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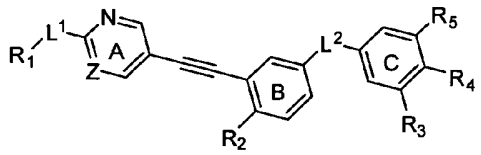
— 包括国际检索报告(条约第 21 条(3))。

(54) Title: HETEROCYCLIC ALKYNYL BENZENE COMPOUNDS AND MEDICAL COMPOSITIONS AND USES THEREOF

(54) 发明名称 : 杂环炔苯类化合物及其药用组合物和应用



（I）

(57) Abstract: Heterocyclic alkynyl benzene compounds of formula (I), pharmaceutically acceptable salts or stereomers thereof, as well as uses in preparing drugs for preventing or treating tumors. The compounds can overcome Gleevec induced drug resistance.

(57) 摘要:

一种如式（I）所示的杂环炔基苯化合物，及其药学上可接受的盐或其立体异构体，以及其在制备治疗或预防肿瘤的药物中的应用。该化合物可以克服 Gleevec 诱发的耐药。

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杂环炔苯类化合物及其药用组合物和应用

技术领域

本发明属于化学医药领域，具体地涉及具有式（I）结构特征的杂环炔苯类化合物或其药学上可接受的盐或立体异构体及其前药分子，含有这种化合物的药物组合物和这些化合物或组合物在制备药物中的应用。

背景技术

肿瘤是目前人类健康和生命的头号杀手，其发病率仅次于心血管类疾病。并且随着环境污染或其它因素的影响，恶性肿瘤的发病率呈快速上升趋势。根据世界卫生组织 2003 年公布的数据，2000 年全球共有恶性肿瘤患者 1000 万，因恶性肿瘤死亡者高达 620 万，占总死亡人数的 12%～25%。预期到 2020 年，全球每年新发病例将达 1500 万。近年来，虽有一些新型的酪氨酸蛋白抑制剂等靶向新药的开发上市，但仍远远无法满足日益增长的临床癌症病人的需要。抗肿瘤药物研发也仍是目前药物研发界的重要研究方向。

肿瘤分子靶向治疗是基于对肿瘤生长密切相关的关键分子通过化学或生物学手段选择性杀伤肿瘤细胞的一种治疗方法。靶向治疗的特点为：特异性高，选择性强，毒副作用较轻；联合应用时，它可加强传统化疗、放疗的疗效，减少术后复发。以 Gleevec（STI571）为代表的靶向药物为肿瘤化疗开创了一个新时代。肿瘤靶向治疗在短短几年内得到了迅速发展。肿瘤靶向治疗的出现已对传统给药观念和模式构成冲击，例如，因毒副作用小靶向药物在 I 期临床试验中往往无法达到剂量限制性毒性和最大耐受剂量；用靶向治疗药物时无需用最大耐受剂量即可达到满意疗效。肿瘤靶向治疗是肿瘤治疗的热点和发展趋势。

蛋白酪氨酸激酶（PTKs）是一类能够催化多种重要蛋白质的酪氨酸残基上的酚羟基发生磷酸化，进而激活功能蛋白的功能的蛋白质酶系。人体内的 520 多种蛋白激酶中大约有一半是酪氨酸激酶（PTKs）。它们在细胞内的信号传导通路中占据了十分重要的地位，调节着细胞体内生长、分化、死亡等一系列生理化过程。蛋白酪氨酸激酶功能失调会引发生物体内的一系列疾病。研究表明，半数以上的原癌基因和癌基因的激活都与蛋白酪氨酸激酶相关。蛋白酪氨酸激酶的异常表达可导致细胞增殖调节发生紊乱，进而导致肿瘤发生。此外，酪氨酸激酶的异常表达还与肿瘤的侵袭和转移，肿瘤新生血管的生成，肿瘤的化疗抗药性密切相关。以酪氨酸激酶为靶点进行抗肿瘤药物研发成为国际上的一个热点，也是各国药物开发机构研究投入的重点。

目前为止，已有数十种蛋白酪氨酸激酶小分子抑制剂和抗体进入临床试验，有的已经上市，并取得了较好的治疗效果。如：用于治疗费城染色体呈阳性慢性髓样白血病（CML）及胃肠间质瘤的 Bcr-Abl 抑制剂 Gleevec；用于治疗非小细胞肺癌的 EGFR 抑制剂 Iressa 和 Tarceva 等。Gleevec 是第一个在了解癌症的病因后合理设计开发，并取得了显著成效的肿瘤治疗药物，它的成功是癌症治疗的一个里程碑。这一重大成就也被美国《科学》杂志列入 2001 年度十大科技新闻。

针对蛋白酪氨酸激酶的特异性小分子抑制物在临床肿瘤治疗中获得的巨大成功进一步证实了蛋白酪氨酸激酶是关键性的治疗靶点，同时也说明其在肿瘤发生中的重要性。有确切证据证明蛋白酪氨酸激酶编码基因突变引起肿瘤发生的例子包括：Bcr-Abl 与慢性粒细胞性白血病(chronic myeloid leukemia, CML)；c-KIT 与胃肠间质瘤(GIST)、系统性肥大细胞增多症(systemic mastocytosis, SM)；PDGFR 和慢性骨髓单核细胞性白血病（chronic myelomonocytic leukemia)、隆突性皮肤纤维肉瘤（dermatofibrosarcoma protuberan)、高嗜酸细胞综合征；Flt3 与部分急性粒细胞性白血病；B-Raf 与黑色素瘤(melanoma)；RET 与甲状腺癌等。此外，c-KIT 与小细胞肺癌有密切关系。

2001 年美国 FDA 批准的用以治疗慢性粒细胞性白血病(CML)的第一个靶向治疗药物 STI571 (Gleevec, Imatinib mesylate, 中文名 “格列卫”，Novartis Pharmaceuticals) 酪氨酸蛋白激酶抑制剂，主要作用于 Bcr-Abl， cKit, PDGFR 等。临床上 STI571 单药治疗可使 98% 的 CML 病人获得临床血液学的缓解，53%获得细胞遗传学缓解。

然而随着 STI571 在临床上的广泛应用，耐药问题日益突出：部分癌症病人对 STI571 天然耐受(primary resistance)；另一部分病人开始用药时有反应，但在用药治疗过程中逐渐出现获得性耐受（secondary resistance)。长期服用的患者易产生耐受性。耐受性是指慢性期患者经 STI571 治疗后未出现完全血液学反应或加速期和急变期患者经 STI571 治疗后未能恢复到慢性期。临床上，急变期（blast-crisis）的 CML、Bcr-Abl 阳性的 ALL 病人对 STI571 耐受较普遍，约 70%的这两类病人在用药 3～6 个月出现对 STI571 耐药。而且一旦出现耐药，病情往往进展迅速。获得性耐受被认为是肿瘤细胞为逃避杀伤的一种防卫，其机制有多种，包括：①靶基因(Bcr-Abl, c-KIT, PDGFR)扩增；②靶基因突变；③靶基因非依赖性肿瘤克隆的形成；④α-1 酸性糖蛋白的产生和多药耐受基因 MDR1 的过度表达。但目前公认的主要机制是靶基因(Bcr-Abl, c-KIT, PDGFR)表达产物激酶域的继发突变（secondary mutation)。研究表明与 STI571 耐受关系明确的靶基因的常见点突变位点包括 Bcr-Abl 的 E255K、E255V、T315I 及 D276G, c-KIT 的 D816V 等。携有这些突变的患者容易复发，预

后不好。有报道指出仅有 50%的转移性胃肠间质瘤（GIST）病人对 STI571 反应，效果可靠，而这部分病人携带有 c-KIT 临膜域 V560G 突变。此外，尚有 50%的转移性 GIST 病人对 STI571 缺乏反应。c-KIT 酪氨酸激酶域的点突变（如 D816V，T315I）则对 STI571 非常耐受。 体外实验表明 STI571 不能抑制携有 D816V c-KIT 以及 T315I 突变株细胞的增殖；携有 D816V c-KIT 的系统性肥大细胞增多症病人对 STI571 也不反应。

如何克服 STI571 抵抗性是当今肿瘤医学的重要课题。寻找新型的酪氨酸激酶小分子抑制物是克服 STI571 抵抗性的的重要途径。例如，最近上市的酪氨酸激酶小分子抑制物 Nilotinib (AMN107) 、Dasatinib（BMS-354825）对部分（而不是全部）STI571 抵抗性 Bcr-Abl 点突变（除 T315I 之外）病例有效。AMN107 结合 Abl 激酶的位置与 STI571 相同，也是竞争性结合到非活化构型的 Abl 激酶，但与 Abl 的亲和力比 STI571 更强，药效约是后者的 10～50 倍。AMN107 对除了 T315I 之外的 15 种点突变细胞有明显的抑制作用，IC_{50} 在 10～1000 nM。与 STI571 和 AMN107 不同，BMS-354825 可以同时结合和抑制未活化和已活化的 Bcr-Abl。BMS-354825 对除了 T315I 之外的 15 种点突变细胞有明显的抑制作用，IC_{50} 在 10～125 nM。但是，AMN107 和 Dasatinib 对 T315I Bcr-Abl 无效，且 AMN107 和 STI571 对 c-KIT D816V 点突变细胞无效。因此，研制出新型的、能有效杀伤 STI571 抵抗性 c-KIT 点突变(D816V)和 Bcr-Abl 点突变（包括 T315I）携带细胞的小分子化合物在全球肿瘤治疗科学界和产业界都显得十分必要和迫切。

事实上，目前的蛋白酪氨酸激酶抑制剂类抗肿瘤药物大多存在着药物诱导抗药性基因突变，并面临着临床适用范围较窄和等问题。因此，开发第二代蛋白酪氨酸激酶抑制剂以克服现有药物耐受并提高临床效果，具有重大意义。

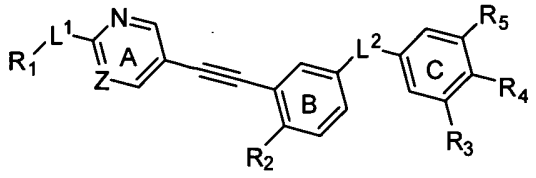
本发明涉及具有式（I）结构特征的杂环炔苯类化合物。该类化合物可有效抑制多种肿瘤细胞的生长，并可以克服现有药物（Gleevec）诱发的耐药，是一类新型的蛋白激酶抑制剂。

发明内容

本发明需要解决的技术问题之一是提供一种新的杂环炔苯类化合物。

解决上述技术问题的技术方案如下：

具有式（Ⅰ）结构特征的杂环炔苯类化合物或者其药学上可接受的盐或立体异构体，或其前药分子：



（Ⅰ）

Z 任选为 CH 或 N；L^1 任选自 NH，-N=，CH；L^2 任选为-CONH-或-NHCO-；

R_1 任选自：

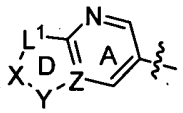
1）H；

2）C_1~C_6 烷基；

3）C_3~C_6 环烷基；

4）被 1 或 2 个羟基取代的 C_1~C_5 烷基；

5）苯基；

6）. 能与 A 环 Z 位形成含 1~3 个 N 原子的含 L^1 的并五元杂环  的基团，其中， L^1 的定义与前述相同，X，Y，Z，任选为 N，CH，D 环为含有 1～3 个氮原子的杂环；

R_2 任选自：

1）H；

2）卤素（F, Cl, Br）；

3) C_1~C_5 烷基；

4) C_3~C_6 环烷基；

5) C_1~C_5 含氟烷基；

R_3 任选自：

1) H；

2) 卤素（F, Cl, Br）；

3) C_1~C_4 烷基；

4) C_3~C_6 环烷基；

5) C_1~C_4 含氟烷基；

R_5 为 H，R_4 任选自：

1). H；

2). $(CH_2)nNR_6R_7$;

3). $(CH_2)n$ –Het^1;

或 R_4 为 H，R_5 任选自：

1). H;

2). Het^2;

其中，n 为 0 或 1，Het^1 为含有 1～3 个 N 的非芳香杂环，Het^2 为含 1～3 个杂原子 N，O，S 的五元芳香杂环，所述非芳香及芳香杂环任一 C 原子或 N 原子在能够被取代的位置可以被烷基，环烷基，或 NR_6R_7 取代；

R_6，R_7 任选自：

1） H;

2）C1~C3 烷基;

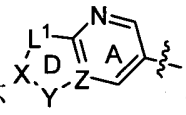
3） C1~C3 含氟烷基;

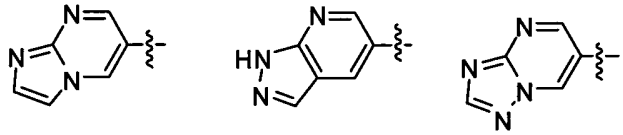
4） C3~C6 环烷基;

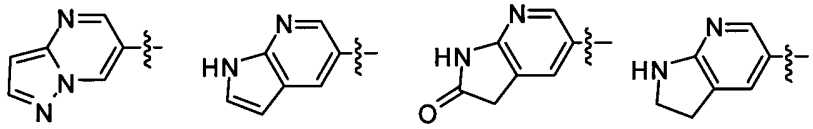
R_6 和 R_7 可通过 C，O， N， S 等原子进一步形成五元，六元，七元或八元环状结构。优选地，所述 Z 为 N，L^1 为 NH，R_1 优选为：

1） 甲基，乙基，异丙基，叔丁基;

2） 环丙基，环丁基，环戊基，环己基。

所述 R_1 与 A 形成的并环  优选为以下结构：





所述 R_2 任选自以下结构：

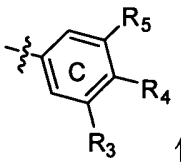
1） H;

2） 甲基，乙基，异丙基，叔丁基;

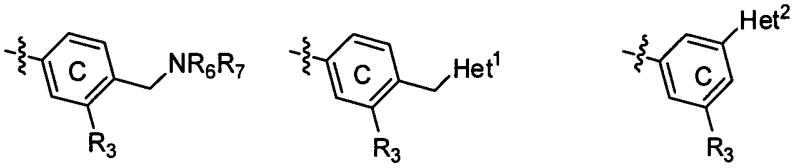
3） 环丙基;

4） F, Cl, Br;

5） 三氟甲基;

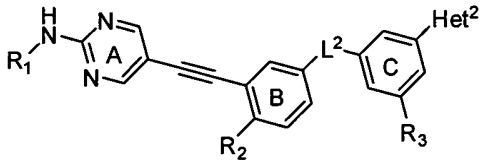


所述 C 环 优选为以下结构：

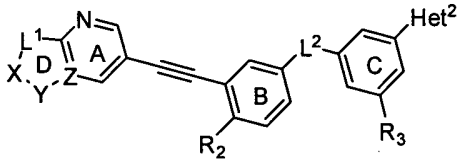


R_3 及 R_6，R_7 的定义与前述相同，Het^1 定义与前述相同，Het^2 选自取代咪唑类化合物、取代吡唑类化合物、取代恶唑类化合物、取代三氮唑类化合物、取代四氢噁唑类化合物、或取代噻唑类化合物。

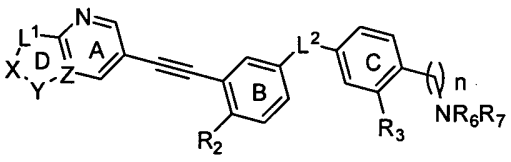
优选地，本申请的另一个实施方案为具有式 I 结构的化合物或其药学上可接受的盐或立体异构体及其前药分子，更优选为：



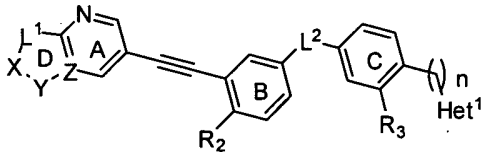
(II)



(III)

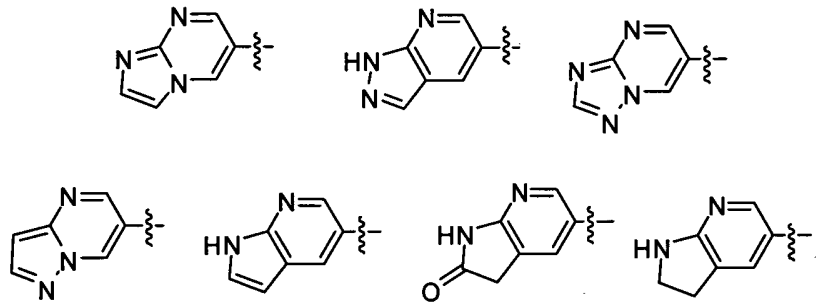


(IV)



(V)

其中，X，Y，Z 任选为 N，CH；D 环为含有 1～3 个氮原子的杂环， D 与 A 所并环优选为以下结构：



R_1，R_2，R_3，R_6，R_7， n 、L^1，L^2，Het^1，Het^2 的定义与上述相同。

本发明的另一目的是提供上述化合物的应用。

上述述化合物及其药学上可接受的盐或立体异构体或其前药分子在制备治疗或预防肿瘤的药物中的应用。

本申请还涉及了利用有效剂量的上述化合物可以用于治疗胃肠间质瘤、组织细胞性淋巴癌、非小细胞肺癌、小细胞肺癌、肺腺癌、肺鳞癌、胰腺癌、乳腺癌、前列腺癌、肝癌、皮肤癌、上皮细胞癌、鼻咽癌、白血病等过渡增殖性疾病。

本发明涉及的杂环炔苯类化合物及其药学上可接受的盐，可以有效抑制多种肿瘤细胞的生长，并对 Bcr-Abl，c-Kit，PDGF 等蛋白酶产生抑制作用，可用于制备抗肿瘤药物，并可以克服现有药物（Gleevec）诱发的耐药。如本领域技术人员所理解的，本申请所涉及的化合物及其药学可接受的盐可用于制备治疗人类及其它哺乳动物的肿瘤等过渡增殖性疾病。

附图说明

图 1 是实施例 1 化合物 D747 的盐酸盐(po,qd)对 K562 细胞肿瘤移植模型动物体重的影响结果示意图；

图 2 是实施例 1 化合物 D747 的盐酸盐(po,qd)对 K562 细胞肿瘤移植模型动物肿瘤体积的影响结果示意图；

图 3 是实施例 21 化合物 D822 的甲磺酸盐(po,qd)对 K562 细胞肿瘤移植模型动物体重的影响结果示意图；

图 4 是实施例 21 化合物 D822 的甲磺酸盐(po,qd)对 K562 细胞肿瘤移植模型动物肿瘤体积的影响结果示意图。

图 5 是实施例 17 化合物 D767 的甲磺酸盐(po,qd)和 D800 甲磺酸盐(po,qd)对 K562 细胞肿瘤移植模型动物体重的影响结果示意图；

图 6 是实施例 17 化合物 D767 的甲磺酸盐(po,qd)和 D800 甲磺酸盐(po,qd)对 K562 细胞肿瘤移植模型动物肿瘤体积的影响结果示意图；

图 7 是实施例 41 的化合物 D824 二甲磺酸盐(po,qd)对 K562 细胞肿瘤移植模型动物体重的影响结果示意图；

图 8 是实施例 41 的化合物 D824 二甲磺酸盐(po,qd)对 K562 细胞肿瘤移植模型动物肿瘤体积的影响结果示意图。

图 9 是实施例 41 的化合物 D824 二甲磺酸盐(po,qd)对 BAF3-T315I 细胞肿瘤移植模型动物体重的影响结果示意图；

图 10 是实施例 41 的化合物 D824 二甲磺酸盐(po,qd)对 BAF3-T315I 细胞肿瘤移植模型动物肿瘤体积的影响结果示意图；

图 11 是实施例 41 的化合物 D824 二甲磺酸盐(po,q2d)对 BAF3-T315I 细胞肿瘤移植模型动物体重的影响结果示意图；

图 12 是实施例 41 的化合物 D824 二甲磺酸盐(po,q2d)对 BAF3-T315I 细胞肿瘤移植模型动物肿瘤体积的影响结果示意图。

图 13 是实施例 48 的化合物 D856 二甲磺酸盐(po,qd)对 K562 细胞肿瘤移植模型动物体重的影响结果示意图；

图 14 是实施例 48 的化合物 D856 二甲磺酸盐(po,qd)对 K562 细胞肿瘤移植模型动物肿瘤体积的影响结果示意图；

图 15 是实施例 34 化合物 D968 的二甲磺酸盐(po,qd)对 K562 细胞肿瘤移植模型动物体重的影响结果示意图；

图 16 是实施例 34 化合物 D968 的二甲磺酸盐(po,qd)对 K562 细胞肿瘤移植模型动物肿瘤体积的影响结果示意图。

具体实施方式

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

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

本文所用术语“杂芳基”代表环中多达6个原子的稳定的单环或每个环中多达6个原子双环碳环，其中至少一个环为芳香环且含有 1- 4 个选自 O 、N 和 S 的杂原子。本定义范围内的杂芳基包括但不限于：咪唑基、三唑基、吡唑基、呋喃基、噻吩基、噁唑基、异噁

唑基、吡嗪基、哒嗪基、吡啶基、嘧啶基、吡咯基。对于下列杂芳基的定义，“杂芳基”也理解为包括任何含有氮的杂芳基的N-氧化物衍生物。在杂芳基取代基是双环的且含有一个环为非芳香性或不含有杂原子的例子中，应理解各自经芳香环或经含杂原子环连接。

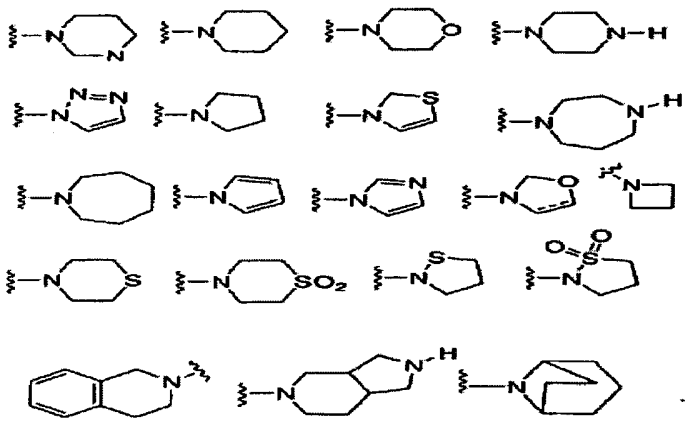
本文中所用术语“杂环”或“杂环基”是指含有1 - 4 个选自O 、N 和S 的杂原子的5元 - 6 元芳香性或非芳香性杂环，且包括双环基团。“杂环基”因此包括上面提及的杂芳基，也包括其二氢化及四氢化类似物。“杂环基”进一步的实例包括但不限于：咪唑基、吲哚基、异噻唑基、异噁唑基、噁二唑基、噁唑基、氧杂环丁烷基（oxetanyl）、吡喃基、吡嗪基、吡唑基、哒嗪基、吡啶基、嘧啶基、吡咯基、喹噁啉基、四唑基、噻二唑基、噻唑基、噻吩基、三唑基、1,4－二噁烷基、吡咯烷基、二氢咪唑基、二氢异噁唑基、二氢异噻唑基、二氢噁二唑基、二氢噁唑基、二氢吡嗪基、二氢吡唑基、二氢吡啶基、二氢嘧啶基、二氢吡咯基、二氢四唑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

在一个实施方案中，杂环选自咪唑基、吡啶基、1-吡咯烷酮、2-哌啶酮、2-嘧啶酮、2-吡咯烷酮、噻吩基、噁唑基、三氮唑基、异噁唑基。

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

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

在某些例子中，定义Het使其可与连接它们的氮共同形成4-7 元单环或每个环为4-7元的双环杂环，且任选含有除氮外一个或两个选自N 、O 和S 的另外的杂原子，所述杂环任选被一个或多个选自R_2的取代基取代。可如此形成的杂环的实例包括但不限于下列的杂环，须牢记杂环任选被一个或多个（且优选一个、两个或三个）选自R_2的取代基取代：



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

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

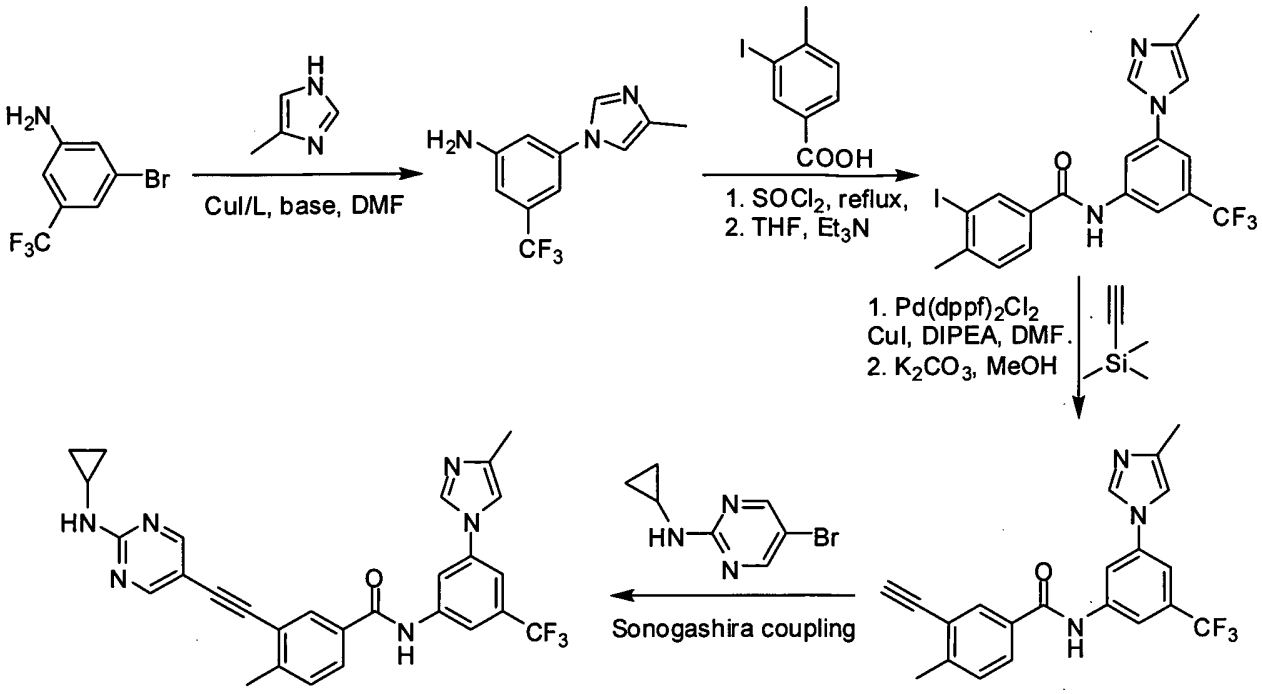
Berg 等，“Pharmaceutical Salts，”*J. Pharm. Sci.*’1977：66：1－19 更详细描述了上文所述药学上可接受的盐及其它典型的药学上可接受的盐的制备。

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

方 案

如方案 A 中所示式（I）中化合物可以由 3-溴－4－三氟甲基苯胺为起始原料通过 5 步反应合成。

方 案 A



在一个实施方案中，本申请提供了一种利用具有式（I）的化合物及其药学可接受的盐治疗人或其它哺乳动物肿瘤等过渡增殖性疾病或症状。

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

在一个实施方案中，本申请所设计的化合物及其药学可接受的盐可以与目前应用的或正处开发阶段的雌激素受体调节剂、雄激素受体调节剂、视网膜样受体调节剂、细胞毒素/细胞抑制剂、抗增殖剂、蛋白转移酶抑制剂、HMG-CoA 还原酶抑制剂、HIV 蛋白激酶抑制剂、逆转录酶抑制剂、血管生成抑制剂、细胞增殖及生存信号抑制剂、干扰细胞周期关卡的药物和细胞凋亡诱导剂，细胞毒类药物、酪氨酸蛋白抑制剂、EGFR 抑制剂、VEGFR 抑制剂、丝氨酸/苏氨酸蛋白抑制剂、Bcr-Abl 抑制剂，c-Kit 抑制剂，Met 抑制剂，Raf 抑制剂, MEK 抑制剂, MMP 抑制剂, 拓扑异构酶抑制剂、组氨酸去乙酰化酶抑制剂、蛋白酶体抑制剂、CDK 抑制剂，Bcl-2 家族蛋白抑制剂，MDM2 家族蛋白抑制剂、IAP 家族蛋白抑制剂、STAT 家族蛋白抑制剂、PI3K 抑制剂、AKT 抑制剂、整联蛋白阻滞剂、干扰素-α、白介素-12、COX-2 抑制剂、p53、p53 激活剂、VEGF 抗体、EGF 抗体等药物联合用药增加其临床效果。

本申请所涉及的化合物及其药学可接受的盐可根据下面的方法用于治疗下列的疾病以及下面没有列出的其它疾病：

1） 一种利用包含本申请所涉及的、具有式（I）结构的化合物及其药学可接受的盐的药用组合物治疗人或其它哺乳动物的乳腺癌的方法。包括但不局限于侵袭性导管癌、侵袭性小叶癌、原位管癌和原位小叶癌。

2） 一种利用包含本申请所涉及的、具有式（I）结构的化合物及其药学可接受的盐的药用组合物治疗人或其它哺乳动物的呼吸道癌的方法。包括但不局限于小细胞＆非小细胞肺癌以及支气管腺瘤和胸膜肺母细胞瘤。

3） 一种利用包含本申请所涉及的、具有式（I）结构的化合物及其药学可接受的盐的药用组合物治疗人或其它哺乳动物的脑癌的方法。包括但不局限于脑干和眼下神经胶质瘤、小脑和大脑星形细胞瘤、室管膜细胞瘤以及神经外胚层和松果瘤体。

4） 一种利用包含本申请所涉及的、具有式（I）结构的化合物及其药学可接受的盐的药用组合物治疗人或其它哺乳动物的雄、雌性生殖器官的肿瘤的方法。雄性生殖器官的肿瘤包括但不限于前列腺和睾丸癌。雌性生殖器官的肿瘤包括但不限于子宫内膜癌、宫颈癌、卵巢癌、阴道癌和外阴癌以及子宫内瘤。

5） 一种利用包含本申请所涉及的、具有式（I）结构的化合物及其药学可接受的盐的药用组合物治疗人或其它哺乳动物的消化道的肿瘤的方法。包括但不限于肛门癌、结肠癌、结肠直道癌、食道癌、胃癌、胰腺癌直肠癌、小肠癌或唾腺癌。

6） 一种利用包含本申请所涉及的、具有式（I）结构的化合物及其药学可接受的盐的药用组合物治疗人或其它哺乳动物的尿道的肿瘤的方法。包括但不限于膀胱癌、阴茎癌、肾癌、肾盂癌、输尿管癌或尿道癌。

7） 一种利用包含本申请所涉及的、具有式（I）结构的化合物及其药学可接受的盐的药用组合物治疗人或其它哺乳动物的眼癌的方法。包括但不限于眼内黑素瘤和视网膜细胞瘤。

8） 一种利用包含本申请所涉及的、具有式（I）结构的化合物及其药学可接受的盐的药用组合物治疗人或其它哺乳动物肝癌的方法。包括但不限于肝细胞瘤（具有或不具有纤维板变化的干细胞癌）、胆管癌（肝内胆管癌）以及混合的肝细胞性胆管癌。

9） 一种利用包含本申请所涉及的、具有式（I）结构的化合物及其药学可接受的盐的药用组合物治疗人或其它哺乳动物皮肤癌的方法。包括但不限于扁平细胞癌、卡波济氏肉瘤、恶性黑素瘤、默克氏细胞皮肤癌以及非黑素瘤细胞癌。

10） 一种利用包含本申请所涉及的、具有式（I）结构的化合物及其药学可接受的盐的药用组合物治疗人或其它哺乳动物头颈癌的方法。包括但不限于喉、下咽、鼻咽、口咽癌以及唇和口腔癌。

11） 一种利用包含本申请所涉及的、具有式（I）结构的化合物及其药学可接受的盐的药用组合物治疗人或其它哺乳动物淋巴瘤的方法。包括但不限于 AIDS 相关淋巴瘤、非何杰金淋巴瘤、皮肤 T 细胞淋巴瘤、何杰森病和中枢神经系统淋巴瘤。

12） 一种利用包含本申请所涉及的、具有式（I）结构的化合物及其药学可接受的盐的药用组合物治疗人或其它哺乳动物肉瘤的方法。包括但不限于软组织肉瘤、骨肉瘤、恶性纤维性组织细胞瘤、林把肉瘤和横纹肌肉瘤。

13） 一种利用包含本申请所涉及的、具有式（I）结构的化合物及其药学可接受的盐的药用组合物治疗人或其它哺乳动物白血病的方法。包括但不限于急性髓样白血病、急性林细胞白血病、慢性淋细胞白血病、慢性骨髓性白血病以及多毛细胞白血病。

服用方式与剂量范围

根据标准药学技术，本发明化合物可单独或在药用组合物中与药学上可接受的受体、辅料或稀释剂组合给予哺乳动物，优选人。可口服或皮下、肌注、腹膜内、静脉、直肠及局部、眼睛、肺部、鼻腔、胃肠外给予化合物。

在一个实施方案中，利用式（I）化合物治疗或控制癌症等患者时，服用剂量范围为在口服 0.1～ 500 毫克/天/公斤体重。适当的给药方式为每日单剂量给药或每日二次、三次、四次等多次给药或利用缓释技术给药。对于多种大型哺乳动物，其优选的剂量范围为 0.1 ～ 1500 毫克/天/公斤体重，优选于 0.5～100 毫克/天/公斤体重。对于平均体重为 70 公斤的病人，其每日剂量为 1 ～ 500 毫克。对于一些特别搞活性化合物，成年病人每日剂量可低达 0.1 毫克/天。

药物代谢物及前药

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

联合用药

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

可以与式I ～II化合物进行药物联用的药物或活性成分包括但不局限为：

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

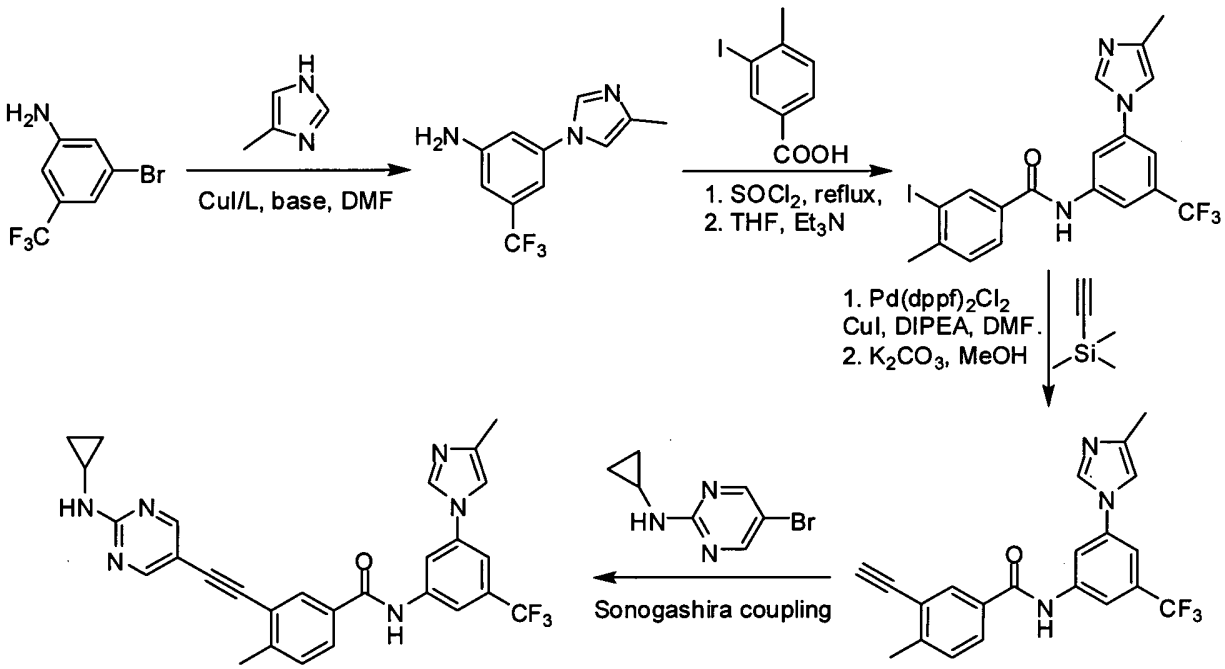
在一个实施方案中，可以与式I ～II化合物进行药物联用的药物或活性成分包括但不局限为：阿地白介素、阿仑膦酸、干扰素、阿曲诺英、别嘌醇、别嘌醇钠、帕洛诺司琼盐酸盐、六甲蜜胺、氨基格鲁米特、氨磷汀、氨柔比星、安丫啶、阿纳托唑、多拉司琼、aranesp 、arglabin 、三氧化二砷、阿诺新、5 -氮胞苷、硫唑嘌呤、卡介苗或 tice 卡介苗、贝他定、醋酸倍他米松、倍他米松磷酸钠制剂、贝沙罗汀、硫酸博来霉素、溴尿甘、bortezomib 、白消安、降钙素、阿来佐单抗注射剂、卡培他滨、卡铂、康士得、cefesone 、西莫白介素、柔红霉素、苯丁酸氮芥、顺铂、克拉屈滨、克拉屈滨、氯屈磷酸、环磷酰胺、阿糖胞苷、达卡巴嗪、放线菌素 D 、柔红霉素脂质体、地塞米松、磷酸地塞米松、戊酸雌二醇、地尼白介素 2 、狄波美、地洛瑞林、地拉佐生、己烯雌酚、大扶康、多西他奇、去氧氟尿苷、阿霉素、屈大麻酚、钬-166-壳聚糖复合物、eligard 、拉布立酶、盐酸表柔比星、阿瑞吡坦、

表阿霉素、阿法依伯汀、红细胞生成素、依铂、左旋咪唑片、雌二醇制剂、 17-β-雌二醇、雌莫司汀磷酸钠、炔雌醇、氨磷汀、羟磷酸、凡毕复、依托泊甙、法倔唑、他莫昔芬制剂、非格司亭、非那司提、非雷司替、氟尿苷、氟康唑、氟达拉滨、 5-氟脱氧尿嘧啶核苷一磷酸盐、 5-氟尿嘧啶、氟甲睾酮、氟他胺、福麦斯坦、 1-β-D-阿糖呋喃糖胞噻啶-5 '-硬脂酰磷酸酯、福莫司汀、氟维司群、丙种球蛋白、吉西他滨、吉妥单抗、甲磺酸伊马替尼、卡氮芥糯米纸胶囊剂、戈舍瑞林、盐酸格拉尼西隆、组氨瑞林、和美新、氢化可的松、赤型-羟基壬基腺嘌呤、羟基脲、替坦异贝莫单抗、伊达比星、异环磷酰胺、干扰素 α 、干扰素 -α2 、干扰素 α- 2A 、干扰素 α-2B 、干扰素 α-nl 、干扰素 α-n3 、干扰素 β、干扰素 γ-la 、白细胞介素-2 、内含子 A 、易瑞沙、依立替康、凯特瑞、硫酸香菇多糖、来曲唑、甲酰四氢叶酸、亮丙瑞林、亮丙瑞林醋酸盐、左旋四咪唑、左旋亚叶酸钙盐、左甲状腺素钠、左甲状腺素钠制剂、洛莫司汀、氯尼达明、屈大麻酚、氮芥、甲钴胺、甲羟孕酮醋酸酯、醋酸甲地孕酮、美法仑、酯化雌激素、 6-巯基嘌呤、美司钠、氨甲蝶呤、氨基乙酰丙酸甲酯、米替福新、美满霉素、丝裂霉素 C 、米托坦、米托葸醌、曲洛司坦、柠檬酸阿霉素脂质体、奈达铂、聚乙二醇化非格司亭、奥普瑞白介素、 neupogen 、尼鲁米特、三苯氧胺、 NSC-631570 、重组人白细胞介素 1-β 、奥曲肽、盐酸奥丹西隆、去氢氢化可的松口服溶液剂、奥沙利铂、紫杉醇、泼尼松磷酸钠制剂、培门冬酶、派罗欣、喷司他丁、溶链菌制剂、盐酸匹鲁卡品、毗柔比星、普卡霉素、叶吩姆钠、泼尼莫司汀、司替泼尼松龙、泼尼松、倍美力、丙卡巴肼、重组人类红细胞生成素、雷替曲塞、利比、依替膦酸铼-186 、美罗华、力度伸-A 、罗莫肽、盐酸毛果芸香碱片剂、奥曲肽、沙莫司亭、司莫司汀、西佐喃、索布佐生、唬钠甲强龙、帕福斯酸、干细胞治疗、链佐星、氯化锶-89 、左旋甲状腺素钠、他莫昔芬、坦舒洛辛、他索那明、tastolactone 、泰索帝、替西硫津、替莫唑胺、替尼泊苷、丙酸睾酮、甲睾酮、硫鸟嘌呤、噻替哌、促甲状腺激素、替鲁膦酸、拓扑替康、托瑞米芬、托西莫单抗、曲妥珠单抗、曲奥舒凡、维 A 酸、甲氨喋呤片剂、三甲基密胺、三甲曲沙、乙酸曲普瑞林、双羟萘酸曲普瑞林、优福定、尿苷、戊柔比星、维司力农、长春碱、长春新碱、长春酰胺、长春瑞滨、维鲁利秦、右旋丙亚胺、净司他丁斯酯、枢复宁、紫杉醇蛋白质稳定制剂、 acolbifene 、干扰素 r-lb 、 affinitak 、氨基喋呤、阿佐昔芬、asoprisnil 、阿他美坦、阿曲生坦、 BAY 43-9006 、阿瓦斯丁、 CCI-779 、 CDC-501 、西乐葆、西妥昔单抗、克立那托、环丙孕酮醋酸酯、地西他滨、 DN-101 、阿霉素-MTC 、dSLIM 、度他雄胺、 edotecarin 、依氟鸟氨酸、依喜替康、芬维 A 胺、组胺二盐酸盐、组氨瑞林水凝胶植入物、钬-166 DOTMP 、伊班膦酸、干扰素 γ、内含子-PEG 、

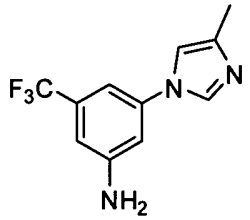
ixabepilone 、匙孔形血蓝蛋白、 L-651582 、兰乐肽、拉索昔芬、 libra 、 lonafamib 、米泼昔芬、米诺屈酸酯、 MS-209 、脂质体 MTP-PE 、 MX-6 、那法瑞林、奈莫柔比星、新伐司他、诺拉曲特、奥利默森、 onco-TCS、osidem 、紫杉醇聚谷氨酸酯、帛米酸钠、PN-401 、 QS-21 、夸西洋、 R - 1549 、雷洛昔芬、豹蛙酶、 13-顺维 A 酸、沙铂、西奥骨化醇、 T- 138067 、 tarceva 、二十二碳六烯酸紫杉醇、胸腺素 αl 、嘎唑呋林、tipifarnib 、替拉扎明、TLK-286 、托瑞米芬、反式 MID-lo7R 、伐司朴达、伐普肽、vatalanib 、维替泊芬、长春氟宁、 Z-100 和唑来膦酸或它们的组合。

以下实施例对本发明做进一步的描述，但该实施例并非用于限制本发明的保护范围。

实施例 1 3-((2-(环丙基胺基)嘧啶-5-取代)乙炔)-4-甲基-N-(3-(4-甲基-1H-咪唑-1-取代)-5-(三氟甲基)苯基)苯甲酰胺



步骤 1. 5-(4-甲基-1*H*-咪唑-1-取代)-3-(三氟甲基)-苯胺（5-(4-methyl-1*H*-imidazol-1-yl)-3-(trifluoromethyl)-benzenamine）



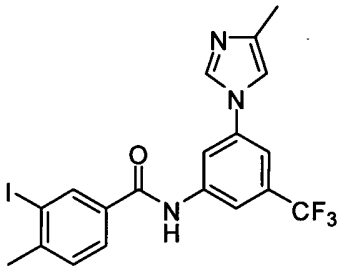
在一端密封的耐压管中，加入 CuI 190mg（1mmol），4-甲基咪唑 1.64g （20mmol），Cs_2CO_3 3.25g （10mmol），氮气置换后加入 3-溴-5-(三氟甲基)苯胺 2.40g (10 mmol),

1-(5,6,7,8-四氢喹啉-8-取代)乙基酮 350mg （2mmol），30mLDMF，密封后于 110℃反应 18h。冷却至室温，减压旋干溶剂，柱层析得产物 2.19g（91%）。

^{1}HNMR (400 MHz, *d*-DMSO), δ 8.06 (s, 1H), 7.35 (s, 1 H), 6.97 (s, 1 H), 6.93 (s, 1 H), 6.81 (s, 1 H), 5.87 (br, 2H), 2.15, (s, 3H).

MS(ESI), m/z: 242 ($M^+ + H^+$).

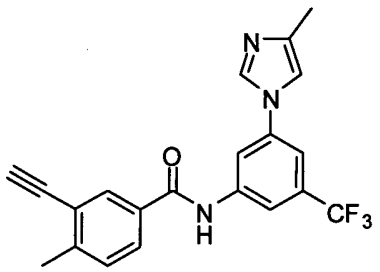
步骤 2. 3-碘-4-甲基-*N*-(3-(4-甲基-1*H*-咪唑-1-取代)-5-(三氟甲基)苯基)苯甲酰胺



将 3-碘-4-甲基苯甲酸 628mg（2.2 mmol）于 20mL$SOCl_2$ 中滴加 2 滴 DMF，回流 2h。减压蒸除 SOCl2，加入 6 mL 无水 THF 溶解，得淡黄色溶液待用。将步骤 1 所得化合物 524mg（2.0 mmol）溶解于 6 mL 无水 THF 中，加入三乙胺 10 mmol，于 0 滴加前述淡黄色溶液，滴加完毕，升至室温反应 1h。加入饱和氯化钠溶液萃灭反应，混合液用乙酸乙酯萃取，萃取所得有机相干燥后减压蒸除溶剂，经柱层析得产物 873 mg（90%）。

MS (ESI), m/z: 486 ($M^+ + H^+$).

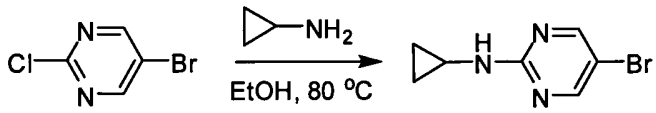
步骤 3. 3-乙炔基-4-甲基-*N*-(3-(4-甲基-1*H*-咪唑-1-取代)-5-(三氟甲基)苯基)苯甲酰胺



在一端密封的耐压管中，加入步骤 2 所得产物 485 mg（1.0 mmol），三甲基硅乙炔 500mg（5.0 mmol），CuI 19mg（0.1mmol），$Pd(dppf)_2Cl_2$ 7mg（0.01 mmol），三乙胺 1mL，乙腈 3mL，氮气置换后密封于 80℃反应 2h。冷却至室温，经 2cm 硅胶短柱过滤，滤渣用乙酸乙酯洗三次，减压旋干溶剂得褐色固体。将所得固体溶解于 5mL 甲醇中，加入 980mg K_2CO_3 室温搅拌 3h，过滤，减压旋干溶剂，柱层析得产物 344 mg（90%）。

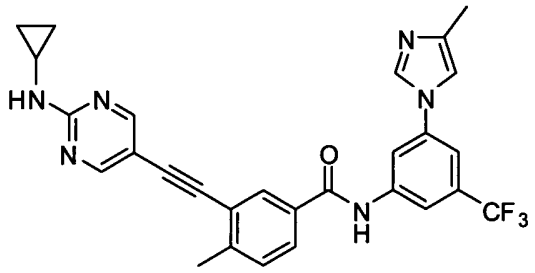
MS (ESI), m/z:384 ($M^+ + H^+$).

步骤 4. 5-溴-*N*-环丙基嘧啶-2-胺（5-bromo-N-cyclopropylpyrimidin-2-amine）



在一端密封的耐压管中，加入 5-溴-2-氯嘧啶 193mg （1.0 mmol），环丙胺 285mg（5.0 mmol），乙醇 3mL，密封后于 80℃反应 3h。冷却至室温，过滤得固体产物 203mg（95%）。MS (ESI), m/z: 215 ($M^+ + H^+$).

步骤 5. 3-((2-(环丙基胺基)嘧啶-5-取代)乙炔)-4-甲基-*N*-(3-(4-甲基-1*H*-咪唑-1-取代)-5-(三氟甲基)苯基)苯甲酰胺 （D747）

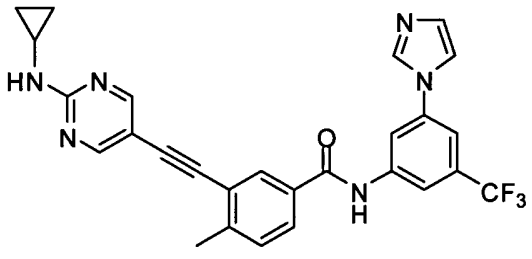


在一端密封的耐压管中，加入步骤 3 所得产物 192 mg（0.5 mmol），步骤 4 所得产物 107mg（0.5 mmol），CuI 19mg（0.1mmol），$Pd(OAc)_2$ 2.2mg（0.01 mmol），PCy_3 2.8mg （0.01 mmol）,DIPEA 193mg（1.5mmol），DMF 3mL，氮气置换后密封于 60℃反应 12h。冷却至室温，经 2cm 硅胶短柱过滤，滤渣用乙酸乙酯洗三次，减压旋干溶剂，柱层析得产物 193 mg（75%）。

^{1}HNMR (400 MHz, *d*-DMSO), δ ppm 10.69 (s, 1H), 8.54 (br, 2H), 8.29 (s, 1H), 8.21 (s, 1H), 8.16 (m, 2 H), 7.93 (m, 2H), 7.73 (s, 1H), 7.52 (m, 2H), 2.77 (m, 1H), 2.53 (s, 3H), 2.18 (s, 3H), 0.71 (m, 2H), 0.53 (m, 2H).

MS (ESI), m/z: 517 ($M^+ + H^+$).

实施例 2 N-(3-(1*H*-咪唑-1-取代)-5-(三氟甲基)苯基)-3-((2-(环丙基胺基)嘧啶-5-取代)乙炔基)-4-甲基苯甲酰胺 (D729)



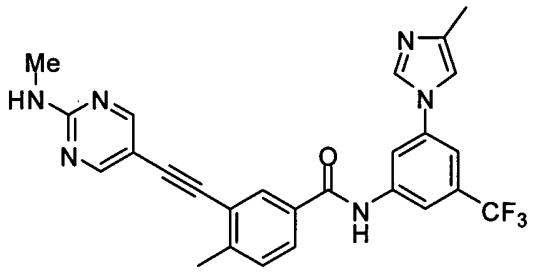
合成方法如实施例 1。

^{1}HNMR (400 MHz, *d*-DMSO), δ ppm 10.73 (s, 1H), 8.55 (br, 2H), 8.33 (d, *J*= 2.4 Hz, 2H), 8.21 (s, 1H), 8.14 (d, J= 1.2 Hz, 1 H), 7.94-7.89 (m, 2H), 7.80-7.76 (m, 2H), 7.53 (d, J= 8.4 Hz,

1H), 7.17 (s, 1H), 2.78-2.73 (m, 1H), 2.53 (s, 3H), 2.18 (s, 3H), 0.73-0.68 (m, 2H), 0.53-0.49 (m, 2H).

MS (ESI), m/z: 503 ($M^+ + H^+$).

实施例 3 4-甲基-*N*-(3-(4-甲基-1*H*-咪唑-1-取代)-5-(三氟甲基)苯基)-3-((2-(甲基胺基)嘧啶-5-取代)乙炔基)苯甲酰胺 (D800)

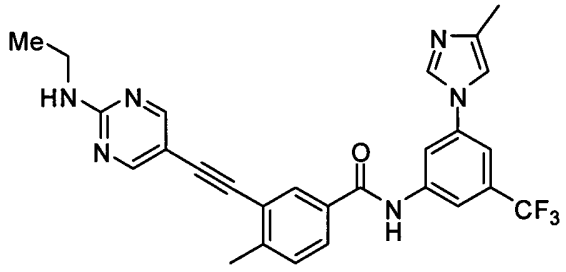


合成方法如实施例 1。

^{1}HNMR (400 MHz, *d*-DMSO), δ ppm 10.69 (s, 1H), 8.29 (m, 2H), 8.20-8.13 (m, 5H), 7.91 (d, *J*= 4.8 Hz, 1H), 7.73-7.66 (m, 2 H), 7.52 (m, 2H), 2.85 (d, *J*= 4.4 Hz, 1H), 2.53 (s, 3H), 2.18 (s, 3H).

MS (ESI), m/z: 491 ($M^+ + H^+$).

实施例 4 3-((2-(乙基胺基)嘧啶-5-取代)乙炔基)-4-甲基-*N*-(3-(4-甲基-1*H*-咪唑-1-取代)-5-(三氟甲基)苯基)苯甲酰胺 (D755)

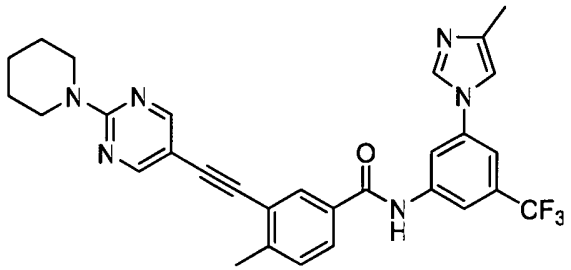


合成方法如实施例 1。

^{1}HNMR (400 MHz, *d*-DMSO), δ ppm 10.69 (s, 1H), 8.52 (br, 2H), 8.29 (s, 1H), 8.21 (d, *J*= 1.6 Hz, 1H), 8.16 (s, 1 H), 8.13 (d, *J*= 1.6 Hz, 1H), 7.91 (m, 1H), 7.75-7.73 (m, 2H), 7.52-7.49 (m, 2H), 3.35-3.29 (m, 2H), 2.52 (s, 3H), 2.18 (s, 3H), 1.15 (t, *J*= 7.2 Hz, 3H).

MS (ESI), m/z: 505 ($M^+ + H^+$).

实施例 5 4-甲基-N-(3-(4-甲基-1H-咪唑-1-取代)-5-(三氟甲基)苯基)-3-((2-(哌啶-1-取代)嘧啶-5-取代)乙炔基)苯甲酰胺（D797）

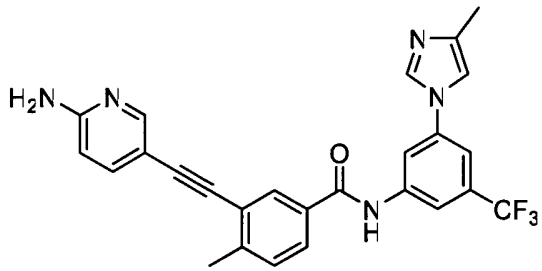


合成方法如实施例 1。

^{1}HNMR (400 MHz, *d*-DMSO), δ 1.51 (4H, s), 1.62 (2H, s), 2.16 (3H, s), 3.77 (4H, s), 7.47 (2H, s), 7.70 (1H, s), 7.88 (1H, d, *J*=6.4 Hz), 8.15 (3H, m), 8.28 (1H, s), 8.53 (2.0H, s), 10.66 (1H, s).

MS(ESI), m/z: 545 ($M^+ + H^+$).

实施例 6 3-((6-氨基吡啶-3-取代)乙炔基)-4-甲基-N-(3-(4-甲基-1*H*-咪唑-1-取代)-5-(三氟甲基)苯基)苯甲酰胺（D827）

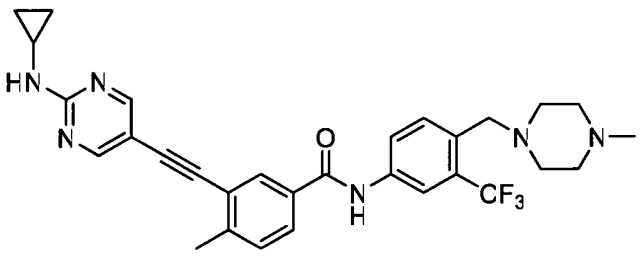


合成方法如实施例 1。

^{1}HNMR (400 MHz, *d*-DMSO), δ 2.53 (3H, s), 6.48 (2H, s), 7.54 (2H, m), 7.74 (1H, s), 7.89 (1H, dd, *J*=8.0, 3.2 Hz), 8.13 (1H, d, *J*=1.6 Hz), 8.18 (2H, s), 8.31 (1.0H, s), 10.68 (1H, s).

MS(ESI), m/z: 476 ($M^+ + H^+$).

实施例 7 3-((2-(环丙基氨基)嘧啶-5-取代)乙炔基)-4-甲基-N-(4-((4-甲基哌嗪-1-取代)甲基)-3-(三氟甲基)苯基)苯甲酰胺（D825）

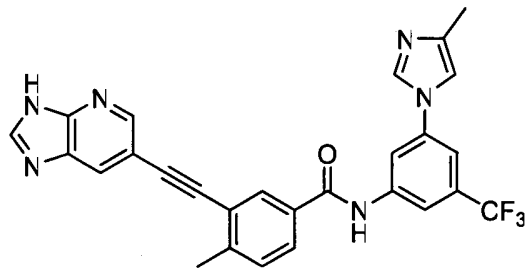


合成方法如实施例 1。

^{1}HNMR (400 MHz, *d*-DMSO), δ 0.51 (2H, s), 0.70 (2H, d, *J*=5.6 Hz), 2.42 (3H, s), 2.72 (3H, s), 2.75 (2H, m), 3.60 (6H, br), 7.48 (1H, d, *J*=7.8 Hz), 7.69 (1H, d, *J*=8.2 Hz), 7.89 (2H, m), 8.09 (2H,m), 8.21 (1H, s), 8.54 (2H, s), 10.51 (1H, s).

MS(ESI), m/z: 549 ($M^+ + H^+$).

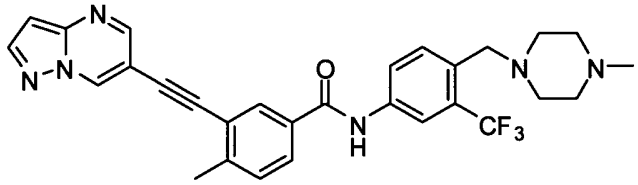
实施例 8 3-((3*H*-咪唑[4,5-b]吡啶-6-取代)乙炔基)-4-甲基-*N*-(3-(4-甲基-1*H*-咪唑-1-取代)-5-(三氟甲基)苯基)苯甲酰胺（D833）



^{1}HNMR (400 MHz, *d*-DMSO), δ 2.18 (3H, s), 2.60 (3H, s), 7.49 (1H, s), 7.55 (1H, d, *J*=8.0 Hz), 7.74 (1H, s), 7.94 (1 H, d, *J*=7.8 Hz), 8.20 (4H, mHz), 8.30 (1H, s), 8.59 (1H, s), 10.72 (1H, s).

MS(ESI), m/z: 501 ($M^+ + H^+$).

实施例 9 4-甲基-N-(4-((4-甲基哌嗪-1-取代)甲基)-3-(三氟甲基)苯基)-3-(吡唑[1,5-a]嘧啶-6-取代乙炔基)苯甲酰胺（D856）

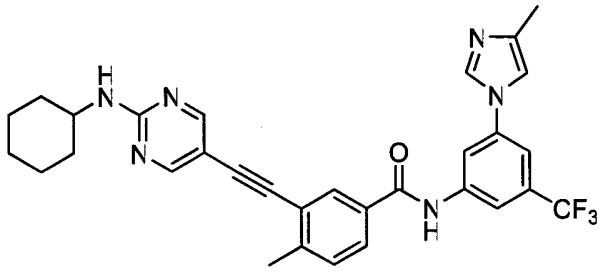


合成方法如实施例 1。

^{1}HNMR (400 MHz, *d*-DMSO), δ 2.17 (3H, s), 2.37 (8H, m), 2.60 (3H, s), 3.57 (2H, s), 6.85 (1H, d, J=2.0 Hz), 7.54 (1H, d, J=8.0 Hz), 7.71 (1H, d, J=8.4 Hz), 7.96 (1H, dd, J= 8.0, 3.29 Hz), 8.06 (1H, d, J=2.00 Hz), 8.21 (2H, dd, J=4.2, 2.0 Hz), 8.34 (1H, d, J=2.0 Hz), 8.72 (1H, d, J=2.0 Hz), 9.58 (1H, d, J=2.00 Hz), 10.56 (1H, s).

MS(ESI), m/z: 533 ($M^+ + H^+$).

实施例 10 3-((2-(环己基氨基)嘧啶-5-取代)乙炔基)-4-甲基-N-(3-(4-甲基-1H-咪唑-1-取代)-5-(三氟甲基)苯基)苯甲酰胺（D828）

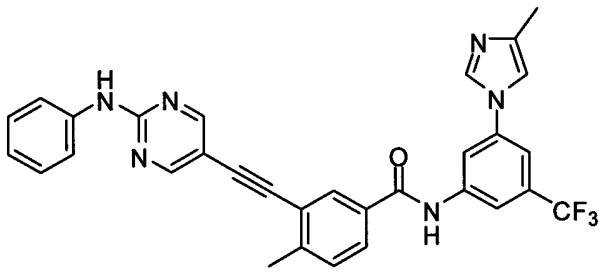


合成方法如实施例 1。

^{1}HNMR (400 MHz, *d*-DMSO), δ 1.23 (4H, m), 1.71 (3H, m), 2.17 (2H, s), 2.54 (3H, s), 4.40 (1 H, q, *J*=7.0 Hz), 7.51 (2H,m), 7.64 (1H, d, *J*=8.0 Hz), 7.72 (1H, s), 7.94 (1H, d, J=7.48 Hz), 8.14 (2H, m), 8.29 (1H, s), 8.49 (1H, s), 8.84 (1H, s), 10.68 (1H, s).

MS(ESI), m/z: 559 ($M^+ + H^+$).

实施例 11 4-甲基-N-(3-(4-甲基-1*H*-咪唑-1-取代)-5-(三氟甲基)苯基)-3-((2-(苯氨基)嘧啶-5-取代)乙炔基)苯甲酰胺 (D809)

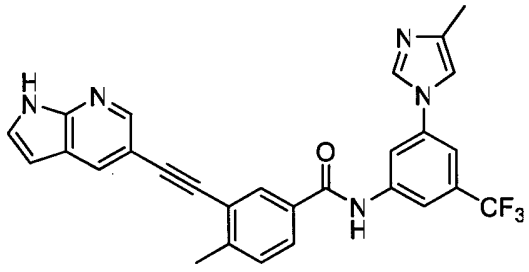


合成方法如实施例 1。

^{1}HNMR (400 MHz, *d*-DMSO), δ 2.18 (3H, s), 2.56 (3H, s), 7.02 (1H, t, *J*=7.2 Hz), 7.32 (2.0H, t, *J*=8.0 Hz), 7.49 (1H, s), 7.54 (1H, d, *J*=8.0 Hz), 7.75 (3H, m), 7.93 (1H, dd, *J*= 8.0, 3.2 Hz), 8.17 (2H, s), 8.21 (1H, s), 8.30 (1H, s), 8.72 (2H, s), 10.06 (1H, s), 10.71 (1H, s).

MS(ESI), m/z: 553 ($M^+ + H^+$).

实施例 12 3-((1*H*-吡咯[2,3-b]吡啶 5-取代)乙炔基)-4-甲基-N-(3-(4-甲基-1H-咪唑-1-取代)-5-(三氟甲基)苯基)苯甲酰胺 (D832)

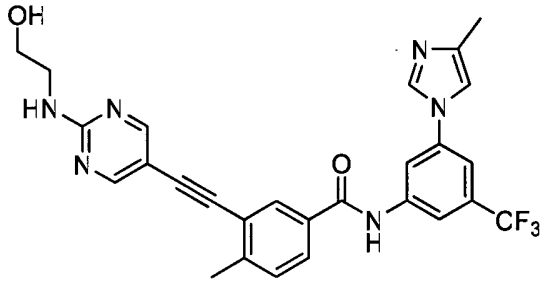


合成方法如实施例 8。

^{1}HNMR (400 MHz, *d*-DMSO), δ 2.18 (3H, s), 2.58 (3H, s), 6.53 (1H, q, J=1.71 Hz), 7.53 (3H, m), 7.73 (1H, s), 7.92 (1H, dd, J= 8.0, 3.2 Hz), 8.20 (3H, m), 8.31 (1H, s), 8.46 (1H, s), 10.70 (1H, s), 11.95 (1H, s).

MS(ESI), m/z: 500 ($M^+ + H^+$).

实施例 13 3-((2-(2-羟基乙胺)嘧啶-5-取代)乙炔基)-4-甲基-N-(3-(4-甲基-1H-咪唑-1-取代)-5-(三氟甲基)苯基)苯甲酰胺（D820）

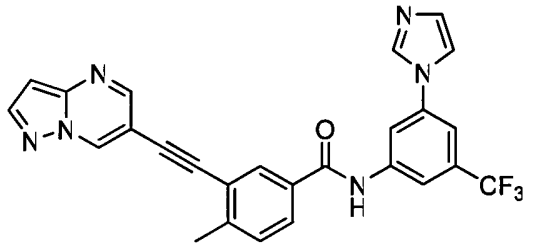


合成方法如实施例 1。

^{1}HNMR (400 MHz, *d*-DMSO), δ 2.19 (3H, s), 2.53 (3H, s), 3.15 (1H, m), 3.41 (2H, m), 3.53 (2H, m), 4.73 (1H, t, J=5.2 Hz), 7.52 (1H, d, J=8.0 Hz), 7.63 (1H, s), 7.74 1H, s), 7.91 (1H, m), 8.00 (1H, s), 8.16 (2H, m), 8.31 (1H, s), 8.52 (1H, s), 10.71 (1H, s).

MS(ESI), m/z: 521 ($M^+ + H^+$).

实施例 14 N-(3-(1H-咪唑-1-取代)-5-(三氟甲基)苯基)-4-甲基-3-(吡唑[1,5-a]嘧啶-6-取代乙炔基)苯甲酰胺（D819）

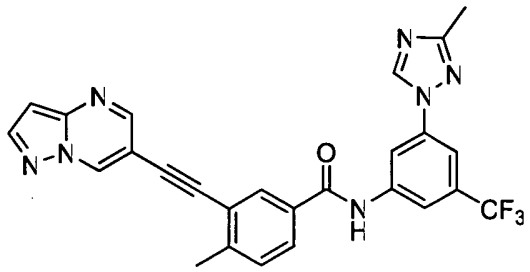


合成方法如实施例 1。

^{1}HNMR (400 MHz, *d*-DMSO), δ 2.61 (3H, s), 6.85 (1.0H, d, *J*=2.0 Hz), 7.21 (1H, s), 7.57 (1H, d, *J*=8.4 Hz), 7.82 (2H, m), 7.98 (1H, dd, J=8.0, 3.2 Hz), 8.23 (2H, m), 8.35 (3H, d, *J*=2.4 Hz), 8.73 (1H, d, *J*=2.00 Hz), 9.59 (1H, d, *J*=2.0 Hz), 10.77 (1H, s).

MS(ESI), m/z: 487 ($M^+ + H^+$).

实施例 15 4-甲基-N-(3-(3-甲基-1H-1,2,4-三氮唑-1-取代)-5-(三氟甲基)苯基)-3-(吡唑[1,5-a]嘧啶-6-取代乙炔基)苯甲酰胺 (D818)

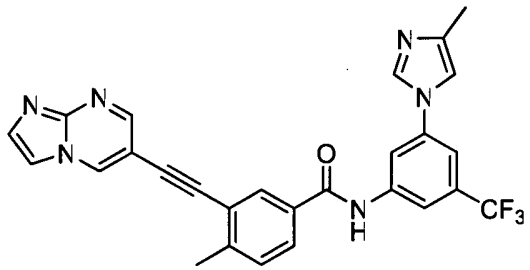


合成方法如实施例 1。

^{1}HNMR (400 MHz, *d*-DMSO), δ 2.40 (3H, s), 2.60 (3H, s), 6.85 (1H, d, J=1.6 Hz), 7.56 (1H, d, J=8.2 Hz), 7.99 (2H, m), 8.26 (2H, m), 8.35 (1H, d, J=2.0 Hz), 8.64 (1H, s), 8.73 (1H, d, J=2.0 Hz), 9.32 (1H, s), 9.58 (1H, d, J=1.2 Hz), 10.80 (1H, s).

MS(ESI), m/z: 502 ($M^+ + H^+$).

实施例 16 3-(咪唑[1,2-a]嘧啶-6-取代乙炔)-4-甲基-N-(3-(4-甲基-1H-咪唑-1-取代)-5-(三氟甲基)苯基)苯甲酰胺 (D799)

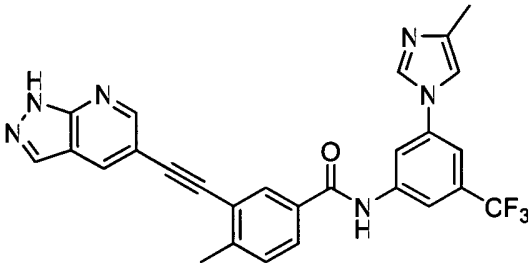


合成方法如实施例 1。

^{1}HNMR (400 MHz, *d*-DMSO), δ 2.19 (3H, s), 2.59 (3H, s), 7.50 (1H, s), 7.57 (1H, d, J=8.2 Hz), 7.74 (1H, s), 7.82 (1H, s), 7.97 (2H, m), 8.17 (1H, s), 8.22 (2H, d, J=2.0 Hz), 8.31 (1H, s), 8.71 (1H, d, J=2.4 Hz), 9.40 (1H, d, J=2.4 Hz), 10.73 (1H, s).

MS(ESI), m/z: 501 ($M^+ + H^+$).

实施例 17 3-((1H-吡唑[3,4-b]吡啶-5-取代)乙炔基)-4-甲基-N-(3-(4-甲基-1H-咪唑-1-取代)-5-(三氟甲基)苯基)苯甲酰胺（D767）

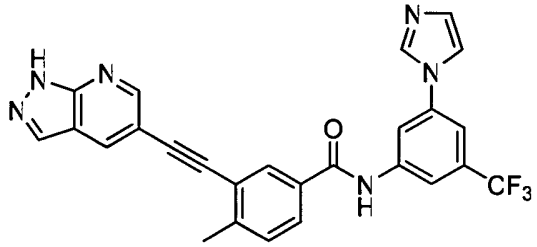


合成方法如实施例 1。

^{1}HNMR (400 MHz, *d*-DMSO), δ 13.95 (s, 1H), 10.72 (s, 1H), 8.75 (s, 1H), 8.54 (s, 1H), 8.31 (s, 1 H), 8.23 (s, 3H), 8.18 (s, 1 H), 7.97 (d, *J*= 8.0 Hz, 1H), 7.75 (s, 1H), 7.57 (d, *J*= 8.0 Hz, 1H), 7.49 (s, 1 H), 2.60 (s, 3H), 2.19 (s, 3H).

MS(ESI), m/z: 501 ($M^+ + H^+$).

实施例 18 3-((1H-吡唑[3,4-b]吡啶-5-取代)乙炔基)-4-甲基-N-(3-(1H-咪唑-1-取代)-5-(三氟甲基)苯基)苯甲酰胺（D831）

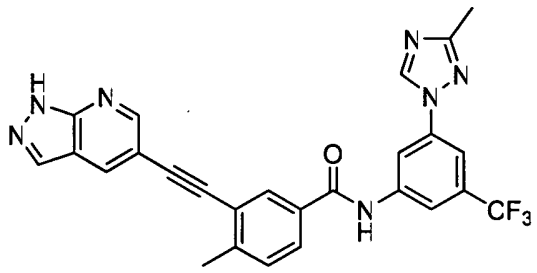


合成方法如实施例 1。

^{1}HNMR (400 MHz, *d*-DMSO), δ 13.92 (s, 1H), 10.72 (s, 1H), 8.72 (d, J=2.0 Hz, 1H), 8.51 (d, J=2.0 Hz, 1H), 8.32 (s, 2 H), 8.21 (s, 3H), 7.95 (d, J= 8.0 Hz, 1 H), 7.79 (d, *J*= 4.0 Hz, 2H), 7.54 (d, J= 8.0 Hz, 1H), 7.16 (s, 1H), 2.58 (s, 3H).

MS(ESI), m/z: 487 ($M^+ + H^+$).

实施例 19 3-((1H-吡唑[3,4-b]吡啶-5-取代)乙炔基)-4-甲基-N-(3-(3-甲基-1H-1,2,4-三氮唑-1-取代)-5-(三氟甲基)苯基)苯甲酰胺（D835）

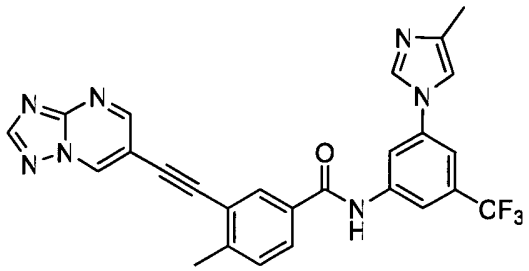


合成方法如实施例 1。

^{1}HNMR (400 MHz, *d*-DMSO), δ 13.92 (s, 1H), 10.76 (s, 1H), 9.30 (s, 1H), 8.73 (d, J=2.0 Hz, 1H), 8.63 (s, 1H), 8.52 (d, J=2.0 Hz, 1H), 8.26 (m, 3 H), 7.97 (m, 2H), 7.55 (d, J= 8.0 Hz, 1 H), 2.58 (s, 3H), 2.38 (s, 3H).

MS(ESI), m/z: 502 ($M^+ + H^+$).

实施例 20 3-([1,2,4]三氮唑[1,5-a]嘧啶-6-取代乙炔基)-4-甲基-N-(3-(4-甲基-1H-咪唑-1-取代)-5-(三氟甲基)苯基)苯甲酰胺 (D798)

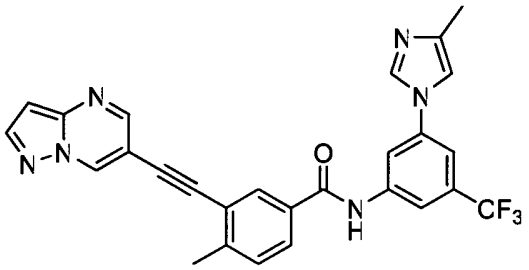


合成方法如实施例 1。

^{1}HNMR (400 MHz, *d*-DMSO), δ 2.17 (3H, s), 2.60 (3H, s), 7.48 (1H, s), 7.58 (1H, d, J=8.4 Hz), 7.74 (1H, s), 7.98 (1H, d, J= 8.0 Hz), 8.15 (1H, s), 8.22 (2H, m), 8.29 (1H, s), 8.78 (1H, s), 9.09 (1H, d, J=2.4 Hz), 9.88 (1H, d, J=2.4 Hz), 10.74 (1H, s).

MS(ESI), m/z: 502 ($M^+ + H^+$).

实施例 21 4-甲基-N-(3-(4-甲基-1H-咪唑-1-取代)-5-(三氟甲基)苯基)-3-(吡唑[1,5-a]嘧啶-6-取代乙炔基)苯甲酰胺 (D822)

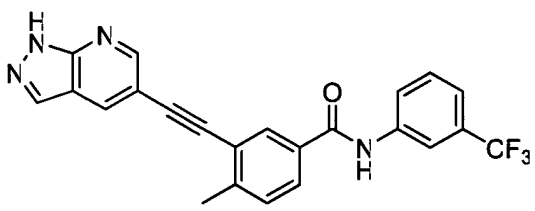


合成方法如实施例 1。

^{1}HNMR (400 MHz, *d*-DMSO), δ 2.18 (3H, s), 2.59 (3H, s), 6.84 (1H, m), 7.49 (1H, s), 7.57 (1H, d, *J*=8.4 Hz), 7.73 (1H, s), 7.98 (1H, dd, J= 8.0, 1.6 Hz), 8.16 (1H, s), 8.21 (2H, d, *J*= 2.0 Hz), 8.28 (1H, s), 8.34 (1H, d, J= 2.4 Hz), 8.71 (1H, d, J= 2.4 Hz), 9.57 (1H, d, J=2.0 Hz), 10.74 (1H, s).

MS(ESI), m/z: 502 ($M^+ + H^+$).

实施例 22 3-((1H-吡唑[3,4-b]吡啶-5-取代)乙炔基)-4-甲基-N-(3-(三氟甲基)苯基)苯甲酰胺 (D821)

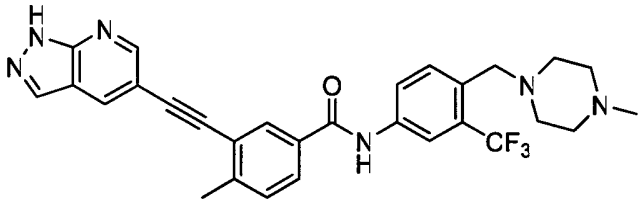


合成方法如实施例 1。

^{1}HNMR (400 MHz, *d*-DMSO), δ 13.94 (s, 1H), 10.59 (s, 1H), 8.75 (d, J=2.0 Hz, 1H), 8.54 (d, J=2.0 Hz, 1H), 8.26 (m, 3 H), 8.10 (d, J= 8.0 Hz, 1H), 7.95 (dd, J= 8.0,2.0 Hz, 1 H), 7.64 (m, 3H), 2.59 (s, 3H).

MS(ESI), m/z: 421 ($M^+ + H^+$).

实施例 23 3-((1H-吡唑[3,4-b]吡啶-5-取代)乙炔基)-4-甲基-N-(4-((4-甲基哌嗪-1-取代)甲基)-3-(三氟甲基)苯基)苯甲酰胺 (D824)

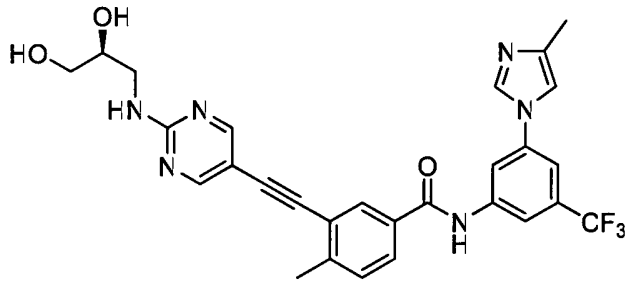


合成方法如实施例 1。

^{1}HNMR (400 MHz, *d*-DMSO), δ 13.92 (s, 1H), 10.55 (s, 1H), 8.72 (d, J=2.0 Hz, 1H), 8.52 (d, J=2.0 Hz, 1H), 8.17 (m, 3 H), 8.10 (d, J= 8.0 Hz, 1H), 7.92 (dd, J= 8.0,2.0 Hz, 1 H), 7.70 (d, J= 8.8 Hz, 1H), 7.53 (d, J= 8.0 Hz, 1H), 3.80 (s, 2H), 3.10 (brs, 8H), 2.71 (s, 3H), 2.57 (s, 3H).

MS(ESI), m/z: 533, ($M^+ + H^+$).

实施例 24 (S)-3-((2-(2,3-二羟基丙胺)嘧啶-5-取代)乙炔基)-4-甲基-N-(3-(4-甲基-1H-咪唑-1-取代)-5-(三氟甲基)苯基)苯甲酰胺（D834）

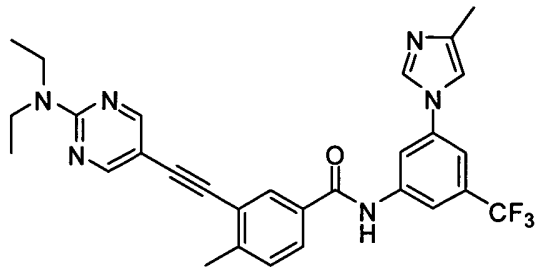


合成方法如实施例 1。

^{1}HNMR (400 MHz, *d*-DMSO), δ 2.31 (3H, s), 2.98 (1H, s), 3.65 (2H, br), 4.57 (1H, s), 4.78 (1H, s), 7.49 (4H, br), 7.70 (1H, br), 7.99 (2H, m), 8.22 (4H, s), 8.50 (2H, s), 10.67 (1H, s).

MS(ESI), m/z: 551 ($M^+ + H^+$).

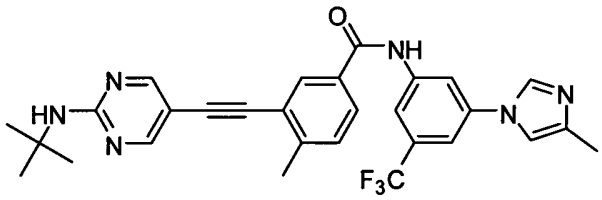
实施例 25 3-((2-(二乙基胺基)嘧啶-5-取代)乙炔基)-4-甲基-*N*-(3-(4-甲基-1*H*-咪唑-1-取代)-5-(三氟甲基)苯基)苯甲酰胺 (D807)



合成方法如实施例 1。

^{1}HNMR (400 MHz, *d*-DMSO), δ ppm 10.65 (s, 1H), 8.54 (br, 2H), 8.29 (s, 1H), 8.18 (m, 3H), 7.88 (d, J= 7.2 Hz, 1 H), 7.70 (s, 1H), 7.48 (m, 2H), 3.62 (m, 4H), 2.52 (s, 3H), 2.17 (s, 3H), 1.17 (t, *J*= 7.2 Hz, 6H). MS (ESI), m/z: 533 ($M^+ + H^+$).

实施例 26 3-((2-(叔丁基胺基)嘧啶-5-取代)乙炔基)-4-甲基-*N*-(3-(4-甲基-1*H*-咪唑-1-取代)-5-(三氟甲基)苯基)苯甲酰胺 (D806)

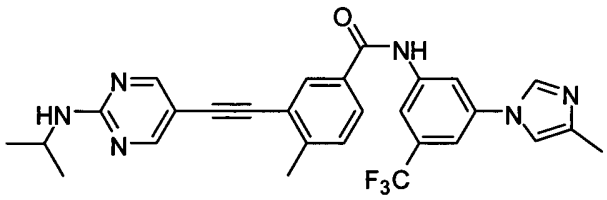


合成方法如实施例 1。

^{1}HNMR (400 MHz, *d*-DMSO), δ 10.69 (s, 1H), 8.51 (s, 2H), 8.29 (s, 1H), 8.20 (s, 1H), 8.16 (s, 1 H), 8.12 (s, 1H), 7.91 (dd, J= 6.8, 1.6 Hz, 1H), 7.73 (s, 1H), 7.52 (m, 2H), 7.38 (s, 1H), 2.55 (s, 3H), 2.18 (s, 3H), 1.39 (s, 9H).

MS(ESI), m/z: 533, ($M^+ + H^+$).

实施例 27 3-((2-(2-异丙基胺基)嘧啶-5-取代)乙炔基)-4-甲基-*N*-(3-(4-甲基-1*H*-咪唑-1-取代)-5-(三氟甲基)苯基)苯甲酰胺 (D752)

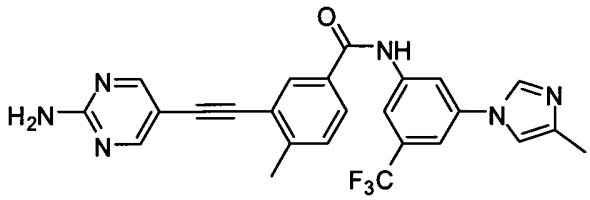


合成方法如实施例 1。

^{1}HNMR (400 MHz, *d*-DMSO), δ 10.69 (s, 1H), 8.51 (s, 2H), 8.29 (s, 1H), 8.20 (s, 1H), 8.16 (s, 1 H), 8.12 (s, 1H), 7.91 (dd, J= 6.8, 1.6 Hz, 1H), 7.73 (s, 1H), 7.52 (d, J= 8.0 Hz, 1H), 7.50 (m, 2H), 4.08 (m, 1H), 2.51 (s, 3H), 2.18 (s, 3H), 1.17 (d, J= 6.4 Hz, 6H).

MS(ESI), m/z: 519, ($M^+ + H^+$).

实施例 28 3-((2-胺基嘧啶-5-取代)乙炔基)-4-甲基-*N*-(3-(4-甲基-1*H*-咪唑-1-取代)-5-(三氟甲基)苯基)苯甲酰胺 (D803)

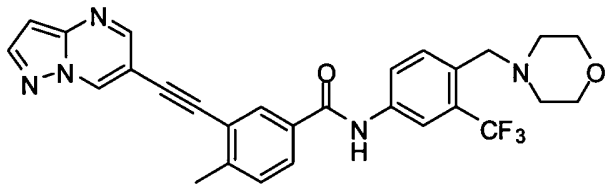


合成方法如实施例 1。

^{1}HNMR (400 MHz, *d*-DMSO), δ 10.69 (s, 1H), 8.48 (s, 2H), 8.31 (m, 2H), 8.16 (s, 1H), 8.13 (s, 1 H), 7.91 (d, J= 7.2 Hz, 1H), 7.74 (s, 1H), 7.51 (s, 2H), 7.20 (m, 2H), 2.52 (s, 3H), 2.19 (s, 3H).

MS(ESI), m/z: 477, ($M^+ + H^+$).

实施例 29 4-甲基-N-(4-(吗啡啉亚甲基)-3-(三氟甲基)苯基)-3-(吡唑[1,5-a]嘧啶-6-取代乙炔基)苯甲酰胺（D931）

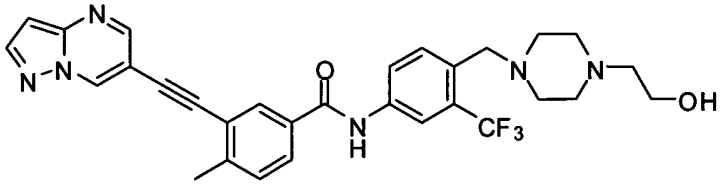


合成方法如实施例 1。

^{1}HNMR (400 MHz, *d*-DMSO), δ 2.39 (4H, brs), 2.59 (3H, s), 3.61 (6H, m), 6.85 (1H, s), 7.55 (1H, d, J=8.4 Hz), 7.72 (1H, d, J=8.4 Hz), 7.94 (1H, dd, J= 8.0, 1.6 Hz), 8.06 (1H, d, J=8.4 Hz), 8.21 (2H, dd, J=4.2, 1.6 Hz), 8.34 (1H, d, J=6.0 Hz), 8.72 (1H, d, J=2.0 Hz), 9.58 (1H, d, J=1.2 Hz), 10.56 (1H, s).

MS(ESI), m/z: 520 ($M^+ + H^+$).

实施例 30 N-(4-((4-(2-羟基乙基)哌嗪-1-取代)甲基)-3-(三氟甲基)苯基)-4-甲基-3-(吡唑[1,5-a]嘧啶-6-取代乙炔)苯甲酰胺（D942）

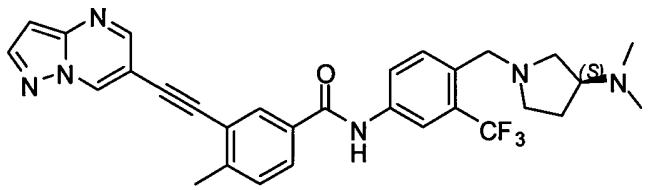


合成方法如实施例 1。

^{1}HNMR (400 MHz, *d*-DMSO), δ 2.39 (10H, m), 2.59 (3H, s), 3.49 (2H, m), 3.56 (2H, s), 4.36 (1H, br), 6.85 (1H, s), 7.55 (1H, d, J=8.0 Hz), 7.72 (1H, d, J=8.8 Hz), 7.94 (1H, dd, J= 8.0, 1.6 Hz), 8.05 (1H, d, J=8.4 Hz), 8.21 (2H, dd, J=4.8, 1.6 Hz), 8.34 (1H, d, J=2.0 Hz), 8.72 (1H, d, J=2.0 Hz), 9.58 (1H, d, J=1.2 Hz), 10.55 (1H, s).

MS(ESI), m/z: 563 ($M^+ + H^+$).

实施例 31 (S)-N-(4-((3-(甲基氨基)吡咯-1-取代)甲基)-3-(三氟甲基)苯基)-4-甲基-3-(吡唑[1,5-a]嘧啶-6-取代乙炔)苯甲酰胺（D940）

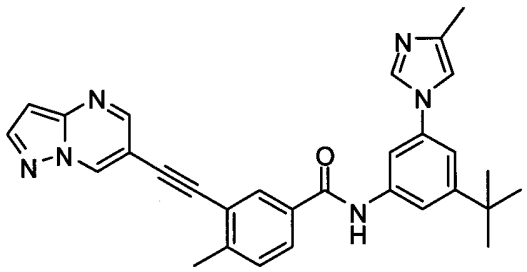


合成方法如实施例 1。

^{1}HNMR (400 MHz, *d*-DMSO), δ 1.62 (1H, m), 1.85 (1H, m), 2.12 (6H, s), 2.38 (1H, m), 2.59 (4H, m), 2.61 (1H, m), 2.83 (1H, m), 3.36 (2H, m), 3.56 (2H, s), 6.84 (1H, s), 7.55 (1H, d, J=8.0 Hz), 7.72 (1H, d, J=8.8 Hz), 7.94 (1H, dd, J= 8.0, 1.6 Hz), 8.05 (1H, d, J=8.4 Hz), 8.19 (2H, s), 8.34 (1H, d, J=2.4 Hz), 8.72 (1H, d, J=2.0 Hz), 9.56 (1H, d, J=1.2 Hz), 10.55 (1H, s).

MS(ESI), m/z: 547 ($M^+ + H^+$).

实施例 32 N-(3-叔丁基-5-(4-甲基-1H-咪唑-1-取代)苯基)-4-甲基-3-(吡唑[1,5-a]嘧啶-6-取代乙炔)苯甲酰胺（D941）

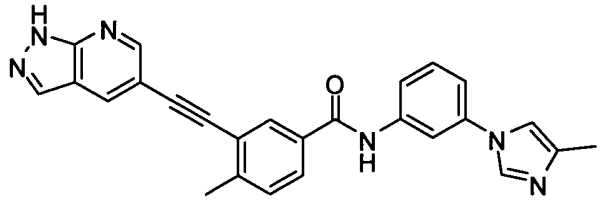


合成方法如实施例 1。

^{1}HNMR (400 MHz, *d*-DMSO), δ 1.34 (9H, s), 2.18 (3H, s), 2.59 (3H, m), 6.84 (1H, s), 7.30 (1H, s), 7.40 (1H, br), 7.55 (1H, d, J=8.0 Hz), 7.38 (1H, s), 7.97 (2H, m), 8.08 (1H, br), 8.21 (1H, d, J=1.6 Hz), 8.34 (1H, d, J=2.4 Hz), 8.72 (1H, d, J=2.0 Hz), 9.57 (1H, d, J=1.2 Hz), 10.42 (1H, s).

MS(ESI), m/z: 489 ($M^+ + H^+$).

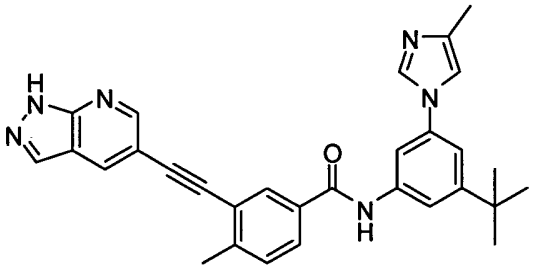
实施例33 3-((1H-吡唑[3,4-b]吡啶-5-取代)乙炔基)-4-甲基-N-(3-(三氟甲基)苯基)苯甲酰胺(D967)



1HNMR (400 MHz, *d*-DMSO), 13.95 (s, 1H), 10.47 (s, 1H), 8.74 (s, 1H), 8.52 (s, 1H), 8.22 (m, 2 H), 8.06 (m, 2H), 7.94 (d, J= 7.6 Hz, 1 H), 7.76 (d, J= 8.0 Hz, 1H), 7.53 (m, 2H), 7.35 (m, 2H), 2.59 (s, 3H), 2.18 (s, 3H).

MS(ESI), m/z: 433 (M+ + H+).

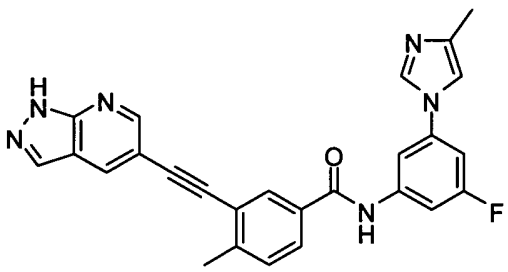
实施例 34 3-((1H-吡唑[3,4-b]吡啶-5-取代)乙炔基)-N-(3-叔丁基-5-(4-甲基-1H-咪唑-1-取代)苯基)-4-甲基苯甲酰胺（D968）



^{1}HNMR (400 MHz, *d*-DMSO), δ 13.95 (s, 1H), 10.42 (s, 1H), 8.75 (s, 1H), 8.54 (s, 1H), 8.23 (m, 2H), 8.07 (s, 1H), 7.96 (m, 2H), 7.75 (s, 1H), 7.54 (d, J= 8.0 Hz, 1 H), 7.31 (s, 2H), 7.30 (d, J= 4.2 Hz, 1 H), 2.59 (s, 3H), 2.18 (s, 3H), 1.34 (s, 9H).

MS(ESI), m/z: 489 ($M^+ + H^+$).

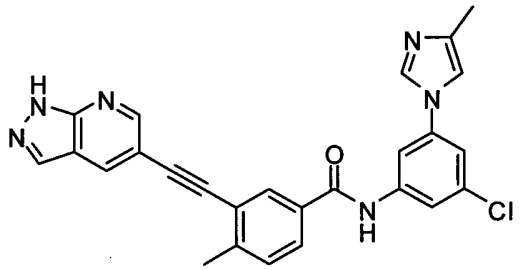
实施例 35 3-((1H-吡唑[3,4-b]吡啶-5-取代)乙炔基)-N-(3-氟-5-(4-甲基-1H-咪唑-1-取代)苯基)-4-甲基苯甲现酰胺（D963）



^{1}HNMR (400 MHz, *d*-DMSO), δ 13.94 (s, 1H), 10.58 (s, 1H), 8.74 (s, 1H), 8.51 (s, 1H), 8.22 (d, J=8.0 Hz, 2H), 8.11 (s, 1H), 7.93 (d, J= 7.6Hz, 1H), 7.83 (s, 1 H), 7.71 (d, J= 7.2 Hz, 1H), 7.54 (d, J= 8.0 Hz, 1 H), 7.39 (s, 1H), 7.33 (d, J= 10 Hz, 1H), 2.58 (s, 3H), 2.17 (s, 3H).

MS(ESI), m/z: 451 ($M^+ + H^+$).

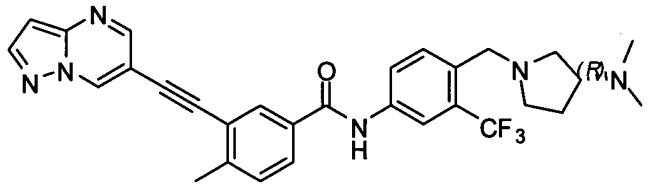
实施例 36 3-((1H-吡唑[3,4-b]吡啶-5-取代)乙炔基)-N-(3-氯-5-(4-甲基-1H-咪唑-1-取代)苯基)-4-甲基苯甲现酰胺（D964）



^{1}HNMR (400 MHz, *d*-DMSO), δ 13.94 (s, 1H), 10.52 (s, 1H), 8.78 (s, 1H), 8.48 (s, 1H), 8.21 (s, 1H), 8.16 (s, 1H), 8.11 (s, 1H), 7.95 (s, 1H), 7.88 (s, 2 H), 7.49 (s, 2H), 7.36 (s, 1 H), 2.57 (s, 3H), 2.15 (s, 3H).

MS(ESI), m/z: 468 ($M^+ + H^+$).

实施例 37 (R)-N-(4-((3-(甲基氨基)吡咯-1-取代)甲基)-3-(三氟甲基)苯基)-4-甲基-3-(吡唑[1,5-a]嘧啶-6-取代乙炔)苯甲酰胺（D943）

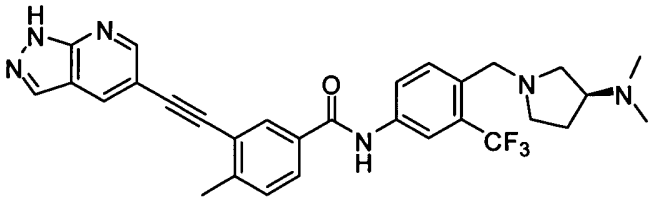


合成方法如实施例 1。

^{1}HNMR (400 MHz, *d*-DMSO), δ 1.62 (1H, m), 1.85 (1H, m), 2.12 (6H, s), 2.37 (1H, m), 2.59 (4H, m), 2.61 (1H, m), 2.83 (1H, m), 3.36 (2H, m), 3.56 (2H, s), 6.84 (1H, s), 7.55 (1H, d, J=8.0 Hz), 7.73 (1H, d, J=8.8 Hz), 7.95 (1H, dd, J= 8.0, 1.6 Hz), 8.05 (1H, d, J=8.4 Hz), 8.19 (2H, s), 8.34 (1H, d, J=2.4 Hz), 8.72 (1H, d, J=2.0 Hz), 9.56 (1H, d, J=1.2 Hz), 10.55 (1H, s).

MS(ESI), m/z: 547 ($M^+ + H^+$).

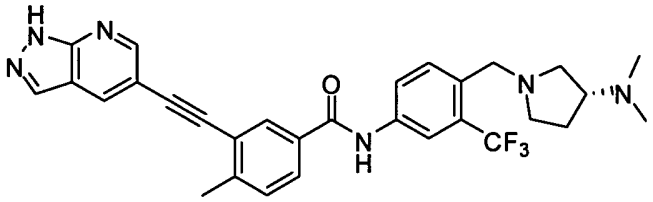
实施例 38 (S)-3-((1H-吡唑[3,4-b]嘧啶-5-取代)乙炔)-N-(4-((3-(二甲基氨基)吡咯-1-取代)甲基)-3-(三氟甲基)苯基)-4-甲基苯甲酰胺（D966）



^{1}HNMR (400 MHz, *d*-DMSO), δ 13.95 (s, 1H), 10.55 (s, 1H), 8.75 (s, 1H), 8.54 (s, 1H), 8.24 (m, 3H), 8.09 (d, J=8.4 Hz, 1H), 7.95 (d, J= 8.4 Hz, 1H), 7.72 (d, J=8.4 Hz, 1 H), 7.55 (d, J= 8.0 Hz, 1H), 3.74 (m, 2H), 3.52 (m, 1H), 3.17 (s, 1H), 2.88 (br, 1H), 2.68 (m, 1H), 2.59 (s, 3H), 2.43 (m, 1H), 2.17 (s, 6H), 1.91 (s, 4H), 1.70 (m, 2H).

MS(ESI), m/z: 547 ($M^+ + H^+$).

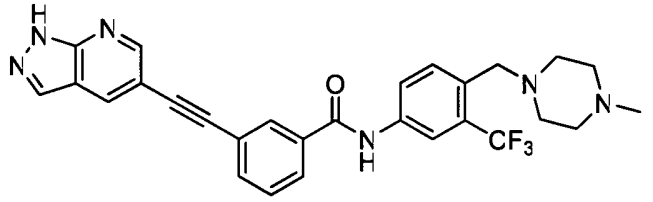
实施例 39 (R)-3-((1H-吡唑[3,4-b]嘧啶-5-取代)乙炔)-N-(4-((3-(二甲基氨基)吡咯-1-取代)甲基)-3-(三氟甲基)苯基)-4-甲基苯甲酰胺（D965）



^{1}HNMR (400 MHz, *d*-DMSO), δ 13.95 (s, 1H), 10.55 (s, 1H), 8.76 (s, 1H), 8.54 (s, 1H), 8.24 (m, 3H), 8.09 (d, J=8.4 Hz, 1H), 7.94 (d, J= 8.4 Hz, 1H), 7.72 (d, J=8.4 Hz, 1 H), 7.54 (d, J= 8.0 Hz, 1H), 3.74 (m, 2H), 3.51 (m, 1H), 3.17 (s, 1H), 2.88 (br, 1H), 2.68 (m, 1H), 2.59 (s, 3H), 2.43 (m, 1H), 2.17 (s, 6H), 1.91 (s, 4H), 1.71 (m, 2H).

MS(ESI), m/z: 547 ($M^+ + H^+$).

实施例 40 3-((1H-吡唑[3,4-b]吡啶-5-取代)乙炔基)-N-(4-((4-甲基哌嗪-1-取代)甲基)-3-(三氟甲基)苯基)苯甲酰胺(D1072)

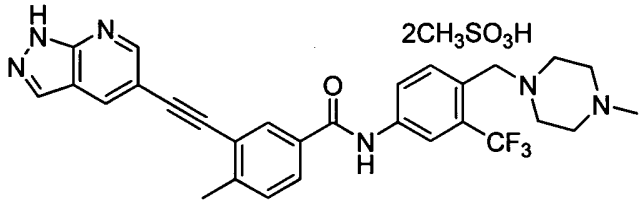


^{1}HNMR (400 MHz, *d*-DMSO), δ ppm 10.62 (s, 1H), 8.73 (d, J=2.0 Hz, 1H), 8.52 (d, J=2.0 Hz, 1H), 8.21-8.23 (m, 3H), 8.07 (d, J=8.4 Hz, 1H), 8.01 (d, J=7.6 Hz, 1H), 7.83 (d, J=7.6 Hz,

1H), 7.72 (d, J=7.6 Hz, 1H), 7.64 (t, J=8.0 Hz, 1H), 3.57 (s, 2H), 2.39 (br, 8H), 2.16 (s, 3H).

MS (ESI), m/z:.519 ($M^+ + H^+$).

实施例 41 3-((1H-吡唑[3,4-b]吡啶-5-取代)乙炔基)-4-甲基-N-(4-((4-甲基哌嗪-1-取代)甲基)-3-(三氟甲基)苯基)苯甲酰胺二甲磺酸盐 (D824 二甲磺酸盐)

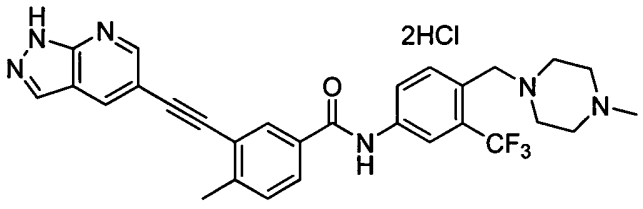


将 3.1g D824 (5.83 mmol) 置于 500 mL 单口瓶中，加入 150 mL 无水乙醇，搅拌下滴加 2.24 g 甲磺酸 (23.31 mmol)，加热至沸，体系变澄清，回流 4h，冷却至室温，有白色固体析出，过滤，滤渣用乙醇洗三次，真空干燥得浅黄色固体 3.86 g (90%)。

1HNMR (400 MHz, d-DMSO), δ ppm 10.66 (s, 1H), 8.73 (d, J=2.0 Hz, 1H), 8.52 (d, J=1.6Hz, 1H), 8.28 (d, J=1.6 Hz, 1H), 8.23 (s, 1H), 8.19 (s, 1H), 8.16 (d, J=7.6 Hz, 1H), 7.92 (dd, J=8.0, 1.6 Hz, 1H), 7.78 (d, J=8.4 Hz, 1H), 7.53 (d, J=8.4 Hz, 1H), 4.00 (s, 2H), 3.19 (br, 6H), 2.85 (s, 3H), 2.77 (br, 2H), 2.58 (s, 3H), 2.41 (s, 6H).

MS (ESI), m/z:.533 , 627

实施例 42 3-((1H-吡唑[3,4-b]吡啶-5-取代)乙炔基)-4-甲基-N-(4-((4-甲基哌嗪-1-取代)甲基)-3-(三氟甲基)苯基)苯甲酰胺二盐酸盐 (D824 二盐酸盐)

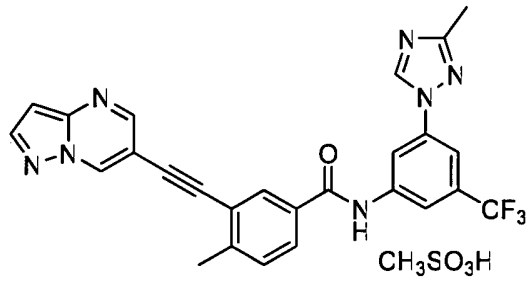


将 3 g D824 (5.64 mmol) 置于 250 mL 三颈瓶中，加入 100 mL 无水乙醇，搅拌下通入现制的干燥的氯化氢气体，体系先变澄清，16h 后有黄色固体析出，过滤，滤渣用乙醇洗三次，真空干燥得浅黄色固体 2.63 g (82 %)。

1HNMR (400 MHz, d-DMSO), δ ppm 11.36 (br, 1H), 10.74 (s, 1H), 8.74 (d, J=2.0 Hz, 1H), 8.53 (d, J=2.0 Hz, 1H), 8.33 (d, J=1.6 Hz, 1H), 8.18-8.23 (m, 3H), 8.04 (br, 1H), 7.96 (dd, J=8.0, 1.6 Hz, 1H), 7.54 (d, J=8.4 Hz, 1H), 4.15 (br, 2H), 3.55 (m, 6H), 3.08 (br, 2H), 2.80 (s, 3H), 2.59 (s, 3H).

MS (ESI), m/z:.533

实施例 43 4-甲基-N-(3-(3-甲基-1H-1,2,4-三氮唑-1-取代)-5-(三氟甲基)苯基)-3-(吡唑[1,5-a]嘧啶-6-取代乙炔基)苯甲酰胺甲磺酸盐 (D818 甲磺酸盐)

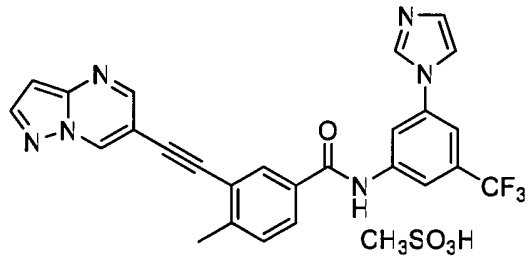


合成方法如实施例 1。

1HNMR (400 MHz, d-DMSO), δ ppm 10.80 (s, 1H), 9.57 (s, 1H), 9.34 (s, 1H), 8.72 (s, 1H), 8.64 (s, 1H), 8.34 (s, 1H), 8.25 (d, J=7.6 Hz, 1H), 7.98 (s, 1H), 7.55 (d, J=7.6 Hz, 1H), 6.84 (s, 1H), 2.60 (s, 3H), 2.39 (s, 3H), 2.38 (s, 3H).

MS (ESI), m/z: 502

实施例 44 N-(3-(1H-咪唑-1-取代)-5-(三氟甲基)苯基)-4-甲基-3-(吡唑[1,5-a]嘧啶-6-取代乙炔基)苯甲酰胺甲磺酸盐 (D819 甲磺酸盐)



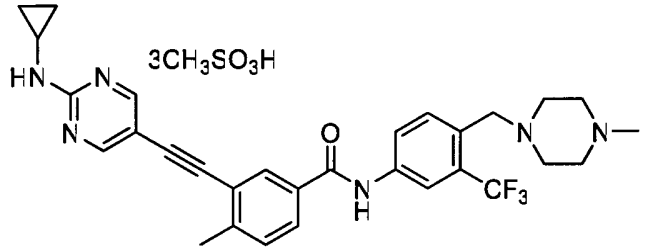
合成方法如实施例 1。

1HNMR (400 MHz, d-DMSO), δ ppm 10.93 (s, 1H), 9.65 (s, 1H), 9.58 (s, 1H), 8.72 (d, J=2.0 Hz, 1H), 8.57 (s, 1H), 8.34 (d, J=2.0 Hz, 1H), 8.30 (s, 1H), 8.24

(s, 1H), 8.00 (s, 1H), 7.98 (s, 1H), 7.89 (s, 1H), 7.58 (d, J=8.0 Hz, 1H), 6.85 (s, 1H), 2.61 (s, 3H), 2.33 (s, 3H).

MS (ESI), m/z: 487

实施例 45 3-((2-(环丙基氨基)嘧啶-5-取代)乙炔基)-4-甲基-N-(4-((4-甲基哌嗪-1-取代)甲基)-3-(三氟甲基)苯基)苯甲酰胺三甲磺酸盐（D825 三甲磺酸盐）

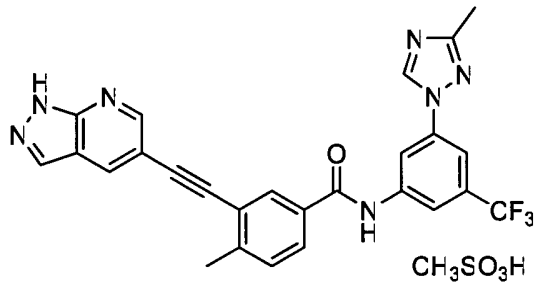


合成方法如实施例 1。

1HNMR (400 MHz, D2O), δ ppm 8.23 (s, 1H), 7.89 (s, 1H), 7.71 (d, J=8.8 Hz, 1H), 7.64 (s, 1H), 7.57 (d, J=8.8 Hz, 1H), 7.52 (d, J=8.0 Hz, 1H), 7.14 (s, 1H), 4.32 (s, 2H), 3.54 (br, 8H), 2.92 (s, 3H), 2.70 (s, 9H), 2.45 (br, 1H), 2.24 (s, 3H), 1.08 (t, J=6.8 Hz, 1H), 0.78 (d, J=6.8 Hz, 2H), 0.49 (s, 2H).

MS (ESI), m/z: 549, 644

实施例 46 3-((1H-吡唑[3,4-b]吡啶-5-取代)乙炔基)-4-甲基-N-(3-(3-甲基-1H-1,2,4-三氮唑-1-取代)-5-(三氟甲基)苯基)苯甲酰胺甲磺酸盐（D835 甲磺酸盐）

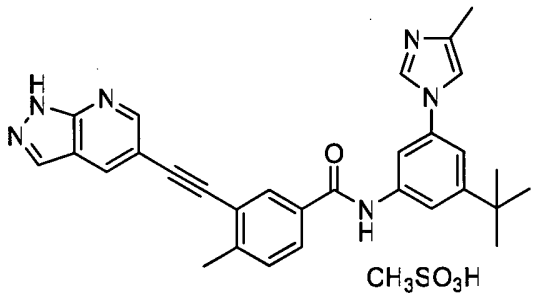


合成方法如实施例 1。

1HNMR (400 MHz, d-DMSO), δ ppm 10.78 (s, 1H), 9.37 (s, 1H), 8.73 (d, J=2.0 Hz, 1H), 8.64 (s, 1H), 8.52 (d, J=1.6 Hz, 1H), 8.22-8.27 (m, 3H), 7.97 (s, 1H), 7.94 (s, 1H), 7.52 (d, J=8.0 Hz, 1H), 2.55 (s, 3H), 2.43 (s, 3H), 2.39 (s, 3H).

MS (ESI), m/z: 502

实施例 47 3-((1H-吡唑[3,4-b]吡啶-5-取代)乙炔基)-N-(3-叔丁基-5-(4-甲基-1H-咪唑-1-取代)苯基)-4-甲基苯甲酰胺甲磺酸盐（D968 甲磺酸盐）

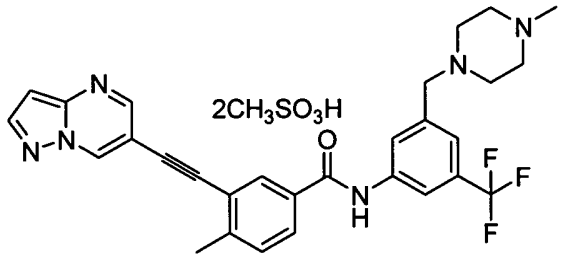


合成方法如实施例 1。

1HNMR (400 MHz, d-DMSO), δ ppm 13.96 (s, 1H), 10.60 (s, 1H), 9.58 (d, J=1.2 Hz, 1H), 8.74 (d, J=2.0 Hz, 1H), 8.54 (d, J=2.0 Hz, 1H), 8.22-8.24 (m, 3H), 8.01 (s, 1H), 7.94 (d, J=8.0 Hz, 1H), 7.85 (s, 1H), 7.55 (d, J=8.0 Hz, 1H), 7.49 (s, 1H), 2.60 (s, 3H), 2.36 (s, 3H), 2.31 (s, 3H), 1.36 (s, 9H).

MS (ESI), m/z: 489

实施例 48 4-甲基-N-(3-((4-甲基哌嗪-1-取代)甲基)-5-(三氟甲基)苯基)-3-(2-(吡唑[1,5-a]吡啶-6-取代) 乙炔基) 苯甲酰胺二甲磺酸盐（D856 二甲磺酸盐）



1HNMR (400 MHz, d-DMSO), δ ppm 10.63 (S,1H) 9.58 (s,1H), 8.72 (d,J=2.0Hz,1H),8.34 (d,J=2.0Hz,1H), 8.25 (d, J=2.0 Hz, 1H), 8.20 (d, J=2.0 Hz, 1H), 8.14 (d, J=8.8 Hz, 1H),7.97 (d, J=8.0 Hz, 1H), 7.75 (d, J=8.4 Hz, 1H), 7.55 (d, J=8.0 Hz, 1H), 6.85 (d, J=1.6 Hz, 1H), 3.82 (s, 2H), 3.41-3.47 (m, 4H), 3.07-3.23 (m, 4H), 2.83 (s, 3H), 2.60 (s, 3H),2.36 (s,6H).

MS (ESI), m/z: 533 , 627

实施例 49

用不同浓度的杂环炔苯类化合物（1×10^{-10}～1×10^{-5} M)分别处理 K562 (慢性白血病),

MOLT-4(急性白血病),U937(慢性白血病)，MEG-01(慢性白血病)，L78（肺癌）, Ba/F3(携带 T315I Bcr/Abl 突变,对 STI571 耐受)等六种细胞，72 小时后 MTT 或者 CCK8，再孵育 4 小时，然后用酶标仪测定其在 570nm(CCK8, 450,650nm)的吸光值。结果发现，杂环炔苯类化合物处理可明显降低各种细胞对 MTT 的吸收，说明杂环炔苯类化合物可显著抑制上述细胞的增殖，尤其是抑制 K562(慢性白血病)，Ba/F3(携带 T315I Bcr/Abl 突变,对 STI571 耐受)细胞的增值，抑制率与药物浓度成正相关。根据杂环炔苯类化合物对这六种细胞的生长抑制作用，我们计算出其半数抑制浓度（IC50）值如表 1 和 2 所描述。(所用化合物分别为实施例 1－40 所制备的化合物，在表 1 中用 Drug No.标号表示)。

表 1. 部分化合物对不同肿瘤细胞生长抑制的 IC_{50}（未特别标注的数据，单位为 μM）

Drug No.	K562 (慢性白血病)	MOLT -4(急性白血病)	U937 (慢性白血病)	MEG-01 (慢性白血病)	K562R	BAF3-T315I	L78 （肺癌）
D729	**2.09 nM**	**5.75**		**6.58**	0. 07269	0. 04968	
D747	**2.6 nM**	**>10**	**11.54**	**7.537**	0. 096	0. 09973	**10.57**
D752	0.003477	12.67	8.988	22.6	*0. 84*	1. 027	>10
D755	7.595nM	>10	>10	>10	0. 22	0. 06097	11.76
D767	0.2081nM	>100nM	>100nM	>100nM	0. 089	0. 00424	11.77nM
D768	2.597nM	>100nM	>100nM	>100nM	0. 16	5. 993	>100nM
D770	99.51nM	>100nM	>100nM	3684nM	0. 16	5. 993	>100nM
D771	128.6nM				1735	>10	>100nM
D797	>100nM	>10nM	>100nM	>100nM	3. 366	12. 95	
D798	33.99nM	>10nM	>100nM	>100nM	1. 222	1. 864	
D799	36.2nM	>100nM	>100nM	>100nM	0. 6118	>10	
D800	1.097nM	>100nM	>100nM	>100nM	0. 08966	0. 09979	
D801	141.3nM	>100nM	>100nM	563806nM	0. 9063	10. 45	
D803	1.517nM	132nM	147.1nM	>100nM	0. 06333	0. 1245/ 0. 08580	
D806	>100nM	>100nM	147.3nM	131.3 nM		1. 894	
D807	128.5 nM	>100nM	126.3nM	>100nM	14. 14	13. 45	

D809	>100nM	>100nM	>100nM	114.9 nM	0. 1769	~ 0. 1022/ 0. 07115	
D818	1.383 nM	>100 nM	>100nM	210.1 nM	0. 1423	0. 3936	
D819	1.504 nM	145.8 nM	2208 nM	122 nM	0. 1456	3. 12	
D820	1.374 nM	134.3 nM	>100nM	>100 nM	0. 03518	0. 2763	
D821	0.7241nM	>100nM			0. 058	0. 01948	
D822	**4.343nM**	**>100nM**			0. 58	1. 104	
D823	>100nM	>100nM			9. 63	>10	
D824	0.4941nM	>100nM			0. 014	0. 001645	
D825	1.882nM	92.89nM			0. 05	0. 0157	
D827	2.683nM	1851nM			0. 059	0. 0298	
D828	30.93nM	>100nM			3. 07	2. 477	
D831	0.4661 nM		7134 nM		0. 054	0. 0368	
D832	7.273 nM		>100nM		0. 2	0. 02184	
D834	8.703 nM		>100nM		0. 19	0. 2151	
D835	0.4018 **nM**		>100nM		0. 026	0. 008578	
D855	0. 03455	>10	7. 167		1. 02	1. 84	
D856	0. 00224	0. 4994	2. 001		0. 067	0. 0108	
D931	>10	7. 429	4. 596		0. 51	2. 754	
D940	0. 0657	0. 9548	0. 7154		0. 032	0. 2447	
D941	0. 002341	0. 3397	0. 6959		0. 41	0. 1022	
D942	0. 003542	0. 6737	1. 298		0. 04404	0. 1016	
D943	0. 008305	1. 626	2. 121		0. 3197	0. 6183	
D963	0. 0009975		>1		0. 07505	0. 2426	
D964	0. 0009378		>1		0. 032	0. 02423	
D965	0. 0005879		0. 8171		0. 0057	0. 006867	
D966	0. 0003239		0. 01854			0. 01381	
D967	0. 000314		5. 832		0. 2066	0. 7981	
D968	0. 0007014		>1		0. 032	0. 006362	

附注：

K562R，imatinb 诱导获得耐药株 ，本申请发明人诱导获得， 可以保证从申请日起 20 年内发放该耐药株。

BAF3-T315I：稳定表达 BCR/ABL（T315I 突变型）的 BAF3 细胞株，本申请发明人构建筛选获得，可以保证从申请日起 20 年内发放该耐药株。

表 2. 部分化合物对白血病 Ba/F3 细胞 (携带 T315I Bcr/Abl 突变,对 STI571 耐受)生长抑制的 IC_{50}（μM）。

Drug No.	Ba/F3 (T315I)
D729	<0.1

实施例 50

5*106 个 K562 细胞接种到 BALB/C-nu 裸鼠的右前腋下，待瘤体增长至 100～200mm^3 大小时分组口服给药，针对不同化合物设置不同剂量组，2mg/kg，5mg/kg，25mg/kg 和 50mg/kg，po，qd， 8~10 只/组，每 2 天称取一次动物体重，量取瘤体积（分组当天记录初始瘤体积和体重）。瘤体积计算公式为：V=π/6* a*b*b。结果发现 D747 盐酸盐和 D822 甲磺酸盐，D767 甲磺酸盐，D800 甲磺酸盐，D824 二甲磺酸盐均不会导致动物体重降低，有效剂量水平表现处动物体重增加，均表现出良好的体内抑制肿瘤生长活性。D747 盐酸盐，D822 甲磺酸盐，D767 甲磺酸盐，D800 甲磺酸盐，D824 二甲磺酸盐分别在 25mg/kg，25mg/kg，25mg/kg，25mg/kg，5mg/kg 的剂量水平均能完全抑制肿瘤的生长，把移植瘤瘤细胞完全杀死，达到移植瘤的完全治愈；D747 盐酸盐和 D822 甲磺酸盐的体内抗肿瘤活性均较 Imatinib 为好。结果见说明书附图 1，2，3，4，5，6，7，8。

实施例 51

2*106 个 BA/F3-BCR/ABL-T315I 细胞接种到 SCID 鼠的右前腋下，待瘤体增长至 300～500mm^3 大小时分组口服给药，设置不同剂量组和给药间隔，50mg/kg，20mg/kg 和 10mg/kg，po，q2d 或者 qd， 8～10 只/组，每 2 天称取一次动物体重，量取瘤体积（分组当天记录初始瘤体积和体重）。瘤体积计算公式为：V= π /6* a*b*b。结果发现 D824 二甲磺酸盐在 20mg/kg，po，qd 或者 q2d 水平均能增加动物体重，基本可以完全抑制移植肿瘤的生长。D856 二甲磺酸盐，D968 甲磺酸盐在 20mg/kg，po，qd 剂量水平均能控制肿瘤的生长。结果见附图 9，10，11，12，13，14，15，16。

实施例 52

大鼠药代动力学和生物利用度试验。SD 大鼠，雌雄各 2 只，单次给药，口服（25mg/kg）和静脉（2.5~10mg/kg）给药，给药后在合适的时间点采集动物血样，肝素抗凝，3000rpm*10min，取上清，-20℃保存备 HPLC-MS 分析。血样采用乙腈沉淀蛋白，12000rpm*10min，上清用于 HPCL-MS 分析。数据采用 DAS2.0 进行参数拟合，分别获得房室模型和非房室模型参数。根据 AUC 数据计算化合物的口服生物利用度。结果见下表，其中 D747,D752,D755,D767,D800, D822, D824，D831，D856，D825 等所对应的药学上可接受的盐均具有合适的药动参数（T1/2 和 BA 等），能够满足体内药效试验需要。

表 3. 部分化合物药代动力学研究结果。

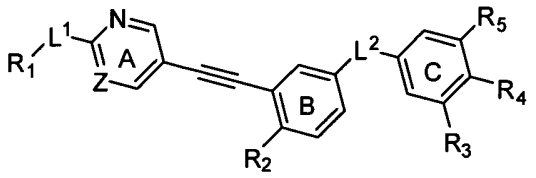
	Adminis-tration route	Animal Number	Dose level mg/kg	AUC(0-∞) ug/L*h	Cmax ug/l	T1/2 (Hr)	Tmax (Hr)	BA(%) 口服生物利用度
D747 盐酸盐	PO	♀2 ♂2	25	251684.381	6205	48.701	4.5	35.3
	IV	♀2 ♂2	10	285187.275	49750	71.753	0.033	
D822 甲磺酸盐	PO	♀2 ♂2	25	10736.39	814	8.04	3	31.2
	IV	♀2 ♂2	10	13754.54	23056.25	3.15	0.033	
D752 甲磺酸盐	PO	♀2 ♂2	20	70411.149	1900	7.548	20	11.54
	IV	♀2 ♂2	10	304881.256	19606.25	43.854	0.033	
D800 盐酸盐	PO	♀2 ♂2	5	35809.5	10975	7.5	0.033	27.1
	IV	♀2 ♂2	25	48574.3	3090	7.8	2	
D767 盐酸盐	PO	♀2 ♂2	25	62208	3615	7.179	7.75	19
	IV	♀2 ♂2	5	65534	15319	5.596	0.033	
D755 盐酸盐	PO	♀2 ♂2	25	23700	1255	8.298	6.25	63.3
	IV	♀2 ♂2	2.5	3745	510	26.181	0.033	
D648 盐酸盐	PO	♀4	25	1471.701	509.25	1.117	1	10.9
	IV	♀4	5	2694.862	2602.5	3.01	0.183	
D856 二甲磺酸盐	PO	♂4	25	31829.108	899.5	22.199	6.5	78
	IV	♂4	5	8165.792	934.375	19.97	0.033	
D753 甲磺酸盐	PO	♀4	25	1080.493	147.05	18.275	4	1.6
	IV	♀4	5	13128.922	7418.75	58.193	0.083	

D680 甲磺酸盐	PO	♀2 ♂2	50	4847.264	862	2.728	2	8.7
	IV	♀2 ♂2	10	11175.59	14168.75	3.699	0.033	
D824 盐酸盐	PO	♂4	25	7108.253	390.5	10.55	6	48.7
	IV	♂4	5	2922.411	1375.625	5.557	0.067	
D767 甲磺酸盐	PO	♂4	25	27850.615	2322.5	5.949	2.75	9.4
	IV	♂4	5	59222.45	14093.75	4.471	0.033	
D835 盐酸盐	PO	♂4	25	3467.961	233	8.813	4	8.1
	IV	♂4	5	8536.548	975.625	16.863	0.033	
D831 甲磺酸盐	PO	♂4	25	73862.101	9515	4.665	2.25	13.8
	IV	♂3	5	107229.516	64250	5.237	0.033	
D824 二甲磺酸盐	PO	♂4	25	12628.23	774.75	8.72	4.25	58.7
	IV	♂4	5	4304.444	2235.625	6.098	0.033	
D825 甲磺酸盐	PO	♂4	25	34561.045	1700	11.492	4.75	58.5
	IV	♂4	5	11819.424	2331.25	11.693	0.033	

以上是针对本发明的可行实施例的具体说明，但该实施例并非用以限制本发明的专利范围，凡未脱离本发明技艺精神所为的等效实施或变更，均应包含于本发明的专利范围中。

权利要求书

1. 具有式（Ⅰ）结构特征的杂环炔苯类化合物或者其药学上可接受的盐或立体异构体或其前药分子：



（Ⅰ）

Z 任选为 CH 或 N；L^1 任选自 NH，-N=，CH；L^2 任选为-CONH-或-NHCO-；

R_1 任选自：

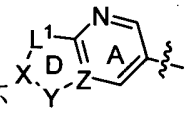
1）H；

2）C_1~C_6 烷基；

3）C_3~C_6 环烷基；

4）被 1 或 2 个羟基取代的 C_1~C_5 烷基；

5）苯基；

6）能与 A 环 Z 位形成含 1~3 个 N 原子的含 L^1 的并五元杂环  的基团，其中， X，Y，Z，任选为 N，CH，D 环为含有 1～3 个氮原子的杂环；

R_2 任选自：

1）H；

2）卤素；

3) C_1~C_5 烷基；

4) C_3~C_6 环烷基；

5) C_1~C_5 含氟烷基；

R_3 任选自：

1) H；

2) 卤素；

3) C_1~C_4 烷基；

4) C_3~C_6 环烷基；

5) C_1~C_4 含氟烷基；

R_5 为 H，R_4 任选自：

1). H;

2). $(CH_2)nNR_6R_7$;

3). $(CH_2)n$ –Het^1;

或 R_4 为 H，R_5 任选自：

1) H;

2) Het^2;

其中，n 为 0 或 1，Het^1 为含有 1～3 个 N 的非芳香杂环， Het^2 为含杂原子 N，O 和/或 S 的五元芳香杂环，所述非芳香及芳香杂环任一 C 原子或 N 原子在能够被取代的位置可以被烷基，环烷基，或 NR_6R_7 取代；

R_6，R_7 任选自：

1） H，

2）C1~C3 烷基；

3） C1~C3 含氟烷基；

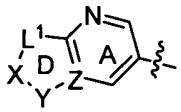
4） C3~C6 环烷基；

或 R_6 和 R_7 通过 C，O， N， S 原子形成五元，六元，七元或八元环状结构。

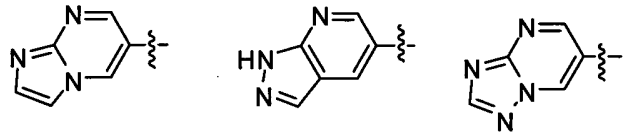
2．根据权利要求 1 所述的杂环炔苯类化合物或者其药学上可接受的盐或立体异构体，其特征是，所述 Z 为 N，L^1 为 NH，R_1 选自：

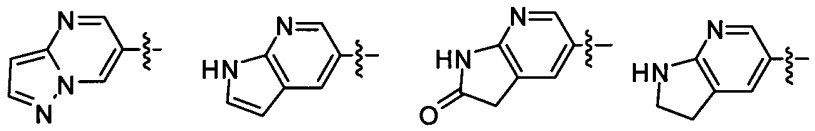
1） 甲基，乙基，异丙基，叔丁基;

2） 环丙基，环丁基，环戊基，环己基。

3．根据权利要求 1 所述的杂环炔苯类化合物或者其药学上可接受的盐或立体异构体，其特征是， 所述 R_1 与 A 形成的并五元杂环 

，为以下结构之一：





。

4．根据权利要求 1 所述的杂环炔苯类化合物或者其药学上可接受的盐或立体异构体，其特征是， 所述 R_2 任选自以下结构：

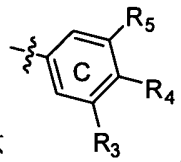
1） H;

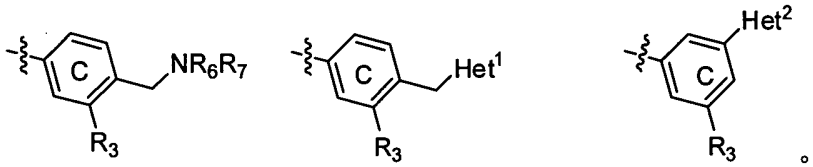
2） 甲基，乙基，异丙基，叔丁基;

3） 环丙基;

4） F, Cl, Br;

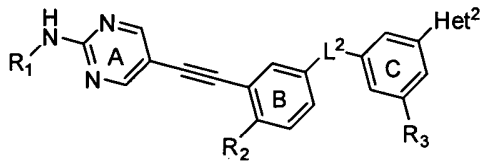
5） 三氟甲基。

5. 根据权利要求 1－4 任一项所述的杂环炔苯类化合物或者其药学上可接受的盐或立体异构体，其特征是，所述 C 环  为以下结构之一：

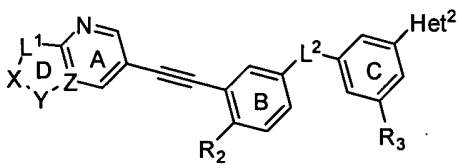


R_3、R_6、R_7、Het^1 的定义与权利要求 1 相同， Het^2 选自取代咪唑类化合物、取代吡唑类化合物、取代恶唑类化合物、取代三氮唑类化合物、取代四氢噁唑类化合物、或取代噻唑类化合物。

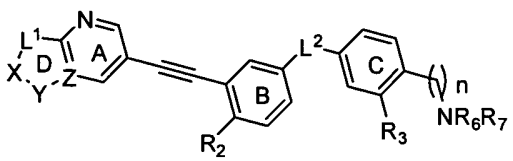
6. 根据权利要求 1 所述的杂环炔苯类化合物或者其药学上可接受的盐或立体异构体，其特征是，所述具有式 I 结构的化合物为以下之一：



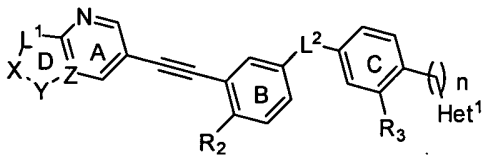
(II)



(III)

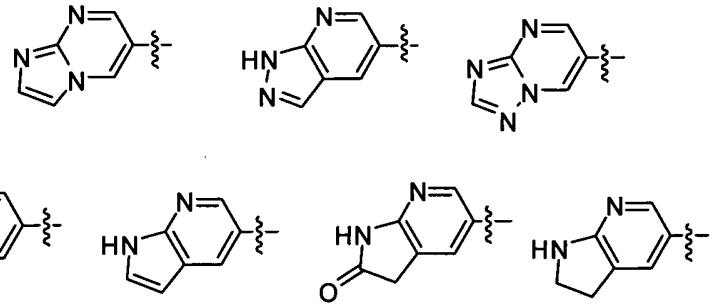


(IV)



(V)

其中，X，Y，Z，任选为 N，CH，D 环为含有 1～3 个氮原子的杂环， D 与 A 环所并环为以下结构之一：



R_1，R_2，R_3，R_6，R_7，L^1，L^2，Het^1，Het^2 的定义与权利要求 1 相同。

7．根据权利要求 6 所述的杂环炔苯类化合物或者其药学上可接受的盐或立体异构体，其特征是，所述杂环炔苯类化合物选自以下化合物：

3-((2-(环丙基胺基)嘧啶-5-取代)乙炔)-4-甲基-N-(3-(4-甲基-1H-咪唑-1-取代)-5-(三氟甲基)苯基)苯甲酰胺、

N-(3-(1H-咪唑-1-取代)-5-(三氟甲基)苯基)-3-((2-(环丙基胺基)嘧啶-5-取代)乙炔基)-4-甲基苯甲酰胺、

4-甲基-N-(3-(4-甲基-1H-咪唑-1-取代)-5-(三氟甲基)苯基)-3-((2-(甲基胺基)嘧啶-5-取代)乙炔基)苯甲酰胺、

3-((2-(乙基胺基)嘧啶-5-取代)乙炔基)-4-甲基-N-(3-(4-甲基-1H-咪唑-1-取代)-5-(三氟甲基)苯基)苯甲酰胺、

4-甲基-N-(3-(4-甲基-1H-咪唑-1-取代)-5-(三氟甲基)苯基)-3-((2-(哌啶-1-取代)嘧啶-5-取代)乙炔基)苯甲酰胺、

3-((6-氨基吡啶-3-取代)乙炔基)-4-甲基-N-(3-(4-甲基-1H-咪唑-1-取代)-5-(三氟甲基)苯基)苯甲酰胺、

3-((2-(环丙基氨基)嘧啶-5-取代)乙炔基)-4-甲基-N-(4-((4-甲基哌嗪-1-取代)甲基)-3-(三氟甲基)苯基)苯甲酰胺、

3-((3H-咪唑[4,5-b]吡啶-6-取代)乙炔基)-4-甲基-N-(3-(4-甲基-1H-咪唑-1-取代)-5-(三氟甲基)苯基)苯甲酰胺、

4-甲基-N-(4-((4-甲基哌嗪-1-取代)甲基)-3-(三氟甲基)苯基)-3-(吡唑[1,5-a]嘧啶-6-取代乙炔基)苯甲酰胺、

3-((2-(环己基氨基)嘧啶-5-取代)乙炔基)-4-甲基-N-(3-(4-甲基-1H-咪唑-1-取代)-5-(三氟甲基)苯基)苯甲酰胺、

4-甲基-N-(3-(4-甲基-1H-咪唑-1-取代)-5-(三氟甲基)苯基)-3-((2-(苯氨基)嘧啶-5-取代)乙炔基)苯甲酰胺、

3-((1H-吡咯[2,3-b]吡啶 5-取代)乙炔基)-4-甲基-N-(3-(4-甲基-1H-咪唑-1-取代)-5-(三氟甲基)苯基)苯甲酰胺、

3-((2-(2-羟基乙胺)嘧啶-5-取代)乙炔基)-4-甲基-N-(3-(4-甲基-1H-咪唑-1-取代)-5-(三氟甲基)苯基)苯甲酰胺、

N-(3-(1H-咪唑-1-取代)-5-(三氟甲基)苯基)-4-甲基-3-(吡唑[1,5-a]嘧啶-6-取代乙炔基)苯甲酰胺、

4-甲基-N-(3-(3-甲基-1H-1,2,4-三氮唑-1-取代)-5-(三氟甲基)苯基)-3-(吡唑[1,5-a]嘧啶-6-取代乙炔基)苯甲酰胺、

3-(咪唑[1,2-a]嘧啶-6-取代乙炔)-4-甲基-N-(3-(4-甲基-1H-咪唑-1-取代)-5-(三氟甲基)苯基)苯甲酰胺、

3-((1H-吡唑[3,4-b]吡啶-5-取代)乙炔基)-4-甲基-N-(3-(4-甲基-1H-咪唑-1-取代)-5-(三氟甲基)苯基)苯甲酰胺、

3-((1H-吡唑[3,4-b]吡啶-5-取代)乙炔基)-4-甲基-N-(3-(1H-咪唑-1-取代)-5-(三氟甲基)苯基)苯甲酰胺、

3-((1H-吡唑[3,4-b]吡啶-5-取代)乙炔基)-4-甲基-N-(3-(3-甲基-1H-1,2,4-三氮唑-1-取代)-5-(三氟甲基)苯基)苯甲酰胺、

3-([1,2,4]三氮唑[1,5-a]嘧啶-6-取代乙炔基)-4-甲基-N-(3-(4-甲基-1H-咪唑-1-取代)-5-(三氟甲基)苯基)苯甲酰胺、

4-甲基-N-(3-(4-甲基-1H-咪唑-1-取代)-5-(三氟甲基)苯基)-3-(吡唑[1,5-a]嘧啶-6-取代乙炔基)苯甲酰胺、

3-((1H-吡唑[3,4-b]吡啶-5-取代)乙炔基)-4-甲基-N-(3-(三氟甲基)苯基)苯甲酰胺、

3-((1H-吡唑[3,4-b]吡啶-5-取代)乙炔基)-4-甲基-N-(4-((4-甲基哌嗪-1-取代)甲基)-3-(三氟甲基)苯基)苯甲酰胺、

(S)-3-((2-(2,3-二羟基丙胺)嘧啶-5-取代)乙炔基)-4-甲基-N-(3-(4-甲基-1H-咪唑-1-取代)-5-(三氟甲基)苯基)苯甲酰胺、

3-((2-(二乙基胺基)嘧啶-5-取代)乙炔基)-4-甲基-N-(3-(4-甲基-1H-咪唑-1-取代)-5-(三氟甲基)苯基)苯甲酰胺、

3-((2-(叔丁基胺基)嘧啶-5-取代)乙炔基)-4-甲基-N-(3-(4-甲基-1H-咪唑-1-取代)-5-(三氟甲基)苯基)苯甲酰胺、

3-((2-(2-异丙基胺基)嘧啶-5-取代)乙炔基)-4-甲基-N-(3-(4-甲基-1H-咪唑-1-取代)-5-(三氟甲

基)苯基)苯甲酰胺、

3-((2-胺基嘧啶-5-取代)乙炔基)-4-甲基-N-(3-(4-甲基-1H-咪唑-1-取代)-5-(三氟甲基)苯基)苯甲酰胺、

4-甲基-N-(4-(吗啡啉亚甲基)-3-(三氟甲基)苯基)-3-(吡唑[1,5-a]嘧啶-6-取代乙炔基)苯甲酰胺

N-(4-((4-(2-羟基乙基)哌嗪-1-取代)甲基)-3-(三氟甲基)苯基)-4-甲基-3-(吡唑[1,5-a]嘧啶-6-取代乙炔)苯甲酰胺、

(S)-N-(4-((3-(甲基氨基)吡咯-1-取代)甲基)-3-(三氟甲基)苯基)-4-甲基-3-(吡唑[1,5-a]嘧啶-6-取代乙炔)苯甲酰胺、

N-(3-叔丁基-5-(4-甲基-1H-咪唑-1-取代)苯基)-4-甲基-3-(吡唑[1,5-a]嘧啶-6-取代乙炔)苯甲酰胺、

3-((1H-吡唑[3,4-b]吡啶-5-取代)乙炔基)-4-甲基-N-(3-(三氟甲基)苯基)苯甲酰胺、

3-((1H-吡唑[3,4-b]吡啶-5-取代)乙炔基)-N-(3-叔丁基-5-(4-甲基-1H-咪唑-1-取代)苯基)-4-甲基苯甲酰胺、

3-((1H-吡唑[3,4-b]吡啶-5-取代)乙炔基)-N-(3-氟-5-(4-甲基-1H-咪唑-1-取代)苯基)-4-甲基苯甲现酰胺、

3-((1H-吡唑[3,4-b]吡啶-5-取代)乙炔基)-N-(3-氯-5-(4-甲基-1H-咪唑-1-取代)苯基)-4-甲基苯甲现酰胺、

(R)-N-(4-((3-(甲基氨基)吡咯-1-取代)甲基)-3-(三氟甲基)苯基)-4-甲基-3-(吡唑[1,5-a]嘧啶-6-取代乙炔)苯甲酰胺、

(S)-3-((1H-吡唑[3,4-b]嘧啶-5-取代)乙炔)-N-(4-((3-(二甲基氨基)吡咯-1-取代)甲基)-3-(三氟甲基)苯基)-4-甲基苯甲酰胺、

(R)-3-((1H-吡唑[3,4-b]嘧啶-5-取代)乙炔)-N-(4-((3-(二甲基氨基)吡咯-1-取代)甲基)-3-(三氟甲基)苯基)-4-甲基苯甲酰胺、

3-((1H-吡唑[3,4-b]吡啶-5-取代)乙炔基)-N-(4-((4-甲基哌嗪-1-取代)甲基)-3-(三氟甲基)苯基)苯甲酰胺、

3-((1H-吡唑[3,4-b]吡啶-5-取代)乙炔基)-4-甲基-N-(4-((4-甲基哌嗪-1-取代)甲基)-3-(三氟甲基)苯基)苯甲酰胺二甲磺酸盐、

3-((1H-吡唑[3,4-b]吡啶-5-取代)乙炔基)-4-甲基-N-(4-((4-甲基哌嗪-1-取代)甲基)-3-(三氟甲基)苯基)苯甲酰胺二盐酸盐、

4-甲基-N-(3-(3-甲基-1H-1,2,4-三氮唑-1-取代)-5-(三氟甲基)苯基)-3-(吡唑[1,5-a]嘧啶-6-取代乙炔基)苯甲酰胺甲磺酸盐、

N-(3-(1H-咪唑-1-取代)-5-(三氟甲基)苯基)-4-甲基-3-(吡唑[1,5-a]嘧啶-6-取代乙炔基)苯甲酰胺甲磺酸盐、

3-((2-(环丙基氨基)嘧啶-5-取代)乙炔基)-4-甲基-N-(4-((4-甲基哌嗪-1-取代)甲基)-3-(三氟甲基)苯基)苯甲酰胺三甲磺酸盐、

3-((1H-吡唑[3,4-b]吡啶-5-取代)乙炔基)-N-(3-叔丁基-5-(4-甲基-1H-咪唑-1-取代)苯基)-4-甲基苯甲酰胺甲磺酸盐、

3-((1H-吡唑[3,4-b]吡啶-5-取代)乙炔基)-4-甲基-N-(3-(3-甲基-1H-1,2,4-三氮唑-1-取代)-5-(三氟甲基)苯基)苯甲酰胺甲磺酸盐、

4-甲基-N-(3-((4-甲基哌嗪-1-取代)甲基)-5-(三氟甲基)苯基)-3-(2-(吡唑[1,5-a]吡啶-6-取代)乙炔基) 苯甲酰胺二甲磺酸盐。

8. 一种治疗肿瘤的药用组合物，其由权利要求 1-7 任一项所述的杂环炔苯类化合物或其药学上可接受的盐或立体异构体或其前药分子与药学上可接受的载体组成。

9. 权利要求 1—7 任一项所述杂环炔苯类化合物及其药学上可接受的盐或立体异构体或其前药分子在制备治疗或预防肿瘤的药物中的应用。

10. 根据权利要求 9 所述的应用，其特征是：所述肿瘤为白血病、胃肠间质瘤、组织细胞性淋巴癌、非小细胞肺癌、小细胞肺癌、肺腺癌、肺鳞癌、胰腺癌、乳腺癌、前列腺癌、肝癌、皮肤癌、上皮细胞癌、鼻咽癌等中的任一种。

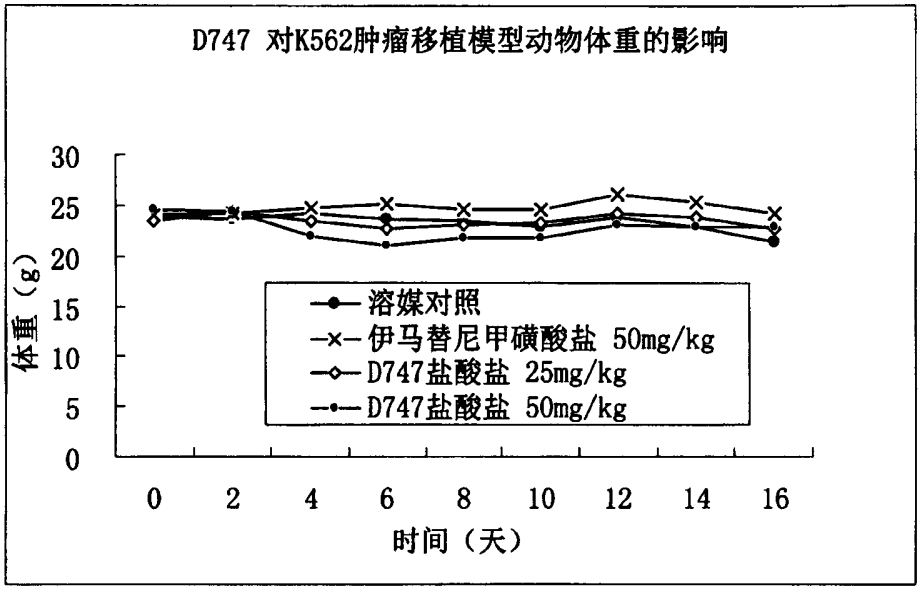

D747 对K562肿瘤移植模型动物体重的影响
体重（g）
30
25
20
15
10
5
0
0
2
4
6
8
10
12
14
16
时间（天）
溶媒对照
伊马替尼甲磺酸盐 50mg/kg
D747盐酸盐 25mg/kg
D747盐酸盐 50mg/kg

图 1

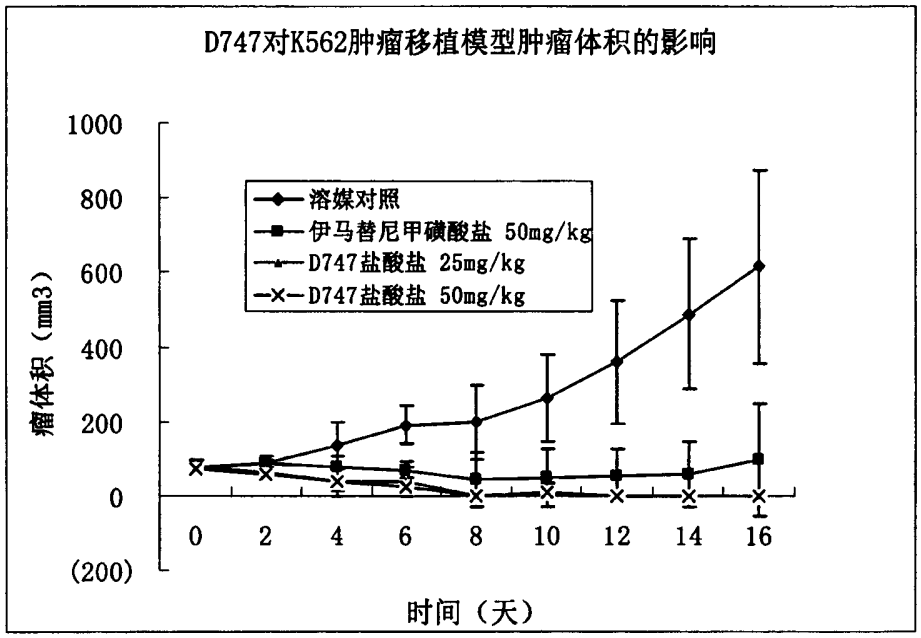

D747对K562肿瘤移植模型肿瘤体积的影响
瘤体积（mm3）
1000
800
600
400
200
0
(200)
0
2
4
6
8
10
12
14
16
时间（天）
溶媒对照
伊马替尼甲磺酸盐 50mg/kg
D747盐酸盐 25mg/kg
D747盐酸盐 50mg/kg

图 2

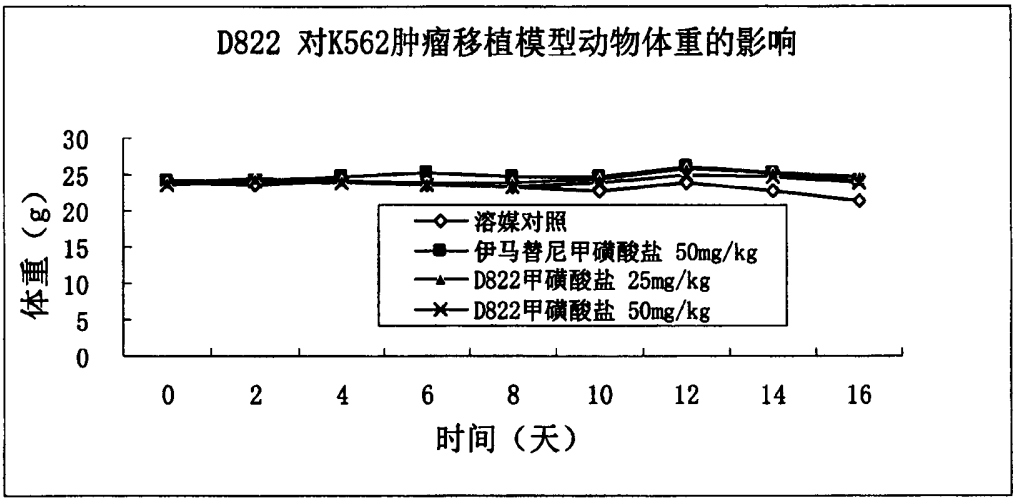

D822 对K562肿瘤移植模型动物体重的影响
体重（g）
30
25
20
15
10
5
0
0
2
4
6
8
10
12
14
16
时间（天）
溶媒对照
伊马替尼甲磺酸盐 50mg/kg
D822甲磺酸盐 25mg/kg
D822甲磺酸盐 50mg/kg

图 3

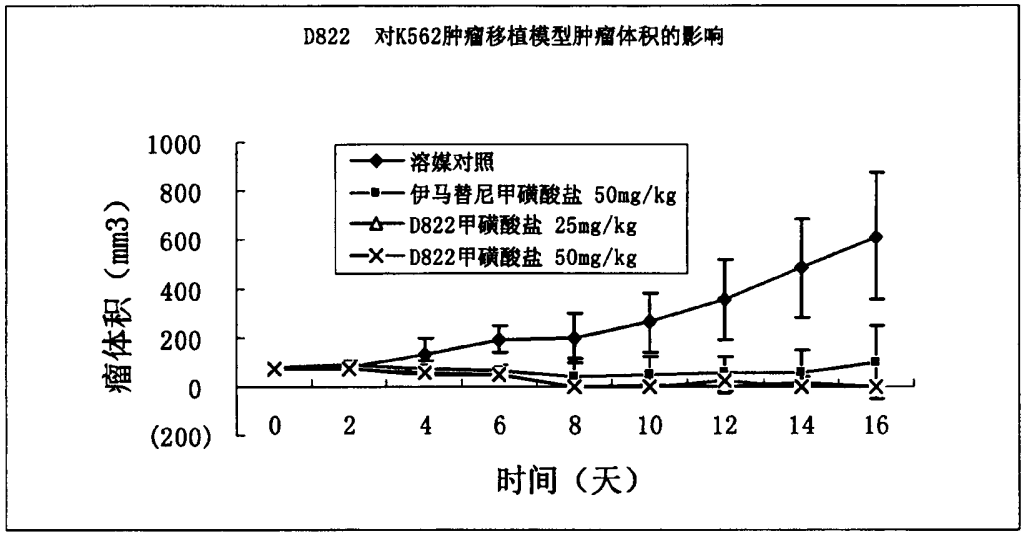

D822 对K562肿瘤移植模型肿瘤体积的影响
瘤体积（mm3）
1000
800
600
400
200
0
(200)
0
2
4
6
8
10
12
14
16
时间（天）
溶媒对照
伊马替尼甲磺酸盐 50mg/kg
D822甲磺酸盐 25mg/kg
D822甲磺酸盐 50mg/kg

图 4

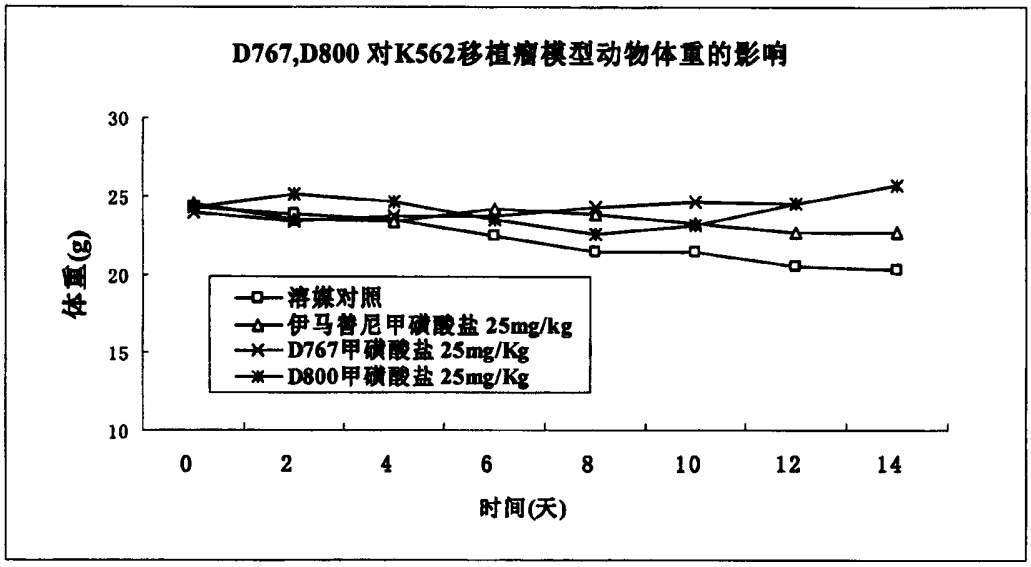

D767,D800 对K562移植瘤模型动物体重的影响
体重(g)
30
25
20
15
10
0
2
4
6
8
10
12
14
时间(天)
溶媒对照
伊马替尼甲磺酸盐 25mg/kg
D767甲磺酸盐 25mg/Kg
D800甲磺酸盐 25mg/Kg

图 5

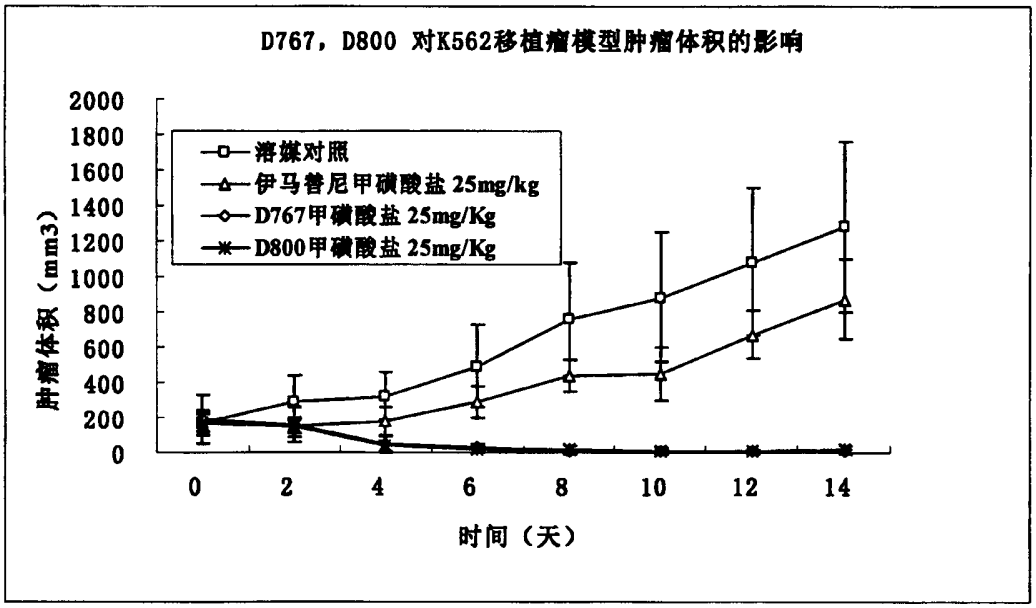

D767，D800 对K562移植瘤模型肿瘤体积的影响
肿瘤体积（mm3）
2000
1800
1600
1400
1200
1000
800
600
400
200
0
0
2
4
6
8
10
12
14
时间（天）
溶媒对照
伊马替尼甲磺酸盐 25mg/kg
D767甲磺酸盐 25mg/Kg
D800甲磺酸盐 25mg/Kg

图 6

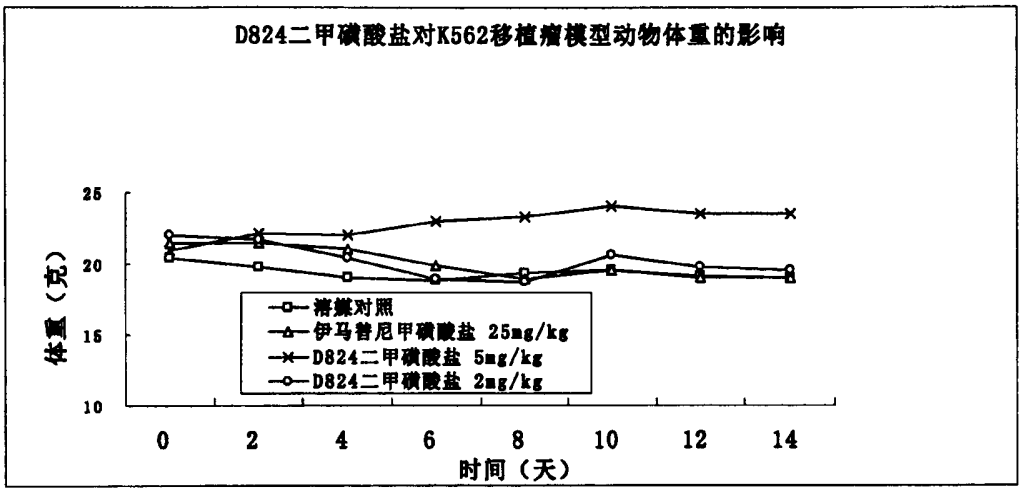

D824二甲磺酸盐对K562移植瘤模型动物体重的影响
体重（克）
25
20
15
10
0
2
4
6
8
10
12
14
时间（天）
溶媒对照
伊马替尼甲磺酸盐 25mg/kg
D824二甲磺酸盐 5mg/kg
D824二甲磺酸盐 2mg/kg

图 7

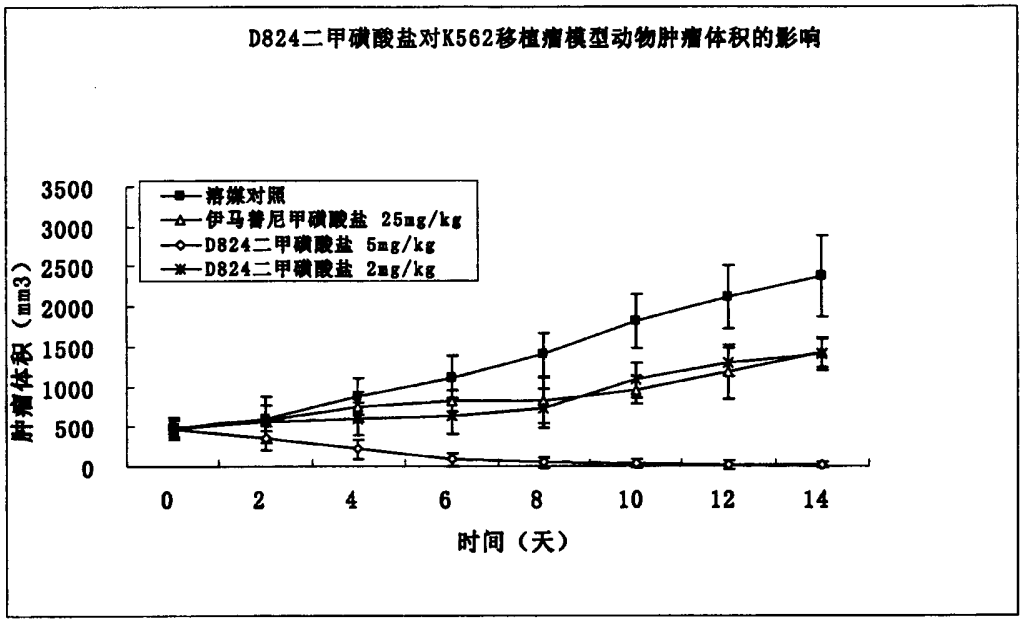

D824二甲磺酸盐对K562移植瘤模型动物肿瘤体积的影响
肿瘤体积（mm3）
3500
3000
2500
2000
1500
1000
500
0
0
2
4
6
8
10
12
14
时间（天）
溶媒对照
伊马替尼甲磺酸盐 25mg/kg
D824二甲磺酸盐 5mg/kg
D824二甲磺酸盐 2mg/kg

图 8

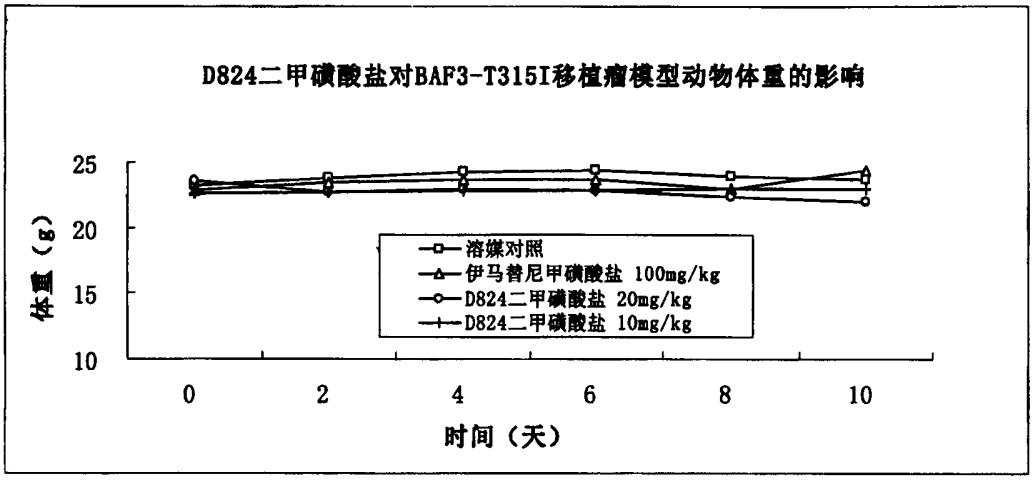

D824二甲磺酸盐对BAF3-T315I移植瘤模型动物体重的影响
体重（g）
25
20
15
10
0
2
4
6
8
10
时间（天）
溶媒对照
伊马替尼甲磺酸盐 100mg/kg
D824二甲磺酸盐 20mg/kg
D824二甲磺酸盐 10mg/kg

图 9

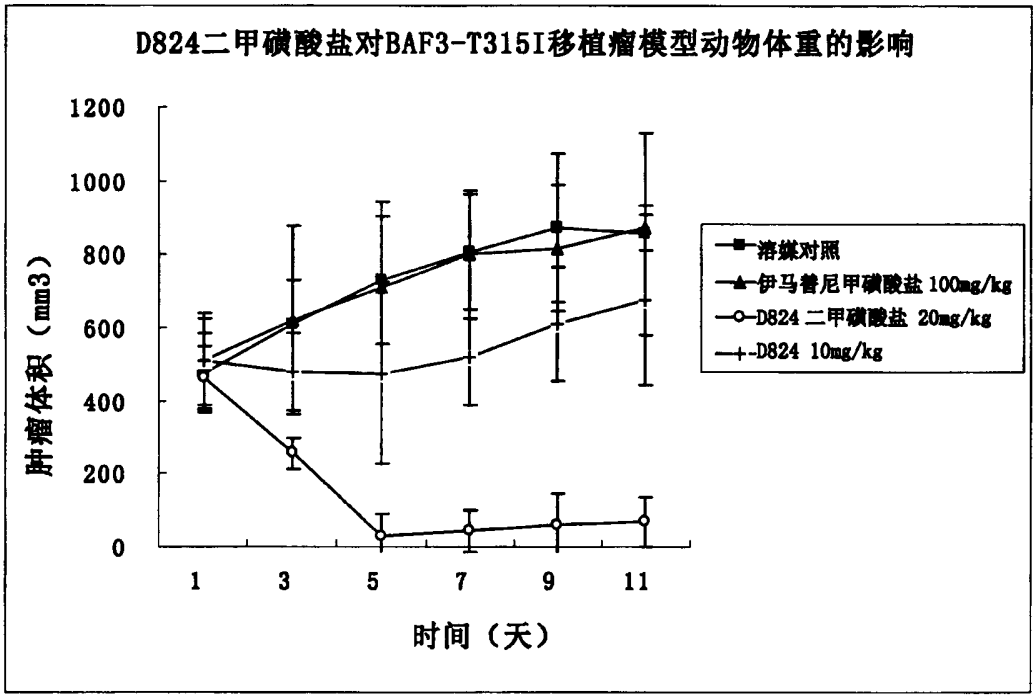

D824二甲磺酸盐对BAF3-T315I移植瘤模型动物体重的影响
肿瘤体积（mm3）
1200
1000
800
600
400
200
0
1
3
5
7
9
11
时间（天）
溶媒对照
伊马替尼甲磺酸盐 100mg/kg
D824 二甲磺酸盐 20mg/kg
D824 10mg/kg

图 10

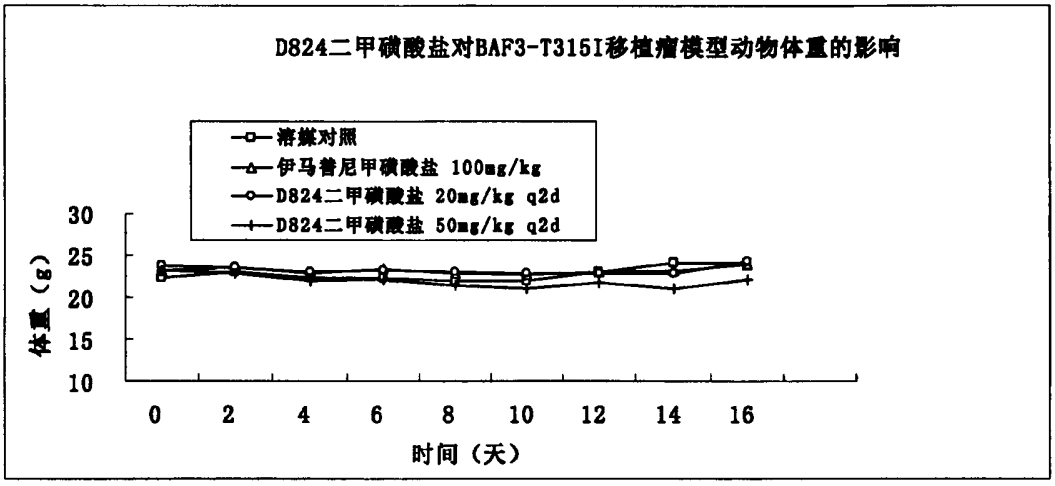

D824二甲磺酸盐对BAF3-T315I移植瘤模型动物体重的影响
溶媒对照
伊马替尼甲磺酸盐 100mg/kg
D824二甲磺酸盐 20mg/kg q2d
D824二甲磺酸盐 50mg/kg q2d
体重（g）
30
25
20
15
10
0
2
4
6
8
10
12
14
16
时间（天）

图 11

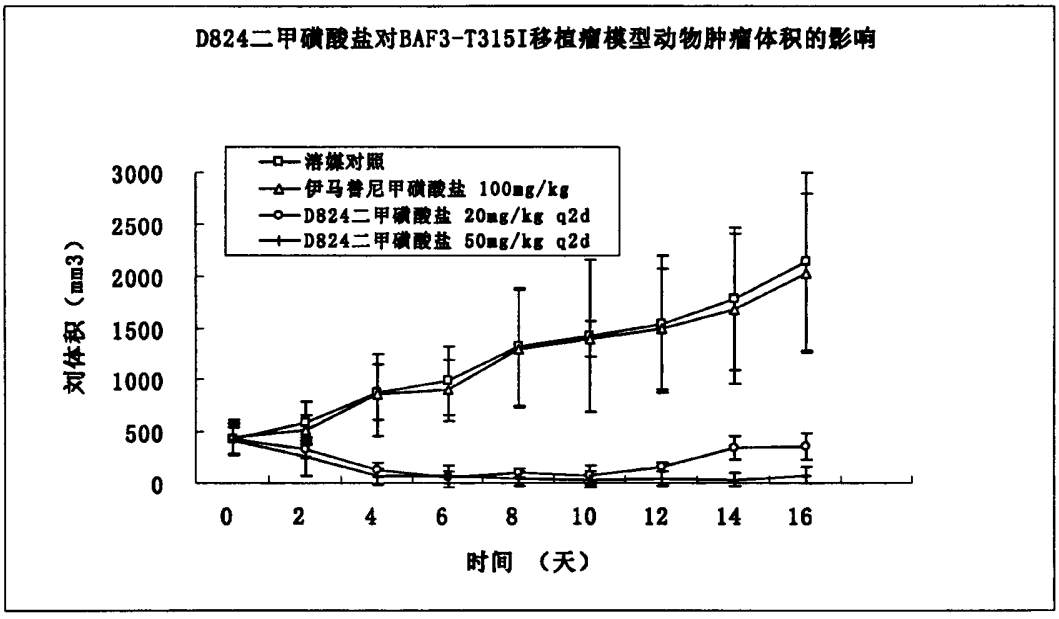

D824二甲磺酸盐对BAF3-T315I移植瘤模型动物肿瘤体积的影响
溶媒对照
伊马替尼甲磺酸盐 100mg/kg
D824二甲磺酸盐 20mg/kg q2d
D824二甲磺酸盐 50mg/kg q2d
瘤体积（mm3）
3000
2500
2000
1500
1000
500
0
0
2
4
6
8
10
12
14
16
时间 （天）

图 12

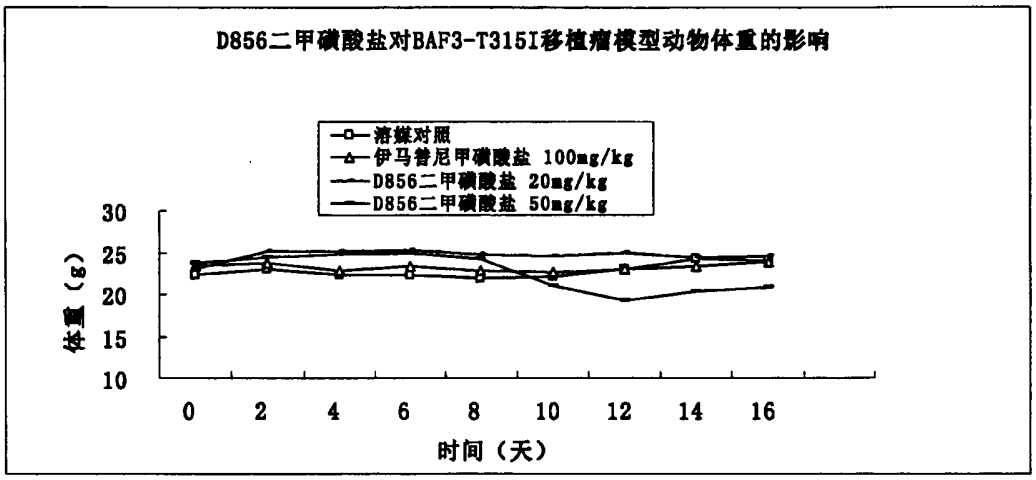

D856二甲磺酸盐对BAF3-T315I移植瘤模型动物体重的影响
溶媒对照
伊马昔尼甲磺酸盐 100mg/kg
D856二甲磺酸盐 20mg/kg
D856二甲磺酸盐 50mg/kg
体重（g）
30
25
20
15
10
0
2
4
6
8
10
12
14
16
时间（天）

图 13

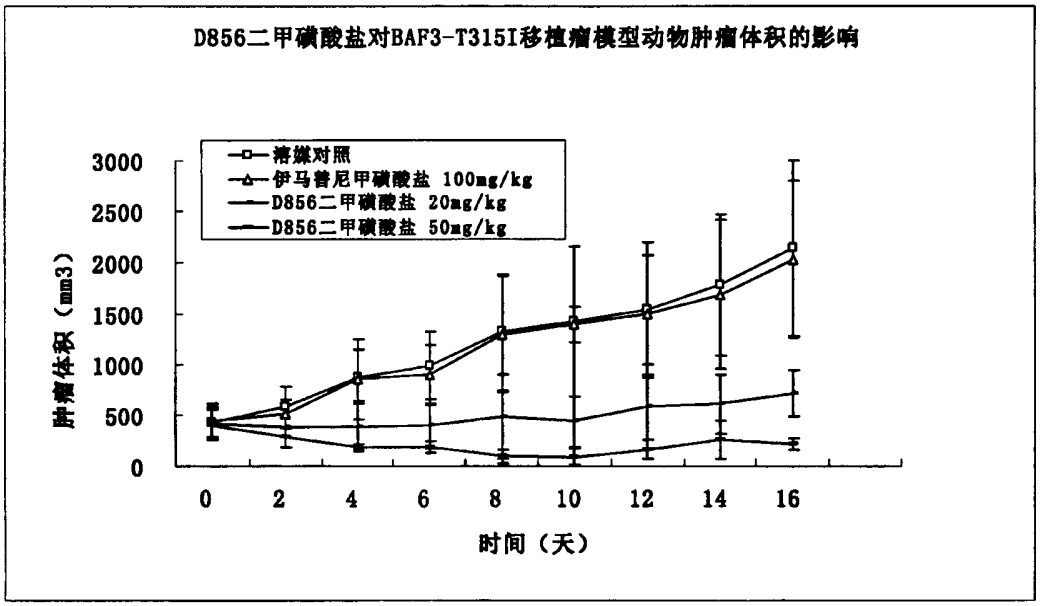

D856二甲磺酸盐对BAF3-T315I移植瘤模型动物肿瘤体积的影响
溶媒对照
伊马昔尼甲磺酸盐 100mg/kg
D856二甲磺酸盐 20mg/kg
D856二甲磺酸盐 50mg/kg
肿瘤体积（mm3）
3000
2500
2000
1500
1000
500
0
0
2
4
6
8
10
12
14
16
时间（天）

图 14

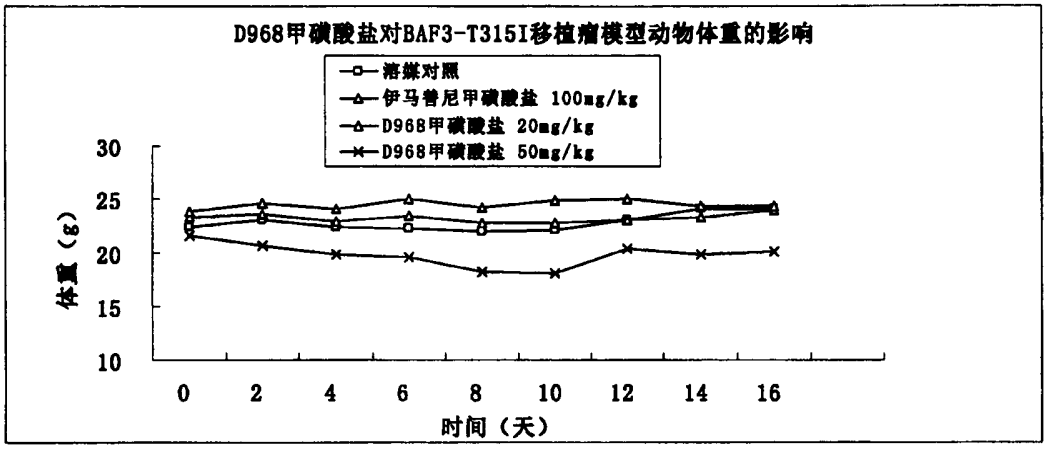

D968甲磺酸盐对BAF3-T315I移植瘤模型动物体重的影响
溶媒对照
伊马替尼甲磺酸盐 100mg/kg
D968甲磺酸盐 20mg/kg
D968甲磺酸盐 50mg/kg
体重（g）
30
25
20
15
10
0
2
4
6
8
10
12
14
16
时间（天）

图 15

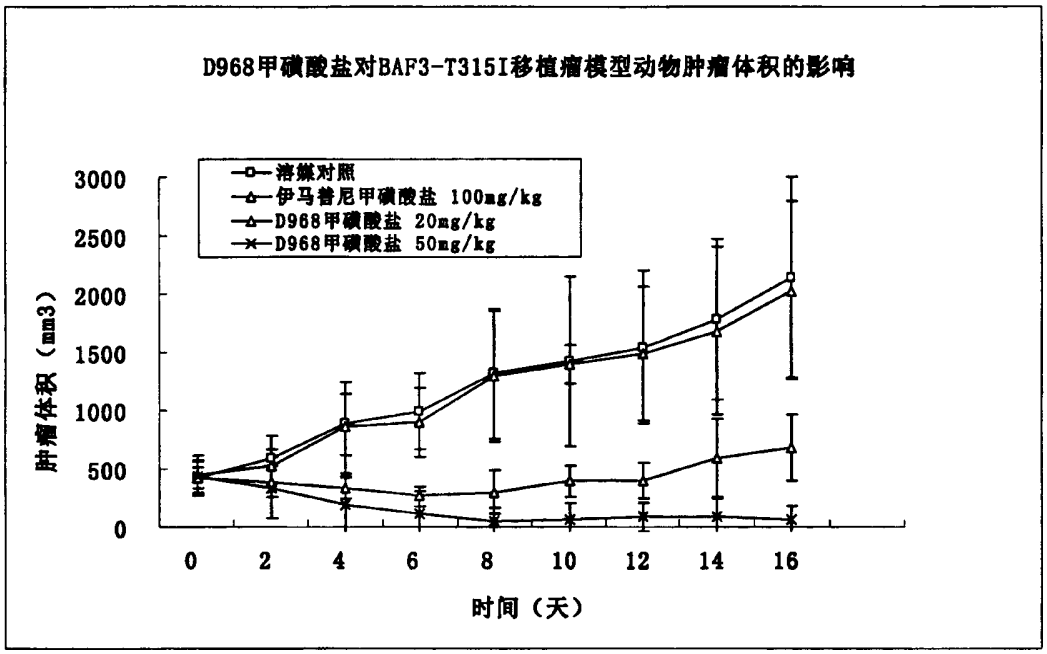

D968甲磺酸盐对BAF3-T315I移植瘤模型动物肿瘤体积的影响
溶媒对照
伊马替尼甲磺酸盐 100mg/kg
D968甲磺酸盐 20mg/kg
D968甲磺酸盐 50mg/kg
肿瘤体积（mm3）
3000
2500
2000
1500
1000
500
0
0
2
4
6
8
10
12
14
16
时间（天）

图 16

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2011/000935

A. CLASSIFICATION OF SUBJECT MATTER

see the extra sheet

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC: C07D 403/-; C07D 401/-; C07D 239/-; C07D 471/-; C07D 487/-; A61K 31/-; A61P 35/-

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Data: CNKI; CPRSABS; VEN; CNTXT; WPITXT; STN

Keyword: heterocyclic; alkynyl; protein; kinase; cancer; tumor; benzamide

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
PX	CN101885722A(GUANGZHOU INSRITUE OF BIOMEDICINE AND HEALTH), 17 Nov. 2010(17.11.2010) The whole description	1-10

☒ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim (S) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&"document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
12 Aug.2011(12.08.2011)	**08 Sep. 2011 (08.09.2011)**
Name and mailing address of the ISA/CN The State Intellectual Property Office, the P.R.China 6 Xitucheng Rd., Jimen Bridge, Haidian District, Beijing, China 100088 Facsimile No. 86-10-62019451	Authorized officer TIAN, Dingding Telephone No. (86-10)62086303

Form PCT/ISA /210 (second sheet) (July 2009)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2011/000935

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO2006044823A2 (AMGEN INC.), 27 Apr. 2006 (27.04.2006) Examples 1-2, 4-5, 7-8, 12, 15, 22-23, 26, 30, 33, 42, 58, 66, 73, 77-V-3, 77-V-4, 78-80, 86, 282, 284, 286-287, 290, 304, 305, 310, 311, 313-316, 321-322, 325, 327, 330, 337, 339, 345, 346, claims 1-49 and pages 74-75 of description	1-10
X	KANSAL, N., et al., A Three Dimensional Pharmacophore Modeling for KDR and Tie-2 Receptor Tyrosine Kinase Inhibitors and Virtual Screening for New Multikinase Inhibitors, QSAR & Combinatorial Science, Vol.28, No.10, pages 1130-1147, 31 Oct. 2009(31.10.2009) Compounds 19a, 20a	1-10
X	CEE,V.J., et al, Alkynylpyrimidine Amide Derivatives as Potent, Selective, and Orally Active Inhibitors of Tie-2 Kinase, Journal of Medicinal Chemistry, Vol.50, No.4, pages 627-640, 25 Jan. 2007(25.01.2007) compounds 6a, 13a, 13b of Table 1, compounds 6a~6g of Table 2, compounds 6f~6p of Table 3, compounds 6l~6n of Table 5	1-10
X	DENG, X.M., et al., Broad spectrum alkynyl inhibitors of T315I Bcr-Abl, Bioorganic & Medicinal Chemistry Letters, Vol.20, No.14, pages 4196-4200,19 May 2010(19.05.2010), Compound 9 of Table 1, Compounds 12, 14, 17-20 of Table 2	1-10
X	HUANG, W.S., et al., Discovery of 3-[2-(Imidazo[1,2-b]pyridazin-3-yl) ethynyl]-4-methyl-N-[4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl]benzamide (AP24534), a Potent, Orally Active Pan-Inhibitor of Breakpoint Cluster Region-Abelson (BCR-ABL) Kinase Including the T315I Gatekeeper Mutant, Journal of Medicinal Chemistry, Vol.53, No.12, pages 4701-4719, 01 Jun. 2010(01.06.2010) Compounds 20a, 20b of Table 4 Compound 12c of Table 2, Compounds 19a, 19c of Table 3, Compounds 20c~20g of Table 4, Table 5	1-10
X	WO2007075869A2 (ARIAD PHARMACEUTICALS,INC.), 05 Jul. 2007 (05.07.2007) Claims 1-22, Examples 1-5, 8-9, 14-19, 21, the table of pages 74-85 of description	1-10

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CN2011/000935

Patent Documents referred in the Report	Publication Date	Patent Family	Publication Date
WO2006044823A2	27.04.2006	EP1802586A2	04.07.2007
		US7776869B2	17.08.2010
		US2010160283A1	24.06.2010
		AU2005295414A1	27.04.2006
		US2006217380A1	28.09.2006
		WO2006044823A3	15.06.2006
WO2007075869A2	05.07.2007	MX2008008152A	30.09.2008
		US2007191376A1	16.08.2007
		WO2007075869A3	29.11.2007
		AU2006331673 A1	05.07.2007
		EP1973545A2	01.10.2008
		IN200802328P2	16.01.2009
		CN101389338A	18.03.2009
		CA2634923A1	05.07.2007
		JP2009521462T	04.06.2009
		KR20080081191A	08.09.2008
CN101885722A	17.11.2010	none	

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2011/000935

CLASSIFICATION OF SUBJECT MATTER

C07D 403/12(2006.01) i
C07D 401/12(2006.01)i
C07D 239/42(2006.01)i
C07D 471/04(2006.01)i
C07D 487/04(2006.01)i
A61K 31/506(2006.01)i
A61K 31/519(2006.01)i
A61K 31/4439(2006.01)i
A61K 31/437(2006.01)i
A61K 31/496(2006.01)i
A61P 35/00(2006.01)i
A61P 35/02(2006.01)i

国际检索报告

国际申请号
PCT/CN2011/000935

A. 主题的分类

参见附加页

按照国际专利分类(IPC)或者同时按照国家分类和 IPC 两种分类

B. 检索领域

检索的最低限度文献(标明分类系统和分类号)

IPC：C07D 403/-; C07D 401/-; C07D 239/-; C07D 471/-; C07D 487/-; A61K 31/-; A61P 35/-

包含在检索领域中的除最低限度文献以外的检索文献

在国际检索时查阅的电子数据库(数据库的名称，和使用的检索词（如使用）)

数据库：CNKI；CPRSABS；VEN；CNTXT；WPITXT；STN

关键词：杂环；炔苯；蛋白激酶；癌症；肿瘤；苯甲酰胺；广州生物医药；heterocyclic；alkynyl；protein；kinase；cancer；tumor；benzamide

C. 相关文件

类　型*	引用文件，必要时，指明相关段落	相关的权利要求
PX	CN101885722A（中国科学院广州生物医药与健康研究院），17.11 月 2010(17.11.2010) 说明书全文	1-10

☒ 其余文件在 C 栏的续页中列出。　　☒ 见同族专利附件。

* 引用文件的具体类型：

"A" 认为不特别相关的表示了现有技术一般状态的文件

"E" 在国际申请日的当天或之后公布的在先申请或专利

"L" 可能对优先权要求构成怀疑的文件，或为确定另一篇引用文件的公布日而引用的或者因其他特殊理由而引用的文件（如具体说明的）

"O" 涉及口头公开、使用、展览或其他方式公开的文件

"P" 公布日先于国际申请日但迟于所要求的优先权日的文件

"T" 在申请日或优先权日之后公布，与申请不相抵触，但为了理解发明之理论或原理的在后文件

"X" 特别相关的文件，单独考虑该文件，认定要求保护的发明不是新颖的或不具有创造性

"Y" 特别相关的文件，当该文件与另一篇或者多篇该类文件结合并且这种结合对于本领域技术人员为显而易见时，要求保护的发明不具有创造性

"&" 同族专利的文件

国际检索实际完成的日期	国际检索报告邮寄日期
12.8 月 2011（12.08.2011）	**08.9 月 2011 (08.09.2011)**
ISA/CN 的名称和邮寄地址： 中华人民共和国国家知识产权局 中国北京市海淀区蓟门桥西土城路 6 号 100088 传真号：　(86-10)62019451	受权官员 田丁丁 电话号码：(86-10) **62086303**

C(续). 相关文件

类　型	引用文件，必要时，指明相关段落	相关的权利要求
X	WO2006044823A2（AMGEN INC.），27.4 月 2006 （27.04.2006） 实施例 1-2，4-5，7-8，12，15，22-23，26，30，33，42，58，66，73，77-V-3，77-V-4，78-80，86，282，284，286-287，290，304，305，310，311，313-316，321-322，325，327，330，337，339，345，346，权利要求 1-49，和说明书第 74-75 页	1-10
X	KANSAL，N.，等，A Three Dimensional Pharmacophore Modeling for KDR and Tie-2 Receptor Tyrosine Kinase Inhibitors and Virtual Screening for New Multikinase Inhibitors, QSAR & Combinatorial Science，第 28 卷，第 10 期，第 1130-1147 页，31.10 月 2009（31.10.2009） 化合物 19a，20a	1-10
X	CEE，V.J.，等，Alkynylpyrimidine Amide Derivatives as Potent, Selective, and Orally Active Inhibitors of Tie-2 Kinase，Journal of Medicinal Chemistry, 第 50 卷，第 4 期, 第 627-640 页，25.1 月 2007（25.01.2007) 表格 1 的化合物 6a，13a，13b，表格 2 的化合物 6a~6g，表格 3 的化合物 6f~6p，表格 5 的化合物 6l~6n	1-10
X	DENG，X.M.，等，Broad spectrum alkynyl inhibitors of T315I Bcr-Abl, Bioorganic & Medicinal Chemistry Letters，第 20 卷，第 14 期, 第 4196-4200 页，19.5 月 2010（19.05.2010） 表格 1 的化合物 9，表格 2 的化合物 12，14，17-20	1-10
X	HUANG，W.S.，等，Discovery of 3-[2-(Imidazo[1,2-b]pyridazin-3-yl)ethynyl]-4-methyl-N-[4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl]benzamide (AP24534), a Potent, Orally Active Pan-Inhibitor of Breakpoint Cluster Region-Abelson (BCR-ABL) Kinase Including the T315I Gatekeeper Mutant，Journal of Medicinal Chemistry，第 53 卷，第 12 期，第 4701-4719 页，01.6 月 2010（01.06.2010） 表 4 的化合物 20a，20b 表格 2 的化合物 12c，表格 3 的化合物 19a，19c，表格 4 的化合物 20c~20g，表格 5	1-10
X	WO2007075869A2（ARIAD PHARMACEUTICALS,INC.)，05.7 月 2007（05.07.2007） 权利要求 1-22，实施例 1-5，8-9，14-19，21，说明书 74-85 页的表格	1-10

国际检索报告
关于同族专利的信息

国际申请号
PCT/CN2011/000935

检索报告中引用的专利文件	公布日期	同族专利	公布日期
WO2006044823A2	27.04.2006	EP1802586A2	04.07.2007
		US7776869B2	17.08.2010
		US2010160283A1	24.06.2010
		AU2005295414A1	27.04.2006
		US2006217380A1	28.09.2006
		WO2006044823A3	15.06.2006
WO2007075869A2	05.07.2007	MX2008008152A	30.09.2008
		US2007191376A1	16.08.2007
		WO2007075869A3	29.11.2007
		AU2006331673 A1	05.07.2007
		EP1973545A2	01.10.2008
		IN200802328P2	16.01.2009
		CN101389338A	18.03.2009
		CA2634923A1	05.07.2007
		JP2009521462T	04.06.2009
		KR20080081191A	08.09.2008
CN101885722A	17.11.2010	无	

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C07D 403/12(2006.01) i

C07D 401/12(2006.01)i

C07D 239/42(2006.01)i

C07D 471/04(2006.01)i

C07D 487/04(2006.01)i

A61K 31/506(2006.01)i

A61K 31/519(2006.01)i

A61K 31/4439(2006.01)i

A61K 31/437(2006.01)i

A61K 31/496(2006.01)i

A61P 35/00(2006.01)i

A61P 35/02(2006.01)i

(19) Europäisches Patentamt
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A61K 31/519 *(2006.01)* ***A61K 31/4439*** *(2006.01)*
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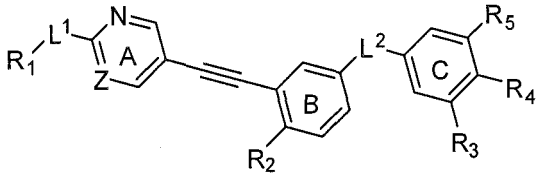
(54) HETEROCYCLIC ALKYNYL BENZENE COMPOUNDS AND MEDICAL COMPOSITIONS AND USES THEREOF

(57) The heterocyclic alkynyl benzene compounds of formula (I), their pharmaceutically acceptable salts and stereoisomers thereof, as well as application in preparing drugs for preventing or treating tumors. The compounds can overcome the clinically induced resistance against Gleevec.



(I)

EP 2 594 567 A1

Description

FILED OF THE INVENTION

[0001] The present invention relates to heterocyclic alkynyl benzene compounds of formula (I), their pharmaceutically acceptable salts and stereoisomers and prodrugs of formula (I), and their applications as the active ingredients for preparing drugs for preventing or treating tumors, particularly, to overcome the clinically induced resistance against Gleevec.

BACKGROUND OF THE INVENTION

[0002] Cancer is the 2nd leading cause after cardiovascular diseases responsible for human death. Because of the environment pollution and other factors, the incidence of malignant tumor is increasing rapidly. Based on WHO's published data of 2003, there are over 100 million patients with malignant tumor in the world. About 6.2 millions patients with malignant tumor die for cancer which accounts for 12%~25% of the total death. It is estimated that the global new cases will reach 15 million per year in 2020. Recently, some novel anticancer drugs of protein tyrosine inhibitors have been developed and achieved great clinical benefits, however, it is still far away from meeting the growing clinical needs of cancer patients. Anticancer drug is still one of the most active areas in the worldwide drug development.

[0003] Molecular targeted cancer therapy is a strategy selectively killing tumor cells through chemical or biological approaches by interfering the key regulators of tumor cell growth. Comparing with the traditional cytotoxic drugs, molecular targeted therapy can selectively modulate key molecules which are closely related to tumor growth and treat patients with high specificity and selectivity, low toxicity and less side effects. It can also enhance the potency by combination with traditional chemotherapy and radiotherapy, and reduce the recurrence after surgery. Gleevec (STI571), the protein tyrosine kinase inhibitor, created a new era of molecular targeted therapy for cancer. The molecular targeted therapy has rapidly developed within these years. The emergence of molecular targeted therapy for cancer has impacted the traditional drug administration concepts and models. For example, because of its low toxicity and less side effects, targeted drugs usually do not reach dose-limited toxicity and maximum tolerated dose in the clinic trial phase I; satisfactory efficacy can be achieved without need for applying maximum tolerated dose for molecular targeted therapy drugs. Targeted cancer therapy is one of the hot issues and developmental tendency of cancer therapy.

[0004] Protein tyrosine kinases (PTKs) can phosphorylate the phenolic hydroxyl groups of tyrosine residues of many important proteins and further activate functions of functional proteins. There are over 520 protein kinases in human body, about half of which are protein tyrosine kinases (PTKs). These proteins play very important roles in the signal transduction pathways inside of cells and modulate a wide range of biological processes of cells including growth, differentiation, death, etc. Disfunction of protein tyrosine kinase will cause a series of diseases. The studies show that half of protooncogenes and activation of oncogenes are related to protein tyrosine kinases. Abnormal expression of protein tyrosine kinase can cause disorder of cell proliferation regulation, and further cause tumors. In addition, abnormal expression of protein tyrosine kinase also closely relates to the tumor invasion and metastasis, the formation of new blood vessels, and resistance against chemotherapy drug. Novel protein tyrosine kinase inhibitor development has been one of the hotest issues in the world, and is also a focal point of all R&D institutions in all countries.

[0005] So far, over tens of small molecular inhibitors and antibodies of protein tyrosine kinase haven advanced into clinical trial, and some of them have been approved for clinical use and achieved excellent therapeutic effect. i.e. BCR-ABL inhibitor Gleevec for treating Philadelphia chromosome positive chronic myeloid leukemia and gastrointestinal stromal tumor; EGFR inhibitor Iressa and Tarceva for treating non-small-cell carcinoma etc. Gleevec is the first tumor drug with significant effect which was designed after knowing the pathogenesis of cancer. This drug is a milestone in molecular targeted cancer therapy. The greatness of Gleevec has been incorporated as one of the top ten science and technology news by SCIENCE magazine of USA in 2001.

[0006] Great success of the approved protein tyrosine kinase inhibitors further validates protein tyrosine kinases as promising molecular targets for clinic cancer therapy, and meanwhile validates its importance in tumor developing. Collective evidences show that protein tyrosine kinases encoded by mutant genes has direct relationship with the occurrence of tumor, such as BCR-ABL with chronic myeloid leukemia, c-Kit with GIST, SCCL and systemic mastocytosis, PDGFR with chronic myelomonocytic leukemia, dermatofibrosarcoma protuberan and hypereosinophilic dyndrome, Flt3 with parts of acute granulocytic leukemia, B-Raf with melanoma, RET with thyroid carcinoma. In addition, c-KIT is also closely related to small cell lung cancer.

[0007] The first targeted therapy drug STI571 (Gleevec, Imatinib mesylate, Chinese name"Geliewei", Novartis Pharmaceuticals), a protein tyrosine kinase inhibitor, was approved by USA FDA in 2001 for treating chronic granulocytic leukemia (CML). This drug mainly targets Bcr-Ab1, cKit, PDGFR etc. In clinic, single drug treatment with STI571 can make 98% of CML patients get relieved in clinical hematology, and 53% of these get relieved in cytogenetics.

[0008] However, emerging acquired resistance has become a major challenge for clinical management of CML

[0009] With the widely application of STI571 in clinic, drug resistance has become a serious problem: part of cancer patients show primary resistance to STI571; some patients show effect at beginning of administration, but gradually show secondary resistance in the process of drug therapy. Resistance means after STI571 treatment, chronic-phase patients do not have complete hematologic response or patients at blast-phase and accelerated phase cannot recover back to chronic phase. In clinic, CML patients in blast-phase and ALL patients with positive BCR-ABL more generally develop resistance. About 70% of the two kinds of patients will develop STI571 resistance after 3~6 month drug administration. And once the resistance happens, the situation gets worse. Resistance is considered one defense by tumor cells to avoid being killed, and has many mechanisms which include: ①target gene (BCR-ABL, c-KIT, PDGFR) amplification; ②target gene mutation; ③ formation of the tumor clone independent of the target genes; ④Production of α-1 acidic glycoprotein and over-expression of multiple drug resistance gene MDR1. However, the major mechanism publically accepted is secondary mutation in the kinase domains of kinase (BCR-ABL, c-KIT, PDGFR). Studies have demonstrated that that the common point mutations closely related to resistance include E255K, E255V, T315I and D276G of BCR-ABL, and D816V of c-KIT, etc. Patients with these mutations can easily have recurrence with bad prognosis. Some reports show that only 50% of patients of metastatic gastrointestinal stromal tumor (GIST), who carry V560G mutation in c-KIT transmembrane domain, respond to STI571 and achieve good efficacy. However, another 50% of patients of metastatic gastrointestinal stromal tumor do not respond to STI571. Point mutation of c-KIT tyrosine kinase (for example D816V, T315I) shows super resistance to STI571. *In vitro* experiments show that STI571 cannot inhibit proliferation of cells carrying c-KIT D816V and T315I mutants; patients of systemic mastocytosis carrying D816V c-KIT do not respond to STI571.

[0010] How to overcome the resistance of STI571 is a major important topic of today's Oncological medical study. Development of new small molecule inhibitors of tyrosine kinase is an important approach to overcome the resistance of STI571. For example, small molecule tyrosine kinase inhibitors, Nilotinib (AMN107), Dasatinib(BMS-354825) which launched to market recently, show effect on part (not all) of patient carrying STI571-resistant BCR-ABL point mutations (exclude T315 mutation). Same as that STI571 does, AMN107 competitively binds to non-active type of Abl kinase. It shows stronger affinity than STI571, and is 10~50 times more patent than STI571. AMN107 displays significant inhibition on cells harboring 15 point mutation except T315I with IC_{50} values in 10~1000 nM. Different from STI571 and AMN107, BMS-354825 can bind and inhibit both the non-activated and the activated BCR-ABL. BMS-354825 displays significant inhibition on cells harboring 15 point mutation except T315I, with IC_{50} values ranging from 10 nM to 125 nM. However, neither AMN107 nor BMS-354825 have effect on BCR-ABL T315I mutant. AMN107 and STI571 have no effect cells have c-KIT D816V point mutation. Therefore, It is urgently needed to develop new small molecule compounds which can efficiently kill the cells with STI571-resistant c-KIT point mutation (D816V) and/or BCR-ABL point mutation (including T315I) for both academia and industry of cancer therapy in the world.

[0011] In fact, most of today's protein tyrosine kinase inhibitor antitumor drugs can induce resistance related gene mutation, and face the problems of narrow clinic application scope. Therefore, development of the second generation of protein tyrosine kinase inhibitor and improvement of the clinic effect are super meaningful.

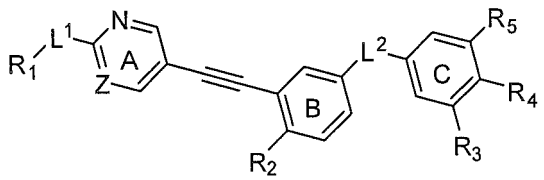
[0012] This invention relates to compounds with formula (I). These compounds can effectively inhibit different kinds of tumor cells, and display inhibitory potency targeting Gleevec- resistant mutants both in vitro and in vivo. These inhibitors represent a new generation of protein tyrosine kinase inhibitors.

SUMMARY OF THE INVENTION

[0013] It is an object of the present invention to provide a new type of heterocyclic alkynyl benzene compounds.

[0014] The technical solutions for solving the problem mentioned above are as followings:

compounds having formula (I) and their pharmaceutical acceptable salts, prodrugs, or stereoisomers:

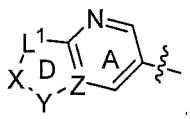


(I)

wherein Z is independently selected as CH or N;
L^1 is independently selected from NH, -N=, CH;
L^2 is independently selected as -CONH- or -NHCO-;

R_1 is independently selected from:

1. H;
2. C_1-C_6 alkyl;
3. C_3~C_6 cycloalkyl;
4. C_1~C_5 alkyl substituted by one or two hydroxyl group(s);
5. Phenyl;
6. Groups which can fuse A ring through L^1 in Z atom site to form fused penta-heterocycles containing 1~3 N atoms like



wherein, L^1 was defined as above; X, Y, Z are independently selected as N, CH; ring D is an aromatic heterocycle containing 1~3 N atoms;

R_2 is independently selected from

1. H;
2. Halogen (F, Cl, Br);
3. C_1~C_5 alkyl;
4. C_3~C_6 cycloalkyl;
5. C_1~C_5 alkyl containing F;

R_3 is independently selected from

1. H;
2. Halogen (F, Cl, Br);
3. C_1~C_4 alkyl;
4. C_3~C_6 cycloalkyl;
5. C_1~C_4 alkyl containing F;

when R_5 is H, R_4 is independently selected from

1. H;
2. $(CH_2)_nNR_6R_7$;
3. $(CH_2)_n$-Het^1;

Or, when R_4 is H, R_5 is independently selected from

1. H;
2. Het^2;

n is independently selected from 0 or 1;
Het^1 is defined as nonaromatic heterocycle containing 1~3 N atoms; Het^2 is defined as aromatic five-menmber heterocycle containing 1~3 hetero atoms like N, O, S; alkyl, cycloalkyl or NR_6R_7 will be incorporated into any C or N position in Het^1 and Het^2 which can be substituted;
R_6 or R_7 is independently selected from:

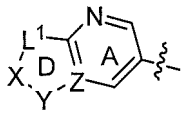
1. H;
2. C_1~C_3 alkyl;
3. C_1~C_3 alkyl containing F;
4. C_3~C_6 cycloalkyl;

R_6 and R_7 can further form penta-, hexa-, hepta- or octatomic ring structure through C, O, N, S atoms.

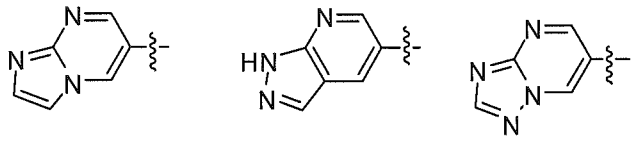
[0015] Preferably, Z is N, L^1 is NH,

R^1 is preferably selected from:

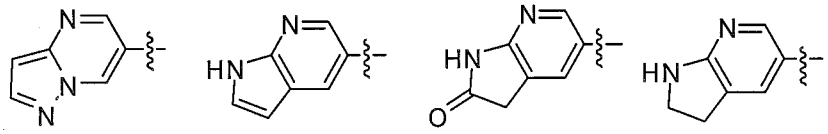
1. methyl, ethyl, isopropyl, tert-butyl;
2. cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl; Preferably R_1 and A form fused ring through as



which is preferably selected



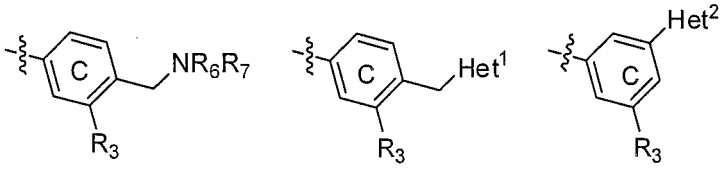
from



[0016] R_2 is selected from:

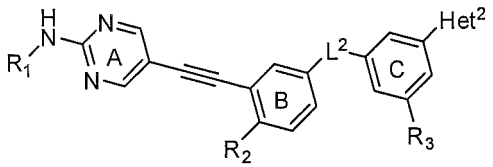
1. H
2. methyl, ethyl, isopropyl, tert-butyl;
3. cyclopropyl;
4. F, Cl, Br;
5. CF_3

[0017] Preferably C ring is selected from:

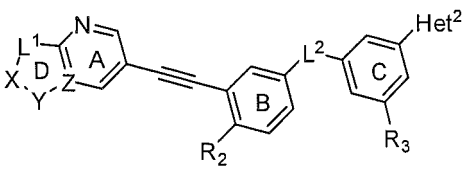


[0018] R_3, R_6, R_7 have the same definition as above mentioned; Het^1 has the same definition as above mentioned, Het^2 is selected from substituted imidazole, substituted pyrazole, substituted oxazole, substituted triazole, substituted oxazolidine, substituted thiazole.

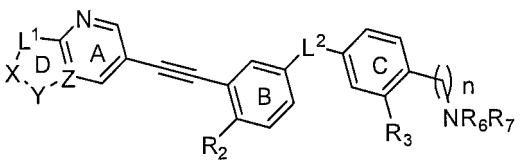
Preferably, in another embodiment, compound having formula (I) and their pharmaceutical acceptable salts, prodrugs, or stereoisomers is more preferably selected from:



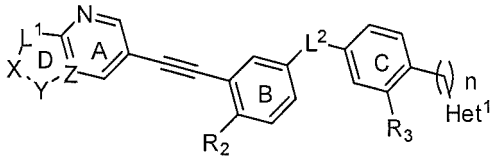
(II)



(III)



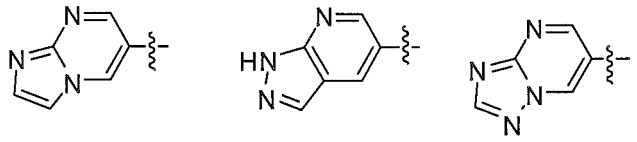
(IV)

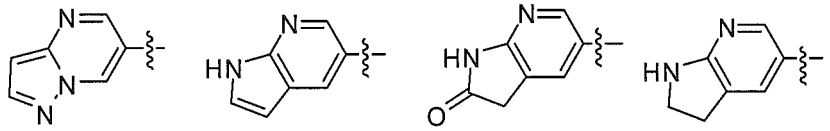


(V)

wherein

X, Y, Z are independently selected from N, CH; D heterocycle contains 1~3 N atoms; the fused ring of D with A ring is selected from:





R_1, R_2, R_3, R_6, R_7, n, L^1, L^2, Het^1, Het^2 have the same definition as above mentioned.

[0019] It is a further object for the present invention to provide the application of above mentioned compounds.

[0020] The compounds mentioned above or their pharmaceutically acceptable salts, stereoisomers or pro-drugs thereof can be used as new therapeutic agents for the treatment or the prevention of cancer.

[0021] The invention also relates to that the above mentioned compounds in effective dose can be used for the treatment of over-proliferative diseases, such as gastrointestinal stromal tumors (GIST), histiocytic lymphoma, non-small cell lung cancer, small cell lung cancer, lung adenocarcinoma, squamous cell lung carcinoma, pancreatic cancer, breast cancer, prostate cancer, liver cancer, skin cancer, squamous cell carcinoma, nasopharyngeal carcinoma, leukemia, and so on.

[0022] The compounds mentioned above and their pharmaceutical acceptable salts of the present invention can inhibit the proliferation of numerous cancers effectively, and inhibit protein kinases including BCR-ABL, c-Kit, PDGF, and can be used as anti-tumor drugs, and overcome the clinically induced resistance against Gleevec. As can be understood by the technical person in the field, the compounds and their pharmaceutical acceptable salts of the present invention can be used for the therapeutic application of over proliferative diseases including human cancers or mammalian cancers.

BRIEF DESCRIPTION OF THE DRAWINGS

[0023]

Fig.1 is the schematic diagram of effect of compound D747 Hydrochloride (po,qd) on body weight in Xenograft model of K562 in Example 1;

Fig.2 is the schematic diagram of effect of compound D747 Hydrochloride (po,qd) on tumor volume in Xenograft model of K562 in Example 1;

Fig.3 is the schematic diagram of effect of compound D822 Mesylate (po,qd) on body weight in Xenograft model of K562 in Example 21;

Fig.4 is the schematic diagram of effect of compound D822 Mesylate (po,qd) on tumor volume in Xenograft model of K5 62 in Example 21;

Fig.5 is the schematic diagram of effect of compound D767 Mesylate (po,qd) and compound D800 Mesylate (po,qd) on body weight in Xenograft model of K562 in Example 17;

Fig.6 is the schematic diagram of effect of compound D767 Mesylate (po,qd) and compound D800 Mesylate (po,qd) on tumor volume in Xenograft model of K562 in Example 17;

Fig.7 is the schematic diagram of effect of compound D824 Mesylate (po,qd) on body weight in Xenograft model of K5 62 in Example 41;

Fig.8 is the schematic diagram of effect of compound D824 Mesylate (po,qd) on tumor volume in Xenograft model of K5 62 in Example 41;

Fig.9 is the schematic diagram of effect of compound D824 Mesylate (po,qd) on body weight in Xenograft model of BAF3-T315I in Example 41;

Fig.10 is the schematic diagram of effect of compound D824 Mesylate (po,qd) on tumor volume in Xenograft model of BAF3-T315I in Example 41;

Fig.11 is the schematic diagram of effect of compound D824 Mesylate (po,q2d) on body weight in Xenograft model of BAF3-T315I in Example 41;

Fig.12 is the schematic diagram of effect of compound D824 Mesylate (po,q2d) on tumor volume in Xenograft model of BAF3-T315I in Example 41;

Fig. 13 is the schematic diagram of effect of compound D856 Mesylate (po,qd) on body weight in Xenograft model of K562 in Example 48;

Fig.14 is the schematic diagram of effect of compound D856 Mesylate (po,qd) on tumor volume in Xenograft model of K562 in Example 48;

Fig.15 is the schematic diagram of effect of compound D968 Mesylate (po,qd) on body weight in Xenograft model of K5 62 in Example 34;

Fig. 16 is the schematic diagram of effect of compound D968 Mesylate (po,qd) on tumor volume in Xenograft model of K562 in Example 34.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

[0024] In the compounds mentioned in the present invention, when any variables (such as R1, R, etc.) appear more than once in any component, the definitions every time they occur are independent from the definitions they appear other times. Also, allow substituent and variable combination, as long as the combination makes stable compounds. The line crossing from the substituent to ring system means the bond indicated can link to any atom of the ring which can be substituted. If the ring system is multiple ring system, it means the bond only connects to any appropriate carbon atom of the adjacent ring. The person with common techniques in the art can choose the compounds substituent and replacement type in order to provide the synthetic compounds that are chemically stable and can be synthesized from easily available materials by the techniques in the field and the methods mentioned below. If the substituent itself is replaced by more than one group, these groups can be in the same carbon atom or different carbon atoms, as long as the structure is stable.

[0025] In this invention, the term "alkyl" and "sub-alkyl" means a branched-chain or straight chain alkyl group with the certain number of carbon atoms. For example, the definition of "C_1-C_5" in "C_1-C_5 alkyl" means straight-chain or branched-chain alkyl group with 1, 2, 3, 4 or 5 carbon atoms. For example, "C_1-C_5 alkyl" includes methyl, ethyl, n-propyl, isopropyl, n-butyl, tert-butyl, isobutyl, pentyl, etc. The term "cycloalkyl" refers to a specific single saturated ring alkyl with the certain number of carbon atoms. For examples, "cycloalkyl" includes cyclopropyl-, methyl-cyclopropyl-, 2, 2-dimethyl-cyclobutyl, 2-ethyl-cyclopentyl-, cyclohexyl etc.

[0026] In this invention, the term of "hetero aryl group" is a stable monocyclic ring with up to six atoms or a stable bicyclic ring in which each ring contains up to six atoms. At least one of the rings is an aromatic ring containing 1~4 atoms selected from O, N or S. Hetero aryl groups include but not limit to: imidazolyl, triazolyl, pyrazolyl, furanyl, thienyl, oxazolyl , isoxazolyl, pyrazinyl, pyridazinyl, pyridyl, pyrimidinyl, pyrrolyl. About the definition of hetero aryl, any hetero aryl N-oxidation derivatives containing N atom should also be added. When hetero aryl substituted group is a bicyclic ring and one of the two rings is non-aromatic or non- hetero-atomcontaining ring, this bicyclic ring is fused through the aromatic ring or hetero atoms.

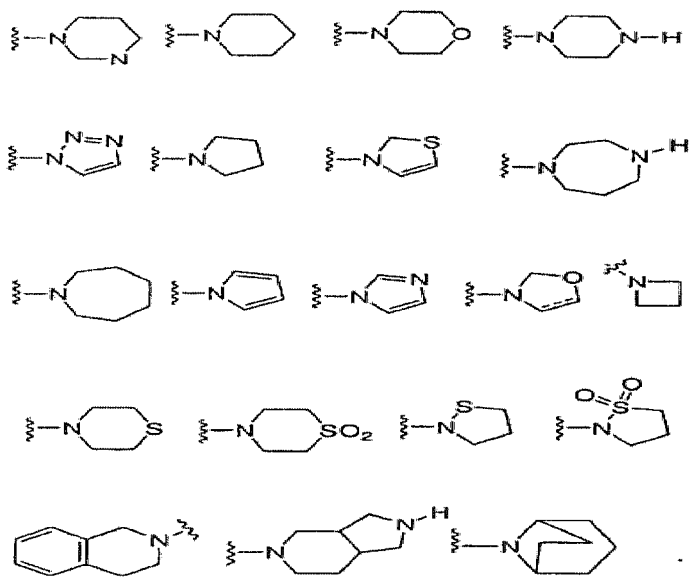
[0027] The term of "Heterocycle" refers to an aromatic or nonaromatic ring containing 5~6 atoms, in which contains 1~4 hetero atoms such as O, N, S. "Heterocycle" includes hetero aromatic ring as mentioned above; it also includes

dihydro and tetrahydro analogs. "Heterocycles" further include but not limit to: imidazolyl, indolyl, isothiazolyl, isoxazolyl, oxadiazolyl, oxazolyl, oxetanyl, pyranyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridyl, pyrimidinyl, pyrrolyl, quinazolinyl, tetrazolyl, thiadiazolyl, thiazolyl, thienyl, triazolyl, 1, 4- alkyl-dioxinyl, alkyl pyrrolidinyl, dihydro-imidazolyl, dihydro-isoxazolyl, dihydro-iso thiazolyl, dihydro-oxadiazolyl, dihydro-oxazolyl, dihydro-pyrazinyl, dihydro-pyrazolyl, dihydro-pyridyl, dihydro-pyrimidinyl, dihydro-pyrrolyl, dihydro-tetrazolyl, dihydro-thiadiazolyl, dihydro-thiazolyl, dihydro-thienyl, dihydro-triazolyl, methylene dioxy-benzophenone acyl , tetrahydrofuranyl, tetrahydrothiopheneyl, and their *N*-oxides etc. The linkage of heterocycle substituent can be achieved through C atom or heteroatom.In one embodiment, heterocycle is selected from imidazolyl" pyridyl, 1-pyrrolidone, 2-piperidone, 2- pyrimidone, 2-pyrrolidone, thienyl, oxazolyl, triazolyl, isoxazolyl, etc.

[0028] As understood by the person skilled in the prior art, "halo" or "halogen" in the present specification means chlorine, fluorine, bromine and iodine.

[0029] Unless specially mentioned, alkyl, cycloalkyl, aryl, hetero aryl, heterocyclic groups can be substituted or not be substituted. For example, C_1 - C_6 alkyl group can be substituted by one, two, or three substitutents selected from OH, halogens, alkoxyl, dialkylamino, or heterocyclic ring such as morpholinyl, piperidinyl groups.

[0030] In an embodiment, Het may form a single ring containing 4~7 atoms or a bicyclic ring in which each ring comprises 4~7 atoms through the N atom which connects the Het, the single ring or bicyclic ring may further comprises 1~2 hetero atoms selected from N, O, S, and said heterocyclecan also be substituted by one or more substituents selected from R_2. The hetero cyclic rings formed include but not limit to the following heterocycles, and it shall be remembered said heterocycle selectively substituted by one or more(preferably one, two or three) substituents selected from R_2:



[0031] The invention relates to the free forms of compounds with formula (I)~(II), and it also relates to their pharmaceutical acceptable salts or steroisomers. The specifc examples in the invention are the protonated salts of amines.

[0032] Therefore, "pharmaceutical acceptable salts" in the invention mean the normal nontoxic salts formed by the basic compounds in the invention with organic acids and inorganic acids. For example, the normal nontoxic salts are from inorganic acids that include hydrochloric acid, hydrobromic acid, sulfuric acid, sulfamic acid, phosphoric acid, nitric acid, and from organic acids that include acetic acid, propionic acid, succinic acid, glycolic acid, stearic acid, lactic acid, malic acid, tartaric acid, lemon acid, ascorbic acid, bashing acid, maleic acid, hydroxy-maleic acid, phenylacetic acid, glutamic acid, benzoic acid, salicylic acid, sulfanilic acid, 2-acetoxy-benzoic acid , p-toluenesulfonic acid, methanesulfonic acid, ethane disulfonic, oxalic acid, hydroxyethyl sulfonic acid, trifluoroacetic acid etc.

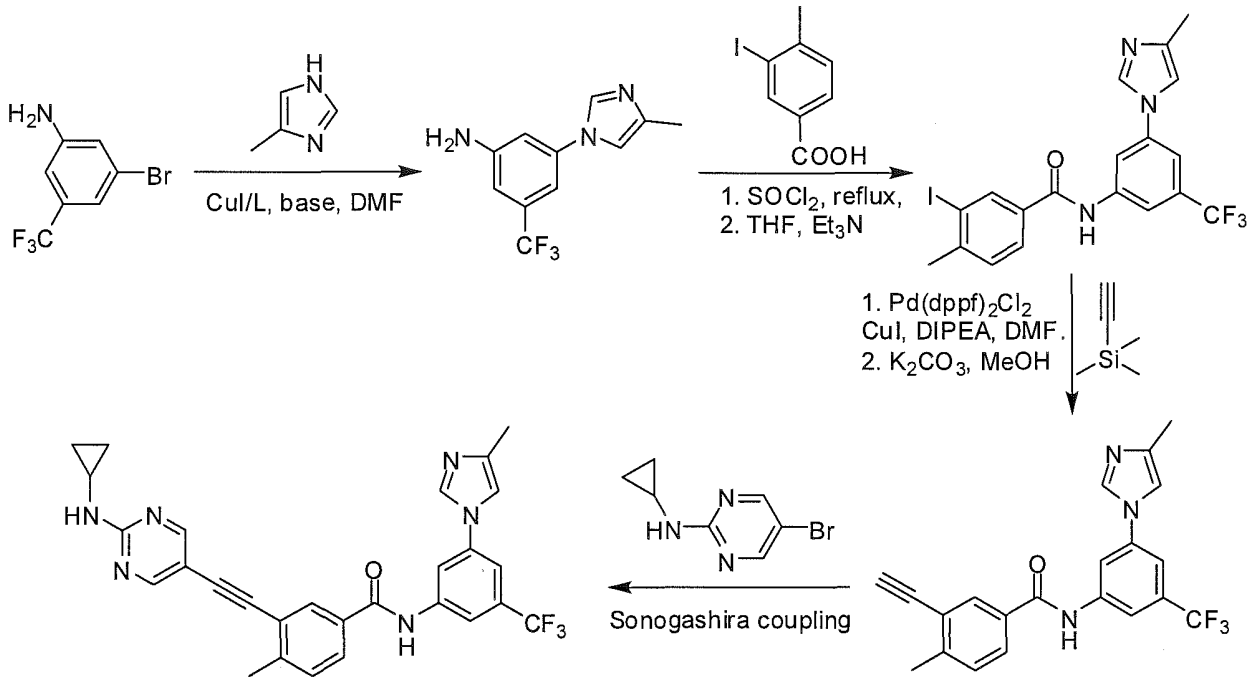
[0033] Berg et al described the preparation of pharmaceutical acceptable salts as above mentioned or other typical pharmaceutical acceptable salts in Pharmaceutical Salts, J. Pharm. Sci. 1977, 66: 1-19 in more details.

[0034] The compounds of the present invention can be prepared by using the following method besides the method which is well validated in the experimental procedures or has been published in articles. Therefore the synthetic scheme below only outlines the examples and does not limit the compounds or any specific substituent. The number of the substituents in the scheme does not need to comply with the number specified in the Claims. And for clear explanation, the formula (I) showing only single substitution can allow compounds with multiple substituents.

[0035] As shown in the scheme A, compounds in formula (I) was synthesized through five steps by using 3-bromo-

5-(trifluoromethyl)benzenamine as the starting material.

Scheme A



[0036] In one embodiment, this present invention provides a method of using compounds in formula (I) and their pharmaceutical acceptable salts for treatment of over proliferative diseases including human cancers or mammalian cancers.

[0037] In one embodiment, the invention also relates to the compounds designed in the present invention and their pharmaceutically acceptable salts which are used for the treatment or the prevention of over proliferative diseases, such as gastrointestinal stromal tumors (GIST), histiocytic lymphoma, non-small cell lung cancer, small cell lung cancer, lung adenocarcinoma, squamous cell lung carcinoma, pancreatic cancer, breast cancer, prostate cancer, liver cancer, skin cancer, squamous cell carcinoma, nasopharyngeal carcinoma, leukemia, and so on.

[0038] In one embodiment, the compounds designed in the present invention and their pharmaceutically acceptable salts can be used in combination with other modulators in clinic or under investigation to strengthen their clinical potency, such as estrogen receptor modulator, androgen receptor modulator, retinoid receptor modulator, cell toxin/cell inhibitor, antiproliferative agent, protein transferase inhibitor, HMG-CoA reductase inhibitor, HIV protein kinase inhibitor, reverse transcriptase inhibitor, angiogenesis inhibitor, cell proliferation and survival signaling inhibitor, interference with the cell cycle checkpoint drug and apoptosis inducing agent, cytotoxic drug, protein tyrosine inhibitor, EGFR, VEGFR inhibitor, serine / threonine protein inhibitor, Bcr-Abl inhibitor, c-Kit inhibitor, Met inhibitor, Raf inhibitor, MEK inhibitor, MMP inhibitor, topoisomerase inhibitor, histidine deacetylase inhibitor, proteasome inhibitor, CDK inhibitor, Bcl-2 family protein inhibitor, MDM2 family protein inhibitor, inhibitors of IAP family proteins, inhibitors of STAT family proteins, PI3K inhibitor, AKT inhibitor, integrin blockade inhibitor, IFN-α, interleukin-12, COX-2 inhibitors, p53, p53 activators, VEGF antibody, EGF antibody, etc.

[0039] The compounds of the present invention and their pharmaceutically acceptable salts can be used to treat the following diseases according to the following methods, as well as other diseases not listed below:

(1) A method for treating breast cancer in a human or other mammalian patient in need of such treatment which comprises administering to the patient a pharmaceutical composition comprising a compound of Formula (I) in present invention and its pharmaceutically acceptable salt. The breast cancers include but are not limited to invasive ductal carcinoma, invasive lobular carcinoma, ductal carcinoma in situ and lobular carcinoma in situ.

(2) A method for treating respiratory tract cancer in a human or other mammalian patient in need of such treatment which comprises administering to the patient a pharmaceutical composition comprising a compound of Formula (I) in present invention and its pharmaceutically acceptable salt. The respiratory tract cancer includes but not limited to small-cell lung cacer, non-small cell lung cancer, bronchial adenoma and pleuropulmonary blastoma.

(3) A method for treating brain cancer in a human or other mammalian patient in need of such treatment which comprises administering to the patient a pharmaceutical composition comprising compound of Formula (I) in the present invention and its pharmaceutically acceptable salt. The brain cancers includes but are not limited to brainstem and subocular glioma, the cerebellum and cerebral astrocytoma, ependymal cell tumor, neuroectodermal and pineal tumor.

(4) A method for treating cancers in the male/female reproductive organism in a human or other mammalian patient in need of such treatment which comprises administering to the patient a pharmaceutical composition comprising a compound of Formula (I) in the present invention and its pharmaceutically acceptable salt. Cancers in the male reproductive organism include but are not limited to prostate cancer and testicular cancer. Cancers in the female reproductive organism include but not limit to endometrial cancer, cervical cancer, ovarian cancer, cancer of the vagina and vulva and uterine tumor;

(5) A method for treating cancers in the alimentary canals in a human or other mammalian patient in need of such treatment which comprises administering to the patient a pharmaceutical composition comprising a compound of Formula (I) in the present invention and its pharmaceutically acceptable salt. Cancers in the alimentary canals include but are not limited to anal cancer, colon cancer, colon cancer, esophageal cancer straight, gastric cancer, pancreatic cancer, small bowel or salivary gland cancer;

(6) A method for treating cancers in the urethra in a human or other mammalian patient in need of such treatment which comprises administering to the patient a pharmaceutical composition comprisinga compound of Formula (I) in the present invention and its pharmaceutically acceptable salt. Cancers in the urethra include but are not limited to bladder cancer, penile cancer, renal cell carcinoma, carcinoma of renal pelvis, ureter cancer or carcinoma of urethra;

(7) A method for treating cancers in the eyes in a human or other mammalian patient in need of such treatment which comprises administering to the patient a pharmaceutical composition comprising a compound of Formula (I) in the present invention and its pharmaceutically acceptable salt. Cancers in the eyes include but are not limited to intraocular melanoma and retinoblastoma;

(8) A method for treating cancers in the liver in a human or other mammalian patient in need of such treatment which comprises administering to the patient a pharmaceutical composition comprising a compound of Formula (I) in the present invention and its pharmaceutically acceptable salt. Cancers in the liver include but are not limited to liver cell tumor (with or without fiber board variations of stem cell carcinoma), bile duct carcinoma (Intrahepatic bile duct carcinoma) and mixed hepatocellular carcinoma of bile duct;

(9) A method for treating cancers in the skin in a human or other mammalian patient in need of such treatment which comprises administering to the patient a pharmaceutical composition comprising a compound of Formula (I) in the present invention and its pharmaceutically acceptable salt. Cancers in the skin include but are not limited to squamous cell carcinomas, Kaposi's sarcoma, malignant melanoma, Merck's cells in skin cancer and melanoma cells cancer;

(10) A method for treating cancers in the head and neck in a human or other mammalian patient in need of such treatment which comprises administering to the patient a pharmaceutical composition comprising a compound of Formula (I) in the present invention and its pharmaceutically acceptable salt. Cancers in the head and neck include but are not limited to the larynx, hypopharynx, nasopharynx, oropharynx cancer and cancer of the mouth and lips;

(11) A method for treating lymphoma cancers in a human or other mammalian patient in need of such treatment which comprises administering to the patient a pharmaceutical composition comprising a compound of Formula (I) in the present invention and its pharmaceutically acceptable salt. Lymphoma cancers include but are not limited to AIDS related lymphoma, non Hochkin lymphoma, cutaneous T cell lymphoma, Hochkin's disease and central nervous system lymphoma;

(12) A method for treating sarcoma cancers in a human or other mammalian patient in need of such treatment which comprises administering to the patient a pharmaceutical composition comprising a compound of Formula (I) in the present invention and its pharmaceutically acceptable salt. Cancers in the eyes include but are not limited to soft tissue sarcomas, osteosarcoma, malignant fibrous histiocytoma, lymphatic sarcoma and rhabdomyosarcoma;

(13) A method for treating leukemia in a human or other mammalian patient in need of such treatment which comprises administering to the patient a pharmaceutical composition comprising a compound of Formula (I) in the present invention and its pharmaceutically acceptable salt. Leukemia include but are not limited to acute myeloid leukemia, acute leukemia, chronic lymphocytic leukemia and forest cell leukemia, chronic myelogenous leukemia and hairy cell leukemia;

Administration and Dose Ranges

[0040] Based on the standard pharmacutical technology, the compound of the present invention can be used alone or in the pharmaceutical combination with pharmaceutical acceptable acceptors, accessories or diluents to a mammal, preferabbly a human. For example, oral, rectal, topical, parenteral, ocular, pulmonary, nasal, and intestines and stomach

may be employed.

[0041] In one embodiment, when treating or controlling cancer of the patient with which compounds of Formula (I) are used, oral daily dosage of the compounds of the present invention administered is from about 0.1~500mg/day/kg body weight. The proper administration is as a single daily dose or as divided doses two to four times a day, or in sustained release form. For most large mammals, the total daily dosage is from about 0.1 ~ 1500 mg/day/kg body weight, preferably from about 0.5 ~ 100 milligrams/day/kg body weight. In the case of a 70 kg adult human, the total daily dose will generally be 0.5 ~ 100 mg/day/kg body weight. In the case of a 70 kg adult human, the total daily dose will generally be from about 1 milligram to about 500 milligrams. For a particularly potent compound, the dosage for an adult human may be as low as 0.1 mg/day.

Metabolites-Prodrugs

[0042] The metabolites of the compounds and their pharmaceutical salts in the present invention, and prodrugs that are converted to the compounds and their pharmaceutical salts in the present invention are comprised in the claims of the present application.

Combination Therapy

[0043] Compounds of Formula I~II may be used in combination with other drugs that are known to be useful in the treatment or amelioration of the diseases or similar diseases. In the combination administration, such other drugs may be administered, by a route administration and in an amount commonly used, and contemporaneously or sequentially with a compound of Formula I~II. When a compound of Formula I~II is used contemporaneously with one or more other drugs, a pharmaceutical composition containing one or more other known drugs and the compound of Formula I~II is preferred. The combination therapy also comprises therapies in which the compound of Formula I~II and one or more other known drugs are administered on overlapping schedules. When used in combination with one or more other drugs, the compound of Formua I~II and the other known drugs may be used in lower dosage than when they are used alone. Drugs or active ingredients used in combination with compounds of Formula I~II comprises but are not limited to: estrogen receptor modulator, androgen receptor modulator, retinoid receptor modulator, cell toxin/cell inhibitor, antiproliferative agents, protein transferase inhibitors, HMG-CoA reductase inhibitors, HIV protein kinase inhibitors, reverse transcriptase inhibitors, angiogenesis inhibitors, cell proliferation and survival signaling inhibitors, interference with the cell cycle checkpoint drugs and apoptosis inducing agent, cytotoxic drugs, protein tyrosine inhibitor, EGFR, VEGFR inhibitors, inhibitors of serine /threonine protein inhibitors, inhibitors of Bcr-Abl, c-Kit inhibitor, Met inhibitors, inhibitors of Raf, MEK inhibitor, MMP inhibitors, inhibitors of topoisomerase, histidine deacetylase inhibitors, proteasome inhibitors, inhibitors of CDK, Bcl-2 family protein inhibitor, MDM2 family protein inhibitors, inhibitors of IAP family proteins, inhibitor of STAT family proteins, PI3K, AKT inhibitors, inhibitors of integrin blockade, IFN-α, interleukin-12, COX-2 inhibitor, p53, p53 activator inhibitor, VEGF antibody, EGF antibody, etc.

[0044] In one embodiment, drugs or active ingredients used in combination with compounds of Formula I~II comprises but are not limited to: Aldesleukin, Alendronate, interferon, Alitretinoin, allopurinol, allopurinol sodium, palonosetron hydrochloride, Hemel, amino glutethimide, amifostine, amrubicin, Ann acridine, anastrozole, dolasetron, Aranesp, arglabin, arsenic trioxide, Aromasin, 5 - N cytidine, azathioprine, BCG or BCG, Bestatin hydrochloride, betamethasone acetate, betamethasone sodium phosphate, Bexarotene, bleomycin sulfate, broxuridine, bortezomib, busulfan, calcitonin, Alemtuzumab Campath, capecitabine, carboplatin, Casodex, cefesone, Seamus IL, DNR, chlorambucil, cisplatin, cladribine, cladribine, chloride phosphoric acid, Cytarabine, cyclophosphamide, Dacarbazine, Actinomycin D, DNX, dexamethasone, dexamethasone phosphate, estradiol valerate, cefdinir interleukin 2, Methylprednisolone acetate, deslorelin, dexrazoxane, diethylstilbestrol, Diflucan, docetaxel, doxorubicin, doxifluridine, dronabinol, chin -166- chitosan complexes, eligard, rasburicase, epirubicin hydrochloride, aprepitant, epirubicin, alfa-epoetin, erythropoietin, Eptaplatin, levamisole, estradiol formulation, 17- β - estradiol, estramustine phosphate sodium, ethinylestradiol, Amifostine, hydroxyl phosphate, Etopophos, etoposide, Fadrozole, tamoxifen, filgrastim, finasteride, floxuridine, fluconazole, fludarabine, 5-fluorine BrdU a phosphate, 5- fluorouracil, fluoxymesterone, flutamide, formestane, Cytarabine hydrochloride, Fotemustine, fulvestrant, immunoglobulin, gemcitabine, gemtuzumab ozogamicin, imatinib mesylate, carmustine capsules, goserelin, hydrocortisone, erythro-hydroxy nonyl adenine, hydroxyurea, Ibritumomab Tiuxetan. Idarubicin, ifosfamide, interferon α, IFN-α2, interferon α-2A,interferon α-2B, interferon α-nl, IFN α-n3, interferon β, interferon γ-la, IL-2, intron A, Iressa, Irinotecan, Kytril, mushroom polysaccharide sulfate, letrozole, leucovorin, leuprolide, leuprorelin acetate, Levamisole, levorotation folinic acid calcium salt, levothyroxine sodium, levothyroxine sodium, lomustine, lonidamine, dronabinol, nitrogen mustard, Mecobalamin, medroxyprogesterone acetate, megestrol acetate, melphalan, esterified estrogens, 6-Mercaptopurine, mesna, methotrexate, aminolevulinic acid methyl ester, miltefosine, minocycline, mitomycin C, mitotane, mitoxantrone anthraquinone, Trilostane, citric acid adriamycin liposome, Nedaplatin, Pegfilgrastim, oprelvekin, neupogen, nilutamide, tamoxifen, NSC-631570, recombinant human interleukin 1- β, octreotide, Ondansetron hydro-

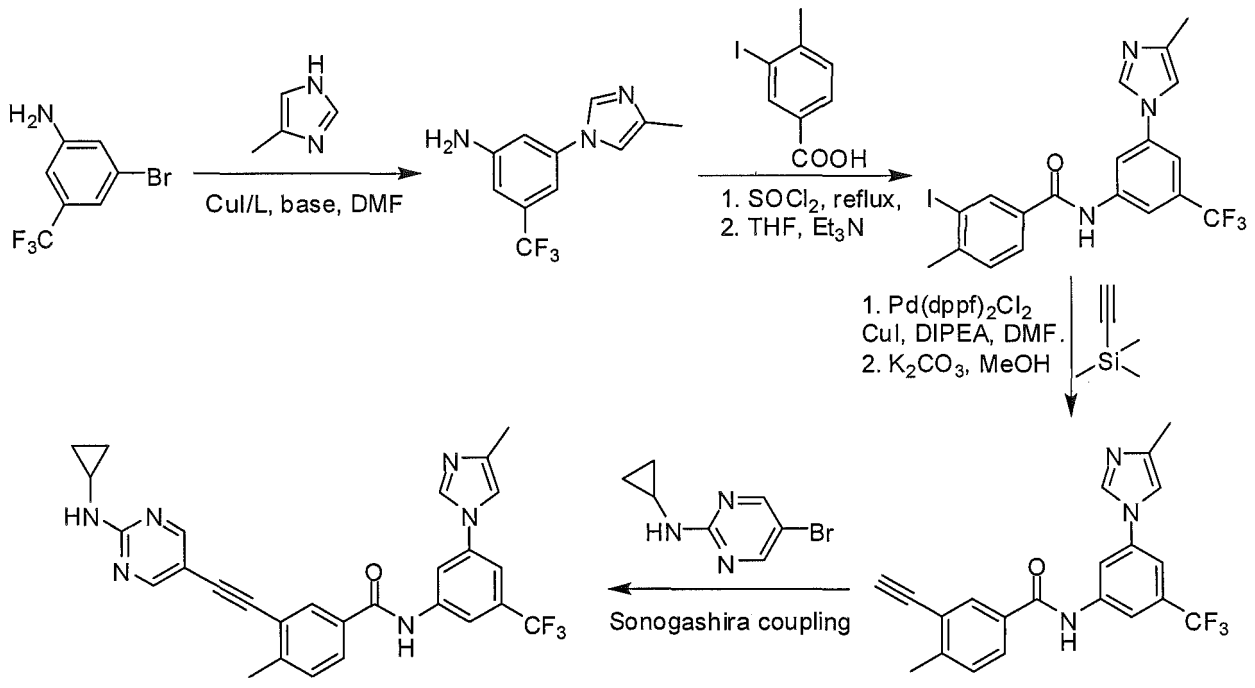
chloride, hydroprednisone oral solution, oxaliplatin, paclitaxel, prednisone, L-asparaginase enzyme sodium phosphate preparation, Pegasys, pentostatin, Picibanil, pilocarpine hydrochloride, adjoin THP, mithramycin, porfimer sodium, prednimustine, Prednisolone Steaglate, prednisolone, Premarin, C kappa umbilical, recombinant human erythropoietin, raltitrexed, Libby, etidronate rhenium-186, rituximab, Redoxon-A, Romo peptide, pilocarpine hydrochloride tablets, octreotide, Sargramostim, semustine, Schizophyllan, sobuzoxane, Methylprednisolone, Paphos acid, stem cell therapy, streptozocin, strontium chloride -89, levothyroxine sodium, tamoxifen, tamsulosin, TNF-alfa, tastolactone, docetaxel, teceleukin, temozolomide, teniposide, propionic acid testosterone, testosterone propionate, thioguanine, thiotepa, thyroid stimulating hormone, Tiludronic acid, topotecan, toremifene, tositumomab, trastuzumab, Treosulfan, Victoria A acid, methotrexate tablets, three methyl melamine, trimetrexate, triptorelin, double hydroxy acetic acidNaphthalene of triptorelin, UFT, uridine, valrubicin, vesnarinone, alkali, vincristine, Vindesine Vinorelbine, virulizin, dextral razoxane, Zinostatin ester, ondansetron, paclitaxel, acolbifene, Interferon r-Ib, affinitak, aminopterin, Arzoxifene, Asoprisnil, atamestane, atrasentan, BAY 43-9006, Avastin, CCI-779, CDC-501, Celebrex, cetuximab, crisnatol, cyproterone acetate, decitabine, DN-101, Doxorubicin-MTC, dSLIM, dutasteride, edotecarin, eflornithine, Exatecan, Fenretinide, histamine hydrochloride, holmium -166 DOTMP, ibandronate, IFN -γ, intron -PEG, ixabepilone, intron keyhole shaped hemocyanin, L-651582, Lanreotide, lasofoxifene, Libra, lonafamib, Miproxifene, MS-209, liposome MTP-PE, MX-6, Nafarelin, Nemorubicin, Neovastat, Nolatrexed, Aolimosen, onco-TCS, osidem, paclitaxel poly glutamic acid ester, pamidronate disodium injection, PN-401, QS-21, R -1549, raloxifene, ranpirnase, 13-cis-Victoria A acid, satraplatin, seocalcitol, T-138067, Tarceva, DHA-PTX, thymosin αl, Pirazofurin, tipifarnib, tirapazamine, TLK-286, toremifene, trans MID-lo7R, valspodar, vapreotide, vatalanib, verteporfin, Vinflunine, Z-100 and Zoledronic acid or their combination.

[0045] Further explanations are made as followings, but those embodiments cannot be used to limit the protection scope of the invention.

Example 1

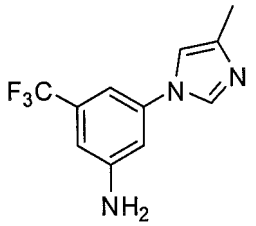
3-(2-(2-(cyclopropylamino)pyrimidin-5-yl)ethynyl)-4-methyl-N-(3-(4-methyl-1H-imidazol-1-yl)-5 -(trifluoromethyl)phenyl)benzamide

[0046]



Step 1. 5-(4-methyl-1*H*-imidazol-1-yl)-3-(trifluoromethyl)-benzenamine

[0047]

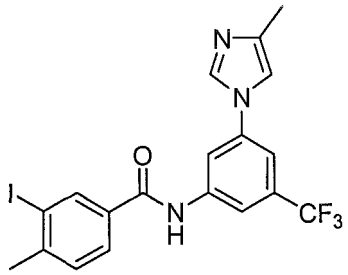


[0048] In a pressure tube with one end sealed, add 190mg CuI (1mmol), 1.64g 4-methyl-1H-imidazole (20mmol), 3.25g Cs_2CO_3(10mmol), and after Nitrogen replacement, add 2.40g 3-bromo-5-(trifluoromethyl)aniline (10 mmol), 350mg 1-(5,6,7,8-tetrahydroquinolin-8-yl)ethanone (2mmol) and 30mL DMF was added into a flask. The mixture was stirred at 110°C for 18 h under sealing. After cooling to room temperature, the solvent was removed under vacuum and the residue was purified by column chromatography to afford 2.19 g desired product (91 %).

[0049] ^{1}H NMR (400 MHz, *d*-DMSO), δ 8.06 (s, 1H), 7.35 (s, 1 H), 6.97 (s, 1 H), 6.93 (s, 1 H), 6.81 (s, 1H), 5.87 (br, 2H), 2.15 (s, 3H). MS (ESI), m/z: 242 ($M^+ + H^+$).

Step 2. 3-iodo-4-methyl-*N*-(3-(4-methyl-1*H*-imidazol-1-yl)-5-(trifluoromethyl)phenyl)benzamide.

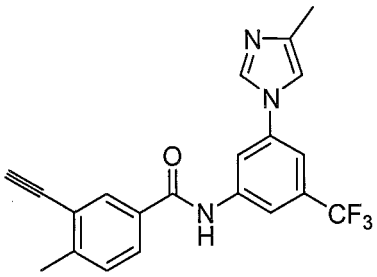
[0050]



[0051] Add 2 drops of DMF into 628 mg 3-iodo-4-methylbenzoic acid (2.2 mmol) in 20 mL $SOCl_2$ and reflux for 2 h. After vacuum evaporation of $SOCl_2$, add 6.0 mL anhydrous THF and get the pale yellow solution. Dissolve the product from step 1, 524 mg 5-(4-methyl-1*H*-imidazol-1-yl)-3-(trifluoromethyl)-benzenamine (2.0 mmol) in 6.0 mL anhydrous THF and add 10 mmol Et_3N, and the pale yellow solution prepared previously is added drop wise till it is all added. The reaction mixture rises to room temperature for 1 hr. The reaction was quenched with addition of brine and extracted with EtOAc. The combined extraction organic layers was dried and concentrated under vacuum, the residue was purified through column chromatography to afford 873 mg desired product. (90%)
MS (ESI), m/z: 486 ($M^+ + H^+$).

Step 3. 3-ethynyl-4-methyl-*N*-(3-(4-methyl-1*H*-imidazol-1-yl)-5-(trifluoromethyl) phenyl)benzamide.

[0052]

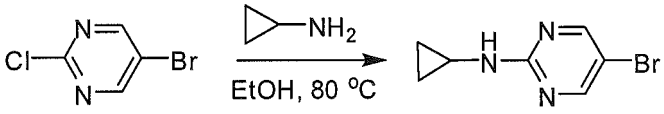


[0053] In a pressure tube with one end sealed, add 485 mg 3-iodo-4-methyl-*N*-(3-(4-methyl-1*H*-imidazol-1-yl)-5-(trifluoromethyl)phenyl)benzamide (1.0 mmol) from Step 2, 500 mg trimethylsilylacetylene (5.0 mmol), 19 mg Cu I (0.1 mmol), 7 mg $Pd(PPh_3)_2Cl_2$ (0.01 mmol), 1.0 mL Et_3N in 3.0 mL acetonitrile, and after Nitrogen replacement, the mixture is stirred at 80 °C for 2 h. After cooling to room temperature, the solution was filtered by 2 cm silica gel column. The

filtration is washed three times with ethyl acetate and is concentrated to brown solid which is further dissolved in 5 mL methanol. The solution is then added with 980 mg K_2CO_3 and stirred at room temperature for 3 h. The solid was filtered off and the solution was concentrated to column chromatography f 344 mg desired product. (90 %)
MS (ESI), m/z: 384 ($M^+ + H^+$),

Step 4. 5-bromo-N-cyclopropylpyrimidin-2-amine

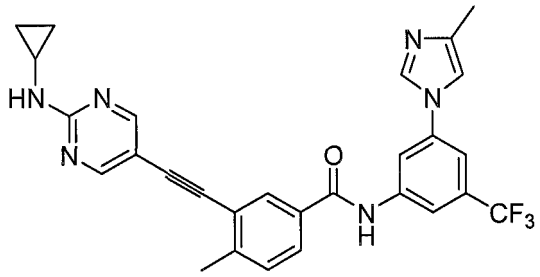
[0054]



[0055] In a pressure tube with one end sealed, add 193 mg 5-bromo-2-chloropyrimidine (1.0 mmol) and 285 mg cyclopropylamine (5.0 mmol) in 3.0 mL ethanol, and the mixture is heated to 80 °Cand stirred for 3 h. The reaction mixture was cooled to room temperature, and 203 mg solid product was collected by filitration for direct useyield: 95%). MS (ESI), m/z: 215 ($M^+ + H^+$).

Step 5. 3-(2-(2-(cyclopropylamino)pyrimidin-5-yl)ethynyl)-4-methyl-*N*-(3-(4-methyl-1*H*-imidazol-1-yl)-5-(trifluoromethyl)phenyl)benzamide (D747)

[0056]



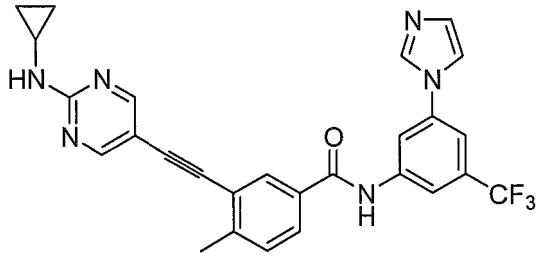
[0057] In a pressure tube with one end sealed, add 192 mg step 3 product, 3-ethynyl-4-methyl-*N*-(3-(4-methyl-1*H*-imidazol-1-yl)-5-(trifluoromethyl) phenyl)benzamide (0.5 mmol), 107 mg Step 4 product, 5-bromo-N-cyclopropylpyrimidin-2-amine (0.5 mmol), 19 mg CuI (0.1 mmol), 2.2 mg $Pd(OAc)_2$ (0.01 mmol), 2.8 mg PCy_3 (0.01 mmol) 3.0 mL DMF, 193 mg DIPEA (1.5 mmol), after nitrogen replacement, the solution is heated to 60 °C for 12 h. After cooling to room temperature, the solid is filtered off by 2 cm silical gel column and washed by ethyl acetate for three times, and the solution was concentrated by vacuum evaporation for 193 mg desired product (75%).

[0058] ^{1}HNMR (400 MHz, *d*-DMSO), δ ppm 10.69 (s, 1H), 8.54 (br, 2H), 8.29 (s, 1H), 8.21 (s, 1H), 8.16 (m, 2 H), 7.93 (m, 2H), 7.73 (s, 1H), 7.52 (m, 2H), 2.77 (m, 1H), 2.53 (s, 3H), 2.18 (s, 3H), 0.71 (m, 2H), 0.53 (m, 2H). MS (ESI), m/z: 517 ($M^+ + H^+$).

Example 2

***N*-(3-(1*H*-imidazol-1-yl)-5-(trifluoromethyl)phenyl)-3-(2-(2-(cyclopropylamino)pyrimidin-5-yl)et hynyl)-4-methylbenzamide (D729)**

[0059]



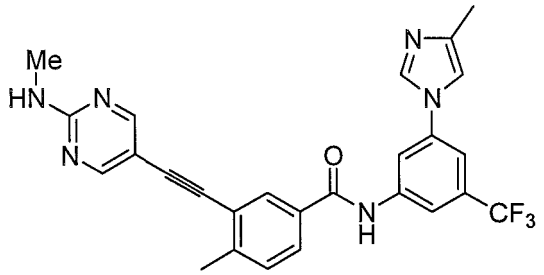
[0060] The compound was synthesized by using the procedure similar to that of Example 1.

[0061] ^{1}HNMR (400 MHz, *d*-DMSO), δ ppm 10.73 (s, 1H), 8.55 (br, 2H), 8.33 (d, *J*= 2.4 Hz, 2H), 8.21 (s, 1H), 8.14 (d, J= 1.2 Hz, 1 H), 7.94-7.89 (m, 2H), 7.80-7.76 (m, 2H), 7.53 (d, J= 8.4 Hz, 1H), 7.17 (s, 1H), 2.78-2.73 (m, 1H), 2.53 (s, 3H), 2.18 (s, 3H), 0.73-0.68 (m, 2H), 0.53-0.49 (m, 2H). MS (ESI), m/z: 503 ($M^+ + H^+$).

Example 3

4-methyl-*N*-(3-(4-methyl-1*H*-imidazol-1-yl)-5-(trifluoromethyl)phenyl)-3-(2-(2-(methylamino)py rimidin-5-yl)ethynyl)benzamide (D800)

[0062]



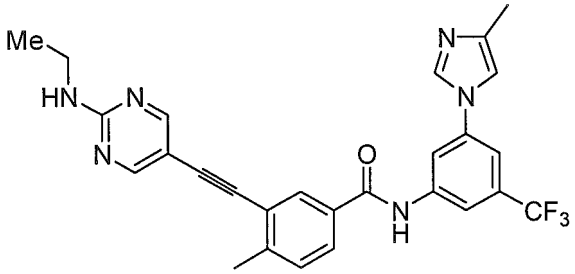
[0063] The compound was synthesized by using the procedure similar to that of Example 1.

[0064] ^{1}HNMR (400 MHz, *d*-DMSO), δ ppm 10.69 (s, 1H), 8.29 (m, 2H), 8.20-8.13 (m, 5H), 7.91 (d, *J*= 4.8 Hz, 1H), 7.73-7.66 (m, 2 H), 7.52 (m, 2H), 2.85 (d, *J*= 4.4 Hz, 1H), 2.53 (s, 3H), 2.18 (s, 3H). MS (ESI), m/z: 491 ($M^+ + H^+$).

Example 4

3-(2-(2-(ethylamino)pyrimidin-5-yl)ethynyl)-4-methyl-*N*-(3-(4-methyl-1*H*-imidazo1-1-yl)-5-(triflu oromethyl)phenyl)benzamide (D755)

[0065]



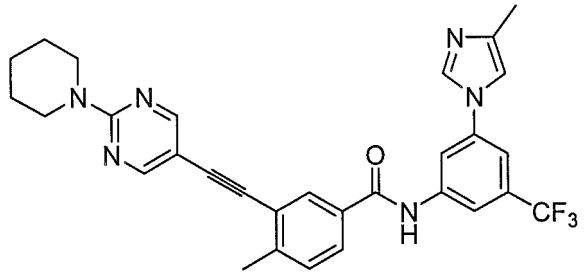
[0066] The compound was synthesized by using the procedure similar to that of Example 1.

[0067] ^{1}HNMR (400 MHz, *d*-DMSO), δ ppm 10.69 (s, 1H), 8.52 (br, 2H), 8.29 (s, 1H), 8.21 (d, *J*= 1.6 Hz, 1H), 8.16 (s, 1 H), 8.13 (d, *J*= 1.6 Hz, 1H), 7.91 (m, 1H), 7.75-7.73 (m, 2H), 7.52-7.49 (m, 2H), 3.35-3.29 (m, 2H), 2.52 (s, 3H), 2.18 (s, 3H), 1.15 (t, *J*= 7.2 Hz, 3H). MS (ESI), m/z: 505 ($M^+ + H^+$).

Example 5

4-methyl-*N*-(3-(4-methyl-1*H*-imidazol-1-yl)-5-(trifluoromethyl)phenyl)-3-(2-(2-(piperidin-1-yl)py rimidin-5-yl)ethynyl)benzamide (D797)

[0068]



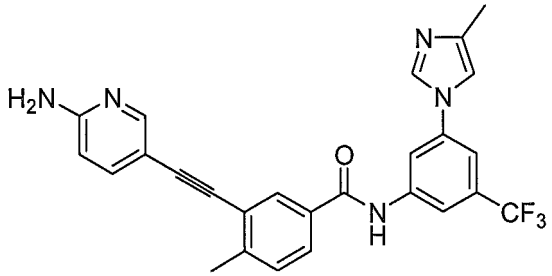
[0069] The compound was synthesized by using theprocedure similar to that of Example 1.

[0070] ^{1}HNMR (400 MHz, *d*-DMSO), δ 1.51 (4H, s), 1.62 (2H, s), 2.16 (3H, s), 3.77 (4H, s), 7.47 (2H, s), 7.70 (1H, s), 7.88 (1H, d, *J*=6.4 Hz), 8.15 (3H, m), 8.28 (1H, s), 8.53 (2H, s), 10.66 (1H, s). MS(ESI), m/z: 545 ($M^+ + H^+$).

Example 6

3-(2-(6-aminopyridin-3-yl)ethynyl)-4-methyl-*N*-(3-(4-methyl-1*H*-imidazol-1-yl)-5-(trifluorometh yl)phenyl)benzamide (D827)

[0071]



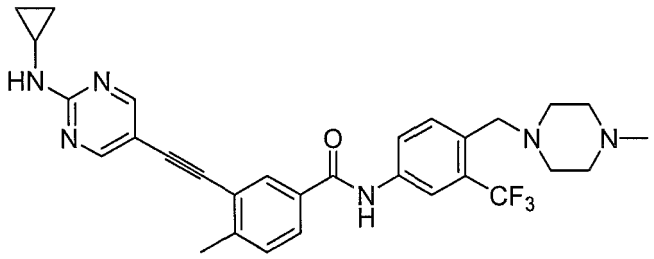
[0072] The compound was synthesized by using the procedure similar to that of Example 1.

[0073] ^{1}HNMR (400 MHz, *d*-DMSO), δ 2.53 (3H, s), 6.48 (2H, s), 7.54 (2H, m), 7.74 (1H, s), 7.89 (1H, dd, *J*=8.0, 3.2 Hz), 8.13 (1H, d, *J*=1.6 Hz), 8.18 (2H, s), 8.31 (1.0H, s), 10.68 (1H, s). MS(ESI), m/z: 476 ($M^+ + H^+$).

Example 7

3-(2-(2-(cyclopropylamino)pyrimidin-5-yl)ethynyl)-4-methyl-*N*-(4-((4-methylpiperazin-1-yl)meth yl)-3-(trifluoromethyl)phenyl)benzamide (D825)

[0074]



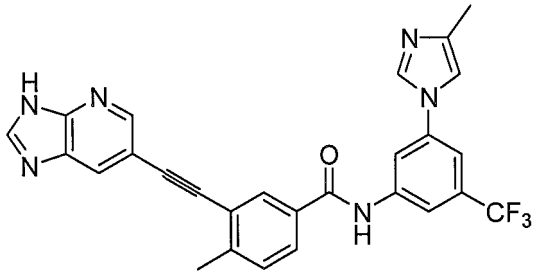
[0075] The compound was synthesized by using the procedure similar to that of Example 1.

[0076] ^{1}HNMR (400 MHz, *d*-DMSO), δ 0.51 (2H, s), 0.70 (2H, d, *J*=5.6 Hz), 2.42 (3H, s), 2.72 (3H, s), 2.75 (2H, m), 3.60 (6H, br), 7.48 (1H, d, *J*=7.8 Hz), 7.69 (1H, d, *J*=8.2 Hz), 7.89 (2H, m), 8.09 (2H,m), 8.21 (1H, s), 8.54 (2H, s), 10.51 (1H, s). MS(ESI), m/z: 549 ($M^+ + H^+$).

Example 8

3-(2-(3*H*-imidazo[4,5-*b*]pyridin-6-yl)ethynyl)-4-methyl-*N*-(3-(4-methyl-1*H*-imidazol-1-yl)-5-(trifl uoromethyl) phenyl)benzamide (D833)

[0077]



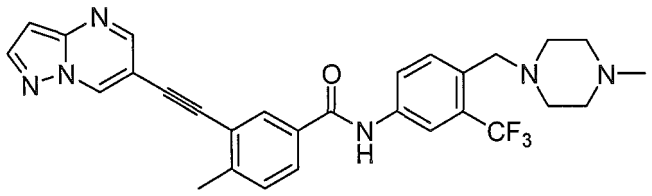
[0078] The compound was synthesized by using the procedure similar to that of Example 1.

[0079] ^{1}HNMR (400 MHz, *d*-DMSO), δ 2.18 (3H, s), 2.60 (3H, s), 7.49 (1H, s), 7.55 (1H, d, *J*=8.0 Hz), 7.74 (1H, s), 7.94 (1 H, d, *J*=7.8 Hz), 8.20 (4H, mHz), 8.30 (1H, s), 8.59 (1H, s), 10.72 (1H, s). MS(ESI), m/z: 501 ($M^+ + H^+$).

Example 9

4-methyl-*N*-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)-3-(2-(pyrazolo[1,5-*a*] pyrimidin-6-yl) ethynyl)benzamide (D856)

[0080]



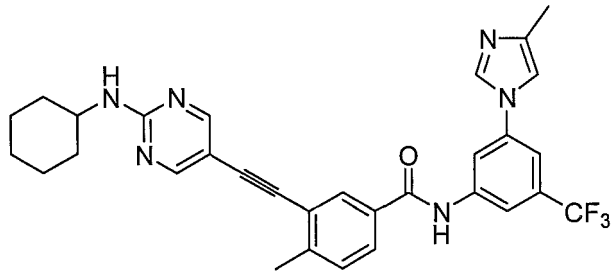
[0081] The compound was synthesized by using the procedure similar to that of Example 1.

[0082] ^{1}HNMR (400 MHz, *d*-DMSO), δ 2.17 (3H, s), 2.37 (8H, m), 2.60 (3H, s), 3.57 (2H, s), 6.85 (1H, d, J=2.0 Hz), 7.54 (1H, d, J=8.0 Hz), 7.71 (1H, d, J=8.4 Hz), 7.96 (1H, dd, J= 8.0, 3.29 Hz), 8.06 (1H, d, J=2.00 Hz), 8.21 (2H, dd, J=4.2, 2.0 Hz), 8.34 (1H, d, J=2.0 Hz), 8.72 (1H, d, J=2.0 Hz), 9.58 (1H, d, J=2.00 Hz), 10.56 (1H, s). MS(ESI), m/z: 533 ($M^+ + H^+$).

Example 10

3-(2-(2-(cyclohexylamino)pyrimidin-5-yl)ethynyl)-4-methyl-*N*-(3-(4-methyl-1*H*-imidazol-1-yl)-5-(trifluoromethyl) phenyl)benzamide (D828)

[0083]



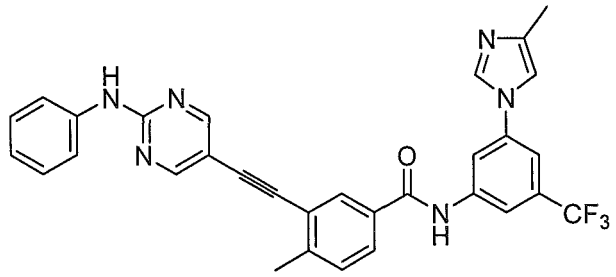
[0084] The compound was synthesized by using the procedure similar to that of Example 1.

[0085] ^{1}HNMR (400 MHz, *d*-DMSO), δ 1.23 (4H, m), 1.71 (3H, m), 2.17 (2H, s), 2.54 (3H, s), 4.40 (1 H, q, *J*=7.0 Hz), 7.51 (2H,m), 7.64 (1H, d, *J*=8.0 Hz), 7.72 (1H, s), 7.94 (1H, d, J=7.48 Hz), 8.14 (2H, m), 8.29 (1H, s), 8.49 (1H, s), 8.84 (1H, s), 10.68 (1H, s). MS(ESI), m/z: 559 ($M^+ + H^+$).

Example 11

4-methyl-*N*-(3-(4-methyl-1*H*-imidazol-1-yl)-5-(trifluoromethyl)phenyl)-3-(2-(2-(phenylamino)pyr imidin-5-yl)ethynyl)benzamide (D809)

[0086]



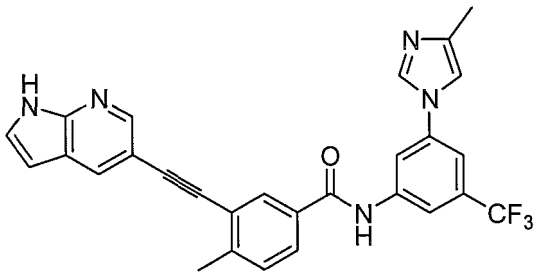
[0087] The compound was synthesized by using the procedure similar to that of Example 1.

[0088] ^{1}HNMR (400 MHz, *d*-DMSO), δ 2.18 (3H, s), 2.56 (3H, s), 7.02 (1H, t, *J*=7.2 Hz), 7.32 (2.0H, t, *J*=8.0 Hz), 7.49 (1H, s), 7.54 (1H, d, *J*=8.0 Hz), 7.75 (3H, m), 7.93 (1H, dd, *J*= 8.0, 3.2 Hz), 8.17 (2H, s), 8.21 (1H, s), 8.30 (1H, s), 8.72 (2H, s), 10.06 (1H, s), 10.71 (1H, s). MS(ESI), m/z: 553 ($M^+ + H^+$).

Example 12

3-(2-(1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)ethynyl)-4-methyl-*N*-(3-(4-methyl-1*H*-imidazol-1-yl)-5-(triflu oromethyl)phenyl)benzamide (D832)

[0089]



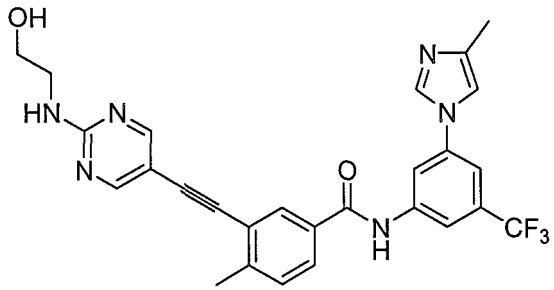
[0090] The compound was synthesized in a similar procedure of Example 8.

[0091] ^{1}HNMR (400 MHz, *d*-DMSO), δ 2.18 (3H, s), 2.58 (3H, s), 6.53 (1H, q, J=1.71 Hz), 7.53 (3H, m), 7.73 (1H, s), 7.92 (1H, dd, J= 8.0, 3.2 Hz), 8.20 (3H, m), 8.31 (1H, s), 8.46 (1H, s), 10.70 (1H, s), 11.95 (1H, s). MS(ESI), m/z: 500 (M^++ H^+).

Example 13

3-(2-(2-(2-hydroxyethylamino)pyrimidin-5-yl)ethynyl)-4-methyl-*N*-(3-(4-methyl-1*H*-imidazol-1-y 1)-5-(trifluoromethyl)phenyl)benzamide (D820)

[0092]



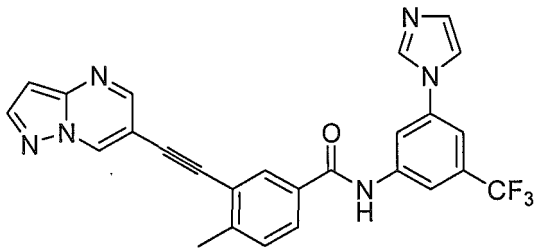
[0093] The compound was synthesized by using the procedure similar to that of Example 1.

[0094] ^{1}HNMR (400 MHz, *d*-DMSO), δ 2.19 (3H, s), 2.53 (3H, s), 3.15 (1H, m), 3.41 (2H, m), 3.53 (2H, m), 4.73 (1H, t, J=5.2 Hz), 7.52 (1H, d, J=8.0 Hz), 7.63 (1H, s), 7.74 1H, s), 7.91 (1H, m), 8.00 (1H, s), 8.16 (2H, m), 8.31 (1H, s), 8.52 (1H, s), 10.71 (1H, s). MS(ESI), m/z: 521 (M^++ H^+).

Example 14

***N*-(3-(1*H*-imidazol-1-yl)-5-(trifluoromethyl)phenyl)-4-methyl-3-(2-(pyrazolo[1,5-*a*]pyrimidin-6-y l)ethynyl)benzamide (D819)**

[0095]



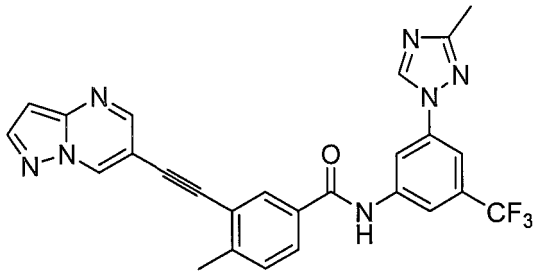
[0096] The compound was synthesized by using the procedure similar to that of Example 1.

[0097] ^{1}HNMR (400 MHz, *d-DMSO),* δ 2.61 (3H, s), 6.85 (1.0H, d, *J*=2.0 Hz), 7.21 (1H, s), 7.57 (1H, d, *J*=8.4 Hz), 7.82 (2H, m), 7.98 (1H, dd, J=8.0, 3.2 Hz), 8.23 (2H, m), 8.35 (3H, d, *J*=2.4 Hz), 8.73 (1H, d, *J*=2.00 Hz), 9.59 (1H, d, *J*=2.0 Hz), 10.77 (1H, s). MS(ESI), m/z: 487 (M^++ H^+).

Example 15

4-methyl-*N*-(3-(3-methyl-1*H*-1,2,4-triazol-1-yl)-5-(trifluoromethyl)phenyl)-3-(2-(pyrazolo[1,5-*a*]p yrimidin-6-yl) ethynyl)benzamide (D818)

[0098]



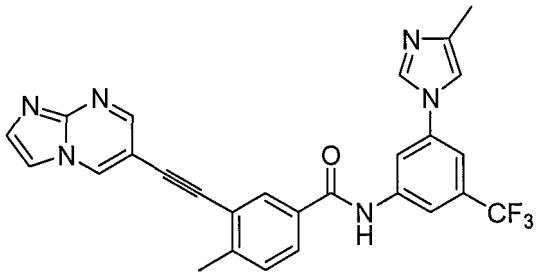
[0099] The compound was synthesized by using the procedure similar to that of Example 1.

[0100] ^{1}HNMR (400 MHz, *d*-DMSO), δ 2.40 (3H, s), 2.60 (3H, s), 6.85 (1H, d, J=1.6 Hz), 7.56 (1H, d, J=8.2 Hz), 7.99 (2H, m), 8.26 (2H, m), 8.35 (1H, d, J=2.0 Hz), 8.64 (1H, s), 8.73 (1H, d, J=2.0 Hz), 9.32 (1H, s), 9.58 (1H, d, J=1.2 Hz), 10.80 (1H, s). MS(ESI), m/z: 502 ($M^+ + H^+$).

Example 16

3-(2-(imidazo[1,2-*a*]pyramidin-6-yl)ethynyl)-4-methyl-*N*-(3-(4-methyl-1*H*-imidazol-1-yl)-5-(triflu oromethyl)phenyl)benzamide (D799)

[0101]



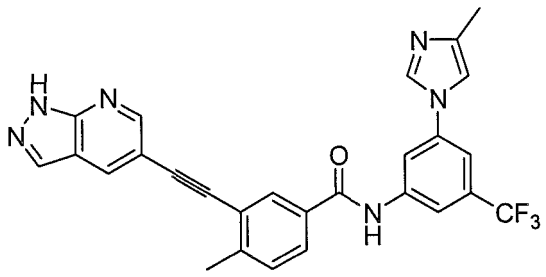
[0102] The compound was synthesized by using the procedure similar to that of Example 1.

[0103] ^{1}HNMR (400 MHz, *d-DMSO),* δ 2.19 (3H, s), 2.59 (3H, s), 7.50 (1H, s), 7.57 (1H, d, J=8.2 Hz), 7.74 (1H, s), 7.82 (1H, s), 7.97 (2H, m), 8.17 (1H, s), 8.22 (2H, d, J=2.0 Hz), 8.31 (1H, s), 8.71 (1H, d, J=2.4 Hz), 9.40 (1H, d, J=2.4 Hz), 10.73 (1H, s). MS(ESI), m/z: 501 ($M^+ + H^+$)

Example 17

3-(2-(1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)ethynyl)-4-methyl-*N*-(3-(4-methyl-1*H*-imidazol-1-yl)-5-(trifl uoromethyl)phenyl)benzamide (D767)

[0104]



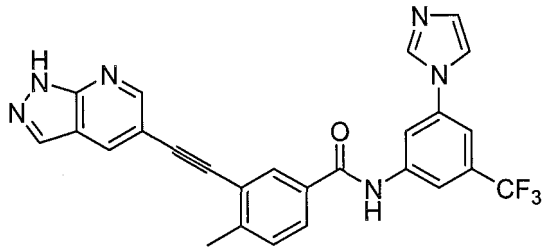
[0105] The compound was synthesized by using the procedure similar to that of Example 1.

[0106] ^{1}HNMR (400 MHz, *d-DMSO),* δ 13.95 (s, 1H), 10.72 (s, 1H), 8.75 (s, 1H), 8.54 (s, 1H), 8.31 (s, 1 H), 8.23 (s, 3H), 8.18 (s, 1 H), 7.97 (d, *J*= 8.0 Hz, 1H), 7.75 (s, 1H), 7.57 (d, *J*= 8.0 Hz, 1H), 7.49 (s, 1 H), 2.60 (s, 3H), 2.19 (s, 3H). MS(ESI), m/z: 501 ($M^+ + H^+$).

Example 18

***N*-(3-(1*H*-imidazol-1-yl)-5-(trifluoromethyl)phenyl)-3-(2-(1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)ethynyl)-4-methylbenzamide (D831)**

[0107]



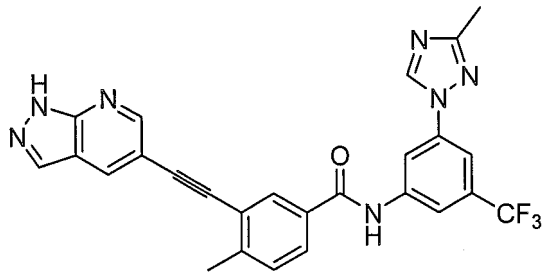
[0108] The compound was synthesized by using the procedure similar to that of Example 1.

[0109] ^{1}HNMR (400 MHz, *d-DMSO),* δ 13.92 (s, 1H), 10.72 (s, 1H), 8.72 (d, J=2.0 Hz, 1H), 8.51 (d, J=2.0 Hz, 1H), 8.32 (s, 2 H), 8.21 (s, 3H), 7.95 (d, J= 8.0 Hz, 1 H), 7.79 (d, *J*= 4.0 Hz, 2H), 7.54 (d, J= 8.0 Hz, 1H), 7.16 (s, 1H), 2.58 (s, 3H). MS(ESI), m/z: 487 ($M^+ + H^+$).

Example 19

3-(2-(1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)ethynyl)-4-methyl-*N*-(3-(3-methyl-1*H*-1,2,4-triazol-1-yl)-5-(trifluoromethyl) phenyl)benzamide (D835)

[0110]



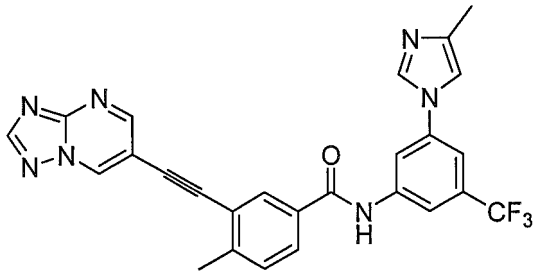
[0111] The compound was synthesized by using the procedure similar to that of Example 1.

[0112] ^{1}HNMR (400 MHz, *d-DMSO),* δ 13.92 (s, 1H), 10.76 (s, 1H), 9.30 (s, 1H), 8.73 (d, J=2.0 Hz, 1H), 8.63 (s, 1H), 8.52 (d, J=2.0 Hz, 1H), 8.26 (m, 3 H), 7.97 (m, 2H), 7.55 (d, J= 8.0 Hz, 1 H), 2.58 (s, 3H), 2.38 (s, 3H). MS(ESI), m/z: 502 ($M^+ + H^+$).

Example 20

3-(2-([1,2,4]triazolo[1,5-*a*]pyrimidin-6-yl)ethynyl)-4-methyl-*N*-(3-(4-methyl-1*H*-imidazol-1-yl)-5-(trifluoromethyl) phenyl)benzamide (D798)

[0113]



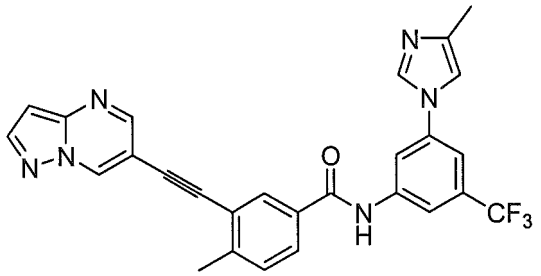
[0114] The compound was synthesized by using the procedure similar to that of Example 1.

[0115] ^{1}HNMR (400 MHz, *d*-DMSO), δ 2.17 (3H, s), 2.60 (3H, s), 7.48 (1H, s), 7.58 (1H, d, J=8.4 Hz), 7.74 (1H, s), 7.98 (1H, d, J= 8.0 Hz), 8.15 (1H, s), 8.22 (2H, m), 8.29 (1H, s), 8.78 (1H, s), 9.09 (1H, d, J=2.4 Hz), 9.88 (1H, d, J=2.4 Hz), 10.74 (1H, s). MS(ESI), m/z: 502 (M^++ H^+).

Example 21

4-methyl-*N*-(3-(4-methyl-1*H*-imidazol-1-yl)-5-(trifluoromethyl)phenyl)-3-(2-(pyrazolo[1,5-*a*]pyri midin-6-yl)ethynyl)benzamide (D822)

[0116]



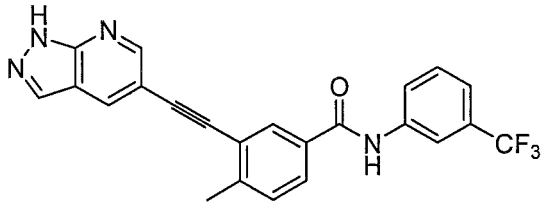
[0117] The compound was synthesized by using the procedure similar to that of Example 1.

[0118] ^{1}HNMR (400 MHz, *d-DMSO),* δ 2.18 (3H, s), 2.59 (3H, s), 6.84 (1H, m), 7.49 (1H, s), 7.57 (1H, d, *J*=8.4 Hz), 7.73 (1H, s), 7.98 (1H, dd, J= 8.0, 1.6 Hz), 8.16 (1H, s), 8.21 (2H, d, *J*= 2.0 Hz), 8.28 (1H, s), 8.34 (1H, d, J= 2.4 Hz), 8.71 (1H, d, J= 2.4 Hz), 9.57 (1H, d, J=2.0 Hz), 10.74 (1H, s). Ms(ESI), m/z: 502 (M^+ + H^+).

Example 22

3-(2-(1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)ethynyl)-4-methyl-*N*-(3-(trifluoromethyl)phenyl)benzamide (D821)

[0119]



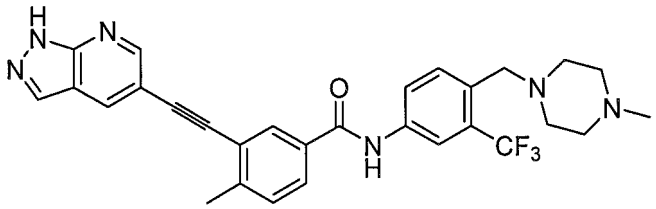
[0120] The compound was synthesized by using the procedure similar to that of Example 1.

[0121] ^{1}HNMR (400 MHz, *d-DMSO),* δ 13.94 (s, 1H), 10.59 (s, 1H), 8.75 (d, J=2.0 Hz, 1H), 8.54 (d, J=2.0 Hz, 1H), 8.26 (m, 3 H), 8.10 (d, J= 8.0 Hz, 1H), 7.95 (dd, J= 8.0,2.0 Hz, 1 H), 7.64 (m, 3H), 2.59 (s, 3H). MS(ESI), m/z: 421 (M^+ + H^+).

Example 23

3-(2-(1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)ethynyl)-4-methyl-*N*-(4-((4-methylpiperazin-1-yl)methyl)-3 -(trifluoromethyl) phenyl)benzamide (D824)

[0122]



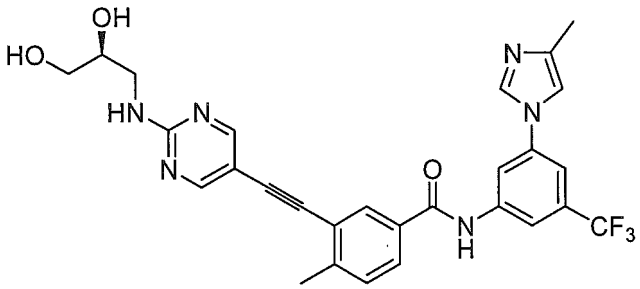
[0123] The compound was synthesized by using the procedure similar to that of Example 1.

[0124] ^{1}HNMR (400 MHz, *d-DMSO),* δ 13.92 (s, 1H), 10.55 (s, 1H), 8.72 (d, J=2.0 Hz, 1H), 8.52 (d, J=2.0 Hz, 1H), 8.17 (m, 3 H), 8.10 (d, J= 8.0 Hz, 1H), 7.92 (dd, J= 8.0,2.0 Hz, 1 H), 7.70 (d, J= 8.8 Hz, 1H), 7.53 (d, J= 8.0 Hz, 1H), 3.80 (s, 2H), 3.10 (brs, 8H), 2.71 (s, 3H), 2.57 (s, 3H). MS(ESI), m/z: 533, (M^++H^+).

Example 24

3-(2-(2-((*S*)-2,3-dihydroxypropylamino)pyrimidin-5-yl)ethynyl)-4-methyl-*N*-(3-(4-methyl-1*H*-imi dazol-1-yl)-5-(trifluoromethyl)phenyl)benzamide (D834)

[0125]



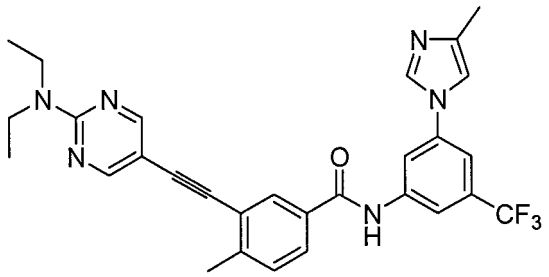
[0126] The compound was synthesized by using the procedure similar to that of Example 1.

[0127] ^{1}HNMR (400 MHz, *d*-DMSO), δ 2.31 (3H, s), 2.98 (1H, s), 3.65 (2H, br), 4.57 (1H, s), 4.78 (1H, s), 7.49 (4H, br), 7.70 (1H, br), 7.99 (2H, m), 8.22 (4H, s), 8.50 (2H, s), 10.67 (1H, s). MS(ESI), m/z: 551 (M^++ H^+).

Example 25

3-(2-(2-(diethylamino)pyrimidin-5-yl)ethynyl)-4-methyl-*N*-(3-(4-methyl-1*H*-imidazol-1-yl)-5-(trif luoromethyl)phenyl)benzamide (D807)

[0128]



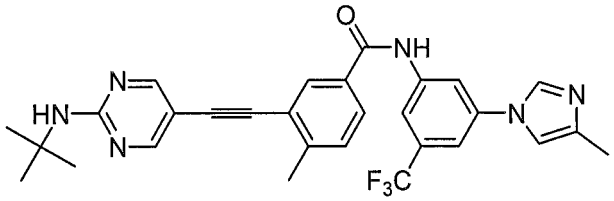
[0129] The compound was synthesized by using the procedure similar to that of Example 1.

[0130] ^{1}HNMR (400 MHz, *d*-DMSO), δ ppm 10.65 (s, 1H), 8.54 (br, 2H), 8.29 (s, 1H), 8.18 (m, 3H), 7.88 (d, J= 7.2 Hz, 1 H), 7.70 (s, 1H), 7.48 (m, 2H), 3.62 (m, 4H), 2.52 (s, 3H), 2.17 (s, 3H), 1.17 (t, *J*= 7.2 Hz, 6H). MS (ESI), m/z: 533 ($M^+ + H^+$).

Example 26

3-(2-(2-(tert-butylamino)pyrimidin-5-yl)ethynyl)-4-methyl-*N*-(3-(4-methyl-1*H*-imidazol-1-yl)-5-(t rifluoromethyl) phenyl)benzamide (D806)

[0131]



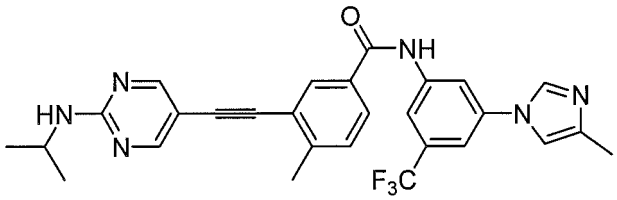
[0132] The compound was synthesized by using the procedure similar to that of Example 1.

[0133] ^{1}HNMR (400 MHz, *d*-DMSO), δ 10.69 (s, 1H), 8.51 (s, 2H), 8.29 (s, 1H), 8.20 (s, 1H), 8.16 (s, 1 H), 8.12 (s, 1H), 7.91 (dd, J= 6.8, 1.6 Hz, 1H), 7.73 (s, 1H), 7.52 (m, 2H), 7.38 (s, 1H), 2.55 (s, 3H), 2.18 (s, 3H), 1.39 (s, 9H). MS (ESI), m/z: 533, (M^++H^+).

Example 27

3-(2-(2-(isopropylamino)pyrimidin-5-yl)ethynyl)-4-methyl-*N*-(3-(4-methyl-1*H*-imidazol-1-yl)-5-(t rifluoromethyl) phenyl)benzamide (D752)

[0134]



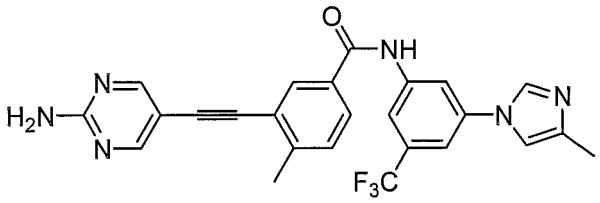
[0135] The compound was synthesized by using the procedure similar to that of Example 1.

[0136] ^{1}HNMR (400 MHz, *d*-DMSO), δ 10.69 (s, 1H), 8.51 (s, 2H), 8.29 (s, 1H), 8.20 (s, 1H), 8.16 (s, 1 H), 8.12 (s, 1H), 7.91 (dd, J= 6.8, 1.6 Hz, 1H), 7.73 (s, 1H), 7.52 (d, J= 8.0 Hz, 1H), 7.50 (m, 2H), 4.08 (m, 1H), 2.51 (s, 3H), 2.18 (s, 3H), 1.17 (d, J= 6.4 Hz, 6H). MS(ESI), m/z: 519, (M^++H^+).

Example 28

3-(2-(2-aminopyrimidin-5-yl)ethynyl)-4-methyl-*N*-(3-(4-methyl-1*H*-imidazol-1-yl)-5-(trifluorome thyl)phenyl)benzamide (D803)

[0137]



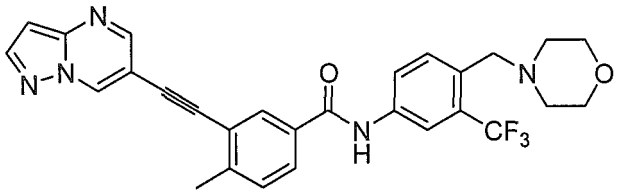
[0138] The compound was synthesized by using the similar procedure similar to that of Example 1.

[0139] ^{1}HNMR (400 MHz, d-DMSO), δ 10.69 (s, 1H), 8.48 (s, 2H), 8.31 (m, 2H), 8.16 (s, 1H), 8.13 (s, 1 H), 7.91 (d, J= 7.2 Hz, 1H), 7.74 (s, 1H), 7.51 (s, 2H), 7.20 (m, 2H), 2.52 (s, 3H), 2.19 (s, 3H). MS(ESI), m/z: 477, ($M^+ + H^+$).

Example 29

4-methyl-*N*-(4-(morpholinomethyl)-3-(trifluoromethyl)phenyl)-3-(2-(pyrazolo[1,5-*a*]pyrimidin-6-yl)ethynyl)benzamide (D931)

[0140]



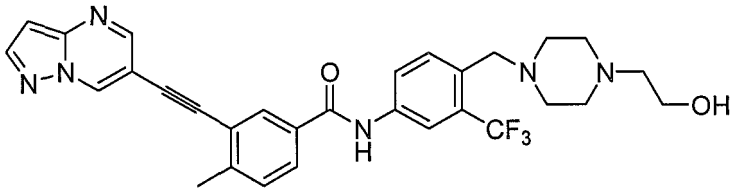
[0141] The compound was synthesized by using the procedure similar to that of Example 1.

[0142] ^{1}HNMR (400 MHz, *d*-DMSO), δ 2.39 (4H, brs), 2.59 (3H, s), 3.61 (6H, m), 6.85 (1H, s), 7.55 (1H, d, J=8.4 Hz), 7.72 (1H, d, J=8.4 Hz), 7.94 (1H, dd, J= 8.0, 1.6 Hz), 8.06 (1H, d, J=8.4 Hz), 8.21 (2H, dd, J=4.2, 1.6 Hz), 8.34 (1H, d, J=6.0 Hz), 8.72 (1H, d, J=2.0 Hz), 9.58 (1H, d, J=1.2 Hz), 10.56 (1H, s). MS(ESI), m/z: 520 (M^++H^+).

Example 30

***N*-(4-((4-(2-hydroxyethyl)piperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)-4-methyl-3-(2-(pyra zolo[1,5-*a*]pyrimidin-6-yl)ethynyl)benzamide (D942)**

[0143]



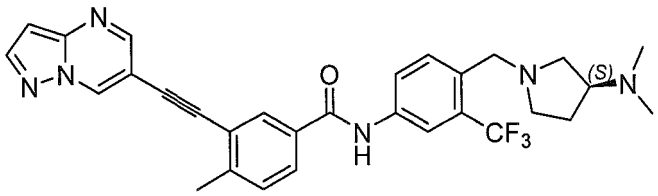
[0144] The compound was synthesized by using the procedure similar to that of Example 1.

[0145] ^{1}HNMR (400 MHz, *d*-DMSO), δ 2.39 (10H, m), 2.59 (3H, s), 3.49 (2H, m), 3.56 (2H, s), 4.36 (1H, br), 6.85 (1H, s), 7.55 (1H, d, J=8.0 Hz), 7.72 (1H, d, J=8.8 Hz), 7.94 (1H, dd, J= 8.0, 1.6 Hz), 8.05 (1H, d, J=8.4 Hz), 8.21 (2H, dd, J=4. 8, 1.6 Hz), 8.34 (1H, d, J=2.0 Hz), 8.72 (1H, d, J=2.0 Hz), 9.58 (1H, d, J=1.2 Hz), 10.55 (1H, s). MS(ESI), m/z: 563 (M^+ +H^+).

Example 31

(*S*)-*N*-(4-((3-(dimethylamino)pyrrolidin-1-yl)methyl)-3-(trifluoromethyl)phenyl)-4-methyl-3-(2-(pyrazolo[1,5-a] pyrimidin-6-yl)ethynyl)benzamide (D940)

[0146]



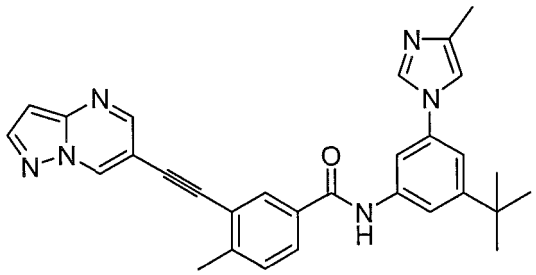
[0147] The compound was synthesized by using the procedure similar to that of Example 1.

[0148] ^{1}HNMR (400 MHz, *d*-DMSO), δ 1.62 (1H, m), 1.85 (1H, m), 2.12 (6H, s), 2.38 (1H, m), 2.59 (4H, m), 2.61 (1H, m), 2.83 (1H, m), 3.36 (2H, m), 3.56 (2H, s), 6.84 (1H, s), 7.55 (1H, d, J=8.0 Hz), 7.72 (1H, d, J=8.8Hz), 7.94 (1H, dd, J= 8.0, 1.6 Hz), 8.05 (1H, d, J=8.4 Hz), 8.19 (2H, s), 8.34 (1H, d, J=2.4 Hz), 8.72 (1H, d, J=2.0 Hz), 9.56 (1H, d, J=1.2 Hz), 10.55 (1H, s). MS(ESI), m/z: 547 ($M^+ + H^+$).

Example 32

***N*-(3-tert-butyl-5-(4-methyl-1*H*-imidazol-1-yl)phenyl)-4-methyl-3-(2-(pyrazolo[1,5-*a*] pyrimidin-6 -yl)ethynyl)benzamide (D941)**

[0149]



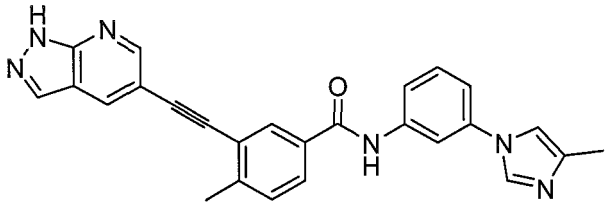
[0150] The compound was synthesized by using the procedure similar to that of Example 1.

[0151] ^{1}HNMR (400 MHz, *d*-DMSO), δ 1.34 (9H, s), 2.18 (3H, s), 2.59 (3H, m), 6.84 (1H, s), 7.30 (1H, s), 7.40 (1H, br), 7.55 (1H, d, J=8.0 Hz), 7.38 (1H, s), 7.97 (2H, m), 8.08 (1H, br), 8.21 (1H, d, J=1.6 Hz), 8.34 (1H, d, J=2.4 Hz), 8.72 (1H, d, J=2.0 Hz), 9.57 (1H, d, J=1.2 Hz), 10.42 (1H, s). MS(ESI), m/z: 489 ($M^+ + H^+$).

Example 33

3-(2-(1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)ethynyl)-4-methyl-*N*-(3-(4-methyl-1*H*-imidazol-1-yl)phenyl)benzamide (D967)

[0152]



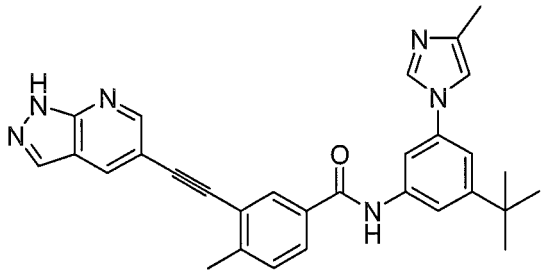
[0153] The compound was synthesized by using the procedure similar to that of Example 1.

[0154] ^{1}HNMR (400 MHz, *d*-DMSO), 13.95 (s, 1H), 10.47 (s, 1H), 8.74 (s, 1H), 8.52 (s, 1H), 8.22 (m, 2 H), 8.06 (m, 2H), 7.94 (d, J= 7.6 Hz, 1 H), 7.76 (d, J= 8.0 Hz, 1H), 7.53 (m, 2H), 7.35 (m, 2H), 2.59 (s, 3H), 2.18 (s, 3H). MS(ESI), m/z: 433 (M+ + H+).

Example 34

3-(2-(1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)ethynyl)-*N*-(3-tert-butyl-5-(4-methyl-1*H*-imidazol-1-yl)phe nyl)-4-methylbenzamide (D968)

[0155]



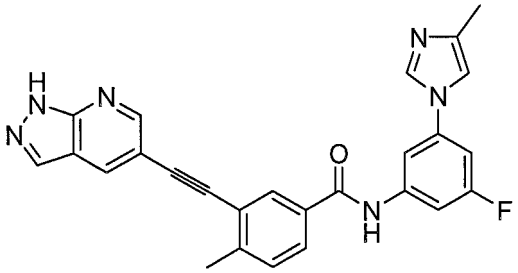
[0156] The compound was synthesized by using the procedure similar to that of Example 1.

[0157] ^{1}HNMR (400 MHz, d-DMSO), δ 13.95 (s, 1H), 10.42 (s, 1H), 8.75 (s, 1H), 8.54 (s, 1H), 8.23 (m, 2H), 8.07 (s, 1H), 7.96 (m, 2H), 7.75 (s, 1H), 7.54 (d, J= 8.0 Hz, 1 H), 7.31 (s, 2H), 7.30 (d, J= 4.2 Hz, 1 H), 2.59 (s, 3H), 2.18 (s, 3H), 1.34 (s, 9H). MS(ESI), m/z: 489 (M^++ H^+).

Example 35

3-(2-(1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)ethynyl)-*N*-(3-fluoro-5-(4-methyl-1*H*-imidazol-1-yl)phenyl) -4-methylbenzamide (D963)

[0158]



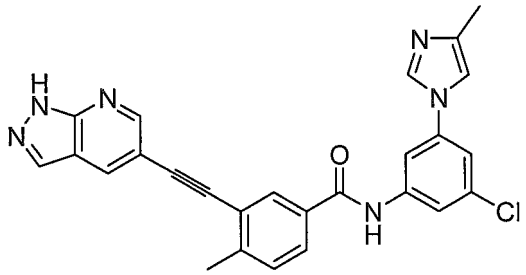
[0159] The compound was synthesized by using the procedure similar to that of Example 1.

[0160] ^{1}HNMR (400 MHz, *d*-DMSO), δ 13.94 (s, 1H), 10.58 (s, 1H), 8.74 (s, 1H), 8.51 (s, 1H), 8.22 (d, J=8.0 Hz, 2H), 8.11 (s, 1H), 7.93 (d, J= 7.6Hz, 1H), 7.83 (s, 1 H), 7.71 (d, J= 7.2 Hz, 1H), 7.54 (d, J= 8.0 Hz, 1 H), 7.39 (s, 1H), 7.33 (d, J= 10 Hz, 1H), 2.58 (s, 3H), 2.17 (s, 3H). MS(ESI), m/z: 451 (M^+ + H^+).

Example 36

3-(2-(1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)ethynyl)-*N*-(3-chloro-5-(4-methyl-1*H*-imidazol-1-yl)phenyl) -4-methylbenzamide (D964)

[0161]



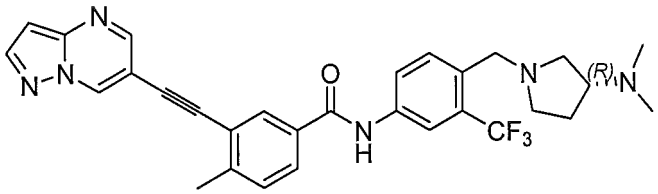
[0162] The compound was synthesized by using the procedure similar to that of Example 1.

[0163] ^{1}HNMR (400 MHz, *d*-DMSO), δ 13.94 (s, 1H), 10.52 (s, 1H), 8.78 (s, 1H), 8.48 (s, 1H), 8.21 (s, 1H), 8.16 (s, 1H), 8.11 (s, 1H), 7.95 (s, 1H), 7.88 (s, 2H), 7.49 (s, 2H), 7.36 (s, 1H), 2.57 (s, 3H), 2.15 (s, 3H). MS(ESI), m/z: 468 ($M^+ + H^+$).

Example 37

(*R*)-*N*-(4-((3-(dimethylamino)pyrrolidin-1-yl)methyl)-3-(trifluoromethyl)phenyl)-4-methyl-3-(2-(pyrazolo[1,5-*a*] pyrimidin-6-yl)ethynyl)benzamide (D943)

[0164]



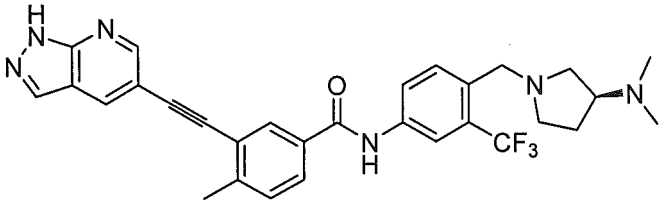
[0165] The compound was synthesized by using the procedure similar to that of Example 1.

[0166] ^{1}HNMR (400 MHz, *d*-DMSO), δ 1.62 (1H, m), 1.85 (1H, m), 2.12 (6H, s), 2.37 (1H, m), 2.59 (4H, m), 2.61 (1H, m), 2.83 (1H, m), 3.36 (2H, m), 3.56 (2H, s), 6.84 (1H, s), 7.55 (1H, d, J=8.0 Hz), 7.73 (1H, d, J=8.8 Hz), 7.95 (1H, dd, J= 8.0, 1.6 Hz), 8.05 (1H, d, J=8.4 Hz), 8.19 (2H, s), 8.34 (1H, d, J=2.4 Hz), 8.72 (1H, d, J=2.0 Hz), 9.56 (1H, d, J=1.2 Hz), 10.55 (1H, s). MS (ESI), m/z: 547 ($M^+ + H^+$).

Example 38

(*S*)-3-(2-(1*H* pyrazolo[3,4-b]pyridin-5-yl)ethynyl)-*N*-(4-((3-(dimethylamino)pyrrolidin-1-yl)meth yl)-3-(trifluoromethyl)phenyl)-4-methylbenzamide (D966)

[0167]



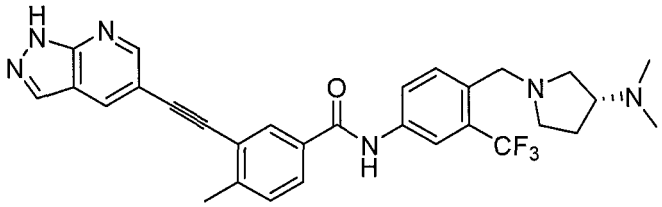
[0168] The compound was synthesized by using the procedure similar to that of Example 1.

[0169] ^{1}HNMR (400 MHz, *d*-DMSO), δ 13.95 (s, 1H), 10.55 (s, 1H), 8.75 (s, 1H), 8.54 (s, 1H), 8.24 (m, 3H), 8.09 (d, J=8.4 Hz, 1H), 7.95 (d, J= 8.4 Hz, 1H), 7.72 (d, J=8.4 Hz, 1 H), 7.55 (d, J= 8.0 Hz, 1H), 3.74 (m, 2H), 3.52 (m, 1H), 3.17 (s, 1H), 2.88 (br, 1H), 2.68 (m, 1H), 2.59 (s, 3H), 2.43 (m, 1H), 2.17 (s, 6H), 1.91 (s, 4H), 1.70 (m, 2H). MS(ESI), m/z: 547 ($M^+ + H^+$).

Example 39

(*R*)-3-(2-(1*H*-pyrazolo[3,4-b]pyridin-5-yl)ethynyl)-*N*-(4-((3-(dimethylamino)pyrrolidin-1-yl)meth yl)-3-(trifluoromethyl)phenyl)-4-methylbenzamide (D965)

[0170]



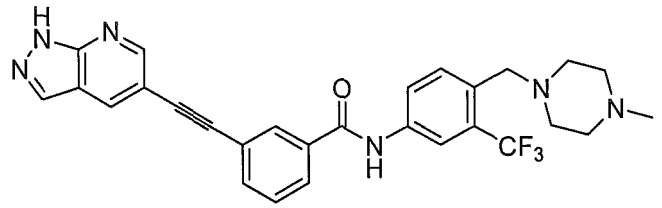
[0171] The compound was synthesized by using the procedure similar to that of Example 1.

[0172] ^{1}HNMR (400 MHz, d-DMSO), δ 13.95 (s, 1H), 10.55 (s, 1H), 8.76 (s, 1H), 8.54 (s, 1H), 8.24 (m, 3H), 8.09 (d, J=8.4 Hz, 1H), 7.94 (d, J= 8.4 Hz, 1H), 7.72 (d, J=8.4 Hz, 1 H), 7.54 (d, J= 8.0 Hz, 1H), 3.74 (m, 2H), 3.51 (m, 1H), 3.17 (s, 1H), 2.88 (br, 1H), 2.68 (m, 1H), 2.59 (s, 3H), 2.43 (m, 1H), 2.17 (s, 6H), 1.91 (s, 4H), 1.71 (m, 2H). MS(ESI), m/z: 547 + H^+).

Example 40

3-(2-(1*H*-pyrazolo[3,4-b]pyridin-5-yl)ethynyl)-*N*-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoro methyl)phenyl) benzamide (D1072)

[0173]



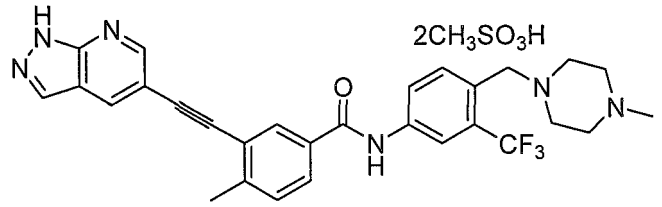
[0174] The compound was synthesized by using the procedure similar to that of Example 1.

[0175] ^{1}HNMR (400 MHz, *d*-DMSO), δ 10.62 (s, 1H), 8.73 (d, J=2.0 Hz, 1H), 8.52 (d, J=2.0 Hz, 1H), 8.21-8.23 (m, 3H), 8.07 (d, J=8.4 Hz, 1H), 8.01 (d, J=7.6 Hz, 1H), 7.83 (d, J=7.6 Hz, 1H), 7.72 (d, J=7.6 Hz, 1H), 7.64 (t, J=8.0 Hz, 1H), 3.57 (s, 2H), 2.39 (br, 8H), 2.16 (s, 3H). MS (ESI), m/z:.519 + H^+).

Example 41

3-(2-(1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)ethynyl)-4-methyl-*N*-(4-((4-methylpiperazin-1-yl)methyl)-3 -(trifluoromethyl) phenyl)benzamide dimesylate (D824 dimesylate)

[0176]



[0177] Add 2.24 g methanesulfonic acid (23.31 mmol) dropwise into 3.1 g D824 (5.83 mmol) in 150 mL ethanol into in a 500 mL round flask. The reaction mixture turns clear when heated to boiling. After refluxing for 4 h, the reaction is

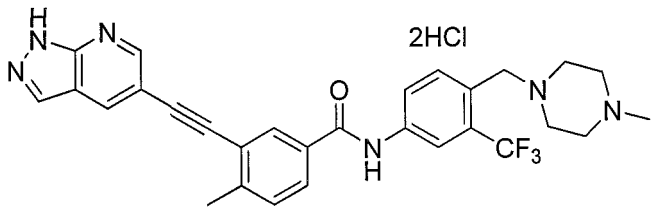
cooled to room temperature, And white solid is collected and washed three times with ethanol after filtration. Then 3.86 g product was obtained as pale yellow solid after further dryness in vacuum (90%)

[0178] ^{1}HNMR (400 MHz, d-DMSO), δ10.66 (s, 1H), 8.73 (d, J=2.0 Hz, 1H), 8.52 (d, J=1.6Hz, 1H), 8.28 (d, J=1.6 Hz, 1H), 8.23 (s, 1H), 8.19 (s, 1H), 8.16 (d, J=7.6 Hz, 1H), 7.92 (dd, J=8.0,1.6 Hz, 1H), 7.78 (d, J=8.4 Hz, 1H), 7.53 (d, J=8.4 Hz, 1H), 4.00 (s, 2H), 3.19 (br, 6H), 2.85 (s, 3H), 2.77 (br, 2H), 2.58 (s, 3H), 2.41 (s, 6H). MS (ESI), m/z:.533 , 627

Example 42

3-(2-(1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)ethynyl)-4-methyl-*N*-(4-((4-methylpiperazin-1-yl)methyl)-3 -(trifluoromethyl) phenyl)benzamide dihydrochloride (D824 dihydrochloride)

[0179]



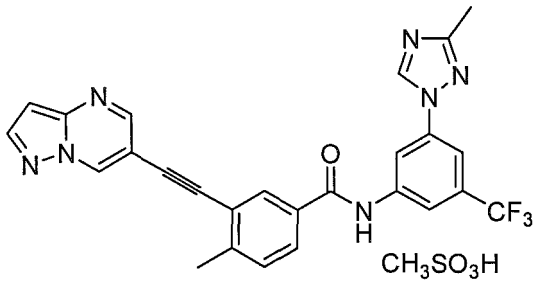
[0180] Add 3.0 g D824 (5.64 mmol) in 100 mL ethanol in a 250 mL round flask , and into hydrochloride gas is pumped into the mixture. The mixture turns clear and after stirring for 16 h, yellow solid is precipitated. The solid was collected and washed three times with ethanol and is dried in vacuum to afford 2.63 g desired product (82%).

[0181] ^{1}HNMR (400 MHz, d-DMSO), δ11.36 (br, 1H), 10.74 (s, 1H), 8.74 (d, J=2.0 Hz, 1H), 8.53 (d, J=2.0 Hz, 1H), 8.33 (d, J=1.6 Hz, 1H), 8.18-8.23 (m, 3H), 8.04 (br, 1H), 7.96 (dd, J=8.0, 1.6 Hz, 1H), 7.54 (d, J=8.4 Hz, 1H), 4.15 (br, 2H), 3.55 (m, 6H), 3.08 (br, 2H), 2.80 (s, 3H), 2.59 (s, 3H). MS (ESI), m/z:.533

Example 43

4-methyl-*N*-(3-(3-methyl-1*H*-1,2,4-triazol-1-yl)-5-(trifluoromethyl)phenyl)-3-(2-(pyrazolo[1,5-*a*]*p* yrimidin-6-yl) ethynyl)benzamide mesylate (D818 mesylate)

[0182]



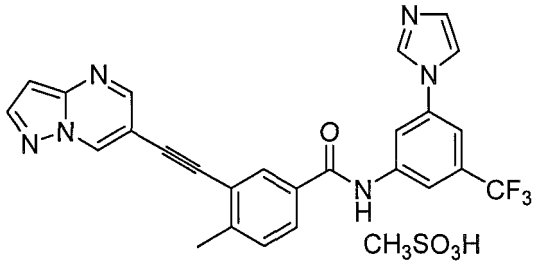
[0183] The compound was synthesized by using the procedure similar to that of Example 41.

[0184] ^{1}HNMR (400 MHz, d-DMSO), δppm 10.80 (s, 1H), 9.57 (s, 1H), 9.34 (s, 1H), 8.72 (s, 1H), 8.64 (s, 1H), 8.34 (s, 1H), 8.25 (d, J=7.6 Hz, 1H), 7.98 (s, 1H), 7.55 (d, J=7.6 Hz, 1H), 6.84 (s, 1H), 2.60 (s, 3H), 2.39 (s, 3H), 2.38 (s, 3H). MS (ESI), m/z: 502

Example 44

***N*-(3-(1*H*-imidazol-1-yl)-5-(trifluoromethyl)phenyl)-4-methyl-3-(2-(pyrazolo[1,5-a]pyrimidin-6-y l)ethynyl)benzamide mesylate (D819 mesylate)**

[0185]



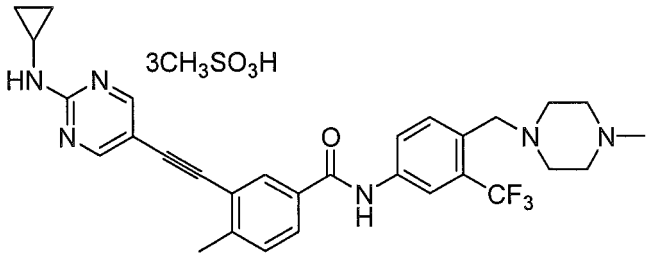
[0186] The compound was synthesized by using the procedure similar to that of Example 41.

[0187] ^{1}HNMR (400 MHz, d-DMSO), δ10.93 (s, 1H), 9.65 (s, 1H), 9.58 (s, 1H), 8.72 (d, J=2.0 Hz, 1H), 8.57 (s, 1H), 8.34 (d, J=2.0 Hz, 1H), 8.30 (s, 1H), 8.24 (s, 1H), 8.00 (s, 1H), 7.98 (s, 1H), 7.89 (s, 1H), 7.58 (d, J=8.0 Hz, 1H), 6.85 (s, 1H), 2.61 (s, 3H), 2.33 (s, 3H). MS (ESI), m/z: 487

Example 45

3-(2-(2-(cyclopropylamino)pyrimidin-5-yl)ethynyl)-4-methyl-*N*-(4-((4-methylpiperazin-1-yl)meth yl)-3-(trifluoromethyl)phenyl)benzamide trimesylate (D825 trimesylate)

[0188]



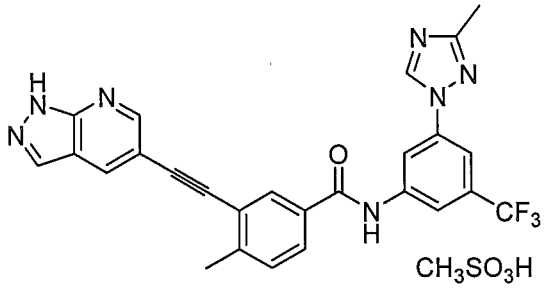
[0189] The compound was synthesized by using the procedure similar to that of Example 41.

[0190] ^{1}HNMR (400 MHz, D20), δ ppm 8.23 (s, 1H), 7.89 (s, 1H), 7.71 (d, J=8.8 Hz, 1H), 7.64 (s, 1H), 7.57 (d, J=8.8 Hz, 1H), 7.52 (d, J=8.0 Hz, 1H), 7.14 (s, 1H), 4.32 (s, 2H), 3.54 (br, 8H), 2.92 (s, 3H), 2.70 (s, 9H), 2.45 (br, 1H), 2.24 (s, 3H), 1.08 (t, J=6.8 Hz, 1H), 0.78 (d, J=6.8 Hz, 2H), 0.49 (s, 2H). MS (ESI), m/z: 549, 644

Example 46

3-(2-(1*H*-pyrazolo[3,4-b]pyridin-5-yl)ethynyl)-4-methyl-*N*-(3-(3-methyl-1*H*-1,2,4-triazol-1-yl)-5-(trifluoromethyl) phenyl)benzamide mesylate (D835 mesylate)

[0191]



[0192] The compound was synthesized by using the procedure similar to that of Example 41.

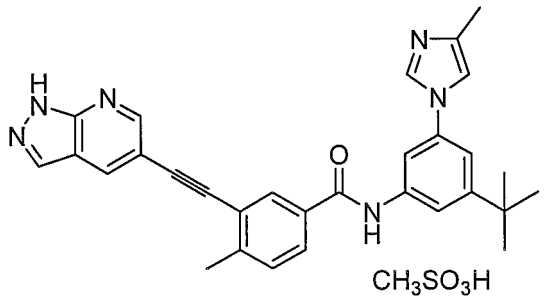
[0193] ^{1}HNMR (400 MHz, d-DMSO), δ ppm 10.78 (s, 1H), 9.37 (s, 1H), 8.73 (d, J=2.0 Hz, 1H), 8.64 (s, 1H), 8.52 (d, J=1.6 Hz, 1H), 8.22-8.27 (m, 3H), 7.97 (s, 1H), 7.94 (s, 1H), 7.52 (d, J=8.0 Hz, 1H), 2.55 (s, 3H), 2.43 (s, 3H), 2.39 (s,

3H). MS (ESI), m/z: 502

Example 47

3-(2-(1*H*-pyrazolo[3,4-b]pyridin-5-yl)ethynyl)-*N*-(3-tert-butyl-5-(4-methyl-1*H*-imidazol-1-yl)phe nyl)-4-methylbenzamide mesylate (D968 mesylate)

[0194]



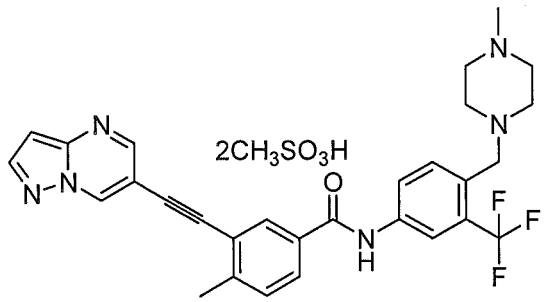
[0195] The compound was synthesized by using the procedure similar to that of Example 41.

[0196] 1HNMR (400 MHz, d-DMSO), δ ppm 13.96 (s, 1H), 10.60 (s, 1H), 9.58 (d, J=1.2 Hz, 1H), 8.74 (d, J=2.0 Hz, 1H), 8.54 (d, J=2.0 Hz, 1H), 8.22-8.24 (m, 3H), 8.01 (s, 1H), 7.94 (d, J=8.0 Hz, 1H), 7.85 (s, 1H), 7.55 (d, J=8.0 Hz, 1H), 7.49 (s, 1H), 2.60 (s, 3H), 2.36 (s, 3H), 2.31 (s, 3H), 1.36 (s, 9H). MS (ESI), m/z: 489

Example 48

4-methyl-N-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)-3-(2-(pyrazolo[1,5-a] pyrimidin-6-yl) ethynyl)benzamide dimesylate (D856 dimesylate)

[0197]



[0198] The compound was synthesized by using the procedure similar to that of Example 41.

[0199] 1HNMR (400 MHz, d-DMSO), δ ppm 10.63 (S,1H) 9.58 (s,1H), 8.72 (d,J=2.0Hz,1H),8.34 (d,J=2.0Hz,1H), 8.25 (d, J=2.0 Hz, 1H), 8.20 (d, J=2.0 Hz, 1H), 8.14 (d, J=8.8 Hz, 1H),7.97 (d, J=8.0 Hz, 1H), 7.75 (d, J=8.4 Hz, 1H), 7.55 (d, J=8.0 Hz, 1H), 6.85 (d, J=1.6 Hz, 1H), 3.82 (s, 2H), 3.41-3.47 (m, 4H), 3.07-3.23 (m, 4H), 2.83 (s, 3H), 2.60 (s, 3H),2.36 (s,6H). MS (ESI), m/z: 533, 627

Example 49

[0200] The heterocyclic alkynyl benzene compounds at different concentrations ($1 \times 10^{-10} \sim 1 \times 10^{-5}$M) were incubated for 72 hours individually applied to 6 cell lines K562 (human CML cell line), MOLT-4 (human ALL cell line), U937 (human CML cell line), MEG-01(human CML cell line), L78 (human lung cancer cell line), Ba/F3-T315I (mice Pro-B cells transformed with Bcr-Ab1T315I and STI571-resistant cell line). After incubation for 72 hrs, cell proliferation was then determined by MTT assay or CCK8 assay, and 4 hr incubation is further conducted, the absorbance at 570 nm (CCK8, 450nm, 650 nm) was measured using enzyme Microplate Reader. The results showed that treatment of the heterocyclic alkynyl benzene compounds could obviously decrease absorption of MTT by all different cells and significantly inhibit the pro-

liferation of the cells mentioned above, especially K562 cells (human CML line) and Ba/F3T315I (mice Pro-B cells transformed with Bcr-AblT315I and STI571-resistant), and the inhibition was dose-dependent. Based on the inhibition potency of the heterocyclic alkynyl benzene compounds on the cell proliferation, IC_{50} values were calculated and summarized in the Table 1 and Table 2 (The compounds used were synthesized by Examples 1-40, and the compounds are marked with Drug No. series in Table 1).

Table 1. IC_{50} values of part of the compounds on the tumor cell proliferation. (The unit is μM if no indication).

Drug No.	K562 (human chronic myelogenous leukemia cell line)	MOLT-4 (Human acute lymphoblastic leukemia cell line	U937 Cell line	MEG-01 1 (Human megakaryoblastic leukaemia cell line)	K562R cells	BAF3-T315I cells	L78 (Lung cancer cell line)
D729	2.09 nM	5.75		6.58	0.07269	0.04968	
D747	2.6 nM	>10	11.54	7.537	0.096	0.09973	10.57
D752	0.003477	12.67	8.988	22.6	*0.84*	1.027	>10
D755	7.595nM	>10	>10	>10	0.22	0.06097	11.76
D767	0.2081nM	>100nM	>100nM	>100nM	0.089	0.00424	11.77nM
D768	2.597nM	>100nM	>100nM	>100nM	0.16	5.993	>100nM
D770	99.51nM	>100nM	>100nM	3684nM	0.16	5.993	>100nM
D771	128.6nM				1735	>10	>100nM
D797	>100nM	>10nM	>100nM	>100nM	3.366	12.95	
D798	33.99nM	>10nM	>100nM	>100nM	1.222	1.864	
D799	36.2nM	>100nM	>100nM	>100nM	0.6118	>10	
D800	1.097nM	>100nM	>100nM	>100nM	0.08966	0.09979	
D801	141.3nM	>100nM	>100nM	563806nM	0.9063	10.45	
D803	1.517nM	132nM	147.1nM	>100nM	0.06333	0.1245/0.08580	
D806	>100nM	>100nM	147.3nM	131.3 nM		1.894	
D807	128.5 nM	>100nM	126.3nM	>100nM	14.14	13.45	
D809	>100nM	>100nM	>100nM	114.9 nM	0.1769	0.1022/0.07115	
D818	1.383 nM	>100 nM	>100nM	210.1 nM	0.1423	0.3936	
D819	1.504 nM	145.8 nM	2208 nM	122 nM	0.1456	3.12	
D820	1.374 nM	134.3 nM	>100nM	>100 nM	0.03518	0.2763	
D821	0.7241nM	>100nM			0.058	0.01948	
D822	4.343nM	>100nM			0.58	1.104	
D823	>100nM	>100nM			9.63	>10	
D824	0.4941nM	>100nM			0.014	0.001645	
D825	1.882nM	92.89nM			0.05	0.0157	
D827	2.683nM	1851nM			0.059	0.0298	
D828	30.93nM	>100nM			3.07	2.477	
D831	0.4661 nM		7134 nM		0.054	0.0368	
D832	7.273 nM		>100nM		0.2	0.02184	
D834	8.703 nM		>100nM		0.19	0.2151	
D835	0.4018 nM		>100nM		0.026	0.008578	

(continued)

Drug No.	K562 (human chronic myelogenous leukemia cell line)	MOLT-4 (Human acute lymphoblastic leukemia cell line	U937 Cell line	MEG-01 1 (Human megakaryoblastic leukaemia cell line)	K562R cells	BAF3-T315I cells	L78 (Lung cancer cell line)
D855	0.03455	>10	7.167		1.02	1.84	
D856	0.00224	0.4994	2.001		0.067	0.0108	
D931	>10	7.429	4.596		0.51	2.754	
D940	0.0657	0.9548	0.7154		0.032	0.2447	
D941	0.002341	0.3397	0.6959		0.41	0.1022	
D942	0.003542	0.6737	1.298		0.04404	0.1016	
D943	0.008305	1.626	2.121		0.3197	0.6183	
D963	0.0009975		>1		0.07505	0.2426	
D964	0.0009378		>1		0.032	0.02423	
D965	0.0005879		0.8171		0.0057	0.006867	
D966	0.0003239		0.01854			0.01381	
D967	0.000314		5.832		0.2066	0.7981	
D968	0.0007014		>1		0.032	0.006362	

[0201] Note: K562R: imatinib-resistant cell line, and was obtained by the patent applicants themselves through induction, and this cell line can be guaranteed to be released within 20 years since the date of the application. Ba/F3-T315: Ba/F3 cell line stably expressing BCR/ABL (mutation of T315I). This cell line was obtained by the patent applicants themselves and can be guaranteed to be released within 20 years since the date of the application.

Table 2. IC_{50} (μM) value of part of the compound on the cell proliferation of Ba/F3 cells (carrying mutation of T315I Bcr-Abl and STI571- resistant).

Drug No.	Ba/F3 (T3151)
D729	<0.1

Example 50

[0202] K562 cells (human CML cell line expressing native Bcr-Abl) were inoculated into the right flank of each BALB/C-nu nude mouse (5×106 cells/ mouse), and when the mean tumor volume reached 100-200 mm^3, mice were grouped and administrated orally. The doses for each compound varied within the range of 0, 2, 5, 25 and 50mg/kg/, po, qd, and each group had 8~10 mice. Tumor volume and body weight were monitored once every 2 days (In each group, the tumor volume and body weight at beginning of the day were recorded). Tumor volume was calculated as π/6*a*b*b.L×W2/2 (a and b are the length and width of the tumor, respectively). The data showed that the hydrochloride form of D747, mesylate form of D822, D767, D800 and dimethylate form of D824 did not cause the body weight loss. These compounds showed good anti-tumor activities and the body weight gain could be observed at the effective doses of these compounds. The hydrochloride form of D747, mesylate forms of D822, D767, D800 and dimethylate form of D824 could completely inhibit the tumor growth at the dose of 25, 25, 25, 25 and 5mg/kg, respectively, and they could eradicate the tumor cells and heal the tumor. The hydrochloride form of D747 and mysylate form of D822 showed better anti-tumor effect than imatinib. The results were shown in Drawings as Figure 1, 2, 3, 4, 5, 6, 7 and 8.

Example 51

[0203] Ba/F3-Bcr/ABL-T315Icells were inoculated into the right flank of each SCID nude mouse (2×106 cells/ mouse). When the mean tumor volume reached 300-500 mm^3, mice were grouped and administered orally. Different dosage group and administration intervals were set, 50mg/kg, 20mg/kg, and 10mg/kg po, q2d or qd, and each group had 8~10

mice. Tumor volume and body weight were monitored once every 2 days (In each group, the tumor volume and body weight at beginning of the day were recorded). Tumor volume was calculated as $\pi/6*a*b*b.L\times W2/2$ (a and b are the length and width of the tumor, respectively). The data showed that the dimesylate form of D824 at the dose of 25 mg/kg, po, q2d or qd could help the body weight gain and almost completely suppressed the tumor growth. The dimesylate forms of D856 and methylate form of D968 could inhibit the tumor growth at the dose of 20mg/kg, , po, q2d or qd . The results were shown in Drawings as Figure 9, 10, 11, 12, 13, 14, 15, 16.

Example 52

[0204] Pharmacokinetics and bioavailability in rats. SD rats (2 males and 2 females) were administrated once through oral gavage (25 mg/kg) or through intravenous injection (2.5~10 mg/kg), respectively. The blood samples were collected at the proper time points after administration, add heparin-anticoagulant, and the supernatants of the blood samples were colleted (3000rpm, 10min) and stored at -20°C for HPLC-MS analysis. After protein-precipitation procedure with acetonitrile, supernatants were collected after 3000rpm, 10min for analysis with HPLC-MS. The data were analyzed with software DAS2.0 to separately acquire the parameters of compartment models and non-compartment models. The bioavailability was calculated according to AUCdata. The corresponding pharmaceutical acceptable salt forms of the compounds D747, D752, D755, D767, D800, D822, D824, D831, D856 and D825 had adequate pharmacokinetics parameters and they are suitable for further *in vivo* pharmacodynamic study. The results are summarized in Table 3.

Table 3 Pharmacokinetics data of some of the compounds.

	Administration route	Animal Number	Dose level mg/kg	AUC(0-∞) ug/L*h	Cmax ug/1	T1/2 (Hr)	Tmax (Hr)	BA(% Oral bioavailability)
D747 hydrochloride salt	PO	♀2 ♂2	25	251684.381	6205	48.701	4.5	35.3
	IV	♀2 ♂2	10	285187.275	49750	71.753	0.033	
D822 mesylate salt	PO	♀2 ♂2	25	10736.39	814	8.04	3	31.2
	IV	♀2 ♂2	10	13754.54	23056.25	3.15	0.033	
D752 mesylate salt	PO	♀2 ♂2	20	70411.149	1900	7.548	20	11.54
	IV	♀2 ♂2	10	304881.256	19606.25	43.854	0.033	
D800 hydrochloride salt	PO	♀2 ♂2	5	35809.5	10975	7.5	0.033	27.1
	IV	♀2 ♂2	25	48574.3	3090	7.8	2	
D767 hydrochloride salt	PO	♀2 ♂2	25	62208	3615	7.179	7.75	19
	IV	♀2 ♂2	5	65534	15319	5.596	0.033	
D755 hydrochloride salt	PO	♀2 ♂2	25	23700	1255	8.298	6.25	63.3
	IV	♀2 ♂2	2.5	3745	510	26.181	0.033	
D648 hydrochloride salt	PO	♂4	25	1471.701	509.25	1.117	1	10.9
	IV	♂4	5	2694.862	2602.5	3.01	0.183	
D856 dimesylate salt	PO	♂4	25	31829.108	899.5	22.199	6.5	78
	IV	♂4	5	8165.792	934.375	19.97	0.033	
D753 mesylate salt	PO	♂4	25	1080.493	147.05	18.275	4	1.6
	IV	♂4	5	13128.922	7418.75	58.193	0.083	
D680 mesylate salt	PO	♀2 ♂2	50	4847.264	862	2.728	2	8.7
	IV	♀2 ♂2	10	11175.59	14168.75	3.699	0.033	

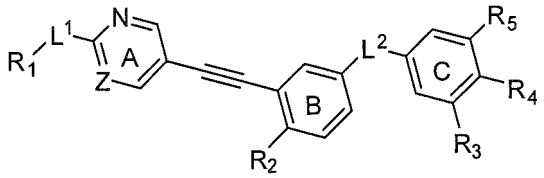
(continued)

	Administration route	Animal Number	Dose level mg/kg	AUC(0-∞) ug/L*h	Cmax ug/1	T1/2 (Hr)	Tmax (Hr)	BA(% Oral bioavailability)
D824 hydrochloride salt	PO	♂4	25	7108.253	390.5	10.55	6	48.7
	IV	♂4	5	2922.411	1375.625	5.557	0.067	
D767 mesylate salt	PO	♂4	25	27850.615	2322.5	5.949	2.75	9.4
	IV	♂4	5	59222.45	14093.75	4.471	0.033	
D835 hydrochloride salt	PO	♂4	25	3467.961	233	8.813	4	8.1
	IV	♂4	5	8536.548	975.625	16.863	0.033	
D831 mesylate salt	PO	♂4	25	73862.101	9515	4.665	2.25	13.8
	IV	♂3	5	107229.516	64250	5.237	0.033	
D824 dimesylate salt	PO	♂4	25	12628.23	774.75	8.72	4.25	58.7
	IV	♂4	5	4304.444	2235.625	6.098	0.033	
D825 mesylate salt	PO	♂4	25	34561.045	1700	11.492	4.75	58.5
	IV	♂4	5	11819.424	2331.25	11.693	0.033	

[0205] The above description is the detail and specific explanation for embodiments of the present invention, but it cannot be understood as the restrictions on the scope of the present invention. It should be noted that one having ordinary skill in the art would make many equivalent modification and improvement within spirit of the present invention, which should be included in the protection scope of the present invention.

Claims

1. Heterocyclic alkynyl benzene compounds having formula (I) and their pharmaceutical acceptable salts, prodrugs, or stereoisomers,

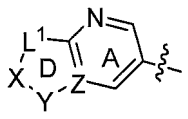


(I)

wherein Z is independently selected as CH or N;
L^1 is independently selected from NH, -N=, CH;
L^2 is independently selected as -CONH- or NHCO-;
R_1 is independently selected from:

1) H;
2) C1~C6 alkyl;
3) C_3~C_6 cycloalkyl;
4) C_1~C_5 alkyl substituted by one or two hydroxyl group(s);
5) Phenyl;
6) Groups which can fuse A ring through L^1 in Z atom site to form fused

penta-heterocycles containing 1~3 N atoms like



Wherein, X, Y, Z are independently selected from N, CH; ring D is an aromatic heterocycle containing 1~3 N atoms;
R_2 is independently selected from

1) H;
2) Halogen;
3) C_1~C_5 alkyl;
4) C_3~C_6 cycloalkyl;
5) C_1~C_5 alkyl containing F;

R_3 is independently selected from:

1) H;
2) Halogen;
3) C_1~C_4 alkyl;
4) C_3~C_6 cycloalkyl;
5) C_1~C_4 alkyl containing F;

when R_5 is H, R_4 is independently selected from

1) H;
2) $(CH_2)_nNR_6R_7$;
3) $(CH_2)_n$-Het^1;

Or, when R_4 is H, R_5 is independently selected as

1) H;
2) Het^2;

wherein, n is independently selected as 0 or 1;
Het^1 is defined as nonaromatic heterocycles containing 1~3 N atoms; Het^2 is defined as aromatic five-menmber heterocycles containing 1~3 hetero atoms like N, O, or S; alkyl, cycloalkyl or NR_6R_7 will be incorporated into any C or N position which can be substituted in Het^1 and Het^2;
R_6 or R_7 is independently selected from:

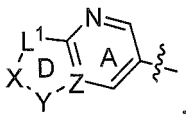
1) H;
2) C_1~C_3 alkyl;
3) C_1~C_3 alkyl containing F;
4) C_3~C_6 cycloalkyl;

Or, R_6 and R_7 can further form penta-, hexa-, hepta- or octatomic ring through C, O, N, S atoms.

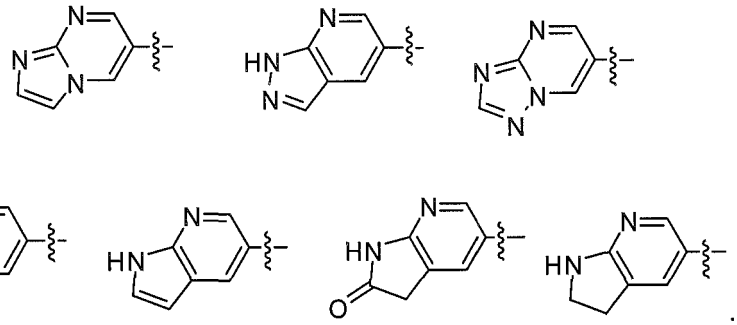
2. Heterocyclic alkynyl benzene compounds and their pharmaceutical acceptable salts, prodrugs, or stereoisomers according to Claim 1,
wherein Z is N, L^1 is NH,
$R^1$is selected from:

1) methyl, ethyl, isopropyl, tert-butyl;
2) cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl.

3. Heterocyclic alkynyl benzene compounds and their pharmaceutical acceptable salts, prodrugs, or stereoisomers according to claim 1, wherein R_1forms fused ring with A ring as



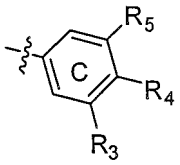
The fused ring is selected as:



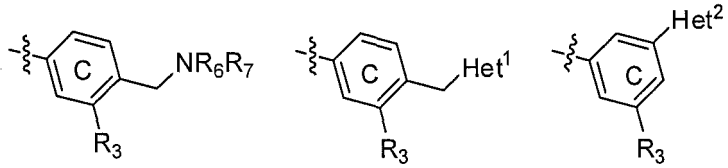
4. Heterocyclic alkynyl benzene compounds and their pharmaceutical acceptable salts, prodrugs,or stereoisomers according to claim 1, wherein,
R_2 is selected from:

1)H
2)methyl, ethyl, isopropyl, tert-butyl;
3)cyclopropyl;
4)F, Cl, Br;
5)CF_3.

5. Heterocyclic alkynyl benzene compounds and their pharmaceutical acceptable salts, prodrugs, or stereoisomers according to claims 1-4, wherein,
C ring

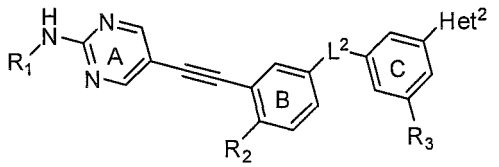


is selected from

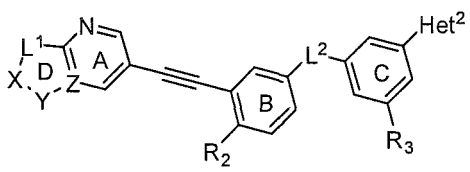


R_3, R_6, R_7 and Het^1 have the same definition as claim 1; Het^2 is selected from substituted imidazole, substituted pyrazole, substituted oxazole, substituted triazole, substituted oxazolidine, or substituted thiazole.

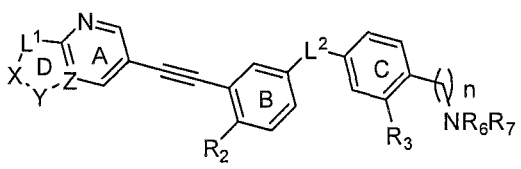
6. Heterocyclic alkynyl benzene compounds and pharmaceutical acceptable salts, prodrugs, or stereoisomers according to claim1, wherein the compounds with formula (I) structure is specially selected from:



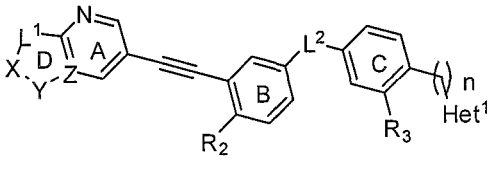
(II)



(III)



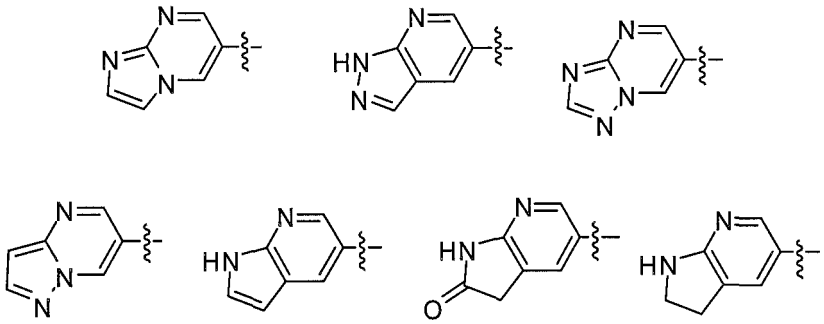
(IV)



(V)

wherein,

X, Y, Z are independently selected from N, CH; D ring is a heterocycle contains 1~3 N atoms; the fused ring of D ring with A ring is selected from:



R_1, R_2, R_3, R_6, R_7, n, L^1, L^2, Het^1, Het^2 have the same definition as claim 1.

7. Heterocyclic alkynyl benzene compounds and pharmaceutical acceptable salts, prodrugs, or stereoisomers according to claim 6, wherein the Heterocyclic alkynyl benzene compound is specially selected from:

3-(2-(2-(cyclopropylamino)pyrimidin-5-yl)ethynyl)-4-methyl-*N*-(3-(4-methyl-1*H*-imidazol-1-yl)-5-(tri fluoromethyl)phenyl)benzamide;
N-(3-(1*H*-imidazol-1-yl)-5-(trifluoromethyl)phenyl)-3-(2-(2-(cyclopropylamino)pyrimidin-5-yl)ethyn yl)-4-methylbenzamide;
4-methyl-*N*-(3-(4-methyl-1H-imidazol-1-yl)-5-(trifluoromethyl)phenyl)-3-(2-(2-(methylamino)pyrimi din-5-yl) ethynyl)benzamide;
3-(2-(2-(ethylamino)pyrimidin-5-yl)ethynyl)-4-methyl-*N*-(3-(4-methyl-1*H*-imidazol-1-yl)-5-(trifluoro methyl)phenyl)benzamide;
4-methyl-N-(3-(4-methyl-1H-imidazol-1-yl)-5-(trifluoromethyl)phenyl)-3-(2-(2-(piperidin-1-yl)pyrimi din-5-yl) ethynyl)benzamide;
3-(2-(6-aminopyridin-3-yl)ethynyl)-4-methyl-N-(3-(4-methyl-1H-imidazol-1-yl)-5-(trifluoromethyl)ph enyl)benzamide;
3-(2-(2-(cyclopropylamino)pyrimidin-5-yl)ethynyl)-4-methyl-N-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)benzamide;
3-(2-(3H-imidazo[4,5-b]pyridin-6-yl)ethynyl)-4-methyl-N-(3-(4-methyl-1H-imidazol-1-yl)-5-(trifluor omethyl)phenyl)benzamide;
4-methyl-N-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)-3-(2-(pyrazolo[1,5-a]pyri midin-6-yl)

ethynyl)benzamide;
3-(2-(2-(cyclohexylamino)pyrimidin-5-yl)ethynyl)-4-methyl-N-(3-(4-methyl-1H-imidazol-1-yl)-5-(trif luoromethyl) phenyl)benzamide;
4-methyl-N-(3-(4-methyl-1H-imidazol-1-yl)-5-(trifluoromethyl)phenyl)-3 -(2-(2-(phenylamino)pyrimi din-5-yl) ethynyl)benzamide;
3-(2-(1H-pyrrolo[2,3-b]pyridin-5-yl)ethynyl)-4-methyl-N-(3-(4-methyl-1H-imidazol-1-yl)-5-(trifluoro methyl)phenyl)benzamide;
3-(2-(2-(2-hydroxyethylamino)pyrimidin-5-yl)ethynyl)-4-methyl-N-(3-(4-methyl-1H-imidazol-1-yl)-5 -(trifluoromethyl)phenyl)benzamide;
N-(3-(1H-imidazol-1-yl)-5-(trifluoromethyl)phenyl)-4-methyl-3-(2-(pyrazolo[1,5-a]pyrimidin-6-yl)eth ynyl)benzamide;
4-methyl-N-(3-(3-methyl-1H-1,2,4-triazol-1-yl)-5-(trifluoromethyl)phenyl)-3-(2-(pyrazolo[1,5-a]pyri midin-6-yl) ethynyl)benzamide;
3-(2-(imidazo[1,2-a]pyrimidin-6-yl)ethynyl)-4-methyl-N-(3-(4-methyl-1H-imidazol-1-yl)-5-(trifluoro methyl)phenyl)benzamide;
3-(2-(1H-pyrazolo[3,4-b]pyridin-5-yl)ethynyl)-4-methyl-N-(3-(4-methyl-1H-imidazol-1-yl)-5-(trifluor omethyl) phenyl)benzamide;
N-(3-(1H-imidazol-1-yl)-5-(trifluoromethyl)phenyl)-3-(2-(1H-pyrazolo[3,4-b]pyridin-5-yl)ethynyl)-4-methylbenzamide;
3-(2-(1H-pyrazolo[3,4-b]pyridin-5-yl)ethynyl)-4-methyl-N-(3-(3-methyl-1H-1,2,4-triazol-1-yl)-5-(trifl uoromethyl) phenyl)benzamide;
3-(2-([1,2,4]triazolo[1,5-a]pyrimidin-6-yl)ethynyl)-4-methyl-N-(3-(4-methyl-1H-imidazol-1-yl)-5-(trif luoromethyl) phenyl)benzamide;
4-methyl-N-(3-(4-methyl-1H-imidazol-1-yl)-5-(trifluoromethyl)phenyl)-3-(2-(pyrazolo[1,5-a]pyrimidi n-6-yl)ethynyl)benzamide;
3-(2-(1H-pyrazolo[3,4-b]pyridin-5-yl)ethynyl)-4-methyl-N-(3-(trifluoromethyl)phenyl)benzamide;
3-(2-(1H-pyrazolo[3,4-b]pyridin-5-yl)ethynyl)-4-methyl-N-(4-((4-methylpiperazin-1-yl)methyl)-3-(tri fluoromethyl)phenyl)benzamide;
3-(2-(2-((S)-2,3-dihydroxypropylamino)pyrimidin-5-yl)ethynyl)-4-methyl-N-(3-(4-methyl-1H-imidaz ol-1-yl)-5-(trifluoromethyl)phenyl)benzamide;
3-(2-(2-(diethylamino)pyrimidin-5-yl)ethynyl)-4-methyl-N-(3-(4-methyl-1H-imidazol-1-yl)-5-(trifluor omethyl) phenyl)benzamide;
3-(2-(2-(tert-butylamino)pyrimidin-5-yl)ethynyl)-4-methyl-N-(3-(4-methyl-1H-imidazol-1-yl)-5-(triflu oromethyl) phenyl)benzamide;
3-(2-(2-(isopropylamino)pyrimidin-5-yl)ethynyl)-4-methyl-N-(3-(4-methyl-1H-imidazol-1-yl)-5-(trifl uoromethyl) phenyl)benzamide;
3-(2-(2-aminopyrimidin-5-yl)ethynyl)-4-methyl-N-(3-(4-methyl-1H-imidazol-1-yl)-5-(trifluoromethyl)phenyl) benzamide;
4-methyl-N-(4-(morpholinomethyl)-3-(trifluoromethyl)phenyl)-3-(2-(pyrazolo[1,5-a]pyrimidin-6-yl)et hynyl)benzamide;
N-(4-((4-(2-hydroxyethyl)piperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)-4-methyl-3-(2-(pyrazolo[1,5-a]pyrimidin-6-yl)ethynyl)benzamide;
(S)-N-(4-((3-(dimethylamino)pyrrolidin-1-yl)methyl)-3-(trifluoromethyl)phenyl)-4-methyl-3-(2-(pyraz olo[1,5-a] pyrimidin-6-yl)ethynyl)benzamide;
N-(3-tert-butyl-5-(4-methyl-1H-imidazol-1-yl)phenyl)-4-methyl-3-(2-(pyrazolo[1,5-a]pyrimidin-6-yl) ethynyl)benzamide;
3-(2-(1H-pyrazolo [3,4-b]pyridin-5-yl)ethynyl)-4-methyl-N-(3-(4-methyl-1H-imidazol-1-yl)phenyl)be nzamide;
3-(2-(1H-pyrazolo[3,4-b]pyridin-5-yl)ethynyl)-N-(3-tert-butyl-5-(4-methyl-1H-imidazol-1-yl)phenyl)-4-methylbenzamide;
3-(2-(1H-pyrazolo[3,4-b]pyridin-5-yl)ethynyl)-N-(3-fluoro-5-(4-methyl-1H-imidazol-1-yl)phenyl)-4-methylbenzamide;
3-(2-(1H-pyrazolo[3,4-b]pyridin-5-yl)ethynyl)-N-(3-chloro-5-(4-methyl-1H-imidazol-1-yl)phenyl)-4-methylbenzamide;
(R)-N-(4-((3-(dimethylamino)pyrrolidin-1-yl)methyl)-3-(trifluoromethyl)phenyl)-4-methyl-3-(2-(pyra zolo[1,5-a] pyrimidin-6-yl)ethynyl)benzamide;
(S)-3-(2-(1H-pyrazolo[3,4-b]pyridin-5-yl)ethynyl)-N-(4-((3-(dimethylamino)pyrrolidin-1-yl)methyl)-3 -(trifluoromethyl)phenyl)-4-methylbenzamide;
(R)-3-(2-(1H-pyrazolo[3,4-b]pyridin-5-yl)ethynyl)-N-(4-((3-(dimethylamino)pyrrolidin-1-yl)methyl)-3-(trifluoro-

methyl)phenyl)-4-methylbenzamide;
3-(2-(1H-pyrazolo[3,4-b]pyridin-5-yl)ethynyl)-N-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromet hyl)phenyl) benzamide;
3-(2-(1H-pyrazolo[3,4-b]pyridin-5-yl)ethynyl)-4-methyl-N-(4-((4-methylpiperazin-1-yl)methyl)-3-(tri fluoro-methyl)phenyl)benzamide bimesylate;
3-(2-(1H-pyrazolo[3,4-b]pyridin-5-yl)ethynyl)-4-methyl-N-(4-((4-methylpiperazin-1-yl)methyl)-3-(trif luoro-methyl)phenyl)benzamide dihydrochloride;
methyl-N-(3-(3-methyl-1H-1,2,4-triazol-1-yl)-5-(trifluoromethyl)phenyl)-3-(2-(pyrazolo[1,5-a]pyrimi din-6-yl) ethynyl)benzamide mesylate;
N-(3-(1H-imidazol-1-yl)-5-(trifluoromethyl)phenyl)-4-methyl-3-(2-(pyrazolo[1,5-a]pyrimidin-6-yl)eth ynyl)benza-mide mesylate;
3-(2-(2-(cyclopropylamino)pyrimidin-5-yl)ethynyl)-4-methyl-*N*-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoro-methyl)phenyl)benzamide trimesylate;
3-(2-(1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)ethynyl)-4-methyl-*N*-(3-(3-methyl-1*H*-1,2,4-triazol-1-yl)-5-(trifl uoromethyl) phenyl)benzamide mesylate;
3-(2-(1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)ethynyl)-*N*-(3-tert-butyl-5-(4-methyl-1*H*-imidazol-1-yl)phenyl)-4-methyl-benzamide mesylate;
4-methyl-N-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)-3-(2-(pyrazolo[1,5-a]pyri midin-6-yl) ethynyl)benzamide dimesylate.

8. A pharmaceutical composition for treating tumors comprising the heterocyclic alkynyl benzene compounds of any one of claims 1-7 or their pharmaceutically acceptable salts, stereoisomers or prodrugs thereof with pharmaceutically acceptable carriers.

9. Use of the heterocyclic alkynyl benzene compound of any one of claims 1-7 or their pharmaceutically acceptable salts, stereoisomers or pro-drugs and the use for preparing drugs for prevention or treatment of cancer.

10. The use according to claim 9, wherein, the cancer type anyone of Leukemia, Gastrointestinal stromal tumors (GIST), Histiocytic lymphoma, Non-small cell lung cancer, Small cell lung cancer, Lung adenocarcinoma, , squamous cell lung carcinoma, pancreatic cancer, breast cancer, prostate cancer, liver cancer, skin cancer, squamous cell carcinoma, nasopharyngeal carcinoma.

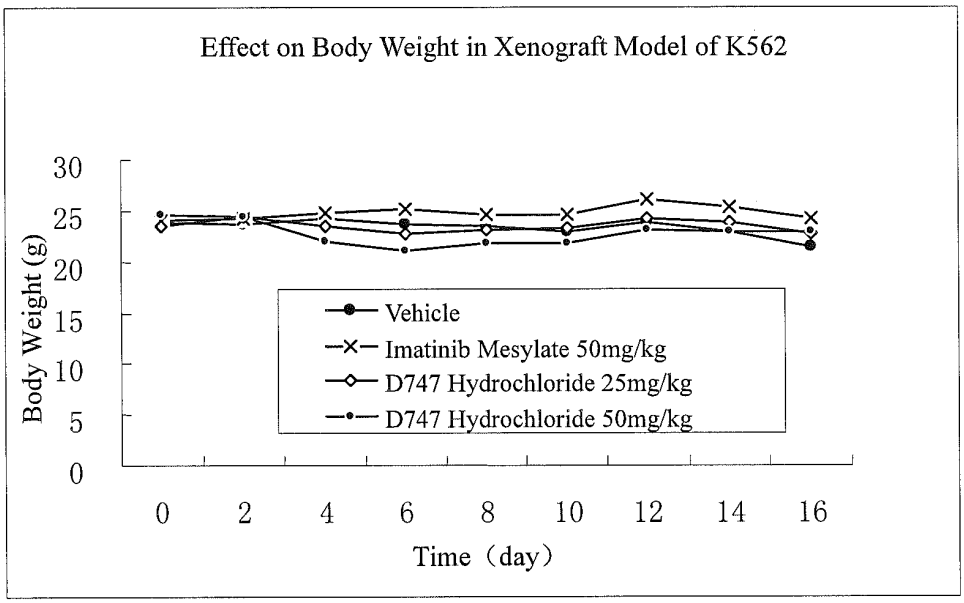

Effect on Body Weight in Xenograft Model of K562
Body Weight (g)
30
25
20
15
10
5
0
0
2
4
6
8
10
12
14
16
Time (day)
Vehicle
Imatinib Mesylate 50mg/kg
D747 Hydrochloride 25mg/kg
D747 Hydrochloride 50mg/kg

Fig. 1

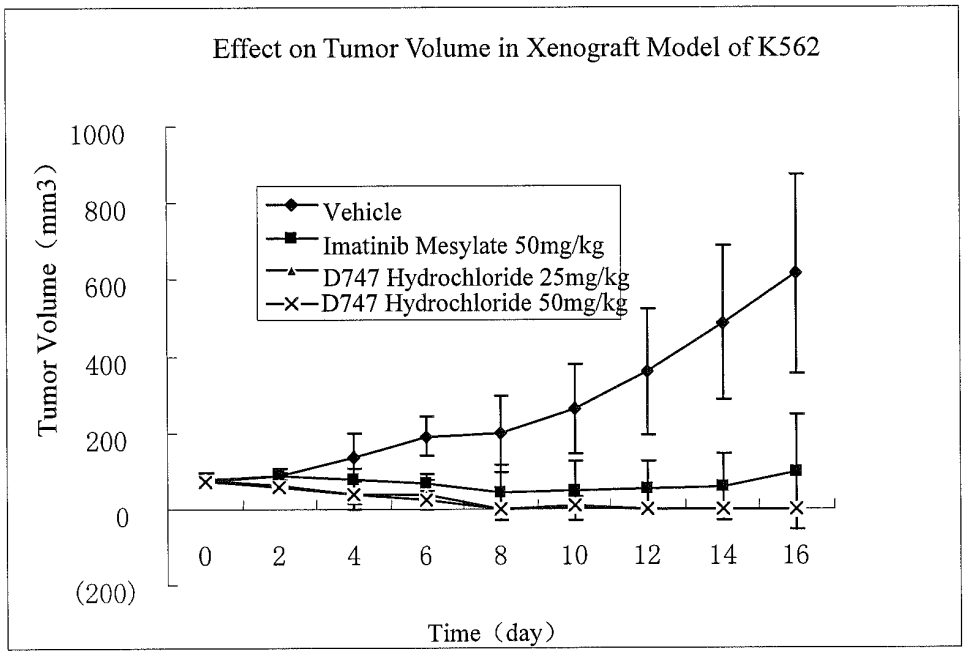

Effect on Tumor Volume in Xenograft Model of K562
Tumor Volume (mm3)
1000
800
600
400
200
0
(200)
0
2
4
6
8
10
12
14
16
Time (day)
Vehicle
Imatinib Mesylate 50mg/kg
D747 Hydrochloride 25mg/kg
D747 Hydrochloride 50mg/kg

Fig. 2

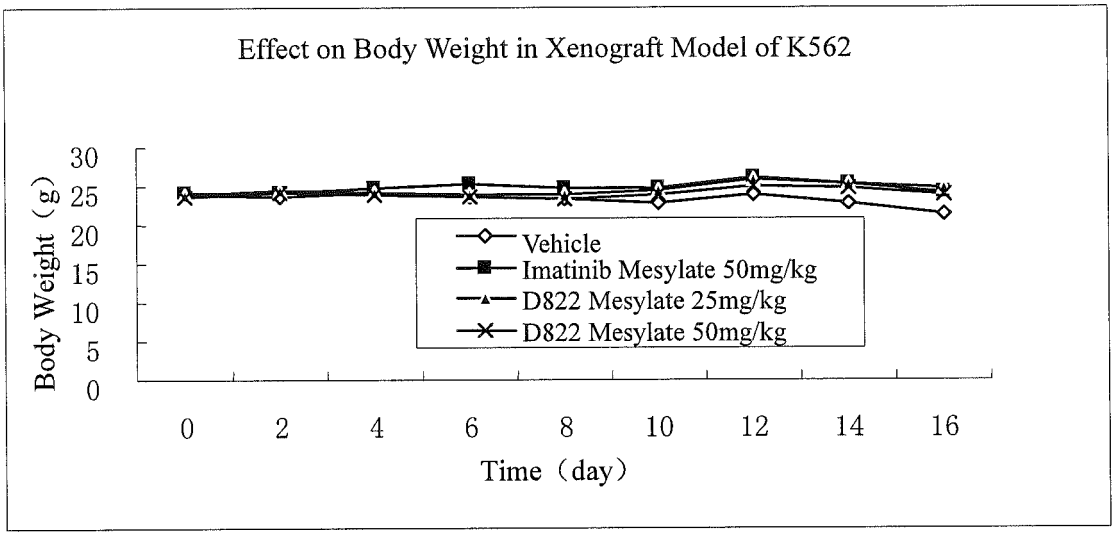

Effect on Body Weight in Xenograft Model of K562
Body Weight (g)
30
25
20
15
10
5
0
0
2
4
6
8
10
12
14
16
Time (day)
Vehicle
Imatinib Mesylate 50mg/kg
D822 Mesylate 25mg/kg
D822 Mesylate 50mg/kg

Fig. 3

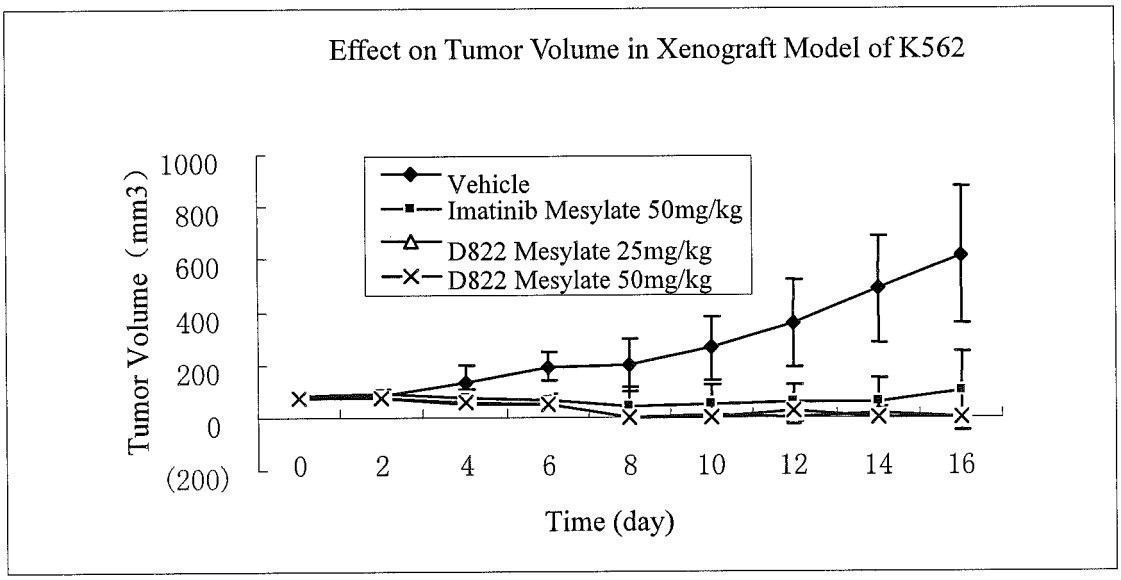

Effect on Tumor Volume in Xenograft Model of K562
Tumor Volume (mm3)
1000
800
600
400
200
0
(200)
0
2
4
6
8
10
12
14
16
Time (day)
Vehicle
Imatinib Mesylate 50mg/kg
D822 Mesylate 25mg/kg
D822 Mesylate 50mg/kg

Fig. 4

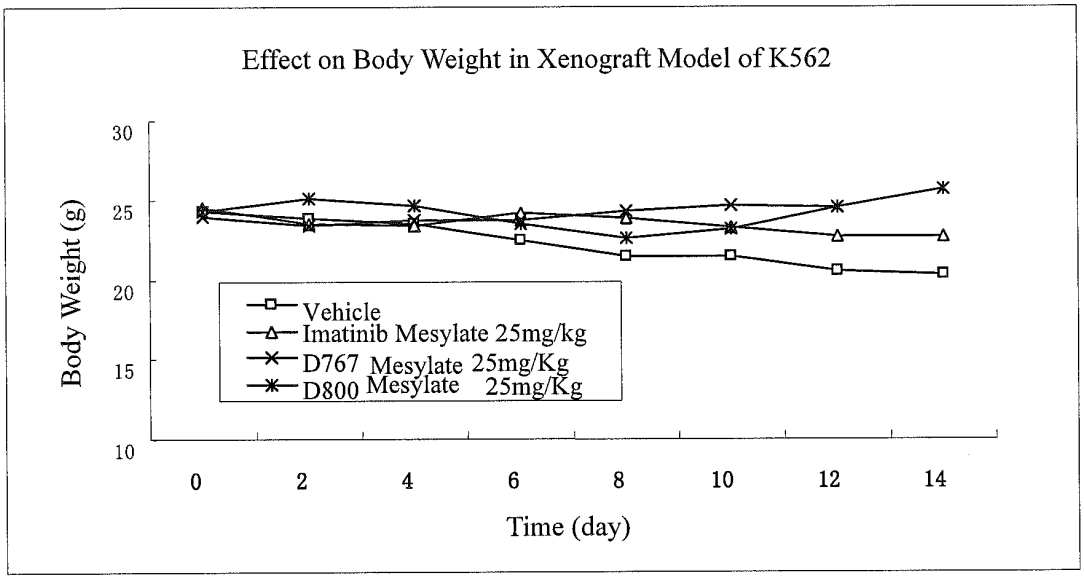

Effect on Body Weight in Xenograft Model of K562
Body Weight (g)
30
25
20
15
10
0
2
4
6
8
10
12
14
Time (day)
Vehicle
Imatinib Mesylate 25mg/kg
D767 Mesylate 25mg/Kg
D800 Mesylate 25mg/Kg

Fig. 5

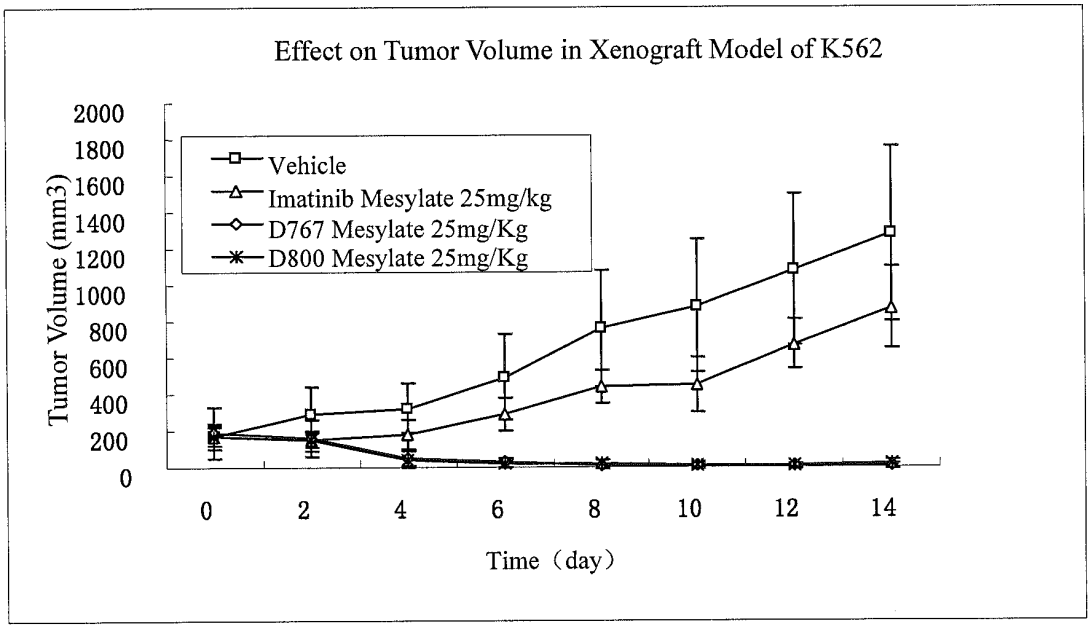

Effect on Tumor Volume in Xenograft Model of K562
Tumor Volume (mm3)
2000
1800
1600
1400
1200
1000
800
600
400
200
0
0
2
4
6
8
10
12
14
Time（day）
Vehicle
Imatinib Mesylate 25mg/kg
D767 Mesylate 25mg/Kg
D800 Mesylate 25mg/Kg

Fig. 6

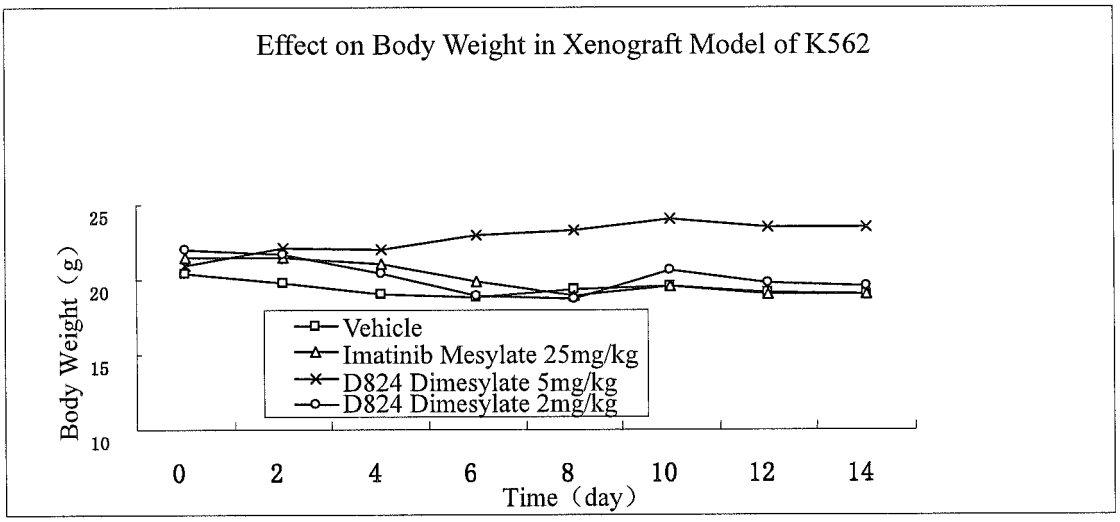

Effect on Body Weight in Xenograft Model of K562
Body Weight (g)
25
20
15
10
0
2
4
6
8
10
12
14
Time (day)
Vehicle
Imatinib Mesylate 25mg/kg
D824 Dimesylate 5mg/kg
D824 Dimesylate 2mg/kg

Fig. 7

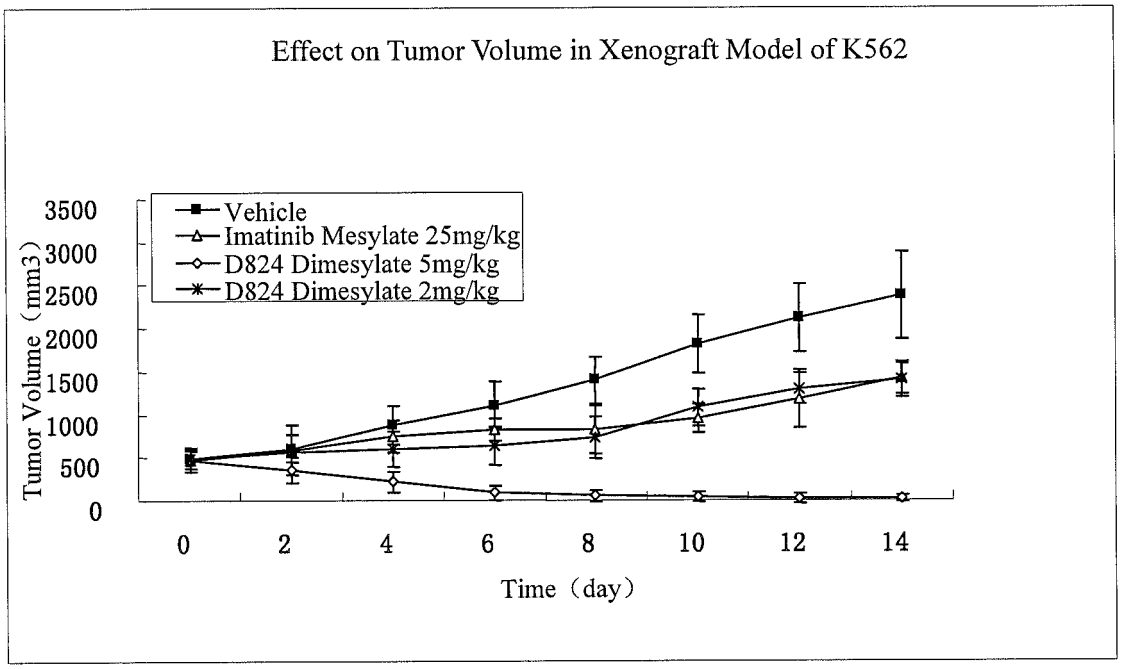

Effect on Tumor Volume in Xenograft Model of K562
Tumor Volume (mm3)
3500
3000
2500
2000
1500
1000
500
0
0
2
4
6
8
10
12
14
Time (day)
Vehicle
Imatinib Mesylate 25mg/kg
D824 Dimesylate 5mg/kg
D824 Dimesylate 2mg/kg

Fig. 8

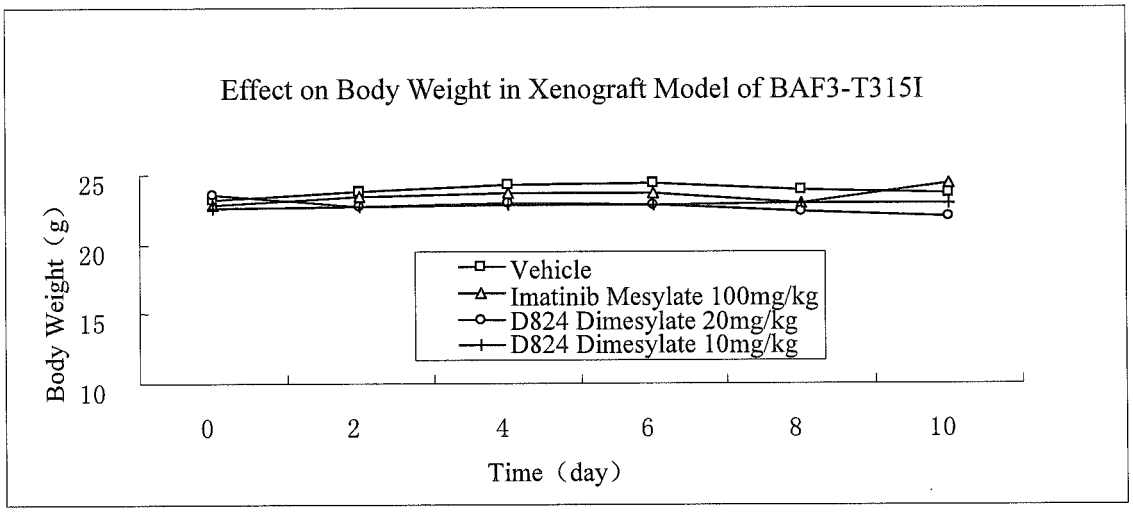

Effect on Body Weight in Xenograft Model of BAF3-T315I
Body Weight (g)
25
20
15
10
0
2
4
6
8
10
Time (day)
Vehicle
Imatinib Mesylate 100mg/kg
D824 Dimesylate 20mg/kg
D824 Dimesylate 10mg/kg

Fig. 9

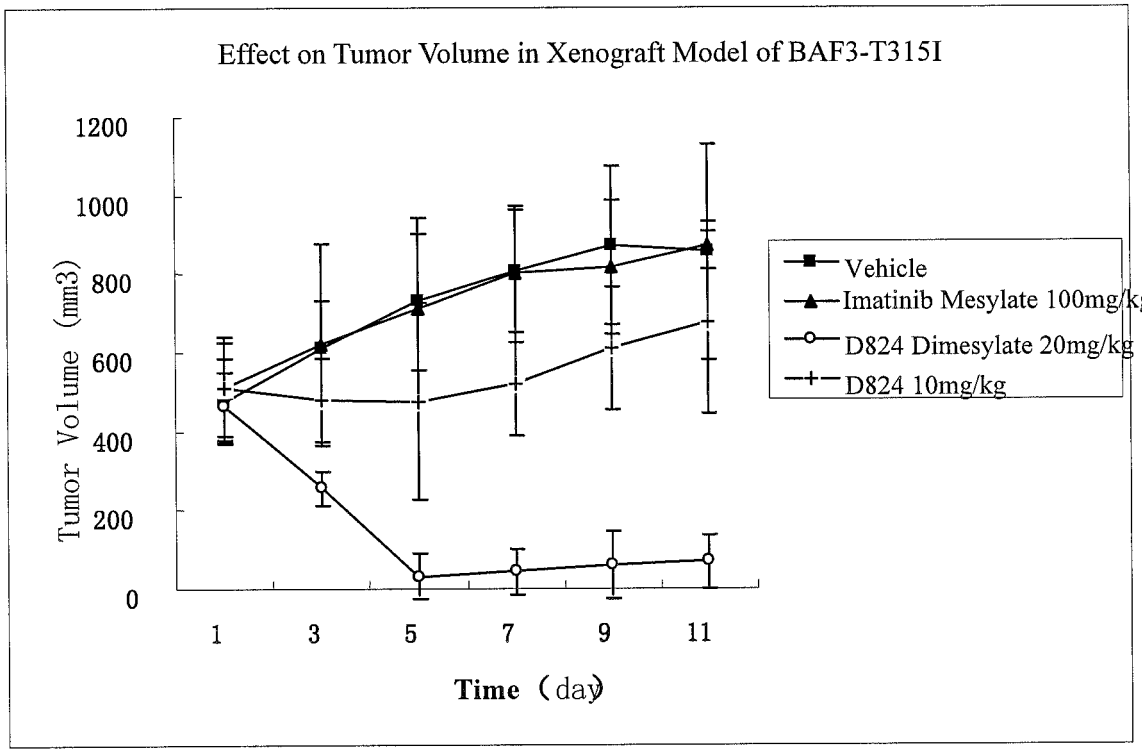

Effect on Tumor Volume in Xenograft Model of BAF3-T315I
Tumor Volume (mm3)
1200
1000
800
600
400
200
0
1
3
5
7
9
11
Time (day)
Vehicle
Imatinib Mesylate 100mg/kg
D824 Dimesylate 20mg/kg
D824 10mg/kg

Fig. 10

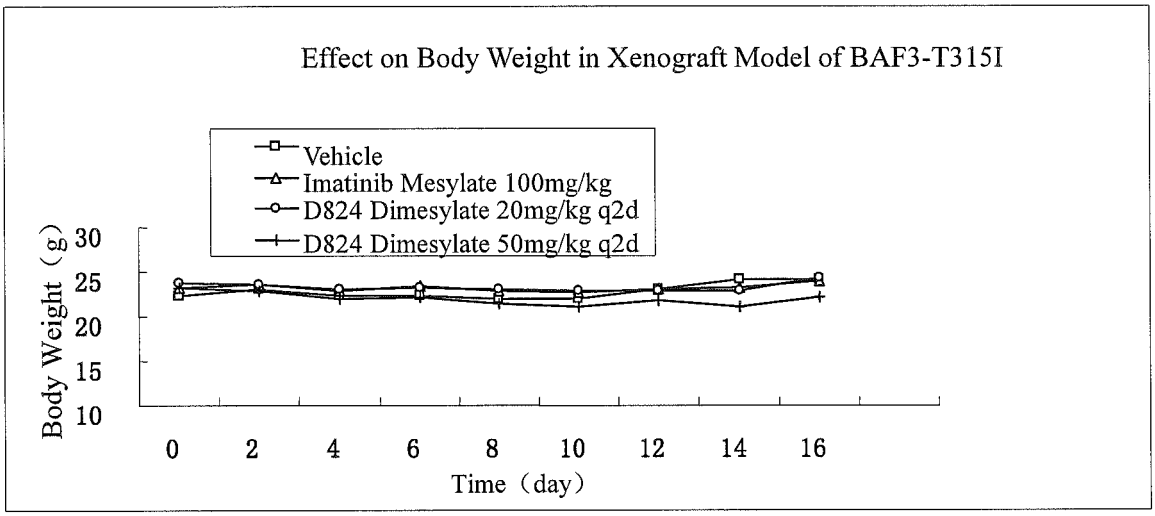

Effect on Body Weight in Xenograft Model of BAF3-T315I
Vehicle
Imatinib Mesylate 100mg/kg
D824 Dimesylate 20mg/kg q2d
D824 Dimesylate 50mg/kg q2d
Body Weight (g)
30
25
20
15
10
0
2
4
6
8
10
12
14
16
Time (day)

Fig. 11

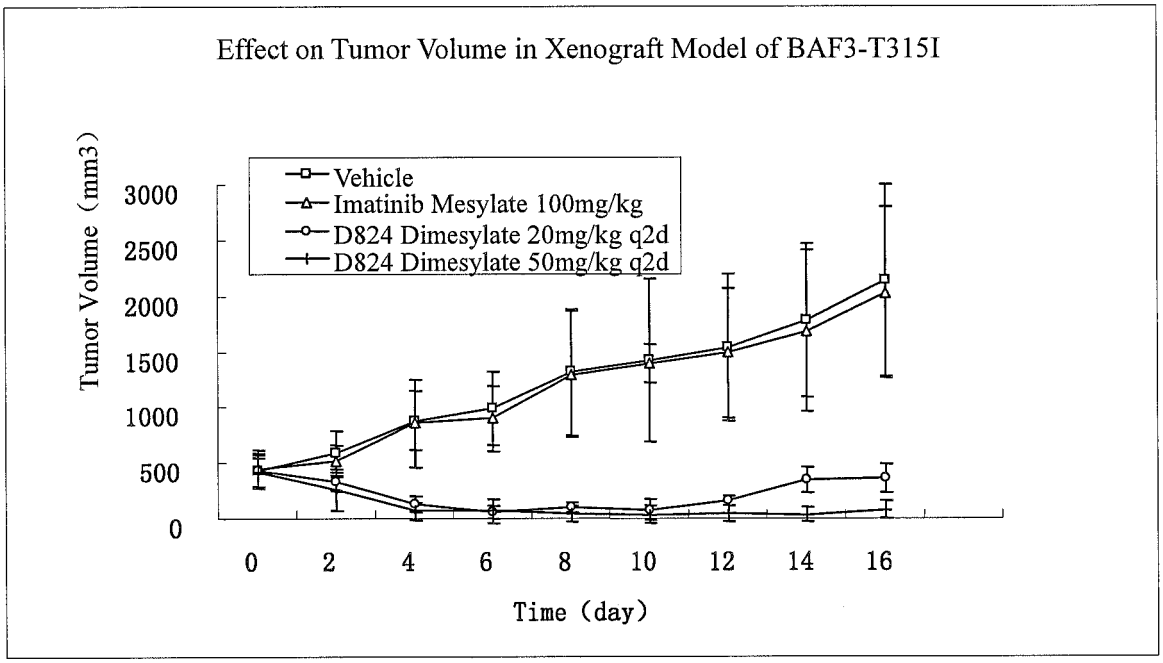

Effect on Tumor Volume in Xenograft Model of BAF3-T315I
Vehicle
Imatinib Mesylate 100mg/kg
D824 Dimesylate 20mg/kg q2d
D824 Dimesylate 50mg/kg q2d
Tumor Volume (mm3)
3000
2500
2000
1500
1000
500
0
0
2
4
6
8
10
12
14
16
Time (day)

Fig. 12

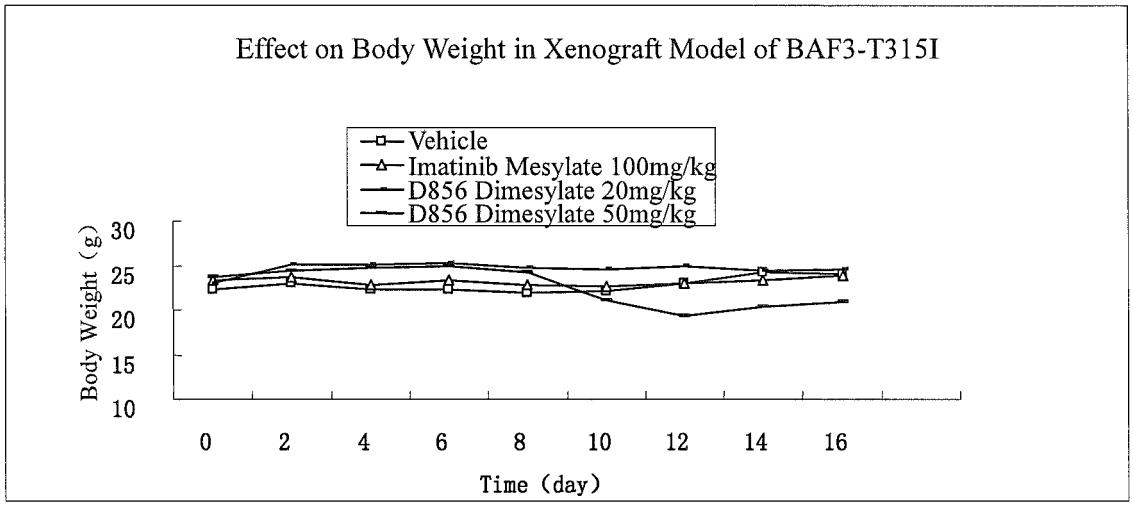

Effect on Body Weight in Xenograft Model of BAF3-T315I
Vehicle
Imatinib Mesylate 100mg/kg
D856 Dimesylate 20mg/kg
D856 Dimesylate 50mg/kg
Body Weight (g)
30
25
20
15
10
0
2
4
6
8
10
12
14
16
Time (day)

Fig. 13

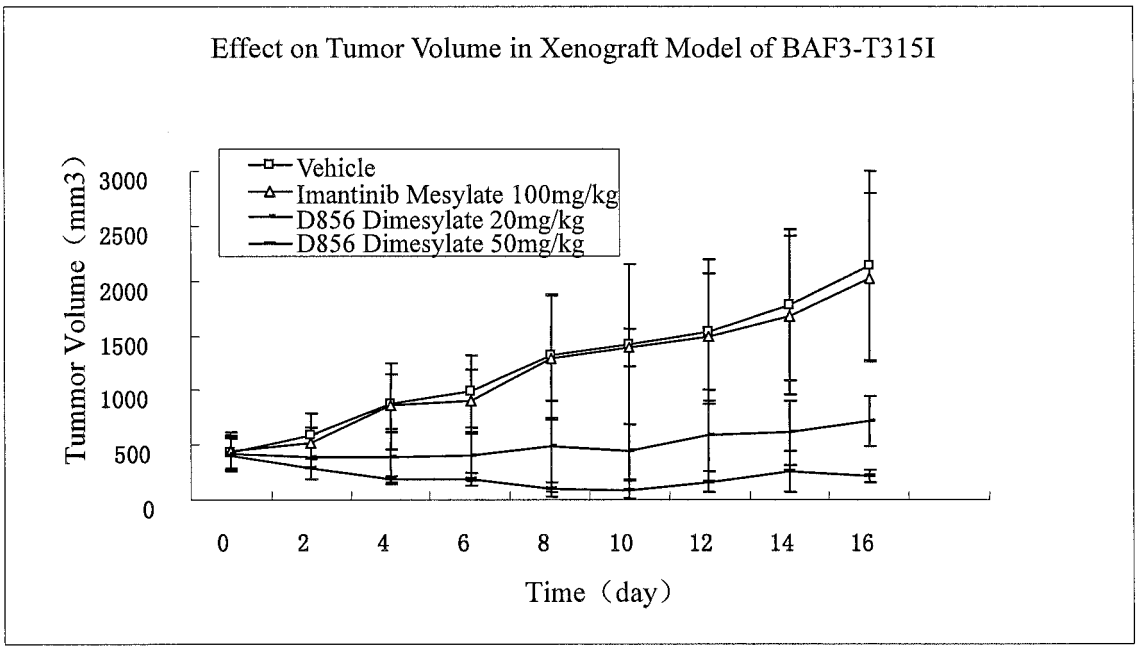

Effect on Tumor Volume in Xenograft Model of BAF3-T315I
Vehicle
Imantinib Mesylate 100mg/kg
D856 Dimesylate 20mg/kg
D856 Dimesylate 50mg/kg
Tummor Volume (mm3)
3000
2500
2000
1500
1000
500
0
0
2
4
6
8
10
12
14
16
Time (day)

Fig.14

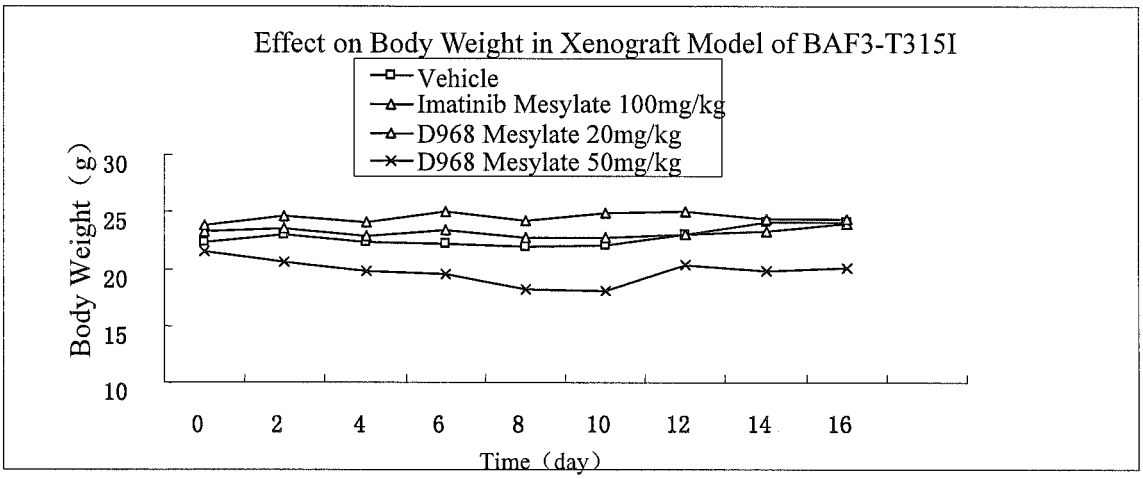

Effect on Body Weight in Xenograft Model of BAF3-T315I
Vehicle
Imatinib Mesylate 100mg/kg
D968 Mesylate 20mg/kg
D968 Mesylate 50mg/kg
Body Weight (g)
30
25
20
15
10
0
2
4
6
8
10
12
14
16
Time (day)

Fig. 15

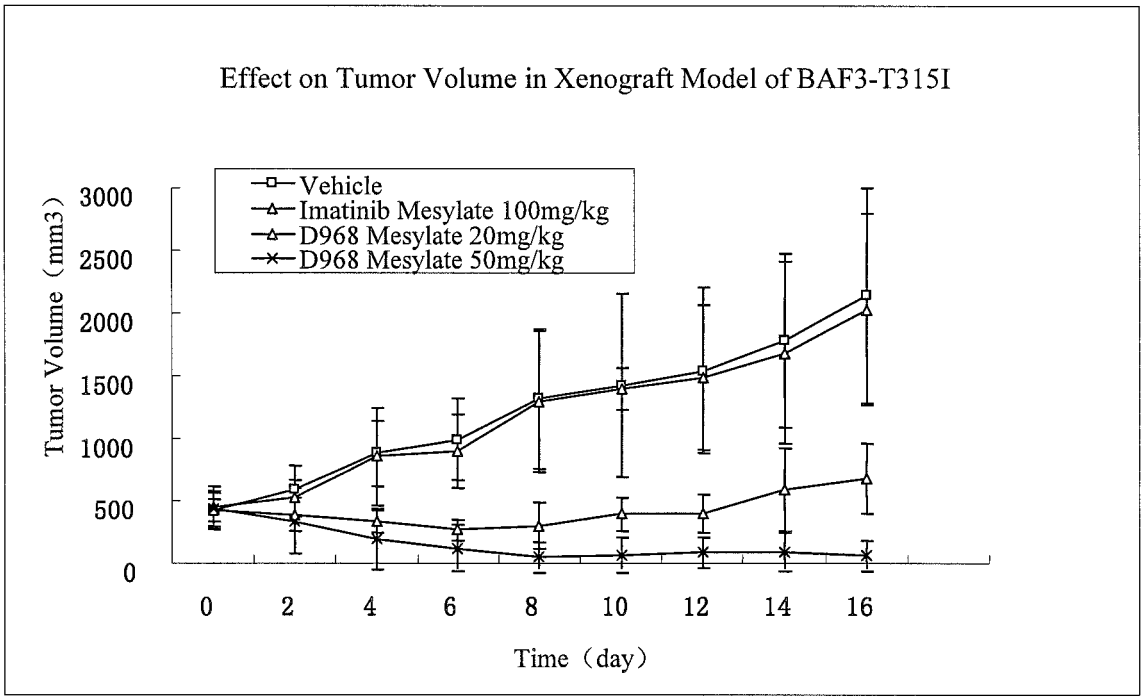

Effect on Tumor Volume in Xenograft Model of BAF3-T315I
Vehicle
Imatinib Mesylate 100mg/kg
D968 Mesylate 20mg/kg
D968 Mesylate 50mg/kg
Tumor Volume (mm3)
3000
2500
2000
1500
1000
500
0
0
2
4
6
8
10
12
14
16
Time (day)

Fig. 16

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2011/000935

A. CLASSIFICATION OF SUBJECT MATTER

see the extra sheet

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC：C07D 403/-; C07D 401/-; C07D 239/-; C07D 471/-; C07D 487/-; A61K 31/-; A61P 35/-

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Data: CNKI; CPRSABS; VEN; CNTXT; WPITXT; STN

Keyword: heterocyclic; alkynyl; protein; kinase; cancer; tumor; benzamide

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
PX	CN101885722A(GUANGZHOU INSRITUE OF BIOMEDICINE AND HEALTH), 17 Nov. 2010(17.11.2010) The whole description	1-10

☒ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

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"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim (S) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&"document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
12 Aug.2011(12.08.2011)	**08 Sep. 2011 (08.09.2011)**
Name and mailing address of the ISA/CN The State Intellectual Property Office, the P.R.China 6 Xitucheng Rd., Jimen Bridge, Haidian District, Beijing, China 100088 Facsimile No. 86-10-62019451	Authorized officer TIAN, Dingding Telephone No. (86-10)62086303

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2011/000935

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO2006044823A2 (AMGEN INC.), 27 Apr. 2006 (27.04.2006) Examples 1-2, 4-5, 7-8, 12, 15, 22-23, 26, 30, 33, 42, 58, 66, 73, 77-V-3, 77-V-4, 78-80, 86, 282, 284, 286-287, 290, 304, 305, 310, 311, 313-316, 321-322, 325, 327, 330, 337, 339, 345, 346, claims 1-49 and pages 74-75 of description	1-10
X	KANSAL, N., et al., A Three Dimensional Pharmacophore Modeling for KDR and Tie-2 Receptor Tyrosine Kinase Inhibitors and Virtual Screening for New Multikinase Inhibitors, QSAR & Combinatorial Science, Vol.28, No.10, pages 1130-1147, 31 Oct. 2009(31.10.2009) Compounds 19a, 20a	1-10
X	CEE,V.J., et al, Alkynylpyrimidine Amide Derivatives as Potent, Selective, and Orally Active Inhibitors of Tie-2 Kinase, Journal of Medicinal Chemistry, Vol.50, No.4, pages 627-640, 25 Jan. 2007(25.01.2007) compounds 6a, 13a, 13b of Table 1, compounds 6a~6g of Table 2, compounds 6f~6p of Table 3, compounds 6l~6n of Table 5	1-10
X	DENG, X.M., et al., Broad spectrum alkynyl inhibitors of T315I Bcr-Abl, Bioorganic & Medicinal Chemistry Letters, Vol.20, No.14, pages 4196-4200,19 May 2010(19.05.2010), Compound 9 of Table 1, Compounds 12, 14, 17-20 of Table 2	1-10
X	HUANG, W.S., et al., Discovery of 3-[2-(Imidazo[1,2-b]pyridazin-3-yl) ethynyl]-4-methyl-N-[4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl]benzamide (AP24534), a Potent, Orally Active Pan-Inhibitor of Breakpoint Cluster Region-Abelson (BCR-ABL) Kinase Including the T315I Gatekeeper Mutant, Journal of Medicinal Chemistry, Vol.53, No.12, pages 4701-4719, 01 Jun. 2010(01.06.2010) Compounds 20a, 20b of Table 4 Compound 12c of Table 2, Compounds 19a, 19c of Table 3, Compounds 20c~20g of Table 4, Table 5	1-10
X	WO2007075869A2 (ARIAD PHARMACEUTICALS,INC.), 05 Jul. 2007 (05.07.2007) Claims 1-22, Examples 1-5, 8-9, 14-19, 21, the table of pages 74-85 of description	1-10

Form PCT/ISA /210 (continuation of second sheet) (July 2009)

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CN2011/000935

Patent Documents referred in the Report	Publication Date	Patent Family	Publication Date
WO2006044823A2	27.04.2006	EP1802586A2	04.07.2007
		US7776869B2	17.08.2010
		US2010160283A1	24.06.2010
		AU2005295414A1	27.04.2006
		US2006217380A1	28.09.2006
		WO2006044823A3	15.06.2006
WO2007075869A2	05.07.2007	MX2008008152A	30.09.2008
		US2007191376A1	16.08.2007
		WO2007075869A3	29.11.2007
		AU2006331673 A1	05.07.2007
		EP1973545A2	01.10.2008
		IN200802328P2	16.01.2009
		CN101389338A	18.03.2009
		CA2634923A1	05.07.2007
		JP2009521462T	04.06.2009
		KR20080081191A	08.09.2008
CN101885722A	17.11.2010	none	

Form PCT/ISA /210 (patent family annex) (July 2009)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2011/000935

CLASSIFICATION OF SUBJECT MATTER

C07D 403/12(2006.01) i
C07D 401/12(2006.01)i
C07D 239/42(2006.01)i
C07D 471/04(2006.01)i
C07D 487/04(2006.01)i
A61K 31/506(2006.01)i
A61K 31/519(2006.01)i
A61K 31/4439(2006.01)i
A61K 31/437(2006.01)i
A61K 31/496(2006.01)i
A61P 35/00(2006.01)i
A61P 35/02(2006.01)i

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REFERENCES CITED IN THE DESCRIPTION

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Non-patent literature cited in the description

- Pharmaceutical Salts. *J. Pharm. Sci.,* 1977, vol. 66, 1-19 **[0033]**

杂环炔苯类化合物及其药用组合物和应用

摘　要

本发明公开了一种具有通式Ⅰ的化合物及其药学上可接受的酸或碱盐或立体异构体，该化合物及其药学上可接受的盐或立体异构体在制备治疗或预防肿瘤的药物中的应用。该类化合物并可以有效克服 Gleevec 诱发的耐药。