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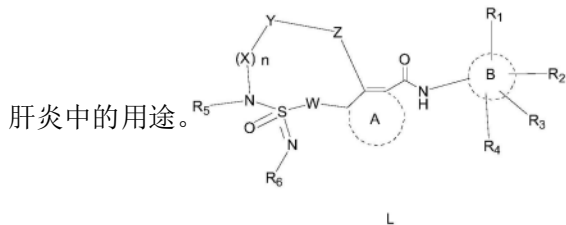
权利要求书2页 说明书138页

(54) 发明名称

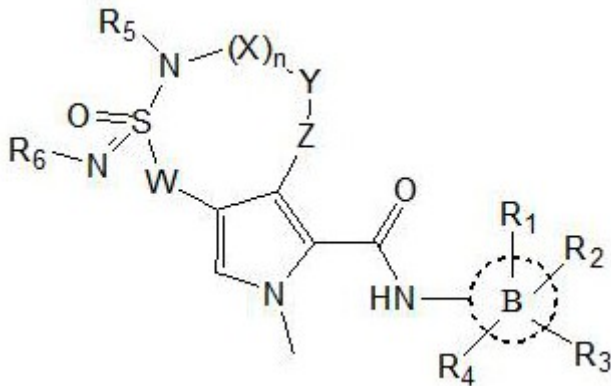
内环硫脒酰胺-芳基酰胺类化合物及其治疗乙型肝炎的用途

(57) 摘要

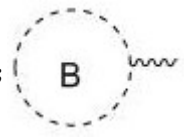
本发明涉及一种内环硫脒酰胺-芳基酰胺类化合物及其治疗乙型肝炎的用途。具体地,本发明公开了一种可作HBV复制抑制剂,其具有化学式(A)所示结构的化合物或其立体异构体或互变异构体,或其药学上可接受的盐,水合物或溶剂化物,各基团的定义详见说明书。本发明还涉及包含上述化合物的药物组合物及其在治疗乙型肝炎中的用途。



1. 一种如式III所示的化合物、或其立体异构体或互变异构体、或其药学上可接受的盐、水合物或溶剂化物:



III其中 $X_1$ 为 $-CR=$ 或 $-N=$ ,  $X_2$ 为 $-NR-$ ; 且所述的R为H或C1-C4的烷基; n为1;



为苯环、或五元或六元芳杂环;

X为 $-CR^aR^b-$ ;

Y为取代或未取代的C1-7亚烷基, 或取代或未取代的C2亚烯基, 其中, 所述的取代基选自下组: C1-C4的烷基、羟基;

Z为无;

W为无;

$R^1, R^2, R^3$ 和 $R^4$ 各自独立地选自下组: H、卤素、氰基、取代或未取代的C1-C4的烷基; 其中, 所述的取代指基团上的氢原子被一个或多个选自下组的取代基取代: 卤素、C1-C4的烷基;

$R^5, R^6$ 各自独立地选自下组: H;

$R^a$ 选自下组: 环丙基、环丙基- $C_1-C_8$ 烷基、卤代苯基- $(CH_2)-$ 、C1-C6烷氧基-苯基- $(CH_2)-$ ;

$R^b$ 为H。

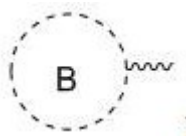
2. 如权利要求1所述的化合物、或其药学上可接受的盐, 其特征在于,  $R^1, R^2, R^3$ 和 $R^4$ 各自独立地选自下组: H、卤素、氰基、取代或未取代的C1-C4的烷基; 其中, 所述的取代指基团上的氢原子被一个或多个选自下组的取代基取代: 卤素。

3. 如权利要求1所述的化合物、或其药学上可接受的盐, 其特征在于,  $R^a$ 选自下组: 环丙基、环丙基- $CH_2-$ 、卤代苯基- $CH_2-$ 、甲氧基-苯基- $CH_2-$ ;

$R^b$ 为H。

4. 如权利要求1所述的化合物、或其药学上可接受的盐, 其特征在于,  $X_1$ 为 $-CR=$ ,  $X_2$ 为-

$NR-$ ; 且所述的R为C1-C4的烷基; n为1;



代的吡啶环;

Y为C2亚烷基或C2亚烯基;

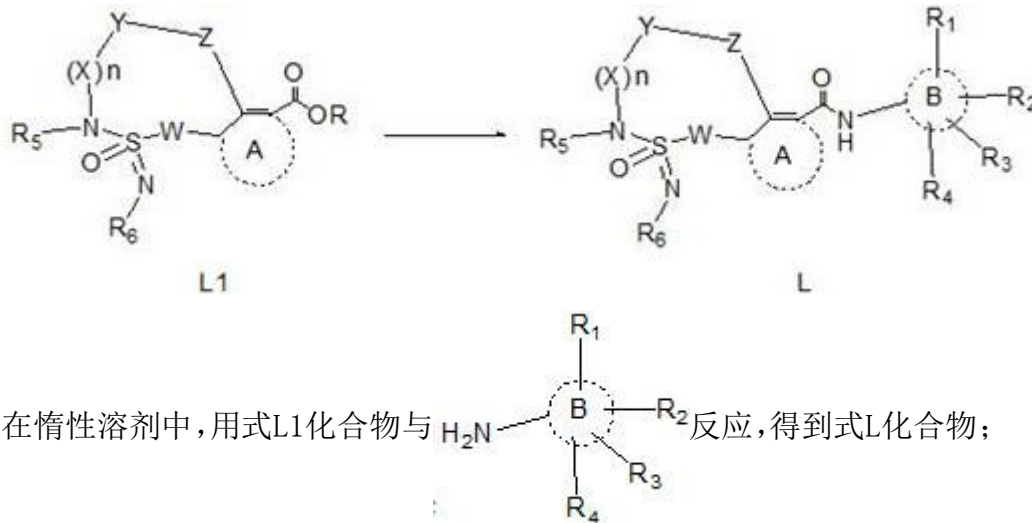
Z为无;

W为无；

$R^1, R^2, R^3$ 和 $R^4$ 各自独立地选自下组：H、卤素、氰基、取代或未取代的C1-C4的烷基；其中，所述的取代指基团上的氢原子被一个或多个选自下组的取代基取代；卤素、C1-C4的烷基；

$R^5, R^6$ 各自独立地选自下组：H、取代或未取代的C<sub>1</sub>-C<sub>8</sub>烷基。

5. 如权利要求1所述的化合物、或其立体异构体或互变异构体，或其药学上可接受的盐、水合物或溶剂化物的制备方法，其特征在于，所示式L化合物为式VII-1所示的化合物，所述方法包括步骤：



其中，所述的OR为离去基团，其余各基团的定义如权利要求1中所述。

6. 一种药物组合物，其特征在于，包含(1)如权利要求1所述的化合物或其立体异构体或互变异构体，或其药学上可接受的盐、水合物或溶剂化物；(2)药学上可接受的载体。

7. 如权利要求1所述的化合物或其立体异构体或互变异构体，或其药学上可接受的盐、水合物或溶剂化物或如权利要求6所述的药物组合物的用途，其特征在于，用于制备预防和/或治疗乙型肝炎病毒感染的药物。

8. 一种乙型肝炎病毒抑制剂，其特征在于，所述抑制剂包含权利要求1所述的化合物、或其立体异构体或互变异构体、或其药学上可接受的盐、水合物或溶剂化物。

9. 一种体外抑制乙型肝炎病毒的方法，其特征在于，包括步骤：将权利要求1所述的化合物、或其立体异构体或互变异构体、或其药学上可接受的盐、水合物或溶剂化物，与乙型肝炎病毒接触，从而抑制乙型肝炎病毒复制。

## 内环硫脒酰胺-芳基酰胺类化合物及其治疗乙型肝炎的用途

### 技术领域

[0001] 本发明属于医药领域,具体地,本发明涉及一种内环硫脒酰胺-芳基酰胺类化合物和其作为药物用于治疗乙型肝炎的用途。

### 背景技术

[0002] 乙型肝炎病毒 (HBV) 是一种有包膜的、部分双链DNA (dsDNA) 的、嗜肝病毒DNA家族 (肝病毒科 (Hepadnaviridae)) 的病毒。它的基因组包含4个重叠阅读框:前核/核基因,聚合酶基因,UM和S基因(它们编码三个包膜蛋白质),以及X基因。在感染前时,该部分双链DNA基因组在宿主细胞核中(开环DNA,rcDNA)转变为共价闭环环状DNA(cccDNA)并且该病毒mRNA进行转录。一旦被壳体化,该前基因组RNA(pgRNA)(其还为核心蛋白和Pol编码)作为模板用于逆转录,这种逆转录在核衣壳中再生该部分dsDNA基因组(rcDNA)。

[0003] HBV在亚洲和非洲的部分地区造成了流行病,并且它在中国是地方性的。HBV已经在全球感染了大约20亿人,其中大约3.5亿人发展成了慢性传染病。该病毒造成了乙型肝炎疾病并且慢性传染病与肝硬化和肝癌的发展的高增加风险相关联。

[0004] 乙型肝炎病毒的传播来源于暴露于传染性的血液或体液,同时在血清中具有高效价DNA的慢性携带者的唾液、泪液以及尿液中检测到了病毒DNA。

[0005] 虽然目前存在一种有效的并且具有良好耐受性的疫苗,但是直接治疗的选择目前还限于干扰素以及以下的抗病毒药:替诺福韦、拉米夫定、阿德福韦、恩替卡韦以及替比夫定。

[0006] 此外,杂芳基二氢嘧啶(HAPs)在组织培养以及动物模型中被鉴别作为一类HBV抑制剂(韦伯(Weber)等人,《抗病毒研究》(Antiviral Res.) 54:69-78)。

[0007] WO 2013/006394(公开于2013年1月10日)和WO 2013/096744(公开于2013年6月27日)还公开了涉及抗HBV活性的氨磺酰基-芳基酰胺。

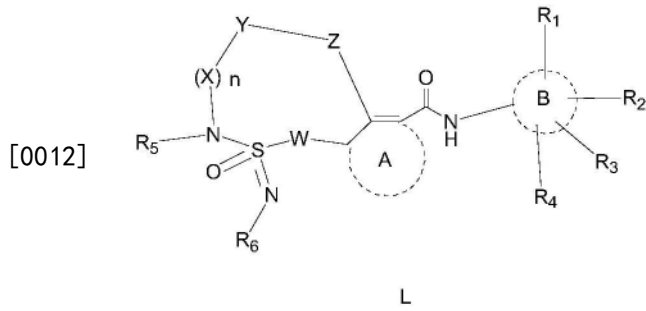
[0008] 然而,在这些直接的HBV抗病毒药中会遇到的是毒性、致突变性、缺乏选择性、疗效差、生物利用度差以及合成困难等问题。

[0009] 因此,为了克服以上缺陷,需要开发具有如效价高、毒性更低等优点的HBV抑制剂。

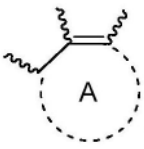
### 发明内容

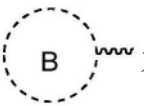
[0010] 本发明的目的是提供一类可用作HBV抑制剂的结构新颖的化合物。

[0011] 本发明第一方面,提供了一种如式L所示的化合物、或其立体异构体或互变异构体、或其药学上可接受的盐、水合物或溶剂化物,



[0013] 其中, n为1、2、3、4、5、6、7、8、9、或10;

[0014]  为取代或未取代的五元或六元环, 其中, 所述的五元或六元环任选地含有一个或多个选自下组的杂原子: O、S、N或P; 所述的取代指基团上的氢原子被一个或多个选自下组的取代基取代: C1-C3烷基 (尤其是甲基)、C3-C4环烷基、氰基, 或卤素;

[0015]  为取代或未取代的五元或六元芳环、或取代或未取代的五元或六元芳杂环;

[0016] X为 $-CR^aR^b-$ ;

[0017] Y为取代或未取代的C1-C7亚烷基, 或取代或未取代的C2-C7亚烯基, 其中, 所述的取代基选自下组: C1-C4的烷基、羟基;

[0018] Z选自下组: O、S、N或P, 或Z为C-C单键 (即Z为无);

[0019] W为NRc或无;

[0020]  $R^1, R^2, R^3$ 和 $R^4$ 各自独立地选自下组: H、卤素、氰基、取代或未取代的C3-C4的环烷基, 取代或未取代的C1-C4的烷基、取代或未取代的C1-C4的烷氧基; 其中, 所述的取代指基团上的氢原子被一个或多个选自下组的取代基取代: 卤素、C1-C4的烷基 (如二氟甲基、二氟乙基、单氟甲基、三氟甲基、三氟甲氧基);

[0021]  $R^5, R^6$ 各自独立地选自下组: H、卤素、-CN、羟基、氨基、羧基、-(C=O)-取代或未取代的C<sub>1</sub>-C<sub>8</sub>烷基、取代或未取代的C<sub>1</sub>-C<sub>8</sub>烷氧基、取代或未取代的C<sub>2</sub>-C<sub>6</sub>烯基、取代或未取代的C<sub>2</sub>-C<sub>6</sub>炔基、取代或未取代的C<sub>1</sub>-C<sub>8</sub>烷胺基、取代或未取代的C<sub>1</sub>-C<sub>8</sub>烷氧基、取代或未取代的C<sub>3</sub>-C<sub>10</sub>环烷基、取代或未取代的具有1-3个选自下组N、S和O的杂原子的3-10元杂环烷基、取代或未取代的C<sub>6</sub>-C<sub>10</sub>芳基、或取代或未取代的具有1-3个选自下组N、S和O的杂原子的5-10元杂芳基;

[0022]  $R^a, R^b$ 各自独立地为H、卤素、-CN、羟基、氨基、羧基、-(C=O)-取代或未取代的C<sub>1</sub>-C<sub>8</sub>烷基、取代或未取代的C<sub>1</sub>-C<sub>8</sub>烷氧基、取代或未取代的C<sub>2</sub>-C<sub>6</sub>烯基、取代或未取代的C<sub>2</sub>-C<sub>6</sub>炔基、取代或未取代的C<sub>1</sub>-C<sub>8</sub>烷胺基、取代或未取代的C<sub>1</sub>-C<sub>8</sub>烷氧基、取代或未取代的C1-C6烷氧基-烷基、取代或未取代的C<sub>3</sub>-C<sub>10</sub>环烷基、取代或未取代的具有1-3个选自下组N、S和O的杂原子的3-10元杂环烷基、取代或未取代的C<sub>6</sub>-C<sub>10</sub>芳基、或取代或未取代的具有1-3个选自下组N、S和O的杂原子的5-10元杂芳基;

[0023] Rc为H、卤素、-CN、羟基、氨基、羧基、-(C=O)-取代或未取代的C<sub>1</sub>-C<sub>8</sub>烷基、取代或未取代的C<sub>1</sub>-C<sub>8</sub>烷氧基、取代或未取代的C<sub>2</sub>-C<sub>6</sub>烯基、取代或未取代的C<sub>2</sub>-C<sub>6</sub>炔基、取代或未取代的

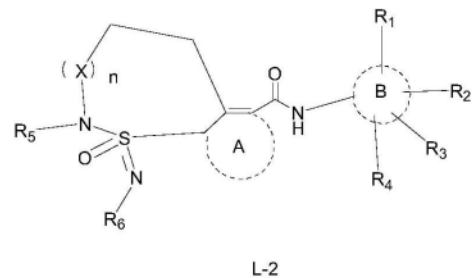
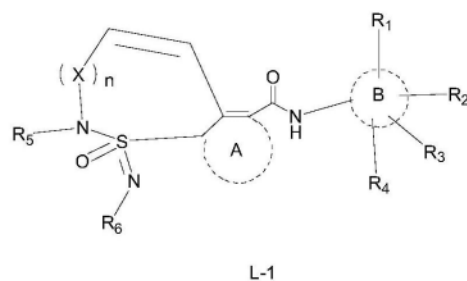
C<sub>1</sub>-C<sub>8</sub>烷基、取代或未取代的C<sub>1</sub>-C<sub>8</sub>烷氧基、取代或未取代的C<sub>3</sub>-C<sub>10</sub>环烷基、取代或未取代的具有1-3个选自下组N、S和O的杂原子的3-10元杂环烷基、取代或未取代的C<sub>6</sub>-C<sub>10</sub>芳基、或取代或未取代的具有1-3个选自下组N、S和O的杂原子的5-10元杂芳基；

[0024] 除非特别说明,所述的“取代”是指被选自下组的一个或多个(例如2个、3个、4个等)取代基所取代:卤素、C1-C6烷基、卤代的C1-C6烷基、C1-C6烷氧基、卤代的C1-C6烷氧基、C3-C8环烷基、卤代的C3-C8环烷基、氧代、-CN、羟基、氨基、羧基、未取代或被一个或多个选自下组的取代基取代的选自下组的基团:C6-C10芳基、卤代的C6-C10芳基、具有1-3个选自N、S和O的杂原子的5-10元杂芳基、卤代的具有1-3个选自N、S和O的杂原子的5-10元杂芳基;所述的取代基选自下组:卤素、C1-C6烷氧基。

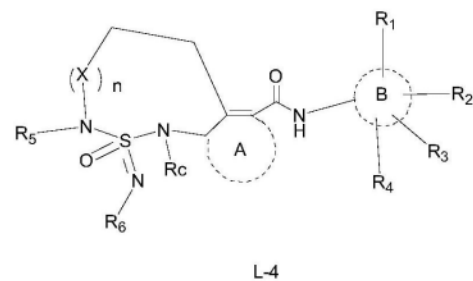
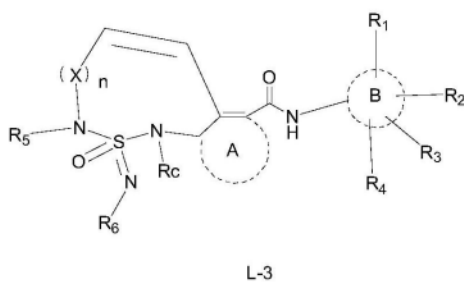
[0025] 在另一优选例中,所述的Y选自下组:C1-C4亚烷基,或取代或未取代的C2-C4亚烯基。

[0026] 在另一优选例中,所述的Ra、Rb各自独立地为取代或未取代的C<sub>1</sub>-C<sub>8</sub>烷基、取代或未取代的C<sub>1</sub>-C<sub>8</sub>烷氧基;其中,所述的取代基选自下组:卤素、羟基、氰基。

[0027] 在另一优选例中,所述化合物具有选自下式L-1、L-2、L-3、L-4所示的结构:



[0028]

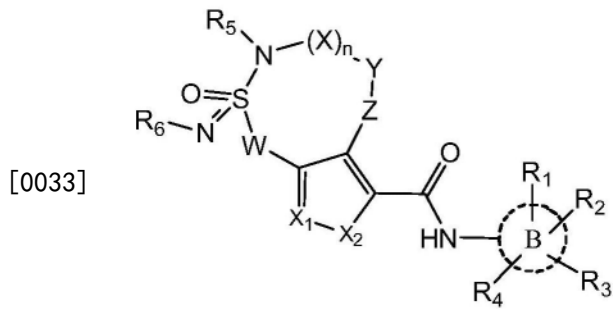


[0029] 各式中,n为1、2、3、4、5、6、7、8、9、10;

[0030] A环、B环、X、R<sub>1</sub>、R<sub>2</sub>、R<sub>3</sub>、R<sub>4</sub>、R<sub>5</sub>、R<sub>6</sub>的定义如本发明第一方面所述。

[0031] 在另一优选例中,所述的Ra、Rb各自独立地为取代或未取代的C<sub>1</sub>-C<sub>8</sub>烷基、取代或未取代的C<sub>1</sub>-C<sub>8</sub>烷氧基;其中,所述的取代基选自下组:卤素、羟基、氰基。

[0032] 在另一优选例中,所述的式I化合物具有如下式II所示的结构:

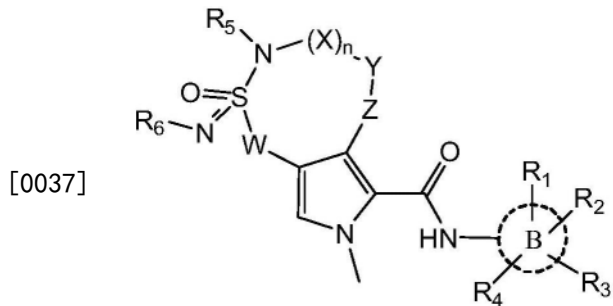


II

[0034] 其中 $X_1$ 为 $-CR=$ 或 $-N=$ ,  $X_2$ 为 $-NR-$ ;且所述的R为H或C1-C4的烷基。

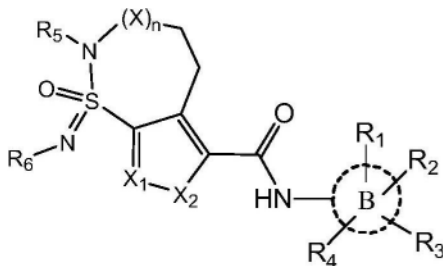
[0035] 在另一优选例中,所述的 $X_2$ 为 $-NCH_3-$ 。

[0036] 在另一优选例中,所述的式I化合物具有以下结构:

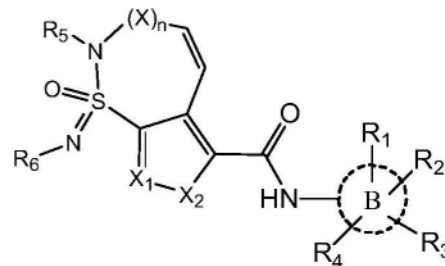


III

[0038] 在另一优选例中,所述的式I化合物具有如下式IV-1或式IV-2所示的结构:

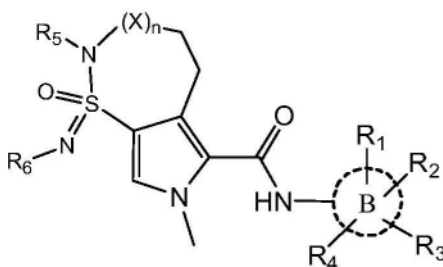


IV-1

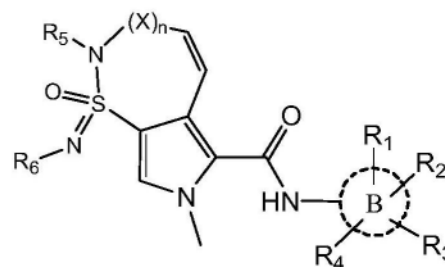


IV-2

[0039]



V-1



V-2

[0040] 在另一优选例中,所述的n为1。

[0041] 在另一优选例中,  $R_a$ 选自下组:取代或未取代的 $C_1-C_8$ 烷基、取代或未取代的 $C_1-C_8$ 烷氧基、取代或未取代的 $C_1-C_6$ 烷氧基-烷基;取代或未取代的 $C_3-C_6$ 环烷基、取代或未取代的 $C_3-C_6$ 环烷基取代的 $C_1-C_4$ 烷基、卤代苯基、取代或未取代的 $C_1-C_6$ 烷氧基-苯基

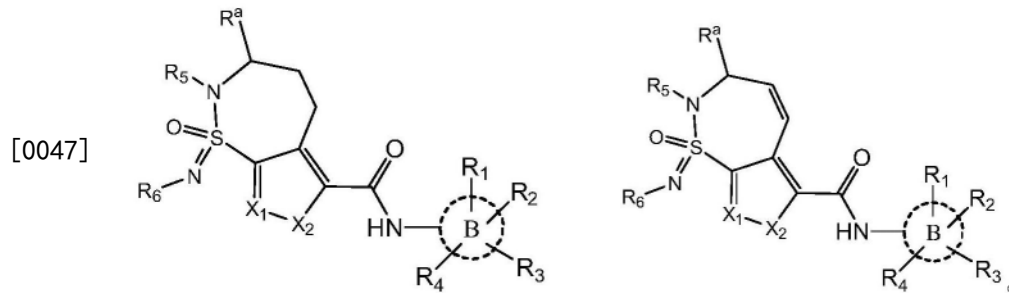
[0042]  $R_b$ 为H。

[0043] 在另一优选例中,所述的Ra选自下组:取代或未取代的C<sub>1</sub>-C<sub>8</sub>烷基;其中,所述的取代指基团上的一个或多个氢原子被选自下组的取代基取代:C1-C4烷氧基、羟基、未取代或被一个或多个选自下组的取代基取代的C6-C10芳基:卤素、C1-C6烷氧基。

[0044] 在另一优选例中,所述的R<sup>a</sup>选自下组:取代或未取代的C3-C6环烷基、取代或未取代的C3-C6环烷基取代的C<sub>1</sub>-C<sub>4</sub>烷基、卤代苯基。

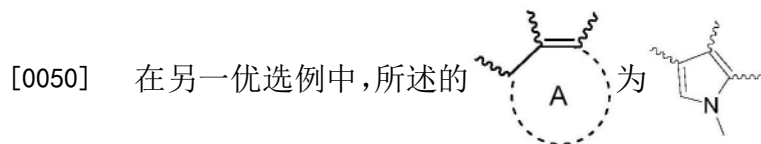
[0045] 在另一优选例中,所述的R<sup>a</sup>选自下组:环丙基、亚甲基-环丙基、4-氟代苯基、4-甲氧基苯基。

[0046] 在另一优选例中,所述的化合物具有如下式所示的结构:



[0048] 在另一优选例中,所述的B环为苯环或吡啶环。

[0049] 在另一优选例中,所述的A环为吡咯环。



[0051] 在另一优选例中,所述的R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>和R<sub>4</sub>各自独立地选自下组:H、卤素、氰基。

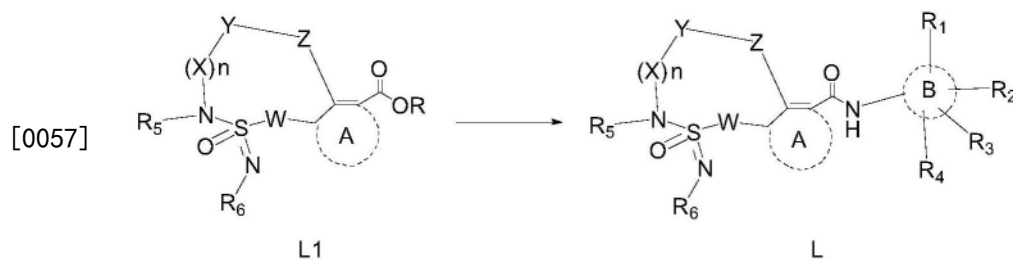
[0052] 在另一优选例中,所述的R<sub>5</sub>选自下组:H、取代或未取代的C<sub>1</sub>-C<sub>8</sub>烷基、取代或未取代的C<sub>3</sub>-C<sub>10</sub>环烷基。

[0053] 在另一优选例中,所述的R<sub>6</sub>选自下组:H、取代或未取代的C<sub>1</sub>-C<sub>8</sub>烷基、取代或未取代的C<sub>3</sub>-C<sub>10</sub>环烷基。

[0054] 在另一优选例中,所述的化合物为如表1中所述的化合物10a1-100c20,其中,Peak1和Peak 2指对映异构体在反相HPLC中的出峰顺序,Peak 1为先出峰的对映异构体,Peak 2为后出峰的对映异构体。

[0055] 在另一优选例中,上表中,HPLC为反相HPLC,其中peak1指极性较大的化合物,peak2指极性较小的化合物。

[0056] 本发明的第二方面,提供了一种如本发明第一方面所述的化合物、或其立体异构体或互变异构体,或其药学上可接受的盐、水合物或溶剂化物的制备方法,所述方法包括步骤:



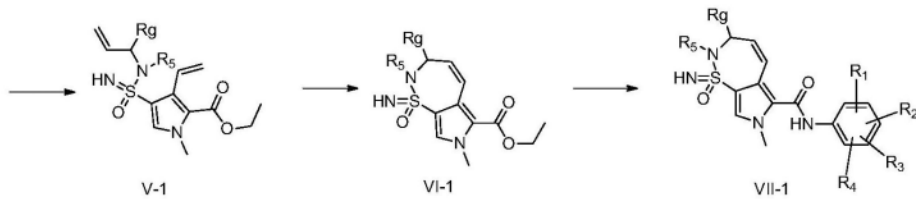
[0058] 在惰性溶剂中,用式L1化合物与  $\text{H}_2\text{N}-\text{B}(\text{R}_1)(\text{R}_2)(\text{R}_3)(\text{R}_4)$  反应,得到式L化合物;

[0059] 其中,所述的R为离去基团,其余各基团的定义如本发明第一方面中所述。

[0060] 在另一优选例中,所示式L化合物为式VII-1所示的化合物,所述的方法包括步骤:



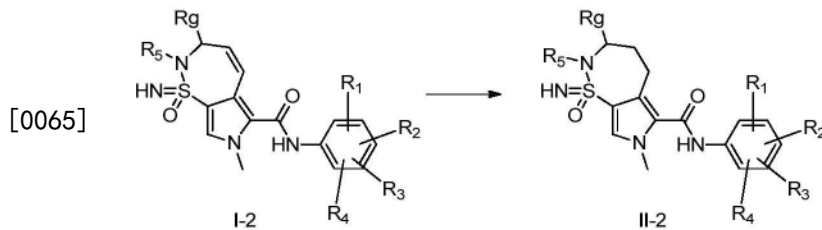
[0061]



[0062] 其中,  $\text{R}_g$  选自下组: H、卤素、-CN、羟基、氨基、羧基、-(C=O)-取代或未取代的  $\text{C}_1-\text{C}_8$  烷基、取代或未取代的  $\text{C}_1-\text{C}_8$  烷基、取代或未取代的  $\text{C}_2-\text{C}_6$  烯基、取代或未取代的  $\text{C}_2-\text{C}_6$  炔基、取代或未取代的  $\text{C}_1-\text{C}_8$  烷胺基、取代或未取代的  $\text{C}_1-\text{C}_8$  烷氧基、取代或未取代的  $\text{C}_3-\text{C}_{10}$  环烷基、取代或未取代的具有1-3个选自下组N、S和O的杂原子的3-10元杂环烷基、取代或未取代的  $\text{C}_6-\text{C}_{10}$  芳基、或取代或未取代的具有1-3个选自下组N、S和O的杂原子的5-10元杂芳基;

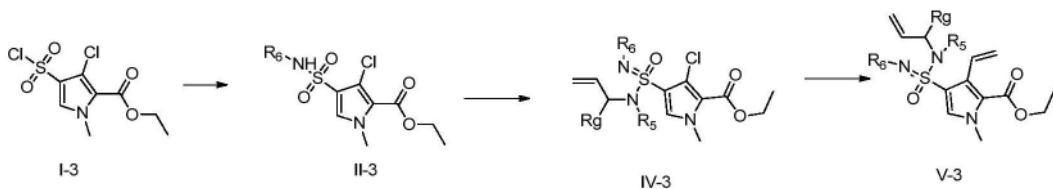
[0063] 各个基团的定义如上文中所述。

[0064] 在另一优选例中,所示式L化合物为式II-2所示的化合物,所述方法包括步骤:

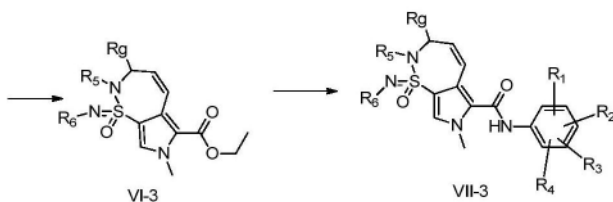


[0066] 各式中,各个基团的定义如上文中所述。

[0067] 在另一优选例中,所示式L化合物为式VII-3所示的化合物,所述方法包括步骤:

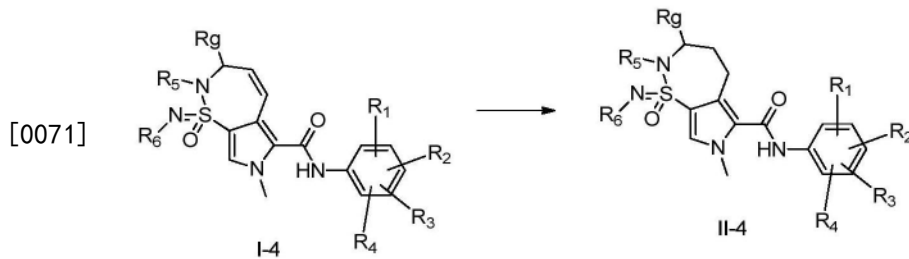


[0068]



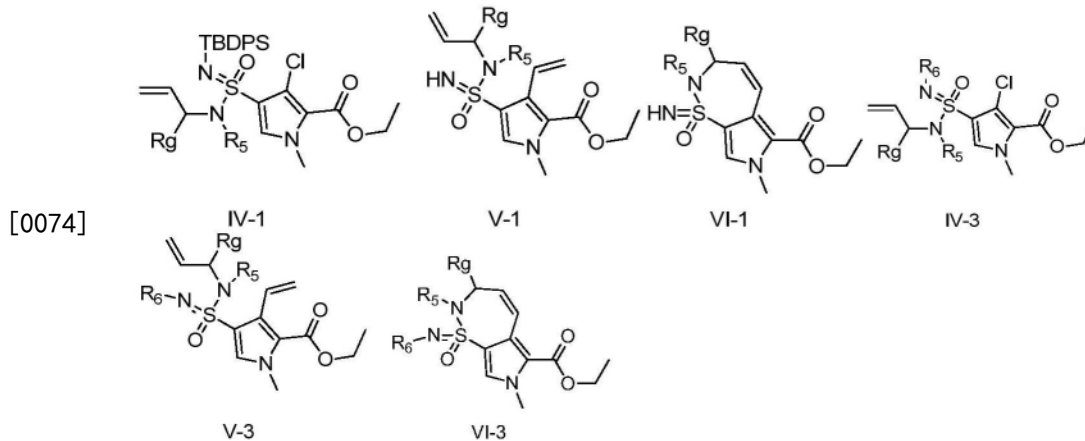
[0069] 各式中,各个基团的定义如上文中所述。

[0070] 在另一优选例中,所示式L化合物为式II-4所示的化合物,所述方法包括步骤:



[0072] 各式中,各个基团的定义如上文中所述。

[0073] 本发明的第三方面,提供了选自下组的化合物:



[0075] 各式中,Rg选自下组:H、卤素、-CN、羟基、氨基、羧基、-(C=O)-取代或未取代的C<sub>1</sub>-C<sub>8</sub>烷基、取代或未取代的C<sub>1</sub>-C<sub>8</sub>烷基、取代或未取代的C<sub>2</sub>-C<sub>6</sub>烯基、取代或未取代的C<sub>2</sub>-C<sub>6</sub>炔基、取代或未取代的C<sub>1</sub>-C<sub>8</sub>烷基胺基、取代或未取代的C<sub>1</sub>-C<sub>8</sub>烷氧基、取代或未取代的C<sub>3</sub>-C<sub>10</sub>环烷基、取代或未取代的具有1-3个选自下组N、S和O的杂原子的3-10元杂环烷基、取代或未取代的C<sub>6</sub>-C<sub>10</sub>芳基、或取代或未取代的具有1-3个选自下组N、S和O的杂原子的5-10元杂芳基;

[0076] 各个基团的定义如本发明第一方面所述。

[0077] 本发明的第四方面,提供了一种药物组合物,包含(1)如本发明第一方面所述的化合物或其立体异构体或互变异构体,或其药学上可接受的盐、水合物或溶剂化物;(2)药学上可接受的载体。

[0078] 本发明的第五方面,提供了一种如本发明第一方面所述的化合物或其立体异构体或互变异构体,或其药学上可接受的盐、水合物或溶剂化物或如本发明第四方面所述的药物组合物的用途,用于制备预防和/或治疗乙型肝炎病毒感染的药物。

[0079] 本发明的第六方面,提供了一种乙型肝炎病毒抑制剂,其特征在于,所述抑制剂包含本发明第一方面所述的化合物、或其立体异构体或互变异构体、或其药学上可接受的盐、水合物或溶剂化物。

[0080] 本发明的第七方面,提供了一种预防和/或治疗乙型肝炎的方法,包括步骤:向所需患者施用本发明第一方面所述的化合物、或其立体异构体或互变异构体、或其药学上可接受的盐、水合物或溶剂化物或本发明第四方面所述的药物组合物。

[0081] 本发明的第八方面,提供了一种抑制乙型肝炎病毒复制的方法,其特征在于,包括步骤:将本发明第一方面所述的化合物、或其立体异构体或互变异构体、或其药学上可接受

的盐、水合物或溶剂化物,与乙型肝炎病毒接触,从而抑制乙型肝炎病毒复制。

[0082] 应理解,在本发明范围内中,本发明的上述各技术特征和在下文(如实施例)中具体描述的各技术特征之间都可以互相组合,从而构成新的或优选的技术方案。限于篇幅,在此不再一一累述。

### 具体实施方式

[0083] 本发明人经过广泛而深入的研究,发现了一类对乙型肝炎具有优异的治疗效果的新型化合物。在此基础上,发明人完成了本发明。

[0084] 定义

[0085] 如本文所用,术语“烷基”包括直链或支链的烷基。例如 $C_1-C_8$ 烷基表示具有1-8个碳原子的直链或支链的烷基,例如甲基、乙基、丙基、异丙基、丁基、异丁基、叔丁基等。

[0086] 如本文所用,术语“烯基”包括直链或支链的烯基。例如 $C_2-C_6$ 烯基指具有2-6个碳原子的直链或支链的烯基,例如乙烯基、烯丙基、1-丙烯基、异丙烯基、1-丁烯基、2-丁烯基、或类似基团。

[0087] 如本文所用,术语“炔基”包括直链或支链的炔基。例如 $C_2-C_6$ 炔基是指具有2-6个碳原子的直链或支链的炔基,例如乙炔基、丙炔基、丁炔基、或类似基团。

[0088] 如本文所用,术语“ $C_3-C_{10}$ 环烷基”指具有3-10个碳原子的环烷基。其可以是单环,例如环丙基、环丁基、环戊基、环己基、或类似基团。也可以是双环形式,例如桥环或螺环形式。

[0089] 如本文所用,术语“ $C_1-C_8$ 烷胺基”是指被 $C_1-C_8$ 烷基所取代的胺基,可以是单取代或双取代的;例如,甲胺基、乙胺基、丙胺基、异丙胺基、丁胺基、异丁胺基、叔丁胺基、二甲胺基、二乙胺基、二丙胺基、二异丙胺基、二丁胺基、二异丁胺基、二叔丁胺基等。

[0090] 如本文所用,术语“ $C_1-C_8$ 烷氧基”是指具有1-8个碳原子的直链或支链的烷氧基;例如,甲氧基、乙氧基、丙氧基、异丙氧基、丁氧基、异丁氧基、叔丁氧基等。

[0091] 如本文所用,术语“具有1-3个选自下组N、S和O的杂原子的3-10元杂环烷基”是指具有3-10个原子的且其中1-3个原子为选自下组N、S和O的杂原子的饱和或部分饱和的环状基团。其可以是单环,也可以是双环形式,例如桥环或螺环形式。具体的实例可以为氧杂环丁烷、氮杂环丁烷、四氢-2H-吡喃基、哌啶基、四氢呋喃基、吗啉基和吡咯烷基等。

[0092] 如本文所用,术语“ $C_6-C_{10}$ 芳基”是指具有6-10个碳原子的芳基,例如,苯基或萘基等类似基团。

[0093] 如本文所用,术语“具有1-3个选自下组N、S和O的杂原子的5-10元杂芳基”指具有5-10个原子的且其中1-3个原子为选自下组N、S和O的杂原子的环状芳香基团。其可以是单环,也可以是稠环形式。具体的实例可以为吡啶基、哒嗪基、嘧啶基、吡嗪基、三嗪基、吡咯基、吡唑基、咪唑基、(1,2,3)-三唑基以及(1,2,4)-三唑基、四唑基、呋喃基、噻吩基、异恶唑基、噻唑基、恶唑基等。

[0094] 本发明所述的基团除非特别说明是“取代的或未取代的”,否则本发明的基团均可被选自下组的取代基所取代:卤素、腈基、硝基、羧基、氨基、 $C_1-C_6$ 烷基-胺基、 $C_1-C_6$ 烷基、 $C_2-C_6$ 烯基、 $C_2-C_6$ 炔基、 $C_1-C_6$ 烷氧基、卤代 $C_1-C_6$ 烷基、卤代 $C_2-C_6$ 烯基、卤代 $C_2-C_6$ 炔基、卤代 $C_1-C_6$ 烷氧基、烯丙基、苄基、 $C_6-C_{12}$ 芳基、 $C_1-C_6$ 烷氧基- $C_1-C_6$ 烷基、 $C_1-C_6$ 烷氧基-羰基、苯氧羰基、

C<sub>2</sub>-C<sub>6</sub>炔基-羰基、C<sub>2</sub>-C<sub>6</sub>烯基-羰基、C<sub>3</sub>-C<sub>6</sub>环烷基-羰基、C<sub>1</sub>-C<sub>6</sub>烷基-磺酰基等。

[0095] 如本文所用,“卤素”或“卤原子”指F、Cl、Br、和I。更佳地,卤素或卤原子选自F、Cl和Br。“卤代的”是指被选自F、Cl、Br、和I的原子所取代。

[0096] 除非特别说明,本发明所描述的结构式意在包括所有的同分异构形式(如对映异构,非对映异构和几何异构体(或构象异构体)):例如含有不对称中心的R、S构型,双键的(Z)、(E)异构体等。因此,本发明化合物的单个立体化学异构体或其对映异构体、非对映异构体或几何异构体(或构象异构体)的混合物都属于本发明的范围。

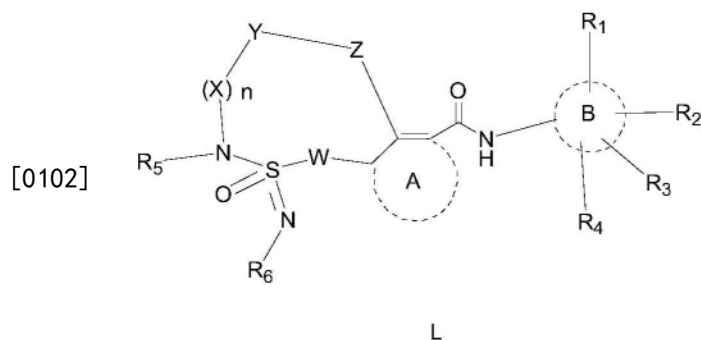
[0097] 如本文所用,术语“互变异构体”表示具有不同能量的结构同分异构体可以超过低能垒,从而互相转化。比如,质子互变异构体(即质子移变)包括通过质子迁移进行互变,如1H-吡唑与2H-吡唑。化合价互变异构体包括通过一些成键电子重组而进行互变。

[0098] 如本文所用,术语“溶剂合物”是指本发明化合物与溶剂分子配位形成特定比例的配合物。

[0099] 如本文所用,术语“水合物”是指本发明化合物与水进行配位形成的配合物。

[0100] 活性成分

[0101] 如本文所用,“本发明化合物”指式L所示的化合物,并且还包括及式L化合物的各种晶型形式、药学上可接受的盐、水合物或溶剂合物:



[0103] 如本文所用,“药学上可接受的盐”指本发明化合物与酸或碱所形成的适合用作药物的盐。药学上可接受的盐包括无机盐和有机盐。一类优选的盐是本发明化合物与酸形成的盐。适合形成盐的酸包括但不限于:盐酸、氢溴酸、氢氟酸、硫酸、硝酸、磷酸等无机酸,甲酸、乙酸、丙酸、草酸、丙二酸、琥珀酸、富马酸、马来酸、乳酸、苹果酸、酒石酸、柠檬酸、苦味酸、甲磺酸、苯甲磺酸,苯磺酸等有机酸;以及天冬氨酸、谷氨酸等酸性氨基酸。

[0104] 在另一优选例中,所述的A环、B环、R<sub>1</sub>、R<sub>2</sub>、R<sub>3</sub>、R<sub>4</sub>、R<sub>5</sub>、R<sub>6</sub>各自独立地为表1中各个化合物所对应的基团。

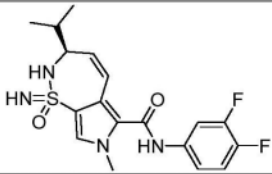
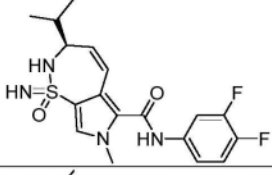
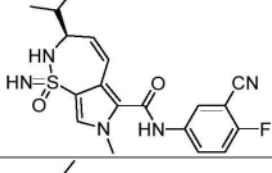
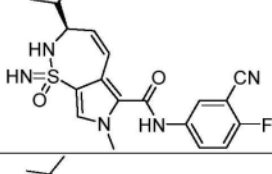
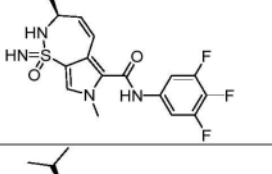
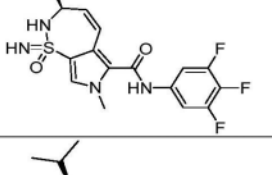
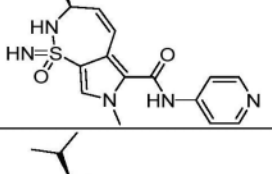
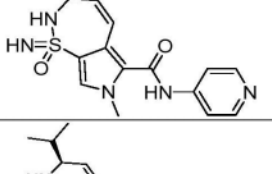
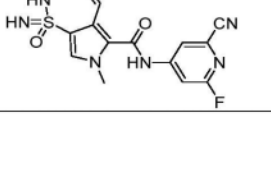
[0105] 优选的本发明化合物如表1所示:

[0106] 表1

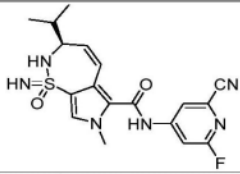
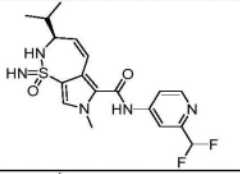
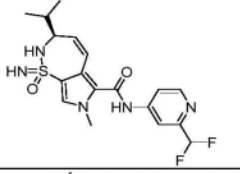
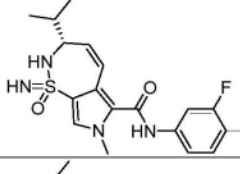
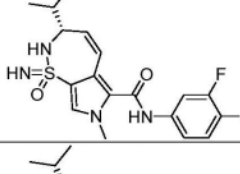
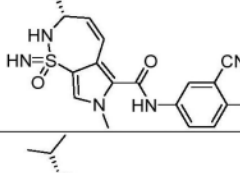
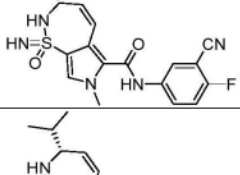
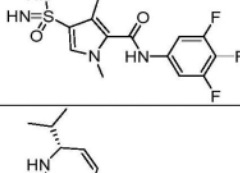
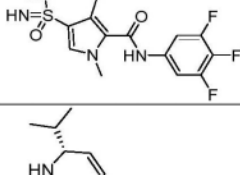
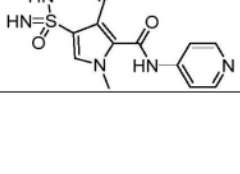
[0107]

编号	结构	质谱 ESI-MS, (M+H)	备注

[0108]

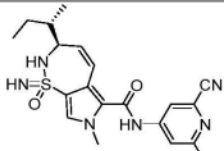
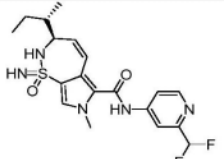
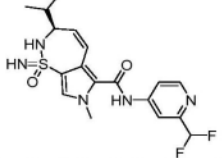
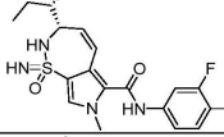
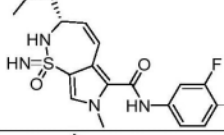
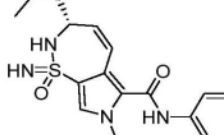
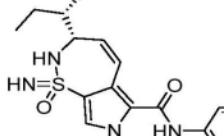
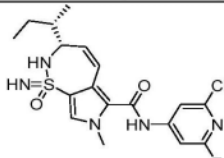
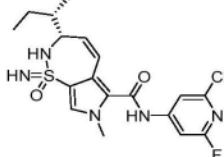
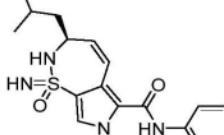
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10a2		395	Peak2 (HPLC)
10b1		402	Peak1 (HPLC)
10b2		402	Peak2 (HPLC)
10c1		413	Peak1 (HPLC)
10c2		413	Peak2 (HPLC)
10d1		360	Peak1 (HPLC)
10d2		360	Peak2 (HPLC)
10e1		403	Peak1 (HPLC)

[0109]

10e2		403	Peak2 (HPLC)
10f1		410	Peak1 (HPLC)
10f2		410	Peak2 (HPLC)
10g1		395	Peak1 (HPLC)
10g2		395	Peak2 (HPLC)
10h1		402	Peak1 (HPLC)
10h2		402	Peak2 (HPLC)
10i1		413	Peak1 (HPLC)
10i2		413	Peak2 (HPLC)
10j1		360	Peak1 (HPLC)

[0110]

10j2		360	Peak2 (HPLC)
10k1		403	Peak1 (HPLC)
10k2		403	Peak2 (HPLC)
10m1		410	Peak1 (HPLC)
10m2		410	Peak2 (HPLC)
10n1		409	Peak1 (HPLC)
10n2		409	Peak2 (HPLC)
10o1		416	Peak1 (HPLC)
10o2		416	Peak2 (HPLC)
10p1		417	Peak1 (HPLC)

10p2		417	Peak2 (HPLC)
10q1		424	Peak1 (HPLC)
10q2		424	Peak2 (HPLC)
10r1		409	Peak1 (HPLC)
10r2		409	Peak2 (HPLC)
10s1		374	Peak1 (HPLC)
10s2		374	Peak2 (HPLC)
10t1		417	Peak1 (HPLC)
10t2		417	Peak2 (HPLC)
10u1		409	Peak1 (HPLC)

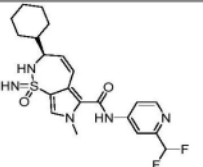
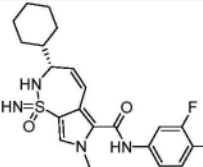
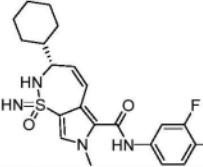
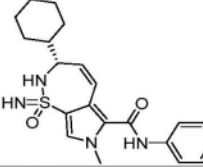
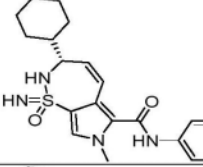
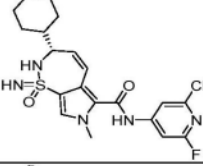
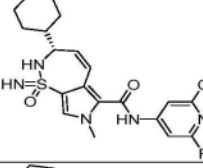
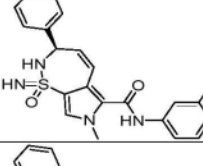
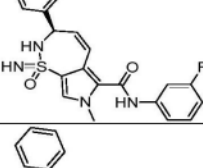
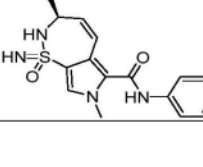
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[0112]

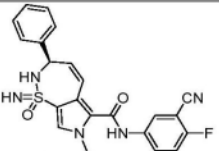
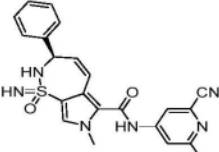
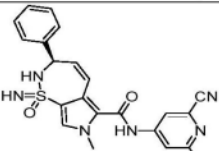
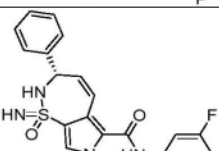
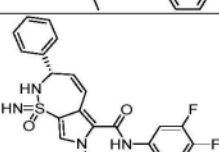
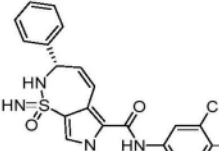
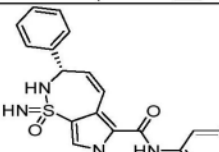
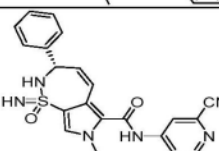
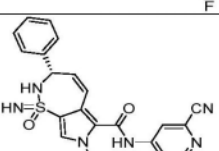
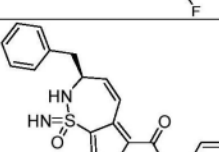
10u2		409	Peak2 (HPLC)
10v1		416	Peak1 (HPLC)
10v2		416	Peak2 (HPLC)
10w1		417	Peak1 (HPLC)
10w2		417	Peak2 (HPLC)
10x1		424	Peak1 (HPLC)
10x2		424	Peak2 (HPLC)
10y1		409	Peak1 (HPLC)
10y2		409	Peak2 (HPLC)
10z1		374	Peak1 (HPLC)

10z2		374	Peak2 (HPLC)
10aa1		417	Peak1 (HPLC)
10aa2		417	Peak2 (HPLC)
10bb1		435	Peak1 (HPLC)
10bb2		435	Peak2 (HPLC)
[0113] 10cc1		442	Peak1 (HPLC)
10cc2		442	Peak2 (HPLC)
10dd1		443	Peak1 (HPLC)
10dd2		443	Peak2 (HPLC)
10ee1		450	Peak1 (HPLC)

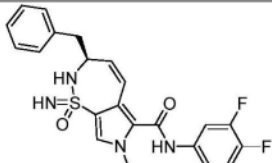
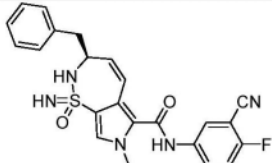
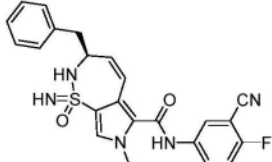
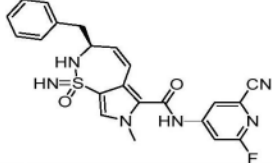
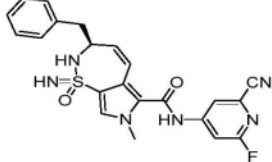
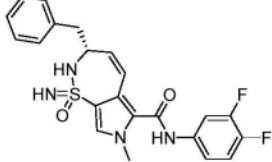
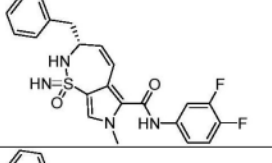
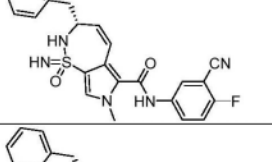
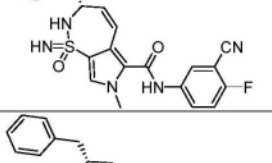
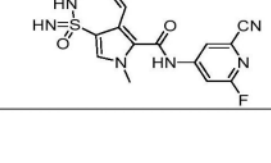
[0114]

10ee2		450	Peak2 (HPLC)
10ff1		435	Peak1 (HPLC)
10ff2		435	Peak2 (HPLC)
10gg1		400	Peak1 (HPLC)
10gg2		400	Peak2 (HPLC)
10hh1		443	Peak1 (HPLC)
10hh2		443	Peak2 (HPLC)
10ii1		429	Peak1 (HPLC)
10ii2		429	Peak2 (HPLC)
10jj1		436	Peak1 (HPLC)

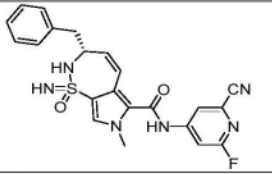
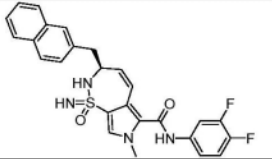
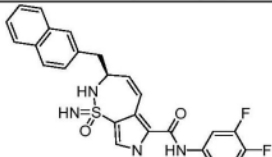
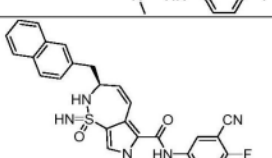
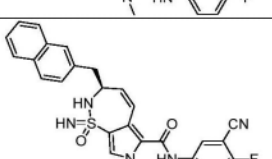
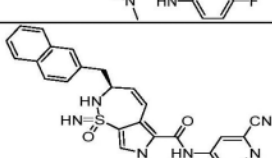
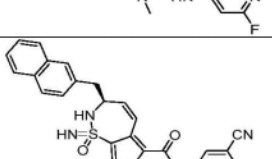
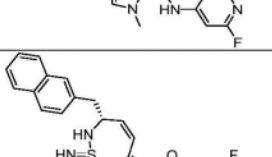
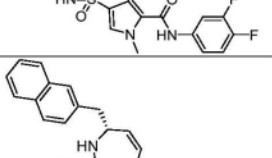
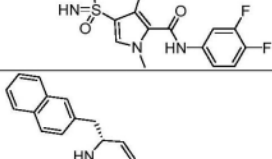
[0115]

10jj2		436	Peak2 (HPLC)
10kk1		437	Peak1 (HPLC)
10kk2		437	Peak2 (HPLC)
10mm1		429	Peak1 (HPLC)
10mm2		429	Peak2 (HPLC)
10nn1		436	Peak1 (HPLC)
10nn2		436	Peak2 (HPLC)
10oo1		437	Peak1 (HPLC)
10oo2		437	Peak2 (HPLC)
10pp1		443	Peak1 (HPLC)

[0116]

10pp2		443	Peak2 (HPLC)
10qq1		450	Peak1 (HPLC)
10qq2		450	Peak2 (HPLC)
10rr1		451	Peak1 (HPLC)
10rr2		451	Peak2 (HPLC)
10ss1		443	Peak1 (HPLC)
10ss2		443	Peak2 (HPLC)
10tt1		450	Peak1 (HPLC)
10tt2		450	Peak2 (HPLC)
10uu1		451	Peak1 (HPLC)

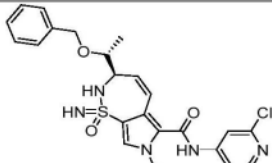
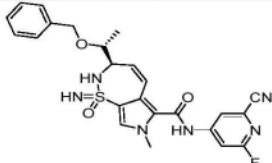
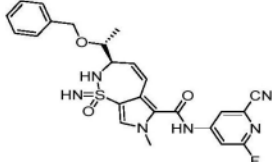
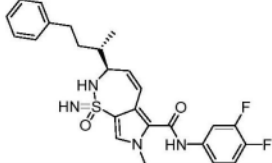
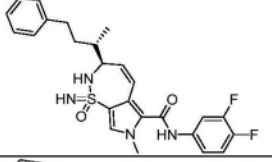
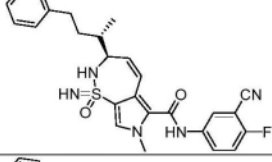
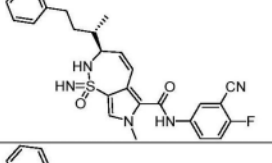
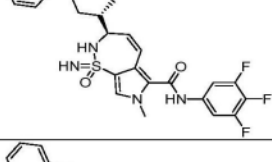
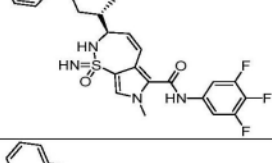
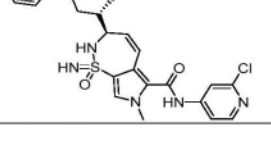
[0117]

10uu2		451	Peak2 (HPLC)
10vv1		493	Peak1 (HPLC)
10vv2		493	Peak2 (HPLC)
10ww1		500	Peak1 (HPLC)
10ww2		500	Peak2 (HPLC)
10xx1		501	Peak1 (HPLC)
10xx2		501	Peak2 (HPLC)
10yy1		493	Peak1 (HPLC)
10yy2		493	Peak2 (HPLC)
10zz1		500	Peak1 (HPLC)

[0118]

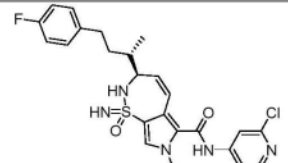
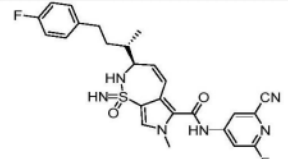
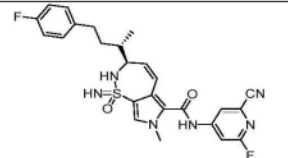
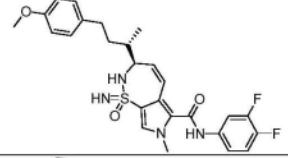
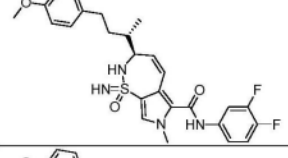
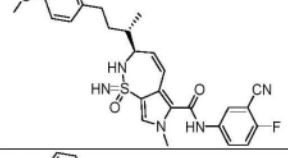
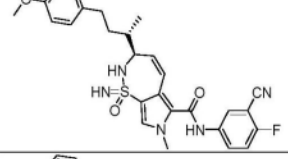
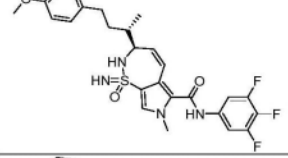
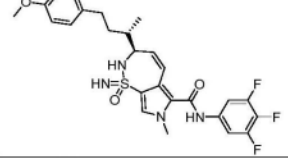
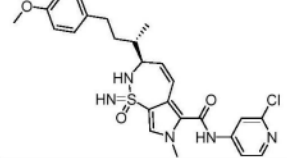
10zz2		500	Peak2 (HPLC)
10aaa1		501	Peak1 (HPLC)
10aaa2		501	Peak2 (HPLC)
10bbb1		487	Peak1 (HPLC)
10bbb2		487	Peak2 (HPLC)
10ccc1		494	Peak1 (HPLC)
10ccc2		494	Peak2 (HPLC)
10ddd1		505	Peak1 (HPLC)
10ddd2		505	Peak2 (HPLC)
10ece1		486	Peak1 (HPLC)

[0119]

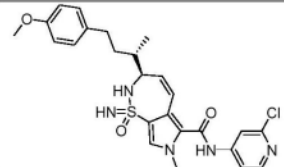
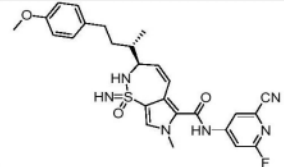
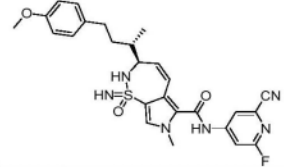
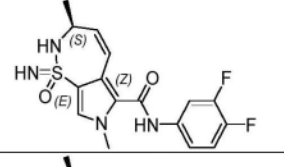
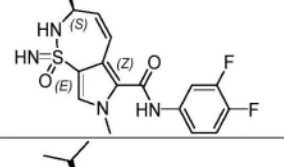
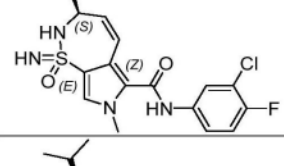
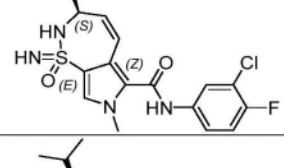
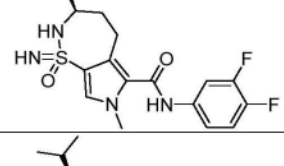
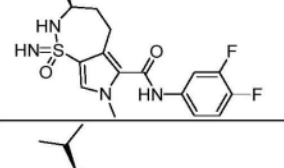
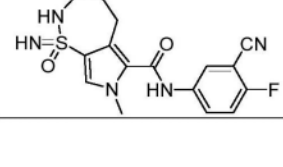
10eee2		486	Peak2 (HPLC)
10fff1		495	Peak1 (HPLC)
10fff2		495	Peak2 (HPLC)
10ggg1		485	Peak1 (HPLC)
10ggg2		485	Peak2 (HPLC)
10hhh1		492	Peak1 (HPLC)
10hhh2		492	Peak2 (HPLC)
10iii1		503	Peak1 (HPLC)
10iii2		503	Peak2 (HPLC)
10jjj1		484	Peak1 (HPLC)

[0120]

10jjj2		484	Peak2 (HPLC)
10kkk1		493	Peak1 (HPLC)
10kkk2		493	Peak2 (HPLC)
10mmm1		503	Peak1 (HPLC)
10mmm2		503	Peak2 (HPLC)
10nnn1		510	Peak1 (HPLC)
10nnn2		510	Peak2 (HPLC)
10ooo1		521	Peak1 (HPLC)
10ooo2		521	Peak2 (HPLC)
10ppp1		502	Peak1 (HPLC)

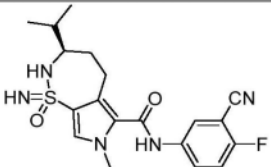
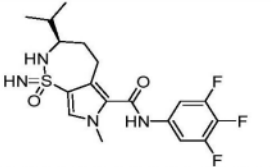
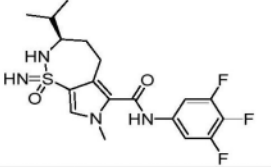
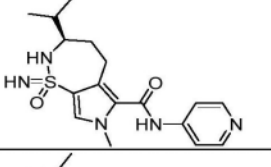
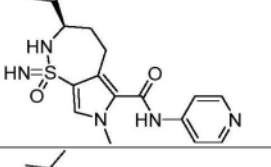
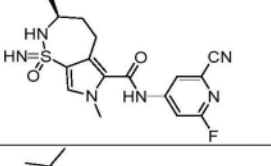
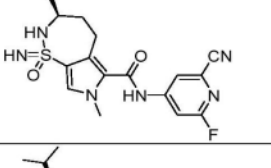
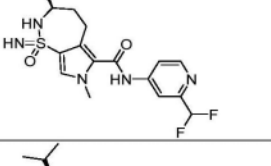
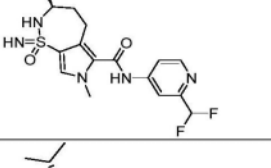
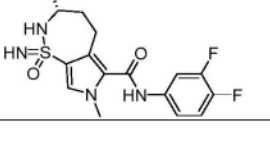
10ppp2		502	Peak2 (HPLC)
10qqq1		511	Peak1 (HPLC)
10qqq2		511	Peak2 (HPLC)
10rrr1		515	Peak1 (HPLC)
10rrr2		515	Peak2 (HPLC)
10sss1		522	Peak1 (HPLC)
10sss2		522	Peak2 (HPLC)
10ttt1		533	Peak1 (HPLC)
10ttt2		533	Peak2 (HPLC)
10uuu1		514	Peak1 (HPLC)

[0121]

10uuu2		514	Peak2 (HPLC)
10vvv1		523	Peak1 (HPLC)
10vvv2		523	Peak2 (HPLC)
10www1		367	Peak1 (HPLC)
10www2		367	Peak2 (HPLC)
10xxx1		411	Peak1 (HPLC)
10xxx2		411	Peak2 (HPLC)
20a1		397	Peak1 (HPLC)
20a2		397	Peak2 (HPLC)
20b1		404	Peak1 (HPLC)

[0122]

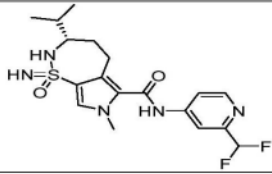
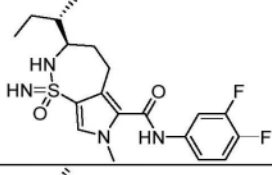
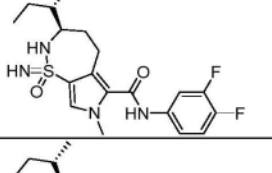
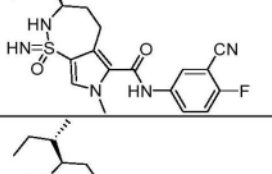
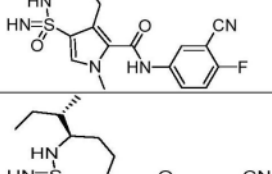
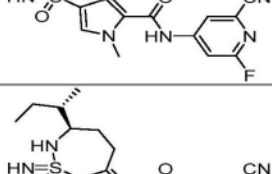
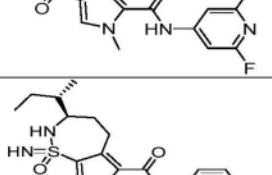
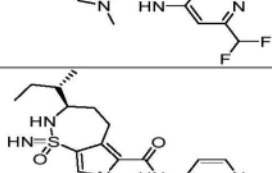
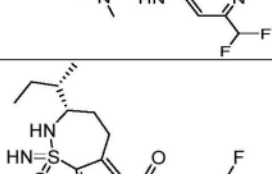
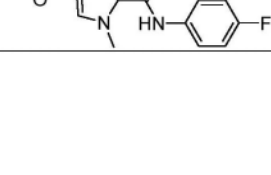
[0123]

20b2		404	Peak2 (HPLC)
20c1		415	Peak1 (HPLC)
20c2		415	Peak2 (HPLC)
20d1		362	Peak1 (HPLC)
20d2		362	Peak2 (HPLC)
20e1		405	Peak1 (HPLC)
20e2		405	Peak2 (HPLC)
20f1		412	Peak1 (HPLC)
20f2		412	Peak2 (HPLC)
20g1		397	Peak1 (HPLC)

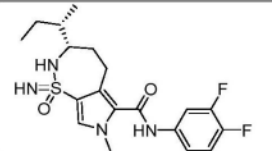
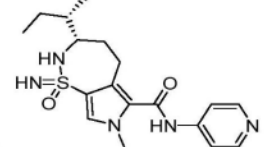
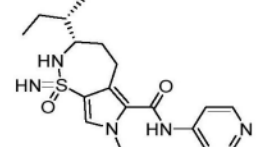
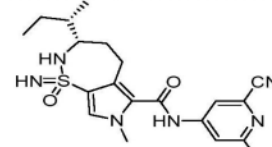
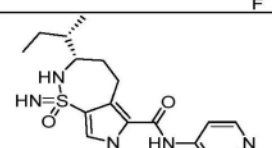
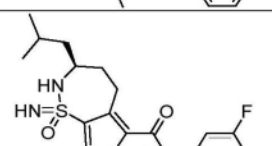
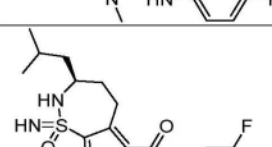
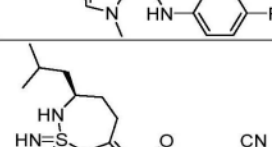
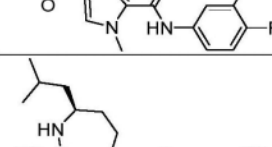
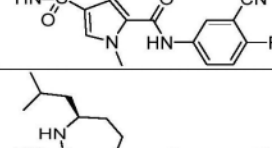
[0124]

20g2		397	Peak2 (HPLC)
20h1		404	Peak1 (HPLC)
20h2		404	Peak2 (HPLC)
20i1		415	Peak1 (HPLC)
20i2		415	Peak2 (HPLC)
20j1		362	Peak1 (HPLC)
20j2		362	Peak2 (HPLC)
20k1		405	Peak1 (HPLC)
20k2		405	Peak2 (HPLC)
20m1		412	Peak1 (HPLC)

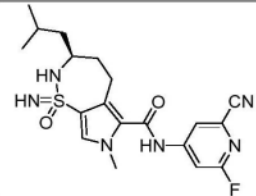
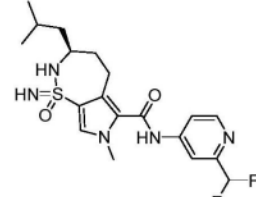
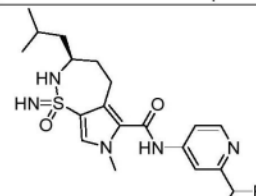
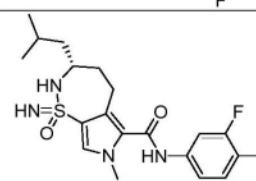
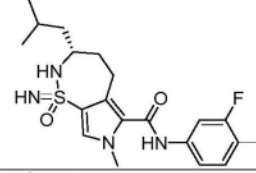
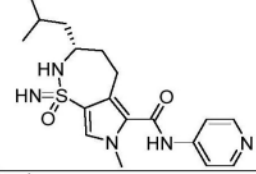
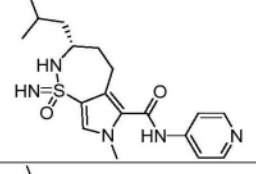
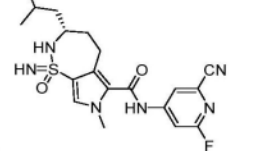
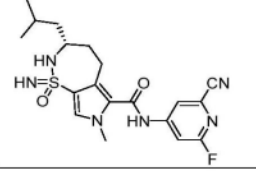
[0125]

10m2		412	Peak2 (HPLC)
20n1		411	Peak1 (HPLC)
20n2		411	Peak2 (HPLC)
20o1		418	Peak1 (HPLC)
20o2		418	Peak2 (HPLC)
20p1		419	Peak1 (HPLC)
20p2		419	Peak2 (HPLC)
20q1		426	Peak1 (HPLC)
20q2		426	Peak2 (HPLC)
20r1		411	Peak1 (HPLC)

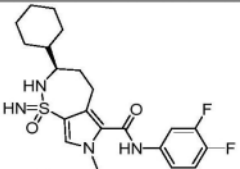
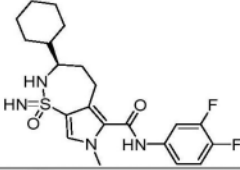
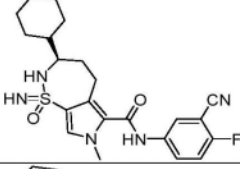
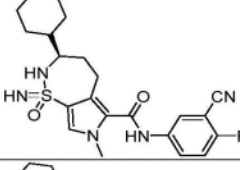
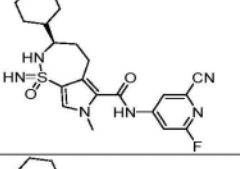
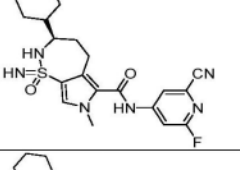
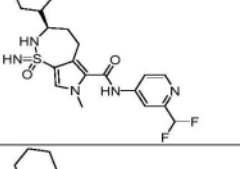
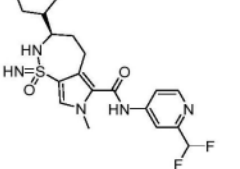
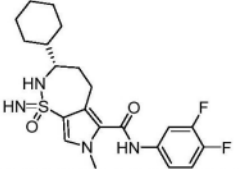
[0126]

20r2		411	Peak2 (HPLC)
20s1		376	Peak1 (HPLC)
20s2		376	Peak2 (HPLC)
20t1		419	Peak1 (HPLC)
20t2		419	Peak2 (HPLC)
20u1		411	Peak1 (HPLC)
20u2		411	Peak2 (HPLC)
20v1		418	Peak1 (HPLC)
20v2		418	Peak2 (HPLC)
20w1		419	Peak1 (HPLC)

[0127]

20w2		419	Peak2 (HPLC)
20x1		426	Peak1 (HPLC)
20x2		426	Peak2 (HPLC)
20y1		411	Peak1 (HPLC)
20y2		411	Peak2 (HPLC)
20z1		376	Peak1 (HPLC)
20z2		376	Peak2 (HPLC)
20aa1		419	Peak1 (HPLC)
20aa2		419	Peak2 (HPLC)

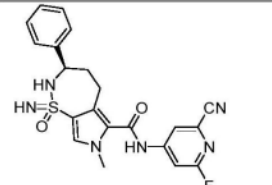
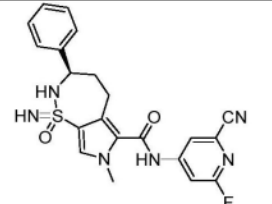
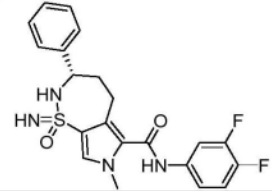
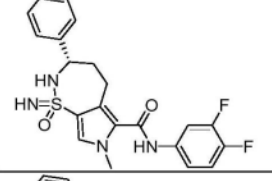
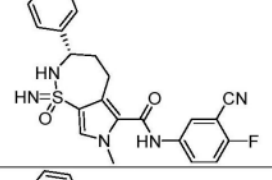
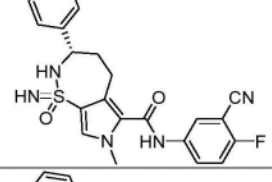
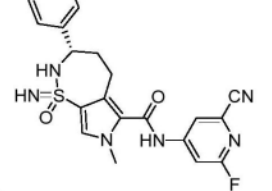
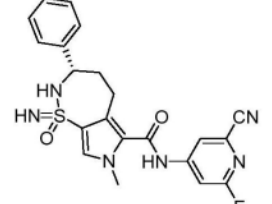
[0128]

20bb1		437	Peak1 (HPLC)
20bb2		437	Peak2 (HPLC)
20cc1		444	Peak1 (HPLC)
20cc2		444	Peak2 (HPLC)
20dd1		445	Peak1 (HPLC)
20dd2		445	Peak2 (HPLC)
20ee1		452	Peak1 (HPLC)
20ee2		452	Peak2 (HPLC)
20ff1		437	Peak1 (HPLC)

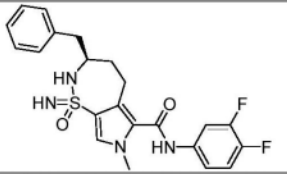
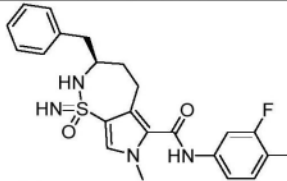
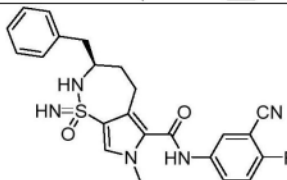
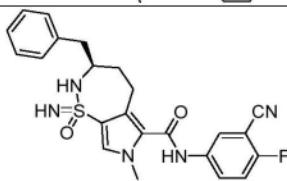
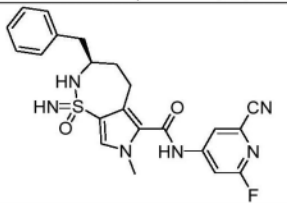
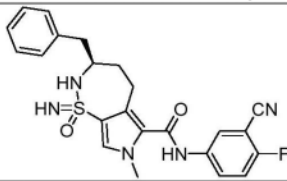
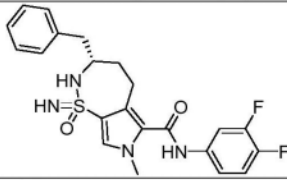
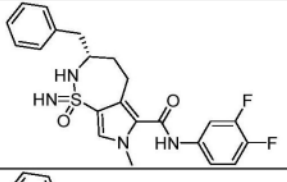
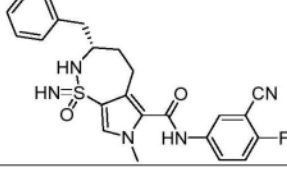
[0129]

20ff2		437	Peak2 (HPLC)
20gg1		402	Peak1 (HPLC)
20gg2		402	Peak2 (HPLC)
20hh1		445	Peak1 (HPLC)
20hh2		445	Peak2 (HPLC)
20ii1		431	Peak1 (HPLC)
20ii2		431	Peak2 (HPLC)
20jj1		438	Peak1 (HPLC)
20jj2		438	Peak2 (HPLC)

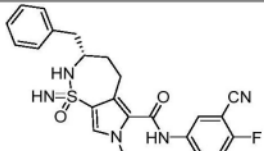
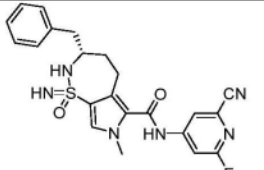
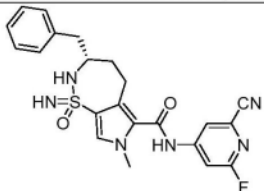
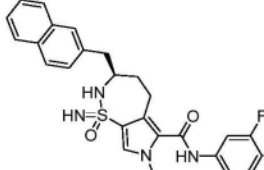
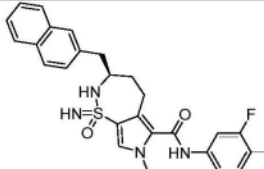
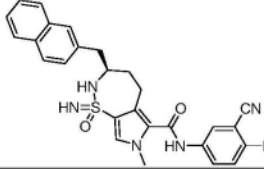
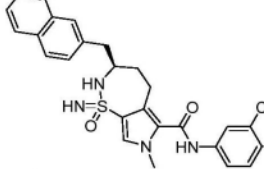
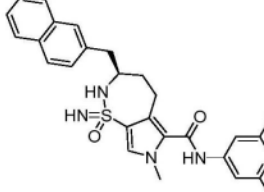
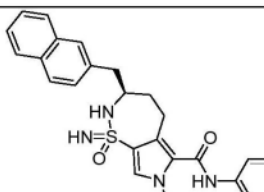
[0130]

20kk1		439	Peak1 (HPLC)
20kk2		439	Peak2 (HPLC)
20mm1		431	Peak1 (HPLC)
20mm2		431	Peak2 (HPLC)
20nn1		438	Peak1 (HPLC)
20nn2		438	Peak2 (HPLC)
20oo1		439	Peak1 (HPLC)
20oo2		439	Peak2 (HPLC)

[0131]

20pp1		445	Peak1 (HPLC)
20pp2		445	Peak2 (HPLC)
20qq1		452	Peak1 (HPLC)
20qq2		452	Peak2 (HPLC)
20rr1		453	Peak1 (HPLC)
20rr2		453	Peak2 (HPLC)
20ss1		445	Peak1 (HPLC)
20ss2		445	Peak2 (HPLC)
20tt1		452	Peak1 (HPLC)

[0132]

20tt2		452	Peak2 (HPLC)
20uu1		453	Peak1 (HPLC)
20uu2		453	Peak2 (HPLC)
20vv1		495	Peak1 (HPLC)
20vv2		495	Peak2 (HPLC)
20ww1		502	Peak1 (HPLC)
20ww2		502	Peak2 (HPLC)
20xx1		503	Peak1 (HPLC)
20xx2		503	Peak2 (HPLC)

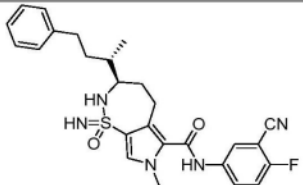
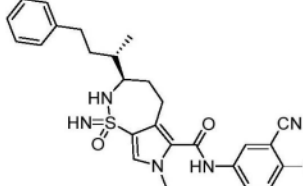
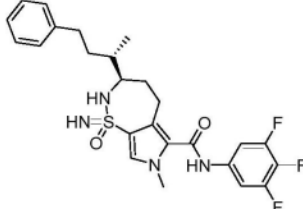
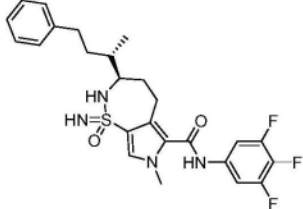
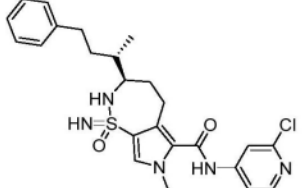
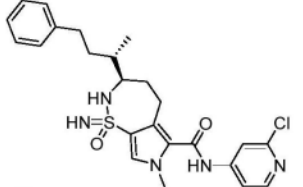
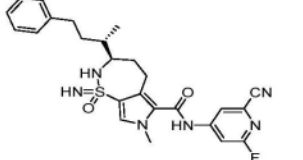
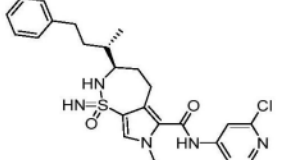
[0133]

20yy1		495	Peak1 (HPLC)
20yy2		495	Peak2 (HPLC)
20zz1		502	Peak1 (HPLC)
20zz2		502	Peak2 (HPLC)
20aaa1		503	Peak1 (HPLC)
20aaa2		503	Peak2 (HPLC)
20bbb1		489	Peak1 (HPLC)
20bbb2		489	Peak2 (HPLC)

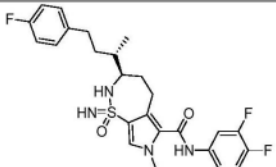
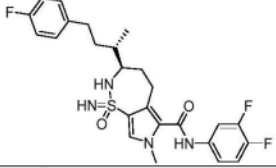
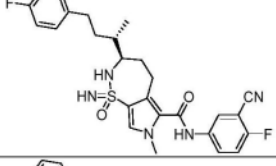
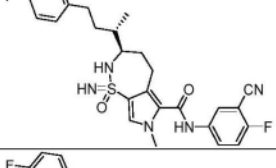
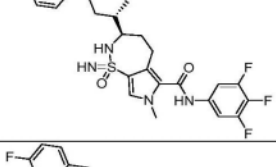
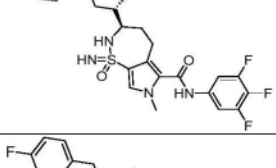
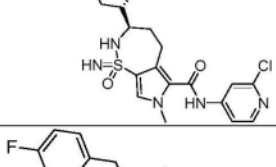
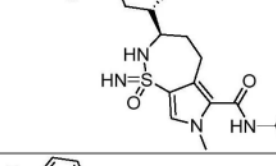
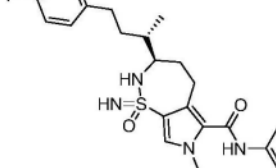
[0134]

20ccc1		496	Peak1 (HPLC)
20ccc2		496	Peak2 (HPLC)
20ddd1		507	Peak1 (HPLC)
20ddd2		507	Peak2 (HPLC)
20eee1		488	Peak1 (HPLC)
20eee2		488	Peak2 (HPLC)
20fff1		497	Peak1 (HPLC)
20fff2		497	Peak2 (HPLC)
20ggg1		486	Peak1 (HPLC)
20ggg2		486	Peak2 (HPLC)

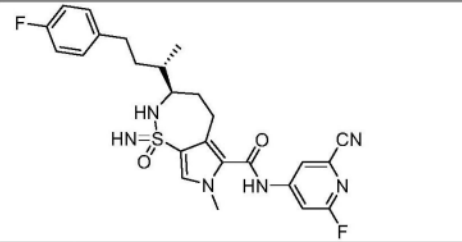
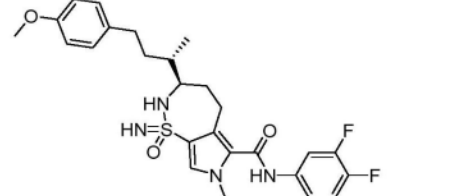
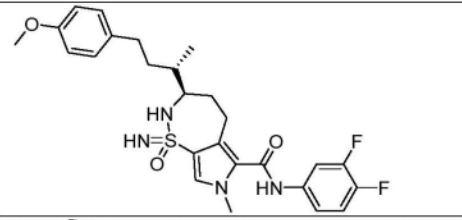
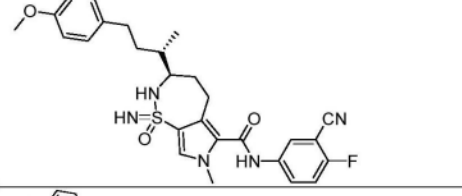
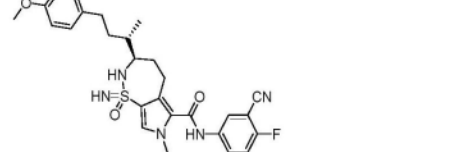
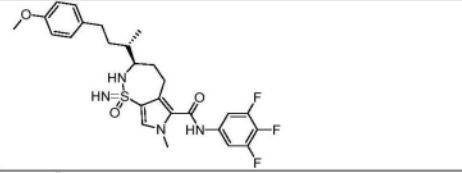
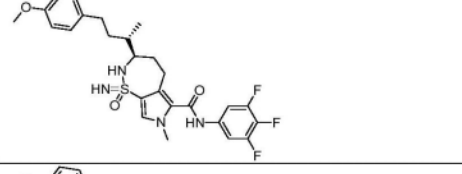
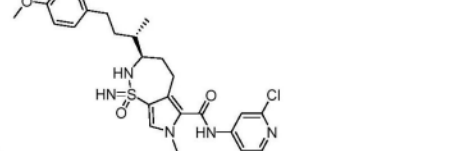
[0135]

20hhh1		494	Peak1 (HPLC)
20hhh2		494	Peak2 (HPLC)
20iii1		505	Peak1 (HPLC)
20iii2		505	Peak2 (HPLC)
20jjj1		486	Peak1 (HPLC)
20jjj2		486	Peak2 (HPLC)
20kkk1		495	Peak1 (HPLC)
20kkk2		495	Peak2 (HPLC)

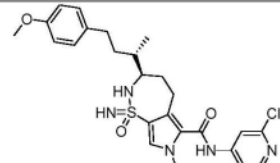
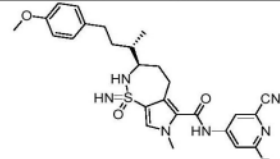
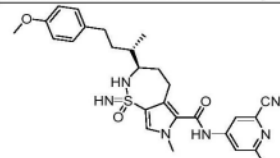
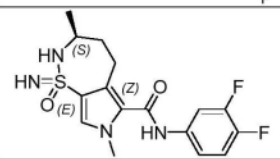
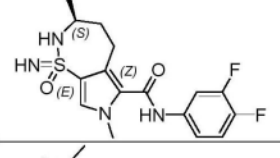
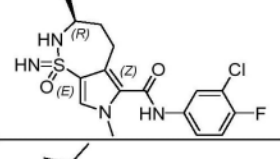
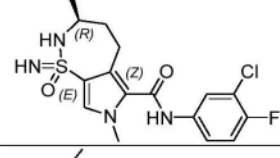
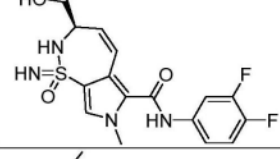
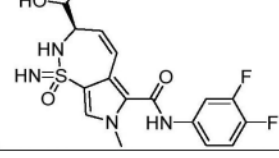
[0136]

20mmm1		505	Peak1 (HPLC)
20mmm2		505	Peak2 (HPLC)
20nnn1		512	Peak1 (HPLC)
20nnn2		512	Peak2 (HPLC)
20ooo1		523	Peak1 (HPLC)
20ooo2		523	Peak2 (HPLC)
20ppp1		504	Peak1 (HPLC)
20ppp2		504	Peak2 (HPLC)
20qqq1		513	Peak1 (HPLC)

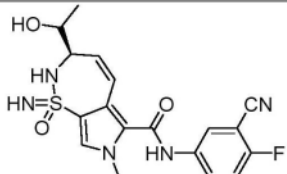
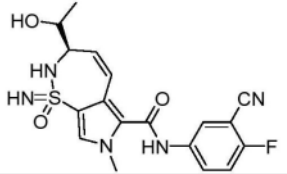
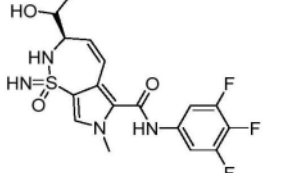
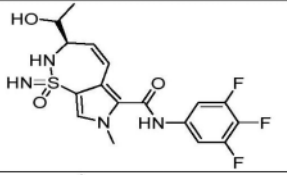
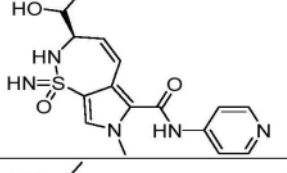
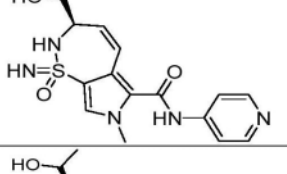
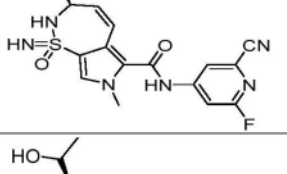
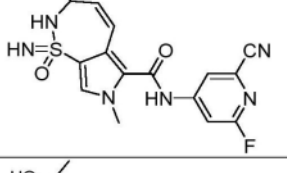
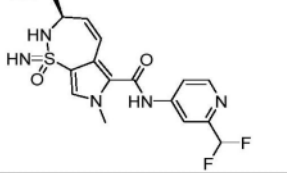
[0137]

20qqq2		513	Peak2 (HPLC)
20rrr1		517	Peak1 (HPLC)
20rrr2		517	Peak2 (HPLC)
20sss1		524	Peak1 (HPLC)
20sss2		524	Peak2 (HPLC)
20ttt1		535	Peak1 (HPLC)
20ttt2		535	Peak2 (HPLC)
20uuu1		516	Peak1 (HPLC)

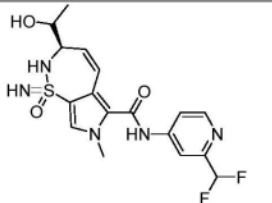
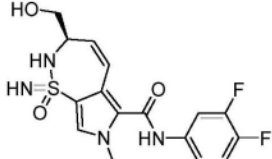
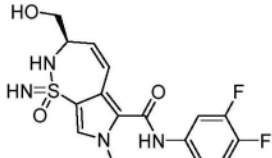
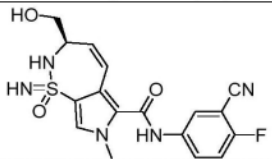
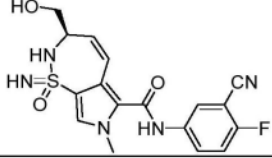
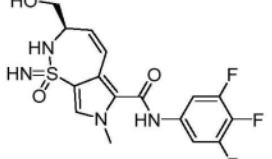
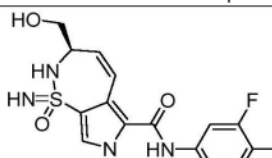
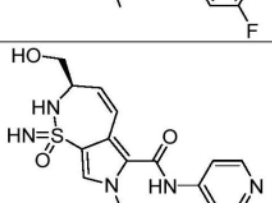
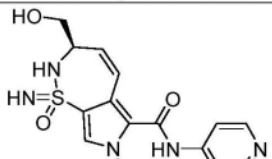
[0138]

20uuu2		516	Peak2 (HPLC)
20vvv1		525	Peak1 (HPLC)
20vvv2		525	Peak2 (HPLC)
20www1		369	Peak1 (HPLC)
20www2		369	Peak2 (HPLC)
20xxx1		413	Peak1 (HPLC)
20xxx2		413	Peak2 (HPLC)
30a1		397	Peak1 (HPLC)
30a2		397	Peak2 (HPLC)

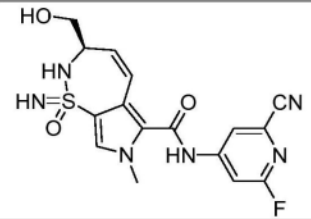
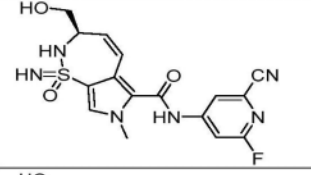
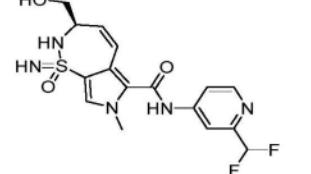
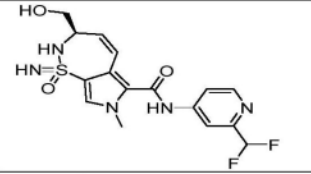
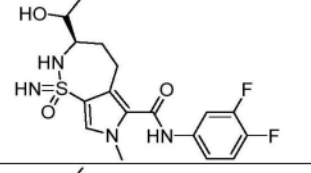
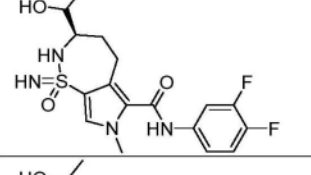
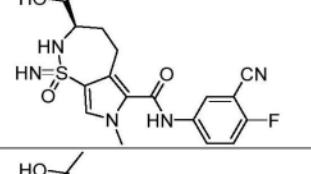
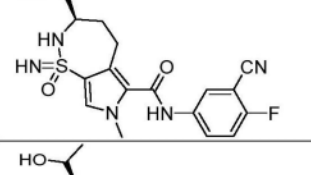
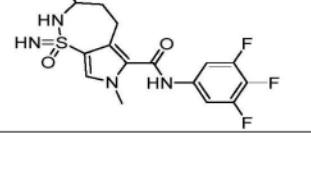
[0139]

30b1		404	Peak1 (HPLC)
30b2		404	Peak2 (HPLC)
30c1		415	Peak1 (HPLC)
30c2		415	Peak2 (HPLC)
30d1		362	Peak1 (HPLC)
30d2		362	Peak2 (HPLC)
30e1		405	Peak1 (HPLC)
30e2		405	Peak2 (HPLC)
30f1		412	Peak1 (HPLC)

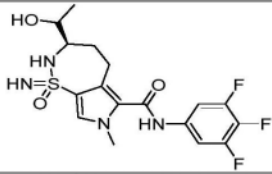
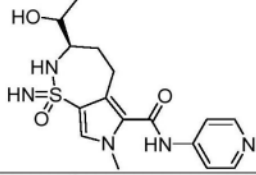
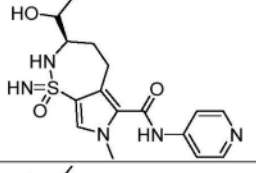
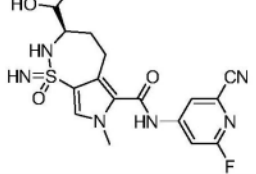
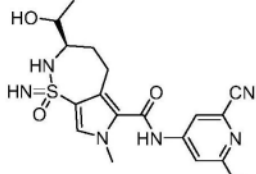
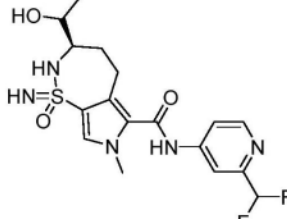
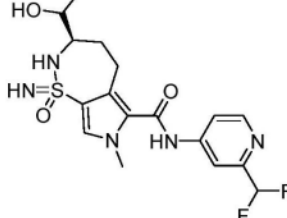
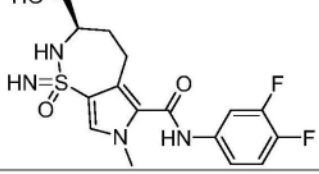
[0140]

30f2		412	Peak2 (HPLC)
30g1		383	Peak1 (HPLC)
30g2		383	Peak2 (HPLC)
30h1		390	Peak1 (HPLC)
30h2		390	Peak2 (HPLC)
30i1		401	Peak1 (HPLC)
30i2		401	Peak2 (HPLC)
30j1		348	Peak1 (HPLC)
30j2		348	Peak2 (HPLC)

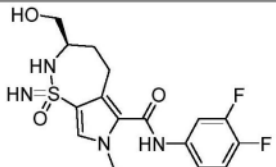
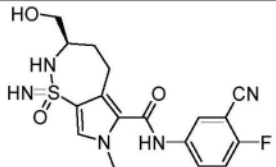
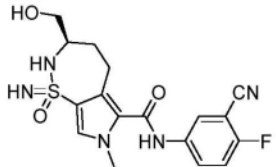
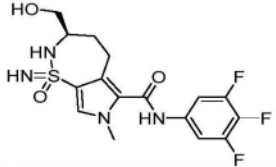
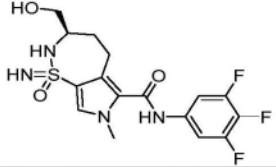
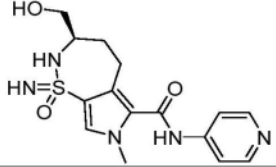
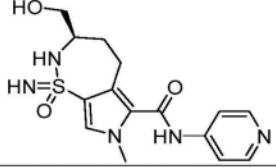
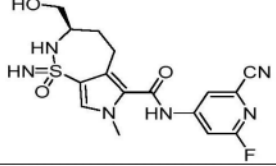
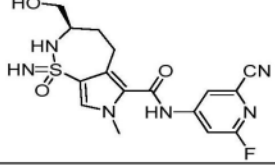
[0141]

30k1		391	Peak1 (HPLC)
30k2		391	Peak2 (HPLC)
30m1		398	Peak1 (HPLC)
30m2		398	Peak2 (HPLC)
40a1		399	Peak1 (HPLC)
40a2		399	Peak2 (HPLC)
40b1		406	Peak1 (HPLC)
40b2		406	Peak2 (HPLC)
40c1		417	Peak1 (HPLC)

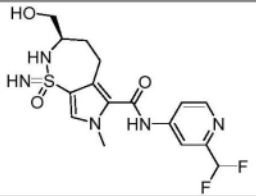
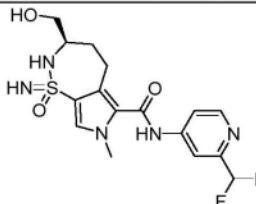
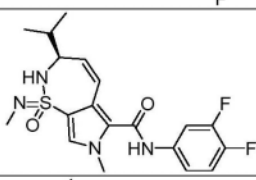
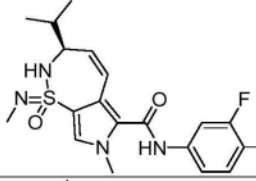
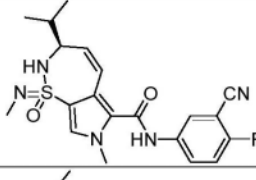
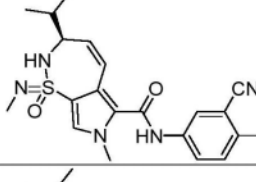
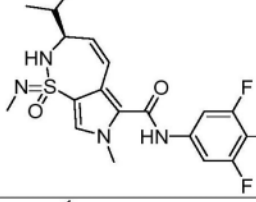
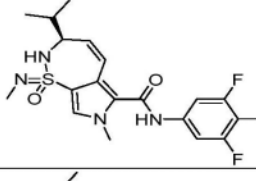
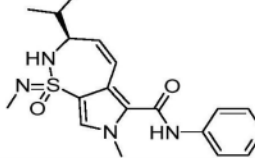
[0142]

40c2		417	Peak2 (HPLC)
40d1		364	Peak1 (HPLC)
40d2		364	Peak2 (HPLC)
40e1		407	Peak1 (HPLC)
40e2		407	Peak2 (HPLC)
40f1		414	Peak1 (HPLC)
40f2		414	Peak2 (HPLC)
40g1		385	Peak1 (HPLC)

[0143]

40g2		385	Peak2 (HPLC)
40h1		392	Peak1 (HPLC)
40h2		392	Peak2 (HPLC)
40i1		403	Peak1 (HPLC)
40i2		403	Peak2 (HPLC)
40j1		350	Peak1 (HPLC)
40j2		350	Peak2 (HPLC)
40k1		393	Peak1 (HPLC)
40k2		393	Peak2 (HPLC)

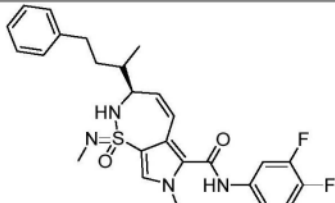
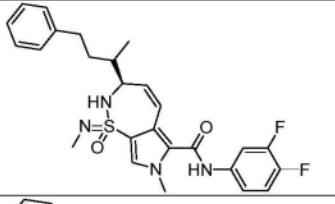
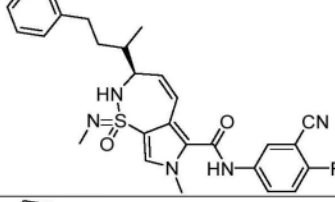
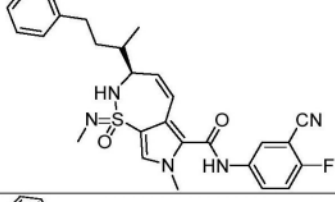
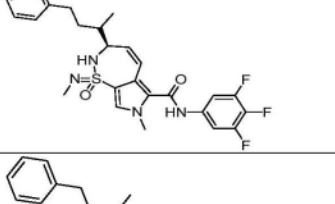
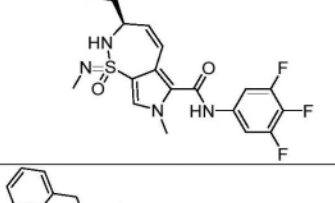
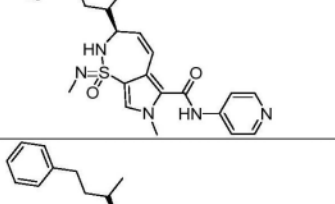
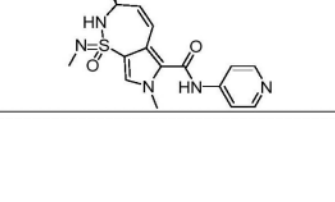
[0144]

40m1		400	Peak1 (HPLC)
40m2		400	Peak2 (HPLC)
50a1		409	Peak1 (HPLC)
50a2		409	Peak2 (HPLC)
50b1		416	Peak1 (HPLC)
50b2		416	Peak2 (HPLC)
50c1		413	Peak1 (HPLC)
50c2		427	Peak2 (HPLC)
50d1		374	Peak1 (HPLC)

[0145]

50d2		360	Peak2 (HPLC)
50e1		417	Peak1 (HPLC)
50e2		417	Peak2 (HPLC)
50f1		423	Peak1 (HPLC)
50f2		423	Peak2 (HPLC)
50g1		430	Peak1 (HPLC)
50g2		430	Peak2 (HPLC)
50h1		442	Peak1 (HPLC)
50h2		442	Peak2 (HPLC)

[0146]

50i1		499	Peak1 (HPLC)
50i2		499	Peak2 (HPLC)
50j1		506	Peak1 (HPLC)
50j2		506	Peak2 (HPLC)
50k1		517	Peak1 (HPLC)
50k2		427	Peak2 (HPLC)
50m1		464	Peak1 (HPLC)
50m2		464	Peak2 (HPLC)

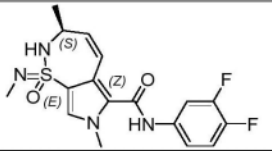
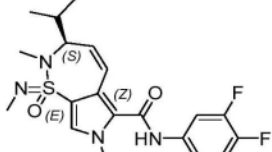
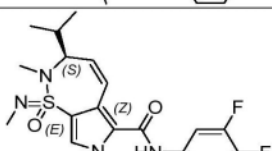
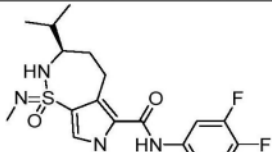
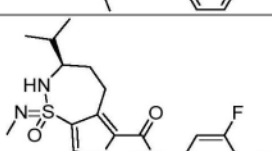
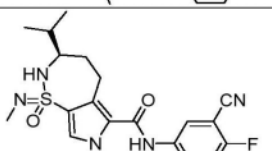
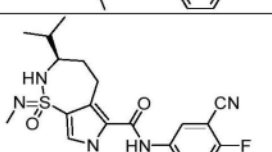
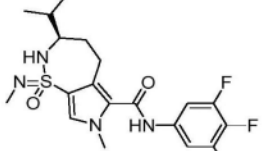
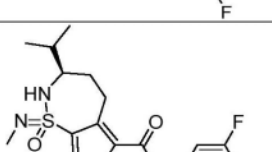
[0147]

50n1		507	Peak1 (HPLC)
50n2		507	Peak2 (HPLC)
50o1		513	Peak1 (HPLC)
50o2		513	Peak2 (HPLC)
50p1		520	Peak1 (HPLC)
50p2		520	Peak2 (HPLC)
50q1		525	Peak1 (HPLC)
50q2		525	Peak2 (HPLC)
50r1		532	Peak1 (HPLC)

[0148]

50r2		532	Peak2 (HPLC)
50s1		430	Peak1 (HPLC)
50s2		430	Peak2 (HPLC)
50t1		444	Peak1 (HPLC)
50t2		444	Peak2 (HPLC)
50u1		458	Peak1 (HPLC)
50u2		458	Peak2 (HPLC)
50v1		456	Peak1 (HPLC)
50v2		456	Peak2 (HPLC)
50w1		381	Peak1 (HPLC)

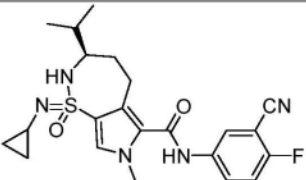
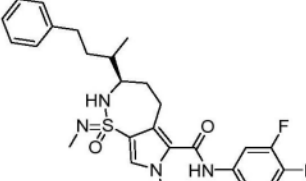
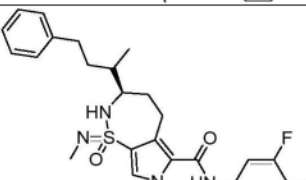
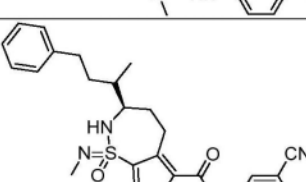
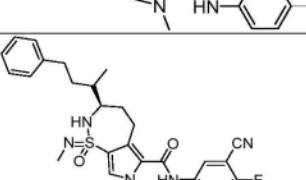
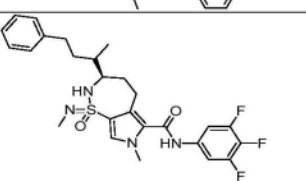
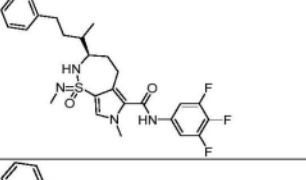
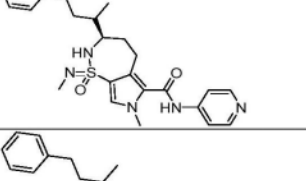
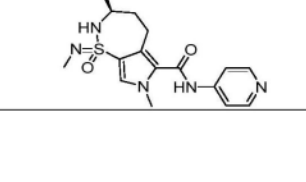
[0149]

50w2		381	Peak2 (HPLC)
50x1		423	Peak1 (HPLC)
50x2		423	Peak2 (HPLC)
60a1		411	Peak1 (HPLC)
60a2		411	Peak2 (HPLC)
60b1		418	Peak1 (HPLC)
60b2		418	Peak2 (HPLC)
60c1		429	Peak1 (HPLC)
60c2		429	Peak2 (HPLC)

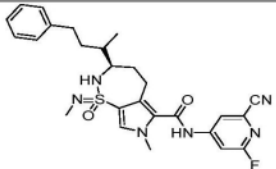
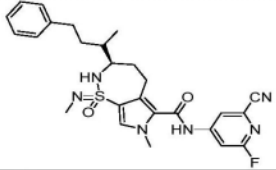
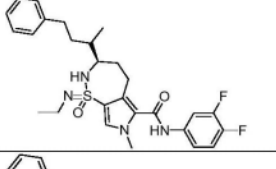
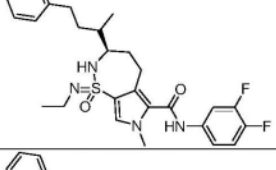
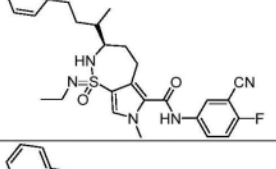
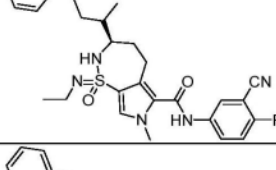
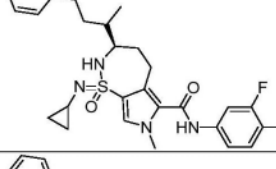
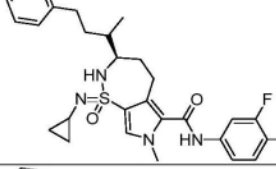
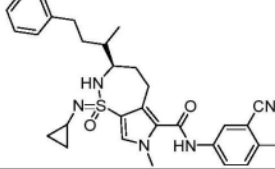
[0150]

60d1		376	Peak1 (HPLC)
60d2		376	Peak2 (HPLC)
60e1		419	Peak1 (HPLC)
60e2		419	Peak2 (HPLC)
60f1		425	Peak1 (HPLC)
60f2		425	Peak2 (HPLC)
60g1		432	Peak1 (HPLC)
60g2		432	Peak2 (HPLC)
60h1		446	Peak1 (HPLC)

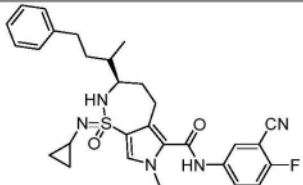
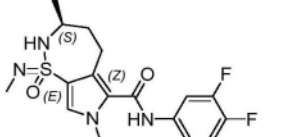
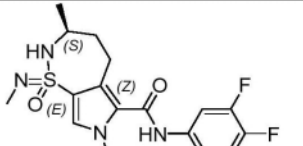
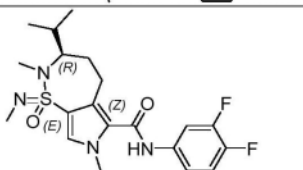
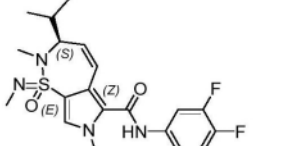
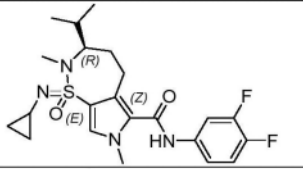
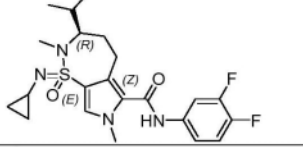
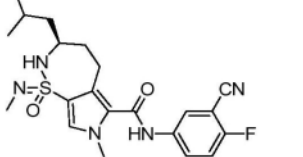
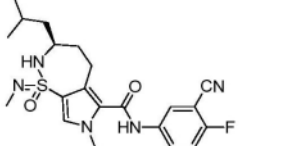
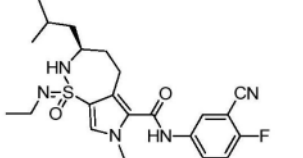
[0151]

60h2		446	Peak2 (HPLC)
60i1		501	Peak1 (HPLC)
60i2		501	Peak2 (HPLC)
60j1		508	Peak1 (HPLC)
60j2		508	Peak2 (HPLC)
60k1		519	Peak1 (HPLC)
60k2		519	Peak2 (HPLC)
60m1		466	Peak1 (HPLC)
60m2		466	Peak2 (HPLC)

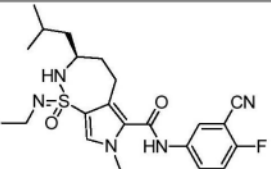
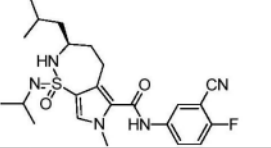
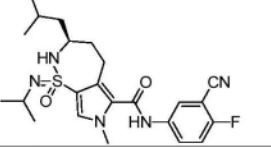
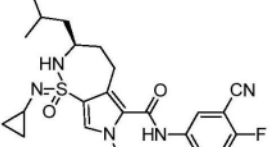
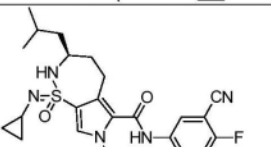
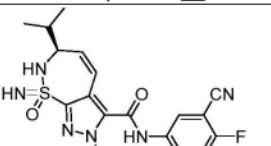
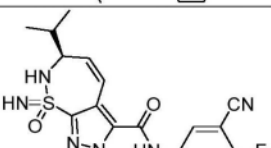
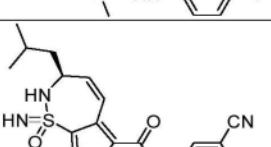
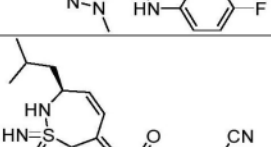
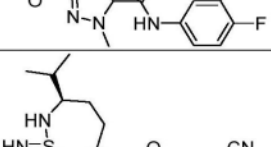
[0152]

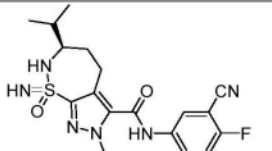
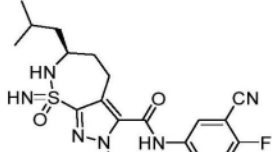
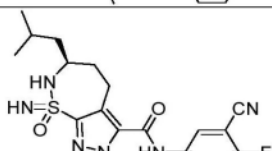
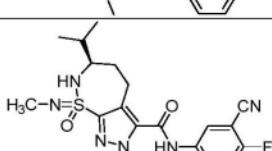
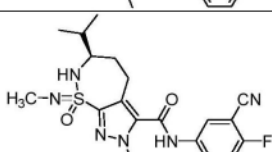
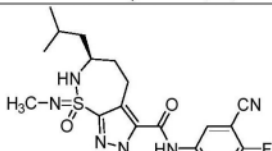
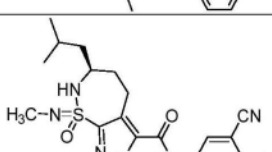
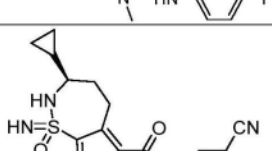
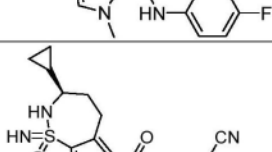
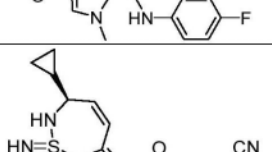
60n1		509	Peak1 (HPLC)
60n2		509	Peak2 (HPLC)
60o1		515	Peak1 (HPLC)
60o2		515	Peak2 (HPLC)
60p1		522	Peak1 (HPLC)
60p2		522	Peak2 (HPLC)
60q1		527	Peak1 (HPLC)
60q2		527	Peak2 (HPLC)
60r1		534	Peak1 (HPLC)

[0153]

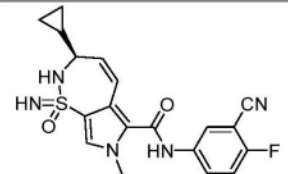
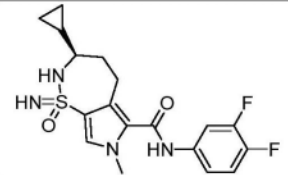
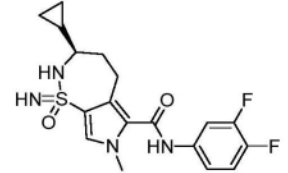
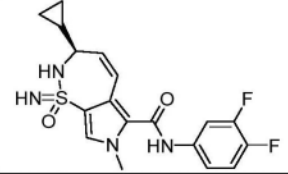
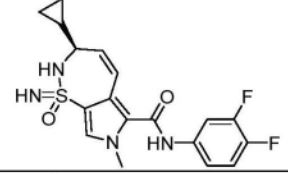
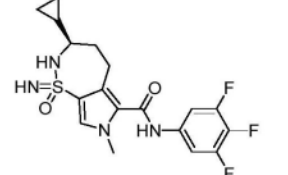
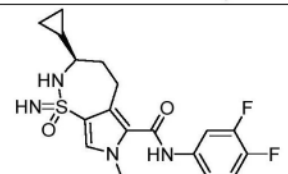
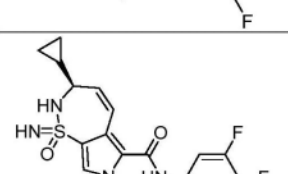
60r2		534	Peak2 (HPLC)
60s1		383	Peak1 (HPLC)
60s2		383	Peak2 (HPLC)
60t1		425	Peak1 (HPLC)
60t2		425	Peak2 (HPLC)
60u1		451	Peak1 (HPLC)
60u2		451	Peak2 (HPLC)
60v1		432	Peak1 (HPLC)
60v2		432	Peak2 (HPLC)
60w1		446	Peak1 (HPLC)

[0154]

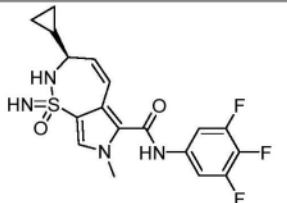
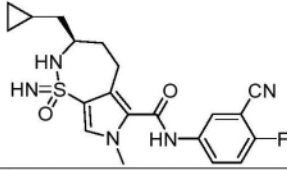
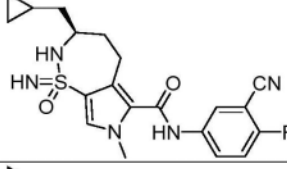
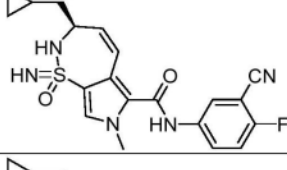
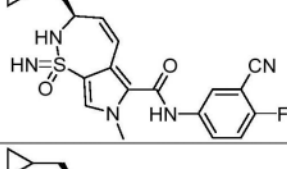
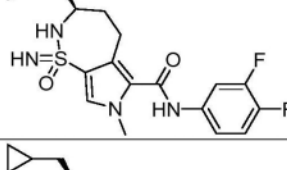
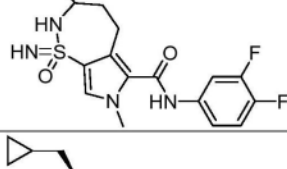
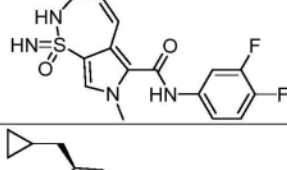
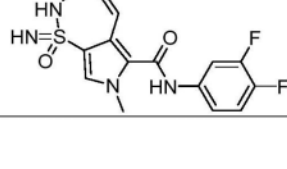
60w2		446	Peak2 (HPLC)
60x1		460	Peak1 (HPLC)
60x2		460	Peak2 (HPLC)
60y1		458	Peak1 (HPLC)
60y2		458	Peak2 (HPLC)
70a1		403	Peak1 (HPLC)
70a2		403	Peak2 (HPLC)
70b1		417	Peak1 (HPLC)
70b2		417	Peak2 (HPLC)
80a1		405	Peak1 (HPLC)

80a2		405	Peak2 (HPLC)
80b1		419	Peak1 (HPLC)
80b2		419	Peak2 (HPLC)
90a1		419	Peak1 (HPLC)
90a2		419	Peak2 (HPLC)
[0155] 90b1		433	Peak1 (HPLC)
90b2		433	Peak2 (HPLC)
100a01		402	Peak1 (HPLC)
100a02		402	Peak2 (HPLC)
100a03		400	Peak1 (HPLC)

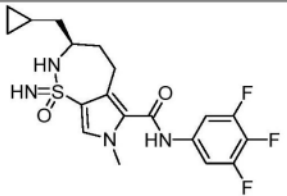
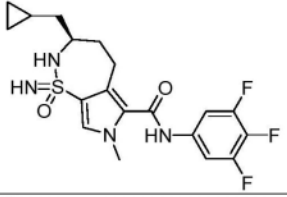
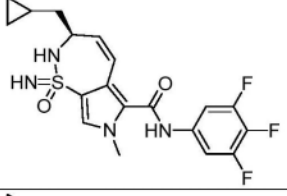
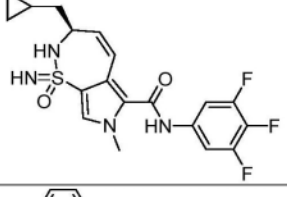
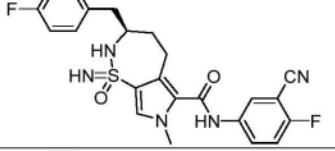
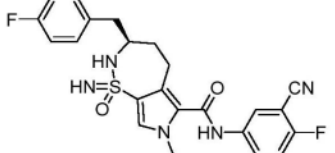
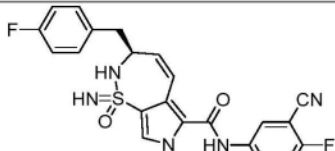
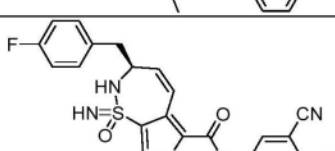
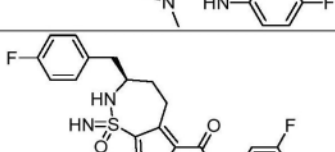
[0156]

100a04		400	Peak2 (HPLC)
100a05		395	Peak1 (HPLC)
100a06		395	Peak2 (HPLC)
100a07		393	Peak1 (HPLC)
100a08		393	Peak2 (HPLC)
100a09		413	Peak1 (HPLC)
100a10		413	Peak2 (HPLC)
100a11		411	Peak1 (HPLC)

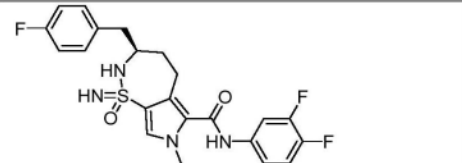
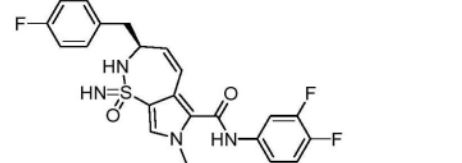
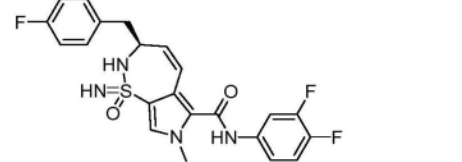
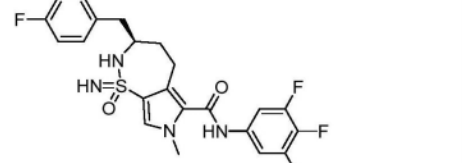
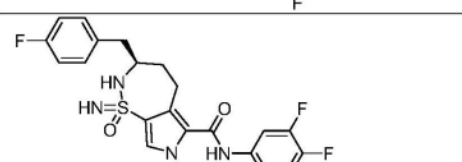
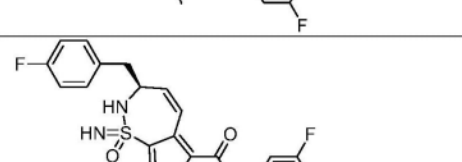
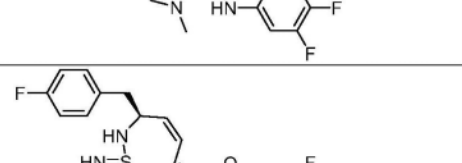
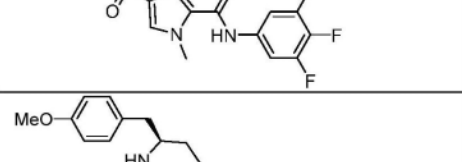
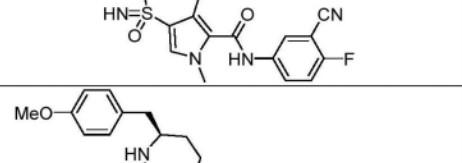
[0157]

100a12		411	Peak2 (HPLC)
100b01		416	Peak1 (HPLC)
100b02		416	Peak2 (HPLC)
100b03		414	Peak1 (HPLC)
100b04		414	Peak2 (HPLC)
100b05		409	Peak1 (HPLC)
100b06		409	Peak2 (HPLC)
100b07		407	Peak1 (HPLC)
100b08		407	Peak2 (HPLC)

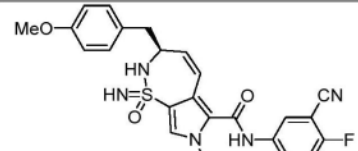
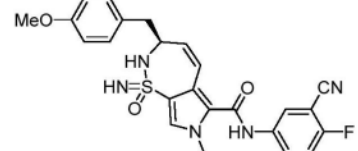
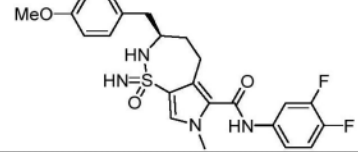
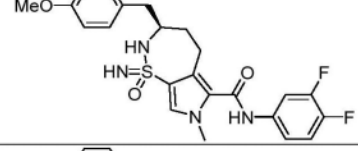
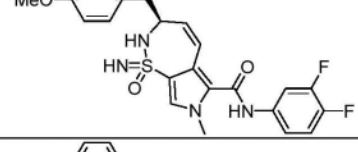
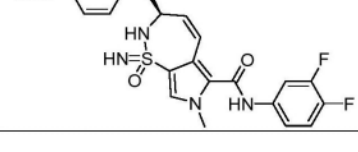
[0158]

100b09		427	Peak1 (HPLC)
100b10		427	Peak2 (HPLC)
100b11		425	Peak1 (HPLC)
100b12		425	Peak2 (HPLC)
100c01		470	Peak1 (HPLC)
100c02		470	Peak2 (HPLC)
100c03		468	Peak1 (HPLC)
100c04		468	Peak2 (HPLC)
100c05		463	Peak1 (HPLC)

[0159]

100c06		463	Peak2 (HPLC)
100c07		461	Peak1 (HPLC)
100c08		461	Peak2 (HPLC)
100c09		481	Peak1 (HPLC)
100c10		481	Peak2 (HPLC)
100c11		479	Peak1 (HPLC)
100c12		479	Peak2 (HPLC)
100c13		482	Peak1 (HPLC)
100c14		482	Peak2 (HPLC)

[0160]

100c15		480	Peak1 (HPLC)
100c16		480	Peak2 (HPLC)
100c17		475	Peak1 (HPLC)
100c18		475	Peak2 (HPLC)
100c19		473	Peak1 (HPLC)
100c20		473	Peak2 (HPLC)

[0161] 药物组合物和施用方法

[0162] 由于本发明化合物具有优异的乙型肝炎病毒 (HBV) 的抑制活性, 因此本发明化合物及其各种晶型, 药学上可接受的无机或有机盐, 水合物或溶剂合物, 以及含有本发明化合物为主要活性成分的药物组合物可用于预防和/或治疗 (稳定、减轻或治愈) 乙型肝炎病毒感染或用于预防和/或治疗 (稳定、减轻或治愈) 乙型肝炎病毒相关疾病 (例如, 乙型肝炎、进展性肝纤维化、导致肝硬化的炎症和坏死、末期肝病、乙基肝癌)。

[0163] 本发明的药物组合物包含安全有效量范围内的本发明化合物及药学上可以接受的赋形剂或载体。其中“安全有效量”指的是: 化合物的量足以明显改善病情, 而不至于产生严重的副作用。通常, 药物组合物含有 1-2000mg 本发明化合物/剂, 更佳地, 含有 10-200mg 本发明化合物/剂。较佳地, 所述的“一剂”为一个胶囊或药片。

[0164] “药学上可接受的载体”指的是: 一种或多种相容性固体或液体填料或凝胶物质, 它们适合于人使用, 而且必须有足够的纯度和足够低的毒性。“相容性”在此指的是组合物中各组份能和本发明化合物以及它们之间相互掺和, 而不明显降低化合物的药效。药学上可以接受的载体部分例子有纤维素及其衍生物 (如羧甲基纤维素钠、乙基纤维素钠、纤维素乙酸酯等)、明胶、滑石、固体润滑剂 (如硬脂酸、硬脂酸镁)、硫酸钙、植物油 (如豆油、芝麻油、花生油、橄榄油等)、多元醇 (如丙二醇、甘油、甘露醇、山梨醇等)、乳化剂 (如吐温®)、润湿剂 (如十二烷基硫酸钠)、着色剂、调味剂、稳定剂、抗氧化剂、防腐剂、无热原水等。

[0165] 本发明化合物或药物组合物的施用方式没有特别限制,代表性的施用方式包括(但并不限于):口服、肠胃外(静脉内、肌肉内或皮下)。

[0166] 用于口服给药的固体剂型包括胶囊剂、片剂、丸剂、散剂和颗粒剂。在这些固体剂型中,活性化合物与至少一种常规惰性赋形剂(或载体)混合,如柠檬酸钠或磷酸二钙,或与下述成分混合:(a) 填料或增容剂,例如,淀粉、乳糖、蔗糖、葡萄糖、甘露醇和硅酸;(b) 粘合剂,例如,羟甲基纤维素、藻酸盐、明胶、聚乙烯基吡咯烷酮、蔗糖和阿拉伯胶;(c) 保湿剂,例如,甘油;(d) 崩解剂,例如,琼脂、碳酸钙、马铃薯淀粉或木薯淀粉、藻酸、某些复合硅酸盐、和碳酸钠;(e) 缓溶剂,例如石蜡;(f) 吸收加速剂,例如,季胺化合物;(g) 润湿剂,例如鲸蜡醇和单硬脂酸甘油酯;(h) 吸附剂,例如,高岭土;和(i) 润滑剂,例如,滑石、硬脂酸钙、硬脂酸镁、固体聚乙二醇、十二烷基硫酸钠,或其混合物。胶囊剂、片剂和丸剂中,剂型也可包含缓冲剂。

[0167] 固体剂型如片剂、糖丸、胶囊剂、丸剂和颗粒剂可采用包衣和壳材制备,如肠衣和其它本领域公知的材料。它们可包含不透明剂,并且,这种组合物中活性化合物或化合物的释放可以延迟的方式在消化道内的某一部分中释放。可采用的包埋组分的实例是聚合物物质和蜡类物质。必要时,活性化合物也可与上述赋形剂中的一种或多种形成微胶囊形式。

[0168] 用于口服给药的液体剂型包括药学上可接受的乳液、溶液、悬浮液、糖浆或酞剂。除了活性化合物外,液体剂型可包含本领域中常规采用的惰性稀释剂,如水或其它溶剂,增溶剂和乳化剂,例知,乙醇、异丙醇、碳酸乙酯、乙酸乙酯、丙二醇、1,3-丁二醇、二甲基甲酰胺以及油,特别是棉籽油、花生油、玉米胚油、橄榄油、蓖麻油和芝麻油或这些物质的混合物等。

[0169] 除了这些惰性稀释剂外,组合物也可包含助剂,如润湿剂、乳化剂和悬浮剂、甜味剂、矫味剂和香料。

[0170] 除了活性化合物外,悬浮液可包含悬浮剂,例如,乙氧基化异十八烷醇、聚氧乙烯山梨醇和脱水山梨醇酯、微晶纤维素、甲醇铝和琼脂或这些物质的混合物等。

[0171] 用于肠胃外注射的组合物可包含生理上可接受的无菌含水或无水溶液、分散液、悬浮液或乳液,和用于重新溶解成无菌的可注射溶液或分散液的无菌粉末。适宜的含水和非水载体、稀释剂、溶剂或赋形剂包括水、乙醇、多元醇及其适宜的混合物。

[0172] 本发明化合物可以单独给药,或者与其他药学上可接受的化合物(例如抗-HBV剂)联合给药。

[0173] 联合给药时,所述药物组合物还包括与一种或多种(2种,3种,4种,或更多种)其他药学上可接受的化合物(例如抗-HBV剂)。该其他药学上可接受的化合物(例如抗-HBV剂)中的一种或多种(2种,3种,4种,或更多种)可与本发明的化合物同时、分开或顺序地用于预防和/或治疗HBV感染或HBV相关疾病。

[0174] 使用药物组合物时,是将安全有效量的本发明化合物适用于需要治疗的哺乳动物(如人),其中施用剂量为药学上认为的有效给药剂量,对于60kg体重的人而言,日给药剂量通常为1~2000mg,优选20~500mg。当然,具体剂量还应考虑给药途径、病人健康状况等因素,这些都是熟练医师技能范围内的。

[0175] 本发明的主要优点包括:

[0176] (1) 本发明的化合物结构新颖且具有优异的抗乙型肝炎病毒感染的作用。本申请中,将

现有的内环亚砷酰胺-芳基酰胺类化合物改造为内环硫脲酰胺-芳基酰胺类化合物,使其能够更好地起到干扰衣壳蛋白组装过程的作用,从而抑制HBV的活性或表达量。

[0177] (2) 本发明的化合物对正常细胞的毒性非常低,因而可以在较大的剂量范围内应用于治疗对象。

[0178] (3) 本发明化合物具有良好的成药性,相较于现有化合物而言,本发明化合物具有更好的溶解度,且在体内实验之中表现出良好的生物利用度,部分化合物的生物利用度达到或超过70%,除此之外,相较于现有化合物,本发明的化合物极易制成药学上可接受的盐,因而有助于进一步形成制剂。

[0179] (4) 本发明化合物以及含有本发明化合物为主要活性成分的药物组合物可用于预防和/或治疗乙型肝炎病毒相关疾病(例如,乙型肝炎、进展性肝纤维化、导致肝硬化的炎症和坏死、末期肝病、乙基肝癌)。

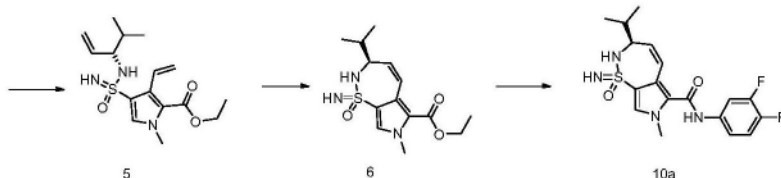
[0180] 下面结合具体实施,进一步阐述本发明。应理解,这些实施例仅用于说明本发明而不适用于限制本发明的范围。下列实施例中未注明具体条件的实验方法,通常按照常规条件,或按照制造厂商所建议的条件。除非另外说明,否则百分比和份数按重量计算。本发明实施例中所用原料或仪器,若非特别说明,均市售可得。

[0181] 下面为10类化合物的合成:

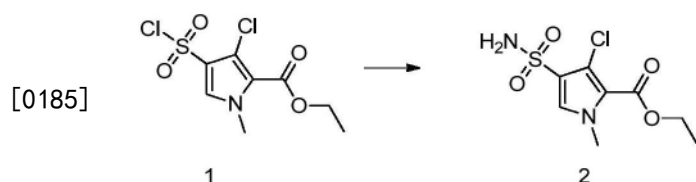
[0182] 实施例1:化合物10a的合成



[0183]

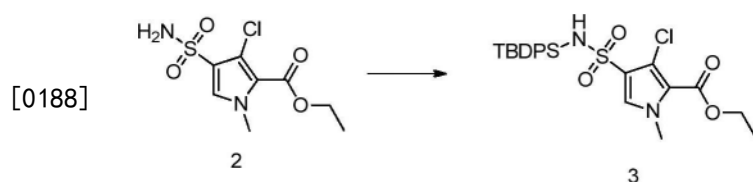


[0184] 步骤1:化合物2的合成



[0186] 将化合物1 (10g) 溶于二氯甲烷 (40mL) 中,室温下将氨水 (30mL) 滴加入反应体系,室温,反应5h,抽滤,滤饼用水 (5mL) 洗涤,得2淡黄色固体5g,MS (M+1=267)。

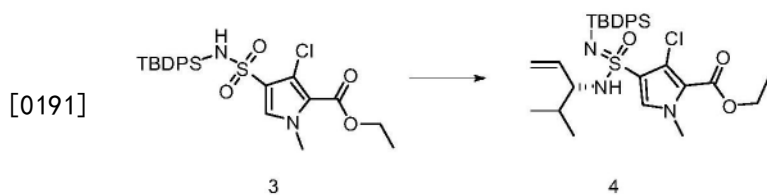
[0187] 步骤2:化合物3的合成



[0189] 将底物2 (5g) 溶于DMF (10mL), 0度下将氢化钠 (1.5g) 加入反应体系,搅拌15min然后将TBDPSCl加入反应体系,反应18h,将反应体系倒入冰水中,乙酸乙酯 (3\*30mL) 萃取,有

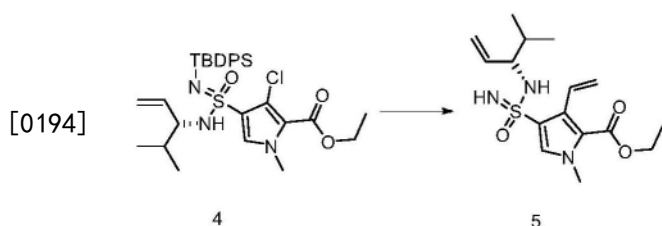
机相干燥、旋干,粗品柱层析(正庚烷:乙酸乙酯=1:4),得产物3(3g)。MS(M+1=505)。

[0190] 步骤3:化合物4的合成



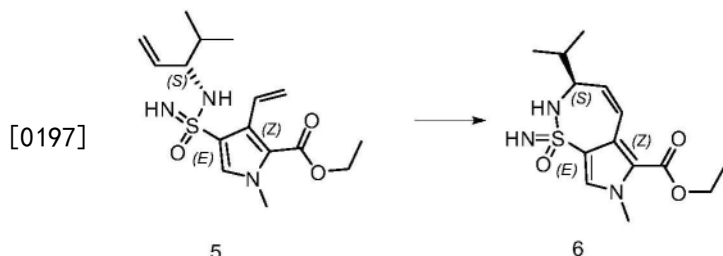
[0192] 将PPh<sub>3</sub>Cl<sub>2</sub>的氯仿溶液(80mL)冷至0度,然后将三乙胺(7mL),搅拌10min后0度下加入化合物3,搅拌20min后,将2-异丙基-3-丙烯胺加入反应体系,室温反应18h,向反应体系中加入水(20mL),乙酸乙酯(3\*25mL)萃取,有机相干燥、旋干,粗品柱层析(正庚烷:乙酸乙酯=1:5),得产物4(1.9g)。MS(M+1=586)。

[0193] 步骤4:化合物5的合成



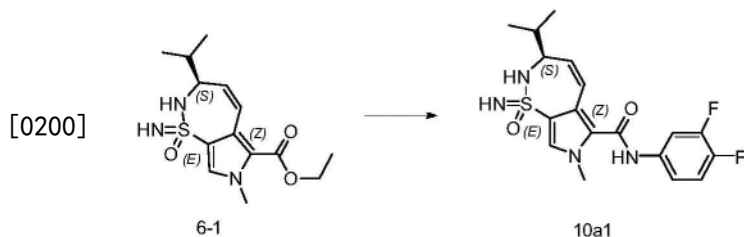
[0195] 将化合物4(1.8g),四三苯基磷钨(100mg),乙烯基硼酸酯(900g),碳酸铯(2.7g),溶于DMF(410mL)中,氮气保护下,100度反应15h,用水溶液淬灭反应,乙酸乙酯萃取,有机相干燥、旋干,所得粗品柱层析(正庚烷:乙酸乙酯=1:5)得化合物5(1.0g)。MS(M+1=340)。

[0196] 步骤5:化合物6的合成



[0198] 将化合物5(1.0g)溶于二氯甲烷(500mL)中,然后将詹氏催化剂(0.1g)加入反应体系,搅拌过夜,将反应液旋干,粗品柱层析(正庚烷:乙酸乙酯=1:3)得化合物6,TLC显示的下点6-1(0.22g),TLC显示的上点6-2(0.27g)MS(M+1=312)。

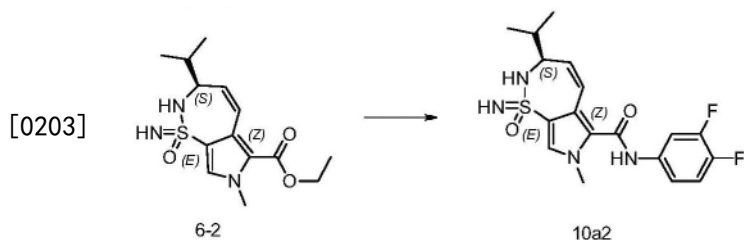
[0199] 步骤6:化合物10a1的合成



[0201] 将化合物6-1(30mg)和4-氟-3-氰基苯胺(20mg)溶于四氢呋喃(5mL)中,降温至0度,然后将NaHMDS(0.2mL)加入反应体系,室温搅拌反应16h,将水加入反应体系,乙酸乙酯(3\*15mL)萃取,有机相用无水硫酸钠干燥,旋干,粗品经柱层析(正庚烷:乙酸乙酯=1:3)目标产物10a1(11mg)。<sup>1</sup>H NMR(400MHz,DMSO-d<sub>6</sub>) δ10.78(s,1H),7.89-7.83(m,1H),7.71(s,

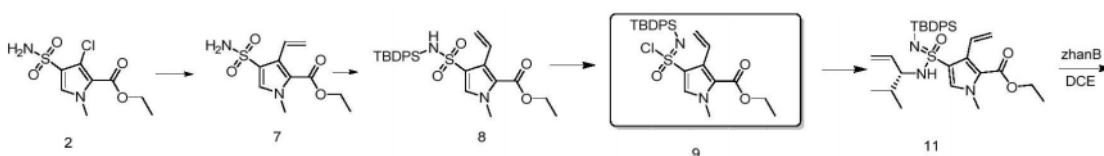
1H), 7.44 (qd, J=4.7, 4.2, 2.5Hz, 2H), 6.54 (dd, J=12.4, 2.7Hz, 1H), 5.75 (dd, J=12.4, 2.8Hz, 1H), 4.0 (dq, J=7.8, 2.6Hz, 1H), 3.74 (s, 3H), 1.97-1.89 (m, 1H), 0.98 (dd, J=12.6, 6.7Hz, 6H). MS (M+1=395)。

[0202] 实施例2:化合物10a2的合成

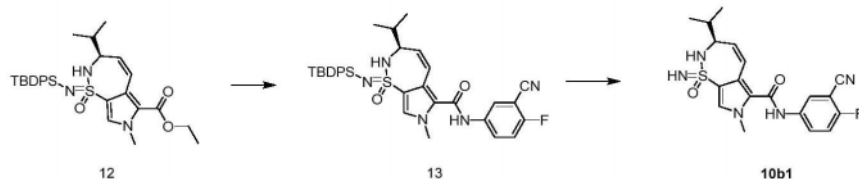


[0204] 根据实施例1的步骤6,只需用化合物6-2代替化合物6-1,其他条件不变,经柱层析(正庚烷:乙酸乙酯=1:1)目标产物10a2 (8mg)。<sup>1</sup>H NMR (400MHz, DMSO-d<sub>6</sub>) δ10.69 (s, 1H), 7.89-7.83 (m, 1H), 7.51 (s, 1H), 7.44 (qd, J=4.7, 4.2, 2.5Hz, 2H), 6.53 (dd, J=12.4, 2.7Hz, 1H), 5.72 (dd, J=12.4, 2.8Hz, 1H), 3.87 (dq, J=7.8, 2.6Hz, 1H), 3.72 (s, 3H), 1.91-1.85 (m, 1H), 0.96 (dd, J=12.6, 6.7Hz, 6H). MS (M+1=395)。

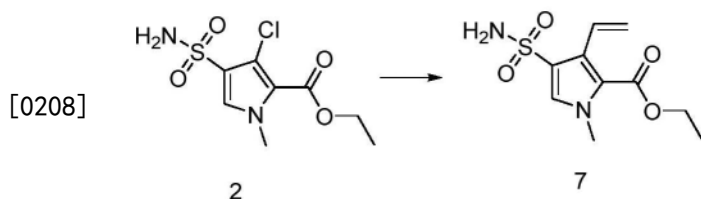
[0205] 实施例3:化合物10b1的合成



[0206]

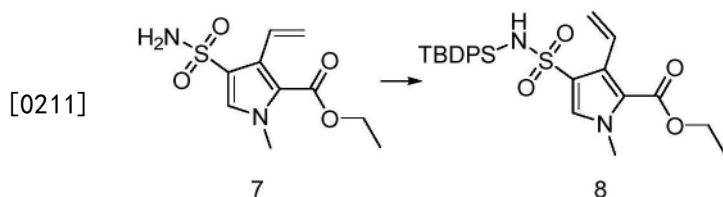


[0207] 步骤1:化合物7的合成



[0209] 将2 (2.5g), 乙烯基硼酸酯 (1.5g), 碳酸钠 (3.5g), 醋酸钡 (120mg) 和Xphos (500mg) 溶于DMF中,氮气保护下,将反应体系至于100度油浴下,反应6h,将水 (50mL) 加入反应体系,乙酸乙酯 (3\*60mL) 萃取,无水硫酸钠干燥,旋干,柱层析得黄色固体1.2g。MS (M+1=259)。

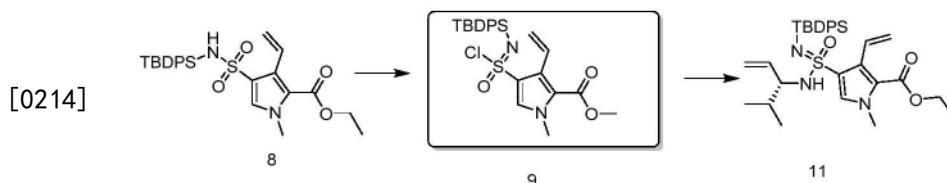
[0210] 步骤2:化合物8的合成



[0212] 将反应体系降温至0度,氢化钠 (180mg) 加入到DMF中,然后搅拌10min,将TBDPSCl (2.7g) 和7 (1.1g) 的DMF溶液,在0度下,滴加入反应体系中,室温反应1.5h。将反应液滴加入

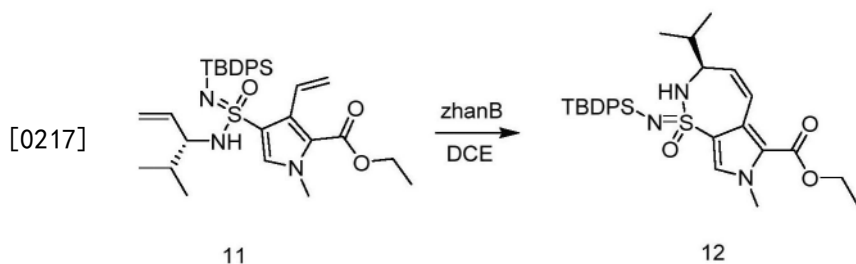
1NHC1和饱和氯化铵的混合溶液中,乙酸乙酯(3\*50mL),无水硫酸钠干燥,有机相旋干,柱层析得白色固体800mg,MS(M+1=497)。<sup>1</sup>H NMR(400MHz,DMSO-d<sub>6</sub>) δ10.78(s,1H),7.62-7.59(m,1H),7.45-7.41(m,1H),7.33-7.29(m,3H),7.13(qd,J=4.7,4.2,2.5Hz,2H),6.16(dd,J=12.4,2.7Hz,1H),5.58(dd,J=12.4,2.8Hz,1H),5.09(s,1H),4.35-4.40(m,2),3.56(s,3H),1.45-1.40(m,3),1.04(s,9H)。

[0213] 步骤3:化合物11的合成



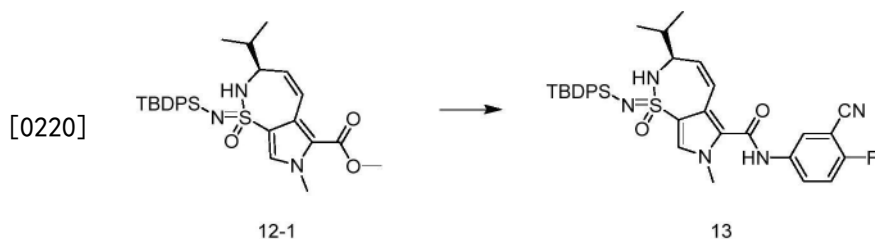
[0215] 将PPh<sub>3</sub>Cl<sub>2</sub>的混合液降温至0度,然后向反应体系中滴加三乙胺(3mL)滴加完毕后,0度反应10min中,然后再想体系内一次性加入固体8(500mg),0度下搅拌20min,最后将异丙基烯丙基胺(200mg)的氯仿溶液加入反应体系,室温反应18h,将硅胶直接加入反应体系,旋干后柱层析得浅黄色油状物650mg。MS(M+1=578)<sup>1</sup>H NMR(400MHz,DMSO-d<sub>6</sub>) δ7.81-7.73(m,4H),7.38-7.32(m,7H),7.06-6.91(m,2H),6.01-5.89(m,1H),5.48-5.33(m,2H),4.92-4.70(m,2H),4.36-4.30(m,2H),3.79(s,1.55H),3.76(s,1.36H),3.50-3.41(m,1H),1.71-1.66(m,0.5H),1.56-1.51(m,0.5H),1.40-1.35(m,3),1.14(s,4.2H),1.12(s,4.5H),0.76-0.73(m,3H),0.68-0.64(m,3H)。

[0216] 步骤4:化合物12的合成



[0218] 将化合物11(650mg)溶于1,2二氯乙烷中,然后zhan1B加入反应体系,然后再氮气保护下,将体系温度升至70度下搅拌24h,将硅胶直接加入反应体系,旋干后柱层析得浅黄色油状物12:TLC显示的下点12-1(0.22g),TLC显示的上点12-2(0.27g)MS(M+1=550)。<sup>1</sup>H NMR(400MHz,DMSO-d<sub>6</sub>) δ7.81-7.74(m,5H),7.40-7.37(m,7H),7.28-7.21(m,1H),6.01-5.89(m,1H),6.99(s,1H),5.77-5.73(m,1H),4.42-4.35(m,2H),4.15-4.11(m,1H),3.80(s,3H),1.91-1.86(m,1H),1.43-1.39(m,3),1.14(s,9H),0.87-0.78(m,6H)。

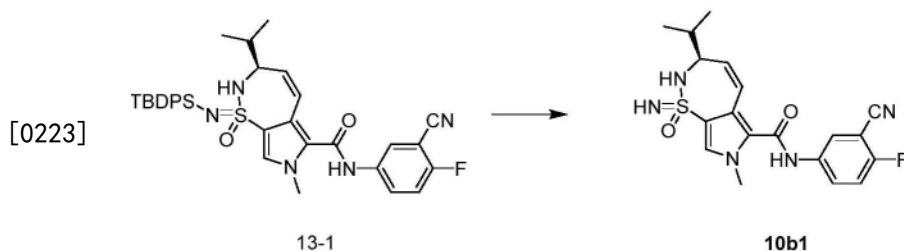
[0219] 步骤5:化合物13的合成



[0221] 将12-1(90mg)(TLC显示的下点)和3,4-二氟苯胺(43mg)溶于THF(8mL)中,然后将体系温度降至0度,将6当量的NaHMDS加入反应体系反应体系,0度反应1h,将水(20mL)加入

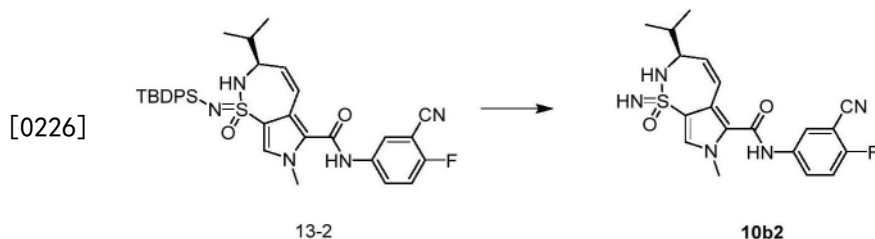
反应体系,乙酸乙酯(3\*30mL)萃取,无水硫酸钠干燥,旋干,柱层析的黄色油状物80mg,MS(M+1=640)。

[0222] 步骤6:化合物10b1的合成



[0224] 将13-1(40mg)(TLC显示的下点)溶于THF(3mL)中,然后将120当量的3HF·TEA滴加入反应体系,室温下反应3天,制备板分离冷冻干燥后得白色固体10b1(4.5mg)。<sup>1</sup>H NMR(400MHz,DMSO-d<sub>6</sub>) δ10.90(s,1H),8.18(dd,J=5.8,2.7Hz,1H),7.99(ddd,J=9.2,4.8,2.7Hz,1H),7.78-7.70(m,2H),7.57(d,J=10.3Hz,1H),6.57(dd,J=12.4,2.7Hz,1H),5.77(dd,J=12.4,2.8Hz,1H),4.07(ddt,J=10.6,5.4,2.7Hz,1H),3.76(s,3H),1.92(tq,J=12.1,6.7,5.6Hz,1H),0.99(dd,J=12.0,6.7Hz,6H)。Ms(ESI)m/z=402(M+1)

[0225] 实施例4:化合物10b2的合成



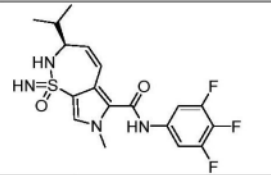
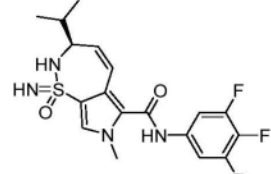
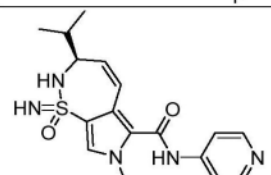
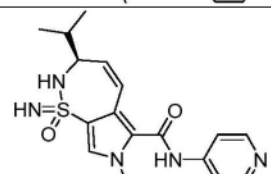
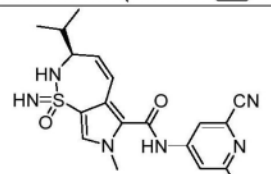
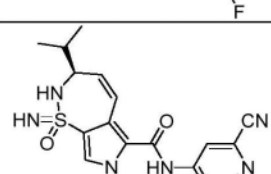
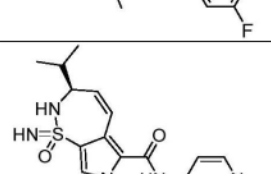
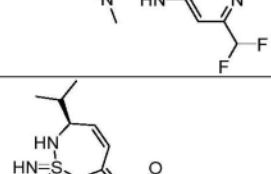
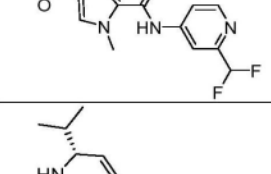
[0227] 根据实施例3的步骤6,只需用化合物13-2(TLC显示的上点)代替化合物13-1(TLC显示的下点),其他条件不变,经柱层析(正庚烷:乙酸乙酯=1:1)目标产物10b2(8mg)。<sup>1</sup>H NMR(400MHz,DMSO-d<sub>6</sub>) δ10.89(s,1H),8.20(dd,J=5.8,2.7Hz,1H),7.97(ddd,J=9.2,4.8,2.7Hz,1H),7.90-7.88(m,2H),7.56(d,J=10.3Hz,1H),6.65(dd,J=12.4,2.7Hz,1H),5.91(dd,J=12.4,2.8Hz,1H),3.80(s,3H),3.69-3.63(m,1H),1.95(tq,J=12.1,6.7,5.6Hz,1H),0.99(dd,J=12.0,6.7Hz,6H)。Ms(ESI)m/z=402(M+1)

[0228] 根据实施例3的合成方法又合成了如下10,30类系列化合物:

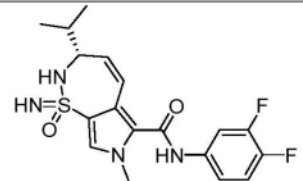
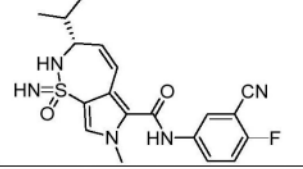
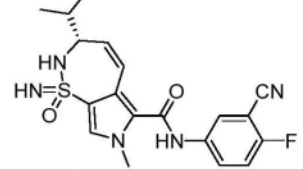
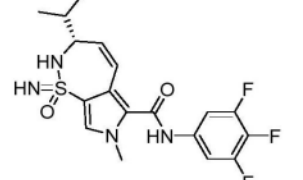
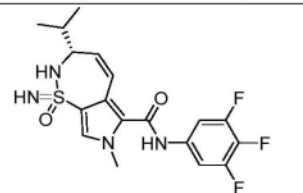
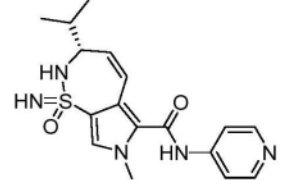
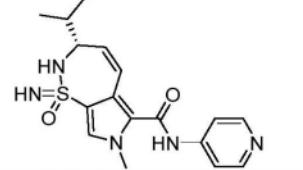
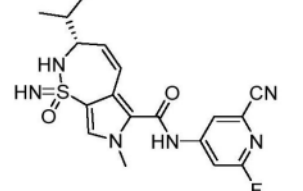
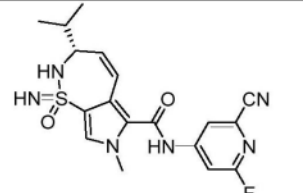
[0229]

编号	结构	质谱ESI-MS, (M+H)	备注
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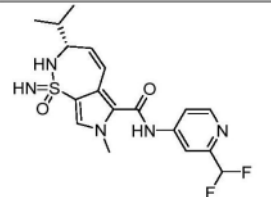
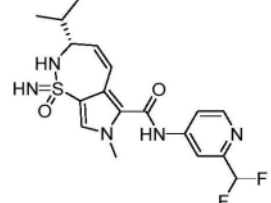
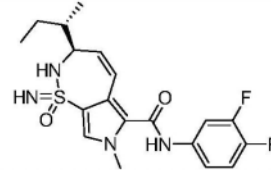
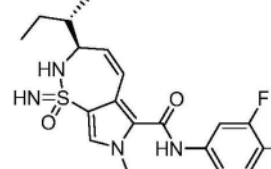
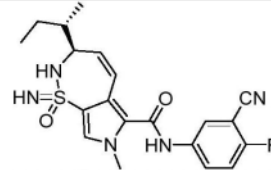
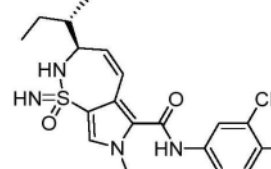
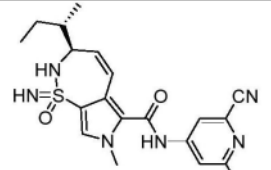
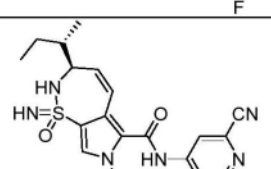
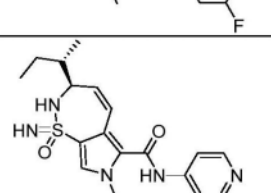
[0230]

10c1		413	Peak1 (HPLC)
10c2		413	Peak2 (HPLC)
10d1		360	Peak1 (HPLC)
10d2		360	Peak2 (HPLC)
10e1		403	Peak1 (HPLC)
10e2		403	Peak2 (HPLC)
10f1		410	Peak1 (HPLC)
10f2		410	Peak2 (HPLC)
10g1		395	Peak1 (HPLC)

[0231]

10g2		395	Peak2 (HPLC)
10h1		402	Peak1 (HPLC)
10h2		402	Peak2 (HPLC)
10i1		413	Peak1 (HPLC)
10i2		413	Peak2 (HPLC)
10j1		360	Peak1 (HPLC)
10j2		360	Peak2 (HPLC)
10k1		403	Peak1 (HPLC)
10k2		403	Peak2 (HPLC)

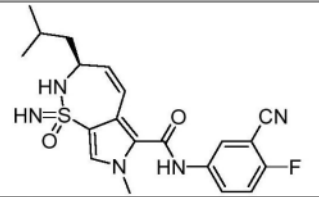
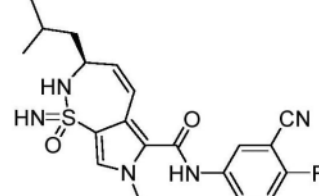
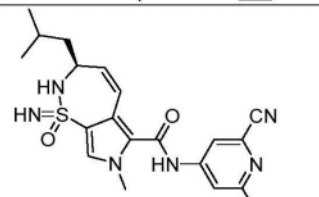
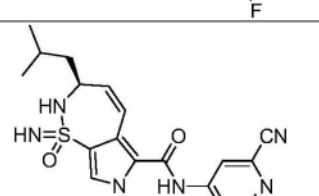
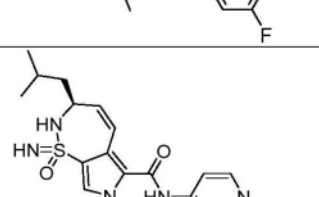
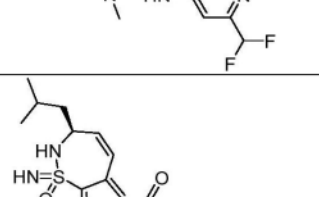
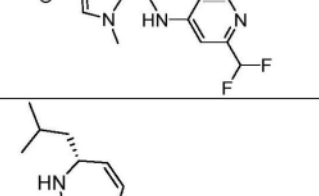
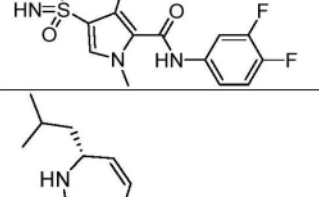
[0232]

10m1		410	Peak1 (HPLC)
10m2		410	Peak2 (HPLC)
10n1		409	Peak1 (HPLC)
10n2		409	Peak2 (HPLC)
10o1		416	Peak1 (HPLC)
10o2		416	Peak2 (HPLC)
10p1		417	Peak1 (HPLC)
10p2		417	Peak2 (HPLC)
10q1		424	Peak1 (HPLC)

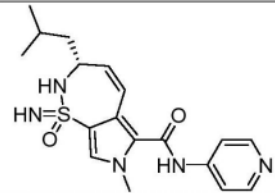
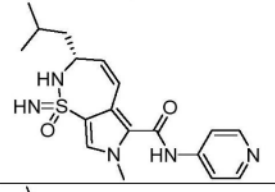
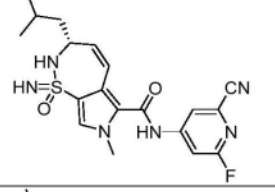
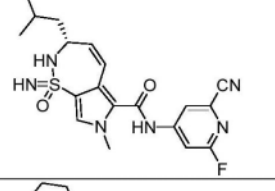
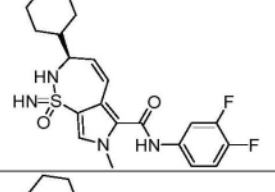
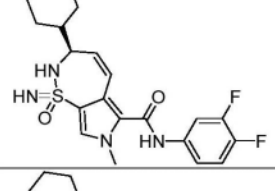
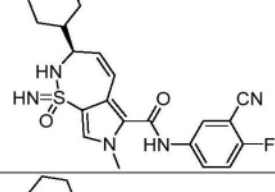
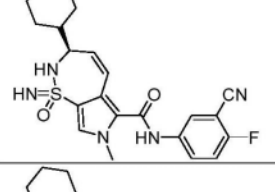
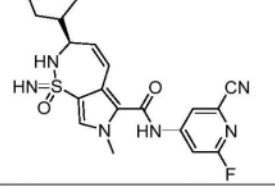
[0233]

10q2		424	Peak2 (HPLC)
10r1		409	Peak1 (HPLC)
10r2		409	Peak2 (HPLC)
10s1		374	Peak1 (HPLC)
10s2		374	Peak2 (HPLC)
10t1		417	Peak1 (HPLC)
10t2		417	Peak2 (HPLC)
10u1		409	Peak1 (HPLC)
10u2		409	Peak2 (HPLC)

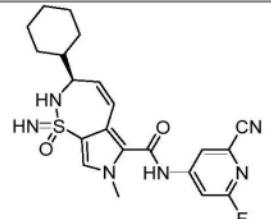
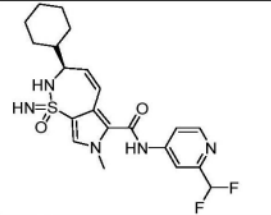
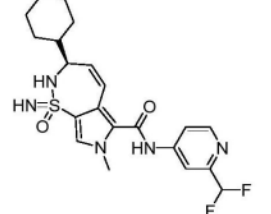
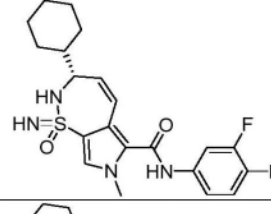
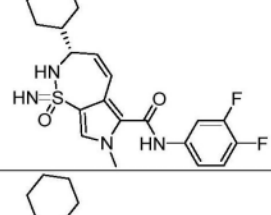
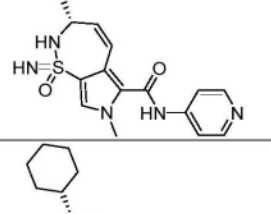
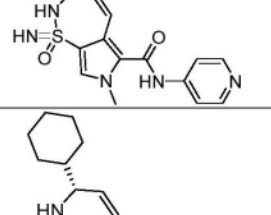
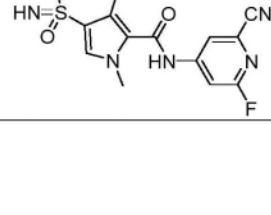
[0234]

10v1		416	Peak1 (HPLC)
10v2		416	Peak2 (HPLC)
10w1		417	Peak1 (HPLC)
10w2		417	Peak2 (HPLC)
10x1		424	Peak1 (HPLC)
10x2		424	Peak2 (HPLC)
10y1		409	Peak1 (HPLC)
10y2		409	Peak2 (HPLC)

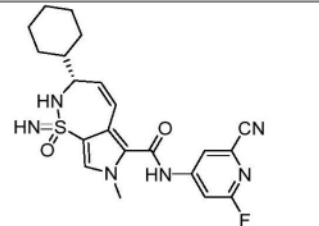
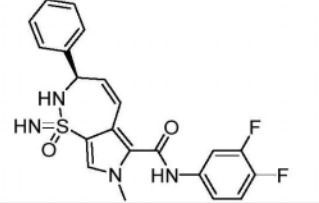
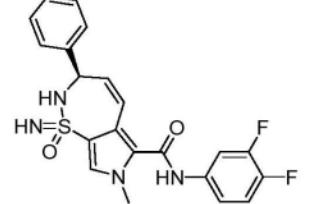
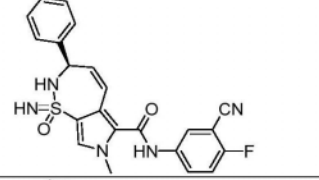
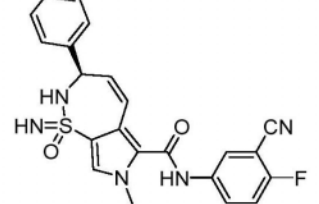
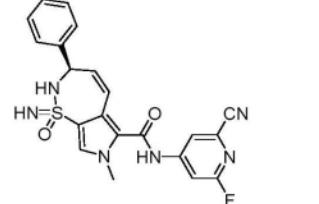
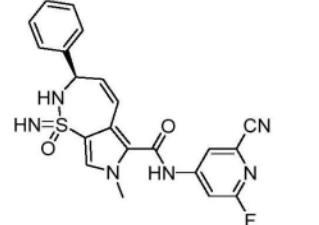
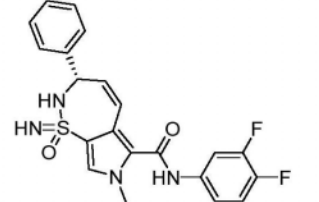
[0235]

10z1		374	Peak1 (HPLC)
10z2		374	Peak2 (HPLC)
10aa1		417	Peak1 (HPLC)
10aa2		417	Peak2 (HPLC)
10bb1		435	Peak1 (HPLC)
10bb2		435	Peak2 (HPLC)
10cc1		442	Peak1 (HPLC)
10cc2		442	Peak2 (HPLC)
10dd1		443	Peak1 (HPLC)

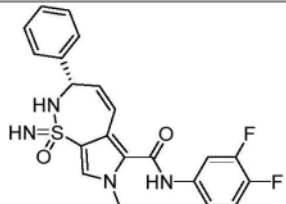
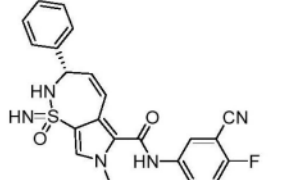
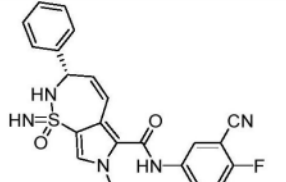
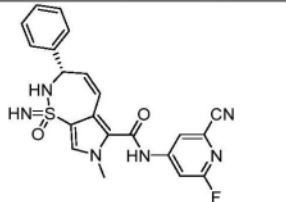
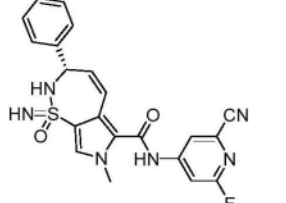
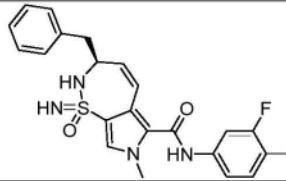
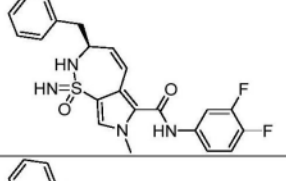
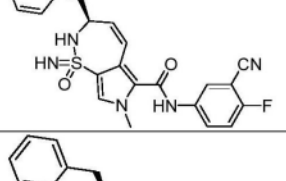
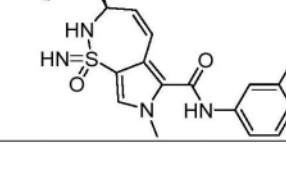
[0236]

10dd2		443	Peak2 (HPLC)
10ee1		450	Peak1 (HPLC)
10ee2		450	Peak2 (HPLC)
10ff1		435	Peak1 (HPLC)
10ff2		435	Peak2 (HPLC)
10gg1		400	Peak1 (HPLC)
10gg2		400	Peak2 (HPLC)
10hh1		443	Peak1 (HPLC)

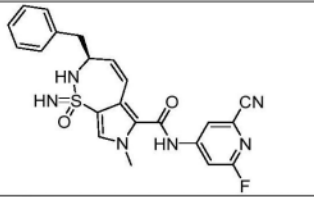
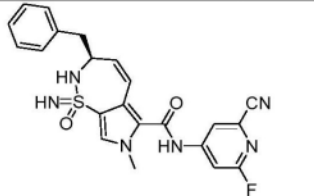
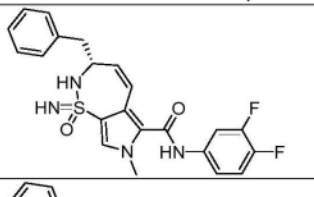
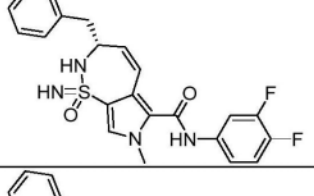
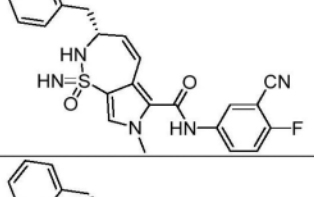
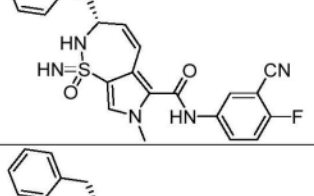
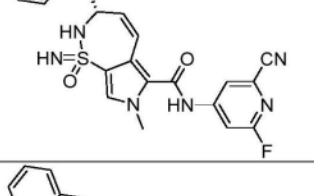
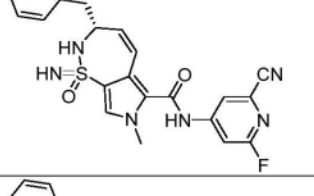
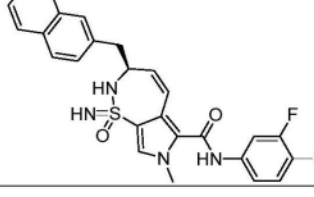
[0237]

10hh2		443	Peak2 (HPLC)
10ii1		429	Peak1 (HPLC)
10ii2		429	Peak2 (HPLC)
10jj1		436	Peak1 (HPLC)
10jj2		436	Peak2 (HPLC)
10kk1		437	Peak1 (HPLC)
10kk2		437	Peak2 (HPLC)
10mm1		429	Peak1 (HPLC)

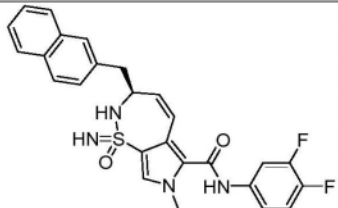
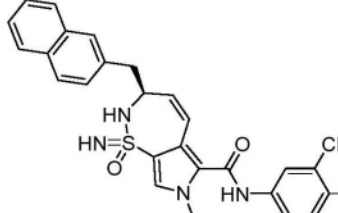
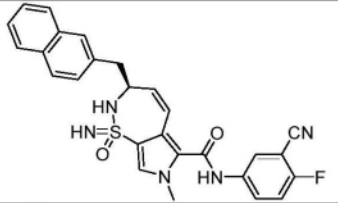
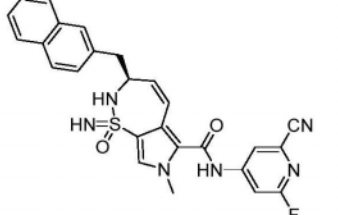
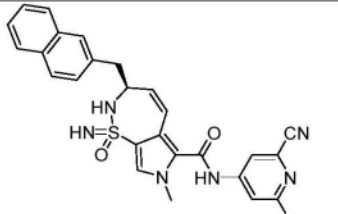
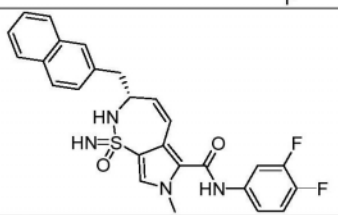
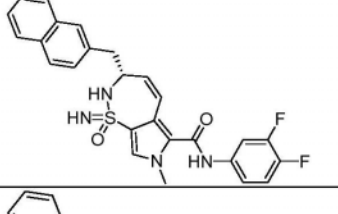
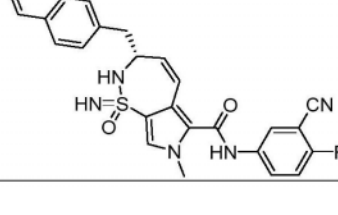
[0238]

10mm2		429	Peak2 (HPLC)
10nn1		436	Peak1 (HPLC)
10nn2		436	Peak2 (HPLC)
10oo1		437	Peak1 (HPLC)
10oo2		437	Peak2 (HPLC)
10pp1		443	Peak1 (HPLC)
10pp2		443	Peak2 (HPLC)
10qq1		450	Peak1 (HPLC)
10qq2		450	Peak2 (HPLC)

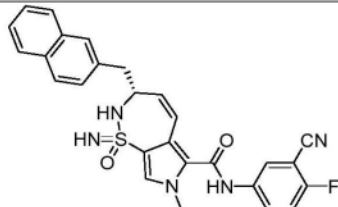
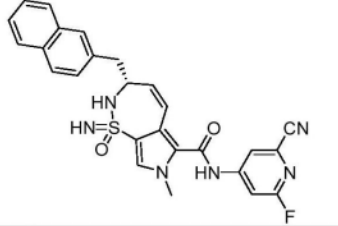
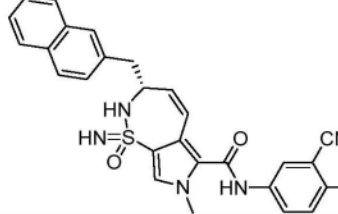
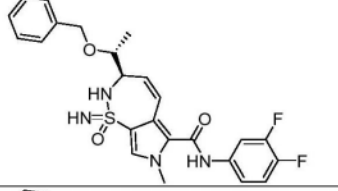
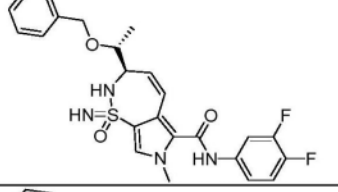
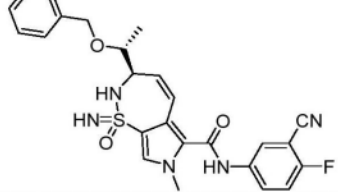
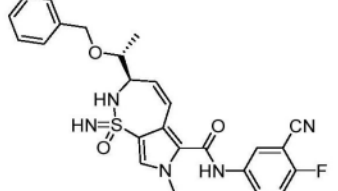
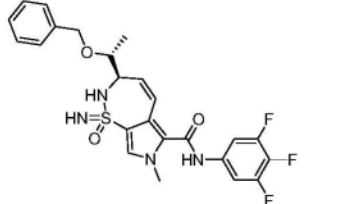
[0239]

10rr1		451	Peak1 (HPLC)
10rr2		451	Peak2 (HPLC)
10ss1		443	Peak1 (HPLC)
10ss2		443	Peak2 (HPLC)
10tt1		450	Peak1 (HPLC)
10tt2		450	Peak2 (HPLC)
10uu1		451	Peak1 (HPLC)
10uu2		451	Peak2 (HPLC)
10vv1		493	Peak1 (HPLC)

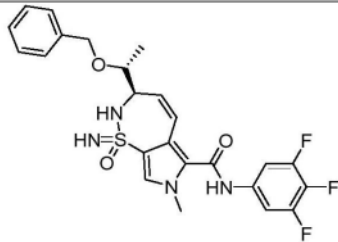
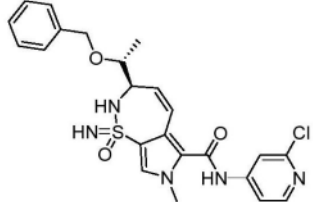
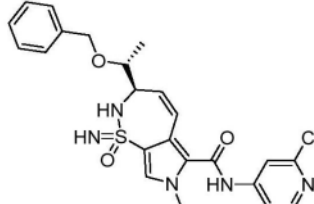
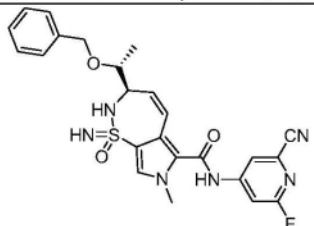
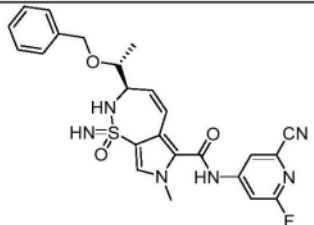
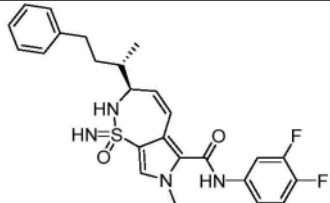
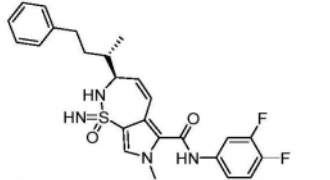
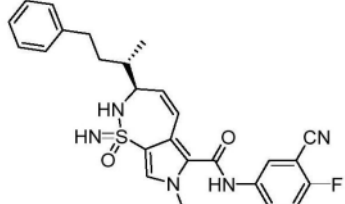
[0240]

10vv2		493	Peak2 (HPLC)
10ww1		500	Peak1 (HPLC)
10ww2		500	Peak2 (HPLC)
10xx1		501	Peak1 (HPLC)
10xx2		501	Peak2 (HPLC)
10yy1		493	Peak1 (HPLC)
10yy2		493	Peak2 (HPLC)
10zz1		500	Peak1 (HPLC)

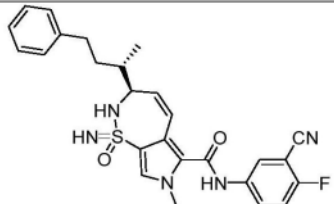
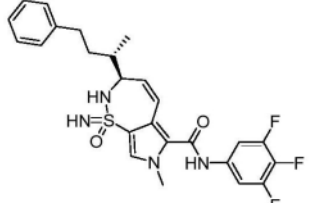
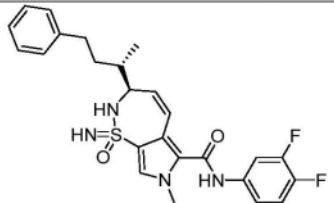
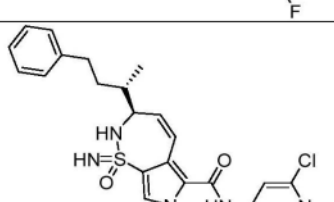
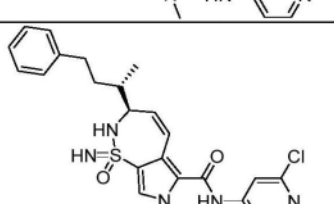
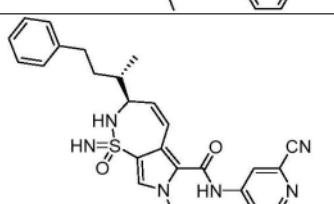
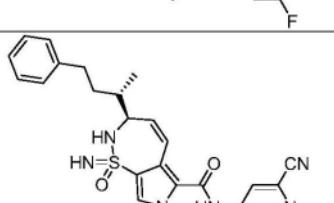
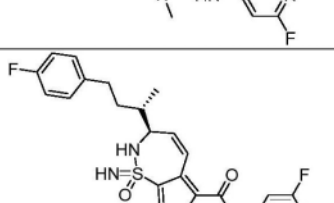
[0241]

10zz2		500	Peak2 (HPLC)
10aaa1		501	Peak1 (HPLC)
10aaa2		501	Peak2 (HPLC)
10bbb1		487	Peak1 (HPLC)
10bbb2		487	Peak2 (HPLC)
10ccc1		494	Peak1 (HPLC)
10ccc2		494	Peak2 (HPLC)
10ddd1		505	Peak1 (HPLC)

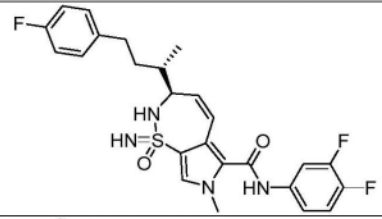
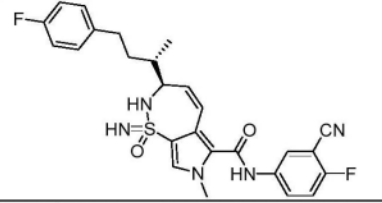
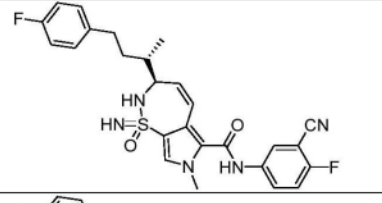
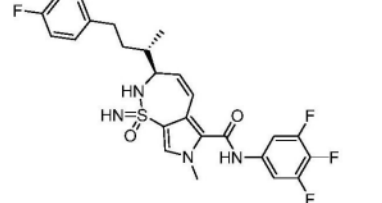
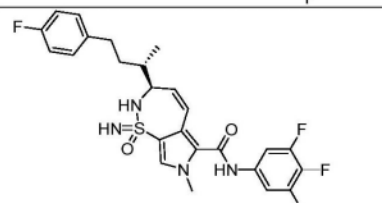
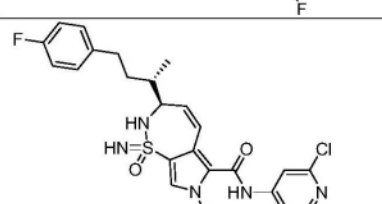
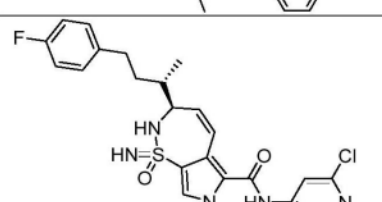
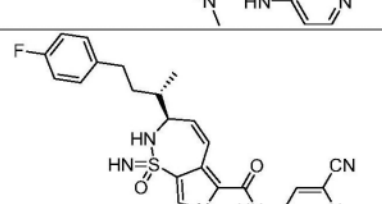
[0242]

10ddd2		505	Peak2 (HPLC)
10eee1		486	Peak1 (HPLC)
10eee2		486	Peak2 (HPLC)
10fff1		495	Peak1 (HPLC)
10fff2		495	Peak2 (HPLC)
10ggg1		485	Peak1 (HPLC)
10ggg2		485	Peak2 (HPLC)
10hhh1		492	Peak1 (HPLC)

[0243]

10hhh2		492	Peak2 (HPLC)
10iii1		503	Peak1 (HPLC)
10iii2		503	Peak2 (HPLC)
10jjj1		484	Peak1 (HPLC)
10jjj2		484	Peak2 (HPLC)
10kkk1		493	Peak1 (HPLC)
10kkk2		493	Peak2 (HPLC)
10mmm1		503	Peak1 (HPLC)

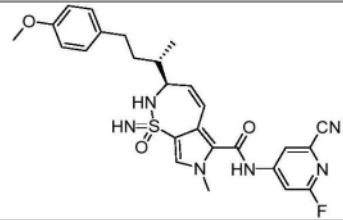
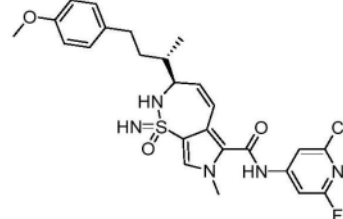
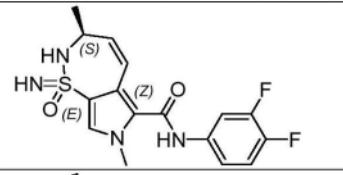
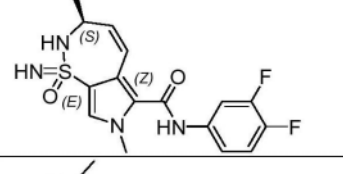
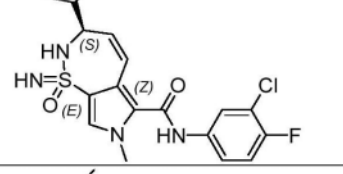
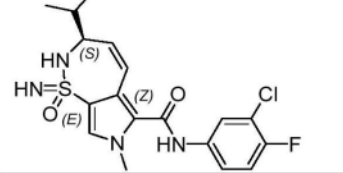
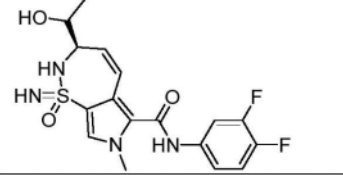
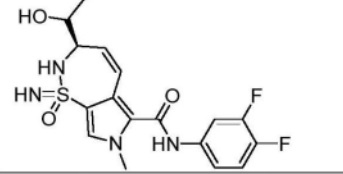
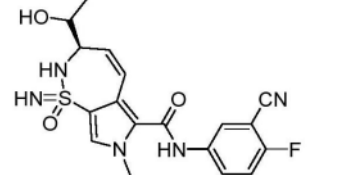
[0244]

10mmm2		503	Peak2 (HPLC)
10nnn1		510	Peak1 (HPLC)
10nnn2		510	Peak2 (HPLC)
10ooo1		521	Peak1 (HPLC)
10ooo2		521	Peak2 (HPLC)
10ppp1		502	Peak1 (HPLC)
10ppp2		502	Peak2 (HPLC)
10qqq1		511	Peak1 (HPLC)

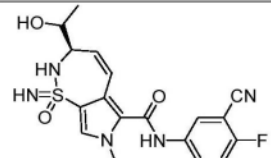
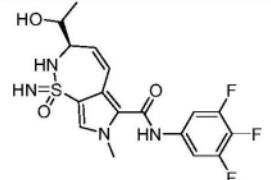
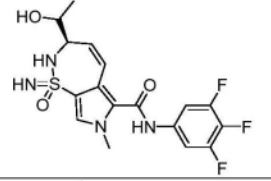
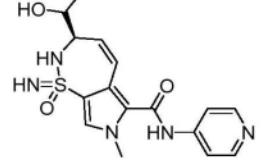
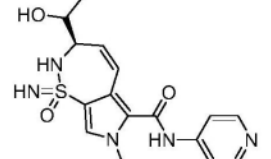
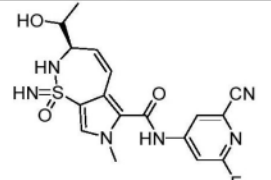
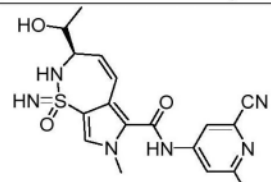
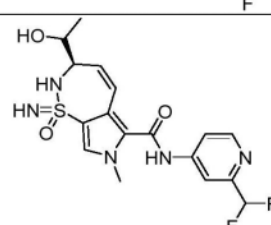
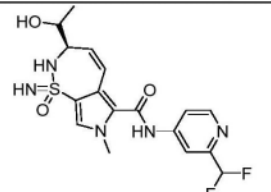
[0245]

10qqq2		511	Peak2 (HPLC)
10rrr1		515	Peak1 (HPLC)
10rrr2		515	Peak2 (HPLC)
10sss1		522	Peak1 (HPLC)
10sss2		522	Peak2 (HPLC)
10ttt1		533	Peak1 (HPLC)
10ttt2		533	Peak2 (HPLC)
10uuu1		514	Peak1 (HPLC)
10uuu2		514	Peak2 (HPLC)

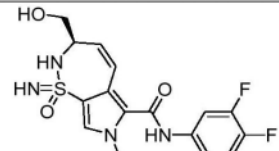
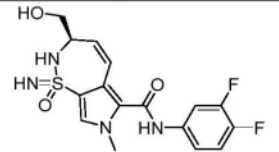
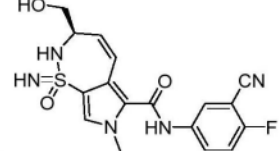
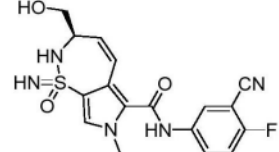
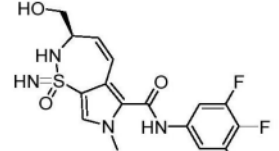
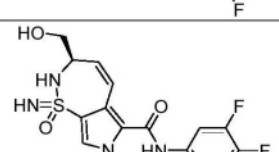
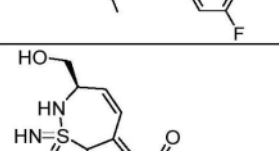
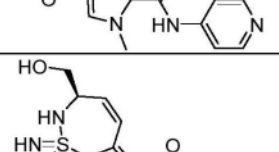
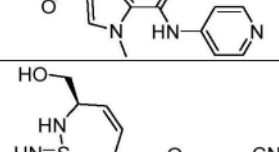
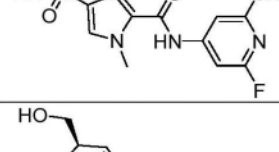
[0246]

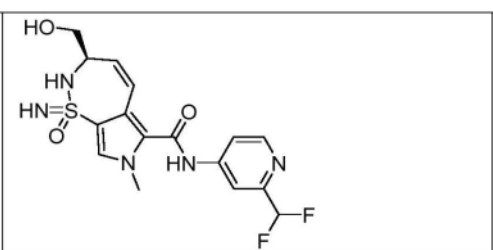
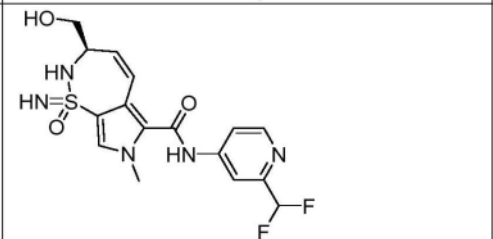
10vvv1		523	Peak1 (HPLC)
10vvv2		523	Peak2 (HPLC)
10www1		367	Peak1 (HPLC)
10www2		367	Peak2 (HPLC)
10xxx1		411	Peak1 (HPLC)
10xxx2		411	Peak2 (HPLC)
30a1		397	Peak1 (HPLC)
30a2		397	Peak2 (HPLC)
30b1		404	Peak1 (HPLC)

[0247]

30b2		404	Peak2 (HPLC)
30c1		415	Peak1 (HPLC)
30c2		415	Peak2 (HPLC)
30d1		362	Peak1 (HPLC)
30d2		362	Peak2 (HPLC)
30e1		405	Peak1 (HPLC)
30e2		405	Peak2 (HPLC)
30f1		412	Peak1 (HPLC)
30f2		412	Peak2 (HPLC)

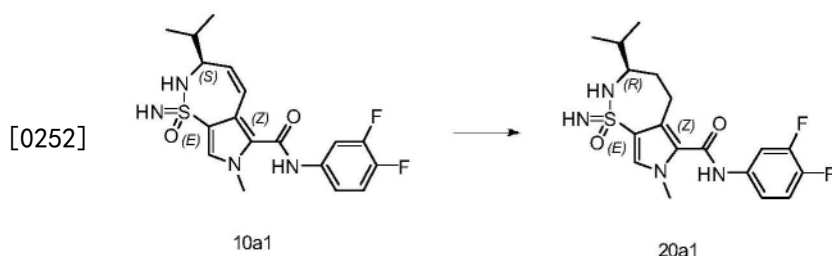
[0248]

30g1		383	Peak1 (HPLC)
30g2		383	Peak2 (HPLC)
30h1		390	Peak1 (HPLC)
30h2		390	Peak2 (HPLC)
30i1		401	Peak1 (HPLC)
30i2		401	Peak2 (HPLC)
30j1		348	Peak1 (HPLC)
30j2		348	Peak2 (HPLC)
30k1		391	Peak1 (HPLC)
30k2		391	Peak2 (HPLC)

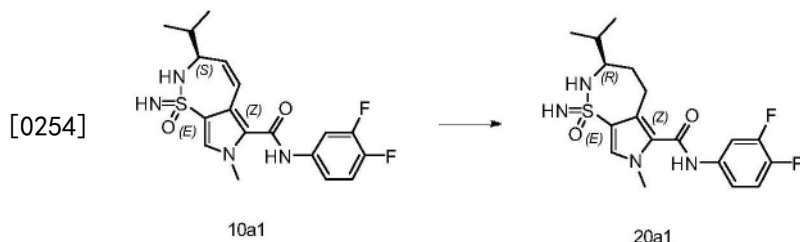
[0249]		398	Peak1 (HPLC)
		398	Peak2 (HPLC)

[0250] 下面为20类化合物的合成:

[0251] 实施例72: 化合物20a1的合成

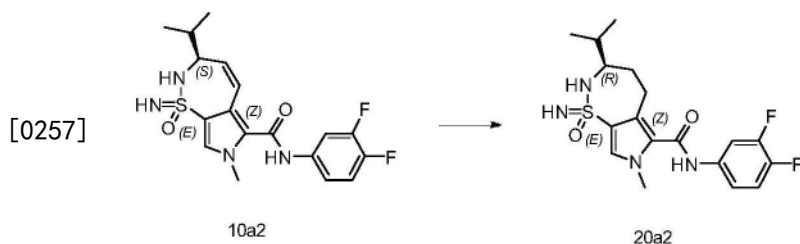


[0253] 步骤1



[0255] 将化合物10a1 (20mg) 溶于甲醇 (5mL), 然后将钯碳 (5mg) 加入反应体系, 氢气保护下室温反应6h, 粗品经柱层析 (正庚烷: 乙酸乙酯=1:3) 目标产物20a1 (11mg)。<sup>1</sup>H NMR (400MHz, DMSO-d<sub>6</sub>) δ10.56 (s, 1H), 7.88-7.83 (m, 1H), 7.63 (s, 2H), 7.46-7.42 (m, 1H), 7.21-6.96 (m, 1H), 3.72 (s, 3H), 3.12-3.09 (m, 1H), 3.00 (dd, J=15.0, 6.7Hz, 1H), 2.89-2.78 (m, 1H), 1.89-1.85 (m, 1H), 1.69-1.50 (m, 1H), 1.43 (q, J=12.0Hz, 1H), 0.92 (dd, J=6.8, 3.5Hz, 6H)。MS (M+1=397)。

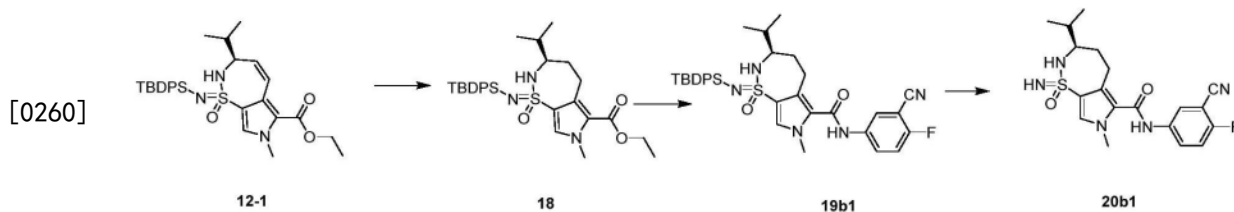
[0256] 实施例73: 化合物20a2的合成



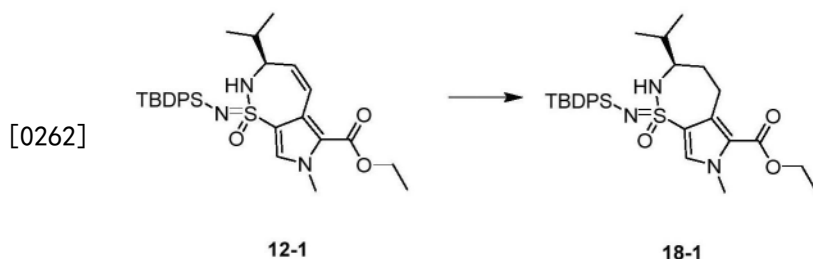
[0258] 根据实施例1的步骤6, 只需用化合物10a2代替化合物10a1, 其他条件不变, 经柱层析 (正庚烷: 乙酸乙酯=1:1) 目标产物20a2 (8mg)。<sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) δ10.67 (s, 1H),

8.20-8.18 (m, 1H), 7.97 (d, J=3.7 Hz, 1H), 7.68-7.59 (m, 1H), 7.55 (d, J=10.3 Hz, 1H), 3.76 (s, 3H), 3.04-2.92 (m, 2H), 2.85 (dd, J=15.0, 6.7 Hz, 1H), 1.90-1.83 (m, 1H), 1.73 (dd, J=14.3, 6.7 Hz, 1H), 1.69-1.50 (m, 1H), 1.45 (q, J=12.0 Hz, 1H), 0.89 (dd, J=6.8, 3.5 Hz, 6H). MS (M+1=397)。

[0259] 实施例74:化合物20b1的合成



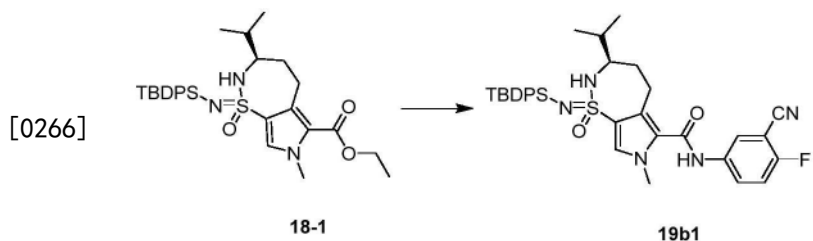
[0261] 步骤1



[0263] 将化合物1 (150mg) 溶于甲醇 (8 mL) 中, 将Pd/C (30 mg) 加入反应体系, 氮气换气三次, 氢气换气三次, 氢气球条件下室温 (25度) 反应18h, TLC检测原料反应完全, 抽滤, 旋干溶剂, 柱层析 (正庚烷:乙酸乙酯=5:1) 得目标产物130 mg

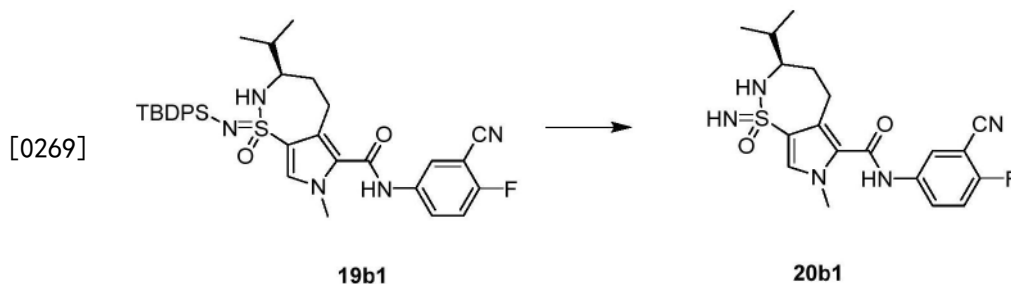
[0264] MS (M+1=552)。

[0265] 步骤2



[0267] 将12-1 (45 mg) 和3-氰基-4-氟苯胺 (23 mg) 溶于THF (6 mL) 中, 然后将体系温度降至0度, 将8当量的NaHMDS加入反应体系, 0度反应1h, 将水 (20mL) 加入反应体系, 乙酸乙酯 (3\*30mL) 萃取, 无水硫酸钠干燥, 旋干, 柱层析的黄色油状物18mg, MS (M+1=640)。

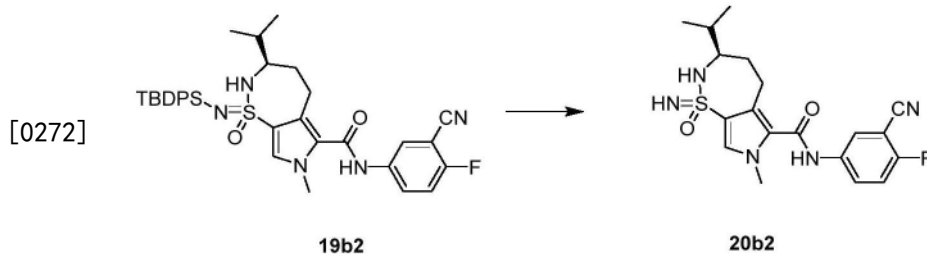
[0268] 步骤3:化合物20b1的合成



[0270] 将2 (18mg) 溶于THF (3mL) 中, 然后将50当量的3HF·TEA滴加入反应体系, 室温下反应3天, 制备板分离冷冻干燥后得白色固体4.0mg目标产物。1H NMR (400MHz, DMSO-d<sub>6</sub>) δ

10.77 (s, 1H), 8.20 (dd, J=5.8, 2.7Hz, 1H), 7.98 (ddd, J=9.2, 4.9, 2.7Hz, 1H), 7.90 (s, 1H), 7.51 (t, J=9.1Hz, 1H), 3.77 (s, 3H), 3.11-3.02 (m, 2H), 2.89-2.87 (m, 1H), 1.97-1.92 (m, 1H), 1.78-1.73 (m, 1H), 1.60-1.51 (m, 1H), 0.96 (dd, J=6.8, 3.4Hz, 6H). Ms (ESI) m/z=404 (M+1)

[0271] 实施例75: 化合物20b2的合成



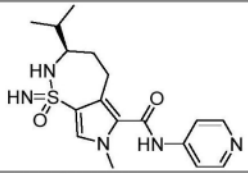
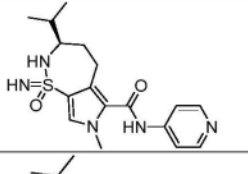
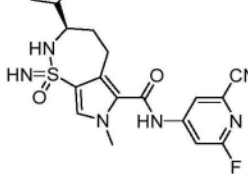
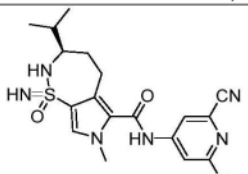
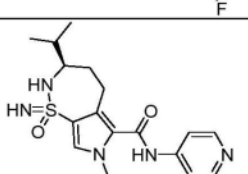
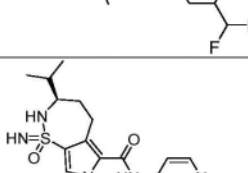
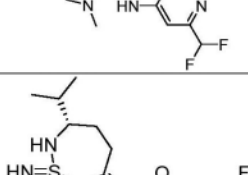
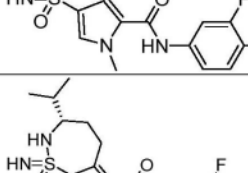
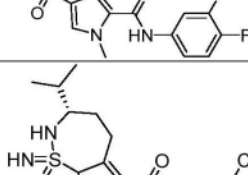
[0273] 根据实施例74的步骤3, 只需用化合物19b2代替化合物19b1, 其他条件不变, 经柱层析(正庚烷: 乙酸乙酯=1:1) 目标产物20b2 (8mg)。<sup>1</sup>H NMR (400MHz, DMSO-d<sub>6</sub>) δ 10.67 (s, 1H), 8.19 (dd, J=5.8, 2.7Hz, 1H), 7.97 (ddd, J=9.2, 4.9, 2.7Hz, 1H), 7.68 (s, 1H), 7.57 (t, J=9.1Hz, 1H), 3.76 (s, 3H), 3.04-2.92 (m, 2H), 2.85-2.83 (m, 1H), 1.90-1.83 (m, 1H), 1.74-1.69 (m, 1H), 1.67-1.46 (m, 1H), 0.89 (dd, J=6.8, 3.4Hz, 6H). Ms (ESI) m/z=404 (M+1)

[0274] 根据实施例72或实施例74的合成方法又合成了如下20, 40类系列化合物:

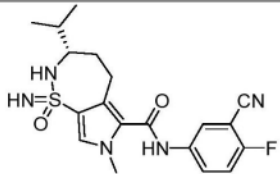
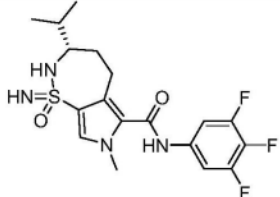
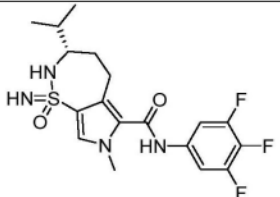
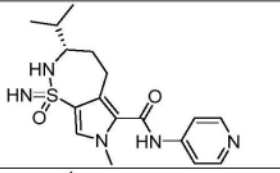
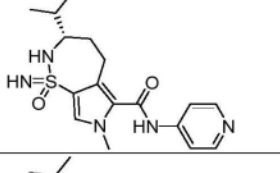
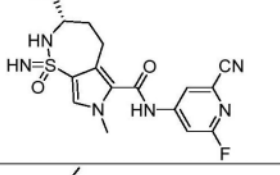
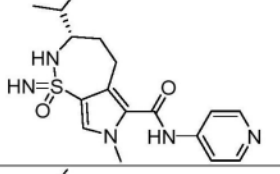
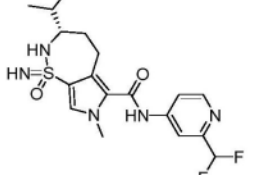
编号	结构	质谱 ESI-MS, (M+H)	备注
20c1		415	Peak1 (HPLC)
20c2		415	Peak2 (HPLC)

[0275]

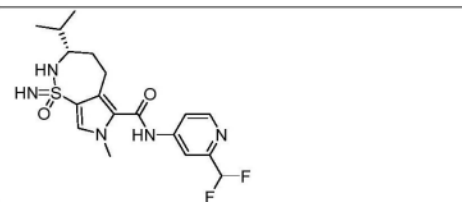
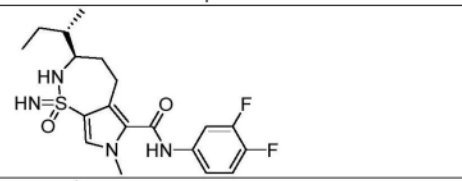
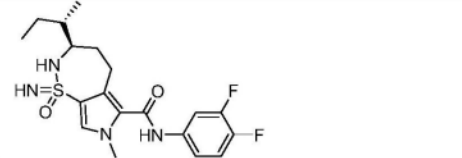
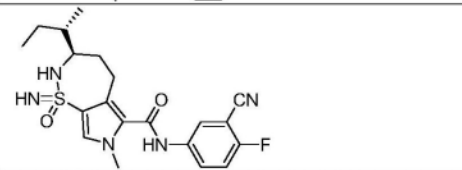
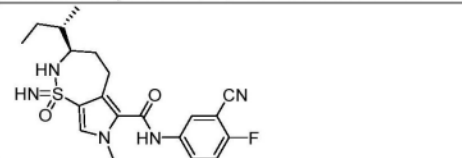
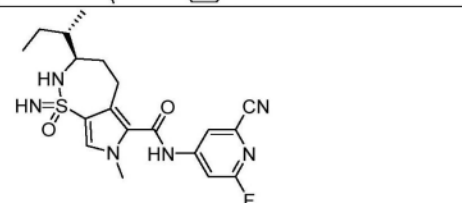
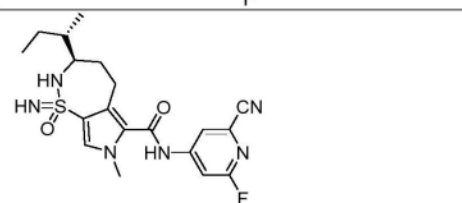
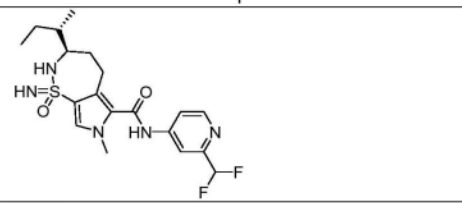
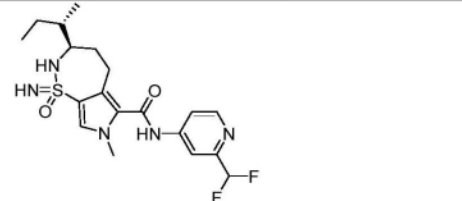
[0276]

20d1		362	Peak1 (HPLC)
20d2		362	Peak2 (HPLC)
20e1		405	Peak1 (HPLC)
20e2		405	Peak2 (HPLC)
20f1		412	Peak1 (HPLC)
20f2		412	Peak2 (HPLC)
20g1		397	Peak1 (HPLC)
20g2		397	Peak2 (HPLC)
20h1		404	Peak1 (HPLC)

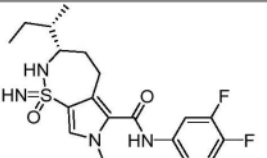
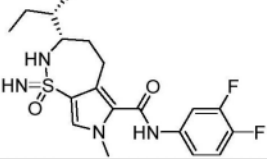
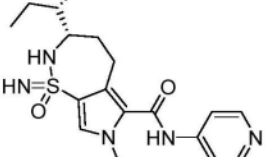
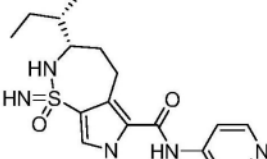
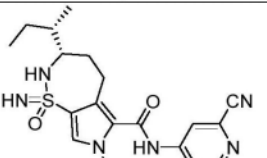
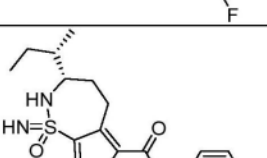
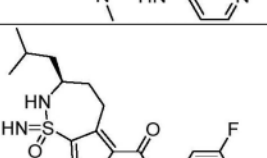
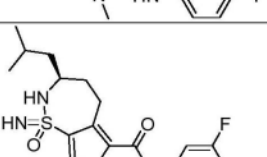
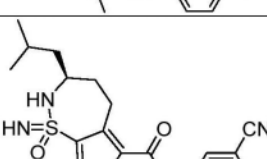
[0277]

20h2		404	Peak2 (HPLC)
20i1		415	Peak1 (HPLC)
20i2		415	Peak2 (HPLC)
20j1		362	Peak1 (HPLC)
20j2		362	Peak2 (HPLC)
20k1		405	Peak1 (HPLC)
20k2		405	Peak2 (HPLC)
20m1		412	Peak1 (HPLC)

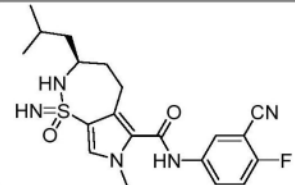
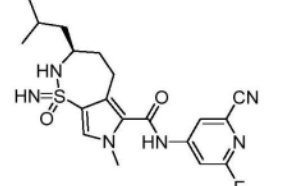
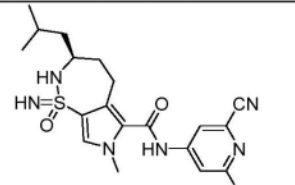
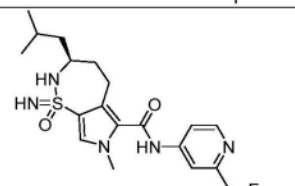
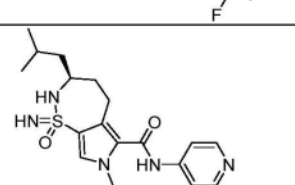
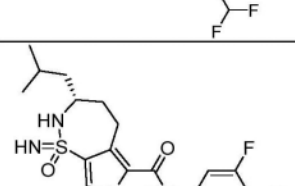
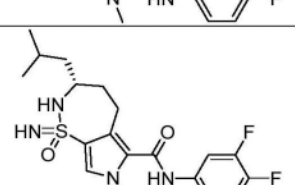
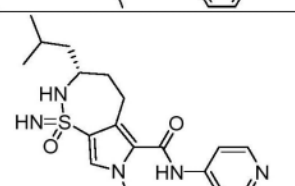
[0278]

10m2		412	Peak2 (HPLC)
20n1		411	Peak1 (HPLC)
20n2		411	Peak2 (HPLC)
20o1		418	Peak1 (HPLC)
20o2		418	Peak2 (HPLC)
20p1		419	Peak1 (HPLC)
20p2		419	Peak2 (HPLC)
20q1		426	Peak1 (HPLC)
20q2		426	Peak2 (HPLC)

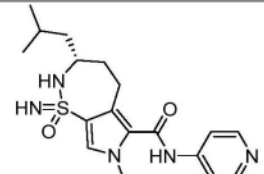
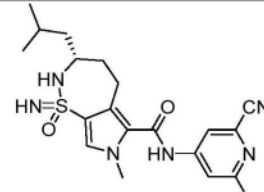
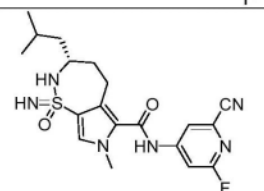
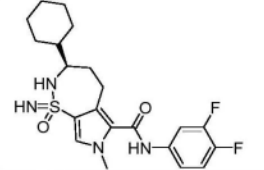
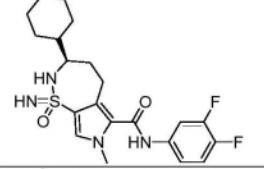
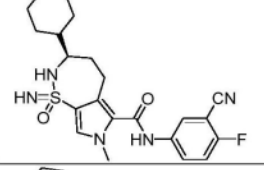
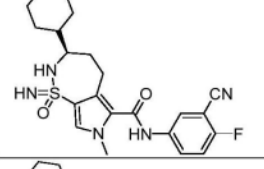
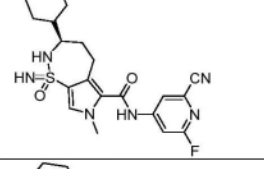
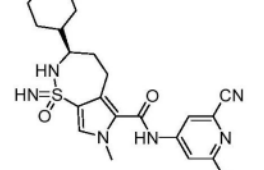
[0279]

20r1		411	Peak1 (HPLC)
20r2		411	Peak2 (HPLC)
20s1		376	Peak1 (HPLC)
20s2		376	Peak2 (HPLC)
20t1		419	Peak1 (HPLC)
20t2		419	Peak2 (HPLC)
20u1		411	Peak1 (HPLC)
20u2		411	Peak2 (HPLC)
20v1		418	Peak1 (HPLC)

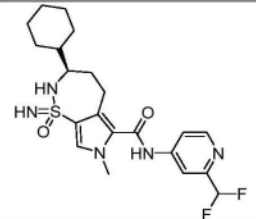
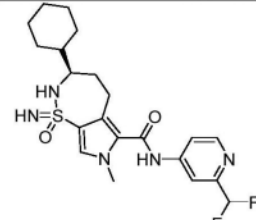
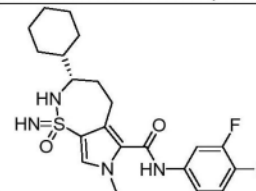
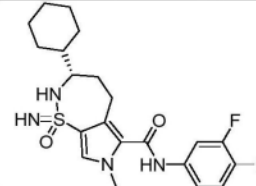
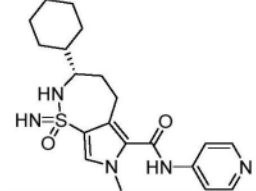
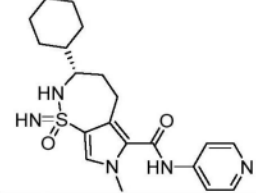
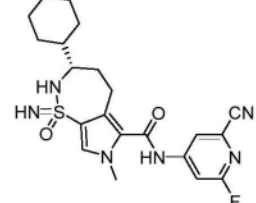
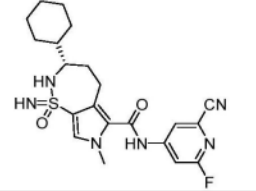
[0280]

20v2		418	Peak2 (HPLC)
20w1		419	Peak1 (HPLC)
20w2		419	Peak2 (HPLC)
20x1		426	Peak1 (HPLC)
20x2		426	Peak2 (HPLC)
20y1		411	Peak1 (HPLC)
20y2		411	Peak2 (HPLC)
20z1		376	Peak1 (HPLC)

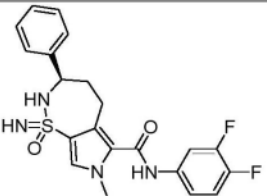
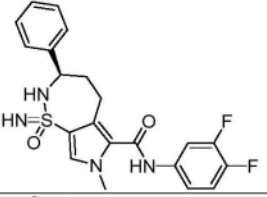
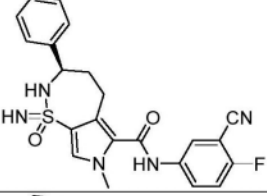
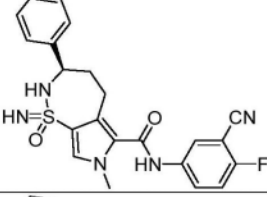
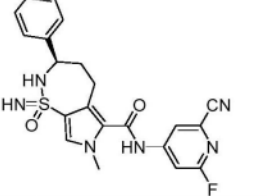
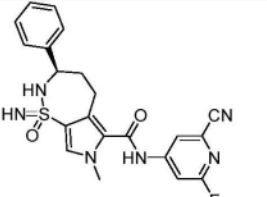
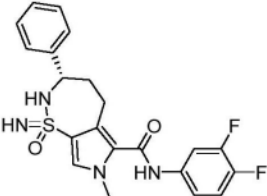
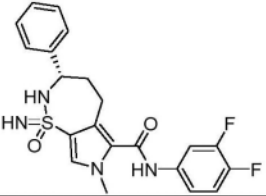
[0281]

20z2		376	Peak2 (HPLC)
20aa1		419	Peak1 (HPLC)
20aa2		419	Peak2 (HPLC)
20bb1		437	Peak1 (HPLC)
20bb2		437	Peak2 (HPLC)
20cc1		444	Peak1 (HPLC)
20cc2		444	Peak2 (HPLC)
20dd1		445	Peak1 (HPLC)
20dd2		445	Peak2 (HPLC)

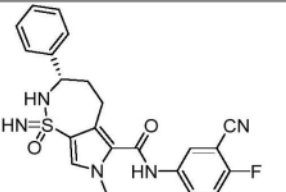
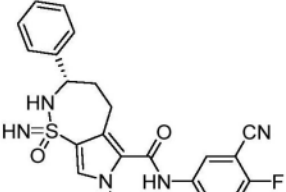
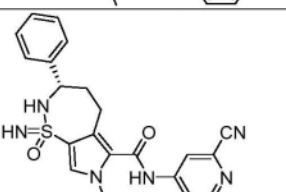
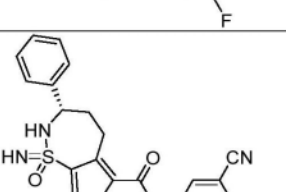
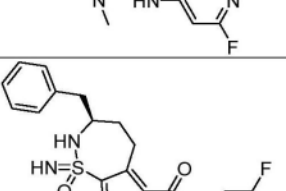
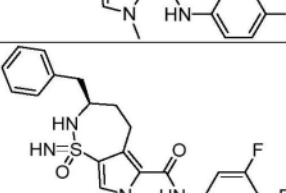
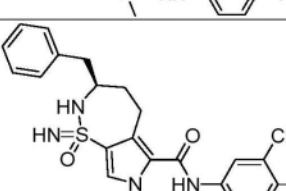
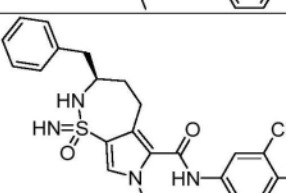
[0282]

20ee1		452	Peak1 (HPLC)
20ee2		452	Peak2 (HPLC)
20ff1		437	Peak1 (HPLC)
20ff2		437	Peak2 (HPLC)
20gg1		402	Peak1 (HPLC)
20gg2		402	Peak2 (HPLC)
20hh1		445	Peak1 (HPLC)
20hh2		445	Peak2 (HPLC)

[0283]

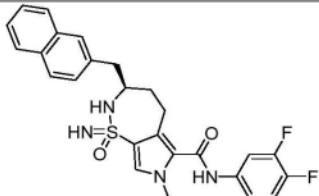
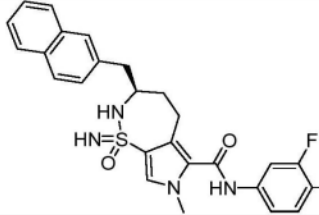
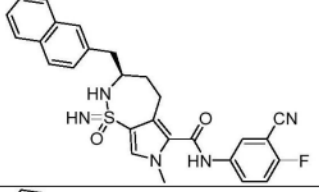
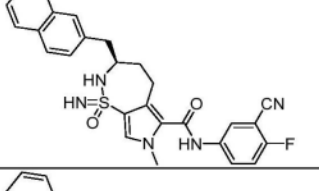
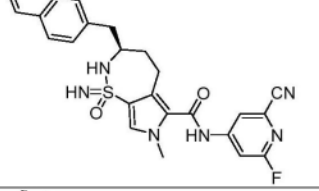
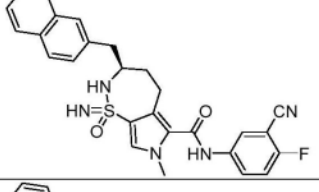
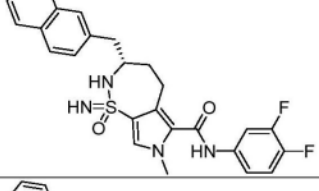
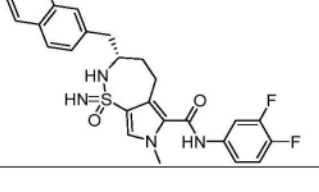
20ii1		431	Peak1 (HPLC)
20ii2		431	Peak2 (HPLC)
20jj1		438	Peak1 (HPLC)
20jj2		438	Peak2 (HPLC)
20kk1		439	Peak1 (HPLC)
20kk2		439	Peak2 (HPLC)
20mm1		431	Peak1 (HPLC)
20mm2		431	Peak2 (HPLC)

[0284]

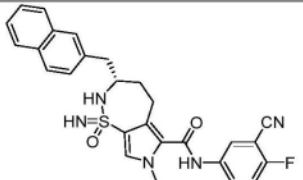
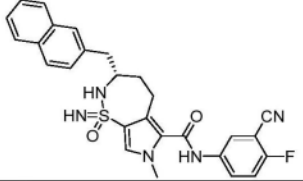
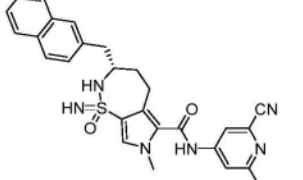
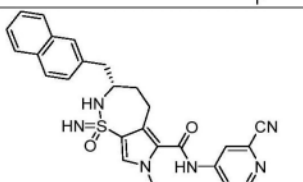
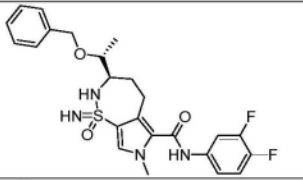
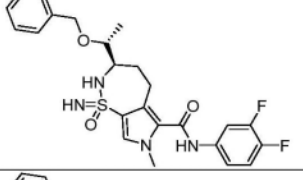
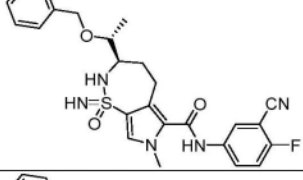
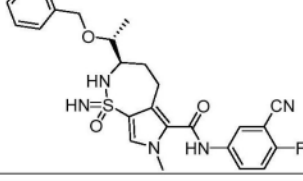
20nn1		438	Peak1 (HPLC)
20nn2		438	Peak2 (HPLC)
20oo1		439	Peak1 (HPLC)
20oo2		439	Peak2 (HPLC)
20pp1		445	Peak1 (HPLC)
20pp2		445	Peak2 (HPLC)
20qq1		452	Peak1 (HPLC)
20qq2		452	Peak2 (HPLC)



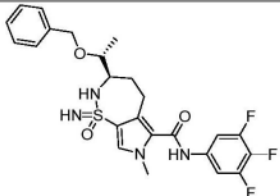
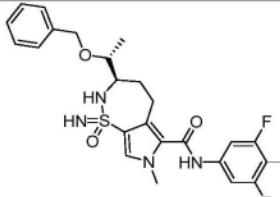
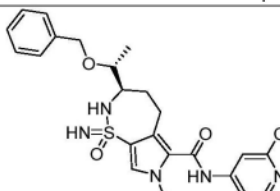
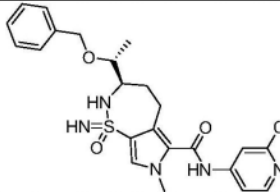
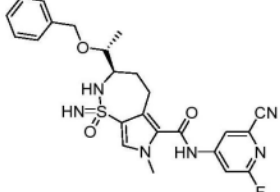
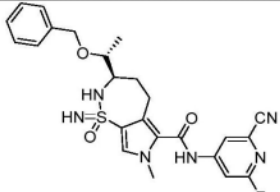
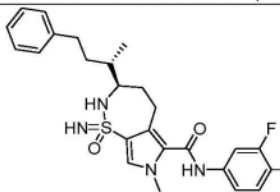
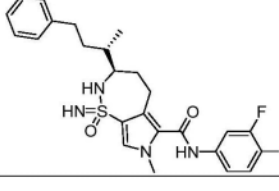
[0286]

20vv1		495	Peak1 (HPLC)
20vv2		495	Peak2 (HPLC)
20ww1		502	Peak1 (HPLC)
20ww2		502	Peak2 (HPLC)
20xx1		503	Peak1 (HPLC)
20xx2		503	Peak2 (HPLC)
20yy1		495	Peak1 (HPLC)
20yy2		495	Peak2 (HPLC)

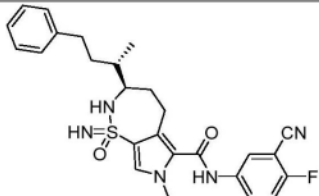
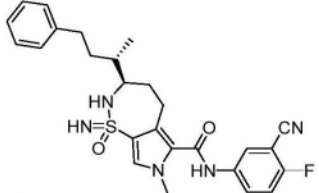
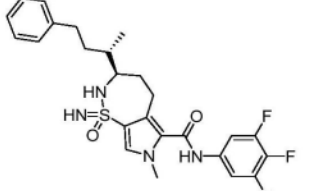
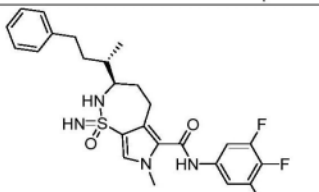
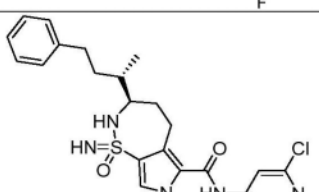
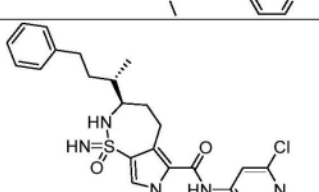
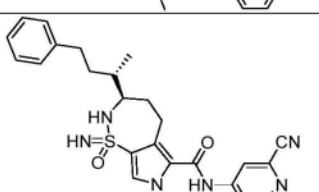
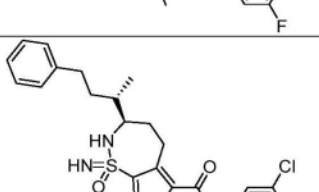
[0287]

20zz1		502	Peak1 (HPLC)
20zz2		502	Peak2 (HPLC)
20aaa1		503	Peak1 (HPLC)
20aaa2		503	Peak2 (HPLC)
20bbb1		489	Peak1 (HPLC)
20bbb2		489	Peak2 (HPLC)
20ccc1		496	Peak1 (HPLC)
20ccc2		496	Peak2 (HPLC)

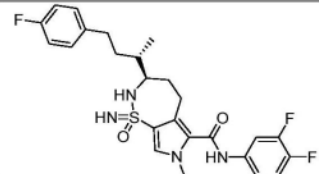
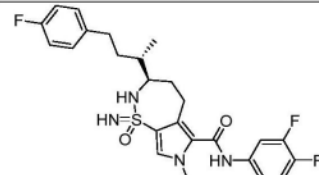
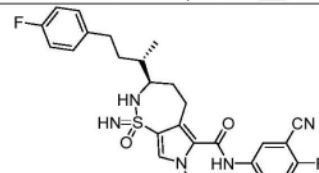
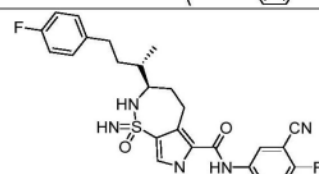
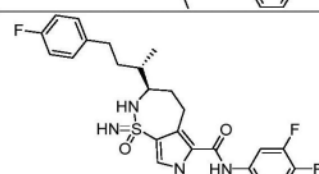
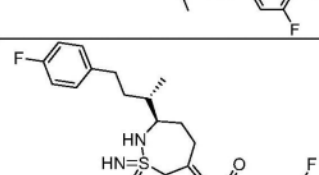
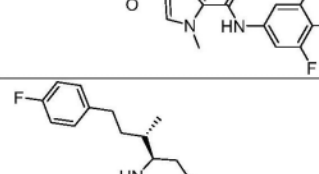
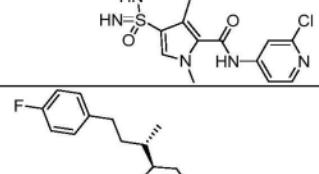
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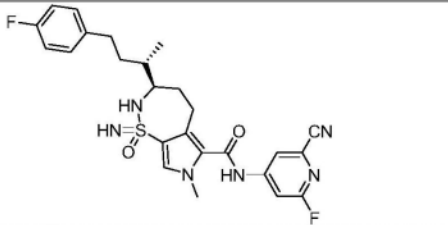
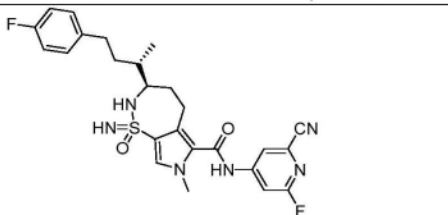
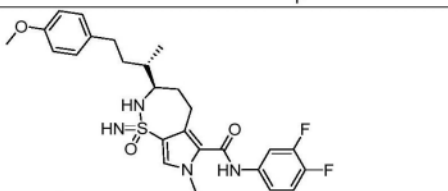
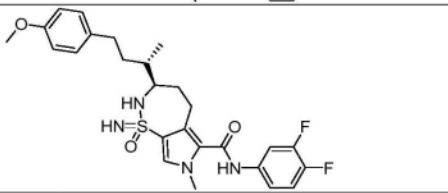
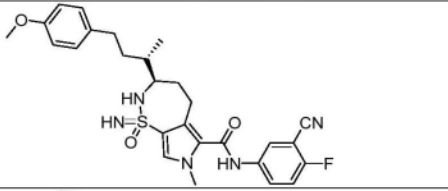
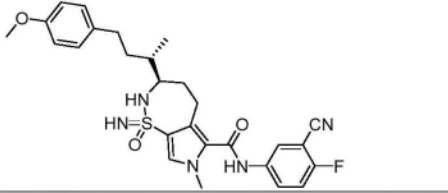
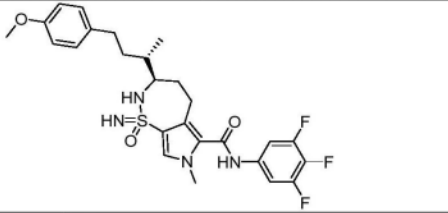
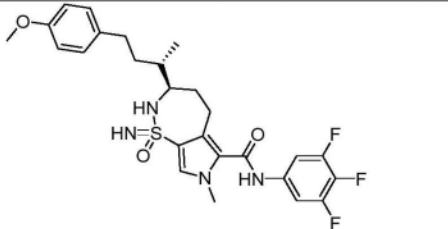
20ddd1		507	Peak1 (HPLC)
20ddd2		507	Peak2 (HPLC)
20eee1		488	Peak1 (HPLC)
20eee2		488	Peak2 (HPLC)
20fff1		497	Peak1 (HPLC)
20fff2		497	Peak2 (HPLC)
20ggg1		486	Peak1 (HPLC)
20ggg2		486	Peak2 (HPLC)

[0289]

20hhh1		494	Peak1 (HPLC)
20hhh2		494	Peak2 (HPLC)
20iii1		505	Peak1 (HPLC)
20iii2		505	Peak2 (HPLC)
20jjj1		486	Peak1 (HPLC)
20jjj2		486	Peak2 (HPLC)
20kkk1		495	Peak1 (HPLC)
20kkk2		495	Peak2 (HPLC)

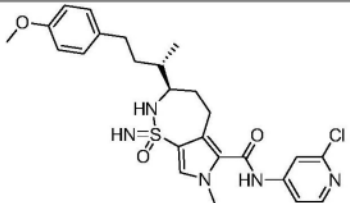
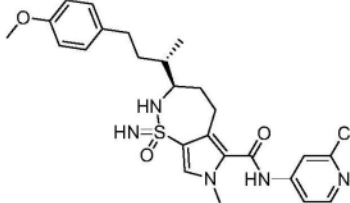
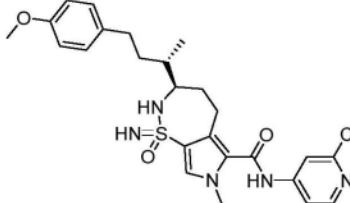
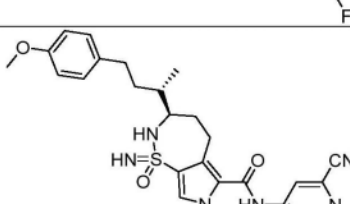
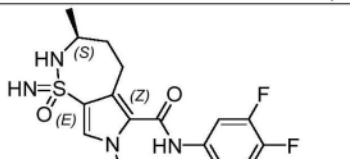
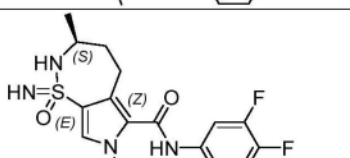
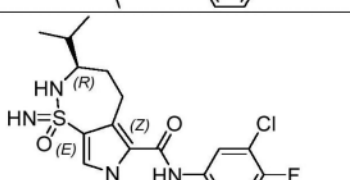
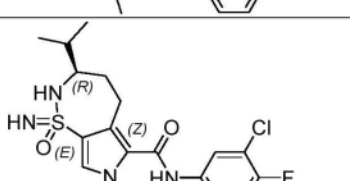
[0290]

20mmm1		505	Peak1 (HPLC)
20mmm2		505	Peak2 (HPLC)
20nnn1		512	Peak1 (HPLC)
20nnn2		512	Peak2 (HPLC)
20ooo1		523	Peak1 (HPLC)
20ooo2		523	Peak2 (HPLC)
20ppp1		504	Peak1 (HPLC)
20ppp2		504	Peak2 (HPLC)

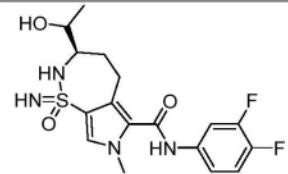
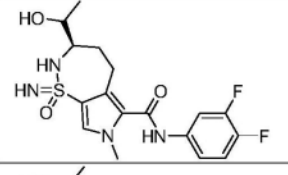
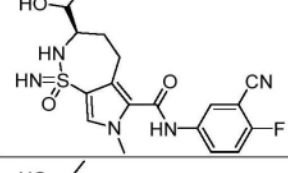
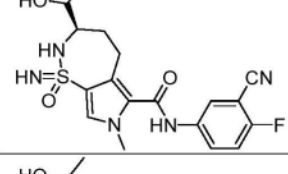
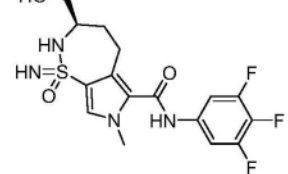
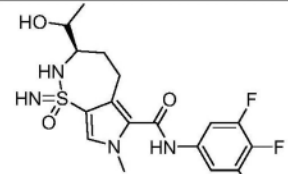
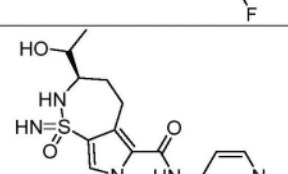
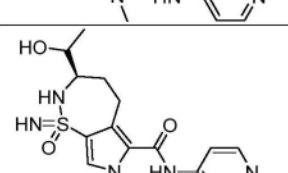
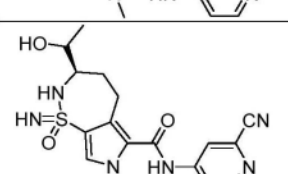
20qqq1		513	Peak1 (HPLC)
20qqq2		513	Peak2 (HPLC)
20rrr1		517	Peak1 (HPLC)
20rrr2		517	Peak2 (HPLC)
20sss1		524	Peak1 (HPLC)
20sss2		524	Peak2 (HPLC)
20ttt1		535	Peak1 (HPLC)
20ttt2		535	Peak2 (HPLC)

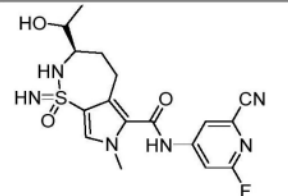
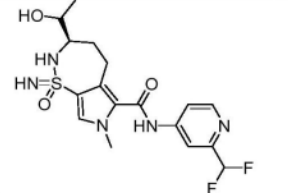
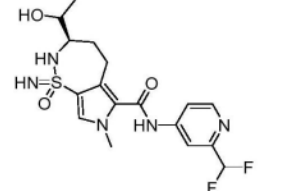
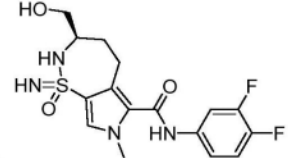
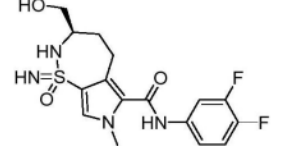
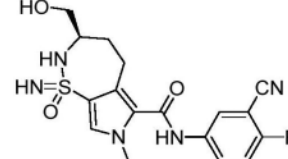
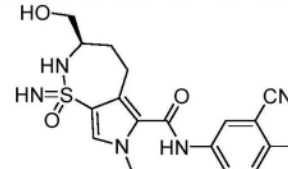
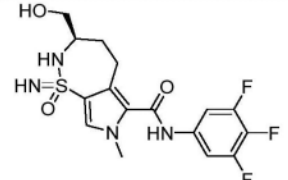
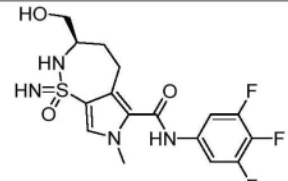
[0291]

[0292]

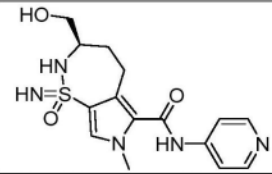
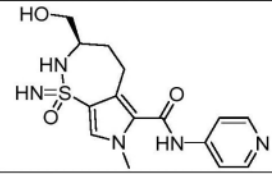
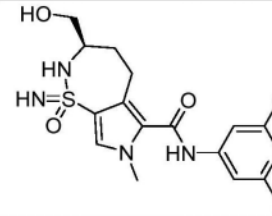
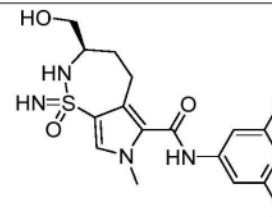
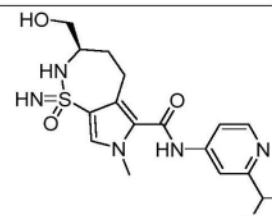
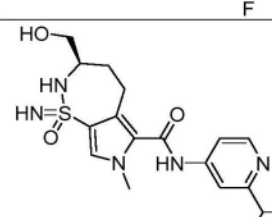
20uuu1		516	Peak1 (HPLC)
20uuu2		516	Peak2 (HPLC)
20vvv1		525	Peak1 (HPLC)
20vvv2		525	Peak2 (HPLC)
20www1		369	Peak1 (HPLC)
20www2		369	Peak2 (HPLC)
20xxx1		413	Peak1 (HPLC)
20xxx2		413	Peak2 (HPLC)

[0293]

40a1		399	Peak1 (HPLC)
40a2		399	Peak2 (HPLC)
40b1		406	Peak1 (HPLC)
40b2		406	Peak2 (HPLC)
40c1		417	Peak1 (HPLC)
40c2		417	Peak2 (HPLC)
40d1		364	Peak1 (HPLC)
40d2		364	Peak2 (HPLC)
40e1		407	Peak1 (HPLC)

40e2		407	Peak2 (HPLC)
40f1		414	Peak1 (HPLC)
40f2		414	Peak2 (HPLC)
40g1		385	Peak1 (HPLC)
40g2		385	Peak2 (HPLC)
40h1		392	Peak1 (HPLC)
40h2		392	Peak2 (HPLC)
40i1		403	Peak1 (HPLC)
40i2		403	Peak2 (HPLC)

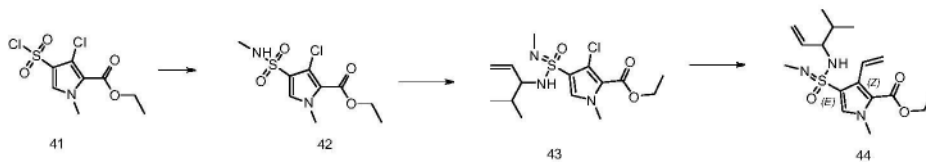
[0294]

40j1		350	Peak1 (HPLC)
40j2		350	Peak2 (HPLC)
40k1		393	Peak1 (HPLC)
40k2		393	Peak2 (HPLC)
40m1		400	Peak1 (HPLC)
40m2		400	Peak2 (HPLC)

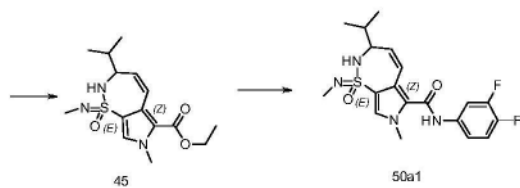
[0295]

[0296] 下面为50类化合物的合成:

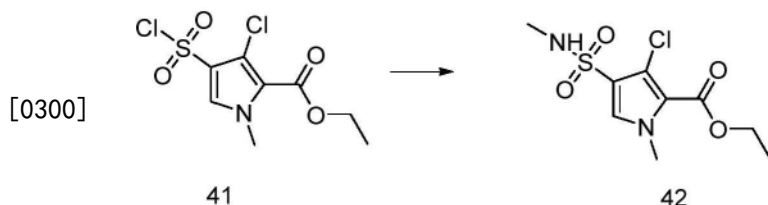
[0297] 实施例167:化合物50a1的合成



[0298]

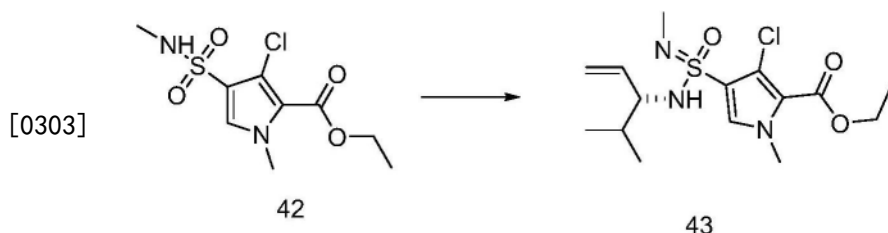


[0299] 步骤1:化合物42的合成



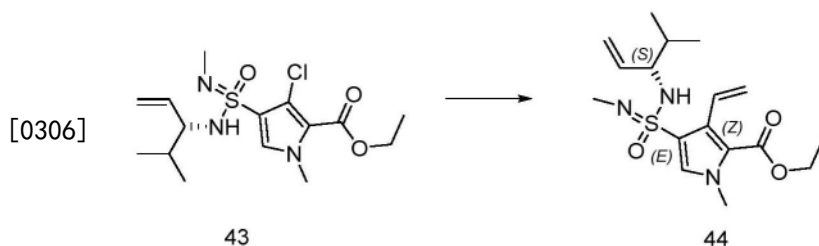
[0301] 将化合物41 (10g) 溶于二氯甲烷 (40mL) 中, 室温下将甲胺水溶液 (30mL) 滴加入反应体系, 室温, 反应5h, 抽滤, 滤饼用水 (5mL) 洗涤, 得42淡黄色固体5g, MS (M+1=281)。

[0302] 步骤2: 化合物43的合成



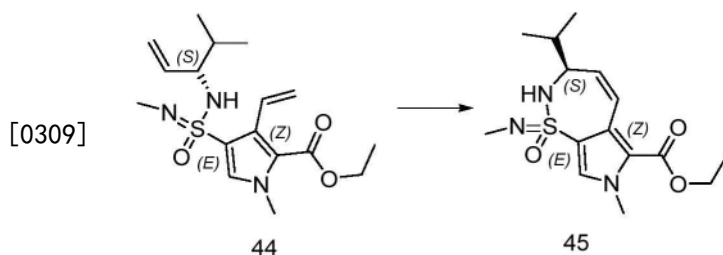
[0304] 将PPh<sub>3</sub>C12的氯仿溶液 (80mL) 冷至0度, 然后将三乙胺 (7mL), 搅拌10min后0度下加入化合物42, (5.0g) 搅拌20min后, 将2-异丙基-3-丙烯胺 (5g) 加入反应体系, 室温反应18h, 向反应体系中加入水 (20mL), 乙酸乙酯 (3\*25mL) 萃取, 有机相干燥、旋干, 粗品柱层析 (正庚烷: 乙酸乙酯=1:5), 得产物43 (400mg)。MS (M+1=362)。

[0305] 步骤3: 化合物44的合成



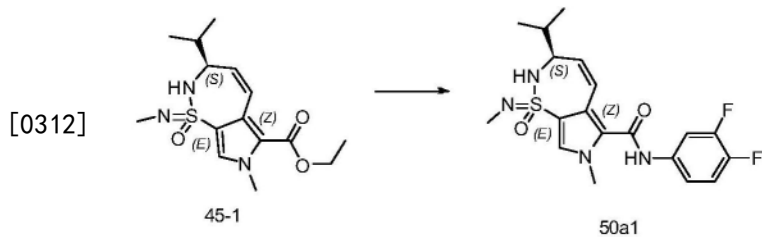
[0307] 将化合物43 (1.8g), 四三苯基磷钡 (100mg), 乙烯基硼酸酯 (900g), 碳酸铯 (2.7g), 溶于DMF (410mL) 中, 氮气保护下, 100度反应15h, 用水溶液淬灭反应, 乙酸乙酯萃取, 有机相干燥、旋干, 所得粗品柱层析 (正庚烷: 乙酸乙酯=1:5) 得化合物44 (0.5g)。MS (M+1=354)。

[0308] 步骤4: 化合物45的合成



[0310] 将化合物44 (1.0g) 溶于二氯甲烷 (500ml) 中, 然后将詹氏催化剂 (0.1g) 加入反应体系, 搅拌过夜, 将反应液旋干, 粗品柱柱层析 (正庚烷: 乙酸乙酯=1:3) 得化合物45。TLC显示的下点45-1 (0.22g), TLC显示的上点45-2 (0.27g) MS (M+1=312)。

[0311] 步骤5: 化合物50a1的合成

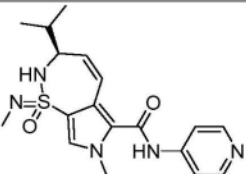
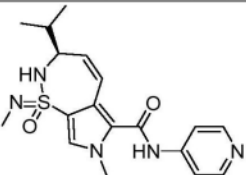
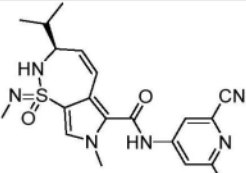
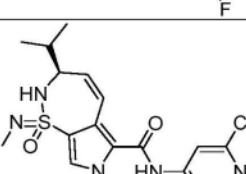
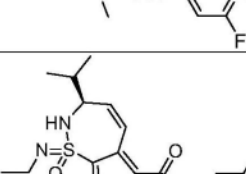
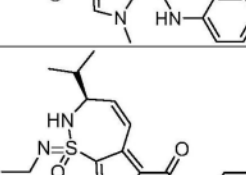
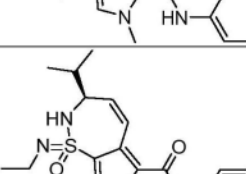
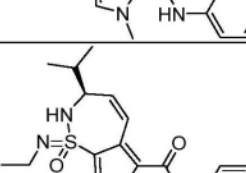
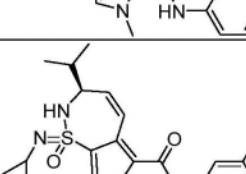


[0313] 将化合物45-1 (30mg) 和4-氟-3-氰基苯胺 (20mg) 溶于四氢呋喃 (5mL) 中, 降温至0度, 然后将NaHMDS (0.2mL) 加入反应体系, 室温搅拌反应16h, 将水加入反应体系, 乙酸乙酯 (3\*15mL) 萃取, 有机相用无水硫酸钠干燥, 旋干, 粗品经柱层析 (正庚烷: 乙酸乙酯=1:3) 目标产物50a1 (11mg)。MS (M+1=409)。

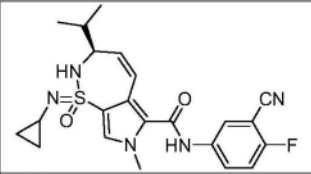
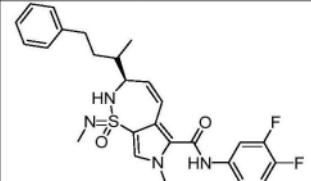
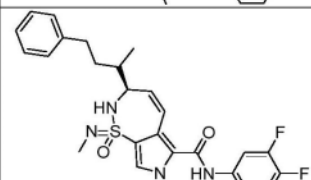
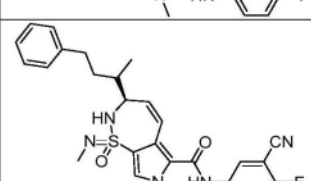
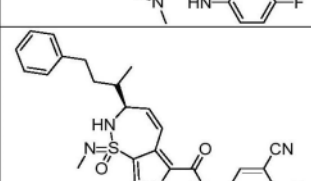
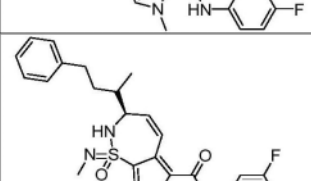
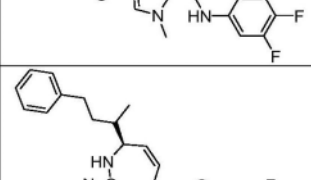
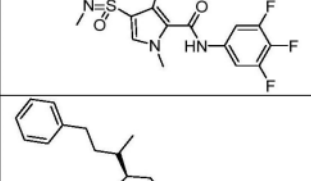
[0314] 根据实施例167的合成方法又合成了如下50类系列化合物:

编号	结构	质谱 ESI-MS, (M+H)	备注
50b1		416	Peak1 (HPLC)
50b2		416	Peak2 (HPLC)
50c1		413	Peak1 (HPLC)
50c2		427	Peak2 (HPLC)

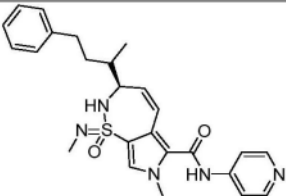
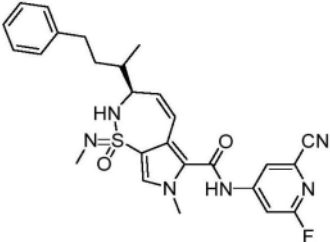
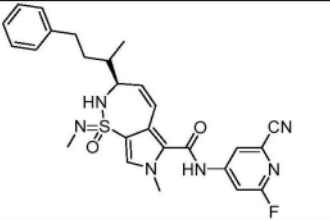
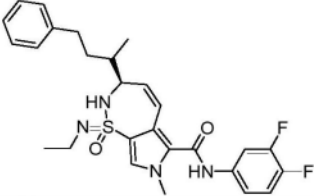
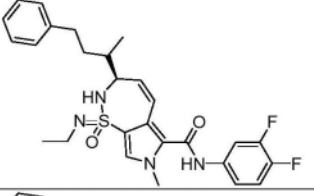
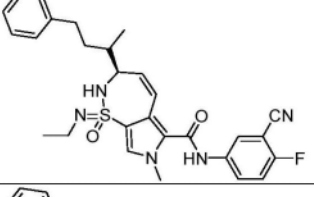
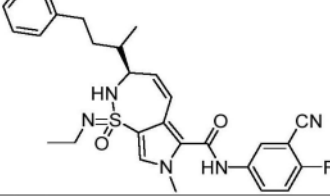
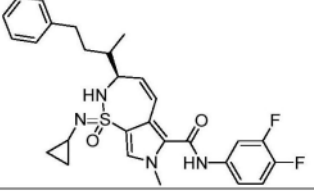
[0316]

50d1		374	Peak1 (HPLC)
50d2		360	Peak2 (HPLC)
50e1		417	Peak1 (HPLC)
50e2		417	Peak2 (HPLC)
50f1		423	Peak1 (HPLC)
50f2		423	Peak2 (HPLC)
50g1		430	Peak1 (HPLC)
50g2		430	Peak2 (HPLC)
50h1		442	Peak1 (HPLC)

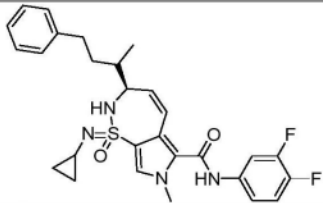
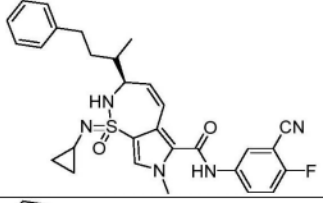
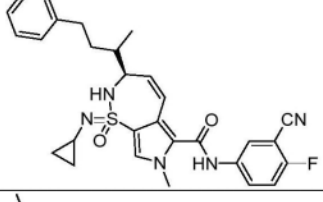
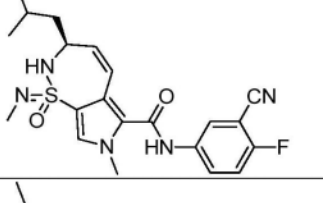
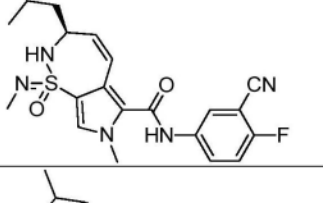
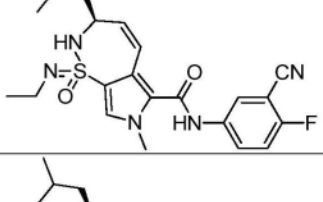
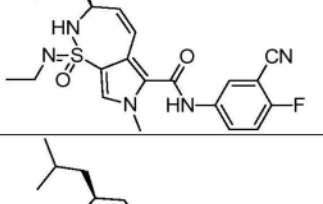
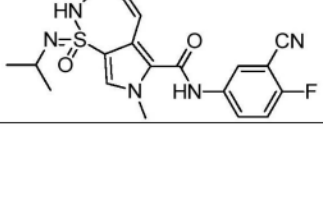
[0317]

50h2		442	Peak2 (HPLC)
50i1		499	Peak1 (HPLC)
50i2		499	Peak2 (HPLC)
50j1		506	Peak1 (HPLC)
50j2		506	Peak2 (HPLC)
50k1		517	Peak1 (HPLC)
50k2		427	Peak2 (HPLC)
50m1		464	Peak1 (HPLC)

[0318]

50m2		464	Peak2 (HPLC)
50n1		507	Peak1 (HPLC)
50n2		507	Peak2 (HPLC)
50o1		513	Peak1 (HPLC)
50o2		513	Peak2 (HPLC)
50p1		520	Peak1 (HPLC)
50p2		520	Peak2 (HPLC)
50q1		525	Peak1 (HPLC)

[0319]

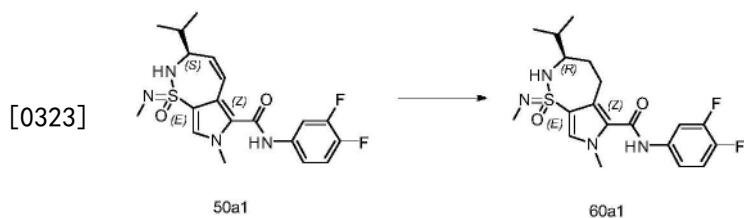
50q2		525	Peak2 (HPLC)
50r1		532	Peak1 (HPLC)
50r2		532	Peak2 (HPLC)
50s1		430	Peak1 (HPLC)
50s2		430	Peak2 (HPLC)
50t1		444	Peak1 (HPLC)
50t2		444	Peak2 (HPLC)
50u1		458	Peak1 (HPLC)

[0320]

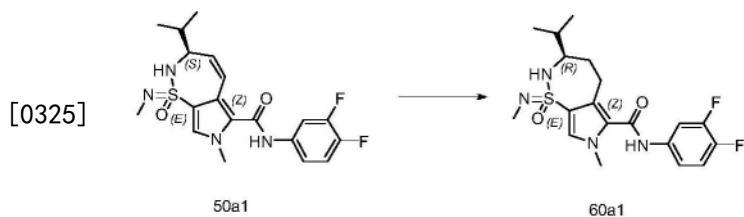
50u2		458	Peak2 (HPLC)
50v1		456	Peak1 (HPLC)
50v2		456	Peak2 (HPLC)
50w1		381	Peak1 (HPLC)
50w2		381	Peak2 (HPLC)
50x1		423	Peak1 (HPLC)
50x2		423	Peak2 (HPLC)

[0321] 下面为60类化合物的合成:

[0322] 实施例186:化合物60a1的合成



[0324] 步骤1



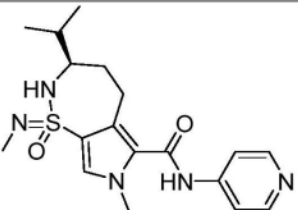
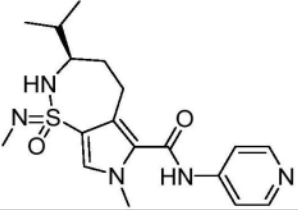
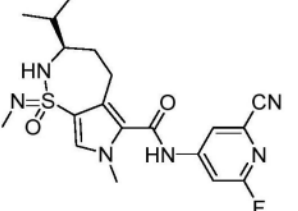
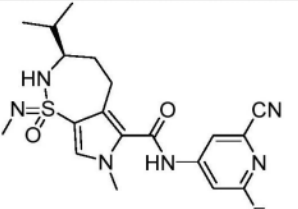
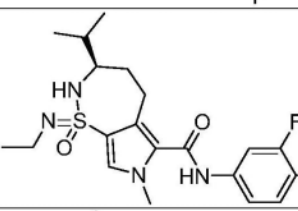
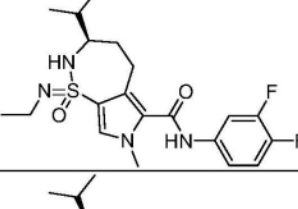
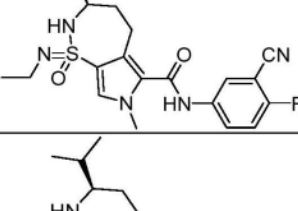
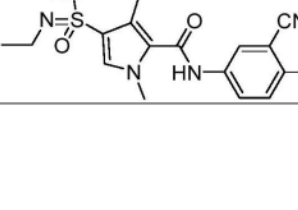
[0326] 将化合物50a1 (20mg) 溶于甲醇 (5mL), 然后将钨碳 (5mg) 加入反应体系, 氢气保护下室温反应6h, 粗品经柱层析 (正庚烷: 乙酸乙酯=1:3) 目标产物60a1 (11mg)。

[0327] MS (M+1=411)

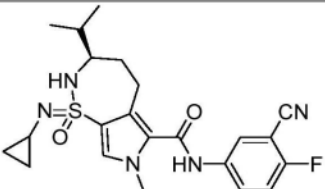
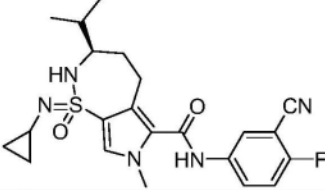
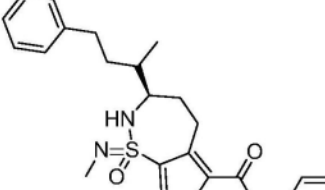
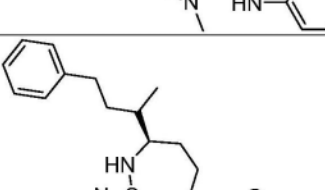
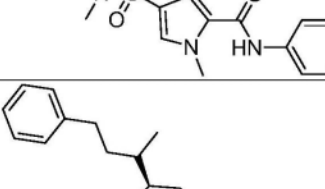
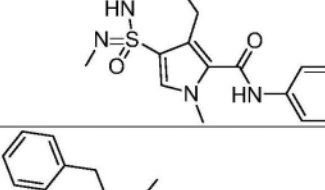
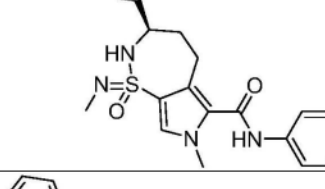
[0328] 根据实施例186的合成方法又合成了如下60类系列化合物:

编号	结构	质谱 ESI-MS, (M+H)	备注
60a2		411	Peak2 (HPLC)
60b1		418	Peak1 (HPLC)
[0329] 60b2		418	Peak2 (HPLC)
60c1		429	Peak1 (HPLC)
60c2		429	Peak2 (HPLC)

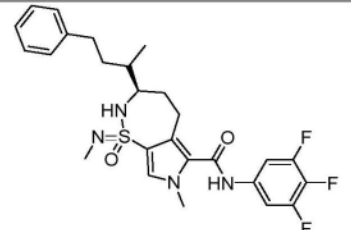
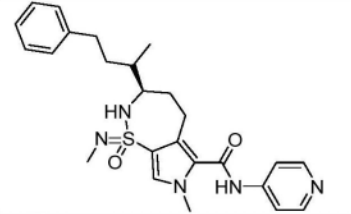
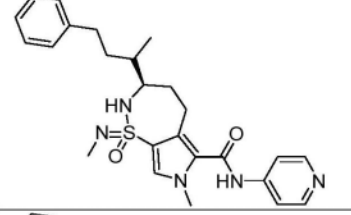
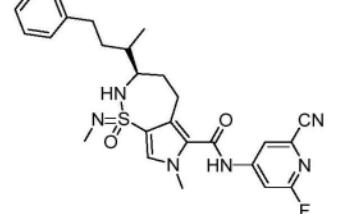
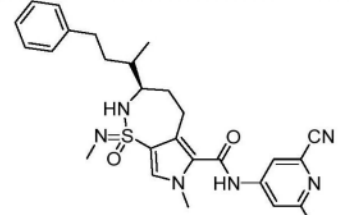
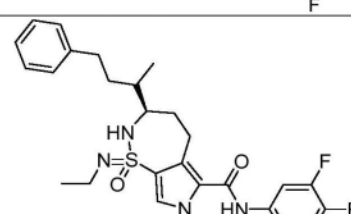
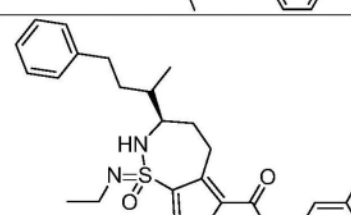
[0330]

60d1		376	Peak1 (HPLC)
60d2		376	Peak2 (HPLC)
60e1		419	Peak1 (HPLC)
60e2		419	Peak2 (HPLC)
60f1		425	Peak1 (HPLC)
60f2		425	Peak2 (HPLC)
60g1		432	Peak1 (HPLC)
60g2		432	Peak2 (HPLC)

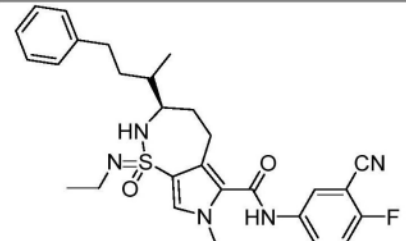
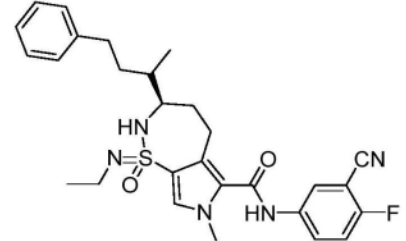
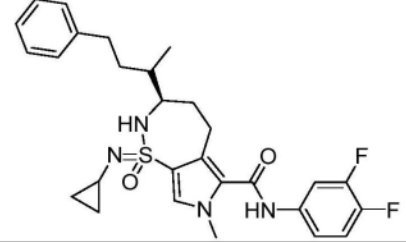
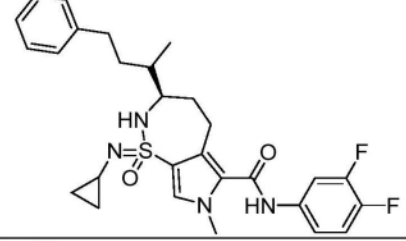
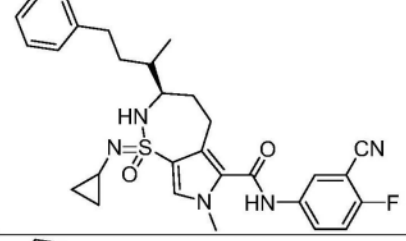
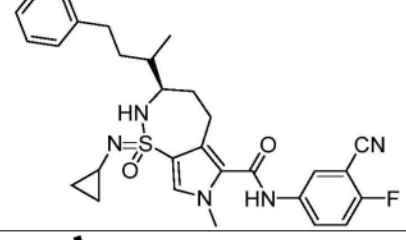
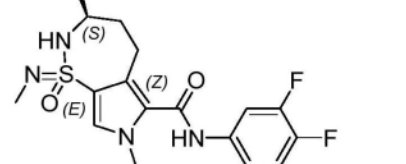
[0331]

60h1		446	Peak1 (HPLC)
60h2		446	Peak2 (HPLC)
60i1		501	Peak1 (HPLC)
60i2		501	Peak2 (HPLC)
60j1		508	Peak1 (HPLC)
60j2		508	Peak2 (HPLC)
60k1		519	Peak1 (HPLC)

[0332]

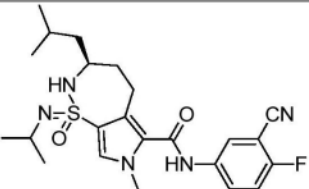
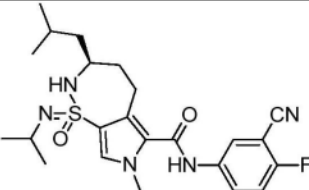
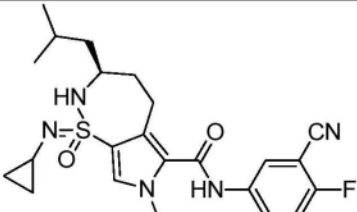
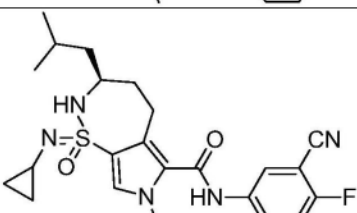
60k2		519	Peak2 (HPLC)
60m1		466	Peak1 (HPLC)
60m2		466	Peak2 (HPLC)
60n1		509	Peak1 (HPLC)
60n2		509	Peak2 (HPLC)
60o1		515	Peak1 (HPLC)
60o2		515	Peak2 (HPLC)

[0333]

60p1		522	Peak1 (HPLC)
60p2		522	Peak2 (HPLC)
60q1		527	Peak1 (HPLC)
60q2		527	Peak2 (HPLC)
60r1		534	Peak1 (HPLC)
60r2		534	Peak2 (HPLC)
60s1		383	Peak1 (HPLC)

[0334]

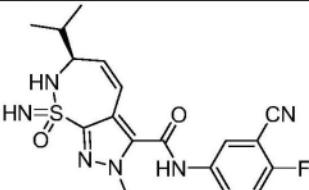
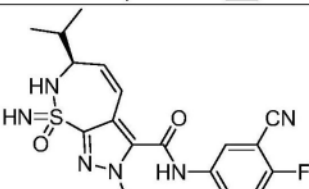
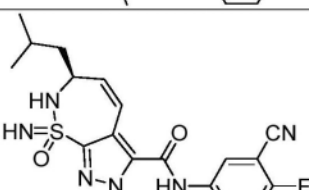
60s2		383	Peak2 (HPLC)
60t1		425	Peak1 (HPLC)
60t2		425	Peak2 (HPLC)
60u1		451	Peak1 (HPLC)
60u2		451	Peak2 (HPLC)
60v1		432	Peak1 (HPLC)
60v2		432	Peak2 (HPLC)
60w1		446	Peak1 (HPLC)
60w2		446	Peak2 (HPLC)

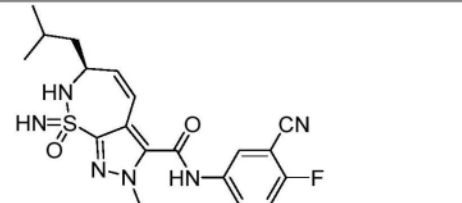
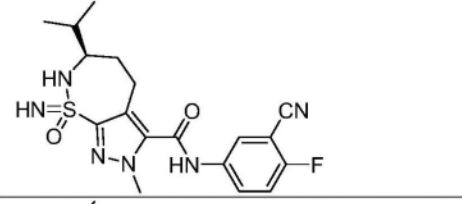
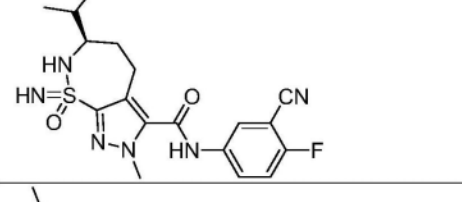
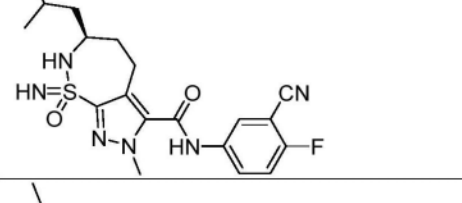
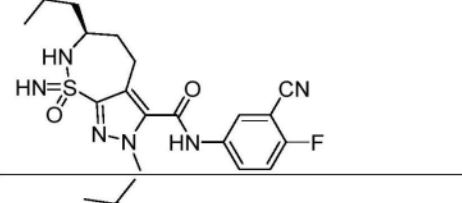
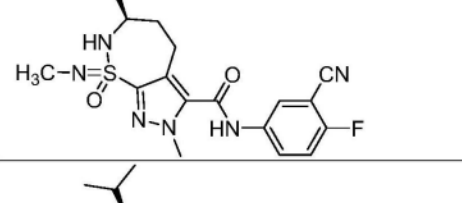
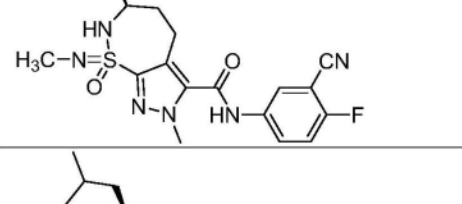
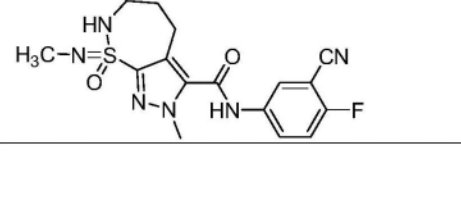
	60x1		460	Peak1 (HPLC)
	60x2		460	Peak2 (HPLC)
[0335]	60y1		458	Peak1 (HPLC)
	60y2		458	Peak2 (HPLC)

[0336] 下面为70、80和90类化合物的合成:

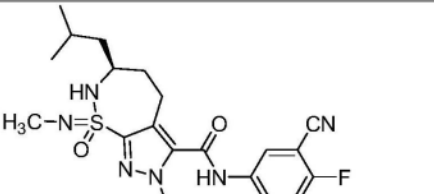
[0337] 实施例234:化合物70a1的合成

[0338] 根据实施例74和实施例167的合成步骤,用吡唑类化合物代替吡咯类化合物可以得到下面列表中的化合物。

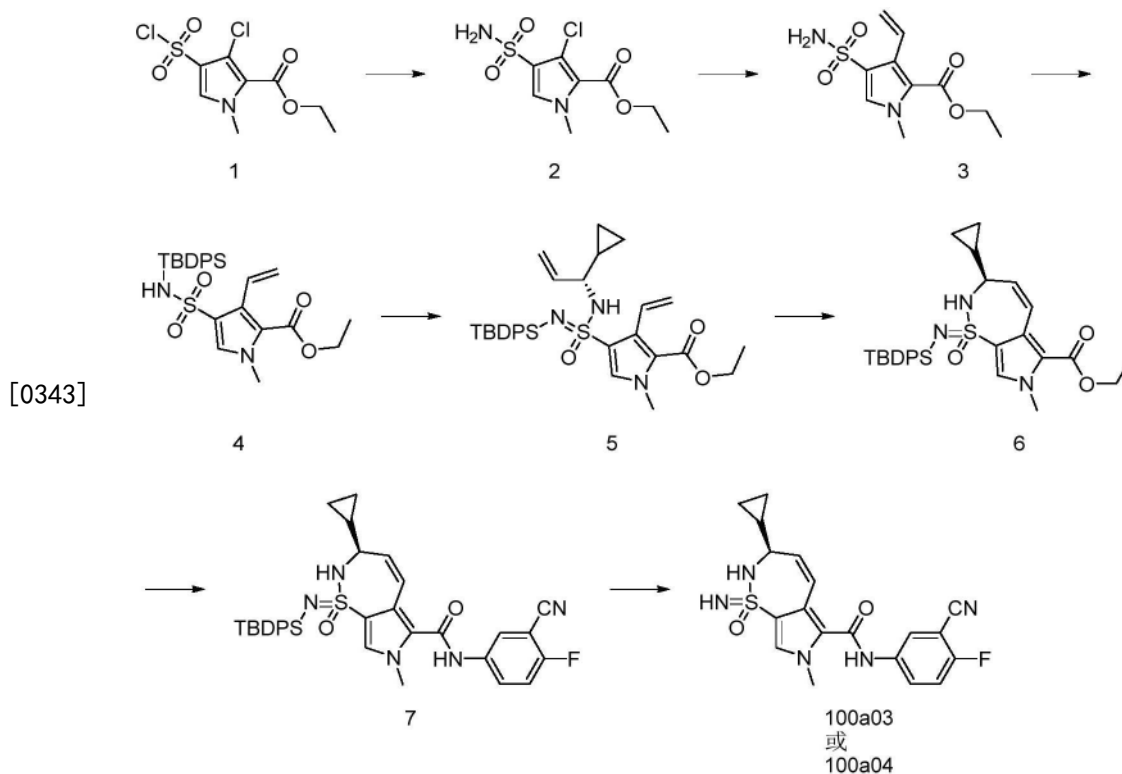
	70a1		403	Peak1 (HPLC)
	70a2		403	Peak2 (HPLC)
[0339]	70b1		417	Peak1 (HPLC)

70b2		417	Peak2 (HPLC)
80a1		405	Peak1 (HPLC)
80a2		405	Peak2 (HPLC)
80b1		419	Peak1 (HPLC)
80b2		419	Peak2 (HPLC)
90a1		419	Peak1 (HPLC)
90a2		419	Peak2 (HPLC)
90b1		433	Peak1 (HPLC)

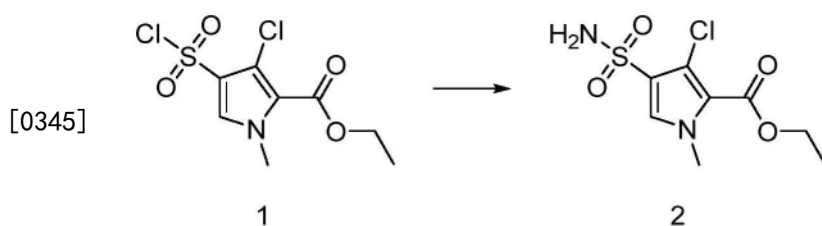
[0340]

[0341]		433	Peak2 (HPLC)
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[0342] 实施例235:化合物100a03和化合物100a04的合成

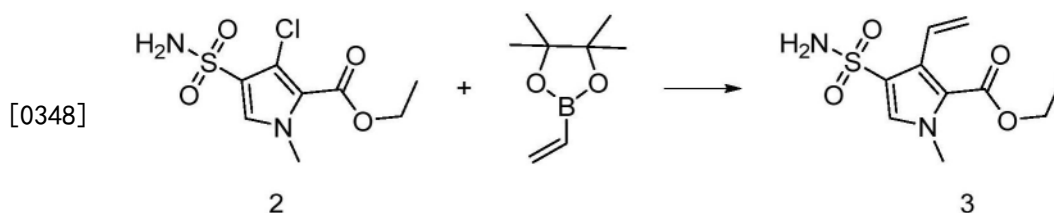


[0344] 步骤1:化合物2的合成



[0346] 将化合物1 (10g) 溶于二氯甲烷 (40mL) 中, 室温下将氨水 (30mL) 滴加入反应体系, 室温, 反应5h, 抽滤, 滤饼用水 (5mL) 洗涤, 得2淡黄色固体5g, MS (M+1=267)。

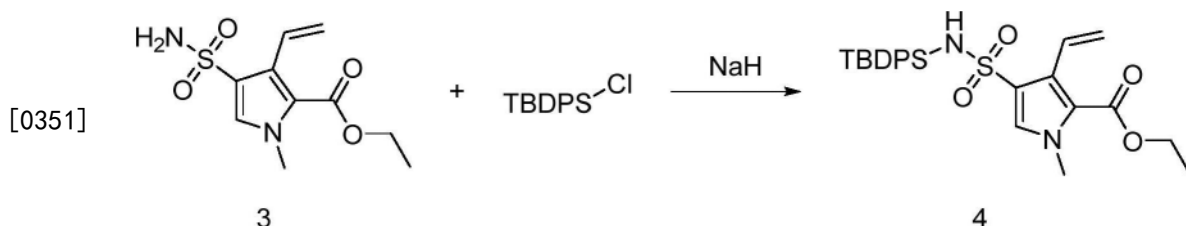
[0347] 步骤2:化合物3的合成



[0349] 将化合物2 (1.8g), XPhos Pd G3 (100mg), 乙烯基硼酸频哪酯 (3.12g), 碳酸铯 (2.7g), 溶于DMF (180mL) / 水 (18mL) 中, 氮气保护下, 100度反应15h, 用水溶液淬灭反应, 乙酸乙酯萃取, 有机相干燥、旋干, 所得粗品柱层析 (正庚烷: 乙酸乙酯=1:5) 得化合物5

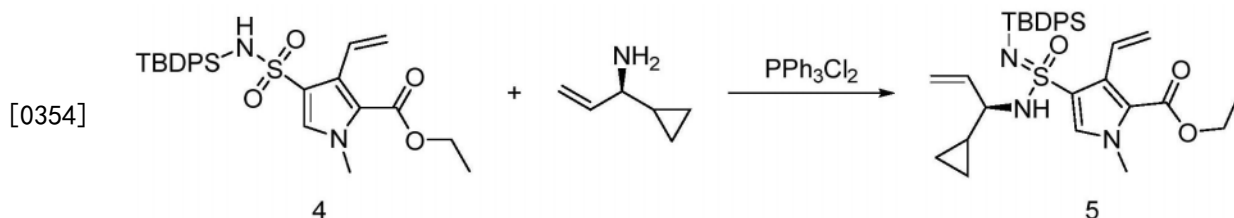
(0.89g), MS ( $M+1=259$ )。

[0350] 步骤3: 化合物4的合成



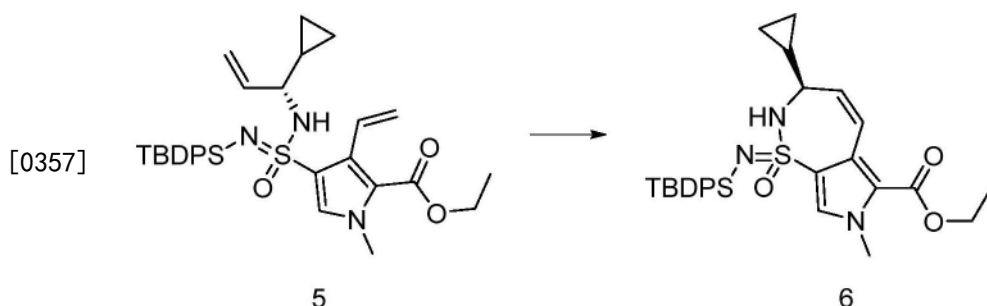
[0352] 将底物3 (5.0g) 溶于DMF (50mL), 0度下将氢化钠 (560mg) 加入反应体系, 搅拌15min 然后将TBDPSCl (6.38g) 加入反应体系, 反应18h, 将反应体系倒入冰水中, 乙酸乙酯 (3\*30mL) 萃取, 有机相干燥、旋干, 粗品柱层析 (正庚烷: 乙酸乙酯=1:4), 得产物4 (9.03g)。<sup>1</sup>H NMR (400MHz, DMSO-*d*<sub>6</sub>) δ 10.78 (s, 1H), 7.62-7.59 (m, 1H), 7.45-7.41 (m, 1H), 7.33-7.29 (m, 3H), 7.13 (qd, *J*=4.7, 4.2, 2.5Hz, 2H), 6.16 (dd, *J*=12.4, 2.7Hz, 1H), 5.58 (dd, *J*=12.4, 2.8Hz, 1H), 5.09 (s, 1H), 4.35-4.40 (m, 2), 3.56 (s, 3H), 1.45-1.40 (m, 3), 1.04 (s, 9H)。MS ( $M+1=497$ )。

[0353] 步骤4: 化合物5的合成



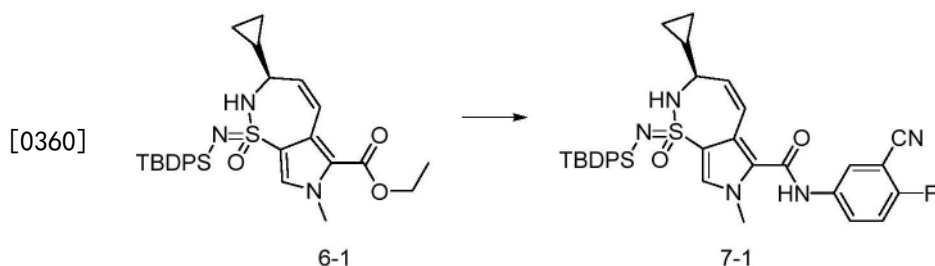
[0355] 将PPh<sub>3</sub>Cl<sub>2</sub> (3.63g) 加入氯仿 (80mL) 中冷至0度, 然后加入三乙胺 (7mL), 搅拌10min 后0度下加入化合物4 (5.00g), 搅拌20min后, 将(R)-1-环丙基丙-2-烯-1-胺 (962mg) 加入反应体系, 室温反应18h, 向反应体系中加水 (20mL), 乙酸乙酯 (3\*30mL) 萃取, 有机相干燥、旋干, 粗品柱层析分离 (正庚烷: 乙酸乙酯=1:5), 得产物5 (3.47g), 为一对差向异构体的混合物。MS ( $M+1=585$ )。

[0356] 步骤5: 化合物6的合成



[0358] 将化合物5 (1.0g) 溶于二氯乙烷 (500mL) 中, 然后将詹氏催化剂 (0.1g) 加入反应体系, 加热回流搅拌过夜, 将反应液旋干, 柱层析 (正庚烷: 乙酸乙酯=1:3) 分离得到两个化合物为硫原子上的手性异构体, TLC显示的上点6-1 (0.35g) MS ( $M+1=548$ ), TLC显示的下点6-2 (0.35g) MS ( $M+1=548$ )。

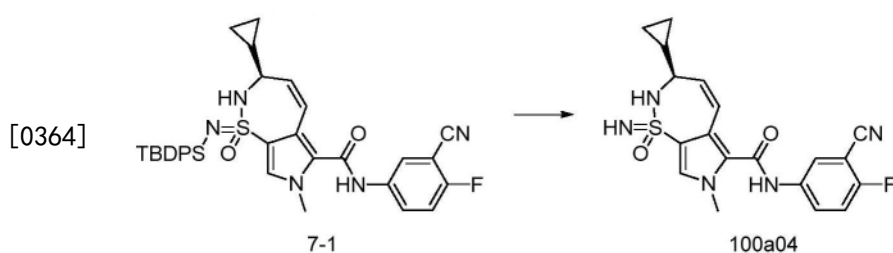
[0359] 步骤6: 化合物7-1的合成



[0361] 将化合物6-1 (30mg) 和4-氟-3-氰基苯胺 (20mg) 溶于四氢呋喃 (5mL) 中, 降温至0度, 然后将NaHMDS (0.2mL) 加入反应体系, 室温搅拌反应16h, 将水加入反应体系, 乙酸乙酯 (3\*15mL) 萃取, 有机相用无水硫酸钠干燥, 旋干, 粗品经柱层析 (正庚烷: 乙酸乙酯=1:3) 目标产物化合物7-1 (11mg)。MS (M+1=638)。

[0362] 用化合物6-2代替化合物6-1按照上述操作可以得到化合物7-2。

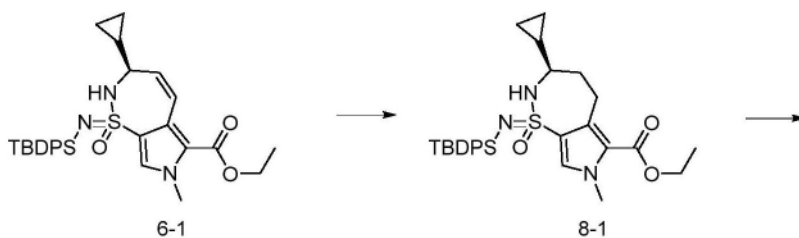
[0363] 步骤7: 化合物100a04的合成



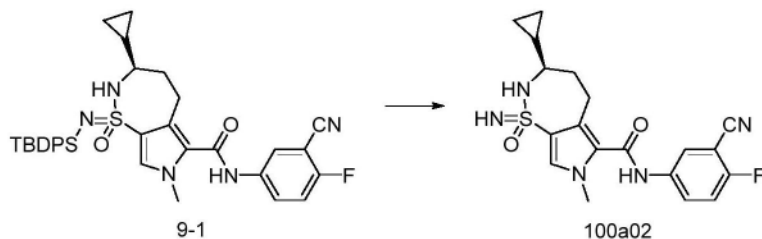
[0365] 将化合物7-1 (40mg) 溶于THF (3mL) 中, 然后将3HF·TEA (1ml) 滴加入反应体系, 室温下反应3天, 制备TLC分离纯化得白色固体化合物100a04 (4.5mg), m/z=400 (M+1)。

[0366] 用化合物7-2代替化合物7-1按照上述操作可以得到化合物100a03。

[0367] 实施例236: 化合物100a2的合成



[0368]



[0369] 步骤1: 化合物8-1的合成

[0370] 将化合物6-1 (500mg) 溶于乙酸乙酯 (10ml) 中, 加入10% Pd/C (200mg), 常温下通氢气反应过夜, 将Pd/C过滤后, 滤液浓缩得到化合物8-1 500mg, 直接用于下步反应。

[0371] 步骤2: 化合物9-1的合成

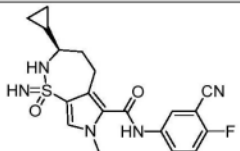
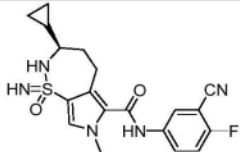
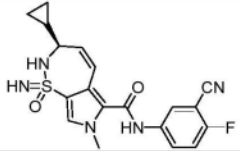
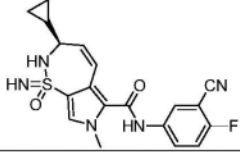
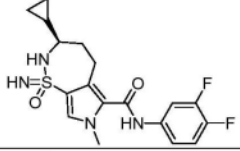
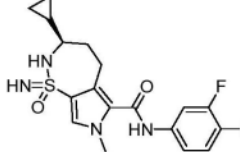
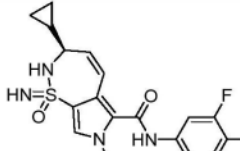
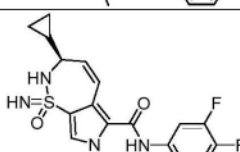
[0372] 参照实施例1中的步骤6合成方法, 用化合物8-1代替化合物6-1可以得到化合物9-1。

[0373] 步骤3: 化合物100a02的合成

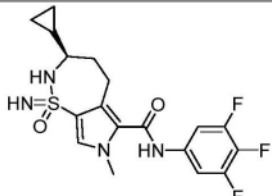
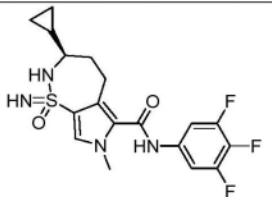
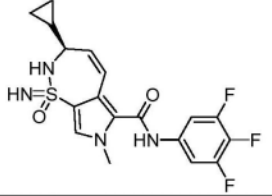
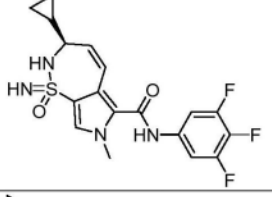
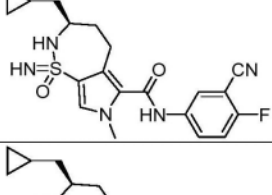
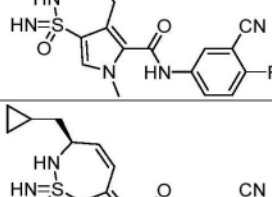
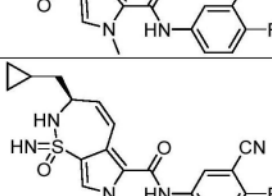
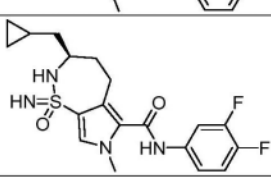
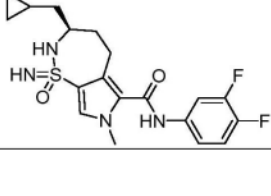
[0374] 参照实施例1中的步骤7合成方法,用化合物9-1代替化合物7-1可以得到化合物100a02。

[0375] 根据实施例235-236的合成方法,替换相应的原料,又合成了下面列表中其他的化合物100a01-100c20。

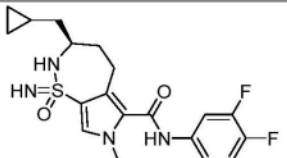
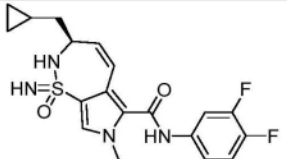
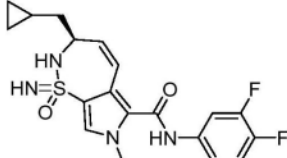
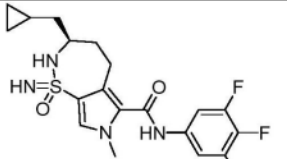
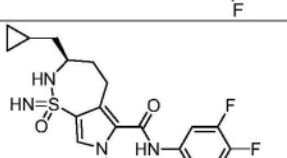
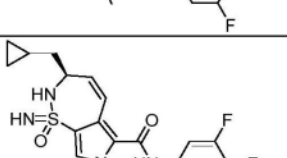
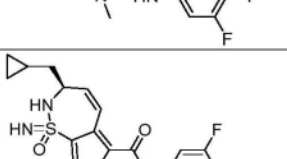
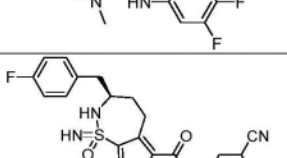
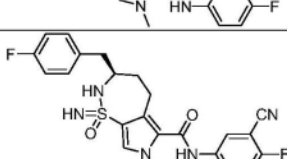
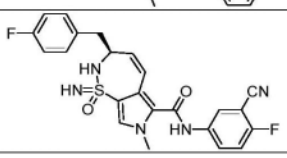
[0376]

100a01		402	Peak1 (HPLC)
100a02		402	Peak2 (HPLC)
100a03		400	Peak1 (HPLC)
100a04		400	Peak2 (HPLC)
100a05		395	Peak1 (HPLC)
100a06		395	Peak2 (HPLC)
100a07		393	Peak1 (HPLC)
100a08		393	Peak2 (HPLC)

[0377]

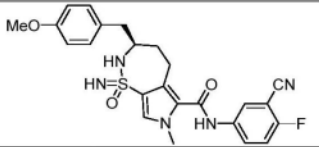
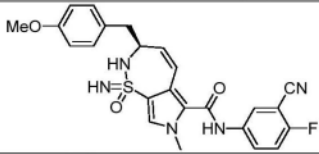
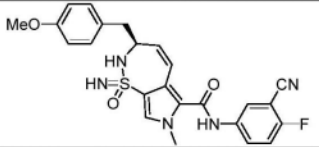
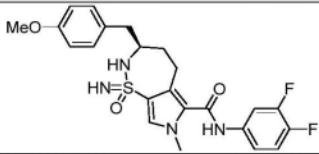
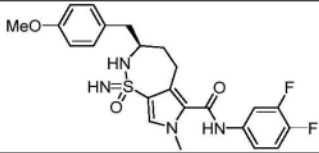
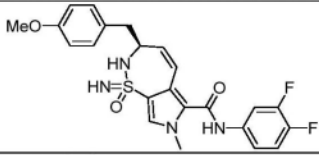
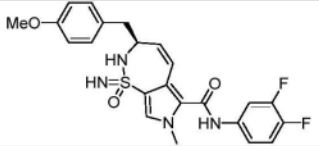
100a09		413	Peak1 (HPLC)
100a10		413	Peak2 (HPLC)
100a11		411	Peak1 (HPLC)
100a12		411	Peak2 (HPLC)
100b01		416	Peak1 (HPLC)
100b02		416	Peak2 (HPLC)
100b03		414	Peak1 (HPLC)
100b04		414	Peak2 (HPLC)
100b05		409	Peak1 (HPLC)

[0378]

100b06		409	Peak2 (HPLC)
100b07		407	Peak1 (HPLC)
100b08		407	Peak2 (HPLC)
100b09		427	Peak1 (HPLC)
100b10		427	Peak2 (HPLC)
100b11		425	Peak1 (HPLC)
100b12		425	Peak2 (HPLC)
100c01		470	Peak1 (HPLC)
100c02		470	Peak2 (HPLC)
100c03		468	Peak1 (HPLC)

[0379]

100c04		468	Peak2 (HPLC)
100c05		463	Peak1 (HPLC)
100c06		463	Peak2 (HPLC)
100c07		461	Peak1 (HPLC)
100c08		461	Peak2 (HPLC)
100c09		481	Peak1 (HPLC)
100c10		481	Peak2 (HPLC)
100c11		479	Peak1 (HPLC)
100c12		479	Peak2 (HPLC)
100c13		482	Peak1 (HPLC)

100c14		482	Peak2 (HPLC)
100c15		480	Peak1 (HPLC)
100c16		480	Peak2 (HPLC)
100c17		475	Peak1 (HPLC)
100c18		475	Peak2 (HPLC)
100c19		473	Peak1 (HPLC)
100c20		473	Peak2 (HPLC)

[0380]

[0381] 生物学实施例--抗-HBV活性实验

[0382] 实验一：体外抗乙肝病毒核衣壳组装活性试验方法

[0383] 主要试剂和原料：

[0384] C150蛋白为药明康德公司表达和纯化；

[0385] BoDIPY®FL购自赛默飞世尔科技公司。

[0386] 蛋白荧光标记：

[0387] 向96孔板每孔加入150μL 2%w/v脱脂牛奶，室温孵育2小时。吸掉脱脂牛奶，用去离子水清洗后烘干，室温保存。将C150蛋白（每管3毫克）用5ml Hitrap脱盐柱脱盐。向每管脱盐后的C150蛋白加入50mM BoDIPY®FL荧光染料20μl混合均匀，4℃避光孵育过夜。用Sephadex G-25凝胶过滤去除未与C150结合的荧光染料。计算C150的荧光标记效率，公式如下：

$$[0388] \quad [\text{BoDIPY}^{\text{®}}\text{FL}] = A_{504} / 78,000 \text{ M}^{-1};$$

$$[0389] \quad [\text{C150Bo}] = (A_{280} - [\text{BoDIPY}^{\text{®}}\text{FL}] \times 1300 \text{ M}^{-1}) / 60,900 \text{ M}^{-1};$$

$$[0390] \quad \text{荧光标记效率} = [\text{BoDIPY}^{\text{®}}\text{FL}] / [\text{C150Bo}];$$

[0391] 其中，

- [0392] [BoDIPY®FL]表示荧光标记的浓度;
- [0393] [C150Bo]表示荧光标记蛋白的浓度;
- [0394] A504表示波长504nm的吸光值;
- [0395] A280表示波长280nm的吸光值;
- [0396]  $M^{-1}$ 表示摩尔浓度的倒数。
- [0397] 化合物稀释:
- [0398] 将化合物母液用DMSO稀释到6mM,再用50mM HEPES稀释到600 $\mu$ M,然后用10%DMSO/50mM HEPES进一步3倍系列稀释8个浓度。
- [0399] 将C150Bo用50mM HEPES稀释到2 $\mu$ M。取37.5 $\mu$ L C150Bo和2.5 $\mu$ L各个浓度的化合物加入到96孔反应板中混匀,室温孵育15分钟。取10 $\mu$ L的750mM NaCl/50mM HEPES加入到反应孔中,NaCl的终浓度为150mM。
- [0400] 0%蛋白组装对照孔,加入10 $\mu$ L的50mM HEPES,NaCl的终浓度为0mM。
- [0401] 100%蛋白组装对照孔,加入10 $\mu$ L的5M NaCl/50mM HEPES,NaCl的终浓度为1M。
- [0402] DMSO终浓度为0.5%,化合物最高终浓度为30 $\mu$ M,C150Bo终浓度为1.5 $\mu$ M。室温孵育1小时。测量荧光信号(激发光485nm;发射光535nm)。
- [0403] 数据分析
- [0404] %蛋白组装 =  $\frac{1 - (\text{样品荧光值} - 1M \text{ NaCl 荧光值})}{(0M \text{ NaCl 荧光值} - 1M \text{ NaCl 荧光值})} \times 100$ 。
- [0405]  $IC_{50}$ 值通过prism软件计算,方程如下:
- [0406]  $Y = \text{Bottom} + (\text{Top} - \text{Bottom}) / (1 + 10^{((\text{Log}IC_{50} - X) * \text{HillSlope})})$ ;
- [0407] 其中,
- [0408] X表示浓度的对数值,Y表示效应值,Y从底部起始以S型拟合至顶部;
- [0409] Bottom表示表示曲线的底部;
- [0410] Top表示Top表示曲线的顶部;
- [0411] HillSlope表示:曲线的最大斜率的绝对值。
- [0412] 实验二:在HepG2.2.15细胞的抗乙肝病毒活性测定
- [0413] 主要试剂:
- [0414] QIAamp 96DNA血液试剂盒(12)(Qiagen,货号51162);
- [0415] FastStart Universal Probe Master(Roche,货号04914058001);
- [0416] Cell-titer Glo检测试剂(Promega,货号G7573)。
- [0417] 化合物稀释:体外抗HBV活性实验和细胞毒性实验所有化合物均3倍系列稀释,8个浓度。受试化合物最终起始浓度为30 $\mu$ M,参照化合物GLS4最终起始浓度为1 $\mu$ M,DMSO终浓度为0.5%。
- [0418] 种HepG2.2.15细胞( $4 \times 10^4$ 细胞/孔)到96孔板,在37 $^{\circ}$ C,5%CO<sub>2</sub>培养过夜。第二天,加入含不同浓度化合物的新鲜培养液到培养孔中。第五天,吸除培养孔中旧的培养液,加入含不同浓度化合物的新鲜培养液。
- [0419] 第八天,收集培养孔中的上清,用于提取上清中的HBV DNA,qPCR检测HepG2.2.15上清中的HBV DNA含量。收集上清后,再向培养孔中补加培养基和Cell-titer Glo试剂,酶标仪检测各孔的化学发光值。

[0420] 活性计算公式如下:

$$[0421] \quad Y = \text{Bottom} + (\text{Top} - \text{Bottom}) / (1 + 10^{((\text{LogIC}_{50} - X) * \text{HillSlope})});$$

[0422] 其中,

[0423] X表示浓度的对数值,Y表示效应值,Y从底部起始以S型拟合至顶部;

[0424] Bottom表示曲线的底部;

[0425] Top表示曲线的顶部;

[0426] HillSlope表示:曲线的最大斜率的绝对值。

[0427] 实验三:细胞毒性测定

[0428] 待测化合物的细胞毒性是使用HepG2细胞进行测试的,将这些细胞在待测化合物存在下孵育4天。使用刃天青测定来评估细胞活力。

[0429] 结果表明:本发明的化合物的体外抗乙肝病毒核衣壳组装活性和抗乙肝病毒活性良好,且细胞毒性低。

[0430] 实验一至实验三的活性数据见表1:

[0431] 表1

[0432]

化合物编号	实验一 蛋白实验 IC <sub>50</sub> (μM)	实验二 细胞实验 EC <sub>50</sub> (nM)	实验三 细胞毒性 CC <sub>50</sub> (nM)
10a1	++	++	>30000
10a2	++	+++	>30000
10b1	++	++	>30000
10b2	++	+++	>30000
10c1	++	++	>30000
10c2	++	+++	>30000
10e1	++	++	>30000
10e2	++	+++	>30000
10f1	++	++	>30000
10f2	++	+++	>30000
10g1	++	++	>30000
10g2	++	+++	>30000
10h1	++	+	>30000
10h2	++	+	>30000
10n1	++	++	>30000
10n2	++	+++	>30000
10o1	++	++	>30000
10o2	++	+++	>30000
10w1	++	++	>30000
10w2	++	+++	>30000
10bb1	++	++	>30000
10bb2	++	+++	>30000

[0433]

10cc1	++	++	>30000
10cc2	++	+++	>30000
10ccc1	++	++	>30000
10ccc2	++	+++	>30000
10ddd1	++	++	>30000
10ddd2	++	+++	>30000
10vvv1	++	++	>30000
10vvv2	++	+++	>30000
20a1	++	++	>30000
20a2	++	+++	>30000
20b1	++	++	>30000
20b2	++	+++	>30000
20c1	++	++	>30000
20c2	++	+++	>30000
20dd1	++	++	>30000
20dd2	++	+++	>30000
20ee1	++	++	>30000
20ee2	++	+++	>30000
20ccc1	++	+++	>30000
20ccc2	++	+++	>30000
20ttt1	++	++	>30000
20ttt2	++	+++	>30000
30a1	++	++	>30000
30a2	++	++	>30000
30b1	++	++	>30000
30b2	++	++	>30000
30c1	++	++	>30000
30c2	++	++	>30000
30g1	++	++	>30000
30g2	++	++	>30000
40a1	++	++	>30000
40a2	++	++	>30000
40b1	++	++	>30000
40b2	++	++	>30000
40g1	++	++	>30000
40g2	++	++	>30000
50a1	++	++	>30000
50a2	++	+++	>30000
50s1	++	++	>30000
50s2	++	+++	>30000
50t1	++	++	>30000
50t2	++	+++	>30000
50u1	++	++	>30000
50u2	++	+++	>30000
50v1	++	++	>30000
50v2	++	+++	>30000

	60a1	++	++	>30000
	60a2	++	+++	>30000
	60g1	++	++	>30000
	60g2	++	+++	>30000
	60h1	++	++	>30000
	60h2	++	+++	>30000
	60v1	++	++	>30000
	60v2	++	+++	>30000
	60w1	++	++	>30000
	60w2	++	+++	>30000
	60x1	++	++	>30000
	60x2	++	+++	>30000
	60y1	++	++	>30000
	60y2	++	+++	>30000
	70a1	++	++	>30000
	70a2	++	+++	>30000
	70b1	++	++	>30000
[0434]	70b2	++	+++	>30000
	80a1	++	++	>30000
	80a2	++	+++	>30000
	80b1	++	++	>30000
	80b2	++	+++	>30000
	90a1	++	++	>30000
	90a2	++	+++	>30000
	90b1	++	++	>30000
	90b2	++	+++	>30000
	100a01	+	++	>30000
	100a02	++	+++	>30000
	100a04	++	+++	>30000
	100b02	++	+++	>30000
	100b04	+	+++	>30000
	100c02	++	+++	>30000
	100c04	+	+++	>30000
	100c14	++	+++	>30000
	100c16	++	+++	>30000

[0435] 表1中:

	实验一	实验二
[0436]	+++表示 $IC_{50} < 1\mu M$ ; ++表示 $IC_{50}$ 为 $1\sim 100\mu M$ ; +表示 $IC_{50}$ 为 $>100\mu M$ 。	++++表示 $EC_{50} < 0.1nM$ ; +++表示 $EC_{50}$ $0.1\sim 100nM$ ; ++表示 $EC_{50}$ 为 $100\sim 1000nM$ ; +表示 $EC_{50}$ 为 $>1000nM$ 。

[0437] 由此可见,本申请的化合物具有优异的抗乙肝病毒活性。

[0438] 此外,对于本发明化合物,经HPLC拆分后,可将基于手性硫原子中心(即 $O=S=N-R_6$ 中的S)的两种构型化合物进行有效分离。本发明人意外地发现,在两种基于手性硫原子中心的两种构型化合物中,极性较小的对映异构体的抑制HBV核衣壳蛋白的活性显著高于

极性较大的对映异构体,在一些实施例中,活性差异可以达到数倍。

[0439] 实验四小鼠PK实验实施例:

[0440] 18只雄性C57小鼠(9只静脉给药,9只口服给药)按照体重随机分组,分别给予受试化合物2mg/kg(静脉给药)和50mg/kg(口服给药)。每组每个时间点取3只小鼠,共取8个时间点(5分钟、15分钟、30分钟、1小时、2小时、4小时、8小时、24小时)。口服生物利用度F的计算方法为 $AUC_{po}/Dose_{po}/AUC_{iv}/Dose_{iv}$ 。

[0441] 用本发明化合物进行给药,结果显示,各个在体内实验之中表现出良好的生物利用度,部分化合物的生物利用度达到或超过70%。

[0442] 在本发明提及的所有文献都在本申请中引用作为参考,就如同每一篇文献被单独引用作为参考那样。此外应理解,在阅读了本发明的上述讲授内容之后,本领域技术人员可以对本发明作各种改动或修改,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。