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(54) Title: FIVE-MEMBERED HETEROCYCLIC COMPOUND, AND PHARMACEUTICAL COMPOSITION THEREOF AND USE THEREOF

(54) 发明名称: 五元杂环类化合物及其药物组合物与应用

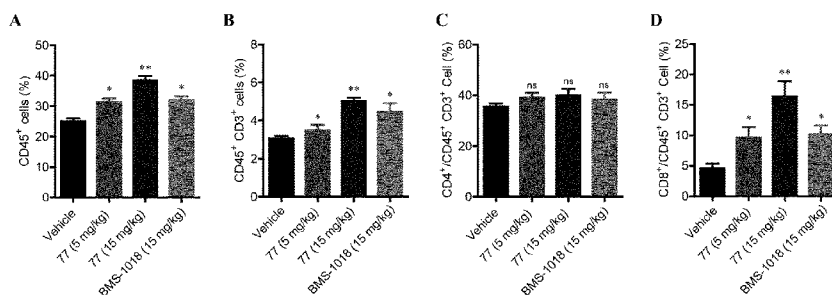
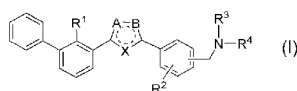


图 4

(57) Abstract: Disclosed in the present invention are a five-membered heterocyclic compound and a pharmaceutical composition thereof and the use thereof. The structure of the five-membered heterocyclic compound is as shown in formula (I). A stereoisomer, a mesomer, a racemate, a prodrug, a crystal, or a pharmaceutically acceptable salt thereof, or a mixture thereof is included. The compound has PD-L1 inhibitory activity, can significantly inhibit PD-1/PD-L1 protein-protein interaction, and blocks a PD-1/PD-L1 signal pathway, and therefore can be used in the preparation of an immunomodulator drug for preventing and/or treating tumors, infectious diseases, inflammatory diseases, autoimmune diseases and organ-graft rejection.

(57) 摘要: 本发明公开了一种五元杂环类化合物及其药物组合物和应用。该五元杂环类化合物的结构如式 (I) 所示, 还包含其立体异构体、内消旋体、外消旋体、前药、结晶、药学上可接受的盐或它们的混合物。该类化合物具有PD-L1抑制活性, 能够显著抑制PD-1/PD-L1蛋白-蛋白相互作用, 阻断PD-1/PD-L1信号通路, 因此可以用于制备预防和/或治疗肿瘤、感染性疾病、炎症性疾病、自身免疫性疾病和器官移植排斥的免疫调节剂药物。

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(81) 指定国(除另有指明, 要求每一种可提供的国家保护): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CV, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IQ, IR, IS, IT, JM, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, MG, MK, MN, MU, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, WS, ZA, ZM, ZW。

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— 包括国际检索报告(条约第 21 条(3))。

## 五元杂环类化合物及其药物组合物与应用

## 技术领域

本发明涉及一种五元杂环类化合物及其药物组合物与应用，尤其涉及一种针对 PD-1/PD-L1 蛋白-蛋白相互作用具有抑制活性的五元杂环类化合物及其药物组合物与应用。

## 背景技术

免疫逃逸是恶性肿瘤的一种基本生物学特征。在正常生理条件下，人体的免疫系统能够识别出异己分子并及时进行清除。但对于肿瘤患者而言，由于机体免疫能力低下和肿瘤细胞特殊的生物学特征，使得肿瘤细胞可以通过各种不同的机制逃避免疫系统的识别和杀灭，最终得以在体内发生与发展。肿瘤免疫逃逸是一个复杂的病理过程，其中由免疫检查点介导的逃逸机制深受人们关注。

免疫检查点是人体内免疫系统的调节器，由一系列共刺激分子和共抑制分子组成，在机体免疫系统中起重要的调控作用。免疫检查点的共刺激分子主要包括 CD27、CD40、OX40、GITR、CD137、OX40 和 ICOS 等，而共抑制分子则主要为 CTLA-4、PD-1、PD-L1、PD-L2、TIM-3、VISTA 和 IDO 等。其中，共刺激分子可以增强机体的免疫应答，从而有利于免疫细胞清除异己分子，而共抑制分子则对免疫应答起着负性调节作用，从而维护机体的免疫稳态，避免过度免疫而造成宿主正常组织的损伤。然而，肿瘤细胞却能够利用免疫检查点而实现免疫逃避。其中，常见的逃避机制便是肿瘤细胞通过诱导自身、抗原呈递细胞（APC）和 T 淋巴细胞等表面过度表达共抑制分子，从而抑制 T 淋巴细胞的激活。其中，程序性死亡受体 1（PD-1）及其配体 PD-L1/2 作为免疫检查点中重要的共抑制分子受到广泛关注，目前 PD-1/PD-L1 作为肿瘤免疫治疗的靶点已得到充分的确证。

PD-1 除了表达在成熟的 T 细胞外，还可以低水平表达在胸腺内的 CD4<sup>+</sup>CD8<sup>+</sup> T 细胞、B 细胞、树突状细胞（DC）和自然杀伤（NK）细胞。PD-1 有两个配体，其中 PD-L1 主要表达在成熟的 T 细胞、B 细胞以及一些非造血类型细胞，但 PD-L1 可以在炎症因子（如 IFN- $\gamma$ 、TNF- $\alpha$  和 VEGF）的诱导下于多种细胞上表达。PD-L2 表达范围相对较窄，主要是在巨噬细胞和 DC 细胞中表达。当 PD-1 与其配体结合后会引发胞质区 ITSM 结构域中的酪氨酸发生磷酸化，从而通过招募 TCR 附近的 SHP-2 磷酸酶，抑制 TCR 近端激酶的活化，导致 TCR-CD3 分子和 Lck 介导的 ZAP-70 磷酸化水平减弱，进而激活其下游信号通路。PD-1/PD-L 对免疫的负调控主要是通过抑制 PI3K-AKT 和 RAS 信号通路，阻断对 T 细胞激活、增殖、功能和生存等具有重要作用的转录因子的活化，如激活蛋白-1（AP-1）、活化 T 细胞的核因子（NFAT）和 NF- $\kappa$ B。另外，还可以通过上调转录因子 BATF 的表达来抑制 T 细胞功能。

在正常生理条件下，PD-1/PD-L 信号通路可以诱导并维持外周组织在免疫反应时的耐受性，以防止组织发生过度免疫应答。当机体处于病理状态下，PD-1/PD-L 信号通路过度激活会抑制免疫刺激因子如 IFN- $\gamma$ 、TNF- $\alpha$  和 IL-2 的分泌与存活蛋白的表达。大量研究表明，PD-1/PD-L 信号通路的异常与病毒感染、糖尿病、神经变性疾病、器官移植排斥和自身免疫性疾病等密切相关。

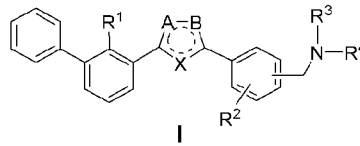
此外，众多研究表明，PD-1/PD-L 信号通路的异常与人类多种肿瘤的发生、发展和预后不良存在密切的关系。在肿瘤微环境中，当 PD-1/PD-L 信号通路被过度激活后，肿瘤细胞可以通过抗凋亡信号以及抑制抗原特异性 T 淋巴细胞的活性而获得生存。另外，使用 PD-1 或 PD-L1 抗体阻断 PD-1/PD-L 信号通路则能够抑制肿瘤细胞的生长。其主要是通过逆转对 T 淋巴细胞信号转导的影响，重新激活 T 淋巴细胞，同时促进效应 T 淋巴细胞和记忆 T 淋巴细胞的生成以及抑制调节性 T 淋巴细胞的分化，最终增强肿瘤微环境内 T 淋巴细胞的免疫杀伤能力，从而达到治疗肿瘤的目的。

目前全球已经有 Keytruda 和 Opdivo 等 10 多款 PD-1/PD-L1 单克隆抗体药物上市，应用于临床治疗恶性黑色素瘤、非小细胞肺癌、胃癌、肝癌、肾癌、膀胱癌等多种实体肿瘤和血液癌症，极大地改善了肿瘤患者预后，打破了许多种类癌症的治疗瓶颈。然而，PD-1/PD-L1 单抗药物存在一些明显的不足。例如，由于其原发性和/或获得性耐药，导致大多数肿瘤患者不能从中获益；由于其缺乏口服生物利用度，无法口服给药，患者依从性差；再加上本身具有的免疫原性容易导致患者出现药源性免疫相关不良事件（irAEs）；此外，由于单克隆抗体的制备和纯化难度大，而且运输不便，导致治疗成本高。这些问题都限制了 PD-1/PD-L1 单抗药物的临床应用。值得一提的是，小分子药物凭借其独有的药代动力学性质和药效学特性，加上其生产成本低，有望解决单抗药物存在的缺陷，因此研发 PD-1/PD-L1 小分子抑制剂具有重要应用价值。然而，该类小分子抑制剂的研发充满着挑战，导致其目前仍处于前期研发阶段，远远落后于单抗药物，因此急需研发活性高且成药性好的新型 PD-L1 小分子抑制剂。

## 发明内容

发明目的：针对现有 PD-1/PD-L1 小分子抑制剂存在的成药性欠佳等不足，本发明旨在提供一种具有显著的 PD-L1 抑制活性的小分子药物及药物组合物和应用。

技术方案：作为本发明的涉及的第一方面，本发明所述的五元杂环类化合物具有式 I 的结构，其还包含其立体异构体、内消旋体、外消旋体、前药、结晶、药学上可接受的盐或它们的混合物，



其中:

(1) 当 X 为 O、A 为 N 时, B 为 C; 当 X 为 O、A 为 C 时, B 为 N 或 C;

(2) 当 X 为 S 时, A、B 为 N 或 C;

(3) 当 X 为 NH、A 为 N 时, B 为 N;

(4) 当 X 为 N、A 为 N 时, B 为 O; 当 X 为 N、A 为 C 时, B 为 O 或 NH; 当 X 为 N, A 为 O 时, B 为 C 或 N;

$R^1$  选自甲基、氰基、羟基或卤素;

$R^2$  选自氢、卤素、硝基、氰基、羟基、 $C_1$ - $C_4$  烷基、 $C_1$ - $C_4$  烷氧基、 $C_1$ - $C_4$  卤代烷基或  $-O(CH_2)_nAr$ ; 其中, n 选自 0-4 的整数; Ar 选自芳基或芳杂环; 所述的芳杂环包含一个或多个选自 O、S 或 N 杂原子; 所述的  $C_1$ - $C_4$  烷基、芳基或芳杂环基被一个或多个 W 基团取代;

W 选自氢、卤素、氰基、羟基、巯基、羧基、 $C_1$ - $C_6$  烷基、 $C_1$ - $C_6$  烷氧基、 $C_1$ - $C_6$  烷氨基或  $C_1$ - $C_6$  卤代烷基;

$R^3$ 、 $R^4$  各自独立地选自氢、 $C_1$ - $C_8$  烷基、 $C_1$ - $C_8$  烷氧基、 $C_1$ - $C_8$  烷基胺基、 $C_3$ - $C_8$  环烷基、5-7 元杂环基或  $R^3$  和  $R^4$  与它们连接的氮原子一起形成 5-7 元杂环基; 所述的杂环基可任选地包含一个或多个选自 O、S 或 N 杂原子; 所述的  $C_1$ - $C_8$  烷基、 $C_1$ - $C_8$  烷氧基、 $C_1$ - $C_8$  烷基胺基、 $C_3$ - $C_8$  环烷基或 5-7 元杂环基被一个或多个 Y 基团取代;

Y 选自氢、卤素、羟基、巯基、甲硫基、羰基、羧基、氨基、胍基、呋喃基、四氢吡咯基、吗啉基、N-甲基哌嗪基、 $C_1$ - $C_4$  烷基、 $-CO_2R^5$ 、 $-NHCOR^5$ 、 $-NR^6R^7$  或  $-CONR^6R^7$ ; 所述的  $C_1$ - $C_4$  烷基被一个或多个羟基或卤素取代;

$R^5$  选自  $C_1$ - $C_8$  烷基;

$R^6$ 、 $R^7$  各自独立地选自氢、 $C_1$ - $C_8$  烷基、 $C_1$ - $C_8$  烷氧基、 $C_3$ - $C_8$  环烷基或  $R^8$  和  $R^9$  与它们连接的氮原子一起形成 5-7 元杂环基; 所述的  $C_1$ - $C_8$  烷基、 $C_1$ - $C_8$  烷氧基、 $C_3$ - $C_8$  环烷基或 5-7 元杂环基被一个或多个 Z 基团取代;

Z 选自氢、卤素、羟基、巯基、羧基、氨基或乙酰胺基。

本发明的小分子化合物具有良好的 PD-1/PD-L1 蛋白-蛋白相互作用的抑制活性, 可以用于治疗和/或预防 PD-1/PD-L1 介导的免疫抑制所引起的各种相关疾病。

优选, 上述结构中:

$R^1$  选自甲基或卤素;

$R^2$  选自氢、硝基或卤素;

$R^3$ 、 $R^4$  各自独立地选自氢、 $C_1$ - $C_5$  烷基或者  $R^3$  和  $R^4$  与它们连接的氮原子一起形成 5-6 元含 N 杂环基; 所述的  $C_1$ - $C_5$  烷基或 5-6 元杂环基被一个或多个 Y 基团取代;

Y 选自氢、羟基、羰基、羧基、胍基、 $C_1$ - $C_4$  烷基、 $-CO_2R^5$ 、 $-NR^6R^7$  或  $-CONR^6R^7$ ;  $C_1$ - $C_4$  烷基被一个或多个氢或羟基取代;

$R^5$  选自  $C_1$ - $C_4$  烷基;

$R^6$ 、 $R^7$  各自独立地选自氢或  $C_1$ - $C_4$  烷基。

优选, 上述结构中:

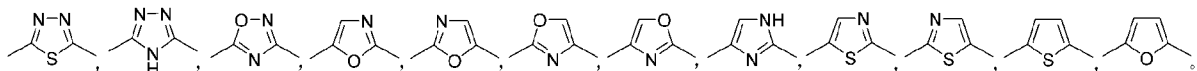
$R^1$  选自甲基或氯;

$R^2$  选自氢、硝基、氟、氯或溴;

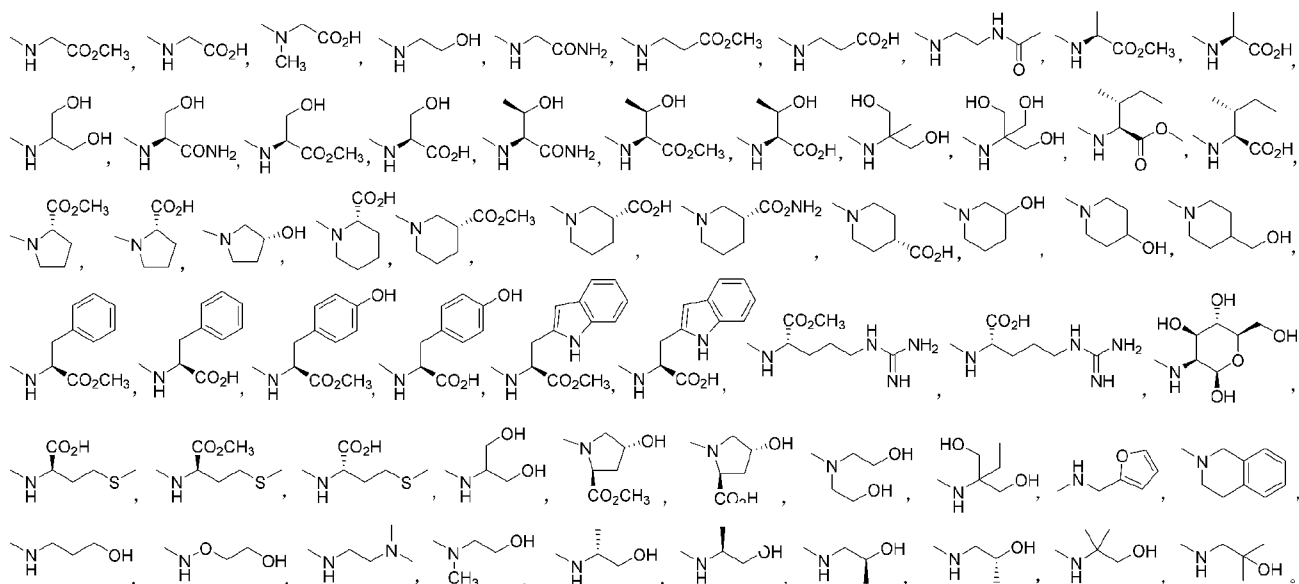
$R^3$ 、 $R^4$  各自独立地选自氢、 $C_1$ - $C_5$  烷基或者  $R^3$  和  $R^4$  与它们连接的氮原子一起形成 5-6 元含一个 N 原子的杂环基; 所述的  $C_1$ - $C_5$  烷基或 5-6 元杂环基被一个或多个 Y 基团取代;

Y 选自氢、羟基、羰基、羧基、胍基、 $C_1$ - $C_4$  烷基、 $-CO_2CH_3$ 、氨基或  $-CONH_2$ ;  $C_1$ - $C_4$  烷基被一个或多个氢或羟基取代。

具体地,  选自以下环系:



 选自以下基团:



更具体地，上述化合物选自以下任一化合物：

- (3-(5-(2-甲基-[1,1'-联苯]-3-基)-1,3,4-噻二唑-2-基)苄基)甘氨酸甲酯 (1m),
- (3-(5-(2-甲基-[1,1'-联苯]-3-基)-1,3,4-噻二唑-2-基)苄基)甘氨酸 (1) 及其盐酸盐 (1s),
- (3-(5-(2-甲基-[1,1'-联苯]-3-基)-1,3,4-噻二唑-2-基)苄基)肌氨酸 (2) 及其盐酸盐 (2s),
- (3-(5-(2-甲基-[1,1'-联苯]-3-基)-1,3,4-噻二唑-2-基)苄基)氨基乙醇 (3) 及其盐酸盐 (3s),
- (3-(5-(2-甲基-[1,1'-联苯]-3-基)-1,3,4-噻二唑-2-基)苄基)甘氨酸胺 (4) 及其盐酸盐 (4s),
- (3-(5-(2-甲基-[1,1'-联苯]-3-基)-1,3,4-噻二唑-2-基)苄基)- $\beta$ -丙氨酸 (5) 及其盐酸盐 (5s),
- N-(2-((3-(5-(2-甲基-[1,1'-联苯]-3-基)-1,3,4-噻二唑-2-基)苄基)氨基)乙基)乙酰胺 (6) 及其盐酸盐 (6s),
- (3-(5-(2-甲基-[1,1'-联苯]-3-基)-1,3,4-噻二唑-2-基)苄基)-L-精氨酸 (7) 及其盐酸盐 (7s),
- (3-(5-(2-甲基-[1,1'-联苯]-3-基)-1,3,4-噻二唑-2-基)苄基)-L-丙氨酸 (8) 及其盐酸盐 (8s),
- (3-(5-(2-甲基-[1,1'-联苯]-3-基)-1,3,4-噻二唑-2-基)苄基)氨基丙烷-1,3-二醇 (9) 及其盐酸盐 (9s),
- (3-(5-(2-甲基-[1,1'-联苯]-3-基)-1,3,4-噻二唑-2-基)苄基)-L-丝氨酸 (10) 及其盐酸盐 (10s),
- (3-(5-(2-甲基-[1,1'-联苯]-3-基)-1,3,4-噻二唑-2-基)苄基)-L-丝氨酸 (11) 及其盐酸盐 (11s),
- (3-(5-(2-甲基-[1,1'-联苯]-3-基)-1,3,4-噻二唑-2-基)苄基)-L-苏氨酸 (12) 及其盐酸盐 (12s),
- (3-(5-(2-甲基-[1,1'-联苯]-3-基)-1,3,4-噻二唑-2-基)苄基)-L-苏氨酸 (13) 及其盐酸盐 (13s),
- 2-甲基-2-((3-(5-(2-甲基-[1,1'-联苯]-3-基)-1,3,4-噻二唑-2-基)苄基)氨基)丙烷-1,3-二醇 (14) 及其盐酸盐 (14s),
- 2-(羟甲基)-2-((3-(5-(2-甲基-[1,1'-联苯]-3-基)-1,3,4-噻二唑-2-基)苄基)氨基)丙烷-1,3-二醇 (15) 及其盐酸盐 (15s),
- (3-(5-(2-甲基-[1,1'-联苯]-3-基)-1,3,4-噻二唑-2-基)苄基)-L-异亮氨酸 (16) 及其盐酸盐 (16s),
- (3-(5-(2-甲基-[1,1'-联苯]-3-基)-1,3,4-噻二唑-2-基)苄基)-L-脯氨酸 (17) 及其盐酸盐 (17s),
- (S)-1-(3-(5-(2-甲基-[1,1'-联苯]-3-基)-1,3,4-噻二唑-2-基)苄基)吡咯烷-3-醇 (18) 及其盐酸盐 (18s),
- (R)-1-(3-(5-(2-甲基-[1,1'-联苯]-3-基)-1,3,4-噻二唑-2-基)苄基)哌啶-3-羧酸 (19) 及其盐酸盐 (19s),
- (4-(5-(2-甲基-[1,1'-联苯]-3-基)-1,3,4-噻二唑-2-基)苄基)甘氨酸 (20) 及其盐酸盐 (20s),
- (4-(5-(2-甲基-[1,1'-联苯]-3-基)-1,3,4-噻二唑-2-基)苄基)氨基乙醇 (21) 及其盐酸盐 (21s),
- (4-(5-(2-甲基-[1,1'-联苯]-3-基)-1,3,4-噻二唑-2-基)苄基)甘氨酸胺 (22) 及其盐酸盐 (22s),
- (4-(5-(2-甲基-[1,1'-联苯]-3-基)-1,3,4-噻二唑-2-基)苄基)- $\beta$ -丙氨酸 (23) 及其盐酸盐 (23s),
- (4-(5-(2-甲基-[1,1'-联苯]-3-基)-1,3,4-噻二唑-2-基)苄基)-L-丝氨酸 (24) 及其盐酸盐 (24s),
- (4-(5-(2-甲基-[1,1'-联苯]-3-基)-1,3,4-噻二唑-2-基)苄基)-L-苏氨酸 (25) 及其盐酸盐 (25s),
- (4-(5-(2-甲基-[1,1'-联苯]-3-基)-1,3,4-噻二唑-2-基)苄基)-L-蛋氨酸 (26) 及其盐酸盐 (26s),
- (R)-1-(4-(5-(2-甲基-[1,1'-联苯]-3-基)-1,3,4-噻二唑-2-基)苄基)哌啶-3-羧酸 (27) 及其盐酸盐 (27s),
- (3-(5-(2-氟-[1,1'-联苯]-3-基)-1,3,4-噻二唑-2-基)苄基)甘氨酸 (28) 及其盐酸盐 (28s),
- (3-(5-(2-溴-[1,1'-联苯]-3-基)-1,3,4-噻二唑-2-基)苄基)甘氨酸 (29) 及其盐酸盐 (29s),
- 4-(5-(2-溴-[1,1'-联苯]-3-基)-1,3,4-噻二唑-2-基)-3-氯苄基)-L-丝氨酸 (30) 及其盐酸盐 (30s),
- (3-(5-(2-氯-[1,1'-联苯]-3-基)-1,3,4-噻二唑-2-基)苄基)甘氨酸 (31) 及其盐酸盐 (31s),
- (3-(5-(2-氯-[1,1'-联苯]-3-基)-1,3,4-噻二唑-2-基)苄基)氨基乙醇 (32) 及其盐酸盐 (32s),

(3-(5-(2-氯-[1,1'-联苯]-3-基)-1,3,4-噻二唑-2-基)苄基)甘氨酸 (33) 及其盐酸盐 (33s),  
(3-(5-(2-氯-[1,1'-联苯]-3-基)-1,3,4-噻二唑-2-基)苄基)-β-丙氨酸 (34) 及其盐酸盐 (34s),  
(3-(5-(2-氯-[1,1'-联苯]-3-基)-1,3,4-噻二唑-2-基)苄基)-L-丙氨酸 (35) 及其盐酸盐 (35s),  
(3-(5-(2-氯-[1,1'-联苯]-3-基)-1,3,4-噻二唑-2-基)苄基)-L-丝氨酸 (36) 及其盐酸盐 (36s),  
(3-(5-(2-氯-[1,1'-联苯]-3-基)-1,3,4-噻二唑-2-基)苄基)-L-丝氨酸 (37) 及其盐酸盐 (37s),  
(R)-1-(3-(5-(2-氯-[1,1'-联苯]-3-基)-1,3,4-噻二唑-2-基)苄基)哌啶-3-羧酸 (38) 及其盐酸盐 (38s),  
(4-(5-(2-氯-[1,1'-联苯]-3-基)-1,3,4-噻二唑-2-基)苄基)甘氨酸 (39) 及其盐酸盐 (39s),  
(4-(5-(2-氯-[1,1'-联苯]-3-基)-1,3,4-噻二唑-2-基)苄基)-L-丙氨酸 (40) 及其盐酸盐 (40s),  
(4-(5-(2-氯-[1,1'-联苯]-3-基)-1,3,4-噻二唑-2-基)苄基)-L-丝氨酸 (41) 及其盐酸盐 (41s),  
(3-氯-5-(5-(2-氯-[1,1'-联苯]-3-基)-1,3,4-噻二唑-2-基)苄基)甘氨酸 (42) 及其盐酸盐 (42s),  
(4-氟-3-(5-(2-甲基-[1,1'-联苯]-3-基)-1,3,4-噻二唑-2-基)苄基)甘氨酸 (43) 及其盐酸盐 (43s),  
(4-溴-3-(5-(2-甲基-[1,1'-联苯]-3-基)-1,3,4-噻二唑-2-基)苄基)甘氨酸 (44) 及其盐酸盐 (44s),  
(4-氯-3-(5-(2-甲基-[1,1'-联苯]-3-基)-1,3,4-噻二唑-2-基)苄基)甘氨酸 (45) 及其盐酸盐 (45s),  
(4-氯-3-(5-(2-甲基-[1,1'-联苯]-3-基)-1,3,4-噻二唑-2-基)苄基)氨基乙醇 (46) 及其盐酸盐 (46s),  
(R)-1-(4-氯-3-(5-(2-甲基-[1,1'-联苯]-3-基)-1,3,4-噻二唑-2-基)苄基)哌啶-3-羧酸 (47) 及其盐酸盐 (47s),  
(2-氯-3-(5-(2-甲基-[1,1'-联苯]-3-基)-1,3,4-噻二唑-2-基)苄基)甘氨酸 (48) 及其盐酸盐 (48s),  
(2-氯-5-(5-(2-甲基-[1,1'-联苯]-3-基)-1,3,4-噻二唑-2-基)苄基)甘氨酸 (49) 及其盐酸盐 (49s),  
(3-氯-5-(5-(2-甲基-[1,1'-联苯]-3-基)-1,3,4-噻二唑-2-基)苄基)甘氨酸 (50) 及其盐酸盐 (50s),  
(3-氯-5-(5-(2-甲基-[1,1'-联苯]-3-基)-1,3,4-噻二唑-2-基)苄基)氨基乙醇 (51) 及其盐酸盐 (51s),  
(3-氯-5-(5-(2-甲基-[1,1'-联苯]-3-基)-1,3,4-噻二唑-2-基)苄基)甘氨酸 (52) 及其盐酸盐 (52s),  
(3-氯-5-(5-(2-甲基-[1,1'-联苯]-3-基)-1,3,4-噻二唑-2-基)苄基)-β-丙氨酸 (53) 及其盐酸盐 (53s),  
(3-氯-5-(5-(2-甲基-[1,1'-联苯]-3-基)-1,3,4-噻二唑-2-基)苄基)-L-丙氨酸 (54) 及其盐酸盐 (54s),  
(3-氯-5-(5-(2-甲基-[1,1'-联苯]-3-基)-1,3,4-噻二唑-2-基)苄基)-L-丝氨酸 (55) 及其盐酸盐 (55s),  
(3-氯-5-(5-(2-甲基-[1,1'-联苯]-3-基)-1,3,4-噻二唑-2-基)苄基)-L-丝氨酸 (56) 及其盐酸盐 (56s),  
(3-氯-5-(5-(2-甲基-[1,1'-联苯]-3-基)-1,3,4-噻二唑-2-基)苄基)-L-苏氨酸 (57) 及其盐酸盐 (57s),  
(3-氯-5-(5-(2-甲基-[1,1'-联苯]-3-基)-1,3,4-噻二唑-2-基)苄基)-L-苏氨酸 (58) 及其盐酸盐 (58s),  
(R)-1-(3-氯-5-(5-(2-甲基-[1,1'-联苯]-3-基)-1,3,4-噻二唑-2-基)苄基)哌啶-3-羧酸 (59) 及其盐酸盐 (59s),  
(3-(5-(2-甲基-[1,1'-联苯]-3-基)-4H-1,2,4-三唑-3-基)苄基)甘氨酸 (60) 及其盐酸盐 (60s),  
(3-(5-(2-甲基-[1,1'-联苯]-3-基)-4H-1,2,4-三唑-3-基)苄基)氨基乙醇 (61) 及其盐酸盐 (61s),  
(3-(5-(2-甲基-[1,1'-联苯]-3-基)-4H-1,2,4-三唑-3-基)苄基)-β-丙氨酸 (62) 及其盐酸盐 (62s),  
(3-(5-(2-甲基-[1,1'-联苯]-3-基)-4H-1,2,4-三唑-3-基)苄基)-L-丝氨酸 (63) 及其盐酸盐 (63s),  
(3-(5-(2-甲基-[1,1'-联苯]-3-基)-4H-1,2,4-三唑-3-基)苄基)-L-苏氨酸 (64) 及其盐酸盐 (64s),  
(R)-1-(3-(5-(2-甲基-[1,1'-联苯]-3-基)-4H-1,2,4-三唑-3-基)苄基)哌啶-3-羧酸 (65) 及其盐酸盐 (65s),  
(4-(5-(2-甲基-[1,1'-联苯]-3-基)-4H-1,2,4-三唑-3-基)苄基)甘氨酸 (66) 及其盐酸盐 (66s),  
N-甲基-N-(4-(5-(2-甲基-[1,1'-联苯]-3-基)-4H-1,2,4-三唑-3-基)苄基)肌氨酸 (67) 及其盐酸盐 (67s),  
(4-(5-(2-甲基-[1,1'-联苯]-3-基)-4H-1,2,4-三唑-3-基)苄基)氨基乙醇 (68) 及其盐酸盐 (68s),  
(4-(5-(2-甲基-[1,1'-联苯]-3-基)-4H-1,2,4-三唑-3-基)苄基)-L-丝氨酸 (69) 及其盐酸盐 (69s),  
(4-(5-(2-甲基-[1,1'-联苯]-3-基)-4H-1,2,4-三唑-3-基)苄基)-L-苏氨酸 (70) 及其盐酸盐 (70s),  
(2-氯-5-(5-(2-甲基-[1,1'-联苯]-3-基)-4H-1,2,4-三唑-3-基)苄基)甘氨酸 (71) 及其盐酸盐 (71s),  
(3-(5-(2-甲基-[1,1'-联苯]-3-基)-1,2,4-噁二唑-3-基)苄基)甘氨酸 (72) 及其盐酸盐 (72s),  
N-(2-((3-(5-(2-甲基-[1,1'-联苯]-3-基)-1,2,4-噁二唑-3-基)苄基)氨基)乙基)乙酰胺 (73) 及其盐酸盐 (73s),  
N-甲基-N-(3-(5-(2-甲基-[1,1'-联苯]-3-基)-1,2,4-噁二唑-3-基)苄基)甘氨酸 (74) 及其盐酸盐 (74s),  
2-((3-(5-(2-甲基-[1,1'-联苯]-3-基)-1,2,4-噁二唑-3-基)苄基)氨基)乙酰胺 (75) 及其盐酸盐 (75s),  
(3-(5-(2-甲基-[1,1'-联苯]-3-基)-1,2,4-噁二唑-3-基)苄基)-L-丙氨酸 (76) 及其盐酸盐 (76s),  
(3-(5-(2-甲基-[1,1'-联苯]-3-基)-1,2,4-噁二唑-3-基)苄基)-L-蛋氨酸 (77) 及其盐酸盐 (77s),  
(3-(5-(2-甲基-[1,1'-联苯]-3-基)-1,2,4-噁二唑-3-基)苄基)-L-亮氨酸 (78) 及其盐酸盐 (78s),  
(3-(5-(2-甲基-[1,1'-联苯]-3-基)-1,2,4-噁二唑-3-基)苄基)-L-异亮氨酸 (79) 及其盐酸盐 (79s),  
(3-(5-(2-甲基-[1,1'-联苯]-3-基)-1,2,4-噁二唑-3-基)苄基)-L-精氨酸 (80) 及其盐酸盐 (80s),  
(3-(5-(2-甲基-[1,1'-联苯]-3-基)-1,2,4-噁二唑-3-基)苄基)-L-苯丙氨酸 (81) 及其盐酸盐 (81s),

(3-(5-(2-甲基-[1,1'-联苯]-3-基)-1,2,4-噁二唑-3-基)苄基)-L-酪氨酸 (82) 及其盐酸盐 (82s),  
(3-(5-(2-甲基-[1,1'-联苯]-3-基)-1,2,4-噁二唑-3-基)苄基)-L-色氨酸 (83) 及其盐酸盐 (83s),  
(3-(5-(2-甲基-[1,1'-联苯]-3-基)-1,2,4-噁二唑-3-基)苄基)-β-丙氨酸 (84) 及其盐酸盐 (84s),  
3-((3-(5-(2-甲基-[1,1'-联苯]-3-基)-1,2,4-噁二唑-3-基)苄基)氨基)丙酰胺 (85) 及其盐酸盐 (85s),  
(3-(5-(2-甲基-[1,1'-联苯]-3-基)-1,2,4-噁二唑-3-基)苄基)-L-脯氨酸 (86) 及其盐酸盐 (86s),  
(2S,4R)-4-羟基-1-(3-(5-(2-甲基-[1,1'-联苯]-3-基)-1,2,4-噁二唑-3-基)苄基)吡咯烷-2-羧酸 (87) 及其盐酸盐 (87s),  
(S)-1-(3-(5-(2-甲基-[1,1'-联苯]-3-基)-1,2,4-噁二唑-3-基)苄基)哌啶-2-羧酸 (88) 及其盐酸盐 (88s),  
(R)-1-(3-(5-(2-甲基-[1,1'-联苯]-3-基)-1,2,4-噁二唑-3-基)苄基)哌啶-3-羧酸 (89) 及其盐酸盐 (89s),  
1-(3-(5-(2-甲基-[1,1'-联苯]-3-基)-1,2,4-噁二唑-3-基)苄基)哌啶-3-甲酰胺 (90) 及其盐酸盐 (90s),  
(R)-1-(3-(5-(2-甲基-[1,1'-联苯]-3-基)-1,2,4-噁二唑-3-基)苄基)哌啶-4-羧酸 (91) 及其盐酸盐 (91s),  
N1,N1-二甲基-N2-(3-(5-(2-甲基-[1,1'-联苯]-3-基)-1,2,4-噁二唑-3-基)苄基)乙基-1,2-二胺 (92) 及其盐酸盐 (92s),  
(3-(5-(2-甲基-[1,1'-联苯]-3-基)-1,2,4-噁二唑-3-基)苄基)氨基乙醇 (93) 及其盐酸盐 (93s),  
2-(甲基(3-(5-(2-甲基-[1,1'-联苯]-3-基)-1,2,4-噁二唑-3-基)苄基)氨基)乙醇 (94) 及其盐酸盐 (94s),  
(R)-2-((3-(5-(2-甲基-[1,1'-联苯]-3-基)-1,2,4-噁二唑-3-基)苄基)氨基)丙醇 (95) 及其盐酸盐 (95s),  
(S)-2-((3-(5-(2-甲基-[1,1'-联苯]-3-基)-1,2,4-噁二唑-3-基)苄基)氨基)丙醇 (96) 及其盐酸盐 (96s),  
(R)-1-((3-(5-(2-甲基-[1,1'-联苯]-3-基)-1,2,4-噁二唑-3-基)苄基)氨基)丙基-2-醇 (97) 及其盐酸盐 (97s),  
(S)-1-((3-(5-(2-甲基-[1,1'-联苯]-3-基)-1,2,4-噁二唑-3-基)苄基)氨基)丙基-2-醇 (98) 及其盐酸盐 (98s),  
2-甲基-2-((3-(5-(2-甲基-[1,1'-联苯]-3-基)-1,2,4-噁二唑-3-基)苄基)氨基)丙醇 (99) 及其盐酸盐 (99s),  
2-甲基-1-((3-(5-(2-甲基-[1,1'-联苯]-3-基)-1,2,4-噁二唑-3-基)苄基)氨基)丙基-2-醇 (100) 及其盐酸盐 (100s),  
3-((3-(5-(2-甲基-[1,1'-联苯]-3-基)-1,2,4-噁二唑-3-基)苄基)氨基)丙醇 (101) 及其盐酸盐 (101s),  
2-((3-(5-(2-甲基-[1,1'-联苯]-3-基)-1,2,4-噁二唑-3-基)苄基)氨基)氧基乙醇 (102) 及其盐酸盐 (102s),  
2-((3-(5-(2-甲基-[1,1'-联苯]-3-基)-1,2,4-噁二唑-3-基)苄基)氨基)丙基-1,3-二醇 (103) 及其盐酸盐 (103s),  
2-甲基-2-((3-(5-(2-甲基-[1,1'-联苯]-3-基)-1,2,4-噁二唑-3-基)苄基)氨基)丙基-1,3-二醇 (104) 及其盐酸盐 (104s),  
2-乙基-2-((3-(5-(2-甲基-[1,1'-联苯]-3-基)-1,2,4-噁二唑-3-基)苄基)氨基)丙基-1,3-二醇 (105) 及其盐酸盐 (105s),  
2-(羟甲基)-2-((3-(5-(2-甲基-[1,1'-联苯]-3-基)-1,2,4-噁二唑-3-基)苄基)氨基)丙基-1,3-二醇 (106) 及其盐酸盐 (106s),  
(3S,4R,5S,6R)-6-(羟甲基)-3-(3-(5-(2-甲基-[1,1'-联苯]-3-基)-1,2,4-噁二唑-3-基)苄基)氨基)四氢-2H-吡喃-2,4,5-三醇 (107) 及其盐酸盐 (107s),  
((3-(5-(2-甲基-[1,1'-联苯]-3-基)-1,2,4-噁二唑-3-基)苄基)氮杂二酰基)二甲醇 (108) 及其盐酸盐 (108s),  
(S)-1-(3-(5-(2-甲基-[1,1'-联苯]-3-基)-1,2,4-噁二唑-3-基)苄基)吡咯烷-3-醇 (109) 及其盐酸盐 (109s),  
1-(3-(5-(2-甲基-[1,1'-联苯]-3-基)-1,2,4-噁二唑-3-基)苄基)哌啶-3-醇 (110) 及其盐酸盐 (110s),  
1-(3-(5-(2-甲基-[1,1'-联苯]-3-基)-1,2,4-噁二唑-3-基)苄基)哌啶-4-醇 (111) 及其盐酸盐 (111s),  
(1-(3-(5-(2-甲基-[1,1'-联苯]-3-基)-1,2,4-噁二唑-3-基)苄基)哌啶-4-基)甲醇 (112) 及其盐酸盐 (112s),  
(3-(5-(2-甲基-[1,1'-联苯]-3-基)-1,2,4-噁二唑-3-基)苄基)-L-丝氨酸 (113) 及其盐酸盐 (113s),  
(3-(5-(2-甲基-[1,1'-联苯]-3-基)-1,2,4-噁二唑-3-基)苄基)-L-苏氨酸 (114) 及其盐酸盐 (114s),  
3-(3-((3,4-二氢异喹啉-2(1H)-基)甲基)苯基)-5-(2-甲基-[1,1'-联苯]-3-基)-1,2,4-噁二唑 (115) 及其盐酸盐 (115s),  
(3-(5-(2-氯-[1,1'-联苯]-3-基)-1,2,4-噁二唑-3-基)苄基)甘氨酸 (116) 及其盐酸盐 (116s),  
(3-(5-(2-氯-[1,1'-联苯]-3-基)-1,2,4-噁二唑-3-基)苄基)-L-丝氨酸 (117) 及其盐酸盐 (117s),  
(4-(5-(2-甲基-[1,1'-联苯]-3-基)-1,2,4-噁二唑-3-基)苄基)甘氨酸 (118) 及其盐酸盐 (118s),  
N-甲基-N-(4-(5-(2-甲基-[1,1'-联苯]-3-基)-1,2,4-噁二唑-3-基)苄基)甘氨酸 (119) 及其盐酸盐 (119s),  
2-((4-(5-(2-甲基-[1,1'-联苯]-3-基)-1,2,4-噁二唑-3-基)苄基)氨基)乙酰胺 (120) 及其盐酸盐 (120s),  
(4-(5-(2-甲基-[1,1'-联苯]-3-基)-1,2,4-噁二唑-3-基)苄基)-L-丙氨酸 (121) 及其盐酸盐 (121s),  
(4-(5-(2-甲基-[1,1'-联苯]-3-基)-1,2,4-噁二唑-3-基)苄基)-L-亮氨酸 (122) 及其盐酸盐 (122s),  
(4-(5-(2-甲基-[1,1'-联苯]-3-基)-1,2,4-噁二唑-3-基)苄基)-L-蛋氨酸 (123) 及其盐酸盐 (123s),  
(4-(5-(2-甲基-[1,1'-联苯]-3-基)-1,2,4-噁二唑-3-基)苄基)-β-丙氨酸 (124) 及其盐酸盐 (124s),  
3-((4-(5-(2-甲基-[1,1'-联苯]-3-基)-1,2,4-噁二唑-3-基)苄基)氨基)丙酰胺 (125) 及其盐酸盐 (125s),  
2-((4-(5-(2-甲基-[1,1'-联苯]-3-基)-1,2,4-噁二唑-3-基)苄基)氨基)丙基-1,3-二醇 (126) 及其盐酸盐 (126s),  
1-(吡喃-2-基)-N-(4-(5-(2-甲基-[1,1'-联苯]-3-基)-1,2,4-噁二唑-3-基)苄基)甲胺 (127) 及其盐酸盐 (127s),  
(4-(5-(2-甲基-[1,1'-联苯]-3-基)-1,2,4-噁二唑-3-基)苄基)-L-脯氨酸 (128) 及其盐酸盐 (128s),

(2S,4R)-4-羟基-1-(3-(5-(2-甲基-[1,1'-联苯]-3-基)-1,2,4-噁二唑-3-基)苄基)吡咯烷-2-羧酸(129)及其盐酸盐(129s),  
(S)-1-(4-(5-(2-甲基-[1,1'-联苯]-3-基)-1,2,4-噁二唑-3-基)苄基)哌啶-2-羧酸(130)及其盐酸盐(130s),  
(3S, 4R, 5S, 6R)-6-(羟甲基)-3-((4-(5-(2-甲基-[1,1'-联苯]-3-基)-1,2,4-噁二唑-3-基)苄基)氨基)四氢-2H-吡喃-2,4,5-  
三醇(131)及其盐酸盐(131s),  
(4-(5-(2-甲基-[1,1'-联苯]-3-基)-1,2,4-噁二唑-3-基)苄基)-L-丝氨酸(132)及其盐酸盐(132s),  
(4-(5-(2-甲基-[1,1'-联苯]-3-基)-1,2,4-噁二唑-3-基)苄基)-L-苏氨酸(133)及其盐酸盐(133s),  
(4-(5-(2-氯-[1,1'-联苯]-3-基)-1,2,4-噁二唑-3-基)苄基)甘氨酸(134)及其盐酸盐(134s),  
(4-(5-(2-氯-[1,1'-联苯]-3-基)-1,2,4-噁二唑-3-基)苄基)-L-丝氨酸(135)及其盐酸盐(135s),  
(3-(3-(2-甲基-[1,1'-联苯]-3-基)-1,2,4-噁二唑-5-基)苄基)-L-丙氨酸(136)及其盐酸盐(136s),  
(3-(3-(2-甲基-[1,1'-联苯]-3-基)-1,2,4-噁二唑-5-基)苄基)-L-丝氨酸(137)及其盐酸盐(137s),  
(3-(3-(2-甲基-[1,1'-联苯]-3-基)-1,2,4-噁二唑-5-基)苄基)氨基丙酸(138)及其盐酸盐(138s),  
(3-(3-(2-甲基-[1,1'-联苯]-3-基)-1,2,4-噁二唑-5-基)苄基)甘氨酸(139)及其盐酸盐(139s),  
(2-((3-(3-(2-甲基-[1,1'-联苯]-3-基)-1,2,4-噁二唑-5-基)苄基)氨基)乙醇(140)及其盐酸盐(140s),  
(3-(3-(2-氟-[1,1'-联苯]-3-基)-1,2,4-噁二唑-5-基)苄基)甘氨酸(141)及其盐酸盐(141s),  
(3-(3-(2-氯-[1,1'-联苯]-3-基)-1,2,4-噁二唑-5-基)苄基)甘氨酸(142)及其盐酸盐(142s),  
(3-(3-(2-溴-[1,1'-联苯]-3-基)-1,2,4-噁二唑-5-基)苄基)甘氨酸(143)及其盐酸盐(143s),  
(4-(3-(2-甲基-[1,1'-联苯]-3-基)-1,2,4-噁二唑-5-基)苄基)甘氨酸(144)及其盐酸盐(144s),  
(4-(3-(2-甲基-[1,1'-联苯]-3-基)-1,2,4-噁二唑-5-基)苄基)-L-丝氨酸(145)及其盐酸盐(145s),  
(3-(5-(2-甲基-[1,1'-联苯]-3-基)噁唑-2-基)苄基)甘氨酸(146)及其盐酸盐(146s),  
(3-(5-(2-甲基-[1,1'-联苯]-3-基)噁唑-2-基)苄基)氨基乙醇(147)及其盐酸盐(147s),  
(3-(5-(2-甲基-[1,1'-联苯]-3-基)噁唑-2-基)苄基)甘氨酸酰胺(148)及其盐酸盐(148s),  
(3-(5-(2-甲基-[1,1'-联苯]-3-基)噁唑-2-基)苄基)-β-丙氨酸(149)及其盐酸盐(149s),  
(3-(5-(2-甲基-[1,1'-联苯]-3-基)噁唑-2-基)苄基)-L-丙氨酸(150)及其盐酸盐(150s),  
(3-(5-(2-甲基-[1,1'-联苯]-3-基)噁唑-2-基)苄基)-L-丝氨酸(151)及其盐酸盐(151s),  
(3-(5-(2-甲基-[1,1'-联苯]-3-基)噁唑-2-基)苄基)-L-苏氨酸(152)及其盐酸盐(152s),  
(R)-1-(3-(5-(2-甲基-1,1'-联苯)-3-基)噁唑-2-基)苄基)哌啶-3-羧酸(153)及其盐酸盐(153s),  
(4-(5-(2-甲基-[1,1'-联苯]-3-基)噁唑-2-基)苄基)甘氨酸(154)及其盐酸盐(154s),  
(4-(5-(2-甲基-[1,1'-联苯]-3-基)噁唑-2-基)苄基)氨基乙醇(155)及其盐酸盐(155s),  
(4-(5-(2-甲基-[1,1'-联苯]-3-基)噁唑-2-基)苄基)-β-丙氨酸(156)及其盐酸盐(156s),  
(R)-1-(4-(5-(2-甲基-[1,1'-联苯]-3-基)噁唑-2-基)苄基)哌啶-3-羧酸(157)及其盐酸盐(157s),  
(2-氯-5-(5-(2-甲基-[1,1'-联苯]-3-基)噁唑-2-基)苄基)甘氨酸(158)及其盐酸盐(158s),  
(R)-1-(2-氯-5-(5-(2-甲基-[1,1'-联苯]-3-基)噁唑-2-基)苄基)哌啶-3-羧酸(159)及其盐酸盐(159s),  
(2-氯-3-(5-(2-甲基-[1,1'-联苯]-3-基)噁唑-2-基)苄基)甘氨酸(160)及其盐酸盐(160s),  
(3-氯-5-(5-(2-甲基-[1,1'-联苯]-3-基)噁唑-2-基)苄基)甘氨酸(161)及其盐酸盐(161s),  
(3-氯-5-(5-(2-甲基-[1,1'-联苯]-3-基)噁唑-2-基)苄基)-L-丙氨酸(162)及其盐酸盐(162s),  
(3-氯-5-(5-(2-甲基-[1,1'-联苯]-3-基)噁唑-2-基)苄基)-L-丝氨酸(163)及其盐酸盐(163s),  
(3-氯-5-(5-(2-甲基-[1,1'-联苯]-3-基)噁唑-2-基)苄基)氨基乙醇(164)及其盐酸盐(164s),  
(4-氯-3-(5-(2-甲基-[1,1'-联苯]-3-基)噁唑-2-基)苄基)甘氨酸(165)及其盐酸盐(165s),  
(4-氯-3-(5-(2-甲基-[1,1'-联苯]-3-基)噁唑-2-基)苄基)-L-丝氨酸(166)及其盐酸盐(166s),  
(4-氯-3-(5-(2-甲基-[1,1'-联苯]-3-基)噁唑-2-基)苄基)-D-丝氨酸(167)及其盐酸盐(167s),  
(4-氟-3-(5-(2-甲基-[1,1'-联苯]-3-基)噁唑-2-基)苄基)甘氨酸(168)及其盐酸盐(168s),  
(4-氟-3-(5-(2-甲基-[1,1'-联苯]-3-基)噁唑-2-基)苄基)-L-丝氨酸(169)及其盐酸盐(169s),  
(4-溴-3-(5-(2-甲基-[1,1'-联苯]-3-基)噁唑-2-基)苄基)甘氨酸(170)及其盐酸盐(170s),  
(4-碘-3-(5-(2-甲基-[1,1'-联苯]-3-基)噁唑-2-基)苄基)甘氨酸(171)及其盐酸盐(171s),  
(4-硝基-3-(5-(2-甲基-[1,1'-联苯]-3-基)噁唑-2-基)苄基)甘氨酸(172)及其盐酸盐(172s),  
(3-氯-4-(5-(2-甲基-[1,1'-联苯]-3-基)噁唑-2-基)苄基)甘氨酸(173)及其盐酸盐(173s),  
(2-氯-4-(5-(2-甲基-[1,1'-联苯]-3-基)噁唑-2-基)苄基)甘氨酸(174)及其盐酸盐(174s),  
(R)-1-(2-氯-4-(5-(2-甲基-[1,1'-联苯]-3-基)噁唑-2-基)苄基)哌啶-3-羧酸(175)及其盐酸盐(175s),  
(2-硝基-4-(5-(2-甲基-[1,1'-联苯]-3-基)噁唑-2-基)苄基)甘氨酸(176)及其盐酸盐(176s),

2-甲氧基-4-(5-(2-甲基-[1,1'-联苯]-3-基)噁唑-2-基)苄基)甘氨酸 (177) 及其盐酸盐 (177s),  
4-(5-(2-甲基-[1,1'-联苯]-3-基)噁唑-2-基)-3-硝基苄基)甘氨酸 (178) 及其盐酸盐 (178s),  
(4-氯-3-(5-(2-氯-[1,1'-联苯]-3-基)噁唑-2-基)苄基)甘氨酸 (179) 及其盐酸盐 (179s),  
4-氯-3-(5-氯-[1,1'-联苯]-3-基)噁唑-2-基)苄基)-L-丝氨酸 (180) 及其盐酸盐 (180s),  
(R)-1-(4-氯-3-(5-氯-[1,1'-联苯]-3-基)噁唑-2-基)苄基)哌啶-3-羧酸 (181) 及其盐酸盐 (181s),  
4-氯-3-(5-(2-氯-[1,1'-联苯]-3-基)噁唑-2-基)苄基)氨基乙醇 (182) 及其盐酸盐 (182s),  
4-氯-3-(5-溴-[1,1'-联苯]-3-基)噁唑-2-基)苄基)甘氨酸 (183) 及其盐酸盐 (183s),  
3-(5-溴-[1,1'-联苯]-3-基)噁唑-2-基)-4-氯苄基)-L-丝氨酸 (184) 及其盐酸盐 (184s),  
5-(5-(2-溴-[1,1'-联苯]-3-基)噁唑-2-基)-2-氯苄基)甘氨酸 (185) 及其盐酸盐 (185s),  
(R)-1-(3-(5-(2-溴-[1,1'-联苯]-3-基)噁唑-2-基)-4-氯苄基)哌啶-3-羧酸 (186) 及其盐酸盐 (186s),  
3-(5-(2-溴-[1,1'-联苯]-3-基)噁唑-2-基)-5-氯苄基)甘氨酸 (187) 及其盐酸盐 (187s),  
4-(5-(2-溴-[1,1'-联苯]-3-基)噁唑-2-基)苄基)甘氨酸 (188) 及其盐酸盐 (188s),  
(4-(5-(2-溴-[1,1'-联苯]-3-基)噁唑-2-基)-3-氯苄基)甘氨酸 (189) 及其盐酸盐 (189s),  
4-(5-(2-溴-[1,1'-联苯]-3-基)噁唑-2-基)-2-氯苄基)甘氨酸 (190) 及其盐酸盐 (190s),  
(3-(2-(2-甲基-[1,1'-联苯]-3-基)噁唑-5-基)苄基)甘氨酸 (191) 及其盐酸盐 (191s),  
(3-(2-(2-甲基-[1,1'-联苯]-3-基)噁唑-5-基)苄基)-L-丝氨酸 (192) 及其盐酸盐 (192s),  
3-((3-(2-(2-甲基-[1,1'-联苯]-3-基)噁唑-5-基)苄基)氨基)丙酸 (193) 及其盐酸盐 (193s),  
(4-(2-(2-甲基-[1,1'-联苯]-3-基)噁唑-5-基)苄基)甘氨酸 (194) 及其盐酸盐 (194s),  
(4-(2-(2-甲基-[1,1'-联苯]-3-基)噁唑-5-基)苄基)-L-丙氨酸 (195) 及其盐酸盐 (195s),  
(4-(2-(2-甲基-[1,1'-联苯]-3-基)噁唑-5-基)苄基)-L-丝氨酸 (196) 及其盐酸盐 (196s),  
(4-(2-(2-甲基-[1,1'-联苯]-3-基)噁唑-5-基)苄基)-L-苏氨酸 (197) 及其盐酸盐 (197s),  
(4-(2-(2-甲基-[1,1'-联苯]-3-基)噁唑-5-基)苄基)-β-丙氨酸 (198) 及其盐酸盐 (198s),  
3-(2-甲基-[1,1'-联苯]-3-基)噁唑-4-基)苄基)甘氨酸 (199) 及其盐酸盐 (199s),  
3-(2-甲基-[1,1'-联苯]-3-基)噁唑-4-基)苄基)-L-丙氨酸 (200) 及其盐酸盐 (200s),  
3-(2-甲基-[1,1'-联苯]-3-基)噁唑-4-基)苄基)-L-丝氨酸 (201) 及其盐酸盐 (201s),  
3-(3-(2-甲基-[1,1'-联苯]-3-基)噁唑-4-基)苄基)-β-丙氨酸 (202) 及其盐酸盐 (202s),  
(R)-1-(3-(2-甲基-[1,1'-联苯]-3-基)噁唑-4-基)苄基)哌啶-3-羧酸 (203) 及其盐酸盐 (203s),  
3-(2-甲基-[1,1'-联苯]-3-基)噁唑-4-基)苄基)氨基乙醇 (204) 及其盐酸盐 (204s),  
3-(2-甲基-[1,1'-联苯]-3-基)噁唑-4-基)苄基)甘氨酸酰胺 (205) 及其盐酸盐 (205s),  
(3-(2-甲基-[1,1'-联苯]-3-基)噁唑-4-基)苄基)-L-丝氨酸酰胺 (206) 及其盐酸盐 (206s),  
4-(2-甲基-[1,1'-联苯]-3-基)噁唑-4-基)苄基)甘氨酸 (207) 及其盐酸盐 (207s),  
4-(2-甲基-[1,1'-联苯]-3-基)噁唑-4-基)苄基)-L-丝氨酸 (208) 及其盐酸盐 (208s),  
4-(2-甲基-[1,1'-联苯]-3-基)噁唑-4-基)苄基)-β-丙氨酸 (209) 及其盐酸盐 (209s),  
(R)-1-(4-(2-甲基-[1,1'-联苯]-3-基)噁唑-4-基)苄基)哌啶-3-羧酸 (210) 及其盐酸盐 (210s),  
4-(2-甲基-[1,1'-联苯]-3-基)噁唑-4-基)苄基)氨基乙醇 (211) 及其盐酸盐 (211s),  
3-(2-氯-[1,1'-联苯]-3-基)噁唑-4-基)苄基)甘氨酸 (212) 及其盐酸盐 (212s),  
3-(2-氯-[1,1'-联苯]-3-基)噁唑-4-基)苄基)-L-丝氨酸 (213) 及其盐酸盐 (213s),  
3-(2-氯-[1,1'-联苯]-3-基)噁唑-4-基)苄基)-L-丙氨酸 (214) 及其盐酸盐 (214s),  
3-(2-氯-[1,1'-联苯]-3-基)噁唑-4-基)苄基)-β-丙氨酸 (215) 及其盐酸盐 (215s),  
(3-氯-(5-(2-氯-[1,1'-联苯]-3-基)噁唑-4-基)苄基)甘氨酸 (216) 及其盐酸盐 (216s),  
(3-氯-(5-(2-氯-[1,1'-联苯]-3-基)噁唑-4-基)苄基)丝氨酸 (217) 及其盐酸盐 (217s),  
(3-[4-(2-甲基-[1,1'-联苯]-3-基)噁唑-2-基)苄基)-L-丙氨酸 (218) 及其盐酸盐 (218s),  
(3-[4-(2-甲基-[1,1'-联苯]-3-基)噁唑-2-基)苄基)-L-丝氨酸 (219) 及其盐酸盐 (219s),  
(3-[4-(2-甲基-[1,1'-联苯]-3-基)噁唑-2-基)苄基)-β-丙氨酸 (220) 及其盐酸盐 (220s),  
(R)-1-(3-[4-(2-甲基-[1,1'-联苯]-3-基)噁唑-2-基)苄基)哌啶-3-羧酸 (221) 及其盐酸盐 (221s),  
(3-[4-(2-甲基-[1,1'-联苯]-3-基)噁唑-2-基)苄基)氨基乙醇 (222) 及其盐酸盐 (222s),  
(3-[4-(2-甲基-[1,1'-联苯]-3-基)噁唑-2-基)苄基)甘氨酸酰胺 (223) 及其盐酸盐 (223s),  
(3-[4-(2-甲基-[1,1'-联苯]-3-基)噁唑-2-基)苄基)-L-丝氨酸酰胺 (224) 及其盐酸盐 (224s),  
(4-(4-(2-甲基-[1,1'-联苯]-3-基)噁唑-2-基)苄基)甘氨酸 (225) 及其盐酸盐 (225s),

(4-(4-(2-甲基-[1,1'-联苯]-3-基)噁唑-2-基)苄基)-L-丝氨酸 (226) 及其盐酸盐 (226s),  
(3-[4-(2-甲基-[1,1'-联苯]-3-基)]-1H-咪唑-2-基)苄基)-L-丙氨酸 (227) 及其盐酸盐 (227s),  
(R)-1-(3-[4-(2-甲基-[1,1'-联苯]-3-基)]-1H-咪唑-2-基)苄基)哌啶-3-羧酸 (228) 及其盐酸盐 (228s),  
(3-[4-(2-甲基-[1,1'-联苯]-3-基)]-1H-咪唑-2-基)苄基)甘氨酸 (229) 及其盐酸盐 (229s),  
(3-[4-(2-甲基-[1,1'-联苯]-3-基)]-1H-咪唑-2-基)苄基)-L-丝氨酸 (230) 及其盐酸盐 (230s),  
(3-(5-(2-甲基-[1,1'-联苯]-3-基)噁唑-2-基)苄基)-L-苏氨酸 (231) 及其盐酸盐 (231s),  
(3-(4-(2-甲基-[1,1'-联苯]-3-基)-1H-咪唑-2-基)苄基)-β-丙氨酸 (232) 及其盐酸盐 (232s),  
(4-(4-(2-甲基-[1,1'-联苯]-3-基)-1H-咪唑-2-基)苄基)-β-丙氨酸 (233) 及其盐酸盐 (233s),  
(4-(4-(2-甲基-[1,1'-联苯]-3-基)-1H-咪唑-2-基)苄基)甘氨酸 (234) 及其盐酸盐 (234s),  
(3-(5-(2-甲基-[1,1'-联苯]-3-基)噁唑-2-基)苄基)甘氨酸 (235) 及其盐酸盐 (235s),  
(3-(5-(2-甲基-[1,1'-联苯]-3-基)噁唑-2-基)苄基)-L-丙氨酸 (236) 及其盐酸盐 (236s),  
(3-(5-(2-甲基-[1,1'-联苯]-3-基)噁唑-2-基)苄基)-L-丝氨酸 (237) 及其盐酸盐 (237s),  
(3-(5-(2-甲基-[1,1'-联苯]-3-基)噁唑-2-基)苄基)-L-苏氨酸 (238) 及其盐酸盐 (238s),  
(3-(5-(2-甲基-[1,1'-联苯]-3-基)噁唑-2-基)苄基)氨基乙醇 (239) 及其盐酸盐 (239s),  
(3-(2-甲基-[1,1'-联苯]-3-基)噁唑-5-基)苄基)甘氨酸 (240) 及其盐酸盐 (240s),  
(3-(2-甲基-[1,1'-联苯]-3-基)噁唑-5-基)苄基)-L-丙氨酸 (241) 及其盐酸盐 (241s),  
(3-(2-甲基-[1,1'-联苯]-3-基)噁唑-5-基)苄基)-L-丝氨酸 (242) 及其盐酸盐 (242s),  
(3-(2-甲基-[1,1'-联苯]-3-基)噁唑-5-基)苄基)-L-苏氨酸 (243) 及其盐酸盐 (243s),  
(3-(2-(2-甲基-[1,1'-联苯]-3-基)噁唑-5-基)苄基)氨基乙醇 (244) 及其盐酸盐 (244s),  
(4-(5-(2-甲基-[1,1'-联苯]-3-基)噁吩-2-基)苄基)甘氨酸 (245) 及其盐酸盐 (245s),  
(4-(5-(2-甲基-[1,1'-联苯]-3-基)噁吩-2-基)苄基)-β-丙氨酸 (246) 及其盐酸盐 (246s),  
(4-(5-(2-甲基-[1,1'-联苯]-3-基)噁吩-2-基)苄基)丝氨酸 (247) 及其盐酸盐 (247s),  
(4-(5-(2-甲基-[1,1'-联苯]-3-基)噁吩-2-基)苄基)-L-苏氨酸 (248) 及其盐酸盐 (248s),  
(R)-1-(4-(5-(2-甲基-[1,1'-联苯]-3-基)噁吩-2-基)苄基)哌啶-3-羧酸 (249) 及其盐酸盐 (249s),  
(3-(5-(2-甲基-[1,1'-联苯]-3-基)噁吩-2-基)苄基)甘氨酸 (250) 及其盐酸盐 (250s),  
(3-(5-(2-甲基-[1,1'-联苯]-3-基)噁吩-2-基)苄基)氨基乙醇 (251) 及其盐酸盐 (251s),  
(3-(5-(2-甲基-[1,1'-联苯]-3-基)噁吩-2-基)苄基)-β-丙氨酸 (252) 及其盐酸盐 (252s),  
(3-(5-(2-甲基-[1,1'-联苯]-3-基)噁吩-2-基)苄基)-L-丙氨酸 (253) 及其盐酸盐 (253s),  
(3-(5-(2-甲基-[1,1'-联苯]-3-基)噁吩-2-基)苄基)-L-丝氨酸 (254) 及其盐酸盐 (254s),  
(3-(5-(2-甲基-[1,1'-联苯]-3-基)噁吩-2-基)苄基)-L-苏氨酸 (255) 及其盐酸盐 (255s),  
(R)-1-(3-(5-(2-甲基-[1,1'-联苯]-3-基)噁吩-2-基)苄基)哌啶-3-羧酸 (256) 及其盐酸盐 (256s),  
(3-(3-(5-(2-甲基-[1,1'-联苯]-3-基)噁吩-2-基)苄基)氨基)哌啶-2,6-二酮 (257) 及其盐酸盐 (257s),  
(4-(5-(2-甲基-[1,1'-联苯]-3-基)呋喃-2-基)苄基)甘氨酸 (258) 及其盐酸盐 (258s),  
(4-(5-(2-甲基-[1,1'-联苯]-3-基)呋喃-2-基)苄基)-L-丝氨酸 (259) 及其盐酸盐 (259s),  
(4-(5-(2-甲基-[1,1'-联苯]-3-基)呋喃-2-基)苄基)-β-丙氨酸 (260) 及其盐酸盐 (260s),  
(3-(5-(2-甲基-[1,1'-联苯]-3-基)呋喃-2-基)苄基)甘氨酸 (261) 及其盐酸盐 (261s),  
(3-(5-(2-甲基-[1,1'-联苯]-3-基)呋喃-2-基)苄基)-L-丝氨酸 (262) 及其盐酸盐 (262s),  
(3-(5-(2-甲基-[1,1'-联苯]-3-基)呋喃-2-基)苄基)-β-丙氨酸 (263) 及其盐酸盐 (263s),  
(R)-1-(3-(5-(2-甲基-[1,1'-联苯]-3-基)呋喃-2-基)苄基)哌啶-3-羧酸 (264) 及其盐酸盐 (264s),  
(3-(5-(2-甲基-[1,1'-联苯]-3-基)呋喃-2-基)苄基)氨基乙醇 (265) 及其盐酸盐 (265s),  
(3-(5-(2-甲基-[1,1'-联苯]-3-基)呋喃-2-基)苄基)-L-苏氨酸 (266) 及其盐酸盐 (266s).

本发明所述的药学上可接受的盐为所述化合物与选自以下任一的酸形成的盐: 盐酸、氢溴酸、硫酸、磷酸、碳酸、甲磺酸、苯磺酸、对甲苯磺酸、萘磺酸、柠檬酸、酒石酸、苹果酸、乳酸、丙酮酸、乙酸、马来酸、琥珀酸、富马酸、水杨酸、苯基乙酸、杏仁酸、阿魏酸。

“药学上可接受的盐”是指化合物的盐, 由具有特定取代基的化合物与相对无毒的酸或碱制备。当化合物中含有相对酸性的官能团时, 可以通过在纯的溶液或合适的惰性溶剂中用足够量的碱与这类化合物的游离体形式接触的方式获得碱加成盐。药学上可接受的碱加成盐包括钠、钾、钙、铵、有机氨或镁盐或类似的盐。当化合物中含有相对碱性的官能团时, 可以通过在纯的溶液或合适的惰性溶剂中用足够量的酸与这类化合物的游离体形式接触的方式获得酸加成盐。药学上可接受的酸加成盐的实例包括无机酸盐, 所述无机酸包括例如盐酸、氢溴酸、硝酸、碳酸 (形

成碳酸盐或碳酸氢盐)、磷酸(形成磷酸盐、磷酸一氢盐、磷酸二氢盐、硫酸(形成硫酸盐或硫酸氢盐)、氢碘酸、亚磷酸等;以及有机酸盐,所述有机酸包括如乙酸、丙酸、异丁酸、马来酸、丙二酸、苯甲酸、琥珀酸、辛二酸、反丁烯二酸、乳酸、扁桃酸、邻苯二甲酸、苯磺酸、对甲苯磺酸、柠檬酸、酒石酸和甲磺酸等类似的酸;有机酸盐还包括氨基酸(如精氨酸等)、葡糖醛酸等有机酸的盐。当某些特定的化合物含有碱性和酸性的官能团,从而可以被转换成任一碱或酸加成盐。优选地,以常规方式使盐与碱或酸接触,再分离母体化合物,由此再生化合物的游离形式。化合物的游离体形式与其各种盐的形式不同之处在于某些物理性质,例如在极性溶剂中的溶解度不同。

“药学上可接受的盐”可由含有酸根或碱基的母体化合物通过常规化学方法合成。一般情况下,这样的盐的制备方法是:在水或有机溶剂或两者的混合物中,经由游离酸或碱形式的这些化合物与化学计量的适当的碱或酸反应来制备。一般地,优选醚、乙酸乙酯、乙醇、异丙醇或乙腈等非水介质。

作为本发明涉及的第二方面,上述化合物可制备为 PD-L1 抑制剂药物以及免疫调节剂药物,具体为预防和/或治疗肿瘤、感染性疾病、炎症性疾病、器官移植排斥和自身免疫性疾病的药物。

作为本发明涉及的第三方面,上述化合物与药学上可接受的载体形成药物组合物,具体制剂形式为片剂、胶囊剂、散剂、丸剂、颗粒剂、注射剂、口服液、糖浆剂、吸入剂、软膏剂、贴剂或栓剂。

“药学上可接受的载体”可为药物生产领域中广泛采用的辅料。辅料主要用于提供一个安全、稳定和功能性药物组合物,还可以提供方法,使受试者接受给药后活性成分以所期望的速率溶出,或促进受试者接受组合物给药后活性成分得到有效吸收。所述的药用辅料可以是惰性填充剂,或者提供某种功能,例如稳定该组合物的整体 pH 值或防止组合物活性成分的降解。所述的药用辅料可以包括下列辅料中的一种或多种:粘合剂、助悬剂、乳化剂、稀释剂、填充剂、成粒剂、胶粘剂、崩解剂、润滑剂、抗粘着剂、助流剂、润湿剂、胶凝剂、吸收延迟剂、溶解抑制剂、增强剂、吸附剂、缓冲剂、螯合剂、防腐剂、着色剂、矫味剂和甜味剂。

所述药物可根据公开的内容使用本领域技术人员已知的任何方法来制备。例如,常规混合、溶解、造粒、乳化、磨细、包封、包埋或冻干工艺。

所述药物可以以任何形式给药,包括注射(静脉内)、粘膜、口服(固体和液体制剂)、吸入、眼部、直肠、局部或胃肠外(输注、注射、植入、皮下、静脉内、动脉内、肌内)给药。所述的药物还可以是控释或缓释剂型(例如脂质体或微球)。固体口服制剂的实例包括但不限于粉末、胶囊、囊片、软胶囊剂和片剂。口服或粘膜给药的液体制剂实例包括但不限于悬浮液、乳液、酏剂和溶液。局部用制剂的实例包括但不限于乳剂、凝胶剂、软膏剂、乳膏剂、贴剂、糊剂、泡沫剂、洗剂、滴剂或血清制剂。胃肠外给药的制剂实例包括但不限于注射用溶液、可以溶解或悬浮在药学上可接受载体中的干粉制剂、注射用悬浮液和注射用乳剂。所述的药物组合物的其它合适制剂的实例包括但不限于滴眼液和其他眼科制剂;气雾剂,如鼻腔喷雾剂或吸入剂;适于胃肠外给药的液体剂型;栓剂以及锭剂。

有益效果:与现有技术相比,本发明具有以下显著优点:

本发明的化合物对 PD-1/PD-L1 蛋白-蛋白相互作用具有很高的抑制活性。药理实验结果表明,这些五元杂环类化合物与 PD-L1 具有很强的结合能力,可以有效地逆转 PD-1/PD-L1 介导的免疫抑制作用,促进 CD8<sup>+</sup> T 淋巴细胞的增殖,提高细胞因子干扰素- $\gamma$  的分泌,减少 CD4<sup>+</sup> CD25<sup>+</sup> Foxp3<sup>+</sup> 调节性 T 细胞的生成,降低 PCNA 蛋白的表达。体内药效学评价结果表明,本发明的化合物能够显著抑制各种肿瘤类型的小鼠移植瘤的生长,而对免疫系统缺陷的裸鼠移植瘤的生长则无影响,说明这些化合物是通过激活宿主免疫应答而起抗肿瘤作用。

#### 附图说明

图 1 为本发明化合物在不同浓度下对 Lewis 肺癌细胞活力的影响;

图 2 为本发明化合物呈剂量依赖性逆转 PD-1/PD-L1 抑制 PBMC 分泌 INF- $\gamma$  的作用;

图 3 为本发明化合物呈剂量依赖性抑制 Lewis 肺癌小鼠移植瘤的生长;

图 4 为本发明化合物对小鼠移植瘤 T 淋巴细胞浸润的影响,其中: A) CD45<sup>+</sup> 细胞; B) CD45<sup>+</sup> CD3<sup>+</sup> 细胞; C) CD4<sup>+</sup> CD45<sup>+</sup> CD3<sup>+</sup> 细胞; D) CD8<sup>+</sup> CD45<sup>+</sup> CD3<sup>+</sup> 细胞。

#### 具体实施方式

下面结合实施例对本发明的技术方案作进一步说明。

试剂与材料:实验所需要的所有试剂未经特别说明均为市售化学纯或分析纯产品。

实施例 1: (3-(5-(2-甲基-[1,1'-联苯]-3-基)-1,3,4-噻二唑-2-基)苄基)甘氨酸 (1) 及其盐酸盐 (1s) 的合成  
2-甲基-[1,1'-联苯]-3-羧酸 (1A) 的合成

将 3-溴-2-甲基苯甲酸 (10.00 g, 46.51 mmol)、苯硼酸 (10.21 g, 83.72 mmol)、碳酸钾 (7.71 g, 55.71 mmol) 和 Pd(PPh<sub>3</sub>)<sub>4</sub> (0.53 g, 0.46 mmol) 加入 100 mL 1,4 二氧六环和 10 mL 水中,氮气保护下 80°C 反应 12 h。减压浓缩,用 4 M HCl 调 pH 至 2,抽滤,干燥,得白色固体 9.53 g,收率 96%。MS (EI) *m/z* 211 [M-H]<sup>-</sup>; <sup>1</sup>H NMR (300 MHz,

Chloroform-*d*)  $\delta$  (ppm) 7.74-7.67 (m, 1H), 7.50-7.38 (m, 3H), 7.38-7.34 (m, 2H), 7.33-7.28 (m, 2H), 2.29 (s, 3H).

#### 2-甲基-[1,1'-联苯]-3-羧酸甲酯 (1B) 的合成

将 1A (9.53g, 44.90mmol) 加入 100mL 甲醇中, 搅拌下滴入 5mL 浓硫酸, 回流反应 4h。冷却, 减压浓缩, 加入 300mL 水, 乙酸乙酯萃取, 饱和食盐水洗涤, 合并有机相, 得黄色油状液体 9.96g, 收率 98%。MS (EI)  $m/z$  225 [M-H]<sup>-</sup>; <sup>1</sup>H NMR (300 MHz, Chloroform-*d*)  $\delta$ (ppm) 7.45-7.32 (m, 4H), 7.30-7.15 (m, 3H), 7.07 (d,  $J$  = 7.5 Hz, 1H), 3.98 (s, 3H), 2.32 (s, 3H).

#### 2-甲基-[1,1'-联苯]-3-碳酰肼 (1C) 的合成

将 1B (9.96g, 44.02mmol) 加入 100 mL 乙醇中, 加入 5 mL 水合肼, 回流反应 5h。冷却, 减压浓缩, 加入 100 mL 冰水, 析出固体, 抽滤, 干燥, 得白色固体 9.24g, 收率 93%。MS (EI)  $m/z$  225 [M-H]<sup>-</sup>; <sup>1</sup>H NMR (300 MHz, Chloroform-*d*)  $\delta$  8.02 (s, 1H), 7.45 (d,  $J$  = 7.5 Hz, 3H), 7.37 (s, 1H), 7.33 (d,  $J$  = 1.8 Hz, 3H), 2.52 (s, 3H).

#### N'-(3-(氯甲基)苯甲酰基)-2-甲基-[1,1'-联苯]-3-甲酰肼 (1D) 的合成

将 3-(氯甲基)苯甲酸 (0.25g, 1.46mmol) 加入 5 mL 无水二氯甲烷中, 滴加 1 mL 草酰氯, 反应 3h, 减压浓缩, 用 3mL 无水二氯甲烷溶解, 滴入经冰浴冷却的 1C (0.32g, 1.33mmol) 和三乙胺 (0.21 g, 1.99 mmol) 二氯甲烷溶液中, 反应 3h, 抽滤, 干燥, 得白色固体 0.45g, 收率 90%。MS (EI)  $m/z$  377 [M-H]<sup>-</sup>; <sup>1</sup>H NMR (300 MHz, Chloroform-*d*)  $\delta$  10.02 (s, 1H), 8.74 (s, 1H), 8.02 (s, 4H), 7.37 (td,  $J$  = 15.0, 13.5, 9.0 Hz, 8H), 4.70 (s, 2H), 2.31 (s, 3H).

#### 2-(3-(氯甲基)苯基)-5-(2-甲基-[1,1'-联苯]-3-基)-1,3,4-噻二唑 (1E) 的合成

将 1D (0.45g, 1.19mmol), 劳森试剂 (0.58g, 1.43mmol) 加入 10 mL 甲苯中, 回流反应 5h。减压浓缩, 乙酸乙酯萃取, 无水硫酸钠干燥, 柱层析纯化[石油醚:乙酸乙酯 = 15:1 (V:V)], 得白色固体 0.32g, 收率 71%。MS (EI)  $m/z$  375 [M-H]<sup>-</sup>; <sup>1</sup>H NMR (300 MHz, Chloroform-*d*)  $\delta$  8.11 (s, 1H), 8.01 (dt,  $J$  = 6.9, 1.8 Hz, 1H), 7.68 (dd,  $J$  = 6.6, 2.4 Hz, 1H), 7.56 (s, 1H), 7.48 (s, 1H), 7.46 (s, 1H), 7.43 (s, 1H), 7.41 (d,  $J$  = 2.7 Hz, 2H), 7.39 (d,  $J$  = 1.8 Hz, 2H), 7.36 (t,  $J$  = 1.5 Hz, 1H), 4.70 (s, 2H), 2.46 (s, 3H).

#### (3-(5-(2-甲基-[1,1'-联苯]-3-基)-1,3,4-噻二唑-2-基)苄基)甘氨酸甲酯 (1m) 的合成

将 1E (0.32g, 0.85mmol), K<sub>2</sub>CO<sub>3</sub> (0.41g, 2.97mmol), 甘氨酸甲酯盐酸盐 (0.27g, 2.12mmol) 加入 5 mL 乙腈中, 回流反应 8h。冷却, 减压浓缩, 乙酸乙酯萃取, 无水硫酸钠干燥, 柱层析纯化[石油醚:乙酸乙酯 = 3:1 (V:V)], 得白色固体 0.15g, 收率 41%。MS (EI)  $m/z$  428 [M-H]<sup>-</sup>; <sup>1</sup>H NMR (300 MHz, Chloroform-*d*)  $\delta$  8.05-7.98 (m, 2H), 7.68-7.63 (m, 1H), 7.51 (s, 1H), 7.48 (s, 1H), 7.45 (s, 1H), 7.43 (s, 1H), 7.36 (t,  $J$  = 6.9 Hz, 5H), 4.24 (s, 2H), 3.98 (s, 3H), 3.77 (s, 2H), 2.33 (s, 3H).

#### (3-(5-(2-甲基-[1,1'-联苯]-3-基)-1,3,4-噻二唑-2-基)苄基)甘氨酸 (1) 的合成

将 1m (0.15g, 0.36mmol), LiOH (25mg, 1.05mmol) 加入 3mL 甲醇中, 室温反应 5 h, 旋除溶剂, 加入 2 mL 水, 用 4 M 盐酸调 pH 至 3, 抽滤, 干燥, 得白色固体 135mg, 收率 92%。MS (ESI)  $m/z$  416 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  8.08 (d,  $J$  = 7.5 Hz, 2H), 7.79 (d,  $J$  = 7.8 Hz, 2H), 7.70 (d,  $J$  = 6.6 Hz, 1H), 7.44 (dd,  $J$  = 11.4, 8.1 Hz, 7H), 4.13 (s, 2H), 3.65 (s, 2H), 2.30 (s, 3H).

#### (3-(5-(2-甲基-[1,1'-联苯]-3-基)-1,3,4-噻二唑-2-基)苄基)甘氨酸盐酸盐 (1s) 的合成

将 1 (32mg, 0.078mmol) 加入 1mL 4 M 1,4-二氧六环盐酸盐溶液中, 室温搅拌过夜, 减压浓缩, 无水乙醚洗涤, 抽滤, 干燥, 得白色固体 27mg, 收率 93%。MS (ESI)  $m/z$  416 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  8.36 (s, 1H), 8.15 (d,  $J$  = 7.2 Hz, 1H), 8.05 (d,  $J$  = 6.9 Hz, 1H), 7.80 (s, 1H), 7.70 (s, 1H), 7.47 (q,  $J$  = 8.1, 7.8 Hz, 5H), 7.37 (d,  $J$  = 6.6 Hz, 3H), 4.21 (s, 2H), 3.75 (s, 2H), 2.23 (s, 3H).

采用与实施例 1 相似的操作, 制得下列化合物:

| 编号 | <sup>1</sup> H-NMR                                                                                                                                                                                                                                                                                                                                           | ESI-MS<br>$m/z$<br>[M+H] <sup>+</sup> |
|----|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------|
| 2  | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) $\delta$ 8.31 (s, 1H), 8.18 (d, $J$ = 7.5 Hz, 1H), 8.11-8.05 (m, 1H), 7.82 (d, $J$ = 7.2 Hz, 1H), 7.73-7.67 (m, 1H), 7.56-7.52 (m, 2H), 7.49 (d, $J$ = 7.2 Hz, 2H), 7.44 (d, $J$ = 5.1 Hz, 1H), 7.39 (d, $J$ = 6.3 Hz, 2H), 4.48 (s, 2H), 4.07 (s, 2H), 2.79 (s, 3H), 2.53 (s, 3H).               | 430                                   |
| 2s | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) $\delta$ 9.21 (s, 1H), 8.31 (s, 1H), 8.18 (d, $J$ = 7.5 Hz, 1H), 8.11-8.05 (m, 1H), 7.82 (d, $J$ = 7.2 Hz, 1H), 7.73-7.67 (m, 1H), 7.56-7.52 (m, 2H), 7.49 (d, $J$ = 7.2 Hz, 2H), 7.44 (d, $J$ = 5.1 Hz, 1H), 7.39 (d, $J$ = 6.3 Hz, 2H), 4.48 (s, 2H), 4.07 (s, 2H), 2.79 (s, 3H), 2.53 (s, 3H). | 430                                   |
| 3  | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) $\delta$ 8.32 (s, 1H), 8.16 (d, $J$ = 7.2 Hz, 2H), 8.11-8.06 (m, 1H), 7.86 (d, $J$ = 6.3 Hz, 1H), 7.54 (d, $J$ = 4.5 Hz, 2H), 7.50 (d, $J$ = 7.2 Hz, 2H), 7.45 (d, $J$ = 6.9 Hz, 1H), 7.40 (d, $J$ = 7.8 Hz, 2H), 5.29 (s, 1H), 4.37 (s, 2H), 3.78 (s,                                            | 402                                   |

|     |                                                                                                                                                                                                                                                                                                                                                                                                                                   |     |
|-----|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|
|     | 2H), 3.07 (s, 2H), 2.54 (s, 3H).                                                                                                                                                                                                                                                                                                                                                                                                  |     |
| 3s  | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 9.14 (s, 1H), 8.16 (d, <i>J</i> = 7.2 Hz, 2H), 8.11-8.06 (m, 1H), 7.86 (d, <i>J</i> = 6.3 Hz, 1H), 7.69 (t, <i>J</i> = 7.8 Hz, 1H), 7.54 (d, <i>J</i> = 4.5 Hz, 2H), 7.50 (d, <i>J</i> = 7.2 Hz, 2H), 7.45 (d, <i>J</i> = 6.9 Hz, 1H), 7.40 (d, <i>J</i> = 7.8 Hz, 2H), 5.29 (s, 1H), 4.37 (s, 2H), 3.78 (s, 2H), 3.07 (s, 2H), 2.54 (s, 3H).                        | 402 |
| 4   | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.35 (s, 1H), 8.17 (d, <i>J</i> = 7.8 Hz, 2H), 8.06 (d, <i>J</i> = 7.5 Hz, 2H), 7.87 (s, 1H), 7.78 (s, 1H), 7.55 (s, 2H), 7.50 (t, <i>J</i> = 7.5 Hz, 3H), 4.30 (s, 2H), 3.66 (s, 2H), 2.53 (s, 3H).                                                                                                                                                                 | 415 |
| 4s  | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 9.47 (s, 1H), 8.35 (s, 1H), 8.17 (d, <i>J</i> = 7.8 Hz, 2H), 8.06 (d, <i>J</i> = 7.5 Hz, 2H), 7.87 (s, 1H), 7.78 (s, 1H), 7.71 (d, <i>J</i> = 7.2 Hz, 1H), 7.55 (s, 2H), 7.50 (t, <i>J</i> = 7.5 Hz, 3H), 4.30 (s, 2H), 3.66 (s, 2H), 2.53 (s, 3H).                                                                                                                  | 415 |
| 5   | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.37 (s, 1H), 8.09 (d, <i>J</i> = 4.2 Hz, 1H), 8.08-8.03 (m, 1H), 7.67 (d, <i>J</i> = 6.9 Hz, 1H), 7.62 (d, <i>J</i> = 7.5 Hz, 1H), 7.54 (d, <i>J</i> = 4.5 Hz, 2H), 7.50 (d, <i>J</i> = 7.2 Hz, 2H), 7.45 (d, <i>J</i> = 6.9 Hz, 1H), 7.40 (d, <i>J</i> = 7.8 Hz, 2H), 4.01 (s, 2H), 2.93-2.85 (m, 2H), 2.54 (s, 3H), 2.46 (t, <i>J</i> = 6.9 Hz, 2H).              | 430 |
| 5s  | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 9.23 (s, 1H), 8.11 (s, 1H), 8.09 (d, <i>J</i> = 4.2 Hz, 1H), 8.05-8.03 (m, 1H), 7.87 (d, <i>J</i> = 6.9 Hz, 1H), 7.72 (d, <i>J</i> = 7.5 Hz, 1H), 7.54 (d, <i>J</i> = 4.5 Hz, 2H), 7.50 (d, <i>J</i> = 7.2 Hz, 2H), 7.44(d, <i>J</i> = 6.9 Hz, 1H), 7.40 (d, <i>J</i> = 7.8 Hz, 2H), 4.01 (s, 2H), 2.93-2.85 (m, 2H), 2.54 (s, 3H), 2.46 (t, <i>J</i> = 6.9 Hz, 2H). | 430 |
| 6   | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.33 (d, <i>J</i> = 10.5 Hz, 1H), 8.14-8.07 (m, 2H), 7.88 (d, <i>J</i> = 7.8 Hz, 1H), 7.66 (t, <i>J</i> = 7.8 Hz, 1H), 7.54 (d, <i>J</i> = 4.5 Hz, 2H), 7.50 (d, <i>J</i> = 7.2 Hz, 2H), 7.45 (d, <i>J</i> = 7.2 Hz, 1H), 7.40 (d, <i>J</i> = 7.8 Hz, 2H), 4.25 (s, 2H), 3.02-2.93 (m, 4H), 2.53 (s, 3H), 1.83 (s, 3H).                                              | 443 |
| 6s  | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.93 (s, 1H), 8.33 (d, <i>J</i> = 10.5 Hz, 1H), 8.14-8.07 (m, 2H), 7.88 (d, <i>J</i> = 7.8 Hz, 1H), 7.66 (t, <i>J</i> = 7.8 Hz, 1H), 7.54 (d, <i>J</i> = 4.5 Hz, 2H), 7.50 (d, <i>J</i> = 7.2 Hz, 2H), 7.45 (d, <i>J</i> = 7.2 Hz, 1H), 7.40 (d, <i>J</i> = 7.8 Hz, 2H), 4.25 (s, 2H), 3.02-2.93 (m, 4H), 2.53 (s, 3H), 1.83 (s, 3H).                                | 443 |
| 7   | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.18 (s, 1H), 8.15-7.98 (m, 2H), 7.67 (d, <i>J</i> = 8.1 Hz, 3H), 7.63-7.45 (m, 7H), 7.40 (dd, <i>J</i> = 12.0, 7.2 Hz, 2H), 4.11-3.90 (m, 2H), 3.15 (d, <i>J</i> = 13.2 Hz, 3H), 2.53 (s, 3H), 1.66 (d, <i>J</i> = 12.6 Hz, 4H).                                                                                                                                    | 515 |
| 7s  | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.62 (s, 1H), 8.18 (s, 1H), 8.15-7.98 (m, 2H), 7.67 (d, <i>J</i> = 8.1 Hz, 3H), 7.63-7.45 (m, 7H), 7.40 (dd, <i>J</i> = 12.0, 7.2 Hz, 2H), 4.11-3.90 (m, 2H), 3.15 (d, <i>J</i> = 13.2 Hz, 3H), 2.53 (s, 3H), 1.66 (d, <i>J</i> = 12.6 Hz, 4H).                                                                                                                      | 515 |
| 8   | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.46 (s, 1H), 8.10 (dd, <i>J</i> = 12.6, 6.0 Hz, 2H), 7.89 (d, <i>J</i> = 7.8 Hz, 1H), 7.55 (d, <i>J</i> = 4.2 Hz, 2H), 7.50 (d, <i>J</i> = 8.1 Hz, 3H), 7.45 (d, <i>J</i> = 5.7 Hz, 1H), 7.40 (d, <i>J</i> = 8.1 Hz, 2H), 4.20 (s, 2H), 3.73 (s, 1H), 2.54 (s, 3H), 1.44 (d, <i>J</i> = 7.2 Hz, 3H).                                                                | 430 |
| 8s  | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.89 (s, 1H), 8.67 (s, 1H), 8.10 (dd, <i>J</i> = 12.6, 6.0 Hz, 2H), 7.96 (d, <i>J</i> = 7.8 Hz, 1H), 7.55 (d, <i>J</i> = 4.2 Hz, 2H), 7.50 (d, <i>J</i> = 8.1 Hz, 3H), 7.45 (d, <i>J</i> = 5.7 Hz, 1H), 7.40 (d, <i>J</i> = 8.1 Hz, 2H), 4.20 (s, 2H), 3.73 (s, 1H), 2.54 (s, 3H), 1.44 (d, <i>J</i> = 7.2 Hz, 3H).                                                  | 430 |
| 9   | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.16 (d, <i>J</i> = 7.8 Hz, 2H), 8.12-8.07 (m, 1H), 7.81 (d, <i>J</i> = 7.8 Hz, 2H), 7.55 (d, <i>J</i> = 4.2 Hz, 2H), 7.50 (d, <i>J</i> = 7.2 Hz, 2H), 7.45 (d, <i>J</i> = 6.9 Hz, 1H), 7.40 (d, <i>J</i> = 6.9 Hz, 2H), 5.34 (s, 2H), 4.34 (s, 2H), 3.75-3.68 (m, 5H), 2.54 (s, 3H).                                                                                | 432 |
| 9s  | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.94 (s, 1H), 8.16 (d, <i>J</i> = 7.8 Hz, 2H), 8.12-8.07 (m, 1H), 7.81 (d, <i>J</i> = 7.8 Hz, 2H), 7.55 (d, <i>J</i> = 4.2 Hz, 2H), 7.50 (d, <i>J</i> = 7.2 Hz, 2H), 7.45 (d, <i>J</i> = 6.9 Hz, 1H), 7.40 (d, <i>J</i> = 6.9 Hz, 2H), 5.34 (s, 2H), 4.34 (s, 2H), 3.75-3.68 (m, 5H), 2.54 (s, 3H).                                                                  | 432 |
| 10  | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.27 (s, 1H), 8.10 (s, 2H), 7.81 (s, 1H), 7.74 (s, 2H), 7.65 (t, <i>J</i> = 7.8 Hz, 1H), 7.50 (s, 1H), 7.48 (s, 1H), 7.45 (s, 2H), 7.43-7.40 (m, 1H), 7.39 (s, 1H), 5.81 (s, 1H), 4.22 (d, <i>J</i> = 6.9 Hz, 2H), 4.01 (s, 1H), 3.53 (d, <i>J</i> = 7.2 Hz, 2H), 2.36 (s, 3H).                                                                                      | 445 |
| 10s | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 9.45 (s, 1H), 8.27 (s, 1H), 8.10 (s, 2H), 7.81 (s, 1H), 7.74 (s, 2H), 7.65 (t, <i>J</i> = 7.8 Hz, 1H), 7.50 (s, 1H), 7.48 (s, 1H), 7.45 (s, 2H), 7.43-7.40 (m, 1H), 7.39 (s, 1H), 5.81 (s, 1H), 4.22 (d, <i>J</i> = 6.9 Hz, 2H), 4.01 (s, 1H), 3.53 (d, <i>J</i> = 7.2 Hz, 2H), 2.36 (s, 3H).                                                                        | 445 |
| 11  | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.35 (d, <i>J</i> = 5.4 Hz, 3H), 7.75 (s, 2H), 7.51 (dd, <i>J</i> = 13.5, 5.4 Hz, 4H), 7.45-7.36 (m, 2H), 7.21 (d, <i>J</i> = 12.3 Hz, 1H), 4.24 (s, 2H), 3.88 (d, <i>J</i> = 12.3 Hz, 2H), 3.74 (s, 1H), 2.53 (s, 3H).                                                                                                                                              | 446 |
| 11s | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.76 (s, 1H), 8.12 (d, <i>J</i> = 5.4 Hz, 3H), 7.51 (dd, <i>J</i> = 13.5, 5.4 Hz, 4H), 7.45-7.36 (m, 2H), 7.32 (s, 2H), 7.21 (d, <i>J</i> = 12.3 Hz, 1H), 4.24 (s, 2H), 3.88 (d, <i>J</i> = 12.3 Hz, 2H), 3.74 (s, 1H), 2.53 (s, 3H).                                                                                                                                | 446 |
| 12  | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.27 (s, 1H), 8.10 (s, 2H), 7.81 (s, 1H), 7.74 (s, 2H), 7.65 (t, <i>J</i> = 7.8 Hz, 1H), 7.50 (s, 1H), 7.48 (s, 1H), 7.45 (s, 2H), 7.43-7.40 (m, 2H), 7.39 (s, 1H), 5.81 (s, 1H), 4.22 (d, <i>J</i> = 6.9 Hz, 2H), 4.01 (s, 1H), 3.53 (d, <i>J</i> = 7.2                                                                                                             | 459 |

|     |                                                                                                                                                                                                                                                                                                                                                                                                                                       |     |
|-----|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|
|     | Hz, 1H), 2.36 (s, 3H), 1.16 (d, $J = 6.3$ Hz, 3H).                                                                                                                                                                                                                                                                                                                                                                                    |     |
| 12s | $^1\text{H}$ NMR (300 MHz, DMSO- $d_6$ ) $\delta$ 9.45 (s, 1H), 8.27 (s, 1H), 8.10 (s, 2H), 7.81 (s, 1H), 7.74 (s, 2H), 7.65 (t, $J = 7.8$ Hz, 1H), 7.50 (s, 1H), 7.48 (s, 1H), 7.45 (s, 2H), 7.43-7.40 (m, 2H), 7.39 (s, 1H), 5.81 (s, 1H), 4.22 (d, $J = 6.9$ Hz, 2H), 4.01 (s, 1H), 3.53 (d, $J = 7.2$ Hz, 1H), 2.36 (s, 3H), 1.16 (d, $J = 6.3$ Hz, 3H).                                                                          | 459 |
| 13  | $^1\text{H}$ NMR (300 MHz, DMSO- $d_6$ ) $\delta$ 8.35 (s, 1H), 8.10 (d, $J = 7.8$ Hz, 1H), 7.74 (s, 2H), 7.65 (t, $J = 7.5$ Hz, 1H), 7.50 (s, 1H), 7.48 (d, $J = 2.4$ Hz, 1H), 7.45 (s, 2H), 7.42 (s, 2H), 7.39 (s, 1H), 4.34 (s, 2H), 4.13 (s, 1H), 3.66 (d, $J = 5.7$ Hz, 1H), 2.36 (s, 3H), 1.23 (d, $J = 6.0$ Hz, 3H).                                                                                                           | 460 |
| 13s | $^1\text{H}$ NMR (300 MHz, DMSO- $d_6$ ) $\delta$ 9.02 (s, 1H), 8.30 (s, 1H), 8.10 (d, $J = 7.8$ Hz, 1H), 7.84 (s, 2H), 7.60 (t, $J = 7.5$ Hz, 1H), 7.50 (s, 1H), 7.48 (d, $J = 2.4$ Hz, 1H), 7.45 (s, 2H), 7.42 (s, 2H), 7.39 (s, 1H), 4.34 (s, 2H), 4.13 (s, 1H), 3.66 (d, $J = 5.7$ Hz, 1H), 2.36 (s, 3H), 1.23 (d, $J = 6.0$ Hz, 3H).                                                                                             | 460 |
| 14  | $^1\text{H}$ NMR (300 MHz, DMSO- $d_6$ ) $\delta$ 8.13 (d, $J = 8.1$ Hz, 3H), 8.10-8.06 (m, 1H), 7.79 (d, $J = 7.8$ Hz, 2H), 7.54 (d, $J = 4.2$ Hz, 2H), 7.49 (d, $J = 7.5$ Hz, 2H), 7.44 (d, $J = 6.9$ Hz, 1H), 7.39 (d, $J = 8.1$ Hz, 2H), 5.45 (s, 2H), 4.22 (s, 2H), 3.61 (s, 4H), 2.53 (s, 3H), 1.24 (s, 3H).                                                                                                                    | 446 |
| 14s | $^1\text{H}$ NMR (300 MHz, DMSO- $d_6$ ) $\delta$ 9.02 (s, 1H), 8.13 (d, $J = 8.1$ Hz, 3H), 8.10-8.06 (m, 1H), 7.79 (d, $J = 7.8$ Hz, 2H), 7.54 (d, $J = 4.2$ Hz, 2H), 7.49 (d, $J = 7.5$ Hz, 2H), 7.44 (d, $J = 6.9$ Hz, 1H), 7.39 (d, $J = 8.1$ Hz, 2H), 5.45 (s, 2H), 4.22 (s, 2H), 3.61 (s, 4H), 2.53 (s, 3H), 1.24 (s, 3H).                                                                                                      | 446 |
| 15  | $^1\text{H}$ NMR (300 MHz, DMSO- $d_6$ ) $\delta$ 9.10 (d, $J = 7.8$ Hz, 3H), 7.83 (d, $J = 7.2$ Hz, 1H), 7.66-7.60 (m, 1H), 7.55-7.52 (m, 2H), 7.49 (d, $J = 7.2$ Hz, 2H), 7.44 (d, $J = 6.9$ Hz, 1H), 7.39 (d, $J = 7.2$ Hz, 2H), 5.49 (s, 3H), 4.35 (s, 2H), 3.67 (s, 6H), 2.53 (s, 3H).                                                                                                                                           | 462 |
| 15s | $^1\text{H}$ NMR (300 MHz, DMSO- $d_6$ ) $\delta$ 8.30 (s, 1H), 8.10 (d, $J = 7.8$ Hz, 3H), 7.83 (d, $J = 7.2$ Hz, 1H), 7.66-7.60 (m, 1H), 7.55-7.52 (m, 2H), 7.49 (d, $J = 7.2$ Hz, 2H), 7.44 (d, $J = 6.9$ Hz, 1H), 7.39 (d, $J = 7.2$ Hz, 2H), 5.49 (s, 3H), 4.35 (s, 2H), 3.67 (s, 6H), 2.53 (s, 3H).                                                                                                                             | 462 |
| 16  | $^1\text{H}$ NMR (300 MHz, DMSO- $d_6$ ) $\delta$ 8.23-8.08 (m, 3H), 7.84-7.67 (m, 3H), 7.63-7.50 (m, 4H), 7.43 (d, $J = 7.2$ Hz, 1H), 7.21 (d, $J = 12.0$ Hz, 1H), 4.16 (s, 2H), 3.93 (s, 3H), 2.56 (s, 3H), 2.31 (d, $J = 5.1$ Hz, 1H), 2.20 (d, $J = 13.2$ Hz, 1H), 1.74 (d, $J = 13.8$ Hz, 2H), 1.34-1.16 (m, 3H), 0.91 (d, $J = 5.1$ Hz, 3H).                                                                                    | 472 |
| 16s | $^1\text{H}$ NMR (300 MHz, DMSO- $d_6$ ) $\delta$ 8.41 (s, 1H), 8.23-8.08 (m, 3H), 7.84-7.67 (m, 3H), 7.63-7.50 (m, 4H), 7.43 (d, $J = 7.2$ Hz, 2H), 7.21 (d, $J = 12.0$ Hz, 1H), 4.16 (s, 2H), 2.56 (s, 3H), 2.31 (d, $J = 5.1$ Hz, 1H), 2.20 (d, $J = 13.2$ Hz, 1H), 1.74 (d, $J = 13.8$ Hz, 2H), 1.34-1.16 (m, 3H), 0.91 (d, $J = 5.1$ Hz, 3H).                                                                                    | 472 |
| 17  | $^1\text{H}$ NMR (300 MHz, DMSO- $d_6$ ) $\delta$ 8.23 (s, 1H), 8.16-8.06 (m, 2H), 7.85 (d, $J = 7.1$ Hz, 1H), 7.66 (d, $J = 7.8$ Hz, 1H), 7.54 (d, $J = 4.2$ Hz, 2H), 7.50 (d, $J = 7.2$ Hz, 2H), 7.45 (d, $J = 7.2$ Hz, 1H), 7.40 (d, $J = 7.8$ Hz, 2H), 4.47 (d, $J = 13.2$ Hz, 1H), 4.25 (d, $J = 13.5$ Hz, 1H), 4.03 (s, 2H), 3.38-3.30 (m, 2H), 3.06 (d, $J = 9.3$ Hz, 1H), 2.53 (s, 3H), 2.41-2.34 (m, 1H), 1.89-1.79 (m, 1H). | 456 |
| 17s | $^1\text{H}$ NMR (300 MHz, DMSO- $d_6$ ) $\delta$ 8.46 (s, 1H), 8.16-8.06 (m, 3H), 7.75 (d, $J = 7.2$ Hz, 1H), 7.66 (d, $J = 7.8$ Hz, 1H), 7.54 (d, $J = 4.2$ Hz, 2H), 7.50 (d, $J = 7.2$ Hz, 2H), 7.45 (d, $J = 7.2$ Hz, 1H), 7.40 (d, $J = 7.8$ Hz, 2H), 4.47 (d, $J = 13.2$ Hz, 1H), 4.25 (d, $J = 13.5$ Hz, 1H), 4.03 (s, 2H), 3.38-3.30 (m, 2H), 3.06 (d, $J = 9.3$ Hz, 1H), 2.53 (s, 3H), 2.41-2.34 (m, 1H), 1.89-1.79 (m, 1H). | 456 |
| 18  | $^1\text{H}$ NMR (300 MHz, DMSO- $d_6$ ) $\delta$ 8.17 (d, $J = 6.3$ Hz, 2H), 8.12-8.06 (m, 2H), 7.90 (d, $J = 7.5$ Hz, 1H), 7.83 (d, $J = 7.5$ Hz, 1H), 7.54 (d, $J = 4.2$ Hz, 2H), 7.49 (d, $J = 7.5$ Hz, 2H), 7.44 (d, $J = 7.2$ Hz, 1H), 7.39 (d, $J = 7.5$ Hz, 2H), 5.46 (s, 1H), 4.41 (s, 2H), 3.26 (d, $J = 12.0$ Hz, 2H), 3.05 (s, 1H), 2.87-2.70 (m, 2H), 2.53 (s, 3H), 1.96-1.79 (m, 2H).                                   | 428 |
| 18s | $^1\text{H}$ NMR (300 MHz, DMSO- $d_6$ ) $\delta$ 9.02 (s, 1H), 8.17 (d, $J = 6.3$ Hz, 2H), 8.12-8.06 (m, 2H), 7.90 (d, $J = 7.5$ Hz, 1H), 7.83 (d, $J = 7.5$ Hz, 1H), 7.54 (d, $J = 4.2$ Hz, 2H), 7.49 (d, $J = 7.5$ Hz, 2H), 7.44 (d, $J = 7.2$ Hz, 1H), 7.39 (d, $J = 7.5$ Hz, 2H), 5.46 (s, 1H), 4.41 (s, 2H), 3.26 (d, $J = 12.0$ Hz, 2H), 3.05 (s, 1H), 2.87-2.70 (m, 2H), 2.53 (s, 3H), 1.96-1.79 (m, 2H).                     | 428 |
| 19  | $^1\text{H}$ NMR (300 MHz, DMSO- $d_6$ ) $\delta$ 8.39 (s, 1H), 8.09 (s, 2H), 8.03-7.94 (m, 1H), 7.69 (d, $J = 8.4$ Hz, 1H), 7.55 (dd, $J = 11.1, 5.7$ Hz, 4H), 7.51-7.45 (m, 2H), 7.41 (t, $J = 6.9$ Hz, 2H), 4.61 (s, 2H), 4.03-3.90 (m, 1H), 3.60 (d, $J = 12.9$ Hz, 1H), 3.20-3.12 (m, 1H), 2.94-2.84 (m, 1H), 2.53 (s, 3H), 2.29 (s, 2H), 1.78 (d, $J = 10.8$ Hz, 1H), 1.49 (s, 2H).                                             | 470 |
| 19s | $^1\text{H}$ NMR (300 MHz, DMSO- $d_6$ ) $\delta$ 8.92 (s, 1H), 8.39 (s, 1H), 8.09 (s, 2H), 8.03-7.94 (m, 1H), 7.69 (d, $J = 8.4$ Hz, 1H), 7.55 (dd, $J = 11.1, 5.7$ Hz, 4H), 7.51-7.45 (m, 2H), 7.41 (t, $J = 6.9$ Hz, 2H), 4.61 (s, 2H), 4.03-3.90 (m, 1H), 3.60 (d, $J = 12.9$ Hz, 1H), 3.20-3.12 (m, 1H), 2.94-2.84 (m, 1H), 2.53 (s, 3H), 2.29 (s, 2H), 1.78 (d, $J = 10.8$ Hz, 1H), 1.49 (s, 2H).                               | 470 |
| 20  | $^1\text{H}$ NMR (300 MHz, DMSO- $d_6$ ) $\delta$ 7.98 (d, $J = 7.8$ Hz, 2H), 7.79 (d, $J = 7.8$ Hz, 2H), 7.70 (d, $J = 6.6$ Hz, 1H), 7.44 (dd, $J = 11.4, 8.1$ Hz, 7H), 4.13 (s, 2H), 3.65 (s, 2H), 2.30 (s, 3H).                                                                                                                                                                                                                    | 416 |

|     |                                                                                                                                                                                                                                                                                                                                                                                                                                    |     |
|-----|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|
| 20s | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.93 (s, 1H), 8.08 (d, <i>J</i> = 7.5 Hz, 2H), 7.79 (d, <i>J</i> = 7.8 Hz, 2H), 7.70 (d, <i>J</i> = 6.6 Hz, 1H), 7.44 (dd, <i>J</i> = 11.4, 8.1 Hz, 7H), 4.13 (s, 2H), 3.65 (s, 2H), 2.30 (s, 3H).                                                                                                                                                                    | 416 |
| 21  | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.32 (s, 1H), 8.16 (d, <i>J</i> = 7.2 Hz, 1H), 8.11-8.06 (m, 1H), 7.86 (d, <i>J</i> = 6.3 Hz, 1H), 7.69 (t, <i>J</i> = 7.8 Hz, 1H), 7.54 (d, <i>J</i> = 4.5 Hz, 2H), 7.50 (d, <i>J</i> = 7.2 Hz, 2H), 7.45 (d, <i>J</i> = 6.9 Hz, 1H), 7.40 (d, <i>J</i> = 7.8 Hz, 2H), 5.29 (s, 1H), 4.37 (s, 2H), 3.78 (s, 2H), 3.07 (s, 2H), 2.54 (s, 3H)                          | 402 |
| 21s | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.76 (s, 1H), 8.32 (s, 1H), 8.16 (d, <i>J</i> = 7.2 Hz, 1H), 8.11-8.06 (m, 1H), 7.86 (d, <i>J</i> = 6.3 Hz, 1H), 7.69 (t, <i>J</i> = 7.8 Hz, 1H), 7.54 (d, <i>J</i> = 4.5 Hz, 2H), 7.50 (d, <i>J</i> = 7.2 Hz, 2H), 7.45 (d, <i>J</i> = 6.9 Hz, 1H), 7.40 (d, <i>J</i> = 7.8 Hz, 2H), 5.29 (s, 1H), 4.37 (s, 2H), 3.78 (s, 2H), 3.07 (s, 2H), 2.54 (s, 3H)            | 402 |
| 22  | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.35 (s, 1H), 8.17 (d, <i>J</i> = 7.8 Hz, 1H), 8.06 (d, <i>J</i> = 7.5 Hz, 2H), 7.87 (s, 1H), 7.78 (s, 1H), 7.71 (d, <i>J</i> = 7.2 Hz, 1H), 7.55 (s, 2H), 7.50 (t, <i>J</i> = 7.5 Hz, 3H), 4.30 (s, 2H), 3.66 (s, 2H), 2.53 (s, 3H).                                                                                                                                 | 415 |
| 22s | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.93 (s, 1H), 8.35 (s, 1H), 8.17 (d, <i>J</i> = 7.8 Hz, 1H), 8.06 (d, <i>J</i> = 7.5 Hz, 2H), 7.87 (s, 1H), 7.78 (s, 1H), 7.71 (d, <i>J</i> = 7.2 Hz, 1H), 7.55 (s, 2H), 7.50 (t, <i>J</i> = 7.5 Hz, 3H), 4.30 (s, 2H), 3.66 (s, 2H), 2.53 (s, 3H).                                                                                                                   | 415 |
| 23  | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.17 (s, 1H), 8.09 (d, <i>J</i> = 4.2 Hz, 1H), 8.08-8.03 (m, 1H), 7.67 (d, <i>J</i> = 6.9 Hz, 1H), 7.62 (d, <i>J</i> = 7.5 Hz, 1H), 7.54 (d, <i>J</i> = 4.5 Hz, 2H), 7.50 (d, <i>J</i> = 7.2 Hz, 2H), 7.45 (d, <i>J</i> = 6.9 Hz, 1H), 7.40 (d, <i>J</i> = 7.8 Hz, 2H), 4.01 (s, 2H), 3.91 (s, 3H), 2.93-2.85 (m, 2H), 2.54 (s, 3H), 2.46 (t, <i>J</i> = 6.9 Hz, 2H). | 430 |
| 23s | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.63 (s, 1H), 8.17 (s, 1H), 8.09 (d, <i>J</i> = 4.2 Hz, 1H), 8.08-8.03 (m, 1H), 7.67 (d, <i>J</i> = 6.9 Hz, 1H), 7.62 (d, <i>J</i> = 7.5 Hz, 1H), 7.54 (d, <i>J</i> = 4.5 Hz, 2H), 7.50 (d, <i>J</i> = 7.2 Hz, 2H), 7.45 (d, <i>J</i> = 6.9 Hz, 1H), 7.40 (d, <i>J</i> = 7.8 Hz, 2H), 4.01 (s, 2H), 2.93-2.85 (m, 2H), 2.54 (s, 3H), 2.46 (t, <i>J</i> = 6.9 Hz, 2H). | 430 |
| 24  | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.02 (d, <i>J</i> = 5.5 Hz, 3H), 7.67 (s, 2H), 7.51 (dd, <i>J</i> = 13.5, 5.5 Hz, 4H), 7.45-7.36 (m, 2H), 7.21 (d, <i>J</i> = 12.3 Hz, 1H), 4.24 (s, 2H), 3.88 (d, <i>J</i> = 12.3 Hz, 2H), 3.74 (s, 1H), 2.53 (s, 3H)                                                                                                                                                | 446 |
| 24s | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.75 (s, 1H), 8.12 (d, <i>J</i> = 5.5 Hz, 3H), 7.77 (s, 2H), 7.51 (dd, <i>J</i> = 13.5, 5.4 Hz, 4H), 7.45-7.36 (m, 2H), 7.21 (d, <i>J</i> = 12.3 Hz, 1H), 4.24 (s, 2H), 3.88 (d, <i>J</i> = 12.3 Hz, 2H), 3.74 (s, 1H), 2.53 (s, 3H)                                                                                                                                  | 446 |
| 25  | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.93 (s, 1H), 8.25 (s, 1H), 8.10 (d, <i>J</i> = 7.8 Hz, 1H), 7.74 (s, 2H), 7.55 (t, <i>J</i> = 7.5 Hz, 1H), 7.50 (s, 1H), 7.48 (d, <i>J</i> = 2.4 Hz, 1H), 7.45 (s, 2H), 7.42 (s, 2H), 7.39 (s, 1H), 4.34 (s, 2H), 4.13 (s, 1H), 3.66 (d, <i>J</i> = 5.7 Hz, 1H), 2.36 (s, 3H), 1.23 (d, <i>J</i> = 6.0 Hz, 3H).                                                      | 474 |
| 25s | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 9.02 (s, 1H), 8.30 (s, 1H), 8.10 (d, <i>J</i> = 7.8 Hz, 1H), 7.74 (s, 2H), 7.65 (t, <i>J</i> = 7.5 Hz, 1H), 7.50 (s, 1H), 7.48 (d, <i>J</i> = 2.4 Hz, 1H), 7.45 (s, 2H), 7.42 (s, 2H), 7.39 (s, 1H), 4.34 (s, 2H), 4.13 (s, 1H), 3.66 (d, <i>J</i> = 5.7 Hz, 1H), 2.36 (s, 3H), 1.23 (d, <i>J</i> = 6.0 Hz, 3H).                                                      | 460 |
| 26  | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.85 (s, 1H), 8.07 (d, <i>J</i> = 8.1 Hz, 2H), 7.64 (d, <i>J</i> = 8.4 Hz, 2H), 7.51 (dd, <i>J</i> = 12.6, 5.7 Hz, 4H), 7.42 (dd, <i>J</i> = 10.5, 7.2 Hz, 2H), 7.30-7.20 (m, 1H), 7.13 (dd, <i>J</i> = 10.5, 7.2 Hz, 1H), 3.99 (s, 2H), 3.28-3.19 (m, 2H), 2.53 (s, 3H), 2.30 (s, 1H), 2.02 (s, 3H), 1.95-1.83 (m, 2H).                                              | 490 |
| 26s | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.94 (s, 1H), 8.07 (d, <i>J</i> = 8.1 Hz, 2H), 7.64 (d, <i>J</i> = 8.4 Hz, 2H), 7.51 (dd, <i>J</i> = 12.6, 5.7 Hz, 4H), 7.42 (dd, <i>J</i> = 10.5, 7.2 Hz, 2H), 7.30-7.20 (m, 1H), 7.13 (dd, <i>J</i> = 10.5, 7.2 Hz, 1H), 3.99 (s, 2H), 3.28-3.19 (m, 2H), 2.53 (s, 3H), 2.30 (s, 1H), 2.02 (s, 3H), 1.95-1.83 (m, 2H).                                              | 490 |
| 27  | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.09 (s, 2H), 8.03-7.94 (m, 1H), 7.69 (d, <i>J</i> = 8.4 Hz, 1H), 7.55 (dd, <i>J</i> = 11.1, 5.6 Hz, 4H), 7.51-7.45 (m, 2H), 7.41 (t, <i>J</i> = 6.9 Hz, 2H), 4.61 (s, 2H), 4.03-3.90 (m, 1H), 3.60 (d, <i>J</i> = 12.9 Hz, 1H), 3.20-3.12 (m, 1H), 2.94-2.84 (m, 1H), 2.53 (s, 3H), 2.29 (s, 2H), 1.78 (d, <i>J</i> = 10.8 Hz, 1H), 1.49 (s, 2H).                    | 470 |
| 27s | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 9.02 (s, 1H), 8.09 (s, 2H), 8.03-7.94 (m, 1H), 7.69 (d, <i>J</i> = 8.4 Hz, 1H), 7.55 (dd, <i>J</i> = 11.1, 5.6 Hz, 4H), 7.51-7.45 (m, 2H), 7.41 (t, <i>J</i> = 6.9 Hz, 2H), 4.61 (s, 2H), 4.03-3.90 (m, 1H), 3.60 (d, <i>J</i> = 12.9 Hz, 1H), 3.20-3.12 (m, 1H), 2.94-2.84 (m, 1H), 2.53 (s, 3H), 2.29 (s, 2H), 1.78 (d, <i>J</i> = 10.8 Hz, 1H), 1.49 (s, 2H).      | 470 |
| 28  | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.36 (s, 1H), 8.15 (d, <i>J</i> = 7.2 Hz, 1H), 8.05 (d, <i>J</i> = 7.5 Hz, 1H), 7.80 (s, 1H), 7.70 (s, 1H), 7.47 (q, <i>J</i> = 8.1, 7.8 Hz, 5H), 7.37 (d, <i>J</i> = 6.6 Hz, 2H), 4.30 (s, 2H), 3.86 (s, 2H).                                                                                                                                                        | 420 |
| 28s | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.91 (s, 1H), 8.36 (s, 1H), 8.15 (d, <i>J</i> = 7.2 Hz, 1H), 8.05 (d, <i>J</i> = 7.5 Hz, 1H), 7.80 (s, 1H), 7.70 (s, 1H), 7.47 (q, <i>J</i> = 8.1, 7.8 Hz, 5H), 7.37 (d, <i>J</i> = 6.6 Hz, 2H), 4.30 (s, 2H), 3.86 (s, 2H).                                                                                                                                          | 420 |
| 29  | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.27 (s, 1H), 8.14 (s, 1H), 7.95 (s, 1H), 7.83-7.54 (m, 5H), 7.45 (d, <i>J</i> = 9.0 Hz, 4H), 4.26 (s, 2H), 3.82 (s, 2H).                                                                                                                                                                                                                                             | 480 |
| 29s | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 9.02 (s, 1H), 8.73 (s, 1H), 8.27 (s, 1H), 8.14 (s, 1H), 7.95 (s, 1H), 7.8-7.54 (m, 5H), 7.45 (d, <i>J</i> = 9.0 Hz, 4H), 4.26 (s, 2H), 3.82 (s, 2H).                                                                                                                                                                                                                  | 480 |

|     |                                                                                                                                                                                                                                                                                                                                                                             |     |
|-----|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|
| 30  | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.02 (d, <i>J</i> = 5.5 Hz, 3H), 7.67 (s, 2H), 7.51 (dd, <i>J</i> = 13.5, 5.5 Hz, 3H), 7.45-7.36 (m, 2H), 7.21 (d, <i>J</i> = 12.3 Hz, 1H), 4.24 (s, 2H), 3.88 (d, <i>J</i> = 12.3 Hz, 2H), 3.74 (s, 1H).                                                                                                      | 544 |
| 30s | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 9.12 (s, 1H), 8.02 (d, <i>J</i> = 5.5 Hz, 4H), 7.67 (s, 2H), 7.51 (dd, <i>J</i> = 13.5, 5.5 Hz, 3H), 7.45-7.36 (m, 2H), 7.21 (d, <i>J</i> = 12.3 Hz, 1H), 4.24 (s, 2H), 3.88 (d, <i>J</i> = 12.3 Hz, 2H), 3.74 (s, 1H).                                                                                        | 544 |
| 31  | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.29 (s, 1H), 8.16 (d, <i>J</i> = 6.6 Hz, 1H), 8.10 (d, <i>J</i> = 7.5 Hz, 1H), 7.74 (s, 1H), 7.62 (s, 3H), 7.47 (s, 5H), 4.27 (s, 2H), 3.81 (s, 2H).                                                                                                                                                          | 436 |
| 31s | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.93 (s, 1H), 8.29 (s, 1H), 8.16 (d, <i>J</i> = 6.6 Hz, 1H), 8.10 (d, <i>J</i> = 7.5 Hz, 1H), 7.74 (s, 1H), 7.62 (s, 3H), 7.47 (s, 5H), 4.27 (s, 2H), 3.81 (s, 2H).                                                                                                                                            | 436 |
| 32  | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.97 (s, 1H), 8.91 (s, 1H), 8.20 (dd, <i>J</i> = 6.6, 2.7 Hz, 1H), 8.14 (d, <i>J</i> = 7.8 Hz, 1H), 7.78 (d, <i>J</i> = 7.5 Hz, 1H), 7.71-7.61 (m, 3H), 7.49 (d, <i>J</i> = 7.8, 6H), 4.30 (s, 2H), 3.71 (t, <i>J</i> = 5.1 Hz, 2H), 3.09-2.91 (m, 2H).                                                        | 422 |
| 32s | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.91 (s, 1H), 8.20 (dd, <i>J</i> = 6.6, 2.7 Hz, 1H), 8.14 (d, <i>J</i> = 7.8 Hz, 1H), 7.78 (d, <i>J</i> = 7.5 Hz, 1H), 7.71-7.61 (m, 3H), 7.49 (d, <i>J</i> = 7.8, 6H), 4.30 (s, 2H), 3.71 (t, <i>J</i> = 5.1 Hz, 2H), 3.09-2.91 (m, 2H).                                                                      | 422 |
| 33  | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.30 (s, 1H), 8.20 (dd, <i>J</i> = 6.6, 2.7 Hz, 1H), 8.15 (d, <i>J</i> = 7.8 Hz, 1H), 7.91 (s, 1H), 7.75 (d, <i>J</i> = 7.8 Hz, 1H), 7.69 (s, 1H), 7.66 (q, <i>J</i> = 3.6 Hz, 3H), 7.59 (s, 1H), 7.54-7.46 (m, 5H), 4.30 (s, 2H), 3.68 (s, 2H).                                                               | 435 |
| 33s | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 9.50 (s, 1H), 8.30 (s, 1H), 8.20 (dd, <i>J</i> = 6.6, 2.7 Hz, 1H), 8.15 (d, <i>J</i> = 7.8 Hz, 1H), 7.91 (s, 1H), 7.75 (d, <i>J</i> = 7.8 Hz, 1H), 7.69 (s, 1H), 7.66 (q, <i>J</i> = 3.6 Hz, 3H), 7.59 (s, 1H), 7.54-7.46 (m, 5H), 4.30 (s, 2H), 3.68 (s, 2H).                                                 | 435 |
| 34  | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.18 (dd, <i>J</i> = 6.9, 2.6 Hz, 1H), 8.13 (d, <i>J</i> = 7.8 Hz, 1H), 7.83 (d, <i>J</i> = 7.5 Hz, 1H), 7.69 (d, <i>J</i> = 3.6 Hz, 1H), 7.65 (d, <i>J</i> = 2.4 Hz, 2H), 7.49 (q, <i>J</i> = 5.4, 4.8 Hz, 6H), 4.28 (s, 2H), 3.13 (t, <i>J</i> = 7.2 Hz, 2H), 2.80 (t, <i>J</i> = 7.2 Hz, 2H).               | 450 |
| 34s | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.83 (s, 1H), 8.18 (dd, <i>J</i> = 6.9, 2.6 Hz, 1H), 8.13 (d, <i>J</i> = 7.8 Hz, 1H), 7.83 (d, <i>J</i> = 7.5 Hz, 1H), 7.69 (d, <i>J</i> = 3.6 Hz, 1H), 7.65 (d, <i>J</i> = 2.4 Hz, 2H), 7.49 (q, <i>J</i> = 5.4, 4.8 Hz, 6H), 4.28 (s, 2H), 3.13 (t, <i>J</i> = 7.2 Hz, 2H), 2.80 (t, <i>J</i> = 7.2 Hz, 2H). | 450 |
| 35  | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.30 (s, 1H), 8.19 (dd, <i>J</i> = 6.6, 2.7 Hz, 1H), 8.12 (d, <i>J</i> = 7.5 Hz, 1H), 7.76 (d, <i>J</i> = 7.5 Hz, 1H), 7.66 (q, <i>J</i> = 6.3, 5.1 Hz, 3H), 7.51 (t, <i>J</i> = 12.4 Hz, 5H), 4.25 (s, 2H), 3.88 (s, 1H), 1.51 (d, <i>J</i> = 6.3 Hz, 3H).                                                    | 450 |
| 35s | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.75 (s, 1H), 8.30 (s, 1H), 8.19 (dd, <i>J</i> = 6.6, 2.7 Hz, 1H), 8.12 (d, <i>J</i> = 7.5 Hz, 1H), 7.76 (d, <i>J</i> = 7.5 Hz, 1H), 7.66 (q, <i>J</i> = 6.3, 5.1 Hz, 3H), 7.51 (t, <i>J</i> = 12.4 Hz, 5H), 4.25 (s, 2H), 3.88 (s, 1H), 1.51 (d, <i>J</i> = 6.3 Hz, 3H).                                      | 450 |
| 36  | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.20 (dd, <i>J</i> = 6.6, 2.7 Hz, 1H), 8.14 (d, <i>J</i> = 7.8 Hz, 1H), 7.75 (d, <i>J</i> = 7.8 Hz, 1H), 7.70 (s, 1H), 7.65 (s, 2H), 7.49 (q, <i>J</i> = 5.1, 3.6 Hz, 7H), 4.29 (s, 2H), 3.87 (d, <i>J</i> = 4.8 Hz, 2H), 3.80 (d, <i>J</i> = 4.8 Hz, 1H).                                                     | 465 |
| 36s | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 9.13 (s, 1H), 8.20 (dd, <i>J</i> = 6.6, 2.7 Hz, 1H), 8.14 (d, <i>J</i> = 7.8 Hz, 1H), 7.75 (d, <i>J</i> = 7.8 Hz, 1H), 7.70 (s, 1H), 7.65 (s, 2H), 7.49 (q, <i>J</i> = 5.1, 3.6 Hz, 7H), 4.29 (s, 2H), 3.87 (d, <i>J</i> = 4.8 Hz, 2H), 3.80 (d, <i>J</i> = 4.8 Hz, 1H).                                       | 465 |
| 37  | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.20 (dd, <i>J</i> = 6.6, 2.7 Hz, 1H), 8.13 (d, <i>J</i> = 7.8 Hz, 1H), 7.76 (d, <i>J</i> = 7.8 Hz, 1H), 7.67 (s, 1H), 7.65 (d, <i>J</i> = 2.4 Hz, 2H), 7.52 (s, 1H), 7.48 (dd, <i>J</i> = 9.0, 2.7 Hz, 5H), 4.34 (s, 2H), 4.04-3.98 (m, 2H), 3.95 (s, 3H), 3.94 (d, <i>J</i> = 4.5 Hz, 1H).                   | 466 |
| 37s | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.93 (s, 1H), 8.20 (dd, <i>J</i> = 6.6, 2.7 Hz, 1H), 8.13 (d, <i>J</i> = 7.8 Hz, 1H), 7.76 (d, <i>J</i> = 7.8 Hz, 1H), 7.67 (s, 1H), 7.65 (d, <i>J</i> = 2.4 Hz, 2H), 7.52 (s, 1H), 7.48 (dd, <i>J</i> = 9.0, 2.7 Hz, 5H), 4.34 (s, 2H), 4.04-3.98 (m, 2H), 3.94 (d, <i>J</i> = 4.5 Hz, 1H).                   | 466 |
| 38  | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.10 (d, <i>J</i> = 7.2 Hz, 2H), 7.87 (d, <i>J</i> = 7.5 Hz, 2H), 7.70 (d, <i>J</i> = 6.6 Hz, 1H), 7.46 (d, <i>J</i> = 6.0 Hz, 3H), 7.42 (s, 2H), 7.38 (s, 2H), 4.40 (s, 2H), 2.98 (dd, <i>J</i> = 6.0, 4.5 Hz, 5H), 1.97 (d, <i>J</i> = 4.5 Hz, 2H), 1.84 (s, 1H), 1.46 (s, 1H).                              | 491 |
| 38s | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.93 (s, 1H), 8.10 (d, <i>J</i> = 7.2 Hz, 2H), 7.87 (d, <i>J</i> = 7.5 Hz, 2H), 7.70 (d, <i>J</i> = 6.6 Hz, 1H), 7.46 (d, <i>J</i> = 6.0 Hz, 3H), 7.42 (s, 2H), 7.38 (s, 2H), 4.40 (s, 2H), 2.98 (dd, <i>J</i> = 6.0, 4.5 Hz, 5H), 1.97 (d, <i>J</i> = 4.5 Hz, 2H), 1.84 (s, 1H), 1.46 (s, 1H).                | 491 |
| 39  | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.29 (s, 1H), 8.16 (d, <i>J</i> = 6.6 Hz, 1H), 8.10 (d, <i>J</i> = 7.5 Hz, 1H), 7.74 (s, 1H), 7.62 (s, 3H), 7.47 (s, 5H), 4.27 (s, 2H), 3.81 (s, 2H).                                                                                                                                                          | 436 |
| 39s | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.93 (s, 1H), 8.29 (s, 1H), 8.16 (d, <i>J</i> = 6.6 Hz, 1H), 8.10 (d, <i>J</i> = 7.5 Hz, 1H), 7.74 (s, 1H), 7.62 (s, 3H), 7.47 (s, 5H), 4.27 (s, 2H), 3.81 (s, 2H).                                                                                                                                            | 436 |
| 40  | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.30 (s, 1H), 8.19 (dd, <i>J</i> = 6.6, 2.7 Hz, 1H), 8.12 (d, <i>J</i> = 7.5 Hz, 1H), 7.76 (d, <i>J</i> = 7.5 Hz, 1H), 7.66 (q, <i>J</i> = 6.3, 5.1 Hz, 3H), 7.51 (t, <i>J</i> = 12.4 Hz, 5H), 4.25 (s, 2H), 3.88 (s, 1H), 1.51 (d, <i>J</i> = 6.3 Hz, 3H).                                                    | 450 |

|     |                                                                                                                                                                                                                                                                                                                                                                                                                               |     |
|-----|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|
| 40s | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.76 (s, 1H), 8.30 (s, 1H), 8.19 (dd, <i>J</i> = 6.6, 2.7 Hz, 1H), 8.12 (d, <i>J</i> = 7.5 Hz, 1H), 7.76 (d, <i>J</i> = 7.5 Hz, 1H), 7.66 (q, <i>J</i> = 6.3, 5.1 Hz, 3H), 7.51 (t, <i>J</i> = 12.4 Hz, 5H), 4.25 (s, 2H), 3.88 (s, 1H), 1.51 (d, <i>J</i> = 6.3 Hz, 3H).                                                                                        | 450 |
| 41  | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.20 (dd, <i>J</i> = 6.6, 2.7 Hz, 1H), 8.13 (d, <i>J</i> = 7.8 Hz, 1H), 7.76 (d, <i>J</i> = 7.8 Hz, 1H), 7.67 (s, 1H), 7.65 (d, <i>J</i> = 2.4 Hz, 2H), 7.52 (s, 1H), 7.48 (dd, <i>J</i> = 9.0, 2.7 Hz, 5H), 4.34 (s, 2H), 4.04-3.98 (m, 2H), 3.94 (d, <i>J</i> = 4.5 Hz, 1H).                                                                                   | 466 |
| 41s | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.78 (s, 1H), 8.20 (dd, <i>J</i> = 6.6, 2.7 Hz, 1H), 8.13 (d, <i>J</i> = 7.8 Hz, 1H), 7.76 (d, <i>J</i> = 7.8 Hz, 1H), 7.67 (s, 1H), 7.65 (d, <i>J</i> = 2.4 Hz, 2H), 7.52 (s, 1H), 7.48 (dd, <i>J</i> = 9.0, 2.7 Hz, 5H), 4.34 (s, 2H), 4.04-3.98 (m, 2H), 3.94 (d, <i>J</i> = 4.5 Hz, 1H).                                                                     | 466 |
| 42  | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.29 (s, 1H), 8.16 (d, <i>J</i> = 6.6 Hz, 1H), 8.10 (d, <i>J</i> = 7.5 Hz, 1H), 7.62 (s, 3H), 7.47 (s, 5H), 4.27 (s, 2H), 3.81 (s, 2H).                                                                                                                                                                                                                          | 484 |
| 42s | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.93 (s, 1H), 8.29 (s, 1H), 8.16 (d, <i>J</i> = 6.6 Hz, 1H), 8.10 (d, <i>J</i> = 7.5 Hz, 1H), 7.62 (s, 3H), 7.47 (s, 5H), 4.27 (s, 2H), 3.81 (s, 2H).                                                                                                                                                                                                            | 470 |
| 43  | <sup>1</sup> H NMR (300 MHz, Chloroform- <i>d</i> ) δ 8.05-7.98 (m, 2H), 7.68-7.63 (m, 1H), 7.51 (s, 1H), 7.45 (s, 1H), 7.43 (s, 1H), 7.36 (t, <i>J</i> = 6.9 Hz, 5H), 4.24 (s, 2H), 3.77 (s, 2H), 2.33 (s, 3H).                                                                                                                                                                                                              | 448 |
| 43s | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.36 (s, 1H), 8.15 (d, <i>J</i> = 7.2 Hz, 1H), 8.05 (d, <i>J</i> = 6.9 Hz, 1H), 7.70 (s, 1H), 7.47 (q, <i>J</i> = 8.1, 7.8 Hz, 5H), 7.37 (d, <i>J</i> = 6.6 Hz, 3H), 4.21 (s, 2H), 3.75 (s, 2H), 2.23 (s, 3H).                                                                                                                                                   | 434 |
| 44  | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.10 (d, <i>J</i> = 8.4 Hz, 1H), 7.75 (dd, <i>J</i> = 7.2, 2.1 Hz, 1H), 7.67 (dd, <i>J</i> = 8.1, 2.4 Hz, 1H), 7.54-7.49 (m, 2H), 7.47 (t, <i>J</i> = 2.4 Hz, 2H), 7.45 (s, 1H), 7.43 (d, <i>J</i> = 1.8 Hz, 2H), 7.40 (s, 1H), 4.28 (s, 2H), 3.91 (s, 2H), 2.36 (s, 3H).                                                                                        | 495 |
| 44s | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.93 (s, 1H), 8.00 (d, <i>J</i> = 8.4 Hz, 1H), 7.75 (dd, <i>J</i> = 7.2, 2.1 Hz, 1H), 7.67 (dd, <i>J</i> = 8.1, 2.4 Hz, 1H), 7.54-7.49 (m, 2H), 7.47 (t, <i>J</i> = 2.4 Hz, 2H), 7.45 (s, 1H), 7.43 (d, <i>J</i> = 1.8 Hz, 2H), 7.40 (s, 1H), 4.28 (s, 2H), 3.91 (s, 2H), 2.36 (s, 3H).                                                                          | 495 |
| 45  | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.56 (d, <i>J</i> = 6.9 Hz, 1H), 7.82 (s, 1H), 7.74 (d, <i>J</i> = 6.9 Hz, 1H), 7.66-7.55 (m, 1H), 7.53-7.42 (m, 5H), 7.40 (s, 2H), 4.29 (s, 2H), 3.87 (s, 2H), 2.34 (s, 3H).                                                                                                                                                                                    | 450 |
| 45s | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.87 (s, 1H), 8.56 (d, <i>J</i> = 6.9 Hz, 1H), 7.82 (s, 1H), 7.74 (d, <i>J</i> = 6.9 Hz, 1H), 7.66-7.55 (m, 1H), 7.53-7.42 (m, 5H), 7.40 (s, 2H), 4.29 (s, 2H), 3.87 (s, 2H), 2.34 (s, 3H).                                                                                                                                                                      | 450 |
| 46  | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.16 (d, <i>J</i> = 7.2 Hz, 1H), 8.11-8.06 (m, 1H), 7.86 (d, <i>J</i> = 6.3 Hz, 1H), 7.69 (t, <i>J</i> = 7.8 Hz, 1H), 7.54 (d, <i>J</i> = 4.5 Hz, 2H), 7.50 (d, <i>J</i> = 7.2 Hz, 2H), 7.45 (d, <i>J</i> = 6.9 Hz, 1H), 7.40 (d, <i>J</i> = 7.8 Hz, 2H), 5.29 (s, 1H), 4.37 (s, 2H), 3.78 (s, 2H), 3.07 (s, 2H), 2.54 (s, 3H).                                  | 437 |
| 46s | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.78 (s, 1H), 8.16 (d, <i>J</i> = 7.2 Hz, 1H), 8.11-8.06 (m, 1H), 7.86 (d, <i>J</i> = 6.3 Hz, 1H), 7.69 (t, <i>J</i> = 7.8 Hz, 1H), 7.54 (d, <i>J</i> = 4.5 Hz, 2H), 7.50 (d, <i>J</i> = 7.2 Hz, 2H), 7.45 (d, <i>J</i> = 6.9 Hz, 1H), 7.40 (d, <i>J</i> = 7.8 Hz, 2H), 5.29 (s, 1H), 4.37 (s, 2H), 3.78 (s, 2H), 3.07 (s, 2H), 2.54 (s, 3H).                    | 437 |
| 47  | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.09 (s, 2H), 8.03-7.94 (m, 1H), 7.69 (d, <i>J</i> = 8.4 Hz, 1H), 7.55 (dd, <i>J</i> = 11.1, 5.4 Hz, 3H), 7.51-7.45 (m, 2H), 7.41 (t, <i>J</i> = 6.9 Hz, 2H), 4.61 (s, 2H), 4.03-3.90 (m, 1H), 3.60 (d, <i>J</i> = 12.9 Hz, 1H), 3.20-3.12 (m, 1H), 2.94-2.84 (m, 1H), 2.53 (s, 3H), 2.29 (s, 2H), 1.78 (d, <i>J</i> = 10.8 Hz, 1H), 1.49 (s, 2H).               | 505 |
| 47s | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.93 (s, 1H), 8.09 (s, 2H), 8.03-7.94 (m, 1H), 7.69 (d, <i>J</i> = 8.4 Hz, 1H), 7.55 (dd, <i>J</i> = 11.1, 5.4 Hz, 3H), 7.51-7.45 (m, 2H), 7.41 (t, <i>J</i> = 6.9 Hz, 2H), 4.61 (s, 2H), 4.03-3.90 (m, 1H), 3.60 (d, <i>J</i> = 12.9 Hz, 1H), 3.20-3.12 (m, 1H), 2.94-2.84 (m, 1H), 2.53 (s, 3H), 2.29 (s, 2H), 1.78 (d, <i>J</i> = 10.8 Hz, 1H), 1.49 (s, 2H). | 505 |
| 48  | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.72 (d, <i>J</i> = 6.9 Hz, 1H), 8.23 (s, 1H), 7.88 (d, <i>J</i> = 6.9 Hz, 1H), 7.56-7.42 (m, 1H), 7.33-7.12 (m, 5H), 7.04 (s, 2H), 4.35 (s, 2H), 3.90 (s, 2H), 2.30 (s, 3H).                                                                                                                                                                                    | 451 |
| 48s | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.93 (s, 1H), 8.72 (d, <i>J</i> = 6.9 Hz, 1H), 8.23 (s, 1H), 7.88 (d, <i>J</i> = 6.9 Hz, 1H), 7.56-7.42 (m, 1H), 7.33-7.12 (m, 5H), 7.04 (s, 2H), 4.35 (s, 2H), 3.90 (s, 2H), 2.30 (s, 3H).                                                                                                                                                                      | 451 |
| 49  | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.24 (d, <i>J</i> = 9.0 Hz, 1H), 7.90 (d, <i>J</i> = 7.5 Hz, 1H), 7.76 (d, <i>J</i> = 7.2 Hz, 1H), 7.69 (t, <i>J</i> = 7.8 Hz, 1H), 7.50 (d, <i>J</i> = 3.9 Hz, 2H), 7.48 (d, <i>J</i> = 3.6 Hz, 3H), 7.43 (s, 2H), 4.46 (s, 2H), 3.85 (s, 3H), 2.37 (s, 3H).                                                                                                    | 451 |
| 49s | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.78 (s, 1H), 8.24 (d, <i>J</i> = 9.0 Hz, 1H), 7.90 (d, <i>J</i> = 7.5 Hz, 1H), 7.76 (d, <i>J</i> = 7.2 Hz, 1H), 7.69 (t, <i>J</i> = 7.8 Hz, 1H), 7.50 (d, <i>J</i> = 3.9 Hz, 2H), 7.48 (d, <i>J</i> = 3.6 Hz, 3H), 7.43 (s, 2H), 4.46 (s, 2H), 3.99 (s, 2H), 2.37 (s, 3H).                                                                                      | 451 |
| 50  | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.20 (d, <i>J</i> = 6.3 Hz, 2H), 7.87 (s, 1H), 7.73 (d, <i>J</i> = 6.3 Hz, 1H), 7.66-7.34 (m, 7H), 4.29 (s, 2H), 3.86 (s, 2H), 2.35 (s, 2H).                                                                                                                                                                                                                     | 451 |

|     |                                                                                                                                                                                                                                                                                                                                                                                                                               |     |
|-----|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|
| 50s | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.93 (s, 1H), 8.20 (d, <i>J</i> = 6.3 Hz, 2H), 7.87 (s, 1H), 7.73 (d, <i>J</i> = 6.3 Hz, 1H), 7.66-7.34 (m, 7H), 4.29 (s, 2H), 3.86 (s, 2H), 2.35 (s, 2H).                                                                                                                                                                                                       | 451 |
| 51  | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.16 (d, <i>J</i> = 7.2 Hz, 1H), 8.11-8.06 (m, 1H), 7.86 (d, <i>J</i> = 6.3 Hz, 1H), 7.69 (t, <i>J</i> = 7.8 Hz, 1H), 7.54 (d, <i>J</i> = 4.5 Hz, 2H), 7.50 (d, <i>J</i> = 7.2 Hz, 2H), 7.45 (d, <i>J</i> = 6.9 Hz, 1H), 7.40 (d, <i>J</i> = 7.8 Hz, 2H), 5.29 (s, 1H), 4.37 (s, 2H), 3.78 (s, 2H), 3.07 (s, 2H), 2.54 (s, 3H).                                  | 437 |
| 51s | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.93 (s, 1H), 8.16 (d, <i>J</i> = 7.2 Hz, 1H), 8.11-8.06 (m, 1H), 7.86 (d, <i>J</i> = 6.3 Hz, 1H), 7.69 (t, <i>J</i> = 7.8 Hz, 1H), 7.54 (d, <i>J</i> = 4.5 Hz, 2H), 7.50 (d, <i>J</i> = 7.2 Hz, 2H), 7.45 (d, <i>J</i> = 6.9 Hz, 1H), 7.40 (d, <i>J</i> = 7.8 Hz, 2H), 5.29 (s, 1H), 4.37 (s, 2H), 3.78 (s, 2H), 3.07 (s, 2H), 2.54 (s, 3H).                    | 437 |
| 52  | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.17 (d, <i>J</i> = 7.8 Hz, 1H), 8.06 (d, <i>J</i> = 7.5 Hz, 2H), 7.87 (s, 1H), 7.78 (s, 1H), 7.71 (d, <i>J</i> = 7.2 Hz, 1H), 7.55 (s, 2H), 7.50 (t, <i>J</i> = 7.5 Hz, 3H), 4.30 (s, 2H), 3.66 (s, 2H), 2.53 (s, 3H).                                                                                                                                          | 450 |
| 52s | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.76 (s, 1H), 8.17 (d, <i>J</i> = 7.8 Hz, 1H), 8.06 (d, <i>J</i> = 7.5 Hz, 2H), 7.87 (s, 1H), 7.78 (s, 1H), 7.71 (d, <i>J</i> = 7.2 Hz, 1H), 7.55 (s, 2H), 7.50 (t, <i>J</i> = 7.5 Hz, 3H), 4.30 (s, 2H), 3.66 (s, 2H), 2.53 (s, 3H).                                                                                                                            | 450 |
| 53  | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.09 (d, <i>J</i> = 4.2 Hz, 1H), 8.08-8.03 (m, 1H), 7.67 (d, <i>J</i> = 6.9 Hz, 1H), 7.62 (d, <i>J</i> = 7.5 Hz, 1H), 7.54 (d, <i>J</i> = 4.5 Hz, 2H), 7.50 (d, <i>J</i> = 7.2 Hz, 2H), 7.45 (d, <i>J</i> = 6.9 Hz, 1H), 7.40 (d, <i>J</i> = 7.8 Hz, 2H), 4.01 (s, 2H), 2.93-2.85 (m, 2H), 2.54 (s, 3H), 2.46 (t, <i>J</i> = 6.9 Hz, 2H).                        | 465 |
| 53s | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.93 (s, 1H), 8.09 (d, <i>J</i> = 4.2 Hz, 1H), 8.08-8.03 (m, 1H), 7.67 (d, <i>J</i> = 6.9 Hz, 1H), 7.62 (d, <i>J</i> = 7.5 Hz, 1H), 7.54 (d, <i>J</i> = 4.5 Hz, 2H), 7.50 (d, <i>J</i> = 7.2 Hz, 2H), 7.45 (d, <i>J</i> = 6.9 Hz, 1H), 7.40 (d, <i>J</i> = 7.8 Hz, 2H), 4.01 (s, 2H), 2.93-2.85 (m, 2H), 2.54 (s, 3H), 2.46 (t, <i>J</i> = 6.9 Hz, 2H).          | 465 |
| 54  | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.10 (dd, <i>J</i> = 12.6, 6.0 Hz, 2H), 7.99 (d, <i>J</i> = 7.8 Hz, 1H), 7.55 (d, <i>J</i> = 4.2 Hz, 2H), 7.50 (d, <i>J</i> = 8.1 Hz, 3H), 7.45 (d, <i>J</i> = 5.7 Hz, 1H), 7.40 (d, <i>J</i> = 8.1 Hz, 2H), 4.20 (s, 2H), 3.73 (s, 1H), 2.54 (s, 3H), 1.44 (d, <i>J</i> = 7.2 Hz, 3H).                                                                          | 465 |
| 54s | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.93 (s, 1H), 8.10 (dd, <i>J</i> = 12.6, 6.0 Hz, 2H), 7.99 (d, <i>J</i> = 7.8 Hz, 1H), 7.55 (d, <i>J</i> = 4.2 Hz, 2H), 7.50 (d, <i>J</i> = 8.1 Hz, 3H), 7.45 (d, <i>J</i> = 5.7 Hz, 1H), 7.40 (d, <i>J</i> = 8.1 Hz, 2H), 4.20 (s, 2H), 3.73 (s, 1H), 2.54 (s, 3H), 1.44 (d, <i>J</i> = 7.2 Hz, 3H).                                                            | 465 |
| 55  | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.27 (s, 1H), 8.10 (s, 2H), 7.74 (s, 2H), 7.65 (t, <i>J</i> = 7.8 Hz, 1H), 7.45 (s, 2H), 7.43-7.40 (m, 2H), 7.39 (s, 1H), 5.81 (s, 1H), 4.22 (d, <i>J</i> = 6.9 Hz, 2H), 4.01 (s, 1H), 3.53 (d, <i>J</i> = 7.2 Hz, 2H), 2.36 (s, 3H).                                                                                                                            | 480 |
| 55s | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 9.45 (s, 1H), 8.27 (s, 1H), 8.10 (s, 2H), 7.74 (s, 2H), 7.65 (t, <i>J</i> = 7.8 Hz, 1H), 7.45 (s, 2H), 7.43-7.40 (m, 2H), 7.39 (s, 1H), 5.81 (s, 1H), 4.22 (d, <i>J</i> = 6.9 Hz, 2H), 4.01 (s, 1H), 3.53 (d, <i>J</i> = 7.2 Hz, 2H), 2.36 (s, 3H).                                                                                                              | 480 |
| 56  | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.12 (d, <i>J</i> = 5.4 Hz, 3H), 7.77 (s, 2H), 7.51 (dd, <i>J</i> = 13.5, 5.4 Hz, 4H), 7.45-7.36 (m, 2H), 4.24 (s, 2H), 3.88 (d, <i>J</i> = 12.3 Hz, 2H), 3.74 (s, 1H), 2.53 (s, 3H).                                                                                                                                                                            | 495 |
| 56s | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.89 (s, 1H), 8.12 (d, <i>J</i> = 5.4 Hz, 3H), 7.77 (s, 2H), 7.51 (dd, <i>J</i> = 13.5, 5.4 Hz, 4H), 7.45-7.36 (m, 2H), 4.24 (s, 2H), 3.88 (d, <i>J</i> = 12.3 Hz, 2H), 3.74 (s, 1H), 2.53 (s, 3H).                                                                                                                                                              | 481 |
| 57  | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.27 (s, 1H), 8.10 (s, 2H), 7.81 (s, 1H), 7.65 (t, <i>J</i> = 7.8 Hz, 1H), 7.50 (s, 1H), 7.45 (s, 2H), 7.43-7.40 (m, 2H), 7.39 (s, 1H), 5.81 (s, 1H), 4.22 (d, <i>J</i> = 6.9 Hz, 2H), 4.01 (s, 1H), 3.53 (d, <i>J</i> = 7.2 Hz, 1H), 2.36 (s, 3H), 1.16 (d, <i>J</i> = 6.3 Hz, 3H).                                                                             | 494 |
| 57s | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 9.45 (s, 1H), 8.27 (s, 1H), 8.10 (s, 2H), 7.81 (s, 1H), 7.65 (t, <i>J</i> = 7.8 Hz, 1H), 7.50 (s, 1H), 7.45 (s, 2H), 7.43-7.40 (m, 2H), 7.39 (s, 1H), 5.81 (s, 1H), 4.22 (d, <i>J</i> = 6.9 Hz, 2H), 4.01 (s, 1H), 3.53 (d, <i>J</i> = 7.2 Hz, 1H), 2.36 (s, 3H), 1.16 (d, <i>J</i> = 6.3 Hz, 3H).                                                               | 494 |
| 58  | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.10 (d, <i>J</i> = 7.8 Hz, 1H), 7.74 (s, 2H), 7.65 (t, <i>J</i> = 7.5 Hz, 1H), 7.50 (s, 1H), 7.48 (d, <i>J</i> = 2.4 Hz, 1H), 7.45 (s, 2H), 7.42 (s, 2H), 7.39 (s, 1H), 4.34 (s, 2H), 4.13 (s, 1H), 3.66 (d, <i>J</i> = 5.7 Hz, 1H), 2.36 (s, 3H), 1.23 (d, <i>J</i> = 6.0 Hz, 3H).                                                                             | 495 |
| 58s | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.75 (s, 1H), 8.10 (d, <i>J</i> = 7.8 Hz, 1H), 7.74 (s, 2H), 7.65 (t, <i>J</i> = 7.5 Hz, 1H), 7.50 (s, 1H), 7.48 (d, <i>J</i> = 2.4 Hz, 1H), 7.45 (s, 2H), 7.42 (s, 2H), 7.39 (s, 1H), 4.34 (s, 2H), 4.13 (s, 1H), 3.66 (d, <i>J</i> = 5.7 Hz, 1H), 2.36 (s, 3H), 1.23 (d, <i>J</i> = 6.0 Hz, 3H).                                                               | 495 |
| 59  | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.09 (s, 2H), 8.03-7.94 (m, 1H), 7.69 (d, <i>J</i> = 8.4 Hz, 1H), 7.55 (dd, <i>J</i> = 11.1, 5.7 Hz, 3H), 7.51-7.45 (m, 2H), 7.41 (t, <i>J</i> = 6.9 Hz, 2H), 4.61 (s, 2H), 4.03-3.90 (m, 1H), 3.60 (d, <i>J</i> = 12.9 Hz, 1H), 3.20-3.12 (m, 1H), 2.94-2.84 (m, 1H), 2.53 (s, 3H), 2.29 (s, 2H), 1.78 (d, <i>J</i> = 10.8 Hz, 1H), 1.49 (s, 2H).               | 505 |
| 59s | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.93 (s, 1H), 8.09 (s, 2H), 8.03-7.94 (m, 1H), 7.69 (d, <i>J</i> = 8.4 Hz, 1H), 7.55 (dd, <i>J</i> = 11.1, 5.7 Hz, 3H), 7.51-7.45 (m, 2H), 7.41 (t, <i>J</i> = 6.9 Hz, 2H), 4.61 (s, 2H), 4.03-3.90 (m, 1H), 3.60 (d, <i>J</i> = 12.9 Hz, 1H), 3.20-3.12 (m, 1H), 2.94-2.84 (m, 1H), 2.53 (s, 3H), 2.29 (s, 2H), 1.78 (d, <i>J</i> = 10.8 Hz, 1H), 1.49 (s, 2H). | 505 |

|                                                                                                                                                                                                                                        |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 5.7 Hz, 3H), 7.51-7.45 (m, 2H), 7.41 (t, $J = 6.9$ Hz, 2H), 4.61 (s, 2H), 4.03-3.90 (m, 1H), 3.60 (d, $J = 12.9$ Hz, 1H), 3.20-3.12 (m, 1H), 2.94-2.84 (m, 1H), 2.53 (s, 3H), 2.29 (s, 2H), 1.78 (d, $J = 10.8$ Hz, 1H), 1.49 (s, 2H). |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

实施例 2: (3-(5-(2-甲基-[1,1'-联苯]-3-基)-4H-1,2,4-三唑-3-基)苄基)甘氨酸 (60) 及其盐酸盐 (60s) 的合成  
3-氨基甲酰苯甲酸甲酯盐酸盐 (2A) 的合成

将 3-氟基苯甲酸甲酯 (7.50 g, 46.54 mmol) 溶于 80 mL 甲醇中, 加入甲醇钠 (2.77 g, 51.19 mmol), 40°C 反应 12h, 再加入氯化铵 (4.98 g, 93.08 mmol), 50°C 反应过夜。冷却, 抽滤, 滤液旋干, 用 PE:EA=5:1 重结晶, 抽滤, 干燥, 得白色固体 6.90 g, 收率 69%。MS (EI)  $m/z$  179  $[M+H]^+$ ;  $^1H$  NMR (300 MHz, Chloroform- $d$ )  $\delta$  7.95 (d,  $J = 6.9$  Hz, 1H), 7.52 (d,  $J = 6.9$  Hz, 1H), 7.39-7.35 (m, 2H) 3.87 (s, 3H).

3-(5-(2-甲基-[1,1'-联苯]-3-基)-4H-1,2,4-三唑-3-基)苯甲酸甲酯 (2B) 的合成

将 2A (3.50g, 16.31mmol) 和甲醇钠 (1.17g, 21.74mmol) 加入 20mL 无水乙醇中, 室温反应 1h, 抽滤, 滤液加入 1C (2.46g, 10.87mmol), 回流搅拌过夜。冷却, 抽滤, 乙酸乙酯萃取, 无水硫酸钠干燥, 柱层析纯化[石油醚:乙酸乙酯 = 20:1 (V:V)], 得白色固体 2.61g, 收率 65%。MS (ESI)  $m/z$  370  $[M+H]^+$ ;  $^1H$  NMR (300 MHz, Chloroform- $d$ )  $\delta$  8.77 (s, 1H), 8.37 (d,  $J = 7.8$  Hz, 1H), 8.23 (d,  $J = 7.8$  Hz, 1H), 8.02 (d,  $J = 6.6$  Hz, 1H), 7.64 (t,  $J = 7.8$  Hz, 1H), 7.51-7.30 (m, 7H), 3.99 (s, 3H), 2.61 (s, 3H).

(3-(5-(2-甲基-[1,1'-联苯]-3-基)-4H-1,2,4-三唑-3-基)苄基)甲醇 (2C) 的合成

将 2B (2.62 g, 7.04 mmol) 加入 30 mL 无水 THF 中, 冰浴冷却下加入  $LiAlH_4$  (0.41 g, 10.56 mmol), 反应 4 h。加入 40 mL 冰水, 抽滤, 干燥, 得白色固体 2.21 g, 收率 94%。MS (ESI)  $m/z$  342  $[M+H]^+$ ;  $^1H$  NMR (300 MHz, Chloroform- $d$ )  $\delta$  8.37 (s, 1H), 8.18 (d,  $J = 7.8$  Hz, 1H), 8.12 (dd,  $J = 7.5, 1.8$  Hz, 1H), 7.83 (d,  $J = 7.8$  Hz, 1H), 7.70 (t,  $J = 7.8$  Hz, 1H), 7.56-7.35 (m, 7H), 4.54 (s, 2H), 2.33 (s, 3H).

3-(5-(2-甲基-[1,1'-联苯]-3-基)-4H-1,2,4-三唑-3-基)苯甲醛 (2D) 的合成

将 2C (2.20 g, 6.44 mmol) 溶于 35mLDMSO 中, 加入 IBX (2.71 g, 9.67 mmol), 室温反应 2 h。乙酸乙酯萃取, 柱层析纯化[石油醚:乙酸乙酯 = 20:1 (V:V)], 得白色固体 1.40 g, 收率 60%。MS (ESI)  $m/z$  340  $[M+H]^+$ ;  $^1H$  NMR (300 MHz, DMSO- $d_6$ )  $\delta$  9.85 (s, 1H), 8.37 (s, 1H), 8.15 (d,  $J = 7.8$  Hz, 1H), 8.07 (dd,  $J = 7.5, 1.8$  Hz, 1H), 7.81 (d,  $J = 7.8$  Hz, 1H), 7.68 (t,  $J = 7.8$  Hz, 1H), 7.62-7.32 (m, 7H), 2.54 (s, 3H).

(3-(5-(2-甲基-[1,1'-联苯]-3-基)-4H-1,2,4-三唑-3-基)苄基)甘氨酸甲酯 (2E) 的合成

将 2D (0.15 g, 0.44 mmol) 加入 5 mL DMF 中, 依次加入甘氨酸甲酯盐酸盐 (0.14 g, 0.89 mmol)、TEA (0.13 g, 1.33 mmol)、冰醋酸 (0.13 g, 2.21 mmol) 和氰基硼氢化钠 (0.14 g, 2.21 mmol), 室温反应 4 h, 加 10 mL 水, 乙酸乙酯萃取, 柱层析纯化[石油醚:乙酸乙酯 = 1:1 (V:V)], 得白色固体 0.12 g, 收率 60%。MS (ESI)  $m/z$  413  $[M+H]^+$ ;  $^1H$  NMR (300 MHz, DMSO- $d_6$ )  $\delta$  8.05-7.98 (m, 2H), 7.68-7.63 (m, 1H), 7.51 (s, 1H), 7.48 (s, 1H), 7.45 (s, 1H), 7.43 (s, 1H), 7.36 (t,  $J = 6.9$  Hz, 5H) 4.24 (s, 2H), 3.98 (s, 3H), 3.77 (s, 2H), 2.33 (s, 3H).

化合物 60 及其盐酸盐 (60s) 的合成

参照实施例 1 的方法, 将 60m 水解制得白色固体 60, 收率 60%。再将 60 与盐酸成盐, 制得白色固体 60s, 收率 94%。MS (ESI)  $m/z$  399  $[M+H]^+$ ;  $^1H$  NMR (300 MHz, DMSO- $d_6$ )  $\delta$  8.93 (s, 1H), 8.86 (s, 1H), 8.36 (s, 1H), 8.15 (d,  $J = 7.2$  Hz, 1H), 8.05 (d,  $J = 6.9$  Hz, 1H), 7.80 (s, 1H), 7.70 (s, 1H), 7.47 (q,  $J = 8.1, 7.8$  Hz, 5H), 7.37 (d,  $J = 6.6$  Hz, 3H), 4.21 (s, 2H), 3.88 (d,  $J = 12.3$  Hz, 2H), 3.74 (s, 1H), 2.23 (s, 3H).

采用与实施例 2 相似的操作, 制得下列化合物:

| 编号  | $^1H$ -NMR                                                                                                                                                                                                                                                                                                                                                 | ESI-MS<br>$m/z$<br>( $M+H$ ) $^+$ |
|-----|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------|
| 61  | $^1H$ NMR (300 MHz, DMSO- $d_6$ ) $\delta$ 8.49 (s, 2H), 7.82 (s, 2H), 7.74 (d, $J = 6.9$ Hz, 2H), 7.48 (d, $J = 3.3$ Hz, 2H), 7.46 (d, $J = 3.3$ Hz, 2H), 7.43 (s, 1H), 7.41 (s, 1H), 5.26 (s, 1H), 4.30 (s, 2H), 3.69 (s, 2H), 3.01 (s, 2H), 2.34 (s, 3H).                                                                                               | 385                               |
| 61s | $^1H$ NMR (300 MHz, DMSO- $d_6$ ) $\delta$ 9.28 (s, 1H), 8.49 (s, 2H), 7.82 (s, 2H), 7.74 (d, $J = 6.9$ Hz, 2H), 7.48 (d, $J = 3.3$ Hz, 2H), 7.46 (d, $J = 3.3$ Hz, 2H), 7.43 (s, 1H), 7.41 (s, 1H), 5.26 (s, 1H), 4.30 (s, 2H), 3.69 (s, 2H), 3.01 (s, 2H), 2.34 (s, 3H).                                                                                 | 385                               |
| 62  | $^1H$ NMR (300 MHz, DMSO- $d_6$ ) $\delta$ 8.37 (s, 1H), 8.09 (d, $J = 4.2$ Hz, 1H), 8.08-8.03 (m, 1H), 7.67 (d, $J = 6.9$ Hz, 1H), 7.62 (d, $J = 7.5$ Hz, 1H), 7.54 (d, $J = 4.5$ Hz, 2H), 7.50 (d, $J = 7.2$ Hz, 2H), 7.45 (d, $J = 6.9$ Hz, 1H), 7.40 (d, $J = 7.8$ Hz, 2H), 4.01 (s, 2H), 2.93-2.85 (m, 2H), 2.54 (s, 3H), 2.46 (t, $J = 6.9$ Hz, 2H). | 413                               |
| 62s | $^1H$ NMR (300 MHz, DMSO- $d_6$ ) $\delta$ 8.78 (s, 1H), 8.31 (d, $J = 8.7$ Hz, 1H), 8.16-8.05 (m, 2H), 7.87 (t, $J = 8.6$ Hz, 1H), 7.71-7.62 (m, 2H), 7.54 (dt, $J = 9.9, 5.4$ Hz, 4H), 7.41 (d, $J = 8.3$ Hz, 2H), 4.24 (s, 2H), 3.11-2.99 (m, 2H), 2.67-2.59 (m, 2H), 2.56 (s, 3H).                                                                     | 413                               |

|     |                                                                                                                                                                                                                                                                                                                                                                                                                          |     |
|-----|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|
| 63  | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.35 (d, <i>J</i> = 5.4 Hz, 3H), 7.75 (s, 2H), 7.51 (dd, <i>J</i> = 13.5, 5.4 Hz, 4H), 7.45-7.36 (m, 2H), 7.21 (d, <i>J</i> = 12.3 Hz, 1H), 4.24 (s, 2H), 3.88 (d, <i>J</i> = 12.3 Hz, 2H), 3.74 (s, 1H), 2.53 (s, 3H).                                                                                                                                     | 429 |
| 63s | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.97 (s, 1H), 8.15 (d, <i>J</i> = 7.8 Hz, 1H), 8.07 (dd, <i>J</i> = 7.5, 1.8 Hz, 2H), 7.81 (d, <i>J</i> = 7.8 Hz, 1H), 7.68 (t, <i>J</i> = 7.8 Hz, 1H), 7.62-7.32 (m, 7H), 4.32 (s, 2H), 4.02-3.94 (m, 1H), 3.89 (d, <i>J</i> = 2.6 Hz, 2H), 2.54 (s, 3H)                                                                                                   | 429 |
| 64  | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.35 (s, 1H), 8.10 (d, <i>J</i> = 7.8 Hz, 1H), 7.74 (s, 2H), 7.65 (t, <i>J</i> = 7.5 Hz, 1H), 7.50 (s, 1H), 7.48 (d, <i>J</i> = 2.4 Hz, 1H), 7.45 (s, 2H), 7.42 (s, 2H), 7.39 (s, 1H), 4.34 (s, 2H), 4.13 (s, 1H), 3.66 (d, <i>J</i> = 5.7 Hz, 1H), 2.36 (s, 3H), 1.23 (d, <i>J</i> = 6.0 Hz, 3H).                                                          | 443 |
| 64s | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.93 (s, 1H), 8.27 (d, <i>J</i> = 10.5 Hz, 1H), 8.14-8.08 (m, 1H), 8.00 (d, <i>J</i> = 7.8 Hz, 1H), 7.75-7.68 (m, 2H), 7.52 (dt, <i>J</i> = 15.0, 6.0 Hz, 5H), 7.42 (d, <i>J</i> = 8.1 Hz, 2H), 4.23 (s, 2H), 3.84-3.71 (m, 2H), 3.28 (s, 1H), 2.56 (s, 3H), 1.47 (d, <i>J</i> = 7.2 Hz, 3H).                                                               | 443 |
| 65  | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.33 (s, 1H), 8.21 (s, 1H), 7.97 (s, 1H), 7.73 (dd, <i>J</i> = 7.2, 1.8 Hz, 2H), 7.51 (dd, <i>J</i> = 6.6, 1.8 Hz, 2H), 7.49-7.46 (m, 2H), 7.45-7.41 (m, 2H), 7.40 (d, <i>J</i> = 1.5 Hz, 1H), 4.46 (s, 2H), 2.97 (s, 4H), 2.35 (s, 3H), 2.01 (s, 1H), 1.86 (s, 2H), 1.46 (s, 2H).                                                                          | 453 |
| 65s | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.93 (s, 1H), 8.33 (s, 1H), 8.21 (s, 1H), 7.97 (s, 1H), 7.73 (dd, <i>J</i> = 7.2, 1.8 Hz, 2H), 7.51 (dd, <i>J</i> = 6.6, 1.8 Hz, 2H), 7.49-7.46 (m, 2H), 7.45-7.41 (m, 2H), 7.40 (d, <i>J</i> = 1.5 Hz, 1H), 4.46 (s, 2H), 2.97 (s, 4H), 2.35 (s, 3H), 2.01 (s, 1H), 1.86 (s, 2H), 1.46 (s, 2H).                                                            | 453 |
| 66  | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 7.98 (d, <i>J</i> = 7.8 Hz, 2H), 7.79 (d, <i>J</i> = 7.8 Hz, 2H), 7.70 (d, <i>J</i> = 6.6 Hz, 1H), 7.44 (dd, <i>J</i> = 11.4, 8.1 Hz, 7H), 4.13 (s, 2H), 3.65 (s, 2H), 2.30 (s, 3H).                                                                                                                                                                        | 399 |
| 66s | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.93 (s, 1H), 7.98 (d, <i>J</i> = 7.8 Hz, 2H), 7.79 (d, <i>J</i> = 7.8 Hz, 2H), 7.70 (d, <i>J</i> = 6.6 Hz, 1H), 7.44 (dd, <i>J</i> = 11.4, 8.1 Hz, 7H), 4.13 (s, 2H), 3.65 (s, 2H), 2.30 (s, 3H).                                                                                                                                                          | 399 |
| 67  | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.31 (d, <i>J</i> = 10.2 Hz, 1H), 8.24-8.15 (m, 1H), 8.13-8.05 (m, 1H), 7.85-7.75 (m, 1H), 7.75-7.66 (m, 1H), 7.55 (dd, <i>J</i> = 11.7, 5.4 Hz, 4H), 7.47 (d, <i>J</i> = 5.7 Hz, 1H), 7.40 (dd, <i>J</i> = 15.6, 6.6 Hz, 2H), 4.49 (s, 2H), 4.09 (s, 2H), 2.81 (s, 3H), 2.53 (s, 3H).                                                                      | 413 |
| 67s | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.93 (s, 1H), 8.31 (d, <i>J</i> = 10.2 Hz, 1H), 8.24-8.15 (m, 1H), 8.13-8.05 (m, 1H), 7.85-7.75 (m, 1H), 7.75-7.66 (m, 1H), 7.55 (dd, <i>J</i> = 11.7, 5.4 Hz, 4H), 7.47 (d, <i>J</i> = 5.7 Hz, 1H), 7.40 (dd, <i>J</i> = 15.6, 6.6 Hz, 2H), 4.49 (s, 2H), 4.09 (s, 2H), 2.81 (s, 3H), 2.53 (s, 3H).                                                        | 413 |
| 68  | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.32 (s, 1H), 8.16 (d, <i>J</i> = 7.2 Hz, 1H), 8.11-8.06 (m, 1H), 7.86 (d, <i>J</i> = 6.3 Hz, 1H), 7.69 (t, <i>J</i> = 7.8 Hz, 1H), 7.54 (d, <i>J</i> = 4.5 Hz, 2H), 7.50 (d, <i>J</i> = 7.2 Hz, 2H), 7.45 (d, <i>J</i> = 6.9 Hz, 1H), 7.40 (d, <i>J</i> = 7.8 Hz, 2H), 5.29 (s, 1H), 4.37 (s, 2H), 3.78 (s, 2H), 3.07 (s, 2H), 2.54 (s, 3H).               | 385 |
| 68s | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.76 (s, 1H), 8.32 (s, 1H), 8.16 (d, <i>J</i> = 7.2 Hz, 1H), 8.11-8.06 (m, 1H), 7.86 (d, <i>J</i> = 6.3 Hz, 1H), 7.69 (t, <i>J</i> = 7.8 Hz, 1H), 7.54 (d, <i>J</i> = 4.5 Hz, 2H), 7.50 (d, <i>J</i> = 7.2 Hz, 2H), 7.45 (d, <i>J</i> = 6.9 Hz, 1H), 7.40 (d, <i>J</i> = 7.8 Hz, 2H), 5.29 (s, 1H), 4.37 (s, 2H), 3.78 (s, 2H), 3.07 (s, 2H), 2.54 (s, 3H). | 385 |
| 69  | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.02 (d, <i>J</i> = 5.5 Hz, 3H), 7.67 (s, 2H), 7.51 (dd, <i>J</i> = 13.5, 5.5 Hz, 4H), 7.45-7.36 (m, 2H), 7.21 (d, <i>J</i> = 12.3 Hz, 1H), 4.24 (s, 2H), 3.88 (d, <i>J</i> = 12.3 Hz, 2H), 3.74 (s, 1H), 2.53 (s, 3H).                                                                                                                                     | 429 |
| 69s | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.75 (s, 1H), 8.12 (d, <i>J</i> = 5.5 Hz, 3H), 7.77 (s, 2H), 7.51 (dd, <i>J</i> = 13.5, 5.4 Hz, 4H), 7.45-7.36 (m, 2H), 7.21 (d, <i>J</i> = 12.3 Hz, 1H), 4.24 (s, 2H), 3.88 (d, <i>J</i> = 12.3 Hz, 2H), 3.74 (s, 1H), 2.53 (s, 3H).                                                                                                                       | 429 |
| 70  | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.25 (s, 1H), 8.10 (d, <i>J</i> = 7.8 Hz, 1H), 7.74 (s, 2H), 7.55 (t, <i>J</i> = 7.5 Hz, 1H), 7.50 (s, 1H), 7.48 (d, <i>J</i> = 2.4 Hz, 1H), 7.45 (s, 2H), 7.42 (s, 2H), 7.39 (s, 1H), 4.34 (s, 2H), 4.13 (s, 1H), 3.66 (d, <i>J</i> = 5.7 Hz, 1H), 2.36 (s, 3H), 1.23 (d, <i>J</i> = 6.0 Hz, 3H).                                                          | 443 |
| 70s | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.75 (s, 1H), 8.30 (s, 1H), 8.10 (d, <i>J</i> = 7.8 Hz, 1H), 7.74 (s, 2H), 7.65 (t, <i>J</i> = 7.5 Hz, 1H), 7.50 (s, 1H), 7.48 (d, <i>J</i> = 2.4 Hz, 1H), 7.45 (s, 2H), 7.42 (s, 2H), 7.39 (s, 1H), 4.34 (s, 2H), 4.13 (s, 1H), 3.66 (d, <i>J</i> = 5.7 Hz, 1H), 2.36 (s, 3H), 1.23 (d, <i>J</i> = 6.0 Hz, 3H).                                            | 443 |
| 71  | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.31 (d, <i>J</i> = 10.2 Hz, 1H), 8.24-8.15 (m, 1H), 8.13-8.05 (m, 1H), 7.85-7.75 (m, 1H), 7.55 (dd, <i>J</i> = 11.7, 5.7 Hz, 4H), 7.40 (dd, <i>J</i> = 15.6, 6.6 Hz, 3H), 4.49 (s, 2H), 4.09 (s, 2H), 2.53 (s, 3H)                                                                                                                                         | 434 |
| 71s | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.79 (s, 1H), 8.42 (s, 1H), 8.18-7.99 (m, 3H), 7.65 (d, <i>J</i> = 6.3 Hz, 1H), 7.60 (d, <i>J</i> = 7.2 Hz, 1H), 7.55-7.48 (m, 3H), 7.41 (d, <i>J</i> = 6.6 Hz, 2H), 3.98 (s, 2H), 3.18 (s, 2H), 2.59 (s, 3H)                                                                                                                                               | 434 |

实施例 3: (3-(5-(2-甲基-[1,1'-联苯]-3-基)-1,2,4-噁二唑-3-基)苄基)甘氨酸 (72) 及其盐酸盐 (72s) 的合成  
3-(N-羟基氨基甲酰)苯甲酸甲酯 (3A) 的合成

将间氨基苯甲酸甲酯(2.61 g, 16.01 mmol)溶于 30 mL 无水乙醇中,搅拌下依次加入盐酸羟胺(3.91 g, 56.02 mmol)和碳酸氢钠(5.30 g, 64.02 mmol),回流反应 12 h。冷却,抽滤,乙酸乙酯萃取,无水硫酸钠干燥,柱层析纯化(PE:EA = 15:1)得到白色固体 2.53 g,收率 80%。MS (ESI)  $m/z$  195  $[M+H]^+$ ;  $^1H$ -NMR (300 MHz, DMSO- $d_6$ ):  $\delta$  (ppm) 8.76-8.68 (m, 2H), 8.49 (s, 1H), 7.89 (s, 1H), 7.28 (s, 1H), 6.90 (s, 1H), 6.68 (s, 1H), 3.98 (s, 3H)。

3-(5-(2-甲基-[1,1'-联苯]-3-基)-1,2,4-噁二唑-3-基)苯甲酸甲酯(3B)的合成

将 1A (4.80 g, 22.71 mmol)、1-羟基苯并三唑 (3.31 g, 24.82 mmol)、1-(3-二甲氨基丙基)-3-乙基碳二亚胺盐酸盐 (4.81 g, 24.80 mmol) 和碳酸钾 (3.41 g, 24.80 mmol) 溶于 50 mL DMF, 室温搅拌 0.5 h, 加入中间体 3A (4.01 g, 20.62 mmol),  $N_2$  保护 110°C 反应 12 h。冷却, 乙酸乙酯萃取, 无水硫酸钠干燥, 柱层析纯化 (PE:EA = 20:1) 得到白色固体 3.51 g, 收率 46%。MS (ESI)  $m/z$  371  $[M+H]^+$ ;  $^1H$  NMR (300 MHz, Chloroform- $d$ )  $\delta$  8.86 (s, 1H), 8.39 (d,  $J$  = 7.8 Hz, 1H), 8.22 (d,  $J$  = 8.0 Hz, 1H), 8.12 (dd,  $J$  = 7.5, 1.8 Hz, 1H), 7.62 (t,  $J$  = 7.8 Hz, 2H), 7.52-7.39 (m, 5H), 7.38-7.33 (m, 1H), 3.99 (s, 3H), 2.63 (s, 3H)。

(3-(5-(2-甲基-[1,1'-联苯]-3-基)-1,2,4-噁二唑-3-基)苯基)甲醇(3C)的合成

参照实施例 2 的方法,将中间体 3B 与  $LiAlH_4$  进行还原反应,得白色固体 3C,收率 81%。MS (ESI)  $m/z$  343  $[M+H]^+$ ;  $^1H$  NMR (300 MHz, Chloroform- $d$ )  $\delta$  8.16 (dd,  $J$  = 7.1, 4.2 Hz, 2H), 8.04-7.98 (m, 1H), 7.62-7.55 (m, 2H), 7.45 (dt,  $J$  = 9.8, 4.3 Hz, 5H), 7.39-7.34 (m, 2H), 4.85 (s, 1H), 4.84 (s, 2H), 2.62 (s, 3H)。

3-(5-(2-甲基-[1,1'-联苯]-3-基)-1,2,4-噁二唑-3-基)苯甲醛(3D)的合成

参照实施例 2 的方法,将中间体 3C 与 IBX 反应,得白色固体 3D,收率 80%。MS (ESI)  $m/z$  341  $[M+H]^+$ ;  $^1H$  NMR (300 MHz, Chloroform- $d$ )  $\delta$  10.12 (s, 1H), 8.20 (s, 3H), 8.02 (d,  $J$  = 7.0 Hz, 1H), 7.45 (t,  $J$  = 6.9 Hz, 5H), 7.36 (d,  $J$  = 6.6 Hz, 2H), 3.99 (s, 3H), 2.63 (s, 3H)。

(3-(5-(2-甲基-[1,1'-联苯]-3-基)-1,2,4-噁二唑-3-基)苯基)甘氨酸甲酯(3E)的合成

参照实施例 2 的方法,将中间体 3E 和甘氨酸甲酯盐酸盐进行还原胺化反应,得白色固体 72m,收率 69%。MS (ESI)  $m/z$  414  $[M+H]^+$ ;  $^1H$  NMR (300 MHz, DMSO- $d_6$ )  $\delta$  8.16 (d,  $J$  = 7.2 Hz, 2H), 8.09 (s, 1H), 7.78 (d,  $J$  = 7.1 Hz, 2H), 7.54 (s, 2H), 7.52-7.46 (m, 3H), 7.40 (d,  $J$  = 6.4 Hz, 2H), 4.26 (s, 2H), 3.9 (s, 3H), 3.83 (s, 2H), 2.54 (s, 3H)。

化合物 72 及其盐酸盐(72s)的合成

参照实施例 1 的方法,将 72m 水解制得白色固体 72,收率 61%。再由 72 与盐酸成盐,制得白色固体 72s,收率 93%。MS (ESI)  $m/z$  400  $[M+H]^+$ ;  $^1H$  NMR (300 MHz, DMSO- $d_6$ )  $\delta$  9.54 (s, 1H), 8.16 (d,  $J$  = 7.2 Hz, 2H), 8.09 (s, 1H), 7.78 (d,  $J$  = 7.1 Hz, 2H), 7.54 (s, 2H), 7.52-7.46 (m, 3H), 7.40 (d,  $J$  = 6.4 Hz, 2H), 4.26 (s, 2H), 3.83 (s, 2H), 2.54 (s, 3H)。

采用与实施例 3 相似的操作,制得下列化合物:

| 编号  | $^1H$ -NMR                                                                                                                                                                                                                                                                                                                                           | ESI-MS<br>$m/z$<br>( $M+H$ ) $^+$ |
|-----|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------|
| 73  | $^1H$ NMR (300 MHz, Chloroform- $d$ ) $\delta$ 8.18 (d, $J$ = 7.9 Hz, 1H), 8.09 (dd, $J$ = 14.0, 7.7 Hz, 2H), 7.82 (d, $J$ = 7.2 Hz, 1H), 7.79-7.73 (m, 1H), 7.59-7.54 (m, 1H), 7.45 (dd, $J$ = 8.6, 3.5 Hz, 4H), 7.33 (d, $J$ = 6.6 Hz, 2H), 4.20 (s, 1H), 3.62 (s, 2H), 3.12 (s, 2H), 2.61 (s, 2H), 2.58 (s, 3H), 2.00 (s, 3H)。                    | 427                               |
| 73s | $^1H$ NMR (300 MHz, Chloroform- $d$ ) $\delta$ 8.93 (s, 1H), 8.18 (d, $J$ = 7.9 Hz, 1H), 8.09 (dd, $J$ = 14.0, 7.7 Hz, 2H), 7.82 (d, $J$ = 7.2 Hz, 1H), 7.79-7.73 (m, 1H), 7.59-7.54 (m, 1H), 7.45 (dd, $J$ = 8.6, 3.5 Hz, 4H), 7.33 (d, $J$ = 6.6 Hz, 2H), 4.20 (s, 1H), 3.62 (s, 2H), 3.12 (s, 2H), 2.61 (s, 2H), 2.58 (s, 3H), 2.00 (s, 3H)。      | 427                               |
| 74  | $^1H$ NMR (300 MHz, DMSO- $d_6$ ) $\delta$ 8.33 (s, 1H), 8.20 (d, $J$ = 7.2 Hz, 1H), 8.09 (q, $J$ = 4.2 Hz, 1H), 7.84 (d, $J$ = 6.0 Hz, 1H), 7.76-7.67 (m, 1H), 7.56 (d, $J$ = 4.2 Hz, 2H), 7.52 (s, 2H), 7.46 (d, $J$ = 6.4 Hz, 1H), 7.41 (d, $J$ = 6.3 Hz, 2H), 4.49 (s, 2H), 4.07 (s, 2H), 3.90 (s, 2H), 2.55 (s, 3H)。                            | 414                               |
| 74s | $^1H$ NMR (300 MHz, DMSO- $d_6$ ) $\delta$ 8.33 (s, 1H), 8.20 (d, $J$ = 7.2 Hz, 1H), 8.09 (q, $J$ = 4.2 Hz, 1H), 7.84 (d, $J$ = 6.0 Hz, 1H), 7.76-7.67 (m, 1H), 7.56 (d, $J$ = 4.2 Hz, 2H), 7.52 (s, 2H), 7.46 (d, $J$ = 6.4 Hz, 1H), 7.41 (d, $J$ = 6.3 Hz, 2H), 4.49 (s, 2H), 4.07 (s, 2H), 2.80 (s, 3H), 2.55 (s, 3H)。                            | 414                               |
| 75  | $^1H$ NMR (300 MHz, DMSO- $d_6$ ) $\delta$ 8.29 (s, 1H), 8.09 (q, $J$ = 4.3 Hz, 2H), 7.94 (d, $J$ = 5.8 Hz, 1H), 7.81 (t, $J$ = 6.4 Hz, 1H), 7.67 (dd, $J$ = 7.8, 4.3 Hz, 1H), 7.52 (dt, $J$ = 14.9, 4.9 Hz, 6H), 7.42-7.36 (m, 2H), 4.23 (d, $J$ = 3.5 Hz, 2H), 3.60 (d, $J$ = 3.8 Hz, 2H), 3.49 (d, $J$ = 4.1 Hz, 1H), 2.53 (s, 3H)。               | 399                               |
| 75s | $^1H$ NMR (300 MHz, DMSO- $d_6$ ) $\delta$ 9.02 (s, 1H), 8.29 (s, 1H), 8.09 (q, $J$ = 4.3 Hz, 2H), 7.94 (d, $J$ = 5.8 Hz, 1H), 7.81 (t, $J$ = 6.4 Hz, 1H), 7.67 (dd, $J$ = 7.8, 4.3 Hz, 1H), 7.52 (dt, $J$ = 14.9, 4.9 Hz, 6H), 7.42-7.36 (m, 2H), 4.23 (d, $J$ = 3.5 Hz, 2H), 3.60 (d, $J$ = 3.8 Hz, 2H), 3.49 (d, $J$ = 4.1 Hz, 1H), 2.53 (s, 3H)。 | 399                               |

|     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |     |
|-----|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|
| 76  | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.28 (s, 1H), 8.14 (d, <i>J</i> = 7.6 Hz, 1H), 8.11-8.07 (m, 1H), 7.98 (d, <i>J</i> = 7.9 Hz, 1H), 7.77-7.72 (m, 1H), 7.68 (d, <i>J</i> = 7.5 Hz, 1H), 7.55 (d, <i>J</i> = 4.6 Hz, 2H), 7.45 (d, <i>J</i> = 5.7 Hz, 1H), 7.40 (d, <i>J</i> = 7.9 Hz, 2H), 7.24 (t, <i>J</i> = 7.0 Hz, 1H), 4.24 (s, 2H), 3.90 (s, 3H), 3.84 (d, <i>J</i> = 7.0 Hz, 1H), 1.48 (d, <i>J</i> = 7.1 Hz, 3H).                                               | 414 |
| 76s | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.97 (s, 1H), 8.28 (s, 1H), 8.14 (d, <i>J</i> = 7.6 Hz, 1H), 8.11-8.07 (m, 1H), 7.98 (d, <i>J</i> = 7.9 Hz, 1H), 7.77-7.72 (m, 1H), 7.68 (d, <i>J</i> = 7.5 Hz, 1H), 7.55 (d, <i>J</i> = 4.6 Hz, 2H), 7.45 (d, <i>J</i> = 5.7 Hz, 1H), 7.40 (d, <i>J</i> = 7.9 Hz, 2H), 7.24 (t, <i>J</i> = 7.0 Hz, 1H), 4.24 (s, 2H), 3.84 (d, <i>J</i> = 7.0 Hz, 1H), 2.54 (s, 3H), 1.48 (d, <i>J</i> = 7.1 Hz, 3H).                                 | 414 |
| 77  | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.17 (s, 1H), 8.10-8.06 (m, 1H), 8.02 (d, <i>J</i> = 7.5 Hz, 1H), 7.62 (t, <i>J</i> = 6.6 Hz, 2H), 7.48 (s, 1H), 7.44 (d, <i>J</i> = 6.8 Hz, 1H), 7.39 (d, <i>J</i> = 7.5 Hz, 3H), 7.08 (d, <i>J</i> = 8.1 Hz, 1H), 6.81 (d, <i>J</i> = 8.4 Hz, 1H), 4.01 (s, 1H), 3.86 (d, <i>J</i> = 13.8 Hz, 2H), 3.66 (s, 3H), 3.26 (d, <i>J</i> = 5.1 Hz, 2H), 2.01 (s, 3H), 1.93-1.83 (m, 2H).                                                   | 474 |
| 77s | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 9.04 (s, 1H), 8.17 (s, 1H), 8.10-8.06 (m, 1H), 8.02 (d, <i>J</i> = 7.5 Hz, 1H), 7.62 (t, <i>J</i> = 6.6 Hz, 2H), 7.48 (s, 1H), 7.44 (d, <i>J</i> = 6.8 Hz, 1H), 7.39 (d, <i>J</i> = 7.5 Hz, 3H), 7.08 (d, <i>J</i> = 8.1 Hz, 1H), 6.81 (d, <i>J</i> = 8.4 Hz, 1H), 4.01 (s, 1H), 3.86 (d, <i>J</i> = 13.8 Hz, 2H), 3.26 (d, <i>J</i> = 5.1 Hz, 2H), 2.53 (s, 3H), 2.01 (s, 3H), 1.93-1.83 (m, 2H).                                     | 474 |
| 78  | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.09 (dd, <i>J</i> = 11.2, 6.2 Hz, 3H), 7.65 (d, <i>J</i> = 8.0 Hz, 2H), 7.54 (d, <i>J</i> = 4.6 Hz, 2H), 7.50 (d, <i>J</i> = 7.0 Hz, 2H), 7.45 (d, <i>J</i> = 6.8 Hz, 1H), 7.40 (d, <i>J</i> = 7.4 Hz, 2H), 4.06 (d, <i>J</i> = 13.0 Hz, 2H), 3.97 (s, 1H), 2.54 (s, 3H), 1.59-1.52 (m, 2H), 1.24 (s, 1H), 0.87 (dd, <i>J</i> = 13.2, 6.5 Hz, 6H).                                                                                    | 456 |
| 78s | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 9.02 (s, 1H), 8.09 (dd, <i>J</i> = 11.2, 6.2 Hz, 3H), 7.65 (d, <i>J</i> = 8.0 Hz, 2H), 7.54 (d, <i>J</i> = 4.6 Hz, 2H), 7.50 (d, <i>J</i> = 7.0 Hz, 2H), 7.45 (d, <i>J</i> = 6.8 Hz, 1H), 7.40 (d, <i>J</i> = 7.4 Hz, 2H), 4.06 (d, <i>J</i> = 13.0 Hz, 2H), 3.97 (s, 1H), 2.54 (s, 3H), 1.59-1.52 (m, 2H), 1.24 (s, 1H), 0.87 (dd, <i>J</i> = 13.2, 6.5 Hz, 6H).                                                                      | 456 |
| 79  | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.04 (d, <i>J</i> = 6.8 Hz, 3H), 7.66 (d, <i>J</i> = 7.8 Hz, 2H), 7.53 (d, <i>J</i> = 4.9 Hz, 2H), 7.51 (d, <i>J</i> = 7.8 Hz, 2H), 7.48 (d, <i>J</i> = 6.0 Hz, 1H), 7.41 (d, <i>J</i> = 7.2 Hz, 2H), 4.07 (d, <i>J</i> = 9.0 Hz, 2H), 3.98 (s, 1H), 2.56 (s, 3H), 1.58-1.53 (m, 2H), 1.42 (t, <i>J</i> = 8.5 Hz, 3H), 1.24 (s, 1H), 0.99 (d, <i>J</i> = 6.8 Hz, 3H).                                                                  | 456 |
| 79s | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.89 (s, 1H), 8.04 (d, <i>J</i> = 6.8 Hz, 3H), 7.66 (d, <i>J</i> = 7.8 Hz, 2H), 7.53 (d, <i>J</i> = 4.9 Hz, 2H), 7.51 (d, <i>J</i> = 7.8 Hz, 2H), 7.48 (d, <i>J</i> = 6.0 Hz, 1H), 7.41 (d, <i>J</i> = 7.2 Hz, 2H), 4.07 (d, <i>J</i> = 9.0 Hz, 2H), 3.98 (s, 1H), 2.56 (s, 3H), 1.58-1.53 (m, 2H), 1.42 (t, <i>J</i> = 8.5 Hz, 3H), 1.24 (s, 1H), 0.99 (d, <i>J</i> = 6.8 Hz, 3H).                                                    | 456 |
| 80  | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.57 (s, 1H), 8.18 (s, 1H), 8.05 (dd, <i>J</i> = 12.0, 5.8 Hz, 2H), 7.68 (d, <i>J</i> = 7.3 Hz, 1H), 7.61-7.55 (m, 3H), 7.54-7.48 (m, 4H), 7.48-7.41 (m, 2H), 7.38 (d, <i>J</i> = 7.0 Hz, 2H), 4.09-3.90 (m, 2H), 3.66 (s, 3H), 3.18 (d, <i>J</i> = 6.6 Hz, 1H), 3.10 (s, 2H), 1.70 (s, 2H), 1.65-1.55 (m, 2H).                                                                                                                        | 499 |
| 80s | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 9.02 (s, 1H), 8.57 (s, 1H), 8.18 (s, 1H), 8.05 (dd, <i>J</i> = 12.0, 5.8 Hz, 2H), 7.68 (d, <i>J</i> = 7.3 Hz, 1H), 7.61-7.55 (m, 3H), 7.54-7.48 (m, 4H), 7.48-7.41 (m, 2H), 7.38 (d, <i>J</i> = 7.0 Hz, 2H), 4.09-3.90 (m, 2H), 3.18 (d, <i>J</i> = 6.6 Hz, 1H), 3.10 (s, 2H), 2.51 (d, <i>J</i> = 2.1 Hz, 3H), 1.70 (s, 2H), 1.65-1.55 (m, 2H).                                                                                       | 499 |
| 81  | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.05 (s, 2H), 7.95 (s, 1H), 7.56-7.45 (m, 7H), 7.39 (d, <i>J</i> = 7.5 Hz, 3H), 7.29 (d, <i>J</i> = 8.1 Hz, 1H), 7.16 (s, 1H), 7.00 (t, <i>J</i> = 7.5 Hz, 1H), 6.89 (t, <i>J</i> = 7.5 Hz, 1H), 3.91 (d, <i>J</i> = 14.0 Hz, 2H), 3.77 (s, 1H), 3.13 (t, <i>J</i> = 10.0 Hz, 1H), 3.06-2.97 (m, 1H), 2.52 (s, 3H).                                                                                                                    | 490 |
| 81s | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.86 (s, 1H), 8.05 (s, 2H), 7.95 (s, 1H), 7.56-7.45 (m, 7H), 7.39 (d, <i>J</i> = 7.5 Hz, 3H), 7.29 (d, <i>J</i> = 8.1 Hz, 1H), 7.16 (s, 1H), 7.00 (t, <i>J</i> = 7.5 Hz, 1H), 6.89 (t, <i>J</i> = 7.5 Hz, 1H), 3.91 (d, <i>J</i> = 14.0 Hz, 2H), 3.77 (s, 1H), 3.13 (t, <i>J</i> = 10.0 Hz, 1H), 3.06-2.97 (m, 1H), 2.52 (s, 3H).                                                                                                      | 490 |
| 82  | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.07 (t, <i>J</i> = 4.6 Hz, 1H), 8.03 (s, 1H), 8.00 (s, 1H), 7.53 (d, <i>J</i> = 4.1 Hz, 2H), 7.48 (dd, <i>J</i> = 7.6, 3.5 Hz, 3H), 7.39 (d, <i>J</i> = 6.6 Hz, 2H), 7.08 (d, <i>J</i> = 8.0 Hz, 1H), 7.01 (d, <i>J</i> = 8.0 Hz, 2H), 6.80 (d, <i>J</i> = 8.0 Hz, 1H), 6.66 (d, <i>J</i> = 8.1 Hz, 2H), 3.90 (d, <i>J</i> = 11.2 Hz, 2H), 3.75 (s, 1H), 2.82 (t, <i>J</i> = 7.0 Hz, 2H), 2.52 (s, 3H).                               | 506 |
| 82s | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 9.22 (s, 1H), 8.07 (t, <i>J</i> = 4.6 Hz, 1H), 8.03 (s, 1H), 8.00 (s, 1H), 7.53 (d, <i>J</i> = 4.1 Hz, 2H), 7.48 (dd, <i>J</i> = 7.6, 3.5 Hz, 3H), 7.39 (d, <i>J</i> = 6.6 Hz, 2H), 7.08 (d, <i>J</i> = 8.0 Hz, 1H), 7.01 (d, <i>J</i> = 8.0 Hz, 2H), 6.80 (d, <i>J</i> = 8.0 Hz, 1H), 6.66 (d, <i>J</i> = 8.1 Hz, 2H), 3.90 (d, <i>J</i> = 11.2 Hz, 2H), 3.75 (s, 1H), 2.82 (t, <i>J</i> = 7.0 Hz, 2H), 2.52 (s, 3H).                 | 506 |
| 83  | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.11-8.06 (m, 2H), 7.97 (t, <i>J</i> = 4.7 Hz, 1H), 7.54 (d, <i>J</i> = 4.8 Hz, 3H), 7.50 (d, <i>J</i> = 5.8 Hz, 4H), 7.45 (d, <i>J</i> = 7.0 Hz, 1H), 7.42-7.38 (m, 2H), 7.30 (d, <i>J</i> = 8.0 Hz, 1H), 7.16-7.13 (m, 1H), 7.02 (t, <i>J</i> = 7.3 Hz, 1H), 6.91 (t, <i>J</i> = 7.2 Hz, 1H), 3.91 (s, 1H), 3.78 (d, <i>J</i> = 13.8 Hz, 2H), 3.10 (d, <i>J</i> = 6.1 Hz, 1H), 3.02 (dd, <i>J</i> = 14.4, 6.6 Hz, 2H), 2.53 (s, 3H). | 529 |
| 83s | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.83 (s, 1H), 8.11-8.06 (m, 2H), 7.97 (t, <i>J</i> = 4.7 Hz, 1H), 7.54 (d, <i>J</i> = 4.8 Hz, 3H), 7.50 (d, <i>J</i> = 5.8 Hz, 4H), 7.45 (d, <i>J</i> = 7.0 Hz, 1H), 7.42-7.38 (m, 2H), 7.30 (d, <i>J</i> = 8.0 Hz, 1H), 7.16-7.13 (m, 1H), 7.02 (t, <i>J</i> = 7.3 Hz, 1H), 6.91 (t, <i>J</i> = 7.2 Hz, 1H), 3.91 (s, 1H), 3.78 (d, <i>J</i> = 13.8 Hz, 2H), 3.10 (d, <i>J</i> = 6.1 Hz, 1H), 3.02 (dd, <i>J</i> = 14.4, 6.6 Hz, 2H), | 529 |

|     |                                                                                                                                                                                                                                                                                                                                                                                                                            |     |
|-----|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|
|     | 2.53 (s, 3H).                                                                                                                                                                                                                                                                                                                                                                                                              |     |
| 84  | <sup>1</sup> H NMR (300 MHz, Chloroform- <i>d</i> ) δ 8.25 (s, 1H), 8.09 (s, 2H), 8.00 (d, <i>J</i> = 7.5 Hz, 1H), 7.69 (s, 1H), 7.55 (d, <i>J</i> = 6.1 Hz, 1H), 7.47-7.39 (m, 4H), 7.35 (d, <i>J</i> = 7.7 Hz, 2H), 4.34-4.21 (m, 2H), 3.24-3.08 (m, 2H), 2.61 (dd, <i>J</i> = 11.2, 6.3 Hz, 2H), 2.52 (s, 3H)                                                                                                           | 414 |
| 84s | <sup>1</sup> H NMR (300 MHz, Chloroform- <i>d</i> ) δ 9.02 (s, 1H), 8.25 (s, 1H), 8.09 (s, 2H), 8.00 (d, <i>J</i> = 7.5 Hz, 1H), 7.69 (s, 1H), 7.55 (d, <i>J</i> = 6.1 Hz, 1H), 7.47-7.39 (m, 4H), 7.35 (d, <i>J</i> = 7.7 Hz, 2H), 4.34-4.21 (m, 2H), 3.24-3.08 (m, 2H), 2.61 (dd, <i>J</i> = 11.2, 6.3 Hz, 2H), 2.52 (s, 3H).                                                                                            | 414 |
| 85  | <sup>1</sup> H NMR (300 MHz, Chloroform- <i>d</i> ) δ 8.25-8.14 (m, 2H), 8.14-8.07 (m, 1H), 7.62-7.54 (m, 2H), 7.53-7.40 (m, 5H), 7.36 (t, <i>J</i> = 8.7 Hz, 2H), 7.10 (s, 2H), 4.08 (s, 1H), 3.16 (dd, <i>J</i> = 14.6, 7.2 Hz, 2H), 2.69-2.58 (m, 4H), 2.21 (s, 3H).                                                                                                                                                    | 413 |
| 85s | <sup>1</sup> H NMR (300 MHz, Chloroform- <i>d</i> ) δ 8.92 (s, 1H), 8.25-8.14 (m, 2H), 8.14-8.07 (m, 1H), 7.62-7.54 (m, 2H), 7.53-7.40 (m, 5H), 7.36 (t, <i>J</i> = 8.7 Hz, 2H), 7.10 (s, 2H), 4.08 (s, 1H), 3.16 (dd, <i>J</i> = 14.6, 7.2 Hz, 2H), 2.69-2.58 (m, 4H), 2.21 (s, 3H).                                                                                                                                      | 413 |
| 86  | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.23 (s, 1H), 8.10 (s, 2H), 7.76-7.62 (m, 2H), 7.59-7.47 (m, 5H), 7.44-7.37 (m, 2H), 4.13 (d, <i>J</i> = 11.6 Hz, 1H), 3.86 (s, 2H), 2.93 (d, <i>J</i> = 10.0 Hz, 1H), 2.54 (s, 3H), 2.31 (s, 1H), 1.95 (s, 2H), 1.82 (s, 1H), 1.23 (s, 1H)                                                                                                                   | 440 |
| 86s | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 9.02 (s, 1H), 8.23 (s, 1H), 8.10 (s, 2H), 7.76-7.62 (m, 2H), 7.59-7.47 (m, 5H), 7.44-7.37 (m, 2H), 4.13 (d, <i>J</i> = 11.6 Hz, 1H), 3.86 (s, 2H), 2.93 (d, <i>J</i> = 10.0 Hz, 1H), 2.54 (s, 3H), 2.31 (s, 1H), 1.95 (s, 2H), 1.82 (s, 1H), 1.23 (s, 1H).                                                                                                    | 440 |
| 87  | <sup>1</sup> H NMR (300 MHz, Chloroform- <i>d</i> ) δ 8.22-8.10 (m, 1H), 7.93 (d, <i>J</i> = 5.3 Hz, 1H), 7.83 (d, <i>J</i> = 6.9 Hz, 1H), 7.57 (dd, <i>J</i> = 15.3, 7.1 Hz, 1H), 7.49-7.40 (m, 1H), 7.32 (d, <i>J</i> = 6.1 Hz, 4H), 7.25-7.11 (m, 3H), 4.79-4.56 (m, 2H), 4.33 (s, 2H), 3.81 (d, <i>J</i> = 12.5 Hz, 2H), 3.29-3.12 (m, 1H), 2.71-2.46 (m, 2H), 2.36 (s, 3H).                                           | 456 |
| 87s | <sup>1</sup> H NMR (300 MHz, Chloroform- <i>d</i> ) δ 8.87 (s, 1H), 8.22-8.10 (m, 1H), 7.93 (d, <i>J</i> = 5.3 Hz, 1H), 7.83 (d, <i>J</i> = 6.9 Hz, 1H), 7.57 (dd, <i>J</i> = 15.3, 7.1 Hz, 1H), 7.49-7.40 (m, 1H), 7.32 (d, <i>J</i> = 6.1 Hz, 4H), 7.25-7.11 (m, 3H), 4.79-4.56 (m, 2H), 4.33 (s, 2H), 3.81 (d, <i>J</i> = 12.5 Hz, 2H), 3.29-3.12 (m, 1H), 2.71-2.46 (m, 2H), 2.36 (s, 3H).                             | 456 |
| 88  | <sup>1</sup> H NMR (300 MHz, Chloroform- <i>d</i> ) δ 8.23 (d, <i>J</i> = 10.5 Hz, 1H), 8.13-8.07 (m, 1H), 8.03-7.94 (m, 1H), 7.70-7.60 (m, 1H), 7.58-7.52 (m, 1H), 7.47-7.39 (m, 5H), 7.33 (d, <i>J</i> = 10.2 Hz, 2H), 4.40 (d, <i>J</i> = 12.9 Hz, 1H), 3.57 (s, 2H), 2.83-2.68 (m, 1H), 2.51 (s, 3H), 2.30 (d, <i>J</i> = 13.4 Hz, 1H), 2.14-1.71 (m, 4H), 1.53-1.35 (m, 1H), 1.27 (s, 1H).                            | 454 |
| 88s | <sup>1</sup> H NMR (300 MHz, Chloroform- <i>d</i> ) δ 9.02 (s, 1H), 8.23 (d, <i>J</i> = 10.5 Hz, 1H), 8.13-8.07 (m, 1H), 8.03-7.94 (m, 1H), 7.70-7.60 (m, 1H), 7.58-7.52 (m, 1H), 7.47-7.39 (m, 5H), 7.33 (d, <i>J</i> = 10.2 Hz, 2H), 4.40 (d, <i>J</i> = 12.9 Hz, 1H), 3.57 (s, 2H), 2.83-2.68 (m, 1H), 2.51 (s, 3H), 2.30 (d, <i>J</i> = 13.4 Hz, 1H), 2.14-1.71 (m, 4H), 1.53-1.35 (m, 1H), 1.27 (s, 1H).              | 454 |
| 89  | <sup>1</sup> H NMR (300 MHz, Chloroform- <i>d</i> ) δ 8.25-8.18 (m, 2H), 8.06 (d, <i>J</i> = 7.3 Hz, 1H), 7.73 (s, 1H), 7.59-7.53 (m, 1H), 7.47-7.39 (m, 5H), 7.34-7.30 (m, 2H), 4.34 (d, <i>J</i> = 12.2 Hz, 1H), 4.12-3.98 (m, 2H), 3.21 (s, 2H), 2.58 (s, 3H), 2.54-2.44 (m, 2H), 1.94 (s, 4H).                                                                                                                         | 454 |
| 89s | <sup>1</sup> H NMR (300 MHz, Chloroform- <i>d</i> ) δ 8.98 (s, 1H), 8.25-8.18 (m, 2H), 8.06 (d, <i>J</i> = 7.3 Hz, 1H), 7.73 (s, 1H), 7.59-7.53 (m, 1H), 7.47-7.39 (m, 5H), 7.34-7.30 (m, 2H), 4.34 (d, <i>J</i> = 12.2 Hz, 1H), 4.12-3.98 (m, 2H), 3.21 (s, 2H), 2.58 (s, 3H), 2.54-2.44 (m, 2H), 1.94 (s, 4H).                                                                                                           | 454 |
| 90  | <sup>1</sup> H NMR (300 MHz, Chloroform- <i>d</i> ) δ 8.29-8.20 (m, 2H), 8.10 (d, <i>J</i> = 6.8 Hz, 1H), 7.93-7.85 (m, 1H), 7.68-7.58 (m, 2H), 7.47 (dd, <i>J</i> = 13.3, 6.6 Hz, 4H), 7.38-7.33 (m, 2H), 5.44 (s, 2H), 4.21-4.12 (m, 1H), 4.09-3.98 (m, 1H), 3.24 (s, 2H), 2.93 (d, <i>J</i> = 8.7 Hz, 1H), 2.70 (d, <i>J</i> = 9.6 Hz, 1H), 2.61 (s, 3H), 2.21 (d, <i>J</i> = 10.3 Hz, 1H), 1.99 (s, 4H).               | 453 |
| 90s | <sup>1</sup> H NMR (300 MHz, Chloroform- <i>d</i> ) δ 9.02 (s, 1H), 8.29-8.20 (m, 2H), 8.10 (d, <i>J</i> = 6.8 Hz, 1H), 7.93-7.85 (m, 1H), 7.68-7.58 (m, 2H), 7.47 (dd, <i>J</i> = 13.3, 6.6 Hz, 4H), 7.38-7.33 (m, 2H), 5.44 (s, 2H), 4.21-4.12 (m, 1H), 4.09-3.98 (m, 1H), 3.24 (s, 2H), 2.93 (d, <i>J</i> = 8.7 Hz, 1H), 2.70 (d, <i>J</i> = 9.6 Hz, 1H), 2.61 (s, 3H), 2.21 (d, <i>J</i> = 10.3 Hz, 1H), 1.99 (s, 4H). | 453 |
| 91  | <sup>1</sup> H NMR (300 MHz, Chloroform- <i>d</i> ) δ 8.23-8.15 (m, 2H), 8.08 (d, <i>J</i> = 8.4 Hz, 1H), 7.67 (d, <i>J</i> = 5.7 Hz, 2H), 7.42 (d, <i>J</i> = 11.7 Hz, 5H), 7.33 (d, <i>J</i> = 5.9 Hz, 2H), 4.10 (s, 2H), 3.29 (s, 2H), 2.75 (s, 2H), 2.63 (d, <i>J</i> = 10.5 Hz, 1H), 2.58 (s, 3H), 2.14 (s, 4H).                                                                                                      | 454 |
| 91s | <sup>1</sup> H NMR (300 MHz, Chloroform- <i>d</i> ) δ 9.54 (s, 1H), 8.23-8.15 (m, 2H), 8.08 (d, <i>J</i> = 8.4 Hz, 1H), 7.67 (d, <i>J</i> = 5.7 Hz, 2H), 7.42 (d, <i>J</i> = 11.7 Hz, 5H), 7.33 (d, <i>J</i> = 5.9 Hz, 2H), 4.10 (s, 2H), 3.29 (s, 2H), 2.75 (s, 2H), 2.63 (d, <i>J</i> = 10.5 Hz, 1H), 2.58 (s, 3H), 2.14 (s, 4H).                                                                                        | 454 |
| 92  | <sup>1</sup> H NMR (300 MHz, Chloroform- <i>d</i> ) δ 8.23-8.16 (m, 2H), 8.10 (d, <i>J</i> = 6.7 Hz, 1H), 7.61 (d, <i>J</i> = 7.9 Hz, 1H), 7.55 (d, <i>J</i> = 7.9 Hz, 1H), 7.52-7.38 (m, 6H), 7.35 (d, <i>J</i> = 6.9 Hz, 2H), 4.05 (s, 2H), 3.77 (d, <i>J</i> = 14.8 Hz, 1H), 3.06 (s, 2H), 2.66 (s, 3H), 2.64-2.56 (m, 6H).                                                                                             | 413 |

|     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |     |
|-----|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|
| 92s | <sup>1</sup> H NMR (300 MHz, Chloroform- <i>d</i> ) δ 9.59 (s, 1H), 8.23-8.16 (m, 2H), 8.10 (d, <i>J</i> = 6.7 Hz, 1H), 7.61 (d, <i>J</i> = 7.9 Hz, 1H), 7.55 (d, <i>J</i> = 7.9 Hz, 1H), 7.52-7.38 (m, 6H), 7.35 (d, <i>J</i> = 6.9 Hz, 2H), 4.05 (s, 2H), 3.77 (d, <i>J</i> = 14.8 Hz, 1H), 3.06 (s, 2H), 2.66 (s, 3H), 2.64-2.56 (m, 6H).                                                                                                                                          | 413 |
| 93  | <sup>1</sup> H NMR (300 MHz, Chloroform- <i>d</i> ) δ 8.21 (d, <i>J</i> = 7.9 Hz, 2H), 8.05 (d, <i>J</i> = 7.5 Hz, 1H), 7.78 (d, <i>J</i> = 7.9 Hz, 2H), 7.49-7.42 (m, 4H), 7.38 (d, <i>J</i> = 7.4 Hz, 2H), 7.32 (t, <i>J</i> = 6.8 Hz, 2H), 4.27 (s, 2H), 3.95 (s, 2H), 3.74 (d, <i>J</i> = 7.3 Hz, 1H), 3.09 (s, 2H), 2.56 (s, 3H).                                                                                                                                                | 386 |
| 93s | <sup>1</sup> H NMR (300 MHz, Chloroform- <i>d</i> ) δ 9.49 (s, 1H), 8.21 (d, <i>J</i> = 7.9 Hz, 2H), 8.05 (d, <i>J</i> = 7.5 Hz, 1H), 7.78 (d, <i>J</i> = 7.9 Hz, 2H), 7.49-7.42 (m, 4H), 7.38 (d, <i>J</i> = 7.4 Hz, 2H), 7.32 (t, <i>J</i> = 6.8 Hz, 2H), 4.27 (s, 2H), 3.95 (s, 2H), 3.74 (d, <i>J</i> = 7.3 Hz, 1H), 3.09 (s, 2H), 2.56 (s, 3H).                                                                                                                                  | 386 |
| 94  | <sup>1</sup> H NMR (300 MHz, Chloroform- <i>d</i> ) δ 8.27 (d, <i>J</i> = 8.0 Hz, 2H), 8.09 (d, <i>J</i> = 7.0 Hz, 1H), 7.97 (d, <i>J</i> = 7.5 Hz, 1H), 7.65 (t, <i>J</i> = 7.6 Hz, 1H), 7.50-7.44 (m, 4H), 7.42-7.39 (m, 1H), 7.37-7.31 (m, 2H), 4.38 (s, 2H), 4.29 (s, 1H), 4.04 (t, <i>J</i> = 4.7 Hz, 2H), 3.24 (t, <i>J</i> = 4.7 Hz, 2H), 2.86 (s, 3H), 2.60 (s, 3H).                                                                                                          | 400 |
| 94s | <sup>1</sup> H NMR (300 MHz, Chloroform- <i>d</i> ) δ 9.54 (s, 1H), 8.27 (d, <i>J</i> = 8.0 Hz, 2H), 8.09 (d, <i>J</i> = 7.0 Hz, 1H), 7.97 (d, <i>J</i> = 7.5 Hz, 1H), 7.65 (t, <i>J</i> = 7.6 Hz, 1H), 7.50-7.44 (m, 4H), 7.42-7.39 (m, 1H), 7.37-7.31 (m, 2H), 4.38 (s, 2H), 4.29 (s, 1H), 4.04 (t, <i>J</i> = 4.7 Hz, 2H), 3.24 (t, <i>J</i> = 4.7 Hz, 2H), 2.86 (s, 3H), 2.60 (s, 3H).                                                                                            | 400 |
| 95  | <sup>1</sup> H NMR (300 MHz, Chloroform- <i>d</i> ) δ 8.25 (s, 1H), 8.15 (d, <i>J</i> = 7.7 Hz, 1H), 8.11-8.05 (m, 1H), 7.71 (d, <i>J</i> = 7.5 Hz, 1H), 7.57-7.50 (m, 2H), 7.49-7.40 (m, 4H), 7.37-7.31 (m, 2H), 4.26 (d, <i>J</i> = 12.7 Hz, 1H), 4.06 (d, <i>J</i> = 12.8 Hz, 1H), 3.81 (d, <i>J</i> = 10.9 Hz, 1H), 3.61 (dd, <i>J</i> = 11.8, 6.8 Hz, 2H), 3.23-3.12 (m, 1H), 2.58 (s, 3H), 1.32 (d, <i>J</i> = 6.3 Hz, 3H).                                                     | 400 |
| 95s | <sup>1</sup> H NMR (300 MHz, Chloroform- <i>d</i> ) δ 9.50 (s, 1H), 8.25 (s, 1H), 8.15 (d, <i>J</i> = 7.7 Hz, 1H), 8.11-8.05 (m, 1H), 7.71 (d, <i>J</i> = 7.5 Hz, 1H), 7.57-7.50 (m, 2H), 7.49-7.40 (m, 4H), 7.37-7.31 (m, 2H), 4.26 (d, <i>J</i> = 12.7 Hz, 1H), 4.06 (d, <i>J</i> = 12.8 Hz, 1H), 3.81 (d, <i>J</i> = 10.9 Hz, 1H), 3.61 (dd, <i>J</i> = 11.8, 6.8 Hz, 2H), 3.23-3.12 (m, 1H), 2.58 (s, 3H), 1.32 (d, <i>J</i> = 6.3 Hz, 3H).                                       | 400 |
| 96  | <sup>1</sup> H NMR (300 MHz, Chloroform- <i>d</i> ) δ 8.22 (s, 1H), 8.15 (d, <i>J</i> = 7.2 Hz, 1H), 8.11-8.06 (m, 1H), 7.65 (d, <i>J</i> = 7.9 Hz, 1H), 7.55 (d, <i>J</i> = 7.8 Hz, 1H), 7.47 (ddd, <i>J</i> = 11.1, 7.5, 3.1 Hz, 4H), 7.42-7.39 (m, 1H), 7.38-7.32 (m, 2H), 4.18 (d, <i>J</i> = 13.8 Hz, 1H), 3.99 (d, <i>J</i> = 12.9 Hz, 2H), 3.76 (d, <i>J</i> = 9.3 Hz, 1H), 3.60-3.48 (m, 1H), 3.13-3.04 (m, 1H), 2.60 (s, 3H), 1.26 (d, <i>J</i> = 6.5 Hz, 3H).               | 400 |
| 96s | <sup>1</sup> H NMR (300 MHz, Chloroform- <i>d</i> ) δ 9.52 (s, 1H), 8.22 (s, 1H), 8.15 (d, <i>J</i> = 7.2 Hz, 1H), 8.11-8.06 (m, 1H), 7.65 (d, <i>J</i> = 7.9 Hz, 1H), 7.55 (d, <i>J</i> = 7.8 Hz, 1H), 7.47 (ddd, <i>J</i> = 11.1, 7.5, 3.1 Hz, 4H), 7.42-7.39 (m, 1H), 7.38-7.32 (m, 2H), 4.18 (d, <i>J</i> = 13.8 Hz, 1H), 3.99 (d, <i>J</i> = 12.9 Hz, 2H), 3.76 (d, <i>J</i> = 9.3 Hz, 1H), 3.60-3.48 (m, 1H), 3.13-3.04 (m, 1H), 2.60 (s, 3H), 1.26 (d, <i>J</i> = 6.5 Hz, 3H). | 400 |
| 97  | <sup>1</sup> H NMR (300 MHz, Chloroform- <i>d</i> ) δ 8.32 (s, 1H), 8.19 (d, <i>J</i> = 7.3 Hz, 1H), 8.07 (d, <i>J</i> = 6.4 Hz, 1H), 7.87 (d, <i>J</i> = 7.5 Hz, 1H), 7.62-7.52 (m, 2H), 7.49-7.39 (m, 4H), 7.37-7.30 (m, 2H), 4.39 (s, 1H), 4.31 (s, 2H), 2.97 (d, <i>J</i> = 11.8 Hz, 2H), 2.90-2.81 (m, 1H), 2.58 (s, 3H), 1.19 (d, <i>J</i> = 6.1 Hz, 3H).                                                                                                                       | 400 |
| 97s | <sup>1</sup> H NMR (300 MHz, Chloroform- <i>d</i> ) δ 9.56 (s, 1H), 8.32 (s, 1H), 8.19 (d, <i>J</i> = 7.3 Hz, 1H), 8.07 (d, <i>J</i> = 6.4 Hz, 1H), 7.87 (d, <i>J</i> = 7.5 Hz, 1H), 7.62-7.52 (m, 2H), 7.49-7.39 (m, 4H), 7.37-7.30 (m, 2H), 4.39 (s, 1H), 4.31 (s, 2H), 2.97 (d, <i>J</i> = 11.8 Hz, 2H), 2.90-2.81 (m, 1H), 2.58 (s, 3H), 1.19 (d, <i>J</i> = 6.1 Hz, 3H).                                                                                                         | 400 |
| 98  | <sup>1</sup> H NMR (300 MHz, Chloroform- <i>d</i> ) δ 8.31 (s, 1H), 8.19 (d, <i>J</i> = 7.3 Hz, 1H), 8.07 (d, <i>J</i> = 6.8 Hz, 1H), 7.87 (d, <i>J</i> = 7.0 Hz, 1H), 7.61-7.52 (m, 2H), 7.49-7.39 (m, 4H), 7.33 (d, <i>J</i> = 7.2 Hz, 2H), 4.35 (s, 1H), 4.30 (s, 2H), 2.97 (d, <i>J</i> = 11.6 Hz, 2H), 2.88-2.79 (m, 1H), 2.58 (s, 3H), 1.19 (d, <i>J</i> = 5.7 Hz, 3H).                                                                                                         | 400 |
| 98s | <sup>1</sup> H NMR (300 MHz, Chloroform- <i>d</i> ) δ 9.61 (s, 1H), 8.31 (s, 1H), 8.19 (d, <i>J</i> = 7.3 Hz, 1H), 8.07 (d, <i>J</i> = 6.8 Hz, 1H), 7.87 (d, <i>J</i> = 7.0 Hz, 1H), 7.61-7.52 (m, 2H), 7.49-7.39 (m, 4H), 7.33 (d, <i>J</i> = 7.2 Hz, 2H), 4.35 (s, 1H), 4.30 (s, 2H), 2.97 (d, <i>J</i> = 11.6 Hz, 2H), 2.88-2.79 (m, 1H), 2.58 (s, 3H), 1.19 (d, <i>J</i> = 5.7 Hz, 3H).                                                                                           | 400 |
| 99  | <sup>1</sup> H NMR (300 MHz, Chloroform- <i>d</i> ) δ 8.29 (s, 1H), 8.07 (dd, <i>J</i> = 14.0, 7.7 Hz, 2H), 7.85 (d, <i>J</i> = 7.3 Hz, 1H), 7.50 (d, <i>J</i> = 8.1 Hz, 1H), 7.43 (dd, <i>J</i> = 14.9, 7.7 Hz, 5H), 7.32 (d, <i>J</i> = 7.0 Hz, 2H), 4.14 (s, 2H), 3.66 (s, 2H), 3.52 (s, 1H), 2.56 (s, 3H), 1.39 (s, 6H).                                                                                                                                                          | 414 |
| 99s | <sup>1</sup> H NMR (300 MHz, Chloroform- <i>d</i> ) δ 9.63 (s, 1H), 8.29 (s, 1H), 8.07 (dd, <i>J</i> = 14.0, 7.7 Hz, 2H), 7.85 (d, <i>J</i> = 7.3 Hz, 1H), 7.50 (d, <i>J</i> = 8.1 Hz, 1H), 7.43 (dd, <i>J</i> = 14.9, 7.7 Hz, 5H), 7.32 (d, <i>J</i> = 7.0 Hz, 2H), 4.14 (s, 2H), 3.66 (s, 2H), 3.52 (s, 1H), 2.56 (s, 3H), 1.39 (s, 6H).                                                                                                                                            | 414 |
| 100 | <sup>1</sup> H NMR (300 MHz, Chloroform- <i>d</i> ) δ 8.22 (d, <i>J</i> = 8.0 Hz, 2H), 8.07 (d, <i>J</i> = 6.9 Hz, 1H), 7.82 (d, <i>J</i> = 8.1 Hz, 2H), 7.50-7.41                                                                                                                                                                                                                                                                                                                    | 414 |

|      |                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |     |
|------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|
|      | (m, 4H), 7.41-7.36 (m, 1H), 7.32 (d, $J = 6.7$ Hz, 2H), 4.57 (s, 1H), 4.34 (s, 2H), 2.91 (s, 2H), 2.57 (s, 3H), 1.41 (s, 6H).                                                                                                                                                                                                                                                                                                                                          |     |
| 100s | <sup>1</sup> H NMR (300 MHz, Chloroform- <i>d</i> ) $\delta$ 9.53 (s, 1H), 8.22 (d, $J = 8.0$ Hz, 2H), 8.07 (d, $J = 6.9$ Hz, 1H), 7.82 (d, $J = 8.1$ Hz, 2H), 7.50-7.41 (m, 4H), 7.41-7.36 (m, 1H), 7.32 (d, $J = 6.7$ Hz, 2H), 4.57 (s, 1H), 4.34 (s, 2H), 2.91 (s, 2H), 2.57 (s, 3H), 1.41 (s, 6H).                                                                                                                                                                 | 414 |
| 101  | <sup>1</sup> H NMR (300 MHz, Chloroform- <i>d</i> ) $\delta$ 8.31 (s, 1H), 8.14 (d, $J = 7.7$ Hz, 1H), 8.03 (d, $J = 7.5$ Hz, 1H), 7.86 (d, $J = 7.5$ Hz, 1H), 7.53 (t, $J = 9.2$ Hz, 2H), 7.47-7.40 (m, 3H), 7.38 (d, $J = 7.3$ Hz, 1H), 7.35-7.28 (m, 2H), 5.73 (s, 1H), 4.26 (s, 2H), 3.78 (t, $J = 5.6$ Hz, 2H), 3.14 (t, $J = 6.2$ Hz, 2H), 2.55 (s, 3H), 2.07-1.96 (m, 2H).                                                                                      | 400 |
| 101s | <sup>1</sup> H NMR (300 MHz, Chloroform- <i>d</i> ) $\delta$ 9.55 (s, 1H), 8.31 (s, 1H), 8.14 (d, $J = 7.7$ Hz, 1H), 8.03 (d, $J = 7.5$ Hz, 1H), 7.86 (d, $J = 7.5$ Hz, 1H), 7.53 (t, $J = 9.2$ Hz, 2H), 7.47-7.40 (m, 3H), 7.38 (d, $J = 7.3$ Hz, 1H), 7.35-7.28 (m, 2H), 5.73 (s, 1H), 4.26 (s, 2H), 3.78 (t, $J = 5.6$ Hz, 2H), 3.14 (t, $J = 6.2$ Hz, 2H), 2.55 (s, 3H), 2.07-1.96 (m, 2H).                                                                        | 400 |
| 102  | <sup>1</sup> H NMR (300 MHz, Chloroform- <i>d</i> ) $\delta$ 8.37 (s, 1H), 8.22 (d, $J = 7.3$ Hz, 2H), 8.11 (d, $J = 6.7$ Hz, 1H), 7.79 (d, $J = 7.6$ Hz, 1H), 7.60-7.54 (m, 2H), 7.50-7.43 (m, 4H), 7.36 (d, $J = 7.5$ Hz, 1H), 4.83 (s, 1H), 4.40 (d, $J = 4.6$ Hz, 2H), 4.39-4.32 (m, 2H), 3.99 (s, 2H), 2.62 (s, 3H).                                                                                                                                              | 402 |
| 102s | <sup>1</sup> H NMR (300 MHz, Chloroform- <i>d</i> ) $\delta$ 9.53 (s, 1H), 8.37 (s, 1H), 8.22 (d, $J = 7.3$ Hz, 2H), 8.11 (d, $J = 6.7$ Hz, 1H), 7.79 (d, $J = 7.6$ Hz, 1H), 7.60-7.54 (m, 2H), 7.50-7.43 (m, 4H), 7.36 (d, $J = 7.5$ Hz, 1H), 4.83 (s, 1H), 4.40 (d, $J = 4.6$ Hz, 2H), 4.39-4.32 (m, 2H), 3.99 (s, 2H), 2.62 (s, 3H).                                                                                                                                | 402 |
| 103  | <sup>1</sup> H NMR (300 MHz, Chloroform- <i>d</i> ) $\delta$ 8.21 (s, 2H), 8.01 (d, $J = 7.8$ Hz, 1H), 7.74-7.65 (m, 2H), 7.51-7.42 (m, 5H), 7.31 (d, $J = 7.1$ Hz, 2H), 4.10 (d, $J = 11.1$ Hz, 2H), 3.80-3.58 (m, 4H), 3.21 (m, 1H), 2.61 (d, $J = 10.5$ Hz, 2H), 2.57 (s, 3H).                                                                                                                                                                                      | 416 |
| 103s | <sup>1</sup> H NMR (300 MHz, Chloroform- <i>d</i> ) $\delta$ 9.63 (s, 1H), 8.21 (s, 2H), 8.01 (d, $J = 7.8$ Hz, 1H), 7.74-7.65 (m, 2H), 7.51-7.42 (m, 5H), 7.31 (d, $J = 7.1$ Hz, 2H), 4.10 (d, $J = 11.1$ Hz, 2H), 3.80-3.58 (m, 4H), 3.21 (m, 1H), 2.61 (d, $J = 10.5$ Hz, 2H), 2.57 (s, 3H).                                                                                                                                                                        | 416 |
| 104  | <sup>1</sup> H NMR (300 MHz, Chloroform- <i>d</i> ) $\delta$ 8.25-8.13 (m, 2H), 8.06 (d, $J = 7.1$ Hz, 1H), 7.75-7.64 (m, 2H), 7.50-7.39 (m, 5H), 7.35-7.29 (m, 2H), 4.10 (d, $J = 12.1$ Hz, 2H), 3.80-3.58 (m, 4H), 2.64 (d, $J = 10.5$ Hz, 2H), 2.57 (s, 3H), 1.16 (s, 3H).                                                                                                                                                                                          | 430 |
| 104s | <sup>1</sup> H NMR (300 MHz, Chloroform- <i>d</i> ) $\delta$ 9.55 (s, 1H), 8.25-8.13 (m, 2H), 8.06 (d, $J = 7.1$ Hz, 1H), 7.75-7.64 (m, 2H), 7.50-7.39 (m, 5H), 7.35-7.29 (m, 2H), 4.10 (d, $J = 12.1$ Hz, 2H), 3.80-3.58 (m, 4H), 2.64 (d, $J = 10.5$ Hz, 2H), 2.57 (s, 3H), 1.16 (s, 3H).                                                                                                                                                                            | 430 |
| 105  | <sup>1</sup> H NMR (300 MHz, Chloroform- <i>d</i> ) $\delta$ 8.18 (d, $J = 8.3$ Hz, 2H), 8.11 (d, $J = 7.3$ Hz, 1H), 7.55 (d, $J = 8.0$ Hz, 2H), 7.47 (dd, $J = 4.7, 2.7$ Hz, 3H), 7.42 (dd, $J = 7.0, 3.5$ Hz, 2H), 7.36 (d, $J = 6.4$ Hz, 2H), 3.82 (s, 2H), 3.67-3.59 (m, 4H), 2.62 (s, 3H), 2.08 (s, 2H), 1.60-1.51 (m, 2H), 0.98 (t, $J = 7.5$ Hz, 3H).                                                                                                           | 444 |
| 105s | <sup>1</sup> H NMR (300 MHz, Chloroform- <i>d</i> ) $\delta$ 9.50 (s, 1H), 8.18 (d, $J = 8.3$ Hz, 2H), 8.11 (d, $J = 7.3$ Hz, 1H), 7.55 (d, $J = 8.0$ Hz, 2H), 7.47 (dd, $J = 4.7, 2.7$ Hz, 3H), 7.42 (dd, $J = 7.0, 3.5$ Hz, 2H), 7.36 (d, $J = 6.4$ Hz, 2H), 3.82 (s, 2H), 3.67-3.59 (m, 4H), 2.62 (s, 3H), 2.08 (s, 2H), 1.60-1.51 (m, 2H), 0.98 (t, $J = 7.5$ Hz, 3H).                                                                                             | 444 |
| 106  | <sup>1</sup> H NMR (300 MHz, Chloroform- <i>d</i> ) $\delta$ 8.21 (s, 1H), 8.16-8.09 (m, 2H), 7.56 (s, 2H), 7.44 (d, $J = 8.3$ Hz, 5H), 7.38-7.33 (m, 2H), 4.83 (s, 3H), 4.00 (s, 1H), 3.84-3.75 (m, 2H), 2.62 (s, 3H), 2.05 (s, 6H).                                                                                                                                                                                                                                  | 446 |
| 106s | <sup>1</sup> H NMR (300 MHz, Chloroform- <i>d</i> ) $\delta$ 9.53 (s, 1H), 8.21 (s, 1H), 8.16-8.09 (m, 2H), 7.56 (s, 2H), 7.44 (d, $J = 8.3$ Hz, 5H), 7.38-7.33 (m, 2H), 4.83 (s, 3H), 4.00 (s, 1H), 3.84-3.75 (m, 2H), 2.62 (s, 3H), 2.05 (s, 6H).                                                                                                                                                                                                                    | 446 |
| 107  | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) $\delta$ 8.12 (dd, $J = 13.0, 5.8$ Hz, 2H), 7.81 (d, $J = 7.0$ Hz, 1H), 7.72-7.64 (m, 1H), 7.57-7.48 (m, 5H), 7.42 (d, $J = 4.2$ Hz, 3H), 5.81 (s, 1H), 5.40 (s, 1H), 5.32 (s, 1H), 4.66-4.31 (m, 3H), 4.12 (d, $J = 9.8$ Hz, 1H), 3.94-3.81 (m, 1H), 3.62 (d, $J = 9.0$ Hz, 2H), 3.52 (d, $J = 7.3$ Hz, 1H), 3.23-3.14 (m, 1H), 2.90 (d, $J = 3.8$ Hz, 1H), 2.78-2.67 (m, 1H), 2.54 (s, 3H).               | 504 |
| 107s | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) $\delta$ 9.57 (s, 1H), 8.12 (dd, $J = 13.0, 5.8$ Hz, 2H), 7.81 (d, $J = 7.0$ Hz, 1H), 7.72-7.64 (m, 1H), 7.57-7.48 (m, 5H), 7.42 (d, $J = 4.2$ Hz, 3H), 5.81 (s, 1H), 5.40 (s, 1H), 5.32 (s, 1H), 4.66-4.31 (m, 3H), 4.12 (d, $J = 9.8$ Hz, 1H), 3.94-3.81 (m, 1H), 3.62 (d, $J = 9.0$ Hz, 2H), 3.52 (d, $J = 7.3$ Hz, 1H), 3.23-3.14 (m, 1H), 2.90 (d, $J = 3.8$ Hz, 1H), 2.78-2.67 (m, 1H), 2.54 (s, 3H). | 504 |
| 108  | <sup>1</sup> H NMR (300 MHz, Chloroform- <i>d</i> ) $\delta$ 8.23-8.15 (m, 2H), 8.10 (d, $J = 7.5$ Hz, 1H), 7.51 (d, $J = 9.3$ Hz, 2H), 7.49-7.39 (m, 6H), 7.35 (d, $J = 6.8$ Hz, 2H), 3.89 (s, 2H), 3.72 (s, 2H), 2.85 (s, 4H), 2.61 (s, 3H).                                                                                                                                                                                                                         | 430 |
| 108s | <sup>1</sup> H NMR (300 MHz, Chloroform- <i>d</i> ) $\delta$ 9.51 (s, 1H), 8.23-8.15 (m, 2H), 8.10 (d, $J = 7.5$ Hz, 1H), 7.51 (d, $J = 9.3$ Hz, 2H), 7.49-7.39 (m, 6H), 7.35 (d, $J = 6.8$ Hz, 2H), 3.89 (s, 2H), 3.72 (s, 2H), 2.85 (s, 4H), 2.61 (s, 3H).                                                                                                                                                                                                           | 430 |

|      |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |     |
|------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|
| 109  | <sup>1</sup> H NMR (300 MHz, Chloroform- <i>d</i> ) δ 8.29-8.21 (m, 2H), 8.08 (d, <i>J</i> = 7.5 Hz, 1H), 7.97 (d, <i>J</i> = 7.6 Hz, 1H), 7.62 (t, <i>J</i> = 7.5 Hz, 1H), 7.44 (dq, <i>J</i> = 10.3, 7.2 Hz, 5H), 7.33 (d, <i>J</i> = 6.6 Hz, 2H), 4.64 (s, 2H), 4.38 (q, <i>J</i> = 13.4 Hz, 2H), 3.60 (q, <i>J</i> = 8.4, 7.7 Hz, 1H), 3.46 (d, <i>J</i> = 12.5 Hz, 1H), 3.35 (d, <i>J</i> = 11.5 Hz, 1H), 3.29-3.16 (m, 1H), 2.59 (s, 3H), 2.38 (td, <i>J</i> = 10.5, 8.3 Hz, 1H), 2.20 (dd, <i>J</i> = 10.0, 6.9 Hz, 1H).               | 413 |
| 109s | <sup>1</sup> H NMR (300 MHz, Chloroform- <i>d</i> ) δ 9.53 (s, 1H), 8.29-8.21 (m, 2H), 8.08 (d, <i>J</i> = 7.5 Hz, 1H), 7.97 (d, <i>J</i> = 7.6 Hz, 1H), 7.62 (t, <i>J</i> = 7.5 Hz, 1H), 7.44 (dq, <i>J</i> = 10.3, 7.2 Hz, 5H), 7.33 (d, <i>J</i> = 6.6 Hz, 2H), 4.64 (s, 2H), 4.38 (q, <i>J</i> = 13.4 Hz, 2H), 3.60 (q, <i>J</i> = 8.4, 7.7 Hz, 1H), 3.46 (d, <i>J</i> = 12.5 Hz, 1H), 3.35 (d, <i>J</i> = 11.5 Hz, 1H), 3.29-3.16 (m, 1H), 2.59 (s, 3H), 2.38 (td, <i>J</i> = 10.5, 8.3 Hz, 1H), 2.20 (dd, <i>J</i> = 10.0, 6.9 Hz, 1H). | 413 |
| 110  | <sup>1</sup> H NMR (300 MHz, Chloroform- <i>d</i> ) δ 8.24 (d, <i>J</i> = 6.7 Hz, 2H), 8.08 (d, <i>J</i> = 7.5 Hz, 1H), 7.82 (s, 2H), 7.42 (dt, <i>J</i> = 14.3, 6.8 Hz, 5H), 7.33 (d, <i>J</i> = 7.1 Hz, 2H), 4.43 (s, 2H), 4.28 (s, 1H), 3.68 (d, <i>J</i> = 15.0 Hz, 1H), 3.35 (s, 1H), 2.89-2.63 (m, 3H), 2.59 (s, 3H), 2.19 (s, 1H), 2.09-1.74 (m, 2H), 1.50 (s, 1H).                                                                                                                                                                    | 426 |
| 110s | <sup>1</sup> H NMR (300 MHz, Chloroform- <i>d</i> ) δ 9.56 (s, 1H), 8.24 (d, <i>J</i> = 6.7 Hz, 2H), 8.08 (d, <i>J</i> = 7.5 Hz, 1H), 7.82 (s, 2H), 7.42 (dt, <i>J</i> = 14.3, 6.8 Hz, 5H), 7.33 (d, <i>J</i> = 7.1 Hz, 2H), 4.43 (s, 2H), 4.28 (s, 1H), 3.68 (d, <i>J</i> = 15.0 Hz, 1H), 3.35 (s, 1H), 2.89-2.63 (m, 3H), 2.59 (s, 3H), 2.19 (s, 1H), 2.09-1.74 (m, 2H), 1.50 (s, 1H).                                                                                                                                                      | 426 |
| 111  | <sup>1</sup> H NMR (300 MHz, Chloroform- <i>d</i> ) δ 8.29-8.15 (m, 2H), 8.13-7.95 (m, 2H), 7.66-7.52 (m, 2H), 7.50-7.35 (m, 5H), 7.31 (d, <i>J</i> = 4.6 Hz, 1H), 4.18 (s, 1H), 3.54 (d, <i>J</i> = 2.9 Hz, 2H), 3.45 (s, 2H), 2.67 (d, <i>J</i> = 8.9 Hz, 2H), 2.57 (s, 3H), 1.92 (s, 4H), 1.71 (s, 1H).                                                                                                                                                                                                                                    | 426 |
| 111s | <sup>1</sup> H NMR (300 MHz, Chloroform- <i>d</i> ) δ 9.50 (s, 1H), 8.29-8.15 (m, 2H), 8.13-7.95 (m, 2H), 7.66-7.52 (m, 2H), 7.50-7.35 (m, 5H), 7.31 (d, <i>J</i> = 4.6 Hz, 1H), 4.18 (s, 1H), 3.54 (d, <i>J</i> = 2.9 Hz, 2H), 3.45 (s, 2H), 2.67 (d, <i>J</i> = 8.9 Hz, 2H), 2.57 (s, 3H), 1.92 (s, 4H), 1.71 (s, 1H).                                                                                                                                                                                                                      | 426 |
| 112  | <sup>1</sup> H NMR (300 MHz, Chloroform- <i>d</i> ) δ 8.28-8.21 (m, 2H), 8.09-8.00 (m, 2H), 7.61 (t, <i>J</i> = 7.7 Hz, 1H), 7.48-7.39 (m, 5H), 7.35-7.30 (m, 2H), 4.24 (s, 2H), 4.12 (s, 1H), 3.39-3.27 (m, 2H), 3.15 (s, 2H), 2.64 (d, <i>J</i> = 16.0 Hz, 2H), 2.58 (s, 3H), 2.43-2.30 (m, 2H), 2.00 (d, <i>J</i> = 13.3 Hz, 2H).                                                                                                                                                                                                          | 440 |
| 112s | <sup>1</sup> H NMR (300 MHz, Chloroform- <i>d</i> ) δ 9.51 (s, 1H), 8.28-8.21 (m, 2H), 8.09-8.00 (m, 2H), 7.61 (t, <i>J</i> = 7.7 Hz, 1H), 7.48-7.39 (m, 5H), 7.35-7.30 (m, 2H), 4.24 (s, 2H), 4.12 (s, 1H), 3.39-3.27 (m, 2H), 3.15 (s, 2H), 2.64 (d, <i>J</i> = 16.0 Hz, 2H), 2.58 (s, 3H), 2.43-2.30 (m, 2H), 2.00 (d, <i>J</i> = 13.3 Hz, 2H).                                                                                                                                                                                            | 440 |
| 113  | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.29 (s, 1H), 8.08 (dd, <i>J</i> = 9.4, 5.8 Hz, 2H), 7.79 (d, <i>J</i> = 7.7 Hz, 1H), 7.62 (t, <i>J</i> = 7.7 Hz, 1H), 7.52 (d, <i>J</i> = 4.5 Hz, 2H), 7.48 (d, <i>J</i> = 7.0 Hz, 2H), 7.44 (d, <i>J</i> = 6.8 Hz, 1H), 7.38 (d, <i>J</i> = 7.7 Hz, 2H), 4.26 (s, 2H), 3.89 (d, <i>J</i> = 18.1 Hz, 2H), 3.71 (d, <i>J</i> = 4.3 Hz, 1H), 2.52 (s, 3H).                                                                                                                        | 430 |
| 113s | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 9.62 (s, 1H), 8.29 (s, 1H), 8.08 (dd, <i>J</i> = 9.4, 5.8 Hz, 2H), 7.79 (d, <i>J</i> = 7.7 Hz, 1H), 7.62 (t, <i>J</i> = 7.7 Hz, 1H), 7.52 (d, <i>J</i> = 4.5 Hz, 2H), 7.48 (d, <i>J</i> = 7.0 Hz, 2H), 7.44 (d, <i>J</i> = 6.8 Hz, 1H), 7.38 (d, <i>J</i> = 7.7 Hz, 2H), 4.26 (s, 2H), 3.89 (d, <i>J</i> = 18.1 Hz, 2H), 3.71 (d, <i>J</i> = 4.3 Hz, 1H), 2.52 (s, 3H).                                                                                                          | 430 |
| 114  | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.22 (s, 1H), 8.11-8.02 (m, 2H), 7.68 (d, <i>J</i> = 7.8 Hz, 1H), 7.60 (t, <i>J</i> = 7.6 Hz, 1H), 7.53 (d, <i>J</i> = 4.5 Hz, 2H), 7.51-7.46 (m, 2H), 7.44 (d, <i>J</i> = 6.6 Hz, 1H), 7.42-7.37 (m, 2H), 4.15 (d, <i>J</i> = 13.5 Hz, 1H), 3.98 (d, <i>J</i> = 13.3 Hz, 2H), 3.17 (d, <i>J</i> = 5.1 Hz, 1H), 2.53 (s, 3H), 1.17 (d, <i>J</i> = 6.3 Hz, 3H).                                                                                                                   | 444 |
| 114s | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 9.52 (s, 1H), 8.22 (s, 1H), 8.11-8.02 (m, 2H), 7.68 (d, <i>J</i> = 7.8 Hz, 1H), 7.60 (t, <i>J</i> = 7.6 Hz, 1H), 7.53 (d, <i>J</i> = 4.5 Hz, 2H), 7.51-7.46 (m, 2H), 7.44 (d, <i>J</i> = 6.6 Hz, 1H), 7.42-7.37 (m, 2H), 4.15 (d, <i>J</i> = 13.5 Hz, 1H), 3.98 (d, <i>J</i> = 13.3 Hz, 2H), 3.17 (d, <i>J</i> = 5.1 Hz, 1H), 2.53 (s, 3H), 1.17 (d, <i>J</i> = 6.3 Hz, 3H).                                                                                                     | 444 |
| 115  | <sup>1</sup> H NMR (300 MHz, Chloroform- <i>d</i> ) δ 8.18 (d, <i>J</i> = 8.1 Hz, 2H), 8.12 (d, <i>J</i> = 6.3 Hz, 1H), 7.58 (d, <i>J</i> = 8.1 Hz, 2H), 7.45 (ddd, <i>J</i> = 15.6, 5.7, 2.6 Hz, 5H), 7.38-7.34 (m, 2H), 3.79 (s, 2H), 3.69 (s, 2H), 2.95 (t, <i>J</i> = 5.6 Hz, 2H), 2.81 (t, <i>J</i> = 5.8 Hz, 2H), 2.62 (s, 3H).                                                                                                                                                                                                         | 458 |
| 115s | <sup>1</sup> H NMR (300 MHz, Chloroform- <i>d</i> ) δ 9.55 (s, 1H), 8.18 (d, <i>J</i> = 8.1 Hz, 2H), 8.12 (d, <i>J</i> = 6.3 Hz, 1H), 7.58 (d, <i>J</i> = 8.1 Hz, 2H), 7.45 (ddd, <i>J</i> = 15.6, 5.7, 2.6 Hz, 5H), 7.38-7.34 (m, 2H), 3.79 (s, 2H), 3.69 (s, 2H), 2.95 (t, <i>J</i> = 5.6 Hz, 2H), 2.81 (t, <i>J</i> = 5.8 Hz, 2H), 2.62 (s, 3H).                                                                                                                                                                                           | 458 |
| 116  | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.30 (s, 1H), 8.19-8.09 (m, 2H), 7.82-7.64 (m, 4H), 7.50 (d, <i>J</i> = 4.5 Hz, 5H), 4.27 (s, 2H), 3.79 (s, 2H).                                                                                                                                                                                                                                                                                                                                                                 | 420 |
| 116s | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 9.51 (s, 1H), 8.30 (s, 1H), 8.19-8.09 (m, 2H), 7.82-7.64 (m, 4H), 7.50 (d, <i>J</i> = 4.5 Hz, 5H), 4.27 (s, 2H), 3.79 (s, 2H).                                                                                                                                                                                                                                                                                                                                                   | 420 |

|      |                                                                                                                                                                                                                                                                                                                                                                                                                                |     |
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| 117  | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.29 (s, 1H), 8.12 (t, <i>J</i> = 6.6 Hz, 2H), 7.79-7.69 (m, 3H), 7.69-7.61 (m, 1H), 7.55-7.46 (m, 5H), 4.24 (s, 2H), 3.85 (q, <i>J</i> = 11.6 Hz, 3H).                                                                                                                                                                                                           | 450 |
| 117s | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 9.55 (s, 1H), 8.29 (s, 1H), 8.12 (t, <i>J</i> = 6.6 Hz, 2H), 7.79-7.69 (m, 3H), 7.69-7.61 (m, 1H), 7.55-7.46 (m, 5H), 4.24 (s, 2H), 3.85 (q, <i>J</i> = 11.6 Hz, 3H).                                                                                                                                                                                             | 450 |
| 118  | <sup>1</sup> H NMR (300 MHz, Chloroform- <i>d</i> ) δ 8.12 (s, 1H), 8.10-8.05 (m, 1H), 7.99 (d, <i>J</i> = 6.7 Hz, 1H), 7.63-7.56 (m, 2H), 7.56-7.44 (m, 5H), 7.40 (t, <i>J</i> = 6.9 Hz, 2H), 3.90 (s, 2H), 3.63 (s, 2H), 2.52 (s, 3H).                                                                                                                                                                                       | 400 |
| 118s | <sup>1</sup> H NMR (300 MHz, Chloroform- <i>d</i> ) δ 9.50 (s, 1H), 8.12 (s, 1H), 8.10-8.05 (m, 1H), 7.99 (d, <i>J</i> = 6.7 Hz, 1H), 7.63-7.56 (m, 2H), 7.56-7.44 (m, 5H), 7.40 (t, <i>J</i> = 6.9 Hz, 2H), 3.90 (s, 2H), 3.63 (s, 2H), 2.52 (s, 3H).                                                                                                                                                                         | 400 |
| 119  | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.10 (t, <i>J</i> = 6.4 Hz, 3H), 7.63 (d, <i>J</i> = 8.0 Hz, 2H), 7.54 (d, <i>J</i> = 4.5 Hz, 2H), 7.49 (d, <i>J</i> = 7.1 Hz, 2H), 7.45 (d, <i>J</i> = 6.6 Hz, 1H), 7.40 (d, <i>J</i> = 7.4 Hz, 2H), 3.97 (s, 2H), 3.49 (s, 2H), 2.53 (s, 3H), 2.45 (s, 3H).                                                                                                     | 414 |
| 119s | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 9.61 (s, 1H), 8.10 (t, <i>J</i> = 6.4 Hz, 3H), 7.63 (d, <i>J</i> = 8.0 Hz, 2H), 7.54 (d, <i>J</i> = 4.5 Hz, 2H), 7.49 (d, <i>J</i> = 7.1 Hz, 2H), 7.45 (d, <i>J</i> = 6.6 Hz, 1H), 7.40 (d, <i>J</i> = 7.4 Hz, 2H), 3.97 (s, 2H), 3.49 (s, 2H), 2.53 (s, 3H), 2.45 (s, 3H).                                                                                       | 414 |
| 120  | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.21 (s, 1H), 8.05 (q, <i>J</i> = 4.8 Hz, 2H), 7.93 (d, <i>J</i> = 7.8 Hz, 1H), 7.85 (t, <i>J</i> = 6.8 Hz, 1H), 7.67 (dd, <i>J</i> = 7.8, 5.3 Hz, 1H), 7.54 (dt, <i>J</i> = 12.9, 6.9 Hz, 6H), 7.42-7.37 (m, 2H), 4.23 (d, <i>J</i> = 5.5 Hz, 2H), 3.65 (d, <i>J</i> = 6.8 Hz, 2H), 3.41 (d, <i>J</i> = 4.1 Hz, 1H), 2.58 (s, 3H).                               | 399 |
| 120s | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 9.55 (s, 1H), 8.21 (s, 1H), 8.05 (q, <i>J</i> = 4.8 Hz, 2H), 7.93 (d, <i>J</i> = 7.8 Hz, 1H), 7.85 (t, <i>J</i> = 6.8 Hz, 1H), 7.67 (dd, <i>J</i> = 7.8, 5.3 Hz, 1H), 7.54 (dt, <i>J</i> = 12.9, 6.9 Hz, 6H), 7.42-7.37 (m, 2H), 4.23 (d, <i>J</i> = 5.5 Hz, 2H), 3.65 (d, <i>J</i> = 6.8 Hz, 2H), 3.41 (d, <i>J</i> = 4.1 Hz, 1H), 2.58 (s, 3H).                 | 399 |
| 121  | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.11-8.07 (m, 3H), 7.63 (d, <i>J</i> = 8.0 Hz, 2H), 7.54 (d, <i>J</i> = 4.3 Hz, 2H), 7.50 (d, <i>J</i> = 7.3 Hz, 2H), 7.45 (d, <i>J</i> = 6.8 Hz, 1H), 7.40 (d, <i>J</i> = 7.7 Hz, 2H), 3.92 (s, 1H), 3.21 (d, <i>J</i> = 7.1 Hz, 2H), 2.54 (s, 3H), 1.27 (d, <i>J</i> = 7.0 Hz, 3H).                                                                             | 414 |
| 121s | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 9.52 (s, 1H), 8.11-8.07 (m, 3H), 7.63 (d, <i>J</i> = 8.0 Hz, 2H), 7.54 (d, <i>J</i> = 4.3 Hz, 2H), 7.50 (d, <i>J</i> = 7.3 Hz, 2H), 7.45 (d, <i>J</i> = 6.8 Hz, 1H), 7.40 (d, <i>J</i> = 7.7 Hz, 2H), 3.92 (s, 1H), 3.21 (d, <i>J</i> = 7.1 Hz, 2H), 2.54 (s, 3H), 1.27 (d, <i>J</i> = 7.0 Hz, 3H).                                                               | 414 |
| 122  | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.09 (dd, <i>J</i> = 11.2, 6.2 Hz, 3H), 7.65 (d, <i>J</i> = 8.0 Hz, 2H), 7.54 (d, <i>J</i> = 4.6 Hz, 2H), 7.50 (d, <i>J</i> = 7.0 Hz, 2H), 7.45 (d, <i>J</i> = 6.8 Hz, 1H), 7.40 (d, <i>J</i> = 7.4 Hz, 2H), 4.06 (d, <i>J</i> = 13.0 Hz, 2H), 3.97 (s, 1H), 2.54 (s, 3H), 1.59-1.52 (m, 2H), 1.24 (s, 1H), 0.87 (dd, <i>J</i> = 13.2, 6.5 Hz, 6H).               | 456 |
| 122s | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 9.53 (s, 1H), 8.09 (dd, <i>J</i> = 11.2, 6.2 Hz, 3H), 7.65 (d, <i>J</i> = 8.0 Hz, 2H), 7.54 (d, <i>J</i> = 4.6 Hz, 2H), 7.50 (d, <i>J</i> = 7.0 Hz, 2H), 7.45 (d, <i>J</i> = 6.8 Hz, 1H), 7.40 (d, <i>J</i> = 7.4 Hz, 2H), 4.06 (d, <i>J</i> = 13.0 Hz, 2H), 3.97 (s, 1H), 2.54 (s, 3H), 1.59-1.52 (m, 2H), 1.24 (s, 1H), 0.87 (dd, <i>J</i> = 13.2, 6.5 Hz, 6H). | 456 |
| 123  | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.07 (d, <i>J</i> = 7.6 Hz, 3H), 7.63 (d, <i>J</i> = 7.7 Hz, 2H), 7.53 (d, <i>J</i> = 4.2 Hz, 2H), 7.49 (d, <i>J</i> = 6.9 Hz, 2H), 7.44 (d, <i>J</i> = 6.4 Hz, 1H), 7.39 (d, <i>J</i> = 7.5 Hz, 2H), 3.85 (s, 1H), 3.23 (s, 2H), 2.59 (t, <i>J</i> = 6.4 Hz, 2H), 2.53 (s, 3H), 2.03 (s, 3H), 1.92-1.85 (m, 2H).                                                 | 474 |
| 123s | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 9.59 (s, 1H), 8.07 (d, <i>J</i> = 7.6 Hz, 3H), 7.63 (d, <i>J</i> = 7.7 Hz, 2H), 7.53 (d, <i>J</i> = 4.2 Hz, 2H), 7.49 (d, <i>J</i> = 6.9 Hz, 2H), 7.44 (d, <i>J</i> = 6.4 Hz, 1H), 7.39 (d, <i>J</i> = 7.5 Hz, 2H), 3.85 (s, 1H), 3.23 (s, 2H), 2.59 (t, <i>J</i> = 6.4 Hz, 2H), 2.53 (s, 3H), 2.03 (s, 3H), 1.92-1.85 (m, 2H).                                   | 474 |
| 124  | <sup>1</sup> H NMR (300 MHz, Chloroform- <i>d</i> ) δ 8.17 (s, 1H), 8.05 (s, 2H), 8.00 (d, <i>J</i> = 7.1 Hz, 1H), 7.64 (s, 1H), 7.54 (d, <i>J</i> = 8.5 Hz, 1H), 7.46-7.38 (m, 4H), 7.34 (d, <i>J</i> = 7.1 Hz, 2H), 4.35-4.28 (m, 2H), 3.21-3.12 (m, 2H), 2.61 (d, <i>J</i> = 6.8 Hz, 2H), 2.58 (s, 3H).                                                                                                                     | 415 |
| 124s | <sup>1</sup> H NMR (300 MHz, Chloroform- <i>d</i> ) δ 9.53 (s, 1H), 8.17 (s, 1H), 8.05 (s, 2H), 8.00 (d, <i>J</i> = 7.1 Hz, 1H), 7.64 (s, 1H), 7.54 (d, <i>J</i> = 8.5 Hz, 1H), 7.46-7.38 (m, 4H), 7.34 (d, <i>J</i> = 7.1 Hz, 2H), 4.35-4.28 (m, 2H), 3.21-3.12 (m, 2H), 2.61 (d, <i>J</i> = 6.8 Hz, 2H), 2.58 (s, 3H).                                                                                                       | 415 |
| 125  | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.30 (s, 1H), 8.15-8.06 (m, 2H), 7.84 (d, <i>J</i> = 7.6 Hz, 1H), 7.67 (d, <i>J</i> = 7.6 Hz, 1H), 7.62 (d, <i>J</i> = 7.4 Hz, 1H), 7.54 (d, <i>J</i> = 4.5 Hz, 2H), 7.49 (d, <i>J</i> = 7.3 Hz, 2H), 7.39 (d, <i>J</i> = 6.8 Hz, 2H), 7.01 (s, 2H), 4.23 (s, 2H), 3.06 (t, <i>J</i> = 7.2 Hz, 2H), 2.63-2.57 (m, 2H), 2.54 (s, 3H).                              | 413 |
| 125s | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 9.57 (s, 1H), 8.30 (s, 1H), 8.15-8.06 (m, 2H), 7.84 (d, <i>J</i> = 7.6 Hz, 1H), 7.67 (d, <i>J</i> = 7.6 Hz, 1H), 7.62 (d, <i>J</i> = 7.4 Hz, 1H), 7.54 (d, <i>J</i> = 4.5 Hz, 2H), 7.49 (d, <i>J</i> = 7.3 Hz, 2H), 7.39 (d, <i>J</i> = 6.8 Hz, 2H), 7.01 (s, 2H), 4.23 (s, 2H), 3.06 (t, <i>J</i> = 7.2 Hz, 2H), 2.63-2.57 (m, 2H), 2.54 (s, 3H).                | 413 |

|      |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |     |
|------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|
| 126  | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.15 (d, <i>J</i> = 7.9 Hz, 2H), 8.09 (t, <i>J</i> = 4.8 Hz, 1H), 7.82 (d, <i>J</i> = 7.3 Hz, 2H), 7.55 (d, <i>J</i> = 4.8 Hz, 2H), 7.50 (d, <i>J</i> = 7.3 Hz, 2H), 7.45 (d, <i>J</i> = 6.6 Hz, 1H), 7.40 (d, <i>J</i> = 7.9 Hz, 2H), 5.34 (s, 2H), 4.35 (s, 2H), 3.75-3.68 (m, 4H), 3.02 (s, 1H), 2.54 (s, 3H).                                                                                                                     | 416 |
| 126s | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 9.51 (s, 1H), 8.15 (d, <i>J</i> = 7.9 Hz, 2H), 8.09 (t, <i>J</i> = 4.8 Hz, 1H), 7.82 (d, <i>J</i> = 7.3 Hz, 2H), 7.55 (d, <i>J</i> = 4.8 Hz, 2H), 7.50 (d, <i>J</i> = 7.3 Hz, 2H), 7.45 (d, <i>J</i> = 6.6 Hz, 1H), 7.40 (d, <i>J</i> = 7.9 Hz, 2H), 5.34 (s, 2H), 4.35 (s, 2H), 3.75-3.68 (m, 4H), 3.02 (s, 1H), 2.54 (s, 3H).                                                                                                       | 416 |
| 127  | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.10 (d, <i>J</i> = 7.2 Hz, 3H), 7.67 (s, 2H), 7.65 (s, 1H), 7.54 (d, <i>J</i> = 3.7 Hz, 2H), 7.51 (s, 1H), 7.49 (s, 1H), 7.47-7.43 (m, 1H), 7.40 (d, <i>J</i> = 7.1 Hz, 2H), 6.46 (s, 2H), 4.47 (s, 1H), 3.99 (s, 2H), 3.94 (s, 2H), 2.54 (s, 3H).                                                                                                                                                                                   | 422 |
| 127s | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 9.55 (s, 1H), 8.10 (d, <i>J</i> = 7.2 Hz, 3H), 7.67 (s, 2H), 7.65 (s, 1H), 7.54 (d, <i>J</i> = 3.7 Hz, 2H), 7.51 (s, 1H), 7.49 (s, 1H), 7.47-7.43 (m, 1H), 7.40 (d, <i>J</i> = 7.1 Hz, 2H), 6.46 (s, 2H), 4.47 (s, 1H), 3.99 (s, 2H), 3.94 (s, 2H), 2.54 (s, 3H).                                                                                                                                                                     | 422 |
| 128  | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.16-8.07 (m, 3H), 7.71 (d, <i>J</i> = 7.8 Hz, 2H), 7.56-7.53 (m, 2H), 7.50 (d, <i>J</i> = 7.1 Hz, 2H), 7.45 (d, <i>J</i> = 6.5 Hz, 1H), 7.40 (d, <i>J</i> = 7.0 Hz, 2H), 4.12 (d, <i>J</i> = 12.9 Hz, 1H), 3.66 (s, 3H), 3.89 (s, 2H), 2.96-2.89 (m, 1H), 2.54 (s, 3H), 2.33-2.26 (m, 1H), 1.94 (dd, <i>J</i> = 12.0, 5.7 Hz, 2H), 1.83 (d, <i>J</i> = 10.1 Hz, 1H), 1.24 (s, 1H).                                                   | 440 |
| 128s | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 9.65 (s, 1H), 8.16-8.07 (m, 3H), 7.71 (d, <i>J</i> = 7.8 Hz, 2H), 7.56-7.53 (m, 2H), 7.50 (d, <i>J</i> = 7.1 Hz, 2H), 7.45 (d, <i>J</i> = 6.5 Hz, 1H), 7.40 (d, <i>J</i> = 7.0 Hz, 2H), 4.12 (d, <i>J</i> = 12.9 Hz, 1H), 3.89 (s, 2H), 2.96-2.89 (m, 1H), 2.54 (s, 3H), 2.33-2.26 (m, 1H), 1.94 (dd, <i>J</i> = 12.0, 5.7 Hz, 2H), 1.83 (d, <i>J</i> = 10.1 Hz, 1H), 1.24 (s, 1H).                                                   | 440 |
| 129  | <sup>1</sup> H NMR (300 MHz, Chloroform- <i>d</i> ) δ 8.22-8.10 (m, 1H), 7.93 (d, <i>J</i> = 5.3 Hz, 1H), 7.83 (d, <i>J</i> = 6.9 Hz, 1H), 7.57 (dd, <i>J</i> = 11.3, 7.1 Hz, 1H), 7.49-7.40 (m, 1H), 7.32 (d, <i>J</i> = 6.1 Hz, 4H), 7.25-7.11 (m, 3H), 4.79-4.56 (m, 2H), 4.33 (s, 2H), 3.81 (d, <i>J</i> = 12.5 Hz, 2H), 3.29-3.12 (m, 1H), 2.71-2.46 (m, 2H), 2.36 (s, 3H).                                                                                                                   | 456 |
| 129s | <sup>1</sup> H NMR (300 MHz, Chloroform- <i>d</i> ) δ 9.50 (s, 1H), 8.22-8.10 (m, 1H), 7.93 (d, <i>J</i> = 5.3 Hz, 1H), 7.83 (d, <i>J</i> = 6.9 Hz, 1H), 7.57 (dd, <i>J</i> = 11.3, 7.1 Hz, 1H), 7.49-7.40 (m, 1H), 7.32 (d, <i>J</i> = 6.1 Hz, 4H), 7.25-7.11 (m, 3H), 4.79-4.56 (m, 2H), 4.33 (s, 2H), 3.81 (d, <i>J</i> = 12.5 Hz, 2H), 3.29-3.12 (m, 1H), 2.71-2.46 (m, 2H), 2.36 (s, 3H).                                                                                                     | 456 |
| 130  | <sup>1</sup> H NMR (300 MHz, Chloroform- <i>d</i> ) δ 8.23 (d, <i>J</i> = 8.1 Hz, 1H), 8.16-8.06 (m, 2H), 7.59-7.50 (m, 2H), 7.44 (dt, <i>J</i> = 7.9, 4.4 Hz, 5H), 7.36 (d, <i>J</i> = 6.8 Hz, 2H), 3.91-3.71 (m, 2H), 2.62 (s, 3H), 2.59-2.54 (m, 1H), 1.83 (s, 6H), 1.29 (d, <i>J</i> = 8.6 Hz, 1H), 0.95-0.78 (m, 1H).                                                                                                                                                                         | 454 |
| 130s | <sup>1</sup> H NMR (300 MHz, Chloroform- <i>d</i> ) δ 9.53 (s, 1H), 8.23 (d, <i>J</i> = 8.1 Hz, 1H), 8.16-8.06 (m, 2H), 7.59-7.50 (m, 2H), 7.44 (dt, <i>J</i> = 7.9, 4.4 Hz, 5H), 7.36 (d, <i>J</i> = 6.8 Hz, 2H), 3.91-3.71 (m, 2H), 2.62 (s, 3H), 2.59-2.54 (m, 1H), 1.83 (s, 6H), 1.29 (d, <i>J</i> = 8.6 Hz, 1H), 0.95-0.78 (m, 1H).                                                                                                                                                           | 454 |
| 131  | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.12 (dd, <i>J</i> = 13.0, 5.8 Hz, 2H), 7.81 (d, <i>J</i> = 7.0 Hz, 1H), 7.72-7.64 (m, 1H), 7.57-7.48 (m, 5H), 7.42 (d, <i>J</i> = 4.2 Hz, 3H), 5.81 (s, 1H), 5.40 (s, 1H), 5.32 (s, 1H), 4.66-4.31 (m, 3H), 4.12 (d, <i>J</i> = 9.8 Hz, 1H), 3.94-3.81 (m, 1H), 3.62 (d, <i>J</i> = 9.0 Hz, 2H), 3.52 (d, <i>J</i> = 7.3 Hz, 1H), 3.23-3.14 (m, 1H), 2.90 (d, <i>J</i> = 3.8 Hz, 1H), 2.78-2.67 (m, 1H), 2.54 (s, 3H).               | 504 |
| 131s | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 9.51 (s, 1H), 8.12 (dd, <i>J</i> = 13.0, 5.8 Hz, 2H), 7.81 (d, <i>J</i> = 7.0 Hz, 1H), 7.72-7.64 (m, 1H), 7.57-7.48 (m, 5H), 7.42 (d, <i>J</i> = 4.2 Hz, 3H), 5.81 (s, 1H), 5.40 (s, 1H), 5.32 (s, 1H), 4.66-4.31 (m, 3H), 4.12 (d, <i>J</i> = 9.8 Hz, 1H), 3.94-3.81 (m, 1H), 3.62 (d, <i>J</i> = 9.0 Hz, 2H), 3.52 (d, <i>J</i> = 7.3 Hz, 1H), 3.23-3.14 (m, 1H), 2.90 (d, <i>J</i> = 3.8 Hz, 1H), 2.78-2.67 (m, 1H), 2.54 (s, 3H). | 504 |
| 132  | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 7.94-7.76 (m, 2H), 7.62-7.54 (m, 1H), 7.40 (d, <i>J</i> = 7.3 Hz, 2H), 7.32 (dd, <i>J</i> = 13.2, 5.9 Hz, 2H), 7.20 (d, <i>J</i> = 7.2 Hz, 2H), 7.08 (t, <i>J</i> = 7.3 Hz, 1H), 6.94 (dt, <i>J</i> = 16.3, 6.4 Hz, 2H), 5.15 (s, 2H), 3.87 (d, <i>J</i> = 11.7 Hz, 2H), 2.96-2.83 (m, 1H), 1.92 (s, 3H).                                                                                                                             | 430 |
| 132s | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 9.50 (s, 1H), 7.94-7.76 (m, 2H), 7.62-7.54 (m, 1H), 7.40 (d, <i>J</i> = 7.3 Hz, 2H), 7.32 (dd, <i>J</i> = 13.2, 5.9 Hz, 2H), 7.20 (d, <i>J</i> = 7.2 Hz, 2H), 7.08 (t, <i>J</i> = 7.3 Hz, 1H), 6.94 (dt, <i>J</i> = 16.3, 6.4 Hz, 2H), 5.15 (s, 2H), 3.87 (d, <i>J</i> = 11.7 Hz, 2H), 2.96-2.83 (m, 1H), 1.92 (s, 3H).                                                                                                               | 430 |
| 133  | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.12 (s, 1H), 8.09 (d, <i>J</i> = 4.8 Hz, 2H), 7.69 (d, <i>J</i> = 8.0 Hz, 2H), 7.54 (d, <i>J</i> = 4.5 Hz, 2H), 7.49 (d, <i>J</i> = 7.1 Hz, 2H), 7.45 (d, <i>J</i> = 6.6 Hz, 1H), 7.41-7.37 (m, 2H), 4.05 (s, 1H), 4.03-3.96 (m, 2H), 3.25 (d, <i>J</i> = 5.4 Hz, 1H), 2.53 (s, 3H), 1.19 (d, <i>J</i> = 6.4 Hz, 3H).                                                                                                                | 444 |
| 133s | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 9.54 (s, 1H), 8.12 (s, 1H), 8.09 (d, <i>J</i> = 4.8 Hz, 2H), 7.69 (d, <i>J</i> = 8.0 Hz, 2H), 7.54 (d, <i>J</i> = 4.5 Hz, 2H), 7.49 (d, <i>J</i> = 7.1 Hz, 2H), 7.45 (d, <i>J</i> = 6.6 Hz, 1H), 7.41-7.37 (m, 2H), 4.05 (s, 1H), 4.03-3.96 (m, 2H), 3.25 (d, <i>J</i>                                                                                                                                                                | 444 |

|      |                                                                                                                                                                                                                                                                                                                                                                                                               |     |
|------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|
|      | = 5.4 Hz, 1H), 2.53 (s, 3H), 1.19 (d, $J = 6.4$ Hz, 3H).                                                                                                                                                                                                                                                                                                                                                      |     |
| 134  | $^1\text{H}$ NMR (300 MHz, DMSO- $d_6$ ) $\delta$ 8.23-8.11 (m, 3H), 7.83-7.67 (m, 4H), 7.57-7.44 (m, 5H), 4.27 (s, 2H), 3.88 (s, 2H).                                                                                                                                                                                                                                                                        | 420 |
| 134s | $^1\text{H}$ NMR (300 MHz, DMSO- $d_6$ ) $\delta$ 9.57 (s, 1H), 8.23-8.11 (m, 3H), 7.83-7.67 (m, 4H), 7.57-7.44 (m, 5H), 4.27 (s, 2H), 3.88 (s, 2H).                                                                                                                                                                                                                                                          | 420 |
| 135  | $^1\text{H}$ NMR (300 MHz, DMSO- $d_6$ ) $\delta$ 8.21-8.05 (m, 3H), 7.83-7.66 (m, 4H), 7.57-7.44 (m, 5H), 4.31 (s, 2H), 4.08-3.86 (m, 3H).                                                                                                                                                                                                                                                                   | 450 |
| 135s | $^1\text{H}$ NMR (300 MHz, DMSO- $d_6$ ) $\delta$ 9.54 (s, 1H), 8.21-8.05 (m, 3H), 7.83-7.66 (m, 4H), 7.57-7.44 (m, 5H), 4.31 (s, 2H), 4.08-3.86 (m, 3H).                                                                                                                                                                                                                                                     | 450 |
| 136  | $^1\text{H}$ NMR (300 MHz, DMSO- $d_6$ ) $\delta$ 8.46 (s, 1H), 8.35 (d, $J = 7.9$ Hz, 1H), 7.98 (dd, $J = 6.4, 2.9$ Hz, 1H), 7.86 (d, $J = 7.7$ Hz, 1H), 7.77 (t, $J = 7.7$ Hz, 1H), 7.51-7.40 (m, 5H), 7.39-7.34 (m, 2H), 4.40 (d, $J = 17.6$ Hz, 2H), 3.90 (d, $J = 7.4$ Hz, 1H), 2.48 (s, 3H), 1.62 (d, $J = 7.2$ Hz, 3H).                                                                                | 414 |
| 136s | $^1\text{H}$ NMR (300 MHz, DMSO- $d_6$ ) $\delta$ 9.56 (s, 1H), 8.46 (s, 1H), 8.35 (d, $J = 7.9$ Hz, 1H), 7.98 (dd, $J = 6.4, 2.9$ Hz, 1H), 7.86 (d, $J = 7.7$ Hz, 1H), 7.77 (t, $J = 7.7$ Hz, 1H), 7.51-7.40 (m, 5H), 7.39-7.34 (m, 2H), 4.40 (d, $J = 17.6$ Hz, 2H), 3.90 (d, $J = 7.4$ Hz, 1H), 2.48 (s, 3H), 1.62 (d, $J = 7.2$ Hz, 3H).                                                                  | 414 |
| 137  | $^1\text{H}$ NMR (400 MHz, Methanol- $d_4$ ) $\delta$ 8.46 (s, 1H), 8.35-8.32 (d, $J = 7.9$ Hz, 1H), 7.98-7.95 (dd, $J = 6.4, 2.9$ Hz, 1H), 7.86-7.82 (d, $J = 7.7$ Hz, 1H), 7.77-7.74 (t, $J = 7.7$ Hz, 1H), 7.51-7.40 (m, 5H), 7.39-7.34 (m, 2H), 4.40-4.35 (d, $J = 17.6$ Hz, 2H), 4.18-4.15 (d, $J = 3.1$ Hz, 2H), 3.83-3.80 (d, $J = 4.0$ Hz, 1H), 3.76-3.74 (dd, $J = 11.5, 5.3$ Hz, 2H).               | 430 |
| 137s | $^1\text{H}$ NMR (400 MHz, Methanol- $d_4$ ) $\delta$ 9.50 (s, 1H), 8.46 (s, 1H), 8.35-8.32 (d, $J = 7.9$ Hz, 1H), 7.98-7.95 (dd, $J = 6.4, 2.9$ Hz, 1H), 7.86-7.82 (d, $J = 7.7$ Hz, 1H), 7.77-7.74 (t, $J = 7.7$ Hz, 1H), 7.51-7.40 (m, 5H), 7.39-7.34 (m, 2H), 4.40-4.35 (d, $J = 17.6$ Hz, 2H), 4.18-4.15 (d, $J = 3.1$ Hz, 2H), 3.83-3.80 (d, $J = 4.0$ Hz, 1H), 3.76-3.74 (dd, $J = 11.5, 5.3$ Hz, 2H). | 430 |
| 138  | $^1\text{H}$ NMR (400 MHz, Methanol- $d_4$ ) $\delta$ 8.52 (s, 1H), 8.37-8.36 (d, $J = 7.9$ Hz, 1H), 7.95-7.93 (dd, $J = 6.4, 2.9$ Hz, 1H), 7.74-7.71 (d, $J = 7.7$ Hz, 1H), 7.68-7.66 (t, $J = 7.7$ Hz, 1H), 7.49-7.39 (m, 5H), 7.37-7.34 (m, 2H), 4.20-4.16 (d, $J = 3.1$ Hz, 2H), 3.75-3.71 (d, $J = 4.0$ Hz, 1H), 3.69-3.66 (dd, $J = 11.5, 5.3$ Hz, 2H).                                                 | 414 |
| 138s | $^1\text{H}$ NMR (400 MHz, Methanol- $d_4$ ) $\delta$ 9.52 (s, 1H), 8.52 (s, 1H), 8.37-8.36 (d, $J = 7.9$ Hz, 1H), 7.95-7.93 (dd, $J = 6.4, 2.9$ Hz, 1H), 7.74-7.71 (d, $J = 7.7$ Hz, 1H), 7.68-7.66 (t, $J = 7.7$ Hz, 1H), 7.49-7.39 (m, 5H), 7.37-7.34 (m, 2H), 4.20-4.16 (d, $J = 3.1$ Hz, 2H), 3.75-3.71 (d, $J = 4.0$ Hz, 1H), 3.69-3.66 (dd, $J = 11.5, 5.3$ Hz, 2H).                                   | 414 |
| 139  | $^1\text{H}$ NMR (300 MHz, DMSO- $d_6$ ) $\delta$ 8.16 (d, $J = 7.2$ Hz, 2H), 8.08 (s, 1H), 7.76 (d, $J = 7.1$ Hz, 2H), 7.54 (s, 2H), 7.52-7.46 (m, 3H), 7.40 (d, $J = 6.4$ Hz, 2H), 4.23 (s, 2H), 3.82 (s, 2H), 2.54 (s, 3H).                                                                                                                                                                                | 400 |
| 139s | $^1\text{H}$ NMR (300 MHz, DMSO- $d_6$ ) $\delta$ 9.54 (s, 1H), 8.16 (d, $J = 7.2$ Hz, 2H), 8.08 (s, 1H), 7.76 (d, $J = 7.1$ Hz, 2H), 7.54 (s, 2H), 7.52-7.46 (m, 3H), 7.40 (d, $J = 6.4$ Hz, 2H), 4.23 (s, 2H), 3.82 (s, 2H), 2.54 (s, 3H).                                                                                                                                                                  | 400 |
| 140  | $^1\text{H}$ NMR (300 MHz, Chloroform- $d$ ) $\delta$ 8.21 (d, $J = 7.9$ Hz, 2H), 8.07 (d, $J = 7.5$ Hz, 1H), 7.74 (d, $J = 7.9$ Hz, 2H), 7.49-7.42 (m, 4H), 7.38 (d, $J = 7.4$ Hz, 2H), 7.32 (t, $J = 6.8$ Hz, 2H), 4.26 (s, 2H), 3.95 (s, 2H), 3.74 (d, $J = 7.3$ Hz, 1H), 3.07 (s, 2H), 2.55 (s, 3H).                                                                                                      | 386 |
| 140s | $^1\text{H}$ NMR (300 MHz, Chloroform- $d$ ) $\delta$ 9.55 (s, 1H), 8.21 (d, $J = 7.9$ Hz, 2H), 8.07 (d, $J = 7.5$ Hz, 1H), 7.74 (d, $J = 7.9$ Hz, 2H), 7.49-7.42 (m, 4H), 7.38 (d, $J = 7.4$ Hz, 2H), 7.32 (t, $J = 6.8$ Hz, 2H), 4.26 (s, 2H), 3.95 (s, 2H), 3.74 (d, $J = 7.3$ Hz, 1H), 3.07 (s, 2H), 2.55 (s, 3H).                                                                                        | 386 |
| 141  | $^1\text{H}$ NMR (300 MHz, DMSO- $d_6$ ) $\delta$ 8.13-8.10 (dd, $J = 14.8, 8.0$ Hz, 2H), 8.05-8.03 (d, $J = 7.4$ Hz, 1H), 7.76-7.74 (t, $J = 7.5$ Hz, 1H), 7.68-7.65 (t, $J = 6.4$ Hz, 1H), 7.61-7.59 (d, $J = 7.4$ Hz, 3H), 7.52-7.50 (t, $J = 7.3$ Hz, 3H), 7.45 (s, 1H), 3.82 (s, 2H), 2.92 (s, 2H).                                                                                                      | 404 |
| 141s | $^1\text{H}$ NMR (300 MHz, DMSO- $d_6$ ) $\delta$ 9.57 (s, 1H), 8.13-8.10 (dd, $J = 14.8, 8.0$ Hz, 2H), 8.05-8.03 (d, $J = 7.4$ Hz, 1H), 7.76-7.74 (t, $J = 7.5$ Hz, 1H), 7.68-7.65 (t, $J = 6.4$ Hz, 1H), 7.61-7.59 (d, $J = 7.4$ Hz, 3H), 7.52-7.50 (t, $J = 7.3$ Hz, 3H), 7.45 (s, 1H), 3.82 (s, 2H), 2.92 (s, 2H).                                                                                        | 404 |
| 142  | $^1\text{H}$ NMR (300 MHz, DMSO- $d_6$ ) $\delta$ 8.26 (s, 1H), 8.10-8.05 (d, $J = 7.7$ Hz, 1H), 7.92-7.86 (d, $J = 6.1$ Hz, 1H), 7.77-7.74 (d, $J = 7.7$ Hz, 1H), 7.70-7.58 (m, 3H), 7.50-7.48 (d, $J = 7.1$ Hz, 5H), 4.05 (s, 2H), 3.18 (s, 2H).                                                                                                                                                            | 420 |
| 142s | $^1\text{H}$ NMR (300 MHz, DMSO- $d_6$ ) $\delta$ 9.51 (s, 1H), 8.26 (s, 1H), 8.10-8.05 (d, $J = 7.7$ Hz, 1H), 7.92-7.86 (d, $J = 6.1$ Hz, 1H), 7.77-7.74 (d, $J = 7.7$ Hz, 1H), 7.70-7.58 (m, 3H), 7.50-7.48 (d, $J = 7.1$ Hz, 5H), 4.05 (s, 2H), 3.18 (s, 2H).                                                                                                                                              | 420 |
| 143  | $^1\text{H}$ NMR (300 MHz, DMSO- $d_6$ ) $\delta$ 8.31 (s, 1H), 8.21-8.15 (d, $J = 10.3$ Hz, 2H), 7.91 (s, 1H), 7.67-7.61 (m, 2H), 7.55 (s, 2H), 7.51-7.50 (d, $J = 8.3$ Hz, 2H), 7.44 (s, 2H), 4.12 (s, 2H), 3.27 (s, 2H).                                                                                                                                                                                   | 464 |
| 143s | $^1\text{H}$ NMR (300 MHz, DMSO- $d_6$ ) $\delta$ 9.53 (s, 1H), 8.31 (s, 1H), 8.21-8.15 (d, $J = 10.3$ Hz, 2H), 7.91 (s, 1H), 7.67-7.61 (m, 2H), 7.55 (s, 2H), 7.51-7.50 (d, $J = 8.3$ Hz, 2H), 7.44 (s, 2H), 4.12 (s, 2H), 3.27 (s, 2H).                                                                                                                                                                     | 464 |

|      |                                                                                                                                                                                                                                                                                                                                                                                                               |     |
|------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|
|      | 7.55 (s, 2H), 7.51-7.50 (d, $J = 8.3$ Hz, 2H), 7.44 (s, 2H), 4.12 (s, 2H), 3.27 (s, 2H).                                                                                                                                                                                                                                                                                                                      |     |
| 144  | $^1\text{H}$ NMR (300 MHz, DMSO- $d_6$ ) $\delta$ 8.16 (d, $J = 7.2$ Hz, 2H), 8.09 (s, 1H), 7.78 (d, $J = 7.1$ Hz, 2H), 7.54 (s, 2H), 7.52-7.46 (m, 3H), 7.40 (d, $J = 6.4$ Hz, 2H), 4.26 (s, 2H), 3.83 (s, 2H), 2.54 (s, 3H).                                                                                                                                                                                | 400 |
| 144s | $^1\text{H}$ NMR (300 MHz, DMSO- $d_6$ ) $\delta$ 9.54 (s, 1H), 8.16 (d, $J = 7.2$ Hz, 2H), 8.09 (s, 1H), 7.78 (d, $J = 7.1$ Hz, 2H), 7.54 (s, 2H), 7.52-7.46 (m, 3H), 7.40 (d, $J = 6.4$ Hz, 2H), 4.26 (s, 2H), 3.83 (s, 2H), 2.54 (s, 3H).                                                                                                                                                                  | 400 |
| 145  | $^1\text{H}$ NMR (400 MHz, Methanol- $d_4$ ) $\delta$ 8.46 (s, 1H), 8.35-8.32 (d, $J = 7.9$ Hz, 1H), 7.98-7.95 (dd, $J = 6.4, 2.9$ Hz, 1H), 7.86-7.82 (d, $J = 7.7$ Hz, 1H), 7.77-7.74 (t, $J = 7.7$ Hz, 1H), 7.51-7.40 (m, 5H), 7.39-7.34 (m, 2H), 4.40-4.35 (d, $J = 17.6$ Hz, 2H), 4.18-4.15 (d, $J = 3.1$ Hz, 2H), 3.83-3.80 (d, $J = 4.0$ Hz, 1H), 3.76-3.74 (dd, $J = 11.5, 5.3$ Hz, 2H).               | 430 |
| 145s | $^1\text{H}$ NMR (400 MHz, Methanol- $d_4$ ) $\delta$ 9.56 (s, 1H), 8.46 (s, 1H), 8.35-8.32 (d, $J = 7.9$ Hz, 1H), 7.98-7.95 (dd, $J = 6.4, 2.9$ Hz, 1H), 7.86-7.82 (d, $J = 7.7$ Hz, 1H), 7.77-7.74 (t, $J = 7.7$ Hz, 1H), 7.51-7.40 (m, 5H), 7.39-7.34 (m, 2H), 4.40-4.35 (d, $J = 17.6$ Hz, 2H), 4.18-4.15 (d, $J = 3.1$ Hz, 2H), 3.83-3.80 (d, $J = 4.0$ Hz, 1H), 3.76-3.74 (dd, $J = 11.5, 5.3$ Hz, 2H). | 430 |

实施例 4: 3-(5-(2-甲基-[1,1'-联苯]-3-基)噁唑-2-基)苄基)甘氨酸 (146) 及其盐酸盐 (146s) 的合成

#### 1-(3-溴-2-甲基苯基)乙烷-1-酮 (4A)

将 1,3-二溴-2-甲基苯 (10.01 g, 40.01 mmol) 溶于 85 mL DMF, 搅拌下加入三丁基(1-乙氧基乙烯)锡 (14.41 g, 40.01 mmol) 和  $\text{Pd}(\text{PPh}_3)_4$  (0.46g, 0.40 mmol), 氮气保护下于 85°C 下反应 12 h。冷却, 乙酸乙酯萃取, 减压浓缩。加入 20 mL 4 M HCl, 室温反应 3 h。乙酸乙酯萃取, 无水硫酸钠干燥, 柱层析纯化[石油醚:乙酸乙酯 = 15:1 (V:V)], 得油状物 8.04 g, 收率 94%。MS (EI)  $m/z$  213  $[\text{M}+\text{H}]^+$ ;  $^1\text{H}$  NMR (300 MHz, Chloroform- $d$ )  $\delta$  7.59 (d,  $J = 7.8$  Hz, 1H), 6.93 (s, 2H), 2.60 (s, 3H), 2.30 (s, 3H)。

#### 1-(2-甲基-[1,1'-联苯]-3-基)乙烷-1-酮 (4B) 的合成

参照实施例 1 的方法, 将 4A 和苯硼酸进行偶联反应, 制得油状物 4B, 收率 87%。MS (EI)  $m/z$  211  $[\text{M}+\text{H}]^+$ ;  $^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ )  $\delta$  7.70 (dd,  $J = 7.2, 2.4$  Hz, 1H), 7.50-7.26 (m, 7H), 2.58 (d,  $J = 2.7$  Hz, 3H), 2.22 (d,  $J = 3.0$  Hz, 3H)。

#### 2-溴-1-(2-甲基-1,1'-联苯)-3-基)乙烷-1-酮 (4C) 的合成

将 4B (1.50 g, 7.13 mmol) 和溴化铜 (3.51 g, 3.51 g) 加入 20 mL 乙酸乙酯中, 回流反应 8 h。冷却, 抽滤, 减压浓缩。加入 10 mL 四氢呋喃、亚磷酸二乙酯 (0.26g, 1.87 mmol) 和三乙胺 (0.21g, 2.06 mmol), 室温反应 2 h。乙酸乙酯萃取, 无水硫酸钠干燥, 柱层析纯化[石油醚:乙酸乙酯 = 20:1 (V:V)], 得白色固体 1.36 g, 收率 65%。MS (EI)  $m/z$  289  $[\text{M}+\text{H}]^+$ ;  $^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ )  $\delta$  7.80 (dd,  $J = 6.3, 2.7$  Hz, 1H), 7.50-7.36 (m, 5H), 7.35-7.26 (m, 2H), 4.91 (s, 2H), 2.21 (s, 3H)。

#### 2-氨基-1-(2-甲基-1,1'-联苯)-3-基)乙烷-1-酮 (4D) 的合成

将 4C (1.21 g, 4.15 mmol) 和二甲酰氨基钠 (0.39g, 4.15 mmol) 加入 15 mL 乙腈中, 75°C 反应 12 h, 趁热抽滤, 减压浓缩, 加入 5 mL 4 M HCl, 回流 1 h。减压浓缩, 乙酸乙酯重结晶, 得白色固体 0.65 g, 收率 70%。MS (EI)  $m/z$  226  $[\text{M}+\text{H}]^+$ ;  $^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ )  $\delta$  8.39 (s, 3H), 7.90-7.84 (m, 1H), 7.53-7.39 (m, 6H), 4.52 (d,  $J = 6.0$  Hz, 2H), 2.28 (s, 3H)。

#### 3-(2-(2-甲基-1,1'-联苯)-3-基)-2-氧代乙基)氨基甲酰基)苯甲酸甲酯 (4E) 的合成

参照实施例 1 的方法, 将 3-(甲氧基羰基)苯甲酸和 4D 进行酰化反应, 制得白色固体 4E, 收率 61%。MS (EI)  $m/z$  388  $[\text{M}+\text{H}]^+$ ;  $^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ )  $\delta$  9.21 (s, 1H), 8.16-7.98 (m, 4H), 7.75 (d,  $J = 8.1$  Hz, 1H), 7.53-7.31 (m, 6H), 4.61 (d,  $J = 5.7$  Hz, 2H), 3.89 (s, 3H), 2.22 (s, 3H)。

#### 3-(5-(2-甲基-1,1'-联苯)-3-基)噁唑-2-基)苯甲酸甲酯 (4F) 的合成

将 4E (0.20 g, 0.51 mmol) 加入 3 mL 乙酸酐中, 加入 4 滴浓硫酸, 80°C 反应 2 h。冷却, 乙酸乙酯萃取, 减压浓缩, 制得白色固体 4F, 收率 62%。MS (EI)  $m/z$  370  $[\text{M}+\text{H}]^+$ ;  $^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ )  $\delta$  8.35-8.09 (m, 4H), 7.95-7.70 (m, 2H), 7.45 (ddt,  $J = 26.4, 19.2, 9.6$  Hz, 7H), 3.91 (d,  $J = 7.5$  Hz, 3H), 2.36 (s, 3H)。

#### 3-(5-(2-甲基-1,1'-联苯)-3-基)噁唑-2-基)苄基)苯基甲醇 (4G) 的合成

参照实施例 2 的方法, 将 4F 和  $\text{LiAlH}_4$  进行还原反应, 制得白色固体 4G, 收率 79%。MS (EI)  $m/z$  342  $[\text{M}+\text{H}]^+$ ;  $^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ )  $\delta$  8.18-8.02 (m, 2H), 7.83 (d,  $J = 10.5$  Hz, 1H), 7.72-7.59 (m, 1H), 7.59-7.34 (m, 8H), 7.29 (s, 1H), 5.36 (s, 1H), 4.59 (s, 2H), 2.35 (s, 3H)。

#### 2-(3-氯甲基)苄基-5-(2-甲基-1,1'-联苯)-3-基)噁唑 (4H) 的合成

将 4G (0.60g, 1.76 mmol) 加入 5 mL 二氯甲烷中, 冰浴冷却下滴加 0.3 mL 氯化亚砷, 室温反应 3 h。乙酸乙酯萃取, 减压浓缩, 得白色固体 0.53 g, 收率 83%。MS (EI)  $m/z$  360  $[\text{M}+\text{H}]^+$ ;  $^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ )  $\delta$  8.18-8.02 (m, 2H), 7.83 (d,  $J = 10.5$  Hz, 1H), 7.72-7.59 (m, 1H), 7.59-7.34 (m, 8H), 7.29 (s, 1H), 4.64 (s, 2H), 2.33 (s, 3H)。

(3-(5-(2-甲基-[1,1'-联苯]-3-基)噁唑-2-基)苄基)甘氨酸甲酯 (4I) 的合成

参照实施例 1 的方法, 将 4H 和甘氨酸甲酯盐酸盐进行缩合反应, 制得白色固体 146m, 收率 58%。MS (EI)  $m/z$  413  $[M+H]^+$ ;  $^1H$  NMR (300 MHz, DMSO- $d_6$ )  $\delta$  8.04 (d,  $J$  = 7.8 Hz, 2H), 7.83 (d,  $J$  = 7.8 Hz, 1H), 7.62 (s, 1H), 7.57-7.35 (m, 8H), 7.29 (dd,  $J$  = 7.5, 1.5 Hz, 1H), 3.80 (s, 2H), 3.64 (s, 3H), 3.35 (s, 2H), 2.36 (s, 3H)。

化合物 146 及其盐酸盐 (146s) 的合成

参照实施例 1 的方法, 将 4I 水解制得 146, 收率 84%。再由 146 与盐酸成盐, 制得 146s, 收率 78%。MS (ESI)  $m/z$  399  $[M+H]^+$ ;  $^1H$  NMR (300 MHz, DMSO- $d_6$ )  $\delta$  8.86 (s, 1H), 8.15 (d,  $J$  = 7.2 Hz, 1H), 8.05 (d,  $J$  = 6.9 Hz, 1H), 7.80 (s, 1H), 7.70 (s, 1H), 7.47 (q,  $J$  = 8.1, 7.8 Hz, 5H), 7.37 (d,  $J$  = 6.6 Hz, 4H), 4.21 (s, 2H), 3.75 (s, 2H), 2.23 (s, 3H)。

采用与实施例 4 相似的操作, 制得下列化合物:

| 编号   | $^1H$ -NMR                                                                                                                                                                                                                                                                                                                                                               | ESI-MS<br>$m/z$<br>( $M+H$ ) $^+$ |
|------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------|
| 147  | $^1H$ NMR (300 MHz, DMSO- $d_6$ ) $\delta$ 8.30 (s, 1H), 8.14 (s, 1H), 7.93-7.83 (m, 2H), 7.72 (s, 1H), 7.47 (dt, $J$ = 15.6, 7.5 Hz, 4H), 7.35 (dd, $J$ = 16.8, 6.9 Hz, 4H), 5.27 (s, 1H), 4.31 (s, 2H), 3.70 (s, 2H), 3.02 (s, 2H), 2.37 (s, 3H)。                                                                                                                      | 385                               |
| 147s | $^1H$ NMR (300 MHz, DMSO- $d_6$ ) $\delta$ 9.27 (s, 1H), 8.30 (s, 1H), 8.14 (s, 1H), 7.93-7.83 (m, 2H), 7.72 (s, 1H), 7.47 (dt, $J$ = 15.6, 7.5 Hz, 4H), 7.35 (dd, $J$ = 16.8, 6.9 Hz, 4H), 5.27 (s, 1H), 4.31 (s, 2H), 3.70 (s, 2H), 3.02 (s, 2H), 2.37 (s, 3H)。                                                                                                        | 385                               |
| 148  | $^1H$ NMR (300 MHz, DMSO- $d_6$ ) $\delta$ 8.28 (s, 1H), 8.13 (d, $J$ = 6.9 Hz, 1H), 7.83 (d, $J$ = 7.5 Hz, 2H), 7.66 (d, $J$ = 4.8 Hz, 2H), 7.56 (s, 2H), 7.47 (d, $J$ = 7.5 Hz, 2H), 7.42 (d, $J$ = 7.8 Hz, 2H), 7.39-7.33 (m, 2H), 7.30 (d, $J$ = 7.5 Hz, 1H), 4.28 (s, 2H), 3.66 (s, 2H), 2.35 (s, 3H)。                                                              | 398                               |
| 148s | $^1H$ NMR (300 MHz, DMSO- $d_6$ ) $\delta$ 9.25 (s, 1H), 8.28 (s, 1H), 8.13 (d, $J$ = 6.9 Hz, 1H), 7.83 (d, $J$ = 7.5 Hz, 2H), 7.66 (d, $J$ = 4.8 Hz, 2H), 7.56 (s, 2H), 7.47 (d, $J$ = 7.5 Hz, 2H), 7.42 (d, $J$ = 7.8 Hz, 2H), 7.39-7.33 (m, 2H), 7.30 (d, $J$ = 7.5 Hz, 1H), 4.28 (s, 2H), 3.66 (s, 2H), 2.35 (s, 3H)。                                                | 398                               |
| 149  | $^1H$ NMR (300 MHz, DMSO- $d_6$ ) $\delta$ 8.76 (s, 1H), 8.05 (s, 1H), 7.92 (dd, $J$ = 14.1, 7.2 Hz, 2H), 7.53 (d, $J$ = 6.9 Hz, 2H), 7.47 (d, $J$ = 7.8 Hz, 3H), 7.43 (s, 1H), 7.38 (q, $J$ = 7.5, 5.7 Hz, 3H), 4.22 (s, 2H), 3.14 (t, $J$ = 7.5 Hz, 2H), 2.71 (t, $J$ = 7.2 Hz, 2H), 2.52 (s, 3H)。                                                                     | 413                               |
| 149s | $^1H$ NMR (300 MHz, DMSO- $d_6$ ) $\delta$ 9.27 (s, 1H), 8.76 (s, 1H), 8.05 (s, 1H), 7.92 (dd, $J$ = 14.1, 7.2 Hz, 2H), 7.53 (d, $J$ = 6.9 Hz, 2H), 7.47 (d, $J$ = 7.8 Hz, 3H), 7.43 (s, 1H), 7.38 (q, $J$ = 7.5, 5.7 Hz, 3H), 4.22 (s, 2H), 3.14 (t, $J$ = 7.5 Hz, 2H), 2.71 (t, $J$ = 7.2 Hz, 2H), 2.52 (s, 3H)。                                                       | 413                               |
| 150  | $^1H$ NMR (300 MHz, DMSO- $d_6$ ) $\delta$ 8.77 (s, 1H), 8.08 (s, 1H), 7.92 (dd, $J$ = 10.8, 6.0 Hz, 3H), 7.53 (d, $J$ = 4.8 Hz, 2H), 7.51-7.44 (m, 3H), 7.43 (s, 1H), 7.39 (d, $J$ = 3.3 Hz, 2H), 4.24 (t, $J$ = 9.3 Hz, 2H), 4.02 (d, $J$ = 7.2 Hz, 1H), 2.52 (s, 3H), 1.53 (d, $J$ = 7.2 Hz, 3H)。                                                                     | 413                               |
| 150s | $^1H$ NMR (300 MHz, DMSO- $d_6$ ) $\delta$ 9.23 (s, 1H), 8.08 (s, 1H), 7.92 (dd, $J$ = 10.8, 6.0 Hz, 2H), 7.53 (d, $J$ = 4.8 Hz, 2H), 7.51-7.44 (m, 3H), 7.43 (s, 1H), 7.39 (d, $J$ = 3.3 Hz, 2H), 7.36 (s, 2H), 4.24 (t, $J$ = 9.3 Hz, 2H), 4.02 (d, $J$ = 7.2 Hz, 1H), 2.52 (s, 3H), 1.53 (d, $J$ = 7.2 Hz, 3H)。                                                       | 413                               |
| 151  | $^1H$ NMR (300 MHz, DMSO- $d_6$ ) $\delta$ 8.24 (s, 1H), 8.09 (d, $J$ = 7.5 Hz, 1H), 7.84 (d, $J$ = 7.5 Hz, 1H), 7.64 (d, $J$ = 14.7 Hz, 4H), 7.51-7.32 (m, 6H), 4.19 (d, $J$ = 3.6 Hz, 2H), 3.83 (d, $J$ = 4.8 Hz, 1H), 3.63 (s, 2H), 2.37 (s, 3H)。                                                                                                                     | 429                               |
| 151s | $^1H$ NMR (300 MHz, DMSO- $d_6$ ) $\delta$ 9.27 (s, 1H), 8.09 (d, $J$ = 7.5 Hz, 1H), 7.84 (d, $J$ = 7.5 Hz, 1H), 7.64 (d, $J$ = 14.7 Hz, 3H), 7.51-7.32 (m, 8H), 4.19 (d, $J$ = 3.6 Hz, 2H), 3.83 (d, $J$ = 4.8 Hz, 1H), 3.63 (s, 2H), 2.37 (s, 3H)。                                                                                                                     | 429                               |
| 152  | $^1H$ NMR (300 MHz, DMSO- $d_6$ ) $\delta$ 8.15 (s, 1H), 8.00 (d, $J$ = 6.3 Hz, 1H), 7.81 (d, $J$ = 7.5 Hz, 1H), 7.63 (s, 1H), 7.54 (d, $J$ = 6.3 Hz, 2H), 7.51-7.32 (m, 6H), 7.28 (d, $J$ = 7.5 Hz, 1H), 4.07 (d, $J$ = 13.5 Hz, 1H), 3.86 (d, $J$ = 13.8 Hz, 2H), 3.62-3.53 (m, 1H), 2.34 (s, 3H), 1.14 (d, $J$ = 6.0 Hz, 3H)。                                         | 444                               |
| 152s | $^1H$ NMR (300 MHz, DMSO- $d_6$ ) $\delta$ 9.15 (s, 1H), 8.15 (s, 1H), 8.00 (d, $J$ = 6.3 Hz, 1H), 7.81 (d, $J$ = 7.5 Hz, 1H), 7.63 (s, 1H), 7.54 (d, $J$ = 6.3 Hz, 2H), 7.51-7.32 (m, 6H), 7.28 (d, $J$ = 7.5 Hz, 1H), 4.07 (d, $J$ = 13.5 Hz, 1H), 3.86 (d, $J$ = 13.8 Hz, 2H), 3.62-3.53 (m, 1H), 2.34 (s, 3H), 1.14 (d, $J$ = 6.0 Hz, 3H)。                           | 444                               |
| 153  | $^1H$ NMR (300 MHz, Methanol- $d_4$ ) $\delta$ 8.09 (s, 2H), 8.03-7.94 (m, 1H), 7.69 (d, $J$ = 8.4 Hz, 1H), 7.55 (dd, $J$ = 11.1, 5.7 Hz, 4H), 7.51-7.45 (m, 3H), 7.41 (t, $J$ = 6.9 Hz, 2H), 4.61 (s, 2H), 4.03-3.90 (m, 1H), 3.60 (d, $J$ = 12.9 Hz, 1H), 3.20-3.12 (m, 1H), 2.94-2.84 (m, 1H), 2.53 (s, 3H), 2.29 (s, 2H), 1.78 (d, $J$ = 10.8 Hz, 1H), 1.49 (s, 2H)。 | 453                               |
| 153s | $^1H$ NMR (300 MHz, Methanol- $d_4$ ) $\delta$ 9.13 (s, 1H), 8.09 (s, 2H), 8.03-7.94 (m, 1H), 7.69 (d, $J$ = 8.4 Hz, 1H), 7.55 (dd, $J$ =                                                                                                                                                                                                                                | 453                               |

|      |                                                                                                                                                                                                                                                                                                                                                                                                                                               |     |
|------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|
|      | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 11.1, 5.7 Hz, 4H), 7.51-7.45 (m, 3H), 7.41 (t, <i>J</i> = 6.9 Hz, 2H), 4.61 (s, 2H), 4.03-3.90 (m, 1H), 3.60 (d, <i>J</i> = 12.9 Hz, 1H), 3.20-3.12 (m, 1H), 2.94-2.84 (m, 1H), 2.53 (s, 3H), 2.29 (s, 2H), 1.78 (d, <i>J</i> = 10.8 Hz, 1H), 1.49 (s, 2H).                                                                                                                      |     |
| 154  | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.04 (d, <i>J</i> = 8.1 Hz, 2H), 7.86-7.80 (m, 1H), 7.62 (s, 1H), 7.53 (s, 1H), 7.50 (d, <i>J</i> = 2.4 Hz, 2H), 7.47 (s, 1H), 7.43 (t, <i>J</i> = 3.6 Hz, 2H), 7.41-7.35 (m, 2H), 7.29 (dd, <i>J</i> = 7.8, 1.5 Hz, 1H), 3.80 (s, 2H), 3.35 (s, 2H), 2.36 (s, 3H).                                                                                                              | 413 |
| 154s | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 9.27 (s, 1H), 8.04 (d, <i>J</i> = 8.1 Hz, 2H), 7.86-7.80 (m, 1H), 7.62 (s, 1H), 7.53 (s, 1H), 7.50 (d, <i>J</i> = 2.4 Hz, 2H), 7.47 (s, 1H), 7.43 (t, <i>J</i> = 3.6 Hz, 2H), 7.41-7.35 (m, 2H), 7.29 (dd, <i>J</i> = 7.8, 1.5 Hz, 1H), 3.80 (s, 2H), 3.35 (s, 2H), 2.36 (s, 3H).                                                                                                | 399 |
| 155  | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.14 (d, <i>J</i> = 8.1 Hz, 2H), 7.83 (d, <i>J</i> = 7.8 Hz, 1H), 7.74 (d, <i>J</i> = 8.1 Hz, 2H), 7.65 (s, 1H), 7.47 (d, <i>J</i> = 7.5 Hz, 2H), 7.41 (d, <i>J</i> = 6.9 Hz, 2H), 7.39-7.34 (m, 2H), 7.29 (d, <i>J</i> = 7.5 Hz, 1H), 4.24 (t, <i>J</i> = 5.7 Hz, 2H), 3.69 (d, <i>J</i> = 5.4 Hz, 2H), 2.99 (d, <i>J</i> = 6.0 Hz, 2H), 2.35 (s, 3H).                          | 385 |
| 155s | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 9.26 (s, 1H), 8.14 (d, <i>J</i> = 8.1 Hz, 2H), 7.83 (d, <i>J</i> = 7.8 Hz, 1H), 7.74 (d, <i>J</i> = 8.1 Hz, 2H), 7.65 (s, 1H), 7.47 (d, <i>J</i> = 7.5 Hz, 2H), 7.41 (d, <i>J</i> = 6.9 Hz, 2H), 7.39-7.34 (m, 2H), 7.29 (d, <i>J</i> = 7.5 Hz, 1H), 4.24 (t, <i>J</i> = 5.7 Hz, 2H), 3.69 (d, <i>J</i> = 5.4 Hz, 2H), 2.99 (d, <i>J</i> = 6.0 Hz, 2H), 2.35 (s, 3H).            | 385 |
| 156  | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.38 (s, 2H), 8.17 (d, <i>J</i> = 7.8 Hz, 2H), 7.85 (d, <i>J</i> = 8.4 Hz, 1H), 7.81-7.65 (m, 3H), 7.40 (m, 5H), 4.27 (d, <i>J</i> = 5.5 Hz, 2H), 3.22-3.10 (m, 2H), 2.73 (s, 2H), 2.37 (d, <i>J</i> = 2.7 Hz, 3H).                                                                                                                                                              | 413 |
| 156s | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 9.23 (s, 1H), 8.17 (d, <i>J</i> = 7.8 Hz, 2H), 7.85 (d, <i>J</i> = 8.4 Hz, 1H), 7.81-7.65 (m, 3H), 7.40 (m, 7H), 4.27 (d, <i>J</i> = 5.5 Hz, 2H), 3.22-3.10 (m, 2H), 2.73 (s, 2H), 2.37 (d, <i>J</i> = 2.7 Hz, 3H).                                                                                                                                                              | 413 |
| 157  | <sup>1</sup> H NMR (300 MHz, Methanol- <i>d</i> <sub>4</sub> ) δ 8.09 (s, 2H), 8.03-7.94 (m, 1H), 7.69 (d, <i>J</i> = 8.4 Hz, 1H), 7.55 (dd, <i>J</i> = 11.1, 5.7 Hz, 4H), 7.51-7.45 (m, 3H), 7.41 (t, <i>J</i> = 6.9 Hz, 2H), 4.61 (s, 2H), 4.03-3.90 (m, 1H), 3.60 (d, <i>J</i> = 12.9 Hz, 1H), 3.20-3.12 (m, 1H), 2.94-2.84 (m, 1H), 2.53 (s, 2H), 2.29 (s, 3H), 1.78 (d, <i>J</i> = 10.8 Hz, 1H), 1.49 (s, 2H).                           | 453 |
| 157s | <sup>1</sup> H NMR (300 MHz, Methanol- <i>d</i> <sub>4</sub> ) δ 8.21 (s, 1H), 8.09 (s, 2H), 8.03-7.94 (m, 1H), 7.69 (d, <i>J</i> = 8.4 Hz, 1H), 7.55 (dd, <i>J</i> = 11.1, 5.7 Hz, 4H), 7.51-7.45 (m, 3H), 7.41 (t, <i>J</i> = 6.9 Hz, 2H), 4.61 (s, 2H), 4.03-3.90 (m, 1H), 3.60 (d, <i>J</i> = 12.9 Hz, 1H), 3.20-3.12 (m, 1H), 2.94-2.84 (m, 1H), 2.53 (s, 2H), 2.29 (s, 3H), 1.78 (d, <i>J</i> = 10.8 Hz, 1H), 1.49 (s, 2H).             | 453 |
| 158  | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.27 (s, 1H), 7.99 (d, <i>J</i> = 8.7 Hz, 1H), 7.84 (d, <i>J</i> = 7.7 Hz, 1H), 7.68-7.60 (m, 2H), 7.48 (d, <i>J</i> = 7.5 Hz, 2H), 7.42 (d, <i>J</i> = 7.5 Hz, 2H), 7.38 (d, <i>J</i> = 7.2 Hz, 2H), 7.30 (d, <i>J</i> = 7.5 Hz, 1H), 3.93 (s, 2H), 2.35 (s, 3H).                                                                                                               | 419 |
| 158s | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.86 (s, 1H), 8.36 (s, 1H), 8.15 (d, <i>J</i> = 7.2 Hz, 1H), 8.05 (d, <i>J</i> = 6.9 Hz, 1H), 7.80 (s, 1H), 7.70 (s, 1H), 7.47 (q, <i>J</i> = 8.1, 7.8 Hz, 5H), 7.37 (d, <i>J</i> = 6.6 Hz, 3H), 4.21 (s, 2H), 2.23 (s, 3H).                                                                                                                                                     | 419 |
| 159  | <sup>1</sup> H NMR (300 MHz, Methanol- <i>d</i> <sub>4</sub> ) δ 8.40 (d, <i>J</i> = 2.1 Hz, 1H), 8.16 (dd, <i>J</i> = 8.4, 2.1 Hz, 1H), 7.83 (d, <i>J</i> = 7.5 Hz, 1H), 7.72 (d, <i>J</i> = 8.4 Hz, 1H), 7.54 (s, 1H), 7.51-7.28 (m, 7H), 4.42 (s, 2H), 3.24 (s, 2H), 2.79 (s, 1H), 2.40 (s, 3H), 2.01 (s, 2H), 1.86 (s, 2H), 0.29 (s, 2H).                                                                                                 | 488 |
| 159s | <sup>1</sup> H NMR (300 MHz, Methanol- <i>d</i> <sub>4</sub> ) δ 9.27 (s, 1H), 8.40 (d, <i>J</i> = 2.1 Hz, 1H), 8.16 (dd, <i>J</i> = 8.4, 2.1 Hz, 1H), 7.83 (d, <i>J</i> = 7.5 Hz, 1H), 7.72 (d, <i>J</i> = 8.4 Hz, 1H), 7.54 (s, 1H), 7.51-7.28 (m, 7H), 4.42 (s, 2H), 3.24 (s, 2H), 2.79 (s, 1H), 2.40 (s, 3H), 2.01 (s, 2H), 1.86 (s, 2H), 0.29 (s, 2H).                                                                                   | 488 |
| 160  | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 7.98 (d, <i>J</i> = 7.9 Hz, 1H), 7.76 (d, <i>J</i> = 5.3 Hz, 3H), 7.51 (d, <i>J</i> = 14.9 Hz, 4H), 7.41 (d, <i>J</i> = 13.3 Hz, 3H), 7.30 (d, <i>J</i> = 7.6 Hz, 1H), 3.80 (s, 2H), 3.35 (s, 2H), 2.36 (s, 3H).                                                                                                                                                                 | 433 |
| 160s | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 9.27 (s, 1H), 7.98 (d, <i>J</i> = 7.9 Hz, 1H), 7.76 (d, <i>J</i> = 5.3 Hz, 3H), 7.51 (d, <i>J</i> = 14.9 Hz, 4H), 7.41 (d, <i>J</i> = 13.3 Hz, 3H), 7.30 (d, <i>J</i> = 7.6 Hz, 1H), 4.00 (s, 2H), 3.35 (s, 2H), 2.36 (s, 3H).                                                                                                                                                   | 433 |
| 161  | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.16 (s, 1H), 7.88 (d, <i>J</i> = 7.8 Hz, 1H), 7.70 (s, 2H), 7.54-7.40 (m, 5H), 7.34 (dd, <i>J</i> = 18.0, 7.5 Hz, 3H), 4.10 (s, 2H), 3.48 (s, 2H), 2.36 (s, 3H).                                                                                                                                                                                                                | 433 |
| 161s | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.93 (s, 1H), 8.16 (s, 1H), 7.88 (d, <i>J</i> = 7.8 Hz, 1H), 7.70 (s, 2H), 7.54-7.40 (m, 5H), 7.34 (dd, <i>J</i> = 18.0, 7.5 Hz, 3H), 4.10 (s, 2H), 3.48 (s, 2H), 2.36 (s, 3H).                                                                                                                                                                                                  | 433 |
| 162  | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.87 (s, 1H), 8.08 (s, 1H), 7.99 (dd, <i>J</i> = 6.0, 3.3 Hz, 1H), 7.92 (d, <i>J</i> = 6.9 Hz, 1H), 7.64-7.60 (m, 2H), 7.55 (d, <i>J</i> = 6.9 Hz, 2H), 7.52 (d, <i>J</i> = 2.4 Hz, 1H), 7.49 (t, <i>J</i> = 2.4 Hz, 2H), 7.47-7.45 (m, 1H), 4.24 (d, <i>J</i> = 4.8 Hz, 2H), 4.03 (q, <i>J</i> = 7.2, 6.3 Hz, 1H), 2.31 (s, 3H), 1.53 (d, <i>J</i> = 7.2 Hz, 3H).               | 447 |
| 162s | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 9.25 (s, 1H), 8.87 (s, 1H), 8.08 (s, 1H), 7.99 (dd, <i>J</i> = 6.0, 3.3 Hz, 1H), 7.92 (d, <i>J</i> = 6.9 Hz, 1H), 7.64-7.60 (m, 2H), 7.55 (d, <i>J</i> = 6.9 Hz, 2H), 7.52 (d, <i>J</i> = 2.4 Hz, 1H), 7.49 (t, <i>J</i> = 2.4 Hz, 2H), 7.47-7.45 (m, 1H), 4.24 (d, <i>J</i> = 4.8 Hz, 2H), 4.03 (q, <i>J</i> = 7.2, 6.3 Hz, 1H), 2.31 (s, 3H), 1.53 (d, <i>J</i> = 7.2 Hz, 3H). | 447 |

|      |                                                                                                                                                                                                                                                                                                                                                                   |     |
|------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|
| 163  | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.11 (s, 1H), 8.02 (s, 1H), 7.88 (d, <i>J</i> = 8.4 Hz, 1H), 7.68 (d, <i>J</i> = 6.0 Hz, 2H), 7.44 (m, 7H), 4.07 (d, <i>J</i> = 15.9 Hz, 2H), 3.96 (d, <i>J</i> = 9.3 Hz, 1H), 3.73-3.67 (m, 2H), 2.36 (s, 3H).                                                                                      | 464 |
| 163s | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 9.16 (s, 1H), 8.11 (s, 1H), 8.02 (s, 1H), 7.88 (d, <i>J</i> = 8.4 Hz, 1H), 7.68 (d, <i>J</i> = 6.0 Hz, 2H), 7.44 (dq, <i>J</i> = 15.9, 7.8, 7.2 Hz, 7H), 4.07 (d, <i>J</i> = 15.9 Hz, 2H), 3.96 (d, <i>J</i> = 9.3 Hz, 1H), 3.73-3.67 (m, 2H), 2.36 (s, 3H).                                         | 464 |
| 164  | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.30 (s, 1H), 8.14 (s, 1H), 7.93-7.83 (m, 2H), 7.72 (s, 1H), 7.47 (dt, <i>J</i> = 15.6, 7.5 Hz, 5H), 7.35 (dd, <i>J</i> = 16.8, 6.9 Hz, 2H), 5.27 (s, 1H), 4.31 (s, 2H), 3.70 (s, 2H), 3.02 (s, 2H), 2.37 (s, 3H).                                                                                   | 420 |
| 164s | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 9.18 (s, 1H), 8.30 (s, 1H), 8.14 (s, 1H), 7.93-7.83 (m, 2H), 7.72 (s, 1H), 7.47 (dt, <i>J</i> = 15.6, 7.5 Hz, 5H), 7.35 (dd, <i>J</i> = 16.8, 6.9 Hz, 2H), 5.27 (s, 1H), 4.31 (s, 2H), 3.70 (s, 2H), 3.02 (s, 2H), 2.37 (s, 3H).                                                                     | 420 |
| 165  | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 7.79 (s, 1H), 7.74 (s, 1H), 7.68 (s, 1H), 7.61 (s, 1H), 7.50 (s, 1H), 7.47 (s, 1H), 7.45 (s, 1H), 7.42 (s, 1H), 7.38 (d, <i>J</i> = 7.8 Hz, 3H), 7.33 (s, 1H), 4.04 (s, 2H), 3.70 (s, 2H), 2.37 (s, 3H).                                                                                             | 434 |
| 165s | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 9.16 (s, 1H), 7.79 (s, 1H), 7.74 (s, 1H), 7.68 (s, 1H), 7.61 (s, 1H), 7.50 (s, 1H), 7.47 (s, 1H), 7.45 (s, 1H), 7.42 (s, 1H), 7.38 (d, <i>J</i> = 7.8 Hz, 3H), 7.33 (s, 1H), 4.04 (s, 2H), 3.73 (s, 2H), 2.37 (s, 3H).                                                                               | 434 |
| 166  | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.28 (s, 1H), 7.80 (d, <i>J</i> = 8.7 Hz, 1H), 7.75 (s, 2H), 7.64 (s, 1H), 7.51-7.42 (m, 5H), 7.33 (s, 2H), 4.20 (s, 2H), 3.83 (s, 2H), 3.76 (s, 1H), 2.37 (s, 3H).                                                                                                                                  | 465 |
| 166s | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 9.27 (s, 1H), 8.28 (s, 1H), 7.80 (d, <i>J</i> = 8.7 Hz, 1H), 7.75 (s, 2H), 7.64 (s, 1H), 7.51-7.42 (m, 5H), 7.33 (s, 2H), 4.20 (s, 2H), 3.83 (s, 2H), 3.76 (s, 1H), 2.37 (s, 3H).                                                                                                                    | 465 |
| 167  | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.33 (s, 1H), 7.81 (d, <i>J</i> = 6.9 Hz, 1H), 7.77-7.68 (m, 3H), 7.48 (dd, <i>J</i> = 13.8, 7.8 Hz, 4H), 7.34 (dd, <i>J</i> = 16.8, 6.9 Hz, 3H), 4.28 (s, 2H), 3.98-3.88 (m, 3H), 2.37 (s, 3H).                                                                                                     | 465 |
| 167s | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.93 (s, 1H), 8.68 (s, 2H), 8.33 (s, 1H), 7.81 (d, <i>J</i> = 6.9 Hz, 1H), 7.77-7.68 (m, 3H), 7.48 (dd, <i>J</i> = 13.8, 7.6 Hz, 3H), 7.34 (dd, <i>J</i> = 16.8, 6.9 Hz, 2H), 4.28 (s, 2H), 3.98-3.88 (m, 3H), 2.37 (s, 3H).                                                                         | 465 |
| 168  | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.35-8.29 (m, 1H), 7.78 (d, <i>J</i> = 8.1 Hz, 1H), 7.73 (s, 1H), 7.52 (s, 1H), 7.47 (d, <i>J</i> = 7.2 Hz, 2H), 7.42 (d, <i>J</i> = 8.1 Hz, 2H), 7.38-7.33 (m, 2H), 7.31 (d, <i>J</i> = 7.5 Hz, 2H), 4.26 (s, 2H), 3.87 (s, 2H), 2.35 (s, 3H).                                                      | 417 |
| 168s | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 9.27 (s, 1H), 8.35-8.29 (m, 1H), 7.78 (d, <i>J</i> = 8.1 Hz, 1H), 7.73 (s, 1H), 7.52 (s, 1H), 7.47 (d, <i>J</i> = 7.2 Hz, 3H), 7.42 (d, <i>J</i> = 8.1 Hz, 2H), 7.38-7.33 (m, 2H), 7.31 (d, <i>J</i> = 7.5 Hz, 1H), 4.26 (s, 2H), 3.87 (s, 2H), 2.35 (s, 3H).                                        | 417 |
| 169  | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.36 (d, <i>J</i> = 6.9 Hz, 1H), 7.79 (d, <i>J</i> = 8.1 Hz, 2H), 7.73 (s, 1H), 7.53-7.50 (m, 1H), 7.47 (d, <i>J</i> = 6.9 Hz, 2H), 7.45-7.40 (m, 2H), 7.39-7.33 (m, 2H), 7.31 (d, <i>J</i> = 7.8 Hz, 1H), 4.04 (s, 2H), 3.98 (t, 1H), 3.56 (s, 2H), 2.35 (s, 3H).                                   | 447 |
| 169s | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 9.59 (d, <i>J</i> = 43.7 Hz, 1H), 8.36 (d, <i>J</i> = 6.9 Hz, 1H), 7.79 (d, <i>J</i> = 8.1 Hz, 2H), 7.73 (s, 1H), 7.53-7.50 (m, 1H), 7.47 (d, <i>J</i> = 6.9 Hz, 2H), 7.45-7.40 (m, 2H), 7.39-7.33 (m, 2H), 7.31 (d, <i>J</i> = 7.8 Hz, 1H), 4.04 (s, 2H), 3.98 (t, 1H), 3.56 (s, 2H), 2.35 (s, 3H). | 447 |
| 170  | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.14 (s, 1H), 7.83 (dd, <i>J</i> = 12.0, 7.8 Hz, 2H), 7.72 (s, 1H), 7.52-7.44 (m, 3H), 7.41 (d, <i>J</i> = 7.5 Hz, 2H), 7.36 (d, <i>J</i> = 7.5 Hz, 2H), 7.29 (d, <i>J</i> = 7.5 Hz, 1H), 4.01 (s, 2H), 3.33 (s, 2H), 2.35 (s, 3H).                                                                  | 478 |
| 170s | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 9.36 (d, <i>J</i> = 12.0 Hz, 1H), 8.14 (s, 1H), 7.83 (dd, <i>J</i> = 12.0, 7.8 Hz, 2H), 7.72 (s, 1H), 7.52-7.44 (m, 3H), 7.41 (d, <i>J</i> = 7.5 Hz, 2H), 7.36 (d, <i>J</i> = 7.5 Hz, 2H), 7.29 (d, <i>J</i> = 7.5 Hz, 1H), 4.01 (s, 2H), 3.33 (s, 2H), 2.35 (s, 3H).                                | 478 |
| 171  | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.21-8.11 (m, 2H), 7.87 (d, <i>J</i> = 7.8 Hz, 1H), 7.74 (s, 1H), 7.47 (d, <i>J</i> = 7.2 Hz, 2H), 7.42 (d, <i>J</i> = 7.5 Hz, 2H), 7.36 (d, <i>J</i> = 7.5 Hz, 3H), 7.31 (d, <i>J</i> = 7.5 Hz, 1H), 4.22 (s, 2H), 3.88 (s, 2H), 2.37 (s, 3H).                                                      | 525 |
| 171s | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 9.29 (s, 1H), 8.21-8.11 (m, 2H), 7.87 (d, <i>J</i> = 7.8 Hz, 1H), 7.74 (s, 1H), 7.47 (d, <i>J</i> = 7.2 Hz, 2H), 7.42 (d, <i>J</i> = 7.5 Hz, 2H), 7.36 (d, <i>J</i> = 7.5 Hz, 3H), 7.31 (d, <i>J</i> = 7.5 Hz, 1H), 4.22 (s, 2H), 3.88 (s, 2H), 2.37 (s, 3H).                                        | 525 |
| 172  | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.38 (s, 1H), 8.11 (d, <i>J</i> = 8.1 Hz, 1H), 7.89 (d, <i>J</i> = 8.1 Hz, 1H), 7.77 (s, 1H), 7.70 (d, <i>J</i> = 7.8 Hz, 1H), 7.46 (dd, <i>J</i> = 15.0, 7.2 Hz, 4H), 7.36 (d, <i>J</i> = 8.1 Hz, 3H), 4.36 (s, 2H), 3.92 (s, 2H), 2.32 (s, 3H).                                                    | 444 |
| 172s | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 9.36 (s, 1H), 8.38 (s, 1H), 8.11 (d, <i>J</i> = 8.1 Hz, 1H), 7.89 (d, <i>J</i> = 8.1 Hz, 1H), 7.77 (s, 1H), 7.70 (d, <i>J</i> = 7.8 Hz, 1H), 7.46 (dd, <i>J</i> = 15.0, 7.2 Hz, 4H), 7.36 (d, <i>J</i> = 8.1 Hz, 3H), 4.36 (s, 2H), 3.92 (s, 2H), 2.32 (s, 3H).                                      | 444 |
| 173  | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.04 (d, <i>J</i> = 8.1 Hz, 2H), 7.86-7.80 (m, 1H), 7.62 (s, 1H), 7.53 (s, 1H), 7.50 (d, <i>J</i> = 2.4 Hz, 2H), 7.47 (s, 1H), 7.43 (t, <i>J</i> = 3.6 Hz, 2H), 7.41-7.35 (m, 2H), 3.35 (s, 2H), 2.36 (s, 3H).                                                                                       | 434 |
| 173s | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 9.37 (s, 1H), 8.04 (d, <i>J</i> = 8.1 Hz, 2H), 7.86-7.80 (m, 1H), 7.62 (s, 1H), 7.53 (s, 1H), 7.50 (d, <i>J</i> = 2.4 Hz, 2H), 7.47 (s, 1H), 7.43 (t, <i>J</i> = 3.6 Hz, 2H), 7.41-7.35 (m, 2H), 3.80 (s, 2H), 3.35 (s, 2H), 2.36 (s, 3H).                                                           | 434 |

|      |                                                                                                                                                                                                                                                                                                                                                             |     |
|------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|
| 174  | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.27 (s, 1H), 7.99 (d, <i>J</i> = 8.6 Hz, 1H), 7.84 (d, <i>J</i> = 7.8 Hz, 1H), 7.68-7.60 (m, 2H), 7.48 (d, <i>J</i> = 7.5 Hz, 2H), 7.42 (d, <i>J</i> = 7.5 Hz, 2H), 7.38 (d, <i>J</i> = 7.5 Hz, 2H), 7.30 (d, <i>J</i> = 7.5 Hz, 1H), 3.93 (s, 2H), 3.22 (s, 2H), 2.35 (s, 3H).               | 434 |
| 174s | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 9.25 (s, 1H), 8.27 (s, 1H), 7.99 (d, <i>J</i> = 8.6 Hz, 1H), 7.84 (d, <i>J</i> = 7.8 Hz, 1H), 7.68-7.60 (m, 2H), 7.48 (d, <i>J</i> = 7.5 Hz, 2H), 7.42 (d, <i>J</i> = 7.5 Hz, 2H), 7.38 (d, <i>J</i> = 7.5 Hz, 2H), 7.30 (d, <i>J</i> = 7.5 Hz, 1H), 3.93 (s, 2H), 3.22 (s, 2H), 2.35 (s, 3H). | 434 |
| 175  | <sup>1</sup> H NMR (300 MHz, Methanol- <i>d</i> <sub>4</sub> ) δ 8.40 (d, <i>J</i> = 2.1 Hz, 1H), 8.16 (dd, <i>J</i> = 8.4, 2.1 Hz, 1H), 7.83 (d, <i>J</i> = 7.5 Hz, 1H), 7.72 (d, <i>J</i> = 8.4 Hz, 1H), 7.54 (s, 1H), 7.51-7.28 (m, 7H), 4.42 (s, 2H), 3.24 (s, 2H), 2.79 (s, 1H), 2.40 (s, 3H), 2.01 (s, 2H), 1.86 (s, 2H), 0.36 (s, 2H).               | 448 |
| 175s | <sup>1</sup> H NMR (300 MHz, Methanol- <i>d</i> <sub>4</sub> ) δ 9.36 (s, 1H), 8.40 (d, <i>J</i> = 2.1 Hz, 1H), 8.16 (dd, <i>J</i> = 8.4, 2.1 Hz, 1H), 7.83 (d, <i>J</i> = 7.5 Hz, 1H), 7.72 (d, <i>J</i> = 8.4 Hz, 1H), 7.54 (s, 1H), 7.51-7.28 (m, 7H), 4.42 (s, 2H), 3.24 (s, 2H), 2.79 (s, 1H), 2.40 (s, 3H), 2.01 (s, 2H), 1.86 (s, 2H), 0.36 (s, 2H). | 448 |
| 176  | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.04 (d, <i>J</i> = 8.1 Hz, 2H), 7.86-7.80 (m, 1H), 7.62 (s, 1H), 7.53 (s, 1H), 7.50 (d, <i>J</i> = 2.4 Hz, 2H), 7.47 (s, 1H), 7.43 (t, <i>J</i> = 3.6 Hz, 2H), 7.41-7.35 (m, 2H), 3.80 (s, 2H), 3.35 (s, 2H), 2.36 (s, 3H).                                                                   | 444 |
| 176s | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 9.02 (s, 1H), 8.04 (d, <i>J</i> = 8.1 Hz, 2H), 7.86-7.80 (m, 1H), 7.62 (s, 1H), 7.53 (s, 1H), 7.50 (d, <i>J</i> = 2.4 Hz, 2H), 7.47 (s, 1H), 7.43 (t, <i>J</i> = 3.6 Hz, 2H), 7.41-7.35 (m, 2H), 3.80 (s, 2H), 3.64(s, 3H), 3.35 (s, 2H), 2.36 (s, 3H).                                        | 444 |
| 177  | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 7.84 (d, <i>J</i> = 6.8 Hz, 1H), 7.70 (d, <i>J</i> = 6.3 Hz, 1H), 7.62 (dd, <i>J</i> = 9.0, 5.2 Hz, 3H), 7.56-7.33 (m, 6H), 7.29 (d, <i>J</i> = 7.2 Hz, 1H), 3.95 (s, 2H), 3.60 (d, <i>J</i> = 35.9 Hz, 2H), 2.35 (s, 3H).                                                                     | 429 |
| 177s | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.94 (s, 1H), 7.84 (d, <i>J</i> = 6.8 Hz, 1H), 7.70 (d, <i>J</i> = 6.3 Hz, 1H), 7.62 (dd, <i>J</i> = 8.9, 5.3 Hz, 3H), 7.56-7.33 (m, 6H), 7.29 (d, <i>J</i> = 7.2 Hz, 1H), 3.95 (s, 2H), 3.60 (d, <i>J</i> = 36.0 Hz, 2H), 2.35 (s, 3H).                                                       | 429 |
| 178  | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.24 (d, <i>J</i> = 8.2 Hz, 1H), 8.12 (s, 1H), 7.92 (d, <i>J</i> = 7.8 Hz, 1H), 7.75 (s, 1H), 7.70 (d, <i>J</i> = 7.8 Hz, 1H), 7.55-7.30 (m, 7H), 4.23 (s, 2H), 3.73 (s, 2H), 2.32 (s, 3H).                                                                                                    | 444 |
| 178s | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 9.36 (s, 1H), 8.24 (d, <i>J</i> = 8.2 Hz, 1H), 8.12 (s, 1H), 7.92 (d, <i>J</i> = 7.8 Hz, 1H), 7.75 (s, 1H), 7.70 (d, <i>J</i> = 7.8 Hz, 1H), 7.55-7.30 (m, 7H), 4.23 (s, 2H), 3.73 (s, 2H), 2.32 (s, 3H).                                                                                      | 444 |
| 179  | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.38 (s, 1H), 8.08 (s, 1H), 8.05-7.99 (m, 1H), 7.78 (d, <i>J</i> = 8.2 Hz, 1H), 7.71 (d, <i>J</i> = 8.2 Hz, 1H), 7.62 (t, <i>J</i> = 7.8 Hz, 2H), 7.49 (s, 3H), 7.48-7.42 (m, 2H), 4.29 (s, 2H), 3.91 (s, 2H).                                                                                 | 453 |
| 179s | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.86 (s, 1H), 8.38 (s, 1H), 8.08 (s, 1H), 8.05-7.99 (m, 1H), 7.78 (d, <i>J</i> = 8.2 Hz, 1H), 7.71 (d, <i>J</i> = 8.2 Hz, 1H), 7.62 (t, <i>J</i> = 7.8 Hz, 2H), 7.49 (s, 3H), 7.48-7.42 (m, 2H), 4.29 (s, 2H), 3.91 (s, 2H).                                                                   | 453 |
| 180  | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.36 (s, 1H), 8.07 (s, 1H), 8.01 (d, <i>J</i> = 8.4 Hz, 1H), 7.73 (d, <i>J</i> = 5.1 Hz, 2H), 7.62 (t, <i>J</i> = 7.6 Hz, 1H), 7.57-7.40 (m, 6H), 4.29 (s, 2H), 3.92 (s, 3H).                                                                                                                  | 484 |
| 180s | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.96 (s, 1H), 8.36 (s, 1H), 8.07 (s, 2H), 8.01 (d, <i>J</i> = 8.4 Hz, 1H), 7.73 (d, <i>J</i> = 5.1 Hz, 2H), 7.62 (t, <i>J</i> = 7.6 Hz, 1H), 7.57-7.40 (m, 5H), 4.29 (s, 2H), 3.94 (m, 3H).                                                                                                    | 484 |
| 181  | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.42 (s, 1H), 8.06 (s, 2H), 7.78 (s, 2H), 7.59 (t, <i>J</i> = 7.8 Hz, 1H), 7.49 (s, 1H), 7.47 (s, 1H), 7.47-7.45 (m, 2H), 7.44 (s, 2H), 4.40 (s, 2H), 2.94 (s, 3H), 2.00 (s, 2H), 1.84 (s, 2H), 1.43 (s, 2H).                                                                                  | 508 |
| 181s | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 9.36 (s, 1H), 8.42 (s, 1H), 8.06 (s, 2H), 7.78 (s, 2H), 7.59 (t, <i>J</i> = 7.8 Hz, 1H), 7.49 (s, 1H), 7.47 (s, 1H), 7.47-7.45 (m, 2H), 7.44 (s, 2H), 4.40 (s, 2H), 2.94 (s, 3H), 2.00 (s, 2H), 1.84 (s, 2H), 1.43 (s, 2H).                                                                    | 508 |
| 182  | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.39 (d, <i>J</i> = 1.8 Hz, 1H), 8.06 (s, 1H), 8.02 (dd, <i>J</i> = 7.8, 1.8 Hz, 1H), 7.75 (d, <i>J</i> = 3.9 Hz, 2H), 7.60 (t, <i>J</i> = 7.8 Hz, 1H), 7.50 (s, 1H), 7.45-7.4 (m, 5H), 5.25 (s, 1H), 4.28 (s, 2H), 3.69 (s, 2H), 3.01 (s, 2H).                                                | 440 |
| 182s | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 9.12 (s, 1H), 8.39 (d, <i>J</i> = 1.8 Hz, 1H), 8.06 (s, 1H), 8.02 (dd, <i>J</i> = 7.8, 1.8 Hz, 1H), 7.75 (d, <i>J</i> = 3.9 Hz, 2H), 7.60 (t, <i>J</i> = 7.8 Hz, 1H), 7.50 (s, 1H), 7.45-7.4 (m, 5H), 5.25 (s, 1H), 4.28 (s, 2H), 3.69 (s, 2H), 3.01 (s, 2H).                                  | 440 |
| 183  | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.33 (s, 1H), 8.07 (s, 1H), 7.89 (s, 1H), 7.77 (s, 1H), 7.69 (d, <i>J</i> = 9.7 Hz, 2H), 7.51-7.38 (m, 6H), 4.28 (s, 2H), 3.90 (s, 2H), 3.68(s, 3H).                                                                                                                                           | 498 |
| 183s | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.95 (s, 1H), 8.33 (s, 1H), 8.07 (s, 1H), 7.89 (s, 1H), 7.77 (s, 1H), 7.69 (d, <i>J</i> = 9.7 Hz, 2H), 7.51-7.38 (m, 6H), 4.28 (s, 2H), 3.90 (s, 2H).                                                                                                                                          | 498 |
| 184  | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.36 (s, 1H), 8.07 (s, 1H), 8.01 (d, <i>J</i> = 8.4 Hz, 1H), 7.73 (d, <i>J</i> = 5.1 Hz, 2H), 7.62 (t, <i>J</i> = 7.6 Hz, 1H), 7.57-7.40 (m, 6H), 4.29 (s, 2H), 3.64(s, 3H).                                                                                                                   | 528 |
| 184s | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.92 (s, 1H), 8.36 (s, 1H), 8.07 (s, 1H), 8.01 (d, <i>J</i> = 8.4 Hz, 1H), 7.73 (d, <i>J</i> = 5.1 Hz, 2H),                                                                                                                                                                                    | 528 |

|      |                                                                                                                                                                                                                                                                                                                      |     |
|------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|
|      | 7.62 (t, $J = 7.6$ Hz, 1H), 7.57-7.40 (m, 6H), 4.29 (s, 2H), 3.94 (m, 3H).                                                                                                                                                                                                                                           |     |
| 185  | $^1\text{H}$ NMR (300 MHz, DMSO- $d_6$ ) $\delta$ 8.48 (s, 1H), 8.16 (d, $J = 8.4$ Hz, 1H), 8.03 (s, 1H), 7.98 (d, $J = 7.8$ Hz, 1H), 7.77 (d, $J = 8.4$ Hz, 1H), 7.63 (t, $J = 7.8$ Hz, 1H), 7.58-7.37 (m, 6H), 4.46 (s, 2H), 4.02-3.95 (m, 2H).                                                                    | 498 |
| 185s | $^1\text{H}$ NMR (300 MHz, DMSO- $d_6$ ) $\delta$ 9.16 (s, 1H), 8.48 (s, 1H), 8.16 (d, $J = 8.4$ Hz, 1H), 8.03 (s, 1H), 7.98 (d, $J = 7.8$ Hz, 1H), 7.77 (d, $J = 8.4$ Hz, 1H), 7.63 (t, $J = 7.8$ Hz, 1H), 7.58-7.37 (m, 6H), 4.46 (s, 2H), 4.02-3.95 (m, 2H)                                                       | 498 |
| 186  | $^1\text{H}$ NMR (300 MHz, DMSO- $d_6$ ) $\delta$ 8.39 (s, 1H), 8.06 (s, 1H), 7.92 (s, 1H), 7.78 (s, 1H), 7.53-7.32 (m, 8H), 2.90 (s, 2H), 2.26 (s, 1H), 1.99 (d, $J = 2.6$ Hz, 3H), 1.83 (d, $J = 1.4$ Hz, 3H), 1.45 (d, $J = 2.3$ Hz, 2H).                                                                         | 552 |
| 186s | $^1\text{H}$ NMR (300 MHz, DMSO- $d_6$ ) $\delta$ 8.95 (s, 1H), 8.39 (s, 1H), 8.06 (s, 1H), 7.92 (s, 1H), 7.78 (s, 1H), 7.53-7.32 (m, 8H), 2.90 (s, 2H), 2.26 (s, 1H), 1.99 (d, $J = 2.6$ Hz, 3H), 1.83 (d, $J = 1.4$ Hz, 3H), 1.45 (d, $J = 2.3$ Hz, 2H).                                                           | 552 |
| 187  | $^1\text{H}$ NMR (300 MHz, DMSO- $d_6$ ) $\delta$ 8.26 (s, 1H), 8.17 (s, 1H), 8.06 (s, 1H), 8.01 (d, $J = 7.2$ Hz, 1H), 7.81 (s, 1H), 7.64 (s, 1H), 7.50 (s, 1H), 7.48 (s, 3H), 7.42 (s, 1H), 7.39 (s, 1H), 4.30 (s, 2H), 3.90 (s, 2H).                                                                              | 498 |
| 187s | $^1\text{H}$ NMR (300 MHz, DMSO- $d_6$ ) $\delta$ 8.97 (s, 1H), 8.26 (s, 1H), 8.17 (s, 1H), 8.06 (s, 1H), 8.01 (d, $J = 7.2$ Hz, 1H), 7.81 (s, 1H), 7.64 (s, 1H), 7.50 (s, 1H), 7.48 (s, 3H), 7.42 (s, 1H), 7.39 (s, 1H), 4.30 (s, 2H), 3.90 (s, 2H).                                                                | 498 |
| 188  | $^1\text{H}$ NMR (300 MHz, DMSO- $d_6$ ) $\delta$ 8.24 (d, $J = 8.2$ Hz, 1H), 8.12 (s, 1H), 7.92 (d, $J = 7.8$ Hz, 1H), 7.75 (s, 1H), 7.70 (d, $J = 7.8$ Hz, 1H), 7.55-7.30 (m, 7H), 4.23 (s, 2H), 3.73 (s, 2H), 3.59 (s, 3H).                                                                                       | 464 |
| 188s | $^1\text{H}$ NMR (300 MHz, DMSO- $d_6$ ) $\delta$ 8.91 (s, 1H), 8.24 (d, $J = 8.2$ Hz, 1H), 8.12 (s, 1H), 7.92 (d, $J = 7.8$ Hz, 1H), 7.75 (s, 1H), 7.70 (d, $J = 7.8$ Hz, 1H), 7.55-7.30 (m, 7H), 4.23 (s, 2H), 3.73 (s, 2H).                                                                                       | 464 |
| 189  | $^1\text{H}$ NMR (300 MHz, DMSO- $d_6$ ) $\delta$ 8.26 (s, 1H), 8.17 (s, 1H), 8.06 (s, 1H), 8.01 (d, $J = 7.2$ Hz, 1H), 7.81 (s, 1H), 7.64 (s, 1H), 7.50 (s, 1H), 7.48 (s, 3H), 7.42 (s, 1H), 7.39 (s, 1H), 4.30 (s, 2H), 3.90 (s, 2H).                                                                              | 498 |
| 189s | $^1\text{H}$ NMR (300 MHz, DMSO- $d_6$ ) $\delta$ 8.95 (s, 1H), 8.26 (s, 1H), 8.17 (s, 1H), 8.06 (s, 1H), 8.01 (d, $J = 7.2$ Hz, 1H), 7.81 (s, 1H), 7.64 (s, 1H), 7.50 (s, 1H), 7.48 (s, 3H), 7.42 (s, 1H), 7.39 (s, 1H), 4.30 (s, 2H), 3.90 (s, 2H).                                                                | 498 |
| 190  | $^1\text{H}$ NMR (300 MHz, DMSO- $d_6$ ) $\delta$ 8.20 (d, $J = 3.9$ Hz, 1H), 8.14 (s, 1H), 8.04 (d, $J = 4.8$ Hz, 3H), 7.68-7.59 (m, 1H), 7.54-7.38 (m, 6H), 4.42 (s, 2H), 4.00-3.94 (m, 2H).                                                                                                                       | 498 |
| 190s | $^1\text{H}$ NMR (300 MHz, DMSO- $d_6$ ) $\delta$ 8.93 (s, 1H), 8.20 (d, $J = 3.9$ Hz, 1H), 8.14 (s, 1H), 8.04 (d, $J = 4.8$ Hz, 3H), 7.68-7.59 (m, 1H), 7.54-7.38 (m, 6H), 4.42 (s, 2H), 4.00-3.94 (m, 2H).                                                                                                         | 498 |
| 191  | $^1\text{H}$ NMR (300 MHz, DMSO- $d_6$ ) $\delta$ 8.06 (d, $J = 7.8$ Hz, 1H), 7.95 (s, 1H), 7.87 (s, 2H), 7.54 (s, 1H), 7.51 (s, 1H), 7.49 (s, 2H), 7.47 (s, 1H), 7.44 (s, 1H), 7.38 (d, $J = 7.8$ Hz, 3H), 4.12 (s, 2H), 3.49 (s, 2H), 2.53 (s, 3H).                                                                | 398 |
| 191s | $^1\text{H}$ NMR (300 MHz, DMSO- $d_6$ ) $\delta$ 8.86 (s, 1H), 8.36 (s, 1H), 8.15 (d, $J = 7.2$ Hz, 1H), 8.05 (d, $J = 6.9$ Hz, 1H), 7.80 (s, 1H), 7.70 (s, 1H), 7.47 (q, $J = 8.1, 7.8$ Hz, 5H), 7.37 (d, $J = 6.6$ Hz, 3H), 4.21 (s, 2H), 3.74 (s, 2H), 2.23 (s, 3H).                                             | 398 |
| 192  | $^1\text{H}$ NMR (300 MHz, DMSO- $d_6$ ) $\delta$ 8.24 (s, 1H), 8.09 (d, $J = 7.5$ Hz, 1H), 7.84 (d, $J = 7.5$ Hz, 1H), 7.64 (d, $J = 14.7$ Hz, 4H), 7.51-7.32 (m, 6H), 4.19 (d, $J = 3.6$ Hz, 2H), 3.83 (d, $J = 4.8$ Hz, 1H), 3.63 (s, 2H), 2.37 (s, 3H).                                                          | 443 |
| 192s | $^1\text{H}$ NMR (300 MHz, DMSO- $d_6$ ) $\delta$ 9.17 (s, 1H), 8.08 (dd, $J = 7.8, 1.5$ Hz, 2H), 7.92-7.87 (m, 2H), 7.57 (d, $J = 5.7$ Hz, 2H), 7.51-7.47 (m, 3H), 7.45 (d, $J = 1.2$ Hz, 1H), 7.43-7.36 (m, 3H), 4.31 (s, 2H), 4.00 (dd, $J = 10.2, 2.4$ Hz, 2H), 3.92 (dd, $J = 12.3, 4.5$ Hz, 1H), 2.55 (s, 3H). | 429 |
| 193  | $^1\text{H}$ NMR (300 MHz, DMSO- $d_6$ ) $\delta$ 8.09 (d, $J = 6.0$ Hz, 2H), 7.90 (d, $J = 8.1$ Hz, 2H), 7.58 (d, $J = 6.0$ Hz, 2H), 7.49 (d, $J = 7.5$ Hz, 2H), 7.43 (d, $J = 7.5$ Hz, 1H), 7.42-7.36 (m, 4H), 4.26 (s, 2H), 3.19-3.12 (m, 2H), 2.76 (t, $J = 7.2$ Hz, 2H), 2.55 (s, 3H).                          | 413 |
| 193s | $^1\text{H}$ NMR (300 MHz, DMSO- $d_6$ ) $\delta$ 9.17 (s, 1H), 8.09 (d, $J = 6.0$ Hz, 3H), 7.90 (d, $J = 8.1$ Hz, 2H), 7.58 (d, $J = 6.0$ Hz, 2H), 7.49 (d, $J = 7.5$ Hz, 2H), 7.43 (d, $J = 7.5$ Hz, 1H), 7.42-7.36 (m, 3H), 4.26 (s, 2H), 3.19-3.12 (m, 2H), 2.76 (t, $J = 7.2$ Hz, 2H), 2.55 (s, 3H).            | 413 |
| 194  | $^1\text{H}$ NMR (300 MHz, DMSO- $d_6$ ) $\delta$ 8.04 (d, $J = 7.8$ Hz, 2H), 7.83 (d, $J = 7.8$ Hz, 1H), 7.62 (s, 1H), 7.57-7.35 (m, 8H), 7.29 (dd, $J = 7.5, 1.5$ Hz, 1H), 3.80 (s, 2H), 3.35 (s, 2H), 2.36 (s, 3H).                                                                                               | 399 |
| 194s | $^1\text{H}$ NMR (300 MHz, Methanol- $d_4$ ) $\delta$ 9.17 (s, 1H), 8.50 (d, $J = 2.6$ Hz, 2H), 7.92 (d, $J = 6.9$ Hz, 3H), 7.65 (s, 2H), 7.44 (s, 2H), 7.41 (s, 4H), 4.28 (s, 2H), 3.55 (s, 2H), 2.55 (s, 3H).                                                                                                      | 399 |
| 195  | $^1\text{H}$ NMR (300 MHz, DMSO- $d_6$ ) $\delta$ 8.77 (s, 1H), 8.08 (s, 1H), 7.92 (dd, $J = 10.8, 6.0$ Hz, 3H), 7.53 (d, $J = 4.8$ Hz, 2H), 7.51-7.44 (m, 3H), 7.43 (s, 1H), 7.39 (d, $J = 3.3$ Hz, 2H), 4.24 (t, $J = 9.3$ Hz, 2H), 4.02 (d, $J = 7.2$ Hz, 1H), 2.52 (s, 3H), 1.53 (d, $J = 7.2$ Hz, 3H).          | 413 |
| 195s | $^1\text{H}$ NMR (300 MHz, DMSO- $d_6$ ) $\delta$ 9.21 (s, 1H), 8.77 (s, 1H), 8.08 (s, 1H), 7.92 (dd, $J = 10.8, 6.0$ Hz, 2H), 7.53 (d, $J = 4.8$ Hz, 2H), 7.51-7.44 (m, 3H), 7.43 (s, 1H), 7.39 (d, $J = 3.3$ Hz, 2H), 7.36 (s, 1H), 4.24 (t, $J = 9.3$ Hz, 2H), 4.02 (d, $J = 7.2$ Hz, 1H),                        | 413 |

|      |                                                                                                                                                                                                                                                                                                             |     |
|------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|
|      | 2.52 (s, 3H), 1.53 (d, $J = 7.2$ Hz, 3H).                                                                                                                                                                                                                                                                   |     |
| 196  | $^1\text{H}$ NMR (300 MHz, DMSO- $d_6$ ) $\delta$ 8.24 (s, 1H), 8.09 (d, $J = 7.5$ Hz, 1H), 7.84 (d, $J = 7.5$ Hz, 1H), 7.64 (d, $J = 14.7$ Hz, 4H), 7.51-7.32 (m, 6H), 4.19 (d, $J = 3.6$ Hz, 2H), 3.83 (d, $J = 4.8$ Hz, 1H), 3.63 (s, 2H), 2.37 (s, 3H).                                                 | 429 |
| 196s | $^1\text{H}$ NMR (300 MHz, DMSO- $d_6$ ) $\delta$ 9.07 (s, 1H), 8.08 (dd, $J = 7.8, 1.2$ Hz, 1H), 7.96 (s, 1H), 7.91 (s, 1H), 7.89 (s, 1H), 7.68 (s, 1H), 7.65 (s, 1H), 7.50 (dd, $J = 7.8, 6.3$ Hz, 3H), 7.45-7.37 (m, 4H), 4.24 (s, 2H), 3.94 (dd, $J = 12.3, 8.1$ Hz, 3H), 2.54 (s, 3H).                 | 429 |
| 197  | $^1\text{H}$ NMR (300 MHz, DMSO- $d_6$ ) $\delta$ 8.08 (dd, $J = 7.8, 1.2$ Hz, 1H), 7.97 (s, 1H), 7.90 (d, $J = 8.1$ Hz, 2H), 7.67 (d, $J = 8.1$ Hz, 2H), 7.51-7.43 (m, 3H), 7.42-7.37 (m, 4H), 4.27-4.21 (m, 2H), 4.20-4.07 (m, 2H), 2.54 (s, 3H), 1.21 (d, $J = 6.3$ Hz, 3H).                             | 434 |
| 197s | $^1\text{H}$ NMR (300 MHz, DMSO- $d_6$ ) $\delta$ 9.17 (s, 1H), 8.08 (dd, $J = 7.8, 1.2$ Hz, 1H), 7.97 (s, 1H), 7.90 (d, $J = 8.1$ Hz, 2H), 7.67 (d, $J = 8.4$ Hz, 2H), 7.51-7.43 (m, 3H), 7.42-7.37 (m, 4H), 4.27-4.21 (m, 2H), 4.20-4.07 (m, 2H), 2.54 (s, 3H), 1.21 (d, $J = 6.3$ Hz, 3H).               | 434 |
| 198  | $^1\text{H}$ NMR (300 MHz, DMSO- $d_6$ ) $\delta$ 8.76 (s, 1H), 8.05 (s, 1H), 7.92 (dd, $J = 14.1, 7.2$ Hz, 2H), 7.53 (d, $J = 6.9$ Hz, 2H), 7.47 (d, $J = 7.8$ Hz, 3H), 7.43 (s, 1H), 7.38 (q, $J = 7.5, 5.7$ Hz, 3H), 4.22 (s, 2H), 3.14 (t, $J = 7.5$ Hz, 2H), 2.71 (t, $J = 7.2$ Hz, 2H), 2.52 (s, 3H). | 413 |
| 198s | $^1\text{H}$ NMR (300 MHz, DMSO- $d_6$ ) $\delta$ 9.21 (s, 1H), 8.09 (d, $J = 6.0$ Hz, 3H), 7.90 (d, $J = 8.1$ Hz, 2H), 7.58 (d, $J = 6.0$ Hz, 2H), 7.49 (d, $J = 7.5$ Hz, 2H), 7.43 (d, $J = 7.5$ Hz, 1H), 7.42-7.36 (m, 3H), 4.26 (s, 2H), 3.19-3.12 (m, 2H), 2.76 (t, $J = 7.2$ Hz, 2H), 2.55 (s, 3H).   | 413 |

实施例 5: 3-(2-甲基-[1,1'-联苯]-3-基)噁唑-4-基)苄基)甘氨酸 (199) 及其盐酸盐 (199s) 的合成

#### 2-甲基-[1,1'-联苯]-3-甲酰胺 (5A) 的合成

将 1C (2.00 g, 9.42 mmol)、氨水 (0.66 g, 18.85 mmol)、2-(7-氮杂苯并三氮唑)-N,N,N',N'-四甲基脲六氟磷酸酯 (5.37 g, 14.13 mmol)、N,N-二异丙基乙胺 (2.44 g, 18.85 mmol) 加入 80 mL DMF, 室温反应过夜。加入 200 mL 水, 抽滤, 干燥, 得白色固体 1.63g, 收率 82%。MS (EI)  $m/z$  212  $[\text{M}+\text{H}]^+$ ;  $^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ )  $\delta$  7.70 (dd,  $J = 7.2, 2.4$  Hz, 1H), 7.50-7.26 (m, 7H), 2.22 (s, 3H).

#### 3-(2-(2-甲基-[1,1'-联苯]-3-基)噁唑-4-基)苯甲酸甲酯 (5B) 的合成

由 5A 进行环合反应制得白色固体 5B, 收率 53%。MS (EI)  $m/z$  370  $[\text{M}+\text{H}]^+$ ;  $^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ )  $\delta$  8.90 (s, 1H), 8.44 (s, 1H), 8.14 (d,  $J = 7.8$  Hz, 1H), 7.94 (t,  $J = 6.6$  Hz, 2H), 7.63 (t,  $J = 7.8$  Hz, 1H), 7.52-7.44 (m, 3H), 7.44-7.35 (m, 4H), 3.89 (s, 3H), 2.52 (s, 3H).

#### 3-(2-甲基-[1,1'-联苯]-3-基)噁唑-4-基)苯基甲醇 (5C) 的合成

参照实施例 2 的方法, 将 5B 和  $\text{LiAlH}_4$  进行还原反应, 制得白色固体 5C, 收率 71%。MS (EI)  $m/z$  342  $[\text{M}+\text{H}]^+$ ;  $^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ )  $\delta$  8.91 (s, 1H), 8.42 (s, 1H), 8.14 (d,  $J = 7.8$  Hz, 1H), 7.94 (t,  $J = 6.6$  Hz, 2H), 7.63 (t,  $J = 7.8$  Hz, 1H), 7.52-7.44 (m, 3H), 7.45-7.34 (m, 4H), 5.27 (s, 2H), 2.52 (s, 3H).

#### 4-(3-氯甲基)苄基-2-(2-甲基-[1,1'-联苯]-3-基)噁唑 (5D) 的合成

参照实施例 4 的方法, 将 5C 进行反应, 制得白色固体 5D, 收率 83%。MS (EI)  $m/z$  360  $[\text{M}+\text{H}]^+$ ;  $^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ )  $\delta$  8.91 (s, 1H), 8.42 (s, 1H), 8.14 (d,  $J = 7.8$  Hz, 1H), 7.94 (t,  $J = 6.6$  Hz, 2H), 7.63 (t,  $J = 7.8$  Hz, 1H), 7.52-7.44 (m, 3H), 7.45-7.34 (m, 4H), 5.27 (s, 2H), 2.52 (s, 3H).

#### 3-(2-甲基-[1,1'-联苯]-3-基)噁唑-4-基)苄基)甘氨酸甲酯 (5E) 的合成

参照实施例 1 的方法, 将 5D 和甘氨酸甲酯盐酸盐进行反应, 制得白色固体 199m, 收率 80%。MS (EI)  $m/z$  413  $[\text{M}+\text{H}]^+$ ;  $^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ )  $\delta$  8.77 (s, 1H), 8.08 (s, 1H), 7.92 (dd,  $J = 10.9, 6.1$  Hz, 2H), 7.53 (d,  $J = 4.8$  Hz, 2H), 7.51-7.44 (m, 3H), 7.43 (s, 1H), 7.39 (d,  $J = 3.3$  Hz, 2H), 7.36 (s, 1H), 3.82 (t,  $J = 9.3$  Hz, 2H), 3.62 (d,  $J = 7.2$  Hz, 2H), 3.89 (s, 3H), 2.35 (s, 3H).

#### 化合物 199 及其盐酸盐 (199s) 的合成

参照实施例 1 的方法, 将 5E 水解制得白色固体 199, 收率 58%。再将 199 与盐酸成盐, 制得白色固体 199s, 收率 88%。MS (ESI)  $m/z$  399  $[\text{M}+\text{H}]^+$ ;  $^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ )  $\delta$  9.02 (s, 1H), 8.36 (s, 1H), 8.15 (d,  $J = 7.2$  Hz, 1H), 8.05 (d,  $J = 6.9$  Hz, 2H), 7.47 (q,  $J = 8.1, 7.8$  Hz, 6H), 7.37 (d,  $J = 6.6$  Hz, 3H), 4.21 (s, 2H), 3.75 (s, 2H), 2.23 (s, 3H).

采用与实施例 5 相似的操作, 制得下列化合物:

| 编号  | $^1\text{H}$ -NMR                                                                                                                            | ESI-MS<br>$m/z$<br>$(\text{M}+\text{H})^+$ |
|-----|----------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------|
| 200 | $^1\text{H}$ NMR (300 MHz, DMSO- $d_6$ ) $\delta$ 8.77 (s, 1H), 8.08 (s, 1H), 7.92 (dd, $J = 10.8, 6.0$ Hz, 2H), 7.53 (d, $J = 4.8$ Hz, 2H), | 413                                        |

|      |                                                                                                                                                                                                                                                                                                                                                                             |     |
|------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|
|      | 7.51-7.44 (m, 3H), 7.43 (s, 1H), 7.39 (d, $J = 3.3$ Hz, 2H), 7.36 (s, 1H), 4.24 (t, $J = 9.3$ Hz, 2H), 4.02 (d, $J = 7.2$ Hz, 1H), 2.52 (s, 3H), 1.53 (d, $J = 7.2$ Hz, 3H).                                                                                                                                                                                                |     |
| 200s | <sup>1</sup> H NMR (300 MHz, DMSO- $d_6$ ) $\delta$ 9.17 (s, 1H), 8.77 (s, 1H), 8.08 (s, 1H), 7.92 (dd, $J = 10.8, 6.0$ Hz, 2H), 7.53 (d, $J = 4.8$ Hz, 2H), 7.51-7.44 (m, 3H), 7.43 (s, 1H), 7.39 (d, $J = 3.3$ Hz, 2H), 7.36 (s, 1H), 4.24 (t, $J = 9.3$ Hz, 2H), 4.02 (d, $J = 7.2$ Hz, 1H), 2.52 (s, 3H), 1.53 (d, $J = 7.2$ Hz, 3H).                                   | 413 |
| 201  | <sup>1</sup> H NMR (300 MHz, DMSO- $d_6$ ) $\delta$ 8.75 (s, 1H), 8.06 (s, 1H), 7.94 (d, $J = 7.6$ Hz, 1H), 7.92-7.85 (m, 1H), 7.51 (d, $J = 5.0$ Hz, 2H), 7.47 (d, $J = 7.4$ Hz, 2H), 7.43 (t, $J = 6.6$ Hz, 2H), 7.40-7.33 (m, 3H), 4.26 (s, 2H), 3.94 (d, $J = 6.0$ Hz, 3H), 2.52 (s, 3H).                                                                               | 429 |
| 201s | <sup>1</sup> H NMR (300 MHz, DMSO- $d_6$ ) $\delta$ 9.17 (s, 1H), 8.75 (s, 1H), 8.06 (s, 1H), 7.94 (d, $J = 7.5$ Hz, 1H), 7.92-7.85 (m, 1H), 7.51 (d, $J = 5.1$ Hz, 2H), 7.47 (d, $J = 7.5$ Hz, 2H), 7.43 (t, $J = 6.6$ Hz, 2H), 7.40-7.33 (m, 3H), 4.26 (s, 2H), 3.94 (d, $J = 6.0$ Hz, 3H), 2.52 (s, 3H).                                                                 | 429 |
| 202  | <sup>1</sup> H NMR (300 MHz, DMSO- $d_6$ ) $\delta$ 8.76 (s, 1H), 8.05 (s, 1H), 7.92 (dd, $J = 14.1, 7.2$ Hz, 2H), 7.53 (d, $J = 6.9$ Hz, 2H), 7.47 (d, $J = 7.8$ Hz, 3H), 7.43 (s, 1H), 7.38 (q, $J = 7.5, 5.7$ Hz, 3H), 4.22 (s, 2H), 3.14 (t, $J = 7.5$ Hz, 2H), 2.71 (t, $J = 7.2$ Hz, 2H), 2.52 (s, 3H).                                                               | 413 |
| 202s | <sup>1</sup> H NMR (300 MHz, DMSO- $d_6$ ) $\delta$ 9.31 (s, 1H), 8.76 (s, 1H), 8.05 (s, 1H), 7.92 (dd, $J = 14.1, 7.2$ Hz, 2H), 7.53 (d, $J = 6.9$ Hz, 2H), 7.47 (d, $J = 7.8$ Hz, 3H), 7.43 (s, 1H), 7.38 (q, $J = 7.5, 5.7$ Hz, 3H), 4.22 (s, 2H), 3.14 (t, $J = 7.5$ Hz, 2H), 2.71 (t, $J = 7.2$ Hz, 2H), 2.52 (s, 3H).                                                 | 413 |
| 203  | <sup>1</sup> H NMR (300 MHz, DMSO- $d_6$ ) $\delta$ 8.76 (s, 1H), 8.13 (s, 1H), 7.94 (d, $J = 7.2$ Hz, 2H), 7.57 (d, $J = 7.5$ Hz, 2H), 7.47 (d, $J = 8.1$ Hz, 3H), 7.42 (s, 1H), 7.36 (s, 1H), 4.37 (s, 2H), 3.55 (s, 1H), 2.95 (s, 3H), 2.51 (s, 3H), 2.02 (d, $J = 13.2$ Hz, 2H), 1.85 (s, 2H), 1.44 (s, 1H).                                                            | 453 |
| 203s | <sup>1</sup> H NMR (300 MHz, DMSO- $d_6$ ) $\delta$ 8.97 (s, 1H), 8.76 (s, 1H), 8.13 (s, 1H), 7.94 (d, $J = 7.2$ Hz, 2H), 7.57 (d, $J = 7.5$ Hz, 2H), 7.47 (d, $J = 8.1$ Hz, 3H), 7.42 (s, 1H), 7.36 (s, 1H), 4.37 (s, 2H), 3.55 (s, 1H), 2.95 (s, 3H), 2.51 (s, 3H), 2.02 (d, $J = 13.2$ Hz, 2H), 1.85 (s, 2H), 1.44 (s, 1H).                                              | 453 |
| 204  | <sup>1</sup> H NMR (300 MHz, DMSO- $d_6$ ) $\delta$ 8.76 (s, 1H), 8.08 (s, 1H), 7.97-7.92 (m, 1H), 7.88 (d, $J = 4.2$ Hz, 1H), 7.53 (d, $J = 5.4$ Hz, 2H), 7.47 (d, $J = 7.5$ Hz, 2H), 7.43 (dd, $J = 7.5, 5.7$ Hz, 2H), 7.40-7.34 (m, 3H), 5.25 (s, 1H), 4.22 (s, 2H), 3.69 (s, 2H), 2.99 (s, 2H), 2.52 (s, 3H).                                                           | 385 |
| 204s | <sup>1</sup> H NMR (300 MHz, DMSO- $d_6$ ) $\delta$ 9.17 (s, 1H), 8.76 (s, 1H), 8.08 (s, 1H), 7.97-7.92 (m, 1H), 7.88 (d, $J = 4.2$ Hz, 1H), 7.53 (d, $J = 5.4$ Hz, 2H), 7.47 (d, $J = 7.5$ Hz, 2H), 7.43 (dd, $J = 7.5, 5.7$ Hz, 2H), 7.40-7.34 (m, 3H), 5.25 (s, 1H), 4.22 (s, 2H), 3.69 (s, 2H), 2.99 (s, 2H), 2.52 (s, 3H).                                             | 385 |
| 205  | <sup>1</sup> H NMR (300 MHz, DMSO- $d_6$ ) $\delta$ 8.75 (s, 1H), 7.94 (d, $J = 7.5$ Hz, 1H), 7.90 (d, $J = 7.5$ Hz, 1H), 7.84 (s, 1H), 7.55 (d, $J = 6.6$ Hz, 2H), 7.50 (d, $J = 6.6$ Hz, 3H), 7.46 (d, $J = 2.7$ Hz, 2H), 7.43 (s, 1H), 7.40 (d, $J = 3.3$ Hz, 1H), 7.39-7.34 (m, 2H), 4.22 (s, 2H), 3.65 (s, 2H), 2.52 (s, 3H).                                          | 398 |
| 205s | <sup>1</sup> H NMR (300 MHz, DMSO- $d_6$ ) $\delta$ 9.31 (s, 1H), 8.75 (s, 1H), 7.94 (d, $J = 7.5$ Hz, 1H), 7.90 (d, $J = 7.5$ Hz, 1H), 7.84 (s, 1H), 7.55 (d, $J = 6.6$ Hz, 2H), 7.50 (d, $J = 6.6$ Hz, 3H), 7.46 (d, $J = 2.7$ Hz, 2H), 7.43 (s, 1H), 7.40 (d, $J = 3.3$ Hz, 1H), 7.39-7.34 (m, 2H), 4.22 (s, 2H), 3.65 (s, 2H), 2.52 (s, 3H).                            | 398 |
| 206  | <sup>1</sup> H NMR (300 MHz, DMSO- $d_6$ ) $\delta$ 8.76 (d, $J = 2.4$ Hz, 1H), 8.05 (s, 1H), 7.92 (d, $J = 15.6$ Hz, 3H), 7.66 (s, 1H), 7.57-7.44 (m, 5H), 7.43 (s, 1H), 7.37 (d, $J = 7.5$ Hz, 3H), 5.57 (s, 1H), 4.20 (s, 2H), 3.84 (s, 2H), 3.74 (s, 1H), 2.52 (s, 3H).                                                                                                 | 428 |
| 206s | <sup>1</sup> H NMR (300 MHz, DMSO- $d_6$ ) $\delta$ 9.35 (s, 1H), 8.76 (d, $J = 2.4$ Hz, 1H), 8.05 (s, 1H), 7.92 (d, $J = 15.6$ Hz, 3H), 7.66 (s, 1H), 7.57-7.44 (m, 5H), 7.43 (s, 1H), 7.37 (d, $J = 7.5$ Hz, 3H), 5.57 (s, 1H), 4.20 (s, 2H), 3.84 (s, 2H), 3.74 (s, 1H), 2.52 (s, 3H).                                                                                   | 428 |
| 207  | <sup>1</sup> H NMR (300 MHz, DMSO- $d_6$ ) $\delta$ 8.81 (s, 1H), 7.93 (t, $J = 6.9$ Hz, 3H), 7.59 (d, $J = 8.1$ Hz, 2H), 7.47 (d, $J = 7.5$ Hz, 2H), 7.45-7.40 (m, 2H), 7.38 (s, 2H), 7.36 (s, 1H), 4.19 (s, 2H), 3.86 (s, 2H), 2.52 (s, 3H).                                                                                                                              | 399 |
| 207s | <sup>1</sup> H NMR (300 MHz, DMSO- $d_6$ ) $\delta$ 9.49 (s, 1H), 8.81 (s, 1H), 7.93 (t, $J = 6.9$ Hz, 3H), 7.59 (d, $J = 8.1$ Hz, 2H), 7.47 (d, $J = 7.5$ Hz, 2H), 7.45-7.40 (m, 2H), 7.38 (s, 2H), 7.36 (s, 1H), 4.19 (s, 2H), 3.86 (s, 2H), 2.52 (s, 3H).                                                                                                                | 399 |
| 208  | <sup>1</sup> H NMR (300 MHz, DMSO- $d_6$ ) $\delta$ 8.01 (s, 1H), 7.81 (dd, $J = 14.2, 7.6$ Hz, 2H), 7.50 (s, 1H), 7.49-7.43 (m, 3H), 7.42 (d, $J = 1.7$ Hz, 1H), 7.38 (dd, $J = 5.1, 2.6$ Hz, 2H), 7.35 (s, 1H), 7.22 (d, $J = 7.5$ Hz, 1H), 7.12 (d, $J = 3.5$ Hz, 1H), 6.90 (d, $J = 3.5$ Hz, 1H), 4.27 (s, 2H), 3.95 (d, $J = 4.6$ Hz, 3H), 2.36 (s, 3H).               | 429 |
| 208s | <sup>1</sup> H NMR (300 MHz, DMSO- $d_6$ ) $\delta$ 9.37 (s, 1H), 8.01 (s, 1H), 7.81 (dd, $J = 14.2, 7.6$ Hz, 2H), 7.50 (s, 1H), 7.49-7.43 (m, 3H), 7.42 (d, $J = 1.7$ Hz, 1H), 7.38 (dd, $J = 5.1, 2.6$ Hz, 2H), 7.35 (s, 1H), 7.22 (d, $J = 7.5$ Hz, 1H), 7.12 (d, $J = 3.5$ Hz, 1H), 6.90 (d, $J = 3.5$ Hz, 1H), 4.27 (s, 2H), 3.95 (d, $J = 4.6$ Hz, 3H), 2.36 (s, 3H). | 429 |

|      |                                                                                                                                                                                                                                                                                                                                                                                                                                 |     |
|------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|
| 209  | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.81 (s, 1H), 7.93 (t, <i>J</i> = 6.9 Hz, 3H), 7.64 (d, <i>J</i> = 7.8 Hz, 2H), 7.52-7.43 (m, 3H), 7.42 (s, 1H), 7.37 (d, <i>J</i> = 7.2 Hz, 3H), 4.18 (s, 2H), 3.11 (s, 2H), 2.76 (d, <i>J</i> = 7.6 Hz, 2H), 2.52 (s, 3H).                                                                                                                                       | 413 |
| 209s | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 9.34 (s, 1H), 8.81 (s, 1H), 7.93 (t, <i>J</i> = 6.9 Hz, 3H), 7.64 (d, <i>J</i> = 7.8 Hz, 2H), 7.52-7.43 (m, 3H), 7.42 (s, 1H), 7.37 (d, <i>J</i> = 7.2 Hz, 3H), 4.18 (s, 2H), 3.11 (s, 2H), 2.76 (d, <i>J</i> = 7.6 Hz, 2H), 2.52 (s, 3H).                                                                                                                         | 413 |
| 210  | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.78 (s, 1H), 7.94 (d, <i>J</i> = 7.8 Hz, 3H), 7.70 (d, <i>J</i> = 7.8 Hz, 2H), 7.49 (d, <i>J</i> = 8.1 Hz, 2H), 7.43 (dd, <i>J</i> = 11.4, 4.2 Hz, 3H), 7.38 (s, 2H), 4.32 (s, 2H), 2.96 (d, <i>J</i> = 12.3 Hz, 2H), 2.82 (s, 2H), 2.52 (s, 3H), 2.01 (s, 2H), 1.86 (s, 2H), 1.44 (s, 1H).                                                                       | 453 |
| 210s | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 9.08 (s, 1H), 8.78 (s, 1H), 7.94 (d, <i>J</i> = 7.8 Hz, 3H), 7.70 (d, <i>J</i> = 7.8 Hz, 2H), 7.49 (d, <i>J</i> = 8.1 Hz, 2H), 7.43 (dd, <i>J</i> = 11.4, 4.2 Hz, 3H), 7.38 (s, 2H), 4.32 (s, 2H), 2.96 (d, <i>J</i> = 12.3 Hz, 2H), 2.82 (s, 2H), 2.52 (s, 3H), 2.01 (s, 2H), 1.86 (s, 2H), 1.44 (s, 1H).                                                         | 453 |
| 211  | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.80 (s, 1H), 7.94 (d, <i>J</i> = 7.2 Hz, 2H), 7.90 (s, 1H), 7.63 (d, <i>J</i> = 8.0 Hz, 2H), 7.47 (d, <i>J</i> = 7.4 Hz, 2H), 7.41 (d, <i>J</i> = 5.0 Hz, 2H), 7.38 (s, 2H), 7.35 (s, 1H), 5.25 (s, 1H), 4.18 (s, 2H), 3.70-3.66 (m, 2H), 2.96 (s, 2H), 2.51 (s, 3H).                                                                                             | 385 |
| 211s | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 9.16 (s, 1H), 8.80 (s, 1H), 7.94 (d, <i>J</i> = 7.2 Hz, 2H), 7.90 (s, 1H), 7.63 (d, <i>J</i> = 8.0 Hz, 2H), 7.47 (d, <i>J</i> = 7.4 Hz, 2H), 7.41 (d, <i>J</i> = 5.0 Hz, 2H), 7.38 (s, 2H), 7.35 (s, 1H), 5.25 (s, 1H), 4.18 (s, 2H), 3.70-3.66 (m, 2H), 2.96 (s, 2H), 2.51 (s, 3H).                                                                               | 385 |
| 212  | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.86 (s, 1H), 8.06 (s, 1H), 7.99 (dd, <i>J</i> = 6.0, 3.3 Hz, 1H), 7.91 (d, <i>J</i> = 6.9 Hz, 1H), 7.64-7.60 (m, 2H), 7.53 (td, <i>J</i> = 5.1, 4.8, 2.4 Hz, 3H), 7.49 (d, <i>J</i> = 3.6 Hz, 3H), 7.47-7.45 (m, 1H), 4.23 (s, 2H), 3.84 (s, 2H).                                                                                                                 | 419 |
| 212s | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 9.16 (s, 1H), 8.86 (s, 2H), 8.06 (s, 1H), 7.99 (dd, <i>J</i> = 6.0, 3.3 Hz, 1H), 7.91 (d, <i>J</i> = 6.9 Hz, 1H), 7.64-7.60 (m, 2H), 7.53 (td, <i>J</i> = 5.1, 4.8, 2.4 Hz, 3H), 7.49 (d, <i>J</i> = 3.6 Hz, 3H), 4.23 (s, 2H), 3.84 (s, 2H).                                                                                                                      | 419 |
| 213  | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.85 (s, 1H), 8.09 (s, 1H), 7.99 (dd, <i>J</i> = 6.0, 3.3 Hz, 1H), 7.90 (d, <i>J</i> = 3.6 Hz, 1H), 7.64-7.60 (m, 2H), 7.54 (d, <i>J</i> = 3.9 Hz, 3H), 7.49 (d, <i>J</i> = 3.3 Hz, 3H), 7.47-7.45 (m, 1H), 4.28 (s, 2H), 3.97 (s, 2H), 3.57 (s, 1H).                                                                                                              | 449 |
| 213s | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 9.02 (s, 1H), 8.85 (s, 1H), 8.09 (s, 1H), 7.99 (dd, <i>J</i> = 6.0, 3.3 Hz, 1H), 7.90 (d, <i>J</i> = 3.6 Hz, 1H), 7.64-7.60 (m, 2H), 7.54 (d, <i>J</i> = 3.9 Hz, 4H), 7.49 (d, <i>J</i> = 3.3 Hz, 3H), 4.28 (s, 2H), 3.97 (s, 2H), 3.57 (s, 1H).                                                                                                                   | 449 |
| 214  | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.87 (s, 1H), 8.08 (s, 1H), 7.99 (dd, <i>J</i> = 6.0, 3.3 Hz, 1H), 7.92 (d, <i>J</i> = 6.9 Hz, 1H), 7.64-7.60 (m, 2H), 7.55 (d, <i>J</i> = 6.9 Hz, 2H), 7.52 (d, <i>J</i> = 2.4 Hz, 1H), 7.49 (t, <i>J</i> = 2.4 Hz, 3H), 7.47-7.45 (m, 1H), 4.24 (d, <i>J</i> = 4.8 Hz, 2H), 4.03 (q, <i>J</i> = 7.2, 6.3 Hz, 1H), 1.53 (d, <i>J</i> = 7.2 Hz, 3H).               | 433 |
| 214s | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 9.16 (s, 1H), 8.87 (s, 1H), 8.08 (s, 1H), 7.99 (dd, <i>J</i> = 6.0, 3.3 Hz, 1H), 7.92 (d, <i>J</i> = 6.9 Hz, 1H), 7.64-7.60 (m, 2H), 7.55 (d, <i>J</i> = 6.9 Hz, 2H), 7.52 (d, <i>J</i> = 2.4 Hz, 1H), 7.49 (t, <i>J</i> = 2.4 Hz, 3H), 7.47-7.45 (m, 1H), 4.24 (d, <i>J</i> = 4.8 Hz, 2H), 4.03 (q, <i>J</i> = 7.2, 6.3 Hz, 1H), 1.53 (d, <i>J</i> = 7.2 Hz, 3H). | 433 |
| 215  | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.86 (s, 1H), 8.12 (s, 1H), 7.99 (dd, <i>J</i> = 6.3, 3.3 Hz, 1H), 7.90 (d, <i>J</i> = 6.9 Hz, 1H), 7.63-7.60 (m, 2H), 7.57 (d, <i>J</i> = 2.4 Hz, 2H), 7.54 (s, 1H), 7.52 (s, 1H), 7.49 (d, <i>J</i> = 3.3 Hz, 3H), 4.23 (s, 2H), 3.14 (t, <i>J</i> = 7.5 Hz, 2H), 2.77 (t, <i>J</i> = 7.5 Hz, 2H).                                                               | 433 |
| 215s | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 9.24 (s, 1H), 8.86 (s, 1H), 8.12 (s, 1H), 7.99 (dd, <i>J</i> = 6.3, 3.3 Hz, 1H), 7.90 (d, <i>J</i> = 6.9 Hz, 1H), 7.63-7.60 (m, 2H), 7.57 (d, <i>J</i> = 2.4 Hz, 2H), 7.54 (s, 1H), 7.52 (s, 1H), 7.49 (d, <i>J</i> = 3.3 Hz, 3H), 4.23 (s, 2H), 3.14 (t, <i>J</i> = 7.5 Hz, 2H), 2.77 (t, <i>J</i> = 7.5 Hz, 2H).                                                 | 433 |
| 216  | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.96 (s, 1H), 8.04 (s, 1H), 8.02-7.97 (m, 2H), 7.65 (s, 1H), 7.62 (d, <i>J</i> = 1.8 Hz, 1H), 7.61 (s, 1H), 7.52 (s, 1H), 7.49 (d, <i>J</i> = 3.6 Hz, 3H), 7.47-7.45 (m, 1H), 4.22 (s, 2H), 3.81 (s, 2H).                                                                                                                                                          | 454 |
| 216s | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 9.19 (s, 1H), 8.96 (s, 1H), 8.04 (s, 1H), 8.02-7.97 (m, 3H), 7.65 (s, 1H), 7.62 (d, <i>J</i> = 1.8 Hz, 1H), 7.61 (s, 1H), 7.52 (s, 1H), 7.49 (d, <i>J</i> = 3.6 Hz, 3H), 4.22 (s, 2H), 3.81 (s, 2H).                                                                                                                                                               | 454 |
| 217  | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.94 (s, 1H), 8.00 (dd, <i>J</i> = 5.7, 3.9 Hz, 1H), 7.93 (d, <i>J</i> = 9.3 Hz, 2H), 7.62 (d, <i>J</i> = 1.8 Hz, 1H), 7.61 (s, 1H), 7.55 (d, <i>J</i> = 1.8 Hz, 1H), 7.52 (d, <i>J</i> = 2.7 Hz, 1H), 7.49 (d, <i>J</i> = 3.3 Hz, 3H), 7.47 (d, <i>J</i> = 1.5 Hz, 1H), 4.12 (s, 2H), 3.78 (t, <i>J</i> = 5.4 Hz, 2H), 2.54 (m, 1H).                              | 484 |
| 217s | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 9.16 (s, 1H), 8.94 (s, 1H), 8.00 (dd, <i>J</i> = 5.7, 3.9 Hz, 1H), 7.93 (d, <i>J</i> = 9.3 Hz, 2H), 7.62 (d, <i>J</i> = 1.8 Hz, 1H), 7.61 (s, 1H), 7.55 (d, <i>J</i> = 1.8 Hz, 1H), 7.52 (d, <i>J</i> = 2.7 Hz, 1H), 7.49 (d, <i>J</i> = 3.3 Hz, 3H), 7.47 (d, <i>J</i> = 1.5 Hz, 1H), 4.12 (s, 2H), 3.78 (t, <i>J</i> = 5.4 Hz, 2H), 2.54 (m, 1H).                | 484 |
| 218  | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.94 (s, 1H), 8.00 (dd, <i>J</i> = 5.7, 3.9 Hz, 1H), 7.93 (d, <i>J</i> = 9.3 Hz, 2H), 7.62 (d, <i>J</i> = 1.8 Hz,                                                                                                                                                                                                                                                  | 413 |

|      |                                                                                                                                                                                                                                                                                                                                                           |      |
|------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------|
|      | 1H), 7.61 (s, 1H), 7.55 (d, $J = 1.8$ Hz, 1H), 7.52 (d, $J = 2.7$ Hz, 1H), 7.49 (d, $J = 3.3$ Hz, 3H), 7.47 (d, $J = 1.5$ Hz, 1H), 4.12 (s, 2H), 3.78 (t, $J = 5.4$ Hz, 2H), 2.54 (m, 1H).                                                                                                                                                                |      |
| 218s | MS (ESI) $m/z$ 413 $[M+H]^+$ ; $^1H$ NMR (300 MHz, DMSO- $d_6$ ) $\delta$ 9.02 (s, 1H), 8.36 (s, 1H), 8.15 (d, $J = 7.2$ Hz, 1H), 8.05 (d, $J = 6.9$ Hz, 2H), 7.80 (s, 1H), 7.70 (s, 1H), 7.47 (q, $J = 8.1$ , 7.8 Hz, 4H), 7.37 (d, $J = 6.6$ Hz, 3H), 4.21 (s, 2H), 3.75-3.65 (m, 1H), 2.23 (s, 3H), 1.53 (d, $J = 4.3$ Hz, 3H)                         | 413  |
| 219  | $^1H$ NMR (300 MHz, DMSO- $d_6$ ) $\delta$ 8.53 (s, 1H), 8.31 (s, 1H), 8.10 (d, $J = 7.5$ Hz, 1H), 7.85 (d, $J = 7.5$ Hz, 1H), 7.67 (dd, $J = 18.0$ , 7.5 Hz, 2H), 7.47 (d, $J = 7.2$ Hz, 2H), 7.38 (q, $J = 7.5$ Hz, 4H), 7.25 (d, $J = 7.5$ Hz, 1H), 5.67 (s, 2H), 4.33 (s, 2H), 3.91 (m, 3H), 2.33 (s, 3H).                                            | 429  |
| 219s | $^1H$ NMR (300 MHz, DMSO- $d_6$ ) $\delta$ 9.02 (s, 1H), 8.53 (s, 1H), 8.31 (s, 1H), 8.10 (d, $J = 7.5$ Hz, 1H), 7.85 (d, $J = 7.5$ Hz, 1H), 7.67 (dd, $J = 18.0$ , 7.5 Hz, 2H), 7.47 (d, $J = 7.2$ Hz, 2H), 7.38 (q, $J = 7.5$ Hz, 4H), 7.25 (d, $J = 7.5$ Hz, 1H), 4.33 (s, 2H), 3.97 (m, 3H), 2.33 (s, 3H).                                            | 429  |
| 220  | $^1H$ NMR (300 MHz, DMSO- $d_6$ ) $\delta$ 8.50 (s, 1H), 8.28 (s, 1H), 8.08 (d, $J = 7.2$ Hz, 1H), 7.83 (d, $J = 8.1$ Hz, 1H), 7.74 (d, $J = 7.2$ Hz, 1H), 7.64 (d, $J = 8.1$ Hz, 1H), 7.54-7.42 (m, 3H), 7.36 (dd, $J = 13.5$ , 7.2 Hz, 3H), 7.23 (d, $J = 8.1$ Hz, 1H), 4.27 (s, 2H), 3.19-3.08 (m, 2H), 2.81-2.69 (m, 2H), 2.31 (s, 3H).               | 413  |
| 220s | $^1H$ NMR (300 MHz, DMSO- $d_6$ ) $\delta$ 9.12 (s, 1H), 8.50 (s, 1H), 8.28 (s, 1H), 8.08 (d, $J = 7.2$ Hz, 1H), 7.83 (d, $J = 8.1$ Hz, 1H), 7.74 (d, $J = 7.2$ Hz, 1H), 7.64 (d, $J = 8.1$ Hz, 1H), 7.54-7.42 (m, 3H), 7.36 (dd, $J = 13.5$ , 7.2 Hz, 3H), 7.23 (d, $J = 8.1$ Hz, 1H), 4.27 (s, 2H), 3.19-3.08 (m, 2H), 2.81-2.69 (m, 2H), 2.31 (s, 3H). | 413  |
| 221  | $^1H$ NMR (300 MHz, DMSO- $d_6$ ) $\delta$ 8.50 (s, 1H), 8.31 (s, 1H), 8.12 (d, $J = 7.5$ Hz, 1H), 7.82 (d, $J = 7.2$ Hz, 2H), 7.65 (t, $J = 7.2$ Hz, 1H), 7.49-7.40 (m, 3H), 7.35 (t, $J = 6.6$ Hz, 3H), 7.23 (d, $J = 7.5$ Hz, 1H), 3.55 (s, 2H), 3.06-2.64 (m, 5H), 2.31 (s, 3H), 1.90 (dd, $J = 34.8$ , 17.1 Hz, 4H).                                 | 453  |
| 221s | $^1H$ NMR (300 MHz, DMSO- $d_6$ ) $\delta$ 9.13 (s, 1H), 8.50 (s, 1H), 8.31 (s, 1H), 8.12 (d, $J = 7.5$ Hz, 1H), 7.82 (d, $J = 7.2$ Hz, 2H), 7.65 (t, $J = 7.2$ Hz, 1H), 7.49-7.40 (m, 3H), 7.35 (t, $J = 6.6$ Hz, 3H), 7.23 (d, $J = 7.5$ Hz, 1H), 3.55 (s, 2H), 3.06-2.64 (m, 5H), 2.31 (s, 3H), 1.90 (dd, $J = 34.8$ , 17.1 Hz, 4H).                   | 453  |
| 222  | $^1H$ NMR (300 MHz, DMSO- $d_6$ ) $\delta$ 8.12 (s, 1H), 7.97 (d, $J = 6.6$ Hz, 1H), 7.85 (d, $J = 6.6$ Hz, 1H), 7.55 (d, $J = 5.4$ Hz, 2H), 7.47 (d, $J = 7.5$ Hz, 2H), 7.38 (td, $J = 9.3$ , 8.2, 4.2 Hz, 5H), 7.25 (d, $J = 6.6$ Hz, 1H), 3.95 (s, 2H), 2.74-2.69 (m, 4H), 2.32 (s, 3H).                                                               | 385  |
| 222s | $^1H$ NMR (300 MHz, DMSO- $d_6$ ) $\delta$ 8.47 (d, $J = 3.3$ Hz, 1H), 8.12 (s, 1H), 7.97 (d, $J = 6.6$ Hz, 1H), 7.85 (d, $J = 6.6$ Hz, 1H), 7.55 (d, $J = 5.4$ Hz, 2H), 7.47 (d, $J = 7.5$ Hz, 2H), 7.38 (td, $J = 9.3$ , 8.2, 4.2 Hz, 5H), 7.25 (d, $J = 6.6$ Hz, 1H), 3.95 (s, 2H), 2.74-2.69 (m, 4H), 2.32 (s, 3H).                                   | 385  |
| 223  | $^1H$ NMR (300 MHz, DMSO- $d_6$ ) $\delta$ 8.51 (d, $J = 1.8$ Hz, 1H), 8.27 (s, 1H), 8.09 (d, $J = 7.5$ Hz, 1H), 7.90-7.80 (m, 2H), 7.65 (dt, $J = 14.4$ , 7.2 Hz, 2H), 7.55 (s, 1H), 7.46 (d, $J = 7.2$ Hz, 2H), 7.37 (q, $J = 7.2$ Hz, 4H), 7.24 (d, $J = 7.5$ Hz, 1H), 4.28 (s, 2H), 3.66 (s, 2H), 2.32 (s, 3H)                                        | 398s |
| 223s | $^1H$ NMR (300 MHz, DMSO- $d_6$ ) $\delta$ 9.43 (s, 1H), 8.51 (d, $J = 1.8$ Hz, 1H), 8.27 (s, 1H), 8.09 (d, $J = 7.5$ Hz, 1H), 7.90-7.80 (m, 2H), 7.65 (dt, $J = 14.4$ , 7.2 Hz, 2H), 7.55 (s, 1H), 7.46 (d, $J = 7.2$ Hz, 2H), 7.37 (q, $J = 7.2$ Hz, 4H), 7.24 (d, $J = 7.5$ Hz, 1H), 4.28 (s, 2H), 3.66 (s, 2H), 2.32 (s, 3H)                          | 398s |
| 224  | $^1H$ NMR (300 MHz, DMSO- $d_6$ ) $\delta$ 8.51 (d, $J = 1.8$ Hz, 1H), 8.27 (s, 1H), 8.09 (d, $J = 7.5$ Hz, 1H), 7.90-7.80 (m, 2H), 7.65 (dt, $J = 14.4$ , 7.2 Hz, 2H), 7.55 (s, 1H), 7.46 (d, $J = 7.2$ Hz, 2H), 7.37 (q, $J = 7.2$ Hz, 4H), 7.24 (d, $J = 7.5$ Hz, 1H), 4.28 (s, 2H), 3.66 (s, 2H), 2.32 (s, 3H)                                        | 428  |
| 224s | $^1H$ NMR (300 MHz, DMSO- $d_6$ ) $\delta$ 9.43 (s, 1H), 8.51 (d, $J = 1.8$ Hz, 1H), 8.27 (s, 1H), 8.09 (d, $J = 7.5$ Hz, 1H), 7.90-7.80 (m, 2H), 7.65 (dt, $J = 14.4$ , 7.2 Hz, 2H), 7.55 (s, 1H), 7.46 (d, $J = 7.2$ Hz, 2H), 7.37 (q, $J = 7.2$ Hz, 4H), 7.24 (d, $J = 7.5$ Hz, 1H), 4.28 (s, 2H), 3.66 (s, 2H), 2.32 (s, 3H)                          | 428  |
| 225  | $^1H$ NMR (300 MHz, DMSO- $d_6$ ) $\delta$ 8.49 (s, 1H), 8.11 (d, $J = 8.1$ Hz, 2H), 7.81 (d, $J = 7.8$ Hz, 1H), 7.71 (d, $J = 8.1$ Hz, 2H), 7.47 (t, $J = 6.9$ Hz, 2H), 7.42-7.32 (m, 4H), 7.24 (d, $J = 7.5$ Hz, 1H), 4.24 (s, 2H), 3.88 (s, 2H), 2.31 (s, 3H).                                                                                         | 399  |
| 225s | $^1H$ NMR (300 MHz, DMSO- $d_6$ ) $\delta$ 9.02 (s, 1H), 8.49 (s, 1H), 8.11 (d, $J = 8.1$ Hz, 2H), 7.81 (d, $J = 7.8$ Hz, 1H), 7.71 (d, $J = 8.1$ Hz, 2H), 7.47 (t, $J = 6.9$ Hz, 2H), 7.42-7.32 (m, 4H), 7.24 (d, $J = 7.5$ Hz, 1H), 4.24 (s, 2H), 3.88 (s, 2H), 2.31 (s, 3H).                                                                           | 399  |
| 226  | $^1H$ NMR (300 MHz, DMSO- $d_6$ ) $\delta$ 8.49 (s, 1H), 8.10 (d, $J = 8.1$ Hz, 2H), 7.81 (d, $J = 8.1$ Hz, 1H), 7.72 (d, $J = 8.1$ Hz, 2H), 7.49-7.43 (m, 2H), 7.40-7.31 (m, 4H), 7.24 (d, $J = 7.5$ Hz, 1H), 4.29 (s, 2H), 3.97 (d, $J = 10.8$ Hz, 2H), 3.92 (d, $J = 3.6$ Hz, 1H), 2.31 (s, 3H).                                                       | 429  |

|      |                                                                                                                                                                                                                                                                                                                                                                   |     |
|------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|
| 226s | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 9.02 (s, 1H), 8.49 (s, 1H), 8.10 (d, <i>J</i> = 8.1 Hz, 2H), 7.81 (d, <i>J</i> = 8.1 Hz, 1H), 7.72 (d, <i>J</i> = 8.1 Hz, 2H), 7.49-7.43 (m, 2H), 7.40-7.31 (m, 4H), 7.24 (d, <i>J</i> = 7.5 Hz, 1H), 4.29 (s, 2H), 3.97 (d, <i>J</i> = 10.8 Hz, 2H), 3.92 (d, <i>J</i> = 3.6 Hz, 1H), 2.31 (s, 3H). | 429 |
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实施例 6: (3-[4-(2-甲基-[1,1'-联苯]-3-基))-1H-咪唑-2-基)苄基)-L-丙氨酸 (227) 及其盐酸盐 (227s) 的合成  
3-(4-(2-甲基-[1,1'-联苯]-3-基))-1H-咪唑-2-基)苯甲酸甲酯 (6A) 的合成

将 2A (2.00 g, 9.23 mmol) 和 K<sub>2</sub>CO<sub>3</sub> (1.93 g, 13.98 mmol) 加入 20 mL 四氢呋喃和 5 mL 水中, 搅拌 0.5h, 加入 4C (2.42 g, 8.39 mmol), 70°C 反应 6 h。冷却, 乙酸乙酯萃取, 无水硫酸钠干燥, 柱层析纯化[石油醚:乙酸乙酯=4:1(V:V)], 得黄色油状物 1.06 g, 收率 52%。MS (EI) *m/z* 367 [M-H]<sup>-</sup>; <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 8.18-8.02 (m, 2H), 7.83 (d, *J* = 10.5 Hz, 1H), 7.72-7.59 (m, 1H), 7.59-7.34 (m, 8H), 7.29 (s, 1H), 3.89 (s, 3H), 2.35 (s, 3H).

(3-[4-(2-甲基-[1,1'-联苯]-3-基))-1H-咪唑-2-基)苯基)甲醇 (6B) 的合成

参照实施例 2 的方法, 将 6A 和 LiAlH<sub>4</sub> 反应, 制得黄色油状物 6B, 收率 94%。MS (EI) *m/z* 339 [M-H]<sup>-</sup>; <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 8.18-8.02 (m, 2H), 7.83 (d, *J* = 10.5 Hz, 1H), 7.72-7.59 (m, 1H), 7.59-7.34 (m, 8H), 7.29 (s, 1H), 4.59 (s, 2H), 2.35 (s, 3H).

2-(3-(氯甲基)苯基)-4-(2-甲基-[1,1'-联苯]-3-基)-1H-咪唑 (6C) 的合成

参照实施例 4 的方法, 将 6B 进行反应, 制得黄色油状物 6C, 收率 97%。MS (EI) *m/z* 357 [M-H]<sup>-</sup>; <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 8.18-8.02 (m, 2H), 7.83 (d, *J* = 10.5 Hz, 1H), 7.72-7.59 (m, 1H), 7.59-7.34 (m, 8H), 7.29 (s, 1H), 4.64 (s, 2H), 2.33 (s, 3H).

(3-[4-(2-甲基-[1,1'-联苯]-3-基))-1H-咪唑-2-基)苄基)-L-丙氨酸甲酯 (227m) 的合成

参照实施例 1 的方法, 将 6C 和 L-丙氨酸甲酯盐酸盐进行反应, 制得黄色油状物 227m, 收率 63%。MS (EI) *m/z* 425 [M-H]<sup>-</sup>; <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 8.43 (s, 1H), 8.31 (d, *J* = 7.8 Hz, 1H), 7.95 (s, 1H), 7.88 (d, *J* = 7.8 Hz, 1H), 7.73 (t, *J* = 7.8 Hz, 1H), 7.63 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.55-7.29 (m, 7H), 3.92 (s, 3H), 3.57 (s, 2H), 3.39 (s, 1H), 2.30 (s, 3H), 1.57 (d, *J* = 7.2 Hz, 3H).

化合物 227 及其盐酸盐 (227s) 的合成

参照实施例 1 的方法, 将 227m 水解制得白色固体 227, 收率 80%。再将 227 与盐酸成盐, 制得白色固体 227s, 收率 88%。MS (ESI) *m/z* 413 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 8.36 (s, 1H), 8.15 (d, *J* = 7.2 Hz, 1H), 8.05 (d, *J* = 6.9 Hz, 2H), 7.80 (s, 1H), 7.70 (s, 1H), 7.47 (q, *J* = 8.1, 7.8 Hz, 5H), 7.37 (d, *J* = 6.6 Hz, 3H), 4.21 (s, 2H), 3.75-3.65 (m, 1H), 2.23 (s, 3H), 1.53 (d, *J* = 4.3 Hz, 3H).

采用与实施例 6 相似的操作, 制得下列化合物:

| 编号   | <sup>1</sup> H-NMR                                                                                                                                                                                                                                                                                                                                          | ESI-MS<br><i>m/z</i><br>(M+H) <sup>+</sup> |
|------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------|
| 228  | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.27 (d, <i>J</i> = 8.0 Hz, 1H), 7.94 (d, <i>J</i> = 7.5 Hz, 2H), 7.75 (t, <i>J</i> = 7.8 Hz, 1H), 7.62 (d, <i>J</i> = 6.9 Hz, 1H), 7.54-7.29 (m, 8H), 3.57 (s, 2H), 2.30 (s, 3H), 2.01 (d, <i>J</i> = 6.9 Hz, 2H), 1.87 (s, 3H), 1.46 (s, 2H), 1.18 (d, <i>J</i> = 7.2 Hz, 2H).               | 452                                        |
| 228s | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 9.02 (s, 1H), 8.27 (d, <i>J</i> = 8.0 Hz, 1H), 7.94 (d, <i>J</i> = 7.5 Hz, 2H), 7.75 (t, <i>J</i> = 7.8 Hz, 1H), 7.62 (d, <i>J</i> = 6.9 Hz, 1H), 7.54-7.29 (m, 8H), 3.57 (s, 2H), 2.30 (s, 3H), 2.01 (d, <i>J</i> = 6.9 Hz, 2H), 1.87 (s, 3H), 1.46 (s, 2H), 1.18 (d, <i>J</i> = 7.2 Hz, 2H). | 452                                        |
| 229  | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.49 (s, 1H), 8.11 (d, <i>J</i> = 8.1 Hz, 2H), 7.81 (d, <i>J</i> = 7.8 Hz, 1H), 7.71 (d, <i>J</i> = 8.1 Hz, 2H), 7.47 (t, <i>J</i> = 6.9 Hz, 2H), 7.42-7.32 (m, 4H), 7.24 (d, <i>J</i> = 7.5 Hz, 1H), 4.24 (s, 2H), 3.88 (s, 2H), 2.31 (s, 3H).                                                | 398                                        |
| 229s | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 9.02 (s, 1H), 8.49 (s, 1H), 8.11 (d, <i>J</i> = 8.1 Hz, 2H), 7.81 (d, <i>J</i> = 7.8 Hz, 1H), 7.71 (d, <i>J</i> = 8.1 Hz, 2H), 7.47 (t, <i>J</i> = 6.9 Hz, 2H), 7.42-7.32 (m, 4H), 7.24 (d, <i>J</i> = 7.5 Hz, 1H), 4.24 (s, 2H), 3.88 (s, 2H), 2.31 (s, 3H).                                  | 398                                        |
| 230  | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.35 (s, 1H), 8.24 (d, <i>J</i> = 7.5 Hz, 1H), 7.95 (s, 1H), 7.84 (s, 1H), 7.70 (s, 1H), 7.61 (s, 1H), 7.49 (s, 2H), 7.42 (d, <i>J</i> = 7.5 Hz, 2H), 7.36 (d, <i>J</i> = 7.2 Hz, 4H), 4.31 (s, 2H), 4.03 (d, <i>J</i> = 11.7 Hz, 2H), 3.94 (s, 1H), 2.28 (s, 3H).                             | 428                                        |
| 230s | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 9.04 (s, 1H), 8.35 (s, 1H), 8.24 (d, <i>J</i> = 7.5 Hz, 1H), 7.95 (s, 1H), 7.84 (s, 1H), 7.70 (s, 1H), 7.61 (s, 1H), 7.49 (s, 2H), 7.42 (d, <i>J</i> = 7.5 Hz, 2H), 7.36 (d, <i>J</i> = 7.2 Hz, 3H), 4.31 (s, 2H), 4.03 (d, <i>J</i> = 11.7 Hz, 2H), 3.94 (s, 1H), 2.28 (s, 3H).               | 428                                        |
| 231  | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.15 (s, 1H), 8.00 (d, <i>J</i> = 6.3 Hz, 1H), 7.81 (d, <i>J</i> = 7.5 Hz, 1H), 7.63 (s, 1H), 7.54 (d, <i>J</i> = 6.3 Hz, 2H), 7.51-7.32 (m, 6H), 7.28 (d, <i>J</i> = 7.5 Hz, 1H), 4.07 (d, <i>J</i> = 13.5 Hz, 1H), 3.86 (d, <i>J</i> = 13.8 Hz, 2H), 3.62-3.53 (m,                           | 442                                        |

|      |                                                                                                                                                                                                                                                                                                                                                                   |     |
|------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|
|      | 1H), 2.34 (s, 3H), 1.14 (d, $J = 6.0$ Hz, 3H).                                                                                                                                                                                                                                                                                                                    |     |
| 231s | <sup>1</sup> H NMR (300 MHz, DMSO- $d_6$ ) $\delta$ 9.15 (s, 1H), 8.15 (s, 1H), 8.00 (d, $J = 6.3$ Hz, 1H), 7.81 (d, $J = 7.5$ Hz, 1H), 7.63 (s, 1H), 7.54 (d, $J = 6.3$ Hz, 2H), 7.51-7.32 (m, 6H), 7.28 (d, $J = 7.5$ Hz, 1H), 4.07 (d, $J = 13.5$ Hz, 1H), 3.86 (d, $J = 13.8$ Hz, 2H), 3.62-3.53 (m, 1H), 2.34 (s, 3H), 1.14 (d, $J = 6.0$ Hz, 3H).           | 442 |
| 232  | <sup>1</sup> H NMR (300 MHz, DMSO- $d_6$ ) $\delta$ 8.50 (s, 1H), 8.28 (s, 1H), 8.08 (d, $J = 7.2$ Hz, 1H), 7.83 (d, $J = 8.0$ Hz, 1H), 7.74 (d, $J = 7.2$ Hz, 1H), 7.64 (d, $J = 8.1$ Hz, 1H), 7.54-7.42 (m, 3H), 7.36 (dd, $J = 13.5, 7.2$ Hz, 3H), 7.23 (d, $J = 8.1$ Hz, 1H), 4.27 (s, 2H), 3.19-3.08 (m, 2H), 2.81-2.69 (m, 2H), 2.31 (s, 3H).               | 412 |
| 232s | <sup>1</sup> H NMR (300 MHz, DMSO- $d_6$ ) $\delta$ 9.02 (s, 1H), 8.50 (s, 1H), 8.28 (s, 1H), 8.08 (d, $J = 7.2$ Hz, 1H), 7.83 (d, $J = 8.0$ Hz, 1H), 7.74 (d, $J = 7.2$ Hz, 1H), 7.64 (d, $J = 8.1$ Hz, 1H), 7.54-7.42 (m, 3H), 7.36 (dd, $J = 13.5, 7.2$ Hz, 3H), 7.23 (d, $J = 8.1$ Hz, 1H), 4.27 (s, 2H), 3.19-3.08 (m, 2H), 2.81-2.69 (m, 2H), 2.31 (s, 3H). | 412 |
| 233  | <sup>1</sup> H NMR (300 MHz, DMSO- $d_6$ ) $\delta$ 8.35 (s, 1H), 8.06 (d, $J = 8.1$ Hz, 2H), 7.80 (s, 1H), 7.67-7.23 (m, 9H), 7.15 (s, 1H), 4.10 (s, 2H), 3.03 (t, $J = 6.9$ Hz, 2H), 2.60 (t, $J = 6.9$ Hz, 2H), 2.34 (s, 3H).                                                                                                                                  | 412 |
| 233s | <sup>1</sup> H NMR (300 MHz, DMSO- $d_6$ ) $\delta$ 8.85 (s, 1H), 8.06 (d, $J = 8.1$ Hz, 2H), 7.80 (s, 1H), 7.67-7.23 (m, 9H), 7.15 (s, 1H), 4.10 (s, 2H), 3.03 (t, $J = 6.9$ Hz, 2H), 2.60 (t, $J = 6.9$ Hz, 2H), 2.34 (s, 3H).                                                                                                                                  | 412 |
| 234  | <sup>1</sup> H NMR (300 MHz, DMSO- $d_6$ ) $\delta$ 8.49 (s, 1H), 8.11 (d, $J = 8.1$ Hz, 2H), 7.81 (d, $J = 7.8$ Hz, 1H), 7.71 (d, $J = 8.1$ Hz, 2H), 7.47 (t, $J = 6.9$ Hz, 2H), 7.42-7.32 (m, 4H), 7.24 (d, $J = 7.5$ Hz, 1H), 4.24 (s, 2H), 3.88 (s, 2H), 2.31 (s, 3H).                                                                                        | 398 |
| 234s | <sup>1</sup> H NMR (300 MHz, DMSO- $d_6$ ) $\delta$ 9.02 (s, 1H), 8.49 (s, 1H), 8.11 (d, $J = 8.1$ Hz, 2H), 7.81 (d, $J = 7.8$ Hz, 1H), 7.71 (d, $J = 8.1$ Hz, 2H), 7.47 (t, $J = 6.9$ Hz, 2H), 7.42-7.32 (m, 4H), 7.24 (d, $J = 7.5$ Hz, 1H), 4.24 (s, 2H), 3.88 (s, 2H), 2.31 (s, 3H).                                                                          | 398 |

实施例 7: 3-(5-(2-甲基-[1,1'-联苯]-3-基)噻唑-2-基)苄基甘氨酸 (235) 及其盐酸盐 (235s) 的合成

3-(5-(2-甲基-[1,1'-联苯]-3-基)噻唑-2-基)苯甲酸甲酯 (7A) 的合成

参照实施例 1 的方法, 将 4E 和劳森试剂进行环合反应, 制得白色固体 7A, 收率 83%。MS (EI)  $m/z$  384 [M-H]<sup>-</sup>; <sup>1</sup>H NMR (300 MHz, Chloroform- $d$ )  $\delta$  8.11 (s, 1H), 8.01 (dt,  $J = 6.9, 1.8$  Hz, 1H), 7.68 (dd,  $J = 6.6, 2.4$  Hz, 1H), 7.56 (s, 1H), 7.48 (s, 1H), 7.46 (s, 1H), 7.43 (s, 1H), 7.41 (d,  $J = 2.7$  Hz, 2H), 7.39 (d,  $J = 1.8$  Hz, 2H), 7.36 (t,  $J = 1.5$  Hz, 2H), 3.90 (s, 3H), 2.46 (s, 3H).

3-(5-(2-甲基-[1,1'-联苯]-3-基)噻唑-2-基)苄基甲醇 (7B) 的合成

参照实施例 2 的方法, 将 7A 和 LiAlH<sub>4</sub> 反应, 制得白色固体 7B, 收率 94%。MS (EI)  $m/z$  356 [M-H]<sup>-</sup>; <sup>1</sup>H NMR (300 MHz, DMSO- $d_6$ )  $\delta$  8.18-8.02 (m, 2H), 7.83 (d,  $J = 10.5$  Hz, 1H), 7.72-7.59 (m, 1H), 7.59-7.34 (m, 8H), 7.29 (s, 1H), 4.59 (s, 2H), 2.35 (s, 3H).

2-(3-氯甲基)苄基-5-(2-甲基-[1,1'-联苯]-3-基)噻唑 (7C) 的合成

参照实施例 4 的方法, 将 7B 进行反应, 制得白色固体 7C, 收率 95%。MS (EI)  $m/z$  374 [M-H]<sup>-</sup>; <sup>1</sup>H NMR (300 MHz, DMSO- $d_6$ )  $\delta$  8.18-8.02 (m, 2H), 7.83 (d,  $J = 10.5$  Hz, 1H), 7.72-7.59 (m, 1H), 7.59-7.34 (m, 8H), 7.29 (s, 1H), 4.64 (s, 2H), 2.33 (s, 3H).

(3-(5-(2-甲基-[1,1'-联苯]-3-基)噻唑-2-基)苄基)甘氨酸甲酯 (235m) 的合成

参照实施例 1 的方法, 将 7C 和甘氨酸甲酯盐酸盐进行反应, 制得白色固体 235m, 收率 76%。MS (EI)  $m/z$  427 [M-H]<sup>-</sup>; <sup>1</sup>H NMR (300 MHz, DMSO- $d_6$ )  $\delta$  8.04 (d,  $J = 7.8$  Hz, 2H), 7.83 (d,  $J = 7.8$  Hz, 1H), 7.62 (s, 1H), 7.57-7.35 (m, 8H), 7.29 (dd,  $J = 7.5, 1.5$  Hz, 1H), 3.80 (s, 2H), 3.64 (s, 3H), 3.35 (s, 2H), 2.36 (s, 3H).

化合物 235 及其盐酸盐 (235s) 的合成

参照实施例 1 的方法, 将 235m 水解制得白色固体 235, 收率 87%。再将 235 与盐酸成盐, 制得白色固体 235s, 收率 90%。MS (ESI)  $m/z$  415 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (300 MHz, DMSO- $d_6$ )  $\delta$  9.02 (s, 1H), 8.36 (s, 1H), 8.15 (d,  $J = 7.2$  Hz, 1H), 8.05 (d,  $J = 6.9$  Hz, 2H), 7.80 (s, 1H), 7.70 (s, 1H), 7.47 (q,  $J = 8.1, 7.8$  Hz, 5H), 7.37 (d,  $J = 6.6$  Hz, 2H), 4.21 (s, 2H), 3.75 (s, 2H), 2.23 (s, 3H).

采用与实施例 7 相似的操作, 制得下列化合物:

| 编号  | <sup>1</sup> H-NMR                                                                                                                                                                                                                                                                                                          | ESI-MS<br>$m/z$<br>(M+H) <sup>+</sup> |
|-----|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------|
| 236 | <sup>1</sup> H NMR (300 MHz, DMSO- $d_6$ ) $\delta$ 8.77 (s, 1H), 8.08 (s, 1H), 7.92 (dd, $J = 10.8, 6.0$ Hz, 2H), 7.53 (d, $J = 4.8$ Hz, 2H), 7.51-7.44 (m, 3H), 7.43 (s, 1H), 7.39 (d, $J = 3.3$ Hz, 2H), 7.36 (s, 1H), 4.24 (t, $J = 9.3$ Hz, 2H), 4.02 (d, $J = 7.2$ Hz, 1H), 2.52 (s, 3H), 1.53 (d, $J = 7.2$ Hz, 3H). | 429                                   |

|      |                                                                                                                                                                                                                                                                                                                                                                                                                                    |     |
|------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|
| 236s | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 9.23 (s, 1H), 8.77 (s, 1H), 8.08 (s, 1H), 7.92 (dd, <i>J</i> = 10.8, 6.0 Hz, 2H), 7.53 (d, <i>J</i> = 4.8 Hz, 2H), 7.51-7.44 (m, 3H), 7.43 (s, 1H), 7.39 (d, <i>J</i> = 3.3 Hz, 2H), 7.36 (s, 1H), 4.24 (t, <i>J</i> = 9.3 Hz, 2H), 4.02 (d, <i>J</i> = 7.2 Hz, 1H), 2.52 (s, 3H), 1.53 (d, <i>J</i> = 7.2 Hz, 3H).                                                   | 429 |
| 237  | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.24 (s, 1H), 8.09 (d, <i>J</i> = 7.5 Hz, 1H), 7.84 (d, <i>J</i> = 7.5 Hz, 1H), 7.64 (d, <i>J</i> = 14.7 Hz, 4H), 7.51-7.32 (m, 6H), 4.19 (d, <i>J</i> = 3.6 Hz, 2H), 3.83 (d, <i>J</i> = 4.8 Hz, 1H), 3.63 (s, 2H), 2.37 (s, 3H).                                                                                                                                    | 445 |
| 237s | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 9.27 (s, 1H), 8.09 (d, <i>J</i> = 7.5 Hz, 1H), 7.84 (d, <i>J</i> = 7.5 Hz, 1H), 7.64 (d, <i>J</i> = 14.7 Hz, 3H), 7.51-7.32 (m, 8H), 4.19 (d, <i>J</i> = 3.6 Hz, 2H), 3.83 (d, <i>J</i> = 4.8 Hz, 1H), 3.63 (s, 2H), 2.37 (s, 3H).                                                                                                                                    | 445 |
| 238  | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.15 (s, 1H), 8.00 (d, <i>J</i> = 6.3 Hz, 1H), 7.81 (d, <i>J</i> = 7.5 Hz, 1H), 7.63 (s, 1H), 7.54 (d, <i>J</i> = 6.3 Hz, 2H), 7.51-7.32 (m, 6H), 7.28 (d, <i>J</i> = 7.5 Hz, 1H), 4.07 (d, <i>J</i> = 13.5 Hz, 1H), 3.86 (d, <i>J</i> = 13.8 Hz, 2H), 3.62-3.53 (m, 1H), 2.34 (s, 3H), 1.14 (d, <i>J</i> = 6.0 Hz, 3H).                                              | 459 |
| 238s | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 9.15 (s, 1H), 8.15 (s, 1H), 8.00 (d, <i>J</i> = 6.3 Hz, 1H), 7.81 (d, <i>J</i> = 7.5 Hz, 1H), 7.63 (s, 1H), 7.54 (d, <i>J</i> = 6.3 Hz, 2H), 7.51-7.32 (m, 6H), 7.28 (d, <i>J</i> = 7.5 Hz, 1H), 4.07 (d, <i>J</i> = 13.5 Hz, 1H), 3.86 (d, <i>J</i> = 13.8 Hz, 2H), 3.62-3.53 (m, 1H), 2.34 (s, 3H), 1.14 (d, <i>J</i> = 6.0 Hz, 3H).                                | 459 |
| 239  | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.14 (d, <i>J</i> = 8.1 Hz, 2H), 7.83 (d, <i>J</i> = 7.8 Hz, 1H), 7.74 (d, <i>J</i> = 8.1 Hz, 2H), 7.65 (s, 1H), 7.47 (d, <i>J</i> = 7.5 Hz, 2H), 7.41 (d, <i>J</i> = 6.9 Hz, 2H), 7.39-7.34 (m, 2H), 7.29 (d, <i>J</i> = 7.5 Hz, 1H), 4.24 (t, <i>J</i> = 5.7 Hz, 2H), 3.69 (d, <i>J</i> = 5.4 Hz, 2H), 2.99 (d, <i>J</i> = 6.0 Hz, 2H), 2.35 (s, 3H).               | 401 |
| 239s | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 9.26 (s, 2H), 8.14 (d, <i>J</i> = 8.1 Hz, 2H), 7.83 (d, <i>J</i> = 7.8 Hz, 1H), 7.74 (d, <i>J</i> = 8.1 Hz, 2H), 7.65 (s, 1H), 7.47 (d, <i>J</i> = 7.5 Hz, 2H), 7.41 (d, <i>J</i> = 6.9 Hz, 2H), 7.39-7.34 (m, 2H), 7.29 (d, <i>J</i> = 7.5 Hz, 1H), 4.24 (t, <i>J</i> = 5.7 Hz, 2H), 3.69 (d, <i>J</i> = 5.4 Hz, 2H), 2.99 (d, <i>J</i> = 6.0 Hz, 2H), 2.35 (s, 3H). | 401 |
| 240  | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.36 (s, 1H), 8.15 (d, <i>J</i> = 7.2 Hz, 1H), 8.05 (d, <i>J</i> = 6.9 Hz, 1H), 7.80 (s, 1H), 7.70 (s, 1H), 7.47 (q, <i>J</i> = 8.1, 7.8 Hz, 4H), 7.37 (d, <i>J</i> = 6.6 Hz, 3H), 4.21 (s, 2H), 3.74 (s, 2H), 2.23 (s, 3H).                                                                                                                                          | 414 |
| 240s | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.77 (s, 1H), 8.08 (s, 1H), 7.92 (dd, <i>J</i> = 10.8, 6.0 Hz, 2H), 7.53 (d, <i>J</i> = 4.8 Hz, 2H), 7.51-7.44 (m, 3H), 7.43 (s, 1H), 7.39 (d, <i>J</i> = 3.3 Hz, 2H), 7.36 (s, 1H), 4.24 (t, <i>J</i> = 9.3 Hz, 2H), 4.02 (d, <i>J</i> = 7.2 Hz, 1H), 3.64 (s, 3H), 2.52 (s, 3H), 1.53 (d, <i>J</i> = 7.2 Hz, 3H).                                                   | 414 |
| 241  | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.77 (s, 1H), 8.08 (s, 1H), 7.92 (dd, <i>J</i> = 10.8, 6.0 Hz, 2H), 7.53 (d, <i>J</i> = 4.8 Hz, 2H), 7.51-7.44 (m, 3H), 7.43 (s, 1H), 7.39 (d, <i>J</i> = 3.3 Hz, 2H), 7.36 (s, 1H), 4.24 (t, <i>J</i> = 9.3 Hz, 2H), 4.02 (d, <i>J</i> = 7.2 Hz, 1H), 2.52 (s, 3H), 1.53 (d, <i>J</i> = 7.2 Hz, 3H).                                                                 | 427 |
| 241s | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 9.23 (s, 1H), 8.77 (s, 1H), 8.08 (s, 1H), 7.92 (dd, <i>J</i> = 10.8, 6.0 Hz, 2H), 7.53 (d, <i>J</i> = 4.8 Hz, 2H), 7.51-7.44 (m, 3H), 7.43 (s, 1H), 7.39 (d, <i>J</i> = 3.3 Hz, 2H), 7.36 (s, 1H), 4.24 (t, <i>J</i> = 9.3 Hz, 2H), 4.02 (d, <i>J</i> = 7.2 Hz, 1H), 2.52 (s, 3H), 1.53 (d, <i>J</i> = 7.2 Hz, 3H).                                                   | 427 |
| 242  | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.24 (s, 1H), 8.09 (d, <i>J</i> = 7.5 Hz, 1H), 7.84 (d, <i>J</i> = 7.5 Hz, 1H), 7.64 (d, <i>J</i> = 14.7 Hz, 4H), 7.51-7.32 (m, 6H), 4.19 (d, <i>J</i> = 3.6 Hz, 2H), 3.83 (d, <i>J</i> = 4.8 Hz, 1H), 3.63 (s, 2H), 2.37 (s, 3H).                                                                                                                                    | 445 |
| 242s | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 9.27 (s, 1H), 8.09 (d, <i>J</i> = 7.5 Hz, 1H), 7.84 (d, <i>J</i> = 7.5 Hz, 1H), 7.64 (d, <i>J</i> = 14.7 Hz, 3H), 7.51-7.32 (m, 8H), 4.19 (d, <i>J</i> = 3.6 Hz, 2H), 3.83 (d, <i>J</i> = 4.8 Hz, 1H), 3.63 (s, 2H), 2.37 (s, 3H).                                                                                                                                    | 445 |
| 243  | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.15 (s, 1H), 8.00 (d, <i>J</i> = 6.3 Hz, 1H), 7.81 (d, <i>J</i> = 7.5 Hz, 1H), 7.63 (s, 1H), 7.54 (d, <i>J</i> = 6.3 Hz, 2H), 7.51-7.32 (m, 6H), 7.28 (d, <i>J</i> = 7.5 Hz, 1H), 4.07 (d, <i>J</i> = 13.5 Hz, 1H), 3.86 (d, <i>J</i> = 13.8 Hz, 2H), 3.62-3.53 (m, 1H), 2.34 (s, 3H), 1.14 (d, <i>J</i> = 6.0 Hz, 3H).                                              | 459 |
| 243s | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 9.15 (s, 1H), 8.15 (s, 1H), 8.00 (d, <i>J</i> = 6.3 Hz, 1H), 7.81 (d, <i>J</i> = 7.5 Hz, 1H), 7.63 (s, 1H), 7.54 (d, <i>J</i> = 6.3 Hz, 2H), 7.51-7.32 (m, 6H), 7.28 (d, <i>J</i> = 7.5 Hz, 1H), 4.07 (d, <i>J</i> = 13.5 Hz, 1H), 3.86 (d, <i>J</i> = 13.8 Hz, 2H), 3.62-3.53 (m, 1H), 2.34 (s, 3H), 1.14 (d, <i>J</i> = 6.0 Hz, 3H).                                | 459 |
| 244  | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.14 (d, <i>J</i> = 8.1 Hz, 2H), 7.83 (d, <i>J</i> = 7.8 Hz, 1H), 7.74 (d, <i>J</i> = 8.1 Hz, 2H), 7.65 (s, 1H), 7.47 (d, <i>J</i> = 7.5 Hz, 2H), 7.41 (d, <i>J</i> = 6.9 Hz, 2H), 7.39-7.34 (m, 2H), 7.29 (d, <i>J</i> = 7.5 Hz, 1H), 4.24 (t, <i>J</i> = 5.7 Hz, 2H), 3.69 (d, <i>J</i> = 5.4 Hz, 2H), 2.99 (d, <i>J</i> = 6.0 Hz, 2H), 2.35 (s, 3H).               | 401 |
| 244s | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 9.26 (s, 2H), 8.14 (d, <i>J</i> = 8.1 Hz, 2H), 7.83 (d, <i>J</i> = 7.8 Hz, 1H), 7.74 (d, <i>J</i> = 8.1 Hz, 2H), 7.65 (s, 1H), 7.47 (d, <i>J</i> = 7.5 Hz, 2H), 7.41 (d, <i>J</i> = 6.9 Hz, 2H), 7.39-7.34 (m, 2H), 7.29 (d, <i>J</i> = 7.5 Hz, 1H), 4.24 (t, <i>J</i> = 5.7 Hz, 2H), 3.69 (d, <i>J</i> = 5.4 Hz, 2H), 2.99 (d, <i>J</i> = 6.0 Hz, 2H), 2.35 (s, 3H). | 401 |

实施例 8: (4-(5-(2-甲基-[1,1'-联苯]-3-基)噻吩-2-基)苄基)甘氨酸 (245) 及其盐酸盐 (245s) 的合成  
2-(3-溴-2-甲基苄基)噻吩 (8A) 的合成

参照实施例 1 的合成, 将 2,5-二溴甲苯和 2-硼酸噻吩为原料, 制得淡黄色油状液体 8A, 收率 89%, 直接投入下一步反应。

#### 2-(2-甲基-[1,1'-联苯]-3-基)噻吩 (8B) 的合成

参照实施例 1 的合成, 将 8A 和苯硼酸进行偶联反应, 制得黄色油状液体 8B, 收率 82%, 直接投入下一步反应。

#### 2-溴-5-(2-甲基-[1,1'-联苯]-3-基)噻吩 (8C) 的合成

将 8B (2.20g, 8.79mmol) 溶于 5mLDMSO 中, 再加入 N-溴代丁二酰亚胺 (1.56g, 8.79mmol), 室温下反应 3h, 反应完成后, 加入 50mL 水, 抽滤, 干燥, 得淡黄色固体 2.62 g, 收率 90%, 直接投入下一步反应。

#### 4-(5-(2-甲基-[1,1'-联苯]-3-基)噻吩-2-基)苯甲醛 (8D) 的合成

将 8C (2.62g, 7.91mmol) 溶于 20mL 二氧六环中, 再依次加入 2mL 水、4-甲酰苯硼酸频那醇酯 (2.38g, 10.3mmol)、碳酸钾 (3.27g, 23.7mmol)、Pd(dppf)Cl<sub>2</sub> (32mg, 0.04mmol)。氮气下 80°C 下反应 8h。冷却, 旋除溶剂, 乙酸乙酯萃取, 无水硫酸钠干燥, 柱层析纯化 (石油醚:乙酸乙酯=5:1 (V: V)), 得淡黄色固体 1.61g, 收率 57%, 直接投入下一步反应。

#### (4-(5-(2-甲基-[1,1'-联苯]-3-基)噻吩-2-基)苄基)甘氨酸甲酯 (245m) 的合成

参照实施例 2 的方法, 将 8D 和甘氨酸甲酯盐酸盐进行还原胺化反应, 制得淡黄色固体 245m, 收率 59%。MS (ESI) *m/z* 428 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 7.76 (d, *J* = 8.1 Hz, 2H), 7.62 (d, *J* = 3.6 Hz, 1H), 7.57 (d, *J* = 8.1 Hz, 3H), 7.52-7.40 (m, 3H), 7.40-7.33 (m, 3H), 7.28-7.21 (m, 2H), 4.18 (s, 2H), 3.91 (s, 3H), 3.83 (s, 2H), 2.27 (s, 3H).

#### 化合物 245 及其盐酸盐 (245s) 的合成

参照实施例 1 的方法, 将 245m 水解制得黄色固体 245, 收率 85%。再将 245 与盐酸成盐, 得淡黄色固体 245s, 收率 96%。MS (ESI) *m/z* 414 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 7.76 (d, *J* = 8.1 Hz, 2H), 7.62 (d, *J* = 3.6 Hz, 1H), 7.57 (d, *J* = 8.1 Hz, 2H), 7.52-7.40 (m, 4H), 7.40-7.33 (m, 3H), 7.28-7.21 (m, 2H), 4.18 (s, 2H), 3.83 (s, 2H), 2.27 (s, 3H).

采用与实施例 8 相似的操作, 制得下列化合物:

| 编号   | <sup>1</sup> H-NMR                                                                                                                                                                                                                                                                                                                                         | ESI-MS<br><i>m/z</i><br>[M+H] <sup>+</sup> |
|------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------|
| 246  | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 7.75 (d, <i>J</i> = 8.1 Hz, 2H), 7.60 (s, 2H), 7.57 (s, 1H), 7.45 (d, <i>J</i> = 6.9 Hz, 3H), 7.40 (d, <i>J</i> = 11.4 Hz, 3H), 7.31 (s, 1H), 7.23 (d, <i>J</i> = 3.3 Hz, 2H), 4.17 (s, 2H), 3.14-3.07 (m, 2H), 2.72 (t, <i>J</i> = 7.2 Hz, 2H), 2.26 (s, 3H).                                | 428                                        |
| 246s | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 9.02 (s, 1H), 7.75 (d, <i>J</i> = 8.1 Hz, 2H), 7.60 (s, 2H), 7.57 (s, 1H), 7.45 (d, <i>J</i> = 6.9 Hz, 3H), 7.40 (d, <i>J</i> = 11.4 Hz, 3H), 7.31 (s, 1H), 7.23 (d, <i>J</i> = 3.3 Hz, 2H), 4.17 (s, 2H), 3.14-3.07 (m, 2H), 2.72 (t, <i>J</i> = 7.2 Hz, 2H), 2.26 (s, 3H).                  | 428                                        |
| 247  | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 7.74 (d, <i>J</i> = 8.1 Hz, 2H), 7.59 (dd, <i>J</i> = 11.7, 6.0 Hz, 3H), 7.49-7.40 (m, 4H), 7.35 (dd, <i>J</i> = 12.3, 7.8 Hz, 3H), 7.26-7.20 (m, 2H), 4.21 (s, 2H), 3.97-3.86 (m, 3H), 2.26 (s, 3H).                                                                                         | 444                                        |
| 247s | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.96 (s, 1H), 7.74 (d, <i>J</i> = 8.1 Hz, 2H), 7.59 (dd, <i>J</i> = 11.7, 6.0 Hz, 3H), 7.49-7.40 (m, 4H), 7.35 (dd, <i>J</i> = 12.3, 7.8 Hz, 3H), 7.26-7.20 (m, 2H), 4.21 (s, 2H), 3.97-3.86 (m, 3H), 2.26 (s, 3H).                                                                           | 444                                        |
| 248  | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 7.76 (d, <i>J</i> = 8.1 Hz, 2H), 7.64 (d, <i>J</i> = 3.6 Hz, 1H), 7.58 (d, <i>J</i> = 8.1 Hz, 2H), 7.50-7.40 (m, 4H), 7.40-7.34 (m, 3H), 7.27-7.23 (m, 2H), 4.27-4.16 (m, 2H), 4.09 (t, <i>J</i> = 6.3 Hz, 1H), 3.54 (s, 1H), 2.27 (s, 3H), 1.21 (d, <i>J</i> = 6.3 Hz, 3H).                  | 458                                        |
| 248s | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 9.12 (s, 1H), 7.76 (d, <i>J</i> = 8.1 Hz, 2H), 7.64 (d, <i>J</i> = 3.6 Hz, 1H), 7.58 (d, <i>J</i> = 8.1 Hz, 2H), 7.50-7.40 (m, 4H), 7.40-7.34 (m, 3H), 7.27-7.23 (m, 2H), 4.27-4.16 (m, 2H), 4.09 (t, <i>J</i> = 6.3 Hz, 1H), 3.54 (s, 1H), 2.27 (s, 3H), 1.21 (d, <i>J</i> = 6.3 Hz, 3H).    | 458                                        |
| 249  | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 7.77 (d, <i>J</i> = 7.5 Hz, 2H), 7.66 (s, 1H), 7.63 (s, 2H), 7.44 (dt, <i>J</i> = 11.4, 6.3 Hz, 4H), 7.35 (dd, <i>J</i> = 11.6, 8.1 Hz, 3H), 7.24 (d, <i>J</i> = 5.1 Hz, 2H), 4.29 (s, 2H), 3.89 (s, 3H), 3.31 (m, 2H), 2.93 (s, 3H), 2.26 (s, 3H), 2.00 (s, 1H), 1.84 (s, 2H), 1.44 (s, 1H). | 482                                        |
| 249s | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 7.77 (d, <i>J</i> = 7.5 Hz, 2H), 7.66 (s, 1H), 7.63 (s, 2H), 7.44 (dt, <i>J</i> = 11.4, 6.3 Hz, 4H), 7.35 (dd, <i>J</i> = 11.6, 8.1 Hz, 3H), 7.24 (d, <i>J</i> = 5.1 Hz, 2H), 4.29 (s, 2H), 3.89 (s, 3H), 3.31 (m, 2H), 2.93 (s, 3H), 2.26 (s, 3H), 2.00 (s, 1H), 1.84 (s, 2H), 1.44 (s, 1H). | 482                                        |
| 250  | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 7.78 (s, 1H), 7.67 (d, <i>J</i> = 9.0 Hz, 2H), 7.55 (d, <i>J</i> = 3.9 Hz, 1H), 7.45 (d, <i>J</i> = 7.2 Hz, 4H), 7.37 (d, <i>J</i> = 7.5 Hz, 4H), 7.27-7.20 (m, 2H), 4.03 (s, 2H), 3.87 (s, 2H), 2.26 (s, 3H).                                                                                | 414                                        |
| 250s | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 9.02 (s, 1H), 7.78 (s, 1H), 7.67 (d, <i>J</i> = 9.0 Hz, 2H), 7.55 (d, <i>J</i> = 3.9 Hz, 1H), 7.45 (d, <i>J</i> =                                                                                                                                                                             | 414                                        |

|      |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |     |
|------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|
|      | 7.2 Hz, 4H), 7.37 (d, $J = 7.5$ Hz, 4H), 7.27-7.20 (m, 2H), 4.03 (s, 2H), 3.87 (s, 2H), 2.26 (s, 3H).                                                                                                                                                                                                                                                                                                                                                                                                                                            |     |
| 251  | $^1\text{H}$ NMR (300 MHz, DMSO- $d_6$ ) $\delta$ 8.11 (d, $J = 8.1$ Hz, 2H), 7.77 (s, 1H), 7.75 (s, 1H), 7.70 (s, 1H), 7.48 (d, $J = 5.7$ Hz, 4H), 7.43 (s, 2H), 7.40 (s, 3H), 5.27 (s, 1H), 4.26 (s, 2H), 3.69 (s, 2H), 2.99 (s, 2H), 2.34 (s, 3H).                                                                                                                                                                                                                                                                                            | 386 |
| 251s | $^1\text{H}$ NMR (300 MHz, DMSO- $d_6$ ) $\delta$ 9.27 (s, 1H), 8.11 (d, $J = 8.1$ Hz, 2H), 7.77 (s, 1H), 7.75 (s, 1H), 7.70 (s, 1H), 7.48 (d, $J = 5.7$ Hz, 4H), 7.43 (s, 2H), 7.40 (s, 3H), 5.27 (s, 1H), 4.26 (s, 2H), 3.69 (s, 2H), 2.99 (s, 2H), 2.34 (s, 3H).                                                                                                                                                                                                                                                                              | 386 |
| 252  | $^1\text{H}$ NMR (300 MHz, DMSO- $d_6$ ) $\delta$ 7.97 (s, 1H), 7.71 (s, 2H), 7.60 (s, 3H), 7.48 (s, 4H), 7.38 (s, 3H), 7.23 (s, 1H), 4.19 (s, 2H), 3.11 (s, 2H), 2.77 (s, 2H), 2.26 (s, 3H).                                                                                                                                                                                                                                                                                                                                                    | 442 |
| 252s | $^1\text{H}$ NMR (300 MHz, DMSO- $d_6$ ) $\delta$ 8.76 (s, 1H), 7.97 (s, 1H), 7.71 (s, 2H), 7.60 (s, 3H), 7.48 (s, 4H), 7.38 (s, 3H), 7.23 (s, 1H), 4.19 (s, 2H), 3.11 (s, 2H), 2.77 (s, 2H), 2.26 (s, 3H).                                                                                                                                                                                                                                                                                                                                      | 428 |
| 253  | $^1\text{H}$ NMR (300 MHz, DMSO- $d_6$ ) $\delta$ 8.30 (s, 1H), 8.19 (dd, $J = 6.6, 2.7$ Hz, 1H), 8.12 (d, $J = 7.5$ Hz, 1H), 7.76 (d, $J = 7.5$ Hz, 1H), 7.66 (q, $J = 6.3, 5.4$ Hz, 3H), 7.51 (t, $J = 12.3$ Hz, 5H), 7.26 (dd, $J = 6.9, 2.4$ Hz, 2H), 4.25 (s, 2H), 3.88 (s, 1H), 2.28 (s, 3H), 1.51 (d, $J = 6.2$ Hz, 3H).                                                                                                                                                                                                                  | 428 |
| 253s | $^1\text{H}$ NMR (300 MHz, DMSO- $d_6$ ) $\delta$ 9.02 (s, 1H), 8.30 (s, 1H), 8.19 (dd, $J = 6.6, 2.7$ Hz, 1H), 8.12 (d, $J = 7.5$ Hz, 1H), 7.76 (d, $J = 7.5$ Hz, 1H), 7.66 (q, $J = 6.3, 5.4$ Hz, 3H), 7.51 (t, $J = 12.3$ Hz, 5H), 7.26 (dd, $J = 6.9, 2.4$ Hz, 2H), 4.25 (s, 2H), 3.88 (s, 1H), 2.28 (s, 3H), 1.51 (d, $J = 6.2$ Hz, 3H).                                                                                                                                                                                                    | 428 |
| 254  | $^1\text{H}$ NMR (300 MHz, DMSO- $d_6$ ) $\delta$ 7.96 (s, 1H), 7.72 (s, 2H), 7.58 (d, $J = 3.5$ Hz, 2H), 7.45 (d, $J = 7.5$ Hz, 4H), 7.38 (s, 3H), 7.24 (d, $J = 3.9$ Hz, 2H), 4.27 (s, 2H), 4.00 (d, $J = 2.1$ Hz, 1H), 3.97-3.91 (m, 2H), 2.26 (s, 3H).                                                                                                                                                                                                                                                                                       | 444 |
| 254s | $^1\text{H}$ NMR (300 MHz, DMSO- $d_6$ ) $\delta$ 9.04 (s, 1H), 7.96 (s, 1H), 7.72 (s, 2H), 7.58 (d, $J = 3.5$ Hz, 2H), 7.45 (d, $J = 7.4$ Hz, 4H), 7.38 (s, 3H), 7.24 (d, $J = 3.8$ Hz, 2H), 4.27 (s, 2H), 4.00 (d, $J = 2.1$ Hz, 1H), 3.97-3.91 (m, 2H), 2.26 (s, 3H).                                                                                                                                                                                                                                                                         | 444 |
| 255  | $^1\text{H}$ NMR (300 MHz, DMSO- $d_6$ ) $\delta$ 7.91 (s, 1H), 7.76 (d, $J = 7.2$ Hz, 1H), 7.59 (d, $J = 3.6$ Hz, 1H), 7.51 (d, $J = 7.4$ Hz, 1H), 7.45 (d, $J = 7.8$ Hz, 4H), 7.40 (s, 1H), 7.37 (d, $J = 4.2$ Hz, 2H), 7.27 (s, 1H), 7.25 (s, 2H), 4.25 (s, 2H), 4.14-4.07 (m, 1H), 3.55 (d, $J = 5.7$ Hz, 1H), 2.28 (s, 3H), 1.21 (d, $J = 6.3$ Hz, 3H).                                                                                                                                                                                     | 458 |
| 255s | $^1\text{H}$ NMR (300 MHz, DMSO- $d_6$ ) $\delta$ 9.10 (s, 1H), 7.91 (s, 1H), 7.76 (d, $J = 7.2$ Hz, 1H), 7.59 (d, $J = 3.6$ Hz, 1H), 7.51 (d, $J = 7.4$ Hz, 1H), 7.45 (d, $J = 7.8$ Hz, 4H), 7.40 (s, 1H), 7.37 (d, $J = 4.2$ Hz, 2H), 7.27 (s, 1H), 7.25 (s, 2H), 4.25 (s, 2H), 4.14-4.07 (m, 1H), 3.55 (d, $J = 5.7$ Hz, 1H), 2.28 (s, 3H), 1.21 (d, $J = 6.3$ Hz, 3H).                                                                                                                                                                       | 458 |
| 256  | $^1\text{H}$ NMR (300 MHz, DMSO- $d_6$ ) $\delta$ 7.99 (s, 1H), 7.80 (d, $J = 7.2$ Hz, 1H), 7.64 (t, $J = 3.9$ Hz, 1H), 7.56 (d, $J = 7.5$ Hz, 1H), 7.51 (d, $J = 3.0$ Hz, 1H), 7.48 (d, $J = 1.8$ Hz, 1H), 7.46 (d, $J = 2.1$ Hz, 1H), 7.45-7.43 (m, 1H), 7.41 (d, $J = 5.7$ Hz, 1H), 7.39 (d, $J = 2.7$ Hz, 1H), 7.37 (d, $J = 4.2$ Hz, 1H), 7.26 (dd, $J = 6.9, 2.4$ Hz, 3H), 4.37 (s, 2H), 3.31 (m, 2H), 2.93 (s, 2H), 2.28 (s, 3H), 2.05 (d, $J = 17.1$ Hz, 1H), 1.87 (s, 2H), 1.51-1.40 (m, 1H), 1.35 (d, $J = 6.9$ Hz, 1H).               | 468 |
| 256s | $^1\text{H}$ NMR (300 MHz, DMSO- $d_6$ ) $\delta$ 9.02 (s, 1H), 7.99 (s, 1H), 7.80 (d, $J = 7.2$ Hz, 1H), 7.64 (t, $J = 3.9$ Hz, 1H), 7.56 (d, $J = 7.5$ Hz, 1H), 7.51 (d, $J = 3.0$ Hz, 1H), 7.48 (d, $J = 1.8$ Hz, 1H), 7.46 (d, $J = 2.1$ Hz, 1H), 7.45-7.43 (m, 1H), 7.41 (d, $J = 5.7$ Hz, 1H), 7.39 (d, $J = 2.7$ Hz, 1H), 7.37 (d, $J = 4.2$ Hz, 1H), 7.26 (dd, $J = 6.9, 2.4$ Hz, 3H), 4.37 (s, 2H), 3.31 (m, 2H), 2.93 (s, 2H), 2.28 (s, 3H), 2.05 (d, $J = 17.1$ Hz, 1H), 1.87 (s, 2H), 1.51-1.40 (m, 1H), 1.35 (d, $J = 6.9$ Hz, 1H). | 468 |
| 257  | $^1\text{H}$ NMR (300 MHz, DMSO- $d_6$ ) $\delta$ 7.95 (d, $J = 1.8$ Hz, 1H), 7.73 (s, 1H), 7.60 (d, $J = 3.6$ Hz, 1H), 7.52-7.45 (m, 3H), 7.45-7.36 (m, 3H), 7.37-7.31 (m, 1H), 7.26 (d, $J = 3.6$ Hz, 1H), 7.25-7.18 (m, 3H), 4.23 (s, 2H), 2.65 (d, $J = 6.0$ Hz, 2H), 2.42 (s, 1H), 2.35 (d, $J = 6.3$ Hz, 1H), 2.28 (s, 3H), 2.11 (d, $J = 12.9$ Hz, 1H).                                                                                                                                                                                   | 467 |
| 257s | $^1\text{H}$ NMR (300 MHz, DMSO- $d_6$ ) $\delta$ 9.27 (s, 1H), 7.95 (d, $J = 1.8$ Hz, 1H), 7.73 (s, 1H), 7.60 (d, $J = 3.6$ Hz, 1H), 7.52-7.45 (m, 3H), 7.45-7.36 (m, 3H), 7.37-7.31 (m, 1H), 7.26 (d, $J = 3.6$ Hz, 1H), 7.25-7.18 (m, 3H), 4.23 (s, 2H), 2.65 (d, $J = 6.0$ Hz, 2H), 2.42 (s, 1H), 2.35 (d, $J = 6.3$ Hz, 1H), 2.28 (s, 3H), 2.11 (d, $J = 12.9$ Hz, 1H).                                                                                                                                                                     | 467 |
| 258  | $^1\text{H}$ NMR (300 MHz, DMSO- $d_6$ ) $\delta$ 7.76 (d, $J = 8.1$ Hz, 2H), 7.62 (d, $J = 3.6$ Hz, 1H), 7.57 (d, $J = 8.1$ Hz, 2H), 7.52-7.40 (m, 4H), 7.40-7.33 (m, 3H), 7.28-7.21 (m, 2H), 4.18 (s, 2H), 3.83 (s, 2H), 2.27 (s, 3H).                                                                                                                                                                                                                                                                                                         | 398 |
| 258s | $^1\text{H}$ NMR (300 MHz, DMSO- $d_6$ ) $\delta$ 8.99 (s, 1H), 7.76 (d, $J = 8.1$ Hz, 2H), 7.62 (d, $J = 3.6$ Hz, 1H), 7.57 (d, $J = 8.1$ Hz, 2H), 7.52-7.40 (m, 4H), 7.40-7.33 (m, 3H), 7.28-7.21 (m, 2H), 4.18 (s, 2H), 3.83 (s, 2H), 2.27 (s, 3H).                                                                                                                                                                                                                                                                                           | 398 |
| 259  | $^1\text{H}$ NMR (400 MHz, DMSO- $d_6$ ) $\delta$ 7.86 (d, $J = 8.0$ Hz, 2H), 7.79 (dd, $J = 8.0, 1.4$ Hz, 1H), 7.62 (d, $J = 8.0$ Hz, 2H), 7.49 (dd, $J = 8.0, 6.5$ Hz, 2H), 7.44-7.36 (m, 4H), 7.23 (dd, $J = 7.7, 1.4$ Hz, 1H), 7.20 (d, $J = 3.4$ Hz, 1H), 6.91 (d, $J = 3.4$ Hz, 1H), 4.24 (s, 2H), 4.03-3.85 (m, 3H), 2.37 (s, 3H).                                                                                                                                                                                                        | 428 |
| 259s | $^1\text{H}$ NMR (400 MHz, DMSO- $d_6$ ) $\delta$ 9.12 (s, 1H), 7.86 (d, $J = 8.0$ Hz, 2H), 7.79 (dd, $J = 8.0, 1.4$ Hz, 1H), 7.62 (d, $J = 8.0$ Hz, 2H), 7.49 (dd, $J = 8.0, 6.5$ Hz, 2H), 7.44-7.36 (m, 4H), 7.23 (dd, $J = 7.7, 1.4$ Hz, 1H), 7.20 (d, $J = 3.4$ Hz, 2H), 6.91 (d, $J =$                                                                                                                                                                                                                                                      | 428 |

|      |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |     |
|------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|
|      | 3.4 Hz, 1H), 4.24 (s, 2H), 4.03-3.85 (m, 3H), 2.37 (s, 3H).                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |     |
| 260  | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 7.88 (d, <i>J</i> = 8.0 Hz, 2H), 7.79 (dd, <i>J</i> = 7.8, 1.3 Hz, 1H), 7.64 (d, <i>J</i> = 8.0 Hz, 2H), 7.48 (t, <i>J</i> = 7.3 Hz, 2H), 7.43-7.36 (m, 4H), 7.25-7.22 (m, 1H), 7.20 (d, <i>J</i> = 3.4 Hz, 2H), 6.91 (d, <i>J</i> = 3.4 Hz, 1H), 4.19 (s, 2H), 3.12 (t, <i>J</i> = 7.4 Hz, 2H), 2.76 (t, <i>J</i> = 7.4 Hz, 2H), 2.37 (s, 3H).                                                                                                                                                             | 412 |
| 260s | <sup>1</sup> H NMR (400 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.95 (s, 1H), 7.88 (d, <i>J</i> = 8.0 Hz, 2H), 7.79 (dd, <i>J</i> = 7.8, 1.3 Hz, 1H), 7.64 (d, <i>J</i> = 8.0 Hz, 2H), 7.48 (t, <i>J</i> = 7.3 Hz, 2H), 7.43-7.36 (m, 4H), 7.25-7.22 (m, 1H), 7.20 (d, <i>J</i> = 3.4 Hz, 1H), 6.91 (d, <i>J</i> = 3.4 Hz, 1H), 4.19 (s, 2H), 3.12 (t, <i>J</i> = 7.4 Hz, 2H), 2.76 (t, <i>J</i> = 7.4 Hz, 2H), 2.37 (s, 3H).                                                                                                                                               | 412 |
| 261  | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 7.98 (s, 1H), 7.81 (dd, <i>J</i> = 18.3, 7.6 Hz, 2H), 7.56-7.42 (m, 4H), 7.37 (qd, <i>J</i> = 7.8, 5.4, 3.6 Hz, 4H), 7.28-7.11 (m, 3H), 6.91 (q, <i>J</i> = 3.9 Hz, 1H), 4.23 (s, 2H), 3.88 (s, 2H), 2.35 (s, 3H).                                                                                                                                                                                                                                                                                          | 398 |
| 261s | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 9.02 (s, 1H), 7.98 (s, 1H), 7.81 (dd, <i>J</i> = 18.5, 7.5 Hz, 2H), 7.56-7.42 (m, 4H), 7.37 (qd, <i>J</i> = 7.8, 5.4, 3.6 Hz, 4H), 7.28-7.11 (m, 3H), 6.91 (q, <i>J</i> = 3.9 Hz, 1H), 4.23 (s, 2H), 3.88 (s, 2H), 2.35 (s, 3H).                                                                                                                                                                                                                                                                            | 398 |
| 262  | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.01 (s, 1H), 7.81 (dd, <i>J</i> = 14.1, 7.5 Hz, 2H), 7.50 (s, 1H), 7.49-7.43 (m, 3H), 7.42 (d, <i>J</i> = 1.8 Hz, 1H), 7.38 (dd, <i>J</i> = 5.1, 2.7 Hz, 2H), 7.35 (s, 1H), 7.22 (d, <i>J</i> = 7.5 Hz, 1H), 7.12 (d, <i>J</i> = 3.6 Hz, 2H), 6.90 (d, <i>J</i> = 3.6 Hz, 1H), 4.27 (s, 2H), 3.95 (d, <i>J</i> = 4.5 Hz, 3H), 2.36 (s, 3H).                                                                                                                                                                | 428 |
| 262s | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.87 (s, 1H), 8.01 (s, 1H), 7.81 (dd, <i>J</i> = 14.1, 7.5 Hz, 2H), 7.50 (s, 1H), 7.49-7.43 (m, 3H), 7.42 (d, <i>J</i> = 1.8 Hz, 1H), 7.38 (dd, <i>J</i> = 5.1, 2.7 Hz, 2H), 7.35 (s, 1H), 7.22 (d, <i>J</i> = 7.5 Hz, 1H), 7.12 (d, <i>J</i> = 3.6 Hz, 2H), 6.90 (d, <i>J</i> = 3.6 Hz, 1H), 4.27 (s, 2H), 3.95 (d, <i>J</i> = 4.5 Hz, 3H), 2.36 (s, 3H).                                                                                                                                                  | 428 |
| 263  | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.04 (s, 1H), 7.87-7.77 (m, 2H), 7.49 (dd, <i>J</i> = 6.9, 4.5 Hz, 3H), 7.45 (s, 1H), 7.43-7.40 (m, 1H), 7.37 (d, <i>J</i> = 2.1 Hz, 2H), 7.35 (d, <i>J</i> = 1.5 Hz, 1H), 7.22 (dd, <i>J</i> = 7.8, 1.5 Hz, 1H), 7.14 (d, <i>J</i> = 3.6 Hz, 1H), 6.90 (d, <i>J</i> = 3.6 Hz, 1H), 4.22 (s, 2H), 3.13 (s, 2H), 2.75 (t, <i>J</i> = 7.5 Hz, 2H), 2.36 (s, 3H).                                                                                                                                              | 412 |
| 263s | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 9.02 (s, 1H), 8.04 (s, 1H), 7.87-7.77 (m, 2H), 7.49 (dd, <i>J</i> = 6.9, 4.5 Hz, 3H), 7.45 (s, 1H), 7.43-7.40 (m, 1H), 7.37 (d, <i>J</i> = 2.1 Hz, 2H), 7.35 (d, <i>J</i> = 1.5 Hz, 1H), 7.22 (dd, <i>J</i> = 7.8, 1.5 Hz, 1H), 7.14 (d, <i>J</i> = 3.6 Hz, 1H), 6.90 (d, <i>J</i> = 3.6 Hz, 1H), 4.22 (s, 2H), 3.13 (s, 2H), 2.75 (t, <i>J</i> = 7.5 Hz, 2H), 2.36 (s, 3H).                                                                                                                                | 412 |
| 264  | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.12 (s, 1H), 7.87 (d, <i>J</i> = 6.3 Hz, 1H), 7.80 (d, <i>J</i> = 7.8 Hz, 1H), 7.53 (d, <i>J</i> = 4.8 Hz, 2H), 7.46 (d, <i>J</i> = 7.2 Hz, 2H), 7.39 (d, <i>J</i> = 12.3 Hz, 3H), 7.35 (s, 1H), 7.22 (d, <i>J</i> = 7.5 Hz, 1H), 7.15 (d, <i>J</i> = 3.3 Hz, 1H), 6.90 (d, <i>J</i> = 3.3 Hz, 1H), 4.36 (s, 2H), 3.55 (s, 1H), 3.39 (d, <i>J</i> = 7.2 Hz, 2H), 2.98 (d, <i>J</i> = 10.2 Hz, 3H), 2.86 (s, 1H), 2.36 (s, 3H), 2.03 (d, <i>J</i> = 13.8 Hz, 1H), 1.86 (s, 2H), 1.45 (s, 1H).               | 452 |
| 264s | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.97 (s, 1H), 8.12 (s, 1H), 7.87 (d, <i>J</i> = 6.3 Hz, 1H), 7.80 (d, <i>J</i> = 7.8 Hz, 1H), 7.53 (d, <i>J</i> = 4.8 Hz, 2H), 7.46 (d, <i>J</i> = 7.2 Hz, 2H), 7.39 (d, <i>J</i> = 12.3 Hz, 3H), 7.35 (s, 1H), 7.22 (d, <i>J</i> = 7.5 Hz, 1H), 7.15 (d, <i>J</i> = 3.3 Hz, 1H), 6.90 (d, <i>J</i> = 3.3 Hz, 1H), 4.36 (s, 2H), 3.55 (s, 1H), 3.39 (d, <i>J</i> = 7.2 Hz, 2H), 2.98 (d, <i>J</i> = 10.2 Hz, 3H), 2.86 (s, 1H), 2.36 (s, 3H), 2.03 (d, <i>J</i> = 13.8 Hz, 1H), 1.86 (s, 2H), 1.45 (s, 1H). | 452 |
| 265  | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 8.06 (d, <i>J</i> = 1.8 Hz, 1H), 7.84 (ddd, <i>J</i> = 11.2, 7.5, 1.5 Hz, 2H), 7.54-7.45 (m, 4H), 7.45-7.35 (m, 4H), 7.24 (dd, <i>J</i> = 7.5, 1.5 Hz, 1H), 7.16 (d, <i>J</i> = 3.6 Hz, 1H), 6.92 (d, <i>J</i> = 3.6 Hz, 1H), 4.24 (t, <i>J</i> = 5.4 Hz, 2H), 3.71 (t, <i>J</i> = 5.4 Hz, 2H), 3.01 (d, <i>J</i> = 6.6 Hz, 2H), 2.37 (s, 3H).                                                                                                                                                              | 384 |
| 265s | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 9.23 (s, 1H), 8.06 (d, <i>J</i> = 1.8 Hz, 1H), 7.84 (ddd, <i>J</i> = 11.2, 7.5, 1.5 Hz, 2H), 7.54-7.45 (m, 4H), 7.45-7.35 (m, 4H), 7.24 (dd, <i>J</i> = 7.5, 1.5 Hz, 1H), 7.16 (d, <i>J</i> = 3.6 Hz, 1H), 6.92 (d, <i>J</i> = 3.6 Hz, 1H), 4.24 (t, <i>J</i> = 5.4 Hz, 2H), 3.71 (t, <i>J</i> = 5.4 Hz, 2H), 3.01 (d, <i>J</i> = 6.6 Hz, 2H), 2.37 (s, 3H).                                                                                                                                                | 384 |
| 266  | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 7.99 (d, <i>J</i> = 1.8 Hz, 1H), 7.90-7.76 (m, 2H), 7.55-7.48 (m, 2H), 7.47-7.41 (m, 3H), 7.40-7.35 (m, 3H), 7.24 (dd, <i>J</i> = 7.5, 1.5 Hz, 1H), 7.14 (d, <i>J</i> = 3.6 Hz, 1H), 6.92 (d, <i>J</i> = 3.6 Hz, 1H), 4.33-4.18 (m, 2H), 4.09 (d, <i>J</i> = 6.3 Hz, 1H), 3.95 (s, 3H), 3.53 (d, <i>J</i> = 5.7 Hz, 1H), 2.37 (s, 3H), 1.21 (d, <i>J</i> = 6.3 Hz, 3H).                                                                                                                                     | 456 |
| 266s | <sup>1</sup> H NMR (300 MHz, DMSO- <i>d</i> <sub>6</sub> ) δ 9.02 (s, 1H), 7.99 (d, <i>J</i> = 1.8 Hz, 1H), 7.90-7.76 (m, 2H), 7.55-7.48 (m, 2H), 7.47-7.41 (m, 3H), 7.40-7.35 (m, 3H), 7.24 (dd, <i>J</i> = 7.5, 1.5 Hz, 1H), 7.14 (d, <i>J</i> = 3.6 Hz, 1H), 6.92 (d, <i>J</i> = 3.6 Hz, 1H), 4.33-4.18 (m, 2H), 4.09 (d, <i>J</i> = 6.3 Hz, 1H), 3.53 (d, <i>J</i> = 5.7 Hz, 1H), 2.37 (s, 3H), 1.21 (d, <i>J</i> = 6.3 Hz, 3H).                                                                                                                                     | 442 |

#### 实施例 9：药理活性评价

##### 1、本发明化合物对 PD-1/PD-L1 蛋白-蛋白相互作用的抑制活性

##### 1.1 实验目的

使用 PD-1/PD-L1 binding assay kit 试剂盒(BPS Bioscience) 检测本发明化合物对 PD-1/PD-L1 蛋白-蛋白相互作用的抑制活性。

1.2 主要实验材料

PD-1/PD-L1 binding assay kit 试剂盒购自 BPS Bioscience, 其中含有 PD-1、PD-L1、Anti-tag1-Eu、Anti-tag2-XL665、Dilute Buffer 和 Detection Buffer 等实验所需的试剂; 384 孔微孔板购自 Perkin Elmer 公司; 阳性药 (BMS-202) 购自 Selleck。

1.3 仪器

离心机 (Eppendorf, 型号: 5430); 酶标仪 (Perkin Elmer, 型号: EnVision)

1.4 实验方法

- (1) 配制 1× Assay buffer。
- (2) 化合物加样: 用 Echo550 仪器按化合物不同浓度梯度转移 200 nL 到 384 反应板中。
- (3) 配制 PD-L1-Biotin 工作液于 1× Assay buffer 中。
- (4)在化合物孔和阳性对照孔分别加 5 μL 的 PD-L1-Biotin 工作液; 在阴性对照孔中加 5 μL 的 Assaybuffer。
- (5) 1000 rpm 离心 30 秒, 室温孵育 15 分钟。
- (6) 配制 PD-1-Eu 和 Dye labeled acceptor 混合液于 1× Assay buffer 中。
- (7) 加入 15 μL PD-1-Eu 和 Dye labeled acceptor 混合液。
- (8) 1000 rpm 离心 30 秒, 室温孵育 90 分钟。
- (9) EnVision 读取 665nm/615nm ratio。根据荧光比值计算化合物对蛋白结合的抑制率。

1.5 数据公式

$$\% \text{ Inhibition} = (1 - \left(\frac{\text{Ratio}_{\text{sample}} - \text{Ratio}_{\text{min}}}{\text{Ratio}_{\text{max}} - \text{Ratio}_{\text{min}}}\right)) \times 100$$

其中: Ratio<sub>sample</sub> 是样品孔的比值; Ratio<sub>min</sub>: 阴性对照孔比值均值; Ratio<sub>max</sub>: 阳性对照孔比值均值, 用 Graphpad 计算化合物 IC<sub>50</sub> 值。

1.6 实验结果

本发明化合物对 PD-1/PD-L 蛋白-蛋白相互作用的抑制活性如表 1 所示。实验结果表明, 本发明的化合物对 PD-1/PD-L1 蛋白-蛋白相互作用具有显著的抑制活性。其中, A 表示 IC<sub>50</sub>= 1 nM-100 nM; B 表示 IC<sub>50</sub>= 100.01 nM-500 nM; C 表示 IC<sub>50</sub>= 500.01 nM-20μM。

表 1. 本发明化合物对 PD-1/PD-L1 相互作用的抑制活性

| 化合物 | IC <sub>50</sub> (nM) | 化合物 | IC <sub>50</sub> (nM) | 化合物  | IC <sub>50</sub> (nM) | 化合物  | IC <sub>50</sub> (nM) |
|-----|-----------------------|-----|-----------------------|------|-----------------------|------|-----------------------|
| 1   | A                     | 64  | A                     | 127s | B                     | 196s | B                     |
| 1s  | 12.4                  | 64s | 16.6                  | 128s | 83.7                  | 197s | B                     |
| 2   | A                     | 65s | B                     | 129s | 41.2                  | 198s | B                     |
| 2s  | 25.2                  | 66s | B                     | 130s | 51.3                  | 199  | A                     |
| 3s  | A                     | 67s | 21.5                  | 132s | A                     | 199s | 12.1                  |
| 4s  | A                     | 68s | A                     | 133s | A                     | 200s | A                     |
| 5s  | A                     | 69s | A                     | 134s | A                     | 201s | A                     |
| 6s  | 87.1                  | 70s | A                     | 135s | A                     | 202s | A                     |
| 7s  | A                     | 71s | 36.6                  | 136s | A                     | 203s | B                     |
| 8   | A                     | 72  | A                     | 137  | A                     | 204s | B                     |
| 8s  | 22.4                  | 72s | 6.5                   | 137s | 37.3                  | 205s | B                     |
| 9s  | A                     | 73  | B                     | 138s | A                     | 206s | B                     |
| 10s | A                     | 73s | 48.5                  | 139s | A                     | 207s | B                     |
| 11s | 20.9                  | 74s | A                     | 140s | A                     | 208s | B                     |
| 12s | A                     | 67s | 21.5                  | 141s | B                     | 209s | B                     |
| 13  | A                     | 68s | A                     | 142s | A                     | 210s | B                     |
| 13s | 9.8                   | 69s | A                     | 143s | A                     | 213  | A                     |
| 14s | A                     | 70s | A                     | 144s | A                     | 213s | A                     |
| 15s | 35.8                  | 71s | 36.6                  | 145s | A                     | 214s | A                     |
| 16s | A                     | 72  | A                     | 146s | A                     | 215s | A                     |
| 17s | 71.3                  | 72s | 6.5                   | 147s | A                     | 216s | A                     |

|     |      |      |       |      |       |      |      |
|-----|------|------|-------|------|-------|------|------|
| 18s | A    | 73   | B     | 148s | A     | 217s | 27.9 |
| 19s | A    | 75   | A     | 149s | 27.9  | 218s | A    |
| 20  | A    | 75s  | 18.9  | 150s | A     | 219  | A    |
| 20s | 12.4 | 76   | A     | 151  | A     | 219s | 19.4 |
| 21s | A    | 76s  | 12.6  | 151s | 16.3  | 220s | B    |
| 22s | B    | 77s  | 26.4  | 152s | A     | 221s | B    |
| 23s | B    | 78s  | A     | 153s | B     | 222s | 12.9 |
| 24s | A    | 79s  | 26.4  | 154s | B     | 223s | B    |
| 25s | 31.9 | 80s  | 35.9  | 155s | B     | 224s | B    |
| 26s | A    | 81s  | 41.2  | 156s | B     | 225s | B    |
| 27s | B    | 82s  | 39.5  | 157s | A     | 226s | B    |
| 28s | A    | 83s  | 41.3  | 158s | A     | 227s | A    |
| 29s | 22.1 | 84s  | 28.7  | 159s | A     | 228s | B    |
| 30s | A    | 85   | A     | 160s | A     | 229  | A    |
| 31s | 19.9 | 85s  | 28.8  | 161s | 45.5  | 229s | 18.0 |
| 32s | A    | 86s  | 62.1  | 162s | A     | 230s | 33.4 |
| 33s | A    | 87s  | 35.9  | 163s | 25.0  | 231s | A    |
| 34s | 34.7 | 88s  | A     | 164s | 18.5  | 232s | B    |
| 35  | A    | 89s  | A     | 165s | 50.1  | 233s | B    |
| 35s | 11.3 | 90s  | A     | 166s | 25.4  | 234s | B    |
| 36s | 74.5 | 91s  | A     | 167  | A     | 235  | A    |
| 37  | A    | 92s  | A     | 167s | 15.9  | 235s | 5.7  |
| 37  | 6.2  | 93s  | 42.6  | 168s | A     | 236s | A    |
| 38s | A    | 94s  | A     | 169s | A     | 237s | A    |
| 39s | 28.9 | 95s  | A     | 170s | A     | 238s | A    |
| 40s | 28.7 | 96s  | A     | 171s | A     | 239s | B    |
| 41s | 28.3 | 97s  | 58.2  | 172s | B     | 240s | A    |
| 42  | A    | 98s  | 121.4 | 173s | A     | 241s | A    |
| 42s | 12.4 | 99s  | 46.4  | 174s | B     | 242s | A    |
| 43s | A    | 100s | 81.7  | 175s | 84.1  | 243s | A    |
| 44s | A    | 101s | 50.5  | 176s | 164.1 | 244s | A    |
| 45s | A    | 102s | 35.3  | 177s | 32.9  | 245s | A    |
| 46s | A    | 103s | 42.9  | 178s | 103.1 | 246s | A    |
| 47s | B    | 104s | 105.1 | 179  | A     | 247s | B    |
| 48  | A    | 105s | 69.2  | 179s | 14.7  | 248s | B    |
| 48s | 10.8 | 106s | 42.5  | 180  | A     | 249s | A    |
| 49s | A    | 107s | 51.2  | 181  | A     | 250  | A    |
| 50  | A    | 108s | 92.5  | 181s | B     | 250s | 16.2 |
| 50s | 7.7  | 109s | 43.3  | 182s | A     | 251s | A    |
| 51s | A    | 110s | 82.8  | 183s | 56.9  | 252s | B    |
| 52s | A    | 111s | 75.4  | 184  | A     | 253s | A    |
| 53  | A    | 112s | 64.2  | 184s | 28.7  | 254s | B    |
| 53s | 4.7  | 113s | 57.4  | 185s | B     | 255s | A    |
| 54s | A    | 114s | A     | 186s | 14.0  | 256s | 21.0 |
| 55s | A    | 115s | 140.6 | 187s | B     | 257s | C    |
| 56  | A    | 116s | 28.1  | 188s | C     | 258s | B    |
| 56s | 7.2  | 117s | 35.7  | 189s | B     | 259s | B    |

|     |      |      |       |      |      |           |      |
|-----|------|------|-------|------|------|-----------|------|
| 57s | A    | 118s | 111.1 | 190s | C    | 260s      | B    |
| 58  | A    | 119s | 120.1 | 191  | A    | 261s      | 35.9 |
| 58s | 27.9 | 120s | 20.1  | 191s | 25.4 | 262s      | A    |
| 59s | B    | 121s | 134.1 | 192  | A    | 263s      | B    |
| 60  | A    | 122s | B     | 192s | A    | 264s      | B    |
| 60s | 15.7 | 123s | 148.2 | 193s | A    | 265s      | B    |
| 61s | B    | 124s | 35.5  | 194  | A    | 266s      | A    |
| 62s | 21.1 | 125s | A     | 194s | 23.4 | BMS-202   | 50.3 |
| 63s | A    | 126s | A     | 195s | B    | BMS-1018* | 32.7 |

\*对照组：BMS-1018 是 WO 2015160641 A2 专利中的第 1018 号化合物。

2、本发明化合物对细胞的毒性实验

为验证本发明化合物是否存在明显的细胞毒性，采用 MTT 法检测本发明化合物对 Lewis 肺癌细胞活力的影响。

2.1 实验方法

于 96 孔板中每孔加入 20  $\mu$ L 4 mg/mL MTT 溶液，放入细胞培养箱孵育 4 小时，将 96 孔板进行离心，小心吸去孔内液体，每孔加入 200  $\mu$ L 二甲基亚砜，放置在摇床上 300 r 振荡 10 min，使紫色结晶物质充分溶解。最后在酶标仪 570 nm 处检测吸光值。根据吸光度用 Bliss 法计算抑制率。

$$IR\% = \frac{(OD_{\text{对照}} - OD_{\text{样品}})}{(OD_{\text{对照}} - OD_{\text{空白}})} \times 100\%$$

2.2 实验结果

实验结果如图 1 所示。结果表明，与模型组相比，本发明化合物 77 在各种检测浓度下对 Lewis 肺癌细胞的活力均没有明显的影响，说明本发明化合物无明显的细胞毒性。

3、本发明化合物对细胞因子 INF- $\gamma$  释放的影响

细胞因子是一类具有效应及调节双重作用的独特分子，在淋巴细胞应答中具有重要的免疫调节作用。活化的人外周血单个核细胞（PBMC）可以释放 IFN- $\gamma$ 、IL-2 和 TNF- $\alpha$  等细胞因子，而当 PBMC 膜上表达的 PD-1 与其配体 PD-L1 结合后将会抑制细胞因子的释放。本实验的目的是检测本发明化合物是否能逆转 PD-1/PD-L1 抑制 PBMC 分泌 INF- $\gamma$  的能力。

3.1 实验方法

使用人淋巴细胞分离液提取人外周血单个核细胞（PBMC），接种到 24 孔板，加入终浓度 1  $\mu$ g/mL 的 anti-CD3/anti-CD28，终浓度为 2  $\mu$ g/mL 配体蛋白和不同剂量的化合物，48 h 后离心取上清 100  $\mu$ L，使用达科公司的 INF- $\gamma$  酶联免疫吸附试剂盒检测上清中 INF- $\gamma$  的表达量。

3.2 实验结果

实验结果如图 2 所示。结果表明，与模型组相比，当加入 anti-CD3/anti-CD28 时能明显促进 INF- $\gamma$  的释放，而加入 PD-L1 后则显著降低 INF- $\gamma$  的水平，表明 PD-1/PD-L1 明显抑制 INF- $\gamma$  的释放。当加入不同浓度的本发明化合物 77 后能够显著提高 INF- $\gamma$  的水平，并且呈现剂量依赖性，说明本发明化合物能够阻断 PD-1/PD-L1 对 PBMC 的抑制作用，从而恢复 T 细胞的活性，进而促进 INF- $\gamma$  的分泌。

4、本发明化合物的药代动力学实验

良好的药物代谢动力学性质是评价一个候选药物成药性的必不可少的参数。为了检验本发明化合物是否具有良好的成药性，选取本发明化合物 77 开展大鼠体内药代动力学实验，BMS-1018 为阳性药。

4.1 实验方法

实验所选动物为 SD 大鼠，体重 200~250 克。化合物 77 和 BMS-1018 的给药剂量分别为口服 10 mg/kg 和静脉注射 2 mg/kg，口服组为 3 只大鼠，静脉注射组为 5 只大鼠。给药后采集 9 个时间点的血浆样品，计算药代动力学参数。

实验当天将 ICR 雄性小鼠按体重随机分为组，每组 3 只。给药前 1 天禁食不禁水 12~14 h，给药后 4 h 给食。每只动物每次通过眼眶取 0.030 mL 血液，EDTAK2 抗凝，采集时间点为：（1）I.G.组：0.0833, 0.25, 0.5, 1, 2, 4, 6, 8, 24 h。（2）I.V.组：给予受试物后 0.25, 0.5, 1, 2, 4, 6, 8, 24 h。血液样本采集后置于冰上，并于 30 分钟内离心分离血浆，分析前存放于 -80  $^{\circ}$ C。

取样品 10  $\mu$ L（从冰箱 -80  $^{\circ}$ C 中取出样品，室温自然溶化后涡旋 30 秒）至 1.5 mL 离心管中，加入 100  $\mu$ L 内标溶液（5.0 ng/mL 维拉帕米，30.0 ng/mL 丁螺环酮和 60.0 ng/mL 地塞米松乙腈溶液），涡旋 60 秒后离心 3 分钟（12000 rpm）；取上清液 75  $\mu$ L 移至装有等体积水的 96 孔进样板上，振荡混匀后 LC-MS/MS 进样分析，进样量为 10  $\mu$ L。

数据采集及控制系统软件为 Analyst1.5.1 软件。图谱样品峰积分方式为自动积分；采用样品峰面积和内标峰面积的比值作为指标，和样品的浓度进行回归。回归方式：线性回归，权重系数为 1/X<sup>2</sup>。药代动力学参数用 WinNonlin Professional v6.3 (Pharsight, USA)用非房室模型分析处理。 $C_{\max}$  为实测的最大血药浓度，血药浓度-时间曲线下面积  $AUC_{(0 \rightarrow t)}$ 由梯形法计算得到， $T_{\max}$  为给药后血药浓度达峰时间。

4.2 实验结果

实验结果如表 2 所示。从表中可以看出，化合物 77 具有良好的药代动力学参数，特别是其具有较长半衰期，并且口服生物利用度达到 23.94%。值得一提的是，BMS-1018 口服给药未能检测到血药浓度，而且其静脉注射的半衰期仅为 0.53 h。这些实验结果表明本发明化合物具有良好的药代动力学性质。

表 2. 大鼠体内药代动力学实验结果

| Administration          | BMS-1018(i.v.) | 77(i.g.)        | 77(i.v.)       |
|-------------------------|----------------|-----------------|----------------|
|                         | (2 mg/kg)      | (10 mg/kg)      | (2 mg/kg)      |
| $T_{1/2}$ (h)           | 0.53 ± 0.05    | 4.36 ± 1.47     | 3.11 ± 0.55    |
| $T_{\max}$ (h)          | -              | 2.19 ± 1.16     | 0.03 ± 0.00    |
| $C_{\max}$ (ng/mL)      | -              | 94.18 ± 35.39   | 145.08 ± 44.20 |
| $AUC_{0-24h}$ (ng•h/mL) | 253.32 ± 13.12 | 520.80 ± 162.15 | 340.60 ± 16.50 |
| CL (mL/min/kg)          | 4312 ± 413     | 12554 ± 6658    | 3155 ± 301     |
| Vss (L/kg)              | 7.11 ± 1.06    | 102.61 ± 4.84   | 15.09 ± 2.30   |
| MRT (h)                 | 1.28 ± 0.21    | 4.45 ± 0.42     | 3.40 ± 0.40    |
| F (%)                   | -              | 23.94 ± 6.60    | -              |

5、本发明化合物的体内药效学评价

增殖细胞核抗原（PCNA）是真核细胞 DNA 合成所必需的一种核蛋白，检测 PCNA 可以客观评价肿瘤细胞的增殖状态。为此，在开展体内药效学评价过程中，利用免疫组化和 TUNEL 分析检测肿瘤组织中的 T 淋巴细胞的浸润以及 IFN- $\gamma$  和 PCNA 水平。以 BMS-1018 作阳性对照组。

5.1 实验方法

小鼠的培养：选择 7~8 周的雌鼠，在 SPF 级动物饲养室饲养一周，每只小鼠体重大约在 18~20 g。

肿瘤细胞的处理：采集处于对数生长期的肿瘤细胞，180 g 离心 5 min（4℃），使用预冷的 PBS 洗 2 次，吹打均匀，终细胞浓度为  $1 \times 10^7$ /mL，冰浴备用。

肿瘤细胞的移植：将 Lewis 肺癌细胞悬浮液接种至 BALB/c 雌鼠右侧腋窝皮下，接种的肿瘤细胞数为  $1 \times 10^6$ /只。每两天使用游标卡尺测量小鼠肿瘤大小一次，称小鼠体重一次。当肿瘤体积均值达到 40 mm<sup>3</sup> 左右时，开始给药。

实验分组和给药方法：移植 Lewis 肺癌细胞的 BALB/c 雌鼠分为 4 组，每组 6 只。模型组（溶剂：PBS + 2%的吐温 20 + 2% DMSO，灌胃给药，每天一次），阳性对照组（BMS-1018，灌胃给药，每天一次，剂量：15 mg/kg），药物处理组 1（化合物 77，灌胃给药，每天一次，剂量：5 mg/kg），药物处理组 2（化合物 77，灌胃给药，每天一次，剂量：15 mg/kg）。

当肿瘤体积达到一定大小后，结束动物实验。称量小鼠体重，对其进行眼球取血，并对小鼠实施安乐死，剥取肿瘤组织，对肿瘤组织进行称重并拍照。同时，将部分组织置于 10%中性固定液中，送样进行石蜡包埋组织、制作石蜡组织切片，并开展 H&E 染色、TUNEL 和免疫组化分析。实验操作参考检测试剂盒说明书。

5.2 实验结果

实验结果如图 3 所示。结果表明，与模型组相比，本发明化合物 77 在 5 mg/kg 和 15 mg/kg 给药剂量下都能显著抑制 Lewis 肺癌小鼠移植瘤的生长，呈现剂量依赖性，并且不影响小鼠的体重。此外，在相同给药剂量下，化合物 77 对移植瘤的抑制活性明显优于对照组 BMS-1018。

免疫组化和 TUNEL 实验结果表明，与模型组相比，化合物 77 在 5 mg/kg 和 15 mg/kg 剂量下都能够显著促进肿瘤组织中 T 淋巴细胞的浸润，并且提高 IFN- $\gamma$  的水平，降低 PCNA 蛋白的表达，而且在 5 mg/kg 剂量下，化合物 77 逆转 PD-1/PD-L1 介导的免疫抑制作用强于 BMS-1018 对照组。

6、本发明化合物对肿瘤微环境 T 淋巴细胞浸润的影响

T 淋巴细胞是人体免疫系统的核心执行者，在肿瘤免疫应答中起重要作用。肿瘤浸润淋巴细胞（TIL）是指那些离开血流进入到肿瘤中的白细胞。当肿瘤微环境中存在大量的肿瘤浸润淋巴细胞时，表明机体启动了对抗肿瘤的免疫反应。PD-1/PD-L1 信号通路的激活会抑制抗肿瘤免疫微环境，导致淋巴细胞的浸润减少。本实验的目的分析本发明化合物对肿瘤微环境中 T 淋巴细胞浸润的影响。

6.1 实验方法

取部分实验 4 中剥取的肿瘤组织,剪碎转入 15 mL 离心管中,加入胶原酶 IV(0.5 mg/mL)、DNA 酶 I(0.5 mg/mL), 37 °C 消化 30 min, 过滤掉剩余组织碎片, 离心重悬细胞后使用不同通道的 CD45、CD3、CD4、CD8 流式抗体避光染色 30 min, 流式细胞仪检测。

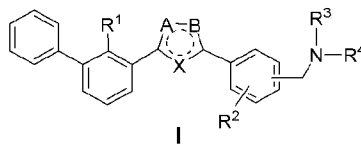
## 6.2 实验结果

实验结果如图 4 所示。结果表明,与模型组相比,化合物 77 在 5 mg/kg 和 15 mg/kg 剂量下能够显著促进 CD45<sup>+</sup> 白细胞、CD45<sup>+</sup> CD3<sup>+</sup> T 淋巴细胞、CD8<sup>+</sup> CD45<sup>+</sup> CD3<sup>+</sup> 细胞毒性 T 细胞的浸润,并且呈现剂量依赖性,而对 CD4<sup>+</sup> CD45<sup>+</sup> CD3<sup>+</sup> 调节性 T 淋巴细胞的影响很弱。此外,在相同剂量下,化合物 77 促进淋巴细胞浸润的能力强于 BMS-1018,特别是对 CD45<sup>+</sup> CD3<sup>+</sup> CD8<sup>+</sup> 细胞毒性 T 淋巴细胞的浸润增加更为突出。这些实验说明本发明的化合物能够有效地逆转 PD-1/PD-L1 介导的免疫抑制作用,重塑抗肿瘤免疫微环境。

本发明的其他化合物在多种肿瘤类型如 CT26、EMT6、B16F1、PAN02、LLC 等小鼠移植瘤模型中表现出显著的抗肿瘤作用,而且这些化合物能够促进淋巴细胞对肿瘤微环境的浸润,提高肿瘤组织中 IFN- $\gamma$  的分泌,降低 PCNA 蛋白的表达。说明本发明化合物能够阻断 PD-1/PD-L1 介导的免疫抑制作用,激活抗肿瘤免疫应答。

## 权 利 要 求 书

1、一种五元杂环类化合物，其特征在于，具有式 I 的结构，还包含其立体异构体、内消旋体、外消旋体、前药、结晶、药学上可接受的盐或它们的混合物，



其中：

(1) 当 X 为 O、A 为 N 时，B 为 C；当 X 为 O、A 为 C 时，B 为 N 或 C；

(2) 当 X 为 S 时，A、B 为 N 或 C；

(3) 当 X 为 NH、A 为 N 时，B 为 N；

(4) 当 X 为 N、A 为 N 时，B 为 O；当 X 为 N、A 为 C 时，B 为 O 或 NH；当 X 为 N，A 为 O 时，B 为 C 或 N；

R<sup>1</sup> 选自甲基、氰基、羟基或卤素；

R<sup>2</sup> 选自氢、卤素、硝基、氰基、羟基、C<sub>1</sub>-C<sub>4</sub> 烷基、C<sub>1</sub>-C<sub>4</sub> 烷氧基、C<sub>1</sub>-C<sub>4</sub> 卤代烷基或 -O(CH<sub>2</sub>)<sub>n</sub>Ar；其中，n 选自 0-4 的整数；Ar 选自芳基或芳杂环；所述的芳杂环包含一个或多个选自 O、S 或 N 杂原子；所述的 C<sub>1</sub>-C<sub>4</sub> 烷基、芳基或芳杂环基被一个或多个 W 基团取代；

W 选自氢、卤素、氰基、羟基、巯基、羰基、C<sub>1</sub>-C<sub>6</sub> 烷基、C<sub>1</sub>-C<sub>6</sub> 烷氧基、C<sub>1</sub>-C<sub>6</sub> 烷氨基或 C<sub>1</sub>-C<sub>6</sub> 卤代烷基；

R<sup>3</sup>、R<sup>4</sup> 各自独立地选自氢、C<sub>1</sub>-C<sub>8</sub> 烷基、C<sub>1</sub>-C<sub>8</sub> 烷氧基、C<sub>1</sub>-C<sub>8</sub> 烷氨基、C<sub>3</sub>-C<sub>8</sub> 环烷基、5-7 元杂环基或 R<sup>3</sup> 和 R<sup>4</sup> 与它们连接的氮原子一起形成 5-7 元杂环基；所述的杂环基可任选地包含一个或多个选自 O、S 或 N 杂原子；所述的 C<sub>1</sub>-C<sub>8</sub> 烷基、C<sub>1</sub>-C<sub>8</sub> 烷氧基、C<sub>1</sub>-C<sub>8</sub> 烷氨基、C<sub>3</sub>-C<sub>8</sub> 环烷基或 5-7 元杂环基被一个或多个 Y 基团取代；

Y 选自氢、卤素、羟基、巯基、甲硫基、羰基、羧基、氨基、胍基、咪唑基、四氢吡咯基、吗啉基、N-甲基哌嗪基、C<sub>1</sub>-C<sub>4</sub> 烷基、-CO<sub>2</sub>R<sup>5</sup>、-NHCOR<sup>5</sup>、-NR<sup>6</sup>R<sup>7</sup> 或 -CONR<sup>6</sup>R<sup>7</sup>；所述的 C<sub>1</sub>-C<sub>4</sub> 烷基被一个或多个羟基或卤素取代；

R<sup>5</sup> 选自 C<sub>1</sub>-C<sub>8</sub> 烷基；

R<sup>6</sup>、R<sup>7</sup> 各自独立地选自氢、C<sub>1</sub>-C<sub>8</sub> 烷基、C<sub>1</sub>-C<sub>8</sub> 烷氧基、C<sub>3</sub>-C<sub>8</sub> 环烷基或 R<sup>8</sup> 和 R<sup>9</sup> 与它们连接的氮原子一起形成 5-7 元杂环基；所述的 C<sub>1</sub>-C<sub>8</sub> 烷基、C<sub>1</sub>-C<sub>8</sub> 烷氧基、C<sub>3</sub>-C<sub>8</sub> 环烷基或 5-7 元杂环基被一个或多个 Z 基团取代；

Z 选自氢、卤素、羟基、巯基、羰基、氨基或乙酰胺基。

2、根据权利要求 1 所述的五元杂环类化合物，其特征在于，所述结构中：

R<sup>1</sup> 选自甲基或卤素；

R<sup>2</sup> 选自氢、硝基或卤素；

R<sup>3</sup>、R<sup>4</sup> 各自独立地选自氢、C<sub>1</sub>-C<sub>5</sub> 烷基或者 R<sup>3</sup> 和 R<sup>4</sup> 与它们连接的氮原子一起形成 5-6 元含 N 杂环基；所述的 C<sub>1</sub>-C<sub>5</sub> 烷基或 5-6 元杂环基被一个或多个 Y 基团取代；

Y 选自氢、羟基、羰基、羧基、胍基、C<sub>1</sub>-C<sub>4</sub> 烷基、-CO<sub>2</sub>R<sup>5</sup>、-NR<sup>6</sup>R<sup>7</sup> 或 -CONR<sup>6</sup>R<sup>7</sup>；C<sub>1</sub>-C<sub>4</sub> 烷基被一个或多个氢或羟基取代；

R<sup>5</sup> 选自 C<sub>1</sub>-C<sub>4</sub> 烷基；

R<sup>6</sup>、R<sup>7</sup> 各自独立地选自氢或 C<sub>1</sub>-C<sub>4</sub> 烷基。

3、根据权利要求 1 所述的五元杂环类化合物，其特征在于，所述结构中：

R<sup>1</sup> 选自甲基或氯；

R<sup>2</sup> 选自氢、硝基、氟、氯或溴；

R<sup>3</sup>、R<sup>4</sup> 各自独立地选自氢、C<sub>1</sub>-C<sub>5</sub> 烷基或者 R<sup>3</sup> 和 R<sup>4</sup> 与它们连接的氮原子一起形成 5-6 元含一个 N 原子的杂环基；所述的 C<sub>1</sub>-C<sub>5</sub> 烷基或 5-6 元杂环基被一个或多个 Y 基团取代；

Y 选自氢、羟基、羰基、羧基、胍基、C<sub>1</sub>-C<sub>4</sub> 烷基、-CO<sub>2</sub>CH<sub>3</sub>、氨基或 -CONH<sub>2</sub>；C<sub>1</sub>-C<sub>4</sub> 烷基被一个或多个氢或羟基取代。

4、根据权利要求 1 所述的五元杂环类化合物，其特征在于，选自以下任一化合物：

(3-(5-(2-甲基-[1,1'-联苯]-3-基)-1,3,4-噻二唑-2-基)苄基)甘氨酸甲酯 (1m)，

(3-(5-(2-甲基-[1,1'-联苯]-3-基)-1,3,4-噻二唑-2-基)苄基)甘氨酸 (1) 及其盐酸盐 (1s)，

(3-(5-(2-甲基-[1,1'-联苯]-3-基)-1,3,4-噻二唑-2-基)苄基)肌氨酸 (2) 及其盐酸盐 (2s)，

(3-(5-(2-甲基-[1,1'-联苯]-3-基)-1,3,4-噻二唑-2-基)苄基)氨基乙醇 (3) 及其盐酸盐 (3s)，

(3-(5-(2-甲基-[1,1'-联苯]-3-基)-1,3,4-噻二唑-2-基)苄基)甘氨酸酰胺 (4) 及其盐酸盐 (4s)，

(3-(5-(2-甲基-[1,1'-联苯]-3-基)-1,3,4-噻二唑-2-基)苄基)-β-丙氨酸 (5) 及其盐酸盐 (5s)，

N-(2-((3-(5-(2-甲基-[1,1'-联苯]-3-基)-1,3,4-噻二唑-2-基)苄基)氨基)乙基)乙酰胺 (6) 及其盐酸盐 (6s),  
(3-(5-(2-甲基-[1,1'-联苯]-3-基)-1,3,4-噻二唑-2-基)苄基)-L-精氨酸 (7) 及其盐酸盐 (7s),  
(3-(5-(2-甲基-[1,1'-联苯]-3-基)-1,3,4-噻二唑-2-基)苄基)-L-丙氨酸 (8) 及其盐酸盐 (8s),  
(3-(5-(2-甲基-[1,1'-联苯]-3-基)-1,3,4-噻二唑-2-基)苄基)氨基丙烷-1,3-二醇 (9) 及其盐酸盐 (9s),  
(3-(5-(2-甲基-[1,1'-联苯]-3-基)-1,3,4-噻二唑-2-基)苄基)-L-丝氨酸 (10) 及其盐酸盐 (10s),  
(3-(5-(2-甲基-[1,1'-联苯]-3-基)-1,3,4-噻二唑-2-基)苄基)-L-丝氨酸 (11) 及其盐酸盐 (11s),  
(3-(5-(2-甲基-[1,1'-联苯]-3-基)-1,3,4-噻二唑-2-基)苄基)-L-苏氨酸 (12) 及其盐酸盐 (12s),  
(3-(5-(2-甲基-[1,1'-联苯]-3-基)-1,3,4-噻二唑-2-基)苄基)-L-苏氨酸 (13) 及其盐酸盐 (13s),  
2-甲基-2-((3-(5-(2-甲基-[1,1'-联苯]-3-基)-1,3,4-噻二唑-2-基)苄基)氨基)丙烷-1,3-二醇 (14) 及其盐酸盐 (14s),  
2-(羟甲基)-2-((3-(5-(2-甲基-[1,1'-联苯]-3-基)-1,3,4-噻二唑-2-基)苄基)氨基)丙烷-1,3-二醇 (15) 及其盐酸盐 (15s),  
(3-(5-(2-甲基-[1,1'-联苯]-3-基)-1,3,4-噻二唑-2-基)苄基)-L-异亮氨酸 (16) 及其盐酸盐 (16s),  
(3-(5-(2-甲基-[1,1'-联苯]-3-基)-1,3,4-噻二唑-2-基)苄基)-L-脯氨酸 (17) 及其盐酸盐 (17s),  
(S)-1-(3-(5-(2-甲基-[1,1'-联苯]-3-基)-1,3,4-噻二唑-2-基)苄基)吡咯烷-3-醇 (18) 及其盐酸盐 (18s),  
(R)-1-(3-(5-(2-甲基-[1,1'-联苯]-3-基)-1,3,4-噻二唑-2-基)苄基)哌啶-3-羧酸 (19) 及其盐酸盐 (19s),  
(4-(5-(2-甲基-[1,1'-联苯]-3-基)-1,3,4-噻二唑-2-基)苄基)甘氨酸 (20) 及其盐酸盐 (20s),  
(4-(5-(2-甲基-[1,1'-联苯]-3-基)-1,3,4-噻二唑-2-基)苄基)氨基乙醇 (21) 及其盐酸盐 (21s),  
(4-(5-(2-甲基-[1,1'-联苯]-3-基)-1,3,4-噻二唑-2-基)苄基)甘氨酸 (22) 及其盐酸盐 (22s),  
(4-(5-(2-甲基-[1,1'-联苯]-3-基)-1,3,4-噻二唑-2-基)苄基)-β-丙氨酸 (23) 及其盐酸盐 (23s),  
(4-(5-(2-甲基-[1,1'-联苯]-3-基)-1,3,4-噻二唑-2-基)苄基)-L-丝氨酸 (24) 及其盐酸盐 (24s),  
(4-(5-(2-甲基-[1,1'-联苯]-3-基)-1,3,4-噻二唑-2-基)苄基)-L-苏氨酸 (25) 及其盐酸盐 (25s),  
(4-(5-(2-甲基-[1,1'-联苯]-3-基)-1,3,4-噻二唑-2-基)苄基)-L-蛋氨酸 (26) 及其盐酸盐 (26s),  
(R)-1-(4-(5-(2-甲基-[1,1'-联苯]-3-基)-1,3,4-噻二唑-2-基)苄基)哌啶-3-羧酸 (27) 及其盐酸盐 (27s),  
(3-(5-(2-氟-[1,1'-联苯]-3-基)-1,3,4-噻二唑-2-基)苄基)甘氨酸 (28) 及其盐酸盐 (28s),  
(3-(5-(2-溴-[1,1'-联苯]-3-基)-1,3,4-噻二唑-2-基)苄基)甘氨酸 (29) 及其盐酸盐 (29s),  
4-(5-(2-溴-[1,1'-联苯]-3-基)-1,3,4-噻二唑-2-基)-3-氯苄基)-L-丝氨酸 (30) 及其盐酸盐 (30s),  
(3-(5-(2-氯-[1,1'-联苯]-3-基)-1,3,4-噻二唑-2-基)苄基)甘氨酸 (31) 及其盐酸盐 (31s),  
(3-(5-(2-氯-[1,1'-联苯]-3-基)-1,3,4-噻二唑-2-基)苄基)氨基乙醇 (32) 及其盐酸盐 (32s),  
(3-(5-(2-氯-[1,1'-联苯]-3-基)-1,3,4-噻二唑-2-基)苄基)甘氨酸 (33) 及其盐酸盐 (33s),  
(3-(5-(2-氯-[1,1'-联苯]-3-基)-1,3,4-噻二唑-2-基)苄基)-β-丙氨酸 (34) 及其盐酸盐 (34s),  
(3-(5-(2-氯-[1,1'-联苯]-3-基)-1,3,4-噻二唑-2-基)苄基)-L-丙氨酸 (35) 及其盐酸盐 (35s),  
(3-(5-(2-氯-[1,1'-联苯]-3-基)-1,3,4-噻二唑-2-基)苄基)-L-丝氨酸 (36) 及其盐酸盐 (36s),  
(3-(5-(2-氯-[1,1'-联苯]-3-基)-1,3,4-噻二唑-2-基)苄基)-L-丝氨酸 (37) 及其盐酸盐 (37s),  
(R)-1-(3-(5-(2-氯-[1,1'-联苯]-3-基)-1,3,4-噻二唑-2-基)苄基)哌啶-3-羧酸 (38) 及其盐酸盐 (38s),  
(4-(5-(2-氯-[1,1'-联苯]-3-基)-1,3,4-噻二唑-2-基)苄基)甘氨酸 (39) 及其盐酸盐 (39s),  
(4-(5-(2-氯-[1,1'-联苯]-3-基)-1,3,4-噻二唑-2-基)苄基)-L-丙氨酸 (40) 及其盐酸盐 (40s),  
(4-(5-(2-氯-[1,1'-联苯]-3-基)-1,3,4-噻二唑-2-基)苄基)-L-丝氨酸 (41) 及其盐酸盐 (41s),  
(3-氯-5-(5-(2-氯-[1,1'-联苯]-3-基)-1,3,4-噻二唑-2-基)苄基)甘氨酸 (42) 及其盐酸盐 (42s),  
(4-氟-3-(5-(2-甲基-[1,1'-联苯]-3-基)-1,3,4-噻二唑-2-基)苄基)甘氨酸 (43) 及其盐酸盐 (43s),  
(4-溴-3-(5-(2-甲基-[1,1'-联苯]-3-基)-1,3,4-噻二唑-2-基)苄基)甘氨酸 (44) 及其盐酸盐 (44s),  
(4-氯-3-(5-(2-甲基-[1,1'-联苯]-3-基)-1,3,4-噻二唑-2-基)苄基)甘氨酸 (45) 及其盐酸盐 (45s),  
(4-氯-3-(5-(2-甲基-[1,1'-联苯]-3-基)-1,3,4-噻二唑-2-基)苄基)氨基乙醇 (46) 及其盐酸盐 (46s),  
(R)-1-(4-氯-3-(5-(2-甲基-[1,1'-联苯]-3-基)-1,3,4-噻二唑-2-基)苄基)哌啶-3-羧酸 (47) 及其盐酸盐 (47s),  
(2-氯-3-(5-(2-甲基-[1,1'-联苯]-3-基)-1,3,4-噻二唑-2-基)苄基)甘氨酸 (48) 及其盐酸盐 (48s),  
(2-氯-5-(5-(2-甲基-[1,1'-联苯]-3-基)-1,3,4-噻二唑-2-基)苄基)甘氨酸 (49) 及其盐酸盐 (49s),  
(3-氯-5-(5-(2-甲基-[1,1'-联苯]-3-基)-1,3,4-噻二唑-2-基)苄基)甘氨酸 (50) 及其盐酸盐 (50s),  
(3-氯-5-(5-(2-甲基-[1,1'-联苯]-3-基)-1,3,4-噻二唑-2-基)苄基)氨基乙醇 (51) 及其盐酸盐 (51s),  
(3-氯-5-(5-(2-甲基-[1,1'-联苯]-3-基)-1,3,4-噻二唑-2-基)苄基)甘氨酸 (52) 及其盐酸盐 (52s),  
(3-氯-5-(5-(2-甲基-[1,1'-联苯]-3-基)-1,3,4-噻二唑-2-基)苄基)-β-丙氨酸 (53) 及其盐酸盐 (53s),  
(3-氯-5-(5-(2-甲基-[1,1'-联苯]-3-基)-1,3,4-噻二唑-2-基)苄基)-L-丙氨酸 (54) 及其盐酸盐 (54s),

(3-氯-5-(5-(2-甲基-[1,1'-联苯]-3-基)-1,3,4-噻二唑-2-基)苄基)-L-丝氨酸 (55) 及其盐酸盐 (55s),  
(3-氯-5-(5-(2-甲基-[1,1'-联苯]-3-基)-1,3,4-噻二唑-2-基)苄基)-L-丝氨酸 (56) 及其盐酸盐 (56s),  
(3-氯-5-(5-(2-甲基-[1,1'-联苯]-3-基)-1,3,4-噻二唑-2-基)苄基)-L-苏氨酸 (57) 及其盐酸盐 (57s),  
(3-氯-5-(5-(2-甲基-[1,1'-联苯]-3-基)-1,3,4-噻二唑-2-基)苄基)-L-苏氨酸 (58) 及其盐酸盐 (58s),  
(R)-1-(3-氯-5-(5-(2-甲基-[1,1'-联苯]-3-基)-1,3,4-噻二唑-2-基)苄基)哌啶-3-羧酸 (59) 及其盐酸盐 (59s),  
(3-(5-(2-甲基-[1,1'-联苯]-3-基)-4H-1,2,4-三唑-3-基)苄基)甘氨酸 (60) 及其盐酸盐 (60s),  
(3-(5-(2-甲基-[1,1'-联苯]-3-基)-4H-1,2,4-三唑-3-基)苄基)氨基乙醇 (61) 及其盐酸盐 (61s),  
(3-(5-(2-甲基-[1,1'-联苯]-3-基)-4H-1,2,4-三唑-3-基)苄基)-β-丙氨酸 (62) 及其盐酸盐 (62s),  
(3-(5-(2-甲基-[1,1'-联苯]-3-基)-4H-1,2,4-三唑-3-基)苄基)-L-丝氨酸 (63) 及其盐酸盐 (63s),  
(3-(5-(2-甲基-[1,1'-联苯]-3-基)-4H-1,2,4-三唑-3-基)苄基)-L-苏氨酸 (64) 及其盐酸盐 (64s),  
(R)-1-(3-(5-(2-甲基-[1,1'-联苯]-3-基)-4H-1,2,4-三唑-3-基)苄基)哌啶-3-羧酸 (65) 及其盐酸盐 (65s),  
(4-(5-(2-甲基-[1,1'-联苯]-3-基)-4H-1,2,4-三唑-3-基)苄基)甘氨酸 (66) 及其盐酸盐 (66s),  
N-甲基-N-(4-(5-(2-甲基-[1,1'-联苯]-3-基)-4H-1,2,4-三唑-3-基)苄基)肌氨酸 (67) 及其盐酸盐 (67s),  
(4-(5-(2-甲基-[1,1'-联苯]-3-基)-4H-1,2,4-三唑-3-基)苄基)氨基乙醇 (68) 及其盐酸盐 (68s),  
(4-(5-(2-甲基-[1,1'-联苯]-3-基)-4H-1,2,4-三唑-3-基)苄基)-L-丝氨酸 (69) 及其盐酸盐 (69s),  
(4-(5-(2-甲基-[1,1'-联苯]-3-基)-4H-1,2,4-三唑-3-基)苄基)-L-苏氨酸 (70) 及其盐酸盐 (70s),  
(2-氯-5-(5-(2-甲基-[1,1'-联苯]-3-基)-4H-1,2,4-三唑-3-基)苄基)甘氨酸 (71) 及其盐酸盐 (71s),  
(3-(5-(2-甲基-[1,1'-联苯]-3-基)-1,2,4-噁二唑-3-基)苄基)甘氨酸 (72) 及其盐酸盐 (72s),  
N-(2-((3-(5-(2-甲基-[1,1'-联苯]-3-基)-1,2,4-噁二唑-3-基)苄基)氨基)乙基)乙酰胺 (73) 及其盐酸盐 (73s),  
N-甲基-N-(3-(5-(2-甲基-[1,1'-联苯]-3-基)-1,2,4-噁二唑-3-基)苄基)甘氨酸 (74) 及其盐酸盐 (74s),  
2-((3-(5-(2-甲基-[1,1'-联苯]-3-基)-1,2,4-噁二唑-3-基)苄基)氨基)乙酰胺 (75) 及其盐酸盐 (75s),  
(3-(5-(2-甲基-[1,1'-联苯]-3-基)-1,2,4-噁二唑-3-基)苄基)-L-丙氨酸 (76) 及其盐酸盐 (76s),  
(3-(5-(2-甲基-[1,1'-联苯]-3-基)-1,2,4-噁二唑-3-基)苄基)-L-蛋氨酸 (77) 及其盐酸盐 (77s),  
(3-(5-(2-甲基-[1,1'-联苯]-3-基)-1,2,4-噁二唑-3-基)苄基)-L-亮氨酸 (78) 及其盐酸盐 (78s),  
(3-(5-(2-甲基-[1,1'-联苯]-3-基)-1,2,4-噁二唑-3-基)苄基)-L-异亮氨酸 (79) 及其盐酸盐 (79s),  
(3-(5-(2-甲基-[1,1'-联苯]-3-基)-1,2,4-噁二唑-3-基)苄基)-L-精氨酸 (80) 及其盐酸盐 (80s),  
(3-(5-(2-甲基-[1,1'-联苯]-3-基)-1,2,4-噁二唑-3-基)苄基)-L-苯丙氨酸 (81) 及其盐酸盐 (81s),  
(3-(5-(2-甲基-[1,1'-联苯]-3-基)-1,2,4-噁二唑-3-基)苄基)-L-酪氨酸 (82) 及其盐酸盐 (82s),  
(3-(5-(2-甲基-[1,1'-联苯]-3-基)-1,2,4-噁二唑-3-基)苄基)-L-色氨酸 (83) 及其盐酸盐 (83s),  
(3-(5-(2-甲基-[1,1'-联苯]-3-基)-1,2,4-噁二唑-3-基)苄基)-β-丙氨酸 (84) 及其盐酸盐 (84s),  
3-((3-(5-(2-甲基-[1,1'-联苯]-3-基)-1,2,4-噁二唑-3-基)苄基)氨基)丙酰胺 (85) 及其盐酸盐 (85s),  
(3-(5-(2-甲基-[1,1'-联苯]-3-基)-1,2,4-噁二唑-3-基)苄基)-L-脯氨酸 (86) 及其盐酸盐 (86s),  
(2S,4R)-4-羟基-1-(3-(5-(2-甲基-[1,1'-联苯]-3-基)-1,2,4-噁二唑-3-基)苄基)吡咯烷-2-羧酸 (87) 及其盐酸盐 (87s),  
(S)-1-(3-(5-(2-甲基-[1,1'-联苯]-3-基)-1,2,4-噁二唑-3-基)苄基)哌啶-2-羧酸 (88) 及其盐酸盐 (88s),  
(R)-1-(3-(5-(2-甲基-[1,1'-联苯]-3-基)-1,2,4-噁二唑-3-基)苄基)哌啶-3-羧酸 (89) 及其盐酸盐 (89s),  
1-(3-(5-(2-甲基-[1,1'-联苯]-3-基)-1,2,4-噁二唑-3-基)苄基)哌啶-3-甲酰胺 (90) 及其盐酸盐 (90s),  
(R)-1-(3-(5-(2-甲基-[1,1'-联苯]-3-基)-1,2,4-噁二唑-3-基)苄基)哌啶-4-羧酸 (91) 及其盐酸盐 (91s),  
N1,N1-二甲基-N2-(3-(5-(2-甲基-[1,1'-联苯]-3-基)-1,2,4-噁二唑-3-基)苄基)乙基-1,2-二胺 (92) 及其盐酸盐 (92s),  
(3-(5-(2-甲基-[1,1'-联苯]-3-基)-1,2,4-噁二唑-3-基)苄基)氨基乙醇 (93) 及其盐酸盐 (93s),  
2-(甲基(3-(5-(2-甲基-[1,1'-联苯]-3-基)-1,2,4-噁二唑-3-基)苄基)氨基)乙醇 (94) 及其盐酸盐 (94s),  
(R)-2-((3-(5-(2-甲基-[1,1'-联苯]-3-基)-1,2,4-噁二唑-3-基)苄基)氨基)丙醇 (95) 及其盐酸盐 (95s),  
(S)-2-((3-(5-(2-甲基-[1,1'-联苯]-3-基)-1,2,4-噁二唑-3-基)苄基)氨基)丙醇 (96) 及其盐酸盐 (96s),  
(R)-1-((3-(5-(2-甲基-[1,1'-联苯]-3-基)-1,2,4-噁二唑-3-基)苄基)氨基)丙基-2-醇 (97) 及其盐酸盐 (97s),  
(S)-1-((3-(5-(2-甲基-[1,1'-联苯]-3-基)-1,2,4-噁二唑-3-基)苄基)氨基)丙基-2-醇 (98) 及其盐酸盐 (98s),  
2-甲基-2-((3-(5-(2-甲基-[1,1'-联苯]-3-基)-1,2,4-噁二唑-3-基)苄基)氨基)丙醇 (99) 及其盐酸盐 (99s),  
2-甲基-1-((3-(5-(2-甲基-[1,1'-联苯]-3-基)-1,2,4-噁二唑-3-基)苄基)氨基)丙基-2-醇 (100) 及其盐酸盐 (100s),  
3-((3-(5-(2-甲基-[1,1'-联苯]-3-基)-1,2,4-噁二唑-3-基)苄基)氨基)丙醇 (101) 及其盐酸盐 (101s),  
2-((3-(5-(2-甲基-[1,1'-联苯]-3-基)-1,2,4-噁二唑-3-基)苄基)氨基)氧基乙醇 (102) 及其盐酸盐 (102s),  
2-((3-(5-(2-甲基-[1,1'-联苯]-3-基)-1,2,4-噁二唑-3-基)苄基)氨基)丙基-1,3-二醇 (103) 及其盐酸盐 (103s),

2-甲基-2-((3-(5-(2-甲基-[1,1'-联苯]-3-基)-1,2,4-噁二唑-3-基)苄基)氨基)丙基-1,3-二醇 (104) 及其盐酸盐 (104s),  
2-乙基-2-((3-(5-(2-甲基-[1,1'-联苯]-3-基)-1,2,4-噁二唑-3-基)苄基)氨基)丙基-1,3-二醇 (105) 及其盐酸盐 (105s),  
2-(羟甲基)-2-((3-(5-(2-甲基-[1,1'-联苯]-3-基)-1,2,4-噁二唑-3-基)苄基)氨基)丙基-1,3-二醇 (106) 及其盐酸盐 (106s),  
(3S,4R,5S,6R)-6-(羟甲基)-3-(3-(5-(2-甲基-[1,1'-联苯]-3-基)-1,2,4-噁二唑-3-基)苄基)氨基)四氢-2H-吡喃-2,4,5-三醇 (107) 及其盐酸盐 (107s),  
((3-(5-(2-甲基-[1,1'-联苯]-3-基)-1,2,4-噁二唑-3-基)苄基)氮杂二酰基)二甲醇 (108) 及其盐酸盐 (108s),  
(S)-1-(3-(5-(2-甲基-[1,1'-联苯]-3-基)-1,2,4-噁二唑-3-基)苄基)吡咯烷-3-醇 (109) 及其盐酸盐 (109s),  
1-(3-(5-(2-甲基-[1,1'-联苯]-3-基)-1,2,4-噁二唑-3-基)苄基)哌啶-3-醇 (110) 及其盐酸盐 (110s),  
1-(3-(5-(2-甲基-[1,1'-联苯]-3-基)-1,2,4-噁二唑-3-基)苄基)哌啶-4-醇 (111) 及其盐酸盐 (111s),  
(1-(3-(5-(2-甲基-[1,1'-联苯]-3-基)-1,2,4-噁二唑-3-基)苄基)哌啶-4-基)甲醇 (112) 及其盐酸盐 (112s),  
(3-(5-(2-甲基-[1,1'-联苯]-3-基)-1,2,4-噁二唑-3-基)苄基)-L-丝氨酸 (113) 及其盐酸盐 (113s),  
(3-(5-(2-甲基-[1,1'-联苯]-3-基)-1,2,4-噁二唑-3-基)苄基)-L-苏氨酸 (114) 及其盐酸盐 (114s),  
3-(3-((3,4-二氢异喹啉-2(1H)-基)甲基)苄基)-5-(2-甲基-[1,1'-联苯]-3-基)-1,2,4-噁二唑 (115) 及其盐酸盐 (115s),  
(3-(5-(2-氯-[1,1'-联苯]-3-基)-1,2,4-噁二唑-3-基)苄基)甘氨酸 (116) 及其盐酸盐 (116s),  
(3-(5-(2-氯-[1,1'-联苯]-3-基)-1,2,4-噁二唑-3-基)苄基)-L-丝氨酸 (117) 及其盐酸盐 (117s),  
(4-(5-(2-甲基-[1,1'-联苯]-3-基)-1,2,4-噁二唑-3-基)苄基)甘氨酸 (118) 及其盐酸盐 (118s),  
N-甲基-N-(4-(5-(2-甲基-[1,1'-联苯]-3-基)-1,2,4-噁二唑-3-基)苄基)甘氨酸 (119) 及其盐酸盐 (119s),  
2-((4-(5-(2-甲基-[1,1'-联苯]-3-基)-1,2,4-噁二唑-3-基)苄基)氨基)乙酰胺 (120) 及其盐酸盐 (120s),  
(4-(5-(2-甲基-[1,1'-联苯]-3-基)-1,2,4-噁二唑-3-基)苄基)-L-丙氨酸 (121) 及其盐酸盐 (121s),  
(4-(5-(2-甲基-[1,1'-联苯]-3-基)-1,2,4-噁二唑-3-基)苄基)-L-亮氨酸 (122) 及其盐酸盐 (122s),  
(4-(5-(2-甲基-[1,1'-联苯]-3-基)-1,2,4-噁二唑-3-基)苄基)-L-蛋氨酸 (123) 及其盐酸盐 (123s),  
(4-(5-(2-甲基-[1,1'-联苯]-3-基)-1,2,4-噁二唑-3-基)苄基)-β-丙氨酸 (124) 及其盐酸盐 (124s),  
3-((4-(5-(2-甲基-[1,1'-联苯]-3-基)-1,2,4-噁二唑-3-基)苄基)氨基)丙酰胺 (125) 及其盐酸盐 (125s),  
2-((4-(5-(2-甲基-[1,1'-联苯]-3-基)-1,2,4-噁二唑-3-基)苄基)氨基)丙基-1,3-二醇 (126) 及其盐酸盐 (126s),  
1-(呋喃-2-基)-N-(4-(5-(2-甲基-[1,1'-联苯]-3-基)-1,2,4-噁二唑-3-基)苄基)甲胺 (127) 及其盐酸盐 (127s),  
(4-(5-(2-甲基-[1,1'-联苯]-3-基)-1,2,4-噁二唑-3-基)苄基)-L-脯氨酸 (128) 及其盐酸盐 (128s),  
(2S,4R)-4-羟基-1-(3-(5-(2-甲基-[1,1'-联苯]-3-基)-1,2,4-噁二唑-3-基)苄基)吡咯烷-2-羧酸 (129) 及其盐酸盐 (129s),  
(S)-1-(4-(5-(2-甲基-[1,1'-联苯]-3-基)-1,2,4-噁二唑-3-基)苄基)哌啶-2-羧酸 (130) 及其盐酸盐 (130s),  
(3S, 4R, 5S, 6R)-6-(羟甲基)-3-((4-(5-(2-甲基-[1,1'-联苯]-3-基)-1,2,4-噁二唑-3-基)苄基)氨基)四氢-2H-吡喃-2,4,5-三醇 (131) 及其盐酸盐 (131s),  
(4-(5-(2-甲基-[1,1'-联苯]-3-基)-1,2,4-噁二唑-3-基)苄基)-L-丝氨酸 (132) 及其盐酸盐 (132s),  
(4-(5-(2-甲基-[1,1'-联苯]-3-基)-1,2,4-噁二唑-3-基)苄基)-L-苏氨酸 (133) 及其盐酸盐 (133s),  
(4-(5-(2-氯-[1,1'-联苯]-3-基)-1,2,4-噁二唑-3-基)苄基)甘氨酸 (134) 及其盐酸盐 (134s),  
(4-(5-(2-氯-[1,1'-联苯]-3-基)-1,2,4-噁二唑-3-基)苄基)-L-丝氨酸 (135) 及其盐酸盐 (135s),  
3-(3-(2-甲基-[1,1'-联苯]-3-基)-1,2,4-噁二唑-5-基)苄基)-L-丙氨酸 (136) 及其盐酸盐 (136s),  
(3-(3-(2-甲基-[1,1'-联苯]-3-基)-1,2,4-噁二唑-5-基)苄基)-L-丝氨酸 (137) 及其盐酸盐 (137s),  
3-(3-(3-(2-甲基-[1,1'-联苯]-3-基)-1,2,4-噁二唑-5-基)苄基)氨基丙酸 (138) 及其盐酸盐 (138s),  
(3-(3-(2-甲基-[1,1'-联苯]-3-基)-1,2,4-噁二唑-5-基)苄基)甘氨酸 (139) 及其盐酸盐 (139s),  
2-((3-(3-(2-甲基-[1,1'-联苯]-3-基)-1,2,4-噁二唑-5-基)苄基)氨基)乙醇 (140) 及其盐酸盐 (140s),  
3-(3-(2-氟-[1,1'-联苯]-3-基)-1,2,4-噁二唑-5-基)苄基)甘氨酸 (141) 及其盐酸盐 (141s),  
(3-(3-(2-氯-[1,1'-联苯]-3-基)-1,2,4-噁二唑-5-基)苄基)甘氨酸 (142) 及其盐酸盐 (142s),  
(3-(3-(2-溴-[1,1'-联苯]-3-基)-1,2,4-噁二唑-5-基)苄基)甘氨酸 (143) 及其盐酸盐 (143s),  
(4-(3-(2-甲基-[1,1'-联苯]-3-基)-1,2,4-噁二唑-5-基)苄基)甘氨酸 (144) 及其盐酸盐 (144s),  
(4-(3-(2-甲基-[1,1'-联苯]-3-基)-1,2,4-噁二唑-5-基)苄基)-L-丝氨酸 (145) 及其盐酸盐 (145s),  
(3-(5-(2-甲基-[1,1'-联苯]-3-基)噁唑-2-基)苄基)甘氨酸 (146) 及其盐酸盐 (146s),  
(3-(5-(2-甲基-[1,1'-联苯]-3-基)噁唑-2-基)苄基)氨基乙醇 (147) 及其盐酸盐 (147s),  
(3-(5-(2-甲基-[1,1'-联苯]-3-基)噁唑-2-基)苄基)甘氨酸酰胺 (148) 及其盐酸盐 (148s),  
(3-(5-(2-甲基-[1,1'-联苯]-3-基)噁唑-2-基)苄基)-β-丙氨酸 (149) 及其盐酸盐 (149s),

3-(5-(2-甲基-[1,1'-联苯]-3-基)噁唑-2-基)苄基)-L-丙氨酸 (150) 及其盐酸盐 (150s),  
3-(5-(2-甲基-[1,1'-联苯]-3-基)噁唑-2-基)苄基)-L-丝氨酸 (151) 及其盐酸盐 (151s),  
(3-(5-(2-甲基-[1,1'-联苯]-3-基)噁唑-2-基)苄基)-L-苏氨酸 (152) 及其盐酸盐 (152s),  
(R)-1-(3-(5-(2-甲基-[1,1'-联苯]-3-基)噁唑-2-基)苄基)哌啶-3-羧酸 (153) 及其盐酸盐 (153s),  
4-(5-(2-甲基-[1,1'-联苯]-3-基)噁唑-2-基)苄基)甘氨酸 (154) 及其盐酸盐 (154s),  
(4-(5-(2-甲基-[1,1'-联苯]-3-基)噁唑-2-基)苄基)氨基乙醇 (155) 及其盐酸盐 (155s),  
(4-(5-(2-甲基-[1,1'-联苯]-3-基)噁唑-2-基)苄基)-β-丙氨酸 (156) 及其盐酸盐 (156s),  
(R)-1-(4-(5-(2-甲基-[1,1'-联苯]-3-基)噁唑-2-基)苄基)哌啶-3-羧酸 (157) 及其盐酸盐 (157s),  
(2-氯-5-(5-(2-甲基-[1,1'-联苯]-3-基)噁唑-2-基)苄基)甘氨酸 (158) 及其盐酸盐 (158s),  
(R)-1-(2-氯-5-(5-(2-甲基-[1,1'-联苯]-3-基)噁唑-2-基)苄基)哌啶-3-羧酸 (159) 及其盐酸盐 (159s),  
2-氯-3-(5-(2-甲基-[1,1'-联苯]-3-基)噁唑-2-基)苄基)甘氨酸 (160) 及其盐酸盐 (160s),  
3-氯-5-(5-(2-甲基-[1,1'-联苯]-3-基)噁唑-2-基)苄基)甘氨酸 (161) 及其盐酸盐 (161s),  
3-氯-5-(5-(2-甲基-[1,1'-联苯]-3-基)噁唑-2-基)苄基)-L-丙氨酸 (162) 及其盐酸盐 (162s),  
3-氯-5-(5-(2-甲基-[1,1'-联苯]-3-基)噁唑-2-基)苄基)-L-丝氨酸 (163) 及其盐酸盐 (163s),  
(3-氯-5-(5-(2-甲基-[1,1'-联苯]-3-基)噁唑-2-基)苄基)氨基乙醇 (164) 及其盐酸盐 (164s),  
4-氯-3-(5-(2-甲基-[1,1'-联苯]-3-基)噁唑-2-基)苄基)甘氨酸 (165) 及其盐酸盐 (165s),  
4-氯-3-(5-甲基-[1,1'-联苯]-3-基)噁唑-2-基)苄基)-L-丝氨酸 (166) 及其盐酸盐 (166s),  
4-氯-3-(5-甲基-[1,1'-联苯]-3-基)噁唑-2-基)苄基)-D-丝氨酸 (167) 及其盐酸盐 (167s),  
4-氟-3-(5-(2-甲基-[1,1'-联苯]-3-基)噁唑-2-基)苄基)甘氨酸 (168) 及其盐酸盐 (168s),  
4-氟-3-(5-(2-甲基-[1,1'-联苯]-3-基)噁唑-2-基)苄基)-L-丝氨酸 (169) 及其盐酸盐 (169s),  
4-溴-3-(5-(2-甲基-[1,1'-联苯]-3-基)噁唑-2-基)苄基)甘氨酸 (170) 及其盐酸盐 (170s),  
4-碘-3-(5-(2-甲基-[1,1'-联苯]-3-基)噁唑-2-基)苄基)甘氨酸 (171) 及其盐酸盐 (171s),  
4-硝基-3-(5-(2-甲基-[1,1'-联苯]-3-基)噁唑-2-基)苄基)甘氨酸 (172) 及其盐酸盐 (172s),  
3-氯-4-(5-(2-甲基-[1,1'-联苯]-3-基)噁唑-2-基)苄基)甘氨酸 (173) 及其盐酸盐 (173s),  
2-氯-4-(5-(2-甲基-[1,1'-联苯]-3-基)噁唑-2-基)苄基)甘氨酸 (174) 及其盐酸盐 (174s),  
(R)-1-(2-氯-4-(5-(2-甲基-[1,1'-联苯]-3-基)噁唑-2-基)苄基)哌啶-3-羧酸 (175) 及其盐酸盐 (175s),  
2-硝基-4-(5-(2-甲基-[1,1'-联苯]-3-基)噁唑-2-基)苄基)甘氨酸 (176) 及其盐酸盐 (176s),  
2-甲氧基-4-(5-(2-甲基-[1,1'-联苯]-3-基)噁唑-2-基)苄基)甘氨酸 (177) 及其盐酸盐 (177s),  
4-(5-(2-甲基-[1,1'-联苯]-3-基)噁唑-2-基)-3-硝基苄基)甘氨酸 (178) 及其盐酸盐 (178s),  
(4-氯-3-(5-(2-氯-[1,1'-联苯]-3-基)噁唑-2-基)苄基)甘氨酸 (179) 及其盐酸盐 (179s),  
4-氯-3-(5-氯-[1,1'-联苯]-3-基)噁唑-2-基)苄基)-L-丝氨酸 (180) 及其盐酸盐 (180s),  
(R)-1-(4-氯-3-(5-氯-[1,1'-联苯]-3-基)噁唑-2-基)苄基)哌啶-3-羧酸 (181) 及其盐酸盐 (181s),  
4-氯-3-(5-(2-氯-[1,1'-联苯]-3-基)噁唑-2-基)苄基)氨基乙醇 (182) 及其盐酸盐 (182s),  
4-氯-3-(5-溴-[1,1'-联苯]-3-基)噁唑-2-基)苄基)甘氨酸 (183) 及其盐酸盐 (183s),  
3-(5-溴-[1,1'-联苯]-3-基)噁唑-2-基)-4-氯苄基)-L-丝氨酸 (184) 及其盐酸盐 (184s),  
5-(5-(2-溴-[1,1'-联苯]-3-基)噁唑-2-基)-2-氯苄基)甘氨酸 (185) 及其盐酸盐 (185s),  
(R)-1-(3-(5-(2-溴-[1,1'-联苯]-3-基)噁唑-2-基)-4-氯苄基)哌啶-3-羧酸 (186) 及其盐酸盐 (186s),  
3-(5-(2-溴-[1,1'-联苯]-3-基)噁唑-2-基)-5-氯苄基)甘氨酸 (187) 及其盐酸盐 (187s),  
4-(5-(2-溴-[1,1'-联苯]-3-基)噁唑-2-基)苄基)甘氨酸 (188) 及其盐酸盐 (188s),  
(4-(5-(2-溴-[1,1'-联苯]-3-基)噁唑-2-基)-3-氯苄基)甘氨酸 (189) 及其盐酸盐 (189s),  
4-(5-(2-溴-[1,1'-联苯]-3-基)噁唑-2-基)-2-氯苄基)甘氨酸 (190) 及其盐酸盐 (190s),  
(3-(2-(2-甲基-[1,1'-联苯]-3-基)噁唑-5-基)苄基)甘氨酸 (191) 及其盐酸盐 (191s),  
(3-(2-(2-甲基-[1,1'-联苯]-3-基)噁唑-5-基)苄基)-L-丝氨酸 (192) 及其盐酸盐 (192s),  
3-((3-(2-(2-甲基-[1,1'-联苯]-3-基)噁唑-5-基)苄基)氨基)丙酸 (193) 及其盐酸盐 (193s),  
(4-(2-(2-甲基-[1,1'-联苯]-3-基)噁唑-5-基)苄基)甘氨酸 (194) 及其盐酸盐 (194s),  
(4-(2-(2-甲基-[1,1'-联苯]-3-基)噁唑-5-基)苄基)-L-丙氨酸 (195) 及其盐酸盐 (195s),  
(4-(2-(2-甲基-[1,1'-联苯]-3-基)噁唑-5-基)苄基)-L-丝氨酸 (196) 及其盐酸盐 (196s),  
(4-(2-(2-甲基-[1,1'-联苯]-3-基)噁唑-5-基)苄基)-L-苏氨酸 (197) 及其盐酸盐 (197s),  
(4-(2-(2-甲基-[1,1'-联苯]-3-基)噁唑-5-基)苄基)-β-丙氨酸 (198) 及其盐酸盐 (198s),

3-(2-甲基-[1,1'-联苯]-3-基)噁唑-4-基)苄基)甘氨酸 (199) 及其盐酸盐 (199s),  
3-(2-甲基-[1,1'-联苯]-3-基)噁唑-4-基)苄基)-L-丙氨酸 (200) 及其盐酸盐 (200s),  
3-(2-甲基-[1,1'-联苯]-3-基)噁唑-4-基)苄基)-L-丝氨酸 (201) 及其盐酸盐 (201s),  
3-(3-(2-甲基-[1,1'-联苯]-3-基)噁唑-4-基)苄基)- $\beta$ -丙氨酸 (202) 及其盐酸盐 (202s),  
(R)-1-(3-(2-甲基-[1,1'-联苯]-3-基)噁唑-4-基)苄基)哌啶-3-羧酸 (203) 及其盐酸盐 (203s),  
3-(2-甲基-[1,1'-联苯]-3-基)噁唑-4-基)苄基)氨基乙醇 (204) 及其盐酸盐 (204s),  
3-(2-甲基-[1,1'-联苯]-3-基)噁唑-4-基)苄基)甘氨酸 (205) 及其盐酸盐 (205s),  
(3-(2-甲基-[1,1'-联苯]-3-基)噁唑-4-基)苄基)-L-丝氨酸 (206) 及其盐酸盐 (206s),  
4-(2-甲基-[1,1'-联苯]-3-基)噁唑-4-基)苄基)甘氨酸 (207) 及其盐酸盐 (207s),  
4-(2-甲基-[1,1'-联苯]-3-基)噁唑-4-基)苄基)-L-丝氨酸 (208) 及其盐酸盐 (208s),  
4-(2-甲基-[1,1'-联苯]-3-基)噁唑-4-基)苄基)- $\beta$ -丙氨酸 (209) 及其盐酸盐 (209s),  
(R)-1-(4-(2-甲基-[1,1'-联苯]-3-基)噁唑-4-基)苄基)哌啶-3-羧酸 (210) 及其盐酸盐 (210s),  
4-(2-甲基-[1,1'-联苯]-3-基)噁唑-4-基)苄基)氨基乙醇 (211) 及其盐酸盐 (211s),  
3-(2-氯-[1,1'-联苯]-3-基)噁唑-4-基)苄基)甘氨酸 (212) 及其盐酸盐 (212s),  
3-(2-氯-[1,1'-联苯]-3-基)噁唑-4-基)苄基)-L-丝氨酸 (213) 及其盐酸盐 (213s),  
3-(2-氯-[1,1'-联苯]-3-基)噁唑-4-基)苄基)-L-丙氨酸 (214) 及其盐酸盐 (214s),  
3-(2-氯-[1,1'-联苯]-3-基)噁唑-4-基)苄基)- $\beta$ -丙氨酸 (215) 及其盐酸盐 (215s),  
(3-氯-(5-(2-氯-[1,1'-联苯]-3-基)噁唑-4-基)苄基)甘氨酸 (216) 及其盐酸盐 (216s),  
(3-氯-(5-(2-氯-[1,1'-联苯]-3-基)噁唑-4-基)苄基)丝氨酸 (217) 及其盐酸盐 (217s),  
(3-[4-(2-甲基-[1,1'-联苯]-3-基)噁唑-2-基)苄基)-L-丙氨酸 (218) 及其盐酸盐 (218s),  
(3-[4-(2-甲基-[1,1'-联苯]-3-基)噁唑-2-基)苄基)-L-丝氨酸 (219) 及其盐酸盐 (219s),  
(3-[4-(2-甲基-[1,1'-联苯]-3-基)噁唑-2-基)苄基)- $\beta$ -丙氨酸 (220) 及其盐酸盐 (220s),  
(R)-1-(3-[4-(2-甲基-[1,1'-联苯]-3-基)噁唑-2-基)苄基)哌啶-3-羧酸 (221) 及其盐酸盐 (221s),  
(3-[4-(2-甲基-[1,1'-联苯]-3-基)噁唑-2-基)苄基)氨基乙醇 (222) 及其盐酸盐 (222s),  
(3-[4-(2-甲基-[1,1'-联苯]-3-基)噁唑-2-基)苄基)甘氨酸 (223) 及其盐酸盐 (223s),  
(3-[4-(2-甲基-[1,1'-联苯]-3-基)噁唑-2-基)苄基)-L-丝氨酸 (224) 及其盐酸盐 (224s),  
(4-[4-(2-甲基-[1,1'-联苯]-3-基)噁唑-2-基)苄基)甘氨酸 (225) 及其盐酸盐 (225s),  
(4-[4-(2-甲基-[1,1'-联苯]-3-基)噁唑-2-基)苄基)-L-丝氨酸 (226) 及其盐酸盐 (226s),  
(3-[4-(2-甲基-[1,1'-联苯]-3-基)-1H-咪唑-2-基)苄基)-L-丙氨酸 (227) 及其盐酸盐 (227s),  
(R)-1-(3-[4-(2-甲基-[1,1'-联苯]-3-基)-1H-咪唑-2-基)苄基)哌啶-3-羧酸 (228) 及其盐酸盐 (228s),  
(3-[4-(2-甲基-[1,1'-联苯]-3-基)-1H-咪唑-2-基)苄基)甘氨酸 (229) 及其盐酸盐 (229s),  
(3-[4-(2-甲基-[1,1'-联苯]-3-基)-1H-咪唑-2-基)苄基)-L-丝氨酸 (230) 及其盐酸盐 (230s),  
(3-(5-(2-甲基-[1,1'-联苯]-3-基)噁唑-2-基)苄基)-L-苏氨酸 (231) 及其盐酸盐 (231s),  
(3-(4-(2-甲基-[1,1'-联苯]-3-基)-1H-咪唑-2-基)苄基)- $\beta$ -丙氨酸 (232) 及其盐酸盐 (232s),  
(4-(4-(2-甲基-[1,1'-联苯]-3-基)-1H-咪唑-2-基)苄基)- $\beta$ -丙氨酸 (233) 及其盐酸盐 (233s),  
(4-(4-(2-甲基-[1,1'-联苯]-3-基)-1H-咪唑-2-基)苄基)甘氨酸 (234) 及其盐酸盐 (234s),  
(3-(5-(2-甲基-[1,1'-联苯]-3-基)噁唑-2-基)苄基)甘氨酸 (235) 及其盐酸盐 (235s),  
3-(5-(2-甲基-[1,1'-联苯]-3-基)噁唑-2-基)苄基)-L-丙氨酸 (236) 及其盐酸盐 (236s),  
3-(5-(2-甲基-[1,1'-联苯]-3-基)噁唑-2-基)苄基)-L-丝氨酸 (237) 及其盐酸盐 (237s),  
3-(5-(2-甲基-[1,1'-联苯]-3-基)噁唑-2-基)苄基)-L-苏氨酸 (238) 及其盐酸盐 (238s),  
3-(5-(2-甲基-[1,1'-联苯]-3-基)噁唑-2-基)苄基)氨基乙醇 (239) 及其盐酸盐 (239s),  
(3-(2-甲基-[1,1'-联苯]-3-基)噁唑-5-基)苄基)甘氨酸 (240) 及其盐酸盐 (240s),  
(3-(2-甲基-[1,1'-联苯]-3-基)噁唑-5-基)苄基)-L-丙氨酸 (241) 及其盐酸盐 (241s),  
(3-(2-甲基-[1,1'-联苯]-3-基)噁唑-5-基)苄基)-L-丝氨酸 (242) 及其盐酸盐 (242s),  
(3-(2-甲基-[1,1'-联苯]-3-基)噁唑-5-基)苄基)-L-苏氨酸 (243) 及其盐酸盐 (243s),  
3-(2-(2-甲基-[1,1'-联苯]-3-基)噁唑-5-基)苄基)氨基乙醇 (244) 及其盐酸盐 (244s),  
(4-(5-(2-甲基-[1,1'-联苯]-3-基)噁吩-2-基)苄基)甘氨酸 (245) 及其盐酸盐 (245s),  
(4-(5-(2-甲基-[1,1'-联苯]-3-基)噁吩-2-基)苄基)- $\beta$ -丙氨酸 (246) 及其盐酸盐 (246s),  
(4-(5-(2-甲基-[1,1'-联苯]-3-基)噁吩-2-基)苄基)丝氨酸 (247) 及其盐酸盐 (247s),

(4-(5-(2-甲基-[1,1'-联苯]-3-基)噻吩-2-基)苄基)-L-苏氨酸 (248) 及其盐酸盐 (248s),  
(R)-1-(4-(5-(2-甲基-[1,1'-联苯]-3-基)噻吩-2-基)苄基)哌啶-3-羧酸 (249) 及其盐酸盐 (249s),  
(3-(5-(2-甲基-[1,1'-联苯]-3-基)噻吩-2-基)苄基)甘氨酸 (250) 及其盐酸盐 (250s),  
(3-(5-(2-甲基-[1,1'-联苯]-3-基)噻吩-2-基)苄基)氨基乙醇 (251) 及其盐酸盐 (251s),  
(3-(5-(2-甲基-[1,1'-联苯]-3-基)噻吩-2-基)苄基)- $\beta$ -丙氨酸 (252) 及其盐酸盐 (252s),  
(3-(5-(2-甲基-[1,1'-联苯]-3-基)噻吩-2-基)苄基)-L-丙氨酸 (253) 及其盐酸盐 (253s),  
(3-(5-(2-甲基-[1,1'-联苯]-3-基)噻吩-2-基)苄基)-L-丝氨酸 (254) 及其盐酸盐 (254s),  
(3-(5-(2-甲基-[1,1'-联苯]-3-基)噻吩-2-基)苄基)-L-苏氨酸 (255) 及其盐酸盐 (255s),  
(R)-1-(3-(5-(2-甲基-[1,1'-联苯]-3-基)噻吩-2-基)苄基)哌啶-3-羧酸 (256) 及其盐酸盐 (256s),  
3-((3-(5-(2-甲基-[1,1'-联苯]-3-基)噻吩-2-基)苄基)氨基)哌啶-2,6-二酮 (257) 及其盐酸盐 (257s),  
(4-(5-(2-甲基-[1,1'-联苯]-3-基)呋喃-2-基)苄基)甘氨酸 (258) 及其盐酸盐 (258s),  
(4-(5-(2-甲基-[1,1'-联苯]-3-基)呋喃-2-基)苄基)-L-丝氨酸 (259) 及其盐酸盐 (259s),  
(4-(5-(2-甲基-[1,1'-联苯]-3-基)呋喃-2-基)苄基)- $\beta$ -丙氨酸 (260) 及其盐酸盐 (260s),  
(3-(5-(2-甲基-[1,1'-联苯]-3-基)呋喃-2-基)苄基)甘氨酸 (261) 及其盐酸盐 (261s),  
(3-(5-(2-甲基-[1,1'-联苯]-3-基)呋喃-2-基)苄基)-L-丝氨酸 (262) 及其盐酸盐 (262s),  
(3-(5-(2-甲基-[1,1'-联苯]-3-基)呋喃-2-基)苄基)- $\beta$ -丙氨酸 (263) 及其盐酸盐 (263s),  
(R)-1-(3-(5-(2-甲基-[1,1'-联苯]-3-基)呋喃-2-基)苄基)哌啶-3-羧酸 (264) 及其盐酸盐 (264s),  
(3-(5-(2-甲基-[1,1'-联苯]-3-基)呋喃-2-基)苄基)氨基乙醇 (265) 及其盐酸盐 (265s),  
(3-(5-(2-甲基-[1,1'-联苯]-3-基)呋喃-2-基)苄基)-L-苏氨酸 (266) 及其盐酸盐 (266s)。

5、根据权利要求 1 所述的五元杂环类化合物,其特征在于,所述药学上可接受的盐为所述化合物与选自以下任一的酸形成的盐:盐酸、氢溴酸、硫酸、磷酸、碳酸、甲磺酸、苯磺酸、对甲苯磺酸、萘磺酸、柠檬酸、酒石酸、苹果酸、乳酸、丙酮酸、乙酸、马来酸、琥珀酸、富马酸、水杨酸、苯基乙酸、杏仁酸、阿魏酸。

6、一种权利要求 1-5 任一所述的五元杂环类化合物在制备 PD-L1 抑制剂药物中的应用。

7、一种权利要求 1-5 任一所述的五元杂环类化合物在制备免疫调节剂药物中的应用。

8、根据权利要求 7 所述的应用,其特征在于,所述免疫调节剂药物为预防和/或治疗肿瘤、感染性疾病、炎症性疾病、器官移植排斥和自身免疫性疾病的药物。

9、一种药物组合物,其特征在于,包括权利要求 1-5 任一所述的五元杂环类化合物以及药学上可接受的载体。

10、根据权利要求 9 所述的药物组合药,其特征在于,其药物制剂形式是片剂、胶囊剂、散剂、丸剂、颗粒剂、注射剂、口服液、糖浆剂、吸入剂、软膏剂、贴剂或栓剂。

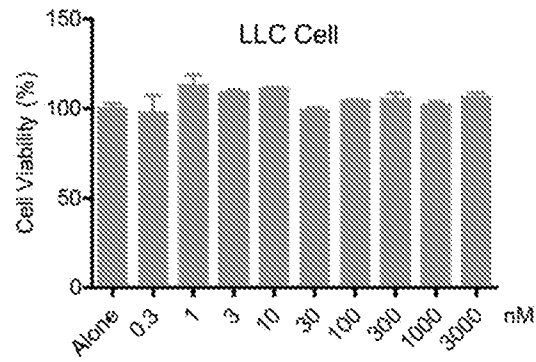


图 1

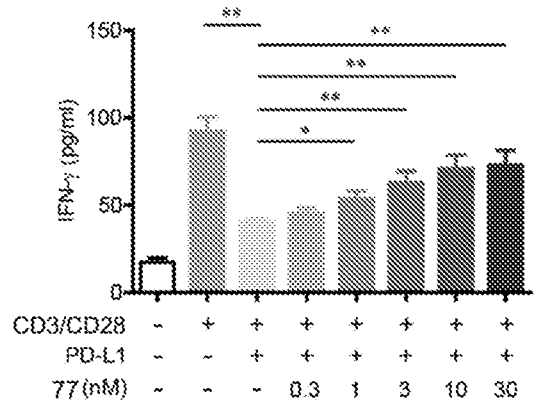


图 2

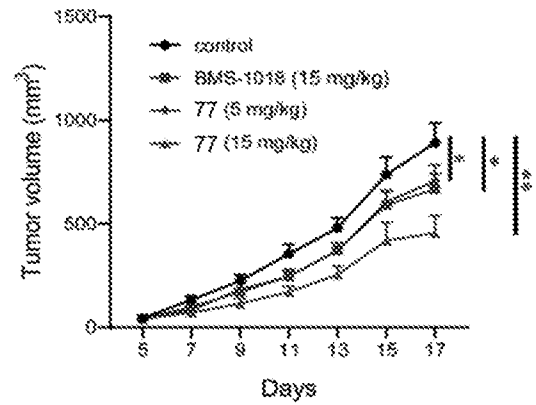


图 3

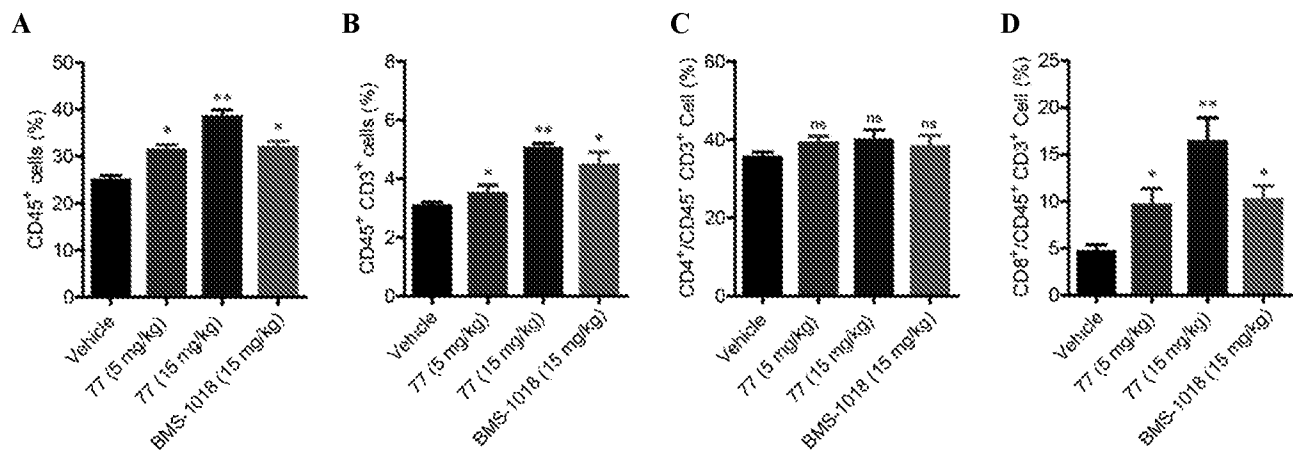


图 4

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/CN2024/072679

**A. CLASSIFICATION OF SUBJECT MATTER**

C07D285/12(2006.01)i; C07D249/08(2006.01)i; C07D401/10(2006.01)i; C07D271/06(2006.01)i; C07D413/12(2006.01)i; C07D413/10(2006.01)i; C07D263/32(2006.01)i; C07D277/28(2006.01)i; C07D333/20(2006.01)i; C07D409/12(2006.01)i; C07D409/10(2006.01)i; C07D307/52(2006.01)i; A61P37/02(2006.01)i; A61P37/06(2006.01)i; A61P35/00(2006.01)i; A61P31/00(2006.01)i; A61P29/00(2006.01)i

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

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

C07D285/-; C07D249/-; C07D401/-; C07D271/-; C07D413/-; C07D/263; C07D277/-; C07D333/-; C07D409/-; C07D307/-; A61P37/-; A61P35/-; A61P31/-; A61P29/-

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

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

CNTEXT; VEN; ENTEXT; WOTXT; USTXT; EPTXT; GBTXT; JPTXT; CNMED; MEDNPL; CNKI; 万方, WANFANG; 百度学术, BAIDU SCHOLAR; 读秀, DUXIU; STN; Web of Science; 苯基, 联苯, 五元杂环类, 式I结构检索, 肿瘤, 感染性疾病, 炎症性疾病, 器官移植排斥, 自身免疫性疾病, 中国药科大学, 赖宜生, 文博杰, 杨帆, 陈西敬, phenyl, biphenyl, five-membered heterocyclic, tumor, infectious disease, inflammatory disease, organ transplant rejection, autoimmune disease, CHINA PHARMACEUTICAL UNIV.

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

| Category* | Citation of document, with indication, where appropriate, of the relevant passages                                                                                                                                                                                                                      | Relevant to claim No. |
|-----------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|
| PX        | CN 116041277 A (CHINA PHARMACEUTICAL UNIVERSITY) 02 May 2023 (2023-05-02)<br>claims 1-10                                                                                                                                                                                                                | 1-10                  |
| A         | AMEDEO Omodei-Salé et al. "A new class of nonhormonal pregnancy-terminating agents. Synthesis and contragestational activity of 3,5-diaryl-s-triazoles"<br><i>Journal of Medicinal Chemistry</i> , Vol. 26, No. (8), 31 August 1983 (1983-08-31), 1189-1192<br>ISSN: 0022-2623,<br>page 1190, number 70 | 1-10                  |
| A         | CN 108292709 A (SUMITOMO CHEMICAL CO., LTD.) 17 July 2018 (2018-07-17)<br>claims 1-12                                                                                                                                                                                                                   | 1-10                  |
| A         | US 2021198222 A1 (SAMSUNG ELECTRONICS CO., LTD.) 01 July 2021 (2021-07-01)<br>claims 1-20                                                                                                                                                                                                               | 1-10                  |



Further documents are listed in the continuation of Box C.



See patent family annex.

\* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance  
"D" document cited by the applicant in the international application  
"E" earlier application or patent but published on or after the international filing date  
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)  
"O" document referring to an oral disclosure, use, exhibition or other means  
"P" document published prior to the international filing date but later than the priority date claimed

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search

25 March 2024

Date of mailing of the international search report

01 April 2024

Name and mailing address of the ISA/CN

China National Intellectual Property Administration (ISA/  
CN)  
China No. 6, Xitucheng Road, Jimenqiao, Haidian District,  
Beijing 100088

Authorized officer

Telephone No.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/CN2024/072679

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages                    | Relevant to claim No. |
|-----------|-------------------------------------------------------------------------------------------------------|-----------------------|
| A         | US 6699896 B1 (WYETH CORP.) 02 March 2004 (2004-03-02)<br>claims 1-24                                 | 1-10                  |
| A         | WO 2021148043 A1 (CHINA PHARMACEUTICAL UNIVERSITY et al.) 29 July 2021<br>(2021-07-29)<br>claims 1-10 | 1-10                  |

**INTERNATIONAL SEARCH REPORT**  
**Information on patent family members**

International application No.

**PCT/CN2024/072679**

| Patent document<br>cited in search report |            |    | Publication date<br>(day/month/year) | Patent family member(s) |             |    | Publication date<br>(day/month/year) |
|-------------------------------------------|------------|----|--------------------------------------|-------------------------|-------------|----|--------------------------------------|
| CN                                        | 116041277  | A  | 02 May 2023                          | None                    |             |    |                                      |
| CN                                        | 108292709  | A  | 17 July 2018                         | EP                      | 3389104     | A1 | 17 October 2018                      |
|                                           |            |    |                                      | EP                      | 3389104     | A4 | 31 July 2019                         |
|                                           |            |    |                                      | EP                      | 3389104     | B1 | 16 September 2020                    |
|                                           |            |    |                                      | JPWO                    | 2017099012  | A1 | 20 September 2018                    |
|                                           |            |    |                                      | JP                      | 6754774     | B2 | 16 September 2020                    |
|                                           |            |    |                                      | WO                      | 2017099012  | A1 | 15 June 2017                         |
|                                           |            |    |                                      | KR                      | 20180091026 | A  | 14 August 2018                       |
|                                           |            |    |                                      | US                      | 2018375034  | A1 | 27 December 2018                     |
| US                                        | 2021198222 | A1 | 01 July 2021                         | US                      | 11691957    | B2 | 04 July 2023                         |
|                                           |            |    |                                      | KR                      | 20210084775 | A  | 08 July 2021                         |
| US                                        | 6699896    | B1 | 02 March 2004                        | US                      | 2004147755  | A1 | 29 July 2004                         |
|                                           |            |    |                                      | US                      | 7141672     | B2 | 28 November 2006                     |
| WO                                        | 2021148043 | A1 | 29 July 2021                         | None                    |             |    |                                      |

A. 主题的分类

C07D285/12(2006.01)i; C07D249/08(2006.01)i; C07D401/10(2006.01)i; C07D271/06(2006.01)i; C07D413/12(2006.01)i; C07D413/10(2006.01)i; C07D263/32(2006.01)i; C07D277/28(2006.01)i; C07D333/20(2006.01)i; C07D409/12(2006.01)i; C07D409/10(2006.01)i; C07D307/52(2006.01)i; A61P37/02(2006.01)i; A61P37/06(2006.01)i; A61P35/00(2006.01)i; A61P31/00(2006.01)i; A61P29/00(2006.01)i

按照国际专利分类(IPC)或者同时按照国家分类和IPC两种分类

B. 检索领域

检索的最低限度文献(标明分类系统和分类号)

C07D285/-; C07D249/-; C07D401/-; C07D271/-; C07D413/-; C07D/263; C07D277/-; C07D333/-; C07D409/-; C07D307/-; A61P37/-; A61P35/-; A61P31/-; A61P29/-

包含在检索领域中的除最低限度文献以外的检索文献

在国际检索时查阅的电子数据库(数据库的名称, 和使用的检索词(如使用))

CNXTX; VEN; ENTXT; WOTXT; USTXT; EPTXT; GBTXT; JPTXT; CNMED; MEDNPL; CNKI; 万方; 百度学术; 读秀; STN; Web of Science:苯基, 联苯, 五元杂环类, 式 I 结构检索, 肿瘤、感染性疾病、炎症性疾病、器官移植排斥, 自身免疫性疾病, 中国药科大学, 赖宜生, 文博杰, 杨帆, 陈西敬, phenyl, biphenyl, five-membered heterocyclic, tumor, infectious disease, inflammatory disease, organ transplant rejection, autoimmune disease, CHINA PHARMACEUTICAL UNIV.

C. 相关文件

| 类 型* | 引用文件, 必要时, 指明相关段落                                                                                                                                                                                                                                                               | 相关的权利要求 |
|------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------|
| PX   | CN 116041277 A (中国药科大学) 2023年5月2日 (2023 - 05 - 02)<br>权利要求1-10                                                                                                                                                                                                                  | 1-10    |
| A    | AMEDEO Omodei-Sal  et al. "A new class of nonhormonal pregnancy-terminating agents. Synthesis and contragestational activity of 3,5-diaryl-s-triazoles"<br>Journal of Medicinal Chemistry, 第26卷, 第8期, 1983年8月31日 (1983 - 08 - 31), 1189-1192<br>ISSN: 0022-2623,<br>第1190页no.70 | 1-10    |
| A    | CN 108292709 A (住友化学株式会社) 2018年7月17日 (2018 - 07 - 17)<br>权利要求1-12                                                                                                                                                                                                               | 1-10    |

☒ 其余文件在C栏的续页中列出。

☒ 见同族专利附件。

★ 引用文件的具体类型:

“A” 认为不特别相关的表示了现有技术一般状态的文件

“D” 申请人在国际申请中引证的文件

“E” 在国际申请日的当天或之后公布的在先申请或专利

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

“O” 涉及口头公开、使用、展览或其他方式公开的文件

“p” 公布日先于国际申请日但迟于所要求的优先权日的文件

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

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

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

“&” 同族专利的文件

国际检索实际完成的日期

2024年3月25日

国际检索报告邮寄日期

2024年4月1日

ISA/CN的名称和邮寄地址

中国国家知识产权局  
中国北京市海淀区蓟门桥西土城路6号 100088

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PCT/ISA/210 表(第2页) (2022年7月)

| C. 相关文件 |                                                                                        |         |
|---------|----------------------------------------------------------------------------------------|---------|
| 类 型*    | 引用文件，必要时，指明相关段落                                                                        | 相关的权利要求 |
| A       | US 2021198222 A1 (SAMSUNG ELECTRONICS CO. LTD.) 2021年7月1日 (2021 - 07 - 01)<br>权利要求1-20 | 1-10    |
| A       | US 6699896 B1 (WYETH CORP.) 2004年3月2日 (2004 - 03 - 02)<br>权利要求1-24                     | 1-10    |
| A       | WO 2021148043 A1 (UNIV. CHINA PHARMA. et al.) 2021年7月29日 (2021 - 07 - 29)<br>权利要求1-10  | 1-10    |

国际检索报告  
关于同族专利的信息

国际申请号  
PCT/CN2024/072679

| 检索报告引用的专利文件 |            |    | 公布日<br>(年/月/日) | 同族专利 |             |    | 公布日<br>(年/月/日) |
|-------------|------------|----|----------------|------|-------------|----|----------------|
| CN          | 116041277  | A  | 2023年5月2日      | 无    |             |    |                |
| CN          | 108292709  | A  | 2018年7月17日     | EP   | 3389104     | A1 | 2018年10月17日    |
|             |            |    |                | EP   | 3389104     | A4 | 2019年7月31日     |
|             |            |    |                | EP   | 3389104     | B1 | 2020年9月16日     |
|             |            |    |                | JPWO | 2017099012  | A1 | 2018年9月20日     |
|             |            |    |                | JP   | 6754774     | B2 | 2020年9月16日     |
|             |            |    |                | WO   | 2017099012  | A1 | 2017年6月15日     |
|             |            |    |                | KR   | 20180091026 | A  | 2018年8月14日     |
|             |            |    |                | US   | 2018375034  | A1 | 2018年12月27日    |
| US          | 2021198222 | A1 | 2021年7月1日      | US   | 11691957    | B2 | 2023年7月4日      |
|             |            |    |                | KR   | 20210084775 | A  | 2021年7月8日      |
| US          | 6699896    | B1 | 2004年3月2日      | US   | 2004147755  | A1 | 2004年7月29日     |
|             |            |    |                | US   | 7141672     | B2 | 2006年11月28日    |
| WO          | 2021148043 | A1 | 2021年7月29日     | 无    |             |    |                |