



(10) 授权公告号 CN 111148740 B

(45) 授权公告日 2023. 08. 25

(21) 申请号 201880033785.9

(22) 申请日 2018.05.18

(65) 同一申请的已公布的文献号
申请公布号 CN 111148740 A

(43) 申请公布日 2020.05.12

(66) 本国优先权数据
201710364986.4 2017.05.22 CN

(85) PCT国际申请进入国家阶段日
2019.11.22

(86) PCT国际申请的申请数据
PCT/CN2018/087446 2018.05.18

(87) PCT国际申请的公布数据
W02018/214812 ZH 2018.11.29

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(51) Int.Cl.

C07D 295/088 (2006.01)

C07D 295/205 (2006.01)

C07D 209/04 (2006.01)

C07D 213/16 (2006.01)

C07D 231/56 (2006.01)

C07C 49/563 (2006.01)

C07C 49/567 (2006.01)

C07C 49/573 (2006.01)

C07C 49/577 (2006.01)

(56) 对比文件

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审查员 周琼

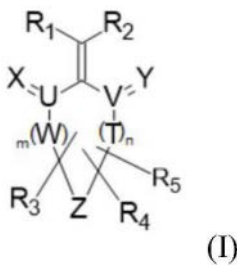
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(54) 发明名称

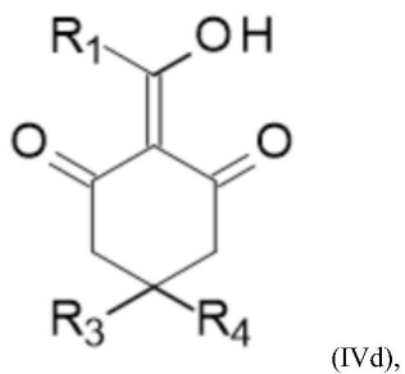
用作自噬调节剂的化合物及其制备方法和
用途

(57) 摘要

本发明涉及用作自噬调节剂的化合物及其
制备方法和用途,具体而言提供了一种通式(I)
所示化合物或其药学上可接受的盐,其是一类自
噬调节剂,特别是哺乳动物ATG8同源物调节剂。

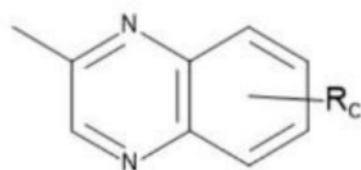
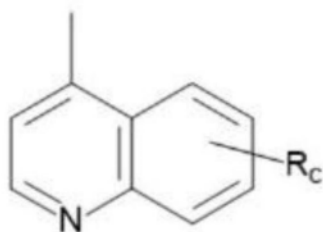
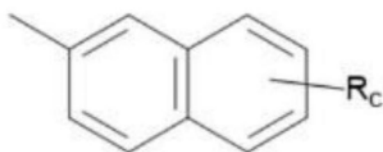
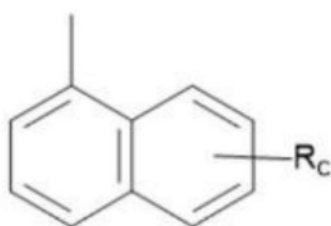
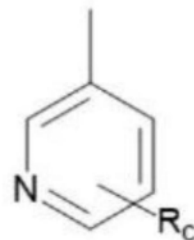
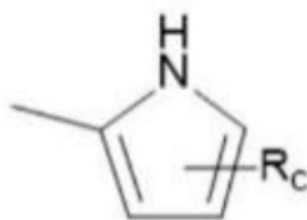
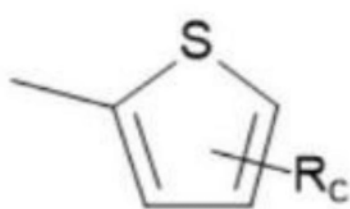
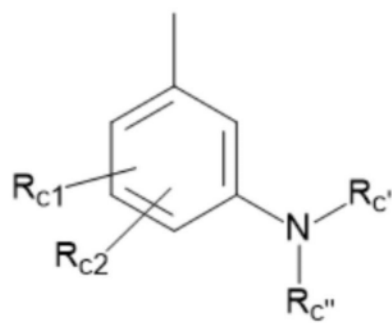
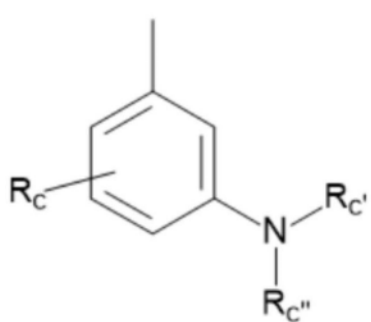


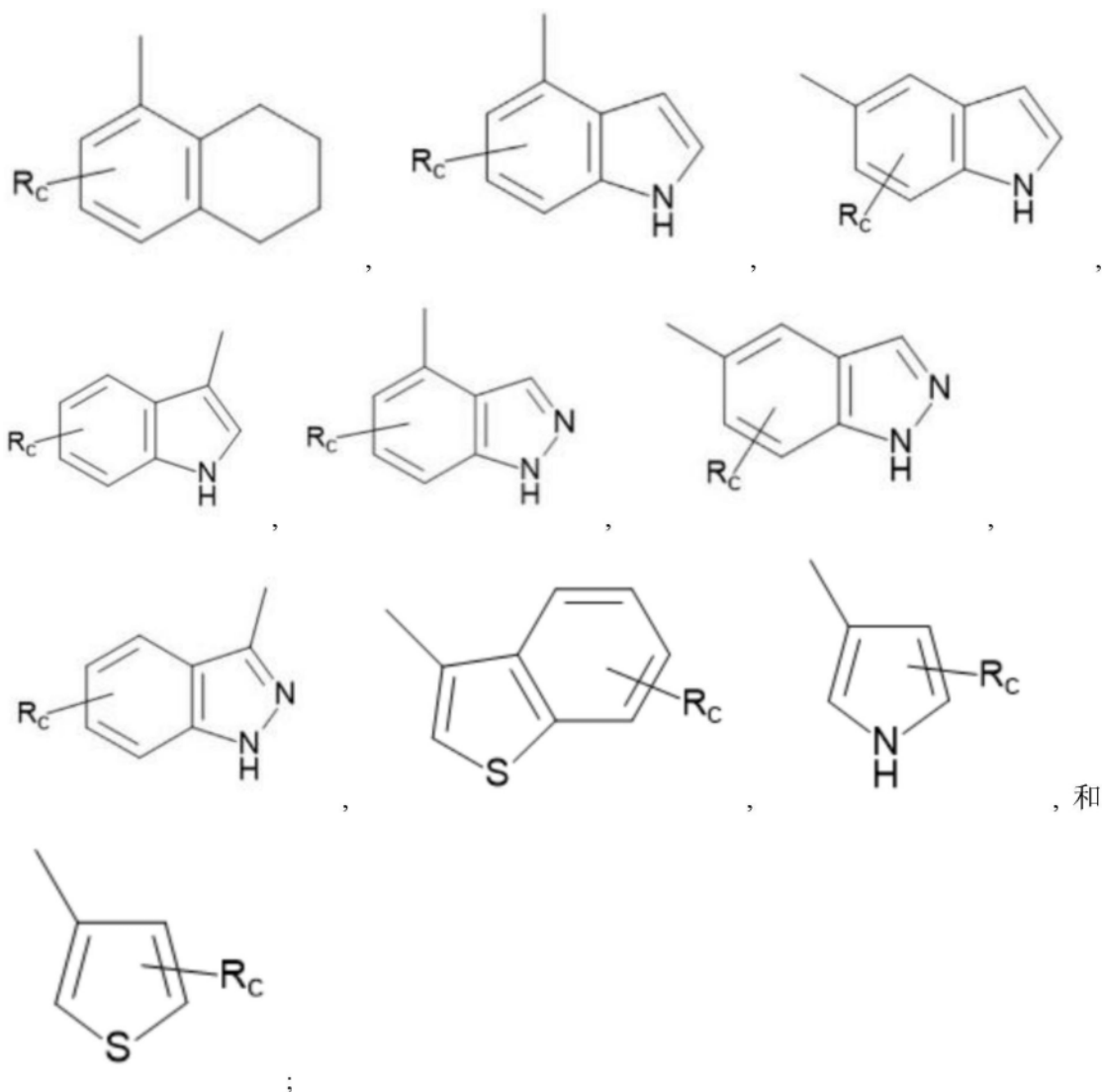
1. 一种通式 (IVd) 所示化合物或其药学上可接受的盐：



其中, R_1 选自氢；

R_3 选自如下基团：

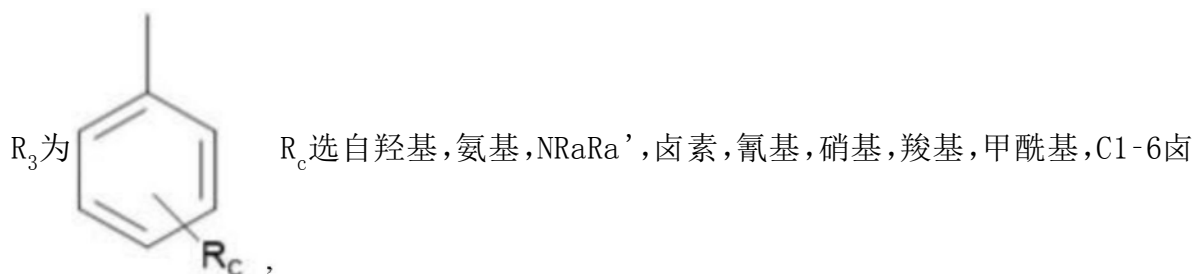




其中,各 R_c , R_{c1} , R_{c2} , R_c' 和 R_c'' 独立地选自氢,羟基,氨基, NR_aR_a' ,卤素,氰基,硝基,羧基,甲酰基,C1-6卤代烷基,C1-6羟基烷基,C1-6杂烷基,C1-6烷氧基,C2-6烯基,C2-6炔基,C6-10芳基,5-10元杂芳基,C3-10环烷基,3-10元杂环烷基,3-7元杂环烯基,C1-6烷基C6-10芳基,5-10元杂芳基C1-6烷基或C1-6烷基5-10元杂芳基;

各 R_a 和 R_a' 独立地为氢或C1-6烷基;

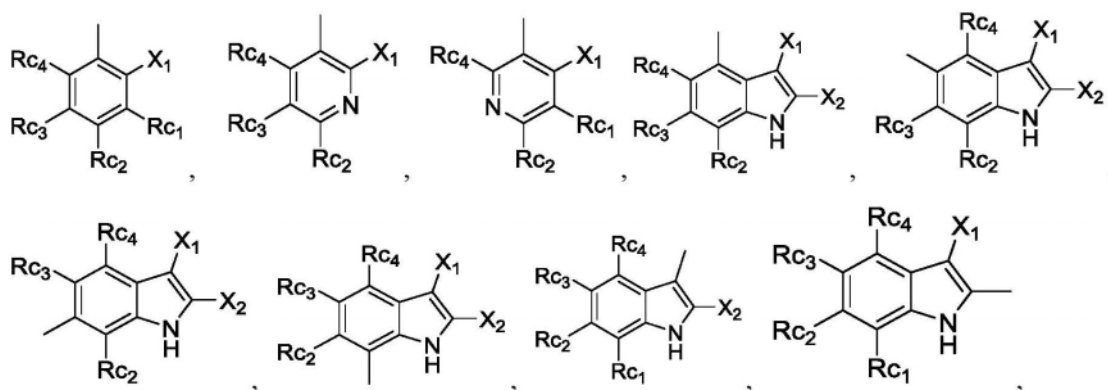
或者



代烷基,C1-6羟基烷基,C1-6杂烷基,C1-6烷氧基,C2-6烯基,C2-6炔基,C6-10芳基,5-10元杂芳基,C3-10环烷基,3-10元杂环烷基,3-7元杂环烯基,C1-6烷基C6-10芳基,5-10元杂芳基C1-6烷基或C1-6烷基5-10元杂芳基;各 R_a 和 R_a' 独立地为氢或C1-6烷基;

或者

R₃选自如下基团：



其中, X₁为F, Cl, Br, I或三氟甲基；

X₂为H, F, Cl, Br或I；

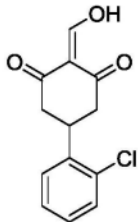
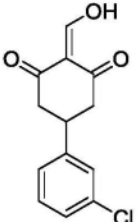
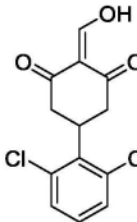
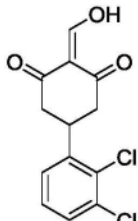
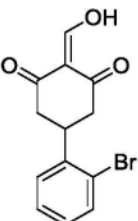
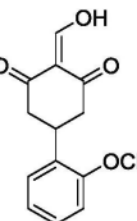
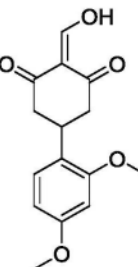
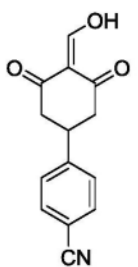
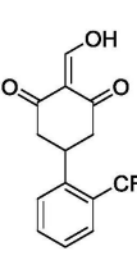
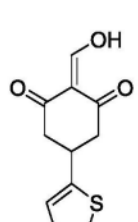
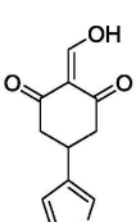
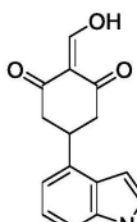
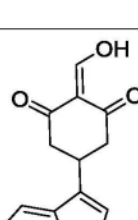
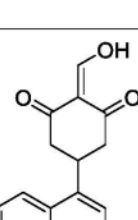
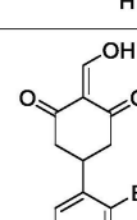
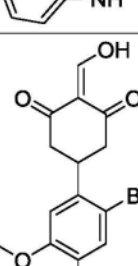
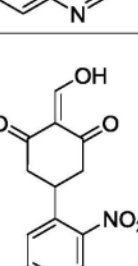
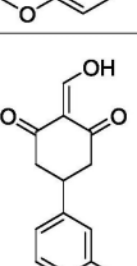
R_{c1}、R_{c2}、R_{c3}或R_{c4}各自独立地选自氢, 羟基, 氨基, NR_aR_a', 卤素, 氰基, 硝基, 羧基, 甲酰基, C1-6卤代烷基, C1-6羟基烷基, C1-6杂烷基, C1-6烷氧基, C2-6烯基, C2-6炔基, C6-10芳基, 5-10元杂芳基, C3-10环烷基, 3-10元杂环烷基, 3-7元杂环烯基, C1-6烷基C6-10芳基, 5-10元杂芳基C1-6烷基或C1-6烷基5-10元杂芳基；

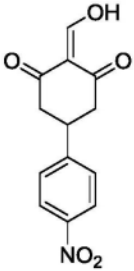
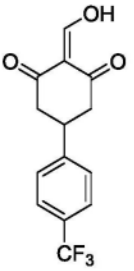
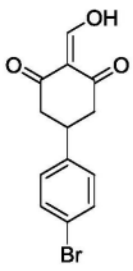
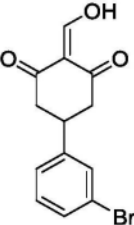
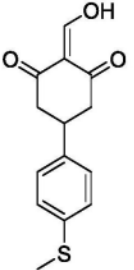
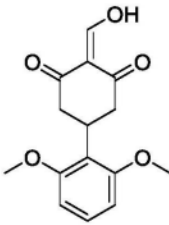
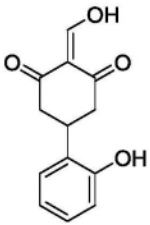
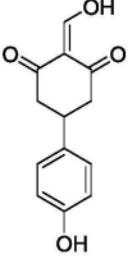
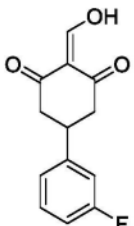
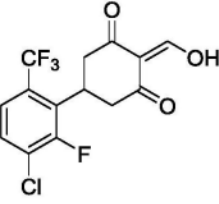
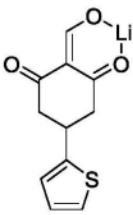
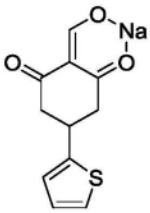
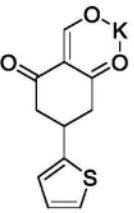
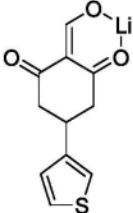
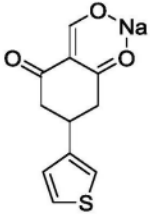
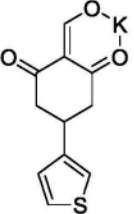
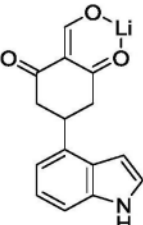
各R_a和R_a'独立地为氢或C1-6烷基；

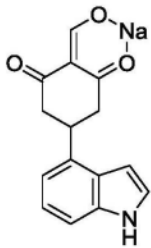
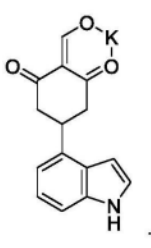
R₄为氢。

2. 化合物或其药学上可接受的盐, 其选自以下化合物或盐：

编号	结构式	编号	结构式	编号	结构式
415		416		417	

418		419		420	
421		422		423	
424		425		426	
427		428		429	
430		431		432	
433		434		435	

436		437		438	
439		440		441	
442		443			
446		447		453	
454		455		456	
457		458		459	

460	 <chem>[Na+].[O-]C1=CC(=O)C(=O)C2=C1C(=O)C(C3=CC4=C(C=C3)C=CC=C4N)C2=O</chem>	461	 <chem>[K+].[O-]C1=CC(=O)C(=O)C2=C1C(=O)C(C3=CC4=C(C=C3)C=CC=C4N)C2=O</chem>	
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3. 一种药物组合物,其包含根据权利要求1-2中任一项所述的化合物或其药学上可接受的盐。

4. 根据权利要求1-2中任一项所述的化合物或其药学上可接受的盐在制备调节细胞自噬的药物中的用途,其中,所述调节细胞自噬的药物是预防或治疗与细胞自噬相关的疾病的药物,所述调节细胞自噬的药物是调节哺乳动物ATG8同源物LC3B的药物。

用作自噬调节剂的化合物及其制备方法和用途

技术领域

[0001] 本发明涉及生物医药领域,具体涉及一类自噬调节剂,特别是哺乳动物ATG8同源物调节剂及其用途。

背景技术

[0002] 细胞自噬是一种细胞内降解的通路,是将细胞内受损或失去功能的蛋白质以及细胞器运输至溶酶体,并进行消化和降解的过程。在生物进化中,细胞自噬是一种保守的过程,从酵母到植物细胞再到哺乳动物细胞,都存在这样的过程。

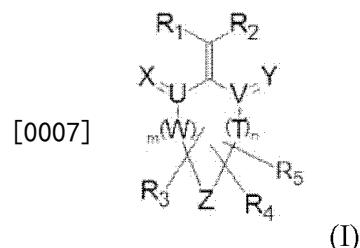
[0003] 现有的研究表明,细胞自噬在维持生理功能如饥饿时提供营养、清除细胞内容物、抗原呈递等方面起着重要的作用,并在癌症、感染性疾病、神经退行性疾病等扮演着重要的角色。细胞自噬在肿瘤的发生发展中起到双刃剑的作用:在肿瘤发生早期,自噬缺陷会增加基因组的不稳定性,促进癌变过程;肿瘤快速生长和转移阶段,自噬可以抵抗应激条件抑制失巢凋亡,维持肿瘤细胞生存。虽然自噬与肿瘤之间的关系在肿瘤发生发展的不同阶段有所不同,但针对进展晚期以及化疗耐药的癌症,细胞自噬调节剂的开发将有重大的价值。

[0004] 目前共有30余项关于调节自噬的药物临床试验,例如单独使用羟氯喹、氯喹或与其他抗肿瘤药物联用评价细胞自噬的抑制对难治性、复发性为主的实体瘤的治疗效果,相关结果可在clinicaltrial.gov官网查询。不过,由于缺乏明确的分子靶标,抗溶酶体抑制剂的副作用以及化学空间改造的方向不明会严重限制该类细胞自噬抑制剂的进一步发展。

[0005] 目前靶向细胞自噬的小分子调节剂主要限于mTOR和溶酶体调节剂,针对细胞自噬相关蛋白,如ATG4和ULK1的小分子调控剂的研究依然处于开发的早期。而最重要的细胞自噬相关蛋白,ATG8及其哺乳动物同源家族蛋白LC3, GABARAP和GATE-16子家族的调控剂均未有任何报道。在人体内,LC3家族有LC3A、LC3B、LC3C, GABARAP家族有GABARAPL和GABARAPL1, GATE-16家族有GABARAPL2。在ATG8的哺乳动物同源蛋白中,LC3B无疑是研究得最为深入的一个,它被认为是细胞自噬的标志物。目前尚未有任何针对LC3B的调控剂的报道,开发LC3B的调控剂对于治疗相关疾病的来说十分迫切。

发明内容

[0006] 本发明提供了一种通式(I)所示化合物或其药学上可接受的盐:



[0008] 其中:

[0009] X和Y各自独立地选自O, S, NR_a , NOH和 CH_2 ;

[0010] U和V各自独立地选自C, S, SO和 POR_a ;

- [0011] W、Z和T各自独立地选自O,S,SO,SO₂,N,NR_a,CO,C,CR_a,和CH₂;
- [0012] m为0,1,2或3;优选为0或1;
- [0013] n为0,1,2或3;优选为0或1;
- [0014] R₁选自氢,氘,C1-6烷基,C1-6羟基烷基,C1-6卤代烷基,未取代或取代的苯基;
- [0015] R₂表示为-J-K-M-Q,其中
- [0016] J为NR_a,NOR_a,O,S或 $\text{—N} \begin{array}{c} \text{A} \\ \text{---} \end{array}$,其中
- [0017] $\text{—N} \begin{array}{c} \text{A} \\ \text{---} \end{array}$ 环为含至少一个氮原子的二价3-10元杂环烷基或二价3-7元杂环烯基;
- [0018] K为共价键,NR_a,CR_cR_c或CR_cR_c,CR_cR_c;
- [0019] M为共价键,CR_cR_c,二价3-10元杂环烷基,二价3-7元杂环烯基或二价5-10元杂芳基;
- [0020] Q为氢,C1-6烷基,C1-6羟基烷基, $\text{—(CH}_2\text{)}_p\text{—C(O)R}_b$, $\text{—(CH}_2\text{)}_p\text{—C(O)NHR}_b$, $\text{—(CH}_2\text{)}_p\text{—C(S)R}_b$, $\text{—(CH}_2\text{)}_p\text{—C(S)NHR}_b$, $\text{—(CH}_2\text{)}_p\text{—SO}_2\text{R}_b$, $\text{—(CH}_2\text{)}_p\text{—SO}_2\text{NHR}_b$;
- [0021] p为0,1,2或3;优选为0或1;
- [0022] 各R_c和R_c'独立地选自氢,羟基,氨基,NRaRa',卤素,氰基,硝基,羧基,甲酰基,酰胺基,酯基,C1-6卤代烷基,C1-6羟基烷基,C1-6杂烷基,C1-6烷氧基,C1-6烷氧基烷基,C2-6烯基,C2-6炔基,C6-10芳基,5-10元杂芳基,C3-10环烷基,3-10元杂环烷基,3-7元杂环烯基,C1-6烷基C6-10芳基,5-10元杂芳基C1-6烷基或C1-6烷基5-10元杂芳基;优选选自氢,羟基,氨基,NRaRa',卤素,羧基,甲酰基,酰胺基,酯基,C1-6卤代烷基,C1-6羟基烷基,C1-6杂烷基,C1-6烷氧基,C3-10环烷基,3-10元杂环烷基,取代或未取代的苯基或吡啶基;
- [0023] R₃、R₄和R₅各自独立地选自氢,羟基,氨基,卤素,氰基,硝基,羧基,甲酰基,酰胺基, —NH—COR_b ,酯基,C1-6烷基,C1-6卤代烷基,C1-6羟基烷基,C1-6杂烷基,C1-6烷氧基,C1-6烷氧基烷基,C2-6烯基,C2-6炔基,未取代或取代的 —CONH—(C6-10芳基) ,未取代或取代的 —CH=CH—(C6-10芳基) ,未取代或取代的C6-10芳基,未取代或取代的5-10元杂芳基,未取代或取代的C3-10环烷基,未取代或取代的3-10元杂环烷基,未取代或取代的3-7元杂环烯基,未取代或取代的C6-10芳基C1-6烷基,未取代或取代的C1-6烷基C6-10芳基,未取代或取代的5-10元杂芳基C1-6烷基,和未取代或取代的C1-6烷基5-10元杂芳基;
- [0024] 或者R₃、R₄和R₅中的两个相邻基团可以连接形成未取代或取代的C6-10芳基,未取代或取代的5-10元杂芳基,未取代或取代的C3-10环烷基或未取代或取代的3-10元杂环烷基;
- [0025] 其中,各R_b独立地为C1-6烷基,C2-6烯基,NHR_a,NR_aR_a',未取代或取代的苯基或3-7元杂环基;
- [0026] 各R_a和R_a'独立地为氢或C1-6烷基;
- [0027] 未取代或取代表示该基团未被取代或者被一个或多个取代基取代,所述取代基选自羟基,氨基,氰基,硝基,羧基,卤素,C1-6烷基,C1-6卤代烷基或C1-6羟基烷基,或者二个相邻取代基可以连接形成C6-10芳基,C5-10杂芳基,C3-10环烷基或C3-10杂环烷基;
- [0028] 并且满足如下条件:
- [0029] (1) 当W、Z或T上被R₃、R₄和R₅中的一个取代时,该W、Z或T是N或CH;
- [0030] (2) 当W、Z或T上被R₃、R₄和R₅中的一个基团取代且该基团与R₃、R₄和R₅中的另一个相

邻基团连接形成未取代或取代的C6-10芳基或未取代或取代的5-10元杂芳基时,该W、Z或T是C;例如,当W被 R_3 取代且 R_3 与相邻的 R_4 连接形成未取代或取代的C6-10芳基或未取代或取代的5-10元杂芳基时,W是C;

[0031] (3)当W、Z或T上被 R_3 、 R_4 和 R_5 中的二个取代时,该W、Z或T是C。

[0032] 优选地,通式(I)中:

[0033] X和Y各自独立地选自O,S或NH;

[0034] U和V各自独立地选自C或S;

[0035] W、Z和T各自独立地选自O,N, NR_a ,CO,C, CR_a ,和 CH_2 ;

[0036] m为0,1或2;

[0037] n为0,1或2;

[0038] R_1 选自氢和氖;

[0039] R_2 表示为-J-K-M-Q,其中

[0040] J为 NR_a , NOR_a ,O,S或 $-N \begin{array}{c} \text{A} \\ \text{---} \end{array}$,其中

[0041] $-N \begin{array}{c} \text{A} \\ \text{---} \end{array}$ 为含至少一个氮原子的二价3-10元杂环烷基或二价3-7元杂环烯基;

[0042] K为共价键, NR_a , CR_cR_c 或 CR_cR_c · CR_cR_c ·;

[0043] M为共价键, CR_cR_c ·,二价3-10元杂环烷基,二价3-7元杂环烯基或二价5-10元杂芳基;

[0044] Q为氢,C1-6烷基,C1-6羟基烷基, $-(CH_2)_p-C(O)R_b$, $-(CH_2)_p-C(O)NHR_b$, $-(CH_2)_p-C(S)R_b$, $-(CH_2)_p-C(S)NHR_b$, $-(CH_2)_p-SO_2R_b$, $-(CH_2)_p-SO_2NHR_b$,其中,

[0045] p为0,1,2或3;优选为0或1;

[0046] 各 R_c 和 R_c' 独立地选自氢,羟基,氨基, $NRaRa'$,卤素,氰基,硝基,羧基,甲酰基,酰胺基,酯基,C1-6卤代烷基,C1-6羟基烷基,C1-6杂烷基,C1-6烷氧基,C1-6烷氧基烷基,C2-6烯基,C2-6炔基,C6-10芳基,5-10元杂芳基,C3-10环烷基,3-10元杂环烷基,3-7元杂环烯基,C1-6烷基C6-10芳基,5-10元杂芳基C1-6烷基或C1-6烷基5-10元杂芳基;优选选自氢,羟基,氨基, $NRaRa'$,卤素,羧基,甲酰基,酰胺基,酯基,C1-6卤代烷基,C1-6羟基烷基,C1-6杂烷基,C1-6烷氧基,C3-10环烷基,3-10元杂环烷基,取代或未取代的苯基或吡啶基;

[0047] R_3 、 R_4 和 R_5 各自独立地选自氢,羟基,氨基,卤素,氰基,硝基,羧基,甲酰基,酰胺基, $NH-COR_b$,酯基,C1-6烷基,C1-6卤代烷基,C1-6羟基烷基,C1-6杂烷基,C1-6烷氧基,C1-6烷氧基烷基,C2-6烯基,C2-6炔基,未取代或取代的 $-CONH-$ (C6-10芳基),未取代或取代的 $-CH=CH-$ (C6-10芳基),未取代或取代的C6-10芳基,未取代或取代的5-10元杂芳基,未取代或取代的C3-10环烷基,未取代或取代的3-10元杂环烷基,未取代或取代的3-7元杂环烯基,未取代或取代的C6-10芳基C1-6烷基,未取代或取代的C1-6烷基C6-10芳基,未取代或取代的5-10元杂芳基C1-6烷基或未取代或取代的C1-6烷基5-10元杂芳基;

[0048] 或者 R_3 、 R_4 和 R_5 中的两个相邻基团可以连接形成未取代或取代的C6-10芳基,未取代或取代的5-10元杂芳基,未取代或取代的C3-10环烷基或未取代或取代的3-10元杂环烷基;

[0049] 其中,各 R_b 独立地为C1-6烷基,C2-6烯基, NHR_a , NR_aR_a' ,未取代或取代的苯基或3-7元杂环基;

[0050] 各 R_a 和 R_a' 独立地为氢或C1-6烷基；

[0051] 未取代或取代表示该基团未被取代或者被一个或多个取代基取代,所述取代基选自羟基,氨基,氰基,硝基,羧基,卤素,C1-6烷基,C1-6卤代烷基和C1-6羟基烷基,或者二个相邻取代基可以连接形成C6-10芳基,5-10元杂芳基,C3-10环烷基或3-10元杂环烷基；

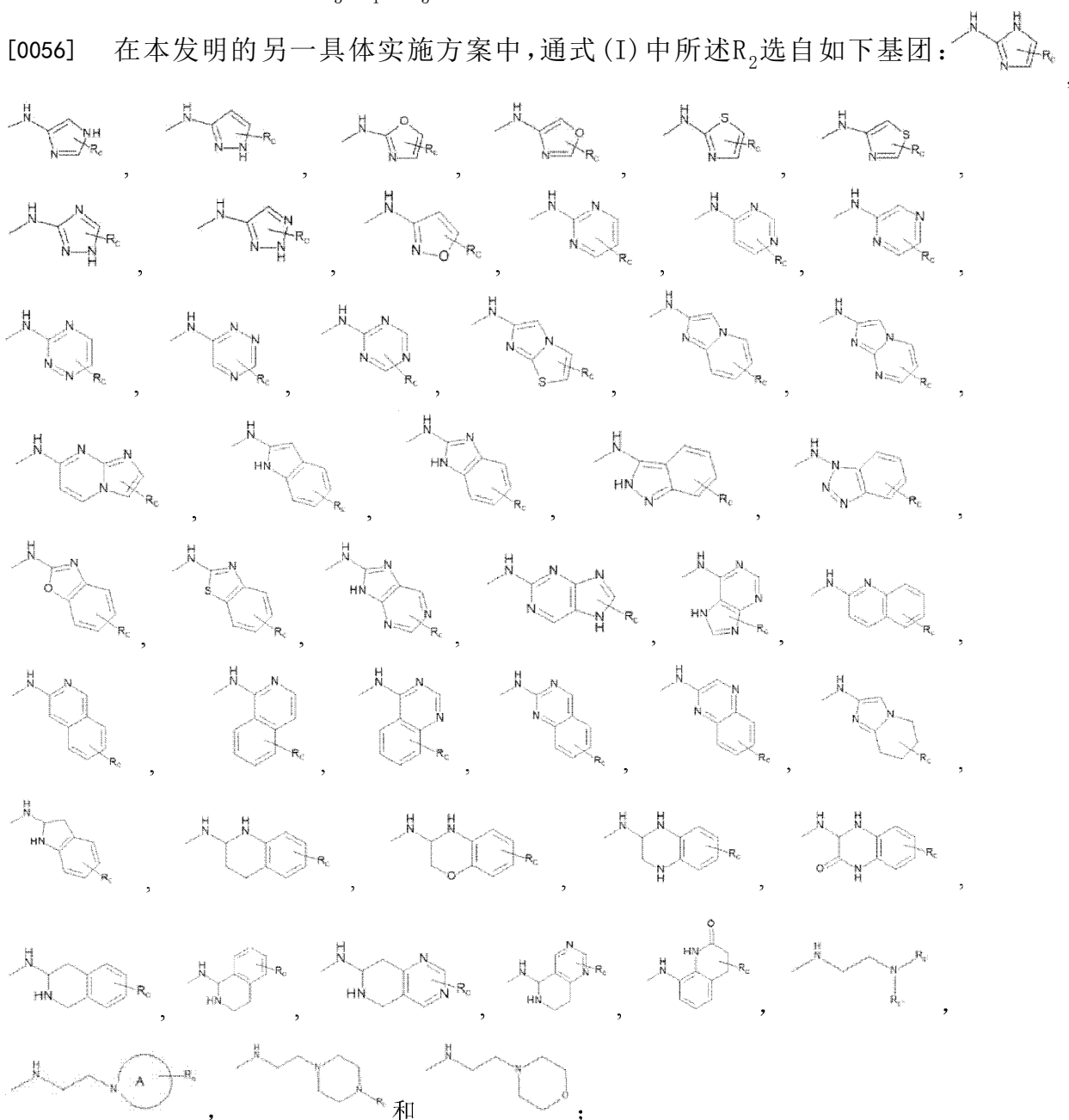
[0052] 并且满足如下条件：

[0053] (1) 当W、Z或T上被 R_3 、 R_4 和 R_5 中的一个取代时,该W、Z或T是N或CH；

[0054] (2) 当W、Z或T上被 R_3 、 R_4 和 R_5 中的一个基团取代且该基团与 R_3 、 R_4 和 R_5 中的另一个相邻基团连接形成未取代或取代的C6-10芳基或未取代或取代的5-10元杂芳基时,该W、Z或T是C；

[0055] (3) 当W、Z或T上被 R_3 、 R_4 和 R_5 中的二个取代时,该W、Z或T是C。

[0056] 在本发明的另一具体实施方案中,通式(I)中所述 R_2 选自如下基团：

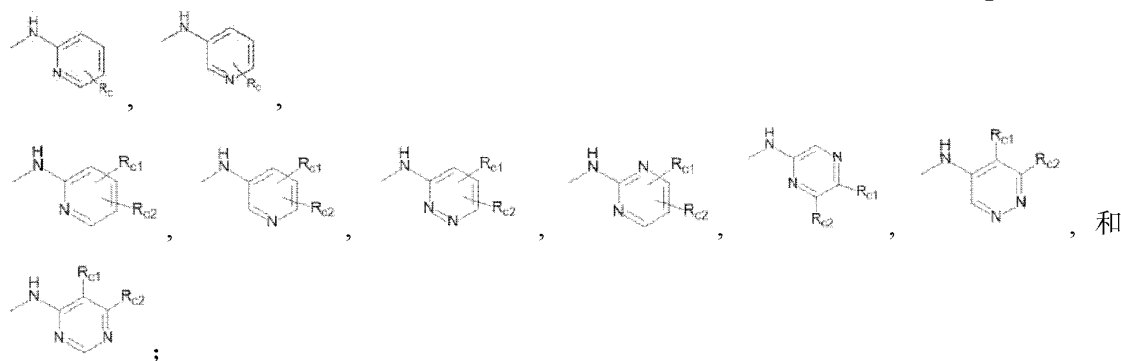


[0057] 其中,A为二价3-10元含氮杂环烷基或二价3-7元含氮杂环烯基；

[0058] R_c , R_c' 和 R_c'' 各自独立地选自氢, 羟基, 氨基, NR_aRa' , 卤素, 氰基, 硝基, 羧基, 甲酰基, 酰胺基, 酯基, C1-6卤代烷基, C1-6羟基烷基, C1-6杂烷基, C1-6烷氧基, C1-6烷氧基烷基, C2-6烯基, C2-6炔基, C6-10芳基, 5-10元杂芳基, C3-10环烷基, 3-10元杂环烷基, 3-7元杂环烯基, C1-6烷基C6-10芳基, 5-10元杂芳基C1-6烷基或C1-6烷基5-10元杂芳基; 优选选自氢, 羟基, 氨基, NR_aRa' , 卤素, 羧基, 甲酰基, 酰胺基, 酯基, C1-6卤代烷基, C1-6羟基烷基, C1-6杂烷基, C1-6烷氧基, C3-10环烷基, 3-10元杂环烷基, 取代或未取代的苯基或吡啶基;

[0059] 各 R_a 和 R_a' 独立地为氢或C1-6烷基。

[0060] 在本发明的另一具体实施方案中, 通式(I)中所述 R_2 选自如下基团:

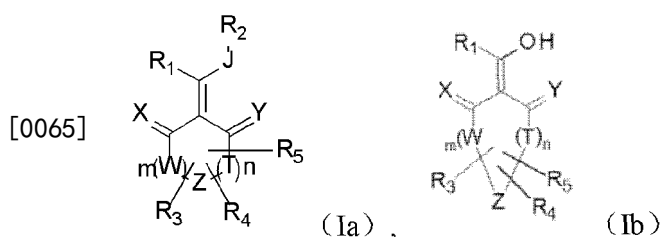


[0061] 其中, R_c , R_{c1} 和 R_{c2} 选自氢, 羟基, 氨基, NR_aRa' , 卤素, 氰基, 硝基, 羧基, 甲酰基, 酰胺基, 酯基, C1-6卤代烷基, C1-6羟基烷基, C1-6杂烷基, C1-6烷氧基, C1-6烷氧基烷基, C2-6烯基, C2-6炔基, C6-10芳基, 5-10元杂芳基, C3-10环烷基, 3-10元杂环烷基, 3-7元杂环烯基, C1-6烷基C6-10芳基, 5-10元杂芳基C1-6烷基或C1-6烷基5-10元杂芳基; 优选选自氢, 羟基, 氨基, NR_aRa' , 卤素, 羧基, 甲酰基, 酰胺基, 酯基, C1-6卤代烷基, C1-6羟基烷基, C1-6杂烷基, C1-6烷氧基, C3-10环烷基, 3-10元杂环烷基, 取代或未取代的苯基或吡啶基;

[0062] 或者 R_{c1} 和 R_{c2} 可以连接形成C6-10芳基, 5-10元杂芳基, C3-10环烷基和3-10元杂环烷基;

[0063] 各 R_a 和 R_a' 独立地为氢或C1-6烷基。

[0064] 在本发明的另一具体实施方案中, 通式(I)化合物选自如下通式(Ia)或(Ib)所示化合物



[0066] 其中, X 和 Y 各自独立地选自O, S或NH;

[0067] W , Z 和 T 各自独立地选自O, N, NR_a , CO, C, CR_a , 或 CH_2 ;

[0068] m 为0, 1或2;

[0069] n 为0, 1或2;

[0070] R_1 选自氢和氘;

[0071] J 为 NR_a , NOR_a , O, S 或 $-N \text{---} A \text{---}$, 其中 $-N \text{---} A \text{---}$ 为含至少一个氮原子的二价3-10元杂

环烷基或二价3-7元杂环烯基；

[0072] R_2' 选自：氢，C1-6烷基、C1-6卤代烷基、C1-6烷氧基、C1-6烷基氨基、C6-10芳基或5-10元杂芳基，C3-10环烷基，3-10元杂环烷基， $-(CH_2)_m-M-Q$ ，

[0073] 其中，M为共价键，二价3-10元杂环烷基，二价3-7元杂环烯基或二价5-10元杂芳基；

[0074] Q为氢，C1-6烷基，C1-6羟基烷基， $-(CH_2)_p-C(O)R_b$ ， $-(CH_2)_p-C(O)NHR_b$ ， $-(CH_2)_p-C(S)R_b$ ， $-(CH_2)_p-C(S)NHR_b$ ， $-(CH_2)_p-SO_2R_b$ ， $-(CH_2)_p-SO_2NHR_b$ ，

[0075] p为0, 1, 2或3；优选为0或1；

[0076] R_3 、 R_4 和 R_5 各自独立地选自氢，羟基，氨基，卤素，氰基，硝基，羧基，甲酰基，酰胺基， $NH-COR_b$ ，酯基，C1-6烷基，C1-6卤代烷基，C1-6羟基烷基，C1-6杂烷基，C1-6烷氧基，C1-6烷氧基烷基，C2-6烯基，C2-6炔基，未取代或取代的 $-CONH-$ (C6-10芳基)，未取代或取代的 $-CH=CH-$ (C6-10芳基)，未取代或取代的C6-10芳基，未取代或取代的5-10元杂芳基，未取代或取代的C3-10环烷基，未取代或取代的3-10元杂环烷基，未取代或取代的3-7元杂环烯基，未取代或取代的C6-10芳基C1-6烷基，未取代或取代的C1-6烷基C6-10芳基，未取代或取代的5-10元杂芳基C1-6烷基或未取代或取代的C1-6烷基5-10元杂芳基；

[0077] 或者 R_3 、 R_4 和 R_5 中的两个相邻基团可以连接形成未取代或取代的C6-10芳基，未取代或取代的5-10元杂芳基，未取代或取代的C3-10环烷基或未取代或取代的3-10元杂环烷基；

[0078] 其中，各 R_b 独立地为C1-6烷基，C2-6烯基， NHR_a ， NR_aR_a' ，未取代或取代的苯基或3-7元杂环基；

[0079] 各 R_a 和 R_a' 独立地为氢或C1-6烷基；

[0080] 未取代或取代表示该基团未被取代或者被一个或多个取代基取代，所述取代基选自羟基，氨基，氰基，硝基，羧基，卤素，C1-6烷基，C1-6卤代烷基和C1-6羟基烷基，或者二个相邻取代基可以连接形成C6-10芳基，5-10元杂芳基，C3-10环烷基或3-10元杂环烷基；

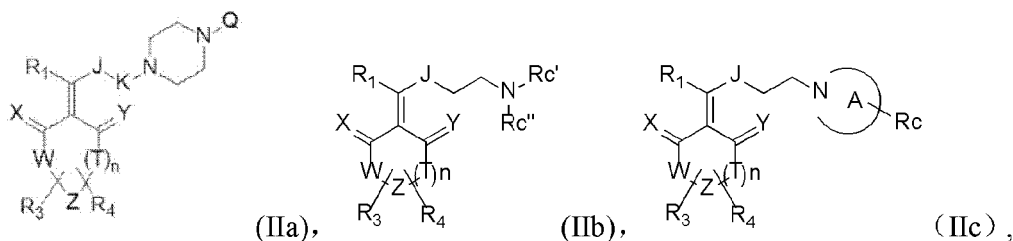
[0081] 并且满足如下条件：

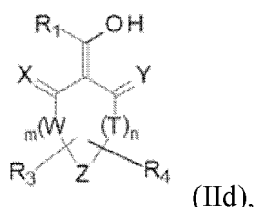
[0082] (1) 当W、Z或T上被 R_3 、 R_4 和 R_5 中的一个取代时，该W、Z或T是N或CH；

[0083] (2) 当W、Z或T上被 R_3 、 R_4 和 R_5 中的一个基团取代且该基团与 R_3 、 R_4 和 R_5 中的另一个相邻基团连接形成未取代或取代的C6-10芳基或未取代或取代的5-10元杂芳基时，该W、Z或T是C；

[0084] (3) 当W、Z或T上被 R_3 、 R_4 和 R_5 中的二个取代时，该W、Z或T是C。

[0085] 在本发明的另一具体实施方案中，通式(I)化合物选自如下通式(IIa)、(IIb)、(IIc)和(IId)所示化合物：





[0086] 其中,X和Y独立地是O,S,NH;

[0087] W、Z和T各自独立地选自O,N,NR_a,CO,C,CR_a,或CH₂;

[0088] n为0,1,2或3;

[0089] R₁选自氢和氘;

[0090] $\text{—N} \begin{array}{c} \text{A} \\ \text{---} \end{array}$ 为二价3-10元含氮杂环烷基或二价3-7元含氮杂环烯基;

[0091] J选自NR_a,NOR_a,O和S;

[0092] K为共价键,NR_a,CR_cR_c,或CR_cR_c.CR_cR_c;

[0093] Q为氢,C1-6烷基,C1-6羟基烷基, $\text{—(CH}_2\text{)}_p\text{—C(O)R}_b$, $\text{—(CH}_2\text{)}_p\text{—C(O)NHR}_b$, $\text{—(CH}_2\text{)}_p\text{—C(S)R}_b$, $\text{—(CH}_2\text{)}_p\text{—C(S)NHR}_b$, $\text{—(CH}_2\text{)}_p\text{—SO}_2\text{R}_b$, $\text{—(CH}_2\text{)}_p\text{—SO}_2\text{NHR}_b$,

[0094] p为0,1,2或3;优选为0或1;

[0095] R_c,R_c'和R_c''各自独立地选自氢,羟基,氨基,NRaRa',卤素,氰基,硝基,羧基,甲酰基,酰胺基,酯基,C1-6卤代烷基,C1-6羟基烷基,C1-6杂烷基,C1-6烷氧基,C1-6烷氧基烷基,C2-6烯基,C2-6炔基,C6-10芳基,5-10元杂芳基,C3-10环烷基,3-10元杂环烷基,3-7元杂环烯基,C1-6烷基C6-10芳基,5-10元杂芳基C1-6烷基或C1-6烷基5-10元杂芳基;优选选自氢,羟基,氨基,NRaRa',卤素,羧基,甲酰基,酰胺基,酯基,C1-6卤代烷基,C1-6羟基烷基,C1-6杂烷基,C1-6烷氧基,C3-10环烷基,3-10元杂环烷基,取代或未取代的苯基或吡啶基;

[0096] R₃和R₄各自独立地选自氢,羟基,氨基,卤素,氰基,硝基,羧基,甲酰基,酰胺基,NH-COR_b,酯基,C1-6烷基,C1-6卤代烷基,C1-6羟基烷基,C1-6杂烷基,C1-6烷氧基,C1-6烷氧基烷基,C2-6烯基,C2-6炔基,未取代或取代的-CONH-(C6-10芳基),未取代或取代的-CH=CH-(C6-10芳基),未取代或取代的C6-10芳基,未取代或取代的5-10元杂芳基,未取代或取代的C3-10环烷基,未取代或取代的3-10元杂环烷基,未取代或取代的3-7元杂环烯基,未取代或取代的C6-10芳基C1-6烷基,未取代或取代的C1-6烷基C6-10芳基,未取代或取代的5-10元杂芳基C1-6烷基或未取代或取代的C1-6烷基5-10元杂芳基;

[0097] 或者R₃和R₄连接形成未取代或取代的C6-10芳基,未取代或取代的5-10元杂芳基,未取代或取代的C3-10环烷基或未取代或取代的3-10元杂环烷基;

[0098] 其中,各R_b独立地为C1-6烷基,C2-6烯基,NHR_a,NR_aR_a',未取代或取代的苯基或3-7元杂环基;

[0099] 各R_a和R_a'独立地为氢或C1-6烷基;

[0100] 未取代或取代表示该基团未被取代或者被一个或多个取代基取代,所述取代基选自羟基,氨基,氰基,硝基,羧基,卤素,C1-6烷基,C1-6卤代烷基和C1-6羟基烷基,或者二个相邻取代基可以连接形成C6-10芳基,5-10元杂芳基,C3-10环烷基或3-10元杂环烷基;

[0101] 并且满足如下条件:

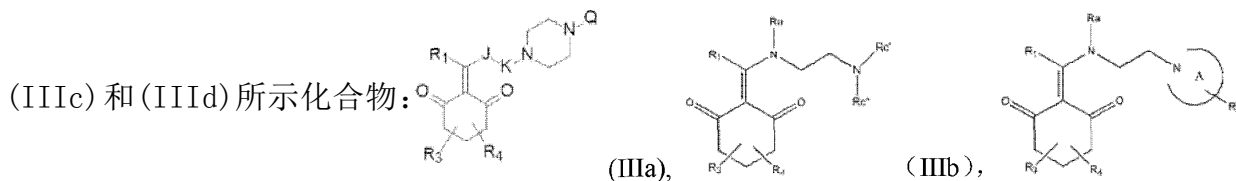
[0102] (1)W/Z或T上被R₃和R₄中一个取代时,该W/Z或T是N或CH;

[0103] (2)W/Z或T上被R₃和R₄中一个取代且R₃和R₄连接形成C6-10芳基或5-10元杂芳基

时,该W、Z或T是C;

[0104] (3)W、Z或T上同时被 R_3 和 R_4 取代时,该W、Z或T是C。

[0105] 在本发明的另一具体实施方案中,通式(I)化合物选自如下通式(IIIa)、(IIIb)、



(IIIc), (IIId),

[0106] 其中, R_1 选自氢,氘,C1-6烷基,C1-6羟基烷基,C1-6卤代烷基,未取代或取代的苯基;优选选自氢和氘;优选为氢;

[0107] J选自NRa,NORa,0或S;

[0108] K为共价键, NR_a , CR_cR_c 或 CR_cR_c , CR_cR_c ;

[0109] $-N \begin{array}{c} \text{A} \end{array} -$ 为二价3-10元含氮杂环烷基或二价3-7元含氮杂环烯基;

[0110] Q为氢,C1-6烷基,C1-6羟基烷基, $-(CH_2)_p-C(O)R_b$, $-(CH_2)_p-C(O)NHR_b$, $-(CH_2)_p-C(S)R_b$, $-(CH_2)_p-C(S)NHR_b$, $-(CH_2)_p-SO_2R_b$ 或 $-(CH_2)_p-SO_2NHR_b$,

[0111] p为0,1,2或3;优选为0或1;

[0112] 各 R_c , R_c 和 R_c 独立地选自氢,羟基,氨基,NRaRa',卤素,氰基,硝基,羧基,甲酰基,酰胺基,酯基,C1-6卤代烷基,C1-6羟基烷基,C1-6杂烷基,C1-6烷氧基,C1-6烷氧基烷基,C2-6烯基,C2-6炔基,C6-10芳基,5-10元杂芳基,C3-10环烷基,3-10元杂环烷基,3-7元杂环烯基,C1-6烷基C6-10芳基,5-10元杂芳基C1-6烷基或C1-6烷基5-10元杂芳基;优选选自氢,羟基,氨基,NRaRa',卤素,羧基,甲酰基,酰胺基,酯基,C1-6卤代烷基,C1-6羟基烷基,C1-6杂烷基,C1-6烷氧基,C3-10环烷基,3-10元杂环烷基,取代或未取代的苯基或吡啶基;

[0113] R_3 和 R_4 各自独立地选自氢,羟基,氨基,卤素,氰基,硝基,羧基,甲酰基,酰胺基,NH-CORb,酯基,C1-6烷基,C1-6卤代烷基,C1-6羟基烷基,C1-6杂烷基,C1-6烷氧基,C1-6烷氧基烷基,C2-6烯基,C2-6炔基,未取代或取代的-CONH-(C6-10芳基),未取代或取代的-CH=CH-(C6-10芳基),未取代或未取代或取代的C6-10芳基,未取代或取代的5-10元杂芳基,未取代或取代的C3-10环烷基,未取代或取代的3-10元杂环烷基,未取代或取代的3-7元杂环烯基,未取代或取代的C6-10芳基C1-6烷基,未取代或取代的C1-6烷基C6-10芳基,未取代或取代的5-10元杂芳基C1-6烷基或未取代或取代的C1-6烷基5-10元杂芳基;

[0114] 或者 R_3 和 R_4 连接形成未取代或取代的C6-10芳基,未取代或取代的5-10元杂芳基,未取代或取代的C3-10环烷基或未取代或取代的3-10元杂环烷基;

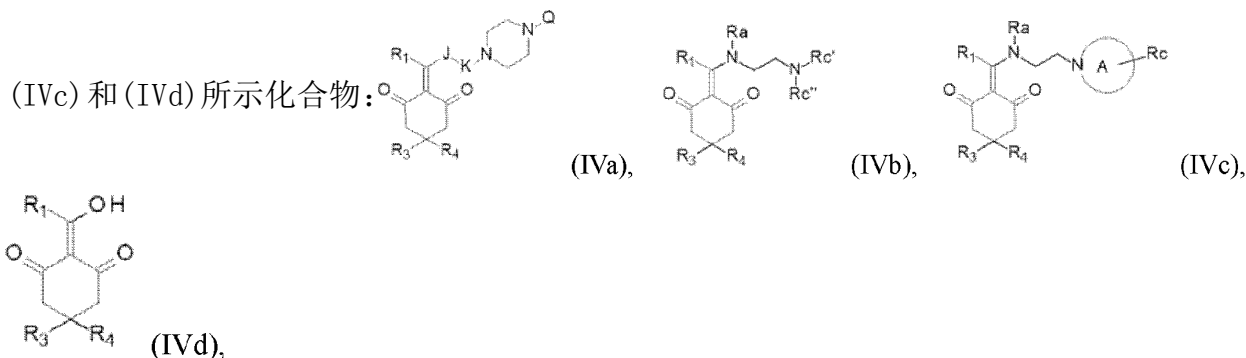
[0115] 其中,各 R_b 独立地为C1-6烷基,C2-6烯基,NHRa,NRaRa',未取代或取代的苯基或3-7元杂环基;

[0116] 各 R_a 和 R_a 独立地为氢或C1-6烷基;

[0117] 未取代或取代表示该基团未被取代或这被一个或多个取代基取代,所述取代基选

自羟基,氨基,氰基,硝基,羧基,卤素,C1-6烷基,C1-6卤代烷基和C1-6羟基烷基,或者二个相邻取代基可以连接形成C6-10芳基,5-10元杂芳基,C3-10环烷基或3-10元杂环烷基。

[0118] 在本发明的另一具体实施方案中,通式(I)化合物选自如下通式(IVa)、(IVb)、



[0119] 其中, R_1 选自氢,氘,C1-6烷基,C1-6羟基烷基,C1-6卤代烷基,未取代或取代的苯基;优选选自氢和氘;优选为氢;

[0120] J为 NR_a , NOR_a ,O或S;

[0121] K为共价键, NR_a , CR_cR_c 或 CR_cR_c , CR_cR_c ;

[0122] $-N(A)-$ 为二价3-10元含氮杂环烷基或二价3-7元含氮杂环烯基;

[0123] Q为氢,C1-6烷基,C1-6羟基烷基, $-(CH_2)_p-C(O)R_b$, $-(CH_2)_p-C(O)NHR_b$, $-(CH_2)_p-C(S)R_b$, $-(CH_2)_p-C(S)NHR_b$, $-(CH_2)_p-SO_2R_b$, $-(CH_2)_p-SO_2NHR_b$,

[0124] p为0,1,2或3;优选为0或1;

[0125] R_c , R_c' 和 R_c'' 各自独立地选自氢,羟基,氨基, $NRaRa'$,卤素,氰基,硝基,羧基,甲酰基,酰胺基,酯基,C1-6卤代烷基,C1-6羟基烷基,C1-6杂烷基,C1-6烷氧基,C1-6烷氧基烷基,C2-6烯基,C2-6炔基,C6-10芳基,5-10元杂芳基,C3-10环烷基,3-10元杂环烷基,3-7元杂环烯基,C1-6烷基C6-10芳基,5-10元杂芳基C1-6烷基或C1-6烷基5-10元杂芳基;优选选自氢,羟基,氨基, $NRaRa'$,卤素,羧基,甲酰基,酰胺基,酯基,C1-6卤代烷基,C1-6羟基烷基,C1-6杂烷基,C1-6烷氧基,C3-10环烷基,3-10元杂环烷基,取代或未取代的苯基或吡啶基;

[0126] R_3 选自氢,羟基,氨基,卤素,氰基,硝基,羧基,甲酰基,酰胺基, $NH-COR_b$,酯基,C1-6烷基,C1-6卤代烷基,C1-6羟基烷基,C1-6杂烷基,C1-6烷氧基,C1-6烷氧基烷基,C2-6烯基,C2-6炔基,未取代或取代的 $-CONH-(C6-10芳基)$,未取代或取代的 $-CH=CH-(C6-10芳基)$,未取代或取代的C6-10芳基,未取代或取代的5-10元杂芳基,未取代或取代的C3-10环烷基,未取代或取代的3-10元杂环烷基,未取代或取代的3-7元杂环烯基,未取代或取代的C6-10芳基C1-6烷基,未取代或取代的C1-6烷基C6-10芳基,未取代或取代的5-10元杂芳基C1-6烷基或未取代或取代的C1-6烷基5-10元杂芳基;

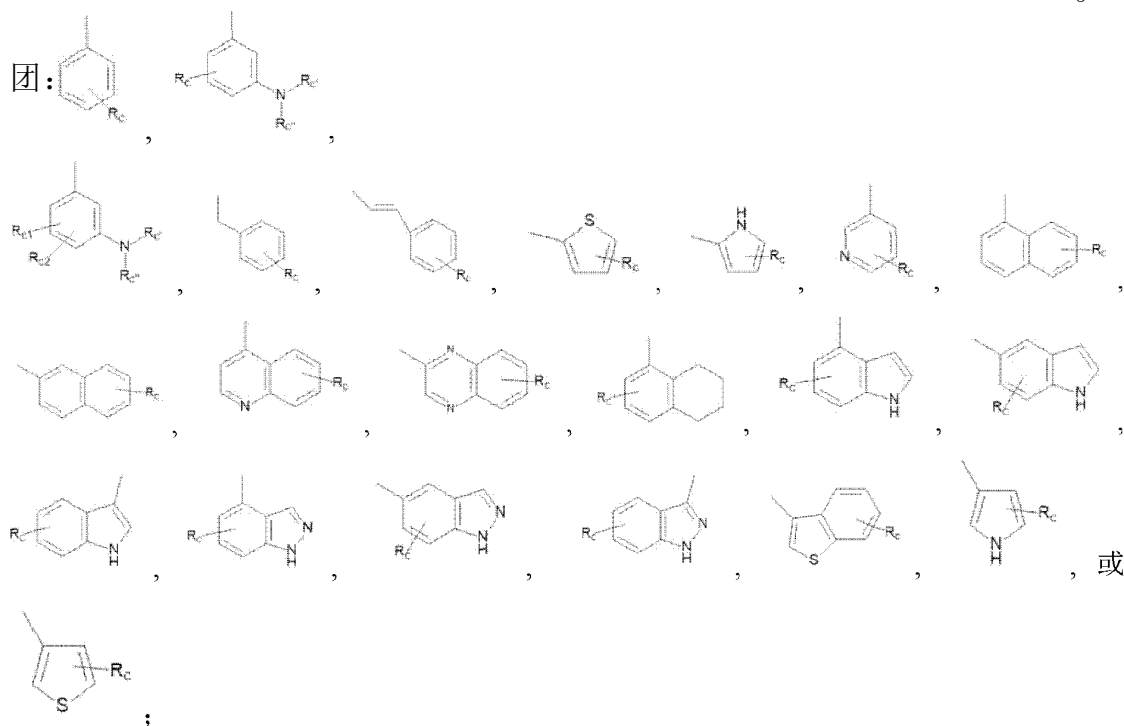
[0127] 其中,各 R_b 独立地为C1-6烷基,C2-6烯基, NHR_a , $NRaR_a'$,未取代或取代的苯基或3-7元杂环基;

[0128] 各 R_a 和 R_a' 独立地为氢或C1-6烷基;

[0129] 未取代或取代表示该基团未被取代或者被一个或多个取代基取代,所述取代基选自羟基,氨基,氰基,硝基,羧基,卤素,C1-6烷基,C1-6卤代烷基和C1-6羟基烷基,或者二个相邻取代基可以连接形成C6-10芳基,5-10元杂芳基,C3-10环烷基或3-10元杂环烷基;

[0130] R_4 选自氢,羟基和C1-6烷基。

[0131] 在本发明的另一具体实施方案中,通式(I), (Ia), (Ib), (IIa), (IIb), (IIc), (IIId), (IIIa), (IIIb), (IIIc), (IIId), (IVa), (IVb), (IVc), (IVd)中所述 R_3 选自如下基团:

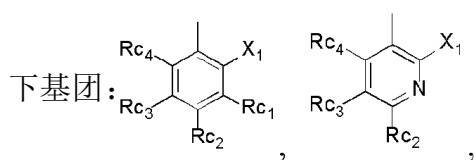


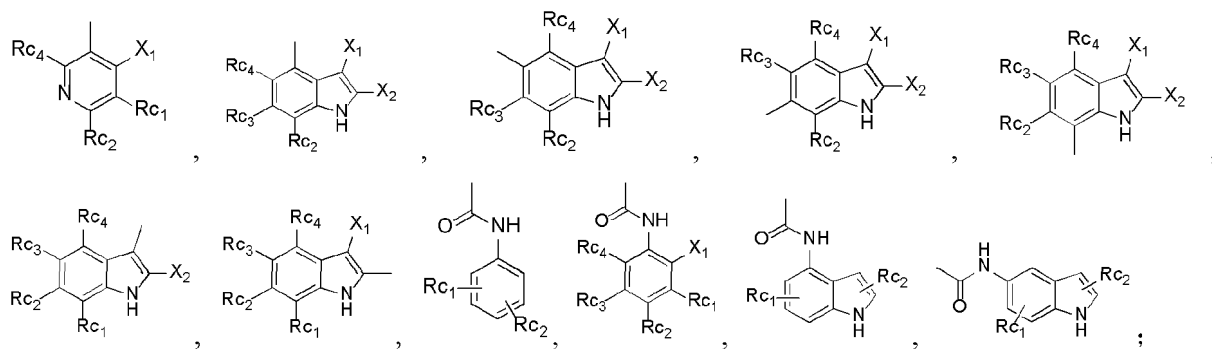
[0132] 其中,各 R_c , R_{c1} , R_{c2} , R_c' 和 R_c'' 独立地选自氢,羟基,氨基, $NRaRa'$, 卤素,氰基,硝基,羧基,甲酰基,酰胺基,酯基, C1-6卤代烷基, C1-6羟基烷基, C1-6杂烷基, C1-6烷氧基, C1-6烷氧基烷基, C2-6烯基, C2-6炔基, C6-10芳基, 5-10元杂芳基, C3-10环烷基, 3-10元杂环烷基, 3-7元杂环烯基, C1-6烷基C6-10芳基, 5-10元杂芳基C1-6烷基或C1-6烷基5-10元杂芳基;优选选自氢,羟基,氨基, $NRaRa'$, 卤素,羧基,甲酰基,酰胺基,酯基, C1-6卤代烷基, C1-6羟基烷基, C1-6杂烷基, C1-6烷氧基, C3-10环烷基, 3-10元杂环烷基, 取代或未取代的苯基或吡啶基;

[0133] 各 R_a 和 R_a' 独立地为氢或C1-6烷基。

[0134] 或者 R_{c1} 和 R_{c2} 可以连接形成C6-10芳基, 5-10元杂芳基, C3-10环烷基或3-10元杂环烷基。

[0135] 在本发明的另一具体实施方案中,通式(I), (Ia), (Ib), (IIa), (IIb), (IIc), (IIId), (IIIa), (IIIb), (IIIc), (IIId), (IVa), (IVb), (IVc), (IVd)中所述 R_3 选自如下基团:





[0136] 其中, X_1 为 F, Cl, Br, I 或三氟甲基;

[0137] X_2 为 H, F, Cl, Br 或 I;

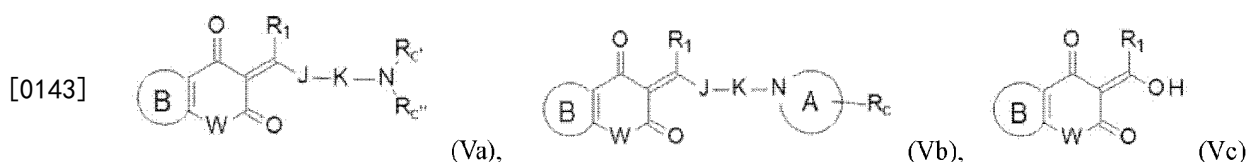
[0138] R_{c1} 、 R_{c2} 、 R_{c3} 或 R_{c4} 各自独立地选自氢, 羟基, 氨基, $NRaRa'$, 卤素, 氰基, 硝基, 羧基, 甲酰基, 酰胺基, 酯基, C1-6 卤代烷基, C1-6 羟基烷基, C1-6 杂烷基, C1-6 烷氧基, C1-6 烷氧基烷基, C2-6 烯基, C2-6 炔基, C6-10 芳基, 5-10 元杂芳基, C3-10 环烷基, 3-10 元杂环烷基, 3-7 元杂环烯基, C1-6 烷基 C6-10 芳基, 5-10 元杂芳基 C1-6 烷基或 C1-6 烷基 5-10 元杂芳基; 优选选自氢, 羟基, 氨基, $NRaRa'$, 卤素, 羧基, 甲酰基, 酰胺基, 酯基, C1-6 卤代烷基, C1-6 羟基烷基, C1-6 杂烷基, C1-6 烷氧基, C3-10 环烷基, 3-10 元杂环烷基, 取代或未取代的苯基或吡啶基;

[0139] 或者 R_{c1} 和 R_{c2} , 或 R_{c2} 和 R_{c3} , 或 R_{c3} 和 R_{c4} 可以连接形成 C6-10 芳基, 5-10 元杂芳基, C3-10 环烷基和 3-10 元杂环烷基;

[0140] 各 R_a 和 R_a' 独立地为氢或 C1-6 烷基。

[0141] 在本发明的另一具体实施方案中, 通式 (I) 中所述 R_4 和 R_5 为氢。

[0142] 在本发明的另一具体实施方案中, 通式 (I) 化合物选自如下通式 (Va), (Vb) 和 (Vc) 所示化合物:



[0144] 其中: W 选自: O, NRa 和 $CHRa$;

[0145] J 为 NR_a , $NORa$, O 或 S;

[0146] K 为共价键, NR_a , CR_cR_c 或 CR_cR_c , CR_cR_c' ;

[0147] R_1 选自氢, 氘, C1-6 烷基, C1-6 羟基烷基, C1-6 卤代烷基, 未取代或取代的苯基; 优选选自氢和氘; 优选为氢;

[0148] A 环为二价 3-10 元含氮杂环烷基或二价 3-7 元含氮杂环烯基;

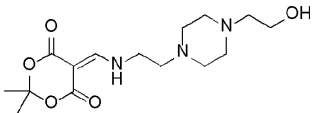
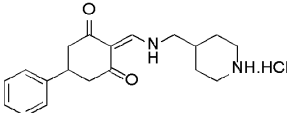
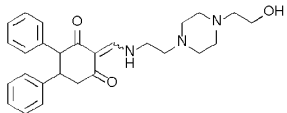
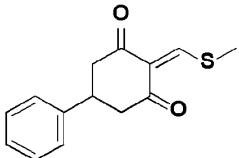
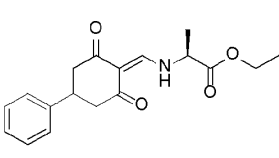
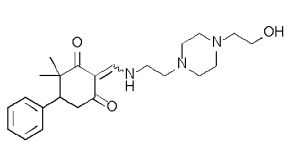
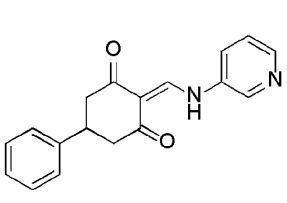
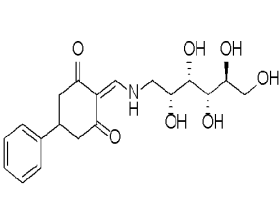
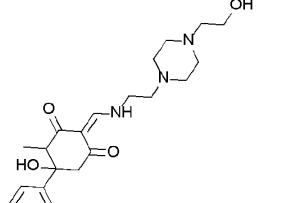
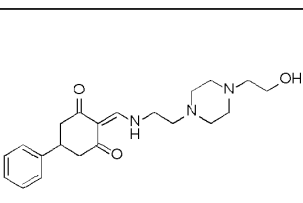
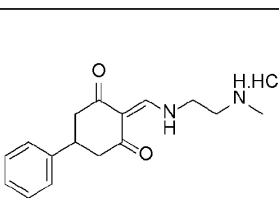
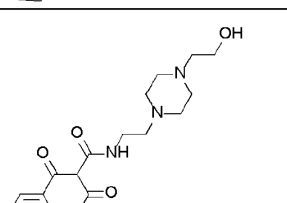
[0149] B 环为未取代或取代的 C6-10 芳基或 5-10 元杂芳基; 优选地, B 环为未取代或取代的 C6-10 芳基, 更优选 B 环为未取代或取代的苯基;

[0150] R_c , R_c' 和 R_c'' 各自独立地选自氢, 羟基, 氨基, $NRaRa'$, 卤素, 氰基, 硝基, 羧基, 甲酰基, 酰胺基, 酯基, C1-6 卤代烷基, C1-6 羟基烷基, C1-6 杂烷基, C1-6 烷氧基, C1-6 烷氧基烷基, C2-6 烯基, C2-6 炔基, C6-10 芳基, 5-10 元杂芳基, C3-10 环烷基, 3-10 元杂环烷基, 3-7 元杂环烯基, C1-6 烷基 C6-10 芳基, 5-10 元杂芳基 C1-6 烷基或 C1-6 烷基 5-10 元杂芳基; 优选选自氢, 羟基, 氨基, $NRaRa'$, 卤素, 羧基, 甲酰基, 酰胺基, 酯基, C1-6 卤代烷基, C1-6 羟基烷基, C1-6 杂烷基, C1-6 烷氧基, C3-10 环烷基, 3-10 元杂环烷基, 取代或未取代的苯基或吡啶基;

[0151] 各R_a独立地选自氢和C1-6烷基。

[0152] 在本发明的另一具体实施方案中,本发明化合物或其药学上可接受的盐优选选自以下化合物或盐:

[0153]

编号	结构式	编号	结构式	编号	结构式
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4A		162		324	
7		163		325	
8		164		326	

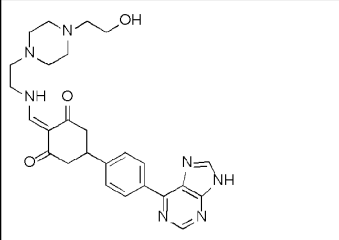
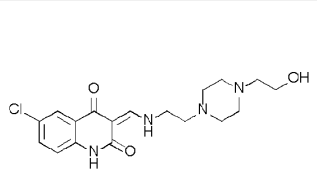
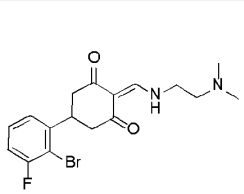
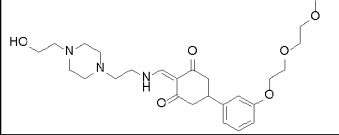
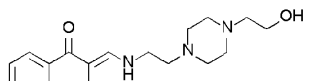
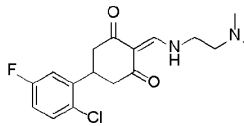
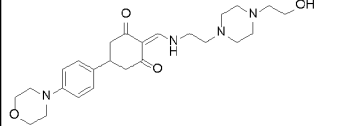
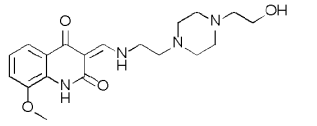
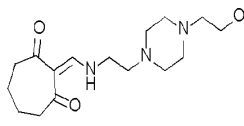
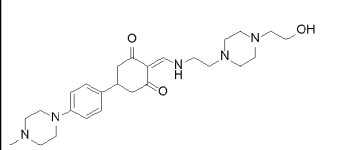
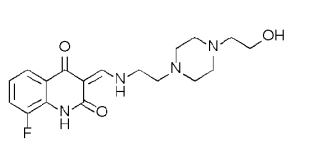
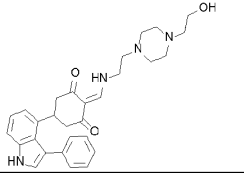
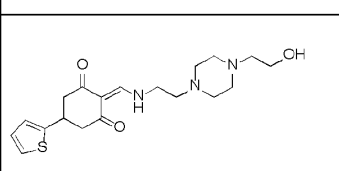
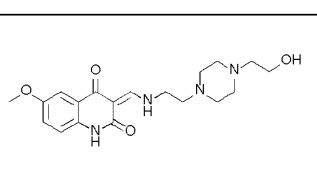
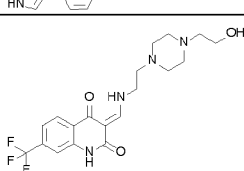
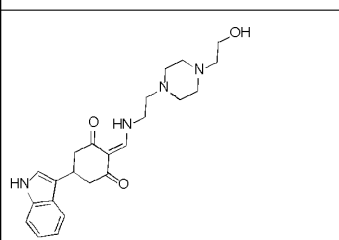
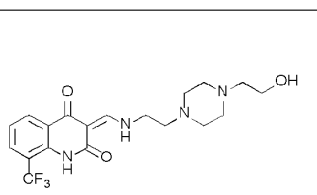
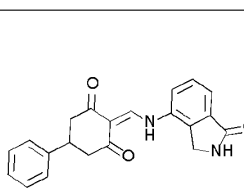
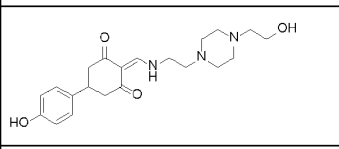
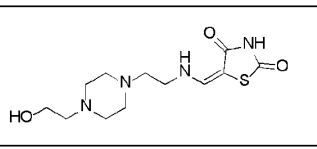
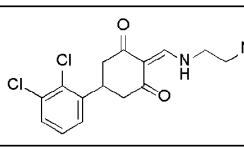
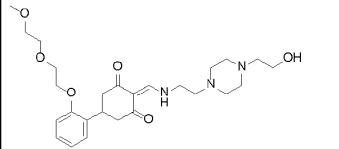
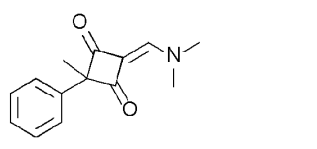
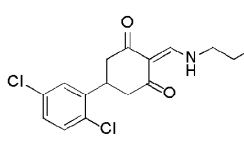
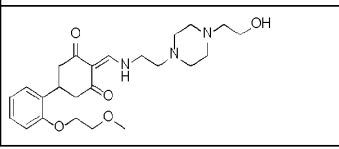
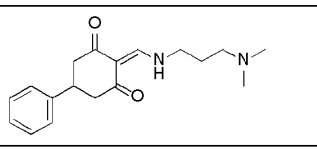
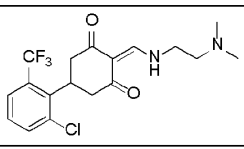
[0154]

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[0156]

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32		191		349	

[0157]

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42		202		358	

[0158]

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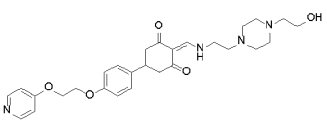
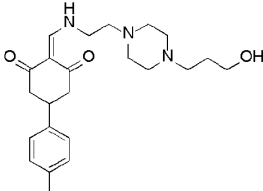
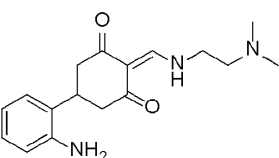
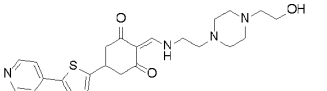
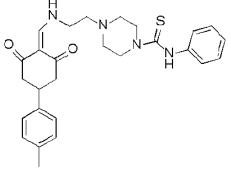
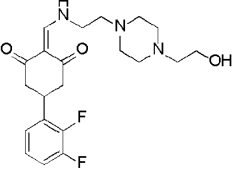
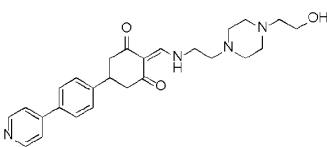
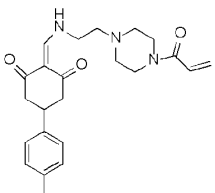
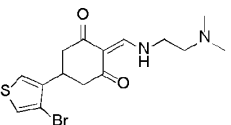
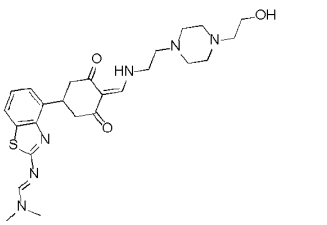
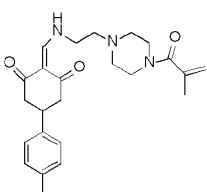
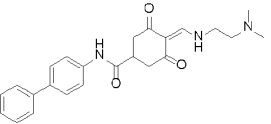
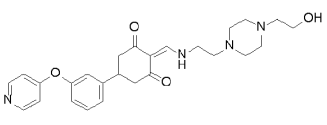
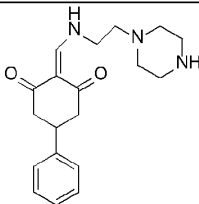
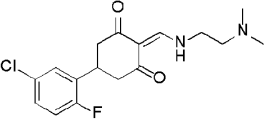
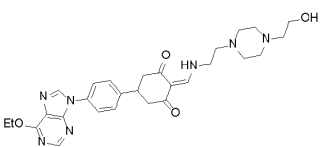
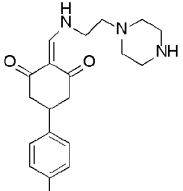
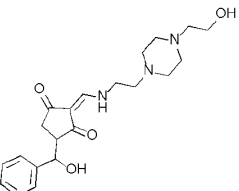
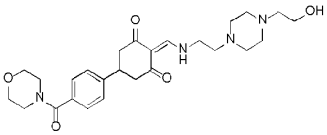
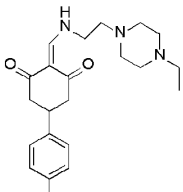
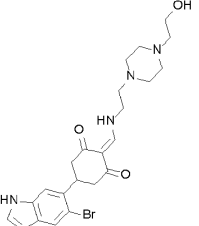
[0159]

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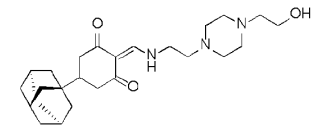
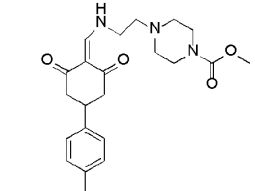
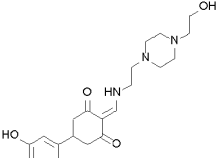
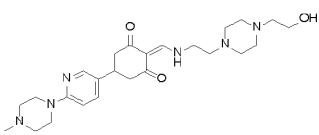
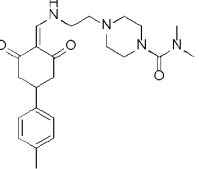
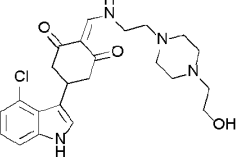
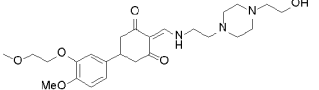
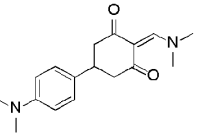
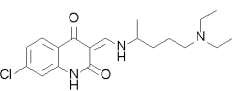
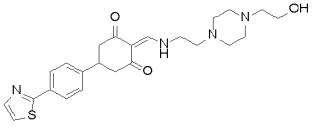
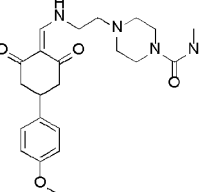
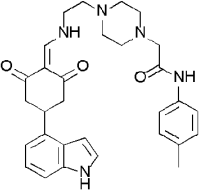
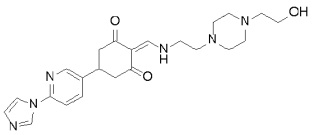
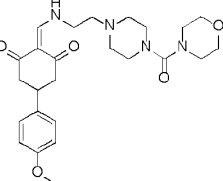
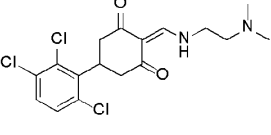
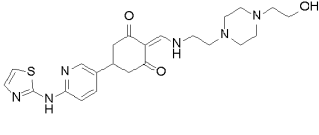
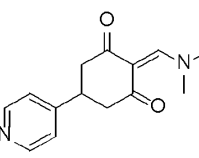
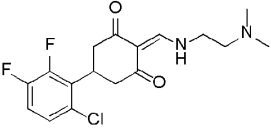
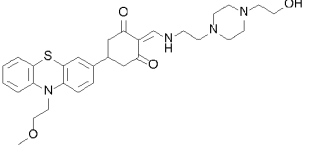
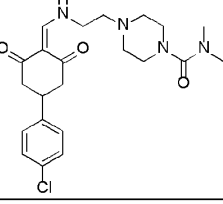
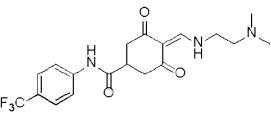
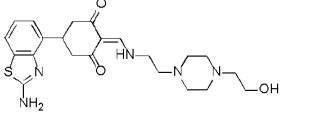
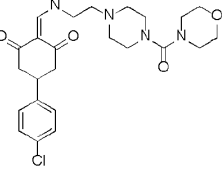
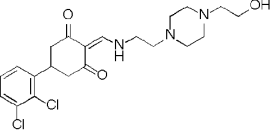
[0160]

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[0161]

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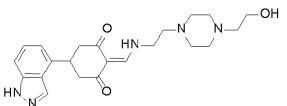
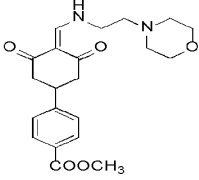
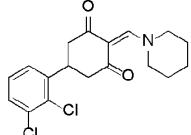
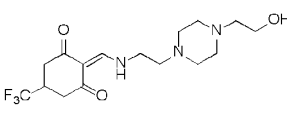
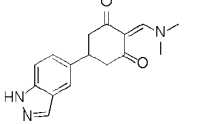
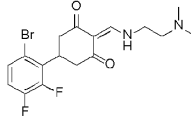
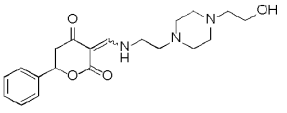
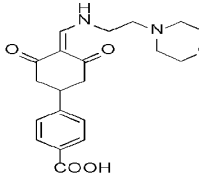
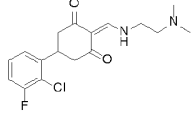
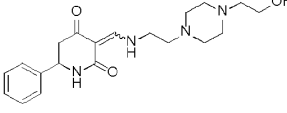
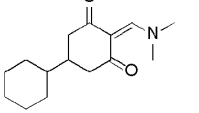
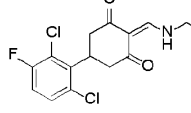
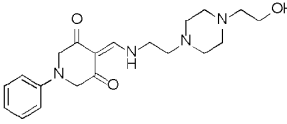
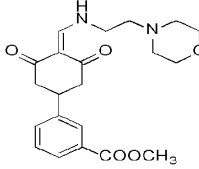
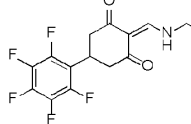
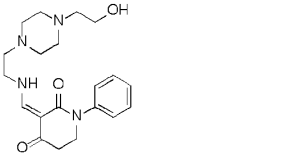
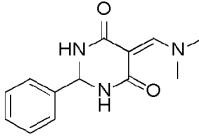
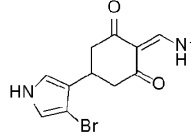
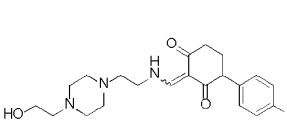
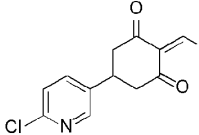
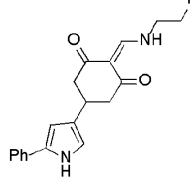
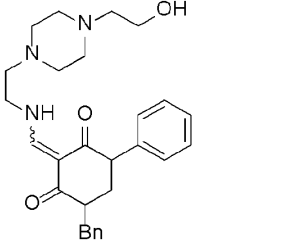
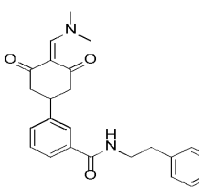
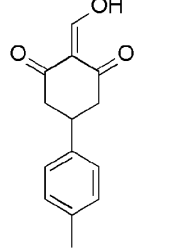
[0162]

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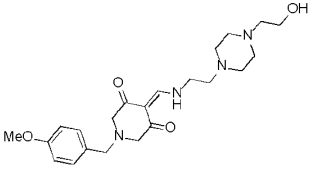
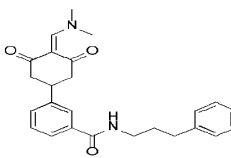
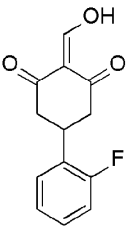
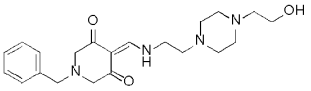
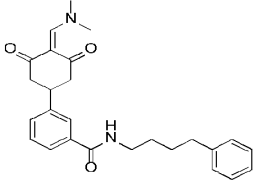
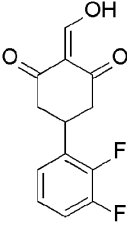
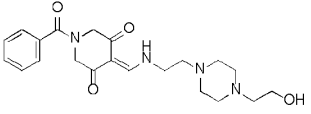
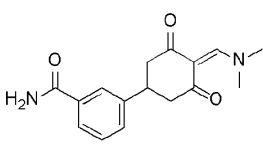
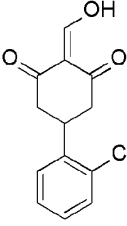
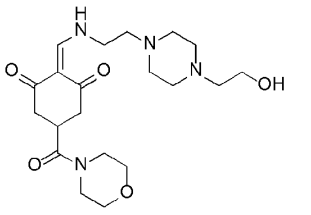
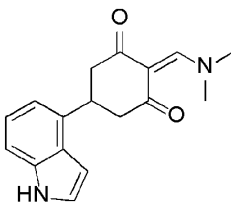
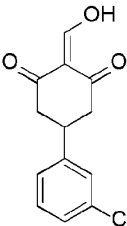
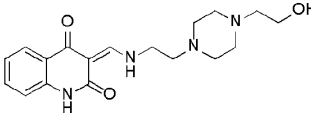
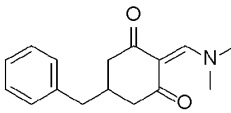
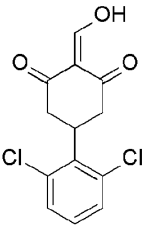
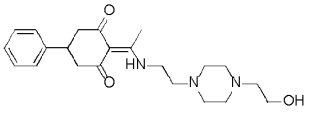
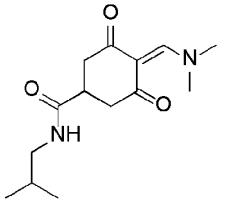
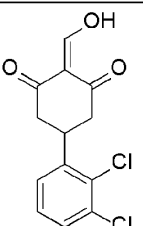
[0163]

86		251		401	
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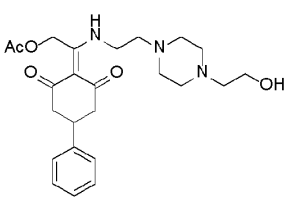
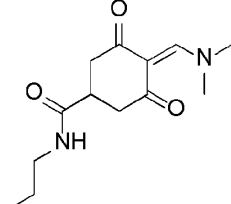
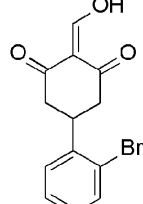
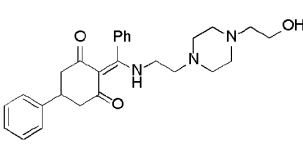
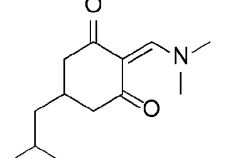
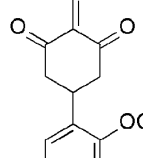
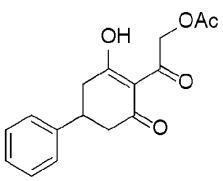
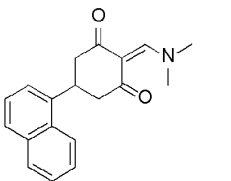
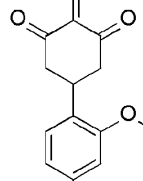
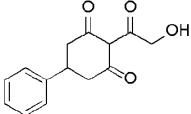
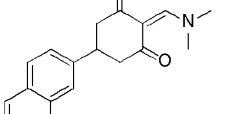
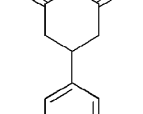
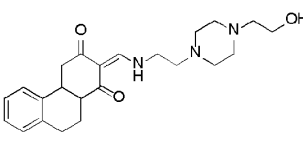
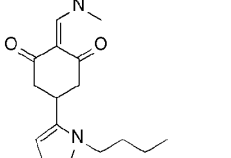
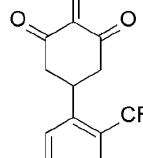
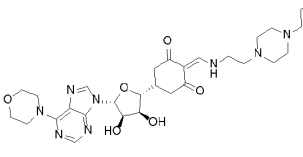
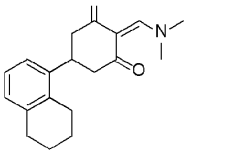
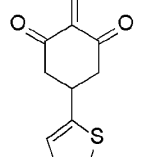
[0164]

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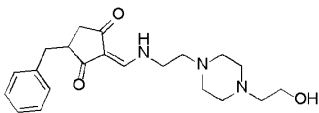
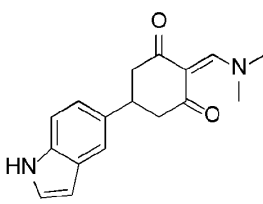
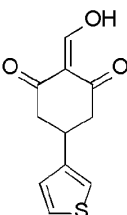
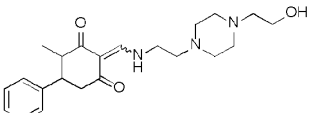
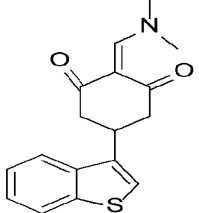
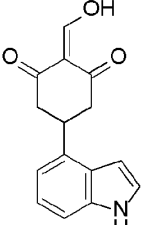
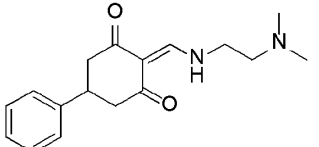
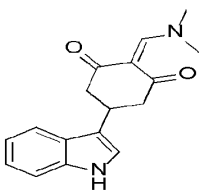
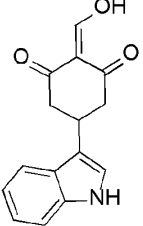
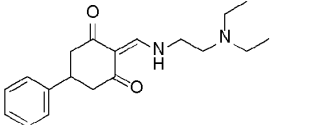
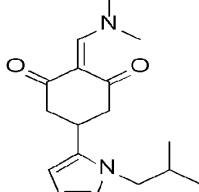
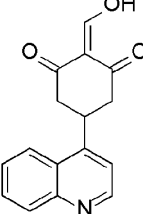
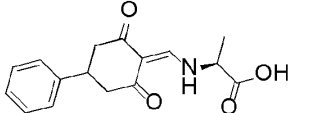
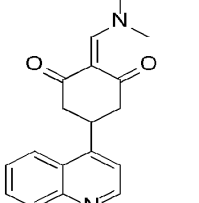
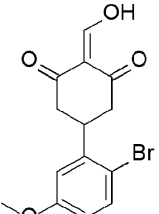
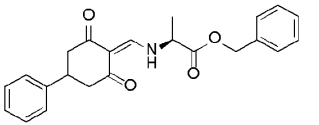
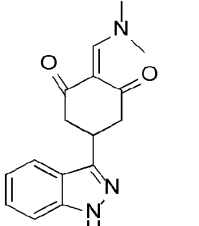
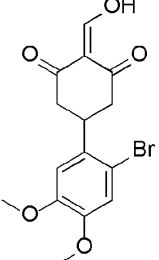
[0165]

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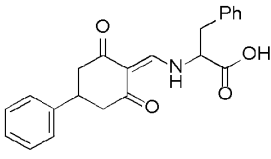
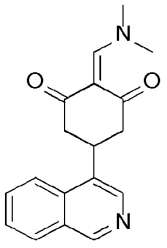
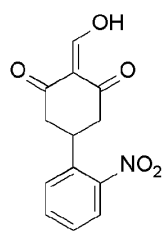
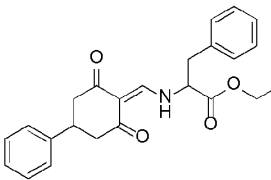
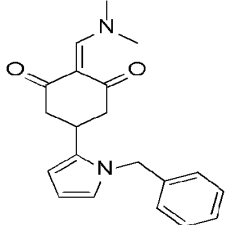
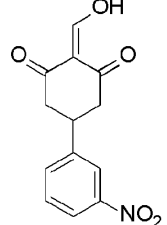
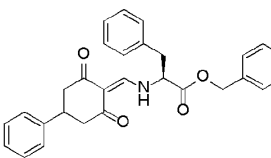
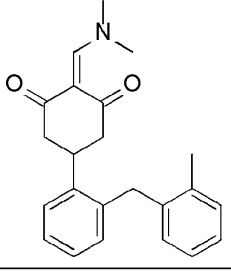
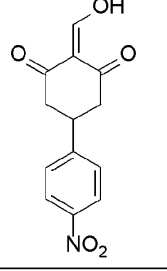
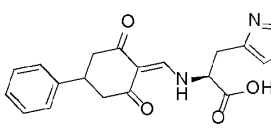
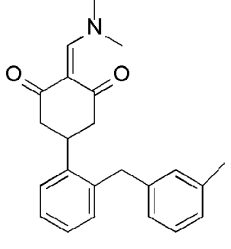
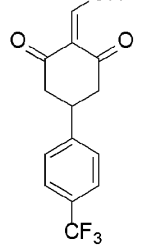
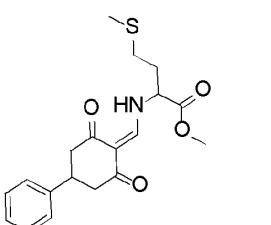
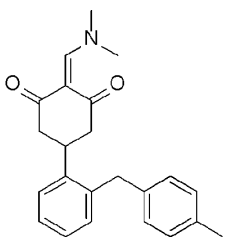
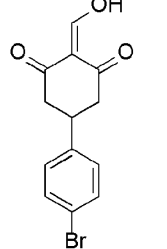
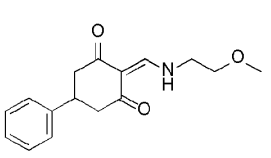
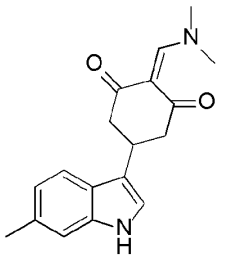
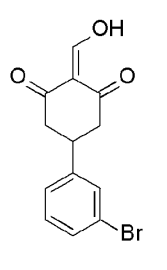
[0166]

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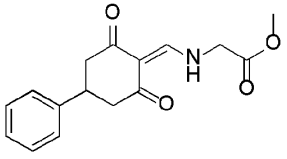
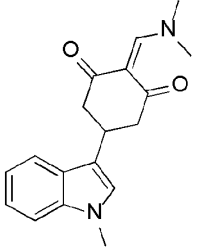
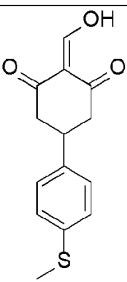
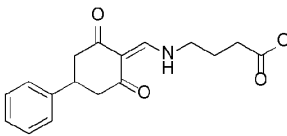
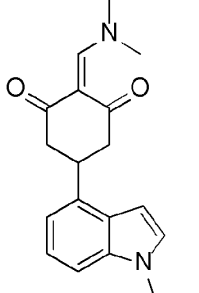
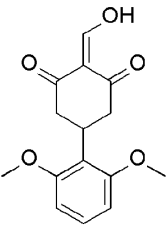
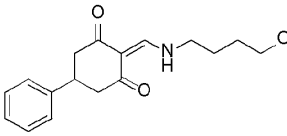
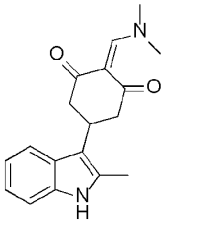
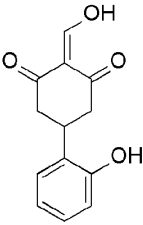
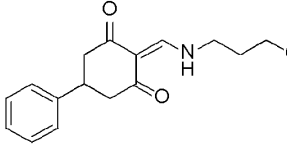
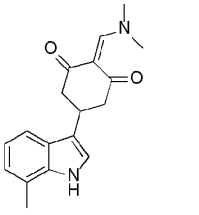
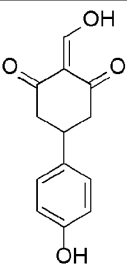
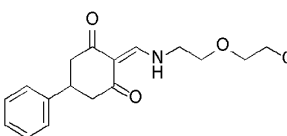
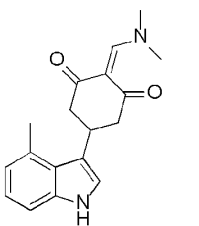
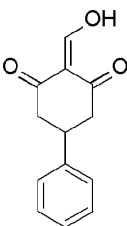
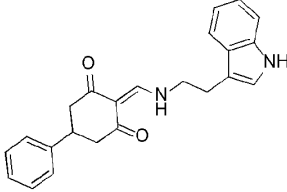
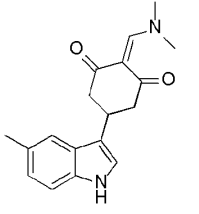
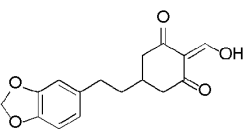
[0167]

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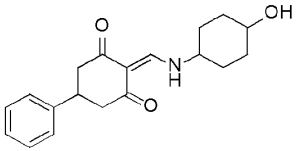
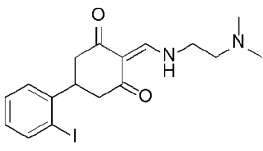
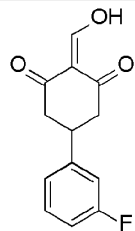
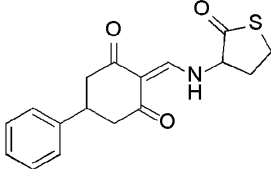
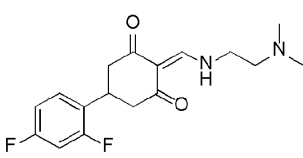
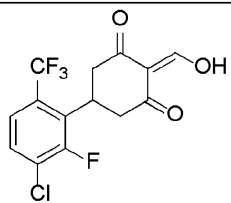
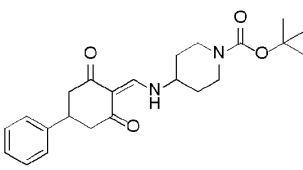
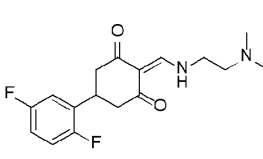
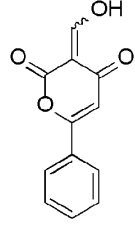
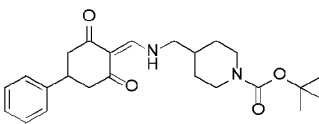
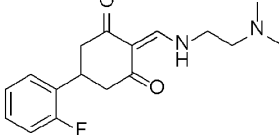
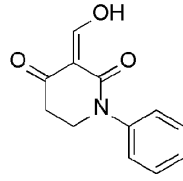
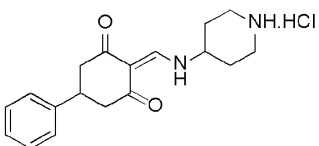
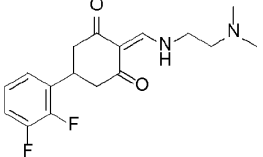
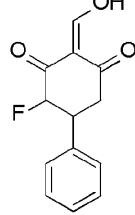
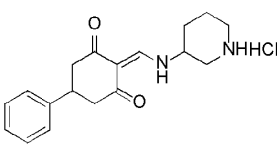
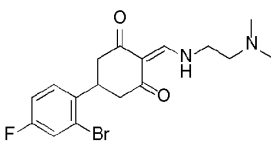
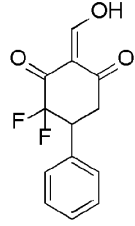
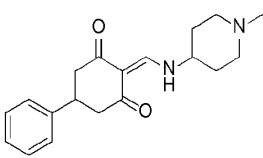
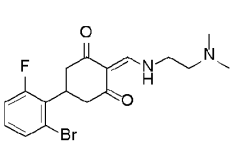
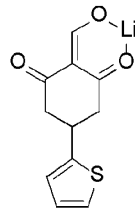
[0168]

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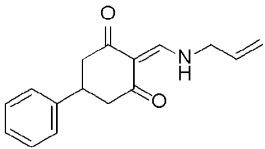
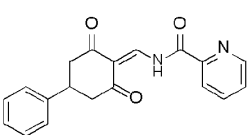
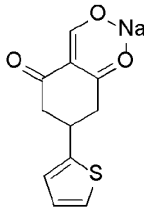
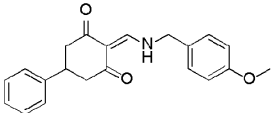
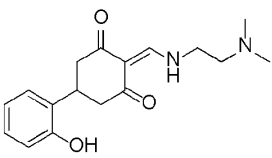
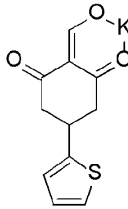
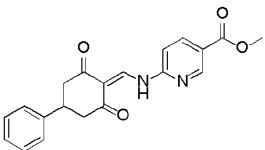
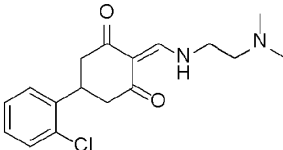
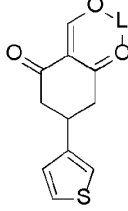
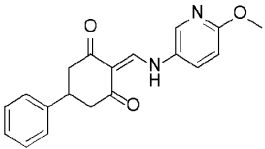
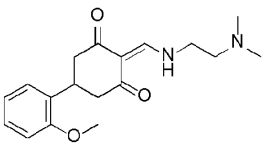
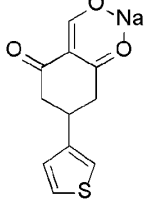
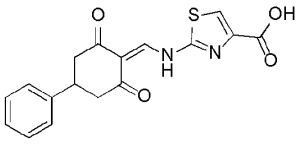
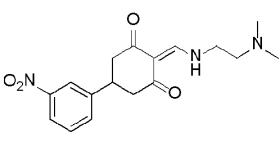
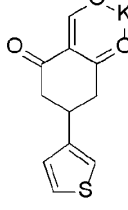
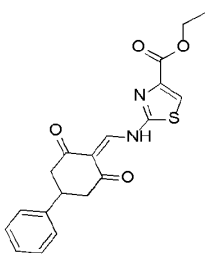
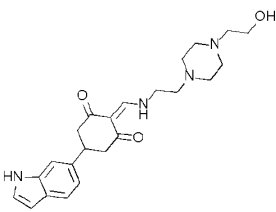
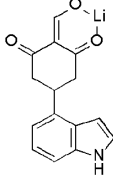
[0169]

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135		299		445	

[0170]

136		300		446	
137		301		447	
138		302		448	
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140		304		451	
141		305		452	
142		306		453	

[0171]

143		307		454	
145		308		455	
146		309		456	
147		310		457	
148		311		458	
149		315		459	

[0172]

150		317		460	
155		318		461	
156		320			
158		321			
160		322			

[0173] 在本发明的另一具体实施方案中,本发明提供了一种药物组合物,其包含根据本发明的化合物或其药学上可接受的盐。所述药物组合物还可以包含药学辅料。

[0174] 在本发明的另一具体实施方案中,本发明提供了根据本发明的化合物或其药学上可接受的盐在制备调节细胞自噬的药物中的用途。

[0175] 在本发明的另一具体实施方案中,所述调节细胞自噬的药物是调节哺乳动物ATG8同源物的药物。

[0176] 在本发明的另一具体实施方案中,所述调节细胞自噬的药物是预防或治疗与细胞自噬,尤其是与哺乳动物ATG8同源物相关的疾病的药物。

[0177] 在本发明的另一具体实施方案中,本发明提供了调节细胞自噬的方法,其包括向有此需要的对象施用根据本发明的化合物或其药学上可接受的盐。

[0178] 在本发明的另一具体实施方案中,所述调节细胞自噬的方法是调节哺乳动物ATG8同源物的方法。

[0179] 在本发明的另一具体实施方案中,所述调节细胞自噬的方法是预防或治疗与细胞自噬,尤其是与哺乳动物ATG8同源物相关的疾病的方法。

[0180] 在本发明的另一具体实施方案中,所述哺乳动物ATG8同源物是LC3B。

[0181] 在本发明的另一具体实施方案中,所述预防或治疗与细胞自噬,尤其是与哺乳动物ATG8同源物相关的疾病选自以下的疾病:肿瘤,心血管疾病,自身免疫性疾病,神经退行性疾病,高血压,骨组织细胞及骨类疾病,克罗恩氏病,急性肾损伤,脑缺血,视网膜疾病,支气管哮喘,Vici综合征,以及感染性疾病。

[0182] 在本发明的另一具体实施方案中,所述肿瘤选自肝癌、肺癌、胰腺癌、乳腺癌、宫颈癌、子宫内膜癌、大肠癌、胃癌、肺癌、鼻咽癌、卵巢癌、前列腺癌、白血病、淋巴瘤、骨髓瘤。

[0183] 在根据本发明的制备调节细胞自噬的药物的用途和调节细胞自噬的方法中,一些优选的化合物选自通式(Ib)化合物,通式(IIId)化合物,通式(IIId)化合物,通式(IVd)化合物,和通式(Vc)化合物,其中,通式(Ib),通式(IIId),通式(IIId),通式(IVd),和通式(Vc)的描述同上;或者一些优选的化合物选自化合物2,化合物3,化合物241,化合物264,化合物449,化合物462,化合物463,和化合物464。

[0184] 应理解,本发明的前述一般性描述和以下详细描述都是示例性和说明性的,旨在提供对所要求保护的本发明的进一步说明。

具体实施方式

[0185] 以下将详细描述本发明的实施例。

[0186] 本发明使用的术语具有其在本技术领域的一般含义。化学名称、通用名称和化学结构可以互换使用以描述相同的结构。无论术语是单独使用还是与其他术语组合使用,这些定义都适用。因此,“C1-6烷基”的定义适用于“C1-6烷基”以及“C1-6羟基烷基”、“C1-6卤代烷基”、“C6-10芳基C1-6烷基”、“C1-6烷基C6-10芳基”、“C1-6烷氧基”等的“C1-6烷基”部分。

[0187] “药物组合物”是指适合于患者用药的组合物。所述组合物可以只含有本发明化合物或含有本发明化合物的混合物,或含有本发明化合物的盐、溶剂合物、前体药物、异构体或互变异构体,或含有与一种或多种药学上可接受的载体或辅料合用的本发明化合物。“患者”包括人类和非人类的动物。所述药物组合物可以是多种形式,如片剂、胶囊、粉剂、糖浆、溶液状、悬浮液和气雾剂等,并可以存在于适宜的固体或液体的载体或稀释液中以及适宜的用于注射或滴注的消毒器具中。

[0188] 本发明的药物组合物的各种剂型可按照药学领域的常规制备方法制备。其制剂配方的单位剂量中包含0.05-200mg通式(I)化合物,优选地,制剂配方的单位剂量中包含0.1mg-100mg通式(I)化合物。

[0189] 本发明的化合物和药物组合物可对哺乳动物临床使用,包括人和动物,可以通过口、鼻、皮肤、肺、或者胃肠道等的给药途径。最优选为口服。最佳优选日剂量为0.01-200mg/kg体重,一次性服用,或0.01-100mg/kg体重分次服用。不管用何种服用方法,个人的最佳剂量应依据具体的治疗而定。通常情况下是从小剂量开始,逐渐增加剂量一直到找到最适合的剂量。

[0190] “卤素”(或卤代基)是指氟、氯、溴或碘。

[0191] “C1-6烷基”是指含有1至6个碳原子的直链或支链烷基,优选为1至4个碳原子的直链或支链烷基。支链是指一个或多个1至4个碳原子的烷基如甲基、乙基或丙基等与直链烷基连接。优选的C1-6烷基包括但不限于甲基、乙基、正丙基、异丙基、正丁基、异丁基和叔丁

基等。

[0192] “C1-6卤代烷基”是指如上定义的C1-6烷基中含有一个或多个卤素原子取代基。

[0193] “C1-6杂烷基”是指如上定义的C1-6烷基中含有一个或多个选自以下基团中的取代基：O、S、N、- (S=O) -、- (O=S=O) -等。

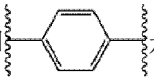
[0194] “C2-6烯基”是指含有2至6个碳原子的直链或支链的烯基，优选含有2至4个碳原子。支链是指一个或多个低级C1-6烷基连接到直链C2-6烯基链上。优选的C2-6烯基包括但不限于乙烯基、丙烯基、正丁烯基、3-甲基丁烯基、正戊烯基等。

[0195] “C1-6亚烷基”是指通过从上述定义的C1-6烷基除去一个氢原子得到的二价基团。优选的C1-6亚烷基包括但不限于亚甲基、亚乙基和亚丙基等。一般地，其可以任选且等同地在此表示为- (C1-6烷基) -，例如-CH₂CH₂-是亚乙基。

[0196] “C2-6炔基”是指含有2至6个碳原子的直链或支链炔基，优选含有2至6个碳原子，更优选含有2至4个碳原子。支链表示一个或多个含有2至4个碳原子的烷基连接到直链炔基链上。优选的C2-6炔基包括但不限于乙炔基、丙炔基、2-丁炔基和3-甲基丁炔基等。

[0197] “亚C2-6烯基”是指通过从上述定义的C2-6烯基中除去一个氢原子而获得的双官能团。优选的亚C2-6烯基包括但不限于-CH=CH-，-C(CH₃)=CH-，-CH=CHCH₂-等。

[0198] “C6-10芳基”是指含有6至10个碳原子的芳族单环或多环系统。优选的C6-10芳基包括但不限于苯基和萘基。

[0199] “C6-10亚芳基”是指通过从上述定义的C6-10芳基除去一个氢原子得到的二价基团，例如是对亚苯基。

[0200] “5-10元杂芳基”是指含有5至10个环原子的芳族单环或多环基团，所述5-10元杂芳基包含选自N、O和S中的1至4个杂原子。优选的5-10元杂芳基含有5至6个环原子。5-10元杂芳基的氮原子可以任选地被氧化成相应的N-氧化物。术语“5-10元杂芳基”还包括与上述定义的C6-10芳基稠环。优选的5-10元杂芳基包括但不限于吡啶基、吡嗪基、呋喃基、噻吩基、嘧啶基、吡啶酮、噁唑基、异噻唑基、噁唑基、噁二唑基、噻唑基、噻二唑基、吡唑基、呋咕基(furazanyl)、吡咯基、三唑基、1,2,4-噻二唑基、哒嗪基、喹啉基、酞嗪基、羟吡啶基、咪唑并[1,2-a]吡啶基、咪唑并[2,1-b]噻唑基、苯并呋咕基(benzofurazanyl)、吡啶基、氮杂吡啶基、苯并咪唑基、苯并噻吩基、喹啉基、咪唑基、噻吩并吡啶基、喹啉基、噻吩并嘧啶基、吡咯并吡啶基、咪唑并吡啶、异喹啉基、苯并吡嗪基、1,2,4-三嗪基、苯并噻唑基其氧化物等。术语“5-10元杂芳基”也指部分饱和的5-10元杂芳基，例如四氢异喹啉基，四氢喹啉基等。

[0201] “C3-10环烷基”是指含有3至10个碳原子，优选3至6个碳原子的非芳族单环或多环基团。优选的单环C3-10环烷基包括但不限于环丙基、环戊基、环己基、环庚基等。优选的多环环烷基包括但不限于[1.1.1]-双环戊烷基、1-癸酰基、降冰片基、金刚烷基等。

[0202] “C3-10环烯基”是指含有3至10个碳原子的非芳族单环或多环基团，其含有至少一个环内碳-碳双键，优选含有3至7个环原子，更优选含有5至7个环原子。优选地所述C3-10环烯基包括但不限于环丙烯基、环丁烯基、环戊烯基、环己烯基、环庚烯基、环庚烷-1,3-二烯基、降冰片烯基等。

[0203] “3-10元杂环烷基”(或“3-10元杂环基”)是指含有3至10个环原子，优选5至10个环

原子,优选5至6个环原子的非芳族饱和单环或多环基团,其中,所述3-10元杂环基包含选自N、O和S中的1至4个杂原子,且环体系中两个的杂原子不会相邻。所述3-10元杂环基的氮或硫原子可以任选地氧化成相应的N-氧化物、S-氧化物或S,S-二氧化物。因此本发明中术语“氧化物”是指相应的N-氧化物、S-氧化物或S,S-二氧化物。“3-10元杂环基”还包括环体系的相同碳原子上的两个可用氢原子同时被单一的基团=O取代(例如羰基),这样的=O基团在本发明中可以称为“氧代”。优选的单环3-10元杂环烷基包括但不限于哌啶基、氧杂环丁烷基、吡咯基、哌嗪基、吗啉基、硫代吗啉基、噻唑烷基、1,4-二噁C1-6烷基、四氢呋喃基、四氢噻吩基、内酰胺基(如吡咯烷酮基)、3至10个环原子的内酯基及其氧化物。

[0204] “3-7元杂环烯基”是指含有3至7个环原子,优选5至6个环原子的非芳族单环或多环基团,其中,所述3-7元杂环烯基包含选自N、O和S中的1至4个杂原子,并且其含有至少一个碳-碳双键或碳-氮双键。环体系中不存在相邻的氧和/或硫原子。在3-7元杂环烯基根名之前的前缀氮杂、氧杂或硫杂是指至少一个氮、氧或硫原子分别地作为环原子。3-7元杂环烯基的氮或硫原子可以任选被氧化成相应的N-氧化物、S-氧化物或S,S-二氧化物。优选的3-7元杂环烯基包含但不限于1,2,3,4-四氢吡啶基、1,2-二氢吡啶基、1,4-二氢吡啶基、1,2,3,6-四氢吡啶基、1,4,5,6-四氢嘧啶基、2-吡咯啉基、3-吡咯啉基、2-咪唑啉基、2-吡唑啉基、二氢咪唑基、二氢噁唑基、二氢恶二唑基、二氢噻唑基、3,4-二氢-2H-吡喃基、二氢呋喃基、氟代二氢呋喃基及其氧化物等。“3-7元杂环烯基”还可是环体系中相同碳原子上的两个可用氢原子同时被单一的基团=O取代(即形成羰基)。

[0205] “C6-10芳基C1-6烷基”(或“C6-10芳基C1-6烷基”)是指由上述定义的C6-10芳基和C1-6烷基连接形成的基团。优选的C6-10芳基C1-6烷基包括但不限于苄基、2-苯乙基和萘甲基。所述C6-10芳基C1-6烷基通过C1-6烷基与母体部分键接。类似地,“5-10元杂芳基C1-6烷基”,“C3-10环烷基C1-6烷基”,“C2-6环烯基C1-6烷基”,“3-10元杂环烷基C1-6烷基”,“3-7元杂环烯基C1-6烷基”等是指如本发明所述的5-10元杂芳基,C2-6环烯基,3-10元杂环烷基,3-7元杂环烯基等通过C1-6烷基与母体部分键接。

[0206] “C1-6烷基C6-10芳基”是指由上述定义的C1-6烷基和C6-10芳基连接形成的基团。优选C1-6烷基C6-10芳基包括但不限于甲苯基。所述C1-6烷基C6-10芳基通过C6-10芳基与母体部分键接。

[0207] “5-10元杂芳基C1-6烷基”是指由上述定义的5-10元杂芳基和C1-6烷基连接形成的基团。优选的C6-10芳基C1-6烷基基团包括但不限于吡啶基甲基和喹啉-3-基甲基。所述5-10元杂芳基C1-6烷基通过C1-6烷基与母体部分键接。

[0208] “C1-6羟基烷基”是指被羟基取代的C1-6烷基基团,其中C1-6烷基如上所述。优选的C1-6羟基烷基包括但不限于羟甲基和2-羟乙基。

[0209] “C1-6烷氧基”是指C1-6烷基-O-基团,通过氧与母体部分键接,其中C1-6烷基如上所述。优选的C1-6烷氧基包括但不限于甲氧基、乙氧基、正丙氧基、异丙氧基和正丁氧基。

[0210] “C1-6烷氧基烷基”是指衍生自本发明所定义的C1-6烷氧基和C1-6烷基的基团,通过C1-6烷基与母体部分键接。

[0211] “酯基”是指-C(O)OR_x,其中R_x是C1-6烷基、C6-10芳基、C6-10芳基C1-6烷基和C3-10环烷基。优选的酯基包括但不限于甲酯基,乙酯基,异丙酯基,叔丁酯基,苯酯基。

[0212] “酰胺基”是指-C(O)NR_yR_{y'},其中R_y和R_{y'}是氢,C1-6烷基、C6-10芳基、C6-10芳基C1-

6烷基或C3-10环烷基。

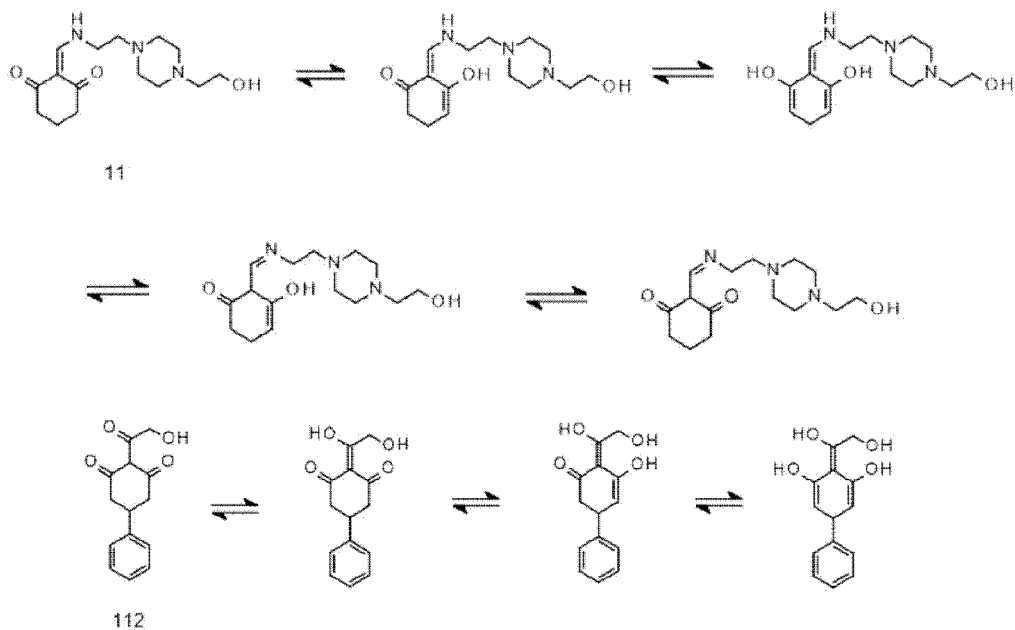
[0213] 本发明任何前述官能团可以是未经取代或被本发明所述取代基取代。术语“取代的”(或取代)是指将指定原子上的一個或多个氢原子替换为从指定基团中选择的基团,条件是不超出指定原子的正常价态,并且取代产生稳定的化合物。只有当所述组合形成稳定化合物时,所述取代基和/或变量的组合才是允许的;“稳定化合物”或“稳定结构”是指具有能够从反应混合物中分离至有用纯度和配置成有效治疗剂的具有充分稳定性的化合物。

[0214] 术语“未取代或取代”表示特定基团未被取代或被一个或多个取代基取代。取代基包括,不局限于,氢,羟基,氨基,氰基,硝基,羧基,卤素,C1-6烷基,C1-6卤代烷基或C1-6羟基烷基。二个相邻取代基可以连接形成C6-10芳基,5-10元杂芳基,C3-10环烷基或3-10元杂环烷基。C6-10芳基,5-10元杂芳基,C3-10环烷基,3-10元杂环烷基,3-7元杂环烯基等基团上的取代包括在基团的任何环部分的取代。

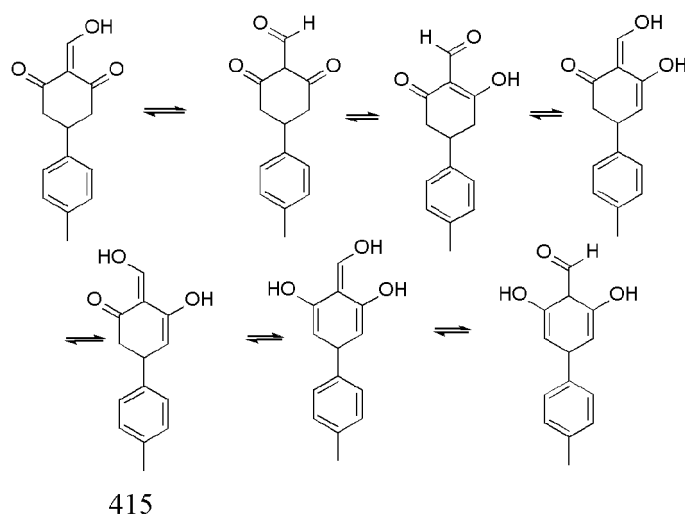
[0215] 在本申请中,如果一个基团是“共价键”,那表明这个基团“不存在”,二个相连的基团通过一个共价键相连。比如说,在“-J-K-M-Q”取代基中,如果K是共价键,那这个取代基就成为“-J-M-Q”。

[0216] 互变异构体是指由于分子中一个原子的质子转移到另一个原子上的现象产生的化合物。互变异构体还指容易从一种异构体形式转化为另一种异构体形式的两种或更多种处于平衡状态的异构体形式。本领域普通技术人员应认识到所有互变异构环原子排列的可能性。这些化合物的所有这些异构形式明确地包括在本发明公开内容中。

[0217] 具体而言,本发明的化合物包括其所有互变异构体,例如酮-烯醇互变异构体。为方便起见,在本发明的详细叙述和权利要求中,这些互变异构体和其混合物部分结构(实施例11,112,和415)如下所示。



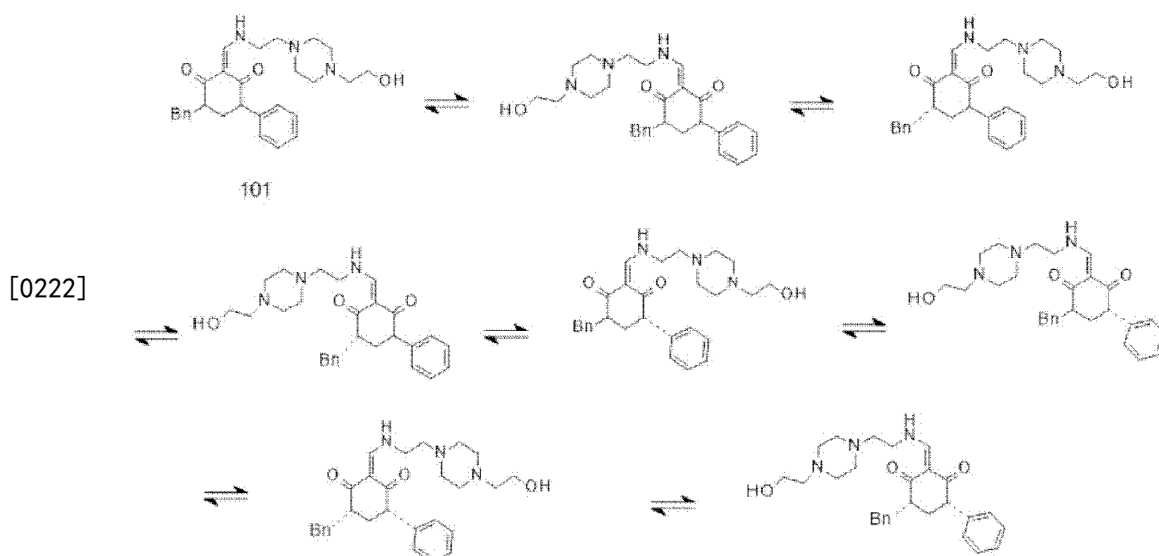
[0218]



[0219] 为方便起见,在本发明中仅示例出了每种化合物的一种互变异构体。应当注意,本发明的化合物包括所有互变异构体。

[0220] 立体异构体是指化合物具有相同分子式,分子中原子连接次序相同但空间排列不同而引起的同分异构。立体异构包括顺反异构、构象异构、对映异构和非对映异构等,其中顺反异构是指由于双键相连的两个碳原子不能绕 σ 键作相对的自由旋转引起的,一般指烯烃的双键,也有C=N双键,N=N双键及环状等化合物的顺反异构。对映异构体是指互为镜像关系的立体异构体;非对映异构体是指分子具有两个或多个手性中心,并且分子间为非镜像的关系的立体异构体。除非另有说明,本说明书旨在包括单独的立体异构体及其混合物。

[0221] 具体而言,本发明的化合物包括其所有异构体,例如非对映异构体和顺/反(Z/E)异构体。本发明公开的化合物101的顺反异构体的实例如下所示。



[0223] 为方便起见,在本发明中仅示例了每种化合物的一种异构体。应当注意,本发明的化合物包括所有的立体异构体。

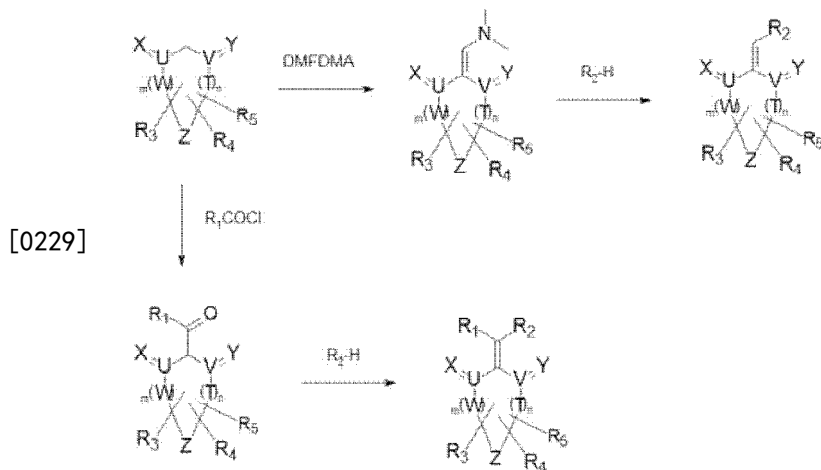
[0224] 本发明的化合物可以与一种或多种金属离子形成金属螯合物。金属离子包括但不限于铜,铁,镁,钙,锌,镍和铂等。如本发明所述,金属螯合物的实例在实施例38中给出。应当注意,本发明的化合物包括所有的金属螯合物。

[0225] 术语“药学上可接受的盐”是指适用于人和/或动物而无过度不良副反应(如毒性、刺激和变态反应),即有合理的效益/风险比的物质。药学上可接受的盐包括无机盐和有机盐,它们可以在本发明化合物的最终分离和纯化期间获得,或者通过游离酸或碱官能团与合适的碱或酸反应成盐。适合形成盐的酸包括但不限于:无机酸如盐酸、磷酸或硫酸,或有机酸如枸橼酸、抗坏血酸、柠檬酸、酒石酸、乳酸、马来酸、丙二酸、富马酸、乙醇酸、琥珀酸、丙酸、乙酸或甲磺酸等。适合形成盐的碱包括但不限于:无机碱如碳酸钠、氢氧化钠、碳酸钾、氢氧化钾、氢氧化锂、醋酸钙、氯化钙或氯化镁等,有机碱如氨基乙醇等。

[0226] 术语“有效量”是指施用的组合物中所含的本发明化合物的量足以调节(例如抑制或激动等)哺乳动物ATG8同源物。

[0227] 本发明化合物可以通过本领域中类似已知的各种方法制备,下述反应流程为制备本发明化合物的可选方案。

[0228] 一般反应流程



[0230] 上述方案中的基团或取代基定义与通式(I)定义相同。化合物可以通过本领域普通技术人员已知的一些参考文献中描述的方法来制备。这些参考文献包括例如: Bioorganic&Medicinal Chemistry Letters, 24(16), 3764-3771, 2014; Chemistry-A European Journal, 20(9), 2445-2448, 2014; Bioorganic&Medicinal Chemistry, 20(2), 1029-1045, 2012; Journal of Organic Chemistry, 82(5), 2630-2640, 2017; Tetrahedron Letters, 49(2008), 4725-4727; Journal of Organic Chemistry, 78(9), 4563-4567, 2013; Heterocycles, 28(2), 1015-35, 1989; Journal of Medicinal Chemistry, 57(10), 3924-3938, 2014; Journal of Organic Chemistry, 66(24), 8000-8009, 2001; and Tetrahedron Letters, 56(45), 6287-6289, 2015.

[0231] 实施例

[0232] 下面结合具体实施例,进一步阐述本发明。应理解,这些实施例仅用于说明本发明而并不用于限制本发明的范围,且本发明不限于这些实施例。本领域的技术人员将容易理解的是,可使用以下制备方法的条件和过程的已知变型来制备这些化合物。本发明中用到的起始反应物未经特别说明,均为商业购买。

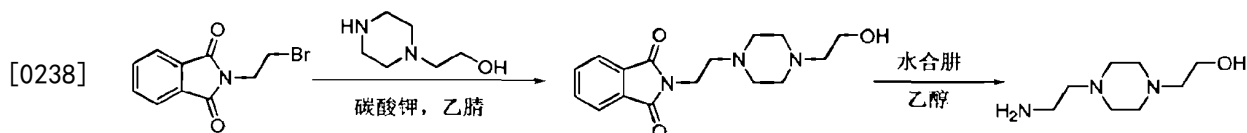
[0233] 缩写:乙腈(MeCN, ACN);水溶液(aq.);溴化苄(BnBr);二碳酸二叔丁酯(Boc₂O);甲基叔丁基醚(t-BuOMe);叔丁醇钾(t-BuOK);叔丁醇钠(t-BuONa);硝酸铈铵(CAN);浓缩的/高浓度的(con.);二氯甲烷(DCM);二异丁基氢化铝(DIBAL-H);二异丙基乙胺(DI(P)EA);4-二甲基氨基吡啶(DMAP);N,N-二甲基甲酰胺二甲基缩醛(DMF-DMA);二甲基甲酰胺(DMF);二甲基亚砜(DMSO);乙酸乙酯(EA或EtOAc);当量(eq.);乙醇(EtOH);乙醇钠(EtONa);克/毫克(g/mg);2-(7-偶氮苯并三氮唑)-N,N,N',N'-四甲基脒六氟磷酸酯(HATU);小时(h, hr, hrs);醋酸(HOAc);升/毫升(L/mL);液相色谱-质谱联用仪(LCMS);二异丙基氨基锂(LDA);甲醇(MeOH);摩尔/毫摩尔(mol/mmol);质谱(MS);甲磺酰氯(MsCl);分钟(min(s));醋酸钠(NaOAc);氮气(N₂);氮溴代丁二酰亚胺(NBS);N-甲基吗啉氧化物(NMO);核磁共振(NMR);钯碳(Pd/C);石油醚(PE);苯甲酰氯(PhCOCl);甲苯(PhMe);三苯基膦(PPh₃);吡啶(Py);1H-苯并三唑-1-氧三吡咯啉六氟磷酸(PyBOP);制备型薄层色谱(Pre-TLC);室温(RT, rt);三乙胺(TEA);四氢呋喃(THF);薄层色谱(TLC);三甲基氯硅烷(TMSCl);1,1'-双二苯基膦二茂铁二氯化钯(Pd(dppf)₂Cl₂)。

[0234] 一般合成方法:

[0235] 除非另有说明,否则所有反应均在惰性气体(如氩气或氮气)环境下进行,使用的市售试剂和无水溶剂无需进行进一步处理。

[0236] 质谱用液相色谱-质谱联用仪(LC-MS)记录(安捷伦6120B型单四级杆液相色谱-质谱联用仪)。核磁共振谱(如氢谱(¹H)、碳谱(¹³C)、磷谱(³¹P)和氟谱(¹⁹F)等)用BrukerAMX-400型、Gemini-300型或AMX-600型核磁共振仪记录,在氘代氯仿、氘代甲醇、氘代水或氘代二甲亚砜等氘代溶剂中记录并以氘代溶剂峰为参考标准。化学位移δ的单位为ppm,耦合常数(J或J)的单位为赫兹(Hz, Hertz),核磁谱中耦合裂分峰表示为:宽单峰(brs)、单峰(s)、二重峰(d)、双二重峰(dd)、三重峰(t)、四重峰(q)和多重峰(m)。

[0237] 实施例1:化合物2-(4-(2-氨基乙基)哌嗪-1-基)乙-1-醇的合成



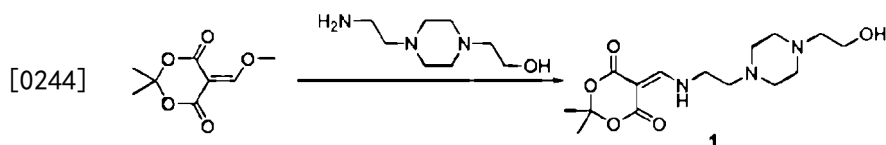
[0239] 步骤1:化合物2-(2-(4-(2-羟乙基)哌嗪-1-基)乙基)异吲哚啉-1,3-二酮的合成

[0240] 将化合物2-(2-溴乙基)异二氢吲哚-1,3-二酮(20.0g,78mmol)、化合物2-(哌嗪-1-基)乙-1-醇(10.2g,78mmol)和碳酸钾(22.0g,156mmol)溶解于100mL乙腈中,上述混合物回流反应3小时。反应完毕,冷却至室温,过滤,滤渣用乙腈(20mL)洗涤,收集滤液,浓缩,经柱层析分离纯化得目标化合物13.45g,产率57%。

[0241] 步骤2:化合物2-(4-(2-氨基乙基)哌嗪-1-基)乙-1-醇的合成

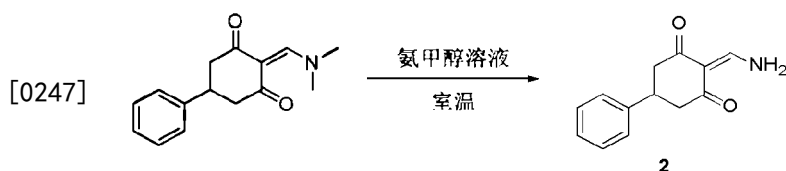
[0242] 将化合物2-{2-[4-(2-羟基-乙基)-哌嗪-1-基]-乙基}-异吲哚啉-1,3-二酮(13.45g,43.67mmol)和水合肼(80%,6mL)溶解于乙醇(130mL)中回流反应4小时。反应完毕,冷却至室温,过滤,滤渣用冷乙醇(20mL×2)洗涤。收集滤液,浓缩得粗品6.5g,不经进一步纯化直接用于下一步反应。

[0243] 实施例2:化合物5-(((2-(4-(2-羟乙基)哌嗪-1-基)乙基)氨基)亚甲基)-2,2-二甲基-1,3-二噁烷-4,6-二酮(化合物1)的合成



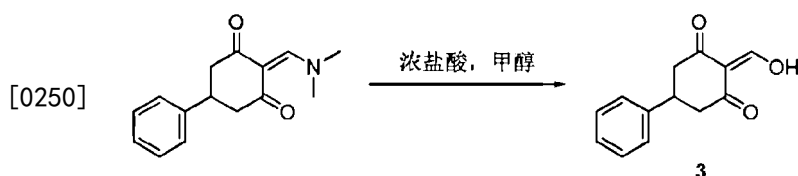
[0245] 将化合物5-(甲氧基亚甲基)-2,2-二甲基-1,3-二噁烷-4,6-二酮(186mg,1mmol)溶于5mL乙醇,加入2-(4-(2-氨基乙基)哌嗪-1-基)乙-1-醇(259.5mg,,1.5mmol),室温反应15分钟,浓缩得粗品,经柱层析分离纯化得目标化合物220mg,产率67.2%。¹H NMR(400MHz,CD₃OD) δ8.22(s,1H),3.67(t,J=6.0Hz,1H),3.58(t,J=5.9Hz,1H),2.57(dt,J=24.7,6.0Hz,1H),1.66(s,1H);LCMS:328.4(M+1)。

[0246] 实施例3:化合物2-(氨基亚甲基)-5-苯基环己烷-1,3-二酮(化合物2)的合成



[0248] 将化合物2-二甲氨基亚甲基-5-苯基环己烷-1,3-二酮(1.1g,4.52mmol)溶于氨的甲醇溶液(7N,50mL),室温搅拌1小时,浓缩得粗品,经柱层析分离得目标化合物900mg,产率93%。化合物2:¹H NMR(400MHz,CD₃OD) δ10.12(br,1H),8.24(br,1H),8.02(q,J=8.8Hz,1H),7.32-7.29(m,4H),7.23-7.17(m,1H),3.31-3.25(m,1H),2.77-2.63(m,2H),2.51-2.45(m,2H);MS:216.1[M+1]。

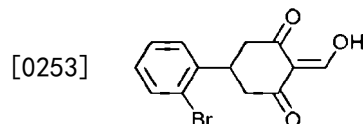
[0249] 实施例4:化合物2-(羟基亚甲基)-5-苯基环己烷-1,3-二酮(化合物3)的合成



[0251] 将化合物2-((二甲氨基)亚甲基)-5-苯基环己烷-1,3-二酮(244mg,1mmol)溶于

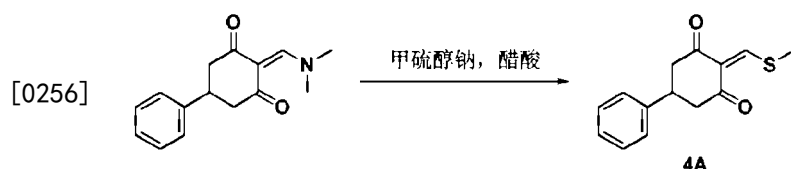
5mL 甲醇, 滴加浓盐酸 (1mL), 室温反应 30 分钟。浓缩得粗品, 经柱层析分离得目标化合物 162mg, 产率 75%。化合物 3: ^1H NMR (400MHz, DMSO- d_6) δ 9.58 (s, 1H), 7.27-7.30 (m, 4H), 7.16-7.19 (m, 1H), 3.14-3.20 (m, 1H), 2.51 (d, $J=16.8\text{Hz}$, 1H), 2.47 (d, $J=9.2\text{Hz}$, 1H), 2.31 (dd, $J=16.0, 4.0\text{Hz}$, 2H); LCMS: 217.1 [M+1]。

[0252] 化合物 5- (2-溴苯基) -2- (羟基亚甲基) 环己烷-1,3-二酮 (化合物 4) 的合成



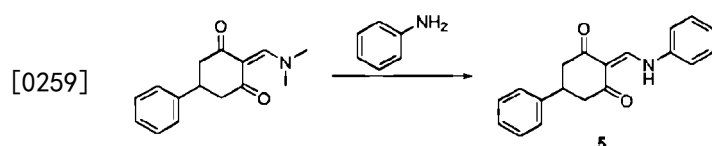
[0254] 化合物 4 的合成方法同化合物 3。化合物 4: ^1H NMR (400MHz, DMSO- d_6) δ 9.34 (dd, $J=9.1, 1.9\text{Hz}$, 1H), 7.60 (d, $J=7.6\text{Hz}$, 1H), 7.49-7.29 (m, 2H), 7.16 (d, $J=7.0\text{Hz}$, 1H), 3.57 (m, 2H), 2.82-2.56 (m, 2H), 2.41 (d, $J=1.8\text{Hz}$, 1H); MS: 297.0 [M+1]。

[0255] 实施例 5: 化合物 2- ((甲硫基) 亚甲基) -5- 苯基环己烷-1,3-二酮 (化合物 4A) 的合成



[0257] 将化合物 2- ((二甲基氨基) 亚甲基) -5- 苯基环己烷-1,3-二酮 (200mg, 0.823mmol) 溶于 5mL 无水乙醇和 5mL DCM 中, 室温加入 1mL 醋酸和甲硫醇钠 (115mg, 1.64mmol), 混合物在封管中室温搅拌 16 小时。补加 1mL 醋酸和甲硫醇钠 (115mg, 1.64mmol), 继续搅拌 16 小时。反应完毕将反应液倒入水中, 二氯甲烷 (DCM) 萃取。合并有机相依次用水和饱和食盐水洗涤, 无水硫酸钠干燥, 浓缩得粗品, 经柱层析分离得目标化合物 15mg, 产率 7%。化合物 4A: ^1H NMR (400MHz, DMSO- d_6) δ 8.75 (s, 1H), 7.33-7.19 (m, 5H), 3.46-3.37 (m, 1H), 2.95-2.86 (m, 2H), 2.72-2.64 (m, 2H), 2.60 (s, 3H); MS: 247.1 [M+1]。

[0258] 实施例 6: 化合物 5- 苯基-2- ((苯基氨基) 亚甲基) 环己烷-1,3-二酮 (化合物 5) 的合成

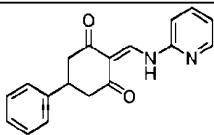
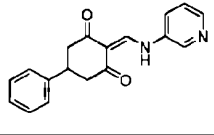


[0260] 将化合物 2- ((二甲基氨基) 亚甲基) -5- 苯基环己烷-1,3-二酮 (200mg, 0.82mmol)、苯胺 (60mg, 0.65mmol) 和醋酸 (0.5mL) 溶解于 10mL 乙醇中, 回流反应 1 小时。冷却至室温, 浓缩得粗品, 经柱层析分离得到目标化合物 150mg, 产率 79%。化合物 5: ^1H NMR (400MHz, DMSO- d_6) δ 8.72 (s, 1H), 7.49-7.41 (m, 4H), 7.35-7.28 (m, 5H), 7.25-7.22 (m, 1H), 3.46-3.40 (m, 1H), 2.95-2.70 (m, 4H); MS: 292.1 [M+1]。

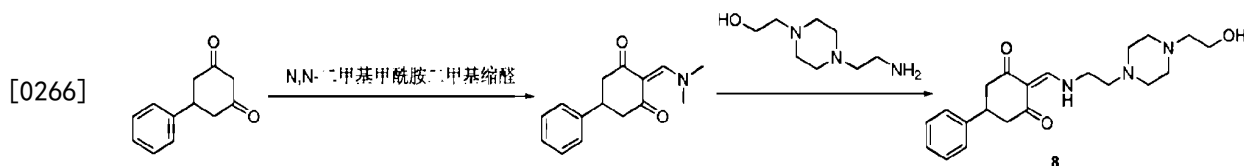
[0261] 实施例 7: 化合物 6 和 7 的合成

[0262] 化合物 6 和 7 的合成方法同化合物 5, 如表 1 所示。

[0263] 表 1: 化合物 6 和 7

#	结构	名称	氢谱(¹ H NMR),质谱(MS)
[0264] 6		5-苯基-2-((吡啶-2-基氨基)亚甲基)环己烷-1,3-二酮	¹ H NMR (400 MHz, CD ₃ OD) δ 9.27(s, 1H), 8.43 (dd, <i>J</i> = 4.8, 1.2Hz, 1H), 7.88-7.84 (m, 1H), 7.35-7.21 (m, 8H), 3.50-3.40 (m, 1H), 2.96-2.72 (m, 4H); MS: 293.1 [M+1].
7		5-苯基-2-((吡啶-3-基氨基)亚甲基)环己烷-1,3-二酮	¹ H NMR (400 MHz, CD ₃ OD) δ 8.72(s, 1H), 8.68 (d, <i>J</i> = 3.2Hz, 1H), 8.45(d, <i>J</i> = 4.4Hz, 1H), 7.99-7.96(m, 1H), 7.55-7.51(m, 1H), 7.63-7.31 (m, 4H), 7.26-7.22 (m, 1H), 3.47-3.41 (m, 1H), 2.97-2.76 (m, 4H); MS: 293.1 [M+1].

[0265] 实施例8:化合物2-(((2-(4-(2-羟乙基)哌嗪-1-基)乙基)氨基)亚甲基)-5-苯基环己烷-1,3-二酮(化合物8)的合成



[0267] 步骤1:化合物2-((二甲基氨基)亚甲基)-5-苯基环己烷-1,3-二酮的合成

[0268] 将化合物5-苯基环己烷-1,3-二酮(5.0g, 26.6mmol)溶于氯仿(25mL)中,加入N,N-二甲基甲酰胺二甲基缩醛(DMF-DMA)(5mL),上述混合物于室温下反应1小时。反应完毕,反应液浓缩,浓缩物用10%乙酸乙酯(EA)/石油醚(PE)匀浆析出沉淀,过滤,将滤渣干燥即得目标化合物4.81g,产率74%。

[0269] 步骤2:化合物2-(((2-(4-(2-羟乙基)哌嗪-1-基)乙基)氨基)亚甲基)-5-苯基环己烷-1,3-二酮(化合物8)的合成

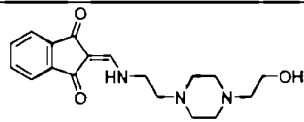
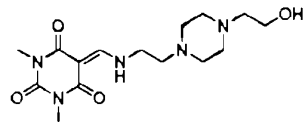
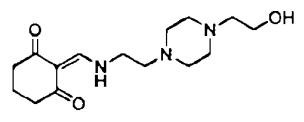
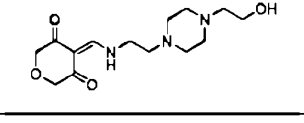
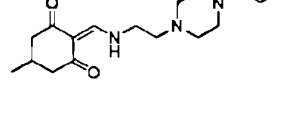
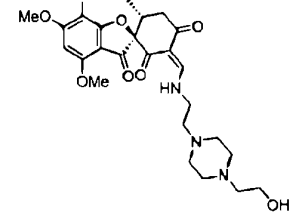
[0270] 将化合物2-(4-(2-氨基乙基)哌嗪-1-基)乙-1-醇(200mg, 1.15mmol)溶于5mL乙醇,加入化合物2-((二甲基氨基)亚甲基)-5-苯基环己烷-1,3-二酮(365mg, 1.5mmol),室温反应30分钟,产生固体,过滤,滤渣用乙醇洗涤,收集滤渣,干燥得目标化合物312mg,产率73%。化合物8:¹H NMR (400MHz, CD₃OD) δ 8.25 (s, 1H), 7.34-7.20 (m, 5H), 3.80 (t, *J* = 5.6Hz, 2H), 3.61 (t, *J* = 5.6Hz, 2H), 3.40-3.30 (m, 1H), 3.06 (br, 4H), 2.98 (t, *J* = 4.4Hz, 2H), 2.85-2.64 (m, 10H); MS: 372.3 [M+1]。

[0271] 实施例9:化合物9-12,14-15

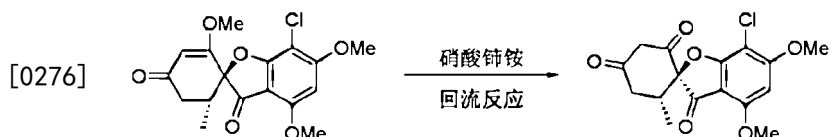
[0272] 除了使用相应的取代1,3-环己二酮或其他具有活泼亚甲基的酮外(例如实施例9-1),化合物9-12和14-15的合成方法同化合物8,如表2所示。

[0273] 表2:化合物9-12和14-15

[0274]

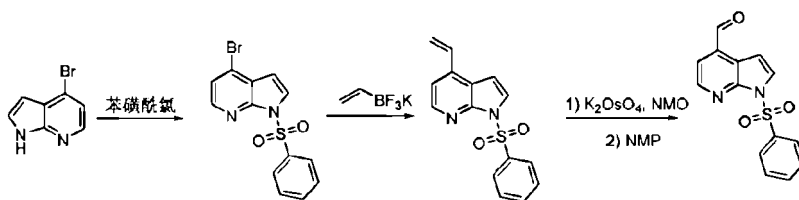
#	结构	名称	氢谱(¹ H NMR),质谱(MS)
9		2-(((2-(4-(2-羟乙基)哌嗪-1-基)乙基)氨基)亚甲基)-1H-茚-1,3(2H)-二酮	¹ H NMR (400 MHz, CD ₃ OD) δ 7.85 (s, 1H), 7.66 (d, <i>J</i> = 2.4 Hz, 4H), 3.72 (t, <i>J</i> = 5.9 Hz, 2H), 3.59 (t, <i>J</i> = 5.9 Hz, 2H), 2.78 – 2.60 (m, 12H); MS: 330.3 [M+1].
10		5-(((2-(4-(2-羟乙基)哌嗪-1-基)乙基)氨基)亚甲基)-1,3-二甲基嘧啶-2,4,6(1H, 3H, 5H)-三酮	¹ H NMR (400 MHz, CD ₃ OD) δ 8.25 (s, 1H), 3.72 (t, <i>J</i> = 5.9 Hz, 2H), 3.62 (t, <i>J</i> = 5.8 Hz, 2H), 3.39 – 3.08 (m, 6H), 2.97 – 2.31 (m, 12H); MS: 400.2 [M+1].
11		2-(((2-(4-(2-羟乙基)哌嗪-1-基)乙基)氨基)亚甲基)环己烷-1,3-二酮	¹ H NMR (400 MHz, CD ₃ OD) δ 8.21 (s, 1H), 3.68 (t, <i>J</i> = 6.0 Hz, 2H), 3.57 (t, <i>J</i> = 5.9 Hz, 2H), 2.61 (dd, <i>J</i> = 15.9, 10.1 Hz, 12H), 2.44 (dd, <i>J</i> = 9.5, 6.6 Hz, 4H), 2.04 – 1.85 (m, 2H); MS: 296.2 [M+1].
12		4-(((2-(4-(2-羟乙基)哌嗪-1-基)乙基)氨基)亚甲基)-2H-吡喃-3,5(4H, 6H)-二酮	¹ H NMR (400 MHz, CD ₃ OD) δ 8.24 (s, 1H), 4.17 (s, 4H), 3.74 (t, <i>J</i> = 5.9 Hz, 2H), 3.64 (t, <i>J</i> = 5.9 Hz, 2H), 2.96 – 2.41 (m, 12H); MS: 298.2 [M+1].
14		2-(((2-(4-(2-羟乙基)哌嗪-1-基)乙基)氨基)亚甲基)-5-甲基环己烷-1,3-二酮	¹ H NMR (400 MHz, CD ₃ OD) δ 8.19 (s, 1H), 3.71 (t, <i>J</i> = 5.9 Hz, 2H), 3.57 (t, <i>J</i> = 5.9 Hz, 2H), 2.84 – 2.54 (m, 12H), 2.49 (d, <i>J</i> = 15.5 Hz, 2H), 2.24-2.02 (m, 3H), 1.05 (d, <i>J</i> = 5.6 Hz, 3H); MS: 310.3 [M+1].
15		(2R, 6'R)-7-氯-3'-(((2-(4-(2-羟乙基)哌嗪-1-基)乙基)氨基)亚甲基)-4,6-二甲氧基-6'-甲基-3H-螺[苯并呋喃-2,1'-环己烷]-2',3,4'-三酮	¹ H NMR (400 MHz, CD ₃ OD) δ 8.25 (d, <i>J</i> = 13.6 Hz, 1H), 6.39 (s, 1H), 4.05 (s, 3H), 3.95 (s, 3H), 3.71 (t, <i>J</i> = 6.0 Hz, 2H), 3.61 (J = 4.8 Hz, 2H), 3.17-3.06 (m, 1H), 2.84-2.49 (m, 14H), 0.94 (d, <i>J</i> = 6.8 Hz, 3H); MS: 522.2 [M+1].

[0275] 实施例9-1: 中间体3-1: (2S, 2'R)-7-氯-4,6-二甲氧基-2'-甲基-3H-螺[苯并呋喃-2,1'-环己烷]3,4',6'-三酮的合成

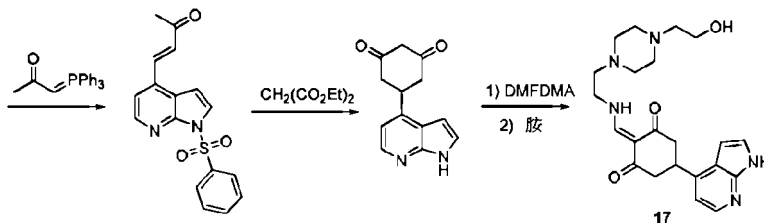


[0277] 化合物(2S, 6'R)-7-氯-2',4,6-三甲氧基-6'-甲基-3H-螺[苯并呋喃-2,1'-环己烷]-2'-烯-3,4'-二酮(1.0g, 2.84mmol)和硝酸铈铵(1.55g, 2.84mmol)溶解于乙腈(40mL)和水(40mL)混合溶剂中加热回流6小时。反应完毕, 降至室温, 倒入水中, EA萃取, 有机相并依次用水和饱和食盐水洗涤, 无水硫酸钠干燥, 浓缩得粗品, 经柱层析分离得到目标化合物880mg, 产率91%。

[0278] 实施例10: 化合物2-(((2-(4-(2-羟乙基)哌嗪-1-基)乙基)氨基)亚甲基)-5-(1H-吡咯并[2,3-b]吡啶-4-基)环己烷-1,3-二酮(化合物17)的合成



[0279]



[0280] 步骤1:化合物4-溴-1-(苯基磺酰基)-1H-吡咯并[2,3-b]吡啶的合成

[0281] 氮气保护下,将化合物4-溴-1H-吡咯并[2,3-b]吡啶(3.0g,15.23mmol)溶于无水四氢呋喃(THF)(50mL)中,在0℃下,向上述混合液分批加入60%氢化钠(800mg,20mmol)并在该温度下搅拌30分钟后,加入苯磺酰氯(3.53g,20mmol),将所得混合物在室温下反应1小时。反应完毕,将反应混合物用冰水在0℃缓慢淬灭,EA萃取,有机相用水洗涤,无水硫酸钠干燥,浓缩,粗品经柱层析分离纯化得目标化合物4.3g,产率84%。

[0282] 步骤2:化合物1-(苯基磺酰基)-4-乙C2-6烯基-1H-吡咯并[2,3-b]吡啶的合成

[0283] 氮气保护下,将化合物4-溴-1-(苯基磺酰基)-1H-吡咯并[2,3-b]吡啶(4.3g,12.8mmol)溶于50mL二氧六环和10mL水中,依次加入Pd(dppf)₂Cl₂(470mg,0.64mmol)、乙烯三氟硼酸钾(2.57g,19.2mmol)和N,N-二异丙基乙胺(DIPEA)(3.23g,25mmol)。上述混合物加热回流2小时,反应完毕降至室温,倒入冰水中,EA萃取,有机相分别用水和饱和食盐水洗涤,干燥,浓缩得粗品,经柱层析分离得目标化合物2.52g,产率70%。

[0284] 步骤3:化合物1-(苯基磺酰基)-1H-吡咯并[2,3-b]吡啶-4-甲醛的合成

[0285] 将化合物1-(苯基磺酰基)-4-乙C2-6烯基-1H-吡咯并[2,3-b]吡啶(2.52g,8.86mmol)溶于50mL丙酮和10mL水,加入N-甲基-N-氧化吗啉(1.56g,13.3mmol)和二水合钨酸钾(100mg),室温反应2小时后,向上述反应液分批加入高碘酸钠(7.56g,35.44mmol),然后继续室温反应1小时。反应完毕倒入水中,EA萃取,有机相分别用水和饱和食盐水洗涤,干燥,浓缩得粗品,经柱层析分离得到目标化合物1.52g,产率60%。

[0286] 步骤4:化合物4-(1-(苯基磺酰基)-1H-吡咯并[2,3-b]吡啶-4-基)丁-3-烯-2-酮的合成

[0287] 将化合物1-(苯基磺酰基)-1H-吡咯并[2,3-b]吡啶-4-甲醛(1.52g,5.3mmol)和1-三苯基膦-2-丙酮(2.55g,8mmol)分别加入到30mL无水THF中,回流反应2小时。反应完毕降至室温,浓缩得粗品,经柱层析分离得到目标化合物1.52g,产率88%。

[0288] 步骤5:化合物5-(1H-吡咯并[2,3-b]吡啶-4-基)环己烷-1,3-二酮的合成

[0289] 将丙二酸二乙酯(970mg,6.06mmol)加入到乙醇钠(412mg,6.06mmol)的乙醇(20mL)溶液中,室温搅拌10分钟,滴加4-(1-(苯基磺酰基)-1H-吡咯并[2,3-b]吡啶-4-基)丁-3-烯-2-酮(1.52g,4.66mmol)的乙醇(10mL)溶液,加热回流1小时。降至室温,加50mL水,用EA(50mL)萃取,水相用3N盐酸调节至pH=2-3,加热回流30分钟。降至室温,用EA萃取,合并的有机相依次用水和饱和食盐水洗涤,干燥,浓缩。粗品经柱层析分离得到目标化合物620mg,产率58.3%。

[0290] 步骤6: 化合物2-(((2-(4-(2-羟乙基)哌嗪-1-基)乙基)氨基)亚甲基)-5-(1H-吡咯并[2,3-b]吡啶-4-基)环己烷-1,3-二酮的合成

[0291] 操作步骤同实施例2。化合物17: ^1H NMR (400MHz, CDCl_3) δ 11.31-11.15 (m, 1H), 9.81 (s, 1H), 8.27 (dd, $J=18.6, 9.6\text{Hz}$, 2H), 7.35 (d, $J=3.4\text{Hz}$, 1H), 6.95 (d, $J=5.0\text{Hz}$, 1H), 6.56 (d, $J=3.5\text{Hz}$, 1H), 3.92-3.77 (m, 1H), 3.73-3.64 (m, 2H), 3.60-3.46 (m, 2H), 3.07-2.53 (m, 17H); MS: 412.4 [M+1]。

[0292] 实施例11: 化合物18-32

[0293] 除了使用相应的溴代C6-10芳基或醛 (如实施例11-1至11-5), 化合物18-32的合成方法同化合物17, 如表3所示。

[0294] 表3: 化合物18-32

#	结构	名称	氢谱(^1H NMR), 质谱(MS)
18		2-(((2-(4-(2-羟乙基)哌嗪-1-基)乙基)氨基)亚甲基)-5-(1H-吡咯并[2,3-b]吡啶-4-基)环己烷-1,3-二酮	^1H NMR (400 MHz, CDCl_3) δ 11.28 – 11.08 (m, 1H), 9.50 (s, 1H), 8.32 (d, $J = 4.0\text{ Hz}$, 1H), 8.20 (d, $J = 14.3\text{ Hz}$, 1H), 7.97 (d, $J = 7.8\text{ Hz}$, 1H), δ 7.14 – 7.07 (m, 2H), 3.85 – 3.62 (m, 3H), 3.52 (m, 2H), 3.02 – 2.65 (m, 17H); MS: 412.2 [M+1].
19		2-(((2-(4-(2-羟乙基)哌嗪-1-基)乙基)氨基)亚甲基)-5-(1-(2-甲氧基乙基)-1H-吡咯并[2,3-b]吡啶-4-基)环己烷-1,3-二酮	^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 11.03 – 10.91 (m, 1H), 8.34 – 8.01 (m, 2H), 7.51 (d, $J = 3.5\text{ Hz}$, 1H), 7.00 (d, $J = 5.0\text{ Hz}$, 1H), 6.64 (d, $J = 3.5\text{ Hz}$, 1H), 4.40 (t, $J = 5.4\text{ Hz}$, 3H), 3.83 – 3.65 (m, 3H), 3.58 (dd, $J = 11.6, 5.8\text{ Hz}$, 4H), 3.49 (dd, $J = 11.4, 5.9\text{ Hz}$, 3H), 3.23 (s, 2H), 2.97 – 2.76 (m, 2H), 2.69 – 2.23 (m, 12H); MS: 470.1 [M+1].
20		2-(((2-(4-(2-羟乙基)哌嗪-1-基)乙基)氨基)亚甲基)-5-(1,10-菲咯啉-3-基)环己烷-1,3-二酮	^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 11.09 – 10.83 (m, 1H), 9.09 (dd, $J = 2.0, 1.0\text{ Hz}$, 1H), 8.47 (dd, $J = 12.3, 4.7\text{ Hz}$, 2H), 8.17 (d, $J = 14.6\text{ Hz}$, 1H), 7.95 (s, 2H), 7.77 (dd, $J = 7.6, 6.9\text{ Hz}$, 2H), 5.20 – 4.90 (m, 1H), 3.94 – 3.52 (m, 6H), 3.14 – 2.83 (m, 7H), 2.85 –

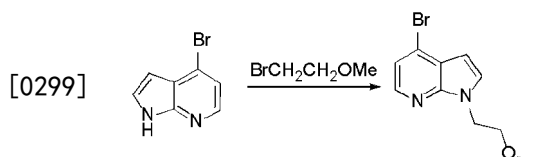
[0296]

			2.62 (m, 4H), 2.57 (s, 4H); MS: 474.3 [M+1].
21		2-(((2-(4-(2-羟乙基)哌嗪-1-基)乙基)氨基)亚甲基)-5-(4-(苯硫基)苯基)环己烷-1,3-二酮	¹ H NMR (400 MHz, CD ₃ OD) δ 8.24 (s, 1H), 7.49 – 6.95 (m, 9H), 3.79 (t, <i>J</i> = 5.4 Hz, 2H), 3.61 (t, <i>J</i> = 5.3 Hz, 2H), 3.43 – 3.32 (m, 1H), 3.11 – 2.87 (m, 6H), 2.85 – 2.58 (m, 10H); MS: 480.2 [M+1].
22		2-(((2-(4-(2-羟乙基)哌嗪-1-基)乙基)氨基)亚甲基)-5-(4-(2-甲基-2H-四唑-5-基)苯基)环己烷-1,3-二酮	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.01 – 10.86 (m, 1H), 8.12 (d, <i>J</i> = 14.6 Hz, 1H), 7.98 (d, <i>J</i> = 8.3 Hz, 2H), 7.49 (d, <i>J</i> = 8.3 Hz, 2H), 4.40 (s, 4H), 3.63 – 3.51 (m, 2H), 3.51 – 3.42 (m, 2H), 3.43 – 3.34 (m, 1H), 2.86 – 2.62 (m, 3H), 2.60 – 2.51 (m, 3H), 2.51 – 2.24 (m, 10H); MS: 454.3 [M+1].
23		5-(2-环丙基-4,5-二甲氧基苯基)-2-(((2-(4-(2-羟乙基)哌嗪-1-基)乙基)氨基)亚甲基)环己烷-1,3-二酮	¹ H NMR (400 MHz, CD ₃ OD) δ 8.28 (s, 1H), 6.88 (s, 1H), 6.67 (s, 1H), 3.99 (dd, <i>J</i> = 10.1, 6.2 Hz, 1H), 3.80 (t, <i>J</i> = 4.0 Hz, 8H), 3.63 (t, <i>J</i> = 5.7 Hz, 2H), 3.18 – 2.39 (m, 16H), 2.01 – 1.78 (m, 1H), 0.90 (dd, <i>J</i> = 8.3, 1.5 Hz, 2H), 0.61 (d, <i>J</i> = 4.0 Hz, 2H); MS: 472.2 [M+1].
24		5-(4-氟-1H-吲哚-3-基)-2-(((2-(4-(2-羟乙基)哌嗪-1-基)乙基)氨基)亚甲基)环己烷-1,3-二酮	¹ H NMR (400 MHz, CD ₃ OD) δ 8.29 (s, 1H), 7.18 (d, <i>J</i> = 8.1 Hz, 1H), 7.11 – 6.99 (m, 2H), 6.71 (dd, <i>J</i> = 11.7, 7.8 Hz, 1H), 3.85 – 3.69 (m, 3H), 3.64 (t, <i>J</i> = 5.7 Hz, 2H), 3.03 – 2.52 (m, 16H); MS: 430.4 [M+1].
25		2-(((2-(4-(2-羟乙基)哌嗪-1-基)乙基)氨基)亚甲基)-5-(8-吗啉代咪唑并[1,2-a]吡嗪-3-基)环己烷-1,3-二酮	¹ H NMR (400 MHz, CD ₃ OD) δ 8.28 (s, 1H), 7.77 (d, <i>J</i> = 4.7 Hz, 1H), 7.43 (d, <i>J</i> = 4.6 Hz, 1H), 7.37 (s, 1H), 4.18 – 4.06 (m, 4H), 3.90 – 3.78 (m, 5H), 3.69 (t, <i>J</i> = 6.0 Hz, 2H), 3.62 (t, <i>J</i> = 5.8 Hz, 2H), 3.01 – 2.73 (m, 5H), 2.59 (m, 11H).
26		5-(6,7-二甲氧基吡啶-4-基)-2-(((2-(4-(2-羟乙基)哌嗪-1-基)乙基)氨基)亚甲基)环己烷-1,3-二酮	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.00 – 10.90 (m, 1H), 9.00 (s, 1H), 8.17 (d, <i>J</i> = 14.6 Hz, 1H), 7.59 (s, 1H), 7.35 (s, 1H), 4.59 – 4.45 (m, 1H), 3.97 (d, <i>J</i> = 4.0 Hz, 6H), 3.74 – 3.52 (m, 4H), 2.85 (ddd, <i>J</i> = 22.8, 16.8, 10.8 Hz, 7H), 2.71 – 2.53 (m, 6H).
27		2-(((2-(4-(2-羟乙基)哌嗪-1-基)乙基)氨基)亚甲基)-5-(噻吩并[2,3-d]咪唑-4-基)环己烷-1,3-二酮	¹ H NMR (400 MHz, CD ₃ OD) δ 8.96 (s, 1H), 8.28 (s, 1H), 7.83 (d, <i>J</i> = 6.1 Hz, 1H), 7.68 (d, <i>J</i> = 6.1 Hz, 1H), 4.22 (td, <i>J</i> = 10.5, 5.2 Hz, 1H), 3.84 – 3.76 (m, 2H), 3.63 (t, <i>J</i> = 5.7 Hz, 2H), 3.15 – 2.87 (m, 8H), 2.85 – 2.59 (m, 8H).
28		2-(((2-(4-(2-羟乙基)哌嗪-1-基)乙基)氨基)亚甲基)-5-(邻甲苯基)环己烷-1,3-二酮	¹ H NMR (400 MHz, CD ₃ OD) δ 8.27 (s, 1H), 7.27-7.11 (m, 4H), 3.69 (t, <i>J</i> = 6.0 Hz, 2H), 3.63-3.55 (m, 3H), 2.78-2.56 (m, 16H), 3.34 (s, 3H); MS: 386.2 [M+1].

[0297]

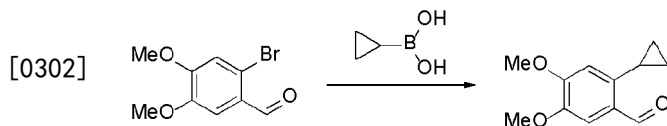
29		2-(((2-(4-(2-羟乙基)哌嗪-1-基)乙基)氨基)亚甲基)-5-甲基-5-苯基环己烷-1,3-二酮	$^1\text{H NMR}$ (400 MHz, CD_3OD) δ 8.07(s, 1H), 7.34-7.25(m, 4H), 7.18-7.14(m, 1H), 3.79(t, $J=5.6\text{Hz}$, 2H), 3.53-3.49(m, 2H), 3.06-2.96(m, 8H), 2.77-2.58(m, 8H), 1.36 (s, 3H)
30		5-((3aR, 4R, 6R, 6aR)-2,2-二甲基-6-(6-吗啉代-9H-嘌呤-9-基)四氢呋喃并[3,4-D][1,3]二氧杂环戊烯-4-基)-2-(((2-(4-(2-羟乙基)哌嗪-1-基)乙基)氨基)亚甲基)环己烷-1,3-二酮	$^1\text{HNMR}$ (400 MHz, CD_3OD) δ 8.25 (s, 1H), 8.17 (m, 2H), 6.14 (d, $J=2.6\text{Hz}$, 1H), 5.42 – 5.31 (m, 1H), 5.08 – 4.99 (m, 1H), 4.26 (s, 4H), 3.95 (m, 1H), 3.84 – 3.68 (m, 6H), 3.57 (m, 2H), 2.90 – 2.70 (m, 6H), 2.61 (s, 7H), 2.46 (m, 5H), 1.57 (s, 3H), 1.37 (s, 3H)
31		2-(((2-(4-(2-羟乙基)哌嗪-1-基)乙基)氨基)亚甲基)-5-(苯氧基甲基)环己烷-1,3-二酮	$^1\text{HNMR}$ (400 MHz, CD_3OD) δ 8.26 (s, 1H), 7.41 – 7.14 (m, 2H), 7.03 – 6.88 (m, 3H), 3.97 (d, $J=5.1\text{Hz}$, 2H), 3.75 (t, $J=5.8\text{Hz}$, 2H), 3.63 (t, $J=5.8\text{Hz}$, 2H), 2.92 – 2.41 (m, 17H); MS: 402.4 [M+1].
32		5-((3-氟苯氧基)甲基)-2-(((2-(4-(2-羟乙基)哌嗪-1-基)乙基)氨基)亚甲基)环己烷-1,3-二酮	$^1\text{HNMR}$ (400 MHz, CD_3OD) δ 8.22 (s, 1H), 7.24 (dd, $J=15.2, 8.1\text{Hz}$, 1H), 6.73 (d, $J=8.2\text{Hz}$, 1H), 6.70 – 6.59 (m, 2H), 3.94 (d, $J=5.1\text{Hz}$, 2H), 3.77 (t, $J=5.6\text{Hz}$, 2H), 3.59 (t, $J=5.7\text{Hz}$, 2H), 2.98-2.91 (m, 5H), 2.79 – 2.32 (m, 12H); MS: 420.4 [M+1].

[0298] 实施例11-1: 中间体11-1: 4-溴-1-(2-甲氧基乙基)-1H-吡咯并[2,3-b]吡啶的合成



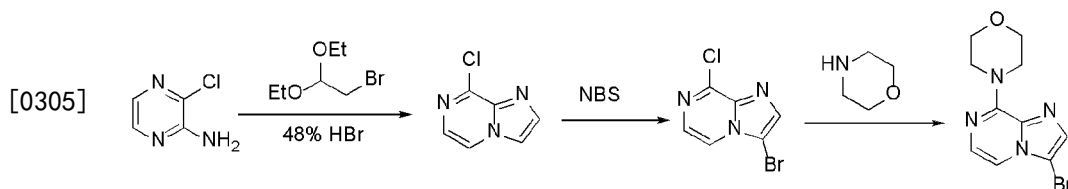
[0300] 将4-溴-7-氮杂吡啶 (3g, 15.2mmol) 溶于30mL无水N,N-二甲基甲酰胺(DMF)中, 0℃下缓慢加入钠氢(60%, 800mg, 20mmol), 该温度下反应30分钟。加入2-溴乙基甲基醚(2.78g, 20mmol), 升至室温反应4小时。反应完毕缓慢倒入冰水中, EA萃取, 有机相依次用水和饱和食盐水洗涤, 干燥, 浓缩。粗品经柱层析分离得目标化合物3.12g, 产率80%。

[0301] 实施例11-2: 中间体11-2: 2-环丙基-4,5-二甲氧基苯甲醛的合成



[0303] 氮气保护下, 将6-溴藜芦醛(1g, 4.08mmol)、环丙基硼酸(515mg, 6mmol)、碳酸钠(1.06g, 10mmol)和四(三苯基膦)钯(100mg, 0.086mmol)加入到二氧六环(15mL)和水(5mL)中, 回流反应过夜。反应完毕降至室温, 倒入冰水中, EA萃取, 有机相依次用水和食盐水洗涤, 干燥, 浓缩。粗品经柱层析分离得目标化合物560mg, 产率66%。

[0304] 实施例11-3: 中间体11-3: 4-(3-溴咪唑并[1,2-a]吡嗪-8-基)吗啉的合成



[0306] 步骤1:化合物8-氯咪唑并[1,2-a]吡嗪的合成

[0307] 将2-溴-1,1-二乙氧基乙烷(22.7g,0.115mol)在48%溴化氢(4.45mL)水溶液中加热回流2小时,然后倒入碳酸氢钠(74.5g)的异丙醇溶液200mL中。混合物搅拌30分钟,过滤,向滤液中加入3-氯吡嗪-2-胺(5.0g,38.6mmol),将混合物在85℃下搅拌4小时。浓缩,加入饱和的碳酸钠溶液并用DCM萃取,将合并的有机层干燥,浓缩,粗品用乙醚重结晶,得粗品5.7g,其不经进一步纯化直接用于下一步反应。

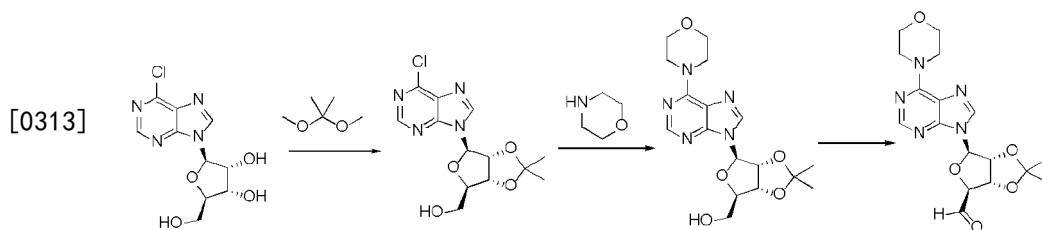
[0308] 步骤2:化合物3-溴-8-氯咪唑并[1,2-a]吡嗪的合成

[0309] 室温下向8-氯咪唑并[1,2-a]吡嗪(5.7g)的DCM(100mL)溶液中分批加入NBS(6.6g,37mmol),室温反应2小时。反应完毕将反应混合物倒入水中,DCM萃取,有机相用水、盐水洗涤,干燥,浓缩得粗品8.0g,其不经进一步纯化直接用于下一步反应。

[0310] 步骤3:化合物4-(3-溴咪唑并[1,2-a]吡嗪-8-基)吗啉的合成

[0311] 将3-溴-8-氯咪唑并[1,2-a]吡嗪(8.0g)、DIPEA(5.7g,44mmol)和吗啉(6.44g,74mmol)的混合物在80℃下反应4小时。反应完毕倒入水中,DCM萃取,有机相用水,盐水洗涤,干燥,浓缩,经柱层析分离得目标化合物5.71g,产率52%。

[0312] 实施例11-4:中间体11-4:(3aS,4S,6R,6aR)-2,2-二甲基-6-(6-吗啉代-9H-嘌呤-9-基)四氢呋喃并[3,4-D][1,3]二氧杂环戊烯-4-甲醛的合成



[0314] 步骤1:化合物((3aR,4R,6R,6aR)-2,2-二甲基-6-(6-吗啉代-9H-嘌呤-9-基)四氢呋喃并[3,4-d][1,3]二氧代-4基)甲醇的合成

[0315] 将6-氯嘌呤核苷(3.0g,10.46mmol)、2,2-二甲氧基丙烷(5.2g,50mmol)和一水合对甲苯磺酸(1.99g,10.46mmol)的丙酮(120mL)溶液回流2小时,反应完毕,将反应混合物倒入冰水中,调节pH至8-9,用DCM萃取,有机相用水洗涤,硫酸钠干燥,浓缩得到目标化合物3.31g,产率96%。

[0316] 步骤2:化合物((3aR,4R,6R,6aR)-2,2-二甲基-6-(6-吗啉代-9H-嘌呤-9-基)四氢呋喃并[3,4-d][1,3]二氧代-4基)甲醇的合成

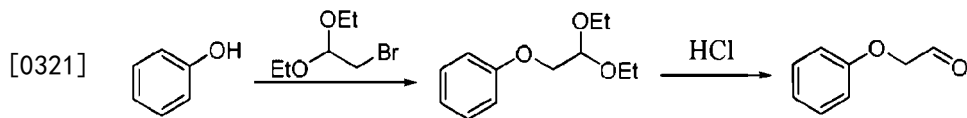
[0317] 将化合物((3aR,4R,6R,6aR)-6-(6-氯-9H-嘌呤-9-基)-2,2-二甲基四氢呋喃并[3,4-D][1,3]二氧杂环戊烯-4-基)甲醇(1.00g,3.06mmol)、吗啉(610mg,7.0mmol)和DIPEA(900mg,7.0mmol)溶于乙腈(20mL)中,回流反应2小时,反应完毕将反应混合物冷却至室温,倒入冰水中,EA萃取,有机相用水洗涤,无水硫酸钠干燥,浓缩,粗品经柱层析分离纯化得目标化合物912mg,产率80%。

[0318] 步骤3:化合物(3aS,4S,6R,6aR)-2,2-二甲基-6-(6-吗啉代-9H-嘌呤-9-基)四氢

呋喃并[3,4-d][1,3]间二氧杂环戊烯-4-甲醛的合成

[0319] 将((3aR,4R,6R,6aR)-2,2-二甲基-6-(6-吗啉代-9H-嘌呤-9-基)四氢呋喃并[3,4-d][1,3]二氧代-4基)甲醇(700mg,1.85mmol)溶于DCM中,0℃下缓慢加入戴斯-马丁氧化剂(2.5mmol),反应液升至室温搅拌2小时。加水稀释,DCM萃取,有机相用饱和食盐水洗涤,干燥,浓缩。粗品经柱层析分离得目标化合物508mg,产率73%。

[0320] 实施例11-5:中间体11-5:2-苯氧基乙醛的合成



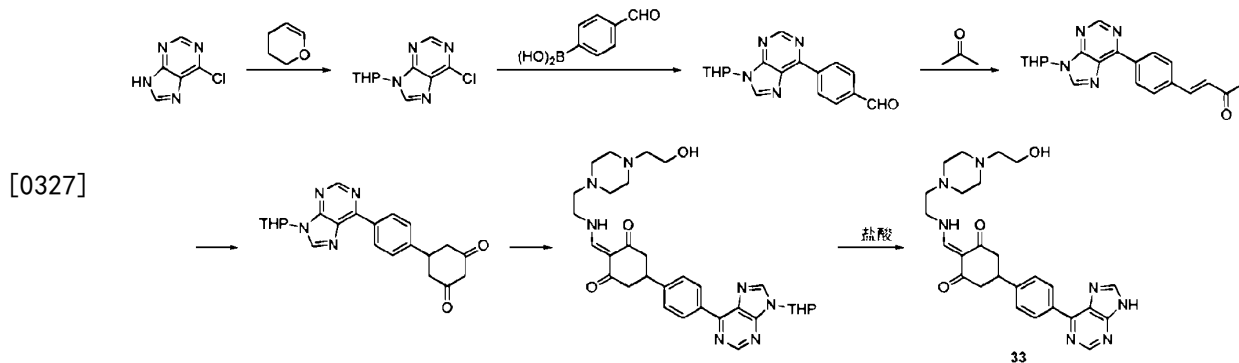
[0322] 步骤1:化合物(2,2-二乙氧基乙氧基)苯的合成

[0323] 将苯酚(0.94g,10mmol)、氯乙醛缩二乙醇(1.52g,10mmol)、碳酸钾(2.77g,20mmol)和碘化钾(500mg)溶解于DMF(15mL)中,上述混合物在100℃下搅拌过夜。反应完毕,将反应混合物冷却至室温,倒入冰水中,用EA萃取,有机相用水洗涤,硫酸钠干燥,浓缩,粗品经柱层析分离纯化得目标化合物1.21g,产率58%。

[0324] 步骤2:化合物2-苯氧基乙醛的合成

[0325] 将(2,2-二乙氧基乙氧基)苯(0.84g,4mmol)溶解于醋酸(5mL)、1N盐酸溶液(2.5mL)和乙醇(EtOH)(20mL)的混合溶液中,加热回流3小时。反应完毕冷却至室温,倒入冰水中,EA萃取,有机相用水洗涤,无水硫酸钠干燥,浓缩,粗品经柱层析分离纯化得目标化合物468mg,产率86%。

[0326] 实施例12:化合物5-(4-(9H-嘌呤-6-基)苯基)-2-(((2-(4-(2-羟乙基)哌嗪-1-基)乙基)氨基)亚甲基)环己烷-1,3-二酮(化合物33)的合成



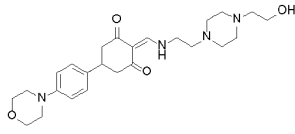
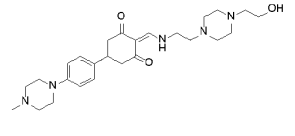
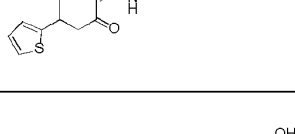
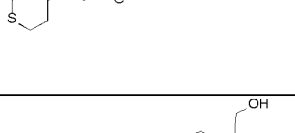
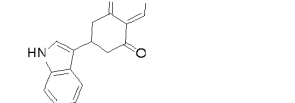
[0328] 步骤1:化合物6-氯-9-(四氢-2H-吡喃-2-基)-9H-嘌呤的合成

[0329] 将6-氯-9H-嘌呤(4.50g,30mmol)、一水合对甲苯磺酸(1.14g,6.0mmol)和3,4-二氢-2H-吡喃(5.05g,60mmol)的EA溶液(200mL)加热回流5小时。反应完毕冷却至室温,倒入冰水中,EA萃取,有机相用水洗涤,硫酸钠干燥,浓缩,粗品经柱层析分离纯化得目标化合物5.72g,产率80%。

[0330] 步骤2:化合物4-(9-(四氢-2H-吡喃-2-基)-9H-嘌呤-6-基)苯甲醛的合成

[0331] 将6-氯-9-(四氢-2H-吡喃-2-基)-9H-嘌呤(5.7g,24mmol)、碳酸钠(5.3g,50mmol)、4-醛基苯硼酸(7.5g,50mmol)和四(三苯基膦)钯(690mg,0.6mmol)溶于二氧六环(200mL)和水(20mL)的混合溶液中,回流反应过夜。反应完毕冷却至室温,倒入冰水中,EA萃取,有机相用水洗涤,硫酸钠干燥,浓缩,粗品经柱层析分离纯化得目标化合物5.51g,产率74%。

[0345] 表4:化合物35-59,61-84

#	结构	名称	氢谱(¹ HNMR),质谱(MS)
35		2-(((2-(4-(2-羟乙基)哌嗪-1-基)乙基)氨基)亚甲基)-5-(4-(吗啉代苯基)环己烷-1,3-二酮	¹ HNMR (400 MHz, CD ₃ OD) δ 8.27 (s, 1H), 7.21 (d, <i>J</i> = 8.1 Hz, 2H), 6.97 (d, <i>J</i> = 8.2 Hz, 2H), 3.86 (s, 4H), 3.75 (t, <i>J</i> = 5.5 Hz, 2H), 3.64 (s, 2H), 3.14 (s, 4H), 2.88 – 2.49 (m, 17H); MS: 457.4 [M+1].
36		2-(((2-(4-(2-羟乙基)哌嗪-1-基)乙基)氨基)亚甲基)-5-(4-(4-甲基哌嗪-1-基)苯基)环己烷-1,3-二酮	¹ HNMR (400 MHz, CD ₃ OD) δ 8.27 (s, 1H), 7.21 (d, <i>J</i> = 8.6 Hz, 2H), 6.98 (d, <i>J</i> = 8.7 Hz, 2H), 3.79 (t, <i>J</i> = 5.7 Hz, 2H), 3.63 (t, <i>J</i> = 5.7 Hz, 2H), 2.92 (s, 4H), 2.89-2.59 (m, 21H), 2.52 (s, 3H); MS: 470.2 [M+1].
37		2-(((2-(4-(2-羟乙基)哌嗪-1-基)乙基)氨基)亚甲基)-5-(噻吩-2-基)环己烷-1,3-二酮	¹ HNMR (400 MHz, CD ₃ OD) δ 8.26 (d, <i>J</i> = 14.4Hz, 1H), 7.27 (br, 1H), 6.95 (br, 1H), 4.09-3.30 (m, 7H), 2.50-2.84 (m, 14H); MS: 378.5 [M+1].
38		2-(((2-(4-(2-羟乙基)哌嗪-1-基)乙基)氨基)亚甲基)-5-(四氢-2H-噻喃-4-基)环己烷-1,3-二酮	¹ H NMR (400 MHz, CD ₃ OD) δ 8.10 (s, 1H), 3.70 (t, <i>J</i> = 5.5 Hz, 2H), 3.50 (t, <i>J</i> = 5.7 Hz, 2H), 2.92 (d, <i>J</i> = 29.8 Hz, 5H), 2.69 – 2.42 (m, 8H), 2.44 – 2.12 (m, 4H), 2.05 – 1.72 (m, 3H), 1.52 – 1.07 (m, 6H); MS: 396.1 [M+1].
39		2-(((2-(4-(2-羟乙基)哌嗪-1-基)乙基)氨基)亚甲基)-5-(1H-吡啶-3-基)环己烷-1,3-二酮	¹ H NMR (400 MHz, CD ₃ OD) δ 8.23 (s, 1H), 7.56 (d, <i>J</i> = 7.8 Hz, 1H), 7.32 (d, <i>J</i> = 8.1 Hz, 1H), 7.08 (t, <i>J</i> = 7.1 Hz, 1H), 7.03 – 6.94 (m, 2H), 3.78 – 3.61 (m, 3H), 3.57 (t, <i>J</i> = 5.7 Hz, 2H), 2.95 – 2.49 (m, 16H); MS: 411.4 [M+1].

[0346]

[0347]

40		2-(((2-(4-(2-羟乙基)吡咯-1-基)乙基)氨基)亚甲基)-5-(4-(羟基苯基)环己烷-1,3-二酮	¹ H NMR (400 MHz, CD ₃ OD) δ 8.27 (s, 1H), 7.13 (d, <i>J</i> = 8.5 Hz, 2H), 6.77 (d, <i>J</i> = 8.6 Hz, 2H), 3.81 (t, <i>J</i> = 5.6 Hz, 2H), 3.64 (t, <i>J</i> = 5.7 Hz, 2H), 3.14 – 2.57 (m, 16H)
41		2-(((2-(4-(2-羟乙基)吡咯-1-基)乙基)氨基)亚甲基)-5-(3-(2-(2-甲氧基乙氧基)乙氧基)苯基)环己烷-1,3-二酮	¹ H NMR (400 MHz, CD ₃ OD) δ 8.26 (s, 1H), 7.23-7.17 (m, 2H), 6.97 (d, <i>J</i> = 8.0 Hz, 1H), 6.92 (t, <i>J</i> = 7.2 Hz, 1H), 4.16 (t, <i>J</i> = 4.4 Hz, 2H), 3.84 (q, <i>J</i> = 4.8 Hz, 4H), 3.73-3.61 (m, 5H), 3.54-3.52 (m, 2H), 3.32-3.26 (m, 9H), 2.93-2.61 (m, 10H); MS: 490.2 [M+1].
42		2-(((2-(4-(2-羟乙基)吡咯-1-基)乙基)氨基)亚甲基)-5-(2-(2-甲氧基乙氧基)苯基)环己烷-1,3-二酮	¹ H NMR (400 MHz, CD ₃ OD) δ 8.27 (s, 1H), 7.24-7.19 (m, 2H), 7.00-6.92 (m, 2H), 4.17 (t, <i>J</i> = 4.0 Hz, 2H), 3.78-3.70 (m, 5H), 3.63 (t, <i>J</i> = 5.2 Hz, 2H), 3.32 (s, 3H), 2.88-2.64 (m, 16H); MS: 446.9 [M+1].
43		5-(呋喃-2-基)-2-(((2-(4-(2-羟乙基)吡咯-1-基)乙基)氨基)亚甲基)环己烷-1,3-二酮	¹ H NMR (400 MHz, CD ₃ OD) δ 8.20 (s, 1H), 7.38 (s, 1H), 7.29 (s, 1H), 6.08 (d, <i>J</i> = 3.2 Hz, 1H), 3.76 (t, <i>J</i> = 6.4 Hz, 2H), 3.58 (t, <i>J</i> = 6.4 Hz, 2H), 3.50-3.44 (m, 1H), 2.94-2.62 (m, 16H); MS: 362.5 [M+1].
44		2-(((2-(4-(2-羟乙基)吡咯-1-基)乙基)氨基)亚甲基)-5-(4-(2-甲氧基乙氧基)苯基)环己烷-1,3-二酮	¹ H NMR (400 MHz, CD ₃ OD) δ 8.23 (s, 1H), 7.19 (t, <i>J</i> = 8.4 Hz, 2H), 6.89 (t, <i>J</i> = 8.8 Hz, 2H), 4.09-4.06 (m, 2H), 3.60 (t, <i>J</i> = 5.6 Hz, 2H), 3.40 (s, 3H), 3.30-3.27 (m, 1H), 3.07 (br, 4H), 2.99 (t, <i>J</i> = 5.6 Hz, 2H), 2.82-2.61 (m, 16H); MS: 446.6 [M+1].
45		2-(((2-(4-(2-羟乙基)吡咯-1-基)乙基)氨基)亚甲基)-5-(4-(2-甲氧基乙氧基)乙氧基)苯基)环己烷-1,3-二酮	¹ H NMR (400 MHz, CD ₃ OD) δ 8.27 (s, 1H), 7.23 (t, <i>J</i> = 8.8 Hz, 2H), 6.93 (t, <i>J</i> = 8.8 Hz, 2H), 4.14-4.12 (m, 2H), 3.86-3.83 (m, 2H), 3.73-3.70 (m, 4H), 3.39 (s, 3H), 3.33-3.27 (m, 1H), 3.07 (br, 4H), 2.99 (t, <i>J</i> = 5.6 Hz, 2H), 2.83-2.56 (m, 16H); MS: 490.6 [M+1].
46		5-(2,4-二甲氧基苯基)-2-(((2-(4-(2-羟乙基)吡咯-1-基)乙基)氨基)亚甲基)环己烷-1,3-二酮	¹ H NMR (400 MHz, CD ₃ OD) δ 8.12 (d, <i>J</i> = 14.6 Hz, 1H), 7.08 (d, <i>J</i> = 8.4 Hz, 1H), 6.54 (d, <i>J</i> = 2.3 Hz, 1H), 6.48 (dd, <i>J</i> = 8.4, 2.3 Hz, 1H), 4.77 (s, 1H), 3.78 (s, 3H), 3.74 (s, 3H), 3.64 – 3.52 (m, 4H), 3.52 – 3.41 (m, 1H), 2.74 – 2.52 (m, 12H), 2.49 – 2.37 (m, 4H); MS: 432.5 [M+1].
47		2-(((2-(4-(2-羟乙基)吡咯-1-基)乙基)氨基)亚甲基)-5-苯基环己烷-1,3-二酮	¹ H NMR (400 MHz, CD ₃ OD) δ 8.21 (s, 1H), 7.35 (d, <i>J</i> = 7.3 Hz, 2H), 7.26 (t, <i>J</i> = 7.5 Hz, 2H), 7.18 (t, <i>J</i> = 7.3 Hz, 1H), 6.46 (d, <i>J</i> = 15.9 Hz, 1H), 6.23 (dd, <i>J</i> = 15.9, 6.8 Hz, 1H), 3.74 – 3.65 (m, 3H), 3.63 – 3.53 (m, 2H), 3.04 – 2.90 (m, 1H), 2.88 (s, 1H), 2.77 – 2.39 (m, 14H); MS: 398.3 [M+1].

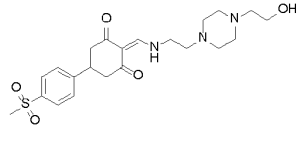
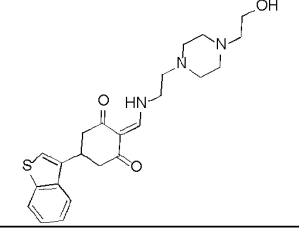
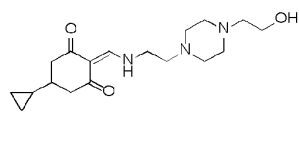
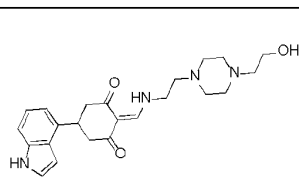
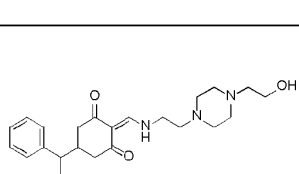
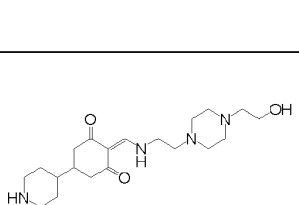
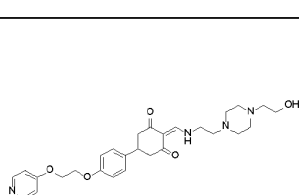
[0348]

48		2-(((2-(4-(2-羟乙基)哌嗪-1-基)乙基)氨基)亚甲基)-5-(4-(三氟甲基)苯基)环己烷-1,3-二酮	¹ H NMR (400 MHz, CD ₃ OD) δ 9.29 (s, 1H), 7.66 (d, <i>J</i> =8.0Hz, 2H), 7.54 (d, <i>J</i> =8.0Hz, 2H), 3.73 (t, <i>J</i> =5.6Hz, 2H), 3.64 (t, <i>J</i> =5.6Hz, 2H), 3.55-3.47 (m, 1H), 2.91-2.83 (m, 16H); MS: 440.6 [M+1].
49		5-(4-氟苯基)-2-(((2-(4-(2-羟乙基)哌嗪-1-基)乙基)氨基)亚甲基)环己烷-1,3-二酮	¹ H NMR (400 MHz, CD ₃ OD) δ 8.28 (s, 1H), 7.36-7.32 (m, 2H), 7.10-7.01 (m, 2H), 3.75 (t, <i>J</i> =5.6Hz, 2H), 3.64 (t, <i>J</i> =5.6Hz, 2H), 3.44-3.36 (m, 1H), 2.87-2.65 (m, 16H); MS: 390.5 [M+1].
50		2-(((2-(4-(2-羟乙基)哌嗪-1-基)乙基)氨基)亚甲基)-5-(4-(三氟甲氧基)苯基)环己烷-1,3-二酮	¹ H NMR (400 MHz, CD ₃ OD) δ 8.24 (s, 1H), 7.39 (d, <i>J</i> = 8.6 Hz, 2H), 7.22 (d, <i>J</i> = 8.1 Hz, 2H), 3.67 (t, <i>J</i> = 6.0 Hz, 2H), 3.59 (t, <i>J</i> = 5.8 Hz, 2H), 3.49 - 3.33 (m, 1H), 2.93 - 2.39 (m, 16H); MS: 456.2 [M+1].
51		2-(((2-(4-(2-羟乙基)哌嗪-1-基)乙基)氨基)亚甲基)-5-(4-(氰基)苯基)环己烷-1,3-二酮	¹ H NMR (400 MHz, CD ₃ OD) δ 8.28 (s, 1H), 7.72 (d, <i>J</i> = 8.3 Hz, 2H), 7.53 (d, <i>J</i> = 8.2 Hz, 2H), 3.75 (t, <i>J</i> = 5.8 Hz, 2H), 3.63 (t, <i>J</i> = 5.8 Hz, 2H), 3.56 - 3.40 (m, 1H), 3.00 - 2.49 (m, 16H); MS: 397.2 [M+1].
52		2-(((2-(4-(2-羟乙基)哌嗪-1-基)乙基)氨基)亚甲基)-5-(4-(三氟甲氧基)苯基)环己烷-1,3-二酮	¹ H NMR (400 MHz, CD ₃ OD) δ 8.742 (d, <i>J</i> = 6.0 Hz, 2H), 8.253 (s, 1H), 7.396 (d, <i>J</i> = 6.0 Hz, 2H), 3.712 (t, <i>J</i> = 6.0 Hz, 2H), 3.606 (d, <i>J</i> = 5.6 Hz, 2H), 3.419-3.496 (m, 1H), 2.873-2.610 (m, 16H); MS: 373.2 [M+1].
53		2-(((2-(4-(2-羟乙基)哌嗪-1-基)乙基)氨基)亚甲基)-5-(吡啶-2-基)环己烷-1,3-二酮	¹ H NMR (400 MHz, CD ₃ OD) δ 8.49 (d, <i>J</i> = 4.0 Hz, 1H), 8.25(s, 1H), 7.80-7.76 (m, 1H), 7.37 (d, <i>J</i> = 7.2Hz, 1H), 7.29-7.26(m, 1H), 3.68 (t, <i>J</i> = 6.0 Hz, 2H), 3.60 (t, <i>J</i> = 6.4 Hz, 2H), 3.56-3.49 (m, 1H), 2.93-2.82 (m, 2H), 2.71-2.54 (m, 14H); MS: 373.5 [M+1].
54		2-(((2-(4-(2-羟乙基)哌嗪-1-基)乙基)氨基)亚甲基)-5-(4-甲氧基萘-1-基)环己烷-1,3-二酮	¹ H NMR (400 MHz, CD ₃ OD) δ 8.27 (d, <i>J</i> = 6.9 Hz, 2H), 8.02 (d, <i>J</i> = 8.5 Hz, 1H), 7.54 (t, <i>J</i> = 7.0 Hz, 1H), 7.49 - 7.40 (m, 1H), 7.31 (d, <i>J</i> = 8.0 Hz, 1H), 6.86 (d, <i>J</i> = 8.1 Hz, 1H), 4.19 - 4.05 (m, 1H), 3.98 (s, 3H), 3.67 (t, <i>J</i> = 6.0 Hz, 2H), 3.64 - 3.53 (m, 2H), 2.92 - 2.47 (m, 16H); MS: 452.3 [M+1].
55		2-(((2-(4-(2-羟乙基)哌嗪-1-基)乙基)氨基)亚甲基)-5-(1-甲基-1H-吡咯-2-基)环己烷-1,3-二酮	¹ H NMR (400 MHz, CD ₃ OD) δ 8.22 (s, 1H), 6.77 - 6.27 (m, 1H), 6.05 - 5.83 (m, 1H), 5.85 - 5.76 (m, 1H), 3.74 (t, <i>J</i> = 5.7 Hz, 2H), 3.64 - 3.53 (m, 5H), 3.50 - 3.37 (m, 1H), 3.06 - 2.45 (m, 16H); MS: 375.3 [M+1].
56		5-(2,3-二氢苯并[b][1,4]二氧杂环己烯-5-基)-2-(((2-(4-(2-羟乙基)哌嗪-1-基)乙基)氨基)亚甲基)环己烷-1,3-二酮	¹ H NMR (400 MHz, CD ₃ OD) δ 8.24 (s, 1H), 6.83 - 6.51 (m, 3H), 4.24 (dd, <i>J</i> = 16.6, 5.0 Hz, 4H), 3.73 (t, <i>J</i> = 5.8 Hz, 2H), 3.64 - 3.47 (m, 3H), 3.05 -

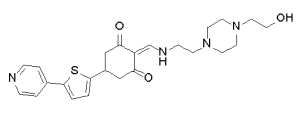
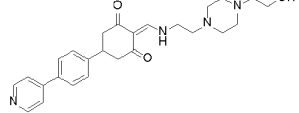
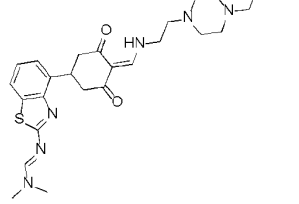
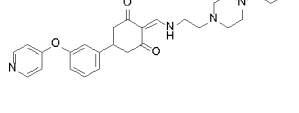
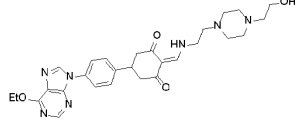
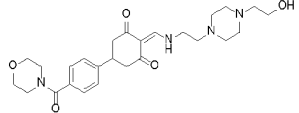
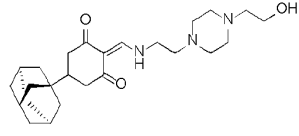
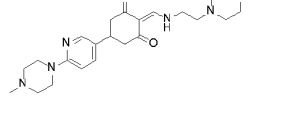
[0349]

		亚甲基)环己烷-1,3-二酮	2.32 (m, 16H); MS: 430.2 [M+1].
57		2-(((2-(4-(2-羟乙基)哌嗪-1-基)乙基)氨基)亚甲基)-5-(噻唑-2-基)环己烷-1,3-二酮	¹ H NMR (400 MHz, CD ₃ OD) δ 8.26 (s, 1H), 7.74 (d, <i>J</i> = 3.3 Hz, 1H), 7.53 (d, <i>J</i> = 3.3 Hz, 1H), 3.97 – 3.83 (m, 2H), 3.74 (t, <i>J</i> = 5.9 Hz, 2H), 3.62 (t, <i>J</i> = 5.8 Hz, 2H), 2.95 (dd, <i>J</i> = 14.4, 6.0 Hz, 4H), 2.80 – 2.54 (m, 12H); MS: 379.3 [M+1].
58		2-(((2-(4-(2-羟乙基)哌嗪-1-基)乙基)氨基)亚甲基)-5-(异喹啉-5-基)环己烷-1,3-二酮	¹ H NMR (400 MHz, CD ₃ OD) δ 9.25 (s, 1H), 8.49 (d, <i>J</i> = 6.1 Hz, 1H), 8.31 (s, 1H), 8.06 (d, <i>J</i> = 6.2 Hz, 1H), 8.03 (d, <i>J</i> = 8.1 Hz, 1H), 7.77 (d, <i>J</i> = 7.2 Hz, 1H), 7.72 – 7.64 (m, 1H), 4.30 – 4.19 (m, 1H), 3.72 (t, <i>J</i> = 5.9 Hz, 2H), 3.64 (t, <i>J</i> = 5.8 Hz, 2H), 2.98 – 2.58 (m, 16H); MS: 423.4 [M+1].
59		2-(((2-(4-(2-羟乙基)哌嗪-1-基)乙基)氨基)亚甲基)-5-(1H-咪唑-4-基)环己烷-1,3-二酮	¹ H NMR (400 MHz, CDCl ₃) δ 11.39 – 10.87 (m, 1H), 9.33 – 8.87 (m, 1H), 8.15 (d, <i>J</i> = 14.4 Hz, 1H), 7.60 (s, 1H), 6.80 (s, 1H), 3.61 (t, <i>J</i> = 5.3 Hz, 2H), 3.55–3.47 (m, 3H), 3.05 – 2.30 (m, 17H); MS: 362.3 [M+1].
61		5-(苝-9-基)-2-(((2-(4-(2-羟乙基)哌嗪-1-基)乙基)氨基)亚甲基)环己烷-1,3-二酮	¹ H NMR (400 MHz, CD ₃ OD) δ 8.54 – 8.42 (m, 3H), 8.40 (s, 1H), 8.06 (d, <i>J</i> = 8.0 Hz, 2H), 7.57 – 7.39 (m, 4H), 5.09 – 4.94 (m, 1H), 3.90 – 3.59 (m, 6H), 2.73 – 2.52 (m, 14H); MS: 472.2 [M+1].
62		2-(((2-(4-(2-羟乙基)哌嗪-1-基)乙基)氨基)亚甲基)-5-(喹啉-4-基)环己烷-1,3-二酮	¹ H NMR (400 MHz, CD ₃ OD) δ 8.80 (d, <i>J</i> = 4.7 Hz, 1H), 8.30 (s, 1H), 8.23 (d, <i>J</i> = 8.4 Hz, 1H), 8.06 (d, <i>J</i> = 8.4 Hz, 1H), 7.78 (d, <i>J</i> = 7.3 Hz, 1H), 7.73 – 7.62 (m, 1H), 7.49 (d, <i>J</i> = 4.8 Hz, 1H), 4.34 (s, 1H), 3.72 (t, <i>J</i> = 5.8 Hz, 2H), 3.63 (t, <i>J</i> = 5.7 Hz, 2H), 3.01 – 2.51 (m, 16H); MS: 423.3 [M+1].
63		2-(((2-(4-(2-羟乙基)哌嗪-1-基)乙基)氨基)亚甲基)-5-(戊-3-基)环己烷-1,3-二酮	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.17 – 10.13 (m, 1H), 8.06 (d, <i>J</i> = 14.6 Hz, 1H), 4.82 (s, 1H), 3.74 – 3.46 (m, 5H), 3.38 (dd, <i>J</i> = 14.0, 7.0 Hz, 2H), 2.74 (s, 5H), 2.57 (s, 3H), 2.36 – 2.09 (m, 4H), 2.01 (s, 1H), 1.91 (s, 1H), 1.46 – 1.13 (m, 4H), 1.05 (t, <i>J</i> = 21.2 Hz, 1H), 0.83 (t, <i>J</i> = 7.3 Hz, 6H); MS: 366.2 [M+1].
64		2-(((2-(4-(2-羟乙基)哌嗪-1-基)乙基)氨基)亚甲基)-5-(四氢-2H-吡喃-4-基)环己烷-1,3-二酮	¹ H NMR (400 MHz, CD ₃ OD) δ 8.18 (s, 1H), 3.95 (dd, <i>J</i> = 11.1, 3.8 Hz, 2H), 3.69 (t, <i>J</i> = 5.9 Hz, 2H), 3.57 (t, <i>J</i> = 5.8 Hz, 2H), 3.37 (t, <i>J</i> = 11.0 Hz, 2H), 2.90 – 2.43 (m, 13H), 2.41 – 2.15 (m, 2H), 1.89 – 1.78 (m, 1H), 1.65 (d, <i>J</i> = 12.2 Hz, 2H), 1.59 – 1.10 (m, 4H); MS: 380.2 [M+1].

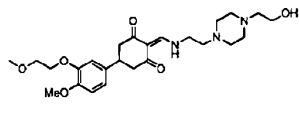
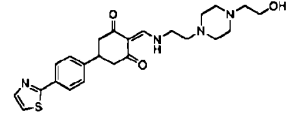
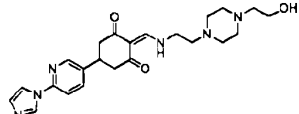
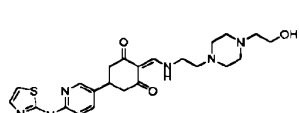
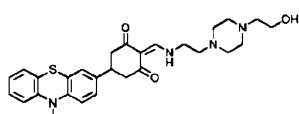
[0350]

65		2-(((2-(4-(2-羟乙基)哌嗪-1-基)乙基)氨基)亚甲基)-5-(4-(甲基磺酰基)苯基)环己烷-1,3-二酮	^1H NMR (400 MHz, CD_3OD) δ 8.29 (s, 1H), 7.95 (d, $J = 8.4$ Hz, 2H), 7.62 (d, $J = 8.4$ Hz, 2H), 3.71 (t, $J = 6.1$ Hz, 2H), 3.64 (t, $J = 5.9$ Hz, 2H), 3.61 – 3.47 (m, 1H), 3.14 (s, 3H), 3.00 – 2.44 (m, 16H); MS: 450.2 [M+1].
66		5-(苯并[b]噻吩-3-基)-2-(((2-(4-(2-羟乙基)哌嗪-1-基)乙基)氨基)亚甲基)环己烷-1,3-二酮	^1H NMR (400 MHz, CD_3OD) δ 8.27 (s, 1H), 7.95 – 7.78 (m, 2H), 7.37 (dt, $J = 19.3, 7.1$ Hz, 2H), 7.30 (s, 1H), 3.89 – 3.79 (m, 1H), 3.77 (t, $J = 5.6$ Hz, 2H), 3.61 (t, $J = 5.8$ Hz, 2H), 3.09 – 2.57 (m, 16H); MS: 428.2 [M+1].
67		5-环丙基-2-(((2-(4-(2-羟乙基)哌嗪-1-基)乙基)氨基)亚甲基)环己烷-1,3-二酮	^1H NMR (400 MHz, CD_3OD) δ 8.19 (s, 1H), 3.70 (t, $J = 5.9$ Hz, 2H), 3.57 (t, $J = 5.8$ Hz, 2H), 2.76 – 2.51 (m, 13H), 2.49 – 2.30 (m, 2H), 1.31 – 1.18 (m, 2H), 0.77 – 0.59 (m, 1H), 0.47 (dd, $J = 5.1, 2.7$ Hz, 2H), 0.14 (d, $J = 4.9$ Hz, 2H); MS: 336.2 [M+1].
68		2-(((2-(4-(2-羟乙基)哌嗪-1-基)乙基)氨基)亚甲基)-5-(1H-吡啶-4-基)环己烷-1,3-二酮	^1H NMR (400 MHz, CD_3OD) δ 8.26 (s, 1H), 7.25 (dd, $J = 14.5, 5.7$ Hz, 2H), 7.05 (t, $J = 7.7$ Hz, 1H), 6.87 (d, $J = 7.2$ Hz, 1H), 6.52 (d, $J = 2.5$ Hz, 1H), 3.85 – 3.74 (m, 1H), 3.71 (t, $J = 5.8$ Hz, 2H), 3.59 (t, $J = 5.8$ Hz, 2H), 3.05 – 2.38 (m, 16H); MS: 411.4 [M+1].
69		2-(((2-(4-(2-羟乙基)哌嗪-1-基)乙基)氨基)亚甲基)-5-(1-苯基乙基)环己烷-1,3-二酮	^1H NMR (400 MHz, CD_3OD) δ 8.16 (d, $J = 10.5$ Hz, 1H), 7.28 (t, $J = 7.4$ Hz, 2H), 7.18 (t, $J = 8.3$ Hz, 3H), 3.78 (t, $J = 5.4$ Hz, 2H), 3.57 (t, $J = 5.6$ Hz, 2H), 3.15 – 2.85 (m, 5H), 2.82 – 2.52 (m, 8H), 2.46 – 1.90 (m, 5H), 1.29 (d, $J = 7.0$ Hz, 3H); MS: 400.2 [M+1].
70		2-(((2-(4-(2-羟乙基)哌嗪-1-基)乙基)氨基)亚甲基)-5-(哌啶-4-基)环己烷-1,3-二酮盐酸盐	^1H NMR (400 MHz, D_2O) δ 8.09 (s, 1H), 3.88 – 3.74 (m, 3H), 3.68 – 3.26 (m, 15H), 2.91 – 2.74 (m, 2H), 2.45 (dd, $J = 17.1, 3.9$ Hz, 2H), 2.27 (s, 2H), 2.02 – 1.75 (m, 3H), 1.59 – 1.44 (m, 1H), 1.43 – 1.21 (m, 2H); MS: 379.2 [M+1].
71		2-(((2-(4-(2-羟乙基)哌嗪-1-基)乙基)氨基)亚甲基)-5-(4-(2-(吡啶-4-基氧基)乙氧基)苯基)环己烷-1,3-二酮	^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 10.92 (d, $J = 14.7$ Hz, 1H), 8.38 (d, $J = 6.2$ Hz, 2H), 8.11 (d, $J = 14.6$ Hz, 1H), 7.21 (d, $J = 8.7$ Hz, 2H), 7.00 (dd, $J = 4.8, 1.5$ Hz, 2H), 6.91 (d, $J = 8.7$ Hz, 2H), 4.69 (s, 1H), 4.38 (dd, $J = 5.6, 2.9$ Hz, 2H), 4.29 (dd, $J = 5.5, 3.1$ Hz, 2H), 3.55 (d, $J = 5.4$ Hz, 4H), 3.28 – 2.31 (m, 17H); MS: 510.2 [M+1].

[0351]

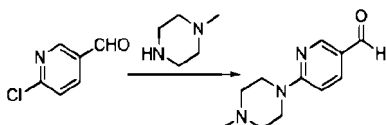
72		2-(((2-(4-(2-羟乙基)哌嗪-1-基)乙基)氨基)亚甲基)-5-(5-(吡啶-4-基)噻吩-2-基)环己烷-1,3-二酮	^1H NMR (400 MHz, CD_3OD) δ 8.47 (dd, $J = 4.8, 1.5$ Hz, 2H), 8.23 (s, 1H), 7.61 (dd, $J = 4.7, 1.6$ Hz, 2H), 7.55 (d, $J = 3.8$ Hz, 1H), 7.00 (d, $J = 3.1$ Hz, 1H), 3.83 – 3.69 (m, 1H), 3.66 (t, $J = 6.0$ Hz, 2H), 3.59 (t, $J = 5.8$ Hz, 2H), 3.00 – 2.71 (m, 4H), 2.66 – 2.42 (m, 12H); MS: 455.3 [M+1].
73		2-(((2-(4-(2-羟乙基)哌嗪-1-基)乙基)氨基)亚甲基)-5-(4-(吡啶-4-基)苯基)环己烷-1,3-二酮	^1H NMR (400 MHz, CD_3OD) δ 8.55 (dd, $J = 4.7, 1.6$ Hz, 2H), 8.25 (s, 1H), 7.77 – 7.66 (m, 4H), 7.46 (d, $J = 8.3$ Hz, 2H), 3.67 (t, $J = 6.0$ Hz, 2H), 3.60 (t, $J = 6.0$ Hz, 2H), 3.45 (m, 1H), 2.67 (m, 16H); MS: 449.5 [M+1].
74		N'-(4-(4-(((2-(4-(2-羟乙基)哌嗪-1-基)乙基)氨基)亚甲基)-3,5-二氧代环己基)苯并[d]基)-N,N-二甲基甲脒	^1H NMR (400 MHz, CD_3OD) δ 8.35 (s, 1H), 8.26 (s, 1H), 7.64 – 7.52 (m, 1H), 7.21 (d, $J = 6.8$ Hz, 1H), 7.15 (t, $J = 7.7$ Hz, 1H), 4.06 (t, $J = 11.6$ Hz, 1H), 3.74 (t, $J = 5.7$ Hz, 2H), 3.61 (t, $J = 5.6$ Hz, 2H), 3.19 (s, 3H), 3.11 (s, 3H), 3.09 – 2.54 (m, 16H); MS: 499.3 [M+1].
75		2-(((2-(4-(2-羟乙基)哌嗪-1-基)乙基)氨基)亚甲基)-5-(3-(吡啶-4-基氧基)苯基)环己烷-1,3-二酮	^1H NMR (400 MHz, CD_3OD) δ 8.41 (dd, $J = 5.0, 1.4$ Hz, 2H), 8.26 (s, 1H), 7.47 (t, $J = 7.9$ Hz, 1H), 7.28 (d, $J = 7.8$ Hz, 1H), 7.14 (s, 1H), 7.04 (dd, $J = 8.1, 1.5$ Hz, 1H), 6.95 (dd, $J = 4.9, 1.5$ Hz, 2H), 3.70 (t, $J = 6.0$ Hz, 2H), 3.62 (t, $J = 5.9$ Hz, 2H), 3.52 – 3.39 (m, 1H), 2.91 – 2.47 (m, 16H); MS: 465.4 [M+1].
76		5-(4-(6-乙氧基-9H-嘌呤-9-基)苯基)-2-(((2-(4-(2-羟乙基)哌嗪-1-基)乙基)氨基)亚甲基)环己烷-1,3-二酮	^1H NMR (400 MHz, CD_3OD) δ 8.48 (s, 1H), 8.43 (s, 1H), 8.18 (s, 1H), 7.69 (d, $J = 8.5$ Hz, 2H), 7.47 (d, $J = 8.5$ Hz, 2H), 4.60 (q, $J = 7.1$ Hz, 2H), 3.67 (t, $J = 5.6$ Hz, 2H), 3.53 (t, $J = 5.7$ Hz, 2H), 3.46 – 3.37 (m, 1H), 2.89 – 2.52 (m, 16H), 1.42 (t, $J = 7.1$ Hz, 3H); MS: 534.3 [M+1].
77		2-(((2-(4-(2-羟乙基)哌嗪-1-基)乙基)氨基)亚甲基)-5-(4-(吗啉-4-羰基)苯基)环己烷-1,3-二酮	^1H NMR (400 MHz, CD_3OD) δ 8.29 (s, 1H), 7.45 (s, 4H), 3.84 – 3.38 (m, 13H), 2.93 – 2.50 (m, 16H); MS: 485.3 [M+1].
78		5-金刚烷-1-基)-2-(((2-(4-(2-羟乙基)哌嗪-1-基)乙基)氨基)亚甲基)环己烷-1,3-二酮	^1H NMR (400 MHz, CD_3OD) δ 8.21 (s, 1H), 3.73 (t, $J = 5.9$ Hz, 2H), 3.61 (t, $J = 5.8$ Hz, 2H), 3.37 (d, $J = 5.3$ Hz, 2H), 2.84 – 2.47 (m, 12H), 2.40 – 2.19 (m, 2H), 2.09 – 1.88 (m, 4H), 1.86 – 1.54 (m, 12H); MS: 430.2 [M+1].
79		2-(((2-(4-(2-羟乙基)哌嗪-1-基)乙基)氨基)亚甲基)-5-(6-(4-甲基哌嗪-1-基)吡啶-3-基)环己烷	^1H NMR (400 MHz, CD_3OD) δ 8.24 (s, 1H), 8.02 (d, $J = 2.2$ Hz, 1H), 7.55 (dd, $J = 8.8, 2.4$ Hz, 1H), 6.82 (d, $J = 8.9$ Hz, 1H), 3.68 (t, $J = 6.0$ Hz, 2H), 3.60 (t, $J = 5.8$ Hz, 2H), 3.53 – 3.49

[0352]

		-1,3-二酮	(m, 4H), 2.76 – 2.50 (m, 21H), 2.34 (s, 3H); MS: 471.3 [M+1].
80		2-(((2-(4-(2-羟乙基)哌嗪-1-基)乙基)氨基)亚甲基)-5-(4-甲氧基-3-(2-甲氧基乙氧基)苯基)环己烷-1,3-二酮	¹ H NMR (400 MHz, CD ₃ OD) δ 8.24(s, 1H), 6.92-6.83(m, 3H), 4.13-4.11(m, 2H), 3.82(s, 3H), 3.76-3.72(m, 4H), 3.60(t, J=5.6Hz, 2H), 3.42(s, 3H), 2.87-2.61(m, 17H); MS: 476.2 [M+1].
81		2-(((2-(4-(2-羟乙基)哌嗪-1-基)乙基)氨基)亚甲基)-5-(4-(噻唑-2-基)苯基)环己烷-1,3-二酮	¹ H NMR (400 MHz, CD ₃ OD) δ 8.26 (s, 1H), 7.92 (d, J = 8.3 Hz, 2H), 7.85 (d, J = 3.2 Hz, 1H), 7.59 (d, J = 3.3 Hz, 1H), 7.44 (d, J = 8.2 Hz, 2H), 3.68 (t, J = 6.2 Hz, 2H), 3.61 (t, J = 9.1 Hz, 2H), 3.45 (m, 2H), 2.62 (m, 15H).
82		5-(6-(1H-咪唑-1-基)吡啶-3-基)-2-(((2-(4-(2-羟乙基)哌嗪-1-基)乙基)氨基)亚甲基)环己烷-1,3-二酮	¹ H NMR (400 MHz, CD ₃ OD) δ 8.50 (s, 1H), 8.44 (d, J = 1.8 Hz, 1H), 8.26 (s, 1H), 7.94 (dd, J = 8.5, 2.1 Hz, 1H), 7.87 (s, 1H), 7.66 (d, J = 8.4 Hz, 1H), 7.14 (s, 1H), 3.67 (t, J = 6.0 Hz, 2H), 3.61 (t, J = 5.9 Hz, 2H), 3.52 (m, 1H), 2.94 – 2.67 (m, 5H), 2.66 – 2.43 (m, 11H).
83		2-(((2-(4-(2-羟乙基)哌嗪-1-基)乙基)氨基)亚甲基)-5-(6-(噻唑-2-基氨基)吡啶-3-基)环己烷-1,3-二酮	¹ H NMR (400 MHz, CD ₃ OD) δ 8.28 – 8.20 (m, 2H), 7.66 (dd, J = 8.6, 2.4 Hz, 1H), 7.31 (d, J = 3.7 Hz, 1H), 7.00 (d, J = 8.6 Hz, 1H), 6.89 (d, J = 3.7 Hz, 1H), 3.82 – 3.77 (m, 2H), 3.60-3.63 (m, 2H), 3.39 (m, 1H), 3.14 – 2.89 (m, 6H), 2.87 – 2.61 (m, 10H).
84		2-(((2-(4-(2-羟乙基)哌嗪-1-基)乙基)氨基)亚甲基)-5-(10-(2-甲氧基乙基)-10H-吩噻嗪-3-基)环己烷-1,3-二酮	¹ H NMR (400 MHz, CD ₃ OD) δ 8.24 (s, 1H), 7.16 (m, 1H), 7.10 (d, J = 7.9 Hz, 2H), 7.05 (s, 1H), 7.00 – 6.88 (m, 3H), 4.08 (t, J = 5.7 Hz, 2H), 3.72 (q, J = 5.8 Hz, 4H), 3.60 (t, J = 5.7 Hz, 2H), 3.32 (s, 5H), 2.83 – 2.49 (m, 15H).

[0353] 实施例13-1:中间体13-1:(6-(4-甲基哌嗪-1-基)吡啶)的合成

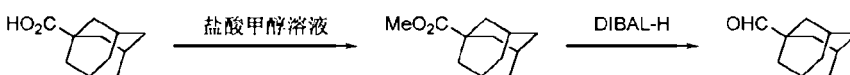
[0354]



[0355] 将6-氯-3-吡啶甲醛(5g, 35.32mmol)和N-甲基哌嗪(15.68L, 141.28mmol)的DMF溶液加热至100℃反应1小时。反应完毕冷却至室温,倒入冰水中,EA萃取,合并的有机相依次用水和饱和食盐水洗涤,干燥,浓缩。粗品经柱层析分离得目标化合物6.32g,产率87%。

[0356] 实施例13-2:中间体13-2:1-金刚烷甲醛的合成

[0357]



[0358] 步骤1:1-金刚烷甲酸甲酯的合成

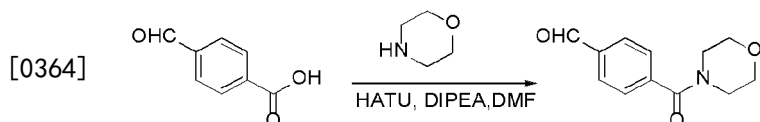
[0359] 1-金刚烷甲酸(5.00g, 27.74mmol)和浓硫酸(0.5ml)溶解于50mL甲醇中,回流反应过夜。

[0360] 反应完毕,将反应混合物冷却至室温,倒入冰水中,DCM萃取,有机相用饱和碳酸氢钠、水和盐水洗涤,硫酸钠干燥,浓缩得到目标化合物粗品4.8g,产率89%。

[0361] 步骤2:1-金刚烷甲醛的合成

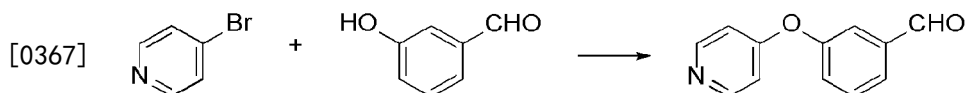
[0362] 氮气保护下,将1-金刚烷甲酸甲酯(3g,15.5mmol)溶于80ml甲苯,降温至-78℃,滴加二异丁基氢化铝(1.5M的甲苯溶液,10.3mL),滴毕升至室温反应1小时。缓慢滴加4N盐酸淬灭反应,倒入冰水中,EA萃取。合并的有机相用饱和食盐水洗涤,干燥,浓缩。粗品经柱层析分离得到目标化合物2.1g,产率82%。

[0363] 实施例13-3:中间体13-3-4-(吗啉-4-羰基)苯甲醛的合成



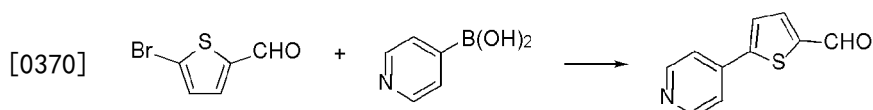
[0365] 将4-甲酰基苯甲酸(5.0g,33.3mmol)溶于无水DMF(10mL)中,依次加入2-(7-偶氮苯并三氮唑)-N,N',N'-四甲基脲六氟磷酸酯(HATU)(17.12g,45mmol)和DIPEA(6.45g,50mmol),室温反应30分钟,加入吗啉(3.92g,45mmol),上述混合物室温继续反应1小时。反应完毕倒入冰水中,EA萃取,有机相用水洗涤,硫酸钠干燥,浓缩,粗品经柱层析分离得目标化合物5.0g,产率68%。

[0366] 实施例13-4:中间体13-4-3-(吡啶-4-基氧基)苯甲醛的合成



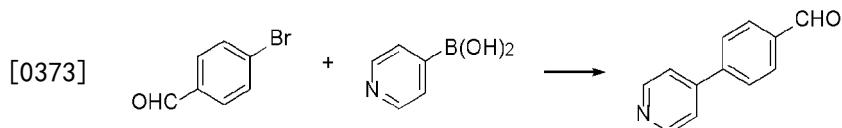
[0368] 将4-溴吡啶(3.1g,40mmol)、3-羟基苯甲醛(40mmol)和碳酸铯(26.1g,80mmol)溶于80mLDMF中,100℃反应过夜。反应完毕冷却至室温,倒入冰水中,EA萃取,有机相依次用水和食盐水洗涤,干燥,浓缩。粗品经柱层析分离得目标化合物1.99g,产率25%。

[0369] 实施例13-5:中间体13-5-5-(吡啶-4-基)噻吩-2-甲醛的合成



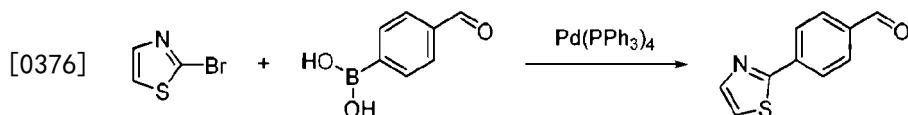
[0371] 氮气保护下,将5-溴-2-噻吩甲醛(3.80g,20.0mmol)、4-[吡啶硼酸(3.0g,24.0mmol)、碳酸钠(3.18g,30.0mmol)、醋酸钯(224.0mg,1.0mmol)和三苯基膦(520.0mg,2.0mmol)溶解于二氧六环和水的混合溶剂(v/v=3:1;80mL)中,回流反应过夜。反应完毕,将反应混合物冷却至室温并倒入冰水中,EA萃取,合并的有机相用水洗涤,硫酸钠干燥,粗品经柱层析分离纯化得目标化合物3.2g,产率85%。

[0372] 实施例13-6:中间体13-6-4-(吡啶-4-基)苯甲醛的合成



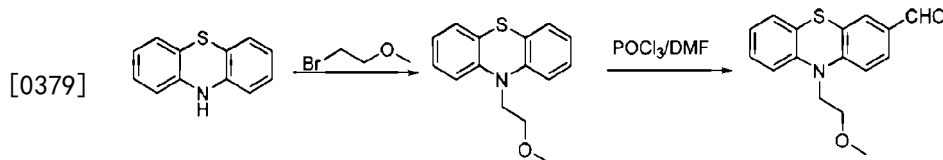
[0374] 氮气保护下,将4-溴苯甲醛(2.78g,15mmol)、4-吡啶硼酸(2.46g,20mmol)、碳酸钠(3.18g,30mmol)和四(三苯基膦)钯(722mg,0.62mmol)溶于二氧六环(40mL)和水(10mL)中,混合物回流反应过夜。反应完毕冷却至室温并倒入冰水中,EA萃取,有机相用水洗涤,干燥,浓缩。粗品经柱层析分离得目标化合物2.23g,产率81%。

[0375] 实施例13-7:中间体13-7:化合物4-(噻唑-2-基)苯甲醛的合成



[0377] 在氮气保护下,将2-溴噻唑(3.0g,18.3mmol)、4-甲醛基苯硼酸(3.3g,22mmol)、碳酸钠(3.88g,36.6mmol)和四(三苯基膦)钯(1.0g,0.865mmol)溶于甲苯/乙醇/水(50mL,v:v=3:1:1)混合溶剂中,回流反应过夜。反应完毕冷却至室温,倒入水中,EA萃取,有机层用硫酸钠干燥,浓缩,柱层析得目标化合物2.24g,产率65%。

[0378] 实施例13-8:中间体13-8:10-(2-甲氧基乙基)-10H-吩噻嗪-3-甲醛的合成



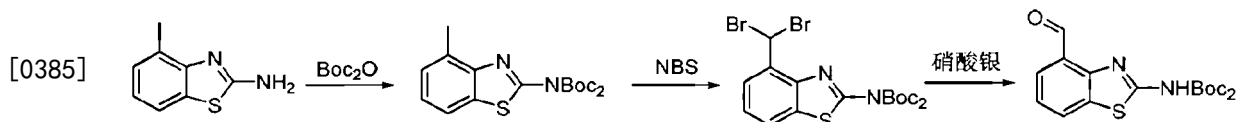
[0380] 步骤1:化合物10-(2-甲氧基乙基)-10H-吩噻嗪的合成

[0381] 氮气保护,0℃下将钠氢(2.4g,2eq)分批加入到吩噻嗪(6g,1eq)的DMF(60mL)溶液中,搅拌30分钟,加入2-溴乙基甲基醚(6.3g,1.5eq)后室温搅拌2小时。加水淬灭反应,DCM萃取,有机层干燥,浓缩,粗品经柱层析分离得目标化合物9g。

[0382] 步骤2:化合物10-(2-甲氧基乙基)-10H-吩噻嗪-3-甲醛的合成

[0383] 氮气保护下,0℃滴加三氯氧磷(10.2mL,5eq)至无水DMF(8g,5eq)中。滴毕,搅拌直到有无色固体生成,随后加入1,2-二氯乙烷(50mL)溶解固体,继续搅拌1小时。滴加10-(2-甲氧基乙基)-10H-吩噻嗪(5.6g,1eq)的1,2-二氯乙烷溶液,并在90℃搅拌2小时。反应完毕,降至室温,加入20%氢氧化钠水溶液调节pH=7,水相用DCM萃取。合并的有机相用无水硫酸钠干燥,浓缩,粗品经柱层析分离得目标化合物5.3g。

[0384] 实施例13-9:中间体13-9:化合物(4-甲酰基苯并[d]噻唑-2-基)氨基甲酸叔丁酯的合成



[0386] 步骤1:化合物(4-甲基苯并[d]噻唑-2-基)氨基甲酸叔丁酯的合成

[0387] 将4-甲基苯并[d]噻唑-2-胺(3.0g,18.3mmol)、二碳酸二叔丁酯(100g,45.7mmol)和DMAP(0.67g,5.5mmol)溶解在DCM(80mL)中,室温反应过夜。反应完毕,将反应混合物倒入冰水中,DCM萃取,合并的有机相用水洗涤,硫酸钠干燥,浓缩,粗品经柱层析分离纯化得目标化合物5.2g,产率78%。

[0388] 步骤2:化合物(4-(二溴甲基)苯并[d]噻唑-2-基)氨基甲酸叔丁酯的合成

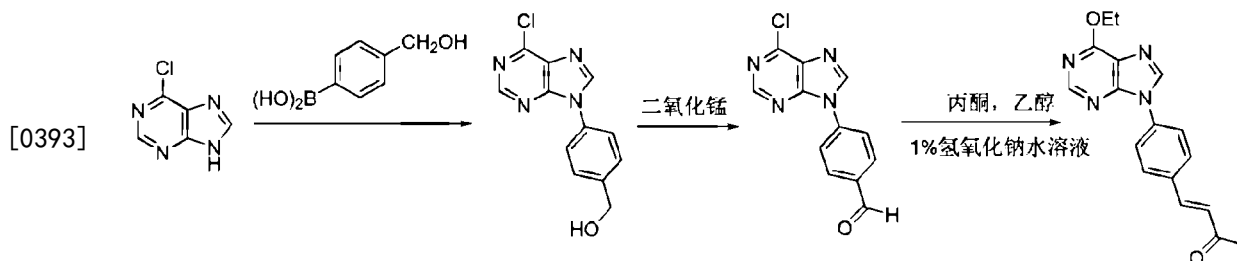
[0389] 将(4-甲基苯并[d]噻唑-2-基)氨基甲酸叔丁酯(5.2g,14.3mmol)、NBS(5.08g,28.5mmol)和AIBN(330mg,2mmol)溶解于四氯化碳30mL中,回流反应过夜。反应完毕,将反应混合物倒入冰水中,DCM萃取,合并的有机相用水洗涤,硫酸盐干燥,浓缩得粗产物4.5g,其不经进一步纯化直接用于下一步反应。

[0390] 步骤3:化合物(4-甲酰基苯并[d]噻唑-2-基)氨基甲酸叔丁酯的合成

[0391] 将化合物(4-(二溴甲基)苯并[d]噻唑-2-基)氨基甲酸叔丁酯(4.5g粗品)和硝酸银(12.2g,71.5mmol)溶解于甲苯(50mL)和DMSO(5mL)混合溶剂中,60℃反应2小时。反应完毕,将反应混合物倒入冰水中,EA萃取,合并的有机相用水洗涤,硫酸钠干燥,浓缩。粗品经柱层析分离纯化得目标化合物1.8g,产率45.2%。

[0392] 实施例13-10:中间体13-10:4-(4-(6-乙氧基-9H-嘌呤-9-基)苯基)丁-3-烯-2-酮

的合成



[0394] 步骤1:化合物4-(6-氯-9H-嘌呤-9-基)苯基)甲醇的合成

[0395] 将6-氯-9H-嘌呤(1.54g, 10.0mmol)、醋酸铜(3.63g, 20mmol)、4-(羟甲基)苯硼酸(3.63g, 20mmol)、1,10-菲咯啉(3.60g, 20mmol)和4A分子筛(1.0g)置于干燥DMF(50mL)溶液中, 40℃反应过夜。反应完毕倒入冰水中, EA萃取, 有机相用水洗涤, 硫酸钠干燥, 浓缩。粗品经柱层析分离纯化得目标化合物1.49g, 产率57%。

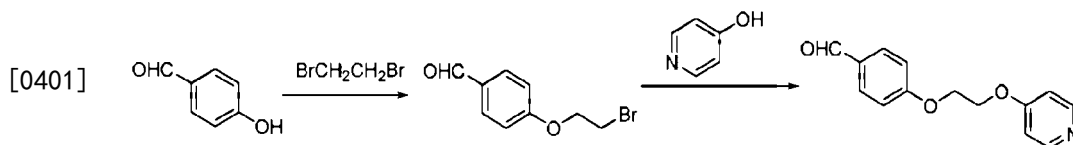
[0396] 步骤2:化合物4-(6-氯-9H-嘌呤-9-基)苯甲醛的合成

[0397] 将4-(6-氯-9H-嘌呤-9-基)苯基)甲醇(900mg, 3.5mmol)和二氧化锰(6.1g, 70mmol)置于80mL DCM中, 室温搅拌1小时。过滤, 滤渣用DCM洗涤, 收集滤液并浓缩得粗品900mg, 其不经纯化直接用于下一步反应。

[0398] 步骤3:化合物4-(4-(6-乙氧基-9H-嘌呤-9-基)苯基)丁-3-烯-2-酮的合成

[0399] 将4-(6-氯-9H-嘌呤-9-基)苯甲醛(900mg, 3.5mmol)和饱和碳酸氢钠水溶液(5ml)加入丙酮(30mL)和乙醇(20mL)中, 加热回流5小时。反应完毕, 降至室温, 倒入冰水中, DCM萃取。合并的有机相用无水硫酸钠干燥, 浓缩, 粗品经柱层析分离得目标化合物490mg, 产率46%。

[0400] 实施例13-11:中间体13-11:4-(2-(吡啶-4-基氧基)乙氧基)苯甲醛的合成



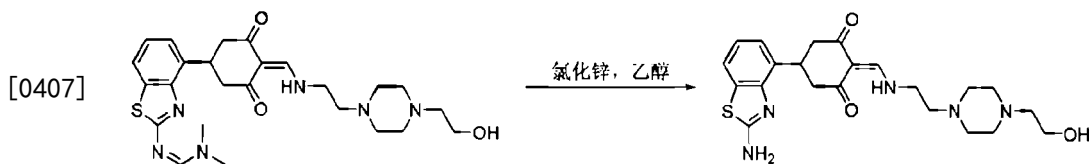
[0402] 步骤1:化合物4-(2-溴乙氧基)苯甲醛的合成

[0403] 将4-羟基苯甲醛(3.0g, 24.6mmol)、碳酸钾(6.90g, 50mmol)和1,2-二溴乙烷(9.4g, 50mmol)溶解于EtOH(85mL)中, 回流反应过夜。反应完毕, 将反应混合物倒入冰水中, EA萃取, 合并的有机相用水洗涤, 硫酸钠干燥, 浓缩。粗品经柱层析分离得目标化合物1.8g, 产率32%。

[0404] 步骤2:化合物4-(2-(吡啶-4-基氧基)乙氧基)苯甲醛的合成

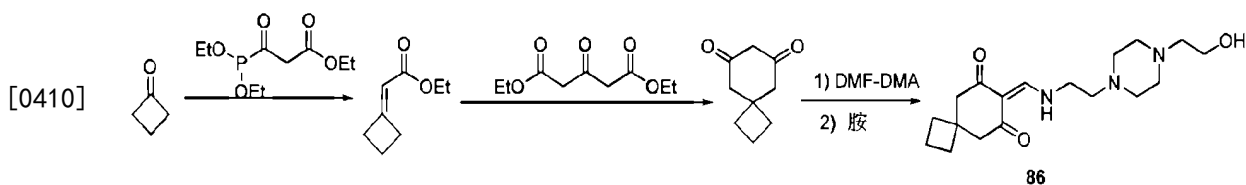
[0405] 将4-(2-溴乙氧基)苯甲醛(1.80g, 7.86mmol)、碳酸铯(4.89g, 15mmol)和4-羟基吡啶(950mg, 10mmol)溶于125mL乙醇中, 回流反应过夜。反应完毕, 降至室温, 倒入冰水中, EA萃取, 合并的有机相用无水硫酸钠干燥, 浓缩, 粗品经柱层析分离得目标化合物400mg, 产率21%。

[0406] 实施例14:化合物5-(2-氨基苯并[d]噻唑-4-基)-2-(((2-(4-(2-羟乙基)哌嗪-1-基)乙基)氨基)亚甲基)环己烷-1,3-二酮(化合物85)的合成



[0408] 将化合物N'- (4- (4- (((2- (4- (2-羟乙基) 哌嗪-1-基) 乙基) 氨基) 亚甲基) -3,5-代环己基) 苯并[d]噻唑-2-基) -N,N-二甲基甲脒(100mg, 0.2mmol) 和氯化锌(1.36g, 10mmol) 溶于5mL无水乙醇中, 回流反应过夜。反应完毕, 冷却, 倒入冰水中, EA萃取, 合并的有机相用无水硫酸钠干燥, 浓缩, 粗品经柱层析分离得目标化合物40mg, 产率45%。化合物85: ^1H NMR (400MHz, CD_3OD) δ 8.27 (s, 1H), 7.48 (d, $J=7.7\text{Hz}$, 1H), 7.14 (d, $J=7.4\text{Hz}$, 1H), 7.03 (t, $J=7.7\text{Hz}$, 1H), 3.92 (s, 1H), 3.75 (t, $J=5.6\text{Hz}$, 2H), 3.62 (t, $J=5.8\text{Hz}$, 2H), 3.10-2.49 (m, 16H); MS: 444.2 [M+1]。

[0409] 实施例15: 化合物7- (((2- (4- (2-羟乙基) 哌嗪-1-基) 乙基) 氨基) 亚甲基) -螺[3.5]壬烷-6,8-二酮(化合物86)的制备



[0411] 步骤1: 化合物2-环亚丁基乙酸乙酯的合成

[0412] 氮气保护, 在0℃下将钠氢(60%, 1.60g, 40mmol) 加入3- (二乙氧基磷基) -3-氧代丙酸乙酯(8.96g, 40mmol) 的无水THF溶液(50mL) 中, 并在该温度下搅拌30分钟后, 加入环丁酮(2.8g, 40mmol) 的无水THF溶液(10mL)。上述混合物在该温度下搅拌2小时, 然后缓慢加入水(10mL), 将所得混合物在室温下再搅拌30分钟。反应完毕, 将反应混合物倒入冰水中, EA萃取, 合并的有机相用水洗涤, 硫酸钠干燥, 浓缩。粗品经柱层析分离纯化得目标化合物4.62g, 产率82.5%。

[0413] 步骤2: 化合物螺[3.5]壬烷-6,8-二酮的合成

[0414] 氮气保护, 在0℃下, 钠氢(60%, 960mg, 24mmol) 加入3-氧代戊二酸二乙酯(2.53g, 12.5mmol) 的无水THF(50mL) 溶液中, 并该温度下搅拌30分钟后, 加入2-环丁基亚乙基酯乙酸乙酯(1.4g, 10mmol) 的无水THF(10mL) 溶液, 室温反应2小时, 然后加入乙醇钠(816mg, 12mmol) 的无水乙醇溶液5mL。上述混合物回流反应5小时, 冷却至50℃, 加入20% KOH溶液(10mL)。将所得混合物在该温度下搅拌过夜, 反应完毕冷却至室温, EA萃取, 将水相调节至1-2, 并在70℃下搅拌2小时。冷却至室温, DCM萃取。将合并的有机相用水洗涤, 硫酸盐干燥, 浓缩。粗品经柱层析分离纯化得目标化合物483mg, 产率32%。

[0415] 步骤3: 化合物7- (((2- (4- (2-羟乙基) 哌嗪-1-基) 乙基) 氨基) 亚甲基) 螺[3.5]壬烷-6,8-二酮的合成

[0416] 操作步骤同实施例2。化合物86: ^1H NMR (CD_3OD , 400MHz) δ 8.16 (s, 1H), 3.67 (t, $J=6.0\text{Hz}$, 2H), 3.56 (t, $J=6.0\text{Hz}$, 2H), 2.59-2.53 (m, 16H), 1.95-1.82 (m, 6H); MS: 336.5 [M+1]。

[0417] 实施例16: 化合物87-94

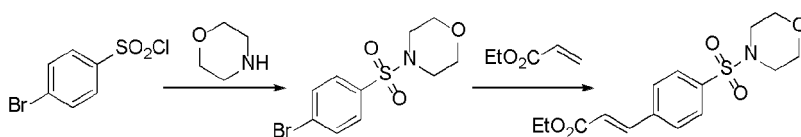
[0418] 除了使用相应的醛、酮或取代的丙烯酸酯外(例如实施例16-1和16-2), 化合物87-94的合成方法同化合物86, 如表5所示。

[0419] 表5:化合物87-94

#	结构	名称	氢谱(¹ HNMR),质谱(MS)
87		5-(4-(1H-咪唑-1-基)苯基)-2-(((2-(4-(2-羟乙基)哌嗪-1-基)乙基)氨基)亚甲基)环己烷-1,3-二酮	¹ HNMR (CD ₃ OD, 400MHz) δ 8.25 (s, 1H), 8.10 (s, 1H), 7.54-7.45 (m, 5H), 7.13 (s, 1H), 3.67 (t, <i>J</i> = 6.0Hz, 2H), 3.60 (t, <i>J</i> = 6.0Hz, 2H), 3.49-3.41 (m, 1H), 2.87-2.52(m, 16H); MS: 438.6 [M+1].
88		2-(((2-(4-(2-羟乙基)哌嗪-1-基)乙基)氨基)亚甲基)-5-(喹啉-2-基)环己烷-1,3-二酮	¹ HNMR (CD ₃ OD, 400MHz): δ 8.89 (s, 1H), 8.24 (s, 1H), 8.07-8.05 (m, 2H), 7.83-7.76 (m, 2H), 3.93-3.88 (m, 1H), 3.67-3.57 (m, 2H), 3.30-3.28 (m, 2H), 3.11-2.91 (m, 2H), 2.88-2.81 (m, 2H), 2.61-2.50 (m, 12H).
89		2-(((2-(4-(2-羟乙基)哌嗪-1-基)乙基)氨基)亚甲基)-5-(6-(2-吗啉代乙氧基)吡啶-3-基)环己烷-1,3-二酮	¹ HNMR (400 MHz, CD ₃ OD) δ 8.25 (s, 1H), 7.57 (d, <i>J</i> = 9.2 Hz, 1H), 7.52 (s, 1H), 6.53 (d, <i>J</i> = 9.3 Hz, 1H), 4.09 (t, <i>J</i> = 6.4 Hz, 2H), 3.72 (t, <i>J</i> = 5.5 Hz, 2H), 3.67 – 3.56 (m, 6H), 3.26 – 3.17 (m, 1H), 2.93 – 2.43 (m, 22H); MS: 502.3 [M+1].
90		2-(((2-(4-(2-羟乙基)哌嗪-1-基)乙基)氨基)亚甲基)-5-(嘧啶-5-基)环己烷-1,3-二酮	¹ HNMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.97 (dd, <i>J</i> = 7.9, 6.7 Hz, 1H), 9.07 (s, 1H), 8.80 (s, 2H), 8.15 (d, <i>J</i> = 14.7 Hz, 1H), 4.35 (t, <i>J</i> = 5.3 Hz, 1H), 3.57 (d, <i>J</i> = 5.7 Hz, 2H), 3.53 – 3.35 (m, 3H), 2.93 – 2.67 (m, 2H), 2.65 – 2.23 (m, 14H); MS: 374.2 [M+1].
91		2-(((2-(4-(2-羟乙基)哌嗪-1-基)乙基)氨基)亚甲基)-5-(2-吗啉代嘧啶-5-基)环己烷-1,3-二酮	¹ HNMR (400 MHz, CD ₃ OD) δ 8.29 (s, 2H), 8.23 (s, 1H), 3.67 (t, <i>J</i> = 6.1 Hz, 1H), 3.59 (t, <i>J</i> = 5.9 Hz, 2H), 2.95 – 2.45 (m, 16H); MS: 459.3 [M+1].
92		2-(((2-(4-(2-羟乙基)哌嗪-1-基)乙基)氨基)亚甲基)-5-(4-(吗啉代)苯基)环己烷-1,3-二酮	¹ HNMR (400 MHz, CD ₃ OD) δ 8.32 (s, 1H), 7.80 (d, <i>J</i> = 8.3 Hz, 2H), 7.64 (d, <i>J</i> = 8.4 Hz, 2H), 3.83 (t, <i>J</i> = 5.6 Hz, 2H), 3.77 – 3.72 (m, 4H), 3.67 (t, <i>J</i> = 5.8 Hz, 2H), 3.63 – 3.51 (m, 1H), 3.05 – 2.97 (m, 6H), 2.97 – 2.67 (m, 14H); MS: 521.3 [M+1].
93		2-(((2-(4-(2-羟乙基)哌嗪-1-基)乙基)氨基)亚甲基)-5-(1H-吡唑-4-基)环己烷-1,3-二酮	¹ H NMR (400 MHz, CD ₃ OD) δ 8.32 (s, 1H), 8.23 (s, 1H), 7.47 (d, <i>J</i> = 8.4 Hz, 1H), 7.41 – 7.33 (m, 1H), 7.06 (d, <i>J</i> = 7.1 Hz, 1H), 3.92 (t, <i>J</i> = 11.0 Hz, 1H), 3.82 (t, <i>J</i> = 5.4 Hz, 2H), 3.66 (t, <i>J</i> = 5.7 Hz, 2H), 3.17 – 2.62 (m, 16H); MS: 412.4 [M+1].
94		2-(((2-(4-(2-羟乙基)哌嗪-1-基)乙基)氨基)亚甲基)-5-(三氟甲基)环己烷-1,3-二酮	¹ H NMR (400 MHz, CD ₃ OD) δ 8.22 (s, 1H), 3.69 (t, <i>J</i> = 5.9 Hz, 2H), 3.59 (t, <i>J</i> = 5.8 Hz, 2H), 3.02 (d, <i>J</i> = 8.2 Hz, 1H), 2.77 – 2.51 (m, 16H); MS: 364.0 [M+1].

[0422] 实施例16-1:中间体16-1:3-(4-(吗啉代磺酰基)苯基)-丙烯酸乙酯的合成

[0423]



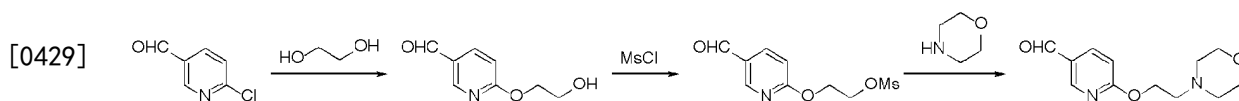
[0424] 步骤1:化合物4-((4-溴苯基)磺酰基)吗啉的合成

[0425] 将4-溴苯磺酰氯(5.0g, 19.6mmol)、三乙胺(TEA)(2.98mL)和吗啉(1.88g, 21.53mmol)溶解在DCM(50mL)中,室温反应30分钟,反应完毕。将反应混合物倒入水中,DCM萃取。合并的有机相用1N盐酸、水和盐水洗涤,干燥,浓缩得粗品5.21g,其不经进一步纯化直接用于下一步反应。

[0426] 步骤2:化合物3-(4-(吗啉代磺酰基)苯基)丙烯酸乙酯的合成

[0427] 氮气保护下,将4-((4-溴苯基)磺酰基)吗啉(2.0g, 6.53mmol)、丙烯酸乙酯(849mg, 8.49mmol)、醋酸钯(43.88mg, 0.2mmol)和三苯基膦(68.89mg, 0.26mmol)加入到3mL三乙胺中,封管中于150度搅拌6小时。冷却,倒入水中,EA萃取。合并的有机相用无水硫酸钠干燥,浓缩,粗品经柱层析分离得到1.8g,产率85%。

[0428] 实施例16-2:中间体16-3:6-(2-吗啉代乙氧基)烟醛的合成



[0430] 步骤1:化合物6-(2-羟基乙氧基)烟醛的合成

[0431] 在室温下将叔丁醇钠(3.49g, 36.3mmol)加入到1,2-乙二醇(30mL)中,搅拌30分钟后,加入6-氯烟醛(4.0g, 28.3mmol),所得混合物在室温下搅拌过夜,然后升温至80℃再搅拌2小时,反应完毕。将反应混合物冷却至室温,倒入冰水中,EA萃取,有机相用水洗涤,干燥,浓缩,粗品经柱层析分离纯化得目标化合物4.01g,产率85%。

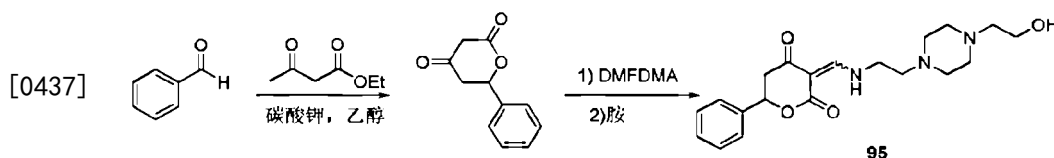
[0432] 步骤2:化合物2-((5-甲酰基吡啶-2-基)氧基)乙基甲磺酸酯的合成

[0433] 将6-(2-羟基乙氧基)烟醛(4g, 24mmol)和TEA(4mL)加入到DCM(90mL)中,于0℃滴加甲磺酰氯(3.66g, 32mmol)的二氯甲烷溶液,滴毕保持在该温度下搅拌30分钟,反应完毕。反应液倒入水中,EA萃取。合并的有机相用无水硫酸钠干燥,浓缩得粗品5.21g,不经进一步纯化直接用于下一步反应。

[0434] 步骤3:化合物6-(2-吗啉代乙氧基)烟醛的制备

[0435] 将2-((5-甲酰基吡啶-2-基)氧基)乙基甲磺酸酯(5.21g, 粗品)、吗啉(4.35g, 50mmol)和碳酸钾(6.91g, 50mmol)加入80mL乙腈中,回流反应过夜。冷却,倒入水中,EA萃取,有机相用无水硫酸钠干燥,浓缩,粗品经柱层析分离得目标化合物2.92g,产率51%。

[0436] 实施例17:化合物3-(((2-(4-(2-羟乙基)哌嗪-1-基)乙基)氨基)亚甲基)-6-苯基二氢-2H-吡喃-2,4(3H)-二酮(化合物95)的合成



[0438] 步骤1:化合物6-苯基二氢-2H-吡喃-2,4(3H)-二酮的制备

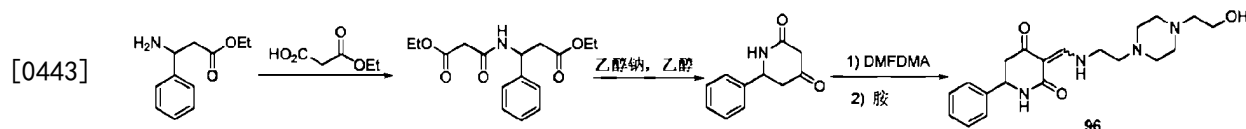
[0439] 将乙酰乙酸乙酯(13.01g, 0.1mol)、碳酸钾(27.64g, 0.2mol)和苯甲醛(10.1mL, 0.1mol)溶解于乙醇(100mL)中,45℃下反应22小时,过滤,滤渣用乙醇洗涤,收集的滤液倒入水中,PE洗涤。收集水相,用6N盐酸酸化至pH 2-3,EA萃取,有机相用水洗涤,硫酸钠干燥,浓缩,粗品经柱层析分离纯化得目标化合物8.87g,产率46.7%。

[0440] 步骤2:化合物3-(((2-(4-(2-羟乙基)哌嗪-1-基)乙基)氨基)亚甲基)-6-苯基二

氢-2H-吡喃-2,4(3H)-二酮的合成

[0441] 合成步骤同实施例2。化合物95: $^1\text{H NMR}$ (400MHz, CD_3OD) δ 8.31 (s, 0.33H), 8.18 (s, 0.67H), 7.46-7.32 (m, 5H), 5.53 (dd, $J=7.2\text{Hz}, 2.4\text{Hz}$, 1H), 3.68 (t, $J=6.0\text{Hz}$, 2H), 3.61-3.58 (m, 2H), 2.98-2.86 (m, 1H), 2.72-2.54 (m, 14H); MS: 374.4[M+1].

[0442] 实施例17A: 3-(((2-(4-(2-羟乙基)哌嗪-1-基)乙基)氨基)亚甲基)-6-苯基哌啶-2,4-二酮(化合物96)的合成



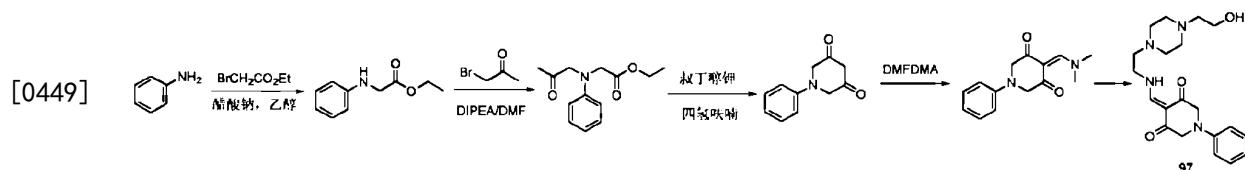
[0444] 步骤1: 化合物3-((3-乙氧基-3-氧代-1-苯基丙基)氨基)-3-氧代丙酸乙酯的合成

[0445] 将3-氨基-3-苯基丙酸乙酯(4.31g, 22.23mmol)、丙二酸单乙酯(4.47g, 33.84mmol)、DIPEA(7.7g, 55.8mmol)和1H-苯并三唑-1-氧三吡咯啉六氟磷酸(PyBOP)(17.42g, 33.84mmol)加入DMF(30mL)中, 室温反应2小时, 反应完毕。倒入水中, EA萃取, 有机相用无水硫酸钠干燥, 浓缩, 粗品经柱层析分离得目标化合物6.05g, 产率88%。

[0446] 步骤2: 化合物6-苯基哌啶-2,4-二酮的合成

[0447] 在0℃下, 将化合物3-((3-乙氧基-3-氧代-1-苯基丙基)氨基)-3-氧代丙酸乙酯(2.0g, 6.51mmol)的甲苯溶液(16mL)滴加至乙醇钠(0.66g, 9.77mmol)的无水乙醇溶液(16mL)中, 回流反应1小时。反应完毕, 将反应混合物倒入水中, pH调节至1-2, EA萃取, 有机相用水和盐水洗涤, 干燥, 浓缩, 所得粗品溶于乙腈/水(v:v=100:1, 16mL)混合溶剂中, 并回流过夜。反应完毕冷却至室温, 倒入冰水中, EA萃取, 有机相用水洗涤, 硫酸钠干燥, 浓缩所得粗品经柱层析分离纯化得目标化合物622mg, 产率50%。化合物96: $^1\text{H NMR}$ (400MHz, CD_3OD) δ 8.09 (s, 0.3H), 8.04 (s, 0.7H), 7.34-7.24 (m, 5H), 4.75-4.72 (m, 1H), 3.72 (t, $J=5.6\text{Hz}$, 2H), 3.55-3.52 (m, 2H), 2.87-2.57 (m, 15H), MS: 373.3[M+1].

[0448] 实施例18: 化合物4-(((2-(4-(2-羟乙基)哌嗪-1-基)乙基)氨基)亚甲基)-1-苯基哌啶-3,5-二酮(化合物97)的合成



[0450] 步骤1: 苯基甘氨酸乙酯的合成

[0451] 将苯胺(5.0g, 53.69mmol)、溴乙酸乙酯(10.76g, 64.43mmol)和醋酸钠(5.29g, 64.43mmol)溶于无水乙醇(120mL)中, 回流反应2小时。反应完毕, 浓缩, 粗品经柱层析分离纯化得目标化合物7.4g, 产率77%。

[0452] 步骤2: 化合物N-(2-氧代丙基)-N-苯基甘氨酸乙酯的合成

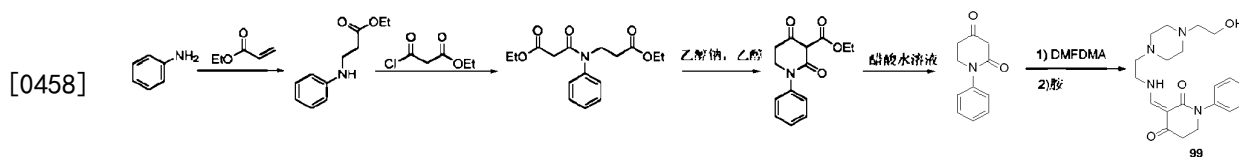
[0453] 将苯基甘氨酸乙酯(2.3g, 12.83mmol)、溴丙酮(2.11g, 25.67mmol)和DIPEA(4.57mL, 25.67mmol)加入到DMF(50mL)中, 110℃反应4小时, 补加溴丙酮(1.06g, 12.8mmol), 继续在110℃反应4小时。降至室温, 倒入水中, EA萃取, 合并的有机相用无水硫酸钠干燥, 浓缩, 粗品经柱层析分离得目标化合物1.3g, 产率43%。

[0454] 步骤3: 化合物1-苯基哌啶-3,5-二酮的合成

[0455] 在0℃下,将叔丁醇钾的THF溶液(2mol/L,3.8mL)滴加至化合物N-(2-氧代丙基)-N-苯基甘氨酸乙酯(1.2g,5.1mmol)的无水THF溶液(50mL)中,上述反应液于室温搅拌3小时。反应完毕,滴加20%醋酸淬灭反应,倒入冰水中,EA萃取,有机相用无水硫酸钠干燥,粗品经柱层析分离得目标化合物600mg,产率62%。

[0456] 步骤4和5:操作步骤同实施例2。化合物97:¹HNMR(400MHz,CD₃OD) δ8.22(s,1H),7.26(t,J=8.0Hz,2H),6.98(d,J=8.0Hz,2H),6.88(t,J=7.3Hz,1H),4.03(d,J=10.9Hz,4H),3.75(t,J=5.8Hz,2H),3.61(t,J=5.7Hz,2H),2.66(dd,J=23.9,18.2Hz,12H);MS:373.3[M+1]。

[0457] 实施例19:化合物3-(((2-(4-(2-羟乙基)哌嗪-1-基)乙基)氨基)亚甲基)-1-苯基哌啶-2,4-二酮(化合物99)的合成



[0459] 步骤1:化合物3-(苯基氨基)丙酸乙酯的合成

[0460] 将苯胺(2.8g,30mmol)、丙烯酸乙酯(3.6g,36mmol)溶解于2mL醋酸中,95℃反应过夜。反应完毕冷却至室温,倒入冰水中,用饱和碳酸钠溶液调PH至9-10,EA萃取,有机相用水洗涤,干燥,浓缩,粗品经柱层析分离得目标化合物5.3g,产率91%。

[0461] 步骤2:化合物3-((3-乙氧基-3-氧代丙基)(苯基)氨基)-3-氧代丙酸乙酯的合成

[0462] 将3-(苯基氨基)丙酸乙酯(5.3g,27.4mmol)、丙二酸单乙酯酰氯(5.35g,35.6mmol)和DIPEA(7.09g,54.8mmol)溶解于DCM(35mL)中,室温反应1小时。反应完毕,将反应混合物倒入冰水中,EA萃取,有机相用水洗涤,干燥,浓缩,粗品经柱层析分离得目标化合物2.1g,产率25%。

[0463] 步骤3:化合物乙基-2,4-二氧代-1-苯基哌啶-3-羧酸乙酯的合成

[0464] 化合物3-((3-乙氧基-3-氧代丙基)(苯基)氨基)-3-氧代丙酸乙酯(2.00g,6.5mmol)和乙醇钠(0.88g,13mmol)溶解于15mL无水乙醇中,室温反应2小时,反应完毕。将反应混合物倒入冰水中,水相用2N盐酸调PH至3-4,EA萃取,有机相用水洗涤,硫酸钠干燥,浓缩,粗品经柱层析分离纯化得目标化合物780mg,产率46%。

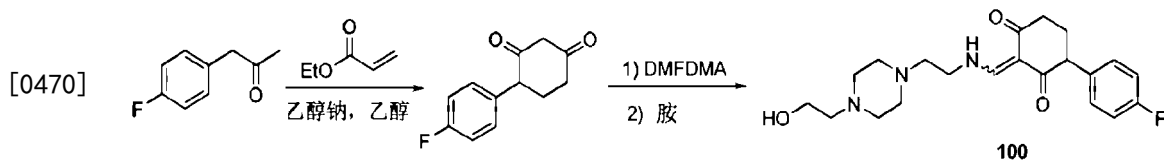
[0465] 步骤4:化合物1-苯基哌啶-2,4-二酮的合成

[0466] 将乙基-2,4-二氧代-1-苯基哌啶-3-羧酸乙酯(780mg,3.0mmol)和醋酸(0.7mL)的水溶液(7mL)在90℃下反应18小时。反应完毕,将反应混合物倒入冰水中,EA萃取,有机相用水洗涤,干燥,浓缩,粗品经柱层析分离得目标化合物510mg,产率90%。

[0467] 步骤5:化合物3-(((2-(4-(2-羟乙基)哌嗪-1-基)乙基)氨基)亚甲基)-1-苯基哌啶-2,4-二酮的合成

[0468] 本步操作步骤同实施例2。化合物99:¹H NMR(400MHz,CD₃OD) δ8.13(d,J=7.1Hz,1H),7.48-7.33(m,2H),7.34-7.15(m,3H),3.90-3.72(m,2H),3.71-3.61(m,2H),3.60-3.46(m,2H),2.83-2.38(m,14H);MS:373.3[M+1]。

[0469] 实施例20:化合物4-(4-氟苯基)-2-(((2-(4-(2-羟乙基)哌嗪-1-基)乙基)氨基)亚甲基)环己-1,3-二酮(化合物100)的合成



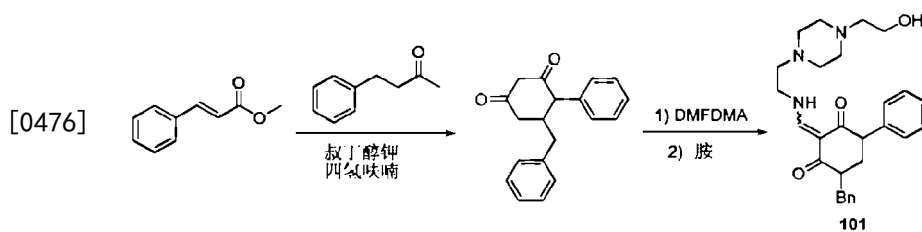
[0471] 步骤1:化合物4-(4-氟苯基)环己烷-1,3-二酮的合成

[0472] 化合物1-(4-氟苯基)丙-2-酮(2.0g, 13.14mmol)、丙烯酸乙酯(1.45g, 14.46mmol)和乙醇钠(893.5mg, 13.14mmol)溶解于无水乙醇20mL中,回流反应过夜。反应完毕,冷却至室温并倒入冰水中,用2N盐酸调PH至3-4,EA萃取,有机相用水洗涤,硫酸钠干燥,浓缩,粗品经柱层析分离纯化得目标化合物620mg,产率23%。

[0473] 步骤2:化合物4-(4-氟苯基)-2-(((2-(4-(2-羟乙基)哌嗪-1-基)乙基)氨基)亚甲基)环己-1,3-二酮的合成

[0474] 操作步骤同实施例2。化合物100:¹H NMR (400MHz, CD₃OD) δ8.30 (d, J=8.8Hz, 1H), 7.28-7.16 (m, 2H), 7.06 (t, J=8.0Hz, 2H), 3.81-3.66 (m, 3H), 3.62 (t, J=5.8Hz, 2H), 2.86-2.43 (m, 14H), 2.27-2.15 (m, 2H)。MS: 390.4 [M+1]。

[0475] 实施例21:化合物4-苄基-2-(((2-(4-(2-羟乙基)哌嗪-1-基)乙基)氨基)亚甲基)-6-苯基环己烷-1,3-二酮(化合物101)的合成



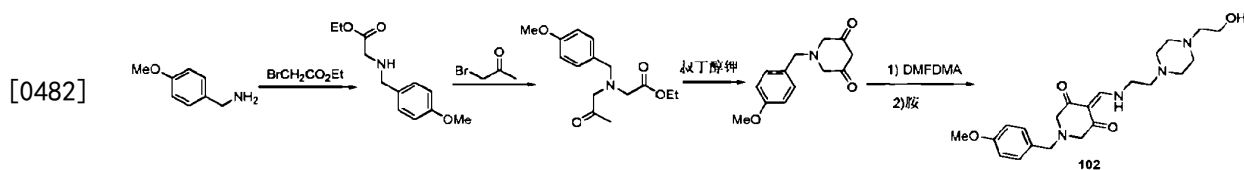
[0477] 步骤1:化合物5-苄基-4-苯基环己烷-1,3-二酮的合成

[0478] 氮气保护,在0℃下,将叔丁醇钾(1.61g, 14.3mmol)加入苄基丙酮(2.5mL, 15.5mmol)的无水THF(20mL)溶液中,搅拌10分钟后,加入肉桂酸甲酯(2g, 12.3mmol),然后继续搅拌30分钟,反应完毕将反应液倒入水中,用2N稀盐酸调节pH至6-7,EA萃取,有机相干燥,浓缩得到3.61g粗品,直接用于下一步反应。

[0479] 步骤2:化合物4-苄基-2-(((2-(4-(2-羟乙基)哌嗪-1-基)乙基)氨基)亚甲基)-6-苯基环己烷-1,3-二酮的合成

[0480] 操作步骤同实施例2。化合物101:¹H NMR (400MHz, CD₃OD) δ8.24 (d, J=5.6Hz, 1H), 7.39-6.98 (m, 9H), 6.91 (d, J=7.4Hz, 1H), 3.72 (t, J=5.8Hz, 2H), 3.60 (t, J=5.7Hz, 2H), 3.46-3.40 (m, 1H), 3.24-3.01 (m, 3H), 2.95-2.56 (m, 13H), 2.49 (dd, J=13.8, 7.6Hz, 1H); MS: 462.3 [M+1]。

[0481] 实施例22:化合物4-(((2-(4-(2-羟乙基)哌嗪-1-基)乙基)氨基)亚甲基)-1-(4-甲氧基苄基)哌啶-3,5-二酮(化合物102)的合成



[0483] 步骤1:化合物乙基(4-甲氧基苄基)甘氨酸酯的合成

[0484] 室温下,2-溴乙酸乙酯(5.00g, 29.94mmol)的无水THF溶液(20mL)在2小时内滴加

至对甲氧基苄胺(9.04g,66mmol)的无水THF溶液(120mL)中,室温反应过夜。反应完毕,将反应混合物倒入水中,用饱和碳酸钠调PH至9-10,EA萃取,有机相用水洗涤,硫酸钠干燥,浓缩,粗品经柱层析分离纯化得目标化合物3.12g,产率47%。

[0485] 步骤2:化合物N-(4-甲氧基苄基)-N-(2-氧代丙基)甘氨酸乙酯的合成

[0486] 将乙基(4-甲氧基苄基)甘氨酸乙酯(3g,13.44mmol)、溴丙酮(7.36g,53.75mmol)和碳酸氢钠(2.26g,26.87mmol)加入到50mL无水乙醇中,加热回流4小时。冷却至室温,浓缩,粗品经柱层析分离得目标化合物700mg,产率19%。

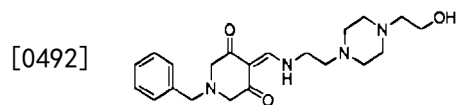
[0487] 步骤3:化合物1-(4-甲氧基苄基)哌啶-3,5-二酮的合成

[0488] 在0℃下,将叔丁醇钾的THF溶液(1mol/L,4mL)滴加至N-(4-甲氧基苄基)-N-(2-氧代丙基)甘氨酸乙酯(700mg,2.51mmol)的无水THF溶液(30mL)中,室温反应3小时,反应完毕。将反应液倒入10%醋酸水溶液中,EA萃取,有机相用无水硫酸钠干燥,浓缩,粗品经柱层析分离得目标化合物220mg,产率38%。

[0489] 步骤4:化合物4-(((2-(4-(2-羟乙基)哌嗪-1-基)乙基)氨基)亚甲基)-1-(4-甲氧基苄基)哌啶-3,5-二酮的合成

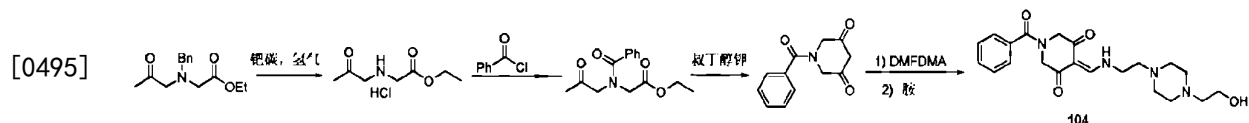
[0490] 操作步骤同实施例2。化合物102:¹H NMR(400MHz,CD₃OD) δ8.19(s,1H),7.24(d,J=8.2Hz,2H),6.89(d,J=8.3Hz,2H),3.86-3.73(m,5H),3.60(s,4H),3.31(s,2H),3.14(d,J=33.6Hz,8H),2.72(m,6H);MS:417.4[M+1]..

[0491] 实施例23:化合物1-苄基-4-(((2-(4-(2-羟乙基)哌嗪-1-基)乙基)氨基)亚甲基)-哌啶-3,5-二酮(化合物103)的合成



[0493] 除了使用苄胺外,化合物103的合成方法同实施例22(化合物102)。化合物103:¹H NMR(400MHz,CD₃OD) δ8.22(s,1H),7.40-7.26(m,5H),3.72(t,J=5.9Hz,2H),3.69(s,2H),3.62(t,J=5.8Hz,2H),3.34(s,2H),3.23(d,J=6.6Hz,1H),2.80-2.54(m,10H);MS:387.4[M+1]。

[0494] 实施例24:化合物1-苯甲酰基-4-(((2-(4-(2-羟乙基)哌嗪-1-基)乙基)氨基)亚甲基)-哌啶-3,5-二酮(化合物104)的合成



[0496] 步骤1:化合物乙基(2-氧代丙基)甘氨酸乙酯盐酸盐的合成

[0497] 将乙基N-苄基-N-(2-氧代丙基)甘氨酸乙酯(4.00g,16.04mmol)、10%钯碳(500mg)和5mL盐酸溶解于100mL乙醇中,置换氢气,室温反应4小时。反应完毕,过滤除去钯碳,乙醇洗涤滤渣,收集滤液并浓缩得粗品3.4g,直接用于下一步反应。

[0498] 步骤2:化合物乙基N-苯甲酰基-N-(2-氧代丙基)甘氨酸乙酯的合成

[0499] 室温下,将TEA(4mL,29mmol)加入到(2-氧代丙基)甘氨酸乙酯(2.78g,粗品)的DCM溶液(100mL)中,随后向上述混合液加入苯甲酰氯(1.65mL,14.23mmol),加毕室温反应4小时。反应完毕倒入水中,DCM萃取,有机相用水洗涤,硫酸钠干燥,浓缩,粗品经柱层析分离纯化得目标化合物1.92g,产率56%。

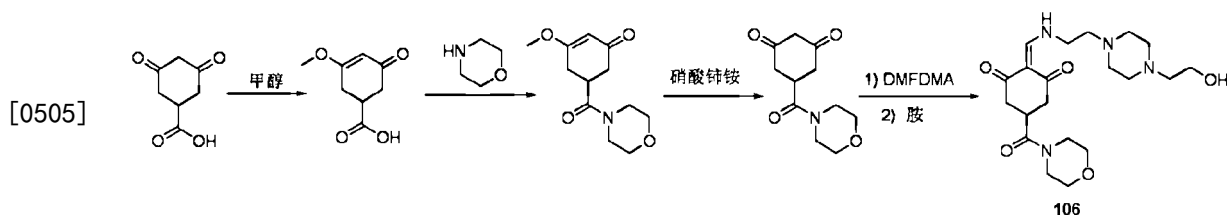
[0500] 步骤3:化合物1-苯甲酰-3,5-二酮的合成

[0501] 在0℃下,将叔丁醇钾的THF溶液(1mol/L,11mL)滴加至乙基N-苯甲酰基-N-(2-氧代丙基)甘氨酸乙酯(1.9g,7.22mmol)的无水THF溶液60mL中,于室温反应3小时。反应完毕,将反应液倒入10%醋酸溶液中,EA萃取,有机相用无水硫酸钠干燥,浓缩,粗品经柱层析分离得目标化合物1.03g,产率66%。

[0502] 步骤4:化合物1-苯甲酰基-4-(((2-(4-(2-羟乙基)哌嗪-1-基)乙基)氨基)亚甲基)哌啶-3,5-二酮的合成

[0503] 最后一步操作步骤同实施例8。化合物104:¹H NMR(400MHz,CD₃OD) δ8.25(s,1H), 7.57-7.45(m,3H), 7.42(dd, J=8.0,1.5Hz,2H), 4.47(s,2H), 4.18(s,2H), 3.73(t, J=5.8Hz,2H), 3.62(t, J=5.8Hz,2H), 2.83-2.58(m,12H); MS:401.4[M+1]。

[0504] 实施例26:化合物2-(((2-(4-(2-羟乙基)哌嗪-1-基)乙基)氨基)亚甲基)-5-(吗啉-4-羰基)环己烷-1,3-二酮(化合物106)的合成



[0506] 步骤1:化合物3-甲氧基-5-氧代环己-3-烯-1-羧酸的合成

[0507] 将化合物3,5-二氧代环己烷羧酸(780mg,5mmol)、一水合对甲苯磺酸(95mg,0.5mmol)溶解于6mL甲醇中,回流反应2小时。反应完毕冷却至室温,将EA加入到混合物中,析出沉淀,过滤得粗品420mg,其不经进一步纯化直接用于下一步反应。

[0508] 步骤2:化合物3-甲氧基-5-(吗啉-4-羰基)环己-2-烯-1-酮的合成

[0509] 将3-甲氧基-5-氧代环己-3-烯-1-羧酸(340mg,粗品)、吗啡啉(310mg,2.4mmol)、DIPEA(390mg,3mmol)和HATU(1.14g,3mmol)加入到12mL无水DMF中,室温搅拌过夜。反应完毕,倒入水中,EA萃取,有机相用无水硫酸钠干燥,浓缩,粗品经柱层析分离得目标化合物140mg,产率15%。

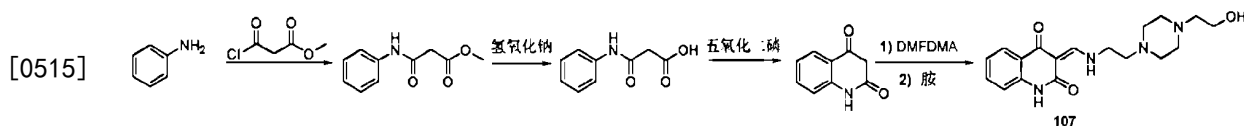
[0510] 步骤3:化合物5-(吗啉-4-羰基)环己烷-1,3-二酮的合成

[0511] 将3-甲氧基-5-(吗啉-4-羰基)环己-2-烯-1-酮(132mg,0.55mmol)和硝酸铈铵(110mg,0.2mmol)加入到乙腈(4mL)和水(4mL)中,加热回流3小时。反应完毕,降至室温,将反应液倒入水中,EA萃取,合并的有机相用无水硫酸钠干燥,浓缩,粗品经柱层析分离得目标化合物112mg,产率90%。

[0512] 步骤4:化合物2-(((2-(4-(2-羟乙基)哌嗪-1-基)乙基)氨基)亚甲基)-5-(吗啉-4-羰基)环己烷-1,3-二酮的合成

[0513] 操作步骤同实施例2。化合物106:¹H NMR(400MHz,CD₃OD) δ8.19(s,1H), 3.75(t, J=5.7Hz,2H), 3.65(dd, J=13.9,4.5Hz,4H), 3.61-3.47(m,7H), 2.88(s,3H), 2.81(t, J=5.8Hz,2H), 2.75-2.42(m,10H)。

[0514] 实施例27:化合物3-(((2-(4-(2-羟乙基)哌嗪-1-基)乙基)氨基)亚甲基)喹啉-2,4(1H,3H)-二酮(化合物107)的合成



[0516] 步骤1:化合物3-氧代-3-(苯基氨基)丙酸甲酯的合成

[0517] 在0℃下,将丙二酸单甲酯酰氯(1.84g,13.5mmol)滴加至苯胺(1.00g,10.74mmol)和TEA(1.42g,14mmol)的乙酸乙酯溶液中,滴毕,在室温下搅拌30分钟。反应完毕,将反应混合物倒入水中,EA萃取,有机相用水洗涤,硫酸钠干燥,浓缩,粗品经柱层析分离得目标化合物1.75g,产率85%。

[0518] 步骤2:化合物3-氧代-3-(苯基氨基)丙酸的合成

[0519] 将3-氧代-3-(苯基氨基)丙酸甲酯(1.00g,5.18mmol)和氢氧化钠(415mg,10.37mmol)的甲醇/水(v:v=3:1,20mL)混合溶液在室温下搅拌1小时。反应完毕,将反应混合物倒入水中,EA萃取。将水相的PH值调节至5-6,DCM萃取。将合并的有机相用水洗涤,硫酸钠干燥,浓缩得粗品820mg,直接用于下一步反应。

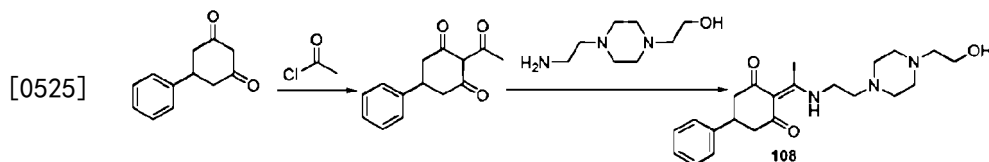
[0520] 步骤3:化合物喹啉-2,4(1H,3H)-二酮的合成

[0521] 将3-氧代-3-(苯基氨基)丙酸(537mg,粗品)加入到6mL甲磺酸中,加热至50℃,分批加入五氧化二磷(852mg)。反应液随后升至75℃搅拌2小时。降至室温,缓慢倒入冰水中,水相用饱和碳酸钠水溶液调节pH至7-8。将析出的固体过滤,收集,干燥得粗品220mg,产率40%,无需纯化直接用于下一步反应。

[0522] 步骤4:化合物3-((2-(4-(2-羟乙基)哌嗪-1-基)乙基)氨基)亚甲基)喹啉-2,4(1H,3H)-二酮的合成

[0523] 操作步骤同实施例2。化合物107:¹H NMR(400MHz,CD₃OD) δ8.57(d,J=36.5Hz,1H), 8.04(d,J=7.5Hz,1H), 7.53(t,J=6.9Hz,1H), 7.16(t,J=8.7Hz,2H), 3.73(m,4H), 2.69(m,11H)。

[0524] 实施例28:化合物2-(1-((2-(4-(2-羟乙基)哌嗪-1-基)乙基)氨基)亚乙基)-5-苯基环己烷-1,3-二酮(化合物108)的合成



[0526] 步骤1:化合物2-乙酰基-5-苯基-1,3-环己二酮的合成

[0527] 室温下,将乙酰氯(4.2g,53.5mmol)滴加至5-苯基-1,3-环己二酮(10.0g,53.1mmol)、DMAP(2.00g,16.4mmol)和DIPEA(7.75g,60mmol)混合物中,回流反应2小时。反应完毕冷却至室温,倒入冰水中,DCM萃取,有机相用水洗涤,硫酸钠干燥,浓缩,粗品经柱层析分离纯化得目标化合物8.51g,产率70%。

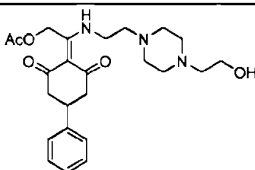
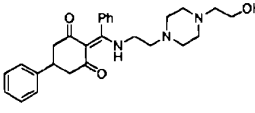
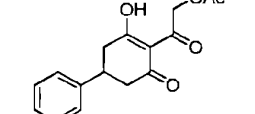
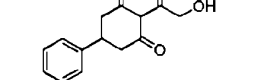
[0528] 步骤2:化合物2-(1-((2-(4-(2-羟乙基)哌嗪-1-基)乙基)氨基)亚乙基)-5-苯基环己烷-1,3-二酮的合成

[0529] 将2-乙酰基-5-苯基-1,3-环己二酮(90mg,0.39mmol)和2-(4-(2-氨基乙基)哌嗪-1-基)乙-1-醇(81mg,0.47mmol)溶解于5mL乙醇中,加热回流1小时。冷却,浓缩,粗品经制备板分离得目标化合物80mg,产率44%。化合物108:¹H NMR(400MHz,DMSO-d₆) δ13.18(s,1H), 7.37-7.26(m,4H), 7.26-7.19(m,1H), 5.00(s,1H), 3.68(s,2H), 3.57(d,J=5.4Hz,2H),

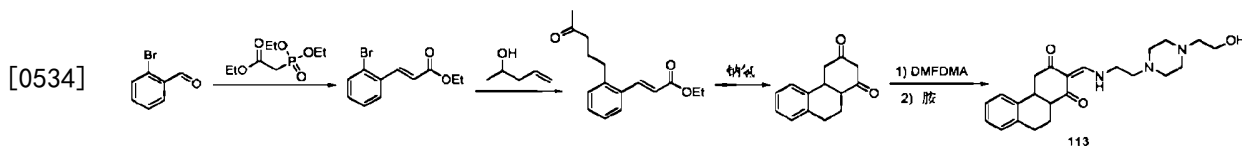
3.31-3.18(m, 2H), 2.91(s, 4H), 2.77-2.58(m, 7H), 2.56(d, $J=4.1$ Hz, 2H), 2.53(s, 3H)。

[0530] 化合物109-112的合成方法同化合物107, 如表6所示。

[0531] 表6: 化合物109-112

#	结构	名称	氢谱(^1H NMR), 质谱(MS)
109		2-((2,6-二氧代-4-苯基亚环己基)-2-((2-(4-(2-羟乙基)哌嗪-1-基)乙基)氨基)乙酸乙酯	^1H NMR (400 MHz, DMSO- d_6) δ 13.13 (s, 1H), 7.29 (s, 4H), 7.20 (s, 1H), 5.33 (s, 2H), 4.82 (s, 1H), 3.60 (d, $J=5.0$ Hz, 4H), 3.24 (d, $J=11.9$ Hz, 2H), 2.98-2.66 (m, 8H), 2.66-2.52 (m, 7H), 2.04 (s, 3H).
110		2-(((2-(4-(2-羟乙基)哌嗪-1-基)乙基)氨基)(苯基)亚甲基)-5-苯基环己烷-1,3-二酮	^1H NMR (400 MHz, DMSO- d_6) δ 13.07 (s, 1H), 7.42 (m, 3H), 7.31 (m, 4H), 7.26-7.14 (m, 3H), 4.91 (s, 1H), 3.62 (s, 2H), 3.32 (m, 5H), 3.12-2.57 (m, 10H), 2.43 (m, 4H).
111		2-(5-羟基-3-氧代-1,2,3,6-四氢-[1,1'-联苯]-4-基)-2-氧代乙酸乙酯	^1H NMR (DMSO- d_6) δ 16.58 (s, 1H), 7.22-7.34 (m, 5H), 5.20 (s, 2H), 3.32-3.46 (m, 1H), 2.68-3.10 (m, 4H), 2.11 (s, 3H); LCMS: 289.1 [M+1].
112		2-(羟基乙基)-5-苯基-环己烷-1,3-二酮	^1H NMR (CD $_3$ OD) δ 7.24-7.36 (m, 6H), 4.73 (s, 2H), 3.35-3.44 (m, 1H), 2.66-2.95 (m, 4H); LCMS: 247.2 [M+1].

[0533] 实施例30: 化合物2-(((2-(4-(2-羟乙基)哌嗪-1-基)乙基)氨基)亚甲基)-4a, 9, 10, 10a-四氢菲咯啉-1,3(2H,4H)-二酮(化合物113)的合成



[0535] 步骤1: 化合物3-(2-溴苯基)丙烯酸乙酯的合成

[0536] 将2-溴苯甲醛(2.0g, 10.8mmol)、磷酰基乙酸三乙酯(2.66g, 11.9mmol)和氢氧化锂(285mg, 11.9mmol)溶于无水THF溶液(14mL), 室温反应3.5小时, 反应完毕将反应混合物倒入冰水中, DCM萃取, 有机相用水洗涤, 硫酸钠干燥, 浓缩, 粗品经柱层析分离纯化得目标化合物2.59g, 产率94%。

[0537] 步骤2: 化合物3-(2-(4-氧代戊基)苯基)丙烯酸乙酯的合成

[0538] 氮气保护下, 将化合物3-(2-溴苯基)丙烯酸乙酯(1.00g, 3.92mmol)、戊-4-烯-2-醇(843mg, 9.8mmol)、醋酸钨(44mg, 0.2mmol)、DIPEA(4.00g, 31mmol)和氯化锂(167mg, 3.94mmol)溶解于干燥DMF溶液(100mL)中, 80℃下反应48小时。反应完毕, 冷却至室温, 倒入冰水中, 用甲基叔丁基醚萃取, 有机相用水洗涤, 硫酸钠干燥, 浓缩, 粗品经柱层析分离纯化得目标化合物612mg, 产率60%。

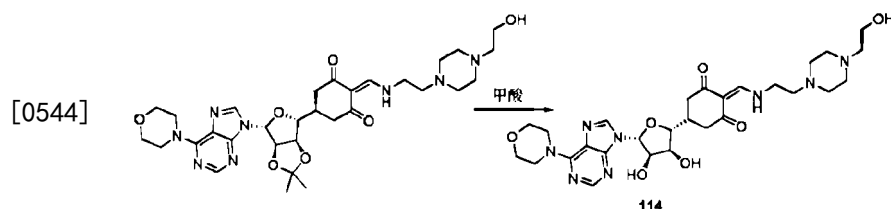
[0539] 步骤3: 化合物4a, 9, 10, 10a-四氢菲咯啉-1,3(2H,4H)-二酮的合成

[0540] 将3-(2-(4-氧代戊基)苯基)丙烯酸乙酯(195mg, 0.75mmol)和钠氢(60%, 100mg, 2.5mmol)溶解于无水THF溶液(12mL)中, 室温反应过夜。反应完毕, 0℃下将反应混合物在缓慢倒入1N盐酸(20mL)中, EA萃取, 有机相用水洗涤, 硫酸钠干燥, 浓缩, 粗品经柱层析分离纯化得目标化合物74mg, 产率46%。

[0541] 步骤4:化合物2-(((2-(4-(2-羟乙基)哌嗪-1-基)乙基)氨基)亚甲基)-4a,9,10,10a-四氢菲咯啉-1,3(2H,4H)-二酮的合成

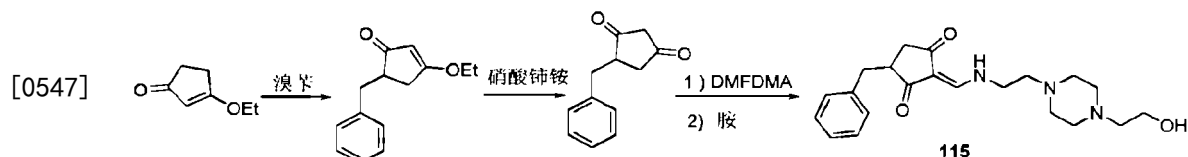
[0542] 操作步骤同实施例2。化合物113: ^1H NMR (400MHz, CD_3OD) δ 8.26 (s, 1H), 7.30 (d, $J=7.6\text{Hz}$, 1H), 7.13 (m, 3H), 3.88-3.77 (m, 2H), 3.63 (t, $J=5.7\text{Hz}$, 2H), 3.28-2.72 (m, 12H), 2.72-2.64 (m, 2H), 2.61-2.35 (m, 3H), 1.62-1.47 (m, 1H)。

[0543] 实施例30B:化合物5-((2R,3S,4R,5R)-3,4-二羟基-5-(6-吗啉代-9H-嘌呤-9-基)四氢呋喃-2-基)-2-(((2-(4-(2-羟乙基)哌嗪-1-基)乙基)氨基)亚甲基)环己烷-1,3-二酮(化合物114)的合成



[0545] 将5-((3AR,4R,6R,6AR)-2,2-二甲基-6-(6-吗啉代-9H-嘌呤-9-基)四氢呋喃并[3,4-D][1,3]二氧杂环戊烯-4-基)-2-(((2-(4-(2-羟乙基)哌嗪-1-基)乙基)氨基)亚甲基)环己-1,3-二酮(120mg, 0.187mmol)加入到1mL甲酸和1mL水中,加热至50℃反应4小时。反应完毕降至室温,倒入冰水中,调节pH至9-10,DCM萃取,有机相用无水硫酸钠干燥,浓缩,粗品经制备板分离得目标化合物73mg,产率65%。化合物114: ^1H NMR (400MHz, CD_3OD) δ 8.24 (s, 1H), 8.19 (s, 1H), 8.15 (s, 1H), 5.94 (d, $J=4.9\text{Hz}$, 1H), 4.72 (t, $J=5.3\text{Hz}$, 1H), 4.38 (s, 1H), 4.26 (s, 4H), 3.88 (t, $J=5.7\text{Hz}$, 1H), 3.82-3.75 (m, 4H), 3.70 (t, $J=5.9\text{Hz}$, 2H), 3.57 (t, $J=5.8\text{Hz}$, 2H), 2.71-2.36 (m, 17H)。

[0546] 实施例31:化合物4-苄基-2-(((2-(4-(2-羟乙基)哌嗪-1-基)乙基)氨基)-亚甲基)环戊烷-1,3-二酮(化合物115)的合成



[0548] 步骤1:化合物5-苄基-3-乙氧基环戊-2-烯-1-酮的合成

[0549] 氮气保护,在-60℃下,将LDA (1mol/L的THF溶液, 5mL, 5mmol)滴加至3-乙氧基环戊-2-烯-1-酮(500mg, 4mmol)的无水THF溶液(15mL)中,在此温度下搅拌30分钟后加入苄溴(855mg, 5mmol),继续反应3小时。反应完毕,将反应混合物倒入饱和氯化铵水溶液中,DCM萃取,有机相用水洗涤,硫酸钠干燥,浓缩,粗品经柱层析分离纯化得目标化合物540mg,产率63%。

[0550] 步骤2:化合物4-苄基环戊烷-1,3-二酮的合成

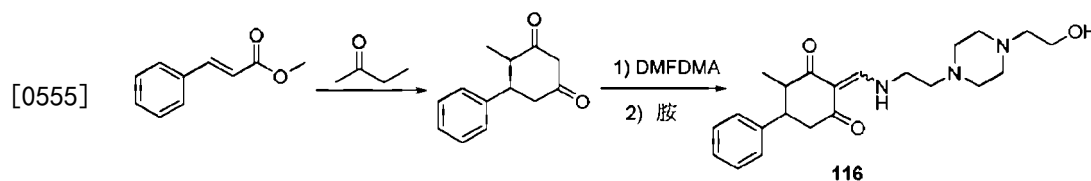
[0551] 将5-苄基-3-乙氧基环戊-2-烯-1-酮(300mg, 1.38mmol)和硝酸钾(152mg, 0.27mmol)加入到5mL乙腈和5mL水中,加热回流4小时。反应完毕降至室温,倒入水中,DCM萃取,有机相干燥,浓缩,粗品经柱层析分离得到160mg,产率62%。

[0552] 步骤3:化合物4-苄基-2-(((2-(4-(2-羟乙基)哌嗪-1-基)乙基)氨基)亚甲基)-环戊烷-1,3-二酮的合成

[0553] 操作步骤同实施例2。化合物115: ^1H NMR (400MHz, CD_3OD) δ 7.86 (s, 1H), 7.27-7.17

(m, 5H), 3.71 (t, J=6.0Hz, 2H), 3.59 (t, J=6.0Hz, 2H), 3.18-3.14 (m, 1H), 2.94-2.88 (m, 1H), 2.74-2.60 (m, 13H), 2.51-2.45 (m, 1H), 2.24-2.18 (m, 1H); MS: 372.2 [M+1].

[0554] 实施例32: 化合物2-(((2-(4-(2-羟乙基)哌嗪-1-基)乙基)氨基)亚甲基)-4-甲基-5-苯基环己烷-1,3-二酮(化合物116)的合成



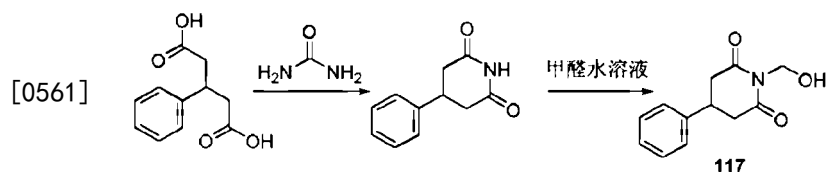
[0556] 步骤1: 化合物4-甲基-5-苯基-1,3-环己二酮的合成

[0557] 氮气保护, 在0℃下将叔丁醇钾(831mg, 7.4mmol)加入到丁-2-酮(5mL)中, 在该温度下搅拌10分钟后, 加入肉桂酸甲酯(1.00g, 6.17mmol)。将反应混合物升温至室温反应30分钟, 反应完毕。将反应混合物倒入冰水中, 用1N盐酸将PH调节至7, EA萃取, 有机相用水洗涤, 干燥, 浓缩, 粗品经柱层析分离得目标化合物510mg, 产率41%。

[0558] 步骤2: 化合物2-(((2-(4-(2-羟乙基)哌嗪-1-基)乙基)氨基)亚甲基)-4-甲基-5-苯基环己烷-1,3-二酮的合成

[0559] 操作步骤同实施例2。化合物116: ^1H NMR (400MHz, CD_3OD) δ 8.35-8.13 (m, 1H), 7.44-7.08 (m, 5H), 3.67 (t, J=6.0Hz, 2H), 3.63-3.55 (m, 2H), 3.06-2.43 (m, 16H), 0.97 (dd, J=12.6, 6.6Hz, 3H); MS: 386.2 [M+1].

[0560] 实施例33: 化合物1-(羟基甲基)-4-苯基哌啶-2,6-二酮(化合物117)的合成



[0562] 步骤1: 化合物4-苯基哌啶-2,6-二酮的合成

[0563] 将3-苯基戊二酸(5.0g, 24mmol)和脲(25g)的混合物在160℃下反应3小时, 反应完毕, 将反应混合物缓慢倒入冰水中, EA萃取, 有机相用水洗涤, 硫酸钠干燥, 浓缩, 粗品经柱层析分离得目标化合物3.6g, 产率79%。

[0564] 步骤2: 化合物1-(羟基甲基)-4-苯基哌啶-2,6-二酮的合成

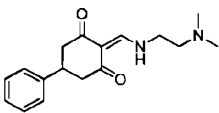
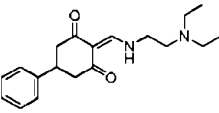
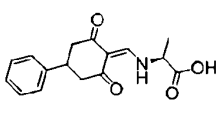
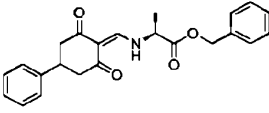
[0565] 将4-苯基哌啶-2,6-二酮(800mg, 4.22mmol)和35%甲醛溶液(10mL)加热至100℃, 直到所有固体溶解。反应完毕降至室温, 倒入水中, EA萃取, 合并的有机相, 无水硫酸钠干燥, 浓缩, 粗品经柱层析分离得目标化合物513mg, 产率55%。化合物117: ^1H NMR ($\text{DMSO}-d_6$) δ 7.31-7.34 (m, 5H), 6.10 (t, J=7.6Hz, 1H), 5.06 (d, J=7.6Hz, 2H), 3.41-3.33 (m, 1H), 2.97-2.90 (m, 2H), 2.82-2.77 (m, 2H); MS: 220.1 [M+1].

[0566] 实施例34: 化合物119-129, 131-143, 145-150, 155-156, 158, 160-165, 169-180, 182-197, 200-233, 236-243, 245-260, 262-274, 276-291, 293-311, 315, 317-318, 320-347和349-414的合成

[0567] 除了使用相应的取代1,3-环己二酮或其他具有活性亚甲基的类似化合物(如实施例9-1), 下列化合物的合成方法同上(如化合物8), 如表7所示。

[0568] 表7

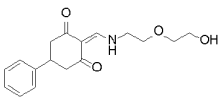
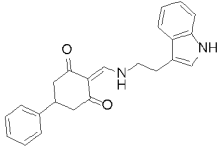
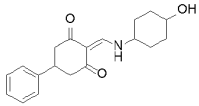
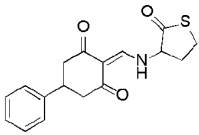
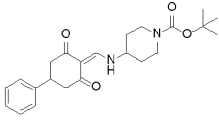
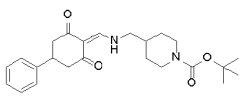
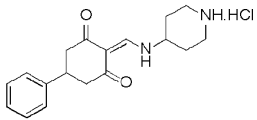
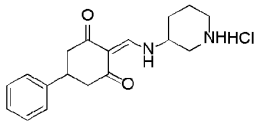
[0569]

#	结构	名称	氢谱(¹ H NMR),质谱(MS)
119		2-(((2-(二甲基氨基)乙基)氨基)亚甲基)-5-苯基环己烷-1,3-二酮	¹ H NMR (400 MHz, CDCl ₃) δ 11.20 (s, 1H), 8.17 (d, <i>J</i> = 14.3 Hz, 1H), 7.34 (t, <i>J</i> = 7.5 Hz, 2H), 7.23 (d, <i>J</i> = 8.3 Hz, 3H), 3.51 (q, <i>J</i> = 6.1 Hz, 2H), 3.36 (ddd, <i>J</i> = 15.7, 10.4, 5.1 Hz, 1H), 2.80 – 2.60 (m, 4H), 2.55 (t, <i>J</i> = 6.2 Hz, 2H), 2.29 (s, 6H).
120		2-(((2-(二乙基氨基)乙基)氨基)亚甲基)-5-苯基环己烷-1,3-二酮	¹ H NMR (400 MHz, CDCl ₃) δ 11.19 (s, 1H), 8.17 (d, <i>J</i> = 14.4 Hz, 1H), 7.33 (t, <i>J</i> = 7.6 Hz, 2H), 7.23 (d, <i>J</i> = 8.0 Hz, 3H), 3.48 (q, <i>J</i> = 6.0 Hz, 2H), 3.36 (ddd, <i>J</i> = 15.7, 10.3, 5.1 Hz, 1H), 2.80 – 2.52 (m, 10H), 1.04 (t, <i>J</i> = 7.1 Hz, 6H).
121		((2,6-二氧代-4-苯基亚环己基)甲基)-L-丙氨酸	¹ H NMR (400 MHz, DMSO-d ₆) δ 11.34 (s, 1H), 9.35 (s, 1H), 8.07 (s, 1H), 7.35 – 7.24 (m, 4H), 7.20 (dd, <i>J</i> = 8.1, 3.8 Hz, 1H), 3.93 (q, <i>J</i> = 6.8 Hz, 1H), 3.34 – 3.22 (m, 1H), 2.77 – 2.58 (m, 2H), 2.47 – 2.40 (m, 2H), 1.32 (d, <i>J</i> = 7.1 Hz, 3H).
122		苄基((2,6-二氧代-4-苯基亚环己基)甲基)-L-丙氨酸酯	¹ H NMR (400 MHz, DMSO-d ₆) δ 11.27 – 11.19 (m, 1H), 8.21 (d, <i>J</i> = 14.1 Hz, 1H), 7.48 – 7.26 (m, 9H), 7.22 (dt, <i>J</i> = 8.5, 4.1 Hz, 1H), 5.22 (d, <i>J</i> = 13.0 Hz, 2H), 4.79 – 4.69 (m, 1H), 2.84 – 2.68 (m, 2H), 2.60 – 2.51 (m, 2H), 1.50 (d, <i>J</i> = 7.2 Hz, 3H).

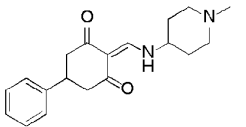
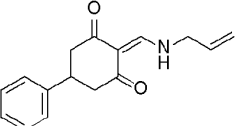
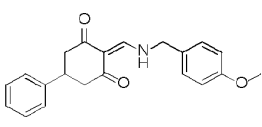
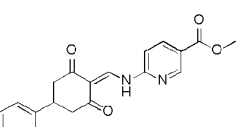
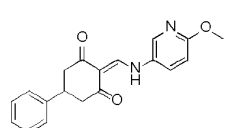
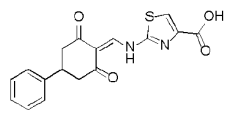
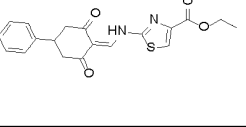
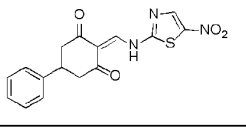
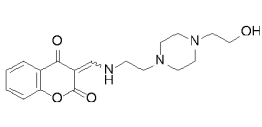
[0570]

123		((2,6-二氧代-4-苯基亚环己基)氨基)苯丙氨酸	^1H NMR (400 MHz, CD_3OD) δ 7.87 (d, J = 5.7 Hz, 1H), 7.34 – 7.15 (m, 10H), 4.60 – 4.52 (m, 1H), 3.39 – 3.31 (m, 2H), 3.16 – 3.06 (m, 1H), 2.76 (dt, J = 8.9, 5.0 Hz, 1H), 2.70 – 2.56 (m, 3H).
124		((2,6-二氧代-4-苯基亚环己基)氨基)苯基丙氨酸乙酯	^1H NMR (400 MHz, CDCl_3) δ 11.38 (s, 1H), 7.84 (dd, J = 13.8, 4.7 Hz, 1H), 7.38 – 7.27 (m, 5H), 7.19 (d, J = 31.7 Hz, 5H), 4.24 (d, J = 6.1 Hz, 3H), 3.30 (dd, J = 18.9, 8.0 Hz, 2H), 3.15 – 3.06 (m, 1H), 2.80 – 2.57 (m, 4H), 1.27 (td, J = 7.1, 3.5 Hz, 3H).
125		苯基((2,6-二氧代-4-苯基亚环己基)氨基)-L-苯丙氨酸	^1H NMR (400 MHz, DMSO-d_6) δ 11.12 (dd, J = 13.7, 9.1 Hz, 1H), 8.03 (d, J = 14.0 Hz, 1H), 7.40 – 7.30 (m, 5H), 7.31 – 7.16 (m, 8H), 7.11 (t, J = 6.4 Hz, 2H), 5.18 (d, J = 3.0 Hz, 2H), 4.99 (dd, J = 14.3, 8.0 Hz, 1H), 3.28 – 3.14 (m, 3H), 2.78 – 2.61 (m, 2H), 2.52 (s, 1H).
126		((2,6-二氧代-4-苯基亚环己基)氨基)-L-组氨酸	^1H NMR (400 MHz, DMSO-d_6) δ 11.27 – 11.09 (m, 1H), 7.95 (d, J = 14.6 Hz, 1H), 7.69 (s, 1H), 7.24 (d, J = 34.3 Hz, 4H), 6.86 (s, 1H), 4.67 (s, 1H), 3.27 (s, 1H), 3.08 (s, 2H), 2.81 – 2.56 (m, 2H), 2.41 (s, 2H).
127		((2,6-二氧代-4-苯基亚环己基)氨基)甲硫氨酸甲基酯	^1H NMR (400 MHz, CDCl_3) δ 11.37 (s, 1H), 8.14 (d, J = 13.6 Hz, 1H), 7.35 (t, J = 7.4 Hz, 2H), 7.23 (d, J = 7.1 Hz, 3H), 4.35 (td, J = 8.9, 4.9 Hz, 1H), 3.81 (d, J = 1.8 Hz, 3H), 3.44 – 3.31 (m, 1H), 2.85 – 2.57 (m, 5H), 2.50 (dd, J = 7.2, 3.5 Hz, 1H), 2.27 (dt, J = 13.2, 7.5 Hz, 1H), 2.19 – 2.02 (m, 4H).
128		2-((2-甲氧基乙基)氨基)亚甲基)-5-苯基环己烷-1,3-二酮	^1H NMR (400 MHz, CDCl_3) δ 11.23 (s, 1H), 8.18 (d, J = 14.2 Hz, 1H), 7.34 (t, J = 7.4 Hz, 2H), 7.23 (d, J = 8.3 Hz, 3H), 3.62 – 3.51 (m, 4H), 3.42 – 3.30 (m, 4H), 2.81 – 2.60 (m, 4H).
129		((2,6-二氧代-4-苯基亚环己基)氨基)甘氨酸甲酯	^1H NMR (400 MHz, CDCl_3) δ 11.27 (s, 1H), 8.10 (d, J = 13.8 Hz, 1H), 7.35 (t, J = 7.4 Hz, 2H), 7.24 (dd, J = 6.5, 5.1 Hz, 3H), 4.20 (d, J = 6.1 Hz, 2H), 3.82 (s, 3H), 3.38 (dd, J = 14.4, 8.2 Hz, 1H), 2.82 – 2.65 (m, 4H).
131		4-(((2,6-二氧代-4-苯基亚环己基)氨基)氨基)丁酸	^1H NMR (400 MHz, DMSO-d_6) δ 12.17 (s, 1H), 10.91 (d, J = 14.6 Hz, 1H), 8.08 (d, J = 14.6 Hz, 1H), 7.34 – 7.14 (m, 5H), 3.46 (q, J = 6.7 Hz, 2H), 3.31 – 3.22 (m, 1H), 2.70 (ddd, J = 33.3, 16.6, 11.8 Hz, 2H), 2.51 (d, J = 3.9 Hz, 1H), 2.44 (s, 1H), 2.21 (t, J = 7.4 Hz, 2H), 1.78 (dd, J = 14.2, 7.0 Hz, 2H).
132		2-((4-羟基丁基)氨基)亚甲基)-5-苯基环己烷-1,3-二酮	^1H NMR (400 MHz, CDCl_3) δ 11.23 (s, 1H), 8.17 (d, J = 14.2 Hz, 1H), 7.33 (t, J = 7.4 Hz, 2H), 7.23 (d, J = 8.2 Hz, 3H), 3.70 (t, J = 6.1 Hz, 2H), 3.50 (q, J = 6.7 Hz, 2H), 3.35 (td, J = 10.8, 5.7 Hz, 1H), 2.82 – 2.58 (m, 4H), 1.84 – 1.71 (m, 2H), 1.68 – 1.56 (m, 2H).
133		2-((3-氯丙基)氨基)亚甲基)-5-苯基环己烷-1,3-二酮	^1H NMR (400 MHz, CDCl_3) δ 11.22 (s, 1H), 8.19 (d, J = 14.0 Hz, 1H), 7.34 (t, J = 7.4 Hz, 2H), 7.26 – 7.20 (m, 3H), 3.63 (dt, J =

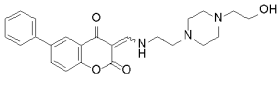
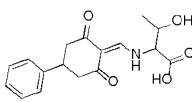
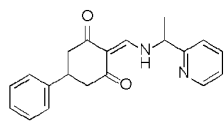
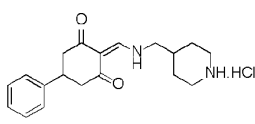
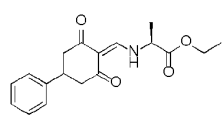
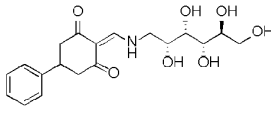
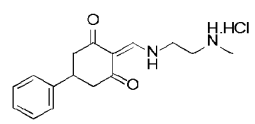
[0571]

		酮	12.1, 6.3 Hz, 4H), 3.42 – 3.30 (m, 1H), 2.82 – 2.60 (m, 4H), 2.18 – 2.06 (m, 2H).
134		2-(((2-(2-羟基乙氧基)乙基)氨基)亚甲基)-5-苯基环己烷-1,3-二酮	¹ HNMR (400 MHz, CDCl ₃) δ 11.32 (s, 1H), 8.24 (d, <i>J</i> = 14.2 Hz, 1H), 7.34 (t, <i>J</i> = 7.4 Hz, 2H), 7.23 (dd, <i>J</i> = 5.9, 4.7 Hz, 3H), 3.80 – 3.73 (m, 2H), 3.69 (t, <i>J</i> = 4.7 Hz, 2H), 3.61 (dd, <i>J</i> = 8.7, 4.4 Hz, 4H), 3.36 (ddd, <i>J</i> = 15.8, 10.6, 5.3 Hz, 1H), 2.82 – 2.58 (m, 4H).
135		2-(((2-(1H-吡咯-3-基)乙基)氨基)亚甲基)-5-苯基环己烷-1,3-二酮	¹ HNMR (400 MHz, DMSO-d ₆) δ 11.01 (d, <i>J</i> = 14.2 Hz, 1H), 10.87 (s, 1H), 8.03 (d, <i>J</i> = 14.6 Hz, 1H), 7.58 (d, <i>J</i> = 7.8 Hz, 1H), 7.35 – 7.25 (m, 5H), 7.22 – 7.17 (m, 1H), 7.15 (d, <i>J</i> = 2.1 Hz, 1H), 7.06 (t, <i>J</i> = 7.5 Hz, 1H), 6.96 (t, <i>J</i> = 7.5 Hz, 1H), 3.74 (dd, <i>J</i> = 13.4, 6.8 Hz, 2H), 3.25 (dd, <i>J</i> = 13.7, 9.9 Hz, 1H), 2.98 (t, <i>J</i> = 7.0 Hz, 2H), 2.74 – 2.58 (m, 2H), 2.46 – 2.38 (m, 2H).
136		2-(((4-羟基环己基)氨基)亚甲基)-5-苯基环己烷-1,3-二酮	¹ HNMR (400 MHz, DMSO-d ₆) δ 11.03 (dd, <i>J</i> = 14.4, 8.1 Hz, 1H), 8.16 (d, <i>J</i> = 14.3 Hz, 1H), 7.35 – 7.25 (m, 4H), 7.24 – 7.16 (m, 1H), 4.60 (d, <i>J</i> = 4.4 Hz, 1H), 3.57 – 3.35 (m, 2H), 3.28 (dt, <i>J</i> = 11.7, 4.0 Hz, 1H), 2.69 (ddd, <i>J</i> = 33.9, 16.6, 11.8 Hz, 2H), 2.54 – 2.50 (m, 1H), 2.47 – 2.41 (m, 1H), 1.82 (t, <i>J</i> = 13.1 Hz, 4H), 1.55 – 1.38 (m, 2H), 1.22 (dd, <i>J</i> = 21.5, 11.0 Hz, 2H).
137		2-(((2-氧代四氢噻吩-3-基)氨基)亚甲基)-5-苯基环己烷-1,3-二酮	¹ HNMR (400 MHz, DMSO-d ₆) δ 10.86 – 10.73 (m, 1H), 8.05 (d, <i>J</i> = 14.5 Hz, 1H), 7.36 – 7.25 (m, 4H), 7.21 (dd, <i>J</i> = 8.3, 4.0 Hz, 1H), 4.74 (dt, <i>J</i> = 12.9, 6.6 Hz, 1H), 3.35 – 3.25 (m, 4H), 2.87 – 2.58 (m, 3H), 2.58 – 2.50 (m, 1H), 2.45 – 2.37 (m, 1H).
138		4-(((2,6-二氧代-4-苯基亚环己基)甲基)氨基)哌啶-1-甲酸叔丁酯	¹ HNMR (400 MHz, CDCl ₃) δ 11.29 (s, 1H), 8.23 (d, <i>J</i> = 14.0 Hz, 1H), 7.34 (t, <i>J</i> = 7.5 Hz, 2H), 7.25 – 7.20 (m, 3H), 4.08 (s, 2H), 3.48 (d, <i>J</i> = 7.1 Hz, 1H), 3.35 (dd, <i>J</i> = 13.5, 8.2 Hz, 1H), 2.91 (t, <i>J</i> = 11.7 Hz, 2H), 2.79 – 2.61 (m, 4H), 1.97 (d, <i>J</i> = 11.0 Hz, 2H), 1.61 (d, <i>J</i> = 8.1 Hz, 2H), 1.46 (s, 9H).
139		4-(((2,6-二氧代-4-苯基亚环己基)甲基)氨基)哌啶-1-甲酸叔丁酯	¹ HNMR (400 MHz, DMSO-d ₆) δ 11.01 – 10.91 (m, 1H), 8.08 (d, <i>J</i> = 14.4 Hz, 1H), 7.30 (dd, <i>J</i> = 7.0, 6.1 Hz, 4H), 7.23 – 7.16 (m, 1H), 3.92 (d, <i>J</i> = 12.4 Hz, 2H), 3.38 (t, <i>J</i> = 6.5 Hz, 2H), 3.30 – 3.25 (m, 1H), 2.70 (ddd, <i>J</i> = 34.4, 16.6, 11.8 Hz, 4H), 2.44 (s, 1H), 1.70 (s, 1H), 1.53 (d, <i>J</i> = 11.4 Hz, 2H), 1.37 (s, 9H), 0.99 (dt, <i>J</i> = 12.0, 8.1 Hz, 2H).
140		5-苯基-2-((哌啶-4-基氨基)亚甲基)环己烷-1,3-二酮盐酸盐	¹ HNMR (400 MHz, CD ₃ OD) δ 8.32 (s, 1H), 7.35 – 7.26 (m, 4H), 7.23 (dd, <i>J</i> = 11.2, 4.3 Hz, 1H), 3.84 (t, <i>J</i> = 11.3 Hz, 1H), 3.49 (d, <i>J</i> = 13.3 Hz, 2H), 3.40 – 3.32 (m, 1H), 3.13 (t, <i>J</i> = 11.6 Hz, 2H), 2.85 – 2.74 (m, 2H), 2.67 (dd, <i>J</i> = 16.7, 4.1 Hz, 2H), 2.25 (d, <i>J</i> = 11.9 Hz, 2H), 1.90 (td, <i>J</i> = 14.1, 4.2 Hz, 2H).
141		5-苯基-2-((哌啶-3-基氨基)亚甲基)环己烷-1,3-二酮盐酸盐	¹ HNMR (400 MHz, DMSO-d ₆) δ 10.88 (dd, <i>J</i> = 14.1, 8.4 Hz, 1H), 9.54 (s, 1H), 9.35 (d, <i>J</i> = 10.1 Hz, 1H), 8.14 (d, <i>J</i> = 14.2 Hz, 1H), 7.33 (dd, <i>J</i> = 7.2, 6.1 Hz, 3H), 7.27 – 7.18

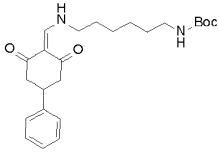
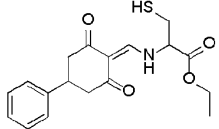
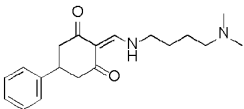
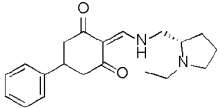
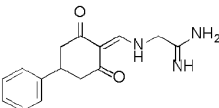
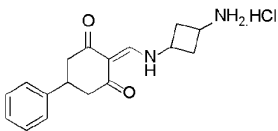
[0572]

			(m, 1H), 5.92 (s, 3H), 3.89 (s, 1H), 3.34 (d, $J = 11.7$ Hz, 1H), 3.19 – 3.05 (m, 2H), 2.72 (d, $J = 12.7$ Hz, 3H), 2.55 (s, 1H), 1.98 (s, 1H), 1.79 (m, 3H).
142		2-(((1-甲基哌啶-4-基)氨基)亚甲基)-5-苯基环己烷-1,3-二酮	^1H NMR (400 MHz, CDCl_3) δ 11.30 (s, 1H), 8.23 (d, $J = 14.1$ Hz, 1H), 7.34 (t, $J = 7.4$ Hz, 2H), 7.23 (d, $J = 8.2$ Hz, 3H), 3.36 (dd, $J = 19.1, 13.2$ Hz, 2H), 2.87 – 2.61 (m, 6H), 2.30 (s, 3H), 2.16 (t, $J = 10.6$ Hz, 2H), 2.00 (d, $J = 13.2$ Hz, 2H), 1.76 (q, $J = 13.7$ Hz, 2H).
143		2-((烯丙氨基)亚甲基)-5-苯基环己烷-1,3-二酮	^1H NMR (400 MHz, CDCl_3) δ 11.21 (s, 1H), 8.17 (d, $J = 14.1$ Hz, 1H), 7.34 (t, $J = 7.4$ Hz, 2H), 7.26 – 7.20 (m, 3H), 5.89 (ddd, $J = 22.2, 11.0, 5.6$ Hz, 1H), 5.34 – 5.26 (m, 2H), 4.04 (t, $J = 5.7$ Hz, 2H), 3.44 – 3.28 (m, 1H), 2.83 – 2.59 (m, 4H).
145		2-(((4-甲氧基苄基)氨基)亚甲基)-5-苯基环己烷-1,3-二酮	^1H NMR (400 MHz, CDCl_3) δ 11.39 (s, 1H), 8.24 (d, $J = 14.1$ Hz, 1H), 7.34 (t, $J = 7.4$ Hz, 2H), 7.26 – 7.14 (m, 5H), 6.93 – 6.86 (m, 2H), 4.53 (d, $J = 6.0$ Hz, 2H), 3.81 (s, 3H), 3.41 – 3.31 (m, 1H), 2.82 – 2.60 (m, 4H).
146		6-(((2,6-二氧代-4-苯基亚环己基)氨基)氨基)烟酸甲酯	^1H NMR (400 MHz, DMSO-d_6) δ 12.44 (d, $J = 10.9$ Hz, 1H), 9.07 (d, $J = 10.8$ Hz, 1H), 8.93 (d, $J = 2.0$ Hz, 1H), 8.30 (dd, $J = 8.6, 2.1$ Hz, 1H), 7.68 (d, $J = 8.6$ Hz, 1H), 7.37 – 7.16 (m, 5H), 3.86 (s, 3H), 3.44 (t, $J = 11.4$ Hz, 1H), 3.03 – 2.79 (m, 2H), 2.67 (t, $J = 16.8$ Hz, 2H).
147		2-(((6-甲氧基吡啶-3-基)氨基)亚甲基)-5-苯基环己烷-1,3-二酮	^1H NMR (400 MHz, DMSO-d_6) δ 12.63 (d, $J = 13.6$ Hz, 1H), 8.40 (d, $J = 13.7$ Hz, 1H), 8.33 (d, $J = 2.8$ Hz, 1H), 7.96 (dd, $J = 9.0, 2.9$ Hz, 1H), 7.38 – 7.25 (m, 4H), 7.25 – 7.18 (m, 1H), 6.87 (d, $J = 8.9$ Hz, 1H), 3.84 (s, 3H), 3.38 (ddd, $J = 15.4, 7.6, 3.9$ Hz, 1H), 2.82 (ddd, $J = 41.2, 16.4, 11.6$ Hz, 2H), 2.61 (dd, $J = 20.6, 16.8$ Hz, 2H).
148		2-(((2,6-二氧代-4-苯基亚环己基)氨基)氨基)噻唑-4-羧酸	^1H NMR (400 MHz, DMSO-d_6) δ 8.71 (s, 1H), 7.87 (s, 1H), 7.28 (t, $J = 21.9$ Hz, 5H), 3.40 (s, 1H), 2.92 – 2.76 (m, 2H), 2.61 (d, $J = 17.2$ Hz, 2H).
149		2-(((2,6-二氧代-4-苯基亚环己基)氨基)氨基)噻唑-4-羧酸乙酯	^1H NMR (400 MHz, CDCl_3) δ 13.15 (d, $J = 12.3$ Hz, 1H), 8.71 (d, $J = 12.4$ Hz, 1H), 7.89 (s, 1H), 7.36 (t, $J = 7.4$ Hz, 2H), 7.31 – 7.18 (m, 3H), 4.42 (q, $J = 7.1$ Hz, 2H), 3.43 (s, 1H), 2.82 (m, 4H), 1.42 (t, $J = 7.1$ Hz, 3H).
150		2-(((5-硝基噻唑-2-基)氨基)亚甲基)-5-苯基环己烷-1,3-二酮	^1H NMR (400 MHz, DMSO-d_6) δ 12.88 (s, 1H), 8.71 (s, 1H), 8.62 (s, 1H), 7.38 – 7.15 (m, 5H), 3.46 (t, $J = 11.6$ Hz, 1H), 3.03 – 2.82 (m, 2H), 2.71 (s, 2H).
155		3-(((2-(4-(2-羟乙基)哌嗪-1-基)乙基)氨基)亚甲基)-5-苯基环己烷-1,3-二酮	^1H NMR (400 MHz, DMSO-d_6) δ 11.54 (s, 1H), 10.29 (s, 1H), 8.49 (dd, $J = 8.2, 5.7$ Hz, 1H), 7.92 (t, $J = 7.5$ Hz, 1H), 7.63 (t, $J = 6.9$ Hz, 1H), 7.28 (dd, $J = 8.4, 5.2$ Hz, 2H), 4.60 (s, 1H), 3.68 (d, $J = 5.5$ Hz, 2H), 3.53 (s,

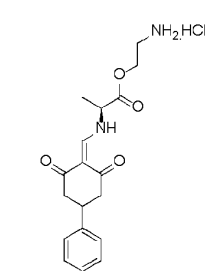
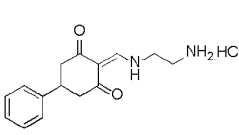
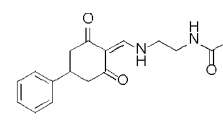
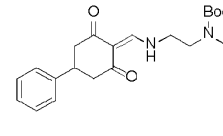
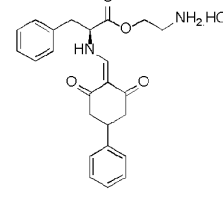
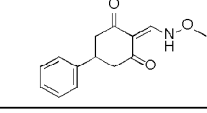
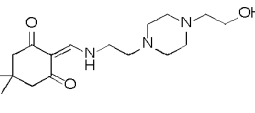
[0573]

		-2,4-二酮	2H), 3.32 (s, 2H), 2.57 – 2.31 (m, 10H).
156		3-(((2-(4-(2-羟乙基)吡啶-1-基)乙基)氨基)亚甲基)-6-苯基色满-2,4-二酮	¹ HNMR (400 MHz, DMSO-d ₆) δ 11.57 (s, 1H), 10.33 (s, 1H), 8.52 (dd, <i>J</i> = 53.2, 15.2 Hz, 1H), 8.16 – 8.07 (m, 1H), 7.93 (d, <i>J</i> = 8.4 Hz, 1H), 7.68 (d, <i>J</i> = 7.3 Hz, 2H), 7.48 (t, <i>J</i> = 7.6 Hz, 2H), 7.38 (t, <i>J</i> = 8.6 Hz, 2H), 4.55 (s, 1H), 3.69 (d, <i>J</i> = 5.5 Hz, 2H), 3.52 (s, 2H), 2.56 (s, 8H).
158		2-((((2,6-二氧代-4-苯基亚环己基)甲基)氨基)-3-羟基丁酸	¹ HNMR (400 MHz, DMSO-d ₆) δ 11.15 (dd, <i>J</i> = 14.6, 8.6 Hz, 1H), 9.29 (s, 1H), 8.02 (d, <i>J</i> = 15.0 Hz, 1H), 7.39 – 7.11 (m, 5H), 3.87 (d, <i>J</i> = 5.1 Hz, 1H), 3.71 (s, 1H), 3.33 – 3.24 (m, 1H), 2.77 – 2.59 (m, 2H), 2.46 (s, 2H), 1.02 (dd, <i>J</i> = 6.1, 2.6 Hz, 3H).
160		5-苯基-2-((((1-(吡啶-2-基)乙基)氨基)亚甲基)环己烷-1,3-二酮	¹ HNMR (400 MHz, DMSO-d ₆) δ 11.59 (s, 1H), 8.59 (d, <i>J</i> = 4.0 Hz, 1H), 8.31 (d, <i>J</i> = 14.4 Hz, 1H), 7.82 (t, <i>J</i> = 7.7 Hz, 1H), 7.41 (d, <i>J</i> = 7.6 Hz, 1H), 7.37 – 7.31 (m, 1H), 7.28 (s, 4H), 7.21 (d, <i>J</i> = 3.3 Hz, 1H), 5.13 – 5.03 (m, 1H), 3.27 (d, <i>J</i> = 11.7 Hz, 1H), 2.80 – 2.62 (m, 2H), 2.52 (s, 1H), 1.54 (d, <i>J</i> = 6.8 Hz, 3H).
161		5-苯基-2-((((吡啶-4-基甲基)氨基)亚甲基)环己烷-1,3-二酮盐酸盐	¹ HNMR (400 MHz, CD ₃ OD) δ 8.21 (s, 1H), 7.35 – 7.19 (m, 5H), 3.50 – 3.32 (m, 5H), 3.00 (td, <i>J</i> = 12.9, 2.8 Hz, 2H), 2.74 (dtd, <i>J</i> = 22.9, 17.0, 12.0 Hz, 4H), 1.96 (t, <i>J</i> = 10.0 Hz, 3H), 1.47 (dd, <i>J</i> = 23.9, 10.8 Hz, 2H).
162		((2,6-二氧代-4-苯基亚环己基)甲基)-L-丙氨酸乙酯	¹ HNMR (400 MHz, CDCl ₃) δ 11.45 (s, 1H), 8.16 (d, <i>J</i> = 13.9 Hz, 1H), 7.34 (t, <i>J</i> = 7.4 Hz, 2H), 7.24 (d, <i>J</i> = 8.2 Hz, 3H), 4.30 – 4.15 (m, 3H), 3.42 – 3.32 (m, 1H), 2.82 – 2.64 (m, 4H), 1.61 (dd, <i>J</i> = 7.2, 1.1 Hz, 3H), 1.31 (td, <i>J</i> = 7.1, 1.5 Hz, 3H).
163		2-((((2R, 3S, 4S, 5S)-2,3,4,5,6-五羟基己基)氨基)亚甲基)-5-苯基环己烷-1,3-二酮	¹ HNMR (400 MHz, DMSO-d ₆) δ 11.05 – 10.96 (m, 1H), 8.08 (d, <i>J</i> = 14.4 Hz, 1H), 7.30 (d, <i>J</i> = 4.4 Hz, 4H), 7.23 – 7.17 (m, 1H), 5.02 (d, <i>J</i> = 4.2 Hz, 1H), 4.50 (d, <i>J</i> = 5.3 Hz, 1H), 4.44 (dd, <i>J</i> = 12.3, 6.3 Hz, 2H), 4.34 (t, <i>J</i> = 5.4 Hz, 1H), 3.68 – 3.53 (m, 4H), 3.50 – 3.36 (m, 4H), 3.28 (d, <i>J</i> = 11.5 Hz, 1H), 2.69 (ddd, <i>J</i> = 31.9, 16.6, 11.8 Hz, 2H).
164		2-((((2-(甲基氨基)乙基)氨基)亚甲基)-5-苯基环己烷-1,3-二酮盐酸盐	¹ HNMR (400 MHz, D ₂ O) δ 8.23 (s, 1H), 7.40 (t, <i>J</i> = 7.4 Hz, 2H), 7.31 (dd, <i>J</i> = 15.6, 7.6 Hz, 3H), 3.88 (t, <i>J</i> = 5.8 Hz, 2H), 3.46 (td, <i>J</i> = 9.8, 4.5 Hz, 1H), 3.37 (t, <i>J</i> = 5.9 Hz, 2H), 2.92 – 2.64 (m, 7H).

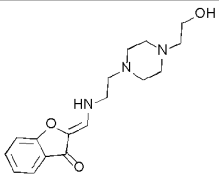
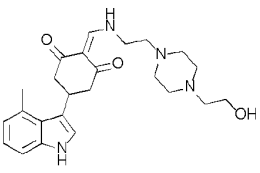
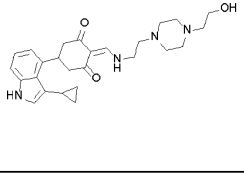
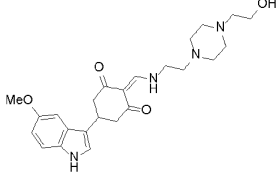
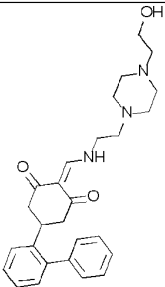
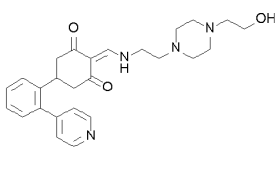
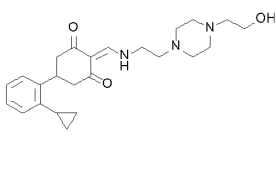
[0574]

165		6-(((2,6-二氧代-4-苯基亚环己基)甲基)氨基)己基)氨基甲酸叔丁酯	¹ HNMR (400 MHz, CDCl ₃) δ 11.21 (s, 1H), 8.16 (d, <i>J</i> = 14.1 Hz, 1H), 7.34 (t, <i>J</i> = 7.4 Hz, 2H), 7.26 – 7.20 (m, 3H), 4.53 (s, 1H), 3.43 (dd, <i>J</i> = 13.4, 6.8 Hz, 2H), 3.39 – 3.31 (m, 1H), 3.11 (d, <i>J</i> = 6.7 Hz, 2H), 2.81 – 2.61 (m, 4H), 1.66 (dd, <i>J</i> = 13.9, 6.4 Hz, 3H), 1.55 – 1.23 (m, 14H).
169		((2,6-二氧代-4-苯基亚环己基)甲基)半胱氨酸乙酯	¹ HNMR (400 MHz, CDCl ₃) δ 11.52 (s, 1H), 8.16 (dd, <i>J</i> = 13.7, 0.7 Hz, 1H), 7.35 (t, <i>J</i> = 7.4 Hz, 2H), 7.25 (dd, <i>J</i> = 6.3, 4.9 Hz, 3H), 4.34 – 4.20 (m, 3H), 3.44 – 3.33 (m, 1H), 3.13 – 2.98 (m, 2H), 2.85 – 2.74 (m, 3H), 2.69 (dd, <i>J</i> = 16.9, 12.1 Hz, 1H), 1.56 (td, <i>J</i> = 9.1, 2.7 Hz, 1H), 1.33 (td, <i>J</i> = 7.1, 2.6 Hz, 3H).
170		2-(((4-(二甲基氨基)丁基)氨基)亚甲基)-5-苯基环己烷-1,3-二酮	¹ HNMR (400 MHz, CD ₃ OD) δ 8.24 (s, 1H), 7.35 – 7.18 (m, 5H), 3.53 (t, <i>J</i> = 6.9 Hz, 2H), 3.35 (ddd, <i>J</i> = 11.6, 8.0, 4.3 Hz, 1H), 2.75 (d, <i>J</i> = 12.0 Hz, 2H), 2.64 (dd, <i>J</i> = 16.8, 4.2 Hz, 2H), 2.42 – 2.34 (m, 2H), 2.26 (s, 6H), 1.68 (dt, <i>J</i> = 14.1, 6.9 Hz, 2H), 1.59 – 1.51 (m, 2H).
171		2-((((S)-1-乙基吡咯烷-2-基)甲基)氨基)亚甲基)-5-苯基环己烷-1,3-二酮	¹ HNMR (400 MHz, CDCl ₃) δ 11.19 (s, 1H), 8.17 (d, <i>J</i> = 14.3 Hz, 1H), 7.34 (t, <i>J</i> = 7.5 Hz, 2H), 7.24 (d, <i>J</i> = 8.0 Hz, 3H), 3.54 – 3.46 (m, 1H), 3.37 (dt, <i>J</i> = 15.7, 5.4 Hz, 2H), 3.24 – 3.17 (m, 1H), 2.85 – 2.61 (m, 6H), 2.35 (dq, <i>J</i> = 13.8, 7.0 Hz, 1H), 2.23 (dt, <i>J</i> = 16.4, 8.3 Hz, 1H), 1.93 (ddd, <i>J</i> = 17.2, 12.5, 8.6 Hz, 1H), 1.79 – 1.63 (m, 2H), 1.60 – 1.49 (m, 1H), 1.13 (t, <i>J</i> = 7.2 Hz, 3H).
172		2-(((2,6-二氧代-4-苯基亚环己基)甲基)氨基)乙酰亚胺酰胺	¹ HNMR (400 MHz, DMSO-d ₆) δ 10.83 (s, 1H), 8.89 (s, 4H), 8.16 (s, 1H), 7.33 (d, <i>J</i> = 4.4 Hz, 4H), 7.27 – 7.20 (m, 1H), 4.44 (s, 2H), 3.34 – 3.27 (m, 1H), 2.84 – 2.67 (m, 2H), 2.56 (d, <i>J</i> = 16.3 Hz, 2H).
173		2-(((3-氨基环丁基)氨基)亚甲基)-5-苯基环己烷-1,3-二酮盐酸盐	¹ HNMR (400 MHz, D ₂ O) δ 8.01 (s, 1H), 7.27 – 7.20 (m, 2H), 7.19 – 7.11 (m, 3H), 4.32 (dt, <i>J</i> = 15.1, 7.4 Hz, 1H), 3.82 (td, <i>J</i> = 8.6, 4.5 Hz, 1H), 3.28 (ddd, <i>J</i> = 15.0, 10.2, 4.6 Hz, 1H), 2.71 – 2.46 (m, 8H).

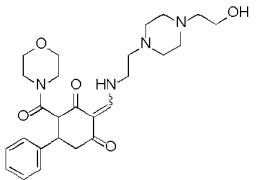
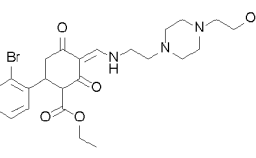
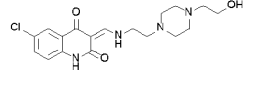
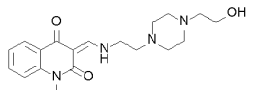
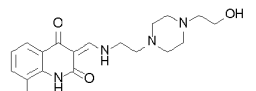
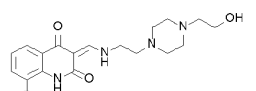
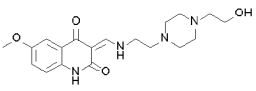
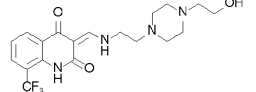
[0575]

174		((2,6-二氧代-4-苯基亚环己基)甲基)-L-丙氨酸盐酸盐	¹ HNMR (400 MHz, DMSO-d ₆) δ 11.24 – 11.13 (m, 1H), 8.31 (s, 2H), 8.21 (d, <i>J</i> = 14.2 Hz, 1H), 8.00 (s, 1H), 7.32 (d, <i>J</i> = 4.4 Hz, 4H), 7.27 – 7.19 (m, 1H), 4.70 (p, <i>J</i> = 7.2 Hz, 1H), 4.45 – 4.35 (m, 1H), 4.33 – 4.24 (m, 1H), 3.58 (dd, <i>J</i> = 9.2, 3.7 Hz, 1H), 3.35 – 3.30 (m, 1H), 3.10 (d, <i>J</i> = 4.5 Hz, 2H), 2.93 – 2.66 (m, 3H), 2.59 – 2.53 (m, 1H), 1.53 (d, <i>J</i> = 7.1 Hz, 3H).
175		2-(((2-氨基乙基)氨基)亚甲基)-5-苯基环己烷-1,3-二酮盐酸盐	¹ HNMR (400 MHz, DMSO-d ₆) δ 10.88 – 10.77 (m, 1H), 8.32 (s, 3H), 8.10 (d, <i>J</i> = 14.4 Hz, 1H), 7.32 (d, <i>J</i> = 4.3 Hz, 4H), 7.28 (dd, <i>J</i> = 37.6, 4.3 Hz, 5H), 7.23 (d, <i>J</i> = 4.3 Hz, 1H), 3.73 (d, <i>J</i> = 6.1 Hz, 2H), 3.31 (tt, <i>J</i> = 11.5, 4.0 Hz, 1H), 3.06 (dd, <i>J</i> = 11.4, 5.6 Hz, 2H), 2.73 (dt, <i>J</i> = 28.6, 14.1 Hz, 2H), 2.53 (d, <i>J</i> = 13.3 Hz, 2H).
176		N-(2-(((2,6-二氧代-4-苯基亚环己基)甲基)氨基)乙基)乙酰胺	¹ HNMR (400 MHz, CDCl ₃) δ 11.21 (s, 1H), 8.14 (d, <i>J</i> = 14.0 Hz, 1H), 7.35 (t, <i>J</i> = 7.4 Hz, 2H), 7.24 (t, <i>J</i> = 6.7 Hz, 3H), 6.03 (s, 1H), 3.59 (dd, <i>J</i> = 11.7, 5.8 Hz, 2H), 3.49 (dd, <i>J</i> = 11.5, 5.7 Hz, 2H), 3.42 – 3.30 (m, 1H), 2.82 – 2.59 (m, 4H), 2.02 (s, 3H).
177		(2-(((2,6-二氧代-4-苯基亚环己基)甲基)氨基)乙基)(甲基)氨基甲酸叔丁酯	¹ HNMR (400 MHz, CDCl ₃) δ 11.22 (s, 1H), 8.12 (d, <i>J</i> = 13.9 Hz, 1H), 7.34 (t, <i>J</i> = 7.4 Hz, 2H), 7.27 – 7.20 (m, 3H), 3.58 (s, 2H), 3.46 (t, <i>J</i> = 5.7 Hz, 2H), 3.41 – 3.29 (m, 1H), 2.89 (s, 3H), 2.81 – 2.60 (m, 4H), 1.46 (s, 9H).
178		((2,6-二氧代-4-苯基亚环己基)甲基)-L-苯丙氨酸盐酸盐的 2-氨基乙基酯	¹ HNMR (400 MHz, DMSO-d ₆) δ 11.14 – 11.02 (m, 1H), 8.31 (s, 3H), 7.97 (d, <i>J</i> = 14.0 Hz, 1H), 7.40 – 7.06 (m, 10H), 4.94 (td, <i>J</i> = 8.9, 4.6 Hz, 1H), 4.41 (dd, <i>J</i> = 12.1, 3.2 Hz, 1H), 4.29 (dd, <i>J</i> = 12.1, 2.6 Hz, 1H), 3.26 (ddd, <i>J</i> = 19.7, 11.0, 3.5 Hz, 2H), 3.13 (s, 2H), 2.82 – 2.61 (m, 2H), 2.54 (s, 1H), 2.44 (s, 2H).
180		2-((甲氧基氨基)亚甲基)-5-苯基环己烷-1,3-二酮	¹ H NMR (400 MHz, DMSO d ₆) δ 12.36(br, 1H), 8.16(s, 1H), 7.32-7.20(m, 5H), 3.83(s, 3H), 3.41-3.33(m, 1H), 2.84-2.77(m, 2H), 2.61-2.57(m, 2H); MS: 246.1 [M+1].
182		2-(((2-(4-(2-羟乙基)哌嗪-1-基)乙基)氨基)亚甲基)-5,5-二甲基环己烷-1,3-二酮	¹ H NMR (400 MHz, CD ₃ OD) δ 8.19(s, 1H), 3.68 (t, <i>J</i> = 6.1 Hz, 2H), 3.58 (t, <i>J</i> = 5.9 Hz, 2H), 2.94 (m, 1H), 2.67-2.47(m, 11H), 2.35 (d, <i>J</i> = 14.8 Hz, 4H) 1.04 (s, 6H); MS: 324.2 [M+1].

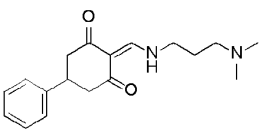
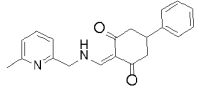
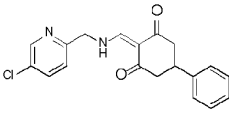
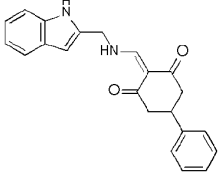
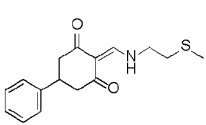
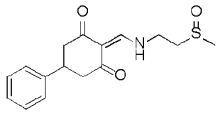
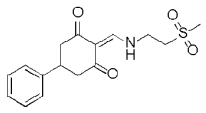
[0576]

183		2-(((2-(4-(2-羟乙基)哌嗪-1-基)乙基)氨基)亚甲基)苯并呋喃-3(2H)-酮	$^1\text{H NMR}$ (400 MHz, CD_3OD) δ 7.73 (d, J = 7.4 Hz, 1H), 7.57 (m, 2H), 7.31 (d, J = 8.8 Hz, 1H), 7.20 (t, J = 7.3 Hz, 1H), 3.77 (t, J = 5.5 Hz, 2H), 3.53 (t, 2H), 2.81 (m, 11H).
184		2-(((2-(4-(2-羟乙基)哌嗪-1-基)乙基)氨基)亚甲基)-5-(4-甲基-1H-咪唑-3-基)环己烷-1,3-二酮	$^1\text{H NMR}$ (400 MHz, CD_3OD) δ 8.26 (s, 1H), 7.16 (d, J = 8.0 Hz, 1H), 7.03 (s, 1H), 6.99 – 6.91 (m, 1H), 6.74 (d, J = 7.2 Hz, 1H), 3.94 (m, 1H), 3.73 (t, J = 5.8 Hz, 2H), 3.61 (t, J = 5.6 Hz, 2H), 2.95 – 2.55 (m, 19H). MS: 426.2 [M+1].
185		5-(3-环丙基-1H-咪唑-4-基)-2-(((2-(4-(2-羟乙基)哌嗪-1-基)乙基)氨基)亚甲基)环己烷-1,3-二酮	$^1\text{H NMR}$ (400 MHz, CD_3OD) δ 8.28 (s, 1H), 7.20 (d, J = 8.0 Hz, 1H), 7.05 (t, J = 7.6 Hz, 1H), 6.96 – 6.87 (m, 2H), 4.65 (s, 1H), 3.71 (dt, J = 25.1, 5.8 Hz, 2H), 3.61 (t, J = 5.7 Hz, 2H), 3.50 (m, 1H), 2.96 – 2.44 (m, 16H), 1.94 (m, 1H), 0.77 (d, J = 7.9 Hz, 2H), 0.61 (d, J = 3.5 Hz, 2H); MS: 451.2 [M+1].
186		2-(((2-(4-(2-羟乙基)哌嗪-1-基)乙基)氨基)亚甲基)-5-(5-甲氧基-1H-咪唑-3-基)环己烷-1,3-二酮	$^1\text{H NMR}$ (400 MHz, CD_3OD) δ 8.24(s, 1H), 7.23 (d, J = 8.8Hz, 1H), 7.04(s, 1H), 6.98(s, 1H), 6.77 (d, J = 8.8Hz, 1H), 3.81-3.76 (m, 5H), 3.66-3.59 (m, 3H), 3.05-2.65 (m, 16H); MS: 441.2 [M+1].
187		5-([1,1'-联苯]-2-基)-2-(((2-(4-(2-羟乙基)哌嗪-1-基)乙基)氨基)亚甲基)环己烷-1,3-二酮	$^1\text{H NMR}$ (400 MHz, DMSO-d_6) δ 10.93 – 10.77 (m, 1H), 8.03 (d, J = 14.7 Hz, 1H), 7.54 (d, J = 7.9 Hz, 1H), 7.44 – 7.23 (m, 6H), 7.14 (d, J = 7.5 Hz, 1H), 3.60 (s, 2H), 3.51 (d, J = 5.8 Hz, 2H), 3.30 (m, 4H), 2.73 (m, 8H), 2.28 (d, J = 14.1 Hz, 3H); MS: 448.2 [M+1].
188		2-(((2-(4-(2-羟乙基)哌嗪-1-基)乙基)氨基)亚甲基)-5-(2-(吡啶-4-基)苯基)环己烷-1,3-二酮	$^1\text{H NMR}$ (400 MHz, DMSO-d_6) δ 10.87 (m, 1H), 8.60 (d, J = 5.5 Hz, 2H), 8.03 (d, J = 14.7 Hz, 1H), 7.59 (d, J = 7.7 Hz, 1H), 7.44 (t, J = 7.1 Hz, 1H), 7.33 (m, 3H), 7.16 (dd, J = 7.5, 0.7 Hz, 1H), 4.35 (ds, 1H), 3.45 (m, 5H), 3.20 (m, 1H), 2.86 – 2.58 (m, 3H), 2.34 (m, 12H); MS: 449.2 [M+1].
189		2-(((2-(4-(2-羟基乙基)哌嗪-1-基)乙基)氨基)亚甲基)-5-(2-(吡啶-4-基)苯基)己烷-1,3-二酮	$^1\text{H NMR}$ (400 MHz, DMSO-d_6) δ 10.94 (d, J = 14.6 Hz, 1H), 8.13 (d, J = 14.6 Hz, 1H), 7.30 (d, J = 7.5 Hz, 1H), 7.13 (dt, J = 18.7, 7.2 Hz, 2H), 6.98 (d, J = 7.0 Hz, 1H), 4.39 (s, 1H), 3.87 (t, J = 12.3 Hz, 1H), 3.56 (d, J = 5.5 Hz, 2H), 3.46 (d, J = 5.9 Hz, 2H), 3.35 (s, 1H), 2.81 – 2.57 (m, 3H), 2.46 – 2.26 (m, 12H), 1.96 (m, 1H), 0.86 (m, 2H), 0.58 (m, 2H).

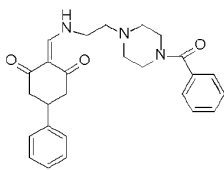
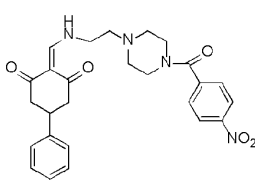
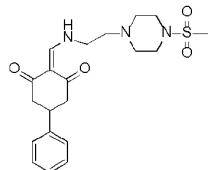
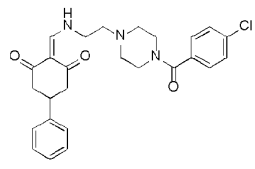
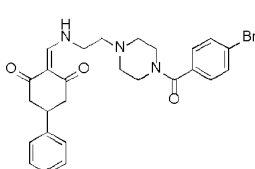
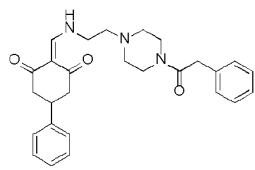
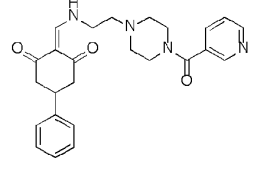
[0577]

190		2-(((2-(4-(2-羟乙基)哌嗪-1-基)乙基)氨基)亚甲基)-4-(吗啉-4-羰基)-5-苯基环己烷-1,3-二酮	¹ HNMR (400 MHz, CDCl ₃) δ 8.29, 8.23 (two singlets, 1H), 7.38-7.22 (m, 5H), 4.46-4.35 (m, 1H), 3.78-3.35 (m, 10H), 3.20-2.55 (m, 16H); MS: 485.3 [M+1].
191		6-(2-溴苯基)-3-(((2-(4-(2-羟乙基)哌嗪-1-基)乙基)氨基)亚甲基)-2,4-二氧代环己烷-1-羧酸乙酯	¹ HNMR (400 MHz, DMSO-d ₆) δ 11.08 – 10.77 (m, 1H), 8.16 (dd, <i>J</i> = 15.0, 6.9 Hz, 1H), 7.60 – 7.51 (m, 2H), 7.37 (t, <i>J</i> = 7.5 Hz, 1H), 7.18 – 7.09 (m, 1H), 4.41 – 4.13 (m, 2H), 4.04 – 3.76 (m, 3H), 3.64 – 3.52 (m, 2H), 3.45 (d, <i>J</i> = 5.0 Hz, 2H), 2.78 – 2.54 (m, 2H), 2.46 – 2.29 (m, 9H), 1.31 – 1.03 (m, 2H), 0.90 (m, 3H); MS: 524.1 [M+1]
192		6-氯-3-(((2-(4-(2-羟乙基)哌嗪-1-基)乙基)氨基)亚甲基)喹啉-2,4(1H, 3H)-二酮	¹ HNMR (400 MHz, CD ₃ OD) δ 8.55 (d, <i>J</i> = 32.6 Hz, 1H), 7.97 (d, <i>J</i> = 2.5 Hz, 1H), 7.49 (d, <i>J</i> = 6.5 Hz, 1H), 7.16 (d, <i>J</i> = 8.7 Hz, 1H), 3.71 (t, <i>J</i> = 5.4 Hz, 4H), 2.67 (m, 12H); MS: 379.1 [M+1].
193		3-(((2-(4-(2-羟乙基)哌嗪-1-基)乙基)氨基)亚甲基)-1-甲基喹啉-2,4(1H, 3H)-二酮	¹ HNMR (400 MHz, CD ₃ OD) δ 8.59 (d, <i>J</i> = 18.0 Hz, 1H), 8.14 (m, 1H), 7.65 (t, <i>J</i> = 7.1 Hz, 1H), 7.42 (d, <i>J</i> = 8.5 Hz, 1H), 7.23 (t, <i>J</i> = 7.6 Hz, 1H), 3.82 – 3.76 (m, 2H), 3.73 (m, 2H), 3.57 (d, <i>J</i> = 3.4 Hz, 3H), 3.02 (m, 6H), 2.84 – 2.61 (m, 6H); MS: 359.2 [M+1].
194		3-(((2-(4-(2-羟乙基)哌嗪-1-基)乙基)氨基)亚甲基)-8-甲氧基喹啉-2,4(1H, 3H)-二酮	¹ HNMR (400 MHz, CD ₃ OD) δ 8.56 (d, <i>J</i> = 32.3 Hz, 1H), 7.61 (d, <i>J</i> = 7.7 Hz, 1H), 7.23 – 7.06 (m, 2H), 3.97 (s, 3H), 3.81 – 3.66 (m, 4H), 2.99 – 2.57 (m, 12H); MS: 375.2 [M+1].
195		8-氟-3-(((2-(4-(2-羟乙基)哌嗪-1-基)乙基)氨基)亚甲基)喹啉-2,4(1H, 3H)-二酮	¹ H NMR (400 MHz, CD ₃ OD) δ 8.57 (d, <i>J</i> = 30.8 Hz, 1H), 7.88 – 7.78 (m, 1H), 7.42 – 7.30 (m, 1H), 7.12 (m, 1H), 3.81 (m, 2H), 3.73 (m, 2H), 3.35 (s, 1H), 3.24 (s, 1H), 3.07 (d, <i>J</i> = 43.1 Hz, 5H), 2.75 (m, 5H); MS: 363.1 [M+1]
196		3-(((2-(4-(2-羟乙基)哌嗪-1-基)乙基)氨基)亚甲基)-6-甲氧基喹啉-2,4(1H, 3H)-二酮	¹ H NMR (400 MHz, DMSO-d ₆) δ 11.68-10.99 (m, 1H), 10.52 (d, <i>J</i> = 29.2 Hz, 1H), 8.43 (t, <i>J</i> = 14.5 Hz, 1H), 7.33 (t, <i>J</i> = 9.2 Hz, 1H), 7.23 – 7.01 (m, 2H), 4.66 (s, 1H), 3.77 (d, <i>J</i> = 19.5 Hz, 3H), 3.65 (m, 2H), 3.55 (s, 2H), 3.35 (s, 4H), 2.55 (m, 8H); MS: 375.2 [M+1].
197		3-(((2-(4-(2-羟乙基)哌嗪-1-基)乙基)氨基)亚甲基)-8-(三氟甲基)喹啉-2,4(1H, 3H)-二酮	¹ HNMR (400 MHz, CD ₃ OD) δ 8.54 (m, 1H), 8.35 (d, <i>J</i> = 7.1 Hz, 1H), 7.89 (d, <i>J</i> = 7.4 Hz, 1H), 7.31 (t, <i>J</i> = 7.9 Hz, 1H), 3.73 (m, 4H), 2.93 – 2.58 (m, 12H).

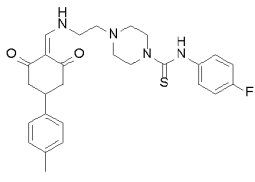
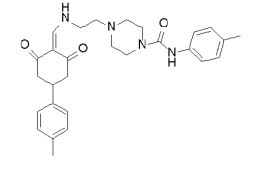
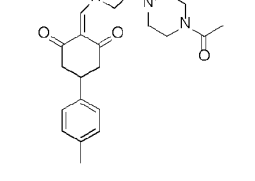
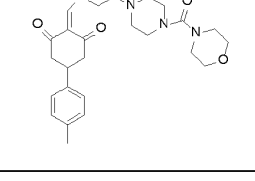
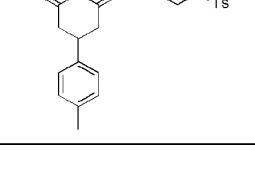
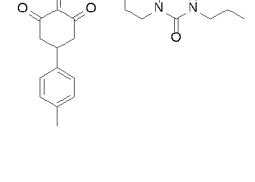
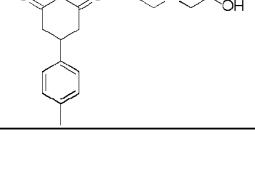
[0578]

		喹啉-2,4(1H, 3H)-二酮	
202		2-(((3-(二甲基氨基)丙基)氨基)亚甲基)-5-苯基环己烷-1,3-二酮	¹ HNMR (400 MHz, CDCl ₃) δ 11.28 (s, 1H), 8.17 (s, 1H), 7.34 (t, <i>J</i> = 7.5 Hz, 2H), 7.24 (dd, <i>J</i> = 8.5, 7.1 Hz, 3H), 3.52 (t, <i>J</i> = 6.6 Hz, 2H), 3.43 – 3.30 (m, 1H), 2.81 – 2.61 (m, 4H), 2.43 (t, <i>J</i> = 6.9 Hz, 2H), 2.28 (s, 6H), 1.84 (p, <i>J</i> = 6.8 Hz, 2H).
203		2-(((6-甲基吡啶-2-基)甲基)氨基)亚甲基)-5-苯基环己烷-1,3-二酮	¹ HNMR (400 MHz, CDCl ₃) δ 11.58 (s, 1H), 8.31 (d, <i>J</i> = 14.2 Hz, 1H), 7.59 (t, <i>J</i> = 7.7 Hz, 1H), 7.34 (t, <i>J</i> = 7.4 Hz, 2H), 7.27 – 7.18 (m, 3H), 7.11 (d, <i>J</i> = 7.7 Hz, 1H), 7.04 (d, <i>J</i> = 7.6 Hz, 1H), 4.68 (d, <i>J</i> = 6.1 Hz, 2H), 3.43 – 3.32 (m, 1H), 2.82 – 2.63 (m, 4H), 2.57 (s, 3H).
204		2-(((5-氯吡啶-2-基)甲基)氨基)亚甲基)-5-苯基环己烷-1,3-二酮	¹ HNMR (400 MHz, CDCl ₃) δ 11.59 (s, 1H), 8.58 (d, <i>J</i> = 2.2 Hz, 1H), 8.30 (d, <i>J</i> = 14.0 Hz, 1H), 7.70 (dd, <i>J</i> = 8.3, 2.5 Hz, 1H), 7.35 (t, <i>J</i> = 7.4 Hz, 2H), 7.27 – 7.19 (m, 4H), 4.71 (d, <i>J</i> = 6.2 Hz, 2H), 3.42 – 3.33 (m, 1H), 2.83 – 2.64 (m, 4H)
205		2-(((1H-吲哚-2-基)甲基)氨基)亚甲基)-5-苯基环己烷-1,3-二酮	¹ HNMR (400 MHz, DMSO-d ₆) δ 11.22 (s, 2H), 8.27 (d, <i>J</i> = 14.1 Hz, 1H), 7.51 (d, <i>J</i> = 7.8 Hz, 1H), 7.39 – 7.35 (m, 1H), 7.33 – 7.28 (m, 4H), 7.24 – 7.17 (m, 1H), 7.13 – 7.05 (m, 1H), 7.01 – 6.96 (m, 1H), 6.39 (d, <i>J</i> = 1.1 Hz, 1H), 4.81 (d, <i>J</i> = 4.7 Hz, 2H), 3.31 (td, <i>J</i> = 7.6, 3.8 Hz, 1H), 2.72 (ddd, <i>J</i> = 31.1, 16.6, 11.7 Hz, 2H), 2.55 – 2.50 (m, 2H)
206		2-(((2-(甲硫基)乙基)氨基)亚甲基)-5-苯基环己烷-1,3-二酮	¹ HNMR (400 MHz, CDCl ₃) δ 11.32 (s, 1H), 8.19 (d, <i>J</i> = 14.0 Hz, 1H), 7.34 (t, <i>J</i> = 7.4 Hz, 2H), 7.24 (d, <i>J</i> = 8.1 Hz, 3H), 3.63 (q, <i>J</i> = 6.4 Hz, 2H), 3.42 – 3.31 (m, 1H), 2.81 – 2.62 (m, 6H), 2.15 (s, 3H)
207		2-(((2-(甲基磺酰基)乙基)氨基)亚甲基)-5-苯基环己烷-1,3-二酮	¹ HNMR (400 MHz, CDCl ₃) δ 11.35 (s, 1H), 8.21 (d, <i>J</i> = 13.8 Hz, 1H), 7.34 (t, <i>J</i> = 7.4 Hz, 2H), 7.24 (t, <i>J</i> = 6.4 Hz, 3H), 4.06 – 3.89 (m, 2H), 3.36 (dd, <i>J</i> = 11.8, 8.7 Hz, 1H), 3.08 – 2.94 (m, 2H), 2.82 – 2.61 (m, 7H).
208		2-(((2-(甲基磺酰基)乙基)氨基)亚甲基)-5-苯基环己烷-1,3-二酮	¹ HNMR (400 MHz, CDCl ₃) δ 11.37 (s, 1H), 8.18 (d, <i>J</i> = 13.7 Hz, 1H), 7.34 (t, <i>J</i> = 7.4 Hz, 2H), 7.23 (d, <i>J</i> = 7.2 Hz, 3H), 3.98 (dd, <i>J</i> = 12.8, 6.4 Hz, 2H), 3.36 (dd, <i>J</i> = 14.2, 8.1 Hz, 3H), 3.00 (s, 3H), 2.83 – 2.63 (m, 4H)

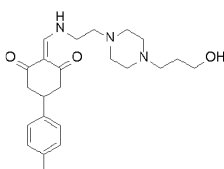
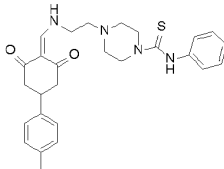
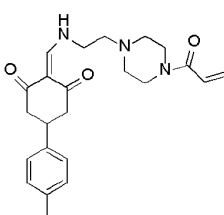
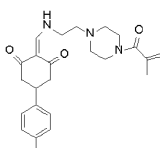
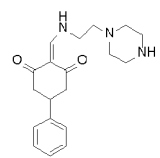
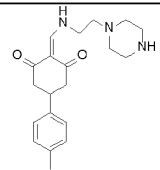
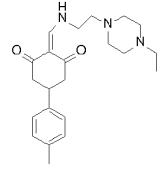
[0580]

216		2-(((2-(4-苯甲酰基哌嗪-1-基)乙基)氨基)亚甲基)-5-苯基环己烷-1,3-二酮	¹ HNMR (300 MHz, CDCl ₃) δ 11.25 (s, 1H), 8.21 (d, <i>J</i> = 14.7 Hz, 1H), 8.10 (d, <i>J</i> = 7.6 Hz, 2H), 7.48 (d, <i>J</i> = 7.7 Hz, 1H), 7.40 (s, 4H), 7.32 (d, <i>J</i> = 7.1 Hz, 1H), 7.23 (d, <i>J</i> = 7.7 Hz, 2H), 3.85 (s, 2H), 3.54 (d, <i>J</i> = 5.8 Hz, 4H), 3.36 (s, 1H), 2.84 – 2.69 (m, 4H), 2.64 (d, <i>J</i> = 13.3 Hz, 4H), 2.48 (s, 2H)
217		2-(((2-(4-(4-硝基苯甲酰基)哌嗪-1-基)乙基)氨基)亚甲基)-5-苯基环己烷-1,3-二酮	¹ HNMR (300 MHz, CDCl ₃) δ 11.26 (s, 1H), 8.29 (d, <i>J</i> = 8.4 Hz, 2H), 8.19 (d, <i>J</i> = 14.3 Hz, 1H), 7.57 (d, <i>J</i> = 8.5 Hz, 2H), 7.33 (d, <i>J</i> = 7.1 Hz, 2H), 7.22 (s, 3H), 3.86 (s, 2H), 3.53 (d, <i>J</i> = 5.8 Hz, 4H), 3.42 (s, 2H), 3.38 – 3.28 (m, 1H), 2.83 – 2.69 (m, 4H), 2.65 (d, <i>J</i> = 6.0 Hz, 4H), 2.47 (s, 2H)
218		2-(((2-(4-(甲基磺酰基)哌嗪-1-基)乙基)氨基)亚甲基)-5-苯基环己烷-1,3-二酮	¹ HNMR (300 MHz, CDCl ₃) δ 11.22 (s, 1H), 8.18 (d, <i>J</i> = 14.3 Hz, 1H), 7.37 – 7.30 (m, 2H), 7.23 (d, <i>J</i> = 7.9 Hz, 3H), 3.60 – 3.46 (m, 2H), 3.36 (d, <i>J</i> = 5.5 Hz, 1H), 3.28 (s, 4H), 2.79 (s, 3H), 2.75 (d, <i>J</i> = 7.5 Hz, 2H), 2.72 – 2.63 (m, 4H), 2.67 – 2.59 (m, 4H)
219		2-(((2-(4-(4-氯苯甲酰基)哌嗪-1-基)乙基)氨基)亚甲基)-5-苯基环己烷-1,3-二酮	¹ HNMR (300 MHz, CDCl ₃) δ 11.25 (s, 1H), 8.18 (d, <i>J</i> = 14.3 Hz, 1H), 7.37 (d, <i>J</i> = 6.6 Hz, 5H), 7.24 (d, <i>J</i> = 12.4 Hz, 4H), 3.81 (s, 2H), 3.51 (s, 4H), 3.40 – 3.29 (m, 1H), 2.83 – 2.67 (m, 4H), 2.65 (s, 2H), 2.62 – 2.35 (m, 4H)
220		2-(((2-(4-(4-溴苯甲酰基)哌嗪-1-基)乙基)氨基)亚甲基)-5-苯基环己烷-1,3-二酮	¹ HNMR (300 MHz, CDCl ₃) δ 11.26 (s, 1H), 8.18 (d, <i>J</i> = 14.1 Hz, 1H), 7.55 (d, <i>J</i> = 7.7 Hz, 2H), 7.38 – 7.27 (m, 4H), 7.23 (d, <i>J</i> = 7.4 Hz, 3H), 3.81 (s, 2H), 3.52 (d, <i>J</i> = 5.7 Hz, 4H), 3.36 (s, 1H), 2.82 – 2.68 (m, 4H), 2.65 (d, <i>J</i> = 6.4 Hz, 2H), 2.51 (d, <i>J</i> = 29.1 Hz, 4H)
221		5-苯基-2-(((2-(4-(2-苯基乙酰基)哌嗪-1-基)乙基)氨基)亚甲基)环己烷-1,3-二酮	¹ HNMR (300 MHz, CDCl ₃) δ 11.19 (s, 1H), 8.16 (d, <i>J</i> = 14.4 Hz, 1H), 7.38 – 7.28 (m, 5H), 7.23 (d, <i>J</i> = 7.7 Hz, 5H), 3.73 (s, 2H), 3.69 (s, 2H), 3.48 (d, <i>J</i> = 5.4 Hz, 4H), 3.35 (s, 1H), 2.81 – 2.63 (m, 4H), 2.57 (t, <i>J</i> = 5.6 Hz, 2H), 2.45 (s, 2H), 2.30 (s, 2H)
222		2-(((2-(4-烟酰基哌嗪-1-基)乙基)氨基)亚甲基)-5-苯基环己烷-1,3-二酮	¹ HNMR (300 MHz, CDCl ₃) δ 11.26 (s, 1H), 8.66 (s, 2H), 8.18 (d, <i>J</i> = 14.4 Hz, 1H), 7.75 (d, <i>J</i> = 7.9 Hz, 1H), 7.35 (dd, <i>J</i> = 15.1, 7.6 Hz, 4H), 7.25 – 7.19 (m, 2H), 3.86 (s, 2H), 3.52 (d, <i>J</i> = 5.4 Hz, 4H), 3.38 (s, 1H), 2.85 – 2.70 (m, 4H), 2.65 (d, <i>J</i> = 6.0 Hz, 4H), 2.51 (t, <i>J</i> = 29.8 Hz, 2H)

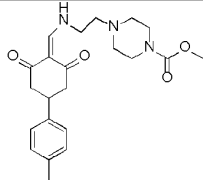
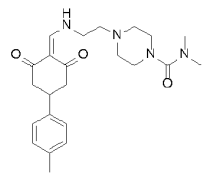
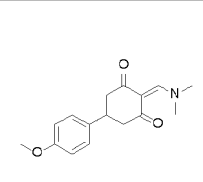
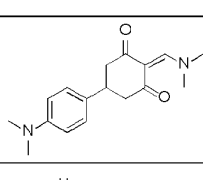
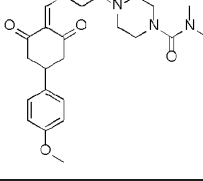
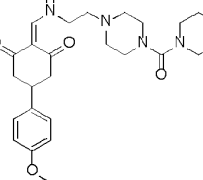
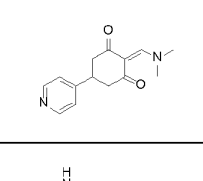
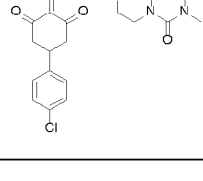
[0581]

223		4-(2-(((2,6-二氧代-4-(对甲苯基)亚环己基)甲基)氨基)乙基)-N-(4-氟苯基)哌嗪-1-硫代甲酰胺	^1H NMR (300 MHz, DMSO) δ 10.93 (s, 1H), 9.28 (s, 1H), 8.14 (d, $J = 14.5$ Hz, 1H), 7.30 – 7.22 (m, 2H), 7.17 (d, $J = 7.8$ Hz, 2H), 7.11 (t, $J = 7.2$ Hz, 4H), 3.85 (s, 2H), 3.59 (s, 4H), 3.31 (s, 3H), 3.27 – 3.17 (m, 1H), 2.79 (m, 4H), 2.65 (d, $J = 6.4$ Hz, 2H), 2.22 (d, $J = 13.5$ Hz, 4H)
224		4-(2-(((2,6-二氧代-4-(对甲苯基)亚环己基)甲基)氨基)乙基)-N-(对甲苯基)哌嗪-1-甲酰胺	^1H NMR (300 MHz, CDCl_3) δ 11.43 – 10.70 (m, 2H), 8.18 (d, $J = 14.1$ Hz, 1H), 7.26 (s, 1H), 7.21 (d, $J = 8.4$ Hz, 1H), 7.17 – 7.05 (m, 3H), 6.26 (s, 1H), 3.54 (s, 2H), 3.40 – 3.26 (m, 1H), 2.70 (dd, $J = 18.3, 9.0$ Hz, 3H), 2.55 (s, 2H), 2.31 (d, $J = 11.6$ Hz, 3H)
225		2-(((2-(4-乙酰基哌嗪-1-基)乙基)氨基)亚甲基)-5-(对甲苯基)环己烷-1,3-二酮	^1H NMR (300 MHz, CDCl_3) δ 11.31 – 11.12 (m, 1H), 8.18 (d, $J = 14.2$ Hz, 1H), 7.13 (d, $J = 2.6$ Hz, 4H), 3.65 (s, 2H), 3.50 (d, $J = 5.7$ Hz, 3H), 3.42 (m, 2H), 3.33 (s, 1H), 2.73 (q, $J = 9.0$ Hz, 4H), 2.62 (d, $J = 5.1$ Hz, 2H), 2.55 – 2.42 (m, 4H), 2.30 (d, $J = 13.6$ Hz, 2H), 2.08 (s, 3H)
226		2-(((2-(4-(吗啉-4-羰基)哌嗪-1-基)乙基)氨基)亚甲基)-5-(对甲苯基)环己烷-1,3-二酮	^1H NMR (300 MHz, CDCl_3) δ 11.25 (m, 1H), 8.17 (d, $J = 14.3$ Hz, 1H), 7.18 – 6.89 (m, 4H), 3.69 – 3.62 (m, 5H), 3.51 (d, $J = 5.8$ Hz, 2H), 3.34 (s, 4H), 3.28 – 3.20 (m, 4H), 2.77 – 2.58 (m, 6H), 2.49 (s, 4H), 2.32 (s, 3H)
227		5-(对甲苯基)-2-(((2-(4-甲苯磺酰基哌嗪-1-基)乙基)氨基)亚甲基)环己烷-1,3-二酮	^1H NMR (300 MHz, CDCl_3) δ 11.05 (s, 1H), 8.09 (d, $J = 14.2$ Hz, 1H), 7.62 (d, $J = 7.5$ Hz, 2H), 7.44 – 7.24 (m, 2H), 7.11 (d, $J = 6.1$ Hz, 4H), 3.45 (d, $J = 4.5$ Hz, 2H), 3.27 (s, 1H), 3.05 (s, 4H), 2.73 – 2.53 (m, 8H), 2.37 (d, $J = 31.3$ Hz, 6H)
228		4-(2-(((2,6-二氧代-4-(对甲苯基)亚环己基)甲基)氨基)乙基)-N-丙基哌嗪-1-甲酰胺	^1H NMR (300 MHz, CDCl_3) δ 11.23 (s, 1H), 8.17 (d, $J = 14.3$ Hz, 1H), 7.20 – 7.07 (m, 4H), 4.47 (s, 1H), 3.49 (dd, $J = 13.7, 8.2$ Hz, 2H), 3.46 – 3.34 (m, 4H), 3.36 – 3.22 (m, 1H), 3.18 (dd, $J = 13.0, 6.6$ Hz, 2H), 2.79 – 2.60 (m, 6H), 2.46 (t, $J = 16.1$ Hz, 4H), 2.32 (s, 3H), 1.62 – 1.38 (m, 2H), 0.89 (dd, $J = 16.1, 8.7$ Hz, 3H)
229		2-(((2-(4-(2-羟乙基)哌嗪-1-基)乙基)氨基)亚甲基)-5-(对甲苯基)环己烷-1,3-二酮	^1H NMR (300 MHz, CDCl_3) δ 11.20 (s, 1H), 8.17 (d, $J = 14.3$ Hz, 1H), 7.14 (d, $J = 8.6$ Hz, 4H), 3.71 – 3.63 (m, 2H), 3.55 – 3.29 (m, 5H), 2.73 – 2.59 (m, 14H), 2.32 (s, 3H)

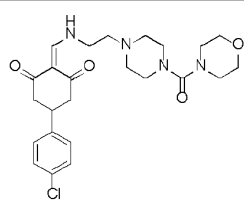
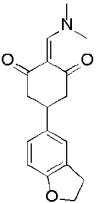
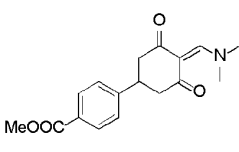
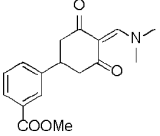
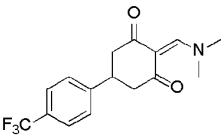
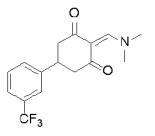
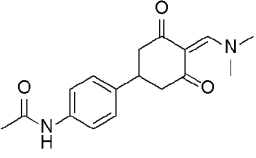
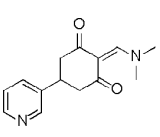
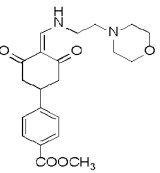
[0582]

230		2-(((2-(4-(3-羟丙基)哌嗪-1-基)乙基)氨基)亚甲基)-5-(对甲苯基)环己烷-1,3-二酮	¹ HNMR (300 MHz, CDCl ₃) δ 11.20 (s, 2H), 8.16 (d, <i>J</i> = 14.4 Hz, 1H), 7.18 – 7.06 (m, 4H), 3.84 – 3.72 (m, 2H), 3.49 (dd, <i>J</i> = 11.6, 5.8 Hz, 2H), 3.31 (d, <i>J</i> = 5.9 Hz, 1H), 2.87 – 2.50 (m, 14H), 2.33 (s, 3H), 1.85 – 1.72 (m, 2H)
231		4-(2-(((2,6-二氧代-4-(对甲苯基)亚环己基)甲基)氨基)乙基)-N-苯基哌嗪-1-硫代甲酰胺	¹ HNMR (300 MHz, CDCl ₃) δ 11.28 (m, 1H), 8.17 (d, <i>J</i> = 14.2 Hz, 1H), 7.32 (d, <i>J</i> = 7.8 Hz, 3H), 7.13 (d, <i>J</i> = 3.2 Hz, 6H), 3.87 (s, 4H), 3.50 (s, 2H), 3.36 – 3.26 (m, 1H), 2.81 – 2.65 (m, 4H), 2.64 (s, 2H), 2.57 (s, 4H), 2.33 (s, 3H)
232		2-(((2-(4-丙烯酰基哌嗪-1-基)乙基)氨基)亚甲基)-5-(对甲苯基)环己烷-1,3-二酮	¹ HNMR (300 MHz, CDCl ₃) δ 11.21 (s, 1H), 8.18 (d, <i>J</i> = 14.4 Hz, 1H), 7.14 (d, <i>J</i> = 10.6 Hz, 4H), 6.55 (dd, <i>J</i> = 16.4, 10.9 Hz, 1H), 6.28 (d, <i>J</i> = 16.8 Hz, 1H), 5.69 (d, <i>J</i> = 10.5 Hz, 1H), 3.73 (s, 2H), 3.57 (d, <i>J</i> = 22.5 Hz, 2H), 3.57 – 3.43 (m, 1H), 3.30 (d, <i>J</i> = 6.0 Hz, 2H), 2.83 – 2.65 (m, 4H), 2.63 (t, <i>J</i> = 5.4 Hz, 2H), 2.55 – 2.42 (m, 4H), 2.33 (s, 3H)
233		2-(((2-(4-甲基丙烯酰基哌嗪-1-基)乙基)氨基)亚甲基)-5-(对甲苯基)环己烷-1,3-二酮	¹ H NMR (300 MHz, CDCl ₃) δ 11.28 (m, 1H), 8.18 (d, <i>J</i> = 14.0 Hz, 1H), 7.15 (d, <i>J</i> = 10.7 Hz, 4H), 5.19 (s, 1H), 5.02 (s, 1H), 3.63 (s, 4H), 3.52 (d, <i>J</i> = 5.8 Hz, 2H), 3.31 (s, 1H), 2.80 – 2.69 (m, 4H), 2.62 (d, <i>J</i> = 5.6 Hz, 2H), 2.49 (s, 4H), 2.33 (s, 3H), 1.94 (s, 3H)
236		5-苯基-2-(((2-(哌嗪-1-基)乙基)氨基)亚甲基)环己烷-1,3-二酮	¹ HNMR (300 MHz, CDCl ₃) δ 11.20 (s, 1H), 8.17 (d, <i>J</i> = 14.0 Hz, 1H), 7.32 (d, <i>J</i> = 7.3 Hz, 2H), 7.24 (t, <i>J</i> = 6.7 Hz, 3H), 3.48 (d, <i>J</i> = 7.0 Hz, 2H), 3.41 (s, 4H), 3.41 (s, 2H), 3.08 (s, 2H), 2.74 (d, <i>J</i> = 7.1 Hz, 2H), 2.64 (s, 4H), 2.52 (s, 1H)
237		2-(((2-(哌嗪-1-基)乙基)氨基)亚甲基)-5-(对甲苯基)环己烷-1,3-二酮	¹ HNMR (300 MHz, CDCl ₃) δ 11.31 – 11.16 (m, 2H), 8.14 (s, 1H), 7.13 (s, 4H), 3.51 (s, 3H), 3.38 – 3.27 (m, 2H), 3.12 (s, 4H), 2.71 (s, 4H), 2.43 (s, 6H), 2.33 (s, 3H)
238		2-(((2-(4-乙基哌嗪-1-基)乙基)氨基)亚甲基)-5-(对甲苯基)环己烷-1,3-二酮	¹ HNMR (300 MHz, CDCl ₃) δ 11.20 (s, 1H), 8.16 (d, <i>J</i> = 14.3 Hz, 1H), 7.13 (s, 4H), 3.45 (t, <i>J</i> = 23.7 Hz, 2H), 3.31 (d, <i>J</i> = 5.3 Hz, 1H), 2.83 – 2.53 (m, 16H), 2.32 (s, 3H), 1.20 (t, <i>J</i> = 7.2 Hz, 3H)

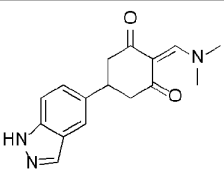
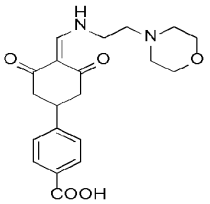
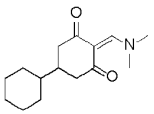
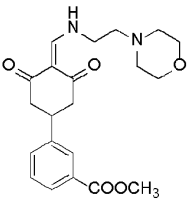
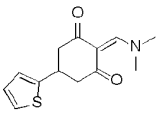
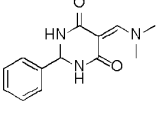
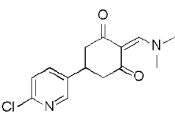
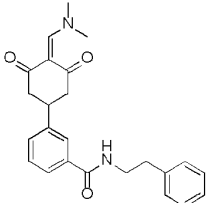
[0583]

239		4-(2-(((2,6-二氧代-4-(对甲苯基)亚环己基)甲基)氨基)乙基)哌嗪-1-甲酸甲酯	^1H NMR (300 MHz, CDCl_3) δ 11.22 (s, 1H), 8.17 (d, $J = 14.3$ Hz, 1H), 7.13 (s, 4H), 3.69 (s, 3H), 3.50 (d, $J = 4.2$ Hz, 6H), 3.29 (d, $J = 5.0$ Hz, 1H), 2.77 – 2.53 (m, 6H), 2.45 (s, 4H), 2.32 (s, 3H)
240		4-(2-(((2,6-二氧代-4-(对甲苯基)亚环己基)甲基)氨基)乙基)-N,N-二甲基哌嗪-1-甲酰胺	^1H NMR (300 MHz, CDCl_3) δ 11.26 (m, 1H), 8.17 (d, $J = 14.2$ Hz, 1H), 7.13 (s, 4H), 3.51 (d, $J = 6.0$ Hz, 2H), 3.30 (s, 5H), 2.81 (s, 4H), 2.72 (d, $J = 6.8$ Hz, 6H), 2.66 – 2.56 (m, 4H), 2.49 (s, 4H), 2.33 (s, 3H)
241		2-((二甲基氨基)亚甲基)-5-(4-甲氧基苯基)环己烷-1,3-二酮	^1H NMR (300 MHz, CDCl_3) δ 8.04 (d, $J = 16.8$ Hz, 1H), 7.16 (d, $J = 8.4$ Hz, 2H), 6.86 (d, $J = 8.5$ Hz, 2H), 3.79 (s, 3H), 3.41 (s, 3H), 3.30 (td, $J = 11.3, 5.7$ Hz, 1H), 3.19 (d, $J = 11.1$ Hz, 3H), 2.69 (qd, $J = 16.7, 8.1$ Hz, 4H)
242		2-((二甲基氨基)亚甲基)-5-(4-(二甲基氨基)苯基)环己烷-1,3-二酮	^1H NMR (300 MHz, CDCl_3) δ 8.07 (s, 1H), 7.12 (d, $J = 8.4$ Hz, 2H), 6.72 (d, $J = 8.6$ Hz, 2H), 3.41 (s, 3H), 3.27 (s, 1H), 3.21 (s, 3H), 2.93 (s, 6H), 2.78 – 2.59 (m, 4H)
245		4-(2-(((4-(4-甲氧基苯基)-2,6-二氧代环己基)甲基)氨基)乙基)-N,N-二甲基哌嗪-1-甲酰胺	^1H NMR (300 MHz, CDCl_3) δ 11.27 (m, 1H), 8.17 (d, $J = 14.4$ Hz, 1H), 7.13 (s, 4H), 3.51 (d, $J = 5.1$ Hz, 2H), 3.30 (s, 5H), 3.10 (q, $J = 7.2$ Hz, 4H), 2.81 (s, 6H), 2.65 (dd, $J = 32.5, 10.9$ Hz, 6H), 2.49 (s, 4H), 2.33 (s, 3H)
246		5-(4-甲氧基苯基)-2-(((2-(4-(吗啉-4-羰基)哌嗪-1-基)乙基)氨基)-亚甲基)环己烷-1,3-二酮	^1H NMR (300 MHz, CDCl_3) δ 11.26 (m, 1H), 8.17 (d, $J = 14.4$ Hz, 1H), 7.13 (s, 4H), 3.72 (s, 2H), 3.67 (t, 8H), 3.52 (s, 1H), 3.35 (s, 4H), 3.27 (d, $J = 11.8$ Hz, 4H), 2.79 – 2.67 (m, 2H), 2.63 (d, $J = 6.2$ Hz, 2H), 2.50 (s, 4H), 2.33 (s, 3H)
247		2-((二甲基氨基)亚甲基)-5-(吡啶-4-基)环己烷-1,3-二酮	^1H NMR (300 MHz, CDCl_3) δ 8.18 (s, 1H), 7.35 (d, $J = 8.3$ Hz, 2H), 7.21 (d, $J = 8.3$ Hz, 2H), 3.38 (s, 3H), 3.39 – 3.28 (m, 1H), 3.11 (s, 3H), 2.63 (qd, $J = 16.5, 8.0$ Hz, 4H)
248		4-(2-(((4-(4-氯苯基)-2,6-二氧代亚环己基)甲基)氨基)乙基)-N,N-二甲基哌嗪-1-甲酰胺	^1H NMR (300 MHz, CDCl_3) δ 11.26 (m, 1H), 8.17 (d, $J = 14.3$ Hz, 1H), 7.29 (t, $J = 7.2$ Hz, 2H), 7.16 (d, $J = 8.1$ Hz, 2H), 3.52 (d, $J = 6.1$ Hz, 2H), 3.30 (s, 5H), 2.81 (s, 6H), 2.78 – 2.64 (m, 4H), 2.64 – 2.58 (m, 2H), 2.49 (s, 4H)

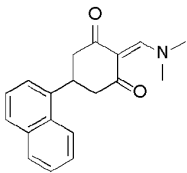
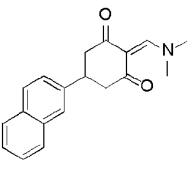
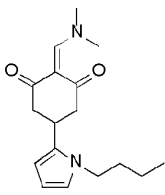
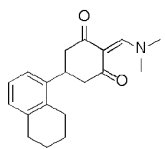
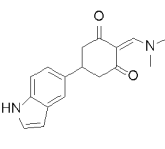
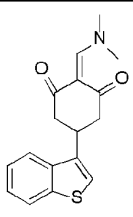
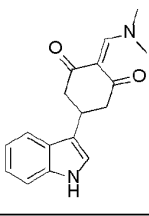
[0584]

249		5-(4-氯苯基)-2-(((2-(4-(吗啉-4-羰基)哌嗪-1-基)乙基)氨基)亚甲基)环己烷-1,3-二酮	¹ HNMR (300 MHz, CDCl ₃) δ 11.22 (s, 1H), 8.17 (d, <i>J</i> = 14.5 Hz, 1H), 7.29 (t, <i>J</i> = 7.7 Hz, 2H), 7.15 (d, <i>J</i> = 8.4 Hz, 2H), 3.66 (d, <i>J</i> = 4.4 Hz, 4H), 3.51 (d, <i>J</i> = 6.0 Hz, 2H), 3.34 (s, 5H), 3.25 (d, <i>J</i> = 4.3 Hz, 4H), 2.79 – 2.55 (m, 6H), 2.49 (s, 4H)
251		5-(2,3-二氢苯并呋喃-5-基)-2-((二甲基氨基)亚甲基)环己烷-1,3-二酮	¹ HNMR (400 MHz, CDCl ₃) δ 8.09 (s, 1H), 7.09 (s, 1H), 6.99 (d, <i>J</i> = 8.1 Hz, 1H), 6.75 (d, <i>J</i> = 8.2 Hz, 1H), 4.58 (t, <i>J</i> = 8.7 Hz, 2H), 3.44 (d, <i>J</i> = 5.0 Hz, 3H), 3.31 (ddd, <i>J</i> = 16.2, 11.6, 4.4 Hz, 1H), 3.26 – 3.16 (m, 5H), 2.70 (qd, <i>J</i> = 16.6, 8.1 Hz, 4H)
252		4-(4-((二甲基氨基)亚甲基)-3,5-二氧代环己基)苯甲酸甲酯	¹ HNMR (400 MHz, CDCl ₃) δ 8.10 (d, <i>J</i> = 5.5 Hz, 1H), 8.02 (d, <i>J</i> = 7.9, 6.1 Hz, 2H), 7.37 – 7.30 (d, 2H), 3.96 – 3.84 (s, 3H), 3.44 (t, <i>J</i> = 8.5 Hz, 4H), 3.24 (s, <i>J</i> = 5.6 Hz, 3H), 2.74 (m, <i>J</i> = 16.9, 5.3 Hz, 4H)
253		3-(4-((二甲基氨基)亚甲基)-3,5-二氧代环己基)苯甲酸甲酯	¹ HNMR (400 MHz, CDCl ₃) δ 8.11 (s, 1H), 7.97 (s, 1H), 7.94 (d, <i>J</i> = 7.1 Hz, 1H), 7.49 – 7.40 (m, 2H), 3.94 (s, 3H), 3.52 – 3.35 (m, 4H), 3.25 (s, 3H), 2.84 – 2.63 (m, 4H)
254		2-((二甲基氨基)亚甲基)-5-(4-(三氟甲基)苯基)环己烷-1,3-二酮	¹ HNMR (400 MHz, CDCl ₃) δ 8.10 (s, 1H), 7.61 (d, <i>J</i> = 8.0 Hz, 2H), 7.38 (d, <i>J</i> = 7.9 Hz, 2H), 3.45 (s, 4H), 3.24 (s, 3H), 2.84 – 2.62 (m, 5H)
255		2-((二甲基氨基)亚甲基)-5-(3-(三氟甲基)苯基)环己烷-1,3-二酮	¹ HNMR (400 MHz, CDCl ₃) δ 8.10 (s, 1H), 7.54 – 7.49 (m, 2H), 7.48 (d, <i>J</i> = 7.8 Hz, 1H), 7.46 (s, 1H), 3.51 – 3.35 (m, 4H), 3.24 (s, 3H), 2.75 (qd, <i>J</i> = 16.5, 8.1 Hz, 4H)
256		N-(4-(4-((二甲基氨基)亚甲基)-3,5-二氧代环己基)苯基)乙酰胺	¹ HNMR (400 MHz, CDCl ₃) δ 8.07 (s, 1H), 7.94 (s, 1H), 7.47 (d, <i>J</i> = 6.8 Hz, 2H), 7.18 (d, <i>J</i> = 6.1 Hz, 2H), 3.40 (s, 3H), 3.33 (m, 1H), 3.21 (s, 3H), 2.69 (q, <i>J</i> = 15.7 Hz, 4H), 2.16 (s, 3H)
257		2-((二甲基氨基)亚甲基)-5-(吡啶-3-基)环己烷-1,3-二酮	¹ HNMR (400 MHz, CDCl ₃) δ 8.56 (s, 1H), 8.53 (d, <i>J</i> = 4.5 Hz, 1H), 8.11 (s, 1H), 7.59 (d, <i>J</i> = 7.9 Hz, 1H), 7.32 – 7.29 (m, 1H), 3.46 (s, 3H), 3.41 (dd, <i>J</i> = 11.2, 4.8 Hz, 1H), 3.25 (s, 3H), 2.82 – 2.71 (m, 4H)
258		4-(4-(((2-吗啉代乙基)氨基)亚甲基)-3,5-二氧代环己基)苯甲酸甲酯	¹ HNMR (400 MHz, CDCl ₃) δ 11.26 (s, 1H), 8.21 (d, <i>J</i> = 14.4 Hz, 1H), 8.03 (d, <i>J</i> = 8.2 Hz, 2H), 7.33 (d, <i>J</i> = 8.2 Hz, 2H), 3.93 (s, 3H), 3.80 – 3.72 (m, 4H), 3.55 (dd, <i>J</i> = 11.9, 6.0 Hz, 2H), 3.46 (dd, <i>J</i> = 10.8, 5.8 Hz, 1H), 2.84 – 2.66 (m, 4H), 2.63 (t, <i>J</i> = 5.9 Hz, 2H), 2.53 (d, <i>J</i> = 4.1 Hz, 4H)

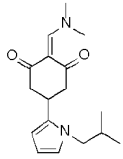
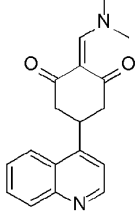
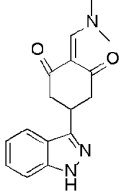
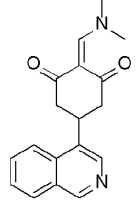
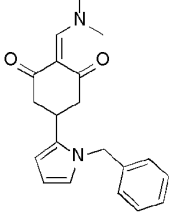
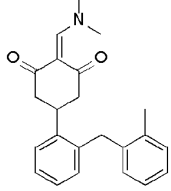
[0585]

259		2-((二甲基氨基)亚甲基)-5-(1H-吲唑-5-基)环己烷-1,3-二酮	¹ HNMR (400 MHz, CDCl ₃) δ 10.85 – 10.35 (m, 1H), 8.14 (s, 1H), 8.06 (s, 1H), 7.74 (d, <i>J</i> = 8.5 Hz, 1H), 7.38 (s, 1H), 7.11 (d, <i>J</i> = 8.0 Hz, 1H), 3.52 (s, 1H), 3.46 (s, 2H), 3.26 (s, 2H), 2.93 – 2.73 (m, 3H)
260		4-(4-(((2-吗啉代乙基)氨基)亚甲基)-3,5-二氧代环己基)苯甲酸	¹ HNMR (400 MHz, CDCl ₃) δ 11.23 (s, 1H), 9.09 – 8.95 (m, 1H), 8.26 (d, <i>J</i> = 14.4 Hz, 1H), 8.06 (d, <i>J</i> = 8.2 Hz, 2H), 7.33 (d, <i>J</i> = 8.0 Hz, 2H), 3.79 (s, 3H), 3.79 (s, 3H), 3.61 (d, <i>J</i> = 5.9 Hz, 2H), 3.42 (s, 1H), 2.84 – 2.62 (m, 5H), 2.60 (s, 3H)
262		4-((二甲基氨基)亚甲基)-[1,1'-双(环己烷)]-3,5-二酮	¹ HNMR (400 MHz, CDCl ₃) δ 8.02 (s, 1H), 3.39 (s, 3H), 3.19 (s, 3H), 2.55 (dd, <i>J</i> = 16.7, 3.8 Hz, 2H), 2.25 (dd, <i>J</i> = 16.6, 12.1 Hz, 2H), 1.94 – 1.83 (m, 1H), 1.75 (d, <i>J</i> = 10.1 Hz, 4H), 1.67 (d, <i>J</i> = 12.0 Hz, 1H), 1.28 – 1.13 (m, 4H), 0.98 (dd, <i>J</i> = 23.2, 12.7 Hz, 2H)
263		3-(4-(((2-吗啉代乙基)氨基)亚甲基)-3,5-二氧代环己基)苯甲酸甲酯	¹ HNMR (400 MHz, CDCl ₃) δ 11.26 (s, 1H), 8.21 (d, <i>J</i> = 14.4 Hz, 1H), 8.03 (d, <i>J</i> = 8.2 Hz, 2H), 7.33 (d, <i>J</i> = 8.2 Hz, 2H), 3.93 (s, 3H), 3.76 (dd, <i>J</i> = 9.4, 4.8 Hz, 4H), 3.55 (dd, <i>J</i> = 11.9, 6.0 Hz, 2H), 3.49 – 3.39 (m, 1H), 2.87 – 2.68 (m, 4H), 2.63 (t, <i>J</i> = 5.9 Hz, 2H), 2.52 (dd, <i>J</i> = 10.3, 5.9 Hz, 4H)
264		2-((二甲基氨基)亚甲基)-5-(噻吩-2-基)环己烷-1,3-二酮	¹ HNMR (400 MHz, CDCl ₃) δ 8.08 (s, 1H), 7.19 (d, <i>J</i> = 5.1 Hz, 1H), 6.99 – 6.92 (m, 1H), 6.88 (d, <i>J</i> = 3.4 Hz, 1H), 3.71 – 3.59 (m, 1H), 3.43 (s, 3H), 3.22 (s, 3H), 2.92 (dd, <i>J</i> = 16.8, 4.2 Hz, 2H), 2.74 (dd, <i>J</i> = 16.8, 10.9 Hz, 2H)
265		5-((二甲基氨基)亚甲基)-2-苯基二氢嘧啶-4,6(1H, 5H)-二酮	¹ HNMR (400 MHz, DMSO) δ 11.53 (s, 2H), 8.34 (s, 1H), 8.06 (t, <i>J</i> = 9.1 Hz, 2H), 7.59 (t, <i>J</i> = 7.1 Hz, 1H), 7.51 (t, <i>J</i> = 7.3 Hz, 2H), 3.51 (s, 3H), 3.29 (s, 3H)
266		5-(6-氯吡啶-3-基)-2-((二甲基氨基)亚甲基)环己烷-1,3-二酮	¹ HNMR (400 MHz, CDCl ₃) δ 8.32 (d, <i>J</i> = 2.2 Hz, 1H), 8.10 (s, 1H), 7.56 (dd, <i>J</i> = 8.2, 2.2 Hz, 1H), 7.32 (d, <i>J</i> = 8.3 Hz, 1H), 3.45 (s, 3H), 3.44 – 3.37 (m, 1H), 3.24 (s, 3H), 2.73 (qd, <i>J</i> = 16.6, 7.9 Hz, 4H)
267		3-(4-((二甲基氨基)亚甲基)-3,5-二氧代环己基)-N-苄基苯甲酰胺	¹ HNMR (400 MHz, CDCl ₃) δ 8.09 (s, 1H), 7.64 (s, 1H), 7.56 – 7.48 (m, 1H), 7.39 – 7.32 (m, 4H), 7.28 – 7.23 (m, 3H), 3.73 (dd, <i>J</i> = 12.9, 6.9 Hz, 2H), 3.44 (d, <i>J</i> = 5.0 Hz, 3H), 3.41 – 3.35 (m, 1H), 3.24 (s, 3H), 2.97 (t, <i>J</i> = 3.4 Hz, 2H), 2.78 – 2.68 (m, 4H)

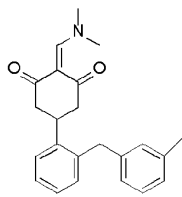
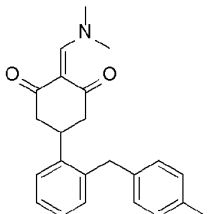
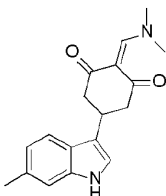
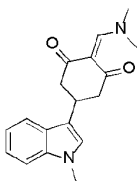
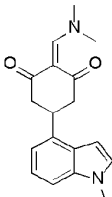
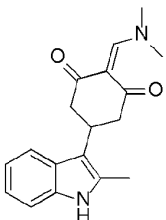
[0587]

			0.90 (d, $J = 6.6$ Hz, 6H)
277		2-((二甲基氨基)亚甲基)-5-(萘-1-基)环己烷-1,3-二酮	$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 8.15 (s, 1H), 8.09 (d, $J = 8.1$ Hz, 1H), 7.92 – 7.88 (m, 1H), 7.78 (d, $J = 8.1$ Hz, 1H), 7.58 – 7.45 (m, 3H), 7.41 (d, $J = 7.0$ Hz, 1H), 4.21 (tt, $J = 11.9, 4.2$ Hz, 1H), 3.46 (d, $J = 8.5$ Hz, 3H), 3.30 (s, 3H), 2.89 (ddd, $J = 28.4, 16.7, 12.3$ Hz, 4H)
278		2-((二甲基氨基)亚甲基)-5-(萘-2-基)环己烷-1,3-二酮	$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 8.12 (s, 1H), 7.87 – 7.80 (m, 3H), 7.69 (s, 1H), 7.53 – 7.45 (m, 2H), 7.42 (dd, $J = 8.5, 1.8$ Hz, 1H), 3.64 – 3.49 (m, 1H), 3.45 (s, 3H), 3.26 (s, 3H), 2.90 – 2.78 (m, 4H)
279		5-(1-丁基-1H-吡咯-2-基)-2-((二甲基氨基)亚甲基)环己烷-1,3-二酮	$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 8.10 (d, $J = 10.7$ Hz, 1H), 6.67 – 6.53 (m, 1H), 6.11 (dd, $J = 6.8, 3.6$ Hz, 1H), 6.00 (d, $J = 37.2$ Hz, 1H), 3.87 – 3.79 (m, 2H), 3.41 (d, $J = 24.1$ Hz, 3H), 3.39 – 3.31 (m, 1H), 3.26 (s, 3H), 2.92 – 2.73 (m, 2H), 2.66 (ddd, $J = 23.2, 11.9, 6.0$ Hz, 2H), 1.80 – 1.64 (m, 2H), 1.41 – 1.32 (m, 2H), 0.99 – 0.87 (m, 3H)
280		2-((二甲基氨基)亚甲基)-5-(5,6,7,8-四氢萘-1-基)环己烷-1,3-二酮	$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 8.10 (s, 1H), 7.15 (t, $J = 7.5$ Hz, 1H), 7.08 (d, $J = 6.7$ Hz, 1H), 7.00 (d, $J = 7.3$ Hz, 1H), 3.59 (p, $J = 8.3$ Hz, 1H), 3.44 (s, 3H), 3.26 (s, 3H), 2.82 (t, $J = 6.2$ Hz, 2H), 2.77 (t, $J = 6.2$ Hz, 2H), 2.67 (d, $J = 8.2$ Hz, 4H), 1.86 – 1.76 (m, 4H)
281		2-((二甲基氨基)亚甲基)-5-(1H-吡咯-5-基)环己烷-1,3-二酮	$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 8.20 (s, 1H), 8.11 (s, 1H), 7.53 (s, 1H), 7.39 (d, $J = 8.6$ Hz, 1H), 7.26 – 7.21 (m, 1H), 7.12 (d, $J = 8.6$ Hz, 1H), 6.55 (s, 1H), 3.47 (dd, $J = 11.1, 5.6$ Hz, 1H), 3.44 (s, 3H), 3.25 (s, 3H), 2.83 (dd, $J = 16.4, 11.2$ Hz, 4H)
282		5-(苯并[b]噻吩-3-基)-2-((二甲基氨基)亚甲基)环己烷-1,3-二酮	$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 8.13 (s, 1H), 7.89 (dd, $J = 7.2, 1.9$ Hz, 1H), 7.80 (dd, $J = 7.0, 1.6$ Hz, 1H), 7.45 – 7.33 (m, 2H), 7.18 (s, 1H), 3.85 – 3.74 (m, 1H), 3.46 (s, 3H), 3.27 (s, 3H), 2.99 (dd, $J = 16.9, 4.1$ Hz, 2H), 2.79 (dd, $J = 16.8, 11.1$ Hz, 2H)
283		2-((二甲基氨基)亚甲基)-5-(1H-吡咯-3-基)环己烷-1,3-二酮	$^1\text{H NMR}$ (400 MHz, DMSO) δ 10.85 (s, 1H), 8.04 (s, 1H), 7.57 (d, $J = 7.8$ Hz, 1H), 7.35 (d, $J = 8.1$ Hz, 1H), 7.15 – 7.03 (m, 2H), 7.03 – 6.89 (m, 1H), 3.61 – 3.49 (m, 1H), 3.42 (s, 3H), 3.10 (s, 3H), 2.68 (qd, $J = 16.2, 7.4$ Hz, 4H)

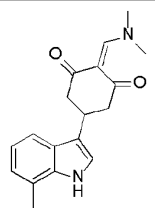
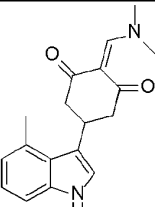
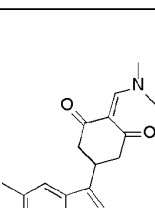
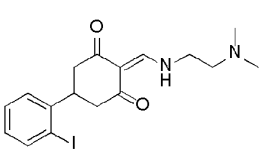
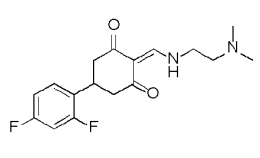
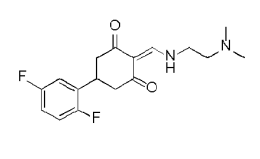
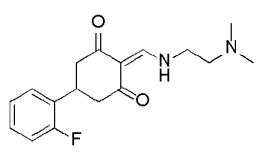
[0588]

284		2-((二甲基氨基)亚甲基)-5-(1-异丁基-1H-吡咯-2-基)环己烷-1,3-二酮	¹ H NMR (400 MHz, CDCl ₃) δ 8.08 (s, 1H), 6.66 – 6.51 (m, 1H), 6.10 (t, <i>J</i> = 3.1 Hz, 1H), 6.02 – 5.85 (m, 1H), 3.63 (d, <i>J</i> = 7.5 Hz, 2H), 3.43 (s, 3H), 3.32 (ddd, <i>J</i> = 15.7, 7.8, 4.0 Hz, 1H), 3.25 (s, 3H), 2.76 (dd, <i>J</i> = 16.9, 4.1 Hz, 2H), 2.68 – 2.58 (m, 2H), 2.02 – 1.98 (m, 1H), 0.96 (dd, <i>J</i> = 15.8, 5.9 Hz, 2H), 0.90 (d, <i>J</i> = 6.6 Hz, 6H)
285		2-((二甲基氨基)亚甲基)-5-(喹啉-4-基)环己烷-1,3-二酮	¹ H NMR (400 MHz, CDCl ₃) δ 8.92 (dd, <i>J</i> = 10.6, 4.4 Hz, 1H), 8.22 – 8.15 (m, 2H), 8.08 (d, <i>J</i> = 8.3 Hz, 1H), 7.76 (dd, <i>J</i> = 16.9, 8.7 Hz, 1H), 7.69 – 7.57 (m, 1H), 4.25 – 4.16 (m, 1H), 3.48 (s, 3H), 3.29 (s, 3H), 2.94 (dd, <i>J</i> = 16.7, 4.1 Hz, 2H), 2.82 (dd, <i>J</i> = 16.6, 11.5 Hz, 2H)
286		2-((二甲基氨基)亚甲基)-5-(1H-吡唑-3-基)环己烷-1,3-二酮	¹ H NMR (400 MHz, CDCl ₃) δ 10.35 (s, 1H), 8.12 (s, 1H), 7.76 (d, <i>J</i> = 8.1 Hz, 1H), 7.50 (d, <i>J</i> = 8.3 Hz, 1H), 7.42 – 7.35 (m, 1H), 7.16 (t, <i>J</i> = 7.5 Hz, 1H), 3.91 (dt, <i>J</i> = 14.7, 4.8 Hz, 1H), 3.41 (s, 3H), 3.23 (s, 3H), 3.05 – 2.95 (m, 4H)
287		2-((二甲基氨基)亚甲基)-5-(喹啉-4-基)环己烷-1,3-二酮	¹ H NMR (400 MHz, CDCl ₃) δ 9.29 (d, <i>J</i> = 4.3 Hz, 1H), 8.58 (t, <i>J</i> = 6.4 Hz, 1H), 8.16 (s, 1H), 7.91 (dd, <i>J</i> = 8.4, 4.6 Hz, 1H), 7.84 (d, <i>J</i> = 6.1 Hz, 1H), 7.63 (s, 1H), 7.61 (t, <i>J</i> = 2.6 Hz, 1H), 4.14 (tt, <i>J</i> = 11.4, 4.1 Hz, 1H), 3.48 (s, 3H), 3.30 (s, 3H), 2.92 (dd, <i>J</i> = 16.6, 4.2 Hz, 2H), 2.83 (dt, <i>J</i> = 16.6, 8.5 Hz, 2H)
288		5-(1-苄基-1H-吡咯-2-基)-2-((二甲基氨基)亚甲基)环己烷-1,3-二酮	¹ H NMR (400 MHz, CDCl ₃) δ 8.03 (d, <i>J</i> = 6.4 Hz, 1H), 7.31 (dd, <i>J</i> = 13.0, 5.6 Hz, 1H), 7.29 – 7.23 (m, 1H), 6.96 (d, <i>J</i> = 6.9 Hz, 2H), 6.69 – 6.60 (m, 1H), 6.22 – 6.12 (m, 1H), 6.05 (dd, <i>J</i> = 3.4, 1.5 Hz, 1H), 5.10 (d, <i>J</i> = 6.7 Hz, 1H), 3.41 (s, 3H), 3.27 – 3.21 (m, 1H), 3.20 (s, 3H), 2.64 (dd, <i>J</i> = 17.9, 5.9 Hz, 4H)
289		2-((二甲基氨基)亚甲基)-5-(2-(2-甲基苄基)苯基)环己烷-1,3-二酮	¹ H NMR (400 MHz, CDCl ₃) δ 8.07 (s, 1H), 7.33 – 7.29 (m, 2H), 7.25 – 7.19 (m, 1H), 7.15 (t, <i>J</i> = 7.3 Hz, 2H), 7.01 (d, <i>J</i> = 7.5 Hz, 1H), 6.91 – 6.83 (m, 2H), 4.04 (s, 2H), 3.60 (tt, <i>J</i> = 12.5, 4.0 Hz, 1H), 3.41 (d, <i>J</i> = 14.6 Hz, 3H), 3.21 (s, 3H), 2.64 (dt, <i>J</i> = 27.4, 13.7 Hz, 2H), 2.52 (dd, <i>J</i> = 16.9, 4.0 Hz, 2H), 2.29 (s, 3H)

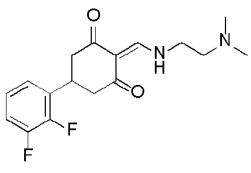
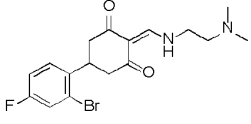
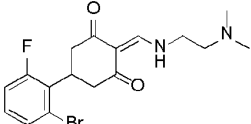
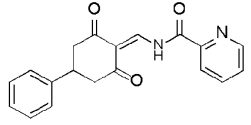
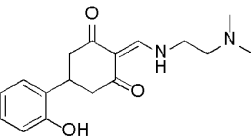
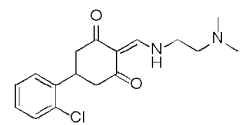
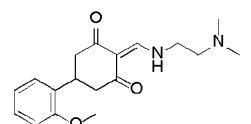
[0589]

290		2-((二甲基氨基)亚甲基)-5-(2-(3-甲基苯基)苯基)环己烷-1,3-二酮	¹ HNMR (400 MHz, CDCl ₃) δ 8.09 (d, <i>J</i> = 11.8 Hz, 1H), 7.41 – 7.30 (m, 2H), 7.18 (t, <i>J</i> = 7.6 Hz, 2H), 7.14 – 7.06 (m, 1H), 6.96 (d, <i>J</i> = 7.5 Hz, 1H), 6.85 (d, <i>J</i> = 7.1 Hz, 1H), 4.01 (s, 2H), 3.59 – 3.50 (m, 2H), 3.44 (d, <i>J</i> = 4.8 Hz, 3H), 3.22 (s, 3H), 2.72 (dd, <i>J</i> = 16.7, 12.1 Hz, 2H), 2.65 – 2.58 (m, 2H), 2.27 (s, 3H)
291		2-((二甲基氨基)亚甲基)-5-(2-(4-甲基苯基)苯基)环己烷-1,3-二酮	¹ HNMR (400 MHz, CDCl ₃) δ 8.07 (s, 1H), 7.30 (t, <i>J</i> = 6.1 Hz, 2H), 7.24 – 7.18 (m, 1H), 7.16 (d, <i>J</i> = 7.2 Hz, 1H), 7.07 (d, <i>J</i> = 7.9 Hz, 2H), 6.96 (d, <i>J</i> = 8.0 Hz, 2H), 4.04 (s, 2H), 3.60 (tt, <i>J</i> = 12.5, 4.2 Hz, 1H), 3.43 (s, 3H), 3.22 (s, 3H), 2.66 (dd, <i>J</i> = 16.8, 12.5 Hz, 2H), 2.53 (dd, <i>J</i> = 17.0, 4.1 Hz, 2H), 2.31 (s, 3H)
293		2-((二甲基氨基)亚甲基)-5-(6-甲基-1H-吡啶-3-基)环己烷-1,3-二酮	¹ HNMR (400 MHz, CDCl ₃) δ 8.11 (s, 1H), 8.03 (s, 1H), 7.54 (d, <i>J</i> = 8.1 Hz, 1H), 7.18 (s, 1H), 6.98 (d, <i>J</i> = 8.2 Hz, 1H), 6.94 (d, <i>J</i> = 2.0 Hz, 1H), 3.67 (td, <i>J</i> = 11.0, 5.4 Hz, 1H), 3.41 (s, 3H), 3.24 (s, 3H), 2.99 (dd, <i>J</i> = 16.9, 4.0 Hz, 2H), 2.77 (dd, <i>J</i> = 16.8, 11.1 Hz, 2H), 2.48 (s, 3H)
294		2-((二甲基氨基)亚甲基)-5-(1-甲基-1H-吡啶-3-基)环己烷-1,3-二酮	¹ HNMR (400 MHz, CDCl ₃) δ 8.12 (s, 1H), 7.67 – 7.63 (m, 1H), 7.32 (dt, <i>J</i> = 8.2, 0.9 Hz, 1H), 7.27 – 7.23 (m, 1H), 7.13 (ddd, <i>J</i> = 8.0, 6.9, 1.1 Hz, 1H), 6.87 (d, <i>J</i> = 0.7 Hz, 1H), 3.77 (s, 3H), 3.70 (ddt, <i>J</i> = 8.5, 4.3, 3.4 Hz, 1H), 3.43 (t, <i>J</i> = 2.1 Hz, 3H), 3.25 (d, <i>J</i> = 0.6 Hz, 3H), 3.02 – 2.94 (m, 2H), 2.77 (dd, <i>J</i> = 16.9, 11.0 Hz, 2H)
295		2-((二甲基氨基)亚甲基)-5-(1-甲基-1H-吡啶-4-基)环己烷-1,3-二酮	¹ HNMR (400 MHz, CDCl ₃) δ 8.14 (s, 1H), 7.28 – 7.21 (m, 2H), 7.09 (d, <i>J</i> = 3.2 Hz, 1H), 7.00 (dd, <i>J</i> = 6.6, 1.0 Hz, 1H), 6.55 (dd, <i>J</i> = 3.2, 0.7 Hz, 1H), 3.87 – 3.76 (m, 4H), 3.47 – 3.41 (m, 3H), 3.27 (t, <i>J</i> = 4.2 Hz, 3H), 2.88 (dd, <i>J</i> = 15.1, 11.4 Hz, 4H).
296		2-((二甲基氨基)亚甲基)-5-(2-甲基-1H-吡啶-3-基)环己烷-1,3-二酮	¹ HNMR (400 MHz, CDCl ₃) δ 8.14 (s, 1H), 7.98 (s, 1H), 7.63 (d, <i>J</i> = 7.9 Hz, 1H), 7.35 – 7.29 (m, 1H), 7.13 (tt, <i>J</i> = 6.4, 1.8 Hz, 1H), 7.07 (ddd, <i>J</i> = 9.2, 5.2, 1.6 Hz, 1H), 3.63 – 3.54 (m, 1H), 3.41 (s, 3H), 3.26 (d, <i>J</i> = 0.5 Hz, 3H), 3.19 (dd, <i>J</i> = 17.2, 13.4 Hz, 2H), 2.72 – 2.65 (m, 2H), 2.40 (d, <i>J</i> = 6.1 Hz, 3H).

[0590]

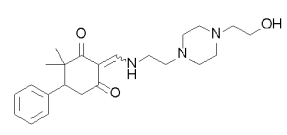
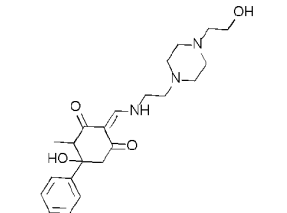
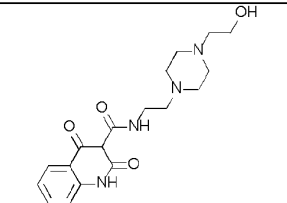
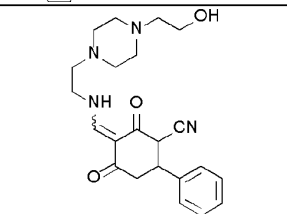
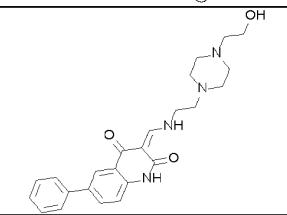
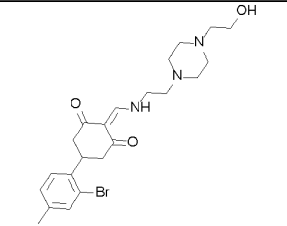
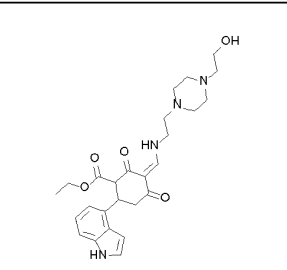
297		2-((二甲基氨基)亚甲基)-5-(7-甲基-1H-吲哚-3-基)环己烷-1,3-二酮	¹ H NMR (400 MHz, CDCl ₃) δ 8.12 (s, 1H), 8.07 (s, 1H), 7.52 (d, <i>J</i> = 7.7 Hz, 1H), 7.10 – 7.05 (m, 1H), 7.05 – 7.01 (m, 2H), 3.79 – 3.64 (m, 1H), 3.42 (s, 3H), 3.25 (s, 3H), 3.00 (dd, <i>J</i> = 16.9, 4.2 Hz, 2H), 2.79 (dd, <i>J</i> = 16.9, 11.2 Hz, 2H), 2.50 (s, 3H)
298		2-((二甲基氨基)亚甲基)-5-(4-甲基-1H-吲哚-3-基)环己烷-1,3-二酮	¹ H NMR (400 MHz, CDCl ₃) δ 8.11 (s, 2H), 7.23 (d, <i>J</i> = 7.9 Hz, 1H), 7.13 – 7.06 (m, 1H), 7.03 (d, <i>J</i> = 2.0 Hz, 1H), 6.91 – 6.86 (m, 1H), 3.97 (tt, <i>J</i> = 11.2, 3.7 Hz, 1H), 3.43 (d, <i>J</i> = 0.4 Hz, 3H), 3.26 (d, <i>J</i> = 0.5 Hz, 3H), 3.02 – 2.95 (m, 2H), 2.79 – 2.64 (m, 6H)
299		2-((二甲基氨基)亚甲基)-5-(5-甲基-1H-吲哚-3-基)环己烷-1,3-二酮	¹ H NMR (400 MHz, CDCl ₃) δ 8.11 (d, <i>J</i> = 5.2 Hz, 2H), 7.45 (d, <i>J</i> = 0.7 Hz, 1H), 7.28 (d, <i>J</i> = 6.6 Hz, 1H), 7.05 (dd, <i>J</i> = 8.3, 1.4 Hz, 1H), 6.97 (d, <i>J</i> = 1.8 Hz, 1H), 3.67 (tt, <i>J</i> = 11.1, 4.2 Hz, 1H), 3.42 (s, 3H), 3.30 – 3.23 (m, 3H), 3.00 (dd, <i>J</i> = 17.0, 4.2 Hz, 2H), 2.77 (dd, <i>J</i> = 16.9, 11.2 Hz, 2H), 2.48 (d, <i>J</i> = 5.1 Hz, 3H)
300		2-(((2-(二甲基氨基)乙基)氨基)亚甲基)-5-(2-碘苯基)环己烷-1,3-二酮	¹ H NMR (400 MHz, CDCl ₃) δ 11.22 (s, 1H), 8.20 (d, <i>J</i> = 14.4 Hz, 1H), 7.86 (dd, <i>J</i> = 7.9, 1.0 Hz, 1H), 7.35 (t, <i>J</i> = 7.6 Hz, 1H), 7.21 (dd, <i>J</i> = 7.8, 1.3 Hz, 1H), 6.98 – 6.91 (m, 1H), 3.66 (tt, <i>J</i> = 12.1, 4.1 Hz, 1H), 3.51 (q, <i>J</i> = 6.0 Hz, 2H), 2.77 (dd, <i>J</i> = 16.7, 4.0 Hz, 2H), 2.69 – 2.52 (m, 4H), 2.29 (s, 6H).
301		5-(2,4-二氟苯基)-2-(((2-(二甲基氨基)乙基)氨基)亚甲基)环己烷-1,3-二酮	¹ H NMR (400 MHz, CDCl ₃) δ 11.22 (s, 1H), 8.18 (d, <i>J</i> = 14.4 Hz, 1H), 7.16 (dd, <i>J</i> = 14.8, 8.5 Hz, 1H), 6.88 – 6.77 (m, 2H), 3.60 (d, <i>J</i> = 9.8 Hz, 1H), 3.51 (q, <i>J</i> = 6.1 Hz, 2H), 2.71 (dd, <i>J</i> = 14.9, 9.7 Hz, 4H), 2.55 (t, <i>J</i> = 6.1 Hz, 2H), 2.29 (s, 6H).
302		5-(2,5-二氟苯基)-2-(((2-(二甲基氨基)乙基)氨基)亚甲基)环己烷-1,3-二酮	¹ H NMR (400 MHz, cdcl ₃) δ 11.22 (s, 1H), 8.19 (d, <i>J</i> = 14.4 Hz, 1H), 7.01 (td, <i>J</i> = 9.6, 4.5 Hz, 1H), 6.95 – 6.87 (m, 2H), 3.64 (ddd, <i>J</i> = 15.7, 10.7, 5.2 Hz, 1H), 3.51 (q, <i>J</i> = 6.0 Hz, 2H), 2.77 – 2.61 (m, 4H), 2.55 (t, <i>J</i> = 6.1 Hz, 2H), 2.29 (s, 6H).
303		2-(((2-(二甲基氨基)乙基)氨基)亚甲基)-5-(2-氟苯基)环己烷-1,3-二酮	¹ H NMR (400 MHz, DMSO-d ₆) δ 10.99 – 10.88 (m, 1H), 8.13 (d, <i>J</i> = 14.7 Hz, 1H), 7.35 (t, <i>J</i> = 7.7 Hz, 1H), 7.32 – 7.23 (m, 1H), 7.16 (d, <i>J</i> = 7.2 Hz, 1H), 7.13 (d, <i>J</i> = 8.2 Hz, 1H), 3.54 (dt, <i>J</i> = 9.1, 4.6 Hz, 3H), 2.70 (ddd, <i>J</i> = 31.8, 16.5, 11.7 Hz, 2H), 2.54 – 2.49 (m, 1H), 2.45 (dd, <i>J</i> = 5.7, 3.7 Hz, 1H), 2.40 (t, <i>J</i> = 5.9 Hz, 2H), 2.15 (s, 6H).

[0591]

304		5-(2,3-二氟苯基)-2-(((2-(二甲基氨基)乙基)氨基)亚甲基)环己烷-1,3-二酮	$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 11.22 (s, 1H), 8.19 (d, $J = 14.4$ Hz, 1H), 7.06 (t, $J = 6.2$ Hz, 2H), 6.97 (dd, $J = 5.4, 3.2$ Hz, 1H), 3.75 – 3.63 (m, 1H), 3.51 (q, $J = 6.0$ Hz, 2H), 2.79 – 2.67 (m, 4H), 2.55 (t, $J = 6.1$ Hz, 2H), 2.29 (s, 6H).
305		5-(2-溴-4-氟苯基)-2-(((2-(二甲基氨基)乙基)氨基)亚甲基)环己烷-1,3-二酮	$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 11.21 (s, 1H), 8.19 (d, $J = 14.4$ Hz, 1H), 7.33 (dd, $J = 8.2, 2.6$ Hz, 1H), 7.21 (dd, $J = 8.7, 5.9$ Hz, 1H), 7.04 (td, $J = 8.3, 2.6$ Hz, 1H), 3.77 (dd, $J = 10.0, 5.9$ Hz, 1H), 3.51 (q, $J = 6.0$ Hz, 2H), 2.77 (d, $J = 2.6$ Hz, 1H), 2.73 (d, $J = 3.1$ Hz, 1H), 2.68 – 2.56 (m, 2H), 2.55 (dd, $J = 11.4, 5.3$ Hz, 2H), 2.29 (s, 6H).
306		5-(2-溴-6-氟苯基)-2-(((2-(二甲基氨基)乙基)氨基)亚甲基)环己烷-1,3-二酮	$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 11.24 (s, 1H), 8.22 (d, $J = 14.4$ Hz, 1H), 7.38 (d, $J = 7.9$ Hz, 1H), 7.10 (td, $J = 8.1, 5.9$ Hz, 1H), 7.06 – 6.98 (m, 1H), 4.00 (tt, $J = 13.5, 3.5$ Hz, 1H), 3.56 – 3.47 (m, 2H), 3.10 (ddd, $J = 30.3, 16.6, 13.7$ Hz, 2H), 2.60 (ddd, $J = 14.7, 3.9, 2.0$ Hz, 2H), 2.54 (t, $J = 6.1$ Hz, 2H), 2.29 (s, 6H).
307		N-((2,6-二氧代-4-苯基亚环己基)甲基)吡啶酰胺	$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 13.92 (d, $J = 12.5$ Hz, 1H), 8.88 (d, $J = 12.9$ Hz, 1H), 8.79 (d, $J = 4.7$ Hz, 1H), 8.29 (d, $J = 7.8$ Hz, 1H), 7.95 (td, $J = 7.7, 1.6$ Hz, 1H), 7.62 – 7.55 (m, 1H), 7.36 (t, $J = 7.4$ Hz, 2H), 7.28 (d, $J = 7.3$ Hz, 1H), 7.24 (s, 2H), 3.50 – 3.40 (m, 1H), 3.01 – 2.77 (m, 4H).
308		2-(((2-(二甲基氨基)乙基)氨基)亚甲基)-5-(2-羟基苯基)环己烷-1,3-二酮	$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 11.25 (d, $J = 14.2$ Hz, 1H), 8.23 (d, $J = 14.5$ Hz, 1H), 7.07 (t, $J = 6.9$ Hz, 2H), 6.88 – 6.81 (m, 2H), 3.69 (s, 1H), 3.53 (q, $J = 6.0$ Hz, 2H), 2.95 – 2.85 (m, 2H), 2.81 – 2.62 (m, 2H), 2.57 (t, $J = 6.1$ Hz, 2H), 2.30 (s, 6H).
309		5-(2-氯苯基)-2-(((2-(二甲基氨基)乙基)氨基)亚甲基)环己烷-1,3-二酮	$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 11.20 (s, 1H), 8.19 (d, $J = 14.3$ Hz, 1H), 7.38 (d, $J = 7.7$ Hz, 1H), 7.25 (s, 2H), 7.21 – 7.14 (m, 1H), 3.85 (s, 1H), 3.51 (d, $J = 6.0$ Hz, 2H), 2.70 (ddd, $J = 23.0, 16.8, 9.6$ Hz, 4H), 2.55 (t, $J = 5.9$ Hz, 2H), 2.29 (s, 6H).
310		2-(((2-(二甲基氨基)乙基)氨基)亚甲基)-5-(2-甲氧基苯基)环己烷-1,3-二酮	$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 11.21 (s, 1H), 8.18 (d, $J = 14.3$ Hz, 1H), 7.23 (td, $J = 8.2, 1.6$ Hz, 1H), 7.15 (dd, $J = 7.6, 1.3$ Hz, 1H), 6.94 (td, $J = 7.5, 0.9$ Hz, 1H), 6.87 (d, $J = 8.2$ Hz, 1H), 3.82 (s, 3H), 3.77 – 3.67 (m, 1H), 3.49 (q, $J = 6.1$ Hz, 2H), 2.77 – 2.66

			(m, 4H), 2.53 (t, $J = 6.2$ Hz, 2H), 2.28 (s, 6H).
311		2 - (((2-(二甲基氨基)乙基)氨基)亚甲基)-5-(3-硝基苯基)环己烷-1,3-二酮	$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 11.21 (s, 1H), 8.20 (d, $J = 14.5$ Hz, 1H), 8.12 (dd, $J = 4.3, 2.0$ Hz, 2H), 7.61 – 7.48 (m, 2H), 3.55 – 3.44 (m, 3H), 2.80 – 2.76 (m, 2H), 2.74 (d, $J = 12.4$ Hz, 1H), 2.71 – 2.65 (m, 1H), 2.55 (t, $J = 6.1$ Hz, 2H), 2.29 (s, 6H).
315		2-(((2-(4-(2-羟乙基)哌嗪-1-基)乙基)氨基)亚甲基)-5-(1H-吡啶-6-基)环己烷-1,3-二酮	$^1\text{H NMR}$ (400 MHz, CD_3OD) δ 8.24 (s, 1H), 7.49 (d, $J = 8.2$ Hz, 1H), 7.27 (s, 1H), 7.19 (d, $J = 3.1$ Hz, 1H), 6.96 (s, 1H), 6.39 (s, 1H), 3.81 (t, $J = 5.4$ Hz, 2H), 3.61 (m, 2H), 3.45 (m, 1H), 3.34 (s, 2H), 3.06 (m, 4H), 2.93 – 2.62 (m, 10H); MS: 411.2 [M+1].
317		3-(((2-(4-(2-羟乙基)哌嗪-1-基)乙基)氨基)亚甲基)-6-(三氟甲基)喹啉-2,4(1H, 3H)-二酮	$^1\text{H NMR}$ (400 MHz, CD_3OD) δ 8.58 (d, $J = 8.5$ Hz, 1H), 8.31 (s, 1H), 7.77 (d, $J = 8.3$ Hz, 1H), 7.32 (d, $J = 8.6$ Hz, 1H), 3.87 – 3.67 (m, 4H), 3.02 (d, $J = 4.0$ Hz, 6H), 2.74 (m, 6H).
318		3-(((2-(4-(2-羟乙基)哌嗪-1-基)乙基)氨基)亚甲基)-8-硝基喹啉-2,4(1H, 3H)-二酮	$^1\text{H NMR}$ (400 MHz, CD_3OD) δ 8.47 (m, 3H), 7.27 (m, 1H), 3.81 (m, 4H), 3.10 (d, $J = 5.3$ Hz, 6H), 2.89 – 2.66 (m, 6H).
320		2-(((2-(4-(2-羟乙基)哌嗪-1-基)乙基)氨基)亚甲基)-5-(2-(三氟甲基)苯基)环己烷-1,3-二酮	$^1\text{H NMR}$ (400 MHz, $\text{DMSO}-d_6$) δ 11.05 – 10.84 (m, 1H), 8.15 (d, $J = 14.8$ Hz, 1H), 7.81 (d, $J = 8.2$ Hz, 1H), 7.67 (t, $J = 7.2$ Hz, 2H), 7.44 (t, $J = 7.6$ Hz, 1H), 4.80 (s, 1H), 3.58 – 3.12 (m, 9H), 3.00 – 2.50 (m, 10H), 2.34 (d, $J = 16.5$ Hz, 2H).
321		3-(((2-(4-(2-羟乙基)哌嗪-1-基)乙基)氨基)亚甲基)-8-苯基喹啉-2,4(1H, 3H)-二酮	$^1\text{H NMR}$ (400 MHz, CD_3OD) δ 8.54 (d, $J = 47.0$ Hz, 1H), 8.09 (d, $J = 7.8$ Hz, 1H), 7.63 – 7.37 (m, 6H), 7.25 (t, $J = 7.7$ Hz, 1H), 3.74 (m, 4H), 3.04 – 2.57 (m, 12H).
322		5-(3-氯-1H-吡啶-4-基)-2-(((2-(4-(2-羟乙基)哌嗪-1-基)乙基)氨基)亚甲基)环己烷-1,3-二酮	$^1\text{H NMR}$ (400 MHz, CD_3OD) δ 8.27 (s, 1H), 7.32 – 7.19 (m, 2H), 7.12 (t, $J = 7.8$ Hz, 1H), 6.96 (d, $J = 7.2$ Hz, 1H), 3.71 (t, $J = 5.9$ Hz, 2H), 3.61 (t, $J = 5.9$ Hz, 2H), 2.92 – 2.48 (m, 17H).
323		2-(((2-(4-(2-羟乙基)哌嗪-1-基)乙基)氨基)亚甲基)-4,5-二苯基环	$^1\text{H NMR}$ (400 MHz, CD_3OD) δ 8.30 (d, $J = 24.8$ Hz, 1H), 7.16-7.05 (m, 10H), 4.04-3.93 (m, 1H), 3.70-3.56 (m, 5H), 3.04-2.99 (m, 1H), 2.69-2.61 (m, 13H); MS: 448.2 [M+1].

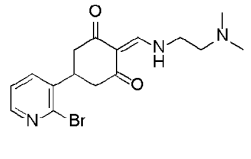
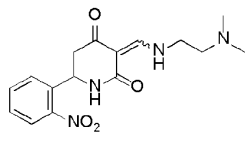
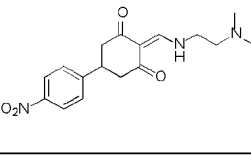
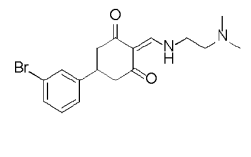
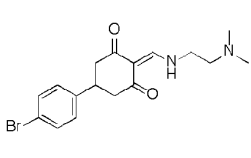
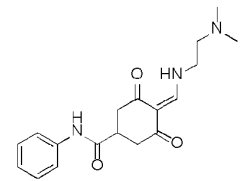
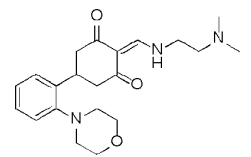
[0593]

		己烷-1,3-二酮	
324		2-(((2-(4-(2-羟乙基)哌嗪-1-基)乙基)氨基)亚甲基)-4,4-二甲基-5-苯基环己烷-1,3-二酮	^1H NMR (400 MHz, CD_3OD) δ 8.27(d, J = 20.4 Hz, 1H), 7.29-7.21(m, 5H), 3.72 (t, J = 5.6 Hz, 2H), 3.62(t, J = 5.6 Hz, 2H), 3.22-3.17 (m, 1H), 3.09-3.00(m, 1H), 2.77-2.56 (m, 13H), 1.12 – 1.00 (m, 6H); MS: 400.2 [M+1].
325		5-羟基-2-(((2-(4-(2-羟乙基)哌嗪-1-基)乙基)氨基)亚甲基)-4-甲基-5-苯基环己烷-1,3-二酮	^1H NMR (400 MHz, DMSO- d_6) δ 10.76 (s, 1H), 8.08 (d, J = 14.8 Hz, 1H), 7.71 (s, 1H), 7.47 (d, J = 7.7 Hz, 2H), 7.32 (t, J = 7.5 Hz, 2H), 7.20 (t, J = 7.2 Hz, 1H), 3.72 (s, 3H), 3.60 (s, 2H), 3.22 – 2.85 (m, 10H), 2.71 (s, 2H), 2.56 (m, 1H), 2.43 (s, 1H), 1.92 (d, J = 12.3 Hz, 1H), 1.07 – 0.71 (m, 3H).
326		N-(2-(4-(2-羟乙基)哌嗪-1-基)乙基)-2,4-二氧代-1,2,3,4-四氢喹啉-3-甲酰胺	^1H NMR (400 MHz, CD_3OD) δ 8.06 (d, J = 8.0 Hz, 1H), 7.64 (t, J = 7.3 Hz, 1H), 7.29 (dd, J = 14.9, 7.7 Hz, 2H), 3.68 (t, J = 6.0 Hz, 2H), 3.57 (t, J = 6.4 Hz, 2H), 2.59 m, 12H).
327		2-(((2-(4-(2-羟乙基)哌嗪-1-基)乙基)氨基)亚甲基)-4-氰基-5-苯基环己烷-1,3-二酮	^1H NMR (400 MHz, CD_3OD) δ 8.35-8.32(m, 1H), 7.40-7.31(m, 5H), 3.84-3.82(m, 2H), 3.66-3.53(m, 3H), 3.28-3.12(m, 6H), 2.88-2.63(m, 10H); MS: 397.2 [M+1].
328		3-(((2-(4-(2-羟乙基)哌嗪-1-基)乙基)氨基)亚甲基)-6-苯基喹啉-2,4-二酮	^1H NMR (400 MHz, DMSO- d_6) δ 11.93 – 11.64 (m, 1H), 10.72-10.02 (m, 2H), 8.48 (m, 1H), 8.23 – 7.16 (m, 7H), 3.67 – 3.31 (m, 10H), 2.94 (m, 6H).
329		5-(2-溴-4-甲基苯基)-2-(((2-(4-(2-羟乙基)哌嗪-1-基)乙基)氨基)亚甲基)环己烷-1,3-二酮	^1H NMR (400 MHz, CD_3OD) δ 8.26 (s, 1H), 7.43 (s, 1H), 7.24 (d, J = 8.0 Hz, 1H), 7.17 (d, J = 8.0 Hz, 1H), 3.71 (m, 3H), 3.61 (t, J = 5.9 Hz, 2H), 2.81 – 2.52 (m, 16H), 2.30 (s, 3H).
330		3-(((2-(4-(2-羟乙基)哌嗪-1-基)乙基)氨基)亚甲基)-6-(1H-咪唑-4-基)-2,4-二氧代环己烷-1-羧酸乙酯	^1H NMR (400 MHz, CD_3OD) δ 8.30 (d, J = 18.1 Hz, 1H), 7.26 (dd, J = 14.0, 5.6 Hz, 2H), 7.05 (t, J = 7.8 Hz, 1H), 6.94 (d, J = 7.3 Hz, 1H), 6.56 (d, J = 3.1 Hz, 1H), 4.09 (m, 2H), 3.96 – 3.83 (m, 2H), 3.77 (t, J = 5.6 Hz, 2H), 3.62 (m, 2H), 2.92 (m, 6H), 2.80 – 2.45 (m, 8H), 0.90 (t, J = 7.1 Hz, 3H).

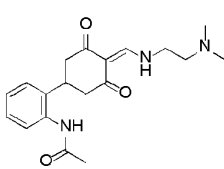
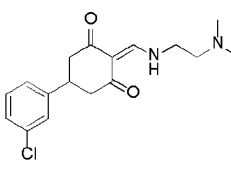
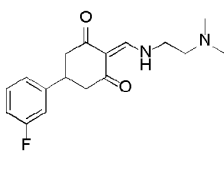
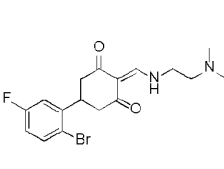
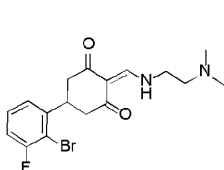
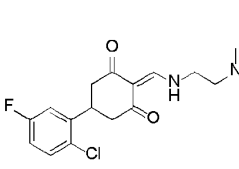
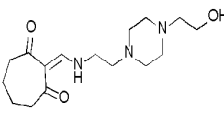
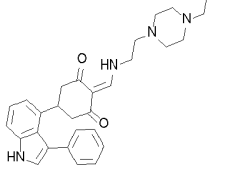
[0594]

331		3-(((2-(4-(2-羟乙基)哌嗪-1-基)乙基)氨基)亚甲基)苯并[h]喹啉-2,4(1H,3H)-二酮	$^1\text{H NMR}$ (400 MHz, CD_3OD) δ 8.61 (d, J = 34.9 Hz, 1H), 8.47 (d, J = 8.1 Hz, 1H), 8.06 (d, J = 8.7 Hz, 1H), 7.91 (d, J = 7.4 Hz, 1H), 7.71 – 7.54 (m, 3H), 3.73 (m, 4H), 2.92 – 2.53 (m, 12H).
332		5-(2-溴-5-(二甲基氨基)苯基)-2-(((2-(4-(2-羟乙基)哌嗪-1-基)乙基)氨基)亚甲基)环己烷-1,3-二酮	$^1\text{H NMR}$ (400 MHz, CD_3OD) δ 8.26 (s, 1H), 7.34 (d, J = 8.9 Hz, 1H), 6.66 (d, J = 3.0 Hz, 1H), 6.56 (dd, J = 8.9, 3.0 Hz, 1H), 3.76 (t, J = 5.7 Hz, 2H), 3.70 (m, 1H), 3.62 (t, J = 5.8 Hz, 2H), 2.99 – 2.56 (m, 22H).
333		3-(((2-(4-(2-羟乙基)哌嗪-1-基)乙基)氨基)亚甲基)-2,4-二氧代-6-苯基环己烷-1-甲酰胺	$^1\text{H NMR}$ (400 MHz, CD_3OD) δ 8.27(d, J = 16.8Hz, 1H), 7.31-7.25(m, 5H), 3.84-3.72(m, 3H), 3.66-3.59(m, 3H), 3.16-3.04(m, 6H), 2.86-2.59(m, 12H); MS: 415.2 [M+1].
334		3-(((2-(4-(2-羟乙基)哌嗪-1-基)乙基)氨基)亚甲基)-2,4-二氧代-6-苯基环己烷-1-甲酸叔丁酯	$^1\text{H NMR}$ (400 MHz, CD_3OD) δ 8.28-8.24(m, 1H), 7.31-7.20(m, 5H), 3.89-3.27(m, 12H), 2.90-2.55(m, 8H), 1.20-1.17(m, 9H); MS: 472.2 [M+1].
335		3-(((2-(4-(2-羟乙基)哌嗪-1-基)乙基)氨基)亚甲基)-2,4-二氧代-6-苯基环己烷-1-甲酸乙酯	$^1\text{H NMR}$ (400 MHz, CD_3OD) δ 8.30-8.25(m, 1H), 7.46-7.12(m, 5H), 4.00-3.87(m, 5H), 3.86-3.11(m, 9H), 2.87-2.57 (m, 8H), 1.01-0.90(m, 3H); MS: 444.2 [M+1].
336		3-(((2-(4-(2-羟乙基)哌嗪-1-基)乙基)氨基)亚甲基)-1-甲基-2,4-二氧代-6-苯基环己烷-1-腈	$^1\text{H NMR}$ (400 MHz, CD_3OD) δ 8.37-8.31(m, 1H), 7.43-7.33(m, 5H), 3.70(t, J = 6.0Hz, 2H), 3.64(t, J = 5.6Hz, 2H), 3.11-3.33(m, 2H), 2.77-2.60(m, 13H), 1.37(br, 3H); MS: 411.2 [M+1].
337		2-(((2-(二甲基氨基)乙基)氨基)亚甲基)-5-(3-甲氧基苯基)环己烷-1,3-二酮	$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 11.21 (s, 1H), 8.18 (d, J = 14.3 Hz, 1H), 7.24 (d, J = 7.6 Hz, 1H), 6.80 (dd, J = 15.9, 7.6 Hz, 3H), 3.80 (s, 3H), 3.52 (dd, J = 12.1, 6.0 Hz, 2H), 3.38 – 3.27 (m, 1H), 2.80 – 2.69 (m, 3H), 2.70 – 2.61 (m, 1H), 2.57 (t, J = 6.1 Hz, 2H), 2.30 (s, 6H).

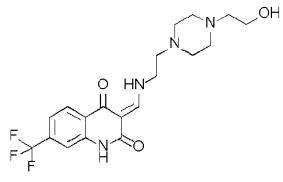
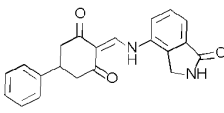
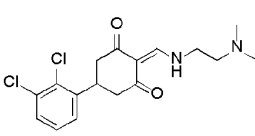
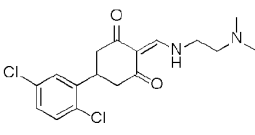
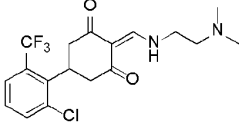
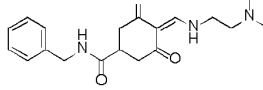
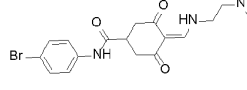
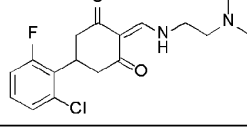
[0595]

338		5-(2- 溴 吡 啶 -3-基)-2-(((2-(二甲基氨基)乙基)氨基)亚甲基)环己烷-1,3-二酮	$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 11.22 (s, 1H), 8.28 (d, $J = 3.0$ Hz, 1H), 8.20 (d, $J = 14.4$ Hz, 1H), 7.54 (d, $J = 7.6$ Hz, 1H), 7.29 (s, 1H), 3.84 – 3.74 (m, 1H), 3.57 – 3.47 (m, 2H), 2.81 (d, $J = 6.7$ Hz, 2H), 2.70 – 2.59 (m, 2H), 2.56 (d, $J = 6.0$ Hz, 2H), 2.31 (s, 6H).
339		3-(((2-(二甲基氨基)乙基)氨基)亚甲基)-6-(2-硝基苯基)哌啶-2,4-二酮	$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 10.70 (s, 1H), 8.09 (d, $J = 14.3$ Hz, 1H), 7.96 (d, $J = 8.0$ Hz, 1H), 7.70 (t, $J = 7.8$ Hz, 1H), 7.64 (t, $J = 7.6$ Hz, 1H), 7.47 (t, $J = 7.5$ Hz, 1H), 5.65 (s, 1H), 5.35 (d, $J = 8.3$ Hz, 1H), 3.47 (dd, $J = 6.7, 5.8$ Hz, 2H), 3.17 – 3.03 (m, 1H), 2.70 (dd, $J = 6.7, 6.9$ Hz, 1H), 2.53 (t, $J = 6.1$ Hz, 2H), 2.28 (s, 6H).
340		2-(((2-(二甲基氨基)乙基)氨基)亚甲基)-5-(4-硝基苯基)环己烷-1,3-二酮	$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 11.21 (s, 1H), 8.20 (dd, $J = 11.7, 6.2$ Hz, 3H), 7.40 (d, $J = 8.5$ Hz, 2H), 3.56 – 3.43 (m, 3H), 2.82 – 2.62 (m, 4H), 2.54 (t, $J = 6.0$ Hz, 2H), 2.29 (s, 6H).
341		5-(3- 溴 苯基)-2-(((2-(二甲基氨基)乙基)氨基)亚甲基)环己烷-1,3-二酮	$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 11.18 (s, 1H), 8.16 (d, $J = 14.4$ Hz, 1H), 7.37 (dd, $J = 4.7, 1.4$ Hz, 2H), 7.17 (dt, $J = 19.2, 7.8$ Hz, 2H), 3.48 (q, $J = 6.0$ Hz, 2H), 3.37 – 3.26 (m, 1H), 2.77 – 2.56 (m, 4H), 2.52 (t, $J = 6.1$ Hz, 2H), 2.27 (s, 6H).
342		5-(4- 溴 苯基)-2-(((2-(二甲基氨基)乙基)氨基)亚甲基)环己烷-1,3-二酮	$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 11.21 (s, 1H), 8.18 (d, $J = 14.4$ Hz, 1H), 7.47 (d, $J = 8.4$ Hz, 2H), 7.12 (d, $J = 8.3$ Hz, 2H), 3.51 (q, $J = 6.0$ Hz, 2H), 3.34 (ddd, $J = 15.9, 11.1, 4.6$ Hz, 1H), 2.80 – 2.58 (m, 4H), 2.55 (t, $J = 6.1$ Hz, 2H), 2.29 (s, 6H).
343		4-(((2-(二甲基氨基)乙基)氨基)亚甲基)-3,5-二氧代的 N-苯基环己烷-1-甲酰胺	$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 11.16 (s, 1H), 8.12 (d, $J = 14.6$ Hz, 1H), 7.92 (s, 1H), 7.56 (d, $J = 7.8$ Hz, 2H), 7.32 (t, $J = 7.8$ Hz, 2H), 7.11 (t, $J = 7.5$ Hz, 1H), 3.45 (d, $J = 6.0$ Hz, 2H), 3.03 – 2.76 (m, 3H), 2.69 (d, $J = 17.1$ Hz, 2H), 2.51 (t, $J = 6.1$ Hz, 2H), 2.25 (s, 6H).
344		2-(((2-(二甲基氨基)乙基)氨基)亚甲基)-5-(2-吗啉代苯基)环己烷-1,3-二酮	$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 11.21 (s, 1H), 8.21 (d, $J = 14.4$ Hz, 1H), 7.27 – 7.12 (m, 4H), 3.96 (dd, $J = 9.8, 5.9$ Hz, 1H), 3.88 – 3.72 (m, 4H), 3.52 (q, $J = 6.0$ Hz, 2H), 2.85 (s, 4H), 2.78 – 2.61 (m, 4H), 2.55 (t, $J = 6.1$ Hz, 2H), 2.29 (s, 6H).

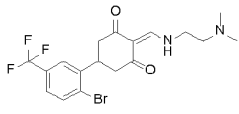
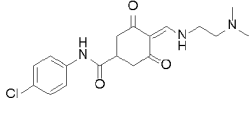
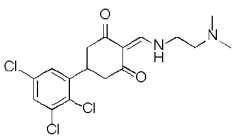
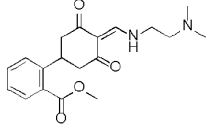
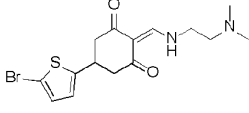
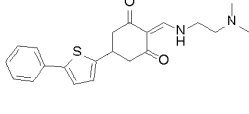
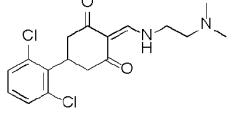
[0596]

345		N-(2-(4-((2-(二甲基氨基)乙基)氨基)亚甲基)-3,5-代环己基)苯基)乙酰胺	¹ H NMR (400 MHz, CDCl ₃) δ 11.15 (s, 1H), 8.12 (d, <i>J</i> = 14.3 Hz, 1H), 7.66 (s, 1H), 7.57 (d, <i>J</i> = 7.4 Hz, 1H), 7.25 (d, <i>J</i> = 4.9 Hz, 3H), 3.51 (t, <i>J</i> = 17.7 Hz, 3H), 2.64 (dd, <i>J</i> = 24.2, 10.9 Hz, 4H), 2.53 (t, <i>J</i> = 5.9 Hz, 2H), 2.27 (s, 6H), 2.18 (s, 3H).
346		5-(3-氯苯基)-2-((2-(二甲基氨基)乙基)氨基)亚甲基)环己烷-1,3-二酮	¹ H NMR (400 MHz, CDCl ₃) δ 11.21 (s, 1H), 8.18 (d, <i>J</i> = 14.4 Hz, 1H), 7.26 – 7.19 (m, 3H), 7.11 (d, <i>J</i> = 7.3 Hz, 1H), 3.53 – 3.47 (m, 2H), 3.39 – 3.28 (m, 1H), 2.70 (dt, <i>J</i> = 33.1, 12.1 Hz, 4H), 2.54 (t, <i>J</i> = 6.1 Hz, 2H), 2.28 (s, 6H).
347		2-((2-(二甲基氨基)乙基)氨基)亚甲基)-5-(3-氟苯基)环己烷-1,3-二酮	¹ H NMR (400 MHz, CDCl ₃) δ 11.21 (s, 1H), 8.18 (d, <i>J</i> = 14.4 Hz, 1H), 7.31 (dd, <i>J</i> = 9.5, 7.0 Hz, 1H), 7.01 (d, <i>J</i> = 7.7 Hz, 1H), 6.97 – 6.91 (m, 2H), 3.51 (q, <i>J</i> = 6.0 Hz, 2H), 3.41 – 3.31 (m, 1H), 2.79 – 2.59 (m, 4H), 2.55 (t, <i>J</i> = 6.1 Hz, 2H), 2.29 (s, 6H).
349		5-(2-溴-5-氟苯基)-2-((2-(二甲基氨基)乙基)氨基)亚甲基)环己烷-1,3-二酮	¹ H NMR (400 MHz, CDCl ₃) δ 11.21 (s, 1H), 8.20 (d, <i>J</i> = 14.4 Hz, 1H), 7.53 (dd, <i>J</i> = 8.8, 5.5 Hz, 1H), 6.97 (dd, <i>J</i> = 9.8, 2.9 Hz, 1H), 6.89 – 6.81 (m, 1H), 3.84 – 3.73 (m, 1H), 3.52 (q, <i>J</i> = 6.0 Hz, 2H), 2.77 (dd, <i>J</i> = 16.5, 3.8 Hz, 2H), 2.67 – 2.50 (m, 4H), 2.29 (s, 6H).
350		5-(2-溴-3-氟苯基)-2-((2-(二甲基氨基)乙基)氨基)亚甲基)环己烷-1,3-二酮	¹ H NMR (400 MHz, CDCl ₃) δ 11.21 (s, 1H), 8.20 (d, <i>J</i> = 14.4 Hz, 1H), 7.32 – 7.27 (m, 1H), 7.03 (t, <i>J</i> = 7.2 Hz, 2H), 3.85 (ddd, <i>J</i> = 15.7, 7.8, 4.1 Hz, 1H), 3.52 (q, <i>J</i> = 6.0 Hz, 2H), 2.81 – 2.59 (m, 4H), 2.56 (t, <i>J</i> = 6.1 Hz, 2H), 2.29 (s, 6H).
351		5-(2-氯-5-氟苯基)-2-((2-(二甲基氨基)乙基)氨基)亚甲基)环己烷-1,3-二酮	¹ H NMR (400 MHz, CDCl ₃) δ 11.22 (s, 1H), 8.20 (d, <i>J</i> = 14.4 Hz, 1H), 7.34 (dd, <i>J</i> = 8.8, 5.3 Hz, 1H), 6.99 – 6.88 (m, 2H), 3.86 – 3.76 (m, 1H), 3.52 (q, <i>J</i> = 6.0 Hz, 2H), 2.76 (dd, <i>J</i> = 16.6, 3.3 Hz, 2H), 2.68 – 2.52 (m, 4H), 2.29 (s, 6H).
352		2-((2-(4-(2-羟乙基)哌啶-1-基)乙基)氨基)亚甲基)环庚烷-1,3-二酮	¹ H NMR (400 MHz, CD ₃ OD) δ 8.08 (s, 1H), 3.72 (t, <i>J</i> = 5.9 Hz, 2H), 3.55 (t, <i>J</i> = 5.9 Hz, 2H), 2.87 – 2.52 (m, 15H), 1.90 – 1.75 (m, 4H). MS: 310.2 [M+1].
353		2-((2-(4-(2-羟乙基)哌啶-1-基)乙基)氨基)亚甲基)-5-(3-苯基-1H-吲哚-4-基)环己烷-1,3-二酮	¹ H NMR (400 MHz, CD ₃ OD) δ 8.10 (s, 1H), 7.39 (dd, <i>J</i> = 8.2, 1.3 Hz, 2H), 7.30 (m, 3H), 7.22 (m, 1H), 7.15 – 7.09 (m, 2H), 6.94 (d, <i>J</i> = 7.3 Hz, 1H), 3.81 – 3.76 (m, 2H), 3.74 (m, 1H), 3.55 (t, <i>J</i> = 5.8 Hz, 2H), 2.97 (m, 6H), 2.76 – 2.57 (m, 8H), 2.48 (m, 2H).

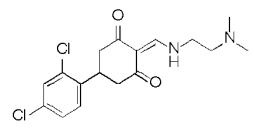
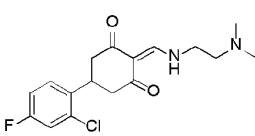
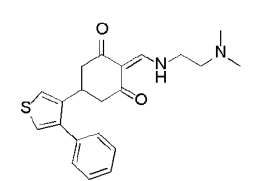
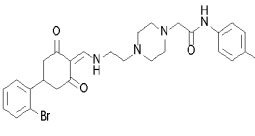
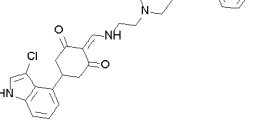
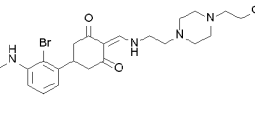
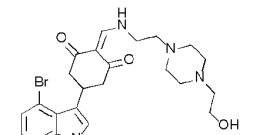
[0597]

			MS: 487.2 [M+1].
354		3-(((2-(4-(2-羟乙基)吡啶-1-基)乙基)氨基)亚甲基)-7-(三氟甲基)喹啉-2,4(1H, 3H)-二酮	¹ H NMR (400 MHz, CD ₃ OD) δ 8.54 (m, 1H), 8.19 (d, <i>J</i> = 8.0 Hz, 1H), 7.48 (s, 1H), 7.39 (d, <i>J</i> = 7.8 Hz, 1H), 3.81 – 3.68 (m, 4H), 2.88 (d, <i>J</i> = 34.6 Hz, 6H), 2.72 (s, 6H). MS: 413.1 [M+1].
355		2-(((1-氧代异吡啶啉-4-基)氨基)亚甲基)-5-苯基环己烷-1,3-二酮	¹ H NMR (400 MHz, DMSO-d ₆) δ 12.87 (s, 1H), 8.73 (s, 1H), 8.63 (m, 1H), 7.86 (m, 1H), 7.56 (s, 2H), 7.33 (s, 4H), 7.24 – 7.18 (m, 1H), 4.50 (s, 2H), 3.43 – 3.39 (m, 1H), 2.97 – 2.89 (m, 1H), 2.86 – 2.77 (m, 1H), 2.65 (m, 2H). MS: 347.1 [M+1]
356		5-(2,3-二氯苯基)-2-(((2-(二甲基氨基)乙基)氨基)亚甲基)环己烷-1,3-二酮	¹ H NMR (400 MHz, CDCl ₃) δ 11.20 (s, 1H), 8.19 (d, <i>J</i> = 14.4 Hz, 1H), 7.38 (dd, <i>J</i> = 7.7, 1.3 Hz, 1H), 7.19 (dt, <i>J</i> = 7.8, 7.1 Hz, 2H), 3.95 – 3.84 (m, 1H), 3.51 (q, <i>J</i> = 6.0 Hz, 2H), 2.77 (m, 2H), 2.63 (m, 2H), 2.54 (t, <i>J</i> = 6.1 Hz, 2H), 2.28 (s, 6H).
357		5-(2,5-二氯苯基)-2-(((2-(二甲基氨基)乙基)氨基)亚甲基)环己烷-1,3-二酮	¹ H NMR (400 MHz, CDCl ₃) δ 11.20 (s, 1H), 8.20 (d, <i>J</i> = 14.4 Hz, 1H), 7.32 (d, <i>J</i> = 8.5 Hz, 1H), 7.23 (d, <i>J</i> = 2.3 Hz, 1H), 7.17 (dd, <i>J</i> = 8.4, 2.2 Hz, 1H), 3.80 (m, 1H), 3.51 (q, <i>J</i> = 6.0 Hz, 2H), 2.79 – 2.51 (m, 6H), 2.29 (s, 6H).
358		5-(2-氯-6-(三氟甲基)苯基)-2-(((2-(二甲基氨基)乙基)氨基)亚甲基)环己烷-1,3-二酮	¹ H NMR (400 MHz, CDCl ₃) δ 11.27 (s, 1H), 8.22 (d, <i>J</i> = 14.4 Hz, 1H), 7.63 (d, <i>J</i> = 7.8 Hz, 1H), 7.56 (d, <i>J</i> = 7.9 Hz, 1H), 7.31 (t, <i>J</i> = 8.0 Hz, 1H), 3.96 (m, 1H), 3.75 – 3.56 (m, 2H), 3.51 (q, <i>J</i> = 6.1 Hz, 2H), 2.61 – 2.41 (m, 4H), 2.29 (s, 6H).
359		N-苄基-4-(((2-(二甲基氨基)乙基)氨基)亚甲基)-3,5-二氧代环己烷-1-甲酰胺	¹ H NMR (400 MHz, CDCl ₃) δ 11.15 (s, 1H), 8.12 (d, <i>J</i> = 14.5 Hz, 1H), 7.36 – 7.26 (m, 3H), 7.24 (s, 2H), 5.84 (s, 1H), 4.45 (d, <i>J</i> = 5.5 Hz, 2H), 3.49 (dd, <i>J</i> = 12.1, 6.0 Hz, 2H), 2.89 – 2.50 (m, 7H), 2.29 (s, 6H).
360		N-(4-溴苯基)-4-(((2-(二甲基氨基)乙基)氨基)亚甲基)-3,5-二氧代环己烷-1-甲酰胺	¹ H NMR (400 MHz, DMSO-d ₆) δ 10.89 (d, <i>J</i> = 14.7 Hz, 1H), 10.13 (s, 1H), 8.09 (d, <i>J</i> = 14.7 Hz, 1H), 7.57 (d, <i>J</i> = 8.9 Hz, 2H), 7.51 – 7.44 (m, 2H), 3.54 (dt, <i>J</i> = 14.5, 7.3 Hz, 2H), 3.15 – 3.04 (m, 1H), 2.64 (m, 1H), 2.55 (m, 3H), 2.42 (t, <i>J</i> = 5.8 Hz, 2H), 2.17 (s, 6H).
361		5-(2-氯-6-氟苯基)-2-(((2-(二甲基氨基)乙基)氨基)亚甲基)环己烷-1,3-二酮	¹ H NMR (400 MHz, CDCl ₃) δ 11.22 (s, 1H), 8.21 (d, <i>J</i> = 14.4 Hz, 1H), 7.17 (dd, <i>J</i> = 7.5, 5.1 Hz, 2H), 7.01 – 6.94 (m, 1H), 4.02 (t, <i>J</i> = 13.3 Hz, 1H), 3.51 (q, <i>J</i> = 6.1 Hz,

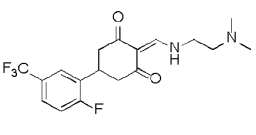
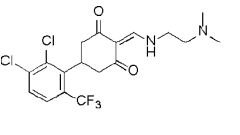
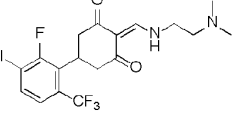
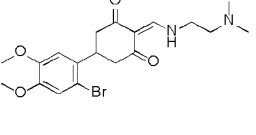
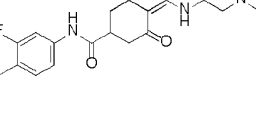
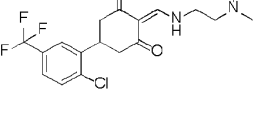
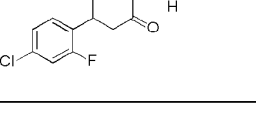
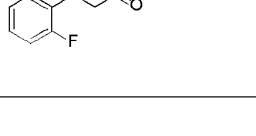
[0598]

		-1,3-二酮	2H), 3.22 – 3.02 (m, 2H), 2.56 (m, 4H), 2.29 (s, 6H).
362		5-(2-溴-5-(三氟甲基)苯基)-2-(((2-(二甲基氨基)乙基)氨基)亚甲基)环己烷-1,3-二酮	¹ H NMR (400 MHz, CDCl ₃) δ 11.21 (s, 1H), 8.20 (d, <i>J</i> = 14.4 Hz, 1H), 7.71 (d, <i>J</i> = 8.2 Hz, 1H), 7.48 (s, 1H), 7.38 (d, <i>J</i> = 8.3 Hz, 1H), 3.86 (s, 1H), 3.52 (q, <i>J</i> = 6.0 Hz, 2H), 2.79 (m, 2H), 2.74 – 2.60 (m, 2H), 2.57 (m, 2H), 2.30 (s, 6H).
363		N-(4-氯苯基)-4-(((2-(二甲基氨基)乙基)氨基)亚甲基)-3,5-二氧代环己烷-1-甲酰胺	¹ H NMR (400 MHz, CDCl ₃) δ 11.17 (s, 1H), 8.38 (s, 1H), 8.12 (d, <i>J</i> = 14.4 Hz, 1H), 7.54 (d, <i>J</i> = 8.5 Hz, 2H), 7.28 (s, 1H), 3.51 – 3.42 (m, 2H), 3.00 – 2.76 (m, 3H), 2.68 (m, 2H), 2.52 (t, <i>J</i> = 6.0 Hz, 2H), 2.25 (s, 6H).
364		2-(((2-(二甲基氨基)乙基)氨基)亚甲基)-5-(2,3,5-三氯苯基)环己烷-1,3-二酮	¹ H NMR (400 MHz, CDCl ₃) δ 11.20 (s, 1H), 8.19 (d, <i>J</i> = 14.5 Hz, 1H), 7.40 (d, <i>J</i> = 2.3 Hz, 1H), 7.15 (d, <i>J</i> = 2.3 Hz, 1H), 3.86 (s, 1H), 3.51 (q, <i>J</i> = 5.9 Hz, 2H), 2.84 – 2.69 (m, 2H), 2.69 – 2.48 (m, 4H), 2.29 (s, 6H).
365		2-(((2-(二甲基氨基)乙基)氨基)亚甲基)-3,5-二氧代环己基)苯甲酸甲酯	¹ H NMR (400 MHz, CDCl ₃) δ 11.18 (s, 1H), 8.18 (d, <i>J</i> = 14.3 Hz, 1H), 7.85 (d, <i>J</i> = 7.7 Hz, 1H), 7.51 (t, <i>J</i> = 7.6 Hz, 1H), 7.39 (d, <i>J</i> = 7.7 Hz, 1H), 7.31 (d, <i>J</i> = 7.6 Hz, 1H), 4.35 – 4.25 (m, 1H), 3.88 (s, 3H), 3.50 (q, <i>J</i> = 6.1 Hz, 2H), 2.80 – 2.71 (m, 2H), 2.71 – 2.60 (m, 2H), 2.54 (t, <i>J</i> = 6.1 Hz, 2H), 2.28 (s, 6H).
366		5-(5-溴噻吩-2-基)-2-(((2-(二甲基氨基)乙基)氨基)亚甲基)环己烷-1,3-二酮	¹ H NMR (400 MHz, CDCl ₃) δ 11.19 (s, 1H), 8.15 (d, <i>J</i> = 14.4 Hz, 1H), 6.87 (d, <i>J</i> = 3.7 Hz, 1H), 6.61 (d, <i>J</i> = 3.7 Hz, 1H), 3.55 (td, <i>J</i> = 10.6, 5.4 Hz, 1H), 3.48 (q, <i>J</i> = 6.0 Hz, 2H), 2.90 – 2.80 (m, 2H), 2.66 (m, 2H), 2.53 (t, <i>J</i> = 6.1 Hz, 2H), 2.27 (s, 6H).
367		2-(((2-(二甲基氨基)乙基)氨基)亚甲基)-5-(5-苯基噻吩-2-基)环己烷-1,3-二酮	¹ H NMR (400 MHz, CDCl ₃) δ 11.19 (s, 1H), 8.17 (d, <i>J</i> = 14.4 Hz, 1H), 7.58 – 7.52 (m, 2H), 7.35 (t, <i>J</i> = 7.6 Hz, 2H), 7.27 (s, 1H), 7.13 (d, <i>J</i> = 3.6 Hz, 1H), 6.82 (dd, <i>J</i> = 3.6, 0.8 Hz, 1H), 3.63 (m, 1H), 3.49 (q, <i>J</i> = 6.1 Hz, 2H), 2.96 – 2.87 (m, 2H), 2.74 (m, 2H), 2.53 (m, 2H), 2.28 (s, 6H).
368		5-(2,6-二氯苯基)-2-(((2-(二甲基氨基)乙基)氨基)亚甲基)环己烷-1,3-二酮	¹ H NMR (400 MHz, CDCl ₃) δ 11.25 (s, 1H), 8.22 (d, <i>J</i> = 14.4 Hz, 1H), 7.32 (s, 2H), 7.12 (t, <i>J</i> = 8.0 Hz, 1H), 4.37 (m, 1H), 3.65 – 3.47 (m, 4H), 2.56 (t, <i>J</i> = 6.1 Hz, 2H), 2.53 – 2.49 (m, 1H), 2.49 – 2.45 (m, 1H), 2.30 (s, 6H).

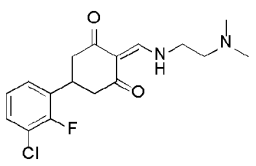
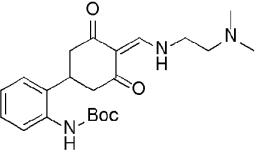
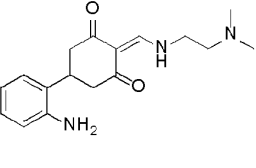
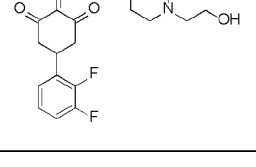
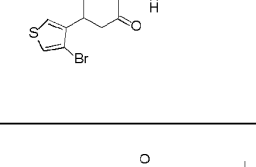
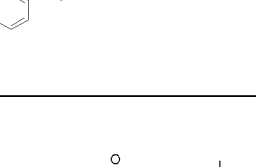
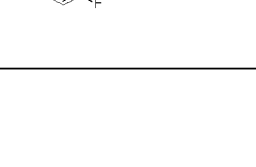
[0599]

369		5-(2,4-二氯苯基)-2-(((2-(二甲基氨基)乙基)氨基)亚甲基)环己烷-1,3-二酮	$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 11.21 (s, 1H), 8.19 (d, $J = 14.4$ Hz, 1H), 7.40 (d, $J = 2.1$ Hz, 1H), 7.25 (dd, $J = 8.4, 2.1$ Hz, 1H), 7.18 (d, $J = 8.4$ Hz, 1H), 3.80 (m, 1H), 3.51 (q, $J = 6.0$ Hz, 2H), 2.78 – 2.70 (m, 2H), 2.69 – 2.58 (m, 2H), 2.55 (t, $J = 6.0$ Hz, 2H), 2.29 (s, 6H).
370		5-(2-氯-4-氟苯基)-2-(((2-(二甲基氨基)乙基)氨基)亚甲基)环己烷-1,3-二酮	$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 11.21 (s, 1H), 8.19 (d, $J = 14.4$ Hz, 1H), 7.22 (dd, $J = 8.7, 5.9$ Hz, 1H), 7.14 (dd, $J = 8.5, 2.7$ Hz, 1H), 6.99 (td, $J = 8.3, 2.7$ Hz, 1H), 3.80 (m, 1H), 3.51 (q, $J = 6.1$ Hz, 2H), 2.79 – 2.70 (m, 2H), 2.69 – 2.58 (m, 2H), 2.55 (t, $J = 6.1$ Hz, 2H), 2.29 (s, 6H).
371		2-(((2-(二甲基氨基)乙基)氨基)亚甲基)-5-(4-苯基噻吩-3-基)环己烷-1,3-二酮	$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 11.12 (s, 1H), 8.10 (d, $J = 14.4$ Hz, 1H), 7.38 (dd, $J = 7.8, 6.2$ Hz, 2H), 7.34 (dd, $J = 5.1, 3.6$ Hz, 1H), 7.32 – 7.27 (m, 2H), 7.16 (d, $J = 3.2$ Hz, 1H), 7.13 – 7.09 (m, 1H), 3.56 – 3.48 (m, 1H), 3.45 (m, 2H), 2.70 – 2.61 (m, 2H), 2.58 (m, 2H), 2.50 (dd, $J = 7.3, 4.9$ Hz, 2H), 2.25 (s, 6H).
372		2-(4-(2-(((4-(2-溴苯基)-2,6-二氧化代亚环己基)甲基)氨基)乙基)哌嗪-1-基)-N-(对甲苯基)乙酰胺	$^1\text{H NMR}$ (400 MHz, CD_3OD) δ 8.28 (s, 1H), 7.60 (d, $J = 7.8$ Hz, 1H), 7.40 (m, 4H), 7.13 (m, 3H), 3.80 (m, 1H), 3.62 (m, 2H), 3.16 (s, 2H), 2.65 (m, 13H), 2.29 (s, 3H).
373		2-(4-(2-(((4-(3-氯-1H-吲哚-4-基)-2,6-二氧化代亚环己基)甲基)氨基)乙基)哌嗪-1-基)-N-(对甲苯基)乙酰胺	$^1\text{H NMR}$ (400 MHz, CD_3OD) δ 8.27 (s, 1H), 7.43 (d, $J = 8.4$ Hz, 2H), 7.30 – 7.20 (m, 2H), 7.11 (t, $J = 7.8$ Hz, 3H), 6.95 (d, $J = 7.3$ Hz, 1H), 4.54 (m, 1H), 3.62 (t, $J = 5.8$ Hz, 2H), 3.16 (s, 2H), 2.83 (m, 4H), 2.65 (s, 9H), 2.29 (s, 3H).
374		5-(2-溴-3-(甲基氨基)苯基)-2-(((2-(4-(2-羟乙基)哌嗪-1-基)乙基)氨基)亚甲基)环己烷-1,3-二酮	$^1\text{H NMR}$ (400 MHz, CD_3OD) δ 8.26 (s, 1H), 7.19 (t, $J = 7.9$ Hz, 1H), 6.61 (dd, $J = 24.0, 7.7$ Hz, 2H), 3.79 (m, 1H), 3.73 (t, $J = 5.8$ Hz, 2H), 3.62 (t, $J = 5.8$ Hz, 2H), 3.35 (s, 1H), 2.86 (s, 3H), 2.70 (m, 15H).
375		5-(4-溴-1H-吲哚-3-基)-2-(((2-(4-(2-羟乙基)哌嗪-1-基)乙基)氨基)亚甲基)环己烷-1,3-二酮	$^1\text{H NMR}$ (400 MHz, CD_3OD) δ 8.26 (s, 1H), 7.34 (dd, $J = 8.1, 0.7$ Hz, 1H), 7.21 – 7.14 (m, 2H), 6.96 (t, $J = 7.9$ Hz, 1H), 4.28 (m, 1H), 3.78 (t, $J = 5.6$ Hz, 2H), 3.61 (t, $J = 5.7$ Hz, 2H), 2.91 (m, 8H), 2.71 (m, 8H).

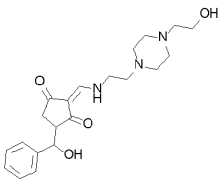
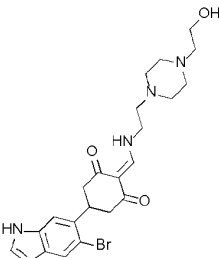
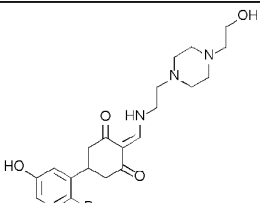
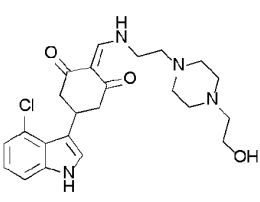
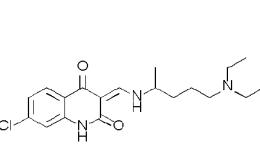
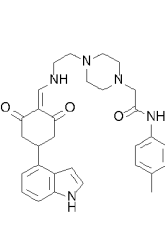
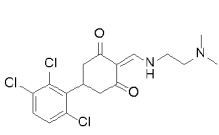
[0600]

376		2-(((2-(2,4-二甲基氨基)乙基)氨基)亚甲基)-5-(2-氟-5-(三氟甲基)苯基)环己烷-1,3-二酮	$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 11.22 (s, 1H), 8.20 (d, $J = 14.4$ Hz, 1H), 7.56 – 7.45 (m, 2H), 7.19 (s, 1H), 3.69 (ddd, $J = 16.3, 10.8, 5.8$ Hz, 1H), 3.52 (q, $J = 6.0$ Hz, 2H), 2.74 (td, $J = 10.9, 6.3$ Hz, 4H), 2.55 (t, $J = 6.1$ Hz, 2H), 2.29 (s, 6H).
377		5-(2,3-二氯-6-(三氟甲基)苯基)-2-(((2-(2-(二甲基氨基)乙基)氨基)亚甲基)环己烷-1,3-二酮	$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 11.28 (s, 1H), 8.23 (d, $J = 14.4$ Hz, 1H), 7.55 (q, $J = 8.6$ Hz, 2H), 4.00 (dd, $J = 11.2, 6.8$ Hz, 1H), 3.75 – 3.57 (m, 2H), 3.52 (q, $J = 6.0$ Hz, 2H), 2.56 (t, $J = 6.1$ Hz, 2H), 2.49 (d, $J = 15.5$ Hz, 2H), 2.30 (s, 6H).
378		5-(3-氯-2-氟-6-(三氟甲基)苯基)-2-(((2-(2-(二甲基氨基)乙基)氨基)亚甲基)环己烷-1,3-二酮	$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 11.24 (s, 1H), 8.22 (d, $J = 14.4$ Hz, 1H), 7.48 – 7.41 (m, 2H), 3.77 (t, $J = 13.2$ Hz, 1H), 3.52 (q, $J = 6.0$ Hz, 2H), 3.20 – 3.01 (m, 2H), 2.64 – 2.60 (m, 1H), 2.59 – 2.53 (m, 3H), 2.29 (s, 6H).
379		5-(2-溴-4,5-二甲氧基苯基)-2-(((2-(2-(二甲基氨基)乙基)氨基)亚甲基)环己烷-1,3-二酮	$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 11.20 (s, 1H), 8.19 (d, $J = 14.4$ Hz, 1H), 7.04 (s, 1H), 6.73 (s, 1H), 3.86 (d, $J = 1.9$ Hz, 6H), 3.74 (tt, $J = 11.9, 4.1$ Hz, 1H), 3.51 (q, $J = 6.1$ Hz, 2H), 2.80 – 2.70 (m, 2H), 2.69 – 2.58 (m, 2H), 2.55 (t, $J = 6.1$ Hz, 2H), 2.29 (s, 6H).
380		4-(((2-(2-(二甲基氨基)乙基)氨基)亚甲基)-N-(3-氟-4-甲基苯基)-3,5-二氧代环己烷-1-甲酰胺	$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 11.24 – 11.12 (m, 1H), 8.16 – 8.06 (m, 2H), 7.44 (d, $J = 13.2$ Hz, 1H), 7.15 – 7.05 (m, 2H), 3.50 – 3.41 (m, 2H), 2.97 – 2.75 (m, 3H), 2.72 – 2.62 (m, 2H), 2.51 (t, $J = 6.0$ Hz, 2H), 2.25 (s, 6H), 2.22 (d, $J = 1.5$ Hz, 3H).
381		5-(2-氯-5-(三氟甲基)苯基)-2-(((2-(2-(二甲基氨基)乙基)氨基)亚甲基)环己烷-1,3-二酮	$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 11.22 (s, 1H), 8.20 (d, $J = 14.5$ Hz, 1H), 7.49 (dt, $J = 8.4, 7.5$ Hz, 3H), 3.93 – 3.84 (m, 1H), 3.52 (q, $J = 6.1$ Hz, 2H), 2.71 (ttdd, $J = 19.8, 12.2, 4.2$ Hz, 4H), 2.56 (t, $J = 6.1$ Hz, 2H), 2.30 (s, 6H).
382		5-(4-氯-2-氟苯基)-2-(((2-(2-(二甲基氨基)乙基)氨基)亚甲基)环己烷-1,3-二酮	$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 11.20 (s, 1H), 8.18 (d, $J = 14.4$ Hz, 1H), 7.11 (dd, $J = 18.1, 8.6$ Hz, 3H), 3.62 (s, 1H), 3.51 (q, $J = 6.0$ Hz, 2H), 2.70 (dd, $J = 14.9, 9.5$ Hz, 4H), 2.55 (t, $J = 6.1$ Hz, 2H), 2.29 (s, 6H).
383		5-(2,6-二氟苯基)-2-(((2-(2-(二甲基氨基)乙基)氨基)亚甲基)环己烷-1,3-二酮	$^1\text{H NMR}$ (400 MHz, cdcl_3) δ 11.21 (s, 1H), 8.19 (d, $J = 14.4$ Hz, 1H), 7.23 – 7.10 (m, 1H), 6.87 (t, $J = 8.5$ Hz, 2H), 3.80 (s, 1H), 3.50 (q, $J = 6.1$ Hz, 2H), 3.05 (ddd, $J = 30.5, 16.9, 13.5$ Hz, 2H), 2.65 – 2.50 (m, 4H), 2.28 (s, 6H).

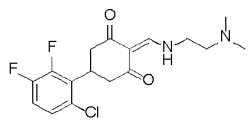
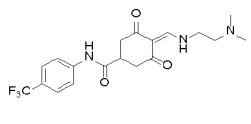
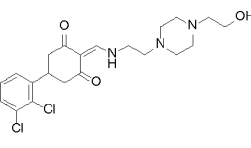
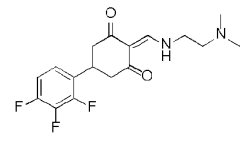
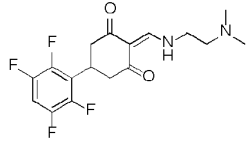
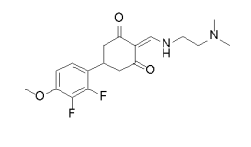
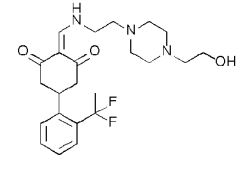
[0601]

384		5-(3-氯-2-氟苯基)-2-(((2-(二甲基氨基)乙基)氨基)亚甲基)环己烷-1,3-二酮	$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 11.21 (s, 1H), 8.19 (d, $J = 14.4$ Hz, 1H), 7.30 (d, $J = 7.5$ Hz, 1H), 7.15 – 7.02 (m, 2H), 3.68 (s, 1H), 3.51 (q, $J = 6.0$ Hz, 2H), 2.72 (dd, $J = 14.7$, 9.5 Hz, 4H), 2.54 (t, $J = 6.1$ Hz, 2H), 2.28 (s, 6H).
385		(2-(4-(((2-(二甲基氨基)乙基)氨基)亚甲基)-3,5-二氧代环己基)苯基)氨基甲酸叔丁酯	$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 11.19 (s, 1H), 8.19 (d, $J = 14.4$ Hz, 1H), 7.62 (d, $J = 7.2$ Hz, 1H), 7.23 (d, $J = 7.3$ Hz, 2H), 7.16 (t, $J = 6.9$ Hz, 1H), 6.27 (s, 1H), 3.51 (dd, $J = 11.9$, 5.9 Hz, 3H), 2.73 – 2.60 (m, 4H), 2.54 (t, $J = 6.1$ Hz, 2H), 2.28 (s, 6H), 1.50 (s, 9H).
386		5-(2-氨基苯基)-2-(((2-(二甲基氨基)乙基)氨基)亚甲基)环己烷-1,3-二酮	$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 11.20 (s, 1H), 8.18 (d, $J = 14.4$ Hz, 1H), 7.07 (t, $J = 7.8$ Hz, 2H), 6.79 (t, $J = 7.5$ Hz, 1H), 6.70 (d, $J = 7.9$ Hz, 1H), 3.64 (s, 2H), 3.50 (dd, $J = 12.0$, 6.0 Hz, 2H), 3.38 – 3.28 (m, 1H), 2.81 – 2.50 (m, 6H), 2.28 (s, 6H).
387		5-(2,3-二氟苯基)-2-(((2-(4-(2-羟乙基)哌嗪-1-基)乙基)氨基)亚甲基)环己烷-1,3-二酮	$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 11.18 (s, 1H), 8.20 (d, $J = 14.5$ Hz, 1H), 7.13 – 7.01 (m, 2H), 6.96 (s, 1H), 3.69 (s, 1H), 3.62 (t, $J = 5.3$ Hz, 2H), 3.56 – 3.47 (m, 2H), 2.73 (dd, $J = 15.9$, 9.4 Hz, 4H), 2.68 – 2.34 (m, 13H).
388		5-(4-溴噻吩-3-基)-2-(((2-(二甲基氨基)乙基)氨基)亚甲基)环己烷-1,3-二酮	$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 11.20 (s, 1H), 8.18 (d, $J = 14.3$ Hz, 1H), 7.28 (d, $J = 3.3$ Hz, 1H), 7.00 (d, $J = 3.0$ Hz, 1H), 3.50 (t, $J = 5.9$ Hz, 3H), 2.84 (t, $J = 10.5$ Hz, 2H), 2.60 (ddd, $J = 22.3$, 14.3, 8.4 Hz, 4H), 2.29 (s, 6H).
389		N-([1,1'-联苯]-4-基)-4-(((2-(二甲基氨基)乙基)氨基)亚甲基)-3,5-二氧代环己烷-1-甲酰胺	$^1\text{H NMR}$ (400 MHz, DMSO-d_6) δ 10.88 (s, 1H), 10.11 (s, 1H), 8.10 (d, $J = 14.5$ Hz, 1H), 7.74 – 7.57 (m, 6H), 7.43 (t, $J = 7.4$ Hz, 2H), 7.33 (d, $J = 7.3$ Hz, 1H), 3.55 (d, $J = 5.6$ Hz, 2H), 3.13 (s, 1H), 2.56 (d, $J = 5.1$ Hz, 4H), 2.43 (s, 2H), 2.18 (s, 6H).
390		5-(5-氯-2-氟苯基)-2-(((2-(二甲基氨基)乙基)氨基)亚甲基)环己烷-1,3-二酮	$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 11.20 (s, 1H), 8.19 (d, $J = 14.4$ Hz, 1H), 7.19 (t, $J = 6.7$ Hz, 2H), 6.99 (t, $J = 9.1$ Hz, 1H), 3.61 (s, 1H), 3.51 (dd, $J = 12.0$, 6.0 Hz, 2H), 2.70 (dd, $J = 17.2$, 10.2 Hz, 4H), 2.55 (t, $J = 6.0$ Hz, 2H), 2.29 (s, 6H).

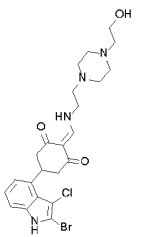
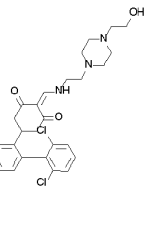
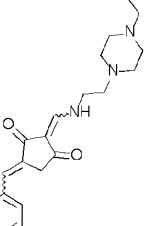
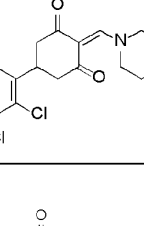
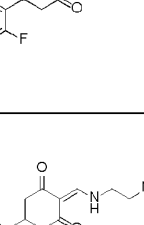
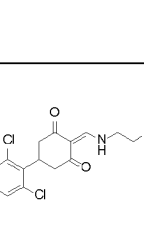
[0602]

391		4-(羟基(苯基)甲基)-2-(((2-(4-(2-羟乙基)吡咯-1-基)乙基)氨基)亚甲基)环戊烷-1,3-二酮	$^1\text{H NMR}$ (400 MHz, CD_3OD) δ 7.77 (s, 1H), 7.26 (m, 5H), 5.13 (d, $J = 6.0$ Hz, 1H), 3.69 (t, $J = 6.0$ Hz, 2H), 3.55 (t, $J = 5.7$ Hz, 2H), 3.13 (m, 1H), 2.69 – 2.46 (m, 12H), 2.33 (m, 2H); MS: 388.2 [M+1].
392		5-(5-溴-1H-吲哚-6-基)-2-(((2-(4-(2-羟乙基)吡咯-1-基)乙基)氨基)亚甲基)环己烷-1,3-二酮	$^1\text{H NMR}$ (400 MHz, CD_3OD) δ 8.27 (s, 1H), 7.78 (s, 1H), 7.37 (s, 1H), 7.25 (d, $J = 3.2$ Hz, 1H), 6.38 (d, $J = 2.4$ Hz, 1H), 3.90 – 3.81 (m, 1H), 3.72 (t, $J = 5.9$ Hz, 2H), 3.62 (t, $J = 5.6$ Hz, 2H), 2.72 (m, 16H); MS: 491.1 [M+1].
393		5-(2-溴-5-羟基苯基)-2-(((2-(4-(2-羟乙基)吡咯-1-基)乙基)氨基)亚甲基)环己烷-1,3-二酮	$^1\text{H NMR}$ (400 MHz, CD_3OD) δ 8.27 (s, 1H), 7.36 (d, $J = 8.6$ Hz, 1H), 6.78 (d, $J = 2.9$ Hz, 1H), 6.60 (dd, $J = 8.7, 2.8$ Hz, 1H), 3.80 – 3.57 (m, 4H), 2.77 (m, 13H); MS: 467.0 [M+1].
394		5-(4-氯-1H-吲哚-3-基)-2-(((2-(4-(2-羟乙基)吡咯-1-基)乙基)氨基)亚甲基)环己烷-1,3-二酮	$^1\text{H NMR}$ (400 MHz, CD_3OD) δ 8.27 (s, 1H), 7.36 – 7.26 (m, 1H), 7.14 (s, 1H), 7.03 (m, 2H), 4.22 – 4.12 (m, 1H), 3.77 (t, $J = 5.7$ Hz, 2H), 3.63 (m, 2H), 3.03 – 2.63 (m, 16H); MS: 445.1 [M+1].
395		7-氯-3-(((5-(二乙基氨基)戊-2-基)氨基)亚甲基)喹啉-2,4(1H, 3H)-二酮	$^1\text{H NMR}$ (400 MHz, CD_3OD) δ 8.55 (s, 1H), 7.97 (d, $J = 8.5$ Hz, 1H), 7.18 (d, $J = 1.7$ Hz, 1H), 7.12 (dd, $J = 8.5, 1.8$ Hz, 1H), 3.81 (s, 1H), 3.06 (m, 6H), 1.75 (d, $J = 5.6$ Hz, 4H), 1.43 (d, $J = 6.6$ Hz, 3H), 1.30 – 1.18 (m, 6H); MS: 364.1 [M+1].
396		2-(4-(2-(((4-(1H-吲哚-4-基)-2,6-二氧代亚环己基)甲基)氨基)乙基)吡咯-1-基)-N-(对甲苯基)乙酰胺	$^1\text{H NMR}$ (400 MHz, CD_3OD) δ 8.28 (s, 1H), 7.43 (d, $J = 8.4$ Hz, 2H), 7.26 (dd, $J = 14.2, 5.7$ Hz, 2H), 7.13 (d, $J = 8.0$ Hz, 2H), 7.06 (t, $J = 7.7$ Hz, 1H), 6.88 (d, $J = 7.3$ Hz, 1H), 6.53 (d, $J = 2.6$ Hz, 1H), 3.79 (m, 1H), 3.63 (m, 2H), 3.16 (s, 2H), 2.99 – 2.85 (m, 2H), 2.82 (m, 2H), 2.65 (s, 9H), 2.29 (s, 3H).
397		2-(((2-(二甲基氨基)乙基)氨基)亚甲基)-5-(2,3,6-三氯苯基)环己烷-1,3-二酮	$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 11.25 (s, 1H), 8.21 (d, $J = 14.4$ Hz, 1H), 7.31 (s, 1H), 7.25 – 7.17 (m, 1H), 4.41 (s, 1H), 3.68 – 3.43 (m, 4H), 2.58 (t, $J = 5.9$ Hz, 2H), 2.48 (d, $J = 16.7$ Hz, 2H), 2.31 (s, 6H).

[0603]

398		5-(6-氯-2,3-二氟苯基)-2-(((2-(二甲基氨基)乙基)氨基)亚甲基)环己烷-1,3-二酮	$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 11.24 (s, 1H), 8.22 (d, $J = 14.4$ Hz, 1H), 7.15 (ddd, $J = 9.0$, 4.6, 2.0 Hz, 1H), 7.04 (dd, $J = 17.4$, 9.0 Hz, 1H), 4.06 – 3.93 (m, 1H), 3.53 (q, $J = 6.0$ Hz, 2H), 3.20 – 3.02 (m, 2H), 2.66 – 2.54 (m, 4H), 2.30 (s, 6H).
399		4-(((2-(二甲基氨基)乙基)氨基)亚甲基)-3,5-二氟代-N-(4-(三氟甲基)苯基)环己烷-1-甲酰胺	$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 11.16 (s, 1H), 8.14 (d, $J = 14.5$ Hz, 2H), 7.70 (d, $J = 8.3$ Hz, 2H), 7.57 (d, $J = 8.7$ Hz, 2H), 3.49 (d, $J = 6.1$ Hz, 2H), 2.97 – 2.66 (m, 5H), 2.53 (t, $J = 6.0$ Hz, 2H), 2.26 (s, 6H).
400		5-(2,3-二氯苯基)-2-(((2-(4-(2-羟乙基)哌嗪-1-基)乙基)氨基)亚甲基)环己烷-1,3-二酮	$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 11.17 (s, 1H), 8.20 (d, $J = 14.4$ Hz, 1H), 7.40 – 7.36 (m, 1H), 7.24 – 7.14 (m, 2H), 3.95 – 3.85 (m, 1H), 3.62 (t, $J = 5.3$ Hz, 2H), 3.52 (dd, $J = 11.9$, 6.0 Hz, 2H), 2.78 (dt, $J = 18.6$, 4.2 Hz, 2H), 2.71 – 2.45 (m, 14H).
401		2-(((2-(二甲基氨基)乙基)氨基)亚甲基)-5-(2,3,4-三氟苯基)环己烷-1,3-二酮	$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 11.21 (s, 1H), 8.19 (d, $J = 14.4$ Hz, 1H), 6.94 (dd, $J = 8.4$, 6.0 Hz, 2H), 3.68 – 3.59 (m, 1H), 3.52 (q, $J = 6.0$ Hz, 2H), 2.70 (m, 4H), 2.56 (t, $J = 6.1$ Hz, 2H).
402		2-(((2-(二甲基氨基)乙基)氨基)亚甲基)-5-(2,3,5,6-四氟苯基)环己烷-1,3-二酮	$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 11.23 (s, 1H), 8.21 (d, $J = 14.4$ Hz, 1H), 7.04 – 6.94 (m, 1H), 3.84 (m, 1H), 3.54 (q, $J = 6.0$ Hz, 2H), 3.12 – 2.94 (m, 2H), 2.67 – 2.53 (m, 4H), 2.31 (s, 6H).
403		5-(2,3-二氟-4-甲氧基苯基)-2-(((2-(二甲基氨基)乙基)氨基)亚甲基)环己烷-1,3-二酮	$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 11.21 (s, 1H), 8.18 (d, $J = 14.4$ Hz, 1H), 6.86 (t, $J = 8.2$ Hz, 1H), 6.71 (t, $J = 7.6$ Hz, 1H), 3.89 (s, 3H), 3.64 – 3.54 (m, 1H), 3.50 (q, $J = 6.0$ Hz, 2H), 2.70 (m, 4H), 2.54 (t, $J = 6.1$ Hz, 2H), 2.28 (s, 6H).
404		5-(2-(1,1-二氟乙基)苯基)-2-(((2-(4-(2-羟乙基)哌嗪-1-基)乙基)氨基)亚甲基)环己烷-1,3-二酮	$^1\text{H NMR}$ (400 MHz, CD_3OD) δ 8.28 (s, 1H), 7.60 (d, $J = 8.0$ Hz, 1H), 7.53 (d, $J = 7.7$ Hz, 1H), 7.48 (t, $J = 7.7$ Hz, 1H), 7.32 (t, $J = 7.7$ Hz, 1H), 3.85 (t, $J = 12.7$ Hz, 1H), 3.77 (t, $J = 5.7$ Hz, 2H), 3.63 (t, $J = 5.7$ Hz, 2H), 3.07 – 2.59 (m, 14H), 2.54 (dd, $J = 17.0$, 3.6 Hz, 2H), 1.98 (t, $J = 18.6$ Hz, 3H).

[0604]

405		5-(2-溴-3-氯-1H-吲哚-4-基)-2-(((2-(4-(2-羟乙基)哌嗪-1-基)乙基)氨基)亚甲基)环己烷-1,3-二酮	$^1\text{H NMR}$ (400 MHz, DMSO- d_6) δ 12.37 (s, 1H), 10.95 (m, 1H), 8.13 (d, $J = 14.6$ Hz, 1H), 7.23 (d, $J = 8.2$ Hz, 1H), 7.12 (t, $J = 7.8$ Hz, 1H), 6.98 (d, $J = 7.3$ Hz, 1H), 4.29 (m, 1H), 3.57 (m, 3H), 3.16 (m, 3H), 2.84 – 2.50 (m, 15H).
406		5-(2', 6'-二氯-[1,1'-联苯]-2-基)-2-(((2-(4-(2-羟乙基)哌嗪-1-基)乙基)氨基)亚甲基)环己烷-1,3-二酮	$^1\text{H NMR}$ (400 MHz, CD_3OD) δ 8.17 (s, 1H), 7.55 (d, $J = 7.6$ Hz, 1H), 7.47 (m, 3H), 7.39 – 7.30 (m, 2H), 7.09 – 7.02 (m, 1H), 3.75 (t, $J = 5.7$ Hz, 2H), 3.56 (t, $J = 5.9$ Hz, 2H), 2.97 – 2.72 (m, 9H), 2.62 (m, 6H), 2.53 (dd, $J = 16.3, 3.1$ Hz, 2H).
407		4-苯亚甲基-2-(((2-(4-(2-羟乙基)哌嗪-1-基)乙基)氨基)亚甲基)环戊烷-1,3-二酮	$^1\text{H NMR}$ (400 MHz, CD_3OD) δ 8.08 (d, $J = 0.5$ Hz, 1H), 7.57 (d, $J = 7.7$ Hz, 2H), 7.40 (m, 4H), 3.97 – 3.86 (m, 4H), 3.39 (m, 10H), 3.28 – 3.13 (m, 4H).
408		5-(2,3-二氯苯基)-2-(哌啶-1-基亚甲基)环己烷-1,3-二酮	$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 8.04 (s, 1H), 7.37 (dd, $J = 7.5, 1.9$ Hz, 1H), 7.23 – 7.11 (m, 2H), 3.91 – 3.80 (m, 1H), 3.80 – 3.55 (m, 4H), 2.77 (m, 2H), 2.60 (m, 2H), 1.84 (m, 4H), 1.74 (m, 2H).
409		5-(6-溴-2,3-二氟苯基)-2-(((2-(二甲基氨基)乙基)氨基)亚甲基)环己烷-1,3-二酮	$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 11.24 (s, 1H), 8.22 (d, $J = 14.4$ Hz, 1H), 7.37 – 7.31 (m, 1H), 6.98 (dd, $J = 17.5, 9.0$ Hz, 1H), 3.96 (t, $J = 13.6$ Hz, 1H), 3.53 (q, $J = 6.1$ Hz, 2H), 3.19 – 2.99 (m, 2H), 2.67 – 2.53 (m, 4H), 2.30 (s, 6H).
410		5-(2-氯-3-氟苯基)-2-(((2-(二甲基氨基)乙基)氨基)亚甲基)环己烷-1,3-二酮	$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 11.22 (s, 1H), 8.20 (d, $J = 14.4$ Hz, 1H), 7.26 – 7.20 (m, 1H), 7.06 (t, $J = 7.8$ Hz, 2H), 3.86 (td, $J = 11.6, 5.8$ Hz, 1H), 3.52 (q, $J = 6.0$ Hz, 2H), 2.80 – 2.60 (m, 4H), 2.56 (t, $J = 6.1$ Hz, 2H), 2.30 (s, 6H).
411		5-(2,6-二氯-3-氟苯基)-2-(((2-(二甲氨基)乙基)氨基)亚甲基)环己烷-1,3-二酮	$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 11.25 (s, 1H), 8.22 (d, $J = 14.4$ Hz, 1H), 7.32 (s, 1H), 7.04 (dd, $J = 8.8, 8.0$ Hz, 1H), 4.35 (s, 1H), 3.66 – 3.45 (m, 4H), 2.55 (t, $J = 6.1$ Hz, 2H), 2.48 (m, 2H), 2.29 (s, 6H).

[0605]

412		2-(((2-(二甲基氨基)乙基)氨基)亚甲基)-5-(全氟苯基)环己烷-1,3-二酮	$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 11.23 (s, 1H), 8.21 (d, $J = 14.5$ Hz, 1H), 3.84 – 3.73 (m, 1H), 3.51 (q, $J = 5.9$ Hz, 2H), 3.09 – 2.90 (m, 2H), 2.61 (dd, $J = 16.6, 2.1$ Hz, 2H), 2.54 (t, $J = 6.0$ Hz, 2H), 2.29 (s, 6H).
413		5-(4-溴-1H-吡咯-3-基)-2-(((2-(二甲基氨基)乙基)氨基)亚甲基)环己烷-1,3-二酮	$^1\text{H NMR}$ (400 MHz, CD_3OD) δ 8.23 (s, 1H), 6.72 (d, $J = 1.8$ Hz, 1H), 6.54 (d, $J = 1.9$ Hz, 1H), 3.61 (t, $J = 6.2$ Hz, 2H), 3.26 (m, 1H), 2.74 (m, 2H), 2.62 (t, $J = 6.2$ Hz, 4H), 2.32 (s, 6H).
414		2-(((2-(二甲基氨基)乙基)氨基)亚甲基)-5-(5-苯基-1H-吡咯-3-基)环己烷-1,3-二酮	$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 11.26 – 11.10 (m, 1H), 8.52 (s, 1H), 8.14 (d, $J = 14.3$ Hz, 1H), 7.49 – 7.40 (m, 2H), 7.34 (t, $J = 7.8$ Hz, 2H), 7.19 (t, $J = 7.4$ Hz, 1H), 6.65 (s, 1H), 6.45 – 6.38 (m, 1H), 3.45 (q, $J = 6.1$ Hz, 2H), 3.35 (m, 1H), 2.84 (m, 2H), 2.66 (m, 2H), 2.51 (t, $J = 6.2$ Hz, 2H), 2.26 (s, 6H).

[0606] 实施例35化合物415-452的合成

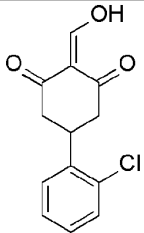
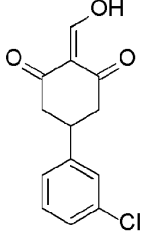
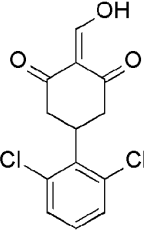
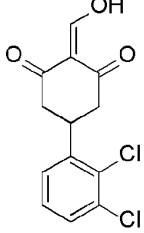
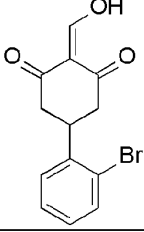
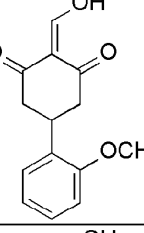
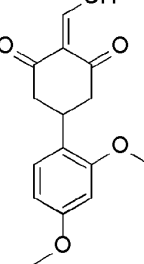
[0607] 除了使用相应的取代1,3-环己二酮外,化合物415-452的合成方法与实施例4或8相同(如化合物3和8),如表8所示。

[0608] 表8:化合物415-452

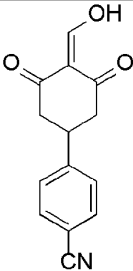
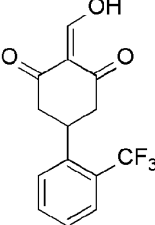
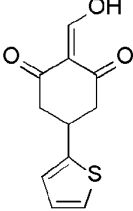
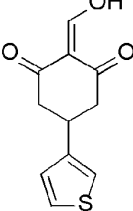
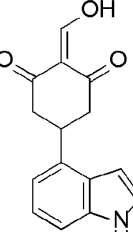
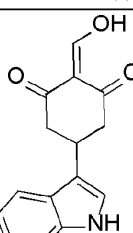
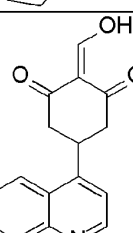
[0609]

#	结构	名称	氢谱($^1\text{H NMR}$),质谱(MS)
415		2-(羟基亚甲基)-5-(4-甲基苯基)环己烷-1,3-二酮	$^1\text{H NMR}$ (400 MHz, $\text{DMSO}-d_6$) δ 9.52 (s, 1H), 7.22 (d, $J = 8.1$ Hz, 2H), 7.14 (d, $J = 8.0$ Hz, 2H), 3.46-3.38 (m, 1H), 2.99 – 2.86 (m, 2H), 2.71 – 2.59 (m, 2H), 2.27 (s, 3H); MS: 229.1 [M-1].
416		2-(羟基亚甲基)-5-(2-氟苯基)环己烷-1,3-二酮	$^1\text{H NMR}$ (400 MHz, $\text{DMSO}-d_6$) δ 9.52 (s, 1H), 7.42 (td, $J = 8.0, 1.7$ Hz, 1H), 7.37 – 7.29 (m, 1H), 7.25 – 7.16 (m, 2H), 3.78-3.70 (m, 1H), 3.01-2.94 (m, 2H), 2.70-2.64 (m, 2H); MS: 235.1 [M+1].
417		2-(羟基亚甲基)-5-(2,3-二氟苯基)环己烷-1,3-二酮	$^1\text{H NMR}$ (400 MHz, $\text{DMSO}-d_6$) δ 9.51 (s, 1H), 7.39-7.32 (m, 1H), 7.29 – 7.19 (m, 2H), 3.85 – 3.71 (m, 1H), 3.03-2.95 (m, 2H), 2.71-2.66 (m, 2H); MS: 253.1 [M+1].

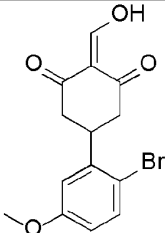
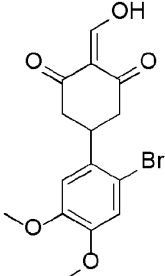
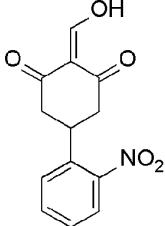
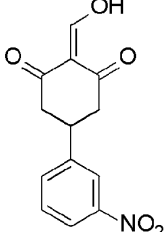
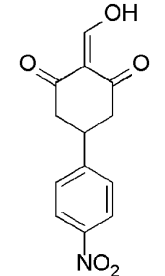
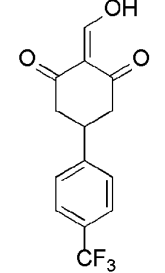
[0610]

418		2-(羟基亚甲基)-5-(2-氯苯基)环己烷-1,3-二酮	$^1\text{H NMR}$ (400 MHz, $\text{DMSO-}d_6$) δ 9.51 (s, 1H), 7.48 (t, $J = 6.9$ Hz, 2H), 7.38 (t, $J = 7.6$ Hz, 1H), 7.31 (m, 1H), 3.88 – 3.78 (m, 1H), 3.07 – 2.93 (m, 2H), 2.67 (m, 2H); MS: 249.1 [M-1].
419		2-(羟基亚甲基)-5-(3-氯苯基)环己烷-1,3-二酮	$^1\text{H NMR}$ (400 MHz, $\text{DMSO-}d_6$) δ 9.52 (s, 1H), 7.45 (s, 1H), 7.35 (m, 3H), 3.50 (m, 1H), 3.03 – 2.92 (m, 2H), 2.67 (d, $J = 13.5$ Hz, 2H); MS: 249.1 [M-1].
420		2-(羟基亚甲基)-5-(2,6-二氯苯基)环己烷-1,3-二酮	$^1\text{H NMR}$ (400 MHz, $\text{DMSO-}d_6$) δ 9.51 (s, 1H), 7.51 (t, $J = 6.9$ Hz, 1H), 7.33 (m, 2H), 4.02 – 3.89 (m, 1H), 3.27 – 3.13 (m, 2H), 2.67 (m, 2H); MS: 283.1 [M-1].
421		2-(羟基亚甲基)-5-(2,3-二氯苯基)环己烷-1,3-二酮	$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 15.89 (s, 1H), 9.66 (s, 1H), 7.43 (dd, $J = 8.0, 1.5$ Hz, 1H), 7.25 (t, $J = 7.9$ Hz, 1H), 7.16 (dd, $J = 7.8, 1.4$ Hz, 1H), 4.01-3.93 (m, 1H), 3.00-2.94 (m, 1H), 2.91 – 2.75 (m, 2H), 2.71-2.64 (m, 1H); MS: 285.0 [M+1].
422		2-(羟基亚甲基)-5-(2-溴苯基)环己烷-1,3-二酮	$^1\text{H NMR}$ (400 MHz, $\text{DMSO-}d_6$) δ 9.52 (s, 1H), 7.65 (d, $J = 7.2$ Hz, 1H), 7.52 – 7.47 (m, 1H), 7.43 (t, $J = 7.3$ Hz, 1H), 7.27 – 7.20 (m, 1H), 3.81 – 3.73 (m, 2H), 3.05 – 2.91 (m, 2H), 2.70-2.65 (m, 2H); MS: 293.0 [M-1].
423		2-(羟基亚甲基)-5-(2-甲氧基苯基)环己烷-1,3-二酮	$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 15.90 (s, 1H), 9.68 (s, 1H), 7.31-7.27 (m, 0.8H), 7.26 – 7.24 (m, 0.2H), 7.15-7.10 (m, 1H), 6.99 – 6.88 (m, 2H), 3.85 (s, 3H), 3.79 – 3.69 (m, 1H), 3.05 – 2.94 (m, 1H), 2.93 – 2.67 (m, 3H); MS: 247.1 [M+1].
424		2-(羟基亚甲基)-5-(2,4-二甲氧基苯基)环己烷-1,3-二酮	$^1\text{H NMR}$ (400 MHz, CD_3OD) δ 9.63 (s, 1H), 7.08 (d, $J = 8.8$ Hz, 1H), 6.53 – 6.55 (m, 1H), 6.51 – 6.45 (m, 1H), 5.49 (s, 1H), 3.82 (d, $J = 2.4$ Hz, 3H), 3.78 (d, $J = 2.4$ Hz, 3H), 3.69 – 3.53 (m, 1H), 3.00 – 2.83 (m, 1H), 2.80 – 2.62 (m, 2H), 2.60 – 2.46 (m, 1H); MS: 277.1 [M+1].

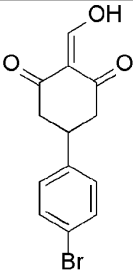
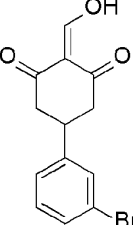
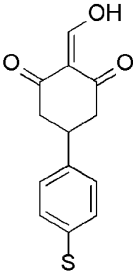
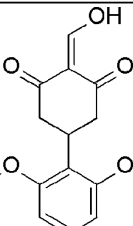
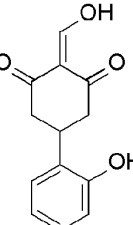
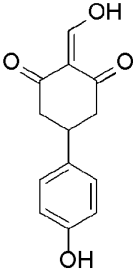
[0611]

425		2-(羟基亚甲基)- 5-(4-氰基苯基)环己烷-1,3-二酮	$^1\text{H NMR}$ (400 MHz, $\text{DMSO}-d_6$) δ 9.52 (s, 1H), 7.83 (d, $J = 8.0$ Hz, 2H), 7.58 (d, $J = 8.0$ Hz, 2H), 3.65 – 3.55 (m, 1H), 3.05-2.96 (m, 2H), 2.73-2.64 (m, 2H); MS: 242.0 [M+1].
426		2-(羟基亚甲基)- 5-(2-三氟甲基苯基)环己烷-1,3-二酮	$^1\text{H NMR}$ (400 MHz, $\text{DMSO}-d_6$): δ 9.52 (s, 1H), 7.87 (d, $J = 8.2$ Hz, 1H), 7.79 – 7.68 (m, 2H), 7.50 (t, $J = 7.7$ Hz, 1H), 3.75-3.61 (m, 1H), 3.25-3.06 (m, 2H), 2.56 (d, $J = 3.8$ Hz, 1H). MS: 283.1 [M-1].
427		2-(羟基亚甲基)- 5-(2-噻吩基)环己烷-1,3-二酮	$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 15.87 (s, 1H), 9.64 (s, 1H), 7.23 (dd, $J = 5.1, 1.1$ Hz, 1H), 6.98-6.96 (m, 1H), 6.89 (dt, $J = 3.5, 1.0$ Hz, 1H), 3.79 – 3.68 (m, 1H), 3.10-3.04 (m, 1H), 2.99 – 2.88 (m, 2H), 2.76-2.69 (m, 1H); MS: 221.1 [M-1].
428		2-(羟基亚甲基)- 5-(3-噻吩基)环己烷-1,3-二酮	$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 15.86 (s, 1H), 9.63 (s, 1H), 7.35 (dd, $J = 4.8, 2.0$ Hz, 1H), 7.06 – 7.03 (m, 1H), 7.00 (dd, $J = 5.2, 1.2$ Hz, 1H), 3.59-3.50 (m, 1H), 3.05-2.96 (m, 1H), 2.93 – 2.81 (m, 2H), 2.72-2.62 (m, 1H); MS: 223.0 [M+1].
429		2-(羟基亚甲基)- 5-(1H-吲哚-4-基)环己烷-1,3-二酮	$^1\text{H NMR}$ (400 MHz, $\text{DMSO}-d_6$) δ 11.17 (s, 1H), 9.55 (s, 1H), 7.35 (t, $J = 2.8$ Hz, 1H), 7.30 (d, $J = 8.0$ Hz, 1H), 7.05 (t, $J = 7.7$ Hz, 1H), 6.89 (d, $J = 7.2$ Hz, 1H), 6.61 (s, 1H), 3.94 – 3.81 (m, 1H), 3.14 – 3.00 (m, 2H), 2.7-2.73 (m, 2H); MS: 254.1 [M-H].
430		2-(羟基亚甲基)- 5-(1H-吲哚-3-基)环己烷-1,3-二酮	$^1\text{H NMR}$ (400 MHz, $\text{DMSO}-d_6$) δ 9.55 (s, 1H), 7.37 (s, 1H), 7.30 -7.05 (m, 4H), 3.96 – 3.83 (m, 1H), 3.15 – 3.01 (m, 2H), 2.71-2.74 (m, 2H); MS: 254.1 [M-H].
431		2-(羟基亚甲基)- 5-(4-喹啉基)环己烷-1,3-二酮	$^1\text{H NMR}$ (400 MHz, $\text{DMSO}-d_6$): δ 9.56 (s, 1H), 8.91 (d, $J = 4.6$ Hz, 1H), 8.34 (d, $J = 8.1$ Hz, 1H), 8.07 (d, $J = 8.4$ Hz, 1H), 7.81 (t, $J = 7.0$ Hz, 1H), 7.68 (t, $J = 7.0$ Hz, 1H), 7.55 (d, $J = 4.7$ Hz, 1H), 4.51-4.39 (m, 1H), 3.15-3.01 (m, 2H), 2.82-2.70 (m, 2H). MS: 266.1 [M-1].

[0612]

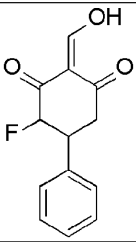
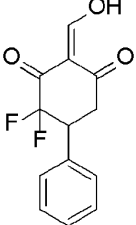
432		2-(羟基亚甲基)-5-(2-溴-5-甲氧基苯基)环己烷-1,3-二酮	$^1\text{H NMR}$ (400 MHz, $\text{DMSO}-d_6$) δ 9.51 (s, 1H), 7.52 (d, $J = 8.8$ Hz, 1H), 7.06 (d, $J = 3.0$ Hz, 1H), 6.83 (dd, $J = 8.8, 3.0$ Hz, 1H), 3.81-3.66 (m, 4H), 3.03-2.96 (m, 2H), 2.66-2.60 (m, 2H). MS: 325.0 [M-1].
433		2-(羟基亚甲基)-5-(2-溴-4,5-二甲氧基苯基)环己烷-1,3-二酮	$^1\text{H NMR}$ (400 MHz, $\text{DMSO}-d_6$) δ 9.53 (s, 1H), 7.14 (s, 1H), 7.08 (s, 1H), 3.78 (s, 3H), 3.76 (s, 3H), 3.70-3.65 (m, 1H), 3.08-2.98 (m, 2H), 2.58-2.55 (m, 2H). MS: 357.1 [M+1].
434		2-(羟基亚甲基)-5-(2-硝基苯基)环己烷-1,3-二酮	$^1\text{H NMR}$ (400 MHz, $\text{DMSO}-d_6$) δ 9.53 (s, 1H), 7.91 (s, 1H), 7.80-7.66 (m, 3H), 3.66-3.56 (m, 1H), 3.06-2.95 (m, 2H), 2.76-2.70 (m, 2H). MS: 260.1 [M-1].
435		2-(羟基亚甲基)-5-(3-硝基苯基)环己烷-1,3-二酮	$^1\text{H NMR}$ (400 MHz, $\text{DMSO}-d_6$) δ 9.55 (s, 1H), 7.88 (s, 1H), 7.83-7.62 (m, 3H), 3.67-3.57 (m, 1H), 3.07-2.96 (m, 2H), 2.75-2.69 (m, 2H). MS: 260.1 [M-1].
436		2-(羟基亚甲基)-5-(4-硝基苯基)环己烷-1,3-二酮	$^1\text{H NMR}$ (400 MHz, $\text{DMSO}-d_6$) δ 9.55 (s, 1H), 7.82 (d, $J = 8.1$ Hz, 2H), 7.69 (d, $J = 8.4$ Hz, 2H), 3.67-3.57 (m, 1H), 3.07-2.96 (m, 2H), 2.75-2.69 (m, 2H). MS: 260.1 [M-1].
437		2-(羟基亚甲基)-5-(4-三氟甲基苯基)环己烷-1,3-二酮	$^1\text{H NMR}$ (400 MHz, $\text{DMSO}-d_6$) δ 9.53 (s, 1H), 7.72 (d, $J = 8.1$ Hz, 2H), 7.59 (d, $J = 8.4$ Hz, 2H), 3.65-3.55 (m, 1H), 3.05-2.94 (m, 2H), 2.73-2.67 (m, 2H). MS: 283.1 [M-1].

[0613]

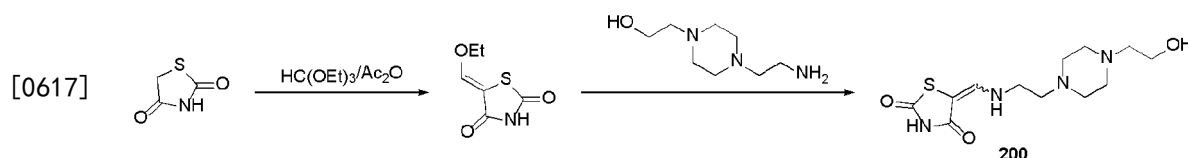
438		2-(羟基亚甲基)-5-(4-溴苯基)环己烷-1,3-二酮	$^1\text{H NMR}$ (400 MHz, $\text{DMSO}-d_6$) δ 9.55 (s, 1H), 7.68 – 7.75 (m, 2H), 7.47 – 7.40 (m, 2H), 3.81 – 3.73 (m, 1H), 3.08 – 2.94 (m, 2H), 2.73-2.68 (m, 2H); MS: 293.0 [M-1].
439		2-(羟基亚甲基)-5-(3-溴苯基)环己烷-1,3-二酮	$^1\text{H NMR}$ (400 MHz, $\text{DMSO}-d_6$) δ 9.52 (s, 1H), 7.65 (s, 1H), 7.65 – 7.58 (m, 3H), 3.81 – 3.73 (m, 1H), 3.07 – 2.91 (m, 2H), 2.70-2.62 (m, 2H); M: 293.0 [M-1].
440		5-(4-甲基硫苯基)-2-(羟基亚甲基)环己烷-1,3-二酮	$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 9.68 (s, 1H), 7.28 (d, $J = 8.5$ Hz, 2H), 7.18 (d, $J = 8.3$ Hz, 2H), 3.45-3.80 (m, 1H), 2.91 (d, $J = 8.3$ Hz, 2H), 2.81-2.76 (m, 1H), 2.71-2.64 (m, 1H), 2.51 (s, 3H); MS: 263.1 [M+1].
441		2-(羟基亚甲基)-5-(2,6-二甲氧基苯基)环己烷-1,3-二酮	$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 9.65 (s, 1H), 7.31-7.10 (m, 3H), 3.88 (s, 3H), 3.86 (s, 3H), 3.79 – 3.69 (m, 1H), 3.05 – 2.94 (m, 1H), 2.93 – 2.67 (m, 3H); MS: 277.1 [M+1].
442		2-(羟基亚甲基)-5-(2-羟基苯基)环己烷-1,3-二酮	$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 9.68 (s, 1H), 7.36-7.11 (m, 4H), 3.75-3.62 (m, 1H), 2.81 (m, 1H), 2.68-2.36 (m, 3H); MS: 233.1 [M+1].
443		2-(羟基亚甲基)-5-(4-羟基苯基)环己烷-1,3-二酮	$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 9.68 (s, 1H), 7.36 (d, $J = 8.5$ Hz, 2H), 7.29 (d, $J = 8.3$ Hz, 2H), 3.55-3.80 (m, 1H), 2.81 (d, $J = 8.3$ Hz, 2H), 2.71-2.65 (m, 1H), 2.60-2.56 (m, 1H); MS: 233.1 [M+1].

[0614]

444		2-(羟基亚甲基)-5-苯基环己烷-1,3-二酮	$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 15.86 (s, 1H), 9.67 (s, 1H), 7.39-7.35 (m, 2H), 7.32 – 7.27 (m, 1H), 7.25 – 7.21 (m, 2H), 3.49 – 3.38 (m, 1H), 2.95 – 2.89 (m, 2H), 2.82 – 2.63 (m, 2H); MS: 217.1 [M+1].
445		2-(羟基亚甲基)-5-(2-(苯并[d][1,3]二氧基-5-基)乙基)-环己烷-1,3-二酮	$^1\text{H NMR}$ (400 MHz, $\text{DMSO}-d_6$) δ 9.48 (s, 1H), 6.86 – 6.73 (m, 2H), 6.66 (dd, $J = 7.9$, 1.5 Hz, 1H), 5.95 (s, 2H), 2.69 – 2.52 (m, 4H), 2.48 – 2.30 (m, 2H), 2.13 – 2.01 (m, 1H), 1.64-1.59 (m, 2H); MS: 289.1 [M+1].
446		2-(羟基亚甲基)-5-(3-氟苯基)环己烷-1,3-二酮	$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 15.88 (s, 1H), 9.66 (s, 1H), 7.37-7.27 (m, 1H), 7.06 – 6.89 (m, 3H), 3.48-3.40 (m, 1H), 2.92-2.89 (m, 2H), 2.83 – 2.74 (m, 1H), 2.70-2.62 (m, 1H); MS: 235.1 [M+1].
447		2-(羟基亚甲基)-5-((2-氟-3-氯-6-三氟甲基)苯基)环己烷-1,3-二酮	$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 15.93 (s, 1H), 9.69 (s, 1H), 7.55 – 7.45 (m, 2H), 3.87 – 3.75 (m, 1H), 3.39-3.31 (m, 1H), 3.11-3.03 (m, 1H), 2.78-2.63 (m, 2H); MS: 337.0 [M+1].
448		3-(羟基亚甲基)-6-苯基-2H-吡喃-2,4(3H)-二酮	$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 14.46 (s, 1H), 9.97 (s, 1H), 7.94 – 7.85 (m, 2H), 7.61-7.50 (m, 3H), 6.59 (s, 1H); MS: 217.1 [M+1].
449		2-(1-羟基亚乙基)-5-苯基环己烷-1,3-二酮	$^1\text{H NMR}$ (400 MHz, $\text{DMSO}-d_6$) δ 18.06 (s, 1H), 7.37 – 7.30 (m, 4H), 7.29 – 7.21 (m, 1H), 3.44-3.37 (m, 1H), 2.96 (br, 2H), 2.71 (br, 2H), 2.55 (s, 3H); MS: 231.1 [M+1].
450		3-(羟基亚甲基)-N-苯基吡咯-2,4-二酮	$^1\text{H NMR}$ (400 MHz, $\text{DMSO}-d_6$) δ 10.00 (s, 1H), 8.03 (t, $J = 14.5$ Hz, 1H), 7.40 – 7.32 (m, 2H), 7.29 (t, $J = 7.4$ Hz, 2H), 7.17 (q, $J = 14.0$, 7.3 Hz, 1H), 3.83 – 3.73 (m, 2H), 3.46 – 3.34 (m, 2H), 2.59 (t, $J = 6.5$ Hz, 1H), 2.54 (t, $J = 6.6$ Hz, 1H).

[0615]		2-(羟基亚甲基)-4-氟-5-(苯基)环己烷-1,3-二酮	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.26 – 8.07 (m, 1H), 7.40 – 7.12 (m, 4H), 5.29 – 5.04 (m, 1H), 3.83 – 3.69 (m, 1H), 2.92 – 2.63 (m, 2H).
		2-(羟基亚甲基)-4,4-二氟-5-(苯基)环己烷-1,3-二酮	¹ H NMR (400 MHz, CD ₃ OD) δ 9.84 (s, 1H), 7.58 (s, 1H), 7.41 – 7.29 (m, 5H), 3.79 – 3.64 (m, 1H), 3.12-3.02 (m, 1H), 2.72 – 2.63 (m, 1H) ; MS: 253.1 [M+1] ⁺

[0616] 实施例36化合物5-(((2-(4-(2-羟乙基)哌嗪-1-基)乙基)氨基)亚甲基)噻唑烷-2,4-二酮(化合物200)的合成



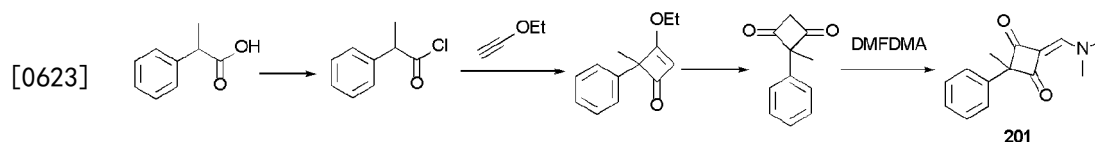
[0618] 步骤1:5-(乙氧基亚甲基)-2,4-噻唑烷二酮的合成

[0619] 将2,4-噻唑烷二酮(2.8g, 23.93mmol)、三乙氧基甲烷(4mL)和乙酸酐(6mL)的混合物加热回流过夜,反应完毕,冷却至室温析出固体,过滤,收集滤液并浓缩,得到目标化合物粗品,不经纯化直接用于下一步反应。

[0620] 步骤2:化合物5-(((2-(4-(2-羟乙基)哌嗪-1-基)乙基)氨基)亚甲基)噻唑烷-2,4-二酮的合成

[0621] 操作步骤同实施例2(化合物1)

[0622] 实施例37化合物4-((二甲基氨基)亚甲基)-2-甲基-2-苯基环丁烷-1,3-二酮(化合物201)的合成



[0624] 步骤1:2-苯基丙酰氯的合成

[0625] 氮气保护,在0℃下,氯化亚砷(4.8g, 40.3mmol)滴加至2-苯基丙酸(2g, 13.3mmol)的DCM(20mL)溶液,滴毕,加入催化量DMF,将混合物回流反应2小时并浓缩,得到2-苯基丙酰氯粗品,直接用于下一步反应。

[0626] 步骤2:化合物3-乙氧基-4-甲基-4-苯基环丁-2-烯-1-酮的合成

[0627] 氮气保护下,将乙氧基乙炔(3.72g, 26.6mmol, 50%w/w己烷溶液)滴加至2-苯基丙酰氯(13.3mmol)的乙醚(40mL)溶液中,向上述混合物滴加TEA(2g, 19.8mmol),室温搅拌30分钟后,将悬浮液加热回流反应24小时。反应完毕,将所得混合物冷却,过滤,滤液浓缩,通过柱层析分离纯化得目标化合物600mg。

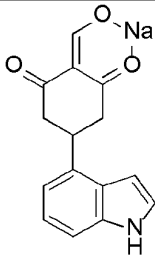
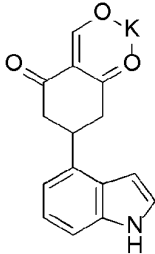
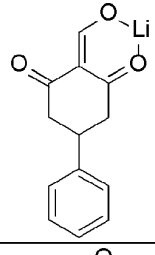
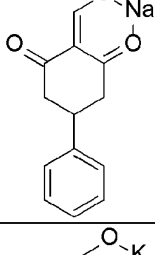
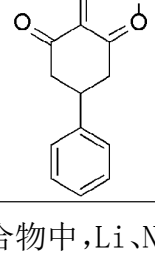
[0628] 步骤3:化合物2-甲基-2-苯基环丁烷-1,3-二酮的合成

[0629] 将化合物3-乙氧基-4-甲基-4-苯基环丁-2-烯-1-酮(350mg, 1.73mmol)溶解在2M

[0642]

#	结构	名称	氢谱(¹ H NMR),质谱(MS)
453		2-(羟基亚甲基)-5-(2-噻吩基)环己烷-1,3-二酮锂盐	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.43 (s, 1H), 7.35 (d, <i>J</i> = 5.0, 1H), 6.97 – 6.93 (m, 1H), 6.92-6.91 (m, 1H), 3.58 – 3.49 (m, 1H), 2.65 – 2.51 (m, 4H); MS: 221.1 [M-Li].
454		2-(羟基亚甲基)-5-(2-噻吩基)环己烷-1,3-二酮钠盐	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.59 (s, 1H), 7.33 (d, <i>J</i> = 4.9 Hz, 1H), 6.97 – 6.92 (m, 1H), 6.91-6.90 (m, 1H), 3.51-3.43 (m, 1H), 2.54-2.40 (m, 4H, Part of the peak is contained in solvent residual peak of DMSO- <i>d</i> ₆); MS: 221.1 [M-Na].
455		2-(羟基亚甲基)-5-(2-噻吩基)环己烷-1,3-二酮钾盐	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.65 (s, 1H), 7.32 (dd, <i>J</i> = 5.1, 1.2 Hz, 1H), 6.94 (dd, <i>J</i> = 5.1, 3.5 Hz, 1H), 6.89 (dt, <i>J</i> = 3.5, 1.1 Hz, 1H), 3.47 – 3.38 (m, 1H), 2.48-2.33 (m, 4H); MS: 221.1 [M-K].
456		2-(羟基亚甲基)-5-(3-噻吩基)环己烷-1,3-二酮锂盐	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.43 (s, 1H), 7.49-7.45 (m, 1H), 7.24-7.20 (m, 1H), 7.14-7.10 (m, 1H), 3.34 – 3.25 (m, 1H), 2.52-2.48 (m, 4H); MS: 223.0 [M+1].
457		2-(羟基亚甲基)-5-(3-噻吩基)环己烷-1,3-二酮钠盐	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.59 (s, 1H), 7.47-7.44 (m, 1H), 7.20 (d, <i>J</i> = 2.8 Hz, 1H), 7.12-7.09 (m, 1H), 3.30-3.21 (m, 1H), 2.46-2.40 (m, 4H); MS: 223.0 [M+1].
458		2-(羟基亚甲基)-5-(3-噻吩基)环己烷-1,3-二酮钾盐	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.64 (s, 1H), 7.47-7.42 (m, 1H), 7.20-7.17 (m, 1H), 7.10-7.06 (m, 1H), 3.28-3.16 (m, 1H), 2.42-2.30 (m, 4H) ; MS: 223.0 [M+1].
459		2-(羟基亚甲基)-5-(1 <i>H</i> -吲哚-4-基)环己烷-1,3-二酮锂盐	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.35 (s, 1H), 7.45 (t, <i>J</i> = 2.8 Hz, 1H), 7.50 (d, <i>J</i> = 8.0 Hz, 1H), 7.15 (t, <i>J</i> = 7.7 Hz, 1H), 7.09 (d, <i>J</i> = 7.2 Hz, 1H), 6.71 (s, 1H), 3.74 – 3.56 (m, 1H), 2.50 – 2.46 (m, 4H) ; MS: 254.1 [M-H].

[0643]

460		2-(羟基亚甲基)-5-(1 <i>H</i> -吲哚-4-基)环己烷-1,3-二酮钠盐	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.51 (s, 1H), 7.47 (t, <i>J</i> = 2.8 Hz, 1H), 7.34 (d, <i>J</i> = 8.0 Hz, 1H), 7.09 (t, <i>J</i> = 7.7 Hz, 1H), 6.93 (d, <i>J</i> = 7.2 Hz, 1H), 6.65 (s, 1H), 3.66 – 3.53 (m, 1H), 2.44 – 2.40 (m, 4H); MS: 254.1 [M-H].
461		2-(羟基亚甲基)-5-(1 <i>H</i> -吲哚-4-基)环己烷-1,3-二酮钾盐	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.56 (s, 1H), 7.45 (t, <i>J</i> = 2.8 Hz, 1H), 7.44 (d, <i>J</i> = 8.0 Hz, 1H), 7.09 (t, <i>J</i> = 7.7 Hz, 1H), 6.93 (d, <i>J</i> = 7.2 Hz, 1H), 6.65 (s, 1H), 3.63 – 3.50 (m, 1H), 2.40 – 2.36 (m, 4H); MS: 254.1 [M-H].
462		2-(羟基亚甲基)-5-苯基环己烷-1,3-二酮锂盐	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.45 (s, 1H), 7.35 – 7.26 (m, 4H), 7.25 – 7.17 (m, 1H), 3.29 – 3.14 (m, 1H), 2.67 – 2.53 (m, 2H), 2.46 – 2.33 (m, 2H).
463		2-(羟基亚甲基)-5-苯基环己烷-1,3-二酮钠盐	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.61 (s, 1H), 7.35 – 7.25 (m, 4H), 7.22 – 7.14 (m, 1H), 3.24 – 3.12 (m, 1H), 2.56 – 2.45 (m, 2H), 2.37 – 2.25 (m, 2H).
464		2-(羟基亚甲基)-5-苯基环己烷-1,3-二酮钾盐	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.66 (s, 1H), 7.33 – 7.24 (m, 4H), 7.22 – 7.13 (m, 1H), 3.17 – 3.09 (m, 1H), 2.48 – 2.37 (m, 2H), 2.31 – 2.22 (m, 2H).

[0644] 在上述化合物中, Li、Na或K与羰基氧形成配位键。

[0645] 实施例41: 利用荧光偏振 (FP) 法测试本发明的化合物对自噬相关蛋白LC3B的调节。

[0646] 荧光偏振 (FP) 法测试实验

[0647] 组蛋白GST-LC3B(终浓度180nM) (SEQ ID NO:1) 和N末端FITC标记肽(SEQ ID NO:2, 序列: FITC-GGDDDWTHLSSKEVD-NH₂, 终浓度18nM) 置于FP缓冲液 (50mM HEPES pH7.5, 0.1mg/mLBSA, 1mM DTT) 中, 向其中加入使用FP缓冲液梯度稀释的化合物, 然后将上述混合物于25℃下在避光孵育。监测荧光偏振值 (PerkinElmer Envision, 发射光波长480nm; 吸收光波长535nm), 并用GraphPad Prism 6.0程序计算IC₅₀值, 测试结果如表8所示。

[0648] 化合物的IC₅₀值表示方法: 100μM < IC₅₀ ≤ 1mM被认为对LC3B的活性较低(+); 化合物15μM < IC₅₀ ≤ 100μM被认为是对LC3B的活性中等(++); 3μM < IC₅₀ ≤ 15μM被认为对LC3B活性较高(+++); IC₅₀ ≤ 3μM被认为对LC3B具有高活性(++++)。本发明化合物的IC₅₀值如表10所

示。

[0649] 表10:化合物IC₅₀

[0650]

编号	IC ₅₀ (μM)	编号	IC ₅₀ (μM)	编号	IC ₅₀ (μM)	编号	IC ₅₀ (μM)	编号	IC ₅₀ (μM)	编号	IC ₅₀ (μM)
1	+	2	+++	4A	+++	7	+++	8	++++	9	+
10	+	11	+	12	+	14	+	15	+++	17	+++
18	+++	19	++	20	+	21	++	22	+	23	+++
24	++++	25	+	26	++	27	++	28	+++	29	+
30	+	31	+++	32	+++	33	++	34	++++	35	++
36	+	37	++++	39	++++	40	++++	41	+++	42	+++
43	+++	44	++	45	++	46	++++	47	+++	48	++++
49	++++	50	++++	51	++	52	++	53	++	54	++++
55	++	56	+++	57	++	58	++	59	+	61	++++
62	+++	63	++	64	+	65	+	66	++++	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	++
99	+	100	++	101	++	102	++	103	++	104	++
106	+	107	++	108	+	109	+	110	+	111	+
112	++	113	+	114	+	115	+++	116	++++	119	++++
120	++++	121	++	122	+	123	+	124	+	125	+
126	++	127	++	128	+	129	++	131	++	132	+
133	+	134	+	135	+	136	+	137	+++	138	+
139	+	140	++	141	+++	142	++	143	++	145	+
146	++	147	++	148	++++	149	++++	150	++++	155	++
156	+++	158	+	160	++	161	+	162	++	163	+
164	+++	165	+	169	+++	170	+++	171	+++	172	+++
173	++	174	++	175	+++	176	+	177	+	178	++
180	+	182	+	183	+	184	+	185	++++	186	+++
187	++++	188	+++	189	++++	190	++	191	++++	192	+++
193	++	194	++	195	+++	196	+++	197	++++	198	++

[0651]

200	+	201	+	202	++	203	+++	204	+	205	+
206	++	207	++	208	++	209	++++	210	++	211	++++
212	++++	213	++++	214	++++	215	++++	216	++++	217	+++
218	++++	219	++++	220	+++	221	++++	222	++++	223	+++
224	++++	225	++++	226	++++	227	+	228	++++	229	++++
230	++++	231	++++	232	++++	233	++++	236	+++	237	+++
238	++++	239	++++	240	++++	241	++++	242	+++	245	++++
246	++++	247	++	248	++++	249	++++	251	++++	252	++++
253	++++	254	++++	255	++++	256	++++	257	++	258	++++
259	++++	260	++++	262	++++	263	++++	264	++++	265	+++
266	+++	267	+++	268	+++	269	+++	270	+++	271	++++
272	+++	273	++	274	++	276	++	277	++++	278	++++
279	+++	280	++++	281	++++	282	++++	283	++++	284	+++
285	+++	286	++++	287	+++	288	+++	289	+++	290	+++
291	+++	293	+++	294	++++	295	+++	296	++++	297	++++
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321	+++	322	++++	323	+++	324	+++	325	++	326	+
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352	+	353	++++	354	++++	355	++++	356	++++	357	++++
358	++++	359	++	360	+++	361	++++	362	++++	363	+++
364	++++	365	++++	366	++++	367	++++	368	++++	369	++++
370	++++	371	++++	372	++++	373	++++	374	++++	375	++++
376	++++	377	++++	378	++++	379	++++	380	+++	381	++++
382	++++	383	++++	384	++++	385	++++	386	++++	387	++++
388	++++	389	++++	390	++++	391	++	392	++++	393	++++
394	++++	395	+++	396	++++	397	++++	398	++++	399	+++
400	++++	401	++++	402	++++	403	++++	404	++++	405	++++
406	++++	407	++	408	+++	409	++++	410	++++	411	++++

[0652]

412	++++	413	+++	414	+++	415	+++	416	++++	417	++++
418	++++	419	++++	420	++++	421	++++	422	++++	423	+++
424	+++	425	++	426	++++	427	+++	428	+++	429	++++
430	++++	431	+++	432	++++	433	++++	434	+++	435	+++
436	+++	437	+++	438	+++	439	+++	440	+++	441	++
442	++	443	++	444	+++	445	++	446	+++	447	++++
448	+++	449	++	450	++	451	+++	452	+++	453	+++
454	+++	455	+++	456	+++	457	+++	458	+++	459	++++
460	++++	461	++++	462	+++	463	+++	464	+++		

[0653] 本发明的化合物表现出对LC3B的活性,并且一些化合物对LC3B具有高活性。这些化合物对ATG8的其它哺乳动物同源物也是有活性的。因此,这些化合物可以调节LC3B和ATG8的其他哺乳动物同源物,用于治疗与自噬相关的疾病。

[0654] 应理解,在不脱离本发明范围和精神的情况下,本领域技术人员可以对本发明进行各种改动或修改,这对于本领域技术人员是显而易见的,这些等价形式同样落于本申请所附权利要求书所限定的范围。

序列表

<110> 微境生物医药科技（上海）有限公司

<120> 用作自噬调节剂的化合物及其制备方法和用途

<160> 2

<170> SIPOSequenceListing 1.0

<210> 1

<211> 356

<212> PRT

<213> （人工序列）

<400> 1

[0001]

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Met Ser Pro Ile Leu Gly Tyr Trp Lys Ile Lys Gly Leu Val Gln Pro
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Thr Arg Leu Leu Leu Glu Tyr Leu Glu Glu Lys Tyr Glu Glu His Leu
          20           25           30
Tyr Glu Arg Asp Glu Gly Asp Lys Trp Arg Asn Lys Lys Phe Glu Leu
          35           40           45
Gly Leu Glu Phe Pro Asn Leu Pro Tyr Tyr Ile Asp Gly Asp Val Lys
          50           55           60
Leu Thr Gln Ser Met Ala Ile Ile Arg Tyr Ile Ala Asp Lys His Asn
65           70           75           80
Met Leu Gly Gly Cys Pro Lys Glu Arg Ala Glu Ile Ser Met Leu Glu
          85           90           95
Gly Ala Val Leu Asp Ile Arg Tyr Gly Val Ser Arg Ile Ala Tyr Ser
          100          105          110
Lys Asp Phe Glu Thr Leu Lys Val Asp Phe Leu Ser Lys Leu Pro Glu
          115          120          125
Met Leu Lys Met Phe Glu Asp Arg Leu Cys His Lys Thr Tyr Leu Asn
          130          135          140
Gly Asp His Val Thr His Pro Asp Phe Met Leu Tyr Asp Ala Leu Asp
145          150          155          160
Val Val Leu Tyr Met Asp Pro Met Cys Leu Asp Ala Phe Pro Lys Leu
          165          170          175
Val Cys Phe Lys Lys Arg Ile Glu Ala Ile Pro Gln Ile Asp Lys Tyr
          180          185          190
Leu Lys Ser Ser Lys Tyr Ile Ala Trp Pro Leu Gln Gly Trp Gln Ala
          195          200          205
Thr Phe Gly Gly Gly Asp His Pro Pro Lys Ser Asp Leu Glu Val Leu
          210          215          220

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	Phe Gln Gly Pro Leu Gly Ser Met Pro Ser Glu Lys Thr Phe Lys Gln	
225	230	240
	Arg Arg Thr Phe Glu Gln Arg Val Glu Asp Val Arg Leu Ile Arg Glu	
	245	255
	Gln His Pro Thr Lys Ile Pro Val Ile Ile Glu Arg Tyr Lys Gly Glu	
	260	270
	Lys Gln Leu Pro Val Leu Asp Lys Thr Lys Phe Leu Val Pro Asp His	
	275	285
	Val Asn Met Ser Glu Leu Ile Lys Ile Ile Arg Arg Arg Leu Gln Leu	
	290	300
	Asn Ala Asn Gln Ala Phe Phe Leu Leu Val Asn Gly His Ser Met Val	
305	310	320
	Ser Val Ser Thr Pro Ile Ser Glu Val Tyr Glu Ser Glu Lys Asp Glu	
[0002]	325	335
	Asp Gly Phe Leu Tyr Met Val Tyr Ala Ser Gln Glu Thr Phe Gly Met	
	340	350
	Lys Leu Ser Val	
	355	
<210>	2	
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<400>	2	
	Gly Gly Asp Asp Asp Trp Thr His Leu Ser Ser Lys Glu Val Asp	
1	5	15