通过硅藻土垫过滤。真空浓缩滤液。通过硅胶柱色谱纯化(0-80%乙酸乙酯的己烷溶液),得到3-(4-甲氧基苄基)-2-甲基-4-氧代-6-((1-(2,2,2-三氟乙基)哌啶-4-基)氧基)-3,4-二氢吡啶并[3,4-d]嘧啶-5-甲腈(C)粗品。

[0370] 实施例1A.10



[0371]

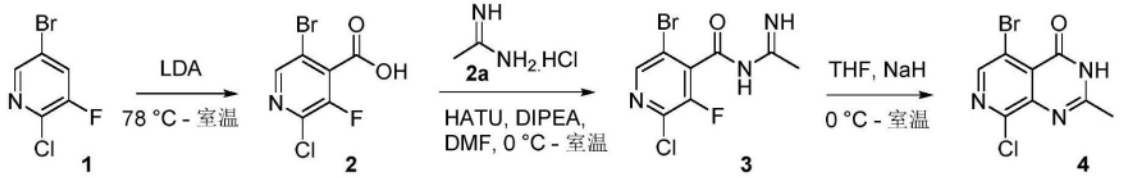


[0372] 在室温下向6-氯-3-(4-甲氧基苄基)-2-甲基-4-氧代-3,4-二氢吡啶并[3,4-d]嘧啶-5-甲腈(1,134mg,0.390mmol)的1,4-二氧六环(3.9mL)溶液中加入苯甲硫醇(1a,0.09mL,0.790mmol),碳酸铯(256mg,0.790mmol),2,2'-双(二苯基膦基)-1,1'-联萘(73mg,0.118mmol)和三(二亚苄基丙酮)二钯(72mg,0.0790mmol)。混合物用氩气鼓泡5min,并在100℃下搅拌2h。混合物用乙酸乙酯稀释,用5%breech的水溶液洗涤,用无水硫酸镁干燥,并在过滤后真空浓缩。用制备HPLC纯化(C_{18}柱,15-85%乙腈的水溶液+0.1%三氟乙酸),得到6-(苄硫基)-3-(4-甲氧基苄基)-2-甲基-4-氧代-3,4-二氢吡啶并[3,4-d]嘧啶-5-甲腈(2)。

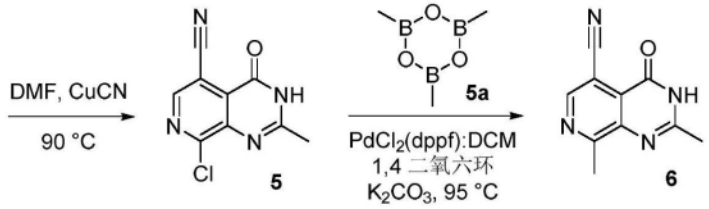
[0373] 在0℃下向6-(苄硫基)-3-(4-甲氧基苄基)-2-甲基-4-氧代-3,4-二氢吡啶并[3,4-d]嘧啶-5-甲腈(2,74mg,0.173mmol)在二氯甲烷(2mL)和水(0.4mL)中的溶液中加入硫酰氯(0.1mL,1.21mmol)。将混合物在室温下搅拌1h。将有机层分离,用无水硫酸镁干燥,并在过滤后真空浓缩,得到5-氰基-3-(4-甲氧基苄基)-2-甲基-4-氧代-3,4-二氢吡啶并[3,4-d]嘧啶-6-磺酰氯(3)粗品。

[0374] 在0℃下,向5-氰基-3-(4-甲氧基苄基)-2-甲基-4-氧代-3,4-二氢吡啶并[3,4-d]嘧啶-6-磺酰氯(3,70mg,0.173mmol)的二氯甲烷(1.7mL)溶液中加入1-甲基哌嗪(0.06mL,0.520mmol)和二异丙基乙胺(0.09mL,0.520mmol)。在室温下搅拌混合物1h后,将混合物用碳酸氢钠水溶液稀释。有机物质用乙酸乙酯萃取两次,用无水硫酸镁干燥,并在过滤后真空浓缩。用制备HPLC纯化(C_{18}柱,15-60%乙腈的水溶液+0.1%三氟乙酸),得到3-(4-甲氧基苄基)-2-甲基-6-((4-甲基哌嗪-1-基)磺酰基)-4-氧代-3,4-二氢吡啶并[3,4-d]嘧啶-5-甲腈(4)。

[0375] 实施例1A.11



[0376]



[0377] 将5-溴-2-氯-3-氟吡啶(1,30.0g,143.6mmol)的四氢呋喃(300mL)溶液冷却至-78℃,并滴加二异丙基氨基锂(2M的THF溶液,78.9mL,157.9mmol)。将该反应混合物在-78℃下搅拌1h。然后将反应混合物用二氧化碳气体吹扫15min,使其在室温下升温。将反应混合物用氯化铵溶液淬灭,并用水稀释。水层用乙酸乙酯洗涤,用6N盐酸溶液酸化,并用15%甲醇的二氯甲烷溶液萃取。将有机层用无水硫酸钠干燥,过滤并浓缩,得到5-溴-2-氯-3-氟异烟酸(2)。

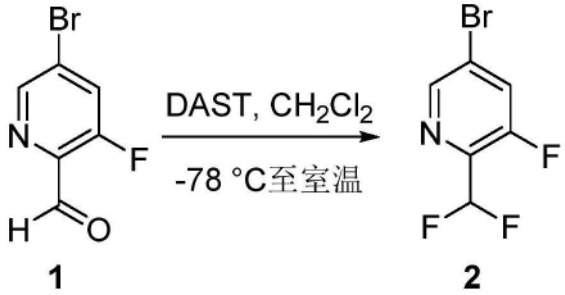
[0378] 在0℃下向5-溴-2-氯-3-氟异烟酸(2,18.0g,71.1mmol)的N,N-二甲基甲酰胺(30mL)溶液中加入乙脒盐酸盐(2a,13.4g,142.3mmol)。然后加入N,N-二异丙基乙胺(110mL,711.0mmol)和1-[双(二甲基氨基)亚甲基]-1H-1,2,3-三唑并[4,5-b]吡啶鎓3-氧化物六氟磷酸盐(40.5g,106.6mmol),并将反应混合物在室温下搅拌2h。在该时间后,将反应混合物用水稀释,并用乙酸乙酯萃取。将有机层用无水硫酸钠干燥,过滤并浓缩,得到5-溴-2-氯-3-氟-N-(1-亚氨基乙基)异烟酰胺(3)粗品。

[0379] 将5-溴-2-氯-3-氟-N-(1-亚氨基乙基)异烟酰胺(3,18.0g)粗品的四氢呋喃(200mL)溶液冷却至0℃,然后分批加入矿物油中的60%氢化钠(7.30g,NaH,184.3mmol),并将反应混合物在室温下搅拌12h。在该时间后,将反应混合物倒入冰冷的水中。水层用5%甲醇的二氯甲烷溶液洗涤,用6N盐酸溶液酸化,并用10%甲醇的二氯甲烷溶液萃取。来自该萃取的有机层用无水硫酸钠干燥,过滤并浓缩,得到粗产物,将其用乙醚洗涤,得到5-溴-8-氯-2-甲基吡啶并[3,4-d]嘧啶-4(3H)-酮(4)。

[0380] 向5-溴-8-氯-2-甲基吡啶并[3,4-d]嘧啶-4(3H)-酮(4,8.0g,29.3mmol)的N,N-二甲基甲酰胺(80.0mL)溶液中加入氰化亚铜(I)(4.1g,46.8mmol)。将反应混合物在90℃下加热3h。在该时间后,将反应混合物冷却,用水稀释,用6N盐酸溶液酸化,并用乙酸乙酯萃取。将有机层浓缩得到粗产物,用40-50%乙酸乙酯的己烷溶液作为洗脱剂,通过硅胶(100-200目)柱色谱将其纯化,得到8-氯-2-甲基-4-氧代-3,4-二氢吡啶并[3,4-d]嘧啶-5-甲腈(5)。

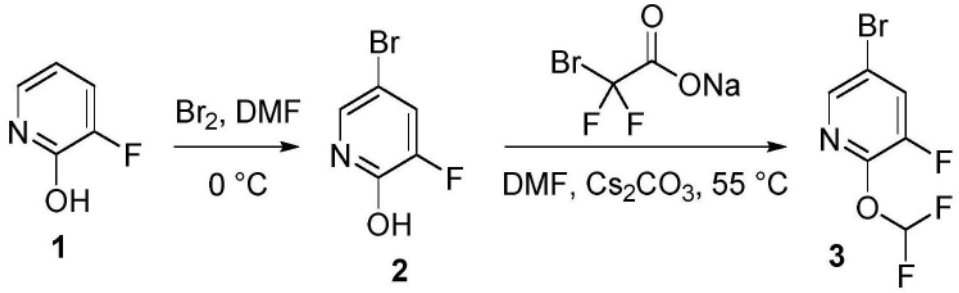
[0381] 在室温下向8-氯-2-甲基-4-氧代-3,4-二氢吡啶并[3,4-d]嘧啶-5-甲腈(5,1.0g,4.55mmol)的1,4-二氧六环(15.0mL)溶液中加入2,4,6-三甲基-1,3,5,2,4,6-三氧杂三硼杂环己烷(5a,1.0mL,7.5mmol),碳酸钾(2.0g,15.0mmol)和水(2mL)。将该反应混合物用氮气脱气10min。然后加入[1,1-双(二苯基膦基)二茂铁]二氯化钯(II)与二氯甲烷的复合物(0.183g,0.225mmol),并将反应混合物在95℃下加热12h。在该时间后,将反应混合物冷却并减压浓缩,得到粗产物,用10%甲醇的二氯甲烷溶液作为洗脱剂,通过硅胶(100-200目)柱色谱将其纯化,得到2,8-二甲基-4-氧代-3,4-二氢吡啶并[3,4-d]嘧啶-5-甲腈(6)。

[0382] 实施例1A.12

[0383] 

[0384] 在-78℃下在氩气下将二乙基氨基三氟化硫(1.44mL,10.4mmol)加入搅拌的5-溴-3-氟吡啶-2-甲醛(1,0.97g,4.75mmol)的DCM(20mL)溶液中。移除冷浴,使反应混合物在氩气下经1.5h升温至室温。将反应混合物倒入搅拌的饱和碳酸氢钠水溶液和冰的混合物中。将得到的混合物在室温下剧烈搅拌1h以完全淬灭反应混合物。分离各相,并将水相用二氯甲烷萃取。合并的有机层用硫酸钠干燥,过滤,在旋转蒸发仪上浓缩,并通过硅胶色谱(0-10%乙酸乙酯的己烷溶液)纯化。将含有期望产物的级分合并,并在室温下在旋转蒸发仪上浓缩。残留物用干燥的THF(5mL)稀释,并在旋转蒸发仪上浓缩。残留物在高真空下干燥2min,得到5-溴-2-(二氟甲基)-3-氟吡啶(2)。

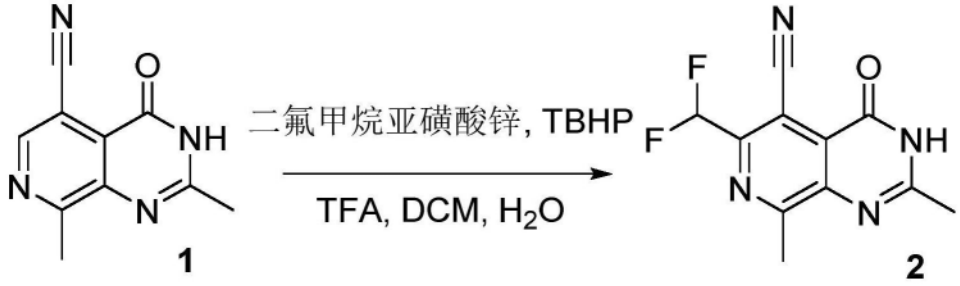
[0385] 实施例1A.13

[0386] 

[0387] 将3-氟吡啶-2-醇(1,20.0g,176.9mmol)的N,N-二甲基甲酰胺(220.0mL)溶液在0℃下冷却,滴加溴(10.30mL,194.6mmol),并将反应混合物在0℃下搅拌2h。完成后,将反应混合物用水稀释,并用乙酸乙酯萃取。将有机层用碳酸氢钠和盐水洗涤,用无水硫酸钠干燥,过滤并浓缩,得到化合物粗品。使用硅胶(100-200目)和2-3%甲醇的二氯甲烷溶液,通过柱色谱纯化化合物粗品,得到5-溴-3-氟吡啶-2-醇(2)。

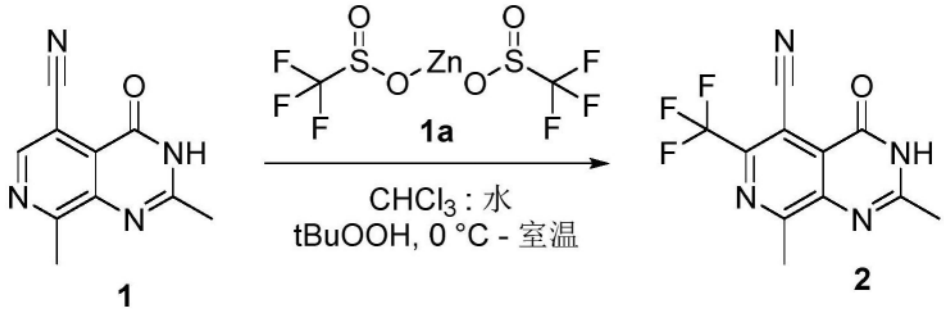
[0388] 向5-溴-3-氟吡啶-2-醇(2,11.0g,57.29mmol)的N,N-二甲基甲酰胺(110mL)溶液中加入碳酸铯(24.59g,74.47mmol)和2-溴-2,2-二氟乙酸钠(17.04g,85.93mmol),并将反应混合物在55℃下加热。完成后,将反应混合物用水稀释,并用乙醚萃取。将有机层用无水硫酸钠干燥,过滤并浓缩,得到化合物粗品。将得到的化合物粗品减压浓缩,得到粗产物,使用硅胶(100-200目)和1-2%乙酸乙酯的己烷溶液,通过柱色谱纯化所述粗产物,得到5-溴-2-(二氟甲氧基)-3-氟吡啶(3)。

[0389] 实施例1A.14

[0390] 

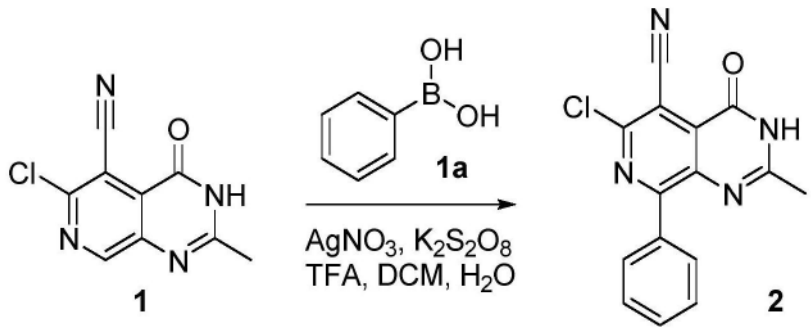
[0391] 向2,8-二甲基-4-氧代-3,4-二氢吡啶并[3,4-d]嘧啶-5-甲腈(1,0.16g,0.8mmol)和二氟甲烷亚磺酸锌(0.472g,1.6mmol)在二氯甲烷和水(4:1,2mL)的混合物中的溶液中加入三氟乙酸(0.06mL,0.8mmol)和叔丁基过氧化氢(0.23mL,2.4mmol)。将该混合物在室温下搅拌16h。在该时间后,将反应混合物减压浓缩,用水稀释,并用二氯甲烷萃取。合并的有机层用水洗涤,然后用盐水洗涤,用无水硫酸钠干燥,过滤并浓缩。用40%乙酸乙酯的已烷溶液作为洗脱剂,通过硅胶(100-200目)快速色谱纯化粗产物。将期望的级分减压浓缩,得到6-(二氟甲基)-2,8-二甲基-4-氧代-3,4-二氢吡啶并[3,4-d]嘧啶-5-甲腈(2)。

[0392] 实施例1A.15

[0393] 

[0394] 将2,8-二甲基-4-氧代-3,4-二氢吡啶并[3,4-d]嘧啶-5-甲腈(1,0.200g,0.99mmol)和双(((三氟甲基)亚磺酰基)氧基)锌(1a,0.662g,1.99mmol)在氯仿(2.0mL)和水(2.0mL)中搅拌,在0℃下加入叔丁基过氧化氢(70%)(0.38mL,2.99mmol)。将反应混合物在室温下搅拌15h。在该时间后,将反应混合物用水稀释,并用乙酸乙酯萃取。将有机层用无水硫酸钠干燥,过滤并浓缩,得到粗产物。用70-80%乙酸乙酯的已烷溶液作为洗脱剂,通过硅胶(100-200目)柱色谱纯化粗品。将期望的级分减压浓缩,得到2,8-二甲基-4-氧代-6-(三氟甲基)-3,4-二氢吡啶并[3,4-d]嘧啶-5-甲腈(2)。

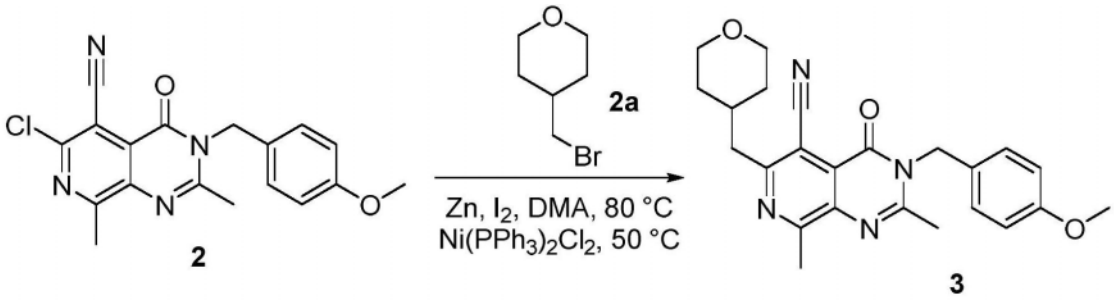
[0395] 实施例1A.16

[0396] 

[0397] 向6-氯-2-甲基-4-氧代-3,4-二氢吡啶并[3,4-d]嘧啶-5-甲腈(1,1.0g,4.54mmol)在二氯甲烷:水(1:1)(20.0mL)中的溶液中加入2,2,2-三氟乙酸(10.4mL,13.63mmol)。将反应混合物在室温下搅拌15min,然后加入苯基硼酸(1a,1.65g,

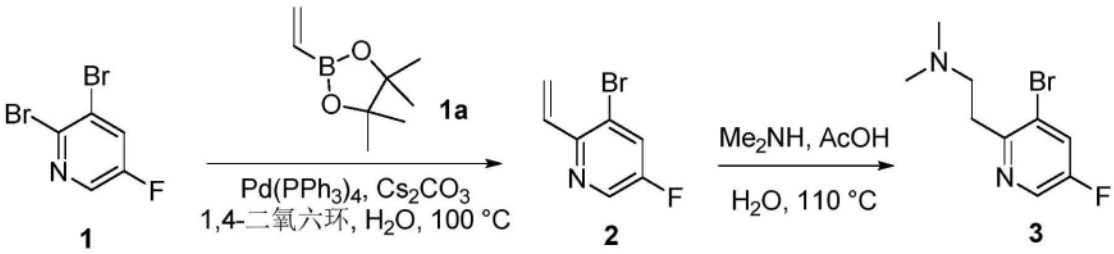
13.63mmol)，并搅拌40min。加入硝酸银(0.154g，0.90mmol)和过硫酸钾(2.45g，9.09mmol)，并将反应混合物在室温下搅拌24h。完成后，将反应混合物用水稀释，并用二氯甲烷萃取。将有机层用无水硫酸钠干燥，过滤并浓缩，得到化合物粗品。粗品用30％乙醚的戊烯溶液洗涤，得到6-氯-2-甲基-4-氧代-8-苯基-3,4-二氢吡啶并[3,4-d]嘧啶-5-甲腈(2)。

[0398] 实施例1A.17

[0399] 

[0400] 将锌粉(<10微米)(37.7mg，0.58mmol)称量到干燥的1打兰(dram)小瓶中并放置在氩气下。加入DMA(0.4mL)，接着加入碘(3.6mg，0.014mmol)。将得到的混合物在室温下在氩气下剧烈搅拌，直到碘的红色消褪(5min)。加入4-(溴甲基)四氢-2H-吡喃(2a，0.072mL，0.56mmol)，将得到的混合物密封，剧烈搅拌，并在80℃下加热23h。冷却至室温后，将反应混合物置于氩气下，并加入6-氯-3-(4-甲氧基苄基)-2,8-二甲基-4-氧代-3,4-二氢吡啶并[3,4-d]嘧啶-5-甲腈(2，49.9mg，0.14mmol)和双(三苯基膦)镍(II)二氯化物(9.2mg，0.014mmol)。将得到的混合物在室温下在氩气下剧烈搅拌2.5h，然后在50℃下2h。将反应混合物用NMP和甲醇稀释，过滤，并通过制备HPLC纯化(15-70％的乙腈在含0.1％TFA的水中的溶液)。将含有期望产物的级分合并，并冻干至干，得到3-(4-甲氧基苄基)-2,8-二甲基-4-氧代-6-((四氢-2H-吡喃-4-基)甲基)-3,4-二氢吡啶并[3,4-d]嘧啶-5-甲腈(3)。

[0401] 实施例1A.18

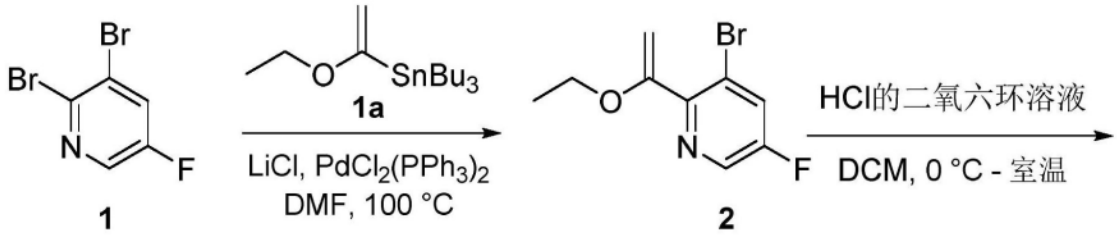
[0402] 

[0403] 在装有搅拌棒的100mL圆底烧瓶中将2,3-二溴-5-氟吡啶(1，3.15g，12.4mmol)，4,4,5,5-四甲基-2-乙烯基-1,3,2-二氧杂硼杂环戊烷(1a，1.93mL，13.6mmol)，碳酸铯(8.86g，27.2mmol)，1,4-二氧六环(24mL)和水(6mL)混合。在真空下除去烧瓶中的气氛，用氩气置换两次。加入四(三苯基膦)钯(0)(0.71g，0.62mmol)，在真空下除去烧瓶中的气氛，并用氩气置换两次。将得到的澄清黄色反应混合物剧烈搅拌，并在100℃下在氩气下加热12h。冷却至室温后，将反应混合物分配于盐水和乙酸乙酯之间。将有机层用硫酸镁干燥，过滤，在旋转蒸发仪上浓缩，并通过硅胶色谱纯化(2-15％乙酸乙酯的己烷溶液)，得到3-溴-5-氟-2-乙烯基吡啶(2)。

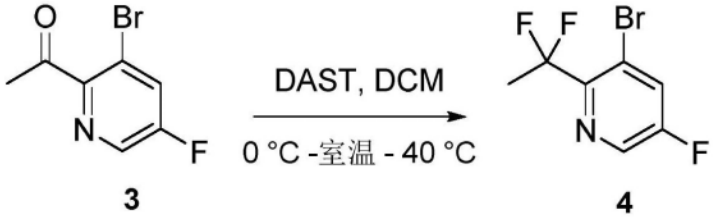
[0404] 将二甲胺(40重量％的水溶液)(34.1mL，108mmol)加入搅拌的3-溴-5-氟-2-乙烯基吡啶(2，2.18g，10.8mmol)的乙酸(14.2mL，248mmol)溶液中。将得到的混合物密封，剧烈搅拌，并在110℃下加热68h。冷却至室温后，反应混合物倒入搅拌的氢氧化钠(9.93g，

248mmol)和碳酸氢钠(4.53g,54.0mmol)在冰水的混合物中。得到的混合物用二氯甲烷萃取三次。合并的有机层用硫酸镁干燥,过滤,在旋转蒸发仪上浓缩,并通过硅胶色谱纯化(0-20%甲醇的二氯甲烷溶液)。将含有期望产物的级分合并,并在旋转蒸发仪上浓缩。残留物在THF中浓缩两次,并在高真空下干燥,得到2-(3-溴-5-氟吡啶-2-基)-N,N-二甲基乙-1-胺(3)。

[0405] 实施例1A.19



[0406]

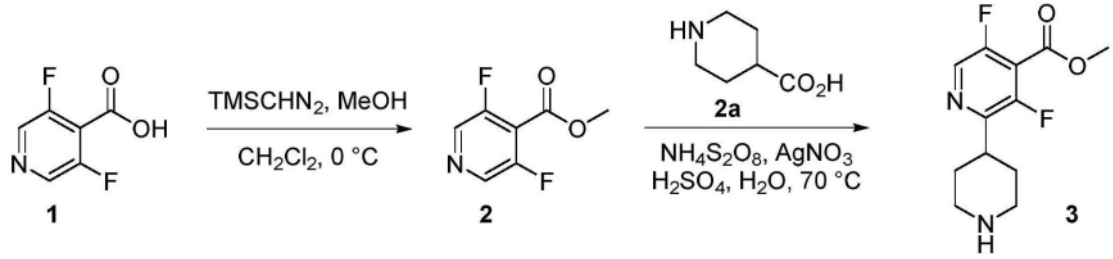


[0407] 将2,3-二溴-5-氟吡啶(1,10.0g,39.2mmol),三丁基(1-乙氧基乙烯基)锡烷(1a,15.5mL,43.1mmol)和氯化锂(4.9g,117.6mmol)的N,N-二甲基甲酰胺(100mL)溶液在氮气下脱气10分钟。然后,加入双(三苯基膦)二氯化钯(II)(1.3g,1.9mmol),并将混合物在100℃下加热4h。将反应混合物冷却,用水稀释,并用乙醚萃取。将合并的有机层用水洗涤,用无水硫酸钠干燥,过滤并浓缩。用硅胶(100-200目)和0-2%乙酸乙酯的己烷溶液,通过柱色谱纯化粗产物,得到3-溴-2-(1-乙氧基乙烯基)-5-氟吡啶(2)。

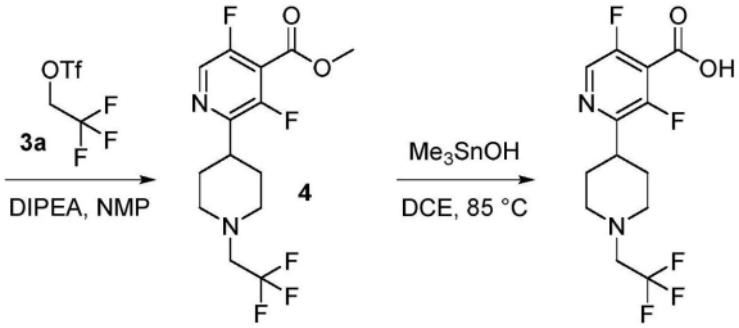
[0408] 将3-溴-2-(1-乙氧基乙烯基)-5-氟吡啶(2,5.7g,23.1mmol)的二氯甲烷(60mL)溶液冷却至0℃,加入盐酸的1,4-二氧六环溶液(4m,10mL),将混合物在室温下搅拌3h。将反应混合物倒入冰冷的水中,用碳酸氢钠中和,并用二氯甲烷萃取。将有机层用无水硫酸钠干燥,过滤并浓缩。用硅胶(100-200目)和0-5%乙酸乙酯的己烷溶液,通过柱色谱纯化粗产物,得到1-(3-溴-5-氟吡啶-2-基)乙-1-酮(3)。

[0409] 将1-(3-溴-5-氟吡啶-2-基)乙-1-酮(3,3.8g,17.4mmol)的二氯甲烷(40mL)溶液冷却至0℃,加入二乙基氨基三氟化硫(23.3mL,174.0mmol);将混合物在室温下搅拌48h,然后在40℃下加热72h。将反应混合物冷却,倒入碎冰中(非常缓慢,分批),用碳酸氢钠中和,并用二氯甲烷萃取。将有机层用无水硫酸钠干燥,过滤并浓缩。用硅胶(100-200目)和0-1%乙酸乙酯的己烷溶液,通过柱色谱纯化粗品,得到3-溴-2-(1,1-二氟乙基)-5-氟吡啶(4)。

[0410] 实施例1A.20



[0411]



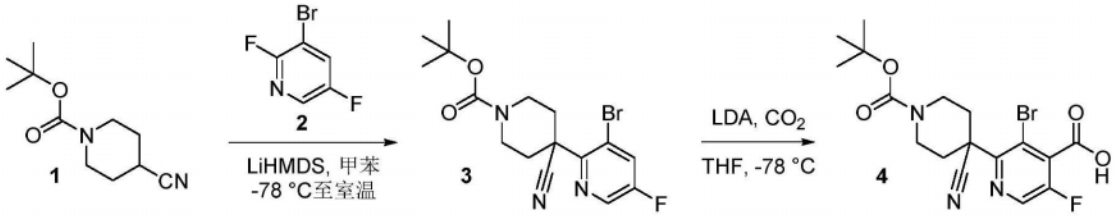
[0412] 在0℃下将(三甲基甲硅烷基)重氮甲烷(2M的乙醚溶液)(19.5mL,39.1mmol)缓慢加入搅拌的3,5-二氟异烟酸(1,5.18g,32.6mmol)在湿甲醇(200mL)中的混合物(未完全溶解)中。将得到的浑浊的混合物在0℃下在空气中剧烈搅拌。在加入过程中观察到冒泡,并持续45min。加入二氯甲烷(100mL),接着加入更多的(三甲基甲硅烷基)重氮甲烷(2M的乙醚溶液)(19.5mL,39.1mmol)。将得到的澄清溶液在0℃下在空气中剧烈搅拌30min。加入更多的(三甲基甲硅烷基)重氮甲烷(2M的乙醚溶液)(19.5mL,39.1mmol),然后再加入更多的(三甲基甲硅烷基)重氮甲烷(2M的乙醚溶液)(19.5mL,39.1mmol),直到LCMS显示原料完全转化。在旋转蒸发仪上除去挥发物。将残留物溶于二氯甲烷中,并通过硅胶色谱纯化(0-50%乙酸乙酯的己烷溶液)(仅在高真空下干燥几秒),得到3,5-二氟异烟酸甲酯(2)。

[0413] 在70℃下将哌啶-4-甲酸(2a,1.20g,9.27mmol),过硫酸铵(2.33g,10.2mmol)和硝酸银(590mg,3.47mmol)的水(8mL)溶液加入搅拌的3,5-二氟异烟酸甲酯(2,802mg,4.63mmol)在3%硫酸水溶液(8mL)中的混合物中。将得到的棕色混合物在70℃下在剧烈搅拌下加热10min(观察到冒泡),然后冷却至室温。将反应混合物在70℃下加热,并加入更多的哌啶-4-甲酸(1.20g,9.27mmol),过硫酸铵(2.33g,10.2mmol)和硝酸银(590mg,3.47mmol)的水(8mL)溶液。将反应混合物在70℃下加热10min,然后冷却至室温。将此总共重复四次。反应混合物用碳酸钾碱化。在旋转蒸发仪上除去所有的挥发物。将残留物与20%甲醇的二氯甲烷溶液一起打浆,并通过硅藻土过滤。滤饼用20%甲醇的二氯甲烷溶液彻底洗涤。将滤液在旋转蒸发仪上与硅胶一起浓缩,并通过硅胶色谱纯化(0-20%甲醇的二氯甲烷溶液),得到3,5-二氟-2-(哌啶-4-基)异烟酸甲酯(3)。

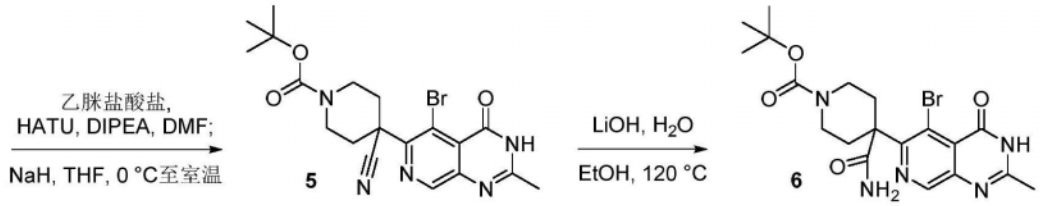
[0414] 在室温下在氩气下将三氟甲磺酸2,2,2-三氟乙酯(3a,1.05mL,7.32mmol)加入搅拌的3,5-二氟-2-(哌啶-4-基)异烟酸甲酯(3,625mg,2.44mmol)和N,N-二异丙基乙胺(3.40mL,19.5mmol)的NMP(10mL)溶液中。将得到的混合物在室温下在氩气下搅拌3h。反应混合物用乙酸乙酯稀释,用盐水洗涤三次,用硫酸镁干燥,过滤,在旋转蒸发仪上浓缩,并通过硅胶色谱纯化(0-50%乙酸乙酯的己烷溶液),得到3,5-二氟-2-(1-(2,2,2-三氟乙基)哌啶-4-基)异烟酸甲酯(4)。

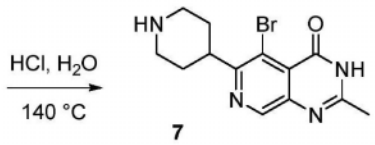
[0415] 在具有搅拌棒的100mL圆底烧瓶中将3,5-二氟-2-(1-(2,2,2-三氟乙基)哌啶-4-基)异烟酸甲酯(4,505mg,1.49mmol),三甲基氢氧化锡(1.08g,5.97mmol)和DCE(10mL)混合。将得到的混合物剧烈搅拌,并在回流冷凝器下在80℃下在氩气下加热1h,然后在85℃下加热3h。在旋转蒸发仪上除去挥发物。将残留物溶于20%甲醇的二氯甲烷溶液中,通过硅胶色谱纯化(0-20%甲醇的二氯甲烷溶液),得到3,5-二氟-2-(1-(2,2,2-三氟乙基)哌啶-4-基)异烟酸(5)。

[0416] 实施例1A.21



[0417]





[0418] 在-78℃下在氩气下将双(三甲基甲硅烷基)氨基锂(1M的甲苯溶液)(2.23mL,2.23mmol)缓慢加入搅拌的4-氰基哌啶-1-甲酸叔丁酯(1,469mg,2.23mmol)和3-溴-2,5-二氟吡啶(2,433mg,2.23mmol)的甲苯(5mL)溶液中。移除冷浴,将得到的橙色溶液在氩气下在搅拌下升温至室温,并在室温下搅拌2h。剧烈搅拌下加入0.2M HCl的水溶液(22.3mL,4.46mmol)。将得到的混合物用乙酸乙酯萃取。将有机层用盐水洗涤,用硫酸镁干燥,过滤,在旋转蒸发仪上浓缩,并通过硅胶色谱纯化(0-50%乙酸乙酯的己烷溶液),得到4-(3-溴-5-氟吡啶-2-基)-4-氰基哌啶-1-甲酸叔丁酯(3)。

[0419] 在0℃下在氩气下将正丁基锂(2.5M的己烷溶液)(0.48mL,1.20mmol)加入搅拌的二异丙胺(0.18mL,1.30mmol)的THF(4mL)溶液中。将得到的浅黄色溶液在0℃下搅拌10min,然后缓慢加入在-78℃下在氩气下搅拌的4-(3-溴-5-氟吡啶-2-基)-4-氰基哌啶-1-甲酸叔丁酯(3,401mg,1.04mmol)的THF(7mL)溶液中。将得到的橙色反应混合物在-78℃下在氩气下搅拌30min,然后用二氧化碳气体鼓泡约1min(橙色消褪)。10min后,加入0.1N氢氧化钠水溶液(1mL)以淬灭反应混合物。将得到的混合物分配于0.1N氢氧化钠水溶液(20mL)和乙醚之间。将有机层用0.1N氢氧化钠水溶液(5mL)再萃取两次。弃去有机物。水层用1N HCl水溶液酸化,然后用乙酸乙酯萃取四次。将有机层用盐水洗涤,用硫酸镁干燥,过滤,在旋转蒸发仪上浓缩,并在高真空下干燥,得到3-溴-2-(1-(叔丁氧基羰基)-4-氰基哌啶-4-基)-5-氟异烟酸(4)。

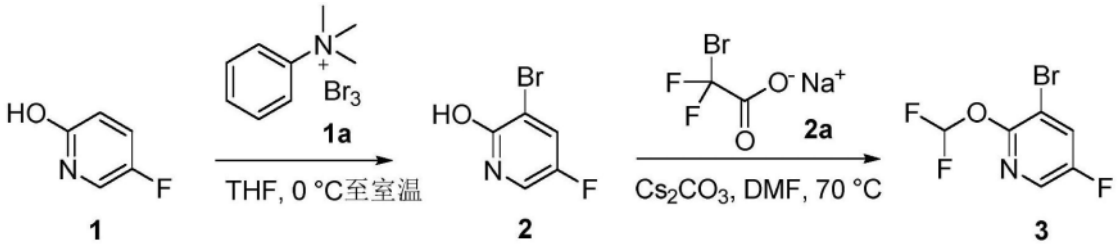
[0420] 在室温下在氩气下将HATU(366mg,0.964mmol)加入搅拌的3-溴-2-(1-(叔丁氧基

羰基)-4-氰基哌啶-4-基)-5-氟异烟酸(4,393mg,0.918mmol)的DMF(6mL)溶液中。2min后,加入N,N-二异丙基乙胺(0.19mL,1.10mmol)。将得到的橙色混合物在室温下在氩气下搅拌20min。加入乙脒盐酸盐(174mg,1.84mmol)和N,N-二异丙基乙胺(0.80mL,4.59mmol)的DMF(3mL)溶液(将其用加热枪加热并用超声处理,使得乙脒完全溶解)。将得到的橙色混合物在室温下在氩气下剧烈搅拌2h。反应混合物用乙酸乙酯稀释,用盐水洗涤四次,用硫酸镁干燥,过滤,并在旋转蒸发仪上浓缩。加入干燥的THF(10mL),并再次在旋转蒸发仪上除去挥发物。将残留物在高真空下干燥10min。将残留物在搅拌下溶于THF(15mL)中,并在氩气下冷却至0℃。加入氢化钠(44.1mg,1.84mmol)。移除冷浴,并将得到的浑浊的橙色混合物在室温下在氩气下剧烈搅拌2.5h。加入氯化铵(147mg,2.75mmol)的水(2mL)溶液,然后将得到的混合物分配于乙酸乙酯和盐水之间。将有机层用硫酸镁干燥,过滤,在旋转蒸发仪上浓缩,并通过硅胶色谱纯化(20-100%乙酸乙酯的己烷溶液),得到4-(5-溴-2-甲基-4-氧代-3,4-二氢吡啶并[3,4-d]嘧啶-6-基)-4-氰基哌啶-1-甲酸叔丁酯(5)。

[0421] 在装有搅拌棒的可密封容器中将4-(5-溴-2-甲基-4-氧代-3,4-二氢吡啶并[3,4-d]嘧啶-6-基)-4-氰基哌啶-1-甲酸叔丁酯(5,313mg,0.698mmol),乙醇(17mL)和氢氧化锂(1M的水溶液)(6.98mL,6.98mmol)混合。将得到的混合物密封,剧烈搅拌,并用油浴在120℃下加热44h。冷却至室温后,将反应混合物用甲醇稀释,并在旋转蒸发仪上浓缩。将残留物溶于NMP,甲醇和乙酸(0.60mL,10.5mmol)中,过滤,并通过制备HPLC纯化(15-60%的乙腈在含0.1%TFA的水中的溶液)。将含有期望产物的级分合并,并冻干至干,得到4-(5-溴-2-甲基-4-氧代-3,4-二氢吡啶并[3,4-d]嘧啶-6-基)-4-氨基甲酰基哌啶-1-甲酸叔丁酯(6)。

[0422] 将搅拌的4-(5-溴-2-甲基-4-氧代-3,4-二氢吡啶并[3,4-d]嘧啶-6-基)-4-氨基甲酰基哌啶-1-甲酸叔丁酯TFA盐(6,186mg,0.321mmol)在6M HCl水溶液(7mL)中的混合物用油浴在140℃下加热2min,然后密封,剧烈搅拌,并用油浴在140℃下加热2h。加入更多的6M HCl水溶液(3mL),用油浴在140℃下继续加热21h。冷却至室温后,将反应混合物用甲醇稀释,过滤,并通过制备HPLC纯化(5-18%的乙腈在含0.1%TFA的水中的溶液)。将含有期望产物的级分装载到来自Phenomenex的Strata X-C离子交换柱。依次用水,乙腈,甲醇,然后用5%氢氧化铵的甲醇溶液冲洗柱。将含有期望产物的洗脱液在旋转蒸发仪上浓缩,并在高真空下干燥,得到5-溴-2-甲基-6-(哌啶-4-基)吡啶并[3,4-d]嘧啶-4(3H)-酮(7)。

[0423] 实施例1A.22

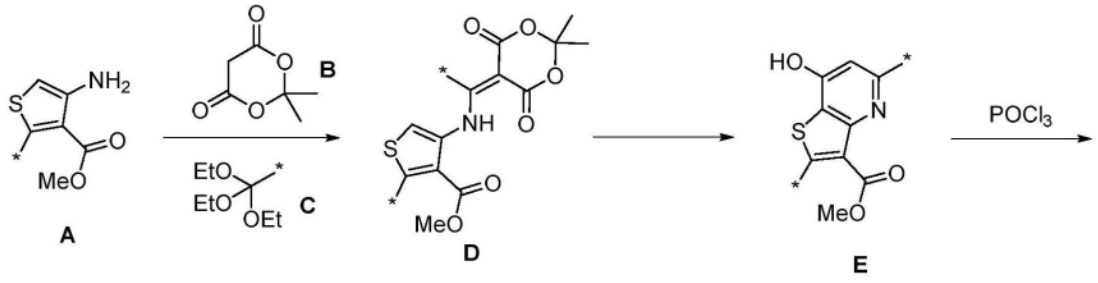
[0424] 

[0425] 在0℃下向5-氟吡啶-2-醇(1,9.00g,0.079mol)的四氢呋喃(290mL)溶液中缓慢加入三甲基苯基三溴化铵(29.9g,0.079mol),并将反应混合物在室温下搅拌16h。16h后,将反应混合物分配于乙酸乙酯和水之间。分离水层,并用乙酸乙酯反萃取。将合并的有机层用5%焦亚硫酸钠溶液和饱和盐水溶液洗涤,用无水硫酸钠干燥,过滤并浓缩,得到粗产物。用硅胶(100-200目)和0-30%乙酸乙酯的己烷溶液,通过柱色谱纯化粗产物,得到3-溴-5-氟吡啶-2-醇(2),为灰白色固体。产率:4.90g,27%;MS(ESI)m/z 189.99[M-1]⁻。

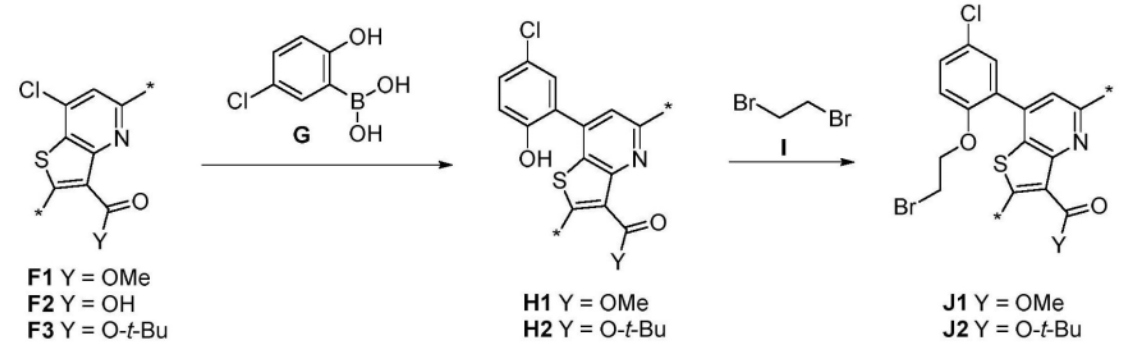
[0426] 向3-溴-5-氟吡啶-2-醇(2,4.10g,0.021mol)的N,N-二甲基甲酰胺(40mL)溶液中加入碳酸铯(3.48g,0.031mol)和2-溴-2,2-二氟乙酸钠(2a,5.05g,0.025mmol),并将反应混合物在70℃下加热4h。完成后,将反应混合物冷却,并分配于乙醚和水之间。分离水层,并用乙醚反萃取。将合并的有机层用水,饱和盐水溶液洗涤,用无水硫酸钠干燥,过滤并浓缩,得到粗产物。用硅胶(100-200目)以及用己烷作为洗脱剂,通过柱色谱纯化粗产物,得到3-溴-2-(二氟甲氧基)-5-氟吡啶(3)。

[0427] 实施例1B.合成右侧的方法

[0428] 实施例1B.1



[0429]



[0430] 将2,2-二甲基-1,3-二氧六环-4,6-二酮(B,1.1当量)和1,1,1-三乙氧基乙烷(C,0.7M)的溶液在90℃下搅拌并加热2h。在90℃下在氩气气氛下分批加入4-氨基噻吩-3-甲酸甲酯(A,1当量)并在90℃下继续加热6h。将反应混合物冷却至室温,加入水,并用乙酸乙酯萃取混合物。将有机层用无水硫酸钠干燥,过滤并真空浓缩。将粗产物与乙醚一起研磨,得到4-((1-(2,2-二甲基-4,6-二氧代-1,3-二氧六环-5-亚基)乙基)氨基)噻吩-3-甲酸甲酯(D)。

[0431] 将4-((1-(2,2-二甲基-4,6-二氧代-1,3-二氧六环-5-亚基)乙基)氨基)噻吩-3-甲酸甲酯(D,1当量)的道式热载体A溶液(0.5M)在235℃下加热4h。完成后,将反应物质冷却至室温,过滤分离沉淀的固体并真空干燥。将获得的固体用乙醚洗涤,得到7-羟基-5-甲基噻吩并[3,2-b]吡啶-3-甲酸甲酯(E)。

[0432] 在室温下向7-羟基-5-甲基噻吩并[3,2-b]吡啶-3-甲酸甲酯(E,1当量)的1,2-二氯乙烷溶液(0.22M)中加入三氯氧磷(3当量)和催化量的N,N-二甲基甲酰胺,并将反应混合物在90℃下加热6h。将反应混合物减压浓缩,用冰冷的水稀释,并用10%氢氧化钠水溶液碱化溶液至pH约7-8,接着用乙酸乙酯萃取。将有机层用无水硫酸钠干燥,过滤,浓缩并通过柱色谱纯化,得到7-氯-5-甲基噻吩并[3,2-b]吡啶-3-甲酸甲酯(F1)。

[0433] 在室温下向7-氯-5-甲基噻吩并[3,2-b]吡啶-3-甲酸甲酯(F1,1当量)在甲醇(1.7M),水(1.7M)和四氢呋喃(0.64M)的混合物中的溶液中加入氢氧化锂一水合物(2当

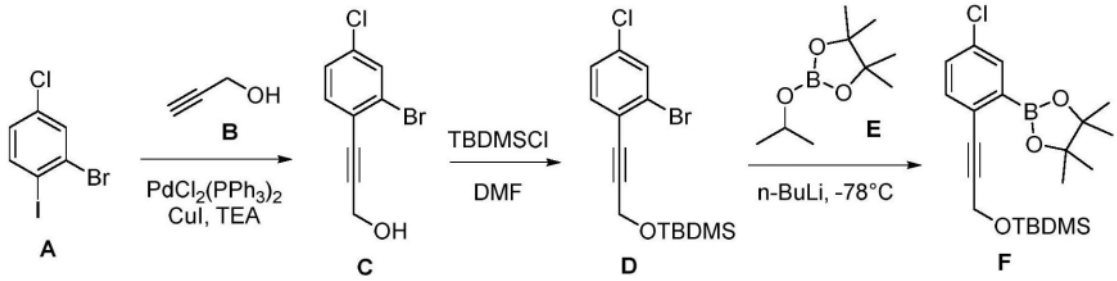
量),并将得到的混合物搅拌2h。过滤固体,将滤液浓缩并与固体合并。将合并的固体用饱和柠檬酸溶液酸化(最多达pH=1)并过滤。得到的固体用甲醇洗涤,接着用乙醚洗涤,并在高真空下干燥,得到7-氯-5-甲基噻吩并[3,2-b]吡啶-3-羧酸(F2)。

[0434] 在室温下向7-氯-5-甲基噻吩并[3,2-b]吡啶-3-羧酸(F2,1当量)的叔丁醇溶液(0.4M)中加入4-二甲基氨基吡啶(1当量)和Boc酸酐(3当量)。将混合物在90℃下搅拌48h,并将反应混合物减压浓缩。将粗产物通过硅胶柱色谱纯化,得到7-氯-5-甲基噻吩并[3,2-b]吡啶-3-甲酸叔丁酯(F3)。

[0435] 在室温下向7-氯-5-甲基噻吩并[3,2-b]吡啶-3-甲酸叔丁酯(F3,1当量)和(5-氯-2-羟基苯基)硼酸(G,1.2当量)在1,4-二氧六环(0.5M)和水(1.2M)中的溶液中加入碳酸钾溶液(2当量),并将反应混合物用氩气脱气20分钟。加入[1,1'-双(二苯基膦基)二茂铁]二氯化钯(II)(0.05当量),并将混合物在90℃下加热2h。将反应混合物冷却至室温并过滤,固体用水洗涤,接着用甲醇洗涤,真空干燥,得到7-(5-氯-2-羟基苯基)-5-甲基噻吩并[3,2-b]吡啶-3-甲酸叔丁酯(H)。

[0436] 在室温下向7-(5-氯-2-羟基苯基)-5-甲基噻吩并[3,2-b]吡啶-3-甲酸叔丁酯(H,1当量)的丙酮溶液(0.28M)中加入碳酸钾(3.5当量)和1,2-二溴乙烷(I,5.0当量),并将反应混合物在40℃下加热12h。然后在室温下加入额外的5.0当量1,2-二溴乙烷,并将混合物加热至45℃。将反应混合物通过烧结漏斗过滤,用丙酮洗涤,将滤液浓缩并通过柱色谱纯化,得到7-(2-(2-溴乙氧基)-5-氯苯基)-5-甲基噻吩并[3,2-b]吡啶-3-甲酸叔丁酯(J)。

[0437] 实施例1B.2

[0438] 

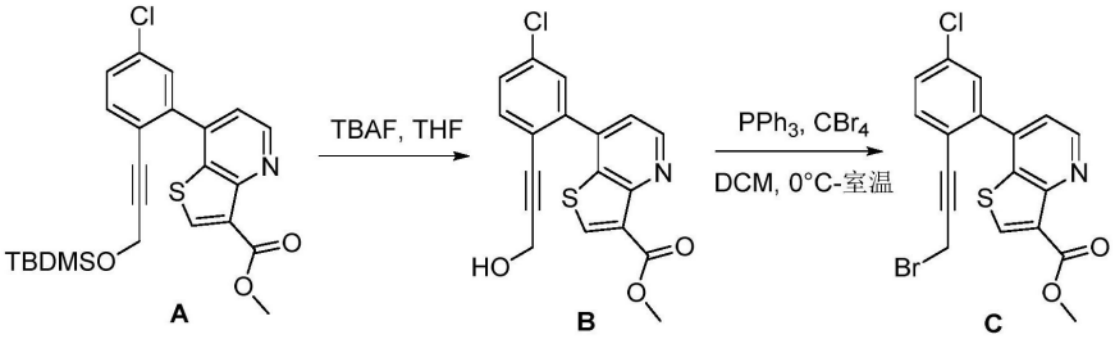
[0439] 将2-溴-4-氯-1-碘苯(A,1当量)和丙-2-炔-1-醇(B,1.3当量)的三乙胺溶液(0.3M)用氩气脱气10min。加入碘化亚铜(I)(0.15当量)和双(三苯基膦)氯化钯(0.08当量),并将反应混合物在室温下搅拌16h。将反应物质减压浓缩,并通过Combi-flash纯化化合物粗品,得到3-(2-溴-4-氯苯基)丙-2-炔-1-醇(C)。

[0440] 在室温下向3-(2-溴-4-氯苯基)丙-2-炔-1-醇(C,1当量)的四氢呋喃溶液(0.8M)中加入咪唑(3当量),4-二甲基氨基吡啶(0.045当量)和叔丁基二甲基氯硅烷(1.2当量),并将反应混合物搅拌24h。反应物质用水稀释,用乙酸乙酯萃取,分离有机层,用无水硫酸钠干燥,并通过Combi-flash纯化,得到((3-(2-溴-4-氯苯基)丙-2-炔-1-基)氧基)(叔丁基)二甲基硅烷(D)。

[0441] 在-78℃下向((3-(2-溴-4-氯苯基)丙-2-炔-1-基)氧基)(叔丁基)二甲基硅烷(D,1当量)的四氢呋喃溶液(0.14M)中滴加正丁基锂(1.23M的己烷溶液,1.3当量),并将混合物在-78℃下搅拌1h。在-78℃下滴加2-异丙氧基-4,4,5,5-四甲基-1,3,2-二氧杂硼杂环戊烷(E,1.2当量)并继续搅拌1h。用冷水淬灭反应,用乙酸乙酯萃取,分离有机层,用无水硫酸钠干燥,浓缩并通过Combi-flash纯化,得到叔丁基((3-(4-氯-2-(4,4,5,5-四甲基-1,3,2-二

氧杂硼杂环戊烷-2-基)苯基)丙-2-炔-1-基)氧基)二甲基硅烷(F)。

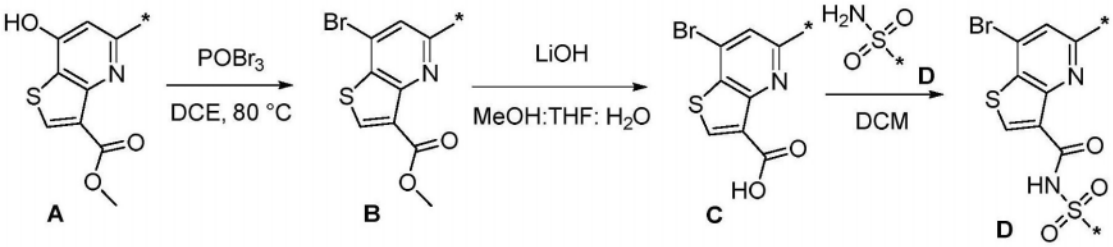
[0442] 实施例1B.3

[0443] 

[0444] 在室温下向7-(2-(3-((叔丁基二甲基甲硅烷基)氧基)丙-1-炔-1-基)-5-氯苯基)噻吩并[3,2-b]吡啶-3-甲酸甲酯(A,1当量)的四氢呋喃溶液(0.21M)中加入四正丁基氟化铵(1.2当量),并将混合物搅拌2h。反应物质用乙酸乙酯稀释,用冷水洗涤,分离有机层,用无水硫酸钠干燥,浓缩,并与乙醚一起研磨,得到7-(5-氯-2-(3-羟基丙-1-炔-1-基)苯基)噻吩并[3,2-b]吡啶-3-甲酸甲酯(B)。

[0445] 在室温下向7-(5-氯-2-(3-羟基丙-1-炔-1-基)苯基)噻吩并[3,2-b]吡啶-3-甲酸甲酯(B,1当量)的二氯甲烷(10.0mL)溶液中加入三苯基膦(1.5当量),并将反应混合物冷却至0℃。加入四溴化碳(1.5当量),并将反应混合物在室温下搅拌3h。将反应物质浓缩并通过Combi-flash纯化,得到7-(2-(3-溴丙-1-炔-1-基)-5-氯苯基)噻吩并[3,2-b]吡啶-3-甲酸甲酯(C)。

[0446] 实施例1B.4

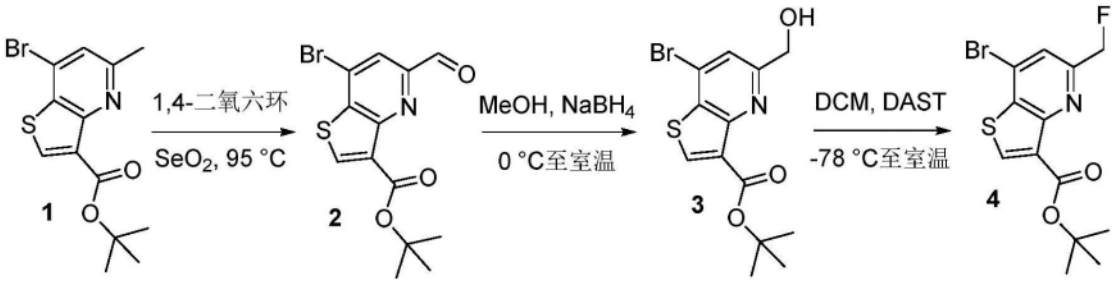
[0447] 

[0448] 将7-羟基-5-甲基噻吩并[3,2-b]吡啶-3-甲酸甲酯(A,1当量)和氧溴化磷(10当量)的1,2-二氯乙烷溶液(0.45M)在80℃下加热16h。将反应混合物冷却至室温,用碳酸氢钠水溶液淬灭,用二氯甲烷萃取,合并的有机层用盐水洗涤,用无水硫酸钠干燥,过滤,浓缩并通过柱色谱纯化,得到7-溴-5-甲基噻吩并[3,2-b]吡啶-3-甲酸甲酯(B)。

[0449] 将7-溴-5-甲基噻吩并[3,2-b]吡啶-3-甲酸甲酯(B,1当量)和氢氧化锂(3当量)在甲醇:四氢呋喃:水溶剂混合物(1:2:1,0.25M)中的溶液在室温下搅拌16h。将反应用水稀释,冷却至0℃,并用1N盐酸酸化至pH约5。过滤沉淀,用戊烷洗涤并干燥,得到7-溴-5-甲基噻吩并[3,2-b]吡啶-3-羧酸(C)。

[0450] 在室温下向7-溴-5-甲基噻吩并[3,2-b]吡啶-3-羧酸(C,1当量)和甲磺酰胺(D,1.5当量)的二氯甲烷溶液(0.16M)中加入N-乙基-N'-(3-二甲基氨基丙基)碳二亚胺盐酸盐(2当量)和N,N-二甲基吡啶-4-胺(2.5当量),并将混合物搅拌16h。将反应用水稀释,冷却至0℃,用1N盐酸酸化至pH约2,并用二氯甲烷萃取。合并的有机层用无水硫酸钠干燥,浓缩并通过柱色谱纯化,得到7-溴-5-甲基-N-(甲基磺酰基)噻吩并[3,2-b]吡啶-3-甲酰胺(E)。

[0451] 实施例1B.5

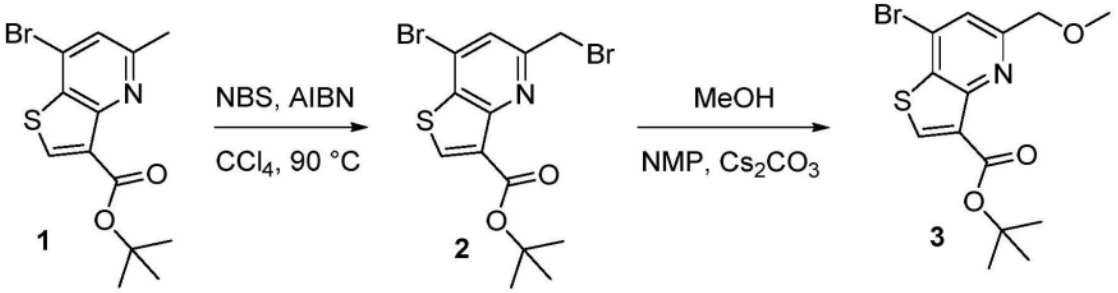
[0452] 

[0453] 向7-溴-5-甲基噻吩并[3,2-b]吡啶-3-甲酸叔丁酯(1,1.50g,4.5mmol)的1,4-二氧六环溶液中加入二氧化硒(0.55g,5.02mmol),并将反应混合物在95℃下加热8h。完成后,将反应混合物经硅藻土床过滤,并用乙酸乙酯洗涤。将获得的滤液减压浓缩,得到粗产物。用硅胶(100-200目)和10%乙酸乙酯的己烷溶液,通过柱色谱纯化获得的粗产物,得到7-溴-5-甲酰基噻吩并[3,2-b]吡啶-3-甲酸叔丁酯(2)。

[0454] 在0℃下向7-溴-5-甲酰基噻吩并[3,2-b]吡啶-3-甲酸叔丁酯(2,0.55g,1.62mmol)的甲醇(6mL)溶液中加入硼氢化钠(0.12g,3.25mmol),并将反应混合物在相同温度下搅拌1小时。完成后,将反应混合物用冰水淬灭,并减压浓缩。将粗材料溶于乙酸乙酯,用水和盐水溶液洗涤,用无水硫酸钠干燥,过滤并浓缩,得到化合物粗品。用硅胶(100-200目)和20%乙酸乙酯的己烷溶液,通过柱色谱纯化获得的化合物粗品,得到7-溴-5-(羟基甲基)噻吩并[3,2-b]吡啶-3-甲酸叔丁酯(3)。

[0455] 在-78℃下向7-溴-5-(羟基甲基)噻吩并[3,2-b]吡啶-3-甲酸叔丁酯(3,0.325g,0.94mmol)的二氯甲烷(5mL)溶液中加入DAST(0.18mL,1.41mmol),并将反应混合物在-78℃下搅拌1小时。完成后,将反应混合物用冰冷的水淬灭,并用二氯甲烷萃取。将有机层用饱和碳酸氢钠溶液洗涤,用无水硫酸钠干燥,过滤并浓缩,得到化合物粗品。用硅胶(100-200目)和10%乙酸乙酯的己烷溶液,通过柱色谱纯化获得的化合物粗品,得到7-溴-5-(氟甲基)噻吩并[3,2-b]吡啶-3-甲酸叔丁酯(4)。

[0456] 实施例1B.6

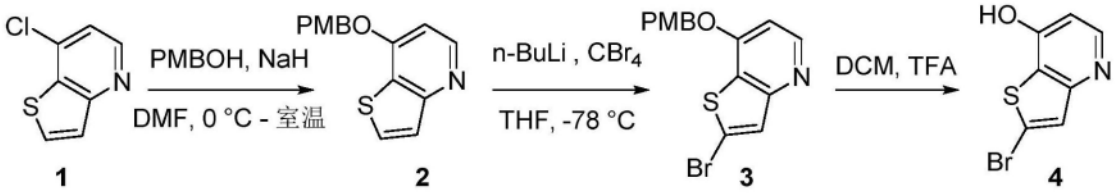
[0457] 

[0458] 将7-溴-5-甲基噻吩并[3,2-b]吡啶-3-甲酸叔丁酯(1,500.0mg,1.523mmol),偶氮二异丁腈(24.98mg,0.152mmol)和N-溴丁二酰亚胺(271.13mg,1.523mmol)的四氯化碳(10mL)溶液在90℃下搅拌5h。完成后,将反应混合物减压浓缩,用二氯甲烷稀释,并加入硅胶。蒸发溶剂。用0-10%甲醇的二氯甲烷溶液作为洗脱剂,通过Isco柱色谱纯化粗品硅胶混合物。将期望的级分减压浓缩,得到7-溴-5-(溴甲基)噻吩并[3,2-b]吡啶-3-甲酸叔丁酯(2)。

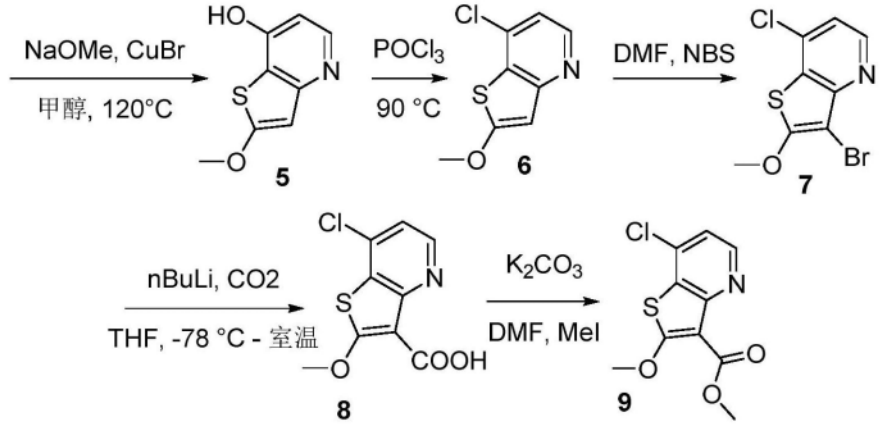
[0459] 在室温下向搅拌的7-溴-5-(溴甲基)噻吩并[3,2-b]吡啶-3-甲酸叔丁酯(2,

0.200g,0.491mmol)在甲醇(0.2mL)和N-甲基吡咯烷酮(2.0mL)中的溶液中加入碳酸铯(0.480g,1.474mmol),并将反应混合物在室温下搅拌8h。完成后,将反应混合物用二氯甲烷稀释,然后加入硅胶。随后蒸发溶剂,然后将自由流动的硅胶装载到柱上,并通过硅胶色谱纯化,用甲醇的二氯甲烷溶液洗脱,得到7-溴-5-(甲氧基甲基)噻吩并[3,2-b]吡啶-3-甲酸叔丁酯(3)。

[0460] 实施例1B.7



[0461]



[0462] 在0℃下向搅拌的4-甲氧基苄醇(8.1g,59.1mmol)的N,N-二甲基甲酰胺(100mL)溶液中加入氢化钠(3.1g,65.0mmol)。将该反应混合物在0℃下搅拌30min。然后在0℃下加入7-氯噻吩并[3,2-b]吡啶(1,10g,59.1mmol),并将反应混合物在室温下搅拌16h。在该时间后,将混合物倒入冰中。过滤收集获得的沉淀并减压干燥,得到7-((4-甲氧基苄基)氧基)噻吩并[3,2-b]吡啶(2)。

[0463] 在-78℃下向搅拌的7-((4-甲氧基苄基)氧基)噻吩并[3,2-b]吡啶(2,8.0g,29.5mmol)的干燥四氢呋喃(250mL)溶液中滴加正丁基锂(2.3M的己烷溶液,38.0mL,64.9mmol)。将该反应混合物在相同温度下搅拌45min。然后在-78℃下加入四溴化碳(9.7g,29.5mmol),并将混合物在相同温度下搅拌1h。在该时间后,用饱和氯化铵水溶液淬灭反应,并用乙酸乙酯萃取。将有机层用水洗涤,用无水硫酸钠干燥,过滤并浓缩。用15%乙酸乙酯的己烷溶液作为洗脱剂,通过硅胶(100-200目)柱色谱纯化粗产物。将期望的级分减压浓缩,得到2-溴-7-((4-甲氧基苄基)氧基)噻吩并[3,2-b]吡啶(3)。

[0464] 将2-溴-7-((4-甲氧基苄基)氧基)噻吩并[3,2-b]吡啶(3,6.5g,18.62mmol)在三氟乙酸和二氯甲烷(1:1,40mL)混合物中的溶液在室温下搅拌8h。在该时间后,将反应混合物减压浓缩。将粗产物在乙醚和戊烷中重结晶,得到2-溴噻吩并[3,2-b]吡啶-7-醇(4)。

[0465] 向2-溴噻吩并[3,2-b]吡啶-7-醇(4,3.5g,15.28mmol)的甲醇(30mL)溶液中加入30%甲醇钠的甲醇溶液(14.0g,甲醇溶液,76.4mmol)和溴化亚铜(I)(0.200g,1.5mmol)。将该反应混合物在120℃下搅拌30h。在该时间后,将反应混合物减压浓缩,用2N盐酸酸化至pH约6,并用10%甲醇的二氯甲烷溶液萃取。将有机层用无水硫酸钠干燥,过滤并浓缩,得到2-

甲氧基噻吩并[3,2-b]吡啶-7-醇(5)。

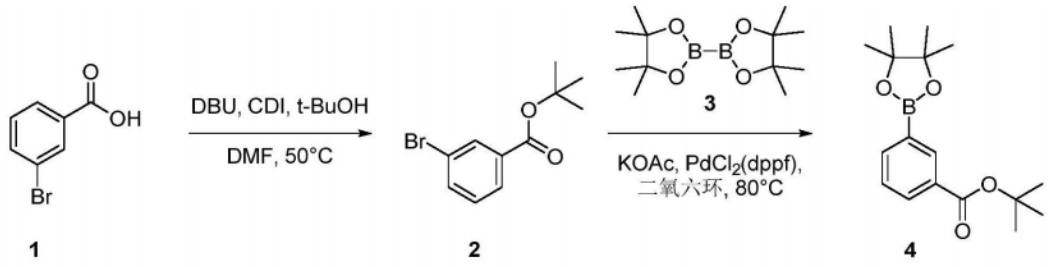
[0466] 将2-甲氧基噻吩并[3,2-b]吡啶-7-醇(5,1.7g,9.39mmol)和磷酰氯(10mL)的混合物在90℃下加热并搅拌6h。在该时间后,将反应混合物用冰淬灭,用50%氢氧化钠水溶液处理,并用乙酸乙酯萃取。将有机层用水洗涤,然后用饱和盐水洗涤,用无水硫酸钠干燥,并减压浓缩。用30%乙酸乙酯的己烷溶液作为洗脱剂,通过Combiflash纯化粗产物。将期望的级分减压浓缩,得到7-氯-2-甲氧基噻吩并[3,2-b]吡啶(6)。

[0467] 在室温下向3-溴-7-氯-2-甲氧基噻吩并[3,2-b]吡啶(6,0.8g,4.02mmol)的N,N-二甲基甲酰胺(10mL)溶液中加入N-溴丁二酰亚胺(1.4g,8.04mmol)。将该反应混合物搅拌30min。然后将反应混合物倒入冰中,并用乙酸乙酯萃取。将有机层用盐水洗涤,用无水硫酸钠干燥,过滤,并减压浓缩至干。用10%乙酸乙酯的己烷溶液作为洗脱剂,通过Combiflash(12g,RediSep柱)纯化粗产物。将期望的级分减压浓缩,得到3-溴-7-氯-2-甲氧基噻吩并[3,2-b]吡啶(7)。

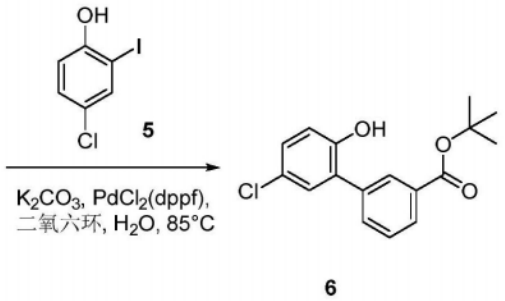
[0468] 在-78℃下向搅拌的3-溴-7-氯-2-甲氧基噻吩并[3,2-b]吡啶(7,0.7g,2.52mmol)的干燥四氢呋喃(10mL)溶液中滴加正丁基锂(2.3M的己烷溶液,1.97mL,4.54mmol)。将该反应混合物在相同温度下搅拌45min。用干燥二氧化碳气体鼓泡通过反应混合物,将其缓慢升温至室温并搅拌16h。将反应混合物用10%柠檬酸水溶液淬灭,并用10%甲醇的二氯甲烷溶液萃取。将有机层用无水硫酸钠干燥,过滤并浓缩,得到7-氯-2-甲氧基噻吩并[3,2-b]吡啶-3-羧酸(8)。

[0469] 在室温下向7-氯-2-甲氧基噻吩并[3,2-b]吡啶-3-羧酸(8,0.5g,2.05mmol)的N,N-二甲基甲酰胺(5.0mL)溶液中加入碳酸钾(0.85g,6.17mmol)和碘甲烷(0.32g,2.26mmol)。将该反应混合物搅拌16h。在该时间后,将反应混合物倒入冰中,并用乙酸乙酯萃取。将有机层用盐水洗涤,用无水硫酸钠干燥,过滤并减压浓缩至干。用2%甲醇的二氯甲烷溶液作为洗脱剂,通过Combiflash(12g,RediSep柱)纯化粗产物。将期望的级分减压浓缩,得到7-氯-2-甲氧基噻吩并[3,2-b]吡啶-3-甲酸甲酯(9)。

[0470] 实施例1B.8



[0471]



[0472] 在室温下向搅拌的3-溴苯甲酸(1,100.0g,497.5mmol)的N,N-二甲基甲酰胺

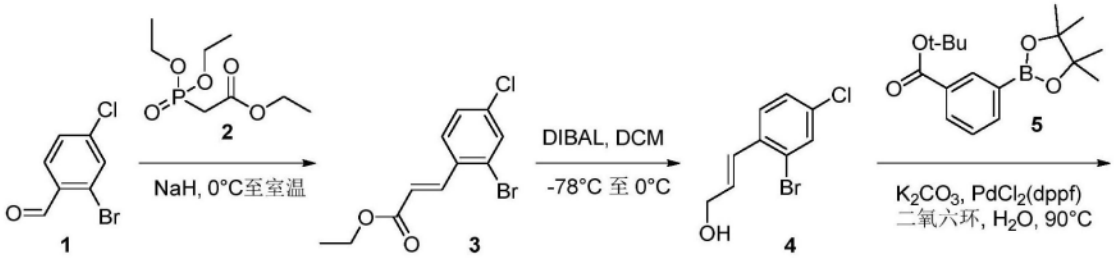
(800mL)溶液中加入羰基二咪唑(112.9g,696.5mmol),并将反应混合物在50℃下加热并搅拌1h。在50℃下加入1,8-二氮杂二环[5.4.0]十一碳-7-烯(105.8g,696.5mmol)和叔丁醇(184.37gm,2487.5mmol),并将反应混合物在50℃下继续搅拌16h。完成后,反应物质用水淬灭,并用乙酸乙酯萃取。将有机层分离,用无水硫酸钠干燥并减压浓缩。用100-200硅胶以及用2%乙酸乙酯的己烷溶液作为洗脱剂,通过柱色谱纯化得到的粗产物。将期望的级分减压浓缩,得到3-溴苯甲酸叔丁酯(2)。

[0473] 将搅拌的3-溴苯甲酸叔丁酯(2,113.0g,439.4mmol),4,4,4',4',5,5,5',5'-八甲基-2,2'-二(1,3,2-二氧杂硼杂环戊烷)(3,167.43g,659.1mmol)和乙酸钾(107.65g,1098.5mmol)的二氧六环(600mL)溶液用氩气脱气30min。然后加入[1,1'-双(二苯基膦基)二茂铁]二氯化钯(II),并将反应混合物在85℃下加热搅拌16h。完成后,将反应物质用水淬灭,并用乙酸乙酯萃取。将有机层分离,用无水硫酸钠干燥并减压浓缩,得到粗物质。用100-200硅胶以及用3%乙酸乙酯的己烷溶液作为洗脱剂,通过柱色谱纯化化合物粗品。将期望的级分减压浓缩,得到3-(4,4,5,5-四甲基-1,3,2-二氧杂硼杂环戊烷-2-基)苯甲酸叔丁酯(4)。

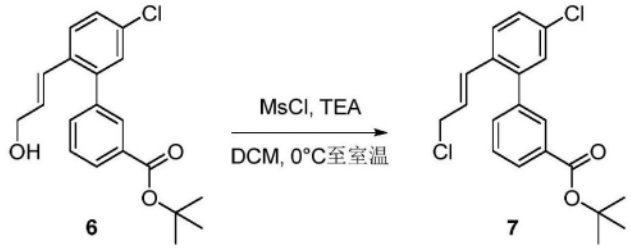
[0474] 将搅拌的4-氯-2-碘苯酚(5,60.0g,235.8mmol),3-(4,4,5,5-四甲基-1,3,2-二氧杂硼杂环戊烷-2-基)苯甲酸叔丁酯(4,100.37g,330.1mmol)和碳酸钾(97.76g,707.4mmol)在二氧六环和水(4:1,1.0L)的混合物中的溶液用氩气脱气30min。在室温下加入双(三苯基膦)二氯化钯(II),并将反应混合物在100℃下搅拌6h。完成后,将反应物质用水淬灭,并用乙酸乙酯萃取。将有机层分离,用无水硫酸钠干燥,并减压浓缩。用100-200硅胶以及用4%乙酸乙酯的己烷溶液作为洗脱剂,通过柱色谱纯化得到的化合物粗品。将期望的级分减压浓缩,得到5'-氯-2'-羟基-[1,1'-联苯]-3-甲酸叔丁酯(6)。

[0475] 在室温下向搅拌的5'-氯-2'-羟基-[1,1'-联苯]-3-甲酸叔丁酯(6,55.0g,180.5mmol)在1N氢氧化钠水溶液(1.1L)中的溶液中加入四丁基溴化铵(8.72g,27.07mmol)和碘化钾(4.49g,27.07mmol),并将反应物质加热至90℃。在90℃下缓慢加入1,2-二溴乙烷(7,57.82mL,667.89mmol),将反应混合物在90℃下搅拌16h。完成后,将反应物质用二氯甲烷萃取。将有机层用硫酸钠干燥,过滤并减压浓缩,得到粗物质。用100-200硅胶和2%乙酸乙酯的己烷溶液,通过柱色谱纯化化合物粗品,得到2'-(2-溴乙氧基)-5'-氯-[1,1'-联苯]-3-甲酸叔丁酯(8)。

[0476] 实施例1B.9



[0477]



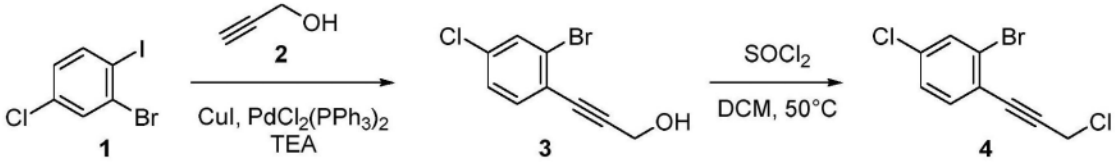
[0478] 在0℃下向搅拌的2-(二乙氧基磷酰基)乙酸乙酯(2,23.01g,102.7mmol)的四氢呋喃(100mL)溶液中加入氢化钠(60%)(5.47g,136.9mmol),并将反应混合物在0℃下搅拌1h。缓慢加入2-溴-4-氯苯甲醛(1,15.0g,68.4mmol)的四氢呋喃(3mL)溶液,并将反应混合物在0℃下搅拌2h。完成后,将反应物质用水淬灭,用乙酸乙酯萃取。将有机层分离,用无水硫酸钠干燥并减压浓缩,得到粗物质。用3%乙酸乙酯的己烷溶液作为洗脱剂,通过Combi-flash纯化粗物质。将期望的级分减压浓缩,得到(E)-3-(2-溴-4-氯苯基)丙烯酸乙酯(3)。

[0479] 向搅拌的(E)-3-(2-溴-4-氯苯基)丙烯酸乙酯(3,2.0g,17.3mmol)的二氯甲烷(15.0mL)溶液中加入二异丁基氢化铝(1M的甲苯溶液)(31.1mL,31.1mmol),并在-78℃下搅拌1h。将反应混合物缓慢升温至室温并搅拌1h。完成后,将反应物质用氯化铵水溶液淬灭,并用二氯甲烷萃取。将有机层分离,用无水硫酸钠干燥并减压浓缩,得到粗物质,用13%乙酸乙酯的己烷溶液作为洗脱剂,通过Combi-flash将其纯化。将期望的级分减压浓缩,得到(E)-3-(2-溴-4-氯苯基)丙-2-烯-1-醇(4)。

[0480] 将搅拌的(E)-3-(2-溴-4-氯苯基)丙-2-烯-1-醇(4,1.5g,6.07mmol),3-(4,4,5,5-四甲基-1,3,2-二氧杂硼杂环戊烷-2-基)苯甲酸叔丁酯(5,2.03g,6.68mmol)和碳酸钾(2.51g,18.2mmol)在二氧六环和水的混合物(4:1)(24.0mL)中的溶液用氩气脱气30min。加入[1,1'-双(二苯基膦基)二茂铁]二氯化钯(II)(0.222g,0.3mmol),并将反应混合物在90℃下加热12h。完成后,将反应物质用水淬灭,并用乙酸乙酯萃取。将有机层分离,用无水硫酸钠干燥并减压浓缩,得到粗物质。用15%乙酸乙酯的己烷溶液作为洗脱剂,通过Combi-flash纯化化合物粗品。将期望的级分减压浓缩,得到(E)-5'-氯-2'-(3-羟基丙-1-烯-1-基)-[1,1'-联苯]-3-甲酸叔丁酯(6)。

[0481] 在0℃下向搅拌的(E)-5'-氯-2'-(3-羟基丙-1-烯-1-基)-[1,1'-联苯]-3-甲酸叔丁酯(6,1.5g,4.34mmol)和三乙胺(1.82mL,13.04mmol)的二氯甲烷溶液中加入甲磺酰氯(0.67mL,8.69mmol),将反应混合物缓慢升温至室温并搅拌16h。完成后,反应物质用水淬灭,并用二氯甲烷萃取。将有机层分离,用无水硫酸钠干燥并减压浓缩,得到粗材料。用10%乙酸乙酯的己烷溶液为洗脱剂,通过Combi-flash纯化化合物粗品,得到(E)-5'-氯-2'-(3-氯丙-1-烯-1-基)-[1,1'-联苯]-3-甲酸叔丁酯(7)。

[0482] 实施例1B.10

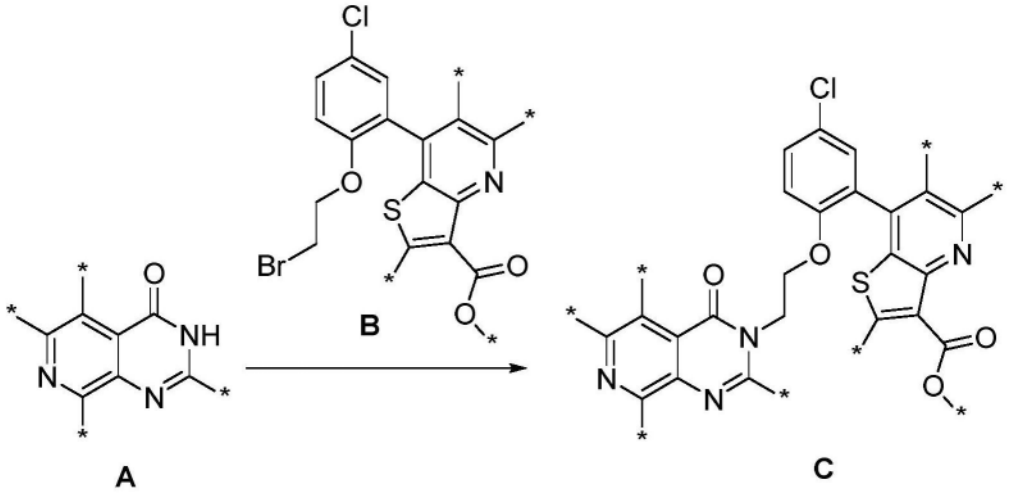
[0483] 

[0484] 将搅拌的2-溴-4-氯-1-碘苯(1,1.0g,3.15mmol),丙-2-炔-1-醇(2,0.2mL,3.47mmol)和碘化亚铜(I)(0.024g,0.126mmol)的三乙胺(30mL)溶液用氩气脱气20min。加入双(三苯基膦)二氯化钯(II)(0.110g,0.15mmol),并将反应混合物在室温下搅拌16h。完成后,将反应物质用水淬灭,并用乙酸乙酯萃取。将有机层分离,用无水硫酸钠干燥并减压浓缩,得到粗材料。用10%乙酸乙酯的己烷溶液作为洗脱剂,通过Combi-flash纯化化合物粗品。将期望的级分减压浓缩,得到3-(2-溴-4-氯苯基)丙-2-炔-1-醇(3),为黄色固体。产率:0.725g,93%,MS未电离化。

[0485] 在0℃下向搅拌的3-(2-溴-4-氯苯基)丙-2-炔-1-醇(3,0.72g,2.93mmol)的二氯甲烷(10mL)溶液中加入氯化亚砜(0.85mL,11.75mmol),并将反应混合物在50℃下加热搅拌16h。完成后,将反应物质减压浓缩,得到粗品,用3%乙酸乙酯的己烷溶液作为洗脱剂,通过Combi-flash将其纯化。将期望的级分减压浓缩,得到2-溴-4-氯-1-(3-氯丙-1-炔-1-基)苯(4)。

[0486] 实施例1C.通用偶联方法

[0487] 实施例1C1

[0488] 

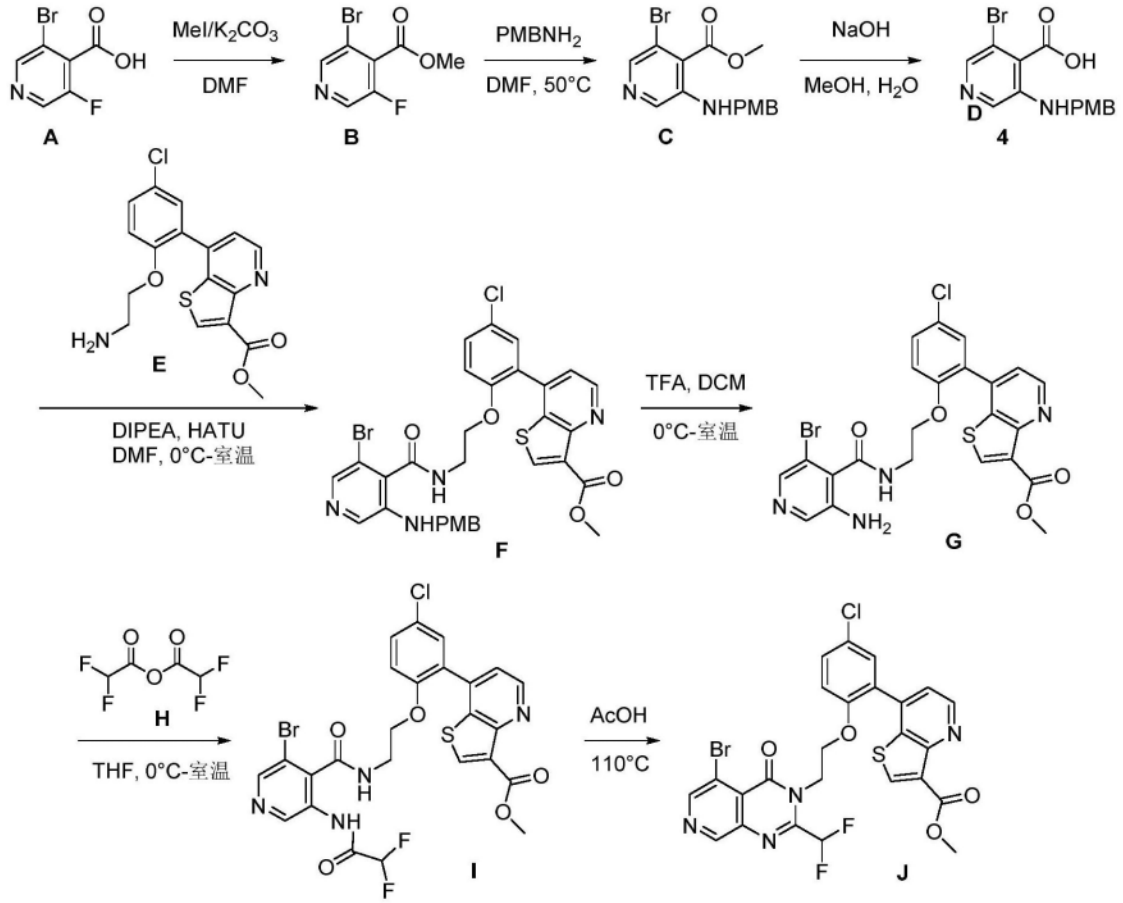
[0489] 向6-氯-2-甲基-4-氧代-3,4-二氢吡啶并[3,4-d]嘧啶-5-甲腈(A,1当量)的N,N-二甲基甲酰胺(0.2M溶液)溶液中加入碳酸钾(3当量)和7-(2-(2-溴乙氧基)-5-氯苯基)噻吩并[3,2-b]吡啶-3-甲酸叔丁酯(B,1当量),并将反应混合物在60℃下加热16h。然后将反应混合物冷却,用水稀释,并用乙酸乙酯萃取2次。将合并的有机层用水洗涤,用无水硫酸钠干燥,过滤并真空浓缩。通过硅胶柱色谱纯化,得到7-(5-氯-2-(2-(6-氯-5-氰基-2-甲基-4-氧代吡啶并[3,4-d]嘧啶-3(4H)-基)乙氧基)苯基)噻吩并[3,2-b]吡啶-3-甲酸叔丁酯(C)。

[0490] 实施例1C2

[0491] 在室温下向6-氯-2-甲基-4-氧代-3,4-二氢吡啶并[3,4-d]嘧啶-5-甲腈(A,1当量)的N,N-二甲基甲酰胺溶液(0.14M)中加入7-(2-(2-溴乙氧基)-5-氯苯基)噻吩并[3,2-b]吡啶-3-甲酸叔丁酯(B,1.3当量),碘化钾(0.2当量)和研磨的碳酸钾(3当量)。将混合物

在50℃下搅拌16h,用水稀释,并用乙酸乙酯萃取2次。将合并的有机层用水洗涤,用无水硫酸镁干燥,并真空浓缩。通过硅胶柱色谱纯化,得到7-(5-氯-2-(2-(6-氯-5-氰基-2-甲基-4-氧代吡啶并[3,4-d]嘧啶-3(4H)-基)乙氧基)苯基)噻吩并[3,2-b]吡啶-3-甲酸叔丁酯(C)。

[0492] 实施例1C.3.可供选择的偶联方法

[0493] 

[0494] 在室温下向3-溴-5-氟异烟酸(A,5.0g,21.92mmol)的二甲基甲酰胺(15mL)溶液中加入碳酸钾(6.07g,43.84mmol)和碘甲烷(2.05mL,32.88mmol),并将反应混合物在室温下搅拌2h。完成后,反应物质用乙酸乙酯稀释,并用冷水洗涤。将有机层分离,用无水硫酸钠干燥,过滤并浓缩,得到粗品。通过快速色谱纯化粗品,用乙酸乙酯的己烷溶液(1-10%)洗脱化合物。将期望的级分减压浓缩,得到3-溴-5-氟异烟酸甲酯(B)。

[0495] 在室温下向3-溴-5-氟异烟酸甲酯(B,4.0g,17.17mmol)的二甲基甲酰胺(15mL)溶液中加入碳酸钾(7.0g,51.51mmol),接着滴加4-甲氧基苄胺(3.52mL,25.0mmol)。将反应混合物在50℃下搅拌16h。完成后,将反应物质用乙酸乙酯稀释,并用冷水洗涤。将有机层分离,用无水硫酸钠干燥,过滤并浓缩,得到粗品。通过快速柱色谱纯化粗品,用乙酸乙酯的己烷溶液(10-20%)洗脱化合物。将期望的级分减压浓缩,得到3-溴-5-((4-甲氧基苄基)氨基)异烟酸甲酯(C)。

[0496] 向3-溴-5-((4-甲氧基苄基)氨基)异烟酸甲酯(C,2.8g,8.0mmol)在甲醇(5.0mL)和水(5.0mL)中的溶液中加入氢氧化钠(0.64g,26.0mmol),并将反应混合物在室温下搅拌6h。完成后,将反应物质浓缩以蒸发甲醇。将水层冷却至0℃,并用2N盐酸酸化(pH约4)。将沉淀的固体过滤并干燥,得到3-溴-5-((4-甲氧基苄基)氨基)异烟酸(D)。

[0497] 在0℃下向3-溴-5-((4-甲氧基苄基)氨基)异烟酸(D,0.9g,26.0mmol)的二甲基甲酰胺(15mL)溶液中加入7-(2-(2-氨基乙氧基)-5-氯苯基)噻吩并[3,2-b]吡啶-3-甲酸甲酯(E,1.16g,32.0mmol)和1-[双(二甲基氨基)亚甲基]-1H-1,2,3-三唑并[4,5-b]吡啶鎓3-氧化物六氟磷酸盐(1.48g,39.0mmol)。在0℃下滴加二异丙基乙胺,将反应混合物在室温下搅拌3h。完成后,将反应物质用乙酸乙酯稀释,并用冷水洗涤。将有机层分离,用无水硫酸钠干燥,过滤并减压浓缩,得到粗品。通过快速柱色谱纯化粗品,用甲醇的二氯甲烷溶液(2-5%)洗脱化合物。将期望的级分减压浓缩,得到7-(2-(2-(3-溴-5-((4-甲氧基苄基)氨基)异烟酰胺基)乙氧基)-5-氯苯基)噻吩并[3,2-b]吡啶-3-甲酸甲酯(F)。

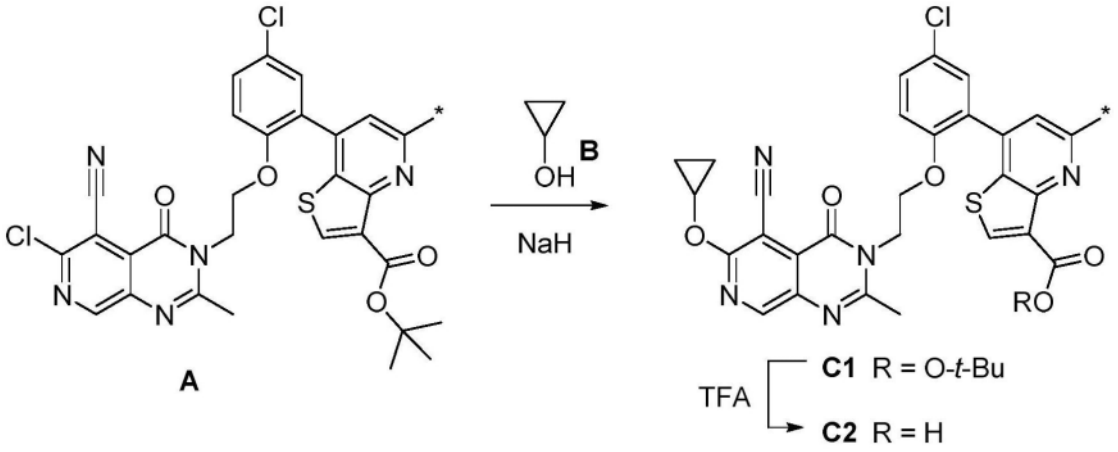
[0498] 在0℃下向7-(2-(2-(3-溴-5-((4-甲氧基苄基)氨基)异烟酰胺基)乙氧基)-5-氯苯基)噻吩并[3,2-b]吡啶-3-甲酸甲酯(F,1.8g,26.0mmol)的二氯甲烷(10mL)溶液中加入三氟乙酸(10mL),并将反应混合物在室温下搅拌2h。完成后,将反应物质浓缩得到粗品。将粗品和乙醚一起研磨,得到7-(2-(2-(3-氨基-5-溴异烟酰胺基)乙氧基)-5-氯苯基)噻吩并[3,2-b]吡啶-3-甲酸甲酯(G)。

[0499] 在0℃下向7-(2-(2-(3-氨基-5-溴异烟酰胺基)乙氧基)-5-氯苯基)噻吩并[3,2-b]吡啶-3-甲酸甲酯(G,1.2g,2.1mmol)的四氢呋喃(10mL)溶液中加入2,2-二氟乙酸酐(H,0.26mL,2.1mmol),并将反应混合物在室温下搅拌1h。完成后,将反应物质浓缩得到粗品。将粗品通过用乙醚洗涤并与乙醚一起研磨来纯化,得到7-(2-(2-(3-溴-5-(2,2-二氟乙酰氨基)异烟酰胺基)乙氧基)-5-氯苯基)噻吩并[3,2-b]吡啶-3-甲酸甲酯(I)。

[0500] 将7-(2-(2-(3-溴-5-(2,2-二氟乙酰氨基)异烟酰胺基)乙氧基)-5-氯苯基)噻吩并[3,2-b]吡啶-3-甲酸甲酯(I,1.0g,1.56mmol)的乙酸(10mL)溶液在110℃下加热并搅拌24h。完成后,减压除去乙酸,得到粗品。通过快速柱色谱纯化粗品,用乙酸乙酯的己烷溶液(50-70%)洗脱化合物。将期望的级分减压浓缩,得到7-(2-(2-(5-溴-2-(二氟甲基)-4-氧代吡啶并[3,4-d]嘧啶-3(4H)-基)乙氧基)-5-氯苯基)噻吩并[3,2-b]吡啶-3-甲酸甲酯(J)。

[0501] 实施例1D.偶联后修饰方法

[0502] 实施例1D.1

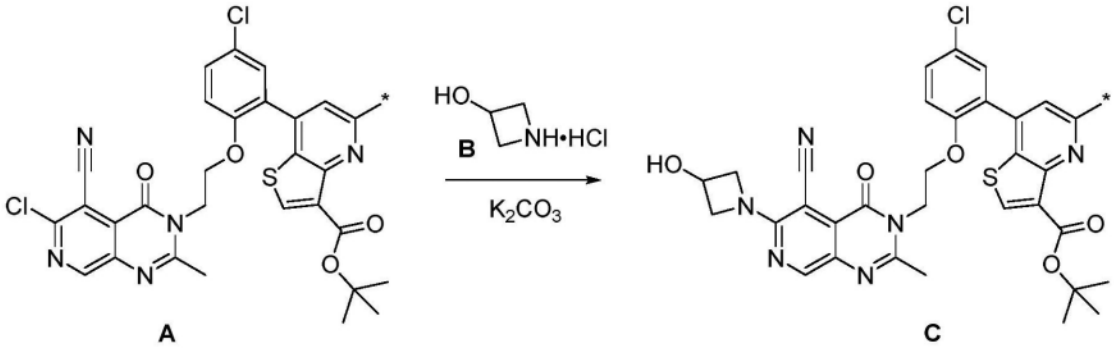
[0503] 

[0504] 向环丙醇(B,2.5当量)的四氢呋喃溶液(0.6M)中加入氢化钠(3当量),并将反应混合物在0℃下搅拌10min。在室温下将7-(5-氯-2-(2-(6-氯-5-氰基-2-甲基-4-氧代吡啶并[3,4-d]嘧啶-3(4H)-基)乙氧基)苯基)-5-甲基噻吩并[3,2-b]吡啶-3-甲酸叔丁酯(A,1当

量)加入反应混合物中,并在120℃下加热6h。将反应混合物冷却至室温,用水稀释,用乙酸乙酯萃取,乙酸乙酯层用硫酸钠干燥,浓缩并在硅胶塞上纯化,得到7-(5-氯-2-(2-(5-氰基-6-环丙氧基-2-甲基-4-氧代吡啶并[3,4-d]嘧啶-3(4H)-基)乙氧基)苯基)-5-甲基噻吩并[3,2-b]吡啶-3-甲酸叔丁酯(C1)。

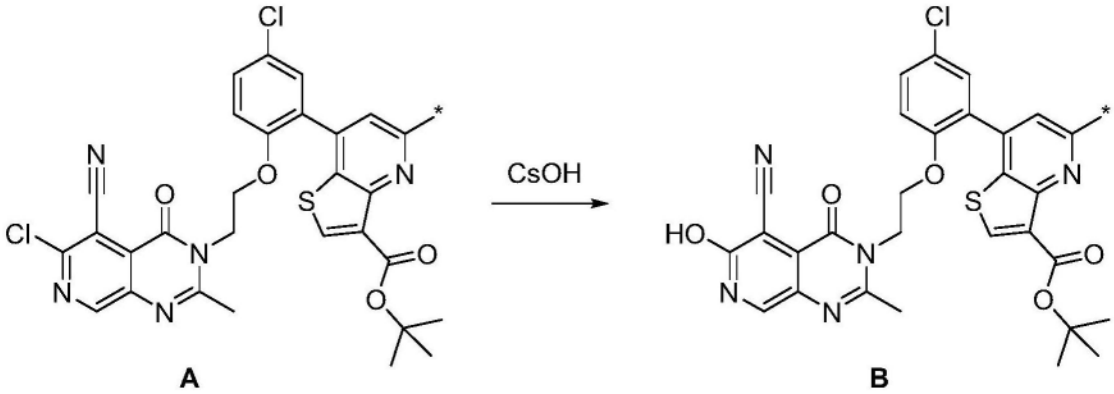
[0505] 在0℃下向7-(5-氯-2-(2-(5-氰基-6-环丙氧基-2-甲基-4-氧代吡啶并[3,4-d]嘧啶-3(4H)-基)乙氧基)苯基)-5-甲基噻吩并[3,2-b]吡啶-3-甲酸叔丁酯(C1,1当量)的二氯甲烷溶液(0.1M)中加入三氟乙酸(0.1M)。将反应缓慢升至室温并搅拌16h。将反应减压浓缩,用乙醚洗涤并通过制备HPLC纯化,得到7-(5-氯-2-(2-(5-氰基-6-环丙氧基-2-甲基-4-氧代吡啶并[3,4-d]嘧啶-3(4H)-基)乙氧基)苯基)-5-甲基噻吩并[3,2-b]吡啶-3-羧酸(C2)。

[0506] 实施例1D.2

[0507] 

[0508] 在室温下向7-(5-氯-2-(2-(6-氯-5-氰基-2-甲基-4-氧代吡啶并[3,4-d]嘧啶-3(4H)-基)乙氧基)苯基)-5-甲基噻吩并[3,2-b]吡啶-3-甲酸叔丁酯(A,1当量)和氮杂环丁烷-3-醇盐酸盐(B,2当量)的DMF溶液(0.16M)中加入碳酸钾(5当量),接着在100℃下在搅拌下加热16h。将反应混合物用水稀释,用乙酸乙酯萃取,并用水和盐水溶液洗涤有机层,用硫酸钠干燥,浓缩并通过快速色谱纯化。得到7-(5-氯-2-(2-(5-氰基-6-(3-羟基氮杂环丁-1-基)-2-甲基-4-氧代吡啶并[3,4-d]嘧啶-3(4H)-基)乙氧基)苯基)-5-甲基噻吩并[3,2-b]吡啶-3-甲酸叔丁酯(C)。

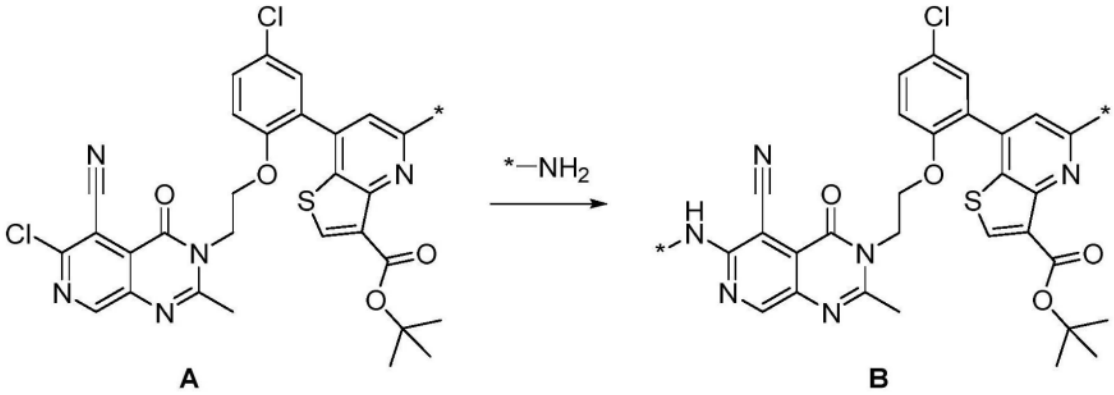
[0509] 实施例1D.3

[0510] 

[0511] 将7-(5-氯-2-(2-(6-氯-5-氰基-2-甲基-4-氧代吡啶并[3,4-d]嘧啶-3(4H)-基)乙氧基)苯基)-5-甲基噻吩并[3,2-b]吡啶-3-甲酸叔丁酯(A,1当量)和氢氧化铯(3当量)的1,4-二氧六环溶液(0.12M)在氮气下脱气5分钟。加入三(二亚苄基丙酮)二钯(0)(0.05当量)和5-(二叔丁基膦基)-1',3',5'-三苯基-1'H-[1,4']联吡唑(0.03当量),并将混合物在

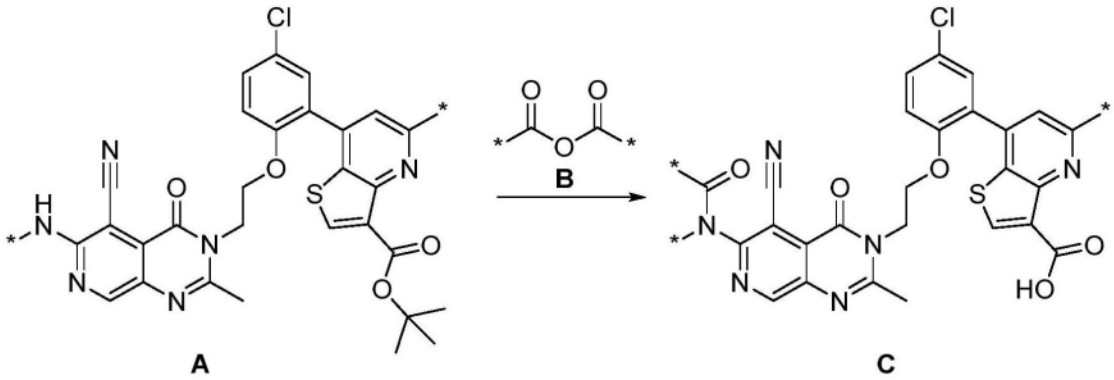
90℃下加热16h。将反应混合物冷却,用水稀释,用乙酸乙酯萃取,并将合并的有机层用无水硫酸钠干燥,过滤并浓缩,得到7-(5-氯-2-(2-(5-氰基-6-羟基-2-甲基-4-氧代吡啶并[3,4-d]嘧啶-3(4H)-基)乙氧基)苯基)-5-甲基噻吩并[3,2-b]吡啶-3-甲酸叔丁酯(B)。

[0512] 实施例1D.4

[0513] 

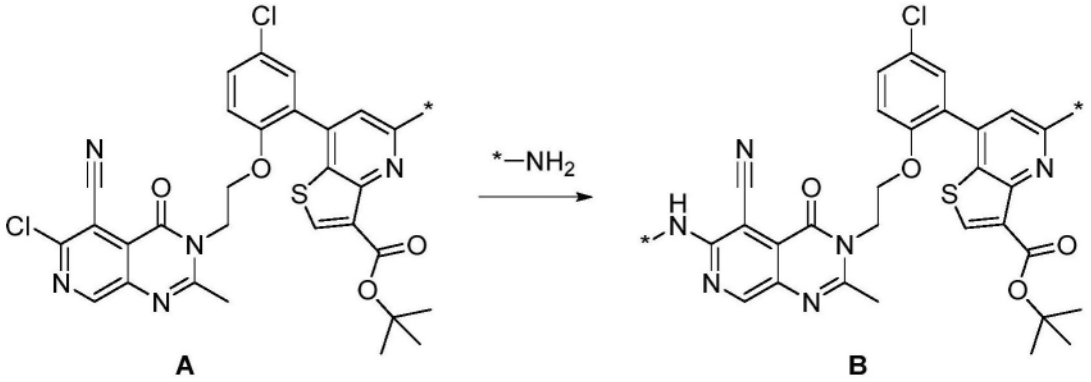
[0514] 将7-(5-氯-2-(2-(6-氯-5-氰基-2-甲基-4-氧代吡啶并[3,4-d]嘧啶-3(4H)-基)乙氧基)苯基)-5-甲基噻吩并[3,2-b]吡啶-3-甲酸叔丁酯(A,1当量)的甲醇氨溶液(20%,0.05M)在密封管中在120℃下加热16h。将反应混合物浓缩,得到7-(2-(2-(6-氨基-5-氰基-2-甲基-4-氧代吡啶并[3,4-d]嘧啶-3(4H)-基)乙氧基)-5-氯苯基)-5-甲基噻吩并[3,2-b]吡啶-3-甲酸叔丁酯(B)。

[0515] 实施例1D.5

[0516] 

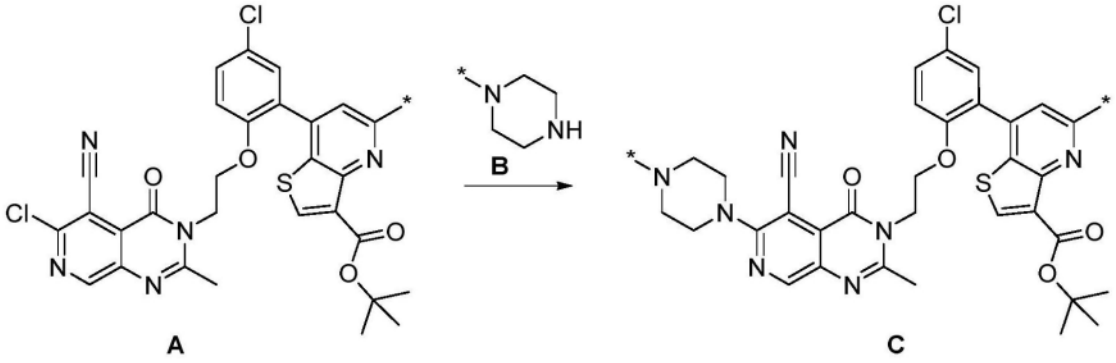
[0517] 在室温下向7-(5-氯-2-(2-(5-氰基-2-甲基-6-(甲基氨基)-4-氧代吡啶并[3,4-d]嘧啶-3(4H)-基)乙氧基)苯基)-5-甲基噻吩并[3,2-b]吡啶-3-甲酸叔丁酯(A,1当量)的乙酸酐溶液(B,0.06M)中加入乙酸(0.24M),并将混合物在120℃下加热27h。将反应混合物在冰上淬灭,用乙酸乙酯萃取,并用无水硫酸钠干燥有机层,过滤,浓缩并通过制备HPLC纯化,得到7-(5-氯-2-(2-(5-氰基-2-甲基-6-(N-甲基乙酰氨基)-4-氧代吡啶并[3,4-d]嘧啶-3(4H)-基)乙氧基)苯基)-5-甲基噻吩并[3,2-b]吡啶-3-羧酸(C)。

[0518] 实施例1D.6

[0519] 

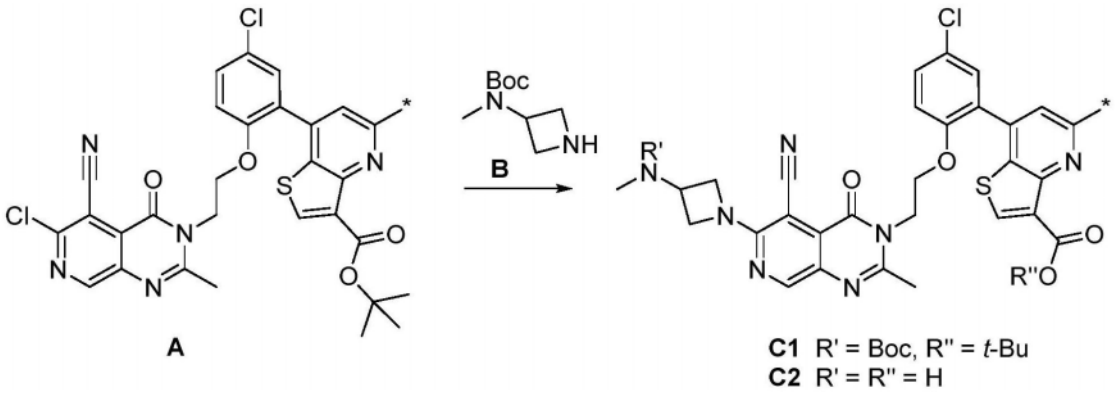
[0520] 将7-(5-氯-2-(2-(6-氯-5-氰基-2-甲基-4-氧代吡啶并[3,4-d]嘧啶-3(4H)-基)乙氧基)苯基)-5-甲基噻吩并[3,2-b]吡啶-3-甲酸叔丁酯(A,1当量)的氨甲醇溶液(20%,0.05M)在密封管中在120℃下加热16h。将反应混合物浓缩,得到7-(2-(2-(6-氨基-5-氰基-2-甲基-4-氧代吡啶并[3,4-d]嘧啶-3(4H)-基)乙氧基)-5-氯苯基)-5-甲基噻吩并[3,2-b]吡啶-3-甲酸叔丁酯(B)。

[0521] 实施例1D.7

[0522] 

[0523] 向7-(5-氯-2-(2-(6-氯-5-氰基-2-甲基-4-氧代吡啶并[3,4-d]嘧啶-3(4H)-基)乙氧基)苯基)-5-乙基噻吩并[3,2-b]吡啶-3-甲酸叔丁酯(A,1当量)的N,N-二甲基甲酰胺溶液(0.05M)中加入1-甲基哌嗪(B,3当量),氟化钾(5当量)和18-冠-6(1当量),并将混合物在90℃下加热3h。将反应混合物冷却,用水稀释,用乙酸乙酯萃取,并用无水硫酸钠干燥合并的有机层,过滤并浓缩,得到7-(5-氯-2-(2-(5-氰基-2-甲基-6-(4-甲基哌嗪-1-基)-4-氧代吡啶并[3,4-d]嘧啶-3(4H)-基)乙氧基)苯基)-5-乙基噻吩并[3,2-b]吡啶-3-甲酸叔丁酯(C)。

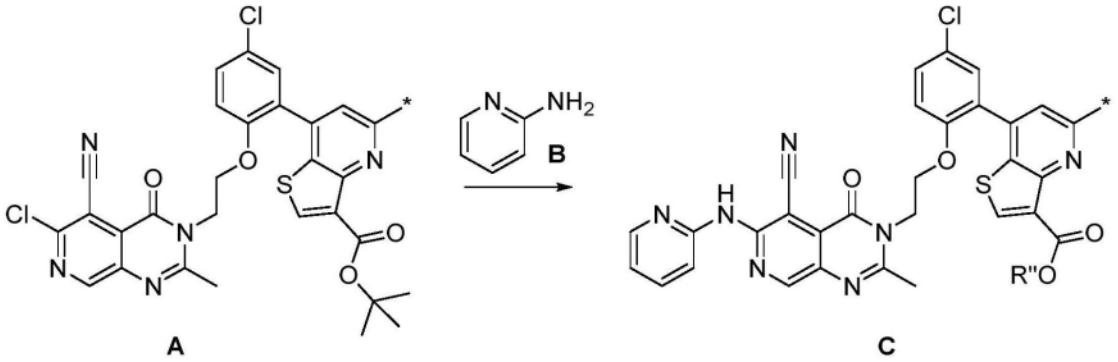
[0524] 实施例1D.8

[0525] 

[0526] 向7-(5-氯-2-(2-(6-氯-5-氰基-2-甲基-4-氧代吡啶并[3,4-d]嘧啶-3(4H)-基)乙氧基)苯基)-5-甲基噻吩并[3,2-b]吡啶-3-羧酸(A,1当量)和氮杂环丁-3-基(甲基)氨基甲酸叔丁酯盐酸盐(B,2当量)的1,4-二氧六环溶液(0.088M)中加入碳酸铯(0.172g,0.530mmol),并将反应混合物在90℃下加热3h。将反应混合物用水稀释,用乙酸乙酯萃取,并用无水硫酸钠干燥有机层,过滤,浓缩并通过柱色谱纯化,得到7-(2-(2-(6-(3-((叔丁氧基羰基)(甲基)氨基)氮杂环丁-1-基)-5-氰基-2-甲基-4-氧代吡啶并[3,4-d]嘧啶-3(4H)-基)乙氧基)-5-氯苯基)-5-甲基噻吩并[3,2-b]吡啶-3-羧酸(C1)。

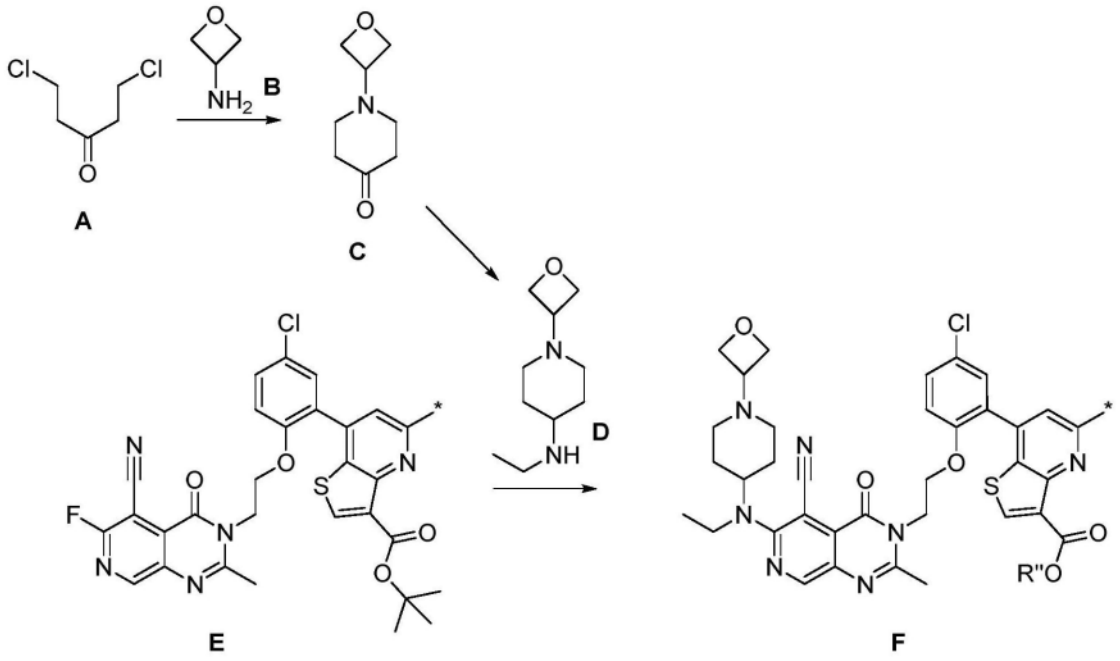
[0527] 在0℃下向7-(2-(2-(6-(3-((叔丁氧基羰基)(甲基)氨基)氮杂环丁-1-基)-5-氰基-2-甲基-4-氧代吡啶并[3,4-d]嘧啶-3(4H)-基)乙氧基)-5-氯苯基)-5-甲基噻吩并[3,2-b]吡啶-3-羧酸(C1,1当量)的二氯甲烷溶液(0.045M)中加入2,2,2-三氟乙酸(0.14M),并将反应混合物在室温下搅拌16h。将反应混合物浓缩并通过制备HPLC纯化,得到7-(5-氯-2-(2-(5-氰基-2-甲基-6-(3-(甲基氨基)氮杂环丁-1-基)-4-氧代吡啶并[3,4-d]嘧啶-3(4H)-基)乙氧基)苯基)-5-甲基噻吩并[3,2-b]吡啶-3-羧酸(C2)。

[0528] 实施例1D.9

[0529] 

[0530] 在配备搅拌棒的螺旋盖小瓶中将7-(2-(2-(6-溴-5-氰基-2-甲基-4-氧代-7-(三氟甲基)喹唑啉-3(4H)-基)乙氧基)-5-氯苯基)-5-甲基噻吩并[3,2-b]吡啶-3-甲酸叔丁酯(A,1当量),3-氨基吡啶(B,1.1当量),xantphos(0.2当量),碳酸铯(3当量)和三(二亚苄基丙酮)二钯(0)(0.2当量)悬浮于1,4-二氧六环(0.047M)中。将反应混合物用氩气吹扫3min,然后密封,并在加热器中在100℃下加热75min。将反应混合物冷却至室温并溶于1:1N,N-二甲基甲酰胺:甲醇溶液中,并通过注射器过滤器过滤。制备HPLC得到7-(5-氯-2-(2-(5-氰基-2-甲基-4-氧代-6-(吡啶-3-基氨基)-7-(三氟甲基)喹唑啉-3(4H)-基)乙氧基)苯基)-5-甲基噻吩并[3,2-b]吡啶-3-甲酸叔丁酯(C)。

[0531] 实施例1D.10

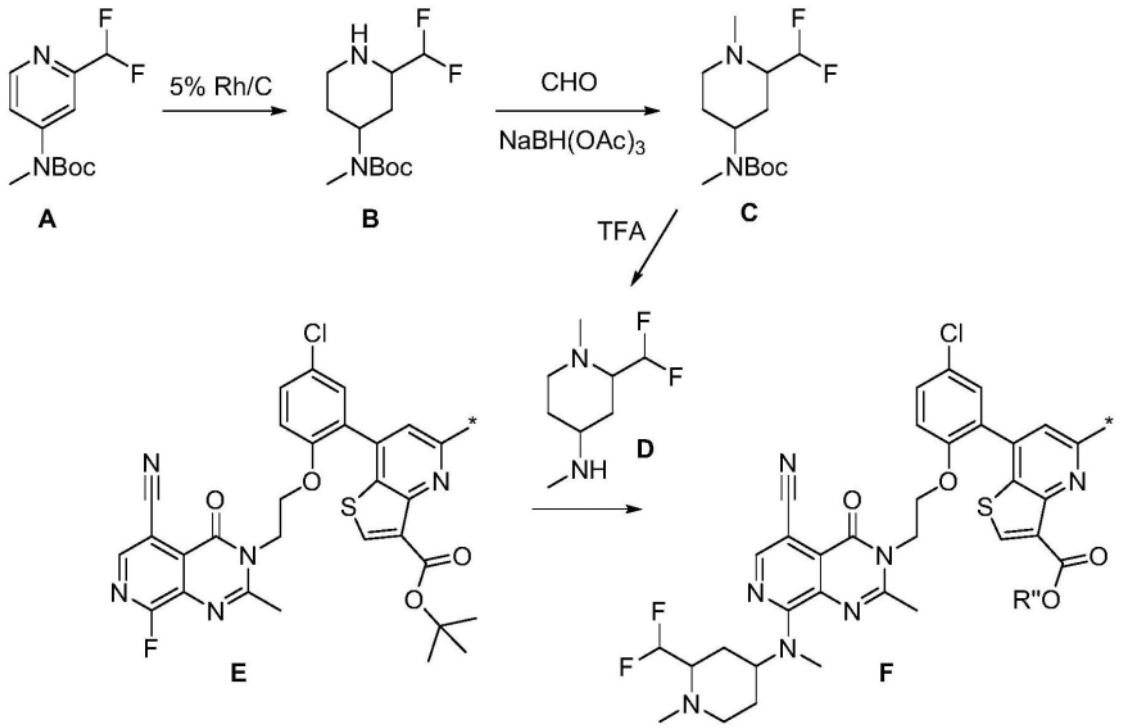
[0532] 

[0533] 在室温下向搅拌的氧杂环丁烷-3-胺(B,1当量),碳酸钠(3.5当量)的甲醇溶液(0.68M)中加入1,5-二氯戊-3-酮(A,1当量),并将反应混合物在75℃下加热3h。将反应混合物冷却至室温,用水稀释,用乙酸乙酯萃取,用硫酸钠干燥乙酸乙酯层,浓缩并在硅胶塞上纯化,得到1-(氧杂环丁烷-3-基)哌啶-4-酮(C)。

[0534] 在室温下向1-(氧杂环丁烷-3-基)哌啶-4-酮(C,0.8g,5.16mmol)的二氯甲烷溶液(0.5M)中加入乙胺(2M的四氢呋喃溶液,1.3当量)和乙酸(10M)。将反应混合物搅拌60min,在0℃下加入三乙酰氧基硼氢化钠(1.3当量)并在室温下搅拌16h。用10%氢氧化钠水溶液淬灭反应,用甲醇的二氯甲烷溶液(5%)萃取,用氯化钠溶液洗涤有机层,用无水硫酸钠干燥,过滤并浓缩,得到N-乙基-1-(氧杂环丁烷-3-基)哌啶-4-胺(D)。

[0535] 在室温下向7-(5-氯-2-(3-(5-氰基-6-氟-2-甲基-4-氧代吡啶并[3,4-d]嘧啶-3(4H)-基)丙-1-炔-1-基)苯基)噻吩并[3,2-b]吡啶-3-甲酸叔丁酯(E,1当量)的乙腈溶液(0.1M)中加入N-乙基-1-(氧杂环丁烷-3-基)哌啶-4-胺(D,2当量)和N,N-二异丙基乙胺(3当量),并将反应混合物在100℃下搅拌30h。将反应冷却至室温,用水淬灭,用乙酸乙酯萃取,用氯化钠溶液洗涤有机层,用无水硫酸钠干燥,过滤,浓缩,并通过Combi flash纯化,得到7-(5-氯-2-(3-(5-氰基-6-(乙基(1-(氧杂环丁烷-3-基)哌啶-4-基)氨基)-2-甲基-4-氧代吡啶并[3,4-d]嘧啶-3(4H)-基)丙-1-炔-1-基)苯基)噻吩并[3,2-b]吡啶-3-甲酸叔丁酯(F)。

[0536] 实施例1D.11

[0537] 

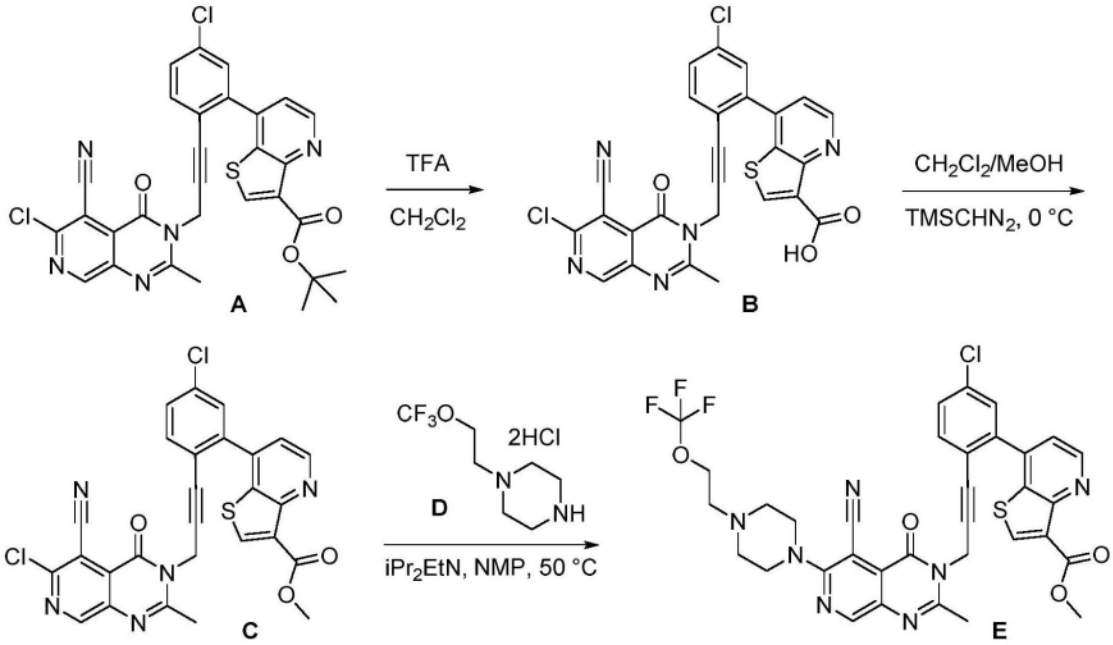
[0538] 在室温下向(2-(二氟甲基)吡啶-4-基)(甲基)氨基甲酸叔丁酯(A,1当量)和乙酸(10当量)的甲醇溶液(0.029M)中加入5%铑碳(rhodium on carbon)(0.5当量),并将混合物在80℃下在80psi下加热15h。将反应混合物过滤并浓缩,得到(2-(二氟甲基)哌啶-4-基)(甲基)氨基甲酸叔丁酯(B)。

[0539] 向(2-(二氟甲基)哌啶-4-基)(甲基)氨基甲酸叔丁酯(B,1当量)的THF溶液(0.19M)中加入甲醛(37%的水溶液,10当量),乙酸(9当量)和分子筛(约3x重量)。将混合物在室温下搅拌30min,加入三乙酰氧基硼氢化钠(sodium triacetoxyboranuide)(361mg,1.7mmol),并将混合物搅拌30min。将反应混合物用甲醇稀释,将残留物通过strata离子交换柱,用水洗脱三次,然后用乙腈洗脱三次,然后用甲醇洗脱三次。通过用二氯甲烷,甲醇和氢氧化铵(50:40:10)的溶液冲洗柱,洗脱(2-(二氟甲基)-1-甲基哌啶-4-基)(甲基)氨基甲酸叔丁酯(C)。

[0540] 将(2-(二氟甲基)-1-甲基哌啶-4-基)(甲基)氨基甲酸叔丁酯(C,1当量)的三氟乙酸溶液(0.006M)在室温下搅拌30min,并将反应混合物浓缩,得到2-(二氟甲基)-N,1-二甲基哌啶-4-胺(D)。

[0541] 将7-(5-氯-2-(2-(5-氰基-8-氟-2-甲基-4-氧代吡啶并[3,4-d]嘧啶-3(4H)-基)乙氧基)苯基)噻吩并[3,2-b]吡啶-3-羧酸(E,1当量),2-(二氟甲基)-N,1-二甲基哌啶-4-胺(D,5当量)和NMP(0.037M)在DIPEA(7当量)中的混合物在室温下搅拌30min。将反应混合物过滤,通过HPLC纯化,得到7-(5-氯-2-(2-(5-氰基-8-((2-(二氟甲基)-1-甲基哌啶-4-基)(甲基)氨基)-2-甲基-4-氧代吡啶并[3,4-d]嘧啶-3(4H)-基)乙氧基)苯基)噻吩并[3,2-b]吡啶-3-羧酸(F)。

[0542] 实施例1D.12

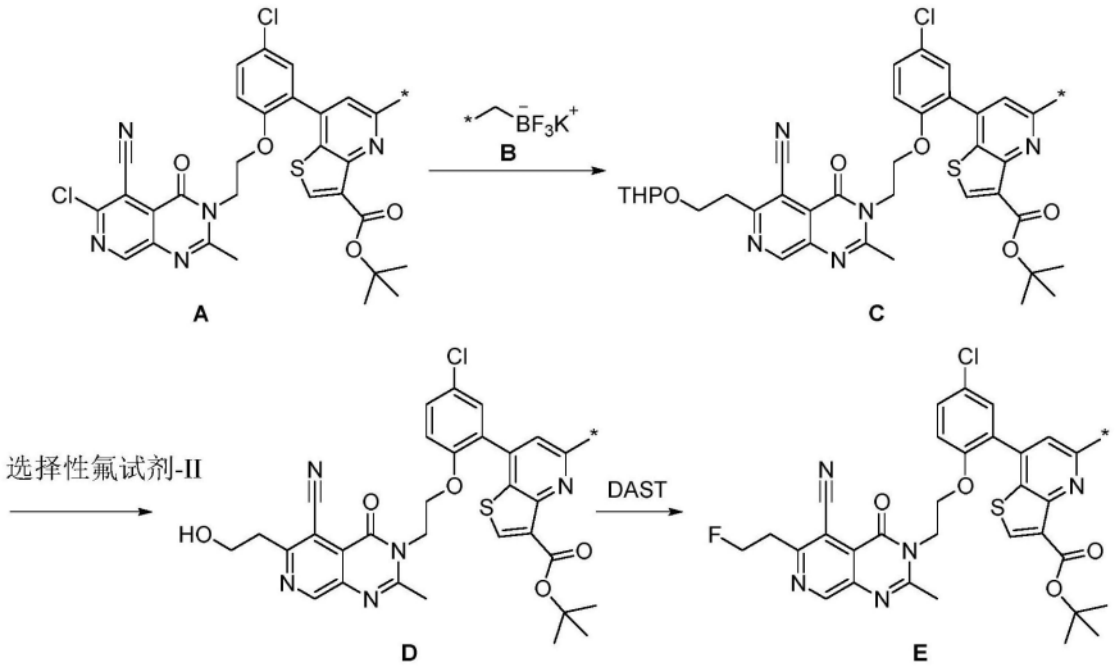
[0543] 

[0544] 在0℃下向7-(5-氯-2-(3-(6-氯-5-氰基-2-甲基-4-氧代吡啶并[3,4-d]嘧啶-3(4H)-基)丙-1-炔-1-基)苯基)噻吩并[3,2-b]吡啶-3-甲酸叔丁酯(A,1当量)的二氯甲烷(40mL)溶液中加入三氟乙酸(0.25M)并在室温下搅拌17h。真空浓缩混合物,加入碳酸氢钠水溶液,并用乙醚洗涤。将水层用3N盐酸溶液酸化,搅拌15min。过滤得到7-(5-氯-2-(3-(6-氯-5-氰基-2-甲基-4-氧代吡啶并[3,4-d]嘧啶-3(4H)-基)丙-1-炔-1-基)苯基)噻吩并[3,2-b]吡啶-3-羧酸(B)。

[0545] 在0℃下向7-(5-氯-2-(3-(6-氯-5-氰基-2-甲基-4-氧代吡啶并[3,4-d]嘧啶-3(4H)-基)丙-1-炔-1-基)苯基)噻吩并[3,2-b]吡啶-3-羧酸(B,1160mg,2.12mmol)在二氯甲烷(0.11M)和甲醇(0.42M)中的溶液中加入三甲基甲硅烷基重氮甲烷(4当量)。在0℃下搅拌10min,用乙酸(3.5M)淬灭反应,浓缩并通过硅胶柱色谱纯化,得到7-(5-氯-2-(3-(6-氯-5-氰基-2-甲基-4-氧代吡啶并[3,4-d]嘧啶-3(4H)-基)丙-1-炔-1-基)苯基)噻吩并[3,2-b]吡啶-3-甲酸甲酯(C)。

[0546] 在室温下向7-(5-氯-2-(3-(6-氯-5-氰基-2-甲基-4-氧代吡啶并[3,4-d]嘧啶-3(4H)-基)丙-1-炔-1-基)苯基)噻吩并[3,2-b]吡啶-3-甲酸甲酯(C,433mg,0.770mmol)的N-甲基-2-吡咯烷酮溶液(0.21M)中加入1-(2-(三氟甲氧基)乙基)哌嗪二盐酸盐(D,1.5当量),并将混合物在50℃下搅拌2h,接着在室温下搅拌17h。混合物用甲醇稀释,过滤并将滤液用制备HPLC纯化,得到7-(5-氯-2-(3-(5-氰基-2-甲基-4-氧代-6-(4-(2-(三氟甲氧基)乙基)哌嗪-1-基)吡啶并[3,4-d]嘧啶-3(4H)-基)丙-1-炔-1-基)苯基)噻吩并[3,2-b]吡啶-3-甲酸甲酯(E)。

[0547] 实施例1D.13

[0548] 

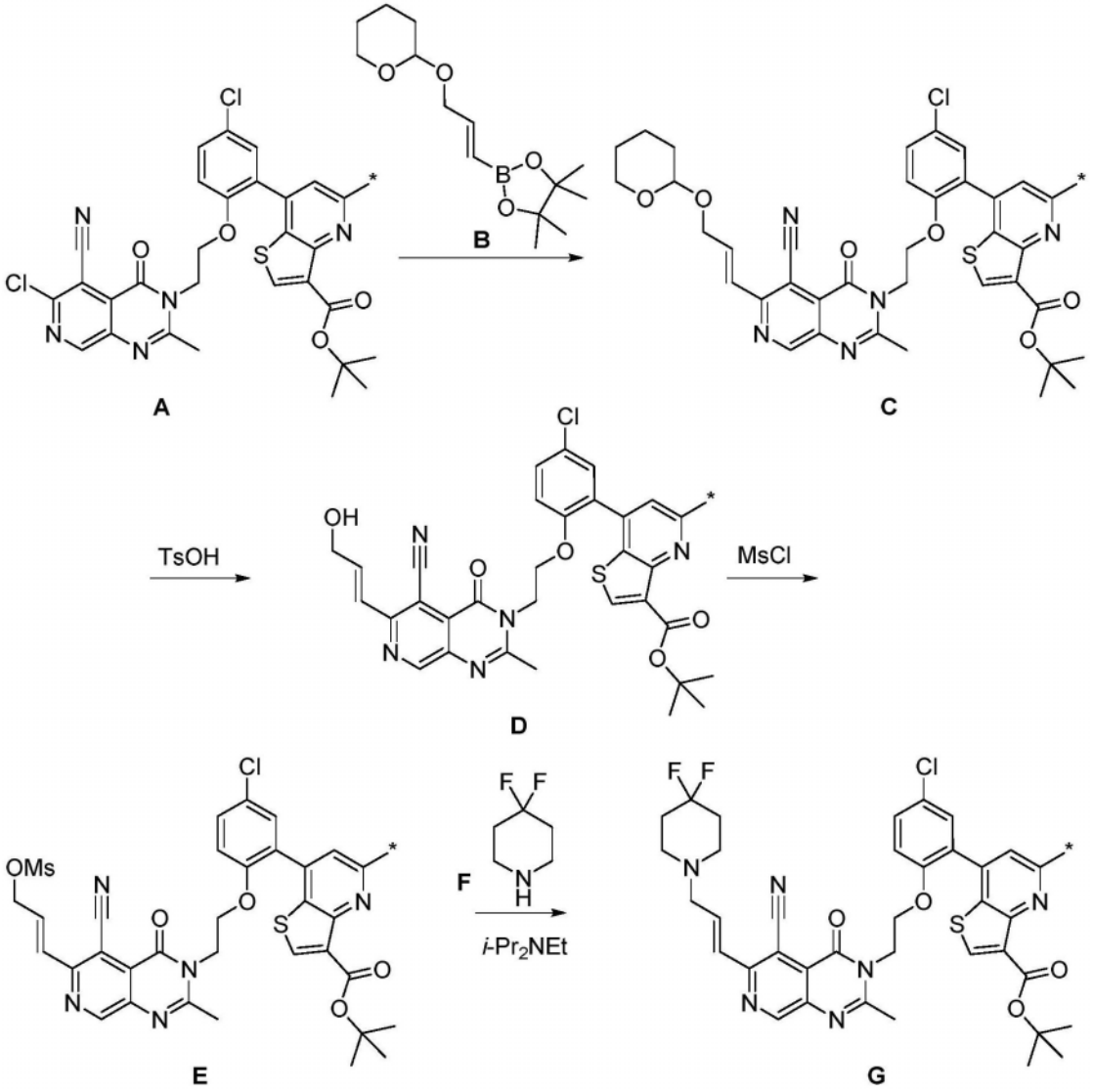
[0549] 向7-(5-氯-2-(2-(6-氯-5-氰基-2-甲基-4-氧代吡啶并[3,4-d]嘧啶-3(4H)-基)乙氧基)苯基)-5-甲基噻吩并[3,2-b]吡啶-3-甲酸叔丁酯(A,1当量)和三氟(2-((四氢-2H-吡喃-2-基)氧基)乙基)硼酸钾(B,1.4当量)在甲苯和水的混合物(2:1,0.7M)中的溶液中加入碳酸铯(2当量),并将反应混合物用氩气脱气15min。加入[1,1'-双(二苯基膦基)二茂铁]二氯化钯(II)(0.1当量),并在100℃下加热16h。将反应物质通过硅藻土过滤,用乙酸乙酯洗涤,用无水硫酸钠干燥滤液,浓缩并通过Combiflash纯化,得到7-(5-氯-2-(2-(5-氰基-2-甲基-4-氧代-6-(2-((四氢-2H-吡喃-2-基)氧基)乙基)吡啶并[3,4-d]嘧啶-3(4H)-基)乙氧基)苯基)-5-甲基噻吩并[3,2-b]吡啶-3-甲酸叔丁酯(C)。

[0550] 在0℃下向搅拌的7-(5-氯-2-(2-(5-氰基-2-甲基-4-氧代-6-(2-((四氢-2H-吡喃-2-基)氧基)乙基)吡啶并[3,4-d]嘧啶-3(4H)-基)乙氧基)苯基)-5-甲基噻吩并[3,2-b]吡啶-3-甲酸叔丁酯(C,1当量)在乙腈和水的混合物(3:1,0.018M)中的溶液中加入选择性氟试剂-II(selectfluor-II)(2当量),并将混合物在室温下搅拌48h。将反应混合物分配于水和乙酸乙酯之间,用硫酸钠干燥有机层并浓缩,得到7-(5-氯-2-(2-(5-氰基-6-(2-羟基乙基)-2-甲基-4-氧代吡啶并[3,4-d]嘧啶-3(4H)-基)乙氧基)苯基)-5-甲基噻吩并[3,2-b]吡啶-3-甲酸叔丁酯(D)。

[0551] 在0℃下向7-(5-氯-2-(2-(5-氰基-6-(2-羟基乙基)-2-甲基-4-氧代吡啶并[3,4-d]嘧啶-3(4H)-基)乙氧基)苯基)-5-甲基噻吩并[3,2-b]吡啶-3-甲酸叔丁酯(D,1当量)的二氯甲烷溶液(0.4M)中加入二乙基氨基三氟化硫(1.5当量),并将混合物在室温下搅拌3h。在0℃下用10%氢氧化钠水溶液淬灭反应物质,用二氯甲烷萃取,用无水硫酸钠干燥有机层并浓缩,得到7-(5-氯-2-(2-(5-氰基-6-(2-氟乙基)-2-甲基-4-氧代吡啶并[3,4-d]嘧啶-3(4H)-基)乙氧基)苯基)-5-甲基噻吩并[3,2-b]吡啶-3-甲酸叔丁酯(E)。

[0552] 实施例1D.14

[0553]



[0554] 在配备搅拌棒的烘干的微波小瓶中将7-(5-氯-2-(2-(6-氯-5-氰基-2-甲基-4-氧代吡啶并[3,4-d]嘧啶-3(4H)-基)乙氧基)苯基)噻吩并[3,2-b]吡啶-3-甲酸叔丁酯(A,1当量),$PdCl_2(PPh_3)_2$(0.18当量)和(E)-4,4,5,5-四甲基-2-(3-((四氢-2H-吡喃-2-基)氧基)丙-1-烯-1-基)-1,3,2-二氧杂硼杂环戊烷(B,1.6当量)悬浮于1,4-二氧六环(0.054M)中。加入碳酸钾水溶液(2.0M,4当量),将密封的小瓶用氩气吹扫5min,并在微波反应器中在100℃下加热4h。将反应混合物用饱和碳酸氢钠水溶液和乙酸乙酯稀释,并将水相用乙酸乙酯萃取三次。合并的有机物质用盐水洗涤,用硫酸镁干燥,过滤并通过硅胶色谱纯化,得到(E)-7-(5-氯-2-(2-(5-氰基-2-甲基-4-氧代-6-(3-((四氢-2H-吡喃-2-基)氧基)丙-1-烯-1-基)吡啶并[3,4-d]嘧啶-3(4H)-基)乙氧基)苯基)噻吩并[3,2-b]吡啶-3-甲酸叔丁酯(C)。

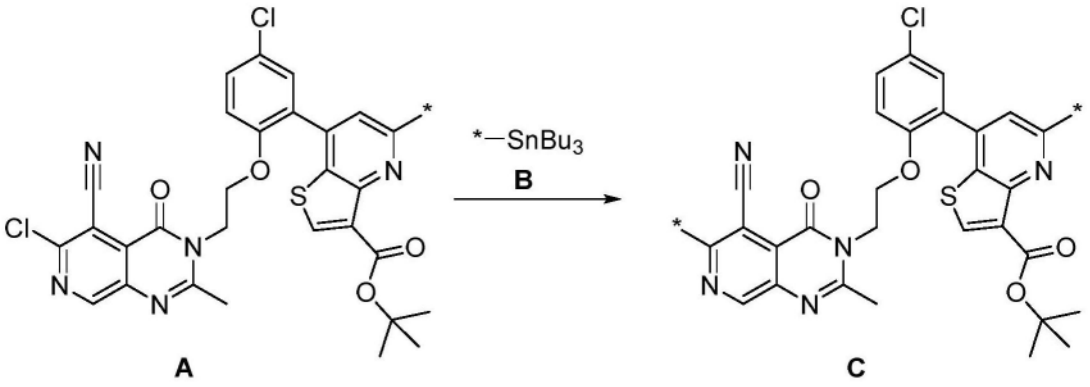
[0555] 在配备搅拌棒的螺旋盖小瓶中将(E)-7-(5-氯-2-(2-(5-氰基-2-甲基-4-氧代-6-(3-((四氢-2H-吡喃-2-基)氧基)丙-1-烯-1-基)吡啶并[3,4-d]嘧啶-3(4H)-基)乙氧基)苯基)噻吩并[3,2-b]吡啶-3-甲酸叔丁酯(C,1当量)悬浮于甲醇(0.05M),四氢呋喃(0.05M)和水(0.05M)中,并将反应混合物在室温下搅拌,同时一批加入对甲苯磺酸(0.35当量)。30min后将温度升至55℃,再搅拌1h。加入水(0.1M),1h后将温度升至80℃,并在该温度下加热8h。

将反应混合物冷却至室温,然后真空除去挥发性溶剂。反应混合物用饱和碳酸氢钠水溶液和乙酸乙酯稀释,分离各层,并将水相用乙酸乙酯萃取三次。合并的有机物质用盐水洗涤,用硫酸镁干燥,将固体过滤并浓缩,得到(E)-7-(5-氯-2-(2-(5-氰基-6-(3-羟基丙-1-烯-1-基)-2-甲基-4-氧代吡啶并[3,4-d]嘧啶-3(4H)-基)乙氧基)苯基)噻吩并[3,2-b]吡啶-3-甲酸叔丁酯(D)。

[0556] 在配备搅拌棒的烘干的螺旋盖小瓶中将(E)-7-(5-氯-2-(2-(5-氰基-6-(3-羟基丙-1-烯-1-基)-2-甲基-4-氧代吡啶并[3,4-d]嘧啶-3(4H)-基)乙氧基)苯基)噻吩并[3,2-b]吡啶-3-甲酸叔丁酯(D,1当量)溶于二氯甲烷(0.086M)中。将反应混合物在0℃下搅拌,同时缓慢加入N,N-二异丙基乙胺(6当量)。然后滴加甲磺酰氯(2.6当量),此时移除冰浴。30min后,将反应混合物用二氯甲烷稀释,用饱和碳酸氢钠水溶液和盐水洗涤,用硫酸镁干燥,过滤并真空除去溶剂,得到(E)-7-(5-氯-2-(2-(5-氰基-2-甲基-6-(3-((甲基磺酰基)氧基)丙-1-烯-1-基)-4-氧代吡啶并[3,4-d]嘧啶-3(4H)-基)乙氧基)苯基)噻吩并[3,2-b]吡啶-3-甲酸叔丁酯(E)。

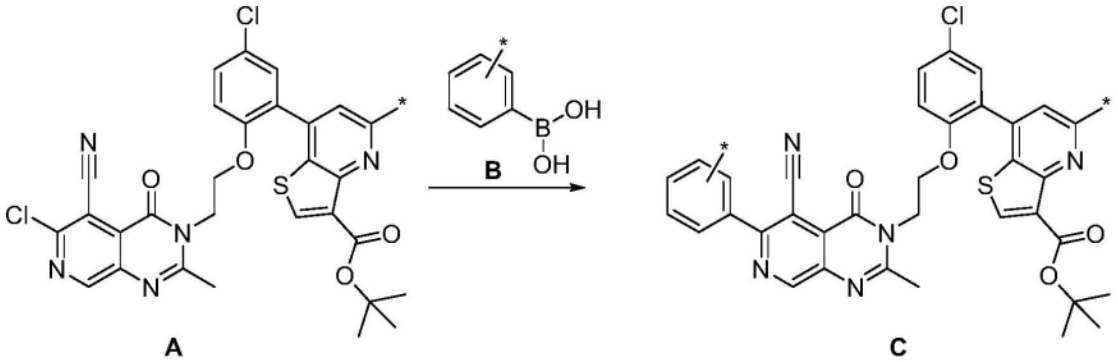
[0557] 在配备搅拌棒的螺旋盖小瓶中将(E)-7-(5-氯-2-(2-(5-氰基-2-甲基-6-(3-((甲基磺酰基)氧基)丙-1-烯-1-基)-4-氧代吡啶并[3,4-d]嘧啶-3(4H)-基)乙氧基)苯基)噻吩并[3,2-b]吡啶-3-甲酸叔丁酯(E,54.5mg,0.07mmol)溶于1,2-二氯乙烷(0.05M)中,并将反应混合物在10℃下搅拌,同时滴加4,4-二氟哌啶(F,3.3当量)。滴加N,N-二异丙基乙胺(6.6当量),5min后将反应混合物升温至室温。15min后将温度升至45℃并继续搅拌3h。将反应混合物冷却至室温,然后真空除去溶剂。将残留物溶于DMF并通过注射器过滤器过滤。制备HPLC得到期望产物,通过将HPLC级分通过strata离子交换柱将其分离,然后用二氯甲烷,甲醇和氢氧化铵的溶液洗涤。除去溶剂,得到(E)-7-(5-氯-2-(2-(5-氰基-6-(3-(4,4-二氟哌啶-1-基)丙-1-烯-1-基)-2-甲基-4-氧代吡啶并[3,4-d]嘧啶-3(4H)-基)乙氧基)苯基)噻吩并[3,2-b]吡啶-3-甲酸叔丁酯(G)。

[0558] 实施例1D.15

[0559] 

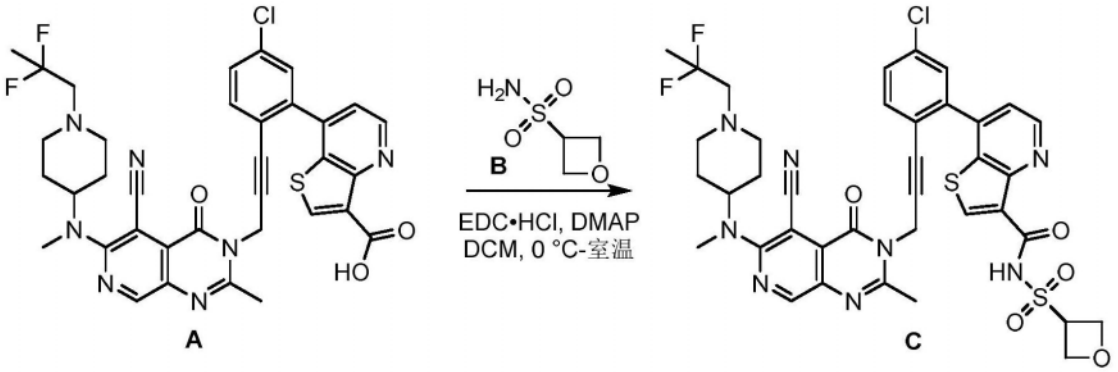
[0560] 将7-(5-氯-2-(2-(6-氯-5-氰基-2-甲基-4-氧代吡啶并[3,4-d]嘧啶-3(4H)-基)乙氧基)苯基)-5-甲基噻吩并[3,2-b]吡啶-3-甲酸叔丁酯(A,1当量),三丁基(甲氧基甲基)锡烷(B,1.5当量)的1-甲基-2-吡咯烷酮溶液(0.1M)用氩气脱气10min,并在室温下加入四(三苯基膦)钯(0)(0.055g,0.048mmol),在130℃下加热10h。将反应混合物冷却至室温,用水稀释,用乙酸乙酯萃取,用硫酸钠干燥乙酸乙酯层,浓缩并通过制备HPLC纯化,得到7-(5-氯-2-(2-(5-氰基-6-(甲氧基甲基)-2-甲基-4-氧代吡啶并[3,4-d]嘧啶-3(4H)-基)乙氧基)苯基)-5-甲基噻吩并[3,2-b]吡啶-3-甲酸叔丁酯(C)。

[0561] 实施例1D.16

[0562] 

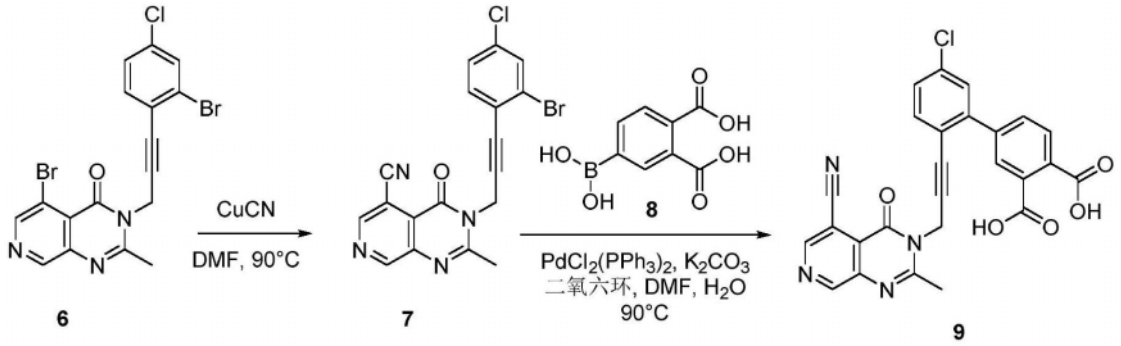
[0563] 向7-(5-氯-2-(2-(6-氯-5-氰基-2-甲基-4-氧代吡啶并[3,4-d]嘧啶-3(4H)-基)乙氧基)苯基)-5-甲基噻吩并[3,2-b]吡啶-3-甲酸叔丁酯(A,1当量)和(2-氟苯基)硼酸(B,1.5当量)的1,4-二氧六环溶液中加入2M碳酸钾水溶液(3当量),并将反应混合物用氩气脱气10min。加入[1,1'-双(二苯基膦基)二茂铁]二氯化钯(II)二氯甲烷复合物(0.05当量),用氩气脱气5min,并将反应混合物在90℃下加热3h。反应混合物用水稀释,用乙酸乙酯萃取,用无水硫酸钠干燥有机层,过滤,浓缩并通过柱色谱纯化,得到7-(5-氯-2-(2-(5-氰基-6-(2-氟苯基)-2-甲基-4-氧代吡啶并[3,4-d]嘧啶-3(4H)-基)乙氧基)苯基)-5-甲基噻吩并[3,2-b]吡啶-3-甲酸叔丁酯(C)。

[0564] 实施例1D.17

[0565] 

[0566] 在0℃下向7-(5-氯-2-(3-(5-氰基-6-((1-(2,2-二氟丙基)哌啶-4-基)(甲基)氨基)-2-甲基-4-氧代吡啶并[3,4-d]嘧啶-3(4H)-基)丙-1-炔-1-基)苯基)噻吩并[3,2-b]吡啶-3-羧酸(A,1当量)和氧杂环丁烷-3-磺酰胺(B,2.5当量)的二氯甲烷溶液(0.07M)中加入1-乙基-3-(3-二甲基氨基丙基)碳二亚胺盐酸盐(2当量)和4-(二甲基氨基)吡啶(2.5当量),并在室温下搅拌12h。将反应混合物用水稀释,用二氯甲烷萃取,有机层用无水硫酸钠干燥,过滤,浓缩并通过制备HPLC纯化,得到7-(5-氯-2-(3-(5-氰基-6-((1-(2,2-二氟丙基)哌啶-4-基)(甲基)氨基)-2-甲基-4-氧代吡啶并[3,4-d]嘧啶-3(4H)-基)丙-1-炔-1-基)苯基)-N-(氧杂环丁烷-3-基磺酰基)噻吩并[3,2-b]吡啶-3-甲酰胺(C)。

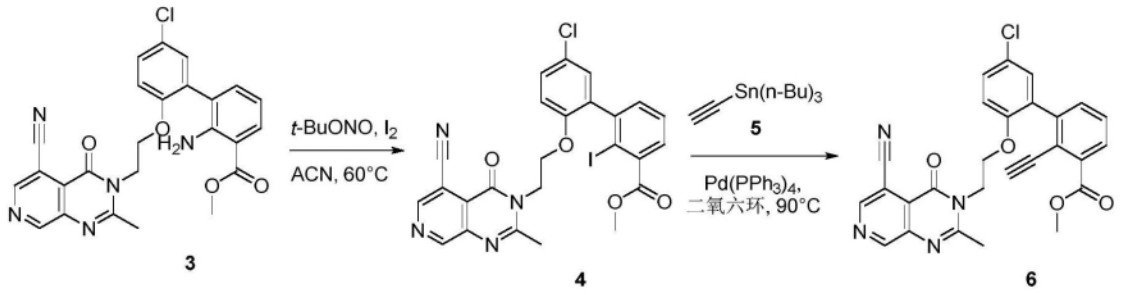
[0567] 实施例1D.18

[0568] 

[0569] 向搅拌的5-溴-3-(3-(2-溴-4-氯苯基)丙-2-炔-1-基)-2-甲基吡啶并[3,4-d]嘧啶-4(3H)-酮(6,0.6g,1.28mmol)的N,N-二甲基甲酰胺溶液中加入氰化亚铜(I)(0.138g,1.53mmol),并将反应混合物在90℃下加热并搅拌16h。完成后,将反应物质用乙酸乙酯稀释,并用冷水洗涤。将有机层分离,用无水硫酸钠干燥并减压浓缩。用50%乙酸乙酯的己烷溶液作为洗脱剂,通过Combi-flash纯化化合物粗品。将期望的级分减压浓缩,得到3-(3-(2-溴-4-氯苯基)丙-2-炔-1-基)-2-甲基-4-氧代-3,4-二氢吡啶并[3,4-d]嘧啶-5-甲腈(7)。

[0570] 将搅拌的3-(3-(2-溴-4-氯苯基)丙-2-炔-1-基)-2-甲基-4-氧代-3,4-二氢吡啶并[3,4-d]嘧啶-5-甲腈(7,0.1g,0.24mmol),4-二羟硼基邻苯二甲酸(8,0.075g,0.36mmol)和碳酸钾(0.099g,0.72mmol)在二氧六环,N,N-二甲基甲酰胺和水的混合物(分别为1.2mL,0.6mL和0.2mL)中的溶液用氩气脱气25min。加入双(三苯基膦)二氯化钯(II),将反应混合物在90℃下加热并搅拌2h。完成后,减压除去挥发物,得到残留物。将该残留物用水稀释,用1N盐酸水溶液酸化,并用乙酸乙酯萃取。将有机层分离,用无水硫酸钠干燥并减压浓缩,得到化合物。该化合物通过制备HPLC纯化,得到5'-氯-2'-(3-(5-氰基-2-甲基-4-氧代吡啶并[3,4-d]嘧啶-3(4H)-基)丙-1-炔-1-基)-[1,1'-联苯]-3,4-二羧酸(9)。

[0571] 实施例1D.18

[0572] 

[0573] 在室温下向2-氨基-5'-氯-2'-(2-(5-氰基-2-甲基-4-氧代吡啶并[3,4-d]嘧啶-3(4H)-基)乙氧基)-[1,1'-联苯]-3-甲酸甲酯(3,1.5g,3.06mmol)的乙腈(40mL)溶液中加入亚硝酸叔丁酯(0.50g,4.8mmol)。在室温下在10min的时间段内滴加碘化亚铜(I)(0.93g,3.06mmol)在乙腈(10mL)中的悬浮液。将反应混合物在60℃下搅拌4h。完成后,将反应混合物用水稀释,并用乙酸乙酯萃取。将有机层用硫代硫酸钠洗涤,用无水硫酸钠干燥,过滤并减压浓缩,得到粗品。用0-40%乙酸乙酯的己烷溶液,通过快速柱色谱纯化粗品,得到5'-氯-2'-(2-(5-氰基-2-甲基-4-氧代吡啶并[3,4-d]嘧啶-3(4H)-基)乙氧基)-2-碘-[1,1'-联苯]-3-甲酸甲酯(4)。

[0574] 将5'-氯-2'-(2-(5-氰基-2-甲基-4-氧代吡啶并[3,4-d]嘧啶-3(4H)-基)乙氧

基)-2-碘-[1,1'-联苯]-3-甲酸甲酯(4,0.57g,0.95mmol)的二氧六环(20mL)溶液用氩气脱气10min。加入三丁基(乙炔基)锡烷(5,0.6g,1.86mmol)和四(三苯基膦)钯(0)(0.076g,0.066mmol),并将反应混合物在90℃下搅拌16h。完成后,将反应混合物用水稀释,并用乙酸乙酯萃取。将有机层用无水硫酸钠干燥,过滤,并减压浓缩至干。用0-40%乙酸乙酯的己烷溶液,通过快速柱色谱纯化粗品,得到5'-氯-2'-(2-(5-氰基-2-甲基-4-氧代吡啶并[3,4-d]嘧啶-3(4H)-基)乙氧基)-2-乙炔基-[1,1'-联苯]-3-甲酸甲酯(6)。

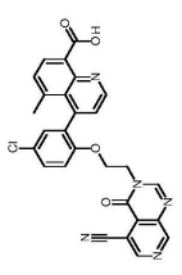
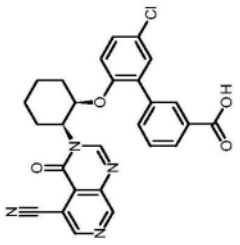
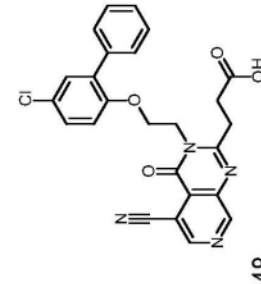
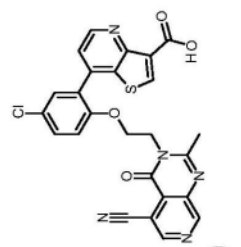
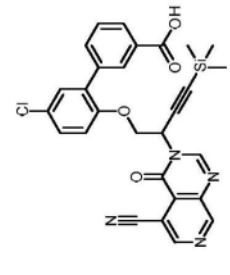
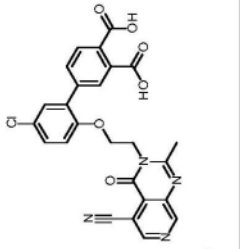
[0575] 使用一种或多种上述通用方法制备的化合物显示在表1中。在提供表征数据的情况下,表征数据在化合物的右侧。

[0576]

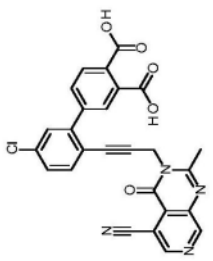
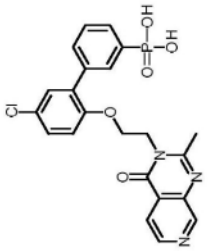
表 1. 7-氮杂-噻吩基吡啶和衍生化合物

化合物	表征	化合物	表征
34	MS (ESI) m/z 447.30 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 12.98 (s, 1H), 9.23 (s, 1H), 9.07 (s, 1H), 8.20 (s, 1H), 7.88 (s, 1H), 7.84 (d, J = 7.68, 1H), 7.61 (d, J = 7.72, 1H), 7.45 - 7.39 (m, 2H), 7.33 (d, J = 2.5 Hz, 1H), 7.21 (d, J = 8.84Hz, 1H), 4.35 (s, 4H)	38	MS (ESI) m/z 529.45 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 12.98 (s, 1H), 9.13 (s, 1H), 7.87-7.85 (m, 2H), 7.56 (d, J = 7.76 Hz, 1H), 7.42-7.38 (m, 2H), 7.29 (d, J = 2.64 Hz, 1H), 7.21 (d, J = 8.92 Hz, 1H), 4.37 (m, 4H), 2.24 (s, 3H)
35	MS (ESI) m/z 462.39 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 9.19 (s, 1H), 9.03 (s, 1H), 8.63 (d, J = 4.8 Hz, 1H), 7.94 (d, J = 0.8 Hz, 1H), 7.59 (dd, J = 4.8 Hz, 1H), 7.48 (dd, J = 4.4 Hz, 1H), 7.409 (d, J = 2.8 Hz, 1H), 7.249 (d, J = 8.8 Hz, 1H), 4.386 (s, 4H), 2.22 (s, 3H)	39	MS (ESI) m/z 554.13 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 9.22 (s, 1H), 9.19 (s, 1H), 8.79 (d, J = 4.8 Hz, 1H), 8.45 (s, 1H), 7.61 (dd, J = 2.64, 8.88, 1H), 7.48 (d, J = 4.8 Hz, 1H), 7.45 (d, J = 2.68 Hz, 1H), 7.37 (d, J = 8.96 Hz, 1H), 6.72-6.46 (t, J = 51.6 Hz, 1H), 4.41 (d, J = 4.64 Hz, 2H), 4.36 (d, J = 4.52 Hz, 2H)
36	MS (ESI) m/z 486.38 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 9.16 (s, 1H), 7.87 (d, J=7.68 Hz, 1H), 7.83 (s, 1H), 7.49 (d, J = 7.68 Hz, 1H), 7.43-7.38 (m, 2H), 7.27 (d, J = 2.6 Hz, 1H), 7.20 (d, J = 8.88 Hz, 1H), 4.39-4.35 (dd, J =12.52 Hz, 4H), 2.29 (s, 3H)	44	MS (ESI) m/z 457.42 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.06 (s, 1H), 9.18 (s, 1H), 9.04 (s, 1H), 7.9-7.83 (m, 1H), 7.76 (s, 1H), 7.72 (d, J = 8.4 Hz, 1H), 7.52-7.44 (m, 3H), 7.36 (d, J = 2.2 Hz, 1H), 6.42 -6.35 (m, 1H), 6.22 (d, J = 16.04 Hz, 1H), 4.82 (d, J = 4.8 Hz, 2H), 2.58 (s, 3H)

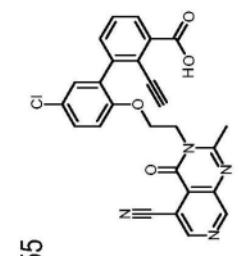
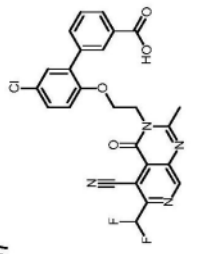
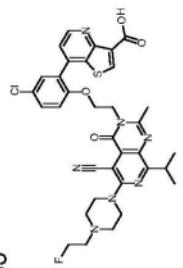
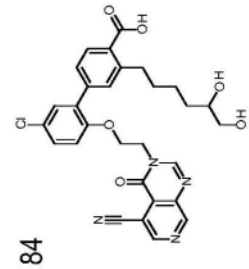
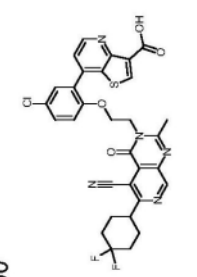
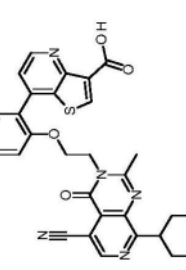
[0577]

 45	MS (ESI) m/z 510.44 [M-1]-; 1H NMR (400 MHz, DMSO-d6) δ 9.01 (s, 1H), 8.98 (s, 1H), 8.96 (d, J = 4.56 Hz, 1H), 8.17 (d, J = 7.52 Hz, 1H), 7.64 (s, 1H), 7.56 (dd, J = 8.92 Hz, 1H), 7.44 (d, J = 4.56 Hz, 1H), 7.30 (d, J = 2.56 Hz, 1H), 7.26 (d, J = 8.96 Hz, 1H), 7.19 (d, J =7.6 Hz, 1H), 4.33-4.29 (m, 2H), 4.24-4.17 (m, 1H), 4.12-4.06 (m, 1H), 1.84 (s, 3H)	 50	MS (ESI) m/z 619.07 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.86 (d, J = 4.4 Hz, 1H), 8.24 (s, 1H), 8.08 (s, 1H), 7.60 (dd, J = 8.8, 2.6 Hz, 1H), 7.51 (d, J = 4.8 Hz, 1H), 7.43 (d, J = 2.6 Hz, 1H), 7.36 (d, J = 8.8 Hz, 1H), 4.41 (t, J = 4.7 Hz, 2H), 4.25 (t, J = 4.7 Hz, 2H), 1.69 (s, 3H)
 48	MS (ESI) m/z 475.16 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 12.16 (s, 1H), 9.18 (s, 1H), 9.05 (s, 1H), 7.36 (dd, J = 8.8 Hz, 1H), 7.28 (t, 2H), 7.24 – 7.18 (m, 5 H), 4.57 (t, 2H), 4.33 (t, 2H), 2.87 (t, 2H) 2.57 (t, 2H)	 140	MS (ESI) m/z 518.50 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 9.029 (d, J = 1.24 Hz, 2H), 8.835 (d, J = 4.76 Hz, 1H), 8.379 (s, 1H), 7.596 (dd, J = 2.6, 8.96 Hz, 1H), 7.48 (d, J = 4.72 Hz, 1H), 7.439 (d, J = 2.52 Hz, 1H), 7.35 (d, J = 9.0 Hz, 1H), 4.403 (t, J = 4.68 Hz, 2H), 4.255 (t, J = 6.04 Hz, 2H), 1.787 (s, 3H)
 49	MS (ESI) m/z 553.18 [M+1]+; 1H NMR (400 MHz, DMSO-d6) d 12.17 (bs, 1H), 8.84 (d, J = 4.76 Hz, 1H), 8.41 (s, 1H), 7.72 (dd, J = 10.68 Hz, 7.56 Hz, 1H),7.60 (dd, J = 8.08, 2.60 Hz, 1H), 7.48 (d, J = 4.76 Hz, 1H), 7.41 (d, J = 2.52 Hz, 1H), 7.36 (d, J = 8.08 Hz, 1H), 4.39 (t, J = 4.64 Hz, 2H). 4.23 (t, J = 4.68 Hz, 2H), 1.77 (s, 3H)	 147	MS (ESI) m/z 505 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 9.16 (s, 1H), 9.00 (s, 1H), 8.139 (m, J = 8.04 Hz, 2H), 7.44 (m, J = 7.92 Hz, 2H), 7.28 (d, J = 2.76 Hz, 1H), 7.19 (d, J = 8.92 Hz ,1H), 4.35 (s, 4H), 2.22 (s, 3H)

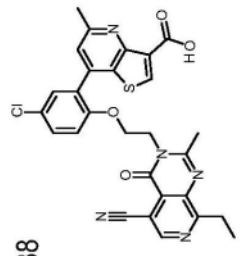
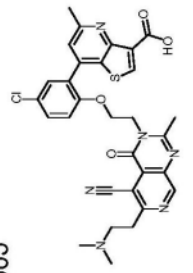
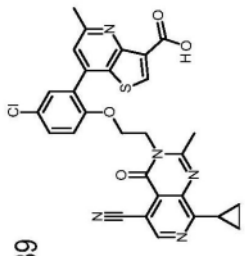
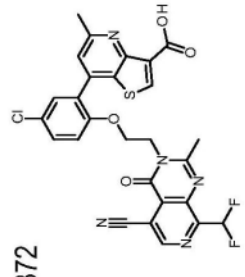
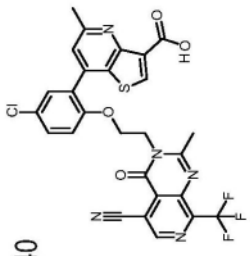
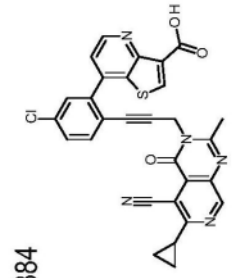
[0578]

149		MS (ESI) m/z 497.38 [M-1]-; 1H NMR (400 MHz, DMSO-d6) δ 9.158 (s, 1H), 9.033 (s, 1H), 8.291 (s, 1H), 8.117 (d, J = 8.2 Hz, 1H), 7.63 (d, J = 8.28 Hz, 1H), 7.6 (dd, J = 1.96, 8.12 Hz, 1H), 7.53 (d, J = 1.96 Hz, 1H), 7.49 (dd, J = 2.2, 8.4 Hz, 1H), 5.05 (s, 2H), 2.35 (s, 3H)	150FC 	MS (ESI) m/z 472 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.9 (s, 1H), 8.62 (d, J = 5.2 Hz, 1H), 7.91 (d, J = 5.16 Hz, 1H), 7.63-7.72 (m, 2H), 7.40-7.44 (m, 3H), 7.24 (d, J = 2.64 Hz, 1H), 7.19 (d, J=8.84, 1H), 4.33-4.37 (m, 4H), 2.28 (s, 3H)
150FA		MS (ESI) m/z 497 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 9.20 (s, 1H), 9.03 (s, 1H), 7.68-7.63 (m, 2H), 7.47-7.38 (m, 3H), 7.23 (d, J = 2.6 Hz, 1H), 7.18 (d, J = 8.88 Hz, 1H), 4.37-4.22 (m, 4H), 2.25 (s, 3H)	151	MS (ESI) m/z 696.11 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 12.69 (bs, 1H), δ 8.92 (d, J = 4.4 Hz, 1H), δ 8.34 (s, 1H), δ 8.09 (s, 1H), δ 7.63-7.57 (m, 2H), δ 7.45 (d, J = 2.0 Hz, 1H), δ 7.36 (d, J = 8.8 Hz, 1H), δ 4.42 (t, 4.8 Hz, 2H), δ 4.24 (t, J = 4.8, 2H), δ 3.56 (s, 3H), δ 1.65 (s, 3H)
150FB		MS (ESI) m/z 539 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 9.19 (s, 1H), 9.03 (s, 1H), 7.25 (d, J = 2.6 Hz, 1H), 7.19 (d, J = 8.8 Hz, 1H),7.63-7.67 (m, 2H), 7.50 (d, J = 6.5 Hz, 1H), 7.41 -7.44 (m, 1H), 7.41 (dd, J =2.8 Hz, J'= 2.6 Hz, 1H), 4.36 (s, 4H), 4.41-4.48 (m, 1H), 2.24 (s, 3H), 1.19 (d, J = 6.2 Hz, 6H)	152	MS (ESI) m/z 579.03 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 12.96 (b, 1H), 8.74(d, J = 4.72 Hz, 1H), 8.62 (s, 1H), 8.13 (d, J = 9.76 Hz, 1H), 7.76 (d, J = 9.76 Hz, 1H), 7.68 (t, J = 2.04 Hz, 1H), 7.53 (d, J = 4.72 Hz, 1H), 7.3 (t, J = 53.68 Hz, 1H), 4.88 (s, 2H), 2.22(s, 3H)

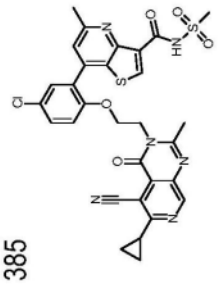
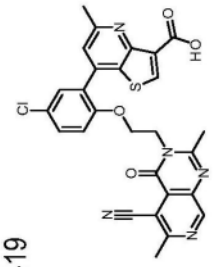
[0579]

155		MS (ESI) m/z 485.13 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 12.89 (bs, 1H), 9.17 (s, 1H), 9.00 (s, 1H), 7.88 (m, 1H), 7.46-7.36 (m, 3H), 7.16-7.12 (m, 2H), 4.32 (bs, 4H), 3.67 (s, 1H), 1.98 (s, 3H)	
157		MS (ESI) m/z 511.48 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 12.87 (s, 1H), 9.23 (s, 1H), 7.88-7.86 (dd, J = 1.28, J = 6.8 Hz, 1H), 7.80 (d, J = 1.6 Hz, 1H), 7.53 (d, J = 7.6 Hz, 1H), 7.45-7.17 (m, 5H), 4.36 (s, 4H), 2.19 (s, 3H)	
183		MS (ESI) m/z 690.4 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 10.15 (s, 1H), 8.79 (d, J = 4.8 Hz, 1H), 8.59 (s, 1H), 7.60 (dd, J = 8.9, 2.7 Hz, 1H), 7.46 (d, J = 4.8 Hz, 1H), 7.44 (d, J = 2.6 Hz, 1H), 7.38 (d, J = 9.0 Hz, 1H), 4.89 (dt, J = 47.1, 4.7 Hz, 2H), 4.44 – 4.33 (m, 3H), 4.23 (t, J = 5.1 Hz, 2H), 3.93 (hept, J = 6.8 Hz, 1H), 3.79 – 3.52 (m, 7H), 1.87 (s, 3H), 1.25 (d, J = 6.8 Hz, 6H)	
184		MS (ESI) m/z 561.16 [M-1]-; 1H NMR (400 MHz, DMSO-d6) δ 9.26 (s, 1H), 9.08 (s, 1H), 8.32 (s, 1H), 7.63 (d, J = 8.4 Hz, 1H), 7.39-7.16 (m, 5H), 4.34 (d, J = 3.6 Hz, 6H), 3.25-3.18 (m, 3H), 2.89 (s, 2H), 1.42 (d, J = 15 Hz, 4H), 1.27-1.18 (m, 2H)	
260		MS (ESI) m/z 636.1 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.99 (s, 1H), 8.82 (d, J = 4.9 Hz, 1H), 8.40 (s, 1H), 7.60 (dd, J = 8.9, 2.7 Hz, 1H), 7.48 (d, J = 4.8 Hz, 1H), 7.44 (d, J = 2.7 Hz, 1H), 7.36 (d, J = 9.0 Hz, 1H), 4.40 (t, J = 5.0 Hz, 2H), 4.25 (t, J = 5.0 Hz, 2H), 3.50 – 3.41 (m, 1H), 2.24 – 1.94 (m, 8H), 1.83 (s, 3H)	
284		MS (ESI) m/z 636.1 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.94 (s, 1H), 8.80 (d, J = 4.8 Hz, 1H), 8.60 (s, 1H), 7.59 (dd, J = 8.9, 2.7 Hz, 1H), 7.49 (d, J = 4.8 Hz, 1H), 7.45 (d, J = 2.7 Hz, 1H), 7.36 (d, J = 9.0 Hz, 1H), 4.42 (t, J = 4.9 Hz, 2H), 4.25 (t, J = 4.9 Hz, 2H), 3.94 – 3.82 (m, 1H), 2.23 – 1.94 (m, 6H), 1.86 (td, J = 12.7, 12.1, 4.2 Hz, 2H), 1.80 (s, 3H)	

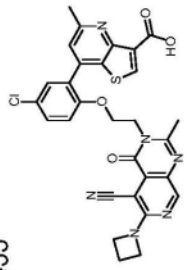
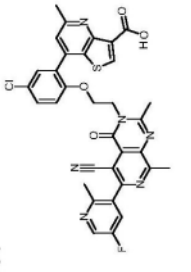
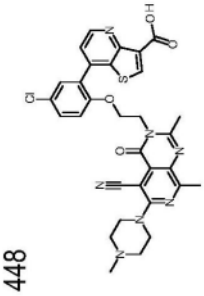
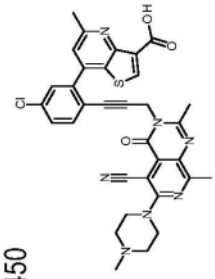
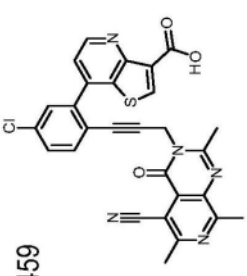
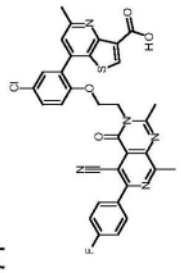
[0580]

338		MS (ESI) m/z 560.1 [M+1]+; 1H-NMR (400 MHz, d6-DMSO) d / ppm = 8.89 (s, 1H), 8.49 (s, 1H), 7.59 (dd, J = 8.9, 2.6 Hz, 1H), 7.43-7.41 (m, 2H), 7.36 (d, J = 8.9 Hz, 1H), 4.43 (t, J = 4.8 Hz, 2H), 4.26 (t, J = 4.8 Hz, 2H), 3.19 (q, J = 7.5 Hz, 2H), 2.69 (s, 3H), 1.93 (s, 3H), 1.27 (t, J = 7.5 Hz, 3H)	365		MS (ESI) m/z 603.3 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 9.58 (s, 1H), 8.96 (s, 1H), 8.34 (s, 1H), 7.60 (dd, J = 8.9, 2.7 Hz, 1H), 7.42 (s, 1H), 7.41 (d, J = 2.7 Hz, 1H), 7.36 (d, J = 9.0 Hz, 1H), 4.41 (t, J = 5.0 Hz, 2H), 4.28 (t, J = 5.1 Hz, 2H), 3.69 – 3.61 (m, 2H), 3.58 – 3.50 (m, 2H), 2.93 (s, 3H), 2.92 (s, 3H), 2.72 (s, 3H), 1.92 (s, 3H)
339		MS (ESI) m/z 572.1; 1H-NMR (400 MHz, d6-DMSO) d / ppm = 8.77 (s, 1H), 8.59 (s, 1H), 7.59 (dd, J = 8.9, 2.6 Hz, 1H), 7.42 (d, J = 2.6 Hz, 1H), 7.41 (s, 1H), 7.36 (d, J = 8.9 Hz, 1H), 4.42 (t, J = 5.0 Hz, 2H), 4.27 (t, J = 5.0 Hz, 2H), 3.21-3.11 (m, 1H), 2.68 (s, 3H), 1.92 (s, 3H), 1.33-1.26 (m, 1H), 1.21-1.15 (m, 1H)	372		MS (ESI) m/z 582.2 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 9.12 (s, 1H), 8.59 (s, 1H), 7.59 (dd, J = 8.9, 2.7 Hz, 1H), 7.52 (t, J= 53.5 Hz, 1H), 7.44 (d, J = 2.6 Hz, 1H), 7.40 (s, 1H), 7.35 (d, J = 9.0 Hz, 1H), 4.42 (t, J = 5.0 Hz, 2H), 4.27 (t, J = 5.0 Hz, 2H), 2.66 (s, 3H), 1.90 (s, 3H)
340		MS (ESI) m/z 600.2 [M+1]+; 1H-NMR (400 MHz, d6-DMSO) d / ppm = 9.11 (s, 1H), 8.63 (s, 1H), 7.60 (dd, J = 8.9, 2.7 Hz, 1H), 7.46-7.44 (m, 2H), 7.36 (d, J = 8.9 Hz, 1H), 4.44 (t, J = 4.9 Hz, 2H), 4.30 (t, J = 4.9 Hz, 2H), 2.70 (s, 3H), 2.05 (s, 3H)	384		MS (ESI) m/z 552.1 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.99 (s, 1H), 8.75 (d, J = 4.8 Hz, 1H), 8.62 (s, 1H), 7.80 – 7.73 (m, 1H), 7.72 – 7.65 (m, 2H), 7.55 (d, J = 4.8 Hz, 1H), 4.86 (s, 2H), 2.67 – 2.61 (m, 1H), 2.09 (s, 3H), 1.29 – 1.15 (m, 4H)

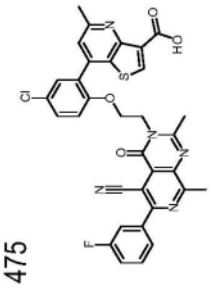
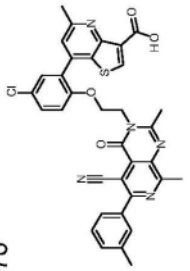
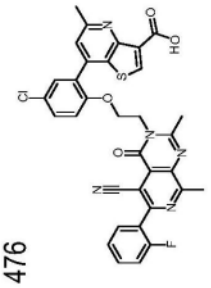
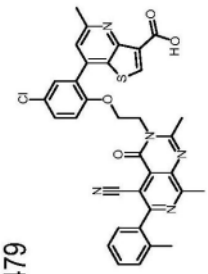
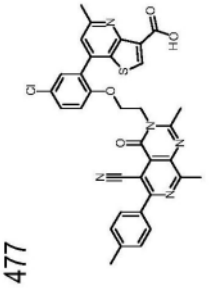
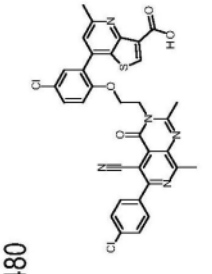
[0581]

385		MS (ESI) m/z 649.1 [M+1]+; ; 1H NMR (400 MHz, DMSO-d6) δ 12.91 (s, 1H), 8.84 (s, 1H), 8.56 (s, 1H), 7.60 (dd, J = 8.9, 2.7 Hz, 1H), 7.43 (s, 1H), 7.40 (d, J = 2.7 Hz, 1H), 7.37 (d, J = 9.0 Hz, 1H), 4.41 (t, J = 5.1 Hz, 2H), 4.25 (t, J = 5.1 Hz, 2H), 3.57 (s, 3H), 2.68 (s, 3H), 2.61 (tt, J = 7.6, 4.9 Hz, 1H), 1.87 (s, 3H), 1.31 – 1.13 (m, 4H)	419		MS (ESI) m/z 546.7 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.89 (s, 1H), 8.38 (s, 1H), 7.59 (dd, J = 8.9, 2.7 Hz, 1H), 7.42 (s, 1H), 7.41 (d, J = 2.6 Hz, 1H), 7.35 (d, J = 8.9 Hz, 1H), 4.40 (t, J = 5.0 Hz, 2H), 4.25 (t, J = 5.0 Hz, 2H), 2.79 (s, 3H), 2.71 (s, 3H), 1.88 (s, 3H)
400		MS (ESI) m/z 644.5 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.47 (s, 1H), 7.59 (dd, J = 8.9, 2.6 Hz, 1H), 7.44 – 7.38 (m, 2H), 7.37 (d, J = 9.0 Hz, 1H), 4.42 (t, J = 5.0 Hz, 2H), 4.25 (t, J = 5.0 Hz, 2H), 3.87 – 3.78 (m, 2H), 3.26 (td, J = 11.7, 2.1 Hz, 2H), 2.96 (d, J = 7.1 Hz, 2H), 2.73 (s, 3H), 2.69 (s, 3H), 2.15 – 2.02 (m, 1H), 1.92 (s, 3H), 1.56 – 1.47 (m, 2H), 1.33 (qd, J = 12.0, 4.4 Hz, 2H)	420		MS (ESI) m/z 588.1 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.92 (s, 1H), 8.46 (s, 1H), 7.59 (dd, J = 8.9, 2.7 Hz, 1H), 7.43 (s, 1H), 7.42 (d, J = 2.5 Hz, 1H), 7.36 (d, J = 9.0 Hz, 1H), 4.39 (t, J = 5.1 Hz, 2H), 4.24 (t, J = 5.1 Hz, 2H), 2.71 (s, 3H), 1.86 (s, 3H), 1.58 (s, 9H)
418		MS (ESI) m/z 572.5 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.84 (s, 1H), 8.42 (s, 1H), 7.59 (dd, J = 8.8, 2.6 Hz, 1H), 7.42 (s, 1H), 7.41 (d, J = 2.6 Hz, 1H), 7.36 (d, J = 9.0 Hz, 1H), 4.40 (t, J = 5.0 Hz, 2H), 4.25 (t, J = 5.0 Hz, 2H), 2.70 (s, 3H), 2.65-2.56 (m, 1H), 1.86 (s, 3H), 1.27-1.14 (m, 4H)	432		MS (ESI) m/z 574.6 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.98 (s, 1H), 8.42 (s, 1H), 7.59 (dd, J = 8.9, 2.6 Hz, 1H), 7.42 (d, J = 2.6 Hz, 1H), 7.42 (s, 1H), 7.35 (d, J = 9.0 Hz, 1H), 4.39 (t, J = 4.9 Hz, 2H), 4.25 (t, J = 5.0 Hz, 2H), 3.64 (hept, J = 6.8 Hz, 1H), 2.70 (s, 3H), 1.87 (s, 3H), 1.33 (d, J = 6.7 Hz, 6H)

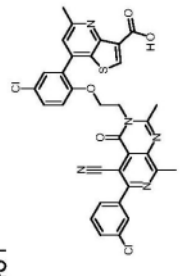
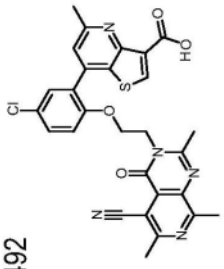
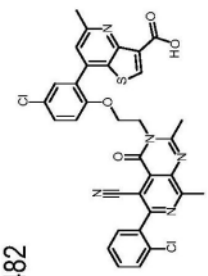
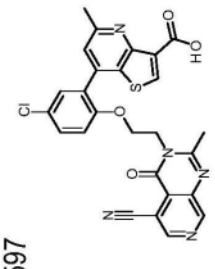
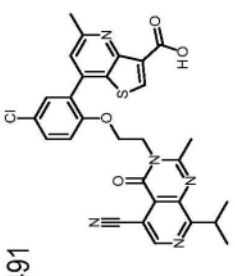
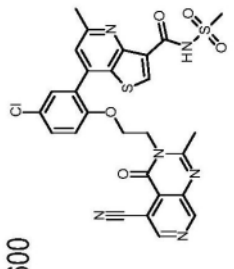
[0582]

435		MS (ESI) m/z 587.6 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.52 – 8.47 (m, 2H), 7.56 (dd, J = 8.9, 2.7 Hz, 1H), 7.40 – 7.35 (m, 2H), 7.31 (d, J = 9.0 Hz, 1H), 4.37 – 4.29 (m, 6H), 4.16 (t, J = 5.1 Hz, 3H), 2.68 (s, 3H), 2.40 – 2.28 (m, 2H), 1.79 (s, 3H)	
441		MS (ESI) m/z 655.5 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.65 (d, J = 2.7 Hz, 1H), 8.48 (s, 1H), 8.06 (dd, J = 9.1, 2.8 Hz, 1H), 7.60 (dd, J = 8.9, 2.7 Hz, 1H), 7.49 – 7.34 (m, 3H), 4.46 (t, J = 5.0 Hz, 2H), 4.30 (t, J = 5.1 Hz, 2H), 2.79 (s, 3H), 2.72 (s, 3H), 2.35 (s, 3H), 2.00 (s, 3H)	
448		MS (ESI) m/z 630.2 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 9.89 (s, 1H), 8.82 (d, J = 4.8 Hz, 1H), 8.48 (s, 1H), 7.61 (dd, J = 9.0, 2.7 Hz, 1H), 7.47 (d, J = 4.8 Hz, 1H), 7.41 – 7.37 (m, 2H), 4.43 (t, J = 5.1 Hz, 2H), 4.33 (d, J = 14.1 Hz, 2H), 4.24 (t, J = 5.1 Hz, 2H), 3.60 (d, J = 11.9 Hz, 2H), 3.33 – 3.19 (m, 2H), 2.91 (d, J = 3.1 Hz, 3H), 2.66 (s, 3H), 1.89 (s, 3H)	
450		MS (ESI) m/z 638.1 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 9.86 (s, 1H), 8.64 (s, 1H), 7.75 (d, J = 8.4 Hz, 1H), 7.69 (dd, J = 8.4, 2.2 Hz, 1H), 7.63 (d, J = 2.1 Hz, 1H), 7.46 (s, 1H), 4.81 (s, 2H), 4.35 (d, J = 14.1 Hz, 2H), 3.62 (d, J = 12.0 Hz, 2H), 3.48 – 3.23 (m, 6H), 2.92 (d, J = 3.5 Hz, 3H), 2.74 (s, 3H), 2.66 (s, 3H), 2.17 (s, 3H)	
459		MS (ESI) m/z 560.1 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.73 (d, J = 4.8 Hz, 1H), 8.63 (s, 1H), 7.76 (d, J = 8.2 Hz, 1H), 7.72 – 7.63 (m, 2H), 7.53 (d, J = 4.8 Hz, 1H), 4.85 (s, 2H), 2.78 (d, J = 10.6 Hz, 6H), 2.15 (s, 3H)	
474		LCMS: 640.2 [M+H]+; 1H NMR (400 MHz, DMSO-d6) δ 8.50 (s, 1H), 7.99 – 7.89 (m, 2H), 7.60 (dd, J = 8.9, 2.7 Hz, 1H), 7.48 – 7.31 (m, 5H), 4.45 (t, J = 5.0 Hz, 2H), 4.28 (t, J = 5.1 Hz, 2H), 2.79 (s, 3H), 2.71 (s, 3H), 1.97 (s, 3H)	

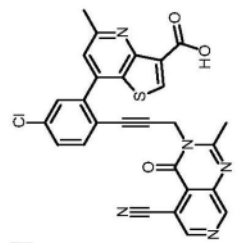
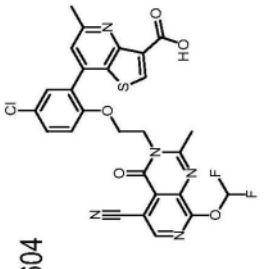
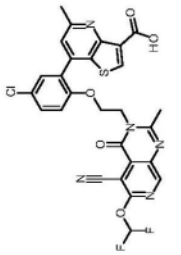
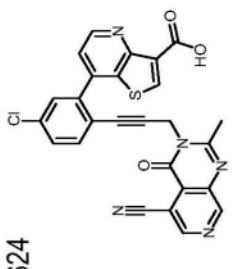
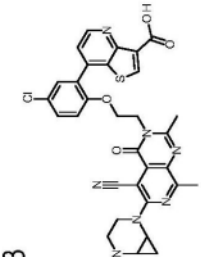
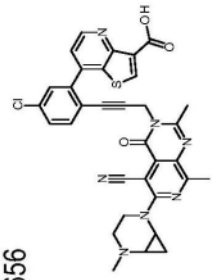
[0583]

475 	LCMS: 640.2 [M+H]+; 1H NMR (400 MHz, DMSO-d6) δ 8.48 (s, 1H), 7.79 – 7.68 (m, 2H), 7.66 – 7.57 (m, 2H), 7.45 – 7.34 (m, 4H), 4.45 (t, J = 5.1 Hz, 2H), 4.29 (t, J = 5.0 Hz, 2H), 2.80 (s, 3H), 2.71 (s, 3H), 1.99 (s, 3H)	478 	LCMS: 636.8 [M+H]+; 1H NMR (400 MHz, DMSO-d6) δ 8.50 (s, 1H), 7.70 – 7.63 (m, 2H), 7.60 (dd, J = 8.9, 2.7 Hz, 1H), 7.48 – 7.33 (m, 5H), 4.45 (t, J = 5.0 Hz, 2H), 4.28 (t, J = 5.0 Hz, 2H), 2.79 (s, 3H), 2.71 (s, 3H), 2.43 (s, 3H), 1.94 (s, 3H)
476 	LCMS: 640.2 [M+H]+; 1H NMR (400 MHz, DMSO-d6) δ 8.57 (s, 1H), 7.72 (td, J = 7.7, 1.9 Hz, 1H), 7.67 – 7.57 (m, 2H), 7.47 – 7.34 (m, 5H), 4.44 (t, J = 5.0 Hz, 2H), 4.28 (t, J = 5.0 Hz, 2H), 2.80 (s, 3H), 2.71 (s, 3H), 1.96 (s, 3H)	479 	LCMS: 636.8 [M+H]+; 1H NMR (400 MHz, DMSO-d6) δ 8.52 (s, 1H), 7.60 (dd, J = 8.9, 2.7 Hz, 1H), 7.44 (dq, J = 3.9, 2.0 Hz, 4H), 7.42 – 7.31 (m, 3H), 4.44 (t, J = 5.0 Hz, 2H), 4.28 (d, J = 4.9 Hz, 2H), 2.77 (s, 3H), 2.71 (s, 3H), 2.18 (s, 3H), 1.90 (s, 3H)
477 	LCMS: 636.7 [M+H]+; ; 1H NMR (400 MHz, DMSO-d6) δ 8.52 (s, 1H), 7.81 – 7.75 (m, 2H), 7.60 (dd, J = 8.9, 2.7 Hz, 1H), 7.46 – 7.32 (m, 5H), 4.45 (t, J = 5.0 Hz, 2H), 4.28 (t, J = 5.1 Hz, 2H), 2.78 (d, J = 0.7 Hz, 3H), 2.71 (s, 3H), 2.42 (s, 3H), 1.94 (s, 3H)	480 	LCMS: 656.4 [M+H]+; 1H NMR (400 MHz, DMSO-d6) δ 8.49 (s, 1H), 7.92 (d, J = 2.1 Hz, 1H), 7.91 (d, J = 2.1 Hz, 1H), 7.68 – 7.63 (m, 2H), 7.60 (dd, J = 8.9, 2.7 Hz, 1H), 7.45 – 7.36 (m, 3H), 4.45 (t, J = 5.0 Hz, 2H), 4.29 (t, J = 4.9 Hz, 2H), 2.79 (s, 3H), 2.70 (s, 3H), 1.97 (s, 3H)

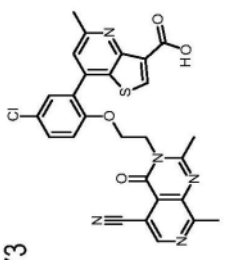
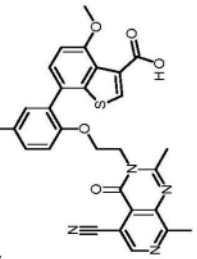
[0584]

481		LCMS: 656.6 [M+H]+; 1H NMR (400 MHz, DMSO-d6) δ 8.46 (s, 1H), 7.94 (td, J = 1.9, 0.6 Hz, 1H), 7.85 (dt, J = 7.1, 1.7 Hz, 1H), 7.67 – 7.57 (m, 3H), 7.45 – 7.36 (m, 3H), 4.46 (t, J = 5.1 Hz, 2H), 4.29 (t, J = 5.0 Hz, 2H), 2.79 (s, 3H), 2.72 (s, 3H), 1.99 (s, 3H)	492		MS (ESI) m/z 560.1 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.48 (s, 1H), 7.59 (dd, J = 8.9, 2.7 Hz, 1H), 7.42 – 7.35 (m, 4H), 4.43 (t, J = 5.1 Hz, 2H), 4.26 (t, J = 5.1 Hz, 2H), 2.72 (d, J = 3.2 Hz, 6H), 2.70 (s, 3H), 1.96 (s, 3H)
482		LCMS: 656.7 [M+H]+; 1H NMR (400 MHz, DMSO-d6) δ 8.54 (s, 1H), 7.70 – 7.63 (m, 2H), 7.62 – 7.52 (m, 3H), 7.46 – 7.41 (m, 2H), 7.38 (d, J = 9.0 Hz, 1H), 4.44 (t, J = 5.0 Hz, 2H), 4.28 (s, 2H), 2.79 (s, 3H), 2.71 (s, 3H), 1.94 (s, 3H)	597		MS (ESI) m/z 532.14 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 9.0 (d, J = 5.6 Hz, 1H), 8.38 (s, 1H), 7.59 (dd, J = 8.8, 2.5 Hz, 1H), 7.41 (d, J = 2.1 Hz, 2H), 7.35 (d, J = 9.0 Hz, 1H), 4.4 (t, J = 4.2 Hz, 2H), 4.26 (t, J = 4.8 Hz, 2H), 2.7 (s, 3H), 1.85 (s, 3H)
491		MS (ESI) m/z 574.5 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.92 (s, 1H), 8.59 (s, 1H), 7.59 (dd, J = 8.9, 2.7 Hz, 1H), 7.50 – 7.41 (m, 2H), 7.35 (d, J = 9.0 Hz, 1H), 4.42 (t, J = 5.0 Hz, 2H), 4.26 (t, J = 5.1 Hz, 2H), 4.12 – 4.00 (m, 1H), 2.68 (s, 3H), 1.94 (s, 3H), 1.26 (d, J = 6.8 Hz, 6H)	600		MS (ESI) m/z 609.11 [M+1; 1H NMR (400 MHz, DMSO-d6) δ 12.94 (s, 1H), 9.01 (d, J = 5.44, 1H), 8.51 (s, 1H), 7.62-7.56 (m, 1H), 7.49-7.31 (m, 3H), 4.41 (s, 2H), 4.26 (s, 2H), 3.58 (s, 3H), 2.69 (s, 3H), 1.91 (s, 3H)

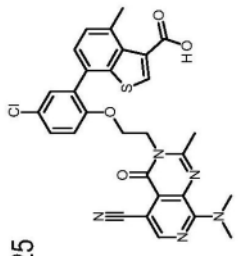
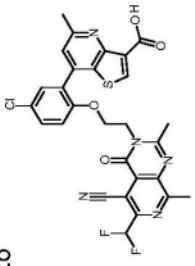
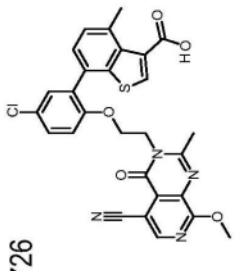
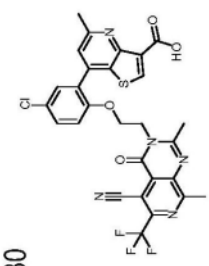
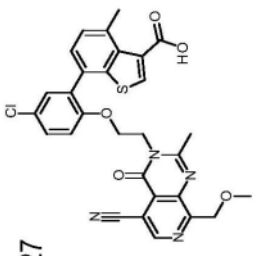
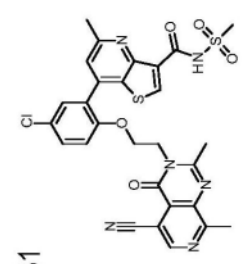
[0585]

601		MS (ESI) m/z 526.12 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 9.14 (s, 1H), 9.08 (s, 1H), 8.61 (s, 1H), 7.75 (d, J = 8.2 Hz, 1H), 7.69-7.66 (m, 2H), 7.46 (s, 1H), 4.87 (s, 2H), 2.61 (s, 3H), 2.16 (s, 3H)	604		MS (ESI) m/z 598.18 [M+1]+; 1H-NMR (400 MHz, DMSO-d6) δ 8.66 (s ,1H), 8.54 (s, 1H), 7.82 (t, J = 71.4 Hz, 1H), 7.60 (dd, J = 2.52, 8.84 Hz, 1H), 7.42 (d, J = 2.5 Hz, 1H), 7.40 (s, 1H), 7.36 (d, J = 8.8 Hz, 1H), 4.42 (t, J = 5.46 Hz, 2H), 4.29 (t, J = 5.46 Hz, 2H), 2.71 (s, 3H), 2.01 (s, 3H)
602		MS (ESI) m/z 598.13 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.78 (s, 1H), 8.40 (s, 1H), 7.85 (t, J = 72.0 Hz, 1H), 7.59 (d, J = 8.92 Hz, 1H), 7.42 (bs, 2H), 7.35 (d, J = 8.96 Hz, 1H), 4.40 (t, J = 5.12 Hz, 2H), 4.25 (t, J = 4.44 Hz, 2H), 2.71 (s, 3H), 1.82 (s, 3H)	624		MS (ESI) m/z 512.02 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 9.15 (s, 1H), 9.06 (s, 1H), 8.74 (d, J = 4.76 Hz, 1H), 8.61 (s, 1H), 7.76 (d, J = 8.96, 1H), 7.70-7.65 (m, 2H), 7.54 (d, J = 4.76, 1H), 4.87 (s, 2H), 2.13 (s, 3H)
603		MS (ESI) m/z 642.4 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 10.85 (s, 1H), 8.82 (d, J = 4.8 Hz, 1H), 8.53 (s, 1H), 7.60 (dd, J = 8.9, 2.7 Hz, 1H), 7.47 (d, J = 4.8 Hz, 1H), 7.42 (d, J = 2.7 Hz, 1H), 7.39 (d, J = 9.0 Hz, 1H), 4.55 – 4.38 (m, 3H), 4.30 – 4.15 (m, 2H), 3.66 – 3.44 (m, 4H), 3.27 – 3.12 (m, 1H), 3.05 – 2.83 (m, 4H), 2.64 (s, 3H), 1.85 (s, 3H), 1.44 – 1.22 (m, 2H)	656		MS (ESI) m/z 636.2 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 10.83 (s, 0H), 8.78 (d, J = 4.8 Hz, 1H), 8.67 (s, 1H), 7.76 (d, J = 8.3 Hz, 1H), 7.69 (dd, J = 8.3, 2.2 Hz, 1H), 7.66 (d, J = 2.1 Hz, 1H), 7.54 (d, J = 4.8 Hz, 1H), 4.91 – 4.76 (m, 2H), 4.57 (d, J = 14.5 Hz, 1H), 3.73 – 3.12 (m, 4H), 3.08 – 2.87 (m, 4H), 2.71 (s, 3H), 2.10 (s, 3H), 1.51 (s, 1H), 1.41 – 1.29 (m, 1H)

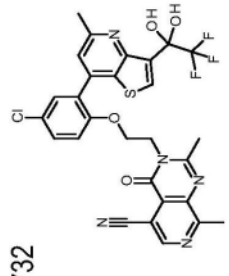
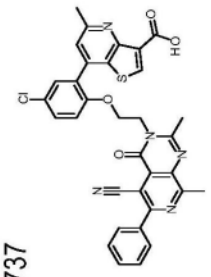
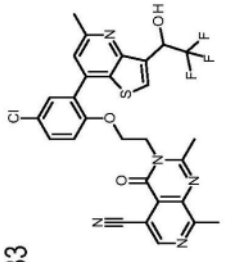
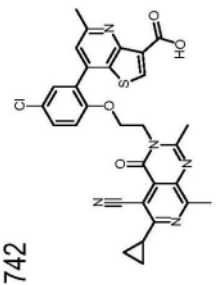
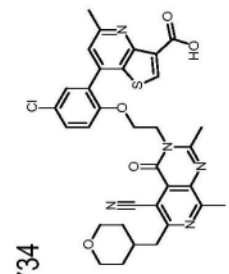
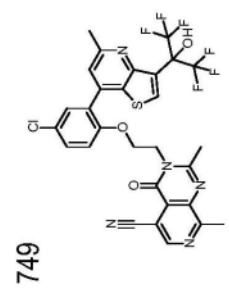
[0586]

673		LCMS (ESI) m/z 546.0 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.80 (s, 1H), 8.44 (s, 1H), 7.56 (dd, J = 8.9, 2.7 Hz, 1H), 7.41 – 7.35 (m, 2H), 7.33 (d, J = 9.0 Hz, 1H), 4.40 (s, 2H), 4.23 (s, 2H), 2.72 (s, 3H), 2.67 (s, 3H), 1.88 (s, 3H)	721		MS (ESI) m/z 560.99 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 12.73 (bs, 1H), 8.85 (s, 1H), 7.68 (s, 1H), 7.47 (dd, J = 2.64, 8.88 Hz, 1H), 7.28 (d, J = 2.60 Hz, 1H), 7.24 (d, J= 8.88 Hz, 1H), 7.19 (d, J = 8.00 Hz, 1H), 6.98 (d, J = 8.16 Hz, 1H), 4.34 (t, J = 4.60 Hz, 2H), 4.24 (t, J = 4.32 Hz, 2H), 3.93 (s, 3H), 2.79 (s, 3H), 1.86 (s, 3H)
674		LCMS (ESI) m/z 531.1 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.85 (s, 1H), 8.82 (dd, J = 4.8, 1.0 Hz, 1H), 8.48 (d, J = 2.0 Hz, 1H), 7.64 – 7.56 (m, 1H), 7.52 – 7.40 (m, 2H), 7.36 (dd, J = 9.0, 4.8 Hz, 1H), 4.43 (t, J = 5.0 Hz, 2H), 4.25 (t, J = 4.9 Hz, 2H), 2.76 (s, 3H), 1.85 – 1.78 (m, 3H)	722		MS (ESI) m/z 544.96 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 12.92 (s, 1H), 8.84 (s, 1H), 7.92 (s, 1H), 7.49 (dd, J=2.48 Hz, J=8.84 Hz, 1H), 7.28-7.24 (m, 3H), 7.13 (d, J = 7.32 Hz, 1H), 4.35 (t, J=4.56 Hz, 2H), 4.21 (t, J=4.48 Hz, 2H), 2.79 (s, 3H), 2.67 (s, 3H), 1.76 (s, 3H)
707		MS (ESI) m/z 616.2 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 9.89 (s, 1H), 8.83 (d, J = 4.8 Hz, 1H), 8.70 (s, 1H), 8.43 (s, 1H), 7.60 (dd, J = 8.9, 2.7 Hz, 1H), 7.47 (d, J = 4.8 Hz, 1H), 7.41 (d, J = 2.7 Hz, 1H), 7.37 (d, J = 9.0 Hz, 1H), 4.40 (t, J = 4.9 Hz, 2H), 4.32 (d, J = 14.2 Hz, 2H), 4.24 (t, J = 5.0 Hz, 2H), 3.61 (d, J = 12.0 Hz, 2H), 3.45 (t, J = 13.1 Hz, 2H), 3.32 – 3.21 (m, 2H), 2.91 (d, J = 3.5 Hz, 3H), 1.84 (s, 3H)	723		MS (ESI) m/z 564.90 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.15 (bs, 1H), 8.52 (s, 1H), 7.97 (s, 1H), 7.53-7.48 (m, 2H), 7.34 (d, J=2.4Hz , 1H), 7.28 (d, J=8.8 Hz, 1H), 7.23 (d, J=7.6 Hz, 1H), 4.36 (t, J=4.44 Hz, 2H), 4.22 (t, J=4.4 Hz, 2H), 2.81 (s, 3H), 1.79 (s, 3H)

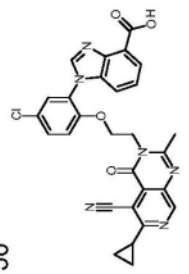
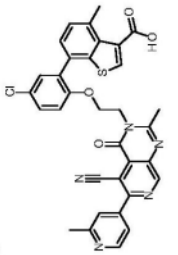
[0587]

725		MS (ESI) m/z 574 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 12.92 (bs, 1H), 8.35 (s, 1H), 7.96 (s, 1H), 7.49 (dd, J = 8.84, 2.48 Hz, 1H), 7.27-7.21 (m, 3H), 7.12 (d, J = 7.32 Hz, 1H), 4.33 (t, J = 4.56 Hz, 2H), 4.17 (t, J = 4.44 Hz, 2H) 3.41 (s, 6H), 2.65 (s, 3H), 1.67 (s, 3H)	728		MS (ESI) m/z 595.96 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.49 (s, 1H) 7.60 (dd, J = 8.88, 2.76 1H), 7.42-7.08 (m, 4H), 4.43 (t, J = 4.68 Hz, 2H), 4.27 (t, J = 4.44 Hz, 2H), 2.79 (s, 3H), 2.70 (s, 3H), 1.91 (s, 3H)
726		MS (ESI) m/z 560.99 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 12.83 (s, 1H), 8.58 (s, 1H), 7.94 (s, 1H), 7.48 (dd, J= 8.88, 2.64 Hz, 1H), 7.28-7.22 (m, 3H), 7.37 (d, J=7.36 Hz, 1H), 4.34 (s, 2H), 4.20 (s, 2H), 4.09 (s, 3H), 2.67 (s, 3H), 1.80 (s, 3H)	730		MS (ESI) m/z 614.03 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.50 (bs, 1H), 8.48 (s, 1H), 7.59 (d, J = 8.72 Hz, 1H), 7.42 (d, J = 4.8 Hz, 2H), 7.37 (d, J = 8.8 Hz, 1H), 4.44 (bs, 2H), 4.29 (bs, 2H), 2.80 (s, 3H), 2.71 (s, 1H), 1.94 (s, 1H
727		MS (ESI) m/z 574.98 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 12.98 (s, 1H), 8.96 (s, 1H), 7.93 (s, 1H), 7.48 (dd, J = 8.88, 2.56 Hz, 1H), 7.28-7.24 (m, 3H), 7.12 (d, J = 7.36, 1H), 4.95 (s, 2H), 4.34 (t, J = 4.4 Hz, 2H), 4.20 (t, J = 4.84 Hz, 2H), 3.41 (s, 3H), 2.66 (s, 3H), 1.74 (s, 3H)	731		MS (ESI) m/z 622.99 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 12.89 (s, 1H), 8.83 (s, 1H), 8.63 (s, 1H), 7.61 (dd, J = 2.44, 8.84 Hz, 1H), 7.45 (s,1H), 7.39 (d, J = 9.4 Hz, 2H), 4.43 (t, J = 4.48 Hz, 2H), 4.28 (t, J = 4.6 Hz, 2H), 3.56 (s, 3H), 2.75 (s, 3H), 2.69 (s, 3H), 2.01 (s, 3H)

[0588]

732		MS (ESI) m/z 616.2 [M+1]+; 1H NMR (400 MHz, DMSO-d6 at high temperature) δ 8.96 (s, 1H), 8.75 (s, 1H), 7.56-7.52 (dd, J = 6.4 Hz, 9.2 Hz, 1H), 7.38 (d, J = 2.8 Hz, 1H), 7.36 (s, 1H), 7.27 (bs, 1H), 4.43 (t, J = 5.2 Hz, 2H), 4.28 (t, J = 4.8 Hz, 2H), 2.73 (s, 3H), 2.63 (s, 3H), 2.00 (s, 3H)	737 	MS (ESI) m/z 622.05 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.51 (bs, 1H), 8.50 (s, 1H), 7.55 (bs, 2H), 7.64-7.45 (m, 4H), 7.42-7.36 (m, 3H), 4.44 (bs, 2H), 4.28 (bs, 2H), 2.78 (s, 3H), 2.69 (s, 3H), 1.94 (s, 3H)
733		MS (ESI) m/z 599.99 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.51 (s, 1H), 8.11 (s, 1H), 7.55-7.52 (dd, J = 2.4, 8.8 Hz, 1H), 7.41 (d, J = 2.4 Hz, 1H), 7.31 (d, J = 9.2 Hz, 1H), 7.19 (s, 1H), 5.74-5.69 (m, 1H), 4.38 (t, J = 4.4 Hz, 2H), 4.26 (t, J = 4.4 Hz, 2H), 2.79 (s, 3H), 2.57 (s, 3H), 1.79 (s, 3H)	742 	MS (ESI) m/z 586.06 [M+1]+; 1H NMR (400 MHz, DMSO-d6): δ 13.5 (bs, 1H), 8.49 (s, 1H), 7.60-7.57 (dd, J = 2.4, 8.8 Hz, 1H), 7.39-7.35 (m, 3H), 4.42 (t, J = 4.4 Hz, 2H), 4.25 (t, J = 3.6 Hz), 2.68 (s, 3H), 2.66 (s, 3H), 1.90 (s, 3H), 1.18-1.16 (m, 4H)
734		MS (ESI) m/z 644.20 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.48 (s, 1H), 7.59 (dd, J = 8.88, 2.44 Hz, 1H), 7.41 (s, 2H), 7.36 (d, J = 8.96, 1H), 4.42 (t, J = 4.52 Hz, 2H), 4.25 (t, J = 4.4 Hz, 2H), 3.79 (t, J = 10.28 Hz, 2H), 3.26 (t, J = 11.36 Hz, 2H), 2.96 (d, J = 6.92 Hz, 2H), 2.73 (s, 3H), 2.69 (s, 3H), 2.09 (bs, 1H), 1.92 (s, 3H), 1.51 (d, J = 11.16 Hz, 2H), 1.39-1.28 (m, 2H)	749 	MS (ESI) m/z 668.00 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 11.6 (bs, 1H), 8.86 (s, 1H), 8.47 (s, 1H), 7.58-7.55 (m, 1H), 7.51 (d, J = 2.4 Hz, 1H), 7.39 (s, 1H), 7.34 (d, J = 8.8 Hz, 1H), 4.41 (t, J = 4.8 Hz, 2H), 4.27 (t, J = 5.20 Hz, 2H), 2.77 (s, 3H), 2.59 (s, 3H), 1.73 (s, 3H)

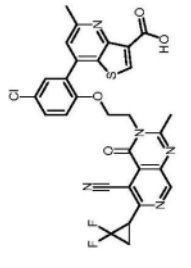
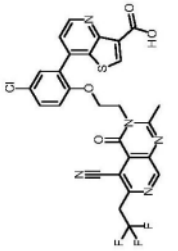
[0589]

756		MS (ESI) m/z 541.2 [M+1]+; 1H-NMR (400 MHz, DMSO-d6) δ 13.42 (bs, 1H), 9.11 (bs, 1H), 8.89 (s, 1H), 7.76 (d, J = 2.16 Hz, 1H), 7.74-7.62 (m, 2H), 7.53-7.38 (m, 2H), 7.11 (t, J = 7.80 Hz, 1H), 4.46 (s, 2H), 4.23 (s, 2H), 2.62-2.57 (m, 1H), 1.89 (s, 3H), 1.29-1.08 (m, 4H)	763		MS (ESI) m/z 622.01 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 12.9 (bs, 1H), 9.19 (s, 1H), 8.76 (d, J= 5.24, 1H), 7.89 (s, 1H), 7.85 (s, 1H), 7.77 (s, 1H), 7.51 (dd, J= 8.84, 2.52 Hz, 1H), 7.29-7.26 (m, 3H), 7.15 (d, J= 7.32 Hz, 1H), 4.36 (t, J= 3.96 Hz, 2H), 4.25 (t, J= 4.96 Hz 2H), 2.68 (s, 3H), 2.65 (s, 3H), 1.78 (s, 3H)
757		MS (ESI) m/z 548.02 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.54 (bs, 1H), 9.02 (s, 1H), 8.44 (d, J = 4.8 Hz 1H), 7.45 (dd, J = 2.8, 8.8 Hz , 1H), 7.26-7.20 (m, 3H), 4.31 (s, 4H), 2.62-2.58 (m, 1H), 2.02 (s, 3H), 1.93 (s, 3H), 1.20 (d , J = 8.0 Hz ,2H), 1.12 (s, 2H)	770		MS (ESI) m/z 588.72 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 9.25 (s, 1H), 8.88 (d, J = 5.64 Hz, 2H), 8.79 (d, J = 4.76 Hz, 1H), 8.63 (s, 1H), 8.00 (d, J = 5.72 Hz, 2H), 7.77 (d, J = 8.08 Hz, 1H), 7.70 -7.68 (m, J = 8.0 Hz, 2H) 7.55 (d, J = 4.76 Hz, 1H), 4.89 (s, 2H), 2.22 (s, 3H)
762		MS (ESI) m/z 607.99 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 12.93 (s, 1H), 9.16 (s, 1H), 8.84 (d, J=5.80, 2H), 7.91 (d, J=5.92 Hz, 2H), 7.80 (s, 1H), 7.50 (dd, J=8.84, 2.56 Hz, 1H), 7.29-7.26 (m, 3H), 7.15 (d, J=7.32 Hz, 1H), 4.36 (t, J=5.64, 2H), 4.25 (t, J=3.80, 2H), 2.68 (s, 3H), 1.79 (s, 3H)	771		MS (ESI) m/z 585.00 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 12.94 (bs, 1H), 8.94 (s, 1H), 7.76 (s, 1H), 7.48 (dd, J = 2.52, 8.76 Hz, 1H), 7.26-7.24 (m, 2H), 7.06 (s, 1H), 4.32 (t, J = 4.48 Hz, 2H), 4.20 (t, J = 5.08 Hz, 2H), 2.62-2.59 (m, 1H), 2.49 (s, 3H), 2.33 (s, 3H), 1.75 (s, 3H), 1.22 (bs, 2H), 1.14 (bs, 2H)

[0590]

772		MS (ESI) m/z 588.02 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.84 (s, 1H), 8.70 (d, J=5.12 Hz, 1H), 7.59 (dd, J=8.88, 2.48 Hz, 1H), 7.42-7.39 (m, 2H), 7.35 (d, J=8.96 Hz, 1H), 4.44 (t, J=4.25 Hz, 2H), 4.29 (t, J=4.28 Hz, 2H), 3.66 (s, 3H), 2.62-2.59 (m, 1H), 1.87 (s, 3H), 1.24-1.19 (m, 4H)	
773		MS (ESI) m/z 590.98 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.16 (bs, 1H), 8.98 (s, 1H), 7.83 (s, 1H), 7.53-7.49 (m, 2H), 7.33-7.22 (m, 3H), 4.34 (t, J = 4.8 Hz, 2H), 4.22 (t, J = 4.4 Hz, 2H), 2.60-2.58 (m, 1H), 1.77 (s, 3H), 1.22-1.15 (m, 4H)	
791		MS (ESI) m/z 574.95 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.57 (bs, 1H), 8.56 (s, 1H), 8.48 (s, 1H), 7.58 (dd, J = 8.8, 2.48 Hz, 1H), 7.41 (d, J = 2.52 Hz, 1H), 7.38 (s, 1H), 7.35 (d, J = 9.4 Hz, 1H), 4.39-4.36 (m, 2H), 4.21-4.18 (m, 2H), 3.25 (s, 6H), 2.70 (s, 3H), 1.80 (s, 3H)	
792		MS (ESI) m/z 565.91 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.84 (s, 1H), 8.39 (s, 1H), 7.59 (dd, J = 8.84, 2.52 Hz, 1H), 7.42 (s, 2H), 7.34 (d, J = 8.96 Hz, 1H), 4.42-4.37 (m, 2H), 4.29-4.24 (m, 2H), 2.71 (s, 3H),.1.81(s, 3H)	
793		MS (ESI) m/z 585.97 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.82 (s, 1H), 8.39 (s, 1H), 7.61 (dd, J= 8.88, 2.68 Hz, 1H), 7.45-7.43 (m, 2H), 7.37 (d, J= 8.96 Hz, 1H), 4.41 (t, J=5.08 Hz, 2H), 4.25 (t, J=5.24 Hz, 2H), 3.02 (q, J=7.56,7.52 Hz, 2H), 2.67 (bs, 1H), 1.83 (s, 3H), 1.35 (t, J= 7.52 Hz, 3H), 1.24-1.19 (m, 4H)	
794		MS (ESI) m/z 571.07 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.00 (bs, 1H), 8.94 (s, 1H), 7.80 (s, 1H), 7.50 (dd, J = 8.84, 2.4 Hz, 1H), 7.26-7.21 (m, 3H), 7.12 (d, J = 7.32 Hz, 1H), 4.34 (t, J = 4.8 Hz, 2H), 4.21 (t, J = 4.44 Hz, 2H), 2.66 (s, 3H), 2.62-2.57 (m, 1H), 1.73 (s, 3H), 1.22 -1.15 (m, 4H)	

[0591]

807		MS (ESI) m/z 608.7 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.97 (s, 1H), 8.41 (s, 1H), 7.60 (dd, J = 8.9, 2.7 Hz, 1H), 7.45 – 7.40 (m, 2H), 7.35 (d, J = 9.0 Hz, 1H), 4.45 – 4.35 (m, 2H), 4.26 (dtt, J = 14.9, 10.4, 5.0 Hz, 2H), 3.54 (td, J = 11.5, 7.9 Hz, 1H), 2.70 (s, 3H), 2.54-2.44 (m,1H), 2.37 – 2.23 (m, 1H), 1.86 (s, 3H)	814		MS (ESI) m/z 600.3 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 9.06 (s, 1H), 8.82 (d, J = 4.8 Hz, 1H), 8.43 (s, 1H), 7.60 (dd, J = 9.0, 2.6 Hz, 1H), 7.47 (d, J = 4.8 Hz, 1H), 7.44 (d, J = 2.6 Hz, 1H), 7.35 (d, J = 8.9 Hz, 1H), 4.40 (t, J = 5.0 Hz, 2H), 4.27 (t, J = 5.0 Hz, 2H), 4.16 (q, J = 10.7 Hz, 2H), 1.83 (s, 3H)
809		MS (ESI) m/z 558.4 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.97 (d, J = 0.6 Hz, 1H), 8.41 (s, 1H), 7.59 (dd, J = 8.9, 2.7 Hz, 1H), 7.42 (d, J = 2.7 Hz, 1H), 7.42 (s, 1H), 7.35 (d, J = 9.0 Hz, 1H), 7.33 – 7.24 (m, 1H), 6.66 (dd, J = 16.7, 1.9 Hz, 1H), 5.88 (dd, J = 10.6, 1.9 Hz, 1H), 4.40 (t, J = 5.1 Hz, 2H), 4.26 (t, J = 5.0 Hz, 2H), 2.70 (s, 3H), 1.83 (s, 3H)	815		MS (ESI) m/z 644.6 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.83 (d, J = 4.8 Hz, 1H), 8.71 (s, 1H), 8.37 (s, 1H), 7.60 (dd, J = 8.9, 2.7 Hz, 1H), 7.47 (d, J = 4.8 Hz, 1H), 7.42 (d, J = 2.7 Hz, 1H), 7.36 (d, J = 9.0 Hz, 1H), 4.40 (t, J = 5.0 Hz, 2H), 4.23 (t, J = 5.0 Hz, 2H), 4.20 – 4.24 (m, 2H), 3.60-3.40 (m, 2H), 3.30 (d, J = 14.1 Hz, 2H), 2.81 (d, J = 4.7 Hz, 3H), 1.79 (s, 3H), 1.43 (s, 3H), 1.38 (s, 3H)
813		MS (ESI) m/z 546.6 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.96 (s, 1H), 8.83 (d, J = 4.9 Hz, 1H), 8.41 (s, 1H), 7.60 (dd, J = 8.9, 2.7 Hz, 1H), 7.49 (d, J = 4.8 Hz, 1H), 7.44 (d, J = 2.6 Hz, 1H), 7.36 (d, J = 9.0 Hz, 1H), 4.40 (t, J = 5.0 Hz, 2H), 4.25 (t, J = 5.0 Hz, 2H), 3.11 (q, J = 7.5 Hz, 2H), 1.81 (s, 3H), 1.34 (t, J = 7.5 Hz, 3H)	816		MS (ESI) m/z 644.6 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.78 (d, J = 4.8 Hz, 1H), 8.72 (s, 1H), 8.58 (s, 1H), 7.60 (dd, J = 8.9, 2.7 Hz, 1H), 7.46 (s, 1H), 7.46 (d, J = 2.2 Hz, 1H), 7.37 (d, J = 9.0 Hz, 1H), 4.45-4.38 (m, 2H), 4.37- 4.28 (m, 2H), 4.22 (t, J = 5.1 Hz, 2H), 3.29 – 3.08 (m, 4H), 2.96 (d, J = 3.9 Hz, 3H), 1.76 (s, 3H), 1.68 (s, 3H), 1.48 (s, 3H)

[0592]

817		MS (ESI) m/z 660.8 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.81 (d, J = 4.8 Hz, 1H), 8.47 (d, J = 9.3 Hz, 2H), 7.60 (dd, J = 8.9, 2.7 Hz, 1H), 7.48 (d, J = 4.8 Hz, 1H), 7.42 (d, J = 2.6 Hz, 1H), 7.38 (d, J = 9.0 Hz, 1H), 4.91 (bs, 2H), 4.78 (bs, 2H), 4.49-4.38 (m, 2H), 4.30-4.14 (m, 2H), 3.55-2.82 (br, 4H), 1.79 (s, 3H), 1.32-0.83 (m, 4H)	820		MS (ESI) m/z 699.5 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.84 (dd, J = 4.9, 0.9 Hz, 1H), 8.71 (s, 1H), 8.42 (d, J = 1.5 Hz, 1H), 7.60 (dd, J = 9.0, 2.7 Hz, 1H), 7.50 (dd, J = 4.9, 2.6 Hz, 1H), 7.43 (d, J = 2.6 Hz, 1H), 7.36 (d, J = 9.0 Hz, 1H), 5.37-5.27 (m, 1H), 4.39 (t, J = 5.0 Hz, 2H), 4.22 (t, J = 5.0 Hz, 2H), 3.43-3.26 (m, 2H), 3.02-2.90 (m, 2H), 2.81-2.69 (m, 2H), 2.12-2.01 (m, 2H), 1.90-1.79 (m, 2H), 1.75 (s, 3H)
818		MS (ESI) m/z 678.6 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.81 (d, J = 4.8 Hz, 1H), 8.49 (s, 1H), 8.40 (s, 1H), 7.60 (dd, J = 8.9, 2.7 Hz, 1H), 7.48 (d, J = 4.9 Hz, 1H), 7.42 (d, J = 2.7 Hz, 1H), 7.37 (d, J = 9.0 Hz, 1H), 6.26 (tt, J = 55.6, 4.2 Hz, 1H), 4.49-4.35 (m, 2H), 4.29 – 4.12 (m, 2H), 3.25 – 2.72 (m, 8H), 1.75 (s, 3H), 0.64-0.53 (m, 2H)	821		MS (ESI) m/z 680.3 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 9.04 (s, 1H), 8.85 (d, J = 4.8 Hz, 1H), 8.39 (s, 1H), 7.61 (dd, J = 8.9, 2.7 Hz, 1H), 7.50 (d, J = 4.8 Hz, 1H), 7.46 (d, J = 2.7 Hz, 1H), 7.37 (d, J = 9.0 Hz, 1H), 4.42 (t, J = 5.0 Hz, 2H), 4.29 (t, J = 5.0 Hz, 2H), 4.05 (br, 2H), 3.62-3.16 (br, 6H), 2.89 (s, 3H), 1.77 (s, 3H)
819		MS (ESI) m/z 617.4 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.79 (d, J = 4.8 Hz, 1H), 8.60 (s, 1H), 8.36 (s, 1H), 7.59 (dd, J = 8.9, 2.7 Hz, 1H), 7.47 (d, J = 4.8 Hz, 1H), 7.44 (d, J = 2.7 Hz, 1H), 7.36 (d, J = 9.0 Hz, 1H), 4.59-4.58 (m, 2H), 4.40 (t, J = 5.1 Hz, 2H), 4.20 (t, J = 5.1 Hz, 2H), 3.84-3.76 (m, 1H), 3.66-3.54 (m, 2H), 1.91 – 1.84 (m, 2H), 1.78 (s, 3H), 1.53-1.41 (m, 2H)	822		MS (ESI) m/z 648.6 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.76 – 8.71 (m, 2H), 8.66 (s, 1H), 7.75 (dd, J = 8.0, 0.9 Hz, 1H), 7.71 – 7.64 (m, 2H), 7.54 (d, J = 4.8 Hz, 1H), 4.81 (s, 2H), 4.59 (bd, J = 16.5 Hz, 4H), 4.41 (s, 4H), 3.08 (br, 1H), 2.09 (s, 3H), 0.81-0.76 (m, 4H)

[0593]

823		MS (ESI) m/z 706.5 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.82 (d, J = 4.8 Hz, 1H), 8.61 (s, 1H), 8.47 (s, 1H), 7.60 (dd, J = 8.9, 2.7 Hz, 1H), 7.46 (d, J = 4.8 Hz, 1H), 7.42 (d, J = 2.7 Hz, 1H), 7.36 (d, J = 9.0 Hz, 1H), 6.22 (t, J = 53.9 Hz, 1H), 4.56 (br, 6H), 4.38 (t, J = 5.0 Hz, 2H), 4.25 (br, 2H), 4.20 (t, J = 5.0 Hz, 2H), 1.79 (s, 3H), 1.32 (s, 6H)	826		MS (ESI) m/z 688.7 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.82 (d, J = 4.9 Hz, 1H), 8.61 (s, 1H), 8.48 (s, 1H), 7.64 – 7.58 (dd, J = 8.9, 2.6 Hz, 1H), 7.47 (d, J = 4.8 Hz, 1H), 7.43 (d, J = 4.4 Hz, 1H), 7.36 (d, J = 9.0 Hz, 1H), 4.71 – 4.42 (m, 8H), 4.38 (t, J = 5.2 Hz, 2H), 4.28 – 4.16 (m, 4H), 1.80 (s, 3H), 1.26 (s, 6H)
824		MS (ESI) m/z 678.4 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.85 (d, J = 4.9 Hz, 1H), 8.60 (s, 1H), 8.50 (s, 1H), 7.60 (dd, J = 8.9, 2.7 Hz, 1H), 7.51 (d, J = 4.9 Hz, 1H), 7.45 (d, J = 2.7 Hz, 1H), 7.37 (d, J = 9.0 Hz, 1H), 6.26 (tt, J = 55.5, 4.2 Hz, 1H), 4.44 – 4.37 (m, 2H), 4.26-4.14 (m, 2H), 3.44 (dd, J = 7.8, 6.6, 4.1 Hz, 2H), 3.19 – 2.84 (m, 6H), 1.74 (s, 3H), 0.81 (q, J = 6.6 Hz, 1H), 0.69 – 0.63 (m, 1H)	827		MS (ESI) m/z 718.4 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.75 (d, J = 4.8 Hz, 1H), 8.72 (s, 1H), 8.66 (s, 1H), 7.76 (d, J = 9.0 Hz, 1H), 7.71 – 7.67 (m, 2H), 7.55 (d, J = 4.8 Hz, 1H), 4.82 (s, 2H), 4.59 – 4.47 (m, 2H), 4.33 – 3.54 (br, 8H), 3.14 (s, 3H), 2.63 (br, 1H), 2.06 (s, 3H)
825		MS (ESI) m/z 686.4 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.78 (d, J = 4.8 Hz, 1H), 8.57 (s, 1H), 8.44 (s, 1H), 7.57 (dd, J = 8.9, 2.7 Hz, 1H), 7.43 (d, J = 4.8 Hz, 1H), 7.39 (d, J = 2.7 Hz, 1H), 7.32 (d, J = 9.0 Hz, 1H), 4.65 (d, J = 48.5 Hz, 2H), 4.45 (br, 4H), 4.35 (t, J = 5.2 Hz, 2H), 4.27 (br, 4H), 4.17 (t, J = 5.2 Hz, 2H), 1.76 (s, 3H), 1.29 (br, 2H), 0.97 (br, 2H)	828		MS (ESI) m/z 710.4 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.75 (d, J = 4.8 Hz, 1H), 8.72 (s, 1H), 8.65 (s, 1H), 7.78 – 7.74 (m, 1H), 7.71 – 7.67 (m, 2H), 7.55 (d, J = 4.8 Hz, 1H), 4.82 (s, 2H), 4.53-4.45 (m, 1H), 4.49 (d, J = 47.2 Hz, 2H), 4.42 – 4.36 (m, 1H), 4.31-4.24 (m, 1H), 4.15-4.07 (m, 1H), 3.99 – 3.92 (m, 1H), 3.15 (s, 3H), 2.79 – 2.40 (m, 4H), 2.06 (s, 3H), 1.24 (d, J = 1.9 Hz, 6H)

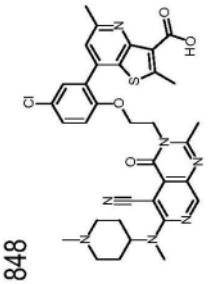
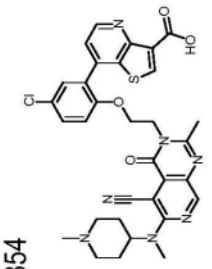
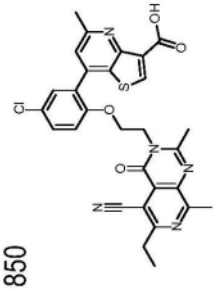
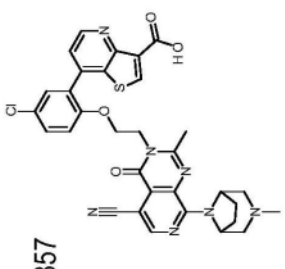
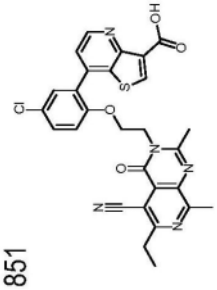
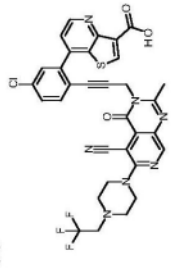
[0594]

829		MS (ESI) m/z 682.5 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.82 (d, J = 4.8 Hz, 1H), 8.58 (s, 1H), 8.46 (s, 1H), 7.60 (dd, J = 8.9, 2.7 Hz, 1H), 7.47 (d, J = 4.8 Hz, 1H), 7.43 (d, J = 2.7 Hz, 1H), 7.35 (d, J = 9.0 Hz, 1H), 4.45 (s, 2H), 4.37 (t, J = 5.1 Hz, 2H), 4.34 (s, 2H), 4.19 (t, J = 5.1 Hz, 2H), 3.98 – 3.87 (m, 1H), 2.76 (s, 3H), 2.69-2.42 (m, 4H), 1.76 (s, 3H), 1.10 – 0.99 (m, 1H), 0.93-0.72 (m, 4H)
830		MS (ESI) m/z 676.6 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.75 (d, J = 4.8 Hz, 1H), 8.71 (s, 1H), 8.66 (s, 1H), 7.77 – 7.74 (m, 1H), 7.71 – 7.66 (m, 2H), 7.54 (d, J = 4.8 Hz, 1H), 4.80 (s, 2H), 4.48 (s, 2H), 4.36 (s, 2H), 3.99 – 3.88 (m, 1H), 2.76 (s, 3H), 2.70 – 2.42 (m, 4H), 2.08 (s, 3H), 1.09-0.99 (m, 1H), 0.92-0.72 (m, 4H)
831		MS (ESI) m/z = 586.3 [M+1]+; 1H-NMR (400 MHz, d6-DMSO) δ /ppm = 8.89 (s, 1H), 8.40 (s, 1H), 7.59 (dd, J = 9.0, 2.6, 1H), 7.43-7.41 (m, 2H), 7.35 (d, J = 9.0 Hz, 1H), 4.39 (t, J = 5.2 Hz, 2H), 4.39 (t, J = 5.2 Hz, 2H), 2.71 (s, 3H), 1.86 (s, 3H), 1.47 (s, 3H), 1.12-1.07 (m, 2H), 0.92-0.88 (m, 2H)
837		MS (ESI) m/z = 652.1 [M+1]+; 1H; -NMR (400 MHz, d6-DMSO) δ /ppm = 8.79 (d, J = 4.8 Hz, 1H), 8.48 (s, 1H), 8.46 (s, 1H), 7.57 (dd, J = 8.9, 2.7 Hz, 1H), 7.44 (d, J = 4.8 Hz, 1H), 7.38 (d, J = 2.7 Hz, 1H), 7.35 (d, J = 8.9 Hz, 1H), 4.94-4.81 (m, 2H), 4.40 (t, J = 4.6 Hz, 2H), 4.28-4.19 (m, 4H), 3.88-3.77 (m, 2H), 1.80 (s, 3H) [剩余的 CH2-质子可能被水峰所掩盖]
838		MS (ESI) m/z = 666.4 [M+1]+; ; 1H-NMR (400 MHz, d6-DMSO) δ /ppm = 8.81 (d, J = 4.8 Hz, 1H), 8.53 (s, 1H), 8.47 (s, 1H), 7.60 (dd, J = 8.8, 2.7 Hz, 1H), 7.47 (d, J = 4.8 Hz, 1H), 7.42 (d, J = 2.7 Hz, 1H), 7.38 (d, J = 8.8 Hz, 1H), 4.85 (bt, J = 12.4 Hz, 2H), 4.42 (t, J = 5.0 Hz, 2H), 4.24 (t, J = 5.0 Hz, 2H), 4.24-4.14 (b, 2H), 2.87-2.71 (b, 3H), 1.83 (s, 3H), 剩余的质子似乎被水峰所掩盖
839		MS (ESI) m/z = 640.0 [M+1]+; 1H-NMR (400 MHz, d6-DMSO) δ /ppm = 9.00 (s, 1H), 8.38 (s, 1H), 7.59 (dd, J = 8.9, 2.8 Hz, 1H), 7.42 (d, J = 2.8 Hz, 1H), 7.41 (s, 1H), 7.35 (d, J = 8.9 Hz, 1H), 4.40 (t, J = 4.9 Hz, 2H), 4.26 (t, J = 4.9 Hz, 2H), 2.70 (s, 3H), 1.90 (s, 3H), 1.63-1.58 (m, 2H), 1.54-1.48 (m, 2H)

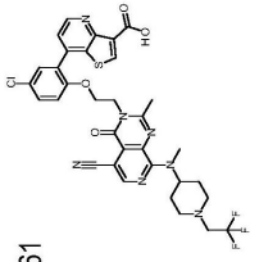
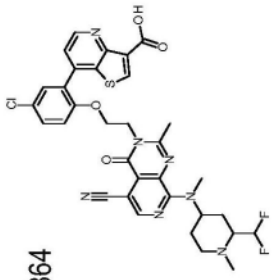
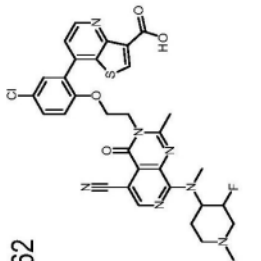
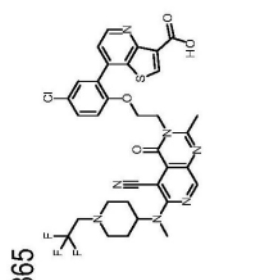
[0595]

840	MS (ESI) m/z = 696.3 [M+1]+; 1H-NMR (400 MHz, d6-DMSO) δ /ppm = 8.78 (d, J = 4.8 Hz, 1H), 8.55 (s, 1H), 8.44 (s, 1H), 7.56 (dd, J = 8.9, 2.7 Hz, 1H), 7.42 (d, J = 4.8 Hz, 1H), 7.39 (d, J = 8.9 Hz, 1H), 4.44 (s, 4H), 4.34 (t, J = 5.0 Hz, 2H), 4.15 (t, J = 5.0 Hz, 2H), 3.89-3.51 (b), 3.12-2.76 (b), 1.73 (s, 3H)	844	MS (ESI) m/z = 712.3 [M+1]+; 1H-NMR (400 MHz, d6-DMSO) δ /ppm = 9.98-9.78 (b, 1H), 8.83 (d, J = 4.9 Hz, 1H), 8.70 (s, 1H), 8.43 (s, 1H), 7.60 (dd, J = 8.9, 2.7 Hz, 1H), 7.48 (d, J = 4.9 Hz, 1H), 7.41 (d, J = 2.7 Hz, 1H), 7.38 (d, J = 8.9 Hz, 1H), 4.41 (t, J = 4.8 Hz, 2H), 4.38-4.28 (m, 2H), 4.24 (t, J = 4.8 Hz, 2H), 3.32-3.21 (m, 部分被水峰所掩盖), 2.47-2.33 (m, 2H), 2.02-1.91 (m,2 H), 1.85 (s, 3H); 剩余的信号被水峰所掩盖
842	MS (ESI) m/z = 610.3 [M+1]+; 1H-NMR (400 MHz, d6-DMSO) δ /ppm = 9.98-9.88 (b, 1H), 8.84 (s, 1H), 8.75 (d, J = 4.8 Hz, 1H), 8.64 (s, 1H), 7.75 (d, J = 8.4 Hz, 1H), 7.71-7.65 (m, 2H), 7.53 (d, J = 4.8 Hz, 1H), 4.83 (s, 2H), 4.36 (bd, J = 14 Hz, 2H), 3.36-3.24 (m, 2H), 2.91 (s, 3H), 2.13 (s, 3H); 剩余的信号被水峰所掩盖	845	MS (ESI) m/z = 726.3 [M+1]+; 1H-NMR (400 MHz, d6-DMSO) δ /ppm = 10.29-9.70 (b, 1H), 8.83 (d, J = 4.7 Hz, 1H), 8.71 (s, 1H), 8.44 (s, 1H), 7.61 (dd, J= 8.9, 2.7 Hz, 1H), 7.48 (d, J = 4.7 Hz, 1H), 7.42 (d, J = 2.7 Hz, 1H), 7.37 (d, J = 8.9 Hz, 1H), 4.41 (t, J = 4.5 Hz, 2H), 4.24 (t, J = 4.5 Hz, 2H), 4.50-3.20 (宽信号, 部分被水峰所掩盖), 2.99 (bq, J = 11 Hz, 2H), 1.85 (s, 3H), 1.52 (s, 6H)
843	MS (ESI) m/z = 712.5 [M+1]+; 1H-NMR (400 MHz, d6-DMSO) δ /ppm = 9.98-9.79 (b, 1H), 8.81 (d, J = 4.9 Hz, 1H), 8.52 (s, 1H), 8.49 (s, 1H), 7.61 (dd, J = 8.9, 2.8 Hz, 1H), 7.48 (d, J = 4.9 Hz, 1H), 7.42 (d, J = 2.8 Hz, 1H), 7.39 (d, J = 8.9 Hz, 1H), 5.21-5.08 (m, 2H), 4.43 (t, J = 5.0 Hz, 2H), 4.23 (t, J = 5.0 Hz, 2H), 3.76-3.62 (m, 部分被水峰所掩盖), 3.38-3.14 (m, 部分被水峰所掩盖), 2.49-2.36 (m, 2H), 2.03-1.93 (m, 2H), 1.83 (s, 3H)	846	MS (ESI) m/z 631.1 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 10.31 (s, 1H), 9.85 (s, 1H), 8.73 (d,J= 8.1 Hz, 1H), 7.60 (dd, J= 8.9, 2.7 Hz, 1H), 7.42 (s, 1H), 7.40 – 7.33 (m, 2H), 5.69 (d, J= 7.2 Hz, 1H), 5.60 – 5.42 (m, 1H), 4.78 (s, 1H), 4.59 – 4.46 (m, 2H), 4.41 (t, J= 5.2 Hz, 2H), 4.29 (q, J= 5.9, 5.4 Hz, 3H), 3.04 – 2.96 (m, 3H), 2.71 (s, 3H), 2.54 (d, J= 6.4 Hz, 3H), 2.11 (d, J= 22.1 Hz, 3H)

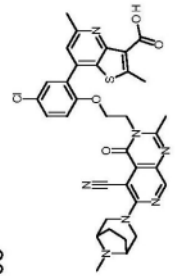
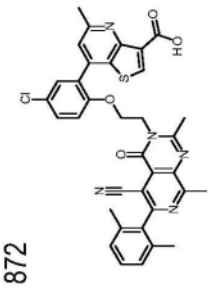
[0596]

848		MS (ESI) m/z 671.9 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.55 (s, 1H), 7.56 (dd,J= 8.9, 2.7 Hz, 1H), 7.38 – 7.29 (m, 4H), 4.61 – 4.42 (m, 1H), 4.36 (t, J= 5.0 Hz, 2H), 4.20 (t, J= 5.0 Hz, 2H), 3.18 – 3.09 (m, 2H), 3.04 (s, 3H), 2.78 (d, J= 4.6 Hz, 3H), 2.67 (s, 4H), 2.17 – 1.94 (m, 3H), 1.92 (s, 3H)	854		MS (ESI) m/z 644.3 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.82 (d, J = 4.8 Hz, 1H), 8.61 (s, 1H), 8.40 (s, 1H), 7.60 (dd, J = 8.9, 2.7 Hz, 1H), 7.47 (d, J = 4.8 Hz, 1H), 7.42 (d, J = 2.7 Hz, 1H), 7.36 (d, J = 9.0 Hz, 1H), 4.39 (t, J = 5.0 Hz, 2H), 4.21 (s, 2H), 3.08 (s, 3H), 2.81 (d, J = 4.7 Hz, 3H), 2.07 (d, J = 8.4 Hz, 5H), 1.77 (s, 3H)
850		LCMS: 574.6 [M+H]+; 1H NMR (400 MHz, DMSO-d6) δ 8.46 (s, 1H), 7.56 (dd, J= 8.9, 2.7 Hz, 1H), 7.40 – 7.28 (m, 3H), 4.39 (t, J= 5.1 Hz, 2H), 4.22 (t, J= 5.0 Hz, 2H), 3.00 (q, J= 7.6 Hz, 2H), 2.70 (s, 3H), 2.66 (s, 3H), 1.90 (s, 3H), 1.28 (t, J= 7.5 Hz, 3H)	857		LCMS: 642.7 [M+H]+; 1H NMR (400 MHz, DMSO-d6) δ 9.57 (s, 1H), 8.80 (d, J = 4.8 Hz, 1H), 8.59 (s, 1H), 8.46 (s, 1H), 7.61 (dd, J = 8.9, 2.7 Hz, 1H), 7.49 – 7.34 (m, 3H), 4.43 (t, J = 5.0 Hz, 2H), 4.24 (d, J= 5.0 Hz, 2H), 3.35 (t, J = 10.8 Hz, 3H), 2.79 (d, J = 3.4 Hz, 3H), 2.23 (s, 2H), 2.08 (d, J = 8.1 Hz, 2H), 1.86 (s, 3H)
851		LCMS: 560.4 [M+H]+; 1H NMR (400 MHz, DMSO-d6) δ 8.78 (d, J = 4.8 Hz, 1H), 8.46 (s, 1H), 7.56 (dd, J = 8.9, 2.7 Hz, 1H), 7.43 (d, J = 4.8 Hz, 1H), 7.39 (d, J = 2.7 Hz, 1H), 7.33 (d, J = 9.0 Hz, 1H), 4.39 (t, J = 5.0 Hz, 2H), 4.21 (t, J = 5.0 Hz, 2H), 3.01 (q, J = 7.5 Hz, 2H), 2.71 (s, 3H), 1.80 (s, 3H), 1.28 (t, J = 7.5 Hz, 3H)	860		LCMS: 678.5 [M+H]+; 1H NMR (400 MHz, DMSO-d6) δ 8.81 – 8.73 (m, 2H), 8.66 (s, 1H), 7.76 (d, J = 9.0 Hz, 1H), 7.69 (dd, J= 6.2, 2.3 Hz, 2H), 7.54 (d, J= 4.8 Hz, 1H), 4.82 (s, 2H), 3.69 (t, J= 4.7 Hz, 4H), 3.30 (q, J= 10.2 Hz, 2H), 2.84 (t, J= 4.8 Hz, 4H), 2.07 (s, 3H)

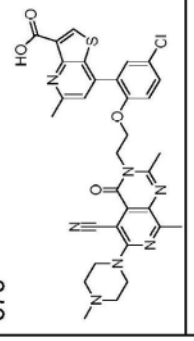
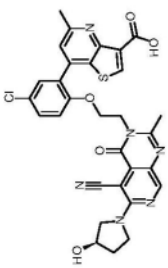
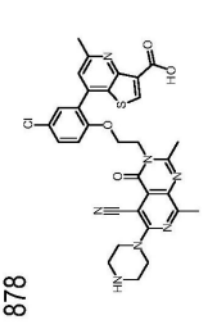
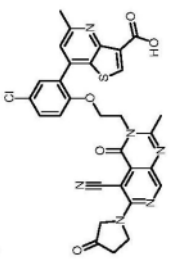
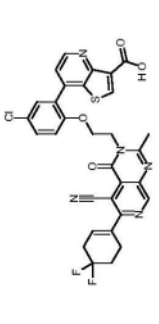
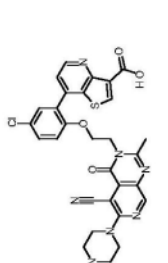
[0597]

861		LCMS: 712.7 [M+H]+; 1H NMR (400 MHz, DMSO-d6) δ 8.79 (d, J = 4.8 Hz, 1H), 8.50 (s, 1H), 8.37 (s, 1H), 7.60 (dd, J = 9.0, 2.7 Hz, 1H), 7.47 (d, J = 4.8 Hz, 1H), 7.43 (d, J = 2.6 Hz, 1H), 7.37 (d, J = 9.0 Hz, 1H), 4.69 (s, 1H), 4.43 (t, J = 5.1 Hz, 2H), 4.22 (d, J = 5.1 Hz, 2H), 3.22 (s, 1H), 3.13 (s, 3H), 3.04 (d, J = 11.2 Hz, 2H), 2.00 – 1.81 (m, 1H), 1.78 (s, 3H)	864		LCMS: 694.5 [M+H]+; 1H NMR (400 MHz, DMSO-d6) δ 8.75 (d, J = 4.9 Hz, 1H), 8.40 (d, J = 2.3 Hz, 2H), 7.58 (dd, J = 8.9, 2.7 Hz, 1H), 7.44 (d, J = 4.8 Hz, 1H), 7.40 – 7.32 (m, 2H), 6.55 (t, J = 52.5 Hz, 2H), 4.89 (s, 1H), 4.48 – 4.32 (m, 2H), 4.21 (t, J = 5.3 Hz, 2H), 3.10 (s, 3H), 2.91 (s, 4H), 2.33 – 2.08 (m, 4H), 2.05 – 1.88 (m, 3H), 1.74 (s, 3H)
862		LCMS: 662.5 [M+H]+; 1H NMR (400 MHz, DMSO-d6) δ 9.80 (s, 1H), 8.80 (d, J = 4.8 Hz, 1H), 8.45 (d, J = 9.3 Hz, J = 8.9, 2.7 Hz, 1H), 7.48 – 7.41 (m, 2H), 7.39 (d, J = 9.0 Hz, 1H), 5.50 (s, 1H),J = 11.4 Hz, 1H), 5.02 (d, J = 12.3 Hz, 1H), 4.44 (q, J = 4.8 Hz, 2H), J = 5.1 Hz, 2H), 3.85 (d, J = 12.3 Hz, 1H), 3.26 (d, J = 1.6 Hz, 3H), 2.87 (d, J = 4.1. 12H), 7.61 (dd, 5.38 (s, 1H), 5.10 (d, 4.25 (t, Hz, 3H), 2.20 – 2.03 (m, 1H), 1.80 (s, 3H)	865		LCMS: 712.6 [M+H]+; 1H NMR (400 MHz, DMSO-d6) δ 8.83 (d, J = 4.8 Hz, 1H), 8.60 (s, 1H), 8.45 (s, 1H), 7.60 (dd, J = 8.9, 2.7 Hz, 1H), 7.48 (d, J = 4.8 Hz, 1H), 7.43 (d, J = 2.7 Hz, 1H), 7.36 (d, J = 9.0 Hz, 1H), 4.38 (t, J = 5.0 Hz, 2H), 4.33 – 4.13 (m, 3H), 3.07 (s, 3H), 2.73 – 2.52 (m, 3H), 2.03 – 1.82 (m, 2H), 1.77 (d, J = 28.9 Hz, 5H), 1.25 (d, J = 16.2 Hz, 1H)
863		LCMS: 670.2 [M+H]+; 1H NMR (400 MHz, DMSO-d6) δ 9.64 (s, 1H), 9.51 (s, 1H), 8.82 – 8.75 (m, 1H), 8.44 – 8.38J = 8.9, 2.6 Hz, 1H), 7.49 (t, J = 5.0 Hz, 1H), 7.44 (dd, J = 9.0, 2.7 Hz, 1H),J = 9.0 Hz, 1H), 5.18 (dq, J = 11.7, 5.8 Hz, 1H), 5.05 (s, 1H), 4.44 (q, J = 5.2 Hz, 2H), J = 5.0 Hz, 2H), 4.05 – 3.78 (m, 2H), 3.17 (d, J = 9.9 Hz, 1H), 3.07 (s, 3H), 2.72 –J = 3.4 Hz, 5H)	866		LCMS: 694.5 [M+H]+; 1H NMR (400 MHz, DMSO-d6) δ 8.83 (d, J = 4.8 Hz, 1H), 8.63 (s, 1H), 8.42 (s, 1H), 7.60 (dd, J = 8.9, 2.7 Hz, 1H), 7.47 (d, J = 4.8 Hz, 1H), 7.43 (d, J = 2.7 Hz, 1H), 7.36 (d, J = 9.0 Hz, 1H), 6.49 (d, J = 52.7 Hz, 1H), 4.64 (d, J = 15.0 Hz, 1H), 4.39 (t, J = 5.0 Hz, 2H), 4.22 (t, J = 5.1 Hz, 2H), 3.09 (s, 3H), 2.94 (s, 3H), 1.76 (s, 3H)

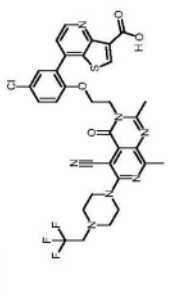
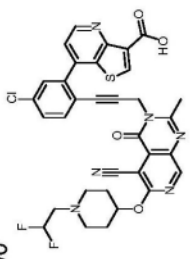
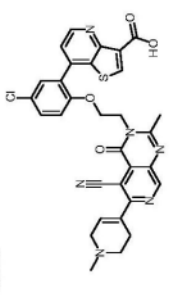
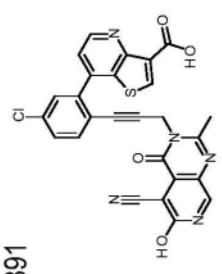
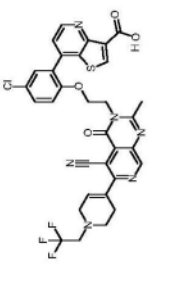
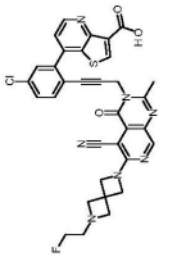
[0598]

868		MS (ESI) m/z 670.5 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 9.50 (s, 1H), 8.64 (s, 1H), 7.56 (dd, J= 8.9, 2.7 Hz, 1H), 7.38 – 7.30 (m, 3H), 4.90 (s, 2H), 4.36 (t, J= 5.1 Hz, 2H), 4.22 (t, J= 5.1 Hz, 2H), 3.56 (d, J= 12.1 Hz, 2H), 3.30 (t, J= 10.9 Hz, 2H), 2.80 (s, 2H), 2.67 (s, 3H), 2.02 (d, J= 2.5 Hz, 4H), 1.93 (s, 3H)	872		LCMS (ESI) m/z 650.8 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.47 (s, 1H), 7.60 (dd, J = 8.9, 2.7 Hz, 1H), 7.49 – 7.45 (m, 2H), 7.38 (d, J = 9.0 Hz, 1H), 7.30 (dd, J = 8.2, 6.9 Hz, 1H), 7.21 – 7.16 (m, 2H), 4.45 (t, J = 5.0 Hz, 2H), 4.26 (t, J = 5.0 Hz, 2H), 2.77 (s, 3H), 2.72 (s, 3H), 2.00 (s, 6H), 1.84 (s, 3H)
869		LCMS: 1.54 Min, 617.5 [M+H]+; 1H NM:R (400 MHz, DMSO-d6) δ 9.07 (s, 1H), 8.80 (s, 1H), 8.72 (s, 1H), 7.60 (dd, J = 8.9, 2.7 Hz, 1H), 7.44 – 7.33 (m, 3H), 5.62 (p, J = 6.2 Hz, 1H), 4.58 – 4.45 (m, 2H), 4.41 (t, J = 5.1 Hz, 2H), 4.25 (dt, J = 20.4, 5.8 Hz, 4H), 2.71 (s, 3H), 2.54 (s, 3H), 2.11 (s, 3H)	873		LCMS (ESI) m/z 637.0 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.48 (s, 1H), 7.60 (dd, J = 8.9, 2.7 Hz, 1H), 7.49 – 7.43 (m, 2H), 7.38 (d, J = 9.0 Hz, 1H), 7.30 (dd, J = 8.2, 6.9 Hz, 1H), 7.19 (d, J = 8.0 Hz, 2H), 4.45 (t, J = 5.0 Hz, 2H), 4.26 (t, J = 4.9 Hz, 2H), 2.77 (s, 3H), 2.72 (s, 3H), 2.00 (s, 6H)
871		LCMS (ESI) m/z 654.8 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.50 (s, 1H), 7.57 (dd, J = 8.9, 2.7 Hz, 1H), 7.51 – 7.39 (m, 3H), 7.34 (d, J = 9.0 Hz, 1H), 7.26 – 7.14 (m, 2H), 4.43 (td, J = 8.9, 7.7, 3.7 Hz, 1H), 4.37 (dd, J = 10.3, 4.5 Hz, 1H), 4.23 (t, J = 5.1 Hz, 2H), 2.75 (s, 3H), 2.68 (s, 3H), 2.12 (s, 3H), 1.83 (s, 3H)	874		LCMS (ESI) m/z 656.0 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 9.36 (s, 1H), 8.54 (s, 1H), 8.30 (dd, J = 9.3, 5.7 Hz, 1H), 7.66 – 7.57 (m, 2H), 7.48 – 7.33 (m, 3H), 6.96 (ddd, J = 8.2, 5.8, 2.3 Hz, 1H), 4.43 (t, J = 5.0 Hz, 2H), 4.24 (t, J = 5.0 Hz, 2H), 2.72 (d, J = 4.6 Hz, 6H), 1.87 (s, 3H)

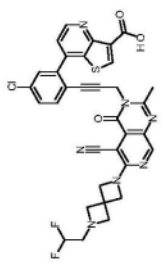
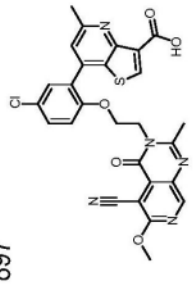
[0599]

875 	LCMS (ESI) m/z 644.1 [M+1]+; 1H NMR (400 MHz, 氯仿-d) δ 8.48 (s, 1H), 7.61 (dd, J = 8.9, 2.7 Hz, 1H), 7.43 (s, 1H), 7.42 – 7.37 (m, 2H), 4.42 (d, J = 5.3 Hz, 2H), 4.33 (s, 1H), 4.30 (s, 1H), 4.25 (d, J = 5.0 Hz, 2H), 3.61 (d, J = 12.2 Hz, 2H), 3.44 (d, J = 13.6 Hz, 4H), 3.24 (d, J = 11.0 Hz, 1H), 2.92 (d, J = 4.4 Hz, 3H), 2.73 (s, 3H), 2.66 (s, 4H), 1.98 (s, 3H)	883 手性 	LCMS (ESI) m/z 617.1 [M+1]+. ; 1H NMR (400 MHz, DMSO-d6) δ 8.53 (s, 1H), 8.47 (d, J = 0.8 Hz, 1H), 7.55 (dd, J = 8.9, 2.7 Hz, 1H), 7.41 – 7.34 (m, 2H), 7.39 – 7.28 (m, 2H), 7.44 – 4.40 (m, 2H), 4.34 (t, J = 5.1 Hz, 2H), 4.16 (t, J = 5.1 Hz, 2H), 3.86 (dd, J = 11.5, 4.8 Hz, 2H), 3.73 (ddd, J = 11.1, 8.1, 3.4 Hz, 1H), 3.54 (d, J = 11.6 Hz, 1H), 2.67 (s, 3H), 2.05 – 1.94 (m, 1H), 1.90 (s, 2H), 1.76 (s, 3H)
878 	LCMS (ESI) m/z 630.1 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.83 (s, 1H), 8.44 (s, 1H), 7.57 (dd, J = 8.9, 2.7 Hz, 1H), 7.41 – 7.31 (m, 2H), 4.39 (d, J = 10.4 Hz, 1H), 4.39 (s, 1H), 4.20 (s, 1H), 3.79 (t, J = 4.9 Hz, 2H), 3.28 (s, 2H), 2.68 (s, 2H), 2.62 (s, 2H), 1.94 (s, 2H)	884 	LCMS (ESI) m/z 614.9 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.61 (s, 1H), 8.45 (s, 1H), 7.56 (dd, J = 8.9, 2.7 Hz, 1H), 7.39 – 7.29 (m, 3H), 4.36 (t, J = 5.1 Hz, 2H), 4.24 (s, 2H), 4.22 – 4.14 (m, 4H), 2.71 (t, J = 7.7 Hz, 2H), 2.68 (s, 3H), 1.86 (s, 3H)
882 	LCMS (ESI) m/z 634.2 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.91 (s, 1H), 8.80 (d, J = 4.8 Hz, 1H), 8.35 (s, 1H), 7.56 (dd, J = 8.9, 2.7 Hz, 1H), 7.47 – 7.38 (m, 2H), 7.32 (d, J = 9.0 Hz, 1H), 6.27 (s, 1H), 4.37 (t, J = 5.0 Hz, 2H), 4.21 (t, J = 4.9 Hz, 2H), 2.87 – 2.75 (m, 4H), 2.22 (dq, J = 14.1, 6.8 Hz, 2H), 1.75 (s, 3H).	885 	LCMS (ESI) m/z 662.1 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.79 (d, J = 4.8 Hz, 1H), 8.46 (s, 1H), 7.57 (dd, J = 9.0, 2.6 Hz, 1H), 7.44 (d, J = 4.8 Hz, 1H), 7.39 – 7.32 (m, 2H), 4.98 – 4.74 (m, 2H), 4.40 (t, J = 5.1 Hz, 2H), 4.29 (s, 2H), 4.21 (t, J = 5.1 Hz, 2H), 3.64 (s, 2H), 3.56 (s, 2H), 3.47 (s, 2H), 3.31 (s, 2H), 2.66 (s, 3H), 1.86 (s, 3H)

[0600]

886		LCMS (ESI) m/z 698.3 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.82 (d, J = 4.9 Hz, 1H), 8.54 (s, 1H), 7.60 (dd, J = 8.8, 2.8 Hz, 1H), 7.48 (d, J = 4.8 Hz, 1H), 7.41 (d, J = 2.7 Hz, 1H), 7.37 (d, J = 9.0 Hz, 1H), 4.41 (s, 2H), 4.21 (s, 2H), 3.65 (s, 5H), 3.29 (q, J = 10.2 Hz, 2H), 2.82 (s, 4H), 2.64 (s, 3H), 1.80 (s, 3H)	890		LCMS (ESI) m/z 469.5 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.87 (s, 1H), 8.76 (d, J = 4.8 Hz, 1H), 8.61 (s, 1H), 7.76 (d, J = 8.2 Hz, 1H), 7.76 – 7.65 (m, 2H), 7.55 (d, J = 4.8 Hz, 1H), 6.51 (t, J = 54 Hz, 1H), 5.43 (s, 1H), 4.84 (s, 2H), 2.28 (s, 2H), 2.18 (s, 1H), 2.12 (s, 3H)
888		LCMS (ESI) m/z 613.4 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 9.92 (s, 1H), 8.98 (s, 1H), 8.83 (d, J = 4.8 Hz, 1H), 8.36 (s, 1H), 7.60 (dd, J = 8.9, 2.7 Hz, 1H), 7.46 (dd, J = 13.2, 3.7 Hz, 2H), 7.36 (d, J = 9.0 Hz, 1H), 6.51 (s, 1H), 4.40 (d, J = 5.3 Hz, 2H), 4.27 (d, J = 5.0 Hz, 2H), 4.14 (d, J = 17.9 Hz, 1H), 3.91 (s, 1H), 3.69 (d, J = 11.9 Hz, 1H), 3.35 (s, 1H), 2.95 (d, J = 4.5 Hz, 6H), 1.81 (s, 3H)	891		LCMS (ESI) m/z 528.1 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.80 (d, J = 4.8 Hz, 1H), 8.69 (s, 1H), 7.76 (d, J = 9.1 Hz, 1H), 7.72 – 7.64 (m, 2H), 7.56 (d, J = 4.8 Hz, 1H), 4.78 (s, 2H), 1.92 (s, 3H)
889		1H NMR (400 MHz, DMSO-d6) δ 8.91 (s, 1H), 8.80 (d, J = 4.8 Hz, 1H), 8.37 (s, 1H), 7.56 (d, J = 8.8 Hz, 1H), 7.43 (d, J = 15.4 Hz, 2H), 7.32 (d, J = 9.0 Hz, 1H), 6.40 (s, 1H), 4.37 (s, 2H), 4.21 (s, 2H), 3.35 (d, J = 9.9 Hz, 1H), 2.91 (s, 3H), 2.66 (s, 1H), 1.75 (s, 3H)	892		LCMS (ESI) m/z 654.1 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 10.05 (s, 1H), 8.73 – 8.67 (m, 2H), 8.63 (s, 1H), 7.72 (dd, J = 8.1, 0.8 Hz, 1H), 7.73 – 7.61 (m, 2H), 7.51 (d, J = 4.8 Hz, 1H), 4.78 (s, 2H), 4.74 – 4.67 (m, 1H), 4.64 – 4.55 (m, 3H), 4.49 (s, 2H), 4.40 (t, J = 6.9 Hz, 4H), 3.59 (d, J = 4.6 Hz, 1H), 3.52 (s, 1H), 2.07 (s, 3H), 1.21 (s, 1H)

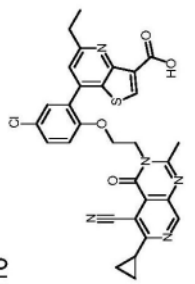
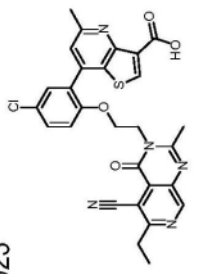
[0601]

893		LCMS (ESI) m/z 672.2 [M+1]+; ; 1H NMR (400 MHz, DMSO-d6) δ 8.75 – 8.67 (m, 2H), 8.63 (s, 1H), 7.72 (dd, J = 8.1, 0.8 Hz, 1H), 7.69 – 7.61 (m, 2H), 7.51 (d, J = 4.8 Hz, 1H), 6.34 (t, J = 52 Hz, 1 H), 4.78 (s, 2H), 4.50 (s, 5H), 4.45 (s, 3H), 3.81 (s, 1H), 2.94 (s, 2H), 2.35 (s, 6H), 2.07 (s, 3H)	897		MS (ESI) m/z 562.07 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.59 (bs, 1H), 8.72 (s, 1H), 8.42 (s, 1H), 7.58 (dd, J = 2.56, 8.72 Hz, 1H), 7.40 (bs, 2H), 7.34 (d, J = 8.92 Hz, 1H), 4.39 (t, J = 4.00 Hz, 2H), 4.39 (t, J = 4.52 Hz, 2H), 4.11 (s, 3H), 2.70 (s, 3H), 1.85 (s, 3H)
894		LCMS (ESI) m/z 720.1 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 10.05 (s, 1H), 8.75 – 8.71 (m, 2H), 8.66 (s, 1H), 7.78 – 7.73 (m, 1H), 7.72 – 7.64 (m, 2H), 7.54 (d, J = 4.8 Hz, 1H), 4.81 (s, 2H), 4.65 (s, 2H), 4.52 (s, 2H), 4.44 (d, J = 3.7 Hz, 4H), 4.37 – 4.29 (m, 2H), 3.61 (s, 2H), 2.10 (s, 3H)	898		MS (ESI) m/z 586.06 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.5 (bs, 1H), 8.49 (s, 1H), 7.60-7.57 (dd, J= 4.0, 8.8 Hz, 1H), 7.39 (m, 3H), 4.44 (t, J = 6.0 Hz, 2H), 4.25 (t, J = 3.6 Hz, 2H), 2.68 (s, 6H), 1.90 (s, 3H), 1.18-1.16 (m, 4H)
895		MS (ESI) m/z 650.4 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 9.78 (s, 1H), 8.85 (s, 1H), 8.75 (d, J = 4.8 Hz, 1H), 8.65 (s, 1H), 7.75 (d, J = 8.4 Hz, 1H), 7.69 (dd, J = 8.4, 2.2 Hz, 1H), 7.66 (d, J = 2.1 Hz, 1H), 7.53 (d, J = 4.8 Hz, 1H), 4.84 (s, 2H), 4.38 (d, J = 14.1 Hz, 2H), 3.75 (d, J = 12.0 Hz, 2H), 3.60 – 3.48 (m, 2H), 3.33 – 3.23 (m, 2H), 3.17 – 3.11 (m, 2H), 2.14 (s, 3H), 1.18 – 1.08 (m, 1H), 0.72 – 0.66 (m, 2H), 0.45 – 0.37 (m, 2H)	900		MS (ESI) m/z 572.02 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.39 (bs, 1H), 8.91 (s, 1H), 8.35 (s, 1H), 8.07 (s, 1H), 7.60-7.57 (dd, J = 7.48, 2.56 Hz, 1H), 7.41 (d, J = 2.52 Hz, 1H), 7.33 (d, J = 8.92 Hz, 1H), 4.41-4.35 (m, 2H), 4.30-4.20 (m, 2H), 3.01 (s, 3H), 2.67-2.60 (m, 1H), 1.81 (s, 3H), 1.28-1.12 (m, 4H)

[0602]

910		MS (ESI) m/z 648.05 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.41 (bs, 1H), 8.64 (s, 1H), 8.08 (d, J = 3.32 Hz, 2H), 7.58 (dd, J = 2.48, 8.84 Hz, 1H), 7.53 (d, J = 2.48 Hz, 3H), 7.42-7.35 (d, J = 2.48 Hz, 1H), 7.35-7.38 (m, 2H), 4.43 (t, J = 5.80 Hz, 2H), 4.28 (t, J = 4.52 Hz, 2H), 2.66-2.55 (m, 1H), 2.55 (s, 3H), 1.95 (s, 3H), 1.23 (d, J = 4.28 Hz, 4H)	913		MS (ESI) m/z 596.04 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.55 (bs, 1H), 9.00 (s, 1H), 8.42 (s, 1H), 7.58 (d, J = 8.68 Hz, 1H), 7.41 (s, 2H), 7.35 (d, J = 8.88 Hz, 1H), 4.40 (t, J = 4.88 Hz, 2H), 4.27 (t, J = 5.4 Hz, 2H), 2.70 (s, 3H), 2.16 (t, J = 19.28 Hz, 3H), 1.89 (s, 3H)
911		MS (ESI) m/z 637.07 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.72 (d, J = 5.2 Hz, 1H), 8.47 (s, 1H), 7.83 (s, 1H), 7.79 (d, J = 4.48 Hz, 1H), 7.60 (dd, J = 2.52, 8.84 Hz, 1H), 7.42-7.34 (m, 3H), 4.45 (t, J = 6.12 Hz, 2H), 4.30 (t, J = 5.72 Hz, 2H), 2.80 (s, 3H), 2.71 (s, 3H), 2.65 (s, 3H), 2.01 (s, 3H)	914		MS (ESI) m/z 582.03 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 9.06 (s, 1H), 8.40 (s, 1H), 7.59 (dd, J= 8.8, 2.5 Hz, 1H), 7.43-7.16 (m, 4H), 4.40 (t, J = 6.0 Hz, 2H), 4.28 (t, J = 2.6 Hz, 2H), 2.70 (s, 2H), 1.84 (s, 3H)
912		MS (ESI) m/z 586.20 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.90 (s, 1H), 8.54 (s, 1H), 7.58 (dd, J = 8.92, 2.44 Hz, 1H), 7.42 (d, J = 2.52 Hz, 1H), 7.40 (s, 1H), 7.35 (d, J = 8.92 Hz, 1H), 4.95 (t, J = 8.68, 1H), 4.41 (t, J = 5.8 Hz, 2H), 4.24 (t, J = 5.84, 2H), 2.68 (s, 3H), 2.37-2.32 (m, 3H), 2.13-2.08 (m, 2H), 1.91 (s, 3H), 1.91 (bs, 2H)	915		MS (ESI) m/z 617.10 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.53 (bs, 1H), 9.02 (s, 1H), 8.36 (s, 1H), 7.59 (dd, J = 8.88 Hz, 2.52 Hz, 1H), 7.41-7.39 (m, 2H), 7.34 (d, J = 8.96 Hz, 1H), 5.72 (d, J = 47.16 Hz, 2H), 4.40 (t, J = 7.44 Hz, 2H), 4.27 (t, J = 4.48 Hz, 2H), 2.69 (s, 3H), 1.88 (s, 3H)

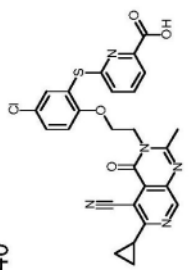
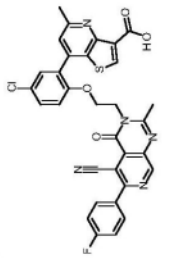
[0603]

916		MS (ESI) m/z 585.97 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.82 (s, 1H), 8.39 (s, 1H), 7.61 (dd, J = 8.88Hz, J = 2.68 Hz, 1H), 7.45-7.43 (m, 2H), 7.37 (d, J = 8.96 Hz, 1H), 4.42-4.39 (m, 2H), 4.26 - 4.23 (m, 2H), 3.02 (q, J = 7.56 Hz, J = 7.52 Hz, 2H), 2.67 (s, 1H), 1.83 (s, 3H), 1.35 (t, J = 7.52 Hz, 3H), 1.24-1.19 (m, 4H)	923		MS (ESI) m/z 560.11 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.95 (s, 1H), 8.35 (s, 1H), 7.59-7.56 (dd, J = 2.4, 8.4 Hz, 1H), 7.41-7.33 (m, 3H), 4.40 (t, J = 4.8 Hz, 2H), 4.26 (t, J = 4.8 Hz, 2H), 3.12 (m, 2H), 2.68 (s, 3H), 1.88 (s, 3H), 1.35 (t, J = 7.2 Hz, 3H)
917		MS (ESI) m/z 590.02 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.01 (s, 1H), 8.86 (s, 1H), 8.43 (s, 1H), 7.60 (dd, J = 2.48, 8.88 Hz, 1H), 7.51 (s, 1H), 7.43 (d, J = 2.52 Hz, 1H), 7.35 (d, J = 8.96, 1H), 5.69 (d, J = 46.8 Hz, 2H), 4.40 (t, J = 3.96 Hz, 2H), 4.23 (t, J = 4.40 Hz, 2H), 2.61-2.57 (m, 1H), 1.77 (s, 3H), 1.23-1.15 (m, 4H)	924		MS (ESI) m/z 690 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.4 (s, 1H), 8.50 (s, 1H), 7.94 (d, J = 7.8 Hz, 1H), 7.89 (t, J = 7.2 Hz, 1H), 7.81 (t, J = 8.4 Hz, 1H), 7.61 (dd, J = 2.4, 8.8 Hz, 1H), 7.43 (s, 2H), 7.38 (d, J = 8.82 Hz, 1H), 4.44 (bs, 2H), 4.27 (bs, 2H), 2.80 (s, 3H), 2.71 (s, 3H), 1.92 (s, 3H)
922		MS (ESI) m/z 540.10 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 12.96 (s, 1H), 8.87 (s, 1H), 7.74 (s, 1H) 7.67 (d, J = 2.3 Hz, 1H), 7.62 (dd, J = 8.84, 2.40 Hz, 1H), 7.35 (d, J =8.92 Hz, 1H), 4.44 (s, 4H), 2.68 (s, 3H), 2.58-2.57 (m, 1H), 1.20-1.14 (m, 4H)	925		MS (ESI) m/z 690.02 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.45 (s, 1H), 8.24 (s, 1H), 8.19 (d, J = 7.76 Hz, 1H), 7.94 (d, J = 7.6 Hz, 1H), 7.84 (t, J = 7.8 Hz, 1H), 7.60 (dd, J = 2.56, 8.8 Hz, 1H), 7.43 (s, 1H), 7.39 (d, J = 2.2 Hz, 2H), 4.46 (t, J = 3.6 Hz, 2H), 4.30 (t, J = 4.4 Hz, 2H), 2.80 (s, 3H), 2.71 (s, 3H), 2.00 (s, 3H)

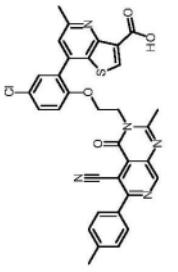
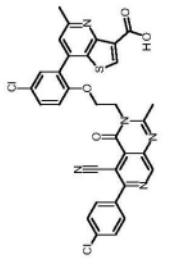
[0604]

926		MS (ESI) m/z 690.02 [M+1] +; 1H NMR (400 MHz, DMSO-d6) δ 13.44 (bs, 1H), 8.49 (s, 1H), 8.10 (d, J = 8.08 Hz, 2H), 7.95 (d, J = 8.20 Hz, 2H), 7.60 (dd, J = 8.88, 2.60 Hz, 1H), 7.43 (s, 1H), 7.42-7.37 (m, 2H), 4.45 (t, J = 4.64 Hz, 2H), 4.30 (t, J = 4.36 Hz, 2H), 2.80 (s, 3H), 2.71 (s, 3H), 1.99 (s, 3H)	929		MS (ESI) m/z 636.20 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.20 (bs, 1H), 9.04 (s, 1H), 8.37 (s, 1H), 7.61-7.56 (m, 1H), 7.44-7.38 (m, 2H), 7.34 (d, J = 8.96 Hz, 1H), 4.40-4.36 (m, 2H), 4.27-4.15 (m, 3H), 2.68 (s, 3H), 2.59-2.56 (m, 1H), 2.32-2.17 (m, 3H), 2.07-2.03 (m, 1H), 1.93-1.83 (m, 4H)
927		MS (ESI) m/z 654.03 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.50 (bs, 1H), 8.48 (s, 1H), 7.60 (dd, J = 2.4, 8.7 Hz, 1H), 7.43-7.37 (m, 5H), 7.30-7.26 (m, 1H), 4.44 (t, J = 5.2 Hz, 2H), 4.27 (t, J = 5.8 Hz, 2H), 2.77 (s, 3H), 2.71 (s, 3H), 2.13 (s, 3H), 1.93 (s, 3H)	930		MS (ESI) m/z 636.20 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.50 (bs, 1H), 8.99 (s, 1H), 8.38 (s, 1H), 7.59 (dd, J = 8.88, 2.52 Hz, 1H),7.40 (s, 2H), 7.35 (d, J = 8.96 Hz, 1H), 4.41-4.36 (m, 2H), 4.31-4.23 (m, 2H), 4.08-4.02 (m, 1H), 2.70 (s, 3H), 2.63-2.57 (m, 2H), 2.38-2.32 (m, 1H), 2.29-2.26 (m, 2H), 2.09-2.05 (m, 1H), 1.91 (s, 3H)
928		MS (ESI) m/z 622.13 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 9.03 (s, 1H), 8.35 (s, 1H), 7.58 (dd, J = 2.52, 8.8 Hz, 1H), 7.39 (t, J = 2.68 Hz, 2H), 7.35 (d, J = 9 Hz, 1H), 4.39 (t, J = 4.4 Hz, 2H), 4.26 (t, J = 4.28 Hz, 2H), 4.04-3.95 (m, 1H), 3.11-3.05 (m, 4H), 2.70 (s, 3H), 1.91 (s, 3H)	931		MS (ESI) m/z 650.13 [M+1] +; 1H NMR (400 MHz, DMSO-d6) δ 8.96 (s, 1H), 8.35 (s, 1H), 7.59 (dd, J = 8.88, 2.56 Hz, 1H), 7.44-7.40 (m, 2H), 7.35 (d, J = 8.96 Hz, 1H), 4.40 (t, J = 4.68 Hz, 2H), 4.25 (t, J = 4.68, 2H), 3.60-3.50 (bs, 1H), 2.70 (s, 3H), 2.40-2.21 (m, 2H), 2.20-2.09 (m, 1H), 2.00.1.80 (m, 6H), 1.68-1.63 (m, 2H)

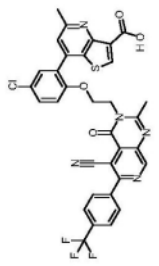
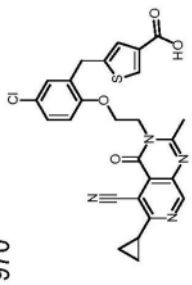
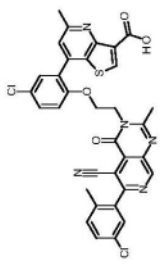
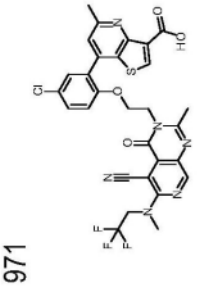
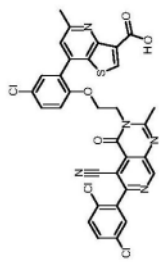
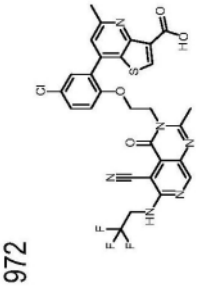
[0605]

940 	MS (ESI) m/z 534.16 [M+1]+;1H NMR (400 MHz, DMSO-d6) δ 13.08 (bs, 1H), 8.82 (s, 1H), 7.61-7.56 (m, 2H), 7.36-7.26 (m, 3H), 6.73 (d, J = 7.88 Hz, 1H), 4.46-4.30 (m, 4H), 2.60-2.59 (m, 合并的, 1H), 2.57 (s, 3H), 1.28-1.10 (m, 4H)	943 	MS (ESI) m/z 626.05 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.55 (bs, 1H), 9.03 (s, 1H), 8.41 (s, 1H), 7.99-7.95 (m, 2H), 7.59 (dd, J = 2.56, 8.88 Hz, 1H), 7.45-7.41 (m, 4H), 7.36 (d, J = 8.96 Hz, 1H), 4.42 (t, J = 4.76 Hz, 2H), 4.28 (t, J = 4.52 Hz, 2H), 2.70 (s, 3H), 1.90 (s, 3H)
941	MS (ESI) m/z 626.17 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.56 (bs, 1H), 9.09 (s, 1H), 8.48 (s, 1H), 7.74-7.71 (m, 1H), 7.65-7.58 (m, 2H), 7.45-7.34 (m, 4H), 7.35 (d, J = 8.8 Hz, 1H), 4.41 (t, J = 4.60 Hz, 2H), 4.28 (t, J = 4.60 Hz, 2H), 2.70 (s, 3H),1.90 (s, 3H)	944	MS (ESI) m/z 622.08 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 9.03 (s, 1H), 8.43 (s, 1H), 7.60 (dd, J = 8.92 Hz, 2.64 Hz, 1H), 7.47-7.35 (m, 7H), 4.42 (t, J = 5.64 Hz, 2H), 4.27 (t, J = 4.4 Hz, 2H), 2.73 (s, 3H), 2.19 (s, 3H), 1.86 (s, 3H)
942	MS (ESI) m/z 626.19 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.55 (bs, 1H), 9.04 (s, 1H), 8.38 (s, 1H), 7.74 (t, J = 6.92 Hz, 2H), 7.67-7.58 (m, 2H), 7.45-7.41 (m, 3H), 7.36 (d, J = 8.76 Hz, 1H), 4.42 (t, J = 4.68 Hz, 2H), 4.28 (t, J = 4.08, Hz, 2H), 2.66 (s, 3H), 1.98 (s, 3H)	945	MS (ESI) m/z 622.05 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 9.02 (s, 1H), 8.41 (s, 1H), 7.90 (s, 1H), 7.68 (s, 1H), 7.58 (dd, J = 8.2, 2.12 Hz, 1H), 7.48-7.35 (m, 5H), 4.42 (t, J = 4.48, 2H), 4.27 (t, J = 5.68, 2H), 2.71 (s, 3H), 2.43 (s, 3H), 1.88 (s, 3H)

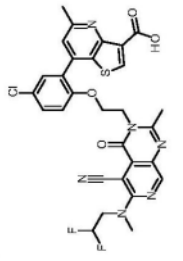
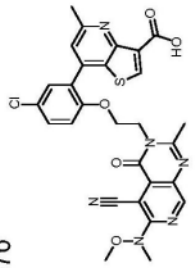
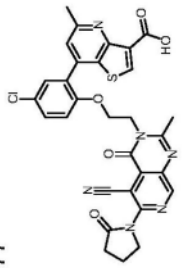
[0606]

946		MS (ESI) m/z 622.08 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.5 (s, 1H), 9.027 (s, 1H), 8.40 (s, 1H), 7.80 (d, J = 8.0 Hz, 2H), 7.58 (dd, J = 2.56 Hz, J = 2.52 Hz, 1H), 7.34- 7.42 (m, 5H), 4.40-4.42 (bs, 2H), 4.26 - 4.28 (bs, 2H), 2.70 (s, 3H), 2.42 (s, 3H), 1.87 (s, 3H)	949		MS (ESI) m/z 642.01 [M+1] +; 1H NMR (400 MHz, DMSO-d6) δ 9.04 (s, 1H), 8.40 (s, 1H), 7.94 (d, J = 8.5 Hz, 2H), 7.67 (d, J = 8.5 Hz, 2H), 7.59 (dd, J = 8.9, 2.6 Hz, 1H), 7.45-7.40 (m, 2H), 7.36 (d, J = 8.9 Hz, 1H), 4.42 (t, J = 8.3 Hz, 2H), 4.28 (t, J = 4.4 Hz, 2H), 2.70 (s, 3H), 1.90 (s, 3H)
947		MS (ESI) m/z 642.01 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.54 (bs, 1H), 9.07 (s, 1H), 8.43 (s, 1H), 7.70-7.68 (m, 2H), 7.66-7.54 (m, 3H), 7.43-7.42 (m, 2H), 7.35 (d, J = 9.0 Hz, 1H), 4.41 (t, J = 6.16 Hz, 2H), 4.27 (t, J = 4.48 Hz, 2H), 2.71 (s, 3H), 1.88 (s, 3H)	950		MS (ESI) m/z 676 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 9.03 (s, 1H), 8.41 (s, 1H), 7.97 (d, J = 7.6 Hz, 1H), 7.91 (t, J = 7.6 Hz, 1H), 7.83 (t, J = 8.0 Hz, 2H), 7.61 (dd, J = 2.8, 8.8 Hz, 1H), 7.44 (s, 1H), 7.36 (d, J = 9.2 Hz) 1H), 4.42 (bs, 1H), 4.27 (bs, 1H), 2.72 (s, 3H), 1.87 (s, 3H)
948		MS (ESI) m/z 642.06 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.50 (bs, 1H), 9.03 (s, 1H), 8.37 (s, 1H), 7.97 (t, J = 2.0 Hz 1H), 7.90-7.84 (m, 1H), 7.67-7.58 (m, 3H), 7.42-7.40 (m, 2H), 7.41 (d, J = 2.6 Hz, 1H), 4.42 (t, J = 5.48 Hz, 2H), 4.28 (t, J = 4.40 Hz, 2H), 2.71 (s, 3H), 1.91 (s, 3H)	951		MS (ESI) m/z 676.10 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 9.06 (s, 1H), 8.37 (s, 1H), 8.27 (s, 1H), 8.22 (d, J = 7.6 Hz ,1H), 7.96 (d, J = 7.4 Hz, 1H), 7.84 (t, J = 7.8 Hz, 1H), 7.60 (dd, J = 2.52, 8.8 Hz, 1H), 7.43 (s, 1H), 7.41 (d, J = 2.5 Hz ,1H), 7.37 (d, J = 8.9 Hz, 1H), 4.43 (t, J = 5.4 Hz, 2H), 4.29 (t, J = 4.96 Hz, 2H), 2.75 (s, 3H), 1.92 (s, 1H)

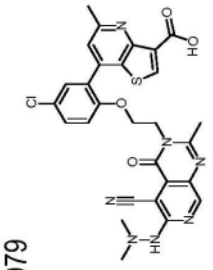
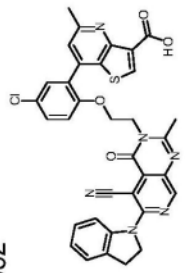
[0607]

952		MS (ESI) m/z 676.01 [M+1] +; 1H NMR (400 MHz, DMSO-d6) δ 13.49 (bs, 1H), 9.07 (s, 1H), 8.41 (s, 1H), 8.13 (d, J = 8.16 Hz, 2H), 7.98 (d, J = 8.28 Hz, 2H), 7.60 (dd, J = 8.92, 2.60 Hz 1H), 7.43-7.40 (m, 2H), 7.36 (d, J = 8.96 Hz 1H), 4.42 (t, J = 6.48 Hz 2H), 4.29 (t, J = 4.48 Hz 2H), 2.71 (s, 3H), 1.92 (s, 3H)	970		MS (ESI) m/z 521.01 [M+1] +; 1H NMR (400 MHz, DMSO-d6) δ 12.47 (bs, 1H), 8.96 (s, 1H), 7.70 (s, 1H), 7.29 (d, J = 8.8 Hz, 1H), 7.17 (s, 1H), 7.10 (d, J = 8.8 Hz, 1H), 6.83 (s, 1H), 4.53 (t, J = 6.4 Hz, 2H), 4.39 (t, J = 4.8 Hz, 2H), 3.99 (s, 2H), 2.65 (s, 3H), 2.57 (bs, 1H), 1.20 (d, J = 7.6 Hz, 2H), 0.93 (d, J = 6.4 Hz, 2H)
953		MS (ESI) m/z 655.99 [M+1]+; ; 1H NMR (400 MHz, DMSO-d6) δ, 9.03(s, 1H), 8.33 (s, 1H), 7.62-7.58 (m, 2H), 7.52 (dd, J = 2.16, 8.24 Hz, 1H), 7.47-7.42 (m, 3H), 7.37 (d, J = 8.92 Hz, 1H), 4.43 (t, J = 4.96 Hz, 2H), 4.29 (t, J = 3.88 Hz, 2H), 2.72 (s, 3H), 2.15 (s, 3H), 1.85 (s, 3H)	971		MS (ESI) m/z 643.13 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.38 (bs, 1H), 8.63 (s, 1H), 8.46 (s, 1H), 7.59 (dd, J = 2.5, 8.9 Hz, 1H), 7.42 (d, J = 2.4 Hz, 1H), 7.36 (s, 1H), 7.34 (s, 1H), 4.76-4.69 (m, 2H), 4.38 (t, J = 4.3 Hz, 2H), 4.21 (t, J = 6.2 Hz, 2H), 3.43 (s, 3H), 2.69 (s, 3H), 1.81 (s, 3H)
954		MS (ESI) m/z 675.95 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 9.06 (s, 1H), 8.36 (s, 1H), 7.90 (s, 1H), 7.74-7.68 (m, 2H), 7.59 (d, J = 6.6 Hz, 1H), 7.42 (s, 2H), 7.35 (d, J = 8.8 Hz, 1H), 4.42 (s, 2H), 4.28 (s, 2H), 2.72 (s, 3H), 1.89 (s, 3H)	972		MS (ESI) m/z 629.09 [M+1]+. ; 1H NMR (400 MHz, DMSO-d6) δ 8.65 (s, 1H), 8.43 (s, 1H), 7.77 (t, J = 6.0 Hz, 1H), 7.57 (d, J = 9.0 Hz, 1H), 7.41 (s, 1H), 7.35 (t, J = 5.3 Hz, 2H), 4.37-4.30 (m, 4H), 4.20 (bs, 2H), 2.68 (s, 3H), 1.78 (s, 3H)

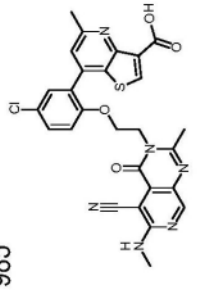
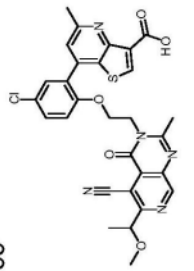
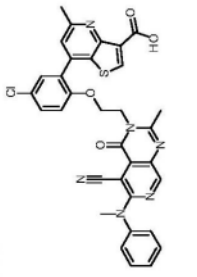
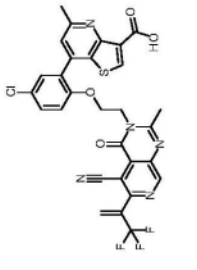
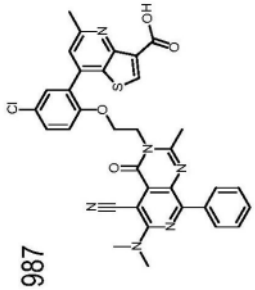
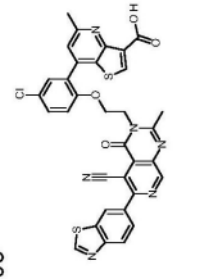
[0608]

973		MS (ESI) m/z 625.11 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.59 (s, 1H), 8.44 (s, 1H), 7.59 (dd, J = 2.56, 6.28 Hz, 1H), 7.40 (bs, 2H), 7.35 (d, J = 8.96 Hz, 1H), 6.38 (tt, J = 4.08, 59.88 Hz, 1H), 4.38 (t, J = 6.20 Hz, 2H), 4.21 (t, J = 4.48 Hz, 2H), 4.16-4.12 (m, 2H), 3.39 (s, 3H), 2.71 (s, 3H), 1.84 (s, 3H)	976		MS (ESI) m/z 591.19 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.75 (s, 1H), 8.23 (bs, 1H), 7.57 (d, J = 8.4 Hz, 1H), 7.38 (s, 1H), 7.33 (m, 2H), 4.37 (t, J = 5.2 Hz, 2H), 4.22 (t, J = 4.0 Hz, 2H), 3.84 (s, 3H), 3.26 (s, 3H), 2.66 (s, 3H), 1.63 (s, 3H)
974		MS (ESI) m/z 611.18 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.60 (s, 1H), 8.47 (s, 1H), 7.60-7.55 (m, 2H), 7.40 (s, 2H), 7.34 (d, J = 8.96 Hz 1H), 6.21 (tt, J = 5.28, 57.68 Hz, 1H), 4.36 (t, J = 4.60 Hz, 2H), 4.20 (t, J = 4.60 Hz, 2H), 3.93-3.86 (m, 2H), 2.70 (s, 3H), 1.80 (s, 3H)	977		MS (ESI) m/z 615.03 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.92 (s, 1H), 8.44 (s, 1H), 7.59 (dd, J1 = 2.5 Hz, J2 = 8.8 Hz, 1H), 7.41-7.40 (m, 2H), 7.35 (d, J = 9.0 Hz, 1H), 4.40 (t, J = 8.8 Hz, 2H), 4.25 (t, J = 9.1 Hz, 2H), 4.08, (t, J = 13.6 Hz, 2H), 2.70 (s, 3H), 2.60-2.58 (m, 2H), 2.20 (t, J = 14.3 Hz, 2H), 1.87 (s, 3H)
975		MS (ESI) m/z 560.11 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 9.14 (s, 1H), 8.61 (s, 1H), 7.62-7.59 (dd, J = 2.4, 8.4 Hz, 1H), 7.46 (s, 1H), 7.42 (d, J = 2.4 Hz, 1H), 7.37 (d, J = 9.2 Hz, 1H), 4.88 (t, J = 9.6 Hz, 2H), 4.40 (t, J = 4.4 Hz, 2H), 4.23 (t, J = 4.8 Hz, 2H), 4.17 (t, J = 9.6 Hz, 2H), 3.52 (s, 1H), 2.66 (s, 3H), 1.86 (s, 3H)	978		MS (ESI) m/z 604.24 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.54 (s, 1H), 8.48 (s, 1H), 7.59 (dd, J = 8.8 Hz, 2.48 Hz, 1H), 7.42-7.39 (m, 2H), 7.35 (d, J = 8.96 Hz, 1H), 4.37 (d, J = 4.48 Hz, 2H), 4.19 (d, J = 4.8 Hz, 2H), 3.05 (s, 3H), 2.70 (s, 3H), 2.53 (s, 6H), 1.78 (s, 3H)

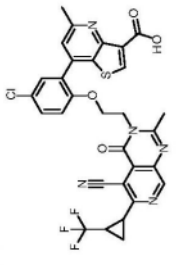
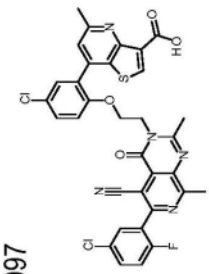
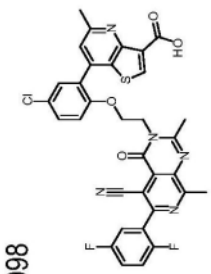
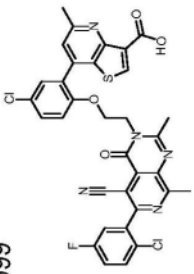
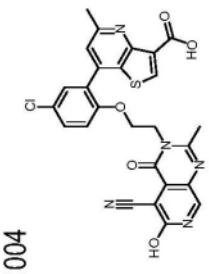
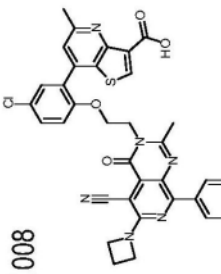
[0609]

979		MS (ESI) m/z 590.16 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.69 (bs, 1H), 8.57 (s, 1H), 8.46 (s, 1H), 7.59 (dd, J = 8.88 Hz, 2.44 Hz, 1H), 7.43-7.41 (m, 2H), 7.34 (d, J = 8.96 Hz, 1H), 4.36 (t, J = 4.28 Hz, 2H), 4.18 (t, J = 4.6 Hz, 2H), 2.70 (s, 9H), 1.71 (s, 3H)	982		MS (ESI) m/z 649.06 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.60 (s, 1H), 8.69 (s, 1H), 8.47 (s, 1H), 7.60 (dd, J = 2.56 Hz, J = 8.88 Hz, 1H), 7.42-7.35 (m, 4H), 7.29 (d, J = 7.25 Hz, 1H), 7.12 (t, J = 7.52 Hz, 1H), 6.96 (t J = 7.24 Hz, 1H), 4.41 (t, J = 5.04 Hz, 2H), 4.34 (t, J = 8.04 Hz, 2H), 4.24 (t, J = 4.76 Hz, 2H), 3.22 (t, J = 7.88 Hz, 2H), 2.71 (s, 3H), 1.83 (s, 3H)
980		MS (ESI) m/z 716.23 [M+1]+; 1H-NMR (400 MHz, DMSO-d6) δ 8.76 (d, J = 3.60 Hz, 1H), 8.68 (s, 1H), 8.59 (s, 1H), 7.74 (d, J = 8.40 Hz, 1H), 7.67-7.64 (m, 2H), 7.43 (d, J = 3.60 Hz, 1H), 4.80 (s, 2H), 4.25 (bs, 1H), 3.83 (s, 3H), 3.10 (s, 3H), 3.02 (d, J = 9.6 Hz, 2H), 2.78-2.71 (m, 2H), 2.39-2.34 (m, 2H), 2.03 (s, 3H), 1.93-1.91 (m, 2H), 1.76-1.05 (m, 5H)	983		MS (ESI) m/z 647.10 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.99 (s, 1H), 8.43 (s, 1H), 7.92 (d, J = 3.36 Hz, 1H), 7.74 (d, J = 8.12 Hz 1H), 7.69 (s, J = 7.60 Hz 1H), 7.61 (dd, J = 8.88, 2.48 Hz 1H), 7.45 (s, 1H), 7.43 (d, J = 2.48 Hz, 1H), 7.37 (d, J = 9.0 Hz, 1H), 7.29-7.20 (m, 2H), 6.84 (d, J = 3.28 Hz, 1H), 4.44 (d, J = 4.48 Hz, 2H), 4.29 (d, J = 4.48 Hz, 2H), 2.70 (s, 3H), 1.87 (s, 3H)
981		MS (ESI) m/z 554.13 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 9.22 (s, 1H), 9.19 (s, 1H), 8.79 (d, J = 4.8 Hz, 1H), 8.45 (s, 1H), 7.61 (dd, J = 2.64, 8.88, 1H), 7.48 (d, J = 4.8 Hz, 1H), 7.45 (d, J = 2.68 Hz, 1H), 7.37 (d, J = 8.96 Hz, 1H), 6.72-6.46 (t, J = 51.6 Hz, 1H), 4.41 (d, J = 4.64 Hz, 2H), 4.36 (d, J = 4.52 Hz, 2H)	984		MS (ESI) m/z 598.05 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.91 (s, 1H), 8.58 (s, 1H), 8.44 (s, 1H), 7.96 (s, 1H), 7.59 (d, J = 8.76 Hz, 1H), 7.42 (s, 2H), 7.35 (d, J = 8.88 Hz, 1H), 6.70 (s, 1H), 4.41 (t, J = 4.12 Hz, 2H), 4.27 (t, J = 4.00 Hz, 2H), 2.71 (s, 3H), 1.83 (s, 3H)

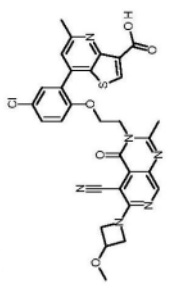
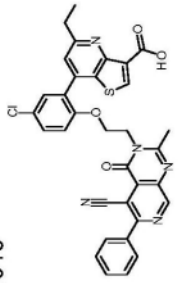
[0610]

985		MS (ESI) m/z 561.13 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.52 (bs, 1H), 8.59 (s, 1H), 8.47 (s, 1H), 7.58 (dd, J = 8.8, 2.12 Hz, 1H), 7.41 (s, 1H), 7.381H), 7.33 (d, J = 8.96 Hz, 1H), 7.28-7.20 (m, 1H), 4.36 (t, J = 5.68 Hz, 2H), 4.18 (t, J = 6.16 Hz, 2H), 2.97 (d, J = 4.24 Hz, 3H), 2.69 (s, 3H), 1.75 (s, 3H)	988		MS (ESI) m/z 590.2 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 9.01 (s, 1H), 8.40 (s, 1H), 7.60 (dd, J = 8.8 Hz, 2.4 Hz, 1H), 7.43-7.42 (m, 2H), 7.35 (d, J = 8.9 Hz, 1H), 4.95-4.90 (m, 1H), 4.39 (s, 2H), 4.23-4.20 (m, 2H), 3.22 (s, 3H), 2.70 (s, 3H), 1.84 (s, 3H), 1.50 (s, 3H)
986		MS (ESI) m/z 637.13 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.59 (bs, 1H), 8.76 (s, 1H), 8.52 (s, 1H), 7.58 (dd, J = 8.84, 2.48 Hz, 1H), 7.43-7.32 (m, 5H), 7.18 (d, J = 8.00 Hz, 2H), 7.12 (t, J = 7.20 Hz, 1H), 4.35 (t, J = 5.48 Hz, 2H), 4.18 (t, J = 3.64 Hz, 2H), 3.53 (s, 3H), 2.72 (s, 3H), 1.78 (s, 3H)	989		MS (ESI) m/z 626.13 [M+1]+; 1H NMR (400 MHz, DMSO-d6 with D2O) δ 9.14 (s, 1H), 7.79 (s, 1H), 7.50 (dd, J = 8.64 Hz, 1.96 Hz, 1H), 7.31 (d, J = 2.56 Hz, 1H), 7.25 (d, J = 8.68 Hz, 1H), 7.04 (s, 1H), 6.63 (s, 1H), 6.41 (s, 1H), 4.33 (s, 2H), 4.25 (s, 2H), 2.66 (s, 3H), 1.82 (s, 3H)
987		MS (ESI) m/z 651.29 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.45 (bs, 1H), 8.69 (s, 1H), 8.62 (s, 1H), 8.13 (t, J = 3.36 Hz, 2H), 7.58 (dd, J = 2.52, 8.84 Hz, 1H), 7.53 -7.51 (m, 3H), 7.42 (d, J = 2.52 Hz, 1H), 7.39-7.36 (m, 2H), 4.41 (t, J = 4.60 Hz, 2H), 4.25 (t, J = 4.4 Hz, 2H), 3.31 (s, 6H), 2.56 (s, 3 H) 1.88 (s, 3H)	993		MS (ESI) m/z 665.02 [M+1]+, ; 1H NMR (400 MHz, DMSO-d6) δ 13.53 (bs, 1H), 9.56 (s, 1H), 9.11 (s, 1H), 8.72 (s, 1H), 8.32 (bs, 1H), 8.28 (d, J = 8.56 Hz, 1H), 8.06 (d, J = 8.48 Hz,1H), 7.59 (dd, J = 8.92Hz, 2.36 Hz, 1H), 7.41 (d, J = 2.28 Hz, 1H), 7.37-7.35 (m, 2H), 4.42 (t, J = 6.24 Hz, 2H), 4.30 (t, J=4.56 Hz, 2H), 2.70 (s, 3H), 1.90 (s, 3H)

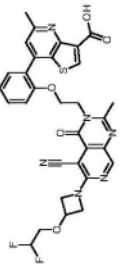
[0611]

994		MS (ESI) m/z 640.13 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.88 (s, 1H), 8.39 (s, 1H), 7.59 (dd, J = 8.88, 2.62 Hz, 1H), 7.41 (t, J = 2.8 Hz, 2H), 7.36 (d, J = 8.8 Hz, 1H), 4.40 (t, J 5.2 Hz, 2H), 4.27 (t, J = 5.2 Hz, 2H), 2.94 (d, 4.4 Hz, 1H), 2.70 (s, 3H), 2.66 - 2.60 (m, 1H), 1.91 (s, 3H), 1.68 (t, 7.2 Hz, 2H)	
997		MS (ESI) m/z 673.99 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.50 (s, 1H), 8.50 (s, 1H), 7.86 (dd, J = 2.56, 6.08 Hz, 1H), 7.70 (dd, J = 4.60, 8.60 Hz, 1H), 7.58 (dd, J = 2.52, 8.92 Hz, 1H), 7.49 (t, J = 9.28 Hz, 2H), 7.42-7.36 (m, 2H), 4.44 (t, J = 4.40 Hz, 2H), 4.29 (t, J = 4.40 Hz, 2H), 2.79 (s, 3H), 2.70 (s, 3H), 2.00 (s, 3H)	
998		MS (ESI) m/z 658.03 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.50 (s, 1H), 8.52 (s, 1H), 7.64-7.61 (m, 1H), 7.60 (dd, J = 2.4, 8.92 Hz, 1H), 7.50-7.47 (m, 2H), 7.42 (bs, 1H), 7.40 (d, J = 2.56 Hz, 1H), 7.37 (d, J = 9.00 Hz, 1H), 4.44 (t, J = 4.72 Hz, 2H), 4.29 (t, J = 4.52 Hz, 2H) 2.79 (s, 3H), 2.70 (s, 3H), 2.06 (s, 3H)	
999		MS (ESI) m/z 674.0 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.50 (bs, 1H), 8.50 (s, 1H), 7.72-7.68 (m, 2H), 7.59 (dd, J = 2.56, 8.92 Hz, 1H), 7.53-7.45 (m, 1H), 7.43-7.41 (m, 2H), 7.34 (d, J = 9.2 Hz, 1H), 4.45 (t, J = 4.96 Hz, 2H), 4.29 (bs, 2H), 2.78 (s, 3H), 2.70 (s, 3H), 1.98 (s, 3H)	
1004		MS (ESI) m/z 548.02 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.62 (bs, 2H), 8.51 (s, 1H), 8.30 (bs, 1H), 7.59 (dd, J = 8.88, 2.52 Hz, 1H), 7.42 (s, 2H), 7.34 (d, J = 9.00 Hz 1H), 4.35 (t, J = 5.48 Hz, 2H), 4.15 (t, J=3.64 Hz, 2H), 2.71 (s, 3H), 1.65 (s, 3H)	
1008		MS (ESI) m/z 663.13 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.68 (s, 1H), 8.10-8.08 (m, 2H), 7.60 (dd, J = 2.4, 6.8 Hz, 2H), 7.51-7.50 (m, 3H), 7.41-7.36 (m, 3H), 4.42 (t, J = 4.8 Hz, 6H), 4.24 (t, J = 4.4 Hz, 2H), 2.57 (s, 3H), 2.42-2.32 (m, 2H), 1.97 (s, 3H)	

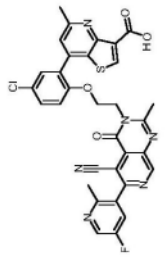
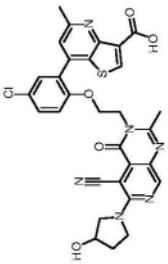
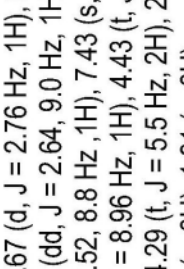
[0612]

1010		MS (ESI) m/z 617.14 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.59 (s, 1H), 8.55 (s, 1H), 8.47 (s, 1H), 7.58 (d, J = 8.72 Hz ,1H), 7.40-7.38 (m, 2H), 7.34 (d, J = 8.76 Hz, 1H), 4.55 (t, J = 6.76 Hz, 2H), 4.36 (m, 3H), 4.18-4.13 (m, 4H), 3.28 (s, 3H), 2.70 (s, 3H), 1.80 (s, 3H)	1016		MS (ESI) m/z 622.14 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.73 (bs, 1H), 9.02 (s, 1H), 8.39 (s, 1H) 7.94-7.87 (m, 2H), 7.61-7.58 (m, 4H), 7.46-7.43 (m, 2H), 7.36 (d, J = 8.96 Hz, 1H), 4.42 (t, J = 5.6 Hz, 2H), 4.27 (t, J= 4.32 Hz, 2H), 3.02 (q, J = 7.52 Hz, 2H), 1.83 (s, 3H) 1.35 (t, J = 7.56 Hz, 3H)
1011		MS (ESI) m/z 603.09 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.55 (s, 1H), 8.48 (s, 1H), 7.59 (dd, J = 2.4, 8.8 Hz 1H), 7.41 (d, J = 2.4 Hz, 1H), 7.39 (s, 1H), 7.35 (d, J = 9.2 Hz 1H), 5.79 (d, J = 5.2 Hz, 1H), 4.58 (m, 3H), 4.36 (bs, 2H), 4.19 (bs, 2H), 4.07 (d, J = 6.8 Hz, 2H), 2.70 (s, 3H), 1.78 (s, 3H)	1037		MS (ESI) m/z 688.18 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 12.86 (bs, 1H), 8.87 (s, 1H), 8.11 (s, 1H), 7.54 (d, J = 8.72 Hz, 1H), 7.36 (s, 1H), 7.30 (d, J = 8.88 Hz, 1H), 7.23 (s, 1H), 4.48 (t, J = 4.4 Hz, 1H), 4.35 (t, J = 4.08, 2H), 4.22 (t, J = 3.24, 2H), 2.66 (s, 3H), 1.80 (s, 3H), 0.86 (d, J = 5.56 Hz, 2H), 0.81 (s, 2H)
1015		MS (ESI) m/z 636.14 [M+1]+1H; NMR (400 MHz, DMSO-d6) δ 13.67 (bs, 1H), 8.50 (s, 1H), 7.87 (m, 2H), 7.61-7.55 (m, 4H), 7.46 (s, 1H), 7.42 (d, J = 2.5 Hz, 1H), 7.37 (s, 1H), 4.45 (t, J = 5.3 Hz, 2H), 4.27 (t, J = 4.6 Hz, 2H), 3.04-2.98 (m, 2H), 2.78 (s, 3H), 1.35 (s, 3H), 1.08 (t, J = 7.5 Hz, 3H)	1038		MS (ESI) m/z 624.06 [M+1] +; 1H NMR (400 MHz, DMSO-d6) δ 13.57 (bs, 1H), 8.62 (s, 1H), 8.44 (s, 1H), 7.60 (dd, J = 8.8 Hz, 2.4 Hz 1H), 7.54-7.46 (m, 2H), 7.45-7.40 (m, 2H), 7.36 (d, J = 8.8 Hz, 1H), 7.35-7.28 m, 3H), 4.41 (t, J = 4.4 Hz, 2H), 4.26 (t, J = 5.2 Hz, 2H), 2.71 (s, 3H), 1.82 (s, 3H)

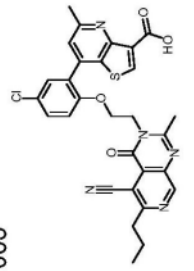
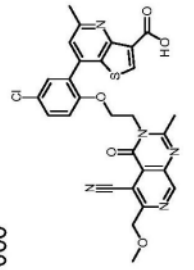
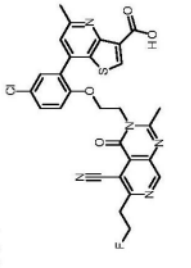
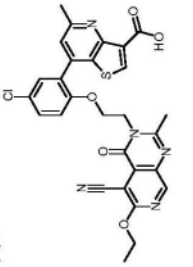
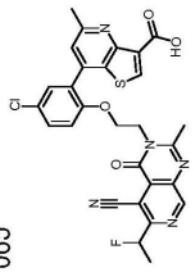
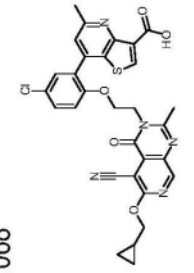
[0613]

1039		MS (ESI) m/z 639.08 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.62 (bs, 1H), 8.71 (s, 1H), 8.59 (d, J = 4 Hz, 1H), 8.43 (s, 1H), 7.89 (t, J = 7.08 Hz, 1H), 7.60-7.57 (m, 2H), 7.40 (s, 2H), 7.39-7.34 (m, 2H), 5.68 (s, 2H), 4.40 (t, J = 5.36 Hz, 2H), 4.24 (t, J = 4.36 Hz,2H), 2.70 (s, 3H), 1.85 (s, 3H)	1043		MS (ESI) m/z 667.13 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.56 (s, 1H), 8.47 (s, 1H), 7.57 (dd, J = 2.52, 8.8 Hz ,1H), 7.40 (t, J = 2.4 Hz, 2H), 7.34 (d, J = 8.84 Hz, 1H), 6.35-6.06 (m, 1H), 4.59 (t, J = 6.24 Hz, 2H), 4.36 (t, J = 4.8 Hz, 2H), 4.18 (d, J = 6.8 Hz, 4H), 3.84-3.75 (m, 2H), 2.70 (s, 3H), 1.80 (s, 3H)
1041		MS (ESI) m/z 653.12 [M+1]+; 1H NMR (400 MHz, DMSO-d6)) δ 8.58 (s, 1H), 8.46 (s, 1H), 7.58 (dd, J = 2.4, 8.8 Hz, 1H), 7.40 (t, J = 2.4 Hz, 2H), 7.35 (d, J = 8.8 Hz, 1H), 7.03-6.65 (m, 1H), 5.12 (t, J = 3.6 Hz, 1H), 4.72 (m, 2H), 4.38 (t, J = 5.2 Hz, 2H), 4.32 (m, 2H), 4.21 (t, J = 4.4 Hz, 2H), 3.40 (s, 1H), 2.71 (s, 3H), 1.83 (s, 3H)	1044		MS (ESI) m/z 685.20 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.58 (bs, 1H), 8.57 (s, 1H), 8.47 (s, 1H), 7.58 (dd, J = 2.48, 8.88 Hz ,1H), 7.40 (d, J = 2.56 Hz, 1H), 7.39 (s, 1H), 7.34 (d, J = 9.00 Hz, 1H), 4.65-4.58 (m, 3H), 4.37 (t, J = 6.08 Hz, 2H), 4.25-4.19 (m, 6H), 2.70 (s, 3H), 1.81 (s, 3H)
1042		MS (ESI) m/z 671.16 [M+1] +; ; 1H NMR (400 MHz, DMSO-d6) δ 8.60 (s, 1H), 8.47 (s, 1H), 7.60 (dd, J = 2.8, 8.8 Hz, 1H), 7.41-7.40 (m, 2H), 7.36 (d, J = 8.8 Hz, 1H), 5.36-5.33 (m, 1H), 4.79-4.75 (m, 2H), 4.43 (t, J = 3.2 Hz, 2H), 4.40 (t, J = 7.6 Hz, 2H), 4.21 (d, J = 4.4 Hz, 2H), 2.17 (s, 3H), 1.85 (s, 3H)	1045		MS (ESI) m/z 659.25 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.59 (bs, 1H), 8.55 (s, 1H), 8.47 (s, 1H), 7.59 (dd, J = 2.48, 8.84 Hz, 1H), 7.41 (d, J = 2.52 Hz, 1H), 7.39 (s, 1H), 7.34 (d, J = 8.96 Hz, 1H), 4.68-4.65 (m, 1H), 4.61-4.57 (m, 2H), 4.34 (t, J = 4.68 Hz, 2H), 4.16 (t, J = 3.72 Hz, 2H), 4.06-4.03 (m, 2H), 2.67 (s, 3H), 1.82 (s, 3H), 1.15 (s, 9H)

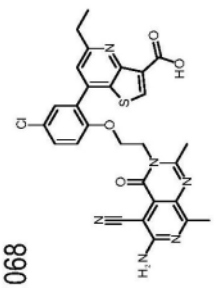
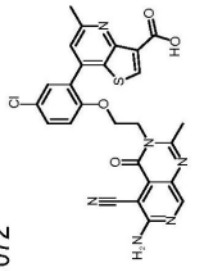
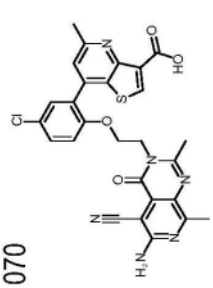
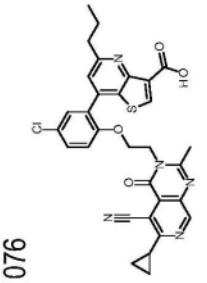
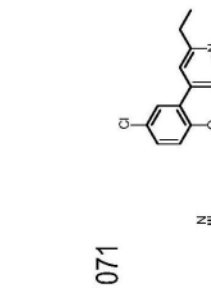
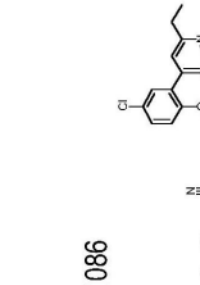
[0614]

1051		MS (ESI) m/z 641.11 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.52 (s, 1H), 9.06 (s, 1H), 8.67 (d, J = 2.76 Hz, 1H), 8.36 (s, 1H), 8.06 (dd, J = 2.64, 9.0 Hz, 1H), 7.60 (dd, J = 2.52, 8.8 Hz ,1H), 7.43 (s, 2H), 7.36 (d, J = 8.96 Hz, 1H), 4.43 (t, J = 5.0 Hz, 2H), 4.29 (t, J = 5.5 Hz, 2H), 2.72 (s, 3H), 2.36 (s, 3H), 1.91 (s, 3H)	1056 	MS (ESI) m/z 617.15 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.55 (s, 1H), 8.50 (s, 1H), 7.59 (dd, J = 8.8 Hz, 2.44 Hz, 1H), 7.42-7.40 (m, 2H), 7.35 (d, J = 9 Hz, 1H), 4.38 (bs, 1H), 4.36 (m, 2H), 4.21-4.18 (m, 2H), 3.93-3.87 (m, 3H), 3.78-3.73 (m,1H), 3.56 (d, J = 11.68 Hz, 1H), 2.70 (s, 3H), 2.04-2.02 (m, 1H), 1.94-1.92 (m, 1H), 1.79 (s, 3H)
1052		MS (ESI) m/z, 640.13 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.51 (bs, 1H), 9.03 (s, 1H), 8.37 (s, 1H), 7.60 (dd, J= 2.40, 8.84 Hz, 1H), 7.43 (bs, 4H), 7.34 (d, J = 8.92 Hz, 1H), 7.32-7.28 (m, 1H), 4.42 (t, J = 4.72 Hz, 2H), 4.27 (t, J = 4.76 Hz, 2H), 2.72 (s, 3H), 2.14 (s, 3H), 1.86 (s, 3H)	1057	MS (ESI) m/z 617.18 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.59 (bs, 1H), 8.56 (s, 1H), 8.47 (s, 1H), 7.58 (d, J = 8.64 Hz, 1H), 7.40 (d, J = 8.84 Hz, 2H), 7.34 (d, J = 8.88 Hz, 1H), 5.70 (bs, 1H) 4.36 (t, J = 6.56 Hz, 2H), 4.20 (m, 6H), 2.70 (s, 3H), 1.77 (s, 3H), 1.47 (s, 3H)
1053		MS (ESI) m/z 603.17 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.94 (s, 1H), 8.38 (s, 1H), 7.59 (d, J=8.72 Hz, 1H), 7.42 (s, J = 2.76, 2H), 7.36 (d, J = 8.96 Hz, 1H), 4.41 (s, 2H), 4.26 (s, 2H), 3.34 (s, 3H), 2.71 (s, 3H), 2.00 (bs, 3H), 1.84 (s, 3H)	1062	MS (ESI) m/z 574.12 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.7 (bs, 1H), 8.92 (s, 1H), 8.35 (s, 1H), 7.60 (d, J = 8.4 Hz, 1H), 7.44-7.43 (m, 2H), 7.36 (d, J = 8.8 Hz, 1H), 4.40 (t, J = 4.4 Hz, 2H), 4.25 (t, J = 4.0 Hz, 2H), 3.12-3.07(m, 2H), 3.03-2.97 (m, 2H), 1.83 (s, 3H), 1.36 (t, J = 7.2 Hz, 6H)

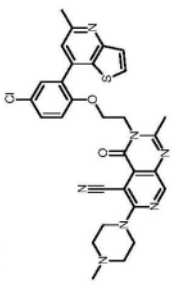
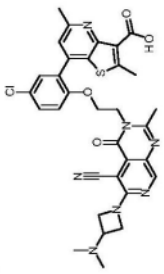
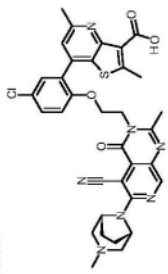
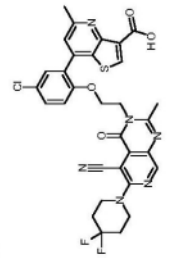
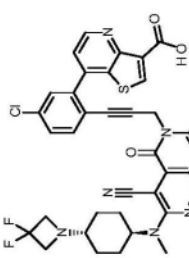
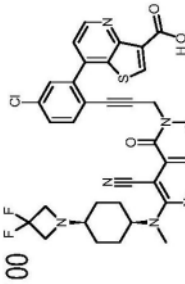
[0615]

1063		MS (ESI) m/z 573.12 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.86 (s, 1H), 8.30 (s, 1H), 7.55 (dd, J = 8.88 Hz, 2.32 Hz, 1H), 7.35-7.30 (m, 3H), 4.36 (t, J = 6.6 Hz, 2H), 4.22 (t, J = 5.12 Hz, 2H), 3.02 (t, J = 7.36 Hz, 2H), 2.71 (s, 3H), 1.90 (s, 3H), 1.80-1.74 (m, 2H),0.93 (t, J=14.6Hz, 3H)	1066		MS (ESI) m/z 576.18 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.58 (s, 1H), 8.98 (s, 1H), 8.35 (s, 1H), 7.58 (s, 1H), 7.41-7.35 (m, 3H), 4.74 (s, 2H), 4.39 (s, 2H), 4.26 (s, 2H), 3.38 (s, 3H) 2.69 (s, 3H), 1.85 (s, 3H)
1064		MS (ESI) m/z 578.19 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.98 (s, 1H), 8.40 (s, 1H), 7.59 (dd, J = 8.88 Hz, 2.62 Hz, 1H), 7.41 (s, 2H), 7.35 (d, J = 8.89 Hz, 1H), 4.94 (dt, J = 48 Hz, 6.0 Hz, 2H), 4.40 (t, J = 5.2 Hz, 2H), 4.26 (t, J = 4.8 Hz, 2H), 3.49 (dt, J = 25 Hz, 6.0 Hz, 2H), 2.70 (s, 3H), 1.89 (s, 3H)	1067		MS (ESI) m/z 576.14 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.69 (s, 1H), 8.42 (s, 1H), 7.57 (dd, J = 2.52, 8.8 Hz, 1H), 7.41 (s, 2H), 7.35 (d, J = 8.92 Hz, 1H), 4.59-4.54 (m, 2H), 4.39 (t, J = 4.4 Hz, 2H), 4.23 (t, J = 4.3 Hz, 2H), 2.71 (s, 3H), 1.84 (s, 3H)
1065		MS (ESI) m/z 578.14 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.50 (bs, 1H), 9.03 (s, 1H), 8.39 (s, 1H), 7.59 (dd, J = 8.8, 2.2 Hz 1H), 7.45-7.38 (m, 2H), 7.35 (d, J = 8.92 Hz, 1H), 6.24-6.15 (dq, J = 47.20, 6.80 Hz, 1H), 4.47-4.35 (m, 2H), 4.35-4.29 (m, 2H), 2.69 (s, 3H), 1.87 (s, 3H), 1.78 (dd, J = 24.4, 6.32 Hz, 3H)	1068		MS (ESI) m/z 602.16 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.70 (bs, 1H), 8.69 (s, 1H), 8.37 (s, 1H), 7.59 (dd, J = 8.88, 2.64 Hz, 1H), 7.40 (d, J = 2.60 Hz, 1H), 7.38 (s, 1H), 7.34 (d, J = 8.96 Hz, 1H), 4.41-4.31 (m, 4H), 4.23 (t, J = 4.60 Hz, 2H), 2.70 (s, 3H), 1.83 (s, 3H), 1.40-1.40 (m, 1H), 0.65-0.58 (m, 2H), 0.46-0.39 (m, 2H)

[0616]

1068		MS (ESI) m/z 561.20 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.59 (bs, 1H), 8.55 (s, 1H), 7.58 (d, J = 8.0 Hz, 1H), 7.40-7.34 (m, 3H), 7.03 (s, 2H), 4.38 (t, J = 5.9 Hz, 2H), 4.17 (t, J = 4.0 Hz, 2H), 2.69 (s, 3H), 2.56 (s, 3H), 1.72 (s, 3H)	1072		MS (ESI) m/z 547.10 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.49 (s, 1H), 8.47 (s, 1H) 7.59 (dd, J = 8.92, 2.44 Hz, 1H), 7.45-7.39 (m, 2H), 7.33 (d, J = 8.92 Hz 1H), 7.21 (bs, 2H), 4.36 (t, J = 6.0 Hz, 2H), 4.17 (t, J = 6.04 Hz, 2H), 2.70 (s, 3H), 1.68 (s, 3H)
1070		MS (ESI) m/z 575.20 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.56 (s, 1H), 7.60 (dd, J = 2.0, 8.8 Hz, 1H), 7.44 (t, J = 3.6 Hz, 2H), 7.36 (d, J = 9.2 Hz, 1H), 7.03 (bs, 2H), 4.40 (bs, 2H), 4.17 (bs, 2H), 3.03 (m, 2H), 2.55 (s, 3H), 1.69 (s, 3H), 2.96 (t, J = 7.6 Hz, 3H)	1076		MS (ESI) m/z 600.18 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.71 (s, 1H), 8.81 (s, 1H), 8.35 (s, 1H), 7.60 (dd, J = 2.4, 8.8 Hz, 1H), 7.43 (s, 1H), 7.36 (d, J = 9.2 Hz, 1H), 4.41 (t, J = 4.8 Hz, 2H), 4.24 (t, J = 4.4 Hz, 2H), 2.96 (t, J = 7.2 Hz, 2H), 2.66 (m, 1H), 1.85-1.75 (m, 5H), 1.23-1.18 (m, 2H), 1.10-1.06 (m, 2H), 1.00 (t, J = 7.2 Hz, 3H)
1071		MS (ESI) m/z 561.21 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.80 (bs, 1H), 8.47 (s, 1H), 8.44 (s, 1H) 7.59 (d, J = 9.20 Hz, 1H), 7.44 (s, 2H), 7.33 (d, J = 9.0 Hz, 1H), 7.21 (bs, 2H), 4.35 (t, J = 5.48 Hz, 2H), 4.16 (t, J = 6.28 Hz, 2H), 3.01 (q, J = 7.52 Hz, 2H), 1.64 (s, 3H), 1.34 (t, J = 7.48 Hz, 3H)	1086		MS (ESI) m/z 644.20 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.70 (bs, 1H), 9.90 (bs, 1H), 8.66 (s, 1H), 8.38 (s, 1H) 7.60 (dd, J = 8.88, 2.36 Hz, 1H), 7.46 (s, 1H), 7.41 (d, J = 2.36 Hz 1H), 7.37 (d, J = 8.96 Hz, 1H), 4.40 (t, J = 4.88 Hz, 2H), 4.31 (d, J = 13.92 Hz, 2H), 4.22 (t, J = 5.84 Hz, 2H), 3.61 (d, J = 11.36 Hz, 2H), 3.44 (t, J = 11.92 Hz, 2H), 3.30-3.28 (m, 2H), 3.02 (q, J = 7.44 Hz, 2H), 2.91 (s, 3H), 1.84 (s, 3H), 1.37 (t, J = 7.52 Hz, 3H)

[0617]

1089		MS (ESI) m/z 586.27 [M+1]+; 1H NMR (400 MHz, DMSO-d6) 8.75 (s, 1H), 7.68 (s, 1H), 7.52 (d, J = 7.0 Hz, 1H), 7.34-7.28 (m, 3H), 7.09 (s, 1H), 4.34 (S, 2H), 4.20 (s , 2H), 3.65 (s, 4H), 2.58 (s, 4H), 2.49 (s, 3H), 2.24 (s, 3H), 1.8 (s, 3H)	
1091		MS (ESI) m/z 644.27 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 14.39 (bs, 1H), 8.62 (s, 1H), 7.59 (dd, J = 2.48, 8.88 Hz ,1H), 7.40-7.38 (m, 2H), 7.35 (d, J = 8.92 Hz, 1H), 4.63-4.59 (m, 2H), 4.47 (bs, 2H), 4.39 (t, J = 4.64 Hz, 2H), 4.23 (t, J = 4.64 Hz, 3H), 2.82 (bs, 6H), 2.70 (s, 3H), 2.54 (s, 3H), 1.94 (s, 3H)	
1092		MS (ESI) m/z 670.20 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.58 (s, 1H), 7.55 (d, J = 8.8 Hz, 1H), 7.33-7.30 (m, 3H), 4.88 (s, 2H), 4.35 (s, 2H), 4.22 (s, 2H), 3.53 (d, J = 12 Hz, 2H), 3.31 (d, J = 11.6 Hz, 2H), 2.79 (s, 3H), 2.66 (s, 3H), 2.46 (s, 3H), 2.05 (s, 7H)	
1097		MS (ESI) m/z 651.21 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.64 (s, 1H), 8.42 (s, 1H), 7.59 (dd, J = 8.8, 2.56 Hz, 1H), 7.41 (s, 2H), 7.36 (d, J = 8.95 Hz, 1H), 4.39 (t, J = 6.9 Hz, 2H), 4.22 (t, J = 4.56 Hz, 2H), 3.87-3.75 (m, 4H), 2.71 (s, 3H), 2.21-2.15 (m, 4H) 1.87 (s, 3H)	
1099		MS (ESI) m/z 325.5 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 7.39 – 7.28 (m, 5H), 7.19 (d, J = 7.9 Hz, 1H), 4.99 (s, 2H), 3.50 (t, J = 12.4 Hz, 4H), 3.29 – 3.17 (m, 1H), 2.04 (t, J = 10.8 Hz, 2H), 1.77 (d, J = 12.4 Hz, 2H), 1.70 (d, J = 12.8 Hz, 2H), 1.15 (dq, J = 12.9, 3.2 Hz, 2H), 0.99 (q, J = 13.3 Hz, 2H)	
1100		MS (ESI) m/z 714.6 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.76 (d, J = 4.7 Hz, 1H), 8.71 (s, 1H), 8.66 (s, 1H), 7.78-7.74 (m, 1H), 7.69 (dd, J = 6.4, 2.2 Hz, 2H), 7.55 (d, J = 4.8 Hz, 1H), 4.92 (br, 4H), 4.82 (s, 2H), 4.33 (br, 2H), 3.13 (s, 3H), 2.07 (s, 3H), 2.03 – 1.61 (m, 8H)	

[0618]

1101	MS (ESI) m/z 670.4 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.83 (d, J = 4.8 Hz, 1H), 8.77 (s, 1H), 8.36 (s, 1H), 7.60 (dd, J = 8.9, 2.7 Hz, 1H), 7.47 (d, J = 4.8 Hz, 1H), 7.44 (d, J = 2.7 Hz, 1H), 7.36 (d, J = 9.0 Hz, 1H), 4.40 (br, 2H), 4.23 (br, 2H), 3.81-3.03 (br, 6H), 1.79 (s, 3H), 1.62 (br, 3H), 1.31 (br, 4H), 0.96 – 0.75 (m, 4H)	1104	MS (ESI) m/z 722.5 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.82 (s, 1H), 8.74 (d, J = 4.7 Hz, 1H), 8.62 (s, 1H), 7.74 (d, J = 8.4 Hz, 1H), 7.71 – 7.61 (m, 2H), 7.43 (d, J = 4.7 Hz, 1H), 4.82 (s, 2H), 4.54 (bs, 2H), 3.86 (s, 3H), 3.68-3.23 (br, 2H), 2.15 (s, 3H). 未看到一些脂族质子
1102	MS (ESI) m/z 664.4 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.90 (s, 1H), 8.75 (d, J = 4.8 Hz, 1H), 8.63 (s, 1H), 7.78 – 7.73 (m, 1H), 7.69 (dd, J = 6.6, 2.2 Hz, 2H), 7.55 (d, J = 4.8 Hz, 1H), 4.85 (d, J = 7.1 Hz, 2H), 3.83-2.97 (br, 6H), 2.12 (s, 3H), 1.63 (br 3H), 1.34 (br, 3H), 1.23 – 0.78 (m, 5H)	1105	MS (ESI) m/z 829.4 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.84 (d, J = 4.9 Hz, 1H), 8.82 (s, 1H), 8.75 (s, 1H), 7.78 (d, J = 9.1 Hz, 1H), 7.71 (dd, J = 6.6, 2.2 Hz, 2H), 7.64 (d, J = 4.9 Hz, 1H), 7.26 – 6.94 (m, 1H), 6.59 (tt, J = 54.1, 4.3 Hz, 2H), 4.84 (s, 2H), 4.56 (br, 1H), 4.48 (td, J = 14.7, 4.3 Hz, 2H), 3.12 (s, 3H), 2.34-1.97 (br, 8H), 1.95 (s, 3H), 1.76 (t, J = 19.4 Hz, 3H)
1103	MS (ESI) m/z 738.3 [M+1]+; 1; H NMR (400 MHz, DMSO-d6) δ 8.77 (d, J = 4.8 Hz, 1H), 8.72 (s, 1H), 8.66 (s, 1H), 7.78 – 7.73 (m, 1H), 7.71-7.67 (m, 2H), 7.55 (d, J = 4.8 Hz, 1H), 6.79 – 6.41 (m, 1H), 4.82 (s, 2H), 4.36 (br, 1H), 3.11 (s, 3H), 2.07 (s, 3H), 2.05-1.82 (br, 2H). 未看到哌啶上的质子	1106	MS (ESI) m/z 710.4 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 10.06 (s, 1H), 8.76 (d, J = 4.8 Hz, 1H), 8.73 (s, 1H), 8.66 (s, 1H), 7.76 (d, J = 9.0 Hz, 1H), 7.71 – 7.66 (m, 2H), 7.55 (d, J = 4.8 Hz, 1H), 5.00 – 4.86 (m, 1H), 4.83 (s, 2H), 4.81-4.68 (m, 1H), 3.78-3.29 (m, 2H), 3.19 (s, 3H), 2.87 (s, 3H), 2.44-2.11 (m, 5H), 2.08 (s, 3H), 2.06-1.77 (m, 5H)

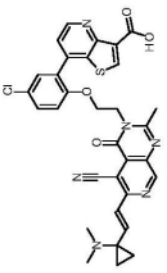
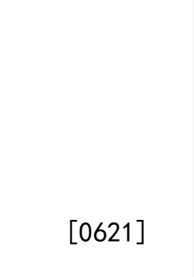
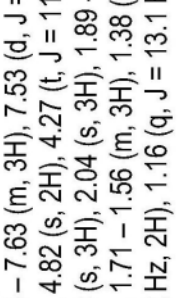
[0619]

1107	MS (ESI) m/z 752.3 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.77 (d, J = 4.8 Hz, 1H), 8.73 (s, 1H), 8.66 (s, 1H), 7.78 – 7.74 (m, 1H), 7.71 – 7.67 (m, 2H), 7.55 (d, J = 4.9 Hz, 1H), 4.82 (s, 2H), 4.38 (br, 1H), 3.11 (s, 3H), 2.08 (s, 3H), 2.07-1.92 (br, 2H), 1.84 (t, J = 20.0 Hz, 3H). 未看到哌啶质子	1110 手性	MS (ESI) m/z 854.4 [M+1]+; ; 1H NMR (400 MHz, DMSO-d6) δ 9.29 (dd, J = 2.4, 0.8 Hz, 1H), 8.92 (dd, J = 4.8, 1.6 Hz, 1H), 8.83 (d, J = 4.9 Hz, 1H), 8.69 (s, 1H), 8.54 (ddd, J = 8.2, 2.4, 1.6 Hz, 1H), 8.47 (s, 1H), 7.77 – 7.67 (m, 3H), 7.66 (dd, J = 2.2, 0.5 Hz, 1H), 7.62 (dd, J = 4.8, 0.4 Hz, 1H), 4.84 (br, 4H), 4.80 (s, 2H), 4.39 – 4.27 (m, 1H), 3.28 (br, 1H), 3.09 (s, 3H), 2.14 – 2.05 (m, 2H), 2.02-1.94 (m, 2H), 1.91 (s, 3H), 1.74 (q, J = 12.2 Hz, 2H), 1.42 (q, J = 11.9 Hz, 2H)
1108 手性	MS (ESI) m/z 791.2 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 12.47 (s, 1H), 8.82 – 8.78 (m, 2H), 8.76 (s, 1H), 7.77 (dd, J = 8.3, 0.6 Hz, 1H), 7.73 – 7.66 (m, 2H), 7.62 (d, J = 4.9 Hz, 1H), 4.83 (s, 2H), 4.78 (br, 4H), 4.36 – 4.22 (m, 2H), 3.54 (s, 3H), 3.09 (s, 3H), 2.12 – 2.02 (m, 2H), 1.98 (s, 3H), 1.80-1.67 (m, 3H), 1.46-1.32 (m, 3H)	1111	MS (ESI) m/z 854.4 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.98 – 8.93 (m, 2H), 8.84 (d, J = 4.9 Hz, 1H), 8.70 (s, 1H), 8.48 (s, 1H), 8.11 – 8.06 (m, 2H), 7.76 (dd, J = 8.4, 0.5 Hz, 1H), 7.70 (dd, J = 8.4, 2.2 Hz, 1H), 7.66 (dd, J = 2.2, 0.5 Hz, 1H), 7.64 (dd, J = 4.9, 0.4 Hz, 1H), 4.84 (br, 4H), 4.81 (s, 2H), 4.38 – 4.25 (m, 1H), 3.28 (br, 1H), 3.08 (s, 3H), 2.15 – 2.06 (m, 2H), 2.01-1.94 (m, 2H), 1.92 (s, 3H), 1.73 (q, J = 12.1 Hz, 2H), 1.41 (q, J = 11.8 Hz, 2H)
1109	MS (ESI) m/z 854.4 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.01 (s, 1H), 8.89 (d, J = 4.8 Hz, 1H), 8.72 (ddd, J = 4.6, 1.7, 0.9 Hz, 1H), 8.66 (s, 1H), 8.59 (s, 1H), 8.27 (dt, J = 8.0, 1.1 Hz, 1H), 8.25 – 8.18 (m, 1H), 7.79 – 7.72 (m, 2H), 7.72 – 7.68 (m, 2H), 7.66 (d, J = 4.9 Hz, 1H), 4.82 (s, 2H), 4.76 (br, 4H), 4.34 – 4.23 (m, 1H), 3.24 (br, 1H), 3.07 (s, 3H), 2.13 – 2.01 (m, 2H), 1.97 (br, 2H), 1.94 (s, 3H), 1.71 (q, J = 12.1 Hz, 2H), 1.38 (q, J = 12.0 Hz, 2H)	1112	MS (ESI) m/z 688.1 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.76 (d, J = 4.8 Hz, 1H), 8.74 (s, 1H), 8.65 (s, 1H), 7.77 – 7.74 (m, 1H), 7.71 – 7.67 (m, 2H), 7.55 (d, J = 4.8 Hz, 1H), 6.52 (t, J = 53.4 Hz, 1H), 4.83 (s, 2H), 4.50 (bs, 1H), 3.11 (s, 3H), 2.25 – 1.98 (m, 7H)

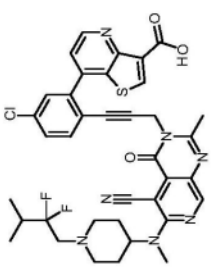
[0620]

1113	MS (ESI) m/z 702.1 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.77 (d, J = 4.7 Hz, 1H), 8.69 (s, 1H), 8.59 (s, 1H), 7.74 (dd, J = 8.1, 0.8 Hz, 1H), 7.68 – 7.64 (m, 2H), 7.44 (d, J = 4.7 Hz, 1H), 6.15 (tt, J = 55.8, 4.4 Hz, 1H), 4.81 (s, 2H), 4.26 (ddt, J = 11.6, 7.7, 4.0 Hz, 1H), 3.84 (s, 3H), 3.10 (s, 3H), 3.03 (d, J = 11.2 Hz, 2H), 2.76 (td, J = 15.7, 4.3 Hz, 2H), 2.33 (t, J = 11.5 Hz, 2H), 2.03 (s, 3H), 1.92 (qd, J = 12.1, 3.9 Hz, 2H), 1.79 (d, J = 11.7 Hz, 2H); 19F NMR (377 MHz, DMSO-d6) δ -118.73 (dt, J = 55.8, 15.7 Hz, 2F)	1117	MS (ESI) m/z 683.3 [M+1]+; 1H NMR (400 MHz, 氯仿-d) δ 9.12 (s, 1H), 8.78 (d, J = 4.8 Hz, 1H), 8.45 (s, 1H), 7.48 (dd, J = 8.9, 2.6 Hz, 1H), 7.32 – 7.27 (m, 2H), 7.03 (d, J = 8.9 Hz, 1H), 4.41 (t, J = 4.9 Hz, 2H), 4.29 (t, J = 4.9 Hz, 2H), 3.64 – 3.48 (m, 6H), 3.13 – 3.01 (m, 2H), 2.46 – 2.32 (m, 2H), 1.89 (s, 3H)
1115	MS (ESI) m/z 683.3 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.94 (s, 1H), 8.79 (d, J = 4.8 Hz, 1H), 8.59 (s, 1H), 7.59 (dd, J = 8.9, 2.7 Hz, 1H), 7.47 (d, J = 4.8 Hz, 1H), 7.45 (d, J = 2.7 Hz, 1H), 7.35 (d, J = 9.0 Hz, 1H), 4.42 (t, J = 4.9 Hz, 2H), 4.25 (t, J = 5.0 Hz, 2H), 3.82 – 3.70 (m, 1H), 3.20 – 3.09 (m, 2H), 2.78 – 2.67 (m, 2H), 1.92 – 1.79 (m, 7H)	1118	MS (ESI) m/z 694.3 [M+1]+; 1H NMR (400 MHz, 氯仿-d) δ 8.75 (s, 1H), 8.71 (d, J = 4.8 Hz, 1H), 8.49 (s, 1H), 7.59 (d, J = 8.4 Hz, 1H), 7.52 (dd, J = 8.4, 2.1 Hz, 1H), 7.40 (d, J = 2.1 Hz, 1H), 7.38 (d, J = 4.9 Hz, 1H), 5.36 (d, J = 7.0 Hz, 2H), 4.77 – 4.64 (m, 3H), 4.34 (d, J = 7.0 Hz, 2H), 3.37 (d, J = 11.5 Hz, 2H), 3.28 (t, J = 12.1 Hz, 2H), 3.19 (s, 3H), 2.84 – 2.70 (m, 2H), 2.44 (s, 3H), 2.34 (d, J = 13.5 Hz, 2H), 1.85 (s, 3H)
1116	MS (ESI) m/z 677.1 [M+1]+; 1H NMR (400 MHz, 氯仿-d) δ 9.16 (s, 1H), 8.78 (d, J = 4.9 Hz, 1H), 8.56 (s, 1H), 7.59 (d, J = 8.4 Hz, 1H), 7.51 (dd, J = 8.4, 2.1 Hz, 1H), 7.46 – 7.41 (m, 2H), 4.81 (s, 2H), 3.66 – 3.38 (m, 5H), 3.01 (t, J = 11.8 Hz, 2H), 2.50 – 2.31 (m, 5H), 2.13 (d, J = 14.0 Hz, 2H)	1119	MS (ESI) m/z 756.2 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.77 (d, J = 4.8 Hz, 1H), 8.72 (s, 1H), 8.66 (s, 1H), 7.76 (d, J = 9.0 Hz, 1H), 7.71 – 7.66 (m, 2H), 7.55 (d, J = 4.8 Hz, 1H), 4.82 (s, 2H), 4.35 – 4.24 (m, 1H), 3.38 – 3.22 (m, 2H), 3.12 – 3.00 (m, 5H), 2.63 – 2.52 (m, 2H), 2.06 (s, 3H), 2.00 – 1.86 (m, 2H), 1.85 – 1.75 (m, 2H)

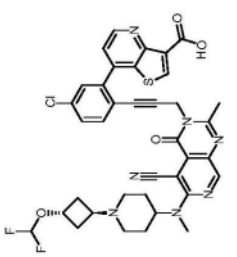
[0621]

1120		MS (ESI) m/z 623.1 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.80 – 8.58 (m, 3H), 7.78 – 7.63 (m, 3H), 7.53 (d, J = 4.8 Hz, 1H), 4.82 (s, 2H), 4.27 (t, J = 11.8 Hz, 1H), 3.09 (s, 3H), 2.04 (s, 3H), 1.89 – 1.75 (m, 4H), 1.71 – 1.56 (m, 3H), 1.38 (q, J = 12.8, 12.2 Hz, 2H), 1.16 (q, J = 13.1 Hz, 1H)	1123		LCMS (ESI) m/z 627.3 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 9.01 (s, 1H), 8.83 (d, J = 4.8 Hz, 1H), 8.38 (s, 1H), 7.67 – 7.58 (m, 2H), 7.48 (d, J = 4.8 Hz, 1H), 7.43 (d, J = 2.7 Hz, 1H), 7.37 (d, J = 9.1 Hz, 1H), 7.04 (d, J = 15.0 Hz, 1H), 4.42 (t, J = 5.0 Hz, 2H), 4.28 (t, J = 5.0 Hz, 2H), 2.98 (s, 6H), 1.86 (s, 3H), 1.53 (s, 2H), 1.35 (s, 2H)
1121		LCMS (ESI) m/z 677.1 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 9.01 (s, 1H), 8.83 (d, J = 4.8 Hz, 1H), 8.36 (s, 1H), 7.60 (dd, J = 8.9, 2.7 Hz, 1H), 7.48 (d, J = 4.8 Hz, 1H), 7.44 (s, 1H), 7.42 – 7.33 (m, 2H), 7.19 (dt, J = 14.8, 7.3 Hz, 1H), 4.41 (t, J = 4.9 Hz, 2H), 4.33 – 4.09 (m, 4H), 2.08 (d, J = 4.4 Hz, 3H), 1.80 (s, 3H)	1124		LCMS (ESI) m/z 677.1 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.92 (s, 1H), 8.84 (dd, J = 4.8, 1.4 Hz, 1H), 8.38 (d, J = 2.2 Hz, 1H), 7.60 (ddd, J = 9.0, 2.7, 0.8 Hz, 1H), 7.50 (s, 1H), 7.51 – 7.41 (m, 1H), 7.35 (d, J = 9.0 Hz, 1H), 7.11 (d, J = 15.4 Hz, 1H), 6.93 (d, J = 15.4 Hz, 1H), 6.06 (tt, J = 56.0, 4.2 Hz, 1H), 4.40 (t, J = 4.9 Hz, 2H), 4.24 (t, J = 4.9 Hz, 2H), 3.19 (td, J = 15.5, 4.2 Hz, 2H), 2.61 (s, 3H), 1.73 (d, J = 1.3 Hz, 3H), 1.16 – 1.13 (m, 2H), 1.12 – 1.01 (m, 2H)
1122		LCMS (ESI) m/z 631.1 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 9.00 (s, 1H), 8.83 (d, J = 4.8 Hz, 1H), 8.37 (s, 1H), 7.60 (dd, J = 8.9, 2.7 Hz, 1H), 7.48 (d, J = 4.8 Hz, 1H), 7.44 (d, J = 2.7 Hz, 1H), 7.36 (d, J = 9.0 Hz, 2H), 7.05 (dt, J = 14.5, 6.8 Hz, 1H), 5.46 (d, J = 57.5 Hz, 1H), 4.56 (s, 2H), 4.46 – 4.32 (m, 4H), 4.26 (t, J = 5.0 Hz, 4H), 1.79 (s, 3H)	1125		LCMS (ESI) m/z 728.1 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.78 – 8.71 (m, 2H), 8.64 (s, 1H), 7.75 (dd, J = 7.9, 1.0 Hz, 1H), 7.71 – 7.64 (m, 2H), 7.54 (d, J = 4.8 Hz, 1H), 4.82 (s, 2H), 2.09 (s, 3H), 0.70 (s, 2H), 0.65 (s, 2H)

[0622]

1126		LCMS (ESI) m/z 734.1 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.79 (d, J = 4.8 Hz, 1H), 8.58 (s, 1H), 8.38 (s, 1H), 7.57 (dd, J = 8.9, 2.7 Hz, 1H), 7.47 – 7.37 (m, 2H), 7.33 (d, J = 9.0 Hz, 1H), 4.49 (bs, 1H), 4.36 (t, J = 4.9 Hz, 2H), 4.18 (t, J = 4.9 Hz, 2H), 2.99 (s, 3 H), 1.73 (s, 3H), 1.51 (ddd, J = 13.2, 8.1, 4.9 Hz, 1H), 0.71 – 0.60 (m, 4H)	1129 	LCMS (ESI) m/z 730.3 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.81 – 8.71 (m, 2H), 8.65 (s, 1H), 7.76 (dd, J = 7.9, 1.0 Hz, 1H), 7.72 – 7.66 (m, 2H), 7.55 (d, J = 4.8 Hz, 1H), 4.83 (s, 2H), 3.11 (s, 3H), 2.40 – 2.18 (m, 2H), 2.11 (s, 4H), 1.03 (d, J = 6.9 Hz, 6H)
1127		LCMS (ESI) m/z 714.4 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.79 (d, J = 4.8 Hz, 1H), 8.54 (s, 1H), 8.34 (s, 1H), 7.57 (dd, J = 8.9, 2.7 Hz, 1H), 7.44 (d, J = 4.8 Hz, 1H), 7.39 – 7.29 (m, 2H), 4.51 (s, 1H), 4.46 – 4.30 (m, 4H), 4.19 (t, J = 5.1 Hz, 2H), 3.50 (d, J = 11.8 Hz, 2H), 3.26 – 3.11 (m, 2H), 3.08 (s, 3H), 2.75 – 2.66 (m, 1H), 2.25 (d, J = 12.7 Hz, 2H), 2.03 (d, J = 12.8 Hz, 2H), 1.79 (s, 3H), 1.07 (d, J = 6.9 Hz, 6H)	1130	LCMS (ESI) m/z 469.5 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.76 – 8.69 (m, 4H), 8.62 (s, 2H), 7.76 – 7.61 (m, 7H), 7.52 (d, J = 4.8 Hz, 2H), 4.79 (s, 5H), 4.51 (s, 1H), 3.71 (s, 1H), 3.34 (s, 1H), 2.07 (s, 8H), 2.01 (s, 1H), 1.22 (s, 14H)
1128		LCMS (ESI) m/z 712.4 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.79 (d, J = 4.8 Hz, 1H), 8.53 (s, 1H), 8.33 (s, 1H), 7.57 (dd, J = 8.9, 2.7 Hz, 1H), 7.44 (d, J = 4.9 Hz, 1H), 7.38 – 7.30 (m, 2H), 4.58 – 4.43 (m, 3H), 4.36 (t, J = 5.1 Hz, 2H), 4.19 (t, J = 5.0 Hz, 2H), 3.52 (d, J = 11.8 Hz, 3H), 3.18 (t, J = 12.7 Hz, 2H), 3.07 (s, 3H), 2.24 (d, J = 12.7 Hz, 2H), 2.17 – 1.95 (m, 3H), 1.80 (s, 3H), 1.06 (dd, J = 23.8, 2.3 Hz, 4H)	1131	LCMS (ESI) m/z 744.1 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.76 (d, J = 4.8 Hz, 1H), 8.68 (d, J = 14.8 Hz, 2H), 7.76 (d, J = 9.0 Hz, 1H), 7.73 – 7.66 (m, 2H), 7.55 (d, J = 4.7 Hz, 1H), 4.82 (s, 2H), 4.21 (d, J = 6.9 Hz, 1H), 3.75 (s, 1H), 3.07 (s, 3H), 3.00 (s, 2H), 2.05 (s, 3H), 1.77 (s, 4H), 0.85 (s, 4H)

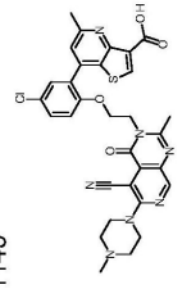
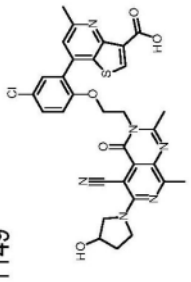
[0623]

1132	LCMS (ESI) m/z 718.1 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.73 (d, J = 4.8 Hz, 1H), 8.70 (s, 1H), 8.61 (s, 1H), 7.72 (d, J = 8.9 Hz, 1H), 7.68 – 7.63 (m, 2H), 7.51 (d, J = 4.8 Hz, 1H), 4.79 (s, 2H), 4.50 (s, 1H), 3.71 (t, J = 13.7 Hz, 7H), 3.08 (s, 3H), 2.22 (s, 2H), 2.06 (s, 3H), 2.03 – 1.91 (m, 2H)	1135 	LCMS (ESI) m/z 744.0 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.75 (d, J = 1.8 Hz, 2H), 8.65 (s, 1H), 7.76 (d, J = 8.2 Hz, 1H), 7.69 (d, J = 8.9 Hz, 2H), 7.55 (d, J = 4.8 Hz, 1H), 6.72 (t, J = 75.2 Hz, 1H), 4.83 (s, 2H), 4.78 (s, 1H), 4.56 (s, 1H), 3.94 (d, J = 8.4 Hz, 1H), 3.57 (d, J = 11.9 Hz, 2H), 3.12 (s, 3H), 3.06 (d, J = 10.5 Hz, 2H), 2.77 – 2.64 (m, 2H), 2.54 (s, 1H), 2.11 (s, 7H). 19F NMR (377 MHz, DMSO-d6) δ -73.82, -82.25 (d, J = 75.1 Hz)
1133	LCMS (ESI) m/z 732.4 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.79 – 8.71 (m, 2H), 8.65 (s, 1H), 7.79 – 7.72 (m, 1H), 7.72 – 7.65 (m, 2H), 7.55 (d, J = 4.8 Hz, 1H), 4.82 (s, 2H), 3.76 (s, 2H), 3.11 (s, 3H), 2.08 (s, 3H)	1136	LCMS: 1.77 Min, 700.2. [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 10.73 (s, 1H), 8.78 – 8.72 (m, 2H), 8.64 (s, 1H), 7.81 – 7.73 (m, 1H), 7.72 – 7.67 (m, 2H), 7.54 (d, J = 4.8 Hz, 1H), 6.40 (t, J = 53.2 Hz, 1H), 4.82 (s, 2H), 4.12 (s, 4H), 3.92 (t, J = 16.0 Hz, 2H), 3.64 (d, J = 31.4 Hz, 4H), 2.06 (s, 3H)
1134	LCMS (ESI) m/z 720.0 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.76 – 8.68 (m, 2H), 8.62 (s, 1H), 7.76 – 7.69 (m, 1H), 7.69 – 7.62 (m, 2H), 7.52 (d, J = 4.8 Hz, 1H), 4.86 – 4.58 (m, 2H), 4.79 (s, 3H), 4.42 (s, 1H), 2.05 (s, 3H), 1.92 (bs, 3H)	1137	LCMS: 1.71 Min, 714.5 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 10.61 (s, 1H), 8.81 – 8.72 (m, 2H), 8.64 (s, 1H), 7.79 – 7.72 (m, 1H), 7.71 – 7.64 (m, 2H), 7.54 (d, J = 4.8 Hz, 1H), 4.82 (s, 2H), 4.32 – 3.89 (m, 6H), 3.64 (m, 4H), 2.07 (d, J = 1.6 Hz, 6H), 2.00 (s, 3H), 1.74 (t, J = 19.6 Hz, 3H)

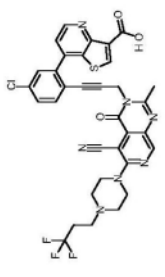
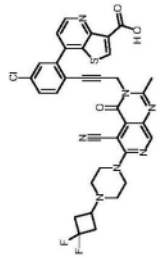
[0624]

1139	MS (ESI) m/z 708.4 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.83 (d, J = 4.8 Hz, 1H), 8.61 (s, 1H), 8.41 (s, 1H), 7.60 (dd, J = 8.9, 2.7 Hz, 1H), 7.47 (d, J = 4.8 Hz, 1H), 7.43 (d, J = 2.7 Hz, 1H), 7.36 (d, J = 9.0 Hz, 1H), 4.39 (t, J = 5.0 Hz, 2H), 4.21 (t, J = 5.0 Hz, 2H), 3.75 – 3.30 (m, 10H), 3.09 (s, 3H), 1.75 (s, 6H)	1142	MS (ESI) m/z 698.4 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.78 – 8.73 (m, 2H), 8.65 (s, 1H), 7.76 (dd, J = 8.1, 0.8 Hz, 1H), 7.72 – 7.66 (m, 2H), 7.55 (d, J = 4.8 Hz, 1H), 4.83 (s, 2H), 4.57 (d, J = 12.1 Hz, 1H), 3.67 (d, J = 12.6 Hz, 2H), 3.48 (dd, J = 22.6, 5.0 Hz, 2H), 3.33 (d, J = 11.5 Hz, 1H), 3.12 (s, 3H), 2.40 – 2.26 (m, 2H), 2.15 – 1.98 (m, 5H), 1.50 (d, J = 21.4 Hz, 6H)
1140	MS (ESI) m/z 706.2 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.77 (d, J = 4.8 Hz, 1H), 8.69 (d, J = 22.6 Hz, 2H), 7.76 (d, J = 9.0 Hz, 1H), 7.71 – 7.66 (m, 2H), 7.55 (d, J = 4.8 Hz, 1H), 4.82 (s, 2H), 4.31 (s, 1H), 3.34 (s, 1H), 3.10 (s, 5H), 2.61 (s, 2H), 2.06 (s, 3H), 1.96 (q, J = 11.8 Hz, 2H), 1.82 (d, J = 12.1 Hz, 2H)	1143	MS (ESI) m/z 842.3 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 1H NMR (400 MHz, DMSO-d6) δ 13.21 (bs, 1H), 9.97 (s, 1H), 8.97 – 8.93 (m, 2H), 8.85 (d, J = 4.9 Hz, 1H), 8.69 (s, 1H), 8.50 (s, 1H), 8.10 – 8.05 (m, 2H), 7.77 (dd, J = 8.4, 0.5 Hz, 1H), 7.70 (dd, J = 8.4, 2.2 Hz, 1H), 7.66 (dd, J = 2.2, 0.5 Hz, 1H), 7.64 (dd, J = 4.9, 0.4 Hz, 1H), 4.82 (s, 2H), 4.57 (s, 1H), 3.96 – 3.26 (m, 4H), 3.11 (s, 3H), 2.26 (s, 2H), 2.04 (dd, J = 20.6, 10.2 Hz, 2H), 1.92 (s, 3H), 1.78 (t, J = 19.5 Hz, 3H)
1141	MS (ESI) m/z 702.2 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.76 (d, J = 4.8 Hz, 1H), 8.74 (s, 1H), 8.65 (s, 1H), 7.78 – 7.74 (m, 1H), 7.71 – 7.67 (m, 2H), 7.55 (d, J = 4.8 Hz, 1H), 4.83 (s, 2H), 3.11 (s, 3H), 2.09 (s, 3H), 1.78 (t, J = 19.5 Hz, 3H)	1144	MS (ESI) m/z 842.4 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.12 (s, 1H), 9.28 (d, J = 2.3 Hz, 1H), 8.92 (d, J = 4.6 Hz, 1H), 8.84 (d, J = 4.9 Hz, 1H), 8.67 (s, 1H), 8.56 – 8.51 (m, 1H), 8.48 (s, 1H), 7.73 (ddd, J = 16.1, 10.9, 8.4 Hz, 3H), 7.66 (d, J = 2.2 Hz, 1H), 7.63 (d, J = 4.9 Hz, 1H), 4.81 (s, 2H), 3.11 (s, 3H), 1.90 (s, 3H)

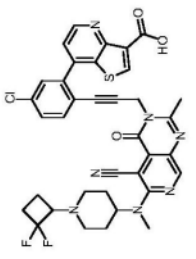
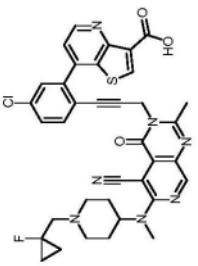
[0625]

1145		MS (ESI) m/z 630.2 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 9.89 (s, 1H), 8.69 (s, 1H), 8.41 (s, 1H), 7.60 (dd, J = 8.9, 2.7 Hz, 1H), 7.42 (s, 1H), 7.40 (d, J = 2.7 Hz, 1H), 7.37 (d, J = 9.0 Hz, 1H), 4.40 (t, J = 5.1 Hz, 2H), 4.31 (d, J = 14.2 Hz, 2H), 4.24 (t, J = 5.1 Hz, 2H), 3.61 (d, J = 12.0 Hz, 2H), 3.45 (t, J = 13.1 Hz, 2H), 3.24 (q, J = 10.2 Hz, 2H), 2.91 (d, J = 3.4 Hz, 3H), 2.72 (s, 3H), 1.90 (s, 3H)	1149		MS (ESI) m/z 631.26 [M+1]+; 1H-NMR (400 MHz, DMSO-d6) δ 13.60 (bs, 1H), 8.56 (s, 1H), 7.58 (dd, J = 8.8, 2.4 Hz, 1H), 7.40 – 7.35 (m, 3H), 5.02 (bs, 1H), 4.39 (s, 2H), 4.19 (s, 2H), 3.90-3.82 (m, 2H), 3.74 (t, J = 8.0 Hz, 1H), 3.54 (d, J = 11.6 Hz 1H), 2.70 (s, 3H), 2.59 (s, 3H), 2.05 – 1.85 (m, 2H), 1.84 (s, 3H)
1146		MS (ESI) m/z 842.4 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 1H NMR (400 MHz, DMSO-d6) δ 13.03 (s, 1H), 8.90 (d, J = 4.9 Hz, 1H), 8.72 (ddd, J = 4.6, 1.7, 0.9 Hz, 1H), 8.65 (s, 1H), 8.60 (s, 1H), 8.30 – 8.25 (m, 1H), 8.21 (td, J = 7.7, 1.7 Hz, 1H), 7.80 – 7.72 (m, 2H), 7.72 – 7.68 (m, 2H), 7.66 (d, J = 4.8 Hz, 1H), 4.83 (s, 2H), 3.09 (s, 3H), 1.94 (s, 3H), 1.77 (t, J = 18.9 Hz, 2H)	1152		MS (ESI) m/z 616.24 [M+1]+; 1H-NMR (400 MHz, DMSO-d6) δ 13.56 (bs, 1H), 9.01 (s, 1H), 8.39 (s, 1H), 7.59 (dd, J = 2.8, 9.2 Hz, 1H), 7.41 (d, J = 2.4 Hz, 1H), 7.39 (s 1H), 7.34 (d, J = 8.8 Hz, 1H), 4.38 (s, 2H) 4.24 (s, 2H), 4.0-3.9 (m, 1H), 3.67-3.61 (m, 1H), 3.19 (s, 3H), 2.69 (bs, 5H), 2.35-2.31 (m, 2H), 1.86 (s, 3H)
1148		MS (ESI) m/z 676.21. [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.22 (bs, 1H), 8.83 (d, J = 4.6 Hz, 1H), 8.49 (s, 1H), 7.94 (d, J = 7.8 Hz, 1H), 7.87 (t, J = 7.4 Hz, 1H), 7.77 (m, 2H), 7.60 (dd, J = 2.4, 8.8 Hz, 1H), 7.47 (d, J = 4.7 Hz, 1H), 7.44 (d, J = 2.4 Hz, 1H), 7.37 (d, J = 8.9 Hz, 1H), 4.44 (s, 2H), 4.27 (s, 2H), 2.77 (s, 3H), 1.85 (s, 3H)	1157		MS (ESI) m/z 789.51 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 12.66 (s, 1H), 8.87 (d, J = 4.8 Hz, 1H), 8.60 (m, 1H), 8.58 (s, 1H), 7.60 (dd, J = 8.8, 2.4 Hz, 1H), 7.54 (d, J = 4.8 Hz, 1H), 7.43 (d, J = 2.4 Hz, 1H), 7.38 (d, J = 9.2 Hz, 1H), 4.39 (t, J = 6.0 Hz, 2H), 4.35-4.25 (m, 1H), 4.19 (t, J = 6.0 Hz, 2H), 3.58 (s, 3H), 3.40-3.20 (m, 2H), 3.07 (s, 5H), 2.65-2.55 (m, 2H), 1.99-1.90 (m, 2H), 1.85-1.79 (m, 2H), 1.74 (s, 3H)

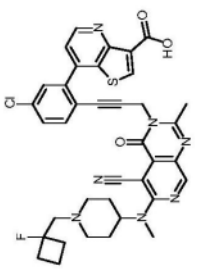
[0626]

1160 	MS (ESI) m/z 692.45 [M+1]+; 1H-NMR (400 MHz, DMSO-d6) δ 13.05 (bs, 1H), 8.83 (s, 1H), 8.75 (d, J = 4.6 Hz, 1H), 8.64 (s, 1H), 7.75 (d, J = 8.2 Hz, 1H), 7.69 (s, 1H), 7.66 (s, 1H), 7.52 (d, J = 4.5 Hz, 1H), 4.83 (s, 2H), 4.31 (bs, 1H), 3.43 (bs, 7H), 2.85 (s, 4H), 2.11 (s, 3H)	1163 	MS (ESI) m/z 686.0 [M+1]+; 1H-NMR (400 MHz, DMSO-d6) δ 13.03 (s, 1H), 8.83 (s, 1H), 8.75 (d, J = 4.8 Hz, 1H), 8.64 (s, 1H), 7.75 (d, J = 8.4 Hz, 1H), 7.70-7.66 (m, 1H), 7.53 (d, J = 4.8 Hz, 1H), 4.72 (s, 2H), 3.80 (bs, 4H), 3.39 (bs, 4H), 3.05-3.02 (m, 5H), 2.16 (s, 3H)
1161	MS (ESI) m/z 708.3 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.84 (s, 1H), 8.76 (d, J = 4.8 Hz, 1H), 8.65 (s, 1H), 7.76 (dd, J = 8.3, 0.5 Hz, 1H), 7.71 – 7.65 (m, 2H), 7.54 (d, J = 4.8 Hz, 1H), 4.84 (s, 2H), 4.53 (s, 2H), 4.06 – 2.83 (m, 8H), 2.13 (s, 3H)	1164	MS (ESI) m/z 694.52 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.82 (d, J = 4.8 Hz, 1H), 8.68 (s, 1H), 8.45 (s, 1H), 7.60 (dd, J = 8.8 Hz, 2.4 Hz, 1H), 7.48 (d, J = 4.8 Hz, 1H), 7.42 (d, J = 2.8 Hz, 1H), 7.36 (d, J = 8.8 Hz, 1H), 4.72-4.54 (m, 2H), 4.39 (bs, 2H), 4.22 (bs, 2H), 3.25-2.78 (m, 10H), 1.81 (s, 3H), 1.45 (bs, 3H)
1162	MS (ESI) m/z 636.25 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.18 (bs, 1H), 8.84 (s, 1H), 8.75 (d, J = 4.8 Hz, 1H), 8.65 (s, 1H), 7.75 (d, J = 8.4 Hz, 1H), 7.70-7.65 (m, 2H), 7.53 (d, J = 4.8 Hz, 1H), 4.84 (s, 2H), 4.38 (m, 2H), 3.79 (m, 2H,), 3.49 (m, 4H), 3.03 (m, 1H), 2.14 (s, 3H), 0.93 (m, 4H)	1165	MS (ESI) m/z, 714.50 [M+1] +; 1H-NMR (400 MHz, DMSO-d6) δ 9.80 (bs, 1H), 8.76 (s, 1H), 8.75 (s, 1H), 8.65 (s, 1H), 7.75 (d, J = 8.4 Hz, 1H), 7.70-7.67 (m, 2H), 7.54 (d, J = 4.8 Hz, 1H), 4.83 (s, 2H), 4.56 (bs, 1H), 3.56 (bs, 4H), 3.11 (bs, 1H), 3.06 (s, 3H), 3.05 (bs, 4H), 2.13 (bs, 4H), 2.11 (s, 3H)

[0627]

1166 	MS (ESI) m/z 714.58 [M+1]+; 1H-NMR (400 MHz, DMSO-d6) δ 8.76-8.74 (m, 2H), 8.65 (s, 1H), 7.75 (d, J = 8.0 Hz, 1H), 7.70-7.67 (m, 2H), 7.55 (d, J = 4.8 Hz, 1H), 4.82 (s, 2H), 4.58-4.38 (m, 2H), 3.11 (s, 3H), 2.90-2.88 (m, 2H), 2.50-2.32 (m, 4H), 2.20-2.15 (m, 5H), 2.12-2.10 (m, 2H)	1169 	MS (ESI) m/z 696.24 [M+1]+; 1H-NMR (400 MHz, DMSO-d6) δ 8.76-8.75 (m, 2H), 8.64 (s, 1H), 7.75 (d, J = 8.4 Hz, 1H), 7.69-7.67 (m, 2H), 7.54 (d, J = 4.8 Hz, 1H), 4.82 (s, 2H), 4.54 (s, 1H), 3.74-3.72 (m, 4H), 3.31-3.29 (m, 2H), 3.12 (s, 3H), 2.28-2.22 (m, 2H), 2.13-2.10 (m, 5H), 1.25 (d, J = 19.6 Hz, 2H), 0.96 (d, J = 8.0 Hz, 2H)
1167	MS (ESI) m/z 668.42 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.08 (bs, 1H), 10.22 (bs, 1H), 8.85 (s, 1H), 8.76 (d, J = 4.8 Hz, 1H), 8.65 (s, 1H), 7.76 (d, J = 8.4 Hz, 1H), 7.69-7.66 (m, 2H), 7.53 (d, J = 4.8 Hz, 1H), 4.83 (s, 2H), 4.39 (d, J = 11.6 Hz, 2H), 3.76 (bs, 6H), 3.43 (bs, 2H), 2.14 (s, 3H), 1.29 (d, J = 18.8 Hz, 2H), 0.99 (d, J = 7.6 Hz, 2H)	1170	MS (ESI) m/z 736.43 [M+1]+; 1H-NMR (400 MHz, DMSO-d6) δ 8.76-.8.74 (m, 2H), 8.64 (s, 1H), 7.75 (d, J = 8.0 Hz, 1H), 7.70-7.67 (m, 2H), 7.54 (d, J = 4.8 Hz, 1H), 4.82 (s, 2H), 4.56-4.52 (m, 3H), 3.67-3.55 (m, 4H), 3.25-3.19 (m, 2H), 3.11 (s, 3H), 2.23-2.20 (m, 2H), 2.17-2.10 (m, 5H)
1168	MS (ESI) m/z 722.51 [M+1] +; 1H NMR (400 MHz, DMSO-d6) δ 8.82 (d, J = 4.8 Hz, 1H), 8.61 (s, 1H), 8.41 (s, 1H), 7.60 (dd, J = 8.8 Hz, 2.4 Hz, 1H), 7.47 (d, J = 4.8 Hz, 1H), 7.43 (d, J = 2.8 Hz, 1H), 7.36 (d, J = 9.2 Hz, 1H), 4.52 (bs, 1H), 4.39 (s, 2H), 4.21 (s, 2H), 3.90-3.82 (m, 1H), 3.36-3.31 (m, 6H), 3.09 (s, 3H), 2.33-2.27 (m, 1H), 2.02-2.07 (m, 4H), 1.79 (s, 3H), 0.99 (t, J = 7.2 Hz, 3H)	1171	MS (ESI) m/z 664.42 [M+1] +; 1H NMR (400 MHz, DMSO-d6) δ 8.76 (d, J = 6.0 Hz, 2H), 8.65 (s, 1H), 7.76 (d, J = 8.0 Hz, 1H), 7.70-7.67 (m, 2H), 7.55 (d, J = 4.8 Hz, 1H), 4.83 (s, 2H), 4.60-4.59 (m, 1H), 3.66 (d, J = 11.6 Hz, 2H), 3.43-3.22 (m, 2H), 3.09 (s, 3H), 2.85 (bs, 1H), 2.10 (s, 7H), 0.95-0.85 (m, 4H)

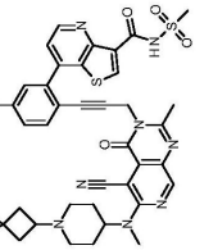
[0628]

1172 手性		MS (ESI) m/z 744.02 [M+1]+; 1H-NMR (400 MHz, DMSO-d6) δ 8.76-8.74 (m, 2H), 8.64 (s, 1H), 7.75 (d, J = 8.4 Hz, 1H), 7.70-7.67 (m, 2H), 7.54 (d, J = 4.8 Hz, 1H), 6.89-6.52 (m, 1H), 4.82 (s, 2H), 4.58-4.45 (m, 2H), 3.48-3.38 (m, 5H), 3.10 (s, 3H), 3.08-3.06 (m, 2H), 2.40.2.38 (m, 2H), 2.20-2.10 (m, 5H)	1174		MS (ESI) m/z 710.42 [M+1]+; 1H-NMR (400 MHz, DMSO-d6) δ 9.40 (bs, 1H), 8.76-8.74 (m, 2H), 8.64 (s, 1H), 7.75 (d, J = 8.0 Hz, 1H), 7.70-7.67 (m, 2H), 7.55 (d, J = 4.8 Hz, 1H), 4.82 (s, 2H), 4.56-4.53 (m, 1H), 3.94-3.80 (m, 4H), 3.66-3.59 (m, 4H), 3.11 (s, 3H), 2.40-2.34 (m, 3H), 2.27-2.24 (m, 1H), 2.10-2.01 (m, 5H), 1.91-1.88 (m, 1H), 1.70-1.63 (m, 1H)
1173a 手性		MS (ESI) m/z 762.47 [M+1]+; 1H-NMR (400 MHz, DMSO-d6) δ 8.77-8.75 (m, 2H), 8.65 (s, 1H), 7.76 (d, J = 8.0 Hz, 1H), 7.70 (d, J = 2.0 Hz, 1H), 7.68 (s, 1H), 7.56 (d, J = 4.8 Hz, 1H), 4.83 (s, 2H), 4.73 (quin, J = 7.2 Hz, 1H), 4.59 (bs, 1H), 3.62 (bs, 4H), 3.41 (bs, 1H), 3.12 (bs, 5H), 2.89 (bs, 2H), 2.11 (bs, 7H)	1175 手性		MS (ESI) m/z 732.40 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.77-8.74 (m, 2H), 8.65 (s, 1H), 7.76 (d, J = 8.4 Hz, 1H), 7.69 (d, J = 1.6 Hz, 1H), 7.68 (s, 1H), 7.55 (d, J = 4.8 Hz, 1H), 4.82 (s, 2H), 4.48 (bs, 1H), 3.65 (m, 4H), 3.10 (s, 3H), 2.50-2.39 (m, 2H), 2.09 (s, 3H), 2.04 (bs, 4H), 1.44-1.33 (m, 2H)
1173b		MS (ESI) m/z 671.41 [M+1] +; 1H-NMR (400 MHz, DMSO-d6) δ 8.76 (d, J = 4.8 Hz, 1H), 8.68 (d, J = 1.6 Hz, 2H), 7.75 (d, J = 8.4 Hz, 1H), 7.70-7.67 (m, 2H), 7.55 (d, J = 4.8 Hz, 1H), 4.82 (s, 3H), 3.38-3.28 (m, 4H), 3.11 (s, 9H), 2.02 (s, 3H), 1.97-1.91 (m, 2H), 1.89-1.83 (m, 2H)	1176		MS (ESI) m/z 720.44 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.77 (d, J = 4.4 Hz, 1H), 8.74 (s, 1H), 8.67 (s, 1H), 7.76 (d, J = 8.8 Hz, 1H), 7.69-7.67 (m, 2H), 7.56 (d, J = 4.8 Hz, 1H), 4.82 (s, 2H), 4.18-4.15 (m, 1H), 3.67-3.64 (m, 2H), 3.29 (bs, 2H), 3.07 (d, J = 9.2 Hz, 2H), 2.60-2.55 (m, 2H), 2.06 (s, 3H), 1.96-1.94 (m, 2H), 1.85-1.82 (m, 2H), 1.11 (t, J = 6.8 Hz, 3H)

[0629]

1177	MS (ESI) m/z 716.60 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.14 (bs, 1H), 8.77 (d, J = 4.4 Hz, 2H), 8.66 (s, 1H), 7.77-7.74 (m, 1H), 7.69-7.68 (m, 2H), 7.56 (d, J = 4.8 Hz, 1H), 4.82 (s, 2H), 4.39 (bs, 1H), 3.63 (bs, 4H), 3.30 (bs, 4H), 2.34 (bs, 2H), 2.08 (s, 5H), 1.75 (t, J = 18.0 Hz, 3H), 1.13 (t, J = 6.8 Hz, 3H)	1182	MS (ESI) m/z 730.45 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.76 (d, J = 4.8 Hz 1H), 8.71 (s, 1H), 8.65 (s, 1H), 7.76-7.74 (m, 1H), 7.69-7.67 (m, 2H), 7.55 (d, J = 4.8 Hz, 1H), 6.46 (t, J = 54.4 Hz, 1H), 4.81 (s, 2H), 4.50 (d, J = 6.8 Hz, 2H), 4.44 (d, J = 6.4 Hz, 2H), 4.32-4.28 (m, 1H), 3.16 (s, 3H), 2.91-2.89 (m, 2H), 2.59-2.53 (m, 2H), 2.05 (s, 3H), 1.89-1.86 (m, 4H)
1180	MS (ESI) m/z 713.37 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 9.62 (bs, 1H), 8.79 (s, 1H), 8.75 (d, J = 4.8 Hz, 1H), 8.65 (s, 1H), 7.75 (d, J = 8.0 Hz, 1H), 7.70-7.68 (m, 2H), 7.54 (d, J = 4.8 Hz, 1H), 4.83 (s, 2H), 4.41-4.39 (d, J = 12.8 Hz, 2H), 3.83-3.69 (m, 4H), 3.23-3.14 (m, 4H), 2.43 (m, 2H), 2.33-2.25 (m, 3H), 2.10 (s, 3H), 1.91-1.88 (m, 2H)	1183	MS (ESI) m/z 821.52 [M+1]+; 1H-NMR (400 MHz, DMSO-d6) δ 12.71 (s, 1H), 8.82 (d, J = 4.8 Hz, 1H), 8.75 (d, J = 2.4 Hz, 2H), 7.77 (d, J = 8.8 Hz, 1H), 7.71-7.68 (m, 2H), 7.62 (d, J = 4.8 Hz, 1H), 5.21 (quin, J = 7.6 Hz, 1H), 4.97-4.90 (m, 4H), 4.82 (s, 2H), 4.59 (m, 1H), 3.69-3.49 (m, 4H), 3.11 (bs, 5H), 2.32 (m, 2H), 1.98 (m, 2H), 1.93 (s, 3H), 1.76 (t, J = 19.6 Hz, 3H)
1181 手性	MS (ESI) m/z 696.32 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 9.74 (bs, 1H), 8.78-8.72 (m, 2H), 8.64 (s, 1H), 7.75 (d, J = 8.1 Hz, 1H), 7.70-7.62 (m, 2H), 7.55 (d, J = 4.8 Hz, 1H), 5.35-5.18 (m, 1H), 4.82 (s, 2H), 4.60-4.52 (m, 1H), 4.04-3.98 (m, 1H), 3.60-3.50 (m, 2H), 3.15-2.95 (m, 5H), 2.80-2.45 (m, 4H), 2.20-2.00 (m, 7H)	1184	MS (ESI) m/z 728.48 [M+1] +; 1H-NMR (400 MHz, DMSO-d6) δ 13.11 (bs, 1H), 8.78-8.76 (m, 2H), 8.65 (s, 1H), 7.76 (d, J = 9.2 Hz, 1H), 7.70-7.68 (m, 2H), 7.56 (d, J = 4.8 Hz, 1H), 4.82 (s, 2H), 4.37 (bs, 1H), 3.75- 3.59 (m, 5H), 3.05 (bs, 6H), 2.15 (bs, 4H), 2.10 (s, 3H), 1.16 (t, J = 6.4 Hz, 3H)

[0630]

1185		MS (ESI) m/z 712.32 [M+1]+; 1H-NMR (400 MHz, DMSO-d6) δ 13.09 (bs, 1H), 8.76-8.74 (m, 2H), 8.64 (s, 1H), 7.75 (d, J = 8.0 Hz, 1H), 7.70-7.67 (m, 2H), 7.54 (d, J = 4.8 Hz, 1H), 4.82-4.75 (m, 6H), 4.55 (bs, 1H), 3.91-3.85 (m, 2H), 3.52-3.35 (m, 4H), 3.10 (s, 3H), 2.32-2.21 (m, 2H), 2.09 (bs, 5H)	1188 	MS (ESI) m/z 791.62 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 12.47 (s, 1H), 8.81-8.78 (m, 3H), 7.77 (d, J = 8.40 Hz, 1H), 7.71-7.67 (m, 2H), 7.62 (d, J = 4.80 Hz, 1H), 4.83 (s, 2H), 4.59 (bs, 1H), 3.74-3.54 (m, 6H), 3.08 (s, 3H), 2.98-2.88 (m, 6H), 2.11-2.05 (m, 4H), 2.00 (s, 3H)
1186		MS (ESI) m/z 694.43 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.78 (d, J = 2.8 Hz, 1H), 8.76 (s, 1H), 8.65 (s, 1H), 7.76 (d, J = 9.2 Hz, 1H), 7.69 (d, J = 6.8 Hz, 2H), 7.55 (d, J = 4.8 Hz, 1H), 4.82 (s, 2H), 4.75 (bs, 4H), 4.38 (bs, 2H), 3.61 (d, J = 6.8 Hz, 2H), 3.52 (bs, 2H), 3.16 (bs, 2H), 2.16-2.10 (m, 7H), 1.15 (t, J = 6.8 Hz, 3H)	1189	MS (ESI) m/z 758.56 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.76-8.74 (m, 2H), 8.64 (s, 1H), 7.76 (d, J = 8.4 Hz, 1H), 7.70-7.67 (m, 2H), 7.55 (d, J = 4.8 Hz, 1H), 6.65 (t, J = 74.4 Hz, 1H), 4.82 (s, 2H), 4.57-4.47 (m, 2H), 3.53 (d, J = 11.6 Hz, 2H), 3.23-3.10 (m, 7H), 2.54-2.49 (m, 2H), 2.32-2.28 (m, 1H), 2.16-2.09 (m, 7H), 2.06-1.91 (m, 2H)
1187		MS (ESI) m/z 715.47 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.75 (d, J = 4.8 Hz, 1H), 8.73 (s, 1H), 8.63 (s, 1H), 7.75 (d, J = 8.8, 1H), 7.68-7.68 (m, 2H), 7.63 (d, J = 4.8 Hz, 1H), 6.69 (t, J = 75.2 Hz, 1H), 4.81 (s, 2H), 4.70 (t, J = 5.6 Hz, 1H), 4.04 (d, J = 13.2 Hz, 2H), 3.60 (t, J = 6.4 Hz, 2H), 3.32-3.27 (m, 2H), 3.00 (t, J = 6.8 Hz, 2H), 2.37 (bs, 1H), 2.05 (s, 3H), 1.80 (d, J = 10.4 Hz, 2H), 1.39-1.32 (m, 2H)	1190	MS (ESI) m/z 716.53 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.09 (bs, 1H), 9.32 (bs, 1H), 8.76-8.74 (m, J = 7.8 Hz, 2H), 8.64 (s, 1H) 7.75 (d, J = 8.2 Hz, 1H), 7.71-7.65 (m, 2H), 7.54 (d, J = 4.8 Hz, 1H), 4.82 (s, 2H), 4.60-4.50 (m, 1H), 3.69 (d, J = 10.4 Hz, 2H), 3.30-311 (m, 4H), 3.10 (s, 3H), 2.50-2.32 (合并的, 2H), 2.20-2.05 (m, 7H), 1.70 (t, J = 19.2 Hz, 3H)

[0631]

1191		MS (ESI) m/z 752.52 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.15 (s, 1H), 8.77-8.741 (m, 2H), 8.66 (s, 1H), 7.75 (d, J = 9.2 Hz, 1H), 7.68 (d, J = 6.0 Hz, 2H), 7.55 (d, J = 4.8 Hz, 1H), 6.57 (t, J = 52.0 Hz, 1H), 4.81 (s, 2H), 4.29 (bs, 1H), 3.64 (d, J = 6.8 Hz, 2H), 3.03 (bs, 4H), 2.50 (s, 2H), 2.06 (s, 3H), 1.98-1.84 (m, 4H), 1.13-1.08 (m, 3H)	1196		MS (ESI) m/z 644.27 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 14.39 (bs, 1H), 8.62 (s, 1H), 7.59 (dd, J = 2.48, 8.88 Hz ,1H), 7.40-7.38 (m, 2H), 7.35 (d, J = 8.92 Hz, 1H), 4.63-4.59 (m, 2H), 4.47 (bs, 2H), 4.39 (t, J = 4.64 Hz, 2H), 4.23 (t, J = 4.64 Hz, 3H), 2.82 (bs, 6H), 2.70 (s, 3H), 2.54 (s, 3H), 1.94 (s, 3H)
1194 手性		MS (ESI) m/z 602.22 [M+1]+; 1H-NMR (400 MHz, DMSO-d6) δ 13.62 (bs, 1H), 9.01 (s, 1H), 8.41 (s, 1H), 7.62-7.57 (m, 2H), 7.41 (d, J = 2.4 Hz, 1H), 7.39 (s, 1H), 7.34 (d, J = 8.0 Hz, 1H), 4.38 (s, 2H), 4.24 (s, 2H), 4.19-4.15 (m, 1H), 3.56 (bs, 1H), 2.68-2.62 (m, 5H), 2.32-2.27 (m, 2H), 1.84 (s, 3H)	1198		MS (ESI) m/z 620.15 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.63 (bs, 1H) 8.55 (s, 1H), 7.59 (dd, J = 8.88, 2.62 Hz, 1H), 7.42 (t, J = 6.0 Hz, 2H), 7.35 (d, J = 8.8 Hz, 1H), 4.40 (d, J = 4.4 Hz, 2H), 4.26 (s, 2H), 4.26 (t, J = 4.8 Hz, 2H), 2.98 - 3.04 (m, 2H), 2.55 (d, J = 4.0 Hz, 1H), 1.93 (s, 3H), 1.13-1.36 (m, 7H)
1195		MS (ESI) m/z 720.41 [M+1]+; 1H-NMR (400 MHz, DMSO-d6) δ 8.76 (d, J = 4.56 Hz, 1H), 8.68 (s, 1H), 8.59 (s, 1H), 7.74 (d, J = 8.12 Hz, 1H), 7.67-7.64 (m, 2H), 7.43 (d, J = 4.64 Hz, 1H), 4.80 (s, 2H), 4.29-4.23 (m, 1H), 3.83 (s, 3H), 3.21 (q, J = 10.08 Hz, 2H), 3.10 (s, 3H), 3.04 (d, J = 11.4 Hz, 2H), 2.54 (bs, 2H), 2.03 (s, 3H), 1.98-1.89 (m, 2H), 1.78 (d, J = 10.52 Hz, 2H)	1199		MS (ESI) m/z 629.24 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.69 (bs, 1H), 8.49 (s, 1H), 7.59 (dd, J = 8.88, 2.62 Hz, 1H), 7.36 - 7.43 (m, 3H), 4.41 (t, J = 6.0 Hz, 2H), 4.20 (t, J = 6.0 Hz, 2H), 4.26 (t, J = 4.8 Hz, 2H), 3.34 (s, 6H), 2.96 - 3.01 (m, 2H), 2.40 (d, J = 4.0 Hz, 1H), 1.81 (s, 3H), 1.31 (t, J = 12.8 Hz, 3H), 1.03 - 1.12 (m, 4H)

[0632]

1202	手性		MS (ESI) m/z 656.33 [M+1]+; 1H NMR (400 MHz, DMSO-d6) 14.39 (bs, 1H), 10.23 (bs, 1H), 8.68 (s, 1H), 7.59 (d, J = 8.0, 2.4 Hz, 1H), 7.45-7.38 (m, 2H), 7.39 (d, J = 8.8 Hz, 1H), 4.87 (d, J = 4.8 Hz, 2H), 4.39 (bs, 2H), 4.23 (bs, 2H), 3.91-3.82 (m, 2H), 3.60-3.49 (m, 2H), 3.00-2.88 (m, 2H), 2.75 (s, 3H), 2.70 (s, 3H), 2.53 (s, 3H), 1.86 (s, 3H)	1216		MS (ESI) m/z 641.37 [M+1]+; 1H-NMR (400 MHz, DMSO-d6) δ 13.75 (bs, 1H), 8.84 (s, 1H), 8.31 (s, 1H), 7.60 (dd, J = 2.52, 8.88 Hz, 1H), 7.45 (s, 1H), 7.41 (d, J = 2.48 Hz, 1H), 7.36 (d, J = 8.96 Hz, 1H), 4.39 (t, J = 4.40 Hz, 2H), 4.26 (t, J = 4.44 Hz, 2H), 3.84 (bs, 2H), 3.52 (bs, 2H), 3.31 (s, 3H), 3.01 (q, J = 7.48 Hz, 2H), 2.97 (bs, 1H), 2.91 (bs, 2H), 1.97 (s, 3H), 1.36 (t, J = 7.56 Hz, 3H)
1203			MS (ESI) m/z 656.33 [M+1]+; 1H NMR (400 MHz, DMSO-d6) 14.39 (bs, 1H), 10.23 (bs, 1H), 8.68 (s, 1H), 7.59 (d, J = 8.0, 2.4 Hz, 1H), 7.45-7.38 (m, 2H), 7.39 (d, J = 8.8 Hz, 1H), 4.87 (d, J = 4.8 Hz, 2H), 4.39 (bs, 2H), 4.23 (bs, 2H), 3.91-3.82 (m, 2H), 3.60-3.49 (m, 2H), 3.00-2.88 (m, 2H), 2.75 (s, 3H), 2.70 (s, 3H), 2.53 (s, 3H), 1.86 (s, 3H)	1217		MS (ESI) m/z 706.31[M+1]+; 1H-NMR (400 MHz, DMSO-d6) δ 13.43 (bs, 1H), 8.59 (s, 1H), 8.16 (d, J = 3.6 Hz, 2H), 7.59 (dd, J = 2.0, 7.2 Hz, 1H), 7.54 (bs, 3H), 7.41 (bs, 3H), 4.45 (bs, 4H), 4.27 (bs, 2H), 3.60 (bs, 2H), 3.48 (bs, 2H), 3.33 (bs, 2H), 2.90 (s, 3H), 2.66 (bs, 3H), 2.008 (s, 3H)
1204			MS (ESI) m/z 554.23 [M+1] +; 1H NMR (400 MHz, DMSO-d6) δ 11.14 (s, 1H), 8.99 (s, 1H), 7.37 (s, 1H), 7.31-7.28 (m, 2H), 7.21 (d, J = 2.4 Hz, 1H), 7.14 (d, J = 9.2 Hz, 1H), 6.92 (s, 1H), 6.38 (bs 1H), 4.33 (bs, 2H), 4.30 (bs, 2H), 3.80 (s, 2H), 2.60 (t, J = 3.6 Hz, 1H), 2.18 (s, 3H), 1.21 (d, J = 7.6 Hz, 2H), 1.12 (bs, 2H)	1219		MS (ESI) m/z 656.26 [M+1]+; 1H-NMR (400 MHz, DMSO-d6) δ 8.56 (s, 1H), 8.41 (s, 1H), 7.58 (dd, J = 2.48, 8.92 Hz, 1H), 7.42 (m, 2H), 7.35 (d, J = 8.9 Hz, 1H), 4.39-4.37 (m, 2H), 4.20-4.19 (m, 2H), 3.36-3.33 (m, 1H), 3.13-3.07 (m, 1H), 3.01 (q, J 7.5 Hz, 2H), 2.75-2.72 (m, 2H), 2.32 (s, 3 H), 2.20-2.15 (m, 1H), 1.75 (s, 3H), 1.34 (t, J = 7.5 Hz, 3H), 0.70-0.65 (m, 2H), 0.55-0.70 (m, 2H)

[0633]

1220		MS (ESI) m/z 642.25 [M+1]+; 1H-NMR (400 MHz, DMSO-d6) δ 13.76 (bs, 1H), 9.42 (bs, 2H), 8.62 (s, 1H), 8.41 (s, 1H), 7.60 (dd, J = 2.4, 8.8 Hz, 1H), 7.46 (s, 1H), 7.42 (d, J = 2.4 Hz, 1H), 7.37 (d, J = 8.8 Hz, 1H), 4.44-4.40 (m, 3H), 4.22 (s, 2H), 3.51-3.38 (m, 1H), 3.41-319 (m, 2H), 3.04 (m, 3H), 1.83 (s, 3H), 1.36 (m, 4H), 0.84 (m, 1H)	1231		MS (ESI) m/z 592.13 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.79-8.77 (m, 2H), 8.15 (s, 1H), 7.57 (dd, J = 2.60, 8.84 Hz, 1H), 7.34-7.32 (m, 3H), 4.38 (t, J = 4.60 Hz, 2H), 4.26 (t, J = 4.56 Hz, 2H), 1.77 (s, 3H), 1.63 (s, 9H)
1227		MS (ESI) m/z 638.14 [M+1]+; 1H-NMR (400 MHz, DMSO-d6) δ 13.56 (bs, 1H), 9.65 (bs, 1H), 9.01 (s, 1H), 8.45 (s, 1H), 7.59 (dd, J = 2.4, 8.8 Hz, 1H), 7.42 (d, J = 2.4 Hz, 2H), 7.36-7.32 (m, 2H), 7.28-7.23 (m, 2H), 4.41 (bs, 2H), 4.26 (bs, 2H), 2.70 (s, 3H), 2.16 (s, 3H), 1.38 (s, 3H)	1232		MS (ESI) m/z 615.03[M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.96 (s, 1H), 8.34 (s, 1H), 7.60 (dd, J = 8.8 Hz, 2.4 Hz, 1H), 7.47 (s, 1H), 7.44 (d, J = 2.4 Hz, 1H), 7.35 (d, J = 8.8 Hz, 1H), 4.40-3.79 (m, 10H), 3.05-3.00 (m, 2H), 2.95 (s, 3H). 1.83 (s, 3H), 1.38-1.34 (t, J = 7.6 Hz, 3H)
1229	手性	MS (ESI) m/z 698.43 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 9.59 (bs, 1H), 8.76 (d, J = 4.8 Hz, 1H), 8.72 (s, 1H), 8.65 (s, 1H), 7.75 (d, J = 9.2 Hz, 1H), 7.70-7.65 (m, 2H), 7.55 (d, J = 4.8 Hz, 1H), 4.90-4.79 (m, 4H), 4.40-4.29 (m, 1H), 3.65-3.35 (m, 3H), 3.09 (s, 3H), 2.85-2.80 (m, 3H), 2.18-1.65 (m, 11H)	1233		MS (ESI) m/z 586.32 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.94 (s, 1H), 8.68 (d, J = 4.80 Hz, 1H), 8.51 (s, 1H), 7.74 (d, J = 8.40 Hz, 1H), 7.67-7.63 (m, 3H), 7.40 (d, J = 4.80 Hz, 1H), 4.88 (s, 2H), 2.18 (s, 3H), 1.59 (s, 9H)

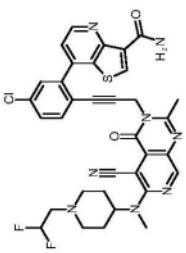
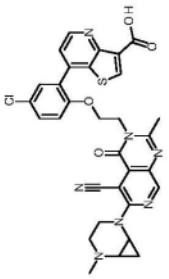
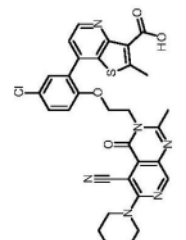
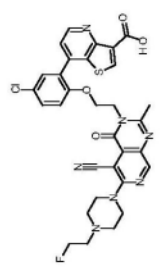
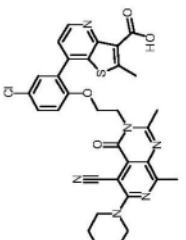
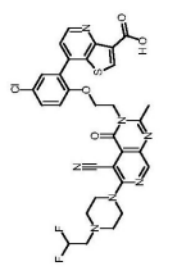
[0634]

1234		MS (ESI) m/z 631.23 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.56 (s, 1H), 8.49 (s, 1H), 7.59 (dd, J = 8.88, 2.50 Hz, 1H), 7.41 (d, J = 2.60 Hz, 1H), 7.40 (s, 1H), 7.35 (d, J = 8.96 Hz, 1H), 4.37 (t, J = 5.00 Hz, 2H), 4.19 (t, J = 5.00 Hz, 2H), 4.11 (bs, 1H), 3.92-3.70 (m, 4H), 3.29 (s, 3H), 2.70 (s, 3H), 2.11-2.04 (m, 2H), 1.81 (s, 3H)	1257		MS (ESI) m/z 572.27 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.86 (s, 1H), 8.65 (d, J = 4.8 Hz, 1H), 7.71 (d, J = 5.2 Hz, 1H), 7.55 (dd, J = 8.8, 2.8 Hz, 1H), 7.44 (d, J = 5.2 Hz, 1H), 7.39 (d, J = 2.4 Hz, 1H), 7.31 (d, J = 9.2 Hz, 1H), 7.21 (d, J = 4.4 Hz, 1H), 4.36–4.23 (m, 6H), 3.60 (d, J = 12.0 Hz, 2H), 3.41 (t, J = 11.6 Hz, 2H), 3.29-3.16 (m, 2H), 2.90 (s, 3H), 1.81 (s, 3H)
1235		MS (ESI) m/z 631.26 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.76 (s, 1H), 8.54 (s, 1H), 8.48 (s, 1H), 7.59 (dd, J =8.8 Hz, 2.4 Hz, 1H) 7.43 (s, 2H), 7.35 (d, J =8.8 Hz, 1H), 5.07 (d, J =2.8 Hz, 1H), 4.41 (bs, 1H), 4.37-4.36 (m, 2H), 4.42 (m, 2H), 3.93-3.87 (m, 2H), 3.79-3.75 (m, 1H), 3.59 (d, J =11.2 Hz, 1H), 3.01 (q, J =7.6 Hz, 2H), 2.04-2.01 (m, 1H), 1.93 (bs, 1H), 1.75 (s, 3H),1.35 (t, J =7.6 Hz, 3H)	1258		MS (ESI) m/z 559.20 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.69 (s, 1H), 8.65 (d, J = 3.8, 1H), 7.75 (d, J = 4.76, 1H), 7.55-7.53 (m, 1H), 7.47 (d, J = 5.0 Hz, 1H), 7.39 (s, 1H), 7.31 (d, J = 8.6 Hz, 1H), 7.21 (d, J = 3.6 Hz, 1H), 5.07 (s, 1H), 4.41 (s, 1H), 4.35 (t, J = 3.6 Hz, 2H), 4.19 (t, J = 5.6 Hz, 2H), 3.89 (t, J = 5.9 Hz, 2H), 3.77-3.73 (m, 1H), 3.58 (d, J = 11.4 Hz, 1H), 2.00-1.98 (m, 1H), 1.93 (bs, 1H), 1.74 (s, 3H)
1236		MS (ESI) m/z 631.23 [M+1]+ ; 1H NMR (400 MHz, DMSO-d6) δ 14.35 (bs, 1H), 8.53 (s, 1H), 7.58 (dd, J = 8.96, 2.36 Hz, 1H), 7.39-7.34 (m, 3H), 4.45-4.36 (m, 3H), 4.21 (t, J = 4.24 Hz, 2H), 3.92-3.86 (m, 2H), 3.78-3.68 (m, 2H), 3.56 (d, J = 12.04 Hz, 1H), 2.70 (s, 3H), 2.53 (s, 3H), 2.22-1.86 (m, 5H)	1264		MS (ESI) m/z 633.24 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.99 (s, 1H), 8.83 (d, J = 4.8 Hz, 1H), 8.37 (s, 1H), 7.61 (d, J = 9.2 Hz, 1H), 7.48 (d, J = 4.8 Hz, 1H), 7.44 (s, 1H), 7.36 (d, J = 8.8 Hz, 1H), 4.41 (t, J = 5.2 Hz, 2H), 4.27 (t, J = 4.0 Hz, 2H), 3.52 (bs, 6H), 3.77-3.25 (m, 2H), 2.92 (d, J = 3.2 Hz, 3H), 1.82 (s , 3H)

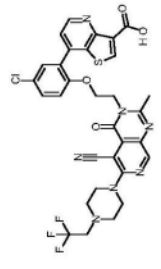
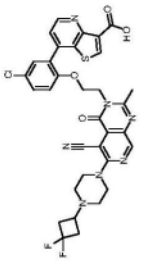
[0635]

1265		1273	
MS (ESI) m/z 642.16 [M+1]+; 1H-NMR (400 MHz, DMSO-d6) δ 9.54 (s, 1H), 8.80 (d, J = 4.8 Hz,1H), 8.55 (s, 1H), 7.57 (dd, J = 2.4, 8.8 Hz ,1H), 7.45 (d, J = 4.8 Hz, 1H), 7.40-7.36 (m, 2H), 4.55 (s, 2H), 4.48 (d, J = 14 Hz, 4H), 4.40 (s, 2H), 4.22 (d, J = 14.4 Hz, 4H), 2.85 (d, J = 4 Hz, 3H), 2.60 (s, 3H), 1.86 (s, 3H)		MS (ESI) m/z 624.30 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.00 (bs, 1H), 8.76 (d, J = 4.80 Hz, 1H), 8.66 (s, 1H), 7.76-7.64 (m, 3H), 7.53 (d, J = 4.80 Hz, 1H), 4.82 (s, 2H), 4.38-4.35 (m, 2H), 3.63-3.60 (m, 2H), 3.48-3.25 (m, 4H), 2.91 (s, 3H), 2.73 (s, 3H), 2.14 (s, 3H)	
1266		1274	
MS (ESI) m/z 629.0 [M+1]+; 1H-NMR (400 MHz, DMSO-d6) δ 8.80 (d, J = 4.8 Hz, 1H), 8.55 (s, 1H), 8.49 (bs, 2H), 7.57 (dd, J = 2.4, 8.8 Hz ,1H), 7.45 (d, J = 4.8 Hz, 1H), 7.40-7.36 (m, 2H), 4.52 (s, 4H), 4.39 (d, J = 4.8 Hz, 2H), 4.22 (d, J = 5.2 Hz, 6H), 2.60 (s, 3H), 1.85 (s, 3H)		MS (ESI) m/z 680.33 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.81 (d, J = 4.72 Hz, 1H), 8.52 (s, 1H), 7.59 (dd, J = 8.88, 2.44 Hz, 1H), 7.44 (d, J = 4.68, 1H), 7.40 (d, J = 2.4 Hz, 1H), 7.36 (d J = 9.0 Hz, 1H), 6.35-6.05 (m, 1H), 4.40 (t, J = 4.48 Hz, 2H), 4.20 (t, J = 4.72 Hz, 2H), 3.64 (s, 4H), 2.87-2.878 (m, 2H), 2.71 (s, 4H), 2.63 (s, 3H), 1.78 (s, 3H)	
1268		1279	
MS (ESI) m/z 678.28 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 9.82 (bs, 1H), 8.74 (d, J = 4.8 Hz, 1H), 8.48 (s, 1H), 8.05 (d, J = 8.4 Hz, 2H), 7.76 (s, 1H), 7.56 (dd, J = 8.8, 2.4 Hz, 1H), 7.41 (d, J = 2.8 Hz, 1H), 7.34 (d, J = 8.9 Hz, 1H), 7.28 (d, J = 4.4 Hz, 1H), 7.10 (d, J = 8.8 Hz, 2H), 4.43-4.36 (m, 2H), 4.27-4.17 (m, 4H), 3.86 (s, 3H), 3.62-3.53 (m, 2H), 3.41-3.29 (m, 2H), 3.21-3.10 (m, 2H), 2.90 (s, 3H), 1.78 (s, 3H)		MS (ESI) m/z 622.22 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 9.01 (s, 1H), 8.82 (d, J = 4.8 Hz, 1H), 8.39 (s, 1H), 7.59 (dd, J = 8.8, 2.4 Hz, 1H), 7.48 (d, J = 4.8 Hz, 1H), 7.42 (d, J = 2.4 Hz, 1H), 7.35 (d, J = 8.8 Hz, 1H), 4.45-4.36 (m, 2H), 4.30-4.20 (m, 2H), 4.15-4.00 (m, 1H), 2.70-2.50 (m, 2H), 2.44-2.20 (m, 3H), 2.14-2.01 (m, 1H), 1.84 (s, 3H)	

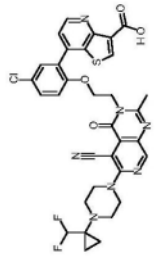
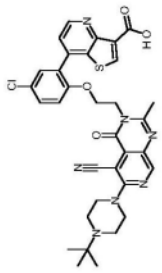
[0636]

1281		MS (ESI) m/z 687.47 [M+1]+; 1H-NMR (400 MHz, DMSO-d6) δ 10.05 (bs, 1H), 8.87 (d, J = 3.2 Hz, 1H), 8.74 (s, 1H), 8.72 (d, J = 4.8 Hz, 1H), 8.47 (s, 1H), 7.75 (d, J = 8.0 Hz, 1H), 7.69 (d, J = 2.0 Hz, 2H), 7.66 (s, 1H), 7.49 (d, J = 4.4 Hz, 1H), 6.53 (tt, J = 5.2, 51.2 Hz, 1H), 4.82 (s, 2H), 4.49 (bs, 1H), 3.64 (bs, 4H), 3.38 (bs, 2H), 3.16 (s, 3H), 2.17 (bs, 2H), 2.04 (bs, 5H)	1301		MS (ESI) m/z 628.33 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 10.82 (bs, 1H), 8.83 (d, J = 4.8 Hz, 1H), 8.67 (s, 1H), 8.46 (s, 1H), 7.60 (dd, J = 8.8, 2.4 Hz, 1H), 7.48 (d, J = 4.8 Hz, 1H), 7.43 (d, J = 2.8 Hz, 1H), 7.37 (d, J = 8.8 Hz, 1H), 4.48 - 4.40 (m, 3H), 4.29-4.19 (m, 2H), 3.45-3.19 (m, 3H), 3.10-2.89 (m, 5H), 1.80 (s, 3H), 1.48-1.27 (m, 2H)
1282		MS (ESI) m/z 630.28 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 14.09 (bs, 1H), 8.77 (d, J = 4.8 Hz, 1H), 8.61 (s, 1H), 7.59 (dd, J = 8.8, 2.4 Hz, 1H), 7.48 (d, J = 4.8 Hz, 1H), 7.40 (d, J = 2.4 Hz, 1H), 7.35 (d, J = 9.2 Hz, 1H), 4.39 (s, 2H), 4.21 (s, 2H), 3.64 (s, 4H), 2.55-2.35 (m, 7H), 2.23 (s, 3H), 1.83 (s, 3H)	1302		MS (ESI) m/z 648.15 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 10.15 (bs, 1H), 8.83 (d, J = 4.8 Hz, 1H), 8.70 (s, 1H), 8.43 (s, 1H), 7.57 (dd, J = 2.4, 8.8 Hz , 1H), 7.47 (d, J = 4.8 Hz, 1H), 7.41-7.36 (m, 2H), 4.95 (s, 1H), 4.84 (s, 1H), 4.39 (d, J = 4.4 Hz, 2H), 4.30 (d, J = 7.6 Hz, 2H), 4.23 (s, 2H), 3.83-3.59 (m, 4H), 3.53-3.34 (m, 4H), 1.83 (s, 3H)
1297		MS (ESI) m/z 644.30 [M+1]+; 1 H NMR (400 MHz, DMSO-d6) δ 13.46 (bs, 1H), 8.66 (d, J = 4.8 Hz, 1H), 7.55 (dd, J = 8.8, 2.4 Hz, 1H), 7.37-7.28 (m, 3H), 4.42-4.34 (m, 2H), 4.21 (s, 2H), 3.63 (bs, 4H), 2.64 (s, 3H), 2.49-2.35 (m, 7H), 2.22 (s, 3H), 1.84 (s, 3H)	1303		MS (ESI) m/z 666.24 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.83 (d, J = 4.8 Hz, 1H), 8.68 (s, 1H), 8.46 (s, 1H), 7.60 (dd, J = 8.8 Hz, 2.4 Hz, 1H), 7.48 (d, J = 4.8 Hz, 1H), 7.42 (d, J = 2.4 Hz, 1H), 7.37-7.35 (m, 1H), 6.46 (t, J = 54.8 Hz, 1H), 4.41-4.38 (m, 2H), 4.28-4.22 (m, 2H), 3.87-3.83 (m, 4H), 3.38-3.32 (m, 2H), 3.24-3.11 (m, 4H), 1.80 (s, 3H)

[0637]

1304		MS (ESI) m/z 684.26 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 11.77 (bs, 1H), 8.81 (d, J = 4.8 Hz, 1H), 8.66 (s, 1H), 8.40 (s, 1H), 7.58 (dd, J = 9.2, 6.8 Hz, 1H), 7.45-7.40 (m, 2H), 7.34 (d, J = 8.8 Hz, 1H), 4.37 (s, 2H), 4.20 (s, 2H), 3.65 (s, 4H), 3.35-3.20 (m, 2H), 2.81 (s, 4H), 1.75 (s, 3H)	1307		MS (ESI) m/z 692.28[M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.31 (bs, 1H), 8.82 (d, J = 4.8 Hz, 1H), 8.68 (s, 1H), 8.43 (s, 1H), 7.59 (dd, J = 2.40, 8.8 Hz, 1H), 7.46 (d, J = 4.4 Hz, 1H), 7.41 (d, J = 2.0 Hz, 1H), 7.36 (d, J = 8.8 Hz, 1H), 4.39 (s, 2H), 4.22 (s, 2H), 3.76 (m, 4H), 3.19-2.93 (m, 8H), 2.32 (m, 1H), 1.80 (s, 3H)
1305		MS (ESI) m/z 666 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.82 (d, J = 4.8 Hz , 1H), 8.70 (s, 1H), 8.43 (s, 1H), 7.61 (dd, J = 2.4, 8.8 Hz, 1H), 7.47 (d, J = 4.8 Hz, 1H), 7.42 (d, J = 2.8 Hz, 1H), 7.37 (d, J = 8.8 Hz, 1H), 6.73-6.46 (m, 1H), 4.39 (s, 2H), 4.34 (s, 1H), 4.23 (s, 2H), 4.18 (s, 1H), 3.56-3.15 (m, 5H), 2.83 (s, 3H), 1.82 (s, 3H)	1308		MS (ESI) m/z 698.28 [M+1] +; 1H NMR (400 MHz, DMSO-d6) δ 13.33 (bs, 1H), 8.82 (d, J = 4.76 Hz, 1H), 8.69 (s, 1H), 8.43 (s, 1H), 7.59 (dd, J = 2.4, 8.8 Hz, 1H), 7.46 (d, J = 4.7 Hz, 1H), 7.41 (d, J = 2.5 Hz, 1H), 7.35 (d, J = 8.9 Hz, 1H) , 4.39 (t, J = 4.8 Hz, 2H), 4.22 (t, J = 4.4 Hz, 2H), 3.38 (bs, 8H), 2.82 (s, 4H), 1.81 (s, 3H)
1306		MS (ESI) m/z 642.35 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.43 (bs, 1H), 8.83 (d, J = 4.8 Hz, 1H), 8.70 (s, 1H), 8.44 (s, 1H), 7.61 (dd, J = 8.8 Hz, J = 2.4 Hz, 1H), 7.48 (d, J = 4.8 Hz, 1H), 7.41-7.38 (m, 2H), 4.41-4.40 (m, 4H), 4.31 (t, J = 2.4 Hz, 2H), 3.47 (bs, 6H), 3.01 (bs, 1H), 1.85 (s, 3H), 1.00-0.88 (bs, 2H)	1309		MS (ESI) m/z 694.37 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.82 (d, J = 4.8 Hz, 1H), 8.67 (s, 1H), 8.45 (s, 1H), 7.59 (dd, J = 2.4, 8.8 Hz, 1H), 7.47 (d, J = 4.8 Hz, 1H), 7.42 (d, J = 2.0 Hz, 1H), 7.36 (d, J = 9.2 Hz, 1H), 6.22 (m, 1H), 4.39 (s, 2H), 4.21 (s, 2H), 3.72 (m, 4H), 2.96 (s, 4H), 1.79 (s, 3H), 1.23 (s, 6H)

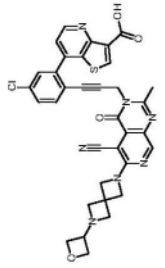
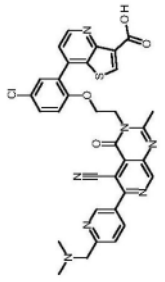
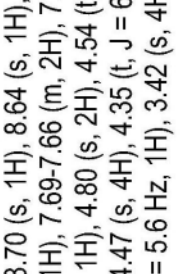
[0638]

1310		MS (ESI) m/z 692.51 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.83 (d, J = 4.8 Hz, 1H), 8.64 (s, 1H), 8.48 (s, 1H), 7.60 (dd, J = 8.8, 2.4 Hz, 1H), 7.49 (d, J = 4.80, 1H), 7.43 (d, J = 2.4 Hz, 1H), 7.35 (d, J = 8.8 Hz, 1H), 6.04 (t, J = 55.6 Hz, 1H), 4.38 (s, 2H), 4.20 (s, 2H), 3.55 (s, 4H), 3.01 (s, 4H), 1.75 (s, 3H), 0.90-078 (m, 4H)	1313 	MS (ESI) m/z 658.37 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 9.43 (bs, 1H), 8.82 (d, J = 4.8 Hz, 1H), 8.70 (s, 1H), 8.41 (s, 1H), 7.60 (dd, J = 8.8 Hz, 2.4 Hz, 1H), 7.47 (d, J = 4.4 Hz, 1H), 7.41-7.36 (m, 2H), 4.42-4.39 (m, 4H), 4.24 (s, 2H), 3.72 (d, J = 12 Hz, 2H), 3.51 (t, J = 12.4 Hz, 2H), 3.19 (d, J = 9.6 Hz, 2H), 1.86 (s, 3H), 1.39 (s, 9H)
1311		MS (ESI) m/z 678.43 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.83 (d, J = 4.8 Hz, 1H), 8.66 (s, 1H), 8.45 (s, 1H) 7.60 (dd, J = 9.2 Hz, 2.8 Hz, 1H), 7.48 (d, J = 4.8 Hz, 1H), 7.42 (d, J = 2.4 Hz, 1H), 7.36 (d, J = 9.2 Hz, 1H), 4.39 (bs, 2H), 4.32 (d, J = 12.8 Hz, 2H), 4.22 (bs, 4H), 3.64 (bs, 1H), 3.38 (bs, 1H), 3.19 (bs, 2H), 2.93 (bs, 2H), 2.15 (bs, 1H), 1.759 (s, 3H)	1314	MS (ESI) m/z 654.34 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.22 (bs, 1H), 8.82 (d, J = 4.7 Hz, 1H), 8.57 (s, 1H), 8.46 (s, 1H), 7.59 (dd, J = 8.8, 2.5 Hz, 1H), 7.45 (d, J = 4.7 Hz, 1H), 7.42 (d, J = 2.4 Hz, 1H), 7.34 (d, J = 9.0 Hz, 1H), 4.41 (s, 4H), 4.36 (s, 2H), 4.18 (s, 2H), 3.49 (bs, 4H), 1.90 (bs, 1H), 1.73 (s, 3H), 0.42-0.20 (m, 4H)
1312		MS (ESI) m/z 680.29 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.22 (bs, 1H), 8.82 (d, J = 4.8 Hz 1H), 8.66 (s, 1H), 8.44 (s, 1H), 7.598 (dd, J = 2.4, 8.8 Hz, 1H), 7.47 (d, J = 4.4 Hz, 1H), 7.42 (d, J = 2.4 Hz, 1H), 7.35 (d, J = 8.8 Hz, 1H), 6.25 (m, 1H), 4.38 (s, 2H), 4.21 (s, 2H), 3.64 (m, 4H), 2.97 (m, 4H), 2.63 (s, 1H), 1.77 (s, 3H), 1.16 (s, 3H)	1315	MS (ESI) m/z 698.12 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.83 (d, J = 4.4 Hz, 1H), 8.65 (s, 1H), 8.47 (s, 1H), 7.60 (dd, J = 8.8, 2.4 Hz, 1H), 7.49 (d, J = 4.8 Hz, 1H), 7.43 (d, J = 2.4 Hz, 1H), 7.35 (d, J = 8.8 Hz, 1H), 4.42-4.34 (m, 2H), 4.20 (s, 2H), 3.63-3.57 (m, 5H), 2.90-2.80 (m, 4H), 1.76 (s, 3H), 1.21 (d, J = 6.8 Hz, 3H)

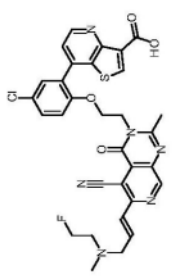
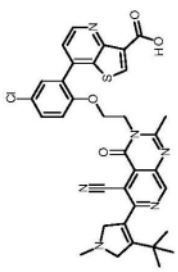
[0639]

1316		MS (ESI) m/z 712.41 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.83 (d, J = 4.8 Hz, 1H), 8.65 (s, 1H), 8.47 (s, 1H), 7.59 (dd, J = 8.8, 2.4 Hz, 1H), 7.48 (d, J = 4.8 Hz, 1H), 7.43 (d, J = 2.4 Hz, 1H), 7.35 (d, J = 8.8 Hz, 1H), 4.41-4.35 (m, 2H), 4.23-4.16 (m, 2H), 3.61 (s, 4H), 2.93 (s, 4H), 1.75 (s, 3H), 1.32 (s, 6H)	1319		MS (ESI) m/z 670.45 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.82 (d, J = 4.76 Hz, 1H), 8.62 (s, 1H), 8.41 (s, 1H), 7.60 (dd, J = 8.9 Hz, 2.4 Hz, 1H), 7.47 (d, J = 4.7 Hz, 1H), 7.42 (d, J = 2.5 Hz, 1H), 7.36 (d, J = 9.0 Hz, 1H), 4.57-4.52 (m, 1H), 4.39 (d, J = 5.6 Hz, 2H), 4.17 (d, J = 5.28, 2H), 3.65 (d, J = 11.44, 2H), 3.95 (bs, 2H), 3.07 (s, 3H), 2.83 (bs, 1H), 2.07 (s, 4H), 1.76 (s, 3H), 0.94-0.85 (m, 4H)
1317		MS (ESI) m/z 676.42 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.23 (bs, 1H), 8.82 (d, J = 4.8 Hz, 1H), 8.64 (s, 1H), 8.45 (s, 1H), 7.59-7.57 (m, 1H), 7.45 (d, J = 4.8 Hz, 1H), 7.42 (d, J = 2.0 Hz, 1H), 7.35 (d, J = 8.8 Hz, 1H), 4.38 (s, 2H), 4.20 (s, 2H), 3.65 (s, 4H), 2.67 (s, 4H), 2.60-2.48 (m, 2H), 1.74 (s, 3H), 1.35 (J = 21.6 Hz, 6H)	1320		MS (ESI) m/z 686.26 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.32 (s, 1H), 8.82 (d, J = 4.8, 1H), 8.61 (s, 1H), 8.40 (s, 1H), 7.59 (dd, J = 2.4, 8.8 Hz, 1H), 7.46 (d, J = 4.8 Hz, 1H), 7.42 (d, J = 2.4 Hz, 1H), 7.36 (d, J = 8.8 Hz, 1H), 4.77-4.76 (m, 4H), 4.55 (bs, 1H), 4.39 (s, 3H), 4.21 (s, 2H), 3.26-3.15 (m, 2H), 3.09-2.97 (m, 5H), 2.21-2.08 (m, 4H), 1.77 (s, 3H)
1318		MS (ESI) m/z 7694.3 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.78 (d, J = 4.8 Hz, 1H), 8.51 (s, 1H), 8.31 (s, 1H), 7.59 (dd, J = 2.4, 8.8 Hz, 1H), 7.45 (d, J = 4.8 Hz, 1H), 7.42 (d, J = 2.4 Hz, 1H), 7.36 (d, J = 9.2 Hz, 1H), 6.54 (t, J = 57.2 Hz, 1H), 4.49 (bs, 2H), 4.39 (bs, 2H), 4.21 (bs, 2H), 3.60 (bs, 4H), 3.08 (t, J = 12.0 Hz, 2H), 3.08 (s, 3H), 2.17 (bs, 1H), 2.03 (bs, 4H) 1.76 (s, 3H)	1321		MS (ESI) m/z 652.12 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.83 (s, 1H), δ 8.74 (d, J = 4.8 Hz, 1H), 8.64 (s, 1H), 7.75 (d, J = 8.4 Hz, 1H), 7.69-7.66 (m, 2H), 7.53 (d, J = 4.4 Hz, 1H), 4.83 (s, 2H), 4.76 (s, 4H), 4.37 (bs, 4H), 4.04 (bs, 1H), 3.34-2.82 (m, 4H), 2.12 (s, 3H)

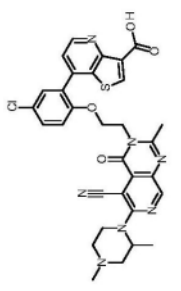
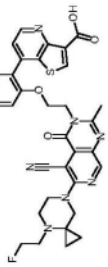
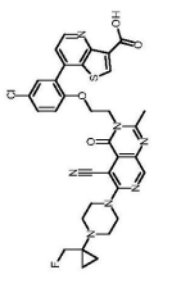
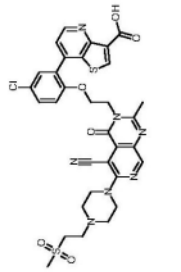
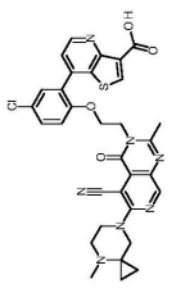
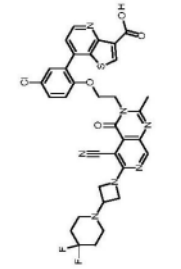
[0640]

1322		MS (ESI) m/z 664.45 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.74 (d, J = 4.8 Hz, 1H), 8.70 (s, 1H), 8.64 (s, 1H), 7.76-7.73 (m, 1H), 7.69-7.66 (m, 2H), 7.52 (d, J = 4.8 Hz, 1H), 4.80 (s, 2H), 4.54 (t, J = 6.4 Hz, 2H), 4.47 (s, 4H), 4.35 (t, J = 6 Hz, 2H), 3.69 (t, J = 5.6 Hz, 1H), 3.42 (s, 4H), 2.0 (s, 3H)	1325		MS (ESI) m/z 652.36 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.23 (bs, 1H), 9.09 (s, 1H), 9.00 (s, 1H), 8.85 (d, J = 4.4 Hz, 1H), 8.38 (s, 1H), 8.31 (d, J = 8.0 Hz, 1H), 7.65 (d, J = 8.0 Hz, 1H), 7.60 (dd, J = 8.8, 2.4 Hz, 1H), 7.47 (d, J = 4.8 Hz, 1H), 7.43 (d, J = 2.4 Hz, 1H), 7.36 (d, J = 8.8 Hz, 1H), 4.42 (s, 2H), 4.28 (s, 2H), 3.66 (s, 2H), 2.26 (s, 6H), 1.83 (s, 3H)
1323		MS (ESI) m/z 630.32 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 9.62 (s, 1H), 8.80 (d, J = 4.8 Hz, 1H), 8.59 (s, 1H), 8.50 (s, 1H), 7.59 (dd, J = 2.4, 8.8 Hz, 1H), 7.45 (d, J = 4.8 Hz, 1H), 7.40 (d, J = 2.4 Hz, 1H), 7.36 (d, J = 9.2 Hz, 1H), 7.19 (s, 1H), 4.41 (t, J = 4.8 Hz, 2H), 4.24 (t, J = 4.8 Hz, 2H), 3.64 (s, 2H), 2.96 (m, 5H), 2.5 (m, 3H), 2.10 (m, 2H), 1.85 (s, 3H)	1326		MS (ESI) m/z 631.39 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.23 (bs, 1H), 8.97 (s, 1H), 8.83 (d, J = 4.8 Hz, 1H), 8.36 (s, 1H), 7.60 (dd, J = 9.2, 2.0 Hz, 1H), 7.47 (d, J = 4.8 Hz, 1H), 7.44 (d, J = 2.4 Hz, 1H), 7.35 (d, J = 8.8 Hz, 1H), 4.81 (d, J = 46.4 Hz, 2H), 4.47-4.38 (m, 4H), 4.26 (s, 2H), 3.65-3.30 (m, 2H), 2.86 (s, 3H), 1.77 (s, 3H)
1324		MS (ESI) m/z 652.29 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 9.17 (s, 1H), 8.85 (d, J = 4.81 Hz, 1H), 8.36 (s, 1H), 7.62-7.59 (m, 2H), 7.47 (d, J = 4.8 Hz, 1H), 7.43 (d, J = 2.8 Hz, 1H), 7.36 (d, J = 8.8 Hz, 1H), 7.06 (bs, 1H), 4.44 (s, 2H), 4.33 (s, 2H), 3.29 (s, 6H), 2.60 (s, 3H), 1.92 (s, 3H)	1327		MS (ESI) m/z 667.38 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.16 (bs, 1H), 8.94 (s, 1H), 8.83 (d, J = 4.8 Hz, 1H), 8.38 (s, 1H), 7.59 (dd, J = 9.2, 2.4 Hz, 1H), 7.47 (d, J = 4.8 Hz, 1H), 7.43 (d, J = 2.4 Hz, 1H), 7.34 (d, J = 8.8 Hz, 1H), 4.39 (s, 2H), 4.25 (s, 2H), 3.88 (s, 2H), 3.37 (q, J = 10.0 Hz, 2H), 2.54 (s, 3H), 1.73 (s, 3H)

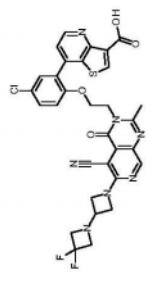
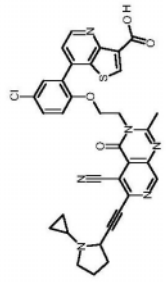
[0641]

1328		MS (ESI) m/z 633.40 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.40 (bs, 1H), 10.08 (bs, 1H), (9.01 (s, 1H), 8.82 (d, J = 4.8 Hz, 1H), 8.36 (s, 1H), 7.60 (dd, J = 8.9, 2.5 Hz, 1H), 7.48 (d, J = 4.7 Hz, 1H), 7.45-7.33 (m, 3H), 7.21-7.18 (m, 1H), 4.88 (d, J = 47.2 Hz, 2H), 4.41 (t, J = 4.9 Hz, 2H), 4.27-4.13 (m, 4H), 3.70-3.55 (m, 合并的, 2H), 2.90 (s, 3H), 1.81 (s, 3H)	1332		MS (ESI) m/z 655.5 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.98 (s, 1H), 8.84 (d, J = 4.8 Hz, 1H), 8.23 (s, 1H), 7.61 (dd, J = 9.2, 2.8 Hz, 1H), 7.46 (d, J = 4.8 Hz, 1H), 7.43 (d, J = 2.4 Hz, 1H), 7.37 (d, J = 9.2 Hz, 1H), 4.42 (bs, 2H), 4.30 (bs, 2H), 2.82 (bs, 2H), 2.72 (s, 6H), 2.61 (bs, 2H) 1.30 (s, 9H)
1329		MS (ESI) m/z 625.37 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.92 (s, 1H), 8.83 (d, J = 4.8 Hz, 1H), 8.34 (s, 1H), 7.59 (dd, J = 8.8, 2.4 Hz, 1H), 7.48 (d, J = 4.4 Hz, 1H), 7.43 (d, J = 2.4 Hz, 1H), 7.35 (d, J = 8.8 Hz, 1H), 4.40 (bs, 2H), 4.25 (bs, 2H), 2.74 (bs, 6H), 1.75 (s, 3H), 1.36 (bs, 4H)	1333		MS (ESI) m/z 676.51 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.33 (bs, 1H), 9.75 (bs, 1H), 8.83 (d, J = 4.8 Hz, 1H), 8.71 (s, 1H), 8.38 (s, 1H), 7.61-7.58 (dd, J = 2.8, 9.2 Hz, 1H), 7.47 (d, J = 4.4 Hz, 1H), 7.42 (d, J = 2.4 Hz, 1H), 7.37 (d, J = 9.2 Hz, 1H), 4.97-4.79 (m, 2H), 4.39 (bs, 2H), 4.22 (bs, 2H), 3.88-3.48 (m, 6H), 1.79 (s, 3H), 1.45 (s, 3H), 1.40 (s, 3H)
1330		MS (ESI) m/z 617.43 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.38 (bs, 1H), 10.15 (bs, 1H), 9.02 (s, 1H), 8.82 (d, J = 4.8 Hz, 1H), 8.34 (s, 1H), 7.60 (dd, J = 2.4, 8.8 Hz, 1H), 7.46 (d, J = 4.4 Hz, 1H), 7.43 (d, J = 2.8 Hz, 1H), 7.35 (d, J = 9.2 Hz, 1H), 5.27 (d, J = 8.0 Hz, 1H), 4.40 (bs, 2H), 4.32-4.23 (m, 2H), 3.94 (t, J = 12.4 Hz, 1H), 3.78 (bs, 2H), 3.49 (bs, 2H), 3.24 (bs, 1H), 2.99 (s, 3H), 1.81 (s, 3H)	1334		MS (ESI) m/z 684.26 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.38 (s, 1H), 8.82 (d, J = 4.8 Hz, 1H), 8.67 (s, 1H), 8.43 (s, 1H), 7.59 (d, J = 7.2 Hz, 1H), 7.47 (d, J = 4.4 Hz, 1H), 7.43 (s, 1H), 7.35 (d, J = 9.2 Hz, 1H), 4.38 (s, 2H), 4.21 (s, 2H), 4.08 (d, J = 11.2 Hz, 1H), 3.82-3.05 (m, 5H), 2.67 (s, 1H), 2.50 (s, 3H), 1.76 (s, 3H)

[0642]

1335		MS (ESI) m/z 630.46[M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 9.85 (s, 1H), 8.85 (d, J = 8.4 Hz, 1H), 8.67 (s, 1H), 8.40 (s, 1H), 7.61 (d, J = 8.8 Hz, 1H), 7.48 (d, J = 4.8 Hz, 1H), 7.41 (m, 2H), 4.74 (bs, 1H), 4.42 (m, 2H), 4.23 (m, 4H), 3.52 (m, 2H), 3.32 (m, 2H). 2.91 (s, 3H), 1.78 (s, 3H), 1.49 (d, J = 6.8 Hz, 3H), 1.04 (d, J = 5.6 Hz, 1H)	1338		MS (ESI) m/z 674.53 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.21 (bs, 1H), 8.83 (d, J = 4.8 Hz, 1H), 8.68 (s, 1H), 8.39 (s, 1H), 7.60 (dd, J = 8.8, 2.0 Hz, 1H), 7.47 (d, J = 4.8 Hz, 1H), 7.43 (d, J = 2.4 Hz, 1H), 7.36 (d, J = 8.8 Hz, 1H), 4.83-4.72 (m, 2H), 4.39 (s, 2H), 4.23 (s, 2H), 3.98-3.53 (m, 8H), 1.77 (s, 3H), 1.03 (bs, 4H)
1336		MS (ESI) m/z 674.50 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.82 (d, J = 4.8 Hz, 1H), 8.67 (s, 1H), 8.45 (s, 1H), 7.60 (dd, J = 9.2, 2.8 Hz, 1H), 7.47 (d, J = 4.8 Hz, 1H), 7.42 (d, J = 2.4 Hz, 1H), 7.36 (d, J = 8.8 Hz, 1H), 4.62 (d, J = 49.6 Hz, 2H), 4.40-4.35 (m, 2H), 4.25-4.15 (m, 2H), 3.75-3.55 (m, 4H), 3.30-3.00 (m, 4H), 1.79 (s, 3H), 1.15-.0.80 (m, 4H)	1339		MS (ESI) m/z 708.26 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.27 (bs, 1H), 8.82 (d, J = 8.0 Hz, 1H), 8.67 (s, 1H), 8.43 (s, 1H), 7.59 (d, J = 6.8 Hz, 1H), 7.46 (d, J = 4.4 Hz, 1H), 7.42 (s, 1H), 7.36 (d, J = 9.2 Hz, 1H), 4.39 (s, 2H), 4.22 (s, 2H), 3.59-3.30 (m, 12H), 3.10 (s, 3H), 1.79 (s, 3H)
1337		MS (ESI) m/z 642.53 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.37 (bs, 1H), 8.82 (d, J = 4.4 Hz, 1H), 8.70 (s, 1H), 8.38 (s, 1H), 7.60 (t, J = 6.8 Hz, 1H), 7.47-7.21 (m, 3H), 4.39 (s, 2H), 4.23 (s, 2H), 4.05 (bs, 2H), 3.93 (bs, 2H), 3.52 (bs, 2H), 2.99 (s, 3H), 1.79 (s, 3H), 1.26-1.07 (m, 4H)	1340		MS (ESI) m/z 692.45 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.83 (d, J = 4.8 Hz, 1H), 8.63 (s, 1H), 8.47 (s, 1H), 7.60 (dd, J = 2.4, 8.8 Hz, 1H), 7.47 (d, J = 4.8 Hz , 1H), 7.43 (d, J = 2.4 Hz, 1H), 7.36 (d, J = 8.8 Hz, 1H), 4.57 (t, J = 8.0 Hz, 2H), 4.38 (bs, 4H), 4.20 (bs, 2H), 3.94 (bs, 1H), 3.07 (bs, 4H), 2.20 (bs, 4H), 1.76 (s, 3H)

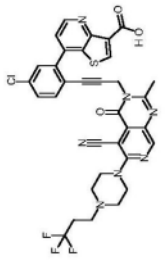
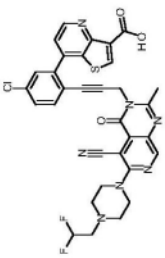
[0643]

1341		MS (ESI) m/z 664.51 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.83 (d, J = 4.8 Hz, 1H), 8.58 (s, 1H), 8.47 (s, 1H), 8.48 (s, 1H), 7.59 (dd, J = 2.4, 8.8 Hz , 1H), 7.47 (d, J = 4.8 Hz, 1H), 7.35 (d, J = 9.2 Hz, 1H), 4.47-4.42 (m, 2H), 4.37 (bs, 2H), 4.18 (bs, 2H), 4.13-4.10 (m, 2H), 3.95-3.74 (m, 5H), 1.74 (s, 3H)	1344		MS (ESI) m/z 651.48 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.96 (s, 1H), 8.83 (d, J = 4.4 Hz, 1H), 8.36 (s, 1H), 7.60 (dd, J = 8.8, 2.4 Hz, 1H), 7.48 (d, J = 4.4 Hz, 1H), 7.44 (d, J = 2.4 Hz, 1H), 7.35 (d, J = 9.2 Hz, 1H), 4.80-4.60 (m, 1H), 4.40 (s, 2H), 4.25 (s, 2H), 3.55-3.30 (m, 合并的, 2H), 2.50-2.30 (m, 1H), 2.22-1.91 (m, 4H), 1.75 (s, 3H), 1.04-0.61 (m, 4H)
1342		MS (ESI) m/z 655.35 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.27 (bs, 1H), 8.83 (d, J = 4.8 Hz, 1H), 8.67 (s, 1H), 8.43 (s, 1H), 7.60 (dd, J = 8.8, 2.4 Hz, 1H), 7.46 (d, J = 4.0 Hz, 1H), 7.43 (d, J = 2.4 Hz, 1H), 7.35 (d, J = 9.2 Hz, 1H), 4.43-4.35 (m, 2H), 4.25-4.15 (m, 2H), 4.13- 4.00 (m, 2H), 3.16- 3.10 (m, 1H), 2.97- 2.83 (m, 4H), 2.48-2.33 (m, 2H), 2.30 (s, 3H), 1.74 (s, 3H)	1345		MS (ESI) m/z 635.42 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.40 (bs. 1H), 9.67 (bs, 1H), 8.96 (s, 1H), 8.82 (d, J = 4.7 Hz, 1H), 8.32 (s, 1H), 7.60 (dd, J = 8.92, 2.36 Hz, 1H), 7.47 (d, J = 4.7 Hz, 1H), 7.43 (d, J = 2.4 Hz, 1H), 7.36 (d, J = 8.9 Hz, 1H), 4.92-4.76 (m, 1H), 4.40 (t, J = 4.4 Hz, 2H), 4.26 (t, J = 5.0 Hz, 2H), 3.62-3.52 (m, 2H), 3.40-3.20 (m, 2H), 3.18 (t, J = 7.24 Hz, 2H), 2.88 (s, 3H), 2.31-2.17 (m, 2H), 1.82 (s, 3H)
1343		MS (ESI) m/z 683.44 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.83 (d, J = 4.8 Hz, 1H), 8.69 (s, 1H), 8.43 (s, 1H), 7.60 (dd, J = 8.8, 2.4 Hz, 1H), 7.48 (d, J = 4.8 Hz, 1H), 7.42 (d, J = 2.4 Hz, 1H), 7.37 (d, J = 8.8 Hz, 1H), 4.40 (s, 2H), 4.23 (s, 2H), 3.95 (s, 2H), 3.57-3.40 (m, 4H), 3.30-3.15 (m, 4H), 1.83 (s, 3H), 1.46 (s, 6H)	1346		MS (ESI) m/z 639.42 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.97 (s, 1H), 8.83 (d, J = 4.7 Hz, 1H), 8.37 (s, 1H), 7.59 (dd, J = 8.9, 2.4 Hz, 1H), 7.47 (d, J = 4.7 Hz, 1H), 7.44 (d, J = 2.4 Hz, 1H), 7.34 (d, J = 9.0 Hz, 1H), 4.65-4.35 (m, 4H), 4.25 (t, J = 3.8 Hz, 2H), 2.85 (bs, 3H), 1.75 (s, 3H), 1.36 (s, 3H), 1.03 (bs, 2H), 0.72 (bs, 2H)

[0644]

1347		MS (ESI) m/z 624.49 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.08 (bs, 1H), 8.86 (s, 1H), 8.79 (d, J = 4.4 Hz, 1H), 8.66 (s, 1H), 7.88 (d, J = 8.4 Hz, 1H), 7.61 (d, J = 8.8 Hz, 1H), 7.52 (s, 1H), 7.42 (d, J = 4.8 Hz, 1H), 6.52-6.38 (m, 1H), 5.89 (d, J = 16.0 Hz, 1H), 4.68 (d, J = 4.0 Hz, 2H), 4.39 (d, J = 13.2 Hz, 1H), 3.11 (t, J = 12.4 Hz, 2H), 2.82-2.65 (m, 1H), 2.40-2.10 (m, 8H), 0.72-0.45 (m, 2H)	1350 手性		MS (ESI) m/z 694.59 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.83 (d, J = 4.8 Hz, 1H), 8.65 (s, 1H), 8.41 (s, 1H), 7.59 (dd, J = 2.0, 8.8 Hz, 1H), 7.48 (d, J = 4.8 Hz, 1H), 7.42 (d, J = 2.0 Hz, 1H), 7.36 (d, J = 8.8 Hz, 1H), 6.15 (bs, 1H), 4.39 (s, 2H), 4.21-4.16 (m, 2H), 4.14 (bs, 2H), 3.01 (bs, 6H), 1.77 (s, 3H), 1.21 (s, 6H)
1348		MS (ESI) m/z 628.18 [M+1]+; ; 1H NMR (400 MHz, DMSO-d6), δ 8.81 (d, J = 4.8 Hz, 1H), δ 8.62 (s, 1H), 8.43 (s, 1H), 7.59 (dd, J = 8.8 Hz, 2.4 Hz, 1H), 7.45-7.42 (m, 2H), 7.35 (d, J = 8.8 Hz, 1H), 4.78 (bs, 1H), 4.37 (t, J = 5.1 Hz, 2H), 4.27 (t, J = 4.5 Hz, 2H), 3.45-3.43 (m, 2H), 3.32-2.8 (m, 4H), 2.75-2.56 (m, 2H), 1.93-1.90 (m, 2H), 1.74 (s, 3H)	1351		MS (ESI) m/z 658.47 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.83 (d, J = 2.36 Hz, 1H), 8.74 (s, 1H), 8.40 (s, 1H), 7.60 (dd, J = 8.9, 2.5 Hz, 1H), 7.47 (d, J = 4.7 Hz, 1H), 7.42 (d, J = 2.5 Hz, 2H), 7.37 (d, J = 9.0 Hz, 2H), 4.66 (d, J = 7.5 Hz, 2H), 4.40 (s, 2H), 4.24 (s, 2H), 4.14 (bs, 4H), 3.40 (s, 2H), 3.06 (s, 3H), 1.82 (s, 3H)
1349		MS (ESI) m/z 715.66 [M+1]+; ; 1H NMR (400 MHz, DMSO-d6) δ 8.89 (s, 1H), 8.82 (d, J = 4.8 Hz, 1H), 8.41 (s, 1H), 7.58 (dd, J = 8.8 Hz, 2.8 Hz, 1H), 7.47 (d, J = 4.8 Hz, 1H), 7.43 (d, J = 2.4 Hz, 1H), 7.34 (d, J = 8.8 Hz, 1H), 4.38 (s, 2H), 4.22 (s, 2H), 4.05 (s, 1H), 3.40-3.32 (m, 2H), 2.93 (s, 2H), 2.66-2.61 (m, 2H), 2.11-2.09 (m, 2H), 1.74 (s, 5H)	1352		MS (ESI) m/z 652.12 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.83 (s, 1H), δ 8.74 (d, J = 4.8 Hz, 1H), 8.64 (s, 1H), 7.75 (d, J = 8.4 Hz, 1H), 7.69-7.66 (m, 2H), 7.53 (d, J = 4.4 Hz, 1H), 4.83 (s, 2H), 4.76 (s, 4H), 4.37 (bs, 4H), 4.04 (bs, 1H), 3.34-2.82 (m, 4H), 2.12 (s, 3H)

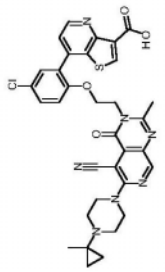
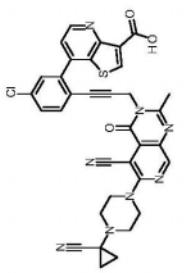
[0645]

1353		MS (ESI) m/z 692.45 [M+1] +; 1H NMR (400 MHz, DMSO-d6) δ 13.05 (bs, 1H), 8.83 (s, 1H), 8.75 (d, J = 4.6 Hz, 1H), 8.64 (s, 1H), 7.75 (d, J = 8.2 Hz, 1H), 7.69 (s, 1H), 7.66 (s, 1H), 7.52 (d, J = 4.6 Hz, 1H), 4.83 (s, 2H), 4.31 (bs, 1H), 3.43 (bs, 7H), 2.85 (s, 4H), 2.11 (s, 3H)	1356		MS (ESI) m/z 660.27 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.05 (bs, 1H), 8.79 (s, 1H), 8.75 (d, J = 4.6 Hz, 1H), 8.65 (s, 1H), 7.75 (d, J = 8.1 Hz, 1H), 7.68 (m, 2H), 7.53 (d, J = 4.6 Hz, 1H), 6.34 (m, 1H), 4.82 (s, 2H), 3.76-2.66 (m, 10H), 2.09 (s, 1H)
1354		MS (ESI) m/z 636.25 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.18 (bs, 1H), 8.84 (s, 1H), 8.75 (d, J = 4.8 Hz, 1H), 8.65 (s, 1H), 7.75 (d, J = 8.4 Hz, 1H), 7.70-7.65 (m, 2H), 7.53 (d, J = 4.8 Hz, 1H), 4.84 (s, 2H), 4.38 (m, 2H), 3.79 (m, 2H,), 3.49 (m, 4H), 3.03 (m, 1H), 2.14 (s, 3H), 0.93 (m, 4H)	1357		MS (ESI) m/z 658.37 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.83 (d, J = 4.8 Hz, 1H), 8.61 (s, 1H), 8.46 (s, 1H), 7.60 (dd, J = 8.8, 2.4 Hz, 1H), 7.47 (d, J = 4.8 Hz, 1H), 7.43 (d, J = 2.6 Hz, 1H), 7.36 (d, J = 9.0 Hz, 1H), 6.33 (t, J = 53.6 Hz, 1H), 5.09 (s, 1H), 4.38 (t, J = 4.3 Hz, 2H), 4.21 (t, J = 5.7, 2H), 4.15-3.80 (m, 7H), 2.21 (bs, 2H), 1.76 (s, 3H)
1355		MS (ESI) m/z 686.0 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.03 (s, 1H), 8.83 (s, 1H), 8.75 (d, J = 4.8 Hz, 1H), 8.64 (s, 1H), 7.75 (d, J = 8.4 Hz, 1H), 7.70-7.66 (m, 1H), 7.53 (d, J = 4.8 Hz, 1H), 4.72 (s, 2H), 3.80 (bs, 4H), 3.39 (bs, 4H), 3.05-3.02 (m, 5H), 2.16 (s, 3H)	1358		MS (ESI) m/z 716.50 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.83 (d, J = 4.8 Hz, 1H), 8.68 (s, 1H), 8.45 (s, 1H), 7.60 (dd, J = 8.8 Hz, 2.4 Hz, 1H), 7.48 (d, J = 4.8 Hz, 1H), 7.37-7.33 (m, 2H), 5.77 (d, J = 46 Hz, 1H), 4.39 (s, 2H), 4.22 (s, 2H), 3.24 (bs, 2H), 3.29-3.15 (m, 8H), 1.79 (s, 3H)

[0646]

1359		MS (ESI) m/z 766.56 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.83 (d, J = 4 Hz, 1H), 8.66 (s, 1H), 8.46 (s, 1H), 7.60 (dd, J = 2.4, 8.8 Hz, 1H), 7.48 (d, J = 4.8 Hz, 1H), 7.43 (d, J = 2.4 Hz, 1H), 7.36 (d, J = 8.8 Hz, 1H), 4.39 (bs, 2H), 4.21 (bs, 2H), 3.68 (bs, 4H), 2.96 (bs, 2H), 2.78 (bs, 4H), 2.46 (s, 1H) 1.77 (s, 3H)
1360		MS (ESI) m/z 726.51 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 9.53 (bs, 1H), 8.83 (d, J = 4.8 Hz, 1H), 8.61 (s, 1H), 8.40 (s, 1H), 7.59 (dd, J = 8.8 Hz, 2.4 Hz, 1H), 7.47 (d, J = 4.4 Hz, 1H), 7.42 (d, J = 2.4 Hz, 1H), 7.36 (d, J = 8.8 Hz, 1H), 4.49 (bs, 1H), 4.52 (bs, 1H), 4.21 (bs, 2H), 3.69 (d, J = 10.4 Hz, 2H), 3.50 (bs, 2H), 3.40 (bs, 2H), 3.21 (s, 3H), 2.89-2.85 (m, 2H), 2.11 (bs, 4H), 1.78 (s, 3H)
1361		MS (ESI) m/z 724.51 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.82 (d, J = 4.8 Hz, 1H), 8.64 (s, 1H), 8.46 (s, 1H), 7.60 (dd, J = 8.8, 2.8 Hz, 1H), 7.48 (d, J = 4.8 Hz, 1H), 7.42 (d, J = 2.4 Hz, 1H), 7.35 (d, J = 8.8 Hz, 1H), 4.37 (s, 2H), 4.20 (s, 2H), 3.63 (bs, 4H), 2.84 (bs, 4H), 2.70-2.50 (m, 2H), 1.77 (s, 3H), 0.84-0.74 (m, 4H)
1362		MS (ESI) m/z 755.45 [M+1] +; 1H NMR (400 MHz, DMSO- d6) δ 12.44 (s, 1H), 8.83-8.79 (m, 3H), 7.76 (d, J = 8.4 Hz, 1H), 7.71- 7.67 (m, 2H), 7.61 (d, J = 4.8 Hz, 1H), 4.82 (s, 2H), 3.75 - 3.60 (m, 4H), 3.56 (s, 3H), 3.31 (q, J = 10.0 Hz, 2H), 2.90 – 2.80 (m, 4H), 2.00 (s, 3H)
1363		MS (ESI) m/z 668.48 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.21 (bs, 1H), 9.37 (bs, 1H), 8.82 (d, J = 4.8 Hz, 1H), 8.67 (s, 1H), 8.37 (s, 1H), 7.59 (dd, J = 8.8, 2.4 Hz, 1H), 7.47 (d, J = 4.8 Hz, 1H), 7.41 (d, J = 2.0 Hz, 1H), 7.36 (d, J = 9.2 Hz, 1H), 4.38 (s, 2H), 4.21 (s, 2H), 3.80-3.50 (m, 2H), 3.20-2.90 (m, 2H), 2.61 (s, 3H), 1.78 (s, 3H), 1.40-0.80 (m, 8H)
1364		MS (ESI) m/z 642.35 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.83 (d, J = 4.8 Hz, 1H), 8.68 (s, 1H), 8.45 (s, 1H), 7.60 (dd, J = 8.8, 2.4 Hz, 1H), 7.47 (d, J = 4.8 Hz, 1H), 7.42 (d, J = 2.4 Hz, 1H), 7.36 (d, J = 8.8 Hz, 1H), 4.87-4.75 (m, 4H), 4.39 (bs, 2H), 4.22 (bs, 2H), 3.56-3.14 (m, 8H), 2.41 (s, 1H), 1.78 (s, 3H)

[0647]

1365		MS (ESI) m/z 656.52 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 9.30 (bs, 1H), 8.83 (d, J = 4.8 Hz, 1H), 8.69 (s, 1H), 8.41 (s, 1H), 7.62-7.59 (dd, J = 2.4, 8.8 Hz, 1H), 7.48 (d, J = 4.8 Hz, 1H), 7.41-7.36 (m, 2H), 4.40 (bs, 4H), 4.24 (bs, 2H), 3.48 (bs, 6H), 1.85 (s, 3H), 1.39 (s, 3H), 1.19 (bs, 2H), 0.82 (bs, 2H)	1368		MS (ESI) m/z 661.35 [M+1]+; ; 1H NMR (400 MHz, DMSO-d6) δ 8.78 (s, 1H), 8.77 (d, J = 3.2 Hz, 1H), 8.67 (s, 1H), 7.76 (d, J = 8.8 Hz, 1H), 7.71-7.65 (m, 2H), 7.55 (d, J = 4.8 Hz, 1H), 4.82 (s, 2H), 3.67 (s, 4H), 2.82 (s, 4H) 2.07 (s, 3H), 1.32-1.27 (m, 2H), 1.17-1.09 (m, 2H)
1366		MS (ESI) m/z 686.46 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.79-8.73 (m, 2H), 8.66 (s, 1H), 7.75 (d, J = 9.2 Hz, 1H), 7.72-7.66 (m, 2H), 7.55 (d, J = 4.8 Hz, 1H), 6.04 (t, J = 55.6 Hz, 1H), 4.82 (s, 2H), 3.59 (s, 4H), 3.02 (s, 4H), 2.06 (s, 3H), 0.90-0.78 (m, 4H)	1369		MS (ESI) m/z 682.51 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.81 (d, J = 4.4 Hz, 1H), 8.60 (s, 1H), 8.47 (s, 1H), 7.60 (dd, J = 9.2, 2.4 Hz, 1H), 7.46 (d, J = 4.4 Hz, 1H), 7.42 (d, J = 2.4 Hz, 1H), 7.35 (d, J = 9.2 Hz, 1H), 4.60 (s, 2H), 4.52 (s, 2H), 4.43-4.38 (m, 4H), 4.33-4.28 (m, 2H), 4.20 (bs, 2H), 3.79 (bs, 1H), 1.89 (t, J = 6.8 Hz, 2H), 1.80 (s, 3H), 1.67-1.58 (m, 4H), 1.47 (t, J = 6.4 Hz, 2H)
1367		MS (ESI) m/z 677.49 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.05 (bs, 1H), 9.99 (bs, 1H), 8.82 (s, 1H), 8.75 (d, J = 4.8 Hz, 1H), 8.65 (s, 1H), 7.75 (d, J = 8.4 Hz, 1H), 7.71-7.66 (m, 2H), 7.54 (d, J = 4.8 Hz, 1H), 4.83 (s, 2H), 4.45 (bs, 2H), 3.62 (bs, 4H), 3.27 (bs, 4H), 2.13 (s, 3H), 1.46 (bs, 6H)	1370		MS (ESI) m/z 684.53 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.83 (d, J = 4.9 Hz, 1H), 8.61 (s, 1H), 8.40 (s, 1H), 7.60 (dd, J = 2.4, 8.8 Hz, 1H), 7.46 (d, J = 4.8 Hz, 1H), 7.42 (d, J = 2.4 Hz, 1H), 7.36 (d, J = 8.8 Hz, 1H), 4.51 (bs, 1H), 4.39 (s, 2H), 4.21 (s, 2H), 3.68 (d, J = 10.4 Hz, 2H), 3.21-3.16 (m, 2H), 3.09 (s, 3H), 3.01 (t, J = 5.6 Hz, 2H), 2.21-2.15 (m, 2H), 2.12-2.06 (m, 2H), 1.77 (s, 3H), 1.10 (bs, 1H), 0.67 (d, J = 7.2 Hz, 2H), 0.44-0.38 (m, 2H)

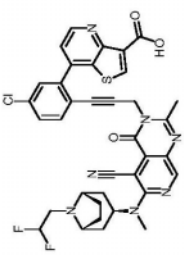
[0648]

1371	MS (ESI) m/z 654.44 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 10.48 (bs, 1H), 8.82 (d, J = 4.8 Hz, 1H), 8.64 (s, 1H), 8.44 (s, 1H), 7.60 (dd, J = 9.2, 2.4 Hz, 1H), 7.47 (d, J = 4.8 Hz, 1H), 7.42 (d, J = 2.4 Hz, 1H), 7.36 (d, J = 8.8 Hz, 1H), 5.25-4.89 (m, 2H), 4.63 (d, J = 10.4 Hz, 2H), 4.38 (s, 2H), 4.21 (s, 2H), 3.98 (bs, 2H), 3.18 (bs, 1H), 2.75 (bs, 2H), 1.78 (s, 3H), 0.86 (bs, 4H)	1390	MS (ESI) m/z 650.1[M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.93 (s, 1H), 8.39 (s, 1H), 7.59 (dd, J = 8.9, 2.7 Hz, 1H), 7.42 (d, J = 2.8 Hz, 2H), 7.35 (d, J = 9.0 Hz, 1H), 6.29 (s, 1H), 4.39 (d, J = 5.0 Hz, 2H), 4.26 (d, J = 4.9 Hz, 2H), 2.91 – 2.78 (m, 4H), 2.71 (s, 3H), 2.35 – 2.15 (m, 2H), 1.85 (s, 3H)
1378	MS (ESI) m/z 608.1	1395	MS (ESI) m/z 714.2 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.81 (d, J = 4.8 Hz, 1H), 8.54 (s, 1H), 8.48 (s, 1H), 7.61 (dd, J = 8.9, 2.7 Hz, 1H), 7.48 (d, J = 4.8 Hz, 1H), 7.43 (d, J = 2.7 Hz, 1H), 7.39 (d, J = 9.0 Hz, 1H), 4.54 (s, 2H), 4.43 (t, J = 5.1 Hz, 2H), 4.24 (t, J = 5.1 Hz, 2H), 3.82 – 3.40 (m, 10H), 1.83 (s, 3H)
1382	MS (ESI) m/z 608.0[M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 1H NMR (400 MHz, DMSO-d6) δ 9.05 (s, 1H), 8.44 (s, 1H), 7.94 – 7.86 (m, 2H), 7.64 – 7.54 (m, 4H), 7.46 – 7.40 (m, 2H), 7.37 (d, J = 9.0 Hz, 1H), 4.42 (d, J = 4.9 Hz, 2H), 4.29 (d, J = 4.9 Hz, 2H), 2.71 (s, 3H), 1.89 (s, 3H)	1396	MS (ESI) m/z 708.3 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.84 (s, 1H), 8.76 (d, J = 4.8 Hz, 1H), 8.65 (s, 1H), 7.76 (dd, J = 8.3, 0.5 Hz, 1H), 7.71 – 7.65 (m, 2H), 7.54 (d, J = 4.8 Hz, 1H), 4.84 (s, 2H), 4.53 (s, 2H), 4.06 – 2.83 (m, 8H), 2.13 (s, 3H)

[0649]

1397		MS (ESI) m/z 708.4 [M+1]+; ; 1H NMR (400 MHz, DMSO-d6) δ 8.82 (d, J = 4.8 Hz, 1H), 8.60 (s, 1H), 8.40 (s, 1H), 7.60 (dd, J = 8.9, 2.7 Hz, 1H), 7.51 – 7.47 (m, 1H), 7.44 (d, J = 2.7 Hz, 1H), 7.36 (d, J = 9.0 Hz, 1H), 6.46 (t, J = 54.6 Hz, 1H), 4.54 (s, 4H), 4.41 (t, J = 4.9 Hz, 2H), 4.21 (t, J = 4.8 Hz, 2H), 4.10 (s, 4H), 2.75 (t, J = 4.7 Hz, 4H), 1.75 (s, 3H)	1400		MS (ESI) m/z = 740.3 [M+1]+; 1H NMR (400 MHz, d6-DMSO) δ 9.59-9.49 (b, 1H), 8.83 (d, J = 4.6 Hz, 1H), 8.70 (s, 1H), 8.42 (s, 1H), 7.61 (dd, J = 8.9, 2.7 Hz, 1H), 7.49 (d, J = 4.8 Hz, 1H), 7.42 (d, J = 2.7 Hz, 1H), 7.38 (d, J = 8.9 Hz, 1H), 4.43-4.36 (m, 2H), 4.24 (t, J = 4.8 Hz, 2H), 3.61-3.49 (m, 2H), 3.34-3.20 (m, 2H), 2.49-2.39 (m, 2H), 2.00-1.92 (m, 2H), 1.85 (s, 3H), 1.39 (s, 6H). 剩余的质子部分被水峰所掩盖
1398		MS (ESI) m/z 650.1 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.93 (s, 1H), 8.39 (s, 1H), 7.59 (dd, J = 8.9, 2.7 Hz, 1H), 7.42 (d, J = 2.8 Hz, 2H), 7.35 (d, J = 9.0 Hz, 1H), 6.29 (s, 1H), 4.39 (d, J = 5.0 Hz, 2H), 4.26 (d, J = 4.9 Hz, 2H), 2.91 – 2.78 (m, 4H), 2.71 (s, 3H), 2.35 – 2.15 (m, 2H), 1.85 (s, 3H)	1401		MS (ESI) m/z = 738.3 [M+1]+; 1H NMR (400 MHz, d6-DMSO) δ 8.83 (d, J = 4.9 Hz, 1H), 8.67 (s, 1H), 8.42 (s, 1H), 7.60 (dd, J = 8.9, 2.7 Hz, 1H), 7.48 (d, J = 4.7 Hz, 1H), 7.42 (d, J = 2.7 Hz, 1H), 7.37 (d, J = 8.9 Hz, 1H), 4.40 (t, J = 4.9 Hz, 2H), 4.23 (t, J = 4.9 Hz, 2H), 2.39-2.25 (m, 2H), 1.82 (s, 3H), 1.40-0.45 (b, 4H). 剩余的质子作为非常宽的信号出现和/或部分被水峰所掩盖
1399		MS (ESI) m/z 842.4 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.03 (s, 1H), 8.90 (d, J = 4.9 Hz, 1H), 8.72 (ddd, J = 4.6, 1.7, 0.9 Hz, 1H), 8.65 (s, 1H), 8.60 (s, 1H), 8.30 – 8.25 (m, 1H), 8.21 (td, J = 7.7, 1.7 Hz, 1H), 7.80 – 7.72 (m, 2H), 7.72 – 7.68 (m, 2H), 7.66 (d, J = 4.8 Hz, 1H), 4.83 (s, 2H), 3.09 (s, 3H), 1.94 (s, 3H), 1.77 (t, J = 18.9 Hz, 2H)	1402		MS (ESI) m/z = 627.3 [M+1]+; 1H NMR (400 MHz, d6-DMSO) δ 10.20-10.10 ppm (b, 1H), 9.15 (s, 1H), 8.74 (d, J = 4.8 Hz, 1H), 8.61 (s, 1H), 7.78-7.75 (m, 1H), 7.71-7.68 (m, 2H), 7.54 (d, J = 4.8 Hz, 1H), 7.42 (d, J = 15 Hz, 1H), 7.19 (dt, J = 7.3, 15 Hz, 1H), 4.97-4.79 (m, 2H), 4.88 (s, 2H), 4.35-4.13 (m, 2H), 3.75-3.53 (m, 2H), 2.91 (s, 3H), 2.15 (s, 3H)

[0650]

1403 手性		MS (ESI) m/z = 686.2 [M+1]+; 1H NMR (400 MHz, d6-DMSO) δ 8.77 (d, J = 4.8 Hz, 1H), 8.71 (s, 1H), 8.65 (s, 1H), 7.77-7.73 (m, 1H), 7.71-7.66 (m, 2H), 7.53 (d, J = 4.8 HZ, 1H), 6.37 (bt, J = 55 Hz, 1H), 4.81 (s, 2H), 3.25 (s, 3H), 2.37-2.18 (b, 2H), 2.11 (s, 3H). 剩余的质子(部分)被水峰所掩盖	1406 手性		MS (ESI) m/z = 714.5 [M+1]+; 1H NMR (400 MHz, d6-DMSO) δ 10.38-10.18 (b, 1H), 8.76 (d, J = 4.7 Hz, 1H), 8.75 (s, 1H), 8.66 (s, 1H), 7.78-7.66 (m, 3H), 7.55 (d, J = 4.7 Hz, 1H), 6.59 (t, J = 52.6 Hz, 1H), 4.82 (s, 2H), 4.78-4.68 (m, 1H), 4.24-4.14 (m, 与水峰重叠), 3.76-3.58 (m, 与水峰重叠), 3.12 (s, 3H), 2.47-2.37 (m, 2H), 2.37-2.26 (m, 2H), 2.21-2.13 (m, 2H), 2.10-2.01 (m, 2H)
1404		MS (ESI) m/z = 674.4 [M+1]+; 1H NMR (400 MHz, d6-DMSO) δ 8.75 (s, 1H), 8.75 (d, J = 4.7 Hz, 1H), 8.59 (s, 1H), 7.74 (dd, J = 8.1, 0.5 Hz, 1H), 7.69-7.64 (m, 2H), 7.43 (dd, J = 4.7, 0.3 Hz, 1H), 6.22 (tt, J = 55.7, 4.4 Hz, 1H), 4.81 (s, 2H), 3.85 (s, 3H), 3.71-3.67 (m, 4H), 2.84 (dt, J = 15.7, 4.2 Hz, 2H), 2.78-2.72 (m, 4H), 2.06 (s, 3H)	1407		MS (ESI) m/z = 686.1 [M+1]+; 1H NMR (400 MHz, d6-DMSO) δ 8.79 (b, 1H), 8.77 (d, J = 4.7 Hz, 1H), 8.67 (s, 1H), 7.79-7.74 (m, 1H), 7.71-7.67 (m, 2H), 7.54 (d, J = 4.7 Hz, 1H), 6.58-5.69 (b, 1H), 4.84 (s, 2H), 3.33 (t, J = 6.6 Hz, 1H), 3.28 (s, 3H), 2.08 (s, 3H). 剩余的质子作为宽的信号出现和/或(部分)被水峰所掩盖
1405		MS (ESI) m/z = 722.5 [M+1]+; 1H NMR (400 MHz, d6-DMSO) δ 8.82 (s, 1H), 8.74 (d, J = 4.7 Hz, 1H), 8.62 (s, 1H), 7.73 (d, J = 8.4 Hz, 1H), 7.67 (dd, J = 8.4, 2.2 Hz, 1H), 7.61 (dd, J = 2.2, 0.4, 1H), 7.43 (d, J = 4.7 Hz, 1H), 4.82 (s, 2H), 4.59-4.53 (m, 2H), 3.86 (s, 3H), 3.69-3.62 (m, 2H), 2.16 (s, 3H). 剩余的质子作为非常宽的信号出现和/或部分被水峰所掩盖	1408		MS (ESI) m/z = 819.2 [M+1]+; 1H NMR (400 MHz, d6-DMSO) δ 12.98 (bs, 1H), 10.80-10.54 (b, 1H), 8.81 (d, J = 4.8 Hz, 1H), 8.79 (s, 1H), 8.75 (s, 1H), 7.77 (dd, J = 8.3, 0.5 Hz, 1H), 7.72-7.66 (m, 2H), 7.63 (d, J = 4.8 Hz, 1H), 6.40 (tt, J = 53.6, 2.8 Hz, 1H), 5.27-5.17 (m, 1H), 5.00-4.90 (m, 4H), 4.82 (s, 2H), 4.12 (bs, 2H), 3.99-3.85 (m, 2H), 3.76-3.55 (m, 4H), 2.11-1.93 (m, 4H), 1.96 (s, 3H)

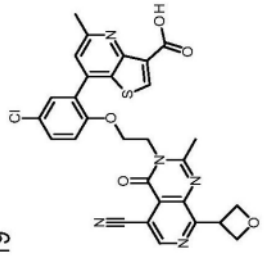
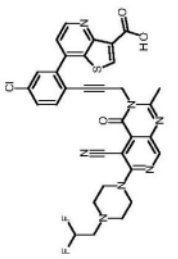
[0651]

1409		MS (ESI) m/z = 840.5 [M+1]+; 1H NMR (400 MHz, d6-DMSO) δ 13.15-12.95 (b, 1H), 10.75-10.55 (b, 1H), 9.26 (dd, J = 2.4, 0.7 Hz, 1H), 8.89 (dd, J = 4.8, 1.6 Hz, 1H), 8.81 (d, J = 4.8 Hz, 1H), 8.61 (s, 1H), 8.52 (ddd, J = 8.1, 2.4, 1.6 Hz, 1H), 8.46 (s, 1H), 7.74-7.64 (m, 3H), 7.62 (dd, J = 2.2, 0.5 Hz, 1H), 7.59 (d, J = 4.8 Hz, 1H), 6.37 (tt, J = 53.7, 3.1 Hz, 1H), 4.77 (s, 2H), 4.10 (bs, 4H), 3.97-3.82 (m, 2H), 3.72-3.50 (m, 4H), 2.07-1.94 (m, 4H), 1.87 (s, 3H)
1410		MS (ESI) m/z = 791.4 [M+1]+; 1H NMR (400 MHz, d6-DMSO) δ 12.44 (s, 1H), 10.60-10.50 (b, 1H), 8.80 (s, 1H), 8.80 (d, J = 4.8 Hz, 1H), 8.78 (s, 1H), 7.77 (dd, J = 8.3, 0.5 Hz, 1H), 7.70 (dd, J = 8.3, 2.1 Hz, 1H), 7.67 (dd, J = 2.1, 0.5 Hz, 1H), 7.62 (d, J = 4.8 Hz, 1H), 4.83 (s, 2H), 4.27-3.90 (m, 6H), 3.79-3.56 (m, 4H 预期的; 部分被水峰所掩盖), 3.55 (s, 3H 预期的; 部分被水峰所掩盖), 2.12-1.95 (m, 4H), 2.00 (s, 3H), 1.73 (t, J = 19 Hz, 3H)
1411		MS (ESI) m/z = 833.3 [M+1]+; 1H NMR (400 MHz, d6-DMSO) δ 12.65 (bs, 1H), 10.59 (bs, 1H), 8.78 (d, J = 4.8 Hz, 1H), 8.75 (s, 1H), 8.71 (s, 1H), 7.74 (dd, J = 8.3, 0.5 Hz, 1H), 7.67 (dd, J = 8.3, 2.1, 1H), 7.64 (dd, J = 2.1, 0.5 Hz, 1H), 7.59 (d, J = 4.8 Hz, 1H), 5.24-5.15 (m, 1H), 4.98-4.85 (m, 4H), 4.79 (s, 2H), 4.21-3.87 (m, 4H),
1412		MS (ESI) m/z = 854.4 [M+1]+; 1H NMR (400 MHz, d6-DMSO) d/ppm = 13.13-13.93 (b, 1H), 10.65-10.49 (b, 1H), 9.26 (dd, J = 2.4, 0.8 Hz, 1H), 8.89 (dd, J = 4.9, 1.6 Hz, 1H), 8.81 (d, J = 4.8 Hz, 1H), 8.61 (s, 1H), 8.52 (ddd, J = 8.1, 2.4, 1.6 Hz, 1H), 8.46 (s, 1H), 7.73 (dd, J = 8.4, 0.4 Hz, 1H), 7.69 (ddd, J = 8.1, 3.3, 0.8 Hz, 1H), 7.66 (dd, J = 8.4, 2.2 Hz, 1H), 7.62 (dd, J = 2.2, 0.4 Hz, 1H), 7.59 (d, J = 4.8 Hz, 1H), 4.77 (s, 2H), 4.24-3.90 (m, 6H 预期的, 与水峰重叠), 3.71-3.51 (m, 4H), 2.08-1.93 (m, 4H), 1.87 (s, 3H), 1.70 (t, J = 19.4 Hz, 3H)
1413		MS (ESI) m/z 702.5 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 10.61 (s, 1H), 8.81 – 8.72 (m, 2H), 8.64 (s, 1H), 7.79 – 7.72 (m, 1H), 7.71 – 7.64 (m, 2H), 7.54 (d, J = 4.8 Hz, 1H), 4.82 (s, 2H), 4.32 – 3.89 (m, 6H), 3.64 (m, 4H), 2.07 (d, J = 1.6 Hz, 6H), 2.00 (s, 3H), 1.74 (t, J = 19.6 Hz, 3H)
1414		LCMS (ESI) m/z 702.5 [M+1]+

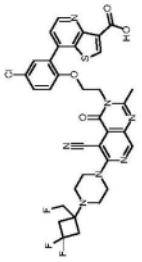
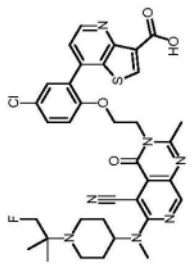
[0652]

	3.74-3.54 (m, 4H), 2.10-1.91 (m, 4H), 1.92 (s, 3H), 1.70 (t, J = 19.3 Hz, 3H)		
1415	MS (ESI) m/z 629.1 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 9.23 (d, J = 22.2 Hz, 1H), 8.78 (m, 1H), 8.44 (d, J = 17.1 Hz, 1H), 8.11 (d, J = 57.3 Hz, 1H), 7.57 (m, 1H), 7.48 – 7.40 (m, 2H), 7.34 (dd, J = 12.2, 9.0 Hz, 1H), 4.39 (m, 2H), 4.26 (d, J = 5.4 Hz, 2H), 3.47 – 3.31 (m, 2H), 3.25 (dd, J = 13.1, 9.7 Hz, 1H), 2.29 (m, 1H), 2.22 – 2.11 (m, 1H), 2.11 – 2.01 (m, 1H), 1.99 (d, J = 2.0 Hz, 3H), 1.82 (d, J = 14.3 Hz, 1H), 1.46 (s, 1H), 1.26 (s, 3H)	1421	MS (ESI) m/z 619.45 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 9.17 (bs, 1H), 7.92 (bs, 1H), 7.52 (d, J = 5.2 Hz, 1H), 7.34-7.27 (m, 2H), 7.14 (bs, 1H), 4.35 (bs, 2H), 4.26 (bs, 2H), 4.04-3.97 (m, 2H), 3.74-3.67 (m, 2H), 2.34 (s, 3H), 1.82 (s , 3H), 1.78 (s, 3H)
1418	MS (ESI) m/z 644.0 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 9.86 (s, 1H), 8.71 (s, 1H), 7.60 (dd, J = 8.9, 2.7 Hz, 1H), 7.40 (s, 1H), 7.39 (d, J = 2.7 Hz, 1H), 7.36 (d, J = 9.0 Hz, 1H), 4.40 (t, J = 5.1 Hz, 2H), 4.31 – 4.22 (m, 4H), 3.62 (d, J = 12.1 Hz, 2H), 3.40 (t, J = 13.0 Hz, 2H), 3.20 (q, J = 11.4 Hz, 2H), 2.90 (s, 3H), 2.70 (s, 3H), 2.53 (s, 3H), 2.00 (s, 3H)	1422	MS (ESI) m/z 676.42 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.23 (bs, 1H), 8.82 (d, J = 4.8 Hz, 1H), 8.64 (s, 1H), 8.45 (s, 1H), 7.59-7.57 (m, 1H), 7.45 (d, J = 4.80, 1H), 7.42 (d, J = 2.0 Hz, 1H), 7.35 (d, J = 8.8 Hz, 1H), 4.38 (s, 2H), 4.20 (s, 2H), 3.65 (s, 4H), 2.67 (s, 4H), 2.60-2.48 (m, 2H), 1.74 (s, 3H), 1.35 (J = 21.6 Hz, 6H)

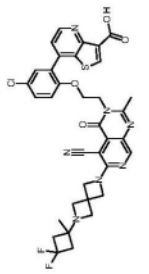
[0653]

1419		MS (ESI) m/z 588.1 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.90 (s, 1H), 8.63 (s, 1H), 7.59 (dd, J = 8.9, 2.7 Hz, 1H), 7.43 (d, J = 2.7 Hz, 1H), 7.41 (s, 1H), 7.36 (d, J = 9.0 Hz, 1H), 6.33 (q, J = 1.6 Hz, 1H), 5.97 (q, J = 1.9 Hz, 1H), 4.54 – 4.48 (m, 2H), 4.42 (t, J = 5.0 Hz, 2H), 4.28 (t, J = 5.1 Hz, 2H), 2.67 (s, 3H), 1.99 (s, 3H)	1423		MS (ESI) m/z 660.27 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.05 (bs, 1H), 8.79 (s, 1H), 8.75 (d, J = 4.64 Hz, 1H), 8.65 (s, 1H), 7.75 (d, J = 8.12 Hz, 1H), 7.68 (m, 2H), 7.53 (d, J = 4.64 Hz, 1H), 6.34 (m, 1H), 4.82 (s, 2H), 3.76-2.66 (m, 10H), 2.09 (s, 1H)
1424		MS (ESI) m/z 662.41 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.84 (d, J = 4.8 Hz, 1H), 8.70 (s, 1H), 8.42 (s, 1H), 7.61 (dd, J = 8.8 Hz, 2.8 Hz, 1H), 7.47 (d, J = 4.4 Hz, 1H), 7.41 (d, J = 2.8 Hz, 1H), 7.37 (d, J = 9.2 Hz, 1H), 4.96-4.67 (m, 2H), 4.40-4.21 (m, 5H), 3.57-3.36 (m, 8H), 1.84 (s, 3H), 1.37 (d, J = 6.0 Hz, 3H)	1427		MS (ESI) m/z 697.51 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 9.01 (s, 1H), 8.82 (d, J = 4.4 Hz, 1H), 8.41 (s, 1H), 7.59 (dd, J = 8.8, 2.8 Hz, 1H), 7.46 (d, J = 4.8 Hz, 1H), 7.43 (d, J = 2.4 Hz, 1H), 7.35 (d, J = 8.8 Hz, 1H), 4.39 (t, J = 4.4 Hz, 2H), 4.24 (t, J = 4.4 Hz, 2H), 3.81-3.75 (m, 1H), 3.31 (bs, 3H), 2.45 (s, 3H), 2.32-2.23 (m, 1H), 2.11-1.93 (m, 3H), 1.92-1.66 (m, 5H)
1425		MS (ESI) m/z 688.50 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.82 (d, J = 4.8 Hz,1H), 8.67 (s, 1H), 8.44 (s, 1H), 7.60 (dd, J = 2.8, 8.8 Hz, 1H), 7.47 (d, J = 4.8 Hz, 1H), 7.41 (d, J = 2.8 Hz, 1H), 7.37 (d, J = 8.8 Hz, 1H), 4.58-4.48 (m, 1H), 4.44-4.41 (m, 2H), 4.39-4.36 (m, 2H), 3.56-3.53 (m, 4H), 3.30-3.28 (m, 1H), 3.17-2.95 (m, 4H), 2.22-2.19 (m, 2H), 1.84 (s, 3H), 1.14-0.77 (m, 4H)	1428		MS (ESI) m/z 702.53 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.83 (d, J = 4.8 Hz, 1H), 8.59 (s, 1H), 8.42 (s, 1H), 7.59 (dd, J = 2.4, 8.8 Hz, 1H), 7.46 (d, J = 4.8 Hz, 1H), 7.43 (d, J = 2.8 Hz, 1H) 7.36 (d, J = 9.2 Hz, 1H), 4.52 (s, 2H), 4.37-4.40 (m, 2H), 4.23-4.26 (m, 1H), 4.18-4.21 (m, 2H), 3.03 (s, 3H), 2.94-2.97 (m, 2H), 2.66-2.72 (m, 2H), 1.71-1.75 (m, 7H), 0.64-0.68 (m, 4H)

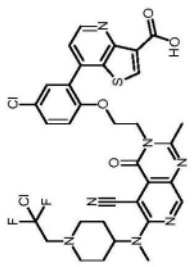
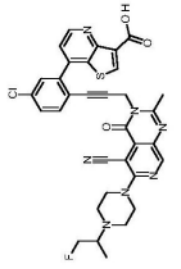
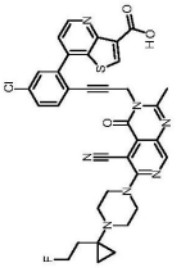
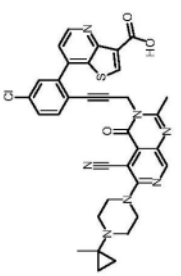
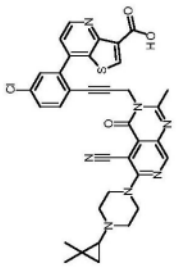
[0654]

1426		MS (ESI) m/z 724.56 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.83 (d, J = 4.8 Hz, 1H), 8.66 (s, 1H), 8.47 (s, 1H), 7.60 (dd, J = 2.4, 8.8 Hz, 1H), 7.49 (d, J = 4.8 Hz, 1H), 7.41 (d, J = 2.8 Hz, 1H), 7.35 (d, J = 9.2 Hz, 1H), 4.74 (s, 1H), 4.63 (s, 1H), 4.39 (t, J = 4.4 Hz, 2H), 4.21 (t, J = 4.4 Hz, 2H), 3.69 (bs, 4H), 2.88 (bs, 4H), 2.72 (bs, 4H), 1.7(s, 3H)	
1429		MS (ESI) m/z 704.54 [M+1]; 1H NMR (400 MHz, DMSO-d6) δ 13.2 (bs, 1H), 9.11 (bs, 1H), 8.83 (d, J = 4.8 Hz, 1H), 8.61 (s, 1H), 8.38 (s, 1H), 7.60 (dd, J = 2.8, 8.8 Hz, 1H), 7.47 (d, J = 4.8 Hz, 1H), 7.42 (d, J = 2.8 Hz, 1H) 7.36 (d, J = 8.8 Hz, 1H), 4.74-4.62 (d, J = 46.8 Hz, 2H), 4.60-4.57 (m, 1H), 4.39 (bs, 2H), 4.21 (bs, 2H), 3.66-3.58 (m, 2H), 3.30-3.24 (m, 2H), 3.09 (s, 3H), 2.26-2.20 (m, 2H), 2.11-2.08 (m, 2H), 1.76 (s, 3H), 1.38 (s, 6H)	
1430		MS (ESI) m/z 720.50 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.84 (d, J = 4.8 Hz, 1H), 8.59 (s, 1H), 8.44 (s, 1H), 7.60 (dd, J = 2.4, 6.4 Hz, 1H), 7.49 (d, J = 4.8 Hz, 1H), 7.44 (d, J = 2.8 Hz, 1H), 7.37 (d, J = 8.8 Hz, 1H), 6.08 (t, J = 55.6 Hz, 1H), 4.38 (d, J = 4.4 Hz, 2H), 4.25 (bs, 1H), 4.19 (bs, 2H), 3.08 (bs, 2H), 3.03 (s, 3H), 2.92 (bs, 2H), 1.77 (bs, 7H), 0.48-0.78 (m, 4H)	
1433		MS (ESI) m/z 708.50 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.82 (d, J = 4.2 Hz, 1H), 8.65 (s, 1H), 8.41 (s, 1H), 7.59 (d, J = 8.6 Hz, 1H), 7.47-7.43 (m, 2H), 7.35 (d, J = 8.8 Hz, 1H), 6.51 (t, J = 53.4 Hz, 1H), 4.38 (s, 4H), 4.21 (s, 2H), 3.07 (bs, 5H), 2.52 (s, 2H), 2.17 (bs, 2H), 2.02 (bs, 2H), 1.75 (s, 3H), 1.11 (t, J = 6.3 Hz, 3H)	
1431		MS (ESI) m/z 722.55 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.83 (d, J = 4.8 Hz, 1H), 8.61 (s, 1H), 8.39 (s, 1H) 7.61 (dd, J = 2.4, 9.2 Hz, 1H), 7.48 (d, J = 4.8 Hz, 1H), 7.42-7.35 (m, 2H), 6.52 (t, J = 52 Hz, 1H), 4.62-4.56 (m, 1H), 4.39 (bs, 2H), 4.21 (bs, 2H,), 3.38-3.34 (m, 4H), 3.09 (s, 3H), 2.32-2.26 (m, 2H), 2.12-2.09 (m, 2H), 1.76 (s, 3H), 1.44 (s, 6H)	
1434		MS (ESI) m/z 667.18 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.32 (bs, 1H), 8.81 (d, J = 4.8 Hz, 1H), 8.60 (s, 1H), 8.46 (s, 1H), 7.60 (dd, J = 9.2, 2.8 Hz, 1H), 7.44 (dd, J = 15.6 Hz, 2H), 7.35 (d, J = 9.2 Hz, 1H), 4.59 (s, 2H), 4.53 (s, 2H), 4.38 (bs, 4H), 4.24-4.20 (m, 4H), 3.91-3.88 (m, 1H), 2.17 (bs, 2H), 2.01 (t, J = 9.6 Hz, 2H), 1.82 (s, 3H), 1.78-1.71 (m, 2H)	

[0655]

1432		MS (ESI) m/z 708.2 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.83 (dd, J = 4.8 Hz, 2 Hz, 1H), 8.61 (d, J = 2 Hz, 1H), 8.40 (s, 1H), 7.61 (d, J = 8.8 Hz, 1H), 7.46 (dd, J = 4.8 Hz, 2 Hz, 1H), 7.43 (d, J = 4.0 Hz, 1H), 7.36 (d, J = 7.2 Hz, 1H), 4.99 (bs, 4H), 4.58 (bs, 1H), 4.39 (s, 2H), 4.21 (s, 2H), 4.0 (bs, 2H), 3.70 (bs, 2H), 3.28 (bs, 1H), 3.09 (s, 3H), 2.33-2.00 (m, 4H), 1.76 (s, 3H)
1435		MS (ESI) m/z 718.48 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.82 (d, J = 4.8 Hz, 1H), 8.61 (s, 1H), 8.47 (s, 1H), 7.60 (dd, J = 9.2, 2.8 Hz, 1H), 7.46 (d, J = 4.8 Hz, 1H), 7.42 (d, J = 2.8 Hz, 1H), 7.36 (d, J = 8.8 Hz, 1H), 4.78-4.59 (m, 4H), 4.40-4.30 (m, 6H), 4.23-4.18 (m, 2H), 3.35-3.15 (m, 2H), 2.80-2.65 (m, 2H), 1.80 (s, 3H), 1.47 (s, 3H)
1436		MS (ESI) m/z 682.52 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.5 (bs, 1H), 9.66 (bs, 1H), 8.80 (d, J = 4.8 Hz, 1H), 8.61 (s, 1H), 8.47 (s, 1H), 7.60 (dd, J = 9.2, 2.8 Hz, 1H), 7.46 (d, J = 4.8 Hz, 1H), 7.42 (d, J = 2.4 Hz, 1H), 7.36 (d, J = 8.8 Hz, 1H), 4.65-4.45 (m, 8H), 4.40-4.35 (m, 2H), 4.25-4.15 (m, 2H), 2.91 (bs, 1H), 1.80 (s, 3H), 1.17 (s, 3H), 1.06 (s, 3H), 0.85-0.55 (m, 2H)
1439		MS (ESI) m/z 692.45 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.83 (d, J = 4.8 Hz, 1H), 8.67 (s, 1H), 8.44 (s, 1H), 7.59 (dd, J = 8.8, 2.4 Hz, 1H), 7.47 (d, J = 4.8 Hz, 1H), 7.43 (d, J = 2.4 Hz, 1H), 7.36 (d, J = 8.8 Hz, 1H), 6.54 (t, J = 54.8 Hz, 1H), 4.38 (d, J = 4.8 Hz, 2H), 4.22 (d, J = 4.8 Hz, 2H), 4.10 (d, J = 12 Hz, 1H), 3.93 (d, J = 12.4 Hz, 1H), 3.41-3.32 (m, 2H), 3.16-3.13 (m, 3H), 2.02 (bs, 1H),1.76 (s, 3H), 0.53-0.41 (m, 4H)
1437		MS (ESI) m/z 667.18 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.32 (bs, 1H), 8.81 (d, J = 4.8 Hz, 1H), 8.60 (s, 1H), 8.46 (s, 1H), 7.60 (dd, J = 9.2, 2.8 Hz, 1H), 7.44 (dd, J = 15.6 Hz, 2H), 7.35 (d, J = 9.2 Hz, 1H), 4.59 (s, 2H), 4.53 (s, 2H), 4.38 (bs, 4H), 4.24- 4.20 (m, 4H), 3.91-3.88 (m, 1H), 2.17 (bs, 2H), 2.01 (t, J = 9.6 Hz, 2H), 1.82 (s, 3H), 1.78-1.71 (m, 2H)
1440		MS (ESI) m/z 693.42 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 9.03 (s, 1H), 8.84 (d, J = 4.8 Hz, 1H), 8.33 (s, 1H), 7.65-7.58 (m, 1H), 7.48 (d, J = 4.8 Hz, 1H), 7.42 (d, J = 2.4 Hz, 1H), 7.36 (d, J = 8.8 Hz, 1H), 6.40 (t, J = 62.4 Hz, 1H), 4.41 (s, 2H), 4.28 (d, J = 5.2 Hz, 2H), 3.51-3.05 (m, 8H), 2.50 (bs, 2H), 1.82 (s, 3H), 1.77 (s, 1H)

[0656]

1438		MS (ESI) m/z 710.17 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.83 (d, J = 4.8 Hz, 1H), 8.67 (s, 1H), 8.46 (s, 1H), 7.60 (dd, J = 8.8 Hz, 2.4 Hz, 1H), 7.49 (d, J = 4.8 Hz, 1H), 7.43 (d, J = 2.8 Hz, 1H), 7.36 (d, J = 8.8 Hz, 1H), 4.39 (d, J = 4.8 Hz, 2H), 4.29 (bs, 2H), 3.96 (dd, J = 14, 5.2 Hz, 1H), 3.87 (bs, 2H), 3.71 (bs, 1H), 3.59 (t, J = 9.2 Hz, 1H), 3.27 (bs, 1H), 2.90 (d, J = 12.8 Hz, 1H), 2.26 (bs, 1H), 1.76 (s, 3H), 0.58 (d, J = 6.4 Hz, 2H), 0.46 (s, 2H)
1441		MS (ESI) m/z 728.40 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.83 (d, J = 4.8 Hz, 1H), 8.59 (s, 1H), 8.44 (s, 1H), 7.60-7.58 (dd, J = 2.4, 8.8 Hz, 1H), 7.48 (d, J = 4.8 Hz, 1H), 7.43 (d, J = 2.4 Hz, 1H), 7.36 (d, J = 8.8 Hz, 1H), 4.38 (bs, 2H), 4.25-4.19 (m, 3H), 3.35-3.30 (m, 2H), 3.07(s, 5H), 2.66-2.59 (m, 2H), 1.92 (d, J = 9.2 Hz, 2H), 1.78-1.72 (m, 5H)
1443		MS (ESI) m/z 656.45 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.07 (s, 1H), 8.75 (d, J = 4.8, 2H), 8.65 (s, 1H), 7.75 (d, J = 8.8 Hz, 1H), 7.68 (d, J = 6.8 Hz, 2H), 7.53 (d, J = 4.8 Hz, 1H), 4.82 (s, 2H), 4.47 (d, J = 44 Hz, 2H), 3.66 (bs, 4H), 2.96 (bs, 1H), 2.74 (s, 3H), 2.07-2.08 (m, 4H), 1.23 (s, 3H)
1446		MS (ESI) m/z 682.44 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.81 (s, 1H), 8.75 (d, J = 4.8 Hz, 1H), 8.66 (s, 1H), 7.75 (d, J = 8.4 Hz, 1H), 7.70-7.67 (m, 2H), 7.54 (d, J = 4.8 Hz, 1H), 4.83 (s, 2H), 4.56-4.41 (m, 2H), 3.77-3.06 (m, 8H), 2.23 (s, 3H), 1.23-0.72 (m, 6H)
1444		MS (ESI) m/z 650.47 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 9.29 (bs, 1H), 8.83 (s, 1H), 8.76 (d, J = 4.8 Hz, 1H), 8.65 (s, 1H), 7.76 (d, J = 8.4 Hz, 1H), 7.70-7.65 (m, 2H), 7.54 (d, J = 4.8 Hz, 1H), 4.83 (s, 2H), 4.46 (bs, 2H), 3.53 (bs, 6H), 2.14 (s, 3H), 1.39 (s, 3H), 1.20 (bs, 2H), 0.83 (bs, 2H)
1447		MS (ESI) m/z 664.45 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 12.99 (bs, 1H), 9.00 (bs, 1H), 8.83 (bs, 1H), 8.75 (d, J = 4.8 Hz, 1H), 8.65 (s, 1H), 7.75 (d, J = 8.4 Hz, 1H), 7.70-7.64 (m, 2H), 7.54 (d, J = 4.8 Hz, 1H), 4.83 (s, 2H), 4.37 (bs, 2H), 3.85-3.40 (m, 6H), 2.90-2.80 (m, 1H), 2.13 (s, 3H), 1.38 (s, 3H), 1.07 (s, 3H), 0.95-0.75 (m, 2H)

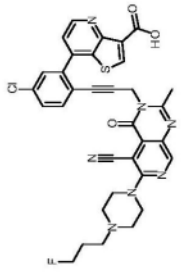
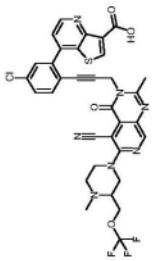
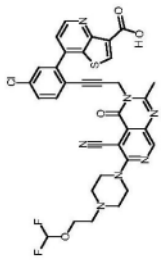
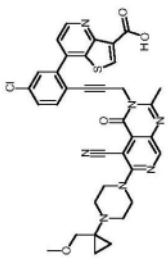
[0657]

1445		MS (ESI) m/z 668.45 [M+1]+; 1; H NMR (400 MHz, DMSO-d6) δ 8.79 (s, 1H), 8.76 (d, J = 4.8 Hz, 1H), 8.66 (s, 1H), 7.75 (d, J = 8.4 Hz, 1H), 7.69-7.67 (m, 2H), 7.54 (d, J = 4.8 Hz, 1H), 4.83 (s, 2H), 4.60 (d, J = 48.4 Hz, 2H), 3.80-3.50 (m, 4H), 3.30-2.80 (m, 4H), 2.09 (s, 3H), 1.20-0.80 (m, 4H)	
1448		MS (ESI) m/z 674.2 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.81 (s, 1H), 8.75 (d, J = 4.4 Hz, 1H), 8.65 (s, 1H), 7.75 (d, J = 8.0 Hz, 1H), 7.69-7.67 (m, 2H), 7.54 (d, J = 4.8 Hz, 1H), 4.91-4.83 (m, 6H), 4.12 (bs, 1H), 3.79 (bs, 4H), 3.27 (bs, 4H), 2.10 (s, 3H)	
1449		MS (ESI) m/z 688.47 [M+1]+; ; 1H NMR (400 MHz, DMSO-d6) δ 8.81 (s, 1H), 8.75 (d, J = 4.8 Hz, 1H), 8.65 (s, 1H), 7.75 (d, J = 8.4 Hz, 1H), 7.69-7.67 (m, 2H), 7.54 (d, J = 4.8 Hz, 1H), 4.83 (s, 2H), 4.72-4.54 (m, 2H), 4.32 (bs, 2H), 3.14-2.67 (m, 8H), 2.10 (s, 3H), 1.48-1.45 (m, 3H)	
1452		MS (ESI) m/z 670.50 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 9.76 (bs, 1H), 8.84 (s, 1H), 8.76 (d, J = 4.4 Hz, 1H), 8.65 (s, 1H), 7.75 (d, J = 8.4 Hz, 1H), 7.70-7.66 (m, 2H), 7.54 (d, J = 4.8 Hz, 2H), 4.83 (s, 2H), 4.72 (d, J = 46.8 Hz, 2H), 4.46 (d, J = 14.0 Hz, 2H), 3.85-3.50 (m, 4H), 3.40-3.30 (m, 2H), 2.15 (s, 3H), 1.40 (s, 6H)	
1450		MS (ESI) m/z 668.42 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 9.74 (bs, 1H), 8.46 (s, 1H), 8.75 (d, J = 4.8 Hz, 1H), 8.65 (s, 1H), 7.76 (d, J = 8.4 Hz, 1H), 7.69-7.66 (m, 2H), 7.54 (d, J = 4.8 Hz, 1H), 5.74 (d, J = 34.0 Hz, 2H), 5.10 (s, 1H), 4.98 (s, 1H), 4.83 (s, 2H), 4.40 (d, J = 20.8 Hz, 2H), 3.96 (bs, 2H), 3.65 (m, 2H), 3.54 (m, 2H), 3.29 (bs, 2H), 2.14 (s, 3H)	
1453		MS (ESI) m/z 670.13 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 9.78 (bs, 1H), 8.83 (s, 1H), 8.75 (d, J = 4.8 Hz, 1H), 8.65 (s, 1H), 7.75 (d, J = 8.4 Hz, 1H), 7.71-7.64 (m, 2H), 7.53 (d, J = 4.8 Hz, 1H), 4.83 (s, 2H), 4.32 (bs, 2H), 3.85-3.30 (m, 8H), 2.13 (s, 3H), 1.50 (d, J = 21.2 Hz, 6H)	

[0658]

1451		1454	
MS (ESI) m/z 664.24 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.84 (s, 1H), 8.75 (d, J = 4.8 Hz, 1H), 8.65 (s, 1H), 7.75 (d, J = 8.4 Hz, 1H), 7.70-7.66 (m, 2H), 7.53 (d, J = 4.8 Hz, 1H), 4.83 (s, 2H), 4.36 (m, 2H), 3.71-3.57 (m, 4H), 3.30-3.18 (m, 4H), 2.15 (s, 3H), 2.21 (s, 3H), 0.60-0.51 (m, 4H)		MS (ESI) m/z 684.48 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.84 (s, 1H), 8.75 (d, J = 4.8 Hz, 1H), 8.65 (s, 1H), 7.75 (d, J = 8 Hz, 1H), 7.70-7.66 (m, 2H), 7.54 (d, J = 4.8 Hz, 1H), 4.83 (s, 2H), 4.74-4.60 (m, 2H), 4.47 (d, J = 13.6 Hz, 2H), 3.75 (d, J = 11.2 Hz, 2H), 3.60-3.53 (m, 2H), 3.31-3.28 (m, 2H), 2.21-2.15 (m, 5H) 1.42 (s, 6H)	
1455		1458	
MS (ESI) m/z 688.32 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.80 (s, 1H), 8.75 (d, J = 4.8 Hz, 1H), 8.66 (s, 1H), 7.75 (d, J = 8.4 Hz, 1H), 7.69-7.67 (m, 2H), 7.54 (d, J = 4.8, 1H), 6.45-6.14 (m, 1H), 4.82 (s, 2H), 3.98-3.69 (m, 4H), 3.17 (m, 4H), 2.11 (s, 3H), 1.29 (s, 6H)		MS (ESI) m/z 706.49 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 12.96 (bs, 1H), 8.84 (s, 1H), 8.76 (d, J = 4.8 Hz, 1H), 8.64 (s, 1H), 7.76 (d, J = 8.4 Hz, 1H), 7.69 (dd, J = 8.4, 2.0 Hz, 1H), 7.65 (d, J = 2.0 Hz, 1H), 7.53 (d, J = 4.8 Hz, 1H), 4.84 (s, 2H), 4.40-4.36 (m, 2H), 3.74-3.72 (m, 2H), 3.29 (bs, 6H), 2.45-2.38 (m, 2H), 2.14 (s, 3H), 1.98-1.93 (m, 2H)	
1456		1459	
MS (ESI) m/z 674.18 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.16 (bs, 1H), 8.84 (s, 1H), 8.75 (d, J = 4.8 Hz, 1H), 8.64 (s, 1H), 7.75 (d, J = 8.4 Hz, 1H), 7.67 (t, J = 8.4 Hz, 2H), 7.53 (d, J = 4.8 Hz, 1H), 6.26 (t, J = 56 Hz, 1H), 4.83 (s, 2H), 4.36 (bs, 2H), 3.73 (bs, 2H), 3.37 (bs, 6H), 2.40 (bs, 2H), 2.13 (s, 3H)		MS (ESI) m/z 642.17 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.85 (s, 1H), 8.76 (d, J = 4.8 Hz, 1H), 8.65 (s, 1H), 7.75 (d, J = 8.0 Hz, 1H), 7.69 (dd, J = 8.4 Hz, 2.0 Hz, 1H), 7.65 (s, 1H), 7.53 (d, J = 4.8 Hz, 1H), 5.12-4.93 (m, 2H), 4.84 (s, 2H), 4.44 (dd, J = 42.4 Hz, 14.4 Hz, 1H), 3.54-3.51 (m, 4H), 3.00 (s, 3H), 2.50-2.43 (m, 1H), 2.14 (s, 3H)	

[0659]

1457		MS (ESI) m/z 656.39 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.84 (s, 2H), 8.75 (d, J = 4.8 Hz, 1H), 8.64 (s, 1H), 7.75 (d, J = 8.4 Hz, 1H), 7.70-7.65 (m, 2H), 7.53 (d, J = 4.8 Hz, 1H), 4.83 (s, 2H), 4.65-4.50 (m, 2H), 4.38 (d, J = 13.6 Hz, 2H), 3.46 (bs, 4H), 3.32 (bs, 4H), 2.19-2.06 (m, 5H)	1460		MS (ESI) m/z 708.44 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.85 (s, 1H), 8.76 (d, J = 4.8 Hz, 1H), 8.65 (s, 1H), 7.75 (d, J = 8.0 Hz, 1H), 7.70-7.66 (m, 2H), 7.53 (d, J = 4.8 Hz, 1H), 4.84 (s, 2H), 4.66-4.36 (m, 5H), 3.91-3.78 (m, 4H), 2.95 (bs, 3H), 2.13 (s, 3H)
1461		MS (ESI) m/z 633.40 [M+1] +; 1H NMR (400 MHz, DMSO-d6) δ 13.05 (bs, 1H), 9.51 (bs, 1H), 9.12 (s, 1H), 8.74 (d, J = 4.8 Hz, 1H), 8.61 (s, 1H), 7.76 (d, J = 9.1 Hz, 1H), 7.81-7.67 (m, 2H), 7.55 (d, J = 4.8 Hz, 1H), 6.56 (s, 1H), 4.87 (s, 2H), 4.30-4.10 (m, 2H), 3.80 (bs, 1H), 3.01 (bs, 4H), 2.19 (s, 3H), 1.10-0.84 (m, 4H)	1464		MS (ESI) m/z 690.43 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.04 (bs, 1H), 8.81-8.75 (m, 2H), 8.65 (s, 1H), 7.75 (d, J = 8.4 Hz, 1H), 7.68 (d, J = 10.0 Hz, 1H), 7.53 (d, J = 4.4 Hz, 1H), 4.83 (s, 2H), 4.36-4.02 (m, 4H), 3.69-3.59 (m, 4H), 3.36-2.9 (m, 4H), 2.11 (s, 3H)
1462		MS (ESI) m/z 639.37 [M+1]+; ; 1H NMR (400 MHz, DMSO-d6) δ 13.07 (bs, 1H), 10.26 (bs, 1H), 9.12 (s, 1H), 8.75 (d, J = 4.8 Hz, 1H), 8.61 (s, 1H), 7.76 (d, J = 8.8 Hz, 1H), 7.71-7.66 (m, 2H), 7.55 (d, J = 4.8 Hz, 1H), 6.57 (s, 1H), 5.00-4.85 (m, 4H), 4.29-3.95 (m, 2H), 3.90-3.80 (m, 2H), 3.60-3.45 (m, 2H), 3.10-2.90 (m, 2H), 2.18 (s, 3H)	1465		MS (ESI) m/z 680.51 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.83 (s,1H), 8.76 (d, J = 4.8 Hz, 1H), 8.65 (s, 1H), 7.75 (d, J = 8.0 Hz, 1H), 7.70-7.67 (m, 2H), 7.55 (d, J = 4.8 Hz, 1H), 4.83 (s, 2H), 4.49-4.43 (m, 2H), 3.76-3.46 (m, 8H), 3.26 (s, 3H), 2.49 (s, 1H), 2.12 (s, 3H), 1.25 (bs, 2H), 0.97 (bs, 2H)

[0660]

1463		MS (ESI) m/z 657.40 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 9.10 (s, 1H), 8.75 (d, J = 4.8 Hz, 1H), 8.62 (s, 1H), 7.76 (d, J = 9.2 Hz, 1H), 7.70-7.68 (m, 2H), 7.54 (d, J = 4.8 Hz, 1H), 6.62-6.34 (m, 2H), 4.86 (s, 2H), 3.41-3.24 (m, 4H), 3.15-2.95 (m, 2H), 2.87 (bs, 2H), 2.16 (s, 3H)	1466		MS (ESI) m/z 674.47 [M+1]+; 1; H NMR (400 MHz, DMSO-d6) δ 8.80 (s, 1H), 8.75 (d, J = 4.8 Hz, 1H), 8.65 (s, 1H), 7.75 (d, J = 8.4 Hz, 1H), 7.69 (bs, 1H), 7.67 (s, 1H), 7.53 (d, J = 4.4 Hz, 1H), 6.31 (t, J = 53.2 Hz, 1H), 4.82 (s, 2H), 3.79 (bs, 4H), 3.11 (bs, 4H), 2.64-2.59 (m, 1H), 2.09 (s, 3H), 1.21 (bs, 3H)
1467		MS (ESI) m/z 686.19 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.77-8.74 (m, 2H), 8.64 (s, 1H), 7.75 (d, J = 9.2 Hz, 1H), 7.69-7.67 (m, 2H), 7.54 (d, J = 4.8 Hz, 1H), 4.82 (s, 2H), 4.57-4.55 (m, 4H), 4.24 (d, 2H), 3.21-3.15 (m, 2H), 2.41 (s, 1H), 2.08-2.04 (m, 5H), 1.55 (s, 2H)	1470		MS (ESI) m/z 674.44 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 9.74 (bs, 1H), 8.83 (d, J = 4.8 Hz, 1H), 8.70 (s, 1H), 8.44 (s, 1H), 7.61-7.58 (dd, J = 2.4, 8.8 Hz, 1H), 7.47 (d, J = 4.8 Hz, 1H), 7.41 (d, J = 2.4 Hz, 1H), 7.38 (d, J = 8.8 Hz, 1H), 5.73 (d, J = 30.4 Hz, 2H), 5.09 (s, 1H), 4.98 (s, 1H), 4.40 (d, J = 4.8 Hz, 2H), 4.31 (bs, 2H), 4.24 (d, J = 4.8 Hz, 2H), 3.96 (bs, 2H), 3.63 (m, 2H), 3.32-3.18 (m, 4H), 1.84 (s, 3H)
1468		MS (ESI) m/z 661.37 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.02 (bs, 1H), 9.07 (s, 1H), 8.76 (s, 1H), 8.61 (s, 1H), 7.76 (d, J = 8.0 Hz, 1H), 7.69 (s, 2H), 7.53 (s, 1H), 4.87 (s, 2H), 3.90 (s, 2H), 3.50-3.30 (m, 合并的, 2H), 2.55 (s, 3H), 2.09 (s, 3H)	1471		MS (ESI) m/z 724.09 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.82 (d, J = 4.8 Hz, 1H), 8.70 (s, 1H), 8.45 (s, 1H), 7.60 (dd, J = 2.4, 8.8 Hz, 1H), 7.46 (d, J = 4.8 Hz, 1H), 7.41 (d, J = 2.4 Hz, 1H), 7.36 (d, J = 8.8 Hz, 1H), 4.39 (s, 2H), 4.32-4.23 (m, 4H), 3.28-2.86 (m, 4H), 1.83 (s, 3H), 1.30-1.21 (m, 4H)

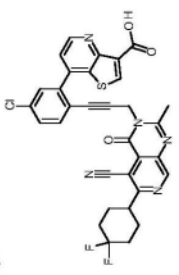
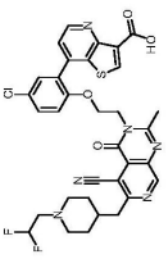
[0661]

1469		MS (ESI) m/z 704.21 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.83 (d, J = 4.9 Hz, 1H), 8.70 (s, 1H), 8.40 (s, 1H), 7.55 (dd, J = 2.4, 8.8 Hz, 1H), 7.50 (d, J = 4.9 Hz, 1H), 7.31 (d, J = 2.8 Hz, 2H), 4.46 (t, J = 4.9 Hz, 2H), 4.34 (t, J = 4.9 Hz, 2H), 4.10 (bs, 4H), 3.72 (bs, 4H), 3.61 (s, 2H), 2.11 (s, 3H), 1.99-1.80 (m, 4H), 1.03 (t, J = 7.4 Hz, 6H)	1472		MS (ESI) m/z 726.18 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.82 (d, J = 4.8 Hz, 1H), 8.66 (bs, 1H), 8.45 (s, 1H), 7.59 (dd, J = 2.4, 9.2 Hz, 1H), 7.47 (d, J = 4.8 Hz, 1H), 7.42 (d, J = 2.4 Hz, 1H), 7.36 (d, J = 9.2 Hz, 1H), 4.38 (s, 2H), 4.21 (s, 2H), 3.75 (bs, 8H), 2.71 (s, 2H), 1.76 (s, 3H), 1.15 (s, 6H)
1473		MS (ESI) m/z 698.22 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.82 (d, J = 4.8 Hz, 1H), 8.69 (bs, 1H), 8.45 (s, 1H), 7.59 (dd, J = 2.4, 9.2 Hz, 1H), 7.45 (d, J = 4.8 Hz, 1H), 7.42 (d, J = 2.4 Hz, 1H), 7.36 (d, J = 9.2 Hz, 1H), 4.39 (s, 2H), 4.22 (s, 4H), 3.54 (bs, 6H), 1.98-1.64 (m, 2H), 1.18 (d, J = 7.2 Hz, 2H), 1.10-1.05 (m, 12H)	1476		MS (ESI) m/z 710.49 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.90 (bs, 1H), 8.81 (d, J = 5.2 Hz, 1H), 8.61 (s, H), 8.47 (s, 1H), 7.60 (dd, J = 8.8, 2.4 Hz, 1H), 7.46 (d, J = 4.8 Hz, 1H), 7.43 (d, J = 2.8 Hz, 1H), 7.36 (d, J = 8.8 Hz, 1H), 4.63 (s, 2H), 4.59-4.47 (m, 6H), 4.38 (t, J = 4.4 Hz, 2H), 4.21 (d, J = 4.8 Hz, 2H), 2.70 (s, 1H), 1.81 (s, 3H), 1.09 (s, 6H), 1.07 (s, 6H)
1474		MS (ESI) m/z 700.44 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.82 (d, J = 5.2 Hz, 1H), 8.60 (s, 1H), 8.43 (s, 1H), 7.59-7.57 (dd, J = 2.4, 10.8 Hz, 1H), 7.49 (d, J = 4.8 Hz, 1H), 7.39 (d, J = 2.4 Hz, 1H), 7.35 (d, J = 9.2 Hz, 1H), 4.36 (s, 2H), 4.19 (s, 2H), 3.65 (m, 4H), 4.44-3.38 (m, 2H), 2.87 (bs, 4H), 1.77 (s, 3H)	1477		MS (ESI) m/z 720.50 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.35 (bs, 1H), 8.82 (d, J = 4.8 Hz, 1H), 8.61 (s, 1H), 8.40 (s, 1H), 7.59 (dd, J = 2.40, 8.8 Hz, 1H), 7.47 (d, J = 4.4 Hz, 1H), 7.42 (d, J = 2.8 Hz, 1H), 7.36 (d, J = 8.8 Hz, 1H), 4.53 (bs, 1H), 4.39 (bs, 2H), 4.21 (bs, 2H), 3.74 (bs, 1H), 3.58 (bs, 2H), 3.09 (bs, 9H), 2.10 (bs, 4H), 1.77 (s, 3H)

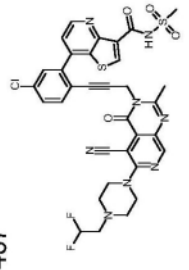
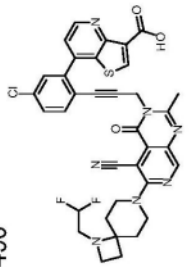
[0662]

1475		MS (ESI) m/z 704.47 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.81 (d, J = 4.8 Hz, 1H), 8.60 (s, 1H), 8.47 (s, 1H), 7.59 (dd, J = 9.2, 2.8 Hz, 1H), 7.46 (d, J = 4.8 Hz, 1H), 7.42 (d, J = 2.4 Hz, 1H), 7.35 (d, J = 9.2 Hz, 1H), 4.53 (bs, 4H),4.45-4.35 (m, 2H), 4.25-4.15 (m, 2H), 3.60-3.45 (m, 1H), 3.20-2.70 (m, 4H), 2.60-2.40 (m, 合并的, 4H), 1.81 (s, 3H)	
1478		MS (ESI) m/z 692.2 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.81 (d, J = 4.8 Hz, 1H), 8.62 (s, 1H), 8.47 (s, 1H), 7.60 (dd, J = 9.2, 2.8 Hz, 1H), 7.45 (d, J = 4.8 Hz, 1H), 7.43 (d, J = 2.4 Hz, 1H), 7.36 (d, J = 9.2 Hz, 1H), 6.41 (t, J = 53.6 Hz, 1H), 4.38-4.37 (m, 2H), 4.21 (s, 2H), 3.91 (bs, 6H), 3.17 (s, 4H), 3.03-2.81 (m, 2H), 1.79 (s, 3H)	
1479		MS (ESI) m/z 663.41 [M+1] +; 1H NMR (400 MHz, DMSO-d6) δ 8.83 (d, J = 4.8 Hz, 1H), 8.72 (s, 1H), 8.37 (s, 1H), 7.60 (d, J = 8.4 Hz, 1H), 7.47 (d, J = 4.4 Hz, 1H), 7.42 (bs, 1H), 7.36 (d, J = 8.8 Hz, 1H), 5.47 (d, J = 48.4 Hz, 1H), 4.93 (bs, 1H), 4.82 (bs, 1H), 4.39 (bs, 2H), 4.24 (bs, 2H), 3.68 (bs, 4H), 3.37-3.27 (m, 4H), 2.29-2.10 (m, 1H), 2.01-1.98 (m, 1H), 1.82-1.77 (m, 3H)	
1482		MS (ESI) m/z 628.33 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.04 (bs, 1H), 9.07 (s, 1H), 8.76 (d, J = 4.8 Hz, 1H), 8.61 (s, 1H), 7.77 (d, J = 9.2 Hz, 1H), 7.69 (t, J = 3.2 Hz, 1H), 7.54 (d, J = 4.4 Hz, 1H), 6.33 (s, 1H), 4.86 (s, 2H), 2.89-2.84 (m, 4H), 2.29-2.22 (m, 2H), 2.14 (s, 3H)	
1480		MS (ESI) m/z 691.44 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 9.00 (s, 1H), 8.84 (d, J = 4.8 Hz, 1H), 8.39 (s, 1H), 7.61-7.58 (dd, J = 2.8, 8.8 Hz, 1H), 7.48-7.45 (dd, J = 10.8, 8.8 Hz, 2H), 7.37 (d, J = 9.2 Hz, 1H), 6.46 (m, 1H), 4.40 (t, 2H), 4.25 (bs, 2H), 3.07-2.97 (m, 8H), 2.22 (m, 2H), 2.06 (s, 3H), 1.79 (s, 3H)	1483		MS (ESI) m/z 753.43 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 12.65 (s, 1H), 9.87 (bs, 1H), 8.90 (d, J = 4.8 Hz, 1H), 8.76 (s, H), 8.55 (s, 1H), 7.63 (dd, J = 8.8, 2.4 Hz, 1H), 7.57 (d, J = 4.8 Hz, 1H), 7.44-7.37 (m, 2H), 4.73 (d, J = 46.0 Hz, 2H), 4.50-4.35 (m, 4H), 4.23 (s, 2H), 3.80-3.50 (m, 7H), 3.45-3.22 (m, 2H), 1.85 (s, 3H), 1.42 (s, 6H)

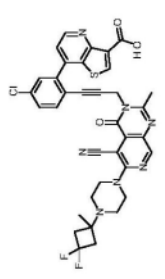
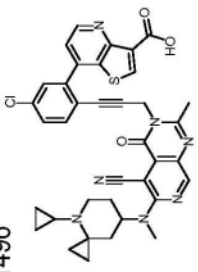
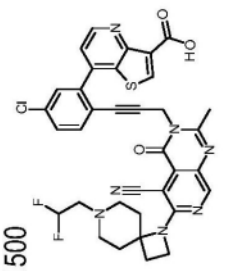
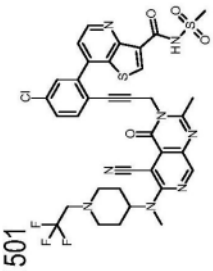
[0663]

1481 	MS (ESI) m/z 630.38 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 9.11 (s, 1H), 8.57 (d, J = 4.8 Hz, 1H), 8.61 (s, 1H), 7.77-7.75 (m, 1H), 7.69 (dd, J = 2.0, 6.8 Hz, 2H), 7.54 (d, J = 4.8 Hz, 1H), 4.86 (s, 2H), 2.53 (s, 1H), 2.17-2.15 (m, 3H), 2.08-2.06 (m, 2H), 2.01 (d, J = 5.6 Hz, 6H)	1484 	MS (ESI) m/z 679.16 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 9.85 (bs, 1H), 8.96 (s, 1H), 8.82 (d, J = 4.8 Hz ,1H), 8.33 (s, 1H), 7.60 (dd, J = 2.4, 8.8 Hz, 2H), 7.47-7.43 (m, 1H), 7.36 (d, J = 8.8 Hz ,1H), 6.66-6.39 (m, 1H), 4.39 (t, J = 4.4 Hz ,2H), 4.25 (bs, 2H), 3.66-3.51 (m, 4H), 3.05 (d, J = 5.6 Hz, 4H), 2.19 (bs, 1H), 1.80 (s, 6H), 1.63-1.60 (m, 2H)
1485	MS (ESI) m/z 639.38 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.96 (s, 1H), 8.82 (d, J = 4.4 Hz, 1H), 8.34 (s, 1H), 7.60 (dd, J = 9.2, 2.8 Hz, 1H), 7.47 (d, J = 4.8 Hz, 1H), 7.43 (d, J = 2.8 Hz, 1H), 7.36 (d, J = 9.2, 1H), 6.36 (t, J = 49.2 Hz, 1H), 4.40 (t, J = 4.8 Hz, 2H), 4.27-4.26 (m, 2H), 3.43 (bs, 4H), 2.73 (bs, 2H), 1.82 (s, 3H)	1488	MS (ESI) m/z 719.44 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 12.45 (s, 1H), 10.12 (bs, 1H), 8.89 (s, 1H), 8.82 (d, J = 4.8 Hz, 1H), 8.79 (s, 1H), 7.77 (d, J = 8.4 Hz, 1H), 7.72-7.69 (m, 1H), 7.66 (d, J = 1.6 Hz, 1H), 7.62 (d, J = 4.8 Hz, 1H), 5.00-4.80 (m, 2H), 4.35 (bs, 2H), 3.82-3.60 (m, 4H), 3.55 (s, 3H), 3.50-3.22 (m, 4H), 2.03 (s, 3H)
1486	MS (ESI) m/z 769.56 [M+1]+	1489	MS (ESI) m/z 698.22 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.80 (s, 1H), 8.75 (d, J = 4.8 Hz, 1H), 8.65 (s, 1H), 7.75 (d, J = 8.4 Hz, 1H), 7.68 (d, J = 9.2 Hz, 2H), 7.53 (d, J = 4.4 Hz, 1H), 4.83 (s, 2H), 3.59 (bs, 2H), 3.09 (bs, 8H), 5.19 (s, 5H), 1.82 (bs, 1H)

[0664]

1487		MS (ESI) m/z 737.44 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 12.44 (bs, 1H), 8.84-8.80 (m, 3H), 7.77 (d, J = 8.4 Hz, 1H), 7.71-7.66 (m, 2H), 7.61 (d, J = 4.8 Hz, 1H), 6.32 (t, J = 52.0 Hz, 1H), 4.83 (s, 2H), 3.75 (bs, 4H), 3.56 (bs, 3H), 2.95 (bs, 6H), 2.01 (s, 3H)	1490 	MS (ESI) m/z 700.41 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 10.35 (s, 1H), 8.78 (s, 1H), 8.75 (d, J = 4.4 Hz, 1H), 8.64 (s, 1H), 7.76 (d, J = 8.0 Hz, 1H), 7.69 (d, J = 9.6 Hz, 2H), 7.54 (d, J = 4.8 Hz, 1H), 6.39 (bs, 1H), 4.83 (s, 2H), 4.37-4.08 (m, 4H), 3.87 (bs, 4H), 3.26 (bs, 2H), 2.18 (bs, 4H), 2.10 (s, 3H)
1491		MS (ESI) m/z 680.42 [M+1]+; 1H NMR (400 MHz, DMSO-d6) d 8.76 (d, J = 4.8 Hz, 1H), 8.68 (d, J = 8.8 Hz, 2H), 7.75 (d, J = 8.8 Hz, 1H), 7.68 (d, J = 6.4 Hz, 2H), 7.55 (d, J = 4.8 Hz, 1H), 4.81 (s, 2H), 3.82 (t, J = 6.8 Hz, 2H), 3.33-3.25 (m, 5H), 2.92 (t, J = 6.8 Hz, 2H), 2.45 (s, 3H), 2.04 (s, 3H)	1494	MS (ESI) m/z 689.42 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.77 (d, J = 4.8 Hz, 1H), 8.73 (s, 1H), 8.66 (s, 1H), 7.76 (d, J = 9.2 Hz, 1H), 7.69-7.68 (m, 2H), 7.55 (d, J = 4.4 Hz, 1H), 4.82 (s, 2H), 4.30 (s, 1H), 3.06-3.01 (m, 7H), 2.06 (s, 3H), 1.86-1.83 (m, 4H), 1.25 (dd, J = 8.0 Hz, 5.6 Hz, 2H), 1.05 (dd, J = 7.2, 4.8 Hz, 2H)
1492		MS (ESI) m/z 633.31 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 9.11 (s, 1H), 8.73 (d, J = 4.8 Hz 1H), 8.59 (s, 1H), 7.76 (d, J = 8.4 Hz, 1H), 7.70-7.67 (m, 2H), 7.54 (d, J = 4.8 Hz, 1H), 6.40 (t, J = 50.8 Hz, 1H), 4.87 (s, 2H), 3.49 (bs, 4H), 3.12-2.77 (m, 5H), 2.17 (s, 3H)	1495	MS (ESI) m/z 638.41 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.79-8.74 (m, 2H), 8.65 (s, 1H), 7.78 (d, J = 8.0 Hz, 1H), 7.70-7.68 (m, 2H), 7.55 (d, J = 4.8 Hz, 1H), 4.83 (s, 2H), 4.54-4.53 (m, 1H), 3.58-3.55 (m, 2H), 3.20 (bs, 2H), 3.01 (s, 3H), 2.83-2.82 (m, 3H), 2.10 (bs, 7H)

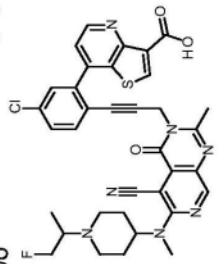
[0665]

1493 	MS (ESI) m/z 700.47 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.82 (s, 1H), 8.75 (d, J = 4.8 Hz, 1H), 8.65 (s, 1H), 7.75 (d, J = 8.0 Hz, 1H), 7.70-7.67 (m, 2H), 7.54 (d, J = 4.8 Hz, 1H), 4.83 (s, 2H), 4.43-3.90 (m, 4H), 3.22-2.87 (m, 8H), 2.13 (s, 3H), 1.46 (s, 3H)	1496 	MS (ESI) m/z 690.46 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.75 (d, J = 4.7 Hz 1H), 8.72 (s, 1H), 8.69 (s, 1H), 7.74 (d, J = 8.2 Hz, 1H), 7.66-7.64 (m, 2H), 7.53 (d, J = 4.6 Hz, 1H), 4.83 (s, 2H), 4.60-4.58 (m, 1H), 3.18 (s, 3H), 3.10-3.00 (m, 1H), 2.27 (s, 3H), 1.60-1.57 (m, 1H), 1.30-1.24 (m, 5H), 0.87-0.67 (m, 8H)
1497	MS (ESI) m/z 694.46 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.76 (d, J = 4.8 Hz, 1H), 8.69 (d, J = 6.8 Hz, 1H), 7.76-7.43 (m, 1H), 7.68 (dd, J = 2.0, 4.0 Hz, 1H), 7.54 (d, J = 4.8 Hz, 1H), 4.81 (s, 2H), 3.73-3.70 (m, 2H), 3.27 (bs, 5H), 2.68-2.64 (m, 2H), 2.41 (s, 3H), 2.05 (s, 3H), 1.90 (t, J = 13.6 Hz, 2H)	1500 	MS (ESI) m/z 700.47 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.74 (d, J = 4.8 Hz, 1H), 8.63 (s, 1H), 8.60 (s, 1H), 7.75 (d, J = 8 Hz, 1H), 7.68-7.66 (m, 2H), 7.51 (d, J = 4.8 Hz, 1H), 6.15 (tt, J = 4.0, 55.6 Hz, 1H), 4.79 (s, 2H), 4.53 (t, J = 7.2 Hz, 2H), 2.89 (d, J = 11.2 Hz, 2H), 2.77-2.67 (m, 4H), 2.21-2.16 (m, 4H), 2.03 (s, 3H), 1.81 (d, J = 11.6 Hz, 2H)
1498	MS (ESI) m/z 595.39 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.11 (bs, 1H), 9.73 (bs, 1H), 9.14 (s, 1H), 8.73 (d, J = 4.8 Hz, 1H), 8.60 (s, 1H), 7.76 (d, J = 9.2 Hz, 1H), 7.71-7.67 (m, 2H), 7.54 (d, J = 4.8 Hz, 1H), 7.39 (d, J = 15.2 Hz, 1H), 7.20-7.10 (m, 1H), 4.88 (s, 2H), 4.16-4.08 (m, 2H), 2.87 (s, 6H), 2.15 (s, 3H)	1501 	MS (ESI) m/z 783.47 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 12.47 (s, 1H), 8.81 (d ,J = 5.6 Hz, 2H), 8.75 (s, 1H), 7.78 (d, J = 8.4 Hz, 1H), 7.71-7.68 (dd, J = 2.0, 10.4 Hz, 2H), 7.62 (d, J = 4.4 Hz, 1H), 4.82 (s, 2H), 4.32 (bs, 1H), 3.55 (s, 3H), 3.31 (bs, 2H), 3.10 (bs, 5H), 2.51 (bs, 2H), 1.97 (bs, 5H), 1.82-1.79 (m, 2H)

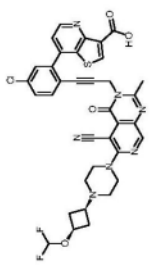
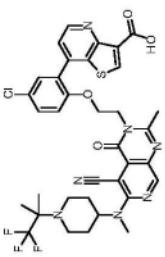
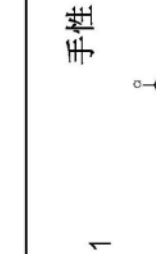
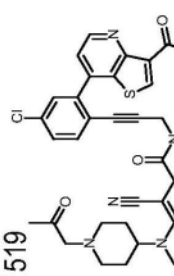
[0666]

1499	MS (ESI) m/z 672.39 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.26 (bs, 1H), 9.90 (bs, 1H), 8.89 (s, 1H), 8.75 (d, J = 4.8 Hz, 1H), 8.69 (s, 1H), 7.76 (d, J = 8.4 Hz, 1H), 7.71-7.66 (m, 2H), 7.55 (d, J = 4.8 Hz, 1H), 6.48 (t, J = 53.2 Hz, 1H), 5.21-5.02 (m, 2H), 4.82 (s, 2H), 4.53 (bs, 4H), 4.20-3.80 (m, 2H), 2.78-2.63 (m, 2H), 2.18 (s, 3H)	1502	MS (ESI) m/z 716.50 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.75 (d, J = 4.8 Hz, 1H), 8.72 (s, 1H), 8.57 (s, 1H), 7.75 (d, J = 9.2 Hz, 1H), 7.68-7.66 (m, 2H), 7.50 (d, J = 4.8 Hz, 1H), 4.82 (s, 2H), 4.28-4.22 (m, 1H), 3.09 (s, 3H), 3.01 (d, J = 11.2 Hz, 2H), 2.75 (t, J = 14.4 Hz, 2H), 2.38 -2.32 (m, 2H), 2.05 (s, 3H), 2.01-1.85 (m, 4H), 1.77 (d, J = 11.6 Hz, 2H), 0.96 (t, J = 7.2 Hz, 3H)
1503	MS (ESI) m/z 718.42 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.08 (bs, 1H), 8.76-8.74 (m, 2H), 8.65 (s, 1H), 7.75 (d, J = 8.0 Hz, 1H), 7.69-7.67 (m, 2H), 7.54 (d, J = 4.8 Hz, 1H), 6.79 (t, J = 74.8 Hz, 1H), 4.82 (s, 2H), 4.56 (bs, 1H), 4.23 (s, 2H), 3.65 (bs, 2H), 3.46 (bs, 2H), 3.26-3.19 (m, 2H), 3.11 (s, 3H), 2.26-2.08 (m, 2H), 2.04 (s, 5H)	1506	MS (ESI) m/z 730.26 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.76-8.74 (m, 2H), 8.65 (s, 1H), 7.75 (d, J = 6.0 Hz, 1H), 7.70-7.67 (m, 2H), 7.55 (d, J = 4.8 Hz, 1H), 4.82 (s, 2H), 4.65-4.60 (m, 1H), 3.91-3.78 (m, 2H), 3.41-3.39 (m, 2H), 3.22 (s, 3H), 2.32-2.26 (m, 2H), 2.24-2.08 (m, 5H), 1.84-1.79 (m, 3H), 1.51 (s, 6H)
1504	MS (ESI) m/z 744.4 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.75 (d, J = 4.8 Hz, 2H), 8.65 (s, 1H), 7.75 (d, J = 8.0 Hz, 1H), 7.70 (d, J = 2.0 Hz, 2H), 7.55 (d, J = 4.8 Hz, 1H), 6.73 (t, J = 75 Hz, 1H), 4.82 (s, 2H), 4.65 (bs, 1H), 4.21 (bs, 2H), 3.09 (s, 3H), 2.70-2.50 (m, 4H), 2.09 (bs, 7H), 1.33 (bs, 2H), 1.12 (bs, 2H)	1507	MS (ESI) m/z 734.30 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.76 (d, J = 4.8 Hz, 1H), 8.71 (s, 1H), 8.66 (s, 1H), 7.76 (d, J = 5.2 Hz, 1H), 7.70-7.67 (m, 2H), 7.55 (d, J = 4.8 Hz, 1H), 4.81 (s, 2H), 4.30-4.06 (m, 2H), 3.53-3.37 (m, 2H), 3.08 (s, 3H), 2.05 (s, 3H), 1.90-1.86 (m, 4H), 1.33 (s, 6H)

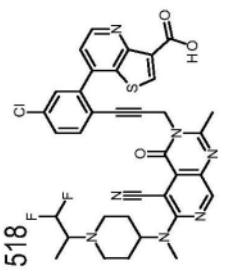
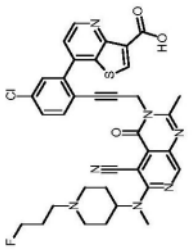
[0667]

1505	MS (ESI) m/z 671.41 [M+1] +; 1H NMR (400 MHz, DMSO-d6) δ 8.76 (d, J = 4.8 Hz, 1H), 8.68 (d, J = 1.6 Hz, 2H), 7.75 (d, J = 8.4 Hz, 1H), 7.70-7.67 (m, 2H), 7.55 (d, J = 4.8 Hz, 1H), 4.82 (s, 3H), 3.38-3.28 (m, 4H), 3.11 (s, 9H), 2.02 (s, 3H), 1.97-1.91 (m, 2H), 1.89-1.83 (m, 2H)	1508 手性 	MS (ESI) m/z, 684.48 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.76 (d, J = 4.8 Hz, 1H), 8.74 (s, 1H), 8.65 (s, 1H), 7.75 (d, J = 8.4 Hz, 1H), 7.69 (d, J = 2.0 Hz, 1H), 7.67 (s, 1H), 7.55 (d, J = 4.8 Hz, 1H), 4.82 (bs, 4H), 4.68-4.62 (m, 2H), 3.60 (bs, 2H), 3.33 (bs, 2H), 3.11 (s, 3H), 2.24 (bs, 2H), 2.13 (bs, 2H), 2.09 (s, 3H), 1.33 (d, J = 6.8 Hz, 3H)
1509	MS (ESI) m/z 704.38 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.06 (bs, 1H), 9.76 (bs, 1H), 8.84 (s,1H), 8.75 (d, J = 4.8 Hz, 1H), 8.64 (s, 1H), 7.75 (d, J = 8.4 Hz, 1H), 7.70-7.65 (m, 2H), 7.53 (d, J = 4.8 Hz, 1H), 6.71 (t, J = 75.6 Hz, 1H), 4.83 (s, 2H), 4.40-4.36 (m, 2H), 3.94 (t, J = 6.0 Hz, 2H), 3.74-3.71 (m, 2H), 3.60-3.20 (m, 6H), 2.14 (s, 3H), 2.10-2.05 (m, 2H)	1512	MS (ESI) m/z 745.4 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 12.65 (s, 1H), 10.01 (bs, 1H), 8.87 (d, J = 4.8 Hz, 1H), 8.62 (s, 1H), 8.60 (s, 1H), 7.61 (dd, J = 8.8, 4.8 Hz, 1H), 7.54 (d, J = 4.8 Hz, 1H), 7.43 (d, J = 2.5 Hz, 1H), 7.38 (d, J = 9.0 Hz, 1H), 4.60 (s, 2H), 4.54 (s, 2H), 4.44-4.37 (m, 4H), 4.28-4.16 (m, 4H), 4.00-3.80 (m, 1H), 3.49 (s, 3H), 2.23-2.14 (m, 2H), 2.09-1.95 (m, 2H), 1.85-1.70 (m, 5H)
1510	MS (ESI) m/z 716.40 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.15 (bs, 1H), 8.79 (s, 1H), 8.75 (d, J = 4.8 Hz, 1H), 8.66 (s, 1H), 7.75 (d, J = 9.1 Hz, 1H), 7.69-7.67 (m, 2H), 7.54 (d, J = 4.8 Hz, 1H), 6.68 (t, J = 75.9 Hz, 1H), 4.82 (s, 2H), 4.01 (bs, 2H), 3.40-2.80 (m, 8H), 2.08 (s, 3H), 1.05-0.65 (m, 4H)	1513	MS (ESI) m/z 724.49 [M+1]+; ; 1H NMR (400 MHz, DMSO-d6) δ 8.82 (d, J = 4.8 Hz, 1H), 8.61 (s, 1H), 8.40 (s, 1H), 7.60 (dd, J = 8.8, 2.4 Hz, 1H), 7.46 (d, J = 4.8 Hz, 1H), 7.42 (d, J = 2.4 Hz, 1H), 7.36 (d, J = 9.2 Hz, 1H), 6.79 (t, J = 75.2 Hz, 1H), 4.54-4.51 (m, 1H), 4.38 (d, J = 4.4 Hz, 2H), 4.28 (d, J = 4.4 Hz, 4H), 3.67-3.63 (m, 2H), 3.45 (bs, 2H), 3.25-3.22 (m, 2H), 3.09 (s, 3H), 2.21-2.15 (m, 2H), 2.08-2.05 (m, 2H), 1.71 (s, 3H)

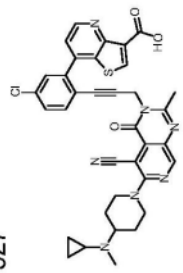
[0668]

1511 手性 	MS (ESI) m/z 716.44 [M+1]+; ; 1H NMR (400 MHz, DMSO-d6) δ 13.01 (bs, 1H), 10.04 (bs, 1H), 8.84 (s, 1H), 8.75 (d, J = 4.8 Hz,1H), 8.64 (s,1H), 7.75 (d, J = 8.4 Hz, 1H), 7.70-7.60 (m, 2H), 7.52 (d, J = 4.4 Hz,1H), 6.71 (t, J = 75.2 Hz, 1H), 4.83 (s, 2H), 4.55-4.36 (m, 3H), 3.70-3.40 (m, 5H), 3.16 (bs, 2H), 2.77 (bs, 2H), 2.50-2.35 (m, 2H), 2.14 (s, 3H)	1514 	MS (ESI) m/z 740.49 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.82 (d, J = 4.8 Hz, 1H), 8.59 (s, 1H), 8.43 (s, 1H), 7.60 (dd, J = 9.2, 2.8 Hz, 1H), 7.48 (d, J = 4.8 Hz, 1H), 7.43 (d, J = 2.4 Hz, 1H), 7.35 (d, J = 8.8 Hz, 1H), 4.38-4.37 (m, 2H), 4.26 (bs, 2H), 4.19 (s,2H), 3.36 (bs, 2H), 3.05 (s, 3H), 1.83 (bs, 4H), 1.73 (s, 4H), 1.33 (s, 6H)
1515 	MS (ESI) m/z 744.51 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.83 (d, J = 4.8 Hz, 1H), 8.60 (s, 1H), 7.85 (dd, J = 8.8 Hz, 2.4 Hz, 1H), 7.48 (d, J = 4.8 Hz, 1H), 7.43 (d, J = 2.8 Hz, 1H), 7.36 (d, J = 9.2 Hz, 1H), 6.57 (t, J = 52 Hz, 1H), 4.38 (d, J = 4.8 Hz, 2H), 4.30-4.02 (m, 3H), 3.30-2.89 (m, 9H), 1.99 (bs, 2H), 1.82 (bs, 2H), 1.74 (s, 3H)	1519 	MS (ESI) m/z 680.45 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.08 (bs, 1H), 8.75 (d, J = 4.8 Hz, 2H), 8.64 (s, 1H), 7.75 (d, J = 8.4 Hz, 1H), 7.69 (d, J = 2 Hz, 2H), 7.5 (d, J = 4.8 Hz, 1H), 4.82 (s, 2H), 4.57 (bs, 2H), 4.34 (bs, 2H), 3.23 (d, J = 11.6 Hz, 2H), 3.19 (s, 1H), 3.11 (s, 3H), 2.31 (m, 2H), 2.21 (s, 3H), 2.10-2.03 (m, 5H)
1516	MS (ESI) m/z 753.18 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 12.66 (s, 1H), 9.81 (bs, 1H), 8.89 (d, J = 4.4 Hz, 1H), 8.75 (s, 1H), 8.57 (s, 1H), 7.59 (dd, J = 2.8, 9.2 Hz, 1H), 7.56 (d, J = 4.8 Hz, 1H), 7.40 (d, J = 8.4 Hz, 2H), 2.26 (s, 2H), 4.23 (s, 4H), 3.80 (bs, 6H), 3.61 (s, 3 H), 3.42 (bs, 2H), 1.81 (s, 3H), 1.53-1.48 (m, 6H)	1520	MS (ESI) m/z 720.44 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.09 (bs, 1H), 8.77-8.75 (m, 2H), 8.65 (s, 1H), 7.76 (d, J = 8.0 Hz, 1H), 7.68 (d, J = 9.2 Hz, 2H), 7.55 (d, J = 4.4 Hz, 1H), 4.83 (s, 2H), 4.55 (bs, 1H), 3.70 (bs, 2H), 3.24 (bs, 4H), 3.11 (bs, 3H), 2.89 (bs, 2H), 2.15-2.11 (m, 7H)

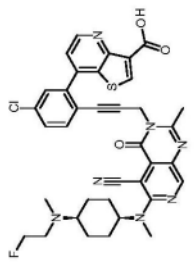
[0669]

1518 	MS (ESI) m/z 702.43 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.75 (d, J = 4.8 Hz, 1H), 8.74 (s, 1H), 8.65 (s, 1H), 7.75 (d, J = 8.4 Hz, 1H), 7.69 (s, 1H), 7.67 (s, 1H), 7.55 (d, J = 4.8 Hz, 1H), 6.53 (t, J = 50.0 Hz, 1H), 4.82 (bs, 2H), 4.57 (d, J = 2.4 Hz, 1H), 3.58 (bs, 2H), 3.36 (bs, 2H), 3.16 (s, 3H), 2.98 (bs, 1H), 2.24 (bs, 2H), 2.08 (bs, 5H), 1.35 (s, 3H)	1521 	MS (ESI) m/z 784.45 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.76-8.75 (m, 2H), 8.65 (s, 1H), 7.75 (d, J = 8.4 Hz, 1H), 7.70-7.67 (m, 2H), 7.54 (d, J = 4.8 Hz, 1H), 4.82 (s, 2H), 4.56 (dt, J = 47.2, 5.6 Hz, 2H), 4.59-4.57 (m, 1H), 3.68-3.55 (m, 2H), 3.21-3.19 (m, 4H), 3.11 (s, 3H), 2.21-2.05 (m, 9H)
1522	MS (ESI) m/z 714.42 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.76 (d, J = 4.8 Hz, 1H), 8.71 (s, 1H), 7.66 (s, 1H), 7.75 (d, J = 9.2 Hz, 1H), 7.68 (t, J = 2.8 Hz, 2H), 7.55 (d, J = 4.8 Hz, 1H), 6.08 (t, J = 56.4 Hz, 1H), 4.81 (s, 2H), 4.09 (bs, 1H), 3.05 (bs, 5H), 2.92 (bs, 2H), 2.05 (s, 3H), 1.79-1.73 (m, 4H), 0.85-0.78 (m, 4H)	1525	MS (ESI) m/z 648.39 [M+1]; 1H NMR (400 MHz, DMSO-d6) δ 8.78 (s, 1H), 8.76 (d, J = 4.4 Hz, 1H), 8.65 (s, 1H), 7.75 (d, J = 8.4 Hz, 1H), 7.70-7.67 (m, 1H), 7.55 (d, J = 4.8 Hz, 1H), 5.13 (bs, 1H), 4.81-4.67 (m, 6H), 3.97 (bs, 2H), 2.77 (bs, 2H), 2.10 (s, 3H), 0.85 (bs, 4H)
1523	MS (ESI) m/z 680.48 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.76 (d, J = 6.4 Hz, 2H), 8.64 (s, 1H), 7.75 (d, J = 8.4 Hz, 1H), 7.70-7.67 (m, 2H), 7.55 (d, J = 4.4 Hz, 1H), 4.82 (s, 2H), 4.80-4.76 (m, 4H), 4.58 (bs, 1H), 4.37 (bs, 1H), 3.55 (d, J = 8.8 Hz, 2H), 3.12 (bs, 5H), 2.15-2.10 (m, 5H), 剩余的质子合并在水分峰中	手性 1526	MS (ESI) m/z 704.41 [M+1] +; 1H NMR (400 MHz, DMSO-d6) δ 13.16 (bs, 1H), 8.79 (s, 1H), 8.75 (d, J = 4.8 Hz, 1H), 8.65 (s, 1H), 7.75 (d, J = 8.3 Hz, 1H), 7.69-7.67 (m, 2H), 7.54 (d, J = 4.8 Hz, 1H), 4.82 (s, 2H), 3.73 bs, 4H), 3.00 (bs, 4H), 2.70-2.50 (m, 合并的, 1H), 2.20-2.07 (m, 1H), 2.08 (s, 3H), 1.03-1.08 (m, 2H)

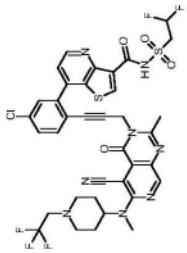
[0670]

1524	MS (ESI) m/z 678.20 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.06 (bs, 1H), 8.75.-8.74 (m, 2H), 8.65 (s, 1H), 7.75 (d, J = 8.4 Hz ,1H), 7.68 (d, J = 8.8 Hz ,2H), 7.54 (d, J = 4.8 Hz, 1H), 4.82 (s, 2H), 4.64 (t, J = 8.4 Hz, 1H), 3.49 (s, 4H), 3.10 (s, 3H), 2.21-2.08 (m, 7H), 1.39 (s, 3H), 1.14 (bs, 2H), 0.81 (bs, 2H)	1527 	MS (ESI) m/z 664.45 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 9.05 (bs, 1H), 8.79 (s, 1H), 8.75 (d, J = 4.8 Hz, 1H), 8.65 (s, 1H), 7.75 (d, J = 8.0 Hz, 1H), 7.71-7.65 (m, 2H), 7.54 (d, J = 4.8 Hz, 1H), 4.83 (s, 2H), 4.39 (d, J = 12.4 Hz, 2H), 3.19 (t, J = 12.0 Hz, 2H), 2.95-2.90 (m, 5H), 2.32-2.28 (m, 2H), 2.10 (s, 3H), 2.00-1.80 (m, 2H), 1.02-0.91 (m, 2H), 0.90-0.81 (m, 2H)
1528	MS (ESI) m/z 625.37 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.77 (d, J = 4.8 Hz, 1H), 8.72 (s, 1H), 8.66 (s, 1H), 7.75 (d, J = 8.8 Hz, 1H), 7.70-7.65 (m, 2H), 7.55 (d, J = 4.8 Hz, 1H), 4.81 (s, 2H), 4.60-4.45 (m, 1H), 4.05-3.95 (m, 2H), 3.65-3.40 (m, 2H), 3.11 (s, 3H), 2.06 (s, 3H), 2.00-1.85 (m, 2H), 1.78 (d, J = 10.8 Hz, 2H)	手性 1531	MS (ESI) m/z 714.45 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.06 (bs, 1H), 10.53 (bs, 1H), 8.77-8.70 (m, 2H), 8.65 (s, 1H), 7.75 (d, J = 4.4 Hz, 1H), 7.69-7.67 (m, 2H), 7.55 (d, J = 4.8 Hz, 1H), 6.49 (t, J = 56.4 Hz, 1H), 4.82 (s, 2H), 4.57 (bs, 2H), 3.80-3.48 (m, 3H), 3.40-3.20 (m, 2H), 3.16 (s, 4H), 3.01-2.70 (m, 2H), 2.02-2.15 (m, 2H), 2.06 (s, 3H), 1.80-1.65 (m, 2H)
1529	MS (ESI) m/z 696.48 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 9.00 (bs, 1H), 8.76-8.74 (m, 2H), 8.65 (s, 1H), 7.76 (d, J = 8.0 Hz, 1H), 7.70-7.67 (m, 2H), 7.75 (d, J = 4.8 Hz, 1H), 4.83 (s, 2H), 4.72-4.66 (m, 2H), 3.65 (bs, 4H), 3.09 (s, 3H), 2.71 (s, 1H), 2.12-2.08 (m, 7H), 1.35 (bs, 2H), 1.16 (bs, 2H)	手性 1532	MS (ESI) m/z 670.30 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 10.05 (bs, 1H), 8.76-8.70 (m, 2H), 8.65 (s, 1H), 7.75 (d, J = 8.8 Hz, 1H), 7.70-7.68 (m, 2H), 7.55 (d, J = 4.8 Hz, 1H), 4.96- 4.68 (m, 4H), 4.01-3.95 (m, 1H), 3.65- 3.28 (m, 3H), 3.22 (s, 3H), 2.82 (s, 3H), 2.80-2.55 (m, 4H), 2.08 (s, 3H)

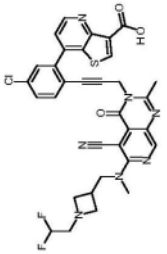
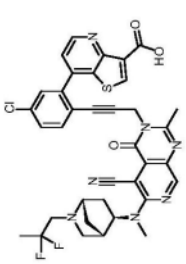
[0671]

1530	MS (ESI) m/z 732.40 [M+1]+; 1H NMR (400 MHz, DMSO- d6) δ 8.76 (d, J = 4.8, 1H), 8.70 (s, 1H), 8.65 (s, 1H), 7.79-7.73 (m, 1H), 7.71-7.65 (m, 2H), 7.55 (d, J = 4.8 Hz, 1H), 4.81 (s, 2H), 4.32-4.20 (m, 1H), 3.12-3.10 (m, 5H), 2.81 (t, J = 11.2 Hz, 2H), 2.05 (s, 3H), 1.85-1.65 (m, 4H), 1.06-0.90 (m, 4H)	1533 手性 	MS (ESI) m/z 698.43 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 9.19 (bs, 1H), 8.76-8.75 (m, 2H), 8.65 (s, 1H), 7.75 (d, J = 8.8 Hz, 1H), 7.70-7.68 (m, 2H), 7.55 (d, J = 8.8 Hz, 1H), 4.95-4.82 (m, 4H), 4.35-4.25 (m, 1H), 3.60-3.40 (m, 3H), 3.12 (s, 3H), 2.95-2.90 (m, 3H), 2.13-1.72 (m, 11H)
1534	MS (ESI) m/z 597.28 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 9.35 (s, 1H), 8.79-8.75 (m, 2H), 7.75 (d, J = 8.0 Hz, 1H), 7.71-7.66 (m, 2H), 7.54 (d, J = 4.4 Hz, 1H), 5.00-4.97 (m, 1H), 4.88 (d, J = 18.4 Hz, 1H), 4.77-4.73 (m, 2H), 4.44 (bs, 1H), 3.89 (d, J = 12.0 Hz, 1H), 3.64 (d, J = 12.0 Hz, 1H), 3.57 (s, 3H), 2.13 (s, 3H)	1537	MS (ESI) m/z 768.43 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.74 (d, J = 5.2 Hz, 1H), 8.70 (s, 1H), 8.63 (s, 1H), 7.83 (bs, 1H), 7.75 (d, J = 8.4 Hz, 1H), 7.70-7.69 (m, 2H), 7.54 (d, J = 4.8 Hz, 1H), 6.74-6.60 (m, 1H), 6.48 (bs, 1H), 4.81 (s, 2H), 4.5-4.25 (m, 2H), 4.15-4.05 (bs, 2H), 3.90 (s, 3H), 3.45-3.3 (bs, 2H), 3.09 (s, 3H), 2.2-2.13 (bs, 2H), 2.06 (s, 3H), 2.05-1.9 (bs, 2H)
1535	MS (ESI) m/z 702.43 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.77 (d, J = 4.4 Hz, 2H), 8.66 (s, 1H), 7.75 (d, J = 9.2 Hz, 1H), 7.70-7.68 (m, 2H), 7.55 (d, J = 4.8 Hz, 1H), 6.51 (bs, 1H), 4.82 (s, 2H), 4.35 (bs, 1H), 3.66-3.51 (m, 6H), 3.06-2.97 (m, 2H), 2.16-2.02 (m, 7H), 1.13 (t, J = 6.8 Hz, 3H)	1538	MS (ESI) m/z 811.19 [M+1]+; ; 1H NMR (400 MHz, DMSO-d6) δ 12.45 (s, 1H), 8.85 (d, J = 4.8 Hz 1H), 8.70 (s, 2H), 8.69 (s, 1H), 7.78-7.69 (m, 3H), 7.63 (d, J = 4.8 Hz, 1H), 4.82 (s, 2H), 4.32 (t, J = 11.6 Hz, 1H), 3.94-3.87 (m, 2H), 3.31 (bs, 2H), 3.10-3.07 (m, 5H), 2.59 (m, 1H), 1.96 (d, J = 9.3 Hz, 2H), 1.90-1.77 (m, 5H), 1.44 (s, 6H)

[0672]

1536		MS (ESI) m/z 768.45 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.76 (d, J = 4.8 Hz, 1H), 8.74 (s, 1H), 8.65 (s, 1H), 7.90 (bs, 1H), 7.76 (d, J = 8.0 Hz, 1H), 7.70 (d, J = 2.0 Hz, 1H), 7.67 (s, 1H), 7.55 (d, J = 4.8 Hz, 1H), 6.61 (bs, 1H), 4.82 (s, 2H), 4.53-4.24 (m, 5H), 3.92 (s, 3H), 3.53 (m, 2H), 3.09 (s, 5H), 2.00 (s, 5H)	1539		MS (ESI) m/z 833.16 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 12.88 (bs, 1H), 8.84-8.83 (m, 2H), 8.73 (s, 1H), 7.77 (d, J = 4.4 Hz, 1H), 7.76-7.69 (m, 2H), 7.63 (d, J = 4.8 Hz, 1H), 6.73-6.46 (tt, J = 54.4, 4.4 Hz, 1H), 4.82 (s, 2H), 4.49 (dt, J = 14.8, 4.0 Hz, 2H), 4.36-4.30 (m, 1H), 3.36 (bs, 2H), 3.10 (s, 5H), 2.66-2.63 (m, 2H), 2.05-1.77 (m, 7H)
1540		MS (ESI) m/z 688.42 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.80-8.74 (m, 2H), 8.65 (s, 1H), 7.75 (d, J = 8.8 Hz, 1H), 7.70-7.66 (m, 1H), 7.55 (d, J = 4.8 Hz, 1H), 6.47 (t, J = 58.0 Hz, 1H), 4.83 (s, 2H), 4.68 (bs, 1H), 3.70-3.40 (m, 4H), 3.16 (s, 3H), 3.08-2.75 (m, 2H), 2.08 (s, 3H), 2.05-1.75 (m, 4H)	1543		MS (ESI) m/z 707.43 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.35 (bs, 1H), 8.38 (d, J = 4.8 Hz, 1H), 8.72 (s, 1H), 8.36 (s, 1H), 7.61 (dd, J = 2.4, 8.8 Hz, 1H), 7.59 (d, J = 2.4 Hz, 1H), 7.48 (d, J = 4.8 Hz, 1H), 7.37 (d, J = 8.8 Hz, 1H), 5.46-5.45 (m, 1H), 4.39 (bs, 2H), 4.24 (bs, 2H), 3.92 (m, 1H), 3.60-3.58 (m, 2H), 3.08-3.05 (m, 8H), 2.14-1.90 (m, 2H), 1.79-1.77 (m, 3H)
1541		MS (ESI) m/z 701.18 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 9.92 (bs, 1H), 8.76 (d, J = 4.8 Hz, 1H), 8.69-8.66 (m, 2H), 7.76 (d, J = 8.8 Hz, 1H), 7.68 (t, J = 3.6 Hz, 2H), 7.55 (d, J = 4.4 Hz, 1H), 6.59 (bs, 1H), 4.81 (s, 2H), 3.72 (d, J = 6.0 Hz, 2H), 3.40 (bs, 4H), 3.33 (s, 3H), 3.11-2.99 (m, 2H), 2.06 (s, 3H), 1.79 (bs, 4H), 1.47 (bs, 1H)	1544 手性		MS (ESI) m/z 714.18 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.76 (d, J = 4.8 Hz, 2H), 8.64 (s, 1H), 7.75 (d, J = 9.2 Hz, 1H), 7.69 (t, J = 8.8 Hz, 2H), 7.54 (d, J = 4.8 Hz, 1H), 6.49 (bs, 1H), 4.82 (s, 2H), 4.49 (s, 1H), 3.75 (bs, 8H), 2.97 (s, 2H), 2.08 (bs, 5H), 1.81 (s, 1H), 1.68 (d, J = 12.8 Hz, 2H)

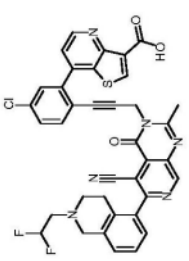
[0673]

1542		MS (ESI) m/z 674.40[M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 9.26 (s, 1H), 8.81 (d, J = 4.8 Hz, 1H), 8.73 (s, 1H), 7.77 (d, J = 8.4 Hz, 1H), 7.72-7.69 (m, 2H), 7.57 (d, J = 4.4 Hz, 1H), 6.42-6.15 (m, 1H), 4.90-4.80 (m, 3H), 4.51-4.46 (m, 1H), 3.87-3.84 (m, 2H), 3.68-3.61 (m, 3H), 3.58-3.37 (m, 2H), 3.25-3.17 (m, 2H), 2.87 (bs, 2H), 2.17 (s, 3H)	1545 手性 	MS (ESI) m/z 714.45 [M+1]+; 1H NMR (400 MHz, DMSO-d6 at 353.1 K) δ 8.15 (s, 1H), 8.77 (d, J = 4.8 Hz, 1H), 8.68 (s, 1H), 7.75 (d, J = 8.4 Hz, 1H), 7.67-7.64 (m, 2H), 7.53 (d, J = 4.8 Hz, 1H), 4.86-4.80 (m, 2H), 4.08-4.05 (m, 1H), 3.09 (s, 3H), 2.98 (m, 3H), 2.18 (s, 3H), 2.06-2.01 (m, 1H), 1.67 (t, J = 18.4 Hz, 3H), 1.38-1.26 (m, 4H)
1546		MS (ESI) m/z 811.16 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 12.43 (s, 1H), 8.82 (d, J = 4.8 Hz, 1H), 8.74 (d, J = 8.0 Hz, 2H), 7.78 (d, J = 8.8 Hz, 1H), 7.70 (d, J = 2.0 Hz, 1H), 7.68 (s, 1H), 7.61 (d, J = 4.8 Hz, 1H), 4.82 (s, 2H), 4.29 (t, J = 23.2 Hz, 1H), 3.22 (q, J = 10.0 Hz, 2H), 3.09 (s, 3H), 3.04 (d, J = 19.2 Hz, 10H), 1.92 (d, J = 8.0 Hz, 5H), 1.78 (d, J = 9.6 Hz, 2H)	1549	MS (ESI) m/z 859.42 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.05 (bs, 1H), 8.93 (d, J = 4.8 Hz, 1H), 8.56 (s, 1H), 8.25 (s, 1H), 8.17 (d, J = 7.6 Hz, 1H), 7.77-7.55 (m, 1H), 7.70-7.63 (m, 4H), 7.55-7.51 (m, 1H), 7.45 (d, J = 7.6 Hz, 1H) 4.82 (s, 2H), 4.29 (bs, 1H), 3.31 (bs, 2H), 3.08 (bs, 5H), 2.67 (s, 3H), 2.63-2.58 (m, 2H), 1.94-1.88 (m, 2H). 1.83 (s, 3H), 1.79-1.76 (m, 2H)
1547		MS (ESI) m/z 809.16 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 12.52 (s, 1H), 8.79 (t, J = 8.0 Hz, 2H), 8.73 (s, 1H), 7.75 (d, J = 8.4 Hz, 1H), 7.70 (d, J = 2 Hz, 2H), 7.60 (d, J = 4.8 Hz, 1H), 4.82 (s, 2H), 4.31 (t, J = 21.2 Hz, 1H), 3.29-3.22 (m, 4H), 3.10 (bs, 5H), 2.50 (s, 1H), 1.94 (d, J = 11.7 Hz, 5H), 1.78 (s, 2H), 1.29 (d, J = 3.8 Hz, 2H), 1.26-1.14 (m, 2H)	1550	MS (ESI) m/z 881.42 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.28 (bs, 1H), 8.94 (d, J = 5.2 Hz, 1H), 8.58 (s, 1H), 8.28 (s, 1H), 8.24-8.19 (m, 1H), 7.77-7.75 (m, 1H), 7.70-7.68 (m, 2H), 7.66 (d, J = 4.8 Hz, 1H), 7.61-7.56 (m, 1H), 7.48-7.40 (m, 1H), 4.80 (s, 2H), 4.37-4.26 (m, 1H), 3.37 (bs, 2H), 3.12-3.10 (m, 2H), 3.07 (s, 3H), 2.66-2.63 (m, 2H), 1.99-1.88 (m, 2H), 1.85-1.74 (m, 5H)

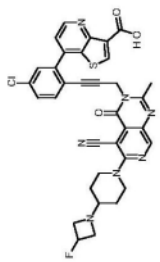
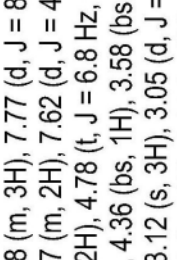
[0674]

1548	MS (ESI) m/z 845.44 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 12.09 (bs, 1H), 8.83 (d, J = 4.8 Hz, 1H), 8.67 (s, 1H), 8.45 (s, 1H), 8.15 (d, J = 7.2 Hz, 2H), 7.78-7.74 (m, 2H), 7.69-7.66 (m, 4H), 7.61 (d, J = 4.8 Hz, 1H), 4.80 (s, 2H), 4.31 (bs, 1H), 3.28 (bs, 2H), 3.09-3.06 (m, 5H), 2.58-2.50 (m, 2H), 1.94 (d, J = 11.2 Hz, 2H), 1.87 (s, 3H), 1.79 (d, 10.4 Hz, 2H)	1551	MS (ESI) m/z 859.42 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.05 (bs, 1H), 8.93 (d, J = 4.8 Hz, 1H), 8.56 (s, 1H), 8.25 (s, 1H), 8.17 (d, J = 7.6 Hz, 1H), 7.77-7.55 (m, 1H), 7.70-7.63 (m, 4H), 7.55-7.51 (m, 1H), 7.45 (d, J = 7.6 Hz, 1H) 4.82 (s, 2H), 4.29 (bs, 1H), 3.31 (bs, 2H), 3.08 (bs, 5H), 2.67 (s, 3H), 2.63-2.58 (m, 2H), 1.94-1.88 (m, 2H). 1.83 (s, 3H), 1.79-1.76 (m, 2H)
1553	MS (ESI) m/z 730.17 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.74 (s, 1H), 8.56 (s, 1H), 7.60-7.73 (m, 1H), 7.67-7.66 (m, 2H), 7.51 (d, J = 4.8 Hz, 1H), 6.14-5.56 (m, 1H), 4.82 (s, 2H), 4.59-4.55 (m, 2H), 4.48 (t, J = 6.4 Hz, 2H), 4.34-4.31 (m, 2H), 4.26-4.21 (m, 1H), 3.14-3.03 (m, 4H), 2.87 (t, J = 12.4 Hz, 1H), 2.07 (s, 3H), 1.76 (d, J = 12.0 Hz, 2H), 1.56-1.48 (m, 2H)	1556 手性	MS (ESI) m/z 700.34 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 10.04 (s, 1H), 8.77-8.74 (m 2H), 8.65 (s, 1H), 7.76 (d, J = 8.4 Hz, 1H), 7.70-7.66 (dd, J = 2.0, 10.4 Hz, 2H), 7.55 (d, J = 4.4 Hz, 1H), 6.54 (bs, 1H), 4.82 (s, 2H), 4.42 (s, 1H), 4.19 (bs, 1H), 3.86-3.59 (bs, 4H), 3.16-2.74 (bs, 4H), 2.11 (s, 5H), 1.97-1.78 (bs, 2H)
1554	MS (ESI) m/z 757.34 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.89 (s, 1H), 8.79 (d, J = 4.8 Hz, 1H), 8.59 (s, 1H), 7.77 (s, 1H), 7.75 (s, 1H), 7.71 (d, J = 2.0 Hz, 1H), 7.68 (bs, 1H), 7.58 (d, J = 4.4 Hz, 1H), 6.29 (t, J = 61.2 Hz, 1H), 4.86 (s, 2H), 4.44 (bs, 2H), 4.04 (bs, 4H), 3.25 (bs, 2H), 2.16 (bs, 4H), 2.10 (bs, 3H)	1557	MS (ESI) m/z 702.35[M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.00 (bs, 1H), 10.03 (bs, 1H), 8.80-8.68 (m, 3H), 7.74-7.63 (m, 3H), 7.59 (d, J = 5.2 Hz, 1H), 6.53 (t, J = 54.4 Hz, 1H), 5.90-5.40 (m, 1H), 4.48 (bs, 1H), 3.81-3.41 (m, 4H), 3.38-3.10 (m, 2H), 3.09 (s, 3H), 2.40-1.95 (m, 7H), 1.47 (t, J = 6.8 Hz, 3H)

[0675]

1555		MS (ESI) m/z 764.14 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 10.13 (bs, 1H), 8.77 (s, 1H), 8.75 (d, J = 7.2 Hz, 1H), 8.65 (s, 1H), 7.76 (s, 1H), 7.70 (d, J = 2.0 Hz, 2H), 7.67-7.54 (m, 6H), 4.82 (s, 2H), 4.56-4.22 (m, 5H), 3.01 (s, 5H), 2.97-2.87 (m, 2H), 2.09 (s, 5H)	1558  MS (ESI) m/z 707.32 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 9.18 (s, 1H), 8.79 (d, J = 4.8 Hz, 1H), 8.64 (s, 1H), 7.77 (d, J = 8.8 Hz, 1H), 7.70-7.68 (m, 2H), 7.56 (d, J = 4.8 Hz, 1H), 7.49-7.44 (m, 2H), 7.36 (bs, 1H), 6.42 (tt, J = 52.4, 7.4 Hz, 1H), 4.90 (s, 2H), 4.38 (bs, 2H), 3.48 (bs, 2H), 3.24 (bs, 2H), 2.86 (bs, 2H), 2.16 (s, 3H)
1559		MS (ESI) m/z 695.2 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 9.22 (bs, 1H), 8.78 (d, J = 4.7 Hz, 1H), 8.65 (s, 1H), 8.00-7.99 (m, 2H), 7.77 (d, J = 9.0 Hz, 1H), 7.70-7.66 (m, 4H), 7.56 (d, J = 4.7 Hz, 1H), 6.43 (t, J = 53.4 Hz, 1H), 4.90 (s, 2H), 4.23 (bs, 2H), 3.41 (bs, 2H), 2.66 (bs, 3H), 2.19 (s, 3H)	1562 MS (ESI) m/z 722.38 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 9.86 (bs, 1H), 8.81 (d, J = 4.8 Hz, 1H), 8.46 (s, 1H), 7.61-7.58 (m, 1H), 7.46 (d, J = 4.8 Hz, 1H), 7.41-7.36 (m, 2H), 4.50 (m, 1H), 4.41 (bs, 2H), 4.21 (bs, 2H), 3.65-3.37 (m, 4H), 3.06 (s, 3H), 2.62 (s, 3H), 2.25 (m, 2H), 2.00 (m, 2H), 1.79-1.69 (m, 8H)
1560		MS (ESI) m/z 703.32 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 11.40 (s, 1H), 9.44 (bs, 1H), 8.73 (s, 1H), 8.68 (d, J = 4.8 Hz, 1H), 8.48 (s, 1H), 7.74-7.72 (m, 1H), 7.66-7.64 (m, 2H), 7.48 (d, J = 4.8 Hz, 1H), 6.45 (b, 1H), 4.80 (s, 2H), 4.49 (bs, 1H), 3.35 (s, 4H), 3.08 (s, 3H), 2.50-2.47 (m, 2H), 2.08 (bs, 2H), 1.99 (s, 5H)	1563 MS (ESI) m/z 722.45 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.59 (s, 1H), 8.41 (bs, 1H), 7.59 (dd, J = 2.4, 8.8 Hz, 1H), 7.42-7.40 (m, 2H), 7.36 (d, J = 9.2 Hz, 1H), 4.53 (bs, 1H), 4.38 (bs, 2H), 4.21 (bs, 2H), 3.84 (bs, 4H), 3.08 (s, 3H), 3.54 (bs, 2H), 2.70 (s, 3H)), 1.99 (bs, 2H), 1.82 (bs, 5H), 1.76 (bs, 3H)

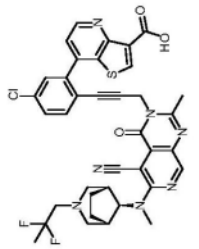
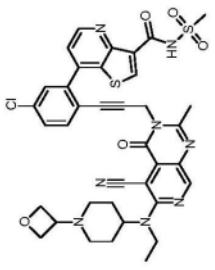
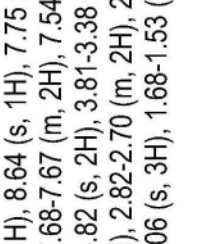
[0676]

1561		MS (ESI) m/z 757.43 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 12.47 (s, 1H), 8.81-8.78 (m, 3H), 7.77 (d, J = 8.4, 1H), 7.72-7.67 (m, 2H), 7.62 (d, J = 4.8 Hz, 1H), 4.83 (s, 2H), 4.78 (t, J = 6.8 Hz, 4H), 4.60 (bs, 1H), 4.36 (bs, 1H), 3.58 (bs, 2H), 3.53 (s, 3H), 3.12 (s, 3H), 3.05 (d, J = 14.0 Hz, 2H), 2.14 (bs, 4H), 1.99 (s, 3H)	1564		MS (ESI) m/z 668.2 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.78 (s, 1H), 8.75 (d, J = 4.8 Hz, 1H), 8.64 (s, 1H), 7.75 (d, J = 9.2 Hz, 1H), 7.67-7.70 (m, 2H), 7.54 (d, J = 4.8 Hz, 1H), 5.45 (d, J = 56.8 Hz, 1H), 4.83 (s, 2H), 4.54-4.29 (m, 5H), 3.52 (bs, 2H), 3.15-3.09 (m, 2H), 2.19-2.09 (m, 5H), 1.60-1.52 (m, 2H)
1565		MS (ESI) m/z 708.44 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.85 (s, 1H), 8.76 (d, J = 4.8 Hz, 1H), 8.65 (s, 1H), 7.75 (d, J = 8.0 Hz, 1H), 7.70-7.66 (m, 2H), 7.53 (d, J = 4.8 Hz, 1H), 4.84 (s, 2H), 4.66-4.36 (m, 5H), 3.91-3.78 (m, 4H), 2.95 (bs, 3H), 2.13 (s, 3H)	1569		MS (ESI) m/z 618.28 [M+1] +; 1H NMR (400 MHz, DMSO-d6) δ 14.24 (bs, 1H), 13.11 (bs, 1H), 9.17 (s, 1H), 8.79 (d, J = 4.80 Hz, 1H), 8.67 (s, 1H), 8.52 (d, J = 7.20 Hz, 2H), 7.76 (d, J = 8.00 Hz, 1H), 7.71-7.68 (m, 2H), 7.53 (d, J = 4.80 Hz, 1H), 7.38 (d, J = 7.20 Hz, 2H), 4.89 (s, 2H), 3.69 (s, 3H), 2.23 (s, 3H)
1566		MS (ESI) m/z 828.47 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.02 (s, 1H), 8.90 (d, J = 4.8 Hz, 1H), 8.71 (d, J = 4.4 Hz, 1H), 8.65 (s, 1H), 8.60 (s, 1H), 8.27-8.18 (m, 2H), 7.77-7.53 (m, 4H), 7.49 (d, J = 5.6 Hz, 1H), 6.66-6.29 (m, 1H), 4.82 (s, 2H), 4.60-4.45 (m, 1H), 3.50-3.15 (m, 6H), 3.09 (s, 3H), 2.30-1.80 (m, 7H)	1571		MS (ESI) m/z 665.43 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 9.00 (s, 1H), 8.82 (d, J = 4.4 Hz, 1H), 8.35 (s, 1H), 7.60 (dd, J= 8.8 Hz, 2.4 Hz, 1H), 7.47 (d, J = 4.8 Hz, 1H), 7.43 (d, J = 2.4 Hz, 1H), 7.36 (d, J = 8.8 Hz, 1H), 6.55 (t, J = 53.2 Hz, 1H), 4.40 (d, J = 4.4 Hz, 2H), 4.26 (s, 2H), 3.87 (bs, 1H), 3.47-3.24 (m, 4H), 2.00-1.89 (m, 4H),1.78 (s, 3H), 1.74-1.67 (m, 2H)

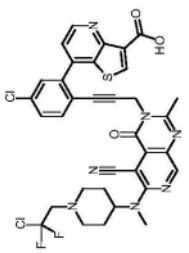
[0677]

1568		MS (ESI) m/z 636.25 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.18 (bs, 1H), 8.84 (s, 1H), 8.75 (d, J = 4.8 Hz,1H), 8.65 (s, 1H), 7.75 (d, J = 8.4 Hz, 1H), 7.70-7.65 (m, 2H), 7.53 (d, J = 4.8 Hz, 1H), 4.84 (s, 2H), 4.38 (m, 2H), 3.79 (m, 2H,), 3.49 (m, 4H), 3.03 (m, 1H), 2.14 (s, 3H), 0.93 (m, 4H)	1572		MS (ESI) m/z 709.45 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 9.18 (s, 1H), 8.77 (d, J = 4.8 Hz, 1H), 8.63 (s, 1H), 7.76 (d, J = 9.2 Hz, 1H), 7.70 (dd, J = 6.4 Hz, 2.0 Hz, 2H), 7.55 (d, J = 4.8 Hz, 1H), 4.89 (s, 2H), 3.78-3.56 (m, 3H), 3.28-3.19 (m, 2H), 3.00-2.79 (m, 2H), 2.08 (s, 3H), 1.98-1.85 (m, 4H)
1573		MS (ESI) m/z 685.39 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 9.06 (s, 1H), 8.75 (d, J = 4.8 Hz, 1H), 8.61 (s, 1H), 7.77-7.75 (m, 1H), 7.70-7.68 (m, 2H), 7.55 (d, J = 4.4 Hz, 1H), 6.60 (bs, 1H), 6.41 (s, 1H), 4.86 (s, 2H), 3.99-3.58 (m, 2H), 3.03-2.76 (m, 4H), 2.54 (s, 3H), 2.29-2.14 (m, 5H), 1.77-1.75 (m, 1H)	1576 手性		[02041] MS (ESI) m/z 714.55 [M+1]+; 1H-NMR (400 MHz, DMSO-d6) δ 8.80 (s, 1H), 8.76 (d, J = 4.8 Hz, 1H), 8.64 (s, 1H), 7.75 (d, J = 8.8 Hz, 1H), 7.68-7.67 (m, 2H), 7.54 (d, J = 4.8 Hz, 1H), 4.82 (s, 2H), 3.81-3.38 (m, 5H), 3.08 (s, 3H), 2.82-2.70 (m, 2H), 2.43-2.33 (m, 2H), 2.06 (s, 3H),1.68-1.53 (m, 7H)
1574		MS (ESI) m/z 659.38 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 9.14 (s, 1H), 8.77 (d, J = 4.8 Hz, 1H), 8.60 (s, 1H), 7.76 (d, J = 18.4 Hz, 1H), 7.70 (d, J=2.0 Hz, 1H), 7.55 (d, J = 4.8 Hz, 2H), 6.55 (t, J = 54.4 Hz, 1H), 4.87 (s, 2H), 3.60-2.87 (m, 7H), 2.17 (s, 3H), 2.04-1.73 (m, 4H)	1577 手性		MS (ESI) m/z 714.49 [M+1]+; 1H-NMR (400 MHz, DMSO-d6) δ 8.80 (s, 1H), 8.76 (d, J = 4.8 Hz, 1H), 8.64 (s, 1H), 7.75 (d, J = 8.8 Hz, 1H), 7.68-7.67 (m, 2H), 7.54 (d, J = 4.8 Hz, 1H), 4.82 (s, 2H), 3.81-3.38 (m, 5H), 3.08 (s, 3H), 2.82-2.70 (m, 2H), 2.43-2.33 (m, 2H), 2.06 (s, 3H), 1.68-1.53 (m, 7H)

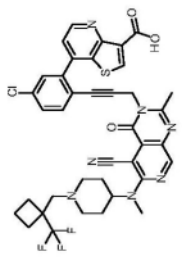
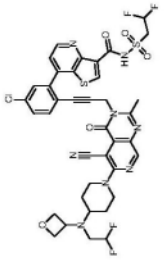
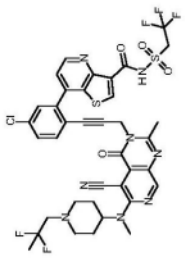
[0678]

1575 手性 	MS (ESI) m/z 728.08 [M+1]+; 1H-NMR (400 MHz, DMSO-d6) δ 8.80 (s, 1H), 8.76 (d, J = 4.8 Hz, 1H), 8.64 (s, 1H), 7.75 (d, J = 8.8 Hz, 1H), 7.68-7.67 (m, 2H), 7.54 (d, J = 4.8 Hz, 1H), 4.82 (s, 2H), 3.81-3.38 (m, 5H), 3.08 (s, 3H), 2.82-2.70 (m, 2H), 2.43-2.33 (m, 2H), 2.06 (s, 3H), 1.68-1.53 (m, 7H)	1578 	MS (ESI) m/z 771.57 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 12.48 (s, 1H), 8.82 (d, J = 4.4 Hz, 2H), 8.78 (s, 1H), 7.75 (d, J = 8.4 Hz, 1H), 7.72-7.67 (m, 2H), 7.63 (d, J = 4.8 Hz, 1H), 4.83 (s, 2H), 4.77-4.75 (m, 4H), 4.44-4.35 (m, 2H), 3.76-3.59 (m, 3H), 3.54 (s, 3H), 3.28-3.19 (m, 1H), 3.02 (bs, 2H), 2.15 (s, 4H), 1.99 (s, 3H), 1.15 (t, J = 6.8 Hz, 3H)
1579 手性 	MS (ESI) m/z 760.64 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.76 (d, J = 4.8 Hz, 1H), 8.17 (s, 1H), 8.66 (s, 1H), 7.76-7.74 (m, 1H), 7.70-7.68 (m, 2H), 7.56 (d, J = 4.8 Hz, 1H), 6.43-4.15 (m, 1H), 4.81 (s, 2H), 4.30 (bs, 1H), 3.54 (bs, 4H), 3.08 (s, 3H), 2.05 (bs, 7H), 1.83-1.67 (m, 6H), 1.17 (bs, 3H)	1583 手性	MS (ESI) m/z 744.52 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.76 (d, J = 4.8 Hz, 1H), 8.70 (s, 1H), 8.66 (s, 1H), 7.75 (d, J = 9.2 Hz, 1H), 7.69-7.68 (m, 2H), 7.55 (d, J = 4.8 Hz, 1H), 4.81 (s, 2H), 4.26-4.23 (m, 1H), 3.12-3.09 (m, 4H), 2.93 (bs, 3H), 2.57-2.52 (m, 2H), 2.06 (s, 3H), 1.89 (bs, 4H), 1.75-1.72 (m, 7H), 1.22 (bs, 2H)
1581 手性	MS (ESI) m/z 702.52 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.74-8.70 (m, 2H), 8.37 (s, 1H), 7.74 (d, J = 8.4 Hz, 1H), 7.67-7.64 (m, 2H), 7.44 (d, J = 4.4 Hz, 1H), 6.16 (t, J = 55.6 Hz, 1H), 4.89-4.84 (m, 3H), 3.081 (bs, 4H), 2.80-2.72 (m, 2H), 2.33 (bs, 3H), 2.07-1.98 (m, 4H), 1.90 (bs, 3H), 1.75-1.71 (m, 1H), 1.41 (t, J = 7.2 Hz, 1H)	1584	MS (ESI) m/z 724.3 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.01 (bs, 1H), 8.76-8.74 (m, 2H), 8.64 (s, 1H), 7.75 (d, J = 8.4 Hz, 1H), 7.70-7.67 (m, 2H), 7.55 (d, J = 4.8 Hz, 1H), 4.82 (s, 2H), 4.74-7.56 (m, 3H), 3.52-3.49 (m, 2H), 3.32-3.26 (m, 4H), 3.11 (s, 3H), 2.26-2.21 (m, 2H), 2.10 (s, 3H), 2.03-1.91 (m, 8H)

[0679]

1582		MS (ESI) m/z 778.66 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.76 (d, J = 4.8 Hz, 1H), 8.73 (s, 1H), 8.65 (s, 1H), 7.75 (d, J = 8.8 Hz, 1H), 7.70-7.67 (m, 2H), 7.55 (d, J = 4.8 Hz, 1H), 4.82 (s, 2H), 4.58 (bs, 2H), 4.24 (bs, 2H), 3.11 (s, 3H), 2.94-2.67 (m, 6H), 2.32-2.08 (m, 9H)	1585 	MS (ESI) m/z 722.42 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.77 (d, J = 4.8 Hz, 1H), 8.71 (s, 1H), 8.66 (s, 1H), 7.76-7.74 (m, 1H), 7.69-7.68 (m, 2H), 7.55 (d, J = 4.8 Hz, 1H), 4.81 (s, 2H), 4.29-4.27 (m, 1H), 3.44 (bs, 2H), 3.17-3.09 (m, 5H), 2.66 (bs, 2H), 2.05 (s, 3H), 1.94 (d, J = 10.4 Hz, 2H),1.80 (d, J = 10.8 Hz, 2H)
1586		MS (ESI) m/z 748.52 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.76 (d, J = 4.8 Hz, 1H), 8.72 (s, 1H), 8.70 (s, 1H), 7.74 (d, J = 8.0 Hz, 1H), 7.70-7.62 (m, 2H), 7.53 (d, J = 4.8 Hz, 1H), 4.84 (s, 2H), 4.48-4.30 (m, 1H), 3.40-2.85 (m, 9H), 2.20-1.75 (m, 7H), 1.20 (s, 6H)	1589	MS (ESI) m/z 791.49 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 12.47 (s, 1H), 9.72 (bs, 1H), 8.81-8.78 (m, 3H), 7.77 (d, J = 8.4 Hz, 1H), 7.72-7.67 (m, 2H), 7.62 (d, J = 4.8 Hz, 1H), 4.83 (s, 2H), 4.59 (bs, 1H), 3.82-3.45 (m, 6H), 3.30-2.95 (m, 9H), 2.20-2.14 (m, 4H), 1.99 (s, 3H)
1587		MS (ESI) m/z 746.54 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.13 (bs, 1H), 8.75 (d, J = 4.8 Hz, 1H), 8.70 (s, 1H), 8.65 (s, 1H), 7.75 (d, J = 9.2 Hz, 1H), 7.68-7.67 (m, 2H), 7.54 (d, J = 4.8 Hz, 1H), 4.81 (s, 2H), 4.26 (bs, 1H), 3.09 (s, 3H), 3.04 (d, J = 10.8 Hz, 2H), 2.70-2.50 (合并的, 2H), 2.10-2.00 (m, 5H), 1.88-1.81 (m, 4H), 0.97 (s, 2H), 0.74 (s, 2H)	1590	MS (ESI) m/z 807.10 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 12.47 (s, 1H), 8.80 (d, J = 5.2 Hz 1H), 8.78 (s, 1H), 8.75 (s, 1H), 7.77 (d, J = 8.4 Hz, 1H), 7.70 (dd, J = 10.4 Hz, 2 Hz, 2H), 7.62 (d, J = 4.8 Hz, 1H), 6.45 (t, J = 54.8 Hz, 1H), 4.82 (s, 2H), 4.50 (d, J = 6.8 Hz, 2H), 4.45 (d, J = 6.8 Hz, 2H), 4.34-4.29 (m, 1H), 3.55 (s, 3H), 3.11 (s, 3H), 2.91 (d, J = 10.8 Hz, 2H), 2.60-2.53 (m, 2H),1.96-1.85 (m, 7H)

[0680]

1588		MS (ESI) m/z 760.61 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.05 (bs, 1H), 9.09 (bs, 1H), 8.80-8.70 (m, 2H), 8.65 (s, 1H), 7.75 (d, J = 8.40 Hz, 1H), 7.71-7.63 (m, 2H), 7.54 (d, J = 4.00 Hz, 1H), 4.82 (s, 2H), 4.56 (bs, 1H), 3.70-3.50 (m, 4H), 3.20-3.20 (合并的, 2H), 3.11 (s, 3H), 2.41-2.20 (m, 6H), 2.18-1.94 (m, 7H)	1591		MS (ESI) m/z 857.53 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.85 (d, J = 5.2 Hz, 1H), 8.81 (s, 1H), 8.75 (s, 1H), 7.78 (d, J = 8.8 Hz, 1H), 7.71-7.69 (m, 2H), 7.64 (d, J = 4.8 Hz, 1H), 6.73-6.58 (m, 1H), 6.15-5.87 (m, 1H), 4.82 (s, 2H), 4.59-4.55 (m, 2H), 4.52-4.47 (m, 4H), 4.35-4.22 (m, 4H), 3.16-3.04 (m, 3H), 2.86 (m, 1H), 1.92 (s, 3H), 1.76 (d, J = 11.2 Hz, 2H), 1.56-1.48 (m, 2H)
1592		MS (ESI) m/z 714.10 [M+1]+; 1H-NMR (400 MHz, DMSO-d6) δ 13.09 (bs, 1H), 8.75-8.74 (m, 2H), 8.64 (s, 1H), 7.75 (d, J = 8.4 Hz, 1H), 7.69-7.67 (m, 2H), 7.53 (d, J = 4.8 Hz, 1H), 4.82 (s, 2H), 4.39 (bs, 2H), 4.01 (bs, 1H), 3.66 (bs, 1H), 3.20-2.95 (m, 5H), 2.72-2.66 (m, 2H), 2.08 (bs, 5H), 1.90-1.60 (m, 4H)	1595		MS (ESI) m/z 847.0 [M+1]+; 1H-NMR (400 MHz, DMSO-d6) δ 13.06 (bs, 1H), 8.85 (d, J = 4.8 Hz, 1H), 8.83 (s, 1H), 8.75 (s, 1H), 7.78 (d, J = 8.80 Hz, 1H), 7.71 (bs, 2H), 7.65 (d, J = 4.80 Hz, 1H), 5.04 (q, J = 9.60 Hz, 2H), 4.83 (s, 2H), 4.59 (bs, 1H), 3.77 (bs, 4H), 3.37 (bs, 2H), 3.11 (s, 3H), 2.26 (bs, 2H), 2.02 (bs, 2H), 1.95 (s, 3H), 1.76 (t, J = 17.6Hz, 3H)
1593		MS (ESI) m/z 851.58 [M+1]+; 1H-NMR (400 MHz, DMSO-d6) δ 13.03 (bs, 1H), 8.87 (d, J = 4.80 Hz, 1H), 8.84 (s, 1H), 8.73 (s, 1H), 7.77 (d, J = 9.20 Hz, 1H), 7.71-7.69 (m, 2H), 7.65 (d, J = 4.80 Hz, 1H), 5.06 (q, J = 9.60 Hz, 2H), 4.82 (s, 2H), 4.32-4.29 (m, 1H), 3.33 (bs, 2H), 3.09 (bs, 5H), 2.58 (bs, 2H), 1.96 (bs, 2H), 1.92 (s, 3H), 1.80 (d, J = 11.2 Hz, 2H)	1596		MS (ESI) m/z 701.0 [M+1]+; 1H-NMR (400 MHz, DMSO-d6 with D2O) δ 8.68 (s, 1H), 8.67 (s, 1H), 8.39 (s, 1H), 7.71 (d, J = 8.4 Hz, 1H), 7.65-7.63 (m, 1H), 7.57 (d, J = 1.6 Hz, 1H), 7.41 (d, J = 4.8 Hz, 1H), 4.73 (s 2H), 4.55-4.49 (m, 1H), 3.80-3.72 (m, 2H), 3.62-3.57 (m, 2H), 3.28 (t, J = 11.6 Hz, 2H), 3.09 (s, 1H), 2.53 (bs, 1H), 2.32-2.20 (m, 2H), 2.06 (bs, 6H), 1.74 (t, J = 19.6 Hz, 3H)

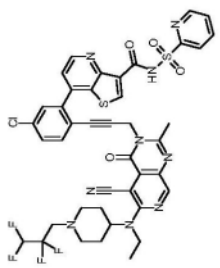
[0681]

1594	MS (ESI) m/z 705.48 [M+1]+; 1H-NMR (400 MHz, DMSO-d6) δ 8.68 (s, 1H), 8.67 (s, 1H), 8.45 (s, 1H), 7.72 (d, J = 8.00 Hz, 1H), 7.65 (d, J = 8.40 Hz, 1H), 7.61 (bs, 1H), 7.44 (d, J = 2.40 Hz, 1H), 4.76 (s, 2H), 4.32 (t, J = 12.00 Hz, 1H), 3.49 (d, J = 8.80 Hz, 2H), 3.18 (d, J = 10.80 Hz, 2H), 3.07 (s, 3H), 2.73 (t, J = 11.2 Hz, 2H), 2.02 (s, 3H), 1.96 (d, J = 13.2 Hz, 2H), 1.85 (d, J = 10.8 Hz, 2H)	1597	MS (ESI) m/z 833.52 [M+1]+; 1H-NMR (400 MHz, DMSO-d6) δ 13.08 (bs, 1H), 8.86-8.84 (m, 2H), 7.79-7.769 (m, 1H), 7.71 (t, J = 2.0 Hz, 2H), 7.66 (d, J = 5.2 Hz, 1H), 6.51 (bs, 1H), 5.08-5.01 (m, 2H), 4.83 (s, 2H), 4.52 (bs, 1H), 3.94 (bs, 2H), 3.41 (bs, 4H), 3.21 (s, 3H), 2.15 (bs, 2H), 2.07 (s, 5H)
1598	MS (ESI) m/z 758.69 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 9.94 (bs, 1H), 8.77 (d, J = 4.8 Hz, 1H), 8.64 (s, 1H), 7.76 (d, J = 8.0 Hz, 1H), 7.69-7.67 (m, 2H), 7.55 (d, J = 4.4 Hz, 1H), 6.43 (bs, 1H), 4.82 (s, 2H), 4.53 (bs, 1H), 3.79 (bs, 4H), 3.39-3.35 (m, 2H), 3.11 (s, 3H), 2.41 (bs, 2H), 2.32-2.26 (m, 2H), 2.09 (s, 7H), 1.86-1.82 (m, 1H), 1.65-1.60 (m, 1H)	1601	MS (ESI) m/z 805.69 [M+1]+; 1H-NMR (400 MHz, DMSO-d6) δ 12.47 (bs, 1H), 8.81 (d, J = 4.8 Hz, 1H), 8.78 (bs, 2H), 7.79 (d, J = 11.6 Hz, 1H), 7.70 (bs, 1H), 7.68 (bs, 1H), 7.63 (d, J = 4.80 Hz, 1H), 4.82 (s, 2H), 4.20 (bs, 1H), 3.65 (q, J = 6.80 Hz, 2H), 3.54 (s, 3H), 2.93-2.90 (m, 2H), 2.69-2.66 (m, 4H), 2.42-2.32 (m, 3H), 1.94 (s, 3H), 1.92-1.89 (m, 4H) 1.11 (t, J = 6.8 Hz, 3H)
1599	[0025] MS (ESI) m/z 638.41 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.79-8.74 (m, 2H), 8.65 (s, 1H), 7.78 (d, J = 8.0 Hz, 1H), 7.70-7.68 (m, 2H), 7.55 (d, J = 4.8 Hz, 1H), 4.83 (s, 2H), 4.54-4.53 (m, 1H), 3.58-3.55 (m, 2H), 3.20 (bs, 2H), 3.01 (s, 3H), 2.83-2.82 (m, 3H), 2.10 (bs, 7H)	1602	手性 MS (ESI) m/z 773.67 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 12.47 (s, 1H), 9.72 (bs, 1H), 8.81-8.78 (m, 3H), 7.77 (d, J = 8.36 Hz, 1H), 7.72-7.67 (m, 2H), 7.62 (d, J = 4.80 Hz, 1H), 5.33-5.14 (dm, 1H), 4.83 (s, 2H), 4.63-4.55 (m, 1H), 4.03-3.97 (m, 1H), 3.60-3.50 (合并的, 3H), 3.11 (s, 3H), 3.09-3.02 (m, 2H), 2.76-2.50 (m, 6H), 2.12-2.07 (m, 4H), 1.99 (s, 3H)

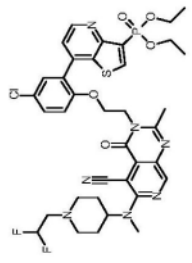
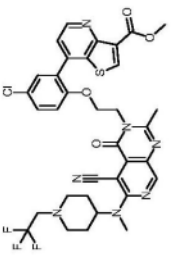
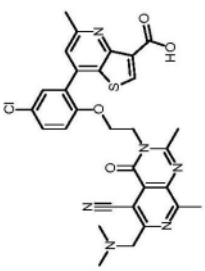
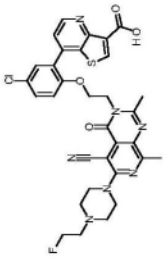
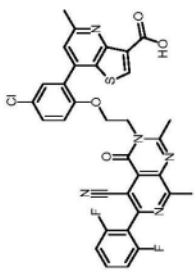
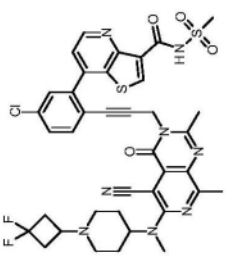
[0682]

1600		MS (ESI) m/z 678.56 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.12 (bs, 1H), 8.83-8.73 (m, 3H), 8.66 (s, 1H), 7.76 (d, J = 8.8 Hz, 1H), 7.70-7.68 (m, 2H), 7.55 (d, J = 4.8 Hz, 1H), 4.83 (s, 2H), 4.40 (bs, 1H), 3.71-3.57 (m, 4H), 3.40-3.20 (合并的, 2H), 2.85 (bs, 1H), 2.18-2.00 (m, 7H), 1.14 (t, J = 6.4 Hz, 3H), 0.98-0.79 (m, 4H)	1603		MS (ESI) m/z 833.74 [M+1]+; 1H-NMR (400 MHz, DMSO-d6) δ 9.86 (bs, 1H), 8.80-8.78 (d, J = 8.80 Hz, 2H), 8.68 (s, 1H), 7.80-7.67 (m, 4H), 4.88 (s, 2H), 4.54 (bs, 1H), 3.66-3.38 (m, 4H), 3.33-3.27 (m, 2H), 3.09 (s, 3H), 2.40-2.25 (m, 2H), 2.12 (s, 3H), 2.10-1.99 (m, 2H), 1.76 (t, J = 19.2 Hz, 3H)
1604		MS (ESI) m/z 793.67 [M+1]+; 1H-NMR (400 MHz, DMSO-d6) δ 12.45 (s, 1H), 8.83 (d, J = 4.8 Hz, 1H), 8.73 (bs, 2H), 7.78 (d, J = 8.4 Hz, 1H), 7.71-7.69 (m, 2H), 7.63 (d, J = 4.8 Hz, 1H), 4.83 (s, 2H), 4.61 (bs, 1H), 3.84 (bs, 1H), 3.69-3.65 (m, 2H), 3.11 (s, 3H), 2.02-1.91 (m, 6H), 1.76 (bs, 4H), 1.38 (t, J = 14.4 Hz, 3H)	1607		MS (ESI) m/z 829.71 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 12.49 (s, 1H), 8.81 (d, J = 4.8 Hz, 1H), 8.78 (d, J = 3.0 Hz, 2H), 7.77 (d, J = 8.16 Hz, 1H), 7.70-7.68 (m, 2H), 7.49 (d, J = 6.36 Hz, 1H), 6.56 (tt, J = 4.16 Hz, J = 88.08 Hz, 1H), 4.82 (s, 2H), 4.22-4.16 (m, 1H), 3.65 (d, J = 6.88 Hz, 2H), 3.55 (s, 3H) 3.04-2.94 (m, 4H), 2.49-2.41 (m, 2H), 1.99-1.89 (m, 5H), 1.78 (d, J = 10.68 Hz, 2H), 1.11 (t, J = 6.72 Hz, 3H)
1605		MS (ESI) m/z 793.67 [M+1]+; 1H-NMR (400 MHz, DMSO-d6) δ 12.45 (s, 1H), 8.83 (d, J = 4.8 Hz, 1H), 8.73 (bs, 2H), 7.78 (d, J = 8.4 Hz, 1H), 7.71-7.69 (m, 2H), 7.63 (d, J = 4.8 Hz, 1H), 4.83 (s, 2H), 4.61 (bs, 1H), 3.84 (bs, 1H), 3.69-3.65 (m, 2H), 3.11 (s, 3H), 2.02-1.91 (m, 6H), 1.76 (bs, 4H), 1.38 (t, J = 14.4 Hz, 3H)	1608		MS (ESI) m/z 871.79 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 12.71 (s, 1H), 8.83 (d, J = 4.8 Hz, 1H), 8.78 (s, 1H), 8.72 (s, 1H), 7.77 (d, J = 8.16 Hz, 1H), 7.71-7.69 (m, 2H), 7.64 (d, J = 4.84 Hz, 1H), 6.58 (tt, J = 52.56 Hz, 5.4 Hz, 1H), 5.25-5.20 (m, 1H), 4.98-4.92 (m, 4H), 4.82 (s, 2H), 4.24 (bs, 1H), 3.95 (bs, 2H), 3.68-3.62 (m, 2H), 3.50-3.10 (m, 4H), 2.01-1.97 (m, 2H), 1.90 (s, 3H), 1.86 (bs, 2H), 1.12 (t, J = 6.8 Hz, 3H)

[0683]

1606		MS (ESI) m/z 821.52 [M+1]+; ; 1H-NMR (400 MHz, DMSO-d6) δ 12.48 (s, 1H), 8.80 (d, J = 4.84 Hz, 1H), 8.78 (d, J = 2.6 Hz, 2H), 7.77 (d, J = 8.31 Hz, 1H), 7.71-7.67 (m, 2H), 7.62 (d, J = 4.80 Hz, 1H), 4.76 (s, 2H), 4.60-4.57 (m, 1H), 3.85-3.58 (m, 4H), 3.49 (s, 3H), 3.32 (t, J = 12 Hz, 2H), 3.10 (s, 3H), 2.32-2.02 (m, 4H), 1.98 (s, 3H), 1.80-1.70 (m, 3H)	1609 	MS (ESI) m/z 892.75 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.05 (s, 1H), 8.91 (d, J = 4.4 Hz, 1H), 8.72 (d, J = 3.6 Hz, 1H), 8.65 (s, 1H), 8.60 (s, 1H), 8.28 (d, J = 8.0 Hz, 1H), 8.21 (t, J = 7.6 Hz, 1H), 7.77-7.75 (m, 2H), 7.70-7.66 (m, 3H), 6.58 (t, J = 52.8 Hz, 1H), 4.82 (s, 2H), 4.23 (bs, 1H), 3.62 (d, J = 7.2 Hz, 2H), 3.16-3.12 (m, 4H), 2.53 (s, 2H), 2.01 (bs, 2H), 1.90-1.84 (m, 5H), 1.09 (t, J = 6.4 Hz, 3H)
1610 手性		MS (ESI) m/z 881.27 [M+1]+; 1H-NMR (400 MHz, DMSO-d6) δ 12.71 (s, 1H), 8.81 (d, J = 4.84 Hz, 1H), 8.77 (s, 1H), 8.76 (s, 1H), 7.77 (d, J = 8.36 Hz, 1H), 7.72-7.67 (m, 2H), 7.62 (d, J = 4.84 Hz, 1H), 5.20-5.16 (m, 1H), 4.97-4.89 (m, 4H), 4.82 (s, 2H), 4.75-4.70 (m, 1H), 4.61-4.57 (m, 1H), 3.54-3.51 (m, 2H), 3.54-3.43 (m, 3H), 3.11 (s, 3H), 3.08-3.06 (m, 2H), 2.87-2.83 (m, 2H), 2.11-2.08 (m, 4H), 1.95 (s, 3H)	1617	MS (ESI) m/z 730.46 [M+1]+; 1H NMR (400 MHz, DMSO-d6 with D2O) δ 8.67 (bs, 2H), 7.95 (d, J = 7.6 Hz, 1H), 7.50 (d, J = 8.4 Hz, 1H), 7.28 (s, 1H), 7.21 (bs, 2H), 6.28 (m, J = 53.6 Hz, 1H), 4.30 (bs, 2H), 4.21-4.00 (m, 3H), 3.29-3.19 (m, 4H), 2.99 (s, 3H), 2.80 (bs, 2H), 2.03 (bs, 2H), 1.86 (bs, 2H), 1.64 (s, 3H)
1611 手性		MS (ESI) m/z 902.74 [M+1]+; 1H-NMR (400 MHz, DMSO-d6) δ 13.02 (s, 1H), 8.89 (d, J = 4.80 Hz, 1H), 8.72 (d, J = 4.40 Hz, 1H), 8.64 (s, 1H), 8.61 (s, 1H), 8.27-8.25 (m, 1H), 8.22-8.18 (m, 1H), 7.77-7.73 (m, 2H), 7.71-7.69 (m, 2H), 7.65 (d, J = 4.80 Hz, 1H), 4.83 (s, 2H), 4.75-4.70 (m, 1H), 4.58 (bs, 1H), 3.67 (bs, 3H), 3.54 (d, J = 10.80 Hz, 2H), 3.42-3.38 (m, 1H), 2.86-2.84 (m, 2H), 2.85 (bs, 2H), 2.45-2.40 (m, 2H), 2.08 (bs, 4H), 1.95 (s, 3H)	1618	MS (ESI) m/z 791.49 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 12.47 (s, 1H), 9.72 (bs, 1H), 8.81-8.78 (m, 3H), 7.77 (d, J = 8.4 Hz, 1H), 7.72-7.67 (m, 2H), 7.62 (d, J = 4.8 Hz, 1H), 4.83 (s, 2H), 4.59 (bs, 1H), 3.82-3.45 (m, 6H), 3.30-2.95 (m, 9H), 2.20-2.14 (m, 4H), 1.99 (s, 3H)

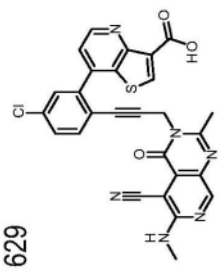
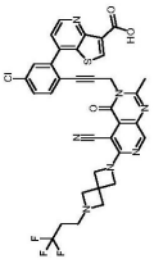
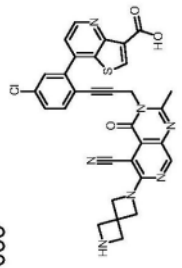
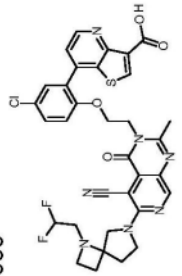
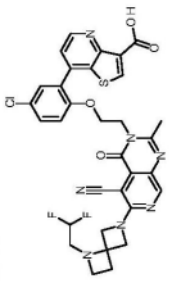
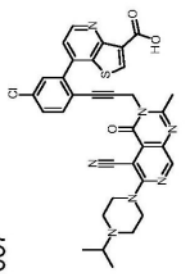
[0684]

1616		MS (ESI) m/z 786.58 [M+1]+ ; 1H NMR (400 MHz, DMSO-d6 with D2O) δ 8.77 (d, J = 4.40 Hz, 1H), 8.68 (s, 1H), 8.19 (d, J = 9.60 Hz, 1H), 7.52 (dd, J = 2.2, 8.8 Hz, 1H), 7.35-7.26 (m, 3H), 6.24 (t, J = 54.4 Hz, 1H), 4.33-4.17 (m, 10H), 3.21 (bs, 3H), 3.03 (s, 3H), 2.70 (bs, 1H), 2.58 (bs, 1H), 1.97 (bs, 2H), 1.82 (bs, 2H), 1.55 (s, 3H), 1.28 (t, J = 6.8 Hz, 6H)
1620		MS (ESI) m/z 726.41 [M+1]+; 1H-NMR (400 MHz, DMSO-d6) δ 8.81 (d, J = 4.0 Hz, 1H), 8.57 (s, 1H), 8.34 (s, 1H), 7.58 (d, J = 7.2, 1H), 7.39-7.33 (m, 3H), 4.37 (bs, 2H), 4.25 (bs, 3H), 3.91 (s, 3H), 3.3; 2-3.30 (m, 2H), 3.07-2.72 (m, 5H), 2.44-2.32 (m, 2H), 1.93-1.74 (bs, 4H), 1.69 (s, 3H)
1621		LCMS: 603.6 [M+H]+; 1H NMR (400 MHz, Methanol-d4) δ 8.31 (s, 1H), 7.54 (dd, J = 8.9, 2.6 Hz, 1H), 7.41 (s, 1H), 7.36 – 7.25 (m, 2H), 4.46 (t, J = 5.1 Hz, 2H), 4.34 (t, J = 5.1 Hz, 2H), 3.13 (s, 6H), 2.89 (s, 3H), 2.83 (s, 3H), 2.24 (s, 3H)
1624		LCMS (ESI) m/z 662.1 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.79 (d, J = 4.8 Hz, 1H), 8.46 (s, 1H), 7.57 (dd, J = 9.0, 2.6 Hz, 1H), 7.44 (d, J = 4.8 Hz, 1H), 7.39 – 7.32 (m, 2H), 4.98 – 4.74 (m, 2H), 4.40 (t, J = 5.1 Hz, 2H), 4.29 (s, 1H), 4.21 (t, J = 5.1 Hz, 2H), 3.64 (s, 3H), 3.56 (s, 1H), 3.47 (s, 1H), 3.31 (s, 2H), 2.63 (s, 3H), 1.86 (s, 3H)
1622		LCMS (ESI) m/z 658.1 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.62 (s, 1H), 7.69 (tt, J = 8.5, 6.6 Hz, 1H), 7.60 (dd, J = 8.9, 2.7 Hz, 1H), 7.48 – 7.43 (m, 2H), 7.40 – 7.32 (m, 3H), 4.43 (t, J = 5.0 Hz, 2H), 4.27 (t, J = 4.9 Hz, 2H), 2.81 (s, 3H), 2.69 (s, 3H), 1.88 (s, 3H)
1625		MS (ESI) m/z 805.29 [M+1]+

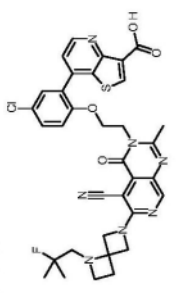
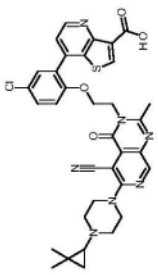
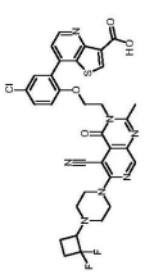
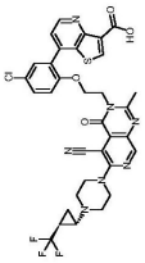
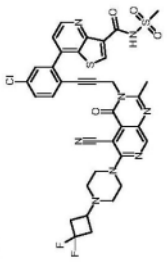
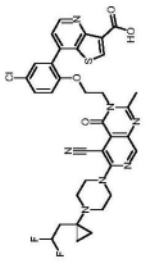
[0685]

1623		LCMS (ESI) m/z 644.1 [M+1]+; 1H NMR (400 MHz, 氯仿-d) δ 8.48 (s, 1H), 7.61 (dd, J = 8.9, 2.7 Hz, 1H), 7.43 (s, 1H), 7.42 – 7.37 (m, 2H), 4.42 (d, J = 5.3 Hz, 2H), 4.33 (s, 1H), 4.30 (s, 1H), 4.25 (d, J = 5.0 Hz, 2H), 3.61 (d, J = 12.2 Hz, 2H), 3.44 (d, J = 13.6 Hz, 4H), 3.24 (d, J = 11.0 Hz, 1H), 2.92 (d, J = 4.4 Hz, 3H), 2.73 (s, 3H), 2.66 (s, 4H), 1.98 (s, 3H)	1626	
1627		MS (ESI) m/z 602.29 [M+1]+	1630		MS (ESI) m/z 618.09 [M+1]+
1628		MS (ESI) m/z 608.3 [M+1]+	1631		

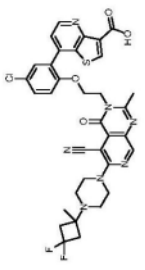
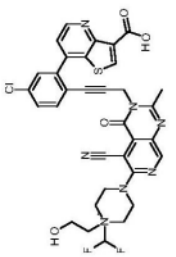
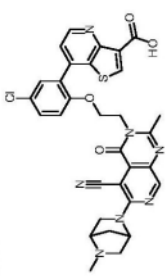
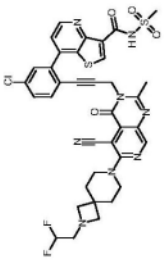
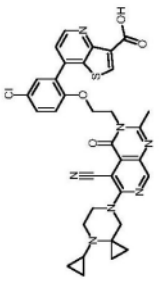
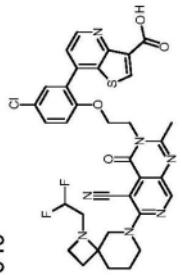
[0686]

1629			
1632		LCMS (ESI) m/z 469.5 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.77 – 8.71 (m, 2H), 8.66 (s, 1H), 7.75 (dd, J = 8.1, 0.8 Hz, 1H), 7.72 – 7.64 (m, 2H), 7.54 (d, J = 4.9 Hz, 1H), 4.81 (s, 2H), 4.63 (s, 2H), 4.53 (s, 2H), 4.44 (s, 2H), 4.39 (s, 2H), 3.36 (s, 4H), 2.73 – 2.62 (m, 1H), 2.10 (s, 3H)
1633		LCMS (ESI) m/z 608.2 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.70 (d, J = 4.7 Hz, 2H), 8.63 (s, 1H), 8.47 (s, 2H), 7.72 (dd, J = 8.1, 0.8 Hz, 1H), 7.68 – 7.61 (m, 2H), 7.50 (d, J = 4.8 Hz, 1H), 4.77 (s, 2H), 4.54 (s, 4H), 4.20 (t, J = 6.2 Hz, 4H), 2.06 (s, 3H), 1.20 (s, 1H)
1636		MS (ESI) m/z 619.45 [M+1]+
1634		MS (ESI) m/z 678.5 [M+1]+
1637		MS (ESI) m/z 638.39 [M+1]+

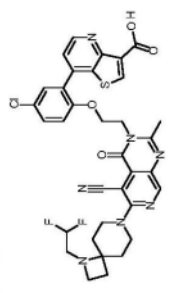
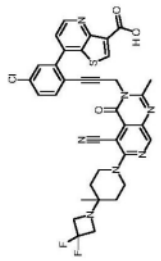
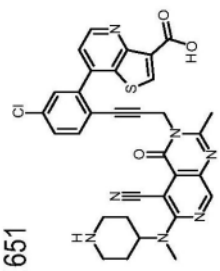
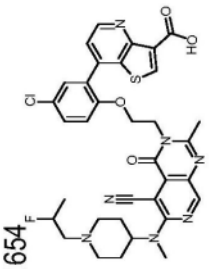
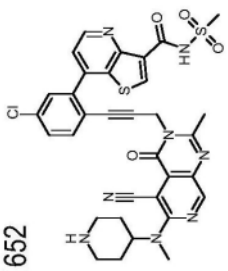
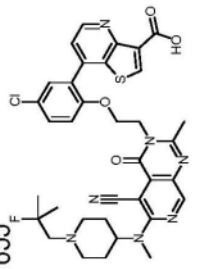
[0687]

1635		MS (ESI) m/z 688.48 [M+1]+	
1638		MS (ESI) m/z 670.50 [M+1]+	
1639		MS (ESI) m/z 706.46 [M+1]+	
1642		MS (ESI) m/z 710.46 [M+1]+	
1640			
1643		MS (ESI) m/z 706.47 [M+1]+	

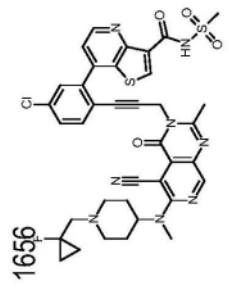
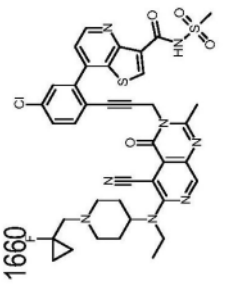
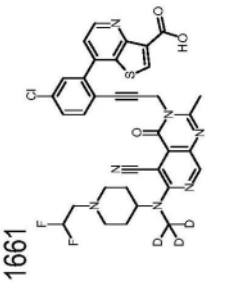
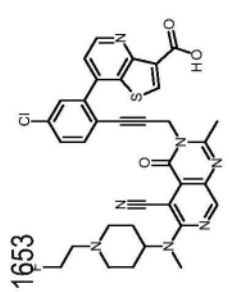
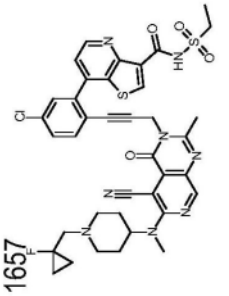
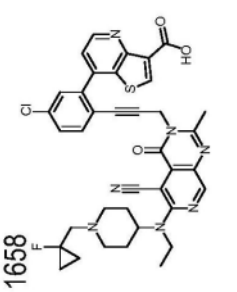
[0688]

1641		MS (ESI) m/z 706.55 [M+1]	
1644		MS (ESI) m/z 690.47 [M+1]+	
1645		MS (ESI) m/z 628.46 [M+1]+	
1648		LCMS: 2.01 Min, 777.3 [M+H]+	
1646		MS (ESI) m/z 668.45 [M+1]+	
1649		MS (ESI) m/z = 706.48 [M+1]+	

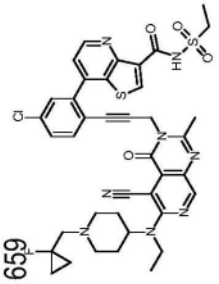
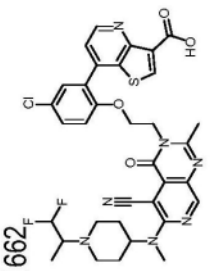
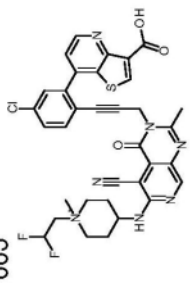
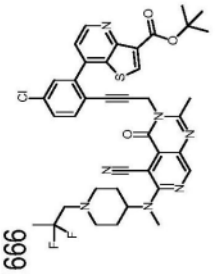
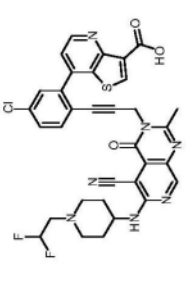
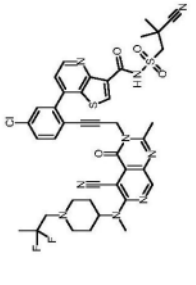
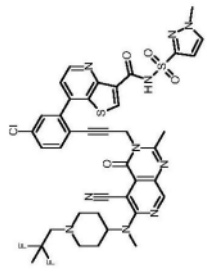
[0689]

1647 	MS (ESI) m/z 706.46 [M+1]	1650 	MS (ESI) m/z 720.47 [M+1]+
1651 		1654 	MS (ESI) m/z, 690.46 [M+1]+
1652 		1655 	MS (ESI) m/z 704.57 [M+1]+

[0690]

		
MS (ESI) m/z 670.43 [M+1]+		
		

[0691]

1659 		1662 	MS (ESI) m/z 708.54 [M+1]+
1663 	MS (ESI) m/z 688.2 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.72 (d, J = 4.8 Hz, 1H), 8.70 (s, 1H), 8.61 (s, 1H), 7.74 – 7.71 (m, 1H), 7.67 – 7.63 (m, 2H), 7.52 (d, J = 4.8 Hz, 1H), 7.03 (d, J = 8.5 Hz, 1H), 6.80 (tt, J = 52.4, 3.5 Hz, 1H), 4.78 (s, 2H), 4.55 – 4.40 (m, 1H), 4.02 (td, J = 14.3, 3.9 Hz, 2H), 3.69 – 3.60 (m, 4H), 3.25 (s, 3H), 2.32 – 2.18 (m, 2H), 2.10 – 2.01 (m, 2H), 2.00 (s, 3H).	1666 	
1664 		1672 	1676 

[0692]

1665	MS (ESI) m/z = 714.5 [M+1]+	1673	1677
1669	1667	1671	1674
1670	1668	1675	1678

[0693]

1686	MS (ESI) m/z 728.47 [M+1]+	
1683	1690 手性	
1679	1687	1684
1680		1681

[0694]

		MS (ESI) m/z 714.55 [M+1]+
	1691 手性	1700
1685	1697	
MS (ESI) m/z 720.47 [M+1]+	MS (ESI) m/z 714.45 [M+1]+	
1682	1688 手性	1689 手性

[0695]

1701 手性	1698	MS (ESI) m/z 878.31 [M+1]+	
1695	1699	1706	
1692	1696		
1693	1694	1702 手性	

[0696]

1703	MS (ESI) m/z 815.32 [M+1]+	1707	1709
1704	MS (ESI) m/z 857.25 [M+1]+	1711	1710
1705	MS (ESI) m/z 878.28 [M+1]+	1708	1714

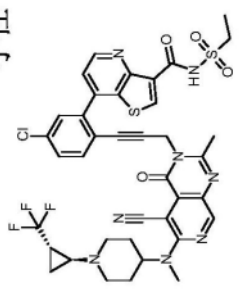
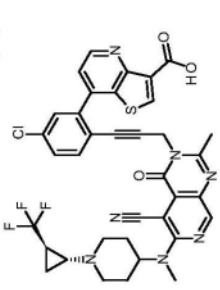
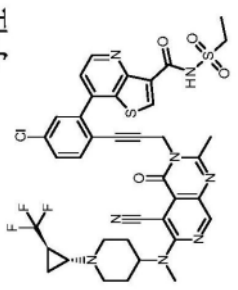
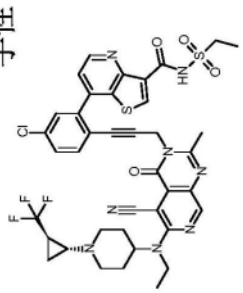
[0697]

1712	1715	1721	
1713	1716	1719	
1717	MS (ESI) m/z 762.2 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.77 (d, J = 4.8 Hz, 1H), 8.75 (s, 1H), 8.65 (s, 1H), 7.76 (d, J = 8.2 Hz, 1H), 7.71 – 7.66 (m, 2H), 7.55 (d, J = 4.8 Hz, 1H), 7.26 (s, 1H), 4.83 (s, 2H), 4.68 – 4.55 (m, 1H), 4.22 (d, J = 13.7 Hz, 1H), 3.99 – 3.71 (m, 7H), 3.20 (s, 3H), 2.70 – 2.61 (m, 2H), 2.42 – 2.30 (m, 2H), 2.18 – 2.00 (m, 5H)	1723	MS (ESI) m/z 726.28 [M+1]+

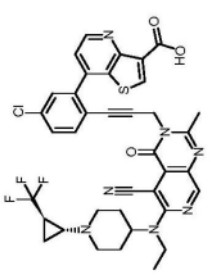
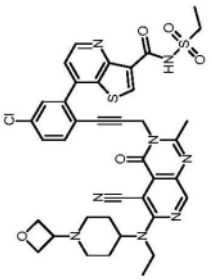
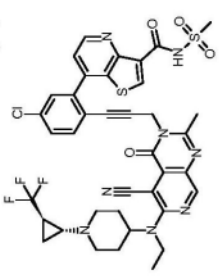
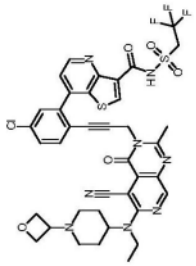
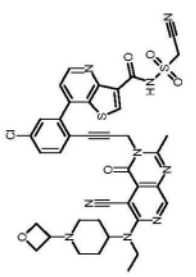
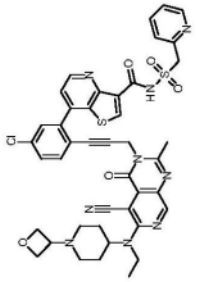
[0698]

1718	1720	1724 Chiral	MS (ESI) m/z 732.18 [M+1]+
1725 手性	MS (ESI) m/z 732.19 [M+1]+	1728 手性	MS (ESI) m/z 809.32 [M+1]+
1722	MS (ESI) m/z 817.25 [M+1]+		

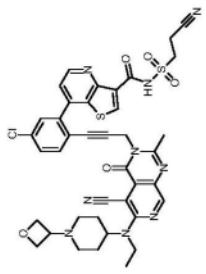
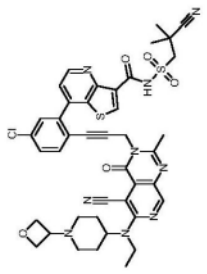
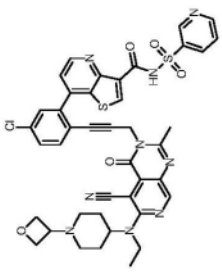
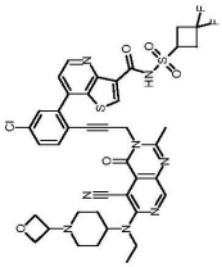
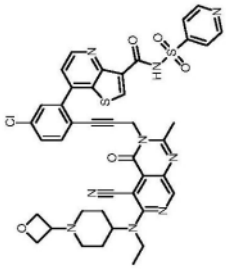
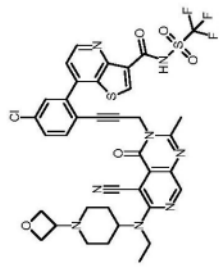
[0699]

1726 手性 	MS (ESI) m/z 823.30 [M+1]+		
1727 手性 	MS (ESI) m/z 732.19 [M+1]+		
1729 手性 	MS (ESI) m/z 823.3 [M+1]+	1732 手性 	MS (ESI) m/z 837.31 [M+1]+

[0700]

1730 手性 	MS (ESI) m/z 746.28 [M+1]+	1733 	MS (ESI) m/z 785.26 [M+1]+
1731 手性 	MS (ESI) m/z 823.27 [M+1]+	1734 	MS (ESI) m/z 839.26 [M+1]+
1735 	MS (ESI) m/z 796.33 [M+1]+	1738 	MS (ESI) m/z 848.33 [M+1]+

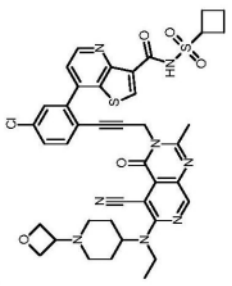
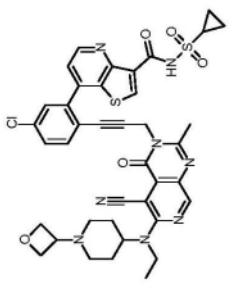
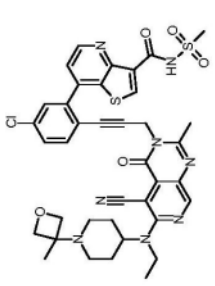
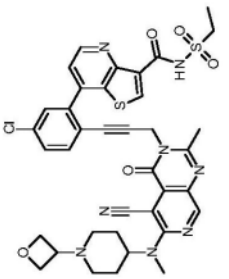
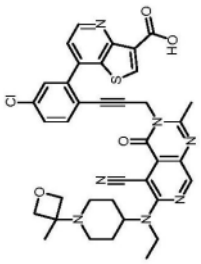
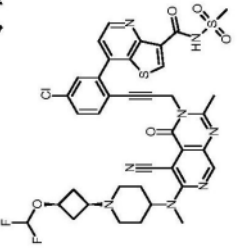
[0701]

1736		MS (ESI) m/z 810.23 [M+1]+	
1737		MS (ESI) m/z 838.32 [M+1]+	
1741		MS (ESI) m/z 834.32 [M+1]+	
1739		MS (ESI) m/z 847.32 [M+1]+	
1740		MS (ESI) m/z 834.36 [M+1]+	
1744		MS (ESI) m/z 825.21 [M+1]+	

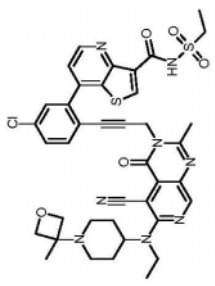
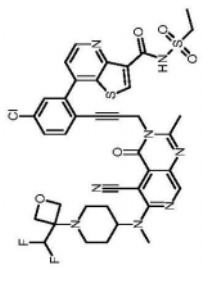
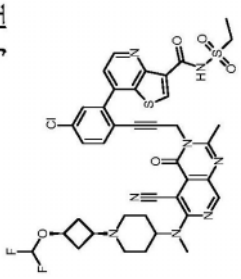
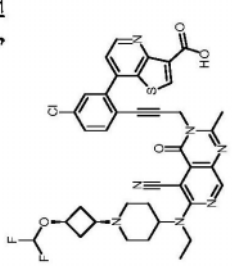
[0702]

1742	MS (ESI) m/z 834.31 [M+1]+	1745	MS (ESI) m/z 821.25 [M+1]+
1743	MS (ESI) m/z 788.18 [M+1]+	1746	MS (ESI) m/z 799.24 [M+1]+
1747	MS (ESI) m/z 813.29 [M+1]+	1750	MS (ESI) m/z 813.22 [M+1]+

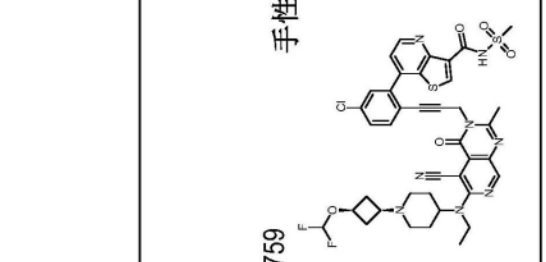
[0703]

1748		MS (ESI) m/z 811.27 [M+1]+	
1749		MS (ESI) m/z 797.29 [M+1]+	
1753		MS (ESI) m/z 785.32 [M+1]+	
1751		MS (ESI) m/z 771.31 [M+1]+	
1752		MS (ESI) m/z 708.23 [M+1]+	
1756	手性 	MS (ESI) m/z 821.28 [M+1]+	

[0704]

1754		MS (ESI) m/z 799.34 [M+1]+	
1755		MS (ESI) m/z 821.31 [M+1]+	
1757	手性 	MS (ESI) m/z 835.45 [M+1]+	
1758	手性 	MS (ESI) m/z 758.28 [M+1]+	

[0705]

1759 手性 	MS (ESI) m/z 835.26 [M+1]+	
1760 手性	MS (ESI) m/z 849.43 [M+1]+	
1761	LCMS (ESI) m/z 821.4 [M+1]+	
1762		LCMS (ESI) m/z 863.3 [M+1]+ ; 1H NMR (400 MHz, DMSO-d6) δ 12.72 (s, 1H), 9.53 (d, J = 9.3 Hz, 1H), 8.83 (d, J = 4.9 Hz, 1H), 8.78 (d, J = 6.8 Hz, 2H), 7.78 (dd, J = 8.3, 0.5 Hz, 1H), 7.77 – 7.66 (m, 2H), 7.64 (d, J = 4.9 Hz, 1H), 6.73 (t, J = 21 Hz, 1H), 5.21 (tt, J = 7.8, 6.2 Hz, 1H), 5.00 – 4.89 (m, 4H), 4.84 (s, 2H), 4.82 – 4.74 (m, 1H), 4.60 (p, J = 8.0 Hz, 1H), 3.94 (q, J = 7.8 Hz, 1H), 3.58 (d, J = 11.8 Hz, 2H), 3.13 (s, 3H), 3.05 (s, 2H), 2.78 – 2.68 (m, 1H), 2.72 (s, 1H), 2.17 – 2.06 (m, 4H), 1.97 (s, 3H)
1763 手性		LCMS (ESI) m/z 884.5 [M+1]+ ; 1H NMR (400 MHz, DMSO-d6) δ 13.02 (s, 1H), 8.90 (d, J = 4.9 Hz, 1H), 8.72 (ddd, J = 4.7, 1.7, 1.0 Hz, 1H), 8.63 (d, J = 13.4 Hz, 2H), 8.27 (dt, J = 7.9, 1.1 Hz, 1H), 8.24 – 8.16 (m, 1H), 7.80 – 7.67 (m, 4H), 7.66 (d, J = 4.8 Hz, 1H), 6.72 (t, J = 76 Hz, 1H), 4.83 (s, 2H), 4.78 (dt, J = 7.3, 3.8 Hz, 1H), 4.58 (d, J = 5.8 Hz, 1H), 3.93 (q, J = 7.6 Hz, 1H), 3.56 (d, J = 11.8 Hz, 2H), 3.04 (s, 1H), 2.72 (dd, J = 14.6, 7.1 Hz, 2H), 2.09 (s, 3H), 1.97 (s, 3H)
1764 手性		LCMS (ESI) m/z 884.5 [M+1]+ ; 1H NMR (400 MHz, DMSO-d6) δ 8.95 – 8.89 (m, 2H), 8.82 (d, J = 4.9 Hz, 1H), 8.65 (s, 1H), 8.47 (s, 1H), 8.07 – 8.01 (m, 2H), 7.77 – 7.58 (m, 3H),6.68 (t, J = 76 Hz, 1H) 4.81 – 4.71 (m, 2H), 4.55 (p, J = 8.0 Hz, 1H), 3.93 – 3.85 (m, 1H), 3.53 (d, J = 11.7 Hz, 2H), 3.01 (s, 1H), 2.77 – 2.63 (m, 2H), 2.07 (s, 3H), 1.90 (s, 2H), 1.90 (d, J = 16.7 Hz, 0H)

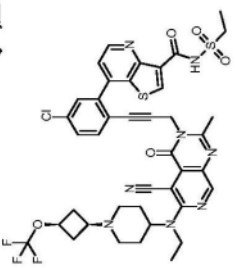
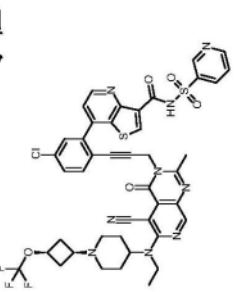
[0706]

1765 手性	LCMS (ESI) m/z 884.5 [M+1]+ ; 1H NMR (400 MHz, DMSO-d6) δ 9.24 (dd, J = 2.5, 0.8 Hz, 1H), 8.89 (dd, J = 4.8, 1.6 Hz, 1H), 8.81 (d, J = 4.9 Hz, 1H), 8.63 (s, 1H), 8.50 (ddd, J = 8.2, 2.4, 1.6 Hz, 1H), 8.46 (s, 1H), 7.76 – 7.64 (m, 3H), 7.64 – 7.57 (m, 2H), 6.69 (t, J = 76 Hz, 1H), 4.76 (d, J = 10.9 Hz, 3H), 4.55 (t, J = 8.0 Hz, 1H), 3.94 – 3.85 (m, 1H), 3.52 (s, 1H), 3.08 (s, 3H), 3.02 (s, 1H), 2.74 – 2.64 (m, 2H), 2.08 (s, 4H), 1.88 (s, 3H)	1768 手性	MS (ESI) m/z 877.29 [M+1]+
1766 手性	MS (ESI) m/z 758.34 [M+1]+	1769 手性	MS (ESI) m/z 898.4 [M+1]+
1767 手性	MS (ESI) m/z 835.33 [M+1]+	1770 手性	MS (ESI) m/z 898.26 [M+1]+

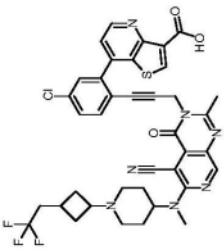
[0707]

1771	手性	MS (ESI) m/z 898.29 [M+1]+	1774	手性	MS (ESI) m/z 902.23 [M+1]+
1772	手性	MS (ESI) m/z 839.28 [M+1]+	1775	手性	MS (ESI) m/z 776.35 [M+1]+
1773	手性	MS (ESI) m/z 902.19 [M+1]+	1776	手性	MS (ESI) m/z 853.3 [M+1]+

[0708]

1777	手性		MS (ESI) m/z 819.33 [M+1]+	1780	手性		MS (ESI) m/z 916.27 [M+1]+
1778	手性		MS (ESI) m/z 895.27 [M+1]+	1781	手性		MS (ESI) m/z 916.27 [M+1]+
1779	手性		MS (ESI) m/z 916.3 [M+1]+	1782	手性		MS (ESI) m/z 762.31 [M+1]+

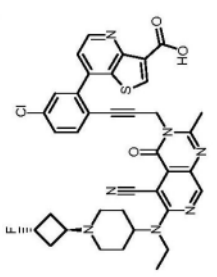
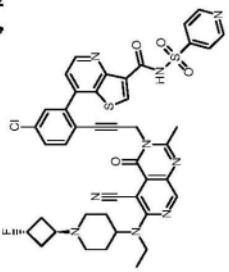
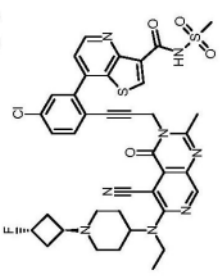
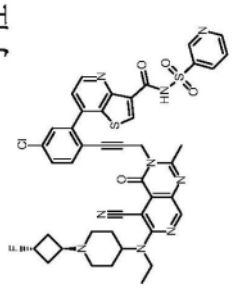
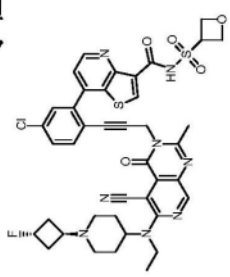
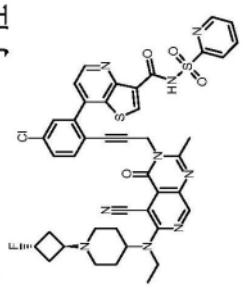
[0709]

1783 手性	MS (ESI) m/z 839.26 [M+1]+	1786 	MS (ESI) m/z 760.31 [M+1]+
1784 手性	MS (ESI) m/z 776.29 [M+1]+	1787	MS (ESI) m/z 837.35 [M+1]+
1785 手性	MS (ESI) m/z 853.37 [M+1]+	1788	MS (ESI) m/z 851.42 [M+1]+

[0710]

1789	MS (ESI) m/z 851.41 [M+1]+	1792 手性	MS (ESI) m/z 836.27 [M+1]+
1790	MS (ESI) m/z 865.46 [M+1]+	1793 手性	MS (ESI) m/z 836.3 [M+1]+
1791 手性	MS (ESI) m/z 815.24 [M+1]+	1794 手性	MS (ESI) m/z 836.33 [M+1]+

[0711]

1795	手性		MS (ESI) m/z 710.25 [M+1]+	1798	手性		MS (ESI) m/z 850.31 [M+1]+
1796	手性		MS (ESI) m/z 787.34 [M+1]+	1799	手性		MS (ESI) m/z 850.34 [M+1]+
1797	手性		MS (ESI) m/z 829.34 [M+1]+	1800	手性		MS (ESI) m/z 850.25 [M+1]+

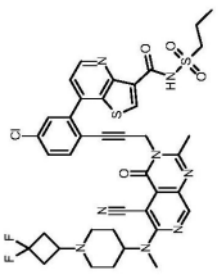
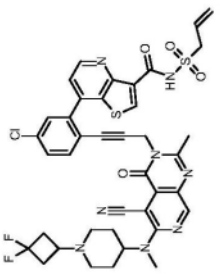
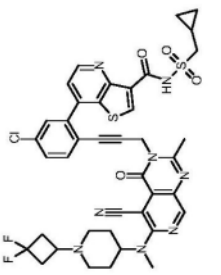
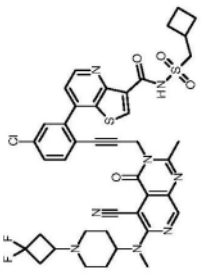
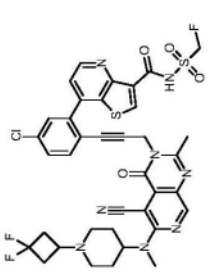
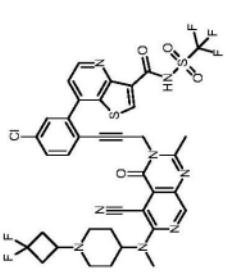
[0712]

1801	MS (ESI) m/z 710.28 [M+1]+	1804	MS (ESI) m/z 797.32 [M+1]+
1802	MS (ESI) m/z 787.28 [M+1]+	1805	MS (ESI) m/z 811.3 [M+1]+
1803	手性 MS (ESI) m/z 801.44 [M+1]+	1806	MS (ESI) m/z 770.31 [M+1]+

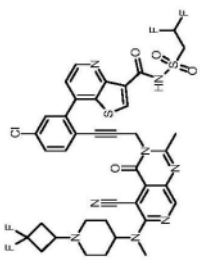
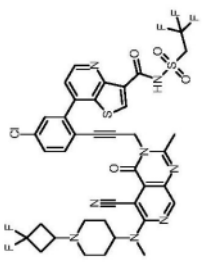
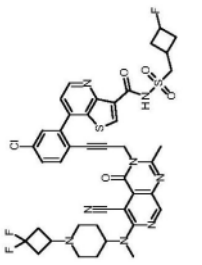
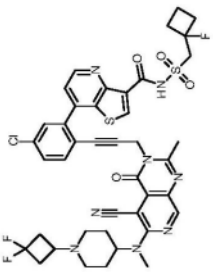
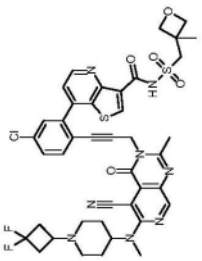
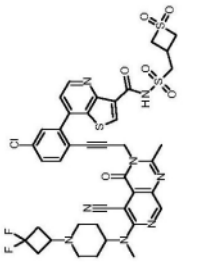
[0713]

1807	MS (ESI) m/z 805.28 [M+1]+	1810	MS (ESI) m/z 831.26 [M+1]+
1808	MS (ESI) m/z 819.358 [M+1]+	1811	MS (ESI) m/z 833.22 [M+1]+
1809	MS (ESI) m/z 817.27 [M+1]+	1812	MS (ESI) m/z 833.39 [M+1]+

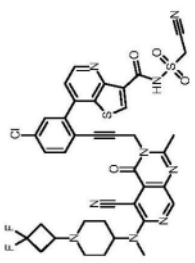
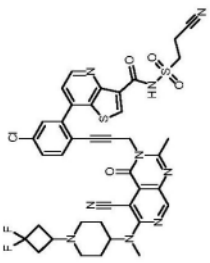
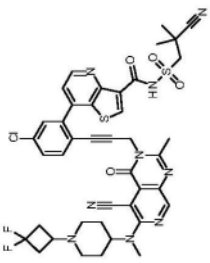
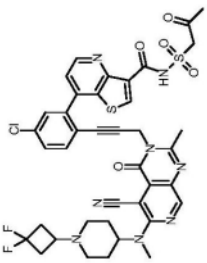
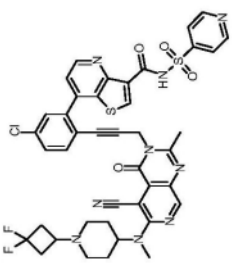
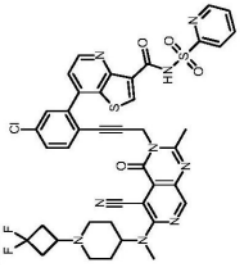
[0714]

1813		MS (ESI) m/z 624.2 [M+1]+	
1814		MS (ESI) m/z 843.32 [M+1]+	
1815		MS (ESI) m/z 787.34 [M+1]+	
1816		MS (ESI) m/z 850.31 [M+1]+	
1817		MS (ESI) m/z 809.22 [M+1]+	
1818		MS (ESI) m/z 845.26 [M+1]+	

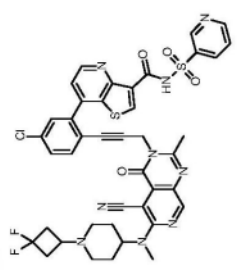
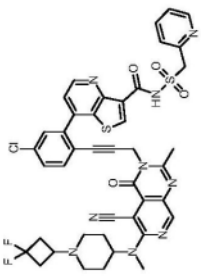
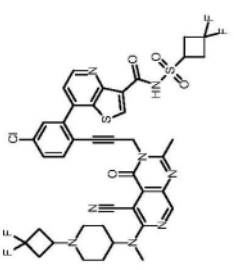
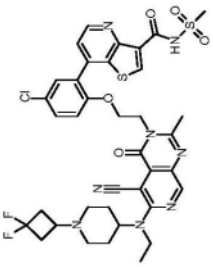
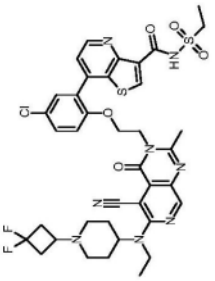
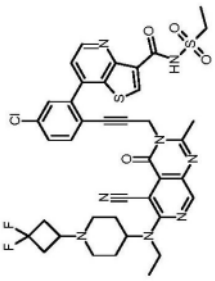
[0715]

1819		MS (ESI) m/z 841.17 [M+1]+	
1820		MS (ESI) m/z 817.25 [M+1]+	
1821		MS (ESI) m/z 863.33 [M+1]+	
1822		MS (ESI) m/z 863.38 [M+1]+	
1823		MS (ESI) m/z 861.36 [M+1]+	
1824		MS (ESI) m/z 895.39 [M+1]+	

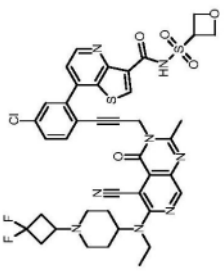
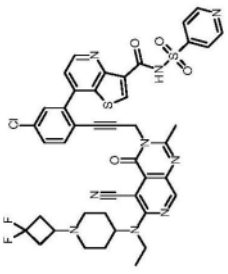
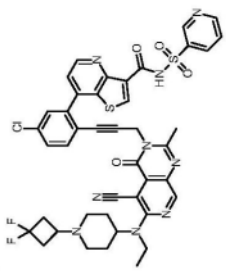
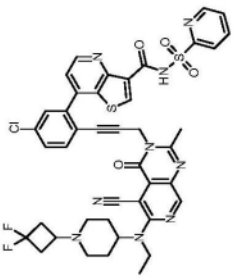
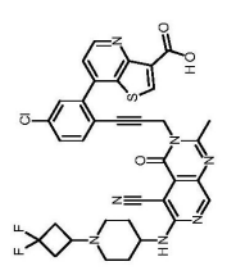
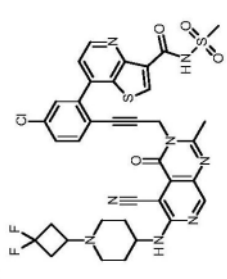
[0716]

1825		MS (ESI) m/z 816.24 [M+1]+	
1826		MS (ESI) m/z 830.3 [M+1]+	
1827		MS (ESI) m/z 858.28 [M+1]+	
1828		MS (ESI) m/z 833.34 [M+1]+	
1829		MS (ESI) m/z 854.26 [M+1]+	
1830		MS (ESI) m/z 854.26 [M+1]+	

[0717]

1831		MS (ESI) m/z 854.22 [M+1]+	
1832		MS (ESI) m/z 868.26 [M+1]+	
1833		MS (ESI) m/z 867.24 [M+1]+	
1834		MS (ESI) m/z 811.4 [M+1]+	
1835		MS (ESI) m/z 825.41 [M+1]+	
1836		MS (ESI) m/z 819.33 [M+1]+	

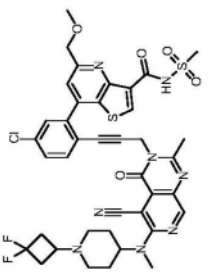
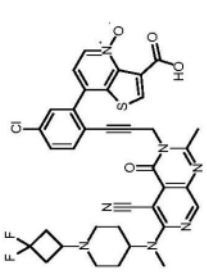
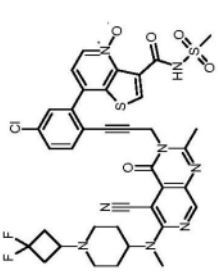
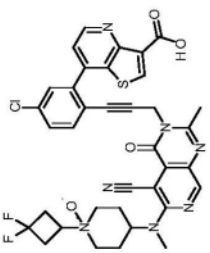
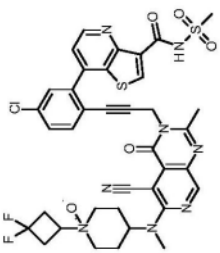
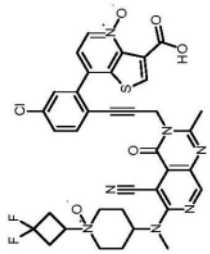
[0718]

1837		MS (ESI) m/z 847.35 [M+1]+	
1838		MS (ESI) m/z 868.26 [M+1]+	
1839		MS (ESI) m/z 868.26 [M+1]+	
1840		MS (ESI) m/z 868.29 [M+1]+	
1841		MS (ESI) m/z 700.33 [M+1]+	
1842		MS (ESI) m/z 777.26 [M+1]+	

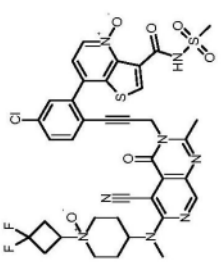
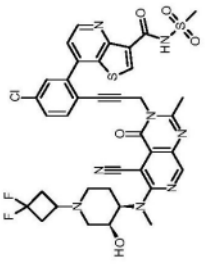
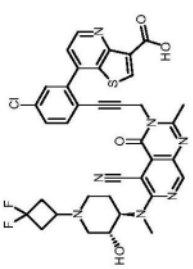
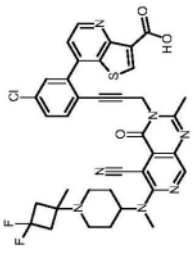
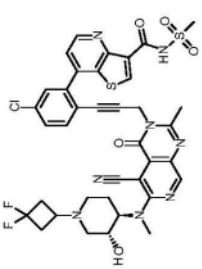
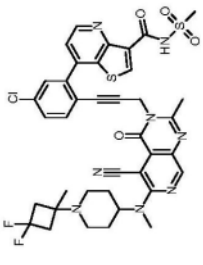
[0719]

1843	MS (ESI) m/z 794.33 [M+1]+	1846	MS (ESI) m/z 805.38 [M+1]+
1844	MS (ESI) m/z 796.44 [M+1]+	1847	MS (ESI) m/z 819.34 [M+1]+
1845	MS (ESI) m/z 841.34 [M+1]+	1848	MS (ESI) m/z 823.3 [M+1]+

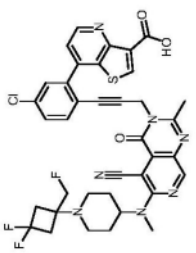
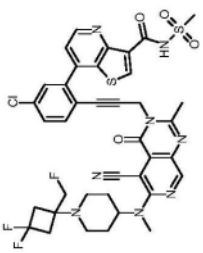
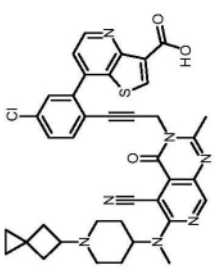
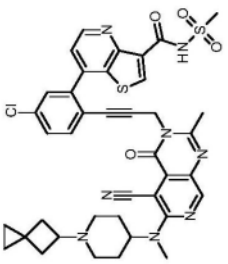
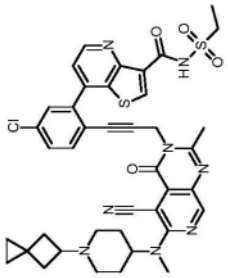
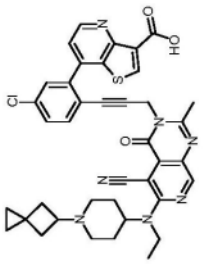
[0720]

1849		MS (ESI) m/z 835.36 [M+1]+	
1850		MS (ESI) m/z 730.34 [M+1]+	
1851		MS (ESI) m/z 807.33 [M+1]+	
1852		MS (ESI) m/z 730.36 [M+1]+	
1853		MS (ESI) m/z 807.18 [M+1]+	
1854		MS (ESI) m/z 746.16 [M+1]+	

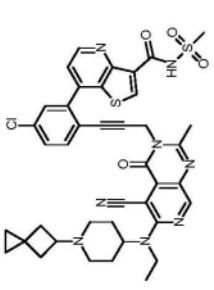
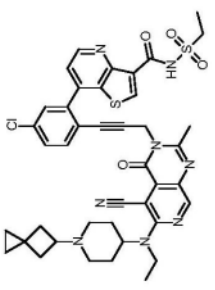
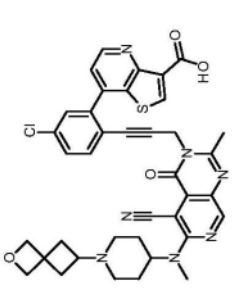
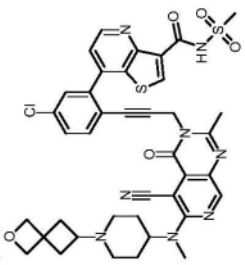
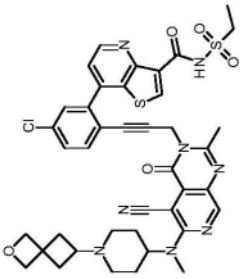
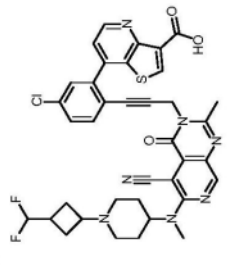
[0721]

1855		MS (ESI) m/z 823.36 [M+1]+	1858 手性		MS (ESI) m/z 807.3 [M+1]+
1856 手性		MS (ESI) m/z 730.37 [M+1]+	1859		MS (ESI) m/z 728.3 [M+1]+
1857 手性		MS (ESI) m/z 807.4 [M+1]+	1860		MS (ESI) m/z 805.32 [M+1]+

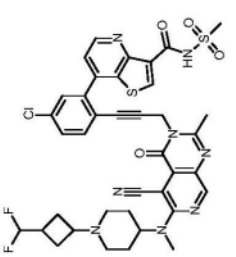
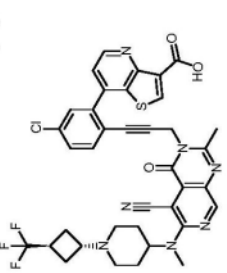
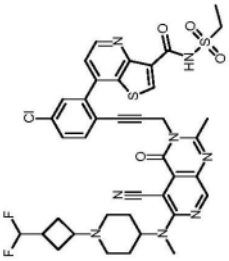
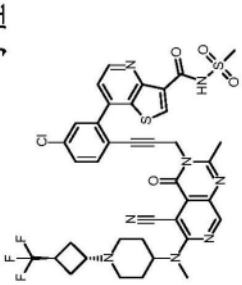
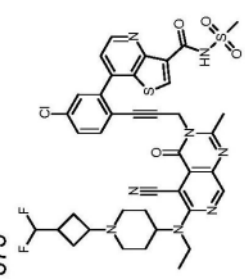
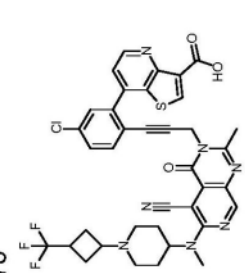
[0722]

1861		MS (ESI) m/z 746.31 [M+1]+	
1862		MS (ESI) m/z 823.39 [M+1]+	
1863		MS (ESI) m/z 704.27 [M+1]+	
1864		MS (ESI) m/z 781.26 [M+1]+	
1865		MS (ESI) m/z 795.37 [M+1]+	
1866		MS (ESI) m/z 718.34 [M+1]+	

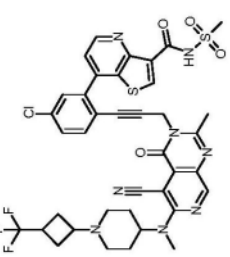
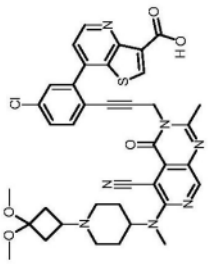
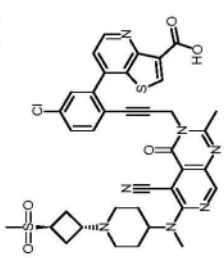
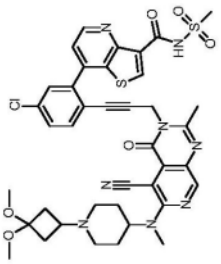
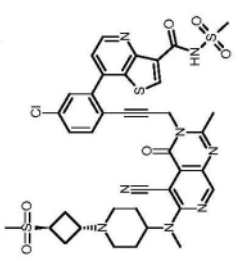
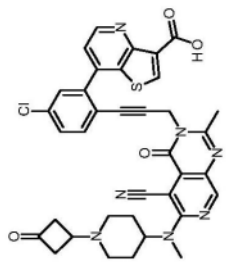
[0723]

1867		MS (ESI) m/z 795.35 [M+1]+	
1868		MS (ESI) m/z 809.44 [M+1]+	
1869		MS (ESI) m/z 720.3 [M+1]+	
1870		MS (ESI) m/z 797.35 [M+1]+	
1871		MS (ESI) m/z 811.4 [M+1]+	
1872		MS (ESI) m/z 728.26 [M+1]+	

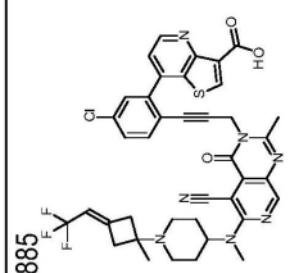
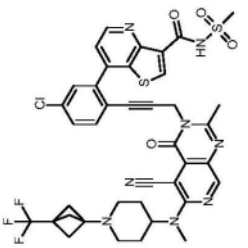
[0724]

1873 	MS (ESI) m/z 805.26 [M+1]+	1876 手性 	MS (ESI) m/z 746.28 [M+1]+
1874 	MS (ESI) m/z 819.46 [M+1]+	1877 手性 	MS (ESI) m/z 823.3 [M+1]+
1875 	MS (ESI) m/z 819.33 [M+1]+	1878 	MS (ESI) m/z 746.34 [M+1]+

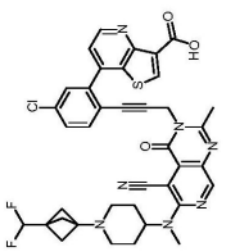
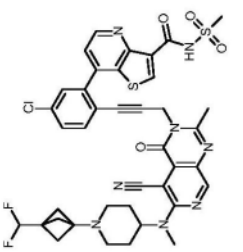
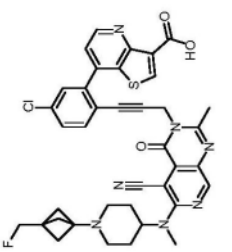
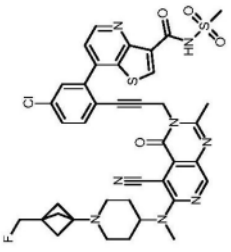
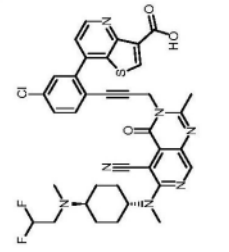
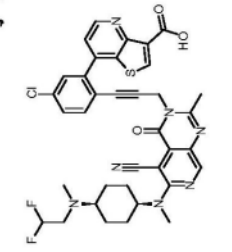
[0725]

1879 	MS (ESI) m/z 823.33 [M+1]+	1882 	MS (ESI) m/z 738.34 [M+1]+
1880 手性 	MS (ESI) m/z 756.29 [M+1]+	1883 	MS (ESI) m/z 815.4 [M+1]+
1881 手性 	MS (ESI) m/z 833.32 [M+1]+	1884 	MS (ESI) m/z 692.31 [M+1]+

[0726]

1885 	MS (ESI) m/z 772.35 [M+1]+	1888 	MS (ESI) m/z 835.26 [M+1]+
1886	MS (ESI) m/z 849.4 [M+1]+	1889	MS (ESI) m/z 754.34 [M+1]+
1887	MS (ESI) m/z 758.28 [M+1]+	1890	MS (ESI) m/z 831.29 [M+1]+

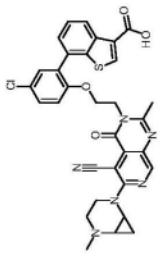
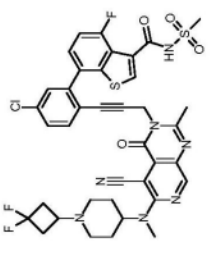
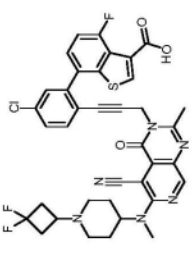
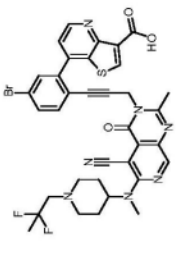
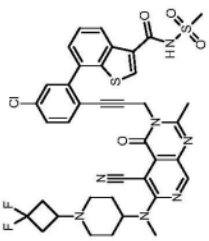
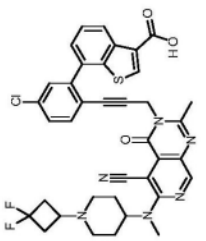
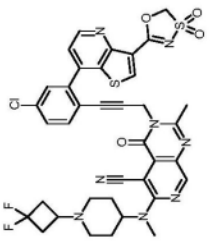
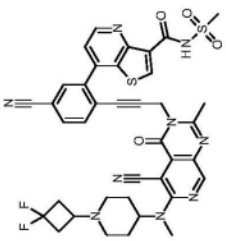
[0727]

1891		MS (ESI) m/z 740.33 [M+1]+	
1892		MS (ESI) m/z 817.32 [M+1]+	
1893		MS (ESI) m/z 722.34 [M+1]+	
1894		MS (ESI) m/z 799.27 [M+1]+	
1895 手性		MS (ESI) m/z 716.5 [M+1]+	
1896 手性		MS (ESI) m/z 716.33 [M+1]+	

[0728]

1897 手性	MS (ESI) m/z 702.46 [M+1]+	1983	MS (ESI) m/z 497.0 [M+1]+
1898	LCMS 1.90 (ESI) m/z 669.3 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.97 (s, 1H), 8.83 (d, J = 4.8 Hz, 1H), 8.40 (s, 1H), 7.59 (dd, J = 8.9, 2.7 Hz, 1H), 7.50 – 7.41 (m, 2H), 7.36 (s, 1H), 7.23 – 7.09 (m, 2H), 4.40 (t, J = 5.0 Hz, 2H), 4.24 (t, J = 4.9 Hz, 2H), 3.55 (d, J = 4.8 Hz, 2H), 3.38 – 3.24 (m, 3H), 2.71 – 2.62 (m, 2H), 2.46 (s, 3H), 2.33 (p, J = 1.9 Hz, 1H), 1.75 (s, 3H)	1984	MS (ESI) m/z 655.19 [M+1]+
1982	MS (ESI) m/z 461.0 [M+1]+	1985	MS (ESI) m/z 734.34 [M+1]+

[0729]

2020		MS (ESI) m/z 627.43 [M+1]+	
2021		MS (ESI) m/z 806.23 [M+1]+	
2022		MS (ESI) m/z 731.29 [M+1]+	
2029		MS (ESI) m/z 746.25 [M+1]+	
2023		MS (ESI) m/z 790.3 [M+1]+	
2024		MS (ESI) m/z 713.31 [M+1]+	
2025		MS (ESI) m/z 789.36 [M+1]+	
2032			

[0730]

2038	MS (ESI) m/z 718.1 [M+1]+	2039	MS (ESI) m/z 734.37 [M+1]+
2042	MS (ESI) m/z 807.38 [M+1]+	2030	MS (ESI) m/z 837.28 [M+1]+
2031	MS (ESI) m/z 705.34 [M+1]+	2041	MS (ESI) m/z 807.38 [M+1]+

[0731] 实施例2.合成7-CF_3-噻吩基吡啶和衍生化合物的通用方法

[0732] 表2中的7-CF3-噻吩基吡啶和衍生化合物可以使用实施例2中描述的方法来合成。

实施例1中描述的许多反应用于合成表2中的化合物。对于一些化合物，下文实施例3中描述的一些反应可用于制备这些化合物。

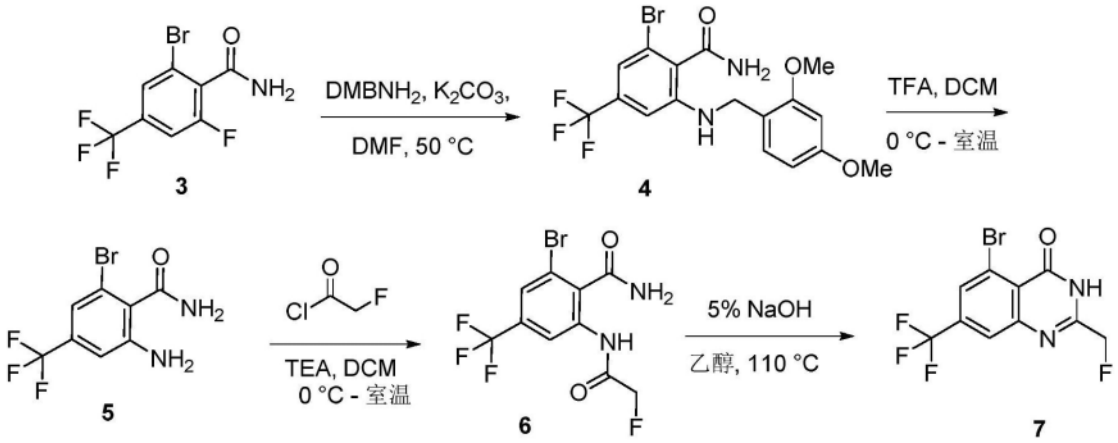
[0733] 实施例2A.合成左侧的方法

[0734] 实施例2A.1

[0735] 

[0736] 在-78℃下在氩气气氛下向二异丙胺(17.8mL,0.123mol)的干燥四氢呋喃(200mL)溶液中滴加正丁基锂(1.6M,66.5mL,0.113mol)。将反应混合物升温至-10℃并搅拌30min。在-78℃下加入1-溴-3-氟-5-(三氟甲基)苯(1,25.0g,0.102mol)的干燥四氢呋喃(50mL)溶液,将混合物在-78℃下搅拌45min。向该反应混合物中吹扫二氧化碳气体15min,并将温度在2h内逐渐升至室温。完成后,将反应混合物冷却至-78℃,并用冰水淬灭。混合物用1N氢氧化钠水溶液碱化,并用乙醚洗涤。水层用2N盐酸酸化至pH约1,并用乙酸乙酯萃取。将有机层分离,用无水硫酸钠干燥,过滤并浓缩,得到2-溴-6-氟-4-(三氟甲基)苯甲酸(2)。

[0737] 实施例2A.2

[0738] 

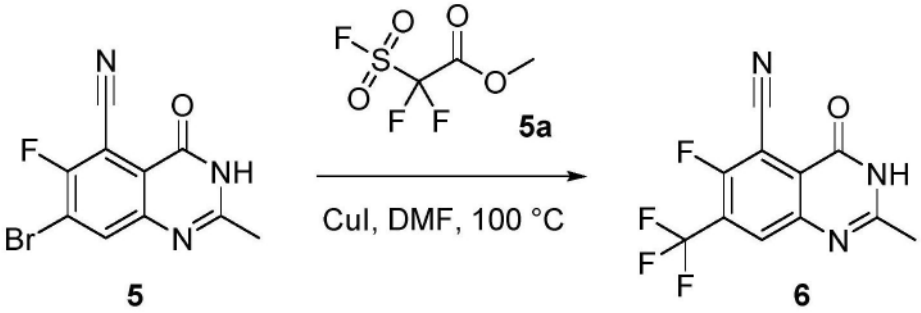
[0739] 在室温下向2-溴-6-氟-4-(三氟甲基)苯甲酰胺(3,4.5g,粗品,15.7mmol)的N,N-二甲基甲酰胺(40mL)溶液中加入碳酸钾(6.5g,47.2mmol)和(2,4-二甲氧基苯基)甲胺(3.1mL,20.45mmol)。将反应混合物加热至50℃并搅拌16h。反应完成后,将反应混合物倒入冰水,并用乙酸乙酯萃取。将有机层用盐水溶液洗涤,用无水硫酸钠干燥,过滤并减压浓缩,得到粗品。用5％甲醇的二氯甲烷溶液作为洗脱剂,通过柱色谱纯化粗品。将期望的级分减压浓缩,得到2-溴-6-((2,4-二甲氧基苄基)氨基)-4-(三氟甲基)苯甲酰胺(4)。

[0740] 向2-溴-6-((2,4-二甲氧基苄基)氨基)-4-(三氟甲基)苯甲酰胺(4,1.0g,2.30mmol)的二氯甲烷(10mL)溶液中加入三氟乙酸(1.8mL,23.0mmol),将混合物搅拌30min。反应完成后,浓缩反应混合物,并将得到的粗品用二氯甲烷稀释,用饱和碳酸氢钠溶液和盐水溶液洗涤,用无水硫酸钠干燥,并减压浓缩,得到粗品。用5％甲醇的二氯甲烷溶液作为洗脱剂,通过柱色谱纯化粗品。将期望的级分减压浓缩,得到2-氨基-6-溴-4-(三氟甲基)苯甲酰胺(5)。

[0741] 在0℃下向2-氨基-6-溴-4-(三氟甲基)苯甲酰胺(5,2.0g,7.06mmol)的二氯甲烷(20mL)溶液中加入三乙胺(2.93mL,21mmol)和2-氟乙酰氯(1.0mL,14.1mmol),并将反应混合物在相同温度下搅拌30min。反应完成后,将反应混合物用冰水稀释,并用二氯甲烷萃取。将有机层用饱和盐水溶液洗涤,用无水硫酸钠干燥并减压浓缩,得到2-溴-6-(2-氟乙酰氨基)-4-(三氟甲基)苯甲酰胺(6)。

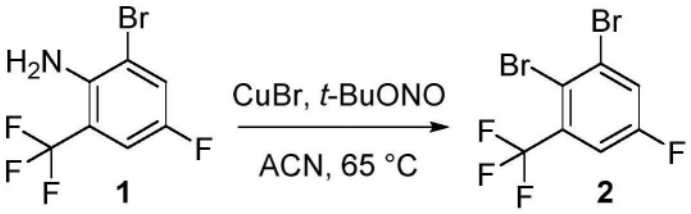
[0742] 向2-溴-6-(2-氟乙酰氨基)-4-(三氟甲基)苯甲酰胺(6,0.600g,1.749mmol)的乙醇(5mL)溶液中加入5%氢氧化钠(4.0mL)。将混合物加热至110℃并搅拌30min。反应完成后,将反应混合物用1N盐酸中和,并用乙酸乙酯萃取。将有机层用饱和盐水溶液洗涤,用无水硫酸钠干燥并减压浓缩,得到粗产物。用硅胶(100-200目)以及用0-5%甲醇的二氯甲烷溶液作为洗脱剂,通过柱色谱纯化粗产物。将期望的级分减压浓缩,得到5-溴-2-(氟甲基)-7-(三氟甲基)喹唑啉-4(3H)-酮(7)。

[0743] 实施例2A.3

[0744] 

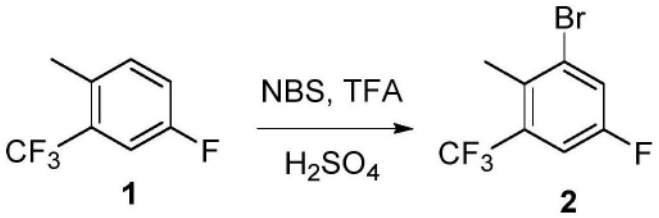
[0745] 向7-溴-6-氟-2-甲基-4-氧代-3,4-二氢喹唑啉-5-甲腈(5,0.200g,0.7mmol)的N,N-二甲基甲酰胺(2mL)溶液中加入碘化亚铜(I)(0.159g,0.84mmol)和2,2-二氟-2-(氟磺酰基)乙酸甲酯(5a,0.403g,2.1mmol),并将反应混合物在100℃下加热16h。完成后,将反应混合物冷却;将水加入反应混合物中,并用乙酸乙酯萃取。将有机层用无水硫酸钠干燥,过滤并浓缩,得到6-氟-2-甲基-4-氧代-7-(三氟甲基)-3,4-二氢喹唑啉-5-甲腈(6)。

[0746] 实施例2A.4

[0747] 

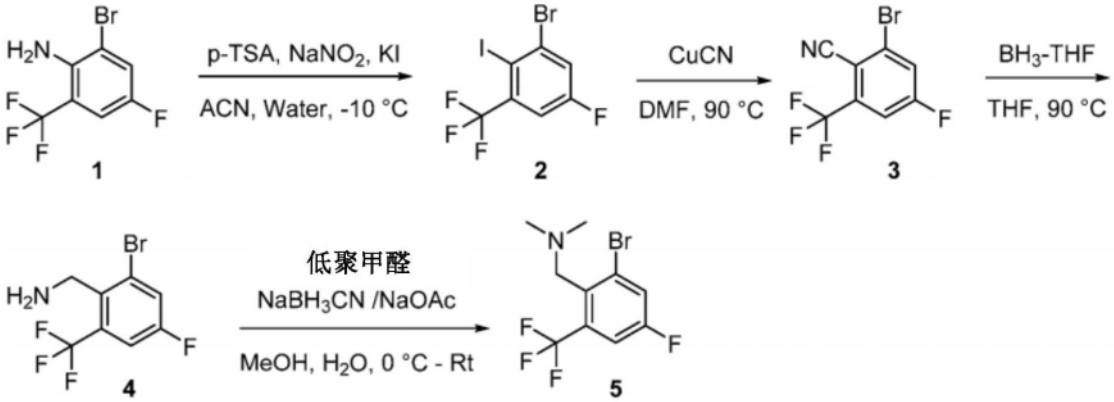
[0748] 将溴化亚铜(I)(89.8g,620.1mmol)和亚硝酸叔丁酯(63.8mL,620.1mmol)在乙腈(2500mL)中的悬浮液在65℃下加热15min。加入2-溴-4-氟-6-(三氟甲基)苯胺(1,100g,387.6momol)的乙腈溶液,并将反应混合物在65℃下加热1h。完成后,反应物质用水淬灭,并用乙酸乙酯萃取。将有机层用无水硫酸钠干燥,过滤并减压浓缩,得到粗物质。用0-5%乙酸乙酯的己烷溶液,在硅胶(100-200目)上通过柱色谱纯化化合物粗品,得到1,2-二溴-5-氟-3-(三氟甲基)苯(2)。

[0749] 实施例2A.5

[0750] 

[0751] 向搅拌的4-氟-1-甲基-2-(三氟甲基)苯(1,1.05g,5.89mmol)的TFA(4mL)溶液中加入硫酸(1.25mL),然后加入N-溴丁二酰亚胺(1.05g,5.89mmol)。将得到的混合物封盖,用铝箔覆盖以避光,并在室温下搅拌过夜。将反应混合物倒入剧烈搅拌的冰水中,然后用己烷萃取。将有机层用盐水洗涤,然后用饱和碳酸氢钠水溶液洗涤。将有机层用硫酸镁干燥,过滤,在旋转蒸发仪上浓缩,并通过硅胶色谱纯化(100%己烷),得到1-溴-5-氟-2-甲基-3-(三氟甲基)苯(2)。

[0752] 实施例2A.6

[0753] 

[0754] 在-10℃下向2-溴-4-氟-6-(三氟甲基)苯胺(1,100.0g,389.2mmol)的乙腈(2500mL)溶液中分批加入对甲苯磺酸(220.9g,1160.1mmol)。在-10℃下加入亚硝酸钠(51.68g,750mmol)和碘化钾(157.7g,949.2mmol)的水(100mL)溶液,并将混合物在-10℃下搅拌45min。完成后,将反应混合物用水淬灭,并用乙酸乙酯萃取(5000mL)。将有机层用饱和硫代硫酸钠水溶液(500mL)洗涤。将有机层分离,用无水硫酸钠干燥,过滤并浓缩,得到1-溴-5-氟-2-碘-3-(三氟甲基)苯(2)。

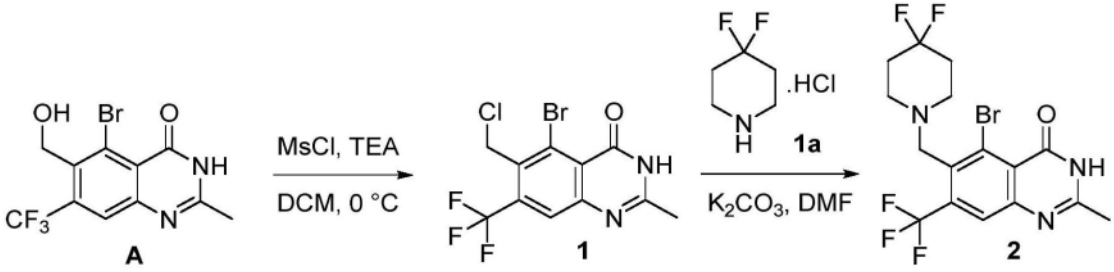
[0755] 在室温下向1-溴-5-氟-2-碘-3-(三氟甲基)苯(2,80.0g,217.3mmol)的N,N-二甲基甲酰胺(500mL)溶液中加入氰化亚铜(I)(19.4g,217.2mmol)。反应混合物在90℃下搅拌12h。完成后,将其冷却至室温,倒入冰水中,并用乙酸乙酯(2.0L)萃取。将有机层用盐水溶液洗涤,用无水硫酸钠干燥,并减压浓缩,得到粗品。用0-5%乙酸乙酯的己烷溶液,通过快速柱色谱纯化化合物粗品,得到2-溴-4-氟-6-(三氟甲基)苯甲腈(3)。

[0756] 在0℃下向2-溴-4-氟-6-(三氟甲基)苯甲腈(3,12.0g,44.9mmol)的四氢呋喃(200mL)溶液中滴加硼烷的四氢呋喃溶液(1M,67mL,67.1mmol)。将反应混合物在90℃下搅拌12h。完成后,将反应混合物倒入冷甲醇中,并减压浓缩。用0-15%乙酸乙酯的己烷溶液,通过快速柱色谱纯化化合物粗品,得到(2-溴-4-氟-6-(三氟甲基)苯基)甲胺(4)。

[0757] 向(2-溴-4-氟-6-(三氟甲基)苯基)甲胺(4,6.0g,22.6mmol)的甲醇(100mL)溶液中加入低聚甲醛(6.0g,200.0mmol)和乙酸钠(5.4g,66.0mmol)的水(10mL)溶液,并在室温下搅拌1h。在0℃下分批加入氰基硼氢化钠(4.03g,66.1mmol)。将反应混合物在室温下搅拌

12h。完成后,将反应混合物减压浓缩。粗残留物用水稀释,并用乙醚萃取(100mL)。用0-15%乙酸乙酯的己烷溶液,通过快速柱色谱纯化化合物粗品,得到1-(2-溴-4-氟-6-(三氟甲基)苯基)-N,N-二甲基甲胺(5)。

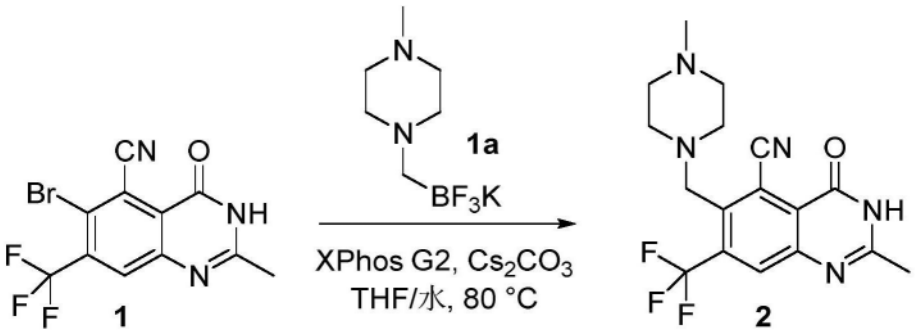
[0758] 实施例2A.7

[0759] 

[0760] 在0℃下向5-溴-6-(羟基甲基)-2-甲基-7-(三氟甲基)喹唑啉-4(3H)-酮(A,0.32g,0.94mmol)的二氯甲烷(6mL)溶液中加入三乙胺(0.39mL,2.84mmol)和甲磺酰氯(0.11mL,1.42mmol),并在0℃下搅拌1h。完成后,将反应混合物用水稀释,并用二氯甲烷萃取。将有机层用水和饱和盐水洗涤,用无水硫酸钠干燥并减压浓缩,得到5-溴-6-(氯甲基)-2-甲基-7-(三氟甲基)喹唑啉-4(3H)-酮(1)。

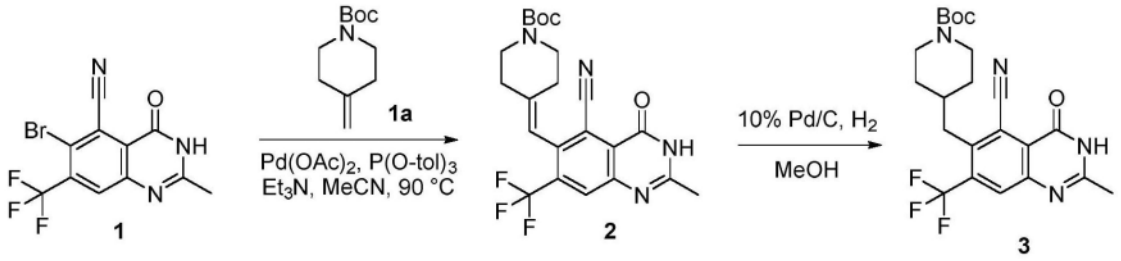
[0761] 在室温下向4,4-二氟哌啶(1a,2.0g,12.7mmol)的N,N-二甲基甲酰胺(10.0mL)溶液中加入碳酸钾(1.06g,7.62mmol),并将混合物搅拌20min。然后在室温下将5-溴-6-(氯甲基)-2-甲基-7-(三氟甲基)喹唑啉-4(3H)-酮(1,0.9g,2.54mmol)加入反应混合物中,并继续搅拌24h。完成后,将反应混合物用水稀释,并用乙酸乙酯萃取。将有机层用水和饱和盐水溶液洗涤,用无水硫酸钠干燥,过滤并浓缩。用硅胶(100-200目)以及用50%乙酸乙酯的己烷溶液作为洗脱剂,通过柱色谱纯化粗产物。将期望的级分减压浓缩,得到5-溴-6-((4,4-二氟哌啶-1-基)甲基)-2-甲基-7-(三氟甲基)喹唑啉-4(3H)-酮(2)。

[0762] 实施例2A.8

[0763] 

[0764] 向6-溴-2-甲基-4-氧代-7-(三氟甲基)-3,4-二氢喹唑啉-5-甲腈(1,50mg,0.151mmol)在四氢呋喃(3mL)和水(0.75mL)中的溶液中加入1-甲基-4-((三氟-λ⁴-硼烷基)甲基)哌嗪钾盐(1a,497mg,2.25mmol),碳酸铯(196mg,0.602mmol)和XPhos氯(2-二环己基膦基-2',4',6'-三异丙基-1,1'-联苯)[2-(2'-氨基-1,1'-联苯)]钯(II)(24mg,0.0301mmol),并将混合物用氩气吹扫5min,然后将其密封并加热至80℃持续15h。完成后,将混合物减压浓缩,得到粗产物。将得到的粗产物通过制备HPLC纯化,得到2-甲基-6-((4-甲基哌嗪-1-基)甲基)-4-氧代-7-(三氟甲基)-3,4-二氢喹唑啉-5-甲腈(2)。

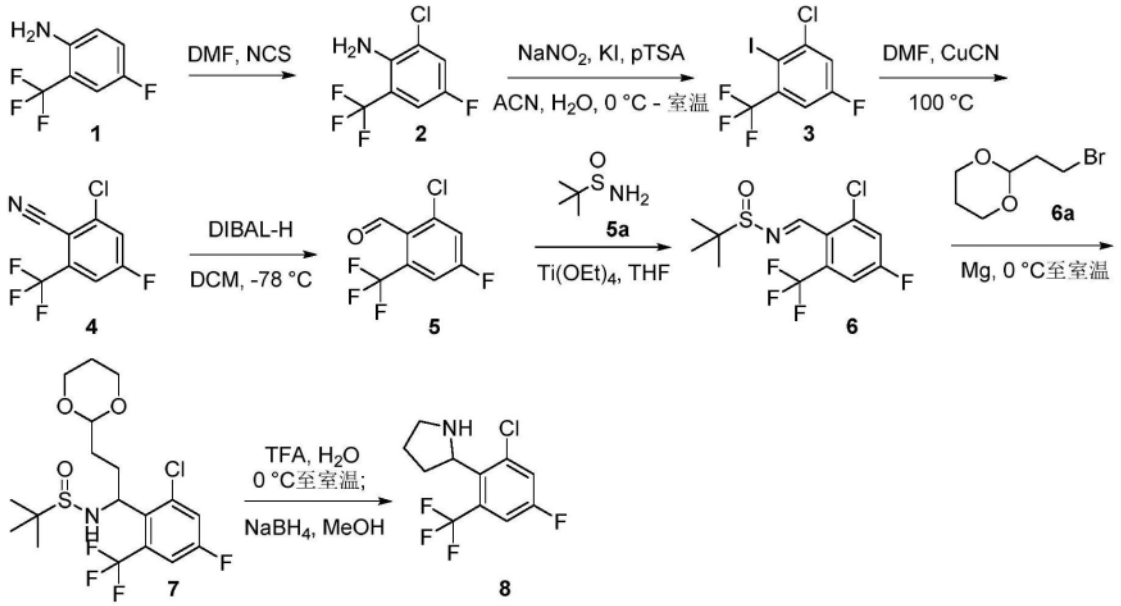
[0765] 实施例2A.9

[0766] 

[0767] 将6-溴-2-甲基-4-氧代-7-(三氟甲基)-3,4-二氢喹唑啉-5-甲腈(1,1.00g,3.02mmol),4-亚甲基哌啶-1-甲酸叔丁酯(1a,5.90g,30.1mmol),三乙胺(1.20mL,9.03mmol)和三(邻甲苯基)膦(0.366g,1.23mmol)的乙腈(10.0mL)溶液用氩气脱气10min。然后将乙酸钯(II)(0.134g,0.60mmol)加入反应混合物中,并继续脱气5min。将反应混合物在90℃下加热24h。在该时间后,将反应混合物冷却至室温,用乙酸乙酯稀释,并减压浓缩至干。用30-50%乙酸乙酯的己烷溶液作为洗脱剂,通过硅胶(100-200目)柱色谱纯化粗产物。将期望的级分减压浓缩,得到4-((5-氰基-2-甲基-4-氧代-7-(三氟甲基)-3,4-二氢喹唑啉-6-基)亚甲基)哌啶-1-甲酸叔丁酯(2)。

[0768] 在室温下向4-((5-氰基-2-甲基-4-氧代-7-(三氟甲基)-3,4-二氢喹唑啉-6-基)亚甲基)哌啶-1-甲酸叔丁酯(2,0.90g,2.0mmol)的甲醇(20mL)溶液中加入10%钯碳(palladium on carbon)(1.35g)。将反应混合物在室温下在氢气气氛下搅拌2h。然后,将反应混合物通过硅藻土过滤。将滤液用乙酸乙酯洗涤并减压浓缩至干,得到粗产物。用3-5%甲醇的二氯甲烷溶液作为洗脱剂,通过硅胶(100-200目)柱色谱纯化粗产物。将期望的级分减压浓缩,得到4-((5-氰基-2-甲基-4-氧代-7-(三氟甲基)-3,4-二氢喹唑啉-6-基)甲基)哌啶-1-甲酸叔丁酯(3)。

[0769] 实施例2A.10

[0770] 

[0771] 在室温下向4-氟-2-(三氟甲基)苯胺(1,100.0g,558.66mmol)的N,N-二甲基甲酰胺(500mL)溶液中加入N-氯代丁二酰亚胺(78.7g,558.66mmol)。将该反应混合物搅拌16h。在该时间后,将混合物用水稀释,并用乙酸乙酯萃取。将有机层用水洗涤,然后用盐水洗涤,用无水硫酸钠干燥,过滤并浓缩。用己烷作为洗脱剂,通过硅胶(100-200目)柱色谱纯化粗

产物。将期望的级分减压浓缩,得到2-氯-4-氟-6-(三氟甲基)苯胺(2)。

[0772] 在-10℃下向2-氯-4-氟-6-(三氟甲基)苯胺(2,43.0g,201.87mmol)的乙腈(200mL)溶液中加入对甲苯磺酸一水合物(115.0g,605.63mmol)。将该反应混合物在相同温度下搅拌15min。将亚硝酸钠(27.85g,403.74mmol)和碘化钾(83.77g,504.67mmol)的水(50mL)溶液滴加到反应混合物,并在-10℃下搅拌30min。然后,将反应混合物用水稀释,用乙酸乙酯萃取。将有机层用饱和硫代硫酸钠水溶液洗涤,然后用盐水洗涤,用无水硫酸钠干燥,过滤并浓缩。用己烷作为洗脱剂,通过硅胶(100-200目)柱色谱纯化粗产物。将期望的级分减压浓缩,得到1-氯-5-氟-2-碘-3-(三氟甲基)苯(3)。

[0773] 向1-氯-5-氟-2-碘-3-(三氟甲基)苯(3,30g,92.6mmol)的N,N-二甲基甲酰胺(200mL)溶液中加入氰化亚铜(I)(12.36g,138.88mmol)。将该反应混合物在100℃下加热16h。在该时间后,将混合物用水稀释,并用乙酸乙酯萃取。将有机层用水和盐水洗涤,用无水硫酸钠干燥,过滤并浓缩。用3%乙酸乙酯的己烷溶液作为洗脱剂,通过硅胶(100-200目)柱色谱纯化粗产物。将期望的级分减压浓缩,得到2-氯-4-氟-6-(三氟甲基)苯甲腈(4)。

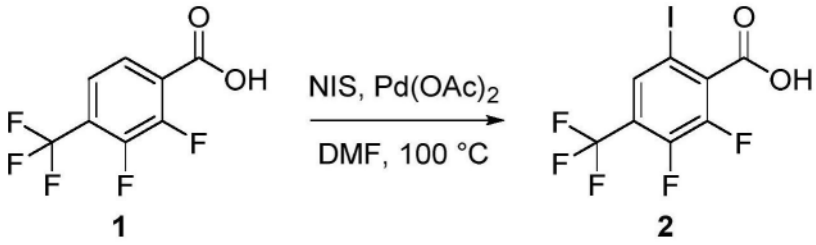
[0774] 在-78℃下向2-氯-4-氟-6-(三氟甲基)苯甲腈(4,15.0g,67.26mmol)的干燥二氯甲烷(150mL)溶液中滴加二异丁基氢化铝(1.0M的甲苯溶液,134.52mL,134.52mmol)。将混合物在相同温度下搅拌30min。然后,将反应混合物用1N盐酸水溶液淬灭,并用二氯甲烷萃取。将有机层用无水硫酸钠干燥,过滤并减压浓缩至干,得到2-氯-4-氟-6-(三氟甲基)苯甲醛(5)。

[0775] 在室温下向2-氯-4-氟-6-(三氟甲基)苯甲醛(5,17.00g,75.22mmol)的四氢呋喃(100mL)溶液中滴加2-甲基丙烷-2-亚磺酰胺(5a,13.65g,112.83mmol)和乙醇钛(34.30mL,150.44mmol)。将该反应混合物在相同温度下搅拌16h。在该时间后,将反应混合物用氯化铵水溶液淬灭,通过硅藻土过滤,并用乙酸乙酯洗涤。将滤液浓缩,用20%乙酸乙酯的己烷溶液作为洗脱剂,通过Combi-flash(40g,Redi-Sep柱)纯化粗残留物。将期望的级分减压浓缩,得到(E)-N-(2-氯-4-氟-6-(三氟甲基)亚苄基)-2-甲基丙烷-2-亚磺酰胺(6)。

[0776] 将镁屑(5.0g)加入干燥四氢呋喃(50mL)中,接着加入碘(0.002g),并将混合物加热至略高于室温。然后加入2-(2-溴乙基)-1,3-二氧六环(6a,9.8mL,72.94mmol),并将混合物加热直到变为无色。然后在室温下将该混合物滴加到(E)-N-(2-氯-4-氟-6-(三氟甲基)亚苄基)-2-甲基丙烷-2-亚磺酰胺(6,12.00g,36.47mmol)的四氢呋喃(50mL)溶液中。将得到的混合物在室温下搅拌1h。然后,将反应混合物用氯化铵水溶液淬灭,并用乙酸乙酯萃取。将有机层用无水硫酸钠干燥并浓缩。用30%乙酸乙酯的己烷溶液作为洗脱剂,通过Combi-flash(40g,Redi-Sep柱)纯化粗残留物。将期望的级分减压浓缩,得到N-(1-(2-氯-4-氟-6-(三氟甲基)苯基)-3-(1,3-二氧六环-2-基)丙基)-2-甲基丙烷-2-亚磺酰胺(7)。

[0777] 将N-(1-(2-氯-4-氟-6-(三氟甲基)苯基)-3-(1,3-二氧六环-2-基)丙基)-2-甲基丙烷-2-亚磺酰胺(7,12.00g,26.96mmol)在三氟乙酸的水溶液(3:1,180mL)在的溶液混合物在室温下搅拌16h。在该时间后,将反应混合物用碳酸氢钠水溶液淬灭,并用乙酸乙酯萃取。将有机层用无水硫酸钠干燥,过滤并浓缩。将固体残留物溶于甲醇,然后在0℃下加入硼氢化钠(8.00g,269.66mmol),并将混合物在室温下搅拌8h。在该时间后,将反应混合物用冰冷的水淬灭,并用乙酸乙酯萃取。将有机层用无水硫酸钠干燥,过滤并减压浓缩至干,得到2-(2-氯-4-氟-6-(三氟甲基)苯基)吡咯烷(8)。

[0778] 实施例2A.11

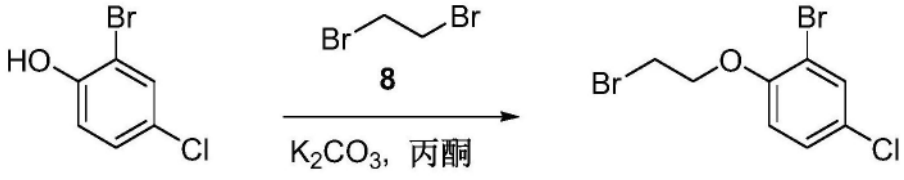
[0779] 

1 2

[0780] 向2,3-二氟-4-(三氟甲基)苯甲酸(1,5g,22.123mmol)的N,N-二甲基甲酰胺(50mL)溶液中加入N-碘代丁二酰亚胺(7.43g,33.185mmol),并用氩气吹扫20min。然后加入乙酸钯(1.48g,6.637mmol),并将反应混合物在100℃下加热48h。完成后,将反应混合物冷却,用水稀释,并用乙酸乙酯萃取。合并的有机层用冷水和盐水溶液洗涤,用无水硫酸钠干燥,过滤并减压浓缩,得到2,3-二氟-6-碘-4-(三氟甲基)苯甲酸(2)。

[0781] 实施例2B.合成右侧的方法

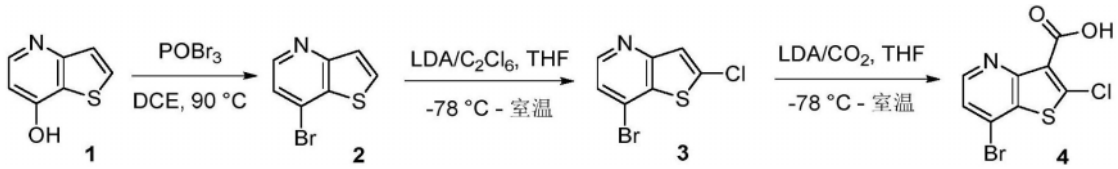
[0782] 实施例2B.1

[0783] 

7 9

[0784] 向2-溴-4-氯苯酚(7,50.0g,241.0mmol)在氢氧化钠水溶液(1M)(1.0L)中的溶液中加入四正丁基溴化铵(11.64g,36.15mmol)和碘化钾(6.00g,36.15mmol)。在85℃下加入1,2-二溴乙烷(8,165.6g,891.7mmol)并在相同温度下搅拌16h。完成后,将反应混合物倒入水中,并用乙酸乙酯萃取。合并的有机层用水和盐水洗涤,用无水硫酸钠干燥,并减压浓缩,得到粗品;通过快速柱色谱纯化(用0-5%乙酸乙酯的己烷溶液)化合物粗品,得到2-溴-1-(2-溴乙氧基)-4-氯苯(9)。

[0785] 实施例2B.2

[0786] 

1 2 3 4

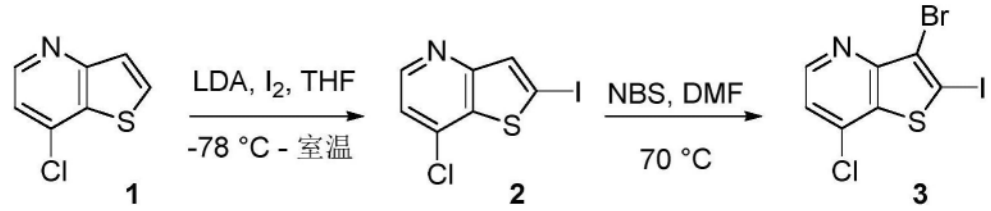
[0787] 将搅拌的噻吩并[3,2-b]吡啶-7-醇(1,2.0g,13.2mmol)在氧溴化磷(7.5g,26.4mmol)和1,2-二氯乙烷中的溶液在90℃下加热12h。反应完成后,将混合物冷却至室温,用饱和碳酸氢钠水溶液淬灭,并用乙酸乙酯萃取。将有机层用盐水洗涤,用无水硫酸钠干燥,过滤并浓缩,得到7-溴噻吩并[3,2-b]吡啶(2)。

[0788] 在-78℃下向搅拌的7-溴噻吩并[3,2-b]吡啶(2,1.5g,7.04mmol)的干燥四氢呋喃(20mL)溶液中加入新制备的二异丙基氨基锂(2.0M的己烷溶液,8.75mL,17.5mmol),并将混合物在相同温度下搅拌1h。滴加六氯乙烷(2.0mL,8.44mmol),并将反应混合物在3h内升温至室温。用氯化铵水溶液淬灭反应,用水稀释,并用乙酸乙酯萃取。将有机层用水和饱和盐水溶液洗涤,用无水硫酸钠干燥,过滤并浓缩。在硅胶塞上纯化粗产物,用乙酸乙酯的己烷溶液(0-10%)洗脱化合物。将期望的级分减压浓缩,得到7-溴-2-氯噻吩并[3,2-b]吡啶

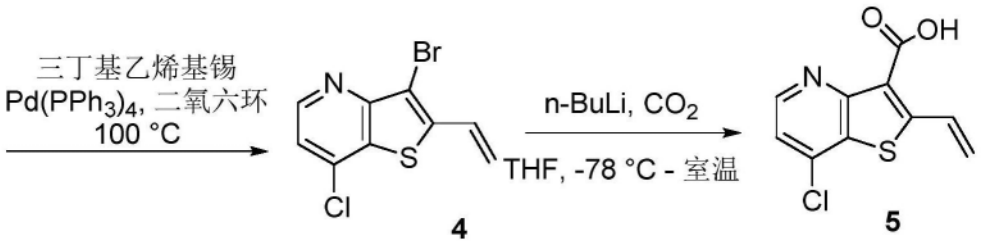
(3)。

[0789] 向7-溴-2-氯噻吩并[3,2-b]吡啶(3,0.5g,2.02mmol)的干燥四氢呋喃(10mL)溶液中,并将混合物冷却至-78℃。滴加二异丙基氨基锂(2M,1.5mL,3.03mmol),并将反应混合物在-78℃下搅拌1h。在相同温度下用二氧化碳气体吹扫通过反应物质20min,并在-78℃下搅拌1h。将反应混合物缓慢升温至0℃,并搅拌30min。完成后,将反应混合物用水淬灭,并用乙酸乙酯洗涤。弃去乙酸乙酯层,水层用柠檬酸水溶液酸化。然后用乙酸乙酯萃取。将有机层分离,用无水硫酸钠干燥,过滤并减压浓缩,得到7-溴-2-氯噻吩并[3,2-b]吡啶-3-羧酸(4)。

[0790] 实施例2B.3



[0791]



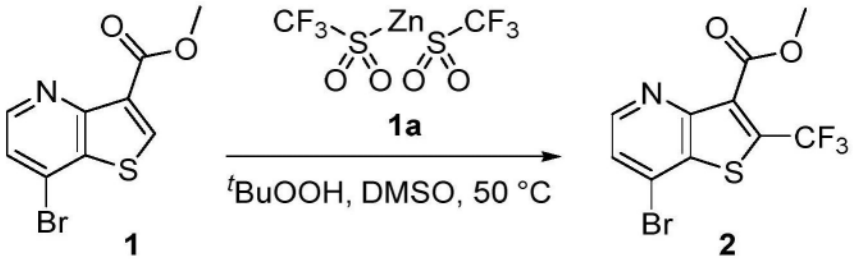
[0792] 在-78℃下向搅拌的7-氯噻吩并[3,2-b]吡啶(1,1.5g,8.9mmol)的干燥四氢呋喃(50mL)溶液中滴加二异丙基氨基锂(11.7mL,19.5mmol),并将混合物在相同温度下搅拌1h。滴加碘(2.25g,8.87mmol溶于四氢呋喃,10mL),并将反应混合物在4h内升温至室温。将其用氯化铵的水溶液淬灭,并用乙酸乙酯萃取。将有机层用水和饱和盐水溶液洗涤,用无水硫酸钠干燥,过滤并减压浓缩至干。用5-10%乙酸乙酯的己烷溶液作为洗脱剂,通过Combiflash(12g,RediSep柱)纯化粗产物。将期望的级分减压浓缩,得到7-氯-2-碘噻吩并[3,2-b]吡啶(2)。

[0793] 在室温下向7-氯-2-碘噻吩并[3,2-b]吡啶(2,1.0g,3.4mmol)的N,N-二甲基甲酰胺(10mL)溶液中加入N-溴代丁二酰亚胺。将反应混合物在70℃下加热搅拌12h。反应完成后,混合物用水稀释,用乙酸乙酯萃取。将有机层用水和饱和盐水溶液洗涤,用无水硫酸钠干燥,过滤,减压浓缩。用5-10%乙酸乙酯的己烷溶液作为洗脱剂,通过Combiflash(12g,RediSep柱)纯化粗产物。将期望的级分减压浓缩,得到3-溴-7-氯-2-碘噻吩并[3,2-b]吡啶(3)。

[0794] 将3-溴-7-氯-2-碘噻吩并[3,2-b]吡啶(3,1.0g,2.7mmol)和三丁基乙烯基锡(1.01mL,3.21mmol)在1,4-二氧六环(10mL)中的悬浮液用氩气脱气10min。在室温下将四(三苯基膦)钯(0)(0.21g,0.19mmol)加入反应混合物,并将混合物在100℃下加热1h。完成后,将反应混合物冷却至室温,用水稀释,并用乙酸乙酯萃取。将乙酸乙酯层用硫酸钠干燥,并减压浓缩至干。在硅胶塞上纯化粗产物,用乙酸乙酯:己烷(1-10%)洗脱化合物。将期望的级分减压浓缩,得到3-溴-7-氯-2-乙烯基噻吩并[3,2-b]吡啶(4)。

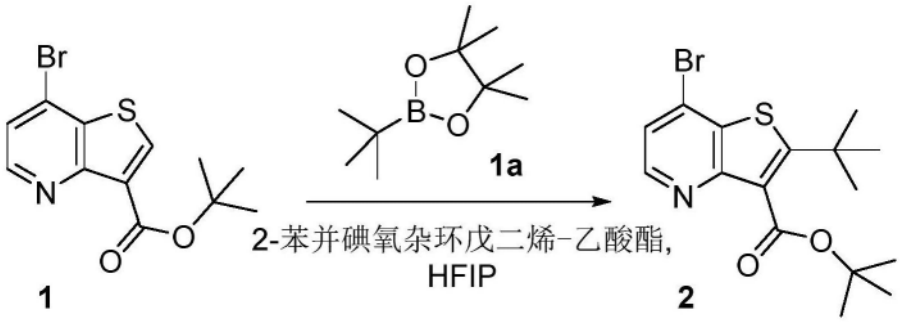
[0795] 在-78℃下向3-溴-7-氯-2-乙烯基噻吩并[3,2-b]吡啶(4,0.6g,2.19mmol)的干燥四氢呋喃(20mL)溶液中滴加正丁基锂(1.7mL,1.3M的己烷溶液,2.19mmol),并将反应混合物在相同温度下搅拌2h。在-78℃下用二氧化碳气体吹扫通过反应混合物30min,并将反应混合物在相同温度下搅拌1h。将反应混合物缓慢升温至0℃并搅拌30min。完成后,将反应混合物用水淬灭,并用乙酸乙酯洗涤。弃去乙酸乙酯层,水层用柠檬酸水溶液酸化,并用乙酸乙酯萃取。将有机层分离,用无水硫酸钠干燥,过滤并减压浓缩,得到7-氯-2-乙烯基噻吩并[3,2-b]吡啶-3-羧酸(5)。

[0796] 实施例2B.4

[0797] 

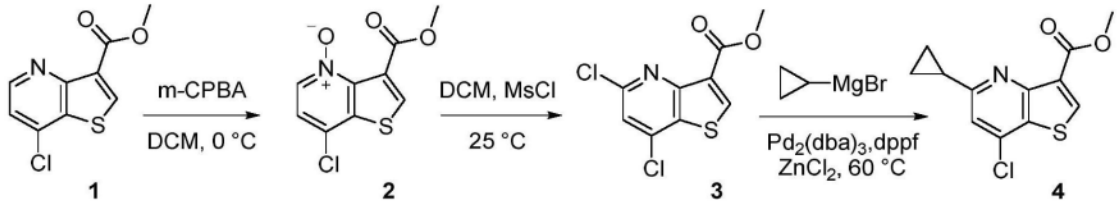
[0798] 在配备搅拌棒的烘干的螺旋盖小瓶中将7-溴噻吩并[3,2-b]吡啶-3-甲酸甲酯(1,68.0mg,0.25mmol)和双(三氟甲基亚磺酰基氧基)锌(1a,139.8mg,0.50mmol)溶于二甲基亚砜(1.71mL)。将混合物在0℃下剧烈搅拌,同时缓慢加入叔丁基过氧化氢(0.09mL,0.92mmol)。加料完成后,移除冰浴,在加热器中将反应混合物加热至50℃持续2.5h,然后冷却至室温。反应混合物用饱和碳酸氢钠水溶液和乙酸乙酯稀释。分离各层,并将水相用乙酸乙酯萃取三次。合并的有机物质用盐水洗涤,并用硫酸镁干燥。将固体过滤,真空除去溶剂得到粗残留物,将其通过硅胶色谱纯化(5至40%乙酸乙酯的己烷溶液),得到7-溴-2-(三氟甲基)噻吩并[3,2-b]吡啶-3-甲酸甲酯(2)。

[0799] 实施例2B.5

[0800] 

[0801] 将7-溴噻吩并[3,2-b]吡啶-3-甲酸叔丁酯(1,150.0mg,0.480mmol),(3-氧代-1λ^{3},2-苯并碘氧杂环戊二烯-1-基)乙酸酯((3-oxo-1λ^{3},2-benziodoxol-1-yl)acetate)(417.5mg,0.950mmol),2-(叔丁基)-4,4,5,5-四甲基-1,3,2-二氧杂硼杂环戊烷(1a,132.0mg,0.720mmol)和三(2,2'-联吡啶基)二氯-钌(II)六水合物(35.7mg,0.048mmol)的六氟异丙醇(1.25mL)溶液在室温下搅拌,并用放置在距离小瓶10cm的60瓦家用灯照射24h。完成后,将反应混合物用二氯甲烷稀释,并加入硅胶。蒸发溶剂。用硅胶(100-200目)以及用0-10%甲醇的二氯甲烷溶液作为洗脱剂,通过快速色谱纯化粗品硅胶混合物。将期望的级分减压浓缩,得到7-溴-2-(叔丁基)噻吩并[3,2-b]吡啶-3-甲酸叔丁酯(2)。

[0802] 实施例2B.6

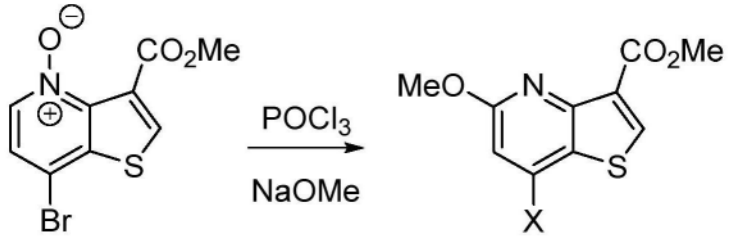
[0803] 

[0804] 在配备搅拌棒的烘干的螺旋盖小瓶中将7-氯噻吩并[3,2-b]吡啶-3-甲酸甲酯(1,0.2g,0.88mmol)溶于二氯甲烷(2.2mL)。将反应混合物在室温下搅拌,同时在2min内分4批加入3-氯过氧苯甲酸(0.24g,1.41mmol)。24h后,将反应混合物倒到硅胶上,并通过硅胶色谱纯化(50-100%乙酸乙酯的己烷溶液,然后10%甲醇的乙酸乙酯溶液),得到7-氯-3-(甲氧基羰基)噻吩并[3,2-b]吡啶4-氧化物(2)。

[0805] 在配备搅拌棒的烘干的螺旋盖小瓶中将7-氯-3-(甲氧基羰基)噻吩并[3,2-b]吡啶4-氧化物(2,0.12g,0.47mmol)溶于二氯甲烷(3.3mL)中。将混合物在室温下搅拌,同时滴加甲磺酰氯(0.18mL,2.36mmol)。3h后,滴加更多的甲磺酰氯(0.18mL,2.36mmol)。4.5h后,将反应混合物升温至40℃,再搅拌16h,然后冷却至室温。将反应混合物倒到硅胶上,并通过硅胶色谱纯化(0-50%乙酸乙酯的己烷溶液),得到5,7-二氯噻吩并[3,2-b]吡啶-3-甲酸甲酯(3)。

[0806] 在配备搅拌棒的烘干的螺旋盖小瓶中将氯化锌溶液(0.5M,0.59mL,0.29mmol)溶于四氢呋喃(1.0mL)中。将反应混合物在室温下搅拌,同时缓慢加入溴(环丙基)镁(0.59mL,0.29mmol)溶液。45min后,缓慢加入5,7-二氯噻吩并[3,2-b]吡啶-3-甲酸甲酯(3,67.0mg,0.25mmol)的四氢呋喃(1.5mL)溶液。1min后,加入$Pd_2(dba)_3$(28.4mg,0.03mmol)和dppf(30.4mg,0.06mmol),随后将反应混合物加热到60℃持续1h。将反应混合物冷却至室温,倒入饱和NH_4Cl水溶液中。水相用乙酸乙酯萃取三次。合并的有机材料用盐水洗涤,用硫酸镁干燥,过滤并真空除去溶剂,得到棕色油状物。通过硅胶色谱纯化(8-29%乙酸乙酯的己烷溶液),得到7-氯-5-环丙基噻吩并[3,2-b]吡啶-3-甲酸甲酯(4)。

[0807] 实施例2B.7

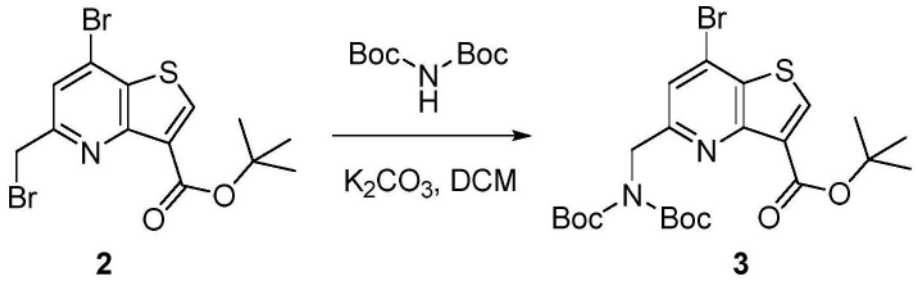
[0808] 

2 **3 (X=Br)/3' (X=Cl)**
(3':3比例约为3:1)

[0809] 将7-溴-3-(甲氧基羰基)噻吩并[3,2-b]吡啶4-氧化物(2,148mg,0.514mmol)溶于氯仿(10mL),并加入$POCl_3$(0.48mL,0.79g,5.1mmol)。将小瓶密封,将混合物在60℃下搅拌4h,然后在室温下过夜。然后将混合物浓缩,溶于DCM,用$NaHCO_3$(水溶液)洗涤,干燥(Na_2SO_4),过滤并浓缩。将粗产物(140mg)溶于THF(9mL),并加入甲醇钠(25%的MeOH溶液,0.12mL,0.12g,0.52mmol)。将混合物在室温下搅拌2.75h,再加入0.13mL NaOMe溶液(25%的MeOH溶液)。30min后,再加入0.04mL NaOMe溶液(25%的MeOH溶液)。再10min后,再加入0.04mL NaOMe溶液(25%的MeOH溶液)。然后将混合物用DCM稀释,并用水洗涤。干燥有机相

(Na_2SO_4),过滤并浓缩。通过柱色谱纯化,得到3'和3的3:1混合物23.9mg。

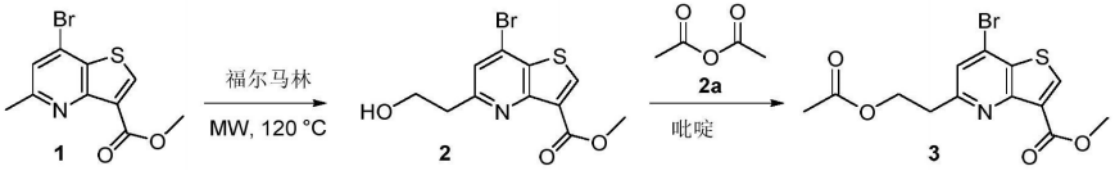
[0810] 实施例2B.8

[0811] 

2 3

[0812] 向7-溴-5-(溴甲基)噻吩并[3,2-b]吡啶-3-甲酸叔丁酯(2,200.0mg,0.491mmol)的N,N-二甲基吡咯烷酮(3mL)溶液中加入N-叔丁氧基羰基氨基甲酸叔丁酯(160.1mg,0.736mmol)和碳酸钾(203.6mg,1.473mmol),并将反应混合物在室温下搅拌24h。完成后,将反应混合物用二氯甲烷稀释,并加入硅胶。蒸发溶剂。用0-10%甲醇的二氯甲烷溶液作为洗脱剂,通过Isco柱色谱纯化粗品硅胶混合物。将期望的级分减压浓缩,得到5-[[双(叔丁氧基羰基)氨基]甲基]-7-溴-噻吩并[3,2-b]吡啶-3-甲酸叔丁酯(3)。

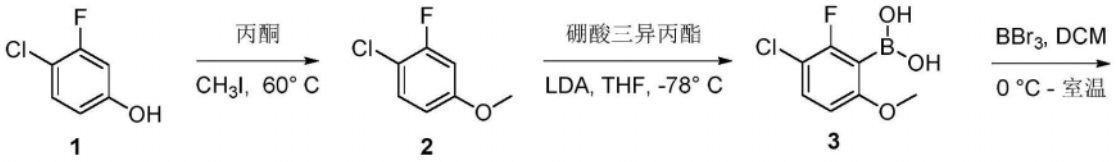
[0813] 实施例2B.9

[0814] 

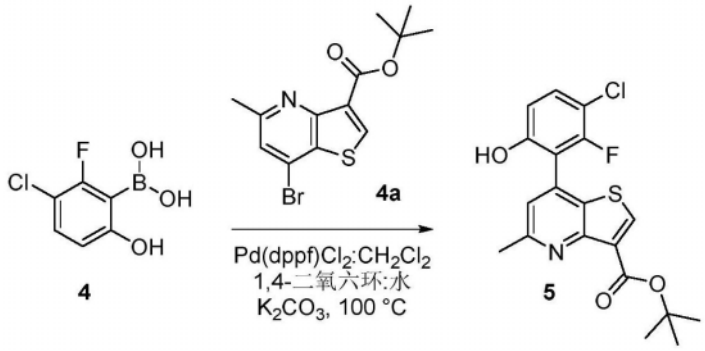
[0815] 将7-溴-5-甲基噻吩并[3,2-b]吡啶-3-甲酸甲酯(1,3.50g,12.3mmol)在福尔马林(37-40%)10mL中的悬浮液在120℃下微波照射1h。1h后,将反应物质冷却,并用乙酸乙酯萃取。原料在1h内未消耗完,微波后处理三次后再次照射反应。通过LCMS监测反应,仍有50%的原料剩余。将反应物质冷却,并用乙酸乙酯萃取。将有机层用无水硫酸钠干燥,并减压浓缩至干。用硅胶(100-200目)和0-40%乙酸乙酯的己烷溶液,通过柱色谱纯化残留物,得到7-溴-5-(2-羟基乙基)噻吩并[3,2-b]吡啶-3-甲酸甲酯(2)。

[0816] 向7-溴-5-(2-羟基乙基)噻吩并[3,2-b]吡啶-3-甲酸甲酯(2,0.32g,1.01mmol)的吡啶(10mL)溶液中,将乙酸酐(0.115mL,1.22mmol)加入反应混合物中。将反应混合物在室温下搅拌16h。在薄层色谱和LCMS上确认反应完成后,将反应混合物用水稀释,并用乙酸乙酯萃取。将有机层用无水硫酸钠干燥,并减压浓缩至干。用50%乙酸乙酯的己烷溶液为洗脱剂,通过combi flash(4g,Redi Sep柱)纯化粗品,得到5-(2-乙酰氧基乙基)-7-溴噻吩并[3,2-b]吡啶-3-甲酸甲酯(3)。

[0817] 实施例2B.10



[0818]



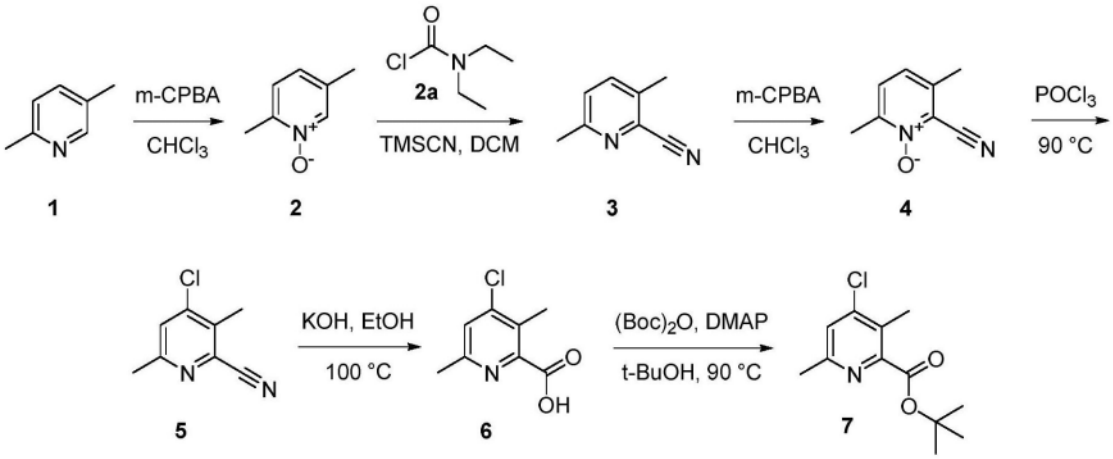
[0819] 在室温下向4-氯-3-氟苯酚(1,3.0g,20.59mmol)的丙酮(30mL)溶液中加入碘甲烷(5.2mL,82.00mmol)和碳酸钾(5.6g,41.00mmol),并将反应混合物在60℃下搅拌12h。在薄层色谱上证实反应完成后,蒸发反应物质,将反应混合物用水稀释,并用乙酸乙酯萃取。将有机层用无水硫酸钠干燥,过滤并浓缩,得到1-氯-2-氟-4-甲氧基苯(2)。

[0820] 在-78℃下向1-氯-2-氟-4-甲氧基苯(2,1.9g,11.84mmol)的四氢呋喃(20mL)溶液中滴加二异丙基氨基锂(2M四氢呋喃溶液)(11.8mL,23.75mmol),并将反应混合物在相同温度下搅拌1h。然后在-78℃下滴加硼酸三异丙酯(3.26mL,14.16mmol)。将反应混合物在室温下搅拌2h。反应完成后,将反应混合物用饱和氯化铵溶液淬灭,并用乙酸乙酯萃取。将有机层用无水硫酸钠干燥,过滤并浓缩,得到化合物粗品。用12gm redisep柱,用80%乙酸乙酯的己烷溶液洗脱,通过combi flash色谱纯化获得的化合物粗品,得到(3-氯-2-氟-6-甲氧基苯基)硼酸(3)。

[0821] 在0℃下向(3-氯-2-氟-6-甲氧基苯基)硼酸(3,0.35g,1.71mmol)的二氯甲烷(5mL)溶液中滴加三溴化硼(0.324mL,3.43mmol),并将反应混合物在室温下搅拌1h。在薄层色谱上确认反应完成后,将反应混合物用冰冷的水淬灭。将固体沉淀过滤并用戊烷洗涤,得到(3-氯-2-氟-6-羟基苯基)硼酸(4)。

[0822] 将7-溴-5-甲基噻吩并[3,2-b]吡啶-3-甲酸叔丁酯(4a,0.230g,0.8mmol),(3-氯-2-氟-6-羟基苯基)硼酸(4,0.30g,1.6mmol)和碳酸钾(0.334g,2.4mmol)在1,4-二氧六环(2.0mL)和水(0.5mL)中的悬浮液用氩气脱气10min。将[1,1'-双(二苯基膦基)二茂铁]二氯化钯(II)与二氯甲烷的复合物(0.03g,0.04mmol)加入上述悬浮液中,并将反应混合物在90℃下搅拌3h。用LCMS和薄层色谱监测反应混合物。完成后,反应物质通过硅藻土床过滤,并用乙酸乙酯洗涤。用4gm redisep柱,用90%乙酸乙酯的己烷溶液洗脱,通过combi flash色谱纯化获得的化合物粗品,得到7-(3-氯-2-氟-6-羟基苯基)-5-甲基噻吩并[3,2-b]吡啶-3-甲酸叔丁酯(5)。

[0823] 实施例2B.11

[0824] 

[0825] 在0℃下在氩气气氛下向2,5-二甲基吡啶(1,10.0g,93.4mmol)的氯仿(100mL)溶液中加入间氯过氧苯甲酸(19.3g,112.1mmol),并将混合物在室温下搅拌16h。完成后,将反应混合物用10%氢氧化钙溶液稀释,将溶液通过硅藻土过滤,将滤液浓缩并干燥,得到2,5-二甲基吡啶1-氧化物(2)。

[0826] 在0℃下在氩气气氛下向2,5-二甲基吡啶1-氧化物(2,10.0g,81.3mmol)的二氯甲烷(100mL)溶液中加入三甲基氰硅烷(11.2g,89.4mmol),在室温下搅拌30分钟,加入二甲基氨基甲酰氯(2a,11.3mL,89.4mmol),并在室温下继续搅拌24h。完成后,将反应混合物用10%碳酸钾溶液淬灭,并用乙酸乙酯萃取。将有机层用无水硫酸钠干燥,并减压浓缩至干。用硅胶(100-200目)以及用30-40%乙酸乙酯的己烷溶液作为洗脱剂,通过柱色谱纯化粗产物。将期望的级分减压浓缩,得到3,6-二甲基吡啶甲腈(3)。

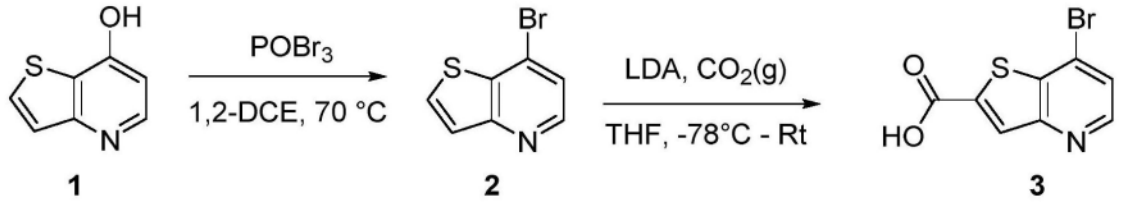
[0827] 在0℃下在氩气气氛下向3,6-二甲基吡啶甲腈(3,7.00g,46.9mmol)的氯仿(70mL)溶液中加入间氯过氧苯甲酸(8.75g,56.6mmol),并在室温下继续搅拌16h。完成后,将反应混合物用10%氢氧化钙溶液稀释并通过硅藻土过滤,将滤液浓缩并干燥,得到2-氰基-3,6-二甲基吡啶1-氧化物(4)。

[0828] 将2-氰基-3,6-二甲基吡啶1-氧化物(4,7.0g,46.9mmol)的磷酰氯(50mL)溶液在90℃下搅拌4h。完成后,将反应混合物浓缩,并用硅胶(100-200目)以及用20-30%乙酸乙酯的己烷溶液作为洗脱剂,通过柱色谱纯化。将期望的级分减压浓缩,得到4-氯-3,6-二甲基吡啶甲腈(5)。

[0829] 将4-氯-3,6-二甲基吡啶甲腈(5,4.0g,24.0mmol)在乙醇(20mL)和10%氢氧化钾溶液(20mL)中的溶液在100℃下搅拌16h。完成后,将反应混合物冷却,用2M盐酸溶液酸化至pH 5,并用乙酸乙酯萃取。将有机层用无水硫酸钠干燥,过滤并减压浓缩至干,得到4-氯-3,6-二甲基吡啶甲酸(6)。

[0830] 在0℃下在氩气气氛下向4-氯-3,6-二甲基吡啶甲酸(6,1.50g,8.10mmol)的叔丁醇(9.0mL)溶液中加入二碳酸二叔丁酯(0.75mL,3.56mmol)和4-二甲基氨基吡啶(1.48g,12.1mmol),并在90℃下搅拌4h。完成后,将反应混合物减压浓缩。用20-30%乙酸乙酯的己烷溶液,通过快速柱色谱纯化化合物粗品,得到4-氯-3,6-二甲基吡啶甲酸叔丁酯(7)。

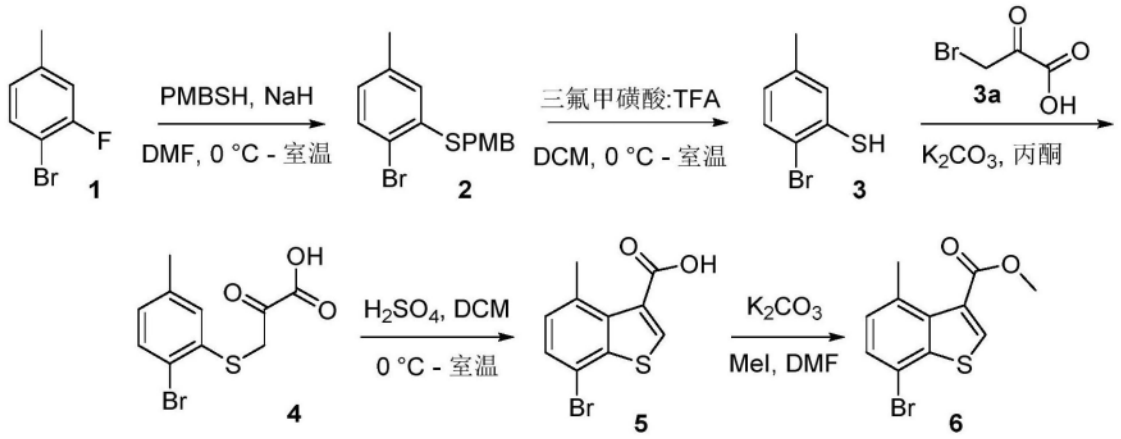
[0831] 实施例2B.12

[0832] 

[0833] 在室温下向搅拌的噻吩并[3,2-b]吡啶-7-醇(1,5.0g,33.07mmol)的1,2-二氯乙烷(50mL)溶液中分批加入氧溴化磷(143.21g,496.09mmol),并将混合物在70℃下搅拌10h。将反应混合物在0℃下冷却,用10%氢氧化钠水溶液碱化,并用二氯甲烷萃取。将有机层用盐水洗涤,用无水硫酸钠干燥,过滤并减压浓缩至干得,到7-溴噻吩并[3,2-b]吡啶(2)。

[0834] 在-78℃下向搅拌的7-溴噻吩并[3,2-b]吡啶(2,4.0g,18.78mmol)的干燥四氢呋喃(40mL)溶液中滴加二异丙基氨基锂(2.0M的己烷溶液,26.30mL,53.60mmol),并将混合物在相同温度下搅拌1h。用二氧化碳气体吹扫通过反应物质15min,将反应混合物在4h内升温至室温。用氯化铵水溶液淬灭反应,用水稀释,并用乙酸乙酯萃取。将有机层用饱和盐水洗涤,用无水硫酸钠干燥,过滤并浓缩,得到7-溴噻吩并[3,2-b]吡啶-2-羧酸(3)。

[0835] 实施例2B.12

[0836] 

[0837] 在0℃下向搅拌的(4-甲氧基苯基)甲硫醇(12.3g,87.77mmol)的N,N-二甲基甲酰胺(150mL)溶液中分批加入氢化钠(4.60g,119.69mmol)。10min后加入1-溴-2-氟-4-甲基苯(1,15.0g,79.79mmol),并将反应在室温下搅拌2h。完成后,将反应倒入冰水中,并用乙酸乙酯萃取。将有机层用水和盐水洗涤,用无水硫酸钠干燥,并减压浓缩,得到粗品。用0-5%乙酸乙酯的己烷溶液作为洗脱剂,通过Combiflash(40g,RediSep柱)纯化粗产物。将期望的级分减压浓缩,得到(2-溴-5-甲基苯基)(4-甲氧基苄基)硫烷(2)。

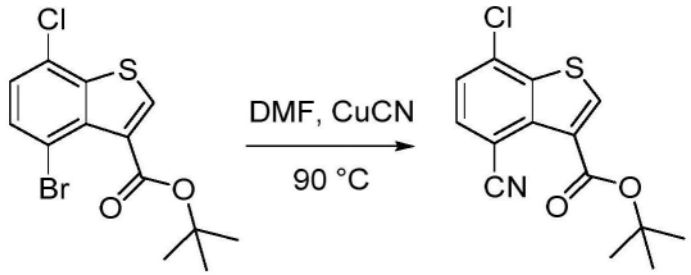
[0838] 在0℃下向(2-溴-5-甲基苯基)(4-甲氧基苄基)硫烷(2,18.0g,55.90mmol)的二氯甲烷(140mL)溶液中滴加三氟乙酸(20mL)和三氟甲磺酸(5mL)在二氯甲烷(40mL)中的混合物,并将反应混合物在室温下搅拌2h。完成后,将反应倒入冰水中,并用二氯甲烷萃取。将有机层用水和盐水洗涤,用无水硫酸钠干燥,减压浓缩,得到粗产物2-溴-5-甲基苯硫醇(3)。

[0839] 在室温下向2-溴-5-甲基苯硫醇(3,4.7g,23.27mmol)的丙酮(47.0mL)溶液中加入碳酸钾(16.0g,116.35mmol),并将混合物搅拌10min。将3-溴-2-氧代丙酸(3a,11.6g,69.80mmol)加入反应混合物,并在室温下搅拌5h。完成后,减压蒸发丙酮;残留物用水稀释,并用乙酸乙酯萃取。将有机层用水和盐水洗涤,用无水硫酸钠干燥并减压浓缩,得到3-((2-溴-5-甲基苯基)巯基)-2-氧代丙酸(4)。

[0840] 向3-((2-溴-5-甲基苯基)巯基)-2-氧代丙酸(4,4.0g,13.89mmol)的二氯甲烷(40.0mL)溶液中加入硫酸(10.0mL),并将反应混合物在室温下搅拌5h。完成后,将反应混合物倒入冰水中,用二氯甲烷萃取。将有机层用水和盐水洗涤,用无水硫酸钠干燥,减压浓缩,得到7-溴-4-甲基苯并[b]噻吩-3-羧酸(5)。

[0841] 在0℃下向7-溴-4-甲基苯并[b]噻吩-3-羧酸(5,3.0g,11.11mmol)的N,N-二甲基甲酰胺(30.0mL)溶液中加入碳酸钾(4.6g,33.33mmol)和碘甲烷(1.4mL,22.22mmol),并将反应混合物在室温下搅拌4h。完成后,将反应物质倒入水中,并用乙酸乙酯萃取。将有机层用水和盐水洗涤,用无水硫酸钠干燥,并减压浓缩;用5%乙酸乙酯的己烷溶液作为洗脱剂,通过快速柱色谱纯化粗产物。将期望的级分减压浓缩,得到7-溴-4-甲基苯并[b]噻吩-3-甲酸甲酯(6)。

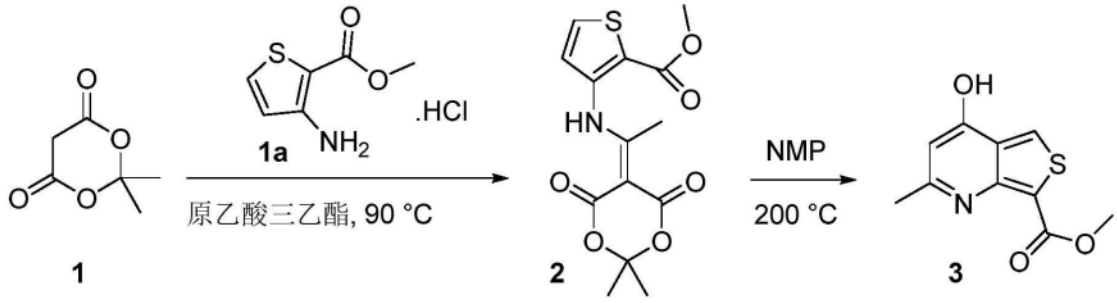
[0842] 实施例2B.13

[0843] 

1 2

[0844] 向4-溴-7-氯苯并[b]噻吩-3-甲酸叔丁酯(1,0.7g,2.01mmol)的N,N-二甲基甲酰胺(2mL)溶液中加入氰化亚铜(I)(0.180g,2.01mmol)。将该反应混合物在90℃下加热2h。在该时间后,反应混合物通过硅藻土过滤,并用乙酸乙酯洗涤。将滤液用水洗涤,然后用盐水洗溶液,用无水硫酸钠干燥,减压浓缩,得到粗产物。用硅胶(100-200目)以及用30-50%乙酸乙酯的己烷溶液作为洗脱剂,通过柱色谱将其纯化。将期望的级分减压浓缩,得到7-氯-4-氰基苯并[b]噻吩-3-甲酸叔丁酯(2)。

[0845] 实施例2B.14

[0846] 

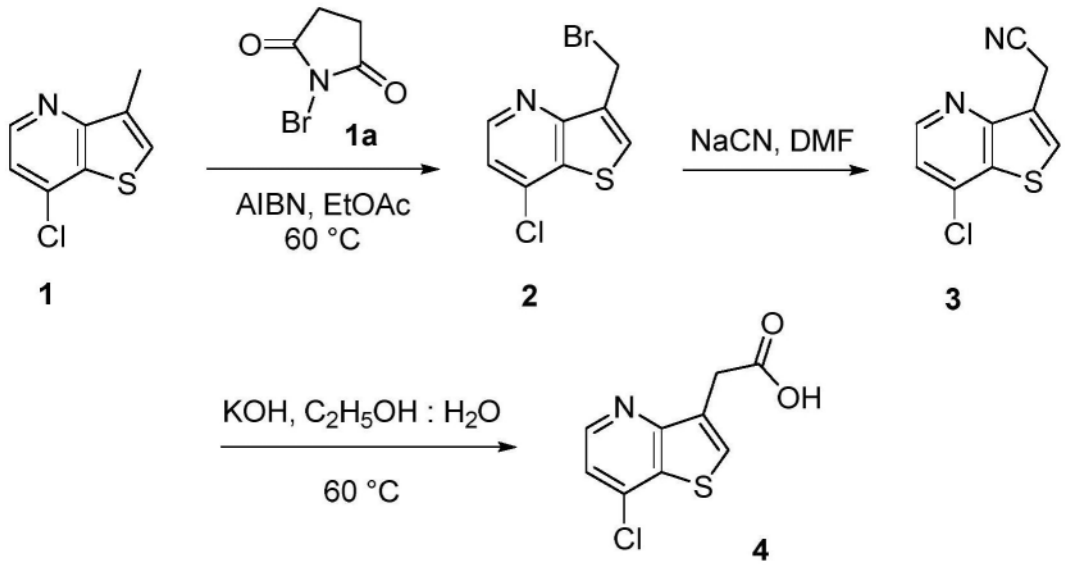
1 2 3

[0847] 在密闭容器中将2,2-二甲基-1,3-二氧六环-4,6-二酮(1,0.41g,2.84mmol)和二乙氧基甲氧基乙烷(50.0mL)的溶液在90℃下搅拌并加热2h。在90℃下在氩气气氛下分批加入3-氨基噻吩-2-甲酸甲酯盐酸盐(1a,0.5g,2.58mmol),并在90℃下继续加热12h。完成后,将反应物质冷却至室温,加入水,并用乙酸乙酯萃取。将有机层用无水硫酸钠干燥,过滤并真空浓缩得到粗品。将粗品与乙醚一起研磨,得到3-((1-(2,2-二甲基-4,6-二氧代-1,3-二氧六环-5-亚基)乙基)氨基)噻吩-2-甲酸甲酯(2)。

[0848] 将3-((1-(2,2-二甲基-4,6-二氧代-1,3-二氧六环-5-亚基)乙基)氨基)噻吩-2-甲酸甲酯(2,0.200g,0.61mmol)的N-甲基吡咯烷酮(15mL)溶液在微波中在200℃下加热

30min。完成后,将反应物质冷却至室温,过滤,粗品固体通过制备HPLC纯化,得到4-羟基-2-甲基噻吩并[3,4-b]吡啶-7-甲酸甲酯(3)。

[0849] 实施例2B.15

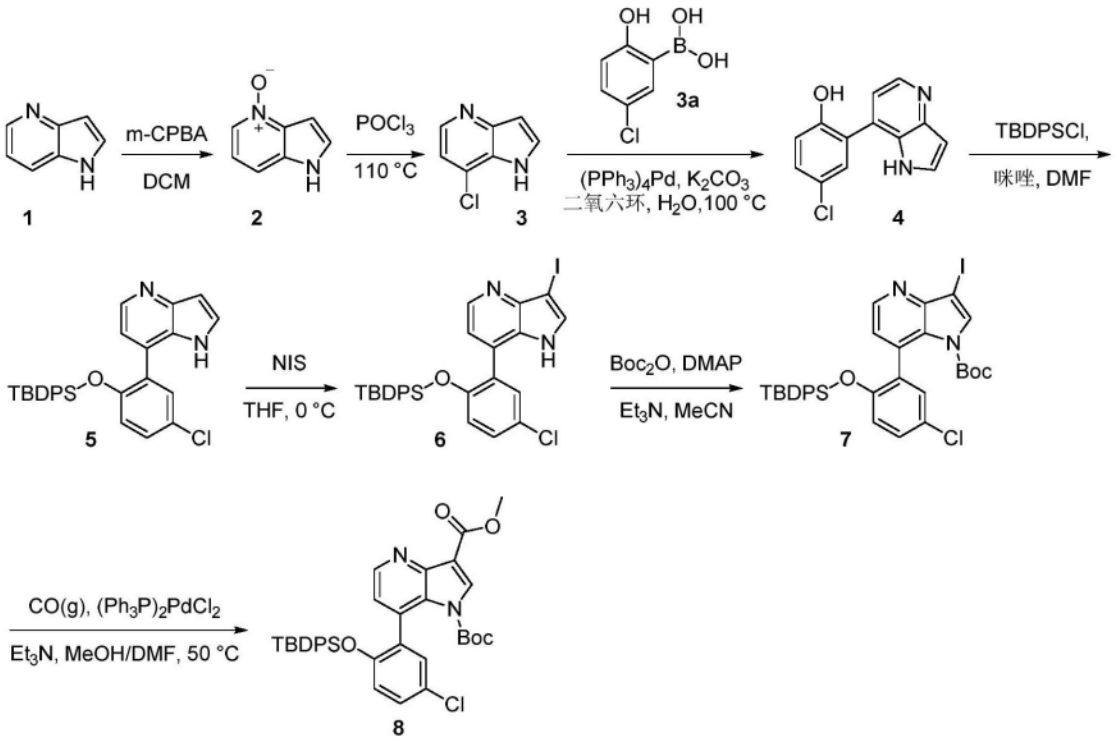
[0850] 

[0851] 在室温下向搅拌的7-氯-3-甲基噻吩并[3,2-b]吡啶(1,1.0g,5.44mmol)的乙酸乙酯(10mL)溶液中加入1-溴吡咯烷-2,5-二酮(1a,1.93g,10.8mmol)和偶氮二异丁腈(0.088g,0.540mmol)。将反应在60℃下搅拌4h。完成后,将反应混合物用水淬灭,并用乙酸乙酯萃取。将有机层用盐水溶液洗涤,用无水硫酸钠干燥,过滤并减压浓缩至干。用1-5%乙酸乙酯的己烷溶液为洗脱剂,通过Combiflash(12g,RediSep柱)纯化粗产物,得到3-(溴甲基)-7-氯噻吩并[3,2-b]吡啶(2)。

[0852] 向3-(溴甲基)-7-氯噻吩并[3,2-b]吡啶(2,1.50g,5.70mmol)的N,N-二甲基甲酰胺(15mL)溶液中加入氰化钠(0.561g,11.40mmol),并将混合物在室温下搅拌3h。完成后,用冰冷的水淬灭反应,用乙酸乙酯萃取。将有机层用冷水洗涤,用无水硫酸钠干燥,过滤并减压浓缩至干,得到2-(7-氯噻吩并[3,2-b]吡啶-3-基)乙腈(3)。

[0853] 向2-(7-氯噻吩并[3,2-b]吡啶-3-基)乙腈(3,1.10g,5.20mmol)在乙醇和水的混合物(1:1,20mL)中的溶液中加入氢氧化钾(2.96g,52.8mmol),并将混合物在60℃下搅拌10h。完成后,将反应混合物浓缩,并用乙醚萃取。水层用1N盐酸水溶液酸化,并用乙酸乙酯萃取。将有机层用饱和盐水溶液洗涤,用无水硫酸钠干燥,过滤并浓缩,得到2-(7-氯噻吩并[3,2-b]吡啶-3-基)乙酸(4)。

[0854] 实施例2B.16

[0855] 

[0856] 在0℃下向1H-吡咯并[3,2-b]吡啶(1,2.5g,21mmol)的DCM(75mL)溶液中缓慢加入m-CPBA(5.69g,25.4mmol)。将混合物从0℃搅拌到室温。16h后,由TLC(SiO_2,10%MeOH/DCM)判断反应完全。将混合物浓缩,残留物通过柱色谱纯化(SiO_2,0-20%MeOH/DCM)。分离产物,为与m-CBA的混合物形式(^{1}H-NMR确认比例约1:0.7)。如此获得的物质1H-吡咯并[3,2-b]吡啶4-氧化物(2)。

[0857] 将1H-吡咯并[3,2-b]吡啶4-氧化物(2,3.64g)的$POCl_3$(30mL,50g,0.32mol)溶液在氩气下回流过夜(油浴,130℃)。然后将混合物小心转移到搅拌的装有碎冰的锥形瓶中。然后将混合物用NaOH(水溶液,12.5%)碱化至pH约8,并过滤收集沉淀的物质。萃取水相(3x EtOAc),将合并的有机相干燥(Na_2SO_4),过滤并浓缩。将沉淀和萃取的物质合并,溶于DCM中,并用$NaHCO_3$(水溶液)洗涤。干燥有机相(Na_2SO_4),过滤并浓缩,得到7-氯-1H-吡咯并[3,2-b]吡啶(3)。

[0858] 反应分两批进行(每批0.80g的(3)),并且将两批合并用于纯化目的。向7-氯-1H-吡咯并[3,2-b]吡啶(3,0.80g,5.2mmol)在1,4-二氧六环(14mL)和水(3.5mL)中的溶液中加入(5-氯-2-羟基苯基)硼酸(3a,1.4g,8.1mmol)和碳酸钾(2.2g,16mmol),并通过用氩气鼓泡通过混合物脱气5min。加入$Pd(PPh_3)_4$(0.61g,0.53mmol),将混合物再脱气5min,然后置于预热的加热器(100℃)中并搅拌20h。然后将混合物冷却至室温。将两批次合并,用水稀释,并用EtOAc萃取。干燥有机相(Na_2SO_4),过滤并浓缩。通过柱色谱纯化(SiO_2,0-20%MeOH/DCM),得到4-氯-2-(1H-吡咯并[3,2-b]吡啶-7-基)苯酚(4)。

[0859] 在0℃下向4-氯-2-(1H-吡咯并[3,2-b]吡啶-7-基)苯酚(4,37mg,0.15mmol)的DMF(0.7mL)溶液中加入咪唑(23mg,0.34mmol)和叔丁基-氯-二苯基-硅烷(0.05mL,0.05g,0.2mmol),并将混合物在室温下搅拌。3h后将混合物用水和EtOAc稀释,并萃取水相(3xEtOAc)。干燥合并的有机相(Na_2SO_4),过滤并浓缩。通过柱色谱纯化(SiO_2,0-40%EtOAc/己烷),得到7-(2-((叔丁基二苯基甲硅烷基)氧基)-5-氯苯基)-1H-吡咯并[3,2-b]吡啶

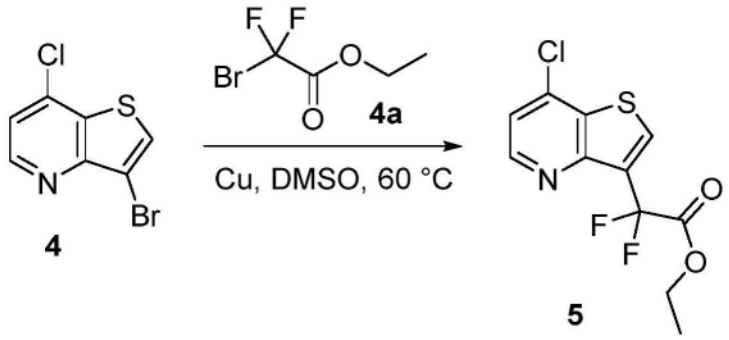
(5)。

[0860] 在0℃下向7-(2-((叔丁基二苯基甲硅烷基)氧基)-5-氯苯基)-1H-吡咯并[3,2-b]吡啶(5;1.08g,2.24mmol)的THF(20mL)溶液中加入N-碘代丁二酰亚胺(503mg,2.24mmol),并将混合物搅拌10min。然后将反应用EtOAc稀释,用$Na_2S_2O_3$(水溶液)和水淬灭并萃取(2xEtOAc)。干燥合并的有机相,过滤并浓缩。通过柱色谱纯化(SiO_2,0-40%EtOAc/己烷),得到7-(2-((叔丁基二苯基甲硅烷基)氧基)-5-氯苯基)-3-碘-1H-吡咯并[3,2-b]吡啶(6)。

[0861] 在0℃下向7-(2-((叔丁基二苯基甲硅烷基)氧基)-5-氯苯基)-3-碘-1H-吡咯并[3,2-b]吡啶(6,990mg,1.63mmol)的MeCN(11mL)溶液中加入三乙胺(0.45mL,0.33g,3.2mmol),二碳酸二叔丁酯(531mg,2.43mmol)的2mL MeCN溶液和4-二甲基氨基吡啶(40mg,0.33mmol),并将混合物在室温下搅拌。1h后加入水,混合物用DCM(3x)萃取。干燥合并的有机相(Na_2SO_4),过滤并浓缩。通过柱色谱纯化(SiO_2,0-20%EtOAc/己烷),得到7-(2-((叔丁基二苯基甲硅烷基)氧基)-5-氯苯基)-3-碘-1H-吡咯并[3,2-b]吡啶-1-甲酸叔丁酯(7)。

[0862] 向7-(2-((叔丁基二苯基甲硅烷基)氧基)-5-氯苯基)-3-碘-1H-吡咯并[3,2-b]吡啶-1-甲酸叔丁酯(7,1.06g,1.49mmol)在甲醇(11mL)和DMF(4mL)中的溶液中加入三乙胺(0.43mL,0.31g,3.1mmol)和$(Ph_3P)_2PdCl_2$(105mg,0.149mmol)。然后将混合物在50℃下在CO气氛下搅拌。18h后将混合物浓缩,通过柱色谱纯化(SiO_2,0-50%EtOAc/己烷),得到7-(2-((叔丁基二苯基甲硅烷基)氧基)-5-氯苯基)-1H-吡咯并[3,2-b]吡啶-1,3-二甲酸1-叔丁酯3-甲酯(8)。

[0863] 实施例2B.17

[0864] 

[0865] 在室温下向3-溴-7-氯噻吩并[3,2-b]吡啶(4,0.30g,1.21mmol)和2-溴-2,2-二氟乙酸乙酯(4a,0.73g,3.62mmol)的二甲基亚砜(12.0mL)溶液中加入铜粉(0.11g,1.81mmol),并将混合物在60℃下加热16h。完成后,反应物质用乙酸乙酯稀释,并通过硅藻土过滤。滤液用水和盐水溶液洗涤,用硫酸钠干燥,过滤并浓缩。用硅胶(100-200目)以及用20-30%乙酸乙酯的己烷溶液作为洗脱剂,通过快速柱色谱纯化粗品。将期望的级分减压浓缩,得到2-(7-氯噻吩并[3,2-b]吡啶-3-基)-2,2-二氟乙酸乙酯(5)。

[0866] 实施例2B.18

[0867] 

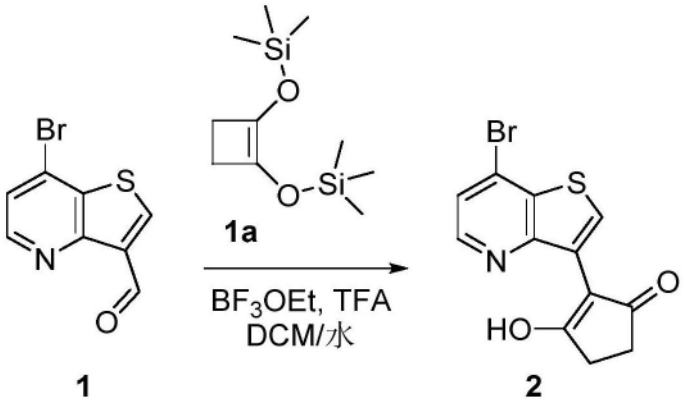
[0868] 在-78℃下向N,N,N',N'-四甲基乙二胺(11.69g,100.42mmol)的四氢呋喃(100mL)

溶液中加入正丁基锂(1.3M的己烷溶液,71.1mL,92.43mmol),然后滴加6,7-二氢-5H-环戊二烯并[b]吡啶(1,10.0g,84.03mmol),并将混合物在-78℃下搅拌45min。然后滴加碳酸二甲酯(1a,8.31g,92.43mmol)的四氢呋喃(10mL)溶液,并将混合物在1h内升至室温。将反应混合物用饱和氯化铵溶液淬灭,并用乙酸乙酯萃取。将合并的有机层用无水硫酸钠干燥,过滤并浓缩。用硅胶(100-200目)以及用0-25%乙酸乙酯的己烷溶液作为洗脱剂,通过柱色谱纯化粗品,得到6,7-二氢-5H-环戊二烯并[b]吡啶-7-甲酸甲酯(2)。

[0869] 在0℃下向6,7-二氢-5H-环戊二烯并[b]吡啶-7-甲酸甲酯(2,2.5g,14.12mmol)的二氯甲烷(30mL)溶液中加入3-氯过氧化苯甲酸(4.85g,28.24mL),并将混合物在相同温度下搅拌30min。完成后,将反应混合物用饱和碳酸氢钠溶液(10mL)淬灭,并用二氯甲烷萃取。将合并的有机层用盐水洗涤,用无水硫酸钠干燥,过滤并浓缩。用硅胶(100-200目)以及用0-10%甲醇的二氯甲烷溶液作为洗脱剂,通过柱色谱纯化粗品。将期望的级分减压浓缩,得到7-(甲氧基羰基)-6,7-二氢-5H-环戊二烯并[b]吡啶1-氧化物(3)。

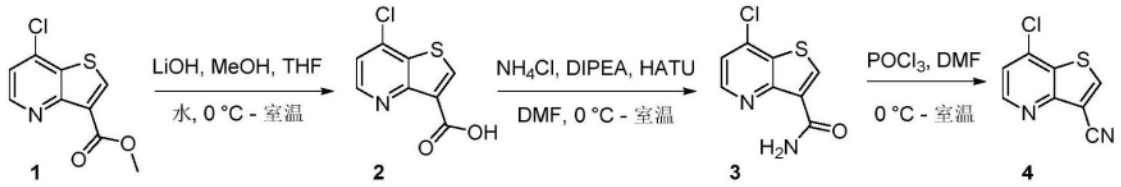
[0870] 向7-(甲氧基羰基)-6,7-二氢-5H-环戊二烯并[b]吡啶1-氧化物(3,1.5g,7.77mmol)的乙腈(25mL)溶液中加入溴化锂(0.67g,7.77mmol)和溴化磷(22.3g,77.72mmol),并将反应混合物在80℃下加热24h。完成后,将反应混合物冷却至0℃,用饱和碳酸氢钠溶液(50mL)淬灭,并用乙酸乙酯萃取。合并的有机层用无水硫酸钠干燥,过滤并浓缩。用硅胶(100-200目)和0-25%乙酸乙酯的己烷溶液,通过柱色谱纯化粗品,得到4-溴-6,7-二氢-5H-环戊二烯并[b]吡啶-7-甲酸甲酯(4)。

[0871] 实施例2B.19

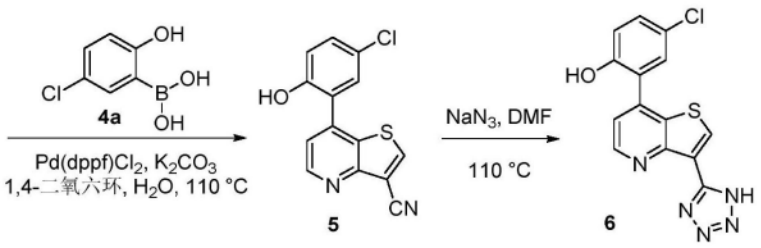
[0872] 

[0873] 向在烘干的螺旋盖小瓶中的7-溴噻吩并[3,2-b]吡啶-3-甲醛(1,36mg,0.148mmol)的DCM(1mL)溶液配备搅拌棒。向混合物中加入乙氧基乙烷三氟硼烷(0.02mL,0.163mmol),在室温下在持续搅拌下缓慢加入。然后滴加1,2-双((三甲基甲硅烷基)氧基)环丁-1-烯(1a,0.06mL,0.222mmol),并将澄清黄色混合物在室温下继续搅拌40min。加入水(0.030mL),接着加入乙氧基乙烷三氟硼烷(0.27mL,2.22mmol),并将反应在室温下搅拌过夜。未观察到转化为频哪醇重排产物,因此加入水和DCM,并将水相用二氯甲烷萃取三次。合并的有机物质用盐水洗涤,并用硫酸镁干燥。将固体过滤并真空除去溶剂,得到粗品黄色残留物。真空浓缩水层。将水层和有机层合并,溶于TFA(3.5mL,0.1480mmol)中,并置于小瓶中,将其密封并在加热器中在70℃下搅拌3h。将反应冷却至室温,真空除去溶剂。制备HPLC(含0.1%TFA的水),得到产物2-(7-溴噻吩并[3,2-b]吡啶-3-基)-3-羟基环戊-2-烯-1-酮(2)。

[0874] 实施例2B.20



[0875]



[0876] 在0℃下向搅拌的7-氯噻吩并[3,2-b]吡啶-3-甲酸甲酯(1,15.0g,65.88mmol)在甲醇,四氢呋喃和水(2:1:1,225mL)中的溶液中加入氢氧化锂(13.82g,329.43mmol),并将反应混合物在室温下搅拌16h。完成后,减压浓缩溶剂,并将水层用1N盐酸水溶液酸化至pH-3。将得到的固体沉淀过滤并用正戊烷洗涤,得到7-氯噻吩并[3,2-b]吡啶-3-羧酸(2)。

[0877] 向7-氯噻吩并[3,2-b]吡啶-3-羧酸(2,12.20g,57.10mmol)的N,N-二甲基甲酰胺(50mL)溶液中加入1-[双(二甲基氨基)亚甲基]-1H-1,2,3-三唑并[4,5-b]吡啶鎓3-氧化物六氟磷酸盐(32.5g,85.65mmol),并将反应混合物搅拌10min。然后将反应混合物冷却至0℃,加入N,N-二异丙基乙胺(29.841mL,171.316mmol)和氯化铵(15.2g,285.52mmol),将反应混合物升温至室温,并搅拌16h。完成后,用冰冷的水淬灭反应,并用乙酸乙酯萃取。将有机层用冷水洗涤,用无水硫酸钠干燥,过滤并减压浓缩至干。将粗产物与戊烷一起研磨并干燥,得到7-氯噻吩并[3,2-b]吡啶-3-甲酰胺(3)。

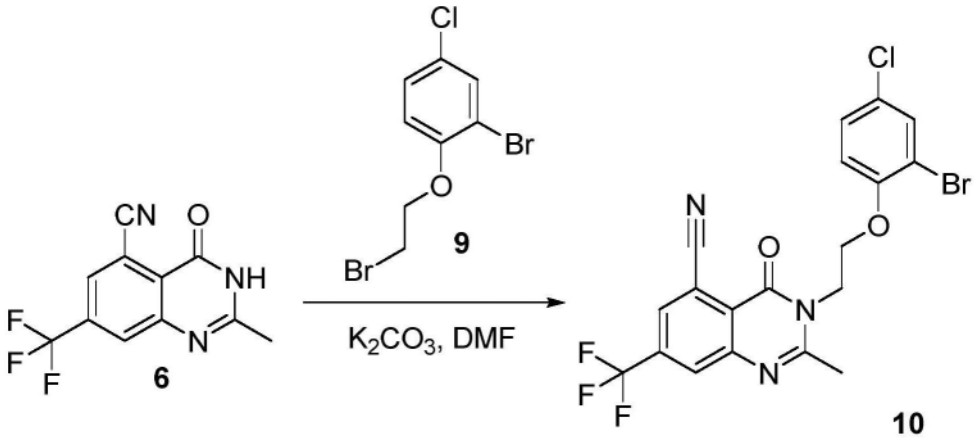
[0878] 在0℃下向7-氯噻吩并[3,2-b]吡啶-3-甲酰胺(3,10.0g,51.37mmol)的N,N-二甲基甲酰胺(100mL)溶液中加入三氯氧磷(48.0mL,513.76mmol)。将反应升温至室温并搅拌16h。完成后,将反应混合物减压浓缩至干。反应混合物用饱和碳酸氢钠溶液碱化到pH-8,并用乙酸乙酯萃取。将有机层用盐水溶液洗涤,用无水硫酸钠干燥,过滤并减压浓缩至干。用0-20%乙酸乙酯的己烷溶液作为洗脱剂,通过Combiflash(40g,RediSep柱)纯化粗产物。将期望的级分减压浓缩,得到7-氯噻吩并[3,2-b]吡啶-3-甲腈(4)。

[0879] 向7-氯噻吩并[3,2-b]吡啶-3-甲腈(4,8.0g,41.10mmol)和(5-氯-2-羟基苯基)硼酸(4a,14.1g,82.20mmol)的1,4-二氧六环(120.0mL)溶液中加入2M碳酸钾(14.2g,102.7mmol)溶液,将反应混合物用氩气脱气10min。然后将[1,1'-双(二苯基膦基)二茂铁]二氯化钯(II)(3.0g,4.11mmol)加入反应混合物中,并将反应混合物在110℃下搅拌2h。完成后,将反应混合物冷却至室温,用水稀释,并用乙酸乙酯萃取。将有机层用盐水溶液洗涤,用无水硫酸钠干燥,过滤并减压浓缩至干。用硅胶(100-200目)以及用0-50%乙酸乙酯的己烷溶液作为洗脱剂,通过柱色谱纯化粗产物。将期望的级分减压浓缩,得到7-(5-氯-2-羟基苯基)噻吩并[3,2-b]吡啶-3-甲腈(5)。

[0880] 在室温下向7-(5-氯-2-羟基苯基)噻吩并[3,2-b]吡啶-3-甲腈(5,5.1g,17.78mmol)的N,N-二甲基甲酰胺(50.0mL)溶液中加入叠氮化钠(5.8g,88.93mmol),并将反应混合物加热至110℃持续36h。完成后,将反应混合物减压浓缩至干。将获得的粗产物与正

戊烷一起研磨得到2-(3-(1H-四氮唑-5-基)噻吩并[3,2-b]吡啶-7-基)-4-氯苯酚(6)。

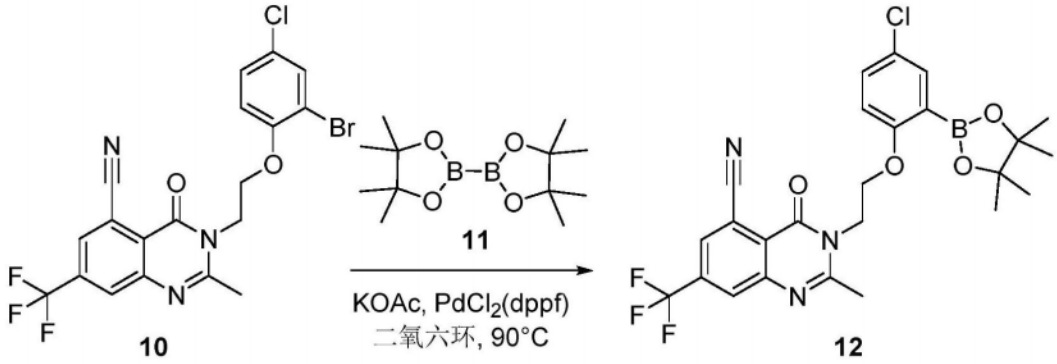
[0881] 实施例2C.通用偶联方法

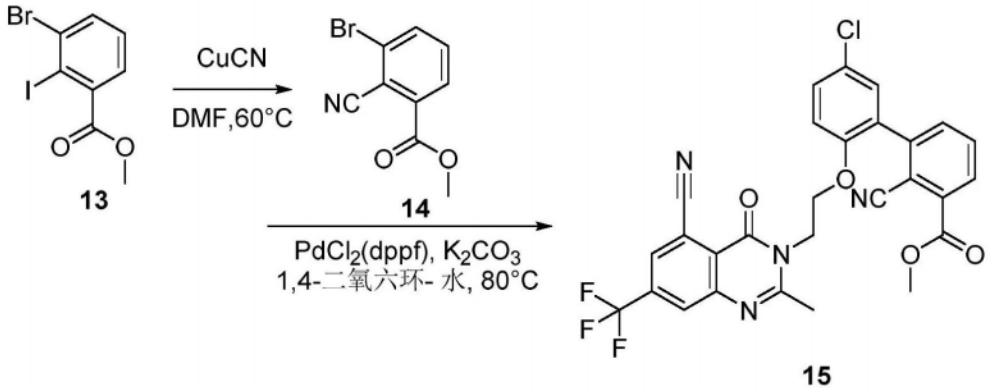
[0882] 

[0883] 在室温下向2-甲基-4-氧代-7-(三氟甲基)-3,4-二氢喹唑啉-5-甲腈(6,0.20g,0.79mmol)的N,N-二甲基甲酰胺(5mL)溶液中加入碳酸钾(0.33g,2.37mmol)。10min后,加入2-溴-1-(2-溴乙氧基)-4-氯-苯(9,0.25g,0.79mmol),并在室温下搅拌16h。完成后,将反应混合物倒入水中,并用乙酸乙酯萃取。合并的有机层用水和盐水洗涤,用无水硫酸钠干燥,并减压浓缩,得到粗品;通过快速柱色谱纯化(用10-70%乙酸乙酯的己烷溶液)化合物粗品,得到3-(2-(2-溴-4-氯-苯氧基)乙基)-2-甲基-4-氧代-7-(三氟甲基)-3,4-二氢喹唑啉-5-甲腈(10)。

[0884] 实施例2D.偶联后修饰方法

[0885] 实施例2D.1



[0886] 

[0887] 将3-(2-(2-溴-4-氯苯氧基)乙基)-2-甲基-4-氧代-7-(三氟甲基)-3,4-二氢喹唑

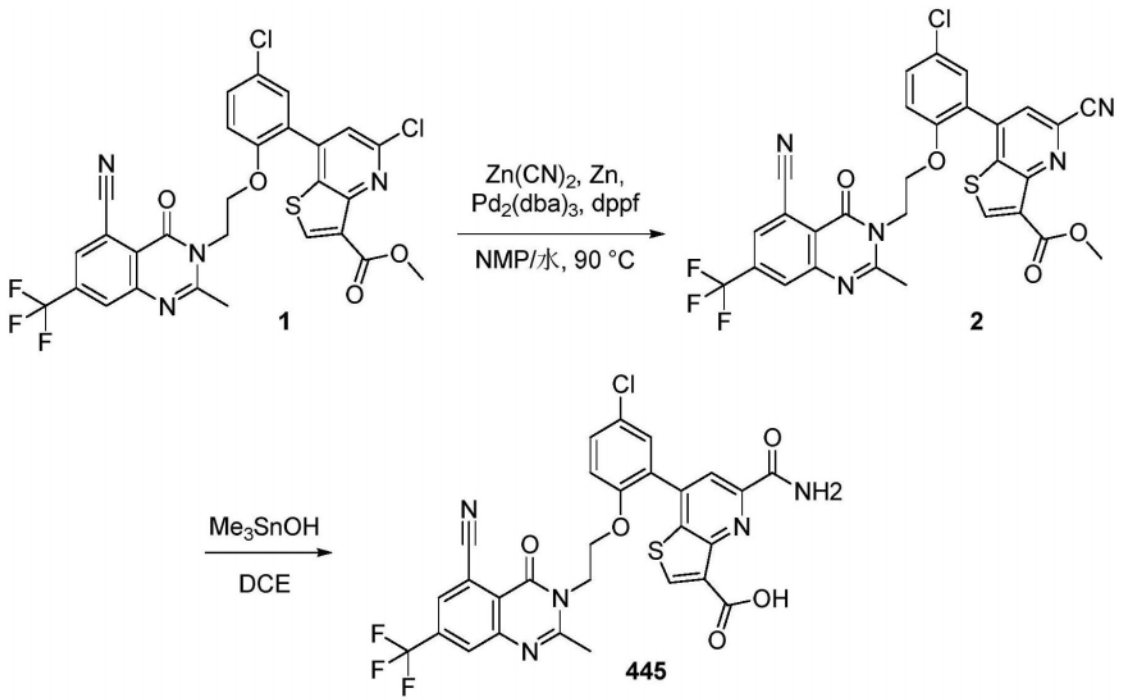
啉-5-甲腈(10,1.8g,3.71mmol),4,4,4',4',5,5,5',5'-八甲基-2,2'-二(1,3,2-二氧杂硼杂环戊烷)(11,1.13g,4.45mmol)和乙酸钾(0.73g,7.42mmol)的1,4-二氧六环(35mL)溶液用氩气脱气10min。加入1,1'-双(二苯基膦基)二茂铁-二氯化钯(II)(0.217g,0.296mmol),并将反应混合物再脱气10min。将反应混合物在90℃下加热并搅拌6h。完成后,将反应混合物用水稀释,并用乙酸乙酯萃取。将有机层用无水硫酸钠干燥,过滤并减压浓缩至干。用40%乙酸乙酯的己烷溶液为洗脱剂,通过快速柱色谱纯化化合物粗品,得到3-(2-(4-氯-2-(4,4,5,5-四甲基-1,3,2-二氧杂硼杂环戊烷-2-基)苯氧基)乙基)-2-甲基-4-氧代-7-(三氟甲基)-3,4-二氢喹唑啉-5-甲腈(12)。

[0888] 向3-溴-2-碘苯甲酸甲酯(13,2.0g,5.88mmol)的N,N-二甲基甲酰胺(20mL)溶液中加入氰化亚铜(I)(0.58g,6.47mmol),并在60℃下加热4h。完成后,反应物质用水稀释(100mL),并用乙酸乙酯萃取。合并的有机层用水和盐水洗涤,用无水硫酸钠干燥,并减压浓缩,得到粗品。通过快速柱色谱纯化化合物粗品(用0-10%乙酸乙酯的己烷溶液),得到3-溴-2-氰基苯甲酸甲酯(14)。

[0889] 在室温下向3-(2-(4-氯-2-(4,4,5,5-四甲基-1,3,2-二氧杂硼杂环戊烷-2-基)苯氧基)乙基)-2-甲基-4-氧代-7-(三氟甲基)-3,4-二氢喹唑啉-5-甲腈(12,0.40g,0.75mmol)和3-溴-2-氰基苯甲酸甲酯(14,0.215g,0.90mmol)在1,4-二氧六环(8mL)和水(2mL)中的溶液中加入碳酸钾(0.313g,2.25mmol)。通过吹扫氩气通过反应物质将反应物质脱气10min。在氩气气氛下加入1,1'-双(二苯基膦基)二茂铁-二氯化钯(II)(0.055g,0.075mmol),将反应混合物在90℃下加热并搅拌3h。完成后,反应物质用水稀释,并用乙酸乙酯萃取;合并的有机层用水和盐水洗涤,用无水硫酸钠干燥,并减压浓缩,得到粗品。通过快速柱色谱纯化化合物粗品(用0-50%乙酸乙酯的己烷溶液),得到5'-氯-2-氰基-2'-(2-(5-氰基-2-甲基-4-氧代-7-(三氟甲基)喹唑啉-3(4H)-基)乙氧基)-[1,1'-联苯]-3-甲酸甲酯(15)。

[0890] 实施例2D.2

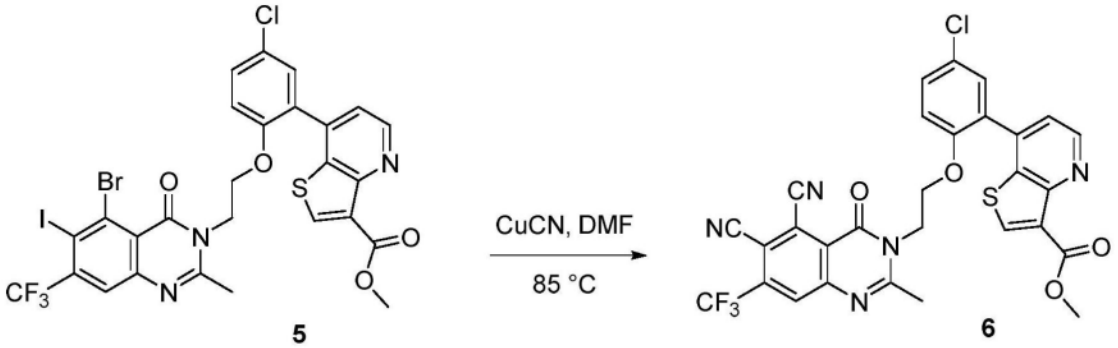
[0891]



[0892] 在微波管中向搅拌的5-氯-7-[5-氯-2-[2-[5-氰基-2-甲基-4-氧代-7-(三氟甲基)喹唑啉-3-基]乙氧基]苯基]噻吩并[3,2-b]吡啶-3-甲酸甲酯(0.050g,0.079mmol)在N-甲基-2-吡咯烷酮和水(9:1,2mL)中的溶液中加入氰化锌(0.011g,0.095mmol)和锌粉(0.030mg,0.034mmol),并将混合物用氩气脱气30min。加入1,1'-双(二苯基膦基)二茂铁(0.0131g,0.023mmol)和三(二亚苄基丙酮)二钯(0)(10.8mg,0.012mmol)后,将小瓶密封然后在80℃的预热的加热器中放置30min。反应完成后,将反应混合物装载到Isco硅胶柱上。通过柱色谱纯化,用0至5%甲醇/二氯甲烷洗脱,得到7-(5-氯-2-(2-(5-氰基-2-甲基-4-氧代-7-(三氟甲基)喹唑啉-3(4H)-基)乙氧基)苯基)-5-氰基噻吩并[3,2-b]吡啶-3-甲酸甲酯(2)。

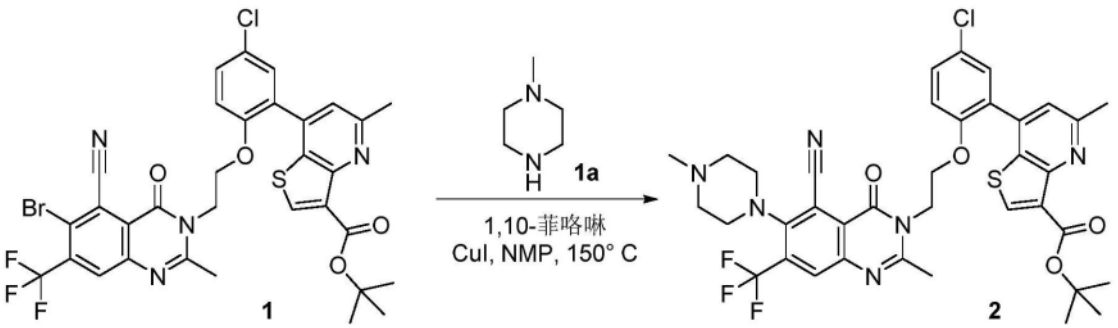
[0893] 在室温下向7-(5-氯-2-(2-(5-氰基-2-甲基-4-氧代-7-(三氟甲基)喹唑啉-3(4H)-基)乙氧基)苯基)-5-氰基噻吩并[3,2-b]吡啶-3-甲酸甲酯(2,25.0mg,0.040mmol)的1,2-二氯乙烷(2mL)溶液中加入三甲基氢氧化锡(0.029g,0.160mmol)。将反应混合物在90℃下加热16h。反应完成后,蒸发有机溶剂,并将粗品用50%二甲基亚砜/甲醇稀释。粗产物通过制备HPLC纯化,得到5-氨基甲酰基-7-(5-氯-2-(2-(5-氰基-2-甲基-4-氧代-7-(三氟甲基)喹唑啉-3(4H)-基)乙氧基)苯基)噻吩并[3,2-b]吡啶-3-羧酸(化合物编号445F)。

[0894] 实施例2D.3

[0895] 

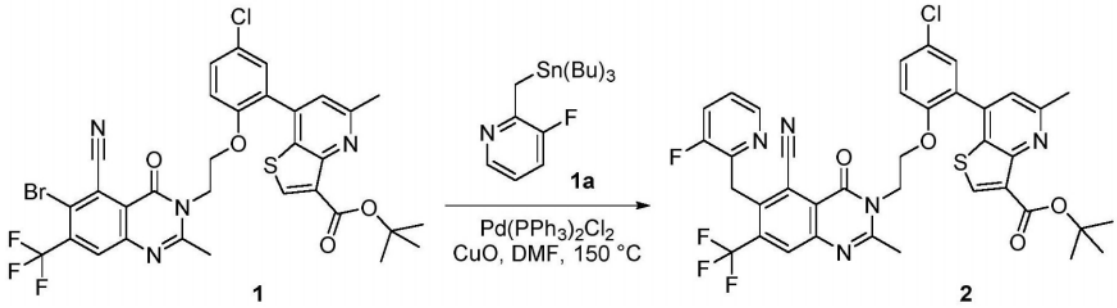
[0896] 向7-(2-(2-(5-溴-6-碘-2-甲基-4-氧代-7-(三氟甲基)喹唑啉-3(4H)-基)乙氧基)-5-氯苯基)噻吩并[3,2-b]吡啶-3-甲酸甲酯(5,0.20g,0.256mmol)的N,N-二甲基甲酰胺溶液中加入氰化亚铜(I)(0.069g,0.770mmol),并在85℃下搅拌2h。完成后,将反应混合物冷却至室温,并倒入冰水中。过滤收集形成的沉淀并干燥。将固体溶于10%甲醇的二氯甲烷溶液中,并使其通过硅藻土床。将滤液减压浓缩,得到7-(5-氯-2-(2-(5,6-二氰基-2-甲基-4-氧代-7-(三氟甲基)喹唑啉-3(4H)-基)乙氧基)苯基)噻吩并[3,2-b]吡啶-3-甲酸甲酯(6)。

[0897] 实施例2D.3

[0898] 

[0899] 向7-(2-(2-(6-溴-5-氰基-2-甲基-4-氧代-7-(三氟甲基)喹唑啉-3(4H)-基)乙氧基)-5-氯苯基)-5-甲基噻吩并[3,2-b]吡啶-3-甲酸叔丁酯(1,0.20g,0.273mmol)的N-甲基-2-吡咯烷酮(5.0mL)溶液中加入1-甲基哌嗪(1a,0.06mL,0.546mmol),并将反应混合物用氩气脱气10min。然后加入碘化亚铜(I)(0.005g,0.027mmol)和1,10-菲咯啉(0.009g,0.054mmol),并将反应混合物在150℃下加热6h。完成后,将反应混合物用水稀释,并用乙酸乙酯萃取。将有机层用无水硫酸钠干燥,过滤并浓缩,得到化合物粗品。用硅胶(100-200目)和3-4%甲醇的二氯甲烷溶液,通过柱色谱纯化获得的化合物粗品,得到7-(5-氯-2-(2-(5-氰基-2-甲基-6-(4-甲基哌嗪-1-基)-4-氧代-7-(三氟甲基)喹唑啉-3(4H)-基)乙氧基)苯基)-5-甲基噻吩并[3,2-b]吡啶-3-甲酸叔丁酯(2)。

[0900] 实施例2D.4

[0901] 

[0902] 在室温下向7-(2-(2-(6-溴-5-氰基-2-甲基-4-氧代-7-(三氟甲基)喹唑啉-3(4H)-基)乙氧基)-5-氯苯基)-5-甲基噻吩并[3,2-b]吡啶-3-甲酸叔丁酯(1,50mg,0.0681mmol)和3-氟-2-((三丁基甲锡烷基)甲基)吡啶(1a,190mg,0.476mmol)的N,N-二甲基甲酰胺(2mL)溶液中加入氧化铜(II)(11mg,0.136mmol)。将反应混合物用氩气吹扫5min,加入双(三苯基膦)二氯化钯(II)(9.6mg,0.0136mmol),然后将容器密封,在150℃下微波1h。完成后,然后将反应混合物装载到Isco装载柱上。用5至80%乙酸乙酯的己烷溶液为洗脱剂,通过柱色谱纯化,产物在约60%乙酸乙酯/己烷中洗脱。将期望的级分减压浓缩,得到7-(5-氯-2-(2-(5-氰基-6-((3-氟吡啶-2-基)甲基)-2-甲基-4-氧代-7-(三氟甲基)喹唑啉-3(4H)-基)乙氧基)苯基)-5-甲基噻吩并[3,2-b]吡啶-3-甲酸叔丁酯(2)。

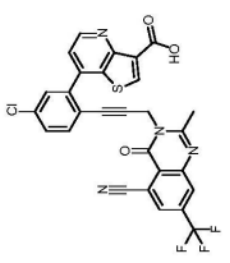
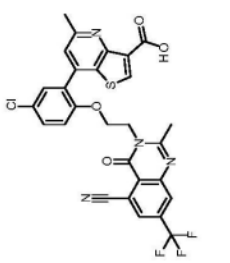
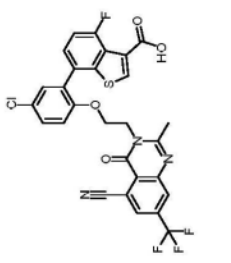
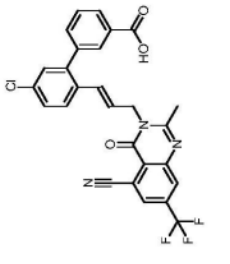
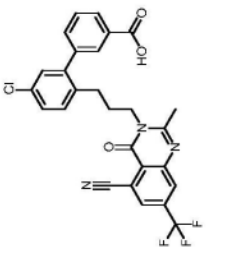
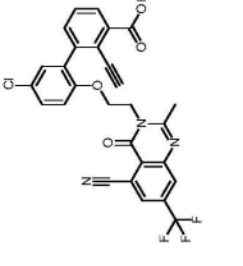
[0903] 使用上述通用方法中的一种或多种制备的化合物示于表2中。在提供表征数据的情况下,表征数据在化合物的右侧。

[0904]

表 2. 7-CF3-噻吩基吡啶和衍生化合物

化合物	表征	化合物	表征
51		MS (ESI) m/z 528.44 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 12.931 (s, 1H), 8.359 (s, 1H), 8.194 (s, 1H), 7.8409 (d, J = 11.6 Hz, 2H), 7.528 (d, J = 7.6 Hz, 1H), 7.412 (m, 2H), 7.278 (d, J = 2.6 Hz, 1H), 7.212 (d, J = 8.8 Hz, 1H), 4.359 (s, 4H), 2.208 (s, 3H)	60		MS (ESI) m/z 527.02 [M-1]-. 1H NMR (400 MHz, DMSO-d6) δ 8.63 (bs, 1H), 8.37(s, 1H), 8.19 (s, 1H), 7.98 (bs, 1H), 7.61 (bs, 1H), 7.48 (d, J = 8.68 Hz, 1H), 7.42 (s, 1H), 7.26 (d, J = 8.92 Hz, 1H), 4.39 (s, 4H), 2.20 (s, 3H)
58		MS (ESI) m/z 553.34 [M+1]+; UPLC: 98.94 %; 1H NMR (400 MHz, DMSO-d6) δ 8.44 (d, J = 3.96, 1H), 8.36 (s, 1H), 8.22 (s, 1H), 7.43 (dd, J = 2.48, 8.88 Hz, 1H), 7.23-7.18 (m, 3H), 4.33 (m, 4H), 4.03 (s, 1H), 2.09 (s, 3H)	61		MS (ESI) m/z 585.13 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.27 (s, 1H), 8.84 (d, J = 4.76, 1H), 8.37 (d, J = 0.96 Hz, 1H), 8.26 (s, 1H), 8.00 (s, 1H), 7.59 (dd, J = 2.64, 8.92 Hz, 1H), 7.48 (d, J = 4.76 Hz, 1H), 7.43 (d, J = 2.6 Hz, 1H), 7.36 (d, J = 8.96, 1H), 4.42-4.23 (m, 4H), 1.74 (s, 3H)
59		MS (ESI) m/z 578.08 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 12.91 (s, 1H), 8.28 (s, 1H), 7.84-7.81 (m, 2H), 7.6-7.2 (m, 6H), 4.37 (s, 4H), 2.21 (s, 3H)	65		MS (ESI) m/z 621.17 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.7935 (d, J = 4.8 Hz, 1H), 8.568 (s, 1H), 8.338 (s, 1H), 8.236 (s, 1H), 7.610 (dd, J = 8.8 Hz, 1H), 7.487 (d, J = 4.8 Hz, 1H), 7.441 (d, J = 2.8 Hz, 1H), 7.372 (d, J = 9 Hz, 1H),6.687-6.429 (m, 1H), 4.431-4.355 (m, 4H)

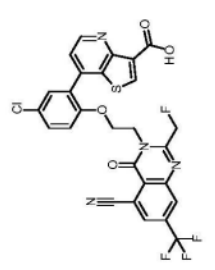
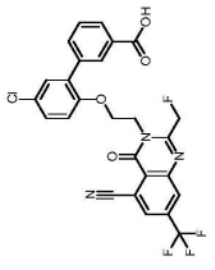
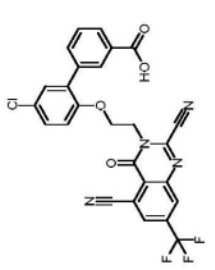
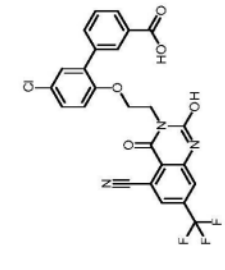
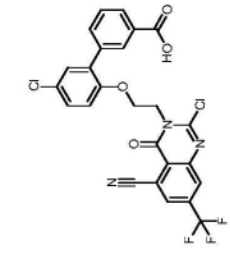
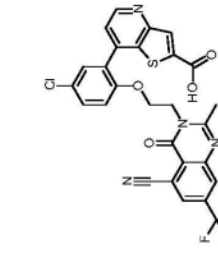
[0905]

120		MS (ESI) m/z 579.15 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.75(d, J = 4.48 Hz, 1H), 8.59 (s, 1H), 8.41 (s, 1H), 8.14 (s, 1H), 7.76 (d, J = 8.8 Hz, 1H), 7.69 (d, J = 6.04 Hz, 2H), 7.56 (d, J = 4.48 Hz, 1H), 4.88(s, 2H), 2.10 (s, 3H)	
121		MS (ESI) m/z 599.14 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.55 (s, 1H), 8.36 (s, 1H), 8.27 (s, 1H), 7.97(s, 1H), 7.60-7.57 (dd, J = 2.52 Hz, 1H), 7.41 (s, 2H), 7.35 (d, J = 8.96 Hz, 1H), 4.40 (t, J = 4.6 Hz, J = 4.48 Hz, 2H), 4.25 (t, J = 4.04 Hz, J = 5.0 Hz, 2H), 2.69 (s, 3H), 1.81 (s, 3H)	
122		MS (ESI) m/z 601.98 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 12.93 (bs, 1H), 8.35 (s, 1H), 8.06 (s, 1H), 7.77 (s, 1H), 7.51(dd, J = 8.88, 2.6 Hz, 1H), 7.29-7.22 (m, 4H), 4.35 (t, J = 4.4 Hz, 2H), 4.24 (t, J = 4.84 Hz, 2H), 1.77 (s, 3H)	
145		MS (ESI) m/z 524.41 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.05 (s, 1H), 8.37 (s, 1H), 8.19 (s, 1H), 7.8480-7.726 (m, 3H), 7.4848-7.454 (m, 3H), 7.36 (s, 1H), 6.43 (d, J = 15.68 Hz, 1H), 6.15 (d, J = 15.68 Hz, 1H), 4.83 (d, J = 3.4 Hz, 2H), 2.56 (s, 3H)	
146		MS (ESI) m/z 526.46 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 12.98 (bs, 1H), 8.35 (d, J = 1.36 Hz, 1H), 8.177 (s, 1H), 7.767 (s, 1H), 7.744 (s, 1H), 7.58-7.557 (m, 1H), 7.467-7.382 (m, 3H), 7.229 (d, J = 6.4 Hz , 1H), 3.933 (t, J = 7.04 Hz, 2H), 2.611 (t, J = 8.44 Hz, 2H), 2.447 (s, 3H), 1.768 (m, 2H)	
156		MS (ESI) m/z 552.22 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 12.92 (bs, 1H), 8.34 (s, 1H), 8.18 (s, 1H), 7.83 (dd, J = 7.64, 1.0 Hz, 1H), 7.44-7.34 (m, 3H), 7.16-7.14 (m, 2H), 4.31 (bs, 4H), 3.73 (s, 1H), 1.98 (s, 3H)	

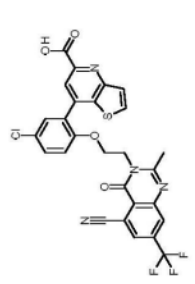
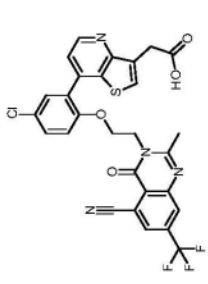
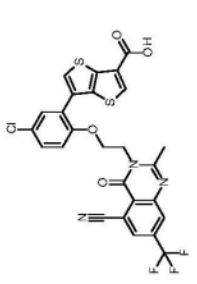
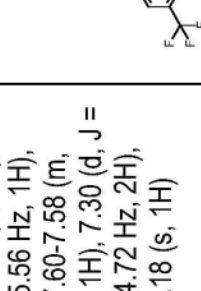
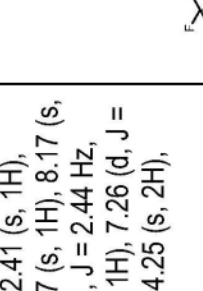
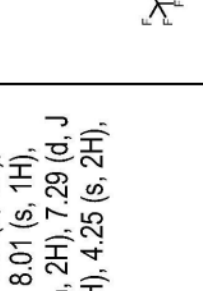
[0906]

158	MS (ESI) m/z 572.49 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.15 (bs, 1H), 8.36 (s, 1H), 8.21 (s, 1H), 7.63 (s, 1H), 7.58 (d, J = 8 Hz, 1H), 7.51 (d, J = 7.6 Hz, 1H), 7.429-7.401 (dd, J = 2.4 Hz, J' = 8.72 Hz, 1H), 7.33 (d, J = 2.4 Hz, 1H), 7.21 (d, J = 8.8 Hz, 1H), 4.37 (s, 4H), 2.25(s, 3H)	164	MS (ESI) m/z 571 [M+1]; 1H NMR (400 MHz, DMSO-d6) δ 8.79(s, 1H), 8.43(d, J = 16.6 Hz, 2H), 8.11(s, 1H), 7.79 (bs, 1H), 7.60(s, 1H), 7.46(m, 2H), 7.35(m, 1H), 4.40(s, 2H), 4.20(s, 2H), 3.89(s, 1H)
159	MS (ESI) m/z 538 [M+1]+. 1H NMR (400 MHz, DMSO-d6) δ 8.43 (s, 1H), 8.29(s, 1H), 8.01 (s, 1H), 7.59 (bs, 1H), 7.38-7.36 (m , 1H), 7.32-7.30 (m, 1H), 7.20 (d, J = 2.56 Hz, 2H), 7.16 (d, J = 8.76 Hz, 1H), 4.26 (s, 4H), 3.8 (s, 1H)	168	MS (ESI) m/z 553.20 [M+1]+. UPLC: 98.95 %; 1H NMR (400 MHz, DMSO-d6) δ 13.65 (s, 1H), 8.37(s, 1H), 8.19 (s, 1H), 8.08 (d, J = 7.68 1H), 7.78-7.76 (t, J = 7.76 Hz, 1H), 7.61 (d, J = 7.24 Hz, 1H), 7.49 (dd, J = 2.4, 8.84 Hz, 1H), 7.28 (d, J = 2.52 Hz, 1H), 7.25 (d, J = 8.92 Hz 1H), 4.32 (m, 4H), 1.95 (s, 3H)
162	MS (ESI) m/z 515.10 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.63 (d, J = 5.04 Hz, 1H), 8.43 (d, J = 1.08 Hz, 1H), 8.27 (s, 1H), 8.23 (s, 1H), 8.03 (s, 1H), 7.67-7.65 (dd, J = 1.52, 4.96 Hz, 1H), 7.49 (d, J = 2.72 Hz, 1H), 7.47 (s, 1H), 7.25 (d, J = 9.28 Hz, 1H), 4.40-4.37 (m, 4H)	169	MS (ESI) m/z 554.24 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 12.77 (bs, 1H), 8.36 (s, 1H), 8.17 (s, 1H), 7.71 (d, J = 7.32 Hz, 1H), 7.36-7.28 (m, 2H), 7.23 (d, J = 7.8 Hz, 1H), 7.10 (d, J = 9.56 Hz, 2H), 6.57-6.50 (q, J = 6.32, 11.64 Hz, 1H), 4.88 (d, J = 11.32 Hz, 1H), 4.64 (d, J = 17.52 Hz, 1H), 4.30 (s, 4H), 2.02 (s, 3H)

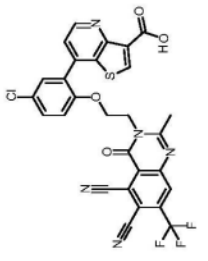
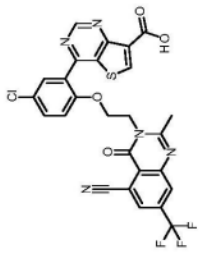
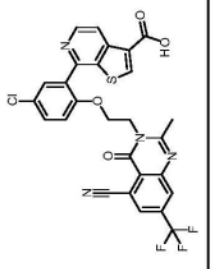
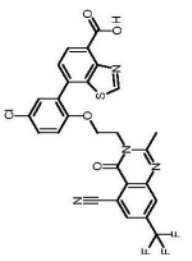
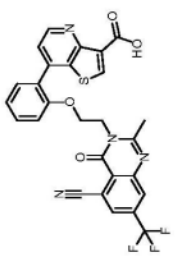
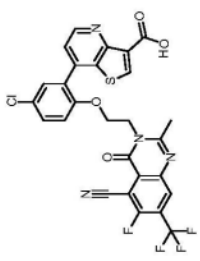
[0907]

181		MS (ESI) m/z 603.04 [M+1]+; 1H-NMR (400 MHz, DMSO-d6) δ 8.83 (s, 1H), 8.50 (s, 1H), 8.33 (s, 1H), 8.15 (s, 1H), 7.60-7.36 (m, 4H), 4.72 (d, J = 44 Hz, 2H), 4.39 (bs, 2H), 4.12 (bs, 2H)	
182		MS (ESI) m/z 546.08 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.40 (s, 1H), 8.30 (s, 1H), 7.87-7.83 (m, 2H), 7.55 (d, J = 7.50 Hz, 1H), 7.45-7.39 (m, 2H), 7.30 (d, J=2.48 Hz, 1H), 7.20 (d, J = 8.0 Hz, 1H), 5.10 (d, J = 45 Hz, 2H), 4.39 (bs, 4H)	
185		MS (ESI) m/z 539.07 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 12.82 (s, 1H), 8.60 (s, 1H), 8.50 (s, 1H), 7.87-7.71 (m, 2H), 7.53-7.51 (d, J = 8 Hz, 1H), 7.43-7.37 (m, 2H), 7.35-7.20 (m, 2H), 4.53 (t, J = 4 Hz, 2H), 4.39 (t, J = 4 Hz, 2H)	
186		MS (ESI) m/z 530.11 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 12.43 (s, 1H), 8.08 (s, 1H), 7.88 (s, 1H), 7.73 (d, J =7.2 Hz, 1H), 7.65 (s, 2H), 7.41-7.33 (m, 3H), 7.22 (d, J=8.72, 1H), 4.30-4.27 (t, J =6 Hz, 2H), 4.22-4.20 (t, J = 5.54 Hz, 2H)	
187		MS (ESI) m/z 548.03 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 12.91 (s, 1H), 8.47 (s, 1H), 8.29 (s, 1H), 7.88 (s, 1H), 7.77 (d, J = 7.50 Hz, 1H), 7.59 (d, J = 7.90 Hz, 1H), 7.42-7.38 (m, 2H), 7.31 (d, J = 2.48 Hz, 1H), 7.22 (d, J = 9.0 Hz, 1H), 4.52 (d, J = 4.72 Hz, 2H), 4.38 (d, J = 4.8 Hz, 2H)	
199		MS (ESI) m/z 584.69 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.50 (s, 1H), 8.72 (d, 4.08 Hz, 1H), 8.29 (s, 1H), 8.08 (s, 1H), 7.70 (s, 1H), 7.58 (dd, J = 2.32, 8.52 Hz, 1H), 7.40 (d, J = 2.36 Hz, 1H), 7.35 (d, J = 8.96 Hz, 2H), 4.42 (s, 2H), 4.26 (s, 2H), 1.81 (s, 3H)	

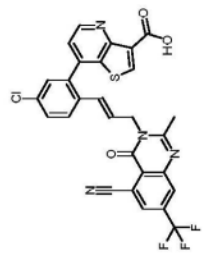
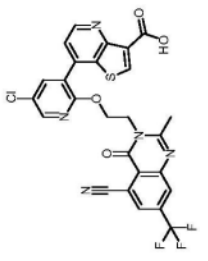
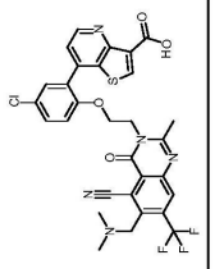
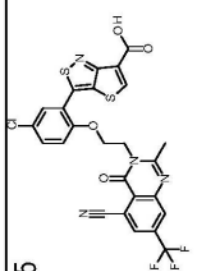
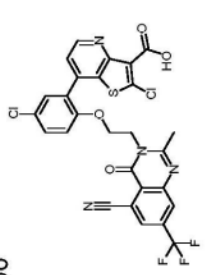
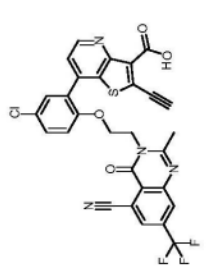
[0908]

201		MS (ESI) m/z 585.16 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 14.04 (b, 1H), 8.30 (s, 1H), 8.25 (d, J = 5.56 Hz, 1H), 7.96 (d, J = 6.4 Hz, 2H), 7.60-7.58 (m, 2H), 7.50 (dd, J = 8.8 Hz, 1H), 7.30 (d, J = 8.84 Hz, 1H), 4.45 (t, J = 4.72 Hz, 2H), 4.36 (t, J = 4.6 Hz, 2H), 2.18 (s, 1H)
202		MS (ESI) m/z 599.18 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 12.41 (s, 1H), 8.66 (d, 4.56 Hz, 1H), 8.37 (s, 1H), 8.17 (s, 1H), 7.56 (m, 2H), 7.40 (d, J = 2.44 Hz, 1H), 7.33 (d, J = 9.04 Hz, 1H), 7.26 (d, J = 4.6 Hz, 1H), 4.38 (s, 2H), 4.25 (s, 2H), 3.84 (s, 2H), 1.78 (s, 3H)
203		MS (ESI) m/z 589.91 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 12.88 (s, 1H), 8.29 (s, 1H), 8.04 (s, 1H), 8.01 (s, 1H), 7.92 (s, 1H), 7.48-7.44 (m, 2H), 7.29 (d, J = 8.8 Hz, 1H), 4.50 (m, 2H), 4.25 (s, 2H), 2.08 (s, 3H)
205		MS (ESI) m/z 599.18 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.79 (d, J = 4.96 Hz, 1H), 8.38 (s, 1H), 7.98 (s, 1H), 7.60 (dd, J = 8.88, 2.6 Hz, 1H), 7.53 (d, J = 4.88 Hz, 1H), 7.43 (d, J = 2.56 Hz, 1H), 7.36 (d, J = 8.96 Hz, 1H), 4.43 (s, 2H), 4.27 (s, 2H), 2.34 (s, 3H), 1.85 (s, 3H)
206		MS (ESI) m/z 619.24 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.82 (d, J = 4.64 Hz, 1H), 8.36 (s, 1H), 8.07 (s, 1H), 7.60 (d, J = 8.84 Hz, 1H), 7.52 (d, J = 4.4 Hz, 1H), 7.41 (s, 1H), 7.34 (d, J = 8.92 Hz, 1H), 4.44 (s, 2H), 4.28 (s, 2H), 1.81 (s, 3H)
210		MS (ESI) m/z 610.15 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.16 (s, 1H), 8.82 (d, J = 4.64 Hz ,1H), 8.41 (d, J = 9.8 Hz , 2H), 7.6 (dd, J =8.92, 2.48 Hz, 1H), 7.45 (dd, J = 9.68 , 4.72 Hz, 2H), 7.37 (d, J = 8.88 Hz, 1H), 4.42 (t, J =5.04 Hz , 2H), 4.27 (t, J= 5.2 Hz , 2H), 1.96 (s, 3H)

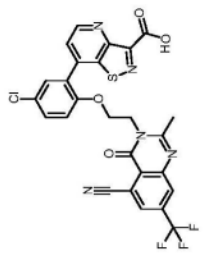
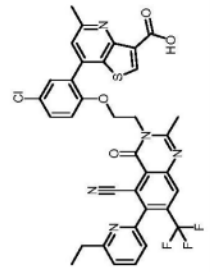
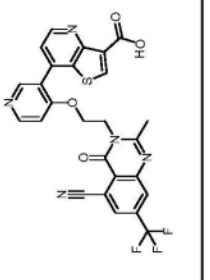
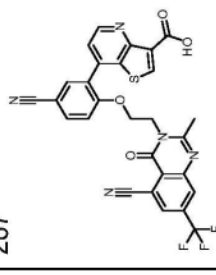
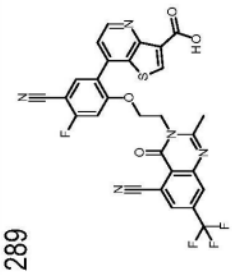
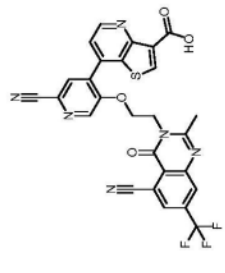
[0909]

214		MS (ESI) m/z 609.05 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.16 (bs, 1H), 8.86 (d, J = 4.6 Hz, 1H), 8.16 (s, 1H), 8.11 (s, 1H), 7.60 (d, J = 8.96 Hz, 1H), 7.49 (d, J = 4.44 Hz, 1H), 7.42 (s, 1H), 7.36 (d, J = 9.04, 1H), 4.42 (bs, 2H), 4.28 (bs, 2H), 1.74 (s, 3H)
215		MS (ESI) m/z 585 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.10 (bs, 1H), 9.33 (s, 1H), 8.38 (s, 2H), 7.98 (s, 1H), 7.64 (dd, J = 8.8, 2.4 Hz, 1H), 7.45 (d, J = 2.4 Hz, 1H), 7.38 (d, J = 9.2 Hz, 1H), 4.45 (s, 2H), 4.27 (s, 2H), 1.77 (s, 3H)
225		MS (ESI) m/z 585.16 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.19 (s, 1H), 8.59 (d, J = 5.56 Hz, 1H), 8.35-8.32 (m, 2H), 8.05 (s, 1H), 7.93 (s, 1H), 7.55 (dd, J = 9.0, 2.56 Hz, 1H), 7.33-7.30 (m, 1H), 4.38 (s, 2H), 4.22 (s, 2H), 1.69 (s, 3H)
226		MS (ESI) m/z 585.39 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.54 (s, 1H), 8.38 (s, 1H), 8.18 (s, 1H), 7.97 (t, J = 6.30 Hz, 2H), 7.55-7.52 (dd, J = 2.24, 2.32 Hz, 1H), 7.46 (d, J = 7.8 Hz, 1H), 7.30-7.25 (m, 2H), 4.45-4.29 (m, 4H), 1.98 (s, 3H)
227		MS (ESI) m/z 551.14 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.83 (d, J = 4.96 Hz, 1H), 8.38 (s, 1H), 8.32 (s, 1H), 8.01 (s, 1H), 7.55 (t, J = 7.16 Hz, 1H), 7.50 (d, J = 4.48 Hz, 1H), 7.34 (t, J = 5.6 Hz, 2H), 7.16 (t, J = 7.40 Hz, 1H), 4.41 (s, 2H), 4.27 (s, 2H), 1.80 (s, 3H)
246		MS (ESI) m/z 603.15 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.77 (d, J = 4.84 Hz, 1H), 8.64 (s, 1H), 8.40 (d, J = 9.16 Hz, 1H), 7.60 (dd, J = 8.92 Hz, 2.6 Hz, 1H), 7.49 (d, J = 4.84 Hz, 1H), 7.45 (d, J = 2.6 Hz, 1H), 7.37 (d, J = 8.96 Hz, 1H), 4.44 (t, J = 4.8 Hz, 2H), 4.29 (t, J = 4.64 Hz, 2H), 1.99 (s, 3H)

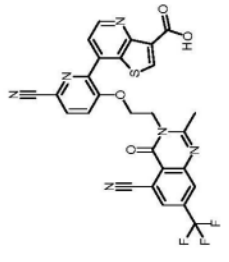
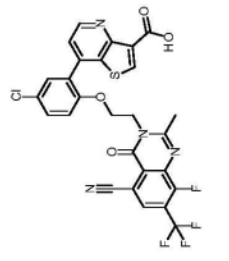
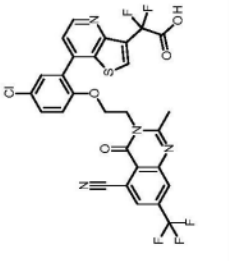
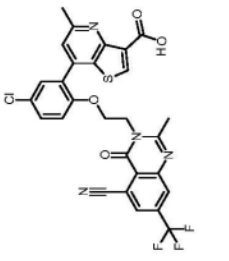
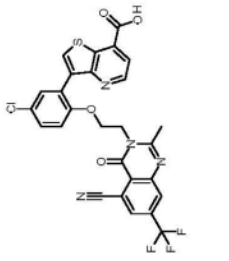
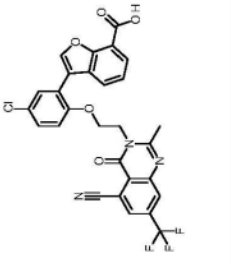
[0910]

255		MS (ESI) m/z 581.20 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.16 (bs, 1H), 8.83 (s, 1H), 7.77 (d, J = 4.4 Hz, 1H), 8.35 (s, 1H), 8.14 (s, 1H), 7.87 (d, J = 8.8 Hz, 1H), 7.61 (d, J = 8.4 Hz, 1H), 7.53 (s, 1H), 7.42 (d, J = 4.4 Hz, 1H), 6.50-6.44 (m, 1H), 5.98 (d, J = 16.0, 1H), 4.73 (d, J = 4.0, 2H), 2.38 (s, 3H)	
259		MS (ESI) m/z 586.14 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.91 (s, 1H), 8.80 (d, J = 4.92 Hz, 1H), 8.39 (d, J = 1.12 Hz, 1H), 8.35 (d, J = 2.80 Hz, 1H), 8.25 (s, 1H), 7.98 (d, J = 2.80 Hz, 1H), 7.49 (d, J = 4.88 Hz, 1H), 4.53 (t, J=5.4 Hz, 2H), 4.41 (t, J = 5.2 Hz, 2H), 2.62 (s, 3H)	
261		MS (ESI) m/z 644.23 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.83-8.79 (m, 3H), 8.29 (s, 1H), 8.22 (s, 1H), 7.93 (s, 1H), 7.84 (d, J = 5.68 Hz, 2H), 7.59 (dd, J = 2.56, J=8.84 Hz, 1H), 7.51 (d, J = 4.8 Hz, 1H), 7.44 (d, J=2.60 Hz, 1H), 7.34 (d, J=8.96 Hz, 1H) 4.38 (t, J = 5.76 Hz, 2H), 4.22 (t, J = 4.60 Hz, 2H), 1.69 (s, 3H)	
265		MS (ESI) m/z 591.15 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 12.98 (bs, 1H), 8.9 (s, 1H), 8.28 (s, 1H), 8.16 (s, 1H), 7.68 (d, J = 2.4 Hz, 1H), 7.6 (dd, J = 8.8, 2.3 Hz, 1H), 7.5 (d, J = 9.0 Hz, 1H), 4.76 (t, J = 5.2 Hz, 2H), 4.57 (t, J = 3.6 Hz, 2H), 2.56 (s, 3H)	
266		MS (ESI) m/z 619.24 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.82 (d, J = 4.64 Hz, 1H), 8.36 (s, 1H), 8.07 (s, 1H), 7.60 (d, J = 8.84 Hz, 1H), 7.52 (d, J = 4.4 Hz, 1H), 7.41 (s, 1H), 7.34 (d, J = 8.92 Hz, 1H), 4.44 (s, 2H), 4.28 (s, 2H), 1.81 (s, 3H)	
267		MS (ESI) m/z 609.20 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.04 (bs, 1H), 8.88 (d, J = 4.8 Hz, 1H), 8.30 (d, J = 1.2 Hz, 1H), 8.03 (d, J = 1.4 Hz, 1H), 7.61-7.56 (m, 2H), 7.42 (d, J = 2.8 Hz, 1H), 7.35 (d, J = 8.8 Hz, 1H), 4.91 (s, 1H), 4.44 (t, J = 4.4 Hz, 2H), 4.26 (d, J = 4.4 Hz, 2H), 1.73 (s, 3H)	

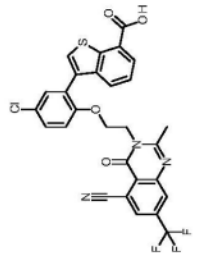
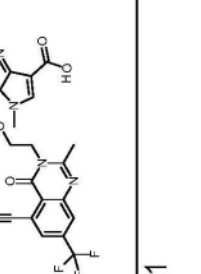
[0911]

272		MS (ESI) m/z 586.17 [M+1]+. 1H NMR (400 MHz, DMSO-d6) δ 13.95 (bs, 1H), 8.98 (d, J = 4.4 Hz, 1H), 8.38 (s, 1H), 8.11 (s, 1H), 7.66 (d, J = 4.0 Hz, 1H), 7.60 (d, J = 9.6 Hz, 1H) 7.49 (s, 1H), 7.36 (d, J = 9.2 Hz, 1H), 4.45 (s, 2H), 4.28 (s, 2H), 1.74 (s, 3H)	
275		MS (ESI) m/z 601.13 [M+1]+; 1H NMR (400 MHz, DMSO-d6) 8.85 (d, J = 4.80 Hz, 1H), 8.39 (s, 1H), 7.89 (s, 1H), 7.60 (dd, J = 8.88, 2.36 Hz, 1H), 7.50 (d, J = 4.80 Hz, 1H), 7.42 (d, J = 2.44 Hz, 1H), 7.35 (d, J = 8.96 Hz, 1H), 4.40 (t, J = 5.28 Hz, 2H). 4.23 (t, J = 4.40 Hz, 2H), 1.71 (s, 3H)	
285		MS (ESI) m/z 552.20 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.91 (d, J = 4.8 Hz, 1H), 8.79 (d, J = 6.2 Hz, 1H), 8.64 (s, 1H), 8.40 (s, 1H), 8.34 (s, 1H), 8.05 (s, 1H), 7.61 (d, J = 3.1 Hz, 1H), 7.55 (d, J = 4.7 Hz, 1H), 4.62 (t, J = 4.2 Hz, 2H), 4.31 (t, J = 4.7 Hz, 2H), 1.75 (s, 3H)	
287		MS (ESI) m/z 576.26 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.28 (bs, 1H), 8.84 (d, J = 4.8 Hz, 1H), 8.38 (s, 1H), 8.26 (s, 1H), 8.05 (dd, J = 8.6, 2.0 Hz, 1H), 8.01 (s, 1H), 7.89 (d, J = 2.0 Hz, 1H), 7.52 (d, J = 3.4 Hz, 1H), 7.5 (s, 1H), 4.51 (t, J = 4.8 Hz, 2H), 4.26 (t, J = 5.9 Hz, 2H), 1.7 (s, 3H)	
289		MS (ESI) m/z 594.14 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.85 (d, J = 4.5 1H), 8.39 (s, 1H), 8.28 (s, 1H), 8.00 (d, J=8.52, 2H), 7.63 (d, J = 11.4 Hz, 1H), 7.49 (d, J = 4.28 Hz, 1H), 4.527 (s, 2H), 4.26 (s, 2H), 1.683 (s, 3H)	
291		MS (ESI) m/z 577.06 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.15 (s, 1H), 8.91 (d, J = 4.72 Hz, 1H), 8.87 (s, 1H), 8.39 (s, 1H), 8.35 (s, 1H), 8.17 (s, 1H), 8.05 (s, 1H), 7.54 (d, J = 4.72 Hz, 1H), 4.66 (s, 2H), 4.27 (s, 2H), 1.79 (s, 3H)	

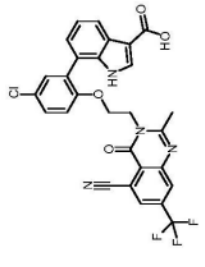
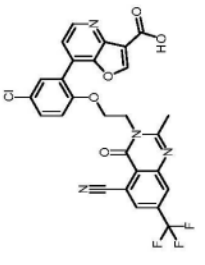
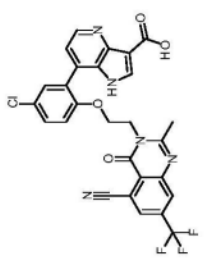
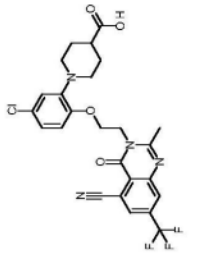
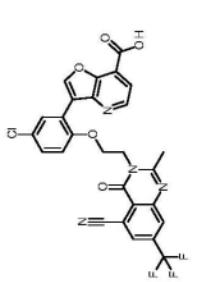
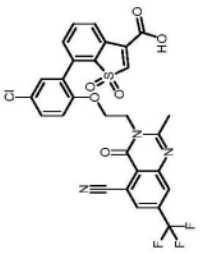
[0912]

292		MS (ESI) m/z 577.0 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.88 (s, 1H), 8.87 (s, 1H), 8.38 (s, 1H), 8.27 (d, J = 8.7 Hz, 1H), 8.22 (s, 1H), 8.1 (d, J = 4.9 Hz, 1H), 8.04 (d, J = 8.7 Hz, 1H), 4.68 (t, J = 4.2 Hz, 2H), 4.55 (t, J = 4.4 Hz, 2H), 2.37 (s, 3H)
294		MS (ESI) m/z 603.17 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.82 (d, J = 4.84 Hz, 1H), 8.45 (s, 1H), 8.37 (d, J = 5.28 Hz, 1H), 7.60 (dd, J = 8.56, 6.72 Hz, 1H), 7.49 (d, J = 4.56 Hz 1H), 7.43 (d, J = 2.04 Hz, 1H), 7.37 (d, J = 8.88 Hz, 1H), 4.42 (t, J = 4.90, 2H), 4.27 (t, J = 4.40 Hz, 2H), 1.86 (s, 3H)
295		MS (ESI) m/z 634.99 [M+1]+;1H NMR (400 MHz, DMSO-d6), δ 8.76 (d, J = 2.68 Hz 1H), 8.35 (s, 1H), 8.10 (s, 1H), 7.74 (s, 1H), 7.58 (dd, J = 9.24, 2.81 Hz, 1H), 7.42 (d, J = 2.80 Hz, 1H), 7.40 (d, J = 4.40 Hz, 1H), 7.34 (d, J = 8.96 Hz, 1H), 4.45-4.37 (m, 2H), 4.30-4.22 (m, 2H), 1.82 (s, 3H)
296		MS (ESI) m/z 599.14 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.55 (s, 1H), 8.36 (s, 1H), 8.27 (s, 1H), 7.97(s, 1H), 7.60-7.57 (dd, J = 2.52, 8.8 Hz, 1H), 7.41 (m, 2H), 7.35 (d, J = 8.96 Hz, 1H), 4.40 (t, J = 5 Hz, 2H), 4.25 (t, J = 5.0 Hz, 2H), 2.69 (s, 3H), 1.82 (s, 3H)
299		MS (ESI) m/z 585.17 [M+1]+. 1H NMR (400 MHz, DMSO-d6) δ 14.22 (bs, 1H), 8.37 (s, 1H), 8.34 (d, J = 4.8 Hz, 1H), 8.18 (s, 1H), 7.98 (s, 1H), 7.47-7.44 (m, 2H), 7.38 (d, J = 2.4 Hz, 1H), 7.25 (d, J = 9.2 Hz, 1H), 4.34 (t, 4.8 Hz, 2H), 4.25 (t, J = 4.4, 2H), 1.97 (s, 3H)
300		MS (ESI) m/z 568.19 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.19 (s, 1H), 8.33 (s,1H), 8.20 (s , 1H), 8.06 (s, 1H), 7.61 (d, J = 7.28 Hz, 1H), 7.51 (d, J = 7.56 Hz, 1H), 7.47 (d, J = 2.32 Hz, 1H), 7.43 (d, J = 2.2 Hz, 1H), 7.28 (d, J = 8.8 Hz, 1H), 6.97 (t, J = 7.56 Hz, 1H,), 4.43(s, 2H), 4.32(s,2H), 2.10 (s, 3H)

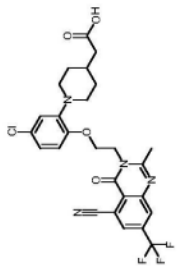
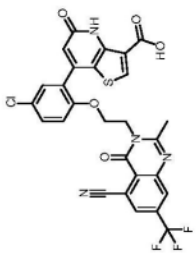
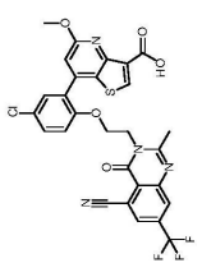
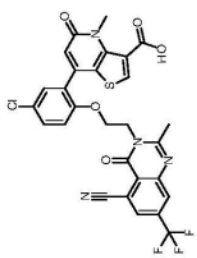
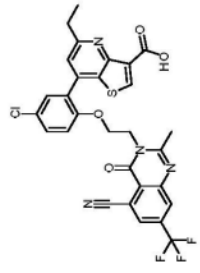
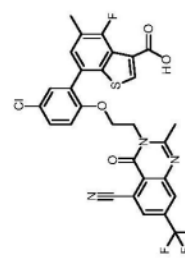
[0913]

301		MS (ESI) m/z 583.99 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.46 (bs, 1H), 8.35 (s, 1H), 7.94 (s, 1H), 7.79 (s, 1H), 7.55 (d, J = 7.32 Hz, 1H), 7.49 (dd, J = 8.80, 2.68 Hz, 1H), 7.32-7.27 (m, 3H), 6.89 (t, J = 7.64 Hz, 1H), 4.30 (t, J = 5.08 Hz, 2H), 4.16 (t, J = 5.12 Hz, 2H), 1.92 (s, 3H)	319		MS (ESI) m/z 585.2 [M+1]+; 1H-NMR (400 MHz, d6-DMSO) / ppm = 13.31 (bs, 1H), 9.59 (s, 1H), 8.37 (s, 1H), 8.34 (d, J = 1.9 Hz, 1H), 7.95-7.94 (m, 1H), 7.91 (s, 1H), 7.54 (dd, J = 8.9, 2.6 Hz, 1H), 7.38 (d, J = 2.6 Hz, 1H), 7.30 (d, J = 8.9 Hz, 1H), 4.36 (t, J = 4.7 Hz, 2H), 4.21 (t, J = 4.7 Hz, 2H), 1.70 (s, 3H)
314		MS (ESI) m/z 585.94 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.25 (s, 1H), 9.18 (s, 1H), 8.33 (s, 1H), 8.24 (s, 1H), 7.97 (s, 1H), 7.62 (dd, J = 8.8, 2.7 Hz, 1H), 7.49 (d, J = 2.32 Hz, 1H), 7.36 (d, J = 9.0 Hz, 1H), 4.44 (t, J = 4.96 Hz, 2H), 4.27 (t, J = 4.96 Hz, 2H), 1.71 (s, 3H)	320		MS (ESI) m/z 582.1 [M+1]+; 1H-NMR (400 MHz, d6-DMSO) / ppm = 8.49 (d, J = 5.1 Hz, 1H), 8.39 (d, J = 1.5 Hz, 1H), 8.15-8.02 (m, 2H), 7.60 (dd, J = 9.1, 2.6 Hz, 1H), 7.41 (d, J = 2.6 Hz, 1H), 7.30 (d, J = 9.1 Hz, 1H), 7.34-7.20 (m, 1H), 4.46-4.33 (m, 2H), 4.28-4.20 (m, 2H), 3.16 (s, 3H), 1.66 (s, 3H)
315		MS (ESI) m/z 591.15 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.54 (s, 1H), 8.33 (s, 1H), 8.11 (s, 1H), 8.01 (s, 1H), 7.67 (d, J = 2.64 Hz, 1H), 7.59 (dd, J = 8.92, 2.68 Hz, 1H), 7.38 (d, J = 9 Hz, 1H), 4.60 (t, J = 5.24 Hz, 2H), 4.37 (t, J = 5.36 Hz, 2H), 2.14 (s, 3H)	321		MS (ESI) m/z 700.1 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 10.16 (s, 1H), 8.87 – 8.81 (m, 1H), 8.24 – 8.17 (m, 1H), 7.98 (s, 1H), 7.61 (dd, J = 8.9, 2.7 Hz, 1H), 7.49 (dd, J = 4.9, 2.0 Hz, 1H), 7.43 (d, J = 2.6 Hz, 1H), 7.37 (d, J = 9.0 Hz, 1H), 4.77 – 4.71 (m, 1H), 4.66 – 4.59 (m, 1H), 4.42 (t, J = 5.0 Hz, 2H), 4.32 – 4.11 (m, 6H), 3.70 – 3.53 (m, 2H), 3.23 – 3.11 (m, 2H), 1.81 (s, 3H)

[0914]

322		325	
[0503] MS (ESI) m/z 567.2 [M+1]+; 1H NMR (400 MHz, d6-DMSO) δ / ppm = 11.04 (d, J = 3.2 Hz, 1H), 8.38-8.37 (m, 1H), 8.10-8.08 (m, 1H), 8.02 (d, J = 8.1 Hz, 1H), 7.45 (dd, J = 8.9 Hz, 2.8 Hz, 1H), 7.25-7.15 (m, 4H), 7.02 (dd, J = 7.2, 1.2 Hz, 1H), 4.40-4.35 (m, 2H), 4.22-4.18 (m, 2H), 1.61 (s, 3H)		MS (ESI) m/z 569.0 [M+1]+; 1H-NMR (400 MHz, d6-DMSO) δ / ppm = 8.98-8.90 (m, 1H), 8.54-8.45 (m, 1H), 8.36-8.31 (m, 1H), 8.23-8.18 (m, 1H), 7.64-7.51 (m, 3H), 7.34-7.27 (m, 1H), 4.43-4.34 (m, 2H), 4.34-4.23 (m, 2H), 1.77 (s, 3H)
323		326	
MS (ESI) m/z 568.0 [M+1]+; 1H-NMR (400 MHz, d6-DMSO) δ / ppm = 13.49 (b, 1H), 8.59 (d, J = 5.6 Hz, 1H), 8.40-8.39 (m, 1H), 8.07-8.05 (m, 1H), 7.87-7.77 (m, 1H), 7.62 (dd, J = 8.9, 2.6 Hz, 1H), 7.60-7.49 (m, 1H), 7.42 (d, J = 2.6 Hz, 1H), 7.34 (d, J = 8.9 Hz, 1H), 4.45 (t, J = 4.6 Hz, 2H), 4.25 (t, J = 4.6 Hz, 2H), 1.76 (s, 3H)		[0506] MS (ESI) m/z 535.1 [M+1]+	
324		327	
MS (ESI) m/z 569.0 [M+1]+; 1H-NMR (400 MHz, d6-DMSO) δ / ppm = 8.80 (s, 1H), 8.65 (d, J = 4.9 Hz, 1H), 8.53 (d, J = 2.7 Hz, 1H), 8.33 (bd, J = 1.7 Hz, 1H), 8.15-8.14 (m, 1H), 7.69 (d, J = 4.9 Hz, 1H), 7.43 (dd, J = 8.9, 2.7 Hz, 1H), 7.30 (d, J = 8.9 Hz, 1H), 4.55-4.52 (m, 4H), 2.45 (s, 3H)		MS (ESI) m/z 616.4 [M+1]+; 1H-NMR (400 MHz, d6-DMSO) δ / ppm = 8.33 (bd, J = 1.7 Hz, 1H), 8.24 (dd, J = 7.8, 0.9 Hz, 1H), 7.95 (s, 1H), 7.76 (dd, J = 7.8, 7.8 Hz, 1H), 7.50 (dd, J = 8.9, 2.6 Hz, 1H), 7.45 (bd, J = 7.8 Hz, 1H), 7.23-7.20 (m, 2H), 7.14 (s, 1H), 4.36-4.21 (m, 4H), 1.84 (s, 3H)	

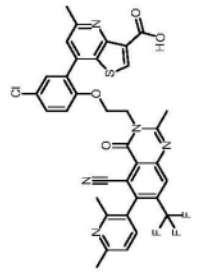
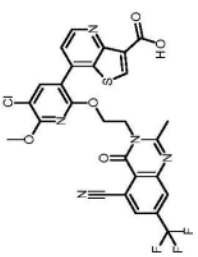
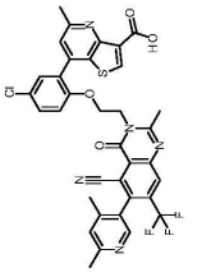
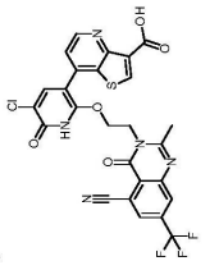
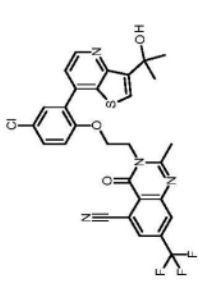
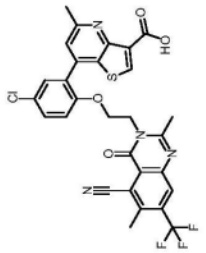
[0915]

328		MS (ESI) m/z 549.3 [M+1]+; 1H-NMR (400 MHz, d6-DMSO) δ / ppm = 8.39 (bd, J = 1.7 Hz, 1H), 8.24-8.22 (m, 1H), 7.01-6.87 (m, 3H), 4.52 (t, J = 4.8 Hz, 2H), 4.35 (t, J = 4.8 Hz, 2H), 3.22-3.16 (m, 2H), 2.80 (s, 3H), 2.50-2.43 (m, 2H), 2.13-2.09 (m, 2H), 1.74-1.57 (m, 3H), 1.27-1.11 (m, 2H)	331		MS (ESI) m/z 601.6 [M+1]+; 1H-NMR (400 MHz, d6-DMSO) δ / ppm = 10.48 (s, 1H), 8.37-8.36 (m, 1H), 7.95 (bs, 1H), 7.78 (bs, 1H), 7.56 (dd, J = 8.7, 2.6, 1H), 7.38 (d, J = 2.6 Hz, 1H), 7.31 (d, J = 8.7 Hz, 1H), 6.36 (bs, 1H), 4.41 (bt, 2H), 4.32 (bt, 2H), 2.15 (s, 3H)
329		MS (ESI) m/z 615.0 [M+1]+; 1H-NMR (400 MHz, d6-DMSO) δ / ppm = 8.36 (bd, J = 1.6 Hz, 1H), 8.12 (s, 1H), 8.01-8.00 (m, 1H), 7.57 (dd, J = 8.9, 2.7 Hz, 1H), 7.39 (d, J = 2.7 Hz, 1H), 7.33 (d, J = 8.9 Hz, 1H), 6.90 (d, J = 0.3 Hz, 1H), 4.40 (t, J = 5.0 Hz, 2H), 4.26 (t, J = 5.0 Hz, 1H), 4.03 (s, 3H), 1.87 (s, 3H)	332		MS (ESI) m/z 615.1 [M+1]+; 1H-NMR (400 MHz, d6-DMSO) δ / ppm = 13.35 (b, 1H), 8.32 (d, J = 1.2 Hz, 1H), 8.06-8.04 (m, 1H), 7.68 (s, 1H), 7.51 (dd, J = 8.8, 2.7 Hz, 1H), 7.32 (d, J = 2.7 Hz, 1H), 7.26 (d, J = 8.8 Hz, 1H), 6.35 (s, 1H), 4.35 (bt, 1H), 4.28 (bt, 1H), 3.65 (s, 3H), 2.06 (s, 3H)
330		MS (ESI) m/z 613.1 [M+1]+; 1H-NMR (400 MHz, d6-DMSO) δ / ppm = 8.37 (bs, 1H), 8.24 (s, 1H), 7.95 (bs, 1H), 7.60 (dd, J = 8.8, 2.6, 1H), 7.47 (s, 1H), 7.43 (d, J = 2.6 Hz, 1H), 7.35 (d, J = 8.8 Hz, 1H), 4.41 (bt, 2H), 4.25 (bt, 2H), 3.01 (q, J = 7.6 Hz, 2H), 1.78 (s, 3H), 1.34 (t, J = 7.6 Hz, 3H)	333		MS (ESI) m/z 616.2 [M+1]+; 1H-NMR (400 MHz, d6-DMSO) δ / ppm = 12.89 (b, 1H), 8.35 (d, J = 1.5 Hz, 1H), 8.07 (bs, 1H), 7.77 (bs, 1H), 7.50 (dd, J = 8.9, 2.7 Hz, 1H), 7.30-7.26 (m, 2H), 7.19 (d, J = 6.0 Hz, 1H), 4.35 (bt, 2H), 4.25 (bt, 2H), 2.33 (s, 3H), 1.83 (s, 3H)

[0916]

341		MS (ESI) m/z 690.1 [M+1]+; 1H-NMR (400 MHz, d6-DMSO) δ / ppm = 8.75 (d, J = 5.3 Hz, 1H), 8.28 (s, 1H), 8.06 (s, 1H), 7.60 (dd, J = 8.9, 2.8 Hz, 1H), 7.59 (s, 1H), 7.52 (bd, J = 5.3 Hz, 1H), 7.45 (s, 1H), 7.42 (d, J = 2.8 Hz, 1H), 7.37 (d, J = 8.9 Hz, 1H), 4.42 (t, J = 5.2 Hz, 2H), 4.28 (t, J = 5.2 Hz, 2H), 2.73 (s, 3H), 2.64 (s, 3H), 1.87 (s, 3H)
342		MS (ESI) m/z 694.2 [M+1]+; 1H-NMR (400 MHz, d6-DMSO) δ / ppm = 8.82 (d, J = 2.8 Hz, 1H), 8.60-8.59 (m, 1H), 8.28 (s, 1H), 8.11-8.06 (m, 1H), 8.07 (s, 1H), 7.60 (dd, J = 8.9, 2.7 Hz, 1H), 7.45 (s, 1H), 7.42 (d, J = 2.7 Hz, 1H), 7.37 (d, J = 8.9 Hz, 1H), 4.43 (t, J = 4.9 Hz, 2H), 4.29 (t, J = 4.9 Hz, 2H), 2.73 (s, 3H), 1.89 (s, 3H)
343		MS (ESI) m/z 694.5 [M+1]+; 1H-NMR (400 MHz, d6-DMSO) δ / ppm = 8.85 (dd, J = 7.5, 5.8 Hz, 1H), 8.79 (d, J = 9.9 Hz, 1H), 8.35 (s, 1H), 8.12 (s, 1H), 7.64 (dd, J = 9.8, 5.8 Hz, 1H), 7.60 (dd, J = 8.9, 2.7 Hz, 1H), 7.47 (s, 1H), 7.43 (d, J = 2.7 Hz, 1H), 7.37 (d, J = 8.9 Hz, 1H), 4.49-4.19 (m, 4H), 2.73 (s, 3H), 1.87 (s, 3H)
344		MS (ESI) m/z 694.2 [M+1]+; 1H-NMR (400 MHz, d6-DMSO) δ / ppm = 8.87 (s, 1H), 8.71 (d, J = 4.7 Hz, 1H), 8.34 (s, 1H), 8.14 (s, 1H), 7.74-7.70 (m, 1H), 7.60 (dd, J = 8.9, 2.7 Hz, 1H), 7.45 (s, 1H), 7.43 (d, J = 2.7 Hz, 1H), 7.36 (d, J = 8.9 Hz, 1H), 4.48-4.20 (m, 4H), 2.72 (s, 3H), 1.87 (s, 3H)
347		MS (ESI) m/z 682.5 [M+1]+; 1H-NMR (400 MHz, d6-DMSO) δ / ppm = 9.32 (s, 1H), 8.71 (s, 1H), 8.30 (s, 1H), 8.05 (s, 1H), 7.60 (dd, J = 8.9, 2.7 Hz, 1H), 7.44 (s, 1H), 7.42 (d, J = 2.7 Hz, 1H), 7.37 (d, J = 8.9 Hz, 1H), 4.42 (t, J = 4.7 Hz, 2H), 4.28 (t, J = 4.7 Hz, 2H), 2.72 (s, 3H), 1.88 (s, 3H)
348		MS (ESI) m/z 682.4 [M+1]+; 1H-NMR (400 MHz, d6-DMSO) δ / ppm = 8.74 (d, J = 1.7 Hz, 1H), 8.31 (s, 1H), 8.06 (s, 1H), 7.67 (d, J = 1.7 Hz, 1H), 7.60 (dd, J = 8.9, 2.7 Hz, 1H), 7.47 (s, 1H), 7.43 (d, J = 2.7 Hz, 1H), 7.36 (d, J = 8.6 Hz, 1H), 4.42 (t, J = 4.9 Hz, 2H), 4.28 (t, J = 4.9 Hz, 2H), 2.74 (s, 3H), 1.86 (s, 3H)

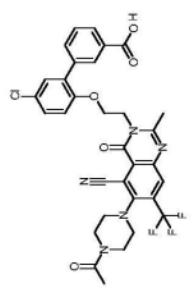
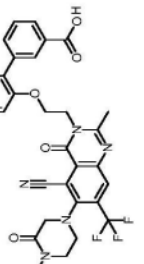
[0917]

349		MS (ESI) m/z 704.3 [M+1]+; 1H-NMR (400 MHz, d6-DMSO) δ / ppm = 8.28 (s, 1H), 8.08 (s, 1H), 7.83-7.77 (m, 1H), 7.60 (dd, J = 9.0, 2.8 Hz, 1H), 7.46 (s, 1H), 7.44 (d, J = 2.8 Hz, 1H), 7.43-7.38 (m, 1H), 7.37 (d, J = 9.0 Hz, 1H), 4.47-4.38 (m, 2H), 4.33-4.19 (m, 2H), 2.73 (s, 3H), 2.59 (s, 3H), 2.22 (s, 3H), 1.84 (s, 3H)	354		MS (ESI) m/z 615.0 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.87 – 8.84 (m, 2H), 7.61 – 7.57 (m, 2H), 7.53 – 7.51 (m, 2H), 7.38 (d, J = 9.0 Hz, 1H), 7.35 (s, 1H), 4.23 (t, J = 5.5 Hz, 2H), 3.74 (t, J = 5.4 Hz, 2H), 2.75 (s, 3H), 1.07 (s, 6H)
350		MS (ESI) m/z 704.5 [M+1]+; 1H-NMR (400 MHz, d_6-DMSO) / ppm = 8.47-8.37 (m, 1H), 8.29 (s, 1H), 8.08 (s, 1H), 7.60 (dd, J = 8.9, 2.7 Hz, 1H), 7.46 (s, 1H), 7.44 (d, J = 2.7 Hz, 1H), 7.43-7.39 (m, 1H), 7.37 (d, J = 8.9 Hz, 1H), 4.47-4.43 (m, 2H), 4.34-4.18 (m, 2H), 2.73 (s, 3H), 2.57 (s, 3H), 2.06 (s, 3H), 1.84 (s, 3H)	356		MS (ESI) m/z 602.3 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 12.34 (s, 1H), 8.82 (d, J = 4.9 Hz, 1H), 8.45 (s, 1H), 8.37 – 8.36 (m, 1H), 8.05 – 8.04 (m, 1H), 7.95 (s, 1H), 7.52 (d, J = 4.9 Hz, 1H), 4.63 (t, J = 5.0 Hz, 2H), 4.31 (t, J = 5.0 Hz, 2H), 1.90 (s, 3H)
352		MS (ESI) m/z 599.2 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.68 (d, J = 4.7 Hz, 1H), 8.38 (dd, J = 1.8, 0.6 Hz, 1H), 8.22 (dt, J = 1.8, 0.8 Hz, 1H), 7.53 (dd, J = 8.9, 2.7 Hz, 1H), 7.42 (s, 1H), 7.39 (d, J = 2.7 Hz, 1H), 7.29 (d, J = 9.0 Hz, 1H), 7.21 (d, J = 4.7 Hz, 1H), 5.43 (s, 1H), 4.37 (t, J = 4.9 Hz, 2H), 4.24 (t, J = 4.9 Hz, 2H), 1.75 (s, 6H), 1.65 (s, 3H)	363		MS (ESI) m/z 613.2 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.25 (s, 1H), 7.92 (s, 1H), 7.60 (dd, J = 8.9, 2.7 Hz, 1H), 7.43 (s, 1H), 7.41 (d, J = 2.7 Hz, 1H), 7.36 (d, J = 9.0 Hz, 1H), 4.41 (t, J = 5.0 Hz, 2H), 4.25 (t, J = 5.0 Hz, 2H), 2.71 (s, 3H), 2.70 (s, 3H), 1.85 (s, 3H)

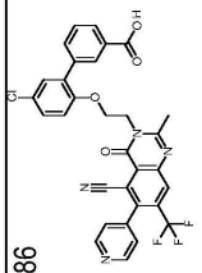
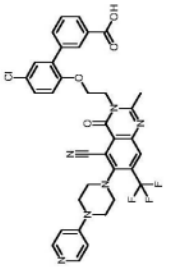
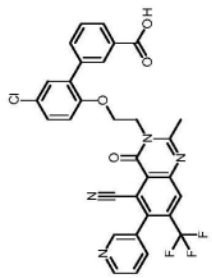
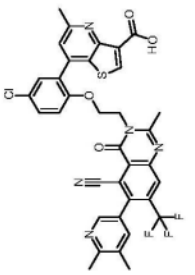
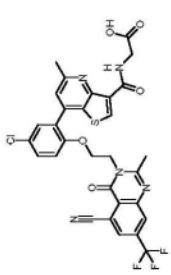
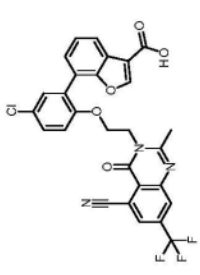
[0918]

364		MS (ESI) m/z 613.1 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.41 (s, 1H), 8.16 (s, 1H), 7.60 (dd, J = 8.9, 2.7 Hz, 1H), 7.43 (s, 1H), 7.41 (d, J = 2.7 Hz, 1H), 7.38 (d, J = 9.0 Hz, 1H), 4.44 (t, J = 5.0 Hz, 2H), 4.26 (t, J = 5.0 Hz, 2H), 2.68 (s, 3H), 2.69 – 2.63 (m, 3H), 1.93 (s, 3H)
375		MS (ESI) m/z 619.4 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.25 (s, 1H), 7.92 – 7.85 (m, 2H), 7.84 (t, J = 1.8 Hz, 1H), 7.54 (dt, J = 7.8, 1.6 Hz, 1H), 7.45 (d, J = 7.6 Hz, 1H), 7.43 – 7.37 (m, 3H), 7.29 (d, J = 2.6 Hz, 1H), 7.21 (d, J = 8.9 Hz, 1H), 4.40 – 4.33 (m, 4H), 2.52 (s, 3H), 2.24 (s, 3H)
373		MS (ESI) m/z 694.2 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 10.09 (s, 1H), 8.25 (d, J = 5.1 Hz, 1H), 7.98 (d, J = 5.3 Hz, 1H), 7.60 (dd, J = 8.9, 2.6 Hz, 1H), 7.44 (s, 1H), 7.42 (d, J = 2.6 Hz, 1H), 7.37 (d, J = 9.0 Hz, 1H), 5.95 (s, 1H), 4.41 (t, J = 5.4 Hz, 2H), 4.26 (t, J = 5.1 Hz, 2H), 4.13 (d, J = 17.4 Hz, 1H), 3.84 (d, J = 17.8 Hz, 1H), 3.02 – 2.88 (m, 5H), 2.73 – 2.66 (m, 5H), 1.87 (s, 3H)
376		MS (ESI) m/z 717.9 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.84 (d, J = 4.8 Hz, 1H), 8.22 (s, 1H), 7.98 (s, 1H), 7.61 (dd, J = 8.9, 2.7 Hz, 1H), 7.49 (d, J = 4.8 Hz, 1H), 7.43 (d, J = 2.6 Hz, 1H), 7.37 (d, J = 9.0 Hz, 1H), 6.38 (tt, J = 53.3, 3.0 Hz, 1H), 4.42 (t, J = 5.1 Hz, 2H), 4.31 – 4.25 (m, 6H), 3.87 (td, J = 16.3, 3.0 Hz, 2H), 3.41 (s, 2H), 3.24 (s, 1H), 1.81 (s, 3H)
374		MS (ESI) m/z 626.2 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 9.74 (s, 1H), 8.15 (s, 1H), 7.83 (dt, J = 7.7, 1.5 Hz, 1H), 7.80 (t, J = 1.8 Hz, 1H), 7.50 (dt, J = 7.7, 1.6 Hz, 1H), 7.45 – 7.38 (m, 2H), 7.28 (d, J = 2.7 Hz, 1H), 7.21 (d, J = 12.3 Hz, 2H), 3.54 (d, J = 11.7 Hz, 2H), 3.19 (d, J = 12.8 Hz, 2H), 3.12 – 2.99 (m, 2H), 2.89 (s, 3H), 2.21 (s, 3H)
377		MS (ESI) m/z 676.3 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.13 (s, 1H), 7.85 – 7.78 (m, 2H), 7.51 (dt, J = 7.7, 1.5 Hz, 1H), 7.44 – 7.37 (m, 2H), 7.28 (d, J = 2.7 Hz, 1H), 7.21 (d, J = 8.9 Hz, 1H), 6.38 (t, J = 54.0 Hz, 1H), 2.20 (s, 3H). 注意：一些脂族信号非常宽且无法积分

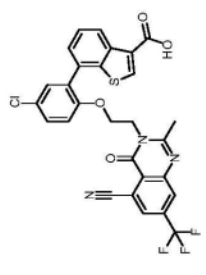
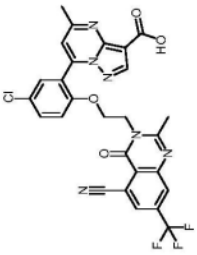
[0919]

378		MS (ESI) m/z 654.1 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.12 (s, 1H), 7.85 – 7.79 (m, 2H), 7.51 (dt, J = 7.7, 1.6 Hz, 1H), 7.44 – 7.37 (m, 2H), 7.27 (d, J = 2.6 Hz, 1H), 7.21 (d, J = 8.9 Hz, 1H), 4.34 (s, 4H), 3.06 – 2.76 (m, 2H), 2.20 (s, 3H), 2.06 (s, 3H) 注意：一些脂族信号非常宽且无法积分	381		MS (ESI) m/z 640.1 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.13 (s, 1H), 7.84 (dt, J = 7.7, 1.5 Hz, 1H), 7.80 (t, J = 1.8 Hz, 1H), 7.51 (dt, J = 7.7, 1.5 Hz, 1H), 7.45 – 7.38 (m, 2H), 7.27 (d, J = 2.6 Hz, 1H), 7.21 (d, J = 8.9 Hz, 1H), 4.35 (s, 4H), 2.92 (s, 3H), 2.19 (s, 3H). 注意：一些脂族信号非常宽且无法积分
379		MS (ESI) m/z 689.2 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.15 (s, 1H), 8.11 (dd, J = 5.6, 1.9 Hz, 1H), 7.87 – 7.79 (m, 3H), 7.51 (dt, J = 7.7, 1.6 Hz, 1H), 7.45 – 7.38 (m, 2H), 7.28 (d, J = 2.7 Hz, 1H), 7.21 (d, J = 8.9 Hz, 2H), 6.85 (t, J = 6.3 Hz, 1H), 4.35 (s, 4H), 2.20 (s, 3H). 注意：一些脂族信号非常宽且无法积分	382		MS (ESI) m/z 688.2 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.13 (s, 1H), 7.87 – 7.80 (m, 2H), 7.52 (dt, J = 7.7, 1.5 Hz, 1H), 7.45 – 7.37 (m, 2H), 7.30 – 7.19 (m, 4H), 7.05 – 6.99 (m, 2H), 6.83 (t, J = 7.3 Hz, 1H), 4.35 (s, 4H), 2.20 (s, 3H). 注意：一些脂族信号非常宽且无法积分
380		MS (ESI) m/z 689.2 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.51 (d, J = 2.9 Hz, 1H), 8.22 (d, J = 5.3 Hz, 1H), 8.15 (s, 1H), 8.08 (dd, J = 8.8, 2.8 Hz, 1H), 7.85 (dt, J = 7.7, 1.5 Hz, 1H), 7.83 – 7.78 (m, 2H), 7.51 (dt, J = 7.7, 1.6 Hz, 1H), 7.45 – 7.38 (m, 2H), 7.28 (d, J = 2.7 Hz, 1H), 7.21 (d, J = 8.9 Hz, 1H), 4.35 (s, 4H), 2.20 (s, 3H). 注意：一些脂族信号非常宽且无法积分	383		MS (ESI) m/z 711.0 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.26 (s, 1H), 7.92 (s, 1H), 7.60 (dd, J = 8.9, 2.7 Hz, 1H), 7.43 (s, 1H), 7.42 (d, J = 2.6 Hz, 1H), 7.36 (d, J = 9.0 Hz, 1H), 4.40 (t, J = 5.1 Hz, 2H), 4.24 (t, J = 5.0 Hz, 2H), 2.94 (s, 3H), 2.72 (s, 3H), 1.82 (s, 3H). 注意：一些脂族信号非常宽且无法积分

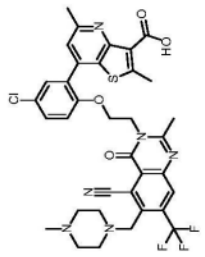
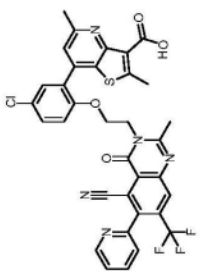
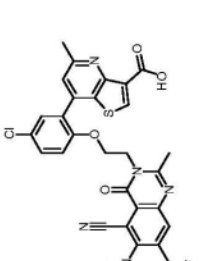
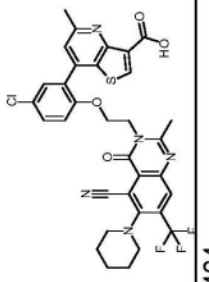
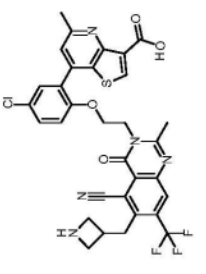
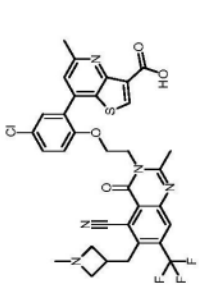
[0920]

386		MS (ESI) m/z 605.1 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.80 (d, J = 5.1 Hz, 2H), 8.29 (s, 1H), 7.86 (dt, J = 7.6, 1.6 Hz, 1H), 7.82 (t, J = 1.8 Hz, 1H), 7.55 – 7.50 (m, 3H), 7.47 – 7.39 (m, 2H), 7.28 (d, J = 2.7 Hz, 1H), 7.22 (d, J = 8.9 Hz, 1H), 4.43 – 4.31 (m, 4H), 2.24 (s, 3H)	
387		MS (ESI) m/z 689.2 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.24 (d, J = 7.4 Hz, 2H), 7.88 (s, 1H), 7.45 – 7.34 (m, 5H), 7.26 (d, J = 2.7 Hz, 1H), 7.19 (d, J = 8.9 Hz, 1H), 7.13 (d, J = 7.1 Hz, 2H), 4.31 (s, 4H), 3.85 – 3.49 (m, 8H), 2.20 (s, 3H)	
388		MS (ESI) m/z 605.2 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.75 (dd, J = 4.9, 1.6 Hz, 1H), 8.62 (s, 1H), 8.28 (s, 1H), 7.91 (dt, J = 7.9, 1.9 Hz, 1H), 7.86 (dt, J = 7.6, 1.5 Hz, 1H), 7.82 (t, J = 1.8 Hz, 1H), 7.62 (dd, J = 7.8, 4.8 Hz, 1H), 7.53 (dt, J = 7.7, 1.5 Hz, 1H), 7.48 – 7.38 (m, 2H), 7.28 (d, J = 2.6 Hz, 1H), 7.22 (d, J = 8.9 Hz, 1H), 4.42 – 4.32 (m, J = 2.5 Hz, 4H), 2.24 (s, 3H)	
389		MS (ESI) m/z 703.9 [M+1]+; ; 1H NMR (400 MHz, DMSO-d6) δ 8.58 (s, 1H), 8.27 (s, 1H), 8.06 (s, 1H), 8.00 (s, 1H), 7.60 (dd, J = 8.9, 2.7 Hz, 1H), 7.46 (s, 1H), 7.42 (d, J = 2.7 Hz, 1H), 7.37 (d, J = 9.0 Hz, 1H), 4.43 (t, J = 5.0 Hz, 2H), 4.28 (t, J = 4.9 Hz, 2H), 2.73 (s, 3H), 2.64 (s, 3H), 2.42 (s, 3H), 1.88 (s, 3H)
398		MS (ESI) m/z 656.0 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 10.16 (t, J = 5.4 Hz, 1H), 8.34 (d, J = 1.7 Hz, 1H), 8.14 (s, 1H), 8.05 (dd, J = 1.8, 0.8 Hz, 1H), 7.58 (dd, J = 8.9, 2.7 Hz, 1H), 7.39 (d, J = 2.7 Hz, 1H), 7.34 (d, J = 9.0 Hz, 1H), 7.33 (s, 1H), 4.40 (t, J = 5.0 Hz, 2H), 4.26 (t, J = 5.0 Hz, 2H), 4.21 (d, J = 5.4 Hz, 2H), 2.69 (s, 3H), 1.84 (s, 3H)
401		MS (ESI) m/z 568.2 [M+H]+; 1H NMR (400 MHz, CD3OD) δ 8.16-8.13 (m, 1H), 8.05-8.02 (m, 1H), 7.97 (s, 1H), 7.90 (dd, J = 7.9, 1.3 Hz, 1H), 7.41 (dd, J = 8.8, 2.7 Hz, 1H), 7.31 (t, J = 7.6 Hz, 1H), 7.23 (d, J = 2.7 Hz, 1H), 7.20 (dd, J = 7.4, 1.3 Hz, 1H), 7.19 (d, J = 8.9 Hz, 1H), 4.40-4.30 (m, 4H), 1.98 (s, 3H)

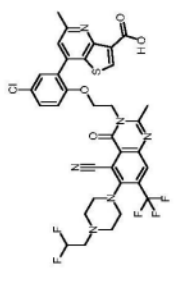
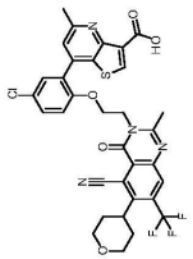
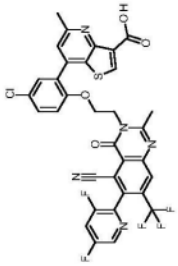
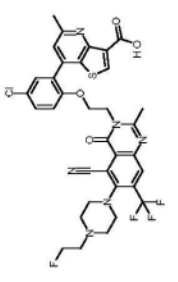
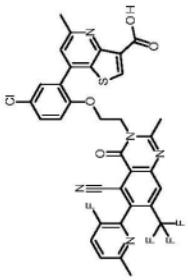
[0921]

402		414	
MS (ESI) m/z 584.3 [M+H]+; 1H NMR (400 MHz, 甲醇-d4) δ 8.52 (dd, J = 8.3, 1.1 Hz, 1H), 8.15 (dd, J = 1.8, 0.6 Hz, 1H), 8.01 (dd, J = 1.7, 0.8 Hz, 1H), 7.77 (s, 1H), 7.51 (dd, J = 8.2, 7.2 Hz, 1H), 7.45 (dd, J = 8.9, 2.7 Hz, 1H), 7.30 – 7.25 (m, 1H), 7.22 (s, 1H), 7.21 – 7.16 (m, 1H), 4.40 (t, J = 4.8 Hz, 2H), 4.31 (t, J = 4.8 Hz, 2H), 1.82 (s, 3H)		MS (ESI) m/z 583.1 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.38 (d, J = 1.8 Hz, 1H), 8.10 (br, 1H), 7.97 (s, 1H), 7.62 (dd, J = 8.9, 2.7 Hz, 1H), 7.53 (d, J = 2.7 Hz, 1H), 7.32 (d, J = 9.0 Hz, 1H), 7.15 (s, 1H), 4.37 (t, J = 4.9 Hz, 2H), 4.25 (t, J = 4.9 Hz, 2H), 2.59 (s, 3H), 1.85 (s, 3H)	
410		415	
MS (ESI) m/z 543.2 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.37 (d, J = 1.7 Hz, 1H), 8.17 (bs, 1H), 7.77 (bd, J = 1.6 Hz, 1H), 7.48 (bd, J = 1.4 Hz, 1H), 7.47 (dd, J = 8.9, 2.7 Hz, 1H), 7.36 (d, J = 2.7 Hz, 1H), 7.25 (d, J = 8.9 Hz, 1H), 4.39 (bs, 4H), 2.51 (s, 3H), 2.24 (s, 3H)		MS (ESI) m/z 599.0 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.83 (bs, 1H), 8.24 (s, 1H), 7.95 (s, 1H), 7.61 (d, J = 8.8 Hz, 1H), 7.50 (bs, 1H), 7.42 (bs, 1H), 7.36 (d, J = 7.8 Hz), 4.40 (bs, 2H), 4.25 (bs, 2H), 2.72 (s, 3H), 1.76 (s, 3H)	
411		416	
MS (ESI) m/z 557.6 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.40 (d, J = 1.7 Hz, 1H), 8.20 (d, J = 1.7 Hz, 1H), 7.49 (dd, J = 8.9, 2.7 Hz, 1H), 7.46-7.40 (br, 2H), 7.37 (d, J = 2.7 Hz, 1H), 7.26 (d, J = 8.9 Hz, 1H), 4.49-4.35 (m, 4H), 3.86 (s, 2H), 2.53 (s, 3H), 2.31 (s, 3H)		MS (ESI) m/z 599.0 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.81 (d, J = 4.6 Hz, 1H), 8.42 (s, 1H), 8.17 (s, 1H), 7.60 (dd, J = 9.4, 2.6 Hz, 1H), 7.49 (d, J = 4.8 Hz, 1H), 7.42 (d, J = 2.7 Hz, 1H), 7.37 (d, J = 9.0 Hz, 1H), 4.44 (t, J = 4.8 Hz, 2H), 4.26 (t, J = 4.8 Hz, 2H), 2.67 (s, 3H), 1.84 (s, 3H)	

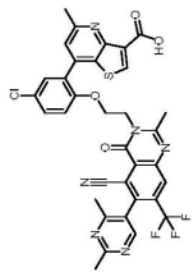
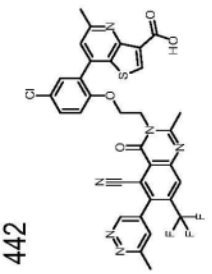
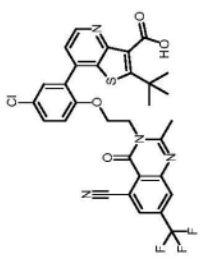
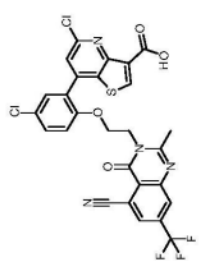
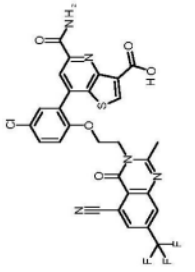
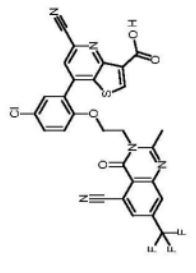
[0922]

417		MS (ESI) m/z 725.2 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 7.94 (s, 1H), 7.60 (dd, J = 8.8, 2.6 Hz, 1H), 7.44 (s, 1H), 7.42 (d, J = 2.7 Hz, 1H), 7.36 (d, J = 9.0 Hz, 1H), 4.42 (t, J = 5.0 Hz, 2H), 4.27 (t, J = 5.0 Hz, 2H), 3.94 (s, 2H), 3.43-3.29 (m, 4H), 2.99-2.82 (m, 4H), 2.78 (d, J = 4.3 Hz, 3H), 2.70 (s, 3H), 2.31 (s, 3H), 1.91 (s, 3H)
421		MS (ESI) m/z 690.7 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.75 (dt, J = 4.8, 1.4 Hz, 1H), 8.08 – 7.99 (m, 2H), 7.65 – 7.53 (m, 3H), 7.45 (s, 1H), 7.42 (d, J = 2.6 Hz, 1H), 7.36 (d, J = 9.0 Hz, 1H), 4.42 (t, J = 4.9 Hz, 2H), 4.28 (br, 2H), 2.72 (s, 3H), 2.48 (s, 3H), 1.94 (s, 3H)
422		MS (ESI) m/z 668.4 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.35 (s, 1H), 7.92 (s, 1H), 7.60 (dd, J = 8.9, 2.7 Hz, 1H), 7.43 (dd, J = 4.3, 1.8 Hz, 2H), 7.36 (d, J = 9.0 Hz, 1H), 4.40 (t, J = 5.0 Hz, 2H), 4.24 (t, J = 5.0 Hz, 2H), 3.37 – 3.28 (m, 4H), 2.70 (s, 3H), 2.10 – 1.99 (m, 4H), 1.82 (s, 3H)
423		MS (ESI) m/z 682.6 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.32 (s, 1H), 7.89 (s, 1H), 7.60 (dd, J = 8.9, 2.7 Hz, 1H), 7.44 (s, 1H), 7.42 (d, J = 2.6 Hz, 1H), 7.36 (d, J = 9.0 Hz, 1H), 5.04 (br, 6H), 4.39 (t, J = 5.0 Hz, 2H), 4.23 (t, J = 5.0 Hz, 2H), 3.21 (br, 4H), 2.71 (s, 3H), 1.80 (s, 3H)
424		MS (ESI) m/z 668.3 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.18 (s, 1H), 7.95 (s, 1H), 7.60 (dd, J = 8.9, 2.7 Hz, 1H), 7.43 (s, 1H), 7.42 (d, J = 2.7 Hz, 1H), 7.37 (d, J = 9.0 Hz, 1H), 4.41 (t, J = 5.0 Hz, 2H), 4.26 (t, J = 5.0 Hz, 2H), 4.11– 3.92 (m, 4H), 3.39 (br, 2H), 3.35-3.21 (m, 1H), 2.71 (s, 3H), 1.85 (s, 3H)
425		MS (ESI) m/z 682.5 [M+1]+; 1H NMR (400 MHz, CDCl3) δ 8.35 (s, 1H), 8.12 (s, 1H), 7.47 (dd, J = 8.9, 2.6 Hz, 1H), 7.26 (s, 1H), 7.18 (s, 1H), 7.03 (d, J = 8.9 Hz, 1H), 4.56 (t, J = 9.0 Hz, 2H), 4.40 (t, J = 4.8 Hz, 2H), 4.29 (t, J = 4.9 Hz, 2H), 3.84 (t, J = 9.6 Hz, 2H), 3.49 (d, J = 6.6 Hz, 2H), 3.45 – 3.29 (m, 1H), 2.89 (s, 3H), 2.80 (s, 3H), 1.89 (s, 3H)

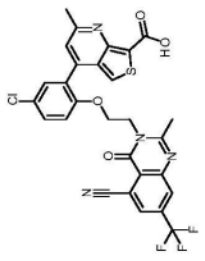
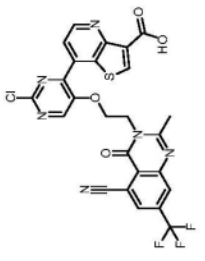
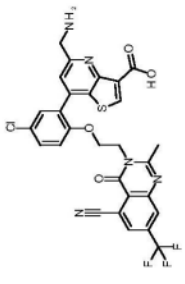
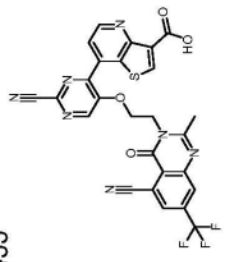
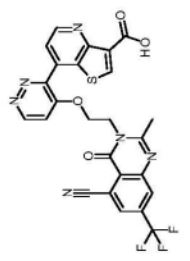
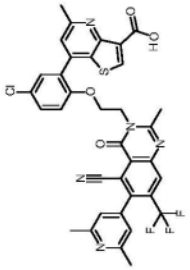
[0923]

428		MS (ESI) m/z 747.7 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.27 (s, 1H), 7.91 (s, 1H), 7.60 (dd, J = 8.9, 2.7 Hz, 1H), 7.43 (s, 1H), 7.42 (d, J = 2.7 Hz, 1H), 7.36 (d, J = 9.0 Hz, 1H), 6.38 (br, 1H), 4.40 (t, J = 5.0 Hz, 2H), 4.24 (t, J = 5.0 Hz, 3H), 4.06-2.83 (br, 10H), 2.71 (s, 3H), 1.83 (s, 3H)	431		MS (ESI) m/z 683.4 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.57 (s, 1H), 8.50 (s, 1H), 7.59 (dd, J = 8.9, 2.7 Hz, 1H), 7.44 (d, J = 2.6 Hz, 1H), 7.40 (s, 1H), 7.37 (d, J = 9.0 Hz, 1H), 4.35 (t, J = 5.1 Hz, 2H), 4.26 (t, J = 5.1 Hz, 2H), 3.98 (dd, J = 11.3, 4.0 Hz, 2H), 3.43 (t, J = 11.3 Hz, 2H), 3.22 (m, 1H), 2.72 (s, 3H), 2.08 (s, 3H), 2.03 – 1.88 (m, 2H), 1.59 (d, J = 12.6 Hz, 2H)
429		MS (ESI) m/z 681.7 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.31 (s, 1H), 7.96 (s, 1H), 7.60 (dd, J = 8.9, 2.7 Hz, 1H), 7.43 (dd, J = 7.3, 2.1 Hz, 2H), 7.36 (d, J = 9.0 Hz, 1H), 5.92 (s, 1H), 4.41 (t, J = 5.0 Hz, 2H), 4.29 – 4.15 (m, 4H), 3.86 (m, 4H), 2.71 (s, 3H), 1.85 (s, 3H)	433		MS (ESI) m/z 712.4 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.80 (d, J = 2.4 Hz, 1H), 8.42 (s, 1H), 8.33 (td, J = 9.1, 2.4 Hz, 1H), 8.17 (s, 1H), 7.59 (dd, J = 8.9, 2.7 Hz, 1H), 7.45 (d, J = 2.4 Hz, 1H), 7.44 (s, 1H), 7.35 (d, J = 9.0 Hz, 1H), 4.40 (t, J = 5.0 Hz, 2H), 4.27 (t, J = 5.1 Hz, 2H), 2.70 (s, 3H), 1.84 (s, 3H)
430		MS (ESI) m/z 729.5 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.25 (s, 1H), 7.93 (s, 1H), 7.61 (dd, J = 8.9, 2.7 Hz, 1H), 7.43 (s, 1H), 7.42 (d, J = 2.7 Hz, 1H), 7.37 (d, J = 9.0 Hz, 1H), 4.95 (t, J = 4.4 Hz, 1H), 4.82 (d, J = 4.6 Hz, 1H), 4.41 (t, J = 5.0 Hz, 2H), 4.25 (t, J = 5.0 Hz, 2H), 3.65-3.03 (br, 10H), 2.72 (s, 3H), 1.85 (s, 3H)	434		MS (ESI) m/z 708.6 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.46 (s, 1H), 8.15 (s, 1H), 7.89 (t, J = 8.9 Hz, 1H), 7.62 – 7.53 (m, 2H), 7.45 (s, 1H), 7.44 (d, J = 2.6, 0.9 Hz, 1H), 7.35 (d, J = 9.0 Hz, 1H), 4.40 (t, J = 5.0 Hz, 2H), 4.28 (d, J = 5.0 Hz, 2H), 2.71 (s, 3H), 2.52 (s, 3H), 1.82 (s, 3H)

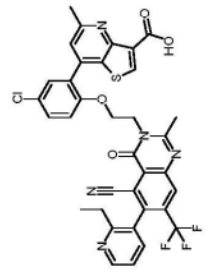
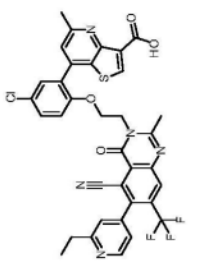
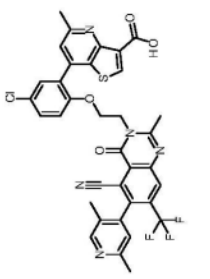
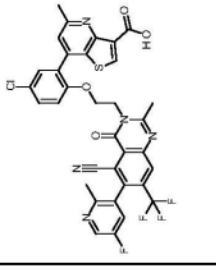
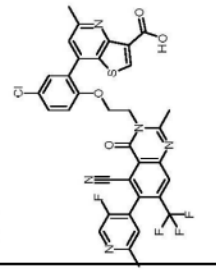
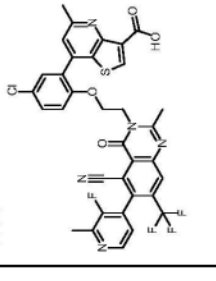
[0924]

437		MS (ESI) m/z 705.0 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.67 (s, 1H), 8.27 (s, 1H), 8.10 (s, 1H), 7.60 (dd, J = 8.9, 2.7 Hz, 1H), 7.46 (s, 1H), 7.43 (d, J = 2.7 Hz, 1H), 7.37 (d, J = 9.0 Hz, 1H), 4.43 (t, J = 5.1 Hz, 2H), 4.28 (tt, J = 9.5, 5.0 Hz, 2H), 2.74 (s, 3H), 2.71 (s, 3H), 2.23 (s, 3H), 1.85 (s, 3H)	
442		MS (ESI) m/z 691.3 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 9.27 (d, J = 2.1 Hz, 1H), 8.26 (s, 1H), 8.08 (s, 1H), 7.85 (d, J = 2.1 Hz, 1H), 7.60 (dd, J = 8.9, 2.6 Hz, 1H), 7.45 (s, 1H), 7.42 (d, J = 2.7 Hz, 1H), 7.37 (d, J = 9.0 Hz, 1H), 4.43 (t, J = 5.0 Hz, 2H), 4.29 (t, J = 5.0 Hz, 2H), 2.77 (s, 3H), 2.73 (s, 3H), 1.89 (s, 3H)	
443		MS (ESI) m/z 604.2 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.58 (d, J= 4.8 Hz, 1H), 8.36 – 8.32 (m, 1H), 8.15 – 8.11 (m, 1H), 7.52 (dd, J= 8.9, 2.7 Hz, 1H), 7.38 (d, J = 2.7 Hz, 1H), 7.29 (d, J = 9.0 Hz, 1H), 7.23 (d, J = 4.8 Hz, 1H), 4.36 (t, J= 5.0 Hz, 2H), 4.25 (d, J= 5.0 Hz, 2H), 1.88 (s, 3H), 1.33 (s, 9H)	
444		MS (ESI) m/z 619.2 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.34 (d, J = 1.9 Hz, 1H), 8.22 (s, 1H), 7.97 (dd, J = 1.9, 0.8 Hz, 1H), 7.56 (dd, J = 8.9, 2.7 Hz, 1H), 7.48 (s, 1H), 7.42 (d, J = 2.7 Hz, 1H), 7.31 (d, J = 9.0 Hz, 1H), 4.37 (t, J = 5.0 Hz, 2H), 4.23 (t, J = 5.0 Hz, 2H), 1.79 (s, 3H)	
445		MS (ESI) m/z 628.7 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.32 (d, J = 1.8 Hz, 1H), 8.25 (s, 1H), 8.01 (d, J = 3.1 Hz, 1H), 7.94 (dd, J = 1.8, 0.9 Hz, 1H), 7.89 (s, 2H), 7.57 (dd, J = 8.9, 2.7 Hz, 1H), 7.43 (d, J = 2.6 Hz, 1H), 7.32 (d, J = 9.0 Hz, 1H), 4.37 (t, J = 5.0 Hz, 2H), 4.20 (t, J = 5.0 Hz, 2H), 1.65 (s, 3H)	
446		MS (ESI) m/z 610.7 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.41 (d, J = 1.1 Hz, 1H), 8.35 (d, J = 1.7 Hz, 1H), 8.01 – 7.97 (m, 2H), 7.58 (ddd, J = 9.1, 2.7, 1.0 Hz, 1H), 7.44 (dd, J = 2.6, 1.0 Hz, 1H), 7.33 (d, J = 9.0 Hz, 1H), 4.38 (t, J = 5.0 Hz, 2H), 4.23 (t, J = 5.0 Hz, 2H), 1.71 (s, 3H)	

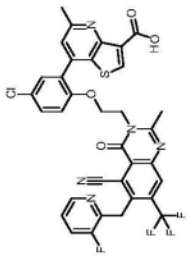
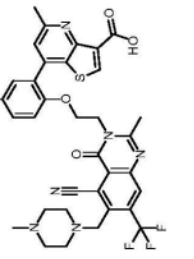
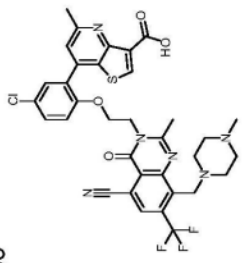
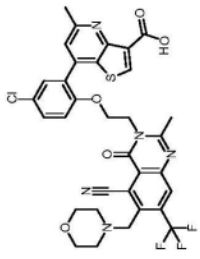
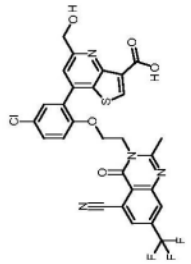
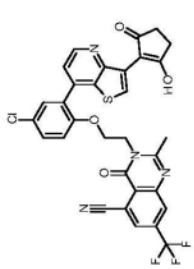
[0925]

447		MS (ESI) m/z 599.14 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.37 – 8.31 (m, 1H), 7.97 (d, J = 1.3 Hz, 1H), 7.95 (dt, J = 1.8, 0.8 Hz, 1H), 7.55 (dd, J = 8.9, 2.7 Hz, 1H), 7.35 – 7.28 (m, 2H), 7.17 (d, J = 0.9 Hz, 1H), 4.36 (t, J = 5.0 Hz, 2H), 4.20 (t, J = 5.0 Hz, 2H), 2.65 (d, J= 0.7 Hz, 3H), 1.86 (s, 3H)	454		MS (ESI) m/z 587.2 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.99 (s, 1H), 8.96 (s, 1H), 8.93 (d, J = 5.0 Hz, 1H), 8.39 – 8.37 (m, 1H), 8.26 (d, J = 5.0 Hz, 1H), 8.24 (dd, J = 1.7, 0.8 Hz, 1H), 4.77 (t, J = 5.1 Hz, 2H), 4.62 (t, J = 5.1 Hz, 2H), 2.53 (s, 3H)
452		MS (ESI) m/z 614.5 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 12.86 (s, 1H), 8.50 – 8.37 (m, 4H), 8.30 (s, 1H), 8.01 (s, 1H), 7.62 (dd, J = 8.9, 2.7 Hz, 1H), 7.57 (s, 1H), 7.40 – 7.35 (m, 2H), 4.44 (q, J = 6.1 Hz, 4H), 4.27 (t, J = 5.2 Hz, 2H), 1.77 (s, 3H)	455		MS (ESI) m/z 578.3 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 9.15 (s, 1H), 8.92 (s, 2H), 8.35 (s, 1H), 8.20 (d, J = 4.9 Hz, 2H), 4.83 (s, 2H), 4.60 (s, 2H), 2.56 (2, 3H)
453		MS (ESI) m/z 552.9 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 9.18 (dd, J = 6.2, 0.7 Hz, 1H), 8.89 – 8.84 (m, 2H), 8.37 – 8.33 (m, 1H), 8.20 (dt, J = 1.8, 0.8 Hz, 1H), 8.07 – 8.03 (m, 1H), 7.66 (dd, J = 6.2, 0.8 Hz, 1H), 4.63 (t, J = 5.0 Hz, 2H), 4.53 (t, J = 5.0 Hz, 2H), 3.88 (s, 1H), 2.33 (s, 3H)	465		LCMS: 704.5 [M+H]+; 1H NMR (400 MHz, DMSO-d6) δ 8.25 (s, 1H), 8.05 (s, 1H), 7.61 (dd, J = 8.9, 2.7 Hz, 1H), 7.50 – 7.33 (m, 4H), 4.42 (t, J = 5.0 Hz, 2H), 4.28 (t, J = 5.0 Hz, 2H), 2.73 (s, 3H), 2.62 (s, 6H), 1.87 (s, 3H)

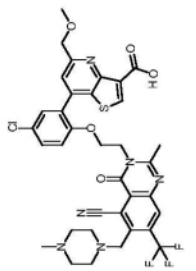
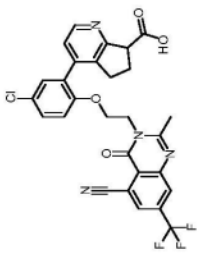
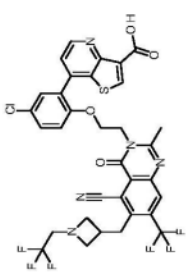
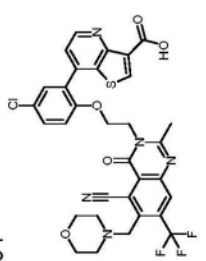
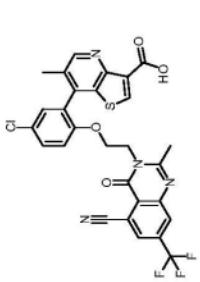
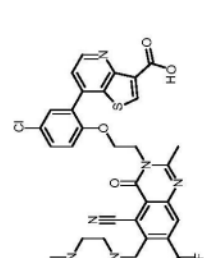
[0926]

466		LCMS: 704.5 [M+H]+; 1H NMR (400 MHz, DMSO-d6) δ 8.74 – 8.65 (m, 1H), 8.32 (s, 1H), 8.09 (s, 1H), 7.80 (d, J = 7.8 Hz, 1H), 7.60 (dd, J = 8.9, 2.7 Hz, 1H), 7.49 – 7.41 (m, 3H), 7.37 (d, J = 9.0 Hz, 1H), 4.52 – 4.10 (m, 2H), 2.73 (s, 3H), 2.45 – 2.35 (m, 2H), 1.85 (s, 3H), 1.15 (t, J = 7.5 Hz, 3H)	
468		LCMS: 704.5 [M+H]+; 1H NMR (400 MHz, DMSO-d6) δ 8.75 (d, J = 5.2 Hz, 1H), 8.29 (s, 1H), 8.06 (s, 1H), 7.60 (dd, J = 8.9, 2.7 Hz, 1H), 7.57 (s, 1H), 7.52 – 7.47 (m, 1H), 7.45 (s, 1H), 7.42 (d, J = 2.6 Hz, 1H), 7.37 (d, J = 9.0 Hz, 1H), 4.42 (t, J = 5.1 Hz, 2H), 4.29 (d, J = 5.2 Hz, 2H), 2.91 (q, J = 7.5 Hz, 2H), 2.73 (s, 3H), 1.87 (s, 3H), 1.29 (t, J = 7.6 Hz, 3H)	
469		LCMS: 704.5 [M+H]+; 1H NMR (400 MHz, DMSO-d6) δ 8.72 (s, 1H), 8.25 (s, 1H), 8.11 (s, 1H), 7.63 – 7.58 (m, 2H), 7.47 (s, 1H), 7.44 (d, J = 2.6 Hz, 1H), 7.37 (d, J = 9.0 Hz, 1H), 4.43 (h, J = 5.9 Hz, 2H), 4.27 (dd, J = 11.3, 5.7 Hz, 1H), 2.74 (s, 3H), 2.64 (s, 3H), 2.08 (s, 3H), 1.84 (s, 3H)	
470		LCMS: 708.5 [M+H]+; 1H NMR (400 MHz, DMSO-d6) δ 8.70 – 8.65 (m, 1H), 8.27 (d, J = 0.9 Hz, 1H), 8.10 (s, 1H), 7.91 (dd, J = 9.0, 2.9 Hz, 1H), 7.60 (ddd, J = 8.9, 2.6, 1.0 Hz, 1H), 7.47 – 7.41 (m, 2H), 7.37 (d, J = 8.9 Hz, 1H), 4.43 (d, J = 4.8 Hz, 2H), 4.37 – 4.17 (m, 2H), 2.74 (d, J = 0.9 Hz, 3H), 2.21 (s, 3H), 1.86 (s, 3H)	
471		LCMS: 708.6 [M+H]+; 1H NMR (400 MHz, DMSO-d6); 1H NMR (400 MHz, DMSO-d6) δ 8.69 (d, J = 0.8 Hz, 1H), 8.30 (s, 1H), 8.11 (s, 1H), 7.61 – 7.57 (m, 1H), 7.55 (d, J = 5.6 Hz, 1H), 7.45 – 7.42 (m, 2H), 7.36 (d, J = 9.0 Hz, 1H), 4.54 – 4.10 (m, 1H), 2.72 (s, 3H), 2.58 (d, J = 1.0 Hz, 3H), 1.86 (s, 3H)	
472		LCMS: 708.6 [M+H]+; 1H NMR (400 MHz, DMSO-d6) δ 8.54 (d, J = 4.8 Hz, 1H), 8.33 (s, 1H), 8.12 (s, 1H), 7.60 (dd, J = 8.9, 2.7 Hz, 1H), 7.51 (t, J = 5.1 Hz, 1H), 7.46 – 7.41 (m, 2H), 7.36 (d, J = 9.0 Hz, 1H), 4.57 – 4.15 (m, 2H), 2.72 (s, 3H), 2.56 (d, J = 3.0 Hz, 3H), 1.87 (s, 3H)	

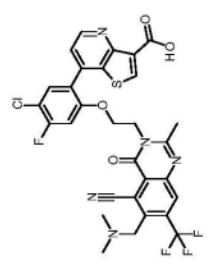
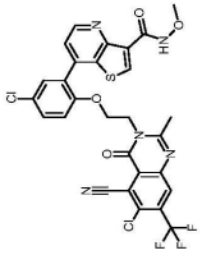
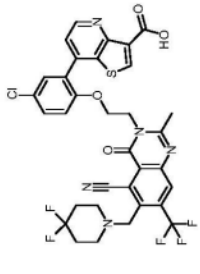
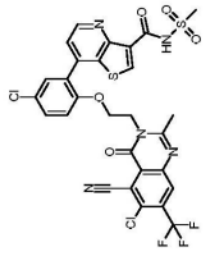
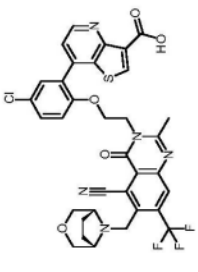
[0927]

473		LCMS: 708.6 [M+H]+; 1H NMR (400 MHz, DMSO-d6) δ 8.27 (s, 1H), 8.17 (dt, J = 4.7, 1.4 Hz, 1H), 7.99 (s, 1H), 7.77 (ddd, J = 9.8, 8.3, 1.3 Hz, 1H), 7.59 (dd, J = 8.9, 2.7 Hz, 1H), 7.45 – 7.40 (m, 2H), 7.36 (dt, J = 8.4, 1.9 Hz, 2H), 4.66 (s, 2H), 4.42 (t, J = 5.0 Hz, 2H), 4.26 (t, J = 5.1 Hz, 2H), 2.70 (s, 3H), 1.86 (s, 3H)	485		MS (ESI) m/z 711.6 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 9.48 (s, 1H), 8.22 (s, 1H), 7.96 (s, 1H), 7.60 (dd, J = 8.9, 2.7 Hz, 1H), 7.43 (d, J = 2.5 Hz, 2H), 7.36 (d, J = 9.0 Hz, 1H), 4.41 (t, J = 5.1 Hz, 2H), 4.26 (d, J = 5.0 Hz, 2H), 3.95 (s, 2H), 3.38 (d, J = 11.4 Hz, 2H), 2.92 (d, J = 11.8 Hz, 4H), 2.78 (d, J = 4.5 Hz, 3H), 2.70 (s, 3H), 1.85 (s, 3H)
483		MS (ESI) m/z 711.6 [M+1]+; ; 1H NMR (400 MHz, DMSO-d6) δ 9.36 (s, 1H), 8.38 (s, 1H), 8.27 (s, 1H), 7.60 (dd, J = 8.9, 2.7 Hz, 1H), 7.46 – 7.34 (m, 3H), 4.43 (d, J = 5.3 Hz, 2H), 4.27 (s, 2H), 4.14 (s, 2H), 3.30 (d, J = 11.8 Hz, 2H), 2.77 (d, J = 20.8 Hz, 7H), 2.68 (s, 3H), 1.88 (s, 3H)	486		MS (ESI) m/z 711.6 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.27 (s, 1H), 7.96 (s, 1H), 7.60 (dd, J = 8.9, 2.7 Hz, 1H), 7.43 (d, J = 2.5 Hz, 2H), 7.36 (d, J = 9.0 Hz, 1H), 4.41 (t, J = 5.0 Hz, 2H), 4.25 (t, J = 5.0 Hz, 2H), 3.89 (s, 2H), 3.53 (s, 4H), 2.70 (s, 3H), 1.83 (s, 3H)
484		MS (ESI) m/z 615.6 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.37 (d, J = 1.7 Hz, 1H), 8.24 (s, 1H), 7.98 – 7.94 (m, 1H), 7.60 (dd, J = 8.9, 2.7 Hz, 1H), 7.53 (s, 1H), 7.41 (d, J = 2.6 Hz, 1H), 7.36 (d, J = 9.0 Hz, 1H), 4.81 (s, 2H), 4.41 (t, J = 5.1 Hz, 2H), 4.25 (t, J = 5.1 Hz, 2H), 1.77 (s, 3H)	487		MS (ESI) m/z 791.5 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.75 (d, J = 5.0 Hz, 1H), 8.50 (s, 1H), 8.33 (d, J = 1.8 Hz, 1H), 7.96 – 7.93 (m, 1H), 7.60 (dd, J = 8.9, 2.7 Hz, 1H), 7.49 (d, J = 5.0 Hz, 1H), 7.44 (d, J = 2.6 Hz, 1H), 7.36 (d, J = 9.0 Hz, 1H), 4.42 (t, J = 5.0 Hz, 2H), 4.26 (t, J = 5.1 Hz, 2H), 2.61 (s, 4H), 1.86 (s, 3H)

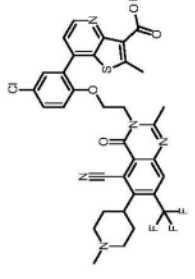
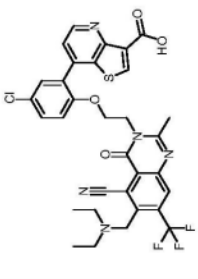
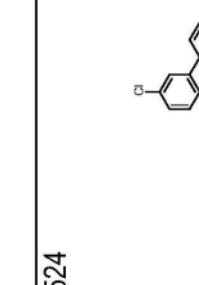
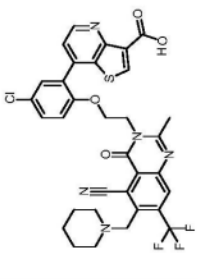
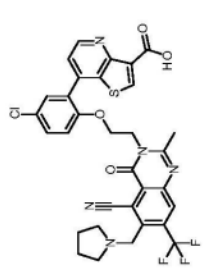
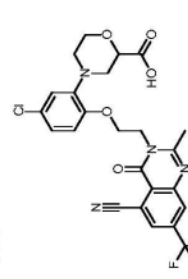
[0928]

489		MS (ESI) m/z 741.8 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 9.47 (s, 1H), 8.21 (s, 1H), 7.97 (s, 1H), 7.60 (dd, J = 8.9, 2.7 Hz, 1H), 7.48 – 7.41 (m, 2H), 7.36 (d, J = 9.0 Hz, 1H), 4.74 (s, 2H), 4.41 (t, J = 5.0 Hz, 2H), 4.25 (t, J = 5.0 Hz, 2H), 3.94 (s, 2H), 2.92 (d, J = 12.0 Hz, 5H), 2.78 (d, J = 4.2 Hz, 3H), 1.77 (s, 3H)	496		MS (ESI) m/z 569.23 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.39 (s, 1H), 8.34 (d, J = 4.28 Hz, 1H), 8.23 (s, 1H), 7.44 (dd, J = 8.80, 2.40 Hz, 1H), 7.25 (d, J = 2.16 Hz, 1H), 7.21 (d, J = 8.84 Hz, 1H), 7.10 (s, 1H), 4.41-4.29 (m, 4H), 4.08 (t, J= 8.48, 1H), 2.12-2.10 (m, 4H), 2.03 (s, 3H)
494		MS (ESI) m/z 735.9 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.85 (d, J = 4.8 Hz, 1H), 8.23 (s, 1H), 7.98 (s, 1H), 7.61 (dd, J = 8.9, 2.7 Hz, 1H), 7.51 (d, J = 4.8 Hz, 1H), 7.43 (d, J = 2.6 Hz, 1H), 7.37 (d, J = 9.0 Hz, 1H), 4.42 (t, J = 4.9 Hz, 2H), 4.26 (t, J = 5.0 Hz, 2H), 4.08 – 3.82 (m, 4H), 3.38 (d, J = 6.2 Hz, 2H), 3.16 – 3.02 (m, 1H), 1.79 (s, 3H)	501		MS (ESI) m/z 684.11 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.84 (d, J= 4.8 Hz, 1H), 8.28(s, 1H), 7.99 (s, 1H), 7.61 (dd, J= 8.92, 2.6 Hz, 1H), 7.51 (d, J= 4.76 Hz, 1H), 7.44 (d, J= 2.6 Hz, 1H), 7.37 (d, J= 9.00 Hz, 1H), 4.42 (t, J= 5.76 Hz, 2H), 4.26 (t, J= 4.36 Hz, 2H), 3.95 (bs, 2H), 3.55 (bs, 4H), 2.56 (bs, 4H), 1.76 (s, 3H)
495		MS (ESI) m/z: 599.01; 1H-NMR (400 MHz, DMSO-d6) δ 8.70 (s, 1H), 8.36 (s, 1H), 8.22 (s, 1H), 8.01 (s, 1H), 7.59-7.56 (m, 1H), 7.37-7.35 (m, 2H), 4.48-4.44 (m, 1H), 4.27-4.20 (m, 3H), 2.08 (s, 3H), 1.17 (s, 3H)	502		MS (ESI) m/z 697.15 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.84 (d, J= 4.76, 1H), 8.23 (s, 1H), 7.98 (s, 1H), 7.61 (dd, J= 8.84, 2.56 Hz, 1H), 7.48 (d, J= 4.76 Hz, 1H), 7.44 (d, J= 2.6 Hz, 1H), 7.37 (d, J= 9.00 Hz, 1H), 4.42 (t, J= 3.8 Hz, 2H), 4.26 (t, J= 5.8, 2H), 3.94 (bs, 2H), 3.40 (d, J=10.68 Hz, 2H), 2.94 (d, J =10.68 Hz, 4H), 2.79 (d, J=3.4 Hz, 3H), 2.50 (m, 2H), 1.77 (s, 3H)

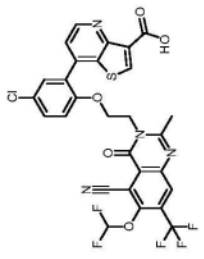
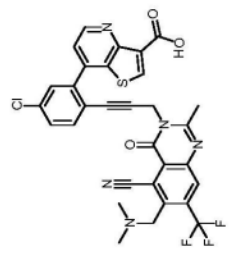
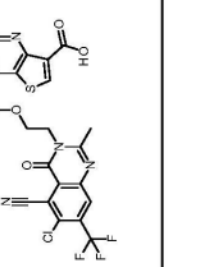
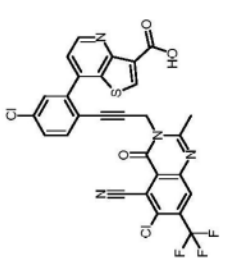
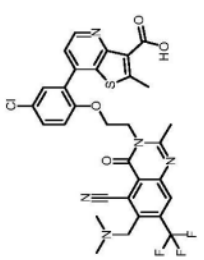
[0929]

503		MS (ESI) m/z 660.1 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.86 (d, J = 4.68 Hz, 1H), 8.11 (s, 1H), 8.07 (s,1H), 7.63 (d, J = 8.36, 1H), 7.57 (d, J = 11.32 Hz, 1H), 7.49 (d, J = 4.72 Hz, 1H), 4.63 (bs, 2H), 4.46 (t, J = 4.64 Hz, 2H), 4.28 (t, J = 4.72 Hz, 2H), 2.89 (bs, 6H), 1.75 (s, 3H)	521		MS (ESI) m/z 648.07 [M+1]+. 1H NMR (400 MHz, DMSO-d6) δ 12.10 (s, 1H), 8.84 (d, J = 4.80 Hz, 1H), 8.12 (s, 1H), 8.09 (S, 1H), 7.59 (dd, J = 8.88, 2.80 1H), 7.46 (d, J = 4.76 Hz, 1H), 7.41 (d, J = 2.60 Hz,1H), 7.34 (d, J = 9.04 Hz, 1H), 4.42-4.38 (m, 2H), 4.28-4.21 (m, 2H), 3.88 (s, 3H), 1.66 (s, 3H)
505		MS (ESI) m/z 637.1 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.86 (d, J = 4.76 Hz, 1H), 8.25 (s, 1H), 8.08 (s, 1H), 7.63 (d, J = 8.32 Hz, 1H), 7.55 (d, J = 11.2 Hz, 1H), 7.50 (d, J = 4.68 Hz, 1H), 4.43 (t, J = 5.00 Hz, 2H), 4.26 (t, J = 4.44 Hz, 2H), 1.68 (s, 3H)	522		MS (ESI) m/z 718.18 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.84 (d, J = 4.16 Hz, 1H), 8.27 (s, 1H), 8.98 (s, 1H), 7.59 (d, J = 8.52 Hz, 1H), 7.50 (d, J = 4.4 Hz, 1H), 7.43 (s, 1H), 7.36 (d, J = 9.08 Hz, 1H), 4.41 (bs, 2H), 4.24 (bs, 2H), 3.94 (s, 2H), 2.61 (s, 4H), 1.92 (s, 4H), 1.76 (s, 3H)
519		MS (ESI) m/z 696.3 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 12.69 (s, 1H), 8.92 (d, J = 4.44 Hz, 1H), 8.34 (s, 1H), 8.09 (s, 1H), 7.65-7.54 (m, 2H), 7.45 (d, J = 1.84 Hz, 1H), 7.36 (d, J = 8.84 Hz, 1H), 4.42 (t, J = 4.68 Hz, 2H), 4.24 (t, J = 5.24 Hz, 2H), 3.56 (s, 3H), 1.65 (s, 3H)	523		MS (ESI) m/z 710.21 [M+1]+; 1H-NMR (400 MHz, DMSO-d6) δ 13.23 (bs, 1H), 8.82 (d, J = 3.2 Hz, 1H), 8.27 (s, 1H), 7.99 (s, 1H), 7.59 (d, J = 8.88 Hz, 1H), 7.50-7.42 (m, 1H), 7.43 (s, 1H) 7.35 (d, J = 8.24 Hz, 1H), 4.41 (s, 2H), 4.24 (s, 2H), 3.84 (s, 1H), 3.50-3.30 (m, 4H), 3.07 (s, 2H), 2.02 (s, 2H), 1.85-1.70 (m, 5H)

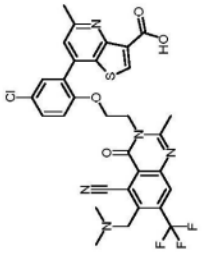
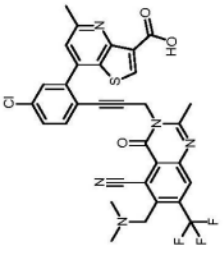
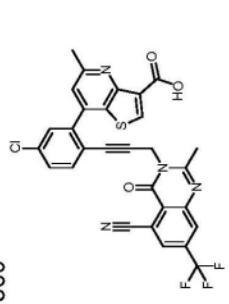
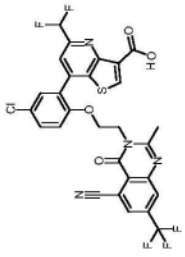
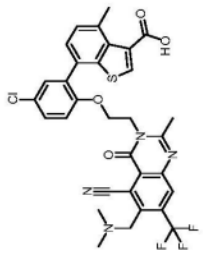
[0930]

524		MS (ESI) m/z 616.13 [M+1]+; 1H-NMR (400 MHz, DMSO-d6) δ 13.27 (bs, 1H), 8.82 (s, J = 4.72 Hz, 1H), 8.17 (s, 1H), 8.00 (s, 1H), 7.58 (dd, J = 8.80, 2.44 Hz, 1H), 7.46 (d, J = 4.76 Hz, 1H), 7.40 (d, J = 2.52 Hz, 1H), 7.35 (d, J = 8.8 Hz, 1H), 5.52 (s, 2H), 4.40 (t, J = 4.28 Hz, 2H), 4.23 (t, J = 5.2 Hz, 2H), 1.73 (s, 3H)	527		MS (ESI) m/z 670.40 [M+1]+; 1H-NMR (400 MHz CD3OD) δ 8.78 (d, J = 4.88 Hz, 1H), 8.27 (s, 1H), 8.20 (s, 1H), 7.57 (dd, J = 2.56, 8.92 Hz, 1H), 7.49 (d, J = 4.92 Hz, 1H), 7.36 (d, J = 2.48 Hz, 1H), 7.32 (d, J = 8.84 Hz, 1H), 4.98 (s, 2H), 4.46 (t, J = 4.76, 2H), 4.37 (t, J = 4.5 Hz, 2H),.3.52-3.47 (m, 4H), 2.03 (s, 3H), 1.48-1.29 (m, 6H)
525		MS (ESI) m/z 692.27 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.83 (s, 1H), 8.23 (s, 1H), 7.97 (s, 1H), 7.65-7.26 (m, 4H), 6.16 (t, J = 56.26 Hz, 1H), 4.40 (s, 2H), 4.24 (s, 2H), 4.04 (s, 2H), 2.94 (t, J = 14.2 Hz, 2H), 2.28 (s, 3H), 1.75 (s, 3H)	528		MS (ESI) m/z 682.19 [M+1]+; 1H NMR (400 MHz, DMSO-d6 + D2O) δ 8.83 (d, J= 4.80 Hz, 1H), 8.21 (s, 1H), 8.06 (s, 1H), 7.61-7.57 (dd, J = 2.48, 8.80 Hz, 1H), 7.48 (d, J = 4.68 Hz, 1H), 7.44 (d, J = 2.48 Hz, 1H), 7.36 (d, J = 8.92 Hz, 1H), 4.58 (m, 2H), 4.40 (t, J = 6.36 Hz, 2H), 4.26 (t, J = 4.52 Hz, 2H)., 3.29 (m, 4H), 1.75 (m, 7H), 1.54 (m, 2H)
526		MS (ESI) m/z 668.20 [M+1]+; 1H-NMR (400 MHz, CD3OD) δ 8.80 (d ,J = 4.84 Hz, 1H), 8.27 (s, 1H), 8.19 (s, 1H), 7.57 (dd, J = 2.96, 9.76 Hz, 1H), 7.49 (d, J = 4.84 Hz, 1H), 7.36 (d, J = 2.36 Hz, 1H), 7.31 (d, J = 8.88 Hz, 1H), 4.98 (s, 2H), 4.46 (t, J = 2.36, 2H), 4.37 (t, J = 4.6 Hz, 2H),.3.74 (s, 4H), 2.20 (s, 3H), 2.03 (s, 3H)	535		MS (ESI) m/z 537.11 [M+1] +. 1H NMR (400 MHz, DMSO-d6) δ 12.77 (bs, 1H), 8.39 (s, 1H), 7.23 (s, 1H), 7.03 (d, J = 8.9 Hz), 6.92 (s, 1H), 4.51 (m, 2H), 4.38 (t, J = 4.8 Hz, 3H), 4.19-4.16 (m, 2H), 3.95 (d, J = 11.2 Hz, 1H), 3.63-3.59 (m, 1H), 3.27 (d, J = 9.6 Hz, 1H), 2.94-2.79 (m, 5H)

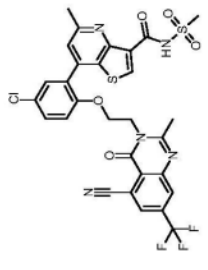
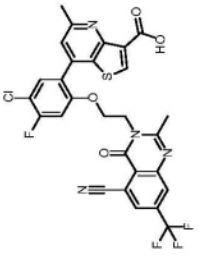
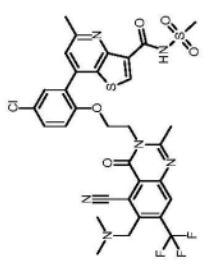
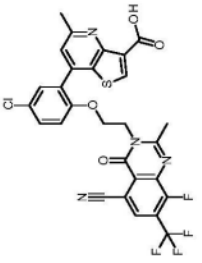
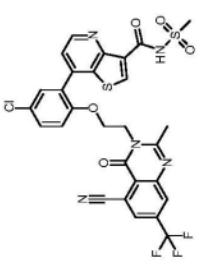
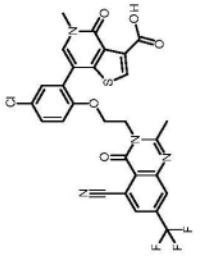
[0931]

549		MS (ESI) m/z 651.08 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.84 (d, J = 4.72 Hz, 1H), 8.22 (s, 1H), 8.07 (s, 1H), 7.61-7.23 (m, 5H), 4.41 (t, J=4.2 Hz, 2H), 4.26 (t, J=4.2 Hz, 2H), 1.72 (s, 3H)	
553		MS (ESI) m/z 636.0 [M+1]+;; 1H NMR (400 MHz, DMSO-d6) δ 8.74 (d, J = 4.7 Hz, 1H), 8.53 (s, 1H), 8.21 (s, 1H), 7.77 (d, J = 8.1 Hz, 1H), 7.7 (d, J = 2.0 Hz, 1H), 7.68 (s, 1H), 7.54 (d, J = 4.7 Hz, 1H), 4.91 (s, 2H), 4.63 (bs, 2H), 2.87 (bs, 6H), 2.11 (s, 3H)	555		MS (ESI) m/z 633. [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.78 (d, J = 4.88, 1H), 8.089 (s, 1H), 7.615 (dd, J=8.92, 8.96, 1H), 7.519 (d, J = 4.88 Hz, 1H), 7.414 (d, J= 2.6, 1H), 7.37 (d, J = 8.96 Hz, 1H), 4.43 (bs, 2H), 4.29 (bs, 2H), 2.41 (s, 3H), 1.89 (s, 3H)
554		MS (ESI) m/z 613.04 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.77 (d, J = 4.8 Hz, 1H), 8.55 (s, 1H), 8.22 (s, 1H), 7.76 (d, J = 8.2 Hz, 1H), 7.7 (d, J = 2.0 Hz, 1H), 7.67 (s, 1H), 7.55 (d, J = 4.7 Hz, 1H), 4.88 (s, 2H), 2.07 (s, 3H)	556		MS (ESI) m/z 656.21 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.79 (d, J=4.76, 1H), 8.088 (s,1H), 7.618 (dd, J=8.84, 8.72, 1H), 7.517 (d, J= 4.84 Hz, 1H), 7.44 (d, J= 2.16, 1H), 7.36 (d, J=8.88 Hz, 1H), 4.602 (bs, 2H), 4.419 (bs, 2H), 4.28 (bs, 2H), 2.84 (bs, 6H), 2.34 (s, 3H), 1.83 (s, 3H)
			558		MS (ESI) m/z 633.10 [M+1]+; 1H-NMR (400 MHz, DMSO-d6) δ 8.24 (s ,1H), 8.03 (s, 1H), 7.61-7.58 (dd, J = 2.52,J = 8.84 Hz, 1H), 7.44 (s, 1H),-7.41 (d, J = 2.52, 1H),7.37 (d, J= 8.92, 1H), 4.42 (t, J = 5.46 Hz, 2H), 4.27 (t, J = 4.32 Hz, 2H), 2.71 (s, 3H),1.79 (s, 3H)

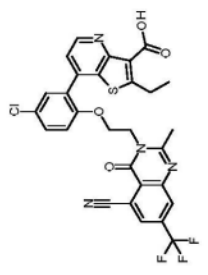
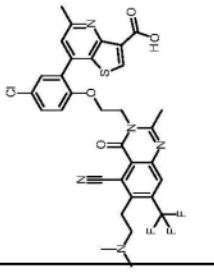
[0932]

559		MS (ESI) m/z 656.15 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.48 (s, 1H), 8.06 (bs, 1H), 8.03 (s, 1H), 7.62 (dd, J = 8.92 Hz, 2.52 Hz, 1 H), 7.45-7.34 (m, 2 H), 7.36 (d, J = 8.32 Hz, 1H), 4.75 (s, 2 H), 4.44 (t, J = 3.6 Hz, 2H), 4.29 (t, J = 5.6 Hz, 2 H), 2.99 (s, 6H), 2.72 (s, 3 H), 1.82 (s, 3 H)	562		MS (ESI) m/z 650.17 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.34 (bs, 1H), 8.73 (d, J = 4.7 Hz, 1H), 8.66 (s, 1H), 8.13 (d, J = 9.7 Hz, 1H), 7.76 (d, J = 9.0 Hz, 1H), 7.68 (m, 1H), 7.53 (d, J = 4.7 Hz, 1H), 7.37 (t, J = 53.7 Hz, 1H), 4.88 (s, 2H), 2.22 (s, 3H)
560		MS (ESI) m/z: 593 [M+1]+; 1H-NMR (400 MHz, DMSO-d6) δ 13.24 (s, 1H), 8.59 (s, 1H), 8.42 (s, 1H), 8.12 (s, 1H), 7.75 (d, J = 8.24 Hz, 1H), 7.68-7.64 (m, 2H), 7.46 (s, 1H), 4.87 (s, 2H), 2.59 (s, 3H), 2.14 (s, 3H)	563		MS (ESI) m/z 635.09 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 12.98 (bs, 1H), 8.37 (s, 1H), 8.28 (s, 1H), 8.00 (s, 1H), 7.67 (s, 1H), 7.60 (dd, J = 1.68, 8.56 Hz, 1H), 7.45 (bs, 1H), 7.35 (d, J = 8.88 Hz, 1H), 7.18 (t, J = 54.84 Hz, 1H), 4.39-4.35 (m, 2H), 4.23-4.20 (m, 2H), 1.67 (s, 3H)
561		MS (ESI) m/z 627.06 [M+1]+; 1H-NMR (400 MHz, DMSO-d6) 13.23 (bs, 1H), 8.54 (s, 1H), 8.20 (s, 1H), 7.75 (d, J = 8.32 Hz, 1H), 7.69 (dd, J = 8.24, 1.96 Hz, 1H), 7.64 (s, 1H), 7.47 (s, 1H), 4.87 (s, 2H). 2.64 (s, 3H), 2.14 (s 3H)	564		MS (ESI) m/z 655.21 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.06 (s, 1H), 9.45 (s, 1H), 8.18 (s, 1H), 7.50 (dd, J=2.52 Hz, J=9.12 Hz, 2H), 7.28-7.25 (m, 2H), 7.15 (d, J = 7.28 Hz, 1H), 4.75 (s, 2H), 4.36 (bs, 2H), 4.24 (bs, 2H), 2.98 (s, 6H), 2.68 (s, 3H), 1.72 (s, 3H)

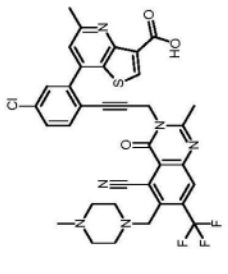
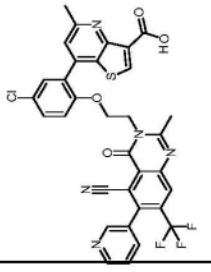
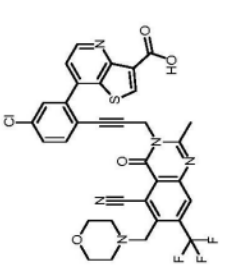
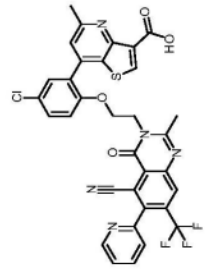
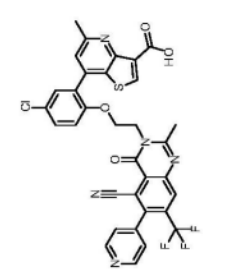
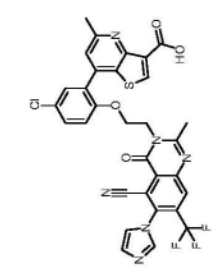
[0933]

565		MS (ESI) m/z 676.11 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.02 (bs, 1H), 8.38 (s, 1H), 8.35 (s, 1H), 7.60 (dd, J = 8.80, 2.40 Hz, 1H), 7.47 (s, 1H), 7.42 (d, J = 2.48 Hz, 1H), 7.35 (d, J = 8.16 Hz, 1H), 4.41 (t, J = 5.0 Hz, 2H), 4. 24 (t, J = 4.72 Hz, 2H), 3.56 (s, 3H), 2.68 (s, 3H), 1.78 (s, 3H)	571		MS (ESI) m/z 617.11 [M+1]+; 1H NMR (400 MHz, MeOD) δ 8.31 (s, 1H), 8.16 (s, 1H), 8.00 (s, 1H), 7.56 (s, 1H),7.51 (d, J = 8.08 Hz, 1H), 7.34 (d, J = 10.84 Hz, 1H), 4.50 (t, J = 4.80 Hz, 2H), 4.38 (t, J = 5.20 Hz, 2H), 2.96 (s, 3H), 2.03 (s, 3H)
568		MS (ESI) m/z 733.16 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.02 (s, 1H), 8.32 (s, 1H), 7.97 (s, 1H), 7.61-7.59 (m, 1H), 7.48 (s, 1H), 7.43 (s, 1H), 7.36 (d, J = 8.8 Hz, 1H), 4.41 (s, 2H), 4.23 (bs, 2H), 3.77 (bs, 2H), 3.55 (s, 3H), 2.69 (s, 3H), 2.22 (s, 6H), 1.75 (s, 3H)	589		MS (ESI) m/z 617.11 [M+1]+; 1H-NMR (400 MHz, DMSO-d6) δ 8.46 (s, 1H), 8.36 (d, J = 5.64 Hz, 1H), 7.60 (dd, J = 8.88, 2.64 Hz, 1H), 7.43-7.39 (m, 2H), 7.36 (d, J = 9.00 Hz, 1H), 4.42 (t, J = 4.52 Hz, 2H), 4.28 (t, J = 4.76 Hz, 2H), 2.69 (s, 3H), 1.94 (s, 3H)
569		MS (ESI) m/z 662.07 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 12.70 (s, 1H), 8.89 (d, J = 4.76 Hz, 1H), 8.39 (s, 2H), 8.02 (s, 1H), 7.63-7.60 (dd, J = 2.56, 2.44 Hz 1H), 7.56 (d, J = 4.72 Hz, 1H), 7.46 (d, J = 2.44 Hz, 1H), 7.36 (d, J = 9.0 Hz, 1H), 4.41 (t, J = 4.4 Hz, 2H), 4.24 (t, J = 3.86 Hz, 2H), 3.56 (s, 3H), 1.73 (s, 3H)	590		MS (ESI) m/z 615.23 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.35 (s, 1H), 7.95-7.93 (m, 3H), 7.57 (dd, J = 2.56, 8.92 Hz, 1H), 7.39 (d, J = 2.52 Hz, 1H), 7.33 (d, J = 9.04 Hz, 1H), 4.39 (t, J = 4.48 Hz, 2H), 4.30 (t, J = 4.36 Hz, 2H), 3.69 (s, 3H), 2.10 (s, 3H)

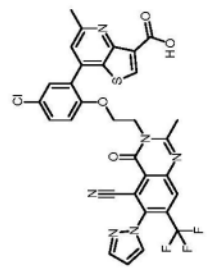
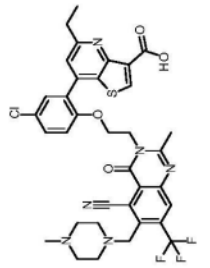
[0934]

591		MS (ESI) m/z 612.91 [M+1]+; 1H-NMR (400 MHz, DMSO-d6) δ 14.09 (bs, 1H), δ 8.77 (d, J = 4.56 Hz, 1H), 8.37 (s, 1H), 7.97 (s, 1H), 7.59 (d, J = 8.48 Hz, 1H), 7.50 (d, J = 4.56 Hz, 1H), 7.42 (bs, 1H), 7.35 (d, J = 8.84 Hz, 1H), 4.42 (t, J = 4.32 Hz, 2H), 4.26 (t, J =3.20 Hz, 2H), 2.85-2.79 (m, 2H), 1.85 (s, 3H), 0.97 (t, J = 7.24 Hz, 3H)	610		MS (ESI) m/z 670.01 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.22 (s, 1H), 7.93 (s, 1H), 7.59 (dd, J = 8.68, 2.16 Hz, 1H), 7.41-7.34 (m, 3H), 4.40 (t, J = 4.76 Hz, 2H), 4.24 (t, J = 4.68 Hz, 2H), 3.20 (d, J = 7.48 Hz, 2H), 2.69 (s, 3H), 2.57 (d, J = 10.48 Hz, 2H), 2.28 (s, 6H), 1.83 (s, 3H)
595		MS (ESI) m/z 629.10 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.37-8.28 (m, 2H), 7.61 (s, 1H), 7.48-7.43 (m, 1H), 7.31-7.26 (m, 2H), 7.05 (bs, 1H), 4.33 (bs, 2H), 4.24 (bs, 2H), 3.81 (s, 2H), 3.01 (s, 2H), 1.80 (s, 3H)	614		MS (ESI) m/z 617.06 [M+1]+; 1H-NMR (400 MHz, DMSO-d6) δ 8.38 (s, 1H), 8.14 (bs, 2H), 7.74 (t, J = 8.56 Hz, 1H), 7.29 (bs, 1H), 7.20 (d, J = 9.08 Hz, 1H), 4.41 (bs, 1H), 4.36 (bs, 1H), 4.23 (s, 2H), 2.66 (s, 3H), 1.70 (s, 3H)
605		MS (ESI) m/z 615.09 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.34 (s, 1H), 8.16 (s, 1H), 7.52 (d, J = 7.44, 1H), 7.36 (s, 1H), 7.29 (d, J = 9.04 Hz, 1H), 6.54 (s, 1H), 6.30 (s, 1H), 4.88 (s, 2H), 4.38 (s, 2H), 4.31 (s, 2H), 2.32 (s, 3H)	615		MS (ESI) m/z 691.19 [M+1]+; ; 1H NMR (400 MHz, DMSO-d6) δ 8.69 (d, J = 4.72 Hz, 1H), 8.48 (s, 1H), 8.06 (s, 1H), 7.73 (d, J = 8.4 Hz, 1H), 7.66 (d, J = 7.1 Hz, 1H), 7.57 (s, 1H), 7.47 (d, J = 4.64, 1H), 4.78 (s, 2H), 3.95 (s, 2H), 3.37 (d, J = 12.5 Hz, 2H), 2.97 (d, J = 10.68 Hz, 4H), 2.75 (s, 3H), 2.58-2.56 (m, 2H), 2.1 (s, 3H)

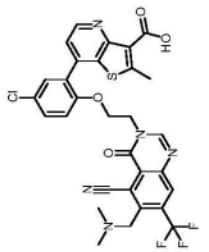
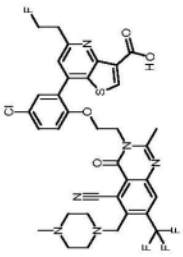
[0935]

616		MS (ESI) m/z 705.23 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.31 (s, 1H), 9.43 (s, 1H), 8.54 (s, 1H), 8.11 (s, 1H), 7.75 (d, J = 8.32 Hz, 1H), 7.69 (dd, J = 8.36, 6.2 Hz, 1H), 7.65 (d, J = 1.96 Hz, 1H), 7.47 (s, 1H), 4.87 (s, 2H), 3.97 (s, 2H), 2.95 (d, J = 10.08 Hz, 4H), 2.80 (s, 3H), 2.66 (s, 3H), 2.62 (s, 4H), 2.17 (s, 3H)	630		MS (ESI) m/z 676.18 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.76 (d, J = 3.7, 1H), 8.69 (s, 1H), 8.31 (s, 1H), 8.05 (s,1H), 7.99 (d, J = 7.8 Hz, 1H), 7.66-7.58 (m, 2H), 7.45 (s, 1H), 7.424 (d, J = 2.56 Hz, 1H), 7.36 (d, J = 8.9, 1H), 4.42 (t, J = 9.2 Hz, 2H), 4.28 (t, J = 9.6 Hz, 2H), 2.73 (s, 3H), 1.87 (s, 3H)
617		MS (ESI) m/z 678.16 [M+1]+; ; 1H NMR (400 MHz, DMSO-d6) δ 8.73 (d, J = 4.76 Hz, 1H), 8.6 (s, 1H), 8.1 (s, 1H), 7.76 (d, J = 8.0 Hz, 1H), 7.69 (d, J = 2.0 Hz, 1H), 7.67 (s, 1H), 7.55 (d, J = 4.76 Hz, 1H), 4.88 (s, 2H), 3.97 (s, 2H), 3.56 (s, 4H), 2.58 (s, 4H), 2.13 (s, 3H)	631		MS (ESI) m/z 676.18 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.74 (d, J = 4.7 Hz, 1H), 8.37 (s, 1H), 8.07 (s, 1H), 8.03 (t, J = 7.8 Hz, 1H), 7.68 (d, J = 7.6 Hz, 1H), 7.61 – 7.52 (m, 2H), 7.43 (s, 2H), 7.36 (d, J = 8.9 Hz, 1H), 4.40 (s, 2H), 4.26 (s, 2H), 2.72 (s, 3H), 1.83 (s, 3H)
629		MS (ESI) m/z 676.18 [M+1]+; ; 1H NMR (400 MHz, DMSO-d6) δ 8.78 (d, J = 5.56 Hz, 2H), 8.25 (s, 1H), 8.09 (s, 1H), 7.59 (dd, J = 7.56 Hz, 2.64 Hz, 1H), 7.53 (d, J = 4.88 Hz, 2H), 7.42-7.40 (m, 2H), 7.36 (d, J = 8.92 Hz, 1H), 4.41 (t, J = 4.76 Hz ,2H), 4.28 (t, J = 4.36 Hz, 2H), 2.72 (s, 3H), 1.86 (s, 3H)	632		MS (ESI) m/z 665.30 [M+1]+; 1H-NMR (400 MHz, DMSO-d6), 13.51 (bs, 1H), 8.26 (s ,1H), 8.09 (s, 1H), 7.98 (s, 1H), 7.60 (dd, J = 2.36, 8.88 Hz, 1H), 7.52 (s, 1H), 7.44 (s, 1H),7.42 (d, J = 2.52 Hz, 1H), 7.37 (d, J = 8.88 Hz, 1H), 7.19 (s, 1H), 4.42 (t, J = 5.28 Hz, 2H), 4.28 (t, J = 4.24 Hz, 2H), 2.73 (s, 3H), 1.87 (s, 3H)

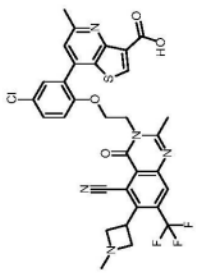
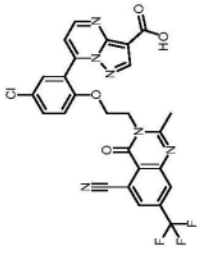
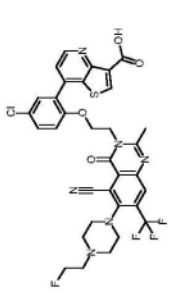
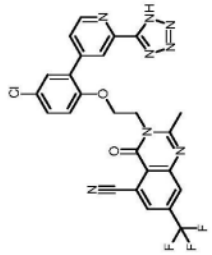
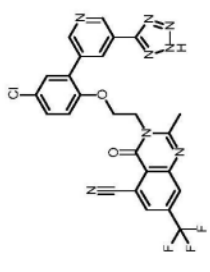
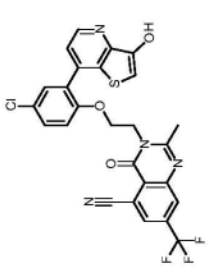
[0936]

633		MS (ESI) m/z 665.23 [M+1]+; 1H-NMR (400 MHz, DMSO-d6) 8.35 (s ,1H), 8.19 (d, J = 2.08 Hz,1H), 8.11 (s, 1H), 7.87 (d, J = 1.52 Hz, 1H), 7.61-7.58 (dd, J = 2.64, 8.88 Hz, 1H), 7.44-7.42 (m, 2H), 7.37 (d, J = 8.88 Hz, 1H), 6.63 (t, J = 2.24 Hz, 1H), 4.41 (t, J = 4.52 Hz, 2H), 4.28 (t, J = 4.12 Hz, 2H), 2.72 (s, 3H), 1.84 (s, 3H)	637		MS (ESI) m/z 725.09 [M+1]+; 1H-NMR (400 MHz, DMSO-d6) δ 8.18 (s,1H), 7.94 (s, 1H), 7.61-7.59 (dd, J = 8.8, 2.4 Hz, 1H), 7.46 (s, 1H), 7.44 (d, J = 2.48 Hz, 1H), 7.36 (d, J = 8.96 Hz, 1H), 4.41 (t, J = 5.2 Hz, 2H), 4.24 (t, J = 5.2 Hz, 2H), 3.94 (s, 2H), 3.40-3.37 (m, 2H), 3.04-2.98 (m, 2H), 2.92 (m, 4H), 2.78 (d, J = 3.52 Hz, 3H), 2.54 (m, 2H), 1.80 (s, 3H), 1.35 (t, J = 7.2 Hz, 3H)
634		MS (ESI) m/z 697.13 [M+1]+; 1H-NMR (400 MHz, DMSO-d6) δ 13.51 (bs, 1H), 9.75 (bs, 1H), 8.23 (s, 1H), 7.92 (s, 1H), 7.61-7.58 (t, J = 6.5 Hz, 1H), 7.42-7.41 (t, J = 6.5 Hz, 2H), 7.37 (d, J = 8.9 Hz, 1H), 4.40 (t, J = 6.2 Hz, 2H), 4.24 (t, J = 6.1 Hz, 2H), 3.83 (m, 2H), 3.49 (m, 2H), 3.24 (m, 2H), 3.03 (m, 2H), 2.28 (s, 3H), 2.71 (s, 3H), 1.82 (s, 3H)	638		MS (ESI) m/z 727.07 [M+1]+; ; 1H NMR (400 MHz, DMSO-d6) δ 12.7 (bs, 1H), 8.09 (s, 1H), 7.98 (s, 1H), 7.59-7.56 (dd, J = 2.8, 9.2 Hz, 1H), 7.40 (d, J = 2.4 Hz, 1H), 7.34 (d, J = 8.8 Hz, 1H), 6.90 (s, 1H), 4.41 (t, J = 6.4 Hz, 2H), 4.28 (t, J = 5.6 Hz, 2H), 4.07 (s, 3H), 3.94 (s, 2H), 3.39 (d, J = 11.2 Hz, 2H), 2.91 (d, J = 11.2 Hz, 4H), 2.78 (d, J = 3.2 Hz, 2H), 2.56 (d, J = 7.6 Hz, 2H), 1.88 (s, 3H)
636		MS (ESI) m/z 642.20 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 12.87 (bs, 1H), 9.92 (s, 1H), 8.39 (s, 1H), 8.29 (s, 1H), 8.03 (s, 1H), 7.62 (dd, J = 2.40, 8.8 Hz, 1H), 7.57 (s, 1H), 7.42 (d, J = 3.28 Hz, 1H), 7.37 (d, J = 8.92 Hz, 1H), 4.63 (bs, 2H), 4.43 (t, J = 4.84 Hz, 2H), 4.26 (t, J = 4.64 Hz, 2H), 2.96 (s, 6H), 1.76 (s, 3H	640		MS (ESI) m/z 751.1 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.85 (d, J = 4.9 Hz, 1H), 8.32 (s, 1H), 7.93 (s, 1H), 7.61 (dd, J = 8.9, 2.7 Hz, 1H), 7.53 (d, J = 4.9 Hz, 1H), 7.43 (d, J = 2.6 Hz, 1H), 7.37 (d, J = 9.0 Hz, 1H), 4.41 (t, J = 4.9 Hz, 2H), 4.24 (t, J = 5.0 Hz, 2H), 3.31 (q, J = 10.1 Hz, 2H), 3.07 – 2.58 (m, 6H), 1.75 (s, 3H). 注意：哌嗪质子非常宽且无法正确积分

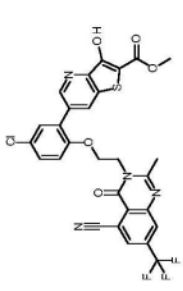
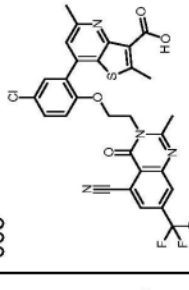
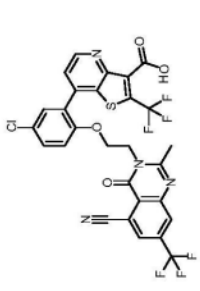
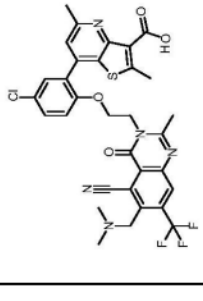
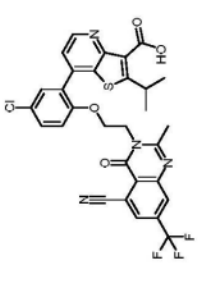
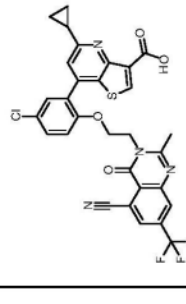
[0937]

641		MS (ESI) m/z 642.08 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.74 (d, J = 4.92 Hz, 1H), 8.15 (s, 1H), 7.86 (s, 1H), 7.61 (dd, J = 8.6, 2.4 Hz, 1H), 7.47 (m, 2H), 7.37 (d, J = 9 Hz, 1H), 4.67 (s, 2H), 4.41 (t, J = 5.28 Hz, 2H), 4.25 (t, J = 4.28 Hz, 2H), 2.88 (s, 6H), 2.53 (s, 3H)	644		MS (ESI) m/z 743.07 [M+1]+.; ; 1H NMR (400 MHz, DMSO-d6) δ 13.2 (bs, 1H), 8.16 (s, 1H), 7.96 (s, 1H), 7.62-7.59 (dd, J = 2.4, 8.8 Hz, 1H), 7.59 (s, 1H), 7.43 (d, J = 2.4 Hz, 1H), 7.37 (d, J = 8.8 Hz, 1H), 4.99 (t, J = 6.0 Hz, 1H), 4.87 (t, J = 6.0 Hz, 1H), 4.42 (t, J = 6.4 Hz, 2H), 4.26 (t, J = 6.8 Hz, 2H), 3.94 (s, 2H), 3.45 (t, J = 6.0 Hz, 2H), 2.93 (m, 4H), 2.78 (s, 3H), 2.50 (m, 2H), 1.76 (s, 3H)
642		MS (ESI) m/z 726.20 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.44 (bs, 1H), 8.27 (s, 1H), 7.95 (s, 1H), 7.59 (dd, J = 8.8, 2.5 Hz, 1H), 7.42-7.41 (m, 2H), 7.35 (d, J = 8.9 Hz, 1H), 4.4 (t, J = 5.9 Hz, 2H), 4.24 (t, J = 5.6 Hz, 2H), 3.83 (s, 2H), 3.47-3.43 (m, 2H), 2.68 (s, 3H), 2.62 (d, J = 10.5 Hz, 2H), 1.89 (d, J = 6.2 Hz, 2H), 1.86 (s, 3H), 1.01 (d, J = 6.2 Hz, 6H)	645		MS (ESI) m/z 729.05 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.04 (bs, 1H), 9.40 (s, 1H), 8.26 (s, 1H), 7.99 (s, 1H), 7.60 (dd, J = 2.28, 8.72 Hz, 1H), 7.53 (bs, 1H), 7.44 (d, J = 2.32 Hz, 1H), 7.36 (d, J = 8.92 Hz, 1H), 5.76-5.65 (d, J = 46.8 Hz, 2H), 4.41 (t, J = 5.16 Hz, 2H), 4.25 (t, J = 5.72 Hz, 2H), 3.94 (s, 2H), 3.40-3.37 (m, 2H), 2.93-2.90 (m, 4H), 2.79 (d, J = 3.32 Hz, 3H), 2.56-2.54 (m, 2H), 1.77 (s, 3H)
643		MS (ESI) m/z 705.27 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.72 (d, J = 4.84 Hz, 1H), 8.05 (s, 1H), 7.75 (d, J = 8.20 Hz, 1H), 7.69 (d, J = 8.48 Hz, 1H), 7.65 (s, 1H), 7.57 (d, J = 4.76 Hz, 1H), 4.88 (s, 2H), 3.86 (s, 2H), 2.50-2.32 (m, 8H, 与 DMSO 中的水分峰合并), 2.17 (s, 3H), 2.10 (s, 3H), 1.23 (s, 3H)	649		MS (ESI) m/z 697.18 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.52 (bs, 2H), 8.22 (s, 1H), 7.59 (s, 1H), 7.61 (dd, J = 2.76, 8.64 Hz , 1H), 7.42 (s, 2H), 7.37 (d, J = 9.0, 1H), 4.42 (t, J = 4.44 Hz, 2H), 4.26 (t, J = 4.96 Hz, 2H), 3.93 (s, 2H), 3.07 (s, 4H), 2.70 (m, 6H), 1.84 (s , 3H)

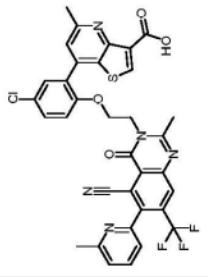
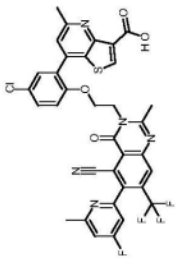
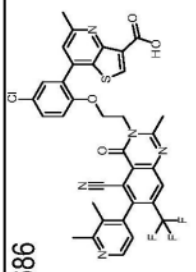
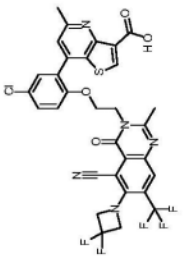
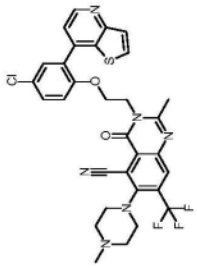
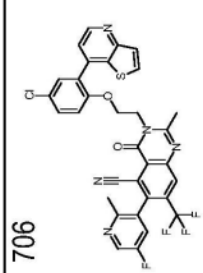
[0938]

652		MS (ESI) m/z 667.97 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.29 (s, 1H), 7.93 (s, 1H), 7.61 (dd, J = 2.56 Hz, 8.8 Hz, 1H), 7.41 (s, 2H), 7.37 (d, J = 9.0 Hz, 1H), 4.39 (m, 2H), 4.26 (m, 3H), 3.96 (bs, 2H), 3.55 (bs, 2H), 2.70 (s, 3H), 2.35 (s, 3H), 1.85 (s, 3H)	661 	LCMS (ESI) m/z 569.1 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.75 (d, J = 4.3 Hz, 1H), 8.37 – 8.31 (m, 1H), 8.07 (dt, J = 1.7, 0.8 Hz, 1H), 7.98 (s, 1H), 7.64 – 7.47 (m, 3H), 7.29 (d, J = 9.0 Hz, 1H), 7.22 (d, J = 4.2 Hz, 1H), 4.35 (t, J = 5.0 Hz, 2H), 4.21 (t, J = 4.9 Hz, 2H), 1.79 (s, 3H)
655		MS (ESI) m/z 715.3 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.84 (d, J = 4.8 Hz, 1H), 8.25 (s, 1H), 7.96 (s, 1H), 7.61 (dd, J = 8.9, 2.7 Hz, 1H), 7.48 (d, J = 4.8 Hz, 1H), 7.43 (d, J = 2.6 Hz, 1H), 7.37 (d, J = 9.0 Hz, 1H), 4.89 (dt, J = 47.3, 4.5 Hz, 2H), 4.41 (t, J = 5.0 Hz, 2H), 4.25 (t, J = 5.0 Hz, 2H), 4.03 – 3.88 (m, 2H), 3.74 – 3.09 (m, 8H), 1.77 (s, 3H)	662 	LCMS (ESI) m/z 553.0 [M+1]+ ; 1H NMR (400 MHz, DMSO-d6) δ 8.71 (dd, J = 5.0, 0.8 Hz, 1H), 8.34 – 8.28 (m, 1H), 8.05 (dd, J = 1.7, 0.8 Hz, 1H), 7.88 (dd, J = 1.8, 0.8 Hz, 1H), 7.57 (dd, J = 5.0, 1.7 Hz, 1H), 7.52 – 7.40 (m, 2H), 7.26 (d, J = 8.9 Hz, 1H), 4.44 – 4.31 (m, 4H), 2.96 (s, 3H), 2.13 (s, 3H).5 (t, J = 4.7 Hz, 2H), 1.69 (s, 3H)
660		LCMS (ESI) m/z 553.1 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 9.14 (d, J = 2.1 Hz, 1H), 8.71 (d, J = 2.1 Hz, 1H), 8.31 (dd, J = 1.8, 0.7 Hz, 1H), 8.23 (t, J = 2.1 Hz, 1H), 7.80 (dd, J = 1.7, 0.8 Hz, 1H), 7.50 – 7.39 (m, 2H), 7.26 (d, J = 8.9 Hz, 1H), 4.43 – 4.31 (m, 4H), 2.11 (s, 3H)	663 	LCMS (ESI) m/z 557.0 [M+1]+ 1H NMR (400 MHz, DMSO-d6) δ 8.60 (d, J = 4.7 Hz, 1H), 8.32 (s, 1H), 8.11 (s, 1H), 7.51 (dd, J = 8.9, 2.7 Hz, 1H), 7.33 (d, J = 2.6 Hz, 1H), 7.28 (d, J = 9.0 Hz, 1H), 7.22 (d, J = 4.4 Hz, 1H), 6.32 (d, J = 1.6 Hz, 1H), 4.34 (s, 2H), 4.23 (s, 2H), 1.81 (s, 3H)

[0939]

664		LCMS (ESI) m/z 615.0 [M+1]+ 1H NMR (400 MHz, DMSO-d6) δ 8.65 (d, J = 1.9 Hz, 1H), 8.35 (d, J = 1.9 Hz, 1H), 8.32 – 8.28 (m, 1H), 8.01 (dd, J = 1.7, 0.8 Hz, 1H), 7.49 – 7.40 (m, 2H), 7.25 (dd, J = 8.6, 0.6 Hz, 1H), 4.36 (dd, J = 11.4, 4.4 Hz, 4H), 3.85 (s, 3H), 2.19 (s, 3H)	668		LCMS (ESI) m/z 613.3 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.33 (d, J = 1.7 Hz, 1H), 7.93 (dt, J = 1.7, 0.8 Hz, 1H), 7.56 (dd, J = 8.9, 2.7 Hz, 1H), 7.42 – 7.29 (m, 2H), 4.39 (t, J = 5.0 Hz, 1H), 4.24 (t, J = 5.0 Hz, 1H), 2.66 (s, 2H), 2.35 (s, 2H), 1.92 (s, 2H)
666		LCMS (ESI) m/z 653.1 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.88 (d, J = 4.7 Hz, 1H), 8.38 – 8.32 (m, 1H), 8.17 – 8.05 (m, 1H), 7.61 – 7.51 (m, 2H), 7.42 (d, J = 2.6 Hz, 1H), 7.32	670		LCMS (ESI) m/z 670.2 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 7.57 (dd, J = 8.9, 2.7 Hz, 1H), 7.43 – 7.36 (m, 2H), 7.32 (d, J = 9.0 Hz, 1H), 4.38 (t, J = 4.9 Hz, 2H), 2.67 (s, 4H), 2.32 (s, 3H), 1.87 (s, 3H)
667		LCMS (ESI) m/z 627.3 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.75 (d, J = 5.0 Hz, 1H), 8.35 (dd, J = 1.7, 0.6 Hz, 1H), 7.97 (dt, J = 1.7, 0.8 Hz, 1H), 7.57 (dd, J = 8.9, 2.7 Hz, 1H), 7.49 (d, J = 5.0 Hz, 1H), 7.42 (d, J = 2.6 Hz, 1H), 7.32 (d, J = 9.0 Hz, 1H), 4.37 (t, J = 5.0 Hz, 1H), 4.23 (t, J = 5.1 Hz, 1H), 3.85 (q, J = 6.8 Hz, 0H), 1.83 (s, 2H), 0.99 (d, J = 6.8 Hz, 3H)	672		LCMS (ESI) m/z 625.9 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.33 (d, J = 1.7 Hz, 1H), 8.17 (s, 1H), 7.92 (d, J = 1.7 Hz, 1H), 7.56 (dd, J = 8.9, 2.7 Hz, 1H), 7.44 – 7.38 (m, 2H), 7.32 (d, J = 9.0 Hz, 1H), 4.36 (t, J = 5.1 Hz, 2H), 4.23 t, J = 5.1 Hz, 2H), 1.78 (s, 3H)

[0940]

675		LCMS (ESI) m/z 690.1 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.36 (s, 1H), 8.03 (s, 1H), 7.87 (t, J = 7.8 Hz, 1H), 7.56 (dd, J = 8.9, 2.7 Hz, 1H), 7.46 – 7.36 (m, 5H), 7.33 (d, J = 9.0 Hz, 1H), 4.37 (s, 2H), 4.24 (s, 2H), 2.69 (s, 3H), 2.50 (s, 4H), 1.80 (s, 3H)	
684		LCMS (ESI) m/z 708.1 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.36 (s, 1H), 8.06 (s, 1H), 7.60 (dd, J = 8.9, 2.7 Hz, 1H), 7.56 (dd, J = 9.3, 2.3 Hz, 1H), 7.43 (dd, J = 6.7, 4.0 Hz, 3H), 7.36 (d, J = 9.0 Hz, 1H), 4.41 (bs, 2H), 4.28 (bs, 2H), 2.73 (s, 3H), 2.56 (s, 3H), 1.85 (s, 3H)	
686		LCMS (ESI) m/z 704.0 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.57 (d, J = 5.4 Hz, 1H), 8.27 (s, 1H), 8.08 (s, 1H), 7.57 (dd, J = 8.9, 2.7 Hz, 1H), 7.50 – 7.38 (m, 3H), 7.33 (d, J = 9.0 Hz, 1H), 4.39 (m, 2H), 4.25 (m 2H), 2.70 (s, 3H), 2.61 (s, 3H), 2.00 (s, 3H), 1.81 (s, 3H)	
687		LCMS (ESI) m/z 690.2 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.34 (s, 1H), 7.85 (s, 1H), 7.60 (dd, J = 8.9, 2.7 Hz, 1H), 7.43 (s, 1H), 7.41 (d, J = 2.7 Hz, 1H), 7.36 (d, J = 9.0 Hz, 1H), 4.86 (t, J = 12.5 Hz, 4H), 4.39 (t, J = 5.0 Hz, 2H), 4.22 (t, J = 5.0 Hz, 2H), 2.72 (s, 3H), 1.79 (s, 3H)	
705		MS (ESI) m/z 639.0 [M+1]+; 1H-NMR (400 MHz, d6-DMSO) δ / ppm = 9.81-9.70 (b, 1H), 8.63 (d, J = 4.7 Hz, 1H), 8.09 (s, 1H), 7.72 (d, J = 5.4 Hz, 1H), 7.56 (dd, J = 8.9, 2.6 Hz, 1H), 7.38 (d, J = 2.6 Hz, 1H), 7.37 (d, J = 5.4 Hz, 1H), 7.33 (d, J = 8.9 Hz, 1H), 7.22 (d, J = 4.7 Hz, 1H), 4.38 (t, J = 4.9 Hz, 2H), 4.27 (t, J = 4.9 Hz, 2H), 3.92-3.82 (m, 2H), 3.59-3.50 (m, 2H), 3.30-3.20 (m, 2H), 3.14-3.01 (m, 2H), 2.91 (bs, 3H), 1.90 (s, 3H)	
706		MS (ESI) m/z 650.8 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.71 – 8.64 (m, 2H), 8.29 (d, J = 0.6 Hz, 1H), 7.90 (dd, J = 9.2, 3.0 Hz, 1H), 7.78 (d, J = 5.6 Hz, 1H), 7.56 (dd, J = 8.9, 2.7 Hz, 1H), 7.48 (d, J = 5.5 Hz, 1H), 7.41 (d, J = 2.7 Hz, 1H), 7.33 (d, J = 8.9 Hz, 1H), 7.26 (d, J = 4.7 Hz, 1H), 4.43 – 4.35 (m, 2H), 4.34 – 4.15 (m, 1H), 2.19 (d, J = 1.0 Hz, 3H), 1.88 (s, 3H)	

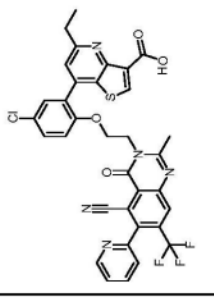
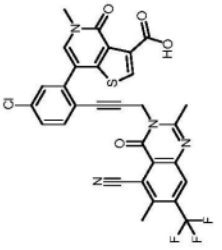
[0941]

708		MS (ESI) m/z 682.0 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.28 (s, 1H), 7.90 (s, 1H), 7.63-7.56 (m, 1H), 7.46-7.38 (m, 2H), 7.35 (d, J = 8.96 Hz, 1H), 4.49-4.32 (m, 2H), 4.31-4.18 (m, 2H), 3.70-3.66 (m, 1H), 3.26-3.22 (m, 2H), 2.69 (s, 3H), 2.32-2.22 (m, 2H), 2.22-2.09 (m, 2H), 2.07 (s, 3H), 1.80 (s, 3H)
713		MS (ESI) m/z 710.17 [M+1]+; 1H NMR (400 MHz, DMSO-d6+D2O) δ 9.18 (bs, 1H), 8.20 (s, 1H), 7.97 (s, 1H), 7.61-7.58 (dd, J = 2.4, 8.8 Hz, 1H), 7.43 (s, 1H), 7.37 (d, J = 9.2 Hz, 1H), 4.42 (t, J = 5.6 Hz, 2H), 4.26 (t, J = 3.6 Hz, 2H), 3.43 (bs, 3H), 3.06 (d, J = 6.8 Hz, 2H), 2.92-2.86 (m, 2H), 2.73-2.70 (m, 3H), 2.02 (bs, 1H), 1.83-1.78 (m, 5H), 1.63-1.54 (m, 2H)
709		MS (ESI) m/z 684.07 [M+1]+; 1H NMR (400 MHz, DMSO-d6) 8.23 (s, 1H), 7.94 (s, 1H), 7.60 (dd, J = 8.80, 2.40 Hz, 1H), 7.44-7.38 (m, 2H), 7.36 (d, J = 8.96 Hz, 1H), 4.40 (t, J = 4.76 Hz, 2H), 4.25 (t, J = 4.24 Hz, 2H), 3.05-3.01 (m, 4H), 2.69 (s, 3H), 2.50-2.30 (m, 6H), 1.91-1.78 (m, 5H)
714		MS (ESI) m/z 696.11 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.50 (bs, 1H), 8.19-8.15 (m, 2H), 7.97 (s, 1H), 7.61-7.58 (dd, J = 2.8, 9.2 Hz, 1H), 7.43-7.42 (m, 2H), 7.37 (d, J = 8.8 Hz, 1H), 4.42 (t, J = 4.8 Hz, 2H), 4.26 (t, J = 4.4 Hz, 2H), 3.29 (d, J = 11.2 Hz, 2H), 3.06 (d, J = 11.2 Hz, 2H), 2.83-2.78 (m, 2H), 2.70 (s, 3H), 2.11-2.01 (m, 1H), 1.82 (s, 3H), 1.75 (d, J = 12.4 Hz, 2H), 1.59-1.50 (m, 2H)
711		MS (ESI) m/z 670.05 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.28 (s, 1H), 7.89 (s, 1H), 7.59 (dd, J = 8.80, 2.40, 1H), 7.45-7.40 (m, 2H), 7.35 (d, J = 8.84 Hz, 1H), 4.39 (t, J = 5.40 Hz, 2H),), 4.30-4.22 (m, 2H) 3.72-3.67 (m, 1H), 2.70 (s, 3H), 2.16 (s, 6H), 1.80 (s, 3H), 1.55 (d, J = 6.68 Hz, 3H)
717		MS (ESI) m/z 621.98 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.69 (d, J = 4.76 Hz, 1H), 8.65 (s, 1H), 8.30 (bs, 2H), 7.75 (d, J= 8.32, 1H), 7.69 (m, 2H), 7.54 (d, J=4.72 Hz, 1H), 4.85 (s, 2H), 4.48 (s, 2H), 2.77 (s, 6H)

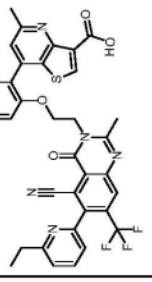
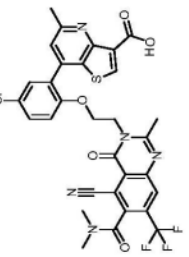
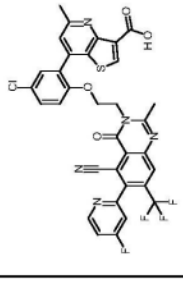
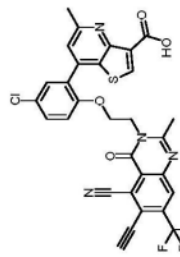
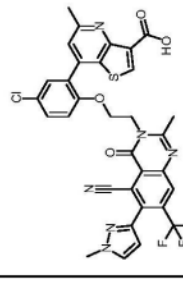
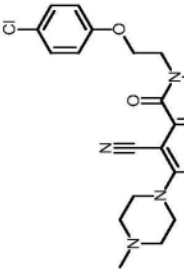
[0942]

719		MS (ESI) m/z 710.06 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 12.99 (s, 1H), 8.10 (s, 1H), 7.65 (s, 1H), 7.49 (dd, J=8.76, 2.48 Hz, 1H), 7.28-7.24 (m, 3H), 7.13 (d, J = 7.32 Hz, 1H), 4.34 (t, J=5.16 Hz, 2H), 4.22 (t, J=5.12 Hz, 2H), 3.93 (s, 2H), 3.37 (d, J=11.32, 2H,), 3.33-3.29 (m, 2H, 与 DMSO 中的水分峰合并), 2.90-2.88 (m, 4H), 2.78 (s, 3H), 2.67 (s, 3H), 1.72 (s, 3H)	738		MS (ESI) m/z 753.46 [M+1]+. ; 1H-NMR (400 MHz, CD3OD) δ 13.50 (bs, 1H), 8.94 (t, J = 8.44 Hz, 1H), 8.21 (s, 1H), 7.96 (s, 1H), 7.57 (dd, J = 2.25, 8.88 Hz, 1H),7.42 (s, 1H), 7.36 (d, J = 8.80 Hz, 1H), 4.41 (t, J = 4.32 Hz, 2H), 4.25 (t, J = 3.24 Hz, 2H), 3.96 (s, 2H),.3.50 (d, J = 10.48 Hz, 2H), 2.95 (d, J = 11.64 Hz, 2H), 2.82 (d, J = 10.52 Hz, 2H), 2.70 (s, 3H), 2.65 (d, J = 11.68 Hz, 2H), 1.85 (s, 3H), 1.30 (s, 9H)
735		MS (ESI) m/z 690.35 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.67 (d, J = 3.72 Hz, 1H), 8.29 (s, 1H), 8.09 (s, 1H), 7.86 (d, J = 7.76 Hz, 1H), 7.60 (dd, J = 2.52, 8.84 Hz, 1H), 7.50 (d, J = 4.96 Hz, 1H), 7.48 (s, 1H), 7.44 (d, J = 2.6 Hz, 1H), 7.38 (d, J = 8.92 Hz, 1H), 4.43 (t, J = 6.12 Hz, 2H), 4.27 (t, J = 5.32, 2H), 2.73 (s, 3H), 2.24 (s, 3H), 1.84 (s, 3H)	739		MS (ESI) m/z 761.12 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.22 (s, 1H), 7.96 (s, 1H), 7.60 (dd, J = 2.44, 8.88 Hz, 1H), 7.43 (s, 1H), 7.42 (s, 1H), 7.36 (d, J = 8.96 Hz, 1H), 6.58-6.31 (m, 1H), 4.41 (t, J = 4.56 Hz, 2H), 4.25 (t, J = 4.64 Hz, 2H), 3.95 (bs, 2H), 3.60-3.45 (m, 2H), 3.32-3.11 (m, 4H), 2.77-2.72 (m, 4H), 2.70 (s, 3H), 1.83 (s, 3H)
736		MS (ESI) m/z 690.04 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.65 (d, J = 4.0 Hz, 1H), 8.56 (s, 1H), 8.29 (s, 1H), 8.09 (s, 1H), 7.60 (dd, J = 8.8, 2.5 Hz, 1H), 7.56 (d, J = 5 Hz, 1H), 7.46 (s, 1H), 7.45 (d, J = 2.5 Hz, 1H), 7.37 (d, J = 8.9 Hz, 1H), 4.43 (bs, 2H), 4.28-4.26 (m, 2H), 2.73 (s, 3H), 2.11 (s, 3H), 1.84 (s, 3H)	740		MS (ESI) m/z 737.12 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.61 (bs, 1H), 9.01 (bs, 1H), 8.23 (s, 1H), 7.96 (s, 1H), 7.59 (dd, J = 8.88, 2.56 Hz, 1H), 7.42 (s, 2H), 7.37 (d, J = 8.96 Hz, 1H), 4.41 (t, J = 4.16 Hz, 2H), 4.25 (t, J = 4.96 Hz, 2H), 3.93 (s, 2H), 3.43 (s, 2H), 3.32-3.29 (m, 2H), 2.98-2.88 (m, 2H), 2.72 (d, J = 3.60, 3H), 2.69 (s, 3H), 2.18-2.16 (m, 2H), 1.91 (d, J = 8.2 Hz, 2H), 1.84 (s, 3H)

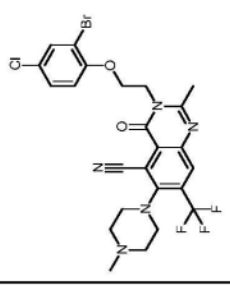
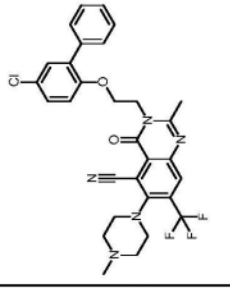
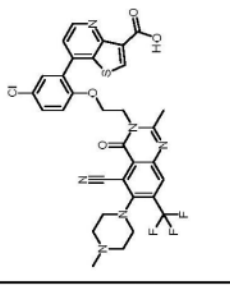
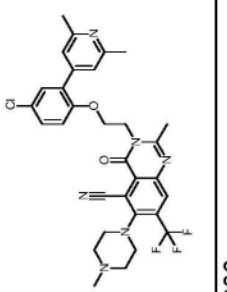
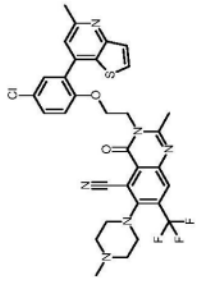
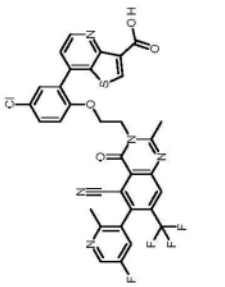
[0943]

747		MS (ESI) m/z 690.06 [M+1]+ ; 1H NMR (400 MHz, DMSO-d6) δ 8.73 (s, 1H), 8.30 (d, J = 10.6 Hz, 1H), 8.07 (t, J = 9.7 Hz, 2H), 7.66 (bs, 1H), 7.57 (s, 2H), 7.44 (bs, 2H), 7.36-7.29 (m, 1H), 4.39 (bs, 2H), 4.26 (bs, 2H), 3.02 (bs, 2H), 1.77 (d, J = 11.0 Hz, 3H), 1.35 (s, 3H)	754		MS (ESI) m/z 622.96 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 16.04 (s, 1H), 8.18 (s, 1H), 8.02 (s, 1H), 8.01 (s, 1H), 7.71 (d, J = 8.36 Hz, 1H), 7.65 (dd, J = 8.36,1.88 Hz, 1H), 7.58 (d, J = 1.72 Hz, 1H), 4.90 (s, 2H) 3.64 (s, 3H), 2.73 (s, 3H), 2.36 (s, 3H)
751		MS (ESI) m/z 693.99 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.86 (s, 1H), 8.71 (d, J = 4.6 Hz, 1H), 8.33 (s, 1H), 8.13 (s, 1H), 7.72 (t, J = 10.4 Hz, 1H), 7.60 (dd, J = 8.84, 2.28 Hz, 1H), 7.45-7.35 (m, 2H), 7.36 (d, J = 8.9 Hz, 1H), 4.44-4.24 (m, 4H), 2.72 (s, 3H), 1.87 (s, 3H)	774		MS (ESI) m/z 703.98 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.59 (s, 1H), 8.32 (s, 1H), 8.05 (s, 1H), 7.92 (d, J = 7.2 Hz, 1H), 7.60 (dd, J = 2.56, 8.88 Hz, 1H), 7.54 (d, J = 8.04 Hz, 1H), 7.45 (s, 1H), 7.42 (d, J = 2.60 Hz, 1H), 7.36 (d, J = 8.96 Hz, 1H) 4.42 (t, J = 4.64 Hz, 2H), 4.27 (t, J = 4.20 Hz, 2H), 2.90 (q, J = 7.52 Hz, 2H), 2.73 (s, 3H), 1.87 (s, 3H), 1.32 (t, J = 7.60 Hz, 3H)
753		MS (ESI) m/z 629.08 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 16.55 (s, 1H), 8.00- 7.83 (m, 3H), 7.60-7.52 (m, 1H), 7.40- 7.28 (m, 2H), 4.49- 4.23 (m, 4H), 3.70 (s, 3H), 2.69 (s, 3H), 2.16 (s, 3H)	775		MS (ESI) m/z 690.05 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.64 (s, 1H), 8.52 (s, 1H), 8.29 (s, 1H), 8.04 (s, 1H), 7.86 (s, 1H), 7.59 (dd, J = 8.84, 2.52 Hz, 1H), 7.45 (s, 1H), 7.41 (d, J = 2.56 Hz , 1H), 7.36 (d, J = 8.96 Hz , 1H), 4.42 (t, J = 5.76 Hz, 2H), 4.28 (t, J = 4.24 Hz, 2H), 2.73 (s, 3H), 2.43 (s, 3H), 1.87 (s, 3H)

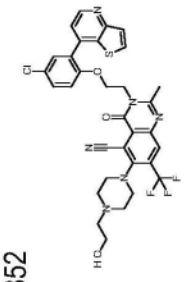
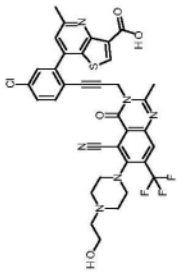
[0944]

776		MS (ESI) m/z 704.04 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.42 (s, 1H), 8.06 (s, 1H), 7.92 (t, J = 7.80 Hz, 1H), 7.59 (dd, J = 8.80, 2.40 Hz, 1H), 7.50-7.39 (m, 4H), 7.36 (d, J = 8.88 Hz, 1H), 4.40 (s, 2H), 4.27 (s, 2H), 2.80 (q, J = 7.44 Hz, 2H), 2.72 (s, 3H), 1.84 (s, 3H), 1.22 (q, J = 7.44 Hz, 3H)	789		MS (ESI) m/z 670.09 [M+1]+; 1H NMR (400 MHz, DMSO-d6 与 D2O) δ 8.24 (s, 1H), 7.97 (s, 1H), 7.56 (dd, J = 8.88, 2.52 Hz, 1H), 7.39-7.37 (m, 2H), 7.31 (d, J = 8.96 Hz, 1H), 4.39-4.34 (m, 2H), 4.22 (bs, 2H), 3.05 (s, 3H), 2.84 (s, 3H), 2.69 (s, 3H), 1.75 (s, 3H)
777		MS (ESI) m/z 693.96 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.85 (dd, J=5.88, 7.96 Hz, 1H), 8.79 (d, J=10.04 Hz, 1H), 8.34 (s, 1H), 8.12 (s, 1H), 7.65-7.58 (m, 2H), 7.45 (s, 1H), 7.43 (d, J=2.56 Hz, 1H), 7.37 (d, J=8.96 Hz, 1H), 4.45-4.26 (m, 4H), 2.72 (s, 3H), 1.87 (s, 3H)	790		MS (ESI) m/z 622.9 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.28 (s, 1H), 7.95 (s, 1H), 7.59 (dd, J=8.84, 2.52 Hz, 1H), 7.42 (s, 1H), 7.41 (d, J=2.56 Hz, 1H), 7.35 (d, J=8.96 Hz, 1H), 5.25 (s, 1H), 4.40 (t, J=4.52 Hz, 2H), 4.25 (t, J=2.44 Hz, 2H), 2.70 (s, 3H), 1.79 (s, 3H)
779		MS (ESI) m/z 679.00 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.37 (s, 1H), 8.02 (s, 1H), 7.87 (d, J= 1.92 Hz, 1H), 7.59 (dd, J = 8.88, 2.62 Hz, 1H), 7.42 (d, J = 3.0 Hz, 2H), 7.35 (d, J = 8.96 Hz, 1H), 6.48 (s, 1H), 4.40 (t, J = 6.04 Hz, 2H), 4.25 (t, J = 5.2 Hz, 2H), 3.93 (s, 3H), 2.70 (s, 3H), 1.82 (s, 3H)	808		MS (ESI) m/z 506.4 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.18 (s, 1H), 7.34 – 7.24 (m, 2H), 6.98 – 6.93 (m, 2H), 4.49 (t, J = 5.2 Hz, 2H), 4.31 (t, J = 5.2 Hz, 2H), 3.85 (t, J = 12.3 Hz, 2H), 3.53 (d, J = 11.8 Hz, 2H), 3.17 (d, J = 12.9 Hz, 2H), 3.05 (d, J = 11.6 Hz, 2H), 2.88 (s, 3H), 2.77 (s, 3H)

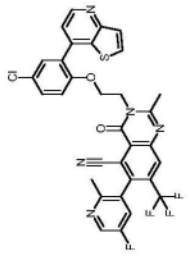
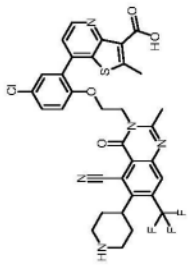
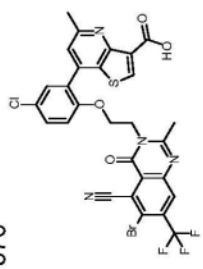
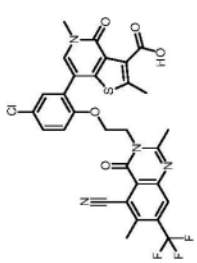
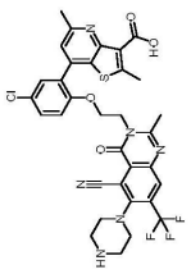
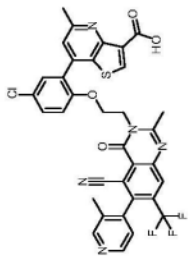
[0945]

832		MS (ESI) m/z = 584.1 [M+1]+; 1H-NMR (400 MHz, d6-DMSO) δ /ppm = 9.85-9.70 (b, 1H), 8.20 (s, 1H), 7.67 (d, J = 2.6 Hz, 1H), 7.40 (dd, J = 8.9, 2.6 Hz, 1H), 7.17 (d, J = 8.9 Hz, 1H), 4.55 (t, J = 4.5 Hz, 2H), 4.39 (t, J = 4.5 Hz, 2H), 3.84 (bt, J = 12.0 Hz, 2H), 3.53 (bd, J = 12.0 Hz, 2H), 3.17 (d, J = 12.5 Hz, 2H), 3.12-2.97 (m, 2H), 2.92-2.84 (m, 6H)
833		MS (ESI) m/z = 582.1 [M+1]+; 1H-NMR (400 MHz, d6-DMSO) δ /ppm = 9.84-9.70 (b, 1H), 8.22 (s, 1H), 7.37 (dd, J = 8.8, 2.7, 1H), 7.34-7.24 (m, 5H), 7.23 (d, J = 2.7 Hz, 1H), 7.17 (d, J = 8.8 Hz, 1H), 4.41-4.30 (m, 4H), 3.86 (bt, J = 12.6 Hz, 2H), 3.54 (bd, J = 11.5 Hz, 2H), 3.18 (d, J = 12.5 Hz, 2H), 3.12-2.99 (m, 2H), 2.89 (bs, 3H), 2.23 (s, 3H)
834		MS (ESI) m/z = 683.3 [M+1]+; 1H-NMR (400 MHz, d6-DMSO) δ /ppm = 9.81-9.69 (b, 1H), 8.84 (d, J = 4.7 Hz, 1H), 8.23 (s, 1H), 7.96 (s, 1H), 7.61 (dd, J = 8.9, 2.7 Hz, 1H), 7.48 (d, J = 4.7 Hz, 1H), 7.43 (d, J = 2.7 Hz, 1H), 7.37 (d, J = 8.9 Hz, 1H), 4.41 (t, J = 5.1 Hz, 2H), 4.25 (t, J = 5.1 Hz, 2H), 3.92-3.82 (m, 2H), 3.57 (bd, J = 11.2 Hz, 2H), 3.26 (bd, J = 13.3 Hz, 2H), 3.15-3.02 (m, 2H), 2.92 (bs, 3H), 1.77 (s, 3H)
835		MS (ESI) m/z = 611.3 [M+1]+; 1H-NMR (400 MHz, d6-DMSO) δ /ppm = 9.98-9.85 (b, 1H), 8.15 (s, 1H), 7.73-7.64 (bs, 2H), 7.55 (dd, J = 8.9, 2.8 Hz, 1H), 7.46 (d, J = 2.8 Hz, 1H), 7.31 (d, J = 8.9 Hz, 1H), 4.43 (bs, 4H), 3.85 (bt, J = 11.1 Hz, 2H), 3.54 (bd, J = 11.4 Hz, 2H), 3.17 (bd, J = 12.8 Hz, 2H), 3.12-2.99 (m, 2H), 2.89 (s, 3H), 2.62 (s, 6H), 2.37 (s, 3H)
836		MS (ESI) m/z = 653.0 [M+1]+; 1H-NMR (400 MHz, d6-DMSO) δ /ppm = 9.85-9.74 (b, 1H), 8.06 (s, 1H), 7.70 (d, J = 5.4 Hz, 1H), 7.55 (dd, J = 8.9, 2.6 Hz, 1H), 7.36 (d, J = 2.6 Hz, 1H), 7.32 (d, J = 8.9 Hz, 1H), 7.25 (d, J = 5.4 Hz, 1H), 7.18 (s, 1H), 4.38 (t, J = 4.7 Hz, 2H), 4.28 (t, J = 4.7 Hz, 2H), 3.87 (bt, J = 13 Hz, 2H), 3.56 (bd, J = 11.7 Hz, 2H), 3.25 (bd, J = 13 Hz, 2H), 3.15-3.01 (m, 2H), 2.91 (bs, 3H), 2.62 (s, 3H), 1.96 (s, 3H)
847		LCMS: 694.4.5 [M+H]+; 1H NMR (400 MHz, DMSO-d6) δ 8.88 (d, J = 4.8 Hz, 1H), 8.67 (d, J = 2.9 Hz, 1H), 8.29 (s, 1H), 8.13 (s, 1H), 7.89 (dd, J = 9.0, 2.8 Hz, 1H), 7.61 (dd, J = 8.9, 2.7 Hz, 1H), 7.53 (d, J = 4.8 Hz, 1H), 7.44 (d, J = 2.7 Hz, 1H), 7.37 (d, J = 9.0 Hz, 1H), 4.43 (q, J = 4.9 Hz, 2H), 4.28 (q, J = 6.6, 5.9 Hz, 2H), 2.22 (s, 3H), 1.79 (s, 3H)

[0946]

852		LCMS: 669.6 [M+H]+; 1H NMR (400 MHz, DMSO-d6) δ 9.70 (s, 1H), 8.59 (d, J = 4.7 Hz, 1H), 8.05 (s, 1H), 7.68 (d, J = 5.5 Hz, 1H), 7.52 (dd, J = 8.9, 2.7 Hz, 1H), 7.38 – 7.26 (m, 3H), 7.18 (d, J = 4.7 Hz, 1H), 4.35 (t, J = 5.2 Hz, 2H), 4.24 (t, J = 4.9 Hz, 2H), 3.92 (d, J = 12.8 Hz, 2H), 3.76 (t, J = 5.2 Hz, 2H), 3.60 (d, J = 12.0 Hz, 2H), 3.23 (dd, J= 26.4, 8.6 Hz, 4H), 3.09 (s, 3H), 1.86 (s, 3H)	856		LCMS: 720.9 [M+H]+; 1H NMR (400 MHz, DMSO-d6) δ 9.81 (d, J = 9.6 Hz, 1H), 8.59 (s, 1H), 8.09 (s, 1H), 7.79 –7.63 (m, 3H), 7.50 (s, 1H), 4.85 (s, 2H), 4.07 – 3.92 (m, 2H), 3.87 – 3.74 (m, 2H), 3.66 (d, J = 11.7 Hz, 2H), 3.29 (d, J = 18.2 Hz, 4H), 3.14 (d, J = 11.5 Hz, 2H), 2.67 (s, 3H), 2.23 (s, 3H)
853		LCMS: 669.6 [M+H]+; 1H NMR (400 MHz, DMSO-d6) δ 8.61 (d, J = 4.7 Hz, 1H), 8.08 (s, 1H), 7.70 (d, J = 5.5 Hz, 1H), 7.52 (dd, J = 8.9, 2.7 Hz, 1H), 7.42 – 7.34 (m, 2H), 7.29 (d, J = 9.0 Hz, 1H), 7.19 (d, J = 4.7 Hz, 1H), 4.43 (t, J = 5.4 Hz, 2H), 4.35 (t, J = 5.0 Hz, 2H), 4.23 (t, J = 5.0 Hz, 2H), 3.14 (s, 5H), 3.01 (s, 2H), 2.83 (s, 5H), 1.83 (s, 3H)	859		LCMS: 707.4 [M+H;]+. 1H NMR (400 MHz, DMSO-d6) δ 9.79 (s, 1H), 8.77 (d, J= 4.8 Hz, 1H), 8.59 (s, 1H), 8.11 (s, 1H), 7.76 (d, J= 8.3 Hz, 1H), 7.72 – 7.66 (m, 2H), 7.57 (d, J= 4.8 Hz, 1H), 4.87 (s, 2H), 3.98 (d, J= 12.8 Hz, 2H), 3.80 (t, J= 5.2 Hz, 2H), 3.72 – 3.53 (m, 2H), 3.39 – 3.21 (m, 4H), 3.21 – 3.03 (m, 1H), 2.16 (s, 3H)
855		MS (ESI) m/z 625.1 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.79 (d, J = 27.2 Hz, 2H), 8.62 (d, J = 4.7 Hz, 1H), 8.08 (s, 1H), 7.72 (d, J = 5.5 Hz, 1H), 7.55 (dd, J = 8.9, 2.7 Hz, 1H), 7.44 – 7.26 (m, 3H), 7.21 (d, J = 4.7 Hz, 1H), 4.38 (t, J = 5.0 Hz, 2H), 4.27 (t, J = 5.0 Hz, 2H), 3.38 (s, 2H), 3.23 (s, 1H), 3.04 (s, 2H), 1.89 (s, 3H)	867		MS (ESI) m/z 732.2 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.22 (s, 1H), 7.91 (s, 1H), 7.60 (dd, J = 8.9, 2.7 Hz, 1H), 7.43 (s, 1H), 7.42 (d, J = 2.7 Hz, 1H), 7.36 (d, J = 9.0 Hz, 1H), 4.40 (t, J = 4.9 Hz, 2H), 4.24 (t, J = 5.0 Hz, 2H), 3.98 (t, J = 11.9 Hz, 2H), 3.50 (d, J = 13.5 Hz, 2H), 3.34 (d, J = 13.5 Hz, 2H), 3.18 (d, J = 12.0 Hz, 2H), 2.72 (s, 3H), 1.81 (s, 3H)

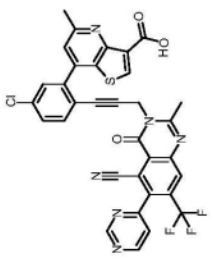
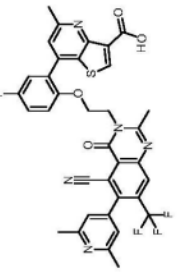
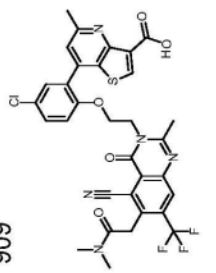
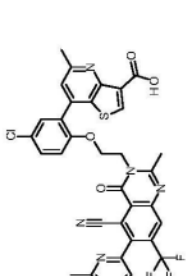
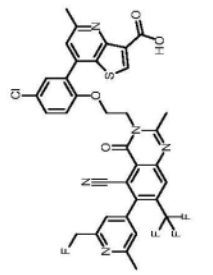
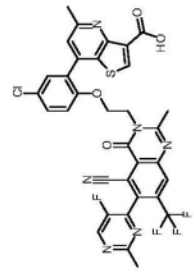
[0947]

870		MS (ESI) m/z 650.8 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.71 – 8.64 (m, 2H), 8.29 (d, J = 0.6 Hz, 1H), 7.90 (dd, J = 9.2, 3.0 Hz, 1H), 7.78 (d, J = 5.6 Hz, 1H), 7.56 (dd, J = 8.9, 2.7 Hz, 1H), 7.48 (d, J = 5.5 Hz, 1H), 7.41 (d, J = 2.7 Hz, 1H), 7.33 (d, J = 8.9 Hz, 1H), 7.26 (d, J = 4.7 Hz, 1H), 4.43 – 4.35 (m, 2H), 4.34 – 4.15 (m, 1H), 2.19 (d, J = 1.0 Hz, 3H), 1.88 (s, 3H)	887		LCMS (ESI) m/z 682.2 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.83 (d, J = 11.8 Hz, 1H), 8.76 (d, J = 4.9 Hz, 1H), 8.41 (d, J = 11.5 Hz, 1H), 7.94 (s, 1H), 7.58 (dd, J= 8.9, 2.7 Hz, 1H), 7.49 (d, J = 4.9 Hz, 1H), 7.39 (d, J = 2.7 Hz, 1H), 7.34 (d, J = 9.0 Hz, 1H), 4.40 (t, J = 5.1 Hz, 2H), 4.22 (t, J = 5.0 Hz, 2H), 3.66 (s, 2H), 3.58 (s, 1H), 3.45 (d, J = 12.3 Hz, 2H), 3.35 (s, 1H), 3.15 – 3.08 (m, 1H), 3.05 (d, J = 12.2 Hz, 1H), 2.75 (d, J = 13.4 Hz, 2H), 2.30 (s, 3H), 1.85 (d, J = 17.3 Hz, 1H), 1.84 (s, 3H
876		LCMS (ESI) m/z 678.8 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.24 (s, 1H), 7.96 (s, 1H), 7.57 (dd, J = 8.9, 2.7 Hz, 1H), 7.43 – 7.36 (m, 2H), 7.33 (d, J = 9.0 Hz, 1H), 4.38 (t, J = 4.9 Hz, 2H), 4.23 (t, J = 4.9 Hz, 2H), 2.68 (s, 3H), 1.76 (s, 3H)	899		MS (ESI) m/z 643.06 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 7.92 (s, 1H), 7.90 (s, 1H), 7.57 (dd, J = 8.80, 2.56 Hz, 1H), 7.31-7.30 (m, 2H), 4.41 (t, J = 4.80 Hz, 2H), 4.33 (t, J= 4.80 Hz, 2H), 3.69 (s, 3H), 2.64 (s, 3H), 2.31(s, 3H), 2.27 (s, 3H)
879		LCMS (ESI) m/z 697.1 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.94 (s, 1H), 8.81 (s, 1H), 7.93 (s, 1H), 7.61 (dd, J = 8.9, 2.7 Hz, 1H), 7.49 – 7.34 (m, 3H), 4.41 (s, 2H), 4.26 (s, 2H), 3.79 (s, 7H), 3.40 (d, J = 12.1 Hz, 2H), 3.18 (d, J = 12.2 Hz, 2H), 3.05 (s, 2H), 2.72 (s, 3H), 2.42 (s, 3H), 1.97 (s, 3H)	901		MS (ESI) m/z 690.05 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.71 (s, 1H), 8.65 (d, J = 4.60 Hz, 1H), 8.29 (s, 1H), 8.10 (s, 1H), 7.60 (d, J = 8.88, 2.44 Hz, 1H), 7.48 (bs, 1H), 7.46 (s, 1H), 7.44 (d, J = 2.48 Hz, 1H), 7.36 (d, J = 8.96 Hz, 1H) 4.42 (t, J = 6.20 Hz, 2H), 4.32-4.22 (m, 2H), 2.73 (s, 3H), 2.07 (s, 3H), 1.84 (s, 3H)

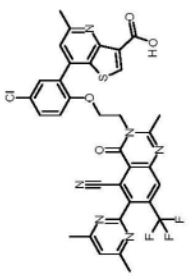
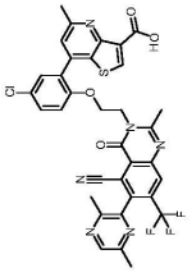
[0948]

902		905	
MS (ESI) m/z 704.06 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.41 (bs, 1H), 8.45 (s, 1H), 8.25 (s, 1H), 8.08 (s, 1H), 7.63-7.57 (m, 2H), 7.46-7.40 (m, 2H), 7.36 (d, J = 8.80 Hz, 1H), 4.45-4.35 (m, 2H), 4.35-4.23 (m, 2H), 2.72 (s, 3H), 2.35 (s, 3H), 2.15 (s, 3H), 1.83 (s, 3H)		MS (ESI) m/z 704.03 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.36 (s, 1H), 8.04 (s, 1H), 7.59 (dd, J = 8.84 Hz, 2.60 Hz, 1H), 7.43 (s, 2H), 7.36 (d, J = 8.96 Hz, 1H), 7.30 (s, 1H), 7.25 (s, 1H), 4.40 (s, 2H), 4.27 (s, 2H), 2.72 (s, 3H), 2.50 (s, 3H), 2.39 (s, 3H), 1.82 (s, 3H)
903		906	
MS (ESI) m/z 704.16 [M+1] +; 1H NMR (400 MHz, DMSO-d6) 8.46 (s, 1H), 8.30 (s, 1H), 8.24 (s, 1H), 7.84 (bs, 1H), 7.58-7.49 (m, 1H), 7.37 (s, 1H), 7.29 (d, J = 8.8 Hz, 1H), 7.16 (s, 1H), 4.37 (t, J = 4.68 Hz, 2H), 4.27 (t, J = 4.2 Hz, 2H), 2.64 (s, 3H), 2.31 (s, 3H), 1.95 (s, 3H), 1.85 (s, 3H)		MS (ESI) m/z 704.03 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.52 (bs, 1H), 8.37 (s, 1H), 8.11 (s, 1H), 7.72 (d, J = 7.88 Hz, 1H), 7.59 (dd, J = 8.88, 2.4 Hz, 1H), 7.45-7.43 (m, 2H), 7.36-7.31 (m, 2H), 4.43 (t, J = 4.36 Hz, 2H), 4.26 (t, J = 5.88 Hz, 2H), 2.72 (s, 3H), 2.46 (s, 3H), 2.04 (s, 3H), 1.80 (s, 3H)	
904		907	
MS (ESI) m/z 704.22 [M+1]+; ; 1H NMR (400 MHz, DMSO-d6) δ 8.38 (s, 1H), 8.04 (s, 1H), 7.73 (d, J= 8.0 Hz, 1H), 7.57 (dd, J = 8.88 Hz, 2.4 Hz, 1H), 7.43 (s, 2H), 7.40 - 7.34 (m, 2H), 4.40 (t, J = 4.48 Hz, 2H), 4.22 (t, J = 5.2 Hz, 2H), 2.72 (s, 3H), 2.50 (s, 3H), 2.36 (s, 3H), 1.82 (s, 3H)		MS (ESI) m/z 679.00 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.56 (bs, 1H), 8.40 (s, 1H), 7.99 (s, 1H), 7.77 (s, 1H), 7.58 (d, J=7.20 Hz, 1H), 7.42-7.34 (m, 4H), 4.39 (s, 2H), 4.25 (s, 2H), 3.77 (s, 3H), 2.69 (s, 3H), 1.82 (s, 3H)	

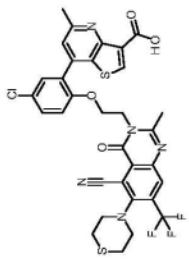
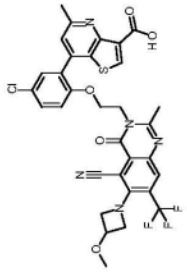
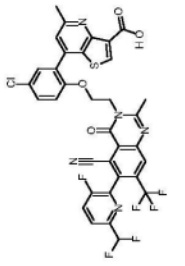
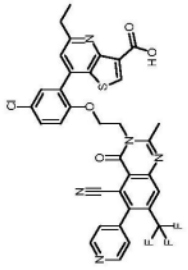
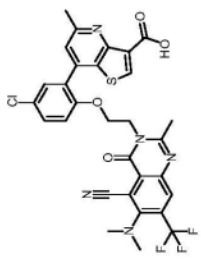
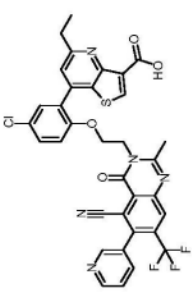
[0949]

908		MS (ESI) m/z 670.97 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 9.44 (s, 1H) 9.15 (d, J = 5.08 Hz, 1H), 8.64 (s, 1H), 8.27 (s, 1H), 7.97 (d, J = 5 Hz, 1H), 7.75 (d, J = 8.4 Hz, 1H), 7.70-7.67 (m, 1H), 7.65 (d, J = 0.84 Hz, 1H), 7.49 (s, 1H), 4.89 (s, 2H), 2.64 (s, 3H), 2.22 (s, 3H)	937		MS (ESI) m/z 688.11 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.28 (s, 1H), 8.06 (s, 1H), 7.41-7.35 (m, 2H), 7.25 (dd, J=8.56, 2.84 Hz, 1H), 4.38 (t, J=4.48 Hz, 2H), 4.27 (t, J=4.32 Hz, 2H), 2.72 (s, 3H), 2.63 (s, 6H), 1.90 (s, 3H)
909		MS (ESI) m/z 684.20 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.57 (bs, 1H), 8.23 (s, 1H), 7.93 (s, 1H), 7.59 (dd, J = 2.44, 8.84 Hz, 1H), 7.41 (d, J = 2.76 Hz, 2H), 7.35 (d, J = 8.96 Hz, 1H), 4.40 (t, J = 4.20 Hz, 2H), 4.25 (t, J = 5.88 Hz, 2H), 4.16 (s, 2H), 3.17 (s, 3H), 2.86 (s, 3H), 2.69 (s, 3H), 1.82 (s, 3H)	963		MS (ESI) m/z 705.26 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.54 (bs, 1H), 8.33 (s, 1H), 8.07 (s, 1H), 7.60 (dd, J = 2.48, 8.90 Hz, 1H), 7.55 (s, 1H), 7.43 -7.42 (m, 2H), 7.36 (d, J = 8.92 Hz, 1H), 4.41 (bs, 2H), 4.27 (bs, 2H), 2.72 (s, 3H), 2.65 (s, 1H), 2.56 (s, 1H), 1.84 (s, 3H)
934		MS (ESI) m/z 722.05 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.5 (bs,1H), 8.24 (s, 1H), 8.05 (s, 1H), 7.59 (dd, J = 8.88, 2.4 Hz, 1H), 7.43 -7.40 (m, 4H), 7.36 (d, J = 9.2 Hz,1H), 5.55 (d, J = 44 Hz, 2H), 4.41 (t, J = 5.2 Hz, 2H), 4.27 (t, J = 5.2 Hz, 2H), 2.72 (s, 3H), 2.58 (s, 3H), 1.84 (s, 3H)	964		MS (ESI) m/z 709.07 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.57 (bs, 1H), 9.14 (s, 1H), 8.41 (s, 1H), 8.19 (s, 1H), 7.60 (dd, J = 2.56, 8.92 Hz, 1H), 7.44-7.43 (m, 2H), 7.36 (d, J = 8.96 Hz, 1H), 4.42 (t, J = 5.20 Hz, 2H), 4.27 (t, J = 4.52 Hz, 2H), 2.73 (s, 3H), 2.70 (s, 3H), 1.82 (s, 3H)

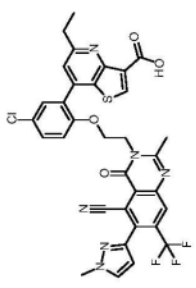
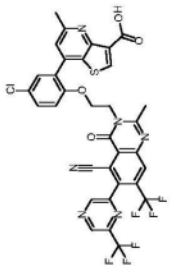
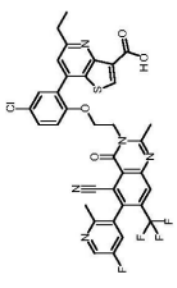
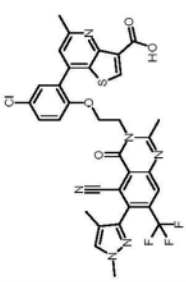
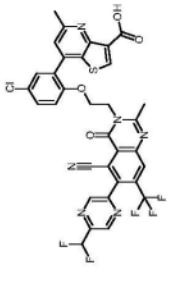
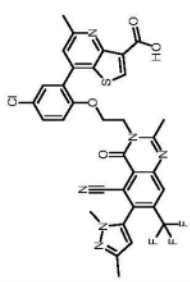
[0950]

965		MS (ESI) m/z 705.10 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.41 (s, 1H), 8.11 (s, 1H), 7.58 (d, J = 8.84 Hz, 1H), 7.46-7.39 (m, 3H), 7.34 (d, J = 8.88 Hz, 1H), 4.39 (t, J = 4.76 Hz, 2H), 4.26 (t, J = 4.44, Hz, 2H), 2.70 (s, 3H), 2.49 (s, 合并的, 6H), 1.77 (s, 3H)	968		MS (ESI) m/z 705.13 [M+1]+; 1H NMR (400 MHz, DMSO-d6) 8.63 (s, 1H), 8.37 (s, 1H), 8.14 (s, 1H), 7.60 (dd, J = 8.88, 2.52 Hz, 1H), 7.48-7.43 (m, 2H), 7.36 (d, J = 8.96 Hz, 1H), 4.48-4.35 (m, 2H), 4.30-4.24 (m, 2H), 2.73 (m, 3H), 2.52 (m, 3H), 2.29 (m, 3H), 1.80 (s, 3H)
966		MS (ESI) m/z 695.07 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.43 (s, 1H) 9.22 (s, 2H), 8.35 (s, 1H), 8.17 (s, 1H), 7.57 (t, J = 6.56 Hz, 1H), 7.42 (d, J = 2.24 Hz, 1H), 7.38 (s, 1H), 7.34 (d, J = 8.88 Hz, 1H), 4.39 (t, J = 2.96 Hz, 2H), 4.27 (t, J = 3.88 Hz, 2H), 2.69 (s, 3H), 1.82 (s, 3H)	969		MS (ESI) m/z 705.12 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.61 (s, 1H), 8.36 (s, 1H), 8.08 (s, 1H), 7.60 (dd, J = 8.80, 2.48 Hz,1H), 7.45-7.42 (m, 2H), 7.36 (d, J = 8.92, 1H), 4.44-4.38 (m, 2H), 4.31-4.23 (m, 2H), 2.72 (s, 3H), 2.66 (s, 3H), 2.57 (s, 3H), 1.84 (s, 3H)
967		MS (ESI) m/z 691.19 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.29 (bs, 1H), 8.16 (bs, 1H), 7.94 (bs, 1H), 7.86-7.83 (m, 1H), 7.59 (d, J = 7.16 Hz, 1H), 7.41-7.28 (m, 3H), 4.41 (bs, 2H), 4.30 (bs, 2H), 2.76 (s, 3H), 2.50 (bs, 3H), 1.86 (bs, 3H)	991		MS (ESI) m/z 714.06 [M-1]-; 1H NMR (400 MHz, DMSO-d6) δ 8.29 (s, 1H), 7.90 (s, 1H), 7.59 (dd, J = 8.84, 2.40 Hz, 1H), 7.46-7.40 (m, 2H), 7.36 (d, J = 9.00, 1H), 4.39 (t, J = 4.48 Hz, 2H), 4.23 (t, J = 4.08 Hz, 3H), 3.60-3.40 (m, 2H), 3.20-3.02 (m, 2H), 3.01-2.80 (m, 1H), 2.70 (s, 3H), 2.30-2.10 (m, 2H), 2.00-2.82 (m, 2H), 1.81 (s, 3H)

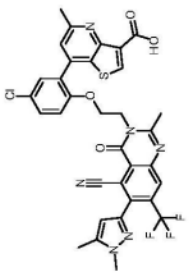
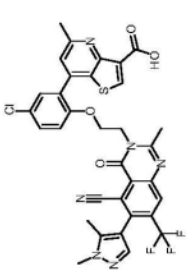
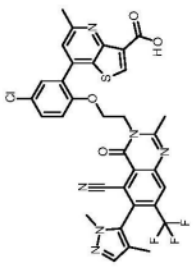
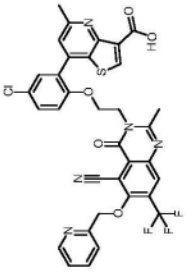
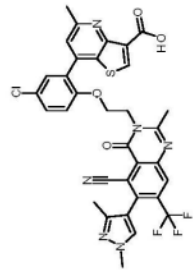
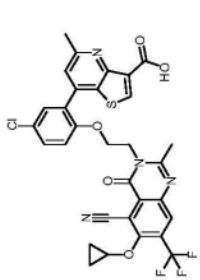
[0951]

992		MS (ESI) m/z 700.13 [M+1]+; 1H NMR (400 MHz, DMSO-d6) 8.26 (s, 1H), 7.89 (s, 1H), 7.63-7.58 (m, 1H), 7.44-7.39 (m, 2H), 7.36 (d, J = 8.8 Hz, 1H), 4.39 (s, 2H), 4.23 (s, 2H), 3.71-3.50 (m, 合并的, 2H), 3.31-3.20 (m, 2H), 2.87-.73 (m, 2H), 2.71 (s, 3H), 2.69-2.60 (m. 2H), 1.80 (s, 3H)	1009		MS (ESI) m/z 684.15 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.56 (s, 1H), 8.39 (s, 1H), 7.77 (s, 1H), 7.58 (dd, J = 2.44, 8.84 Hz, 1H), 7.41-7.39 (m, 2H), 7.35 (d, J = 8.96 Hz, 1H), 4.65-4.62 (m, 2H), 4.37 (bs, 2H), 4.32-4.27 (m, 3H), 4.18 (bs, 2H), 3.37 (s, 3H), 2.70 (s, 3H), 1.74 (s, 3H)
995		MS (ESI) m/z 744.09 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 12.20 (bs, 1H), 8.35 (s, 1H), 8.29-8.25 (m, 1H), 8.22 (s, 1H), 8.09-8.06 (m, 1H), 7.57 (d, J = 9.24 Hz, 1H), 7.43-7.33 (m, 3H), 7.07 (t, J = 54.36 Hz, 1H), 4.39 (bs, 2H), 4.27 (bs, 2H), 2.69 (s, 3H), 1.83 (s, 3H)	1012		MS (ESI) m/z 690.14 [M+1]+; ; 1H NMR (400 MHz, DMSO-d6): δ 13.74 (s, 1H), 8.71 (d, J = 5.0 Hz, 2H), 8.26 (s,1H), 8.041 (s, 1H), 7.61 (dd, J = 7.2.24 Hz, J = 2.20 Hz,1H), 7.54 (d, J = 4.64 Hz, 2H), 7.48 (s, 1H), 7.44 (d, J = 2.24 Hz, 1H), 7.38 (d, J = 8.88 Hz, 1H), 4.43 (t, J = 4.52 Hz, 2H), 4.27 (t, J = 4.44 Hz, 2H), 3.06 (m, 2H), 1.80 (s, 3H), 1.39 (t, J = 7.52 Hz, 3H)
996		MS (ESI) m/z 642.01 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.33 (s, 1H), 7.89 (s, 1H), 7.59 (dd, J = 2.60, 8.88 Hz, 1H), 7.43 (s, 1H), 7.42 (d, J = 2.64 Hz, 1H), 7.36 (d, J = 8.96 Hz, 1H), 4.39 (t, J = 4.68 Hz, 2H), 4.23 (t, J = 4.64 Hz, 2H), 2.94 (s, 6H), 2.70 (s, 3H), 1.81 (s, 3H)	1013		MS (ESI) m/z 690.14 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.76 (d, J = 4.12 Hz, 1H), 8.69 (s, 1H), 8.26 (s, 1H), 8.04 (s, 1H), 7.98 (d, J = 7.68 Hz, 1H), 7.65-7.59 (m, 2H), 7.49 (s, 1H), 7.44 (d, J = 2.48 Hz, 1H), 7.38 (d, J = 8.96 Hz, 1H), 4.43 (t, J = 4.52 Hz, 2H), 4.27 (t, J = 4.44 Hz, 2H), 3.06 (m, 2H), 1.80 (s, 3H), 1.39 (t, J = 7.52 Hz, 3H)

[0952]

1014		MS (ESI) m/z 693.16 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.32 (s, 1H), 8.00 (s, 1H), 7.87 (d, J = 2.56 Hz, 1H), 7.60 (dd, J = 2.56, 8.88 Hz, 1H), 7.46 (s, 1H), 7.44 (d, J = 2.44 Hz, 1H), 7.35 (d, J = 9.00 Hz, 1H), 6.48 (s, 1H), 4.40 (t, J = 4.56 Hz, 2H), 4.24 (t, J = 4.72 Hz, 2H), 3.93 (s, 3H), 3.02 (q, J = 7.36, 2H), 1.76 (s, 3H), 1.35 (t, J = 7.52 Hz, 3H)	1026		MS (ESI) m/z 745.11 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 9.51 (s, 1H), 9.49 (s, 1H), 8.36 (s, 1H), 8.15 (s, 1H), 7.61 (dd, J = 2.48, 8.8 Hz, 1H), 7.44-7.42 (m, 2H), 7.37 (d, J = 8.8 Hz, 1H), 4.42 (bs, 2H), 4.30 (bs, 2H), 2.72 (s, 3H), 1.89 (s, 3H)
1017		MS (ESI) m/z 722.14 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.72 (bs, 1H), 8.67 (d, J = 2.68 Hz, 1H), 8.22 (s, 1H), 8.08 (s, 1H), 7.90 (d, J = 6.68 Hz, 1H), 7.59 (dd, J = 2.48, 8.92 Hz, 1H), 7.49 (s, 1H), 7.44 (d, J = 2.48 Hz, 1H), 7.36 (d, J = 9.0 Hz, 1H), 4.41 (t, J = 3.88 Hz, 2H), 4.28 (bs, 2H), 3.04 (q, J = 7.2 Hz, 2H), 2.21 (s, 3H), 1.79 (s, 3H), 1.39 (t, J = 7.2 Hz, 3H)	1027		MS (ESI) m/z 693.14 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.37 (s, 1H), 8.04 (s, 1H), 7.65 (s, 1H), 7.59 (dd, J=8.92 Hz, 1.48 Hz, 1H), 7.44 (s, 2H), 7.36 (s, 1H),4.41 (s, 2H), 4.25 (s, 2H), 3.86 (s, 3H), 2.71 (s, 3H), 1.86 (s, 3H), 1.79 (s, 3H)
1025		MS (ESI) m/z 727.10 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.54 (bs, 1H), 9.24 (s, 1H), 9.22 (s, 1H), 8.34 (s, 1H), 8.14 (s, 1H), 7.60 (dd, J = 2.52, 8.84 Hz, 1H), 7.43-7.17 (m, 4H), 4.42 (bs, 2H), 4.28 (bs, 2H), 2.72 (s, 3H), 1.87 (s, 3H)	1028		MS (ESI) m/z 693.16 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.57 (s, 1H), 8.32 (s, 1H), 8.07 (s, 1H), 7.61(dd, J = 2.56 Hz, J = 8.88 Hz, 1H), 7.45-7.43 (m, 2H), 7.37 (d, J = 9.00 Hz, 1H), 6.27 (s, 1H), 4.41 (bs, 3H), 4.27 (bs, 2H), 3.55 (s, 3H), 2.72 (s, 3H), 2.23 (s, 3H), 1.84 (s, 3H)

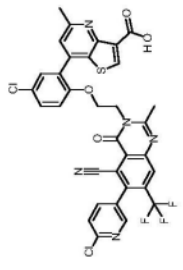
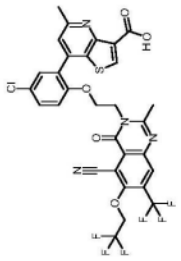
[0953]

1029		MS (ESI) m/z 693.00 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.55 (bs, 1H), 8.34 (s, 1H), 8.01 (s, 1H), 7.59 (dd, J = 8.88, 2.4 Hz, 1H), 7.43- 7.41 (m, 3H), 7.35 (d, J = 8.8 Hz, 1H), 4.40 (t, J = 6.04 Hz, 2H), 4.25 (t, J = 5.2 Hz, 2H), 3.83 (s, 3H), 2.70 (s, 3H), 2.10 (s, 3H), 1.83 (s, 3H)	1032		MS (ESI) m/z 693.10 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.33 (s, 1H), 8.01 (s, 1H), 7.60 (dd, J = 9.92, 3.32 Hz, 1H), 7.45-7.39 (m, 3H), 7.36 (d, J = 8.88 Hz, 1H), 4.46-4.45 (m, 2H), 4.30-4.20 (m, 2H), 3.83 (s, 3H), 2.70 (s, 3H), 2.10 (s, 3H), 1.83 (s, 3H)
1030		MS (ESI) m/z 693.12 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.55 (bs, 1H), 8.26 (s, 1H), 8.10 (s, 1H), 7.61 (dd, J1=6.48, J2=2.28 Hz 1H), 7.45-7.43 (m, 3H), 7.38 (d, J=8.88 Hz, 1H), 4.42 (bs, 2H), 4.26 (bs, 2H), 3.57 (s, 3H), 2.72 (s, 3H), 1.82 (s, 6H)	1033		MS (ESI) m/z 706.14 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.60 (d, J = 4.4 Hz, 1H), 8.28 (s, 1H), 8.00-7.95 (m, 2H), 7.72 (d, J = 7.72 Hz, 1H), 7.60 (dd, J = 8.88, 2.56 Hz, 1H), 7.46-7.39 (m, 3H), 7.37 (d, J = 8.96 Hz, 1H), 5.45 (s, 2H), 4.42 (t, J = 3.8 Hz, 2H), 4.25 (t, J = 4.3 Hz, 2H), 2.72 (s, 3H), 1.80 (s, 3H)
1031		MS (ESI) m/z 693.13 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.56 (bs, 1H), 8.34 (s, 1H), 8.00 (s, 1H), 7.77 (s, 1H), 7.59 (dd, J = 8.84, 2.40 Hz, 1H), 7.43 (s, 2H), 7.36 (d, J = 8.96 Hz, 1H), 4.48-4.36 (m, 2H), 4.35-4.19 (m, 2H), 3.86 (s, 3H), 2.70 (s, 3H), 1.97 (s, 3H), 1.84 (s, 3H)	1034		MS (ESI) m/z 655.18 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.54 (bs, 1H), 8.29 (s, 1H), 7.90 (s, 1H), 7.59 (dd, J = 8.92, 2.32 Hz, 1H), 7.42 (s, 2H), 7.36 (d, J = 8.92 Hz, 1H), 4.77-4.70 (m, 1H), 4.40 (t, J = 6.64 Hz, 2H), 4.23 (t, J = 5.12 Hz, 2H), 2.70 (s, 3H), 1.76 (s, 3H), 0.92-0.75 (m, 4H)

[0954]

1035	MS (ESI) m/z 792.25 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.45 (bs, 1H), 8.44 (d, J = 2.52 Hz, 1H), 8.38 (d, J = 3.32 Hz, 1H), 8.34 (s, 1H), 8.11 (s, 1H), 7.60 (dd, J = 2.55, 8.88 Hz, 1H), 7.49-7.42 (m, 4H), 7.35 (d, J = 8.90 Hz, 1H), 4.41 (t, J = 5.24 Hz, 2H), 4.05 (t, J = 4.0 Hz, 2H), 2.72 (s, 3H), 1.77 (s, 3H)	1049	MS (ESI) m/z 639.16 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.27 (s, 1H), 7.90 (s, 1H), 7.59 (dd, J = 8.84, 2.40 Hz, 1H), 7.44-7.39 (m, 2H), 7.35 (d, J = 8.92 Hz, 1H), 4.38 (t, J = 5.56 Hz, 2H), 4.24 (t, J = 6.04 Hz, 2H), 2.69 (s, 3H), 2.30-2.18 (m, 1H) 1.83 (s, 3H), 1.26-1.12 (m, 2 h), 1.00-0.90 (m, 2H)
1036	MS (ESI) m/z 629.11 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.27 (s, 1H), 7.91 (s, 1H), 7.60 (dd, J = 8.92, 2.56 Hz, 1H), 7.43 (s, 1H),, 7.42, (d, J = 2.80 Hz, 1H), 7.36 (d, J = 8.96 Hz, 1H), 4.40 (t, J = 4.72 Hz, 2H), 4.24 (t, J = 4.48 Hz, 2H), 4.13 (s, 3H), 2.71 (s, 3H), 1.78 (s, 3H)	1055	MS (ESI) m/z 684.16 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.55 (s, 1H), 8.40 (s, 1H), 7.77 (s, 1H), 7.59 (dd, J = 2.28 Hz, J = 8.84 Hz, 1H), 7.42 (d, J = 2.40 Hz, 1H), 7.40 (s, 1H), 7.35 (d, J = 8.88, 1H), 5.72 (s, 1H), 4.39-4.30 (m, 6H), 4.18 (t, J = 6.68, 2H), 2.70 (s, 3H), 1.73 (s, 3H), 1.45 (s, 3H)
1046	MS (ESI) m/z 639.16 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.27 (s, 1H), 7.90 (s, 1H), 7.59 (dd, J = 8.84, 2.40 Hz, 1H), 7.44-7.39 (m, 2H), 7.35 (d, J = 8.92 Hz, 1H), 4.38 (t, J = 5.56 Hz, 2H), 4.24 (t, J = 6.04 Hz, 2H), 2.69 (s, 3H), 2.30-2.18 (m, 1H) 1.83 (s, 3H), 1.26-1.12 (m, 2 h), 1.00-0.90 (m, 2H)	1058	MS (ESI) m/z 706.19 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.49 (bs, 1H), 8.27 (s, 1H), 8.05 (s, 1H), 7.56-7.48 (m, 2H), 7.39 (s, 1H), 4.41 (t, J = 5.52 Hz, 2H), 4.27 (t, J = 5.04 Hz), 2.72 (s, 3H), 2.61 (s, 6H), 1.86 (s, 3H)

[0955]

1059		MS (ESI) m/z 710.5 [M+1]+; 1H NMR (400 MHz, DMSO-d6) 8.57 (d, J = 1.6 Hz, 1H), 8.27 (s, 1H), 8.10-8.03 (m, 2H), 7.79 (d, J = 8.2 Hz,1H), 7.60 (dd, J = 8.8, 2.6 Hz, 1H), 7.45 (s, 1H), 7.42 (d, J = 2.6 Hz, 1H), 7.36 (d, J = 8.9 Hz, 1H), 4.42 (t, J = 4.24 Hz, 2H), 4.28 (t, J = 5.4 Hz, 2H), 2.73 (s, 3H), 1.87 (s, 3H)	1074		MS (ESI) m/z 697.14 [M+1]+; 1H NMR (400 MHz, DMSO-d6) 8.21(s, 1H), 7.96 (s, 1H), 7.59 (d, J = 8.96 Hz, 1H), 7.43 (s, 1H), 7.41 (s, 1H), 7.36 (d, J = 8.96 Hz, 1H), 5.00 (q, J = 8.40 Hz, 2H), 4.41 (t, J = 5.24 Hz, 2H), 4.25 (t, J = 4.8 Hz, 2H), 2.72 (s, 3H), 1.79 (s, 3H)
1060		MS (ESI) m/z 667.06 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.53 (bs, 1H), 8.35 (d, J = 2.68 Hz, 1H), 8.29 (s, 1H), 8.08 (s, 1H), 7.60 (dd, J = 8.84, 2.36 Hz, 1H), 7.46-7.40 (m, 3H), 7.36 (d, J = 8.96 Hz, 1H), 4.50-4.20 (m, 4H), 3.86 (s, 3H), 2.72 (s, 3H), 2.12 (s, 3H), 1.86 (s, 3H)	1075		MS (ESI) m/z 711.15 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.24 (s, 1H), 8.06 (s, 1H), 7.59 (d, J = 8.84 Hz, 1H), 7.43 (d, J = 5.5 Hz, 2H), 7.36 (d, J = 8.9 Hz, 1H), 4.46-3.64 (m, 10H), 2.82 (s, 3H), 2.71 (s, 3H), 1.85 (s, 3H)
1073		MS (ESI) m/z 643.20 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.27 (s, 1H), 7.91 (s, 1H), 7.59 (dd, J = 8.84 Hz, 2.56 Hz, 1H), 7.43-7.41 (m, 2H), 7.36 (d, J = 8.96 Hz, 1H), 4.40-4.35 (m, 4H), 4.23 (t, J = 4.16 Hz, 2H), 2.70 (s, 3H), 1.78 (s, 3H), 1.46 (t, J = 6.96 Hz, 3H)	1079		MS (ESI) m/z 767.24 [M+1]+; 1H NMR (400 MHz, DMSO-d6 与 D2O) δ 8.00 (d, J = 6.4 Hz, 2H), 7.53 (d, J = 7.2 Hz, 1H), 7.33 (s, 1H), 7.27 (d, J = 8.4 Hz, 1H), 7.19 (s, 1H), 4.33 (bs, 2H), 4.20 (bs, 2H), 2.54 (s, 3H), 2.19 (s, 3H), 1.67 (s, 3H)

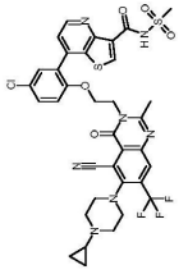
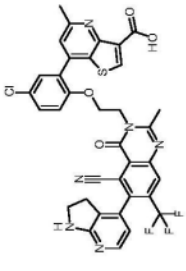
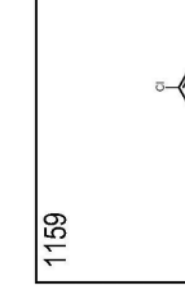
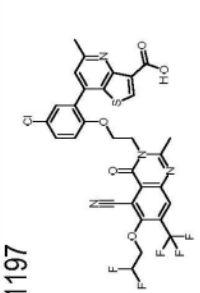
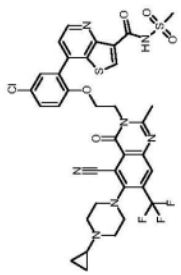
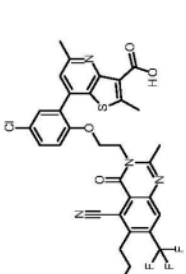
[0956]

1080		MS (ESI) m/z 751.17 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.06 (s, 1H), 7.94 (s, 1H), 7.53 (dd, J = 8.76, 2.16 Hz, 1H), 7.40 (d, J = 2.16 Hz, 1H), 7.29 (d, J = 8.92 Hz, 1H), 7.19 (s, 1H), 7.00 (d, J = 6.52, Hz, 1H), 5.76-5.68 (m, 1H), 4.40-4.30 (m, 2H), 4.30-4.15 (m, 2H), 3.70-3.45 (m, 2H), 3.10-2.70 (m, 2H), 2.60 (s, 3H), 2.35-1.90 (m, 7H), 1.69 (s, 3H)	1085		MS (ESI) m/z 711.21 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.19 (s, 1H), 7.91 (s, 1H), 7.61 (dd, J = 8.9 Hz, 2.44 Hz, 1H), 7.47 (s, 1H), 7.43 (d, J = 2.4 Hz, 1H), 7.36 (d, J = 8.9 Hz, 1H), 4.40 (t, J = 5.0 Hz, 2H), 4.24 (t, J = 4.0 Hz, 2H), 3.86 (t, J = 9.2 Hz, 2H), 3.55 (bs, 2H), 3.32 (bs, 2H), 3.10 (bs, 2H), 3.02 (q, J = 15.0 Hz, 2H), 2.89 (s, 3H), 1.79 (s, 3H), 1.36 (t, J = 7.5 Hz, 3H)
1081		MS (ESI) m/z 805.02 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.67 (d, J = 2.76 Hz, 1H), 8.26 (s, 1H), 8.12 (s, 1H), 7.97 (d, J = 6.76 Hz, 1H), 7.57 (dd, J = 2.56, 8.8 Hz, 1H), 7.36 (t, J = 2.56 Hz, 2H), 7.28 (s, 1H), 4.41-4.21 (m, 6H), 2.82 (bs, 2H), 2.64 (s, 3H), 2.50 (s, 4H), 2.19 (s, 3H), 1.91 (s, 3H), 1.69 (s, 4H)	1087		MS (ESI) m/z 725.29 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 14.50 (bs, 1H), 7.92 (s, 1H), 7.60 (dd, J = 2.52, 9.28 Hz, 1H), 7.47 (s, 1H), 7.43 (d, J = 2.28 Hz, 1H), 7.36 (d, J = 8.88 Hz, 2H), 4.40 (t, J = 5.56 Hz, 2H), 4.24 (t, J = 5.76 Hz, 2H), 3.86 (t, J = 11.28 Hz, 2H), 3.56 (d, J = 11.44 Hz, 2H), 3.21-3.18 (m, 2H), 3.08 (d, J = 10.4 Hz, 2H), 3.01 (q, J = 7.6 Hz, 2H), 2.90 (bs, 3H), 2.37 (s, 3H), 1.90 (s, 3H), 1.36 (t, J = 7.6 Hz, 3H)
1082		MS (ESI) m/z, 867.35 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.42 (s, 1H), 7.96 (s, 1H), 7.57 (dd, J = 2.52, 8.88 Hz, 1H), 7.36 (d, J = 2.52 Hz, 1H), 7.32 (d, J = 9.0 Hz, 1H), 7.27 (s, 1H), 6.94-6.90 (m, 1H), 4.61-4.56 (m, 1H), 4.37 (bs, 2H), 4.23 (bs, 2H), 3.60 (bs, 2H), 2.95 (bs, 2H), 2.63 (s, 3H), 2.24 (s, 4H), 1.84 (bs, 2H), 1.75 (s, 3H), 1.63 (d, J = 5.36 Hz, 6H), 1.44-1.39 (m, 4H), 1.33-1.20 (m, 4H)	1088		MS (ESI) m/z 708.25 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ13.60 (s, 1H), 10.02 (bs,1H), 8.21 (d, J = 5.4 Hz, 1H), 7.97 (d, J = 5.48 Hz, 1H), 7.62 (d, J = 2.28 Hz, 1H), 7.47 (s, 1H), 7.43 (d, J = 2.24 Hz, 1H), 7.37 (d, J = 8.96 Hz, 1H), 5.95 (s, 1H), 4.42 (bs, 2H), 4.39 (bs, 2H), 4.26 (d, J = 4.55 Hz, 1H), 3.85-3.65 (m, 2H), 3.4-3.33 (m, 1H), 3.04-2.99 (m, 6H), 2.67 (bs, 1H), 1.86 (s, 3H), 1.36 (t, J = 7.52, 3H)

[0957]

1093	MS (ESI) m/z 697.18 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.79 (d, J = 4.9 Hz, 1H), 7.95 (s, 1H), 7.61 (dd, J = 2.5, 8.8 Hz, 1H), 7.52 (d, J = 4.8 Hz, 1H), 7.37 (d, J = 2.5 Hz, 1H), 7.37 (d, J = 9.0 Hz, 1H), 4.42 (t, J = 4.8 Hz, 2H), 4.26 (t, J = 4.3 Hz, 2H), 3.90-3.83 (m, 2H), 3.57-3.54 (m, 2H), 3.21-3.18 (m, 2H), 3.10-3.08 (m, 2H), 2.91 (s, 3H), 2.39 (s, 3H), 1.85 (s, 3H)	1154	MS (ESI) m/z 620.27 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 12.79 (bs, 1H), 8.17 (s, 1H), 7.91 (s, 1H), 7.67-7.62 (m, 3H), 7.51 (bs, 2H), 7.37 (bs, 1H), 5.02 (s, 2H), 3.87-3.45 (m, 4H), 3.21-2.91 (m, 4H), 3.02 (bs, 3H), 2.85 (bs, 3H)
1151	MS (ESI) m/z 760.31 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 12.56 (bs, 1H), 8.89 (d, J = 4.8 Hz, 1H), 8.36 (s, 1H), 7.97 (s, 1H), 7.60 (dd, J = 8.8, 2.4 Hz, 1H), 7.53 (d, J = 4.8 Hz, 1H), 7.45 (d, J = 2.8 Hz, 1H), 7.36 (d, J = 9.2 Hz, 1H), 4.45-4.38 (m, 2H), 4.26-4.19 (m, 2H), 3.80-3.40 (m, 5H), 3.20-2.75 (m, 4H), 2.65-2.50 (s, 2H), 2.27 (s, 3H), 1.68 (s, 3H)	1156	MS (ESI) m/z 765.30 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.26 (bs, 1H), 8.82 (d, J = 4.8 Hz, 1H), 8.28 (s, 1H), 7.93 (s, 1H), 7.59 (d, J = 8.8 Hz, 1H), 7.46 (d, J = 4.4 Hz, 1H), 7.42 (s, 1H), 7.35 (d, J = 10.8 Hz, 1H), 4.39 (bs, 2H), 4.23 (bs, 2H), 3.63 (bs, 2H), 3.31 (bs, 2H), 2.95 (m, 4H), 2.60 (t, J = 7.2 Hz, 4H), 1.71 (s, 3H)
1153	MS (ESI) m/z 683.16 [M+1]+; 1H NMR (400 MHz, DMSO-d6) 13.12 (bs, 1H), 8.85 (d, J = 4.8 Hz, 1H), 8.23 (s, 1H), 7.99 (s, 1H), 7.60 (d, J = 9.2, 2.4 Hz, 1H), 7.49 (d, J = 4.8 Hz, 1H), 7.42 (d, J = 2.4 Hz, 1H), 7.36 (d, J = 9.2 Hz, 1H), 5.00 (q, J = 8.4 Hz, 2H), 4.41 (s, 2H), 4.25 (s, 2H), 1.73 (s, 3H)	1158	MS (ESI) m/z 721.16 [M+1]+; 1H-NMR (400 MHz, DMSO-d6) δ 8.84 (d, J = 4.8 Hz, 1H), 8.41 (s, 1H), 7.83 (s, 1H), 7.60 (dd, J = 2.4, 8.4 Hz, 1H), 7.44 (d, J = 2.4 Hz, 1H), 7.36 (d, J = 8.8 Hz, 1H), 4.71 (s, 2H), 4.63 (s, 2H), 4.40-4.20 (m, 8H), 3.05 (bs, 1H), 1.73 (s, 3H), 0.79-0.77 (m, 4H)

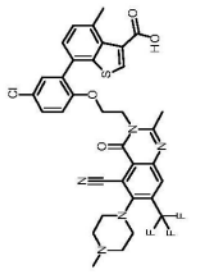
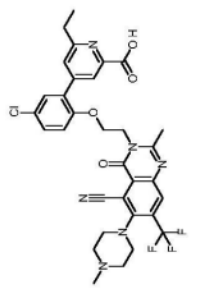
[0958]

1159		MS (ESI) m/z 709.12 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.83 (d, J = 4.4 Hz, 1H), 8.23 (s, 1H), 7.96 (s, 1H), 7.60 (dd, J = 6.4 Hz, 2.4 Hz, 1H), 7.48 (d, J = 4.8 Hz, 1H), 7.42 (d, J = 2.4 Hz, 1H), 7.36 (d, J = 8.8 Hz, 1H), 4.40 (s, 2H), 4.24 (s, 2H), 3.85 (s, 4H), 3.29 (bs, 4H), 3.12 (bs, 1H), 1.76 (s, 3H), 1.01 (s, 2H), 0.85 (s, 2H)	1192		MS (ESI) m/z 717.23 [M+1]+; 1H NMR (400 MHz, DMSO) δ 13.50 (bs, 1H), 8.27 (s, 1H), 8.05 (s, 1H), 7.81 (d, J = 8.0 Hz, 1H), 7.59 (dd, J = 8.0, 4.0 Hz, 1H), 7.43 (s, 2H), 7.36 (d, J = 8.0 Hz, 1H), 6.66 (s, 1H), 6.42 (d, J = 4.0 Hz, 1H), 4.41 (s, 2H), 4.26 (s, 2H), 3.46 (t, J = 8.0 Hz, 2H), 2.83-2.60 (m, 5H), 1.84 (s, 3H)
1178		MS (ESI) m/z 715.47 [M+1]+; 1H-NMR (400 MHz, DMSO-d6) δ 8.77 (d, J = 5.2 Hz, 1H), 8.66 (s, 1H), 7.93 (s, 1H), 7.75 (d, J = 8.4 Hz, 1H), 7.70-7.66 (m, 2H), 7.56 (d, J = 4.4 Hz, 1H), 4.82 (s, 2H), 4.73-4.41 (m, 8H), 3.05 (bs, 1H), 2.11 (s, 3H), 0.77 (bs, 4H)	1197		MS (ESI) m/z 679.22 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.46 (bs, 1H), 8.23 (s, 1H), 7.94 (s, 1H), 7.59 (d, J = 8.0 Hz, 1H), 7.42 (s, 1H), 7.41 (d, J = 2.4 Hz, 1H), 7.35 (d, J = 8.0 Hz, 1H), 6.46 (t, J = 52.0 Hz, 1H), 4.70-4.60 (m, 2H), 4.41 (s, 2H), 4.24 (s, 2H), 2.71 (s, 3H), 1.79 (s, 3H)
1179		MS (ESI) m/z 786.04 [M+1]+. 1H-NMR (400 MHz, DMSO-d6) δ 12.70 (s, 1H), 8.94 (d, J = 4.8 Hz, 1H), 8.31 (s, 1H), 7.97 (s, 1H), 7.63-7.58 (m, 2H), 7.45 (d, J = 2.40 Hz, 1H), 7.37 (d, J = 9.20 Hz, 1H), 4.42 (bs, 2H), 4.22 (bs, 2H), 3.86-3.66 (m, 4H), 3.57 (s, 3H), 3.28-3.122 (m, 5H), 1.67 (s, 3H), 2.01-0.84 (m, 4H)	1200		MS (ESI) m/z 684.22 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 14.29 (bs, 1H), δ 10.03 (bs, 1H), δ 7.98 (s, 1H), δ 7.61 (dd, J = 9.0 Hz, 2.46 Hz, 1H), 7.43 (s, 1H), 7.42 (s, 1H), 7.35 (d, J = 9.2 Hz , 1H), 4.41 (t, J = 5.1 Hz, 2H), 4.28 (t, J = 4.5 Hz, 2H), 3.42 (bs, 2H), 3.32 (bs, 2H), 2.93 (s, 6H), 2.70 (s, 3H), 2.34 (s, 3H), 1.96 (s, 3H)

[0959]

1206		MS (ESI) m/z 723.34 [M+1]+; 1H-NMR (400 MHz, DMSO-d6) δ 8.82 (d, J = 4.6 Hz, 1H), 8.19 (s, 1H), 7.90 (s ,1H), 7.58 (dd, J = 2.48, 8.92 Hz, 1H), 7.38 (d, J = 3.16 Hz, 1H), 7.33 (d, J = 8.96 Hz, 1H), 4.39 (t, J = 5.4 Hz, 2H), 4.22 (t, J = 5.2 Hz, 2H), 3.89 (s, 3H), 3.80-3.40 (m, 4H), 3.10-2.90 (m, 4H), 1.69 (s, 3H), 0.47-0.35 (m, 4H)
1207		MS (ESI) m/z 779.28 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 14.32 (bs, 1H), 7.90 (s, 1H), 7.60 (dd, J = 2.6, 8.9 Hz, 1H), 7.41 (m, 2H), 7.36 (d, J = 8.9 Hz, 1H), 4.40 (s, 2H), 4.26 (s, 2H), 3.66 (m, 2H), 3.20 (m, 2H), 2.97 (m, 2H), 2.70 (s, 3H), 2.66 (m, 1H), 2.49 (s, 3H), 2.44 (s, 3H), 1.97 (s, 3H)
1212		MS (ESI) m/z 677.23 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.11 (bs, 1H), 8.77 (d, J = 4.8 Hz, 1H), 8.59 (s, 1H), 8.11 (s, 1H), 7.76 (d, J = 8.4 Hz, 1H), 7.71-7.67 (m, 2H), 7.56 (d, J = 4.8 Hz, 1H), 4.86 (s, 2H), 3.89-3.86 (m, 2H), 3.59-3.56 (m, 2H), 3.29 (d, J = 11.6 Hz, 2H), 3.11 (bs, 2H), 2.92 (s, 3H), 2.17 (s, 3H)
1213		MS (ESI) m/z 691.29 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.31 (s, 1H), 9.77 (s, 1H), 8.58 (s, 1H), 8.09 (s, 1H), 7.76 -7.64 (m, 3H), 7.50 (s, 1H), 4.84 (s, 2H), 3.93-3.88 (m, 2H), 3.61-3.58 (m, 2H), 3.32-3.29 (m, 2H), 3.12 (bs, 2H), 2.92 (s, 3H), 2.67 (s, 3H), 2.23 (s, 3H)
1214		MS (ESI) m/z 700.25 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 12.83 (bs, 1H), 8.01 (s, 1H), 7.79 (s, 1H), 7.52-7.50 (m, 1H), 7.29-7.20 (m, 4H), 4.34 (bs, 2H), 4.22 (bs, 2H), 3.60-3.38 (m, 2H), 3.25 (bs, 2H), 3.19-2.98 (m, 4H), 2.24 (s, 3H), 1.79 (s, 3H)
1215		MS (ESI) m/z 713.31 [M+1]+;1H NMR (400 MHz, DMSO-d6) δ 13.66 (bs, 1H), 9.74 (bs, 1H), 8.22 (s, 1H), 7.92 (s, 1H), 7.60-7.54 (m, 2H), 7.44 (s, 1H), 4.39 (bs, 2H), 4.23 (bs, 2 H), 3.86 (m, 2H), 3.58 (m, 2H), 3.26-2.98 (m, 6H), 2.89 (s, 3H), 1.79 (s, 3H), 1.35 (t, J = 7.6 Hz, 3H)

[0960]

1218		MS (ESI) m/z 696.26 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 12.98 (s, 1H), 8.02 (s, 1H), 7.66 (s, 1H), 7.50 (dd, J = 2.4 Hz, J = 8.8 Hz, 1H), 7.27-7.25 (m, 3H), 7.13 (d, J = 7.6 Hz, 1H), 4.34 (t, J = 4.8 Hz, 2H), 4.22 (t, J = 4.8 Hz, 2H), 3.86 (t, J = 10.8, 2H), 3.55-3.53 (m, 2H), 3.24-3.21 (m, 2H), 3.07 (bs, 2H), 2.89 (s, 3H), 2.68 (s, 3H), 1.7 (s, 3H)	1223		MS (ESI) m/z 655.38 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 12.89 (bs, 1H), 9.74 (bs, 1H), 8.10 (s, 1H), 7.72 (s, 1H), 7.48-7.44 (m, 2H), 7.36 (d, J = 2.4 Hz, 1H), 7.24 (d, J = 9.2 Hz, 1H), 4.37 (s, 4H), 4.02-4.00 (m, 2H), 3.91-3.75 (m, 2H), 3.54 (d, J = 10.4 Hz, 2H), 3.19 (d, J = 12.0 Hz, 2H), 3.15-2.98 (m, 2H), 2.89 (s, 3H), 2.80 (q, J = 8.0 Hz, 2H), 2.29 (s, 3H), 1.22 (t, J = 7.6 Hz, 3H)
1221		MS (ESI) m/z 627.19 [M+1]+ ; 1H NMR (400 MHz, DMSO-d6) δ 13.02 (bs, 1H), 9.72 (bs, 1H), 8.58 (d, J = 4.4 Hz, 1H), 8.15 (s, 1H), 7.90 (s, 1H), 7.54 (d, J = 4.2 Hz, 1H), 7.48 (dd, J = 8.8, 2.5 Hz, 1H), 7.40 (d, J = 2.4 Hz, 1H), 7.25 (d, J = 9.6 Hz, 1H), 4.39 (s, 4H), 3.85 (t, J = 11.3 Hz, 2H), 3.52 (t, J = 11.2 Hz, 2H), 3.21 (d, J = 11.8 Hz, 2H), 3.07 (bs, 2H), 2.89 (s, 3H), 2.24 (s, 3H)	1224		MS (ESI) m/z 656.30 [M+1] +; 1H NMR (400 MHz, DMSO-d6) δ 12.93 (bs, 1H), 8.05 (s, 1H), 7.52 (s, 1H), 7.46 (dd, J = 8.8, 2.4 Hz, 1H), 7.34 (d, J = 2.4 Hz, 1H), 7.23 (d, J = 8.8 Hz, 1H), 6.95 (s, 1H), 4.36 (bs, 4H), 3.91 (s, 3H), 3.75-3.50 (m, 2H), 3.20-2.70 (m, 6H), 2.26 (s, 3H), 2.24 (s, 3H)
1222		MS (ESI) m/z 641.28 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 9.73 (bs, 1H), 8.10 (s, 1H), 7.70 (s, 1H), 7.50-7.40 (m, 2H), 7.35 (d, J = 2.8 Hz, 1H), 7.25 (d, J = 9.2 Hz, 1H), 4.38 (s, 4H), 3.85 (t, J = 22.8 Hz, 2H), 3.54 (d, J = 11.2 Hz, 2H), 3.21 (d, J = 11.6 Hz, 2H), 3.13-2.98 (m, 2H), 2.89 (s, 3H), 2.26 (s, 3H)	1225		MS (ESI) m/z 670.31 [M+1] +; 1H NMR (400 MHz, DMSO-d6) δ 12.39 (bs, 1H), 8.04 (s, 1H), 7.42 (dd, J = 8.0, 4.0 Hz, 1H), 7.28 (d, J = 4.0 Hz, 1H), 7.20 (d, J = 8.0 Hz, 1H), 7.09 (s, 1H), 6.63 (s, 1H), 4.34 (s, 4H), 3.82-3.35 (m, 4H), 2.99 (s, 6H), 2.95-2.69 (m, 4H), 2.24 (s, 3H), 2.22 (s, 3H)

[0961]

1226		MS (ESI) m/z 655.29 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 12.93 (bs, 1H), 8.09 (s, 1H), 7.46-7.44 (dd, J = 2.0, 8.8 Hz, 1H), 7.21-7.16 (m, 2H), 7.08 (s, 1H), 4.30 (bs, 4H), 3.78 (bs, 2H), 3.14 (m, 4H), 2.91 (bs, 2H), 2.74 (s, 3H), 2.45 (s, 3H), 2.02 (s, 3H), 1.88 (s, 3H)
1228		MS (ESI) m/z 707.30 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.87 (d, J = 4 Hz, 1H), 8.19 (s, 1H), 7.68 (s, 1H), 7.60-7.58 (dd, J = 2.4, 8.8 Hz, 1H), 7.45 (t, J = 4 Hz, 2H), 7.37 (d, J = 8.8 Hz, 1H), 4.41 (bs, 2H), 4.23 (bs, 2H), 3.86-2.64 (m, 8H), 2.32 (s, 3H), 1.74 (s, 3H)
1237		MS (ESI) m/z 729.25 [M+1]+; 1H NMR (400 MHz, DMSO-d6) 13.62 (bs, 1H), 7.96 (s, 1H), 7.63-7.60 (dd, J = 2.4, 8.8 Hz, 1H), 7.52 (s, 1H), 7.43 (d, J = 2.4 Hz, 1H), 7.37 (d, J = 8.8 Hz, 1H), 5.79 (d, J = 46.4 Hz, 2H), 4.41 (bs, 2H), 4.26 (bs, 2H), 3.89 (t, J = 12.4 Hz, 2H), 3.56 (t, J = 10.4 Hz, 2H), 3.20 (t, J = 12.8 Hz, 2H), 3.09 (bs, 2H), 2.90 (s, 3H), 2.39 (s, 3H), 1.88 (s, 3H)
1238		MS (ESI) m/z 741.31 [M+1]+; 1H NMR (400 MHz, DMSO-d6) 13.98 (bs, 1H), 7.93 (s, 1H), 7.62-7.60 (m, 1H), 7.48 (s, 1H), 7.43 (bs, 1H), 7.37 (d, J = 8.8 Hz, 1H), 4.75 (s, 2H), 4.41 (bs, 2H), 4.25 (bs, 2H), 3.57 (t, J = 12.0 Hz, 2H), 3.44 (bs, 2H), 3.40 (s, 3H), 3.21 (t, J = 10.8 Hz, 2H), 3.10 (bs, 2H), 2.90 (s, 3H), 2.39 (s, 3H), 1.89 (s, 3H)
1239		MS (ESI) m/z 733.30 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.02 (bs, 1H), 8.83 (d, J = 4.8 Hz, 1H), 8.27 (s, 1H), 7.94 (s, 1H), 7.60 (dd, J = 8.8, 2.8 Hz 1H), 7.48 (d, J = 4.8 Hz, 1H), 7.42 (d, J = 2.8 Hz, 1H), 7.36 (d, J = 8.8 Hz, 1H), 6.47-6.19 (m, 1H), 4.40 (s, 2H), 4.24 (s, 2H), 3.70-3.50 (合并的, 2H), 3.30-2.80 (m, 8H), 1.75 (s, 3H)
1241		MS (ESI) m/z 725.25 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.77 (bs, 1H), 8.83 (d, J = 4.64 Hz, 1H), 8.24 (s, 1H), 7.96 (s, 1H), 7.11 (dd, J = 8.9 Hz, 2.16 Hz, 1H), 7.48 (d, J = 4.6 Hz, 1H), 7.43 (s, 1H), 7.36 (d, J = 9.0 Hz, 1H), 4.74 (bs, 4H), 4.59 (bs, 1H), 4.41 (s, 2H), 4.25 (s, 2H), 4.07 (bs, 2H), 3.54 (bs, 2H), 3.30 (bs, 2H), 2.93 (bs, 2H), 1.76 (s, 3H)

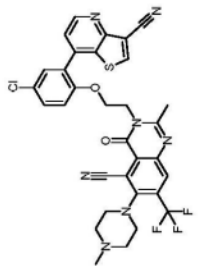
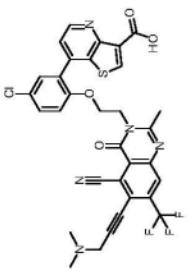
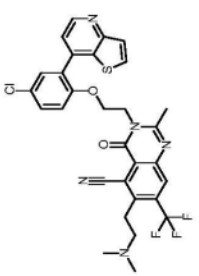
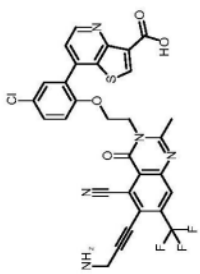
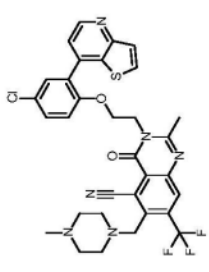
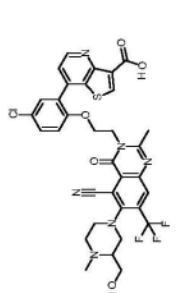
[0962]

1242		1245		MS (ESI) m/z 739.32 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.46 (s, 1H), 8.24 (s, 1H), 7.92 (s, 1H), 7.60 (d, J = 8.8 Hz, 1H), 7.42 (d, J = 6 Hz, 2H), 7.36 (d, J = 8.8 Hz, 1H), 4.78-4.73 (m, 4H), 4.59 (bs, 1H), 4.40 (s, 2H), 4.25 (s, 2H), 3.91 (bs, 4H), 3.29 (bs, 2H), 2.92 (bs, 2H), 2.72 (s, 3H), 1.84 (s , 3H)	MS (ESI) m/z 664.29 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.90 (d, J = 4.4 Hz, 1H), 8.41 (s, 1H), 8.10 (s, 1H), 7.60 (dd, J = 8.8, 2.4 Hz, 1H), 7.56 (d, J = 4.8 Hz, 1H), 7.43 (d, J = 2.4 Hz, 1H), 7.35 (d, J = 8.8 Hz, 1H), 4.43-4.43 (m, 2H), 4.24 (s, 2H), 3.65-3.49 (m, 2H), 2.99-2.89 (m, 4H), 2.74 (s, 2H), 2.24 (s, 3H), 1.69 (s, 3H)
1243		1246		MS (ESI) m/z 727.33 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 9.81 (s, 1H), 8.84 (d, J = 4.8 Hz, 1H), 8.26 (s, 1H), 7.96 (s, 1H), 7.62 (dd, J = 2.4, 9.2 Hz, 1H), 7.47 (d, J = 4.8 Hz, 1H), 7.43 (d, J = 2.4 Hz, 1H), 7.37 (d, J = 8.8 Hz, 1H), 4.42 (t, J = 4.8 Hz, 2H), 4.26 (t, J = 4.8 Hz, 2H), 3.95 (bs, 2H), 3.71 (m, 2H), 3.58 (m, 2H), 3.44 (m, 2H), 3.35 (s, 3H), 3.12 (d, J = 10 Hz, 2H), 3.12 (t, J = 10 Hz, 2H), 1.77 (s, 3H)	MS (ESI) m/z 673.24 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.68 (s, 1H), 8.08 (s, 1H), 7.56 (d, J = 7.84, 1H), 7.45 (s, 1H), 7.37-7.31 (m, 3H), 4.40 (s, 2H), 4.27 (s, 2H), 3.72-3.51 (m, 2H), 2.90 (bs, 4H), 2.25 (s, 5H), 1.83 (s, 3H)
1244		1247		MS (ESI) m/z 663.27 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 9.71 (bs, 1H), 8.73 (d, J = 4.4 Hz, 1H), 8.12 (s, 1H), 7.62 (s, 1H), 7.56 (dd, J = 8.8, 2.4 Hz, 1H), 7.38-7.31 (m, 3H), 4.68 (s, 1H), 4.40 (s, 2H), 4.26 (s, 2H), 3.86 (t, J = 12.0 Hz, 2H), 3.54 (d, J = 11.6 Hz, 2H), 3.22 (d, J = 12.8 Hz, 2H), 3.15-3.00 (m, 2H), 2.91 (s, 3H), 1.82 (s, 3H)	MS (ESI) m/z 673.19 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.77 (d, J = 4.8 Hz, 1H), 8.01 (s, 1H), 7.58 (dd, J = 2.8, 8.8 Hz, 1H), 7.51 (s, 1H), 7.41 (d, J = 4.8 Hz, 1H), 7.37 (d, J = 2.4 Hz, 1H), 7.34 (d, J = 6.8 Hz, 1H), 4.39 (t, J = 4.8 Hz, 2H), 4.24 (t, J = 4.0 Hz, 2H), 3.62 (bs, 2H), 2.81 (bs, 6H), 2.24 (s, 3H), 1.79 (s, 3H)

[0963]

1248		MS (ESI) m/z 653.30 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.54 (s, 1H), 8.06 (s, 1H), 7.52 (s, 1H), 7.31 (t, J = 9.9 Hz, 2H), 7.13 (s, 1H), 7.06 (s, 1H), 4.36 (s, 2H), 4.26 (s, 2H), 3.91-3.42 (m, 2H), 3.22-2.71 (m, 4H), 2.63-2.21 (m, 5H), 2.12 (s, 3H), 1.86 (s, 3H)	
1249		MS (ESI) m/z 653.31 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 9.73 (bs, 1H), 8.66 (d, J = 4.8 Hz, 1H), 8.05 (s, 1H), 7.55 (dd, J = 8.8, 2.4 Hz, 1H), 7.34-7.31 (m, 2H), 7.24 (d, J = 4.8 Hz, 1H), 7.13 (s, 1H), 4.41-4.34 (m, 2H), 4.30-4.20 (m, 2H), 3.87 (t, J = 11.6 Hz, 2H), 3.56 (d, J = 11.6 Hz, 2H), 3.26 (d, J = 12.0 Hz, 2H), 3.15-3.00 (m, 2H), 2.91 (s, 3H), 2.36 (s, 3H), 1.81 (s, 3H)	
1250		MS (ESI) m/z 640.24 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 9.74 (bs, 1H), 9.16 (s, 1H), 8.07 (s, 1H), 8.01 (d, J = 5.32 Hz, 1H), 7.62 (dd, J = 8.9, 2.6 Hz, 1H), 7.46 (d, J = 2.6 Hz, 1H) 7.42 (d, J = 5.4 Hz, 1H) 7.36 (d, J = 9.0 Hz, 1H), 4.43 (t, J = 4.9 Hz, 2H), 4.29 (t, J = 4.32 Hz, 2H), 3.87 (t, J = 11.2 Hz, 2H), 3.55 (d, J = 11.6 Hz, 2H), 3.25 (d, 12.36 Hz, 2H), 3.15-3.00 (m, 2H), 2.90 (s, 3H), 1.93 (s, 3H)	
1251		MS (ESI) m/z 640.27 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 9.10 (s, 1H), 8.84 (d, J = 4.5 Hz, 1H), 8.05 (s, 1H), 7.58 (dd, J = 9.0 Hz, 2.5 Hz, 1H), 7.55 (d, J = 4.5 Hz, 1H), 7.47 (d, J = 2.5 Hz, 1H), 7.35 (d, J = 8.9 Hz, 1H), 4.43 (t, J = 4.16 Hz, 2H), 4.27 (t, J = 4.36 Hz, 2H), 3.61 (bs, 4H), 2.96 (bs, 4H), 2.24 (s, 3H), 1.88 (s, 3H)	
1252		MS (ESI) m/z 667.36 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.60 (d, J = 4.7 Hz, 1H),), 8.01 (s, 1H), 7.54-7.51 (dd, J = 8.8, J = 2.5 Hz, 1H), 7.30 (m, 2H), 7.18 (d, J = 4.6 Hz, 1H), 4.37 (t, J = 12.7 Hz, 2H), 4.23 (t, J = 3.4 Hz, 2H), 3.64 (m, 4H), 2.89 (m, 4H), 2.23 (s, 6H), 1.97 (s, 3H), 1.79 (s, 3H)	
1253		MS (ESI) m/z 671.22 [M+1] +; 1H NMR (400 MHz, DMSO-d6) δ 8.01 (s, 1H), 7.78 (d, J = 5.6 Hz, 1H), 7.57 (dd, J = 2.80, 8.8 Hz, 1H), 7.39 (d, J = 2.8 Hz, 1H), 7.37 (d, J = 9.6 Hz, 1H), 7.34-7.31 (m, 2H), 5.59 (d, J = 46.8 Hz, 2H), 4.36 (t, J = 4.4 Hz, 2H), 4.25 (t, J = 4.0 Hz, 2H), 3.61 (bs, 2H), 2.93 (bs, 2H), 2.50 (bs, 2H), 2.25 (bs, 5H), 1.85 (s, 3H)	

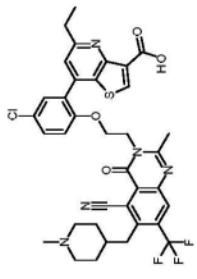
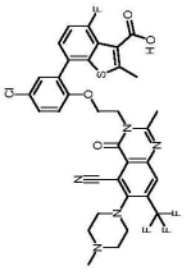
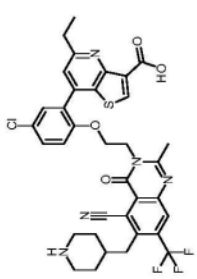
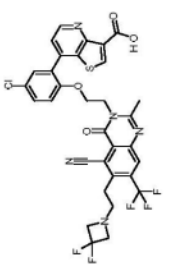
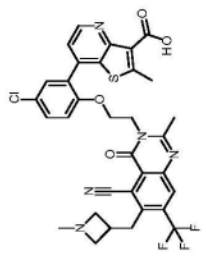
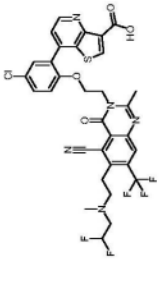
[0964]

1254		MS (ESI) m/z 664.26 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.83 (d, J = 4.8 Hz, 1H), 8.48 (s, 1H), 8.03 (s, 1H), 7.61 (dd, J = 2.4, 11.2 Hz, 1H), 7.50 (d, J = 4.8 Hz, 1H), 7.43 (d, J = 2.4 Hz, 1H), 7.37 (d, J = 8.8 Hz, 1H), 4.40 (bs, 2H), 4.26 (bs, 2H), 3.57 (m, 2H), 3.02 (m, 4H), 2.60 (m, 2H), 2.24 (s, 3H), 1.76 (s, 3H)	1259 	MS (ESI) m/z 666.25 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.38 (d, J = 4.0 Hz 1H), 8.20 (s, 1H), 8.02 (s, 1H), 7.58 (d, J = 6.4 Hz, 1H), 7.42 (d, J = 9.2 Hz, 2H), 7.33 (d, J = 8.8 Hz 1H), 4.39 (s, 2H), 4.23 (s, 2H), 3.67 (s, 2H), 2.32 (s, 6H), 1.68 (s, 3H)
1255		MS (ESI) m/z 612.23 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 9.99 (bs, 1H), δ 8.63 (d, J = 4.8 Hz, 1H), δ 8.10 (s, 1H), 7.66 (d, J = 5.6 Hz, 1H), 7.54 (dd, J = 8.7 Hz, 2.5 Hz, 1H), 7.37 (d, J = 2.4 Hz, 1H), 7.33-31 (m, 2H), 7.21 (d, J = 4.4 Hz, 1H), 4.37 (t, J = 5.1 Hz, 2H), 4.27 (t, J = 4.5 Hz, 2H), 3.45-3.43 (m, 2H), 3.32 (bs, 2H), 2.95 (s, 6H), 1.96 (s, 3H)	1260 	MS (ESI) m/z 638.08 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.28 (s, 1H), 8.84 (d, J = 4.8 Hz, 1H), 8.47 (bs, 3H), 8.31 (s, 1H), 8.04 (s, 1H), 7.61 (dd, J = 8.8, 2.4 Hz, 1H), 7.49 (d, J = 4.4 Hz, 1H), 7.44 (d, J = 2.8 Hz, 1H), 7.37 (d, J = 9.2 Hz, 1H), 4.41 (bs, 2H), 4.27 (bs, 4H), 1.74 (s, 3H)
1256		MS (ESI) m/z 653.27 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.63 (d, J = 4.8 Hz, 1H), 8.05 (s, 1H), 7.72 (d, J = 5.6 Hz, 1H), 7.55 (dd, J = 2.4, 8.8 Hz, 1H), 7.42 (d, J = 5.6, Hz, 1H), 7.39 (d, J = 2.4 Hz, 1H), 7.32 (d, J = 8.8 Hz, 1H), 7.22 (d, J = 4.4 Hz, 1H), 4.38 (t, J = 4.4 Hz, 2H), 4.25 (t, J = 5.2 Hz, 2H), 3.85 (s, 2H), 2.47 (m, 4H), 2.27 (m, 4H), 1.83 (s, 3H), 1.23 (s, 3H)	1261 	MS (ESI) m/z 713. 27 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.25 (bs, 1H), 9.60 (bs, 1H), 8.84 (d, J = 4.8 Hz , 1H), 8.21 (s, 1H), 7.95 (s, 1H), 7.61 (dd, J = 2.4, 8.8 Hz, 1H), 7.48 (d, J = 4.8 Hz, 1H), 7.42 (d, J = 2.4 Hz, 1H), 7.36 (d, J = 9.2 Hz, 1H), 5.69 (bs, 1H), 4.41 (s, 2H), 4.24 (s, 2H), 3.95-3.89 (m, 3H), 3.63-3.58 (m, 2H), 3.22-3.30 (m, 6H), 2.96-2.89 (m, 4H), 1.75 (s, 3H)

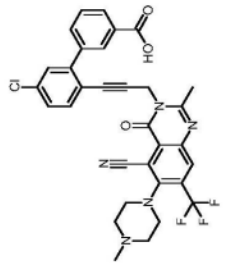
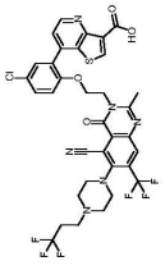
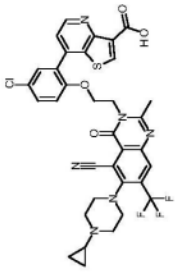
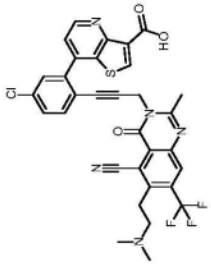
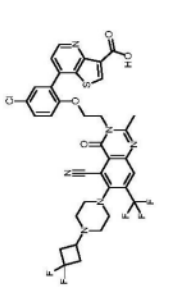
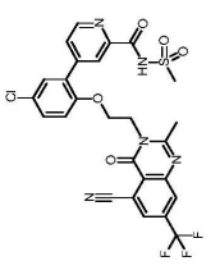
[0965]

1262		1270	
MS (ESI) m/z 749.29 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.37 (bs, 1H), 8.84 (d, J = 4.8 Hz, 1H), 8.24 (s, 1H), 7.94 (s, 1H), 7.59 (dd, J = 2.4, 8.8 Hz, 1H), 7.48 (d, J = 4.8 Hz, 1H), 7.42 (d, J = 2.4 Hz, 1H), 7.36 (d, J = 9.2 Hz, 1H), 4.40 (s, 2H), 4.23 (s, 2H), 3.96 (m, 2H), 3.48 (m, 4H), 3.24 (m, 1H), 2.96 (s, 3H), 1.72 (s, 3H)		MS (ESI) m/z 691.31 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.11 (bs, 1H), 8.7 (d, J = 4.7 Hz, 1H), 8.62 (s, 1H), 8.26 (s, 1H), 7.76 (d, J = 8.1 Hz, 1H), 7.72-7.66 (m, 2H), 7.25 (d, J = 4.7 Hz, 1H), 5.01-4.45 (m, 2H), 4.20-3.82 (m, 4H), 3.70-3.45 (m, 2H), 2.88 (s, 3H), 2.16 (s, 3H)	
1263		1271	
MS (ESI) m/z 682.0 [M+1]+; ; 1H NMR (400 MHz, DMSO-d6) δ 8.28 (s, 1H), 7.90 (s, 1H), 7.63-7.56 (m, 1H), 7.46-7.38 (m, 2H), 7.35 (d, J = 8.96 Hz, 1H), 4.49-4.32 (m, 2H), 4.31-4.18 (m, 2H), 3.70-3.66 (m, 1H), 3.26-3.22 (m, 2H), 2.69 (s, 3H), 2.32-2.22 (m, 2H), 2.22-2.09 (m, 2H), 2.07 (s, 3H), 1.80 (s, 3H)		MS (ESI) m/z 691.28 [M+1]+; ; 1H NMR (400 MHz, DMSO-d6) δ 13.75 (bs, 1H), 9.75 (bs, 1H), 8.74 (d, J = 4.8 Hz, 1H), 8.11 (s, 1H), 7.76-7.69 (m, 2H), 7.65 (s, 1H), 7.58 (d, J = 4.8 Hz, 1H), 4.86 (s, 2H), 3.89 (t, J = 22.4 Hz, 2H), 3.59 (d, J = 11.2 Hz, 2H), 3.30 (d, J = 11.2 Hz, 2H), 3.11 (d, J = 8 Hz, 2H), 2.92 (bs, 3H), 2.64 (s, 3H), 2.22 (s, 3H)	
1269		1272	
MS (ESI) m/z 699.27 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.12 (bs, 1H), 8.94 (s, 1H), 8.91 (d, J = 4.8 Hz, 1H), 8.15 (s, 1H), 7.75 (d, J = 9.2 Hz, 1H), 7.57 (d, J = 4.4 Hz, 1H), 7.49 (bs, 2H), 4.18 (t, J = 6.0 Hz, 2H), 3.87 (bs, 2H), 3.54 (d, J = 12.4 Hz, 2H), 3.33 (bs, 2H), 3.22 (d, J = 11.6 Hz, 2H), 3.08 (bs, 2H), 2.90 (s, 3H), 2.52 (s, 3H)		MS (ESI) m/z 711.31 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.8 (d, J = 4.8 Hz, 1H), 8.09 (s, 1H), 7.60 (dd, J = 8.8 Hz, 2.4 Hz, 1H), 7.50 (d, J = 4.8 Hz, 1H), 7.44 (d, J = 2.4 Hz, 1H), 7.35 (d, J = 8.8 Hz 1H), 4.42 (bs, 2H), 4.28 (bs, 2H), 4.08-3.55 (m, 6H), 2.87 (s, 3H), 2.37 (s, 3H), 1.82 (s, 3H)	

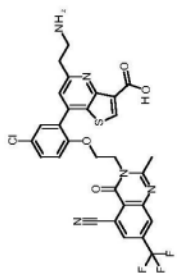
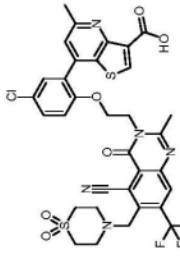
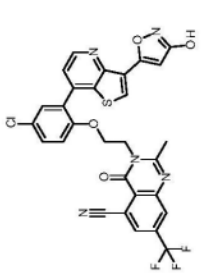
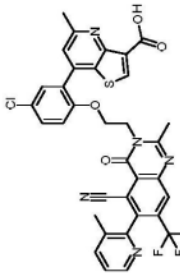
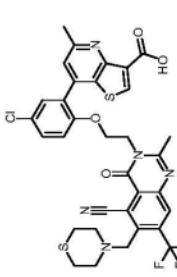
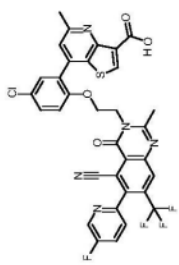
[0966]

1275		MS (ESI) m/z 724.28 [M+1]+; 1H NMR (400 MHz, DMSO-d6) 13.73 (bs, 1H), 8.17 (s, 1H), 7.96 (s, 1H), 7.62-7.59 (dd, J = 2.8, 9.2 Hz, 1H), 7.47-7.44 (m, 2H), 7.37 (d, J = 8.8 Hz, 1H), 4.41 (bs, 2H), 4.24 (bs, 2H), 3.43-3.40 (m, 2H), 3.23-2.86 (m, 6H), 2.73 (s, 3H), 2.02 (bs, 1H), 1.79 (bs, 5H), 1.64-1.55 (m, 2H), 1.37 (t, J = 7.6 Hz, 3H)	1286		MS (ESI) m/z 714.39 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.23 (bs, 1H), 8.14 (s, 1H), 7.52 (dd, J = 8.8 Hz, 2.5 Hz, 1H), 7.27-7.25 (m, 2H), 7.23-7.21 (m, 2H), 4.34-4.33 (m, 2H), 4.27-4.25 (m, 2H), 3.87 (t, J = 12.3 Hz, 2H), 3.55-3.53 (m, 2H), 3.18-3.15 (m, 2H), 3.08-3.06 (m, 2H), 2.89 (s, 3H), 2.04 (s, 3H), 1.83 (s, 3H)
1276		MS (ESI) m/z 710.27 [M+1]+; ; 1H NMR (400 MHz, DMSO-d6) δ 13.70 (bs, 1H), 8.45 (bs, 1H), 8.17 (s, 1H), 7.96 (s, 1H), 7.61-7.59 (dd, J = 6.8, 8.8 Hz, 1H), 7.46-7.43 (m, 2H), 7.37 (d, J = 8.8 Hz, 1H), 4.41 (bs, 2H), 4.24 (bs, 2H), 3.30 (m, 2H), 3.06-2.98 (m, 4H), 2.84 (m, 2H), 2.08 (bs, 1H), 1.79 (s, 3H), 1.75 (d, J = 13.6 Hz, 2H), 1.60 (t, J = 10.0 Hz, 2H), 1.37 (t, J = 7.6 Hz, 3H)	1287		MS (ESI) m/z 704.27 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.83 (d, J = 4.8 Hz, 1H), 8.20 (s, 1H), 7.98 (s, 1H), 7.60 (dd, J = 8.8 Hz, 2.4 Hz, 1H), 7.49 (d, J = 4.4 Hz, 1H), 7.42-7.36 (m, 2H), 4.41 (bs, 6H), 4.24 (s, 2H), 3.31 (d, J = 6.4 Hz, 2H), 3.21 (d, J = 4.8 Hz, 2H), 1.81 (s, 3H)
1283		MS (ESI) m/z 682.22 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 14.06 (bs, 1H), 8.79 (d, J = 5.2 Hz, 1H), 7.97 (d, J = 5.2 Hz, 1H), 7.61 (dd, J = 2.8, 9.2 Hz, 1H), 7.52 (d, J = 4.8 Hz, 1H), 7.9 (d, J = 2.4 Hz, 1H), 7.38 (d, J = 9.2 Hz, 1H), 4.42 (bs, 2H), 4.27 (bs, 2H), 4.20 (d, J = 6.0 Hz, 2H), 4.02 (d, J = 8.0 Hz, 2H), 3.95 (bs, 1H), 3.38 (d, J = 5.6 Hz, 2H), 2.85 (d, J = 4.8 Hz, 3H), 2.33 (s, 3H), 1.88 (s, 3H)	1288		MS (ESI) m/z 706.37 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.83 (d, J = 4.4 Hz 1H), 8.21 (s, 1H), 7.98 (s, 1H) 7.59 (dd, J = 8.9, 2.6 Hz, 1H), 7.49 (d, J = 4.8 Hz 1H), 7.42 (d, J = 2.8 Hz, 1H), 7.36 (d, J = 8.8 Hz, 1H), 6.18 - 6.46 (m, 1H), 4.41 (t, J = 6.02 Hz, 2H), 4.25 (t, J = 8.0 Hz, 2H), 3.39 (s, 4H), 3.09 (s, 2H), 2.73 (s, 3H), 1.77 (s, 3H)

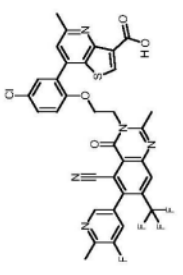
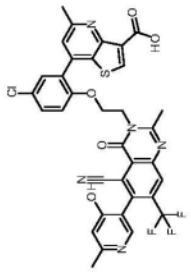
[0967]

1289		MS (ESI) m/z 620.27 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 12.79 (bs, 1H), 8.17 (s, 1H), 7.91 (s, 1H), 7.67-7.62 (m, 3H), 7.51 (bs, 2H), 7.37 (bs, 1H), 5.02 (s, 2H), 3.87-3.45 (m, 4H), 3.21-2.91 (m, 4H), 3.02 (bs, 3H), 2.85 (bs, 3H)	1293		MS (ESI) m/z 765.30 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.26 (bs, 1H), 8.82 (d, J = 4.8 Hz, 1H), 8.28 (s, 1H), 7.93 (s, 1H), 7.59 (d, J = 8.8 Hz, 1H), 7.46 (d, J = 4.4 Hz, 1H), 7.42 (s, 1H), 7.35 (d, J = 10.8 Hz, 1H), 4.39 (bs, 2H), 4.23 (bs, 2H), 3.63 (bs, 2H), 3.31 (bs, 2H), 2.95 (m, 4H), 2.60 (t, J = 7.2 Hz, 4H), 1.71 (s, 3H)
1291		MS (ESI) m/z 709.12 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.83 (d, J = 4.4 Hz, 1H), 8.23 (s, 1H), 7.96 (s, 1H), 7.60 (dd, J = 6.4 Hz, 2.4 Hz, 1H), 7.48 (d, J = 4.8 Hz, 1H), 7.42 (d, J = 2.4 Hz, 1H), 7.36 (d, J = 8.8 Hz, 1H), 4.40 (s, 2H), 4.24 (s, 2H), 3.85 (s, 4H), 3.29 (bs, 4H), 3.12 (bs, 1H), 1.76 (s, 3H), 1.01 (s, 2H), 0.85 (s, 2H)	1298		MS (ESI) m/z 650.26 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.06 (bs, 1H), 8.75 (d, J = 4.8 Hz, 1H), 8.57 (s, 1H), 8.14 (s, 1H), 7.77 (d, J = 8.0 Hz, 1H), 7.70-7.66 (m, 2H), 7.55 (d, J = 4.8 Hz, 1H), 4.88 (s, 2H), 3.38-3.23 (m, 4H), 3.18-3.08 (m, 2H), 2.78 (s, 6H), 2.16 (s, 3H)
1292		MS (ESI) m/z 759.38 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.30 (bs, 1H), 8.83 (d, J = 4.8 Hz, 1H), 8.25 (s, 1H), 7.96 (s, 1H), 7.60 (dd, J = 6.4, 9.2 Hz, 1H), 7.47 (d, J = 4.8 Hz, 1H), 7.42 (d, J = 2.4 Hz, 1H), 7.36 (d, J = 8.8 Hz, 1H), 4.40 (s, 2H), 4.24 (s, 2H), 3.85-3.52 (m, 5H), 3.02 (m, 8H), 1.75 (m, 3H)	1372		MS (ESI) m/z 606.1 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.63 (dd, J = 5.0, 0.8 Hz, 1H), 8.38 (d, J = 1.7 Hz, 1H), 8.26 (dd, J = 1.7, 0.8 Hz, 1H), 8.03 (dd, J = 1.7, 0.8 Hz, 1H), 7.70 (dd, J = 5.0, 1.8 Hz, 1H), 7.57 – 7.39 (m, 2H), 7.27 (d, J = 8.9 Hz, 1H), 4.40 (s, 4H), 3.39 (s, 3H), 2.23 (s, 3H)

[0968]

1374		MS (ESI) m/z 628.2 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.36 (d, J = 1.7 Hz, 1H), 8.25 (s, 3H), 7.99 (d, J = 1.7 Hz, 1H), 7.60 (dd, J = 8.9, 2.7 Hz, 1H), 7.45 (s, 1H), 7.39 – 7.34 (m, 2H), 4.41 (d, J = 5.1 Hz, 2H), 4.27 (t, J = 5.1 Hz, 2H), 3.41 (d, J = 6.0 Hz, 2H), 3.28 (t, J = 6.5 Hz, 2H), 1.83 (s, 3H)	1377		MS (ESI) m/z 746.4 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.31 (s, 1H), 8.16 (s, 1H), 7.60 (dd, J = 8.9, 2.7 Hz, 1H), 7.45 – 7.34 (m, 3H), 5.49 (d, J = 22.9 Hz, 2H), 4.58 (t, J = 13.1 Hz, 2H), 4.42 (s, 2H), 4.29 (s, 2H), 3.82 (s, 2H), 2.72 (s, 3H), 1.84 (s, 3H)
1375		MS (ESI) m/z 624.0 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 11.41 (s, 1H), 8.83 (d, J = 4.7 Hz, 1H), 8.34 (d, J = 1.6 Hz, 1H), 7.95 (s, 1H), 7.81 (d, J = 1.6 Hz, 1H), 7.59 (dd, J = 8.9, 2.7 Hz, 1H), 7.45 – 7.39 (m, 2H), 7.35 (d, J = 9.0 Hz, 1H), 6.92 (s, 1H), 4.40 (d, J = 5.0 Hz, 2H), 4.25 (t, J = 4.9 Hz, 2H), 1.74 (s, 3H)	1380		MS (ESI) m/z 690.1 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.60 – 8.48 (m, 1H), 8.37 (s, 1H), 8.12 (s, 1H), 7.86 (d, J = 7.8 Hz, 1H), 7.60 (dd, J = 8.9, 2.8 Hz, 1H), 7.52 – 7.42 (m, 3H), 7.36 (d, J = 9.0 Hz, 1H), 4.50 – 4.34 (m, 2H), 4.27 (d, J = 5.4 Hz, 2H), 2.72 (s, 3H), 2.10 (s, 3H), 1.81 (s, 3H)
1376		MS (ESI) m/z 714.3 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.27 (s, 1H), 7.95 (s, 1H), 7.60 (dd, J = 8.9, 2.7 Hz, 1H), 7.46 – 7.40 (m, 2H), 7.36 (d, J = 9.0 Hz, 1H), 4.40 (d, J = 5.0 Hz, 2H), 4.25 (s, 2H), 3.91 (s, 2H), 2.70 (s, 5H), 2.58 (s, 2H), 1.83 (s, 3H)	1381		MS (ESI) m/z 694.0 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.87 (s, 1H), 8.76 – 8.65 (m, 1H), 8.34 (s, 1H), 8.14 (s, 1H), 7.73 (t, J = 5.5 Hz, 1H), 7.60 (dd, J = 8.9, 2.6 Hz, 1H), 7.49 – 7.40 (m, 2H), 7.37 (d, J = 9.0 Hz, 1H), 4.50 – 4.18 (m, 4H), 2.72 (s, 3H), 1.87 (s, 3H)

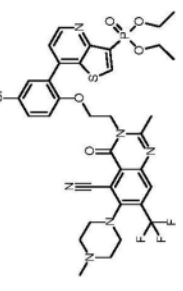
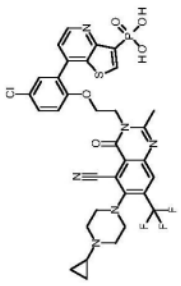
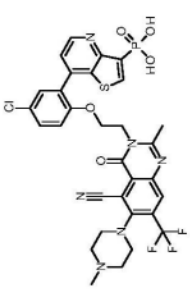
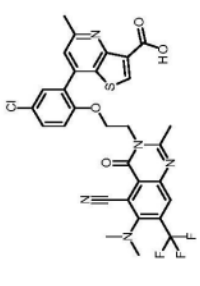
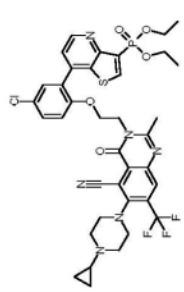
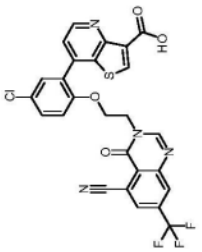
[0969]

1383		MS (ESI) m/z 708.2 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.42 (s, 1H), 8.28 (s, 1H), 8.05 (s, 1H), 7.98 – 7.90 (m, 1H), 7.60 (dd, J = 8.9, 2.7 Hz, 1H), 7.47 – 7.40 (m, 2H), 7.37 (d, J = 9.0 Hz, 1H), 4.42 (t, J = 5.0 Hz, 2H), 4.29 (d, J = 4.9 Hz, 2H), 2.73 (s, 3H), 2.58 (d, J = 2.9 Hz, 3H), 1.88 (s, 3H)	1389		MS (ESI) m/z 706.2 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 10.03 (s, 1H), 9.47 (s, 1H), 9.18 (s, 1H), 8.23 (s, 1H), 7.60 (dd, J = 8.9, 2.7 Hz, 1H), 7.49 (s, 1H), 7.41 (d, J = 9.0 Hz, 1H), 7.30 (d, J = 2.7 Hz, 1H), 7.19 (s, 1H), 4.53 (t, J = 5.2 Hz, 2H), 4.15 (t, J = 5.2 Hz, 2H), 2.67 (d, J = 0.7 Hz, 3H), 2.33 (s, 3H), 2.29 (s, 3H)
1384		MS (ESI) m/z 728.0 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.72 (d, J = 9.9 Hz, 1H), 8.31 (s, 1H), 8.13 (s, 1H), 8.03 (d, J = 9.1 Hz, 1H), 7.60 (dd, J = 8.9, 2.7 Hz, 1H), 7.45 (s, 1H), 7.43 (d, J = 2.7 Hz, 1H), 7.36 (d, J = 9.0 Hz, 1H), 4.53 – 4.20 (m, 4H), 2.72 (s, 3H), 1.88 (s, 3H)	1391		MS (ESI) m/z 711.0 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.13 (s, 1H), 7.93 (s, 1H), 7.58 (dd, J = 8.9, 2.7 Hz, 1H), 7.39 – 7.31 (m, 2H), 7.28 (s, 1H), 4.40 (s, 2H), 4.26 (s, 2H), 3.87 (s, 5H), 3.57 (d, J = 11.7 Hz, 2H), 3.27 (d, J = 12.9 Hz, 2H), 3.09 (d, J = 10.7 Hz, 2H), 2.91 (d, J = 4.2 Hz, 3H), 2.66 (s, 3H), 1.83 (s, 3H)
1388		MS (ESI) m/z 708.1 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.63 – 8.59 (m, 1H), 8.33 (s, 1H), 8.11 (s, 1H), 7.60 (dd, J = 8.9, 2.7 Hz, 1H), 7.50 (d, J = 10.7 Hz, 1H), 7.45 (s, 1H), 7.43 (d, J = 2.7 Hz, 1H), 7.36 (d, J = 9.0 Hz, 1H), 4.53 – 4.02 (m, 4H), 2.72 (s, 3H), 2.62 (s, 3H), 1.85 (s, 3H)	1392		MS (ESI) m/z 740.9 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 9.79 (s, 1H), 7.93 (s, 1H), 7.61 (dd, J = 8.9, 2.7 Hz, 1H), 7.44 (s, 1H), 7.41 (d, J = 2.7 Hz, 1H), 7.37 (d, J = 9.0 Hz, 1H), 5.35 (s, 1H), 4.41 (t, J = 5.0 Hz, 2H), 4.26 (t, J = 5.0 Hz, 2H), 3.97 (t, J = 12.1 Hz, 2H), 3.79 (t, J = 5.2 Hz, 2H), 3.64 (d, J = 11.8 Hz, 2H), 3.15 (dd, J = 29.0, 12.1 Hz, 4H), 2.71 (s, 3H), 2.43 (s, 3H), 1.97 (s, 3H)

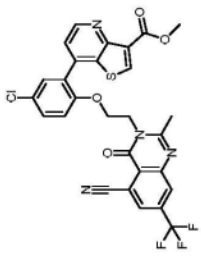
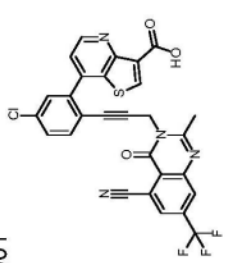
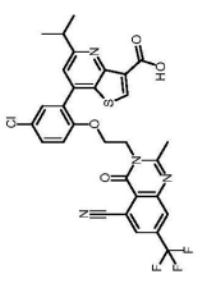
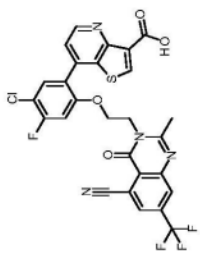
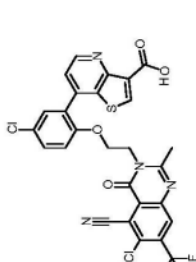
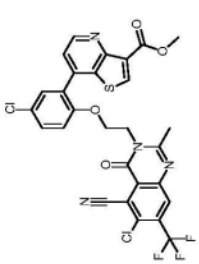
[0970]

1393		[01858] MS (ESI) m/z 741.0 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.59 (s, 2H), 7.93 (s, 1H), 7.60 (dd, J = 8.9, 2.7 Hz, 1H), 7.43 (s, 1H), 7.41 (d, J = 2.7 Hz, 1H), 7.36 (d, J = 9.0 Hz, 1H), 4.42 (t, J = 5.6 Hz, 4H), 4.26 (t, J = 5.0 Hz, 2H), 3.16 (s, 4H), 3.00 (s, 2H), 2.82 (s, 4H), 2.70 (s, 3H), 2.40 (s, 3H), 1.92 (s, 3H)
1417		MS (ESI) m/z 708.1 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 10.05 (s, 1H), 8.04 – 7.95 (m, 1H), 7.61 (dd, J = 8.9, 2.7 Hz, 1H), 7.45 (s, 1H), 7.41 (d, J = 2.7 Hz, 1H), 7.37 (d, J = 9.0 Hz, 1H), 6.54 (s, 1H), 5.91 (s, 1H), 4.42 (t, J = 5.1 Hz, 2H), 4.34 – 4.21 (m, 2H), 4.13 (d, J = 17.4 Hz, 1H), 3.84 (d, J = 16.9 Hz, 1H), 3.70 – 3.57 (m, 1H), 3.40 – 3.27 (m, 1H), 3.02 – 2.89 (m, 3H), 2.71 (s, 3H), 2.64 (s, 1H), 2.41 (s, 3H), 1.98 (s, 3H)
1394		MS (ESI) m/z 696.4 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 9.77 (s, 1H), 9.59 (s, 1H), 8.15 (d, J = 5.8 Hz, 1H), 7.94 (d, J = 2.2 Hz, 1H), 7.61 (dd, J = 8.9, 2.7 Hz, 1H), 7.47 (s, 1H), 7.44 (d, J = 2.6 Hz, 1H), 7.37 (d, J = 9.0 Hz, 1H), 4.42 (t, J = 5.0 Hz, 2H), 4.35 – 4.18 (m, 3H), 4.01 (dt, J = 22.5, 10.9 Hz, 2H), 3.11 (d, J = 8.1 Hz, 1H), 3.01 (q, J = 7.5 Hz, 2H), 2.86 (dd, J = 11.5, 5.1 Hz, 2H), 1.81 (s, 3H), 1.36 (t, J = 7.5 Hz, 3H)
1420		MS (ESI) m/z 723.2 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 9.37 (s, 1H), 7.78 (s, 1H), 7.60 (dd, J = 8.9, 2.7 Hz, 1H), 7.42 – 7.40 (m, 2H), 7.36 (d, J = 8.9 Hz, 1H), 4.70 (s, 2H), 4.61 (s, 2H), 4.49 – 4.39 (m, 2H), 4.38 (t, J = 5.0 Hz, 2H), 4.27 – 4.17 (m, 4H), 2.82 (d, J = 5.2 Hz, 3H), 2.70 (s, 3H), 1.92 (s, 3H)
1416		MS (ESI) m/z 711.0 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 9.75 (s, 1H), 7.93 (s, 1H), 7.61 (dd, J = 8.9, 2.7 Hz, 1H), 7.44 (s, 1H), 7.41 (d, J = 2.7 Hz, 1H), 7.37 (d, J = 9.0 Hz, 1H), 4.40 (t, J = 4.9 Hz, 2H), 4.26 (t, J = 5.0 Hz, 2H), 3.86 (t, J = 12.3 Hz, 2H), 3.56 (d, J = 11.4 Hz, 3H), 3.20 (d, J = 12.6 Hz, 2H), 3.09 (q, J = 11.2 Hz, 2H), 2.95 – 2.87 (m, 3H), 2.71 (s, 3H), 2.42 (s, 3H), 1.96 (s, 3H)
1570		MS (ESI) m/z 715.47 [M+1]+; 1H-NMR (400 MHz, DMSO-d6) δ 8.77 (d, J = 5.2 Hz, 1H), 8.66 (s, 1H), 7.93 (s, 1H), 7.75 (d, J = 8.4 Hz, 1H), 7.70-7.66 (m, 2H), 7.56 (d, J = 4.4 Hz, 1H), 4.82 (s, 2H), 4.73-4.41 (m, 8H), 3.05 (bs, 1H), 2.11 (s, 3H), 0.77 (bs, 4H)

[0971]

1612		1615	
MS (ESI) m/z 775.53 [M+1]+; 1H NMR (400 MHz, DMSO-d6 与 D2O) δ 8.75 (d, J = 4.68 Hz 1H), 8.10 (d, J = 9.44 Hz, 1H), 8.03 (s, 1H), 7.53 (dd, J = 2.56, 8.92 Hz, 1H), 7.34 (d, J = 2.60 Hz, 1H), 7.31 (d, J = 4.68 Hz, 1H), 7.27 (d, J = 9.0 Hz, 1H), 4.35 (bs, 2H), 4.25-4.20 (m, 6H), 3.55 (bs, 2H), 2.93 (bs, 2H), 2.50 (bs, 2H), 2.20 (s, 5H), 1.58 (s, 3H), 1.27 (t, J = 7.04 Hz, 6H)		MS (ESI) m/z 745.50 [M+1]+; 1H NMR (400 MHz, DMSO-d6 与 D2O) δ 8.63 (d, J = 4.80 Hz, 1H), 8.12 (s, 1H), 7.98 (d, J = 8.80 Hz, 1H), 7.49 (dd, J = 2.40, 8.80 Hz, 1H), 7.32 (d, J = 2.40 Hz, 1H), 7.23 (d, J = 9.20 Hz, 1H), 7.14 (d, J = 4.4 Hz, 1H), 4.31 (s, 2H), 4.20 (s, 2H), 3.49 (bs, 3H), 2.84 (bs, 4H), 1.75 (bs, 2H), 1.70 (s, 3H), 0.44 (d, J = 6.00 Hz, 2H), 0.38 (bs, 2H)
1613		1619	
MS (ESI) m/z 719.52 [M+1]+ ; 1H NMR (400 MHz, DMSO-d6 与 D2O) δ 8.60 (d, J = 4.00 Hz 1H), 8.14 (s, 1H), 7.97 (d, J = 8.80 Hz, 1H), 7.49 (dd, J = 2.40, 8.80 Hz, 1H), 7.34 (d, J = 2.00 Hz, 1H), 7.24 (d, J = 9.20 Hz, 1H), 7.13 (d, J = 4.80 Hz, 1H), 4.32 (bs, 2H), 4.21 (bs, 2H), 3.67 (bs, 2H), 3.11 (bs, 4H), 2.76 (bs, 2H), 2.59 (s, 3H), 1.74 (s, 3H)		MS (ESI) m/z 642.01[M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.33 (s, 1H), 7.89 (s, 1H), 7.59 (dd, J = 2.60, 8.88 Hz, 1H), 7.43 (s, 1H), 7.42 (d, J = 2.64 Hz, 1H), 7.36 (d, J = 8.96 Hz, 1H), 4.39 (t, J = 4.68 Hz, 2H), 4.23 (t, J = 4.64 Hz, 2H), 2.94 (s, 6H), 2.70 (s, 3H), 1.81 (s, 3H)	
1614		1899	
MS (ESI) m/z 801.60 [M+1]+; 1H NMR (400 MHz, DMSO-d6 与 D2O) δ 8.75 (d, J = 4.80 Hz, 1H), 8.09 (d, J = 9.60 Hz, 1H), 8.03 (s, 1H), 7.53 (dd, J = 2.40, 8.80 Hz, 1H), 7.33-7.30 (m, 2H), 7.26 (d, J = 8.80 Hz, 1H), 4.34 (s, 2H), 4.23-4.19 (m, 6H), 3.50 (bs, 2H), 2.79 (bs, 5H), 1.67 (bs, 2H), 1.58 (s, 3H), 1.27 (t, J = 6.80 Hz, 6H), 0.43 (bs, 2H), 0 .35 (bs, 2H)		MS (ESI) m/z 571 [M+1]; 1H NMR (400 MHz, DMSO-d6) δ 8.79 (s, 1H), 8.43 (d, J=16.6 Hz, 2H), 8.11 (s, 1H), 7.79 (bs, 1H), 7.60 (s, 1H), 7.46 (m, 2H), 7.35 (m, 1H), 4.40 (s, 2H), 4.20 (s, 2H), 3.89 (s, 1H)	

[0972]

1900		MS (ESI) m/z 599.1 [M+1]	
1901		MS (ESI) m/z 579.15 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.75(d, J =4.48 Hz, 1H), 8.59 (s, 1H), 8.41 (s, 1H), 8.14 (s, 1H), 7.76 (d, J=8.8 Hz, 1H), 7.69 (d, J=6.04 Hz, 2H), 7.56 (d, J=4.48 Hz, 1H), 4.88(s, 2H), 2.10 (s, 3H)
1902		MS (ESI) m/z 627.8 [M+1]+	
1903		MS (ESI) m/z 603.21 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.84 (d, J = 4.8 Hz, 1H), 8.38 (bs, 1H), 8.28 (s, 1H), 8.01 (bs, 1H), 7.63 (d, J = 8.4 Hz, 1H), 7.54 (d, J = 11.4 Hz, 1H), 7.49 (d, J = 4.8 Hz, 1H), 4.43 (t, J = 4.4 Hz, 2H), 4.25 (t, J = 4.4 Hz, 2H), 1.73 (s, 3H)
1904		MS (ESI) m/z 619.07 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.86 (d, J = 4.4 Hz, 1H), 8.24 (s, 1H), 8.08 (s, 1H), 7.60 (dd, J = 8.8, 2.6 Hz, 1H), 7.51 (d, J = 4.8 Hz, 1H), 7.43 (d, J = 2.6 Hz, 1H), 7.36 (d, J = 8.8 Hz, 1H), 4.41 (t, J = 4.7 Hz, 2H), 4.25 (t, J = 4.7 Hz, 2H), 1.69 (s, 3H)
1905		MS (ESI) m/z 633.04 [M+1]+	

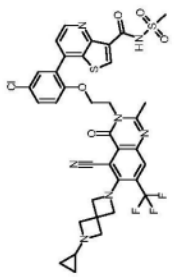
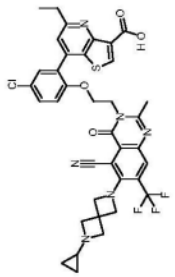
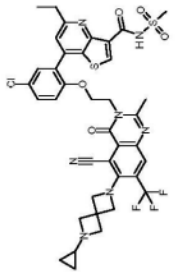
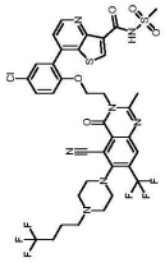
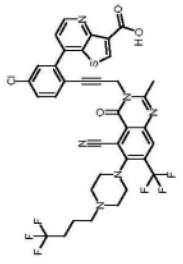
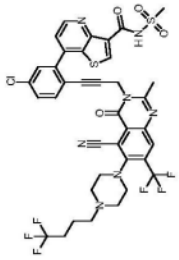
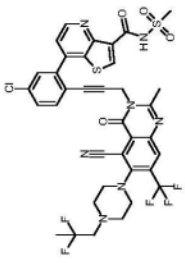
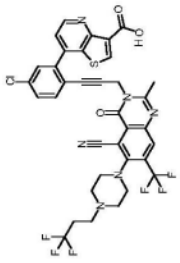
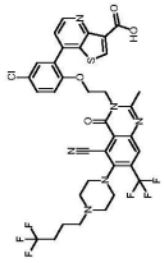
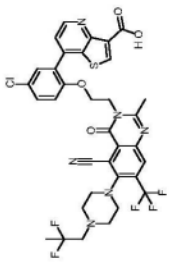
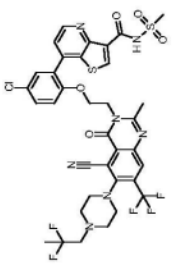
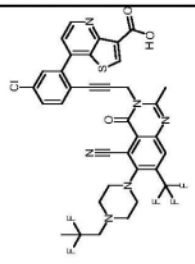
[0973]

1906		1907	
	MS (ESI) m/z 656.15 [M+1]		MS (ESI) m/z 724.6 [M+1]+
1908		1909	
	MS (ESI) m/z 722.0 [M+1]+		MS (ESI) m/z 708.1 [M+1]+
1910		1911	
	MS (ESI) m/z 690.3 [M+1]+		

[0974]

1912	MS (ESI) m/z 773.3 [M+1]+	1915	1918
1913	MS (ESI) m/z 850.3 [M+1]+	1916	1919
1914		1917	1920

[0975]

1930	1931	1932	
			
1927	1928	1929	
			
1924	1925	1926	
			
1921	1922	1923	
			

[0976]

1933	2015	2019	MS (ESI) m/z 624.0 [M+1]+
1934	2016	2028	MS (ESI) m/z 747.2 [M+1]+
1994	2018	2036	MS (ESI) m/z 615.1 [M+1]+
2037	MS (ESI) m/z 626.05 [M+1]+		

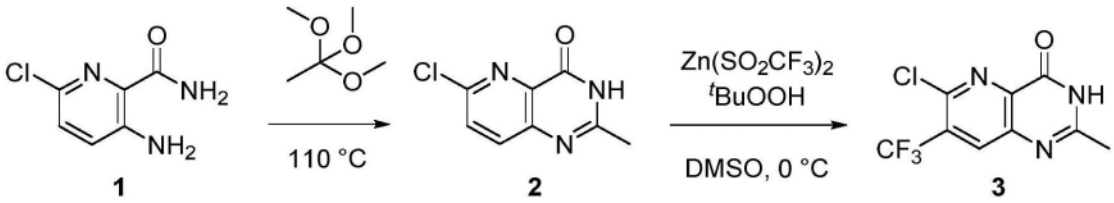
[0977] 实施例3.合成其他化合物的通用方法

[0978] 表3中的化合物可以使用实施例3中描述的方法来合成。实施例1和2中描述的许多

反应也用于合成表3中的化合物。

[0979] 实施例3A.合成左侧的方法

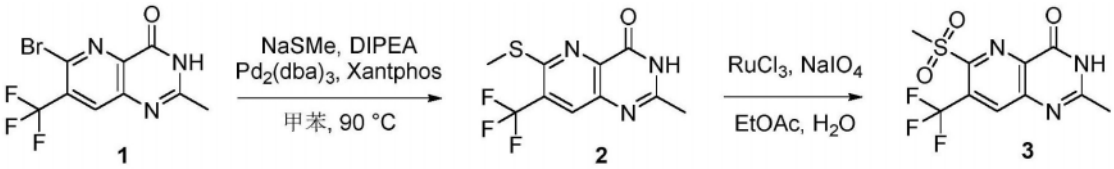
[0980] 实施例3A.1

[0981] 

[0982] 在配备搅拌棒的火焰干燥的圆底烧瓶中将3-氨基-6-氯吡啶甲酰胺(1,3.00g,16.6mmol)溶于1,1,1-三乙氧基乙烷(45mL,16.6mmol)。将反应混合物加热到110℃持续90min,然后冷却至10℃,并用冷醚稀释。将固体过滤,并用冷醚洗涤数次。将固体真空干燥,得到6-氯-2-甲基吡啶并[3,2-d]嘧啶-4(3H)-酮(2)。

[0983] 在配备搅拌棒的圆底烧瓶中将6-氯-2-甲基吡啶并[3,2-d]嘧啶-4(3H)-酮(2,1.00g,5.1mmol)溶于DMSO(30mL)中。将反应混合物在10℃下搅拌,同时一批加入双(三氟甲基磺酰基)锌(4.23g,12.8mmol)。然后通过加料漏斗滴加叔丁基过氧化氢(3.53mL,19.2mmol)。5min后,将反应混合物升温至室温,再过5min后将其升温至50℃持续6.5h。将反应混合物冷却至室温,然后反应混合物用饱和碳酸氢钠和乙酸乙酯稀释。分离各层,并将水相用乙酸乙酯萃取三次。合并的有机物质用盐水洗涤,并用硫酸镁干燥。将固体过滤并真空除去溶剂,得到6-氯-2-甲基-7-(三氟甲基)吡啶并[3,2-d]嘧啶-4(3H)-酮(3)。

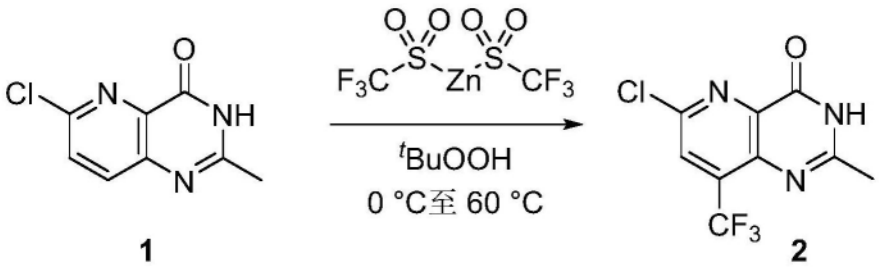
[0984] 实施例3A.2

[0985] 

[0986] 将6-溴-2-甲基-7-(三氟甲基)吡啶并[3,2-d]嘧啶-4(3H)-酮(1,0.3g,0.977mmol),甲硫醇钠(0.102g,1.46mmol),N,N-二异丙基乙胺(0.378g,2.93mmol)和Xantphos(0.056g,0.097mmol)的甲苯(3mL)溶液用氩气脱气10min。然后加入三(二亚苄基丙酮)二钯(0)(0.042g,0.048mmol),并将混合物用氩气再脱气5min。将反应混合物在90℃下搅拌2h。在该时间后,将反应混合物用水稀释,并用乙酸乙酯萃取。将有机层用无水硫酸钠干燥,过滤并减压浓缩至干,得到粗产物。用硅胶(100-200目)以及用60-80%乙酸乙酯的己烷溶液为洗脱剂,通过快速柱色谱将其纯化,得到2-甲基-6-(甲硫基)-7-(三氟甲基)吡啶并[3,2-d]嘧啶-4(3H)-酮(2)。

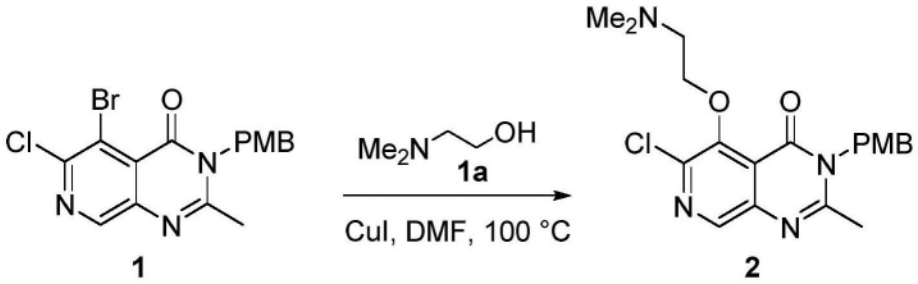
[0987] 向2-甲基-6-(甲硫基)-7-(三氟甲基)吡啶并[3,2-d]嘧啶-4(3H)-酮(2,0.2g,0.727mmol)在乙酸乙酯(4.0mL)和水(1.0mL)中的溶液中加入氯化钌(III)(0.007g,0.0363mmol),接着加入高碘酸钠(0.929g,4.36mmol)。将反应混合物在室温下搅拌30min。在该时间后,将反应混合物过滤,并将滤液减压浓缩,得到粗产物。通过戊烷洗涤将其纯化,得到2-甲基-6-(甲基磺酰基)-7-(三氟甲基)吡啶并[3,2-d]嘧啶-4(3H)-酮(3)。

[0988] 实施例3A.3

[0989] 

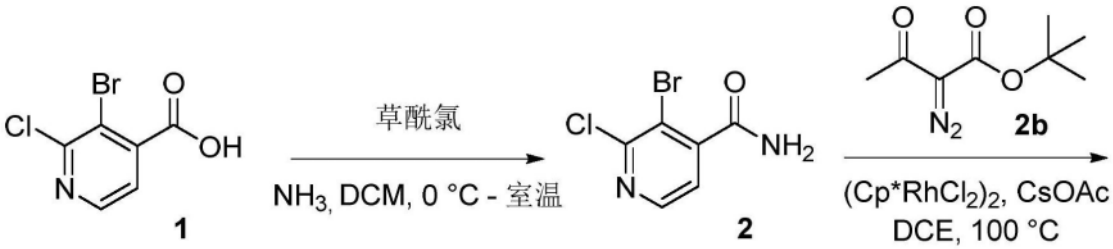
[0990] 在配备搅拌棒的圆底烧瓶中将6-氯-2-甲基吡啶并[3,2-d]嘧啶-4(3H)-酮(1,1.00g,5.1mmol)溶于二甲基亚砜(30mL)。将反应混合物在10℃下搅拌,同时一批加入双(三氟甲基磺酰基)锌(4.23g,12.8mmol)。然后通过加料漏斗滴加叔丁基过氧化氢(3.53mL,19.2mmol)。5min后将反应混合物升温至室温,再过5min后将其升温至50℃持续6.5h。将反应混合物冷却至室温,然后用饱和碳酸氢钠水溶液和乙酸乙酯稀释。分离各层,并将水相用乙酸乙酯萃取三次。合并的有机物质用盐水洗涤,并用硫酸镁干燥。将固体过滤并真空除去溶剂,得到6-氯-2-甲基-8-(三氟甲基)吡啶并[3,2-d]嘧啶-4(3H)-酮(2)的混合物。

[0991] 实施例3A.4

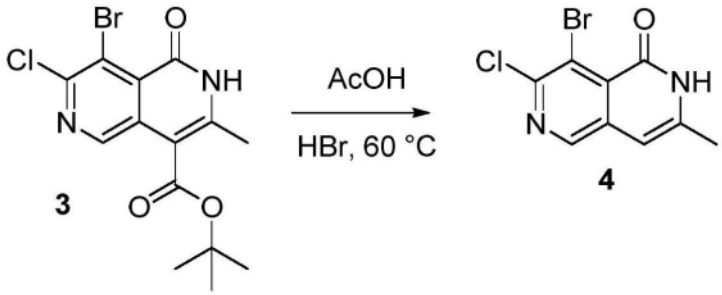
[0992] 

[0993] 在装有搅拌棒的可密封容器中将5-溴-6-氯-3-(4-甲氧基苄基)-2-甲基吡啶并[3,4-d]嘧啶-4(3H)-酮(1,50mg,0.13mmol)和碘化亚铜(I)(26.5mg,0.139mmol)混合,并悬浮于1mL 2-(二甲基氨基)乙-1-醇(1a)中。将得到的混合物用氩气吹扫3min,然后密封,剧烈搅拌,并在100℃下加热。10min后LCMS显示原料完全消耗完。将混合物冷却至室温并浓缩。将残留物溶于MeCN/DMSO,并通过制备HPLC纯化(MeCN/水+0.1%TFA),得到6-氯-5-(2-(二甲基氨基)乙氧基)-3-(4-甲氧基苄基)-2-甲基吡啶并[3,4-d]嘧啶-4(3H)-酮(2)。

[0994] 实施例3A.5



[0995]

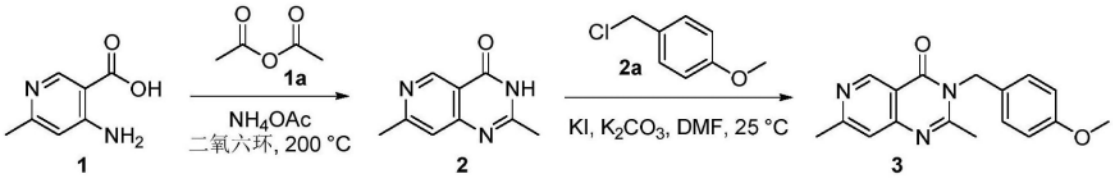


[0996] 在0℃下向3-溴-2-氯异烟酸(1,3.0g,12.76mmol)的二氯甲烷(20mL)溶液中加入N,N-二甲基甲酰胺(0.09mL,1.27mmol),接着加入草酰氯(1.7mL,19.14mmol)。然后将反应混合物在-25℃下搅拌2h。完成后,将反应混合物减压蒸发至干。粗反应混合物用二氯甲烷稀释(10mL),并以逐滴方式倒入冰冷的氨水中。将沉淀的固体通过烧结漏斗过滤并真空干燥,得到3-溴-2-氯异烟酰胺(2)。

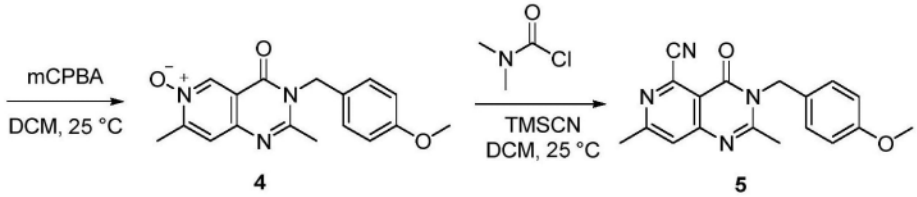
[0997] 在室温下在氮气气氛下向3-溴-2-氯异烟酰胺(2,2.5g,10.68mmol),五甲基环戊二烯基氯化铑(III)二聚体(0.33g,0.53mmol)和乙酸铯(1.02g,5.34mmol)的1,2-二氯乙烷(25mL)溶液中加入2-重氮-3-氧代丁酸叔丁酯(2b,2.96g,16.00mmol)。将反应混合物加热至100℃持续16h。完成后,将反应混合物冷却至室温,减压浓缩至干,接着用醚和戊烷洗涤,得到8-溴-7-氯-3-甲基-1-氧代-1,2-二氢-2,6-萘啶-4-甲酸叔丁酯(3)。

[0998] 向8-溴-7-氯-3-甲基-1-氧代-1,2-二氢-2,6-萘啶-4-甲酸叔丁酯(3,3.0g,8.00mmol)中加入30%氢溴酸的乙酸溶液(30mL),并将反应混合物在80℃下搅拌16h。完成后,用冰冷的水淬灭反应,并用乙酸乙酯萃取。将有机层用冷水洗涤,用无水硫酸钠干燥,过滤并减压浓缩至干,得到8-溴-7-氯-3-甲基-2,6-萘啶-1(2H)-酮(4)粗品。

[0999] 实施例3A.6



[1000]



[1001] 在配备搅拌棒的烘干的微波小瓶中将4-氨基-6-甲基烟酸(1,700mg,4.6mmol)和乙酸铵(1.58g,20.6mmol)溶于1,4-二氧六环(8mL)和乙酸酐(1a,1.74mL,18.4mmol)中。将反应混合物在微波反应器中在200℃下搅拌24h。真空除去溶剂。加入乙酸乙酯,将沉淀过

滤,并用乙酸乙酯洗一次。将固体真空干燥,得到2,7-二甲基吡啶并[4,3-d]嘧啶-4(3H)-酮(2)。

[1002] 在配备搅拌棒的烘干的螺旋盖小瓶中将2,7-二甲基吡啶并[4,3-d]嘧啶-4(3H)-酮(2,92mg,0.50mmol)和1-(氯甲基)-4-甲氧基苯(2a,0.08mL,0.60mmol)溶于N,N-二甲基甲酰胺(2.5mL)中。将反应混合物在室温下搅拌,同时依次加入碳酸钾(137.9mg,1mmol)和碘化钾(16.5mg,0.10mmol)。20h后,将反应混合物用乙酸乙酯稀释,然后用50:50水:盐水溶液洗涤,然后再用100%盐水洗涤两次。然后将有机物质用硫酸镁干燥,过滤,真空除去溶剂。通过硅胶色谱纯化(25-100%乙酸乙酯的己烷溶液),得到3-(4-甲氧基苄基)-2,7-二甲基吡啶并[4,3-d]嘧啶-4(3H)-酮(3)。

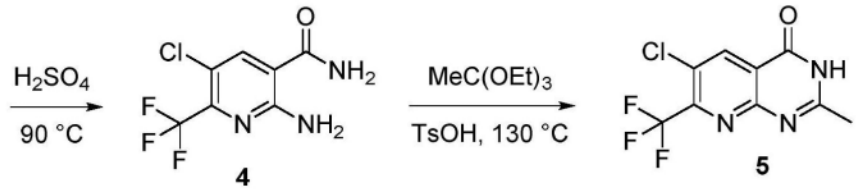
[1003] 在配备搅拌棒的烘干的螺旋盖小瓶中将3-(4-甲氧基苄基)-2,7-二甲基吡啶并[4,3-d]嘧啶-4(3H)-酮(3,109mg,0.37mmol)溶于二氯甲烷(2mL)中。将反应混合物在0℃下搅拌,同时缓慢加入3-氯过氧苯甲酸(84mg,0.49mmol)。5min后将反应混合物升温至室温。3h后将反应混合物用饱和碳酸氢钠水溶液和二氯甲烷稀释。分离各层,并将水相用二氯甲烷萃取一次。将合并的有机物质用盐水洗涤,并用硫酸镁干燥。将固体过滤,真空除去溶剂得到3-(4-甲氧基苄基)-2,7-二甲基-4-氧代-3,4-二氢吡啶并[4,3-d]嘧啶6-氧化物(4)。

[1004] 在配备搅拌棒的烘干的螺旋盖小瓶中将3-(4-甲氧基苄基)-2,7-二甲基-4-氧代-3,4-二氢吡啶并[4,3-d]嘧啶6-氧化物(4,25mg,0.06mmol)溶于二氯甲烷(1mL)中。将反应混合物在25℃下搅拌,然后依次加入三甲基氰硅烷(0.04mL,0.32mmol)和N,N-二甲基氨基甲酰氯(0.03mL,0.32mmol)。45min后将反应混合物升温至45℃。14h后将反应混合物冷却至室温,并真空除去溶剂。通过硅胶色谱纯化(25-80%乙酸乙酯的二氯甲烷溶液),得到3-(4-甲氧基苄基)-2,7-二甲基-4-氧代-3,4-二氢吡啶并[4,3-d]嘧啶-5-甲腈(5)。

[1005] 实施例3A.7



[1006]



[1007] 将5-氯-6-(三氟甲基)吡啶-2-胺(1,100mg,0.51mmol)和N-溴代丁二酰亚胺(91mg,0.51mmol)的MeCN(4mL)溶液在80℃下加热1hr。在该时间后,将反应混合物浓缩,用水稀释,并用乙酸乙酯萃取。将合并的有机层用水和盐水溶液洗涤,用硫酸钠干燥并浓缩。然后将粗物质直接装载到Isco装载柱上。用5至40%乙酸乙酯的己烷溶液为洗脱剂,通过柱色谱纯化,产物在约20%乙酸乙酯/己烷中洗脱。将期望的级分减压浓缩,得到3-溴-5-氯-6-(三氟甲基)吡啶-2-胺(2)。

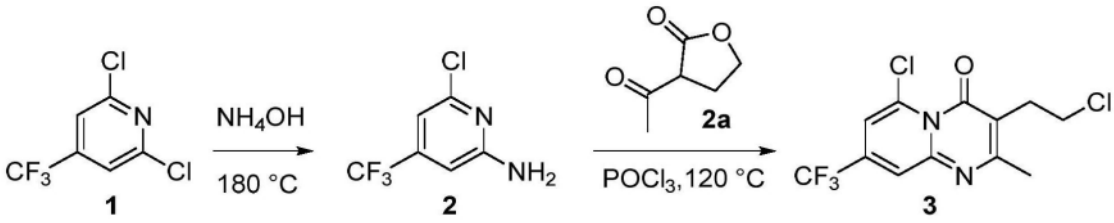
[1008] 将3-溴-5-氯-6-(三氟甲基)吡啶-2-胺(2,50mg,0.18mmol)和二氰基锌(24mg,0.19mmol)的NMP(3mL)溶液用氩气吹扫5-min,然后加入Pd(PPh3)4(21mg,0.018mmol)。将混合物在微波中在120℃下加热30min。完成后,将反应混合物直接装载到硅胶柱上。用0至

20％甲醇的二氯甲烷溶液为洗脱剂,通过柱色谱纯化,产物在约10％甲醇/二氯甲烷中洗脱。将期望的级分减压浓缩,得到2-氨基-5-氯-6-(三氟甲基)烟腈(3)。

[1009] 在圆底烧瓶中将2-氨基-5-氯-6-(三氟甲基)烟腈(3,550mg,2.5mmol)溶于浓缩硫酸(1mL)中,并将混合物在90℃下搅拌15min。在该时间后,停止反应,并将混合物冷却至室温。将反应混合物倒入冰水,并用饱和碳酸氢钠溶液调节至pH 8。过滤收集沉淀,用冷水洗涤并在高真空下干燥,得到2-氨基-5-氯-6-(三氟甲基)烟酰胺(4)。

[1010] 在小瓶中将2-氨基-5-氯-6-(三氟甲基)烟酰胺(4,65mg,0.27mmol),1,1,1-三乙氧基乙烷(0.13mL,1.09mmol)和乙醇(2mL)的溶液在油浴中加热至120℃持续3h。在该时间后,将反应混合物用50％DMSO/MeOH稀释,过滤,并将粗品通过HPLC纯化(C18,制备柱,5-35％MeCN/水+0.1％TFA),得到6-氯-2-甲基-7-(三氟甲基)吡啶并[2,3-d]嘧啶-4(3H)-酮(5)。

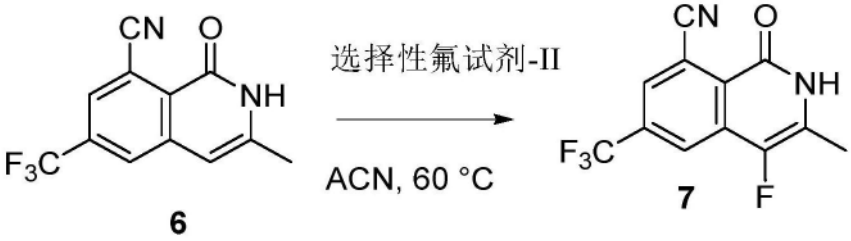
[1011] 实施例3A.8

[1012] 

[1013] 将2,6-二氯-4-(三氟甲基)吡啶(1,10.0g,4.6mmol)和氢氧化铵(50mL)的溶液在180℃下加热4h。完成后,将反应混合物过滤,用水洗涤并干燥,得到6-氯-4-(三氟甲基)吡啶-2-胺(2)。

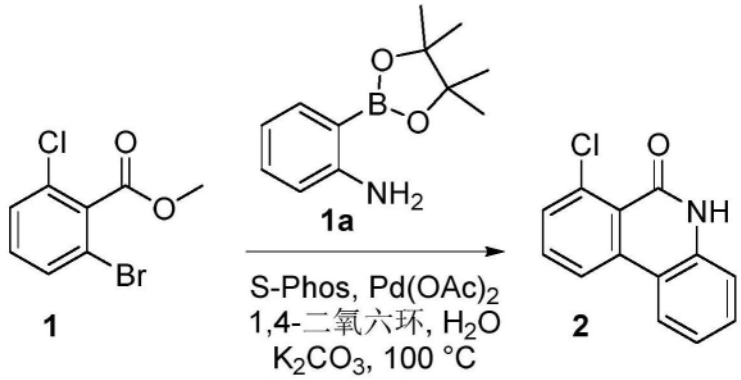
[1014] 在室温下向6-氯-4-(三氟甲基)吡啶-2-胺(2,2.2g,1.0mmol)在氧氯化磷(5mL)中的混合物加入3-乙酰基二氢呋喃-2(3H)-酮(2a,0.256g,2.0mmol),接着在20℃下加热搅拌1.5h。完成后,将反应混合物倒入碎冰中,并用乙酸乙酯萃取。将有机层用无水硫酸钠干燥,减压浓缩至干,得到6-氯-3-(2-氯乙基)-2-甲基-8-(三氟甲基)-4H-吡啶并[1,2-a]嘧啶-4-酮(3)。

[1015] 实施例3A.9

[1016] 

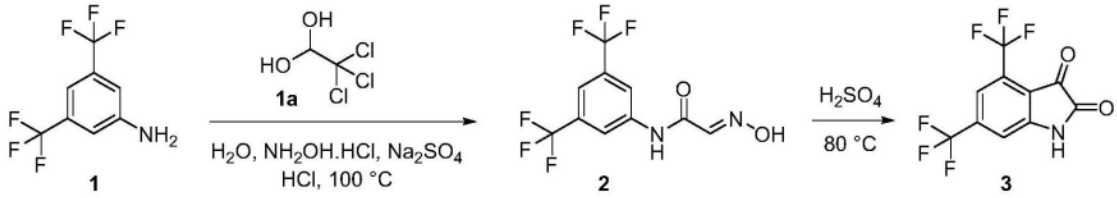
[1017] 向3-甲基-1-氧代-6-(三氟甲基)-1,2-二氢异喹啉-8-甲腈(6,0.2g,0.793mmol)的乙腈(2mL)溶液中加入1-氯甲基-4-氟-1,4-二氮杂二环(diazoniabicyclo)[2.2.2]辛烷双(四氟硼酸盐)或选择性氟试剂(selectfluor)(0.42g,1.190mmol)和催化量的乙酸,并且将反应混合物在60℃下搅拌8h。完成后,将反应混合物用水淬灭,并用乙酸乙酯萃取。将有机层用盐水溶液洗涤,用无水硫酸钠干燥,过滤并减压浓缩。用硅胶(100-200目)以及用0-40％乙酸乙酯的已烷溶液作为洗脱剂,通过柱色谱纯化粗品。将期望的级分减压浓缩,得到4-氟-3-甲基-1-氧代-6-(三氟甲基)-1,2-二氢异喹啉-8-甲腈(7)。

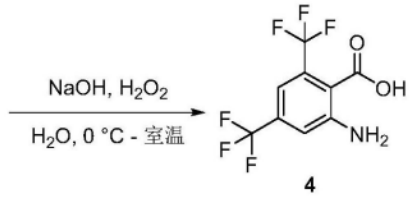
[1018] 实施例3A.10

[1019] 

[1020] 将一瓶1,4-二氧六环用氩气吹扫10min。在配备搅拌棒的烘干的螺旋盖小瓶中将2-溴-6-氯苯甲酸甲酯(1,257.7mg,1.0mmol),SPhos(37.0mg,0.09mmol),乙酸钯(II)(6.7mg,0.03mmol),碳酸钾(276.9mg,2.0mmol)和2-(4,4,5,5-四甲基-1,3,2-二氧杂硼杂环戊烷-2-基)苯胺(1a,257.7mg,1.0mmol)溶于1,4-二氧六环(2mL)和水(0.20mL)中。将小瓶密封,并将反应混合物用氩气吹扫5min。将反应混合物在100℃下剧烈搅拌13h。然后将反应混合物冷却至室温并用水稀释(20mL)。将固体过滤,得到粘稠黄色半固体,将其溶于二氯甲烷(20mL)中并再次过滤。收集并干燥剩余的白色固体,得到7-氯菲啶-6(5H)-酮(2)。

[1021] 实施例3A.11



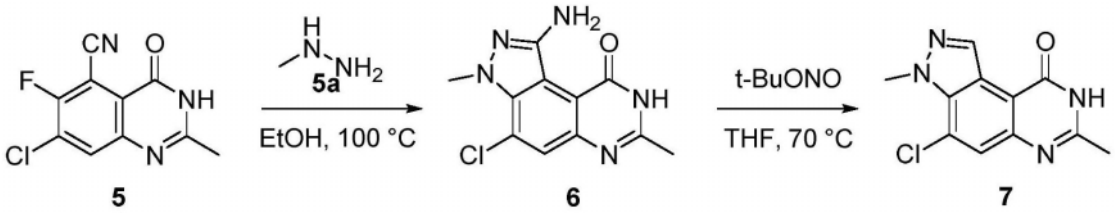
[1022] 

[1023] 在室温下向搅拌的3,5-双(三氟甲基)苯胺(1,10g,43.64mmol)和402f(1a,8.66g,52.37mmol)的水(90mL)溶液中加入羟胺盐酸盐(10.91g,157.11mmol),接着加入硫酸钠(13.63g,96.01mmol),并将混合物在相同温度下搅拌10min。缓慢加入浓盐酸(10.0mL)。将反应混合物加热至回流16h,并冷却至室温。将形成的固体沉淀过滤,用乙醚洗涤并真空干燥,得到(E)-N-(3,5-双(三氟甲基)苯基)-2-(羟基亚氨基)乙酰胺(2)。

[1024] 将(E)-N-(3,5-双(三氟甲基)苯基)-2-(羟基亚氨基)乙酰胺(2,8.0g,26.65mmol)的浓硫酸(60.0mL)溶液加热至85℃并搅拌4h。完成后,用冰冷的水淬灭反应。获得固体,过滤,用水洗涤并真空干燥,得到4,6-双(三氟甲基)二氢吲哚-2,3-二酮(3)。

[1025] 在0℃下向搅拌的4,6-双(三氟甲基)二氢吲哚-2,3-二酮(3,6.5g,22.96mmol)的1N氢氧化钠溶液(120.0mL)溶液中滴加过氧化氢溶液(30%的水溶液,9.10mL,80.36mmol)。将反应升温至室温并搅拌4h。完成后,将反应混合物用1N盐酸淬灭,并用乙酸乙酯萃取。将有机层用盐水洗涤,用无水硫酸钠干燥,过滤并减压浓缩至干,得到2-氨基-4,6-双(三氟甲基)苯甲酸(4)。

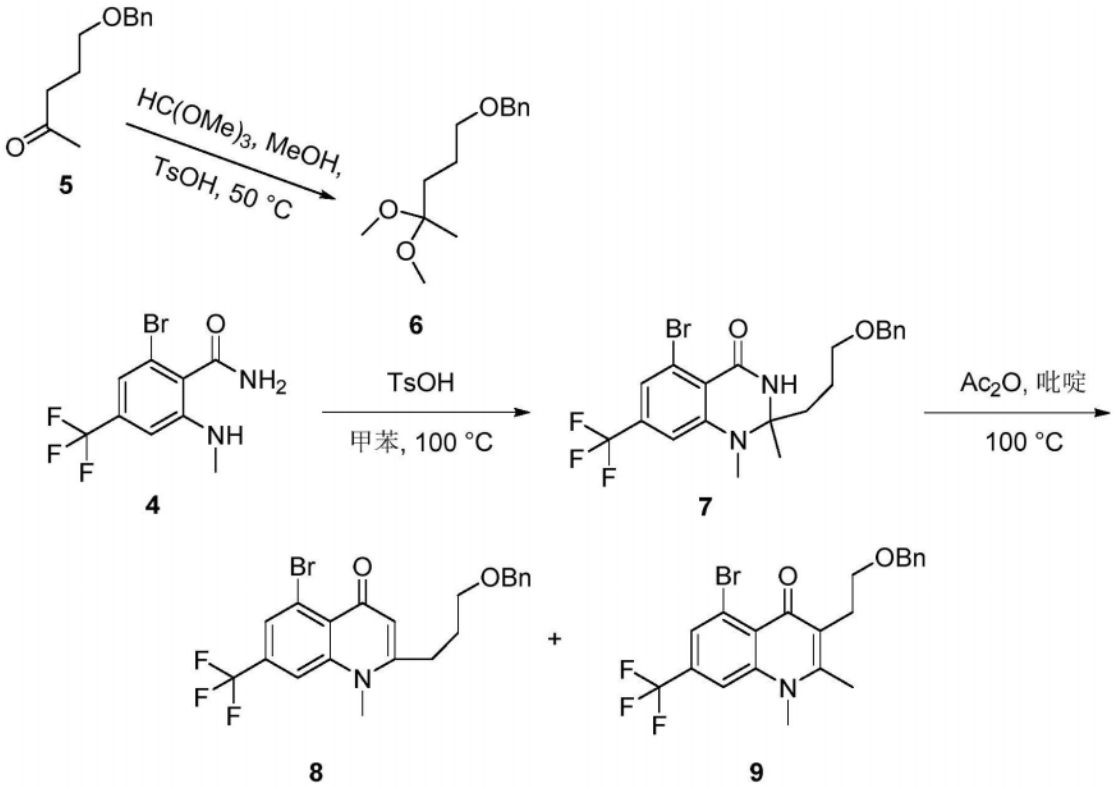
[1026] 实施例3A.12

[1027] 

[1028] 向7-氯-6-氟-2-甲基-4-氧代-3,4-二氢喹唑啉-5-甲腈(5,0.280g,1.17mmol)的乙醇(3mL)溶液中加入甲基肼(7,0.33mL,5.85mmol)。将该混合物在100℃下加热16h。将反应混合物冷却,过滤收集获得的沉淀并干燥,得到1-氨基-4-氯-3,7-二甲基-3,8-二氢-9H-吡唑并[4,3-f]喹唑啉-9-酮(6)。

[1029] 向1-氨基-4-氯-3,7-二甲基-3,8-二氢-9H-吡唑并[4,3-f]喹唑啉-9-酮(6,0.100g,0.37mmol)的四氢呋喃(2mL)溶液中加入亚硝酸叔丁酯(0.14mL,1.1mmol)。将该混合物在70℃下加热16h。将反应混合物冷却,用水稀释,并用10%甲醇的二氯甲烷溶液萃取。将有机层用无水硫酸钠干燥,过滤并浓缩。用0-70%乙酸乙酯的己烷溶液为洗脱剂,通过硅胶(100-200目)柱色谱纯化粗产物,得到4-氯-3,7-二甲基-3,8-二氢-9H-吡唑并[4,3-f]喹唑啉-9-酮(7)。

[1030] 实施例3A.13

[1031] 

[1032] 在室温下在氩气下在回流冷凝器下将对甲苯磺酸一水合物(74.7mg,0.39mmol)加入搅拌的5-苄氧基戊-2-酮(5,3.02g,15.7mmol)在甲醇(15mL)和原甲酸三甲酯(3.44mL,31.4mmol)中的溶液中。将得到的反应混合物在50℃下在氩气下在回流冷凝器下加热1.5h。冷却至室温后,加入甲醇钠(25重量%的甲醇溶液)(0.18mL,0.78mmol),然后在旋转蒸发仪上除去大部分的溶剂。将残留物分配于乙酸乙酯和其中含有少量0.1N NaOH的盐水之间。将

有机层用盐水洗涤,用硫酸镁干燥,过滤,在旋转蒸发仪上浓缩,并在高真空下干燥,得到(((4,4-二甲氧基戊基)氧基)甲基)苯(6)粗品。

[1033] 在具有搅拌棒的100mL圆底烧瓶中将2-溴-6-(甲基氨基)-4-(三氟甲基)苯甲酰胺(4,1.11g,3.7mmol),(((4,4-二甲氧基戊基)氧基)甲基)苯(6,1.33g,5.6mmol),对甲苯磺酸一水合物(35.5mg,0.19mmol)和甲苯(20mL)混合,剧烈搅拌,并在100℃下在氩气下加热40min。在旋转蒸发仪上除去大部分挥发物。残留物通过硅胶色谱纯化(10-80%乙酸乙酯的己烷溶液),得到2-(3-(苄氧基)丙基)-5-溴-1,2-二甲基-7-(三氟甲基)-2,3-二氢喹唑啉-4(1H)-酮(7)。

[1034] 在装有搅拌棒的可密封容器中将2-(3-(苄氧基)丙基)-5-溴-1,2-二甲基-7-(三氟甲基)-2,3-二氢喹唑啉-4(1H)-酮(7,1.64g,3.48mmol),乙酸酐(11.1mL,118mmol)和吡啶(1.12mL,13.9mmol)混合,密封,搅拌,并用加热器在110℃下加热16h。在旋转蒸发仪上除去大部分挥发物。将残留物溶于乙酸乙酯中,并通过硅胶色谱纯化(30-90%乙酸乙酯的己烷溶液),得到2-(3-(苄氧基)丙基)-5-溴-1-甲基-7-(三氟甲基)喹啉-4(1H)-酮(8)和3-(2-(苄氧基)乙基)-5-溴-1,2-二甲基-7-(三氟甲基)喹啉-4(1H)-酮(9)。

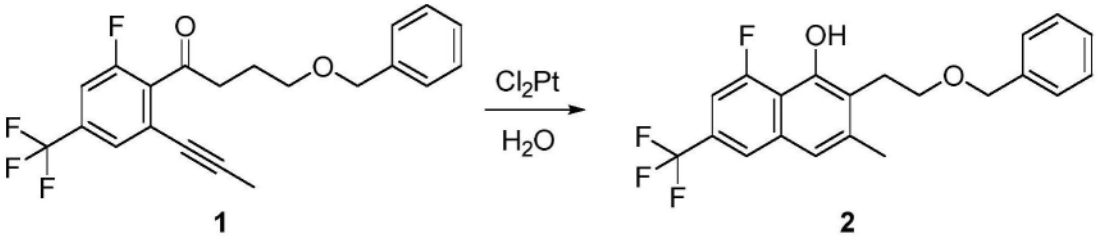
[1035] 实施例3A.14

[1036] 

[1037] 在0℃下向4-(4-甲基哌嗪-1-基)-5-(三氟甲基)苯-1,2-二胺(3,12.0g,43.7mmol)的乙醇(120mL)溶液中加入丙酮酸乙酯(10.0g,87.5mmol),并将反应混合物在室温下搅拌3h。完成后,将反应混合物冷却至0℃,过滤并用乙醚洗涤,将其减压干燥,得到3-甲基-7-(4-甲基哌嗪-1-基)-6-(三氟甲基)喹喔啉-2(1H)-酮(4)。

[1038] 在室温下向3-甲基-7-(4-甲基哌嗪-1-基)-6-(三氟甲基)喹喔啉-2(1H)-酮(4,4.3g,13.1mmol)溶液中加入磷酰氯(43mL)。然后将反应混合物在90℃下搅拌6h。完成后,将反应混合物用冰冷的水淬灭,用1N盐酸水溶液调节至pH 8,用乙酸乙酯萃取,用无水硫酸钠干燥,过滤并减压浓缩,得到粗物质。用4%甲醇的二氯甲烷溶液作为洗脱剂,通过Combiflash(12g,Redi Sep柱)纯化化合物粗品。将期望的级分减压浓缩,得到2-氯-3-甲基-7-(4-甲基哌嗪-1-基)-6-(三氟甲基)喹喔啉(5)。

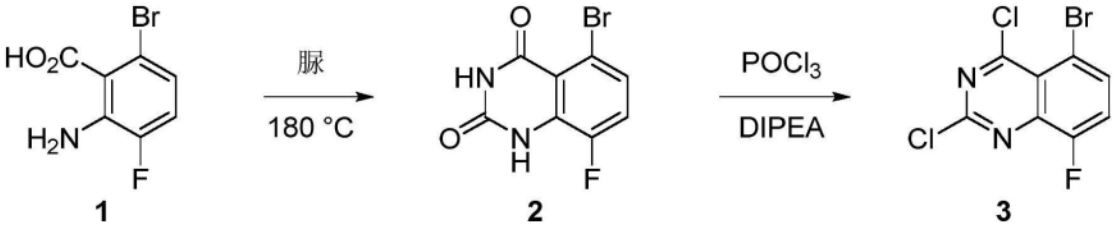
[1039] 实施例3A.15

[1040] 

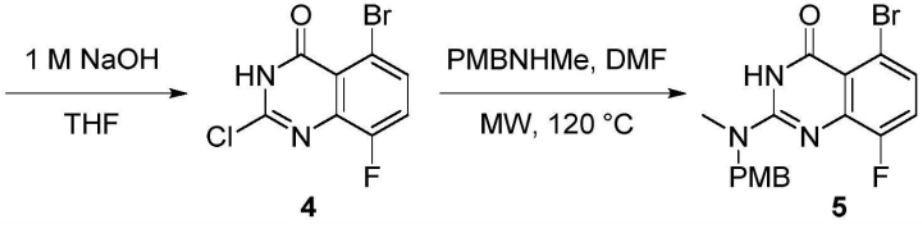
[1041] 向4-苄氧基-1-[2-氟-6-丙-1-炔基-4-(三氟甲基)苯基]丁-1-酮(1,50.mg,0.13200mmol)在1,4-二氧六环(1mL)和水(0.01mL,0.79000mmol)中的溶液中加入二氯化铂(3.52mg,0.01320mmol),并用CO(29.6mg,1.06mmol)鼓泡通过反应混合物5min。将混合物在25℃下搅拌30min,接着加热至100℃持续12h,后处理后得到2-(2-(苄氧基)乙基)-8-氟-3-

甲基-6-(三氟甲基)萘-1-酚(2)。

[1042] 实施例3A.16



[1043]



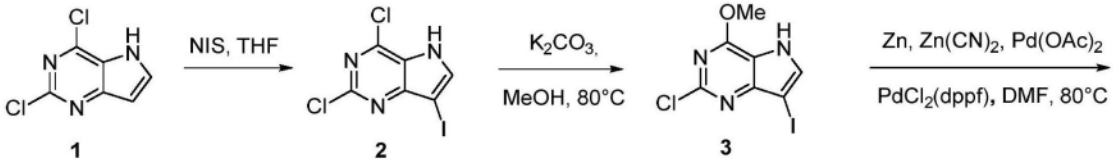
[1044] 将2-氨基-6-溴-3-氟苯甲酸(2.00g,8.55mmol)和脲(4.00g,66.60mmol)的混合物在180℃下加热3h,然后冷却至80℃。加入水(7-10mL)。将反应在回流下搅拌10m。将得到的混合物冷却至室温并过滤。将深棕色固体用水和乙醚洗涤并真空干燥,得到5-溴-8-氟喹唑啉-2,4(1H,3H)-二酮(2)。

[1045] 向5-溴-8-氟喹唑啉-2,4(1H,3H)-二酮(2,445mg,1.72mmol)的氧氯化磷(6.2mL)溶液中滴加N,N-二异丙基乙胺(1.20mL,6.89mmol)。将反应在120℃下搅拌过夜。将得到的混合物冷却至室温并与甲苯共沸。粗品用乙酸乙酯稀释并用水洗涤。合并的有机层用硫酸钠干燥,倾析并浓缩。将粗品通过柱色谱纯化(硅胶,乙酸乙酯/已烷=0-10%),得到5-溴-2,4-二氯-8-氟喹唑啉(3)。

[1046] 向5-溴-2,4-二氯-8-氟喹唑啉(3,395mg,1.33mmol)的四氢呋喃(2mL)溶液中加入1M氢氧化钠溶液(6.70mL,6.70mmol)。将反应在室温下搅拌1h 45min。将得到的混合物用乙酸酸化至约pH 4。过滤沉淀,用乙醚洗涤并真空干燥,得到5-溴-2-氯-8-氟喹唑啉-4(3H)-酮(4)。

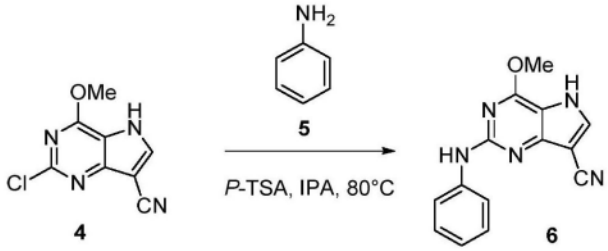
[1047] 向5-溴-2-氯-8-氟喹唑啉-4(3H)-酮(4,100mg,0.36mmol)的N,N-二甲基甲酰胺(2mL)溶液中加入1-(4-甲氧基苯基)-N-甲基甲胺(68uL,0.45mmol)。将反应在120℃下用微波处理10m。将得到的混合物冷却至室温并静置90min。将沉淀过滤并用乙醚洗涤。将滤液浓缩并和乙酸乙酯一起研磨。将合并的固体真空干燥,得到5-溴-8-氟-2-((4-甲氧基苄基)(甲基)氨基)喹唑啉-4(3H)-酮(5)。

[1048] 实施例3A.17



1 2 3

[1049]



4 6

[1050] 向2,4-二氯-5H-吡咯并[3,2-d]嘧啶(1,25.0g,132.9mmol)的四氢呋喃(250mL)溶液中在10min的时间段内分批加入N-碘代丁二酰亚胺(35.89g,159.5mmol),并将反应混合物在室温下搅拌30h。完成后,将反应混合物用水淬灭,并用乙酸乙酯萃取。将有机层用水洗涤,分离,用无水硫酸钠干燥并减压浓缩,得到2,4-二氯-7-碘-5H-吡咯并[3,2-d]嘧啶(2)。

[1051] 向2,4-二氯-7-碘-5H-吡咯并[3,2-d]嘧啶(2,30.0g,95.5mmol)的甲醇(600mL)溶液中在10min的时间段内分批加入碳酸钾(39.62g,286.7mmol),并将反应混合物在80℃下搅拌24h。完成后,将反应混合物浓缩,用水稀释,并用乙酸乙酯萃取。将有机层用水洗涤,分离,用无水硫酸钠干燥,并减压浓缩,得到粗品。将粗品与乙醚一起研磨,得到2-氯-7-碘-4-甲氧基-5H-吡咯并[3,2-d]嘧啶(3)。

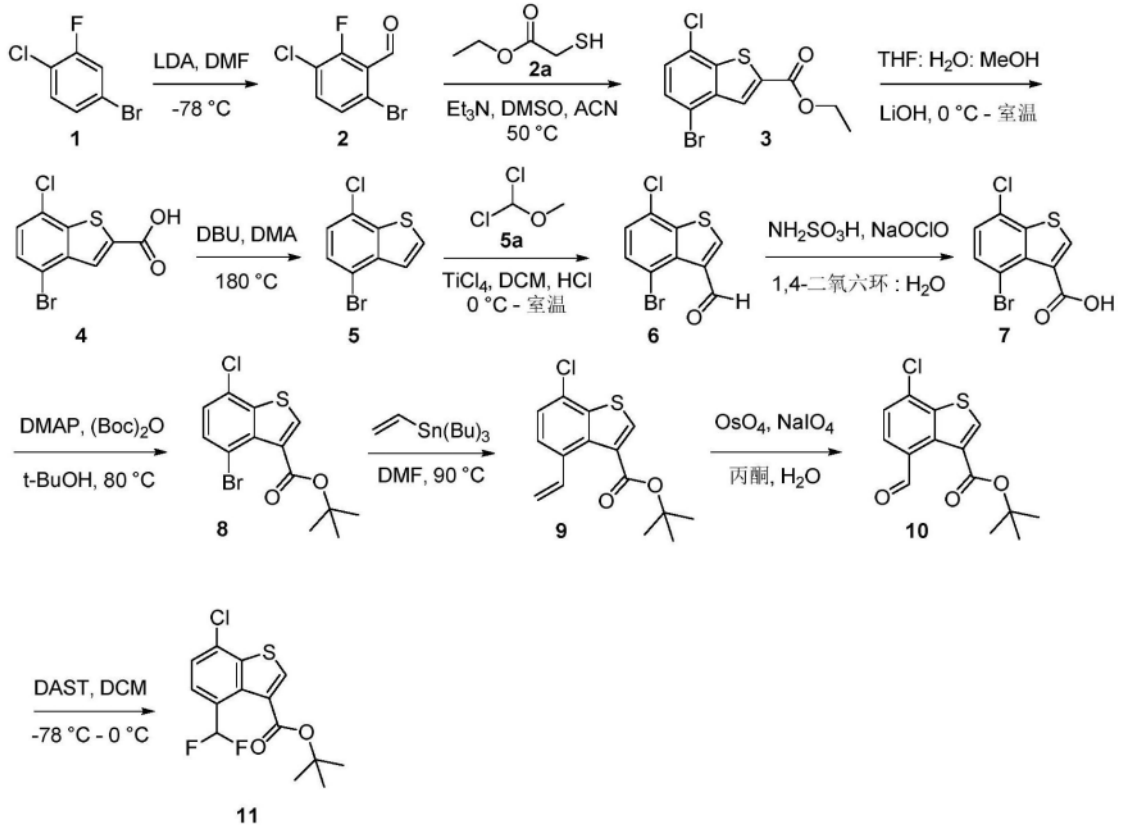
[1052] 在室温下向2-氯-7-碘-4-甲氧基-5H-吡咯并[3,2-d]嘧啶(3,24.0g,77.54mmol)的N,N-二甲基甲酰胺(240mL)溶液中加入氰化锌(9.11g,77.54mmol),乙酸锌(14.22g,77.54mmol)和锌粉(2.02g,31.01mmol)。将反应混合物用氩气脱气15min。加入[1,1'-双(二苯基膦基)二茂铁]钯(II)(5.67g,7.75mmol)和乙酸钯(0.87g,3.87mmol),并将混合物在80℃下加热1h。完成后,将反应物质用乙酸乙酯稀释并用冷水洗涤。将有机层分离,用无水硫酸钠干燥,过滤并浓缩,得到粗品。用0-50%乙酸乙酯的已烷溶液作为洗脱剂,通过硅胶柱色谱(100-200目)纯化粗品。将期望的级分真空浓缩,得到2-氯-4-甲氧基-5H-吡咯并[3,2-d]嘧啶-7-甲腈(4)。

[1053] 向2-氯-4-甲氧基-5H-吡咯并[3,2-d]嘧啶-7-甲腈(4,10.0g,47.9mmol)的异丙醇(100mL)溶液中加入苯胺(5,43.76mL,479.3mmol)和对甲苯磺酸一水合物(10.93g,57.48mmol)。将反应混合物在80℃下搅拌16h。完成后,将反应混合物用水淬灭,并用乙酸乙酯萃取。将有机层用水和盐水洗涤,用无水硫酸钠干燥,并减压浓缩,得到粗品。粗品与正戊烷和乙醚一起研磨并在高真空下干燥,得到4-甲氧基-2-(苯基氨基)-5H-吡咯并[3,2-d]嘧啶-7-甲腈(6)。

[1054] 实施例3B.合成右侧的方法

[1055] 实施例3B.1

[1056]



[1057] 将4-溴-1-氯-2-氟苯(1,20.0g,95.69mmol)的四氢呋喃(200mL)溶液在-78℃下冷却,然后将二异丙基氨基锂(2M的四氢呋喃溶液)(57.2mL,114.83mmol)滴加到混合物中并将反应混合物在-78℃下搅拌1h。然后在15min内在-78℃下滴加N,N-二甲基甲酰胺(20.0mL)并将反应混合物搅拌30min。完成后,将反应混合物用氯化铵溶液淬灭,用水稀释,并用乙醚萃取。将有机层用无水硫酸钠干燥,过滤并浓缩,得到化合物粗品。将获得的化合物粗品用戊烷洗涤,得到6-溴-3-氯-2-氟苯甲醛(2)。

[1058] 在0℃下向6-溴-3-氯-2-氟苯甲醛(2,18.0g,75.94mmol)在乙腈(180.0mL)和二甲基亚砜(48.0mL)中的溶液中加入三乙胺(31.96mL,227.84mmol),接着加入2-巯基乙酸乙酯(2a,18.2g,151.89mmol),并在50℃下继续搅拌4h。完成后,将反应混合物用水稀释,用乙酸乙酯萃取,用1N盐酸,水和盐水溶液洗涤。将有机层用硫酸钠干燥,并减压浓缩至干。与乙醇一起研磨,过滤并干燥,得到4-溴-7-氯苯并[b]噻吩-2-甲酸乙酯(3)。

[1059] 向4-溴-7-氯苯并[b]噻吩-2-甲酸乙酯(3,18.0g,56.42mmol)在四氢呋喃:水:甲醇(90.0mL:45mL:45mL)中的溶液中加入氢氧化锂(13.54g,564.26mmol),并将反应混合物继续搅拌2h。完成后,将反应混合物倒入冷的1N盐酸水溶液中并用乙酸乙酯萃取,用水和盐水溶液洗涤。将有机层用无水硫酸钠干燥,并减压浓缩至干。与醚一起研磨,过滤并干燥,得到4-溴-7-氯苯并[b]噻吩-2-羧酸(4)。

[1060] 向4-溴-7-氯苯并[b]噻吩-2-羧酸(4,15.0g,51.90mmol)的N,N-二甲基乙酰胺(150.0mL)溶液中加入1,8-二氮杂二环(5.4.0)十一碳-7-烯(39.55g,259.51mmol),并将混合物在180℃下加热4h。完成后,将反应混合物冷却至室温,用水稀释,用1N盐酸酸化,用乙酸乙酯萃取,并用水和盐水溶液洗涤。将有机层用无水硫酸钠干燥并减压浓缩至干,得到4-溴-7-氯苯并[b]噻吩(5)。

[1061] 在0℃下向4-溴-7-氯苯并[b]噻吩(5,4.00g,16.19mmol)的二氯甲烷(100.0mL)溶液中加入二氯(甲氧基)甲烷(5a,4.59g,24.29mmol),接着在相同温度下加入四氯化钛(2.79g,24.29mmol),并将反应混合物在室温下继续搅拌16h。完成后,将反应混合物用1N盐酸水溶液淬灭并继续搅拌2h,用水稀释,用二氯甲烷萃取,用水和盐水溶液洗涤。将有机层用无水硫酸钠干燥,并减压浓缩至干。用硅胶(100-200目)以及用0-10%乙酸乙酯的己烷溶液作为洗脱剂,通过快速色谱纯化粗产物。将期望的级分减压浓缩,得到4-溴-7-氯苯并[b]噻吩-3-甲醛(6)。

[1062] 在室温下向4-溴-7-氯苯并[b]噻吩-3-甲醛(6,2.50g,9.12mmol)在1,4-二氧六环(24.0mL)和水(8.0mL)(比例3:1)中的溶液中加入亚氯酸钠(1.24g,13.68mmol),接着加入氨基磺酸(5.30g,54.74mmol),并将混合物继续搅拌16h。完成后,将反应混合物减压浓缩;将残留物用2N盐酸酸化至pH-2,用乙酸乙酯萃取,用水和盐水溶液洗涤。将有机层用无水硫酸钠干燥,并减压浓缩至干。将残留物与正戊烷一起研磨,过滤并干燥,得到4-溴-7-氯苯并[b]噻吩-3-羧酸(7)。

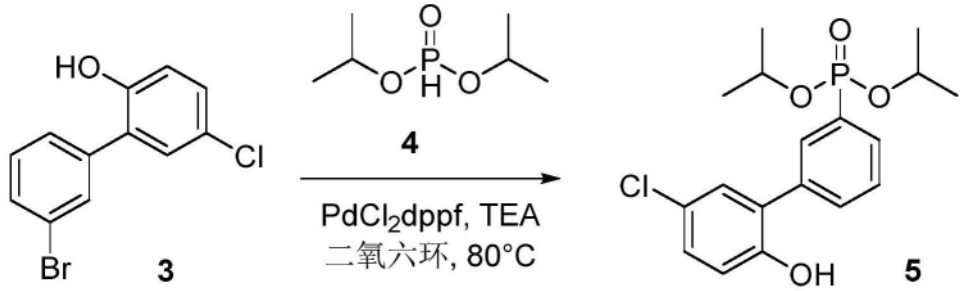
[1063] 在室温下向4-溴-7-氯苯并[b]噻吩-3-羧酸(7,1.40g,4.81mmol)的叔丁醇(15.0mL)溶液中加入二碳酸二叔丁酯(2.0g,9.62mmol),接着加入二甲基氨基吡啶(0.586g,4.81mmol)。将溶液在90℃下加热并继续搅拌16h。完成后,将反应混合物减压浓缩;用水稀释,用乙酸乙酯萃取,用水和盐水溶液洗涤。将有机层用硫酸钠干燥并减压浓缩至干。用硅胶(100-200目)并通过用5-10%乙酸乙酯的己烷溶液梯度洗脱,通过快速色谱纯化粗品。将期望的级分减压浓缩,得到4-溴-7-氯苯并[b]噻吩-3-甲酸叔丁酯(8)。

[1064] 将4-溴-7-氯苯并[b]噻吩-3-甲酸叔丁酯(8,1.10g,3.17mmol)和三丁基(乙烯基)锡烷(1.20g,3.80mmol)的N,N-二甲基甲酰胺(11mL)溶液用氩气脱气15min。将双(三苯基膦)二氯化钯(0.222g,0.3170mmol)加入反应混合物中并在90℃下加热2h。将反应混合物冷却至室温,用乙酸乙酯和水稀释。将有机层分离,用盐水洗涤,用无水硫酸钠干燥,过滤并减压浓缩,得到粗品。用硅胶(100-200目),用2.0-5.0%乙酸乙酯的己烷溶液作为洗脱剂,通过柱色谱纯化粗品。将期望的级分减压浓缩,得到7-氯-4-乙烯基苯并[b]噻吩-3-甲酸叔丁酯(9)。

[1065] 将7-氯-4-乙烯基苯并[b]噻吩-3-甲酸叔丁酯(9,0.6g,2.04mmol)在丙酮(10mL)和水(2mL)中的溶液冷却至0℃,加入四氧化锇(4%水溶液)(1.3mL,0.2040mmol),接着加入高碘酸钠(1.3g,6.12mmol)。将混合物在室温下搅拌1h。完成后,将反应混合物过滤,并将滤液减压浓缩,得到粗产物。通过戊烷洗涤纯化粗品,得到7-氯-4-甲酰基苯并[b]噻吩-3-甲酸叔丁酯(10)。

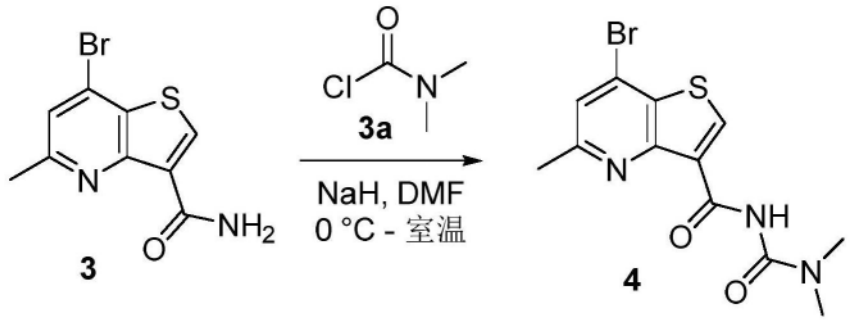
[1066] 在0℃下向搅拌的7-氯-4-甲酰基苯并[b]噻吩-3-甲酸叔丁酯(10,0.550g,1.85mmol)的二氯甲烷(10mL)溶液中加入二乙基氨基三氟化硫(0.503g,2.77mmol)。将反应在室温下升温并搅拌4h。完成后,将反应混合物减压浓缩,得到粗品。用硅胶(100-200目)以及用5.0-10.0%乙酸乙酯的己烷溶液作为洗脱剂,通过柱色谱纯化粗品。将期望的级分减压浓缩,得到7-氯-4-(二氟甲基)苯并[b]噻吩-3-甲酸叔丁酯(11)。

[1067] 实施例3B.2

[1068] 

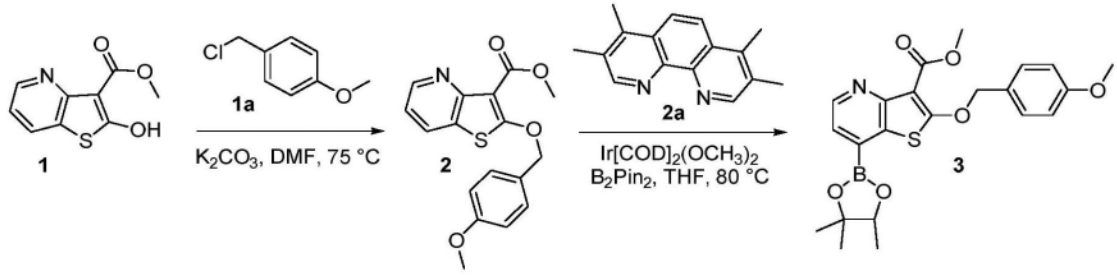
[1069] 将3'-溴-5-氯-[1,1'-联苯]-2-酚(3,0.5g,1.7mmol),膦酸二异丙酯(4,0.585g,3.5mmol)和三乙胺(0.533g,5.2mmol)的异丙醇溶液用氩气脱气10min,接着加入双(二苯基膦基)二茂铁-二氯化钯(II)二氯甲烷复合物,并将反应混合物在100℃下搅拌16h。完成后,减压除去挥发物。用30%乙酸乙酯己烷,通过快速柱色谱纯化粗品得到(5'-氯-2'-羟基-[1,1'-联苯]-3-基)膦酸二异丙酯(5)。

[1070] 实施例3B.3

[1071] 

[1072] 在0℃下向7-溴-5-甲基噻吩并[3,2-b]吡啶-3-甲酰胺(3,1.50g,5.55mmol)的N,N-二甲基甲酰胺(20mL)溶液中加入氢化钠并搅拌10min。然后加入二甲基氨基甲酰氯(3a,0.71g,6.66mmol)并将混合物在室温下搅拌2h。完成后,将反应混合物用乙酸乙酯稀释,用冷水和盐水洗涤,用无水硫酸钠干燥,过滤并浓缩。将粗产物与乙醚和戊烷一起研磨并干燥,得到7-溴-N-(二甲基氨基甲酰基)-5-甲基噻吩并[3,2-b]吡啶-3-甲酰胺(4)。

[1073] 实施例3B.4

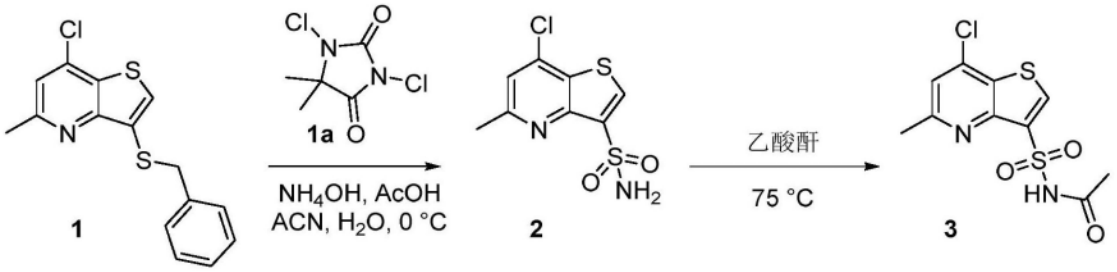
[1074] 

[1075] 在配备搅拌棒的烘干的螺旋盖小瓶中将2-羟基噻吩并[3,2-b]吡啶-3-甲酸甲酯(1,748mg,3.6mmol)溶于N,N-二甲基甲酰胺(20mL)中。加入碳酸钾(210mg,1.52mmol),接着滴加1-(氯甲基)-4-甲氧基苯(1a,0.42mL,4.2mmol)。将小瓶密封并加热到75℃。22h后加入另外的4-甲氧基苄基氯(0.42mL,4.2mmol)和碳酸钾(946.2mg,6.8mmol),并将反应混合物在75℃下继续搅拌。3h后将反应混合物冷却至室温并用乙酸乙酯和水稀释。分离各层,并将水相用乙酸乙酯萃取两次。合并的有机物质用盐水洗涤,用硫酸镁干燥,过滤并在真空下除去溶剂,得到深棕色油状物。通过硅胶色谱纯化,用己烷和乙酸乙酯洗脱,得到2-((4-甲氧

基苄基)氧基)噻吩并[3,2-b]吡啶-3-甲酸甲酯(2)。

[1076] 将一瓶四氢呋喃用氩气吹扫1h。向配备搅拌棒的烘干的微波小瓶中装入双(频哪醇合)二硼(308.4mg,1.21mmol),2-((4-甲氧基苄基)氧基)噻吩并[3,2-b]吡啶-3-甲酸甲酯(2,381mg,1.16mmol),3,4,7,8-四甲基-1,10-菲咯啉(2a,21.8mg,0.093mmol)和(1Z,5Z)-环辛-1,5-二烯;甲氧基铱(30.6mg,0.046mmol)。加入四氢呋喃(2.3mL),将小瓶密封并放置在氩气气氛下,然后在油浴中在80℃下搅拌,16h后,将反应混合物冷却至室温并真空除去溶剂。粗残留物不经进一步纯化用于随后的反应。2-((4-甲氧基苄基)氧基)-7-(4,4,5-三甲基-1,3,2-二氧杂硼杂环戊烷-2-基)噻吩并[3,2-b]吡啶-3-甲酸甲酯(3)。

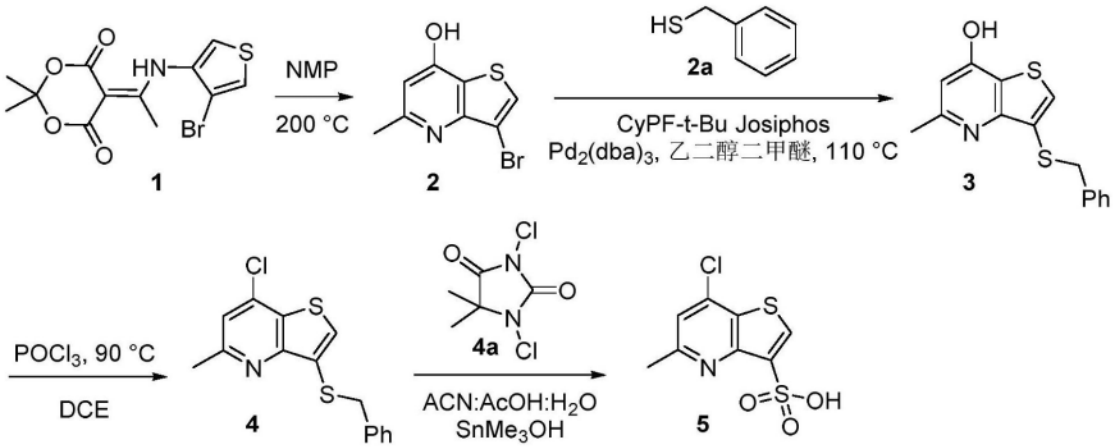
[1077] 实施例3B.5

[1078] 

[1079] 在0℃下向3-(苄硫基)-7-氯-5-甲基噻吩并[3,2-b]吡啶(1,0.7g,2.3mmol)在乙腈,乙酸和水的混合物(40:2:1)(10.0mL)中的溶液中加入在0℃下的1,3-二氯-5,5-二甲基咪唑烷-2,4-二酮(1a,0.9g,4.60mmol),并将混合物搅拌1h。在0℃下将氢氧化铵(35%水溶液,6.0mL)加入反应混合物中并继续搅拌2h。完成后,将反应混合物用水稀释,并用乙酸乙酯萃取。将有机层用水和饱和盐水洗涤,用无水硫酸钠干燥,过滤并浓缩。将粗产物用正戊烷洗涤,得到7-氯-5-甲基噻吩并[3,2-b]吡啶-3-磺酰胺(2)。

[1080] 在室温下向甲基7-氯-5-甲基噻吩并[3,2-b]吡啶-3-磺酰胺(2,0.50g,1.9mmol)的乙酸酐(6.0mL)溶液中加入氯化锌(0.08g,0.57mmol),并将混合物在75℃下加热并搅拌16h。完成后,将反应混合物用水稀释,并用乙酸乙酯萃取。将有机层用水和饱和盐水洗涤,用无水硫酸钠干燥,过滤并浓缩。通过用乙醚和正戊烷洗涤纯化粗产物,得到N-((7-氯-5-甲基噻吩并[3,2-b]吡啶-3-基)磺酰基)乙酰胺(3)。

[1081] 实施例3B.6

[1082] 

[1083] 将5-(1-((4-溴噻吩-3-基)氨基)亚乙基)-2,2-二甲基-1,3-二氧六环-4,6-二酮(1,0.250g,0.722mmol)的N-甲基吡咯烷酮(2mL)溶液在微波中在200℃下加热30min。完成

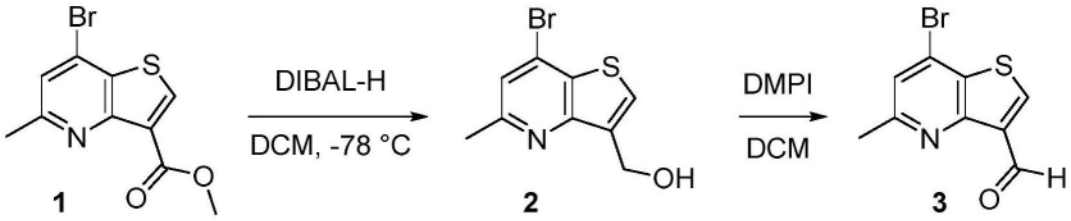
后,将反应混合物用二氯甲烷稀释,然后加入硅胶。然后蒸发溶剂,然后将自由流动的硅胶装载到Isco柱上并通过硅胶色谱纯化,用甲醇/乙酸乙酯洗脱。将期望的级分减压浓缩,得到3-溴-5-甲基噻吩并[3,2-b]吡啶-7-醇(2)。

[1084] 在室温下向3-溴-5-甲基噻吩并[3,2-b]吡啶-7-醇(2,177mg,0.725mmol),苯甲硫醇(2a,0.361g,2.91mmol)和N,N-二异丙基乙胺(0.379mL,2.15mmol)的乙二醇二甲醚(4mL)溶液中加入预混合的三(二亚苄基丙酮)二钯(0)(132mg,0.145mmol)和(R)-1-[(S_p)-2-(二环己基膦基)二茂铁]乙基二叔丁基膦(80mg,0.145mmol)的乙二醇二甲醚(1mL)溶液。将反应混合物用氩气吹扫5min,并将混合物在110℃下加热15h。完成后,将反应混合物用二氯甲烷稀释,然后加入硅胶。随后蒸发溶剂,然后将自由流动的硅胶装载到Isco柱上并通过硅胶色谱纯化,用乙酸乙酯/已烷洗脱。将期望的级分减压浓缩,得到3-(苄硫基)-5-甲基噻吩并[3,2-b]吡啶-7-醇(3)。

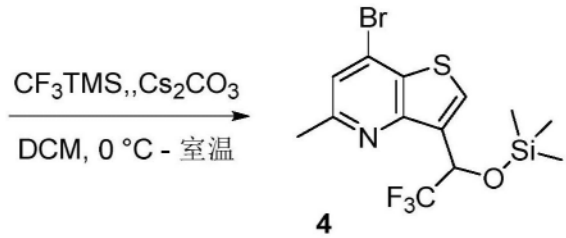
[1085] 在室温下向3-(苄硫基)-5-甲基噻吩并[3,2-b]吡啶-7-醇(3,0.100g,0.347mmol)的1,2-二氯乙烷(3.0mL)溶液中加入三氯氧磷(0.1mL,1.04mmol)和催化量的N,N-二甲基甲酰胺(0.050mL)。将反应混合物在90℃下加热2h。完成后,将反应混合物用二氯甲烷稀释,然后加入硅胶。随后蒸发溶剂,然后将自由流动的硅胶装载到Isco柱上并通过硅胶色谱纯化,用甲醇/二氯甲烷洗脱得到3-(苄硫基)-7-氯-5-甲基噻吩并[3,2-b]吡啶(4)。

[1086] 将3-(苄硫基)-7-氯-5-甲基噻吩并[3,2-b]吡啶(4,50mg,0.163mmol)和1,3-二氯-5,5-二甲基-咪唑烷-2,4-二酮(4a,64mg,0.329mmol)在乙腈(3mL)/水(2mL)/乙酸(0.4mL)的混合物中的溶液在室温下搅拌1h。然后向混合物中加入羟基(三甲基锡烷)(295mg,1.63mmol),然后在50℃下搅拌15h。然后将反应混合物浓缩得到7-氯-5-甲基噻吩并[3,2-b]吡啶-3-磺酸(5)粗品。

[1087] 实施例3B.7



[1088]



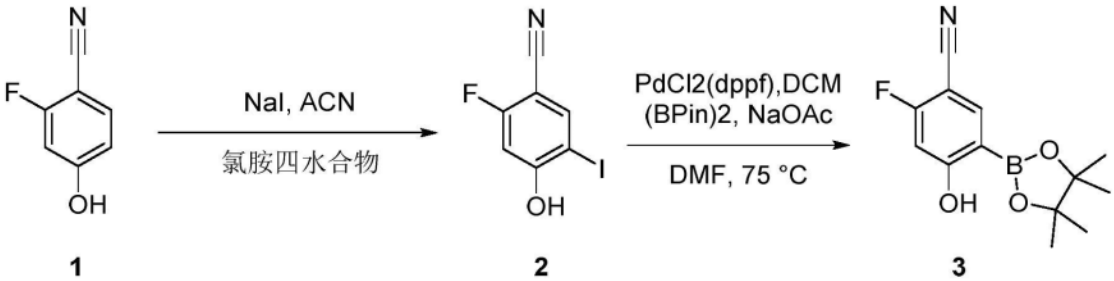
[1089] 在-78℃下向7-溴-5-甲基噻吩并[3,2-b]吡啶-3-甲酸甲酯(1,3.00g,10.4mmol)的二氯甲烷(30.0mL)溶液中加入二异丁基氢化铝(10.40mL,15.7mmol)。将反应混合物在该温度下搅拌3h。在该时间后,将反应混合物用水稀释并用二氯甲烷萃取。将有机层用水洗涤,然后用盐水洗涤,用无水硫酸钠干燥,并减压浓缩至干,得到(7-溴-5-甲基噻吩并[3,2-b]吡啶-3-基)甲醇(2)。

[1090] 在0℃下向(7-溴-5-甲基噻吩并[3,2-b]吡啶-3-基)甲醇(2,1.70g,3.87mmol)的

二氯甲烷(20.0mL)溶液中加入1,1,1-三(乙酰氧基)-1,1-二氢-1,2-苯并碘氧杂环戊二烯-3-(1H)-酮(3.28g,7.75mmol)。将反应混合物在室温下搅拌3h。在该时间后,将反应混合物通过硅藻土过滤并用二氯甲烷洗涤。将滤液减压浓缩至干,得到粗产物。用30-50%乙酸乙酯的己烷溶液作为洗脱剂,通过硅胶(100-200目)柱色谱将其纯化。将期望的级分减压浓缩,得到7-溴-5-甲基噻吩并[3,2-b]吡啶-3-甲醛(3)。

[1091] 在0℃下向7-溴-5-甲基噻吩并[3,2-b]吡啶-3-甲醛(3,0.50g,1.95mmol)的二氯甲烷(5.0mL)溶液中加入三氟甲基三甲基硅烷(0.416g,2.92mmol)和碳酸铯(3.17g,9.75mmol)。将反应混合物在室温下搅拌1h。然后,将反应混合物用水稀释并用二氯甲烷萃取。将有机层用水洗涤,然后用盐水洗溶液,用无水硫酸钠干燥,并减压浓缩至干,得到7-溴-5-甲基-3-(2,2,2-三氟-1-((三甲基甲硅烷基)氧基)乙基)噻吩并[3,2-b]吡啶(4)。

[1092] 实施例3B.8

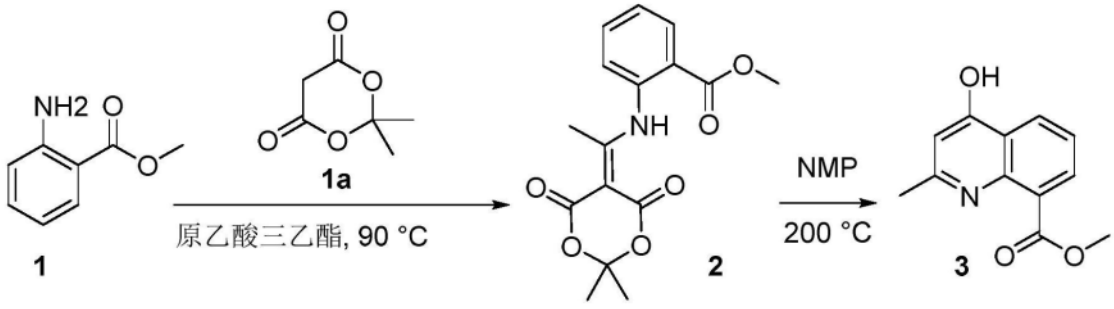
[1093] 

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[1094] 向搅拌的2-氟-4-羟基苯甲腈(1,20g,145.0mmol)的乙腈(80mL)溶液中加入碘化钠(24g,160.0mmol)和氯胺四水合物(chloramine tetrahydrate)(45g,160.0mmol)并在室温下搅拌16h。将反应混合物用水稀释,并用乙酸乙酯萃取。将有机层用水和饱和盐水洗涤,用无水硫酸钠干燥,过滤并浓缩。用硅胶(100-200目)以及用10%乙酸乙酯的己烷溶液作为洗脱剂,通过柱色谱纯化粗产物。将期望的级分减压浓缩,得到2-氟-4-羟基-5-碘苯甲腈(2)。

[1095] 在室温下向2-氟-4-羟基-5-碘苯甲腈(2,7.0g,26.6mmol)的1,4-二氧六环(70mL)溶液中加入乙酸钠(4.36g,53.23mmol)和双频哪醇合二硼(20.26g,79.8mmol),并将混合物用氩气脱气10min。将[1,1'-双(二苯基膦基)二茂铁]二氯化钯二氯甲烷复合物(1.9g,2.66mmol)加入反应混合物中并再脱气15min。将反应混合物在75℃下加热16h。完成后,将反应物质用水稀释,并用乙酸乙酯萃取。将有机层用盐水洗涤,用无水硫酸钠干燥,过滤并减压浓缩至干。用20%乙酸乙酯的己烷溶液作为洗脱剂,通过Combiflash(12g,RediSep柱)纯化粗产物。将期望的级分减压浓缩,得到2-氟-4-羟基-5-(4,4,5,5-四甲基-1,3,2-二氧杂硼杂环戊烷-2-基)苯甲腈(3)。

[1096] 实施例3B.9

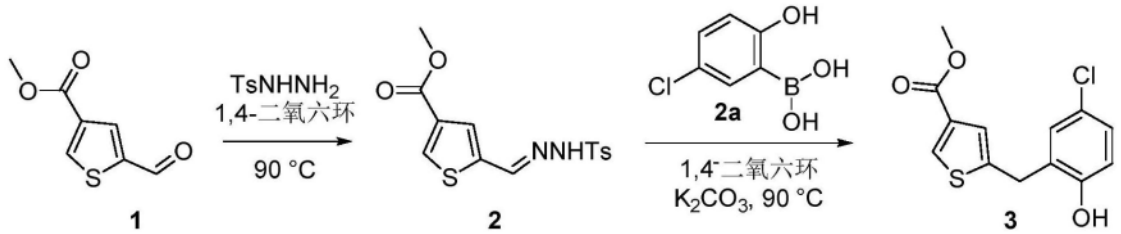
[1097] 

1 2 3

[1098] 将2,2-二甲基-1,3-二氧六环-4,6-二酮(1a,1.048g,7.27mmol)和1,1,1-三乙氧基乙烷(10.0mL)的溶液在密闭容器中在90℃下加热搅拌2h。在90℃下在氩气气氛下分批加入2-氨基苯甲酸甲酯(1,1g,6.62mmol),并继续在90℃下加热6h。完成后,将反应物质冷却至室温,加入水并用乙酸乙酯萃取。将有机层用无水硫酸钠干燥,过滤并真空浓缩得到粗品。2-((1-(2,2-二甲基-4,6-二氧代-1,3-二氧六环-5-亚基)乙基)氨基)苯甲酸甲酯(2)粗品。

[1099] 将2-((1-(2,2-二甲基-4,6-二氧代-1,3-二氧六环-5-亚基)乙基)氨基)苯甲酸甲酯(2,0.900g,2.82mmol)的N-甲基吡咯烷酮(1mL)溶液在微波中在200℃下加热30min。完成后,将反应混合物用二氯甲烷稀释,然后加入硅胶。随后蒸发溶剂,然后将自由流动的硅胶装载到Isco柱上并通过硅胶色谱纯化,用甲醇/乙酸乙酯洗脱。将期望的级分减压浓缩,得到4-羟基-2-甲基喹啉-8-甲酸甲酯(3)。

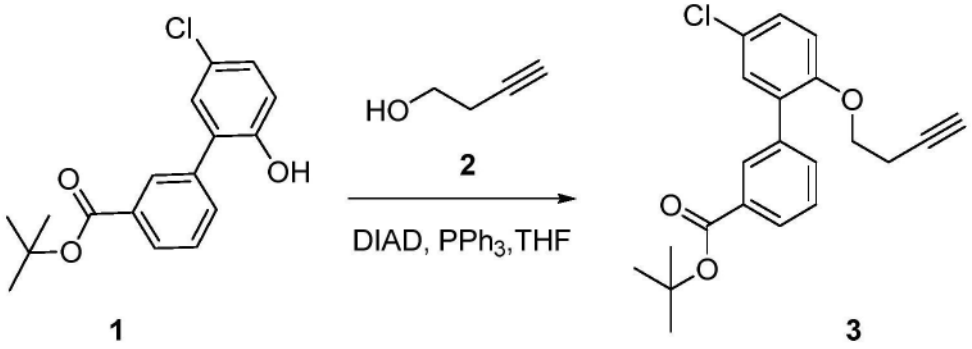
[1100] 实施例3B.10

[1101] 

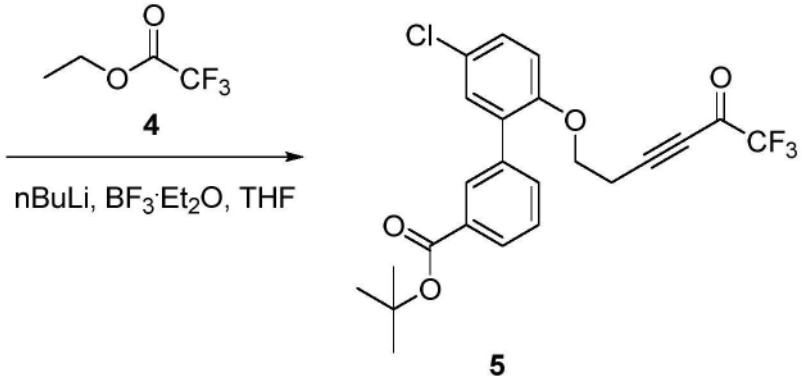
[1102] 将5-甲酰基噻吩-3-甲酸甲酯(1,2.00g,11.7mmol)和4-甲基苯磺酰肼(2.19g,11.7mmol)的1,4-二氧六环(20mL)溶液在90℃下加热16h。将反应混合物在室温下冷却,减压浓缩,得到粗品。将粗品用乙醚洗涤并真空干燥,得到(Z)-5-((2-对甲苯磺酰基亚肼基)甲基)噻吩-3-甲酸甲酯(2)。

[1103] 将(Z)-5-((2-对甲苯磺酰基亚肼基)甲基)噻吩-3-甲酸甲酯(2,0.50g,1.47mmol)溶液中加入(5-氯-2-羟基苯基)硼酸(2a,0.307g,1.77mmol)和碳酸钾(0.40g,2.94mmol)在1,4-二氧六环:水(4:1,5mL)中的溶液,并将反应混合物在90℃下搅拌16h。完成后,将反应混合物用水稀释,并用乙酸乙酯萃取。将有机层用无水硫酸钠干燥,过滤并减压浓缩至干,得到粗品。用硅胶(100-200目)以及用10-20%乙酸乙酯的己烷溶液为洗脱剂,通过快速柱色谱纯化粗品,得到5-(5-氯-2-羟基苄基)噻吩-3-甲酸甲酯(3)。

[1104] 实施例3B.11



[1105]



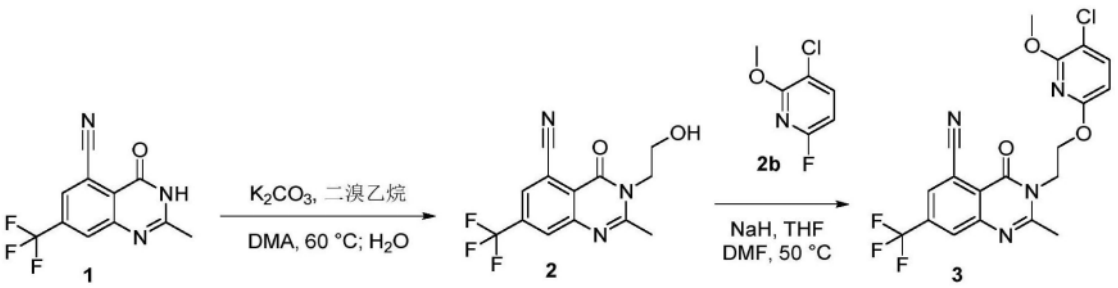
[1106] 在5℃下通过注射器在约2min内向5'-氯-2'-羟基-[1,1'-联苯]-3-甲酸叔丁酯(1,2.65g,8.7mmol),丁-3-炔-1-醇(2,0.66mL,8.7mmol)和三苯基膦(2.28g,8.7mmol)在四氢呋喃(14mL)中的冷却溶液中加入偶氮二甲酸二异丙酯(1.71mL,8.7mmol)。15min后将其升温至室温并再搅拌18h。真空除去溶剂,并将残留物通过自动快速色谱纯化,用己烷和乙酸乙酯洗脱,得到2'-(丁-3-炔-1-基氧基)-5'-氯-[1,1'-联苯]-3-甲酸叔丁酯(3)。

[1107] 在火焰干燥的圆底烧瓶中装入2,2,2-三氟乙酸乙酯(4,0.26mL,2.18mmol)和四氢呋喃(13mL)。将其冷却至-78℃并滴加三氟化硼乙醚(0.29mL,2.32mmol)。50min后缓慢加入2'-(丁-3-炔-1-基氧基)-5'-氯-[1,1'-联苯]-3-甲酸叔丁酯(3,460mg,1.29mmol),接着缓慢加入正丁基锂溶液(2.5M的己烷溶液,0.62mL,1.55mmol)。1h后通过在-78℃下缓慢加入饱和氯化铵水溶液淬灭反应。将溶液升温至室温并加入乙酸乙酯。分离各层,并将水相用乙酸乙酯萃取两次。合并的有机物质用盐水洗涤,用硫酸镁干燥,过滤并浓缩。通过自动快速色谱纯化,用己烷和乙酸乙酯洗脱,得到5'-氯-2'-((6,6,6-三氟-5-氧代己-3-炔-1-基)氧基)-[1,1'-联苯]-3-甲酸叔丁酯(5)。

[1108] 实施例3C.通用偶联方法

[1109] 实施例3C.1

[1110]



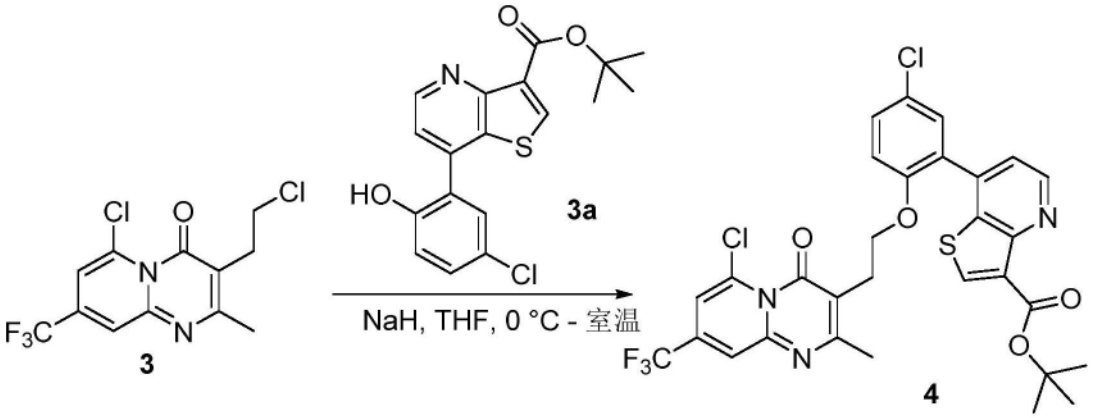
[1111] 在0℃下将甲醇钠(25重量%的甲醇溶液)(3.16mL,13.8mmol)加入搅拌的3-氯-2,6-二氟-吡啶(2a,2.01g,13.4mmol)的甲醇(5mL)溶液中。移除冷浴并将得到的浑浊的混合

物在室温下在氩气下搅拌35min。将反应混合物倒入水(100mL)中。真空过滤收集固体,用水彻底洗涤,并用真空抽吸风干30min。将固体在高真空下干燥,得到3-氯-6-氟-2-甲氧基吡啶(2b)。

[1112] 在室温下在氩气下将碳酸钾(1.82g,13.2mmol)加入搅拌的2-甲基-4-氧代-7-(三氟甲基)-3,4-二氢喹唑啉-5-甲腈(1,835mg,3.30mmol)和1,2-二溴乙烷(2.84mL,33.0mmol)的DMA(15mL)溶液中。将得到的混合物在60℃下在氩气下加热3h。加入水(0.59mL,33.0mmol)。将得到的混合物在60℃下在氩气下加热1h 15min。冷却至室温后,将反应混合物分配于乙酸乙酯和水之间。将有机层用盐水洗涤三次,用硫酸镁干燥,过滤,在旋转蒸发仪上浓缩并通过硅胶色谱纯化(20-90%乙酸乙酯的己烷溶液),得到3-(2-羟基乙基)-2-甲基-4-氧代-7-(三氟甲基)-3,4-二氢喹唑啉-5-甲腈(2)。

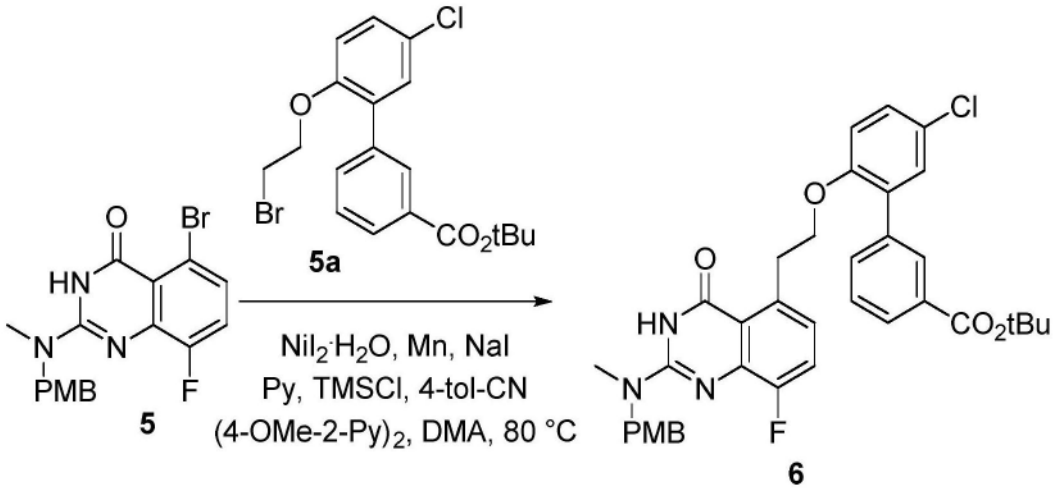
[1113] 在氩气下在搅拌下将3-(2-羟基乙基)-2-甲基-4-氧代-7-(三氟甲基)-3,4-二氢喹唑啉-5-甲腈(2,390mg,1.31mmol)溶于DMF(4mL)中。加入THF(6mL)并将得到的溶液冷却至-78℃。加入氢化钠(34.6mg,1.44mmol)并将得到的浑浊的混合物在-78℃下在氩气下搅拌10min。加入3-氯-6-氟-2-甲氧基吡啶(2b,254mg,1.57mmol)并移除冷浴。将得到的混合物在室温下在氩气下搅拌20min,然后在氩气下在回流冷凝器下在50℃下加热2.5h。冷却至室温后,将得到的混合物分配于乙酸乙酯和盐水与饱和氯化铵水溶液的混合物之间。将有机层再用盐水洗涤两次,在旋转蒸发仪上与硅胶一起浓缩,并通过硅胶色谱纯化(0-100%乙酸乙酯的己烷溶液),得到不纯的3-(2-((5-氯-6-甲氧基吡啶-2-基)氧基)乙基)-2-甲基-4-氧代-7-(三氟甲基)-3,4-二氢喹唑啉-5-甲腈(3)。

[1114] 实施例3C.2

[1115] 

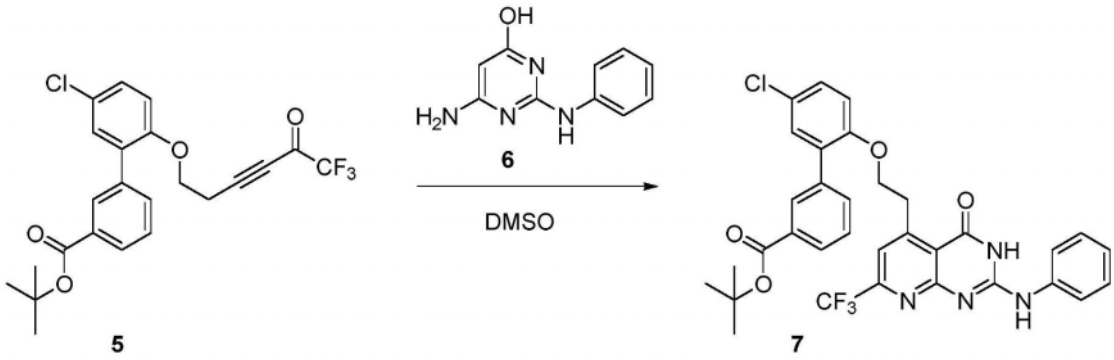
[1116] 在0℃下向7-(5-氯-2-羟基苯基)噻吩并[3,2-b]吡啶-3-甲酸叔丁酯(3a,2.0g,5.5mmol)的四氢呋喃(15mL)溶液中加入氢化钠(0.276g,6.9mmol),并将混合物搅拌0.5h。将6-氯-3-(2-氯乙基)-2-甲基-8-(三氟甲基)-4H-吡啶并[1,2-a]嘧啶-4-酮(3,1.5g,4.6mmol)的四氢呋喃溶液加入反应混合物中并搅拌16h。完成后,将反应混合物倒入碎冰中并用乙酸乙酯萃取。将有机层用无水硫酸钠干燥,并减压浓缩至干。用0-50%乙酸乙酯的己烷溶液作为洗脱剂,通过柱色谱纯化得到的化合物粗品;将含有期望产物的级分减压蒸馏出来,得到7-(5-氯-2-(2-(6-氯-2-甲基-4-氧代-8-(三氟甲基)-4H-吡啶并[1,2-a]嘧啶-3-基)乙氧基)苯基)噻吩并[3,2-b]吡啶-3-甲酸叔丁酯(4)。

[1117] 实施例3C.3

[1118] 

[1119] 向5-溴-8-氟-2-((4-甲氧基苄基)(甲基)氨基)喹唑啉-4(3H)-酮(5,95mg,0.23mmol),2'-(2-溴乙氧基)-5'-氯-[1,1'-联苯]-3-甲酸叔丁酯(5a,99mg,0.24mmol),碘化镍(II)水合物(30mg,0.08mmol),碘化钠(17mg,0.12mmol),对甲苯腈(11mg,0.09mmol)和4,4'-二甲氧基-2,2'-联吡啶(20mg,0.09mmol)在新脱气(sparged)的N,N-二甲基乙酰胺(1.2mL)的混合物中加入三甲基氯硅烷(1滴),吡啶(1滴)和锰(25mg,0.46mmol)。将反应在80℃下搅拌过夜。将得到的混合物冷却至室温并通过硅藻土垫过滤。滤液用乙酸乙酯和水萃取。将合并的有机层用硫酸钠干燥,倾析并浓缩。通过柱色谱(硅胶,乙酸乙酯/己烷=0-40%)纯化粗品,得到5'-氯-2'-(2-(8-氟-2-((4-甲氧基苄基)(甲基)氨基)-4-氧代-3,4-二氢喹唑啉-5-基)乙氧基)-[1,1'-联苯]-3-羧酸(6)。

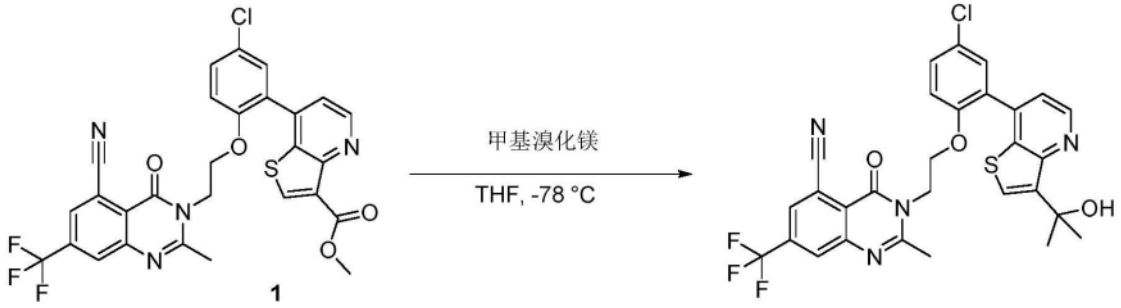
[1120] 实施例3C.4

[1121] 

[1122] 将6-氨基-2-(苯基氨基)嘧啶-4-醇(6,114mg,0.45mmol)溶于二甲基亚砜(1.1mL)中,一批加入5'-氯-2'-((6,6,6-三氟-5-氧代己-3-炔-1-基)氧基)-[1,1'-联苯]-3-甲酸叔丁酯(5,203mg,0.45mmol)。将neon溶液在室温下搅拌19h。将反应混合物用水稀释并过滤。将固体在真空烘箱中干燥2h,得到5'-氯-2'-(2-(4-氧代-2-(苯基氨基)-7-(三氟甲基)-3,4-二氢吡啶并[2,3-d]嘧啶-5-基)乙氧基)-[1,1'-联苯]-3-甲酸叔丁酯(7)。

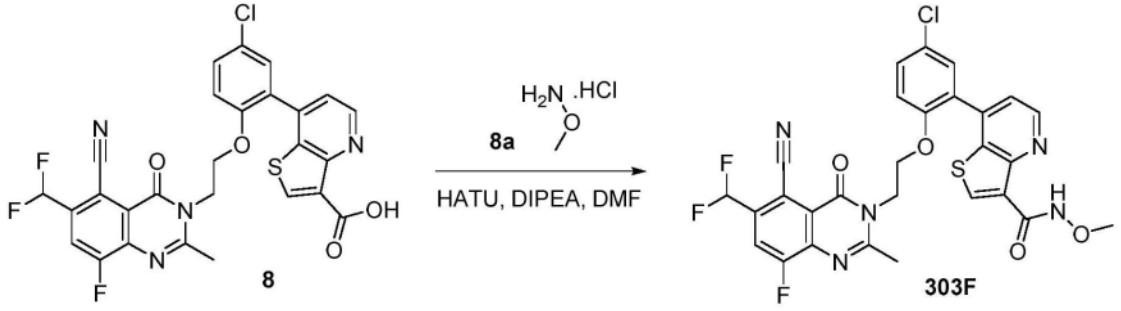
[1123] 实施例3D.偶联后修饰方法

[1124] 实施例3D.1

[1125] 

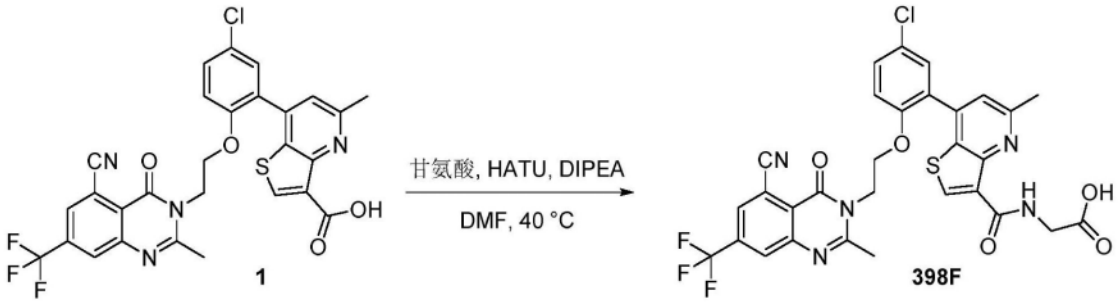
[1126] 在-78℃下在氩气下将甲基溴化镁(3M的乙醚溶液)(0.051mL,0.152mmol)加入搅拌的7-(5-氯-2-(2-(5-氰基-2-甲基-4-氧代-7-(三氟甲基)喹唑啉-3(4H)-基)乙氧基)苯基)噻吩并[3,2-b]吡啶-3-甲酸甲酯(1,30.3mg,0.051mmol)的THF(2.5mL)溶液中。反应混合物快速变为深黄色。20min后,将反应混合物用饱和氯化铵水溶液(0.5mL)淬灭,用水(0.5mL稀释)并分配于乙酸乙酯和盐水之间。将有机层用硫酸镁干燥,过滤,在旋转蒸发仪上浓缩并在高真空下在40℃下干燥45min,得到橙色残留物。将其在搅拌下溶于THF(2.5mL)并在氩气下冷却至-78℃。加入甲基溴化镁(3M的乙醚溶液)(0.051mL,0.152mmol)并将反应混合物在-78℃下在氩气下搅拌20min。将反应混合物用饱和氯化铵水溶液(0.5mL)淬灭,用水(0.5mL)稀释并分配于乙酸乙酯和盐水之间。将有机层用硫酸镁干燥,过滤,在旋转蒸发仪上浓缩并通过制备HPLC(15-57%的乙腈在含0.1%TFA的水中的溶液)纯化。将含有期望产物的级分合并,并用饱和碳酸氢钠水溶液中和。在旋转蒸发仪上除去乙腈。将残留水相用二氯甲烷萃取三次。合并的有机层用硫酸钠干燥,过滤,并在旋转蒸发仪上浓缩。将残留物溶于乙腈和水中并冻干至干,得到3-(2-(4-氯-2-(3-(2-羟基丙-2-基)噻吩并[3,2-b]吡啶-7-基)苯氧基)乙基)-2-甲基-4-氧代-7-(三氟甲基)-3,4-二氢喹唑啉-5-甲腈(化合物编号352F)。

[1127] 实施例3D.2

[1128] 

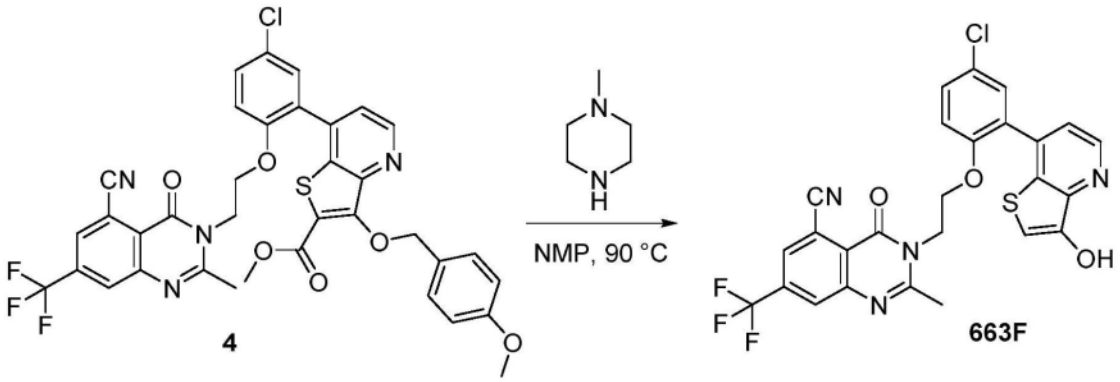
[1129] 向7-(5-氯-2-(2-(5-氰基-6-(二氟甲基)-8-氟-2-甲基-4-氧代喹唑啉-3(4H)-基)乙氧基)苯基)噻吩并[3,2-b]吡啶-3-羧酸(8,0.10g,0.171mmol)的N,N-二甲基甲酰胺(2.0mL)溶液中加入1-[双(二甲基氨基)亚甲基]-1H-1,2,3-三唑并[4,5-b]吡啶鎓3-氧化物六氟磷酸盐(0.098g,0.256mmol),并将混合物在室温下搅拌15min。将反应混合物冷却至0℃,加入N,N-二异丙基乙胺(0.12mL,0.684mmol)和O-甲基羟胺盐酸盐(8a,0.017g,0.205mmol),并将混合物在室温下搅拌1.5h。完成后,将反应混合物用乙酸乙酯稀释,用冷水和盐水溶液洗涤,用无水硫酸钠干燥,并减压浓缩。通过制备HPLC纯化粗品,得到7-(5-氯-2-(2-(5-氰基-6-(二氟甲基)-8-氟-2-甲基-4-氧代喹唑啉-3(4H)-基)乙氧基)苯基)-N-甲氧基噻吩并[3,2-b]吡啶-3-甲酰胺(化合物编号303F)。

[1130] 实施例3D.3

[1131] 

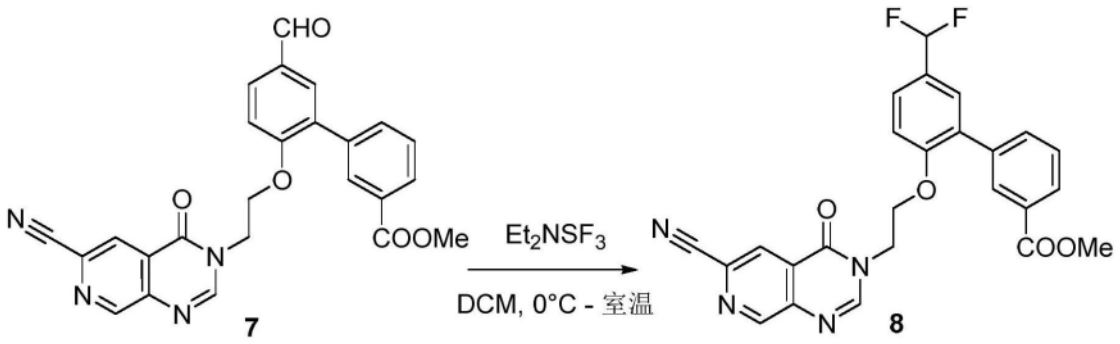
[1132] 在室温下在氩气下将N,N-二异丙基乙胺(0.028mL,0.163mmol)加入搅拌的7-(5-氯-2-(2-(5-氰基-2-甲基-4-氧代-7-(三氟甲基)喹唑啉-3(4H)-基)乙氧基)苯基)-5-甲基噻吩并[3,2-b]吡啶-3-羧酸(1,32.5mg,0.054mmol)和HATU(22.7mg,0.060mmol)在DMF(0.3mL)中的混合物中。所有固体在5min内溶解,然后很快沉淀出大量固体。20min后加入甘氨酸(6.1mg,0.081mmol),接着加入更多的DMF(0.2mL)。将得到的混合物密封并在室温下剧烈搅拌20min。加入更多的甘氨酸(18.0mg,0.240mmol)。将得到的混合物密封,剧烈搅拌,用加热器在40℃下加热14h。将反应混合物用甲醇稀释,过滤,并通过制备HPLC纯化(20-70%的乙腈在含0.1%TFA的水中的溶液)。合并含有期望产物的级分并冻干至干,得到(7-(5-氯-2-(2-(5-氰基-2-甲基-4-氧代-7-(三氟甲基)喹唑啉-3(4H)-基)乙氧基)苯基)-5-甲基噻吩并[3,2-b]吡啶-3-羰基)甘氨酸(化合物编号398F)。

[1133] 实施例3D.4

[1134] 

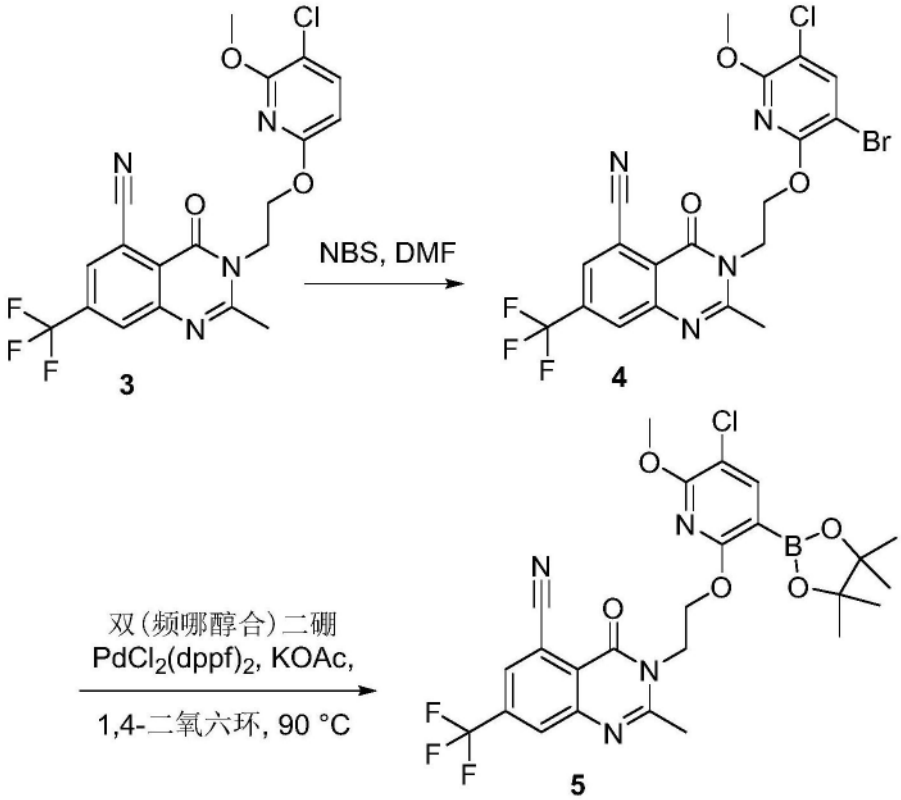
[1135] 在配备搅拌棒的螺旋盖小瓶中将1-甲基哌嗪(0.05mL,0.73mmol)和7-(5-氯-2-(2-(5-氰基-2-甲基-4-氧代-7-(三氟甲基)喹唑啉-3(4H)-基)乙氧基)苯基)-3-((4-甲氧基苄基)氧基)噻吩并[3,2-b]吡啶-2-甲酸甲酯(4,82mg,0.11mmol)溶于N-甲基吡咯烷酮(1.8mL)中。将小瓶密封,并在加热器中在145℃下加热4.5h。将反应混合物冷却至室温。将反应混合物用乙酸乙酯稀释,通过硅藻土过滤,并真空除去挥发性溶剂。将残留物质用二甲基亚砜稀释并通过RP-HPLC纯化,得到3-(2-(4-氯-2-(3-羟基噻吩并[3,2-b]吡啶-7-基)苯氧基)乙基)-2-甲基-4-氧代-7-(三氟甲基)-3,4-二氢喹唑啉-5-甲腈(化合物编号663F)。

[1136] 实施例3D.5

[1137] 

[1138] 在0℃下向2'-(2-(6-氰基-4-氧代吡啶并[3,4-d]嘧啶-3(4H)-基)乙氧基)-5'-甲酰基-[1,1'-联苯]-3-甲酸甲酯(7,0.10g,0.22mmol)的二氯甲烷(8mL)溶液中加入二乙基氨基三氟化硫(0.052g,0.33mmol)。将反应混合物在室温下搅拌16h。完成后,将反应混合物在0℃下用10%氢氧化钠水溶液淬灭至pH约7,并用二氯甲烷(50mL)萃取。将有机层用水(50mL)和盐水(20mL)洗涤,用无水硫酸钠干燥,并减压浓缩,得到粗品。用10-50%乙酸乙酯的己烷溶液,通过combiflash柱(4g,Redisep)纯化粗品,得到2'-(2-(6-氰基-4-氧代吡啶并[3,4-d]嘧啶-3(4H)-基)乙氧基)-5'-(二氟甲基)-[1,1'-联苯]-3-甲酸甲酯(8)。

[1139] 实施例3D.6

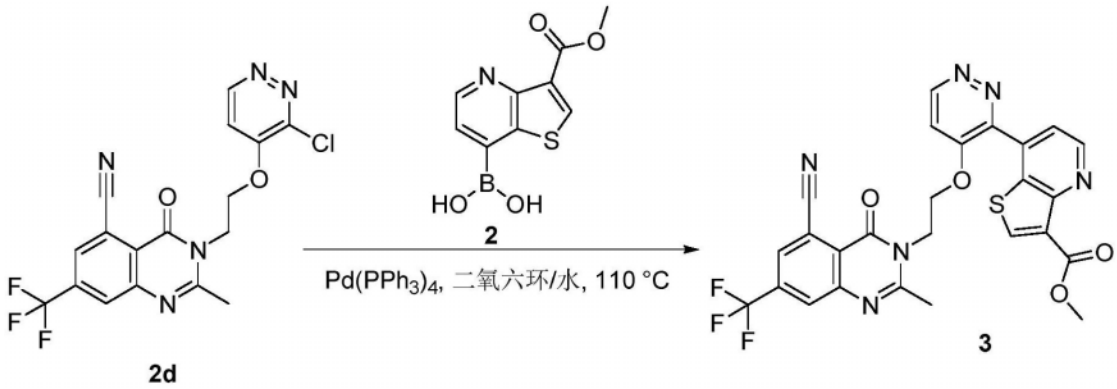
[1140] 

[1141] 在室温下将N-溴代丁二酰亚胺(39.2mg,0.22mmol)加入搅拌的3-(2-((5-氯-6-甲氧基吡啶-2-基)氧基)乙基)-2-甲基-4-氧代-7-(三氟甲基)-3,4-二氢喹唑啉-5-甲腈(3,92mg,0.21mmol)的DMF(1mL)溶液中。将得到的澄清黄色反应混合物封盖并在室温下搅拌3.5h。加入更多的N-溴代丁二酰亚胺(19.0mg,0.11mmol),将反应混合物封盖并在室温下搅拌2h。反应混合物用乙酸乙酯稀释并用盐水洗涤三次。将有机层用硫酸镁干燥,过滤,在旋转蒸发仪上浓缩,并通过硅胶色谱纯化(0-100%乙酸乙酯的己烷溶液),得到3-(2-((3-溴-

5-氯-6-甲氧基吡啶-2-基)氧基)乙基)-2-甲基-4-氧代-7-(三氟甲基)-3,4-二氢喹唑啉-5-甲腈(4)。

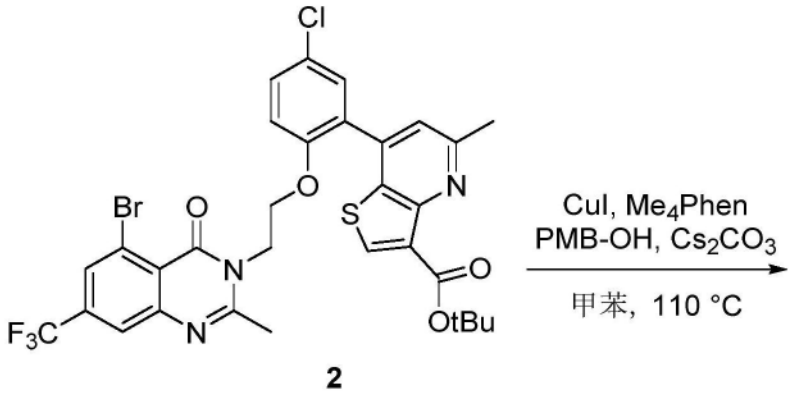
[1142] 在具有搅拌棒的1打兰小瓶中将3-(2-((3-溴-5-氯-6-甲氧基吡啶-2-基)氧基)乙基)-2-甲基-4-氧代-7-(三氟甲基)-3,4-二氢喹唑啉-5-甲腈(4,76.3mg,0.147mmol),乙酸钾(43.4mg,0.44mmol),双(频哪醇合)二硼(44.9mg,0.177mmol),$PdCl_2(dppf).CH_2Cl_2$(12mg,0.015mmol)和1,4-二氧六环(0.5mL)混合,并用氩气吹扫1min。将得到的混合物密封,剧烈搅拌,并用加热器在90℃下加热3h。将反应混合物直接装载到硅胶装载柱并通过硅胶色谱纯化(0-80%乙酸乙酯的己烷溶液),得到不纯的3-(2-((5-氯-6-甲氧基-3-(4,4,5,5-四甲基-1,3,2-二氧杂硼杂环戊烷-2-基)吡啶-2-基)氧基)乙基)-2-甲基-4-氧代-7-(三氟甲基)-3,4-二氢喹唑啉-5-甲腈(5)。

[1143] 实施例3D.7

[1144] 

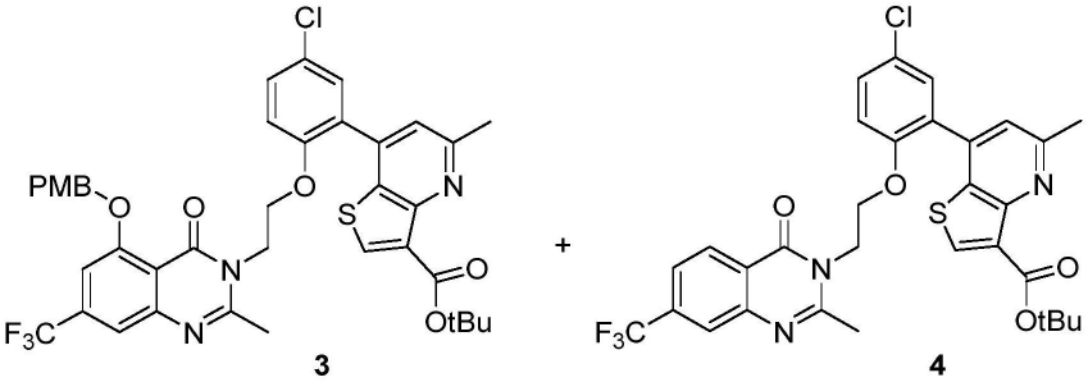
[1145] 在室温下向3-(2-((3-氯哒嗪-4-基)氧基)乙基)-2-甲基-4-氧代-7-(三氟甲基)-3,4-二氢喹唑啉-5-甲腈(2d,20.0mg,0.049mmol),甲基(3-(甲氧基羰基)噻吩并[3,2-b]吡啶-7-基)硼酸(2,15.58mg,0.049mmol)和碳酸钾(0.15mL,0.150mmol)的1,4-二氧六环(1.5mL)溶液中加入四(三苯基膦)钯(0)(5.64mg,0.0049mmol),并通过用氩气鼓泡通过混合物将其脱气5min。将反应混合物加热至90℃持续16h。反应完成后,将反应用水稀释并用乙酸乙酯萃取。将有机层用水和饱和盐水溶液洗涤,用无水硫酸钠干燥,过滤并减压浓缩至干。用1-5%甲醇的二氯甲烷溶液作为洗脱剂,通过Combiflash(12g,RediSep柱)纯化粗产物,得到7-(4-(2-(5-氰基-2-甲基-4-氧代-7-(三氟甲基)喹唑啉-3(4H)-基)乙氧基)哒嗪-3-基)噻吩并[3,2-b]吡啶-3-甲酸甲酯(3)。

[1146] 实施例3D.8



2

[1147]



3 4

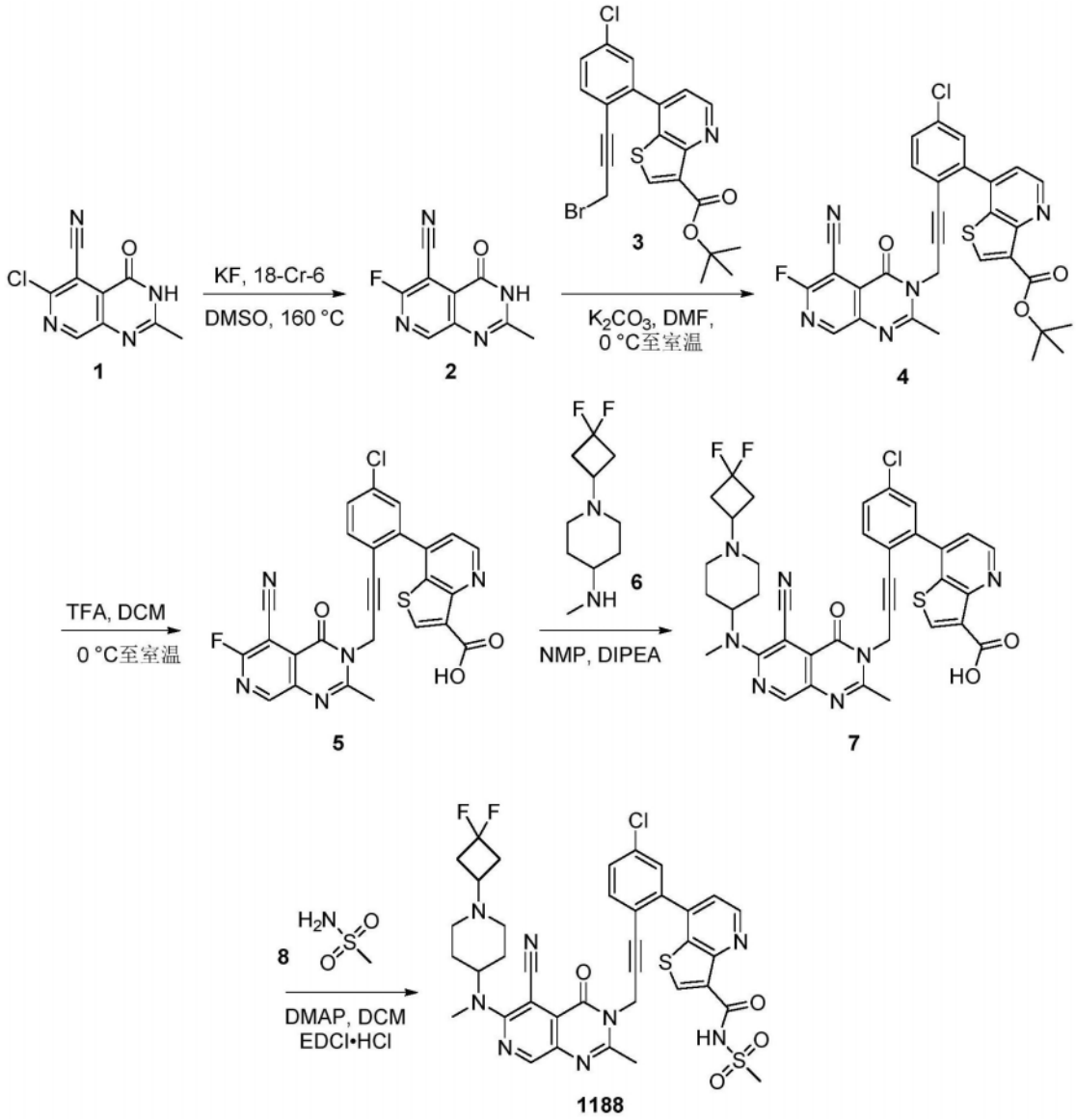
[1148] 向火焰干燥的小瓶中装入7-(2-(2-(5-溴-2-甲基-4-氧代-7-(三氟甲基)喹唑啉-3(4H)-基)乙氧基)-5-氯苯基)-5-甲基噻吩并[3,2-b]吡啶-3-甲酸叔丁酯(2,106mg,0.150mmol),3,4,7,8-四甲基-1,10-菲咯啉(10.8mg,0.0457mmol),碘化亚铜(I)(6.2mg,0.033mmol)和碳酸铯(94mg,0.290mmol)。将小瓶抽真空并回充氩气两次。加入甲苯(1.4mL)和(4-甲氧基苯基)甲醇(29uL,33mg,0.24mmol),并将混合物脱气5min,然后在110℃下搅拌。4h后,将混合物冷却至室温并且再搅拌14h,随后用EtOAc释稀,然后用水洗涤。萃取水相(3x EtOAc),干燥合并的有机相(Na_2SO_4),过滤并浓缩。通过柱色谱纯化(SiO_2,0-50%EtOAc/己烷),得到产物7-(5-氯-2-(2-(5-((4-甲氧基苄基)氧基)-2-甲基-4-氧代-7-(三氟甲基)喹唑啉-3(4H)-基)乙氧基)苯基)-5-甲基噻吩并[3,2-b]吡啶-3-甲酸叔丁酯(3)和7-(5-氯-2-(2-(2-甲基-4-氧代-7-(三氟甲基)喹唑啉-3(4H)-基)乙氧基)苯基)-5-甲基噻吩并[3,2-b]吡啶-3-甲酸叔丁酯(4)的61mg的约1:1的混合物。

[1149] 使用一种或多种上述通用方法制备的化合物显示在表3中。在提供表征数据的情况下,表征数据在化合物的右侧。

[1150] 实施例4.具体实施例

[1151] 实施例4A.化合物1188,7-(5-氯-2-(3-(5-氰基-6-((1-(3,3-二氟环丁基)哌啶-4-基)(甲基)氨基)-2-甲基-4-氧代吡啶并[3,4-d]嘧啶-3(4H)-基)丙-1-炔-1-基)苯基)-N-(甲基磺酰基)噻吩并[3,2-b]吡啶-3-甲酰胺的合成

[1152]



[1153] 将6-氯-2-甲基-4-氧代-3,4-二氢吡啶并[3,4-d]嘧啶-5-甲腈(1,10.0g,45.45mmol)的二甲基亚砜(200mL)溶液用氩气吹扫10分钟。将18-冠-6醚(17.99g,68.18mmol)和氟化钾(13.2g,227.25mmol)加入反应混合物并继续吹扫5分钟。然后将反应混合物在预热的油浴中在160℃下搅拌2h。将反应混合物冷却,倒入冰冷的水中并用乙酸乙酯萃取。将乙酸乙酯层用盐水溶液洗涤,用无水硫酸钠干燥并减压浓缩,得到粗产物。将得到的粗产物与乙醚一起研磨并干燥,得到纯的6-氟-2-甲基-4-氧代-3,4-二氢吡啶并[3,4-d]嘧啶-5-甲腈(2),为浅棕色固体。产率:7.3g,78%;MS(ESI)m/z 205.14[M+1]+。

[1154] 在0℃下向6-氟-2-甲基-4-氧代-3,4-二氢吡啶并[3,4-d]嘧啶-5-甲腈(2,3.70g,18.13mmol)和碳酸钾(4.96g,36.27mmol)的N,N-二甲基甲酰胺(74.0mL)溶液中加入7-(2-(3-溴丙-1-炔-1-基)-5-氯苯基)噻吩并[3,2-b]吡啶-3-甲酸叔丁酯(3,5.85g,12.69mmol),并将反应混合物在1h的时间段内升温至室温。完成后,将反应混合物倒到冰冷的水中。将沉淀出的固体过滤并干燥,得到粗产物。用硅胶(100-200目)和80至90%乙酸乙酯的己烷溶液作为洗脱剂,通过柱色谱纯化粗产物。将期望的级分减压浓缩,得到固体。将获得的固体与甲醇一起研磨并干燥,得到7-(5-氯-2-(3-(5-氰基-6-氟-2-甲基-4-氧代吡

啶并[3,4-d]嘧啶-3(4H)-基)丙-1-炔-1-基)苯基)噻吩并[3,2-b]吡啶-3-甲酸叔丁酯(4),为淡黄色固体。产率:4.25g,40%;MS(ESI)m/z 586.32[M+1]+。1H NMR(400MHz,DMSO-d6)δ8.94(s,1H),8.68(d,J=4.80Hz,1H),8.51(s,1H),7.74(d,J=8.40Hz,1H),7.67-7.63(m,3H),7.40(d,J=4.80Hz,1H),4.88(s,2H),2.18(s,3H),1.59(s,9H)。

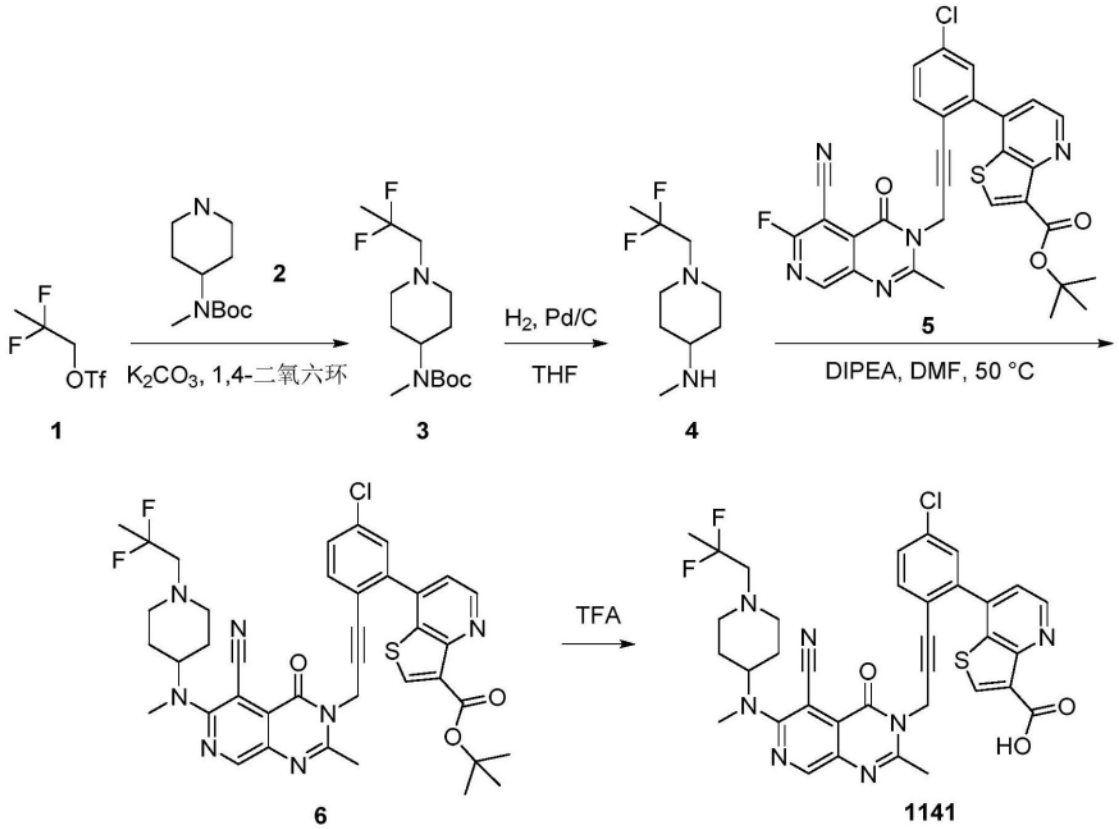
[1155] 向7-(5-氯-2-(3-(5-氰基-6-氟-2-甲基-4-氧代吡啶并[3,4-d]嘧啶-3(4H)-基)丙-1-炔-1-基)苯基)噻吩并[3,2-b]吡啶-3-甲酸叔丁酯(4,0.13g,0.22mmol)的二氯甲烷(1.0mL)溶液中加入2,2,2-三氟乙酸(1.0mL),并将反应混合物在室温下搅拌6h。完成后,将反应混合物减压浓缩,得到固体。将获得的固体与乙醚一起研磨并干燥,得到7-(5-氯-2-(3-(5-氰基-6-氟-2-甲基-4-氧代吡啶并[3,4-d]嘧啶-3(4H)-基)丙-1-炔-1-基)苯基)噻吩并[3,2-b]吡啶-3-羧酸(5),为灰白色固体。产率:0.090g,81%;MS(ESI)m/z 530.12[M+1]+。1H-NMR(400MHz,DMSO-d6)δ8.92(s,1H),8.75(d,J=5.44Hz,1H),8.59(s,1H),7.76(d,J=8.44Hz,1H),7.69-7.68(m,2H),7.52(d,J=4.36Hz,1H),4.87(s,2H),2.13(s,3H)。

[1156] 向7-(5-氯-2-(3-(5-氰基-6-氟-2-甲基-4-氧代吡啶并[3,4-d]嘧啶-3(4H)-基)丙-1-炔-1-基)苯基)噻吩并[3,2-b]吡啶-3-羧酸(5,0.10g,0.189mmol)和1-(3,3-二氟环丁基)-N-甲基哌啶-4-胺(6,0.077g,0.37mmol)的N-甲基-2-吡咯烷酮(1.5mL)溶液中加入N,N-二异丙基乙胺(0.064mL,0.37mmol)。将反应混合物在室温下搅拌72h。完成后,将反应混合物直接用制备HPLC纯化,得到7-(5-氯-2-(3-(5-氰基-6-((1-(3,3-二氟环丁基)哌啶-4-基)(甲基)氨基)-2-甲基-4-氧代吡啶并[3,4-d]嘧啶-3(4H)-基)丙-1-炔-1-基)苯基)噻吩并[3,2-b]吡啶-3-羧酸(7),为黄色固体。产率:0.050g,44%;MS(ESI)m/z,714.50[M+1]+;1H-NMR(400MHz,DMSO-d6)δ9.80(bs,1H),8.76(s,1H),8.75(s,1H),8.65(s,1H),7.75(d,J=8.4Hz,1H),7.70-7.67(m,2H),7.54(d,J=4.8Hz,1H),4.83(s,2H),4.56(bs,1H),3.56(bs,4H),3.11(bs,1H),3.06(s,3H),3.05(bs,4H),2.13(bs,4H),2.11(s,3H)。

[1157] 在0℃下向7-(5-氯-2-(3-(5-氰基-6-((1-(3,3-二氟环丁基)哌啶-4-基)(甲基)氨基)-2-甲基-4-氧代吡啶并[3,4-d]嘧啶-3(4H)-基)丙-1-炔-1-基)苯基)噻吩并[3,2-b]吡啶-3-羧酸(7,1.70g,2.377mmol)和甲磺酰胺(8,0.564g,5.94mmol)的二氯甲烷(17.0mL)溶液中加入1-乙基-3-(3-二甲基氨基丙基)碳二亚胺盐酸盐(0.737g,4.754mmol)和4-(二甲基氨基)吡啶(0.725g,5.94mmol)。将反应混合物在室温下搅拌14h。完成后,将反应混合物用水稀释并用二氯甲烷萃取。将有机层用无水硫酸钠干燥,过滤并浓缩,得到化合物粗品。化合物粗品用制备HPLC纯化,得到7-(5-氯-2-(3-(5-氰基-6-((1-(3,3-二氟环丁基)哌啶-4-基)(甲基)氨基)-2-甲基-4-氧代吡啶并[3,4-d]嘧啶-3(4H)-基)丙-1-炔-1-基)苯基)-N-(甲基磺酰基)噻吩并[3,2-b]吡啶-3-甲酰胺(化合物编号1188),为黄色固体。产率:1.20g,63%;MS(ESI)m/z 791.62$[M+1]^+$;^{1}H-NMR(400MHz,DMSO-d_6)δ12.47(s,1H),8.81-8.78(m,3H),7.77(d,J=8.40Hz,1H),7.71-7.67(m,2H),7.62(d,J=4.80Hz,1H),4.83(s,2H),4.59(bs,1H),3.74-3.54(m,6H),3.08(s,3H),2.98-2.88(m,6H),2.11-2.05(m,4H),2.00(s,3H)。

[1158] 实施例4B.化合物1141,7-(5-氯-2-(3-(5-氰基-6-((1-(2,2-二氟丙基)哌啶-4-基)(甲基)氨基)-2-甲基-4-氧代吡啶并[3,4-d]嘧啶-3(4H)-基)丙-1-炔-1-基)苯基)噻吩并[3,2-b]吡啶-3-羧酸的合成

[1159]



[1160] 在氩气下在具有搅拌棒的100mL圆底烧瓶中将甲基(哌啶-4-基)氨基甲酸苄酯(2,0.990g,3.99mmol),三氟甲磺酸2,2-二氟丙酯(1,1.09g,4.78mmol),碳酸钾(1.10g,7.97mmol)和1,4-二氧六环(15mL)混合。将得到的混合物在室温下在氩气下剧烈搅拌17h。将反应混合物通过硅藻土过滤,并将滤饼用乙酸乙酯彻底洗涤。在旋转蒸发仪上浓缩滤液。将残留物溶于二氯甲烷中并通过硅胶色谱(5-60%乙酸乙酯的己烷溶液)纯化,得到(1-(2,2-二氟丙基)哌啶-4-基)(甲基)氨基甲酸苄酯(3),为无色油状物。产率:958mg,74%;MS(ESI)m/z 327.3[M+1]+;^{1}H NMR(400MHz,氯仿-d)δ7.40-7.27(m,5H),5.14(s,2H),4.12-3.81(m,1H),2.99(d,J=11.2Hz,2H),2.82(s,3H),2.66(t,J=13.7Hz,2H),2.32(bs,2H),1.86-1.68(m,2H),1.70-1.50(m,5H)。

[1161] 在100mL圆底烧瓶中在搅拌下将(1-(2,2-二氟丙基)哌啶-4-基)(甲基)氨基甲酸苄酯(3,255mg,0.781mmol)溶于THF(15mL)。连接真空/氩气/氢气组合歧管,去除烧瓶中的气氛并用氩气置换两次。加入10%钯碳(41.6mg,0.039mmol),去除烧瓶中的气氛并用氢气置换两次。将得到的混合物在氢气下在室温下剧烈搅拌45min。将反应混合物通过硅藻土过滤,并将滤饼用乙醚彻底洗涤。在室温下在旋转蒸发仪上浓缩滤液,得到1-(2,2-二氟丙基)-N-甲基哌啶-4-胺(4),为具有一些黑碳杂质的无色油状物。产率:150mg,定量产率;MS(ESI)m/z 193.2[M+1]+;^{1}H NMR(400MHz,氯仿-d)δ2.94-2.86(m,2H),2.65(t,J=13.6Hz,2H),2.42(s,3H),2.38-2.21(m,3H),1.88-1.79(m,2H),1.62(t,J=18.7Hz,3H),1.42-1.30(m,2H);^{19}F NMR(377MHz,氯仿-d)δ-91.92(qt,J=19.0,13.6Hz,2F)。

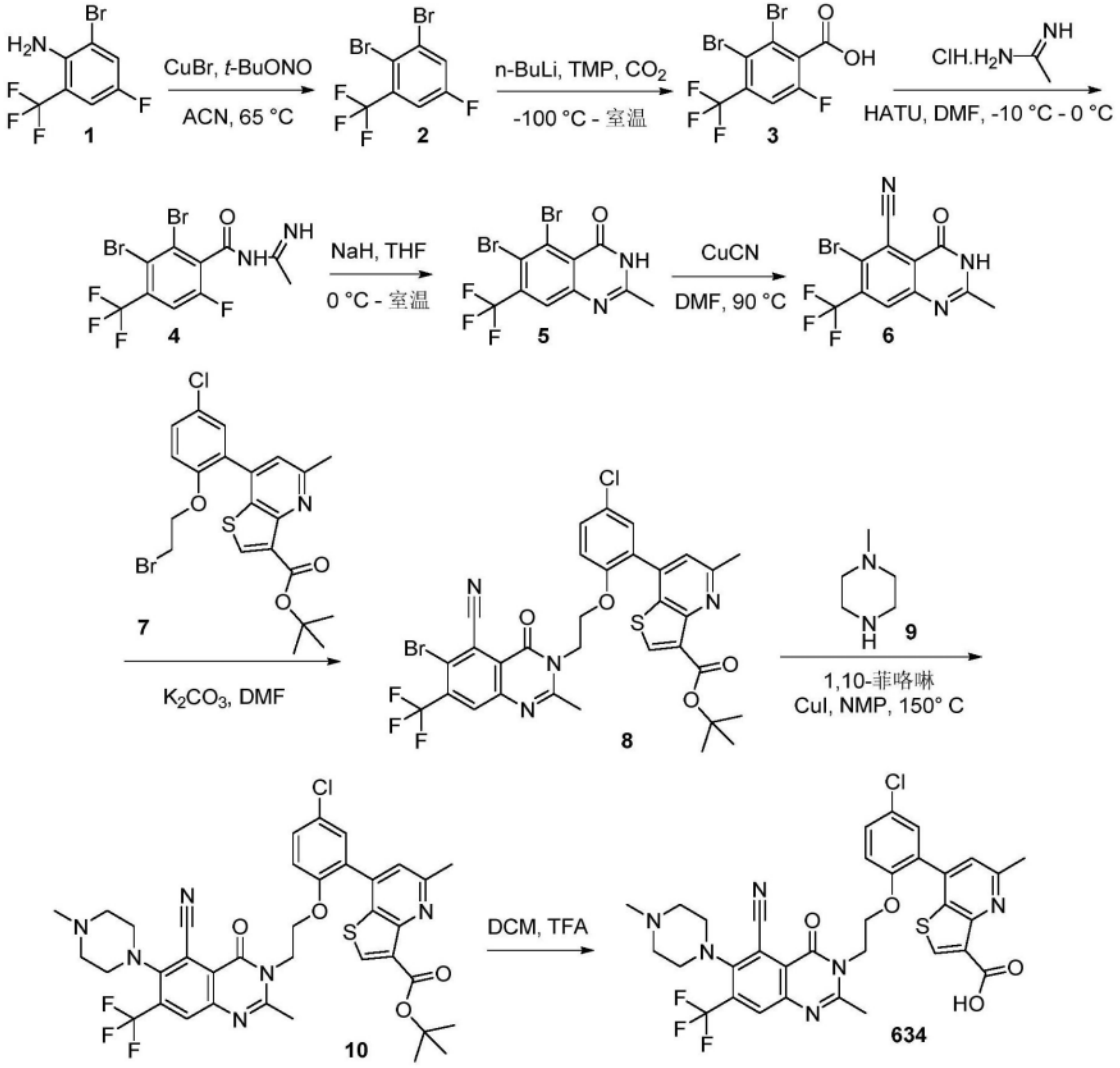
[1162] 将7-(5-氯-2-(3-(5-氰基-6-氟-2-甲基-4-氧代吡啶并[3,4-d]嘧啶-3(4H)-基)丙-1-炔-1-基)苯基)噻吩并[3,2-b]吡啶-3-甲酸叔丁酯(5,100mg,0.17mmol),1-(2,2-二氟丙基)-N-甲基哌啶-4-胺(4,98mg,0.51mmol)和N,N-二异丙基乙胺(0.3mL,1.71mmol)在

N,N-二甲基甲酰胺(2mL)中的混合物在50℃下搅拌过周末。将得到的混合物浓缩并通过柱色谱(硅胶,乙酸乙酯/二氯甲烷=0-40%)纯化,得到7-(5-氯-2-(3-(5-氰基-6-((1-(2,2-二氟丙基)哌啶-4-基)(甲基)氨基)-2-甲基-4-氧代吡啶并[3,4-d]嘧啶-3(4H)-基)丙-1-炔-1-基)苯基)噻吩并[3,2-b]吡啶-3-甲酸叔丁酯(6),为黄色固体。产率:98mg,76%;MS(ESI)m/z 758.2$[M+1]^+$。

[1163] 将7-(5-氯-2-(3-(5-氰基-6-((1-(2,2-二氟丙基)哌啶-4-基)(甲基)氨基)-2-甲基-4-氧代吡啶并[3,4-d]嘧啶-3(4H)-基)丙-1-炔-1-基)苯基)噻吩并[3,2-b]吡啶-3-甲酸叔丁酯(6;97mg,0.13mmol)溶于三氟乙酸(3mL)中。将反应在室温下搅拌5h。将得到的混合物浓缩。粗品经反相HPLC(C18,乙腈/水=15-45%)纯化,得到7-(5-氯-2-(3-(5-氰基-6-((1-(2,2-二氟丙基)哌啶-4-基)(甲基)氨基)-2-甲基-4-氧代吡啶并[3,4-d]嘧啶-3(4H)-基)丙-1-炔-1-基)苯基)噻吩并[3,2-b]吡啶-3-羧酸(1141),为黄色固体。产率:68mg,75%;MS(ESI)m/z 702.2$[M+1]^+$;^{1}H NMR(400MHz,DMSO-d_6)δ8.76(d,J=4.8Hz,1H),8.74(s,1H),8.65(s,1H),7.78-7.74(m,1H),7.71-7.67(m,2H),7.55(d,J=4.8Hz,1H),4.83(s,2H),3.11(s,3H),2.09(s,3H),1.78(t,J=19.5Hz,3H)。

[1164] 实施例4C.化合物634,7-(5-氯-2-(2-(5-氰基-2-甲基-6-(4-甲基哌嗪-1-基)-4-氧代-7-(三氟甲基)喹唑啉-3(4H)-基)乙氧基)苯基)-5-甲基噻吩并[3,2-b]吡啶-3-羧酸的合成

[1165]



[1166] 将溴化亚铜(I)(89.8g,620.1mmol)和亚硝酸叔丁酯(63.8mL,620.1mmol)在乙腈(2500mL)中的悬浮液在65℃下加热15min。加入2-溴-4-氟-6-(三氟甲基)苯胺(1,100g,387.6mmol)的乙腈溶液并将反应混合物在65℃下加热1h。完成后,将反应物质用水淬灭并用乙酸乙酯萃取。将有机层用无水硫酸钠干燥,过滤并减压浓缩,得到粗物质。用0-5%乙酸乙酯的己烷溶液,通过柱色谱在硅胶(100-200目)上纯化化合物粗品,得到1,2-二溴-5-氟-3-(三氟甲基)苯(2)为灰白色固体。产率:70.0g,55%;LCMS中无电离;^{1}H NMR(400MHz,$CDCl_3$)δ7.60(dd,J=7.32,2.84,1H),7.43(dd,J=8.24,2.80,1H)。

[1167] 在-78℃下在氩气气氛下向2,2,6,6-四甲基哌啶(7.09mL,43.61mmol)的干燥四氢呋喃(100mL)溶液中滴加正丁基锂(1.2M,27.25mL,32.71mmol)。将反应混合物升温至0℃并搅拌30min。将其再次冷却至-78℃,并在-100℃下加入1,2-二溴-5-氟-3-(三氟甲基)苯(2,10.0g,31.15mol)的干燥四氢呋喃(70mL)溶液,并将反应混合物在-100℃下搅拌45min。在该温度下将二氧化碳气体鼓泡通过反应物质15min,并将其在2h内逐渐升温至室温。完成后,将反应混合物用水淬灭并用乙醚洗涤。水层用6N盐酸水溶液酸化至pH约3-2,用乙酸乙酯萃取,洗涤有机层,用无水硫酸钠干燥,过滤并减压浓缩,得到2,3-二溴-6-氟-4-(三氟甲基)苯甲酸(3),为棕色固体。产率:10.0g,粗品,87%;MS(ESI)m/z 362.9[M-1]$^-$。

[1168] 在-10℃下向2,3-二溴-6-氟-4-(三氟甲基)苯甲酸(3,27.0g,75.8mmol)和乙脒盐

酸盐(4,9.31g,98.5mmol)的N,N-二甲基甲酰胺(180mL)溶液中加入O-(7-氮杂苯并三唑-1-基)-N,N,N',N'-四甲基脲六氟磷酸盐(36.5g,98.5mmol)和N,N-二异丙基乙胺(32.25mL,221.9mmol),并在0℃下搅拌3h。完成后,将反应物质用冰水淬灭,并用乙酸乙酯萃取。将有机层用无水硫酸钠干燥,并减压浓缩至干。将残留物用戊烷洗涤,得到2,3-二溴-6-氟-N-(1-亚氨基乙基)-4-(三氟甲基)苯甲酰胺(4),为棕色胶。产率:30g(粗品);MS(ESI))m/z 404.8[M+1]$^+$。

[1169] 在0℃下向2,3-二溴-6-氟-N-(1-亚氨基乙基)-4-(三氟甲基)苯甲酰胺(4,30.0g,74.4mmol)的四氢呋喃(250mL)溶液中加入氢化钠(60%)(5.9g,148.8mmol),升温至室温并在室温下继续搅拌16h。完成后,将反应混合物用水淬灭,并用乙酸乙酯萃取。将有机层用无水硫酸钠干燥,并减压浓缩至干。将残留物用乙醚洗涤,得到5,6-二溴-2-甲基-7-(三氟甲基)喹唑啉-4(3H)-酮(5),为白色固体。产率:9.95g,35%;MS(ESI)m/z 383.01[M-1]$^-$。

[1170] 在室温下向搅拌的5,6-二溴-2-甲基-7-(三氟甲基)喹唑啉-4(3H)-酮(5,6.0g,15.62mmol)的二甲基甲酰胺(90mL)溶液中加入氰化亚铜(I)(1.53g,17.18mmol),并将反应混合物在90℃下加热并搅拌2h。完成后,将反应物质冷却至室温,用乙酸乙酯稀释,并用水和1N盐酸水溶液洗涤。分离有机层,用硫酸钠干燥并减压浓缩。用70%乙酸乙酯的己烷溶液作为洗脱剂,通过Combi flash(40g,Redi Sep柱)纯化化合物粗品。将期望的级分减压浓缩,得到6-溴-2-甲基-4-氧代-7-(三氟甲基)-3,4-二氢喹唑啉-5-甲腈(6),为黄色固体。产率:3.2g,62.7%;MS(ESI)m/z 330.06[M-1]$^-$。

[1171] 在室温下向搅拌的6-溴-2-甲基-4-氧代-7-(三氟甲基)-3,4-二氢喹唑啉-5-甲腈(6,2.0g,6.0mmol)的N,N-二甲基甲酰胺(25.0mL)溶液中加入碳酸钾(2.48g,18.0mmol),并将混合物搅拌20min。然后在室温下将7-(2-(2-溴乙氧基)-5-氯苯基)-5-甲基噻吩并[3,2-b]吡啶-3-甲酸叔丁酯(7,2.91g,6.0mmol)加入反应混合物中,并继续搅拌16h。完成后,将反应混合物用水稀释,并用乙酸乙酯萃取。将有机层用水和饱和盐水洗涤,用无水硫酸钠干燥,过滤并浓缩。用硅胶(100-200目)以及用70%乙酸乙酯的己烷溶液作为洗脱剂,通过柱色谱纯化粗产物。将期望的级分减压浓缩,得到7-(2-(2-(6-溴-5-氰基-2-甲基-4-氧代-7-(三氟甲基)喹唑啉-3(4H)-基)乙氧基)-5-氯苯基)-5-甲基噻吩并[3,2-b]吡啶-3-甲酸叔丁酯(8),为白色固体。产率:1.7g,70%;MS(ESI)m/z 731.14[M-1]$^-$。

[1172] 向7-(2-(2-(6-溴-5-氰基-2-甲基-4-氧代-7-(三氟甲基)喹唑啉-3(4H)-基)乙氧基)-5-氯苯基)-5-甲基噻吩并[3,2-b]吡啶-3-甲酸叔丁酯(8,0.20g,0.273mmol)的N-甲基-2-吡咯烷酮(5.0mL)溶液中加入1-甲基哌嗪(9,0.06mL,0.546mmol),并将反应混合物用氩气脱气10min。然后加入碘化亚铜(I)(0.005g,0.027mmol)和1,10-菲咯啉(0.009g,0.054mmol)并将反应混合物在150℃下加热6h。完成后,将反应混合物用水稀释,并用乙酸乙酯萃取。将有机层用无水硫酸钠干燥,过滤并浓缩,得到化合物粗品。用硅胶(100-200目)和3-4%甲醇的二氯甲烷溶液,通过柱色谱纯化得到的化合物粗品,得到7-(5-氯-2-(2-(5-氰基-2-甲基-6-(4-甲基哌嗪-1-基)-4-氧代-7-(三氟甲基)喹唑啉-3(4H)-基)乙氧基)苯基)-5-甲基噻吩并[3,2-b]吡啶-3-甲酸叔丁酯(10),为白色固体。产率:0.08g,39%;MS(ESI)m/z,751.23[M-1]$^-$。

[1173] 在0℃下向7-(5-氯-2-(2-(5-氰基-2-甲基-6-(4-甲基哌嗪-1-基)-4-氧代-7-(三氟甲基)喹唑啉-3(4H)-基)乙氧基)苯基)-5-甲基噻吩并[3,2-b]吡啶-3-甲酸酯(10,

0.10g,0.132mmol)的二氯甲烷(1.5mL)溶液中加入2,2,2-三氟乙酸(0.5mL),并将反应混合物在室温下搅拌12h。完成后,将反应混合物减压浓缩,得到化合物粗品。用制备HPLC纯化化合物粗品,得到7-(5-氯-2-(2-(5-氰基-2-甲基-6-(4-甲基哌嗪-1-基)-4-氧代-7-(三氟甲基)喹唑啉-3(4H)-基)乙氧基)苯基)-5-甲基噻吩并[3,2-b]吡啶-3-羧酸(634),为白色固体。产率:0.020g,21%;MS(ESI)m/z 697.13$[M+1]^+$。^{1}H-NMR(400MHz,DMSO-d_6)δ13.51(bs,1H),9.75(bs,1H),8.23(s,1H),7.92(s,1H),7.61-7.58(t,J=6.5Hz,1H),7.42-7.41(t,J=6.5Hz,2H),7.37(d,J=8.92Hz,1H),4.40(t,J=6.16Hz,2H),4.24(t,J=6.12,2H),3.83(m,2H),3.49(m,2H),3.24(m,2H),3.03(m,2H),2.28(s,3H),2.71(s,3H),1.82(s,3H)。

[1174]

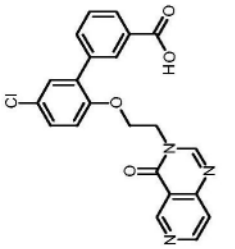
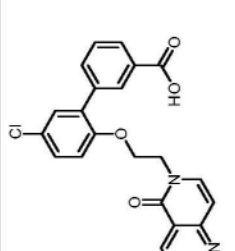
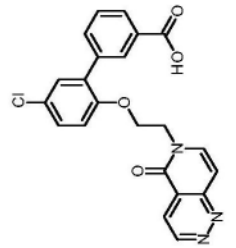
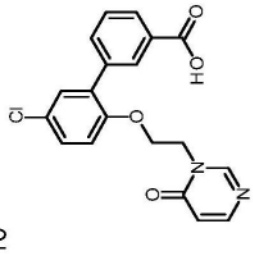
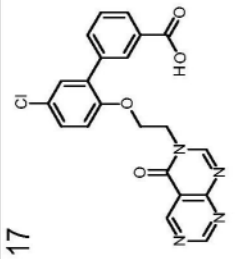
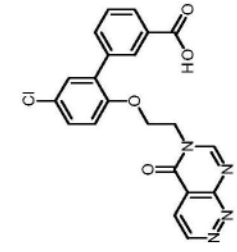
表 3. 其他化合物

化合物	表征	化合物	表征
1		MS (ESI) m/z 436.26 [M+1]+; UPLC: 99.88 %; 1H NMR (400 MHz, DMSO-d6) δ 12.94 (s, 1H), 8.95 (s, 1H), 8.59 (d, J = 5.2 Hz, 1H), 7.89-7.86 (m, 2H), 7.82 (s, 1H), 7.50 (d, J = 7.6 Hz, 1H), 7.43-7.38 (m, 2H), 7.27 (d, J = 2.6 Hz, 1H), 7.19 (d, J = 8.92 Hz, 1H), 4.34 (s, 4H), 2.23 (s, 3H)	4		MS (ESI) m/z 439.2 [M+1]+; UPLC: 96.95 %; 1H NMR (400 MHz, DMSO-d6) δ 13.07 (bs, 1H), 8.00 (s, 1H), 7.95 (s, 1H), 7.87 (d, J = 7.8 Hz, 1H), 7.80-7.75 (m, 1H), 7.60 (d, J = 7.8 Hz, 1H), 7.45 (s, 1H), 7.43-7.38 (m, 2H), 7.35 (d, J = 2.6 Hz, 1H), 7.29-7.24 (m, 1H), 7.20 (d, J = 8.8 Hz, 1H), 4.29 (dd, J = 14.0, 4.44 Hz, 4H)
2		MS (ESI) m/z 437.16 [M+1]+; UPLC: 97.10 %; 1H NMR (400 MHz, DMSO-d6) δ 12.97 (s, 1H), 7.99 (s, 1H), 7.93 (s, 1H), 7.87 (d, J = 7.7 Hz, 1H), 7.77-7.75 (m, 1H), 7.71-7.68 (m, 2H), 7.57 (d, J = 7.7 Hz, 1H), 7.41-7.38 (m, 2H), 7.34 (d, J = 3.7 Hz, 1H), 7.20 (d, J = 8.8 Hz, 1H), 4.32 (s, 4H)	5		MS (ESI) m/z 421.21 [M+1]+; UPLC: 97.35 %; 1H NMR (400 MHz, DMSO-d6) δ 13.05 (s, 1H), 9.01 (s, 1H), 8.62 (d, J = 5.3 Hz, 1H), 7.97-7.96 (m, 2H), 7.90 (d, J = 7.8 Hz, 1H), 7.60 (d, J = 7.8 Hz, 1H), 7.45-7.39 (m, 2H), 7.34 (d, J = 2.6 Hz, 1H), 7.27 (d, J = 7.4 Hz, 1H), 7.20 (d, J = 8.92 Hz, 1H), 6.50 (d, J = 7.32 Hz, 1H), 4.32-4.30 (m, 4H)
3		MS (ESI) m/z 439.25 [M+1]+; UPLC: 99.82 %; 1H NMR (400 MHz, DMSO-d6) δ 12.85 (bs, 1H), 8.17-8.14 (m, 1H), 8.03 (s, 1H), 7.93 (s, 1H), 7.88 (d, J = 7.8 Hz, 1H), 7.58 (d, J = 7.6 Hz, 1H), 7.42-7.36 (m, 4H), 7.34 (d, J = 2.5 Hz, 1H), 7.20 (d, J = 7.7 Hz, 1H), 4.32-4.30 (m, 4H)	6		MS (ESI) m/z 421.21 [M+1]+; UPLC: 97.08 %; 1H NMR (400 MHz, DMSO-d6) δ 13.04 (s, 1H), 9.31 (s, 1H), 8.69 (d, J = 4.72 Hz, 1H), 7.95 (s, 1H), 7.89 (d, J = 7.56 Hz, 1H), 7.61-7.57 (m, 1H), 7.42-7.38 (m, 2H), 7.34 (s, 1H), 7.20 (d, J = 8.76 Hz, 1H), 6.40 (d, J = 7.2 Hz, 1H), 4.31 (s, 4H)

[1175]

7	MS (ESI) m/z 421.18 [M+1]+; UPLC: 99.14 %; 1H NMR (400 MHz, DMSO-d6) δ 13.03 (s, 1H), 8.76 (s, 1H), 8.07 (d, J = 8.04 Hz, 1H), 7.98 (s, 1H), 7.91 (d, J = 7.8 Hz, 1H), 7.69-7.66 (m, 1H), 7.62 (d, J = 7.76 Hz, 1H), 7.44 (t, J = 7.72 Hz, 1H), 7.40-7.34 (m, 2H), 7.23-7.19 (m, 2H), 6.37 (d, J = 7.2 Hz, 1H), 4.32 (s, 4H)	10	MS (ESI) m/z 421.21 [M+1]+; UPLC: 99.17 %; 1H NMR (400 MHz, DMSO-d6) δ 8.89-8.87 (m, 1H), 8.48 (dd, J = 8.0, 1.5 Hz, 1H), 7.99 (s, 1H), 7.90 (d, J = 7.7 Hz, 1H), 7.55 (d, J = 7.7 Hz, 1H), 7.49-7.33 (m, 5H), 7.19 (d, J = 8.7 Hz, 1H), 6.43 (d, J = 7.56 Hz, 1H), 4.30 (s, 4H)
8	MS (ESI) m/z 583.31 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 12.46 (bs, 1H), 8.84 (d, J = 4.4 Hz, 1H), 8.47 (s, 1H), 7.85 (s, 1H), 7.71-7.22 (m, 6H), 4.39-4.37 (m, 2H), 4.23-4.20 (m, 2H), 1.73 (s, 3H)	11	MS (ESI) m/z 421.21 [M+1]+; UPLC: 98.51 %; 1H NMR (400 MHz, DMSO-d6) δ 12.98 (bs, 1H), 8.11 (dd, J = 8.0, 1.2 Hz, 1H), 8.10 (s, 1H), 7.94 (s, 1H), 7.89 (d, J = 7.6 Hz, 1H), 7.83-7.78 (m, 1H), 7.63 (d, J = 8.0 Hz, 1H), 7.54-7.50 (m, 2H), 7.41-7.37 (m, 2H), 7.35 (d, J = 2.6 Hz, 1H), 7.20 (d, J = 8.8 Hz, 1H), 4.32 (s, 4H)
9	MS (ESI) m/z 420.37 [M+1]+; UPLC: 99.10 %; 1H NMR (400 MHz, DMSO-d6) δ 13.07 (s, 1H), 8.18 (d, J = 8.04 Hz, 1H), 8.00 (s, 1H), 7.92 (d, J =7.7 Hz, 1H), 7.68 (t, J = 7.0 Hz, 1H), 7.63-7.58 (m, 2H), 7.50-7.42 (m, 2H), 7.40-7.34 (m, 2H), 7.20 (d, J = 8.7 Hz, 1H), 7.13 (d, J = 7.3 Hz, 1H), 6.37 (d, J = 7.36 Hz, 1H), 4.31-4.27 (m, 4H).	12	MS (ESI) m/z 422.22 [M+1]+; UPLC: 97.46 %; 1H NMR (400 MHz, DMSO-d6) δ 13.02 (bs, 1H), 8.94 (d, J = 2.72 Hz, 1H), 8.49 (dd, J = 7.84, 1.6 Hz, 1H), 8.25 (s, 1H), 7.96 (s, 1H), 7.87 (d, J = 7.68 Hz, 1H), 7.60-7.53 (m, 2H), 7.48-7.34 (m, 3H), 7.20 (d, J = 8.72 Hz, 1H), 4.33 (s, 4H)

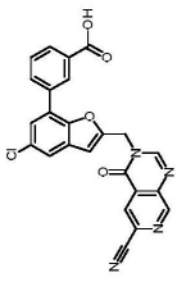
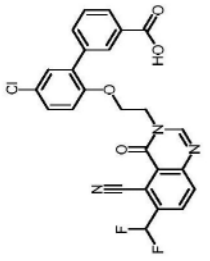
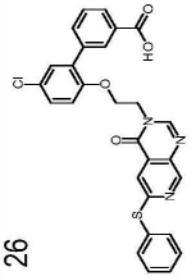
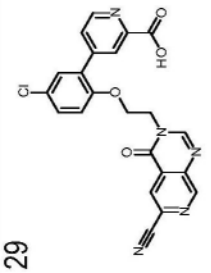
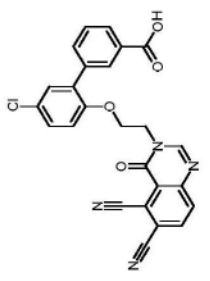
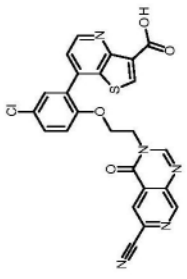
[1176]

13		MS (ESI) m/z 422.18 [M+1]+; UPLC: 98.27 %; 1H NMR (400 MHz, DMSO-d6) δ 12.94 (bs, 1H), 9.26 (s, 1H), 8.82 (d, J = 5.6 Hz, 1H), 8.19 (s, 1H), 7.92 (s, 1H), 7.86 (d, J = 7.7 Hz, 1H), 7.59-7.54 (m, 2H), 7.41-7.37 (m, 2H), 7.33 (d, J = 2.6 Hz, 1H), 7.20 (d, J = 8.8 Hz, 1H), 4.33 (s, 4H)
14		MS (ESI) m/z 422.24 [M+1]+; UPLC: 93.73 %; 1H NMR (400 MHz, DMSO-d6) δ 9.39 (s, 1H), 9.30 (s, 1H), 7.94 (s, 1H), 7.87 (d, J = 7.9 Hz, 1H), 7.66 (d, J = 7.6 Hz, 1H), 7.58 (d, J = 7.4 Hz, 1H), 7.44-7.38 (m, 2H), 7.32 (s, 1H), 7.20 (d, J = 8.8 Hz, 1H), 6.38 (d, J = 7.5 Hz, 1H), 4.32 (s, 4H)
15		MS (ESI) m/z 422.18 [M+1]+; UPLC: 96.38 %; 1H NMR (400 MHz, DMSO-d6) δ 13.03 (bs, 1H), 9.43 (d, J = 5.4 Hz, 1H), 8.19 (d, J = 5.0 Hz, 1H), 7.95 (s, 1H), 7.88 (d, J = 6.6 Hz, 1H), 7.60 (d, J = 7.7 Hz, 1H), 7.50 (d, J = 7.6 Hz, 1H), 7.45-7.33 (m, 3H), 7.20 (d, J = 8.8 Hz, 1H), 6.76 (d, J = 7.4 Hz, 1H), 4.34-4.31 (m, 4H)
16		MS (ESI) m/z 642.21 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.86 (d, J = 4.7 Hz, 1H), 8.11 (s, 1H), 8.07 (s, 1H), 7.63 (dd, J = 8.8, 2.3 Hz, 1H), 7.51 (d, J = 4.8 Hz, 1H), 7.43 (d, J = 2.5 Hz, 1H), 7.39 (d, J = 9.1 Hz, 1H), 4.67 (bs, 2H), 4.45 (t, J = 5.2 Hz 2H), 4.29 (t, J = 3.9 Hz 2H), 2.93 (s, 6H), 1.78 (s, 3H)
17		MS (ESI) m/z 423.23 [M+1]+; UPLC: 92.07 %; 1H NMR (400 MHz, DMSO-d6) δ 9.43 (s, 1H). 9.39 (s, 1H), 8.58 (s, 1H), 7.86 (s, 1H), 7.85 (d, J = 7.7 Hz, 1H), 7.58 (d, J = 7.7 Hz, 1H), 7.41-7.37 (m, 2H), 7.33 (d, J = 2.6 Hz, 1H), 7.20 (d, J = 8.8 Hz, 1H), 4.31 (s, 4H)
18		MS (ESI) m/z 423.23 [M+1]+; UPLC: 99.81 %; 1H NMR (400 MHz, DMSO-d6) δ 13.07 (bs, 1H), 9.48 (d, J = 5.0 Hz, 1H), 8.33 (s, 1H), 8.23 (d, J =5.1 Hz, 1H), 7.93 (s, 1H), 7.86 (d, J = 7.8 Hz, 1H), 7.62 (d, J = 6.2 Hz, 1H), 7.44-7.34 (m, 3H), 7.20 (d, J = 8.8 Hz, 1H), 4.33 (s, 4H)

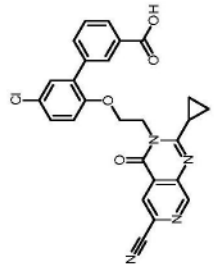
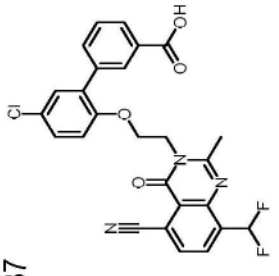
[1177]

19		MS (ESI) m/z 423.23 [M+1]+; UPLC: 96.78 %; 1H NMR (400 MHz, DMSO-d6) δ 8.99 (d, J = 2.0 Hz, 1H), 8.85 (d, J = 2.0 Hz, 1H), 8.32 (s, 1H), 7.95 (s, 1H), 7.86 (d, J = 7.8 Hz, 1H), 7.58 (d, J = 7.7 Hz, 1H), 7.40-7.36 (m, 2H), 7.34 (d, J = 2.7 Hz, 1H), 7.20 (d, J = 8.8 Hz, 1H), 4.36-4.35 (m, 4H)
20		MS (ESI) m/z 422.22 [M+1]+; UPLC: 97.46 %; 1H NMR (400 MHz, DMSO-d6) δ 12.98 (bs, 1H), 8.74 (d, J = 8.0 Hz, 1H), 8.36 (s, 1H), 7.98 (d, J = 8.1 Hz, 1H), 7.94 (s, 1H), 7.84 (d, J = 7.8 Hz, 1H), 7.62 (d, J = 7.7 Hz, 1H), 7.42-7.38 (m, 2H), 7.35 (d, J = 2.6 Hz, 1H), 7.20 (d, J = 8.8 Hz, 1H), 4.35 (s, 4H)
21		MS (ESI) m/z 422.18 [M+1]+; UPLC: 98.77 %; 1H NMR (400 MHz, DMSO-d6) δ 12.96 (bs, 1H), 8.79 (dd, J = 4.1, 1.1 Hz, 1H), 8.06-8.04 (m, 2H), 7.93 (s, 1H), 7.88 (d, J = 7.7 Hz, 1H), 7.81-7.78 (m, 1H), 7.60-7.58 (m, 1H), 7.42-7.38 (m, 2H), 7.34 (d, J = 2.6 Hz, 1H), 7.21 (d, J = 8.8 Hz, 1H), 4.34 (s, 4H)
22		MS (ESI) m/z 585.30 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.80 (d, J = 4.8 Hz, 1H), 8.44 (s, 1H), 8.04 (d, J = 9.72 Hz, 1H), 7.61-7.59 (dd, J = 2.56 Hz, J = 2.64 Hz, 1H), 7.50-7.36 (m, 4H), 4.42 (t, J = 4.56 Hz, 2H), 4.28 (t, J = 4.64 Hz, 2H), 1.87 (s, 3H)
23		MS (ESI) m/z 438.28 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 9.10 (s, 1H), 8.53 (s, 1H), 8.29 (s, 1H), 7.93 (s, 1H), 7.89 (d, J = 7.6 Hz , 1H), 7.83 (dd, J = 2.12, 8.44 Hz, 1H), 7.77 (d, J = 1.96 Hz, 1H), 7.56 (d, J = 7.72 Hz, 1H), 7.43 (t, J = 15.5 Hz, 1H), 7.33 (d, J = 8.64 Hz, 1H), 4.44 (d, J = 4.84 Hz, 2H), 4.40 (d, J = 4.68 Hz, 2H)
24		MS (ESI) m/z 485.37 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 12.74 (s, 1H), 9.11 (s, 1H), 8.56 (s, 1H), 8.01 (s, 1H), 7.74-7.77 (m, 1H), 7.32-7.40 (m, 3H), 7.13-7.16 (m, 2H), 4.29 (s, 4H), 1.55 (s, 3H)

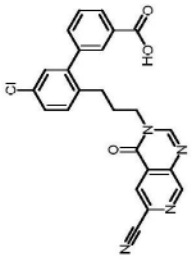
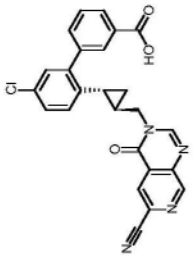
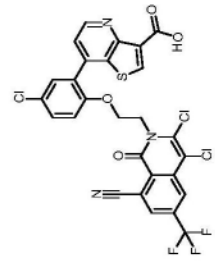
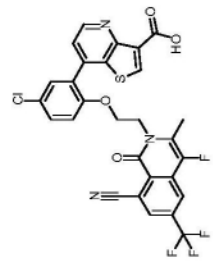
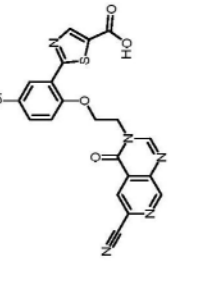
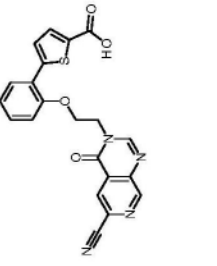
[1178]

25		28	
MS (ESI) m/z 457.23 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.05 (s, 1H), 9.19 (s, 1H), 8.86 (s, 1H), 8.62 (s, 1H), 8.34 (s, 1H), 7.99-8.07 (m, 2H), 7.72 (s, 1H), 7.58-7.63 (m, 2H), 7.04 (s, 1H), 5.48 (s, 2H)		MS (ESI) m/z 496.36 [M+1]+ UPLC: 99.32 %; 1H NMR (400 MHz, DMSO-d6) δ 12.97 (s, 1H), 8.17-8.15 (m, 2H), 8.04 (d, J=8.56 Hz, 1H), 7.90-7.89 (m, 1H), 7.84-7.82 (m, 1H), 7.61-7.58 (m, 1H), 7.52-7.25 (m, 4H), 7.21 (d, J=8.88 Hz, 1H), 4.35 (s, 4H)	
26		29	
MS (ESI) m/z 530.0 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.01 (s, 1H), 8.88 (s, 1H), 8.02 (s, 1H), 7.58-7.90 (m, 2H), 7.64 (s, 2H), 7.54 (s, 4H), 7.30-7.36 (m, 4H), 7.16 (s, 1H), 4.26 (s, 4H)		MS (ESI) m/z 448.31 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 9.09 (s, 1H), 8.63(d, J = 4.47Hz, 1H), 8.53 (s, 1H), 8.31 (s, 1H), 7.99 (s, 1H), 7.63 (d, J = 3.64 Hz, 1H), 7.49-7.45 (m, 2H), 7.25 (d, J = 8.68 Hz, 1H), 4.38 (m, 4H)	
27		30	
MS (ESI) m/z 471.32 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.06 (s, 1H), 8.38 (s, 1H), 8.20 (s, 1H), 8.039 (d, J =8.56 1H), 7.87-7.86 (m, 1H), 7.82-7.81 (m, 1H), 7.62-7.58 (m, 1H), 7.43 - 7.39 (m, 2H), 7.33 (d, J = 2.64 Hz, 1H), 7.21 (d, J = 8.84 Hz, 1H), 4.35 (s, 4H)		MS (ESI) m/z 504.39 [M+1]+. UPLC: 99.59 %; 1H NMR (400 MHz, DMSO-d6) δ 8.96 (s, 1H), 8.81(d, J = 4.88 Hz, 1H), 8.55 (s, 1H), 8.45 (s, 1H), 7.91 (s, 1H), 7.61-7.59 (dd, J = 2.60, 8.88 Hz, 1H), 7.49-7.46 (m, 2H), 7.35 (d, J = 8.96 Hz, 1H), 4.40-4.38 (t, J = 5.00 Hz, 2H), 4.25-4.23 (t, J = 4.84 Hz, 2H)	

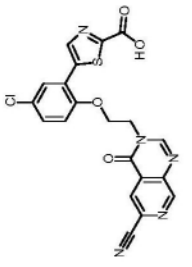
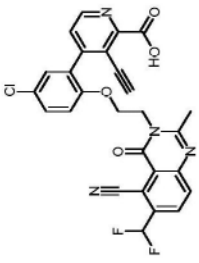
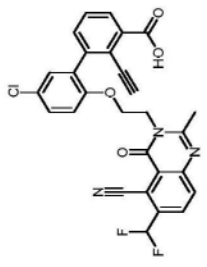
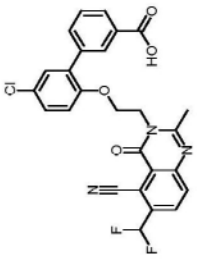
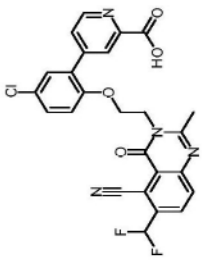
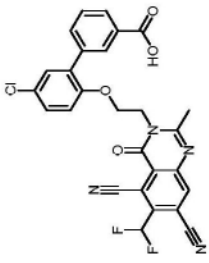
[1179]

31		MS (ESI) m/z 457.36 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 12.92 (s, 1H), 8.92 (s, 1H), 8.42 (s, 1H), 7.86 (s, 1H), 7.81 (d, J = 11.08 Hz, 1H), 7.57 (d, J = 7.8 Hz, 1H), 7.42-7.37 (m, 2H), 7.30 (d, J = 2.72 Hz, 1H), 7.21 (d, J = 8.88 Hz, 1H), 4.61 (t, J = 5.12 Hz, 2H), 4.42 (t, J = 10.08 Hz, 2H), 2.11-2.05 (m, 1H), 1.03-0.99 (m, 2H), 0.77-0.72 (m, 2H).	37		MS (ESI) m/z 510.40 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 12.95 (s, 1H), 8.13 (d, J = 8.0 Hz, 1H), 8.06 (d, J = 7.6 Hz, 1H), 7.83-7.84 (m, 2H), 7.36-7.72 (m, 4H), 7.27-7.28 (m, 1H), 7.21 (d, J = 8.8 Hz, 1H), 4.35 (s, 4H), 2.22 (s, 3H)
32		MS (ESI) m/z 515.33 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.03 (s, 1H), 9.13 (s, 1H), 8.32 (s, 1H), 8.23 (s, 1H), 7.92 (s, 1H), 7.86 (t, J = 5.76 Hz, 2H), 7.61 (d, J = 7.72 Hz, 1H), 7.43-7.39 (m, 2H), 7.34 (d, J = 2.44 Hz, 1H), 7.2 (d, J = 8.84 Hz, 1H), 4.35 (m, 4H), 2.59 (s, 3H)	40		MS (ESI) m/z 603.21 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.84 (d, J = 4.8 Hz, 1H), 8.38 (bs, 1H), 8.28 (s, 1H), 8.01 (bs, 1H), 7.63 (d, J = 8.4 Hz, 1H), 7.54 (d, J = 11.4 Hz, 1H), 7.49 (d, J = 4.8 Hz, 1H), 4.43 (t, J = 4.4 Hz, 2H), 4.25 (t, J = 4.4 Hz, 2H), 1.73 (s, 3H)
33		MS (ESI) m/z 511.34 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.66 (s, 1H), 7.84 (d, J = 7.6 Hz, 2H), 7.74-7.47 (t, J = 5.6 Hz, 1H), 7.43-7.36 (m, 3H), 7.25 (d, J = 2.4 Hz, 1H), 7.17 (d, J = 8.8 Hz, 1H), 4.37 (d, J = 4.4 Hz ,2H), 4.33 (d, J = 3.6 Hz, 2H), 2.89 (s, 3H)	41		MS (ESI) m/z 441.24 [M-1]-; 1H NMR (400 MHz, DMSO-d6) δ 13.06 (s, 1H), 9.1 (s, 1H), 8.6 (s, 1H), 8.57 (s, 1H), 7.84 (d, J = 5.6 Hz , 1H), 7.75 (s, 1H), 7.69 (d, J = 8.3 Hz, 1H), 7.50 -7.44 (m, 3H), 7.36 (d, J = 1.76 Hz, 1H), 6.46 -6.39 (m, 1H), 6.27 (d, J = 16.09 Hz, 1H), 4.73 (d, J = 5.12 Hz, 2H)

[1180]

42		MS (ESI) m/z 445.39 [M+1]+ UPLC: 99.76 %; 1H NMR (400 MHz, DMSO-d6) δ 13.01 (s, 1H), 9.12(s, 1H), 8.51 (s, 1H), 8.47 (s, 1H), 7.69 (s, 1H), 7.64-7.62 (m, 1H), 7.48 (d, J=7.72 Hz, 1H), 7.41-7.34 (m, 3H), 7.19 (s, 1H), 3.90-3.87 (m, 2H), 2.55-2.50 (m, 2H), 1.80-1.74 (m, 2H)
43		MS (ESI) m/z 457.36 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.08 (b, 1H), 9.14(s, 1H), 8.56 (d, J = 4.52 Hz, 2H), 7.92 (d, J = 7.44 Hz, 1H), 7.88 (s, 1H), 7.62-7.54 (m, 2H), 7.34 (dd, J = 8.44 Hz, 1H), 7.23 (d, J = 2.2 Hz, 1H), 7.03 (d, J = 8.48 Hz, 1H), 4.02-3.97 (m, 1H), 3.79-3.74 (m, 1H), 1.94 (q, J = 6.68 Hz, 1H), 1.61 (q, J = 6.76 Hz, 1H), 1.07 (t, J = 7.04 Hz, 2H)
46		MS (ESI) m/z 638.09 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.16 (s, 1H), 8.82 (d, J = 4.84 Hz, 1H), 8.57 (s, 1H), 8.21 (s, 1H), 8.13 (s, 1H), 7.62-7.59 (dd, J = 2.48 Hz, J = 2.44 Hz, 1H), 7.53 (d, J = 4.8 Hz, 1H), 7.40-7.30 (m, 2H), 4.51-4.46 (m, 4H)
47		MS (ESI) m/z 558.95 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.36 (s, 1H), 8.85 (d, J = 4.68 Hz, 1H), 8.57 (d, J = 1.16 Hz, 1H), 8.23 (d, J = 1.23 Hz, 1H), 8.17 (s, 1H), 7.61-7.58 (dd, J = 2.72 Hz, J = 2.68 Hz, 1H), 7.49 (d, J = 4.72 Hz, 1H), 7.40 (d, J = 2.72 Hz, 1H), 7.36 (d, J = 8.96 Hz, 1H), 4.40 (t, J = 4.40 Hz, J = 4.76 Hz, 2H), 4.18 (t, J = 4.44 Hz, J = 4.28 Hz, 2H), 1.48 (d, J = 3.52 Hz, 3H)
52		MS (ESI) m/z 454.33 [M+1]+. 1H NMR (400 MHz, DMSO-d6) δ 9.12 (s, 1H), 8.69 (s, 1H), 8.56 (s, 1H), 8.20 (d, J = 2.64 Hz, 1H), 8.06 (s, 1H), 7.51 (dd, J = 8.88 Hz, 1H), 7.37 (d, J = 9 Hz, 1H), 4.68 (t, J = 5.52 Hz, 2H), 4.54 (t, J = 5.48 Hz, 2H)
53		MS (ESI) m/z 453.31 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 12.99 (b, 1H), 9.09(s, 1H), 8.60 (s, 1H), 8.53 (s, 1H), 7.83 (d, J = 2.52 Hz, 1H), 7.62 (d, J = 4.04 Hz, 1H), 7.55 (d, J = 4 Hz, 1H), 7.42-7.40 (m, 1H), 7.31 (d, J = 8.96 Hz, 1H), 4.61 (t, J = 5.36 Hz, 2H), 4.58 (t, J = 5.28 Hz, 2H)

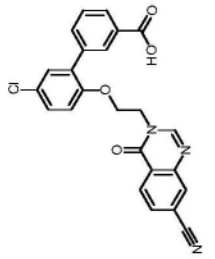
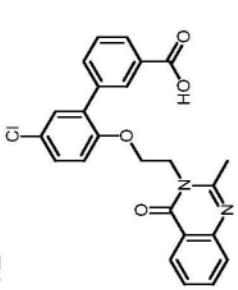
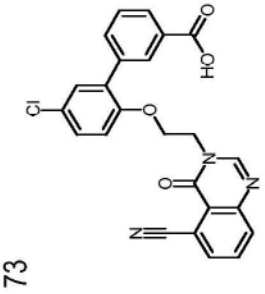
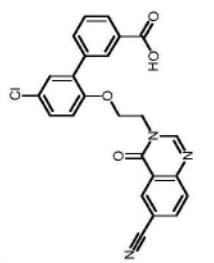
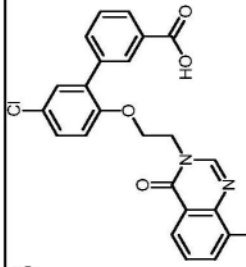
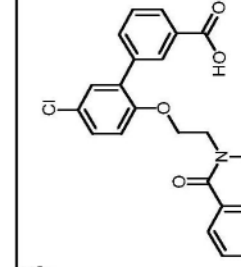
[1181]

54		MS (ESI) m/z 454.36 [M+1]+. 1H NMR (400 MHz, DMSO-d6) δ 9.13 (s, 1H), 8.63 (s, 1H), 8.57 (s, 1H), 8.25 (bs, 1H), 7.79 (s, 1H), 7.38 (dd, J = 8.72 Hz, 1H), 7.24 (d, J = 8.8 Hz, 1H), 4.50 (t, J = 2.96 Hz, 4H).	57		MS (ESI) m/z 535.17 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.41 (s, 1H), 8.13(d, J = 8.72 Hz, 1H), 7.99 (d, J = 8.6 Hz, 1H), 7.49-7.19 (m, 5H), 4.32 (s, 4H), 4.06 (s, 1H), 2.08 (s, 3H)
55		MS (ESI) m/z 534.37 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 12.94 (s, 1H), 8.11 (d, J = 8.56 Hz, 1H), 7.96 (d, J = 8.52 Hz, 1H), 7.82 (d, J = 7.68 Hz, 1H), 7.48-7.21 (m, 4H), 7.15 (d, J = 9.48 Hz, 2H), 4.30 (s, 4H), 3.75 (s, 1H), 1.98 (s, 3H)	62		MS (ESI) m/z 508.04 [M-1]-. UPLC: 98.04 %; 1H NMR (400 MHz, DMSO-d6) δ 12.92 (s, 1H), 8.13(d, J = 8.64 Hz, 1H), 7.97 (d, J = 8.56 Hz, 1H), 7.86 (d, J = 7.84 Hz, 1H), 7.83 (s, 1H), 7.53-7.20 (m, 6H), 4.35 (s, 4H), 2.20 (s, 3H)
56		MS (ESI) m/z 510.73 [M+1]+; UPLC: 99.83 %; 1H NMR (400 MHz, DMSO-d6) δ 12.91 (s, 1H), 8.61(d, J = 4.56 Hz, 1H), 8.14 (d, J = 8.60 Hz, 1H), 7.98 (d, J = 8.44 Hz, 2H), 7.59-7.58 (m, 1H), 7.51-7.23 (m, 4H), 4.39 (s, 4H), 2.22 (s, 3H)	63		MS (ESI) m/z 535.26 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.57 (s, 1H), 7.84-7.79 (m, 2H), 7.61-7.36 (m, 4H), 7.24 (s, 1H), 7.18 (d, J = 8.88 Hz, 1H), 4.34 (s, 4H), 2.17 (s, 3H)

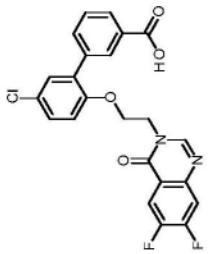
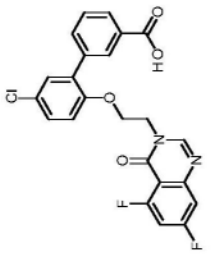
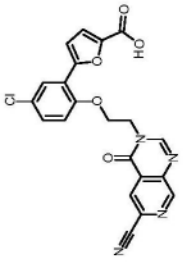
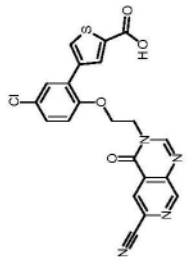
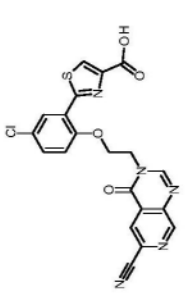
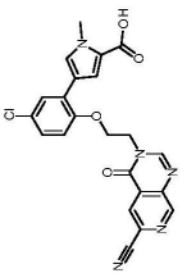
[1182]

64	MS (ESI) m/z 560.18 [M+1]+. 1H NMR (400 MHz, DMSO-d6) δ 12.93 (bs, 1H), 8.12 (s, 1H), 7.85-7.83(m, 2H), 7.63-7.19 (m, 7H), 4.35 (s, 4H), 2.21 (s, 3H)	68	MS (ESI) m/z 424.24 [M+1]+; UPLC: 97.94 %; 1H NMR (400 MHz, DMSO-d6) δ 12.98 (bs, 1H), 7.95-7.91 (m, 2H), 7.78 (s, 1H), 7.58-7.55 (m, 1H), 7.44 (t, J = 7.6 Hz, 1H), 7.38 (dd, J = 8.8, 2.4 Hz, 1H), 7.34 (d, J = 2.4 Hz, 1H), 7.19 (d, J = 8.8 Hz, 1H), 7.09 (d, J = 3.2 Hz, 1H), 6.43 (d, J = 3.2 Hz, 1H), 4.27 (s, 4H), 3.66 (s, 3H)
66	MS (ESI) m/z 445.13 [M-1]-; UPLC: 93.91 %; 1H NMR (400 MHz, DMSO-d6) δ 12.94 (s, 1H), 9.09 (s, 1H), 8.52 (s, 1H), 8.26 (s, 1H), 7.85-7.83 (m, 2H), 7.58 (d, J = 7.84 Hz, 1H), 7.44-7.39 (m, 2H), 7.32 (d, J = 2.60 Hz, 1H), 7.20 (d, J = 8.88 Hz, 1H) 4.35 (s, 4H)	69	MS (ESI) m/z 424.27 [M+1]+; UPLC: 98.50 %; 1H NMR (400 MHz, DMSO-d6) δ 8.00 (s, 1H), 7.89 (d, J = 7.6 Hz, 1H), 7.78 (s, 1H), 7.51 (d, J = 7.6 Hz, 1H), 7.42-7.34 (m, 4H), 7.18 (d, J = 8.8 Hz, 1H), 6.28 (d, J = 2.8 Hz, 1H), 4.28 (s, 4H), 3.97 (s, 3H)
67	MS (ESI) m/z 423.16 [M+1]+; UPLC: 97.88 %; 1H NMR (400 MHz, DMSO-d6) δ 12.98 (bs, 1H), 8.02 (s, 1H), 7.92-7.91 (m, 3H), 7.56-7.55 (m, 1H), 7.44 (t, J = 8.0 Hz, 1H), 7.39 (dd, J = 8.8, 2.8 Hz, 1H), 7.33 (d, J = 2.4 Hz, 1H), 7.2 (d, J = 8.8 Hz, 1H), 4.32-4.29 (m, 4H), 3.69 (s, 3H)	70	MS (ESI) m/z 450.27 [M+1]+; UPLC: 96.87 %; 1H NMR (400 MHz, DMSO-d6) δ 12.98 (bs, 1H), 8.97 (s, 1H), 8.60 (d, J = 5.2 Hz, 1H), 7.89-7.87 (m, 3H), 7.54-7.52 (m, 1H), 7.43-7.37 (m, 2H), 7.28 (d, J = 2.8 Hz, 1H), 7.18 (d, J = 8.8 Hz, 1H), 4.37-4.24 (m, 4H), 2.60-2.49 (m, 2H), 0.97 (t, J = 7.2 Hz, 3H)

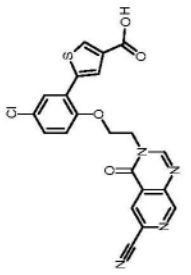
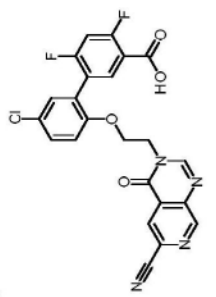
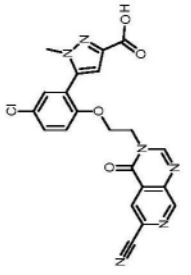
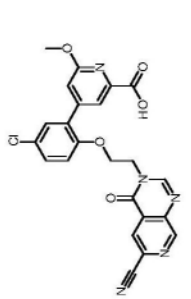
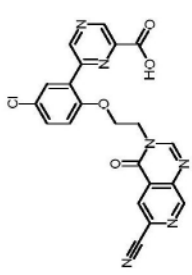
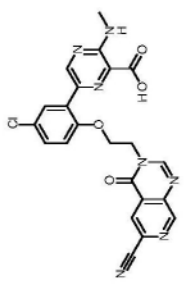
[1183]

71		MS (ESI) m/z 450.27 [M+1]+; UPLC: 96.87 %; 1H NMR (400 MHz, DMSO-d6) δ 12.98 (bs, 1H), 8.97 (s, 1H), 8.60 (d, J = 5.2 Hz, 1H), 7.89-7.87 (m, 3H), 7.54-7.52 (m, 1H), 7.43-7.37 (m, 2H), 7.28 (d, J = 2.8 Hz, 1H), 7.18 (d, J = 8.8 Hz, 1H), 4.37-4.24 (m, 4H), 2.60-2.49 (m, 2H), 0.97 (t, J = 7.2 Hz, 3H)
72		MS (ESI) m/z 435.22 [M+1]+; UPLC: 95.85 %; 1H NMR (400 MHz, DMSO-d6) δ 12.98 (bs, 1H), 8.05 (d, J = 8.0 Hz, 1H), 7.91-7.89 (m, 2H), 7.78 (t, J = 7.2 Hz, 1H), 7.56 (d, J = 8.0 Hz, 1H), 7.52-7.37 (m, 4H), 7.29 (d, J = 2.4 Hz, 1H), 7.19 (d, J = 8.8 Hz, 1H), 4.33 (s, 4H), 2.22 (s, 3H)
73		LCMS Purity: 96.35 %, MS: m/z 444.18 [M-1]-; 1H NMR (DMSO-d6, 400 mHz) δ 12.96 (bs, 1H), 8.09 (s, 1H), 8.02 (m, 1H), 7.92 (m, 3H), 7.85 (d, J = 7.8 Hz, 1H), 7.60 (d, J = 7.8 Hz, 1H), 7.41-7.39 (m, 2H), 7.33 (d, J = 2.7 Hz, 1H), 7.21 (d, J = 8.8 Hz, 1H), 4.33 (m, 4H)
74		MS (ESI) m/z 446.22 [M+1]+; UPLC: 97.68 %; 1H NMR (400 MHz, DMSO-d6) δ 12.95 (bs, 1H), 8.21 (d, J = 8.2 Hz, 1H), 8.15 (s, 1H), 8.09 (s, 1H), 7.89-7.84 (m, 3H), 7.57 (d, J = 7.7 Hz, 1H), 7.41-7.38 (m, 2H), 7.33 (d, J = 2.5 Hz, 1H), 7.20 (d, J = 8.8 Hz, 1H), 4.39-4.32 (m, 4H)
75		MS (ESI) m/z 446.25 [M+1]+; UPLC: 97.45 %; 1H NMR (400 MHz, DMSO-d6) δ 12.96 (s, 1H), 8.36-8.31 (m, 2H), 8.24 (s, 1H), 7.90 (s, 1H), 7.83 (d, J = 7.8 Hz, 1H), 7.65 (t, J = 7.8 Hz, 1H), 7.55 (d, J = 7.8 Hz, 1H), 7.41-7.33 (m, 3H), 7.21 (d, J = 8.8 Hz, 1H), 4.34 (s, 4H)
76		MS (ESI) m/z 439.21 [M+1]+; UPLC: 99.71 %; 1H NMR (400 MHz, DMSO-d6) δ 8.08 (s, 1H), 7.94-7.85 (m, 3H), 7.70-7.68 (m, 1H), 7.58 (d, J = 7.86 Hz, 1H), 7.53-7.48 (m, 1H), 7.40-7.29 (m, 3H), 7.20 (d, J = 8.8 Hz, 1H), 4.33 (s, 4H)

[1184]

77		MS (ESI) m/z 457.25 [M+1]+; UPLC: 95.49 %; 1H NMR (400 MHz, DMSO-d6) δ 12.95 (bs, 1H), 8.07-7.96 (m, 2H), 7.89-7.85 (m, 2H), 7.72-7.67 (m, 1H), 7.57 (d, J = 7.8 Hz, 1H), 7.43-7.38 (m, 2H), 7.32 (d, J = 2.6 Hz, 1H), 7.20 (d, J = 8.8 Hz, 1H), 4.33-4.30 (m, 4H)
78		MS (ESI) m/z 457.21 [M+1]+; UPLC: 95.45 %; 1H NMR (400 MHz, DMSO-d6) δ 12.96 (bs, 1H), 8.01 (s, 1H), 7.92 (s, 1H), 7.87 (d, J = 7.8 Hz, 1H), 7.60 (d, J = 7.8 Hz, 1H), 7.44-7.7.33 (m, 4H), 7.28-7.25 (m, 1H), 7.20 (d, J = 9.6 Hz, 1H), 4.31-4.25 (m, 4H)
79		MS (ESI) m/z 437.2 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 9.13 (s, 1H), 8.74 (s, 1H), 8.60 (s, 1H), 7.69 (d, J = 2.6 Hz, 1H), 7.40 (dd, J = 8.84 Hz, 2.64 Hz, 1H), 7.24 (d, J = 8.96 Hz, 1H), 7.15 (bs, 1H), 7.03(d, J = 3.32 Hz, 1H), 4.53 (s, 4H)
80		MS (ESI) m/z 453.20 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 9.13 (s, 1H), 8.56 (s, 2H), 7.87 (s, 1H), 7.72 (s, 1H), 7.51 (d, J = 2.56 Hz, 1H), 7.31 (dd, J = 8.8 Hz, 2.56 Hz, 1H), 7.15 (d, J = 8.92 Hz, 1H), 4.45 (t, J = 4.76 Hz, 2H), 4.41 (t, J = 4.72 Hz, 2H)
81		MS (ESI) m/z 454.29 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.17 (bs, 1H), 9.14 (s, 1H), 8.75 (s, 1H), 8.59 (s, 1H), 8.20 (bs, 2H), 7.51 (d, J = 8.00 Hz, 1H), 7.35 (d, J = 8.96 Hz, 1H), 4.66 (bs, 2H), 4.55 (bs, 2H)
82		MS (ESI) m/z 450.29 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 12.23 (bs, 1H), 9.13 (s, 1H), 8.67 (s, 1H), 8.57 (s, 1H), 7.49 (d, J = 2.44 Hz, 1H), 7.41 (bs, 1H), 7.17-7.14 (m, 1H), 7.09 (d, J = 8.2 Hz, 1H), 7.04 (bs, 1H), 4.49 (t, J = 4.32 Hz, 2H), 4.46 (t, J = 4.56 Hz, 2H), 3.84 (s, 3H)

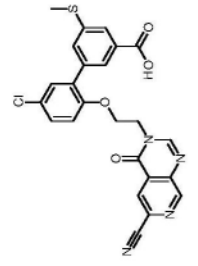
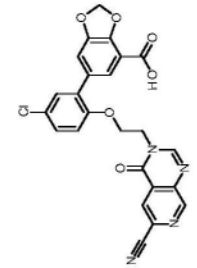
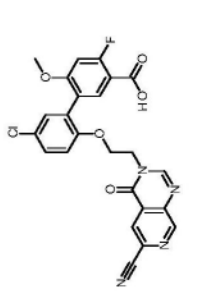
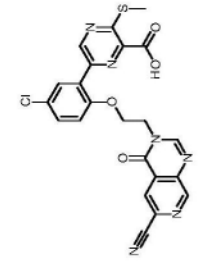
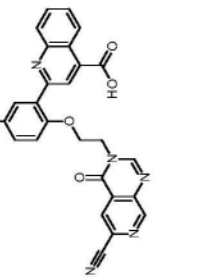
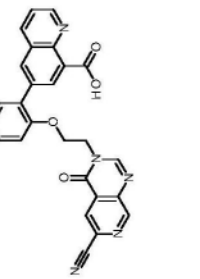
[1185]

83		MS (ESI) m/z 453.31 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 12.74 (s, 1H), 9.12 (s, 1H), 8.63 (s, 1H), 8.56 (s, 1H), 8.09 (bs, 1H), 7.77 (d, J = 2.68 Hz, 2H), 7.36 (dd, J = 8.8 Hz, 2.4 Hz, 1H), 7.25 (d, J = 8.8 Hz, 1H), 4.55 (t, J = 4.8 Hz, 2H), 4.48 (t, J = 5.2 Hz, 2H)	86		MS (ESI) m/z 483.24 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.27 (s, 1H), 9.10 (s, 1H), 8.52 (s, 1H), 8.22 (s, 1H), 7.64 (t, J = 8.32 Hz, 1H),7.46 (dd, J = 8.8 Hz, 2.56 Hz, 1H), 7.31 (d, J = 2.52 Hz, 1H), 7.21-7.18 (m, 2H), 4.32(s, 4H)
84		MS (ESI) m/z 451.30 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 12.60 (bs, 1H), 9.09 (s, 1H), 8.52 (s, 1H), 8.25 (s, 1H), 7.52 (dd, J = 8.76 Hz, 2.6 Hz, 1H), 7.34 (d, J = 2.64 Hz, 1H), 7.24 (d, J = 8.92 Hz, 1H), 6.52 (s, 1H), 4.36 (s, 4H), 3.56 (s, 3H)	87		MS (ESI) m/z 478.30 [M+1]+;1H NMR (400 MHz, DMSO-d6) δ 9.08 (s, 1H), 9.08 (s, 1H), 8.51 (s, 1H), 8.37 (s, 1H), 7.57 (s, 1H), 7.45 (dd, J = 8.76 Hz, 2.6 Hz, 1H), 7.38 (d, J = 2.72 Hz, 1H), 7.23 (d, J = 8.88 Hz, 1H), 6.87 (bs, 1H), 4.38 (bs, 4H), 3.88 (s, 3H)
85		MS (ESI) m/z 449.36 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 9.09 (s, 1H), 8.98 (bs, 2H), 8.54 (s, 1H), 8.43 (bs, 1H), 7.67 (bs, 1H), 7.51 (d, J = 8.8 Hz, 1H), 7.26 (d, J = 7.84 Hz, 1H), 4.44 (s, 4H)	88		MS (ESI) m/z 478.30 [M+1]+; 1H NMR (400 mHz, DMSO-d6) δ 13.10 (s, 1H), 9.06 (s, 1H), 8.57 (s, 1H), 8.53 (s, 1H), 8.47 (s, 1H), 8.11-8.08 (m, 1H), 7.73 (d, J = 2.68 Hz, 1H), 7.37 (dd, J = 8.76 Hz, 2.68Hz, 1H), 7.21 (d, J = 8.88 Hz, 1H), 4.44 (s, 4H), 2.95 (d, J = 4.24 Hz, 3H)

[1186]

89		MS (ESI) m/z 483.24 [M+1]+;1H NMR (400 MHz, DMSO-d6) δ 13.31 (s, 1H), 9.08 (s, 1H), 8.51 (s, 1H), 8.22 (s, 1H), 7.81-7.77 (m, 1H), 7.51-7.48 (m, 2H), 7.35 (d, J = 2.6 Hz, 1H), 7.23 (d, J = 8.92 Hz, 1H), 4.36-4.33 (m, 4H)	
90		MS (ESI) m/z 479.35 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 9.12 (s, 1H), 8.58 (s, 1H), 8.56 (s, 1H), 8.41 (bs, 1H), 7.63 (bs, 1H), 7.41 (dd, J = 8.8 Hz, 2.4 Hz, 1H), 7.21 (d, J = 9.2 Hz, 1H), 4.47-4.43 (m, 4H), 3.90 (s, 3H)	
91		MS (ESI) m/z 483.22 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.83 (bs, 1H), 9.11(s, 1H), 8.54 (s, 1H), 8.23 (s, 1H), 7.46-7.43 (m, 1H), 7.35 (bs, 1H), 7.28 (d, J = 2.56 Hz, 1H), 7.20 (d, J = 8.96 Hz, 1H), 7.07 (t, J = 9.12 Hz, 1H), 4.32 (s, 4H)	
92		MS (ESI) m/z 487.31 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 12.41 (bs, 1H), 9.07 (s, 1H), 8.47 (s, 1H), 7.96 (s, 1H), 7.65 (dd, J = 8.12 Hz, 1.72 Hz, 1H), 7.43-7.40 (m, 2H), 7.19-7.17 (m, 2H), 6.79 (d, J = 8.2 Hz, 1H), 4.26 (s, 4H), 1.44-1.38 (m, 1H), 0.70-0.47 (m, 4H)	
93		MS (ESI) m/z 472.23 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.50 (bs, 1H), 9.05 (s, 1H), 8.49 (s, 1H), 8.20 (s, 1H), 8.16 (s, 1H), 8.07 (t, J = 1.48 Hz, 1H), 8.01 (t, J = 1.48 Hz, 1H), 7.45 (dd, J = 8.8 Hz, 2.68 Hz, 1H), 7.41 (d, J = 2.6 Hz, 1H), 7.24 (d, J = 8.8 Hz, 1H), 4.38-4.33 (m, 4H)	
94		MS (ESI) m/z 472.37 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.87 (bs, 1H), 9.10 (s, 1H), 8.54 (s, 1H), 8.31 (bs, 1H), 7.98 (bs, 1H), 7.72 (bs, 1H), 7.62 (bs, 1H), 7.45 (dd, J = 8.4, 2.0 Hz, 1H), 7.39 (d, J = 2.4 Hz, 1H), 7.22 (d, J = 8.8 Hz, 1H), 4.35 (s, 4H)	

[1187]

95		MS (ESI) m/z 493.24 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.04 (bs, 1H), 9.04 (s, 1H), 8.47 (s, 1H), 8.24 (s, 1H), 7.56 (bs, 2H), 7.41 (dd, J = 8.8 Hz, 2.52 Hz, 1H), 7.34-7.32 (m, 2H), 7.22 (d, J = 8.84 Hz, 1H), 4.37-4.33 (m, 4H), 2.45 (s, 3H)	
96		MS (ESI) m/z 491.20 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 12.97 b(s, 1H), 9.09 (s, 1H), 8.52 (s, 1H), 8.31 (s, 1H), 7.36 (dd, J = 8.72, 2.56 Hz, 1H), 7.24 (d, J = 2.64 Hz, 1H), 7.17 (d, J = 8.88 Hz, 1H), 7.13 (d, J = 1.64 Hz, 1H), 7.01 (d, J = 1.64 Hz, 1H), 6.16 (s, 2H), 4.35 (s, 4H)		
97		MS (ESI) m/z 495.31 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 9.08 (s, 1H), 8.50 (s, 1H), 8.13 (s, 1H), 7.41-7.35 (m, 2H), 7.14-7.12 (m, 2H), 6.78 (d, J = 12.88 Hz, 1H), 4.27 (t, J = 4.2 Hz, 2H), 4.25 (t, J = 4.08 Hz, 2H), 3.62 (s, 3H)		
98		MS (ESI) m/z 495.31 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.56 (bs, 1H), 9.07 (d, J = 0.68 Hz, 1H), 8.91 (s, 1H), 8.53 (s, 1H), 8.48 (s, 1H), 7.74 (d, J = 2.8 Hz, 1H), 7.49 (dd, J = 8.92 Hz, 2.72 Hz, 1H), 7.28 (d, J = 9.0 Hz, 1H), 4.48-4.44 (m, 4H), 2.41 (s, 3H)	
99		MS (ESI) m/z 498.33 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.78 (bs, 1H), 8.83 (s, 1H), 8.73 (d, J = 7.84 Hz, 1H), 8.33 (s, 2H), 8.19 (s, 1H), 8.07 (d, J = 7.8 Hz, 1H), 7.85-7.81 (m, 1H), 7.76-7.72 (m, 2H), 7.52 (dd, J = 8.76, 2.64 Hz, 1H), 7.32 (d, J = 8.92 Hz, 1H), 4.49 (t, J = 4.92 Hz, 2H), 4.37 (t, J = 4.88 Hz, 2H)		
100		MS (ESI) m/z 498.33 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 9.15 (d, J = 3.12 Hz, 1H), 8.78 (s, 1H), 8.65 (d, J = 7.24 Hz, 1H), 8.47 (d, J = 1.76 Hz, 1H), 8.30 (bs, 2H), 8.15 (s, 1H), 7.89-7.86 (m, 1H), 7.52-7.49 (m, 2H), 7.30 (d, J = 8.8 Hz, 1H), 4.42 (t, J = 4.88 Hz, 2H), 4.32 (t, J = 4.72 Hz, 2H).		

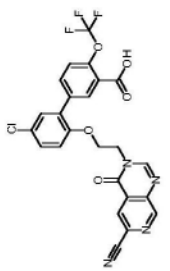
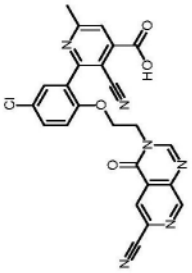
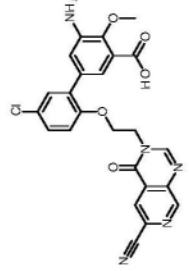
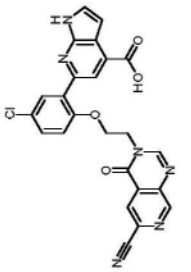
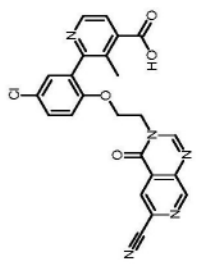
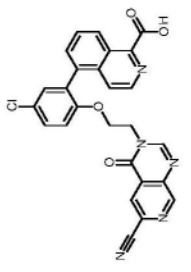
[1188]

101	MS (ESI) *m/z* 501.29 $[M+1]^+$; ^{1}H NMR (400 mHz, DMSO-d_6) δ 9.11 (s, 1H), 8.53 (s, 1H), 8.34 (s, 1H), 7.46 (dd, *J* = 8.88, 2.6 Hz, 1H), 7.36 (t, *J* = 6.8 Hz, 1H), 7.27 (d, *J* = 2.68 Hz, 1H), 7.20 (d, *J* = 8.92 Hz, 2H), 4.34 (s, 4H)	104	MS (ESI) m/z 489.37 $[M+1]^+$; 1H NMR (400 MHz, DMSO-d6) δ 12.61 (bs, 1H), 9.09 (s, 1H), 8.52 (s, 1H), 8.37 (s, 1H), 7.48 (bs, 1H), 7.37 (bs, 1H), 7.33 (dd, J = 8.80, 2.60 Hz, 1H), 7.23 (d, J = 2.60 Hz, 1H), 7.15 (d, J = 8.80 Hz, 1H), 4.66 (t, J = 8.72 Hz, 2H), 4.35 (bs, 4H), 3.22 (t, J = 8.68 Hz, 2H)
102	MS (ESI) m/z 501.29 $[M+1]^+$; 1H NMR (400 mHz, DMSO-d6) δ 12.88 (s, 1H), 8.87 (s, 1H), 8.50 (s, 1H), 8.31 (s, 1H), 8.21 (s, 1H), 7.69 (s, 1H), 7.64 (s, 1H), 7.43-7.40 (m, 1H), 7.34 (d, J = 2.16 Hz, 1H), 7.25 (d, J = 8.76 Hz, 1H), 4.40 (t, J = 4.68 Hz, 2H), 4.31 (t, J = 4.52 Hz, 2H), 4.23 (s, 3H)	105	MS (ESI) m/z 503.38 $[M+1]^+$; 1H NMR (400 mHz, DMSO-d6) δ 9.03 (s, 1H), 8.49 (s, 1H), 8.26 (bs, 1H), 7.85 (s, 1H), 7.74 (bs, 1H), 7.53 (s, 1H), 7.38 (d, J = 8.6 Hz, 1H), 7.31 (d, J = 2.4 Hz, 1H), 7.19 (d, J = 9.16 Hz, 1H), 4.33 (s, 4H), 1.27 (s, 9H)
103	MS (ESI) m/z 504.35 $[M+1]^+$; 1H NMR (400 MHz, DMSO-d6) δ 13.58 (s, 1H), 11.07 (s, 1H), 9.03 (d, J = 0.68 Hz, 1H), 8.44 (s, 1H), 8.36 (d, J = 8.68 Hz, 1H), 8.32 (s, 1H), 7.84 (d, J = 2.2 Hz, 1H), 7.50 (dd, J = 8.64, 2.12 Hz, 1H), 7.38 (dd, J = 8.88, 2.72 Hz, 1H), 7.27 (d, J = 2.6 Hz, 1H), 7.20 (d, J = 8.84 Hz, 1H), 4.35 (s, 4H), 2.19 (s, 3H)	106	MS (ESI) m/z 491.31 $[M+1]^+$; 1H NMR (400 MHz, DMSO-d6) δ 9.06 (s, 1H), 8.51 (s, 1H), 8.30 (s, 1H), 7.73 (bs, 1H), 7.68 (bs, 1H), 7.39-7.36 (m, 2H), 7.29 (d, J = 2.6 Hz, 1H), 7.18 (d, J = 8.88 Hz, 1H), 4.64 (t, J = 5.12 Hz, 1H), 4.34 (s, 4H), 3.62 (t, J = 5.92 Hz, 2H), 2.76 (t, J = 6.64 Hz, 2H)

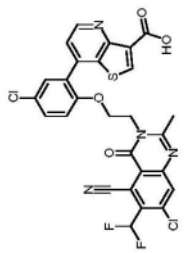
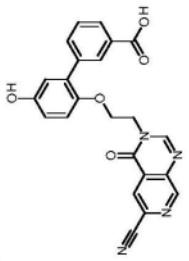
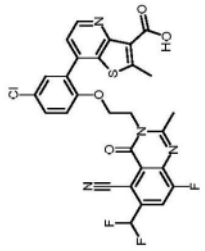
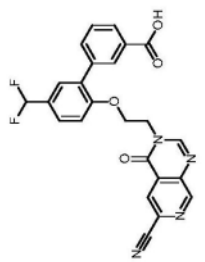
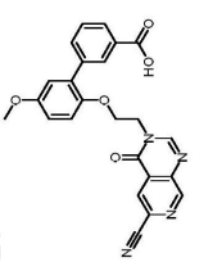
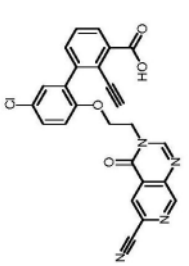
[1189]

107		110		MS (ESI) m/z 514.40 [M+1]+; 1H NMR (400 MHz, DMSO-d6) 13.11 (bs, 1H), 9.03 (s, 1H), 8.48 (s, 1H), 8.17 (s, 1H), 7.97 (t, J = 1.68 Hz, 1H), 7.82 (t, J = 1.36 Hz, 1H), 7.71 (t, J = 1.60 Hz, 2H), 7.43 (dd, J = 8.88, 2.76 Hz, 1H), 7.23 (d, J = 8.92 Hz, 1H), 4.36-4.32 (m, 4H), 1.72 (s, 6H)
108		111		MS (ESI) m/z 513.32 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.20 (bs, 1H), 9.08 (d, J = 0.6 Hz, 1H), 8.54 (d, J = 0.64 Hz, 1H), 8.30 (s, 1H), 7.78 (d, J = 2.24 Hz, 1H), 7.59 (dd, J = 8.44, 2.28 Hz, 1H), 7.41-7.38 (m, 1H), 7.34 (d, J = 2.6 Hz, 1H), 7.21-7.19 (m, 2H), 7.18 (t, J = 67.48 Hz, 1H), 4.35 (s, 4H).
109		112		MS (ESI) m/z 525.31 [M+1]+; 1H NMR (400 mHz, DMSO-d6) δ 13.50 (s, 1H), 9.02 (s, 1H), 8.47 (s, 1H), 8.30 (t, J = 1.6 Hz, 1H), 8.18 (s, 1H), 8.13 (s, 2H), 7.50-7.48 (m, 1H), 7.46 (s, 1H), 7.26 (d, J = 8.8 Hz, 1H), 4.39-4.38 (m, 2H), 4.33-4.32 (m, 2H), 3.32 (s, 3H)
107	MS (ESI) m/z 507.29 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 12.79 (s, 1H), 9.05 (s, 1H), 8.50 (s, 1H), 8.28 (s, 1H), 7.38-7.35 (m, 1H),7.31 (d, J = 2.6 Hz, 1H), 7.18-7.16 (m, 2H), 7.10 (d, J = 1.8 Hz, 1H), 4.34 (bs, 4H), 3.80 (s, 3H)), 3.76 (s , 3H)
108	MS (ESI) m/z 511.18 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 9.06 (s, 1H), 8.52(s, 1H), 8.36 (s, 1H), 7.57 (d, J = 2.12 Hz, 1H), 7.54 (bs, 1H), 7.38 (dd J = 8.88 Hz, 2.72 Hz, 1H), 7.33 (d, J = 2.60 Hz, 2H), 7.18(d, J = 8.8 Hz, 1H), 4.36 (s, 4H), 3.89 (s, 3H)
109	MS (ESI) m/z 498.25 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.98 (bs, 1H), 9.05 (s, 1H), 8.71 (s, 1H), 8.51 (s, 1H), 8.40 (s, 1H), 8.28 (s, 1H), 7.77 (t, J = 54.52 Hz, 1H), 7.49-7.45 (m, 2H), 7.23 (d, J = 8.76 Hz, 1H), 4.38 (s, 4H).

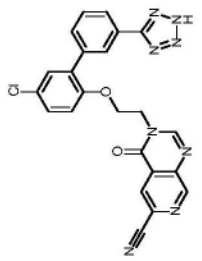
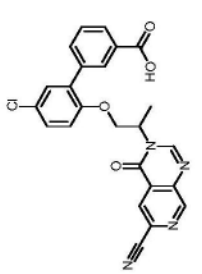
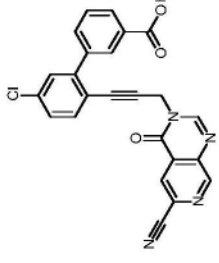
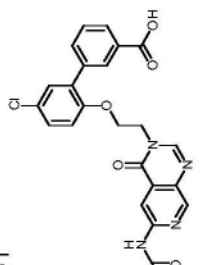
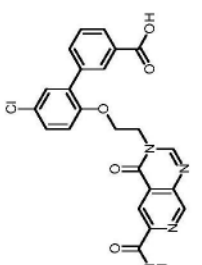
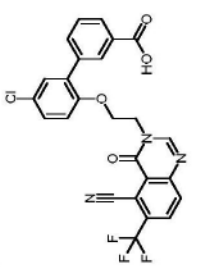
[1190]

113		MS (ESI) m/z 531.29 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 9.10 (s, 1H), 8.57 (s, 1H), 8.54 (bs, 1H), 7.74 (bs, 1H), 7.37-7.32 (m, 2H), 7.30 (d, J = 2.52 Hz, 1H), 7.16 (d, J = 8.88 Hz, 1H), 7.09 (d, J = 8.04 Hz, 1H), 4.39 (t, J = 4.76 Hz, 2H), 4.34 (t, J = 4.68 Hz, 2H)	116		MS (ESI) m/z 487.39 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 9.10 (s, 1H), 8.54 (s, 1H), 8.11 (s, 1H), 7.68 (bs, 1H), 7.51 (dd, J = 8.8, 2.4 Hz, 1H), 7.31 (d, J = 2.8 Hz, 1H), 7.22 (d, J = 8.8 Hz, 1H), 4.33 (s, 4H), 2.50 (s, 3H)
114		MS (ESI) m/z 492.36 [M+1]+;1H NMR (400 MHz, DMSO-d6) δ 12.58 (bs, 1H), 9.07 (s, 1H), 8.55 (s, 1H), 8.35 (s, 1H), 7.32 (d, J = 7.16 Hz, 1H), 7.22 (s, 1H), 7.12 (d, J = 8.88 Hz, 1H), 6.92 (s, 1H), 6.87 (s, 1H), 5.10 (bs, 2H), 4.38 (bs, 2H), 4.30 (bs, 2H), 3.76 (s, 3H)	117		MS (ESI) m/z 487.31 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.27 (bs, 1H), 11.92 (s, 1H), 8.91 (s, 1H), 8.40 (bs, 1H), 8.37 (s, 1H), 7.99 (s, 1H), 7.74 (d, J = 2.64 Hz, 1H), 7.68 (t, J = 2.84 Hz, 1H), 7.42 (dd, J = 8.88, 2.8 Hz, 1H), 7.26 (d, J = 8.76 Hz, 1H), 6.84 (t, J = 1.96 Hz, 1H), 4.47 (t, J = 4.72 Hz, 2H), 4.38 (t, J = 4.64 Hz, 2H)
115		MS (ESI) m/z 462.35 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 9.11 (s, 1H), 8.56 (s, 1H), 8.19 (d, J = 3.72 Hz, 1H), 8.12 (s, 1H), 7.41 (dd, J = 8.8, 2.8 Hz, 1H), 7.23 (bs, 1H), 7.16-7.14 (m, 2H), 4.28 (bs, 4H), 2.03 (s, 3H)	118		MS (ESI) m/z 498.41 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.97 (s, 1H), 8.56 (d, J = 8.56 Hz, 1H), 8.40 (s, 1H), 8.02 (d, J = 5.72 Hz, 1H), 7.70 (t, J = 7.08 Hz, 1H), 7.62-7.60 (m, 2H), 7.54 (dd, J = 8.76, 2.64 Hz, 1H), 7.29-7.26 (m, 2H), 7.18 (d, J = 5.64 Hz, 1H), 4.33-4.23 (m, 2H), 4.17-4.09 (m, 2H)

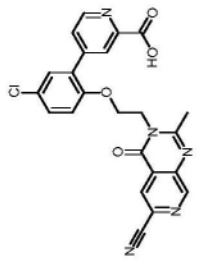
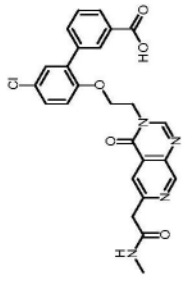
[1191]

119		MS (ESI) m/z 601.13 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 12.92 (bs, 1H), 8.83 (d, J = 4.64 Hz, 1H), 8.38 (s, 1H), 7.87 (s, 1H), 7.59 (dd, J = 8.76, 2.24 Hz, 1H), 7.51 (t, J = 52.0 Hz, 1H), 7.49 (d, J = 4.68 Hz, 1H), 7.43 (d, J = 2.28 Hz, 1H), 7.35 (d, J = 8.96 Hz, 1H), 4.39 (t, J = 5.56 Hz, 2H). 4.23 (t, J = 4.92 Hz, 2H), 1.73 (s, 3H)	125		UPLC: MS (ESI) m/z 429.28 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 9.20 (bs, 1H), 9.10 (s, 1H), 8.51 (s, 1H), 8.37 (s, 1H), 7.87 (s, 1H), 7.69 (d, J = 7.68 Hz, 1H), 7.42 (d, J = 7.76 Hz, 1H), 7.25 (t, J = 7.64 Hz, 1H), 6.96 (d, J = 8.68 Hz, 1H), 6.71-6.68 (dd, J = 2.96 Hz, J=2.92 Hz, 1H), 6.65 (d, J=2.8 Hz, 1H), 4.30 (t, J = 4.8 Hz, 2H), 4.17 (t, J = 4.88 Hz, 2H)
123		MS (ESI) m/z 599.53 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.77 (d, J = 4.92 Hz, 1H), 8.08 (d, J = 9.72 Hz, 1H), 7.60(dd, J = 8.88, 2.64 Hz, 1H), 7.53 (d, J = 4.96 Hz, 1H), 7.41 (d, J = 2.56 Hz,1H), 7.38 (t, J = 64.56 Hz, 1H), 7.35 (d, J = 1.72 Hz, 1H), 4.44 (t, J = 5.40 Hz, 2H), 4.23 (t, J = 4.84 Hz, 2H), 2.49 (s, 3H), 1.96 (s, 3H)	126		MS (ESI) m/z 463.36 [M+1]+; UPLC: 99.75 %; 1H NMR (400 MHz, DMSO-d6) δ 13.01 (s, 1H), 9.10 (s, 1H), 8.53 (s, 1H), 8.29 (s, 1H), 7.89 (s, 1H), 7.86 (d, J =7.76 Hz, 1H), 7.58 (t, J = 8.20 Hz, 2H), 7.48 (s, 1H), 7.44 (t, J = 7.68 Hz, 1H) 7.30 (d, J = 8.60 Hz, 1H), 7.14-6.86 (m, 1H), 4.42-4.38 (m, 4H)
124		UPLC: MS (ESI) m/z 443.28 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 9.10 (s, 1H), 8.51(s, 1H), 8.41(s, 1H), 7.94 (s, 1H), 7.73 (d, J = 7.52 Hz, 1H), 7.41 (d, J = 7.68 Hz, 1H), 7.25 (t, J = 7.52 Hz, 1H), 7.06 (d, J = 8.76 Hz, 1H), 6.88-6.85(dd, J = 2.84 Hz, J = 2.72 Hz, 1H), 6.82 (d, J = 2.92 Hz, 1H), 4.34 (t, J = 4.6 Hz, J = 4.88 Hz 2H), 4.23 (d, J = 4.48 Hz), 3.72 (s, 3H)	127		MS (ESI) m/z 471.32 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 12.94 (bs, 1H), 9.10 (s, 1H), 8.51 (s, 1H), 7.99 (s, 1H), 7.78 (dd, J = 7.56, 11.2 Hz, 1H), 7.43-7.34 (m, 3H), 7.17-7.15 (m, 2H), 4.28 (s, 4H), 3.80 (s, 1H)

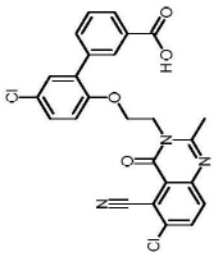
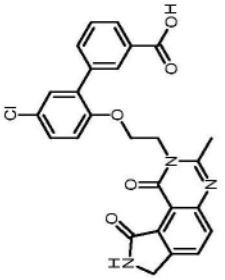
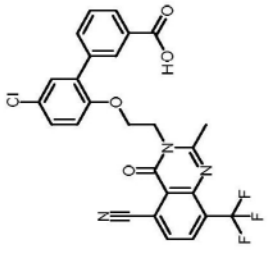
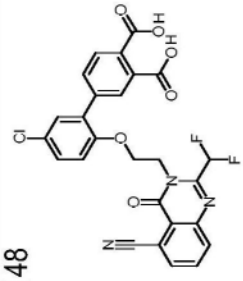
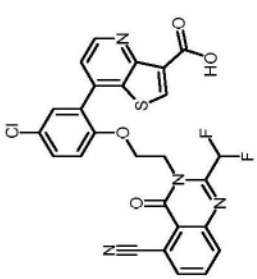
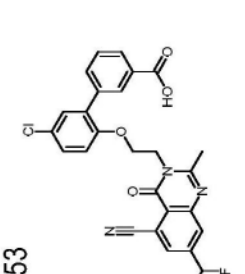
[1192]

128		MS (ESI) m/z 471.29 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 16.5 (bs, 1H), 8.92 (s, 1H), 8.47(s, 1H), 8.23 (s, 1H), 7.97 (d, J = 1.48 Hz, 2H),7.55-7.51 (m, 2H), 7.43 (dd, J = 2.56 Hz, J = 2.68 Hz 1H), 7.39 (d, J = 2.6 Hz, 1H), 7.23 (d, J = 8.76 Hz, 1H), 4.36 (s, 4H)	
129		MS (ESI) m/z 461.21 [M+1]+. UPLC: 99.41 %; 1H NMR (400 MHz, DMSO-d6) δ 12.88 (s, 1H), 9.02 (s, 1H), 8.45 (s, 1H), 8.40 (s, 1H), 7.75 (s, 1H), 7.57 (d, J =7.76 Hz, 1H), 7.44-7.38 (m, 2H), 7.29 (d, J = 2.60 Hz, 1H), 7.23 (d, J = 8.88 Hz, 1H) 7.16 (t, J = 7.72 Hz, 1H), 5.14-5.09 (m, 1H), 4.53-4.49 (m, 1H), 4.42-4.37 (m, 1H), 1.43 (d, J = 6.96 Hz, 3H)	
130		MS (ESI) m/z 439.10 [M-1]-; 1H NMR (400 MHz, DMSO-d6) δ 12.83 (bs,1H), 9.17 (s,1H), 8.56 (d, J = 8.44 Hz, 2H), 7.96 (s, 1H), 7.71-7.68 (m, 2H), 7.62 (d, J = 8.36 Hz, 1H), 7.53 (d, J = 2.04 Hz, 1H), 7.51-7.58 (dd, J = 2.08 Hz, J= 2.20 Hz, 1H), 7.37 (t, J = 7.68 Hz, 1H), 4.91 (s, 2H)	
131		MS (ESI) m/z 479.32 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.03 (bs, 1H), 10.82 (s, 1H), 8.79 (s, 1H), 8.62 (s, 1H), 7.98 (s, 1H), 7.95 (s, 1H),7.87 (d, J = 7.76 Hz, 1H), 7.58 (d, J = 7.56 Hz, 1H), 7.42-7.38 (m, 2H), 7.34 (d, J = 2.76 Hz, 1H), 7.19 (d, J = 8.92 Hz, 1H), 4.32 (s, 4H), 2.13 (s, 3H)	
132		MS (ESI) m/z 479.35 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 9.01 (s, 1H), 8.90 (d, J = 4.8 Hz, 1H), 8.49 (s, 1H), 8.17 (s, 1H), 7.92 (s, 1H), 7.86 (d, J= 7.6 Hz, 1H), 7.61 (d, J = 8.0 Hz, 1H), 7.43-7.38 (m, 2H), 7.34 (d, J = 2.4 Hz, 1H), 7.21 (d, J = 8.8 Hz, 1H), 4.35 (s, 4H), 2.93 (s, 3H)	
133		MS (ESI) m/z 514 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 12.9 (s, 1H), 8.29(d, J = 8.72 Hz, 1H), 8.19 (s, 1H), 8.07 (d, J = 8.64 Hz, 1H), 7.88 (s, 1H), 7.83 (d, J = 7.76 Hz ,1H), 7.60 (d, J = 7.76 Hz ,1H), 7.38-7.42 (m, J = 8.32 Hz, 2H), 7.33 (d, J = 2.68 Hz, 1H), 7.22 (d, J = 8.8 Hz,1H), 4.3 (s, 4H)	

[1193]

134		137	
MS (ESI) m/z 462 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 12.9 (b, 1H), 9.04(s, 1H), 8.63 (d, J = 4.96 Hz, 1H), 8.48 (s, 1H), 7.915 (s, 1H), 7.56 (dd, J = 1.52 Hz, J = 4.96Hz ,1H), 7.484 (dd, J = 1.68, 8.92 Hz, 1H), 7.40 (d, J = 2.6 Hz, 1H), 7.24 (d, J = 8.92 Hz, 1H), 4.385 (s, 4H), 2.278 (s, 3H)		MS (ESI) m/z 493.44 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 12.96 (s,1H), 8.92 (s, 1H), 8.08 (s, 1H), 8.04 (d, J = 4.32 Hz, 1H), 7.93 (s, 1H),7.89 (s, 1H), 7.86 (s, 1H), 7.56 (d, J = 6.88 Hz, 1H), 7.40-7.36 (m, 2H), 7.33 (d, J = 2.56 Hz, 1H), 7.20 (d, J = 8.84 Hz, 1H), 4.328 (s, 4H), 3.75 (s, 2H), 2.59 (d, J = 4.6 Hz, 3H)	
135		138	
UPLC: MS (ESI) m/z 518.43 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.86 (s, 1H), 8.84 (d, J = 4.8 Hz, 1H), 8.43 (s, 1H), 8.36 (s, 1H), 7.60-7.57 (dd, J = 2.6 Hz, J = 2.6 Hz, 1H), 7.47 (d, J = 4.76 Hz, 1H), 7.43 (d, J = 2.6 Hz, 1H), 7.33(d, J = 8.96 Hz, 1H), 4.38 (t, J = 4.8 Hz, 2H), 4.25 (t, J = 4.76, 5.0 Hz, 2H), 1.81 (s, 3H)		MS (ESI) m/z 436.10 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 12.97 (s,1H), 8.89 (s, 1H), 8.04 (s, 1H), 7.90 (s, 1H), 7.86 (d, J = 7.72 Hz, 1H), 7.76 (s, 1H),7.57 (d, J = 1.28 Hz, 1H), 7.409-7.37 (m, 2H), 7.333-7.326 (m, 2H), 7.20 (d, J = 8.88 Hz, 1H), 4.34 (s, 4H), 2.607 (s, 3H).	
136		139	
MS (ESI) m/z 488.32 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 12.96 (bs, 1H), 8.93 (s, 1H), 8.67 (s, 1H), 8.32 (s, 1H), 8.06 (s, 1H), 7.928-7.86 (m, 3H), 7.61 (d, J = 7.2 Hz, 1H), 7.45-7.39 (m, 2H), 7.341 (s, 1H), 7.21 (d, J = 8.4 Hz, 1H), 6.62 (s, 1H), 4.35 (s, 4H)		MS (ESI) m/z 496.35 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 12.927 (bs, 1H), 8.187 (s, 1H), 8.158 (s, 1H), 8.079 (s, 1H), 7.91 (s, 1H), 7.83 (d, J = 7.8 Hz, 1H), 7.599 (d, J = 7.96 Hz, 1H), 7.419-7.08 (m, 5H), 4.349 (s, 4H)	

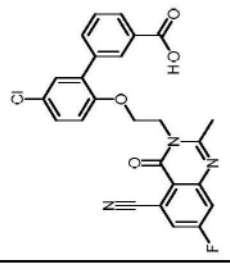
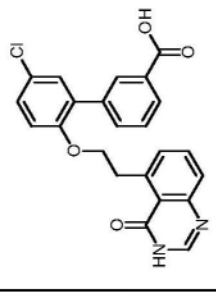
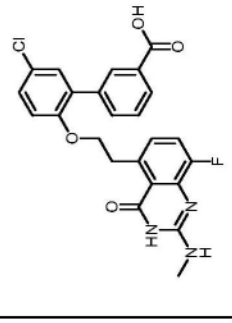
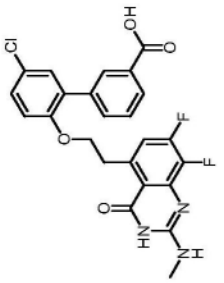
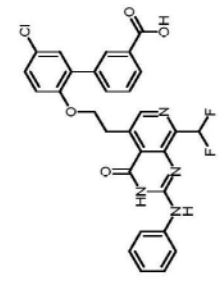
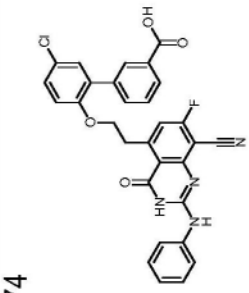
[1194]

141		MS (ESI) m/z 494.34 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 12.931 (bs, 1H), 8.061(d, J = 8.88 Hz, 1H), 7.875-7.82 (m, 3H), 7.517 (d, J = 7.4 Hz, 1H), 7.425-7.386 (m, 2H), 7.276 (d, J = 2.28 Hz, 1H), 7.205 (d, J = 8.8 Hz, 1H), 4.343 (s, 4H), 2.173 (s, 3H)	144		MS (ESI) m/z 662.39 [M+1]+; 1H NMR (400 MHz, DMSO-d6):δ 12.63 (s, 1H), 8.86 (d, J = 4.8 Hz, 1H), 8.54 (s, 1H), 8.06 (d, J = 9.8 Hz, 1H), 7.63-7.60 (dd, J = 2.5, 2.6 Hz, 1H), 7.55 (d, J = 4.8 Hz, 1H), 7.42-7.36 (m, 3H), 4.44 (t, J = 6.1 Hz, 2H), 4.28 (t, J = 5.8 Hz, 2H), 3.53 (s, 3H), 1.90 (s, 3H)
142		MS (ESI) m/z 528.44 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 12.9 (s, 1H), 8.28(d, J = 7.92 Hz, 1H), 8.08 (d, J = 7.84 Hz, 1H), 7.92 (s, 1H), 7.85 (d, J = 7.76 Hz, 1H), 7.53 (d, J = 7.76 Hz ,1H), 7.33-7.41 (m, 2H), 7.28 (d, J = 4.4 Hz, 1H), 7.21 (d, J = 8.8 Hz, 1H), 4.3 (s, 4H), 2.24 (s, 3H)	148		MS (ESI) m/z 540.47 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.10 (bs, 1H), 8.15-8.13 (m, 1H), 8.07-8.00 (m, 2H), 7.70 (d, J = 1.3 Hz, 1H), 7.63-7.58 (m, 2H), 7.44-7.42 (dd, J = 2.6, 8.7 Hz, 1H), 7.39 (d, J = 2.6 Hz, 1H), 7.2 (d, J = 8.9 Hz, 1H), 7.08-6.82 (t, J = 51.9 Hz, 1H), 4.43 (t, J = 6.1 Hz, 2H), 4.34 (t, J = 5.5 Hz, 2H)
143		MS (ESI) m/z 553.44 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.77 (s, 1H), 8.42 (s, 1H), 8.12 (d, J = 6.84 Hz, 1H), 7.99 (t, J = 6.8 Hz, 1H), 7.89 (d, J = 7.28 Hz, 1H), 7.72 (d, J = 4.16 Hz, 1H), 7.47-7.44 (m, 2H), 7.37(d, J = 8.08 Hz, 1H), 6.59 (t, J = 51.6 Hz, 1H), 4.41(s, 2H), 4.34 (s, 2H)	153		MS (ESI) m/z 510.40 [M+1] +; 1H NMR (400 MHz, DMSO-d6) δ 12.94 (bs, 1H), 8.12 (s, 1H), 8.00 (s, 1H), 7.89-7.84 (m, 2H), 7.53 (d, J = 7.6 Hz, 1H), 7.41-7.20 (m, 5H), 4.35 (m, 4H), 2.20 (s, 3H)

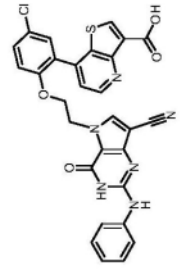
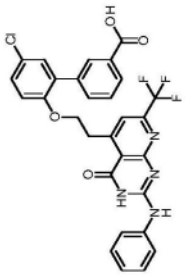
[1195]

154	MS (ESI) m/z 528.08 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.37 (s, 1H), 7.87 (d, J = 7.72 Hz, 1H), 7.81 (s, 1H), 7.54 (d, J = 7.88 Hz, 1H), 7.45 (m, 2H), 7.27 (d, J = 4 Hz, 1H), 7.27 (d, J = 8 Hz, 1H),4.39 (m, 4H), 2.21(s, 3H)	163	MS (ESI) m/z 521.15 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.40 (b, 1H), 8.49(d, J = 4.84 Hz, 1H), 8.14 (d, J = 6.28 Hz, 1H), 8.07-8.02 (m, 2H), 7.49 (m, 1H), 7.43 (d, J = 4.88 Hz, 1H), 7.28 (d, J = 2.2 Hz, 1H), 7.23 (d, J = 8.92 Hz, 1H), 6.71 (t, J = 52.2 Hz, 1H) 4.38-4.33 (m, 4H), 4.19 (s, 1H)
160	MS (ESI) m/z 567.16 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.82 (d, J = 4.76 Hz, 1H), 8.40 (s, 1H), 8.12 (d, J = 8.6 Hz, 1H), 7.82 (d, J = 8.52 Hz, 1H), 7.59 (dd, J = 2.4, 8.92 Hz, 1H), 7.50-7.23 (m, 4H), 4.42-4.23 (m, 4H), 1.79 (s, 3H)	165	MS (ESI) m/z 520.17 [M+1]+. 1H NMR (400 MHz, DMSO-d6) δ 12.91 (bs, 1H), 8.12(d, J = 6.68 Hz, 1H), 8.04-7.98 (m, 2H), 7.78-7.76 (m, 1H), 7.42-7.37 (m, 3H), 7.20-7.07 (m, 2H), 6.68-6.42 (t, J = 52.32 Hz, 1H), 4.36-4.30 (m, 4H), 3.90 (s, 1H)
161	MS (ESI) m/z 497.87 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.64 (d, J = 4.92 Hz, 1H), 8.20 (s, 1H), 8.163 (d, J = 8.6, 1H), 8.0474 (t, J = 8.4 Hz 2H), 7.67 (dd, J = 1.4, 6.4 Hz, 1H), 7.65 (m, 4H), 4.39(m, 4H)	166	MS (ESI) m/z 497.15 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.59 (s, 1H), 8.15 (d, J = 5.56 Hz, 1H), 8.07-7.99 (m, 3H), 7.645 (s, 1H), 7.51-7.46 (m, 2H), 7.23 (d, J = 8.92 Hz, 1H), 7.04-6.78 (m, 2H), 4.44-4.38 (m, 4H)

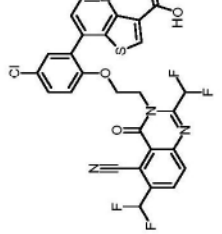
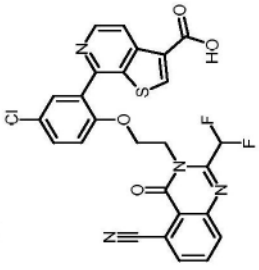
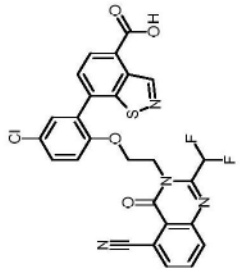
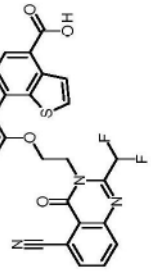
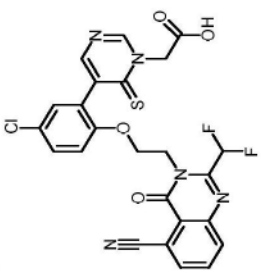
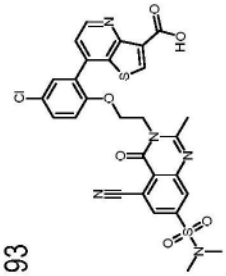
[1196]

167		MS (ESI) m/z 478.15 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 12.912 (bs, 1H), 8.028 (d, J = 8.84 Hz, 1H), 7.879 (d, J = 7.72 Hz, 2H), 7.813 (s, 1H), 7.696 (d, J = 9.36 Hz, 1H), 7.52 (d, J = 7.48 Hz, 1H), 7.449-7.394 (m, 2H), 7.283 (s, 1H), 7.2079 (d, J = 8.8 Hz, 1H), 4.334 (m, 4H), 2.163 (s, 3H)	
170		MS (ESI) m/z 421.2 [M+1]+; 1H NMR (500 MHz, DMSO-d6) δ 13.01 (bs, 1H), 12.21 (bs, 1H), 8.13 (s, 1H), 8.03 (s, 1H), 7.94 (d, J = 7.5 Hz, 1H), 7.62-7.61 (m, 1H), 7.55-7.50 (m, 3H), 7.35-7.34 (m, 2H), 7.20-7.17 (m, 2H), 4.27 (t, J = 6.5 Hz, 2H), 3.62 (t, J = 6.5 Hz, 2H)	
171		MS (ESI) m/z 468.2 [M+1]+; 1H NMR (300 MHz, DMSO-d6) δ 8.03 (s, 1H), 7.93 (d, J = 7.5 Hz, 1H), 7.64 (d, J = 7.5 Hz, 1H), 7.54-7.49 (m, 1H), 7.37-7.34 (m, 2H), 7.27-7.16 (m, 2H), 6.78-6.73 (m, 1H), 4.20 (t, J = 6.5 Hz, 2H), 3.47 (t, J = 6.5 Hz, 2H), 2.87 (d, J = 3.3 Hz, 3H)	
172		MS (ESI) m/z 486.2 [M+1]+. 1H NMR (300 MHz, DMSO-d6) δ 13.00 (bs, 1H), 11.10 (bs, 1H), 8.04 (s, 1H), 7.93 (d, J = 7.5 Hz, 1H), 7.63 (d, J = 7.8 Hz, 1H), 7.51-7.46 (m, 1H), 7.38-7.34 (m, 2H), 7.18 (d, J = 8.4 Hz, 2H), 6.75-6.68 (m, 1H), 6.43 (bs, 1H), 4.24-4.20 (m, 2H), 3.49-3.46 (m, 2H), 2.84 (d, J = 4.8 Hz, 3H)	
173		MS (ESI) m/z 563.4 [M+1]+; 1H NMR (300 MHz, DMSO-d6) δ 12.16 (bs, 1H), 10.34 (bs, 1H), 8.13 (s, 1H), 7.31 (s, 1H), 7.21 (s, 1H), 7.19 (d, J = 7.5 Hz, 1H), 6.87 (d, J = 7.5 Hz, 2H), 6.76-6.75 (m, 1H), 6.68-6.54 (m, 5H), 6.37 (d, J = 8.1 Hz, 1H), 6.29-6.24 (m, 1H), 3.48 (t, J = 6.6 Hz, 2H), 2.74 (t, J = 6.3 Hz, 2H)	
174		MS (ESI) m/z 555.31 [M+1]+; UPLC: 97.62 %; 1H NMR (400 MHz, DMSO-d6) δ 13.00 (bs, 1H), 10.97 (bs, 1H), 9.04 (s, 1H), 8.01 (s, 1H), 7.92 (d, J = 7.76 Hz, 1H), 7.82 (d, J = 7.92 Hz, 2H), 7.60 (d, J = 7.60 Hz, 1H), 7.45 (t, J = 7.68 Hz, 1H), 7.39-7.33 (m, 4H), 7.18 (d, J = 8.84 Hz, 1H), 7.12-7.07 (m, 1H), 6.86 (d, J = 10.32 Hz, 1H), 4.30 (t, J = 5.96 Hz, 2H), 3.59 (t, J = 5.84 Hz, 2H	

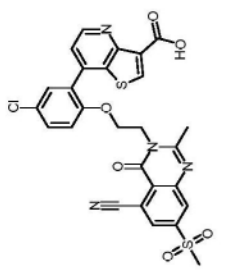
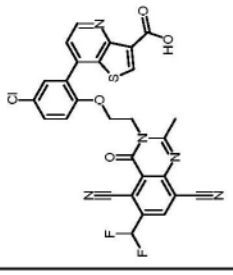
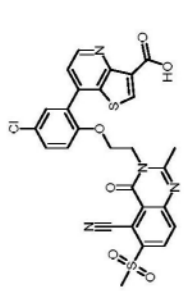
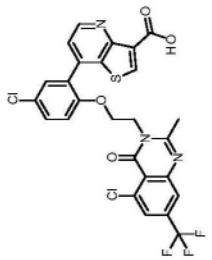
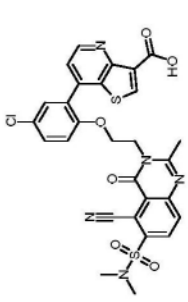
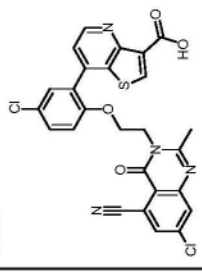
[1197]

175		MS (ESI) m/z 583.21 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 10.68 (bs, 1H), 8.90 (s, 1H), 8.79 (d, J = 4.96 Hz, 1H), 8.57 (s, 1H), 7.66 (d, J = 7.72 Hz, 2H), 7.57-7.60 (dd, J = 2.68 Hz, J = 2.56 Hz, 1H), 7.52 (d, J = 2.56 Hz, 1H), 7.43 (s, 1H), 7.37-7.32 (m, 4H), 7.01-7.07 (m 1H), 4.51 (d, J = 4.72 Hz, 2H), 4.23 (t, J = 4.56 Hz, 2H)	178		LCMS (ESI) m/z 581.2 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 12.94 (bs, 1H), 11.10 (bs, 1H), 8.91 (s, 1H), 8.06 (s, 1H), 7.90 (d, J = 6.0 Hz, 1H), 7.71 (d, J = 5.7 Hz, 2H), 7.63 (d, J = 8.0 Hz, 1H), 7.45 (t, J = 6.0 Hz, 1H), 7.41-7.34 (m, 5H) 7.26 (s, 1H), 7.19 (d. J = 6.8 Hz, 1H), 7.11 (t, J = 6.0 Hz, 1H), 4.35 (m, 2H), 3.68 (m, 2 H)
176		MS (ESI) m/z 513.32 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.0 (bs, 1H), 11.02 (bs, 1H), 8.91 (s, 1H), 8.38 (s, 1H), 8.02 (s, 1H), 7.93 (d, J = 7.6 Hz, 1H), 7.74 (d, J = 7.16 Hz, 2H), 7.60 (d, J = 7.44 Hz, 1H), 7.50 (t, J =7.56 Hz, 1H), 7.38-7.34 (m, 4H), 7.19 (d, J = 8.80 Hz, 1H), 7.07 (t, J = 7.32 Hz, 1H), 6.88 (s, 1H), 4.30 (t, J = 6.0 Hz, 2H), 3.56 (d, J = 5.72 Hz, 2H)	179		MS (ESI) m/z 538.4 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 12.99 (b, 1H), 11.20 (s, 1H), 9.09 (s, 1H), 8.11 (s, 1H), 8.00-8.01 (m, 1H), 7.94-7.91 (m, 1H), 7.84 (d, J = 8 Hz, 2H), 7.58-7.55 (m, 1H), 7.48 (t, J = 8 Hz, 1H), 7.40-7.34 (m, 4H), 7.18 (d, J = 9 Hz, 1H), 7.13-7.09 (m, 1H), 4.31 (t, J = 6 Hz, 2H), 3.57 (t, J = 6 Hz, 2H)
177		MS (ESI m/z 544.12 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 12.99 (s, 1H), 11.73(s, 1H), 8.07 (s, 1H), 7.999-7.995 (t, J = 1.64 Hz, 1H), 7.94-7.91 (td, J = 9.08, J = 1.36 Hz, 1H), 7.56-7.53 (td, J = 7.80, J = 1.64 Hz, 1H), 7.47-7.44 (t, J = 7.68 Hz, 1H), 7.39-7.34 (m, 3H), 7.16 (d, J = 8.88 Hz, 1H), 4.33-4.24 (m, 4H), 3.56-3.53 (t, J = 6.0, 2H)	180		MS (ESI) m/z 598.1 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.83 (d, J = 4.8 Hz, 1H), 8.51 (s, 1H), 8.27 – 8.26 (m, 1H), 8.16 (dd, J = 1.5, 0.6 Hz, 1H), 7.56 (dd, J = 8.9, 2.7 Hz, 1H), 7.49 (d, J = 4.8 Hz, 1H), 7.41 (d, J = 2.7 Hz, 1H), 7.37 (d, J = 9.0 Hz, 1H), 4.23 (t, J = 6.1 Hz, 2H), 3.62 (s, 3H), 2.89 (t, J = 6.1 Hz, 2H), 1.85 (s, 3H)

[1198]

188		MS (ESI) m/z 603.15 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.80-8.74 (m, 1H), 8.44-8.42 (m, 1H), 8.22 (d, J = 8.8, 1H), 8.02 (d, J = 8.8 HZ, 1H), 7.65-7.58 (m, 1H), 7.55-7.28 (m, 4H), 6.73-6.42 (m, 1H), 4.42(s, 2H), 4.34 (s, 2H)	
189		MS (ESI) m/z 553.14 [M+1]+; UPLC: 98.14 %; 1H NMR (400 MHz, DMSO-d6) δ 13.149 (s, 1H), 8.54 (d, J = 5.48, 1H), 8.21 (d, J = 5.2 Hz, 1H), 8.174 (s, 1H), 8.13 (d, J = 7.32 Hz, 1H), 7.96-8.00 (t, J = 7.64 Hz, 1H), 7.91 (d, J = 8.12 Hz, 1H), 7.59-7.56 (dd, J = 2.6, 8.84 Hz, 1H), 7.36-7.33 (m, 2H), 6.63-6.37 (t, J = 52.08 Hz, 1H), 4.40 (d, J = 4.68, 2H), 4.32 (d, J = 4.68, 2H)	
190		MS (ESI) m/z 553.14 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.61 (m, 1H), 9.29 (s, 1H), 8.11-8.07 (t, J = 7.48 Hz, 2H), 8.04-8.00 (t, J = 7.52 Hz, 1H), 7.93 (d, J = 8.2 Hz, 1H), 7.60-7.55 (m, 2H), 7.41 (d, J = 2.52 Hz, 1H), 7.54 (d, J = 8.96 Hz, 1H), 6.68-6.43 (t, J = 51.88 Hz, 1H), 4.40 (d, J = 4.76, 2H), 4.33 (d, J = 4.64, 2H)	
191		MS (ESI) m/z 550.33 [M-1]-; 1H NMR (400 MHz, DMSO-d6) δ 13.07 (s, 1H), 8.10 (d, J = 7.56 Hz, 1H), 8.005 (t, J = 8.38 Hz, 2H), 7.93 (t, J = 4.28 Hz, 2H), 7.55-7.52 (m, 1H), 7.49 (d, J = 5.6 Hz, 1H), 7.34 (t, J = 3.96 Hz, 1H), 7.30 (d, J = 5.52, 1H), 7.27 (s, 1H), 6.44 (t, J = 5.2 Hz, 1H), 4.35 (t, J = 5.52 Hz, 2H), 4.28 (t, J = 4.42 Hz, 2H)	
192		MS (ESI) m/z 542.2 [M-1]-; 1H NMR (400 MHz, DMSO-d6) δ 8.60 (s, 1H), 8.16-8.14 (m, 1H), 8.09-8.03 (m, 2H), 7.76 (s, 1H), 7.39-7.36 (dd, J = 2.60, 2.64 Hz, 1H), 7.13 (d, J = 8.84 Hz ,1H), 7.06 (d, J = 2.6 Hz, 1H), 6.91 (s, 1H), 4.72-4.64 (m, 2H), 4.39 (s, 2H), 4.29 (s, 2H)	
193		MS (ESI) m/z 542.2 [M-1]-; 1H NMR (400 MHz, DMSO-d6) δ 8.60 (s, 1H), 8.16-8.14 (m, 1H), 8.09-8.03 (m, 2H), 7.76 (s, 1H), 7.39-7.36 (dd, J = 2.60, 2.64 Hz, 1H), 7.13 (d, J = 8.84 Hz ,1H), 7.06 (d, J = 2.6 Hz, 1H), 6.91 (s, 1H), 4.72-4.64 (m, 2H), 4.39 (s, 2H), 4.29 (s, 2H)	

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194		MS (ESI) m/z 595.18 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.83 (d, J = 4.5 Hz, 1H), 8.39 (s, 1H), 8.31 (s, 1H), 8.12 (s, 1H), 7.59 (d, J = 8.8 Hz, 1H), 7.48 (d, J = 4.7 Hz, 1H), 7.43 (s, 1H), 7.35 (d, J = 9.1 Hz, 1H), 4.41 (t, J = 4.0 Hz, 2H), 4.24 (t, J = 5.5 Hz, 2H), 1.74 (s, 3H)	197		MS (ESI) m/z 592.22 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.81 (d, J = 4.76 Hz, 1H), 8.67 (s, 1H), 8.55 (s, 1H), 7.61 (dd, J = 2.44, 8.96 Hz, 1H), 7.51-7.24 (m, 4H), 4.43 (s, 2H), 4.31 (s, 2H), 1.98 (s, 3H)
195		MS (ESI) m/z 595.27 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.83 (d, J = 4.7 Hz, 1H), 8.417 (s, 1H), 8.35 (d, J = 8.72 Hz, 1H), 7.87 (d, J = 8.76, 1H), 7.60 (dd, J = 8.8 Hz 2.44 Hz, 1H), 7.48 (d, J = 4.68 Hz, 1H), 7.43 (d, J = 2.44 Hz, 1H), 7.36 (d, J = 9.0 Hz, 1H), 4.405 (d, J = 4.1 Hz, 2H), 4.269 (s, 2H), 3.539 (s, 3H), 1.83 (s, 3H)	198		MS (ESI) m/z 592.01 [M-1]-; 1H NMR (400 MHz, DMSO-d6) δ 8.85 (d, J = 4.84 Hz, 1H), 8.39 (s, 1H), 7.78 (s, 1H), 7.66 (s, 1H), 7.61-7.58 (dd, J = 2.52 Hz, 6.36 Hz, 1H), 7.53 (d, J = 4.80 Hz, 1H), 7.44 (d, J = 2.56 Hz, 1H), 7.354 (d, J = 9.00 Hz, 1H), 4.38-4.36 (m, 2H), 4.20-4.18 (m, 2H), 1.74 (s, 3H)
196		MS (ESI) m/z 624.18 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.84 (d, J = 4.8 Hz, 1H), 8.43 (s, 1H), 8.26 (d, J = 8.76 Hz, 1H), 7.82 (d, J = 8.76, 1H), 7.60 (dd, J = 8.8 Hz, 2.64 Hz, 1H), 7.52 (d, J = 4.8 Hz, 1H), 7.46 (d, J = 2.6 Hz, 1H), 7.36 (d, J = 8.96 Hz, 1H), 4.41(t, J = 4.48 Hz, 2H), 4.25 (t, J = 4.68 Hz , 2H), 2.85 (s, 6H). 1.76 (s, 3H)	200		MS (ESI) m/z 551.26 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.83 (d, J = 4.76 Hz, 1H), 8.38 (s, 1H), 8.11 (s, 1H), 7.73 (d, J = 1.6 Hz, 1H), 7.59 (dd, J = 8.8, 2.3 Hz, 1H), 7.49 (d, J = 4.7 Hz, 1H), 7.43 (d, J = 2.3 Hz, 1H), 7.35 (d, J = 9.0 Hz, 1H), 4.39 (t, J = 4.4 Hz, 2H), 4.22 (t, J = 5.7 Hz, 2H), 1.74 (s, 3H)

[1200]

204	MS (ESI) m/z 595.21 [M+1]+; UPLC: 99.31 %; 1H NMR (400 MHz, DMSO-d6) δ 9.25 (s, 1H), 9.10(s, 2H), 8.75 (d, J = 4.8 Hz, 1H), 8.55 (s, 1H), 8.10-8.03 (q, 2H), 7.61-7.58 (dd, J = 2.6 Hz, 2.6 Hz 1H),7.49 (d, J = 4.76 Hz, 1H), 7.44 (d, J = 8.12, 1H), 7.38 (d, J = 8.92 Hz, 1H), 4.46 (t, J = 4.84 Hz, 2H), 4.28 (t, J = 6.44 Hz, 2H), 1.93 (s, 3H)	209	MS (ESI) m/z 585.06 [M+1]+; UPLC: 99.28 %; 1H NMR (400 MHz, DMSO-d6) δ 13.20 (s, 1H), 8.80 (d, J = 4.72 Hz, 1H), 8.54(s, 1H), 8.39 (s,1H), 7.60-7.58 (dd, J =2.32, 2.24 Hz, 1H), 7.45-7.42 (dd, J = 4.76, 2.64 Hz, 2H), 7.36 (d, J =8.92 Hz, 1H), 4.38 (s, 2H), 4.23 (s, 2H), 1.86 (s, 3H).
207	MS (ESI) m/z 585.08 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.31 (bs, 1H), 8.83 (d, J = 4.7 Hz, 1H), 8.36 (s, 1H), 7.92 (s, 1H), 7.59 (dd, J = 8.8, 2.5 Hz, 1H), 7.47 (d, J = 4.7 Hz, 1H), 7.42 (d, J = 2.5 Hz, 1H), 7.35 (d, J = 8.8 Hz, 1H), 4.39 (t, J = 5.6 Hz, 2H), 4.23 (t, J = 4.8 Hz, 2H), 1.72 (s, 3H)	211	MS (ESI) m/z 541.16 [M+1]+; UPLC: 99.9 %; 1H NMR (400 MHz, DMSO-d6) δ 8.81 (d, J = 4.80 Hz, 1H), 8.65 (s, 1H), 8.05 (d, J = 7.76 1H), 7.89 (d, J = 7.72, 1H), 7.60 (d, J = 2.4 Hz, 1H), 7.46 (d, J = 2.44 Hz, 2H), 7.36 (d, J = 9 Hz, 1H), 4.75 (s, 1H), 4.40 (s, 2H), 4.26 (s, 2H), 1.93 (s, 3H)
208	MS (ESI) m/z 594.02 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.33 (bs, 1H), 8.83 (d, J = 4.6 Hz, 1H), 8.44 (s, 1H), 7.61-7.57 (m, 2H), 7.47-7.42 (m, 2H), 7.33 (d, J = 8.5 Hz, 1H), 4.35 (bs, 2H), 4.17 (bs, 2H), 1.71 (s, 3H)	212	MS (ESI) m/z 542.12 [M+1]+; UPLC: 99.61 %; 1H NMR (400 MHz, DMSO-d6) δ 13.34 (bs, 1H), 8.83 (d, J = 4.56 Hz, 1H), 8.47(s, 1H), 8.32 (s, 1H), 8.15 (s,1H), 7.60-7.57 (dd, J = 3.52,1.72 Hz,1H), 7.46 (d, J = 4.60 Hz, 1H), 7.42 (d, J = 2.32 Hz, 1H), 7.34 (d, J = 8.96 Hz, 1H), 4.41-4.39 (t, J = 5.28 Hz, 2H), 4.25-4.22 (t, J = 5.04 Hz, 2H), 1.77 (s, 3H)

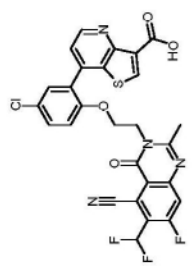
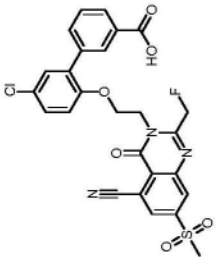
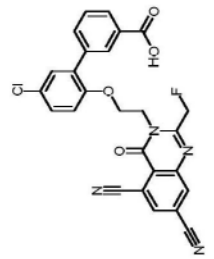
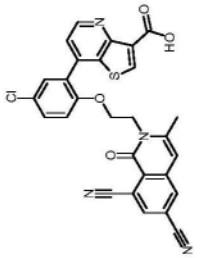
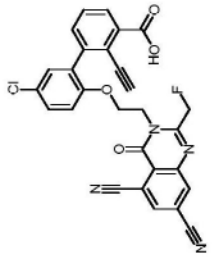
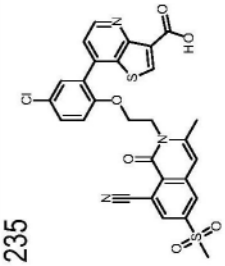
[1201]

213		MS (ESI) m/z 541.16 [M+1]+; UPLC: 99.87 %; 1H NMR (400 MHz, DMSO-d6) δ 13.34 (bs, 1H), 8.83 (d, J = 4.84 Hz, 1H), 8.38 (s, 1H), 8.02 (s, 1H), 7.74 (s,1H), 7.60-7.57 (dd, J = 8.84, 2.36 Hz,1H), 7.47-7.43 (dd, J = 11.20, 4.8 Hz, 2H), 7.34 (d, J = 8.92 Hz, 1H), 4.71 (s, 1H), 4.38 (s, 2H), 4.21 (s, 2H), 1.72 (s, 3H)
216		MS (ESI) m/z 644.23 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.83-8.79 (m, 3H), 8.29 (s, 1H), 8.22 (s, 1H), 7.93 (s, 1H), 7.84 (d, J = 5.68 Hz, 2H), 7.59 (dd, J = 2.56, J=8.84 Hz, 1H), 7.51 (d, J = 4.8 Hz, 1H), 7.44 (d, J=2.60 Hz, 1H), 7.34 (d, J=8.96 Hz, 1H) 4.38 (t, J = 5.76 Hz, 2H), 4.22 (t, J = 4.60 Hz, 2H), 1.69 (s, 3H)
217		MS (ESI) m/z 581.08 [M+1]+. 1H NMR (400 MHz, DMSO-d6) δ 13.39 (bs, 1H), 8.84 (d, J = 4.4 Hz, 1H), 8.26 (s, 1H), 8.13 (s, 1H), 7.81 (s, 1H), 7.59 (dd, J = 8.8, 2.4 Hz, 1H), 7.49 (d, J = 7.2 Hz, 1H), 7.43 (d, J = 2.4 Hz, 1H), 7.35 (d, J = 8.8 Hz, 1H), 4.40 (t, J = 5.9 Hz, 2H), 4.23 (t, J = 4.8 Hz, 2H), 2.14 (t, J = 19.6 Hz, 3H), 1.72 (s, 3H)
218		MS (ESI) m/z 618.02 [M+1]+. 1H NMR (400 MHz, DMSO-d6) δ 13.2 (s, 1H), 8.85-8.84 (d, J = 4.0 Hz, 1H), 8.47 (s, 1H), 8.21 (s, 1H), 8.01 (s, 1H), 7.59-7.58 (d, J=4.0 Hz, 1H), 7.51-7.50 (d, J = 4.0 Hz, 1H), 7.39-7.38 (m, 2H), 4.46-4. (bs, 2H), 4.31 (bs, 2H), 1.76 (s, 3H)
219		MS (ESI) m/z 628.23 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 12.65 (bs, 1H), 8.83 (d, J = 4.76 Hz, 1H), 8.31 (s, 1H), 8.03 (d, J = 3.84 Hz, 2H), 7.60-7.57 (dd, J = 2.4 Hz 6.36 Hz, 1H), 7.48 (d, J = 4.72 Hz, 1H), 7.43 (d, J = 2.44 Hz, 1H), 7.35 (d, J = 8.96 Hz, 1H), 4.38-4.35 (m, 2H), 4.25-4.22 (m, 2H), 1.77 (s, 3H)
220		MS (ESI) m/z 610.05 [M+1]+. 1H NMR (400 MHz, DMSO-d6) δ 13.2 (s, 1H), 8.83-8.82 (d, J = 4, 1H), 8.20 (s, 1H), 7.93-7.87 (m, 2H), 7.60-7.57 (m, 1H), 7.46-7.42 (m, 2H), 7.35-7.33 (d, J = 8 Hz, 1H), 4.36-4.38 (t, J = 4 Hz, 2H), 4.25-4.24 (t, J = 4 Hz, 2H), 1.78 (s, 3H)

[1202]

221		MS (ESI) m/z 592.03 [M+1]+. 1H NMR (400 MHz, DMSO-d6) δ 8.83 (d, J=4.8 Hz, 1H), 8.41 (s, 1H), 7.81 (s, 1H), 7.60-7.57 (dd, J=8.0, 2.52 Hz, 1H), 7.49 (d, J=4.7 Hz, 1H), 7.44 (d, J=2.52 Hz, 1H), 7.37-7.33 (m, 2H), 5.90 (s, 1H), 4.36-4.34 (t, J=7.52 Hz, 2H), 4.18-4.15 (t, J=7.96 Hz, 2H), 1.7 (s, 3H)
222		MS (ESI) m/z 607.03 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.82 (d, J = 4.84 Hz, 1H), 8.39 (s, 1H), 7.60-7.57 (m, 1H), 7.49 (d, J = 4.84 Hz, 1H), 7.43 (d, J = 2.6 Hz, 1H), 7.39 (s, 1H), 7.35 (s, 1H), 7.25 (s, 1H), 4.35-4.34 (t, J = 4.72 Hz, 2H),4.20-4.18 (t, J = 4.32 Hz, 2H), 2.46 (s, 3H), 1.75(s, 3H)
223		MS (ESI) m/z 638.04 [M+1]. 1H NMR (400 MHz, DMSO-d6) δ 13.2 (s, 1H), 8.83 (s, 1H), 8.32 (s, 1H), 8.23 (s, 1H), 8.09 (s, 1H), 7.59-7.57 (d, J = 8 Hz, 1H), 7.43 (d, J = 12 Hz, 2H), 7.34 (d, J=8 Hz, 1H), 4.43-4.41 (t, J=4.0 Hz, 2H), 4.31-4.29(t, J=4.0 Hz, 2H), 3.61(s, 3H), 1.93 (s, 3H)
224		MS (ESI) m/z 599.14 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.3 (s, 1H), 8.83 (d, J = 4 Hz, 1H), 8.66 (s, 1H), 8.36 (s, 1H), 8.32 (s, 1H), 7.60-7.58 (d, J = 8.0 Hz, 1H), 7.46 (d, J = 4.0 Hz, 1H), 7.40 (s, 1H), 7.35 (d, J = 12 Hz, 1H), 4.42-4.40 (t, J = 4.0 Hz, 2H), 4.28-4.26 (t, J = 5.6 Hz, 2H), 1.82 (s, 3H)
228		MS (ESI) m/z 540.16 [M-1]-; 1H NMR (400 MHz, DMSO-d6) δ 8.83 (d, J = 4.8 Hz, 1H), 8.35 (t, J = 4.18 Hz, 2H), 7.78 (d, J = 8.6 Hz, 1H), 7.61-7.58 (dd, J = 2.56, 2.56 Hz, 1H), 7.49 (d, J = 4.72 Hz, 1H), 7.42 (d, J = 2.56 Hz, 1H), 7.36 (d, J = 8.96 Hz, 1H), 4.40 (d, J = 4.64 Hz, 2H), 4.26 (d, J = 4.32 Hz, 2H), 1.79 (s, 3H)
229		MS (ESI) m/z 595.18 [M+1]+; UPLC: 99.8 %; 1H NMR (400 MHz, DMSO-d6) δ 8.83 (d, J = 4.80 Hz, 1H), 8.76 (s, 1H), 8.37 (d, J = 7.92, 1H), 8.10 (d, J = 7.88, 1H), 7.59 (dd, J = 2.04, 3.76 Hz, 1H), 7.44-7.47 (m, 2H), 7.37 (d, J = 8.92 Hz, 1H), 4.34 (s, 2H), 4.29 (s, 2H), 3.62 (s, 3H), 2.061 (s, 3H)

[1203]

230		MS (ESI) m/z 585.05 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.19 (bs, 1H), 8.83 (d, J = 4.8 Hz, 1H), 8.40 (s, 1H), 7.64-7.54 (m, 2H), 7.48-7.28 (m, 4H), 4.40 (t, J = 5.7 Hz, 2H), 4.24 (t, J = 5.2 Hz, 2H), 1.76 (s, 3H)	233  MS (ESI) m/z 556.20 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.10 (s,1H), 8.49 (s, 1H), 8.40 (s, 1H), 7.87 (s, 1H), 7.83 (s, 1H), 7.55 (d, J = 7.6 Hz, 1H), 7.44-7.39 (m, 2H), 7.28 (d, J = 2.4 Hz, 1H), 7.20 (d, J=8.84, 1H), 5.13 (d, J = 45.76 Hz, 2H), 4.33-4.31 (m, 4H), 3.46 (s, 3H)
231		MS (ESI) m/z 503.25 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.57 (s, 1H), 8.54 (s, 1H), 7.88 (d, J = 7.24 Hz, 1H), 7.81 (s, 1H), 7.48 (d, J = 7.16 Hz, 1H), 7.39 (m, 2H), 7.26 (s, 1H), 5.08 (d, J = 45.84 Hz, 2H), 4.31 (s, 4H)	234  MS (ESI) m/z 541.29 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.83 (d, J = 4.76 Hz, 1H), 8.36 (d, J = 3.88 Hz, 2H), 8.19 (d, J = 1.08 Hz, 1H), 7.5996-7.5708 (m, 1H), 7.45 (d, J = 4.76 Hz, 1H), 7.41 (d, J = 2.6 Hz, 1H), 7.35 (d, J = 8.96 Hz, 1H), 6.02 (s, 1H), 4.39 (d, J = 4.76 Hz, 2H), 4.2060 (s, 2H), 1.63 (s, 3H)
232		MS (ESI) m/z 527.16 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 12.96 (s, 1H), 8.58 (d, J = 0.68, 1H), 8.46 (s, 1H), 7.88 (d, J = 7.56 Hz, 1H), 7.47 (t, J = 7.72, 1H), 7.41-7.38 (m, 2H), 7.16 (d, J = 8.92, 1H), 7.13 (d, J = 2.52 ,1H), 5.02 (d, J = 46.24 Hz, 2H), 4.28 (s, 4H), 3.73(s, 1H)	235  MS (ESI) m/z 594.36 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.3202 (bs, 1H), 8.84 (d, J = 4.76 Hz, 1H), 8.34 (s, 1H), 8.31 (d, J = 1.4 Hz, 1H), 8.22 (d, J = 1.36 Hz, 1H), 7.6002-7.5717 (m, 1H), 7.46 (d, J = 4.76 Hz, 1H), 7.44 (d, J = 2.52 Hz, 1H), 7.36 (d, J = 8.96 Hz, 1H), 6.18 (s, 1H), 4.4153 (t, J = 5.32 Hz, 2H), 4.2160 (t, J = 5.4 Hz, 2H), 3.4635 (s, 3H), 1.6167 (s, 3H)

[1204]

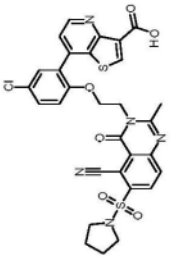
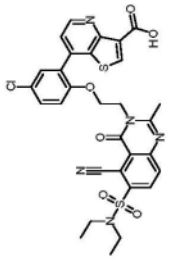
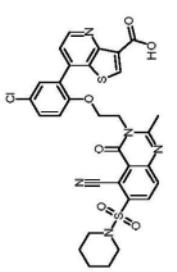
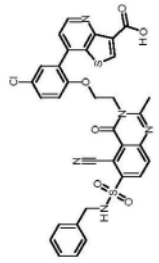
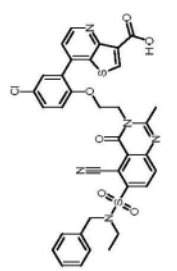
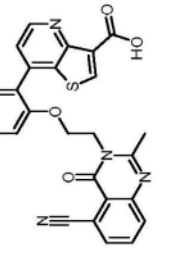
236		239	
MS (ESI) m/z 583.31 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.4 (bs, 1H), 8.82 (d, J = 4.8 Hz, 1H), 8.40 (s, 1H), 7.86 (d, J = 9.2 Hz, 1H), 7.77 (d, J = 9.2 Hz, 1H), 7.69-7.32 (m, 5H), 4.40-4.38 (m, 2H), 4.24-4.21 (m, 2H), 1.74 (s, 3H)		MS (ESI) m/z 576.04 [M+1]+; 1H-NMR (400 MHz, DMSO-d6) 8.82 (d, J = 4.8, 1H), 8.75 (s, 1H), 8.55 (s, 1H), 7.61 (dd, J = 2.48 Hz, 8.8 Hz, 1H), 7.48 (d, J = 4.8 Hz, 1H), 7.44 (d, J = 2.36 Hz, 1H), 7.38 (d, J = 8.92, 1H), 4.42 (t, J = 4.64 Hz, 2H), 4.29 (t, J = 4.32 Hz, 2H), 1.95 (s, 3H)	
237		240	
MS (ESI) m/z 624.32 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.87 (s, 1H), 8.85 (d, J = 4.48 Hz, 1H), 8.34 (d, J = 7.72 Hz, 1H), 8.03 (d, J = 7.92, 1H), 7.59 (d, J = 8.8 Hz , 1H), 7.51 (d, J = 1.96 Hz, 1H), 7.48 (d, J = 4.56 Hz, 1H), 7.35 (d, J = 9 Hz, 1H), 4.41(t, J = 4 Hz, 2H), 4.29 (t, J = 4.28 Hz , 2H), 2.84 (s, 6H). 1.99 (s, 3H)		MS (ESI) m/z 560.21 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.24 (bs, 1H), 8.80 (d, J = 4.60 Hz, 1H), 8.68 (d, J = 8.84 Hz, 1H), 8.51 (s, 1H), 7.59 (dd, J = 6.64 Hz, 2.8 Hz, 1H), 7.45 (d, J = 4.76 Hz, 1H), 7.43 (d, J = 2.28 Hz, 1H), 7.37 (d, J = 8.84 Hz, 1H), 4.42 (t, J = 4.96 Hz, 2H), 4.28 (t, J = 5.04 Hz, 2H), 1.95 (s, 3H)	
238		241	
MS (ESI) m/z 610.19 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.85 (m, 2H), 8.30 (d, J = 7.76Hz, 1H), 8.03 (d, J = 7.72 Hz, 1H), 7.58 (d, J = 8.8Hz, 1H), 7.52 (d, J = 1.76 Hz , 1H), 7.45 (d, J = 4.44 Hz, 1H), 7.35 (d, J = 8.84 Hz, 1H), 4.41(t, J = 4.6 Hz, 2H), 4.29 (t, J = 4.96 Hz , 2H), 2.54 (d, J = 5.92 Hz, 3H). 2.11 (s, 3H)		MS (ESI) m/z 553.18 [M+1]+; 1H NMR (400 MHz, DMSO-d6) 8.83 (d, J = 4.76 Hz, 1H), 8.47 (s, 1H), 8.09 (t, J = 9.48 Hz, 1H), 7.60 (dd, J = 2.16, 8.8 Hz, 1H), 7.51 (d, J = 4.64 Hz, 1H), 7.41 (d, J = 2.16 Hz, 1H), 7.37 (d, J = 8.92 Hz, 1H), 4.42 (bs, 2H). 4.26 (bs, 2H), 1.84 (s, 3H)	

[1205]

242		245		MS (ESI) m/z 535.14 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.33 (bs, 1H), 8.83 (d, J = 4.8 Hz, 1H), 8.4 (s, 1H), 7.93 (t, J = 9.0 Hz, 1H), 7.76 (dd, J = 9.0, 5.0 Hz, 1H), 7.59 (dd, J = 8.8, 2.5 Hz, 1H), 7.51 (d, J = 4.8 Hz, 1H), 7.43 (d, J = 2.5 Hz, 1H), 7.36 (d, J = 8.9 Hz, 1H), 4.4 (t, J = 4.8 Hz, 2H), 4.23 (t, J = 4.7 Hz, 2H), 1.73 (s, 3H)
243		247		MS (ESI) m/z 658.02 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.85 (d, J = 4.84 Hz, 1H), 8.42 (s, 1H), 7.88 (s, 1H), 7.60 (dd, J = 2.4, 8.88 Hz, 1H), 7.52 (d, J = 4.8 Hz, 1H), 7.45 (d, J = 2.4 Hz, 1H), 7.36 (d, J = 9.2 Hz, 1H), 4.41 (t, J = 4.72 Hz, 2H), 4.23 (t, J = 4.44 Hz, 2H), 2.96 (s, 6H), 1.71 (s, 3H)
244		248		MS (ESI) m/z 636.23 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.84 (d, J = 4.76 Hz, 1H), 8.43 (s, 1H), 8.26 (d, J = 8.72 Hz, 1H), 7.84 (d, J = 8.72 Hz, 1H), 7.61 (dd, J = 8.92, 2.6 Hz, 1H), 7.51 (d, J = 4.76 Hz, 1H), 7.46 (d, J = 2.6 Hz, 1H), 7.37 (d, J = 9.0 Hz, 1H), 4.41 (t, J = 5.6 Hz, 2H), 4.25 (t, J = 5.52 Hz, 2H), 3.96 (t, J = 7.52 Hz, 4H), 2.19-2.11 (m, 2H), 1.76 (s, 3H)

242	MS (ESI) m/z 569.11 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.84 (d, J = 4.68 Hz, 1H), 8.36 (s, 1H), 7.91 (d, J = 6.84 Hz, 1H), 7.60 (dd, J = 2.28 Hz, 8.84 Hz, 1H), 7.48 (d, J = 4.68 Hz, 1H), 7.42 (d, J = 2.32 Hz, 1H), 7.35 (d, J = 8.96 Hz, 1H), 4.39 (t, J = 5.64 Hz, 2H), 4.22 (t, J = 5.64 Hz, 2H), 1.73 (s, 3H)
243	MS (ESI) m/z 581.08 [M+1]+. 1H NMR (400 MHz, DMSO-d6) δ 12.35 (bs, 1H), 8.84 (d, J = 4.8 Hz, 1H), 8.40 (s, 1H), 7.65 (d, J = 9.6 Hz, 1H), 7.60 (dd, J = 8.8, 2.4 Hz, 1H), 7.49 (d, J = 4.8 Hz, 1H), 7.42 (d, J = 2.8 Hz, 1H), 7.36 (d, J = 8.8 Hz, 1H), 4.40-4.38 (m, 2H), 4.24-4.22 (m, 2H), 1.75 (s, 3H)
244	MS (ESI) m/z 551.16 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.83 (d, J = 4.76 Hz, 1H), 8.39 (s, 1H), 8.06 (d, J = 8.88,1H), 7.68 (d, J = 8.8, 1H), 7.58-7.61 (m, 1H), 7.50 (d, J = 4.56 Hz, 1H), 7.43 (d, J = 2.52 Hz, 1H), 7.39 (d,J = 9.0 Hz, 1H), 4.40 (s, 2H), 4.23 (s, 2H), 1.74 (s, 3H)
245	
247	
248	

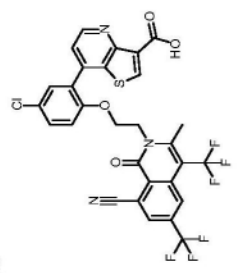
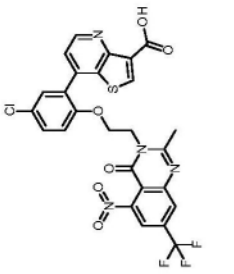
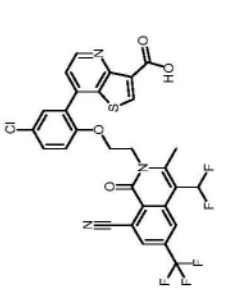
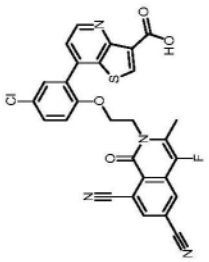
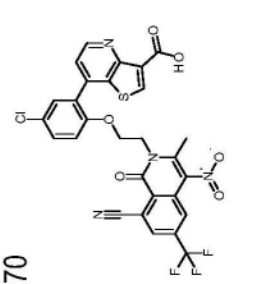
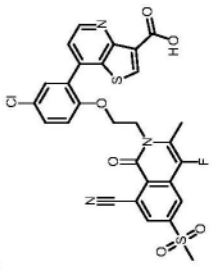
[1206]

249		MS (ESI) m/z 650.15 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.83 (d, J = 4.8 Hz, 1H), 8.40 (s, 1H), 8.28 (d, J = 8.72 Hz, 1H), 7.82 (d, J = 8.76 Hz, 1H), 7.60 (dd, J = 8.92, 2.56 Hz, 1H), 7.50 (d, J = 4.76 Hz, 1H), 7.45 (d, J = 2.6 Hz, 1H), 7.36 (d, J = 9.0 Hz, 1H), 4.40 (t, J = 5.24 Hz, 2H), 4.25 (t, J = 1.96 Hz, 2H),3.36 (t, J = 6.48 Hz, 4H), 1.83 (t, J = 6.52, 4H), 1.75 (s, 3H)
250		MS (ESI) m/z 652.16 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.84 (d, J = 4.84 Hz, 1H), 8.43 (s, 1H), 8.31 (d, J = 8.76 Hz, 1H), 7.81 (d, J = 8.8, Hz, 1H), 7.61 (dd, J = 2.72, 8.92 Hz, 1H), 7.52 (d, J = 4.84 Hz, 1H), 7.46 (d, J = 2.72 Hz, 1H), 7.36 (d, J = 9.04 Hz, 1H), 4.41 (t, J = 4.56 Hz, 2H), 4.24 (t, J = 4.5 Hz, 2H), 3.41(d, J = 7.04 Hz, 4H), 1.74 (s, 3H), 1.10 (t, J = 7.04 Hz, 6H)
251		MS (ESI) m/z 663.32 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.84 (d, J = 4.76 Hz, 1H), 8.41 (s, 1H), 8.26 (d, J = 8.76 Hz, 1H), 7.82 (d, J = 8.72 Hz, 1H),7.60 (dd, J = 8.8, 2.52 Hz, 1H),7.50 (d, J = 4.76 Hz, 1H),7.46 (d, J = 2.45 Hz, 1H),7.36 (d, J = 8.96 Hz, 1H), 4.40 (bs, 2H), 4.23 (bs, 2H), 3.20 (d, J = 5.2 Hz,4H), 1.75 (s, 3H), 1.55 (s, 4H), 1.46 (d, J = 3.64 Hz, 2H)
252		MS (ESI) m/z 686.21 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.83 (d, J = 4.8 Hz, 1H), 8.72 (t, J = 6.1, 1H), 8.4 (s, 1H) 8.20 (d, J = 8.7, 1H), 7.73 (d, J = 8.7 Hz, 1H), 7.60 (dd, J = 2.1, 8.92 Hz, 1H), 7.46 (m, 2H), 7.37 (d, J = 9 Hz, 1H), 7.1 (m, 4H), 7.07 (t, J = 7.1 Hz, 1H), 4.39 (d, J = 4.56, 2H), 4.24 (m, 4H), 1.72 (s, 3H)
253		MS (ESI) m/z 714.20 [M+1]+; 1H NMR (400 MHz, DMSO-d6) 8.84 (d, J = 4.8 Hz, 1H), 8.41 (s, 1H), 8.33 (d, J = 8.76 Hz, 1H), 7.80 (d, J = 8.76 Hz, 1H), 7.62 (dd, J = 2.68, 8.90 Hz, 1H), 7.51 (d, J = 4.80 Hz, 1H), 7.44 (d, J = 2.60 Hz, 1H), 7.38 (d, J = 9.00 Hz, 1H),7.35-7.28 (m, 4H), 7.15-7.20 (m, 1H), 4.59 (s, 2H), 4.40 (t, J = 4.64 Hz, 2H), 4.25 (t, J = 4.36 Hz, 2H), 3.30 (q, J = 6.92 Hz, 2H), 1.75 (s, 3H), 0.91 (t, J = 7.12 Hz, 3H).
254		MS (ESI) m/z 517.17 [M+1]+; UPLC: 98.39 %; 1H NMR (400 MHz, DMSO-d6) δ 13.42 (s, 1H), 8.82 (d, J= 4.72 Hz, 1H), 8.37(s, 1H), 7.95 (d, J = 6.52 Hz, 1H), 7.91-7.87 (t, 1H), 7.70 (d, J = 8.16, Hz 1H), 7.60-7.57 (dd, J = 2.48 Hz, 1H), 7.47 (d, J = 4.76 Hz, 1H), 7.43 (d, J = 2.52 Hz, 1H), 7.35 (d, J = 8.96 Hz, 1H), 4.41-4.22 (m, 4H), 1.77 (s, 3H)

[1207]

256		MS (ESI) m/z 581.07 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.22 (bs, 1H), 8.83 (s, 1H), 8.80 (d, J = 4.8 Hz, 1H), 8.10 (s, 1H), 7.87 (d, J = 8.4 Hz, 1H), 7.62 (dd, J = 8.4, 2.0 Hz, 1H), 7.52 (d, J = 2.0 Hz, 1H), 7.43 (d, J = 4.8 Hz, 1H), 6.48-6.41 (m, 1H), 5.97 (d, J = 16.0 Hz, 1H), 4.70 (d, J = 4.4 Hz, 2H), 2.36 (s, 3H)	
257		MS (ESI) m/z 579.06 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.76 (d, J = 4.7 Hz, 1H), 8.62 (s, 1H), 8.09 (s, 1H), 7.76 (d, J = 8.4 Hz, 1H), 7.69 (d, J = 2.0 Hz, 1H), 7.67 (s, 1H), 7.55 (d, J = 4.8 Hz, 1H), 4.85 (s, 2H), 2.09 (s, 3H)	
258		MS (ESI) m/z 536.11 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.74 (d, J = 4.7 Hz, 1H), 8.6 (s, 1H), 8.51 (d, J = 1.4 Hz, 1H), 8.32 (d, J = 1.4 Hz, 1H), 7.76 (d, J = 9.1 Hz, 1H), 7.68 (m, 2H), 7.53 (d, J = 4.7 Hz, 1H), 4.86 (s, 2H), 2.13 (s, 3H).	
262		MS (ESI) m/z 601.02 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 12.53 (bs, 1H), 8.86 (d, J = 4.8 Hz, 1H), 8.46 (s, 1H), 8.06 (d, J = 4.6 Hz, 2H), 7.60 (dd, J = 8.8, 2.6 Hz, 1H), 7.52 (d, J = 4.7 Hz, 1H), 7.40 (d, J = 2.5 Hz, 1H), 7.36 (d, J = 8.9 Hz, 1H), 4.41 (m, 2H), 4.19 (m, 2H), 1.46 (d, J = 3.3 Hz, 3H)	
263		MS (ESI) m/z 608.02 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.21 (bs, 1H), 8.87 (d, J = 4.7 Hz, 1H), 8.56 (s, 1H), 8.11 (s, 1H), 8.01 (s, 1H), 7.61 (dd, J = 8.8, 2.8 Hz, 1H), 7.52 (d, J = 4.8 Hz, 1H), 7.39-7.37 (m, 2H), 4.45 (m, 2H), 4.33 (m, 2H), 1.92 (s, 3H)	
264		MS (ESI) m/z 601.15 [M+1]+. 1H NMR (400 MHz, DMSO-d6) δ 8.84 (d, J = 4.8 Hz, 1H), 8.33 (d, J = 1.6 Hz, 1H), 8.30 (s, 1H), 7.96 (d, J = 1.2 Hz 1H), 7.60 (dd, J = 8.8, 2.4 Hz, 1H), 7.50 (d, J = 4.8 Hz, 1H), 7.43 (d, J = 2.4 Hz, 1H), 7.35 (d, J = 8.8 Hz, 1H), 4.40 (t, J = 4.8 Hz, 2H), 4.24 (t, J = 4.8 Hz, 2H), 1.73 (s, 3H)	

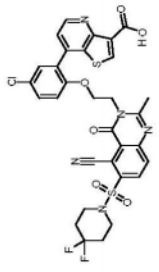
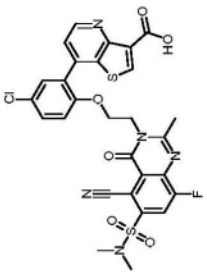
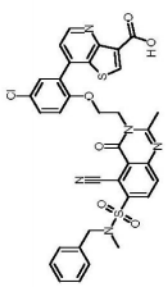
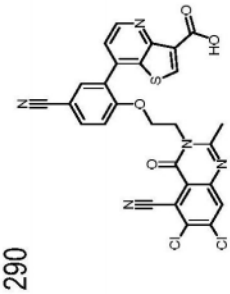
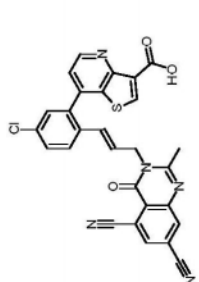
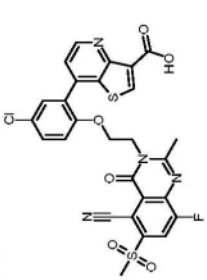
[1208]

268		MS (ESI) m/z 652.05 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.81 (d, J = 4.80 Hz, 1H), 8.50 (s, 1H), 8.24 (s, 1H), 8.08 (s, 1H), 7.60 (dd, J = 2.60, 2.64 Hz, 1H), 7.52 (d, J = 4.76 Hz, 1H), 7.42-7.38 (m, 2H), 4.47 (bs, 2H), 4.39 (bs, 2H), 1.89 (s, 3H)	271		MS (ESI) m/z 605.04 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.30 (bs, 1H), 8.84 (d, J = 4.68 Hz, 1H), 8.36 (s, 1H), 8.35 (d, J = 1.38 Hz, 1H), 7.98 (s, 1H), 7.58 (dd, J = 2.60, 2.60 Hz, 1H), 7.47 (d, J = 4.72 Hz, 1H), 7.43 (d, J = 2.60 Hz, 1H), 7.33 (d, J = 8.96 Hz, 1H), 4.33 (t, J = 4.79 Hz, 2H), 4.20 (t, J = 4.94 Hz, 2H), 1.75 (s, 3H)
269		MS (ESI) m/z 634.05 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.21 (bs, 1H), 8.77 (d, J = 4.84 Hz, 1H), 8.43 (s, 1H), 8.41 (s, 1H), 8.36 (s, 1H), 7.60-7.58 (m, 1H), 7.48 (d, J = 4.72 Hz, 1H), 7.44-7.17 (m, 3H), 4.45 (t, J = 4.47 Hz, 2H), 4.35 (t, J = 4.35 Hz, 2H), 1.99 (s, 3H)	273		MS (ESI) m/z 558.95 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.86-8.85 (d, J = 4.8 Hz, 1H), 8.57 (d, J = 1.2 Hz, 1H), 8.23 (d, J = 1.2 Hz, 1H), 8.17 (s, 1H), 7.61-7.58 (dd, J = 2.8, 8.8 Hz, 1H), 7.50-7.49 (d, J = 4.8 Hz, 1H), 7.40 (d, J = 2.8 Hz, 1H), 7.37-7.35 (d, J = 8.8 Hz, 1H), 4.40 (d, J = 4.4 Hz, 2H), 4.18 (t, J 4.4 Hz, 2H), 1.49 (d, J = 3.6 Hz, 3H)
270		MS (ESI) m/z 629.04 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.21 (bs, 1H), 8.80 (d, J = 4.80 Hz, 1H), 8.54 (s, 1H), 8.33 (s, 1H), 7.94 (s, 1H), 7.62-7.59 (m, 1H), 7.50 (d, J = 4.76 Hz, 1H), 7.42-7.38 (m, 2H), 4.47 (t, J =4.47 Hz, 2H), 4.36 (t, J = 4.36 Hz, 2H), 1.85 (s, 3H)	274		MS (ESI) m/z 611.97 [M+1]+. 1H NMR (400 MHz, DMSO-d6) δ 8.87 (d, J = 4.7 Hz, 1H), 8.47 (s, 1H), 8.23 (s, 1H), 8.12 (s, 1H), 7.59 (d, J = 9.3 Hz, 1H), 7.52 (d, J = 4.5 Hz, 1H), 7.41 (s, 1H), 7.37 (d, J = 8.9 Hz, 1H), 4.42 (t, J = 5.2 Hz, 2H), 4.19 (t, J = 5.2 Hz, 2H), 3.52 (s, 3H), 1.46 (s, 3H)

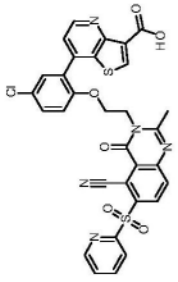
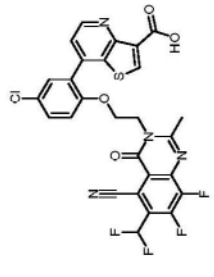
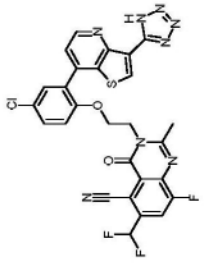
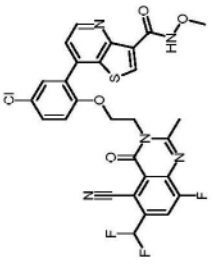
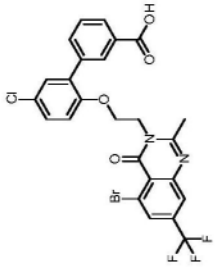
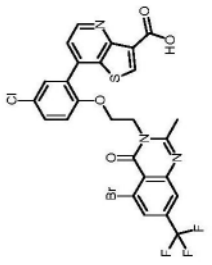
[1209]

276		MS (ESI) m/z 559.95 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 12.81 (bs, 1H), 8.85 (d, J = 4.76 Hz, 1H), 8.39 (s, 1H), 7.69 (d, J = 9.60 Hz, 1H), 7.60 (dd, J = 8.84, 2.48 Hz, 1H), 7.50 (d, J = 4.76 Hz, 1H), 7.42 (d, J = 2.56 Hz, 1H), 7.36 (d, J = 8.96 Hz, 1H), 4.40 (t, 4.40 Hz, 2H), 4.25 (t, J = 4.80, 2H), 1.80 (s, 3H)
277		MS (ESI) m/z 629.53 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.35 (bs, 1H), 8.84 (d, J = 4.8 Hz, 1H), 8.32 (s, 1H), 8.21 (s, 1H), 7.60 (dd, J = 8.8, 2.4 Hz, 1H), 7.49 (d, J = 4.8 Hz, 1H), 7.42 (d, J = 2.8 Hz, 1H), 7.37 (d, J = 8.8 Hz, 1H), 4.42 (t, J = 4.4 Hz, 2H), 4.25 (t, J = 5.2 Hz, 2H), 1.71 (s, 3H)
278		MS (ESI) m/z 613.09 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.21 (bs, 1H), 8.84 (d, J = 3.28 Hz, 1H), 8.26 (s, 1H), 8.07 (d, J = 5.96 Hz, 1H), 7.59 (d, J = 7.96 Hz, 1H), 7.47 (bs, 1H), 7.41 (s, 1H), 7.36 (d, J = 8.68 Hz, 1H), 4.42 (s, 2H), 4.24 (s, 2H), 3.58 (s, 3H),1.72 (s, 3H)
279		MS (ESI) m/z 613.19 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.85 (d, J = 4.72 Hz, 1H), 8.43 (s, 1H), 7.64 (d, J = 11.36 Hz, 1H), 7.60 (dd, J = 8.88, 2.56 Hz, 1H), 7.48 (d, J = 4.8 Hz, 1H), 7.42 (d, J = 2.6 Hz, 1H), 7.36 (d, J = 9.0 Hz, 1H), 4.40 (t, J = 5.0 Hz, 2H), 4.24 (t, J = 4.64, 2H), 3.58 (s, 3H), 1.78 (s, 3H)
280		MS (ESI) m/z 642.15 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.86 (d, J = 4.84 Hz, 1H), 8.31 (s, 1H), 8.05 (d, J = 6.32 Hz, 1H), 7.59 (dd, J = 8.88, 2.56 Hz, 1H), 7.51 (d, J = 4.84 Hz, 1H), 7.45 (d, J = 2.56 Hz, 1H), 7.35 (d, J = 9.0 Hz, 1H), 4.40 (t, J = 4.60 Hz, 2H), 4.22 (t, J = 4.32 Hz, 2H), 2.94 (s, 6H), 1.62 (s, 3H)
281		MS (ESI) m/z 641.95 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.85 (d, J = 4.76 Hz, 1H), 8.40 (s, 1H), 7.64 (d, J = 11.52 Hz, 1H), 7.60 (dd, J = 2.60, 8.96 Hz, 1H), 7.48 (d, J = 4.76 Hz, 1H), 7.44 (d, J = 2.64 Hz, 1H), 7.36 (d, J = 8.92 Hz, 1H), 4.39 (t, J = 4.4 Hz, 2H), 4.22 (t, J = 4.36, 2H), 2.92 (s, 6H), 1.77 (s, 3H)

[1210]

282		MS (ESI) m/z 700.01 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.84 (d, J = 4.84 Hz, 1H), 8.41 (s, 1H), 8.32 (d, J = 8.76 Hz, 1H), 7.81 (d, J = 8.76, Hz, 1H), 7.61 (dd, J = 2.60, 8.92 Hz, 1H), 7.50 (d, J = 4.80 Hz, 1H), 7.46 (d, J = 2.68 Hz, 1H), 7.36 (d, J = 9.04 Hz, 1H), 4.41 (bs, 2H), 4.24 (bs, 2H), 3.41(m, 4H), 2.14 -2.07 (m, 4H), 1.76 (s, 3H)	288		MS (ESI) m/z 642.18 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.84 (d, J = 4.56 Hz, 1H), 8.45 (s, 1H), 8.11 (d, J = 5.2 Hz, 1H), 7.61 (d, J = 7 Hz, 1H), 7.52 (d, J = 4.52 Hz, 1H), 7.45 (d, J = 2.12 Hz, 1H), 7.37 (d, J= 8.68 Hz, 1H), 4.42 (t, J = 4.6 Hz, 2H), 4.27 (t, J = 6.32 Hz, 2H), 2.89 (s, 6H), 1.83 (s, 3H)
283		MS (ESI) m/z 700.22 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.85 (d, J = 4.84 Hz, 1H), 8.41 (s, 1H), 8.34 (d, J = 8.8 Hz, 1H), 7.82 (d, J = 8.8, Hz, 1H), 7.61 (dd, J = 2.72, 8.92 Hz, 1H), 7.505 (d, J = 4.84 Hz, 1H), 7.46 (d, J = 2.72 Hz, 1H), 7.36 (m, 6H), 4.48 (s, 2H), 4.41 (t, J = 4.56 Hz, 2H), 4.24 (t, J = 4.56 Hz, 2H), 2.76 (s, 3H), 1.74 (s, 3H)	290		MS (ESI) m/z 576.13 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.26 (bs, 1H), 8.87 (d, J = 4.6 Hz, 1H), 8.37 (s, 1H), 8.05 (dd, J = 8.7, 2.0 Hz, 1H), 7.93 (s, 1H), 7.88 (d, J = 2.0 Hz, 1H), 7.52 (d, J = 3.1 Hz, 1H), 7.5 (s, 1H), 4.5 (t, J = 4.8 Hz, 2H), 4.25 (t, J = 4.6 Hz, 2H), 1.69 (s, 3H)
286		MS (ESI) m/z 538.22 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.85 (s, 1H), 8.80 (d, J = 4.8 Hz, 1H), 8.43 (d, J = 0.8 Hz, 1H), 8.33 (d, J = 0.8 Hz, 1H), 7.62 (dd, J = 8.8, 2.0 Hz, 1H), 7.52 (d, J = 2.0 Hz, 1H), 7.45 (d, J = 4.8, 1H), 6.49-6.42 (m,1H), 5.97 (d, J = 16 Hz, 1H), 4.71 (d, J = 4.8 Hz, 1H), 2.39 (s 3H)	293		MS (ESI) m/z 613.15 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.81 (d, J = 4.80 Hz, 1H), 8.75 (bs, 1H), 8.30 (d, J = 8.36 Hz, 1H), 7.60 (dd, J = 8.96, 6.52, Hz, 1H), 7.90-7.42 (m, 2H), 7.38 (d, J = 8.88 Hz, 1H), 4.43 (t, J = 5.84 Hz, 2H), 4.30 (t, J = 4.24 Hz, 2H), 3.67 (s, 3H), 2.11 (s, 3H)

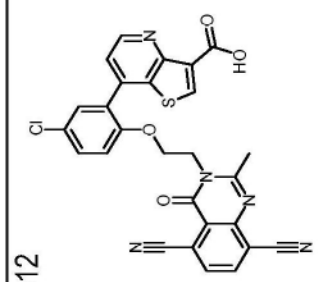
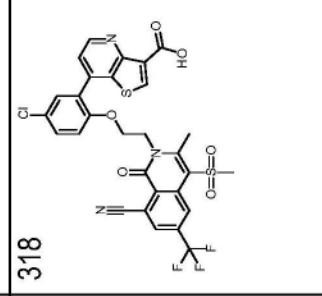
[1211]

297		MS (ESI) m/z 658.33 [M+1]+; 1H NMR (400 MHz, DMSO-d6): δ 13.34 (bs, 1H), 8.80 (d, J = 4.7 Hz, 1H), 8.65 (d, J = 4.32 Hz, 1H), 8.61 (d, J = 8.72 Hz, 1H), 8.48 (s, 1H), 8.37 (d, J = 7.88 Hz, 1H), 8.26 (t, J = 7.76 Hz, 1H), 7.96 (d, J = 8.76 Hz, 1H), 7.77-7.74 (m, 1H), 7.58-7.55 (m, 1H), 7.46-7.44 (m, 2H), 7.30 (d, J = 8.96 Hz, 1H), 4.34 (d, J = 4.68 Hz, 2H), 4.20 (d, J = 4.40 Hz, 2H), 1.75 (s, 3H)
298		MS (ESI) m/z 602.95 [M+1]+; 1H-NMR (400 MHz, DMSO-d6) δ 13.13 (bs, 1H), 8.82 (d, J = 4.76 Hz ,1H), 8.41 (s, 1H), 7.60 (dd, J = 2.64, 8.92 Hz, 1H), 7.48-7.34 (m, 4H), 4.42 (t, J = 4.6 Hz, 2H), 4.26 (t, J = 4.0 Hz, 2H), 1.85 (s, 3H)
302		MS (ESI) m/z 609.60 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.90 (d, J = 4.6 Hz, 1H), 8.38 (s, 1H), 7.89 (d, J = 9.76 Hz, 1H), 7.60 (dd, J = 2,4, 8.84 Hz, 1H), 7.50 (d, J = 4.60 Hz, 1H), 7.47-7.20 (m, 3H), 4.43 (t, J = 4.80 Hz, 2H), 4.26 (t, J = 4.88 Hz, 2H), 1.83 (s, 3H)
303		MS (ESI) m/z 613.08 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 12.03 (s, 1H), 8.78 (d, J = 4.84 Hz, 1H), 8.32 (s, 1H), 8.05 (s, J = 9.60, 1H), 7.59 (dd, J = 8.96, 2.56 Hz, 1H), 7.49-7.35 (m, 4H), 4.41 (m, 2H), 4.27 (m, 2H), 3.86 (s, 3H), 1.89 (s, 3H)
304		MS (ESI) m/z 583.20 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 12.96 (s,1H), 7.95 (s, 1H), 7.86-7.85 (m, 3H), 7.53 (d, J = 7.96, 1H), 7.43-7.38 (m, 2H), 7.28 (d, J = 2.6, 1H), 7.20 (d, J = 8.8 Hz, 1H), 4.30 (s, 4H), 2.18 (s, 3H)
305		MS (ESI) m/z 638.07 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.21 (bs, 1H), 8.83 (s, 1H), 8.35 (s, 1H), 7.94 (s, 1H), 7.71 (s, 1H), 7.58 (dd, J = 2.44, 8.88 Hz, 1H), 7.47 (bs, 1H), 7.43 (s, 1H), 7.33 (d, J = 8.96 Hz, 1H), 4.35 (t, J = 5.32 Hz, 2H), 4.18 (t, J = 5.08 Hz, 2H), 1.71 (s, 3H)

[1212]

306		309		MS (ESI) m/z 614.07 [M+1]+. 1H NMR (400 MHz, DMSO-D2O) δ 8.76 (s, 1H), 8.21 (s, 1H), 8.03 (s, 1H), 7.87 (s, 1H), 7.53 (d, J = 12 Hz, 1H), 7.41 (s, 1H), 7.30-7.26 (m, 2H), 4.34 (s, 2H), 4.17 (s, 2H), 3.41 (s, 3H), 1.50 (s, 3H)
307		310		MS (ESI) m/z 577.08 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.90 (d, J = 4.68 Hz, 1H), 8.39 (s, 1H), 7.61-7.58 (m, 1H), 7.48 (d, J = 4.64 Hz, 1H), 7.44-7.35 (m, 3H), 4.40 (t, J = 5.18 Hz, 2H), 4.22 (t, J = 4.48 Hz, 2H), 1.73 (s, 3H)
308		311		MS (ESI) m/z 629.98 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 12.68 (s, 1H), 8.90 (d, J = 4.80 Hz, 1H), 8.53 (s, 1H), 7.72 (dd, J =7.60, 10.68 Hz, 1H), 7.61 (dd, J = 2.56, 8.88 Hz, 1H), 7.56 (d, J = 4.84 Hz, 1H), 7.44 (d, J = 2.64 Hz, 1H), 7.37 (d, J = 9.0 Hz, 1H), 4.41 (t, J = 4.56 Hz, 2H), 4.23 (t, J = 4.60 Hz, 2H), 3.57 (s, 3H), 1.74 (s, 3H)
				MS (ESI) m/z 581.97 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 12.09 (s, 1H), 8.83 (d, J = 4.76 Hz, 1H), 8.26 (s, 1H), 7.73 (dd, J = 7.24, 10.48 Hz, 1H), 7.59 (dd, J = 2.48, 8.88 Hz, 1H), 7.44 (d, J = 4.72 Hz, 1H), 7.40 (d, J = 2.52 Hz, 1H), 7.35 (d, J = 9.04 Hz, 1H), 4.38 (t, J = 4.28 Hz, 2H), 4.22 (t, J = 4.56 Hz, 2H), 3.88 (s, 3H), 1.75 (s, 3H)
				MS (ESI) m/z 592.10 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.83 (d, J = 4.72 Hz, 1H), 8.29 (s, 1H), 7.62-7.60 (m, 2H), 7.48 (d, J = 4.76 Hz, 1H), 7.43 (d, J = 2.60 Hz, 1H), 7.37 (d, J = 8.96 Hz, 1H), 4.59 (s, 2H), 4.41 (t, J = 4.68 Hz, 2H), 4.25 (t, J = 4.68 Hz, 2H), 2.95 (s, 6H), 1.81 (s, 3H)

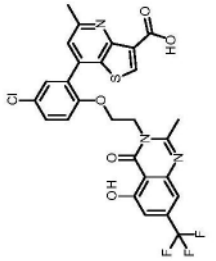
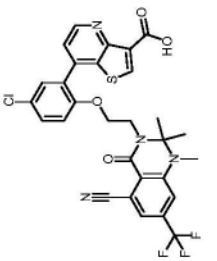
[1213]

312		MS (ESI) m/z 541.97 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.23 (bs, 1H), 8.8 (d, J = 4.8 Hz, 1H), 8.52 (s, 1H), 8.4 (d, J = 7.8 Hz, 1H), 8.06 (d, J = 7.8 Hz, 1H), 7.59 (dd, J = 8.9, 2.6 Hz, 1H), 7.46 (d, J = 4.8 Hz, 1H), 7.44 (d, J = 2.5 Hz, 1H), 7.36 (d, J = 8.9 Hz, 1H), 4.42 (t, J = 4.6 Hz, 2H), 4.28 (t, J = 4.9 Hz, 2H), 1.97 (s, 3H).	317		MS (ESI) m/z 559.99 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.34 (bs, 1H), 8.81 (d, J = 4.4 Hz, 1H), 8.45 (s, 1H), 8.28 (s, 2H), 8.20 (s, 1H), 7.87 (s, 1H), 7.59-7.57 (m, 1H), 7.50-7.40 (m, 2H), 7.35 (d, J = 8.8 Hz, 1H), 4.49-4.30 (m, 2H), 4.29-4.15 (m, 2H), 1.77 (s, 3H)
313		MS (ESI) m/z 600.97 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.23 (bs, 1H), 8.77 (d, J = 4.76 Hz, 1H), 8.55 (s, 1H), 8.02 (d, J = 8.28 Hz, 1H), 7.92 (d, J = 7.24 Hz, 1H), 7.58 (dd, J = 2.56, 8.88 Hz, 1H), 7.46-7.44 (m, 2H), 7.35 (d, J = 8.96 Hz, 1H), 4.41 (t, J = 5.32 Hz, 2H), 4.26 (t, J = 4.52 Hz, 2H), 1.90 (s, 3H).	318		MS (ESI) m/z 662.04 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 9.03 (s, 1H), 8.78 (d, J = 4.76 Hz, 1H), 8.47 (s, 1H), 8.43 (s, 1H), 7.60-7.58 (m, 1H), 7.47-7.44 (m, 2H), 7.38 (d, J = 8.92 Hz, 1H), 4.44 (s, 4H), 3.27 (s, 3H), 2.33 (s, 3H)
316		MS (ESI) m/z 560.39 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.83 (d, J = 4.8 Hz, 1H), 8.40 (s, 1H), 8.17 (s, 1H), 7.92 (d, J = 8.36 Hz, 2H), 7.69 (d, J = 8.52 Hz, 1H), 7.60-7.58 (m, 1H), 7.48 (d, J = 4.84 Hz, 1H), 7.44 (d, J = 2.68 Hz, 1H), 7.35 (d, J = 8.96 Hz, 1H), 4.39 (t, J = 4.48 Hz, 2H), 4.23 (t, J = 4.48 Hz, 2H), 1.72 (s, 3H)	334		MS (ESI) m/z 586.3 [M+1]+; 1H-NMR (400 MHz, d6-DMSO) δ / ppm = 9.20 (b, 2H), 8.30 (s, 1H), 7.60 (dd, J = 8.9, 2.7 Hz, 1H), 7.55 (s, 1H), 7.44 (s, 1H), 7.39-7.35 (m, 2H), 4.53-4.48 (m, 2H), 4.41 (bt, 2H), 4.26 (bt, 2H), 3.57 (2H; 通过 HSQC 观察, 在 1H-NMR 中信号被水峰所掩盖), 3.22 (bt, 2H), 2.73 (s, 3H), 1.97 (s, 3H)

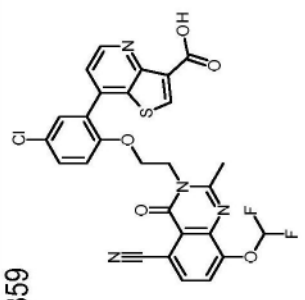
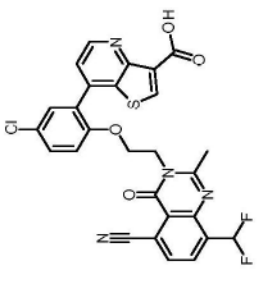
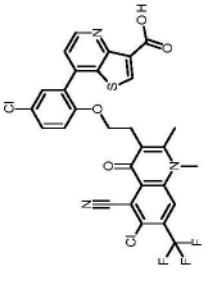
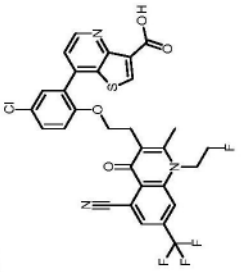
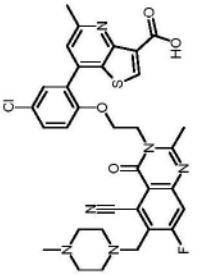
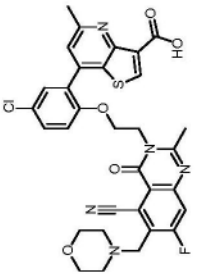
[1214]

335		345a		MS (ESI) m/z 676.6 [M+1]+; 1H-NMR (400 MHz, d6-DMSO) δ / ppm = 8.31 (s, 1H), 8.19 (s, 1H), 8.07-8.04 (m, 1H), 7.93-7.88 (m, 1H), 7.80-7.74 (m, 2H), 7.59 (dd, J = 8.9, 2.6 Hz, 1H), 7.45 (s, 1H), 7.42 (d, J = 2.6 Hz, 1H), 7.35 (d, J = 8.9 Hz, 1H), 4.41 (t, J = 4.8 Hz, 2H), 4.27 (t, J = 4.8 Hz, 2H), 2.74 (s, 3H), 1.82 (s, 3H)
336		345b		MS (ESI) m/z 694.1 [M+1]+; 1H-NMR (400 MHz, d6-DMSO) δ / ppm = 8.29 (s, 1H), 8.07 (s, 1H), 8.01-7.95 (b, 1H), 7.88 (dd, J = 7.7, 1.7 Hz, 1H), 7.65-7.55 (m, 3H), 7.46-7.39 (m, 3H), 7.33 (d, J = 9.0 Hz, 1H), 7.21-7.15 (b, 1H), 4.40 (t, J = 4.7 Hz, 2H), 4.27-4.20 (b, 2H), 2.74 (s, 3H), 1.74 (s, 3H)
337		346		MS (ESI) m/z 600.7 [M+1]+; 1H-NMR (400 MHz, d6-DMSO) δ / ppm = 10.30 (b, 1H), 8.27 (bs, 1H), 7.63-7.58 (m, 1H), 7.52 (bs, 1H), 7.45-7.34 (m, 4H), 4.88-4.12 (m, 6H), 3.04 (s, 3H), 2.72 (s, 3H), 1.92 (s, 3H) [剩余的信号被水峰或溶剂峰所掩盖]
				MS (ESI) m/z 600.3 [M+1]+; 1H-NMR (400 MHz, d6-DMSO) δ / ppm = 10.46-10.14 (b, 1H), 8.26 (s, 1H), 7.60 (dd, J = 9.0, 2.8 Hz, 1H), 7.54 (s, 1H), 7.43 (s, 1H), 7.40-7.35 (m, 2H), 4.93-3.38 (m, 6H; 部分被水峰所掩盖), 4.43-4.35 (b, 2H), 3.38-3.27 (b, 2H), 3.10 (s, 3H), 2.73 (s, 3H), 1.93 (s, 3H)
				MS (ESI) m/z 575.0 [M+1]+; 1H-NMR (400 MHz, d6-DMSO) δ / ppm = 9.07 (d, J = 1.9 Hz, 1H), 8.30 (s, 1H), 8.16 (d, J = 1.9 Hz, 1H), 7.59 (dd, J = 8.9, 2.6 Hz, 1H), 7.43-7.41 (m, 2H), 7.35 (d, J = 8.9 Hz, 1H), 4.39 (t, J = 5.0 Hz, 2H), 4.26 (t, J = 5.0 Hz, 2H), 2.70 (s, 3H), 1.80 (s, 3H)

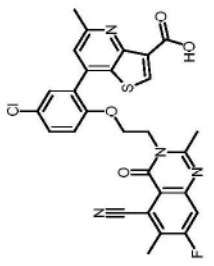
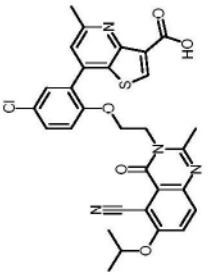
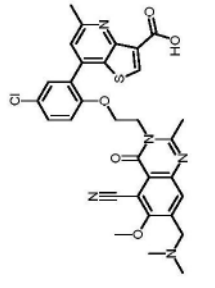
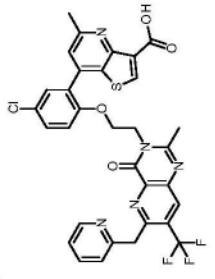
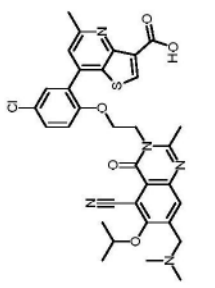
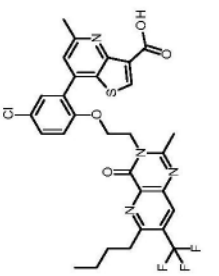
[1215]

351a		MS (ESI) m/z 590.0 [M+1]+; 1H-NMR (400 MHz, d6-DMSO) d / ppm = 11.72 (s, 1H), 8.44 (s, 1H), 7.59 (dd, J = 8.9, 2.7 Hz, 1H), 7.42 (d, J = 2.7 Hz, 1H), 7.40 (s, 1H), 7.34 (d, J = 8.9 Hz, 1H), 7.17-7.16 (m, 1H), 7.07-7.05 (m, 1H), 4.40 (t, J = 4.9 Hz, 1H), 4.25 (t, J = 4.9 Hz, 2H), 2.68 (s, 3H), 1.88 (s, 3H)	355		MS (ESI) m/z 615.0 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.87 – 8.84 (m, 2H), 7.61 – 7.57 (m, 2H), 7.53 – 7.51 (m, 2H), 7.38 (d, J = 9.0 Hz, 1H), 7.35 (s, 1H), 4.23 (t, J = 5.5 Hz, 2H), 3.74 (t, J = 5.4 Hz, 2H), 2.75 (s, 3H), 1.07 (s, 6H)
351b		MS (ESI) m/z 574.0 [M+1]+; 1H-NMR (400 MHz, d6-DMSO) d / ppm = 8.35 (s, 1H), 8.18-8.14 (m, 1H), 7.76-7.71 (m, 1H), 7.58 (dd, J = 8.9, 2.8 Hz, 1H), 7.42 (d, J = 2.8 Hz, 1H), 7.40 (s, 1H), 7.34 (d, J = 8.9 Hz, 1H), 4.38 (t, J = 4.9 Hz, 2H), 4.24 (t, J = 4.9 Hz, 2H), 2.69 (s, 3H), 1.84 (s, 3H)	357		MS (ESI) m/z 598.1 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.83 (d, J = 4.8 Hz, 1H), 8.51 (s, 1H), 8.27 – 8.26 (m, 1H), 8.16 (dd, J = 1.5, 0.6 Hz, 1H), 7.56 (dd, J = 8.9, 2.7 Hz, 1H), 7.49 (d, J = 4.8 Hz, 1H), 7.41 (d, J = 2.7 Hz, 1H), 7.37 (d, J = 9.0 Hz, 1H), 4.23 (t, J = 6.1 Hz, 2H), 3.62 (s, 3H), 2.89 (t, J = 6.1 Hz, 2H), 1.85 (s, 3H)
353		MS (ESI) m/z 584.2 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.77 (d, J = 4.9 Hz, 1H), 8.61 (s, 1H), 8.18 – 8.17 (m, 1H), 8.16 – 8.15 (m, 1H), 7.67 (s, 1H), 7.59 (dd, J = 8.9, 2.7 Hz, 1H), 7.47 (s, 1H), 7.46 (d, J = 2.3 Hz, 1H), 7.38 (d, J = 9.0 Hz, 1H), 4.30 (t, J = 6.2 Hz, 2H), 3.70 (s, 3H), 2.71 (t, J = 6.2 Hz, 2H)	358		MS (ESI) m/z 585.2 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.76 (d, J = 4.8 Hz, 1H), 8.63 (s, 1H), 8.24 (d, J = 7.9 Hz, 1H), 8.06 (d, J = 7.8 Hz, 1H), 7.59 (dd, J = 8.9, 2.7 Hz, 1H), 7.48 – 7.43 (m, 2H), 7.37 (d, J = 9.0 Hz, 1H), 4.44 (t, J = 5.1 Hz, 2H), 4.29 (t, J = 5.1 Hz, 2H), 1.98 (s, 3H).

[1216]

359		MS (ESI) m/z 583.1 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.78 (d, J = 4.3 Hz, 1H), 8.55 (s, 1H), 7.97 (d, J = 8.3 Hz, 1H), 7.67 (d, J = 8.2 Hz, 1H), 7.60 (dd, J = 9.0, 2.6 Hz, 1H), 7.52 – 7.29 (m, 4H), 4.42 (t, J = 4.2 Hz, 2H), 4.26 (t, J = 4.4 Hz, 2H), 1.92 (s, 3H)	
360		MS (ESI) m/z 567.1 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.77 (d, J = 4.8 Hz, 1H), 8.55 (s, 1H), 8.12 (d, J = 7.9 Hz, 1H), 8.06 (d, J = 7.8 Hz, 1H), 7.59 (dd, J = 8.9, 2.7 Hz, 1H), 7.51 (t, J = 54.6 Hz, 1H). 7.44 (d, J = 2.7 Hz, 1H), 7.43 (d, J = 4.7 Hz, 1H), 7.36 (d, J = 9.0 Hz, 1H), 4.42 (t, J = 5.0 Hz, 2H), 4.25 (t, J = 5.0 Hz, 2H), 1.84 (s, 3H)	
361		MS (ESI) m/z 632.2 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.83 (d, J = 4.8 Hz, 1H), 8.45 (s, 1H), 8.28 (s, 1H), 7.57 (dd, J = 8.9, 2.7 Hz, 1H), 7.48 (d, J = 4.8 Hz, 1H), 7.39 (d, J = 2.7 Hz, 1H), 7.36 (d, J = 9.0 Hz, 1H), 4.24 (t, J = 5.9 Hz, 2H), 3.60 (s, 3H), 2.89 (t, J = 5.9 Hz, 2H), 1.80 (s, 3H)	
362		MS (ESI) m/z 630.2 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.83 (d, J = 4.8 Hz, 1H), 8.71 (s, 1H), 8.36 (s, 1H), 8.18 (d, J = 1.2 Hz, 1H), 7.57 (dd, J = 8.9, 2.7 Hz, 1H), 7.53 (d, J = 4.8 Hz, 1H), 7.46 (d, J = 2.7 Hz, 1H), 7.38 (d, J = 9.0 Hz, 1H), 4.76 (t, J = 4.4 Hz, 1H), 4.73 – 4.66 (m, 1H), 4.64 (s, 2H), 4.21 (t, J = 6.3 Hz, 2H), 2.93 (t, J = 6.3 Hz, 2H), 2.02 (s, 3H)	
366		MS (ESI) m/z 661.1 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 9.43 (s, 1H), 8.34 (s, 1H), 7.60 (dd, J = 8.9, 2.6 Hz, 1H), 7.48 (d, J = 10.1 Hz, 1H), 7.46 – 7.39 (m, 2H), 7.36 (d, J = 8.9 Hz, 1H), 4.39 (t, J= 4.9 Hz, 2H), 4.24 (t, J = 5.0 Hz, 2H), 3.83 (s, 2H), 3.06 – 2.92 (m, 4H), 2.77 (d, J = 4.0 Hz, 3H), 2.71 (s, 3H), 1.88 (s, 3H)	
367		MS (ESI) m/z 648.3 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.34 (s, 1H), 7.60 (dd, J = 8.9, 2.7 Hz, 1H), 7.55 (d, J = 10.1 Hz, 1H), 7.43 (s, 1H), 7.42 (d, J = 2.6 Hz, 1H), 7.36 (d, J = 9.0 Hz, 1H), 4.40 (t, J = 5.1 Hz, 2H), 4.25 (t, J = 5.1 Hz, 3H), 3.70 (bs, 4H), 2.99 (bs, 4H), 2.72 (s, 3H), 1.88 (s, 3H)	

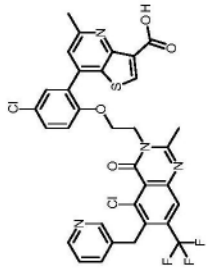
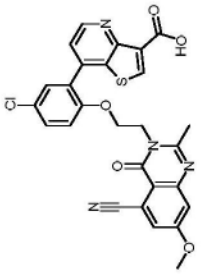
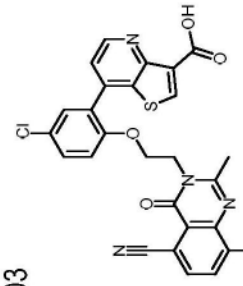
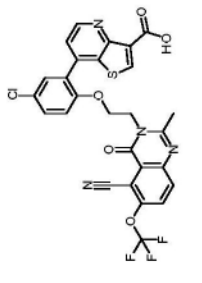
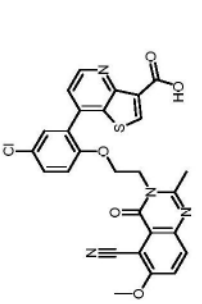
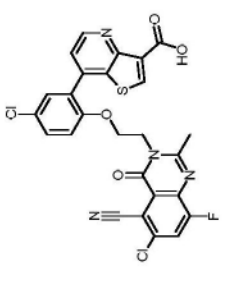
[1217]

368		MS (ESI) m/z 563.3 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.39 (s, 1H), 7.60 (dd, J = 9.0, 2.7 Hz, 1H), 7.44 – 7.39 (m, 3H), 7.36 (d, J = 9.0 Hz, 1H), 4.39 (t, J = 5.1 Hz, 2H), 4.24 (t, J = 5.1 Hz, 2H), 2.72 (s, 3H), 2.50 (s, 3H), 1.91 (s, 3H)	371		MS (ESI) m/z 589.1 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.42 (s, 1H), 7.76 (d, J = 9.4 Hz, 1H), 7.63 (d, J = 9.2 Hz, 1H), 7.59 (dd, J = 8.9, 2.7 Hz, 1H), 7.44 – 7.39 (m, 2H), 7.36 (d, J = 9.0 Hz, 1H), 4.92 (hept, J = 6.0 Hz, 1H), 4.38 (t, J = 5.1 Hz, 2H), 4.21 (t, J = 5.1 Hz, 2H), 2.71 (s, 3H), 1.79 (s, 3H), 1.37 (d, J = 6.0 Hz, 6H)
369		MS (ESI) m/z 618.4 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 9.37 (s, 1H), 8.50 (s, 1H), 7.96 (s, 1H), 7.60 (dd, J = 8.9, 2.7 Hz, 1H), 7.44 (s, 1H), 7.41 (d, J = 2.6 Hz, 1H), 7.38 (d, J = 9.0 Hz, 1H), 4.64 (d, J = 4.6 Hz, 2H), 4.43 (t, J = 5.0 Hz, 2H), 4.27 (t, J = 4.9 Hz, 2H), 2.79 (d, J = 4.0 Hz, 6H), 2.70 (s, 3H), 1.99 (s, 3H)	390		MS (ESI) m/z 666.3 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.29 (s, 1H), 8.17 (s, 1H), 8.03 (s, 1H), 7.58 (dd, J = 8.9, 2.7 Hz, 1H), 7.51 (s, 1H), 7.43 – 7.39 (m, 2H), 7.33 (d, J = 9.0 Hz, 1H), 4.68 (s, 2H), 4.37 (t, J = 4.4 Hz, 2H), 4.21 (t, J = 4.5 Hz, 2H), 2.71 (s, 3H), 1.79 (s, 3H)
370		MS (ESI) m/z 646.3 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 9.36 (s, 1H), 8.53 (s, 1H), 7.96 (s, 1H), 7.60 (dd, J= 8.9, 2.7 Hz, 1H), 7.44 (s, 1H), 7.42 (d, J = 2.6 Hz, 1H), 7.38 (d, J = 9.0 Hz, 1H), 4.89 (hept, J = 6.0 Hz, 1H), 4.62 (d, J = 4.9 Hz, 2H), 4.42 (t, J = 5.0 Hz, 2H), 4.26 (t, J = 5.0 Hz, 2H), 2.78 (d, J = 4.3 Hz, 6H), 2.69 (s, 3H), 1.93 (s, 3H), 1.42 (d, J = 6.0 Hz, 6H)	391		MS (ESI) m/z 631.1 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.31 (s, 1H), 8.05 (s, 1H), 7.59 (dd, J = 8.9, 2.7 Hz, 1H), 7.45 (s, 1H), 7.42 (d, J = 2.7 Hz, 1H), 7.36 (d, J = 9.0 Hz, 1H), 4.40 (t, J = 5.0 Hz, 2H), 4.24 (t, J = 5.0 Hz, 2H), 3.01 – 2.93 (m, 2H), 2.71 (s, 3H), 1.81 (s, 3H), 1.79 – 1.70 (m, 2H), 1.42 (h, J = 7.4 Hz, 2H), 0.93 (t, J = 7.3 Hz, 3H)

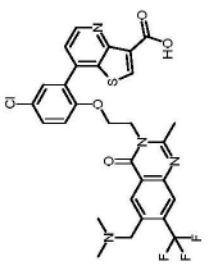
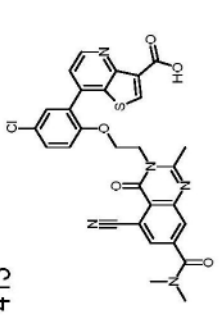
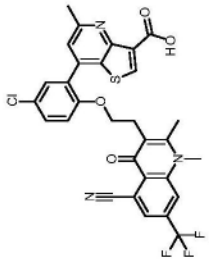
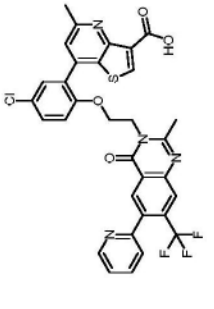
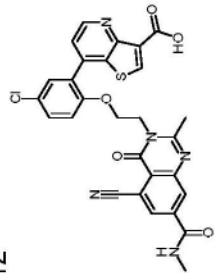
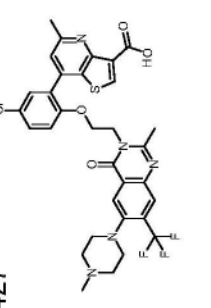
[1218]

392		395		MS (ESI) m/z 656.1 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.66 (dd, J = 5.0, 1.7 Hz, 1H), 8.41 (s, 1H), 7.92 – 7.87 (m, 2H), 7.60 (dd, J = 8.9, 2.7 Hz, 1H), 7.52 (dd, J = 7.7, 4.9 Hz, 1H), 7.45 (s, 1H), 7.44 (d, J = 2.7 Hz, 1H), 7.37 (d, J = 9.0 Hz, 1H), 4.41 (t, J = 5.0 Hz, 2H), 4.32 – 4.18 (m, 2H), 2.73 (s, 3H), 2.29 (s, 3H), 1.86 (s, 3H)	MS (ESI) m/z 674.1 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.66 (d, J = 2.8 Hz, 1H), 8.40 (s, 1H), 7.98 (dd, J = 9.1, 2.9 Hz, 1H), 7.90 (s, 1H), 7.60 (dd, J = 8.9, 2.7 Hz, 1H), 7.45 (s, 1H), 7.43 (d, J = 2.6 Hz, 1H), 7.37 (d, J = 9.0 Hz, 1H), 4.42 (t, J = 5.1 Hz, 2H), 4.35 – 4.17 (m, 2H), 2.74 (s, 3H), 2.25 (s, 3H), 1.89 (s, 3H)
393		396		MS (ESI) m/z 670.0 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.39 (s, 1H), 7.87 (s, 1H), 7.69 (s, 2H), 7.60 (dd, J = 8.9, 2.7 Hz, 1H), 7.44 (s, 1H), 7.42 (d, J = 2.7 Hz, 1H), 7.37 (d, J = 9.0 Hz, 1H), 4.41 (t, J = 5.1 Hz, 2H), 4.27 (t, J = 5.0 Hz, 2H), 2.73 (s, 3H), 2.70 (s, 6H), 1.91 (s, 3H)	MS (ESI) m/z 656.0 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.76 (s, 1H), 8.42 (s, 1H), 7.86 (s, 1H), 7.64 – 7.56 (m, 2H), 7.52 (d, J = 5.0 Hz, 1H), 7.43 (s, 1H), 7.42 (d, J = 2.6 Hz, 1H), 7.37 (d, J = 9.0 Hz, 1H), 4.41 (t, J = 5.1 Hz, 2H), 4.26 (t, J = 5.0 Hz, 2H), 2.73 (s, 3H), 2.64 (s, 3H), 1.90 (s, 3H)
394		397		MS (ESI) m/z 685.1 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.44 (s, 1H), 8.24 (d, J = 2.0 Hz, 1H), 7.88 (d, J = 9.6 Hz, 1H), 7.83 (s, 1H), 7.60 (dd, J = 8.9, 2.7 Hz, 1H), 7.43 (s, 1H), 7.41 (d, J = 2.6 Hz, 1H), 7.37 (d, J = 9.0 Hz, 1H), 7.10 (d, J = 9.2 Hz, 1H), 4.40 (t, J = 5.1 Hz, 2H), 4.26 (t, J = 5.0 Hz, 2H), 3.21 (s, 6H), 2.73 (s, 3H), 1.92 (s, 3H)	MS (ESI) m/z 660.1 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.80 (d, J = 2.8 Hz, 1H), 8.63 (t, J = 1.7 Hz, 1H), 8.43 (s, 1H), 8.12 (ddd, J = 9.6, 2.8, 1.7 Hz, 1H), 7.87 (s, 1H), 7.60 (dd, J = 8.9, 2.7 Hz, 1H), 7.43 (s, 1H), 7.41 (d, J = 2.6 Hz, 1H), 7.37 (d, J = 9.0 Hz, 1H), 4.41 (t, J = 5.1 Hz, 2H), 4.31 – 4.23 (m, 3H), 2.73 (s, 3H), 1.94 (s, 3H)

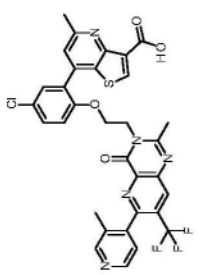
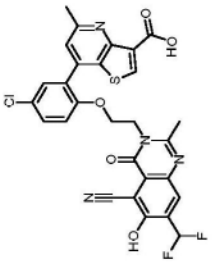
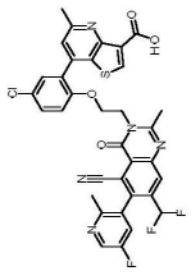
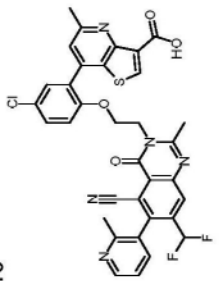
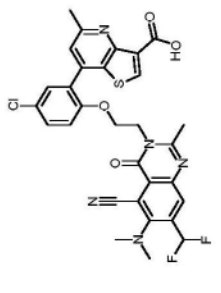
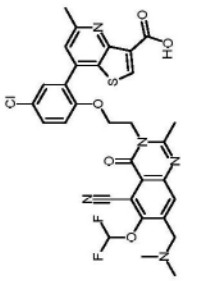
[1219]

399		405		MS (ESI) m/z 547.2 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.86 (d, J = 4.9 Hz, 1H), 8.38 (s, 1H), 7.60 (dd, J = 8.9, 2.6 Hz, 1H), 7.57 (d, J = 2.5 Hz, 1H), 7.54 (d, J = 4.9 Hz, 1H), 7.43 (d, J = 2.7 Hz, 1H), 7.36 (d, J = 9.0 Hz, 1H), 7.11 (d, J = 2.5 Hz, 1H), 4.39 (t, J = 5.0 Hz, 2H), 4.20 (t, J = 5.0 Hz, 2H), 3.99 (s, 3H), 1.72 (s, 3H).	MS (ESI) 699.3 m/z [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 9.02 – 8.95 (m, 2H), 8.67 (tt, J = 7.7, 1.3 Hz, 1H), 8.36 (s, 1H), 8.22 – 8.15 (m, 2H), 7.85 (s, 1H), 7.59 (dd, J = 8.9, 2.7 Hz, 1H), 7.45 – 7.40 (m, 2H), 7.35 (d, J = 9.0 Hz, 1H), 6.22 (s, 2H), 4.37 (t, J = 4.9 Hz, 2H), 4.22 (t, J = 5.0 Hz, 2H), 2.71 (s, 3H), 1.87 (s, 3H)
403		406		MS (ESI) m/z 601.1 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.83 (d, J = 4.9 Hz, 1H), 8.44 (s, 1H), 8.05-8.00 (m, 1H), 7.84 (d, J = 9.1 Hz, 1H), 7.60 (dd, J = 8.9, 2.7 Hz, 1H), 7.51 (d, J = 4.9 Hz, 1H), 7.45 (d, J = 2.6 Hz, 1H), 7.36 (d, J = 9.0 Hz, 1H), 4.41 (t, J = 4.9 Hz, 2H), 4.25 (t, J = 4.9 Hz, 2H), 1.78 (s, 3H)	MS (ESI) m/z 547.1 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.82 (d, J = 4.8 Hz, 1H), 8.33 (s, 1H), 7.88 (d, J = 8.4 Hz, 1H), 7.59 (dd, J = 8.9, 2.7 Hz, 1H), 7.48 (d, J = 4.8 Hz, 1H), 7.41 (d, J = 2.6 Hz, 1H), 7.37 (dd, J = 8.9, 2.9 Hz, 2H), 4.42 (t, J = 5.1 Hz, 2H), 4.24 (t, J = 5.1 Hz, 2H), 3.97 (s, 3H), 1.83 (s, 3H)
404		407		MS (ESI) m/z 569.1 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.82 (d, J = 4.8 Hz, 1H), 8.48 (s, 1H), 8.17 (d, J = 9.5 Hz, 1H), 7.60 (dd, J = 8.9, 2.6 Hz, 1H), 7.50 (d, J = 4.8 Hz, 1H), 7.43 (d, J = 2.7 Hz, 1H), 7.37 (d, J = 9.0 Hz, 1H), 4.42 (t, J = 5.0 Hz, 2H), 4.26 (t, J = 5.0 Hz, 2H), 1.84 (s, 3H)	MS (ESI) m/z 547.2 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.82 (d, J = 4.8 Hz, 1H), 8.41 (s, 1H), 7.76 (d, J = 9.3 Hz, 1H), 7.70 (d, J = 9.3 Hz, 1H), 7.59 (dd, J = 8.9, 2.7 Hz, 1H), 7.47 (d, J = 4.8 Hz, 1H), 7.42 (d, J = 2.6 Hz, 1H), 7.36 (d, J = 8.9 Hz, 1H), 4.39 (t, J = 5.0 Hz, 2H), 4.21 (t, J = 5.0 Hz, 2H), 4.04 (s, 3H), 1.74 (s, 3H)

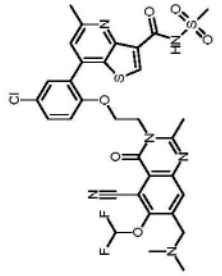
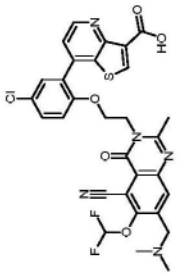
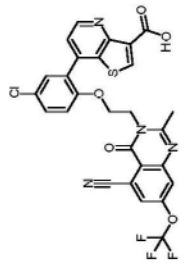
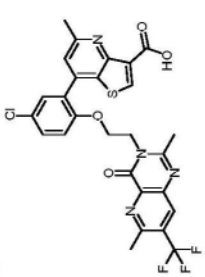
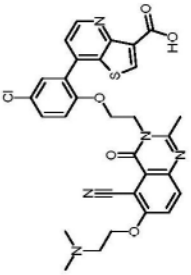
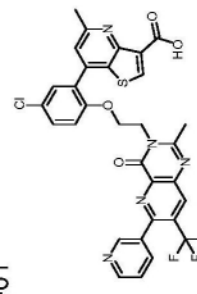
[1220]

408		MS (ESI) m/z 617.2 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.83 (d, J = 4.8 Hz, 1H), 8.54 (s, 1H), 8.19 (s, 1H), 7.80 (s, 1H), 7.60 (dd, J = 8.9, 2.7 Hz, 1H), 7.47 (d, J = 4.8 Hz, 1H), 7.43 (d, J = 2.7 Hz, 1H), 7.36 (d, J = 8.9 Hz, 1H), 4.57 (bs, 2H), 4.40 (t, J = 5.0 Hz, 2H), 4.26 (t, J = 5.0 Hz, 2H), 2.87 (s, 6H), 1.80 (s, 3H)	413		MS (ESI) m/z 588.2 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.83 (d, J = 4.8 Hz, 1H), 8.37 (s, 1H), 7.98 (d, J = 1.4 Hz, 1H), 7.65 (d, J = 2.0 Hz, 1H), 7.60 (dd, J = 8.9, 2.6 Hz, 1H), 7.48 (d, J = 4.8 Hz, 1H), 7.45 (d, J = 2.7 Hz, 1H), 7.35 (d, J = 9.0 Hz, 1H), 4.40 (t, J = 5.3 Hz, 2H), 4.23 (t, J = 5.3 Hz, 2H), 3.05 (s, 3H), 3.01 (s, 3H), 1.69 (s, 3H)
409		MS (ESI) m/z 612.2 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.55 (s, 1H), 8.26 (s, 1H), 8.16 (bd, J = 1.1 Hz, 1H), 7.56 (dd, J = 8.9, 2.7 Hz, 1H), 7.44 (s, 1H), 7.40 (d, J = 2.6 Hz, 1H), 7.37 (d, J = 9.0 Hz, 1H), 4.23 (t, J = 6.1 Hz, 2H), 3.63 (s, 3H), 2.90 (t, J = 6.1 Hz, 2H), 2.70 (s, 3H), 1.94 (s, 3H).	426		MS (ESI) m/z 651.6 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.70 (m, 1H), 8.41 (s, 1H), 8.03 (s, 1H), 7.99 (tdd, J = 7.7, 3.1, 1.8 Hz, 1H), 7.85 (s, 1H), 7.66 (d, J = 7.8 Hz, 1H), 7.59 (dd, J = 8.9, 2.7 Hz, 1H), 7.51 (m, 1H), 7.43 (d, J = 2.6 Hz, 1H), 7.42 (d, J = 2.7 Hz, 1H), 7.34 (d, J = 9.0 Hz, 1H), 4.39 (t, J = 5.0 Hz, 2H), 4.26 (t, J = 5.0 Hz, 2H), 2.69 (s, 3H), 1.85 (s, 3H)
412		MS (ESI) m/z 573.9 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.81 (d, J = 4.9 Hz, 2H), 8.45 (s, 1H), 8.26 (bs, 1H), 8.16 (bs, 1H), 7.59 (dd, J = 8.8, 2.6 Hz, 1H), 7.46 (bs, 1H), 7.44 (bs, 1H), 7.35 (d, J = 9.0 Hz, 1H), 4.40 (t, J = 5.3 Hz, 2H), 4.24 (t, J = 5.3 Hz, 2H), 2.87 (d, J = 4.5 Hz, 3H), 1.78 (s, 3H)	427		MS (ESI) m/z 672.5 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.27 (s, 1H), 7.98 (s, 1H), 7.70 (s, 1H), 7.59 (dd, J = 8.9, 2.7 Hz, 1H), 7.41 (d, J = 2.6 Hz, 1H), 7.39 (s, 1H), 7.35 (d, J = 9.0 Hz, 1H), 4.39 (t, J = 5.1 Hz, 2H), 4.24 (t, J = 5.0 Hz, 3H), 3.59-3.50 (m, 2H), 3.26-3.10 (m, 6H), 2.93 (s, 3H), 2.69 (s, 3H), 1.84 (s, 3H)

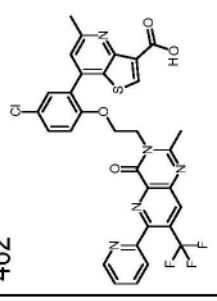
[1221]

436		MS (ESI) m/z 666.5 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.71 (bs, 2H), 8.33 (s, 1H), 8.32 (s, 1H), 7.59 (dd, J = 8.9, 2.7 Hz, 1H), 7.54 (br, 1H), 7.45 (s, 1H), 7.44 (d, J = 2.6 Hz, 1H), 7.36 (d, J = 9.0 Hz, 1H), 4.40 (t, J = 4.5 Hz, 2H), 4.27 (d, J = 4.5 Hz, 2H), 2.74 (s, 3H), 2.06 (bs, 3H), 1.84 (s, 3H)	439b		MS (ESI) m/z 597.0 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.44 (s, 1H), 7.72 (s, 1H), 7.59 (dd, J = 8.9, 2.7 Hz, 1H), 7.42 (d, J = 2.7 Hz, 1H), 7.41 (s, 1H), 7.35 (d, J = 9.0 Hz, 1H), 7.15 (t, J = 54.2 Hz, 1H), 4.38 (t, J = 5.0 Hz, 3H), 4.21 (t, J = 5.0 Hz, 3H), 2.69 (s, 3H), 1.78 (s, 3H)
438		MS (ESI) m/z 690.2 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.65 (d, J = 2.9 Hz, 1H), 8.41 (s, 1H), 7.98 (s, 1H), 7.88 (dd, J = 9.0, 2.9 Hz, 1H), 7.60 (dd, J = 8.9, 2.7 Hz, 1H), 7.45 (s, 1H), 7.43 (d, J = 2.7 Hz, 1H), 7.37 (d, J = 9.0 Hz, 1H), 6.89 (t, J = 53.7 Hz, 1H), 4.48-4.38 (m, 2H), 4.37 – 4.19 (m, 2H), 2.73 (s, 3H), 2.18 (s, 3H), 1.89 (s, 3H)	440		MS (ESI) m/z 671.9 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.73 (dd, J = 5.2, 1.7 Hz, 1H), 8.41 (s, 1H), 7.98 (bd, J = 5.9 Hz, 2H), 7.64 – 7.56 (m, 2H), 7.45 (s, 1H), 7.44 (d, J = 2.7 Hz, 1H), 7.37 (d, J = 9.0 Hz, 1H), 6.84 (t, J = 53.7 Hz, 1H), 4.48 – 4.37 (m, 2H), 4.37 – 4.16 (m, 2H), 2.72 (s, 3H), 2.27 (s, 3H), 1.87 (s, 3H).
439a		MS (ESI) m/z 624.1 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.44 (s, 1H), 7.77 (s, 1H), 7.59 (dd, J = 8.9, 2.7 Hz, 1H), 7.42 (d, J = 2.7 Hz, 1H), 7.41 (s, 1H), 7.36 (d, J = 9.0 Hz, 1H), 7.16 (t, J = 54.4 Hz, 1H), 4.39 (t, J = 5.0 Hz, 2H), 4.22 (t, J = 5.0 Hz, 2H), 2.97 (s, 6H), 2.69 (s, 3H), 1.82 (s, 3H)	449		MS (ESI) m/z 656.6 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.36 (s, 1H), 8.05 (s, 1H), 7.70 – 7.17 (m, 5H), 4.49 (s, 2H), 4.42 (t, J = 5.0 Hz, 2H), 4.27 (t, J = 5.0 Hz, 2H), 2.86 (s, 6H), 2.72 (s, 3H), 1.87 (s, 3H)

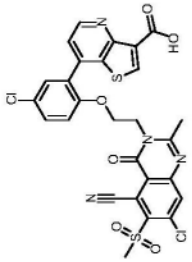
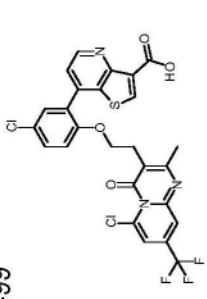
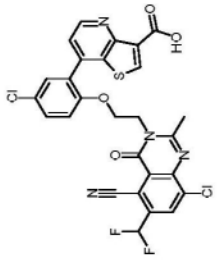
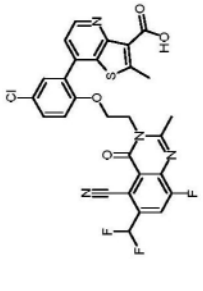
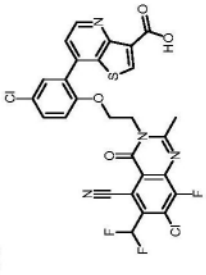
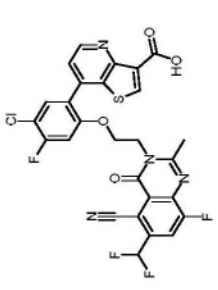
[1222]

451		MS (ESI) m/z 731.3 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.08 (s, 1H), 9.79 (s, 1H), 8.40 (s, 1H), 7.97 (s, 1H), 7.62 (dd, J = 8.9, 2.7 Hz, 1H), 7.51 (s, 1H), 7.44 – 7.36 (m, 2H), 7.25 (s, 1H), 4.51 (s, 2H), 4.43 (d, J = 5.3 Hz, 2H), 4.27 (d, J = 5.1 Hz, 2H), 3.56 (s, 3H), 2.85 (s, 6H), 2.74 (s, 3H), 1.83 (s, 3H)	
458		MS (ESI) m/z 640.1 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.78 (d, J = 4.8 Hz, 1H), 8.39 (s, 1H), 8.04 (s, 1H), 7.63 – 7.17 (m, 5H), 4.54 – 4.42 (m, 2H), 4.39 (t, J = 5.0 Hz, 2H), 4.24 (t, J = 5.0 Hz, 2H), 2.83 (s, 6H), 1.79 (s, 3H)	
456		MS (ESI) m/z 601.2 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.80 (d, J = 4.7 Hz, 1H), 8.35 (s, 1H), 8.07 – 8.03 (m, 1H), 7.60 – 7.56 (m, 1H), 7.55 (d, J = 2.7 Hz, 1H), 7.45 (d, J = 4.8 Hz, 1H), 7.41 (d, J = 2.7 Hz, 1H), 7.32 (d, J = 9.0 Hz, 1H), 4.36 (t, J = 5.0 Hz, 2H), 4.20 (t, J = 5.0 Hz, 2H), 1.70 (s, 3H)	
460		LCMS: 708.6 [M+H]+ ; 1H NMR (400 MHz, DMSO-d6) δ 8.25 (s, 1H), 8.05 (s, 1H), 7.59 (dd, J = 8.9, 2.7 Hz, 1H), 7.44 – 7.38 (m, 2H), 7.35 (d, J = 8.9 Hz, 1H), 4.38 (t, J = 5.0 Hz, 2H), 4.24 (t, J = 5.0 Hz, 2H), 2.75 (d, J = 1.6 Hz, 3H), 2.69 (s, 3H), 1.78 (s, 3H)	
457		MS (ESI) m/z 604.2 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.78 (d, J = 4.8 Hz, 1H), 8.36 (s, 1H), 7.78 (d, J = 9.3 Hz, 1H), 7.70 (d, J = 9.2 Hz, 1H), 7.57 (dd, J = 9.0, 2.7 Hz, 1H), 7.44 (d, J = 4.8 Hz, 1H), 7.39 (d, J = 2.7 Hz, 1H), 7.33 (d, J = 9.0 Hz, 1H), 4.68 – 4.55 (m, 2H), 4.36 (t, J = 5.1 Hz, 2H), 4.20 (d, J = 5.2 Hz, 2H), 3.62 (s, 2H), 2.96 – 2.87 (m, 7H), 1.77 (s, 3H)	
461		LCMS: 652.5 [M+H]+; 1H NMR (400 MHz, DMSO-d6) δ 8.76 (s, 2H), 8.34 (s, 1H), 8.28 (s, 1H), 8.01 (d, J = 7.9 Hz, 1H), 7.61 (d, J = 11.7, 8.4, 3.8 Hz, 2H), 7.46 – 7.41 (m, 2H), 7.36 (d, J = 9.0 Hz, 1H), 4.41 (t, J = 5.0 Hz, 2H), 4.27 (t, J = 5.0 Hz, 2H), 2.72 (s, 3H), 1.84 (s, 3H)	

[1223]

462		LCMS: 652.5.6 [M+H]+; 1H NMR (400 MHz, DMSO-d6) δ 8.69 (dd, J = 4.9, 1.6 Hz, 1H), 8.40 (s, 1H), 8.30 (s, 1H), 8.03 (td, J = 7.7, 1.8 Hz, 1H), 7.84 (d, J = 8.0 Hz, 1H), 7.61 – 7.52 (m, 2H), 7.45 – 7.41 (m, 2H), 7.35 (d, J = 9.0 Hz, 1H), 4.40 (t, J = 5.0 Hz, 2H), 4.27 (t, J = 5.1 Hz, 2H), 2.70 (s, 3H), 1.82 (s, 3H)
463		LCMS: 666.6 [M+H]+; 1H NMR (400 MHz, DMSO-d6) δ 8.76 (d, J = 5.5 Hz, 1H), 8.31 (d, J = 6.8 Hz, 2H), 7.67 (s, 1H), 7.59 (dd, J = 8.9, 2.8 Hz, 2H), 7.45 – 7.41 (m, 2H), 7.35 (d, J = 9.0 Hz, 1H), 4.40 (t, J = 5.0 Hz, 2H), 4.27 (t, J = 5.0 Hz, 2H), 2.73 (s, 3H), 2.67 (s, 3H), 1.84 (s, 3H)
464		LCMS: 652.5 [M+H]+; 1H NMR (400 MHz, DMSO-d6); 1H NMR (400 MHz, DMSO-d6) δ 8.84 (s, 2H), 8.35 (s, 1H), 8.30 (s, 1H), 7.69 (d, J = 5.5 Hz, 2H), 7.59 (dd, J = 8.9, 2.7 Hz, 1H), 7.46 – 7.41 (m, 2H), 7.36 (d, J = 9.0 Hz, 1H), 4.40 (t, J = 4.9 Hz, 2H), 4.27 (t, J = 4.9 Hz, 2H), 2.73 (s, 3H), 1.84 (s, 3H)
467		LCMS: 651.8 [M+H]+; 1H NMR (400 MHz, DMSO-d6) δ 8.36 (s, 1H), 8.24 (s, 1H), 7.59 (dd, J = 8.9, 2.7 Hz, 1H), 7.53 (s, 5H), 7.43 (d, J = 3.1 Hz, 2H), 7.36 (d, J = 9.0 Hz, 1H), 4.40 (t, J = 5.0 Hz, 2H), 4.26 (t, J = 4.9 Hz, 2H), 2.71 (s, 3H), 1.83 (s, 3H)
488		LCMS: 635.9 [M+H]+; 1H NMR (400 MHz, 甲醇-d4) δ 8.40 (s, 1H), 7.93 (d, J = 9.8 Hz, 1H), 7.58 – 7.51 (m, 2H), 7.42 (d, J = 2.6 Hz, 1H), 7.29 (d, J = 8.9 Hz, 1H), 7.23 (s, 1H), 4.48 (t, J = 4.8 Hz, 2H), 4.40 (t, J = 4.7 Hz, 2H), 2.91 (s, 3H), 2.11 (s, 3H)
490		MS (ESI) m/z 593.7 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.14 (dd, J = 7.3, 1.5 Hz, 1H), 8.04 (d, J = 9.7 Hz, 1H), 7.61 (dd, J = 8.9, 2.7 Hz, 1H), 7.58 (s, 1H), 7.51 – 7.46 (m, 1H), 7.39 (s, 1H), 7.36 (d, J = 4.1 Hz, 1H), 7.33 (d, J = 2.6 Hz, 1H), 7.31 – 7.25 (m, 1H), 7.22 (s, 0H), 4.50 – 4.08 (m, 4H), 2.78 (s, 3H), 1.84 (s, 3H)

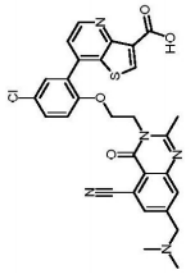
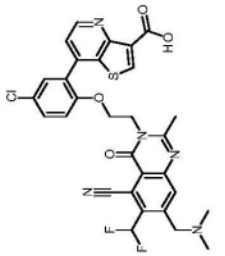
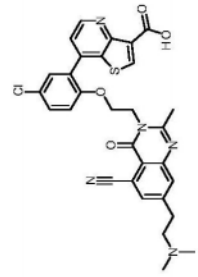
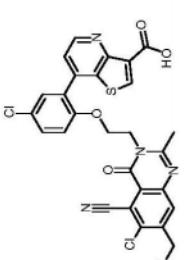
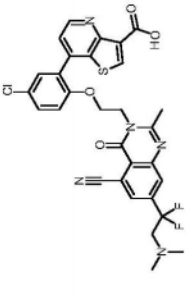
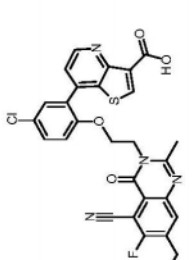
[1224]

493		MS (ESI) m/z 627.12 [M-1]-; 1H NMR (400 MHz, DMSO-d6) δ 13.29 (bs, 1H), 8.84 (d, J = 4.68, 1H), 8.38 (s, 1H), 7.89 (s, 1H), 7.60 (dd, J = 2.56, 9.3 Hz, 1H), 7.47 (d, J = 4.6 Hz, 1H), 7.42 (d, J = 1.96 Hz, 1H),7.34 (d, J = 8.84 Hz, 1H) 4.39 (t, J = 4.7 Hz, 2H), 4.23 (t, J = 4.76, 2H), 3.60 (s, 3H), 1.75 (s, 3H)	499		MS (ESI) m/z 593.13 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 9.03 (s, 1 H), 8.85 (d, J = 4.8 Hz, 1H), 7.83 (d, J = 3.6 Hz, 2H), 7.64 (s, 1H), 7.60 (dd, J = 8.8Hz, 2.46 Hz, 1H), 7.32 (d, J = 8.8 Hz, 1H), 6.98 (s, 1H), 3.63 (t, J = 6.8 Hz, 2H), 2.90 (t, J = 7.2 Hz, 2H), 2.39 (s, 3H)
497		MS (ESI) m/z 619.47 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.80 (d, J = 4.8 Hz, 1H), 8.54 (s, 1H), 8.28 (s, 1H), 7.60 (dd, J = 8.88, 2.68 Hz 1H), 7.47-7.21 (m, 4H), 4.42 (t, J = 5.12, 2H), 4.28 (t, J = 4.88 Hz, 2H), 1.89 (s, 3H)	500		MS (ESI) m/z 599.53 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.77 (d, J = 4.92 Hz, 1H), 8.08 (d, J = 9.72 Hz, 1H), 7.61 (dd, J = 8.80, 2.64 Hz, 1H), 7.53 (d, J = 4.96 Hz, 1H), 7.49-7.22 (m, 3H), 4.44 (t, J = 5.40 Hz, 2H), 4.29 (t, J = 4.84 Hz, 2H). 2.60-2.40 (合并的, 3H), 1.96 (s, 3H)
498		MS (ESI) m/z 619.47 [M+1]+. 1H NMR (400 MHz, DMSO-d6) δ 8.82 (d, J = 4.8Hz, 1H), 8.44 (s, 1H), 7.66-7.59 (m, 5H), 4.42 (t, J = 9.04 Hz, 2H), 4.27 (t, J = 8.6Hz, 2H), 1.84 (s, 3H)	504		MS (ESI) m/z 603.0 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.82 (d, J = 4.80 Hz, 1H), 8.46 (s, 1H), 8.05 (d, J = 9.60 Hz, 1H), 7.65 (d, J = 8.32 Hz, 1H), 7.56 (d, J = 11.32 Hz, 1H), 7.51-7.36 (m, 2H), 4.45 (t, J = 4.72 Hz, 2H), 4.28 (t, J = 6.96 Hz, 2H), 1.86 (s, 3H)

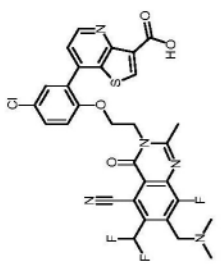
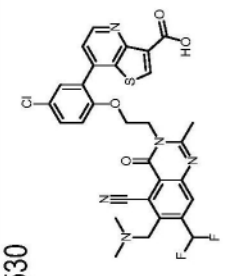
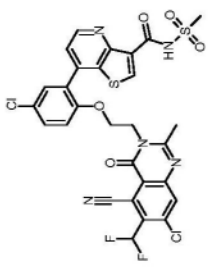
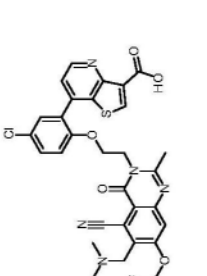
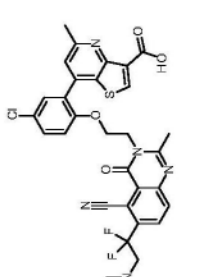
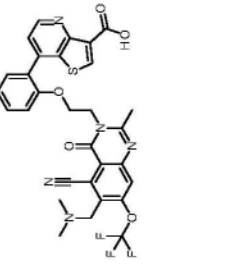
[1225]

506		509	
MS (ESI) m/z 571.10 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.84 (d, J = 4.48 Hz, 1H), 8.41 (s, 1H), 7.74-7.70 (m, 1H), 7.62 (d, J = 8.36 Hz, 1H), 7.55 (d, J = 11.28 Hz, 1H), 7.48 (d, J = 4.48 Hz, 1H), 4.42 (t, J = 4.20 Hz, 2H). 4.23 (t, J = 4.20 Hz, 2H), 1.75 (s, 3H)		MS (ESI) m/z 608.16 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.24 (bs, 1H), 8.82 (d, J = 4.72 Hz, 1H), 8.35 (bs, 1H), 7.79 (bs, 1H), 7.60 (dd, J = 2.44, 8.84 Hz, 1H), 7.47 (d, J = 4.72 Hz, 1H), 7.42 (d, J = 2.56 Hz, 1H), 7.35 (d, J = 8.92 Hz, 1H), 4.39 (t, J = 5.4 Hz, 2H), 4.23 (t, J = 6.12 Hz, 2H), 3.75 (bs, 2H), 2.26 (bs, 6H), 1.77 (s, 3H)	
507		510	
MS (ESI) m/z 588.17 [M+1]+; 1H-NMR (400 MHz, DMSO-d6) δ 13.30 (bs, 1H), 9.71 (bs, 1H), 8.81 (d, J = 4.76 Hz ,1H), 8.35 (s, 1H), 7.91(d, J = 8.52 Hz,1H),7.68 (d, J = 8.4 Hz, 1H), 7.60 (dd, J = 2.40, 8.84 Hz, 1H), 7.46 (d, J = 4.72 Hz, 1H),7.42 (d, J = 2.5 Hz, 1H) ,7.37 (d, J = 8.88 Hz, 1H), 4.40 (s, 2H), 4.25 (s, 2H), 3.4-3.41 (m, 2H), 3.33 (t, J = 3.84 Hz ,2H), 2.92 (s, 6H) ,1.83 (s, 3H)		MS (ESI) m/z 599.1 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ, 8.84 (d, J = 4.76 Hz, 1H), 8.26 (s, 2H), 7.61 (dd, J = 8.84, 2.52 Hz, 1H), 7.48 (d, J = 4.76, Hz, 1H), 7.43 (d, J = 2.56 Hz, 1H), 7.37 (d, J = 8.96 Hz, 1H), 4.55 (bs, 2H), 4.42 (bs, 2H), 4.27 (b s, 2H), 2.90 (bs, 6H), 1.82 (s, 3H)	
508		511	
MS (ESI) m/z 592.16 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 10.23 (bs, 1H), 8.81 (d, J = 4.60 Hz, 1H), 8.34 (s, 1H), 8.09 (d, J = 10.08 Hz, 1H), 7.61-7.58 (m, 1H), 7.48 (d, J = 4.64 Hz, 1H), 7.42 (d, J = 2.0 Hz, 1H), 7.38 (d, J = 8.88 Hz, 1H), 4.58 (bs, 2H), 4.43 (t, J = 6.08 Hz, 2H), 4.28 (t, J = 5.24 Hz, 2H), 2.90 (s, 6H), 1.87 (s, 3H)		MS (ESI) m/z 598.21 [M+1]+; 1H-NMR (400 MHz, DMSO-d6) δ 8.84 (d, J = 4.72 Hz,1H), 8.32 (s, 1H), 8.24 (s, 1H), 7.59 (dd, J = 2.44, 2.48 Hz, 1H), 7.45 (d, J = 4.72 Hz, 1H), 7.40-7.36 (m, 2H), 6.06 (s, 1H), 4.59 (bs, 2H), 4.43 (t, J = 4.36 Hz, 2H), 4.24 (t, J = 4.68 Hz, 2H), 2.93 (bs, 6H), 1.69 (s, 3H)	

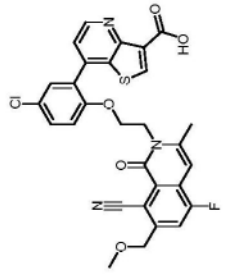
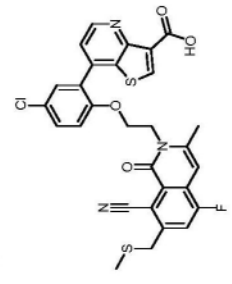
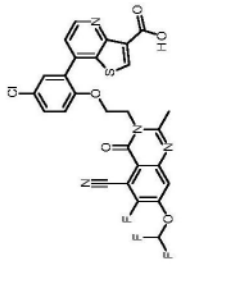
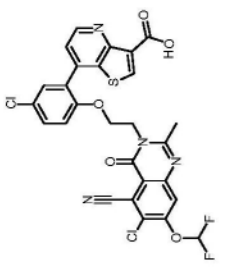
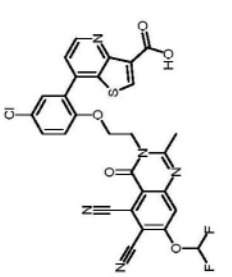
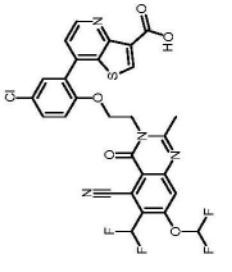
[1226]

512		MS (ESI) m/z 574.38.[M+1]+; 1H-NMR (400 MHz, DMSO-d6) δ 9.96 (bs, 1H), 8.82 (d, J = 4.72 Hz ,1H), 8.36 (s, 1H), 8.08 (s, 1H), 7.83 (s, 1H), 7.61 (dd, J = 2.32, 8.84 Hz, 1H), 7.49 (d, J = 4.68 Hz),7.44 (d, J= 2.32, 1H),7.38 (d = 8.96 Hz), 4.46 (s, 2H), 4.41 (t, J = 5.12 Hz, 2H), 4.25 (t, J = 5.08 Hz, 2H), 2.83 (s, 6H), 1.79 (s, 3H)	515		MS (ESI) m/z 624.14 [M+1]+. 1H-NMR (400 MHz, DMSO-d6) δ 9.69 (bs, 1H), 8.80 (d, J = 4.4 Hz, 1H), 8.46 (s, 1H), 8.05 (bs, 1H), 7.68-7.35 (m, 5H), 4.64 (bs, 2H), 4.41 (s, 2H), 4.26 (s, 2H), 2.83 (bs, 6H), 1.79 (s, 3H)
513		MS (ESI) m/z 588.22 [M+1]+. 1H-NMR (400 MHz, DMSO-d6) δ.9.49 (bs, 1H), 8.86 (dd, J = 4.76, 8.85 Hz, 1H), 8.28 (s, 1H), 7.97 (s, 1H), 7.60 (s, 1H),7.59 (d, J = 7.59 Hz, 1H), 7.45 (d, J = 2.28, Hz, 1H), 7.42 (d, J = 2.52 Hz, 1H), 7.35 (d, J = 8.92 Hz, 1H), 4.40 (t, J = 5.76 Hz, 2H), 4.22 (t, J = 6.32 Hz, 2H), 3.51 (t, J = 4.56. Hz, 2H), 3.18 (t, J = 8.0 Hz, 2H), 2.88 (s, 6H), 1.75 (s, 3H)	516		MS (ESI) m/z 607.9 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.81 (d, J = 4.76 Hz, 1H), 8.39 (s, 1H), 7.75 (s, 1H), 7.59 (dd, J = 8.8, 2.4 Hz, 1H), 7.46 (d, J = 4.76 Hz, 1H), 7.42 (d, J = 2.56 Hz, 1H), 7.35 (d, J = 9.0 Hz, 1H), 4.39 (t, J = 5.8 Hz, 2H), 4.23 (t, J = 5.3 Hz, 2H), 3.63 (s, 2H), 2.28 (s, 6H), 1.77 (s, 3H)
514		MS (ESI) m/z 623.97 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.82 (bs, 1H), 8.20 (s, 1H), 8.08 (s, 1H), 7.88 (s, 1H), 7.56 (d, J = 9.0 Hz, 1H), 7.45-7.36 (m, 2H), 7.32 (d, J = 8.92 Hz, 1H), 4.37 (t, J = 4.44 Hz, 2H) 4.23 (t, J = 4.08 Hz, 2H), 3.21 (t, J = 14.48 Hz, 2H), 2.25 (s, 6H), 1.75 (s, 3H).	517		MS (ESI) m/z 592.02 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 9.98 (bs, 1H), 8.81 (d, J = 4.68 Hz, 1H), 8.41 (s, 1H), 8.00 (d, J = 6.56 Hz, 1H), 7.60 (dd, J = 8.76, 2.28 Hz, 1H), 7.47 (d, J = 4.68 Hz, 1H), 7.42 (d, J = 2.23 Hz, 1H), 7.37 (d, J = 8.96 Hz, 1H), 4.53 (s, 2H), 4.41 (t, J = 6.24 Hz, 2H), 4.26 (t, J = 6.28 Hz, 2H), 2.89 (s, 6H), 1.80 (s, 3H)

[1227]

518		MS (ESI) m/z 642.14 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.79 (d, J = 4.4 Hz, 1H), 8.45 (s, 1H), 7.49 (m, 5H), 4.63 (bs, 2H), 4.43 (bs, 2H), 4.29 (bs, 2H), 2.83 (bs, 6H), 1.86 (s, 3H)	530		MS (ESI) m/z 623.97 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.28 (bs, 1H), 8.80 (d, J = 4.72 Hz, 1H), 8.27 (s, 1H), 7.95 (s, 1H), 7.62-7.32 (m, 5H), 4.62 (s, 2H), 4.41 (t, J = 4.92 Hz, 2H), 4.26 (t, J = 5.40 Hz, 2H), 2.87 (s, 6H), 1.79 (s, 3H)
520		MS (ESI) m/z 678.03 [M+1]+. 1H NMR (400 MHz, DMSO-d6) δ 12.65 (bs, 1H), 8.89 (d, J = 4.12 Hz, 1H), 8.48 (s, 1H), 7.90 (s, 1H), 7.65-7.35 (m, 5H), 4.40 (t, J = 5.18 Hz, 2H), 4.23 (t, J = 6.72 Hz, 2H), 3.56 (s, 3H), 1.71 (s, 3H)	531		MS (ESI) m/z 640.12 [M+1]+; 1H-NMR (400 MHz, DMSO-d6) δ 13.40 (bs, 1H), 9.88 (bs,1H), 8.83 (d, J = 4.48 Hz ,1H), 8.34 (s, 1H),7.74-7.35 (m, 6H), 4.54 (s, 2H), 4.41 (t, J = 5.6 Hz, 2H), 4.25 (t, J = 5.6 Hz, 2H), 2.94 (s, 6H), 1.76 (s, 3H)
529		MS (ESI) m/z 638.20 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.59 (bs, 1H), 8.38 (s, 1H), 8.04 (d, J = 8.72 Hz, 1H), 7.77 (d, J = 8.20 Hz, 1H), 7.80-7.55 (m, 1H), 7.42-7.40 (m, 2H), 7.35 (d, J = 9.00 Hz, 1H), 4.40 (t, J = 4.52 Hz, 2H), 4.25 (t, J = 5.16 Hz, 2H), 2.69 (s, 3H), 2.60-2.20 (合并的, 8H), 1.83 (s, 3H)	532		MS (ESI) m/z 658.20 [M+1]+. 1H NMR (400 MHz, DMSO-d6) δ 10.03 (bs, 1H), 8.84 (d, J = 3.04 Hz, 1H), 8.28 (s, 1H), 7.60 (bs, 2H), 7.47-7.35 (m, 3H), 4.59 (s, 2H), 4.41 (t, J = 4.92 Hz, 2H), 4.26 (t, J = 4.72 Hz, 2H), 2.90 (s, 6H), 1.76 (s, 3H)

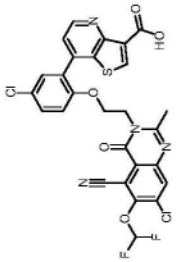
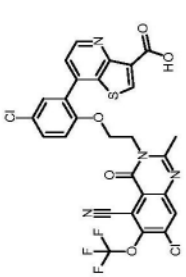
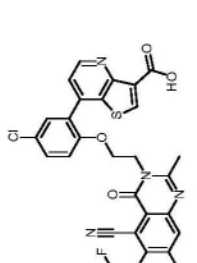
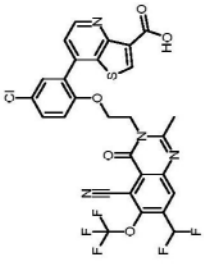
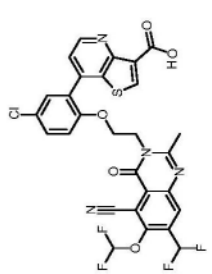
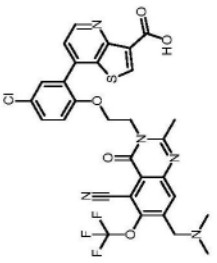
[1228]

533		MS (ESI) m/z 578.18 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.82 (d, J = 4.76 Hz, 1H), 8.37 (s, 1H), 7.67 (d, J = 10.08Hz, 1H), 7.59-7.56 (dd, J = 2.6, 2.56 Hz, 1H), 7.45 (d, J = 4.64 Hz, 1H), 7.40-7.35 (m, 2H), 5.97 (s, 1H), 4.69 (s, 2H), 4.40 (t, J = 4.64 Hz, 2H), 4.21 (t, J = 4.64 Hz, 2H), 3.42 (s, 3H), 1.68 (s, 3H)
534		MS (ESI) m/z 594.04. [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.81 (d, J = 4.72 Hz, 1H), 8.37 (s, 1H), 7.73 (d, J = 10.16 Hz, 1H), 7.58-7.56 (dd, J = 2.48, 2.28 Hz, 1H), 7.44-7.37 (m, 3H), 5.98 (s, 1H) 4.40 (t, J = 5.30 Hz, 2H), 4.20 (t, J = 4.54 Hz, 2H), 3.98 (s, 2H), 2.04 (s, 3H), 1.66 (s, 3H)
536		MS (ESI) m/z 601.05 [M+1]+. 1H NMR (400 MHz, DMSO-d6) δ 8.85 (d, J = 4.72 Hz, 1H), 8.47 (s, 1H), 7.72-7.34 (m, 6H), 4.39 (t, J = 6.4 Hz, 2H), 4.22 (t, J = 6.4 Hz, 2H), 1.71 (s, 3H)
537		MS (ESI) m/z 615.03 [M-1] ; 1H NMR (400 MHz, DMSO-d6) δ 8.85 (d, J = 4.5 Hz, 1H), 8.49 (s, 1H), 7.76-7.33 (m, 6H), 4.88 (t, J = 5.4 Hz, 2H), 4.23 (t, J = 6.1 Hz, 2H), 1.69 (s, 3H)
538		MS (ESI) m/z 608.15 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.39 (bs, 1H), 8.85 (d, J = 4.7 Hz, 1H), 8.43 (s, 1H), 7.83-7.33 (m, 6H), 4.39 (bs, 2H), 4.25 (bs, 2H), 1.72 (s, 3H)
539		MS (ESI) m/z 633.2 [M+1]+. 1H NMR (400 MHz, DMSO-d6) δ 13.49 (bs, 1H), 8.84 (d, J = 4.8 Hz, 1H), 8.49 (s, 1H), 7.75-7.24 (m, 7H), 4.39 (t, J = 4.16 Hz, 2H), 4.24 (t, J = 5.0 Hz, 2H), 1.70 (s, 3H)

[1229]

540		MS (ESI) m/z 651.13 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.85 (d, J = 4.76 Hz, 1H), 8.48 (s, 1H), 7.78-7.48 (m, 4H), 7.44 (d, J = 2.6 Hz, 1H), 7.36 (d, J = 9.0 Hz, 1H), 4.39 (t, J = 4.56 Hz, 2H), 4.29 (t, J = 4.52 Hz, 2H), 1.70 (s, 3H)
541		MS (ESI) m/z 649.16 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.85 (d, J = 4.76, 1H), 8.47 (s, 1H), 7.93 (s, 1H), 7.93 (s, 1H), 7.59 (dd, J = 8.88, 2.52 ,1H), 7.48-6.83 (m, 5H), 4.38 (t, J = 5.48 Hz, 2H), 4.22 (t, J=4.84, 2H), 1.73(s, 3H)
542		MS (ESI) m/z 635.09 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.33 (bs, 1H), 8.83 (d, J = 4.76 Hz, 1H), 8.367 (s, 1H), 7.76 (d, J = 1.32, 1H), 7.58 (dd, J = 2.6 Hz, J = 8.88 Hz, 1H), 7.48 (d, J = 4.76 Hz, 1H), 7.43 (d, J = 1.76 Hz, 1H) 7.34 (d, J = 8.92 Hz, 1H), 4.39 (s, 2H), 4.23 (s, 2H), 1.74 (s, 3H)
543		MS (ESI) m/z 626.11 [M+1]+; 1H-NMR (400 MHz, DMSO-d6) δ 8.85 (d, J = 4.76 Hz, 1H), 8.34 (s, 1H), 7.76 (s, 1H), 7.60 (dd, J =8.80, 2.44 Hz, 1H), 7.49 (d, J = 4.68 Hz, 1H), 7.43 (d, J = 2.48 Hz, 1H), 7.35 (d, J = 8.96 Hz, 1H) 4.40 (t, J = 4.32 Hz, 2H), 4.25 (t, J = 4.12 Hz, 2H), 1.74 (s, 3H)
544		MS (ESI) m/z 626.11 [M+1]+; 1H-NMR (400 MHz, DMSO-d6) δ 8.85 (d, J = 4.76 Hz, 1H), 8.34 (s, 1H), 7.76 (s, 1H), 7.60 (dd, J =8.80, 2.44 Hz, 1H), 7.49 (d, J = 4.68 Hz, 1H), 7.43 (d, J = 2.48 Hz, 1H), 7.35 (d, J = 8.96 Hz, 1H) 4.40 (t, J = 4.32 Hz, 2H), 4.25 (t, J = 4.12 Hz, 2H), 1.74 (s, 3H)
545		MS (ESI) m/z 601.18 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.82 (d, J = 4.76 Hz, 1H), 8.44 (s, 1H), 7.69 (d, J = 10.76 Hz, 1H), 7.60 (dd, J = 2.64, 8.76 Hz, 1H), 7.48 (d, J = 4.68 Hz, 1H), 7.42 (d, J = 2.68 Hz, 1H), 7.41 (t, J = 71.52 Hz, 1H), 7.35 (d, J = 8.92 Hz, 1H), 4.38 (t, J = 4.44 Hz, 2H), 4.23 (t, J = 4.44 Hz, 2H), 1.77 (s, 3H)

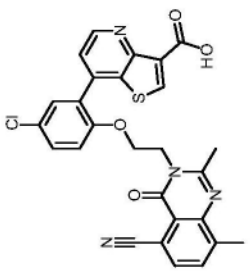
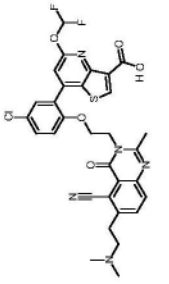
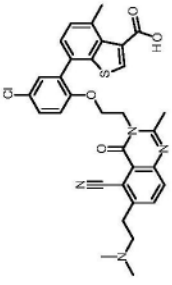
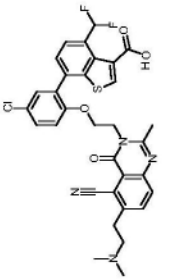
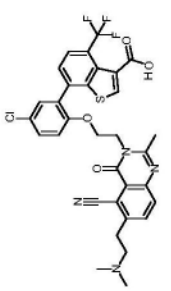
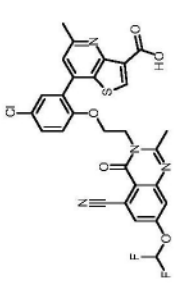
[1230]

546		MS (ESI) m/z 617.13 [M+1]+. 1H NMR (400 MHz, DMSO-d6) δ 8.84 (d, J = 4.68 Hz, 1H), 8.41 (s, 1H), 7.92 (s, 1H), 7.60 (dd, J = 2.60, 9.52 Hz, 1H), 7.50 (d, J = 4.56 Hz, 1H), 7.42 (d, J = 1.84 Hz, 1H), 7.36 (bs, 1H), 7.35 (t, J = 71.96 Hz, 1H), 4.39 (t, J = 5.08 Hz, 2H), 4.23 (t, J = 5.08 Hz, 2H), 1.76 (s, 3H)	550		MS (ESI) m/z 635.09 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8. 84 (d, J = 4.8 Hz, 1H), 8.41 (s, 1H), 8.00 (s, 1H), 7.60 (dd, J =2.52 Hz, 8.84 Hz, 1H), 7.50 (d, J = 4.76, 1H), 7.45 (d, J = 2.48, 1H), 7.36 (d, J = 8.96 Hz, 1H), 4.40 (t, J = 4.48 Hz, 2H), 4.24 (t, J = 4.32 Hz, 2H), 1.75 (s, 3H)
547		MS (ESI) m/z 608.10 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.25 (bs, 1H), 8.86-8.79 (m, 1H), 8.60-8.49 (m, 2H), 7.72-7.33 (m, 5H), 4.46-4.36 (m, 2H), 4.33-4.24 (m, 2H), 1.94 (s, 3H)	551		MS (ESI) m/z 650.9 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.82 (d, J = 4.76 Hz, 1H), 8.38 (s, 1H), 8.04 (s, 1H), 7.59 (dd, J = 8.92, 2.40 Hz, 1H), 7.48-7.19 (m, 4H), 4.40 (t, J = 5.6 Hz, 2H), 4.25 (t, J = 5.6 Hz, 2), 1.76 (s, 3H).
548		MS (ESI) m/z 633.07 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.77 (d, J = 4.76 Hz, 1H), 8.57 (s, 1H), 8.04 (s, 1H), 7.81-7.35 (m, 6H), 4.41 (t, J = 5.04 Hz, 2H), 4.25 (t, J = 4.84 Hz, 2H), 1.81 (s, 3H)	552		MS (ESI) m/z 658.16 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.80 (d, J = 4.7Hz, 1H), 8.48 (s, 1H), 8.17 (s, 1H), 7.62-7.59 (m, 1H), 7.46 (t, J = 4.2Hz, 2H), 7.37 (d, J = 8.9Hz, 1H), 4.5 (bs, 2H), 4.41 (t, J = 4.3Hz, 2H), 4.26 (t, J = 4.3Hz, 2H), 2.86 (s, 6H), 1.80 (s, 3H).

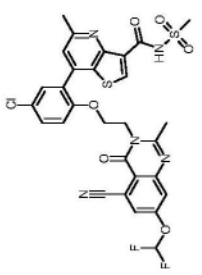
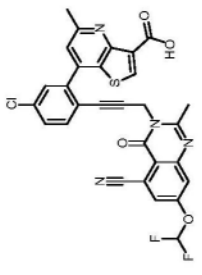
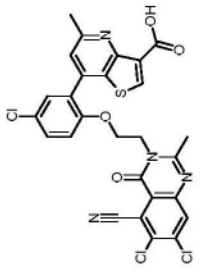
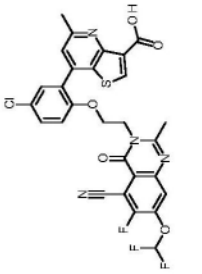
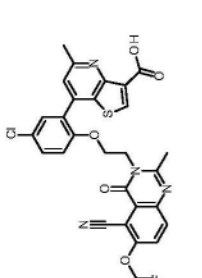
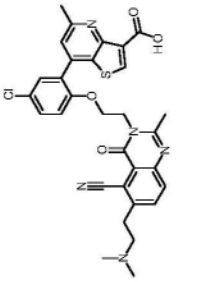
[1231]

557	MS (ESI) m/z 579.03 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 12.96 (bs, 1H), 8.73 (d, J = 4.7 Hz, 1H), 8.66 (s, 1H), 8.13 (d, J = 9.7 Hz, 1H), 7.76 (d, J = 9.0 Hz, 1H), 7.68 (m, 2H), 7.53 (d, J = 4.7 Hz, 1H), 7.37 (t, J = 53.7 Hz, 1H), 4.88 (s, 2H), 2.22 (s, 3H)	570	MS (ESI) m/z 676.14 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 12.34 (bs, 1H), 8.80 (s, 1H), 8.12 (d, J = 10.0 Hz, 1H), 7.56 (dd, J = 8.8 Hz 2.80 Hz, 1H), 7.49-7.22 (m, 4H), 4.38 (t, J = 5.20 Hz, 2H), 4.245 (t, J = 4.40 Hz , 2H), 2.63 (s, 3H). 1.98 (s, 3 H), 1.75 (s, 3H)
566	MS (ESI) m/z 676.15 [M+1]+.1H NMR (400 MHz, DMSO-d6) δ 12.93 (bs, 1H), 8.06 (d, J = 9.72 Hz, 1H), 7.60 (dd, J = 8.80, 2.40 Hz, 1H), 7.48-7.22 (m, 4H), 4.43 (t, J = 4.6 Hz, 2H), 4. 28 (t, J = 4.8Hz, 2H), 3.5 (s, 3H), 2.69 (s, 3H), 1.94 (s, 3H)	572	MS (ESI) m/z 531.22 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.80 (d, J = 4.72 Hz, 1H), 8.39 (s, 1H), 7.83 (d, J = 8.64 Hz, 1H), 7.58 (d, J = 8.64 Hz, 2H), 7.48 (d, J = 4.84 Hz, 1H), 7.42 (d, J = 2.52 Hz, 1H), 7.35 (d, J = 9.0 Hz, 1H), 4.41-4.38 (m, 2H), 4.24-4.23 (m, 2H), 2.60 (s, 3H), 1.79 (s, 3H)
567	MS (ESI) m/z 644.09 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 12.99 (s, 1H), 8.48 (s, 1H), 7.73 (dd, J = 7.88, 10.80 Hz, 1H), 7.60 (dd, J = 2.44, 8.88 Hz, 1H), 7.48 (s, 1H), 7.40 (d, J = 2.60 Hz, 1H), 7.36 (d, J = 9.2 Hz, 1H), 4.41 (t, J = 5.12 Hz, 2H). 4.23 (t, J = 4.28 Hz, 2H), 3.57 (s, 3H), 2.71 (s, 3H), 1.80 (s, 3H)	573	MS (ESI) m/z 531.18 [M+1]+; 1H-NMR (400 MHz, DMSO-d6) δ 8.82 (d, J = 4.04 Hz ,1H), 8.30 (s, 1H), 7.79 (s, 1H), 7.58 (d, J = 8.88 Hz, 1H), 7.46 (m, 2H), 7.41 (m, 2H), 7.35 (d, J = 9.08 Hz, 1H), 4.35 (s, 2H), 4.19 (s, 2H), 2.49 (s, 3H), 1.81 (s, 3H)

[1232]

574		MS (ESI) m/z 531.2 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.26 (bs, 1H), 8.80 (d, J= 4.68 Hz, 1H), 8.43(s, 1H), 7.82 (d, J = 7.56, 1H), 7.55 (d, J = 7.68, 1H), 7.59 (dd, J = 2.44, 2.48 Hz,1H), 7.46 (d, J = 4.68 Hz, 1H), 7.41 (d, J = 2.4 Hz, 1H), 7.37 (d, J = 8.96 Hz, 1H), 4.42 (s, 2H), 4.23 (s, 2H), 3.38 (s, 3H), 1.815 (s, 3H)	
575		MS (ESI) m/z 654.14 [M+1]+. 1H NMR (400 MHz, DMSO-d6) δ, 8.27 (s, 1H), 8.04-7.67 (3, 2H), 7.63 (d, J = 8.4 Hz, 1H), 7.59-7.56 (m, 1H), 7.42 (m, 1H), 7.35 (d, J = 9.2 Hz, 1H), 7.10 (s, 1H), 4.39 (t, J = 4.8 Hz, 2H), 4.24 (t, J = 5.6 Hz, 2H), 3.07(t, J = 7.2 Hz, 2H), 2.58 (t, J = 7.2 Hz, 2H), 2.22 (s, 6H), 1.75 (s, 3H)	
576		MS (ESI) m/z 601.30 [M+1]+., 1H-NMR (400 MHz, DMSO-d6) δ 12.96 (bs, 1H), 7.90 (d, J = 8.44 Hz, 1H), 7.83 (s, 1H), 7.78 (d, J = 8.44 Hz, 1H),7.48 (dd, J = 2.44, 8.76 Hz,1H), 7.27-7.22 (m, 3H), 7.10 (d, J = 7.28 Hz, 1H), 4.32 (t, J = 4.8 Hz, 2H), 4.20 (t, J = 4.8 Hz, 2H), 2.86 (s, 6H), 2.68 (s, 3H), 1.72 (s, 3H)	
577		MS (ESI) m/z 637.22 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.16-7.87 (m, 3H), 7.33 (d, J = 9.2 Hz, 1H), 7.66 (d, J = 8.5 Hz, 1H), 7.53 (dd, J = 2.6, 8.8 Hz, 1H), 7.37-7.30 (m, 3H), 4.31 (t, J = 5.6 Hz, 2H), 4.17 (t, J = 5.6 Hz, 2H), 3.09 (t, J = 6.9 Hz, 2H), 2.56 (t, J = 6.8 Hz, 2H), 2.32 (s, 6H), 1.73 (s, 3H)	
578		MS (ESI) m/z 655.24 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.00 (s, 1H), 7.88-7.85 (m, 2H), 7.68 (d, J = 8.48 Hz, 1H), 7.54 (dd, J = 2.60, 8.88 Hz, 1H), 7.41-7.38 (m, 2H), 7.30 (d, J = 8.92 Hz, 1H), 4.34 (t, J = 4.36 Hz, 2H), 4.19 (t, J = 4.96 Hz, 2H), 3.07 (t, J = 7.20 Hz, 2H), 2.65-2.62 (m, 2H), 2.27 (s, 6H), 1.66 (s, 3H)	
579		MS (ESI) m/z 597.17 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.66 (bs, 1H), 8.43 (s, 1H), 7.84 (s, 1H), 7.71-7.33 (m, 6H), 4.39-4.37 (m, 2H), 4.23-4.21 (m, 2H), 2.70 (s, 3H), 1.81 (s, 3H)	

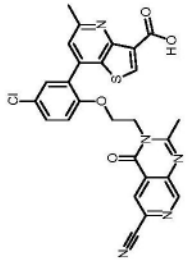
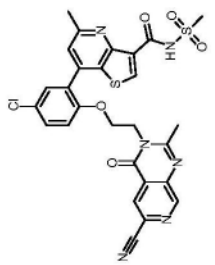
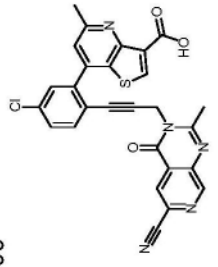
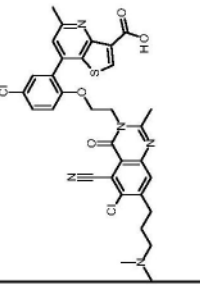
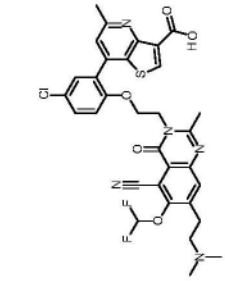
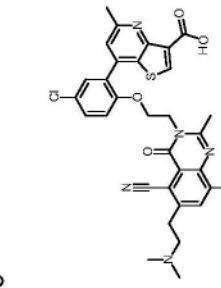
[1233]

580		MS (ESI) m/z 674.19 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.07 (bs, 1H), 8.44 (s, 1H), 7.85 (s, 1H), 7.71 to 7.41 (m, 4H), 7.36 to 7.32 (m, 2H), 4.4 (bs, 2H), 4.21 (bs, 2H), 3.56 (s, 3H), 2.71 (s, 3H), 1.79 (s, 3H)	MS (ESI) m/z 615.05 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.5 (bs, 1H), 8.41 (s, 1H), 8.02 (d, J = 8.8 Hz, 1H), 7.81 (d, J = 9.08, 1H), 7.59 (dd, J = 2.44, 8.80, 1H), 7.42-7.41 (m, 1H), 7.35 (d, J = 8.96, 1H), 4.39 (t, J = 5.08 Hz, 2H), 4.24 (t, J = 4.52, 2H), 2.69 (s, 3H), 1.83 (s, 3H)
581		MS (ESI) m/z 674.19 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.07 (bs, 1H), 8.44 (s, 1H), 7.85 (s, 1H), 7.71 to 7.41 (m, 4H), 7.36 to 7.32 (m, 2H), 4.4 (bs, 2H), 4.21 (bs, 2H), 3.56 (s, 3H), 2.71 (s, 3H), 1.79 (s, 3H)	MS (ESI) m/z 602.18 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 9.74 (bs, 1H), 8.33 (s, 1H), 7.91 (d, J = 8.8 Hz, 1H), 7.67 (d, J = 8.4 Hz, 1H), 7.61-7.58 (m, 1H), 7.41-7.35 (m, 3H), 4.41 (t, J = 4.8 Hz, 2H), 4.26 (t, J = 5.6 Hz, 2H), 3.41 (t, J = 9.6 Hz, 2H), 3.37 (t, J = 3.2 Hz, 2H), 2.91 (s, 6H), 2.70 (s, 3H), 1.87 (s, 3H)
582		MS (ESI) m/z 599.27 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.55 (bs, 1H), 8.37 (s, 1H), 7.89 (s, 1H), 7.60 (dd, J = 1.88 Hz, 8.84 Hz, 1H), 7.41 (s, 2H), 7.35 (d, J = 8.84 Hz, 1H), 4.40-4.38 (m , 2H), 4.24-4.22 (m, 2H), 2.70 (s, 3H), 1.82 (s, 3H)	585		MS (ESI) m/z 615.29 [M+1]+ ; 1H NMR (400 MHz, DMSO-d6) δ 13.68 (bs, 1H), 8.43 (s, 1H), 7.60-7.55 (m, 2H), 7.54 (t, J = 71.72 Hz, 1H), 7.43 (s, 1H), 7.40 (d, J = 4.00 Hz, 1H), 7.34 (d, J = 9.04 Hz, 1H), 4.38 (t, J = 4.68 Hz, 2H), 4.23 (t, J = 4.60 Hz, 2H), 2.71 (s, 3H), 1.78 (s, 3H)
583			
584			

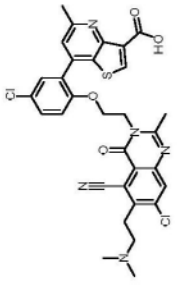
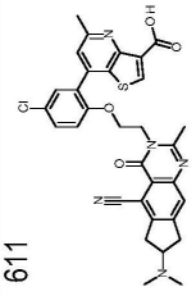
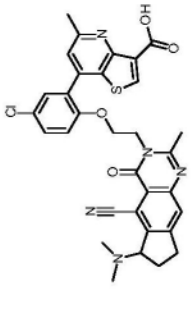
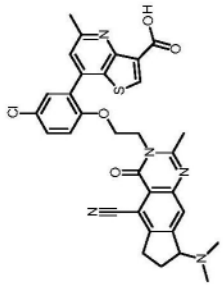
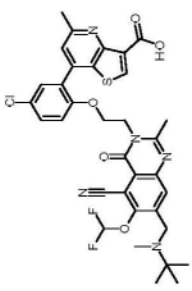
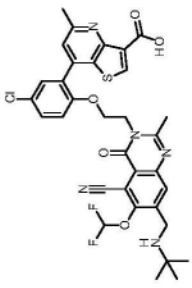
[1234]

586	MS (ESI) m/z 615.07 [M+1]+. 1H-NMR (400 MHz, DMSO-d6) δ 8.39 (s, 1H), 7.83 (s, 1H), 7.63-7.34 (m, 5H), 4.40 (t, J = 4.0 Hz, 2H), 4.25 (t, J = 4.4 Hz, 2H), 2.70 (s, 3H), 1.83 (s, 3H)	592	MS (ESI) m/z 668.20 [M+1]+; UPLC: 92.22 %; 1H NMR (400 MHz, DMSO-d6) δ: 8.32 (s, 1H), 7.78-7.33 (m, 6H), 4.38 (t, J = 4.7 Hz, 2H), 4.22 (t, J = 4.3 Hz, 2H), 3.06-3.04 (m, 2H), 2.76-2.69 (m, 5H), 2.23 (s, 6H), 1.82 (s, 3H)
587	MS (ESI) m/z 599.20 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.5 (s, 1H), 8.44 (s, 1H), 8.04 (d, J = 9.24 Hz, 1H), 7.62-7.58 (m, 1H), 7.47-7.21 (m, 4H), 4.41 (bs, 2H), 4.28 (bs, 2H), 2.69 (s, 3H), 1.94 (s, 3H)	593	MS (ESI) m/z [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.61 (s, 1H), 8.01 (d, J = 9.60 Hz, 1H), 7.88 (s, 1H), 7.67 (dd, J = 8.96, 2.52 Hz, 1H), 7.51 (d, J = 2.52 Hz, 1H), 7.49-7.22 (m, 2H), 4.46 (t, J = 4.84 Hz, 2H), 4.33 (t, J = 4.52 Hz, 2H), 2.94 (s, 3H), 2.07 (s, 3H)
588	MS (ESI) m/z 581.17 [M-1]-; 1H NMR (400 MHz, DMSO-d6) δ 8.47 (s, 1H), 8.15 (d, J = 9.32 Hz, 1H), 7.59 (dd, J = 2.44, 8.88 Hz, 1H), 7.40-7.35 (m, 3H), 4.41 (t, J = 6.24 Hz, 2H), 4.27 (t, J = 5.44 Hz, 2H), 2.70 (s, 3H), 1.93 (s, 3H)	594	MS (ESI) m/z 669 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 11.93 (s, 1H), 8.45 (s, 1H), 8.01 (d, J = 9.76 Hz, 1H), 7.59 (dd, J = 8.88, 2.40, 1H), 7.47-7.20 (m, 4H), 4.40 (t, J = 4.36 Hz, 2H), 4.28 (t, J = 4.76 Hz, 2H), 3.11 (bs, 6H), 2.67 (s, 3H), 1.99 (s, 3H)

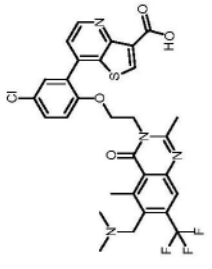
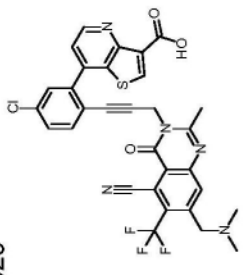
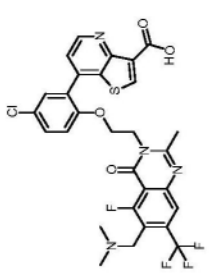
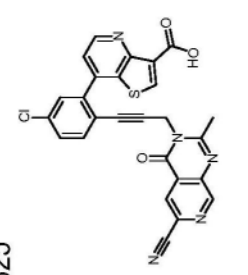
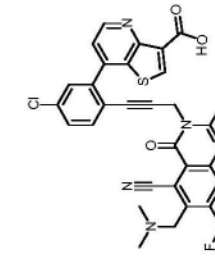
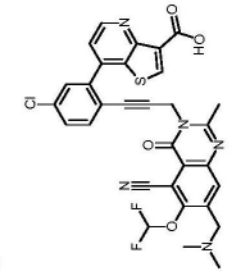
[1235]

596		MS (ESI) m/z 532.14 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.85 (s, 1H), 8.42 (s, 1H), 8.37 (s, 1H), 7.59 (dd, J=8.84 Hz, 2.56 Hz, 1H), 7.41 (t, J= 4.44 Hz, 2H), 7.33 (d, J=8.92, 1H), 4.38 (t, J=6.12Hz, 2H), 4.27 (t, J=6.2 Hz, 2H), 2.70 (s, 3H), 1.86 (s, 3H)	
598		MS (ESI) m/z 608.90 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 12.95 (s, 1H), 8.86 (s, 1H), 8.50 (s, 1H), 8.42 (s, 1H), 7.60 (dd, J = 7.24 Hz, 2.64Hz, 1H), 7.45 (s, 1H), 7.41 (d, J = 2.6 Hz, 1H), 7.35 (d, J = 8.96 Hz, 1H), 4.26 (t, J = 6.04 Hz, 2H), 4.26 (t, J = 4.52 Hz, 2H), 3.59 (s, 3H), 2.71 (s, 3H), 1.88 (s, 3H)	
599		MS (ESI) m/z 526.15 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 9.02 (bs, 1H), 8.45 (bs, 2H), 7.74 (s, 1H), 7.67 (d, J = 8.4 Hz, 2H), 7.40 (bs, 1H), 4.88 (s, 2H), 2.66 (s, 3H), 2.19 (s, 3H),	
606		MS (ESI) m/z 650.24 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.75 (bs, 1H), 9.50-9.30 (m, 1H), 8.29 (s, 1H), 7.64 (s, 1H), 7.60 (dd, J = 8.92, 2.56 Hz, 1H), 7.45 (s, 1H), 7.40 (d, J = 2.56 Hz, 1H), 7.36 (d, J = 9.0 Hz, 1H), 4.40 (t, J = 5.04 Hz, 2H), 4.24 (t, J = 4.48 Hz, 2H), 3.28-3.15 (m, 2H), 2.93 (t, J = 7.64 Hz, 2H), 2.83 (d, J = 4.60, 6H), 2.72 (s, 3H), 2.18-2.07 (m, 2H), 1.84 (s, 3H)	
607		MS (ESI) m/z 668.24 [M+1]+; UPLC: 97.83 %; 1H NMR (400 MHz, DMSO-d6) δ 8.25 (s, 1H), 7.66 (s, 1H), 7.58 (dd, J = 8.68 Hz, J = 2.36 Hz, 1H), 7.47-7.12 (m, 4H), 4.41 (t, J = 4.5 Hz, 2H), 4.24 (t, J = 4.3 Hz, 2H), 3.46 (t, J = 6.0 Hz, 2H), 3.18 (t, J = 8.0 Hz, 2H), 2.89 (s, 6H), 2.70 (s, 3H), 1.81 (s, 3H)	
608		MS (ESI) m/z 620.22 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.44 (s, 1H), 7.81 (d, J = 10.8 Hz, 1H), 7.58 (dd, J = 2.36 Hz, 9.0 Hz, 1H), 7.39-7.35 (m, 3H), 4.40 (t, J = 4.88 Hz, 2H), 4.25 (t, J = 4.44 Hz, 2H), 3.07 (t, J = 7.36 HZ, 2H), 2.69 (s, 5H), 2.28 (s, 6H), 1.94 (s, 3H)	

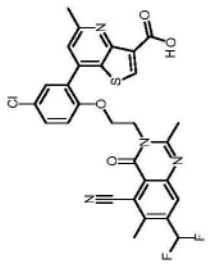
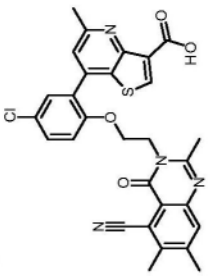
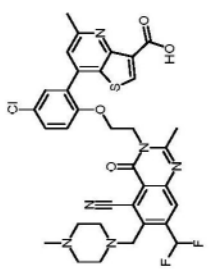
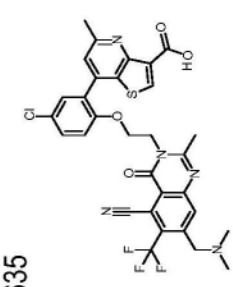
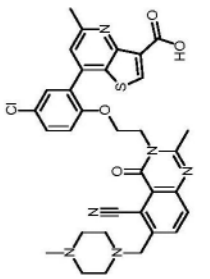
[1236]

609		MS (ESI) m/z 636.04 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.32 (s, 1H), 7.74 (s, 1H), 7.59-7.57 (m, 1H), 7.40-7.33 (m, 3H), 4.38 (t, J = 5.0 Hz, 2H), 4.22 (t, J = 3.92 Hz, 2H), 3.50 (s, 2H), 3.21 (t, J = 7.96 Hz, 2H) 2.69 (s, 3H), 2.26 (s, 6H), 1.84 (s, 3H)
611		MS (ESI) m/z 614.21 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.24 (s, 1H), 7.61 (dd, J1=2.5 Hz, J2 =8.8 Hz, 1H), 7.48 (s, 1H), 7.42 (s, 1H),7.38 (s, 1H), 7.36 (S, 1H), 4.40 (S , 2H), 4.39-4.30 (m, 1H),4.20 (s, 2H), 3.61-3.54 (m, 2H), 3.45-3.20 (m, 2H), 2.9 (s, 6H), 2.71 (s, 3H), 1.93 (s, 3H)
612		MS (ESI) m/z 614.2 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.63 (bs, 1H), 9.72 (bs, 1H), 8.16 (s, 1H), 7.61-7.59 (m, 2H), 7.44-7.36 (m, 3H), 5.19-5.08 (m, 1H), 4.50-4.35 (m, 2H), 4.35-4.18 (m, 2H), 3.23-3.07 (m, 2H), 2.93-2.73 (m, 6H), 2.73 (s, 3H), 1.90 (s, 1H)
613		MS (ESI) m/z 614.24 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.35 (s, 1H), 7.59-7.56 (dd, J = 2.52, 2.56 Hz, 1H), 7.48 (s, 1H), 7.40 (d, J = 2.4 Hz, 1H), 7.36-7.33 (m, 2H), 4.49 (t, J = 7.52 Hz, 1H), 4.41-4.19 (m, 4H), 3.14-2.98 (m, 2H), 2.67. (s, 3H), 2.20 (s, 6H), 2.12-2.05 (m, 2H), 1.89 (s, 3H)
618		MS (ESI) m/z 696.40 [M+1]+; 1H-NMR (400 MHz, DMSO-d6) δ 13.57 (bs, 1H), 8.41 (s ,1H), 7.90 (s, 1H), 7.60-7.57(dd, J = 2.25, 8.8 Hz, 1H), 7.41-7.32 (m, 4H), 4.39 (t, J = 5.28 Hz, 2H), 4.23 (t, J = 5.28 Hz, 2H), 3.71 (s, 2H), 2.68 (s, 3H), 2.11 (s, 3H), 1.82 (s, 3H), 1.15 (s, 9H)
619		MS (ESI) m/z 682.24 [M+1]+; 1H-NMR (400 MHz, DMSO-d6) δ 8.83 (bs, 1H), 8.36 (s ,1H), 8.01 (s, 1H), 7.69-7.33 (m, 5H), 4.42 (t, J = 4.72 Hz, 2H), 4.28 (m, 4H), 2.72 (s, 3H). 1.92 (s, 3H). 1.42 (s, 9H)

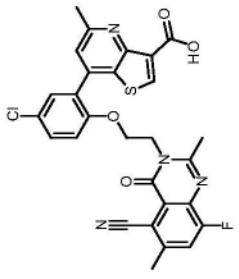
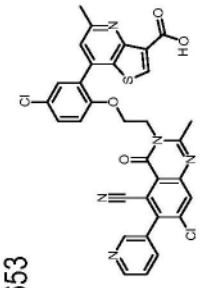
[1237]

620		MS (ESI) m/z 631.21 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.82 (d, J = 4.76 Hz, 1H), 8.24 (s, 1H), 7.67 (s, 1H), 7.61 (dd, J = 2.64, J = 8.88 Hz, 1H), 7.47 (d, J = 4.80 Hz, 1H), 7.43 (d, J = 2.64 Hz, 1H), 7.35 (d, J = 9.04 Hz, 1H), 4.65 (s, 2H), 4.39 (t, J = 4.48 Hz, 2H), 4.21 (t, J = 4.32 Hz, 2H), 2.87 (s, 6H), 1.77 (s, 3H)	623		MS (ESI) m/z 636.00 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.76 (s, 1H), 8.59 (s, 1H), 8.06 (s, 1H), 7.76 (d, J = 8.92, 1H), 7.68 (d, J = 1.8 Hz, 2H), 7.53 (s, 1H), 4.87 (s, 2H), 3.70 (s, 2H), 2.23 (s, 6H), 2.12 (s, 3H)
621		MS (ESI) m/z 634.99 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.84 (d, J=4.74 Hz, 1H), 8.25 (s, 1H), 7.65 (s, 1H), 7.60 (dd, J=8.84, 2.48 Hz, 1H), 7.48 (d, J = 4.72 Hz, 1H), 7.43 (d, J=2.48, 1H), 7.35 (d, J=8.96, 1H), 4.55(, 2H), 4.39 (bs, 2H), 4.24 (bs, 2H), 2.92 (s, 6H), 1.78 (s, 3H).	625		MS (ESI) m/z 512.12 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 9.0 (s, 1H), 8.74 (d, J = 4.8 Hz, 1H), 8.6 (s, 1H), 8.43 (s, 1H), 7.75 (d, J = 8.9 Hz, 1H), 7.68 (m, 2H), 7.51 (d, J = 4.6 Hz, 1H), 4.87 (s, 2H), 2.17 (s, 3H)
622		MS (ESI) m/z 617.93 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.72 (d, J = 4.72 Hz, 1H), 8.60 (s, 1H), 8.09 (s, 1H), 7.76 (d, J = 8.92 Hz, 1H), 7.69-7.65 (m, 2H), 7.54-7.38 (m, 2H), 4.90 (s, 2H), 4.63 (bs, 2H), 2.88 (s, 6H), 2.14 (s, 3H)	626		MS (ESI) m/z 634.10 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.14 (bs, 1H), 8.74 (d, J = 4.72 Hz, 1H), 8.65 (s, 1H), 8.19 (s, 1H), 7.77-7.60 (m, 3H), 7.57-7.24 (m, 2H), 4.88 (s, 2H), 4.53 (s, 2H), 2.88 (s, 6H), 2.16 (s, 3H)

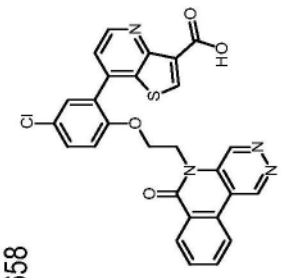
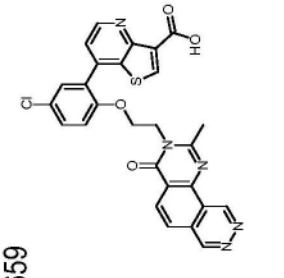
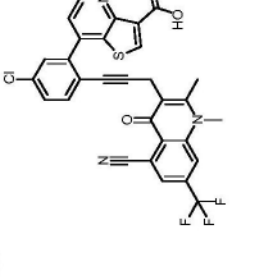
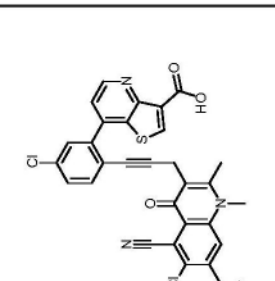
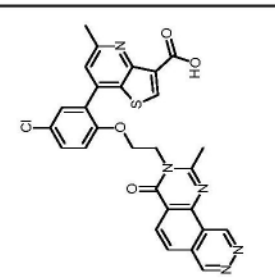
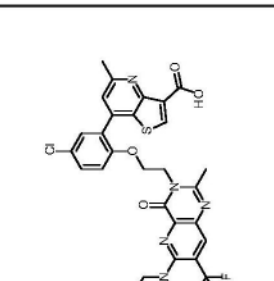
[1238]

627		MS (ESI) m/z 594.95 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.36 (s, 1H), 7.80 (s, 1H), 7.60 (dd, J=2.36, J=2.52,1H), 7.20 – 7.40 (m, 4H), 4.40 (bs, 2H), 4.25 (bs, 2H), 2.68 (s, 3H), 2.65 (s , 3H), 1.88 (s, 3H)	MS (ESI) m/z 667.15 [M+1]+. 1H NMR (400 MHz, DMSO-d6) δ 8.35 (s, 1H), 7.74 (bs, 1H), 7.59 (dd, J = 2.46 Hz, 8.88 Hz, 1H), 7.49-7.31 (m, 4H), 4.39 (bs, 2H), 4.23 (bs, 2H), 3.58 (bs, 2H), 3.02 (q, J = 7.52 Hz, 2H), 2.25(s, 6H), 1.78 (s, 3H), 1.35 (t, J= 7.24 Hz, 3H)
628		MS (ESI) m/z 559.06 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.34 (s, 1H), 7.59 (dd, J = 2.6 Hz, 2.56 Hz, 1H), 7.44 (s, 1H), 7.35-7.39 (m, 3H), 4.39 (s, 2H), 4.23 (s, 2H), 2.70 (s, 3H), 2.51 (s, 3H), 2.437 (s, 3H), 1.9 (s, 3H)	646  MS (ESI) m/z 693.21 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ, 9.41 (bs, 1H), 8.33 (s, 1H), 7.86 (s, 1H), 7.69-7.35 (m, 5H), 4.41 (t, J = 6.4 Hz, 2H), 4.26 (t, J = 6.4 Hz, 2H), 4.00 (s, 2H), 3.41 (d, J = 12.0 Hz, 2H), 3.02-2.94 (m, 4H), 2.79 (d, J = 3.6 Hz, 3H), 2.64 (s, 3H),2.49 (bs, 2H), 1.85 (s, 3H)
635		MS (ESI) m/z 656.12 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.48 (s, 1H), 8.38 (s, 1H), 7.92 (s, 1H), 7.59 (dd, J = 8.88, 2.52 Hz, 1H), 7.40-7.34 (m, 3H), 4.39 (t, J = 4.6 Hz, 2H), 4.25 (t, J = 4.6 Hz, 2H), 3.68 (s, 2H), 2.69 (s, 3H), 2.22 (s, 6H), 1.90 (s, 3H)	647  MS (ESI) m/z 642.99 [M+1]+; 1H-NMR (400 MHz, DMSO-d6) δ 8.37 (s, 1H), 7.92 (d, J = 8.52 Hz, 1H), 7.64 (d, J = 8.48 Hz, 1H), 7.58 (dd, J = 8.84, 2.44 Hz, 1H), 7.41-7.34(m, 3H), 4.42-4.37 (m, 2H), 4.27-4.21 (m, 2H), 3.75 (s, 3H), 2.68 (s, 3H), 2.50-2.30 (m, 6H), 2.21-2.16 (s, 4H), 1.85 (s, 3H)

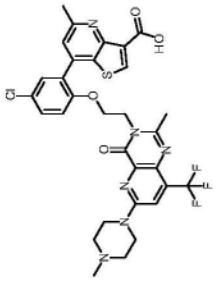
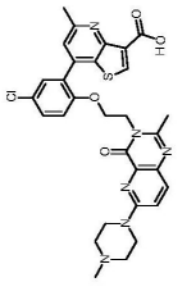
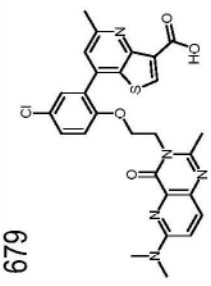
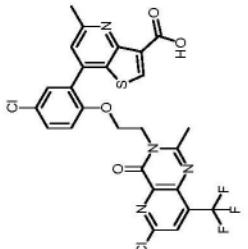
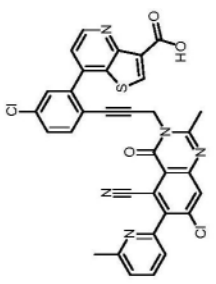
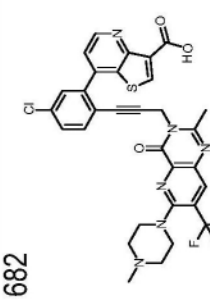
[1239]

648		MS (ESI) m/z 599.20 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.45 (s, 1H), 7.77 (d, J = 10.56 Hz, 1H), 7.60 (m, 1H), 7.40-7.35 (m, 3H), 4.41 (bs, 2H), 4.26 (bs, 2H), 2.69 (s, 3H), 2.58 (s, 3H), 1.98 (s, 3H)	653		MS (ESI) m/z 642.01 [M+1]+; 1H NMR (400 MHz, DMSO-d6) 8.76-8.73 (m, 2H), 8.45 (s, 1H), 8.03 (d, J = 7.84 Hz, 1H), 7.86 (s,1H), 7.67-7.64 (m, 1H), 7.59 (dd, J = 8.8, 2.44 Hz, 1H), 7.45-7.40 (m, 2H), 7.36 (d, J = 8.96 Hz, 1H), 4.40 (t, J = 4.28 Hz, 2H), 4.26 (t, J = 3.76 Hz, 2H), 2.72 (s, 3H), 1.90 (s, 3H)
650		MS (ESI) m/z 602.03 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.36 (s, 1H), 7.86 (s, 1H), 7.61 (dd, J = 8.92 Hz, 2.48 Hz, 1H), 7.43 (s, 1H), 7.41 (d, J = 2.52, 1H), 7.38 (d, J = 9.00 Hz, 1H), 4.54 (s, 2H), 4.43 (t, J = 5.72 , 2H), 4.27 (t, J = 4.2 Hz, 2H), 2.87 (s, 6H), 2.71 (s, 3H), 2.67 (s, 3H), 1.95 (s, 3H)	654		MS (ESI) m/z 608.35 [M+1]+; 1H-NMR (400 MHz, DMSO-d6) δ 9.20 (bs, 1H), 8.74 (bs ,1H), 8.45 (d, J = 7.96 Hz, 1H), 8.39 (s, 1H), 8.32 (s, 1H), 8.00 (s, 1H), 7.66 (m, 1H), 7.61-7.57 (dd, J = 2.26, 8.56 Hz, 1H),7.45 (s, 1H), 7.41 (d, J = 2.48 Hz, 1H), 7.38 (d, J = 8.96 Hz, 1H), 4.44 (t, J = 5.20 Hz, 2H), 4.26 (t, J = 4.60 2H), 2.71 (s, 3H), 1.84 (s, 3H),
651		MS (ESI) m/z 721.31 [M+1]+; 1H-NMR (400 MHz, DMSO-d6) δ 8.81 (d, J = 8.80 Hz, 1H), 8.47 (s ,1H), 8.23 (s, 1H), 8.03 (s, 1H), 7.61 (dd, J = 2.52, 8.84 Hz 1H), 7.47-7.19 (m, 4H), 4.41-4.40 (m, 6H), 4.21 (s, 2H), 4.10 (s, 3H), 2.67 (s, 3H). 1.82 (s, 3H)	657		LCMS (ESI) m/z 552.3 [M+H]+; 1H NMR (400 MHz, DMSO-d6) δ 8.70 (dd, J = 8.7, 1.1 Hz, 1H), 8.62 (d, J = 4.8 Hz, 1H), 8.25 (d, J = 8.6 Hz, 1H), 8.16 (s, 1H), 8.07 (dd, J = 7.4, 1.1 Hz, 1H), 7.95 (dd, J = 8.3, 7.4 Hz, 1H), 7.55 (dd, J = 8.9, 2.7 Hz, 1H), 7.38 (d, J = 1Hz, 1H), 7.36 (d, J = 5.2 Hz, 1H), 7.33 (d, J = 2.3 Hz, 1H), 7.16 – 7.06 (m, 2H), 7.01 – 6.92 (m, 1H), 4.56 – 4.50 (m, 4H)

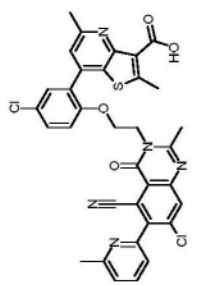
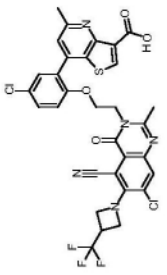
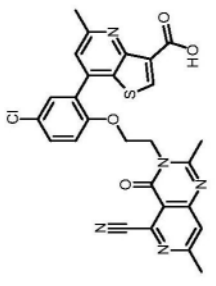
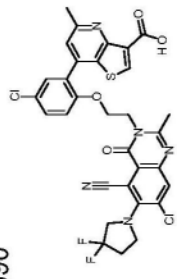
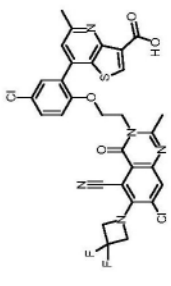
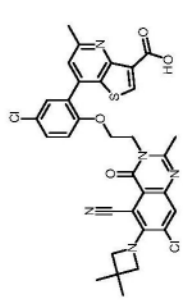
[1240]

658		LCMS (ESI) m/z 529.1 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 9.78 (s, 1H), 9.10 (s, 1H), 8.62 – 8.51 (m, 2H), 8.25 (dd, J = 8.0, 1.3 Hz, 1H), 8.08 (s, 1H), 7.95 (ddd, J = 8.3, 7.2, 1.4 Hz, 1H), 7.80 (ddd, J = 8.1, 7.3, 1.1 Hz, 1H), 7.56 (dd, J = 9.0, 2.7 Hz, 1H), 7.37 (d, J = 9.0 Hz, 1H), 7.33 – 7.26 (m, 2H), 4.61 (t, J = 5.2 Hz, 2H), 4.50 (t, J = 5.1 Hz, 2H)
659		LCMS (ESI) m/z 543.9 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 10.20 – 10.15 (m, 1H), 9.83 (s, 1H), 8.76 (d, J = 4.8 Hz, 1H), 8.36 (d, J = 8.5 Hz, 1H), 8.21 (s, 1H), 8.03 (d, J = 8.5 Hz, 1H), 7.55 (dd, J = 8.9, 2.7 Hz, 1H), 7.43 – 7.30 (m, 2H), 4.42 (d, J = 5.1 Hz, 1H), 4.30 (t, J = 4.9 Hz, 1H), 2.44 – 2.38 (m, 1H), 1.94 (s, 3H)
665		LCMS (ESI) m/z 592.1 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.68 (d, J = 4.8 Hz, 1H), 8.67 (s, 1H), 8.33 (s, 1H), 8.17 (s, 1H), 7.64 (d, J = 8.4 Hz, 1H), 7.62 – 7.56 (m, 2H), 7.46 (d, J = 4.8 Hz, 1H), 3.76 (s, 3H), 3.49 (s, 2H), 2.03 (s, 4H)
669		LCMS (ESI) m/z 626.1 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.73 – 8.63 (m, 2H), 8.35 (s, 1H), 7.68 – 7.53 (m, 3H), 7.47 (d, J = 4.8 Hz, 1H), 3.77 (s, 1H), 2.05 (d, J = 4.3 Hz, 1H), 2.04 (s, 1H)
671		LCMS (ESI) m/z 558.1 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 10.23 (d, J = 0.7 Hz, 1H), 9.92 (d, J = 1.5 Hz, 1H), 8.41 (d, J = 8.5 Hz, 1H), 8.28 (s, 1H), 8.09 (dd, J = 8.6, 0.7 Hz, 1H), 7.59 (dd, J = 8.9, 2.7 Hz, 1H), 7.47 – 7.34 (m, 3H), 4.46 (s, 5H), 4.34 (s, 5H), 2.65 (s, 3H), 2.04 (s, 3H)
676		LCMS (ESI) m/z 673.1 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.30 (s, 1H), 8.10 (s, 1H), 7.56 (dd, J = 8.9, 2.7 Hz, 1H), 7.42 – 7.35 (m, 2H), 7.31 (d, J = 9.0 Hz, 1H), 4.35 (t, J = 5.1 Hz, 2H), 4.19 (t, J = 4.9 Hz, 2H), 3.19 (m, 4H), 2.88 (d, J = 4.1 Hz, 3H), 2.67 (s, 3H), 1.75 (s, 3H)

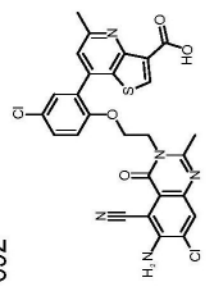
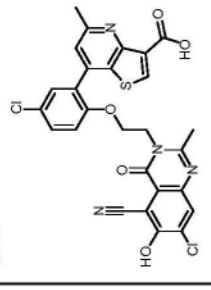
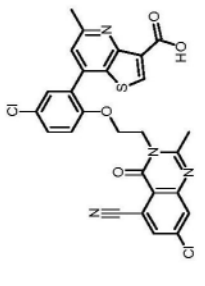
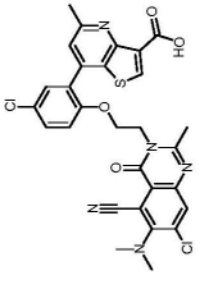
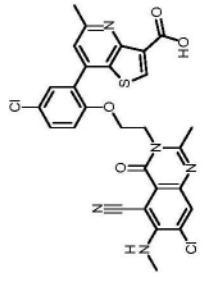
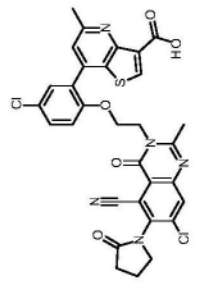
[1241]

677		LCMS (ESI) m/z 673.2 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 9.78 (s, 1H), 8.31 (s, 1H), 8.09 (s, 1H), 7.56 (dd, J = 8.9, 2.7 Hz, 1H), 7.42 – 7.35 (m, 2H), 7.31 (d, J = 9.0 Hz, 1H), 4.35 (t, J = 5.0 Hz, 2H), 4.19 (d, J = 10.1 Hz, 1H), 3.58 (d, J = 11.8 Hz, 4H), 3.29 – 3.13 (m, 4H), 2.88 (d, J = 3.4 Hz, 3H), 2.67 (s, 3H), 1.75 (s, 3H)	
678		LCMS (ESI) m/z 605.0 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 9.78 (s, 1H), 7.66 – 7.51 (m, 1H), 7.47 – 7.36 (m, 1H), 7.37 – 7.27 (m, 1H), 4.52 (d, J = 13.9 Hz, 1H), 4.33 (t, J = 5.1 Hz, 1H), 4.16 (t, J = 5.1 Hz, 1H), 3.54 (d, J = 11.8 Hz, 1H), 3.20 (d, J = 13.0 Hz, 1H), 3.18 – 3.03 (m, 1H), 2.84 (d, J = 3.6 Hz, 2H), 2.67 (s, 1H), 1.73 (s, 1H)	
679		LCMS (ESI) m/z 550.2 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.50 (s, 1H), 7.62 – 7.52 (m, 2H), 7.43 (d, J = 2.7 Hz, 1H), 7.40 – 7.30 (m, 2H), 7.19 (d, J = 9.2 Hz, 1H), 4.36 (t, J = 5.0 Hz, 2H), 4.18 (t, J = 5.0 Hz, 2H), 3.12 (s, 6H), 2.70 (s, 3H), 1.73 (s, 3H)	
680		LCMS (ESI) m/z 609.0 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.59 (s, 1H), 8.16 (s, 1H), 7.56 (dd, J = 8.9, 2.6 Hz, 1H), 7.45 – 7.38 (m, 2H), 7.33 (d, J = 9.0 Hz, 1H), 4.40 (t, J = 5.0 Hz, 2H), 4.24 (t, J = 5.1 Hz, 2H), 4.11 (s, 1H), 2.67 (s, 3H), 1.96 (s, 3H (m, 2H), 7.43 (d, J = 2.7 Hz, 1H), 7.40 – 7.30 (m, 2H), 7.19 (d, J = 9.2 Hz, 1H), 4.36 (t, J = 5.0 Hz, 2H), 4.18 (t, J = 5.0 Hz, 2H), 3.12 (s, 6H), 2.70 (s, 3H), 1.73 (s, 3H)	
681		LCMS (ESI) m/z 650.7 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.69 (s, 1H), 8.00 (s, 1H), 7.96 (t, J = 7.8 Hz, 1H), 7.75 (d, J = 8.3 Hz, 1H), 7.71 – 7.63 (m, 2H), 7.54 (d, J = 7.7 Hz, 1H), 7.48 (s, 1H), 7.44 (d, J = 7.8 Hz, 1H), 4.86 (s, 2H), 2.64 (s, 3H), 2.56 (s, 3H), 2.17 (s, 3H)	
682		LCMS (ESI) m/z 653.2 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 9.86 (s, 1H), 8.75 (d, J = 4.8 Hz, 1H), 8.60 (s, 1H), 8.29 (s, 1H), 7.75 (d, J = 9.2 Hz, 1H), 7.71 – 7.65 (m, 2H), 7.54 (d, J = 4.8 Hz, 1H), 4.86 (s, 2H), 3.64 (dd, J = 24.2, 12.1 Hz, 5H), 3.30 (d, J = 13.5 Hz, 7H), 2.92 (s, 3H), 2.12 (s, 3H)	

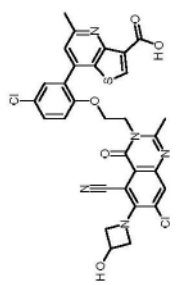
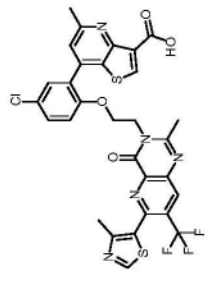
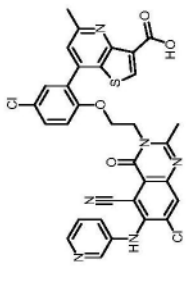
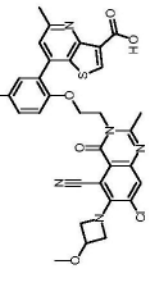
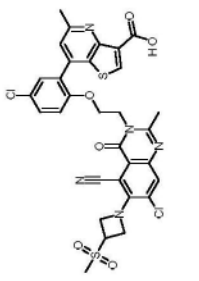
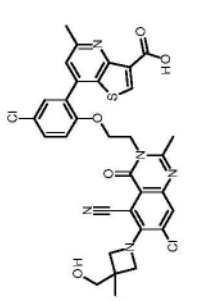
[1242]

683		LCMS (ESI) m/z 670.1 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 7.89 (t, J = 7.8 Hz, 1H), 7.78 (s, 1H), 7.56 (dd, J = 8.9, 2.7 Hz, 1H), 7.45 – 7.35 (m, 4H), 7.33 (d, J = 9.0 Hz, 1H), 4.38 (t, J = 5.0 Hz, 2H), 2.68 (s, 3H), 2.53 (d, J = 11.1 Hz, 6H), 1.93 (s, 3H)	689		LCMS (ESI) m/z 688.0 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.47 (d, J = 0.4 Hz, 1H), 7.59 (dd, J = 8.9, 2.7 Hz, 1H), 7.51 (s, 1H), 7.42 (s, 1H), 7.41 (d, J = 2.7 Hz, 1H), 7.36 (d, J = 8.9 Hz, 1H), 4.84 (t, J = 9.3 Hz, 2H), 4.63 (dd, J = 9.6, 5.0 Hz, 2H), 4.37 (t, J = 5.1 Hz, 2H), 4.18 (t, J = 5.1 Hz, 2H), 3.67 (d, J = 9.1 Hz, 0H), 2.73 (s, 3H), 1.81 (s, 3H)
685		LCMS (ESI) m/z 546.9 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.36 (s, 1H), 7.60 (dd, J = 8.9, 2.7 Hz, 1H), 7.45 – 7.38 (m, 3H), 7.36 (d, J = 9.0 Hz, 1H), 4.39 (d, J = 5.1 Hz, 2H), 4.26 (d, J = 5.1 Hz, 2H), 2.71 (s, 3H), 2.64 (s, 3H), 1.90 (s, 3H)	690		LCMS (ESI) m/z 670.2 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.47 (d, J = 0.4 Hz, 1H), 7.59 (dd, J = 8.9, 2.7 Hz, 1H), 7.51 (s, 1H), 7.42 (s, 1H), 7.41 (d, J = 2.7 Hz, 1H), 7.36 (d, J = 8.9 Hz, 1H), 4.84 (t, J = 9.3 Hz, 2H), 4.63 (dd, J = 9.6, 5.0 Hz, 2H), 4.37 (t, J = 5.1 Hz, 2H), 4.18 (t, J = 5.1 Hz, 2H), 3.67 (d, J = 9.1 Hz, 0H), 2.73 (s, 3H), 1.81 (s, 3H)
688		LCMS (ESI) m/z 656.1, 658.1 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.44 (s, 1H), 7.59 (dd, J = 8.9, 2.7 Hz, 1H), 7.55 (s, 1H), 7.43 – 7.38 (m, 2H), 7.36 (d, J = 9.0 Hz, 1H), 5.03 (t, J = 12.6 Hz, 4H), 4.38 (m, 2H), 4.19 (m, 2H), 2.72 (s, 3H), 1.83 (s, 3H)	691		LCMS (ESI) m/z 648.2 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 7.56 (dd, J = 8.9, 2.7 Hz, 1H), 7.45 – 7.27 (m, 3H), 4.33 (t, J = 5.0 Hz, 2H), 4.28 (bs, 2H), 4.14 (t, J = 5.0 Hz, 2H), 2.69 (s, 2H), 1.76 (s, 2H), 1.27 (s, 3H)

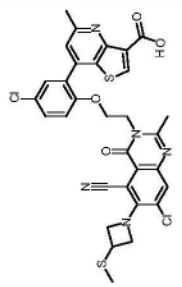
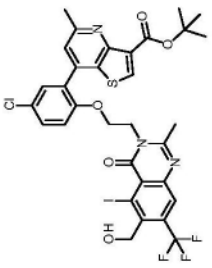
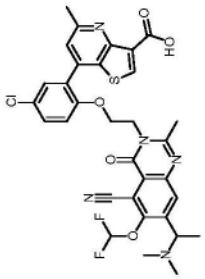
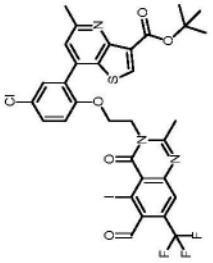
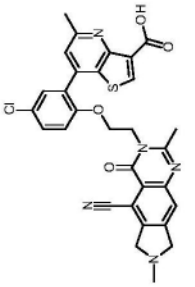
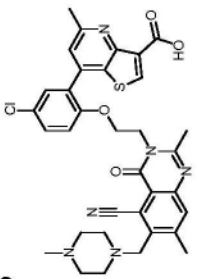
[1243]

692		LCMS (ESI) m/z 580.1 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.41 (s, 1H), 7.60 – 7.51 (m, 2H), 7.43 – 7.34 (m, 2H), 7.31 (d, J = 9.0 Hz, 1H), 6.45 (s, 2H), 4.33 (t, J = 5.0 Hz, 2H), 4.15 (t, J = 4.9 Hz, 2H), 2.67 (s, 3H), 1.69 (s, 3H)	695		LCMS (ESI) m/z 581.2 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.42 (s, 1H), 7.69 (s, 1H), 7.59 (dd, J = 8.9, 2.7 Hz, 1H), 7.43 – 7.39 (m, 2H), 7.35 (d, J = 9.0 Hz, 1H), 4.37 (t, J = 5.0 Hz, 2H), 4.20 (d, J = 5.1 Hz, 2H), 2.70 (s, 3H), 1.74 (s, 3H)
693		LCMS (ESI) m/z 567.0 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.39 (s, 1H), 8.10 (d, J = 2.1 Hz, 1H), 7.71 (d, J = 2.0 Hz, 1H), 7.59 (dd, J = 8.9, 2.7 Hz, 1H), 7.44 – 7.40 (m, 2H), 7.35 (d, J = 9.0 Hz, 1H), 4.39 (t, J = 5.1 Hz, 2H), 4.23 (t, J = 5.1 Hz, 2H), 2.71 (s, 3H), 1.83 (s, 3H)	696		LCMS (ESI) m/z 608.0]M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.44 (d, J = 0.4 Hz, 1H), 7.65 (s, 1H), 7.59 (dd, J = 8.9, 2.7 Hz, 1H), 7.46 – 7.39 (m, 2H), 7.36 (d, J = 9.0 Hz, 1H), 4.38 (s, 2H), 4.20 (s, 2H), 3.03 (s, 6H), 2.72 (s, 3H), 1.81 (s, 3H)
694		LCMS (ESI) m/z 594.2 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.46 (d, J = 0.4 Hz, 1H), 7.59 (dd, J = 8.9, 2.7 Hz, 1H), 7.54 (s, 1H), 7.44 – 7.40 (m, 2H), 7.35 (d, J = 8.9 Hz, 1H), 6.57 (d, J = 13.4 Hz, 1H), 4.37 (t, J = 5.0 Hz, 4H), 4.18 (t, J = 5.0 Hz, 2H), 3.24 (s, 3H), 2.72 (s, 3H), 1.74 (s, 3H)	697		LCMS (ESI) m/z 648.2 [M+1]+; 1H NMR (400 MHz, 甲醇-d4) δ 8.44 (s, 1H), 7.83 (s, 1H), 7.54 (dd, J = 8.9, 2.6 Hz, 1H), 7.52 (s, 1H), 7.33 (d, J = 2.6 Hz, 1H), 7.29 (d, J = 8.9 Hz, 1H), 4.53 – 4.28 (m, 2H), 4.06 – 3.97 (m, 2H), 3.92 – 3.84 (m, 2H), 2.87 (s, 3H), 2.65 (t, J = 7.8 Hz, 2H), 2.40 (q, J = 7.5 Hz, 2H), 2.04 (s, 3H)

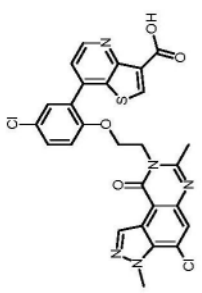
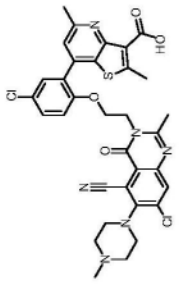
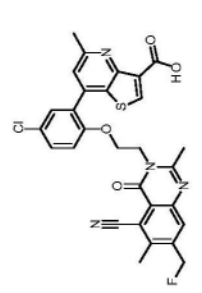
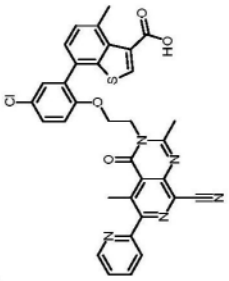
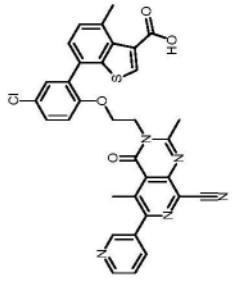
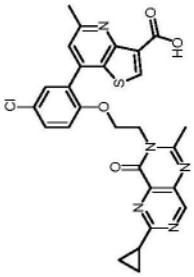
[1244]

698		LCMS (ESI) m/z 636.3 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.45 (s, 1H), 7.55 (dd, J = 8.9, 2.7 Hz, 1H), 7.43 (s, 1H), 7.41 – 7.28 (m, 3H), 4.79 (ddd, J = 9.4, 6.7, 1.3 Hz, 2H), 4.43 (tt, J = 6.7, 4.2 Hz, 1H), 4.36 – 4.24 (m, 4H), 4.14 (t, J = 5.1 Hz, 2H), 2.68 (s, 3H), 1.74 (s, 3H)	
699		LCMS (ESI) m/z 659.3 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.48 (s, 1H), 7.59 (dd, J = 8.9, 2.7 Hz, 1H), 7.46 (s, 1H), 7.44 – 7.39 (m, 2H), 7.35 (d, J = 9.0 Hz, 1H), 4.89 – 4.75 (m, 2H), 4.50 – 4.45 (m, 2H), 4.36 (t, J = 5.0 Hz, 2H), 4.31 (dd, J = 10.5, 4.2 Hz, 2H), 4.17 (t, J = 5.1 Hz, 2H), 2.72 (s, 3H), 1.77 (s, 3H)	
700		LCMS (ESI) m/z 656.9 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 9.31 (s, 1H), 8.46 (s, 1H), 8.32 (s, 1H), 8.25 (s, 1H), 7.87 (s, 1H), 7.66 – 7.60 (m, 2H), 7.60 (dd, J = 8.9, 2.7 Hz, 1H), 7.47 – 7.40 (m, 2H), 7.36 (d, J = 9.0 Hz, 1H), 4.40 (t, J = 5.0 Hz, 2H), 4.24 (t, J = 4.9 Hz, 2H), 2.71 (s, 3H), 1.80 (s, 3H)	
701		LCMS (ESI) m/z 650.1 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.44 (s, 1H), 7.55 (dd, J = 8.9, 2.7 Hz, 1H), 7.44 (s, 1H), 7.40 – 7.28 (m, 3H), 4.76 (dd, J = 10.0, 6.5 Hz, 2H), 4.38 (dd, J = 9.8, 3.5 Hz, 2H), 4.32 (d, J = 5.3 Hz, 2H), 4.22 – 4.12 (m, 3H), 3.25 (s, 3H), 2.68 (s, 3H), 1.75 (s, 3H)	
702		LCMS (ESI) m/z 698.1 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.48 (s, 1H), 7.59 (dd, J = 8.9, 2.6 Hz, 1H), 7.52 (s, 1H), 7.44 – 7.32 (m, 3H), 4.90 (t, J = 9.4 Hz, 2H), 4.79 (dd, J = 10.1, 4.9 Hz, 2H), 4.43 – 4.31 (m, 3H), 4.18 (t, J = 5.0 Hz, 2H), 3.12 (s, 3H), 2.72 (s, 3H), 1.80 (s, 3H)	
703		LCMS (ESI) m/z 664.1 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.43 (s, 1H), 7.55 (dd, J = 8.9, 2.7 Hz, 1H), 7.41 (s, 1H), 7.40 – 7.34 (m, 2H), 7.31 (d, J = 9.0 Hz, 1H), 4.40 (d, J = 8.7 Hz, 2H), 4.32 (t, J = 5.0 Hz, 2H), 4.19 – 4.09 (m, 4H), 3.40 (s, 2H), 2.67 (s, 3H), 1.72 (s, 3H), 1.22 (s, 3H)	

[1245]

704		LCMS (ESI) m/z 666.4 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 7.58 (s, 1H), 7.51 (d, J = 9.8 Hz, 2H), 7.34 (s, 1H), 7.28 (d, J = 9.1 Hz, 1H), 7.17 (s, 1H), 6.66 (bs, 1H), 4.89 (t, J = 8.8 Hz, 2H), 4.39 (s, 2H), 4.93 - 4.36 (m, 2H), 4.30 (s, 2H), 4.15 (s, 3H), 3.72 (s, 1H), 2.62 (s, 3H), 2.51 (s, 2H), 2.12 (s, 3H), 1.84 (s, 4H), 1.73 (d, J = 8.4 Hz, 3H)	715		MS (ESI) m/z 786.00 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.27 (s, 1H), 7.70 (s, 1H), 7.54 (dd, J = 8.84, 2.48 Hz, 1H), 7.36 (d, J = 2.52 Hz, 1H), 7.30 (d, J = 8.96 Hz, 1H), 7.20 (s, 1H), 5.09 (t, J= 4.6 Hz, 1H), 4.89 (d, J = 3.88 Hz, 2H), 4.33 (d, J= 4.52 Hz, 2H), 4.19 (s, 2H), 2.62 (s, 3H), 1.69 (s, 3H), 1.61 (s, 9H)
710		MS (ESI) m/z 668.20 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 10.10 (bs, 1H), 8.35 (s, 1H), 8.12 (s, 1H), 7.61 (dd, J = 2.56, 8.84 Hz, 1H), 7.56-7.21 (m, 4H), 4.84-4.82 (m, 1H), 4.47-4.17 (m, 4H), 2.90 (s, 3H), 2.71 (s, 3H), 2.66 (s, 3H), 1.78 (s, 6H)	716		MS (ESI) m/z 784.32 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 10.10 (s, 1H), 8.29 (s, 1H), 7.79 (s, 1H), 7.54 (dd, J = 8.8, 2.5 Hz, 1H), 7.36 (d, J = 2.52 Hz, 1H), 7.30 (d, J = 8.92 Hz, 1H), 7.21 (s, 1H), 4.35 (t, J = 4.28 Hz, 2H), 4.20 (t, J = 4.0 Hz, 2H), 2.62 (s, 3H), 1.73 (s, 3H), 1.61 (s, 9H)
712		MS (ESI) m/z 586.04 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 10.95 (bs, 1H), 8.30 (s, 1H), 7.66 (s, 1H), 7.60 (dd, J = 8.84, 2.56 Hz, 1H), 7.42 (s, 1H), 7.39-7.35 (m, 2H), 4.92 (bs, 4H), 4.40 (t, J = 4.40 Hz, 2H), 4.26 (t, J = 4.80 Hz, 2H), 3.13 (s, 3H), 2.71 (s, 3H), 1.93 (s, 3H)	718		MS (ESI) m/z 657.11 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.54 (bs, 1H), 8.30 (s, 1H), 7.58 (dd, J=8.92 Hz, 2.6 Hz, 1H), 7.48 (s, 1H), 7.39-7.34 (m, 3H), 4.38 (t, J = 5.88 Hz, 2H), 4.22 (t, J = 4.32 Hz, 2H), 3.75 (s, 2H), 2.68 (s, 3H), 2.56 (s, 3H), 2.45 (bs, 4H,), 2.28 (bs, 4H), 2.12 (s, 3H), 1.89 (s, 3H)

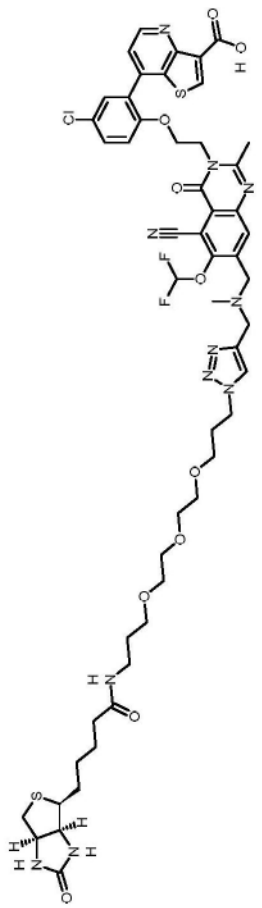
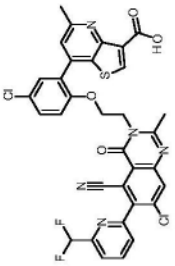
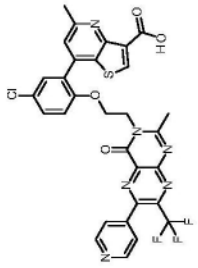
[1246]

720		MS (ESI) m/z 579.93 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.80 (d, J = 4.88 Hz, 1H), 8.48 (s, 1H), 8.32 (s, 1H), 7.59 (dd, J = 8.92, 2.68 Hz, 1H), 7.50-7.44 (m, 2H), 7.40 (d, J = 2.6 Hz, 1H), 7.35 (d, J = 8.96 Hz, 1H), 4.49-4.38 (m, 5H), 4.33-4.27 (m, 2H), 1.85 (s, 3H)	741		MS (ESI) m/z 677.17 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 14.31 (bs, 1H), 7.71 (bs, 1H), 7.60 (dd, J = 2.48, 8.8 Hz 1H), 7.41 (s, 1H), 7.39-7.18 (m, 2H), 4.38 (t, J = 4.12 Hz, 2H), 4.24 (t, J = 4.6 Hz, 2 H), 3.81-3.21 (m, 8H), 2.93 (s, 3H), 2.71 (s, 3H), 2.50 (s, 3H), 2.02 (s, 3H)
724		MS (ESI) m/z 577.00 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.36 (s, 1H), 7.64 (s, 1H), 7.59 (dd, J=8.8 Hz, 2.56 Hz, 1H), 7.39-7.35 (m, 3H), 5.68 (d, 46.72 Hz, 2H), 4.40 (t, 4.40 Hz, 2H), 4.25 (t, 4.56 Hz, 2H), 2.69 (s, 3H), 2.53 (s, 3H), 1.95 (s, 3H)	743		MS (ESI) m/z 622.01 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.69 (d, J=3.88 Hz, 1H), 8.02 (t, J = 6.20 Hz, 1H), 7.81 (d, J = 7.76 Hz, 2H), 7.51-7.47 (m, 2H), 7.30-7.08 (m, 3H), 7.03 (bs, 1H), 4.32 (t, J = 6.04 Hz, 2H), 4.21 (t, J = 5.4 Hz, 2H), 2.76 (s, 3H), 2.66 (s, 3H), 1.93 (s, 3H)
729		MS (ESI) m/z 622.01 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.82 (bs, 1H), 8.71 (bs, 1H), 8.07 (d, J=7.84 Hz, 1H), 7.93 (s, 1H), 7.62-7.56 (m, 1H), 7.53-7.49 (m, 1H), 7.30-7.28 (m, 3H), 7.12 (d, J=7.6 Hz, 1H), 4.42 (t, J = 4.76 Hz, 2H), 4.21 (t, J = 6.16 Hz, 2H), 2.72 (s, 3H), 2.66 (s, 3H), 1.93 (s, 3H)	744		MS (ESI) m/z 579.36 [M+1]+; 1H-NMR (400 MHz, DMSO-d6) δ 13.59 (bs, 1H), 8.90 (s, 1H), 8.44 (s, 1H), 7.57 (d, J = 8.84 Hz, 1H), 7.41 (s, 1H), 7.38 (s, 1H), 7.33 (d, J = 8.84 Hz, 1H), 4.39 (t, J = 5.4 Hz, 2H), 4.21 ((t, J = 4.32 Hz, 2H)), 2.68 (s, 3H), 2.35-2.32 (m, 1H), 1.78 (s, 3H), 1.29-1.07 (m, 4H)

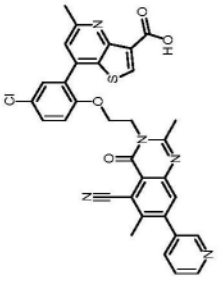
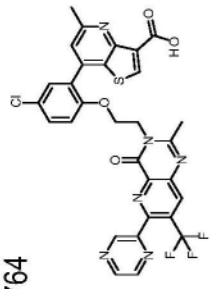
[1247]

745	MS (ESI) m/z 522.26 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.58 (bs, 1H), 9.04 (s, 1H), 8.47 (s, 1H), 7.59 (dd, J = 2.48, 8.88 Hz, 1H), 7.40 (t, J = 2.68 Hz, 2H), 7.35 (d, J = 8.92 Hz, 1H), 4.40 (t, J = 4.32 Hz, 2H), 4.23 (t, J = 5.04, 2H), 2.69 (s, 6H), 1.81 (s, 3H)	750	MS (ESI) m/z 695.96 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.48 (s, 1H), 7.62 (s, 1H), 7.69-7.56 (m, 1H), 7.42 (d, J = 2.44 Hz, 1H), 7.39 (s, 1H), 7.34 (d, J = 8.84 Hz, 1H), 4.35 (t, J = 4.84 Hz, 2H), 4.26 (t, J = 7.52 Hz, 4H), 4.16 (t, J= 4.36 Hz, 2H), 2.70 (s, 3H), 2.31-2.27 (m, 2H), 1.73 (s, 3H)
746	MS (ESI) m/z 536.27 [M+1] +; 1H-NMR NMR (400 MHz, DMSO-d6) δ 13.58 (bs, 1H), 8.49 (s, 1H), 7.59 (d, J = 8.72 Hz, 1H), 7.40-7.38 (m, 2H), 7.35 (d, J = 8.84 Hz, 1H), 4.39 (bs, 2H), 4.22 (bs, 2H), 2.69 (s, 3H), 2.67 (s, 3H), 2.65 (s, 3H), 1.82 (s, 3H)	752	MS (ESI) m/z 620.00 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.45 (s, 1H), 7.58 (dd, J = 2.56, 8.80 Hz, 1H), 7.46 (s, 1H), 7.40 (d, J = 2.56 Hz, 1H), 7.38 (s, 1H), 7.34 (d, J = 9.04 Hz, 1H), 4.60 (t, J= 7.60 Hz, 4H), 4.35 (t, J = 5.12 Hz, 2H), 4.16 (t, J = 4.12 Hz, 2H), 2.70 (s, 3H), 2.32-2.26 (m, 2H), 1.77 (s, 3H)
748	MS (ESI) m/z 571.01 [M+1]+. 1H-NMR (400 MHz, DMSO-d6) δ 8.34 (s, 1H), 7.59 (dd, J = 8.80, 2.80 Hz 1H), 7.44-7.40 (m, 2H), 7.40-7.34 (m, 2H), 4.39 (t, J = 4.96 Hz, 2H), 4.24 (t, J = 4.52 Hz, 2H), 3.10 (t, J = 7.12 Hz, 4H), 2.71 (s, 3H), 2.21-2.14 (m, 2H), 1.96 (s, 3H)		

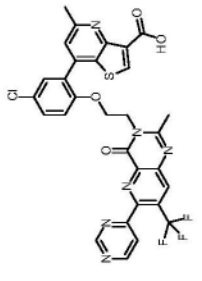
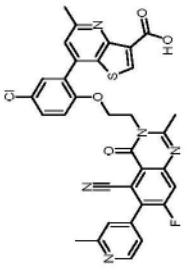
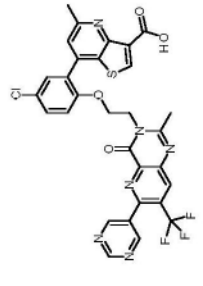
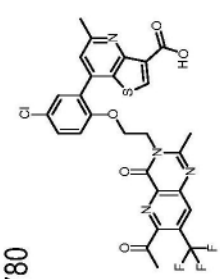
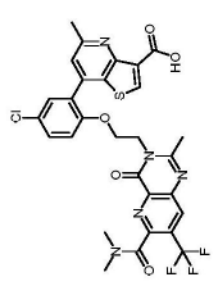
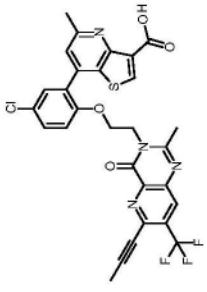
[1248]

755		MS (ESI) m/z 1136.89 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.81 (d, J = 4.8 Hz, 1H), 8.41 (s, 1H), 8.20 (s, 1H), 7.98 (s, 1H), 7.72 (bs, 1H), 7.61-7.58 (m, 1H), 7.54-7.35 (m, 5H), 6.40 (s, 1H), 6.35 (s, 1H), 4.46-4.12 (m, 11H), 3.47-3.33 (m, 13H), 3.04-3.01 (m, 4H), 2.66-2.50 (m, 4H), 2.03-2.00 (m, 4H), 1.81 (s, 3H), 1.58-1.55 (m, 4H), 1.47-1.43 (m, 4H), 1.25-1.20 (m, 2H)	
758		MS (ESI) m/z 692.00 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.56 (bs, 1H), 8.47 (s, 1H), 8.28 (t, J = 7.84 Hz, 1H), 7.94 (d, J = 7.72 Hz, 1H), 7.91-7.86 (m, 2H), 7.59 (dd, J = 8.88, 2.56 Hz, 1H), 7.44-7.39 (m, 2H), 7.35 (d, J = 8.96 Hz, 1H), 7.04 (t, J = 54.68 Hz, 1H), 4.39 (t, J = 4.64 Hz, 2H), 4.25 (t, J = 5.44 Hz, 2H), 2.71 (s, 3H), 1.86 (s, 3H)	761		MS (ESI) m/z 651.05 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.49 (s, 1H), 8.80 (d, J = 5.8Hz, 2H), 8.57 (s, 1H), 7.63 (d J = 5.56 Hz, 2H), 7.59 (dd, J = 8.92 Hz, 2.56, 1H), 7.44 (d, J = 2.6 Hz, 1H), 7.40 (s, 1H), 7.36 (d, J=8.96, 1H), 4.42 (t, J = 5.4 Hz, 2H), 4.32 (t, J = 4.24 Hz, 2H), 2.71 (s, 3H), 2.00 (s, 3H)

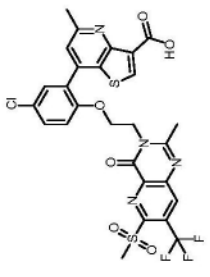
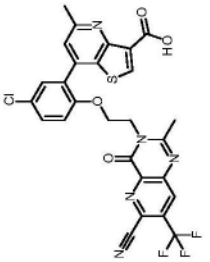
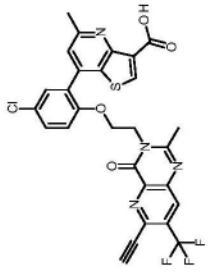
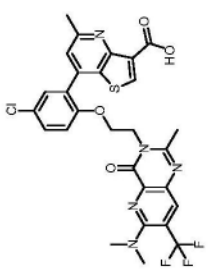
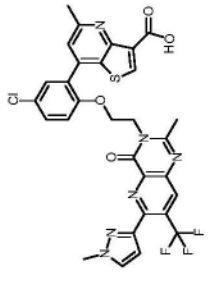
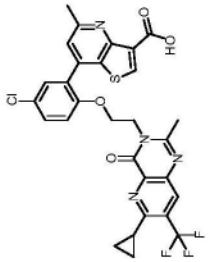
[1249]

759		MS (ESI) m/z 622.07 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.63 (bs, 1H), 8.77 (s, 1H), 8.71 (s, 1H), 8.35 (s, 1H), 8.03 (d, J = 6.96 Hz, 1H), 7.61-7.59 (m, 2H), 7.52 (s, 1H), 7.43-7.36 (m, 3H), 4.42 (t, J = 5.76 Hz, 2H), 4.26 (t, J = 5.48 Hz, 2H), 2.71 (s, 3H), 2.5 (s, 3H, 不可见，与水分峰合并), 1.87 (s, 3H)	764		MS (ESI) m/z 652.95 [M+1]+, 1H NMR (400 MHz, DMSO-d6) δ 13.57 (bs, 1H), 9.09 (s, 1H), 8.84 (d, J = 2.44 Hz, 1H), 8.80 (bs, 1H), 8.37 (s, 1H), 8.35 (s, 1H), 7.58 (dd, J = 2.56, 8.88 Hz, 1H), 7.43 (bs, 2H), 7.35 (d, J= 8.96 Hz, 1H), 4.41 (t, J = 4.96 Hz, 2H), 4.28 (t, J = 4.36 Hz, 2H), 2.70 (s, 3H), 1.83 (s, 3H)
760		MS (ESI) m/z 589.98 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.51 (s, 1H), 7.59 (dd, J = 8.88, 2.6 Hz, 1H), 7.42 (d J = 2.56 Hz, 1H), 7.39 (s, 1H), 7.35 (d, J = 8.96 Hz, 1H), 4.40 (t, J = 4.72 Hz, 2H), 4.28 (t, J = 4.8 Hz, 2H), 2.79 (s, 3H), 2.69 (s, 3H), 1.98 (s, 3H)	765		MS (ESI) m/z 652.95 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.61 (bs, 1H), 9.02 (d, J = 4.92 Hz, 2H), 8.40 (s, 1H), 8.34 (s, 1H), 7.70 (t, J = 4.92 Hz, 1H), 7.58 (dd, J = 8.92, 2.52 Hz, 1H), 7.43 (d, J = 2.48 Hz, 1H), 7.41 (s, 1H), 7.34 (d, J = 8.96 Hz, 1H), 4.39-4.37 (m, 2H), 4.30-4.23 (m, 2H), 2.69 (s, 3H), 1.80 (s, 3H)
766		MS (ESI) m/z 630.01 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.40 (s, 1H), 7.89 (s, 1H), 7.59 (dd, J = 90.20, 2.52 Hz, 1H), 7.42 (s, 2H), 7.34 (d, J = 8.96 Hz, 1H), 4.36 (t, J = 5.64 Hz, 2H), 4.22-4.18 (m, 6H), 2.70 (s, 3H), 2.36-2.30 (m, 2H), 1.72 (s, 3H)	769		MS (ESI) m/z 667.07 [M+1]+ ; 1H NMR (400 MHz, DMSO-d6) δ 13.57 (bs, 1H), 8.95 (d, J = 5.12 Hz, 1H), 8.37 (s, 1H), 8.33 (s, 1H), 7.75 (d, J = 5.08 Hz, 1H), 7.59 (dd, J = 2.52, 8.84 Hz, 1H), 7.42 (t, J = 2.64 Hz, 2H), 7.35 (d, J = 8.96 Hz, 1H), 4.40 (t, J = 6.64 Hz, 2H), 4.27 (t, J = 6.6 Hz, 2H), 2.71 (s, 6H), 1.81 (s, 3H)

[1250]

767		MS (ESI) m/z 652.92 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.57 (bs, 1H) 9.35 (d, J = 0.88 Hz, 1H), 9.08 (d, J = 5.16 Hz, 1H), 8.37 (s, 1H), 8.35 (s, 1H), 7.98 (dd, J = 4.04, 1.52 Hz, 1H), 7.59 (dd, J = 9.20, 2.40, Hz, 1H), 7.43-7.41 (m, 2H), 7.35 (d, J = 8.96 Hz, 1H), 4.40 (t, J = 3.76 Hz, 2H), 4.27 (t, J = 4.48 Hz, 2H), 2.70 (s, 3H), 1.83 (s, 3H)	778		MS (ESI) m/z 639.97 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.80 (d, J = 5.28 Hz, 1H), 8.43 (s, 1H), 7.76 (s, 1H), 7.70 (d, J = 4.88, 1H), 7.61-7.58 (m, 2H), 7.43 (s, 1H), 7.41 (d, J = 2.48 Hz, 1H), 7.37 (d, J = 8.96 Hz, 1H), 4.41 (t, J = 5.32 Hz, 2H), 4.27 (t, J = 4.28 Hz, 2H), 2.73 (s, 3H), 2.67 (s, 3H), 1.94 (s, 3H)
768		MS (ESI) m/z 653.01 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.55 (bs, 1H), 9.38 (s, 1H), 9.03 (s, 2H), 8.31 (d, J = 2.88 Hz, 1H), 7.59 (dd, J = 8.80, 2.40 Hz, 1H), 7.43-7.41 (m, 2H), 7.35 (d, J = 8.96 Hz, 1H), 4.41 (t, J = 4.80 Hz, 2H), 4.27 (t, J = 4.80 Hz, 2H), 2.72 (s, 3H), 1.85 (s, 3H)	780		MS (ESI) m/z 616.97 [M+1]+;1H NMR (400 MHz, DMSO-d6) δ 13.58 (s, 1H), 8.32 (s, 1H), 8.25 (s, 1H), 7.60 (dd, J = 2.56, 8.84 Hz 1H), 7.42-7.41 (m, 2H), 7.36 (d, J = 8.96 Hz, 1H), 4.41 (t, J = 4.56 Hz, 2H), 4.28 (t, J = 4.28 Hz, 2H), 2.72 (s, 3H), 2.71 (s, 3H), 1.81 (s, 3H)
781		MS (ESI) m/z 646.02 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.38 (s, 1H), 8.27 (s, 1H), 7.62-7.57 (dd, J = 2.6, 8.8 Hz, 1H), 7.44-7.43 (m, 2H), 7.36 (d, J = 9.2 Hz, 1H), 4.39 (t, J = 4.4 Hz, 2H), 4.25 (t, J = 4.4 Hz, 2H), 3.06 (s, 3H), 2.79 (s, 3H), 2.71 (s, 3H), 1.78 (s, 3H)	784		MS (ESI) m/z 612.97 [M+1]+; 1H-NMR (400 MHz, DMSO-d6) δ 8.28 (s, 1H), 8.08 (s ,1H), 7.59 (dd, J = 2.48, 8.88 Hz, 1H), 7.41 (d, J = 2.6 Hz, 2H), 7.35 (d, J = 8.96 Hz, 1H), 4.37 (t, J = 4.48 Hz, 2H), 4.23 (t, J = 4.92 Hz, 2H), 2.69 (s, 3H), 2.19 (s, 3H), 1.76 (s, 3H)

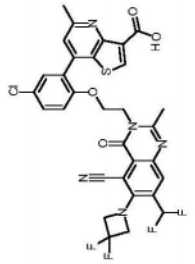
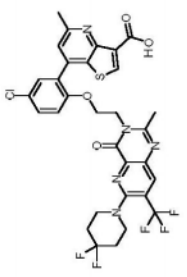
[1251]

782		MS (ESI) m/z 653.03 [M+1]+. 1H NMR (400 MHz, DMSO-d6) δ 13.5 (bs, 1H), 8.40 (s, 1H), 8.32 (s, 1H), 7.59 (d, J = 8.0 Hz, 1H), 7.41 (s, 2H), 7.33 (d, J = 9.0 Hz, 1H), 4.40 (bs, 2H), 4.27 (bs, 2H), 3.54 (s, 3H), 2.70 (s, 3H), 1.78 (s, 3H)	785		MS (ESI) m/z 600.0 [M+1]+. 1H-NMR (400 MHz, DMSO-d6)) δ 8.33 (s, 1H), 8.24 (s ,1H), 7.60 (dd, J = 2.52, 8.84 Hz, 1H), 7.43 (s, 1H), 7.41 (d, J = 2.52 Hz, 1H), 7.35 (d, J = 8.96 Hz, 1H), 4.40 (t, J = 4.4 Hz, 2H), 4.27 (t, J = 6.0 Hz, 2H), 2.70 (s, 3H), 1.75 (s, 3H)
783		MS (ESI) m/z 598.95 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.57 (bs, 1H), 8.29 (s, 1H), 8.13 (s, 1H), 7.60-7.57 (dd, J = 8.84, 2.4 Hz, 2H), 7.41 (d, J = 3.48 Hz 1H), 7.34 (d, J = 8.92 Hz, 1H), 4.89 (s, 1H), 4.38 (t, J = 3.84 Hz, 2H), 4.24 (t, J = 4.52 Hz, 2H), 2.69 (s, 3H), 1.76 (s, 3H)	786		MS (ESI) m/z 615.29 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.41 (s, 1H), 8.00 (s, 1H), 7.59 (d, J = 7.72 Hz, 1H), 7.42 (d, J = 1.92 Hz, 1H), 7.40 (s, 1H), 7.34 (d, J = 9.04 Hz, 1H), 4.37 (t, J = 4.12 Hz, 2H), 4.19 (t, J = 5.04 Hz, 2H), 3.01 (s, 6H), 2.69 (s, 1H), 1.72 (s, 3H)
787		MS (ESI) m/z 654.99 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.60 (bs, 1H), 8.35 (s, 1H), 8.20 (s, 1H), 7.82 (d, J = 1.96 Hz, 1H), 7.58 (dd, J = 8.88, 2.48 Hz, 1H), 7.42 (d, J = 2.52 Hz, 1H), 7.40 (s, 1H), 7.34 (d, J = 8.96 Hz, 1H), 6.70 (d, J = 2.0 Hz, 1H), 4.39 (t, J = 4.40 Hz, 2H), 4.25 (t, J = 4.00 Hz, 2H), 3.94 (s, 3H), 2.68 (s, 3H), 1.77 (s, 3H)	795		MS (ESI) m/z 615.04 [M+1]+ ; 1H NMR (400 MHz, DMSO-d6) δ 13.58 (bs, 1H), 8.32 (s, 1H), 8.03 (s, 1H), 7.59 (dd, J = 2.40, 8.76 Hz, 1H), 7.42 (d, J = 2.52 Hz, 1H), 7.39 (s, 1H), 7.33 (d, J = 8.96 Hz, 1H), 4.37 (bs, 2H), 4.21 (bs, 2H), 2.68 (s, 3H), 2.37-2.32 (m, 1H), 1.76 (s, 3H), 1.19-1.13 (m,4H)

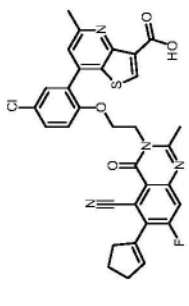
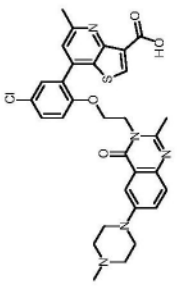
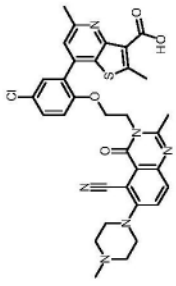
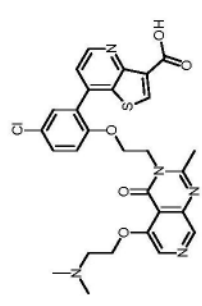
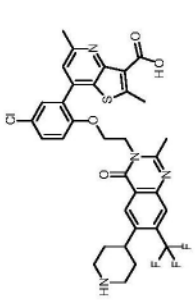
[1252]

788Fa		MS (ESI) m/z 676.01 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 11.58 (s, 1H), 8.43 (d, J = 5.0 Hz, 1H), 8.21 (d, J = 6.6 Hz, 2H), 8.11 (d, J = 7.56 Hz, 1H), 7.62 (s, 1H), 7.60-7.56 (m, 1H), 7.43 (d, J = 2.6 Hz, 2H), 7.35 (d, J = 8.8 Hz, 2H), 4.40 (t, J = 6.7 Hz, 2H), 4.24 (t, J = 5.0 Hz, 2H), 2.58 (s, 3H), 1.71 (s, 3H)
796		MS (ESI) m/z 644.27 [M+1]+; 1H-NMR (400 MHz, DMSO-d6) δ 13.60 (bs, 1H), 8.34 (s, 1H), 8.02 (s ,1H), 7.59 (dd, J = 2.52, 8.88 Hz, 1H), 7.41 (d, J = 2.52 Hz, 1H),7.39 (s, 1H), 7.35 (d, J = 8.96 Hz, 1H), 5.03 (s, 4H), 4.37 (t, J = 5.28 Hz, 2H), 4.23 (t, J = 6.32 Hz, 2H), 2.70 (s, 3H), 1.75 (s, 3H)
788Fb		MS (ESI) m/z 694.03 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 12.69 (s, 1H), 8.63 (d, J = 4.9 Hz, 1H), 8.40 (s, 1H), 7.80 (s, 1H), 7.75 (s, 1H), 7.61 (d, J = 7.4 Hz, 1H), 7.52 (dd, J = 2.4, 4.9 Hz, 1H), 7.45 (s, 1H), 7.37 (s, 2H), 7.31-7.29 (m, 1H), 7.26 (s, 2H), 4.35 (bs, 2H), 4.24 (bs, 2H), 2.58 (s, 3H), 1.75 (s, 3H)
797		MS (ESI) m/z 644.0 [M-1]-; 1H-NMR (400 MHz, DMSO-d6)) δ 13.59 (bs, 1H), 8.39 (s, 1H), 7.90 (s ,1H), 7.59 (dd, J = 2.44, 8.88 Hz, 1H), 7.41 (d, J = 2.48 Hz, 1H), 7.38 (s, 1H), 7.33 (d, J = 8.96 Hz, 1H), 5.70 (d, J = 5.84 Hz, 1H), 4.57-4.56 (m , 1H), 4.38-4.32 (m, 4H), 4.18 (d, J = 4.2 Hz, 2H), 3.96-3.92 (m, 2H), 2.68 (s, 3H), 1.71 (s, 3H)
798		MS (ESI) m/z 725.97 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.45 (s, 1H), 7.66 (s, 1H), 7.58 (dd, J = 8.88, 2.56 Hz 1H), 7.43-7.38 (m, 2H), 7.35 (d, J = 8.96 Hz, 1H), 4.37 (t, J = 6.00 Hz, 2H), 4.20 (t, J = 4.28 Hz, 2H), 3.55-3.44 (m, 4H), 2.70 (s, 3H), 2.05-1.94 (m, 4H), 1.81 (s, 3H)	801		MS (ESI) m/z 686.30 [M+1]+ ; 1H NMR (400 MHz, DMSO-d6) δ 13.58 (bs, 1H), 8.38 (s, 1H), 8.02 (s, 1H), 7.59 (dd, J = 2.60, 8.92 Hz, 1H), 7.42 (d, J = 2.56 Hz, 1H), 7.39 (s, 1H), 7.33 (d, J = 8.96 Hz, 1H), 4.37 (t, J = 4.64 Hz, 2H), 4.20 (t, J = 5.56 Hz, 2H), 3.23 (t, J = 5.16 Hz, 4H), 2.68 (s, 3H), 1.78 (s, 3H), 1.48 (t, J = 5.2 Hz, 4H), 0.99 (s, 6H)

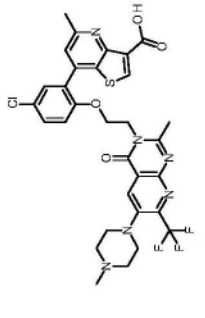
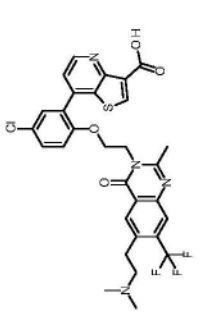
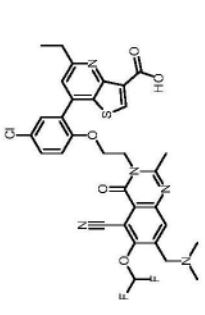
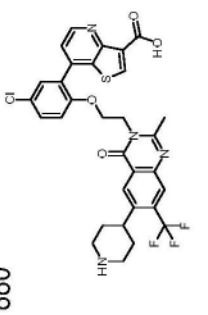
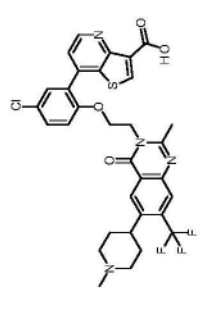
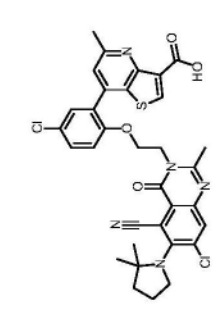
[1253]

799		802	
MS (ESI) m/z 671.94 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.55 (bs, 1H), 8.42 (s, 1H), 7.69 (s, 1H), 7.58 (dd, J = 2.36, 8.84 Hz, 1H), 7.40 (d, J = 2.52 Hz, 1H), 7.39 (s, 1H), 7.35 (d, J = 9.00 Hz, 1H), 7.33 (t, J = 54.04 Hz, 1H), 4.92 (t, J = 12.44 Hz, 4H), 4.38 (t, J = 5.36 Hz, 2H), 4.20 (t, J = 5.80 Hz, 2H), 2.70 (s, 3H), 1.82 (s, 3H)		MS (ESI) m/z 694.06 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.57 (bs, 1H), 8.33 (s, 1H), 8.10 (s, 1H), 7.58 (d, J = 7.08, 1H), 7.41-7.32 (m, 3H), 4.38 (t, J = 3.64 Hz, 2H), 4.21 (t, J = 5.68 Hz, 2H), 3.35 (t, J = 5.08 Hz, 4H), 2.68 (s, 3H), 2.14 (t, J = 13.4 Hz, 4H), 1.76 (s, 3H)	
800		803	
MS (ESI) m/z 672.15 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.38 (s, 1H), 8.03 (s, 1H), 7.59 (dd, J = 2.56, 8.88 Hz, 1H), 7.42 (d, J = 2.56 Hz, 1H), 7.39 (s, 1H), 7.33 (d, J = 8.96 Hz, 1H), 4.37 (t, J = 5.48 Hz, 2H), 4.20 (t, J = 4.32 Hz, 2H), 3.55 (d, J = 12.44 Hz, 2H), 2.90 (t, J = 11.90 Hz, 2H), 2.68 (s, 3H), 1.74-1.72 (m, 5H), 1.58 (bs, 1H), 1.31-1.23 (m, 2H), 0.97 (d, J = 6.44 Hz, 3H)		MS (ESI) m/z 725.97 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.38 (s, 1H), 8.06 (s, 1H), 7.58 (d, J = 8.60 Hz, 1H), 7.41 (s, 2H), 7.34 (d, J = 8.96 Hz, 1H), 4.38 (t, J = 5.16 Hz, 2H), 4.21 (t, J = 5.52 Hz, 2H), 3.62 (d, J = 12.52 Hz, 2H), 2.97 (t, J = 12.12 Hz, 2H), 2.70 (s, 3H), 1.94 (d, J = 11.96 Hz, 2H), 1.76 (s, 3H), 1.64-159 (m, 2H)	
804		810	
MS (ESI) m/z 681.96 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.56 (s, 1H), 8.59 (d, J = 3.56, 1H), 8.35 (s, 1H), 8.14 (s, 1H) 7.87 (t, J = 6.92 Hz, 1H), 7.59-7.53 (m, 2H), 7.42-7.40 (m, 2H), 7.38-7.33 (m, 2H), 5.66 (s, 2H), 4.39 (t, J = 4.36 Hz, 2H), 4.22 (t, J = 4.04 Hz, 2H), 2.70 (s, 3H), 1.75 (s, 3H)		MS (ESI) m/z 605.8 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.49 (d, J = 0.8 Hz, 1H), 8.44 (s, 1H), 7.58 (dd, J = 8.9, 2.7 Hz, 1H), 7.42 (d, J = 2.7 Hz, 1H), 7.36 (s, 1H), 7.34 (d, J = 9.0 Hz, 1H), 7.11 (d, J = 0.9 Hz, 1H), 4.48 (d, J = 12.6 Hz, 2H), 4.36 (t, J = 5.1 Hz, 2H), 4.21 (t, J = 5.1 Hz, 2H), 3.56 (bd, J = 11.0 Hz, 2H), 3.25-3.04 (m, 4H), 2.88 (d, J = 3.5 Hz, 3H), 2.69 (s, 3H), 1.83 (s, 3H)	

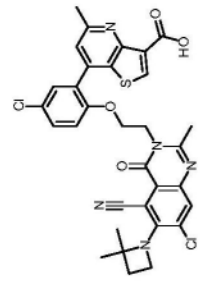
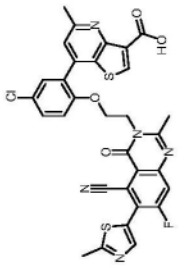
[1254]

805		MS (ESI) m/z 614.99 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.44 (s, 1H), 7.59 (dd, J = 8.80, 2.40 Hz, 1H), 7.43-7.41 (m, 3H), 7.36 (d, J = 8.80 Hz, 1H), 6.19 (s, 1H), 4.38 (t, J = 4.92 Hz, 2H), 4.22 (t, J = 6.00 Hz, 2H), 2.78-2.50 (m, 5H), 2.09-2.01 (m, 4H), 1.86 (s, 3H)	811		MS (ESI) m/z 604.8 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.44 (s, 1H), 7.57 (td, J = 8.9, 2.8 Hz, 2H), 7.42 (d, J = 2.7 Hz, 1H), 7.39 – 7.27 (m, 4H), 4.36 (t, J = 5.1 Hz, 2H), 4.22 (t, J = 5.0 Hz, 2H), 3.97 (d, J = 13.2 Hz, 2H), 3.57 (d, J = 12.3 Hz, 2H) 3.29 – 3.13 (m, 2H), 3.04 (t, J = 12.6 Hz, 2H), 2.89 (d, J = 4.0 Hz, 3H), 2.68 (s, 3H), 1.82 (s, 3H).
806		MS (ESI) m/z 583.01 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 12.89 (bs, 1H), 8.07 (bs, 1H), 7.89 (d, J = 7.6 Hz, 1H), 7.85 (s, 1H), 7.52-7.12 (m, 6H), 4.35 (s, 4H), 4.13 (s, 2H), 2.56 (bs, 6H), 2.14 (s, 3H)	812		MS (ESI) m/z 643.6 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 7.70 (d, J = 9.0 Hz, 1H), 7.64 – 7.57 (m, 2H), 7.43 – 7.34 (m, 3H), 4.41 (t, J = 5.0 Hz, 2H), 4.24 (t, J = 5.1 Hz, 2H), 3.82 – 3.55 (m, 4H), 3.25 (bd, J = 9.1 Hz, 4H), 2.92 (s, 3H), 2.70 (s, 3H), 2.48 (s, 3H), 1.95 (s, 3H)
841		MS (ESI) m/z = 580.3 [M+1]+; 1H-NMR (400 MHz, d6-DMSO) δ /ppm = 9.74-9.62 (b, 1H), 8.84 (d, J = 4.7 Hz, 1H), 8.52 (s, 1H), 8.44 (s, 1H), 8.38 (s, 1H), 7.59 (dd, J = 8.9, 2.7 Hz, 1H), 7.46-7.43 (m, 2H), 7.32 (d, J = 8.9 Hz, 1H), 4.54 (t, J = 4.4 Hz, 2H), 4.34 (t, J = 4.9 Hz, 2H), 4.18 (t, J = 4.9 Hz, 2H), 3.61-3.56 (m, 2H), 2.98 (d, J = 4.4 Hz, 6H), 1.80 (s, 3H)	877		LCMS (ESI) m/z 671.1 [M+1]+. 1H NMR (400 MHz, DMSO-d6) δ 8.62 (s, 1H), 8.18 (d, J = 8.8 Hz, 1H), 8.07 (s, 1H), 7.63 (s, 1H), 7.56 (dd, J = 8.9, 2.7 Hz, 1H), 7.41 – 7.28 (m, 2H), 4.37 (t, J = 5.0 Hz, 1H), 4.22 (d, J = 5.0 Hz, 1H), 3.38 (d, J = 12.0 Hz, 1H), 3.09 (d, J = 12.0 Hz, 1H), 2.67 (s, 2H), 2.17 (s, 2H), 1.94 (t, J = 11.8 Hz, 1H), 1.81 (s, 3H)

[1255]

849		LCMS: 672.9 [M+H]+; 1H NMR (400 MHz, DMSO-d6) δ 9.79 (s, 1H), 8.48 (s, 1H), 8.41 (s, 1H), 7.60 (dd, J = 8.9, 2.7 Hz, 1H), 7.43 (d, J = 2.7 Hz, 1H), 7.40 – 7.31 (m, 2H), 4.41 (t, J = 5.1 Hz, 2H), 4.27 (t, J = 5.2 Hz, 2H), 3.37 – 3.12 (m, 6H), 2.93 (d, J = 2.7 Hz, 3H), 2.69 (s, 3H), 1.99 (s, 3H)
858		LCMS: 631.4 [M+H]+; 1H NMR (400 MHz, DMSO-d6) δ 9.77 – 9.57 (m, 1H), 8.79 (d, J = 4.8 Hz, 1H), 8.19 (s, 1H), 8.11 (s, 1H), 7.70 (s, 1H), 7.56 (dd, J = 8.9, 2.7 Hz, 1H), 7.41 (dd, J = 12.9, 3.7 Hz, 2H), 7.32 (d, J = 9.0 Hz, 1H), 4.36 (t, J = 5.1 Hz, 2H), 4.22 (t, J = 5.0 Hz, 2H), 3.34 (t, J = 6.2 Hz, 2H), 3.20 (dd, J = 11.3, 5.4 Hz, 2H), 2.88 (d, J = 4.3 Hz, 6H), 1.78 (s, 3H)
896		MS (ESI) m/z 668.21 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.34 (s, 1H), 7.74 (bs, 1H), 7.60 (dd, J = 2.4, 8.8 Hz, 1H), 7.49-7.13 (m, 4H), 4.39 (bs, 2H), 4.23 (bs, 2H), 3.58 (bs, 2H), 3.03-2.98 (m, 2H), 2.25 (bs, 6H), 1.78 (s, 3H), 1.37 (t, J = 7.6 Hz, 3H)
880		LCMS (ESI) m/z 643.1 [M+1]+. 1H NMR (400 MHz, DMSO-d6) δ 8.77 (d, J = 4.8 Hz, 1H), 8.26 (s, 1H), 8.20 (s, 1H), 8.06 (s, 1H), 7.70 (s, 1H), 7.56 (dd, J = 8.9, 2.7 Hz, 1H), 7.45 – 7.37 (m, 2H), 7.32 (d, J = 9.0 Hz, 1H), 4.36 (t, J = 5.0 Hz, 2H), 4.21 (t, J = 5.1 Hz, 2H), 3.19 (s, 1H), 3.09 (d, J = 11.9 Hz, 2H), 1.94 (q, J = 13.5, 12.6 Hz, 4H), 1.79 (s, 3H)
881		LCMS (ESI) m/z 657.0 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.78 (d, J = 4.8 Hz, 1H), 8.24 (s, 1H), 8.02 (s, 1H), 7.70 (s, 1H), 7.56 (dd, J = 8.9, 2.7 Hz, 1H), 7.45 – 7.37 (m, 2H), 7.32 (d, J = 9.0 Hz, 1H), 4.36 (t, J = 5.0 Hz, 2H), 4.21 (t, J = 5.0 Hz, 2H), 3.21 – 3.11 (m, 3H), 2.82 (d, J = 4.6 Hz, 3H), 1.99 (s, 3H), 1.78 (s, 3H)
920		MS (ESI) m/z 662.15 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.38 (s, 1H), 7.74 (d, J = 8.72 Hz, 1H), 7.57 (dd, J = 2.12, 8.76 Hz, 1H), 7.41 (d, J = 2.08 Hz, 1H), 7.39 (bs, 1H), 7.34(d, J = 8.92 Hz, 1H), 4.37 (bs, 2H), 4.19 (bs, 2H), 3.60-3.57 (m, 1H), 3.47-3.41 (m, 1H), 2.69 (s, 3H), 2.10-2.05 (m, 2H), 1.89-1.86 (m, 2H), 1.79 (s, 3H), 1.25 (s, 3H), 1.12 (s, 3H)

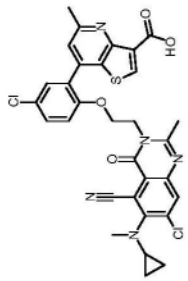
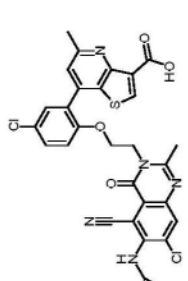
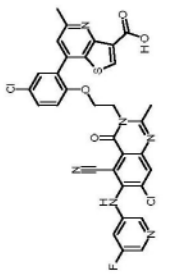
[1256]

918		MS (ESI) m/z 648.12 [M+1]+;1H NMR (400 MHz, DMSO-d6) δ 13.32 (bs, 1H), 8.37 (s, 1H), 7.62-7.57 (m, 2H), 7.42-7.33 (m, 3H), 4.41-4.37 (m, 4H), 4.18 (s, 2H), 2.69 (s, 3H), 2.25 (t, J=7.52 Hz, 2H), 1.74 (s, 3H), 1.53 (s, 6H).	921		MS (ESI) m/z 646.03 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.45 (s, 1H), 8.02 (s, 1H), 7.59 (dd, J = 2.56 Hz, J = 8.88 Hz, 1H), 7.55 (d, J = 10.16 Hz, 1H), 7.43 (s, 1H), 7.41 (d, J = 2.56 Hz, 1H), 7.36 (d, J = 8.96 Hz, 1H), 4.40 (t, J = 5.88 Hz, 2H), 4.25 (t, J = 4.44 Hz, 2H), 2.79 (s, 3H), 2.72 (s, 3H), 1.90 (s, 3H)
919		MS (ESI) m/z 684.04 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.40 (s, 1H), 7.68 (s, 1H), 7.59 (dd, J = 2.48, 8.84 Hz, 1H), 7.40 (bs, 2H), 7.35 (d, J = 8.92 Hz, 1H), 4.38 (t, J = 5.92 Hz, 2H), 4.22 (t, J = 6.52 Hz, 2H), 3.45 (t, J = 5.96 Hz, 4H), 2.71 (s, 3H), 2.21-2.16 (m, 4H), 1.86 (s, 3H)	932		MS (ESI) m/z 654.10 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.41 (s, 1H), 7.69-7.55 (m, 4H), 7.43 (s, 1H), 7.40 (d, J = 2.52 Hz, 1H), 7.32 (d, J = 8.96 Hz, 1H), 4.44-4.38 (m, 2H) 4.26 (t, J=5.40 Hz, 2H), 2.73 (s, 3H), 2.65 (s, 6H), 1.93 (s, 3H)
933		MS (ESI) m/z 668.23 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.39 (s, 1H), 7.79 (s, 1H), 7.60 (dd, J = 8.84, 2.6 Hz, 1H), 7.51 (bs, 2H), 7.42 (s, 1H), 7.40 (d, J = 2.56 Hz, 1H), 7.37 (d, J= 9 Hz, 1H), 5.32 (d, J= 46.4 Hz, 2H), 4.41 (t, J = 3.04 Hz, 2H), 4.27 (t, J = 5.12 Hz, 2H), 2.72 (s, 3H), 2.64 (s, 6H), 1.96 (s, 3H)	938		MS (ESI) m/z 633.05 [M+1]+.1H NMR (400 MHz, DMSO-d6) δ 13.56 (s, 1H), 8.38 (s, 1H), 8.14 (s, 1H), 7.57 (bs, 1H), 7.42-7.33 (m, 3H), 5.36 (bs, 1H), 4.39 (bs, 2H), 4.23 (bs, 2H), 2.67 (s, 3H), 1.79 (s, 3H), 1.58 (s, 6H)

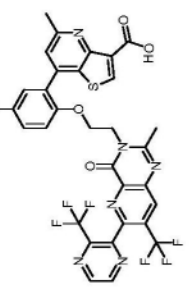
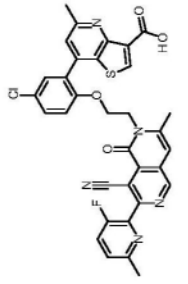
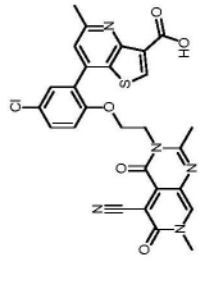
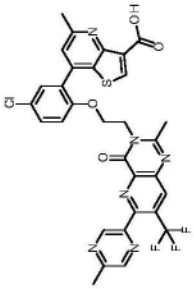
[1257]

935		MS (ESI) m/z 625.09 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.59 (bs, 1H), 8.46 (s, 1H), 7.58-7.51 (m, 7H), 7.42 (s, 2H), 7.37 (d, J = 8.44 Hz, 1H), 4.40 (t, J = 3.72, 2H), 4.25 (t, J = 5.12, 2H), 2.72 (s, 3H), 1.85 (s, 3H).
936		MS (ESI) m/z 646.04 [M+1]+, 1H NMR (400 MHz, DMSO-d6) δ 9.29 (s, 1H), 8.45 (s, 1H), 7.61-7.57 (m, 2H), 7.43 (bs, 2H), 7.33 (t, J=19.2Hz, 1H), 4.40 (t, J=5.68 Hz, 2H), 4.25 (d, J=4.48 Hz, 2H), 2.72 (s, 3H), 2.30 (s, 3H), 1.85 (s, 3H).
956		MS (ESI) m/z 636.11 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.47 (s, 1H), 8.38 (s, 1H), 7.73 (s, 1H), 7.58 (dd, J = 2.32 Hz, J = 8.80 Hz, 1H), 7.43 (d, J = 2.28 Hz, 1H), 7.40 (s, 1H), 7.35 (d, J = 8.96 Hz, 1H), 4.55 (s, 1H), 4.37 (t, J = 5.12 Hz, 2H), 4.19 (t, J = 6.04 Hz, 2H), 2.69 (s, 3H), 1.74 (s, 3H), 1.32 (s, 9H)
939		MS (ESI) m/z 671.98 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.61 (bs, 1H), 9.19 (s, 1H), 8.35 (s, 1H), 7.58 (dd, J = 8.88, 2.56 Hz, 1H), 7.44 (s, 2H), 7.35 (d, J =9.0 Hz, 1H), 4.40 (t, J=5.0 Hz, 2H), 4.26 (t, J = 5.44, 2H), 2.72 (s, 3H), 2.20 (s, 3H), 1.81 (s, 3H)
955		MS (ESI) m/z 650.12 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.54 (s, 1H), 8.34 (s, 1H), 7.72 (s, 1H), 7.58 (dd, J = 1.48 Hz, J = 7.80 Hz, 1H), 7.42 (d, J = 1.76 Hz, 1H), 7.40 (s, 1H), 7.50 (d, J = 8.88, 1H), 4.38 (t, J = 5.80, 2H), 4.20 (t, J = 4.32, 2H), 2.90 (s, 3H), 2.70 (s, 3H), 1.77 (s, 3H), 1.25 (s, 9H)
959		MS (ESI) m/z 685.17 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.58 (s, 1H), 8.41 (s, 1H), 8.17 (s, 1H), 7.92 (s, 1H), 7.62-7.59 (m, 3H), 7.44 (s, 2H), 7.37 (d, J = 8.96 Hz, 1H), 4.40 (t, J = 2.76 Hz, 2H), 4.26 (t, J = 3.72 Hz, 2H), 3.44 (s, 3H), 2.73 (s, 3H), 2.57 (s, 3H), 1.85 (s, 3H)

[1258]

957		MS (ESI) m/z 634.13 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.4 (s, 1H), 8.39 (s, 1H), 7.69 (s, 1H), 7.59 (dd, J = 8.84, 2.44 Hz, 1H), 7.42 (d, J = 2.4 Hz, 1H), 7.38 (s, 1H), 7.35 (d, J = 8.92 Hz, 1H), 4.37 (bs, 2H), 4.19 (bs, 2H), 3.08 (t, J = 10.36 Hz, 1H), 3.02 (s, 3H), 2.69 (s, 3H), 1.78 (s, 3H), 0.63 (d, J = 4.92 Hz, 2H), 0.37 (bs, 2H)	MS (ESI) m/z 671.27 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 9.25 (s, 1H), 8.45 (s, 1H), 8.20 (d, J = 2.20, 1H), 7.86 (s, 1H), 7.69 (s, 1H), 7.60 (dd, J = 2.32 Hz, J = 8.72 Hz, 2H), 7.43-7.42 (m, 2H), 7.36 (d, J = 8.92 Hz, 1H), 4.39 (t, J = 5.56 Hz, 2H), 4.24 (t, J = 3.56 Hz, 2H), 2.71 (s, 3H), 2.55 (s, 3H), 1.81 (s, 3H)
958		MS (ESI) m/z 620.03 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ8.46 (s, 1H), 7.59 (d, J = 2.2Hz, 1H), 7.54 (s, 1H), 7.43 (d, J = 2.4 Hz, 2H), 7.36 (d, J = 8.92 Hz, 1H), 6.66 (s, 1H), 4.36 (bs, 2H), 4.10 (bs, 2H), 3.16 (d, J = 6.84 Hz, 1H), 2.70 (s, 3H), 1.80 (s, 3H), 0.867-0.82 (m, 2H), 0.65-0.62 (m, 2H)	MS (ESI) m/z 689.15 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.43 (s, 1H), 8.01 (s, 1H), 7.91 (s, 1H), 7.79 (s, 1H), 7.59 (d, J = 8.80 Hz, 1H), 7.44 (s, 2H), 7.36 (d, J = 8.80 Hz, 1H), 7.04 (d, J = 12.04 Hz, 1H), 4.39 (s, 2H), 4.25 (s, 2H), 3.39 (s , 3H), 2.73 (s, 3H), 1.80 (s, 3H)
962		MS (ESI) m/z 675.07 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 9.07 (s, 1H), 8.45 (s, 1H), 8.09 (s, 1H), 8.03 (d, J = 2.04, 1H), 7.85 (s, 1H), 7.59 (dd, J = 8.84 Hz, 2.36 Hz, 1H), 7.44 (s, 2H), 7.36 (d, J = 8.92 Hz, 1H), 7.04 (d, J = 11.12 Hz, 1H), 4.39 (t, J = 4.64 Hz, 2H), 4.22 (t, J = 4.48 Hz, 2H), 2.72 (s, 3H), 1.75 (s, 3H)	1001		MS (ESI) m/z [M+1]+, 1H NMR (400 MHz, DMSO-d6) δ 9.08 (s, 1H), 8.64 (s, 1H), 8.38 (s, 1H), 8.02 (d, J = 6.96 Hz,1H), 7.59 (d, J = 6.76 Hz, 1H), 7.39-7.35 (m, 3H), 6.18 (s, 1H), 4.37 (s, 2H), 4.22 (s, 2H), 2.68 (s, 3H), 2.30 (s, 3H),1.78 (s, 3H), 1.05 (t, J = 7.16 Hz, 1H).

[1259]

990		MS (ESI) m/z 721.31 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.63 (bs, 1H), 9.18 (s, 1H), 9.13 (s, 1H), 8.46 (s, 1H), 8.32 (s, 1H), 7.58 (dd, J = 2.52, 8.88 Hz, 1H), 7.44 -7.43 (m, 2H), 7.34 (d, J = 8.96 Hz, 1H), 4.39 (t, J = 5.00 Hz, 2H), 4.26 (t, J = 4.36 Hz, 2H), 2.70 (s, 3H), 1.82 (s, 3H)	MS (ESI) m/z 574 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.52 (bs, 1H), 8.57 (s, 1H), 8.49 (s, 1H), 7.57 (d, J = 8.52Hz, 1H), 7.39-7.33 (m, 3H), 5.91 (s,1H), 4.37 (t, J = 5.08 Hz, 2H), 4.16 (t, J = 4.04 Hz, 2H), 3.21 (s, 6H), 2.70 (s, 3H), 1.63 (s, 3H)
1000		MS (ESI) m/z [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 9.12 (s, 1H), 8.49 (s, 1H), 7.86 (t, J = 9.12 Hz, 1H), 7.74-7.66 (m, 2H), 7.54-7.38 (m, 3H),6.21 (s, 1H), 4.40 (t, J = 4.48, 2H), 4.24 (t, J = 4.64, 2H), 2.69 (s, 3H), 2.54 (s, 3H), 1.69 (s, 3H).	MS (ESI) m/z 586.13 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.49 (bs, 1H), 8.56 (s, 1H), 8.48 (s, 1H), 7.56 (d, J = 8.84 Hz, 1H), 7.39 (s, 1H), 7.40-7.33 (m, 2 H), 5.89 (s, 1H), 4.37-4.32 (m, 6H), 4.15 (t, J = 5.36 Hz, 2H), 2.69 (s, 3H), 1.69 (s, 3H), 2.38-2.32 (m, 2H)
1005		MS (ESI) m/z 562.18 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.64 (bs, 1H), 8.58 (s, 1H), 8.56 (s, 1H), 7.62-7.56 (m, 1H), 7.43-.7.39 (m, 2H), 7.34 (d, J = 8.92 Hz, 1H), 4.35 (t, J = 4.68 Hz, 2H), 4.41 (t, J = 4.48 Hz, 2H), 3.70 (s, 3H), 2.72 (s, 3H), 1.71 (s, 3H)	1018  MS (ESI) m/z 667.06 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.58 (bs, 1H), 8.95 (s, 1H), 8.68 (s, 1H), 8.36 (s, 1H), 8.32 (s, 1H), 7.58 (dd, J = 8.92, 2.40 Hz, 1H), 7.42 (s, 2H), 7.35 (d, J = 8.92 Hz, 1H), 4.40 (s, 2H), 4.27 (s, 2H), 2.70 (s, 3H), 2.62 (s, 3H), 1.81 (s, 3H)

[1260]

1006		MS (ESI) m/z 632.03 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.51 (s, 1H), 8.48 (s, 1H), 7.91 (s, 1H), 7.63-7.56 (m, 2H), 7.46-7.40 (m, 2H), 7.35 (d, J = 8.96 Hz, 1H), 4.39 (t, J = 5.96 Hz, 2H), 4.24 (t, J = 5.44 Hz, 2H), 2.71 (s, 3H), 1.81 (s, 3H)
1007		MS (ESI) m/z 591.10 [M+1]+ ; 1H NMR (400 MHz, DMSO-d6) δ 13.58 (bs, 1H), 8.69 (s, 1H), 8.46 (s, 1H), 7.59 (dd, J = 2.52, 8.64 Hz, 1H), 7.43-7.42 (m, 3H), 7.34 (s, 1H), 7.32 (s, 1H), 4.34 (t, J = 5.04 Hz, 2H), 4.15(t, J = 4.68 Hz, 2H), 2.70 (s, 3H), 1.69 (s, 3H)
1019		MS (ESI) m/z 667.16 [M+1]+; 1H NMR (400 MHz, DMSO-d6) 13.60 (s,1H), 8.72 (d, J = 2.36 Hz, 1H), 8.61 (s, 1H), 8.39 (s, 1H), 8.37 (s, 1H), 7.58 (dd, J = 8.76, 2.36 Hz, 1H), 7.47-7.40 (m, 2H), 7.35 (d, J = 8.96 Hz, 1H), 4.40 (t, J = 4.3 Hz, 2H), 4.26 (t, J = 4.8 Hz, 2H), 2.71 (s, 3H), 2.35(s, 3H), 1.82 (s, 3H)
1020		MS (ESI) m/z 703.10 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.56 (bs, 1H), 9.24 (s, 1H), 9.12 (s, 1H), 8.37 (d, J = 7.00 Hz, 2H), 7.60 (dd, J = 2.44, 8.88 Hz, 1H), 7.42-7.13 (m, 4H), 4.42 (t, J = 5.68 Hz, 2H), 4.28 (t, J = 5.16 Hz, 2H), 2.71 (s, 3H) 1.84 (s, 3H)
1021		MS (ESI) m/z 721.05 [M-1]-; 1H NMR (400 MHz, DMSO-d6) δ 9.51 (s, 1H), 9.41 (s, 1H), 8.39 (s, 1H), 8.36 (s, 1H), 7.59 (dd, J = 2.0, 8.8 Hz, 1H), 7.42 (s, 1H), 7.36 (d, J = 8.8 Hz, 1H, 4.41 (bs, 2H), 4.29 (bs, 2H), 2.69 (s, 3H), 1.83 (s, 3H)
1024		MS (ESI) m/z 701.10 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.74 (s, 1H), 8.39 (s, 1H), 8.35 (s, 1H), 7.58 (dd, J=8.9, 2.3 Hz, 1H), 7.44 (s, 2H), 7.34 (d, J=8.9 Hz, 1H), 4.39 (t, J=9.5 Hz, 2H), 4.26 (t, J=4.5 Hz, 2H), 3.21 (s, 3H), 2.64 (s, 3H), 1.82 (s, 3H)

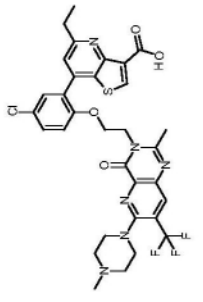
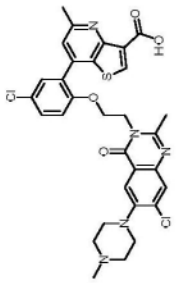
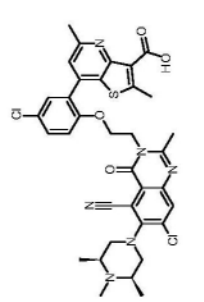
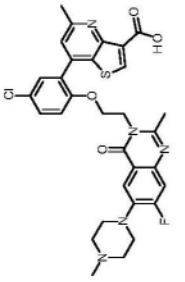
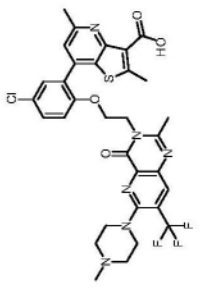
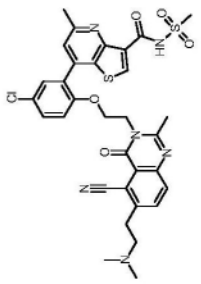
[1261]

1022		1040		MS (ESI) m/z 650.13 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.54 (bs, 1H), 8.34 (s, 1H), 7.59-7.52 (m, 1H), 7.50-7.45 (m, 5H), 7.40 (bs, 2H), 7.35 (d, J = 8.92 Hz, 1H), 6.99 (s, 1H), 4.36 (t, J = 5.24 Hz, 2H), 4.18 (t, J = 4.84 Hz, 2H), 2.71 (s, 3H), 2.70 (s, 6H), 1.79 (s, 3H)
1023		1047		MS (ESI) m/z 619.12 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.50 (s, 1H), 8.37 (s, 1H), 7.66 (s, 1H), 7.57 (dd, J = 2.32 Hz, J = 6.64 Hz, 1H), 7.41-7.34 (m, 3H), 4.37 (bs, 2H), 4.33-4.28 (m, 1H), 4.22 (bs, 2H), 2.81-2.73 (m, 2H), 2.69 (s, 3H), 2.50-2.48 (m, 2H), 2.10-2.03 (m, 1H), 2.01-1.84(m, 1H), 1.84 (s, 3H)
1048		1061		MS (ESI) m/z 672.07 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.50 (bs, 1H), 8.44 (s, 1H), 8.30 (s, 1H), 7.88 (dd, J = 8.56, 2.16 Hz, 1H), 7.87 (s, 1H), 7.59 (dd, J = 8.88, 2.16 Hz, 1H), 7.42 (s, 2H), 7.36 (d, J = 8.88 Hz, 1H), 7.03 (d, J = 8.52 Hz, 1H), 4.40 (t, J = 5.56 Hz, 2H), 4.25 (t, J = 5.20 Hz, 2H), 3.95 (s, 3H), 2.71 (s, 3H), 1.89 (s, 3H)
1024		1041		MS (ESI) m/z 681.06. [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.62 (bs, 1H), 8.59 (s, 1H), 8.40 (s, 1H), 8.35 (s, 1H), 7.58 (dd, J = 2.48, 8.88 Hz, 1H), 7.43 (d, J = 2.5 Hz, 1H),7.43 (s, 1H), 7.34 (d, J = 8.96 Hz, 1H), 4.39 (t, J = 4.39 Hz, 2H), 4.26 (t, J = 4.12 Hz, 2H), 2.71 (s, 6H), 2.29 (s, 3H), 1.81 (s, 1H)
1025		1042		MS (ESI) m/z 681.21 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.48 (s, 1H), 8.39 (s, 1H), 8.34 (s, 1H), 7.58 (dd, J = 8.88, 2.56 Hz, 1H), 7.44 (d, J = 2.84 Hz, 2H), 7.35 (d, J = 8.92 Hz, 1H), 4.39 (t, J = 9.4 Hz, 2H), 4.26 (t, J = 8.32 Hz, 2H), 2.71 (s, 3H), 2.57 (s, 3H), 2.30 (s, 3H), 1.81 (s, 3H)
1049		1062		MS (ESI) m/z 621.09 [M+1] +; 1H NMR (400 MHz, DMSO-d6)) δ 13.49 (bs, 1H), 8.34 (s, 1H), 7.76 (s, 1H), 7.65-7.34 (m, 5H), 4.39 (t, J = 5.8 Hz, 2H), 4.23 (t, J = 5.2 Hz, 2H), 2.69 (s, 3H), 2.20-2.09 (m, 1H), 1.85 (s, 3H), 1.25-1.18 (m, 2H), 0.97-0.88 (m, 2H)

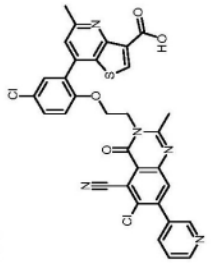
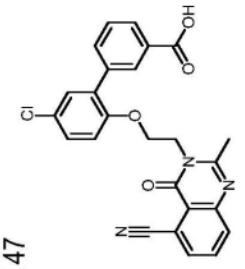
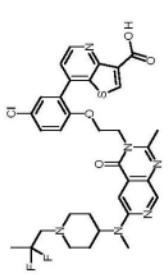
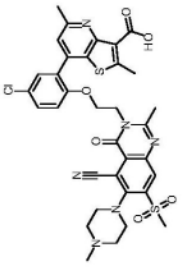
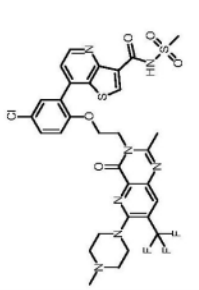
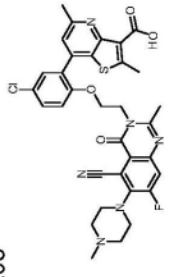
[1262]

1050		MS (ESI) m/z 605.09 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.51 (bs, 1H), 8.34 (s, 1H), 7.68 (s, 1H), 7.58 (dd, J = 8.64, 1.96 Hz, 1H), 7.44-7.38 (m, 2H), 7.35 (d, J = 8.92 Hz, 1H), 4.37 (s, 2H), 4.21 (s, 2H), 2.69 (s, 3H), 2.08-2.03 (m, 1H), 1.84 (s, 3H), 1.26-1.20 (m, 2H), 0.92-0.86 (m, 2H)	1077		MS (ESI) m/z, 580.08 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.85 (s, 1H), 8.50 (s, 1H), 7.58 (dd, J = 2.56, 11.44 Hz, 1H), 7.48 (d, J = 1.76 Hz, 1H), 7.42-7.41 (m, 2H), 7.34 (d, J = 8.96 Hz, 1H), 7.23 (d, J = 2.56 Hz, 1H), 7.18 (bs, 2H), 4.35 (t, J = 5.28 Hz, 2H), 4.24 (t, J = 4.76 Hz, 2H), 2.99 (q, J = 7.48 Hz, 2H), 1.34 (t, J = 7.52 Hz, 3H)
1054		MS (ESI) m/z 650.08 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.01 (s, 1H), 8.42 (s, 1H), 7.65 (s, 1H), 7.59 (dd, J = 10.96 Hz, 8.88 Hz, 1H), 7.33- 7.41 (m, 3H), 5.02 (s, 1H), 4.44 (s, 1H), 4.36 (bs, 2H), 4.19 (bs, 2H), 3.74-3.79 (m, 2H), 3.43-3.47 (m, 1H), 3.33 (s, 1H), 2.69 (s, 3H), 2.07-2.15 (m, 1H), 1.75-1.86 (m, 1H), 1.80 (s, 3H)	1078		MS (ESI) m/z 581.07 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.75 (bs, 1H), 8.53 (s, 1H), 7.72 (d, J = 1.60 Hz, 1H), 7.58 (dd, J = 2.56, 8.88 Hz, 1H), 7.46 (bs, 1H), 7.42 (d, J = 2.56 Hz, 2H), 7.34 (d, J = 8.96 Hz, 1H), 7.30 (d, J = 1.76 Hz, 1H), 4.35 (t, J = 5.16 Hz, 2H), 4.10 (t, J = 5.04 Hz, 2H), 2.99 (q, J = 7.48 Hz, 2H), 1.34 (t, J = 7.56 Hz, 3H)
1083		MS (ESI) m/z 686.21 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.23 (s, 1H), 7.98 (s, 1H), 7.67 (s, 1H), 7.59 (dd, J = 2.52 Hz, J = 8.84 Hz, 1H), 7.43 (bs, 2H), 7.35 (d, J = 8.96 Hz, 1H), 4.39 (t, J = 6.20 Hz, 2H), 4.23 (t, J = 6.32 Hz, 2H), 3.56 (d, J = 9.80 Hz, 2H), 3.25-3.13 (m, 6H), 2.99 (q, J = 7.52 Hz, J = 15.04 Hz, 2H), 2.93 (bs, 3H), 1.79 (s, 3H), 1.35 (t, 7.56 Hz, 3H)	1090b		MS (ESI) m/z 689.25 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 14.28 (bs, 1H), 7.58 (dd, J = 2.28, 8.84 Hz, 1H), 7.41 (bs, 1H), 7.38 (d, J = 2.36 Hz, 1H), 7.34 (d, J = 8.92 Hz, 1H), 6.99 (d, J = 8.28 Hz, 1H), 4.38 (t, J = 5.04 Hz, 2H), 4.19 (t, J = 4.68 Hz, 2H), 3.55 (d, J = 11.64 Hz, 2H), 2.79-2.73 (m, 2H), 2.70 (s, 3H), 2.39 (s, 3H), 2.37-2.34 (m, 2H), 2.23 (s, 3H), 1.86 (s, 3H), 1.10 (d, J = 6.00 Hz, 6H)

[1263]

1084		1094	
MS (ESI) m/z 687.16 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.72 (bs, 1H), 8.30 (s, 1H), 8.10 (s, 1H), 7.59 (dd, J = 2.5, 9.1 Hz, 1H), 7.45 (s, 2H), 7.34 (d, J = 8.9 Hz, 1H), 4.38 (bs, 2H), 4.21 (bs, 2H), 3.59 (bs, 4H), 3.25 (bs, 4H), 3.03-2.97 (m, 2H), 2.90 (s, 3H), 1.72 (s, 3H), 1.34 (t, J = 7.52 Hz, 3H)		MS (ESI) m/z 675.07 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.57 (s, 1H), 8.38 (s, 1H), 7.58 (s, 2H), 7.41-7.33 (m, 3H), 4.36 (s, 2H), 4.21 (s, 2H), 3.55 (bs, 4H), 3.24 (bs, 2H), 3.06 (bs, 2H), 2.91 (s, 3H), 2.69 (s, 3H), 1.82 (s, 3H)	
1090a		1095	
MS (ESI) m/z 705.26 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 14.28 (bs, 1H), 7.60 (bs, 1H), 7.58 (dd, J = 2.64, 8.96 Hz, 1H), 7.39 (bs, 1H), 7.38 (d, J = 2.60 Hz, 1H), 7.35 (d, J = 9.00 Hz, 1H), 4.37 (t, J = 4.56 Hz, 2H), 4.23 (t, J = 4.16 Hz, 2H), 3.17-3.12 (m, 5H), 2.70 (s, 3H), 2.43-2.38 (m, 4H), 2.22 (s, 3H), 1.96 (s, 3H), 1.03 (d, J = 6.08 Hz, 6H)		MS (ESI) m/z 711.15 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.42 (s, 1H), 7.57 (dd, J = 8.8, 2.5 Hz, 1H), 7.45-7.41 (m, 2H), 7.36-7.32 (m, 2H), 7.12 (d, J = 13.2 Hz, 1H), 4.35 (t, J = 9.2 Hz, 2H), 4.20 (t, J = 9.3 Hz, 2H), 3.14 (bs, 4H), 2.69 (s, 3H), 2.50 (bs, 4H), 1.79 (s, 3H), 1.23 (s, 3H)	
1096		1138	
MS (ESI) m/z 687.25 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 14.36 (bs, 1H), 8.00 (s, 1H), 8.32 (s, 1H), 7.60 (dd, J = 2.20, 8.68 Hz, 1H), 7.41 (s, 1H), 7.34 (d, J = 8.92 Hz, 1H), 4.40 (t, J = 4.32 Hz, 2H), 4.20 (t, J = 3.92 Hz, 2H), 3.23 (bs, 4H), 2.69 (s, 3H), 2.49 (bs, 4H), 2.35 (s, 3H), 2.23 (s, 3H), 1.77 (s, 3H)		MS (ESI) m/z 679.1 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 12.98 (s, 1H), 8.41 (s, 1H), 7.88 (d, J = 8.5 Hz, 1H), 7.67 (d, J = 8.5 Hz, 1H), 7.61 (dd, J = 8.9, 2.7 Hz, 1H), 7.46 – 7.37 (m, 3H), 4.42 (t, J = 5.1 Hz, 2H), 4.25 (t, J = 5.1 Hz, 2H), 3.56 (s, 3H), 3.45 – 3.37 (m, 2H), 3.37 – 3.29 (m, 2H), 2.91 (d, J = 4.5 Hz, 6H), 2.70 (s, 3H), 1.91 (s, 3H)	

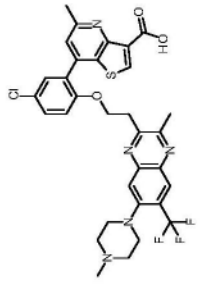
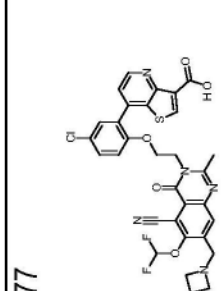
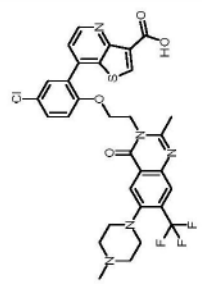
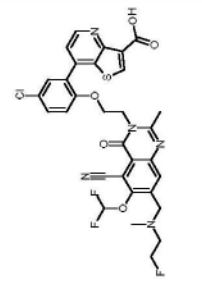
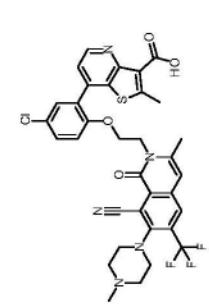
[1264]

1098		MS (ESI) m/z 642.01 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.84 (s, 1H), 8.73 (d, J = 3.7 Hz, 1H), 8.24 (s, 1H), 8.13 (d, J = 7.8 Hz 1H), 7.75 (s, 1H), 7.63-7.57 (m, 2H), 7.40-7.35 (m, 3H), 4.42 (t, J = 5.1 Hz, 2H), 4.27 (t, J = 4.8 Hz, 2H), 2.69 (s, 3H), 1.83 (s, 3H)	1147 	MS (ESI) m/z 460.1 [M+1]+; 1H NMR (300 MHz, DMSO-d6) δ 12.95 (s, 1H), 8.00 – 7.82 (m, 5H), 7.56 – 7.49 (m, 1H), 7.45 – 7.36 (m, 2H), 7.29 (d, J = 2.7 Hz, 1H), 7.21 (d, J = 8.9 Hz, 1H), 4.34 (s, 4H), 2.19 (s, 3H)
1114		MS (ESI) m/z 683.3 [M+1]+; 1H NMR (400 MHz, 氯仿-d) δ 8.79 (d, J = 4.9 Hz, 1H), 8.66 (d, J = 0.9 Hz, 1H), 8.30 (s, 1H), 7.48 (dd, J = 8.9, 2.6 Hz, 1H), 7.32 (d, J = 4.9 Hz, 1H), 7.24 (d, J = 2.6 Hz, 1H), 7.07 (d, J = 8.9 Hz, 1H), 6.87 (d, J = 0.9 Hz, 1H), 5.23 – 5.13 (m, 1H), 4.37 (t, J = 5.0 Hz, 2H), 4.28 (t, J = 5.0 Hz, 2H), 3.88 (d, J = 12.0 Hz, 2H), 3.57 (t, J = 14.3 Hz, 2H), 3.34 – 3.24 (m, 2H), 2.97 (s, 3H), 2.51 – 2.36 (m, 2H), 2.08 – 2.02 (m, 5H), 1.80 (t, J = 19.0 Hz, 3H)	1150 	MS (ESI) m/z 721.29 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 14.35 (s, 1H), 9.78 (s, 1H), 8.12 (s, 1H), 7.62 (dd, J = 8.8, 2.5 Hz, 1H), 7.45-7.42 (m, 2H), 7.38 (d, 1H), 4.41 (t, J = 4.5 Hz, 2H), 4.26 (t, J = 8.9 Hz, 2H), 3.90 (m, 2H), 3.57 (s, 5H), 3.23 (m, 4H), 2.90 (s, 3H), 2.72 (s, 3H), 2.47 (s, 3H), 1.99 (s, 3H)
1155		MS (ESI) m/z 735.80 [M+1] ;1H NMR (400 MHz, DMSO-d6) δ 12.50 (bs, 1H), 8.87 (d, J = 4.7 Hz, 1H), 8.47 (s, 1H), 8.12 (s, 1H), 7.60 (dd, J = 2.4, 8.9 Hz, 1H), 7.53 (d, J = 4.7 Hz, 1H), 7.45 (d, J = 2.4 Hz, 1H), 7.35 (d, J = 8.9 Hz, 1H), 4.39 (t, J = 5.1 Hz, 2H), 4.20 (t, J = 4.5 Hz, 2H), 3.51 (s, 3H), 3.28 (bs, 4H), 2.55 (bs, 4H), 2.28 (s, 3H), 1.69 (s, 3H)	1205 	MS (ESI) m/z 661.24 [M+1]+. 1H NMR (400 MHz, DMSO-d6) δ 14.29 (bs, 1H), 7.58 (d, J = 6.8 Hz, 1H), 7.44-7.34 (m, 4H), 4.38 (t, J = 4.8 Hz, 2H), 4.26 (t, J = 5.2 Hz, 2H), 2.68 (s, 3H), 2.54 (s, 3H), 2.52-2.45 (m, 8H), 2.24 (s, 3H), 1.98 (s, 3H)

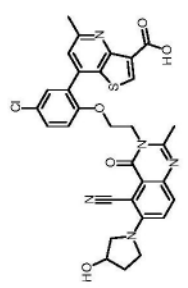
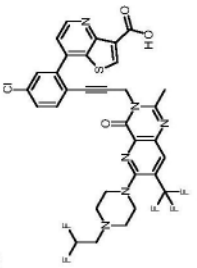
[1265]

1193	MS (ESI) m/z 639.26 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.68 (s, 1H), 7.59-7.58 (m, 6H), 7.42-7.36 (m, 3H), 4.41 (t, J = 4.0 Hz, 2H), 4.25 (t, J = 4.0, Hz, 2H), 3.20 (s, 3H), 2.66 (s, 3H), 2.03 (s, 3H)	1208	MS (ESI) m/z 673.30 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 14.41 (bs, 1H), 7.59 (dd, J = 8.8, 2.4 Hz, 1H), 7.41 (s, 1H), 7.40-7.32 (m, 2H), 6.96 (s, 1H), 4.39 (s, 2H), 4.19 (s, 2H), 4.00 (s, 3H), 3.26 (s, 4H), 2.71 (s, 3H), 2.55-2.45 (合并的, 4H), 2.40 (s, 3H), 2.28 (s, 3H), 1.91 (s, 3H)
1201	MS (ESI) m/z 719.23 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 14.24 (bs, 1H), 7.65 (s, 1H), 7.57 (d, J = 7.2 Hz, 1H), 7.37-7.33 (m, 3H), 4.38 (s, 2H), 4.26 (s, 2H), 2.68 (s, 6H), 2.5-2.47 (m, 8H), 1.93 (s, 3H), 1.06 (s, 9H)	1209	MS (ESI) m/z 682.30 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.43 (s, 1H), 7.96 (s, 1H), 7.93 (s, 1H), 7.58 (dd, J = 8.8, 2.4 Hz, 1H), 7.42-7.34 (m, 3H), 4.39 (s, 2H), 4.22 (s, 2H), 3.52 (s, 3H), 3.04 (s, 4H), 2.68 (s, 3H), 2.50 (合并的, 4H), 2.26 (s, 3H), 1.87 (s, 3H)
1210	MS (ESI) m/z 672.17 [M+1]+; 1H NMR (400 MHz, DMSO-d6), δ 8.79 (d, J = 4.8 Hz, 1H), 8.02 (s, 1H), 7.68 (s, 1H), 7.59 (dd, J = 9.2 Hz, 2.4 Hz, 1H), 7.51 (d, J = 4.8 Hz, 1H), 7.42 (d, J = 2.4 Hz, 1H), 7.35 (d, J = 9.2 Hz, 1H), 4.40 (bs, 2H), 4.24 (bs, 2H), 3.56-3.54 (m, 2H), 3.20-3.12 (m, 6H), 2.93 (s, 3H), 2.23 (s, 3H), 1.78 (s, 3H)	1240	MS (ESI) m/z 682.34 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.14 (bs, 1H), 8.82 (d, J = 4.8, 1H), 8.32 (s, 1H), 8.05 (s, 1H), 7.57 (d, J = 6.4 Hz, 1H), 7.42 (d, J = 5.2 Hz, 2H), 7.35 (d, J = 9.2 Hz, 1H), 6.07 (s, 1H), 4.39 (s, 2H), 4.19 (s, 2H), 3.67 (bs, 4H), 2.87 (bs, 4H), 2.23 (s, 3H), 1.61 (s, 3H)

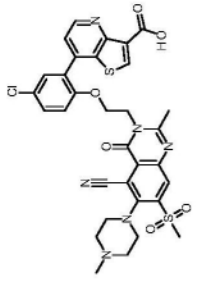
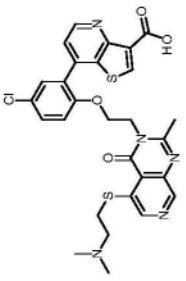
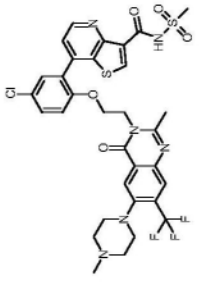
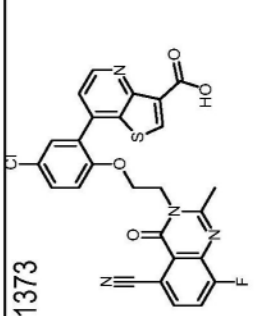
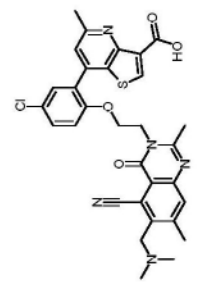
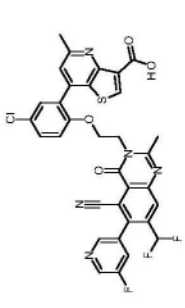
[1266]

1211		1267	
MS (ESI) m/z 656.26 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.24 (s, 1H), 8.27 (s, 1H), 8.08 (s, 1H), 7.56 (dd, J = 8.4 Hz, 2.4 Hz, 1H), 7.40 (s, 1H), 7.33 (s, 1H), 7.30 (d, J = 14.8 Hz, 1H), 7.25 (s, 1H), 4.53-3.38 (m, 4H), 4.25-3.16 (m, 4H), 3.01-2.98 (m, 2H), 2.89 (s, 3H), 2.86 (s, 3H), 2.69-2.60 (m, 2H), 2.26 (s, 3H)		MS (ESI) m/z 683.35 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 10.14 (bs, 1H), 8.83 (d, J = 4.8 Hz, 1H), 8.54 (s, 1H), 8.52 (d, J = 2.8 Hz, 1H), 7.91 (s, 1H), 7.62-7.55 (m, 2H), 7.46-7.43 (m, 2H), 7.30 (d, J = 8.9 Hz, 1H), 4.66-4.56 (m, 2H), 4.22 (s, 2H), 4.15-4.06 (m, 2H), 2.96 (s, 6H), 2.06 (s, 3H), 1.77 (s, 3H)	
1230		1277	
MS (ESI) m/z 660.24 [M+2]+; 1H NMR (400 MHz, DMSO-d6), δ 8.1 (d, J = 4.8 Hz, 1H), 8.30 (s, 1H), 7.95 (s, 1H), 7.70 (s, 1H), 7.58 (dd, J = 8.8, 2.4 Hz, 1H), 7.45-7.42 (m, 2H), 7.34 (d, J = 9.2 Hz, 1H), 4.38 (bs, 2H), 4.23 (bs, 2H), 3.0 (bs, 8H), 2.50 (bs, 3H), 1.78 (bs, 3H)		MS (ESI) m/z 688.19 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.82 (d, J = 4.8 Hz, 1H), 8.38 (s, 1H), 7.76 (s, 1H), 7.59 (dd, J = 2.4, 8.8 Hz, 1H), 7.50-7.20 (m, 4H), 4.39 (d, J = 4.4 Hz, 2H), 4.23 (bs, 2H), 4.05 (s, 2H), 3.85 (t, J = 12.4 Hz, 4H), 1.78 (s, 3H)	
1278		1285	
MS (ESI) m/z 672.23 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.29 (bs, 1H), 8.81 (d, J = 4.8 Hz, 1H), 8.39 (s, 1H), 7.82 (s, 1H), 7.58 (dd, J = 8.8, 6.4 Hz 1H), 7.52–7.15 (m, 4H), 4.59 (d, J = 47.2 Hz, 2H), 4.40 (s, 2H), 4.23 (s, 2H), 3.76 (s, 2H), 2.89-2.71 (m, 2H), 2.30 (s, 3H), 1.79 (s, 3H)		MS (ESI) m/z 696.35 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.93 (bs, 1H), 8.78 (d, J = 4.8 Hz, 1H), 8.10 (s, 1H), 7.59 (dd, J = 8.8 Hz, 2.8 Hz, 1H), 7.48 (d, J = 4.8 Hz, 1H), 7.41 (d, J = 2.8 Hz, 1H), 7.36 (d, J = 8.8 Hz, 1H), 6.13 (s, 1H), 4.41 (bs, 2H), 4.22 (bs, 2H), 3.93-3.87 (m, 2H), 3.54 (d, J = 10.8 Hz, 2H), 3.16 (d, J = 12.8 Hz, 2H), 3.09-3.06 (m, 2H), 2.90 (s, 3H), 2.37 (s, 3H), 1.70 (s, 3H)	

[1267]

1280		1290	
MS (ESI) m/z 616.25 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.50 (s, 1H), 7.58 (dd, J = 8.8, 2.4 Hz, 1H), 7.44-7.31 (m, 5H), 4.46-4.34 (m, 3H), 4.19 (s, 2H), 3.87-3.77 (m, 2H), 3.54 (t, J = 7.20, 1H), 3.36 (d, J = 10.4 Hz, 1H), 2.70 (s, 3H), 2.08-1.86 (m, 2H), 1.78 (s, 3H)		MS (ESI) m/z 703.31 [M+1] +; 1H NMR (400 MHz, DMSO-d6) δ 8.75 (d, J = 4.8 Hz, 1H), 8.62 (s, 1H), 8.25 (s, 1H), 7.75 (d, J = 8.8 Hz, 1H), 7.69 (t, J = 3.2 Hz, 2H), 7.55 (d, J = 4.8 Hz, 1H), 6.43 (t, J = 54.4 Hz, 1H), 4.85 (s, 2H), 3.44 (s, 6H), 3.18 (bs, 4H), 2.09 (s, 3H)	
1284		1294	
MS (ESI) m/z 697.27 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 14.00 (bs, 1H), 10.10 (bs, 1H), 8.77 (d, J = 4.8 Hz, 1H), 8.53 (d, J = 2.4 Hz, 1H), 7.96 (s, 1H), 7.64-7.54 (m, 2H), 7.47-7.46 (m, 2H), 7.29 (d, J = 8.9 Hz, 1H), 4.65-4.56 (m, 2H), 4.23 (s, 2H), 4.15-4.10 (m, 2H), 2.94 (s, 6H), 2.57 (s, 3H), 2.06 (s, 3H), 1.83 (s, 3H)		MS (ESI) m/z 707.32 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 14.03 (bs, 1H), 9.79 (bs, 1H), 8.79 (d, J = 4.8 Hz, 1H), 8.13 (s, 1H), 7.63-7.60 (dd, J = 2.4, 8.8 Hz, 1H), 7.53 (d, J = 4.8 Hz, 1H), 7.44 (d, J = 2.4 Hz, 1H), 7.38 (d, J = 8.8 Hz, 1H), 4.42 (bs, 2H), 4.25 (bs, 2H), 3.93 (t, J = 12.0 Hz, 2H), 3.59-3.57 (m, 5H), 3.34-23 (m, 4H), 2.91 (s, 3H), 2.44 (s, 3H), 1.88 (s, 3H)	
1295		1300	
MS (ESI) m/z 707.34 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 13.58 (bs, 1H), 8.39 (s, 1H), 8.10 (s, 1H), 7.61-7.58 (dd, J = 2.8, 8.8 Hz, 1H), 7.42 (s, 2H), 7.38 (d, J = 9.2 Hz, 1H), 4.41 (t, J = 4.8 Hz, 2H), 4.24 (t, J = 4.4 Hz, 2H), 3.74 (bs, 2H), 3.57 (s, 3H), 3.08 (bs, 4H), 2.87 (m, 2H), 2.71 (s, 3H), 2.32 (s, 3H), 1.87 (s, 3H)		MS (ESI) m/z 735.80 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 12.50 (bs, 1H), 8.87 (d, J = 4.7 Hz, 1H), 8.47 (s, 1H), 8.12 (s, 1H), 7.60 (dd, J = 2.4, 8.9 Hz, 1H), 7.53 (d, J = 4.7 Hz, 1H), 7.45 (d, J = 2.4 Hz, 1H), 7.35 (d, J = 9.0 Hz, 1H), 4.39 (t, J = 5.1 Hz, 2H), 4.20 (t, J = 4.6 Hz, 2H), 3.51 (s, 3H), 3.28 (bs, 4H), 2.55 (bs, 4H), 2.28 (s, 3H), 1.69 (s, 3H)	

[1268]

1296		1331	
MS (ESI) m/z 693.35; 1H NMR (400 MHz, DMSO-d6) δ 13.50 (bs, 1H), 9.78 (bs, 1H), 8.84 (d, J = 4.8 Hz, 1H), 8.33 (s, 1H), 8.13 (s, 1H), 7.61 (dd, J = 8.4, 2.4, Hz, 1H), 7.49 (d, J = 4.7 Hz, 1H), 7.44 (d, J = 2.4 Hz, 1H), 7.36 (d, J = 8.1 Hz, 1H), 4.49-4.39 (m, 2H), 4.30-4.20 (m, 2H), 3.95-3.85 (m, 2 Hz), 3.62-3.50 (m, 5H), 3.40 (d, J = 12.0 Hz, 2H), 3.29-3.19 (m, 2H), 2.92 (s, 3H), 1.79 (s, 3H)		MS (ESI) m/z 596.2 [M+1] +; 1H NMR (400 MHz, DMSO-d6) δ 13.39 (bs, 1H), 9.59 (s, 1H), 8.82 (d, J = 4.8 Hz, 1H), 8.54 (s, 1H), 8.45 (s, 1H), 8.44 (s, 1H), 7.60-7.57 (dd, J = 2.4, 8.8 Hz, 1H), 7.44 (t, J = 8.3 Hz, 2H), 7.33 (d, J = 8.8 Hz, 1H), 4.34 (d, J = 4.4 Hz, 2H), 4.19 (s, 2H), 3.43 (s, 4H), 2.90 (s, 6H), 1.83 (s, 3H)
1299		1373	
MS (ESI) m/z 735.36 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 12.58 (bs, 1H), 8.83 (d, J = 4.8 Hz, 1H), 8.36 (s, 1H), 7.97 (s, 1H), 7.74 (s, 1H), 7.56 (d, J = 8.4 Hz, 1H), 7.44 (d, J = 8.4 Hz, 2H), 7.33 (d, J = 8.8 Hz, 1H), 4.39 (s, 2H), 4.22 (s, 2H), 3.42 (s, 2H), 3.31 (m, 4H), 2.95 (m, 4H), 2.10 (s, 3H), 1.77 (s, 3H)		MS (ESI) m/z 535.0 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.82 (d, J = 4.8 Hz, 1H), 8.44 (s, 1H), 7.99 (dd, J = 8.4, 4.5 Hz, 1H), 7.77 (dd, J = 9.6, 8.4 Hz, 1H), 7.60 (dd, J = 8.9, 2.7 Hz, 1H), 7.49 (d, J = 4.8 Hz, 1H), 7.43 (d, J = 2.7 Hz, 1H), 7.37 (d, J = 9.0 Hz, 1H), 4.42 (t, J = 5.1 Hz, 2H), 4.26 (t, J = 5.1 Hz, 2H), 1.87 (s, 3H)
1379		1387	
MS (ESI) m/z 602.3 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 9.57 (s, 1H), 8.16 (s, 1H), 7.66 – 7.51 (m, 2H), 7.49 – 7.33 (m, 3H), 4.63 (s, 2H), 4.42 (t, J = 5.1 Hz, 2H), 4.25 (t, J = 5.0 Hz, 2H), 2.96 (s, 6H), 2.73 (s, 3H), 2.62 (s, 3H), 1.90 (s, 3H)		MS (ESI) m/z 676.1 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.80 (d, J = 2.6 Hz, 1H), 8.57 (s, 1H), 8.40 (s, 1H), 8.04 (ddd, J = 9.4, 2.8, 1.7 Hz, 1H), 7.95 (s, 1H), 7.60 (dd, J = 8.9, 2.7 Hz, 1H), 7.47 – 7.32 (m, 3H), 6.93 (t, J = 53.7 Hz, 1H), 4.42 (t, J = 5.0 Hz, 2H), 4.29 (dd, J = 5.3, 1.9 Hz, 2H), 2.73 (s, 3H), 1.92 (s, 3H)	

[1269]

1385	MS (ESI) m/z 686.1 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.36 (s, 1H), 7.95 (s, 1H), 7.63 – 7.51 (m, 3H), 7.44 – 7.40 (m, 2H), 7.36 (d, J = 9.0 Hz, 1H), 6.90 (t, J = 53.7 Hz, 3H), 4.42 (t, J = 5.0 Hz, 2H), 4.28 (t, J = 5.0 Hz, 2H), 2.72 (s, 3H), 2.66 (s, 6H), 1.89 (s, 3H)	1935	
1386	MS (ESI) m/z 672.0 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 8.76 (d, J = 5.4 Hz, 1H), 8.39 (s, 1H), 7.95 (s, 1H), 7.62 – 7.57 (m, 2H), 7.56 – 7.51 (m, 1H), 7.44 – 7.40 (m, 2H), 7.36 (d, J = 9.0 Hz, 1H), 6.88 (t, J = 53.8 Hz, 1H), 4.41 (t, J = 5.0 Hz, 2H), 4.28 (t, J = 4.8 Hz, 2H), 2.72 (s, 3H), 2.65 (s, 3H), 1.89 (s, 3H)	1936	
1937		1940	1943
			1946

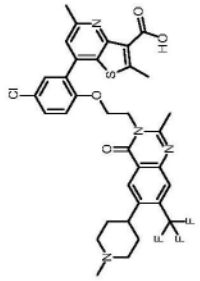
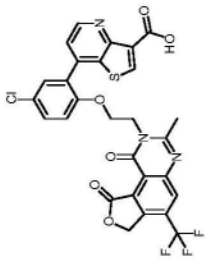
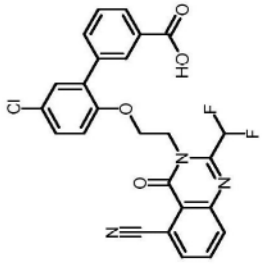
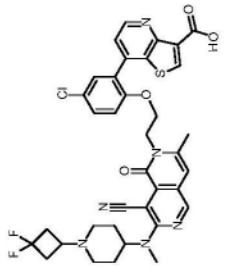
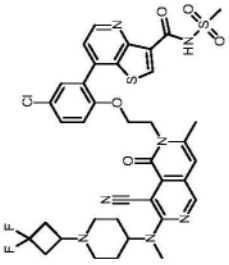
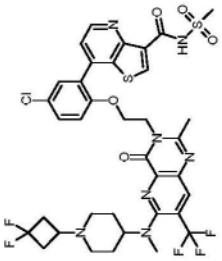
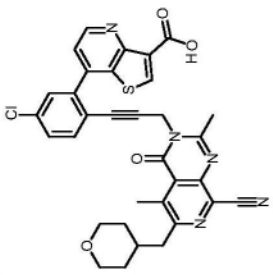
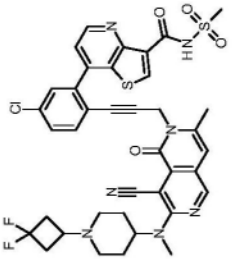
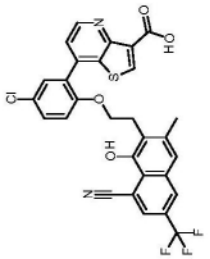
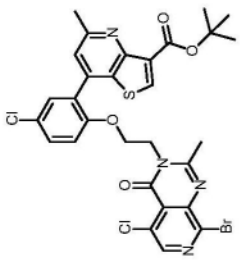
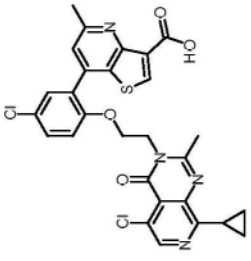
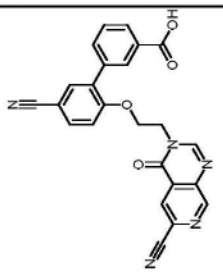
[1270]

1938	1941	1944	1947
1939	1942	1945	1948
1949	1952	1955	1958

[1271]

1959	1960	1970	
1956	1957	1967	
1953	1954	1964	
1950	1951	1961	

[1272]

1971	1972	1986
		
1968	1969	1979
		
1965	1966	1976
		
1962	1963	2026
		

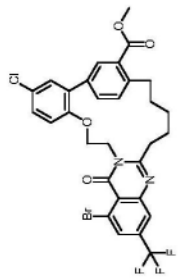
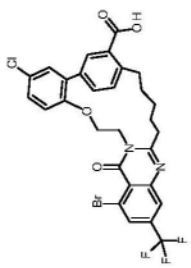
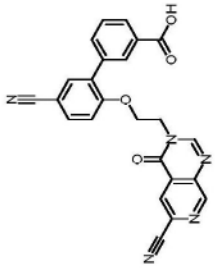
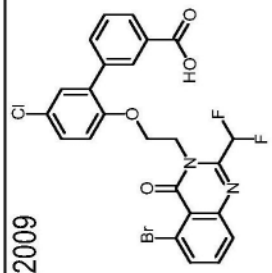
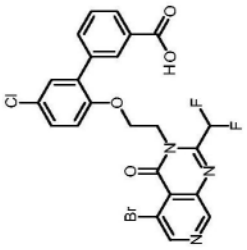
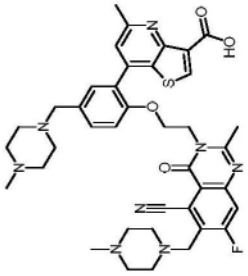
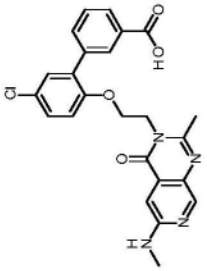
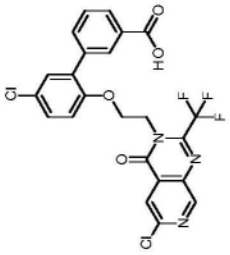
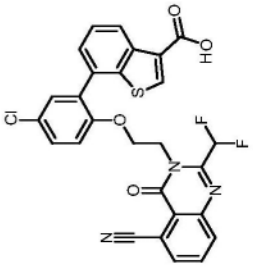
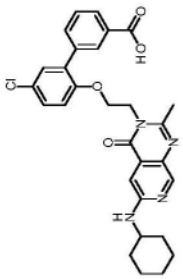
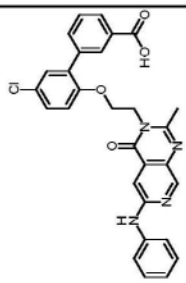
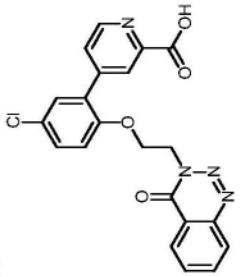
[1273]

1987	1988	1999	
1980	1981	1996	
1977	1978	1992	
1974	1975	1989	

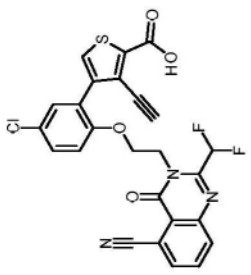
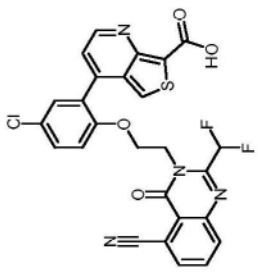
[1274]

2000	2001	2011	
1997	1998	2008	
1993	1995	2005	
1990	1991	2002	

[1275]

2012 	2013 	2026 
2009 	2010 	2027 
2006 	2007 	2017 
2003 	2004 	2014 

[1276]

MS (ESI) m/z 526.15 [M+1]+		
2034 	MS (ESI) m/z 553.33 [M+1]+	
	2035 	

[1277] 实施例5.生物学研究

[1278] 实施例5A.荧光偏振

[1279] 使用荧光偏振竞争测定筛选化合物的eIF4E结合效力。所有结合反应均在含有20mM Tris pH 7.5,100mM NaCl,1mM DTT和0.02％Tween-20的荧光偏振缓冲液(FPB)中进行。最终结合反应包含75nM重组eIF4E(Beryllium,定制订单),20nM EDA-m^7GDP-ATTO-550(Jena Bioscience,NU-827-550)和不同浓度的目标抑制性化合物。每个反应中的最终DMSO浓度为1％。

[1280] eIF4E蛋白与EDA-m^7GDP-ATTO-550在FPB中以2X浓度预孵育5分钟,然后添加化合物。在100％DMSO中使用3倍连续稀释制备化合物(100X),随后在FPB中以1:50稀释以产生2X储备液。将50μl 2X eIF4E/EDA-m^7GDP-ATTO-550转移到96孔半面积黑色平底聚苯乙烯板的孔中。加入50μl 2X测试化合物,在避光的同时使结合反应在室温下平衡30分钟。使用Victor 2多重标记计数器(Perkin Elmer)检测荧光偏振信号,并使用来自8点化合物稀释系列的数据计算实现50％的eIF4E/EDA-m^7GDP-ATTO-550结合抑制(IC50)所需的浓度。

[1281] 这些测定的结果列于下表4A和4B中。在表4A中,小于0.05μM的IC_{50}值被标记为“+++”,1到0.05μM的IC_{50}值被标记为“++”,大于1μM的IC_{50}值被标记为“+”。计算的IC_{50}值显示在表4B中。ND＝未确定。

表 4A

[1282]

化合物	eIF4E FP
1	++
2	+
3	+
4	+
5	+
6	+
7	+
8	+++
9	+
10	+
11	+
12	+
13	+
14	+
15	+
16	++++
17	++
18	++
19	++
20	+
21	++
22	+++
23	++
24	++
25	+
26	++
27	++
28	++
29	++
30	++
31	++
32	++
33	++
34	++
35	+++
36	ND
37	+++
38	++
39	++
40	+++
41	+
42	+
43	+
44	++
45	+
46	++
47	+++
48	++
49	+++
50	+++
51	+++
52	+
53	++
54	+
55	+++
56	+++
57	+++
58	++
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60	+++
61	+++
62	+++
63	+++
64	++
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67	+
68	+
69	+
70	++
71	++
72	+
73	++
74	++
75	+
76	+
77	+
78	+
79	+
80	++
81	+
82	+
83	+
84	+
85	+
86	+
87	+
88	+
89	+
90	+
91	++
92	+
93	+
94	+
95	+
96	+
97	+
98	++
99	+
100	+
101	+
102	+
103	++
104	++
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110	+
111	++
112	+
113	++
114	++
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123	+++
124	+
125	+
126	+
127	++
128	++
129	+
130	+
131	++
132	++
133	++
134	++
135	ND
136	++
137	++
138	++
139	+++
140	++
141	+++
142	++
143	+++
144	+++
145	++
146	++
147	+++
148	+++
149	++
150A	++
150B	++
150C	++
151	+++
152	+++
153	++
154	++
155	+++
156	+++
157	ND
158	+++
159	+++
160	+++
161	++
162	+++
163	++
164	ND
165	++
166	+++
167	++
168	+++
169	++
170	++
171	++
172	++
173	++
174	++
175	+++
176	+++
177	+++
178	++
179	+++
180	+++
181	++
182	+++
183	++
184	++
185	++
186	++
187	+++
188	++
189	+
190	++
191	++
192	+
193	+++
194	+++
195	+++
196	+++
197	++
198	++
199	++
200	+++
201	++
202	+++
203	++
204	+++
205	++
206	++
207	+++
208	++
209	+++
210	++
211	+++
212	+++
213	+++

[1283]

化合物	eIF4E FP	化合物	eIF4E FP	化合物	eIF4E FP	化合物	eIF4E FP	化合物	eIF4E FP
214	+++	258	+++	302	++	345	+++	388	+++
215	++	259	++	303	++	346	+++	389	+++
216	++	260	+++	304	+	347	+++	390	+++
217	++	261	+++	305	++	348	+++	391	+++
218	+++	262	+++	306	++	349	+++	392	+++
219	++	263	+++	307	++	350	+++	393	+++
220	++	264	+++	308	++	351	++	394	+++
221	++	265	++	309	++	351	++	395	+++
222	++	266	+++	310	++	352	+	396	+++
223	++	267	++	311	++	353	++	397	+++
224	+++	268	+++	312	++	354	++	398	++
225	++	269	+++	313	+++	355	++	399	++
226	++	270	+++	314	+++	356	+	400	+++
227	++	271	+++	315	++	357	+++	401	+++
228	+++	272	+++	316	+++	358	++	402	++
229	+++	273	+++	317	+++	359	+++	403	+++
230	+++	274	+++	318	+++	360	+++	404	+++
231	+++	275	+++	319	++	361	++	405	+++
232	+++	276	+++	320	+++	362	++	406	+++
233	+++	277	+++	321	+++	363	+++	407	+++
234	+++	278	+++	322	++	364	++	408	+++
235	+++	279	+++	323	++	365	+++	409	+++
236	+++	280	+++	324	++	366	+++	410	++
237	++	281	+++	325	++	367	+++	411	++
238	+++	282	+++	326	+	368	+++	412	++
239	+++	283	+++	327	+++	369	+++	413	+++
240	+++	284	+++	328	+	370	+++	414	+++
241	+++	285	++	329	+++	371	+++	415	+++
242	+++	286	++	330	+++	372	+++	416	+++
243	+++	287	+++	331	ND	373	+++	417	+++
244	+++	288	+++	332	+++	374	+++	418	+++
245	+++	289	+++	333	ND	375	++	419	+++
246	+++	290	+++	334	+++	376	+++	420	+++
247	++	291	++	335	++	377	++	421	+++
248	++	292	++	336	+++	378	+++	422	+++
249	+++	293	++	337	+++	379	+++	423	+++
250	+++	294	+++	338	+++	380	+++	424	+++
251	+++	295	++	339	+++	381	ND	425	+++
252	+++	296	+++	340	+++	382	ND	426	+++
253	+++	297	+++	341	+++	383	ND	427	+++
254	+++	298	++	342	+++	384	+++	428	+++
255	++	299	+++	343	+++	385	+++	429	+++
256	++	300	+++	344	+++	386	+++	430	+++
257	++	301	++	345	+++	387	++	431	++

[1284]

化合物	eIF4E FP	化合物	eIF4E FP	化合物	eIF4E FP	化合物	eIF4E FP	化合物	eIF4E FP
432	+++	475	+++	519	+++	563	+++	607	+++
433	+++	476	+++	520	+++	564	+++	608	+++
434	+++	477	+++	521	++	565	+++	609	+++
435	+++	478	+++	522	+++	566	+++	610	+++
436	+++	479	+++	523	+++	567	+++	611	+++
437	+++	480	+++	524	+++	568	+++	612	+++
438	+++	481	+++	525	+++	569	+++	613	+++
439	+++	482	+++	526	++	570	+++	614	++
439	+++	483	+++	527	+++	571	++	615	+++
440	+++	484	+++	528	+++	572	+++	616	+++
441	+++	485	+++	529	+++	573	++	617	+++
442	+++	486	+++	530	+++	574	++	618	+++
443	++	487	++	531	+++	575	+++	619	+++
444	+++	488	+++	532	+++	576	+++	620	+++
445	++	489	+++	533	++	577	+++	621	++
446	++	490	++	534	+++	578	+++	622	+++
447	++	491	+++	535	++	579	+++	623	+++
448	+++	492	+++	536	+++	580	+++	624	+++
449	+++	493	++	537	+++	581	+++	625	++
450	+++	494	++	538	+++	582	+++	626	+++
451	+++	495	++	539	+++	583	+++	627	+++
452	+++	496	+	540	+++	584	+++	628	+++
453	+	497	+++	541	+++	585	+++	629	+++
454	++	498	+++	542	+++	586	+++	630	++
455	++	499	++	543	+++	587	+++	631	+++
456	+++	500	+++	544	+++	588	+++	632	+++
457	+++	501	+++	545	+++	589	+++	633	+++
458	+++	502	+++	546	+++	590	+++	634	+++
459	+++	503	+++	547	++	591	+++	635	+++
460	+++	504	+++	548	+++	592	+++	636	+++
461	+++	505	+++	549	+++	593	+++	637	+++
462	+++	506	++	550	++	594	+	638	+++
463	+++	507	+++	551	+++	595	+++	639	+++
464	+++	508	+++	552	++	596	+++	640	+++
465	+++	509	++	553	+++	597	+++	641	+++
466	+++	510	++	554	+++	598	++	642	+++
467	+++	511	++	555	+++	599	++	643	+++
468	+++	512	++	556	+++	600	+++	644	+++
469	+++	513	+++	557	+++	601	++	645	+++
470	+++	514	+++	558	+++	602	+++	646	+++
471	+++	515	+++	559	+++	603	+++	647	+++
472	+++	516	+++	560	+++	604	++	648	+++
473	+++	517	+++	561	++	605	ND	649	+++
474	+++	518	+++	562	+++	606	+++	650	+++

[1285]

化合物	eIF4E FP	化合物	eIF4E FP	化合物	eIF4E FP	化合物	eIF4E FP	化合物	eIF4E FP
651	+++	695	+++	739	+++	783	+++	826	+++
652	+++	696	+++	740	+++	784	+++	827	+++
653	+++	697	+++	741	+++	785	+++	828	+++
654	+++	698	+++	742	+++	786	+++	829	+++
655	+++	699	+++	743	++	787	+++	830	+++
656	+++	700	+++	744	+++	788Fa	+	831	+++
657	+++	701	+++	745	+++	788Fb	+++	832	ND
658	+	702	+++	746	+++	789	+++	833	++
659	+++	703	+++	747	+++	790	+++	834	+++
660	++	704	++	748	+++	791	+++	835	+++
661	+++	705	+++	749	+	792	+++	836	+++
662	++	706	++	750	+++	793	+++	837	+++
663	++	707	+++	751	++	794	+++	838	+++
664	++	708	++	752	+++	795	+++	839	+++
665	+++	709	++	753	+++	796	+++	840	+++
666	++	710	+++	754	+++	797	+++	841	++
667	+++	711	++	755	+++	798	+++	842	+++
668	+++	712	+++	756	+++	799	+++	843	+++
669	+++	713	+++	757	++	800	+++	844	+++
670	+++	714	+++	758	+++	801	+++	845	+++
671	++	715	ND	759	++	802	+++	846	+++
672	++	716	ND	760	+++	803	++	847	+++
673	+++	717	++	761	+++	804	+++	848	+++
674	+++	718	+++	762	+++	805	+++	849	+++
675	+++	719	+++	763	+++	806	+++	850	+++
676	+++	720	++	764	+++	807	+++	851	+++
677	+++	721	+++	765	+++	808	++	852	+++
678	++	722	+++	766	+++	809	+++	853	+++
679	++	723	+++	767	+++	810	+++	854	+++
680	++	724	+++	768	+++	811	++	855	+++
681	+++	725	+++	769	+++	812	+++	856	+++
682	+++	726	++	770	+++	813	+++	857	+++
683	+++	727	+++	771	+++	814	ND	858	+++
684	+++	728	+++	772	+++	815	+++	859	+++
685	+++	729	++	773	+++	816	+++	860	+++
686	+++	730	++	774	+++	817	+++	861	+++
687	+++	731	+++	775	+++	818	+++	862	+++
688	+++	732	++	776	+++	819	+++	863	+++
689	+++	733	+	777	++	820	+++	864	+++
690	+++	734	+++	778	+++	821	+++	865	+++
691	+++	735	++	779	+++	822	+++	866	+++
692	+++	736	+++	780	+++	823	+++	867	+++
693	+++	737	+++	781	+++	824	+++	868	+++
694	+++	738	+++	782	+++	825	+++	869	+++

[1286]

化合物	eIF4E FP	化合物	eIF4E FP	化合物	eIF4E FP	化合物	eIF4E FP	化合物	eIF4E FP
870	++	914	+++	958	+++	1002	+++	1046	+++
871	+++	915	+++	959	+++	1003	+++	1047	+++
872	+++	916	+++	960	+++	1004	+++	1048	+++
873	+++	917	+++	961	+++	1005	+++	1049	+++
874	+++	918	+++	962	+++	1006	+++	1050	+++
875	+++	919	+++	963	+++	1007	+++	1051	+++
876	++	920	+++	964	+++	1008	+++	1052	+++
877	++	921	++	965	++	1009	+++	1053	+++
878	+++	922	++	966	+++	1010	+++	1054	+++
879	+++	923	+++	967	+++	1011	+++	1055	+++
880	++	924	+++	968	+++	1012	+++	1056	+++
881	+++	925	+++	969	+++	1013	+++	1057	+++
882	+++	926	+++	970	++	1014	+++	1058	+++
883	+++	927	+++	971	++	1015	+++	1059	+++
884	+++	928	+++	972	+++	1016	+++	1060	++
885	+++	929	+++	973	++	1017	+++	1061	+++
886	+++	930	+++	974	+++	1018	+++	1062	+++
887	+++	931	+++	975	+++	1019	+++	1063	+++
888	+++	932	+++	976	+++	1020	+++	1064	+++
889	+++	933	++	977	+++	1021	+++	1065	+++
890	+++	934	+++	978	+++	1022	+++	1066	++
891	+++	935	+++	979	+++	1023	+++	1067	+++
892	+++	936	ND	980	+++	1024	+++	1068	+++
893	+++	937	+++	981	+++	1025	+++	1069	+++
894	+++	938	+++	982	+++	1026	+++	1070	+++
895	+++	939	+++	983	+++	1027	+++	1071	++
896	+++	940	++	984	+++	1028	+++	1072	+++
897	+++	941	+++	985	+++	1029	+++	1073	++
898	+++	942	+++	986	+++	1030	+++	1074	+++
899	+++	943	+++	987	+++	1031	+++	1075	+++
900	+++	944	+++	988	+++	1032	+++	1076	+++
901	+++	945	+++	989	+++	1033	+++	1077	++
902	+++	946	+++	990	+++	1034	+++	1078	++
903	+++	947	+++	991	+++	1035	+++	1079	ND
904	+++	948	+++	992	++	1036	+++	1080	++
905	+++	949	+++	993	+++	1037	+++	1081	+
906	+++	950	+++	994	+++	1038	+++	1082	++
907	+++	951	+++	995	+++	1039	+++	1083	+++
908	+++	952	+++	996	+++	1040	+++	1084	+++
909	+++	953	+++	997	+++	1041	+++	1085	++
910	+++	954	+++	998	+++	1042	+++	1086	+++
911	+++	955	+++	999	+++	1043	+++	1087	+++
912	+++	956	+++	1000	+++	1044	+++	1088	++
913	+++	957	+++	1001	+++	1045	+++	1089	++

[1287]

化合物	eIF4E FP
1090	+++
1090	++
1091	++
1092	+++
1093	++
1094	++
1095	+++
1096	+++
1097	+++
1098	+++
1099	+++
1100	+++
1101	+++
1102	+++
1103	+++
1104	++
1105	+++
1106	+++
1107	+++
1108	+++
1109	+++
1110	+++
1111	+++
1112	+++
1113	++
1114	+++
1115	+++
1116	+++
1117	+++
1118	+++
1119	+++
1120	+++
1121	+++
1122	+++
1123	+++
1124	+++
1125	+++
1126	+++
1127	+++
1128	+++
1129	+++
1130	+++
1131	+++
1132	+++

化合物	eIF4E FP
1133	+++
1134	+++
1135	+++
1136	+++
1137	+++
1138	+++
1139	ND
1140	+++
1141	+++
1142	+++
1143	+++
1144	+++
1145	+++
1146	+++
1147	+++
1148	+++
1149	+++
1150	+++
1151	+++
1152	+++
1153	+++
1154	+++
1155	+++
1156	+++
1157	+++
1158	+++
1159	+++
1160	+++
1161	+++
1162	+++
1163	+++
1164	+++
1165	+++
1166	+++
1167	+++
1168	+++
1169	+++
1170	+++
1171	+++
1172	+++
1173	+++
1173	+++
1174	+++
1175	+++

化合物	eIF4E FP
1176	+++
1177	+++
1178	+++
1179	+++
1180	+++
1181	+++
1182	+++
1183	+++
1184	+++
1185	+++
1186	+++
1187	+++
1188	+++
1189	+++
1190	+++
1191	+++
1192	+++
1193	+++
1194	+++
1195	+++
1196	+++
1197	+++
1198	+++
1199	+++
1200	+++
1201	+++
1202	+++
1203	+++
1204	++
1205	++
1206	+++
1207	++
1208	+++
1209	++
1210	+++
1211	++
1212	+++
1213	+++
1214	+++
1215	+++
1216	+++
1217	+++
1218	+++
1219	+++

化合物	eIF4E FP
1220	+++
1221	+++
1222	+++
1223	+++
1224	++
1225	+++
1226	+++
1227	+++
1228	+++
1229	+++
1230	+++
1231	ND
1232	+++
1233	ND
1234	+++
1235	+++
1236	+++
1237	+++
1238	+++
1239	+++
1240	+++
1241	+++
1242	+++
1243	+++
1244	+++
1245	+++
1246	++
1247	+++
1248	++
1249	++
1250	++

表 4B

[1288]

化合物.	IC_{50}(μM)
1	0.281
2	3.10
3	4.72
4	3.52
5	7.64
6	7.39
7	12.0
8	>30.0
9	>30.0
10	6.51
11	6.85
12	2.39
13	1.07
14	>3.00
15	1.74
16	46.1
17	0.721
18	0.832
19	0.838
20	1.07
21	0.575
22	0.0249
23	0.624
24	0.184
25	12.6
26	0.919
27	0.149
28	0.0616
29	0.211
30	0.164
31	0.751
32	0.190
33	0.203
34	0.0885
35	0.0443
36	ND
37	0.0396
38	0.0555
39	0.116
40	0.540
41	3.44
42	19.8
43	>10.0
44	0.0731
45	2.89
46	0.0672
47	0.0224
48	0.631
49	>3.00
50	>3.00
51	0.0213
52	>3.00
53	0.931
54	2.28
55	0.0216
56	0.00789
57	0.0128
58	0.0502
59	0.0215
60	0.0147
61	0.0265
62	0.0249
63	0.0258
64	0.0625
65	0.0241
66	0.187
67	3.22
68	64.3
69	26.8
70	0.432
71	0.636
72	3.10
73	0.0832
74	0.423
75	1.40
76	2.30
77	1.44
78	1.63
79	1.65
80	0.110
81	4.22
82	1.66
83	2.56
84	1.25
85	1.85
86	49.7
87	1.16
88	1.68
89	>3.00
90	1.23
91	0.287
92	>3.00
93	1.40
94	1.42
95	2.86
96	2.10
97	>3.00
98	0.564
99	3.42
100	3.48
101	43.8
102	4.82
103	0.747
104	0.586
105	>3.00
106	1.38
107	3.82
108	11.2
109	19.2
110	26.9
111	0.434
112	>3.00
113	0.804
114	0.333
115	>3.00
116	>3.00
117	>3.00
118	0.416
119	0.0199
120	0.0357
121	0.0375
122	0.0244
123	0.0365
124	9.13
125	>3.00
126	8.36
127	0.0770
128	0.970
129	3.10
130	1.42
131	0.600
132	0.624
133	0.0665
134	0.116
135	ND
136	0.199
137	0.904
138	0.279
139	0.0346
140	0.0500
141	0.0442
142	0.152
143	0.0167
144	0.132
145	0.0959
146	0.259
147	0.0147
148	0.0205
149	0.110
150FA	0.0631
150FB	0.143
150FC	0.124
151	1.05
152	>3.00
153	0.0540
154	0.0972
155	0.0455
156	0.00420
157	ND
158	0.0483
159	0.0309
160	0.00883
161	0.0904
162	0.0287
163	0.0955
164	0.0164
165	0.106
166	0.0350
167	0.101
168	0.0372
169	0.234
170	0.845
171	0.194
172	0.0923
173	0.141
174	0.0521
175	0.0204
176	0.0415
177	0.0268
178	0.140
179	0.0206
180	0.0477
181	0.0623
182	0.0438
183	0.0502
184	0.144
185	0.0949
186	0.344
187	0.0483
188	0.0632
189	1.57
190	0.301
191	0.144
192	1.31
193	0.0209
194	0.0358
195	0.0274
196	0.0257
197	0.0524
198	0.124
199	0.143
200	0.0435

[1289]

化合物.	IC_{50}(μM)	化合物.	IC_{50}(μM)	化合物.	IC_{50}(μM)	化合物.	IC_{50}(μM)	化合物.	IC_{50}(μM)
201	0.354	242	0.0203	283	0.0406	324	0.0933	363	0.0228
202	0.0474	243	0.0432	284	0.0196	325	0.0520	364	0.107
203	0.0806	244	0.0312	285	0.0725	326	1.44	365	0.0190
204	0.0444	245	0.0256	286	0.183	327	0.0437	366	0.00666
205	0.101	246	0.0430	287	0.0478	328	1.32	367	0.00287
206	0.229	247	0.0611	288	0.0461	329	0.0464	368	0.0411
207	0.0213	248	0.0523	289	0.0191	330	0.0477	369	0.00132
208	0.103	249	0.0198	290	0.0427	331	ND	370	0.0121
209	0.0470	250	0.0437	291	0.0995	332	0.0377	371	0.0200
210	0.0910	251	0.0311	292	0.203	333	0.0249	372	0.00734
211	0.0354	252	0.0420	293	0.0639	334	0.0104	373	0.00643
212	0.0400	253	0.0460	294	0.0229	335	0.0569	374	0.0205
213	0.0356	254	0.0204	295	0.167	336	0.0279	375	0.0580
214	0.0122	255	0.0785	296	0.0375	337	0.0257	376	0.0127
215	0.137	256	0.104	297	0.0363	338	0.0453	377	0.0612
216	0.0628	257	0.0692	298	0.101	339	0.0268	378	0.0451
217	0.0554	258	0.0377	299	0.0223	340	0.00501	379	0.0267
218	0.0169	259	>1.00	300	0.0243	341	0.0450	380	0.0297
219	0.109	260	0.0204	301	0.0576	342	0.0474	381	ND
220	0.213	261	0.0420	302	0.0776	343	0.0418	382	ND
221	0.113	262	0.0224	303	0.498	344	0.0321	383	ND
222	0.0674	263	0.0127	304	1.60	345a	0.0432	384	0.0209
223	0.950	264	0.0246	305	0.431	345b	0.0253	385	0.0395
224	0.0110	265	0.0771	306	0.0912	346	0.0181	386	0.0254
225	0.147	266	0.0266	307	0.0594	347	0.0321	387	0.619
226	0.0707	267	0.0741	308	0.811	348	0.0154	388	0.00629
227	0.507	268	0.0341	309	0.0525	349	0.00584	389	0.0123
228	0.0235	269	0.0156	310	0.0977	350	0.0142	390	0.00175
229	0.0222	270	0.0464	311	0.0555	351a	0.885	391	0.00352
230	0.0149	271	0.0132	312	0.0756	351b	0.0936	392	0.0251
231	0.0129	272	0.0229	313	0.0345	352	1.27	393	0.0118
232	0.0163	273	0.0302	314	0.0428	353	0.101	394	0.0218
233	0.0289	274	0.0188	315	0.582	354	>1.00	395	0.00968
234	0.0185	275	0.0365	316	0.0204	355	0.146	396	0.0181
235	0.0166	276	0.0228	317	0.0171	356	1.22	397	0.0105
236	0.0203	277	0.0307	318	0.00292	357	0.0477	398	0.149
237	0.0548	278	0.0127	319	0.0535	358	0.0863	399	0.0699
238	0.0380	279	0.0178	320	0.0435	359	0.0489	400	0.00468
239	0.0286	280	0.0412	321	0.00489	360	0.0426	401	0.0474
240	0.00978	281	0.0375	322	0.116	361	0.0684	402	0.124
241	0.00487	282	0.0171	323	0.0826	362	0.0722	403	0.0126

[1290]

化合物.	IC_{50}(μM)	化合物.	IC_{50}(μM)	化合物.	IC_{50}(μM)	化合物.	IC_{50}(μM)	化合物.	IC_{50}(μM)
404	0.0101	444	0.0308	485	0.00859	526	0.0641	567	0.0117
405	0.0197	445	0.0931	486	0.0305	527	0.0248	568	0.0141
406	0.0114	446	0.0573	487	0.114	528	0.0271	569	0.00200
407	0.0331	447	0.0848	488	0.0265	529	0.00578	570	0.00557
408	0.0311	448	0.00420	489	0.0208	530	0.00665	571	0.0548
409	0.0133	449	0.0196	490	0.178	531	0.0429	572	0.0306
410	0.0626	450	0.00784	491	0.0229	532	0.0451	573	0.0547
411	0.193	451	0.0360	492	0.0297	533	0.0627	574	0.0575
412	0.0701	452	0.0466	493	0.0942	534	0.0302	575	0.0257
413	0.0346	453	2.32	494	0.0856	535	0.244	576	0.0177
414	0.0205	454	0.0511	495	0.237	536	0.0488	577	0.0394
415	0.0143	455	0.473	496	1.06	537	0.0466	578	0.0320
416	0.0230	456	0.0109	497	0.0397	538	0.0223	579	0.0302
417	0.0197	457	0.0112	498	0.0242	539	0.0472	580	0.0242
418	0.00907	458	0.0368	499	>1.00	540	0.0140	581	0.00608
419	0.00108	459	0.0415	500	0.0365	541	0.0491	582	0.0127
420	0.00960	460	0.0255	501	0.0257	542	0.0202	583	0.0159
421	0.0171	461	0.00615	502	0.0384	543	0.0382	584	0.0235
422	0.0115	462	0.0105	503	0.00867	544	0.0282	585	0.0296
423	0.00884	463	0.00886	504	0.0229	545	0.00781	586	0.0500
424	0.00408	464	0.0214	505	0.0436	546	0.0436	587	0.0255
425	0.0112	465	0.0151	506	0.0689	547	0.134	588	0.0493
426	0.0412	466	0.00930	507	0.0490	548	0.0472	589	0.00445
427	0.0250	467	0.0180	508	0.0152	549	0.0193	590	0.00226
428	0.00745	468	0.00436	509	0.125	550	0.0878	591	0.0449
429	0.0382	469	0.00225	510	0.0505	551	0.0292	592	0.0103
430	0.00900	470	0.0128	511	0.0880	552	0.0509	593	0.0329
431	0.226	471	0.0288	512	0.0718	553	0.0134	594	1.35
432	0.0258	472	0.0236	513	0.0116	554	0.0318	595	0.0248
433	0.00415	473	0.0145	514	0.0399	555	0.0108	596	0.0377
434	0.00776	474	0.0135	515	0.0460	556	0.0227	597	0.0468
435	0.0167	475	0.0170	516	0.0344	557	0.00640	598	0.0572
436	0.00717	476	0.0339	517	0.0357	558	0.0272	599	0.0616
437	0.00621	477	0.00973	518	0.0164	559	0.00869	600	0.0142
438	0.00916	478	0.0132	519	0.0378	560	0.00477	601	0.0520
439a	0.00287	479	0.0135	520	0.0183	561	0.0562	602	0.0102
439b	0.0320	480	0.00739	521	0.623	562	0.00878	603	0.0117
440	0.00499	481	0.0105	522	0.0227	563	0.0144	604	0.0707
441	0.0204	482	0.0354	523	0.0239	564	0.0405	605	ND
442	0.0177	483	0.0421	524	0.0128	565	0.0297	606	0.00412
443	0.128	484	0.0116	525	0.0347	566	0.0164	607	0.00550

[1291]

化合物.	IC_{50}(μM)	化合物.	IC_{50}(μM)	化合物.	IC_{50}(μM)	化合物.	IC_{50}(μM)	化合物.	IC_{50}(μM)
608	0.0186	649	0.0150	690	0.00595	731	0.00597	772	0.0141
609	0.0331	650	0.0283	691	0.00717	732	0.874	773	0.0102
610	0.0139	651	0.0218	692	0.00597	733	1.73	774	0.00829
611	0.00776	652	0.00668	693	0.0150	734	0.00468	775	0.0483
612	0.0438	653	0.0227	694	0.0191	735	0.0580	776	0.0365
613	0.00789	654	0.00312	695	0.00105	736	0.0170	777	0.0533
614	0.167	655	0.0135	696	0.00894	737	0.0123	778	0.0000702
615	0.0163	656	0.0334	697	0.0102	738	0.0193	779	0.00954
616	0.00245	657	0.0457	698	0.00340	739	0.0308	780	0.00960
617	0.0397	658	1.29	699	0.0121	740	0.0392	781	0.00312
618	0.00298	659	0.0264	700	0.0224	741	0.0152	782	0.00403
619	0.00634	660	0.258	701	0.0192	742	0.0325	783	0.0148
620	0.0369	661	0.0121	702	0.0127	743	0.188	784	0.0137
621	0.0600	662	0.144	703	0.00318	744	0.0133	785	0.0182
622	0.0438	663	0.332	704	0.0890	745	0.0333	786	0.0192
623	0.00477	664	0.153	705	0.0191	746	0.0367	787	0.0109
624	0.00402	665	0.0165	706	0.140	747	0.0189	788Fa	1.94
625	0.0780	666	0.268	707	0.0178	748	0.0163	788Fb	0.00435
626	0.0104	667	0.0467	708	0.0878	749	>100	789	0.00896
627	0.00672	668	0.00776	709	0.0567	750	0.0415	790	0.0178
628	0.0285	669	0.0364	710	0.0316	751	0.0698	791	0.00359
629	0.00639	670	0.0180	711	0.0775	752	0.0276	792	0.00244
630	0.0502	671	0.0777	712	0.0196	753	0.0138	793	0.00481
631	0.00341	672	0.106	713	0.0314	754	0.0172	794	0.00341
632	0.0120	673	0.0253	714	0.0472	755	0.0101	795	0.0121
633	0.0129	674	0.00927	715	ND	756	0.0432	796	0.00327
634	0.00562	675	0.00777	716	ND	757	0.137	797	0.00679
635	0.0106	676	0.00622	717	0.0730	758	0.0131	798	0.00986
636	0.0332	677	0.00544	718	0.0201	759	0.0529	799	0.00935
637	0.0166	678	0.0538	719	0.0285	760	0.00644	800	0.0324
638	0.00446	679	0.160	720	0.199	761	0.0258	801	0.0170
639	0.00157	680	0.0566	721	0.0206	762	0.0337	802	0.0359
640	0.0240	681	0.0174	722	0.0380	763	0.00519	803	0.161
641	0.0333	682	0.00621	723	0.0287	764	0.0106	804	0.0188
642	0.00363	683	0.0403	724	0.0377	765	0.00919	805	0.0136
643	0.000832	684	0.0150	725	0.0382	766	0.0451	806	0.00358
644	0.00497	685	0.0176	726	0.0530	767	0.00751	807	0.0210
645	0.0313	686	0.0265	727	0.0294	768	0.0224	808	0.0524
646	0.0414	687	0.0135	728	0.0310	769	0.0239	809	0.0160
647	0.0198	688	0.0228	729	0.0925	770	0.0140	810	0.00547
648	0.0246	689	0.0115	730	0.0510	771	0.0128		

[1292]

化合物.	IC_{50}(μM)	化合物.	IC_{50}(μM)	化合物.	IC_{50}(μM)	化合物.	IC_{50}(μM)	化合物.	IC_{50}(μM)
811	0.157	852	0.0214	893	0.0201	934	0.0136	975	0.0148
812	0.0300	853	0.0319	894	0.0216	935	0.0196	976	0.0190
813	0.00404	854	0.0119	895	0.0229	936	ND	977	0.0144
814	ND	855	0.00477	896	0.00157	937	0.00136	978	0.0207
815	0.00331	856	0.0137	897	0.00140	938	0.00244	979	0.00948
816	0.00687	857	0.00462	898	0.0325	939	0.0121	980	0.0156
817	0.00724	858	0.00728	899	0.00744	940	0.470	981	0.0416
818	0.0131	859	0.00559	900	0.0112	941	0.0200	982	0.0204
819	0.0282	860	0.0103	901	0.0456	942	0.00693	983	0.0189
820	0.0136	861	0.0246	902	0.0142	943	0.0147	984	0.0115
821	0.0142	862	0.0209	903	0.0112	944	0.0462	985	0.00669
822	0.0107	863	0.0455	904	0.00419	945	0.0389	986	0.0169
823	0.0115	864	0.0479	905	0.00938	946	0.0277	987	0.0136
824	0.0136	865	0.0284	906	0.0176	947	0.0237	988	0.0219
825	0.0143	866	0.0168	907	0.00776	948	0.0183	989	0.0198
826	0.0124	867	0.00661	908	0.00326	949	0.0373	990	0.0322
827	0.00572	868	0.0172	909	0.0132	950	0.0172	991	0.0121
828	0.00572	869	0.0254	910	0.0175	951	0.0436	992	0.0561
829	0.00453	870	0.140	911	0.0171	952	0.0450	993	0.0156
830	0.0128	871	0.0164	912	0.00898	953	0.0134	994	0.0234
831	0.0123	872	0.0204	913	0.0162	954	0.00829	995	0.0157
832	ND	873	0.0157	914	0.0207	955	0.0102	996	0.0316
833	0.111	874	0.0415	915	0.0184	956	0.0165	997	0.0122
834	0.0316	875	ND	916	0.00481	957	0.00581	998	0.0451
835	0.0293	876	0.0733	917	0.0110	958	0.0135	999	0.0163
836	0.00233	877	0.234	918	0.00437	959	0.0148	1000	0.0167
837	0.0134	878	0.00963	919	0.0177	960	0.0396	1001	0.0312
838	0.0387	879	0.00731	920	0.00576	961	0.0211	1002	0.00237
839	0.0296	880	0.0679	921	0.0696	962	0.00315	1003	0.0134
840	0.0104	881	0.0204	922	0.0894	963	0.00784	1004	0.0225
841	>1.00	882	0.00662	923	0.00371	964	0.00332	1005	0.0334
842	0.0209	883	0.0128	924	0.0143	965	0.118	1006	0.0182
843	0.0131	884	0.00585	925	0.0431	966	0.00358	1007	0.0482
844	0.0233	885	0.0307	926	0.0183	967	0.0122	1008	0.0153
845	0.0127	886	0.0105	927	0.00634	968	0.00895	1009	0.00623
846	0.0379	887	0.0201	928	0.0387	969	0.00556	1010	0.00529
847	0.0440	888	0.0402	929	0.0225	970	0.166	1011	0.00715
848	0.0269	889	0.0124	930	0.00688	971	0.0578	1012	0.00894
849	0.0145	890	0.0125	931	0.0137	972	0.00977	1013	0.0185
850	0.0177	891	0.0137	932	0.0178	973	0.0850	1014	0.0256
851	0.00602	892	0.0360	933	0.122	974	0.0236	1015	0.0197

[1293]

化合物.	IC_{50}(μM)	化合物.	IC_{50}(μM)	化合物.	IC_{50}(μM)	化合物.	IC_{50}(μM)	化合物.	IC_{50}(μM)
1016	0.00111	1057	0.0125	1097	0.0388	1138	0.0237	1178	0.0229
1017	0.00826	1058	0.0397	1098	0.0156	1139	ND	1179	0.0147
1018	0.00671	1059	0.0111	1099	0.0375	1140	0.00614	1180	0.0162
1019	0.0308	1060	0.0509	1100	0.0335	1141	0.0189	1181	0.0137
1020	0.0234	1061	0.00854	1101	0.00720	1142	0.0130	1182	0.0136
1021	0.0211	1062	0.00663	1102	0.0192	1143	0.0246	1183	0.0232
1022	0.0424	1063	0.0312	1103	0.0148	1144	0.0344	1184	0.00932
1023	0.0498	1064	0.0162	1104	0.631	1145	0.0331	1185	0.0176
1024	0.0242	1065	0.0186	1105	0.0217	1146	0.0144	1186	0.0201
1025	0.0300	1066	0.0574	1106	0.0174	1147	0.0446	1187	0.0186
1026	0.0155	1067	0.0105	1107	0.0105	1148	0.0356	1188	0.0124
1027	0.0315	1068	0.0278	1108	0.0291	1149	0.00419	1189	0.0134
1028	0.00614	1069	0.00152	1109	0.0134	1150	0.00460	1190	0.00730
1029	0.00766	1070	0.0320	1110	0.00720	1151	0.0190	1191	0.0128
1030	0.0144	1071	0.0540	1111	0.00571	1152	0.00380	1192	0.0488
1031	0.0116	1072	0.0372	1112	0.0199	1153	0.0380	1193	0.0102
1032	0.00620	1073	0.0581	1113	0.140	1154	0.0140	1194	0.0153
1033	0.0200	1074	0.0174	1114	0.0499	1155	0.0181	1195	0.0131
1034	0.0379	1075	0.00664	1115	0.00677	1156	0.0351	1196	0.0306
1035	0.0197	1076	0.0245	1116	0.0171	1157	0.0220	1197	0.00593
1036	0.00351	1077	0.245	1117	0.0134	1158	0.0158	1198	0.0130
1037	0.0119	1078	0.347	1118	0.0140	1159	0.0147	1199	0.0182
1038	0.0389	1079	0.0559	1119	0.0146	1160	0.0172	1200	0.0148
1039	0.0217	1080	0.105	1120	0.00951	1161	0.0195	1201	0.0228
1040	0.0300	1081	1.04	1121	0.00926	1162	0.0216	1202	0.0197
1041	0.00621	1082	0.903	1122	0.0146	1163	0.0248	1203	0.00915
1042	0.0265	1083	0.0440	1123	0.0215	1164	0.0267	1204	0.150
1043	0.00398	1084	0.0150	1124	0.0132	1165	0.0223	1205	0.199
1044	0.00531	1085	0.0543	1125	0.0145	1166	0.0286	1206	0.0325
1045	0.0382	1086	0.0384	1126	0.0266	1167	0.0173	1207	0.121
1046	0.0380	1087	0.0392	1127	0.0129	1168	0.0130	1208	0.0489
1047	0.0212	1088	0.0533	1128	0.0239	1169	0.0153	1209	0.0980
1048	0.0137	1089	0.618	1129	0.0107	1170	0.0171	1210	0.0483
1049	0.00935	1090a	0.0383	1130	0.00439	1171	0.0130	1211	>1.00
1050	0.0195	1090b	0.503	1131	0.0147	1172	0.0142	1212	0.0442
1051	0.00502	1091	0.0914	1132	0.0133	1173a	0.0192	1213	0.0427
1052	0.00546	1092	0.0427	1133	0.0170	1173b	0.0130	1214	0.00508
1053	0.00508	1093	0.0586	1134	0.0153	1174	0.00932	1215	0.0257
1054	0.0186	1094	0.0716	1135	0.0343	1175	0.0221	1216	0.0103
1055	0.0117	1095	0.0465	1136	0.0170	1176	0.0343	1217	0.0242
1056	0.0161	1096	0.0335	1137	0.0174	1177	0.0342	1218	0.0131

[1294]

化合物.	IC_{50}(μM)	化合物.	IC_{50}(μM)	化合物.	IC_{50}(μM)	化合物.	IC_{50}(μM)	化合物.	IC_{50}(μM)
1219	0.00399	1260	0.0130	1301	0.0155	1342	0.0304	1383	0.00503
1220	0.0131	1261	0.0336	1302	0.0307	1343	0.0406	1384	0.00686
1221	0.0300	1262	0.0106	1303	0.0366	1344	0.0183	1385	0.00724
1222	0.00302	1263	0.0106	1304	0.0185	1345	0.0345	1386	0.0128
1223	0.00279	1264	0.0124	1305	0.0265	1346	0.0197	1387	0.0228
1224	0.0760	1265	0.0115	1306	0.0389	1347	0.0414	1388	0.0362
1225	0.00312	1266	0.00907	1307	0.0542	1348	0.0122	1389	1.19
1226	0.00663	1267	>1.00	1308	0.0415	1349	0.0365	1390	ND
1227	0.0128	1268	0.472	1309	0.0372	1350	0.0351	1391	0.0376
1228	0.00111	1269	0.0666	1310	0.0213	1351	0.0160	1392	0.0265
1229	0.0107	1270	0.0399	1311	0.0133	1352	0.0216	1393	0.0132
1230	0.0103	1271	0.0131	1312	0.00829	1353	0.0172	1394	0.00474
1231	ND	1272	0.0281	1313	0.0426	1354	0.0216	1395	0.0296
1232	0.00449	1273	0.00748	1314	0.0181	1355	0.0248	1396	0.0195
1233	ND	1274	0.0402	1315	0.0131	1356	0.0232	1397	0.0147
1234	0.0302	1275	0.0587	1316	0.0328	1357	0.0159	1398	0.0140
1235	0.00632	1276	0.0135	1317	0.0335	1358	0.0183	1399	0.0144
1236	0.0339	1277	0.0384	1318	0.0344	1359	0.0397	1400	0.0278
1237	0.00668	1278	0.0106	1319	0.0136	1360	0.0168	1401	0.0127
1238	0.0130	1279	0.00891	1320	0.0277	1361	0.0213	1402	0.00658
1239	0.0182	1280	0.00426	1321	0.0602	1362	0.0141	1403	0.00876
1240	0.0155	1281	0.117	1322	0.0112	1363	0.0429	1404	0.482
1241	0.0173	1282	0.0382	1323	0.0730	1364	0.0247	1405	0.631
1242	0.00885	1283	0.0335	1324	0.0237	1365	0.0341	1406	0.0266
1243	0.00555	1284	>1.00	1325	0.0271	1366	0.0143	1407	0.0247
1244	0.0194	1285	0.0413	1326	0.0128	1367	0.0149	1408	0.0176
1245	0.0156	1286	0.0342	1327	0.0193	1368	0.0199	1409	0.0108
1246	0.106	1287	0.0424	1328	0.0248	1369	0.0132	1410	0.0180
1247	0.0355	1288	0.0367	1329	0.0352	1370	0.0199	1411	0.0175
1248	0.0607	1289	0.0140	1330	0.0130	1371	0.0151	1412	0.00671
1249	0.0759	1290	0.149	1331	0.0918	1372	0.0807	1413	0.0517
1250	0.0758	1291	0.0412	1332	0.0345	1373	0.0267	1414	0.0153
1251	0.00477	1292	0.0523	1333	0.0262	1374	0.0561	1415	0.0168
1252	0.222	1293	0.0351	1334	0.0513	1375	0.0839	1416	0.0127
1253	0.00840	1294	0.0559	1335	0.0128	1376	0.0136	1417	0.0249
1254	0.0265	1295	0.0134	1336	0.0130	1377	0.0440	1418	0.00910
1255	0.150	1296	0.0270	1337	0.0519	1378	0.0300	1419	0.00676
1256	0.0247	1297	0.0378	1338	0.00950	1379	0.0180	1420	0.00633
1257	0.0525	1298	0.0383	1339	0.0364	1380	0.0266	1421	0.0366
1258	0.0615	1299	0.0321	1340	0.0442	1381	0.00796	1422	0.0335
1259	0.00538	1300	0.0181	1341	0.0215	1382	0.0216	1423	0.0232

[1295]

化合物.	IC_{50}(μM)	化合物.	IC_{50}(μM)	化合物.	IC_{50}(μM)	化合物.	IC_{50}(μM)	化合物.	IC_{50}(μM)
1424	0.0292	1466	0.0179	1507	0.0160	1549	0.0262	1593	0.0616
1425	0.0130	1467	0.0110	1508	0.0174	1550	0.0229	1594	0.442
1426	0.0117	1468	0.0350	1509	0.0375	1551	0.0220	1595	0.0548
1427	0.0143	1469	0.0230	1510	0.0201	1553	0.0129	1596	0.654
1428	0.0122	1470	0.0308	1511	0.0232	1554	0.0151	1597	0.0221
1429	0.0178	1471	0.0142	1512	0.0122	1555	0.0239	1598	0.0375
1430	0.0228	1472	0.0289	1513	0.0134	1556	0.0499	1599	0.0167
1431	0.0198	1473	0.0169	1514	0.0517	1557	0.00677	1600	0.0203
1432	0.0212	1474	0.0138	1515	0.0321	1558	0.0690	1601	0.00805
1433	0.0274	1475	0.00720	1516	0.0170	1559	0.0134	1602	0.00388
1434	0.0290	1476	0.0162	1518	0.0107	1560	0.00631	1603	0.00212
1435	0.0264	1477	0.0181	1519	0.0153	1561	0.0130	1604	0.00396
1436	0.0295	1478	0.0130	1520	0.0179	1562	0.0168	1605	0.00378
1437	0.0373	1479	0.0167	1521	0.0183	1563	0.0130	1606	0.00460
1438	0.0408	1480	ND	1522	0.0177	1564	0.0106	1607	0.0146
1439	0.0128	1481	0.0208	1523	0.0131	1565	0.00799	1608	0.00659
1440	0.0690	1482	0.0166	1524	0.0125	1566	0.00439	1609	0.00488
1441	0.0298	1483	0.0137	1525	0.0151	1568	0.0216	1610	0.00602
1443	0.0316	1484	0.0229	1526	0.0112	1569	0.0195	1611	0.00385
1444	0.0252	1485	0.0229	1527	0.0156	1570	0.0229	1612	0.0137
1445	0.0320	1486	0.0107	1528	0.00631	1571	0.0205	1613	0.0161
1446	0.0140	1487	0.0254	1529	0.0201	1572	0.0200	1614	0.0314
1447	0.0316	1488	0.0123	1530	0.0335	1573	0.0222	1615	0.0147
1448	0.0260	1489	0.0137	1531	0.0134	1574	0.0134	1616	0.0115
1449	0.0170	1490	0.0291	1532	0.0112	1575	0.0147	1617	0.0156
1450	0.0134	1491	0.0290	1533	0.0217	1576	0.0179	1618	0.0124
1451	0.0217	1492	0.0201	1534	0.0158	1577	0.0133	1619	0.0316
1452	0.0391	1493	0.00683	1535	0.0174	1578	0.0203	1620	0.0179
1453	0.0146	1494	0.0247	1536	0.0183	1579	0.0303	1621	0.0721
1454	0.00615	1495	0.00709	1537	0.0189	1581	0.0143	1622	0.0173
1455	0.0211	1496	0.0325	1538	0.0145	1582	0.0192	1623	ND
1456	0.0184	1497	0.0129	1539	0.0125	1583	0.0582	1624	0.00417
1457	0.0180	1498	0.0291	1540	0.0195	1584	0.0369	1625	ND
1458	0.0191	1499	0.0275	1541	0.0106	1585	0.0152	1626	0.0303
1459	0.0207	1500	0.0170	1542	0.0186	1586	0.0318	1627	ND
1460	0.00799	1501	0.0205	1543	0.0205	1587	0.0397	1628	ND
1461	0.0138	1502	0.0262	1544	0.0131	1588	0.0264	1629	ND
1462	0.0201	1503	0.0192	1545	0.0275	1589	0.0124	1630	ND
1463	0.0229	1504	0.0136	1546	0.0134	1590	0.0360	1631	0.0161
1464	0.0134	1505	0.0130	1547	0.0152	1591	0.0362	1632	0.0424
1465	0.0236	1506	0.0274	1548	0.0362	1592	0.0203	1633	0.0526

[1296]

化合物.	IC_{50}(μM)	化合物.	IC_{50}(μM)	化合物.	IC_{50}(μM)	化合物.	IC_{50}(μM)	化合物.	IC_{50}(μM)
1634	0.0174	1675	0.00411	1716	ND	1757	ND	1798	ND
1635	0.0215	1676	0.00433	1717	0.0134	1758	ND	1799	ND
1636	0.0388	1677	0.0129	1718	ND	1759	ND	1800	ND
1637	0.0177	1678	0.0280	1719	ND	1760	ND	1801	ND
1638	0.0388	1679	0.0293	1720	ND	1761	0.00565	1802	ND
1639	0.0305	1680	0.0233	1721	ND	1762	0.0250	1803	ND
1640	ND	1681	0.00827	1722	ND	1763	0.0233	1804	ND
1641	0.0189	1682	0.0151	1723	ND	1764	0.0190	1805	ND
1642	0.0245	1683	0.0183	1724	0.00407	1765	0.0123	1806	ND
1643	0.0188	1684	ND	1725	ND	1766	ND	1807	0.0104
1644	0.0145	1685	ND	1726	ND	1767	0.0174	1808	0.00540
1645	0.0232	1686	ND	1727	0.00384	1768	0.0313	1809	0.00757
1646	0.0263	1687	ND	1728	ND	1769	0.0164	1810	0.0129
1647	0.0196	1688	0.0127	1729	ND	1770	0.0175	1811	0.0127
1648	0.0133	1689	0.0222	1730	ND	1771	0.0266	1812	0.0184
1649	0.0183	1690	0.0274	1731	ND	1772	0.00607	1813	ND
1650	0.0107	1691	0.0179	1732	ND	1773	0.0475	1814	ND
1651	ND	1692	ND	1733	0.00811	1774	0.0450	1815	ND
1652	ND	1693	ND	1734	0.0194	1775	0.0321	1816	ND
1653	0.0265	1694	ND	1735	0.0336	1776	0.00365	1817	0.0258
1654	0.0210	1695	ND	1736	0.0126	1777	ND	1818	0.0130
1655	0.0134	1696	ND	1737	0.0143	1778	ND	1819	0.00440
1656	ND	1697	ND	1738	0.0255	1779	0.0351	1820	0.0122
1657	ND	1698	ND	1739	0.0333	1780	0.0109	1821	ND
1658	ND	1699	ND	1740	0.0126	1781	0.00832	1822	ND
1659	ND	1700	ND	1741	0.0110	1782	ND	1823	ND
1660	ND	1701	ND	1742	0.00543	1783	ND	1824	ND
1661	ND	1702	ND	1743	0.00687	1784	ND	1825	0.0171
1662	0.0221	1703	0.00600	1744	0.0115	1785	ND	1826	0.0184
1663	0.0141	1704	0.00654	1745	0.0110	1786	ND	1827	0.0148
1664	ND	1705	0.00480	1746	0.0108	1787	ND	1828	ND
1665	0.0146	1706	0.0121	1747	0.0165	1788	ND	1829	0.00627
1666	ND	1707	0.0157	1748	0.0175	1789	ND	1830	0.00806
1667	0.0122	1708	0.0162	1749	0.0164	1790	ND	1831	0.00500
1668	0.00567	1709	0.0284	1750	0.0161	1791	0.0101	1832	0.0205
1669	0.00917	1710	ND	1751	ND	1792	0.00924	1833	0.0148
1670	0.00568	1711	ND	1752	ND	1793	0.00729	1834	ND
1671	0.00414	1712	ND	1753	ND	1794	0.00928	1835	ND
1672	0.0132	1713	0.0158	1754	ND	1795	0.00896	1836	ND
1673	0.00722	1714	ND	1755	ND	1796	ND	1837	ND
1674	0.00650	1715	ND	1756	ND	1797	ND	1838	0.0123

[1297]

化合物.	IC_{50}(μM)	化合物.	IC_{50}(μM)	化合物.	IC_{50}(μM)	化合物.	IC_{50}(μM)	化合物.	IC_{50}(μM)
1839	0.0345	1880	ND	1921	ND	1962	ND	2003	0.264
1840	0.0264	1881	ND	1922	ND	1963	0.241	2004	0.639
1841	ND	1882	ND	1923	ND	1964	0.0498	2005	0.364
1842	ND	1883	ND	1924	ND	1965	0.0864	2006	0.611
1843	ND	1884	ND	1925	ND	1966	ND	2007	>300
1844	ND	1885	ND	1926	ND	1967	ND	2008	0.0961
1845	ND	1886	ND	1927	ND	1968	ND	2009	2.15
1846	ND	1887	ND	1928	ND	1969	ND	2010	1.19
1847	ND	1888	ND	1929	ND	1970	0.0672	2011	0.529
1848	ND	1889	ND	1930	0.00481	1971	0.0519	2012	ND
1849	ND	1890	ND	1931	0.0197	1972	0.0180	2013	>10.0
1850	ND	1891	ND	1932	0.00840	1973	0.0143	2014	12.2
1851	ND	1892	ND	1933	0.0346	1974	0.0513	2015	0.0511
1852	ND	1893	ND	1934	0.0385	1975	0.109	2016	0.613
1853	ND	1894	ND	1935	0.0801	1976	1.85	2017	0.0506
1854	ND	1895	0.0127	1936	0.0374	1977	>1.00	2018	0.0244
1855	ND	1896	0.0122	1937	0.0382	1978	0.0253	2019	0.0249
1856	ND	1897	0.0131	1938	0.0463	1979	ND	2020	0.0330
1857	ND	1898	0.0613	1939	0.0245	1980	ND	2021	ND
1858	ND	1899	0.0164	1940	0.0349	1981	0.0238	2022	ND
1859	ND	1900	2.70	1941	0.0616	1982	0.0364	2023	ND
1860	ND	1901	0.0357	1942	0.182	1983	0.0826	2024	ND
1861	ND	1902	0.0842	1943	0.0424	1984	ND	2025	ND
1862	ND	1903	0.0298	1944	0.0249	1985	ND	2026	0.656
1863	ND	1904	0.0369	1945	0.0449	1986	0.0785	2027	>1.00
1864	ND	1905	0.881	1946	0.0447	1987	1.29	2028	>1.00
1865	ND	1906	ND	1947	0.0297	1988	0.0495	2029	ND
1866	ND	1907	0.405	1948	0.0356	1989	0.0890	2030	ND
1867	ND	1908	0.00517	1949	0.0216	1990	0.0581	2031	ND
1868	ND	1909	0.0292	1950	0.0417	1991	>300	2032	ND
1869	ND	1910	0.0474	1951	0.0199	1992	0.490	2034	0.00620
1870	ND	1911	0.00403	1952	ND	1993	0.412	2035	0.0723
1871	ND	1912	0.00596	1953	0.0893	1994	0.0418	2036	0.0384
1872	ND	1913	0.0229	1954	0.0170	1995	0.0593	2037	>1.00
1873	ND	1914	ND	1955	ND	1996	0.189	2038	ND
1874	ND	1915	ND	1956	ND	1997	0.0775	2039	ND
1875	ND	1916	ND	1957	ND	1998	0.409	2041	ND
1876	ND	1917	ND	1958	ND	1999	0.482	2042	ND
1877	ND	1918	ND	1959	0.0463	2000	18.2		
1878	ND	1919	ND	1960	43.2	2001	65.8		
1879	ND	1920	ND	1961	0.211	2002	0.259		

[1298] 实施例5B.细胞增殖测定

[1299] MDA-MB-361细胞在CO_2培养箱中在37℃下维持在补充10％FBS和1X青霉素/链霉素溶液的DMEM中。对于细胞增殖测定,将指数生长的细胞以每孔2,000个细胞接种在96孔平底白色聚苯乙烯板(ThermoFisher)中并培养过夜。第二天,从1或10μM(如所示)的最高浓度开

始,以9点3倍稀释系列将化合物与DMSO对照一起添加。样品中的最终DMSO浓度为0.1%。

[1300] 细胞在CO_2培养箱中在37℃下孵育最多6天小时。根据制造商的说明,使用来自Promega(Madison,WI)的CELLTITER-GLO®试剂在处理当天测量未处理细胞的基线活力,并在处理6天小时后测量增殖。使用以下公式相对于DMSO对照(对照的百分比)计算对化合物的响应:对照(DMSO)的百分比=[($CTG_{细胞}$+抑制剂)/($CTG_{DMSO对照}$)]x100。使用Prism(GraphPad软件)绘制数据,IC_{50}和E_{max}值是由4参数可变斜率非线性回归模型计算的。结果如以下和图1-3中所示。

[1301]

化合物	平均IC50(nM)	n
1188	46.8*	7
634	3.8	3
1141	361	2

[1302] *95%CI(nM)35.1-62.2,E_{max}(%),90.2

[1303] 可以组合上述各种实施方案以提供另外的实施方案。在本说明书中提到的和/或在申请数据表中列出的所有美国专利,美国专利申请公开案,美国专利申请,外国专利,外国专利申请和非专利出版物通过引用整体并入本文。如果需要,可以修改实施方案的方面以采用各种专利,申请和公开案的构思,以提供另外的实施方案。

[1304] 根据以上详细描述,可以对实施方案进行这些和其他改变。一般而言,在以下权利要求中,所使用的术语不应被解释为将权利要求限制到在说明书和权利要求中公开的特定实施方案,而应被解释为包括所有可能的实施方案连同这些权利要求所享有的等价方案的全部范围。因此,权利要求不受本公开内容的限制。

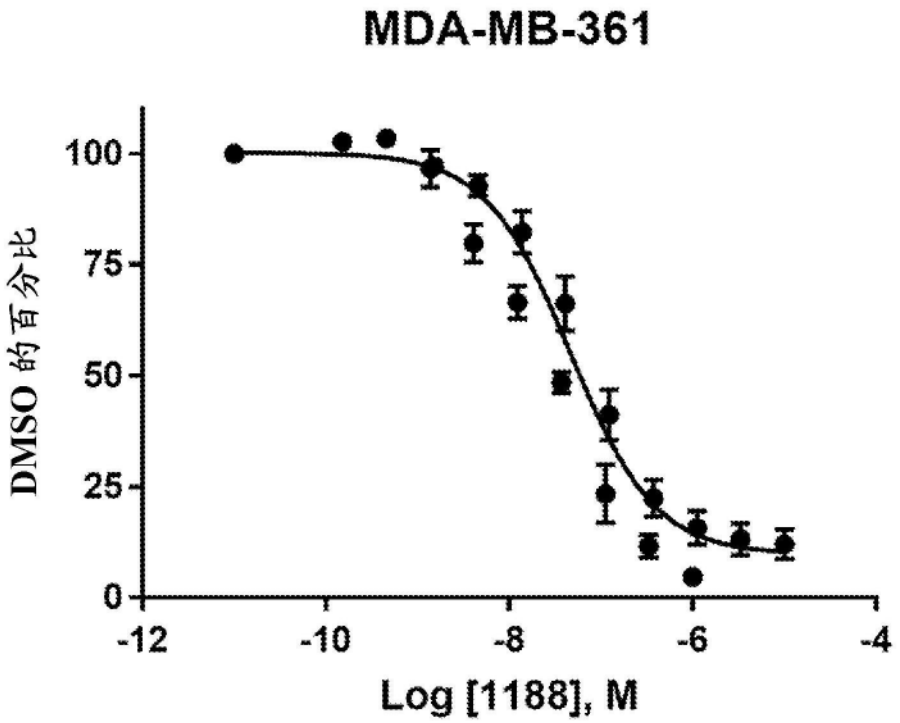

MDA-MB-361
DMSO 的百分比
100
75
50
25
0
-12
-10
-8
-6
-4
Log [1188], M

图1

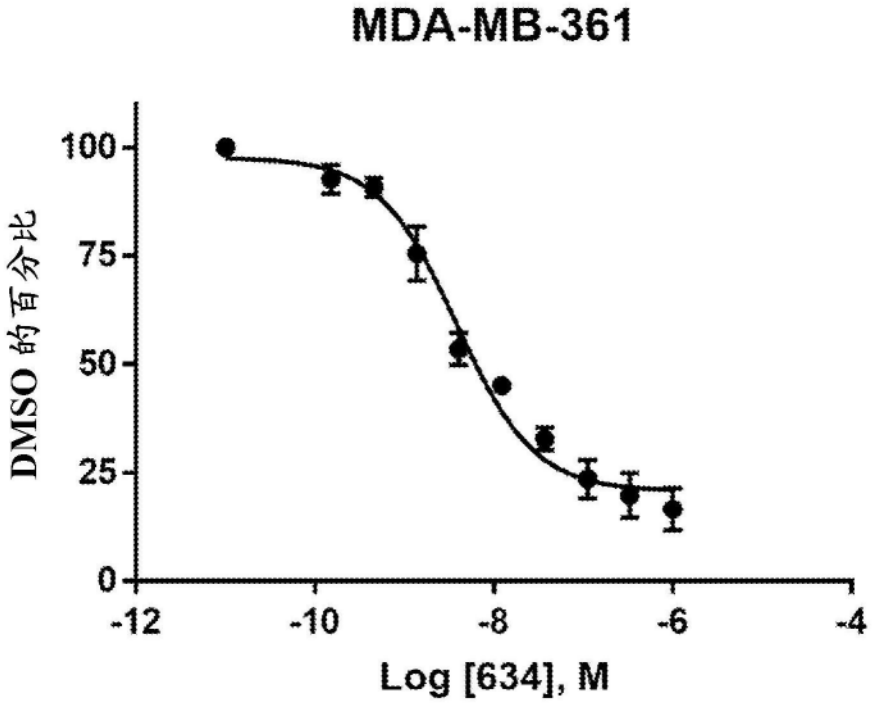

MDA-MB-361
DMSO 的百分比
100
75
50
25
0
-12
-10
-8
-6
-4
Log [634], M

图2

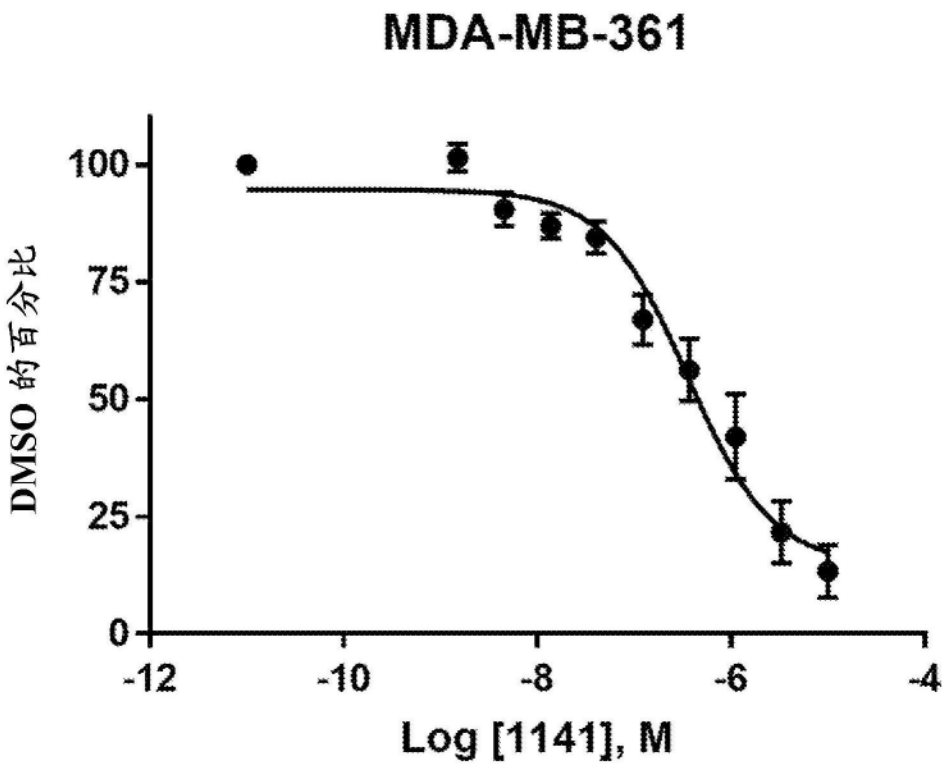


图3