202128696

(19)中華民國智慧財產局

(12)發明說明書公開本 (11)公開編號：TW 202128696 A

(43)公開日： 中華民國 110 (2021) 年 08 月 01 日

(21)申請案號：109136411 (22)申請日： 中華民國 109 (2020) 年 10 月 21 日

(51)Int. Cl.： *C07D487/04 (2006.01)* *A61K31/519 (2006.01)* *A61P35/00 (2006.01)*

(30)優先權：2019/10/22 美國 62/924,214

(71)申請人：昊運股份有限公司 (中華民國) ALPHALA CO., LTD. (TW)
臺北市大同區承德路 2 段 83 之 2 號

(72)發明人：鍾政和 CHUNG, CHENG HO (TW) ；曾喜樑 TSENG, SHI LIANG (TW) ；劉柏賢 LIOU, BO SIAN (TW)

(74)代理人：蘇建太；吳爾軒

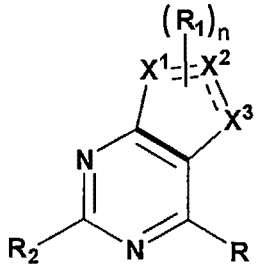
申請實體審查：有 申請專利範圍項數：33 項 圖式數：0 共 261 頁

(54)名稱

嘧啶醯胺化合物及其用途

(57)摘要

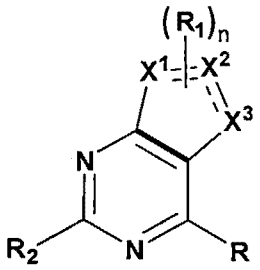
本發明揭示一種如下式(I)之化合物或其立體異構物、互變異構物、或其藥學上可接受之鹽類：



(I)

其中本文定義了每個變數 R、R_1、R_2、X_1、X_2、X_3 及 n。本發明還揭示使用式(I)之化合物或其鹽類以及含有該化合物之醫藥組成物用於治療癌症的方法。

Disclosed are compounds of formula (I) below or a stereoisomer, a tautomer, or a pharmaceutically acceptable salt thereof:

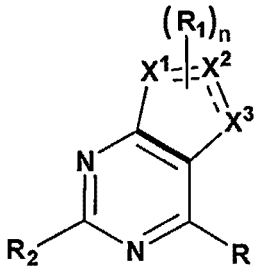


(I),

in which each of variables each of variables R, R_1, R_2, X_1, X_2, X_3 and n is defined herein. Also disclosed is a method for treating a cancer with a compound of formula (I) or a salt thereof and a pharmaceutical composition containing same.

特徵化學式：

TW 202128696 A



(I)

202128696

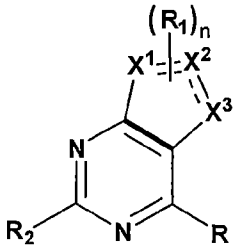
【發明摘要】

【中文發明名稱】嘧啶醯胺化合物及其用途

【英文發明名稱】PYRIMIDINE AMIDE COMPOUNDS AND USE THEREOF

【中文】

本發明揭示一種如下式(I)之化合物或其立體異構物、互變異構物、或其藥學上可接受之鹽類：

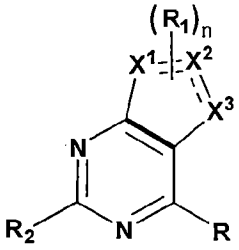


(I)

其中本文定義了每個變數R、R_1、R_2、X_1、X_2、X_3及n。本發明還揭示使用式(I)之化合物或其鹽類以及含有該化合物之醫藥組成物用於治療癌症的方法。

【英文】

Disclosed are compounds of formula (I) below or a stereoisomer, a tautomer, or a pharmaceutically acceptable salt thereof:



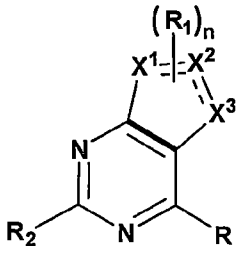
(I),

in which each of variables each of variables R, R_1, R_2, X_1, X_2, X_3 and n is defined herein. Also disclosed is a method for treating a cancer with a compound of formula (I) or a salt thereof and a pharmaceutical composition containing same.

【指定代表圖】無

【代表圖之符號簡單說明】無

【特徵化學式】



(I)

【發明說明書】

【中文發明名稱】嘧啶醯胺化合物及其用途

【英文發明名稱】PYRIMIDINE AMIDE COMPOUNDS AND USE THEREOF

【技術領域】

【0001】本揭露係關於可抑制腫瘤細胞生長之化合物、包括該化合物之醫藥組成物、以及該化合物或醫藥組成物之用途。

【先前技術】

【0002】近年來，發現食品或食品添加劑以及環境汙染可能是近年來引起癌症的原因或催化劑。並非偶然地，於已開發國家及全世界也發生了同樣的事件，癌症的高發生率為令人關注的警訊。根據美國癌症協會發布的數據，癌症已被證實是對公共健康的最大威脅。

【0003】一般用於治療癌症的方法包含手術、放射療法、化學療法及免疫療法。近年來，已經開發了幾種透過新的抗癌機制用於癌症治療的治療劑，並且已經證實透過使用這些治療劑治療可以提高患者的存活率。已知治療劑可透過例如抑制細胞週期進程、血管生成、法尼基轉移酶及酪胺酸激酶來治療癌症。

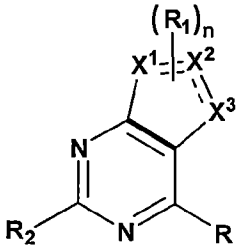
【0004】儘管已知某些藥劑對癌症展現出治療功效，但是這些藥劑仍有其限制。例如，有的抗癌藥僅對特定癌症具有治療功效，例如用於治療肺癌的抗癌藥不一定對乳癌有治療功效。此外，抗癌藥的治療功效還取決於腫瘤細胞的位置、患者的遺傳變異、以及藥物的副作用。另外，癌細胞可透過淋巴系統或血液循環系統從其原始部位擴散至患者的另一器官，從而引起轉移性癌症。

【0005】 由於罹患癌症的風險通常隨著年齡增加，隨著壽命的延長和大眾生活方式的改變，癌症的發生率也有增加的趨勢。因此，長期以來仍未滿足用於癌症治療及預防的新藥物的需求。

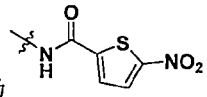
【發明內容】

【0006】 本揭露係關於某些可以抑制腫瘤細胞生長之化合物。

【0007】 本揭露的一態樣涉及下式(I)之化合物或其立體異構物、互變異構物、或其藥學上可接受之鹽類：



(I)

【0008】 於此式中，X_1、X_2及X_3各自獨立為C、N、O或S，但條件為X_1、X_2及X_3中不超過兩個為N、O或S；R_1各自獨立地選自由氫、鹵素、烷基、烷氧基、環烷基、雜環烷基、芳基或雜芳基所組成之群組，其中烷基、烷氧基、環烷基、雜環烷基、芳基及雜芳基各自選擇性地以一至三個選自由鹵素、羥基、硝基、氰基、$-NR_aR_b$、$-C(=O)R_c$、$-C(=O)OR_d$、選擇性地以一至四個鹵素取代之雜環烷基、選擇性地以一至三個鹵素或$-NR_aR_b$取代之芳基、選擇性地以一至三個鹵素取代之烷基、及選擇性地以一至三個鹵素或烷氧基取代之烷氧基所組成之群組之基團取代，其中R_a及R_b各自獨立為氫、烷基或丙烯醯胺，且R_c及R_d各自獨立為氫、烯基、或選擇性地以一至三個鹵素或選擇性地更以烷氧基取代之烷氧基取代的烷基；R及R_2中之一者為 

；R及R_2中之另一者為$-OR_3$、$-NHR_4$、$-SR_5$、烯基、炔基、芳基、雜芳基、環烷基、雜環烷基、與雜環

烷基稠合之芳基、環烯基或環胺，其中烯基、炔基、芳基、雜芳基、環烷基、雜環烷基及環烯基各自選擇性地以一至三個選自由鹵素、羥基、硝基、氰基、$-NR_eR_f$、$-C(=O)R_g$、$-C(=O)OR_h$、$-SO_2R_i$、$-OSiR_j$、烯基、雜環烷基、選擇性地以一至三個鹵素選擇性取代之烷基或以一至三個鹵素選擇性取代之烷氧基取代的芳基、選擇性地以一至三個鹵素、$-NR_eR_f$或$-OR_k$取代之烷基、及選擇性地以一至四個鹵素、羥基、$-NR_eR_f$或選擇性地更以烷氧基取代之烷氧基取代的烷氧基所組成之群組之基團取代，其中R_e及R_f各自獨立為氫或選擇性地以烷氧基取代之烷基，R_g及R_h各自獨立為氫、烷基或烯基，R_i為烷基，R_j為烷基，且R_k為氫、芳基、或選擇性地更被烷氧基選擇性地取代之烷氧基取代的烷基；R_3及R_5各自獨立為烷基、環烷基或芳基，其中烷基、環烷基或芳基選擇性地以一至四個選自由鹵素、選擇性地以一至四個鹵素取代之烷基、選擇性地以一至三個鹵素或烷氧基取代之烷氧基、$-NR_lR_m$、及雜環烷基所組成之群組之基團取代，其中R_l及R_m各自獨立為氫或烷基；R_4為烷基、環烷基或$-SO_2R_n$，其中R_n為氫、烷基或芳基，且烷基或芳基各自選擇性地以一至三個鹵素取代；以及n為1、2或3。

【0009】 本文中的術語「烷基」是指含有1-12個碳原子的直鏈或支鏈烴基(例如，C_1-C_{10}、C_1-C_8及C_1-C_6)。實例包含甲基、乙基、正丙基、異丙基、正丁基、異丁基、及叔丁基。

【0010】 本文中的術語「烯基」是指具有至少一個雙鍵的直鏈或支鏈烴基，並且包含例如具有至少一個雙鍵的直鏈或支鏈的C_{2-12}烴基、具有至少一個雙鍵的直鏈或支鏈的C_{2-8}烴基、或具有至少一個雙鍵的直鏈或支鏈C_{2-6}烴基。烯基的實例包含但不限於乙烯基、丙烯基或丁烯基。

【0011】 本文中的術語「炔基」是指含有2-20個碳原子的直鏈或支鏈一價或二價烴(例如，C_2-C_{16}、C_2-C_{12}、C_2-C_8、C_2-C_6及C_2-C_4)及一或以上個三鍵。炔基

的實例包含但不限於乙炔基、亞乙炔基、1-丙炔基、1-丁炔基及2-丁炔基、以及1-甲基-2-丁炔基。

【0012】 術語「環烷基」是指具有3-12(例如3-10及3-7)個碳原子的飽和及部分不飽和的單環、雙環、三環、或四環烴基。實例包含環丙基、環丁基、環戊基、環戊烯基、環己基、環己烯基、環庚基及環辛基。

【0013】 術語「雜環烷基」是指具有一或以上個雜原子(例如：O、N、P及S)的非芳香族5-8元單環、8-12元雙環、或11-14元三環系統。實例包含哌嗪基(piperazinyl)、咪唑啶基(imidazolidinyl)、氮雜環庚烷(azepanyl)、吡咯烷基、二氫噻二唑基、二噁烷基、嗎啉基、四氫吡喃基(tetrahydropyranyl)及四氫呋喃基。

【0014】 術語「環烯基」包含環狀不飽和烴基，其包含3至18個碳原子(C_{3-18})、3至12個碳原子(C_{3-12})或3至8個碳原子(C_{3-8})。環烯基的實例包含但不限於環戊烯基、環己烯基或環庚烯基。

【0015】 術語「烷氧基(alkoxy)」或「烷氧基(alkyloxy)」是指-O-烷基。 實例包含甲氧基、乙氧基、丙氧基及異丙氧基。

【0016】 術語「鹵素」是指氟、氯、溴、或碘基。

【0017】 術語「胺基」是指衍生自胺的基團，其為未被取代或被烷基、芳基、環烷基、雜環烷基、或雜芳基單/雙取代。

【0018】 術語「芳基」是指6個碳的單環、10個碳的雙環、14個碳的三環芳香族環系統。芳基的實例包含苯基、萘基、及蒽基。

【0019】 術語「雜芳基」是指具有一或以上個雜原子(例如：O、N、P及S)的芳香族5-8元單環、8-12元雙環、或11-14元三環系統。實例包含苯硫基、三唑基、噁唑基(oxazolyl)、噻二唑基、四唑基、吡唑基、吡啶基、呋喃基、咪唑基、苯並咪唑基、嘧啶基、噻吩基、喹啉基、吲哚基、噻唑基、及苯並噻唑基。

【0020】本文提及的烷基、烯基、炔基、環烷基、環烯基、雜環烷基、烷氧基、芳基、及雜芳基包含取代及未取代之基團兩者。環烷基、雜環烷基、烷氧基、芳基、及雜芳基上可能的取代基包含但不限於C_{1-6}烷基、C_{2-6}烯基、C_{2-6}炔基、C_{3-12}環烷基、C_{3-12}環烯基、C_{1-12}雜環烷基、C_{1-12}雜環烯基、C_{1-6}烷氧基、芳基、芳氧基、雜芳基、雜芳氧基、胺基、C_{1-6}烷基胺基、C_{1-20}二烷基胺基、芳基胺基、二芳基胺基、C_{1-6}烷基磺胺基(alkylsulfonamino)、芳基磺胺基(arylsulfonamino)、C_{1-6}烷基亞胺基(alkylimino)、芳基亞胺基(arylimino)、C_{1-6}烷基亞磺胺基(alkylsulfonimino)、芳基亞磺胺基(arylsulfonimino)、羥基、鹵素、硫基、C_{1-6}烷硫基、芳硫基、C_{1-6}烷基磺醯基、芳基磺醯基、醯基胺基(acylamino)、胺基醯基(aminoacyl)、胺基硫醯基、醯胺基(amido)、甲脒基(amidino)、胍基、脲基、硫脲基、氰基、硝基、亞硝基、疊氮基、醯基、硫醯基、醯氧基、羧基、及羧酸酯。另一方面，烷基上可能的取代基包含除了C_{1-6}烷基以外的所有上述取代基。環烷基、雜環烷基、芳基、及雜芳基也可以彼此稠合。

【0021】除了上述式(I)的化合物，如果可適用它們的藥學上可接受之鹽類及溶劑化物也被本揭露所涵蓋。可以在陰離子與化合物上帶正電荷的基團(例如胺基)之間形成鹽類。適合的陰離子的實例包含氯離子、溴離子、碘離子、硫酸根、硝酸根、磷酸根、檸檬酸根、甲磺酸根、三氟乙酸根、乙酸根、蘋果酸根(malate)、甲苯磺酸根(tosylate)、酒石酸根、富馬酸根(fumurate)、谷胺酸根、葡醣醛酸根(glucuronate)、乳酸根、戊二酸根、及順丁烯二酸根(maleate)。也可以在陽離子與帶負電荷的基團之間形成鹽類。適合的陽離子的實例包含鈉離子、鉀離子、鎂離子、鈣離子、及銨陽離子(諸如四甲銨離子(tetramethylammonium ion))。鹽類更包含含有季氮原子的鹽類。溶劑化物是指在活性化合物與藥學上可接受之溶劑之間形成的複合物。藥學上可接受之溶劑的實例包含水、乙醇、異丙醇、乙酸乙酯、乙酸、及乙醇胺。

【0022】 本揭露的另一態樣是用於治療癌症的醫藥組成物。

【0023】 醫藥組成物含有上述式(I)之化合物中之一者或其藥學上可接受之鹽類及藥學上可接受之載體、賦形劑或稀釋劑。

【0024】 本揭露還涵蓋了這種組成物在製備用於治療癌症的藥物中之用途。

【0025】 用於口服給藥的組成物可以是任何口服可接受的劑型，包含膠囊、錠劑、乳劑及水懸浮液、分散液、及溶液。對於錠劑而言，常用的載體包含乳糖及玉米澱粉，通常還添加諸如硬脂酸鎂的潤滑劑。對於以膠囊形式的口服給藥，有用的稀釋劑包含乳糖及乾燥的玉米澱粉。當口服給藥水懸浮液或乳劑時，可以將活性成分懸浮或溶解在與乳化劑或懸浮劑結合的油相中，如果需要，可以添加某些甜味劑、調味劑或著色劑。口服固體劑型可透過噴霧乾燥技術來製備；熱熔擠出策略、微粉化、及奈米研磨技術。

【0026】 可以根據藥物製劑領域中眾所周知的技術來製備鼻用氣霧劑或吸入組成物。例如，可以使用本領域已知的苯甲醇或其他適合的防腐劑、吸收促進劑、碳氟化合物、及/或其他增溶劑或分散劑，將這種組成物製備為在鹽水中的溶液。具有活性化合物之組成物也可以以栓劑的形式用於直腸給藥。

【0027】 醫藥組成物中的載體、賦形劑及稀釋劑在與組成物的活性成分之相容性上須為「可接受的」(且較佳能夠穩定活性成分)，並且對要被治療的主體無害。可以將一或以上種增溶劑用作藥物賦形制以傳遞活性化合物。其他載體的實例包含膠體氧化矽、硬脂酸鎂、纖維素、硫酸月桂酯鈉(sodium lauryl sulfate)、以及D&C Yellow #10。

【0028】 治療癌症的方法仍在本揭露的範圍內。

【0029】 該方法包含給予需求主體有效量式(I)之化合物或其藥學上可接受之鹽類。

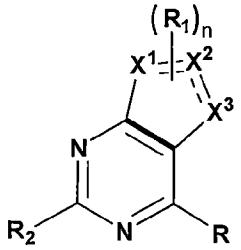
【0030】上述化合物或含有一或以上種上述化合物的醫藥組成物可以以口服、胃腸外、透過吸入噴霧、局部、直腸、鼻、頰、口腔、或經由植入儲藏器的方式給予主體。本文中的術語「腸胃外」包含皮下、皮內、靜脈內、肌肉內、關節內、動脈內、滑膜內(intrasynovial)、胸骨內、脊椎內(intrathecal)、病灶內、及顱內注射或輸注技術。

【0031】術語「治療(treating、treat或treatment)」是指將化合物施用於或給予主體，以治癒、緩解、減輕、改變、矯正(remedy)、改善、或影響疾病、症狀、或其傾向(predisposition)。「有效量」是指賦予主體期望的效果所需的化合物之量。如本領域技術人員所知，有效量取決於給藥途徑、賦形劑用法、以及與其他治療方法(諸如其他活性劑的使用)共同使用的可能性而變化。

【0032】下文描述中闡述了本揭露的一或以上個實施例的細節。根據描述及申請權利範圍，本揭露的其他特徵、目的、以及優點將是顯而易見的。

【實施方式】

【0033】本揭露的一實施例為式(I)之化合物或其立體異構物、互變異構物、或其藥學上可接受之鹽類：



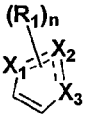
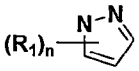
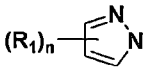
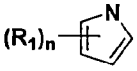
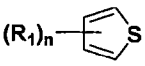
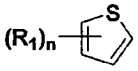
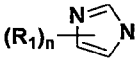
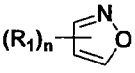
(I)

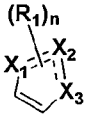
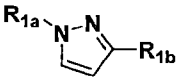
其中每個變數R、R_1、R_2、X_1、X_2、X_3及n的定義如「發明內容」段落所述。

【0034】R_1可以透過將各種肼(hydrazine)衍生物縮合成稠合的芳香族雜環5元環來產生。此外，也可以透過Mitsunobu反應或透過簡單取代反應來建構。Mitsunobu反應使用三苯磷(triphenylphosphine)及偶氮二甲酸酯

(azodicarboxylate)(諸如偶氮二甲酸二乙酯(diethyl azodicarboxylate, DEAD)或偶氮二甲酸二異丙酯(diisopropyl azodicarboxylate, DIAD)以將醇轉化為各種官能團(諸如酯的有機反應))，醇與磷反應形成良好的離去基，然後以經典的S_N2親核試劑取代的方式進行立體化學轉化，形成碳-碳鍵衍生物。

【0035】 R_2可以透過Suzuki合成，而Sonogashira反應是一種在有機合成中用於形成碳-碳鍵的交叉偶合反應(cross-coupling reaction)，其使用鈀催化劑作為催化劑以在末端炔烴(terminal alkyne)與芳基雜芳基或乙烯基鹵化物之間形成碳-碳鍵，並在雜芳族取代中被NR、OR、SR親核試劑取代。

【0036】 本揭露的另一實施例是前述實施例中的化合物或其立體異構物、互變異構物、或其藥學上可接受之鹽類，其中  可為  、  、  、  、  、  或  ，其中n可為1或2。

【0037】 本揭露的另一實施例是前述實施例中的任一項的化合物或其立體異構物、互變異構物、或其藥學上可接受之鹽類，其中  可為  ，其中R_{1a}及R_{1b}可各自獨立地選自由氫、鹵素、烷基、烷氧基、環烷基、雜環烷基、芳基或雜芳基所組成之群組，其中烷基、烷氧基、環烷基、雜環烷基、芳基及雜芳基各自選擇性地以一至三個選自由鹵素、羥基、硝基、氰基、$-NR_aR_b$、$-C(=O)R_c$、$-C(=O)OR_d$、選擇性地以一至四個鹵素取代之雜環烷基、選擇性地以一至三個鹵素或$-NR_aR_b$取代之芳基、選擇性地以一至三個鹵素取代之烷基、及選擇性地以一至三個鹵素或烷氧基取代之烷氧基所組成之群組之基團取代，其中R_a及R_b各自獨立為氫、烷基或丙烯醯胺，且R_c及R_d各自獨立為氫、烯基、或選擇性地以一至三個鹵素或選擇性地更以烷氧基取代之烷氧基取代的烷基。

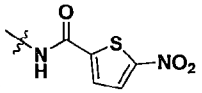
【0038】本揭露的另一實施例是前述實施例中的任一項的化合物或其立體異構物、互變異構物、或其藥學上可接受之鹽類，其中R_{1b}可為氫或烷基。

【0039】本揭露的另一實施例是前述實施例中的任一項的化合物或其立體異構物、互變異構物、或其藥學上可接受之鹽類，其中R_{1b}可為氫。

【0040】本揭露的另一實施例是前述實施例中的任一項的化合物或其立體異構物、互變異構物、或其藥學上可接受之鹽類，其中R_{1a}可為烷基、芳基、雜芳基、環烷基或雜環烷基，其中烷基、環烷基、雜環烷基、芳基及雜芳基各自選擇性地以一至三個選自由F、Cl、羥基、氰基、$-NR_aR_b$、$-C(=O)R_c$、$-C(=O)OR_d$、選擇性地以一至四個F或Cl取代之雜環烷基、選擇性地以一至三個F、Cl或$-NR_aR_b$取代之芳基、選擇性地以一至三個F、Cl取代之烷基、及選擇性地以一至三個F、Cl或烷氧基取代之烷氧基所組成之群組之基團取代，其中R_a為氫或烷基，R_b為烷基或丙烯醯胺，R_c為烷基或烯基，R_d為選擇性地以一至三個F、Cl或選擇性地更以烷氧基取代之烷氧基取代的烷基。

【0041】本揭露的另一實施例是前述實施例中的任一項的化合物或其立體異構物、互變異構物、或其藥學上可接受之鹽類，其中R_{1a}可為烷基、苄基、苯基、吡啶基、吡咯烷基、環戊基、環己基、環庚基或哌啶基，其中烷基選擇性地以羥基、氰基、二烷基胺基、選擇性地以一或兩個F取代之雜環烷基、或選擇性地以烷氧基取代之烷氧基取代，苄基選擇性地以一個F取代，苯基選擇性地以一或兩個F、Cl、$-NR_aR_b$、選擇性地以三個F取代之烷基、或選擇性地以一至三個F取代之烷氧基取代，吡啶基選擇性地被三個F選擇性地取代之烷基取代，吡咯烷基以烷基、$-C(=O)R_c$或$-C(=O)R_d$取代，環戊基、環己基及環庚基選擇性地以一或兩個F、Cl或烷基取代，以及哌啶基選擇性地以烷基、$-C(=O)R_c$、或$-C(=O)OR_d$取代，其中R_a為氫，R_b為丙烯醯胺，R_c為烷基或烯基，R_d為選擇性地以一至三個F、Cl或選擇性地更以烷氧基取代之烷氧基取代的烷基。

【0042】本揭露的另一實施例是前述實施例中的任一項的化合物或其立體異構物、互變異構物、或其藥學上可接受之鹽類，其中R_{1a}可為苄基、苯基、吡啶基、吡咯烷基、環戊基、環己基、環庚基或哌啶基，其中苄基選擇性地以一個F取代，苯基選擇性地以一或兩個F、Cl、$-NR_aR_b$、選擇性地以三個F取代之烷基、或選擇性地以一至三個F取代之烷氧基取代，吡啶基選擇性地被三個F選擇性地取代之烷基取代，吡咯烷基以烷基、$-C(=O)R_c$或$-C(=O)OR_d$取代，環戊基、環己基及環庚基選擇性地以一或兩個F或烷基取代，以及哌啶基選擇性地以烷基、$-C(=O)R_c$、或$-C(=O)OR_d$取代，其中R_a為氫，R_b為丙烯醯胺，R_c為烷基或烯基，R_d為選擇性地以一至三個F或選擇性地更以烷氧基取代之烷氧基取代的烷基。

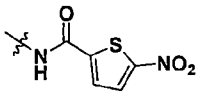
【0043】本揭露的另一實施例是前述實施例中的任一項的化合物或其立體異構物、互變異構物、或其藥學上可接受之鹽類，其中R可為  。

【0044】本揭露的另一實施例是前述實施例中的任一項的化合物或其立體異構物、互變異構物、或其藥學上可接受之鹽類，其中R_2可為$-OR_3$、$-NHR_4$、$-SR_5$、烯基、炔基、芳基、雜芳基、環烷基、雜環烷基、與雜環烷基稠合的芳基或環烯基，其中烯基、炔基、芳基、雜芳基、環烷基、雜環烷基及環烯基各自選擇性地以一至三個選自由F、Cl、羥基、氰基、$-NR_eR_f$、$-C(=O)R_g$、$-C(=O)OR_h$、$-SO_2R_i$、$-OSiR_j$、烯基、雜環烷基、選擇性地被一至三個F、Cl選擇性取代之烷基或以一至三個F、Cl選擇性取代之烷氧基取代的芳基、選擇性地以一至三個F、Cl、$-NR_eR_f$或$-OR_k$取代之烷基、及選擇性地以一至四個F、Cl、羥基、$-NR_eR_f$或選擇性地更以烷氧基取代之烷氧基取代的烷氧基所組成之群組之基團取代，其中R_e及R_f各自獨立為氫或選擇性地以烷氧基取代之烷基，R_g及R_h各自獨立為氫、烷基、或烯基，R_i為烷基，R_j為烷基，及R_k為氫、芳基、或選擇

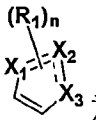
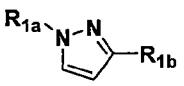
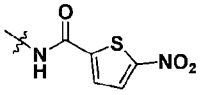
性地更被烷氧基選擇性地取代之烷氧基取代的烷基；R_3及R_5各自獨立為烷基、環烷基或芳基，其中烷基、環烷基或芳基選擇性地以一至四個選自由F、Cl、選擇性地以一至四個F或Cl取代之烷基、選擇性地以一至三個F、Cl或烷氧基取代之烷氧基、$-NR_lR_m$、及雜環烷基所組成之群組之基團取代，其中R_l及R_m各自獨立為氫或烷基；以及R_4為烷基、環烷基或$-SO_2R_n$，其中R_n為氫、烷基或芳基，且烷基或芳基各自選擇性地以一至三個F或Cl取代。

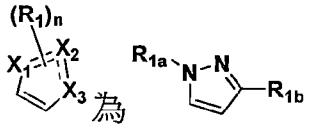
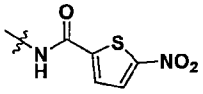
【0045】本揭露的另一實施例是前述實施例中的任一項的化合物或其立體異構物、互變異構物、或其藥學上可接受之鹽類，其中R_2可為$-OR_3$、$-NHR_4$、$-SR_5$、苯乙烯基、苯乙炔基、環己基、環己烯基、苯基、苯並二噁唑基(benzodioxolyl)、苯並二噁烷基(benzodioxinyl)、苯並呋喃基、呋喃基、苯硫基、噁唑基、咪唑基、吡唑基、噁二唑基、氮雜環丁烷基、吡咯烷基、哌啶基、嗎啉基、哌嗪基(piperazinyl)、嘧啶基、或吡啶基，其中苯乙烯基選擇性地被一至三個F或烷氧基取代之烷基取代，苯乙炔基選擇性地被一至三個F選擇性取代之烷基或一至三個F選擇性取代之烷氧基取代，環己基選擇性地以一至三個烷基取代，環己烯基選擇性地以一至三個烷基取代，苯基選擇性地以一至三個選自由F、Cl、氰基、二烷基胺基、$-C(=O)R_g$、$-C(=O)OR_h$、$-SO_2R_i$、選擇性地以一至三個F、二烷基胺基或烷氧基取代之烷基、及選擇性地以一至三個F或選擇性地更以烷氧基取代之烷氧基取代的烷氧基所組成之群組之基團取代，苯硫基選擇性地以Cl或烷基取代，噁唑基選擇性地以一或兩個烷基取代，吡唑基選擇性地被一至三個F選擇性地取代之烷基取代，噁二唑基選擇性地以烷基取代，氮雜環丁烷基選擇性地以一或兩個F或$-OSiR_j$取代，吡咯烷基選擇性地以羥基、氰基、烯基、$-C(=O)OR_h$、一至兩個F、或選擇性地以羥基、苯氧基或選擇性地更被烷氧基選擇性地取代之烷氧基取代之烷氧基取代的烷基取代，哌啶基選擇性地以烷基、一或兩個F、$-C(=O)R_g$取代，嗎啉基選擇性地以一至三個烷基取代；哌嗪

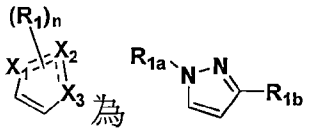
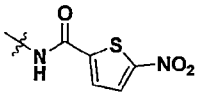
基(piperazinyl)選擇性地以烷基取代，以及吡啶基選擇性地以一或兩個選自由F、Cl、氰基、哌啶基、嗎啉基、$-NR_eR_f$、選擇性地以三至四個F取代之烷基、及選擇性地以一至四個F、羥基、二烷基胺基或選擇性地更以烷氧基取代之烷氧基取代的烷氧基所組成之群組之基團取代，其中R_e為烷基，R_f為選擇性地以烷氧基取代之烷基，R_g為氫、烷基或烯基，R_h為氫或烷基，R_i為烷基，且R_j為烷基；R_3為苯基、環烷基或烷基，其中苯基選擇性地以F、嗎啉基、選擇性地以一至三個F取代之烷氧基、或選擇性地以一至三個F取代之烷基取代，且烷基選擇性地以一至四個F、嗎啉基、二烷基胺基、或選擇性地以烷氧基取代之烷氧基取代；R_4為烷基、環烷基或$-SO_2R_n$，其中R_n為選擇性地以一至三個Cl取代之苯基；以及R_5為選擇性地以Cl取代之苯基。

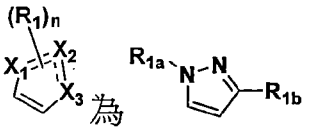
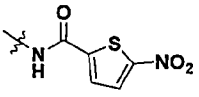
【0046】本揭露的另一實施例是前述實施例中的任一項的化合物或其立體異構物、互變異構物、或其藥學上可接受之鹽類，其中R_2可為  。

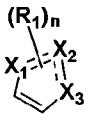
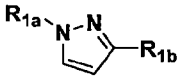
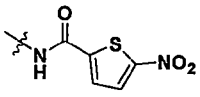
【0047】本揭露的另一實施例是前述實施例中的任一項的化合物或其立體異構物、互變異構物、或其藥學上可接受之鹽類，其中R可為苯基或嗎啉基，且苯基選擇性地以烷基或選擇性地以一至三個F取代之烷氧基取代。

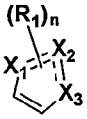
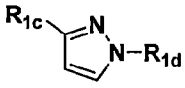
【0048】本揭露的另一實施例是前述實施例中的任一項的化合物或其立體異構物、互變異構物、或其藥學上可接受之鹽類，其中  為  ，其中R_{1a}為烷基且R_{1b}為氫；R為  ；以及R_2為苯乙烯基或苯基，其中苯基以一至三個F取代之烷基取代或以一至三個F取代之烷氧基取代，且苯乙烯基被一至三個F取代之烷基取代。

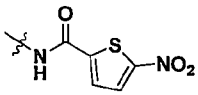
【0049】本揭露的另一實施例是前述實施例中的任一項的化合物或其立體異構物、互變異構物、或其藥學上可接受之鹽類，其中  為，其中R_{1b}為氫，且R_{1a}為選擇性地以一或兩個F、Cl、丙烯醯胺基、選擇性地以三個F取代之烷基或選擇性地以三個F取代之烷氧基取代的苯基；R為  ；以及R_2為$-OR_3$、苯基、苯並二噁唑基、苯硫基、吡唑基、吡咯烷基、嘧啶基或吡啶基，其中苯基選擇性地以一或兩個選自由F、Cl、氰基、選擇性地以一至三個F取代之烷基、及選擇性地以一至三個F取代之烷氧基所組成之群組之基團取代，吡唑基選擇性地以烷基取代，吡咯烷基以$-C(=O)OR_h$、一至兩個F、或以羥基、苯氧基或烷氧基取代之烷基取代，吡啶基選擇性地以一或兩個選自由F、Cl、氰基、哌啶基、烷基、及選擇性地以二烷基胺基或選擇性地更以烷氧基取代之烷氧基取代的烷氧基所組成之群組之基團取代，R_3為選擇性地以二烷基胺基取代之烷基，以及R_h為烷基。

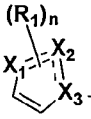
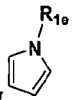
【0050】本揭露的另一實施例是前述實施例中的任一項的化合物或其立體異構物、互變異構物、或其藥學上可接受之鹽類，其中  為，其中R_{1b}為氫，且R_{1a}為以一至三個F取代之烷基取代的吡啶基；R為  ；以及R_2為以一或兩個F或Cl取代之苯基。

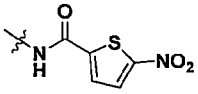
【0051】本揭露的另一實施例是前述實施例中的任一項的化合物或其立體異構物、互變異構物、或其藥學上可接受之鹽類，其中  為，其中R_{1b}為氫，R_{1a}為以$-C(=O)OR_d$取代之哌啶基，且R_d為烷基；R為  ；以及R_2為以Cl或$-C(=O)OR_h$取代之苯基，其中R_h為烷基。

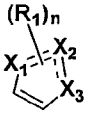
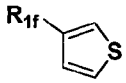
【0052】本揭露的另一實施例是前述實施例中的任一項的化合物或其立體異構物、互變異構物、或其藥學上可接受之鹽類，其中  為  ，其中R_{1b}為氫，且R_{1a}為選擇性地以一或兩個F或烷基取代之環己基；R為  ；以及R_2為苯基或吡啶基，其中苯基以一或兩個F、Cl、或–C(=O)OR_h取代，其中R_h為烷基，且吡啶基以F、Cl或烷氧基取代。

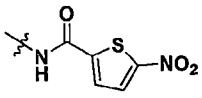
【0053】本揭露的另一實施例是前述實施例中的任一項的化合物或其立體異構物、互變異構物、或其藥學上可接受之鹽類，其中  可為  ，其中R_{1c}及R_{1d}分別為烷基。

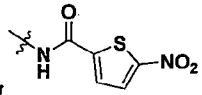
【0054】本揭露的另一實施例是前述實施例中的任一項的化合物或其立體異構物、互變異構物、或其藥學上可接受之鹽類，其中R可為  ，且R_2為苯基，其中苯基選擇性地以F、選擇性地以一至三個F取代之烷基或選擇性地以一至三個F取代之烷氧基取代。

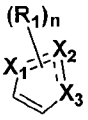
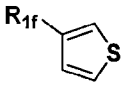
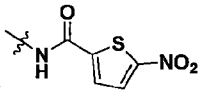
【0055】本揭露的另一實施例是前述實施例中的任一項的化合物或其立體異構物、互變異構物、或其藥學上可接受之鹽類，其中  可為  ，其中R_{1e}為烷基。

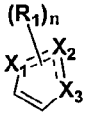
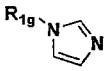
【0056】本揭露的另一實施例是前述實施例中的任一項的化合物或其立體異構物、互變異構物、或其藥學上可接受之鹽類，其中R可為  ，且R_2為選擇性地以烷基取代之苯基。

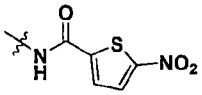
【0057】本揭露的另一實施例是前述實施例中的任一項的化合物或其立體異構物、互變異構物、或其藥學上可接受之鹽類，其中  可為  ，其中R_{1f}為烷基或選擇性地以鹵素或烷基取代之芳基。

【0058】本揭露的另一實施例是前述實施例中的任一項的化合物或其立體異構物、互變異構物、或其藥學上可接受之鹽類，其中R_{1f}可為烷基，R_2可為  ，且R可為苯基，其中苯基選擇性地被一至三個F選擇性地取代之烷氧基取代。

【0059】本揭露的另一實施例是前述實施例中的任一項的化合物或其立體異構物、互變異構物、或其藥學上可接受之鹽類，其中R_{1f}可為烷基或選擇性地以F或烷基取代之苯基，R可為  ，且R_2可為$-OR_3$、吡咯烷基或苯基，其中吡咯烷基選擇性地以一或兩個F取代，苯基選擇性地以一至三個選自由F、Cl、二烷基胺基、選擇性地以一至三個F取代之烷基、以及選擇性地以一至三個F取代之烷氧基所組成之群組之基團取代，且R_3為選擇性地以烷基取代之苯基。

【0060】本揭露的另一實施例是前述實施例中的任一項的化合物或其立體異構物、互變異構物、或其藥學上可接受之鹽類，其中  為  ，其中R_{1f}為烷基，R為  ，且R_2為苯基，其中苯基選擇性地被一至三個F取代之烷基取代或選擇性地以一至三個F取代之烷氧基取代。

【0061】本揭露的另一實施例是前述實施例中的任一項的化合物或其立體異構物、互變異構物、或其藥學上可接受之鹽類，其中  可為  ，其中R_{1g}可為環烷基或選擇性地以–C(=O)OR_d取代之雜環烷基，且R_d為烷基。

【0062】本揭露的另一實施例是前述實施例中的任一項的化合物或其立體異構物、互變異構物、或其藥學上可接受之鹽類，其中R_{1g}可為哌啶基或環己基，R可為  ，且R_2可為選擇性地以F取代之苯基或選擇性地以F或烷氧基取代之吡啶基。

【0063】本揭露的另一實施例可為選自由列出於下表1至表10中的化合物1-1至1-33、化合物2-1至2-8、化合物3-1至3-12、化合物4-1至4-22、化合物5-1至5-57、化合物6-1至6-145、化合物7-1至7-19、化合物8-1至8-16、化合物9-1至9-13及化合物10-1至10-72所組成之群組中之化合物或其立體異構物、互變異構物、或其藥學上可接受之鹽類。

【0064】本揭露的再另一實施例可為選自由化合物1-4至1-5、化合物1-11、化合物1-22、化合物1-27、化合物4-2、化合物4-5、化合物5-6、化合物5-18、化合物5-28至5-33、化合物5-35、化合物5-39、化合物5-40、化合物5-42、化合物5-44、化合物5-45、化合物5-47、化合物5-49、化合物5-56、化合物6-4、化合物6-11、化合物6-18、化合物6-19、化合物6-24至6-28、化合物6-35、化合物6-36、化合物6-39、化合物6-43、化合物6-45、化合物6-46、化合物6-50至6-54、化合物6-57至6-58、化合物6-66、化合物6-69、化合物6-71、化合物6-75、化合物6-85、化合物6-89至6-91、化合物6-104、化合物6-106、化合物6-108、化合物6-110至6-112、化合物6-114至6-121、化合物6-125、化合物6-127至6-128、化合物6-130、化合物6-133、化合物6-135、化合物6-137、化合物7-1、化合物7-3、化合物7-6、

化合物7-13、化合物7-19、化合物9-3、化合物9-5、化合物10-13、化合物10-14、化合物10-18、化合物10-23、化合物10-32、化合物10-40、化合物10-55、化合物10-57、以及化合物10-64所組成之群組中之化合物或其立體異構物、互變異構物、或其藥學上可接受之鹽類。

【0065】本揭露之化合物可含有不對稱或對掌性(chiral)中心，並且以不同立體異構(stereoisomeric)的形式存在。除非另有說明，否則本揭露之化合物之所有立體異構的形式及其混合物、包含外消旋(racemic)混合物是在本發明的範圍內。此外，本揭露之化合物也可以以不同的幾何(geometric)及位置(positional)異構物存在。例如，順式(cis-forms)及反式(trans-forms)以及具有雙鍵或稠合環(fused ring)之化合物的混合物也在本發明的範圍內。

【0066】非鏡向異構物(Diastereomeric)混合物可以透過任何方法(諸如透過層析法(chromatography)及/或分級結晶(fractional crystallization))分離成他們個別的非鏡向異構物。鏡向異構物(Enantiomers)可透過使用對掌性HPLC管柱分離，或透過與適合的具旋光性的化合物(optically active compound)反應將鏡向異構混合物轉化為非鏡向異構混合物來分離非鏡向異構物，並將個別的非鏡向異構物轉化為純鏡向異構物。可透過不對稱轉變(asymmetric transformation)、透過使用具旋光性的起始材料或透過使用旋光性試劑、催化劑、基質或溶劑的不對稱合成，將立體異構物轉化為另一種立體異構物來合成特定的立體異構物。

【0067】本揭露還包括一種醫藥組成物，包括(1)本揭露之化合物或其立體異構物、互變異構物、或其藥學上可接受之鹽類；以及(2)藥學上可接受之載體、賦形劑或稀釋劑。該組成物還可包括至少一種額外的藥物，例如抗癌藥物。本揭露之化合物或其藥學上可接受之鹽類或組成物可用於製備抑制腫瘤細胞生長或治療癌症的藥物。

【0068】本揭露還包括用於治療癌症的方法，包括給予需求主體有效量的本揭露之化合物或其立體異構物、互變異構物、或其藥學上可接受之鹽類的步驟。

【0069】本揭露還涵蓋了抑制腫瘤細胞生長的方法，包括給予需求主體有效量的本揭露的化合物或其立體異構物、互變異構物、或其藥學上可接受之鹽類的步驟。

【0070】於本揭露中，前述主體可為哺乳類動物，例如人類。

【0071】於本揭露中，本揭露的化合物或其立體異構物、互變異構物、或其藥學上可接受之鹽類可以抑制腫瘤細胞的生長，從而達到治療癌症的目的。癌症的實例包括但不限於胃癌、結腸癌(colon cancer)、大腸直腸癌(colorectal cancer)、乳癌、肺癌、前列腺癌、膀胱癌、胰腺癌、肝癌、子宮癌(uterine cancer)、子宮頸癌(cervical caner)、子宮內膜癌、食道癌、白血病、淋巴瘤、腎臟癌、骨肉瘤(osteosarcoma)、卵巢癌、皮膚癌、小腸癌、胸腺癌、甲狀腺癌、神經系統癌、骨癌、腦癌、或頭頸癌。

【0072】本揭露的化合物或其立體異構物、互變異構物、或其藥學上可接受之鹽類可與至少一種額外的藥物(諸如抗癌藥物)合併施用。給藥製劑可以是例如(a)一種單一製劑，包括本揭露之化合物或其立體異構物、互變異構物、或其藥學上可接受之鹽類、藥學上可接受之載體、賦形劑或稀釋劑以及至少一種額外的藥物；或是(b)兩種製劑以任何順序同時或依序給藥，其中一種製劑包括本揭露之化合物或其立體異構物、互變異構物、或其藥學上可接受之鹽類、藥學上可接受載體、賦形劑或稀釋劑，另一種製劑包括至少一種額外的藥物。

【0073】適合的抗癌劑可包含賀癌平(Herceptin)、利妥昔(Rituximab)、多烯紫杉醇(Docetaxel)、凱希得平(Capecitabine)、西妥昔單抗(Cetuximab)、吉非替

尼(Gefitinib)、PD-1、索拉非尼甲苯磺酸(Sorafenib tosylate)或伊馬替尼(Imatinib)，但本揭露不限於此。本領域已知的任何其他抗癌劑也可以用於本揭露中。

【0074】 合成式(I)之化合物的方法為本領域眾所周知的。例如參見R. Larock, Comprehensive Organic Transformations (2nd Ed., VCH Publishers 1999); P. G. M. Wuts以及T. W. Greene, Greene's Protective Groups in Organic Synthesis(4th Ed., John Wiley and Sons 2007)、L. Fieser and M. Fieser, Fieser and Fieser's Reagents for Organic Synthesis (John Wiley and Sons 1994)、L. Paquette, ed., Encyclopedia of Reagents for Organic Synthesis (2nd ed., John Wiley and Sons 2009)、P. Roszkowski, J.K. Maurin, Z.、Czarnocki "Enantioselective synthesis of (R)-(–)-praziquantel (PZQ)" Tetrahedron: Asymmetry 17 (2006) 1415–1419、以及L. Hu, S. Magesh, L. Chen, T. Lewis, B. Munoz, L. Wang "Direct inhibitors of keap1-nrf2 interaction as antioxidant inflammation modulators," WO2013/067036。

【0075】 由此製備的式(I)之化合物首先可以使用體外測定法(例如NCI-60篩選平台或MTS方法)來篩選。隨後可以使用本領域已知的體內測定法對其進行評估。可以進一步測試選定化合物，以驗證其在疾病相關功效及不良反應模型中的功效。可以根據結果決定適當的劑量範圍及給藥途徑。

【0076】 下列實施例清楚地展現本揭露的前述及其他技術內容、特徵及/或效果。透過具體實施例的闡述，人們將進一步理解本揭露為達到上述目的而採用的技術手段及效果。此外，由於本文所揭露的內容應由本領域技術人員容易理解且可實施，因此，不脫離本揭露的概念的所有相等改變或修改應由所附申請專利範圍所涵蓋。

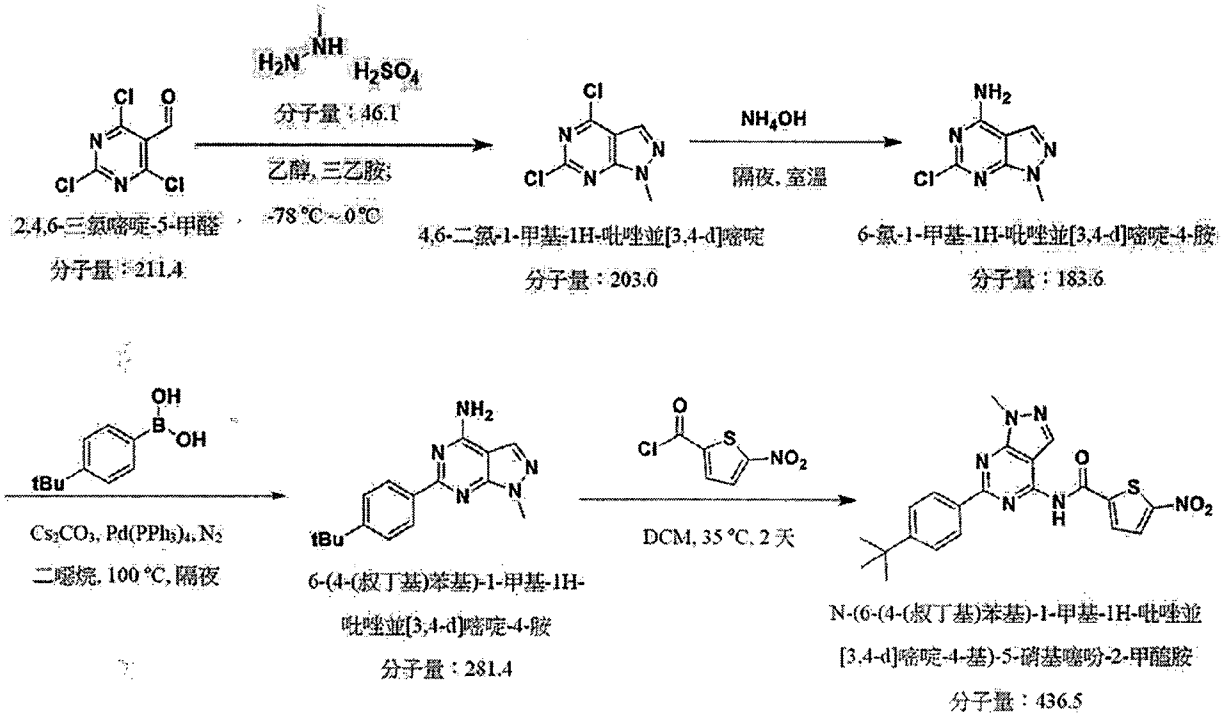
【0077】 無須進一步闡述，相信本領域的技術人員可基於以上描述最大程度地利用本揭露。因此，以下具體實施例被解釋為僅是說明性的，而不以任何方式限制本揭露的其餘部分。本文所引用的所有出版物透過全文併入做為參考。

【0078】 以下描述用於合成本揭露的示例性化合物的方法。

【0079】 除非另有說明，否則所有使用的起始材料都是可商購並按供應原樣使用。在經火焰乾燥的玻璃器皿中進行需要無水條件的反應，並在氬氣或氮氣氣氛下冷卻。除非另有說明，否則反應在氬氣或氮氣下進行，並透過分析薄層(analytical thin-layer)層析法進行監測，該薄層層析法在預塗有由默克公司提供的矽膠60 F254的玻璃背板(5 cm_10 cm)上進行。產生的層析圖的可視化是透過在紫外燈(λ=254 nm)下觀察，然後浸入含有乙酸(3%體積百分濃度)的茚三酮(Ninhydrin)(0.3%體積百分濃度)的nBuOH溶液或磷鉬酸(2.5%體積百分濃度)的乙醇溶液，並用熱風槍焦化(charring)。在如下使用之前，將反應的溶劑在氬氣或氮氣氣氛下乾燥：藉由乾燥分子篩5A(LC technology solution Inc)的管柱乾燥THF、甲苯、及DCM。DMF透過氫化鈣乾燥或可商購無水的DMF。常規使用快速層析法純化及分離產物混合物，以由RediSep提供的RediSep Rf矽膠一次性快速層析管柱Gold®20-40 / 40-60微米矽膠及可重複使用的RediSep RfGold®C18反相層析管柱20-40微米。沖提液(Eluent)系統以體積百分濃度表示。於Bruker AVIII(400 MHz)上記錄^{13}C及^{1}H NMR光譜。使用氯仿-d或二甲基亞碸-d6及CD_3OD作為溶劑，且使用TMS(δ 0.00 ppm)作為內標準品(internal standard)。化學位移數值(Chemical shift values)以相對於TMS的ppm(δ)單位表示。多重態(Multiplicities)紀錄為s(單重態)、br s(寬單重態)、d(雙重態)、t(三重態)、q(四重態)、dd(雙重雙重態)、dt(雙重三重態)、m(多重態)。耦合常數(Coupling constants)(J)以Hz表示。使用Thermo LTQ XL質譜儀紀錄電噴物質譜(Electrospray mass spectra, ESMS)。光譜數據紀錄為m/z值。

【0080】 在製備本發明之化合物時，可能需要保護中間物的遠端官能基(例如伯胺或仲胺)。根據遠端官能基的性質及製備方法的條件，對此類保護的需求可能有所不同。適合的胺基保護基團(NHPg)包括例如乙醯基、三氟乙醯基、叔

丁氧羰基(tbutoxycarbonyl, BOC)、9-芴基亞甲基氧羰基(9-fluorenylmethyleneoxycarbonyl, Fmoc)以及苄氧羰基(CBz)。相似地，「羥基保護基」是指阻斷或保護羥基官能基的羥基的取代基。適合的羥基保護基(OPg)包括例如烯丙基(allyl)、乙醯基、甲矽烷基、苄基、對甲氧基苄基(paramethoxy benzyl)、三苯甲基(trityl)等。本領域技術人員可以容易地確定是否需要這種保護。



【0081】 實驗步驟

【0082】 步驟1：環化(Cyclization)

【0083】 向溶於冷卻至-78°C的EtOH(50 ml)的2,4,6-三氯嘧啶-5-甲醛(2,4,6-trichloropyrimidine-5-carbaldehyde)(3.71 g，17.5 mmol)的溶液中加入甲基肼(methyl hydrazine)(0.93 ml，17.5 mmol)及TEA(8 ml)。將混合物在-78°C下攪拌30分鐘，然後在0°C下攪拌2小時。將溶液在不加熱的情況下真空濃縮。向減小體積的溶液中加入乙酸乙酯，且溶液以飽和碳酸氫鈉溶液洗滌，並在不加熱的情況下真空濃縮。用小的矽膠塞過濾(2：1 = EtOAc：Hex)，並濃縮得到所需為黃

色固體的產物4,6-二氯-1-甲基-1H-吡唑並[3,4-d]嘧啶(4,6-Dichloro-1-methyl-1H-pyrazolo[3,4-d]pyrimidine)(2.84 g，80%)。

【0084】 步驟2：胺化(Amination)

【0085】 向反應燒瓶中的4,6-二氯-1-甲基-1H-吡唑並[3,4-d]嘧啶(4,6-Dichloro-1-methyl-1H-pyrazolo[3,4-d]pyrimidine)(2.84 g，14 mmol)懸浮液中加入THF(56 ml)，等待固體完全溶解。然後加入20 g 30%銨溶液，並在室溫(25°C)下反應24小時，然後將60 ml水倒入溶液中，抽氣過濾得到為黃色固體粉末的6-氯-1-甲基-1H-吡唑並[3,4-d]嘧啶-4-胺(6-chloro-1-methyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine)(2.17g，85%)。

【0086】 步驟3：Suzuki耦合反應

【0087】 使用6個交替的真空/氮氣沖洗循環向100 ml玻璃燒瓶中的6-氯-1-甲基-1H-吡唑並[3,4-d]嘧啶-4-胺(6-chloro-1-methyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine)(1.84 g，10 mmol)、4-(叔丁基)苯基硼酸(4-(tert-butyl)phenyl boronic acid)(2.67 g，15 mmol)、四(三苯基膦)鈀(Tetrakis (triphenylphosphine) palladium)(0)(1.16 g，1 mmol)、1,4-二噁烷(40 ml)、水(2 ml)及碳酸銫水溶液(2.0 M，20 ml，40 mmol)的懸浮液進行脫氧。將反應混合物加熱至100°C持續16小時。冷卻至室溫後，將矽藻土(Celite)粉末倒入燒瓶中，並在室溫下攪拌10分鐘，然後抽氣過濾，將濾液分配在乙酸乙酯(80 ml)與飽和碳酸氫鈉水溶液(30 ml)之間。分離各層，並用鹽水(30 ml)洗滌有機層，經硫酸鈉乾燥、過濾，並減壓濃縮。殘餘物透過矽膠層析法純化(0-25%正己烷/乙酸乙酯，線性梯度)，得到為黃色粉末的6-(4-(叔丁基)苯基)-1-甲基-1H-吡唑並[3,4-d]嘧啶-4-胺(6-(4-(tert-butyl)phenyl)-1-methyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine)(2.25 g，80%)。

【0088】 步驟4：醯胺化(Amidation)反應

【0089】 由羰基酸醯胺化形成的N-(6-(4-(叔丁基)苯基)-1-甲基-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺(N-(6-(4-(tert-butyl)phenyl)-1-methyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

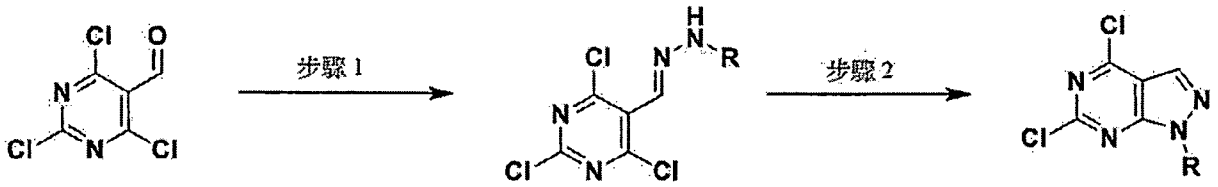
【0090】 向6-(4-(叔丁基)苯基)-1-甲基-1H-吡唑並[3,4-d]嘧啶-4-胺(6-(4-(tert-butyl)phenyl)-1-methyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine)(843 mg，3.00 mmol)的吡啶(6ml)溶液中，加入5-硝基噻吩-2-羰基氯(5-nitrothiophene-2-carbonyl chloride)(900 mg，4.68 mmol)。將反應混合物在環境溫度攪拌15小時。加入水，且產物用乙酸乙酯萃取。分離有機層，乾燥(無水硫酸鈉)並真空蒸發。產物透過矽膠管柱層析法純化(己烷-乙酸乙酯梯度沖提液)，並用己烷及丙酮再結晶(recrystallization)，得到標題化合物。產量980 mg(75%)。為黃色粉末的N-(6-(4-(叔丁基)苯基)-1-甲基-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺(N-(6-(4-(tert-butyl)phenyl)-1-methyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)。

【0091】 實驗步驟

【0092】 透過縮合及閉環反應進行環化

【0093】 向溶於50 ml乙醇並透過冰浴冷卻至0°C的2,4,6-三氯嘧啶-5-甲醛(2,4,6-trichloropyrimidine-5-carbaldehyde)(3.7 g，17.5 mmol)溶液中加入鹽酸苯肼(phenylhydrazine hydrochloride)(2.53 g，17.5 mmol)及8 ml TEA。將混合物在0°C下攪拌30分鐘，並自發地達到環境溫度。將溶液在不加熱的情況下真空濃縮。向減小體積的溶液中加入乙酸乙酯，且溶液用飽和碳酸氫鈉溶液洗滌，並在不加熱的情況下真空濃縮。用小的矽膠塞過濾(EtOAc：Hex = 2：1)並濃縮，得到

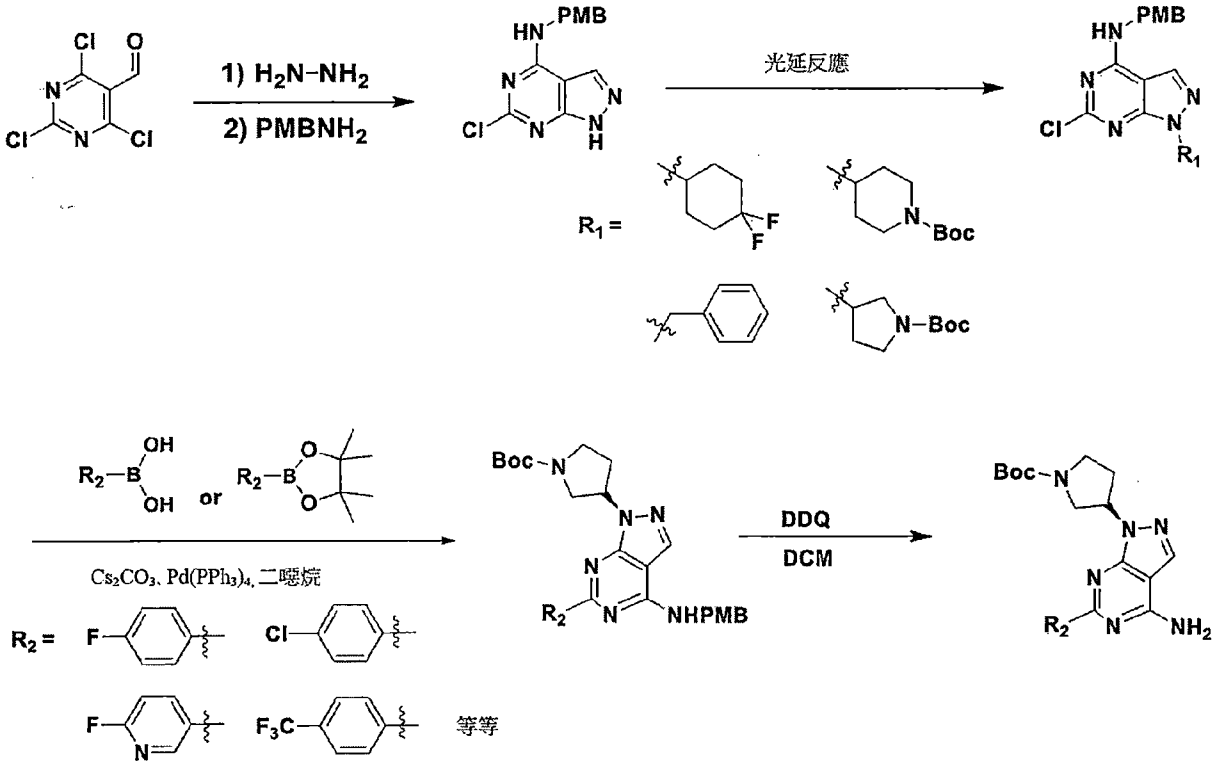
黃色固體的所需為產物4,6-二氯-1-苯基-1H-吡唑並[3，4-d]嘧啶(4,6-dichloro-1-phenyl-1H-pyrazolo[3,4-d] pyrimidine)(3.94 g，85%)。

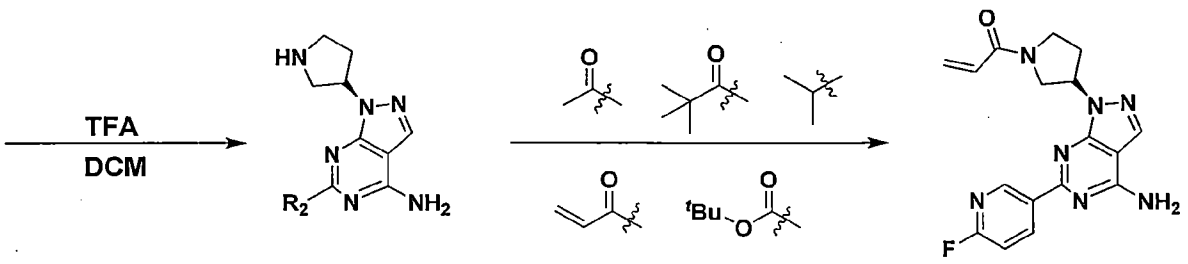


步驟 1 條件				步驟 2 條件			
肼(hydrazine)(1 當量)	溶劑	溫度(°C)	時間	溶劑	基質*a	溫度(°C)	時間
甲肼硫酸鹽 (Methylhydrazine sulfate)	乙醇	-78	20 分鐘	乙醇	3 當量	-78 to 0	1 小時
異丙肼鹽酸鹽 (*iso*-Propylhydrazine hydrochloride)	乙醇	-78	20 分鐘	乙醇	3 當量	-78 to 0	1 小時
叔丁肼鹽酸鹽 (*tert*-Butylhydrazine hydrochloride)	乙醇	-78	20 分鐘	乙醇	3 當量	-78 to 0	1 小時
2-羥乙基肼(2-Hydroxyethyl hydrazine)	乙醇	-78	20 分鐘	乙醇	3 當量	-78 to 0	1 小時
氰乙基肼 (Cyanoethylhydrazine)	乙醇	-78	20 分鐘	乙醇	3 當量	-78 to 0	1 小時
二甲基胺基乙基肼二鹽酸鹽(Dimethylaminoethyl hydrazine dihydrochloride)	乙醇	-78	20 分鐘	乙醇	3 當量	-78 to 0	1 小時
鹽酸苯肼(Phenylhydrazine hydrochloride)	乙醇	-78	20 分鐘	乙醇	3 當量	-78 to 0	1 小時
4-叔丁基苯肼鹽酸鹽 (4-tert-Butylphenyl hydrazine hydrochloride)	乙醇	-78	30 分鐘	乙醇	3 當量	-78 to 0	1 小時
2,4-二氯苯肼鹽酸鹽 (2,4-Dichlorophenylhydrazine hydrochloride)	二噁烷	0	1 小時	二噁烷	3 當量	100	5 天
3,4-二氯苯肼鹽酸鹽 (3,4-Dichlorophenylhydrazine hydrochloride)	二噁烷	0	1 小時	二噁烷	3 當量	100	3 天
4-氯苯肼鹽酸鹽 (4-Chlorophenylhydrazine Hydrochloride)	二噁烷	0	1 小時	二噁烷	3 當量	0 至室溫	1 天
3-氯-6-肼基噠嗪 (3-Chloro-6-hydrazinopyridazine)	ACN	-10	16 小時	ACN	無	回流	16 小時
2-肼基-5-(三氟甲基)吡啶 (2-Hydrazinyl-5-(trifluoromethyl)pyridine)	DMF	室溫	1 天	二噁烷	0	110	1 天

3-氯苯肼鹽酸鹽 (3-Chlorophenylhydrazine hydrochloride)	二噁烷	室溫	1天	二噁烷	1.3當量	回流	2天
3-氟苯肼鹽酸鹽 (3-Fluorophenylhydrazine hydrochloride)	ACN	室溫	1天	ACN	1當量	回流	1天
4-氟苯肼鹽酸鹽 (4-Fluorophenylhydrazine hydrochloride)	DMF	室溫	1天	二噁烷	無	100	1天
4-(三氟甲基)苯肼 (4-(Trifluoromethyl)phenyl hydrazine)	二噁烷	室溫	1天	二噁烷	1當量	回流	1天
4-三氟甲氧基苯肼鹽酸鹽 (4-Trifluoromethoxyphenyl hydrazine hydrochloride)	DMF	室溫	1天	二噁烷	0	100	1天
4-硝基苯肼鹽酸鹽 (4-Nitrophenylhydrazine hydrochloride)	ACN	室溫	1天	ACN	1當量	回流	4天
4-甲氧基苯肼鹽酸鹽 (4-methoxyphenylhydrazine hydrochloride)	二噁烷	0~室溫	12小時	二噁烷	0	回流	4小時

*a：使用TEA或DIPEA作為基質





【0094】 透過Mitsunobu反應形成N-C鍵

【0095】 4-(6-氯-4-((4-甲氧基苄基)胺基)-1H-吡唑並[3,4-d]嘧啶-1-基)哌啶-1-甲酸叔丁酯(tert-butyl 4-(6-chloro-4-((4-methoxybenzyl)amino)-1H-pyrazolo[3,4-d] pyrimidin-1-yl)piperidine-1-carboxylate)的形成。

【0096】 在N_2下向火焰乾燥的圓底瓶中加入在無水四氫呋喃(anhydrous tetrahydrofuran)(175 ml)中的6-氯-N-(4-甲氧基苄基)-1H-吡唑並[3,4-d]嘧啶-4-胺(6-chloro-N-(4-methoxy benzyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine)(4.35 g，15mmol)、4-羥基-1-哌啶甲酸叔丁酯(t-butyl 4-hydroxy-1-piperidinecarboxylate)(3.96 g，20 mmol)、以及PPh_3(5.24 g，20 mmol)。將混合物冷卻至0°C，並逐滴加入在四氫呋喃(tetrahydrofuran)(30 ml)中的偶氮二甲酸二異丙基酯(diisoproyl azodicarboxylate, DIAD)(4.0 ml，20 mmol)。使混合物回溫至室溫，並攪拌整夜。然後將反應物過濾，並移至DCM。濾出不溶物。將濾液濃縮，移至DCM，並置於冰箱5小時。濾出形成的晶體，並透過矽膠層析法(5-12%甲醇/DCM)純化濾液，得到純的4-(6-氯-4-((4-甲氧基苄基)胺基)-1H-吡唑並[3,4-d]嘧啶-1-基)哌啶-1-甲酸叔丁酯(tert-butyl 4-(6-chloro-4-((4-methoxybenzyl)amino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidine-1-carboxylate)(4.78g，70%)。

【0097】 Suzuki耦合反應

【0098】 4-(6-(4-氯苯基)-4-((4-甲氧基苄基)胺基)-1H-吡唑並[3,4-d]嘧啶-1-基)哌啶-1-羧酸酯

(4-(6-(4-chlorophenyl)-4-((4-methoxybenzyl)amino)-1H-pyrazolo[3,4-d] pyrimidin-1-yl)piperidine-1-carboxylate)的形成。

【0099】 使用6個交替的真空/氮氣沖洗循環向100 ml玻璃燒瓶中的4-(6-氯-4-((4-甲氧基苄基)胺基)-1H-吡唑並[3,4-d]嘧啶-1-基)哌啶-1-甲酸叔丁酯(tert-butyl 4-(6-chloro-4-((4-methoxybenzyl)amino) -1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidine-1-carboxylate) (4.73 g, 10 mmol)、4-氯苯基硼酸(4-chlorophenyl boronic acid)(1.87g，12 mmol)、四(三苯基膦)鈀(Tetrakis (triphenylphosphine) palladium)(0)(1.16g，1 mmol)、1,4-二噁烷(1,4-dioxane)(100 ml)、水(40 ml)、及碳酸銫水溶液(1.0 M，40 ml，40 mmol)的懸浮液進行脫氧。將反應混合物加熱至90°C持續16小時。冷卻至室溫後，將矽藻土(Celite)粉末倒入燒瓶中，並在室溫下攪拌10分鐘，然後抽氣過濾，將濾液分配在乙酸乙酯(160 ml)與飽和碳酸氫鈉水溶液(80 ml)之間。分離各層，並用鹽水(80 ml)洗滌有機層，經硫酸鈉乾燥、過濾，並減壓濃縮。殘餘物透過矽膠層析法純化(0-35%正己烷/乙酸乙酯，線性梯度)，得到為黃色粉末的4-(6-(4-氯苯基)-4-((4-甲氧基苄基)胺基)-1H-吡唑並[3,4-d]嘧啶-1-基)哌啶-1-甲酸叔丁酯(tert-butyl 4-(6-(4-chloro phenyl)-4-((4-methoxybenzyl)amino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidine-1 -carboxylate)(4.23 g，77%)。

【0100】 透過DDQ去保護(Deprotection)

【0101】 4-(4-胺基-6-(4-氯苯基)-1H-吡唑並[3,4-d]嘧啶-1-基)哌啶-1-甲酸叔丁酯(tert-butyl 4-(4-amino-6-(4-chlorophenyl)-1H-pyrazolo[3,4-d] pyrimidin-1-yl)piperidine-1-carboxylate)的形成

【0102】 向在反應燒瓶中的4-(6-(4-(氯苯基)-4-((4-甲氧基苄基)胺基)-1H-吡唑並[3,4-d]嘧啶-1-基)哌啶-1-甲酸叔丁酯(tert-butyl 4-(6-(4-chlorophenyl)-4-((4-methoxybenzyl)amino)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidine-1-carboxylate)(4.12 g，7.5 mmol)及DDQ(2.04 g，9.0 mmol)的混合物中倒入125 ml DCM、25 ml水(H_2O)，並在室溫下攪拌整夜。反應結束後，加入DCM及碳酸氫鈉水溶液進行萃取，使用DCM(150 ml x3)萃取水層，使用無水硫酸鎂去除水，並用矽藻土(Celite)過濾並濃縮，然後使用矽膠管柱層析法(10% EA/DCM)，得到為白色固體的4-(4-胺基-6-(4-氯苯基)-1H-吡唑並[3,4-d]嘧啶-1-基)哌啶-1-甲酸叔丁酯(tert-butyl 4-(4-amino -6-(4-chlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidine-1-carboxylate)2.54 g(產率79%)。

【0103】 透過TFA去保護 (Deprotection)

【0104】 (S)-6-(6-氟吡啶-3-基)-1-(吡咯烷-3-基)-1H-吡唑並[3,4-d]嘧啶-4-胺((S)-6-(6-fluoropyridin-3-yl)-1-(pyrrolidin-3-yl)-1H-pyrazolo[3,4-d] pyrimidin-4-amine)的形成

【0105】 於室溫下，向20 ml DCM中的(S)-3-(4-胺基-6-(6-氟吡啶-3-基)-1H-吡唑並[3,4-d]嘧啶-1-基)吡咯烷-1-甲酸叔丁酯(tert-butyl (S)-3-(4-amino-6-(6-fluoropyridin-3-yl)-1H -pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidine-1-carboxylate)(2.00 g，5 mmol)溶液逐滴加入5 ml TFA持續1小時。用LCMS判斷反應後，濃縮以去除溶劑，加入EA，並透過加入10%氫氧化鈉調整至pH=11，使用EA(100 ml x3)萃取水層，使用無水硫酸鎂去除收集的有機層中的水，過濾並濃縮，得到為黃色固體的(S)-6-(6-氟吡啶-3-基)-1-(吡咯烷-3-基)-1H-吡唑並[3,4-d]嘧啶-4-胺

((S)-6-(6-fluoropyridin-3-yl)-1-(pyrrolidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine)1.28 g(86%)。

【0106】以丙烯醯氯(acryloyl chloride)醯胺化(Amidation)

【0107】(S)-1-(3-(4-胺基-6-(6-氟吡啶-3-基)-1H-吡唑並[3,4-d]嘧啶-1-基)吡咯烷-1-基)丙-2-烯-1-酮((S)-1-(3-(4-amino-6-(6-fluoropyridin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one)的形成

【0108】於透過冰浴降至0°C的情況下將TEA(2.02 g，20 mmol)及丙烯醯氯(acryloyl chloride)加入至在50 ml TFA中的(S)-6-(6-氟吡啶-3-基)-1-(吡咯烷-3-基)-1H-吡唑並[3,4-d]嘧啶-4-胺((S)-6-(6-fluoropyridin-3-yl)-1-(pyrrolidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine)(1.20 g，4 mmol)的溶液中。將所得混合物攪拌50分鐘，然後用8 ml甲醇使混合物結束反應，然後萃取並濃縮混合物，並透過矽膠管柱層析法(0-10%甲醇的DCM溶液)純化，得到為淡黃色固體的(S)-1-(3-(4-胺基-6-(6-氟吡啶-3-基)-1H-吡唑並[3,4-d]嘧啶-1-基)吡咯烷-1-基)丙-2-烯-1-酮((S)-1-(3-(4-amino-6-(6-fluoropyridin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one)1.06 g(75 %)

【0109】胺化(Amination)

【0110】向反應燒瓶中的4,6-二氯-1-苯基-1H-吡唑並[3,4-d]嘧啶(3.71 g，14 mmol)的懸浮液中加入60 ml THF，等待固體完全溶解。然後加入20 g、30%的銨溶液，並在室溫(25°C)下反應24小時。將60 ml水倒入溶液中、抽氣過濾，得到為黃色固體粉末的6-氯-1-甲基-1H-吡唑並[3,4-d]嘧啶-4-胺(6-chloro-1-methyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine)(2.93 g，85%)。

【0111】 N-烷基化(N-Alkylation)

【0112】 6-(3,3-二氟吡咯烷-1-基)-1-苯基-1H-吡唑並[3,4-d]嘧啶-4-胺(6-(3,3-difluoropyrrolidin-1-yl)-1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine)的形成

【0113】 在100 ml玻璃燒瓶中的6-氯-1-苯基-1H-吡唑並[3,4-d]嘧啶-4-胺(6-chloro-1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine)(2.46 g，10 mmol)、3,3-二氟吡咯烷鹽酸鹽(3,3-Difluoropyrrolidine hydrochloride)(2.15 g，15 mmol)、1,4-二噁烷(1,4-dioxane)(50 ml)、碳酸銫(Cesium carbonate)(13.03 g，40 mmol)的懸浮液。將反應混合物加熱至100°C持續16小時，然後冷卻至環境溫度，並透過抽氣過濾，除去濾液，並用乙酸乙酯(60 ml)萃取三次。分離各層，用鹽水(30ml)洗滌有機層，經硫酸鈉乾燥、過濾，並減壓濃縮。殘餘物透過矽膠層析法純化(正己烷/0-30%乙酸乙酯，線性梯度)，得到為淺黃色粉末的6-(3,3-二氟吡咯烷-1-基)-1-苯基-1H-吡唑並[3,4-d]嘧啶-4-胺(6-(3,3-difluoropyrrolidin-1-yl)-1-phenyl-1H-pyrazolo[3,4-d] pyrimidin-4-amine)(2.66 g，83%)。

【0114】 醯胺化(Amidation)

【0115】 透過羰基酸的醯胺化形成N-(6-(3,3-二氟吡咯烷-1-基)-1-苯基-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺(N-(6-(3,3-difluoropyrrolidin-1-yl)-1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

【0116】 向在30 ml THF中的6-(3,3-二氟吡咯烷-1-基)-1-苯基-1H-吡唑並[3,4-d]嘧啶-4-胺(6-(3,3-difluoropyrrolidin-1-yl)-1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine)(948 mg，3.00 mmol)及三乙胺(triethyamine)(2.06 ml)的溶液中加入5-硝

基噻吩-2-羰基氯(5-nitrothiophene-2-carbonyl chloride)(900 mg，4.68 mmol)。將反應混合物在環境溫度攪拌15小時。加入水，並將產物用乙酸乙酯萃取。分離有機層，乾燥(無水硫酸鈉)並真空蒸發。產物透過矽膠管柱層析法純化(己烷-乙酸乙酯梯度)，並再結晶(DCM及甲醇)，得到標題化合物。產量為1060 mg(75%)，為黃色粉末的N-(6-(4-(叔丁基)苯基)-1-甲基-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺(N-(6-(4-(tert-butyl)phenyl)-1-methyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)。

【0117】烷氧基化(Alkoxylation)

【0118】形成6-(4-氟苯氧基)-1-苯基-1H-吡唑並[3,4-d]嘧啶-4-胺(6-(4-fluorophenoxy)-1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine)

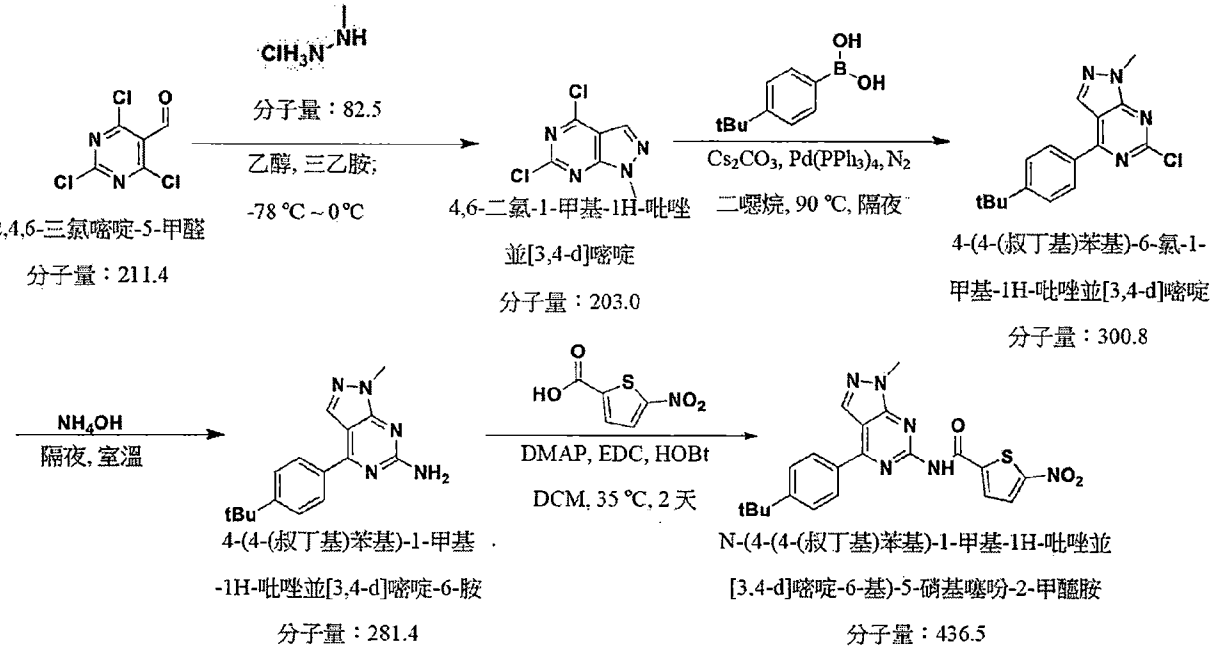
【0119】在100 ml玻璃燒瓶中的6-氯-1-苯基-1H-吡唑並[3,4-d]嘧啶-4-胺(6-chloro-1-phenyl-1H-pyrazolo[3,4-d]pyrimidin- 4-amine)(2.46 g，10 mmol)、4-氟苯酚(4-fluorophenol)(1.68 g，15 mmol)、1,4-二噁烷(1,4-dioxane)(50 ml)、碳酸銫(Cesium carbonate)(13.03 g，40 mmol)的懸浮液。將反應混合物加熱至100°C持續16小時。冷卻至室溫後，抽氣過濾、除去濾液，並用乙酸乙酯(60 ml x3)萃取。分離各層，用鹽水(30 ml)洗滌有機層，經硫酸鈉乾燥、過濾，並減壓濃縮。殘餘物透過矽膠層析法純化(正己烷/0-25%乙酸乙酯，線性梯度)，得到為淡黃色粉末的6-(4-氟苯氧基)-1-苯基-1H-吡唑並[3,4-d]嘧啶-4-胺(6-(4-fluorophenoxy)-1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine)(2.60 g，81%)。

【0120】醯胺化(Amidation)

【0121】透過羰基酸的醯胺化形成N-(6-(4-氟苯氧基)-1-苯基-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺(N-(6-(4-fluorophenoxy)-1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

【0122】 向在30 ml THF中的6-(3,3-二氟吡咯烷-1-基)-1-苯基-1H-吡唑並[3,4-d]嘧啶-4-胺

(6-(3,3-difluoropyrrolidin-1-yl)-1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine)(948 mg，3.00 mmol)及三乙胺(triethyamine)(2.06 ml)的溶液中加入5-硝基噻吩-2-羰基氯(5-nitrothiophene-2-carbonyl chloride)(900 mg，4.68 mmol)。將反應混合物在環境溫度攪拌15小時。加入水，且產物用乙酸乙酯萃取。分離有機層，乾燥(無水硫酸鈉)並真空蒸發。產物透過矽膠管柱層析法純化(己烷-乙酸乙酯梯度沖提液)，並用DCM及甲醇再結晶，得到標題化合物。產量為1100 mg(77%)形成為黃色粉末的N-(6-(4-氟苯氧基)-1-苯基-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺(N-(6-(4-fluorophenoxy)-1-phenyl-1H-pyrazolo [3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)。



【0123】 實驗步驟

【0124】 將溶解在乙醇(50 ml)中的2,4,6-三氯嘧啶-5-甲醛(2,4,6-trichloropyrimidine-5-carbaldehyde)(3.7 g，17.5 mmol)的溶液冷卻至-78°C，加入甲基肼(methyl hydrazine)(0.93 ml，17.5 mmol)及TEA(8 ml)。將混合物在-78°C

下攪拌30分鐘，然後在0°C下放置2小時。將溶液在不加熱的情況下真空濃縮。向減小體積的溶液中加入乙酸乙酯，且溶液用飽和碳酸氫鈉溶液洗滌，並在不加熱的情況下真空濃縮。以小的矽膠塞(2：1 = EtOAc：Hex)過濾並濃縮，得到所需為黃色固體的產物4,6-二氯-1-甲基-1H-吡唑並[3,4-d]嘧啶(4,6-Dichloro-1-methyl- 1H-pyrazolo[3,4-d]pyrimidine)(2.84 g，80%)。

【0125】 4-(4-(叔丁基)苯基)-6-氯-1-甲基-1H-吡唑並[3,4-d]嘧啶(4-(4-(tert-butyl)phenyl)-6-chloro-1-methyl-1H-pyrazolo[3,4-d]pyrimidine)的形成

【0126】 Suzuki耦合反應

【0127】 使用5個交替的真空/氮氣沖洗循環向在100 mL玻璃燒瓶中的4,6-二氯-1-甲基-1H-吡唑並[3,4-d]嘧啶(4,6-dichloro-1-methyl-1H-pyrazolo[3,4-d]pyrimidine)(2.03 g，10 mmol)、4-(叔丁基)苯基硼酸(4-(tert-butyl)phenyl boronic acid)(2.67 g，15 mmol)、四(三苯基膦)鈀(Tetrakis (triphenylphosphine) palladium)(0)(1.16 g，1 mmol)、1,4-二噁烷(1,4-dioxane)(40 ml)、水(2 ml)、及碳酸銫水溶液(aqueous Cesium carbonate solution)(2.0 M，20 ml，40 mmol)的懸浮液進行脫氧。將反應混合物加熱至90°C持續15小時。冷卻至室溫後，將矽藻土(Celite)粉末倒入燒瓶中，並在室溫攪拌10分鐘，然後抽氣過濾，並將濾液分配在乙酸乙酯(80 ml)與飽和碳酸氫鈉水溶液(30 ml)之間。分離各層，用鹽水(30ml)洗滌有機層，經硫酸鈉乾燥、過濾，並減縮濃縮。殘餘物透過矽膠層析法純化(0-25%正己烷/乙酸乙酯，線性梯度)，得到為黃色粉末的4-(4-(叔丁基)苯基)-6-氯-1-甲基-1H-吡唑並[3,4-d]嘧啶(4-(4-(tert-butyl)phenyl)-6-chloro-1-methyl-1H-pyrazolo[3,4-d]pyrimidine)(2.55 g，85%)。

【0128】 4-(4-(叔丁基)苯基)-1-甲基-1H-吡唑並[3,4-d]嘧啶-6-胺(4-(4-(tert-butyl)phenyl)-1-methyl-1H-pyrazolo[3,4-d]pyrimidin-6-amine)

【0129】 胺化(Amination)

【0130】 向反應燒瓶中的4,6-二氯-1-甲基-1H-吡唑並[3,4-d]嘧啶(4,6-Dichloro-1-methyl-1H-pyrazolo[3,4-d]pyrimidine)(2.11 g，7 mmol)的懸浮液中加入32 ml THF，等待固體完全溶解，然後加入10 g、30%的銨溶液，並在室溫(25°C)下反應24小時。將60 ml水倒入溶液中，抽氣過濾得到為黃色固體粉末的4-(4-(叔丁基)苯基)-1-甲基-1H-吡唑並[3,4-d]嘧啶-6-胺(4-(4-(tert-butyl)phenyl)-1-methyl-1H-pyrazolo[3,4-d]pyrimidin-6-amine) (1.58 g，80 %)。

【0131】 醯胺化(Amidation)

【0132】 透過羰基酸的醯胺化形成N-(4-(4-(叔丁基)苯基)-1-甲基-1H-吡唑並[3,4-d]嘧啶-6-基)-5-硝基噻吩-2-甲醯胺

【0133】 向在吡啶(6ml)中的4-(4-(叔丁基)苯基)-1-甲基-1H-吡唑並[3,4-d]嘧啶-6-胺(4-(4-(tert-butyl)phenyl)-1-methyl-1H-pyrazolo[3,4-d]pyrimidin-6-amine)(843 mg，3.00 mmol)的溶液中加入5-硝基噻吩-2-羰基氯(5-nitrothiophene-2-carbonyl chloride)(900 mg，4.68 mmol)。將反應混合物在環境溫度攪拌15小時，加入水，產物用乙酸乙酯萃取。分離有機層，乾燥(無水硫酸鈉)，並真空蒸發。產物透過矽膠管柱層析法純化(己烷-乙酸乙酯梯度)，並再結晶(己烷及丙酮)，得到標題化合物。產量為1021 mg(78%)，為黃色粉末的N-(4-(4-(叔丁基)苯基)-1-甲基-1H-吡唑並[3,4-d]嘧啶-6-基)-5-硝基噻吩-2-甲醯胺(N-(4-(4-(tert-butyl)phenyl)-1-methyl-1H-pyrazolo[3,4-d]pyrimidin-6-yl)-5-nitrothiophene-2-carboxamide)。

【0134】 於體外MTS測定法中評估式(I)之化合物

【0135】 細胞存活率的測量是基於NCI-60篩選方法(Nat. Rev. Cancer 6, 813–823, 2006)。簡而言之，將細胞以最佳接種密度接種至96孔盤中。24小時後，

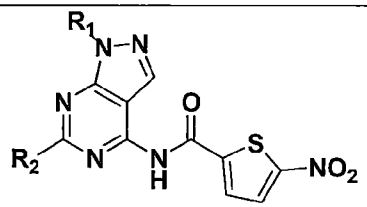
透過MTS測定法(Promega)處理接種Hep3B細胞株的兩個孔盤中之一者以確定初始時間的細胞存活率(Tz)。將化合物以2倍連續稀釋液添加，以提供總共5種藥物濃度和DMSO對照。將孔盤再培養2天，然後透過MTS測定法[在5個濃度量(Ti)的藥物存在下的對照成長量(C)及測試成長量]來測量細胞存活率。由[(Ti-Tz)/Tz]x100=-50計算得出LC_{50}，這是在藥物治療結束時與開始時相比減少50%的藥物濃度。

【0136】表1-10中製備的化合物以三種體外測定法進行測試，表1-10顯示Hep3B的結果，SW480及NCI-H460的結果顯示於下表11中。於本文中，Hep3B是指肝癌細胞株，SW480是指結腸直腸癌細胞株，而NCI-H460是指人類肺癌細胞株。

【0137】於表1至表10所示的化合物中，如果某些化合物的合成步驟與前述化合物的合成步驟相似，則不再重複詳細的合成步驟。

【0138】下表1至表10中顯示了式(I)之化合物的結構與體外活性。發現多數揭露的化合物抑制Hep3B細胞(肝癌細胞株)的生長。

【0139】表1

			
化合物	R_1	R_2	Hep3B LC_{50}
1-1	甲基	4-(叔丁基)苯基	1.80
1-2	甲基	4-乙氧基苯基	3.24
1-3	甲基	苯並呋喃-2-基	NA
1-4	甲基	4-(三氟甲基)苯基	NA
1-5	甲基	4-(三氟甲氧基)苯基	NA

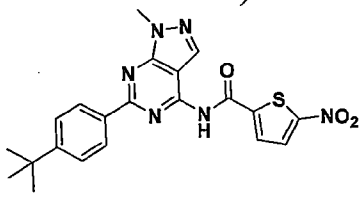
1-6	甲基	3-(三氟甲氧基)苯基	1.47
1-7	甲基	4-(叔丁氧基)苯基	1.51
1-8	甲基	2-(三氟甲氧基)苯基	2.53
1-9	甲基	4-(叔戊基)苯基	1.50
1-10	甲基	4-(二甲基胺基)苯基	>5
1-11	甲基	4-(三氟甲基)苯乙烯基	1.71
1-12	甲基	4-甲氧基苯乙烯基	> 5
1-13	甲基	4-(三氟甲基)苯基)乙炔基	2.03
1-14	甲基	4-(三氟甲氧基)苯基)乙炔基	1.67
1-15	甲基	苯氧基	NA
1-16	甲基	4-氟苯氧基	NA
1-17	甲基	4-(三氟甲氧基)苯氧基	NA
1-18	甲基	3-(三氟甲基)苯氧基	1.99
1-19	甲基	2-(二甲基胺基)乙氧基	NA
1-20	甲基	4-嗎啉基苯氧基 (4-morpholinophenoxy)	NA
1-21	甲基	嗎啉基(morpholino)	NA
1-22	異丙基	4-(三氟甲氧基)苯基	0.73
1-23	異丙基	4-(叔丁基)苯基	1.57
1-24	異丙基	4-(三氟甲基)苯基	0.90
1-25	叔丁基	4-(叔丁基)苯基	4.11
1-26	叔丁基	4-(三氟甲基)苯基	0.79
1-27	叔丁基	4-(三氟甲氧基)苯基	0.61
1-28	2-羥乙基	4-(三氟甲氧基)苯基	4.03
1-29	2-氰乙基	4-(三氟甲氧基)苯基	NA
1-30	2-嗎啉基乙基 (2- morpholinoethyl)	4-(三氟甲氧基)苯基	1.70
1-31	2-(二甲基胺基)乙基	4-(三氟甲氧基)苯基	1.86
1-32	2-(3,3-二氟吡咯烷-1-基)乙基	4-(三氟甲氧基)苯基	0.77

1-33	2-(2-乙氧基乙氧基)乙基 (2-(2-ethoxyethoxy)ethyl)	4-氟苯基	NA

【0140】化合物1-1

N-(6-(4-(叔丁基)苯基)-1-甲基-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(6-(4-(tert-butyl)phenyl)-1-methyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

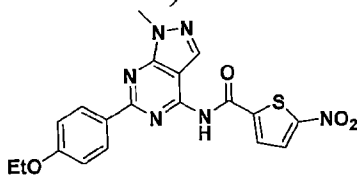


^{1}H NMR (400MHz, $CDCl_3$): δ 15.33 (br. s., 1H), 8.36 (br. s., 1H), 8.13-8.26 (m, 2H), 7.90 (d, J = 4.4 Hz, 1H), 7.77 (d, J = 4.4 Hz, 1H), 7.58 (d, J = 8.3 Hz, 2H), 4.13 (s, 3H), 1.37 (s, 9H). MS(M+1):437.

【0141】化合物1-2

N-(6-(4-乙氧基苯基)-1-甲基-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(6-(4-ethoxyphenyl)-1-methyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

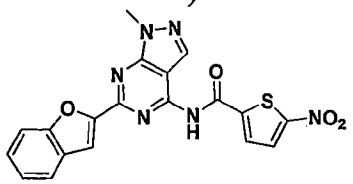


^{1}H NMR (400MHz, DMSO-d_6): δ 11.82 (br. s., 1H), 8.43-8.54 (m, J = 8.8 Hz, 2H), 8.30-8.40 (m, 2H), 8.24 (d, J = 4.4 Hz, 1H), 7.02-7.13 (m, 2H), 4.13 (q, J = 7.2 Hz, 2H), 4.07 (s, 3H), 1.37 (t, J = 6.8 Hz, 3H). MS(M+1):425.

【0142】化合物1-3

N-(6-(苯並呋喃-2-基)-1-甲基-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(6-(benzofuran-2-yl)-1-methyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

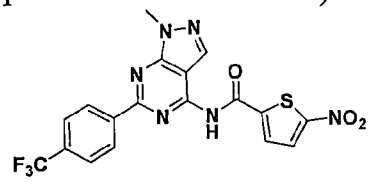


^{1}H NMR (400MHz, DMSO-d_6): δ 12.18 (br. s., 1H), 8.29-8.41 (m, 2H), 8.24 (d, J = 4.4 Hz, 1H), 7.79-7.89 (m, 2H), 7.76 (d, J = 7.8 Hz, 1H), 7.47 (t, J = 7.8 Hz, 1H), 7.35 (t, J = 7.6 Hz, 1H), 4.10 (s, 3H). MS(M+1):421.

【0143】化合物 1-4

N-(1-甲基-6-(4-(三氟甲基)苯基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(1-methyl-6-(4-(trifluoromethyl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

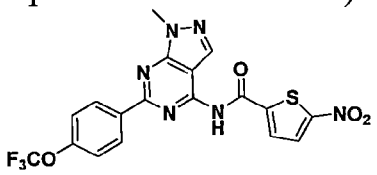


^{1}H NMR (400MHz, DMSO-d_6): δ 11.99 (br. s., 1H), 8.69-8.77 (m, J = 8.3 Hz, 2H), 8.40 (s, 1H), 8.36 (d, J = 4.4 Hz, 1H), 8.24 (d, J = 4.4 Hz, 1H), 7.89-7.99 (m, J = 8.3 Hz, 2H), 4.11 (s, 3H). MS(M+1):449.

【0144】化合物 1-5

N-(1-甲基-6-(4-(三氟甲氧基)苯基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(1-methyl-6-(4-(trifluoromethoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

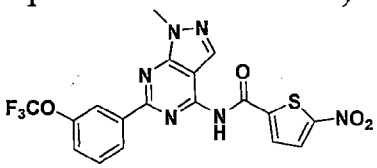


^{1}H NMR (400MHz, DMSO-d_6): δ 11.94 (br. s., 1H), 8.57-8.68 (m, 2H), 8.32-8.41 (m, 2H), 8.24 (d, J = 4.4 Hz, 1H), 7.50-7.61 (m, J = 8.3 Hz, 2H), 4.09 (s, 3H).
MS(M+1) :465

【0145】化合物 1-6

N-(1-甲基-6-(3-(三氟甲氧基)苯基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(1-methyl-6-(3-(trifluoromethoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

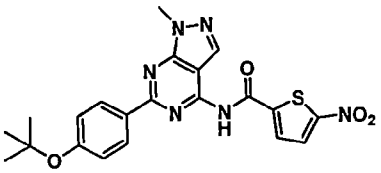


^{1}H NMR (400MHz, DMSO-d_6): δ 11.85 (br. s., 1H), 8.55 (d, J = 7.8 Hz, 1H), 8.42 (s, 1H), 8.38 (s, 1H), 8.34 (d, J = 4.4 Hz, 1H), 8.23 (d, J = 4.4 Hz, 1H), 7.71 (t, J = 8.1 Hz, 1H), 7.55-7.60 (m, 1H), 4.08 (s, 3H).MS(M+1):465.

【0146】化合物 1-7

N-(6-(4-(叔丁氧基)苯基)-1-甲基-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(6-(4-(tert-butoxy)phenyl)-1-methyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

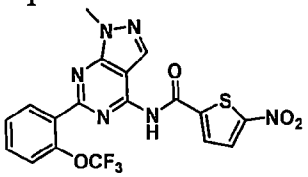


^{1}H NMR (400MHz, DMSO-d_6): δ 11.88 (br. s., 1H), 8.41-8.50 (m, J = 8.8 Hz, 2H), 8.32-8.40 (m, 2H), 8.24 (d, J = 4.4 Hz, 1H), 7.08-7.19 (m, 2H), 4.08 (s, 3H), 1.39 (s, 9H). MS(M+1):453.

【0147】化合物 1-8

N-(1-甲基-6-(2-(三氟甲氧基)苯基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(1-methyl-6-(2-(trifluoromethoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

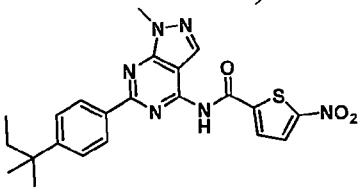


^{1}H NMR (400MHz, DMSO-d_6): δ 12.09 (br. s., 1H), 8.43 (s, 1H), 8.34 (d, J = 4.4 Hz, 1H), 8.22 (d, J = 4.4 Hz, 1H), 8.13 (dd, J = 7.8, 2.0 Hz, 1H), 7.64-7.72 (m, 1H), 7.48-7.64 (m, 2H), 4.05 (s, 3H). MS(M+1):465.

【0148】化合物 1-9

N-(1-甲基-6-(4-(叔戊基)苯基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(1-methyl-6-(4-(tert-pentyl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

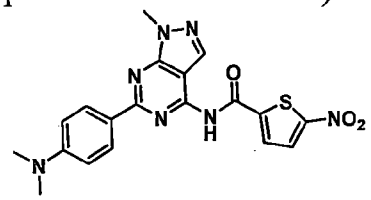


^{1}H NMR (400MHz, DMSO-d_6): δ 11.93 (br. s., 1H), 8.46 (d, J = 8.3 Hz, 2H), 8.31-8.43 (m, 2H), 8.25 (d, J = 4.4 Hz, 1H), 7.52 (d, J = 8.3 Hz, 2H), 4.09 (s, 3H), 1.60-1.76 (m, 2H), 1.31 (s, 6H), 0.66 (t, J = 7.3 Hz, 3H). MS(M+1):451.

【0149】化合物 1-10

N-(6-(4-(二甲基胺基)苯基)-1-甲基-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(6-(4-(dimethylamino)phenyl)-1-methyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

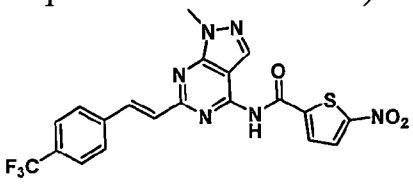


^{1}H NMR (400MHz, DMSO-d_6): δ 11.73 (s, 1H), 8.32-8.45 (m, 3H), 8.27 (s, 1H), 8.24 (d, J = 4.4 Hz, 1H), 6.82 (d, J = 8.8 Hz, 2H), 4.04 (s, 3H), 3.03 (s, 6H). MS(M+1): 424.

【0150】化合物 1-11

(E)-N-(1-甲基-6-(4-(三氟甲基)苯乙烯基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

((E)-N-(1-methyl-6-(4-(trifluoromethyl)styryl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

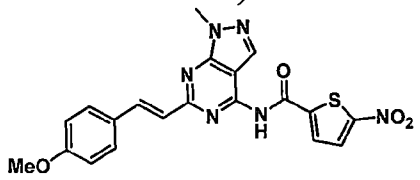


^{1}H NMR (400MHz, DMSO-d_6): δ 11.98 (br. s., 1H), 8.28-8.38 (m, 2H), 8.20 (d, J = 4.4 Hz, 1H), 8.07 (d, J = 16.1 Hz, 1H), 7.89-7.98 (m, J = 8.3 Hz, 2H), 7.72-7.80 (m, J = 8.3 Hz, 2H), 7.41 (d, J = 16.1 Hz, 1H), 4.03 (s, 3H). MS(M+1):475.

【0151】化合物 1-12

(E)-N-(6-(4-甲氧基苯乙烯基)-1-甲基-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

((E)-N-(6-(4-methoxystyryl)-1-methyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

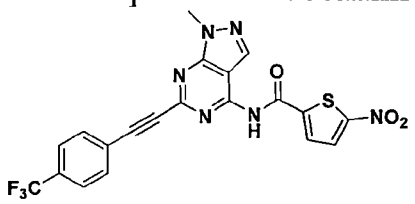


^{1}H NMR (400MHz, DMSO-d_6): δ 11.92 (br. s., 1H), 8.32 (s, 2H), 8.22 (d, J = 4.4 Hz, 1H), 8.03 (d, J = 16.1 Hz, 1H), 7.60-7.73 (m, 2H), 7.16 (d, J = 16.1 Hz, 1H), 6.88 - 7.08 (m, 2H), 4.03 (s, 3H), 3.81 (s, 3H). MS(M+1):437.

【0152】化合物 1-13

N-(1-甲基-6-((4-(三氟甲基)苯基)乙炔基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(1-methyl-6-((4-(trifluoromethyl)phenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

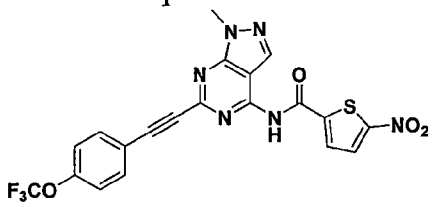


^{1}H NMR (400MHz, DMSO-d_6):δ 12.28 (s, 1H), 8.40 (s, 1H), 8.34 (d, J = 4.4 Hz, 1H), 8.18 (d, J = 4.4 Hz, 1H), 7.72-7.92 (m, 4H), 4.03 (s, 3H). MS(M+1):473.

【0153】化合物 1-14

N-(1-甲基-6-((4-(三氟甲氧基)苯基)乙炔基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(1-methyl-6-((4-(trifluoromethoxy)phenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

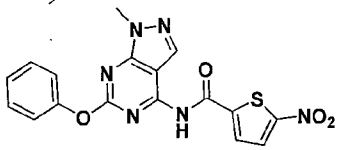


^{1}H NMR (400MHz, DMSO-d_6):δ 12.32 (br. s., 1H), 8.42 (s, 1H), 8.35 (d, J = 4.4 Hz, 1H), 8.21 (d, J = 4.4 Hz, 1H), 7.77-7.86 (m, 2H), 7.49 (d, J = 7.8 Hz, 2H), 4.05 (s, 3H). MS(M+1):489.

【0154】化合物 1-15

N-(1-甲基-6-苯氧基-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(1-methyl-6-phenoxy-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

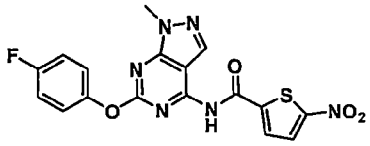


^{1}H NMR (400MHz, DMSO-d_6): δ 12.17 (s, 1H), 8.31-8.34 (m, 2H), 8.21 (d, J = 4.4 Hz, 1H), 7.43-7.50 (m, 2H), 7.24-7.32 (m, 3H), 3.80 (s, 3H). MS (M+1) : 397.

【0155】化合物 1-16

N-(6-(4-氟苯氧基)-1-甲基-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(6-(4-fluorophenoxy)-1-methyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

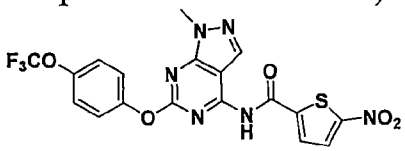


^{1}H NMR (400MHz, DMSO-d_6): δ 12.14 (s, 1H), 8.29-8.33 (m, 2H), 8.20 (d, J = 4.9 Hz, 1H), 7.24-7.38 (m, 5H), 3.79 (s, 3H). MS (M+1) : 415.

【0156】化合物 1-17

N-(1-甲基-6-(4-(三氟甲氧基)苯氧基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(1-methyl-6-(4-(trifluoromethoxy)phenoxy)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

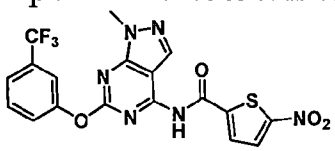


^{1}H NMR (400MHz, DMSO-d_6): δ 12.15 (s, 1H), 8.33 (s, 1H), 8.31 (d, J = 4.9 Hz, 1H), 8.20 (d, J = 4.4 Hz, 1H), 7.46 (s, 4H), 3.81 (s, 3H). MS (M+1): 481.

【0157】化合物 1-18

N-(1-甲基-6-(3-(三氟甲基)苯氧基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(1-methyl-6-(3-(trifluoromethyl)phenoxy)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

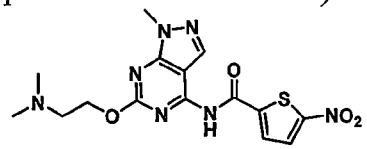


^{1}H NMR (400MHz, DMSO-d_6): δ 12.20 (s, 1H), 8.34 (s, 1H), 8.31 (d, J = 4.9 Hz, 1H), 8.21 (d, J = 4.4 Hz, 1H), 7.62-7.77 (m, 4H), 3.80 (s, 3H). MS (M+1) : 465.

【0158】化合物 1-19

N-(6-(2-(二甲基胺基)乙氧基)-1-甲基-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(6-(2-(dimethylamino)ethoxy)-1-methyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

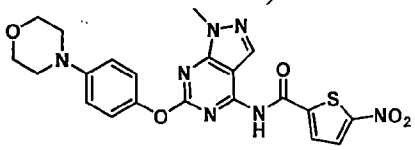


^{1}H NMR (400MHz, DMSO-d_6): δ 8.28-8.33 (m, 2H), 8.22 (d, J = 4.4 Hz, 1H), 4.71-4.79 (m, 2H), 3.95 (s, 3H), 3.52-3.60 (m, 2H), 2.87 (s, 6H). MS (M+1) : 392.

【0159】化合物 1-20

N-(1-甲基-6-(4-嗎啉基苯氧基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(1-methyl-6-(4-morpholinophenoxy)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

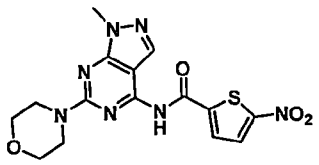


^{1}H NMR (400MHz, DMSO-d_6): δ 12.12 (br. s., 1H), 8.31 (d, J = 4.4 Hz, 1H), 8.30 (s, 1H), 8.20 (d, J = 4.4 Hz, 1H), 7.12-7.19 (m, J = 9.3 Hz, 2H), 6.96-7.03 (m, J = 9.3 Hz, 2H), 3.80 (s, 3H), 3.72-3.78 (m, 4H), 3.08-3.15 (m, 4H). MS (M+1) : 482.

【0160】化合物 1-21

N-(1-甲基-6-嗎啉基-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(1-methyl-6-morpholino-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

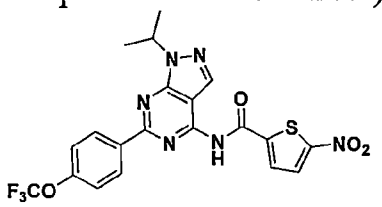


^{1}H NMR (400MHz, DMSO-d_6): δ 11.36 (br. s., 1H), 8.27 (d, J = 4.4 Hz, 1H), 8.20 (d, J = 4.4 Hz, 1H), 8.07 (s, 1H), 3.77-3.88 (m, 7H), 3.66-3.72 (m, 4H). MS(M+1):390.

【0161】化合物 1-22

N-(1-異丙基-6-(4-(三氟甲氧基)苯基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(1-isopropyl-6-(4-(trifluoromethoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

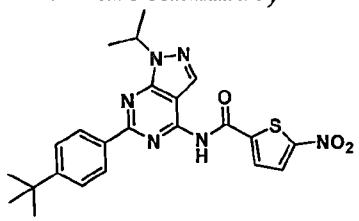


^{1}H NMR (400MHz, DMSO-d_6): δ 11.94 (s, 1H), 8.53-8.74 (m, 2H), 8.34-8.50 (m, 2H), 8.24 (d, J = 4.4 Hz, 1H), 7.57 (d, J = 7.8 Hz, 2H), 5.13-5.43 (m, 1H), 1.55 (d, J = 6.8 Hz, 6H). MS(M+1):493.

【0162】化合物 1-23

N-(6-(4-(叔丁基)苯基)-1-異丙基-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(6-(4-(tert-butyl)phenyl)-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

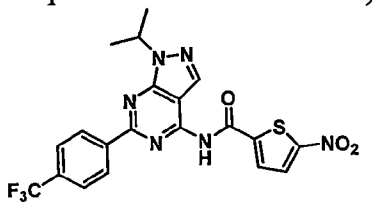


^{1}H NMR (400MHz, DMSO-d_6): δ 11.90 (s, 1H), 8.43-8.53 (m, J = 8.3 Hz, 2H), 8.31-8.43 (m, 2H), 8.25 (d, J = 4.4 Hz, 1H), 7.47-7.67 (m, J = 8.3 Hz, 2H), 5.18-5.37 (m, 1H), 1.56 (d, J = 6.8 Hz, 6H), 1.35 (s, 9H). MS(M+1):465.

【0163】化合物 1-24

N-(1-異丙基-6-(4-(三氟甲基)苯基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(1-isopropyl-6-(4-(trifluoromethyl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

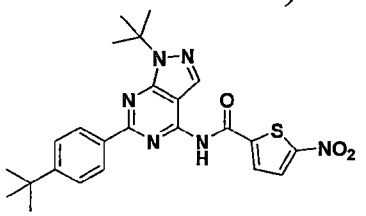


^{1}H NMR (400MHz, DMSO-d_6): δ 11.95 (s, 1H), 8.62-8.78 (m, J = 8.3 Hz, 2H), 8.30-8.44 (m, 2H), 8.22 (d, J = 4.4 Hz, 1H), 7.86-7.99 (m, J = 8.3 Hz, 2H), 5.29 (quin, J = 6.7 Hz, 1H), 1.56 (d, J = 6.8 Hz, 6H). MS(M+1):477.

【0164】化合物 1-25

N-(1-(叔丁基)-6-(4-(叔丁基)苯基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(1-(tert-butyl)-6-(4-(tert-butyl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

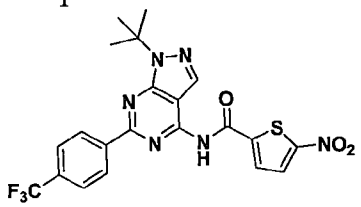


^{1}H NMR (400MHz, DMSO-d_6): δ 11.91 (br. s., 1H), 8.36-8.58 (m, J = 8.3 Hz, 2H), 8.17-8.36 (m, 3H), 7.51-7.76 (m, J = 8.3 Hz, 2H), 1.84 (s, 9H), 1.35 (s, 9H). MS(M+1):479.

【0165】化合物 1-26

N-(1-(叔丁基)-6-(4-(三氟甲基)苯基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(1-(tert-butyl)-6-(4-(trifluoromethyl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

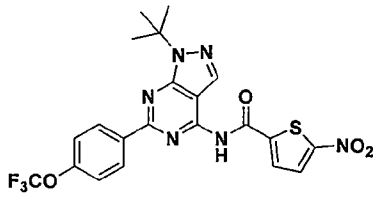


^{1}H NMR (400MHz, DMSO-d_6): δ 11.95 (s, 1H), 8.59-8.76 (m, J = 7.8 Hz, 2H), 8.29-8.42 (m, 2H), 8.23 (d, J = 4.4 Hz, 1H), 7.87-8.11 (m, J = 8.3 Hz, 2H), 1.84 (s, 9H). MS(M+1): 491.

【0166】化合物 1-27

N-(1-(叔丁基)-6-(4-(三氟甲氧基)苯基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(1-(tert-butyl)-6-(4-(trifluoromethoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

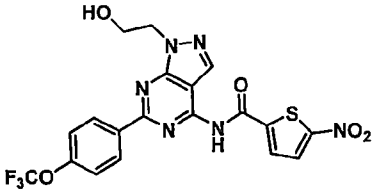


^{1}H NMR (400MHz, DMSO-d_6): δ 11.87 (br. s., 1H), 8.59 (d, J = 8.8 Hz, 2H), 8.34 (d, J = 4.4 Hz, 1H), 8.29 (d, J = 1.5 Hz, 1H), 8.18-8.24 (m, 1H), 7.50-7.60 (m, 2H), 1.82 (s, 9H). MS(M+1):507.

【0167】化合物 1-28

N-(1-(2-羥乙基)-6-(4-(三氟甲氧基)苯基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(1-(2-hydroxyethyl)-6-(4-(trifluoromethoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

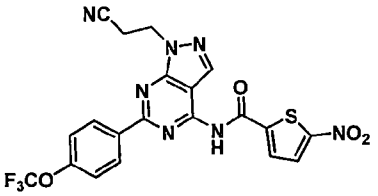


^{1}H NMR (400MHz, DMSO-d_6): δ 11.95 (br. s., 1H), 8.59-8.69 (m, 2H), 8.41 (s, 1H), 8.37 (d, J = 4.4 Hz, 1H), 8.25 (d, J = 4.4 Hz, 1H), 7.57 (d, J = 7.8 Hz, 2H), 4.90 (t, J = 5.6 Hz, 1H), 4.55 (t, J = 5.6 Hz, 2H), 3.92 (d, J = 5.9 Hz, 2H). MS(M+1):495.

【0168】化合物 1-29

N-(1-(2-氰乙基)-6-(4-(三氟甲氧基)苯基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(1-(2-cyanoethyl)-6-(4-(trifluoromethoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

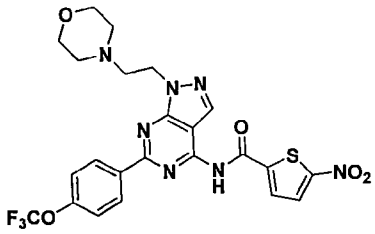


^{1}H NMR (400MHz, DMSO-d_6): δ 12.01 (br. s., 1H), 8.57-8.73 (m, 2H), 8.47 (s, 1H), 8.37 (d, J = 4.9 Hz, 1H), 8.25 (d, J = 4.4 Hz, 1H), 7.49-7.64 (m, J = 8.3 Hz, 2H), 4.71-4.83 (m, 2H), 3.25 (t, J = 6.4 Hz, 2H). MS(M+1):504.

【0169】化合物 1-30

N-(1-(2-嗎啉基乙基)-6-(4-(三氟甲氧基)苯基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(1-(2-morpholinoethyl)-6-(4-(trifluoromethoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

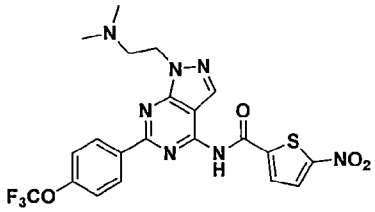


^{1}H NMR (400MHz, DMSO-d_6):δ 11.95 (br. s., 1H), 8.57-8.68 (m, 2H), 8.40 (s, 1H), 8.36 (d, J = 4.4 Hz, 1H), 8.25 (d, J = 4.9 Hz, 1H), 7.46-7.64 (m, J = 8.3 Hz, 2H), 4.64 (t, J = 6.1 Hz, 2H), 3.37-3.50 (m, 4H), 2.84 (t, J = 6.1 Hz, 2H), 2.45-2.55 (m, 4H). MS(M+1):564

【0170】化合物 1-31

N-(1-(2-(二甲基胺基)乙基)-6-(4-(三氟甲氧基)苯基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(1-(2-(dimethylamino)ethyl)-6-(4-(trifluoromethoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

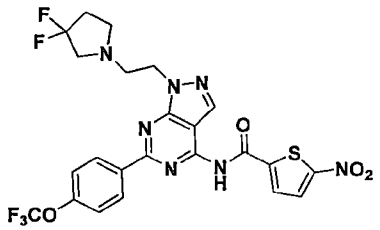


^{1}H NMR (400MHz, DMSO-d_6):δ 12.08 (br. s., 1H), 10.38 (br. s., 1H), 8.61-8.78 (m, 2H), 8.47-8.58 (m, 1H), 8.37-8.47 (m, 1H), 8.26 (d, J = 4.4 Hz, 1H), 7.58 (d, J = 7.8 Hz, 2H), 4.95 (t, J = 6.1 Hz, 2H), 3.71 (t, J = 6.1 Hz, 2H), 2.87 (s, 6H).MS(M+1):558.

【0171】化合物 1-32

N-(1-(2-(3,3-二氟吡咯烷-1-基)乙基)-6-(4-(三氟甲氧基)苯基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(1-(2-(3,3-difluoropyrrolidin-1-yl)ethyl)-6-(4-(trifluoromethoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

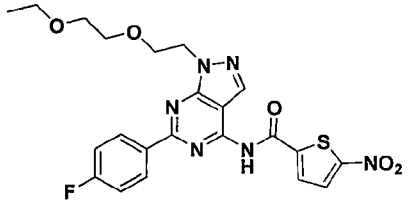


^{1}H NMR (400MHz, DMSO-d_6):δ 11.95 (br. s., 1H), 8.54-8.73 (m, 2H), 8.41 (s, 1H), 8.36 (d, J = 4.4 Hz, 1H), 8.25 (d, J = 4.4 Hz, 1H), 7.50-7.61 (m, 2H), 4.62 (t, J = 6.1 Hz, 2H), 2.92-3.06 (m, 4H), 2.77 (t, J = 7.1 Hz, 2H), 2.01-2.19 (m, 2H). MS(M+1):584.

【0172】化合物 1-33

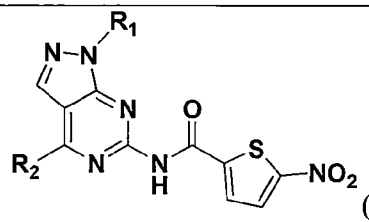
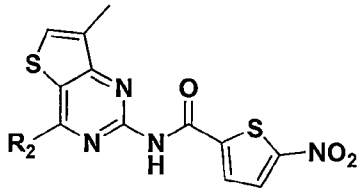
N-(1-(2-(2-乙氧基乙氧基)乙基)-6-(4-氟苯基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(1-(2-(2-ethoxyethoxy)ethyl)-6-(4-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)



【0173】^{1}H NMR (400MHz, DMSO-d_6): δ 11.86 (s, 1H), 8.58-8.54 (m, 2H), 8.38-8.34 (m, 2H), 8.22 (d, J = 4.4 Hz, 1H), 7.38 (t, J = 8.8 Hz, 2H), 4.64 (t, J = 5.6 Hz, 2H), 3.95 (t, J = 5.6 Hz, 2H), 3.54-3.51 (m, 2H), 3.35-3.32 (m, 2H), 3.25 (q, J = 6.8 Hz, 2H), 0.93 (t, J = 6.8 Hz, 3H). MS(M+1): 501. 黃色固體。

【0174】表2

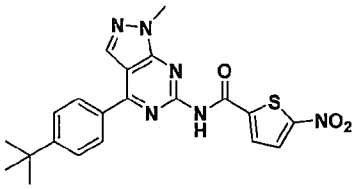
	 (A)  (B)

化合物	R_1	R_2	Hep3B LC_{50}
式(A)			
2-1	甲基	4-(叔丁基)苯基	3.13
2-2	甲基	4-(三氟甲氧基)苯基	NA
2-3	異丙基	4-(三氟甲氧基)苯基	4.02
2-4	叔丁基	4-(三氟甲氧基)苯基	3.05
2-5	叔丁基	4-(叔丁基)苯基	12.88
2-6	甲基	嗎啉基	NA
式(B)			
2-7	—	3-(三氟甲氧基)苯基	3.43
2-8	—	4-(三氟甲氧基)苯基	1.71

【0175】化合物 2-1

N-(4-(4-(叔丁基)苯基)-1-甲基-1H-吡唑並[3,4-d]嘧啶-6-基)-5-硝基噻吩-2-甲醯胺

(N-(4-(4-(tert-butyl)phenyl)-1-methyl-1H-pyrazolo[3,4-d]pyrimidin-6-yl)-5-nitrothiophene-2-carboxamide)

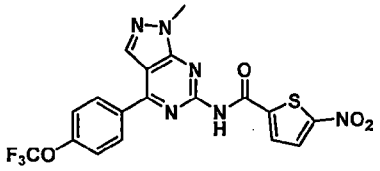


^{1}H NMR (400MHz, DMSO-d_6): δ 11.66 (s, 1H), 8.66 (s, 1H), 8.27-8.35 (m, 2H), 8.17-8.27 (m, 2H), 7.61-7.70 (m, 2H), 4.04 (s, 3H), 1.36 (s, 9H). MS(M+1):437.

【0176】化合物 2-2

N-(1-甲基-4-(4-(三氟甲氧基)苯基)-1H-吡唑並[3,4-d]嘧啶-6-基)-5-硝基噻吩-2-甲醯胺

(N-(1-methyl-4-(4-(trifluoromethoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-yl)-5-nitrothiophene-2-carboxamide)

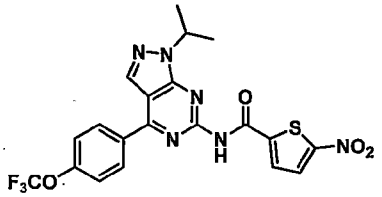


^{1}H NMR (400MHz, DMSO-d_6): δ 11.72 (s, 1H), 8.69 (s, 1H), 8.43-8.52 (m, 2H), 8.17-8.28 (m, 2H), 7.57-7.67 (m, J = 8.3 Hz, 2H), 4.04 (s, 3H). MS(M+1):465.

【0177】化合物 2-3

N-(1-異丙基-4-(4-(三氟甲氧基)苯基)-1H-吡唑並[3,4-d]嘧啶-6-基)-5-硝基噻吩-2-甲醯胺

(N-(1-isopropyl-4-(4-(trifluoromethoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-yl)-5-nitrothiophene-2-carboxamide)

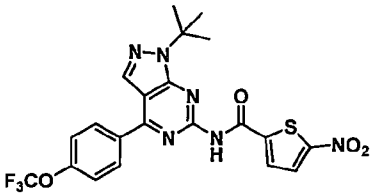


^{1}H NMR (400MHz, DMSO-d_6): δ 11.71 (s, 1H), 8.68 (s, 1H), 8.37-8.57 (m, 2H), 8.11-8.29 (m, 2H), 7.51-7.71 (m, 2H), 5.01-5.24 (m, 1H), 1.54 (d, J = 6.8 Hz, 6H). MS(M+1):493.

【0178】化合物 2-4

N-(1-(叔丁基)-4-(4-(三氟甲氧基)苯基)-1H-吡唑並[3,4-d]嘧啶-6-基)-5-硝基噻吩-2-甲醯胺

(N-(1-(tert-butyl)-4-(4-(trifluoromethoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-yl)-5-nitrothiophene-2-carboxamide)

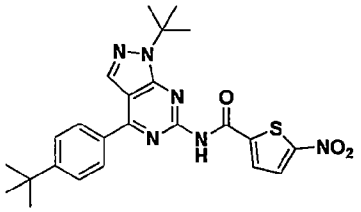


^{1}H NMR (400MHz, DMSO-d_6): δ 11.63 (s, 1H), 8.58 (s, 1H), 8.42 (d, J = 8.8 Hz, 2H), 8.14-8.34 (m, 2H), 7.63 (d, J = 7.8 Hz, 2H), 1.80 (s, 9H). MS(M+1):507.

【0179】化合物 2-5

N-(1-(叔丁基)-4-(4-(叔丁基)苯基)-1H-吡唑並[3,4-d]嘧啶-6-基)-5-硝基噻吩-2-甲醯胺

(N-(1-(tert-butyl)-4-(4-(tert-butyl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-6-yl)-5-nitrothiophene-2-carboxamide)

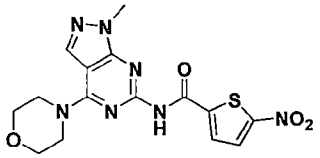


^{1}H NMR (400MHz, DMSO-d_6): δ 11.58 (s, 1H), 8.55 (s, 1H), 8.11-8.32 (m, 4H), 7.57-7.72 (m, 2H), 1.80 (s, 9H), 1.36 (s, 9H). MS(M+1):479.

【0180】化合物 2-6

N-(1-甲基-4-嗎啉基-1H-吡唑並[3,4-d]嘧啶-6-基)-5-硝基噻吩-2-甲醯胺

(N-(1-methyl-4-morpholino-1H-pyrazolo[3,4-d]pyrimidin-6-yl)-5-nitrothiophene-2-carboxamide)

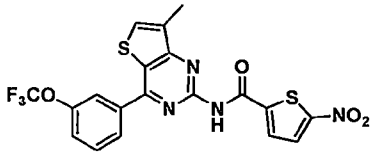


^{1}H NMR (400MHz, DMSO-d_6): δ 11.10 (s, 1H), 8.25 (s, 1H), 8.16 (d, J = 3.4 Hz, 2H), 3.93 (d, J = 4.9 Hz, 4H), 3.88 (s, 3H), 3.68-3.78 (m, 4H). MS(M+1):390.

【0181】化合物 2-7

N-(7-甲基-4-(3-(三氟甲氧基)苯基)噻吩並[3,2-d]嘧啶-2-基)-5-硝基噻吩-2-甲醯胺

(N-(7-methyl-4-(3-(trifluoromethoxy)phenyl)thieno[3,2-d]pyrimidin-2-yl)-5-nitrothiophene-2-carboxamide)

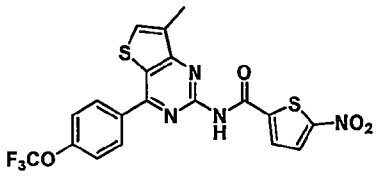


^{1}H NMR (400MHz, DMSO-d_6): δ 11.73 (br. s., 1H), 8.27 (d, J = 1.5 Hz, 1H), 8.18-8.26 (m, 3H), 8.14 (s, 1H), 7.84 (t, J = 8.1 Hz, 1H), 7.63-7.73 (m, 1H), 2.47 (d, J = 1.0 Hz, 3H). MS(M+1):481.

【0182】化合物 2-8

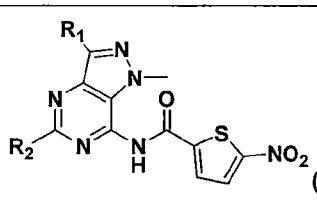
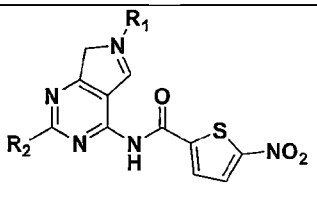
N-(7-甲基-4-(4-(三氟甲氧基)苯基)噻吩並[3,2-d]嘧啶-2-基)-5-硝基噻吩-2-甲醯胺

(N-(7-methyl-4-(4-(trifluoromethoxy)phenyl)thieno[3,2-d]pyrimidin-2-yl)-5-nitrothiophene-2-carboxamide)



^{1}H NMR (400MHz, DMSO-d_6): δ 11.74 (br. s., 1H), 8.31-8.38 (m, 2H), 8.27 (d, J = 1.0 Hz, 1H), 8.22 (q, J = 4.4 Hz, 2H), 7.69 (d, J = 7.8 Hz, 2H), 2.47 (d, J = 1.0 Hz, 3H), MS(M+1): 481.

【0183】表3

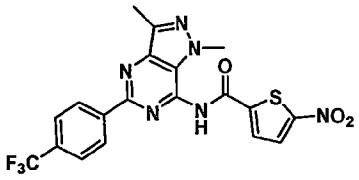
	 (A)  (B)		
化合物	R_1	R_2	Hep3B LC_{50}
式(A)			
3-1	甲基	4-(三氟甲基)苯基	2.22
3-2	甲基	3-(三氟甲基)苯基	0.86
3-3	甲基	4-(三氟甲氧基)苯基	1.92
3-4	甲基	3-(三氟甲氧基)苯基	1.51
3-5	正丙基	4-(三氟甲氧基)苯基	NA
3-6	正丙基	4-(三氟甲基)苯基	NA

3-7	正丙基	4-(叔丁基)苯基	NA
3-8	正丙基	苯基	NA
3-9	正丙基	4-氟苯基	NA
式(B)			
3-10	甲基	4-(叔丁基)苯基	10
3-11	乙基	4-(叔丁基)苯基	7.64
3-12	異丙基	4-(叔丁基)苯基	>10

【0184】化合物 3-1

N-(1,3-二甲基-5-(4-(三氟甲基)苯基)-1H-吡唑並[4,3-d]嘧啶-7-基)-5-硝基噻吩-2-甲醯胺

(N-(1,3-dimethyl-5-(4-(trifluoromethyl)phenyl)-1H-pyrazolo[4,3-d]pyrimidin-7-yl)-5-nitrothiophene-2-carboxamide)

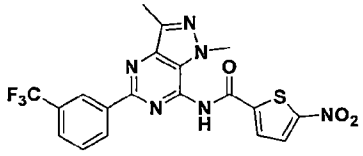


^{1}H NMR (400MHz, DMSO-d_6): δ 11.89 (br. s., 1H), 8.61 (br. s., 2H), 8.07-8.26 (m, 2H), 7.91 (d, J = 7.8 Hz, 2H), 4.20 (s, 3H), 2.72 (s, 3H). MS(M+1): 463.

【0185】化合物 3-2

N-(1,3-二甲基-5-(3-(三氟甲基)苯基)-1H-吡唑並[4,3-d]嘧啶-7-基)-5-硝基噻吩-2-甲醯胺

(N-(1,3-dimethyl-5-(3-(trifluoromethyl)phenyl)-1H-pyrazolo[4,3-d]pyrimidin-7-yl)-5-nitrothiophene-2-carboxamide)

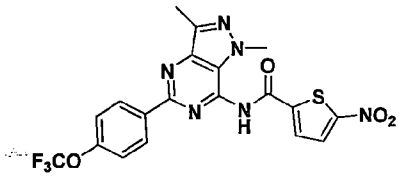


^{1}H NMR (400MHz, DMSO-d_6): δ 11.91 (br. s., 1H), 8.69 (br. s., 2H), 8.10-8.35 (m, 2H), 7.87 (d, J = 7.8 Hz, 1H), 7.79 (t, J = 7.8 Hz, 1H), 4.19 (s, 3H), 2.72 (s, 3H). MS(M+1): 463.

【0186】化合物 3-3

N-(1,3-二甲基-5-(4-(三氟甲氧基)苯基)-1H-吡唑並[4,3-d]嘧啶-7-基)-5-硝基噻吩-2-甲醯胺

(N-(1,3-dimethyl-5-(4-(trifluoromethoxy)phenyl)-1H-pyrazolo[4,3-d]pyrimidin-7-yl)-5-nitrothiophene-2-carboxamide)

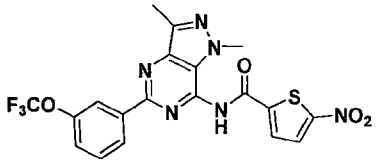


^{1}H NMR (400MHz, DMSO-d_6): δ 11.87 (br. s., 1H), 8.50 (br. s., 2H), 8.04-8.29 (m, 2H), 7.53 (d, J = 7.8 Hz, 2H), 4.18 (s, 3H), 2.70 (s, 3H). MS(M+1): 479.

【0187】化合物 3-4

N-(1,3-二甲基-5-(3-(三氟甲氧基)苯基)-1H-吡唑並[4,3-d]嘧啶-7-基)-5-硝基噻吩-2-甲醯胺

(N-(1,3-dimethyl-5-(3-(trifluoromethoxy)phenyl)-1H-pyrazolo[4,3-d]pyrimidin-7-yl)-5-nitrothiophene-2-carboxamide)

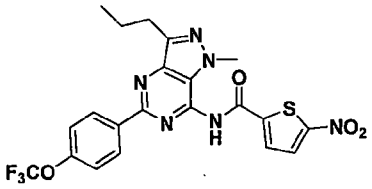


^{1}H NMR (400MHz, DMSO-d_6): δ 11.84 (br. s., 1H), 8.46 (br. s., 1H), 8.30 (br. s., 1H), 8.06-8.26 (m, 2H), 7.68 (t, J = 7.6 Hz, 1H), 7.50 (d, J = 6.8 Hz, 1H), 4.19 (s, 3H), 2.71 (s, 3H). MS(M+1): 479.

【0188】化合物 3-5

N-(1-甲基-3-丙基-5-(4-(三氟甲氧基)苯基)-1H-吡唑並[4,3-d]嘧啶-7-基)-5-硝基噻吩-2-甲醯胺

(N-(1-methyl-3-propyl-5-(4-(trifluoromethoxy)phenyl)-1H-pyrazolo[4,3-d]pyrimidin-7-yl)-5-nitrothiophene-2-carboxamide)

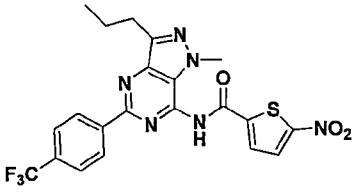


^{1}H NMR (400MHz, DMSO-d_6):δ8.42 (d, J = 7.3 Hz, 2H), 8.21 (d, J = 4.4 Hz, 1H), 8.02 (br. s., 1H), 7.57 (d, J = 8.8 Hz, 2H), 4.20 (br. s., 3H), 2.97 (t, J = 7.3 Hz, 2H), 1.87 (dq, J = 14.8, 7.6 Hz, 2H), 1.00 (t, J = 7.3 Hz, 3H). MS(M+1): 507.

【0189】化合物 3-6

N-(1-甲基-3-丙基-5-(4-(三氟甲基)苯基)-1H-吡唑並[4,3-d]嘧啶-7-基)-5-硝基噻吩-2-甲醯胺

(N-(1-methyl-3-propyl-5-(4-(trifluoromethyl)phenyl)-1H-pyrazolo[4,3-d]pyrimidin-7-yl)-5-nitrothiophene-2-carboxamide)

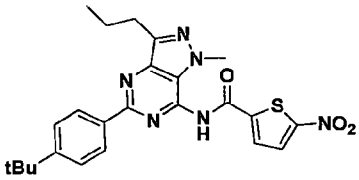


^{1}H NMR (400MHz, DMSO-d_6):δ 12.13 (br. s., 1H), 8.54 (br. s., 2H), 8.25 (d, J = 4.4 Hz, 1H), 8.13 (br. s., 1H), 7.96 (d, J = 8.3 Hz, 2H), 4.16 (br. s., 3H), 3.00 (t, J = 7.3 Hz, 2H), 2.00-1.80 (m, 2H), 1.01 (t, J = 7.3 Hz, 3H). MS(M+1): 491.

【0190】化合物 3-7

N-(5-(4-(叔丁基)苯基)-1-甲基-3-丙基-1H-吡唑並[4,3-d]嘧啶-7-基)-5-硝基噻吩-2-甲醯胺

(N-(5-(4-(tert-butyl)phenyl)-1-methyl-3-propyl-1H-pyrazolo[4,3-d]pyrimidin-7-yl)-5-nitrothiophene-2-carboxamide)

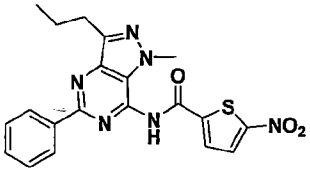


^{1}H NMR (400MHz, DMSO-d_6):δ 8.21 (br. s., 2H), 8.05-8.17 (m, 1H), 7.75 (s, 1H), 7.56 (br. s., 2H), 4.26 (br. s., 3H), 2.91 (t, J = 7.3 Hz, 2H), 1.77-1.94 (m, 2H), 1.34 (s, 9H), 0.99 (t, J = 7.3 Hz, 3H). MS(M+1): 479.

【0191】化合物 3-8

N-(1-甲基-5-苯基-3-丙基-1H-吡唑並[4,3-d]嘧啶-7-基)-5-硝基噻吩-2-甲醯胺

(N-(1-methyl-5-phenyl-3-propyl-1H-pyrazolo[4,3-d]pyrimidin-7-yl)-5-nitrothiophene-2-carboxamide)

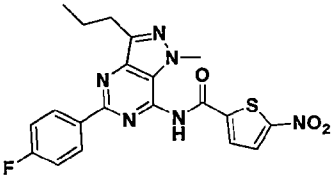


^{1}H NMR (400MHz, DMSO-d_6): δ 8.26 (br. s., 2H), 8.01-8.22 (m, 1H), 7.92 (br. s., 1H), 7.58 (d, J = 6.8 Hz, 3H), 4.27 (br. s., 3H), 2.95 (t, J = 7.6 Hz, 2H), 1.86 (sxt, J = 7.5 Hz, 2H), 0.99 (t, J = 7.3 Hz, 3H). MS(M+1): 423. 黃色固體。

【0192】化合物 3-9

N-(5-(4-氟苯基)-1-甲基-3-丙基-1H-吡唑並[4,3-d]嘧啶-7-基)-5-硝基噻吩-2-甲醯胺

(N-(5-(4-fluorophenyl)-1-methyl-3-propyl-1H-pyrazolo[4,3-d]pyrimidin-7-yl)-5-nitrothiophene-2-carboxamide)

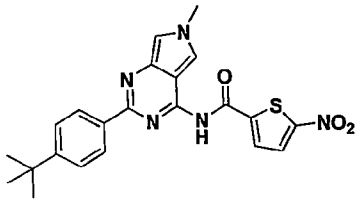


^{1}H NMR (400MHz, DMSO-d_6): δ 8.31 (br. s., 2H), 8.22 (d, J = 4.4 Hz, 1H), 8.03 (br. s., 1H), 7.44 (br. s., 2H), 4.22 (br. s., 3H), 2.96 (t, J = 7.3 Hz, 2H), 1.86 (sxt, J = 7.3 Hz, 2H), 1.00 (t, J = 7.3 Hz, 3H). MS(M+1): 441. 黃色固體。

【0193】化合物 3-10

N-(2-(4-(叔丁基)苯基)-6-甲基-6H-吡咯並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(2-(4-(tert-butyl)phenyl)-6-methyl-6H-pyrrolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

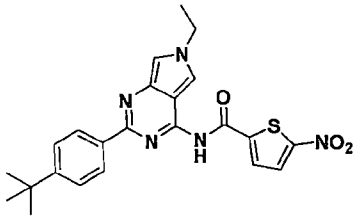


^{1}H NMR (400MHz, DMSO-d_6): δ 8.07-8.13 (m, J = 7.8 Hz, 2H), 8.05 (d, J = 4.4 Hz, 1H), 7.89 (d, J = 2.0 Hz, 1H), 7.85 (br. s., 1H), 7.66-7.73 (m, J = 8.3 Hz, 2H), 7.43 (d, J = 2.0 Hz, 1H), 4.14 (s, 3H), 1.40 (s, 9H). MS (M+1) : 436. 淡黃色固體。

【0194】化合物 3-11

N-(2-(4-(叔丁基)苯基)-6-乙基-6H-吡咯並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(2-(4-(tert-butyl)phenyl)-6-ethyl-6H-pyrrolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

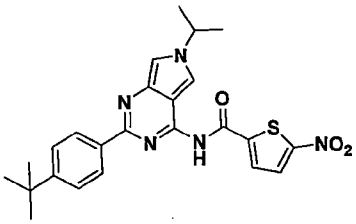


^{1}H NMR (400MHz, DMSO-d_6): δ 14.36 (br. s., 1H), 8.24 (s, 1H), 8.13 (br. s., 1H), 7.88-8.08 (m, 2H), 7.80 (br. s., 1H), 7.44-7.73 (m, 3H), 4.30 (d, J = 6.8 Hz, 2H), 1.49 (t, J = 7.1 Hz, 3H), 1.23-1.41 (m, 9H). MS(M+1):450. 黃色固體。

【0195】化合物 3-12

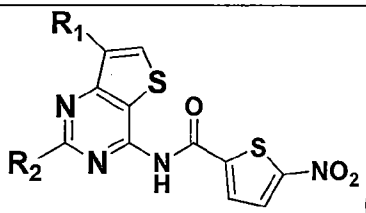
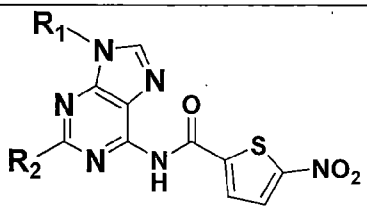
N-(2-(4-(叔丁基)苯基)-6-異丙基-6H-吡咯並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(2-(4-(tert-butyl)phenyl)-6-isopropyl-6H-pyrrolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)



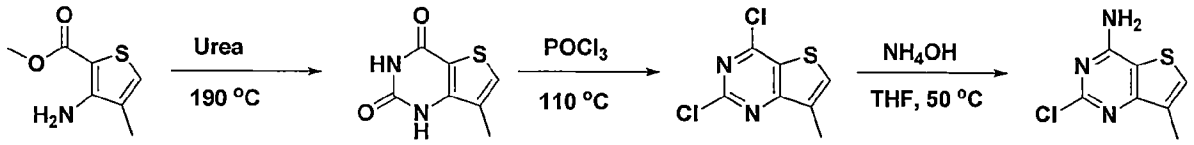
^{1}H NMR (400MHz, DMSO-d_6): δ 14.24 (s, 1H), 8.17 (d, J = 4.4 Hz, 1H), 8.07 (br. s., 2H), 7.99 (br. s., 1H), 7.94 (br. s., 1H), 7.72 (d, J = 2.0 Hz, 1H), 7.62 (d, J = 8.3 Hz, 2H), 4.71 (quin, J = 6.6 Hz, 1H), 1.56 (d, J = 6.4 Hz, 6H), 1.34 (s, 9H). MS(M+1): 464. 黃色固體。

【0196】表4

	 (C)  (D)		
化合物	R_1	R_2	Hep3B LC_{50} (uM)
式(C)			
4-1	甲基	4-(叔丁基)苯基	1.15
4-2	甲基	4-(三氟甲基)苯基	0.97
4-3	甲基	3-(三氟甲基)苯基	0.88
4-4	甲基	4-(三氟甲氧基)苯基	0.89
4-5	甲基	3-(三氟甲氧基)苯基	0.79
4-6	甲基	3,5-雙(三氟甲基)苯基	0.42

4-7	甲基	3-氟苯基	1.28
4-8	甲基	4-氟苯基	1.70
4-9	甲基	3,4,5-三氟苯基	>10
4-10	甲基	4-(二甲基胺基)苯基	>10
4-11	甲基	3,3-二氟吡咯烷-1-基	3.18
4-12	甲基	4-(叔丁基)苯氧基	1.34
4-13	甲基	2-氟-5-(三氟甲基)苯基	1.70
4-14	甲基	2-氟-4-(三氟甲基)苯基	1.35
4-15	苯基	4-氟苯基	0.62
4-16	苯基	4-氯-3-氟苯基	0.56
4-17	苯基	2-氟-5-(三氟甲基)苯基	0.86
4-18	3-氟苯基	4-氟苯基	0.49
4-19	4-(叔丁基)苯基	4-氟苯基	0.67
式(D)			
4-20	4-哌啶-1-甲酸叔丁酯 (tert-butyl 4-piperidine-1-carboxylate)	4-氟苯基	>1.25
4-21	環己基	6-氟吡啶-3-基	NA
4-22	環己基	6-乙氧基吡啶-3-基	NA

【0197】 2-氯-7-甲基噻吩並[3,2-d]嘧啶-4-胺(2-chloro-7-methylthieno[3,2-d]pyrimidin-4-amine)的合成



三步驟合成2-氯-7-甲基噻吩並[3,2-d]嘧啶-4-胺(2-chloro-7-methylthieno[3,2-d]pyrimidin-4-amine)

【0198】 向3-胺基-4-甲基噻吩-2-甲酸甲酯(methyl 3-amino-4-methylthiophene-2-carboxylate)(20.6 g，120 mmol)的溶液中加入36

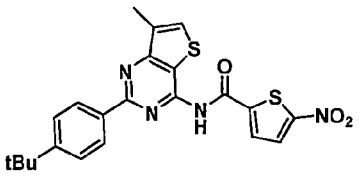
g(600 mmol)脲(urea)，並將所得混合物在200°C下加熱1.5小時。使混合物恢復至室溫，並向其中加入DMF(360 ml)，接著迴流加熱1小時。在反應完成後，將冰水加入混合物中，並過濾因此沉澱的結晶，得到(19.8 g，90%)的7-甲基噻吩並[3,2-d]-嘧啶-2,4(1H,3H)-二酮(7-methylthieno[3,2-d]-pyrimidine-2,4(1H,3H)-dione)。

【0199】 向7-甲基噻吩並[3,2-d]-嘧啶-2,4(1H,3H)-二酮(18.3 g，100 mmol)的溶液中加入153.0 g(1 mol)的氧氯化磷(phosphorus oxychloride)，並將所得混合物迴流加熱8小時。在反應完成後，將冰水加入反應混合物中，並過濾因此沉澱的晶體，得到(15.4 g，70%)的2,4-二氯-7-甲基噻吩並[3,2-d]嘧啶(2,4-dichloro-7-methylthieno[3,2-d]pyrimidine)。

【0200】 向在反應燒瓶中的2,4-二氯-7-甲基噻吩並[3,2-d]嘧啶(2,4-dichloro-7-methylthieno[3,2-d]pyrimidine)(8.8 g，40 mmol)的懸浮液中加入100 ml四氫呋喃，等待固體完全溶解。然後加入100 g、30%的銨溶液，並在室溫下反應24小時。將60 ml水倒入溶液中，抽氣過濾，得到為黃色固體粉末的2-氯-7甲基噻吩並[3,2-d]嘧啶-4-胺(2-chloro-7-methylthieno[3,2-d]pyrimidin-4-amine)(6.8 g，85%)。

【0201】 化合物 4-1

N-(2-(4-(叔丁基)苯基)-7-甲基噻吩並[3,2-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺(N-(2-(4-(tert-butyl)phenyl)-7-methylthieno[3,2-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

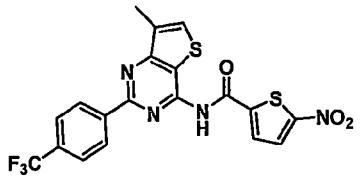


^{1}H NMR (400MHz, DMSO-d_6): δ 11.97 (br. s., 1H), 8.46 (d, J = 8.3 Hz, 2H), 8.24 (d, J = 4.4 Hz, 1H), 8.08 (d, J = 1.5 Hz, 1H), 7.59 (d, J = 8.3 Hz, 2H), 3.28 (br. s., 3H), 1.35 (s, 9H), MS(M+1): 453.

【0202】化合物 4-2

N-(7-甲基-2-(4-(三氟甲基)苯基)噻吩並[3,2-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(7-methyl-2-(4-(trifluoromethyl)phenyl)thieno[3,2-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

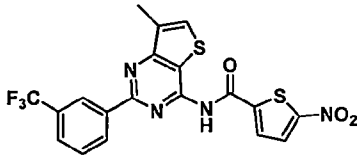


^{1}H NMR (400MHz, DMSO-d_6): δ 12.06 (br. s., 1H), 8.68-8.80 (m, J = 7.8 Hz, 2H), 8.32 (d, J = 4.4 Hz, 1H), 8.25 (d, J = 4.4 Hz, 1H), 8.14 (d, J = 1.5 Hz, 1H), 7.91-8.02 (m, J = 8.3 Hz, 2H), 2.53 (d, J = 1.0 Hz, 3H). MS(M+1): 465

【0203】化合物 4-3

N-(7-甲基-2-(3-(三氟甲基)苯基)噻吩並[3,2-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(7-methyl-2-(3-(trifluoromethyl)phenyl)thieno[3,2-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

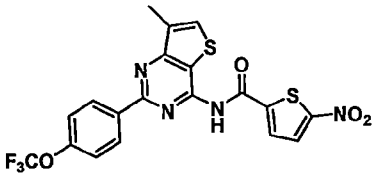


^{1}H NMR (400MHz, DMSO-d_6):δ 12.01 (br. s., 1H), 8.73-8.93 (m, 2H), 8.32 (d, J = 4.4 Hz, 1H), 8.25 (d, J = 4.4 Hz, 1H), 8.14 (d, J = 1.0 Hz, 1H), 7.93 (d, J = 7.8 Hz, 1H), 7.84 (t, J = 7.6 Hz, 1H), 2.52 (d, J = 1.0 Hz, 3H). MS(M+1): 465.

【0204】化合物 4-4

N-(7-甲基-2-(4-(三氟甲氧基)苯基)噻吩並[3,2-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(7-methyl-2-(4-(trifluoromethoxy)phenyl)thieno[3,2-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

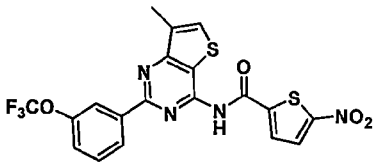


^{1}H NMR (400MHz, DMSO-d_6): δ 12.03 (br. s., 1H), 8.50-8.78 (m, 2H), 8.16-8.38 (m, 2H), 8.11 (d, J = 1.0 Hz, 1H), 7.57 (d, J = 7.8 Hz, 2H), 2.49 (br. s., 3H). MS(M+1): 481.

【0205】化合物 4-5

N-(7-甲基-2-(3-(三氟甲氧基)苯基)噻吩並[3,2-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(7-methyl-2-(3-(trifluoromethoxy)phenyl)thieno[3,2-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

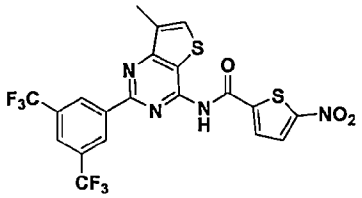


^{1}H NMR (400MHz, DMSO-d_6): δ 11.97 (s, 1H), 8.58 (d, J = 7.8 Hz, 1H), 8.43 (s, 1H), 8.31 (d, J = 4.4 Hz, 1H), 8.25 (d, J = 4.4 Hz, 1H), 8.14 (d, J = 1.0 Hz, 1H), 7.73 (t, J = 8.1 Hz, 1H), 7.52-7.60 (m, 1H), 2.51 (d, J = 1.0 Hz, 7H). MS(M+1): 481.

【0206】化合物 4-6

N-(2-(3,5-雙(三氟甲基)苯基)-7-甲基噻吩並[3,2-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

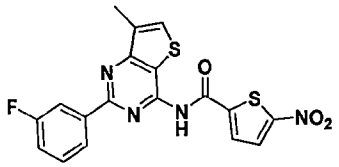
(N-(2-(3,5-bis(trifluoromethyl)phenyl)-7-methylthieno[3,2-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)



^{1}H NMR (400MHz, DMSO-d_6): δ 12.01 (br. s., 1H), 9.07 (s, 2H), 8.30 (d, J = 4.4 Hz, 2H), 8.24 (d, J = 4.4 Hz, 1H), 8.15 (d, J = 1.0 Hz, 1H), 2.52 (s, 2H). MS(M+1): 533.

【0207】 化合物 4-7

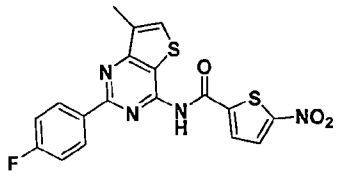
N-(2-(3-氟苯基)-7-甲基噻吩並[3,2-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺 (N-(2-(3-fluorophenyl)-7-methylthieno[3,2-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)



^{1}H NMR (400MHz, DMSO-d_6): δ 11.94 (br. s., 1H), 8.39 (d, J = 7.8 Hz, 1H), 8.18 - 8.33 (m, 3H), 8.11 (d, J = 1.0 Hz, 1H), 7.63 (td, J = 8.1, 6.4 Hz, 1H), 7.33-7.45 (m, 1H), 2.51 (s, 3H). MS(M+1): 415.

【0208】 化合物 4-8

N-(2-(4-氟苯基)-7-甲基噻吩並[3,2-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺 (N-(2-(4-fluorophenyl)-7-methylthieno[3,2-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

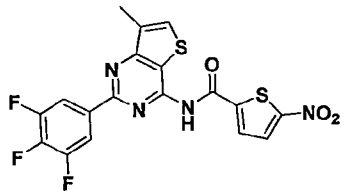


^{1}H NMR (400MHz, DMSO-d_6): δ 11.95 (br. s., 1H), 8.50-8.66 (m, 2H), 8.30 (d, J = 4.4 Hz, 1H), 8.24 (d, J = 4.4 Hz, 1H), 8.10 (d, J = 1.0 Hz, 1H), 7.31-7.50 (m, 2H), 2.50 (s, 3H). MS(M+1): 415.

【0209】 化合物 4-9

N-(7-甲基-2-(3,4,5-三氟苯基)噻吩並[3,2-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(7-methyl-2-(3,4,5-trifluorophenyl)thieno[3,2-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

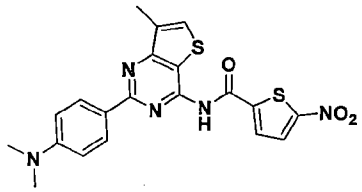


^{1}H NMR (400MHz, DMSO-d_6): δ 11.94 (br. s., 1H), 8.28-8.36 (m, 3H), 8.25-8.27 (m, 1H), 8.14 (d, J = 1.0 Hz, 1H), 2.50 (s, 3H). MS(M+1): 451.

【0210】化合物 4-10

N-(2-(4-(二甲基胺基)苯基)-7-甲基噻吩並[3,2-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(2-(4-(dimethylamino)phenyl)-7-methylthieno[3,2-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

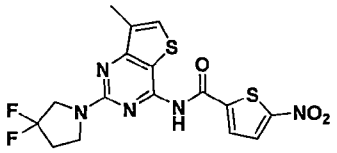


^{1}H NMR (400MHz, DMSO-d_6): δ 11.85 (br. s., 1H), 8.33-8.51 (m, 2H), 8.30 (br. s., 1H), 8.24 (d, J = 3.9 Hz, 1H), 8.01 (br. s., 1H), 6.84 (d, J = 8.8 Hz, 2H), 3.02 (s, 6H), 2.47 (d, J = 1.0 Hz, 3H). MS(M+1): 440.

【0211】化合物 4-11

N-(2-(3,3-二氟吡咯烷-1-基)-7-甲基噻吩並[3,2-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(2-(3,3-difluoropyrrolidin-1-yl)-7-methylthieno[3,2-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

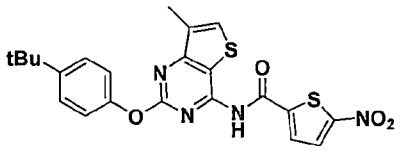


^{1}H NMR (400MHz, DMSO-d_6): δ 11.59 (br. s., 1H), 8.16-8.30 (m, 2H), 7.87 (d, J = 1.0 Hz, 1H), 3.89-4.07 (m, 2H), 3.84 (t, J = 7.3 Hz, 2H), 2.52-2.67 (m, 3H), 2.30 (d, J = 1.0 Hz, 3H), MS(M+1): 426.

【0212】化合物 4-12

N-(2-(4-(叔丁基)苯氧基)-7-甲基噻吩並[3,2-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(2-(4-(tert-butyl)phenoxy)-7-methylthieno[3,2-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

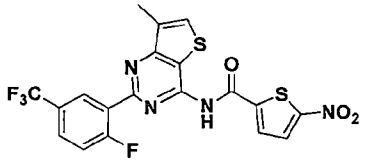


^{1}H NMR (400MHz, DMSO-d_6):δ 12.07 (s, 1H), 8.21-8.25 (m, 1H), 8.18-8.21 (m, 1H), 8.05 (d, J = 1.0 Hz, 1H), 7.34-7.55 (m, 2H), 7.10-7.25 (m, 2H), 2.26 (s, 3H), 1.31 (s, 9H). MS(M+1): 469.

【0213】化合物 4-13

N-(2-(2-氟-5-(三氟甲基)苯基)-7-甲基噻吩並[3,2-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(2-(2-fluoro-5-(trifluoromethyl)phenyl)-7-methylthieno[3,2-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

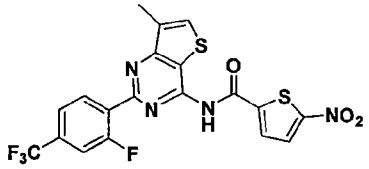


^{1}H NMR (400MHz, DMSO-d_6): δ 12.12 (br. s., 1H), 8.48 (dd, J = 6.8, 2.4 Hz, 1H), 8.27 (d, J = 4.4 Hz, 1H), 8.17-8.25 (m, 1H), 8.16 (d, J = 1.5 Hz, 1H), 7.88-8.05 (m, 1H), 7.65 (t, J = 9.5 Hz, 1H), 2.47 (d, J = 1.0 Hz, 3H). MS(M+1): 483. 黃色固體。

【0214】化合物 4-14

N-(2-(2-氟-4-(三氟甲基)苯基)-7-甲基噻吩並[3,2-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(2-(2-fluoro-4-(trifluoromethyl)phenyl)-7-methylthieno[3,2-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

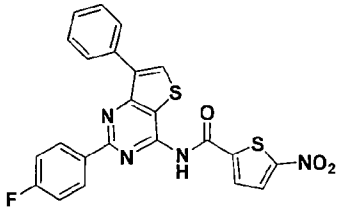


^{1}H NMR (400MHz, DMSO-d_6): δ 12.18 (br. s., 1H), 8.32 (t, J = 7.8 Hz, 1H), 8.23-8.28 (m, 1H), 8.18-8.23 (m, 1H), 8.15 (d, J = 1.0 Hz, 1H), 7.86 (d, J = 10.3 Hz, 1H), 7.79 (d, J = 8.3 Hz, 1H), 2.46 (d, J = 1.0 Hz, 3H). MS(M+1): 483. 黃色固體。

【0215】化合物 4-15

N-(2-(4-氟苯基)-7-苯基噻吩並[3,2-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(2-(4-fluorophenyl)-7-phenylthieno[3,2-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

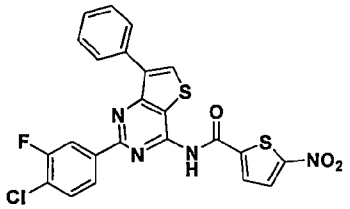


^{1}H NMR (400MHz, DMSO-d_6): δ 12.08 (s, 1H), 8.69 (s, 1H), 8.56 (dd, J = 8.8, 5.4 Hz, 2H), 8.34 (d, J = 4.4 Hz, 1H), 8.27 (d, J = 4.4 Hz, 1H), 8.09-8.21 (m, 2H), 7.51-7.62 (m, 2H), 7.36-7.49 (m, 3H). MS(M+1): 477. 黃色固體。

【0216】化合物 4-16

N-(2-(4-氯-3-氟苯基)-7-苯基噻吩並[3,2-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(2-(4-chloro-3-fluorophenyl)-7-phenylthieno[3,2-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

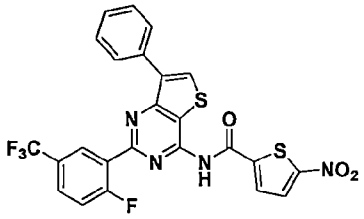


^{1}H NMR (400MHz, DMSO-d_6): δ 12.09 (s, 1H), 8.69-8.74 (m, 1H), 8.31-8.40 (m, 3H), 8.23-8.30 (m, 1H), 8.06-8.18 (m, 2H), 7.76-7.88 (m, 1H), 7.51-7.64 (m, 2H), 7.40-7.50 (m, 1H). MS(M+1): 511. 黃色固體。

【0217】化合物 4-17

N-(2-(2-氟-5-(三氟甲基)苯基)-7-苯基噻吩並[3,2-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(2-(2-fluoro-5-(trifluoromethyl)phenyl)-7-phenylthieno[3,2-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

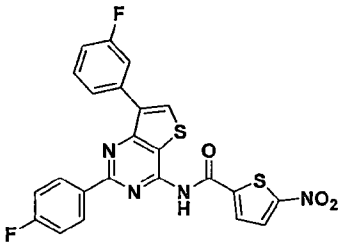


^{1}H NMR (400MHz, DMSO-d_6): δ 12.21 (br. s., 1H), 8.77 (s, 1H), 8.58 (dd, J = 6.8, 2.4 Hz, 1H), 8.32 (d, J = 4.4 Hz, 1H), 8.25 (d, J = 4.4 Hz, 1H), 8.14-8.20 (m, 2H), 8.00 (dt, J = 8.2, 3.5 Hz, 1H), 7.63-7.73 (m, 1H), 7.47-7.56 (m, 2H), 7.38-7.46 (m, 1H). MS(M+1):545.灰白色固體。

【0218】化合物 4-18

N-(7-(3-氟苯基)-2-(4-氟苯基)噻吩並[3,2-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(7-(3-fluorophenyl)-2-(4-fluorophenyl)thieno[3,2-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

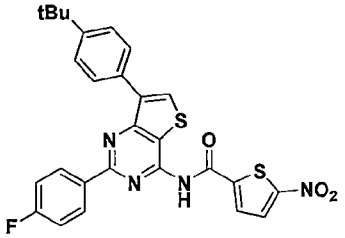


^{1}H NMR (400MHz, DMSO-d_6): δ 12.09 (s, 1H), 8.81 (s, 1H), 8.55 (dd, J = 8.8, 5.9 Hz, 2H), 8.34 (d, J = 4.4 Hz, 1H), 8.26 (d, J = 4.4 Hz, 1H), 8.04-8.09 (m, 1H), 8.02 (d, J = 7.8 Hz, 1H), 7.60 (td, J = 7.9, 6.6 Hz, 1H), 7.38-7.49 (m, 2H), 7.17-7.33 (m, 1H) MS(M+1): 495. 橘色固體。

【0219】化合物 4-19

N-(7-(4-(叔丁基)苯基)-2-(4-氟苯基)噻吩並[3,2-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(7-(4-(tert-butyl)phenyl)-2-(4-fluorophenyl)thieno[3,2-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

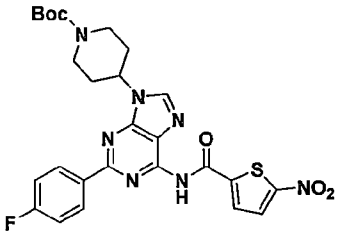


^{1}H NMR (400MHz, DMSO-d_6): δ 12.09 (br. s., 1H), 8.63 (s, 1H), 8.57 (dd, J = 8.8, 5.9 Hz, 2H), 8.28-8.35 (m, 1H), 8.19-8.28 (m, 1H), 8.04-8.17 (m, 2H), 7.52-7.65 (m, 2H), 7.43 (t, J = 8.8 Hz, 2H), 1.37 (s, 9H). MS(M+1): 533. 黃色固體。

【0220】化合物 4-20

4-(2-(4-氟苯基)-6-(5-硝基噻吩-2-甲醯胺基)-9H-嘌呤-9-基)哌啶-1-甲酸叔丁酯(tert-butyl

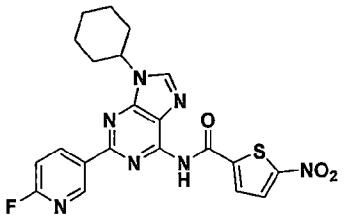
4-(2-(4-fluorophenyl)-6-(5-nitrothiophene-2-carboxamido)-9H-purin-9-yl)piperidine-1-carboxylate)



^{1}H NMR (400MHz, DMSO-d_6): δ 11.76 (br. s., 1H), 8.65 (s, 1H), 8.43-8.58 (m, 2H), 8.15-8.28 (m, 2H), 7.27-7.46 (m, 2H), 4.73-4.89 (m, 1H), 4.16 (d, J = 11.7 Hz, 2H), 3.00 (br. s., 2H), 2.06-2.25 (m, 4H). MS(M+1):568. 黃色固體。

【0221】 化合物 4-21

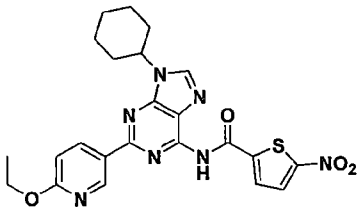
N-(9-環己基-2-(6-氟吡啶-3-基)-9H-嘌呤-6-基)-5-硝基噻吩-2-甲醯胺 (N-(9-cyclohexyl-2-(6-fluoropyridin-3-yl)-9H-purin-6-yl)-5-nitrothiophene-2-carbox amide)



^{1}H NMR (400MHz, DMSO-d_6): δ 11.82 (s, 1H), 9.22 (d, J = 2.4 Hz, 1H), 8.89 (td, J = 8.3, 2.4 Hz, 1H), 8.68 (s, 1H), 8.23 (q, J = 4.4 Hz, 2H), 7.38 (dd, J = 8.8, 2.4 Hz, 1H), 4.56- 4.69 (m, 1H), 1.99-2.18 (m, 4H), 1.82-1.97 (m, 2H), 1.75 (d, J = 13.2 Hz, 1H), 1.41-1.61 (m, 2H), 1.25-1.40 (m, 1H). MS(M+1): 468. 卡其色固體。

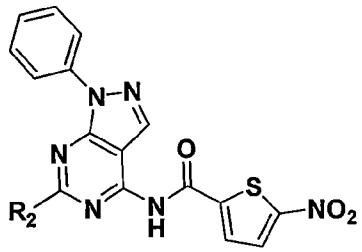
【0222】 化合物 4-22

N-(9-環己基-2-(6-乙氧基吡啶-3-基)-9H-嘌呤-6-基)-5-硝基噻吩-2-甲醯胺 (N-(9-cyclohexyl-2-(6-ethoxypyridin-3-yl)-9H-purin-6-yl)-5-nitrothiophene-2-carbox amide)



^{1}H NMR (400MHz, DMSO-d_6): δ 11.76 (br. s., 1H), 9.18 (d, J = 2.4 Hz, 1H), 8.55-8.68 (m, 2H), 8.16-8.27 (m, 2H), 6.90-7.02 (m, 1H), 4.52-4.68 (m, 1H), 4.33-4.46 (m, 2H), 1.97-2.20 (m, 4H), 1.91 (t, J = 6.6 Hz, 2H), 1.75 (d, J = 12.2 Hz, 1H), 1.52 (q, J = 12.9 Hz, 2H), 1.30-1.42 (m, 4H). MS(M+1): 494. 卡其色固體。

【0223】表5

		
化合物	R_2	Hep3B LC50 (uM)
5-1	哌啶-4-基	>5.0
5-2	1-丙烯醯基哌啶-4-基	2.47
5-3	吡咯烷-1-基	4.91
5-4	(*S*)-吡咯烷基-3-醇-基	1.01
5-5	(*R*)-3-氰基吡咯烷-1-基	0.50
5-6	3,3-二氟吡咯烷-1-基	0.53
5-7	嗎啉基	1.46
5-8	(2*S*，6*R*)-2,6-二甲基嗎啉基	1.71
5-9	4-(氯苯基)磺醯胺基	> 6.0
5-10	2-(2-乙氧基乙氧基)乙氧基	> 5.0
5-11	2-(二甲基胺基)乙氧基	4.13
5-12	2-嗎啉基乙氧基	>3.0
5-13	苯氧基	>5.0
5-14	4-氟苯氧基	>5.0
5-15	苯硫基	>5.0
5-16	4-(氯苯基)硫基	0.36
5-17	呋喃-2-基	0.40

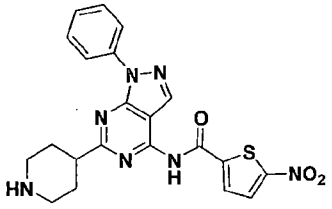
5-18	噻吩-2-基	0.58
5-19	5-氯噻吩-2-基	0.17
5-20	噻吩-3-基	1.11
5-21	3,5-二甲基異噁唑-4-基(3,5-dimethylisoxazol-4-yl)	0.76
5-22	3-(三氟甲基)-1H-吡唑-1-基	0.38
5-23	苯基	0.43
5-24	嘧啶-5-基	0.96
5-25	2-氟苯基	0.46
5-26	3-氟苯基	0.41
5-27	4-氟苯基	0.27
5-28	6-氟吡啶-3-基	0.13
5-29	3-氯苯基	0.21
5-30	4-氯苯基	0.35
5-31	6-氯吡啶-3-基	0.10
5-32	4-氰苯基	0.11
5-33	6-氰基吡啶-3-基	0.30
5-34	6-甲基吡啶-3-基	0.85
5-35	6-甲氧基吡啶-3-基	0.18
5-36	4-甲氧基苯基	0.60
5-37	4-(叔丁基)苯基	0.78
5-38	3-(三氟甲基)苯基	0.45
5-39	4-(三氟甲基)苯基	0.32
5-40	4-(三氟甲氧基)苯基	0.43
5-41	3-(二甲基胺基)苯基	0.45
5-42	6-(6-(哌啶-1-基)吡啶-3-基	0.51
5-43	6-嗎啉並吡啶-3-基(6-morpholinopyridin-3-yl)	0.57
5-44	3,4-二氟苯基	0.25
5-45	2,4-二氟苯基	0.44
5-46	4-氯-3-氟苯基	0.24
5-47	4-氯-2-氟苯基	0.13

5-48	3,4-二氯苯基	0.41
5-49	2,4-二氯苯基	0.27
5-50	2-氟-5-(三氟甲基)苯基	0.35
5-51	2-氟-4-(三氟甲基)苯基	0.37
5-52	3-氟-4-(三氟甲基)苯基	>1.25
5-53	3,4,5-三氟苯基	>1.25
5-54	6-(2-甲氧基乙氧基)吡啶-3-基	0.34
5-55	6-(2-乙氧基乙氧基)吡啶-3-基	0.49
5-56	6-(2,2,3,3-四氟丙氧基)吡啶-3-基	0.40
5-57	6-(2-(2-乙氧基乙氧基)乙氧基)吡啶-3-基	0.79

【0224】化合物 5-1

5-硝基-N-(1-苯基-6-(哌啶-4-基)-1H-吡唑並[3,4-d]嘧啶-4-基)噻吩-2-甲醯胺

(5-nitro-N-(1-phenyl-6-(piperidin-4-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)thiophene-2-carboxamide)

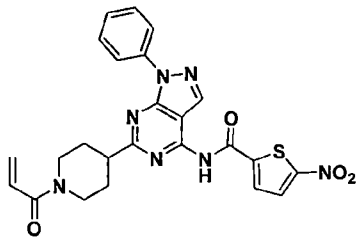


^{1}H NMR (400MHz, DMSO-d_6): δ 8.36 (s, 1H), 8.29-8.24 (m, 2H), 8.07 (d, J = 4.4 Hz, 1H), 7.66 (d, J = 3.9 Hz, 1H), 7.54 (t, J = 7.9 Hz, 2H), 7.31 (t, J = 7.3 Hz, 1H), 3.38- 3.36 (m, 2H), 3.07-3.02 (m, 3H), 2.15-2.02 (m, 4H). MS(M+1): 450. 黃色固體。

【0225】化合物 5-2

N-(6-(1-丙烯醯基哌啶-4-基)-1-苯基-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(6-(1-acryloylpiperidin-4-yl)-1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitro thiophene-2-carboxamide)

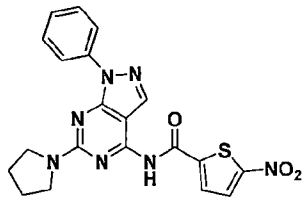


^{1}H NMR (400MHz, DMSO-d_6): δ 12.11 (s, 1H), 8.58 (s, 1H), 8.30 (brs, 1H), 8.23- 8.20 (m, 3H), 7.60 (t, J = 7.8 Hz, 2H), 7.40 (t, J = 7.4 Hz, 1H), 6.87 (dd, J =16.6, 10.3 Hz, 1H), 6.12 (dd, J = 16.6, 2.5 Hz, 1H), 5.69 (dd, J = 10.3, 2.5 Hz, 1H), 4.55-4.52 (m, 1H), 4.21-4.17 (m, 1H), 3.27-3.21 (m, 2H), 2.91-2.84 (m, 1H), 2.12-2.08 (m, 2H), 1.83-1.78 (m, 2H). MS(M+1): 504. 黃色固體。

【0226】化合物 5-3

5-硝基-N-(1-苯基-6-(吡咯烷-1-基)-1H-吡唑並[3,4-d]嘧啶-4-基)噻吩-2-甲醯胺

(5-nitro-N-(1-phenyl-6-(pyrrolidin-1-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)thiophene-2-carboxamide)

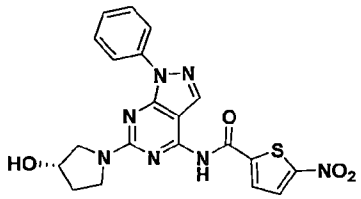


^{1}H NMR (400MHz, DMSO-d_6): δ 8.35 (dd, J = 8.8, 1.0 Hz, 2H), 8.05 (t, J = 2.2 Hz, 2H), 7.64 (d, J = 4.4 Hz, 1H), 7.44-7.52 (m, 2H), 7.21 (t, J = 7.3 Hz, 1H), 3.54-3.62 (m, 4H), 1.90-1.97 (m, 4H). MS(M+1):436.

【0227】化合物 5-4

(S)-N-(6-(3-羥基吡咯烷-1-基)-1-苯基-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

((S)-N-(6-(3-hydroxypyrrolidin-1-yl)-1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

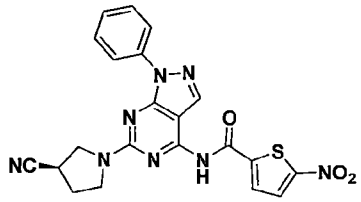


^{1}H NMR (400MHz, DMSO-d_6): δ 11.56 (s, 1H), 8.30-8.20 (m ,5H), 7.53 (t, J = 7.8 Hz, 2H), 7.29 (t, J = 7.3 Hz, 1H), 5.00 (d, J = 3.5 Hz, 1H), 4.42 (s, 1H), 3.70-3.60 (m, 4H), 2.09-1.99 (m, 1H), 1.94 (brm, 1H). MS(M+1): 452. 黃色固體。

【0228】化合物 5-5

(R)-N-(6-(3-氰基吡咯烷-1-基)-1-苯基-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

((R)-N-(6-(3-cyanopyrrolidin-1-yl)-1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

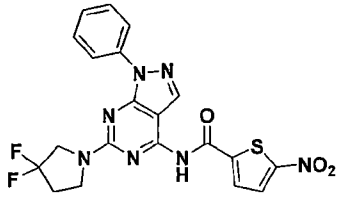


^{1}H-NMR (DMSO-d_6, 400 MHz) : δ 11.62 (s, 1H), 8.31-8.22 (m, 5H), 7.55 (t, J = 7.8 Hz, 2H), 7.32 (t, J = 7.4 Hz, 1H), 4.00-3.59 (m, 5H), 2.52-2.38 (m, 1H), 2.33-1.91 (m, 2H). MS(M+1): 461. 黃色固體。

【0229】化合物 5-6

N-(6-(3,3-二氟吡咯烷-1-基)-1-苯基-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(6-(3,3-difluoropyrrolidin-1-yl)-1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

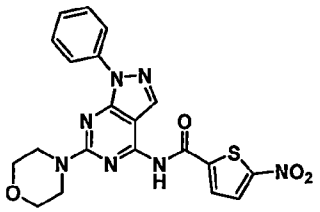


^{1}H NMR (400MHz, DMSO-d_6): δ 11.63 (br. s., 1H), 8.33 (s, 1H), 8.30 (d, J = 4.4 Hz, 1H), 8.25 (d, J = 7.3 Hz, 2H), 8.22 (d, J = 4.4 Hz, 1H), 7.55 (dd, J = 8.3, 7.3 Hz, 2H), 7.29 - 7.35 (m, 1H), 4.05 (t, J = 13.2 Hz, 2H), 3.88 (t, J = 7.1 Hz, 2H), 2.59 (tt, J = 14.2, 7.3 Hz, 2H). MS(M+1):472.

【0230】化合物 5-7

N-(6-嗎啉基-1-苯基-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(6-morpholino-1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

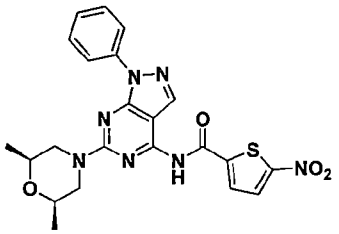


^{1}H NMR (400MHz, DMSO-d_6): δ 11.52 (br. s., 1H), 8.33 (s, 1H), 8.29 (d, J = 4.4 Hz, 1H), 8.23 (d, J = 4.4 Hz, 1H), 8.19 (dd, J = 8.8, 1.0 Hz, 2H), 7.50-7.58 (m, 2H), 7.28- 7.35 (m, 1H), 3.82-3.90 (m, 4H), 3.68-3.76 (m, 4H). MS (M+1) : 452.

【0231】化合物 5-8

N-(6-((2S，6R)-2,6-二甲基嗎啉基)-1-苯基-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

N-(6-((2S,6R)-2,6-dimethylmorpholino)-1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide

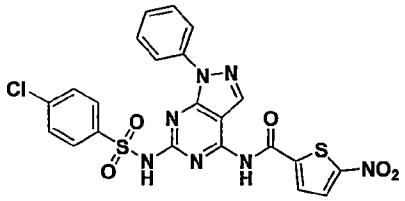


^{1}H NMR (400MHz, DMSO-d_6): δ 11.46 (s, 1H), 8.30 (s, 1H), 8.28 (d, J = 4.4 Hz, 1H), 8.20 (d, J = 4.4 Hz, 1H), 8.17 (d, J = 7.3 Hz, 2H), 7.54 (t, J = 8.1 Hz, 2H), 7.31 (t, J = 7.6 Hz, 1H), 4.62 (d, J = 12.2 Hz, 2H), 3.55-3.67 (m, 2H), 2.64 (dd, J = 13.2, 10.8 Hz, 2H), 1.19 (s, 3H), 1.18 (s, 3H). MS(M+1):480.橘色固體。

【0232】化合物 5-9

N-(6-((4-氯苯基)磺醯胺基)-1-苯基-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(6-((4-chlorophenyl)sulfonamido)-1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

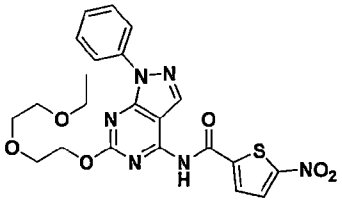


^{1}H NMR (400MHz, DMSO-d_6): δ 12.06 (br. s., 1H), 11.95 (br. s., 1H), 8.42 (s, 1H), 8.29 (br. s., 1H), 8.23 (d, J = 4.4 Hz, 1H), 8.04 (d, J = 8.3 Hz, 2H), 7.96 (d, J = 7.8 Hz, 2H), 7.52-7.66 (m, 4H), 7.35-7.46 (m, 1H). MS(M+1):590.奶油色固體。

【0233】化合物 5-10

N-(6-(2-(2-乙氧基乙氧基)乙氧基)-1-苯基-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(6-(2-(2-ethoxyethoxy)ethoxy)-1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

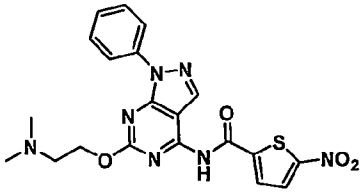


^{1}H NMR (400MHz, DMSO-d_6): δ 12.12 (br. s., 1H), 8.52 (s, 1H), 8.32 (d, J = 4.4 Hz, 1H), 8.21 (d, J = 4.4 Hz, 1H), 8.17 (dd, J = 8.8, 1.0 Hz, 2H), 7.53-7.61 (m, 2H), 7.33- 7.41 (m, 1H), 4.50-4.59 (m, 2H), 3.77-3.85 (m, 2H), 3.59 (dd, J = 5.9, 3.9 Hz, 2H), 3.45-3.50 (m, 2H), 3.40 (q, J = 6.8 Hz, 2H), 1.03-1.10 (m, 3H). MS(M+1):499. 黃色固體。

【0234】化合物 5-11

N-(6-(2-(二甲基胺基)乙氧基)-1-苯基-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(6-(2-(dimethylamino)ethoxy)-1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

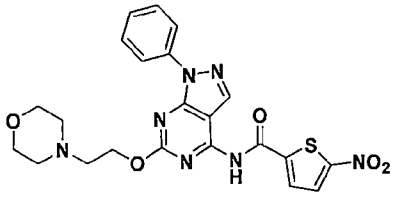


^{1}H NMR (400MHz, DMSO-d_6): δ 8.57 (s, 1H), 8.32 (d, J = 4.9 Hz, 1H), 8.24 (d, J = 4.4 Hz, 1H), 8.16 (d, J = 7.8 Hz, 2H), 7.60 (t, J = 7.8 Hz, 2H), 7.38-7.45 (m, 1H), 4.74 -4.83 (m, 2H), 3.57-3.65 (m, 2H), 2.88 (s, 6H). MS (M+1) : 454.

【0235】化合物 5-12

N-(6-(2-嗎啉基乙氧基)-1-苯基-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(6-(2-morpholinoethoxy)-1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

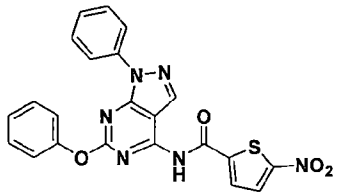


^{1}H NMR (400MHz, DMSO-d_6): δ 8.54 (s, 1H), 8.34 (d, J = 4.4 Hz, 1H), 8.23 (d, J = 4.4 Hz, 1H), 8.17 (dd, J = 8.8, 1.0 Hz, 2H), 7.54-7.62 (m, 2H), 7.39 (t, J = 7.3 Hz, 1H), 4.58 (t, J = 5.4 Hz, 2H), 3.56 (br. s., 4H), 2.82 (br. s., 2H). MS(M+1):496.

【0236】化合物 5-13

5-硝基-N-(6-苯氧基-1-苯基-1H-吡唑並[3,4-d]嘧啶-4-基)噻吩-2-甲醯胺

(5-nitro-N-(6-phenoxy-1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)thiophene-2-carboxamide)

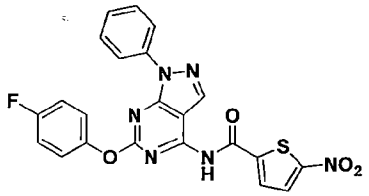


^{1}H NMR (400MHz, DMSO-d_6): δ 12.29 (s, 1H), 8.56 (s, 1H), 8.33 (d, J = 4.4 Hz, 1H), 8.21 (d, J = 4.4 Hz, 1H), 7.98 (dd, J = 8.6, 1.2 Hz, 2H), 7.45-7.55 (m, 2H), 7.38-7.45 (m, 2H), 7.25-7.38 (m, 4H). MS(M+1):459. 灰色固體。

【0237】化合物 5-14

N-(6-(4-氟苯氧基)-1-苯基-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(6-(4-fluorophenoxy)-1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

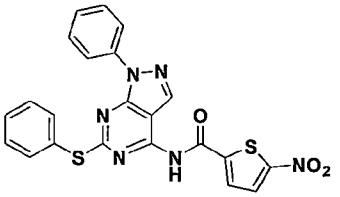


^{1}H NMR (400MHz, DMSO-d_6): δ 12.29 (br. s., 1H), 8.56 (s, 1H), 8.33 (d, J = 4.4 Hz, 1H), 8.22 (d, J = 4.4 Hz, 1H), 7.96-8.00 (m, 2H), 7.37-7.48 (m, 4H), 7.28-7.37 (m, 3H). MS(M+1):477. 灰色固體。

【0238】化合物 5-15

5-硝基-N-(1-苯基-6-(苯硫基)-1H-吡唑並[3,4-d]嘧啶-4-基)噻吩-2-甲醯胺

(5-nitro-N-(1-phenyl-6-(phenylthio)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)thiophene-2-carboxamide)

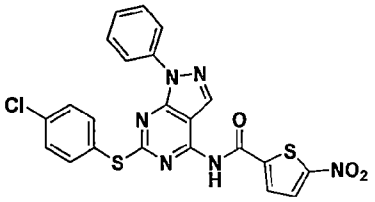


^{1}H NMR (400MHz, DMSO-d_6): δ 12.27 (s, 1H), 8.50 (s, 1H), 8.33 (d, J = 4.4 Hz, 1H), 8.19 (d, J = 4.4 Hz, 1H), 7.81-7.91 (m, 2H), 7.69-7.81 (m, 2H), 7.53-7.69 (m, 3H), 7.18-7.39 (m, 3H). MS(M+1):475.黃褐色固體。

【0239】化合物 5-16

N-(6-((4-氯苯基)硫基)-1-苯基-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(6-((4-chlorophenyl)thio)-1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

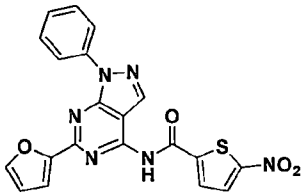


^{1}H NMR (400MHz, DMSO-d_6): δ 12.44 (s, 1H), 8.47 (s, 1H), 8.04-8.21 (m, 2H), 7.82-7.99 (m, 2H), 7.68-7.81 (m, 2H), 7.56-7.68 (m, 2H), 7.22-7.43 (m, 3H). MS(M+1):509. 黃色固體。

【0240】化合物 5-17

N-(6-(呋喃-2-基)-1-苯基-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(6-(furan-2-yl)-1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

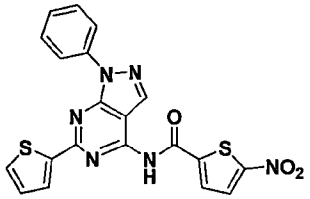


^{1}H NMR (400MHz, DMSO-d_6): δ 12.20 (br. s., 1H), 8.57 (s, 1H), 8.38 (d, J = 4.4 Hz, 1H), 8.19-8.32 (m, 3H), 8.01 (d, J = 1.0 Hz, 1H), 7.58-7.68 (m, 2H), 7.47 (d, J = 2.9 Hz, 1H), 7.39-7.46 (m, 1H), 6.77 (dd, J = 3.4, 2.0 Hz, 1H). MS(M+1):433. 淺卡其色固體。

【0241】化合物 5-18

5-硝基-N-(1-苯基-6-(噻吩-2-基)-1H-吡唑並[3,4-d]嘧啶-4-基)噻吩-2-甲醯胺

(5-nitro-N-(1-phenyl-6-(thiophen-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)thiophene-2-carboxamide)

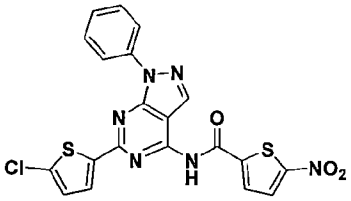


^{1}H NMR (400MHz, DMSO-d_6): δ 12.07 (br. s., 1H), 8.57 (s, 1H), 8.38 (d, J = 4.4 Hz, 1H), 8.25-8.30 (m, 2H), 8.24 (d, J = 4.4 Hz, 1H), 8.11 (dd, J = 3.7, 1.2 Hz, 1H), 7.84 (dd, J = 4.9, 1.5 Hz, 1H), 7.59-7.67 (m, 2H), 7.39-7.45 (m, 1H), 7.27 (dd, J = 5.1, 3.7 Hz, 1H). MS(M+1):449. 淺卡其色固體。

【0242】化合物 5-19

N-(6-(5-氯噻吩-2-基)-1-苯基-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(6-(5-chlorothiophen-2-yl)-1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

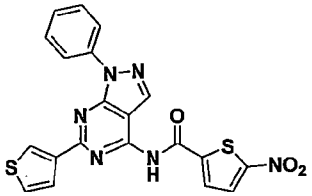


^{1}H NMR (400MHz, DMSO-d_6): δ 12.07 (br. s., 1H), 8.58 (s, 1H), 8.36 (d, J = 4.4 Hz, 1H), 8.22-8.28 (m, 3H), 7.93 (d, J = 3.9 Hz, 1H), 7.60-7.66 (m, 2H), 7.38-7.45 (m, 1H), 7.29 (d, J = 4.4 Hz, 1H). MS(M+1): 483. 黃色固體。

【0243】化合物 5-20

5-硝基-N-(1-苯基-6-(噻吩-3-基)-1H-吡唑並[3,4-d]嘧啶-4-基)噻吩-2-甲醯胺

(5-nitro-N-(1-phenyl-6-(thiophen-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)thiophene-2-carboxamide)

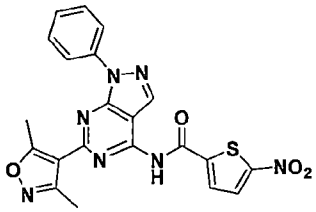


^{1}H NMR (400MHz, DMSO-d_6): δ 12.01 (br. s., 1H), 8.57 (s, 1H), 8.51 (dd, J = 2.9, 1.0 Hz, 1H), 8.37 (d, J = 4.4 Hz, 1H), 8.28-8.33 (m, 2H), 8.23 (d, J = 4.4 Hz, 1H), 7.94 (dd, J = 4.9, 1.0 Hz, 1H), 7.71 (dd, J = 5.1, 3.2 Hz, 1H), 7.59-7.67 (m, 2H), 7.37-7.45 (m, 1H). MS(M+1):449. 黃褐色固體。

【0244】化合物 5-21

N-(6-(3,5-二甲基異噁唑-4-基)-1-苯基-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(6-(3,5-dimethylisoxazol-4-yl)-1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

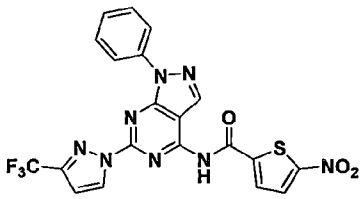


^{1}H NMR (400MHz, DMSO-d_6): δ 11.78 (s, 1H), 8.61 (s, 1H), 8.29-8.33 (m, 1H), 8.25-8.29 (m, 1H), 8.18 (d, J = 8.3 Hz, 2H), 7.61 (t, J = 7.8 Hz, 2H), 7.38-7.47 (m, 1H), 2.90 (s, 3H), 2.63 (s, 3H). MS(M+1):462. 褐色固體。

【0245】化合物 5-22

5-硝基-N-(1-苯基-6-(3-(三氟甲基)-1H-吡唑-1-基)-1H-吡唑並[3,4-d]嘧啶-4-基)噻吩-2-甲醯胺

(5-nitro-N-(1-phenyl-6-(3-(trifluoromethyl)-1H-pyrazol-1-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)thiophene-2-carboxamide)

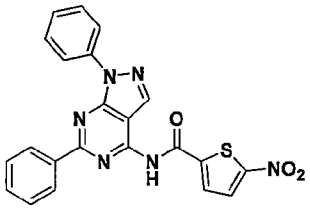


^{1}H NMR (400MHz, DMSO-d_6): δ 12.40 (s, 1H), 8.90-8.94 (m, 1H), 8.61 (s, 1H), 8.37 (d, J = 4.4 Hz, 1H), 8.21 (d, J = 4.4 Hz, 1H), 8.18 (dd, J = 8.6, 1.2 Hz, 2H), 7.57-7.65 (m, 2H), 7.39-7.46 (m, 1H), 7.12 (d, J = 2.9 Hz, 1H). MS(M+1):501. 淡黃色固體。

【0246】化合物 5-23

N-(1,6-二苯基-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(1,6-diphenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

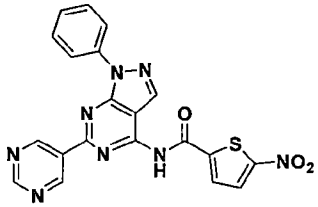


^{1}H NMR (400MHz, DMSO-d_6): δ 12.00 (br. s., 1H), 8.61 (s, 1H), 8.50-8.57 (m, 2H), 8.37 (d, J = 4.4 Hz, 1H), 8.29 (dd, J = 8.8, 1.0 Hz, 2H), 8.23 (d, J = 4.4 Hz, 1H), 7.61-7.67 (m, 2H), 7.54-7.61 (m, 3H), 7.38-7.45 (m, 1H). MS(M+1):443. 黃色固體。

【0247】化合物 5-24

5-硝基-N-(1-苯基-6-(嘧啶-5-基)-1H-吡唑並[3,4-d]嘧啶-4-基)噻吩-2-甲醯胺

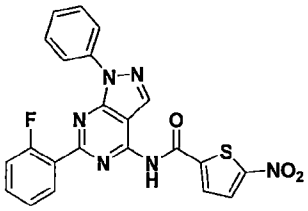
(5-nitro-N-(1-phenyl-6-(pyrimidin-5-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)thiophene-2-carboxamide)



^{1}H NMR (400MHz, DMSO-d_6): δ 12.10 (br. s., 1H), 9.72 (s, 2H), 9.37 (s, 1H), 8.67 (s, 1H), 8.36 (d, J = 4.4 Hz, 1H), 8.22-8.33 (m, 3H), 7.57-7.72 (m, 2H), 7.36-7.50 (m, 1H). MS(M+1):445. 淺卡其色固體。

【0248】化合物 5-25

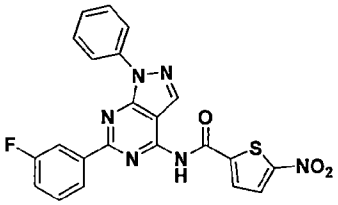
N-(6-(2-氟苯基)-1-苯基-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺 (N-(6-(2-fluorophenyl)-1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)



^{1}H NMR (400MHz, DMSO-d_6): δ 12.21 (br. s., 1H), 8.66 (s, 1H), 8.38 (d, J = 3.9 Hz, 1H), 8.30 (d, J = 7.8 Hz, 2H), 8.22-8.25 (m, 1H), 8.18-8.22 (m, 1H), 7.6 (t, J = 8.1 Hz, 3H), 7.40 (t, J = 7.6 Hz, 3H). MS(M+1):461.

【0249】化合物 5-26

N-(6-(3-氟苯基)-1-苯基-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺 (N-(6-(3-fluorophenyl)-1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

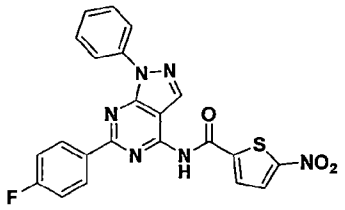


^{1}H NMR (400MHz, DMSO-d_6): δ 11.99 (s, 1H), 8.64 (s, 1H), 8.34-8.40 (m, 2H), 8.21-8.30 (m, 4H), 7.59-7.68 (m, 3H), 7.39-7.46 (m, 2H). MS(M+1):461.

【0250】化合物 5-27

N-(6-(4-氟苯基)-1-苯基-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(6-(4-fluorophenyl)-1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

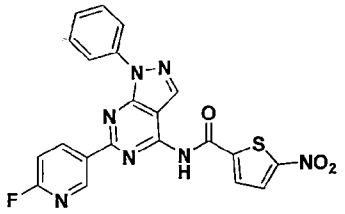


^{1}H NMR (400MHz, DMSO-d_6): δ 11.95 (s, 1H), 8.59 (s, 1H), 8.55 (dd, J = 8.8, 5.9 Hz, 2H), 8.36 (d, J = 4.4 Hz, 1H), 8.20-8.28 (m, 3H), 7.62 (t, J = 7.8 Hz, 2H), 7.35-7.45 (m, 3H), MS(M+1):461.

【0251】化合物 5-28

N-(6-(6-氟吡啶-3-基)-1-苯基-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(6-(6-fluoropyridin-3-yl)-1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

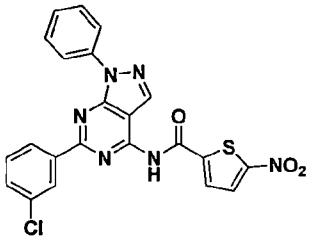


^{1}H NMR (400MHz, DMSO-d_6): δ 12.06 (br. s., 1H), 9.30 (d, J = 2.4 Hz, 1H), 8.93 (td, J = 8.3, 2.4 Hz, 1H), 8.65 (s, 1H), 8.36 (d, J = 4.4 Hz, 1H), 8.21-8.34 (m, 3H), 7.55-7.70 (m, 2H), 7.35-7.48 (m, 2H). MS(M+1): 462. 黃色固體。

【0252】化合物 5-29

N-(6-(3-氯苯基)-1-苯基-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(6-(3-chlorophenyl)-1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

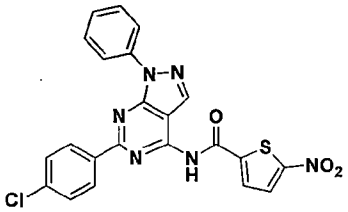


^{1}H NMR (400MHz, DMSO-d_6): δ 12.04 (s, 1H), 8.66 (s, 1H), 8.50-8.56 (m, 1H), 8.48 (dt, J = 7.0, 1.9 Hz, 1H), 8.39 (d, J = 4.4 Hz, 1H), 8.21-8.32 (m, 3H), 7.55-7.75 (m, 4H), 7.32-7.51 (m, 1H). MS(M+1): 477. 黃色固體。

【0253】化合物 5-30

N-(6-(4-氯苯基)-1-苯基-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(6-(4-chlorophenyl)-1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

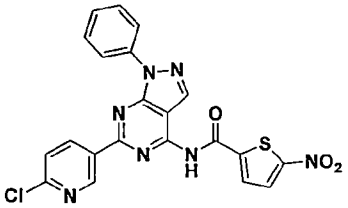


^{1}H NMR (400MHz, DMSO-d_6):δ 12.06 (br. s., 1H), 8.64 (s, 1H), 8.51-8.58 (m, 2H), 8.37 (d, J = 4.4 Hz, 1H), 8.25-8.31 (m, 3H), 7.61-7.71 (m, 4H), 7.38-7.49 (m, 1H) MS(M+1):474.

【0254】化合物 5-31

N-(6-(6-氯吡啶-3-基)-1-苯基-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(6-(6-chloropyridin-3-yl)-1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

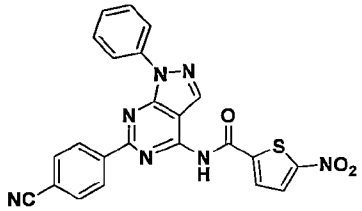


【0255】 ^{1}H NMR (400MHz, DMSO-d_6): δ 12.13 (s, 1H), 9.49 (d, J = 2.4 Hz, 1H), 8.83 (dd, J = 8.3, 2.4 Hz, 1H), 8.70 (s, 1H), 8.40 (d, J = 4.4 Hz, 1H), 8.25-8.32 (m, 3H), 7.79 (d, J = 8.3 Hz, 1H), 7.64-7.69 (m, 2H), 7.42-7.48 (m, 1H). MS(M+1): 478. 橘色固體。

【0256】 化合物 5-32

N-(6-(4-氰基苯基)-1-苯基-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(6-(4-cyanophenyl)-1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

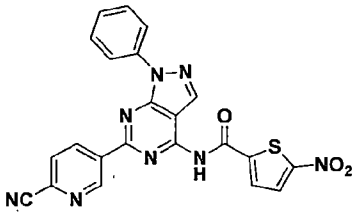


^{1}H NMR (400MHz, DMSO-d_6): δ 12.07 (br. s., 1H), 8.62-8.69 (m, 3H), 8.36 (d, J = 4.4 Hz, 1H), 8.21-8.28 (m, 3H), 8.01-8.09 (m, 2H), 7.61-7.68 (m, 2H), 7.41-7.48 (m, 1H). MS(M+1): 468. 淺卡其色固體。

【0257】 化合物 5-33

N-(6-(6-氰基吡啶-3-基)-1-苯基-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(6-(6-cyanopyridin-3-yl)-1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

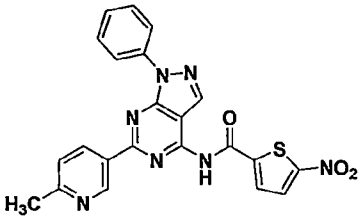


^{1}H NMR (400MHz, DMSO-d_6): δ 12.00 (br. s., 1H), 9.66 (d, J = 1.5 Hz, 1H), 8.83- 8.91 (m, 1H), 8.61 (s, 1H), 8.33 (d, J = 4.4 Hz, 1H), 8.17-8.25 (m, 4H), 7.55-7.64 (m, 2H), 7.36-7.45 (m, 1H). MS(M+1):469. 紅色固體。

【0258】化合物 5-34

N-(6-(6-甲基吡啶-3-基)-1-苯基-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(6-(6-methylpyridin-3-yl)-1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

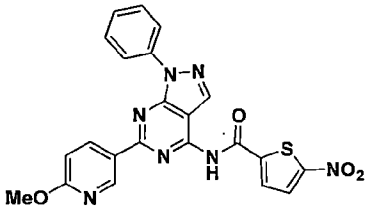


^{1}H NMR (400MHz, DMSO-d_6): δ 12.06 (br. s., 1H), 9.54 (d, J = 2.0 Hz, 1H), 8.59 -8.70 (m, 2H), 8.37 (d, J = 4.4 Hz, 1H), 8.16-8.34 (m, 3H), 7.64 (t, J = 8.1 Hz, 2H), 7.30-7.54 (m, 2H), 2.52-2.61 (m, 3H). MS(M+1): 458. 深橘色固體。

【0259】化合物 5-35

N-(6-(6-甲氧基吡啶-3-基)-1-苯基-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(6-(6-methoxypyridin-3-yl)-1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

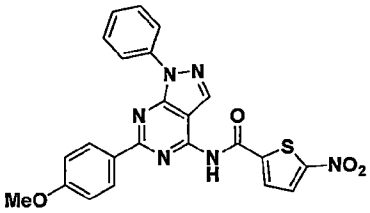


^{1}H NMR (400MHz, DMSO-d_6): δ 11.87 (s, 1H), 9.22 (d, J = 2.4 Hz, 1H), 8.54-8.64 (m, 2H), 8.26-8.20 (m, 4H), 7.60 (t, J = 7.8 Hz, 2H), 7.39 (t, J = 7.8 Hz, 1H), 6.96 (d, J = 8.8 Hz, 1H), 3.94 (s, 3H). MS(M+1): 474. 黃色固體。

【0260】化合物 5-36

N-(6-(4-甲氧基苯基)-1-苯基-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(6-(4-methoxyphenyl)-1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

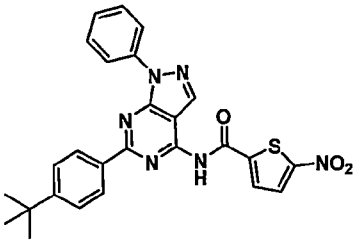


^{1}H NMR (400MHz, DMSO-d_6): δ 11.98 (br. s., 1H), 8.60 (s, 1H), 8.40-8.58 (m, J = 8.8 Hz, 2H), 8.38 (d, J = 4.4 Hz, 1H), 8.30 (dd, J = 8.8, 1.0 Hz, 2H), 8.26 (d, J = 4.4 Hz, 1H), 7.58-7.70 (m, 2H), 7.38-7.48 (m, 1H), 7.08-7.20 (m, 2H), 3.87 (s, 3H) MS(M+1): 473. 黃色固體。

【0261】化合物 5-37

N-(6-(4-(叔丁基)苯基)-1-苯基-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(6-(4-(tert-butyl)phenyl)-1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

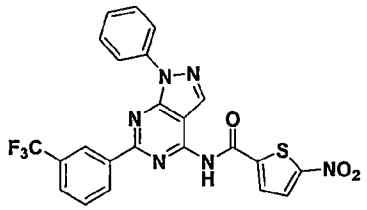


^{1}H NMR (400MHz, DMSO-d_6): δ 12.04 (br. s., 1H), 8.62 (s, 1H), 8.48 (d, J = 8.8 Hz, 2H), 8.40 (d, J = 4.4 Hz, 1H), 8.32 (d, J = 7.8 Hz, 2H), 8.26 (d, J = 4.4 Hz, 1H), 7.58-7.68 (m, 4H), 7.40-7.47 (m, 1H), 1.35 (s, 9H). MS (M+1) : 499. 黃色固體。

【0262】化合物 5-38

5-硝基-N-(1-苯基-6-(3-(三氟甲基)苯基)-1H-吡唑並[3,4-d]嘧啶-4-基)噻吩-2-甲醯胺

(5-nitro-N-(1-phenyl-6-(3-(trifluoromethyl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)thiophene-2-carboxamide)

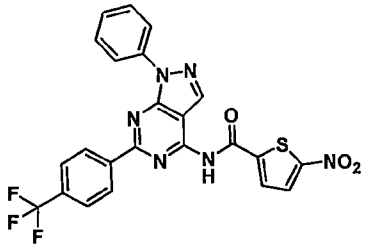


^{1}H NMR (400MHz, DMSO-d_6): δ 12.07 (br. s., 1H), 8.77-8.85 (m, 2H), 8.66 (s, 1H), 8.38 (d, J = 4.4 Hz, 1H), 8.23-8.31 (m, 3H), 7.96 (d, J = 7.8 Hz, 1H), 7.85 (t, J = 7.8 Hz, 1H), 7.65 (t, J = 8.1 Hz, 2H), 7.41-7.48 (m, 1H). MS(M+1):511. 黃色固體。

【0263】化合物 5-39

5-硝基-N-(1-苯基-6-(4-(三氟甲基)苯基)-1H-吡唑並[3,4-d]嘧啶-4-基)噻吩-2-甲醯胺

(5-nitro-N-(1-phenyl-6-(4-(trifluoromethyl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)thiophene-2-carboxamide)

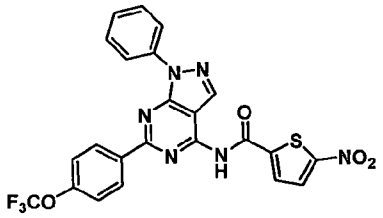


^{1}H NMR (400MHz, DMSO-d_6): δ 12.05 (s, 1H), 8.64-8.70 (m, J = 7.8 Hz, 2H), 8.61 (s, 1H), 8.37 (d, J = 4.4 Hz, 1H), 8.21-8.27 (m, 3H), 7.90-7.96 (m, J = 8.3 Hz, 2H), 7.58-7.66 (m, 2H), 7.40-7.46 (m, 1H). MS (M+1) : 511. 淡黃色固體。

【0264】化合物 5-40

5-硝基-N-(1-苯基-6-(4-(三氟甲氧基)苯基)-1H-吡唑並[3,4-d]嘧啶-4-基)噻吩-2-甲醯胺

(5-nitro-N-(1-phenyl-6-(4-(trifluoromethoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)thiophene-2-carboxamide)

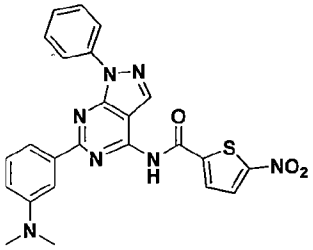


^{1}H NMR (400MHz, DMSO-d_6): δ 12.08 (s, 1H), 8.60-8.68 (m, 3H), 8.38 (d, J = 4.4 Hz, 1H), 8.23-8.32 (m, 3H), 7.61-7.68 (m, 2H), 7.59 (d, J = 8.3 Hz, 2H), 7.40-7.48 (m, 1H), MS (M+1) : 527. 淡黃色固體。

【0265】 化合物 5-41

N-(6-(3-(二甲基胺基)苯基)-1-苯基-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(6-(3-(dimethylamino)phenyl)-1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

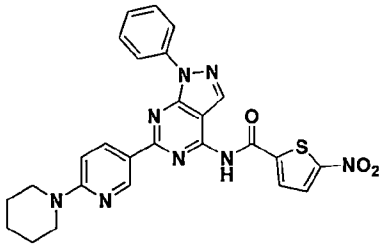


^{1}H NMR (400MHz, DMSO-d_6): δ 11.95 (br. s., 1H), 8.60 (br. s., 1H), 8.27-8.48 (m, 3H), 8.23 (br. s., 1H), 7.94 (br. s., 1H), 7.86 (d, J = 7.3 Hz, 1H), 7.63 (t, J = 7.3 Hz, 2H), 7.30-7.53 (m, 2H), 6.94 (d, J = 8.3 Hz, 1H), 3.02 (s, 6H). MS(M+1): 486. 磚紅色固體。

【0266】 化合物 5-42

5-硝基-N-(1-苯基-6-(6-(哌啶-1-基)吡啶-3-基)-1H-吡唑並[3,4-d]嘧啶-4-基)噻吩-2-甲醯胺

(5-nitro-N-(1-phenyl-6-(6-(piperidin-1-yl)pyridin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)thiophene-2-carboxamide)

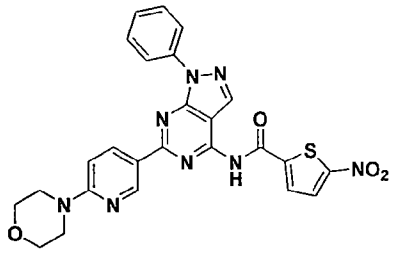


^{1}H NMR (400MHz, DMSO-d_6): δ 11.92 (br. s., 1H), 9.23 (d, J = 2.0 Hz, 1H), 8.55 (s, 1H), 8.49 (dd, J = 9.3, 2.4 Hz, 1H), 8.35 (d, J = 4.4 Hz, 1H), 8.31 (d, J = 7.3 Hz, 2H), 8.25 (d, J = 4.4 Hz, 1H), 7.59-7.67 (m, 2H), 7.36-7.44 (m, 1H), 6.97 (d, J = 8.8 Hz, 1H), 3.61-3.72 (m, 4H), 1.65 (d, J = 4.9 Hz, 2H), 1.58 (d, J = 3.9 Hz, 4H). MS(M+1): 527. 黃色固體。

【0267】化合物 5-43

N-(6-(6-嗎啉基吡啶-3-基)-1-苯基-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(6-(6-morpholinopyridin-3-yl)-1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

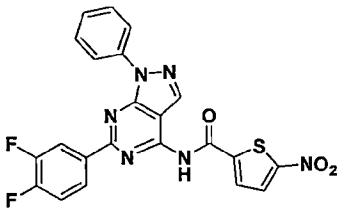


^{1}H NMR (400MHz, DMSO-d_6): δ 11.82 (br. s., 1H), 9.22 (d, J = 2.0 Hz, 1H), 8.52 (s, 1H), 8.50 (dd, J = 9.3, 2.4 Hz, 1H), 8.34 (d, J = 4.4 Hz, 1H), 8.27 (dd, J = 8.6, 1.2 Hz, 2H), 8.21 (d, J = 4.4 Hz, 1H), 7.57-7.64 (m, 2H), 7.35-7.42 (m, 1H), 6.95 (d, J = 9.3 Hz, 1H), 3.68-3.75 (m, 4H), 3.55-3.64 (m, 4H). MS(M+1):529. 黃綠色固體。

【0268】化合物 5-44

N-(6-(3,4-二氟苯基)-1-苯基-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(6-(3,4-difluorophenyl)-1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

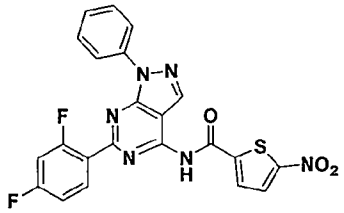


^{1}H NMR (400MHz, DMSO-d_6): δ 11.96 (br. s., 1H), 8.63 (s, 1H), 8.41 (ddd, J = 12.0, 8.1, 2.0 Hz, 1H), 8.32-8.38 (m, 2H), 8.21-8.30 (m, 3H), 7.60-7.69 (m, 3H), 7.39-7.46 (m, 1H). MS(M+1):479. 黃色固體。

【0269】化合物 5-45

N-(6-(2,4-二氟苯基)-1-苯基-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(6-(2,4-difluorophenyl)-1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

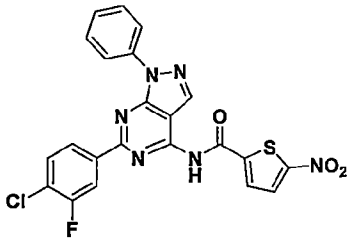


^{1}H NMR (400MHz, DMSO-d_6): δ 12.13 (br. s., 1H), 8.64 (s, 1H), 8.33-8.42 (m, 1H), 8.24-8.33 (m, 3H), 8.22 (d, J = 4.4 Hz, 1H), 7.54-7.66 (m, 2H), 7.36-7.49 (m, 2H), 7.23-7.36 (m, 1H). MS(M+1):479. 黃色固體。

【0270】化合物 5-46

N-(6-(4-氯-3-氟苯基)-1-苯基-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(6-(4-chloro-3-fluorophenyl)-1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitro thiophene-2-carboxamide)

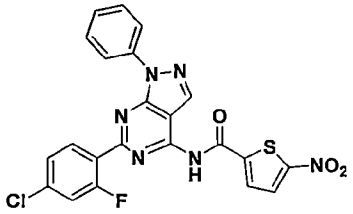


^{1}H NMR (400MHz, DMSO-d_6): δ 11.97 (br. s., 1H), 8.63 (s, 1H), 8.28-8.42 (m, 4H), 8.19-8.28 (m, 3H), 7.80 (t, J = 7.8 Hz, 1H), 7.57-7.69 (m, 2H), 7.37-7.48 (m, 1H). MS(M+1):495. 黃色固體。

【0271】化合物 5-47

N-(6-(4-氯-2-氟苯基)-1-苯基-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(6-(4-chloro-2-fluorophenyl)-1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitro thiophene-2-carboxamide)

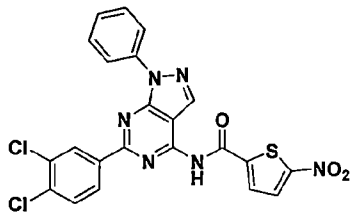


^{1}H NMR (DMSO-d_6) : δ 12.11 (br. s., 1H), 8.62 (d, J = 1.0 Hz, 1H), 8.34 (d, J = 4.4 Hz, 1H), 8.23-8.31 (m, 3H), 8.21 (d, J = 4.4 Hz, 1H), 7.55-7.65 (m, 3H), 7.46-7.52 (m, 1H), 7.36-7.43 (m, 1H). MS(M+1): 495. 黃褐色固體。

【0272】化合物 5-48

N-(6-(3,4-二氯苯基)-1-苯基-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(6-(3,4-dichlorophenyl)-1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)



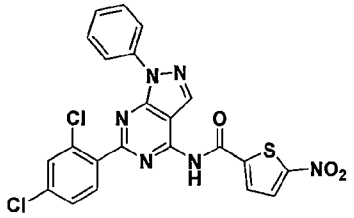
^{1}H NMR (400MHz, DMSO-d_6): δ 11.96 (br. s., 1H), 8.60 (d, J = 2.0 Hz, 1H), 8.59 (s, 1H), 8.36-8.39 (m, 1H), 8.35 (d, J = 4.4 Hz, 1H), 8.23 (d, J = 4.4 Hz, 1H), 8.16-8.21 (m, 2H), 7.80 (d, J = 8.8 Hz, 1H), 7.57-7.64 (m, 2H), 7.38-7.44 (m, 1H).

MS(M+1) :511. 褐色固體。

【0273】化合物 5-49

N-(6-(2,4-二氯苯基)-1-苯基-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(6-(2,4-dichlorophenyl)-1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

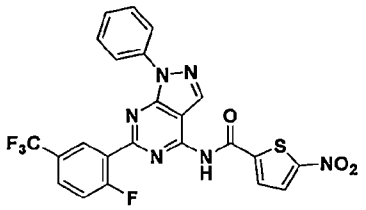


^{1}H NMR (400MHz, DMSO-d_6): δ 12.32 (br. s., 1H), 8.69 (s, 1H), 8.36 (d, J = 4.4 Hz, 1H), 8.19-8.26 (m, 3H), 7.94 (d, J = 8.3 Hz, 1H), 7.82 (d, J = 2.0 Hz, 1H), 7.55-7.66 (m, 3H), 7.37-7.44 (m, 1H). MS(M+1):512. 黃色固體。

【0274】化合物 5-50

N-(6-(2-氟-5-(三氟甲基)苯基)-1-苯基-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(6-(2-fluoro-5-(trifluoromethyl)phenyl)-1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

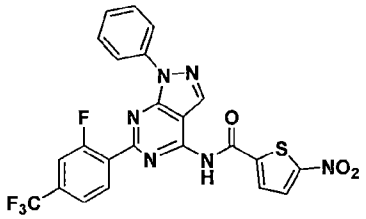


^{1}H NMR (400MHz, DMSO-d_6): δ 12.20 (br. s., 1H), 8.69 (s, 1H), 8.62 (dd, J = 6.8, 2.4 Hz, 1H), 8.36 (d, J = 4.4 Hz, 1H), 8.30 (dd, J = 8.6, 1.2 Hz, 2H), 8.25 (d, J = 4.4 Hz, 1H), 7.98-8.08 (m, 1H), 7.65-7.73 (m, 1H), 7.58-7.65 (m, 2H), 7.39-7.45 (m, 1H) MS(M+1): 529. 淡黃色固體。

【0275】化合物 5-51

N-(6-(2-氟-4-(三氟甲基)苯基)-1-苯基-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(6-(2-fluoro-4-(trifluoromethyl)phenyl)-1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

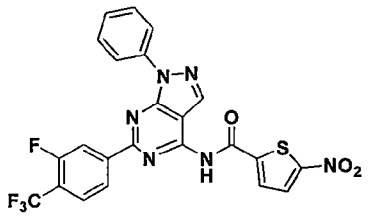


^{1}H NMR (400MHz, DMSO-d_6): δ 12.16 (br. s., 1H), 8.60 (s, 1H), 8.28-8.46 (m, 2H), 8.13-8.28 (m, 3H), 7.85 (d, J = 10.8 Hz, 1H), 7.76 (d, J = 8.3 Hz, 1H), 7.50-7.63 (m, 2H), 7.32-7.43 (m, 1H). MS(M+1):529. 淺卡其色固體。

【0276】化合物 5-52

N-(6-(3-氟-4-(三氟甲基)苯基)-1-苯基-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(6-(3-fluoro-4-(trifluoromethyl)phenyl)-1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

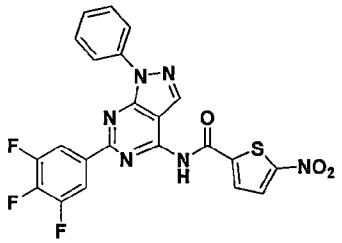


^{1}H NMR (400MHz, DMSO-d_6): δ 12.10 (br. s., 1H), 8.69 (s, 1H), 8.41-8.55 (m, 2H), 8.35 (d, J = 4.4 Hz, 1H), 8.21-8.31 (m, 3H), 8.04 (t, J = 8.1 Hz, 1H), 7.61-7.72 (m, 2H), 7.41-7.51 (m, 1H). MS(M+1):529. 黃色固體。

【0277】化合物 5-53

5-硝基-N-(1-苯基-6-(3,4,5-三氟苯基)-1H-吡唑並[3,4-d]嘧啶-4-基)噻吩-2-甲醯胺

(5-nitro-N-(1-phenyl-6-(3,4,5-trifluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)thiophene-2-carboxamide)

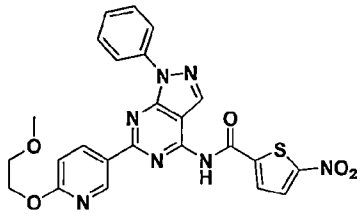


^{1}H NMR (DMSO-d_6): δ 11.79 (br. s., 1H), 8.56 (s, 1H), 8.30 (d, J = 4.4 Hz, 1H), 8.22 (d, J = 4.4 Hz, 1H), 8.10-8.21 (m, 4H), 7.59 (t, J = 7.8 Hz, 2H), 7.35-7.43 (m, 1H) MS(M+1):497. 黃褐色固體。

【0278】化合物 5-54

N-(6-(6-(2-甲氧基乙氧基)吡啶-3-基)-1-苯基-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(6-(6-(2-methoxyethoxy)pyridin-3-yl)-1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

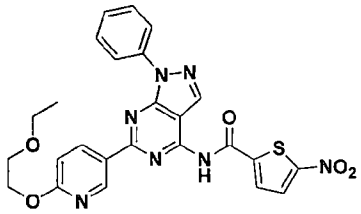


^{1}H NMR (400MHz, DMSO-d_6): δ 11.96 (br. s., 1H), 9.26 (d, J = 2.4 Hz, 1H), 8.68 (dd, J = 8.8, 2.4 Hz, 1H), 8.60 (s, 1H), 8.36 (d, J = 4.4 Hz, 1H), 8.28 (d, J = 7.3 Hz, 2H), 8.25 (d, J = 4.4 Hz, 1H), 7.59-7.68 (m, 2H), 7.37-7.46 (m, 1H), 7.02 (d, J = 8.8 Hz, 1H), 4.43-4.52 (m, 2H), 3.70 (dd, J = 5.4, 3.9 Hz, 2H). MS(M+1):518. 黃色固體。

【0279】化合物 5-55

N-(6-(6-(2-乙氧基乙氧基)吡啶-3-基)-1-苯基-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(6-(6-(2-ethoxyethoxy)pyridin-3-yl)-1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

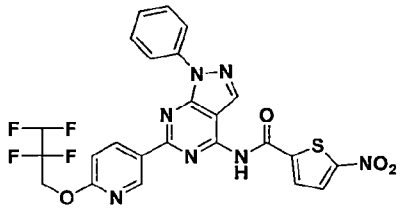


^{1}H NMR (400MHz, DMSO-d_6): δ 11.84 (br. s., 1H), 9.20 (d, J = 2.4 Hz, 1H), 8.62 (dd, J = 8.3, 2.4 Hz, 1H), 8.54 (s, 1H), 8.32 (d, J = 4.4 Hz, 1H), 8.24 (dd, J = 8.8, 1.0 Hz, 2H), 8.20 (d, J = 4.4 Hz, 1H), 7.55-7.64 (m, 2H), 7.34-7.42 (m, 1H), 6.97 (d, J = 7.8 Hz, 1H), 4.44 (dd, J = 5.6, 4.4 Hz, 2H), 3.68-3.77 (m, 2H), 3.51 (q, J = 7.0 Hz, 2H), 1.14 (t, J = 7.0 Hz, 3H). MS(M+1):532. 黃色固體。

【0280】化合物 5-56

5-硝基-N-(1-苯基-6-(6-(2,2,3,3-四氟丙氧基)吡啶-3-基)-1H-吡唑並[3,4-d]嘧啶-4-基) 噻吩-2-甲醯胺

(5-nitro-N-(1-phenyl-6-(6-(2,2,3,3-tetrafluoropropoxy)pyridin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)thiophene-2-carboxamide)

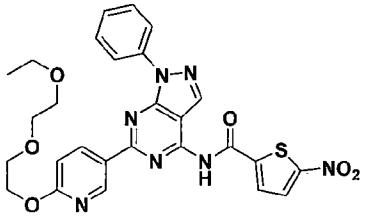


^{1}H NMR (400MHz, DMSO-d_6): δ 12.03 (br. s., 1H), 9.31 (d, J = 2.4 Hz, 1H), 8.77- 8.82 (m, 1H), 8.65 (s, 1H), 8.37 (d, J = 4.4 Hz, 1H), 8.28-8.34 (m, 2H), 8.25-8.28 (m, 1H), 7.62-7.70 (m, 2H), 7.40-7.48 (m, 1H), 7.18 (d, J = 9.3 Hz, 1H), 6.71 (t, J = 5.4 Hz, 1H), 4.98 (t, J = 13.9 Hz, 2H). MS(M+1):574. 黃色固體。

【0281】化合物 5-57

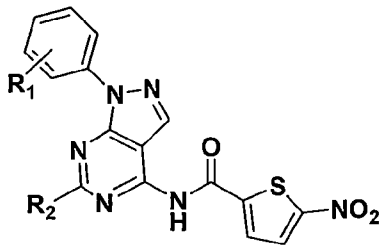
N-(6-(6-(2-(2-乙氧基乙氧基)乙氧基)吡啶-3-基)-1-苯基-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(6-(6-(2-(2-ethoxyethoxy)ethoxy)pyridin-3-yl)-1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)



^{1}H NMR (400MHz, DMSO-d_6): δ 11.88 (br. s., 1H), 9.22 (d, J = 2.0 Hz, 1H), 8.64 (dd, J = 8.8, 2.4 Hz, 1H), 8.56 (s, 1H), 8.33 (d, J = 4.4 Hz, 1H), 8.25 (dd, J = 8.8, 1.0 Hz, 2H), 8.21 (d, J = 4.4 Hz, 1H), 7.57-7.65 (m, 2H), 7.35-7.43 (m, 1H), 6.99 (d, J = 9.3 Hz, 1H), 4.46 (dd, J = 5.4, 3.9 Hz, 2H), 3.78 (dd, J = 5.4, 3.9 Hz, 2H), 3.57-3.63 (m, 2H), 3.48-3.53 (m, 2H), 3.44 (q, J = 6.8 Hz, 2H), 1.05-1.13 (m, 3H). MS(M+1):576. 米色固體。

【0282】表6

			
化合物	R_1	R_2	Hep3B LC_{50} (uM)
6-1	2-甲基	2-(羥甲基)吡咯烷-1-基	>3
6-2	2-甲基	6-氟吡啶-3-基	>3
6-3	4-甲基	2-(羥甲基)吡咯烷-1-基	0.87
6-4	4-甲基	4-氟苯基	0.28
6-5	4-甲基	6-氟吡啶-3-基	0.11
6-6	4-甲基	6-甲氧基吡啶-3-基	0.40
6-7	4-甲基	4-氯苯基	0.29
6-8	4-甲基	4-(三氟甲基)苯基	0.35
6-9	4-甲基	苯並[d][1,3]二氧雜-5-基(benzo[d][1,3]dioxol-5-yl)	0.40
6-10	4-甲基	2,3-二氫苯並[b][1,4]二噁英-6-基 (2,3-dihydrobenzo[b][1,4]dioxin-6-yl)	0.62
6-11	4-甲基	2,4-二氟苯基	0.28
6-12	4-甲基	6-(2-甲氧基乙氧基)吡啶-3-基	0.26
6-13	4-甲基	6-(2-乙氧基乙氧基)吡啶-3-基	0.51
6-14	4-甲基	6-(2-(2-乙氧基乙氧基)乙氧基)吡啶-3-基	0.22
6-15	4-甲氧基	環己胺基(cyclohexylamino)	>1.25
6-16	4-甲氧基	環己氧基	1.36
6-17	4-甲氧基	6-甲基吡啶-3-基	0.19
6-18	4-甲氧基	4-氟苯基	0.18
6-19	4-甲氧基	6-氟吡啶-3-基	0.06
6-20	4-甲氧基	4-氯苯基	0.32
6-21	4-甲氧基	6-氯吡啶-3-基	0.12
6-22	4-甲氧基	4-氯-2-氟苯基	0.38

6-23	4-甲氧基	3,4-二氟苯基	0.17
6-24	4-甲氧基	苯並[d][1,3]二氧雜-5-基(benzo[d][1,3]dioxol-5-yl)	0.19
6-25	4-甲氧基	6-丙氧基吡啶-3-基	0.21
6-26	4-甲氧基	6-(2-甲氧基乙氧基)吡啶-3-基	0.22
6-27	4-甲氧基	6-(2-乙氧基乙氧基)吡啶-3-基	0.21
6-28	4-甲氧基	6-(2-(2-乙氧基乙氧基)乙氧基)吡啶-3-基	0.19
6-29	4-甲氧基	4,4-二甲基環己-1-烯-1-基	0.82
6-30	4-甲氧基	4,4-二甲基環己基	1.32
6-31	3-氯	2-(羥甲基)吡咯烷-1-基	>1.25
6-32	3-氯	L-脯胺酸甲酯	0.56
6-33	3-氯	噻吩-3-基	0.29
6-34	3-氯	3-氟苯基	0.19
6-35	3-氯	4-氟苯基	0.11
6-36	3-氯	6-氟吡啶-3-基	0.09
6-37	3-氯	3-氯苯基	0.23
6-38	3-氯	4-氯苯基	0.38
6-39	3-氯	苯並[d][1,3]二氧雜-5-基(benzo[d][1,3]dioxol-5-yl)	0.27
6-40	3-氯	3-(三氟甲氧基)苯基	0.48
6-41	3-氯	2-氟-4-(三氟甲基)苯基	0.32
6-42	3-氯	2,4-雙(三氟甲基)苯基	0.76
6-43	3-氯	6-(2-甲氧基乙氧基)吡啶-3-基	0.09
6-44	3-氯	6-(2-乙氧基乙氧基)吡啶-3-基	0.45
6-45	3-氯	6-(2-(2-乙氧基乙氧基)乙氧基)吡啶-3-基	0.22
6-46	4-氯	3-甲基-1H-吡唑-1-基	0.16
6-47	4-氯	哌啶-1-基	0.71
6-48	4-氯	4-氟苯基	0.18
6-49	4-氯	4-氯苯基	0.17
6-50	4-氯	苯並[d][1,3]二氧雜-5-基(benzo[d][1,3]dioxol-5-yl)	0.16
6-51	4-氯	6-(2-甲氧基乙氧基)吡啶-3-基	0.05
6-52	4-氯	6-(2-乙氧基乙氧基)吡啶-3-基	0.22

6-53	4-氯	6-(2-(2-乙氧基乙氧基)乙氧基)吡啶-3-基	0.13
6-54	4-三氟甲基	6-氟吡啶-3-基	0.13
6-55	4-三氟甲基	4-氯苯基	0.78
6-56	4-三氟甲基	6-(2-(2-乙氧基乙氧基)乙氧基)吡啶-3-基	0.20
6-57	4-叔丁基	甲氧基	0.70
6-58	4-叔丁基	2-(二甲基胺基)乙氧基	0.69
6-59	4-叔丁基	2,2,3,3-四氟丙氧基	0.50
6-60	4-叔丁基	2-嗎啉基乙氧基	0.89
6-61	4-叔丁基	2-(2-乙氧基乙氧基)乙氧基	0.54
6-62	4-叔丁基	吡咯烷-1-基	0.71
6-63	4-叔丁基	哌啶-1-基	1.92
6-64	4-叔丁基	3-甲基哌啶-1-基	1.07
6-65	4-叔丁基	3,3-二氟氮雜環丁烷-1-基(3,3-difluoroazetidin-1-yl)	0.32
6-66	4-叔丁基	3,3-二氟吡咯烷-1-基	0.13
6-67	4-叔丁基	4,4-二氟哌啶-1-基	0.73
6-68	4-叔丁基	2-亞甲基吡咯烷-1-基	1.44
6-69	4-叔丁基	L-脯胺酸甲酯	0.44
6-70	4-叔丁基	L-脯胺醯(L-prolinyl)	>1.25
6-71	4-叔丁基	2-(羥甲基)吡咯烷-1-基	0.28
6-72	4-叔丁基	2-((2-(2-乙氧基乙氧基)乙氧基)甲基)吡咯烷-1-基	0.67
6-73	4-叔丁基	4-(叔丁基)哌嗪-1-基	0.65
6-74	4-叔丁基	1H-咪唑-1-基	0.33
6-75	4-叔丁基	1H-吡唑-1-基	0.24
6-76	4-叔丁基	5-(叔丁基)-1,3,4-噁二唑-2-基	0.31
6-77	4-叔丁基	3-甲基-1H-吡唑-1-基	0.25
6-78	4-叔丁基	4-(三氟甲基)-1H-吡唑-1-基	0.57
6-79	4-叔丁基	2-氟苯基	0.69
6-80	4-叔丁基	3-氟苯基	0.78
6-81	4-叔丁基	4-氟苯基	0.94
6-82	4-叔丁基	6-甲氧基吡啶-3-基	0.38

6-83	4-叔丁基	6-(2-(2-乙氧基乙氧基)乙氧基)吡啶-3-基	0.41
6-84	4-三氟甲氧基	TBSO-氮雜環丁烷-1-基(TBSO-azetidin-1-yl)	1.11
6-85	4-三氟甲氧基	3,3-二氟吡咯烷-1-基	0.20
6-86	4-三氟甲氧基	4-(叔丁基)苯基	3.46
6-87	4-三氟甲氧基	4-(叔戊基)苯基	>2
6-88	4-三氟甲氧基	4-(三氟甲基)苯基	0.42
6-89	3-氟	4-氟苯基	0.12
6-90	3-氟	6-氟吡啶-3-基	0.14
6-91	3-氟	4-氯苯基	0.18
6-92	3-氟	苯並[d][1,3]二氧雜-5-基(benzo[d][1,3]dioxol-5-yl)	0.45
6-93	3-氟	6-((2-甲氧基乙基)(甲基)胺基)吡啶-3-基	0.40
6-94	3-氟	6-(2-甲氧基乙氧基)吡啶-3-基	0.28
6-95	3-氟	6-(2-乙氧基乙氧基)吡啶-3-基	0.29
6-96	3-氟	6-(2-(2-乙氧基乙氧基)乙氧基)吡啶-3-基	0.35
6-97	4-氟	3,3-二氟吡咯烷-1-基	0.57
6-98	4-氟	4,4-二氟哌啶-1-基	0.43
6-99	4-氟	(2S,6R)-2,6-二甲基嗎啉基	0.61
6-100	4-氟	L-脯胺酸甲酯(Methyl L-prolinate)	0.74
6-101	4-氟	L-脯胺酸乙酯(Ethyl L-prolinate)	>1.25
6-102	4-氟	(S)-2-(羥甲基)吡咯烷-1-基	1.30
6-103	4-氟	(S)-2-(甲氧基甲基)吡咯烷-1-基	0.78
6-104	4-氟	(S)-2-(乙氧基甲基)吡咯烷-1-基	0.38
6-105	4-氟	2-(丙氧基甲基)吡咯烷-1-基	0.42
6-106	4-氟	(S)-2-(苯氧基甲基)吡咯烷-1-基	0.43
6-107	4-氟	噻吩-3-基	0.37
6-108	4-氟	3-甲基-1H-吡唑-1-基	0.09
6-109	4-氟	3-(三氟甲基)-1H-吡唑-1-基	0.38

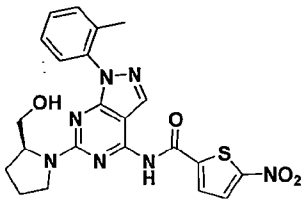
6-110	4-氟	苯基	0.23
6-111	4-氟	吡啶-3-基	0.09
6-112	4-氟	嘧啶-5-基	0.22
6-113	4-氟	2-氟苯基	0.40
6-114	4-氟	3-氟苯基	0.20
6-115	4-氟	4-氟苯基	0.22
6-116	4-氟	6-氟吡啶-3-基	0.09
6-117	4-氟	3-氯苯基	0.15
6-118	4-氟	4-氯苯基	0.25
6-119	4-氟	6-氯吡啶-3-基	0.08
6-120	4-氟	6-甲基吡啶-3-基	0.25
6-121	4-氟	6-甲氧基吡啶-3-基	0.07
6-122	4-氟	4-(三氟甲基)苯基	0.28
6-123	4-氟	4-(三氟甲氧基)苯基	0.34
6-124	4-氟	苯並[d] [1,3]二氧雜-5-基(benzo[d][1,3]dioxol-5-yl)	0.55
6-125	4-氟	3,4-二氟苯基	0.10
6-126	4-氟	2,4-二氟苯基	0.35
6-127	4-氟	4-氯-3-氟苯基	0.15
6-128	4-氟	4-氯-2-氟苯基	0.07
6-129	4-氟	4-氯-2-乙氧基苯基	>3
6-130	4-氟	6-(2-(二甲基胺基)乙氧基)吡啶-3-基	0.26
6-131	4-氟	6-((2-甲氧基乙基)(甲基)胺基)吡啶-3-基	0.37
6-132	4-氟	4-丙氧基苯基	0.43
6-133	4-氟	6-丙氧基吡啶-3-基	0.16
6-134	4-氟	6-(2-羥基乙氧基)吡啶-3-基	0.22
6-135	4-氟	6-(2-甲氧基乙氧基)吡啶-3-基	0.22
6-136	4-氟	6-(2-乙氧基乙氧基)吡啶-3-基	0.26
6-137	4-氟	6-(2-(2-乙氧基乙氧基)乙氧基)吡啶-3-基	0.18
6-138	4-氟	2-氟-4-(2-甲氧基乙氧基)苯基	> 1.25
6-139	4-氟	6-(2-(2-乙氧基乙氧基)乙氧基)-4-甲基吡啶-3-基	0.21

6-140	4-氟	4-氯-2-(2-(2-乙氧基乙氧基)乙氧基)苯基	4.83
6-141	4-氟	6-嗎啉基吡啶-3-基	0.42
6-142	4-氟	4,4-二甲基環己-1-烯-1-基	0.74
6-143	4-氟	4-甲基環己基	1.02
6-144	4-氟	4,4-二甲基環己-1-烯-1-基	0.55
6-145	4-氟	4,4-二甲基環己基	0.89

【0283】化合物 6-1

(S)-N-(6-(2-(羥甲基)吡咯烷-1-基)-1-(鄰-甲苯基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩 -2-甲醯胺

((S)-N-(6-(2-(hydroxymethyl)pyrrolidin-1-yl)-1-(o-tolyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

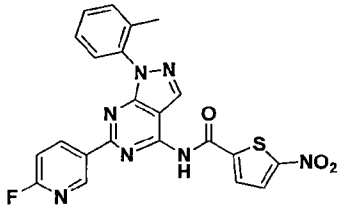


^{1}H NMR (400MHz, DMSO-d_6): δ 11.46 (br. s., 1H), 8.29 (br. s., 1H), 8.23 (br. s., 2H), 7.30-7.47 (m, 4H), 4.62 (br. s., 1H), 4.23 (br. s., 1H), 4.01 (br. s., 1H), 3.50 (br. s., 4H), 2.17 (s, 3H), 1.85-2.07 (m, 3H), 1.76-1.85 (m, 1H). MS(M+1): 480. 黃色固體。

【0284】化合物 6-2

N-(6-(6-氟吡啶-3-基)-1-(鄰-甲苯基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(6-(6-fluoropyridin-3-yl)-1-(o-tolyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)



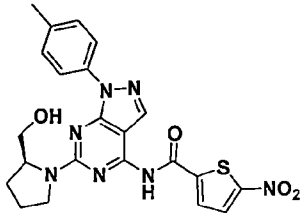
^{1}H NMR (400MHz, DMSO-d_6):δ 12.11 (br. s., 1H), 9.17 (d, J = 2.4 Hz, 1H), 8.76 (td, J = 8.3, 2.4 Hz, 1H), 8.66 (s, 1H), 8.38 (d, J = 4.4 Hz, 1H), 8.27 (d, J = 4.4 Hz, 1H), 7.49-7.59 (m, 3H), 7.41-7.49 (m, 1H), 7.35 (dd, J = 8.8, 2.4 Hz, 1H), 2.16 (s, 3H)

MS(M+1):476. 淺黃色固體。

【0285】化合物 6-3

(S)-N-(6-(2-(羥甲基)吡咯烷-1-基)-1-(對-甲苯基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩 -2-甲醯胺

((S)-N-(6-(2-(hydroxymethyl)pyrrolidin-1-yl)-1-(p-tolyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

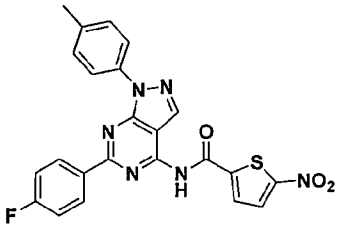


^{1}H NMR (400MHz, DMSO-d_6): δ 11.46 (br. s., 1H), 8.26 (br. s., 1H), 8.19-8.24 (m, 2H), 8.08-8.15 (m, J = 8.3 Hz, 2H), 7.24-7.38 (m, J = 8.3 Hz, 2H), 4.73 (br. s., 1H), 4.25 (br. s., 1H), 3.49-3.74 (m, 4H), 2.32-2.43 (m, 3H), 1.93-2.13 (m, 3H), 1.91 (br. s., 1H). MS(M+1): 480. 黃色固體。

【0286】化合物 6-4

N-(6-(4-氟苯基)-1-(對-甲苯基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(6-(4-fluorophenyl)-1-(p-tolyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

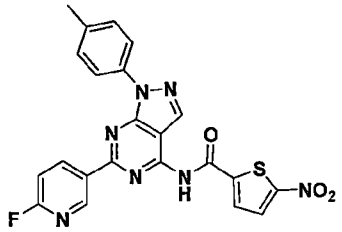


^{1}H NMR (400MHz, DMSO-d_6): δ 12.03 (br. s., 1H), 8.51-8.66 (m, 3H), 8.36 (d, J = 4.4 Hz, 1H), 8.26 (d, J = 4.4 Hz, 1H), 8.06-8.19 (m, 2H), 7.35-7.52 (m, 4H), 2.41 (s, 3H). MS(M+1):475. 黃色固體。

【0287】化合物 6-5

N-(6-(6-氟吡啶-3-基)-1-(對-甲苯基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(6-(6-fluoropyridin-3-yl)-1-(p-tolyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

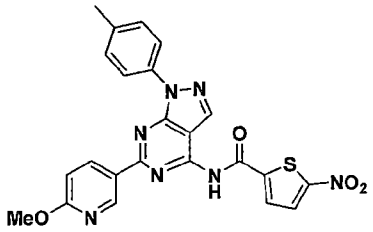


^{1}H NMR (400MHz, DMSO-d_6): δ 12.11 (br. s., 1H), 9.30 (d, J = 2.4 Hz, 1H), 8.94 (td, J = 8.3, 2.4 Hz, 1H), 8.63 (s, 1H), 8.31 (d, J = 4.4 Hz, 1H), 8.25 (d, J = 4.4 Hz, 1H), 8.10-8.20 (m, 2H), 7.39-7.49 (m, 3H), 2.41 (s, 3H). MS(M+1):476. 淺卡其色固體。

【0288】化合物 6-6

N-(6-(6-甲氧基吡啶-3-基)-1-(對-甲苯基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(6-(6-methoxypyridin-3-yl)-1-(p-tolyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)



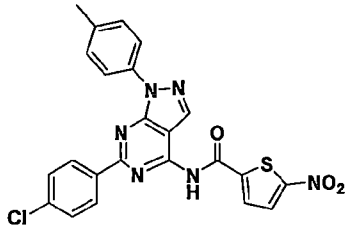
^{1}H NMR (400MHz, DMSO-d_6): δ 11.97 (br. s., 1H), 9.27 (d, J = 2.4 Hz, 1H), 8.67 (dd, J = 8.6, 2.2 Hz, 1H), 8.57 (s, 1H), 8.35 (d, J = 4.4 Hz, 1H), 8.25 (d, J = 4.9 Hz, 1H),

8.09-8.18 (m, J = 8.8 Hz, 2H), 7.38-7.47 (m, J = 8.3 Hz, 2H), 7.01 (d, J = 8.3 Hz, 1H), 3.96 (s, 3H), 2.40 (s, 3H). MS(M+1):488. 黃色固體。

【0289】化合物 6-7

N-(6-(4-氯苯基)-1-(對-甲苯基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(6-(4-chlorophenyl)-1-(p-tolyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

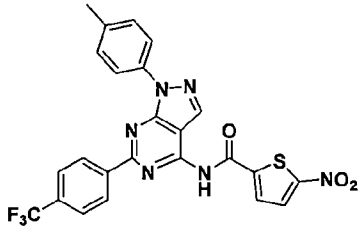


^{1}H NMR (400MHz, DMSO-d_6): δ 12.05 (br. s., 1H), 8.61 (s, 1H), 8.49-8.57 (m, 2H), 8.34 (d, J = 4.4 Hz, 1H), 8.26 (d, J = 4.4 Hz, 1H), 8.08-8.16 (m, 2H), 7.63-7.71 (m, 2H), 7.45 (d, J = 7.8 Hz, 2H), 2.42 (s, 3H). MS(M+1):491. 銀色固體。

【0290】化合物 6-8

5-硝基-N-(1-(對-甲苯基)-6-(4-(三氟甲基)苯基)-1H-吡唑並[3,4-d]嘧啶-4-基)噻吩-2-甲醯胺

(5-nitro-N-(1-(p-tolyl)-6-(4-(trifluoromethyl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)thiophene-2-carboxamide)

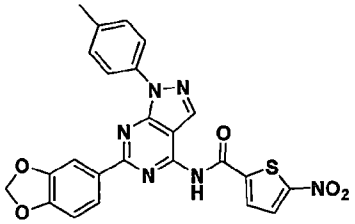


^{1}H NMR (400MHz, DMSO-d_6): δ 12.10 (br. s., 1H), 8.70 (d, J = 8.3 Hz, 2H), 8.63 (s, 1H), 8.37 (d, J = 4.4 Hz, 1H), 8.26 (d, J = 4.4 Hz, 1H), 8.08-8.17 (m, 2H), 7.91-7.99 (m, J = 8.3 Hz, 2H), 7.44 (d, J = 8.3 Hz, 2H), 2.42 (s, 3H). MS(M+1):525. 銀色固體。

【0291】化合物 6-9

N-(6-(苯並[d] [1,3]二氧雜-5-基)-1-(對-甲苯基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩 -2-甲醯胺

(N-(6-(benzo[d][1,3]dioxol-5-yl)-1-(p-tolyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

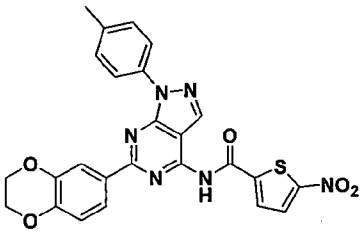


^{1}H NMR (400MHz, DMSO-d_6): δ 11.84 (br. s., 1H), 8.54 (s, 1H), 8.34 (d, J = 4.4 Hz, 1H), 8.24 (d, J = 4.4 Hz, 1H), 8.06-8.16 (m, 3H), 7.96 (d, J = 1.5 Hz, 1H), 7.42 (d, J = 8.3 Hz, 2H), 7.09 (d, J = 8.3 Hz, 1H), 6.14 (s, 2H), 2.40 (s, 3H). MS(M+1):501. 黃色固體。

【0292】化合物 6-10

N-(6-(2,3-二氫苯並[b] [1,4]二噁英-6-基)-1-(對-甲苯基)-1H-吡唑並[3,4-d]嘧啶-4-基) -5-硝基噻吩-2-甲醯胺

(N-(6-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-(p-tolyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

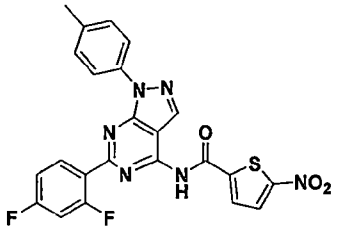


^{1}H NMR (400MHz, DMSO-d_6): δ 11.91 (br. s., 1H), 8.55 (s, 1H), 8.35 (d, J = 4.4 Hz, 1H), 8.25 (d, J = 4.4 Hz, 1H), 8.06-8.15 (m, J = 8.3 Hz, 2H), 7.98-8.06 (m, 2H), 7.40-7.49 (m, J = 8.3 Hz, 2H), 7.03 (d, J = 8.3 Hz, 1H), 4.24-4.39 (m, 4H), 2.40 (s, 3H).MS(M+1): 515. 卡其色固體。

【0293】 化合物 6-11

N-(6-(2,4-二氟苯基)-1-(對-甲苯基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(6-(2,4-difluorophenyl)-1-(p-tolyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

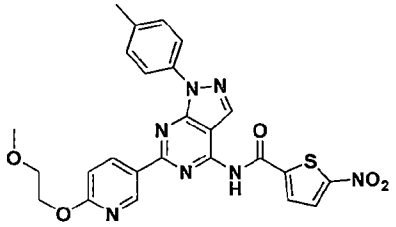


^{1}H NMR (400MHz, DMSO-d_6): δ 12.14 (br. s., 1H), 8.61 (s, 1H), 8.34 (d, J = 4.4 Hz, 1H), 8.29 (td, J = 8.8, 6.8 Hz, 1H), 8.23 (d, J = 4.4 Hz, 1H), 8.06-8.17 (m, 2H), 7.44 (ddd, J = 11.4, 9.2, 2.4 Hz, 1H), 7.35-7.41 (m, J = 8.3 Hz, 2H), 7.22-7.34 (m, 1H), 2.38 (s, 4H). MS(M+1):493. 淺黃色固體。

【0294】 化合物 6-12

N-(6-(6-(2-甲氧基乙氧基)吡啶-3-基)-1-(對-甲苯基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2 -甲醯胺

(N-(6-(6-(2-methoxyethoxy)pyridin-3-yl)-1-(p-tolyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)



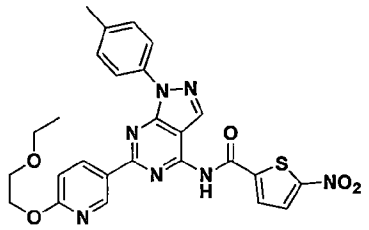
^{1}H NMR (400MHz, DMSO-d_6): δ11.91 (br. s., 1H), 9.23 (d, J = 2.4 Hz, 1H), 8.64 (dd, J = 8.8, 2.4 Hz, 1H), 8.55 (s, 1H), 8.33 (d, J = 4.9 Hz, 1H), 8.23 (d, J = 4.4 Hz, 1H), 8.04- 8.15 (m, J = 8.3 Hz, 2H), 7.36-7.46 (m, J = 8.8 Hz, 2H), 7.00 (d, J = 8.3 Hz, 1H),

4.33- 4.55 (m, 2H), 3.63-3.77 (m, 2H), 3.32 (s, 3H), 2.39 (s, 3H). MS(M+1): 532. 卡其色固體。

【0295】化合物 6-13

N-(6-(6-(2-乙氧基乙氧基)吡啶-3-基)-1-(對-甲苯基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2 -甲醯胺

(N-(6-(6-(2-ethoxyethoxy)pyridin-3-yl)-1-(p-tolyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

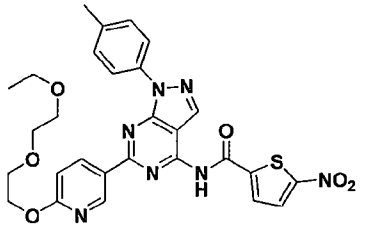


^{1}H NMR (400MHz, DMSO-d_6): δ 11.89 (br. s., 1H), 9.22 (d, J = 2.4 Hz, 1H), 8.63 (dd, J = 8.6, 2.2 Hz, 1H), 8.54 (s, 1H), 8.34 (d, J = 4.4 Hz, 1H), 8.23 (d, J = 4.4 Hz, 1H), 8.05- 8.13 (m, J = 8.3 Hz, 2H), 7.36-7.47 (m, J = 8.3 Hz, 2H), 7.00 (d, J = 8.8 Hz, 1H), 4.46 (dd, J = 5.6, 4.2 Hz, 2H), 3.70-3.78 (m, 2H), 3.51 (q, J = 6.8 Hz, 2H), 2.39 (s, 3H), 1.14 (t, J = 6.8 Hz, 3H). MS(M+1): 546. 黃色固體。

【0296】化合物 6-14

N-(6-(6-(2-(2-乙氧基乙氧基)乙氧基)吡啶-3-基)-1-(對-甲苯基)-1H-吡唑並[3,4-d]嘧啶-4-基)- 5-硝基噻吩-2-甲醯胺

(N-(6-(6-(2-(2-ethoxyethoxy)ethoxy)pyridin-3-yl)-1-(p-tolyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

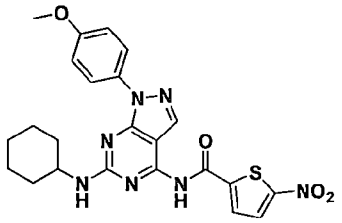


^{1}H NMR (400MHz, DMSO-d_6):δ 11.87 (br. s., 1H), 9.21 (d, J = 2.0 Hz, 1H), 8.62 (dd, J = 8.8, 2.4 Hz, 1H), 8.53 (s, 1H), 8.33 (d, J = 4.4 Hz, 1H), 8.22 (d, J = 4.4 Hz, 1H), 8.03-8.15 (m, 2H), 7.36-7.44 (m, J = 8.3 Hz, 2H), 6.98 (d, J = 9.3 Hz, 1H), 4.46 (dd, J = 5.4, 3.9 Hz, 2H), 3.78 (dd, J = 5.4, 3.9 Hz, 2H), 3.58-3.64 (m, 2H), 3.47-3.55 (m, 2H), 3.44 (q, J = 6.8 Hz, 2H), 2.38 (s, 3H), 1.10 (t, J = 6.8 Hz, 3H). MS(M+1):590. 黃色固體。

【0297】化合物 6-15

N-(6-(環己基胺基)-1-(4-甲氧基苯基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(6-(cyclohexylamino)-1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

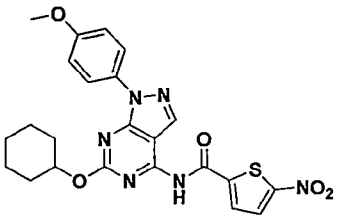


^{1}H NMR (400MHz, DMSO-d_6): δ 11.68 (br., 1H), 8.12-8.29 (m, 2H), 8.05 (d, J = 8.3 Hz, 3H), 7.29 (br., 1H), 7.08 (d, J = 8.8 Hz, 2H), 3.82 (s, 4H), 1.93 (d, J = 18.6 Hz, 2H), 1.68- 1.83 (m, 2H), 1.62 (d, J = 11.7 Hz, 1H), 1.34 (br. s., 4H), 1.23 (br. s., 1H). MS(M+1):494. 黃色固體。

【0298】化合物 6-16

N-(6-(環己氧基)-1-(4-甲氧基苯基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(6-(cyclohexyloxy)-1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

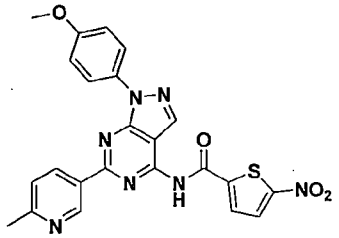


^{1}H NMR (400MHz, DMSO-d_6): δ 12.08 (br. s., 1H), 8.48 (s, 1H), 8.32 (d, J = 4.4 Hz, 1H), 8.23 (d, J = 4.4 Hz, 1H), 7.98-8.07 (m, J = 9.3 Hz, 2H), 7.09-7.18 (m, J = 9.3 Hz, 2H), 5.02-5.15 (m, 1H), 3.83 (s, 3H), 2.00 (d, J = 3.9 Hz, 2H), 1.75 (d, J = 5.9 Hz, 2H), 1.50- 1.67 (m, 3H), 1.34-1.50 (m, 3H). MS(M+1):495. 黃色固體。

【0299】化合物 6-17

N-(1-(4-甲氧基苯基)-6-(6-甲基吡啶-3-基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(1-(4-methoxyphenyl)-6-(6-methylpyridin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

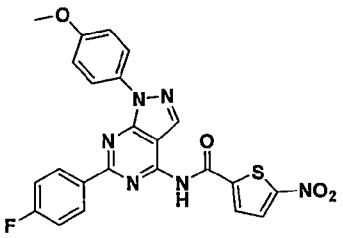


^{1}H NMR (400MHz, DMSO-d_6): δ 11.91 (s, 1H), 9.47 (d, J = 2.4 Hz, 1H), 8.59 (dd, J = 8.1, 2.2 Hz, 1H), 8.52 (s, 1H), 8.34 (d, J = 4.4 Hz, 1H), 8.21 (d, J = 4.4 Hz, 1H), 8.09 (d, J = 9.3 Hz, 2H), 7.42 (d, J = 8.3 Hz, 1H), 7.15 (d, J = 8.8 Hz, 2H), 3.84 (s, 3H), 2.55 (s, 3H). MS(M+1):488.橘色固體。

【0300】化合物 6-18

N-(6-(4-氟苯基)-1-(4-甲氧基苯基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(6-(4-fluorophenyl)-1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

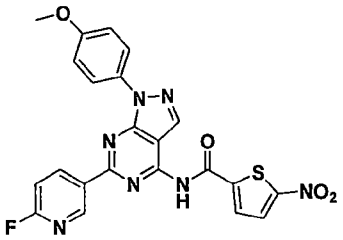


^{1}H NMR (400MHz, DMSO-d_6): δ 12.04 (br. s., 1H), 8.54-8.62 (m, 3H), 8.36 (d, J = 4.4 Hz, 1H), 8.26 (d, J = 4.4 Hz, 1H), 8.09-8.17 (m, 2H), 7.37-7.47 (m, 2H), 7.17-7.24 (m, 2H), 3.86 (s, 3H). MS(M+1):491. 黃色固體。

【0301】化合物 6-19

N-(6-(6-氟吡啶-3-基)-1-(4-甲氧基苯基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(6-(6-fluoropyridin-3-yl)-1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

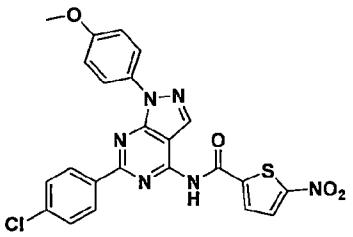


^{1}H NMR (400MHz, DMSO-d_6): δ 12.06 (br. s., 1H), 9.30 (d, J = 2.0 Hz, 1H), 8.93 (td, J = 8.2, 2.2 Hz, 1H), 8.63 (s, 1H), 8.37 (d, J = 4.4 Hz, 1H), 8.26 (d, J = 4.4 Hz, 1H), 8.09-8.18 (m, J = 9.3 Hz, 2H), 7.42 (dd, J = 8.8, 2.4 Hz, 1H), 7.15-7.24 (m, J = 9.3 Hz, 2H), 3.86 (s, 3H). MS(M+1):492. 黃色固體。

【0302】化合物 6-20

N-(6-(4-氯苯基)-1-(4-甲氧基苯基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(6-(4-chlorophenyl)-1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

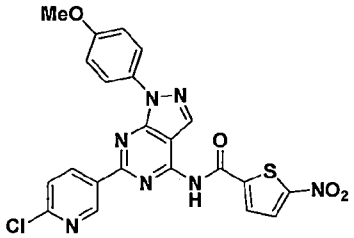


^{1}H NMR (400MHz, DMSO-d_6): δ 11.98 (br. s., 1H), 8.56 (s, 1H), 8.46-8.52 (m, J = 8.3 Hz, 2H), 8.37 (d, J = 4.4 Hz, 1H), 8.24 (d, J = 4.4 Hz, 1H), 8.06-8.12 (m, J = 8.8 Hz, 2H), 7.63 (d, J = 8.3 Hz, 2H), 7.17 (d, J = 9.3 Hz, 2H), 3.85 (s, 3H). MS(M+1) : 507. 黃色固體。

【0303】化合物 6-21

N-(6-(6-氯吡啶-3-基)-1-(4-甲氧基苯基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(6-(6-chloropyridin-3-yl)-1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

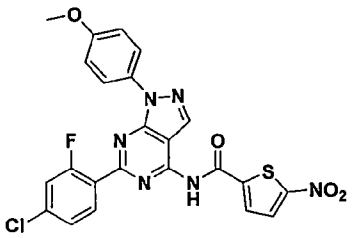


^{1}H NMR (400MHz, DMSO-d_6): δ 12.07 (br. s., 1H), 9.44 (d, J = 2.4 Hz, 1H), 8.79 (dd, J = 8.3, 2.4 Hz, 1H), 8.63 (s, 1H), 8.38 (d, J = 4.4 Hz, 1H), 8.08-8.17 (m, 2H), 7.76 (d, J = 8.8 Hz, 1H), 7.15-7.23 (m, 2H), 3.79-3.90 (m, 3H). MS(M+1):508.黑色固體。

【0304】化合物 6-22

N-(6-(4-氯-2-氟苯基)-1-(4-甲氧基苯基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(6-(4-chloro-2-fluorophenyl)-1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

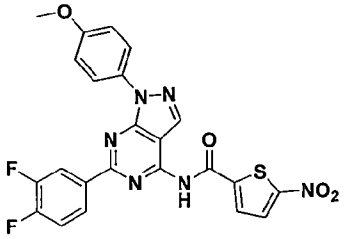


^{1}H NMR (400MHz, DMSO-d_6): δ 12.12 (br. s., 1H), 8.59 (s, 1H), 8.35 (d, J = 4.4 Hz, 1H), 8.19-8.27 (m, 2H), 8.11 (d, J = 8.8 Hz, 2H), 7.62 (dd, J = 10.8, 2.0 Hz, 1H), 7.49 (dd, J = 8.3, 2.0 Hz, 1H), 7.13 (d, J = 9.3 Hz, 2H), 3.83 (s, 3H). MS(M+1):525. 黃色固體。

【0305】化合物 6-23

N-(6-(3,4-二氟苯基)-1-(4-甲氧基苯基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(6-(3,4-difluorophenyl)-1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

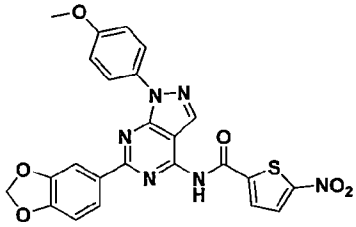


^{1}H NMR (400MHz, DMSO-d_6): δ 11.89 (br. s., 1H), 8.56 (s, 1H), 8.28-8.41 (m, 3H), 8.24 (d, J = 4.4 Hz, 1H), 8.04-8.11 (m, 2H), 7.62 (dt, J = 10.3, 8.6 Hz, 1H), 7.11-7.21 (m, 2H), 3.85 (s, 3H). MS(M+1):509. 橘色固體。

【0306】化合物 6-24

N-(6-(苯並[d] [1,3]二氧雜-5-基)-1-(4-甲氧基苯基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩 -2-甲醯胺

(N-(6-(benzo[d][1,3]dioxol-5-yl)-1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

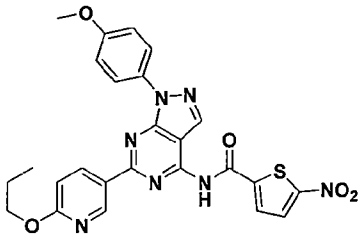


^{1}H NMR (400MHz, DMSO-d_6): δ 11.87 (s, 1H), 8.56 (s, 1H), 8.37 (d, J = 4.4 Hz, 1H), 8.26 (d, J = 4.4 Hz, 1H), 8.08-8.18 (m, 3H), 7.98 (d, J = 1.5 Hz, 1H), 7.19 (d, J = 9.3 Hz, 2H), 7.11 (d, J = 8.3 Hz, 1H), 6.15 (s, 2H), 3.86 (s, 3H). MS(M+1):517. 橘色固體。

【0307】化合物 6-25

N-(1-(4-甲氧基苯基)-6-(6-丙氧基吡啶-3-基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(1-(4-methoxyphenyl)-6-(6-propoxypyridin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

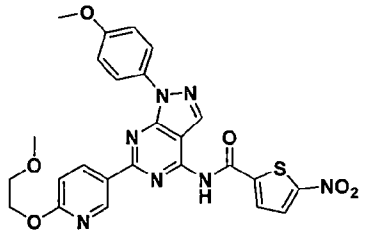


^{1}H NMR (400MHz, DMSO-d_6): δ 11.90 (br. s., 1H), 9.23 (d, J = 2.0 Hz, 1H), 8.64 (dd, J = 8.8, 2.4 Hz, 1H), 8.54 (s, 1H), 8.35 (d, J = 4.4 Hz, 1H), 8.24 (d, J = 4.4 Hz, 1H), 8.09-8.15 (m, 2H), 7.13-7.21 (m, 2H), 6.96 (d, J = 8.8 Hz, 1H), 4.30 (t, J = 6.6 Hz, 2H), 3.85 (s, 3H), 1.77 (sxt, J = 7.1 Hz, 2H), 0.99 (t, J = 7.6 Hz, 3H). MS(M+1):532. 橘色固體。

【0308】化合物 6-26

N-(6-(6-(2-(甲氧基乙氧基)吡啶-3-基)-1-(4-甲氧基苯基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2 -甲醯胺

(N-(6-(6-(2-methoxyethoxy)pyridin-3-yl)-1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

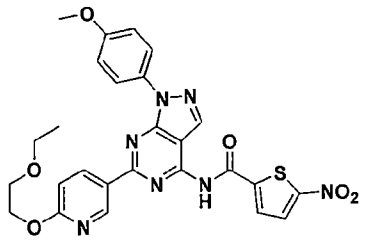


^{1}H NMR (400MHz, DMSO-d_6): δ 11.90 (br. s., 1H), 9.23 (d, J = 2.0 Hz, 1H), 8.65 (dd, J = 8.8, 2.4 Hz, 1H), 8.54 (s, 1H), 8.35 (d, J = 4.4 Hz, 1H), 8.24 (d, J = 4.4 Hz, 1H), 8.08-8.15 (m, 2H), 7.13-7.20 (m, 2H), 7.00 (d, J = 8.8 Hz, 1H), 4.42-4.52 (m, 2H), 3.85 (s, 3H), 3.66-3.72 (m, 2H). MS(M+1):548. 橘色固體。

【0309】化合物 6-27

N-(6-(6-(2-乙氧基乙氧基)吡啶-3-基)-1-(4-甲氧基苯基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2 -甲醯胺

(N-(6-(6-(2-ethoxyethoxy)pyridin-3-yl)-1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

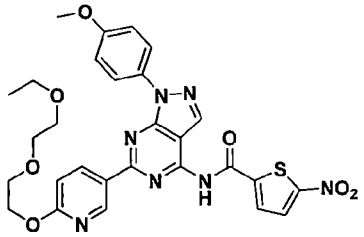


^{1}H NMR (400MHz, DMSO-d_6): δ 11.85 (br. s., 1H), 9.21 (d, J = 2.0 Hz, 1H), 8.62 (dd, J = 8.6, 2.2 Hz, 1H), 8.51 (s, 1H), 8.33 (d, J = 4.4 Hz, 1H), 8.22 (d, J = 4.4 Hz, 1H), 8.05-8.14 (m, 2H), 7.10-7.19 (m, 2H), 6.98 (d, J = 8.8 Hz, 1H), 4.45 (dd, J = 5.4, 3.9 Hz, 2H), 3.84 (s, 3H), 3.73 (dd, J = 5.4, 3.9 Hz, 2H), 3.51 (q, J = 6.8 Hz, 2H), 1.09- 1.17 (m, 3H). MS(M+1):562. 黃色固體。

【0310】化合物 6-28

N-(6-(6-(2-(2-乙氧基乙氧基)乙氧基)吡啶-3-基)-1-(4-甲氧基苯基)-1H-吡唑並[3,4-d]嘧啶-4-基)- 5-硝基噻吩-2-甲醯胺

(N-(6-(6-(2-(2-ethoxyethoxy)ethoxy)pyridin-3-yl)-1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

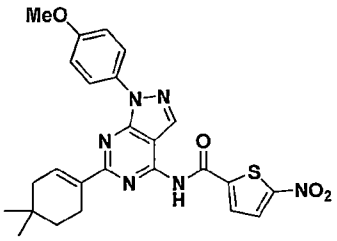


^{1}H NMR (400MHz, DMSO-d_6): δ 11.79 (br. s., 1H), 9.17 (d, J = 2.0 Hz, 1H), 8.59 (dd, J = 8.8, 2.4 Hz, 1H), 8.48 (s, 1H), 8.31 (d, J = 4.4 Hz, 1H), 8.20 (d, J = 4.4 Hz, 1H), 8.04-8.11 (m, J = 8.8 Hz, 2H), 7.09-7.16 (m, J = 9.3 Hz, 2H), 6.95 (d, J = 8.3 Hz, 1H), 4.44 (dd, J = 5.6, 4.2 Hz, 2H), 3.83 (s, 3H), 3.75-3.80 (m, 2H), 3.57-3.62 (m, 2H), 3.48-3.53 (m, 2H), 3.43 (q, J = 6.8 Hz, 2H), 1.10 (t, J = 7.1 Hz, 3H). MS(M+1):606. 黃色固體。

【0311】化合物 6-29

N-(6-(4,4-二甲基環己-1-烯-1-基)-1-(4-甲氧基苯基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩- 2-甲醯胺

(N-(6-(4,4-dimethylcyclohex-1-en-1-yl)-1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)



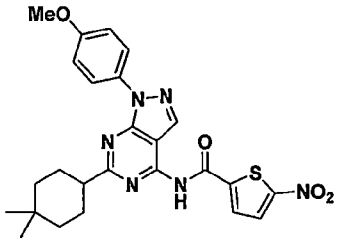
^{1}H NMR (400MHz, DMSO-d_6):δ 11.78 (br. s., 1H), 8.49 (s, 1H), 8.32 (br. s., 1H), 8.22 (d, J = 4.4 Hz, 1H), 8.02-8.18 (m, J = 8.8 Hz, 2H), 7.37 (br. s., 1H), 7.07-7.21 (m,

2H), 3.83 (s, 3H), 2.63 (br. s., 2H), 2.02-2.19 (m, 2H), 1.52 (t, J = 6.4 Hz, 2H), 0.96 (s, 6H). MS(M+1): 505. 黃色固體。

【0312】化合物 6-30

N-(6-(4,4-二甲基環己基)-1-(4-甲氧基苯基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(6-(4,4-dimethylcyclohexyl)-1-(4-methoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

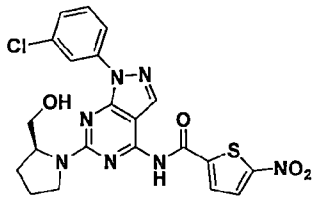


^{1}H NMR (400MHz, DMSO-d_6):δ 12.07 (br. s., 1H), 8.52 (s, 1H), 8.28 (br. s., 1H), 8.21 (d, J = 4.4 Hz, 1H), 7.96-8.11 (m, J = 8.8 Hz, 2H), 7.06-7.20 (m, 2H), 3.84 (s, 3H), 2.76-2.85 (m, 1H), 1.77-1.94 (m, 4H), 1.50 (d, J = 12.7 Hz, 2H), 1.34 (td, J = 12.6, 5.1 Hz, 2H), 0.97 (d, J = 3.4 Hz, 6H). MS(M+1): 507. 黃色固體。

【0313】化合物 6-31

(S)-N-(1-(3-氯苯基)-6-(2-(羥甲基)吡咯烷-1-基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩 -2-甲醯胺

((S)-N-(1-(3-chlorophenyl)-6-(2-(hydroxymethyl)pyrrolidin-1-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)



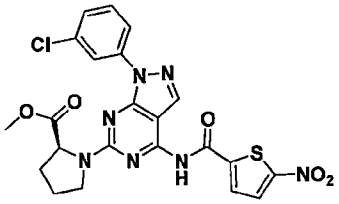
^{1}H NMR (400MHz, DMSO-d_6): δ 11.53 (br. s., 1H), 8.44 (br. s., 1H), 8.25-8.36 (m, 3H), 8.18-8.25 (m, 1H), 7.56 (t, J = 8.3 Hz, 1H), 7.30-7.38 (m, 1H), 4.73 (br. s., 1H), 4.26 (br. s., 1H), 3.66 (br. s., 4H), 2.06 (d, J = 13.2 Hz, 3H), 1.92 (d, J = 6.8 Hz, 1H).

MS(M+1):500. 橘色固體。

【0314】化合物 6-32

(1-(3-氯苯基)-4-(5-硝基噻吩-2-甲醯胺基)-1H-吡唑並[3,4-d]嘧啶-6-基)-L-脯胺酸甲酯

(methyl (1-(3-chlorophenyl)-4-(5-nitrothiophene-2-carboxamido)-1H-pyrazolo[3,4-d]pyrimidin-6-yl)-L-prolinate)



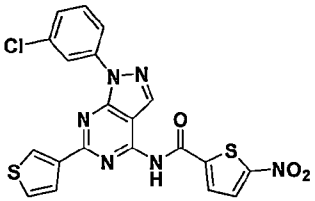
^{1}H NMR (400MHz, DMSO-d_6): δ 11.66 (br. s., 1H), 8.24-8.35 (m, 3H), 8.16-8.24 (m, 2H), 7.53 (t, J = 8.1 Hz, 1H), 7.36 (d, J = 7.8 Hz, 1H), 4.57-4.64 (m, 1H), 3.71-3.88 (m, 2H), 3.57-3.71 (m, 3H), 2.41 (dt, J = 8.2, 4.0 Hz, 1H), 1.93-2.15 (m, 3H).

MS(M+1): 528. 黃色固體。

【0315】化合物 6-33

N-(1-(3-氯苯基)-6-(噻吩-3-基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(1-(3-chlorophenyl)-6-(thiophen-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

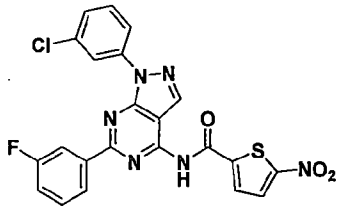


^{1}H NMR (400MHz, DMSO-d_6): δ 12.10 (s, 1H), 8.63 (s, 1H), 8.53 (dd, J = 2.9, 1.0 Hz, 1H), 8.37-8.43 (m, 3H), 8.27 (d, J = 4.4 Hz, 1H), 7.91-7.97 (m, 1H), 7.73-7.78 (m, 1H), 7.68 (t, J = 8.1 Hz, 1H), 7.49 (dd, J = 7.8, 2.4 Hz, 1H). MS(M+1): 483.淡綠色固體。

【0316】化合物 6-34

N-(1-(3-氯苯基)-6-(3-氟苯基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(1-(3-chlorophenyl)-6-(3-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

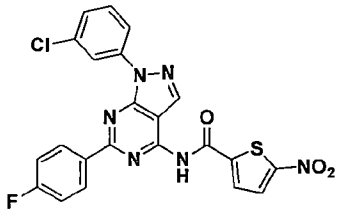


^{1}H NMR (400MHz, DMSO-d_6): δ 12.06 (br. s., 1H), 8.67 (s, 1H), 8.39 (t, J = 2.0 Hz, 1H), 8.33-8.38 (m, 3H), 8.22-8.28 (m, 2H), 7.62-7.72 (m, 2H), 7.48-7.52 (m, 1H), 7.45 (td, J = 8.6, 2.4 Hz, 1H). MS(M+1): 495. 黃色固體。

【0317】化合物 6-35

N-(1-(3-氯苯基)-6-(4-氟苯基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(1-(3-chlorophenyl)-6-(4-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

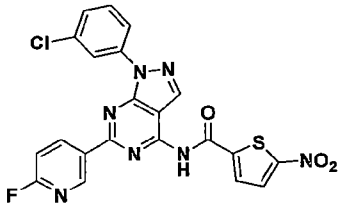


^{1}H NMR (400MHz, DMSO-d_6): δ 12.01 (br. s., 1H), 8.60 (s, 1H), 8.48-8.57 (m, 2H), 8.30-8.37 (m, 3H), 8.24 (d, J = 4.4 Hz, 1H), 7.60-7.68 (m, 1H), 7.44-7.49 (m, 1H), 7.37-7.44 (m, 2H). MS(M+1): 495. 黃色固體。

【0318】化合物 6-36

N-(1-(3-氯苯基)-6-(6-氟吡啶-3-基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(1-(3-chlorophenyl)-6-(6-fluoropyridin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

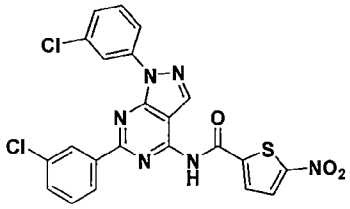


^{1}H NMR (400MHz, DMSO-d_6): δ 12.06 (br. s., 1H), 9.27 (d, J = 2.4 Hz, 1H), 8.89 (td, J = 8.1, 2.4 Hz, 1H), 8.64 (s, 1H), 8.28-8.40 (m, 3H), 8.25 (d, J = 4.4 Hz, 1H), 7.66 (t, J = 8.1 Hz, 1H), 7.45-7.49 (m, 1H), 7.43 (dd, J = 8.6, 2.7 Hz, 1H). MS(M+1): 496. 淡黃色固體。

【0319】化合物 6-37

N-(1,6-雙(3-氯苯基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(1,6-bis(3-chlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

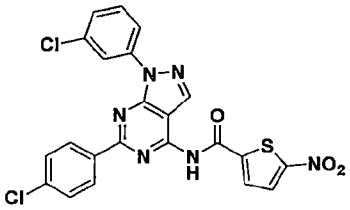


^{1}H NMR (400MHz, DMSO-d_6): δ 12.07 (br. s., 1H), 8.67 (s, 1H), 8.51-8.55 (m, 1H), 8.45 (dt, J = 7.0, 1.9 Hz, 1H), 8.39 (t, J = 2.2 Hz, 1H), 8.37 (d, J = 4.4 Hz, 1H), 8.32 (ddd, J = 8.3, 2.0, 1.0 Hz, 1H), 8.26 (d, J = 4.4 Hz, 1H), 7.61-7.71 (m, 3H), 7.47-7.52 (m, 1H). MS(M+1): 511. 淡黃色固體。

【0320】化合物 6-38

N-(1-(3-氯苯基)-6-(4-氯苯基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(1-(3-chlorophenyl)-6-(4-chlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

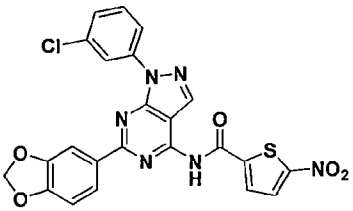


^{1}H NMR (400MHz, DMSO-d_6): δ 12.02 (br. s., 1H), 8.62 (s, 1H), 8.44-8.54 (m, 2H), 8.37 (d, J = 4.4 Hz, 1H), 8.29-8.35 (m, 2H), 8.25 (d, J = 4.4 Hz, 1H), 7.60-7.71 (m, 3H), 7.43-7.50 (m, 1H). MS(M+1): 511. 淡黃色固體。

【0321】化合物 6-39

N-(6-(苯並[d] [1,3]二氧雜-5-基)-1-(3-氯苯基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩 -2-甲醯胺

(N-(6-(benzo[d][1,3]dioxol-5-yl)-1-(3-chlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

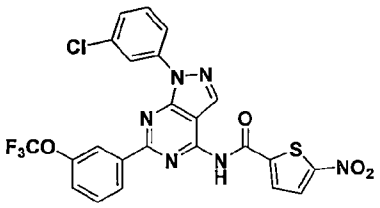


^{1}H NMR (400MHz, DMSO-d_6): δ 11.93 (br. s., 1H), 8.59 (s, 1H), 8.39 (t, J = 2.0 Hz, 1H), 8.29-8.35 (m, 2H), 8.25 (d, J = 4.4 Hz, 1H), 8.13 (dd, J = 8.3, 1.5 Hz, 1H), 7.96 (d, J = 1.5 Hz, 1H), 7.66 (t, J = 8.3 Hz, 1H), 7.41-7.50 (m, 1H), 7.12 (d, J = 8.3 Hz, 1H), 6.15 (s, 2H). MS(M+1):521. 橘色固體。

【0322】化合物 6-40

N-(1-(3-氯苯基)-6-(3-(三氟甲氧基)苯基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(1-(3-chlorophenyl)-6-(3-(trifluoromethoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

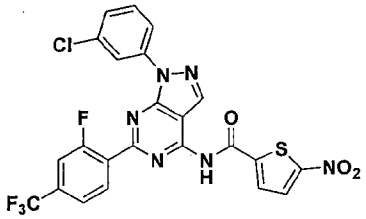


^{1}H NMR (400MHz, DMSO-d_6): δ 12.02 (s, 1H), 8.64 (s, 1H), 8.51 (dt, J = 7.8, 1.2 Hz, 1H), 8.38-8.45 (m, 2H), 8.36 (d, J = 4.4 Hz, 1H), 8.17-8.31 (m, 2H), 7.74 (t, J = 8.1 Hz, 1H), 7.65 (t, J = 8.1 Hz, 1H), 7.55-7.62 (m, 1H), 7.40-7.52 (m, 1H). MS(M+1): 561. 黃色固體。

【0323】化合物 6-41

N-(1-(3-氯苯基)-6-(2-氟-4-(三氟甲基)苯基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(1-(3-chlorophenyl)-6-(2-fluoro-4-(trifluoromethyl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

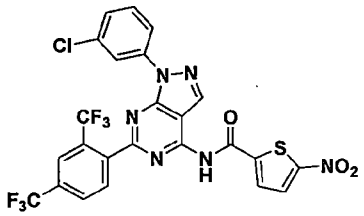


^{1}H NMR (400MHz, DMSO-d_6): δ 12.27 (br. s., 1H), 8.69 (s, 1H), 8.43-8.50 (m, 2H), 8.36 (d, J = 4.4 Hz, 1H), 8.29 (dd, J = 8.3, 1.5 Hz, 1H), 8.24 (d, J = 4.4 Hz, 1H), 7.92 (d, J = 10.8 Hz, 1H), 7.82 (d, J = 8.3 Hz, 1H), 7.63 (t, J = 8.1 Hz, 1H), 7.44-7.49 (m, 1H). MS(M+1):563. 灰白色固體。

【0324】化合物 6-42

N-(6-(2,4-雙(三氟甲基)苯基)-1-(3-氯苯基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(6-(2,4-bis(trifluoromethyl)phenyl)-1-(3-chlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

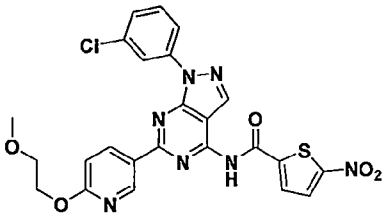


^{1}H NMR (400MHz, DMSO-d_6): δ 12.43 (s, 1H), 8.77 (s, 1H), 8.32-8.40 (m, 2H), 8.27-8.32 (m, 2H), 8.23 (d, J = 4.4 Hz, 1H), 8.14-8.22 (m, 2H), 7.58-7.64 (m, 1H), 7.42-7.51 (m, 1H). MS(M+1): 613. 白色固體。

【0325】化合物 6-43

N-(1-(3-氯苯基)-6-(6-(2-甲氧基乙氧基)吡啶-3-基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2 -甲醯胺

(N-(1-(3-chlorophenyl)-6-(6-(2-methoxyethoxy)pyridin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

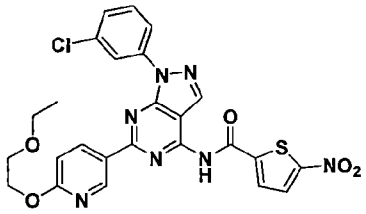


^{1}H NMR (400MHz, DMSO-d_6): δ 11.88 (br. s., 1H), 9.18 (d, J = 2.0 Hz, 1H), 8.60 (dd, J = 8.8, 2.4 Hz, 1H), 8.56 (s, 1H), 8.26-8.38 (m, 3H), 8.23 (d, J = 4.4 Hz, 1H), 7.63 (t, J = 8.3 Hz, 1H), 7.38-7.47 (m, 1H), 6.99 (d, J = 8.8 Hz, 1H), 4.43-4.53 (m, 2H), 3.65-3.78 (m, 2H), 3.34 (s, 3H). MS(M+1): 552. 淺黃色固體。

【0326】化合物 6-44

N-(1-(3-氯苯基)-6-(6-(2-乙氧基乙氧基)吡啶-3-基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2 -甲醯胺

(N-(1-(3-chlorophenyl)-6-(6-(2-ethoxyethoxy)pyridin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

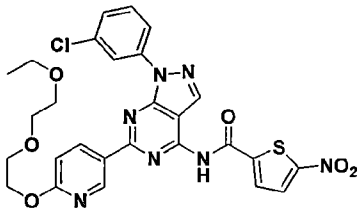


^{1}H NMR (400MHz, DMSO-d_6): δ 11.91 (br. s., 1H), 9.19 (d, J = 2.4 Hz, 1H), 8.61 (dd, J = 8.8, 2.4 Hz, 1H), 8.56 (s, 1H), 8.28 - 8.37 (m, 3H), 8.23 (d, J = 4.4 Hz, 1H), 7.63 (t, J = 8.3 Hz, 1H), 7.41-7.49 (m, 1H), 7.00 (d, J = 8.8 Hz, 1H), 4.46 (dd, J = 5.6, 4.2 Hz, 2H), 3.70-3.79 (m, 2H), 3.52 (q, J = 6.8 Hz, 2H), 1.14 (t, J = 7.1 Hz, 3H). MS(M+1): 566. 淺黃色固體。

【0327】化合物 6-45

N-(1-(3-氯苯基)-6-(6-(2-(2-乙氧基乙氧基)乙氧基)吡啶-3-基)-1H-吡唑並[3,4-d]嘧啶-4-基)- 5-硝基噻吩-2-甲醯胺

(N-(1-(3-chlorophenyl)-6-(6-(2-(2-ethoxyethoxy)ethoxy)pyridin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

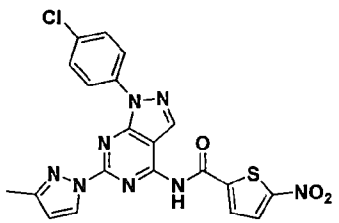


^{1}H NMR (400MHz, DMSO-d_6): δ 11.80 (br. s., 1H), 9.12 (d, J = 2.4 Hz, 1H), 8.40- 8.59 (m, 2H), 8.13-8.40 (m, 4H), 7.51-7.69 (m, 1H), 7.33-7.49 (m, 1H), 6.95 (d, J = 8.8 Hz, 1H), 4.38- 4.50 (m, 2H), 3.74-3.83 (m, 2H), 3.57-3.63 (m, 2H), 3.48-3.54 (m, 2H), 3.44 (q, J = 6.8 Hz, 2H), 1.10 (t, J = 7.1 Hz, 3H). MS(M+1): 610. 褐色固體。

【0328】化合物 6-46

N-(1-(4-氯苯基)-6-(3-甲基-1H-吡唑-1-基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2- 甲醯胺

(N-(1-(4-chlorophenyl)-6-(3-methyl-1H-pyrazol-1-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

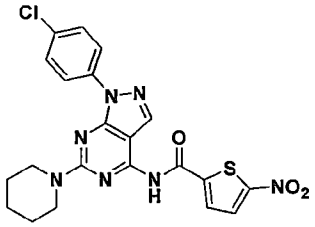


^{1}H NMR (400MHz, DMSO-d_6): δ 12.34 (br. s., 1H), 8.56-8.73 (m, 2H), 8.20-8.41 (m, 4H), 7.65-7.73 (m, 2H), 6.44-6.52 (m, 1H), 2.32-2.36 (m, 3H). MS(M+1): 481. 黃色固體。

【0329】化合物 6-47

N-(1-(4-氯苯基)-6-(哌啶-1-基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(1-(4-chlorophenyl)-6-(piperidin-1-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

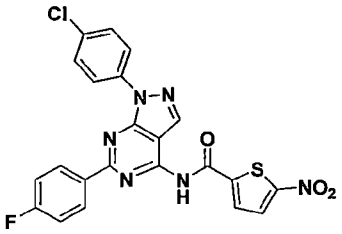


^{1}H NMR (400MHz, DMSO-d_6): δ 11.49 (br. s., 1H), 8.27-8.34 (m, 2H), 8.19-8.27 (m, 3H), 7.58-7.65 (m, 2H), 3.89 (d, J = 5.4 Hz, 4H), 1.64-1.72 (m, 2H), 1.53-1.64 (m, 4H). MS(M+1): 484. 橘色固體。

【0330】化合物 6-48

N-(1-(4-氯苯基)-6-(4-氟苯基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

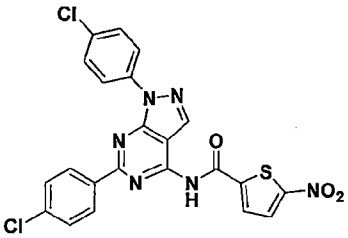
(N-(1-(4-chlorophenyl)-6-(4-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)



^{1}H NMR (400MHz, DMSO-d_6): δ 8.64 (s, 1H), 8.54-8.63 (m, 2H), 8.29-8.41 (m, 3H), 8.26 (d, J = 4.4 Hz, 1H), 7.71 (d, J = 8.8 Hz, 2H), 7.43 (t, J = 8.8 Hz, 2H). MS(M+1): 495. 黃橘色固體。

【0331】化合物 6-49

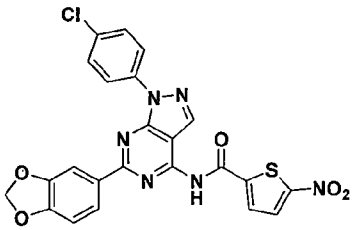
N-(1,6-雙(4-氯苯基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺 (N-(1,6-bis(4-chlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)



^{1}H NMR (400MHz, DMSO-d_6): δ 12.14 (br. s., 1H), 8.65 (s, 1H), 8.55 (d, J = 8.3 Hz, 2H), 8.34 (d, J = 8.8 Hz, 3H), 8.25 (d, J = 4.4 Hz, 1H), 7.71 (d, J = 8.8 Hz, 2H), 7.66 (d, J = 8.3 Hz, 2H), MS(M+1): 511.卡其色固體。

【0332】化合物 6-50

N-(6-(苯並[d] [1,3]二氧雜-5-基)-1-(4-氯苯基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩 -2-甲醯胺 (N-(6-(benzo[d][1,3]dioxol-5-yl)-1-(4-chlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

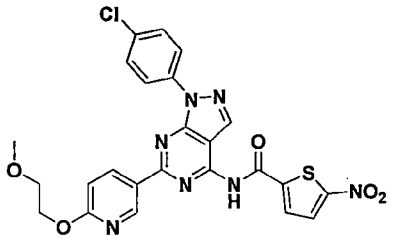


^{1}H NMR (400MHz, DMSO-d_6): δ 11.94 (br. s., 1H), 8.62 (s, 1H), 8.33-8.38 (m, 3H), 8.23 (d, J = 4.4 Hz, 1H), 8.18 (dd, J = 8.3, 2.0 Hz, 1H), 8.02 (d, J = 2.0 Hz, 1H), 7.65-7.75 (m, 2H), 7.09 (d, J = 8.3 Hz, 1H), 6.15 (s, 2H). MS(M+1):521. 淺橘色固體。

【0333】化合物 6-51

N-(1-(4-氯苯基)-6-(6-(2-甲氧基乙氧基)吡啶-3-基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2 -甲醯胺

(N-(1-(4-chlorophenyl)-6-(6-(2-methoxyethoxy)pyridin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

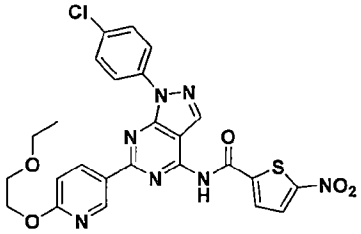


^{1}H NMR (400MHz, DMSO-d_6): δ 11.97 (br. s., 1H), 9.27 (d, J = 2.0 Hz, 1H), 8.69 (dd, J = 8.8, 2.4 Hz, 1H), 8.60 (s, 1H), 8.29-8.39 (m, 3H), 8.25 (d, J = 4.4 Hz, 1H), 7.66-7.75 (m, 2H), 7.01 (d, J = 8.3 Hz, 1H), 4.48 (dd, J = 5.6, 3.7 Hz, 2H), 3.66-3.77 (m, 2H), 3.32 (s, 3H). MS(M+1):552.卡其色固體。

【0334】化合物 6-52

N-(1-(4-氯苯基)-6-(6-(2-乙氧基乙氧基)吡啶-3-基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2 -甲醯胺

(N-(1-(4-chlorophenyl)-6-(6-(2-ethoxyethoxy)pyridin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

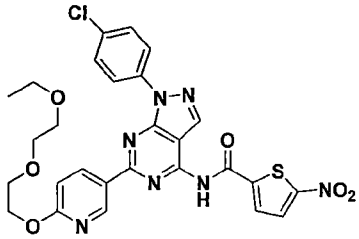


^{1}H NMR (400MHz, DMSO-d_6): δ 11.92 (br. s., 1H), 9.23 (d, J = 2.4 Hz, 1H), 8.65 (dd, J = 8.8, 2.4 Hz, 1H), 8.57 (s, 1H), 8.28-8.37 (m, 3H), 8.24 (d, J = 4.4 Hz, 1H), 7.61-7.72 (m, 2H), 6.99 (d, J = 8.8 Hz, 1H), 4.37-4.50 (m, 2H), 3.69-3.80 (m, 2H), 3.52 (q, J = 7.2 Hz, 2H), 1.08-1.19 (m, 3H). MS(M+1): 566. 卡其色固體。

【0335】 化合物 6-53

N-(1-(4-氯苯基)-6-(6-(2-(2-乙氧基乙氧基)乙氧基)吡啶-3-基)-1H-吡唑並[3,4-d]嘧啶-4-基)- 5-硝基噻吩-2-甲醯胺

(N-(1-(4-chlorophenyl)-6-(6-(2-(2-ethoxyethoxy)ethoxy)pyridin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

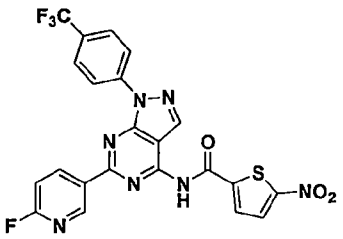


^{1}H NMR (400MHz, DMSO-d_6):δ 11.91 (br. s., 1H), 9.23 (d, J = 2.0 Hz, 1H), 8.64 (dd, J = 8.3, 2.4 Hz, 1H), 8.56 (s, 1H), 8.26-8.39 (m, 3H), 8.23 (d, J = 4.4 Hz, 1H), 7.60-7.71 (m, 2H), 6.98 (d, J = 8.3 Hz, 1H), 4.42-4.52 (m, 2H), 3.74-3.84 (m, 2H), 3.58-3.66 (m, 2H), 3.49-3.55 (m, 2H), 3.44 (q, J = 6.8 Hz, 2H), 1.07-1.13 (m, 3H). MS (M+1):610. 褐色固體。

【0336】 化合物 6-54

N-(6-(6-氟吡啶-3-基)-1-(4-(三氟甲基)苯基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(6-(6-fluoropyridin-3-yl)-1-(4-(trifluoromethyl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

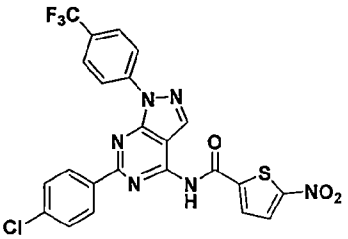


^{1}H NMR (400MHz, DMSO-d_6):δ 12.08 (s, 1H), 9.38 (s, 1H), 8.94-9.07 (m, 1H), 8.73 (s, 1H), 8.57-8.66 (m, J = 8.3 Hz, 2H), 8.40 (d, J = 4.4 Hz, 1H), 8.20-8.17 (d, J = 4.4 Hz, 1H), 7.88-7.99 (m, J = 8.3 Hz, 2H), 7.33 (d, J = 7.3 Hz, 1H). MS(M+1):530. 白褐色固體。

【0337】化合物 6-55

N-(6-(4-氯苯基)-1-(4-(三氟甲基)苯基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(6-(4-chlorophenyl)-1-(4-(trifluoromethyl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

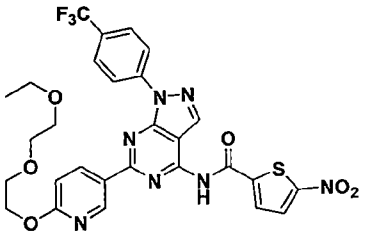


^{1}H NMR (400MHz, DMSO-d_6): δ 12.12 (br. s., 1H), 8.70 (s, 2H), 8.59 (t, J = 7.8 Hz, 3H), 8.37 (br. s., 1H), 8.27 (br. s., 1H), 8.02 (d, J = 7.8 Hz, 2H), 7.67 (d, J = 8.3 Hz, 2H). MS(M+1):545. 薰衣草色固體。

【0338】化合物 6-56

N-(6-(6-(2-(2-乙氧基乙氧基)乙氧基)吡啶-3-基)-1-(4-(三氟甲基)苯基)-1H-吡唑並[3,4-d]嘧啶-4- yl)-5-硝基噻吩-2-甲醯胺

(N-(6-(6-(2-(2-ethoxyethoxy)ethoxy)pyridin-3-yl)-1-(4-(trifluoromethyl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

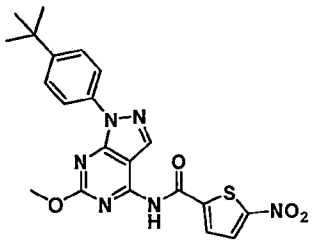


^{1}H NMR (400MHz, DMSO-d_6): δ 11.98 (br. s., 1H), 9.29 (br. s., 1H), 8.71 (d, J = 7.8 Hz, 1H), 8.64 (s, 1H), 8.54-8.63 (m, J = 7.8 Hz, 2H), 8.35 (d, J = 3.9 Hz, 1H), 8.25 (d, J = 3.9 Hz, 1H), 7.93-8.06 (m, J = 7.8 Hz, 2H), 7.01 (d, J = 8.8 Hz, 1H), 4.48 (br. s., 2H), 3.79 (br. s., 2H), 3.57-3.62 (m, 2H), 3.50-3.54 (m, 2H), 3.44 (d, J = 6.8 Hz, 2H), 1.10 (t, J = 6.8 Hz, 3H). MS(M+1):644. 黃色固體。

【0339】化合物 6-57

N-(1-(4-(叔丁基)苯基)-6-甲氧基-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(1-(4-(tert-butyl)phenyl)-6-methoxy-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

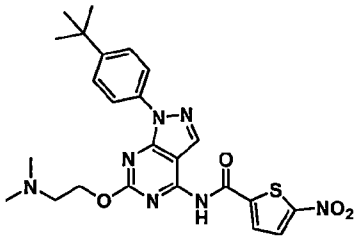


^{1}H NMR (400MHz, DMSO-d_6): δ 12.14 (br. s., 1H), 8.50 (s, 1H), 8.33 (d, J = 4.4 Hz, 1H), 8.21 (d, J = 4.4 Hz, 1H), 8.08-8.14 (m, J = 8.8 Hz, 2H), 7.56-7.63 (m, J = 8.8 Hz, 2H), 4.05 (s, 3H), 1.34 (s, 9H). MS (M+1) : 453. 淺黃色固體。

【0340】化合物 6-58

N-(1-(4-(叔丁基)苯基)-6-(2-(二甲基胺基)乙氧基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2- 甲醯胺

(N-(1-(4-(tert-butyl)phenyl)-6-(2-(dimethylamino)ethoxy)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

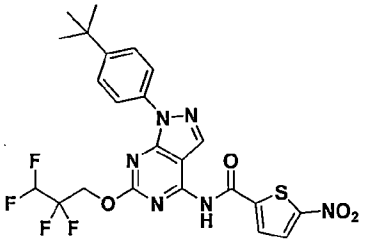


^{1}H NMR (400MHz, DMSO-d_6): δ 12.14 (br. s., 1H), 9.58 (br. s., 1H), 8.55 (s, 1H), 8.32 (d, J = 4.4 Hz, 1H), 8.24 (d, J = 4.4 Hz, 1H), 8.03-8.10 (m, J = 8.8 Hz, 2H), 7.57-7.63 (m, J = 8.8 Hz, 2H), 4.78 (dd, J = 5.6, 4.2 Hz, 2H), 3.58-3.66 (m, 2H), 2.89 (s, 6H), 1.35 (s, 9H). MS (M+1) : 510. 黃色固體。

【0341】化合物 6-59

N-(1-(4-(叔丁基)苯基)-6-(2,2,3,3-四氟丙氧基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩 -2-甲醯胺

(N-(1-(4-(tert-butyl)phenyl)-6-(2,2,3,3-tetrafluoropropoxy)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

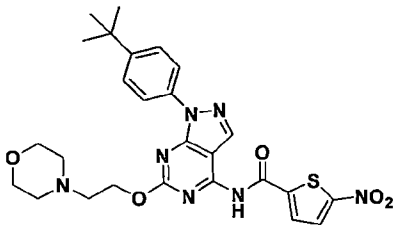


^{1}H NMR (400MHz, DMSO-d_6): δ 12.24 (s, 1H), 8.58 (s, 1H), 8.34 (d, J = 4.4 Hz, 1H), 8.23 (d, J = 4.4 Hz, 1H), 8.03-8.09 (m, J = 8.3 Hz, 2H), 7.57-7.63 (m, J = 8.8 Hz, 2H), 6.68 (t, J = 5.4 Hz, 1H), 5.03 (t, J = 13.9 Hz, 2H), 1.35 (s, 9H). MS(M+1):553.

【0342】化合物 6-60

N-(1-(4-(叔丁基)苯基)-6-(2-嗎啉基乙氧基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(1-(4-(tert-butyl)phenyl)-6-(2-morpholinoethoxy)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

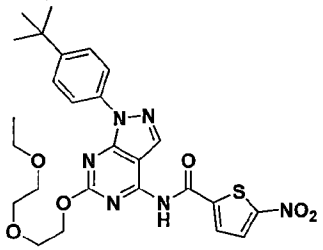


^{1}H NMR (400MHz, DMSO-d_6): δ 8.51 (s, 1H), 8.32 (d, J = 4.4 Hz, 1H), 8.22 (d, J = 4.4 Hz, 1H), 8.04-8.11 (m, J = 8.8 Hz, 2H), 7.56-7.62 (m, J = 8.8 Hz, 2H), 4.55 (t, J = 5.6 Hz, 2H), 3.52-3.58 (m, 4H), 2.76 (t, J = 5.6 Hz, 2H), 1.34 (s, 9H). MS(M+1):552.

【0343】化合物 6-61

N-(1-(4-(叔丁基)苯基)-6-(2-(2-乙氧基乙氧基)乙氧基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩- 2-甲醯胺

(N-(1-(4-(tert-butyl)phenyl)-6-(2-(2-ethoxyethoxy)ethoxy)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

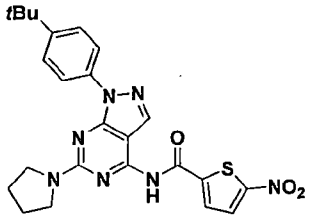


^{1}H NMR (400MHz, DMSO-d_6): δ 12.11 (br. s., 1H), 8.51 (s, 1H), 8.32 (d, J = 4.9 Hz, 1H), 8.21 (d, J = 4.4 Hz, 1H), 8.05-8.10 (m, J = 8.8 Hz, 2H), 7.56-7.61 (m, J = 8.8 Hz, 2H), 4.52-4.59 (m, 2H), 3.79-3.85 (m, 2H), 3.57-3.63 (m, 2H), 3.46-3.51 (m, 2H), 3.41 (q, J = 7.2 Hz, 2H), 1.34 (s, 9H), 1.04-1.10 (m, 3H). MS(M+1):555.淺綠色固體。

【0344】化合物 6-62

N-(1-(4-(叔丁基)苯基)-6-(吡咯烷基-1-基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(1-(4-(tert-butyl)phenyl)-6-(pyrrolidin-1-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

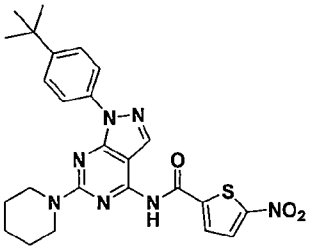


^{1}H NMR (400MHz, DMSO-d_6): δ 8.20-8.28 (m, J = 8.8 Hz, 2H), 8.04 (d, J = 4.4 Hz, 1H), 8.02 (s, 1H), 7.61 (d, J = 3.9 Hz, 1H), 7.46-7.52 (m, J = 8.8 Hz, 2H), 3.58 (t, J = 6.6 Hz, 4H), 1.89-1.99 (m, 4H), 1.32 (s, 9H). MS(M+1):492.

【0345】化合物 6-63

N-(1-(4-(叔丁基)苯基)-6-(哌啶-1-基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(1-(4-(tert-butyl)phenyl)-6-(piperidin-1-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

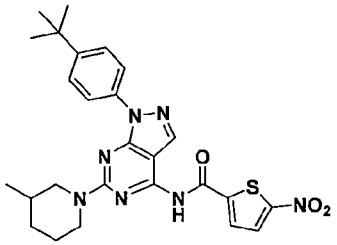


^{1}H NMR (400MHz, DMSO-d_6): δ 11.46 (br. s., 1H), 8.29 (d, J = 4.4 Hz, 1H), 8.26 (s, 1H), 8.23 (d, J = 4.4 Hz, 1H), 8.06-8.15 (m, 2H), 7.49-7.60 (m, 2H), 3.89 (d, J = 4.9 Hz, 4H), 1.66 (br. s., 2H), 1.53-1.64 (m, 4H), 1.33 (s, 9H). MS(M+1):506.

【0346】化合物 6-64

N-(1-(4-(叔丁基)苯基)-6-(3-甲基哌啶-1-基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2 -甲醯胺

(N-(1-(4-(tert-butyl)phenyl)-6-(3-methylpiperidin-1-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

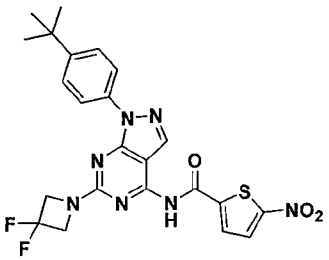


^{1}H NMR (400MHz, DMSO-d_6): δ 11.45 (s, 1H), 8.20-8.32 (m, 3H), 8.06-8.16 (m, 2H), 7.49 - 7.62 (m, 2H), 4.68 (d, J = 12.7 Hz, 2H), 3.01 (t, J = 11.7 Hz, 1H), 2.64 -2.79 (m, 1H), 1.82 (d, J = 12.2 Hz, 1H), 1.67-1.79 (m, 1H), 1.61 (dd, J = 10.5, 3.7 Hz, 1H), 1.47 (q, J = 12.2 Hz, 1H), 1.14-1.29 (m, 1H), 0.96 (d, J = 6.4 Hz, 3H). MS(M+1) : 520.

【0347】化合物 6-65

N-(1-(4-(叔丁基)苯基)-6-(3,3-二氟氮雜環丁烷-1-基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩 -2-甲醯胺

(N-(1-(4-(tert-butyl)phenyl)-6-(3,3-difluoroazetidin-1-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

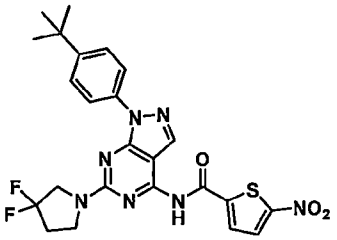


^{1}H NMR (400MHz, DMSO-d_6): δ 11.90 (s, 1H), 8.34 (s, 1H), 8.31 (d, J = 4.4 Hz, 1H), 8.20 (d, J = 4.9 Hz, 1H), 8.06-8.12 (m, J = 8.8 Hz, 2H), 7.51-7.58 (m, J = 8.8 Hz, 2H), 4.60 (t, J = 12.5 Hz, 4H), 1.33 (s, 9H). MS(M+1):514.

【0348】化合物 6-66

N-(1-(4-(叔丁基)苯基)-6-(3,3-二氟吡咯烷-1-基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩 -2-甲醯胺

(N-(1-(4-(tert-butyl)phenyl)-6-(3,3-difluoropyrrolidin-1-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)



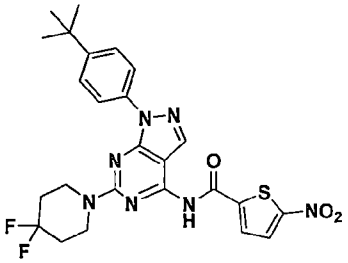
^{1}H NMR (400MHz, DMSO-d_6): δ 11.62 (br. s., 1H), 8.28-8.33 (m, 2H), 8.23 (d, J = 4.9 Hz, 1H), 8.13-8.19 (m, J = 8.8 Hz, 2H), 7.53-7.60 (m, J = 8.8 Hz, 2H), 4.06 (t, J = 13.0 Hz, 2H), 3.88 (t, J = 7.3 Hz, 2H), 2.59 (tt, J = 14.3, 7.2 Hz, 2H), 1.34 (s, 9H).

MS (M+1) : 528. 黃色固體。

【0349】化合物 6-67

N-(1-(4-(叔丁基)苯基)-6-(4,4-二氟哌啶-1-基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩 -2-甲醯胺

(N-(1-(4-(tert-butyl)phenyl)-6-(4,4-difluoropiperidin-1-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

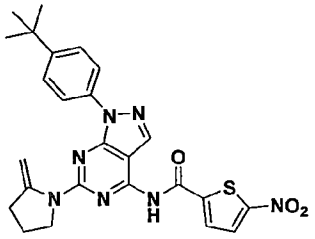


^{1}H NMR (400MHz, DMSO-d_6): δ 11.56 (br. s., 1H), 8.32 (s, 1H), 8.30 (d, J = 4.4 Hz, 1H), 8.23 (d, J = 4.4 Hz, 1H), 8.09 (d, J = 8.8 Hz, 2H), 7.57 (d, J = 8.8 Hz, 2H), 4.03 (t, J = 5.4 Hz, 4H), 1.99-2.17 (m, 4H), 1.34 (s, 9H). MS(M+1):542. 黃色固體。

【0350】化合物 6-68

N-(1-(4-(叔丁基)苯基)-6-(2-亞甲基吡咯烷-1-基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2 -甲醯胺

(N-(1-(4-(tert-butyl)phenyl)-6-(2-methylenepyrrolidin-1-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)



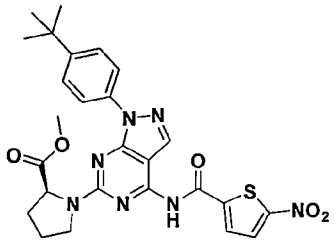
^{1}H NMR (400MHz, DMSO-d_6): δ 8.55 (s, 1H), 8.12 (d, J = 4.4 Hz, 1H), 7.87-8.00 (m, J = 8.3 Hz, 2H), 7.78 (d, J = 4.4 Hz, 1H), 7.53-7.61 (m, J = 8.8 Hz, 2H), 4.39-4.52 (m, 1H), 4.27-4.37 (m, 1H), 4.14-4.26 (m, 1H), 3.61-3.75 (m, 1H), 2.06-2.19 (m, 1H), 2.02 (br. s., 1H), 1.85-1.99 (m, 1H), 1.57-1.74 (m, 1H), 1.33 (s, 9H).

MS(M+1):504.黃色固體。

【0351】化合物 6-69

(1-(4-(叔丁基)苯基)-4-(5-硝基噻吩-2-甲醯胺基)-1H-吡唑並[3,4-d]嘧啶-6-基)-L-脯胺酸甲酯

(methyl(1-(4-(tert-butyl)phenyl)-4-(5-nitrothiophene-2-carboxamido)-1H-pyrazolo[3,4-d]pyrimidin-6-yl)-L-prolinate)



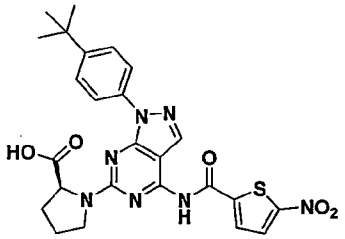
^{1}H NMR (400MHz, DMSO-d_6): δ 11.64 (br. s., 1H), 8.21-8.35 (m, 3H), 8.03-8.13 (m, J = 8.8 Hz, 2H), 7.46-7.60 (m, 2H), 4.57 (dd, J = 8.6, 3.7 Hz, 1H), 3.82 (br. s., 2H), 3.61-3.68 (m, 3H), 2.40 (br. s., 1H), 2.03 (d, J = 3.4 Hz, 3H), 1.34 (s, 9H).

MS(M+1):550. 黃色固體。

【0352】化合物 6-70

(1-(4-(叔丁基)苯基)-4-(5-硝基噻吩-2-甲醯胺基)-1H-吡唑並[3,4-d]嘧啶-6-基)-L-脯胺酸

((1-(4-(tert-butyl)phenyl)-4-(5-nitrothiophene-2-carboxamido)-1H-pyrazolo[3,4-d]pyrimidin-6-yl)-L-proline)

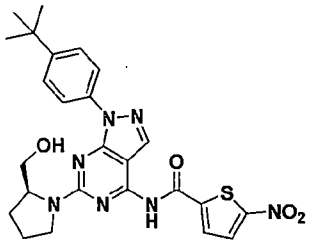


^{1}H NMR (400MHz, DMSO-d_6): δ 12.63 (br. s., 1H), 11.63 (br. s., 1H), 8.12-8.36 (m, 5H), 7.39-7.62 (m, 2H), 4.48 (dd, J = 8.6, 3.7 Hz, 1H), 3.80 (t, J = 5.4 Hz, 2H), 3.61-3.74 (m, 1H), 2.25-2.45 (m, 2H), 1.87-2.16 (m, 3H), 1.33 (s, 9H). MS(M+1):536 黃色固體。

【0353】化合物 6-71

(S)-N-(1-(4-(叔丁基)苯基)-6-(2-(羥甲基)吡咯烷-1-基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

((S)-N-(1-(4-(tert-butyl)phenyl)-6-(2-(hydroxymethyl)pyrrolidin-1-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

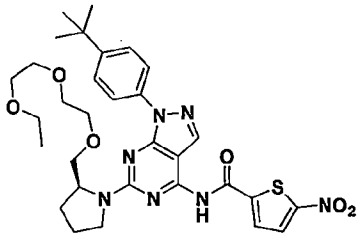


^{1}H NMR (400MHz, DMSO-d_6): δ 11.48 (br. s., 1H), 8.15-8.38 (m, 5H), 7.54 (d, J = 9.3 Hz, 2H), 4.77 (br. s., 1H), 4.26 (br. s., 1H), 3.53-3.83 (m, 4H), 1.84-2.14 (m, 4H), 1.33 (s, 9H). MS(M+1):522. 黃色固體。

【0354】化合物 6-72

(S)-N-(1-(4-(叔丁基)苯基)-6-(2-((2-(2-乙氧基乙氧基)乙氧基)甲基)吡咯烷-1-基)-1H-吡唑並[3 ，4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

((S)-N-(1-(4-(tert-butyl)phenyl)-6-(2-((2-(2-ethoxyethoxy)ethoxy)methyl)pyrrolidin-1-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

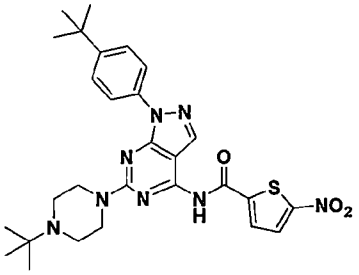


^{1}H NMR (400MHz, DMSO-d_6): δ 11.51 (br. s., 1H), 8.28 (br. s., 1H), 8.24 (s, 1H), 8.21 (d, J = 3.9 Hz, 1H), 8.12-8.19 (m, J = 8.3 Hz, 2H), 7.46-7.57 (m, J = 8.3 Hz, 2H), 4.36 (br. s., 1H), 3.78 (br. s., 1H), 3.63 (br. s., 3H), 3.53 (br. s., 3H), 3.44-3.50 (m, 3H), 3.42 (d, J = 4.9 Hz, 2H), 3.37 (q, J = 7.0 Hz, 2H), 2.03 (br. s., 3H), 1.92 (br. s., 1H), 1.33 (s, 9H), 1.05 (t, J = 7.1 Hz, 3H). MS(M+1):638. 橘色固體。

【0355】化合物 6-73

N-(1-(4-(叔丁基)苯基)-6-(4-(叔丁基)哌嗪-1-基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(1-(4-(tert-butyl)phenyl)-6-(4-(tert-butyl)piperazin-1-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

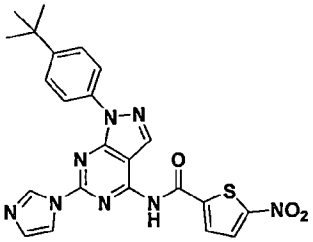


^{1}H NMR (400MHz, DMSO-d_6):δ 11.68 (br. s., 1H), 8.31-8.37 (m, 2H), 8.23 (d, J = 4.4 Hz, 1H), 8.06-8.12 (m, 2H), 7.49-7.60 (m, 2H), 4.91 (d, J = 11.7 Hz, 2H), 3.65 (br. s., 4H), 3.06 (d, J = 8.8 Hz, 2H), 1.38 (br. s., 9H), 1.34 (s, 9H). MS(M+1):563. 黃色固體。

【0356】化合物 6-74

N-(1-(4-(叔丁基)苯基)-6-(1H-咪唑-1-基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2 -甲醯胺

(N-(1-(4-(tert-butyl)phenyl)-6-(1H-imidazol-1-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

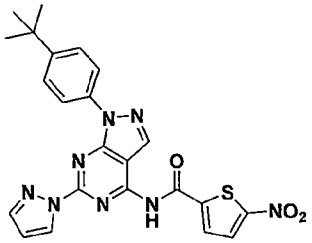


^{1}H NMR (400MHz, DMSO-d_6): δ 12.16 (br. s., 1H), 8.69 (s, 1H), 8.64 (s, 1H), 8.34 (d, J = 4.4 Hz, 1H), 8.26 (d, J = 4.4 Hz, 1H), 8.11-8.18 (m, J = 8.8 Hz, 2H), 8.05 (t, J = 1.2 Hz, 1H), 7.61-7.68 (m, J = 8.8 Hz, 2H), 7.19 (s, 1H), 1.36 (s, 9H). MS(M+1):489 黃色固體。

【0357】 化合物 6-75

N-(1-(4-(叔丁基)苯基)-6-(1H-吡唑-1-基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2 -甲醯胺

(N-(1-(4-(tert-butyl)phenyl)-6-(1H-pyrazol-1-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

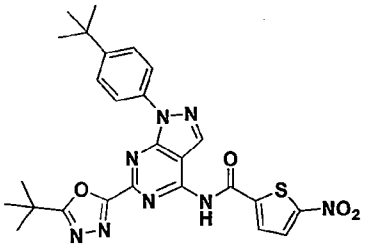


^{1}H NMR (400MHz, DMSO-d_6): δ 8.81 (br. s., 1H), 8.51 (br. s., 1H), 8.14-8.24 (m, J = 8.8 Hz, 2H), 8.09 (br. s., 1H), 7.74 (br. s., 2H), 7.55-7.67 (m, J = 8.3 Hz, 2H), 6.65 (br. s., 1H), 1.36 (s, 9H). MS(M+1):489. 黃色固體。

【0358】 化合物 6-76

N-(6-(5-(叔丁基)-1,3,4-噁二唑-2-基)-1-(4-(叔丁基)苯基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(6-(5-(tert-butyl)-1,3,4-oxadiazol-2-yl)-1-(4-(tert-butyl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

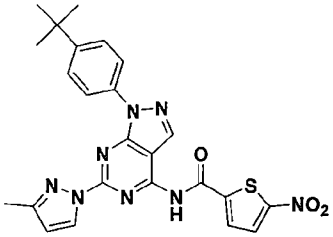


^{1}H NMR (400MHz, DMSO-d_6): δ 12.52 (s, 1H), 8.68 (s, 1H), 8.36 (br. s., 1H), 8.23 (d, J = 4.4 Hz, 1H), 8.01-8.19 (m, J = 8.8 Hz, 2H), 7.55-7.77 (m, J = 8.3 Hz, 2H), 1.48 (s, 9H), 1.36 (s, 9H). MS(M+1):547. 白色固體。

【0359】化合物 6-77

N-(1-(4-(叔丁基)苯基)-6-(3-甲基-1H-吡唑-1-基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5 -硝基噻吩-2-甲醯胺

(N-(1-(4-(tert-butyl)phenyl)-6-(3-methyl-1H-pyrazol-1-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

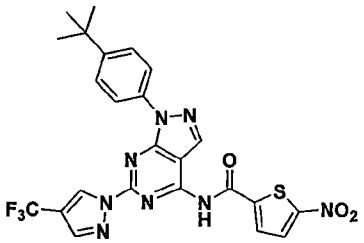


^{1}H NMR (400MHz, DMSO-d_6): δ 12.31 (br. s., 1H), 8.65 (d, J = 2.9 Hz, 1H), 8.56 (s, 1H), 8.35 (d, J = 4.4 Hz, 1H), 8.23 (d, J = 4.4 Hz, 1H), 7.90-8.15 (m, 2H), 7.44-7.69 (m, 2H), 6.47 (d, J = 2.4 Hz, 1H), 2.33 (s, 3H), 1.36 (s, 9H). MS(M+1): 503. 黃色固體。

【0360】化合物 6-78

N-(1-(4-(叔丁基)苯基)-6-(4-(三氟甲基)-1H-吡唑-1-基)-1H-吡唑並[3,4-d]嘧啶-4-基) -5-硝基噻吩-2-甲醯胺

(N-(1-(4-(tert-butyl)phenyl)-6-(4-(trifluoromethyl)-1H-pyrazol-1-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

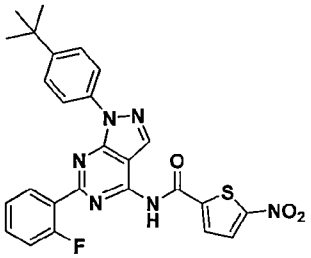


^{1}H NMR (400MHz, DMSO-d_6): δ 12.33 (br. s., 1H), 9.25 (s, 1H), 8.66 (s, 1H), 8.37 (s, 1H), 8.21-8.31 (m, 2H), 8.11-8.19 (m, 2H), 7.61-7.69 (m, 2H), 1.37 (s, 9H). MS(M+1) :557.

【0361】化合物 6-79

N-(1-(4-(叔丁基)苯基)-6-(2-氟苯基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(1-(4-(tert-butyl)phenyl)-6-(2-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

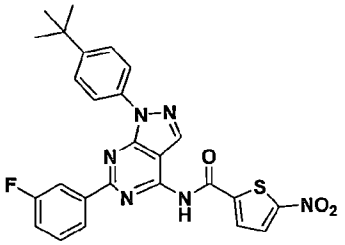


^{1}H NMR (400MHz, DMSO-d_6): δ 12.17 (br. s., 1H), 8.64 (s, 1H), 8.36 (d, J = 4.4 Hz, 1H), 8.13-8.31 (m, 4H), 7.55-7.68 (m, 3H), 7.35-7.47 (m, 2H), 1.35 (s, 9H). MS(M+1):517.

【0362】化合物 6-80

N-(1-(4-(叔丁基)苯基)-6-(3-氟苯基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(1-(4-(tert-butyl)phenyl)-6-(3-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

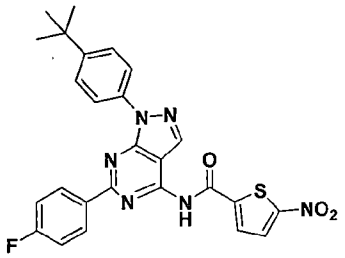


^{1}H NMR (400MHz, DMSO-d_6): δ 12.03 (br. s., 1H), 8.53 - 8.66 (m, 3H), 8.36 (d, J = 4.4 Hz, 1H), 8.26 (d, J = 4.4 Hz, 1H), 8.12-8.23 (m, 2H), 7.60-7.71 (m, 2H), 7.39-7.49 (m, 2H), 1.37 (s, 9H). MS(M+1):517.

【0363】化合物 6-81

N-(1-(4-(叔丁基)苯基)-6-(4-氟苯基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(1-(4-(tert-butyl)phenyl)-6-(4-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

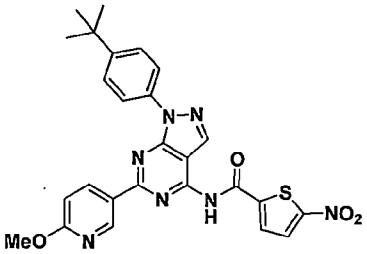


^{1}H NMR (400MHz, DMSO-d_6): δ 12.00 (br. s., 1H), 8.63 (s, 1H), 8.33-8.42 (m, 2H), 8.21-8.29 (m, 2H), 8.14-8.21 (m, 2H), 7.60-7.69 (m, 3H), 7.37-7.47 (m, 1H), 1.37 (s, 9H). MS(M+1):517.

【0364】化合物 6-82

N-(1-(4-(叔丁基)苯基)-6-(6-甲氧基吡啶-3-基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2 -甲醯胺

(N-(1-(4-(tert-butyl)phenyl)-6-(6-methoxypyridin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

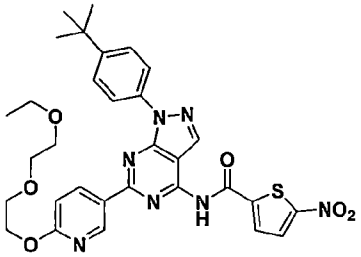


^{1}H NMR (400MHz, DMSO-d_6): δ 11.90 (d, J = 6.3 Hz, 1H), 9.52-9.24 (m ,1H), 8.66-8.53 (m, 2H), 8.34-8.14 (m, 4H), 7.61 (d, J = 6.8 Hz, 2H), 6.99-6.96 (m, 1H), 3.94 (s, 3H), 1.35 (s, 9H). MS(M+1): 530. 黃褐色固體。

【0365】 化合物 6-83

N-(1-(4-(叔丁基)苯基)-6-(6-(2-(2-乙氧基乙氧基)乙氧基)吡啶-3-基)-1H-吡唑並[3,4-d]嘧啶- 4-基)-5-硝基噻吩-2-甲醯胺

(N-(1-(4-(tert-butyl)phenyl)-6-(6-(2-(2-ethoxyethoxy)ethoxy)pyridin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

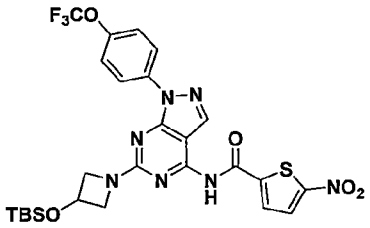


^{1}H NMR (400MHz, DMSO-d_6): δ 11.92 (br. s., 1H), 9.25 (d, J = 2.0 Hz, 1H), 8.67 (dd, J = 8.8, 2.4 Hz, 1H), 8.56 (s, 1H), 8.34 (d, J = 4.4 Hz, 1H), 8.23 (d, J = 4.4 Hz, 1H), 8.08-8.20 (m, 2H), 7.57-7.69 (m, 2H), 7.01 (d, J = 8.8 Hz, 1H), 4.47 (dd, J = 5.6, 4.2 Hz, 2H), 3.78 (dd, J = 5.4, 3.9 Hz, 2H), 3.56-3.64 (m, 2H), 3.47-3.53 (m, 2H), 3.43 (q, J = 6.8 Hz, 2H), 1.36 (s, 9H), 1.10 (t, J = 7.1 Hz, 3H). MS(M+1):632.白色固體。

【0366】 化合物 6-84

N-(6-(3-((叔丁基二甲基甲矽烷基)氧基)氮雜環丁烷-1-基)-1-(4-(三氟甲氧基)苯基)-1H-吡唑並[3,4-d]嘧啶-4-基 -5-硝基噻吩-2-甲醯胺

(N-(6-(3-((tert-butyldimethylsilyl)oxy)azetidin-1-yl)-1-(4-(trifluoromethoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

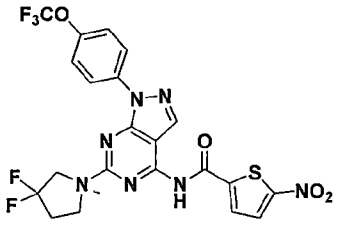


^{1}H NMR (400MHz, DMSO-d_6):δ 11.75 (br. s., 1H), 8.33-8.42 (m, 2H), 8.27-8.33 (m, 2H), 8.21 (d, J = 4.4 Hz, 1H), 7.55 (d, J = 8.3 Hz, 2H), 4.74-4.87 (m, 1H), 4.44 (dd, J = 9.8, 6.4 Hz, 2H), 3.93 (dd, J = 9.8, 4.4 Hz, 2H), 0.82-0.96 (m, 9H), 0.05-0.13 (m, 6H). MS(M+1):636.

【0367】化合物 6-85

N-(6-(3,3-二氟吡咯烷-1-基)-1-(4-(三氟甲氧基)苯基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2 -甲醯胺

(N-(6-(3,3-difluoropyrrolidin-1-yl)-1-(4-(trifluoromethoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

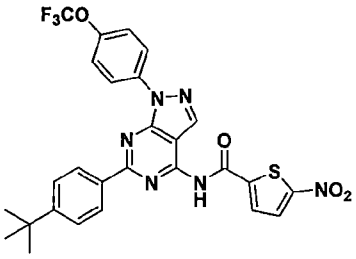


^{1}H NMR (400MHz, DMSO-d_6): δ 11.65 (br. s., 1H), 8.40 (d, J = 9.3 Hz, 2H), 8.35 (s, 1H), 8.31 (d, J = 4.4 Hz, 1H), 8.22 (d, J = 4.4 Hz, 1H), 7.55 (d, J = 8.8 Hz, 2H), 4.06 (t, J = 13.2 Hz, 2H), 3.88 (t, J = 7.3 Hz, 2H), 2.52-2.68 (m, 2H). MS(M+1):556.

【0368】化合物 6-86

N-(6-(4-(叔丁基)苯基)-1-(4-(三氟甲氧基)苯基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2- 甲醯胺

(N-(6-(4-(tert-butyl)phenyl)-1-(4-(trifluoromethoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)



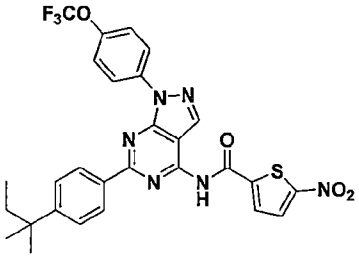
^{1}H NMR (400MHz, DMSO-d_6): δ 12.06 (br. s., 1H), 8.62 (s, 1H), 8.43-8.55 (m, 4H), 8.38 (d, J = 4.4 Hz, 1H), 8.25 (d, J = 4.4 Hz, 1H), 7.54-7.73 (m, 4H), 1.35 (s, 9H).

MS(M+1):583.

【0369】化合物 6-87

5-硝基-N-(6-(4-(叔戊基)苯基)-1-(4-(三氟甲氧基)苯基)-1H-吡唑並[3,4-d]嘧啶-4-基)噻吩-2 -甲醯胺

(5-nitro-N-(6-(4-(tert-pentyl)phenyl)-1-(4-(trifluoromethoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)thiophene-2-carboxamide)



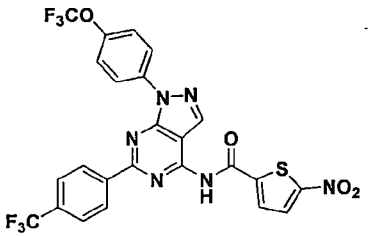
^{1}H NMR (400MHz, DMSO-d_6):δ 12.04 (br. s., 1H), 8.63 (s, 1H), 8.42-8.51 (m, 4H), 8.38 (d, J = 4.4 Hz, 1H), 8.25 (d, J = 4.4 Hz, 1H), 7.65 (d, J = 8.3 Hz, 2H), 7.55 (d, J = 8.3 Hz, 2H), 1.69 (q, J = 7.3 Hz, 2H), 1.32 (s, 6H), 0.67 (t, J = 7.3 Hz, 3H).

MS(M+1) :597.

【0370】化合物 6-88

5-硝基-N-(1-(4-(三氟甲氧基)苯基)-6-(4-(三氟甲基)苯基)-1H-吡唑並[3,4-d]嘧啶-4-基)噻吩-2-甲醯胺

(5-nitro-N-(1-(4-(trifluoromethoxy)phenyl)-6-(4-(trifluoromethyl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)thiophene-2-carboxamide)

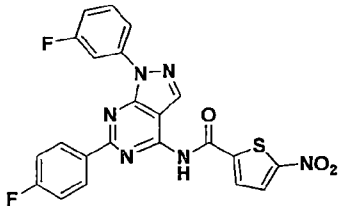


^{1}H NMR (400MHz, DMSO-d_6):δ 12.15 (br. s., 1H), 8.70-8.78 (m, J = 7.8 Hz, 2H), 8.68 (s, 1H), 8.40-8.48 (m, 2H), 8.38 (d, J = 4.4 Hz, 1H), 8.26 (d, J = 4.4 Hz, 1H), 7.91-8.00 (m, J = 8.3 Hz, 2H), 7.65 (d, J = 8.3 Hz, 2H). MS(M+1):595. 淺黃色固體。

【0371】化合物 6-89

N-(1-(3-氟苯基)-6-(4-氟苯基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(1-(3-fluorophenyl)-6-(4-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

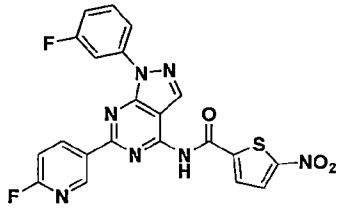


^{1}H NMR (400MHz, DMSO-d_6): δ 11.99 (br. s., 1H), 8.43-8.64 (m, 3H), 8.35 (d, J = 4.4 Hz, 1H), 8.07-8.29 (m, 3H), 7.58-7.77 (m, 1H), 7.41 (t, J = 8.8 Hz, 2H), 7.12-7.35 (m, 1H). MS(M+1):479. 淺黃色固體。

【0372】化合物 6-90

N-(1-(3-氟苯基)-6-(6-氟吡啶-3-基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(1-(3-fluorophenyl)-6-(6-fluoropyridin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

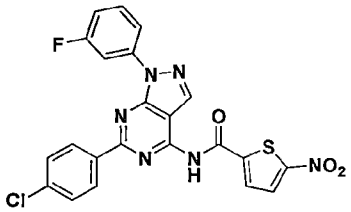


^{1}H NMR (400MHz, DMSO-d_6) :δ 11.97 (br. s., 1H), 9.21 (d, J = 2.4 Hz, 1H), 8.84 (td, J = 8.1, 2.4 Hz, 1H), 8.54-8.64 (m, 1H), 8.28 (d, J = 4.4 Hz, 1H), 8.19-8.24 (m, 1H), 8.17 (dd, J = 8.3, 1.5 Hz, 1H), 8.06 (dt, J = 11.0, 2.1 Hz, 1H), 7.63 (td, J = 8.3, 6.4 Hz, 1H), 7.38 (dd, J = 8.6, 2.7 Hz, 1H), 7.22 (td, J = 8.6, 2.4 Hz, 1H). MS(M+1): 480. 淺黃色固體。

【0373】化合物 6-91

N-(6-(4-氯苯基)-1-(3-氟苯基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(6-(4-chlorophenyl)-1-(3-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

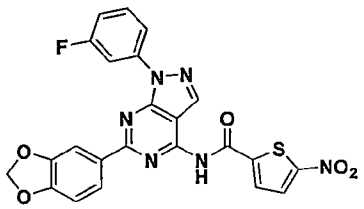


^{1}H NMR (400MHz, DMSO-d_6): δ 11.99 (br. s., 1H), 8.61 (s, 1H), 8.45-8.51 (m, 2H), 8.36 (d, J = 4.4 Hz, 1H), 8.24 (d, J = 4.4 Hz, 1H), 8.18 (dd, J = 8.3, 1.5 Hz, 1H), 8.11 (dt, J = 10.8, 2.4 Hz, 1H), 7.60-7.70 (m, 3H), 7.19-7.29 (m, 1H). MS(M+1):495. 黃綠色固體。

【0374】化合物 6-92

N-(6-(苯並[d] [1,3]二氧雜-5-基)-1-(3-氟苯基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩 -2-甲醯胺

(N-(6-(benzo[d][1,3]dioxol-5-yl)-1-(3-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

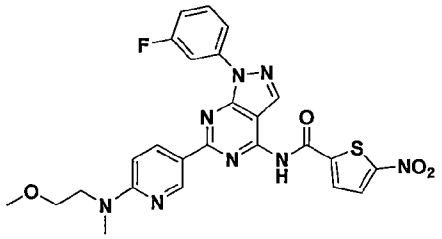


^{1}H NMR (400MHz, DMSO-d_6): δ 11.84 (s, 1H), 8.56 (s, 1H), 8.34 (d, J = 4.4 Hz, 1H), 8.23 (d, J = 4.4 Hz, 1H), 8.16-8.21 (m, 1H), 8.07-8.15 (m, 2H), 7.93 (d, J = 1.5 Hz, 1H), 7.65 (td, J = 8.3, 6.8 Hz, 1H), 7.23 (td, J = 8.1, 2.4 Hz, 1H), 7.09 (d, J = 8.3 Hz, 1H), 6.14 (s, 2H). MS(M+1):505. 黃色固體。

【0375】化合物 6-93

N-(1-(3-氟苯基)-6-(6-((2-甲氧基乙基)(甲基)胺基)吡啶-3-基)-1H-吡唑並[3,4-d]嘧啶-4-基) -5-硝基噻吩-2-甲醯胺

(N-(1-(3-fluorophenyl)-6-(6-((2-methoxyethyl)(methyl)amino)pyridin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

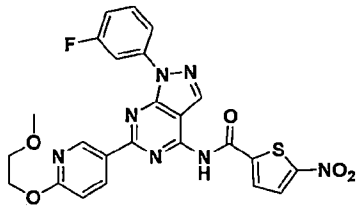


^{1}H NMR (400MHz, DMSO-d_6):δ 11.86 (br. s., 1H), 9.20 (d, J = 2.4 Hz, 1H), 8.54 (s, 1H), 8.45 (dd, J = 9.0, 2.2 Hz, 1H), 8.35 (d, J = 4.4 Hz, 1H), 8.20-8.26 (m, 2H), 8.16 (dt, J = 10.9, 2.4 Hz, 1H), 7.66 (td, J = 8.3, 6.8 Hz, 1H), 7.18-7.26 (m, 1H), 6.79 (d, J = 9.3 Hz, 1H), 3.80 (t, J = 5.6 Hz, 2H), 3.56 (t, J = 5.6 Hz, 2H), 3.28 (s, 3H), 3.13 (s, 3H). MS(M+1): 549. 橘色固體。

【0376】化合物 6-94

N-(1-(3-氟苯基)-6-(6-(2-甲氧基乙氧基)吡啶-3-基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2 -甲醯胺

(N-(1-(3-fluorophenyl)-6-(6-(2-methoxyethoxy)pyridin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

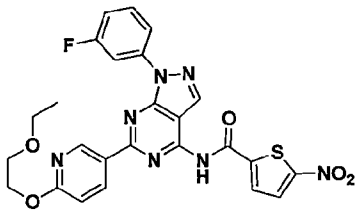


^{1}H NMR (400MHz, DMSO-d_6): δ 12.00 (br. s., 1H), 9.25 (d, J = 1.5 Hz, 1H), 8.66 (dd, J = 8.8, 2.4 Hz, 1H), 8.61 (s, 1H), 8.36 (d, J = 4.4 Hz, 1H), 8.20-8.26 (m, 2H), 8.13 (dt, J = 10.9, 2.4 Hz, 1H), 7.67 (td, J = 8.3, 6.8 Hz, 1H), 7.20-7.29 (m, 1H), 7.03 (d, J = 8.8 Hz, 1H), 4.43-4.52 (m, 2H), 3.65-3.73 (m, 2H), 3.33 (s, 3H). MS(M+1):536. 亮黃色固體。

【0377】化合物 6-95

N-(6-(6-(2-乙氧基乙氧基)吡啶-3-基)-1-(3-氟苯基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2 -甲醯胺

(N-(6-(6-(2-ethoxyethoxy)pyridin-3-yl)-1-(3-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

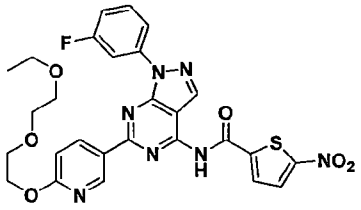


^{1}H NMR (400MHz, DMSO-d_6): δ 11.96 (br. s., 1H), 9.23 (d, J = 2.4 Hz, 1H), 8.65 (dd, J = 8.8, 2.4 Hz, 1H), 8.59 (s, 1H), 8.33 (d, J = 4.4 Hz, 1H), 8.18-8.26 (m, 2H), 8.12 (dt, J = 10.9, 2.4 Hz, 1H), 7.66 (td, J = 8.3, 6.4 Hz, 1H), 7.24 (td, J = 8.2, 2.2 Hz, 1H), 7.03 (d, J = 8.8 Hz, 1H), 4.47 (dd, J = 5.4, 3.9 Hz, 2H), 3.74 (dd, J = 5.4, 3.9 Hz, 2H), 3.52 (q, J = 7.2 Hz, 2H), 1.10-1.19 (m, 3H). MS(M+1):550. 黃色固體。

【0378】化合物 6-96

N-(6-(6-(2-(2-乙氧基乙氧基)乙氧基)吡啶-3-基)-1-(3-氟苯基)-1H-吡唑並[3,4-d]嘧啶-4-基)- 5-硝基噻吩-2-甲醯胺

(N-(6-(6-(2-(2-ethoxyethoxy)ethoxy)pyridin-3-yl)-1-(3-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

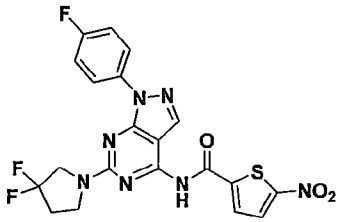


^{1}H NMR (400MHz, DMSO-d_6) :δ 11.80 (br. s., 1H), 9.12 (d, J = 2.4 Hz, 1H), 8.55 (dd, J = 8.8, 2.4 Hz, 1H), 8.49 (s, 1H), 8.11-8.35 (m, 4H), 7.49-7.64 (m, 1H), 7.32-7.41 (m, 1H), 6.95 (d, J = 8.8 Hz, 1H), 4.37-4.50 (m, 2H), 3.69-3.85 (m, 2H), 3.56-3.64 (m, 2H), 3.48- 3.54 (m, 2H), 3.44 (q, J = 6.8 Hz, 2H), 1.10 (t, J = 7.1 Hz, 3H). MS(M+1): 594. 黃色固體。

【0379】化合物 6-97

N-(6-(3,3-二氟吡咯烷-1-基)-1-(4-氟苯基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(6-(3,3-difluoropyrrolidin-1-yl)-1-(4-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)



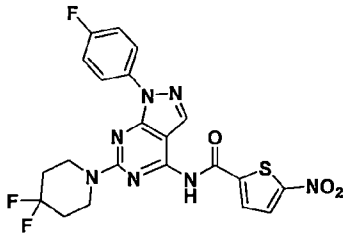
^{1}H NMR (400MHz, DMSO-d_6):δ 11.65 (br. s., 1H), 8.15-8.41 (m, 5H), 7.27-7.46 (m, 2H), 4.05 (t, J = 13.0 Hz, 2H), 3.88 (t, J = 7.3 Hz, 2H), 2.54-2.68 (m, 2H).

MS(M+1):490.

【0380】化合物 6-98

N-(6-(4,4-二氟哌啶-1-基)-1-(4-氟苯基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(6-(4,4-difluoropiperidin-1-yl)-1-(4-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

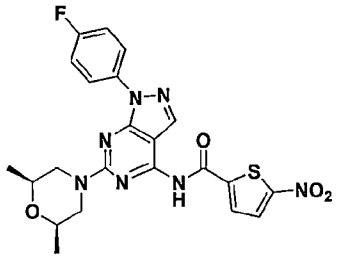


^{1}H NMR (400MHz, DMSO-d_6): δ 11.57 (s, 1H), 8.27-8.37 (m, 2H), 8.12-8.27 (m, 3H), 7.29-7.45 (m, 2H), 4.03 (t, J = 5.6 Hz, 4H), 1.95-2.16 (m, 4H). MS(M+1):504.

【0381】化合物 6-99

N-(6-((2S,6R)-2,6-二甲基嗎啉基)-1-(4-氟苯基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2- 甲醯胺

(N-(6-((2S,6R)-2,6-dimethylmorpholino)-1-(4-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

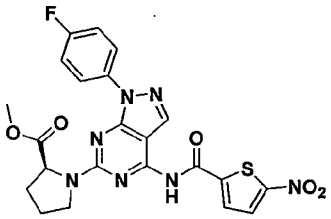


^{1}H NMR (400MHz, DMSO-d_6): δ 11.50 (s, 1H), 8.26-8.37 (m, 2H), 8.10-8.26 (m, 3H), 7.23-7.53 (m, 2H), 4.63 (d, J = 10.8 Hz, 2H), 3.61 (ddd, J = 10.6, 6.2, 2.7 Hz, 2H), 2.65 (dd, J = 13.2, 10.8 Hz, 2H), 1.09-1.28 (m, 6H). MS(M+1):498. 深黃色固體。

【0382】化合物 6-100

(1-(4-氟苯基)-4-(5-硝基噻吩-2-甲醯胺基)-1H-吡唑並[3,4-d]嘧啶-6-基)-L-脯胺酸甲酯(methyl

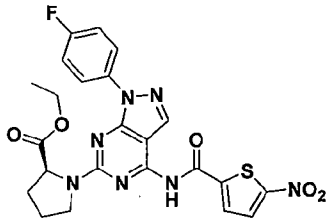
(1-(4-fluorophenyl)-4-(5-nitrothiophene-2-carboxamido)-1H-pyrazolo[3,4-d]pyrimidin-6-yl)-L-prolinate)



^{1}H NMR (400MHz, DMSO-d_6): δ 11.65 (br. s., 1H), 8.15-8.34 (m, 5H), 7.30-7.44 (m, 2H), 4.56 (dd, J = 8.6, 3.7 Hz, 1H), 3.81 (t, J = 6.1 Hz, 2H), 3.64 (s, 3H), 2.28-2.46 (m, 1H), 1.88-2.14 (m, 3H). MS(M+1):512. 黃色固體。

【0383】化合物 6-101

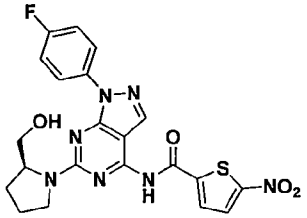
(1-(4-氟苯基)-4-(5-硝基噻吩-2-甲醯胺基)-1H-吡唑並[3,4-d]嘧啶-6-基)-L-脯胺酸乙酯(ethyl (1-(4-fluorophenyl)-4-(5-nitrothiophene-2-carboxamido)-1H-pyrazolo[3,4-d] pyrimidin-6-yl)-L-prolinate)



^{1}H NMR (400MHz, DMSO-d_6): δ 11.60 (br. s., 1H), 8.13-8.36 (m, 5H), 7.26-7.44 (m, 2H), 4.58 (dd, J = 8.3, 3.4 Hz, 1H), 3.94-4.19 (m, 2H), 3.65-3.90 (m, 2H), 2.29-2.47 (m, 1H), 2.02 (d, J = 3.4 Hz, 3H), 1.04-1.22 (m, 3H). MS(M+1):526. 橘色固體。

【0384】化合物 6-102

(S)-N-(1-(4-氟苯基)-6-(2-(羥甲基)吡咯烷-1-基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩 -2-甲醯胺 ((S)-N-(1-(4-fluorophenyl)-6-(2-(hydroxymethyl)pyrrolidin-1-yl)-1H-pyrazolo[3,4-d] pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

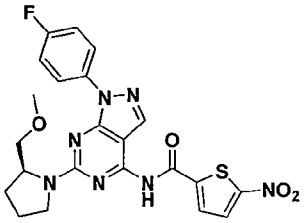


^{1}H NMR (400MHz, DMSO-d_6): δ 11.54 (br. s., 1H), 8.24-8.35 (m, 4H), 8.22 (d, J = 4.4 Hz, 1H), 7.37 (t, J = 8.8 Hz, 2H), 4.26 (br. s., 1H), 3.51-3.80 (m, 5H), 1.85-2.15 (m, 4H). MS(M+1):484. 黃色固體。

【0385】化合物 6-103

(S)-N-(1-(4-氟苯基)-6-(2-(甲氧基甲基)吡咯烷-1-基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩 -2-甲醯胺

((S)-N-(1-(4-fluorophenyl)-6-(2-(methoxymethyl)pyrrolidin-1-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

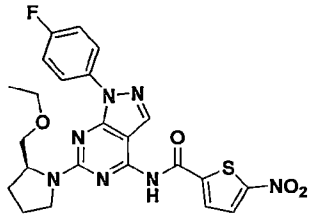


^{1}H NMR (400MHz, DMSO-d_6): δ 11.51 (br. s., 1H), 8.23-8.33 (m, 4H), 8.20 (d, J = 4.4 Hz, 1H), 7.35 (t, J = 8.8 Hz, 2H), 4.35 (br. s., 1H), 3.52-3.76 (m, 3H), 3.39-3.49 (m, 1H), 2.02 (br. s., 3H), 1.78-1.97 (m, 1H). MS(M+1):498. 黃色固體。

【0386】化合物 6-104

(S)-N-(6-(2-(乙氧基甲基)吡咯烷-1-基)-1-(4-氟苯基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩 -2-甲醯胺

((S)-N-(6-(2-(ethoxymethyl)pyrrolidin-1-yl)-1-(4-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

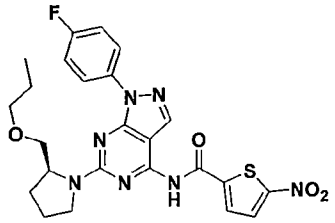


^{1}H NMR (400MHz, DMSO-d_6): δ 11.52 (br. s., 1H), 8.23-8.38 (m, 4H), 8.19-8.23 (m, 1H), 7.35 (t, J = 8.1 Hz, 2H), 4.36 (br. s., 1H), 3.72 (d, J = 7.8 Hz, 1H), 3.63 (br. s., 2H), 3.38-3.56 (m, 3H), 2.03 (br. s., 3H), 1.92 (d, J = 6.4 Hz, 1H), 1.11 (t, J = 7.1 Hz, 3H). MS(M+1):512. 黃色固體。

【0387】化合物 6-105

(S)-N-(1-(4-氟苯基)-6-(2-(丙氧基甲基)吡咯烷-1-基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩 -2-甲醯胺

((S)-N-(1-(4-fluorophenyl)-6-(2-(propoxymethyl)pyrrolidin-1-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

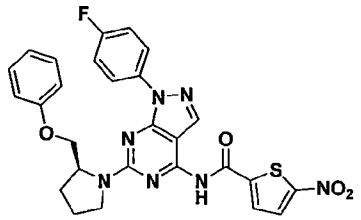


^{1}H NMR (400MHz, DMSO-d_6): δ 11.51 (br. s., 1H), 8.16-8.36 (m, 5H), 7.25-7.43 (m, 2H), 4.25-4.46 (m, 1H), 3.71 (dd, J = 9.0, 2.7 Hz, 1H), 3.63 (br. s., 2H), 3.33-3.51 (m, 3H), 1.96-2.15 (m, 3H), 1.92 (br. s., 1H), 1.43-1.56 (m, 2H), 0.85 (t, J = 7.3 Hz, 3H). MS(M+1):526.橘色固體。

【0388】化合物 6-106

(S)-N-(1-(4-氟苯基)-6-(2-(苯氧基甲基)吡咯烷-1-基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩 -2-甲醯胺

((S)-N-(1-(4-fluorophenyl)-6-(2-(phenoxymethyl)pyrrolidin-1-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

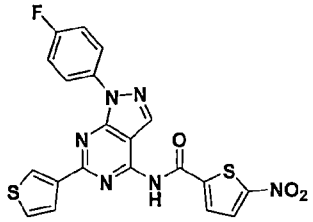


^{1}H NMR (400MHz, DMSO-d_6): δ 11.51 (br. s., 1H), 8.27 (s, 2H), 8.20 (d, J = 3.9 Hz, 2H), 7.37 (br. s., 1H), 7.20-7.29 (m, 2H), 7.06 (br. s., 1H), 6.97 (d, J = 7.8 Hz, 2H), 6.91 (t, J = 6.8 Hz, 1H), 4.41 (br. s., 1H), 4.32 (d, J = 4.9 Hz, 1H), 4.06 (t, J = 8.6 Hz, 1H), 3.71 (br. s., 2H), 2.14 (br. s., 3H), 1.99 (br. s., 1H). MS(M+1):560. 黃色固體。

【0389】化合物 6-107

N-(1-(4-氟苯基)-6-(噻吩-3-基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(1-(4-fluorophenyl)-6-(thiophen-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

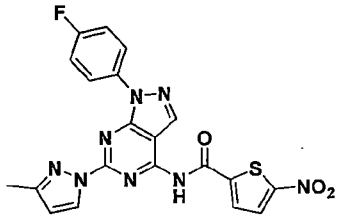


^{1}H NMR (400MHz, DMSO-d_6): δ 12.03 (s, 1H), 8.57 (s, 1H), 8.52-8.51 (m, 1H), 8.36 (d, J = 7.8 Hz, 1H), 8.35-8.29 (m, 2H), 8.24 (d, J = 8.8 Hz, 1H), 7.96-7.94 (m, 1H), 7.73-7.71 (m, 1H), 7.48-7.43 (m, 2H). MS(M+1): 467. 黃色固體。

【0390】化合物 6-108

N-(1-(4-氟苯基)-6-(3-甲基-1H-吡唑-1-基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2- 甲醯胺

(N-(1-(4-fluorophenyl)-6-(3-methyl-1H-pyrazol-1-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

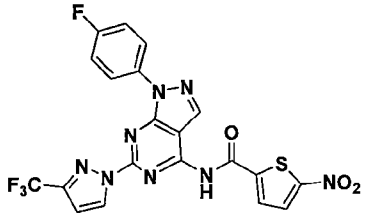


^{1}H NMR (400MHz, DMSO-d_6): δ 12.33 (br. s., 1H), 8.66 (d, J = 2.4 Hz, 1H), 8.59 (s, 1H), 8.36 (d, J = 4.4 Hz, 1H), 8.15-8.33 (m, 3H), 7.34-7.58 (m, 2H), 6.48 (d, J = 2.4 Hz, 1H), 2.33 (s, 3H). MS(M+1): 465. 黃色固體。

【0391】化合物 6-109

N-(1-(4-氟苯基)-6-(3-(三氟甲基)-1H-吡唑-1-基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩- 2-甲醯胺

(N-(1-(4-fluorophenyl)-6-(3-(trifluoromethyl)-1H-pyrazol-1-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

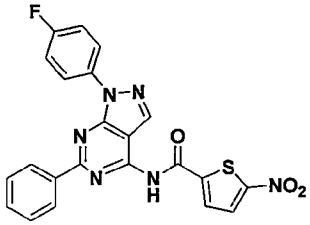


^{1}H NMR (400MHz, DMSO-d_6): δ 12.47 (s, 1H), 8.91-9.06 (m, 1H), 8.67 (s, 1H), 8.39 (d, J = 4.4 Hz, 1H), 8.14-8.29 (m, 3H), 7.37-7.55 (m, 2H), 7.15 (d, J = 2.9 Hz, 1H). MS(M+1):519. 淺黃色固體。

【0392】化合物 6-110

N-(1-(4-氟苯基)-6-苯基-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(1-(4-fluorophenyl)-6-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

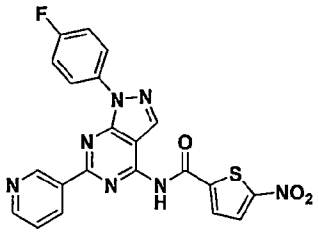


^{1}H NMR (400MHz, DMSO-d_6): δ 12.02 (br. s., 1H), 8.62 (s, 1H), 8.44-8.59 (m, 2H), 8.16-8.44 (m, 4H), 7.55-7.69 (m, 3H), 7.40-7.55 (m, 2H). MS(M+1):461.

【0393】化合物 6-111

N-(1-(4-氟苯基)-6-(吡啶-3-基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(1-(4-fluorophenyl)-6-(pyridin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

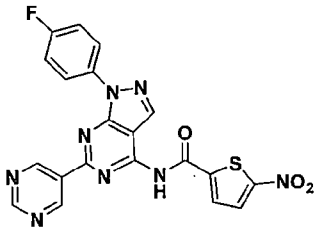


^{1}H NMR (400MHz, DMSO-d_6): δ 12.08 (br. s., 1H), 9.65-9.69 (m, 1H), 8.77-8.81 (m, 1H), 8.74-8.77 (m, 1H), 8.65 (s, 1H), 8.37 (d, J = 4.4 Hz, 1H), 8.28-8.34 (m, 2H), 8.26 (d, J = 4.4 Hz, 1H), 7.59-7.65 (m, 1H), 7.45-7.53 (m, 2H). MS(M+1):462. 黃色固體。

【0394】化合物 6-112

N-(1-(4-氟苯基)-6-(嘧啶-5-基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(1-(4-fluorophenyl)-6-(pyrimidin-5-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

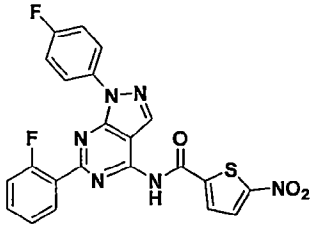


^{1}H NMR (400MHz, DMSO-d_6): δ 12.12 (br. s., 1H), 9.74 (s, 2H), 9.38 (s, 1H), 8.68 (s, 1H), 8.18-8.45 (m, 4H), 7.38 - 7.59 (m, 2H). MS(M+1): 463. 卡其色固體。

【0395】化合物 6-113

N-(6-(2-氟苯基)-1-(4-氟苯基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(6-(2-fluorophenyl)-1-(4-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

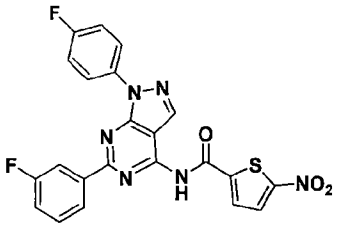


^{1}H NMR (400MHz, DMSO-d_6): δ 12.19 (br. s., 1H), 8.65 (s, 1H), 8.13-8.41 (m, 5H), 7.54-7.67 (m, 1H), 7.33-7.54 (m, 4H). MS(M+1):479. 白色固體。

【0396】化合物 6-114

N-(6-(3-氟苯基)-1-(4-氟苯基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(6-(3-fluorophenyl)-1-(4-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

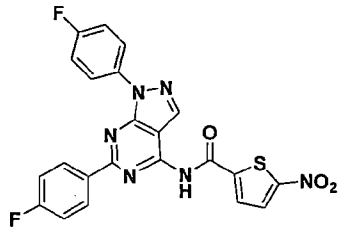


^{1}H NMR (400MHz, DMSO-d_6): δ 11.97 (br. s., 1H), 8.61 (s, 1H), 8.14-8.39 (m, 6H), 7.62 (td, J = 8.1, 5.9 Hz, 1H), 7.36-7.55 (m, 3H). MS(M+1):479. 卡其色固體。

【0397】化合物 6-115

N-(1,6-雙(4-氟苯基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(1,6-bis(4-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

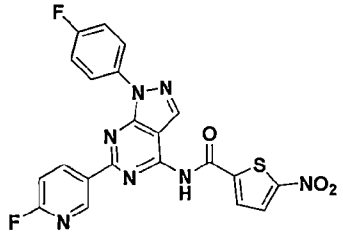


^{1}H NMR (400MHz, DMSO-d_6): δ 12.02 (br. s., 1H), 8.52-8.66 (m, 3H), 8.37 (d, J = 4.4 Hz, 1H), 8.17-8.33 (m, 3H), 7.31-7.55 (m, 4H). MS(M+1):479. 黃色固體。

【0398】化合物 6-116

N-(1-(4-氟苯基)-6-(6-氟吡啶-3-基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(1-(4-fluorophenyl)-6-(6-fluoropyridin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

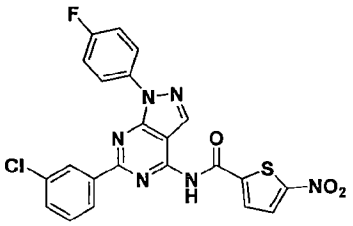


^{1}H NMR (400MHz, DMSO-d_6): δ 12.05 (s, 1H), 9.28 (s, 1H), 8.94-8.90 (m, 1H), 8.83 (d, J = 7.8 Hz, 1H), 8.63 (s, 1H), 8.39 (d, J = 8.8 Hz, 1H), 8.30-8.25 (m, 3H), 7.91-7.88 (m, 1H), 7.42-7.39 (m, 1H). MS(M+1): 480. 黃色固體。

【0399】化合物 6-117

N-(6-(3-氯苯基)-1-(4-氟苯基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(6-(3-chlorophenyl)-1-(4-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

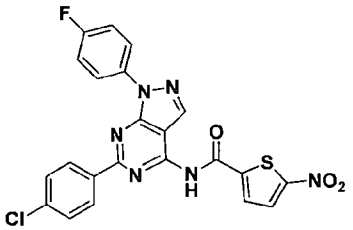


^{1}H NMR (400MHz, DMSO-d_6): δ 12.01 (s, 1H), 8.64 (s, 1H), 8.53-8.52 (m, 1H), 8.47-8.45 (m, 1H), 8.38 (d, J = 7.8 Hz, 1H), 8.29-8.26 (m, 3H), 7.67-7.60 (m, 2H), 7.51-7.47 (m, 2H). MS(M+1): 495. 黃色固體。

【0400】化合物 6-118

N-(6-(4-氯苯基)-1-(4-氟苯基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(6-(4-chlorophenyl)-1-(4-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

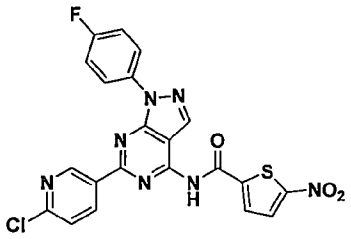


^{1}H NMR (400MHz, DMSO-d_6): δ 12.00 (br. s., 1H), 8.60 (s, 1H), 8.47-8.53 (m, 2H), 8.37 (d, J = 4.4 Hz, 1H), 8.23-8.29 (m, 3H), 7.60-7.67 (m, 2H), 7.43-7.50 (m, 2H). MS(M+1): 495. 黃色固體。

【0401】化合物 6-119

N-(6-(6-氯吡啶-3-基)-1-(4-氟苯基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(6-(6-chloropyridin-3-yl)-1-(4-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

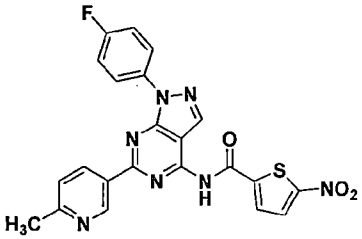


^{1}H NMR (400MHz, DMSO-d_6): δ 12.06 (br. s., 1H), 9.43 (d, J = 2.4 Hz, 1H), 8.77 (dd, J = 8.3, 2.4 Hz, 1H), 8.63 (s, 1H), 8.36 (d, J = 4.4 Hz, 1H), 8.23-8.30 (m, 3H), 7.73 (d, J = 8.3 Hz, 1H), 7.46 (t, J = 8.8 Hz, 2H). MS(M+1):496. 黃色固體。

【0402】化合物 6-120

N-(1-(4-氟苯基)-6-(6-甲基吡啶-3-基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(1-(4-fluorophenyl)-6-(6-methylpyridin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

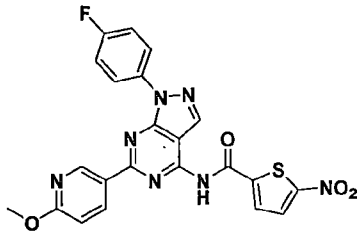


^{1}H NMR (400MHz, DMSO-d_6): δ 12.05 (br. s., 1H), 9.54 (d, J = 2.0 Hz, 1H), 8.66 (dd, J = 8.1, 2.2 Hz, 1H), 8.63 (s, 1H), 8.38 (d, J = 4.4 Hz, 1H), 8.27-8.34 (m, 2H), 8.26 (d, J = 4.4 Hz, 1H), 7.43-7.54 (m, 3H), 2.58 (s, 3H). MS(M+1): 476. 琥珀色固體。

【0403】化合物 6-121

N-(1-(4-氟苯基)-6-(6-甲氧基吡啶-3-基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(1-(4-fluorophenyl)-6-(6-methoxypyridin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

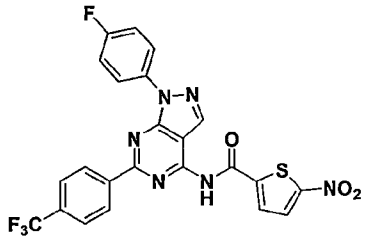


^{1}H NMR (400MHz, DMSO-d_6): δ 11.90 (s, 1H), 9.24 (d, J = 2.4 Hz, 1H), 8.63 (dd, J = 8.8, 2.4 Hz, 1H), 8.55 (s, 1H), 8.34 (d, J = 4.4 Hz, 1H), 8.28 (dd, J = 9.3, 4.9 Hz, 2H), 8.23 (d, J = 4.4 Hz, 1H), 7.44 (t, J = 8.8 Hz, 2H), 6.97 (d, J = 8.8 Hz, 1H), 3.94 (s, 3H). MS(M+1): 492. 黃色固體。

【0404】化合物 6-122

N-(1-(4-氟苯基)-6-(4-(三氟甲基)苯基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(1-(4-fluorophenyl)-6-(4-(trifluoromethyl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

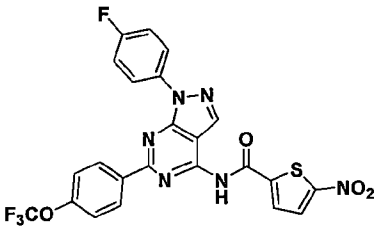


^{1}H NMR (400MHz, DMSO-d_6): δ 12.06 (s, 1H), 8.62-8.69 (m, J = 8.3 Hz, 2H), 8.60 (s, 1H), 8.37 (d, J = 4.4 Hz, 1H), 8.13-8.28 (m, 3H), 7.84-7.99 (m, J = 8.3 Hz, 2H), 7.45 (t, J = 8.8 Hz, 2H). MS(M+1):529.

【0405】化合物 6-123

N-(1-(4-氟苯基)-6-(4-(三氟甲氧基)苯基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(1-(4-fluorophenyl)-6-(4-(trifluoromethoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

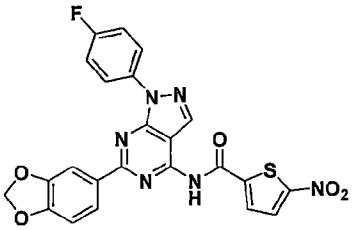


^{1}H NMR (400MHz, DMSO-d_6):δ 12.11 (br. s., 1H), 8.52-8.74 (m, 3H), 8.22-8.42 (m, 4H), 7.58 (d, J = 7.8 Hz, 2H), 7.49 (t, J = 8.8 Hz, 2H). MS(M+1):545. 黃色固體。

【0406】化合物 6-124

N-(6-(苯並[d] [1,3]二氧雜-5-基)-1-(4-氟苯基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩 -2-甲醯胺

(N-(6-(benzo[d][1,3]dioxol-5-yl)-1-(4-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

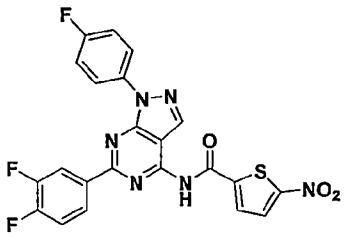


^{1}H NMR (400MHz, DMSO-d_6): δ 11.90 (br. s., 1H), 8.58 (s, 1H), 8.35 (d, J = 4.4 Hz, 1H), 8.23-8.34 (m, 3H), 8.14 (dd, J = 8.3, 1.5 Hz, 1H), 7.98 (d, J = 1.5 Hz, 1H), 7.43-7.53 (m, 2H), 7.10 (d, J = 7.8 Hz, 1H), 6.15 (s, 2H). MS(M+1): 505. 淺黃色固體。

【0407】化合物 6-125

N-(6-(3,4-二氟苯基)-1-(4-氟苯基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩 -2-甲醯胺

(N-(6-(3,4-difluorophenyl)-1-(4-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

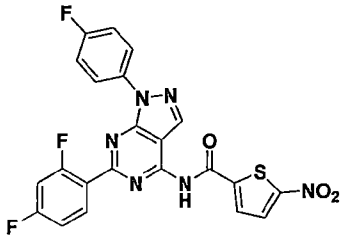


^{1}H NMR (400MHz, DMSO-d_6): δ 11.95 (br. s., 1H), 8.61 (s, 1H), 8.31-8.44 (m, 3H), 8.18-8.30 (m, 3H), 7.58-7.70 (m, 1H), 7.47 (t, J = 8.8 Hz, 2H). MS(M+1):497. 褐色固體。

【0408】化合物 6-126

N-(6-(2,4-二氟苯基)-1-(4-氟苯基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(6-(2,4-difluorophenyl)-1-(4-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

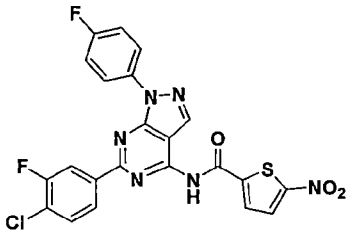


^{1}H NMR (400MHz, DMSO-d_6): δ 12.20 (br. s., 1H), 8.60 (s, 1H), 8.23-8.35 (m, 3H), 8.18-8.23 (m, 2H), 7.38-7.49 (m, 3H), 7.29 (td, J = 8.3, 2.4 Hz, 1H). MS(M+1):497. 灰白色固體。

【0409】化合物 6-127

N-(6-(4-氯-3-氟苯基)-1-(4-氟苯基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(6-(4-chloro-3-fluorophenyl)-1-(4-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

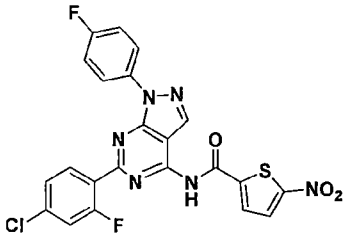


^{1}H NMR (400MHz, DMSO-d_6): δ 11.97 (br. s., 1H), 8.61 (s, 1H), 8.29-8.39 (m, 3H), 8.20-8.29 (m, 3H), 7.78 (t, J = 8.1 Hz, 1H), 7.36-7.53 (m, 2H). MS(M+1):513. 淺卡其色固體。

【0410】化合物 6-128

N-(6-(4-氯-2-氟苯基)-1-(4-氟苯基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(6-(4-chloro-2-fluorophenyl)-1-(4-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

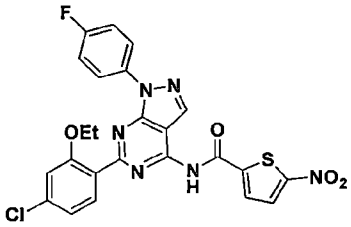


^{1}H NMR (400MHz, DMSO-d_6): δ 12.15 (br. s., 1H), 8.63 (s, 1H), 8.36 (d, J = 4.4 Hz, 1H), 8.20-8.32 (m, 4H), 7.63 (dd, J = 11.0, 2.2 Hz, 1H), 7.50 (dd, J = 8.3, 2.0 Hz, 1H), 7.39-7.48 (m, 2H). MS(M+1): 513. 黃褐色固體。

【0411】化合物 6-129

N-(6-(4-氯-2-乙氧基苯基)-1-(4-氟苯基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(6-(4-chloro-2-ethoxyphenyl)-1-(4-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

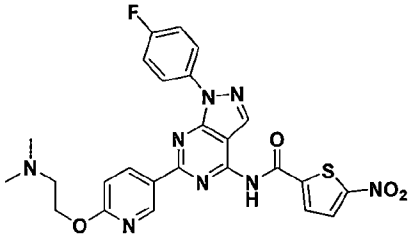


^{1}H NMR (400MHz, DMSO-d_6): δ 8.53 (s, 1H), 8.33 (dd, J = 9.0, 5.1 Hz, 2H), 7.82-8.20 (m, 3H), 7.41 (t, J = 8.8 Hz, 2H), 7.27 (s, 1H), 7.14 (d, J = 8.8 Hz, 1H), 4.19 (br. s., 2H), 1.30 (t, J = 7.1 Hz, 3H). MS(M+1): 539. 淺黃色固體。

【0412】化合物 6-130

N-(6-(6-(2-(二甲基胺基)乙氧基)吡啶-3-基)-1-(4-氟苯基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5- 硝基噻吩-2-甲醯胺

(N-(6-(6-(2-(dimethylamino)ethoxy)pyridin-3-yl)-1-(4-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

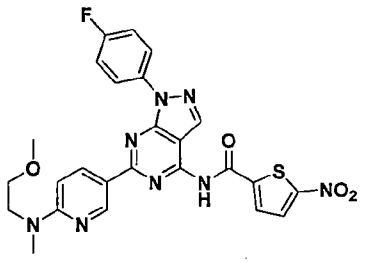


^{1}H NMR (400MHz, D_2O+DMSO-d_6) : δ 9.14 (d, J = 2.1 Hz, 1H), 8.62 (dd, J = 8.8, 2.1 Hz, 1H), 8.43 (s, 1H), 8.22 (d, J = 4.4 Hz, 1H), 8.18-8.14 (m, 2H), 8.10 (d, J = 4.4 Hz, 1H), 7.36 (t, J = 8.8 Hz, 2H), 6.99 (d, J = 8.8 Hz, 1H), 4.66-4.63 (m, 2H), 3.56-3.53 (m, 2H), 2.88 (s, 6H). MS-ESI (M+1): 549. 黃色固體。

【0413】化合物 6-131

N-(1-(4-氟苯基)-6-(6-((2-甲氧基乙基)(甲基)胺基)吡啶-3-基)-1H-吡唑並[3,4-d]嘧啶-4-基) -5-硝基噻吩-2-甲醯胺

(N-(1-(4-fluorophenyl)-6-(6-((2-methoxyethyl)(methyl)amino)pyridin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

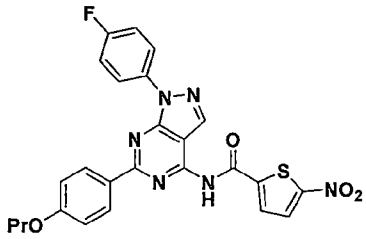


^{1}H NMR (400MHz, DMSO-d_6): δ 11.82 (br. s., 1H), 9.18 (d, J = 2.0 Hz, 1H), 8.50 (s, 1H), 8.44 (dd, J = 9.3, 2.4 Hz, 1H), 8.24-8.37 (m, 3H), 8.22 (d, J = 4.4 Hz, 1H), 7.44 (t, J = 8.8 Hz, 2H), 6.75 (d, J = 9.3 Hz, 1H), 3.78 (t, J = 5.6 Hz, 2H), 3.55 (t, J = 5.9 Hz, 2H), 3.27 (s, 3H), 3.12 (s, 3H). MS(M+1):549. 橘色固體。

【0414】化合物 6-132

N-(1-(4-氟苯基)-6-(4-丙氧基苯基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(1-(4-fluorophenyl)-6-(4-propoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

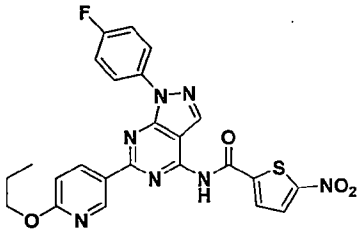


^{1}H NMR (400MHz, DMSO-d_6): δ 11.99 (br. s., 1H), 8.58 (s, 1H), 8.39 - 8.54 (m, 2H), 8.29 - 8.39 (m, 3H), 8.26 (d, J = 4.4 Hz, 1H), 7.38 - 7.65 (m, 2H), 6.99 - 7.23 (m, 2H), 4.04 (t, J = 6.6 Hz, 2H), 1.79 (tt, J = 7.0, 6.6 Hz, 2H), 1.02 (t, J = 7.0 Hz, 3H). MS(M+1): 519. 黃色固體。

【0415】化合物 6-133

N-(1-(4-氟苯基)-6-(6-丙氧基吡啶-3-基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(1-(4-fluorophenyl)-6-(6-propoxypyridin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

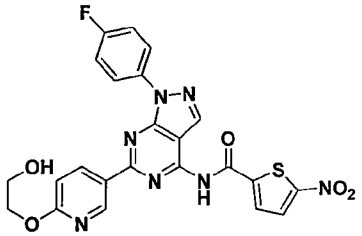


^{1}H NMR (400MHz, DMSO-d_6) : δ 11.84 (brs, 1H), 9.19 (d, J = 2.1 Hz, 1H), 8.60 (dd, J = 8.8, 2.1 Hz, 1H), 8.52 (s, 1H), 8.32 (d, J = 4.4 Hz, 1H), 8.28-8.23 (m, 2H), 8.21 (d, J = 4.4 Hz, 1H), 7.42 (t, J = 8.8 Hz, 2H), 6.92 (d, J = 8.8 Hz, 1H), 4.28 (t, J = 6.8 Hz, 2H), 1.80- 1.71 (m, 2H), 0.99 (t, J = 6.8 Hz, 3H). MS(M+1): 520. 黃色固體。

【0416】化合物 6-134

N-(1-(4-氟苯基)-6-(6-(2-羥基乙氧基)吡啶-3-基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(1-(4-fluorophenyl)-6-(6-(2-hydroxyethoxy)pyridin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

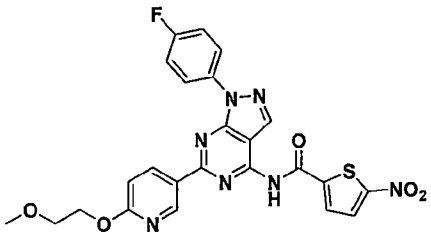


^{1}H NMR (400MHz, DMSO-d_6) : δ 9.21 (d, J = 2.0 Hz, 1H), 8.62 - 8.76 (m, 1H), 8.37 - 8.43 (m, 2H), 8.33 - 8.37 (m, 1H), 8.06 (d, J = 3.9 Hz, 1H), 7.58 (d, J = 3.9 Hz, 1H), 7.37 - 7.48 (m, 2H), 6.93 (d, J = 9.3 Hz, 1H), 4.88 (br. s., 1H), 4.30 - 4.44 (m, 2H), 3.76 (t, J = 4.9 Hz, 2H). MS(M+1): 522. 橘色固體。

【0417】化合物 6-135

N-(1-(4-氟苯基)-6-(6-(2-甲氧基乙氧基)吡啶-3-基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(1-(4-fluorophenyl)-6-(6-(2-methoxyethoxy)pyridin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

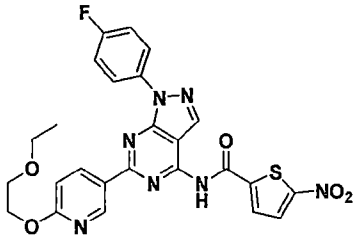


^{1}H NMR (400MHz, DMSO-d_6): δ 11.62 (s, 1H), 9.04 (d, J = 1.0 Hz, 1H), 8.45 (dd, J = 8.3, 1.8 Hz, 1H), 8.37 (s, 1H), 8.24-8.12 (m ,4H),7.32 (t, J = 8.3 Hz, 2H), 6.85 (d, J = 8.8 Hz, 1H), 4.40-4.38 (m, 2H), 3.69-3.66 (m, 2H), 3.34 (s, 3H). MS(M+1): 536. 黃色固體。

【0418】化合物 6-136

N-(6-(6-(2-乙氧基乙氧基)吡啶-3-基)-1-(4-氟苯基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(6-(6-(2-ethoxyethoxy)pyridin-3-yl)-1-(4-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

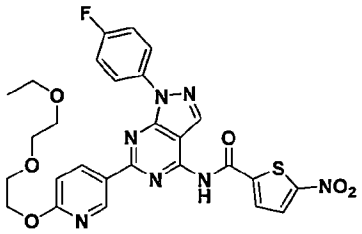


^{1}H NMR (400MHz, DMSO-d_6) : δ 11.89 (br. s., 1H), 9.21 (d, J = 2.0 Hz, 1H), 8.63 (dd, J = 8.8, 2.4 Hz, 1H), 8.54 (s, 1H), 8.18-8.38 (m, 4H), 7.34 - 7.52 (m, 2H), 6.98 (d, J = 8.3 Hz, 1H), 4.45 (dd, J = 5.6, 4.2 Hz, 2H), 3.73 (dd, J = 5.6, 4.2 Hz, 2H), 3.52 (q, J = 6.8 Hz, 2H), 1.14 (t, J = 6.8 Hz, 3H). MS(M+1): 550. 黃色固體。

【0419】化合物 6-137

N-(6-(6-(2-(2-乙氧基乙氧基)乙氧基)吡啶-3-基)-1-(4-氟苯基)-1H-吡唑並[3,4-d]嘧啶-4-基)- 5-硝基噻吩-2-甲醯胺

(N-(6-(6-(2-(2-ethoxyethoxy)ethoxy)pyridin-3-yl)-1-(4-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

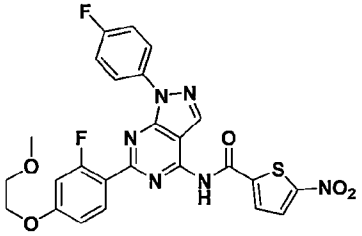


^{1}H NMR (400MHz, DMSO-d_6): δ 11.95 (s, 1H), 9.23 (d, J = 2.4 Hz, 1H), 8.66 (dd, J = 8.8, 2.4 Hz, 1H), 8.56 (s, 1H), 8.33-8.22 (m, 4H), 7.45 (t, J = 8.8 Hz, 2H), 6.99 (d, J = 8.8 Hz, 1H), 4.47-4.45 (m, 2H), 3.79-3.77 (m, 2H), 3.60-3.58 (m, 2H), 3.51-3.49 (m, 2H), 3.43 (q, J = 6.8 Hz, 2H), 1.09 (t, J = 6.8 Hz, 3H). MS(M+1): 594. 黃色固體。

【0420】化合物 6-138

N-(6-(2-氟-4-(2-甲氧基乙氧基)苯基)-1-(4-氟苯基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(6-(2-fluoro-4-(2-methoxyethoxy)phenyl)-1-(4-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

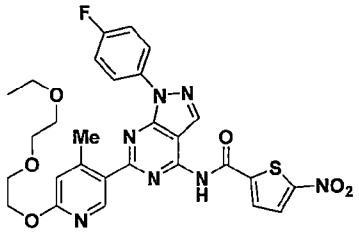


^{1}H NMR (400MHz, DMSO-d_6): δ 12.14 (br. s., 1H), 8.61 (s, 1H), 8.18-8.42 (m, 5H), 7.37-7.53 (m, 2H), 6.92-7.08 (m, 2H), 4.22 (dd, J = 5.1, 3.7 Hz, 2H), 3.62-3.76 (m, 2H), 3.33 (s, 3H). MS(M+1): 553. 亮黃色固體。

【0421】化合物 6-139

N-(6-(6-(2-(2-乙氧基乙氧基)乙氧基)-4-甲基吡啶-3-基)-1-(4-氟苯基)-1H-吡唑並[3,4-d]嘧啶-4- yl)-5-硝基噻吩-2-甲醯胺

(N-(6-(6-(2-(2-ethoxyethoxy)ethoxy)-4-methylpyridin-3-yl)-1-(4-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

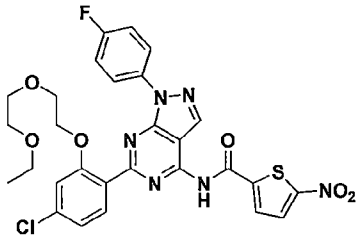


^{1}H NMR (400MHz, DMSO-d_6): δ 11.93 (s, 1H), 8.11 (s, 1H), 8.55 (s, 1H), 8.30 (d, J = 4.2 Hz, 1H), 8.19-8.15 (m, 1H), 7.42-7.38 (m, 2H), 6.79 (s, 1H), 4.43-4.41 (m, 2H), 3.77-3.74 (m, 2H), 3.60-3.57 (m, 2H), 3.51-3.49 (m, 2H), 3.43 (q, J = 6.8 Hz, 2H), 2.63(s, 3H), 1.10 (t, J = 6.8 Hz, 3H). MS(M+1): 608. 黃色固體。

【0422】化合物 6-140

N-(6-(4-氯-2-(2-(2-乙氧基乙氧基)乙氧基)苯基)-1-(4-氟苯基)-1H-吡唑並[3,4-d]嘧啶-4-基)- 5-硝基噻吩-2-甲醯胺

(N-(6-(4-chloro-2-(2-(2-ethoxyethoxy)ethoxy)phenyl)-1-(4-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

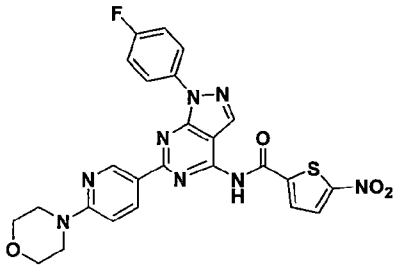


^{1}H NMR (400MHz, DMSO-d_6): δ 12.26 (br. s., 1H), 8.65 (s, 1H), 8.13-8.41 (m, 4H), 7.83 (br. s., 1H), 7.45 (t, J = 8.8 Hz, 2H), 7.37 (br. s., 1H), 7.20 (d, J = 7.3 Hz, 1H), 4.26 (br. s., 2H), 3.70 (br. s., 2H), 3.38 (br. s., 2H), 3.15-3.26 (m, 4H), 0.91 (t, J = 6.8 Hz, 3H). MS(M+1): 628. 黃色固體。

【0423】化合物 6-141

N-(1-(4-氟苯基)-6-(6-嗎啉並吡啶-3-基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(1-(4-fluorophenyl)-6-(6-morpholinopyridin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

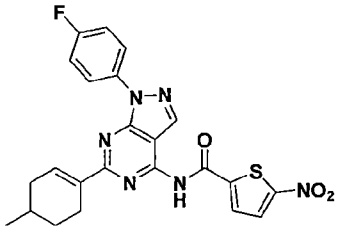


^{1}H NMR (400MHz, DMSO-d_6): δ 11.95 (br. s., 1H), 9.27 (d, J = 2.0 Hz, 1H), 8.53-8.58 (m, 2H), 8.30-8.37 (m, 3H), 8.25 (d, J = 4.4 Hz, 1H), 7.44-7.52 (m, 2H), 7.00 (d, J = 8.8 Hz, 1H), 3.69-3.78 (m, 4H), 3.58-3.67 (m, 4H). MS(M+1):547. 褐色固體。

【0424】化合物 6-142

N-(1-(4-氟苯基)-6-(4-甲基環己-1-烯-1-基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(1-(4-fluorophenyl)-6-(4-methylcyclohex-1-en-1-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

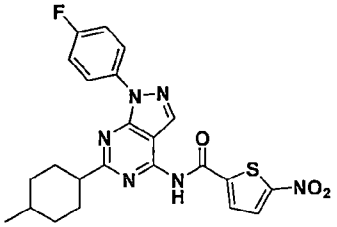


^{1}H NMR (400MHz, DMSO-d_6):δ 11.85 (br. s., 1H), 8.52 (s, 1H), 8.15-8.41 (m, 4H), 7.32-7.53 (m, 3H), 2.82 (d, J = 17.1 Hz, 1H), 2.36-2.48 (m, 2H), 1.81-2.03 (m, 2H), 1.74 (br. s., 1H), 1.23-1.42 (m, 1H), 1.02 (d, J = 6.4 Hz, 3H). MS(M+1): 479. 淡黃色固體。

【0425】化合物 6-143

N-(1-(4-氟苯基)-6-(4-甲基環己基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(1-(4-fluorophenyl)-6-(4-methylcyclohexyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

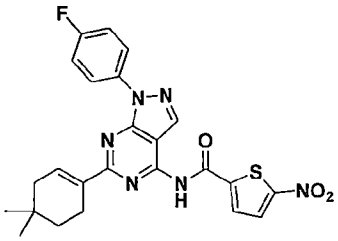


^{1}H NMR (400MHz, DMSO-d_6)(*cis* and *trans*):δ 12.03 (br. s., 1H), 8.55 (s, 2H), 8.31 (br. s., 2H), 8.09-8.28 (m, 7H), 7.37-7.53 (m, 4H), 3.04 (tt, J = 7.9, 4.0 Hz, 1H), 2.84 (tt, J = 11.9, 3.2 Hz, 1H), 2.14 (br. s., 2H), 2.06 (d, J = 11.2 Hz, 2H), 1.57-1.86 (m, 9H), 1.34- 1.52 (m, 3H), 1.03-1.18 (m, 2H), 0.89-1.00 (m, 6H). MS(M+1): 481. 淡黃色固體。

【0426】化合物 6-144

N-(6-(4,4-二甲基環己-1-烯-1-基)-1-(4-氟苯基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩- 2-甲醯胺

(N-(6-(4,4-dimethylcyclohex-1-en-1-yl)-1-(4-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

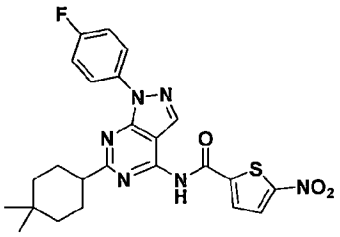


^{1}H NMR (400MHz, DMSO-d_6): δ 11.90 (br. s., 1H), 8.54 (s, 1H), 8.17-8.42 (m, 4H), 7.34-7.57 (m, 3H), 2.66 (br. s., 2H), 2.13 (br. s., 2H), 1.54 (t, J = 6.4 Hz, 2H), 0.98 (s, 6H). MS(M+1): 493. 淡黃色固體。

【0427】化合物 6-145

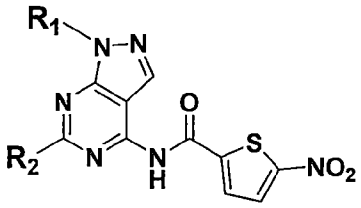
N-(6-(4,4-二甲基環己基)-1-(4-氟苯基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(6-(4,4-dimethylcyclohexyl)-1-(4-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)



^{1}H NMR (400MHz, DMSO-d_6): δ 12.23 (br. s., 1H), 8.55 (s, 1H), 8.16-8.41 (m, 4H), 7.37-7.55 (m, 2H), 2.73-2.90 (m, 1H), 1.75-1.99 (m, 4H), 1.51 (d, J = 12.7 Hz, 2H), 1.36 (td, J = 12.5, 4.9 Hz, 2H), 0.98 (d, J = 4.9 Hz, 6H). MS(M+1): 495. 白色固體。

【0428】表7

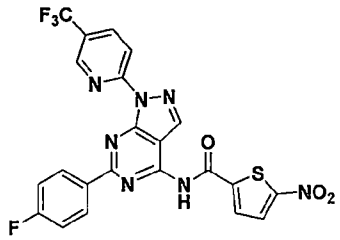
			
化合物	R_1	R_2	Hep3B LC_{50} (uM)
7-1	5-(三氟甲基)吡啶-2-基	4-氟苯基	0.26
7-2	5-(三氟甲基)吡啶-2-基	6-氟吡啶-3-基	0.15
7-3	5-(三氟甲基)吡啶-2-基	4-氯苯基	0.13
7-4	5-(三氟甲基)吡啶-2-基	4-(三氟甲基)苯基	0.22
7-5	5-(三氟甲基)吡啶-2-基	4-(三氟甲氧基)苯基	0.31
7-6	5-(三氟甲基)吡啶-2-基	2,4-二氟苯基	0.15
7-7	5-(三氟甲基)吡啶-2-基	6-(2-(2-乙氧基乙氧基)乙氧基) 吡啶-3-基	0.50
7-8	吡啶-2-基	4-氟苯基	0.58
7-9	2,4-二氯苯基	4-氟苯基	0.37
7-10	2,4-二氯苯基	6-氟吡啶-3-基	>1.25

7-11	3,4-二氯苯基	(S)-2-(羥甲基)吡咯烷-1-基	0.51
7-12	2,4-二氟苯基	4-氟苯基	0.43
7-13	2,4-二氟苯基	6-氟吡啶-3-基	0.13
7-14	2,4-二氟苯基	4-氯苯基	0.58
7-15	苄基	6-氯吡啶-3-基	1.2
7-16	苄基	4-氯苯基	> 1.25
7-17	苄基	6-甲基吡啶-3-基	> 1.25
7-18	3-氟苄基	6-甲氧基吡啶-3-基	> 1.25
7-19	4-丙烯醯胺基苯基	4-氟苯基	0.19

【0429】化合物 7-1

N-(6-(4-氟苯基)-1-(5-(三氟甲基)吡啶-2-基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(6-(4-fluorophenyl)-1-(5-(trifluoromethyl)pyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)



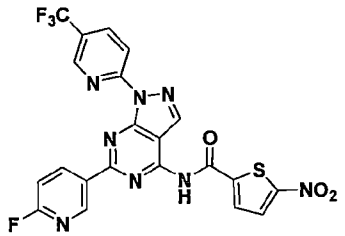
^{1}H NMR (400MHz, DMSO-d_6): δ 12.11 (s, 1H), 9.08 (s, 1H), 8.47-8.76 (m, 5H), 8.39 (d, J = 4.4 Hz, 1H), 8.28 (d, J = 4.4 Hz, 1H), 7.43 (t, J = 8.6 Hz, 2H).

MS(M+1):530. 淺黃色固體。

【0430】化合物 7-2

N-(6-(6-氟吡啶-3-基)-1-(5-(三氟甲基)吡啶-2-基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩 -2-甲醯胺

(N-(6-(6-fluoropyridin-3-yl)-1-(5-(trifluoromethyl)pyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

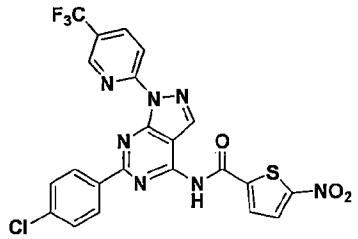


^{1}H NMR (400MHz, DMSO-d_6): δ 12.17 (brs, 1H), 9.36 (d, J = 2.4 Hz, 1H), 9.09 (s, 1H), 9.02-8.97 (m, 1H), 8.76 (s, 1H), 8.68 (d, J = 8.8 Hz, 1H), 8.57-8.55 (m, 1H), 8.37 (d, J = 4.4 Hz, 1H), 8.27 (d, J = 4.4 Hz, 2H), 7.45-7.42 (m, 1H). MS(M+1): 531. 白色固體。

【0431】化合物 7-3

N-(6-(4-氯苯基)-1-(5-(三氟甲基)吡啶-2-基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(6-(4-chlorophenyl)-1-(5-(trifluoromethyl)pyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

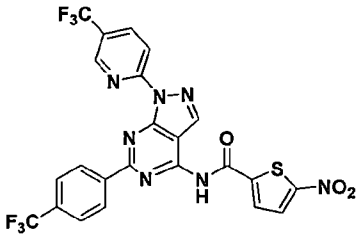


^{1}H NMR (400MHz, DMSO-d_6): δ 12.12 (s, 1H), 9.08 (s, 1H), 8.72 (s, 1H), 8.60-8.69 (m, 1H), 8.50-8.60 (m, 3H), 8.39 (d, J = 4.4 Hz, 1H), 8.27 (d, J = 4.4 Hz, 1H), 7.61- 7.74 (m, 2H). MS(M+1):546. 淺黃色固體。

【0432】化合物 7-4

5-硝基-N-(6-(4-(三氟甲基)苯基)-1-(5-(三氟甲基)吡啶-2-基)-1H-吡唑並[3,4-d]嘧啶-4-基)噻吩 -2-甲醯胺

(5-nitro-N-(6-(4-(trifluoromethyl)phenyl)-1-(5-(trifluoromethyl)pyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)thiophene-2-carboxamide)

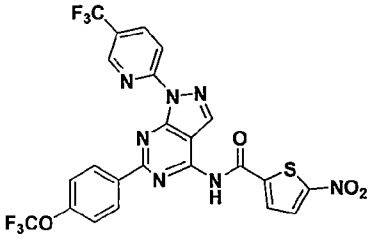


^{1}H NMR (400MHz, DMSO-d_6): δ 12.21 (br. s., 1H), 9.08 (s, 1H), 8.74 (t, J = 4.2 Hz, 3H), 8.64 (d, J = 8.8 Hz, 1H), 8.51-8.60 (m, 1H), 8.38 (d, J = 4.4 Hz, 1H), 8.27 (d, J = 4.4 Hz, 1H), 7.96 (d, J = 8.3 Hz, 2H). MS(M+1):580.乳白色固體。

【0433】化合物 7-5

5-硝基-N-(6-(4-(三氟甲氧基)苯基)-1-(5-(三氟甲基)吡啶-2-基)-1H-吡唑並[3,4-d]嘧啶-4-基)噻吩 -2-甲醯胺

(5-nitro-N-(6-(4-(trifluoromethoxy)phenyl)-1-(5-(trifluoromethyl)pyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)thiophene-2-carboxamide)

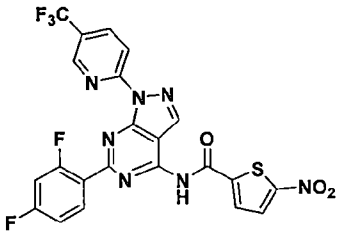


^{1}H NMR (400MHz, DMSO-d_6): δ 12.16 (br. s., 1H), 9.08 (s, 1H), 8.72 (s, 1H), 8.66 (dd, J = 9.0, 2.2 Hz, 3H), 8.55 (dd, J = 8.6, 2.2 Hz, 1H), 8.38 (d, J = 4.4 Hz, 1H), 8.27 (d, J = 4.4 Hz, 1H), 7.58 (d, J = 7.8 Hz, 2H). MS(M+1):596. 白色固體。

【0434】化合物 7-6

N-(6-(2,4-二氟苯基)-1-(5-(三氟甲基)吡啶-2-基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2 -甲醯胺

(N-(6-(2,4-difluorophenyl)-1-(5-(trifluoromethyl)pyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

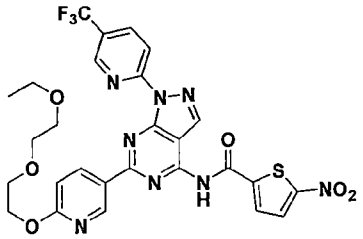


^{1}H NMR (400MHz, DMSO-d_6): δ 12.25 (br. s., 1H), 9.05 (s, 1H), 8.73 (s, 1H), 8.67 (d, J = 8.3 Hz, 1H), 8.54 (dd, J = 8.8, 2.4 Hz, 1H), 8.37 (d, J = 4.4 Hz, 1H), 8.17-8.34 (m, 2H), 7.46 (t, J = 2.2 Hz, 1H), 7.32 (d, J = 2.4 Hz, 1H). MS(M+1):548. 白色固體。

【0435】 化合物 7-7

N-(6-(6-(2-(2-乙氧基乙氧基)乙氧基)吡啶-3-基)-1-(5-(三氟甲基)吡啶-2-基)-1H-吡唑並[3,4-d] 嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(6-(6-(2-(2-ethoxyethoxy)ethoxy)pyridin-3-yl)-1-(5-(trifluoromethyl)pyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

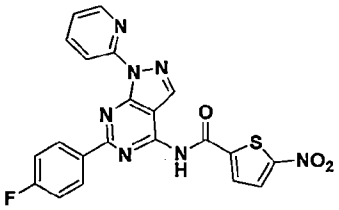


^{1}H NMR (400MHz, DMSO-d_6): δ 11.96 (s, 1H), 9.25 (d, J = 2.4 Hz, 1H), 9.02 (s, 1H), 8.68-8.64 (m, 3H), 8.53-8.50 (m, 1H), 8.34 (d, J = 8.8 Hz, 1H), 8.23 (d, J = 8.8 Hz, 1H), 6.98 (d, J = 8.8 Hz, 1H), 4.47-4.45 (m, 2H), 3.79-3.77 (m, 2H), 3.60-3.58 (m, 2H), 3.52-3.49 (m, 2H), 3.43 (q, J = 6.8 Hz, 2H), 1.10 (t, J = 6.8 Hz, 3H). MS(M+1): 645. 黃色固體。

【0436】 化合物 7-8

N-(6-(4-氟苯基)-1-(吡啶-2-基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(6-(4-fluorophenyl)-1-(pyridin-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

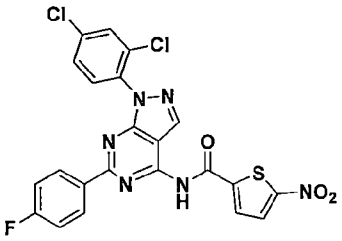


^{1}H NMR (400MHz, DMSO-d_6):δ 12.04 (br. s., 1H), 8.67-8.71 (m, 1H), 8.65 (s, 1H), 8.53-8.60 (m, 2H), 8.39 (d, J = 4.4 Hz, 1H), 8.23-8.30 (m, 2H), 8.11-8.18 (m, 1H), 7.52 (ddd, J = 7.3, 4.9, 1.0 Hz, 1H), 7.35-7.45 (m, 2H). MS(M+1):462. 黃色固體。

【0437】化合物 7-9

N-(1-(2,4-二氯苯基)-6-(4-氟苯基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(1-(2,4-dichlorophenyl)-6-(4-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

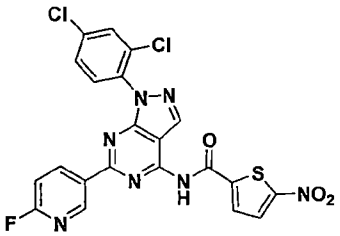


^{1}H NMR (400MHz, DMSO-d_6): δ 12.10 (br. s., 1H), 8.65 (s, 1H), 8.39-8.48 (m, 2H), 8.37 (d, J = 4.4 Hz, 1H), 8.26 (d, J = 4.4 Hz, 1H), 8.02 (d, J = 2.4 Hz, 1H), 7.81 (d, J = 8.3 Hz, 1H), 7.73 (dd, J = 8.8, 2.4 Hz, 1H), 7.32-7.41 (m, 2H). MS(M+1):530.淺卡其色固體。

【0438】化合物 7-10

N-(1-(2,4-二氯苯基)-6-(6-氟吡啶-3-基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(1-(2,4-dichlorophenyl)-6-(6-fluoropyridin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

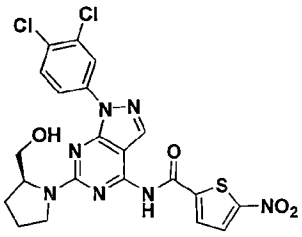


^{1}H NMR (400MHz, DMSO-d_6): δ 12.19 (br. s., 1H), 9.18 (d, J = 2.4 Hz, 1H), 8.78 (td, J = 8.3, 2.4 Hz, 1H), 8.68 (s, 1H), 8.31 (d, J = 4.4 Hz, 1H), 8.26 (d, J = 4.4 Hz, 1H), 8.02 (d, J = 2.4 Hz, 1H), 7.81 (d, J = 8.3 Hz, 1H), 7.68-7.78 (m, 1H), 7.35 (dd, J = 8.8, 2.4 Hz, 1H). MS(M+1): 530. 淺卡其色固體。

【0439】化合物 7-11

(S)-N-(1-(3,4-二氯苯基)-6-(2-(羥甲基)吡咯烷-1-基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5 -硝基噻吩-2-甲醯胺

((S)-N-(1-(3,4-dichlorophenyl)-6-(2-(hydroxymethyl)pyrrolidin-1-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

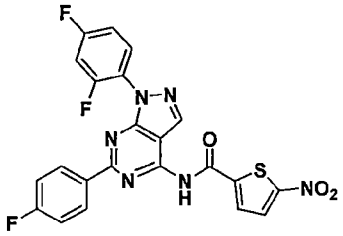


^{1}H NMR (400MHz, DMSO-d_6): δ 11.54 (br. s., 1H), 8.63 (br. s., 1H), 8.25-8.34 (m, 2H), 8.18-8.25 (m, 1H), 7.77 (d, J = 8.8 Hz, 1H), 4.73 (br. s., 1H), 4.25 (d, J = 16.6 Hz, 1H), 3.65 (br. s., 4H), 1.98-2.18 (m, 3H), 1.91 (br. s., 1H). MS(M+1): 534.卡其色固體

【0440】化合物 7-12

N-(1-(2,4-二氟苯基)-6-(4-氟苯基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(1-(2,4-difluorophenyl)-6-(4-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

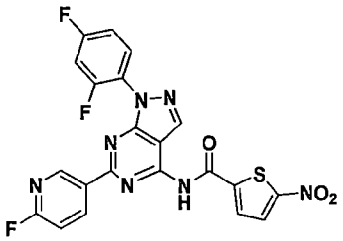


^{1}H NMR (400MHz, DMSO-d_6):δ 12.08 (br. s., 1H), 8.65 (s, 1H), 8.42-8.51 (m, 2H), 8.37 (d, J = 4.4 Hz, 1H), 8.26 (d, J = 4.4 Hz, 1H), 7.88 (td, J = 8.8, 5.9 Hz, 1H), 7.63-7.73 (m, 1H), 7.32-7.44 (m, 3H). MS(M+1): 497. 黃色固體。

【0441】化合物 7-13

N-(1-(2,4-二氟苯基)-6-(6-氟吡啶-3-基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(1-(2,4-difluorophenyl)-6-(6-fluoropyridin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

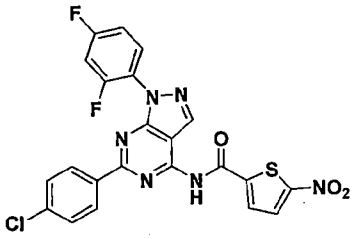


^{1}H NMR (400MHz, DMSO-d_6): δ 12.14 (br. s., 1H), 9.21 (d, J = 2.4 Hz, 1H), 8.80 (td, J = 8.4, 2.4 Hz, 1H), 8.69 (s, 1H), 8.38 (d, J = 4.4 Hz, 1H), 8.27 (d, J = 4.4 Hz, 1H), 7.90 (td, J = 8.4, 6.0 Hz, 1H), 7.60-7.76 (m, 1H), 7.31-7.47 (m, 2H). MS(M+1): 498. 白色固體。

【0442】化合物 7-14

N-(6-(4-氯苯基)-1-(2,4-二氟苯基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(6-(4-chlorophenyl)-1-(2,4-difluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

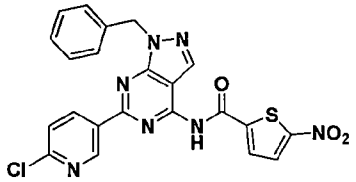


^{1}H NMR (400MHz, DMSO-d_6): δ 12.09 (br. s., 1H), 8.65 (s, 1H), 8.31-8.50 (m, 3H), 8.25 (d, J = 4.4 Hz, 1H), 7.88 (td, J = 8.8, 5.9 Hz, 1H), 7.55-7.73 (m, 3H), 7.31-7.45 (m, 1H). MS(M+1): 513. 黃色固體。

【0443】化合物 7-15

N-(1-苄基-6-(6-氯吡啶-3-基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(1-benzyl-6-(6-chloropyridin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

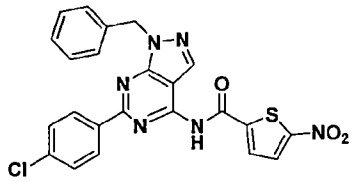


^{1}H NMR (400MHz, DMSO-d_6):δ 12.03 (br. s., 1H), 9.48 (d, J = 2.0 Hz, 1H), 8.85 (dd, J = 8.3, 2.4 Hz, 1H), 8.46 (s, 1H), 8.32 (d, J = 4.4 Hz, 1H), 8.24 (d, J = 4.4 Hz, 1H), 7.75 (d, J = 8.3 Hz, 1H), 7.19-7.46 (m, 5H), 5.74 (s, 2H). MS(M+1): 492. 檸檬綢色固體。

【0444】化合物 7-16

N-(1-苄基-6-(4-氯苯基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(1-benzyl-6-(4-chlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

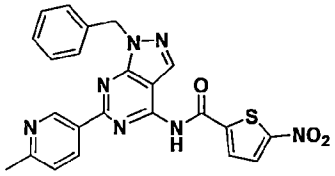


^{1}H NMR (400MHz, DMSO-d_6): δ 11.97 (br. s., 1H), 8.49-8.61 (m, 2H), 8.43 (s, 1H), 8.36 (d, J = 4.4 Hz, 1H), 8.25 (d, J = 4.4 Hz, 1H), 7.57-7.72 (m, 2H), 7.22-7.39 (m, 5H), 5.73 (s, 2H). MS(M+1): 491. 亮黃色固體。

【0445】化合物 7-17

N-(1-苄基-6-(6-甲基吡啶-3-基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(1-benzyl-6-(6-methylpyridin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

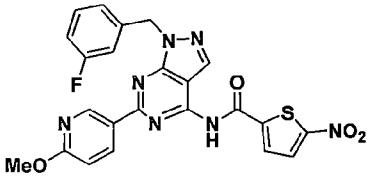


^{1}H NMR (400MHz, DMSO-d_6): δ 11.97 (s, 1H), 9.56 (d, J = 2.0 Hz, 1H), 8.66-8.79 (m, 1H), 8.44 (s, 1H), 8.38 (d, J = 4.4 Hz, 1H), 8.25 (d, J = 4.4 Hz, 1H), 7.47 (d, J = 7.8 Hz, 1H), 7.22-7.41 (m, 5H), 5.73 (s, 2H), 2.58 (s, 3H). MS(M+1): 472. 卡其色固體。

【0446】化合物 7-18

N-(1-(3-氟苄基)-6-(6-甲氧基吡啶-3-基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(1-(3-fluorobenzyl)-6-(6-methoxypyridin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)



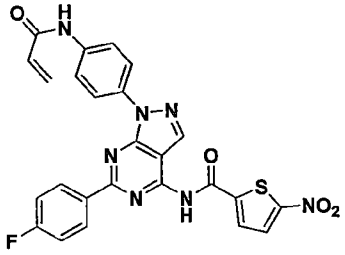
^{1}H NMR (400MHz, DMSO-d_6): δ 11.94 (br. s., 1H), 9.31 (d, J = 2.4 Hz, 1H), 8.72 (dd, J = 8.8, 2.4 Hz, 1H), 8.43 (s, 1H), 8.36 (d, J = 4.4 Hz, 1H), 8.25 (d, J = 4.4 Hz, 1H),

7.39 (td, J = 7.9, 6.1 Hz, 1H), 7.06-7.23 (m, 3H), 7.01 (d, J = 9.3 Hz, 1H), 5.74 (s, 2H), 3.96 (s, 3H). MS(M+1): 506. 亮黃色固體。

【0447】化合物 7-19

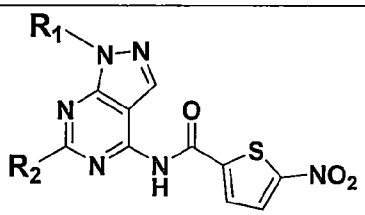
N-(1-(4-丙烯醯胺基苯基)-6-(4-氟苯基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(1-(4-acrylamidophenyl)-6-(4-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)



^{1}H NMR (400MHz, DMSO-d_6): δ 11.97 (br. s., 1H), 10.34 (s, 1H), 8.51-8.61 (m, 3H), 8.37 (d, J = 4.4 Hz, 1H), 8.24 (d, J = 4.4 Hz, 1H), 8.16-8.22 (m, J = 8.8 Hz, 2H), 7.87- 7.95 (m, J = 8.8 Hz, 2H), 7.40 (t, J = 9.0 Hz, 2H), 6.49 (dd, J = 17.1, 10.3 Hz, 1H), 6.31 (dd, J = 17.1, 2.0 Hz, 1H), 5.80 (dd, J = 9.8, 2.0 Hz, 1H). MS(M+1):530. 黃色固體。

【0448】表8

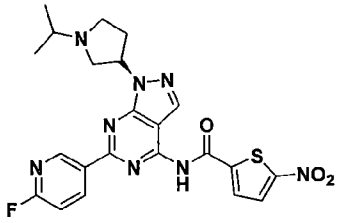
			
化合物	R_1	R_2	Hep3B LC_{50} (uM)
8-1	(S)-1-異丙基吡咯烷-3-基	6-氟吡啶-3-基	>3
8-2	(S)-N-1-乙醯基吡咯烷-3-基	6-氟吡啶-3-基	>3

8-3	(S)-N-1-丙烯醯基吡咯烷-3-基	6-氟吡啶-3-基	> 3
8-4	(S)-N-1-三甲基乙醯基吡咯烷-3-基 ((S)-N-1-pivaloylpyrrolidin-3-yl)	6-氟吡啶-3-基	1.49
8-5	(S)-3-吡咯烷-1-甲酸乙酯	6-氟吡啶-3-基	>2
8-6	(R)-3-吡咯烷-1-甲酸乙酯	6-氟吡啶-3-基	>2
8-7	(S)-3-吡咯烷-1-甲酸叔丁酯	6-氟吡啶-3-基	1.49
8-8	環戊基	6-氟吡啶-3-基	1.17
8-9	環戊基	4-氯苯基	0.94
8-10	環戊基	4-氟苯基	0.83
8-11	環戊基	6-氟吡啶-3-基	NA
8-12	環戊基	4-甲酯苯甲酸(4-methyl benzoate)	0.47
8-13	(1*R*,5*S*)-3,3,5-三甲基環己基	4-氟苯基	0.90
8-14	(1*R*,5*S*)-3,3,5-三甲基環己基	6-氟吡啶-3-基	0.62
8-15	(1*R*,5*S*)-3,3,5-三甲基環己基	4-氯苯基	1.27
8-16	(1*R*,5*S*)-3,3,5-三甲基環己基	6-氯吡啶-3-基	0.59

【0449】化合物 8-1

(S)-N-(6-(6-氟吡啶-3-基)-1-(1-異丙基吡咯烷-3-基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5- 硝基噻吩-2-甲醯胺

((S)-N-(6-(6-fluoropyridin-3-yl)-1-(1-isopropylpyrrolidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

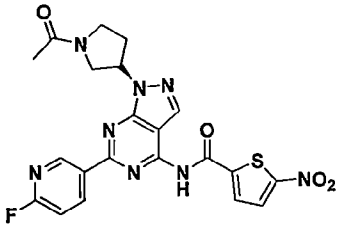


^{1}H NMR (400MHz, DMSO-d_6): δ 11.84 (br. s., 1H), 9.30 (d, J = 2.4 Hz, 1H), 8.96 (td, J = 8.3, 2.4 Hz, 1H), 8.42 (s, 1H), 8.25-8.32 (m, 1H), 8.18-8.25 (m, 1H), 7.40 (dd, J = 8.6, 2.7 Hz, 1H), 5.51-5.69 (m, 1H), 2.90 (d, J = 19.1 Hz, 3H), 2.58 (br. s., 1H), 2.25-2.47 (m, 3H), 1.09 (d, J = 6.4 Hz, 6H). MS(M+1): 497. 深橘色固體。

【0450】化合物 8-2

(S)-N-(1-(1-乙醯基吡咯烷-3-基)-6-(6-氟吡啶-3-基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5- 硝基噻吩-2-甲醯胺

((S)-N-(1-(1-acetylpyrrolidin-3-yl)-6-(6-fluoropyridin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

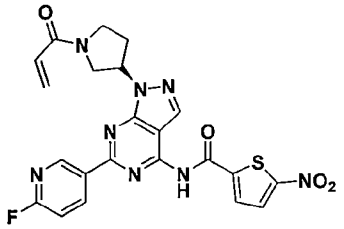


^{1}H NMR (400MHz, DMSO-d_6): δ 12.01 (br. s., 1H), 9.32 (dd, J = 5.4, 2.4 Hz, 1H), 8.89-9.05 (m, 1H), 8.45 (d, J = 5.4 Hz, 1H), 8.33 (d, J = 4.4 Hz, 1H), 8.25 (d, J = 4.4 Hz, 1H), 7.42 (dd, J = 8.6, 2.7 Hz, 1H), 3.57-4.11 (m, 5H), 2.38-2.60 (m, 2H), 1.99 (s, 3H). MS(M+1): 497. 白色固體。

【0451】化合物 8-3

(S)-N-(1-(1-(丙烯醯基吡咯烷基-3-基)-6-(6-氟吡啶-3-基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5- 硝基噻吩-2-甲醯胺

((S)-N-(1-(1-acryloylpyrrolidin-3-yl)-6-(6-fluoropyridin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)



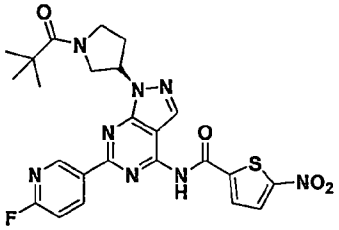
^{1}H NMR (400MHz, DMSO-d_6): δ 12.01 (br. s., 1H), 9.21-9.43 (m, 1H), 8.86-9.06 (m, 1H), 8.45 (d, J = 3.4 Hz, 1H), 8.34 (dd, J = 4.4, 1.5 Hz, 1H), 8.25 (d, J = 4.4 Hz, 1H), 7.42 (dd, J = 8.6, 2.7 Hz, 1H), 6.51-6.75 (m, 1H), 6.18 (ddd, J = 17.1, 7.8, 2.4 Hz, 1H),

5.62- 5.83 (m, 2H), 3.59-4.23 (m, 4H), 2.25-2.64 (m, 2H). MS(M+1): 509.玫瑰棕色固體。

【0452】化合物 8-4

(S)-N-(6-(6-氟吡啶-3-基)-1-(1-三甲基乙醯基吡咯烷-3-基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5- 硝基噻吩-2-甲醯胺

((S)-N-(6-(6-fluoropyridin-3-yl)-1-(1-pivaloylpyrrolidin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

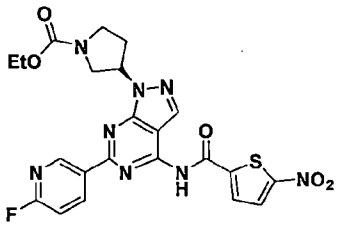


^{1}H NMR (400MHz, DMSO-d_6): δ 11.93 (br. s., 1H), 9.29 (d, J = 2.4 Hz, 1H), 8.94 (td, J = 8.3, 2.4 Hz, 1H), 8.41 (s, 1H), 8.34 (d, J = 4.4 Hz, 1H), 8.23 (d, J = 4.4 Hz, 1H), 7.40 (dd, J = 8.6, 2.7 Hz, 1H), 5.65 (br. s., 1H), 4.00 (br. s., 2H), 3.83 (br. s., 2H), 2.44 (br. s., 2H), 1.19 (s, 9H). MS(M+1): 539. 白色固體。

【0453】化合物 8-5

(S)-3-(6-(6-氟吡啶-3-基)-4-(5-硝基噻吩-2-甲醯胺基)-1H-吡唑並[3,4-d]嘧啶-1-基)吡咯烷- 1-甲酸乙酯

(ethyl (S)-3-(6-(6-fluoropyridin-3-yl)-4-(5-nitrothiophene-2-carboxamido)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidine-1-carboxylate)

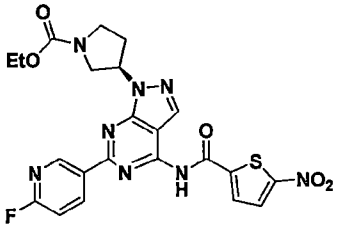


^{1}H NMR (400MHz, DMSO-d_6): δ 11.94 (s, 1H), 9.28 (d, J = 2.4 Hz, 1H), 8.93 (td, J = 8.3, 2.4 Hz, 1H), 8.41 (s, 1H), 8.34 (d, J = 4.4 Hz, 1H), 8.23 (d, J = 4.4 Hz, 1H), 7.40

(dd, J = 8.6, 2.7 Hz, 1H), 5.68 (br. s., 1H), 4.06 (quin, J = 7.1 Hz, 2H), 3.86-3.95 (m, 1H), 3.75 (dd, J = 11.2, 4.4 Hz, 1H), 3.48-3.71 (m, 2H), 2.30-2.48 (m, 2H), 1.19 (dt, J = 16.6, 7.3 Hz, 3H). MS(M+1):527.實木色固體。

【0454】化合物 8-6

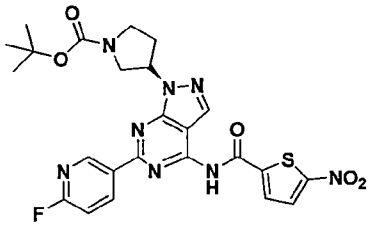
(R)-3-(6-(6-氟吡啶-3-基)-4-(5-硝基噻吩-2-甲醯胺基)-1H-吡唑並[3,4-d]嘧啶-1-基)吡咯烷- 1-甲酸乙酯(ethyl (R)-3-(6-(6-fluoropyridin-3-yl)-4-(5-nitrothiophene-2-carboxamido)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidine-1-carboxylate)



^{1}H NMR (400MHz, DMSO-d_6): δ 11.99 (br. s., 1H), 9.31 (d, J = 2.4 Hz, 1H), 8.95 (td, J = 8.3, 2.4 Hz, 1H), 8.44 (s, 1H), 8.34 (d, J = 4.4 Hz, 1H), 8.25 (d, J = 4.4 Hz, 1H), 7.41 (dd, J = 8.6, 2.7 Hz, 1H), 5.70 (br. s., 1H), 4.01-4.15 (m, 2H), 3.85-3.97 (m, 1H), 3.71-3.78 (m, 1H), 3.64 (d, J = 6.8 Hz, 1H), 3.57 (d, J = 6.4 Hz, 1H), 2.26-2.48 (m, 2H), 1.19 (dt, J = 16.9, 7.0 Hz, 3H). MS(M+1):527. 淺黃色固體。

【0455】化合物 8-7

(S)-3-(6-(6-氟吡啶-3-基)-4-(5-硝基噻吩-2-甲醯胺基)-1H-吡唑並[3,4-d]嘧啶-1-基 吡咯烷-1-甲酸叔丁酯(tert-butyl (S)-3-(6-(6-fluoropyridin-3-yl)-4-(5-nitrothiophene-2-carboxamido)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidine-1-carboxylate)

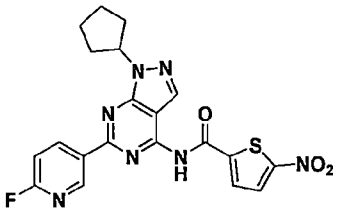


^{1}H NMR (400MHz, DMSO-d_6): δ 12.01 (br. s., 1H), 9.32 (d, J = 2.4 Hz, 1H), 8.96 (td, J = 8.3, 2.4 Hz, 1H), 8.44 (s, 1H), 8.32 (d, J = 4.4 Hz, 1H), 8.25 (d, J = 4.4 Hz, 1H), 7.41 (dd, J = 8.6, 2.7 Hz, 1H), 5.68 (br. s., 1H), 3.82-3.91 (m, 1H), 3.56-3.72 (m, 2H), 3.50 (br. s., 1H), 2.34-2.48 (m, 2H), 1.38-1.48 (m, 9H). MS(M+1): 555. 淡黃色固體。

【0456】化合物 8-8

N-(1-環戊基-6-(6-氟吡啶-3-基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(1-cyclopentyl-6-(6-fluoropyridin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

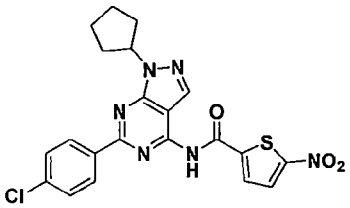


^{1}H NMR (400MHz, DMSO-d_6): δ 11.91 (br. s., 1H), 9.30 (d, J = 2.4 Hz, 1H), 8.95 (td, J = 8.3, 2.4 Hz, 1H), 8.41 (s, 1H), 8.31-8.39 (m, 1H), 8.24 (d, J = 4.4 Hz, 1H), 7.40 (dd, J = 8.6, 2.7 Hz, 1H), 5.46 (quin, J = 7.3 Hz, 1H), 2.13-2.27 (m, 2H), 2.00-2.13 (m, 2H), 1.83- 2.00 (m, 2H), 1.68-1.83 (m, 2H). MS(M+1): 454. 卡其色固體。

【0457】化合物 8-9

N-(6-(4-氯苯基)-1-環戊基-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(6-(4-chlorophenyl)-1-cyclopentyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)



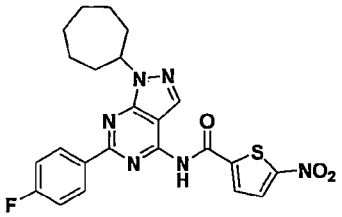
^{1}H NMR (400MHz, DMSO-d_6): δ 11.87 (br. s., 1H), 8.45-8.62 (m, 2H), 8.30-8.45 (m, 2H), 8.21 (d, J = 4.4 Hz, 1H), 7.56-7.71 (m, 2H), 5.43 (quin, J = 7.2 Hz, 1H), 2.12-

2.26 (m, 2H), 1.99-2.12 (m, 2H), 1.82-1.99 (m, 2H), 1.63-1.82 (m, 2H). MS(M+1): 469. 淺黃色固體。

【0458】化合物 8-10

N-(1-環庚基-6-(4-氟苯基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(1-cycloheptyl-6-(4-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

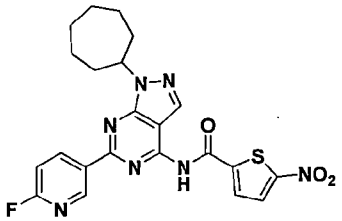


^{1}H NMR (400MHz, DMSO-d_6): δ 11.91 (br. s., 1H), 8.54-8.62 (m, 2H), 8.37 (s, 1H), 8.33 (d, J = 4.4 Hz, 1H), 8.24 (d, J = 4.4 Hz, 1H), 7.34-7.46 (m, 2H), 5.12 (tt, J = 9.6, 4.8 Hz, 1H), 2.10-2.24 (m, 2H), 2.00-2.10 (m, 2H), 1.79-1.95 (m, 2H), 1.56-1.79 (m, 6H). MS(M+1):481. 卡其色固體。

【0459】化合物 8-11

N-(1-環庚基-6-(6-氟吡啶-3-基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(1-cycloheptyl-6-(6-fluoropyridin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

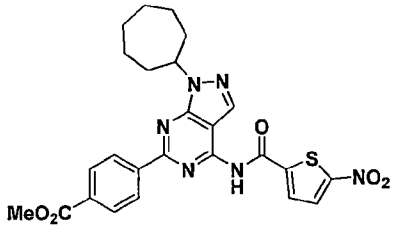


^{1}H NMR (400MHz, DMSO-d_6): δ 11.92 (br. s., 1H), 9.31 (d, J = 2.4 Hz, 1H), 8.95 (td, J = 8.3, 2.4 Hz, 1H), 8.40 (s, 1H), 8.35 (d, J = 4.4 Hz, 1H), 8.24 (d, J = 4.4 Hz, 1H), 7.40 (dd, J = 8.6, 2.7 Hz, 1H), 5.13 (tt, J = 9.6, 4.8 Hz, 1H), 2.10-2.23 (m, 2H),

1.98-2.10 (m, 2H), 1.78-1.91 (m, 2H), 1.55-1.78 (m, 6H). MS(M+1):482. 卡其色固體。

【0460】化合物 8-12

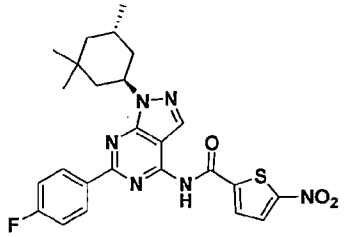
4-(1-環庚基-4-(5-硝基噻吩-2-甲醯胺基)-1H-吡唑並[3,4-d]嘧啶-6-基)苯甲酸甲酯(methyl 4-(1-cycloheptyl-4-(5-nitrothiophene-2-carboxamido)-1H-pyrazolo[3,4-d] pyrimidin-6-yl)benzoate)



^{1}H NMR (400MHz, DMSO-d_6): δ 11.97 (br. s., 1H), 8.64-8.71 (m, J = 8.8 Hz, 2H), 8.39 (s, 1H), 8.36 (d, J = 4.4 Hz, 1H), 8.24 (d, J = 4.4 Hz, 1H), 8.09-8.20 (m, J = 8.3 Hz, 2H), 5.15 (tt, J = 9.5, 4.9 Hz, 1H), 3.91 (s, 3H), 2.10-2.22 (m, 2H), 1.99-2.10 (m, 2H), 1.78-1.92 (m, 2H), 1.55-1.78 (m, 6H). MS(M+1):521. 灰色固體。

【0461】化合物 8-13

N-(6-(4-氟苯基)-1-(((1R,5S)-3,3,5-三甲基環己基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩- 2-甲醯胺(N-(6-(4-fluorophenyl)-1-((1R,5S)-3,3,5-trimethylcyclohexyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)



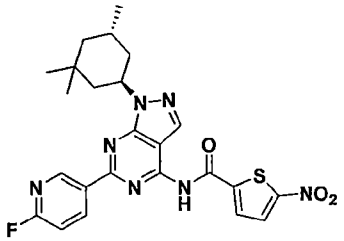
^{1}H NMR (400MHz, DMSO-d_6): δ 11.88 (br. s., 1H), 8.57 (dd, J = 8.8, 5.9 Hz, 2H), 8.32- 8.42 (m, 2H), 8.25 (d, J = 4.4 Hz, 1H), 7.35-7.48 (m, 2H), 5.04-5.17 (m, 1H),

2.37-2.47 (m, 2H), 2.32 (dd, J = 14.2, 5.9 Hz, 1H), 1.67 (dd, J = 13.7, 4.4 Hz, 1H), 1.53-1.62 (m, 1H), 1.47 (dd, J = 12.7, 3.9 Hz, 1H), 1.10-1.16 (m, 1H), 1.08 (d, J = 6.8 Hz, 3H), 0.99 (s, 3H), 0.59 (s, 3H). MS(M+1): 509. 黃色固體。

【0462】化合物 8-14

N-(6-(6-氟吡啶-3-基)-1-((1R,5S)-3,3,5-三甲基環己基)-1H-吡唑並[3,4-d]嘧啶-4-基)- 5-硝基噻吩-2-甲醯胺

(N-(6-(6-fluoropyridin-3-yl)-1-((1R,5S)-3,3,5-trimethylcyclohexyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

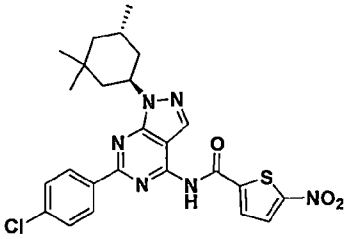


^{1}H NMR (400MHz, DMSO-d_6): δ 11.94 (br. s., 1H), 9.29 (d, J = 2.4 Hz, 1H), 8.93 (td, J = 8.3, 2.4 Hz, 1H), 8.41 (s, 1H), 8.33 (d, J = 4.4 Hz, 1H), 8.24 (d, J = 4.4 Hz, 1H), 7.42 (dd, J = 8.8, 2.4 Hz, 1H), 5.09-5.18 (m, 1H), 2.36-2.45 (m, 2H), 2.29 (dd, J = 13.9, 6.1 Hz, 1H), 1.68 (dd, J = 13.7, 3.9 Hz, 1H), 1.54-1.63 (m, 1H), 1.47 (d, J = 9.3 Hz, 1H), 1.11-1.18 (m, 1H), 1.08 (d, J = 6.8 Hz, 3H), 0.99 (s, 3H), 0.60 (s, 3H). MS(M+1): 510. 淺黃色固體。

【0463】化合物 8-15

N-(6-(4-氯苯基)-1-((1R,5S)-3,3,5-三甲基環己基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩- 2-甲醯胺

(N-(6-(4-chlorophenyl)-1-((1R,5S)-3,3,5-trimethylcyclohexyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

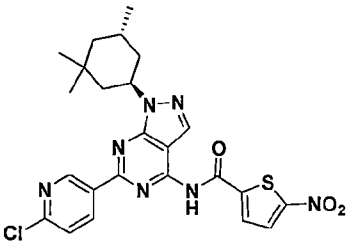


^{1}H NMR (400MHz, DMSO-d_6): δ 11.89 (s, 1H), 8.45-8.59 (m, J = 8.8 Hz, 2H), 8.31-8.42 (m, 2H), 8.24 (d, J = 4.4 Hz, 1H), 7.56-7.72 (m, 2H), 5.04-5.20 (m, 1H), 2.36-2.45 (m, 2H), 2.31 (dd, J = 13.7, 5.9 Hz, 1H), 1.67 (dd, J = 13.7, 4.4 Hz, 1H), 1.51-1.62 (m, 1H), 1.46 (dd, J = 13.0, 3.2 Hz, 1H), 1.09-1.16 (m, 1H), 1.07 (d, J = 6.8 Hz, 3H), 0.98 (s, 3H), 0.58 (s, 3H).MS(M+1): 525. 黃色固體。

【0464】化合物 8-16

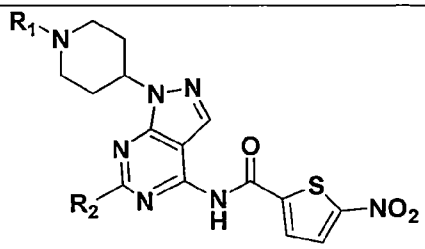
N-(6-(6-氯吡啶-3-基)-1-((1R,5S)-3,3,5-三甲基環己基)-1H-吡唑並[3,4-d]嘧啶-4-基)- 5-硝基噻吩-2-甲醯胺

(N-(6-(6-chloropyridin-3-yl)-1-((1R,5S)-3,3,5-trimethylcyclohexyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)



^{1}H NMR (400MHz, DMSO-d_6): δ 11.96 (s, 1H), 9.45 (d, J = 2.0 Hz, 1H), 8.80 (dd, J = 8.3, 2.4 Hz, 1H), 8.43 (s, 1H), 8.36 (d, J = 4.4 Hz, 1H), 8.25 (d, J = 4.4 Hz, 1H), 7.77 (d, J = 8.3 Hz, 1H), 5.04-5.22 (m, 1H), 2.35-2.45 (m, 2H), 2.29 (dd, J = 13.9, 6.1 Hz, 1H), 1.68 (dd, J = 13.9, 4.2 Hz, 1H), 1.59 (s, 1H), 1.43-1.50 (m, 1H), 1.05-1.17 (m, 4H), 0.99 (s, 3H), 0.60 (s, 3H). MS(M+1): 526. 黃綠色固體。

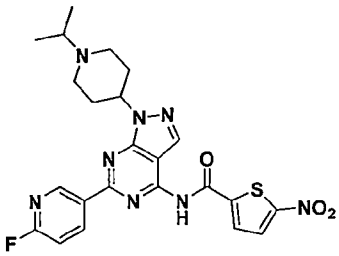
【0465】表9

			
化合物	R_1	R_2	Hep3B LC_{50} (uM)
9-1	異丙基	6-氟吡啶-3-基	1.25
9-2	甲酸乙酯	6-氟吡啶-3-基	> 5
9-3	叔丁氧羰基(BOC)	4-苯甲酸甲酯	0.42
9-4	叔丁氧羰基(BOC)	6-氟吡啶-3-基	0.93
9-5	叔丁氧羰基(BOC)	4-氯苯基	0.45
9-6	丙烯醯基	6-氟吡啶-3-基	1.25
9-7	丁醯基	6-氟吡啶-3-基	> 5
9-8	三甲基乙醯基(Pivaloyl)	6-氟吡啶-3-基	1.90
9-9	4,4,4-三氟甲酸丁酯	4-氯苯基	1.07
9-10	2-(2-乙氧基乙氧基)甲酸乙酯	噻吩-2-基	> 3
9-11	2-(2-乙氧基乙氧基)甲酸乙酯	4-氯苯基	> 1.25
9-12	2-甲氧基甲酸乙酯	4-氯苯基	1.86
9-13	2-乙氧基甲酸乙酯	4-氯苯基	1.62

【0466】化合物 9-1

N-(6-(6-氟吡啶-3-基)-1-(1-異丙基哌啶-4-基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(6-(6-fluoropyridin-3-yl)-1-(1-isopropylpiperidin-4-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

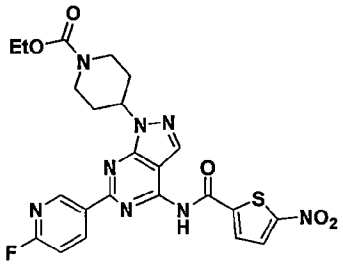


^{1}H NMR (400MHz, DMSO-d_6): δ 11.63 (br. s., 1H),9.30 (d, J = 2.0 Hz, 1H), 8.94 (td, J = 8.3, 2.4 Hz, 1H), 8.38 (s, 1H), 8.14-8.31 (m, 2H), 7.39 (dd, J = 8.6, 2.7 Hz, 1H), 4.92 (br. s., 1H), 3.05 (br. s., 2H), 2.93 (br. s., 1H), 2.45-2.65 (m, 2H), 2.17-2.29 (m, 2H), 1.94- 2.07 (m, 2H), 1.08 (d, J = 6.8 Hz, 6H). MS(M+1): 511.淺黃色固體。

【0467】化合物 9-2

4-(6-(6-氟吡啶-3-基)-4-(5-硝基噻吩-2-甲醯胺基)-1H-吡唑[3,4-d]嘧啶-1-基)哌啶-1-甲酸乙酯

(ethyl 4-(6-(6-fluoropyridin-3-yl)-4-(5-nitrothiophene-2-carboxamido)-1H-pyrazolo [3,4-d]pyrimidin-1-yl)piperidine-1-carboxylate)

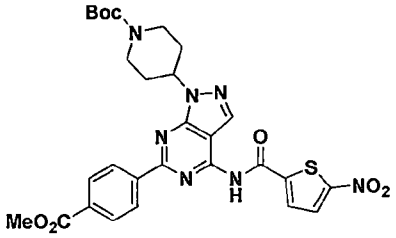


^{1}H NMR (400MHz, DMSO-d_6): δ 12.05 (br. s., 1H), 9.31 (s, 1H), 8.96 (t, J = 7.6 Hz, 1H), 8.40 (s, 1H), 8.23 (br. s., 2H), 7.41 (d, J = 8.3 Hz, 1H), 5.15 (br. s., 1H), 3.98-4.26 (m, 4H), 3.13 (br. s., 2H), 2.08-2.03 (m., 4H), 1.22 (t, J = 7.1 Hz, 3H). MS(M+1): 541. 黃綠色固體。

【0468】化合物 9-3

4-(6-(4-(甲氧基羰基)苯基)-4-(5-硝基噻吩-2-甲醯胺基)叔丁基-1H-吡唑並[3,4-d]嘧啶-1-基)哌啶-1-甲酸叔丁酯

(tert-butyl 4-(6-(4-(methoxycarbonyl)phenyl)-4-(5-nitrothiophene-2-carboxamido)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidine-1-carboxylate)

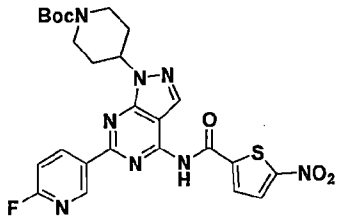


^{1}H NMR (DMSO-d_6, 400 MHz): δ 11.97 (br. s., 1H), 8.57-8.70 (m, 2H), 8.38 (s, 1H), 8.36 (d, J = 4.4 Hz, 1H), 8.23 (d, J = 4.4 Hz, 1H), 8.07-8.17 (m, 2H), 4.97-5.21 (m, 1H), 4.12 (d, J = 12.2 Hz, 2H), 3.90 (s, 3H), 3.07 (brs., 2H), 1.94-2.14 (m, 4H), 1.45 (s, 9H). MS(M+1): 608. 黃色固體。

【0469】化合物 9-4

4-(6-(6-氟吡啶-3-基)-4-(5-硝基噻吩-2-甲醯胺基)-1H-吡唑並[3,4-d]嘧啶-1-基)哌啶-1- 甲酸叔丁酯

(tert-butyl 4-(6-(6-fluoropyridin-3-yl)-4-(5-nitrothiophene-2-carboxamido)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidine-1-carboxylate)

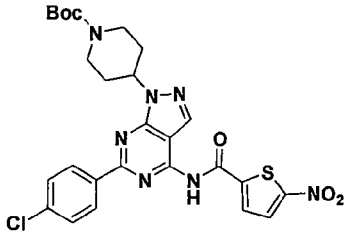


^{1}H NMR (400MHz, DMSO-d_6): δ 11.90 (s, 1H), 9.28 (d, J = 2.4 Hz, 1H), 8.92 (t, J = 8.3, 1H), 8.38 (s, 1H), 8.32 (d, J = 4.4 Hz, 1H), 8.21 (d, J = 4.4 Hz, 1H), 7.38 (dd, J = 8.3 , 2.7 Hz, 1H), 5.15-5.07 (m, 1H), 4.13-4.10 (brm, 2H), 3.06 (brs, 2H), 2.08-1.98 (m, 4H), 1.44 (s, 9H). MS(M+1): 569. 黃色固體。

【0470】化合物 9-5

4-(6-(4-氯苯基)-4-(5-硝基噻吩-2-甲醯胺基)-1H-吡唑並[3,4-d]嘧啶-1-基)哌啶-1-甲酸叔丁酯

(tert-butyl 4-(6-(4-chlorophenyl)-4-(5-nitrothiophene-2-carboxamido)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidine-1-carboxylate)

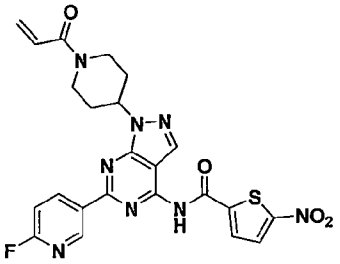


^{1}H NMR (400MHz, DMSO-d_6): δ 11.96 (br. s., 1H), 8.48-8.61 (m, 2H), 8.40 (s, 1H), 8.34 (d, J = 4.9 Hz, 1H), 8.24 (d, J = 4.4 Hz, 1H), 7.61-7.69 (m, 2H), 5.02-5.19 (m, 1H), 4.12 (d, J = 12.2 Hz, 2H), 3.07 (br. s., 2H), 1.94-2.13 (m, 4H), 1.45 (s, 9H). MS(M+1): 584. 淺黃色固體。

【0471】化合物 9-6

N-(1-(1-丙烯醯基哌啶-4-基)-6-(6-氟吡啶-3-基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2- 甲醯胺

(N-(1-(1-acryloylpiperidin-4-yl)-6-(6-fluoropyridin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

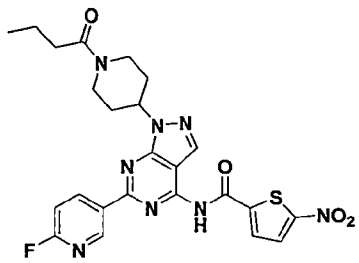


^{1}H NMR (400MHz, DMSO-d_6): δ 11.98 (br. s., 1H), 9.32 (d, J = 2.4 Hz, 1H), 8.96 (td, J = 8.3, 2.4 Hz, 1H), 8.43 (s, 1H), 8.34 (d, J = 4.4 Hz, 1H), 8.25 (d, J = 4.4 Hz, 1H), 7.42 (dd, J = 8.8, 2.4 Hz, 1H), 6.90 (dd, J = 16.6, 10.8 Hz, 1H), 6.16 (dd, J = 16.6, 2.4 Hz, 1H), 5.75 (s, 1H), 5.72 (dd, J = 10.3, 2.4 Hz, 1H), 5.25 (t, J = 7.1 Hz, 1H), 4.58 (d, J = 13.7 Hz, 1H), 4.25 (d, J = 13.2 Hz, 1H), 3.43 (td, J = 7.1, 4.9 Hz, 1H), 2.92-3.10 (m, 1H), 1.97-2.20 (m, 4H). MS(M+1): 523. 金菊色粉末。

【0472】化合物 9-7

N-(1-(1-丁醯基哌啶-4-基)-6-(6-氟吡啶-3-基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2- 甲醯胺

(N-(1-(1-butyrylpiperidin-4-yl)-6-(6-fluoropyridin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

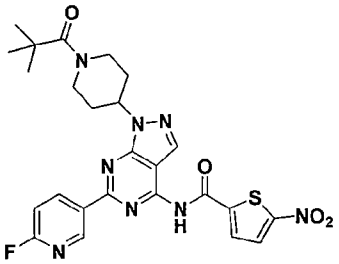


^{1}H NMR (400MHz, DMSO-d_6): δ 11.95 (br. s., 1H), 9.31 (d, J = 2.4 Hz, 1H), 8.95 (td, J = 8.3, 2.4 Hz, 1H), 8.41 (s, 1H), 8.34 (d, J = 4.4 Hz, 1H), 8.24 (d, J = 4.4 Hz, 1H), 7.41 (dd, J = 8.6, 2.7 Hz, 1H), 5.13-5.31 (m, 1H), 4.57 (d, J = 13.2 Hz, 1H), 4.06 (d, J = 13.7 Hz, 1H), 2.87 (t, J = 11.5 Hz, 1H), 2.28-2.44 (m, 2H), 1.57 (sxt, J = 7.3 Hz, 2H), 0.93 (t, J = 7.3 Hz, 3H). MS(M+1):539. 卡其色固體。

【0473】化合物 9-8

N-(6-(6-氟吡啶-3-基)-1-(1-三甲基乙醯基哌啶-4-基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2- 甲醯胺

(N-(6-(6-fluoropyridin-3-yl)-1-(1-pivaloylpiperidin-4-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

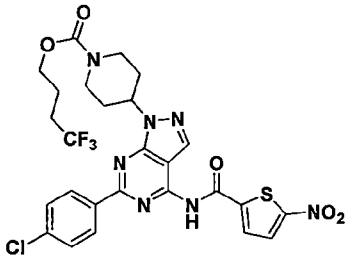


^{1}H NMR (400MHz, DMSO-d_6): δ 11.92 (br. s., 1H), 9.29 (d, J = 2.4 Hz, 1H), 8.93 (td, J = 8.3, 2.4 Hz, 1H), 8.39 (s, 1H), 8.34 (d, J = 4.9 Hz, 1H), 8.23 (d, J = 4.4 Hz, 1H), 7.40 (dd, J = 8.6, 2.7 Hz, 1H), 5.13-5.26 (m, 1H), 4.45 (d, J = 13.2 Hz, 2H), 3.05-3.18 (m, 2H), 1.99-2.13 (m, 4H), 1.25 (s, 9H). MS(M+1): 553. 淺卡其色固體。

【0474】化合物 9-9

4-(6-(4-氯苯基)-4-(5-硝基噻吩-2-甲醯胺基)-1H-吡唑並[3,4-d]嘧啶-1-基)哌啶-1-甲酸 4,4,4-三氟丁酯

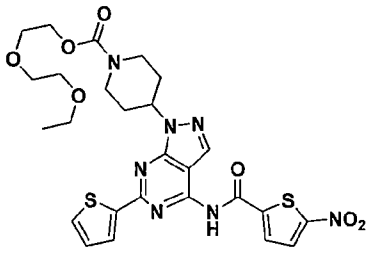
(4,4,4-trifluorobutyl 4-(6-(4-chlorophenyl)-4-(5-nitrothiophene-2-carboxamido)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidine-1-carboxylate)



^{1}H NMR (400MHz, DMSO-d_6): δ 11.95 (br. s., 1H), 8.50-8.61 (m, 2H), 8.40 (s, 1H), 8.35 (d, J = 4.4 Hz, 1H), 8.24 (d, J = 4.4 Hz, 1H), 7.57-7.70 (m, 2H), 5.15 (dt, J = 10.4, 5.3 Hz, 1H), 4.04-4.25 (m, 4H), 3.15 (br. s., 2H), 2.27-2.45 (m, 2H), 1.96-2.19 (m, 4H), 1.75-1.90 (m, 2H). MS(M+1): 638. 淺黃色固體。

【0475】化合物 9-10

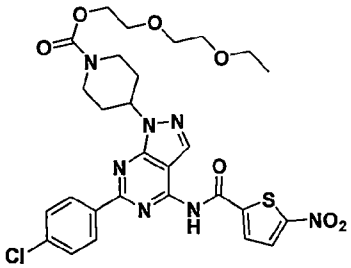
4-(4-(5-硝基噻吩-2-甲醯胺基)-6-(噻吩-2-基)-1H-吡唑並[3,4-d]嘧啶-1-基)哌啶 -1-甲酸 2-(2-乙氧基乙氧基)乙酯(2-(2-ethoxyethoxy)ethyl 4-(4-(5-nitrothiophene-2-carboxamido)-6-(thiophen-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidine-1-carboxylate)



^{1}H NMR (400MHz, DMSO-d_6): δ 11.93 (s, 1H), 8.36 (d, J = 4.4 Hz, 1H), 8.33 (s, 1H), 8.23 (d, J = 4.4 Hz, 1H), 8.06-8.10 (m, 1H), 7.80 (dd, J = 5.1, 1.2 Hz, 1H), 7.25 (dd, J = 4.9, 3.4 Hz, 1H), 4.91-5.13 (m, 1H), 4.05-4.27 (m, 4H), 3.60-3.68 (m, 2H), 3.53-3.59 (m, 2H), 3.46-3.50 (m, 2H), 3.43 (q, J = 7.2 Hz, 2H), 3.14 (br. s., 2H), 1.97-2.14 (m, 4H), 1.09 (t, J = 7.1 Hz, 3H). MS(M+1): 616. 黃色固體。

【0476】化合物 9-11

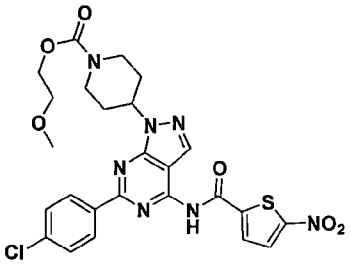
4-(6-(4-氯苯基)-4-(5-硝基噻吩-2-甲醯胺基)-1H-吡唑並[3,4-d]嘧啶-1-基)哌啶-1-甲酸 2-(2-乙氧基乙氧基)乙酯(2-(2-ethoxyethoxy)ethyl 4-(6-(4-chlorophenyl)-4-(5-nitrothiophene-2-carboxamido)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidine-1-carboxylate)



^{1}H NMR (400MHz, DMSO-d_6): δ 11.95 (s, 1H), 8.55 (d, J = 8.8 Hz, 2H), 8.4 (s, 1H), 8.34 (d, J = 4.4 Hz, 1H), 8.24 (d, J = 4.4 Hz, 1H), 7.65 (d, J = 8.8 Hz, 2H), 5.19-5.12 (m, 1H), 4.18-4.14 (m, 4H), 3.65-3.4 (m, 8H), 3.15 (br. s, 1H), 2.09-2.01 (m 4H), 1.09 (t, J = 6.9 Hz, 3H). MS(M+1): 644. 黃褐色固體。

【0477】化合物 9-12

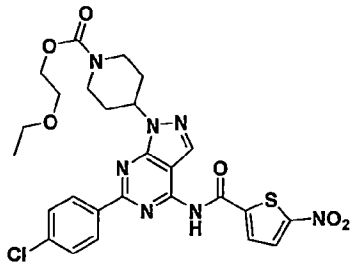
4-(6-(4-氯苯基)-4-(5-硝基噻吩-2-甲醯胺基)-1H-吡唑並[3,4-d]嘧啶-1-基)哌啶-1-甲酸 2-甲氧基乙酯(2-methoxyethyl 4-(6-(4-chlorophenyl)-4-(5-nitrothiophene-2-carboxamido)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidine-1-carboxylate)



^{1}H NMR (400MHz, DMSO-d_6): δ 11.93 (br. s., 1H), 8.48-8.58 (m, 2H), 8.39 (s, 1H), 8.35 (d, J = 4.4 Hz, 1H), 8.24 (d, J = 4.4 Hz, 1H), 7.58-7.69 (m, 2H), 5.15 (dt, J = 10.3, 5.1 Hz, 1H), 4.06-4.23 (m, 4H), 3.48-3.61 (m, 2H), 3.29 (s, 3H), 3.13 (d, J = 16.1 Hz, 2H), 1.97- 2.13 (m, 4H). MS(M+1): 586. 黃色固體。

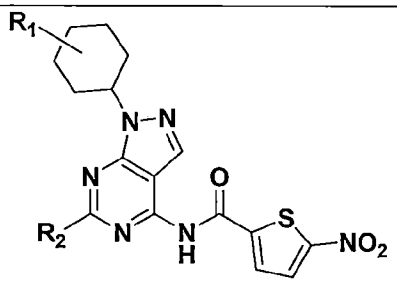
【0478】化合物 9-13

4-(6-(4-氯苯基)-4-(5-硝基噻吩-2-甲醯胺基)-1H-吡唑並[3,4-d]嘧啶-1-基)哌啶-1-甲酸 2-乙氧基乙酯(2-ethoxyethyl 4-(6-(4-chlorophenyl)-4-(5-nitrothiophene-2-carboxamido)-1H-pyrazolo [3,4-d]pyrimidin-1-yl)piperidine-1-carboxylate)



^{1}H NMR (400MHz, DMSO-d_6): δ 11.93 (br. s., 1H), 8.47-8.59 (m, 2H), 8.30-8.44 (m, 2H), 8.23 (d, J = 4.4 Hz, 1H), 7.59-7.70 (m, 2H), 5.06-5.22 (m, 1H), 4.05-4.28 (m, 4H), 3.52-3.67 (m, 2H), 3.48 (q, J = 7.2 Hz, 2H), 3.15 (br. s., 2H), 1.96-2.14 (m, 4H), 1.03-1.16 (m, 3H). MS(M+1): 600. 淺黃色固體。

【0479】表10



化合物	R_1	R_2	Hep3B LC_{50} (uM)
10-1	氫	3,3-二氟吡咯烷-1-基	1.25
10-2	氫	4,4-二氟哌啶-1-基	3.12
10-3	氫	2-(羥甲基)吡咯烷-1-基	>5.0
10-4	氫	呋喃-2-基	1.19

10-5	氫	噻吩-2-基	0.75
10-6	氫	噻吩-3-基	1.03
10-7	氫	5-甲基噻吩-2-基	1.53
10-8	氫	5-氯噻吩-2-基	0.49
10-9	氫	3,5-二甲基異噁唑-4-基	1.07
10-10	氫	吡啶-3-基	0.99
10-11	氫	2-氟苯基	1.94
10-12	氫	3-氟苯基	0.95
10-13	氫	4-氟苯基	0.70
10-14	氫	6-氟吡啶-3-基	0.89
10-15	氫	2-氟吡啶-4-基	1.17
10-16	氫	3-氯苯基	0.61
10-17	氫	4-氯苯基	0.53
10-18	氫	6-氯吡啶-3-基	0.68
10-19	氫	6-甲基吡啶-3-基	1.13
10-20	氫	4-氰基苯基	1.20
10-21	氫	6-甲氧基吡啶-3-基	1.12
10-22	氫	5-甲氧基吡啶-3-基	1.16
10-23	氫	6-乙氧基吡啶-3-基	0.57
10-24	氫	4-(三氟甲基)苯基	0.64
10-25	氫	6-(三氟甲基)吡啶-3-基	
10-26	氫	4-(三氟甲氧基)苯基	0.68
10-27	氫	4-甲醯基苯基	0.84
10-28	氫	4-乙醯基苯基	1.93
10-29	氫	4-((二甲胺基)甲基)苯基	1.51
10-30	氫	4-(甲氧基甲基)苯基	0.84
10-31	氫	3-苯甲酸甲酯	0.58
10-32	氫	4-苯甲酸甲酯	0.40
10-33	氫	4-苯甲酸乙酯	0.54
10-34	氫	4-(甲磺醯基)苯基	0.93

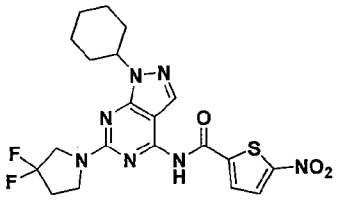
10-35	氫	4-(叔丁基)苯基	1.33
10-36	氫	苯並[d][1,3]二氧雜-5-基	2.12
10-37	氫	2,3-二氫苯並[b][1,4]二噁英-6-基	1.94
10-38	氫	6-嗎啉並吡啶-3-基	NA
10-39	氫	2,4-二氟苯基	1.24
10-40	氫	3,4-二氟苯基	0.32
10-41	氫	3,5-二氟苯基	0.79
10-42	氫	2,4-二氯苯基	>1.25
10-43	氫	3,4-二氯苯基	0.77
10-44	氫	3-氯-4-乙氧基苯基	>2.0
10-45	氫	4-氯-2-氟苯基	0.87
10-46	氫	2-氯-4-氟苯基	1.03
10-47	氫	5-氯-2-氟苯基	0.63
10-48	氫	3,4-二甲氧基苯基	0.97
10-49	氫	6-(2,2,2-三氟乙氧基)吡啶-3-基	0.63
10-50	氫	4-(2-甲氧基乙氧基)苯基	2.64
10-51	氫	6-(2-甲氧基乙氧基)吡啶-3-基	0.96
10-52	氫	6-(2,2,3,3-四氟丙氧基)吡啶-3-基	0.42
10-53	氫	6-(2-(2-乙氧基乙氧基)乙氧基)吡啶-3-基	1.23
10-54	4,4-二氟(4,4-difluoro)	4-氟苯基	0.92
10-55	4,4-二氟(4,4-difluoro)	6-氟吡啶-3-基	0.71
10-56	4,4-二氟(4,4-difluoro)	4-氯苯基	0.77
10-57	4,4-二氟(4,4-difluoro)	6-氯吡啶-3-基	0.57
10-58	4,4-二氟(4,4-difluoro)	4-(三氟甲基)苯基	0.61
10-59	4,4-二氟(4,4-difluoro)	4-乙氧基苯基	1.28
10-60	4,4-二氟(4,4-difluoro)	4-丙氧基苯基	0.83
10-61	4,4-二甲基	4-氟苯基	0.55
10-62	4,4-二甲基	6-氟吡啶-3-基	0.71
10-63	4,4-二甲基	4-氯苯基	0.86
10-64	4,4-二甲基	6-氯吡啶-3-基	0.57

10-65	4,4-二甲基	4-氯-2-氟苯基	0.58
10-66	4,4-二甲基	苯並[d][1,3]二氧雜-5-基	0.61
10-67	4,4-二甲基	4-氟苯基	0.65
10-68	4,4-二甲基	6-氟吡啶-3-基	0.97
10-69	4,4-二甲基	4-氯苯基	0.86
10-70	4,4-二甲基	6-氯吡啶-3-基	0.96
10-71	4,4-二甲基	4-苯甲酸甲酯	0.69
10-72	4,4-二甲基	4-氯-2-氟苯基	0.76

【0480】化合物 10-1

N-(1-環己基-6-(3,3-二氟吡咯烷-1-基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(1-cyclohexyl-6-(3,3-difluoropyrrolidin-1-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

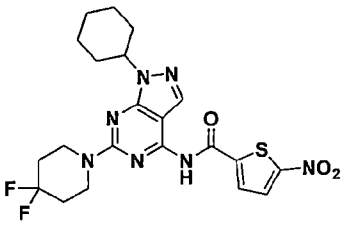


^{1}H NMR (400MHz, DMSO-d_6): δ 11.50 (br. s., 1H), 8.28 (d, J = 4.4 Hz, 1H), 8.21 (d, J = 4.4 Hz, 1H), 8.06 (s, 1H), 4.50-4.60 (m, 1H), 4.01 (t, J = 13.2 Hz, 2H), 3.83 (t, J = 7.3 Hz, 2H), 2.52-2.63 (m, 2H), 1.82-1.97 (m, 6H), 1.70 (d, J = 12.7 Hz, 1H), 1.38-1.52 (m, 2H), 1.19-1.34 (m, 1H). MS(M+1):478. 淺黃色固體。

【0481】化合物 10-2

N-(1-環己基-6-(4,4-二氟哌啶-1-基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(1-cyclohexyl-6-(4,4-difluoropiperidin-1-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

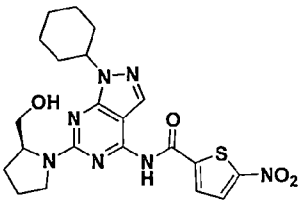


^{1}H NMR (400MHz, DMSO-d_6): δ 11.44 (br. s., 1H), 8.24-8.30 (m, 1H), 8.22 (d, J = 4.4 Hz, 1H), 8.07 (s, 1H), 4.54 (dt, J = 9.8, 4.9 Hz, 1H), 4.00 (t, J = 5.6 Hz, 4H), 1.96-2.14 (m, 4H), 1.80-1.96 (m, 6H), 1.66-1.76 (m, 1H), 1.37-1.51 (m, 2H), 1.18-1.31 (m, 1H). MS(M+1):492. 淺黃色固體。

【0482】化合物 10-3

(S)-N-(1-環己基-6-(2-(羥甲基)吡咯烷-1-基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

((S)-N-(1-cyclohexyl-6-(2-(hydroxymethyl)pyrrolidin-1-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

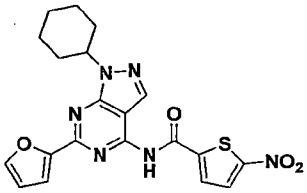


^{1}H NMR (400MHz, DMSO-d_6): δ 8.12-8.38 (m, 2H), 7.98 (s, 1H), 4.78 (br. s., 1H), 4.40 -4.58 (m, 1H), 4.21 (br. s., 1H), 3.66 (br. s., 1H), 3.45-3.63 (m, 3H), 1.79-2.08 (m, 10H), 1.69 (d, J = 13.2 Hz, 1H), 1.32-1.51 (m, 2H), 1.15-1.32 (m, 1H). MS(M+1):472. 橘色固體。

【0483】化合物 10-4

N-(1-環己基-6-(呋喃-2-基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(1-cyclohexyl-6-(furan-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

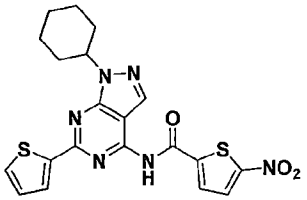


^{1}H NMR (400MHz, DMSO-d_6): δ 12.06 (br. s., 1H), 8.35 (d, J = 4.4 Hz, 1H), 8.32 (s, 1H), 8.22 (d, J = 4.4 Hz, 1H), 7.98 (s, 1H), 7.40 (d, J = 2.9 Hz, 1H), 6.74 (dd, J = 3.4, 2.0 Hz, 1H), 4.75-4.87 (m, 1H), 1.92-2.05 (m, 4H), 1.89 (d, J = 13.2 Hz, 2H), 1.73 (d, J = 12.7 Hz, 1H), 1.45-1.62 (m, 2H), 1.23-1.38 (m, 1H). MS(M+1):439. 卡其色固體。

【0484】化合物 10-5

N-(1-環己基-6-(噻吩-2-基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(1-cyclohexyl-6-(thiophen-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

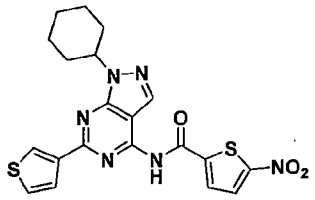


^{1}H NMR (400MHz, DMSO-d_6): δ 11.96 (br. s., 1H), 8.33 (d, J = 4.4 Hz, 1H), 8.30 (s, 1H), 8.23 (d, J = 4.4 Hz, 1H), 8.07 (dd, J = 3.9, 1.5 Hz, 1H), 7.79 (dd, J = 4.9, 1.0 Hz, 1H), 7.20-7.28 (m, 1H), 4.77 (dt, J = 15.6, 7.8 Hz, 1H), 1.81-2.04 (m, 6H), 1.74 (d, J = 12.7 Hz, 1H), 1.43-1.60 (m, 2H), 1.21-1.38 (m, 1H). MS(M+1):455. 卡其色固體。

【0485】化合物 10-6

N-(1-環己基-6-(噻吩-3-基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(1-cyclohexyl-6-(thiophen-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

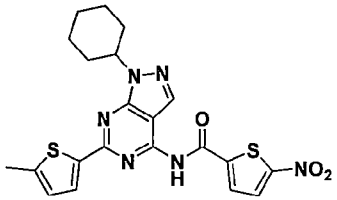


^{1}H NMR (400MHz, DMSO-d_6): δ 11.93 (br. s., 1H), 8.46 (d, J = 2.9 Hz, 1H), 8.29- 8.37 (m, 2H), 8.24 (d, J = 4.4 Hz, 1H), 7.94 (d, J = 4.9 Hz, 1H), 7.69 (dd, J = 5.1, 3.2 Hz, 1H), 4.78-4.91 (m, 1H), 1.94-2.06 (m, 4H), 1.89 (d, J = 12.7 Hz, 2H), 1.74 (d, J = 12.7 Hz, 1H), 1.45-1.60 (m, 2H), 1.23-1.39 (m, 1H). MS(M+1):455. 卡其色固體。

【0486】化合物 10-7

N-(1-環己基-6-(5-甲基噻吩-2-基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(1-cyclohexyl-6-(5-methylthiophen-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

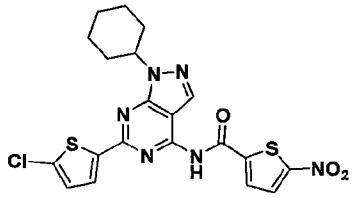


^{1}H NMR (400MHz, DMSO-d_6): δ 11.86 (br. s., 1H), 8.32-8.40 (m, 1H), 8.27 (s, 1H), 8.17-8.24 (m, 1H), 7.87 (d, J = 3.4 Hz, 1H), 6.93 (dd, J = 3.4, 1.0 Hz, 1H), 4.66-4.79 (m, 1H), 2.53 (s, 3H), 1.93-2.04 (m, 4H), 1.89 (d, J = 13.2 Hz, 2H), 1.73 (d, J = 12.7 Hz, 1H), 1.42-1.56 (m, 2H), 1.20-1.36 (m, 1H). MS(M+1):469. 黃色固體。

【0487】化合物 10-8

N-(6-(5-氯噻吩-2-基)-1-環己基-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(6-(5-chlorothiophen-2-yl)-1-cyclohexyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

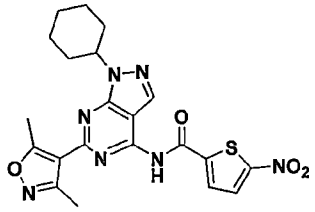


^{1}H NMR (400MHz, DMSO-d_6): δ 11.91 (br. s., 1H), 8.28-8.41 (m, 2H), 8.23 (d, J = 4.4 Hz, 1H), 7.90 (d, J = 3.9 Hz, 1H), 7.26 (d, J = 3.9 Hz, 1H), 4.75 (t, J = 7.3 Hz, 1H), 1.93-2.08 (m, 4H), 1.89 (d, J = 13.2 Hz, 2H), 1.73 (d, J = 12.7 Hz, 1H), 1.40-1.60 (m, 2H), 1.15-1.36 (m, 1H). MS(M+1):489. 黃色固體。

【0488】化合物 10-9

N-(1-環己基-6-(3,5-二甲基異噁唑-4-基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(1-cyclohexyl-6-(3,5-dimethylisoxazol-4-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

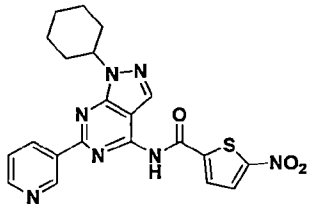


^{1}H NMR (400MHz, DMSO-d_6): δ 11.65 (br. s., 1H), 8.34 (s, 1H), 8.23-8.30 (m, 2H), 4.74 (dt, J = 15.7, 7.8 Hz, 1H), 2.88 (s, 3H), 2.60-2.69 (m, 3H), 1.94-2.05 (m, 4H), 1.89 (d, J = 13.2 Hz, 2H), 1.73 (d, J = 13.2 Hz, 1H), 1.41-1.57 (m, 2H), 1.24-1.36 (m, 1H). MS(M+1):468.卡其色固體。

【0489】化合物 10-10

N-(1-環己基-6-(吡啶-3-基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(1-cyclohexyl-6-(pyridin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

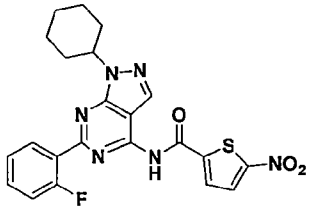


^{1}H NMR (400MHz, DMSO-d_6): δ 11.95 (br. s., 1H), 9.67 (d, J = 1.5 Hz, 1H), 8.69 -8.86 (m, 2H), 8.41 (s, 1H), 8.36 (d, J = 4.4 Hz, 1H), 8.25 (d, J = 4.4 Hz, 1H), 7.55 -7.67 (m, 1H), 4.80-5.01 (m, 1H), 1.94-2.08 (m, 4H), 1.83-1.94 (m, 2H), 1.74 (d, J = 13.2 Hz, 1H), 1.48-1.66 (m, 2H), 1.23-1.39 (m, 1H). MS(M+1):450.卡其色固體。

【0490】化合物 10-11

N-(1-環己基-6-(2-氟苯基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(1-cyclohexyl-6-(2-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

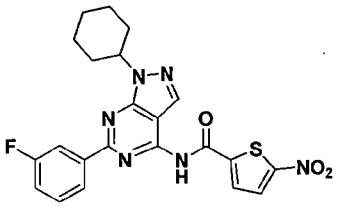


^{1}H NMR (400MHz, DMSO-d_6): δ 12.08 (br. s., 1H), 8.41 (s, 1H), 8.34 (br. s., 1H), 8.22 (d, J = 4.4 Hz, 1H), 8.01-8.12 (m, 1H), 7.55-7.67 (m, 1H), 7.30-7.43 (m, 2H), 4.81 (dt, J = 15.4, 7.9 Hz, 1H), 1.92-2.09 (m, 4H), 1.88 (d, J = 13.2 Hz, 2H), 1.66 -1.79 (m, 1H), 1.43- 1.57 (m, 2H), 1.22-1.35 (m, 1H). MS(M+1):467. 淺卡其色固體。

【0491】化合物 10-12

N-(1-環己基-6-(3-氟苯基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(1-cyclohexyl-6-(3-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

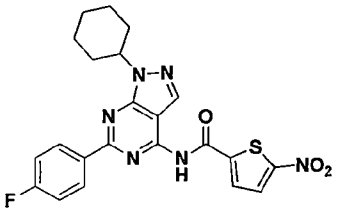


^{1}H NMR (400MHz, DMSO-d_6): δ 8.34-8.47 (m, 2H), 8.18-8.34 (m, 3H), 7.62 (td, J = 7.9, 6.1 Hz, 1H), 7.40 (td, J = 8.4, 2.2 Hz, 1H), 4.84-4.96 (m, 1H), 1.94-2.08 (m, 4H), 1.85- 1.94 (m, 2H), 1.74 (d, J = 12.7 Hz, 1H), 1.56 (d, J = 8.3 Hz, 2H), 1.25-1.37 (m, 1H). MS(M+1):467.卡其色固體。

【0492】化合物 10-13

N-(1-環己基-6-(4-氟苯基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(1-cyclohexyl-6-(4-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

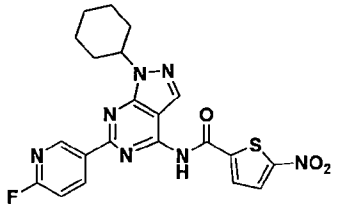


^{1}H NMR (400MHz, DMSO-d_6): δ 11.88 (br. s., 1H), 8.53-8.64 (m, 2H), 8.32-8.42 (m, 2H), 8.25 (d, J = 4.4 Hz, 1H), 7.34-7.47 (m, 2H), 4.83-4.96 (m, 1H), 1.95-2.10 (m, 4H), 1.91 (d, J = 13.2 Hz, 2H), 1.69-1.81 (m, 1H), 1.46-1.64 (m, 2H), 1.24-1.39 (m, 1H). MS(M+1):467.

【0493】化合物 10-14

N-(1-環己基-6-(6-氟吡啶-3-基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(1-cyclohexyl-6-(6-fluoropyridin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

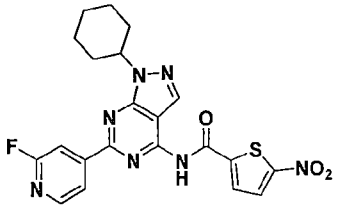


^{1}H NMR (400MHz, DMSO-d_6): δ 11.95 (br. s., 1H), 9.31 (d, J = 2.4 Hz, 1H), 8.96 (td, J = 8.3, 2.4 Hz, 1H), 8.41 (s, 1H), 8.34 (d, J = 4.4 Hz, 1H), 8.25 (d, J = 4.4 Hz, 1H), 7.41 (dd, J = 8.6, 2.7 Hz, 1H), 4.91 (t, J = 6.8 Hz, 1H), 1.94-2.05 (m, 4H), 1.85-1.94 (m, 2H), 1.74 (d, J = 12.7 Hz, 1H), 1.47-1.61 (m, 2H), 1.30 (d, J = 12.7 Hz, 1H). MS(M+1): 468. 淺黃色固體。

【0494】化合物 10-15

N-(1-環己基-6-(2-氟吡啶-4-基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(1-cyclohexyl-6-(2-fluoropyridin-4-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

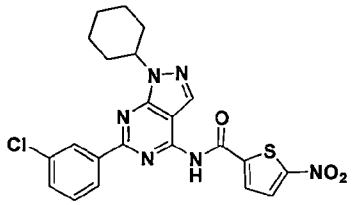


^{1}H NMR (400MHz, DMSO-d_6): δ 12.00 (br. s., 1H), 8.43-8.52 (m, 2H), 8.31-8.38 (m, 2H), 8.25 (d, J = 4.4 Hz, 1H), 8.09 (s, 1H), 4.88-4.99 (m, 1H), 1.96-2.06 (m, 4H), 1.90 (d, J = 12.7 Hz, 2H), 1.71-1.80 (m, 1H), 1.49-1.61 (m, 2H), 1.26-1.38 (m, 1H). MS (M+1): 468. 淺黃色固體。

【0495】化合物 10-16

N-(6-(3-氯苯基)-1-環己基-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(6-(3-chlorophenyl)-1-cyclohexyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

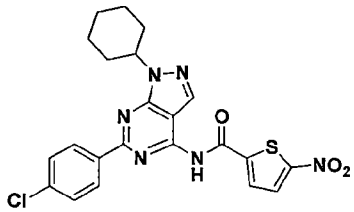


^{1}H NMR (400MHz, DMSO-d_6): δ 11.90 (br. s., 1H), 8.50-8.63 (m, 1H), 8.45-8.50 (m, 1H), 8.39 (s, 1H), 8.34 (d, J = 4.4 Hz, 1H), 8.24 (d, J = 4.4 Hz, 1H), 7.53-7.69 (m, 2H), 4.82-4.97 (m, 1H), 1.93-2.10 (m, 4H), 1.90 (d, J = 13.2 Hz, 2H), 1.74 (d, J = 13.2 Hz, 1H), 1.45-1.64 (m, 2H), 1.21-1.41 (m, 1H). MS(M+1): 483. 白色固體。

【0496】化合物 10-17

N-(6-(4-氯苯基)-1-環己基-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(6-(4-chlorophenyl)-1-cyclohexyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

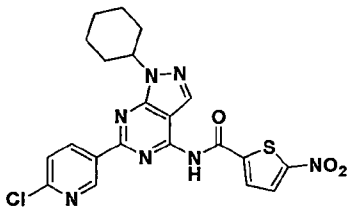


^{1}H NMR (400MHz, DMSO-d_6): δ 11.88 (br. s., 1H), 8.49-8.55 (m, 2H), 8.30-8.41 (m, 2H), 8.22 (d, J = 4.4 Hz, 1H), 7.58-7.69 (m, 2H), 4.82-4.92 (m, 1H), 1.92-2.03 (m, 4H), 1.89 (d, J = 13.7 Hz, 2H), 1.69-1.81 (m, 1H), 1.44-1.62 (m, 2H), 1.22-1.37 (m, 1H).MS(M+1): 483. 黃色固體。

【0497】化合物 10-18

N-(6-(6-氯吡啶-3-基)-1-環己基-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(6-(6-chloropyridin-3-yl)-1-cyclohexyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

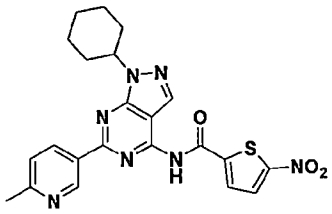


^{1}H NMR (400MHz, DMSO-d_6): δ 11.97 (br. s., 1H), 9.46 (d, J = 2.4 Hz, 1H), 8.82 (dd, J = 8.3, 2.4 Hz, 1H), 8.42 (s, 1H), 8.35 (d, J = 4.4 Hz, 1H), 8.25 (d, J = 4.4 Hz, 1H), 7.75 (d, J = 8.3 Hz, 1H), 4.77-5.01 (m, 1H), 1.94-2.07 (m, 4H), 1.83-1.94 (m, 2H), 1.74 (d, J = 12.7 Hz, 1H), 1.44-1.64 (m, 2H), 1.20-1.39 (m, 1H). MS(M+1): 484. 淺黃色固體。

【0498】化合物 10-19

N-(1-環己基-6-(6-甲基吡啶-3-基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(1-cyclohexyl-6-(6-methylpyridin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

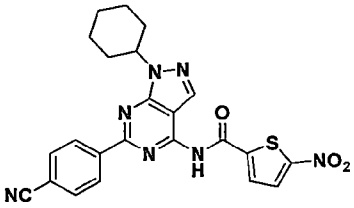


^{1}H NMR (400MHz, DMSO-d_6): δ 11.95 (br. s., 1H), 9.54 (d, J = 2.0 Hz, 1H), 8.68 (dd, J = 8.1, 2.2 Hz, 1H), 8.38 (s, 1H), 8.34 (d, J = 4.4 Hz, 1H), 8.24 (d, J = 4.4 Hz, 1H), 7.46 (d, J = 8.3 Hz, 1H), 4.81-4.98 (m, 1H), 2.58 (s, 3H), 1.95-2.05 (m, 4H), 1.90 (d, J = 13.2 Hz, 2H), 1.74 (d, J = 12.7 Hz, 1H), 1.46-1.62 (m, 2H), 1.21-1.36 (m, 1H). MS(M+1): 464. 黃色固體。

【0499】化合物 10-20

N-(6-(4-氰基苯基)-1-環己基-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(6-(4-cyanophenyl)-1-cyclohexyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

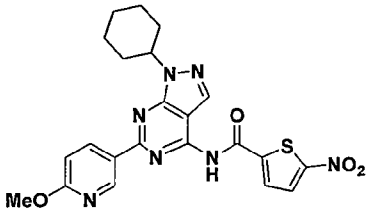


^{1}H NMR (400MHz, DMSO-d_6): δ 11.96 (br. s., 1H), 8.65-8.73 (m, 2H), 8.41 (s, 1H), 8.35 (d, J = 4.4 Hz, 1H), 8.24 (d, J = 4.4 Hz, 1H), 8.01-8.09 (m, 2H), 4.84-4.96 (m, 1H), 1.95- 2.07 (m, 4H), 1.90 (d, J = 13.2 Hz, 2H), 1.70-1.81 (m, 1H), 1.48-1.62 (m, 2H), 1.25-1.40 (m, 1H). MS(M+1): 474. 淺卡其色固體。

【0500】化合物 10-21

N-(1-環己基-6-(6-甲氧基吡啶-3-基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(1-cyclohexyl-6-(6-methoxypyridin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

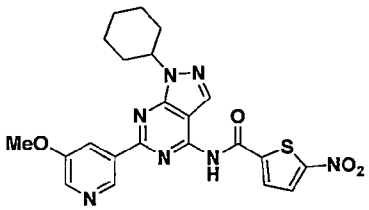


^{1}H NMR (400MHz, DMSO-d_6): δ 11.85 (br. s., 1H), 9.28 (d, J = 2.0 Hz, 1H), 8.69 (dd, J = 8.8, 2.4 Hz, 1H), 8.31-8.39 (m, 2H), 8.23 (d, J = 4.4 Hz, 1H), 7.00 (d, J = 8.8 Hz, 1H), 4.79-4.93 (m, 1H), 3.95 (s, 3H), 1.93-2.08 (m, 4H), 1.89 (d, J = 13.2 Hz, 2H), 1.70-1.79 (m, 1H), 1.43-1.61 (m, 2H), 1.20-1.36 (m, 1H). MS(M+1): 480. 淺卡其色固體。

【0501】化合物 10-22

N-(1-環己基-6-(5-甲氧基吡啶-3-基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(1-cyclohexyl-6-(5-methoxypyridin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

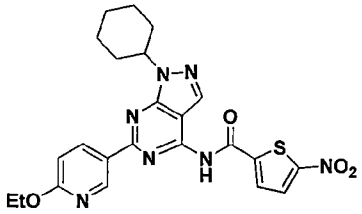


^{1}H NMR (400MHz, DMSO-d_6) : δ 11.92 (br. s., 1H), 9.29 (s, 1H), 8.47 (d, J = 2.4 Hz, 1H), 8.41 (s, 1H), 8.36 (d, J = 4.4 Hz, 1H), 8.27-8.34 (m, 1H), 8.25 (d, J = 4.4 Hz, 1H), 4.92 (t, J = 7.1 Hz, 1H), 3.97 (s, 3H), 1.95-2.03 (m, 4H), 1.90 (d, J = 12.7 Hz, 2H), 1.74 (d, J = 13.2 Hz, 1H), 1.48-1.61 (m, 2H), 1.24-1.36 (m, 1H). MS(M+1): 480. 金菊色粉末。

【0502】化合物 10-23

N-(1-環己基-6-(6-乙氧基吡啶-3-基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(1-cyclohexyl-6-(6-ethoxypyridin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

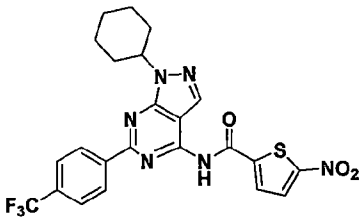


^{1}H NMR (400MHz, DMSO-d_6): δ 11.84 (br. s., 1H), 9.26 (d, J = 2.0 Hz, 1H), 8.68 (dd, J = 8.8, 2.4 Hz, 1H), 8.30-8.41 (m, 2H), 8.23 (d, J = 4.4 Hz, 1H), 6.96 (d, J = 8.8 Hz, 1H), 4.86 (t, J = 6.8 Hz, 1H), 4.40 (q, J = 7.3 Hz, 2H), 1.93-2.07 (m, 4H), 1.89 (d, J = 13.7 Hz, 2H), 1.74 (d, J = 12.7 Hz, 1H), 1.44-1.63 (m, 2H), 1.36 (t, J = 6.8 Hz, 3H), 1.20-1.33 (m, 1H). MS(M+1):494. 褐色固體。

【0503】化合物 10-24

N-(1-環己基-6-(4-(三氟甲基)苯基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(1-cyclohexyl-6-(4-(trifluoromethyl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

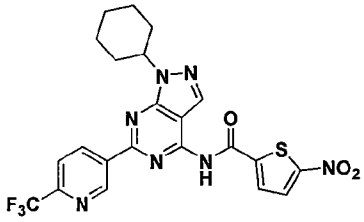


^{1}H NMR (400MHz, DMSO-d_6): δ 11.99 (br. s., 1H), 8.69-8.78 (m, J = 8.3 Hz, 2H), 8.41 (s, 1H), 8.36 (d, J = 4.4 Hz, 1H), 8.24 (d, J = 4.4 Hz, 1H), 7.91-7.99 (m, J = 8.3 Hz, 2H), 4.86-4.97 (m, 1H), 1.94-2.09 (m, 4H), 1.83-1.94 (m, 2H), 1.75 (d, J = 12.7 Hz, 1H), 1.46 -1.62 (m, 2H), 1.25-1.41 (m, 1H). MS(M+1):517.黃褐色固體。

【0504】化合物 10-25

N-(1-環己基-6-(6-(三氟甲基)吡啶-3-基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(1-cyclohexyl-6-(6-(trifluoromethyl)pyridin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

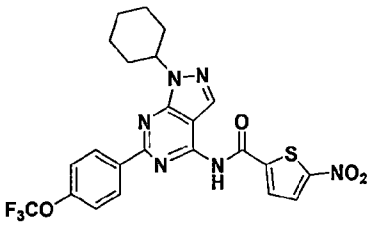


^{1}H NMR (400MHz, DMSO-d_6): δ 12.01 (br. s., 1H), 9.72-9.83 (m, 1H), 9.03 (dd, J = 8.1, 1.7 Hz, 1H), 8.41-8.49 (m, 1H), 8.36 (d, J = 4.4 Hz, 1H), 8.24 (d, J = 4.4 Hz, 1H), 8.10-8.16 (m, 1H), 4.83-5.00 (m, 1H), 1.95-2.11 (m, 4H), 1.90 (d, J = 13.2 Hz, 2H), 1.75 (d, J = 12.7 Hz, 1H), 1.45-1.62 (m, 2H), 1.25-1.39 (m, 1H). MS(M+1): 518. 卡其色固體。

【0505】化合物 10-26

N-(1-環己基-6-(4-(三氟甲氧基)苯基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(1-cyclohexyl-6-(4-(trifluoromethoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

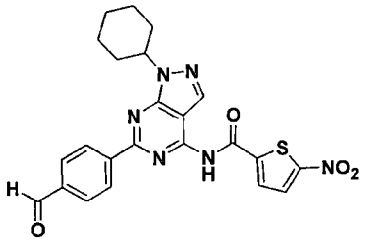


^{1}H NMR (400MHz, DMSO-d_6): δ 11.94 (br. s., 1H), 8.59-8.68 (m, 2H), 8.30-8.40 (m, 2H), 8.23 (d, J = 4.4 Hz, 1H), 7.49-7.63 (m, J = 8.3 Hz, 2H), 4.81-4.95 (m, 1H), 1.94-2.09 (m, 4H), 1.89 (d, J = 12.7 Hz, 2H), 1.69-1.82 (m, 1H), 1.44-1.61 (m, 2H), 1.23-1.37 (m, 1H). MS(M+1):533. 卡其色固體。

【0506】化合物 10-27

N-(1-環己基-6-(4-甲醯基苯基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(1-cyclohexyl-6-(4-formylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

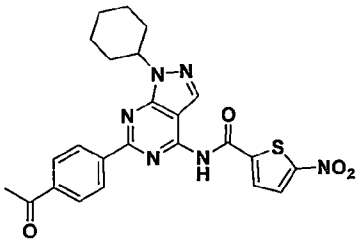


^{1}H NMR (400MHz, DMSO-d_6): δ 11.98 (br. s., 1H), 10.13 (s, 1H), 8.66-8.79 (m, J = 8.3 Hz, 2H), 8.34-8.47 (m, 2H), 8.25 (d, J = 4.4 Hz, 1H), 8.03-8.20 (m, J = 8.3 Hz, 2H), 4.79- 5.03 (m, 1H), 1.96-2.09 (m, 4H), 1.83-1.96 (m, 2H), 1.75 (d, J = 13.2 Hz, 1H), 1.43-1.68 (m, 2H), 1.21-1.41 (m, 1H). MS(M+1): 477. 黃色固體。

【0507】化合物 10-28

N-(6-(4-乙醯基苯基)-1-環己基-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(6-(4-acetylphenyl)-1-cyclohexyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

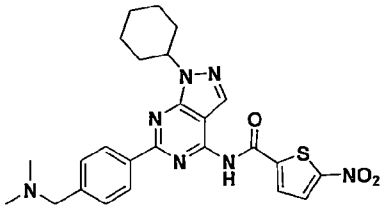


^{1}H NMR (DMSO-d6, 400 MHz): δ 11.97 (brs., 1H), 8.56-8.74 (m, J = 8.3 Hz, 2H), 8.31-8.45 (m, 2H), 8.25 (d, J = 4.4 Hz, 1H), 8.05-8.20 (m, J = 8.3 Hz, 2H), 4.83-4.99 (m, 1H), 2.66 (s, 3H), 1.95-2.06 (m, 4H), 1.91 (d, J = 12.7 Hz, 2H), 1.75 (d, J = 13.2 Hz, 1H), 1.43-1.66 (m, 2H), 1.21-1.40 (m, 1H). MS(M+1): 491. 黃色固體。

【0508】化合物 10-29

N-(1-環己基-6-(4-((二甲基胺基)甲基)苯基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(1-cyclohexyl-6-(4-((dimethylamino)methyl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

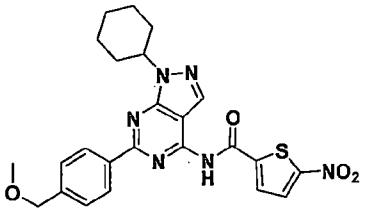


^{1}H NMR (400MHz, DMSO-d_6): δ 11.93 (br. s., 1H), 8.53-8.66 (m, J = 8.3 Hz, 2H), 8.32-8.49 (m, 2H), 8.26 (d, J = 4.4 Hz, 1H), 7.65-7.79 (m, J = 7.8 Hz, 2H), 4.91 (dt, J = 15.3, 7.8 Hz, 1H), 4.32 (br. s., 2H), 2.71 (s, 6H), 1.94-2.08 (m, 4H), 1.90 (d, J = 13.2 Hz, 2H), 1.75 (d, J = 13.2 Hz, 1H), 1.43-1.63 (m, 2H), 1.26-1.41 (m, 1H). MS(M+1): 506. 卡其色固體。

【0509】化合物 10-30

N-(1-環己基-6-(4-(甲氧基甲基)苯基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(1-cyclohexyl-6-(4-(methoxymethyl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

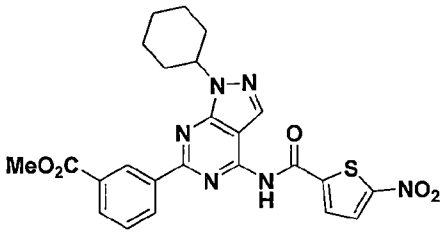


^{1}H NMR (400MHz, DMSO-d_6): δ 11.91 (br. s., 1H), 8.48-8.59 (m, J = 8.3 Hz, 2H), 8.33-8.41 (m, 2H), 8.24 (d, J = 4.4 Hz, 1H), 7.44-7.57 (m, J = 8.3 Hz, 2H), 4.82-4.99 (m, 1H), 4.52 (s, 2H), 3.35 (s, 3H), 1.93-2.09 (m, 4H), 1.90 (d, J = 13.2 Hz, 2H), 1.71-1.81 (m, 1H), 1.47-1.62 (m, 2H), 1.26-1.37 (m, 1H). MS(M+1): 493.卡其色固體。

【0510】化合物 10-31

3-(1-環己基-4-(5-硝基噻吩-2-甲醯胺基)-1H-吡唑並[3,4-d]嘧啶-6-基)苯甲酸甲酯(methyl

3-(1-cyclohexyl-4-(5-nitrothiophene-2-carboxamido)-1H-pyrazolo[3,4-d]pyrimidin-6-yl)benzoate)

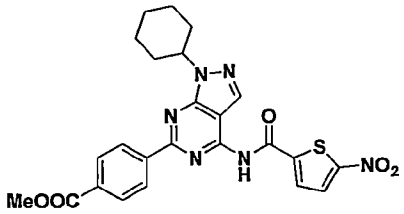


^{1}H NMR (400MHz, DMSO-d_6): δ 12.01 (br. s., 1H), 9.10 (t, J = 1.7 Hz, 1H), 8.73-8.84 (m, 1H), 8.31-8.42 (m, 2H), 8.24 (d, J = 4.9 Hz, 1H), 8.10-8.17 (m, 1H), 7.73 (t, J = 7.8 Hz, 1H), 4.85-4.98 (m, 1H), 3.93 (s, 3H), 1.96-2.12 (m, 4H), 1.90 (d, J = 13.2 Hz, 2H), 1.75 (d, J = 12.7 Hz, 1H), 1.46-1.64 (m, 2H), 1.25-1.39 (m, 1H).

MS(M+1):507. 卡其色固體。

【0511】化合物 10-32

4-(1-環己基-4-(5-硝基噻吩-2-甲醯胺基)-1H-吡唑並[3,4-d]嘧啶-6-基)苯甲酸甲酯(methyl 4-(1-cyclohexyl-4-(5-nitrothiophene-2-carboxamido)-1H-pyrazolo[3,4-d] pyrimidin-6-yl)benzoate)

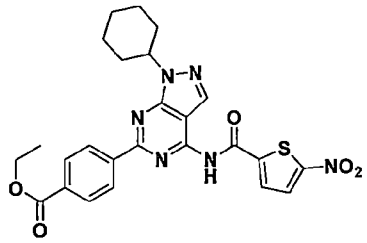


^{1}H NMR (400MHz, DMSO-d_6): δ 12.02 (br. s., 1H), 8.61-8.71 (m, J = 8.3 Hz, 2H), 8.38-8.45 (m, 1H), 8.34 (d, J = 4.4 Hz, 1H), 8.24 (d, J = 4.4 Hz, 1H), 8.10-8.20 (m, 2H), 4.83-5.01 (m, 1H), 3.82-3.98 (m, 3H), 1.95-2.07 (m, 4H), 1.84-1.95 (m, 2H), 1.75 (d, J = 13.2 Hz, 1H), 1.48-1.63 (m, 2H), 1.23-1.39 (m, 1H). MS(M+1):507. 淺卡其色固體。

【0512】化合物 10-33

4-(1-環己基-4-(5-硝基噻吩-2-甲醯胺基)-1H-吡唑並[3,4-d]嘧啶-6-基)苯甲酸乙酯 1285

(ethyl 4-(1-cyclohexyl-4-(5-nitrothiophene-2-carboxamido)-1H-pyrazolo[3,4-d] pyrimidin-6-yl)benzoate 1285)



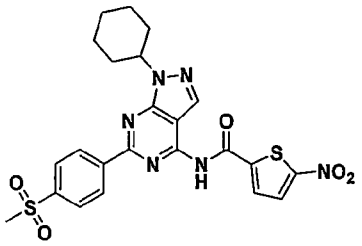
^{1}H NMR (400MHz, DMSO-d_6): δ 12.00 (br. s., 1H), 8.61-8.72 (m, J = 8.3 Hz, 2H), 8.39 (s, 1H), 8.35 (d, J = 4.4 Hz, 1H), 8.24 (d, J = 4.4 Hz, 1H), 8.11-8.20 (m, J = 8.3 Hz, 2H), 4.86-4.98 (m, 1H), 4.37 (q, J = 7.2 Hz, 2H), 1.96-2.14 (m, 4H), 1.90 (d, J

= 13.2 Hz, 2H), 1.75 (d, J = 13.2 Hz, 1H), 1.47-1.65 (m, 2H), 1.36 (t, J = 7.1 Hz, 3H), 1.24-1.34 (m, 1H). MS(M+1): 521. 黃色固體。

【0513】化合物 10-34

N-(1-環己基-6-(4-(甲基磺醯基)苯基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(1-cyclohexyl-6-(4-(methylsulfonyl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

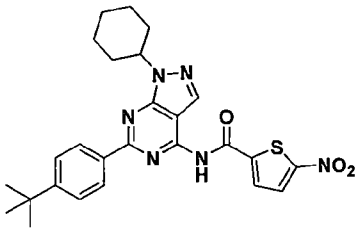


^{1}H NMR (400MHz, DMSO-d_6): δ 12.00 (br. s., 1H), 8.67-8.80 (m, 2H), 8.40 (s, 1H), 8.36 (d, J = 4.4 Hz, 1H), 8.24 (d, J = 4.4 Hz, 1H), 8.10-8.18 (m, 2H), 4.85-4.96 (m, 1H), 3.30 (s, 3H), 1.95-2.09 (m, 4H), 1.90 (d, J = 13.2 Hz, 2H), 1.68-1.82 (m, 1H), 1.47-1.64 (m, 2H), 1.23-1.40 (m, 1H). MS(M+1):527. 淡黃色固體。

【0514】化合物 10-35

N-(6-(4-(叔丁基)苯基)-1-環己基-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(6-(4-(tert-butyl)phenyl)-1-cyclohexyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)



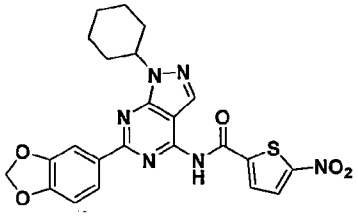
^{1}H NMR (400MHz, DMSO-d_6): δ 11.89 (br. s., 1H), 8.45 (d, J = 8.3 Hz, 2H), 8.35- 8.39 (m, 1H), 8.34 (s, 1H), 8.23 (d, J = 4.4 Hz, 1H), 7.53-7.63 (m, 2H), 4.86 (dt, J

= 15.3, 7.8 Hz, 1H), 1.94-2.09 (m, 4H), 1.90 (d, J = 13.2 Hz, 2H), 1.68-1.81 (m, 1H), 1.46-1.60 (m, 2H), 1.31-1.40 (m, 9H), 1.23-1.31 (m, 1H). MS(M+1): 505. 淡黃色固體。

【0515】化合物 10-36

N-(6-(苯並[d][1,3]二氧雜-5-基)-1-環己基-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(6-(benzo[d][1,3]dioxol-5-yl)-1-cyclohexyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

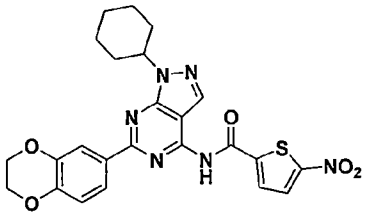


^{1}H NMR (400MHz, DMSO-d_6): δ 11.78 (br. s., 1H), 8.27-8.39 (m, 2H), 8.24 (d, J = 4.4 Hz, 1H), 8.15 (dd, J = 8.1, 1.7 Hz, 1H), 8.02 (d, J = 1.5 Hz, 1H), 7.10 (d, J = 8.3 Hz, 1H), 6.14 (s, 2H), 4.81-4.94 (m, 1H), 1.94-2.06 (m, 4H), 1.89 (d, J = 13.2 Hz, 2H), 1.70-1.81 (m, 1H), 1.45-1.62 (m, 2H), 1.23-1.37 (m, 1H). MS(M+1): 493. 淺橘色固體。

【0516】化合物 10-37

N-(1-環己基-6-(2,3-二氫苯並[b][1,4]二噁英-6-基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩 -2-甲醯胺

(N-(1-cyclohexyl-6-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

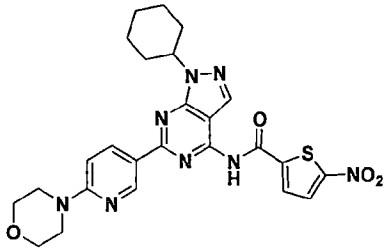


^{1}H NMR (400MHz, DMSO-d_6): δ 11.80 (br. s., 1H), 8.30-8.40 (m, 2H), 8.24 (d, J = 4.4 Hz, 1H), 8.01-8.08 (m, 2H), 7.00-7.06 (m, 1H), 4.85 (dt, J = 15.3; 7.8 Hz, 1H), 4.27-4.40 (m, 4H), 1.95-2.05 (m, 4H), 1.89 (d, J = 13.2 Hz, 2H), 1.70-1.79 (m, 1H), 1.45-1.64 (m, 2H), 1.19-1.39 (m, 1H). MS(M+1): 507. 黃色固體。

【0517】化合物 10-38

N-(1-環己基-6-(6-嗎啉並吡啶-3-基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(1-cyclohexyl-6-(6-morpholinopyridin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

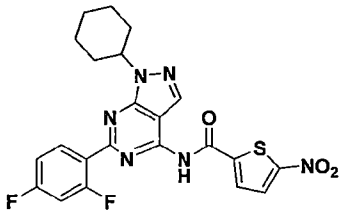


^{1}H NMR (400MHz, DMSO-d_6): δ 11.82 (br. s., 1H), 9.26 (d, J = 2.4 Hz, 1H), 8.55 (dd, J = 8.8, 2.4 Hz, 1H), 8.28-8.38 (m, 2H), 8.23 (d, J = 4.4 Hz, 1H), 6.98 (d, J = 8.8 Hz, 1H), 4.76-4.91 (m, 1H), 3.66-3.82 (m, 4H), 3.55-3.66 (m, 4H), 1.92-2.08 (m, 4H), 1.89 (d, J = 12.7 Hz, 2H), 1.69-1.81 (m, 1H), 1.46-1.61 (m, 2H), 1.22-1.40 (m, 1H). MS(M+1):535. 黃色固體。

【0518】化合物 10-39

N-(1-環己基-6-(2,4-二氟苯基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(1-cyclohexyl-6-(2,4-difluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

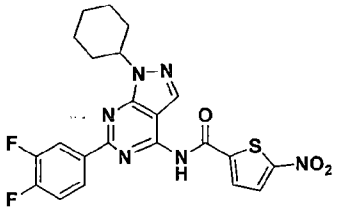


^{1}H NMR (400MHz, DMSO-d_6): δ 12.05 (br. s., 1H), 8.39 (s, 1H), 8.33 (d, J = 3.9 Hz, 1H), 8.10-8.25 (m, 2H), 7.41 (td, J = 10.3, 2.4 Hz, 1H), 7.22-7.34 (m, 1H), 4.79 (dt, J = 15.3, 7.8 Hz, 1H), 1.92-2.05 (m, 4H), 1.88 (d, J = 13.2 Hz, 2H), 1.65-1.77 (m, 1H), 1.39-1.61 (m, 2H), 1.17-1.35 (m, 1H). MS(M+1):485. 卡其色固體。

【0519】化合物 10-40

N-(1-環己基-6-(3,4-二氟苯基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(1-cyclohexyl-6-(3,4-difluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

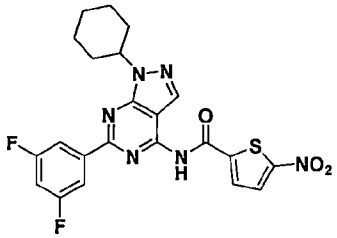


^{1}H NMR (400MHz, DMSO-d_6): δ 11.90 (br. s., 1H), 8.47 (ddd, J = 12.0, 8.1, 2.0 Hz, 1H), 8.35-8.43 (m, 2H), 8.32 (d, J = 4.4 Hz, 1H), 8.25 (d, J = 4.4 Hz, 1H), 7.65 (dt, J = 10.4, 8.5 Hz, 1H), 4.83-4.98 (m, 1H), 1.94-2.04 (m, 4H), 1.90 (d, J = 12.7 Hz, 2H), 1.74 (d, J = 13.2 Hz, 1H), 1.47-1.61 (m, 2H), 1.25-1.36 (m, 1H). MS(M+1):485. 淺黃色固體。

【0520】化合物 10-41

N-(1-環己基-6-(3,5-二氟苯基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(1-cyclohexyl-6-(3,5-difluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

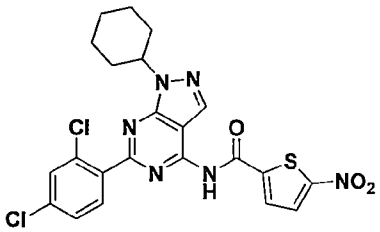


^{1}H NMR (400MHz, DMSO-d_6): δ 11.87 (br. s., 1H), 8.42 (s, 1H), 8.34 (d, J = 4.4 Hz, 1H), 8.25 (d, J = 4.4 Hz, 1H), 8.12-8.21 (m, 2H), 7.47 (tt, J = 9.0, 2.4 Hz, 1H), 4.89-5.00 (m, 1H), 1.95-2.06 (m, 4H), 1.89 (d, J = 12.7 Hz, 2H), 1.74 (d, J = 13.2 Hz, 1H), 1.50-1.63 (m, 2H), 1.24-1.37 (m, 1H). MS(M+1):485.卡其色固體。

【0521】化合物 10-42

N-(1-環己基-6-(2,4-二氯苯基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(1-cyclohexyl-6-(2,4-dichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

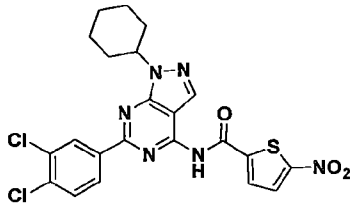


^{1}H NMR (400MHz, DMSO-d_6) : δ 12.17 (br. s., 1H), 8.43 (s, 1H), 8.33 (d, J = 4.4 Hz, 1H), 8.20 (d, J = 4.4 Hz, 1H), 7.85 (d, J = 8.3 Hz, 1H), 7.78 (d, J = 2.4 Hz, 1H), 7.60 (dd, J = 8.3, 2.0 Hz, 1H), 4.64-4.85 (m, 1H), 1.91-2.06 (m, 4H), 1.86 (d, J = 13.2 Hz, 2H), 1.61-1.74 (m, 1H), 1.34-1.59 (m, 2H), 1.17-1.34 (m, 1H). MS(M+1):517. 黃色固體。

【0522】化合物 10-43

N-(1-環己基-6-(3,4-二氯苯基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(1-cyclohexyl-6-(3,4-dichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

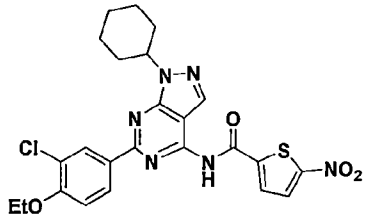


^{1}H NMR (400MHz, DMSO-d_6): δ 11.91 (br. s., 1H), 8.69 (d, J = 2.0 Hz, 1H), 8.47 (dd, J = 8.3, 2.0 Hz, 1H), 8.40 (s, 1H), 8.35 (d, J = 4.4 Hz, 1H), 8.24 (d, J = 4.9 Hz, 1H), 7.78- 7.91 (m, 1H), 4.82-4.97 (m, 1H), 1.92-2.09 (m, 4H), 1.89 (d, J = 13.2 Hz, 2H), 1.74 (d, J = 12.7 Hz, 1H), 1.47-1.65 (m, 2H), 1.26-1.40 (m, 1H). MS(M+1):517. 黃色固體。

【0523】化合物 10-44

N-(6-(3-氯-4-乙氧基苯基)-1-環己基-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(6-(3-chloro-4-ethoxyphenyl)-1-cyclohexyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

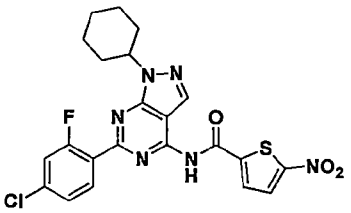


^{1}H NMR (400MHz, DMSO-d_6): δ 11.81 (br. s., 1H), 8.54 (d, J = 2.0 Hz, 1H), 8.44 (dd, J = 8.6, 2.2 Hz, 1H), 8.30-8.39 (m, 2H), 8.23 (d, J = 4.4 Hz, 1H), 7.31 (d, J = 8.8 Hz, 1H), 4.82-4.94 (m, 1H), 4.23 (q, J = 6.8 Hz, 2H), 1.93-2.10 (m, 4H), 1.89 (d, J = 13.2 Hz, 2H), 1.69- 1.79 (m, 1H), 1.47-1.62 (m, 2H), 1.41 (t, J = 6.8 Hz, 3H), 1.23-1.36 (m, 1H). MS(M+1):527. 淺卡其色固體。

【0524】化合物 10-45

N-(6-(4-氯-2-氟苯基)-1-環己基-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(6-(4-chloro-2-fluorophenyl)-1-cyclohexyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

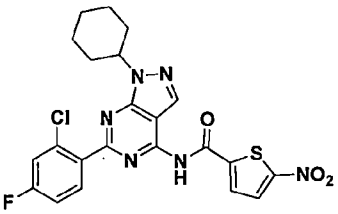


^{1}H NMR (400MHz, DMSO-d_6): δ 12.08 (br. s., 1H), 8.40 (s, 1H), 8.32 (d, J = 4.4 Hz, 1H), 8.22 (d, J = 4.4 Hz, 1H), 8.12-8.19 (m, 1H), 7.61 (dd, J = 10.8, 2.0 Hz, 1H), 7.49 (dd, J = 8.3, 2.0 Hz, 1H), 4.79 (dt, J = 15.3, 7.8 Hz, 1H), 1.94-2.07 (m, 4H), 1.88 (d, J = 12.7 Hz, 2H), 1.72 (d, J = 12.7 Hz, 1H), 1.42-1.58 (m, 2H), 1.23-1.39 (m, 1H). MS(M+1):501. 淺黃色固體。

【0525】化合物 10-46

N-(6-(2-氯-4-氟苯基)-1-環己基-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(6-(2-chloro-4-fluorophenyl)-1-cyclohexyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

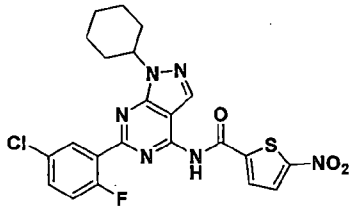


^{1}H NMR (400MHz, DMSO-d_6): δ 12.17 (br. s., 1H), 8.42 (s, 1H), 8.32 (d, J = 4.4 Hz, 1H), 8.20 (d, J = 4.4 Hz, 1H), 7.87 (dd, J = 8.6, 6.1 Hz, 1H), 7.53-7.67 (m, 1H), 7.39 (td, J = 8.4, 2.7 Hz, 1H), 4.78 (t, J = 7.1 Hz, 1H), 1.92-2.05 (m, 4H), 1.86 (d, J = 12.7 Hz, 2H), 1.65- 1.76 (m, 1H), 1.38-1.58 (m, 2H), 1.21-1.38 (m, 1H). MS(M+1):501. 淺黃色固體。

【0526】化合物 10-47

N-(6-(5-氯-2-氟苯基)-1-環己基-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(6-(5-chloro-2-fluorophenyl)-1-cyclohexyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

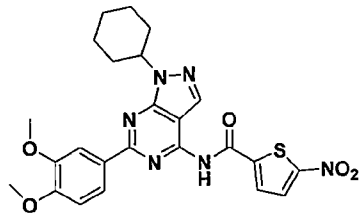


^{1}H NMR (400MHz, DMSO-d_6): δ 12.01 (br. s., 1H), 8.40 (s, 1H), 8.33 (d, J = 4.4 Hz, 1H), 8.21 (d, J = 4.4 Hz, 1H), 8.17 (dd, J = 6.4, 2.9 Hz, 1H), 7.60-7.68 (m, 1H), 7.44 (dd, J = 10.3, 8.8 Hz, 1H), 4.72-4.86 (m, 1H), 1.93-2.05 (m, 4H), 1.87 (d, J = 13.2 Hz, 2H), 1.66- 1.77 (m, 1H), 1.40-1.57 (m, 2H), 1.20-1.36 (m, 1H). MS(M+1):501. 黃色固體。

【0527】化合物 10-48

N-(1-環己基-6-(3,4-二甲氧基苯基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(1-cyclohexyl-6-(3,4-dimethoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

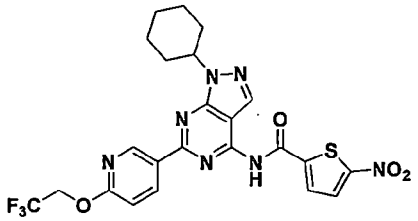


^{1}H NMR (400MHz, DMSO-d_6): δ 11.81 (br. s., 1H), 8.34 (d, J = 4.4 Hz, 1H), 8.32 (s, 1H), 8.22 (d, J = 4.4 Hz, 1H), 8.15 (dd, J = 8.6, 1.7 Hz, 1H), 8.09 (d, J = 2.0 Hz, 1H), 7.13 (d, J = 8.8 Hz, 1H), 4.78-4.92 (m, 1H), 3.90 (s, 3H), 3.86 (s, 3H), 1.94-2.07 (m, 4H), 1.89 (d, J = 13.2 Hz, 2H), 1.68-1.79 (m, 1H), 1.43-1.63 (m, 2H), 1.22-1.36 (m, 1H). MS(M+1):509. 黃色固體。

【0528】化合物 10-49

N-(1-環己基-6-(6-(2,2,2-三氟乙氧基)吡啶-3-基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2 -甲醯胺

(N-(1-cyclohexyl-6-(6-(2,2,2-trifluoroethoxy)pyridin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

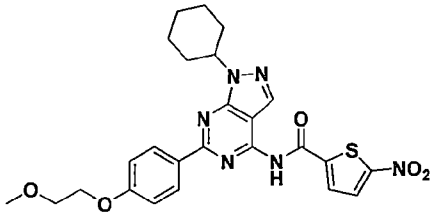


^{1}H NMR (400MHz, DMSO-d_6): δ 11.89 (br. s., 1H), 9.29 (d, J = 2.4 Hz, 1H), 8.79 (dd, J = 8.8, 2.4 Hz, 1H), 8.30-8.44 (m, 2H), 8.25 (d, J = 4.4 Hz, 1H), 7.19 (d, J = 8.3 Hz, 1H), 5.11 (q, J = 8.8 Hz, 2H), 4.79-4.97 (m, 1H), 1.94-2.08 (m, 4H), 1.89 (d, J = 12.2 Hz, 2H), 1.74 (d, J = 12.7 Hz, 1H), 1.46-1.66 (m, 2H), 1.25-1.39 (m, 1H). MS(M+1): 548. 黃色固體。

【0529】化合物 10-50

N-(1-環己基-6-(4-(2-甲氧基乙氧基)苯基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(1-cyclohexyl-6-(4-(2-methoxyethoxy)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)



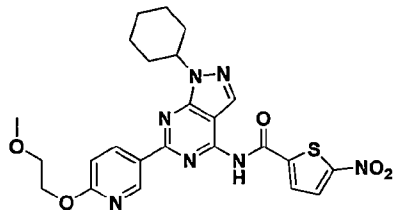
^{1}H NMR (400MHz, DMSO-d_6): δ 11.83 (br. s., 1H), 8.45-8.53 (m, J = 8.3 Hz, 2H), 8.37 (d, J = 3.9 Hz, 1H), 8.34 (s, 1H), 8.25 (d, J = 4.4 Hz, 1H), 7.09-7.17 (m, J = 8.8 Hz, 2H), 4.87 (dt, J = 15.9, 7.7 Hz, 1H), 4.20 (dd, J = 5.6, 3.7 Hz, 2H), 3.68-3.75 (m,

2H), 1.95- 2.04 (m, 4H), 1.86-1.95 (m, 2H), 1.74 (d, J = 13.2 Hz, 1H), 1.46-1.60 (m, 2H), 1.28-1.37 (m, 1H). MS(M+1): 523. 黃色固體。

【0530】化合物 10-51

N-(1-環己基-6-(6-(2-甲氧基乙氧基)吡啶-3-基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(1-cyclohexyl-6-(6-(2-methoxyethoxy)pyridin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

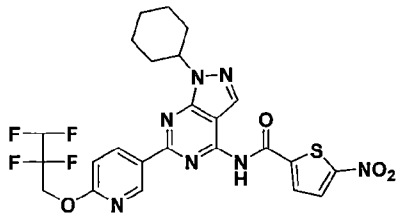


^{1}H NMR (400MHz, DMSO-d_6): δ 11.85 (br. s., 1H), 9.25 (d, J = 2.0 Hz, 1H), 8.69 (dd, J = 8.8, 2.4 Hz, 1H), 8.35 (t, J = 2.2 Hz, 2H), 8.23 (d, J = 4.4 Hz, 1H), 7.01 (d, J = 8.8 Hz, 1H), 4.81-4.94 (m, 1H), 4.39-4.54 (m, 2H), 3.70 (dd, J = 5.4, 3.9 Hz, 2H), 3.32 (s, 5H), 1.94-2.07 (m, 4H), 1.89 (d, J = 13.2 Hz, 2H), 1.74 (d, J = 13.2 Hz, 1H), 1.46-1.61 (m, 2H), 1.24-1.37 (m, 1H). MS(M+1): 524. 黃色固體。

【0531】化合物 10-52

N-(1-環己基-6-(6-(2,2,3,3-四氟丙氧基)吡啶-3-基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩 -2-甲醯胺

(N-(1-cyclohexyl-6-(6-(2,2,3,3-tetrafluoropropoxy)pyridin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)



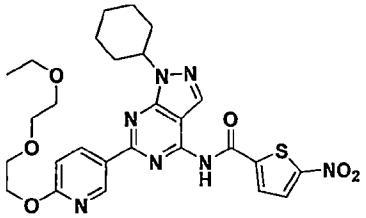
^{1}H NMR (400MHz, DMSO-d_6): δ 11.94 (br. s., 1H), 9.29 (d, J = 2.0 Hz, 1H), 8.79 (dd, J = 8.6, 2.2 Hz, 1H), 8.37 (s, 1H), 8.29 (d, J = 4.4 Hz, 1H), 8.24 (d, J = 4.4 Hz, 1H),

7.16 (d, J = 8.8 Hz, 1H), 6.71 (t, J = 5.4 Hz, 1H), 4.92-5.05 (m, 2H), 4.81-4.92 (m, 1H), 1.95-2.08 (m, 4H), 1.90 (d, J = 13.2 Hz, 2H), 1.74 (d, J = 12.7 Hz, 1H), 1.45-1.61 (m, 2H), 1.30 (q, J = 13.0 Hz, 1H). MS(M+1):580. 淺黃色固體。

【0532】化合物 10-53

N-(1-環己基-6-(6-(2-(2-乙氧基乙氧基)乙氧基)吡啶-3-基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩- 2-甲醯胺

(N-(1-cyclohexyl-6-(6-(2-(2-ethoxyethoxy)ethoxy)pyridin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

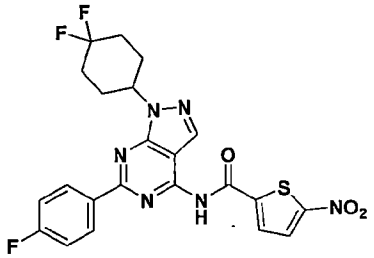


^{1}H NMR (400MHz, DMSO-d_6): δ 11.88 (br. s., 1H), 9.27 (d, J = 2.4 Hz, 1H), 8.71 (dd, J = 8.8, 2.4 Hz, 1H), 8.29-8.39 (m, 2H), 8.24 (d, J = 4.4 Hz, 1H), 7.02 (d, J = 8.8 Hz, 1H), 4.82-4.92 (m, 1H), 4.48 (dd, J = 5.6, 4.2 Hz, 2H), 3.76-3.83 (m, 2H), 3.57-3.64 (m, 2H), 3.46-3.53 (m, 2H), 3.39-3.46 (m, 2H), 1.94-2.08 (m, 4H), 1.89 (d, J = 12.7 Hz, 2H), 1.69 -1.79 (m, 1H), 1.46-1.62 (m, 2H), 1.23-1.36 (m, 1H), 1.05-1.13 (m, 3H). MS(M+1): 582. 黃色固體。

【0533】化合物 10-54

N-(1-(4,4-二氟環己基)-6-(4-氟苯基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(1-(4,4-difluorocyclohexyl)-6-(4-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

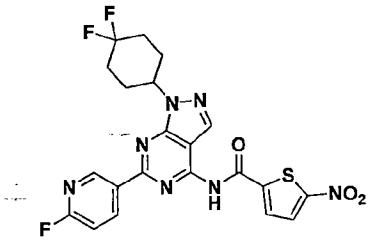


^{1}H NMR (400MHz, DMSO-d_6): δ 11.93 (br. s., 1H), 8.53-8.66 (m, 2H), 8.40 (s, 1H), 8.35 (d, J = 4.4 Hz, 1H), 8.25 (d, J = 4.4 Hz, 1H), 7.33-7.47 (m, 2H), 5.06-5.23 (m, 1H), 2.15- 2.36 (m, 6H), 2.09 (br. s., 2H). MS(M+1): 503. 淡黃色固體。

【0534】化合物 10-55

N-(1-(4,4-二氟環己基)-6-(6-氟吡啶-3-基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(1-(4,4-difluorocyclohexyl)-6-(6-fluoropyridin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

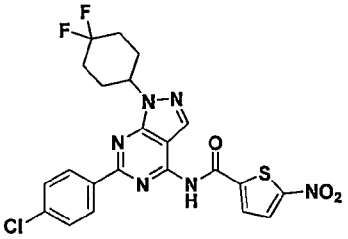


^{1}H NMR (400MHz, DMSO-d_6): δ 11.90 (s, 1H), 9.30 (d, J = 2.4 Hz, 1H), 8.93 (td, J = 8.3, 2.4 Hz, 1H), 8.40 (s, 1H), 8.34 (d, J = 4.4 Hz, 1H), 8.22 (d, J = 4.4 Hz, 1H), 7.40 (dd, J = 8.3, 2.4 Hz, 1H), 5.03-5.25 (m, 1H), 2.15-2.34 (m, 6H), 2.01-2.15 (m, 2H). MS(M+1): 504. 白色固體。

【0535】化合物 10-56

N-(6-(4-氯苯基)-1-(4,4-二氟環己基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(6-(4-chlorophenyl)-1-(4,4-difluorocyclohexyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

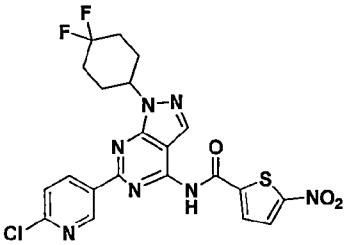


^{1}H NMR (400MHz, DMSO-d_6): δ 11.93 (br. s., 1H), 8.49-8.62 (m, 2H), 8.29-8.42 (m, 2H), 8.23 (d, J = 4.4 Hz, 1H), 7.59-7.71 (m, 2H), 5.15 (d, J = 3.9 Hz, 1H), 2.15-2.34 (m, 6H), 2.09 (br. s., 2H). MS(M+1): 519. 白色固體。

【0536】 化合物 10-57

N-(6-(6-氯吡啶-3-基)-1-(4,4-二氟環己基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(6-(6-chloropyridin-3-yl)-1-(4,4-difluorocyclohexyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

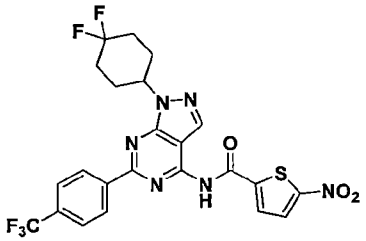


^{1}H NMR (400MHz, DMSO-d_6): δ 11.99 (br. s., 1H), 9.47 (d, J = 2.0 Hz, 1H), 8.83 (dd, J = 8.3, 2.4 Hz, 1H), 8.41-8.48 (m, 1H), 8.35 (d, J = 4.4 Hz, 1H), 8.25 (d, J = 4.4 Hz, 1H), 7.77 (d, J = 8.3 Hz, 1H), 5.12-5.25 (m, 1H), 2.16-2.1 (m, 8H). MS(M+1): 520. 玫瑰棕固體。

【0537】 化合物 10-58

N-(1-(4,4-二氟環己基)-6-(4-(三氟甲基)苯基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(1-(4,4-difluorocyclohexyl)-6-(4-(trifluoromethyl)phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

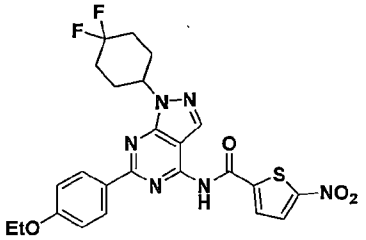


^{1}H NMR (400MHz, DMSO-d_6): δ 12.02 (br. s., 1H), 8.65-8.81 (m, J = 8.3 Hz, 2H), 8.43 (s, 1H), 8.36 (d, J = 4.4 Hz, 1H), 8.24 (d, J = 4.4 Hz, 1H), 7.86-8.02 (m, J = 8.3 Hz, 2H), 5.05-5.28 (m, 1H), 2.16-2.36 (m, 6H), 2.11 (br. s., 2H). MS(M+1): 553. 白色固體。

【0538】化合物 10-59

N-(1-(4,4-二氟環己基)-6-(4-乙氧基苯基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(1-(4,4-difluorocyclohexyl)-6-(4-ethoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

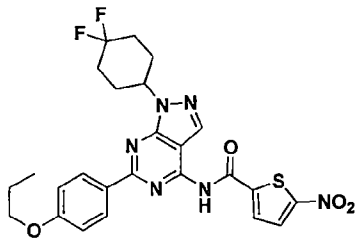


^{1}H NMR (400MHz, DMSO-d_6): δ 11.87 (br. s., 1H), 8.42 8.54 (m, J = 8.8 Hz, 2H), 8.29- 8.39 (m, 2H), 8.24 (d, J = 4.4 Hz, 1H), 7.02-7.15 (m, 2H), 5.04-5.20 (m, 1H), 4.14 (q, J = 6.8 Hz, 2H), 2.15-2.37 (m, 6H), 2.08 (br. s., 2H), 1.37 (t, J = 6.8 Hz, 3H). MS(M+1): 529. 亮黃色固體。

【0539】化合物 10-60

N-(1-(4,4-二氟環己基)-6-(4-丙氧基苯基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(1-(4,4-difluorocyclohexyl)-6-(4-propoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

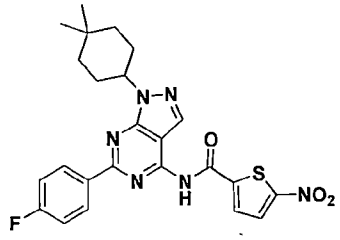


^{1}H NMR (400MHz, DMSO-d_6): δ 11.89 (br. s., 1H), 8.49 (d, J = 8.8 Hz, 2H), 8.28-8.38 (m, 2H), 8.24 (d, J = 4.4 Hz, 1H), 7.02-7.19 (m, 2H), 5.05-5.20 (m, 1H), 4.04 (t, J = 6.6 Hz, 2H), 2.14-2.37 (m, 6H), 2.08 (br. s., 2H), 1.68-1.84 (m, 2H), 1.01 (t, J = 7.6 Hz, 3H). MS(M+1): 543. 亮黃色固體。

【0540】化合物 10-61

N-(1-(4,4-二甲基環己基)-6-(4-氟苯基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(1-(4,4-dimethylcyclohexyl)-6-(4-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

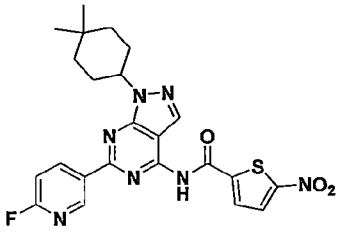


^{1}H NMR (400MHz, DMSO-d_6): δ 11.90 (br. s., 1H), 8.48-8.64 (m, 2H), 8.29-8.40 (m, 2H), 8.24 (d, J = 4.4 Hz, 1H), 7.32-7.49 (m, 2H), 4.74-4.90 (m, 1H), 2.23 (qd, J = 12.5, 4.6 Hz, 2H), 1.73-1.86 (m, 2H), 1.43-1.62 (m, 4H), 1.04-1.12 (m, 3H), 1.01 (s, 3H). MS(M+1): 495. 亮黃色固體。

【0541】化合物 10-62

N-(1-(4,4-二甲基環己基)-6-(6-氟吡啶-3-基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(1-(4,4-dimethylcyclohexyl)-6-(6-fluoropyridin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

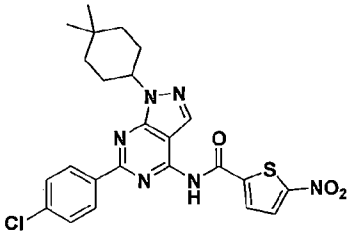


^{1}H NMR (400MHz, DMSO-d_6): δ 11.96 (s, 1H), 9.30 (d, J = 2.4 Hz, 1H), 8.94 (t, J = 8.3, 1H), 8.41 (s, 1H), 8.34 (d, J = 4.4 Hz, 1H), 8.23 (d, J = 4.4 Hz, 1H), 7.40 (dd, J = 8.3 , 2.7 Hz, 1H), 4.89-4.82 (m, 1H), 2.27-2.20 (m, 2H), 1.82-1.80 (m, 2H), 1.54-1.48 (m, 4H), 1.07 (s, 3H), 1.01 (s, 3H). MS(M+1): 496. 黃色固體。

【0542】化合物 10-63

N-(6-(4-氯苯基)-1-(4,4-二甲基環己基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(6-(4-chlorophenyl)-1-(4,4-dimethylcyclohexyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

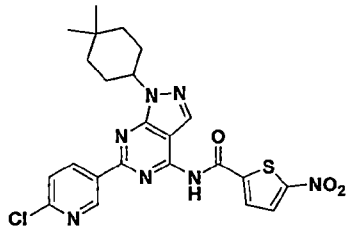


^{1}H NMR (400MHz, DMSO-d_6): δ 11.89 (br. s., 1H), 8.45-8.58 (m, 2H), 8.30-8.40 (m, 2H), 8.22 (d, J = 4.4 Hz, 1H), 7.54-7.71 (m, 2H), 4.72-4.89 (m, 1H), 2.09-2.31 (m, 2H), 1.70-1.86 (m, 2H), 1.42-1.59 (m, 4H), 1.03-1.11 (m, 3H), 1.00 (s, 3H). MS(M+1): 511. 亮黃色固體。

【0543】化合物 10-64

N-(6-(6-氯吡啶-3-基)-1-(4,4-二甲基環己基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(6-(6-chloropyridin-3-yl)-1-(4,4-dimethylcyclohexyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

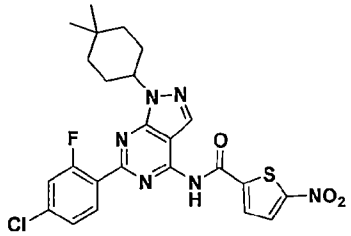


^{1}H NMR (400MHz, DMSO-d_6): δ 11.96 (s, 1H), 9.44 (d, J = 1.7 Hz, 1H), 8.81 (dd, J = 8.8, 2.4 Hz, 1H), 8.41 (s,1H), 8.35 (d, J = 4.4 Hz, 1H), 8.24 (d, J = 4.4 Hz, 1H), 7.74 (d, J = 8.8 Hz, 1H), 4.88-4.80 (m, 1H), 2.26-2.16 (m, 2H), 1.82-1.79 (m, 2H), 1.54-1.48 (m, 4H), 1.06 (s, 3H), 1.01 (s, 3H). MS(M+1): 512. 黃色固體。

【0544】化合物 10-65

N-(6-(4-氯-2-氟苯基)-1-(4,4-二甲基環己基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(6-(4-chloro-2-fluorophenyl)-1-(4,4-dimethylcyclohexyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

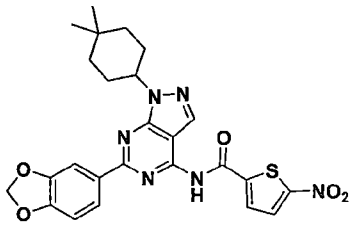


^{1}H NMR (400MHz, DMSO-d_6): δ 12.05 (br. s., 1H), 8.37-8.46 (m, 1H), 8.34 (d, J = 4.4 Hz, 1H), 8.09-8.27 (m, 2H), 7.61 (dd, J = 10.8, 2.0 Hz, 1H), 7.49 (dd, J = 8.3, 2.0 Hz, 1H), 4.73 (tt, J = 11.9, 4.3 Hz, 1H), 2.24 (qd, J = 12.7, 3.9 Hz, 2H), 1.73-1.87 (m, 2H), 1.39- 1.60 (m, 4H), 1.05 (s, 3H), 0.99 (s, 3H). MS(M+1): 529. 黃色固體。

【0545】化合物 10-66

N-(6-(苯並[d][1,3]二氧雜-5-基)-1-(4,4-二甲基環己基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5 -硝基噻吩-2-甲醯胺

(N-(6-(benzo[d][1,3]dioxol-5-yl)-1-(4,4-dimethylcyclohexyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

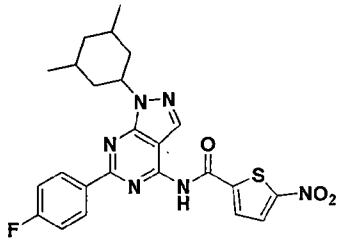


^{1}H NMR (400MHz, DMSO-d_6): δ 11.76 (br. s., 1H), 8.27-8.40 (m, 2H), 8.23 (d, J = 4.4 Hz, 1H), 8.14 (dd, J = 8.3, 1.5 Hz, 1H), 8.01 (d, J = 1.5 Hz, 1H), 7.09 (d, J = 8.3 Hz, 1H), 6.13 (s, 2H), 4.72-4.85 (m, 1H), 2.22 (qd, J = 12.2, 5.4 Hz, 2H), 1.71-1.86 (m, 2H), 1.42-1.61 (m, 4H), 1.07 (s, 3H), 1.00 (s, 3H). MS(M+1): 521. 黃色固體。

【0546】化合物 10-67

N-(1-(3,5-二甲基環己基)-6-(4-氟苯基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(1-(3,5-dimethylcyclohexyl)-6-(4-fluorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

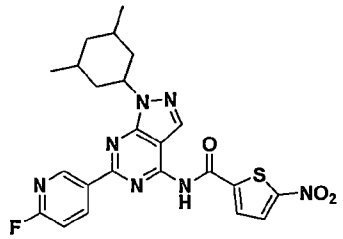


^{1}H NMR (400MHz, DMSO-d_6): δ 11.88 (br. s., 1H), 8.52-8.66 (m, 2H), 8.32-8.40 (m, 2H), 8.24 (d, J = 4.4 Hz, 1H), 7.32-7.46 (m, 2H), 4.97 (tt, J = 11.7, 3.9 Hz, 1H), 1.94 (d, J = 11.7 Hz, 2H), 1.68-1.86 (m, 3H), 1.60 (q, J = 12.1 Hz, 2H), 0.97 (d, J = 6.4 Hz, 6H), 0.64-0.80 (m, 1H). MS(M+1):495. 淺綠色固體。

【0547】化合物 10-68

N-(1-(3,5-二甲基環己基))-6-(6-氟吡啶-3-基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(1-(3,5-dimethylcyclohexyl)-6-(6-fluoropyridin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)



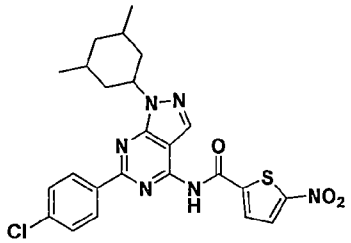
^{1}H NMR (400MHz, DMSO-d_6): δ 11.94 (br. s., 1H), 9.31 (d, J = 2.4 Hz, 1H), 8.96 (td, J = 8.3, 2.4 Hz, 1H), 8.41 (s, 1H), 8.34 (d, J = 4.4 Hz, 1H), 8.25 (d, J = 4.4 Hz, 1H), 7.41 (dd, J = 8.8, 2.4 Hz, 1H), 4.90-5.08 (m, 1H), 1.86-2.05 (m, 2H), 1.74 (t, J = 9.3 Hz, 3H), 1.61 (q, J = 11.9 Hz, 2H), 0.97 (d, J = 6.4 Hz, 6H), 0.74 (d, J = 11.7 Hz, 1H)

MS(M+1): 496. 淺黃色固體。

【0548】化合物 10-69

N-(6-(4-氯苯基)-1-(3,5-二甲基環己基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(6-(4-chlorophenyl)-1-(3,5-dimethylcyclohexyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)

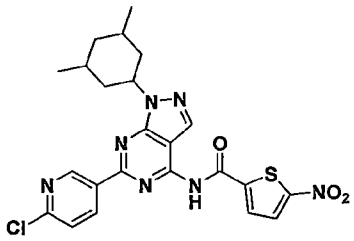


^{1}H NMR (400MHz, DMSO-d_6): δ 11.90 (br. s., 1H), 8.47-8.56 (m, J = 8.3 Hz, 2H), 8.29- 8.42 (m, 2H), 8.24 (d, J = 4.4 Hz, 1H), 7.56-7.73 (m, J = 8.8 Hz, 2H), 4.84-5.08 (m, 1H), 1.93 (d, J = 12.2 Hz, 2H), 1.72 (d, J = 11.2 Hz, 3H), 1.60 (q, J = 12.1 Hz, 2H), 0.96 (d, J = 6.4 Hz, 6H), 0.65-0.80 (m, 1H). MS(M+1):511. 淺黃色固體。

【0549】化合物 10-70

N-(6-(6-氯吡啶-3-基)-1-(3,5-二甲基環己基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

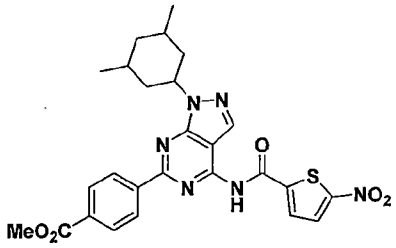
(N-(6-(6-chloropyridin-3-yl)-1-(3,5-dimethylcyclohexyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)



^{1}H NMR (400MHz, DMSO-d_6): δ 11.94 (br. s., 1H), 9.44 (d, J = 2.4 Hz, 1H), 8.80 (dd, J = 8.3, 2.4 Hz, 1H), 8.40 (s, 1H), 8.34 (d, J = 4.4 Hz, 1H), 8.24 (d, J = 4.4 Hz, 1H), 7.60- 7.81 (m, 1H), 4.98 (tt, J = 11.7, 3.9 Hz, 1H), 1.94 (d, J = 12.2 Hz, 2H), 1.68-1.82 (m, 3H), 1.60 (q, J = 12.2 Hz, 2H), 0.97 (d, J = 6.4 Hz, 6H), 0.66-0.79 (m, 1H). MS(M+1): 512. 淺黃色固體。

【0550】化合物 10-71

4-(1-(3,5-二甲基環己基)-4-(5-硝基噻吩-2-甲醯胺基)-1H-吡唑並[3,4-d]嘧啶-6-基)苯甲酸甲酯(methyl 4-(1-(3,5-dimethylcyclohexyl)-4-(5-nitrothiophene-2-carboxamido)-1H-pyrazolo[3,4-d]pyrimidin-6-yl)benzoate)

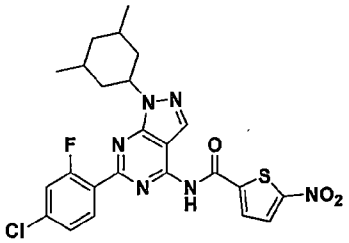


^{1}H NMR (400MHz, DMSO-d_6): δ 12.00 (br. s., 1H), 8.57-8.71 (m, J = 7.8 Hz, 2H), 8.31-8.44 (m, 2H), 8.25 (d, J = 4.4 Hz, 1H), 8.09-8.21 (m, J = 7.8 Hz, 2H), 5.01 (t, J = 11.2 Hz, 1H), 3.91 (s, 3H), 1.95 (d, J = 11.7 Hz, 2H), 1.68-1.84 (m, 3H), 1.49-1.68 (m, 2H), 0.98 (d, J = 5.9 Hz, 6H), 0.74 (d, J = 12.2 Hz, 1H). MS(M+1): 535. 淺黃色固體。

【0551】化合物 10-72

N-(6-(4-氯-2-氟苯基)-1-(3,5-二甲基環己基)-1H-吡唑並[3,4-d]嘧啶-4-基)-5-硝基噻吩-2-甲醯胺

(N-(6-(4-chloro-2-fluorophenyl)-1-(3,5-dimethylcyclohexyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-nitrothiophene-2-carboxamide)



^{1}H NMR (400MHz, DMSO-d_6): δ 12.08 (br. s., 1H), 8.36-8.45 (m, 1H), 8.32 (d, J = 4.4 Hz, 1H), 8.22 (d, J = 4.4 Hz, 1H), 8.15 (t, J = 8.3 Hz, 1H), 7.61 (dd, J = 10.8, 2.0 Hz, 1H), 7.49 (dd, J = 8.6, 1.7 Hz, 1H), 4.78-4.97 (m, 1H), 1.93 (d, J = 11.7 Hz, 2H), 1.52-1.81 (m, 5H), 0.95 (d, J = 5.9 Hz, 6H), 0.61-0.83 (m, 1H). MS(M+1):529. 淺黃色固體。

【0552】表11中顯示式(I)的示例性化合物的體外活性。結果表明本揭露之化合物確實具有抑制各種腫瘤細胞生長的功效。

【0553】表11

化合物	SW480 LC_{50} (μM)	NCI-H460 LC_{50} (μM)
1-4	6.19	3.56
1-5	4.32	2.85
1-11	2.24	2.62
1-22	5.38	2.18
1-27	4.14	1.99
4-2	10.06	1.65
4-5	3.51	2.45
5-6	1.96	1.46
5-18	2.43	0.46
5-28	0.59	0.28
5-29	0.66	0.95
5-30	2.69	0.54
5-31	0.86	0.41

5-32	2.77	1.16
5-33	0.60	1.80
5-35	1.11	0.65
5-39	>10C	1.25
5-40	5.42	0.93
5-42	0.89	1.67
5-44	1.62	4.64
5-45	1.11	2.18
5-47	0.61	0.29
5-49	3.75	1.22
5-56	0.73	1.10
6-4	1.51	0.68
6-5	0.65	0.91
6-11	0.67	0.33
6-18	1.24	0.27
6-19	0.45	0.22
6-28	3.44	0.68
6-35	0.52	0.50
6-36	2.80	0.67
6-39	3.18	1.07
6-45	0.58	0.57
6-53	1.04	1.09
6-54	0.34	0.33
6-57	1.24	2.75
6-58	4.09	3.97
6-66	>10	0.41
6-69	0.89	2.76
6-71	0.98	0.44
6-75	5.48	1.28
6-85	0.68	0.56
6-89	0.81	0.71
6-90	0.54	0.56
6-104	0.65	0.86
6-106	0.50	1.65
6-110	1.25	1.41
6-111	>4	1.87
6-112	0.81	0.97
6-114	0.84	0.35
6-115	1.91	1.13
6-116	0.55	0.50
6-117	0.91	0.60
6-118	2.18	0.98

6-119	0.69	0.53
6-120	0.51	1.34
6-121	0.63	0.48
6-125	2.28	0.35
6-127	1.06	0.45
6-128	0.57	0.31
6-130	2.90	3.81
6-133	0.43	0.49
6-135	0.69	0.56
7-1	>20	8.63
7-3	0.53	0.40
9-3	2.72	1.22
9-5	2.78	1.30
10-13	1.73	2.62
10-14	1.71	0.91
10-18	0.95	0.85
10-23	1.66	3.01
10-32	1.21	1.72
10-40	1.04	1.16
10-55	1.06	0.94
10-57	1.34	1.30

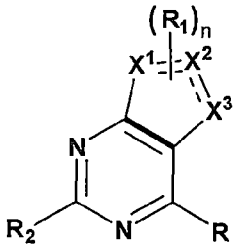
【0554】其他實施例

【0555】本說明書中揭露的所有特徵可以以任何組合結合。本說明書中揭露的每個特徵可以由具有相同、等同或相似目的的替代特徵取代。因此，除非另有明確說明，否則所揭露的每個特徵僅是一通用系列等同或相似特徵的示例。

【0556】此外，根據上文描述，本領域技術人員可以輕易地確定本揭露的基本特徵，並且在不脫離本揭露的精神及範圍的情況下，可以對本揭露進行各種變化和修改以使其適應各種用途和條件。因此，其他實施例也在本申請專利範圍之內。

【發明申請專利範圍】

【請求項1】　一種式(I)之化合物或其立體異構物、互變異構物、或其藥學上可接受之鹽類：

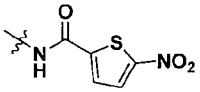


(I)

其中，

X_1、X_2及X_3各自獨立為C、N、O或S，但條件為X_1、X_2及X_3中不超過兩個為N、O或S；

R_1各自獨立地選自由氫、鹵素、烷基、烷氧基、環烷基、雜環烷基、芳基或雜芳基所組成之群組，其中烷基、烷氧基、環烷基、雜環烷基、芳基及雜芳基各自選擇性地以一至三個選自由鹵素、羥基、硝基、氰基、$-NR_aR_b$、$-C(=O)R_c$、$-C(=O)OR_d$、選擇性地以一至四個鹵素取代之雜環烷基、選擇性地以一至三個鹵素或$-NR_aR_b$取代之芳基、選擇性地以一至三個鹵素取代之烷基、及選擇性地以一至三個鹵素或烷氧基取代之烷氧基所組成之群組之基團取代，其中R_a及R_b各自獨立為氫、烷基或丙烯醯胺，且R_c及R_d各自獨立為氫、烯基、或選擇性地以一至三個鹵素或選擇性地更以烷氧基取代之烷氧基取代的烷基；

R及R_2中之一者為  ；

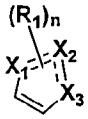
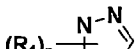
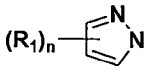
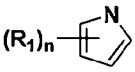
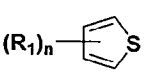
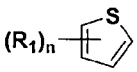
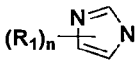
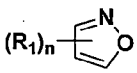
R及R_2中之另一者為$-OR_3$、$-NHR_4$、$-SR_5$、烯基、炔基、芳基、雜芳基、環烷基、雜環烷基、與雜環烷基稠合之芳基、環烯基或環胺，其中烯基、炔基、芳基、雜芳基、環烷基、雜環烷基及環烯基各自選擇性地以一至三個選自由鹵

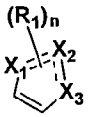
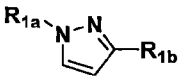
素、羥基、硝基、氰基、$-NR_eR_f$、$-C(=O)R_g$、$-C(=O)OR_h$、$-SO_2R_i$、$-OSiR_j$、烯基、雜環烷基、選擇性地以一至三個鹵素選擇性取代之烷基或以一至三個鹵素選擇性取代之烷氧基取代的芳基、選擇性地以一至三個鹵素、$-NR_eR_f$或$-OR_k$取代之烷基、及選擇性地以一至四個鹵素、羥基、$-NR_eR_f$或選擇性地更以烷氧基取代之烷氧基取代的烷氧基所組成之群組之基團取代，其中R_e及R_f各自獨立為氫或選擇性地以烷氧基取代之烷基，R_g及R_h各自獨立為氫、烷基或烯基，R_i為烷基，R_j為烷基，且R_k為氫、芳基、或選擇性地更被烷氧基選擇性地取代之烷氧基取代的烷基；

R_3及R_5各自獨立為烷基、環烷基或芳基，其中烷基、環烷基或芳基選擇性地以一至四個選自由鹵素、選擇性地以一至四個鹵素取代之烷基、選擇性地以一至三個鹵素或烷氧基取代之烷氧基、$-NR_lR_m$、及雜環烷基所組成之群組之基團取代，其中R_l及R_m各自獨立為氫或烷基；

R_4為烷基、環烷基或$-SO_2R_n$，其中R_n為氫、烷基或芳基，且烷基或芳基各自選擇性地以一至三個鹵素取代；以及

n為1、2或3。

【請求項2】　如請求項1所述的化合物，其中  為  、  、  、  、  、  或  ，其中n為1或2。

【請求項3】　如請求項1所述的化合物，其中  為  ，其中R_{1a}及R_{1b}各自獨立地選自由氫、鹵素、烷基、烷氧基、環烷基、雜環烷基、芳基或雜芳基所組成之群組，其中烷基、烷氧基、環烷基、雜環烷基、芳基及雜芳基各自選擇性地以一至三個選自由鹵素、羥基、硝基、氰基、$-NR_aR_b$、$-C(=O)R_c$、$-C(=O)OR_d$、選擇性地以一至四個鹵素取代之雜環烷基、選擇性地以一至三個鹵素或$-NR_aR_b$取代之芳基、選擇性地以一至三個鹵素取代之烷基、及選擇性地以一至三個鹵素或烷氧基取代之烷氧基所組成之群組之基團取代，其中R_a及R_b各自獨立為氫、烷基或丙烯醯胺，且R_c及R_d各自獨立為氫、烯基、或選擇性地以一至三個鹵素或選擇性地更以烷氧基取代之烷氧基取代的烷基。

【請求項4】　如請求項3所述的化合物，其中R_{1b}為氫或烷基。

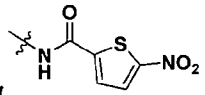
【請求項5】　如請求項4所述的化合物，其中R_{1b}為氫。

【請求項6】　如請求項5所述的化合物，其中R_{1a}為烷基、芳基、雜芳基、環烷基或雜環烷基，其中烷基、環烷基、雜環烷基、芳基及雜芳基各自選擇性地以一至三個選自由F、Cl、羥基、氰基、$-NR_aR_b$、$-C(=O)R_c$、$-C(=O)OR_d$、選擇性地以一至四個F或Cl取代之雜環烷基、選擇性地以一至三個F、Cl或$-NR_aR_b$取代之芳基、選擇性地以一至三個F、Cl取代之烷基、及選擇性地以一至三個F、Cl或烷氧基取代之烷氧基所組成之群組之基團取代，其中R_a為氫或烷基，R_b為烷基或丙烯醯胺，R_c為烷基或烯基，R_d為選擇性地以一至三個F、Cl或選擇性地更以烷氧基取代之烷氧基取代的烷基。

【請求項7】　如請求項6所述的化合物，其中R_{1a}為烷基、苄基、苯基、吡啶基、吡咯烷基、環戊基、環己基、環庚基或哌啶基，其中烷基選擇性地以羥

基、氰基、二烷基胺基、選擇性地以一或兩個F取代之雜環烷基、或選擇性地以烷氧基取代之烷氧基取代，苄基選擇性地以一個F取代，苯基選擇性地以一或兩個F、Cl、$-NR_aR_b$、選擇性地以三個F取代之烷基、或選擇性地以一至三個F取代之烷氧基取代，吡啶基選擇性地被三個F選擇性地取代之烷基取代，吡咯烷基以烷基、$-C(=O)R_c$或$-C(=O)R_d$取代，環戊基、環己基及環庚基選擇性地以一或兩個F、Cl或烷基取代，以及哌啶基選擇性地以烷基、$-C(=O)R_c$、或$-C(=O)OR_d$取代，其中R_a為氫，R_b為丙烯醯胺，R_c為烷基或烯基，R_d為選擇性地以一至三個F、Cl或選擇性地更以烷氧基取代之烷氧基取代的烷基。

【請求項8】　如請求項7所述的化合物，其中R_{1a}為苄基、苯基、吡啶基、吡咯烷基、環戊基、環己基、環庚基或哌啶基，其中苄基選擇性地以一個F取代，苯基選擇性地以一或兩個F、Cl、$-NR_aR_b$、選擇性地以三個F取代之烷基、或選擇性地以一至三個F取代之烷氧基取代，吡啶基選擇性地被三個F選擇性地取代之烷基取代，吡咯烷基以烷基、$-C(=O)R_c$或$-C(=O)OR_d$取代，環戊基、環己基及環庚基選擇性地以一或兩個F或烷基取代，以及哌啶基選擇性地以烷基、$-C(=O)R_c$、或$-C(=O)OR_d$取代，其中R_a為氫，R_b為丙烯醯胺，R_c為烷基或烯基，R_d為選擇性地以一至三個F或選擇性地更以烷氧基取代之烷氧基取代的烷基。

【請求項9】　如請求項3所述的化合物，其中R為  。

【請求項10】　如請求項9所述的化合物，其中R_2為$-OR_3$、$-NHR_4$、$-SR_5$、烯基、炔基、芳基、雜芳基、環烷基、雜環烷基、與雜環烷基稠合的芳基或環烯基，其中烯基、炔基、芳基、雜芳基、環烷基、雜環烷基及環烯基各自選擇性地以一至三個選自由F、Cl、羥基、氰基、$-NR_eR_f$、$-C(=O)R_g$、$-C(=O)OR_h$、

$-SO_2R_i$、$-OSiR_j$、烯基、雜環烷基、選擇性地被一至三個F、Cl選擇性取代之烷基或以一至三個F、Cl選擇性取代之烷氧基取代的芳基、選擇性地以一至三個F、Cl、$-NR_eR_f$或$-OR_k$取代之烷基、及選擇性地以一至四個F、Cl、羥基、$-NR_eR_f$或選擇性地更以烷氧基取代之烷氧基取代的烷氧基所組成之群組之基團取代，其中R_e及R_f各自獨立為氫或選擇性地以烷氧基取代之烷基，R_g及R_h各自獨立為氫、烷基、或烯基，R_i為烷基，R_j為烷基，及R_k為氫、芳基、或選擇性地更被烷氧基選擇性地取代之烷氧基取代的烷基；

R_3及R_5各自獨立為烷基、環烷基或芳基，其中烷基、環烷基或芳基選擇性地以一至四個選自由F、Cl、選擇性地以一至四個F或Cl取代之烷基、選擇性地以一至三個F、Cl或烷氧基取代之烷氧基、$-NR_lR_m$、及雜環烷基所組成之群組之基團取代，其中R_l及R_m各自獨立為氫或烷基；以及

R_4為烷基、環烷基或$-SO_2R_n$，其中R_n為氫、烷基或芳基，且烷基或芳基各自選擇性地以一至三個F或Cl取代。

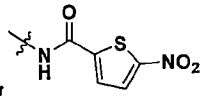
【請求項11】　如請求項10所述的化合物，其中R_2為$-OR_3$、$-NHR_4$、$-SR_5$、苯乙烯基、苯乙炔基、環己基、環己烯基、苯基、苯並二噁唑基、苯並二噁烷基、苯並呋喃基、呋喃基、苯硫基、噁唑基、咪唑基、吡唑基、噁二唑基、氮雜環丁烷基、吡咯烷基、哌啶基、嗎啉基、哌嗪基(piperazinyl)、嘧啶基、或吡啶基，其中苯乙烯基選擇性地被一至三個F或烷氧基取代之烷基取代，苯乙炔基選擇性地被一至三個F選擇性取代之烷基或一至三個F選擇性取代之烷氧基取代，環己基選擇性地以一至三個烷基取代，環己烯基選擇性地以一至三個烷基取代，苯基選擇性地以一至三個選自由F、Cl、氰基、二烷基胺基、$-C(=O)R_g$、$-C(=O)OR_h$、$-SO_2R_i$、選擇性地以一至三個F、二烷基胺基或烷氧基取代之烷基、

及選擇性地以一至三個F或選擇性地更以烷氧基取代之烷氧基取代的烷氧基所組成之群組之基團取代，苯硫基選擇性地以Cl或烷基取代，噁唑基選擇性地以一或兩個烷基取代，吡唑基選擇性地被一至三個F選擇性地取代之烷基取代，噁二唑基選擇性地以烷基取代，氮雜環丁烷基選擇性地以一或兩個F或$-OSiR_j$取代，吡咯烷基選擇性地以羥基、氰基、烯基、$-C(=O)OR_h$、一至兩個F、或選擇性地以羥基、苯氧基或選擇性地更被烷氧基選擇性地取代之烷氧基取代之烷氧基取代的烷基取代，哌啶基選擇性地以烷基、一或兩個F、$-C(=O)R_g$取代，嗎啉基選擇性地以一至三個烷基取代；哌嗪基(piperazinyl)選擇性地以烷基取代，以及吡啶基選擇性地以一或兩個選自由F、Cl、氰基、哌啶基、嗎啉基、$-NR_eR_f$、選擇性地以三至四個F取代之烷基、及選擇性地以一至四個F、羥基、二烷基胺基或選擇性地更以烷氧基取代之烷氧基取代的烷氧基所組成之群組之基團取代，其中R_e為烷基，R_f為選擇性地以烷氧基取代之烷基，R_g為氫、烷基或烯基，R_h為氫或烷基，R_i為烷基，且R_j為烷基；

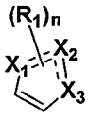
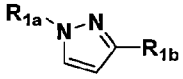
R_3為苯基、環烷基或烷基，其中苯基選擇性地以F、嗎啉基、選擇性地以一至三個F取代之烷氧基、或選擇性地以一至三個F取代之烷基取代，且烷基選擇性地以一至四個F、嗎啉基、二烷基胺基、或選擇性地以烷氧基取代之烷氧基取代；

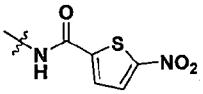
R_4為烷基、環烷基或$-SO_2R_n$，其中R_n為選擇性地以一至三個Cl取代之苯基；以及

R_5為選擇性地以Cl取代之苯基。

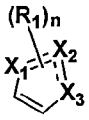
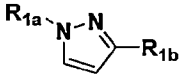
【請求項12】　如請求項3所述的化合物，其中R_2為  。

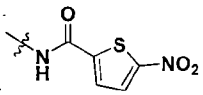
【請求項13】　如請求項12所述的化合物，其中R為苯基或嗎啉基，且苯基選擇性地以烷基或選擇性地以一至三個F取代之烷氧基取代。

【請求項14】　如請求項1所述的化合物，其中  為  ，其中R_{1a}為烷基且R_{1b}為氫；

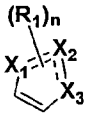
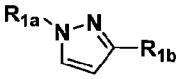
R為  ；以及

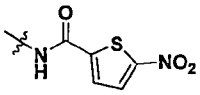
R_2為苯乙烯基或苯基，其中苯基以一至三個F取代之烷基取代或以一至三個F取代之烷氧基取代，且苯乙烯基被一至三個F取代之烷基取代。

【請求項15】　如請求項1所述的化合物，其中  為  ，其中R_{1b}為氫，且R_{1a}為選擇性地以一或兩個F、Cl、丙烯醯胺基、選擇性地以三個F取代之烷基或選擇性地以三個F取代之烷氧基取代的苯基；

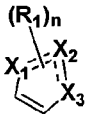
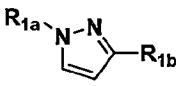
R為  ；以及

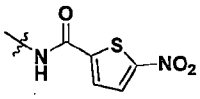
R_2為$-OR_3$、苯基、苯並二噁唑基、苯硫基、吡唑基、吡咯烷基、嘧啶基或吡啶基，其中苯基選擇性地以一或兩個選自由F、Cl、氰基、選擇性地以一至三個F取代之烷基、及選擇性地以一至三個F取代之烷氧基所組成之群組之基團取代，吡唑基選擇性地以烷基取代，吡咯烷基以$-C(=O)OR_h$、一至兩個F、或以羥基、苯氧基或烷氧基取代之烷基取代，吡啶基選擇性地以一或兩個選自由F、Cl、氰基、哌啶基、烷基、及選擇性地以二烷基胺基或選擇性地更以烷氧基取代之烷氧基取代的烷氧基所組成之群組之基團取代，R_3為選擇性地以二烷基胺基取代之烷基，以及R_h為烷基。

【請求項16】　如請求項1所述的化合物，其中  為  ，其中R_{1b}為氫，且R_{1a}為以一至三個F取代之烷基取代的吡啶基；

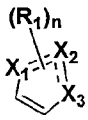
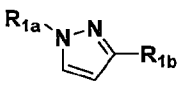
R為  ；以及

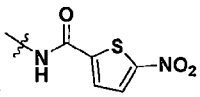
R_2為以一或兩個F或Cl取代之苯基。

【請求項17】　如請求項1所述的化合物，其中  為  ，其中R_{1b}為氫，R_{1a}為以–C(=O)OR_d取代之哌啶基，且R_d為烷基；

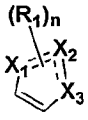
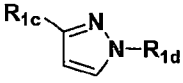
R為  ；以及

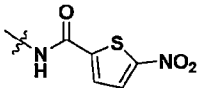
R_2為以Cl或–C(=O)OR_h取代之苯基，其中R_h為烷基。

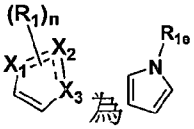
【請求項18】　如請求項1所述的化合物，其中  為  ，其中R_{1b}為氫，且R_{1a}為選擇性地以一或兩個F或烷基取代之環己基；

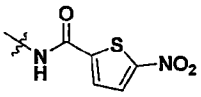
R為  ；以及

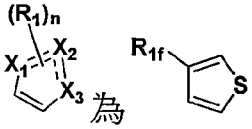
R_2為苯基或吡啶基，其中苯基以一或兩個F、Cl、或–C(=O)OR_h取代，其中R_h為烷基，且吡啶基以F、Cl或烷氧基取代。

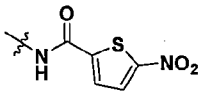
【請求項19】　如請求項1所述的化合物，其中  為  ，其中R_{1c}及R_{1d}分別為烷基。

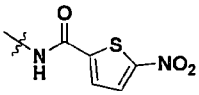
【請求項20】　如請求項19所述的化合物，其中R為  ，且R_2為苯基，其中苯基選擇性地以F、選擇性地以一至三個F取代之烷基或選擇性地以一至三個F取代之烷氧基取代。

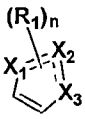
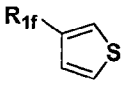
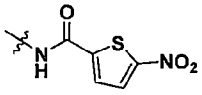
【請求項21】　如請求項1所述的化合物，其中  為，其中R_{1e}為烷基。

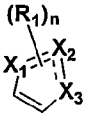
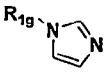
【請求項22】　如請求項21所述的化合物，其中R為  ，且R_2為選擇性地以烷基取代之苯基。

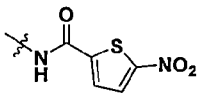
【請求項23】　如請求項1所述的化合物，其中  為，其中R_{1f}為烷基或選擇性地以鹵素或烷基取代之芳基。

【請求項24】　如請求項23所述的化合物，其中R_{1f}為烷基，R_2為  ，且R為苯基，其中苯基選擇性地被一至三個F選擇性地取代之烷氧基取代。

【請求項25】　如請求項23所述的化合物，其中R_{1f}為烷基或選擇性地以F或烷基取代之苯基，R為  ，且R_2為$-OR_3$、吡咯烷基或苯基，其中吡咯烷基選擇性地以一或兩個F取代，苯基選擇性地以一至三個選自由F、Cl、二烷基胺基、選擇性地以一至三個F取代之烷基、以及選擇性地以一至三個F取代之烷氧基所組成之群組之基團取代，且R_3為選擇性地以烷基取代之苯基。

【請求項26】　如請求項1所述的化合物，其中  為  ，其中R_{1f}為烷基，R為  ，且R_2為苯基，其中苯基選擇性地被一至三個F取代之烷基取代或選擇性地以一至三個F取代之烷氧基取代。

【請求項27】　如請求項1所述的化合物，其中  為  ，其中R_{1g}為環烷基或選擇性地以$-C(=O)OR_d$取代之雜環烷基，且R_d為烷基。

【請求項28】　如請求項27所述的化合物，其中R_{1g}為哌啶基或環己基，R為  ，且R_2為選擇性地以F取代之苯基或選擇性地以F或烷氧基取代之吡啶基。

【請求項29】　如請求項1所述的化合物，其中該化合物為選自由化合物1-1至1-33、化合物2-1至2-8、化合物3-1至3-12、化合物4-1至4-22、化合物5-1至5-57、化合物6-1至6-145、化合物7-1至7-19、化合物8-1至8-16、化合物9-1至9-13及化合物10-1至10-72所組成之群組中之任一者。

【請求項30】　如請求項1所述的化合物，其中該化合物為選自由化合物1-4至1-5、化合物1-11、化合物1-22、化合物1-27、化合物4-2、化合物4-5、化合物5-6、化合物5-18、化合物5-28至5-33、化合物5-35、化合物5-39、化合物5-40、化合物5-42、化合物5-44、化合物5-45、化合物5-47、化合物5-49、化合物5-56、化合物6-4、化合物6-11、化合物6-18、化合物6-19、化合物6-24至6-28、化合物6-35、化合物6-36、化合物6-39、化合物6-43、化合物6-45、化合物6-46、化合物6-50至6-54、化合物6-57至6-58、化合物6-66、化合物6-69、化合物6-71、化合

物6-75、化合物6-85、化合物6-89至6-91、化合物6-104、化合物6-106、化合物6-108、化合物6-110至6-112、化合物6-114至6-121、化合物6-125、化合物6-127至6-128、化合物6-130、化合物6-133、化合物6-135、化合物6-137、化合物7-1、化合物7-3、化合物7-6、化合物7-13、化合物7-19、化合物9-3、化合物9-5、化合物10-13、化合物10-14、化合物10-18、化合物10-23、化合物10-32、化合物10-40、化合物10-55、化合物10-57、以及化合物10-64所組成之群組中之任一者。

【請求項31】 一種醫藥組成物，包括：

如請求項1所述之化合物或其立體異構物、互變異構物、或其藥學上可接受之鹽類；以及

一藥學上可接受之載體。

【請求項32】 一種治療癌症之方法，包括：給予一需求主體一有效量的如請求項1所述的化合物或其立體異構物、互變異構物、或其藥學上可接受之鹽類。

【請求項33】 如請求項32所述的方法，其中該癌症選自由胃癌、大腸癌、結腸直腸癌、乳癌、肺癌、前列腺癌、膀胱癌、胰腺癌、肝癌、子宮癌、子宮頸癌、子宮內膜癌、食道癌、白血病、淋巴瘤、腎臟癌、骨肉瘤、卵巢癌、皮膚癌、小腸癌、胸腺癌、甲狀腺癌、神經系統癌、骨癌、腦癌、及頭頸癌所組成之群組。