

一类PRMT5抑制剂及其用途

5 技术领域

本发明涉及药物化合物领域，具体地，本发明提供了一类用于抑制PRMT5的化合物，及其用于药物组合物的用途。

背景技术

10 基因表达的表现遗传调控是蛋白质产生和细胞分化的重要生物学决定因素，在许多人类疾病中起着重要的致病作用。

表观遗传调控涉及遗传物质的可遗传修饰而不改变其核苷酸序列。通常，表观遗传调控由DNA和蛋白质(例如组蛋白)的选择性和可逆修饰(例如甲基化)介导，这些修饰控制染色质转录活性和非活性状态之间的构象转变。这些共价修饰可以由甲基转移酶(例如
15 PRMT5)等酶控制，其中许多与可能导致人类疾病的特定遗传改变有关。PRMT5在增殖性疾病、代谢性疾病和血液疾病等疾病中发挥作用。

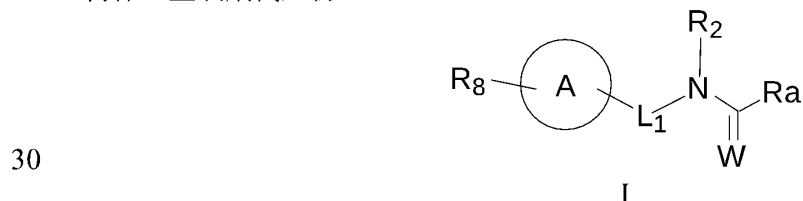
PRMT5是一种已知的细胞必需基因，条件性PRMT5敲除和siRNA敲除研究表明，正常组织中的PRMT5抑制与一系列疾病相关(例如，全血细胞减少症、不孕症、骨骼肌丧失、心脏肥大)。因此，需要新的策略来利用这种代谢脆弱性并优先针对MTAP无效肿瘤中的
20 PRMT5，同时在正常组织中保留PRMT5(MTAPWT)。用MTA协同小分子抑制剂靶向PRMT5可以优先靶向PRMT5的MTA结合状态，富含MTAP无效肿瘤细胞，同时提供优于MTAP完整且MTA水平低的正常细胞的治疗指数。

因此，本领域需要提供新的靶向MTAP无效肿瘤中的PRMT5的小分子化合物。

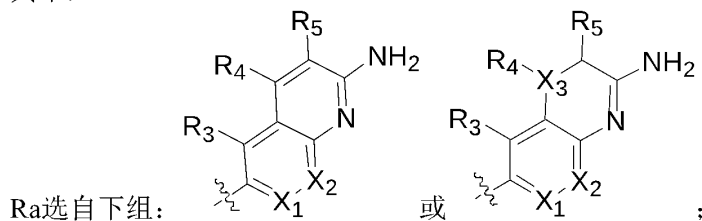
25 发明内容

本发明的目的是提供一类新的靶向MTAP无效肿瘤中的PRMT5的小分子化合物。

本发明的第一方面，提供了一种如下式I所示的化合物，或其药学上可接受的立体异构体、盐或氘代产物：



其中，



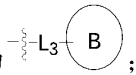
W为O或S;

X₁、X₂各自独立地选自下组: CR、N; X₃为N;

所述的L₁选自下组: 化学键、-O-、-CHR-、-C(R)R-;

- 5 A环选自下组: 取代或未取代的8-12元的稠合二环杂环基(包括碳环或杂环, 优选为五并六环)、取代或未取代的7-10元的稠合二环杂芳基(优选为五并六环);

R₈选自下组: H、卤素、氰基、氨基、硝基、羟基、巯基、醛基、羧基、C₂-C₆炔

基、SF₅、取代或未取代或卤代的C₁-C₆烷基、或R₈为 ;

所述的L₃选自下组: 化学键、-O-、-CHR-、-C(R)R-、羰基、S、-NH-;

- 10 B环选自下组: 取代或未取代的苯环、取代或未取代的5-6元的杂芳环、取代或未取代的C₃-C₆碳环(包括饱和或部分不饱和的情况)、取代或未取代的3-7元的杂环(包括饱和或部分不饱和的情况);

R₂选自下组: R₇、-L₂R₇; 其中, 所述的L₂选自下组: -O-、-CHR-、-C(R)R-、羰基;

- 15 其中R₇选自下组: 氢或无、取代或未取代的C₁-C₆烷基、取代或未取代的C₆₋₁₀的芳环、取代或未取代的5-12元的杂芳环、取代或未取代的C₃-C₁₀碳环(包括饱和或部分不饱和的情况, 包括单环、稠环、螺环或桥环)、取代或未取代的3-10元的杂环(包括饱和或部分不饱和的情况, 包括单环、稠环、螺环或桥环);

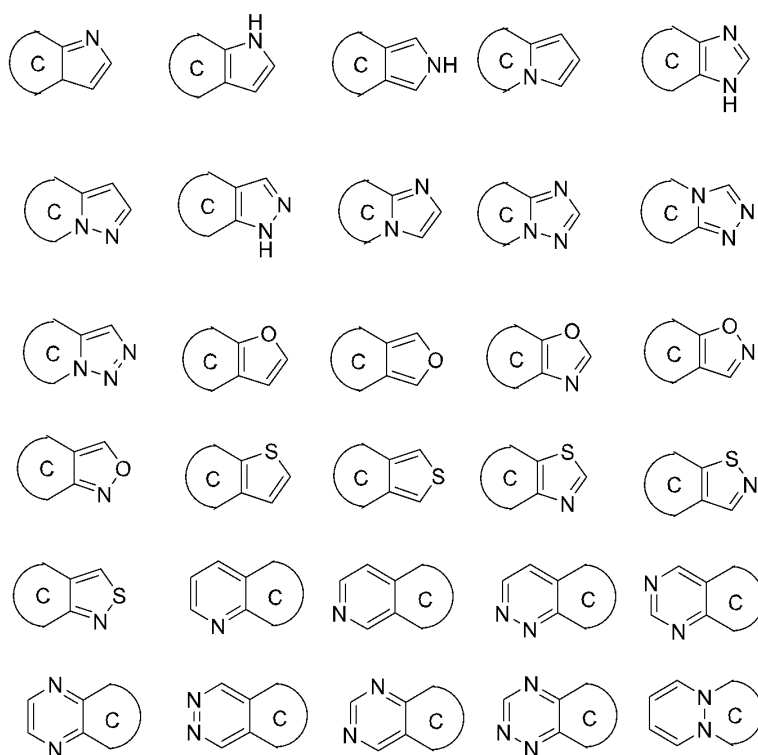
R₃选自下组: H、卤素、氰基、取代或未取代的C₁-C₆烷基;

- 20 R₄和R₅各自独立地选自下组: H、卤素、氰基、取代或未取代的C₁-C₆烷基、取代或未取代的C₁-C₆烷氧基、取代或未取代的C₃-C₆碳环(包括饱和或部分不饱和的情况)、取代或未取代的3-6元的杂环; 或R₄和R₅与相连的环原子共同形成5-12元饱和或不饱和环, 且所述的环可以是取代或未取代的;

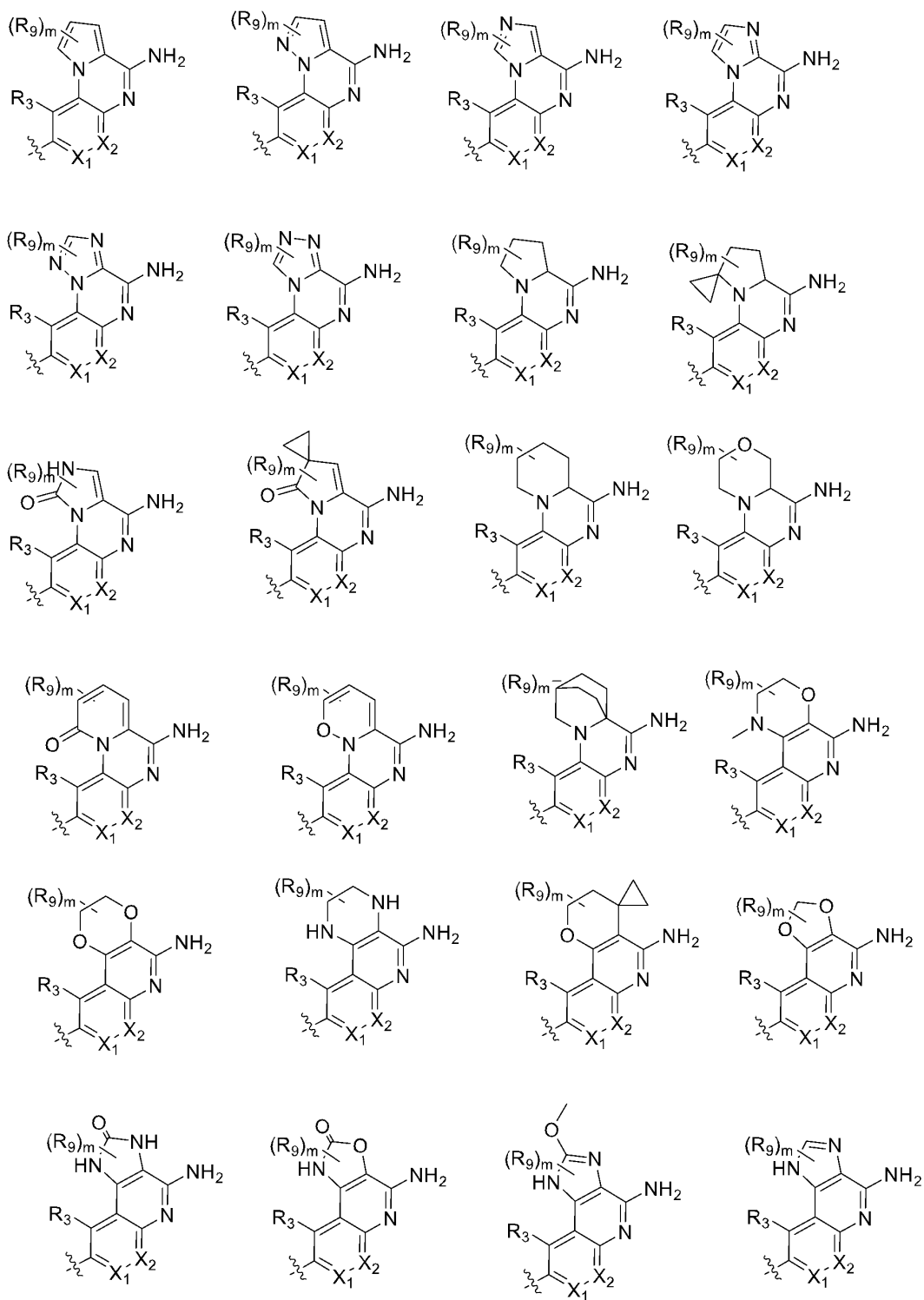
R为H、卤素、取代或未取代的C₁-C₄烷基, 取代或未取代的C₁-C₄烷氧基、取代或未取代C₃-C₆环烷基;

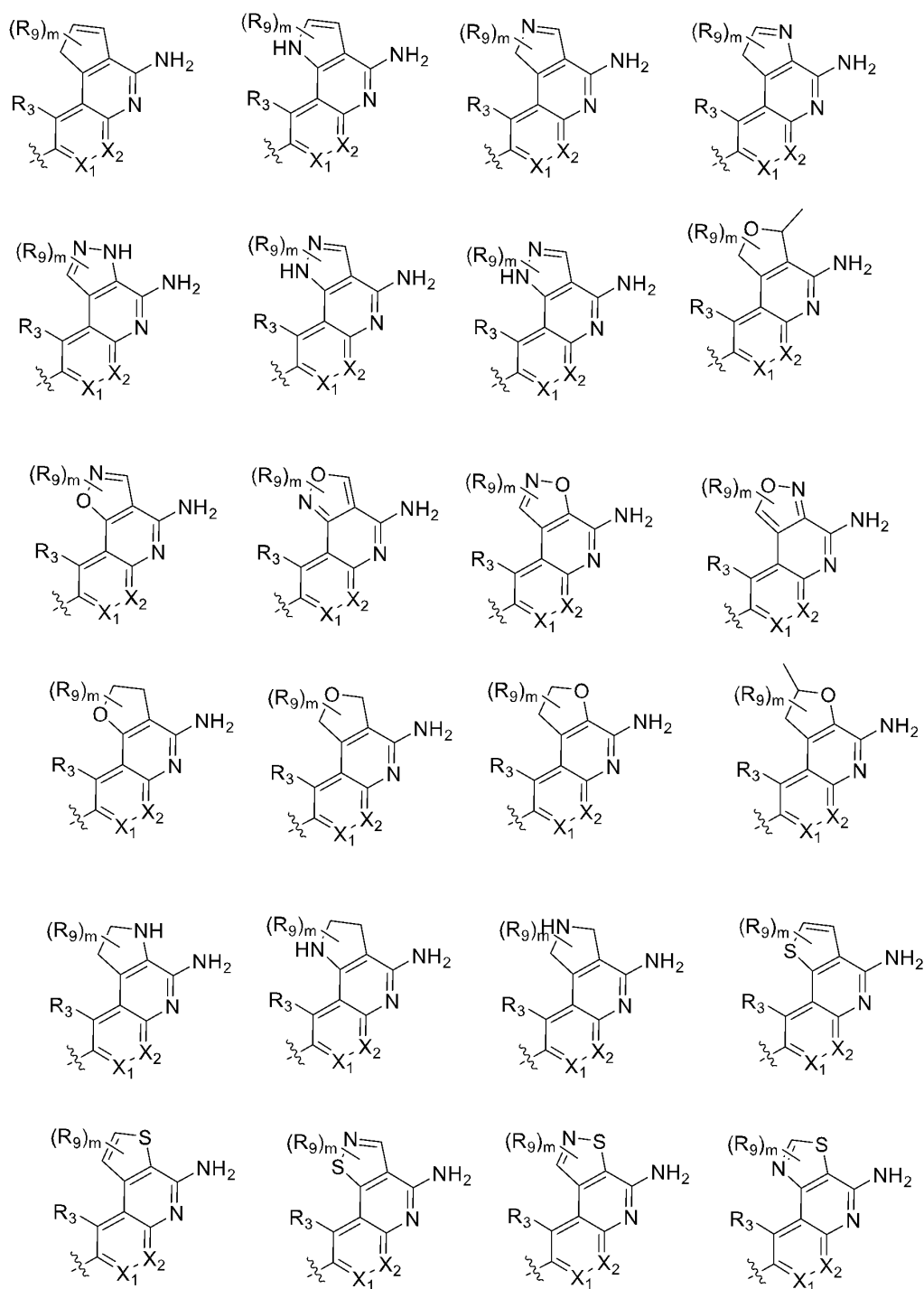
- 25 除非特别说明, 上述各式中, 所述的取代指对应基团上的氢原子被一个或多个选自下组的取代基所取代: 氘、氚、卤素、羟基、羧基、巯基、苄基、C₁-C₁₂烷氧基羰基、C₁-C₆醛基、氨基、C₁-C₆酰胺基、硝基、氰基、未取代或卤代的C₁-C₆烷基、未取代或卤代的C₃-C₈环烷基、C₂-C₁₀烯基、C₁-C₆烷氧基、C₁-C₆烷基-胺基、C₆-C₁₀芳基、五元或六元杂芳基、五元或六元非芳香性杂环基、-O-(C₆-C₁₀芳基)、-O-(五元或六元杂芳基)、C₁-C₁₂烷氨基羰基、未取代或卤代的C₂-C₁₀酰基、磺酰基(-SO₂-OH)、磷酰基(-PO₃-OH)、未取代或卤代的C₁-C₄烷基-S(O)₂-、未取代或卤代C₁-C₄烷基-SO-。
- 30

在另一优选例中, 所述的A环具有选自下组的结构:



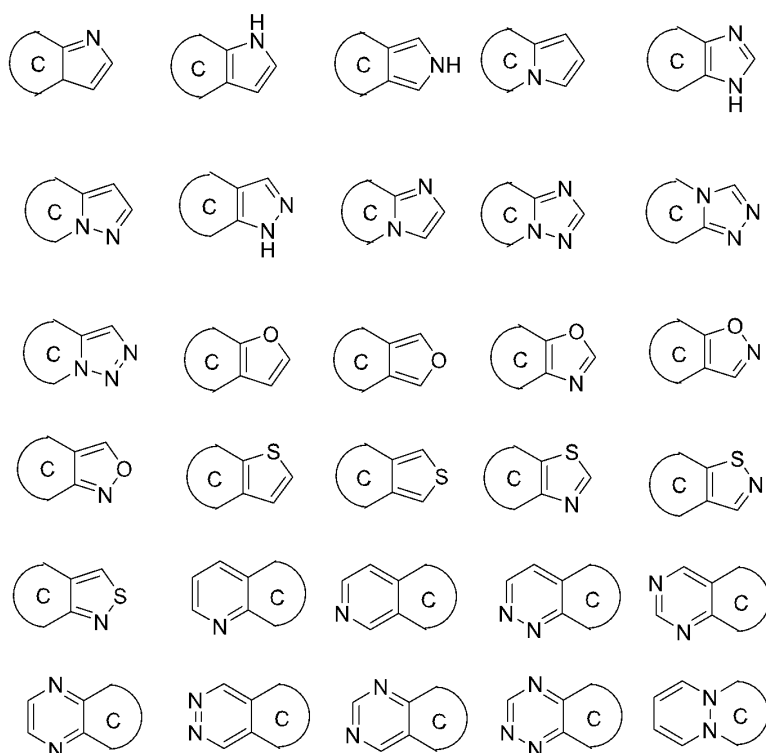
在另一优选例中，所述的Ra选自下组：





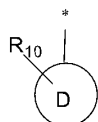
其中, 所述的R₉选自下组: 氦、氖、卤素、羟基、羧基、未取代或卤代的C₁-C₆烷基、未取代或卤代的C₁-C₆烷氧基、未取代或取代的C₁-C₆烷基-OH、-NH(未取代或卤代的C₁-C₆烷基)、-N(未取代或卤代的C₁-C₆烷基)₂; m选自0、1、2或3。

5 在另一优选例中, 所述的L₁为-CH₂-、-CH(CH₃)-; A环选自下组:



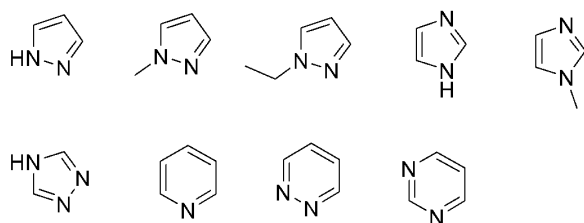
其中，C环选自下组：取代或未取代的苯环、取代或未取代的5-6元的杂芳环、取代或未取代的C₃-C₆碳环(包括饱和或部分不饱和的情况)、取代或未取代的3-6元的杂环(包括饱和或部分不饱和的情况)。

5 在另一优选例中，所述的R₂为邻位取代的5、6元杂芳环，如下式：

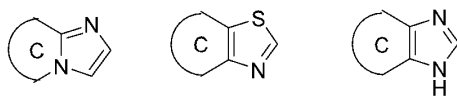


邻位取代基R₁₀为氢、氘、卤素、卤代或未卤代的C₁-C₃烷基，卤代或未卤代的C₁-C₃烷氧基。

10 较佳地，D环选自下组：取代或未取代的苯环、取代或未取代的5-6元的杂芳环，更佳地，D环选自下组：



且A环选自下组：取代或未取代的8-12元的稠合二环杂环基(包括碳环或杂环，优选为五并六环)、取代或未取代的7-10元的稠合二环杂芳基(优选为五并六环)。较佳的，A环选自下组：



15

其中，C环选自下组：取代或未取代的苯环、取代或未取代的5-6元的杂芳环；所

述的 R_8 为 CF_3 。

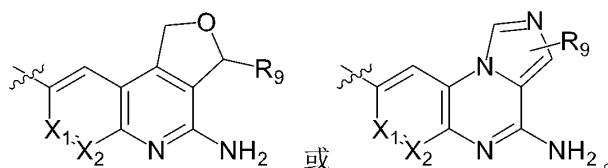
在另一优选例中,所述的 R_2 选自下组: R_7 、 $-L_2R_7$;其中,所述的 L_2 选自下组: $-O-$ 、 $-CHR-$ 、羰基、 S 、 $-NH-$;其中 R_7 选自下组:取代或未取代的 C_1-C_6 烷基、取代或未取代的 C_6-10 的芳环、取代或未取代的5-12元的杂芳环。

- 5 在另一优选例中,所述的 R_7 选自下组:取代或未取代的 C_1-C_6 烷基、取代或未取代的苯环、取代或未取代的5-7元的杂芳环。

在另一优选例中, R_2 选自下组: R_7 、 $-(CHR)R_7$;其中 R_7 选自下组:取代或未取代的 C_6-10 的芳环、取代或未取代的5-12元的杂芳环。

- 10 在另一优选例中,所述的 R_2 为取代或未取代的5-7元杂芳环;且所述的A环选自下组:、取代或未取代的7-10元的稠合二环杂芳基;所述的 R_8 为 CF_3 。

在另一优选例中,所述的 R_a 具有如下式所示的结构:



- 15 本发明的第二方面,提供了一种药物组合物,所述的药物组合物含有治疗有效量的如前述任一方面所述的化合物、其可药用的盐、外消旋体、光学异构体、立体异构体或互变异构体中的一种或多种,以及一种或多种可药用的载体、赋形剂、佐剂、辅料和/或稀释剂。

- 20 本发明的第三方面,提供了一种如前述任一方面所述的化合物、其外消旋体、光学异构体或可药用盐在制备治疗或预防与PRMT5的基因水平异常或表达异常(如对应的核酸突变、缺失,或所述的甲基转移酶产生异位或融合或过高表达)相关的疾病的药物中的用途。

在另一优选例中,所述的疾病选自下组:所述疾病或病症卵巢癌、肺癌、淋巴瘤、胶质母细胞瘤、结肠癌、黑色素瘤、胃癌、胰腺癌或膀胱癌。

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

具体实施方式

- 30 本发明人通过广泛而深入的研究,首次意外地发现一类具有PRMT5调节作用的化合物。在此基础上完成了本发明。

术语

在本发明中,所述卤素为F、Cl、Br或I。

- 35 在本发明中,除非特别指出,所用术语具有本领域技术人员公知的一般含义。本发明中,如果没有特别指明,所有化学式意在涵盖可能的任何光学或几何异构体(例如R型、S型或外消旋体,或者烯烃的顺反异构体等)。

在本发明中,术语“ C_1-C_6 烷基”是指具有1至6个碳原子的直链或支链烷基,非限制性地包括甲基、乙基、丙基、异丙基、丁基、异丁基、仲丁基、叔丁基、戊基和己

基等；优选乙基、丙基、异丙基、丁基、异丁基、仲丁基和叔丁基。

在本发明中，术语“C1-C6烷氧基”是指具有1至6个碳原子的直链或支链烷氧基，非限制性地包括甲氧基、乙氧基、丙氧基、异丙氧基和丁氧基等。

5 在本发明中，术语“C2-C6烯基”是指具有2至6个碳原子的含有一个双键的直链或支链烯基，非限制性地包括乙烯基、丙烯基、丁烯基、异丁烯基、戊烯基和己烯基等。

在本发明中，术语“C2-C6炔基”是指具有2至6个碳原子的含有一个三键的直链或支链炔基，非限制性地包括乙炔基、丙炔基、丁炔基、异丁炔基、戊炔基和己炔基等。

10 在本发明中，术语“C3-C10环烷基”是指在环上具有3至10个碳原子的环状烷基，非限制性地包括环丙基、环丁基、环戊基、环己基、环庚基、环辛基和环癸基等。术语“C3-C8环烷基”、“C3-C7环烷基”、和“C3-C6环烷基”具有类似的含义。

在本发明中，术语“C3-C10环烯基”是指在环上具有3至10个碳原子的环状烯基，非限制性地包括环丙烯基、环丁烯基、环戊烯基、环己烯基、环庚烯基、环辛烯基和环癸烯基等。术语“C3-C7环烯基”具有类似的含义。

15 在本发明中，术语“C1-C12烷氧羰基”是指在烷基链上具有1至12个碳原子的烷氧羰基，非限制性地包括甲氧羰基、乙氧羰基、丙氧羰基、异丙氧羰基、叔丁氧羰基、苄氧羰基等。

在本发明中，术语“C1-C12烷氨基羰基”是指在烷基链上具有1至12个碳原子的烷氨基羰基，非限制性地包括甲氨基羰基、乙氨基羰基、丙氨基羰基、异丙氨基羰基、叔丁氨基羰基、苄氨基羰基、二甲氨基羰基等。

20 在本发明中，术语“芳环”或“芳基”具有相同的含义，优选地“芳基”为“C6-C12芳基”或“C6-C10芳基”。术语“C6-C12芳基”是指在环上不含杂原子的具有6至12个碳原子的芳香族环基，如苯基、萘基等。术语“C6-C10芳基”具有类似的含义。

25 在本发明中，术语“芳香杂环”或“杂芳基”具有相同的含义，指包含一个或多个杂原子的杂芳族基团。这里所指的杂原子包括氧、硫和氮。例如呋喃基、噻吩基、吡啶基、吡唑基、吡咯基、N-烷基吡咯基、嘧啶基、吡嗪基、咪唑基、四唑基等。所述杂芳基环可以稠合于芳基、杂环基或环烷基环上，其中与母体结构连接在一起的环为杂芳基环。杂芳基可以是任选取代的或未取代的。

30 在本发明中，术语“3-12元杂环基”是指在环上含有1~3个选自氧、硫和氮中的杂原子的饱和或不饱和的3-12元环基，例如二氧杂环戊基等。术语“3-7元杂环基”具有类似的含义。

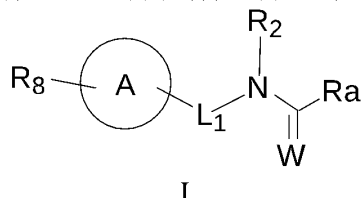
35 在本发明中，术语“取代”指特定的基团上的一个或多个氢原子被特定的取代基所取代。特定的取代基为在前文中相应描述的取代基，或各实施例中所出现的取代基。除非特别说明，某个取代的基团可以在该基团的任何可取代的位点上具有一个选自特定组的取代基，所述的取代基在各个位置上可以是相同或不同的。环状取代基，例如杂环烷基，可以与另一个环相连，例如环烷基，从而形成螺二环系，例如，两个环具有一个共用碳原子。本领域技术人员应理解，本发明所预期的取代基的组合是那些稳定的或化学上可实现的组合。所述取代基例如(但不限于)：C1-8烷基、C2-8烯基、C2-8炔基、C3-8环烷基、3-至12-元杂环基，芳基、杂芳基、卤素、羟基、羧基(-COOH)、C1-8醛基、C2-10酰基、C2-10酯基、C1-C12烷氧羰基、氨基、烷氧基、C1-10磺酰基等。

40 当采用例如“C1-8”或类似表述时，指该基团可以具有1个、2个、3个、4个、5个、6个、7个、或8个碳原子。

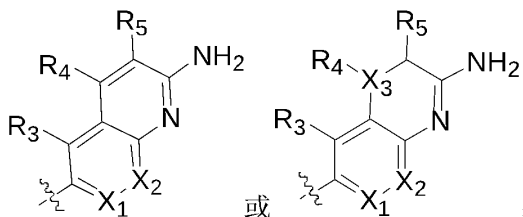
当采用例如“3-12元”或类似表述时，指该基团可以具有3个、4个、5个、6个、7个、8个、9个、10个、11个、或12个作为环原子的碳原子或杂原子。

PRMT5调节剂化合物

5 本发明中提供了一类具有PRMT5调节活性的化合物：



其中，



Ra选自下组：

W为O或S；

X₁、X₂各自独立地选自下组：CR、N；X₃为N；

所述的L₁选自下组：化学键、-O-、-CHR-、-C(R)R-；

A环选自下组：取代或未取代的8-12元的稠合二环杂环基(包括碳环或杂环，优选为五并六环)、取代或未取代的7-10元的稠合二环杂芳基(优选为五并六环)；

15 R₈选自下组：H、卤素、氰基、氨基、硝基、羟基、巯基、醛基、羧基、C₂-C₆炔

基、SF₅、取代或未取代或卤代的C₁-C₆烷基、或R₈为 ；

所述的L₃选自下组：化学键、-O-、-CHR-、-C(R)R-、羰基、S、-NH-；

B环选自下组：取代或未取代的苯环、取代或未取代的5-6元的杂芳环、取代或未取代的C₃-C₆碳环(包括饱和或部分不饱和的情况)、取代或未取代的3-7元的杂环(包括饱和或部分不饱和的情况)；

20 R₂选自下组：R₇、-L₂R₇；其中，所述的L₂选自下组：-O-、-CHR-、-C(R)R-、羰基；

其中R₇选自下组：氢或无、取代或未取代的C₁-C₆烷基、取代或未取代的C₆₋₁₀的芳环、取代或未取代的5-12元的杂芳环、取代或未取代的C₃-C₁₀碳环(包括饱和或部分不饱和的情况，包括单环、稠环、螺环或桥环)、取代或未取代的3-10元的杂环(包括饱和或部分不饱和的情况，包括单环、稠环、螺环或桥环)；

25 R₃选自下组：H、卤素、氰基、取代或未取代的C₁-C₆烷基；

R₄和R₅各自独立地选自下组：H、卤素、氰基、取代或未取代的C₁-C₆烷基、取代或未取代的C₁-C₆烷氧基、取代或未取代的C₃-C₆碳环(包括饱和或部分不饱和的情况)、取代或未取代的3-6元的杂环；或R₄和R₅与相连的环原子共同形成5-12元饱和或不饱和环，且所述的环可以是取代或未取代的；

30 R为H、卤素、取代或未取代的C₁-C₄烷基，取代或未取代的C₁-C₄烷氧基、取代或未取代C₃-C₆环烷基；

除非特别说明，上述各式中，所述的取代指对应基团上的氢原子被一个或多个选

- 自下组的取代基所取代：氘、氚、卤素、羟基、羧基、巯基、苄基、C₁-C₁₂烷氧基羰基、C₁-C₆醛基、氨基、C₁-C₆酰胺基、硝基、氰基、未取代或卤代的C₁-C₆烷基、未取代或卤代的C₃-C₈环烷基、C₂-C₁₀烯基、C₁-C₆烷氧基、C₁-C₆烷基-胺基、C₆-C₁₀芳基、五元或六元杂芳基、五元或六元非芳香性杂环基、-O-(C₆-C₁₀芳基)、-O-(五元或六元杂芳基)、C₁-C₁₂烷氨基羰基、未取代或卤代的C₂-C₁₀酰基、磺酰基(-SO₂-OH)、磷酰基(-PO₃-OH)、未取代或卤代的C₁-C₄烷基-S(O)₂-、未取代或卤代C₁-C₄烷基-SO-。

药物组合物和施用方法

- 由于本发明化合物具有优异的甲基转移酶抑制的活性，因此本发明化合物及其各种晶型，药学上可接受的无机或有机盐，水合物或溶剂合物，以及含有本发明化合物为主要活性成分的药物组合物可用于治疗、预防以及缓解由于甲基转移酶(例如PRMT5)的活性或表达量异常引起的相关疾病。

- 本发明的药物组合物包含安全有效量范围内的本发明化合物或其药理上可接受的盐及药理上可以接受的赋形剂或载体。其中“安全有效量”指的是：化合物的量足以明显改善病情，而不至于产生严重的副作用。通常，药物组合物含有1-2000mg本发明化合物/剂，更佳地，含有5-200mg本发明化合物/剂。较佳地，所述的“一剂”为一个胶囊或药片。

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

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

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

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

用于口服给药的液体剂型包括药学上可接受的乳液、溶液、悬浮液、糖浆或酞剂。

除了活性化合物外，液体剂型可包含本领域中常规采用的惰性稀释剂，如水或其它溶剂，增溶剂和乳化剂，例知，乙醇、异丙醇、碳酸乙酯、乙酸乙酯、丙二醇、1,3-丁二醇、二甲基甲酰胺以及油，特别是棉籽油、花生油、玉米胚油、橄榄油、蓖麻油和芝麻油或这些物质的混合物等。

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

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

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

用于局部给药的本发明化合物的剂型包括软膏剂、散剂、贴剂、喷射剂和吸入剂。活性成分在无菌条件下与生理上可接受的载体及任何防腐剂、缓冲剂，或必要时可能需要的推进剂一起混合。

15 本发明化合物可以单独给药，或者与其他药学上可接受的化合物联合给药。在一些优选的实施方式中，本发明的化合物可以与其他小分子化合物一同形成PROTAC，或者与其他大分子化合物例如单抗共同形成ADC施用。

20 使用药物组合物时，是将安全有效量的本发明化合物适用于需要治疗的哺乳动物(如人)，其中施用剂量为药学上认为的有效给药剂量，对于60kg体重的人而言，日给药剂量通常为1~2000mg，优选5~500mg。当然，具体剂量还应考虑给药途径、病人健康状况等因素，这些都是熟练医师技能范围内的。

25 下面结合具体实施例，进一步阐述本发明。应理解，这些实施例仅用于说明本发明而并不用于限制本发明的范围。下列实施例中未注明具体条件的实验方法，通常按照常规条件，或按照制造厂商所建议的条件。除非另外说明，否则百分比和份数按重量计算。

各个缩写的定义如下所示：

Xantphos	4,5-双二苯基膦-9,9-二甲基氧杂蒽
NBS	N-溴代琥珀酰亚胺
Pd(dppf)Cl ₂	1,1'-双二苯基膦二茂铁二氯化钯
Pd ₂ (dba) ₃	三二亚苄基丙酮二钯
Pd(dba) ₂	双(二亚苄基丙酮)钯
BINAP	1,1'-联萘-2,2'-双二苯膦
X-Phos	2-二环己基膦-2',4',6'-三异丙基联苯
tBuXPhos	2-二叔丁基膦基-2',4',6'-三异丙基联苯
tBuXPhos Pd G3	甲烷磺酸(2-二叔丁基膦基-2',4',6'-三异丙基-1,1'-联苯基)(2'-氨基-1,1'-联苯-2-基)钯(II)
EDCI	1-(3-二甲氨基丙基)-3-乙基碳二亚胺盐酸盐
HOBt	1-羟基苯并三唑
LDA	二异丙基氨基锂
HATU	2-(7-氮杂苯并三氮唑)-N,N,N',N'-四甲基脲六氟磷酸酯

原料可以通过商业途径获得或者通过本领域已经已知或者公开的方法制备获得。

中间体和化合物的纯化采用正相或反向色谱法或者重结晶等常规的化学实验操作进行。正相色谱法为预装填硅胶色谱柱或者制备薄层色谱。硅胶色谱柱主要为玻璃柱或者快速制备色谱仪。正相色谱法的流动相从石油醚/乙酸乙酯，二氯甲烷/甲醇或者其它合适的溶剂中选择及配比进行洗脱。反相制备液相色谱采用 C18 柱，用制备型液相色谱仪或者快速制备色谱仪进行，214nm 和 254nm 或者制备型液相色谱-质谱联用仪器检测，以含 0.1%盐酸的水/乙腈、水/乙腈、含 0.1%碳酸氢铵的水/乙腈、含 0.1%甲酸的水/乙腈、含 0.1%氨水/乙腈、含 0.1%三氟乙酸的水/乙腈或者其它合适的溶剂体系作为流动相进行梯度洗脱。

中间体和化合物结构表征采用核磁共振(NMR)和质谱(LCMS)的方法。核磁共振所用到的核磁共振波谱仪为 Bruker Ascend 400 或者 Varian 400 或者 ZKNJ BIXI-1 300MHz 或者 Bruker Avance III 400 MHz 或者 Bruker AVANCE Neo 400 MHz。所用溶剂为氘代二甲亚砜、氘代氯仿、氘代甲醇或者其它标注的氘代溶剂。光谱数据以模式报告：化学位移 δ (峰裂数, 耦合常数 J(Hz), 氢数目)。四甲基硅烷作为化学位移的内标, 并把它的化学位移定为零 (δ , 0 ppm)。一些缩写的含义为: s(单峰), d(双重峰), t(三重峰), q(四重峰), m(多重峰), br(宽峰)。

中间体和化合物结构表征中液相色谱-质谱联用(LCMS)代表性的方法如下:

方法一: 在偶联有 6120 单四级杆质谱仪的 Agilent LC1260 系统上进行

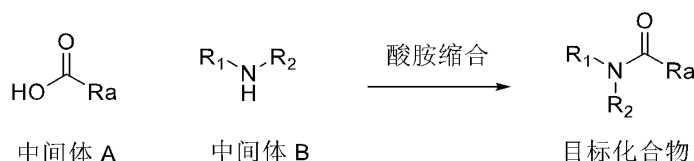
柱: Waters CORTECS C-18, 2.7 μ m, 4.6*30 mm。溶剂 A: 0.05%甲酸水溶液, 溶剂 B: 0.05% 甲酸的乙腈溶液, 历时一分钟 5%乙腈到 95%乙腈, 保持一分钟, 共 2.5 分钟; 流速: 1.8 mL/min; 柱温 40 $^{\circ}$ C。

柱: XSelect CSH C18, 3.5 μ m, 4.6*50 mm。溶剂 A: 0.05%氨水溶液, 溶剂 B: 0.05%氨的乙腈溶液, 历时一分钟内 5%乙腈到 95%乙腈, 保持一分钟, 共 2.5 分钟; 流速: 1.8 mL/min; 柱温 40 $^{\circ}$ C。

方法二: 在偶联有四极杆质谱仪的 Agilent LC/MSD 1200 系统上进行。

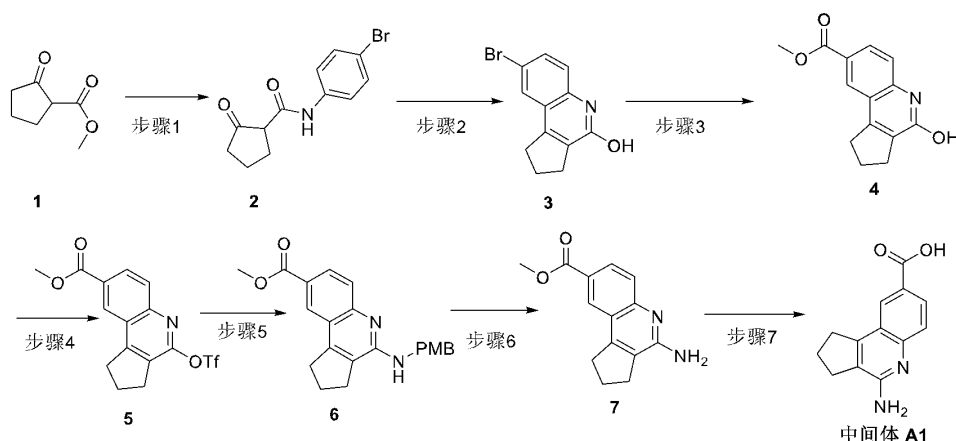
柱: ODS2000 (50 $\times$ 4.6 mm, 5 μ m) (ES (+) 或 (-) 电离模式), 温度 30 $^{\circ}$ C; 流速 1.5 mL/min。

实施例合成通用方法:



通用方法: 中间体A1的合成

合成路线:



步骤 1: N-(4-溴苯基)-2-氧代环戊烷-1-甲酰胺(2)

2-氧代环戊烷-1-羧酸甲酯(50g, 0.35mol)和 4-溴苯胺(121g, 0.70mol)在甲苯(300mL)中的混合物在 110°C 搅拌 12 小时。然后将混合物加入 2 M HCl 水溶液(100 mL)并用水(300 mL)稀释。反应用乙酸乙酯(300mL×3)萃取。有机层用盐水(200mL×3)洗涤, 无水硫酸钠干燥。然后过滤有机相并减压浓缩。残余物通过硅胶色谱法纯化, 用 EA/PE 溶液在 20 分钟内从 0%洗脱到 30%, 得到 N-(4-溴苯基)-2-氧代环戊烷-1-甲酰胺(25g, 产率 21%), 为浅黄色坚硬的固体。LC-MS: Rt = 1.257 min, (ESI) m/z. $[M+H]^+$ 283.0, $[M+2+H]^+$ 285.0; $C_{12}H_{12}BrNO_2$

步骤 2: 8-溴-2,3-二氢-1H-环戊二烯[c]喹啉-4-醇(3)

N-(4-溴苯基)-2-氧代环戊烷-1-甲酰胺(25.0g, 0.088mol)在浓硫酸(100mL)中的混合物在 100°C 搅拌 12 小时。将混合物倒入冰水(500mL)中。添加 $NaHCO_3$ 直到 pH 7~8。过滤形成的沉淀物并用一些冷甲醇(50mL)洗涤。过滤滤液。将合并的固体干燥并从乙醇(20mL)中重结晶以获得浅棕色固体状的 8-溴-2,3-二氢-1H-环戊二烯[c]喹啉-4-醇(6g, 26% 产率)。LC-MS: Rt = 1.299 min, (ESI) m/z. $[M+H]^+$ 264.0; $[M+2+H]^+$ 266.0, $C_{12}H_{10}BrNO$

步骤 3: 4-羟基-2,3-二氢-1H-环戊二烯[c]喹啉-8-羧酸甲酯(4)

8-溴-2,3-二氢-1H-环戊二烯[c]喹啉-4-醇(6.0 g, 23 mmol), Et₃N (6.9 g, 68 mmol) 和 Pd(dppf)Cl₂ (3.3 g, 4.4 mmol)在 MeOH(100mL)中的 4.40mmol)在 100°C 和 CO 气氛下搅拌 12 小时。减压浓缩混合物。残余物通过硅胶色谱法纯化, 在 20 分钟内用 MeOH 的 DCM 溶液从 0%洗脱到 10%, 得到 4-羟基-2,3-二氢-1H-环戊二烯[c]喹啉-8-甲酸甲酯(3 g, 54%产率)为棕色固体。LC-MS: Rt = 1.183 min, (ESI) m/z. $[M+H]^+$ 244.09, $C_{14}H_{13}NO_3$

步骤 4: 4-(((三氟甲基)磺酰基)氧基)-2,3-二氢-1H-环戊二烯[c]喹啉-8-羧酸甲酯(5)

向 4-羟基-2,3-二氢-1H-环戊二烯并[c]喹啉-8-羧酸甲酯(9.3 g, 0.038 mol)和吡啶(9.1 g, 0.11 mmol)在 DCM (200 mL) 中的溶液中加入三氟甲磺酸酐(21.6 g, 0.076 mol)在 0 °C。然后将混合物在 20°C 搅拌 12 小时。用 $NaHCO_3(aq.)$ (200 mL) 淬灭反应, 然后用 DCM (200 mL × 3) 萃取。有机溶液用盐水(200mL)洗涤。有机相用 Na_2SO_4 干燥并过滤。减压浓缩滤液。残余物通过硅胶色谱法纯化, 用 EA 的 PE 溶液在 20 分钟内从 0% 洗脱到 30%, 得到甲基 4-(((三氟甲基)磺酰基)氧基)-2,3-二氢-1H-环戊[c]喹啉- 8-羧酸盐(11.0 g, 77%产率), 为黄色固体。¹H NMR (400 MHz, $CDCl_3$)

δ 8.57 (d, $J = 2.0$ Hz, 1H), 8.30 (dd, $J = 8.8, 2.0$ Hz, 1H), 8.08 (d, $J = 8.8$ Hz, 1H), 4.01 (s, 3H), 3.43 (t, $J = 8.0$ Hz, 2H), 3.21 (t, $J = 8.0$ Hz, 2H), 2.55 – 2.32 (m, 2H). LC-MS: Rt = 1.544 min, (ESI) m/z. 376.1 $[M+H]^+$. $C_{15}H_{12}F_3NO_5S$ 375.04.

步骤 5: 4-((4-甲氧基苄基)氨基)-2,3-二氢-1H-环戊二烯[c]喹啉-8-羧酸甲酯(6)

- 5 向搅拌的 4-(((三氟甲基)磺酰基)氧基)-2,3-二氢-1H-环戊[c]喹啉-8-甲酸甲酯(11.0 g, 29 mmol)在二恶烷(100 mL)中的溶液中加入 20℃ 下的 CS_2CO_3 (28.6 g, 88 mmol)、 $Pd_2(dba)_3$ (2.7 g, 2.93 mmol)、Xantphos (3.4 g, 5.86 mmol)和 $PMBNH_2$ (6.0 g, 0.044 mmol)。将反应混合物在 N_2 气氛下在 110℃ 搅拌 12 小时。过滤混合物，减压浓缩滤液。将残余物通过硅胶色谱法纯化，用 MeOH 的 DCM 溶液在 20 分钟内从 0% 洗脱
- 10 到 5%，得到甲基 4-((4-甲氧基苄基)氨基)-2,3-二氢-1H-环戊二[c]喹啉-8-羧酸盐(8.1 g, 76% 收率)，为黄色固体。 1H NMR (400 MHz, $CDCl_3$) δ 8.33 (d, $J = 2.0$ Hz, 1H), 8.11 (dd, $J = 8.8, 2.0$ Hz, 1H), 7.79 (d, $J = 8.8$ Hz, 1H), 7.36 (d, $J = 8.8$ Hz, 2H), 6.89 (d, $J = 8.8$ Hz, 2H), 4.79 (s, 2H), 3.95 (s, 3H), 3.80 (s, 3H), 3.24 (t, $J = 8.0$ Hz, 2H), 2.80 (t, $J = 8.0$ Hz, 2H), 2.36 – 2.19 (m, 2H). LC-MS: Rt = 1.036 min, (ESI) m/z. 363.1 $[M+H]^+$.
- 15 $C_{22}H_{22}N_2O_3$ 362.16.

步骤 6: 4-氨基-2,3-二氢-1H-环戊二烯[c]喹啉-8-羧酸甲酯(7)

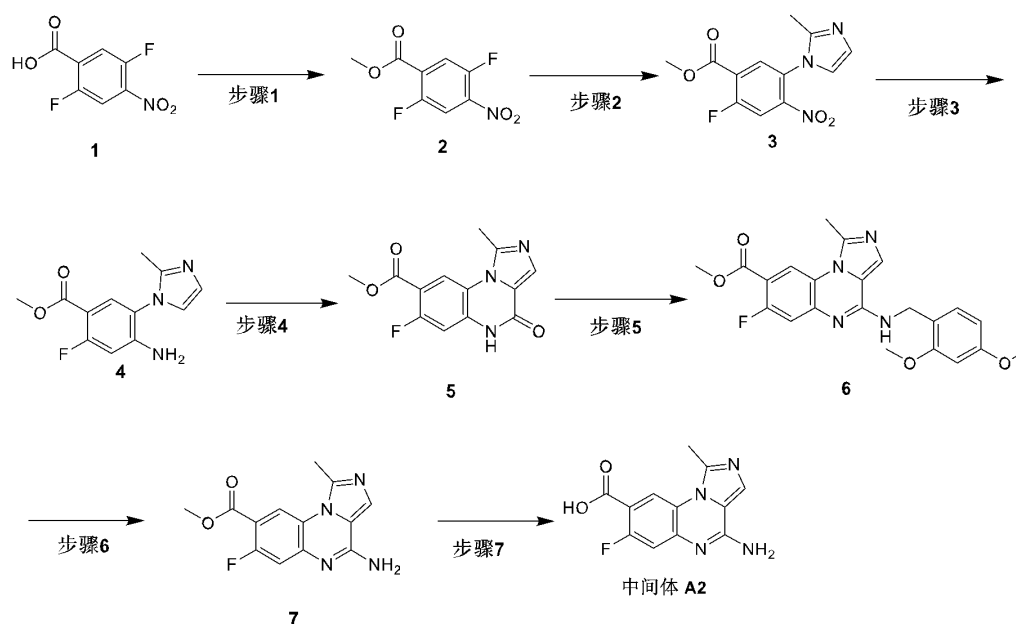
- 将 4-((4-甲氧基苄基)氨基)-2,3-二氢-1H-环戊二[c]喹啉-8-甲酸甲酯(8.1 g, 20 mmol)在 CF_3COOH (50 mL) 中的溶液在 70℃ 下搅拌 12 小时。然后除去溶剂，并将残余物溶解在 DCM(200 mL)中。有机相用 $NaHCO_3$ (aq.) (300 mL) 洗涤并用
- 20 Na_2SO_4 干燥。然后过滤混合物，减压浓缩滤液。将残余物通过硅胶色谱法纯化，用 MeOH 的 DCM 溶液在 20 分钟内从 0% 洗脱到 5%，得到 4-氨基-2,3-二氢-1H-环戊二烯[c]喹啉-8-甲酸甲酯(4.6 g, 85 % 产率)为黄色固体。LC-MS: Rt = 0.921 min, (ESI) m/z. 243.1 $[M+H]^+$. $C_{14}H_{14}N_2O$ 242.11.

步骤 7: 4-氨基-2,3-二氢-1H-环戊二烯[c]喹啉-8-羧酸(中间体 A1)

- 25 将 4-氨基-2,3-二氢-1H-环戊二烯并[c]喹啉-8-羧酸甲酯(0.60 g, 2.31 mmol)在 HCl (4 mol/L 在 H_2O 中) (20 mL)中的溶液在 95℃ 搅拌 12 小时。然后除去溶剂，残余物为 4-氨基-2,3-二氢-1H-环戊[c]喹啉-8-羧酸(500 mg, 88% 收率)，为白色固体，用于下一步一步无需进一步纯化。 1H NMR (400 MHz, $DMSO-d_6$) δ 8.65 (s, 2H), 8.31 (s, 1H), 8.22 (d, $J = 8.0$ Hz, 1H), 7.83 (d, $J = 8.0$ Hz, 2H), 3.32 (t, $J = 8.0$ Hz, 2H), 2.95 (t, $J = 8.0$
- 30 Hz, 2H), 2.34 – 2.20 (m, 2H). LC-MS: Rt = 0.763 min, (ESI) m/z. 229.1 $[M+H]^+$. $C_{13}H_{12}N_2O_2$ 228.09.

通用方法：中间体 A2 的合成

合成路线：



步骤 1: 2,5-二氟-4-硝基苯甲酸甲酯 (2)

将 2,5-二氟-4-硝基苯甲酸(1) (50g, 246.18 毫摩尔, 1 当量)溶解在甲醇中 (500 毫升), 再在 0 摄氏度下加入二氯亚砷(43.93 克, 369.28 毫摩尔, 26.79 毫升, 1.5 当量)。反应液在 40 摄氏度下反应 16 小时。LCMS 显示反应完全。反应液减压浓缩至干。加入 300 毫升的水稀释后用 1 升乙酸乙酯萃取三次。有机相用饱和食盐水(400 毫升)洗涤, 用无水硫酸镁干燥, 过滤滤液减压浓缩至干。粗品在 25 摄氏度下用石油醚打浆 60 分钟得到白色固体 2,5-二氟-4-硝基苯甲酸甲酯(2) (103 克, 474.38 毫摩尔, 96.35% 收率)。HNMR: ES23714-64-P1A, ¹H NMR (400 MHz, CHLOROFORM-d) δ ppm 7.89 (td, J=9.51, 5.63 Hz, 2 H) 4.00 (s, 3 H)。¹⁹F NMR (376 MHz, CHLOROFORM-d) δ ppm -110.27 (s, 1 F) -121.56 (m, 1 F)

步骤 2: 2-氟-5-(2-甲基-1H-咪唑-1-基)-4-硝基苯甲酸甲酯 (3)

将 2,5-二氟-4-硝基苯甲酸甲酯 (2) (80 克, 368.45 毫摩尔, 1 当量), 2-甲基-1H-咪唑(36.30 克, 442.14 毫摩尔, 1.2 当量) 溶解在二甲基亚砷中 (1.2 升)。反应液在 50 摄氏度下反应 16 小时。LCMS 显示反应完全。反应液中加入 4 升的水稀释后用乙酸乙酯 4.5L 萃取。有机相用饱和食盐水(3 升)洗涤, 用无水硫酸镁干燥, 过滤滤液减压浓缩至干。粗品用甲基叔丁基醚在 25 摄氏度下打浆 60 分钟 (25.5 克)。(2)。母液经柱层析色谱纯化(二氧化硅, 50%四氢呋喃在石油醚中)得到黄色液体再经甲基叔丁基醚在 25 摄氏度下打浆 60 分钟得到黄色固体 (8.23 克)。黄色固体 2-氟-5-(2-甲基-1H-咪唑-1-基)-4-硝基苯甲酸甲酯 (3) (25.5 克, 91.32 毫摩尔, 24.79% 收率) 2,5-二氟-4-硝基苯甲酸甲酯 (2)(原料回收) (20.34 克, 93.68 毫摩尔, 25.43% 收率)。黄色固体 2-氟-5-(2-甲基-1H-咪唑-1-基)-4-硝基苯甲酸甲酯 (3) (8.2 克, 29.07 毫摩尔, 7.89% 收率, 99% 纯度) HNMR: ES23714-67-P1A1, ¹H NMR (400 MHz, DMSO-d₆) δ ppm 8.39 (d, J=9.90 Hz, 1 H) 8.08 - 8.20 (m, 1 H) 7.23 (d, J=1.32 Hz, 1 H) 6.92 (s, 1 H) 3.91 (s, 3 H) 2.12 (s, 3 H)。¹⁹F NMR (376 MHz, DMSO-d₆) δ ppm -105.45 (br s, 1 F)

步骤 3: 4-氨基-2-氟-5-(2-甲基-1H-咪唑-1-基)苯甲酸甲酯 (4)

将 2-氟-5-(2-甲基-1H-咪唑-1-基)-4-硝基苯甲酸甲酯 (3) (13.9 克, 49.78 毫摩尔, 1 当量) 溶解在四氢呋喃中 (300 毫升), 在氢气氛围下加入氢氧化钡碳(2.8 克, 49.78 毫摩尔, 20% 纯度, 1 当量)。反应体系用氢气置换 3 次。反应液在氢气 (1 当量) (50 psi) 氛围下加热到 50 摄氏度反应 32 小时。LCMS 显示反应完全。反应液在硅藻土上过滤, 滤饼用 300 毫升乙酸乙酯洗四遍。滤液在减压下浓缩至干, 得到灰色固体。粗品直接用于投下一步。4-氨基-2-氟-5-(2-甲基-1H-咪唑-1-基)苯甲酸甲酯 (4) (12 克, 48.15 毫摩尔, 96.72% 收率)。¹H NMR (400 MHz, DMSO-d₆) Shift 7.46 (d, J=7.63 Hz, 1H), 7.07 (d, J=1.38 Hz, 1H), 6.93 (d, J=1.25 Hz, 1H), 6.59 (d, J=13.51 Hz, 1H), 6.15 (br s, 2H), 3.68-3.77 (m, 3H), 2.01-2.12 (m, 3H)。¹⁹F NMR (376 MHz, DMSO-d₆) Shift -109.31--108.47 (m, 1F)。

步骤 4: 7-氟-1-甲基-4-氧-4,5-二氢咪唑并[1,5-a]喹喔啉-8-甲酸甲酯 (5)

在 25 摄氏度下将 4-氨基-2-氟-5-(2-甲基-1H-咪唑-1-基)苯甲酸甲酯 (4) (12 克, 48.15 毫摩尔, 1 当量) 加入 1-甲基-2-吡咯烷酮, 再加入 1,1-羰基二咪唑(19.52 克, 120.37 毫摩尔, 2.5 当量)。反应液加热到 115 摄氏度反应 16 小时。LCMS 显示反应完全。两个批次反应液合并处理。反应液中加入 600 毫升乙酸乙酯和 600 毫升的水在 25 摄氏度下打浆 16 小时。浆液在减压下过滤, 滤饼用 100 毫升的乙酸乙酯洗。固体在减压下浓缩得到灰色固体 7-氟-1-甲基-4-氧-4,5-二氢咪唑并[1,5-a]喹喔啉-8-甲酸甲酯 (5) (24.1 克, 87.56 毫摩尔, 86.60% 收率)。粗品直接用于投下一步反应。¹H NMR (400 MHz, DMSO-d₆) Shift 11.71 (br s, 1H), 8.40 (d, J=6.38 Hz, 1H), 7.76 (s, 1H), 7.08 (d, J=11.38 Hz, 1H), 3.88 (s, 3H), 2.89 (s, 3H)。¹⁹F NMR (376 MHz, DMSO-d₆) Shift -111.43--110.58 (m, 1F)。

步骤 5: 4-((2,4-二甲氧基苄基)氨基)-7-氟-1-甲基咪唑并[1,5-a]喹喔啉-8-甲酸甲酯 (6)

将 7-氟-1-甲基-4-氧-4,5-二氢咪唑并[1,5-a]喹喔啉-8-甲酸甲酯 (5) (12.0 克, 43.60 毫摩尔, 1.0 当量), 2,4-二甲氧基苄胺(10.9 克, 65.19 毫摩尔, 9.82 毫升, 1.50 当量) 和 1,8-二氮杂二环[5.4.0]十一烷-7-烯(19.92 克, 130.80 毫摩尔, 19.72 毫升, 3.0 当量)加入乙腈中 (240 毫升)。在 15~20 摄氏度下分批加入 苯并三唑-1-氧代-三(二甲氨基磷)六氟磷盐(25.07 克, 56.68 毫摩尔, 1.3 当量)。反应液微微放热, 反应液变均匀, 固体析出。氮气保护下反应液在 15~20 摄氏度下反应 16 小时。LCMS 显示起始物料消耗完全并检测到的目标化合物。反应悬浮液在减压下过滤并用 100 毫升乙腈洗涤滤饼。收集固体并在减压下抽干得到灰白色固体 4-((2,4-二甲氧基苄基)氨基)-7-氟-1-甲基咪唑并[1,5-a]喹喔啉-8-甲酸甲酯 (6) (15.3 克, 36.05 毫摩尔, 82.68% 收率)。LCMS ES15882-1146-P1A: (ESI) m/z= 425.3[M+1]⁺; RT= 1.721 min. ¹H NMR (400 MHz, DMSO-d₆) Shift 8.49 (d, J=7.00 Hz, 1H), 8.45 (t, J=5.57 Hz, 1H), 7.95 (s, 1H), 7.23 (d, J=12.51 Hz, 1H), 7.18 (d, J=8.38 Hz, 1H), 6.58 (d, J=2.38 Hz, 1H), 6.47 (dd, J=2.38, 8.38 Hz, 1H), 4.66 (d, J=5.25 Hz, 2H), 3.88 (s, 3H), 3.82 (s, 3H), 3.73 (s, 3H), 2.93 (s, 3H)。¹⁹F NMR (376.5 MHz, DMSO-d₆) Shift -113.02, , ,

步骤 6: 4-氨基-7-氟-1-甲基咪唑并[1,5-a]喹喔啉-8-甲酸甲酯(7)

将 4-((2,4-二甲氧基苄基)氨基)-7-氟-1-甲基咪唑并[1,5-a]喹喔啉-8-甲酸甲酯 (6) (16.3 克, 38.40 毫摩尔, 1.0 当量) 加入二氯甲烷(50 毫升)中, 再加入三氟乙酸(250 毫升)。反应液加热到 50 摄氏度反应 16 小时。LCMS 显示起始物料消耗完全并检测到的目标化合。反应液在减压下浓缩至干, 得到紫色固体 4-氨基-7-氟-1-甲基咪唑并

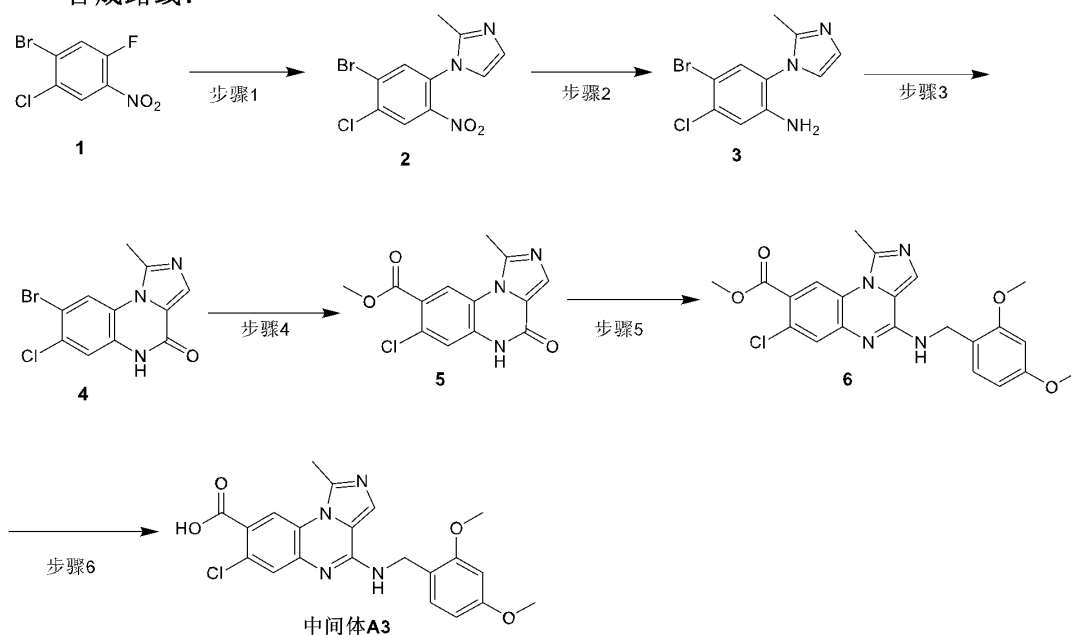
[1,5-a]喹啉-8-甲酸甲酯(7) (28.3 克, 粗品) 粗品直接用于投下一步反应。LCMS ES15882-1150-P1A: (ESI) $m/z=275.3$ $[M+1]^+$; RT= 0.607 min

步骤 7: 4-氨基-7-氟-1-甲基咪唑并[1,5-a]喹啉-8-羧酸 (中间体 A2)

- 将 4-氨基-7-氟-1-甲基咪唑并[1,5-a]喹啉-8-甲酸甲酯 (7)(上一步粗品) (28.3 克, 38.70 毫摩尔, 1 当量)加入四氢呋喃(80 毫升) 和甲醇中(80 毫升)。将氢氧化钠 (7.74 克, 193.48 毫摩尔, 5 当量)溶解在水中(80 毫升)后加入反应液。反应液加热到 50 摄氏度反应 4 小时。LCMS 检测到所需化合物。将反应液冷却到 20 摄氏度后, 在减压下浓缩除去有机溶剂, 残留物用水比甲醇 10 比 1(300 毫升)稀释后, 在硅藻土上过滤, 滤饼用水比甲醇 10 比 1(300 毫升)反复洗涤三次。合并所有的滤液, 减压浓缩除去甲醇。残留物用醋酸调节 pH 至 5~6。得到的浆液在 15~20 摄氏度下搅拌 12 小时, 减压下过滤得到的固体用水洗涤。收集固体经冷冻干燥后得到白色固体。4-氨基-7-氟-1-甲基咪唑并[1,5-a]喹啉-8-羧酸 (中间体 A2) (9.9 克, 37.55 毫摩尔, 97.05% 收率, 98.71% 纯度)。LCMS ES15882-1154-P1C: (ESI) $m/z=261.1$ $[M+1]^+$; RT= 0.422 min。¹H NMR (400 MHz, DMSO- d_6) Shift 13.15 (br s, 1H), 8.53 (d, J=7.04 Hz, 1H), 7.85 (s, 1H), 7.68 (s, 2H), 7.16 (d, J=12.10 Hz, 1H), 2.94 (s, 3H)

通用方法: 中间体 A3 的合成

合成路线:



步骤 1: 1-(5-溴-4-氯-2-硝基-苯基)-2-甲基-咪唑 (2)

- 将 1-溴-2-氯-5-氟-4-硝基苯 (1) (3 克, 11 毫摩尔, 1 当量) 加入到 2-甲基-1H-咪唑 (1.2 克, 14 毫摩尔, 1.2 当量) 的乙腈 (50 毫升) 溶液中, 随后将碳酸钾 (4 克, 29 毫摩尔, 2.5 当量) 加入到反应液中。升温到 80 摄氏度并搅拌 16 小时。检测到原料反应完全, 目标产物生成。减压浓缩除去乙腈, 加入水 (40 毫升), 用乙酸乙酯萃取 (3 x 50 毫升)。用无水硫酸镁干燥, 过滤滤液减压浓缩至干, 经柱层析色谱纯化(二氧化硅, 35%四氢呋喃在石油醚中)得到白色固体 1-(5-溴-4-氯-2-硝基-

苯基)-2-甲基-咪唑 (2) (4 克)。H NMR: ¹H NMR (400 MHz, DMSO-d₆) δ 8.55 (s, 1H), 8.32 (s, 1H), 7.22 (d, J=1.32 Hz, 1H), 6.91 (d, J=1.32 Hz, 1H), 2.08-2.23 (m, 3H).

步骤 2: 4-溴-5-氯-2-(2-甲基咪唑-1-基)苯胺 (3)

将 1-(5-溴-4-氯-2-硝基-苯基)-2-甲基-咪唑 (2) (3.5 克, 11 毫摩尔, 1 当量) 溶解在水 (8 毫升), 乙醇 (16 毫升)与四氢呋喃 (16 毫升)的混合溶液中, 将氯化铵 (8.9 克, 166 毫摩尔, 15 当量)加入到反应液中, 升温到 70 摄氏度把铁粉 (2.5 克, 44 毫摩尔, 4 当量)加入到反应液中。反应在 90 摄氏度下搅拌 2 小时。LC-MS 检测到原料反应完全, 目标产物生成。反应液在硅藻土下过滤并用乙酸乙酯洗涤(40 毫升 x3)。减压除去溶剂得到黑色固体 4-溴-5-氯-2-(2-甲基咪唑-1-基)苯胺 (3) (3.1 克, 10.8 毫摩尔, 98% 产率)。H NMR: ¹H NMR (400 MHz, DMSO-d₆) δ 7.41 (s, 1H), 7.12 (s, 1H), 7.07 (s, 1H), 6.99 (s, 1H), 5.45 (s, 2H), 2.13 (s, 3H).

步骤 3: 8-溴-7-氯-1-甲基-5-氢-咪唑 [1, 5-a] 喹恶啉-4-酮 (4)

将 4-溴-5-氯-2-(2-甲基咪唑-1-基)苯胺 (3) (3 克, 10.5 毫摩尔, 1 当量)和 1,1-羰基二咪唑(2.6 克, 15.7 毫摩尔, 1.5 当量)依次溶解在 1,2-二氯苯 (30 毫升) 溶液中。反应液在 130 摄氏度下搅拌 16 小时。LC-MS 检测到原料反应完全, 目标产物生成。反应液在乙酸乙酯和水(2/1 15 毫升)的溶液中搅拌 30 分钟后过滤得到滤饼, 滤饼在真空下浓缩得到黑色固体 8-溴-7-氯-1-甲基-5-氢-咪唑 [1, 5-a] 喹恶啉-4-酮 (4) (2.2 克, 7 毫摩尔, 67% 产率)。H NMR: ¹H NMR (400 MHz, DMSO-d₆) δ 8.04 (s, 1H), 7.33 (d, J=3.30 Hz, 2H), 2.83 (s, 3H)

步骤 4: 7-氯-1-甲基-4-氧代-5H-咪唑 [1, 5-a] 喹啉-8-羧酸甲酯 (5)

将 8-溴-7-氯-1-甲基-5-氢-咪唑 [1, 5-a] 喹恶啉-4-酮 (4) (500 毫克, 1.6 毫摩尔, 1 当量) 溶解在乙醇 (5 毫升)溶液中加入 1.8-二氮杂二环[5.4.0]十一十一烷-7-烯 (365 毫克, 2.4 毫摩尔, 362 微升, 1.5 当量)置换三次氮气, 将四氟硼酸三丁基磷(46 毫克, 160 微摩尔, 0.1 当量), 六羰基钼 (232 毫克, 880 微摩尔, 118 微升, 0.55 当量)和醋酸钨(36 毫克, 160 微摩尔, 0.1 当量)。反应在 90 摄氏度下搅拌两小时。LC-MS 检测原料反应完全, 目标产物生成。将反应液减压除去乙醇, 加入水(10 毫升), 用乙酸乙酯 30 毫升 (10 毫升 * 3)萃取。用无水硫酸镁干燥, 过滤, 减压浓缩至干。通过柱层析色谱纯化(二氧化硅, 30%四氢呋喃在石油醚中)得到黄色固体 7-氯-1-甲基-4-氧代-5H-咪唑 [1, 5-a] 喹啉-8-羧酸甲酯 (5) (500 毫克)。

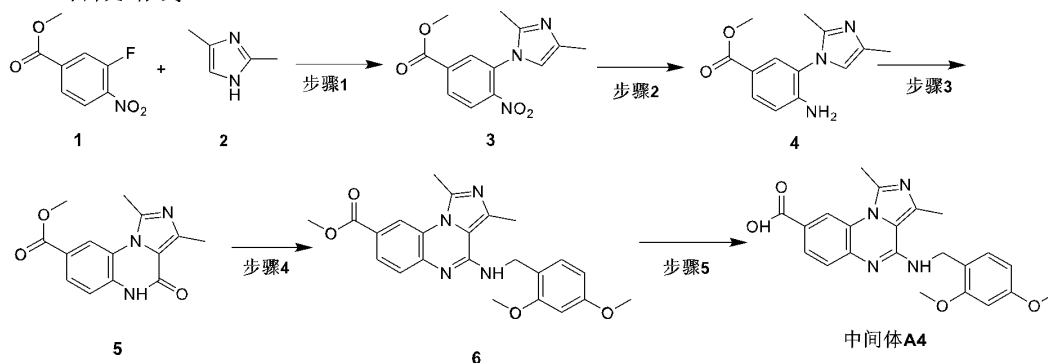
步骤 5: 7-氯-4-((2,4-二甲氧基苄基)氨基)-1-甲基咪唑并[1,5-a]喹啉-8-羧酸甲酯 (6)将 7-氯-1-甲基-4-氧代-5H-咪唑 [1, 5-a] 喹啉-8-羧酸甲酯 (5) (480 毫克, 1.6 毫摩尔, 1 当量) 溶解在乙腈中 (5 毫升) 加入 2,4-二甲氧基苄胺 (341 毫克, 2 毫摩尔, 306 微升, 1.3 当量), 苯并三唑-1-氧代-三(二甲氨基磷)六氟磷盐(1 克, 2.4 毫摩尔, 1.5 当量)和 1.8-二氮杂二环[5.4.0]十一十一烷-7-烯 (1.2 克, 7.9 毫摩尔, 1.2 毫升, 5 当量)。反应在室温下搅拌 16 小时。LC-MS 检测原料反应完全, 目标产物生成。将反应液减压除去乙腈, 加入水(8 毫升), 用乙酸乙酯 30 毫升 (10 毫升 * 3)萃取。用无水硫酸镁干燥, 过滤, 减压浓缩至干。通过柱层析色谱纯化(二氧化硅, 30%四氢呋喃在石油醚中)得到黄色固体 7-氯-4-((2,4-二甲氧基苄基)氨基)-1-甲基咪唑并[1,5-a]喹啉-8-羧酸甲酯 (6) (500 毫克, 1.1 毫摩尔, 70 % 产率)。

步骤 6: 7-氯-4-((2,4-二甲氧基苄基)氨基)-1-甲基咪唑并[1,5-a]喹啉-8-羧酸 (中间体 A3)

- 将 7-氯-4-((2,4-二甲氧基苄基)氨基)-1-甲基咪唑并[1,5-a]喹喔啉-8-羧酸甲酯 (6) (500 毫克, 1.1 毫摩尔, 1 当量) 溶解在水 (5 毫升) 和乙醇 (5 毫升) 中, 加入氢氧化钠 (132 毫克, 3.3 毫摩尔, 3 当量)。反应液在 50 摄氏度下搅拌 5 小时。LCMS 检测原料反应完全, 目标产物生成。反应液加入 6 摩尔盐酸 (0.5 毫升) 减压浓缩至干, 粗品直接用于下一步, 得到白色固体 7-氯-4-((2,4-二甲氧基苄基)氨基)-1-甲基咪唑并[1,5-a]喹喔啉-8-羧酸 (中间体 A3) (350 毫克, 820 微摩尔, 74.6 % 产率)。

通用方法: 中间体 A4 的合成

合成路线:



10

步骤 1: 3-(2,4-二甲基咪唑-1-基)-4-硝基苯甲酸甲酯

- 将 3-氟-4-硝基苯甲酸甲酯 (1) (2.00 克, 10.04 毫摩尔, 1 当量) 加到乙腈中 (40 当量) 加碳酸钾 (4.16 克, 30.13 毫摩尔, 3 当量) 和 2,4-二甲基-1H-咪唑 (2) (965 毫克, 10.04 毫摩尔, 1 当量), 反应液 85 摄氏度反应 16 小时。LC-MS 显示原料消耗完全, 目标产物生成。反应液减压浓缩至干, 残留物用二氯甲烷 (80 当量) 稀释, 过滤, 滤液用硫酸镁干燥, 过滤, 减压浓缩至干得黄色固体 3-(2,4-二甲基咪唑-1-基)-4-硝基苯甲酸甲酯 (3) (2.6 克, 9.45 毫摩尔, 94.05 % 产率), 粗品直接用于下一步, 不需要进一步纯化。

步骤 2: 4-氨基-3-(2,4-二甲基咪唑-1-基)苯甲酸甲酯

- 将 3-(2,4-二甲基咪唑-1-基)-4-硝基苯甲酸甲酯 (3) (2.5 克, 9.08 毫摩尔, 1 当量) 溶解在乙醇 (20 当量), 四氢呋喃 (20 当量) 和水 (10 当量) 中, 室温下加铁粉 (5.07 克, 90.82 毫摩尔, 10 当量) 和氯化铵 (2.43 克, 45.41 毫摩尔, 5 当量)。反应液 90 摄氏度反应 16 小时。LC-MS 显示原料消耗完全, 目标产物生成。反应液过滤, 减压浓缩至干, 残留物用水稀释 (50 当量), 用乙酸乙酯萃取 (40 当量*3), 合并有机相用硫酸镁干燥, 过滤, 减压浓缩至干得黄色固体 4-氨基-3-(2,4-二甲基咪唑-1-基)苯甲酸甲酯 (4) (1.9 克, 6.13 毫摩尔, 67.49 % 产率, 79.13 % 纯度), 粗品直接用于下一步, 不需要进一步纯化。LCMS: ES19974-375-P1C2, (ESI) m/z=246.1 [M+1]⁺; RT=0.61 min, purity: 79.13 %

步骤 3: 1,3-二甲基-4-氧代-4,5-二氢咪唑并[1,5-a]喹喔啉-8-甲酸甲酯

- 4-氨基-3-(2,4-二甲基咪唑-1-基)苯甲酸甲酯 (4) (500 毫克, 2.04 毫摩尔, 1 当量) 和 1,1-羰基二咪唑 (495 毫克, 3.06 毫摩尔, 1.5 当量) 溶解在 1,2-二氯苯中 (10 当量), 反应液在氮气保护下 120 摄氏度反应 16 小时。LC-MS 显示原料消耗完全, 目标产物生成。反应液抽滤, 滤饼用水打浆, 减压干燥得棕色固体 1,3-二甲基-4-氧代-

4,5-二氢咪唑并[1,5-a]喹喔啉-8-甲酸甲酯 (5) (460 毫克, 1.62 毫摩尔, 79.48% 产率, 95.55% 纯度), 粗品直接用于下一步, 不需要进一步纯化。

LCMS: ES19974-392-P1B1, (ESI) m/z = 272.0 $[M+1]^+$; RT=0.61 min, purity: 95.55%

- 5 步骤 4: 4-((2,4-二甲氧基苄基)氨基)-1,3-二甲基咪唑并[1,5-a]喹喔啉-8-甲酸甲酯
将二甲基-4-氧代-4,5-二氢咪唑并[1,5-a]喹喔啉-8-甲酸甲酯 (5) (700 毫克, 2.58 毫摩尔, 1 当量) 溶在乙腈中(25 当量), 加苯并三唑-1-氧代-三(二甲氨基磷)六氟磷酸盐 (1.83 g, 4.13 毫摩尔, 1.6 当量)和 1,8-二氮杂二环[5.4.0]十一-7-烯 (1.96 g, 12.90 毫摩尔, 1.94 当量, 5 当量), 反应液室温反应 0.5 小时, 将(2,4-二甲氧基苄基)甲胺 (647.2 毫克, 3.87 毫摩尔, 583.1 微升, 1.5 当量)加到反应液中, 反应液 50 摄氏度反应 15.5 小时。LC-MS 显示原料消耗完全, 目标产物生成。反应液过滤, 滤饼减压干燥得棕色固体 4-((2,4-二甲氧基苄基)氨基)-1,3-二甲基咪唑并[1,5-a]喹喔啉-8-甲酸甲酯 (6) (900 毫克, 2.08 毫摩尔, 80.57% 产率, 97.13% 纯度), 粗品直接用于下一步, 不需要进一步纯化。LCMS: ES19974-397-P1B1, (ESI) m/z = 421.1
- 10 [M+1]⁺; RT=0.78 min, purity: 97.13%

15 步骤 5: 4-((2, 4-二甲氧基苄基)氨基)-1, 3-二甲基咪唑并[1, 5-a]喹喔啉-8-羧酸

- 将 4-((2,4-二甲氧基苄基)氨基)-1,3-二甲基咪唑并[1,5-a]喹喔啉-8-甲酸甲酯(6) (850 毫克, 2.02 毫摩尔, 1 当量)溶解在甲醇(10 当量), 四氢呋喃(10 当量)和水中(5 当量)加氢氧化锂(424.2 毫克, 10.11 毫摩尔, 5 当量)。反应液 50 摄氏度反应 16 小时。LC-MS 显示原料消耗完全, 目标产物生成。反应液减压浓缩至干, 残留物加醋酸调节 pH=6-7, 过滤, 滤饼减压干燥得棕色固体 4-((2, 4-二甲氧基苄基)氨基)-1, 3-二甲基咪唑并[1, 5-a]喹喔啉-8-羧酸 (中间体 A4) (800 毫克, 1.97 毫摩尔, 97.37% 产率), 粗品直接用于下一步, 不需要进一步纯化。

25

通用方法: 中间体 A5 和中间体 A5b

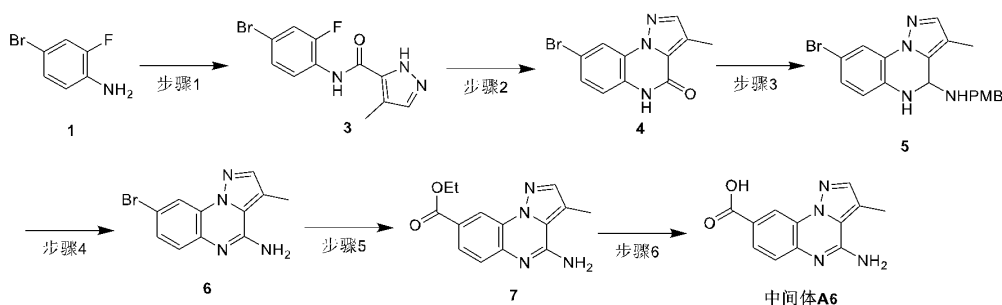


- 30 中间体A5为已知化合物。中间体A5通过SFC分离(条件: 色谱柱: DAICEL CHIRALPAK IC(250 mm * 30 mm, 10 μ m); 流动相: [MeOH(0.1% IPAm)]; B%: 42% - 42%, 15 min)先后得到呈白色固体状的中间体A5a (600mg, 2.46mmol, 40.00% 收率) 和呈白色固体状的中间体A5b(600mg, 2.46mmol, 40.00% 收率)。注: 手型中心非绝对构型, 按照SFC分离先后顺序指定。

- 35 中间体A5a: ¹H NMR (400 MHz, DMSO- d_6) δ 8.07 (d, J = 1.9 Hz, 1H), 7.98 (dd, J = 1.9, 8.8 Hz, 1H), 7.54 (d, J = 8.8 Hz, 1H), 6.74 (s, 2H), 5.47 - 5.35 (m, 2H), 5.34 - 5.25 (m, 1H), 1.41 (d, J = 6.0 Hz, 3H). LC-MS, $[MH]^+$ 245.0

中间体A5b: ¹H NMR (400 MHz, DMSO- d_6) δ 8.05 (d, J = 1.8 Hz, 1H), 7.98 (dd, J = 1.9, 8.8 Hz, 1H), 7.52 (d, J = 8.8 Hz, 1H), 6.68 (s, 2H), 5.46 - 5.35 (m, 2H), 5.33 - 5.26 (m, 1H), 1.41 (d, J = 6.1 Hz, 3H) LC-MS, $[MH]^+$ 245.0

通用方法：中间体 A6 的合成
合成路线：



5 步骤 1：N-(4-溴-2-氟苯基)-4-甲基-1H-吡唑-5-甲酰胺(3)

向 4-溴-2-氟苯胺(5.78g, 30.4mmol, 1当量)和 4-甲基-1H-吡唑-5-甲酸(4.60g, 36.5mmol, 1.2当量)在 Py(120mL)中的溶液中添加 POCl₃(4.66g, 30.4mmol, 2.82mL, 1 eq)在 0℃ 下搅拌 1 h。LC-MS (ET63399-4-R1A1)显示起始材料完全消耗, 并检测到一个具有所需 m/z 的主峰。将反应混合物用冰水(200mL)猝灭, 然后用乙酸乙酯(60mL × 6)萃取。将合并的有机层用盐水(30.0mL)洗涤, 经 Na₂SO₄ 干燥, 过滤并减压浓缩, 得到残余物。将粗产物用乙酸乙酯(50.0mL)研磨, 得到呈白色固体的 N-(4-溴-2-氟苯基)-4-甲基-1H-吡唑-5-甲酰胺(3) (7.09g, 23.8mmol, 78.2% 产率)。¹H NMR (400 MHz, DMSO-*d*₆) δ 13.26 (br s, 1H) 9.52 (s, 1H) 7.92 (t, *J* = 8.52 Hz, 1H) 7.70 (s, 1H) 7.62 (dd, *J* = 10.31, 1.85 Hz, 1H) 7.41 (br d, *J* = 8.70 Hz, 1H) 2.25 (s, 3H)。LC-MS; [MH]⁺ 298.0

15 步骤 2：8-溴-3-甲基吡唑并[1,5-a]喹啉-4(5H)-酮 (4)

向 N-(4-溴-2-氟苯基)-4-甲基-1H-吡唑-5-甲酰胺 (3) (7.09g, 23.8mmol, 1当量)在 DMA(70mL)中的溶液中添加 NaH(1.43g, 35.7mmol, 60% 纯度, 1.5当量)。将混合物在 120℃ 搅拌 16 小时。LC-MS 显示起始材料完全消耗, 并且一个主峰具有所需的 m/z。将反应混合物用饱和氯化铵(300mL)猝灭, 收集沉淀物并用水(50mL)洗涤, 然后减压浓缩, 得到呈白色固体状的 8-溴-3-甲基吡唑并[1,5-a]喹啉-4(5H)-酮 (4) (6.50g, 粗品)。¹H NMR (400 MHz, DMSO-*d*₆) δ 8.11 (d, *J* = 2.00 Hz, 1H) 7.91 (s, 1H) 7.52 (dd, *J* = 8.63, 2.00 Hz, 1H) 7.28 (d, *J* = 8.63 Hz, 1H) 2.42 (s, 3H)。LC-MS; [MH]⁺ 278.0

步骤 3：8-溴-N-(4-甲氧基苄基)-3-甲基-4,5-二氢吡唑并[1,5-a]喹啉-4-胺 (5)

向 8-溴-3-甲基吡唑并[1,5-a]喹啉-4(5H)-酮 (4) (1.00g, 3.60mmol, 1当量)在 MeCN(10.0mL)中的溶液中添加 PMBNH₂ (1.23g, 8.99mmol, 1.16mL, 2.5当量)、BOP(3.18g, 7.19mmol, 2当量)和 DBU(2.74 克, 18.0 毫摩尔, 2.71 毫升, 5 当量)。将混合物在 50℃ 搅拌 16 小时。LC-MS 显示起始材料完全消耗, 并且一个主峰具有所需的 m/z。将反应混合物用饱和氯化铵(10.0mL)和乙醇(5.00mL)稀释。收集沉淀物并用水(10.0mL)洗涤, 然后减压浓缩, 得到呈黄色固体状的 8-溴-N-(4-甲氧基苄基)-3-甲基-4,5-二氢吡唑并[1,5-a]喹啉-4-胺 (5) (1.09g, 粗品)。¹H NMR (400 MHz, DMSO-*d*₆) δ 8.20 (d, *J* = 1.88 Hz, 1H) 7.95 (s, 1H), 7.44-7.48 (m, 2H) 7.38 (d, *J* = 8.63 Hz, 2H) 7.28 (br s, 1H) 6.87 (d, *J* = 8.75 Hz, 2H) 4.70 (d, *J* = 5.88 Hz, 2H) 3.71 (s, 3H) 2.53 (s, 3H)。LC-MS; [MH]⁺ 399.0

步骤 4：8-溴-3-甲基吡唑并[1,5-a]喹啉-4-胺 (6)

35 将 8-溴-N-(4-甲氧基苄基)-3-甲基-4,5-二氢吡唑并[1,5-a]喹啉-4-胺 (5) (500mg,

1.26mmol, 1当量)在TFA(5mL)中的溶液在60℃搅拌12小时。LC-MS显示起始材料完全消耗,并且一个主峰具有所需的 m/z 。将反应混合物减压浓缩,得到化合物8-溴-3-甲基吡唑并[1,5-a]喹喔啉-4-胺 (6) (400mg, 粗品), 为黄色固体。LC-MS: $[MH]^+$ 277.0

步骤 5: 4-氨基-3-甲基吡唑并[1,5-a]喹喔啉-8-甲酸乙酯 (7)

5 向8-溴-3-甲基吡唑并[1,5-a]喹喔啉-4-胺 (6) (400mg, 1.08mmol, 1当量)的EtOH(4mL)溶液中添加Mo(CO)₆ (143mg, 541μmol, 72.9μL, 0.5当量)、DBU(659mg, 4.33 mmol, 652 μL, 4 eq)、(t-Bu)₃PBF₄ (94.2 mg, 325 μmol, 0.3 eq) 和 Pd(OAc)₂ (36.5 mg, 162 μmol, 0.15 eq)。将混合物在90℃搅拌12小时。LC-MS (ET63399-28-R1A1)显示起始材料完全消耗并且检测到所需的质量。将反应混合物用饱和氯化铵(10mL)

10 和乙醇(10mL)稀释。收集沉淀并用水(10.0mL)洗涤, 然后减压浓缩以得到呈黄色固体的4-氨基-3-甲基吡唑并[1,5-a]喹喔啉-8-甲酸乙酯 (7) (250mg, 925μmol, 85.4%产率)。LC-MS; $[MH]^+$ 271.1

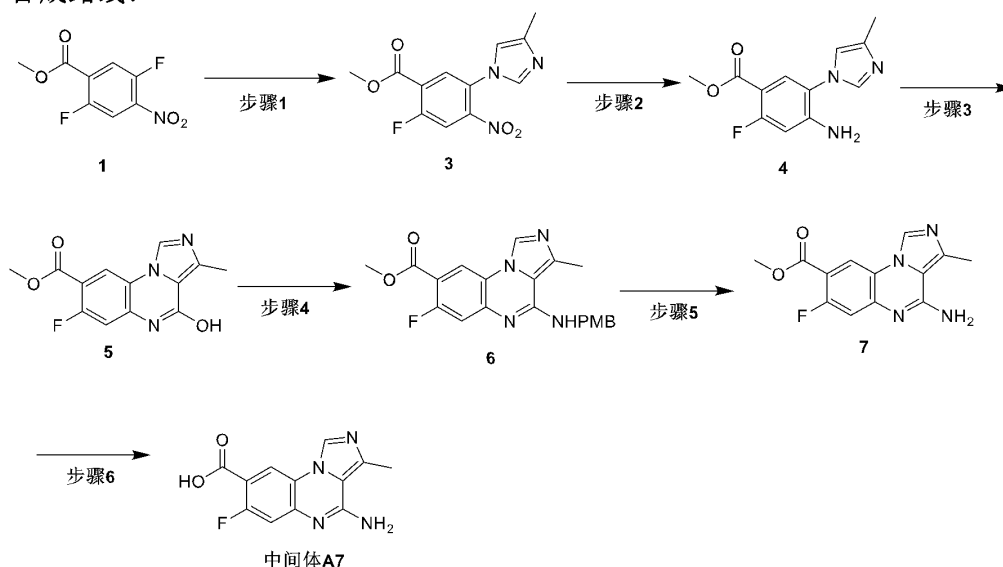
步骤 6: 4-氨基-3-甲基吡唑并[1,5-a]喹喔啉-8-甲酸 (中间体 A6)

15 向4-氨基-3-甲基吡唑并[1,5-a]喹喔啉-8-甲酸乙酯(7) (250mg, 925μmol, 1当量)在EtOH(3mL)和H₂O(1mL)中的溶液中添加LiOH·H₂O(116mg, 2.77mmol, 3当量)。将混合物在25℃搅拌12小时。LC-MS (ET63399-32-R1A1)显示起始材料完全消耗并且检测到所需的质量。将反应混合物浓缩, 用水(10mL)稀释, 用DCM(10.0mL×3)洗涤以除去杂质。用1M HCl调节水相至pH=5, 收集沉淀并通过制备型HPLC纯化(柱: Phenomenex Luna C18 75*30mm*3μm; 流动相: [水(FA)-ACN]; B%: 1%-35%, 8分钟, UV 220nm和254nm), 得到呈黄色固体的4-氨基-3-甲基吡唑并[1,5-a]喹喔啉-8-甲酸 (中间体A6) (60.0mg, 248μmol, 26.8%产率)。¹H NMR (400 MHz, DMSO-*d*₆) δ 12.94 (br s, 1H) 8.67 (d, *J* = 1.96 Hz, 1H) 7.96 (s, 1H) 7.89 (dd, *J* = 8.44, 1.96 Hz, 1H) 7.52 (d, *J* = 8.44 Hz, 1H) 7.19 (br s, 2H) 2.49 (br s, 3H)。LC-MS, $[MH]^+$ 243.1

20

25 **通用方法: 中间体 A7 的合成**

合成路线:



步骤 1: 2-氟-5-(4-甲基-1H-咪唑-1-基)-4-硝基苯甲酸甲酯 (3)

将 2,5-二氟-4-硝基苯甲酸甲酯(20.0g, 92.1mmol, 1 当量)和 5-甲基-1H-咪唑(7.56g, 92.1mmol, 1 当量)在 DMSO(200mL)中的混合物在 50℃搅拌 12 小时。LCMS 显示剩余起始材料并检测到所需质量。将残余物用 H₂O(400mL)稀释并用 EtOAc(200mL×3)萃取。将合并的有机层用盐水(200mL)洗涤,经 Na₂SO₄ 干燥,过滤并减压浓缩,得到残余物。

- 5 将残余物通过柱色谱法(SiO₂, 石油醚/乙酸乙酯=20/1 至 0/1)纯化,得到呈黄色固体的化合物 2-氟-5-(4-甲基-1H-咪唑-1-基)-4-硝基苯甲酸甲酯 (9.30g, 33.3mmol, 34.2%产率)。LC-MS (ESI) m/z = 280.1 [M+H]⁺

步骤 2: 4-氨基-2-氟-5-(4-甲基-1H-咪唑-1-基)苯甲酸甲酯 (4)

- 10 向 2-氟-5-(4-甲基-1H-咪唑-1-基)-4-硝基苯甲酸甲酯(9.30g, 33.3mmol, 1 当量)和 NH₄Cl(26.7g, 499mmol, 15 当量)在 EtOH(90.0mL)/THF(90.0mL)/H₂O(45.0mL)中的溶液中添加 Fe 粉末(7.44 克, 133 毫摩尔, 4 当量)。将混合物在 80℃搅拌 2 小时。LCMS 显示起始材料已消耗并且检测到所需质量。过滤反应混合物,用水(300mL)稀释滤液并用 EtOAc(200mL×3)萃取。将合并的有机层用盐水(100mL)洗涤,用 Na₂SO₄ 干燥,减压浓缩,得到化合物 4-氨基-2-氟-5-(4-甲基-1H-咪唑-1-基)苯甲酸甲酯(8.00g, 32.1mmol, 95.2
- 15 %收率),为黄色固体。LC-MS (ESI) m/z = 250.0 [M+H]⁺

步骤 3: 7-氟-4-羟基-3-甲基咪唑并[1,5-a]喹啉-8-甲酸甲酯 (5)

- 将 4-氨基-2-氟-5-(4-甲基-1H-咪唑-1-基)苯甲酸甲酯(500 mg, 2.01 mmol, 1 eq)和 CDI(487 mg, 2.41 mmol, 1.2 eq)放入微波管中的 1,2-二氯苯(20.0 mL)中。将密封管在微波下于 150℃加热 3 小时。进行 11 次平行反应。LCMS 显示起始材料已消耗并且检测到所需质量。过滤反应混合物,减压干燥滤饼,得到残余物。将粗产物与 MTBE (20.0 mL)在 25° C 下研磨 30 分钟以得到呈黄色固体的 7-氟-4-羟基-3-甲基咪唑并[1,5-a]喹啉-8-甲酸甲酯 (6.00 g, 21.80 mmol, 85.0%收率)。LC-MS (ESI) m/z = 276.0 [M+H]⁺
- 20

步骤 4: 7-氟-4-((4-甲氧基苄基)氨基)-3-甲基咪唑并[1,5-a]喹啉-8-甲酸甲酯 (6)

- 25 向 7-氟-4-羟基-3-甲基咪唑并[1,5-a]喹啉-8-甲酸甲酯 5(6.00g, 21.8mmol, 1 当量)在 MeCN(120mL)中的溶液中添加 BOP(19.2g, 43.6mmol, 2 当量)、DBU(16.5g, 109mmol, 16.4mL, 5 当量)和 PMBNH₂(7.48 克, 54.5 毫摩尔, 7.05 毫升, 2.5 当量)。将混合物在 70℃搅拌 16 小时。LCMS 显示起始材料完全消耗并且检测到所需质量。将反应混合物用饱和氯化铵(20.0mL)稀释。滤饼用水(10.0mL)洗涤并减压浓缩,得到呈黄色固体的 7-氟-4-((4-甲氧基苄基)氨基)-3-甲基咪唑并[1,5-a]喹啉-8-甲酸甲酯 6(5.00g, 12.6mmol, 50.0
- 30 %产率)。LC-MS (ESI) m/z = 395.1 [M+H]⁺

步骤 5: 4-氨基-7-氟-3-甲基咪唑并[1,5-a]喹啉-8-甲酸甲酯 (6)

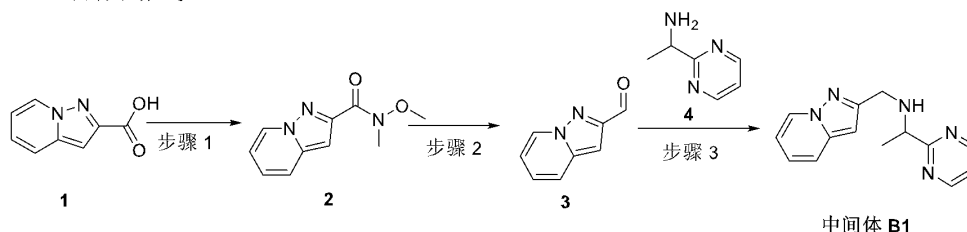
- 将 7-氟-4-((4-甲氧基苄基)氨基)-3-甲基咪唑并[1,5-a]喹啉-8-甲酸甲酯 6(2.00g, 5.07mmol, 1 当量)在 TFA(20.0mL)中的溶液在 75℃搅拌 16 小时。LCMS 显示起始材料已消耗并且检测到所需质量。将反应混合物减压浓缩,得到呈黄色固体状的 4-氨基-7-氟-3-甲基咪唑并[1,5-a]喹啉-8-甲酸甲酯 7(1.39g, 粗品)。LC-MS (ESI) m/z = 275.0 [M+H]⁺
- 35

步骤 6: 4-氨基-7-氟-3-甲基咪唑并[1,5-a]喹啉-8-甲酸 (中间体 A7)

- 向 4-氨基-7-氟-3-甲基咪唑并[1,5-a]喹啉-8-甲酸甲酯 7(1.39g, 5.07mmol, 1 当量)在 EtOH(15mL)/H₂O(5.00mL)中的溶液中添加 LiOH(638mg, 15.2mmol, 3 当量)。将混合物在 25℃搅拌 12 小时。LCMS 表明起始材料已消耗并且检测到具有所需质量的一个主峰。将反应混合物用 H₂O(20.0mL)稀释并用(DCM 10.0mL×2)萃取以除去杂质。用 2M HCl 将水层调节至 pH=6,收集沉淀物并减压干燥,得到呈白色固体的 4-氨基-7-氟-3-甲基咪唑并
- 40

[1,5-a]喹啉-8-甲酸(中间体 A7) (1.30g, 5.00mmol, 98.5%产率)。¹H NMR (400MHz, DMSO-d₆) δ 13.15 (br s, 1H), 9.12 (s, 1H), 8.56 (br d, *J* = 6.4 Hz, 1H), 7.35 (br s, 2H), 7.13 (br d, *J* = 12.1 Hz, 1H), 2.62 (s, 3H). LC-MS (ESI) *m/z* = 261.0 [M+H]⁺

5 通用方法：中间体 B1 的合成 合成路线：



步骤 1：N-甲氧基-N-甲基吡啶并[1,5-a]吡啶-2-甲酰胺(1)

向吡啶并[1,5-a]吡啶-2-羧酸(2.0 g, 12.3 mmol)和 HATU(7.0 g, 18.5 mmol)的 DMF(100 mL)溶液中加入 Et₃N(6.2 g, 61.7 mmol)和甲氧基(甲基)胺(1.9 g, 30.83 mmol), 25 °C。然后将混合物在 25 °C 搅拌 12 小时。用水(100mL)淬灭反应, 然后用 EA(100mL×3)萃取。有机溶液用盐水(100mL)洗涤。有机相用 Na₂SO₄ 干燥并过滤。减压浓缩滤液。将残余物通过硅胶色谱法纯化, 用 MeOH 的 DCM 溶液在 20 分钟内从 0%洗脱到 10%, 得到 N-甲氧基-N-甲基吡啶并[1,5-a]吡啶-2-甲酰胺(2.01 g, 79%产率)为黄色固体。LC-MS: *R*_t = 1.049 min, (ESI) *m/z*. [M+H]⁺ 206.1; C₁₀H₁₁N₃O₂.

步骤 2：吡啶并[1,5-a]吡啶-2-甲醛(3)

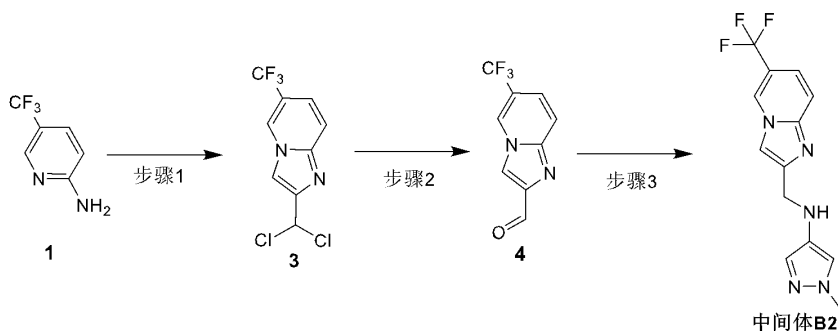
在 -60 °C 向 N-甲氧基-N-甲基吡啶并[1,5-a]吡啶-2-甲酰胺(1.5 g, 7.31 mmol)的 THF(20 mL)溶液中加入 LiAlH₄(439 mg, 10.96 mmol)。然后将混合物在 -60 °C 搅拌 2 小时。用水(40mL)淬灭反应并过滤。减压浓缩滤液。将残余物通过硅胶色谱法纯化, 用 DCM 中的 MeOH 在 20 分钟内从 0%洗脱到 10%, 得到黄色油状的吡啶并[1,5-a]吡啶-2-甲醛(450mg, 42%产率)。LC-MS: *R*_t = 1.071 min, (ESI) *m/z*. [M+H]⁺ 147.1; C₈H₆N₂O

步骤 3：N-(吡啶并[1,5-a]吡啶-2-基甲基)-1-(嘧啶-2-基)乙烷-1-胺(中间体 B1)

向吡啶并[1,5-a]吡啶-2-甲醛(100mg, 0.68mmol)的 MeOH(5mL)溶液中加入 1-(嘧啶-2-基)乙胺(126mg, 1.03mmol)和 NaBH₃CN(86 毫克, 1.37 毫摩尔), 在 25 °C 下反应。然后将混合物在 25 °C 搅拌 2 小时。用水(1mL)淬灭反应, 减压浓缩溶剂。将残余物通过硅胶色谱法纯化, 用 MeOH 的 DCM 溶液在 20 分钟内从 0%洗脱到 5%, 得到 N-(吡啶并[1,5-a]吡啶-2-基甲基)-1-(嘧啶-2-基)乙胺(40 毫克, 23% 产率), 为黄色油状物。LC-MS: *R*_t = 0.521 min, (ESI) *m/z*. [M+H]⁺ 254.2; C₁₄H₁₅N₅

通用方法：中间体 B2 合成

合成路线：



步骤 1: 2-二氯甲基-6-三氟甲基咪唑并[1, 2-a]吡啶(3)

5-(三氟甲基)吡啶-2-胺 (1) (30 克, 185 毫摩尔, 1 当量), 氯苯 (450 毫升) 和 1, 1, 3-三氯-2-丙酮 (45 克, 277 毫摩尔, 1.5 当量)的混合物在 135 摄氏度反应 4 小时。LCMS 检测到目标产物生成。反应液用碳酸钠调 pH 到 8 左右, 用乙酸乙酯萃取 (500 毫升 * 3), 合并有机相用硫酸镁干燥, 过滤滤液减压浓缩至干, 经柱层析色谱纯化(二氧化硅, 15%乙酸乙酯在石油醚中)得到黄色固体 2-二氯甲基-6-三氟甲基咪唑并[1, 2-a]吡啶 (3) (30 克, 111 毫摩尔, 60% 产率)。H NMR: ES19506-784-P1A, ¹H NMR (400 MHz, DMSO-d₆) δ 9.24 (s, 1H), 8.27 (s, 1H), 7.79 (d, J=9.68 Hz, 1H), 7.65 (s, 1H), 7.56 (dd, J=1.65, 9.57 Hz, 1H).

步骤 2: 6-(三氟甲基)咪唑并[1, 2-a]吡啶-2-甲醛(4)

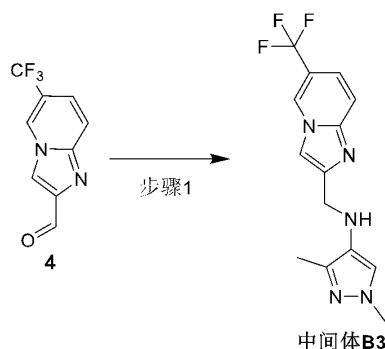
将 2-二氯甲基-6-三氟甲基咪唑并[1, 2-a]吡啶(3) (30 克, 111 毫摩尔, 1 当量), 水(600 毫升), 碳酸钙(33 克, 334 毫摩尔, 3 当量)升温至 100 摄氏度反应 2 小时。LCMS 检测到目标产物生成。反应液加硅藻土和乙酸乙酯(600 毫升), 室温搅拌 30 分钟, 过滤, 用乙酸乙酯萃取(600 毫升*2)。合并有机相用硫酸镁干燥, 过滤, 滤液减压浓缩至干得棕色固体 6-(三氟甲基)咪唑并[1, 2-a]吡啶-2-甲醛(4) (35 克), 粗品直接用于下一步, 不需要进一步纯化。H NMR: ES19506-789-P1A1, ¹H NMR (400 MHz, CHLOROFORM-d) δ 10.09-10.29 (m, 1H), 8.59 (s, 1H), 8.27 (s, 1H), 7.82 (br d, J=9.46 Hz, 1H), 7.44 (br d, J=9.02 Hz, 1H).

步骤 3: 1-甲基-N-((6-(三氟甲基)咪唑并[1,2-a]吡啶-2-基)甲基)-1H-吡啶-4-胺(中间体 B2)

向 6-(三氟甲基)咪唑并[1, 2-a]吡啶-2-甲醛(4)(100mg, 467μmol, 1 当量)在 DCM(2.00mL)中的溶液中添加 KOAc(91.7mg, 934μmol, 2当量)和 1-甲基-1H-吡啶-4-胺(45.4mg, 467μmol, 1当量)在 -5℃ 下, 将反应混合物在 -5℃ 下搅拌 1 小时。然后添加 NaBH(OAc)₃(198mg, 934μmol, 2当量)并在 -5℃ 下再搅拌 3 小时。LCMS (ET63219-45-P1A1)显示 Cpd.4 完全消耗并且 LCMS 上显示几个新峰。将反应混合物用饱和 Na₂CO₃ 水溶液(3.00mL)稀释并用二氯甲烷(2.00mL×4)萃取。将合并的有机层用 Na₂SO₄ 干燥, 减压浓缩, 得到残余物。通过制备型 TLC(乙酸乙酯/甲醇=8/1)纯化残余物, 得到呈黄色固体的 1-甲基-N-((6-(三氟甲基)咪唑并[1,2-a]吡啶-2-基)甲基)-1H-吡啶-4-胺(中间体 B2)(80.0mg, 271μmol, 58.0% 产率)。¹H NMR (400 MHz, CDCl₃) δ 8.47 (s, 1H), 7.69 (d, J=9.5 Hz, 1H), 7.64 (s, 1H), 7.35 (d, J=1.5, 9.5 Hz, 1H), 7.30 (s, 2H), 6.97 (s, 1H), 4.39 (s, 2H), 3.81 (s, 3H); LC-MS, [MH]⁺ 217.0.

通用方法: 中间体 B3 的合成

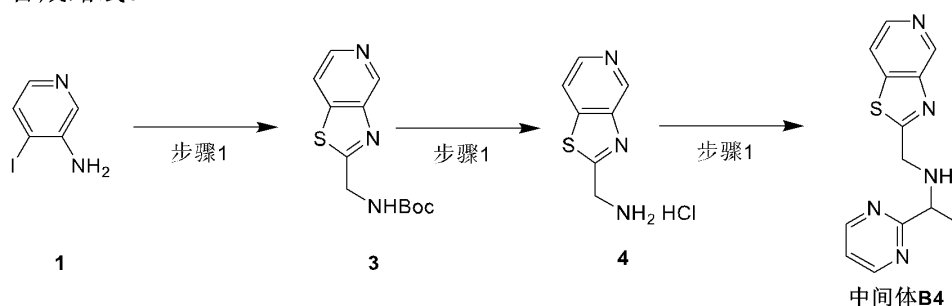
合成路线:



步骤 1: 1,3-二甲基-N-((6-(三氟甲基)咪唑并[1,2-a]吡啶-2-基)甲基)-1H-吡唑-4-胺(中间体 B3)

将 6-(三氟甲基)咪唑并[1,2-a]吡啶-2-甲醛(4) (10 克, 46 毫摩尔, 1 当量)和 1,3-二甲基吡唑-4-胺(6 克, 56 毫摩尔, 1.2 当量)溶解在二氯甲烷(150 毫升)中, 加醋酸(3 克, 56 毫摩尔, 3 毫升, 1.2 当量), 反应液在 25 摄氏度反应 1 小时, 加三乙酰氧基硼氢化钠(25 克, 117 毫摩尔, 2.5 当量), 反应液在 25℃反应 3 小时, LCMS 检测到目标产物生产。反应液用 200 毫升碳酸氢钠淬灭, 用乙酸乙酯萃取(150 毫升*2)。合并有机相用 400 毫升饱和食盐水洗涤, 硫酸镁干燥, 过滤, 滤液减压浓缩至干。经柱层析色谱纯化(二氧化硅, 35%乙酸乙酯: 乙醇(3:1)在石油醚中)得到棕色固体 1,3-二甲基-N-(6-(三氟甲基)咪唑并[1,2-a]吡啶-2-基)甲基)-1H-吡唑-4-胺(中间体 B3) (14 克, 45 毫摩尔, 97% 产率)。H NMR: ES19506-795-P1A, ¹H NMR (400 MHz, DMSO-d₆) δ 9.19 (s, 1H), 7.92 (s, 1H), 7.67 (d, J=9.46 Hz, 1H), 7.41 (dd, J=1.76, 9.46 Hz, 1H), 6.93 (s, 1H), 4.56 (br s, 1H), 4.17 (br d, J=3.96 Hz, 2H), 3.52-3.61 (m, 3H), 2.04 (s, 3H). LCMS: ES19506-795-P1B, (ESI) m/z=310.3 (M+1)⁺, RT= 0.64 min.

通用方法: 中间体 B4 的合成
合成路线:



步骤 1: (噻唑并[4,5-c]吡啶-2-基甲基)氨基甲酸叔丁酯(3)

向 4-碘吡啶-3-胺(20.0g, 90.9mmol, 1 当量)和(2-氨基-2-硫代乙基)氨基甲酸叔丁酯 (20.7g, 109mmol, 1.2 当量)在 MeCN(200mL)中的溶液中添加 Pd2(dba)₃(4.16g, 4.55mmol, 0.05 当量)、DPPF(10.1g, 18.2mmol, 0.2 当量)和 CaO(10.2g, 182mmol, 3.09mL, 2 当量), 将混合物在 N₂ 下于 80℃搅拌 16 小时。LCMS 显示起始材料完全消耗并且检测到所需质量。过滤反应混合物, 减压浓缩滤液, 得到残余物。通过柱色谱法(石油醚/乙酸乙酯=30/1 至 1/1)纯化残余物, 得到呈棕色固体的(噻唑并[4,5-c]吡啶-2-基甲基)氨基甲

酸叔丁酯(3)(17g, 64.0mmol, 70.5%收率)。¹H NMR (400 MHz, CHLOROFORM-d) δ 9.28 (s, 1H), 8.53 (d, J = 5.4 Hz, 1H), 7.84 (d, J = 5.4 Hz, 1H), 5.41 (br s, 1H), 4.77 (br d, J = 5.8 Hz, 2H), 1.50 (s, 9H); LC-MS, $[MH]^+$ 266.1

步骤 2: 噻唑并[4,5-c]吡啶-2-基甲基胺盐酸盐(4)

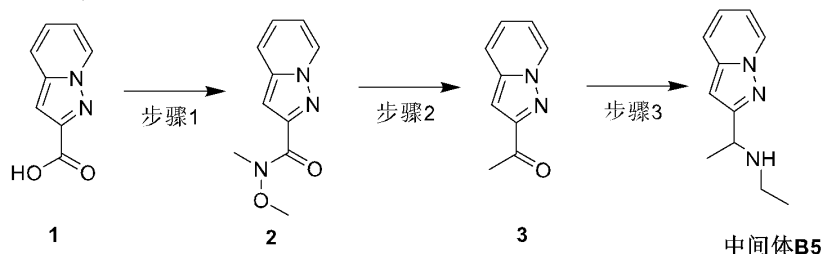
5 向(噻唑并[4,5-c]吡啶-2-基甲基)氨基甲酸叔丁酯(3)(3g, 11.3mmol, 1当量)在DCM(15mL)中的溶液中添加HCl/EtOAc(4M, 15mL)。将混合物在25℃搅拌16小时。LCMS (ET63218-11-P1A2)显示起始材料已消耗并且检测到所需质量。将反应混合物减压浓缩, 得到噻唑并[4,5-c]吡啶-2-基甲基胺盐酸盐(4)(2g, 粗品, HCl), 为浅黄色固体。LC-MS, $[MH]^+$ 166.1

10 **步骤 3: 1-(噻唑-2-基)-N-(噻唑并[4,5-c]吡啶-2-基甲基)乙-1-胺(中间体 B4)**

向噻唑并[4,5-c]吡啶-2-基甲基胺盐酸盐(4)(2g, 9.92mmol, 1当量)和1-(噻唑-2-基)乙烷-1-酮(1.21g, 9.92mmol, 1当量)在DCM(20mL)中的溶液中添加KOAc(1.17g, 11.9mmol, 1.2当量)。将混合物在25℃搅拌0.5小时, 然后在25℃将NaBH(OAc)₃(2.73g, 12.9mmol, 1.3当量)添加至上述混合物, 将混合物在25℃搅拌2小时。LCMS显示起始材料已消耗并且检测到所需质量。用饱和NaHCO₃将混合物调节至pH=8-9, 然后用DCM(20mL×3)萃取。将有机相减压浓缩, 得到残余物。将残余物通过柱色谱法(SiO₂, 二氯甲烷/甲醇=50/1至10/1)纯化, 得到呈棕色油状的1-(噻唑-2-基)-N-(噻唑并[4,5-c]吡啶-2-基甲基)乙-1-胺(中间体B4)(320mg, 1.18mmol, 11.9%产率)。¹H NMR (400 MHz, CHLOROFORM-d) δ = 9.22 (s, 1H), 8.74 (d, J = 4.9 Hz, 2H), 8.50 (d, J = 5.4 Hz, 1H), 7.85 (d, J = 5.4 Hz, 1H), 7.22 (t, J = 4.9 Hz, 1H), 4.27 (d, J = 16.4 Hz, 1H), 4.16 - 4.04 (m, 2H), 1.54 (d, J = 6.9 Hz, 3H); LC-MS, $[MH]^+$ 272.0

通用方法: 中间体 B5 的合成

合成路线:



25 **步骤 1: 吡唑并[1,5-a]吡啶-2-甲酸(2)**

向吡唑并[1,5-a]吡啶-2-甲酸(10.0g, 61.67mmol, 1当量)和HATU(28.14g, 74.01mmol, 1.2当量)、DIEA(31.88g, 246.69mmol, 4当量)在DCM(500mL)中的溶液中添加N,O-二甲基羟胺盐酸盐(12.03克, 123.35毫摩尔, 2当量)。将混合物在25℃搅拌16小时。LCMS (ET63565-18-P1A)表明起始材料完全消耗并且检测到产物。将反应混合物减压浓缩, 得到残余物。通过柱色谱法(石油醚/乙酸乙酯=1/1至0/1)纯化残余物, 得到呈白色固体的化合物吡唑并[1,5-a]吡啶-2-甲酸(2)(12.1g, 58.9mmol, 产率95.6%)。¹H NMR (400 MHz, CHLOROFORM-d) δ 8.49 (d, J = 7.1 Hz, 1H), 7.57 (d, J = 8.9 Hz, 1H), 7.15 (dd, J = 7.3, 8.4 Hz, 1H), 7.00 (s, 1H), 6.85 (t, J = 6.9 Hz, 1H), 3.79 (s, 3H), 3.49 (s, 3H); LC-MS, $[MH]^+$ 206.22.

30 **步骤 2: 1-(吡唑并[1,5-a]吡啶-2-基)乙烷-1-酮(3)**

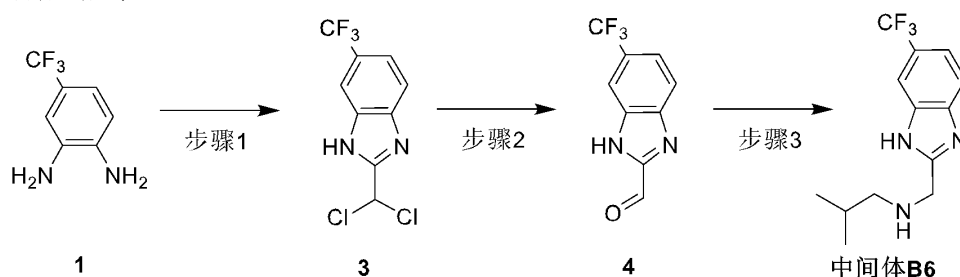
在-60℃下向吡唑并[1,5-a]吡啶-2-甲酸(2)(2g, 9.75mmol, 1 当量)的 THF(20.0mL)溶液中添加 MeLi(11.70mL, 1.2 当量), 然后将混合物在 25℃下搅拌 16 小时。N₂ 下 hr。LCMS (ET63565-13-P1A1)表明起始材料完全消耗并且检测到产物。将残余物通过柱色谱法(石油醚/乙酸乙酯=50/1 至 3/1)纯化, 得到呈白色固体的 1-(吡唑并[1,5-a]吡啶-2-基)乙烷-1-酮(3)(277mg, 1.73mmol, 17.7%收率)。LC-MS, [MH]⁺ 161.1.

步骤 3: N-乙基-1-(吡唑并[1,5-a]吡啶-2-基)乙-1-胺(中间体 B5)

将 1-(吡唑并[1,5-a]吡啶-2-基)乙烷-1-酮(3) (0.1 g, 624.33 μmol, 1 eq)和乙胺(112.58 mg, 2.50 mmol, 163.39 μL, 4 eq) 在 DCM (2 mL)中的混合物在-60℃搅拌 0.5 h, 然后在 0℃下将 NaBH₄(264.64mg, 1.25mmol, 2 当量)添加到混合物中并在 N₂ 气氛下在 25℃下搅拌 16 小时。LCMS (ET63565-9-P1A2)表明起始材料完全消耗并且检测到产物。将反应混合物用 H₂O(5mL)淬灭, 并用 DCM(5mL×3)稀释, 将合并的有机层减压浓缩, 得到残余物。通过制备型 TLC(DCM:MeOH=10:1)纯化残余物以得到呈白色固体的 N-乙基-1-(吡唑并[1,5-a]吡啶-2-基)乙-1-胺(中间体 B5)(50mg, 264μmol, 42.3 % 收率)。¹H NMR (400 MHz, CHLOROFORM-d) δ 8.39 (br d, *J* = 6.9 Hz, 1H), 7.46 (br d, *J* = 8.5 Hz, 1H), 7.12-7.03 (m, 1H), 6.70 (br t, *J* = 6.8 Hz, 1H), 6.44 (s, 1H), 4.13 (br d, *J* = 6.8 Hz, 1H), 3.32-3.21 (m, 1H), 2.77-2.56 (m, 2H), 1.53 (d, *J* = 6.6 Hz, 4H), 1.17-1.14 (m, 3H); LC-MS, [MH]⁺ 190.1.

通用方法: 中间体 B6 的合成

合成路线:



步骤 1: 2-(二氯甲基)-6-(三氟甲基)-1H-苯并[d]咪唑(3)

将 4-(三氟甲基)苯-1,2-二胺 (5 g, 28.3 mmol, 1 eq) 和 2,2-二氯乙酸 (7.32 g, 56.7 mmol, 4.66 mL, 2 eq) 在 HCl (125 mL) (4 M) 中的混合物在 100℃下搅拌 10 分钟。16 小时。LCMS (ET60224-68-P1A)显示 Cpd.1 被消耗并且检测到所需的质量。过滤反应混合物并用水洗涤滤饼。将合并的滤液用 DCM(20ml×3)萃取。将合并的有机层用盐水(100mL)洗涤, 经 MgSO₄ 干燥, 过滤并减压浓缩, 得到残余物。将残余物通过柱色谱法(石油醚/乙酸乙酯=20/1 至 5/1)纯化, 得到呈黄色油状的化合物 2-(二氯甲基)-6-(三氟甲基)-1H-苯并[d]咪唑(3)(4.4g, 16.3mmol, 收率 57.6%)。¹H NMR (400 MHz, CHLOROFORM-d) δ 8.01 (s, 1H), 7.79 (d, *J* = 8.6 Hz, 1H), 7.66 (d, *J* = 8.2 Hz, 1H), 7.26 (s, 1H); LCMS: [M+H]⁺ 268.9

步骤 2: 6-(三氟甲基)-1H-苯并[d]咪唑-2-甲醛(4)

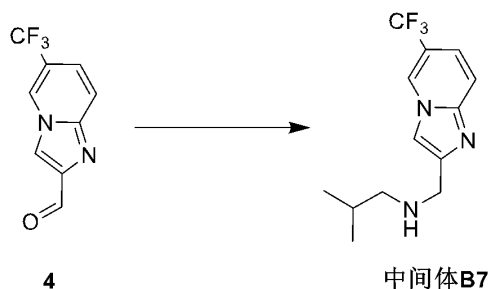
向 2-(二氯甲基)-6-(三氟甲基)-1H-苯并[d]咪唑(3)(1g, 3.72mmol, 1 当量)在 H₂O(20mL)中的悬浮液中添加 CaCO₃ (1.12g, 11.1mmol, 3 当量)。将混合物在 100℃搅拌 8 小时。LCMS (ET60224-74-P1B) 显示 Cpd.3 被消耗并且检测到所需的质量。将反应混合物用 H₂O(50mL)稀释并用乙酸乙酯(30mL×3)萃取。将合并的有机层减压浓缩, 得到呈白色固体的 6-(三氟甲基)-1H-苯并[d]咪唑-2-甲醛(4)(310mg, 1.45mmol, 38.9%产率)。¹H NMR (400 MHz, DMSO-d₆) δ 14.28-13.59 (m, 1H), 10.02 (s, 1H), 8.40-8.30 (m, 2H), 8.23-8.05 (m,

3H), 8.00 (dd, $J = 5.4, 8.5$ Hz, 1H), 7.89 (br s, 1H), 7.83-7.61 (m, 3H), 7.34 (br d, $J = 7.9$ Hz, 1H), 7.27 (d, $J = 7.6$ Hz, 1H); LCMS: $[M+H]^+$ 215.2

步骤 3: 2-甲基-N-((6-(三氟甲基)-1H-苯并[d]咪唑-2-基)甲基)丙-1-胺(中间体 B6)

在 25°C 下, 向 6-(三氟甲基)-1H-苯并[d]咪唑-2-甲醛(4)(0.31g, 1.45mmol, 1 当量)和
 5 2-甲基丙-1-胺 (105mg, 1.45mmol, 143uL, 1 当量)在 DCM(6.2mL)中的溶液中添加
 KOAc(170mg, 1.74mmol, 1.2 eq)。将混合物在 25°C 搅拌 0.5 小时, 然后在 25°C 将
 NaBH(OAc)₃ (398mg, 1.88mmol, 1.3 当量)添加至上述混合物, 将混合物在 25°C 搅拌 15.5
 小时。LCMS (ET60224-77-P1A)显示 Cpd.4 被消耗并且检测到所需的质量。将反应混合物
 10 用 H₂O(10mL)稀释并用 DCM(2mL×3)萃取。将合并的有机层用盐水(10mL)洗涤, 经
 MgSO₄干燥, 过滤并减压浓缩, 得到残余物。通过制备型 TLC(石油醚/乙酸乙酯=0/1)纯化
 残余物, 得到呈无色油状的 2-甲基-N-((6-(三氟甲基)-1H-苯并[d]咪唑-2-基)甲基)丙-1-胺(中
 间体 B6)(100mg, 368umol, 25.4%收率, 100%纯度)。¹H NMR (400 MHz, CHLOROFORM-
 d) 7.80 (s, 1H), 7.56 (d, $J = 8.4$ Hz, 1H), 7.43 (d, $J = 8.5$ Hz, 1H), 4.07 (s, 2H), 2.45 (d, $J = 6.8$
 Hz, 2H), 1.82-1.68 (m, 1H), 0.89 (d, $J = 6.6$ Hz, 6H); LCMS: $[M+H]^+$ 272.0

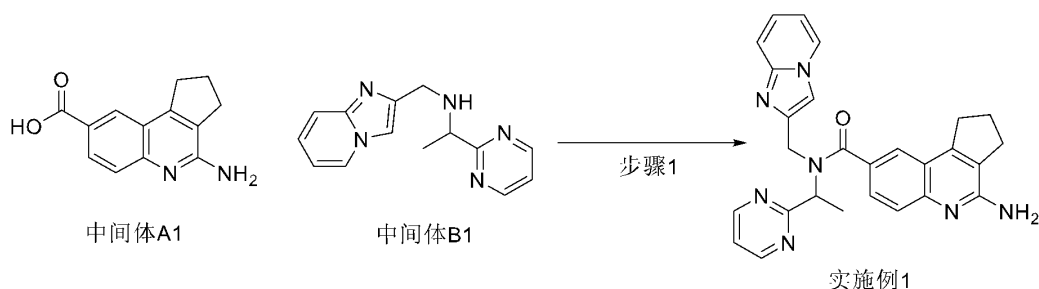
通用方法: 中间体 B7 的合成



步骤: 2-甲基-N-((6-(三氟甲基)咪唑并[1,2-a]吡啶-2-基)甲基)丙-1-胺(中间体 B7)

向 2-甲基丙-1-胺(68.3mg, 933umol, 92.8uL, 1 当量)和 6-(三氟甲基)咪唑并[1,2-a]吡
 20 啶-2-甲醛(0.2g, 933umol, 1 当量)在 DCM(4mL)中的溶液中添加 KOAc(109mg, 1.12mmol,
 1.2 当量)在 25°C 下, 将混合物在 25°C 下搅拌 0.5 小时, 然后在 25°C 下将 NaBH(OAc) 3
 (257mg, 1.21mmol, 1.3 当量)添加到上述混合物中, 将混合物 25°C 搅拌 15.5 小时。LCMS
 (ET60224-75-P1A) 显示 Cpd.4 被消耗并且检测到所需的质量。将反应混合物用
 H₂O(10mL)稀释并用 DCM(2mL×3)萃取以除去杂质。将水层用饱和 Na₂CO₃ 碱化至
 25 pH=8, 然后用 DCM(10mL*3)萃取。将合并的有机层经 MgSO₄干燥, 过滤并减压浓
 缩, 得到呈无色油状的 Cpd.A6(108mg, 398umol, 42.6%收率, 100%纯度)。¹H NMR
 (400 MHz, CHLOROFORM-d) δ 8.49 (s, 1H), 7.70-7.62 (m, 2H), 7.33 (br d, $J = 9.2$ Hz, 1H),
 4.01 (s, 2H), 2.54 (d, $J = 6.7$ Hz, 2H), 1.84 (quind, $J = 6.6, 13.3$ Hz, 1H), 0.97 (d, $J = 6.6$ Hz, 6H);
 LC-MS, $[MH]^+$ 272.0.

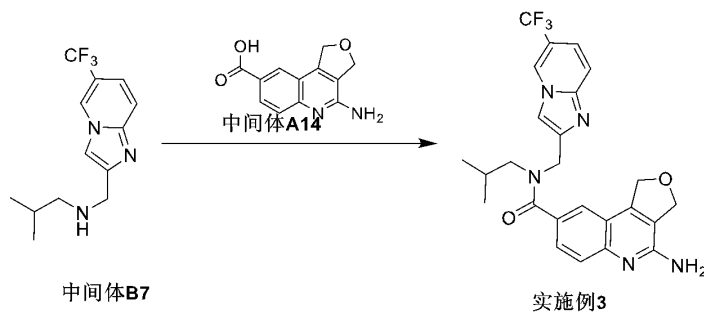
实施例 1 的合成



步骤 1: 4-氨基-N-(吡唑并[1,5-a]吡啶-2-基甲基)-N-(1-(嘧啶-2-基)乙基)-2,3-二氢-1H-环戊二烯[c]喹啉-8-甲酰胺(实施例 1)

将 4-氨基-2,3-二氢-1H-环戊二烯[c]喹啉-8-甲酸(80 mg, 0.35 mmol)在 SOCl_2 (2 mL)中的溶液在 70°C 下搅拌 12 小时。将溶剂浓缩至干, 直接用于下一步反应。在 N-(吡唑并[1,5-a]吡啶-2-基甲基)-1-(嘧啶-2-基)乙烷-1-胺(35 mg, 0.14 mmol)和 Et_3N (140 mg, 1.38)的溶液在 0°C 下, 在 THF(15 mL)中加入 4-氨基-2,3-二氢-1H-环戊二[c]喹啉-8-碳酰氯(80 mg, 0.32 mmol)。然后将混合物在 25°C 搅拌 12 小时。用 NaHCO_3 (aq.) (20 mL)淬灭反应, 然后用 EA (20 mL $\times$ 3)萃取。有机溶液用盐水(20mL)洗涤。有机相用 Na_2SO_4 干燥并过滤。减压浓缩滤液。将残余物通过硅胶色谱法纯化, 用 DCM 中的 MeOH 在 20 分钟内从 0% 洗脱到 5%, 得到 4-氨基-N-(吡唑并[1,5-a]吡啶-2-基甲基)-N-(1-(嘧啶-2-基)乙基)-2,3-二氢-1H-环戊二烯[c]喹啉-8-甲酰胺(2.3 mg, 4% 产率)为黄色固体(实施例 1)。 ^1H NMR (400 MHz, MeOD) δ 8.75 (s, 2H), 8.40 (s, 2H), 7.87 – 7.61 (m, 2H), 7.55 (d, $J = 8.8$ Hz, 1H), 7.32 (s, 1H), 7.18 (s, 1H), 6.83 (s, 1H), 6.51 (s, 1H), 5.68 (s, 1H), 5.40 (s, 1H), 4.73 – 4.53 (m, 2H), 3.24 (s, 2H), 2.94 (s, 2H), 2.41 – 2.13 (m, 2H), 1.84 – 1.65 (m, 3H)。LC-MS: $R_t = 0.981$ min, (ESI) m/z . 464.2 $[\text{M}+\text{H}]^+$. $\text{C}_{27}\text{H}_{25}\text{N}_7\text{O}$

实施例 3 的合成

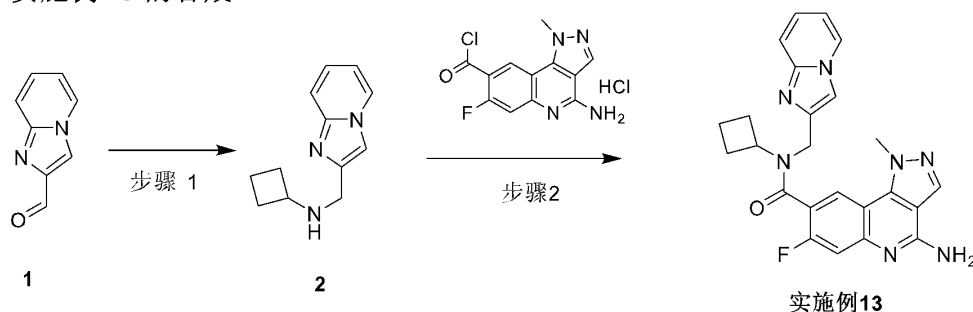


步骤: 4-氨基-N-异丁基-N-((6-(三氟甲基)咪唑并[1,2-a]吡啶-2-基)甲基)-1,3-二氢咪喃并[3,4-c]喹啉-8-甲酰胺(实施例 3)

向 4-氨基-1,3-二氢咪喃并[3,4-c]喹啉-8-甲酸(中间体 A14)(30 mg, 130 μmol , 1 eq) 和 2-甲基-N-((6-(三氟甲基)咪唑并[1,2-a]吡啶-2-基)甲基)丙-1-胺(中间体 B7)(35.3 mg, 130 μmol , 1 eq)在 DMF(2 mL) 中的混合物中添加 TCFH (43.8 mg, 156 μmol , 1.2 eq) 和 NMI(32.1mg, 390 μmol , 3 当量), 将混合物在 N_2 气氛下在 20°C 搅拌 16 小时。LC-MS 显示大部分起始材料已消耗, 并且检测到所需的 m/z 。将反应混合物减压浓缩, 残余物通过制备型 HPLC 纯化(柱: Waters Xbridge BEH C18 100*30mm*10 μm ; 流动相: [水(NH_4HCO_3)-ACN]; B%: 30%–60%, 8 分钟, UV 220&254 nm), 得到白色固体状的 4-氨基-N-异丁基

-N-((6-(三氟甲基)咪唑并[1,2-a]吡啶-2-基)甲基)-1,3-二氢呋喃并[3,4-c]喹啉-8-甲酰胺(实施例 3)(37 mg, 76.5 μ mol, 58.7%产率, 100%纯度)。 ^1H NMR (400 MHz, DMSO- d_6) δ = 9.20 (br s, 1H), 7.96 (br s, 1H), 7.91 - 7.63 (m, 2H), 7.48 (br d, J = 9.4 Hz, 2H), 7.56 (br d, J = 6.4 Hz, 1H), 6.66 (br s, 2H), 5.27 (br d, J = 0.9 Hz, 2H), 5.00 (br s, 2H), 4.86 - 4.51 (m, 2H), 3.30 - 3.19 (m, 2H), 2.16 - 1.90 (m, 1H), 1.00 - 0.61 (m, 6H); LC-MS, $[\text{MH}]^+$.484.2

实施例 13 的合成



步骤 1: (N-咪唑并[1, 2-a]吡啶-2-基甲基)环丁胺 (2)

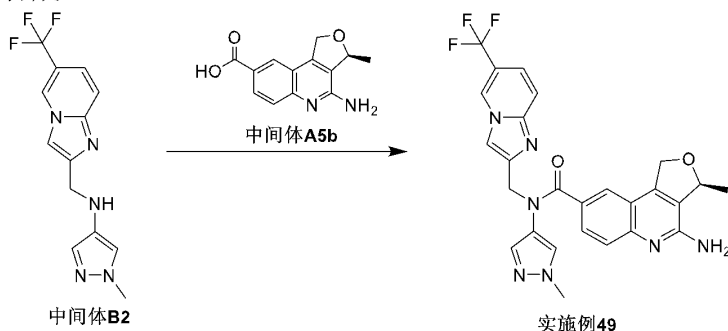
将咪唑并[1, 2-a]吡啶-2-甲醛(1)(300 毫克, 2.05 毫摩尔, 1 当量), 环丁胺(300 毫克, 4.22毫摩尔, 361.45 微升, 2.05 当量)溶解在甲醇中(5 毫升), 室温搅拌12小时, 加硼氢化钠 (118 毫克, 3.12 毫摩尔, 1.52 当量)室温搅拌4小时。LCMS检测到原料消耗完全, 目标产物生成。反应液加醋酸萃灭(60 微升), 减压浓缩至干, 加10%碳酸钠水溶液(25 毫升)和二氯甲烷/乙醇(10:1, 25 毫升)。分液, 水相用二氯甲烷/乙醇萃取 (10:1, 25 毫升*3), 合并有机相, 用硫酸钠干燥, 过滤, 减压浓缩至干得到棕色浆状物N-咪唑并[1,2-a]吡啶-2-基甲基)环丁胺 (2) (401毫克, 粗品) LCMS ES15882-916-P1A: (ESI) m/z = 202.2 $[\text{M}+1]^+$; RT= 1.249min

^1H NMR (400 MHz, CHLOROFORM- d) Shift 8.02-8.09 (m, 1H), 7.46-7.57 (m, 2H), 7.13 (ddd, J =1.22, 6.79, 8.99 Hz, 1H), 6.73 (dt, J =0.98, 6.79 Hz, 1H), 3.88 (s, 2H), 3.29-3.47 (m, 1H), 2.15-2.27 (m, 2H), 1.57-1.84 (m, 4H)

步骤 2: 4-氨基-N-环丁基-7-氟-N-咪唑并[1, 2-a]吡啶-2-基甲基)-1-甲基吡唑并[4, 3-c]喹啉-8-甲酰胺(实施例 13)

将N-咪唑并[1, 2-a]吡啶-2-基甲基)环丁胺 (2) (60 毫克, 298.11 微摩尔, 1 当量)和N-乙基-N-异丙基-2-丙胺(193 毫克, 1.50 毫摩尔, 261.29 微升, 5.03 当量)溶解在四氢呋喃中(5 毫升)加4-氨基-7-氟-1-甲基吡唑并[4, 3-c]喹啉-8-甲酰氯(104 毫克, 295.80 微摩尔, 9.92e-1 当量, 2盐酸盐), 反应液室温搅拌16小时。LCMS 检测原料消耗完全, 目标产物生成。反应液减压浓缩至干, 用二甲基亚砜稀释经反相制备液相色谱纯化(碱性条件; Boston Prime C18 柱子150*30毫米*5微米; 流动相: [水 (氨水 v/v)-乙腈]; B%梯度: 28%-48%, 9分钟)。得白色固体4-氨基-N-环丁基-7-氟-N-咪唑并[1, 2-a]吡啶-2-基甲基)-1-甲基吡唑并[4, 3-c]喹啉-8-甲酰胺(实施例 13) (72 毫克, 161.69 微摩尔, 54.24% 产率, 99.59% 纯度)。 ^1H NMR (400 MHz, DMSO- d_6) Shift 8.40-8.61 (m, 1H), 8.11-8.38 (m, 2H), 7.73-7.90 (m, 1H), 7.44-7.58 (m, 1H), 7.13-7.42 (m, 4H), 6.87 (t, J =6.65 Hz, 1H), 3.86-5.01 (m, 6H), 2.04-2.31 (m, 3H), 1.78-1.96 (m, 1H), 1.26-1.68 (m, 2H). ^{19}F NMR (376.5 MHz, DMSO- d_6) Shift -116.26, -116.59

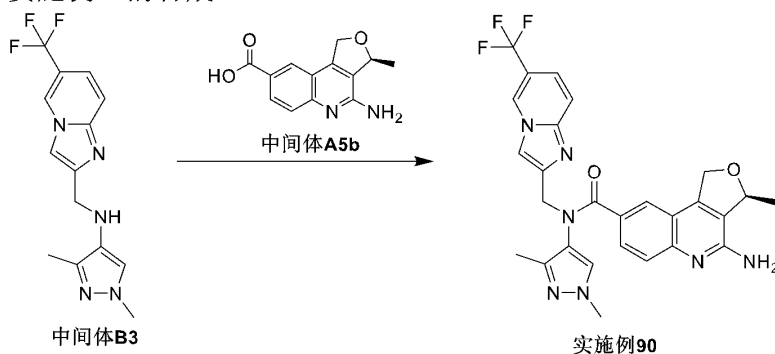
实施例49的合成



步骤: (S)-4-氨基-3-甲基-N-((1-甲基-1H-吡唑-4-基)-N-((6-(三氟甲基)咪唑并[1,2-a]吡啶-2-基))甲基)-1,3-二氢咪喃并[3,4-c]喹啉-8-甲酰胺(实施例49)

- 5 向1-甲基-N-((6-(三氟甲基)咪唑并[1,2-a]吡啶-2-基)甲基)-1H-吡唑-4-胺(中间体B2)(500 mg, 1.69 mmol, 1.00 eq)和(S)-4-氨基-3-甲基-1,3-二氢咪喃并[3,4-c]喹啉-8-甲酸(中间体A5b)(434 mg, 1.78 mmol, 1.05 eq)的DMF (5.00 mL)溶液中添加TCFH (713 mg, 2.54 mmol, 1.50 eq) 和NMI(695 毫克, 8.47 毫摩尔, 675 微升, 5.00 当量)。将混合物在25℃搅拌16小时。LC-MS (ET68149-2-P1A1)显示A29保留并检测到所需质量。
- 10 溶液通过制备型HPLC纯化(色谱柱: Waters Xbridge BEH C18 250 * 50 mm * 10 μm; 流动相: [水(NH₄HCO₃ 10 mM)- ACN]; B%: 20% - 45%, 10 分钟, UV 220 & 254 nm), 得到白色固体状的 (S)-4-氨基-3-甲基-N-((1-甲基-1H-吡唑-4-基)-N-((6-(三氟甲基)咪唑并[1,2-a]吡啶-2-基))甲基)-1,3-二氢咪喃并[3,4-c]喹啉-8-甲酰胺(实施例49)(285 mg, 535 μmol, 31.6% 产率, 97.9% 纯度)。
- 15 ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.18 (s, 1H), 8.03 (s, 1H), 7.73 (d, *J* = 9.5 Hz, 1H), 7.69-7.49 (m, 2H), 7.46 (dd, *J* = 1.3, 9.4 Hz, 2H), 7.42-6.94 (m, 2H), 6.61 (s, 2H), 5.43-5.35 (m, 1H), 5.27-5.19 (m, 1H), 5.18-5.10 (m, 1H), 5.05 (s, 2H), 3.66 (br s, 3H), 1.38 (d, *J* = 6.3 Hz, 3H); LC-MS, [MH]⁺ 522.2.

实施例90的合成

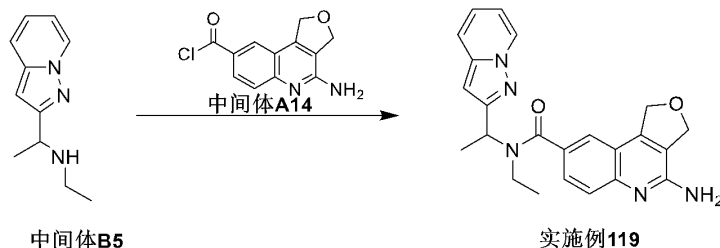


- 20 步骤: (S)-4-氨基-N-((1,3-二甲基咪唑并[1,2-a]吡啶-4-基)-3-甲基-N-((6-三氟甲基)咪唑并[1,2-a]吡啶-2-基)甲基)-1,3-二氢咪喃并[3,4-c]喹啉-8-甲酰胺 (实施例90)

- (S)-4-氨基-3-甲基-1,3-二氢咪喃并[3,4-c]喹啉-8-羧酸 (中间体A5b) (3.12 克, 12.76 毫摩尔, 1 当量), 1,3-二甲基-N-((6-(三氟甲基)咪唑并[1,2-a]吡啶-2-基)甲基)-1H-吡唑-4-胺 (中间体B1) (3.95 克, 12.77 毫摩尔, 1.0 当量) 和1-甲基吡咯烷-2-酮 (30 毫升) 的混合物加 N,N,N,N-四甲基氯甲脒六氟磷酸盐 (4.30 克, 15.32 毫摩尔, 1.2 当量)和N-甲基咪唑 (3.14 克, 38.29 毫摩尔, 3.05 毫升, 3.0 当量), 反应液室温搅拌16小时。LCMS 检测到原
- 25

料消耗完全, 目标产物生成。反应液用乙腈 (10 毫升) 和水 (10 毫升) 稀释, 过滤, 滤液通过反相制备液相色谱纯化 (柱子: C18 150×40毫米; 流动相: [水(氨水+碳酸氢铵)-乙腈]; 梯度: 17%-57%)。馏分冻干后得到白色固体 (S)-4-氨基-N-(1, 3-二甲基吡唑-4-基)-3-甲基-N-(6-三氟甲基)咪唑并[1, 2-a]吡啶-2-基)甲基)-1, 3-二氢呋喃并[3, 4-c]喹啉-8-甲酰胺 (实施例90) (100% 纯度)。HNMR: ES13683-1863-P1A, ¹H NMR (400 MHz, DMSO-d₆) Shift 9.21 (s, 1H), 8.05 (br s, 1H), 7.71 (br d, J=9.24 Hz, 1H), 7.59 (s, 1H), 7.28-7.57 (m, 4H), 6.63 (s, 2H), 5.33-5.49 (m, 1H), 5.07-5.30 (m, 2H), 4.99 (br s, 2H), 3.59 (s, 3H), 1.66 (br s, 3H), 1.38 (d, J=6.16 Hz, 3H)。FNMR: ¹⁹F NMR (376 MHz, DMSO-d₆) Shift -60.41 (br s, 1F)。LCMS: ES13683-1863-P1C, (ESI) m/z= 536.3 [M+1]⁺, RT=0.802 min

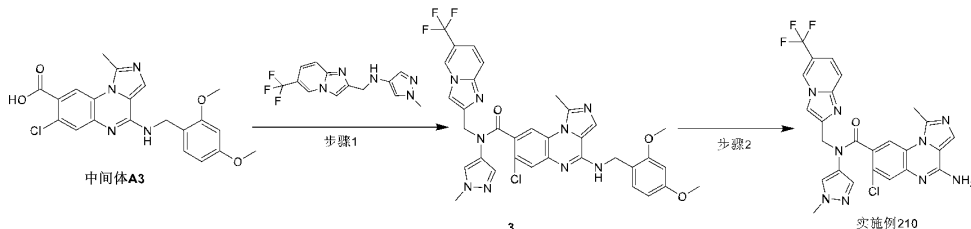
实施例119的合成



步骤: 4-氨基-N-乙基-N-(1-(吡唑并[1,5-a]吡啶-2-基)乙基)-1,3-二氢呋喃并[3,4-c]喹啉-8-甲酰胺(实施例119)

- 在 0℃ 下向 N-乙基-1-(吡唑并[1,5-a]吡啶-2-基)乙-1-胺 (中间体 B5)(50mg, 264.19μmol, 1eq) 的 THF(1mL) 溶液中添加 DIEA(136.58mg, 1.06mmol, 184.06μL, 4eq) 和 4-氨基-1,3-二氢呋喃并[3,4-c]喹啉-8-碳酰氯(65.69mg, 264.19μmol, 1eq)。0℃, 然后将混合物在 N₂ 气氛下在 0℃ 搅拌 1 小时。LCMS 表明起始材料完全消耗并且检测到产物。将反应混合物减压浓缩, 得到残余物。残余物通过制备型 HPLC 纯化 (柱: Waters Xbridge BEH C18 100*30 mm*10 μm; 流动相: [水(NH₄HCO₃)-ACN]; B%: 10%-50%, 8 分钟, UV220&254 nm) 得到白色固体状的 4-氨基-N-乙基-N-(1-(吡唑并[1,5-a]吡啶-2-基)乙基)-1,3-二氢呋喃并[3,4-c]喹啉-8-甲酰胺(实施例119)(41.9mg, 104μmol, 39.5% 收率)。¹H NMR (400 MHz, DMSO-d₆) δ 8.69 (d, J = 7.0 Hz, 1H), 7.82-7.50 (m, 4H), 7.36-7.14 (m, 1H), 6.88 (s, 1H), 6.69 (s, 3H), 5.42-5.18 (m, 3H), 5.02 (br s, 2H), 1.82-1.54 (m, 3H), 1.18 - 0.83 (m, 3H); LC-MS, [MH]⁺ 402.1.

实施例210的合成



- 步骤1: 7-氯-4-[(2,4-二甲氧基苯基)氨基氨基]-1-甲基-N-(1-甲基吡唑-4-基)-N-[[6-(三氟甲基)咪唑并[1,2-a]吡啶-2-基]甲基]咪唑并[1,5-a]喹啉-8-甲酰胺 (3)

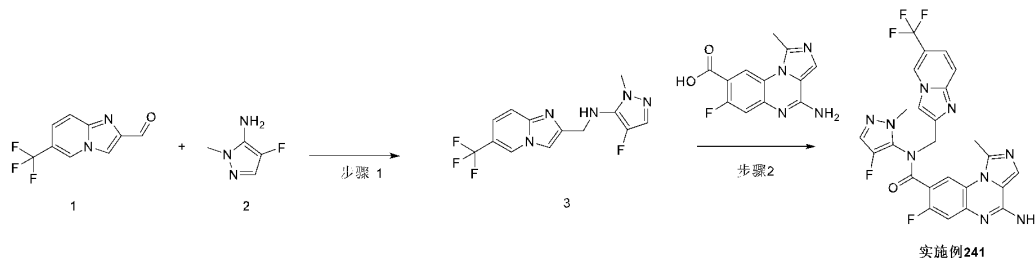
将 7-氯-4-((2,4-二甲氧基苯基)氨基)-1-甲基咪唑并[1,5-a]喹啉-8-羧酸 (中间体 A3) (145 毫克, 339 微摩尔, 1 当量) 加入 1-甲基-N-[[6-(三氟甲基)咪唑并[1,2-a]吡啶-2-

基]甲基]吡啶-4-胺(中间体B2) (100毫克, 339微摩尔, 1当量)的到乙腈(2 毫升)溶液中, 溶解后依次加入N,N,N,N-四甲基氯甲脒六氟磷酸盐 (285毫克, 1毫摩尔, 3当量)和N-甲基咪唑 (139毫克, 1.7毫摩尔, 135微升, 5当量)。反应在50摄氏度下搅拌16小时。LC-MS检测到原料反应完全, 目标产物生成。反应液过滤后减压浓缩得到粗产物。粗产物经柱层析分离纯化(二氧化硅, 10%甲醇在二氯甲烷中)得到黄色油状7-氯-4-[(2,4-二甲氧基苯基)甲基氨基]-1-甲基-N-(1-甲基吡啶-4-基)-N-[[6-(三氟甲基)咪唑并[1,2-a]吡啶-2-基]甲基]咪唑并[1,5-a]喹啉-8-甲酰胺 (3) (130毫克, 185微摩尔, 54.5%产率)。

步骤2: 4-氨基-7-氯-1-甲基-N-(1-甲基-1-氢-吡啶-4-基)-N-((6-(三氟甲基)咪唑并[1,2-a]吡啶-2-基)甲基)咪唑并[1,5-a]喹啉-8-甲酰胺 (实施例210)

7-氯-4-[(2,4-二甲氧基苯基)甲基氨基]-1-甲基-N-(1-甲基吡啶-4-基)-N-[[6-(三氟甲基)咪唑并[1,2-a]吡啶-2-基]甲基]咪唑并[1,5-a]喹啉-8-甲酰胺 (3) (120毫克, 170微摩尔, 1当量) 加入到 三氟乙酸 (0.4毫升)和二氯甲烷(1毫升) 的混合溶液中并溶解。反应在50摄氏度下搅拌16小时。LC-MS显示原料反应完全有目标产物生成。反应经减压浓缩至干。通过反相制备液相色谱纯化(Boston Prime C18柱子, 5微米二氧化硅30毫米直径, 150毫米长度, 使用水和乙腈的极性递减的混合物作为洗脱液)得到白色4-氨基-7-氯-1-甲基-N-(1-甲基-1-氢-吡啶-4-基)-N-((6-(三氟甲基)咪唑并[1,2-a]吡啶-2-基)甲基)咪唑并[1,5-a]喹啉-8-甲酰胺 (实施例210) (30毫克, 53微摩尔, 31%产率, 98.0%纯度)。¹H NMR (400 MHz, DMSO-d₆) δ 9.15-9.31 (m, 1H), 8.33 (s, 1H), 8.07-8.16 (m, 1H), 7.92-8.03 (m, 1H), 7.76-7.86 (m, 1H), 7.58-7.75 (m, 2H), 7.41-7.55 (m, 3H), 7.18-7.33 (m, 1H), 4.71-5.17 (m, 2H), 3.53-3.83 (m, 3H), 2.80-2.97 (m, 3H)。LCMS: (ESI) m/z=554.2 (M+1)⁺, RT= 1.544 min, purity of 98.7 %。

实施例241的合成



步骤1: 4-氟-2-甲基-N-[[6-(三氟甲基)咪唑并[1,2-a]吡啶-2-基]甲基]吡啶-3-胺 (3)

将6-(三氟甲基)咪唑并[1,2-a]吡啶-2-甲醛 (1) (700毫克, 3.27毫摩尔, 1当量)溶解在甲醇(14毫升)中, 加入4-氟-1-甲基-1H-吡啶-5-胺 (2) (402.61毫克, 3.50毫摩尔, 1.07当量)和冰醋酸 (255.18毫克, 4.25毫摩尔, 243.26 微升, 1.3当量), 反应在25摄氏度下搅拌1小时。再加入氰基硼氢化钠(616.24 毫克, 9.81 毫摩尔, 3 当量), 25摄氏度下搅拌15小时。LC-MS检测到原料反应完全, 目标产物生成。反应液浓缩旋干, 加入14毫升2摩尔/升的碳酸钠水溶液和14毫升乙酸乙酯, 分液, 用乙酸乙酯萃取(14毫升*3), 有机相用无水硫酸镁干燥, 过滤, 滤液减压浓缩至干, 经柱层析色谱纯化(12克+4克硅胶柱, 洗脱液 0~30% 乙酸乙酯:乙醇 3:1/石油醚, 流速30毫升/分钟), 减压浓缩得到浅黄色固体4-氟-2-甲基-N-[[6-(三氟甲基)咪唑并[1,2-a]吡啶-2-基]甲基]吡啶-3-胺 (3) (970毫克, 3.10毫摩尔, 94.73%产率)。LCMS: ES13685-1213-P1A, (ESI) m/z = 314.0[M+1]⁺; RT= 1.537 min。NMR: ES13685-1213-R2A, ¹H NMR (400 MHz,

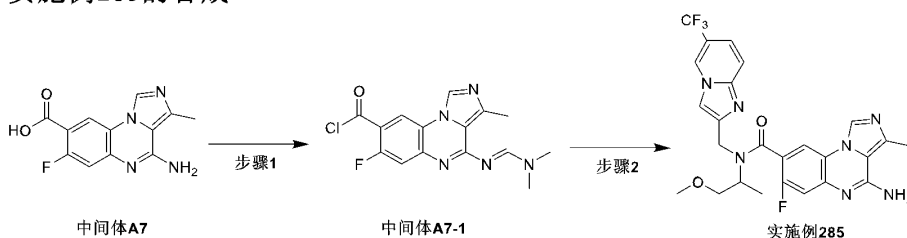
CHLOROFORM-d) 7.11 (d, J=4.38 Hz, 1H), 3.57 (s, 3H), 3.24 (br s, 2H)。HNMR: ES13685-1213-R2A, 19F NMR (376 MHz, CHLOROFORM-d) -185.48 (s, 1F)

步骤2: 4-氟-2-甲基-N-[[6-(三氟甲基)咪唑并[1,2-a]吡啶-2-基]甲基]吡啶-3-胺 (实施例241)

- 5 向反应液4-氨基-7-氟-甲基-咪唑并[1,5-a]喹啉-8-羧酸 (500毫克, 1.92 毫摩尔, 1当量), 4-氟-2-甲基-N-[[6-(三氟甲基)咪唑并[1,2-a]吡啶-2-基]甲基]吡啶-3-胺 (3) (601.89毫克, 1.92毫摩尔, 1当量)和N,N-二异丙基乙胺(993.30毫克, 7.69毫摩尔, 1.34毫升, 4当量)溶解在1-甲基-2-吡咯烷酮(10毫升)中, 加入2-氯-1, 3-二甲基-4, 5-二氢咪唑-1-氯化物(487.23毫克, 2.88毫摩尔, 1.5当量)。反应在50摄氏度下搅拌16小时。LC-MS检测
- 10 有47%原料剩余, 36%目标产物生成。再加入2-氯-1, 3-二甲基-4, 5-二氢咪唑-1-氯化物 (74.71毫克, 441.93 微摩尔, 0.23 当量)。反应在50摄氏度下搅拌16小时, LC-MS检测有49%原料剩余, 38%目标产物生成。通过反相制备液相色谱纯化(Boston Prime C18柱子, 5微米二氧化硅30毫米直径, 150毫米长度, 使用水(含有0.05%甲酸)和乙腈(20%-40%)的极性递减的混合物作为洗脱液)得到浅黄色固体。核磁检测有部分成甲酸盐, 粗品再通过反相制备液相色谱纯化(Boston Prime C18柱子, 5微米二氧化硅30毫米直径, 150毫米长度, 使用水(含有0.05%氨水)和乙腈(32%-52%)的极性递减的混合物作为洗脱液)得到白色固体4-氨基-7-氟-N-(4-氟-2-甲基-吡啶-3-基)-1-甲基-N-[[6-(三氟甲基)咪唑并[1,2-a]吡啶-2-基]甲基]咪唑并[1,5-a]喹啉-8-甲酰胺 (实施例241) (155毫克, 276.26微摩尔, 14.38% 产率)。LCMS: ES13685-1217-P1D1, (ESI) m/z= 556.1 [M+1]
- 20 +; RT= 1.929minNMR: ES13685-1217-P1B, 1H NMR (400 MHz, DMSO-d6) 9.28 (br s, 1H), 8.10 (br s, 1H), 7.92 (br s, 1H), 7.82 (s, 1H), 7.73 (d, J=9.76 Hz, 1H), 7.55 (s, 2H), 7.47 (br d, J=8.63 Hz, 1H), 7.29 (br s, 1H), 7.11 (br d, J=10.38 Hz, 1H), 5.19 (br s, 1H), 5.04-5.14 (m, 1H), 3.59 (s, 3H), 2.86 (br s, 3H)。NMR: ES13685-1217-P1B, 19F NMR (376 MHz, DMSO-d6) -60.47 (s, 3F), -118.15 (s, 1F), -173.54 (s, 1F)

25

实施例285的合成



步骤1: (E)-4-(((二甲基氨基)亚甲基)氨基)-7-氟-3-甲基咪唑并[1,5-a]喹啉-8-碳酰氯(中间体A7-1)

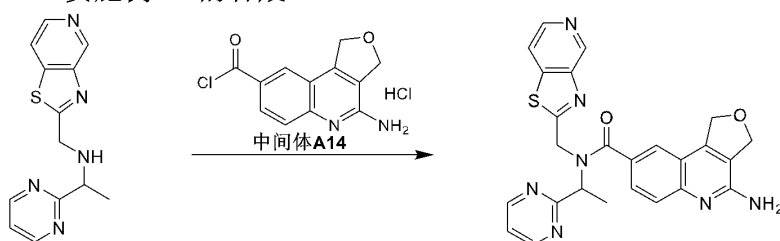
- 30 向4-氨基-7-氟-3-甲基咪唑并[1,5-a]喹啉-8-甲酸 (中间体A7) (270mg, 1.04mmol, 1当量)在DCM(3.00mL)中的搅拌溶液中添加HCl/二恶烷(4M, 778uL, 3当量)。将混合物在25℃搅拌0.5小时。然后将反应混合物浓缩, 用甲苯(10mL x 3)蒸并干燥, 将粗产物溶解在DCM(3.00mL)中, 并冷却至0° C, 加入草酰二氯(790mg, 6.23mmol, 544uL, 在0℃下滴加6当量)和DMF(75.8毫克, 1.04毫摩尔, 79.8uL, 1当量)。将混合物在25℃
- 35 搅拌12小时。LCMS表明起始材料已消耗并且检测到具有所需质量的一个主峰。将反应混合物浓缩, 用正己烷(10mL x 3)蒸煮并减压干燥, 得到呈黄色固体状的(E)-4-(((二甲基氨基)亚甲基)氨基)-7-氟-3-甲基咪唑并[1,5-a]喹啉-8-碳酰氯(中间体A7-1) (340mg,

粗品)。LC-MS (ESI) $m/z = 330.0 [M+H]^+$

步骤2: 4-氨基-7-氟-N-(1-甲氧基丙-2-基)-3-甲基-N-((6-(三氟甲基)咪唑并[1,2-a]吡啶-2-基)甲基)咪唑 [1,5-a]喹喔啉-8-甲酰胺 (实施例285)

在0°C下, 向1-甲氧基-N-((6-(三氟甲基)咪唑并[1,2-a]吡啶-2-基)甲基)丙-2-胺(50.0 mg, 174 μmol , 1 eq) 和 DIEA (89.9 mg, 696 μmol , 121 μL , 4 eq)的THF (1.00 mL)溶液中添加 中间体A7-1 (63.9 mg, 191 μmol , 1.1 eq)。将混合物在25°C搅拌3小时。在25°C下通过添加MeOH(1.00mL)猝灭反应混合物, 并减压浓缩, 得到残余物。将残余物溶解于MeOH(1mL)和NH₃/MeOH(7M, 1mL)中。将混合物在70°C搅拌2小时。LCMS表明起始材料已消耗并且检测到具有所需质量的一个主峰。将反应混合物减压浓缩, 残余物通过制备型HPLC纯化(柱: Waters Xbridge BEH C18 100*30 mm*10 μm ; 流动相: [水(NH₄HCO₃)-ACN]; B%: 30%-60%, 8分钟, UV 220 nm & 254 nm), 得到黄色固体状的 4-氨基-7-氟-N-(1-甲氧基丙-2-基)-3-甲基-N-((6-(三氟甲基)咪唑并[1,2-a]吡啶-2-基)甲基)咪唑 [1,5-a]喹喔啉-8-甲酰胺 (实施例285) (58.1 mg, 109 μmol , 64.2% 产率)。¹H NMR (400MHz, DMSO-d₆) δ 9.29-8.54 (m, 2H), 8.18-7.78 (m, 2H), 7.66 (br s, 1H), 7.38 (br d, $J = 7.9$ Hz, 1H), 7.13 (br s, 1H), 6.72 (br s, 2H), 4.95-4.39 (m, 2H), 4.22-3.82 (m, 1H), 3.52 (br s, 2H), 3.31-3.10 (m, 3H), 2.63 (s, 3H), 1.21 (br s, 3H) LC-MS (ESI) $m/z = 530.2 [M+H]^+$

实施例304的合成



20 中间体B4

实施例304

步骤: 4-氨基-N-(1-(咪唑啉-2-基)乙基)-N-(咪唑并[4,5-c]吡啶-2-基甲基)-1,3-二氢呋喃并[3,4-c]喹啉-8-甲酰胺(实施例304)

在0°C下, 向1-(咪唑啉-2-基)-N-(咪唑并[4,5-c]吡啶-2-基甲基)乙-1-胺(中间体B4) (27 mg, 99.6 μmol , 1 eq)的THF(1 mL)溶液中添加DIEA (51.5 mg, 398 μmol , 69.4 μL , 4 eq)和 4-氨基-1,3-二氢呋喃并[3,4-c]喹啉-8-甲酰胺盐酸盐(28.4 mg, 99.6 μmol , 1 eq, HCl)。将混合物在25°C搅拌2小时。LCMS显示起始材料完全消耗并且检测到所需质量。将混合物用MeOH(2mL)猝灭并减压浓缩, 得到残余物。残余物通过制备型HPLC纯化(柱: Waters Xbridge Prep OBD C18 150*40 mm*10 μm ; 流动相: [水(NH₄HCO₃)-ACN]; B%: 15%-55%, 8分钟, UV220 nm&254 nm)得到白色固体状的4-氨基-N-(1-(咪唑啉-2-基)乙基)-N-(咪唑并[4,5-c]吡啶-2-基甲基)-1,3-二氢呋喃并[3,4-c]喹啉-8-甲酰胺(实施例304)(19mg, 38.9 μmol , 39.0%产率, 98.9%纯度)。¹H NMR (400 MHz, DMSO-d₆) δ 9.26 - 9.11 (m, 1H), 8.81 (d, $J = 4.9$ Hz, 2H), 8.49 (br d, $J = 1.1$ Hz, 1H), 8.13 (br d, $J = 5.1$ Hz, 1H), 7.74 - 7.57 (m, 3H), 7.42 (t, $J = 4.9$ Hz, 1H), 6.73 (br s, 2H), 5.50 - 5.09 (m, 4H), 5.00 (br s, 2H), 4.96 - 4.87 (m, 1H), 1.68 (br d, $J = 7.0$ Hz, 3H); LC-MS, $[M+H]^+$ 484.2

35

以下化合物基于通用方法合成, 产物对应结构见表 1, 表征见表 2:

表 2

	HNMR/LCMS		HNMR/LCMS
1	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.82 – 8.78 (m, 2H), 8.50 (d, <i>J</i> = 6.4 Hz, 1H), 8.02 – 7.67 (m, 2H), 7.64 – 7.37 (m, 4H), 7.29 – 7.10 (m, 1H), 6.84 (s, 1H), 6.43 (s, 2H), 5.39 (s, 1H), 4.91–4.32 (m, 2H), 3.29 – 3.02 (m, 1H), 2.95 – 2.76 (m, 3H), 2.45 – 1.89 (m, 2H), 1.64 (d, <i>J</i> = 6.4 Hz, 3H). ¹⁹ F NMR (377 MHz, DMSO) δ - 60.66 (s, 1H). LC-MS: Rt = 0.858 min, (ESI) <i>m/z</i> . [M+H] ⁺ 465.3; C ₂₇ H ₂₅ N ₇ O	2	¹ H NMR (400 MHz, dmsO- <i>d</i> ₆) δ 8.90 – 8.71 (m, 1H), 8.53 (s, 3H), 8.00 – 7.76 (m, 1H), 7.59 – 7.43 (m, 3H), 7.23 (s, 2H), 5.64 – 5.45 (m, 1H), 5.30 – 5.09 (m, 1H), 5.06 – 4.99 (m, 1H), 4.95 – 4.89 (m, 1H), 3.29 – 3.18 (m, 2H), 3.00 – 2.77 (m, 2H), 2.31 (s, 1H), 2.03 (s, 1H), 1.79 – 1.20 (m, 3H). LC-MS: Rt = 0.918 min, (ESI) <i>m/z</i> . [M+H] ⁺ , 464.2. C ₂₇ H ₂₅ N ₇ O.
3	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ = 9.20 (br s, 1H), 7.96 (br s, 1H), 7.91 – 7.63 (m, 2H), 7.48 (br d, <i>J</i> = 9.4 Hz, 2H), 7.56 (br d, <i>J</i> = 6.4 Hz, 1H), 6.66 (br s, 2H), 5.27 (br d, <i>J</i> = 0.9 Hz, 2H), 5.00 (br s, 2H), 4.86 – 4.51 (m, 2H), 3.30 – 3.19 (m, 2H), 2.16 – 1.90 (m, 1H), 1.00 – 0.61 (m, 6H) LC-MS: Rt = 2.688 min, (ESI) <i>m/z</i> . [M+H] ⁺ 484.2; C ₂₅ H ₂₄ F ₃ N ₅ O ₂	4	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ = 9.35 – 9.08 (m, 1H), 8.74 – 8.35 (m, 1H), 8.29 – 8.17 (m, 1H), 8.12 – 7.96 (m, 1H), 7.83 – 7.69 (m, 1H), 7.66 – 7.54 (m, 2H), 7.53 – 7.45 (m, 1H), 7.18 – 7.01 (m, 2H), 4.94 – 4.48 (m, 2H), 4.43 – 4.10 (m, 3H), 3.30 – 3.21 (m, 2H), 2.23 – 1.92 (m, 1H), 1.06 – 0.58 (m, 6H) LC-MS: Rt = 2.684 min, (ESI) <i>m/z</i> . [M+H] ⁺ 496.3; C ₂₅ H ₂₄ F ₃ N ₇ O
5	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.81 (br s, 2H), 8.49 (br d, <i>J</i> = 6.1 Hz, 1H), 7.91 (br s, 1H), 7.65 (br d, <i>J</i> = 8.6 Hz, 2H), 7.58 – 7.48 (m, 1H), 7.59 – 7.35 (m, 1H), 7.29 – 7.10 (m, 1H), 6.92 – 6.78 (m, 1H), 6.59 (br s, 2H), 5.47 – 5.33 (m, 2H), 5.32 – 5.17 (m, 1H), 5.15 – 4.95 (m, 1H), 4.94 – 4.22 (m, 2H), 1.62 (d, <i>J</i> = 7.1 Hz, 3H), 1.38 (br d, <i>J</i> = 2.2 Hz, 3H) LC-MS: Rt = 2.172 min, (ESI) <i>m/z</i> . [M+H] ⁺ 480.3; C ₂₇ H ₂₅ N ₇ O ₂	6	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ = 8.52 (d, <i>J</i> = 6.8 Hz, 1H), 8.15 – 7.83 (m, 2H), 7.77 – 7.60 (m, 1H), 7.55 (br d, <i>J</i> = 5.6 Hz, 2H), 7.25 (br s, 1H), 6.89 (br t, <i>J</i> = 6.6 Hz, 1H), 6.65 (s, 2H), 5.36 – 5.20 (m, 2H), 4.99 (br s, 2H), 4.77 – 4.53 (m, 2H), 3.47 – 3.40 (m, 2H), 1.12 (br t, <i>J</i> = 6.9 Hz, 3H) LC-MS: Rt = 2.080 min, (ESI) <i>m/z</i> . [M+H] ⁺ 388.1; C ₂₂ H ₂₁ N ₅ O ₂
7	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ = 8.60 – 8.44 (m, 1H), 8.30 – 7.73 (m, 2H), 7.71 – 7.43 (m, 3H), 7.39 – 7.15 (m, 1H), 6.98 – 6.79 (m, 1H), 6.73 – 6.46 (m, 2H), 5.58 – 5.03 (m, 3H), 4.86 – 4.38 (m, 2H), 3.26 – 3.24 (m, 2H), 1.50 – 1.29 (m, 3H), 1.22 – 0.99 (m, 3H) LC-MS: Rt = 2.043 min, (ESI) <i>m/z</i> . [M+H] ⁺ 402.2; C ₂₃ H ₂₃ N ₅ O ₂	8	¹ H NMR (400MHz, DMSO- <i>d</i> ₆) Shift = 8.80 (d, <i>J</i> =4.9 Hz, 2H), 8.49 (d, <i>J</i> =6.8 Hz, 1H), 7.99 – 7.66 (m, 1H), 7.80 (br s, 2H), 7.59 (br d, <i>J</i> =8.3 Hz, 1H), 7.52 – 7.31 (m, 3H), 7.18 (br s, 1H), 6.85 (br t, <i>J</i> =6.6 Hz, 1H), 6.45 (br s, 2H), 5.46 – 5.27 (m, 1H), 5.04 – 4.06 (m, 2H), 2.20 (br s, 3H), 1.64 (br d, <i>J</i> =6.9 Hz, 3H). LC-MS: Rt = 1.493 min, (ESI) <i>m/z</i> . [M+H] ⁺ 438.1; C ₂₅ H ₂₃ N ₇ O
9	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) Shift 8.10–8.59 (m, 3H), 7.68–7.97 (m, 1H), 7.52 (br d, <i>J</i> =8.78 Hz, 1H), 7.19–7.38 (m, 4H), 6.88 (t, <i>J</i> =6.65 Hz, 1H), 4.94–5.15 (m, 2H), 4.49–4.93 (m, 5H), 4.04–4.41 (m, 3H). LC-MS: Rt = 1.188 min, (ESI) <i>m/z</i> . [M+H] ⁺ 446.2; C ₂₃ H ₂₀ FN ₇ O ₂	10	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) Shift 8.70 (br s, 1H), 8.50 (br d, <i>J</i> =6.00 Hz, 1H), 8.14–8.32 (m, 1H), 7.92 (br s, 1H), 7.56 (br d, <i>J</i> =8.76 Hz, 1H), 7.35 (br d, <i>J</i> =11.51 Hz, 1H), 7.24 (br s, 3H), 6.90 (br t, <i>J</i> =6.25 Hz, 1H), 5.92 (br s, 1H), 5.08 (br d, <i>J</i> =6.13 Hz, 1H), 4.36 (br s, 3H), 3.47 (br d, <i>J</i> =7.00 Hz, 1H), 3.13 (br s, 1H), 1.70 (br s, 1H), 1.52–1.64 (m, 2H), 1.09 (br s, 3H), 0.79 (br s, 1H). LC-MS: Rt = 1.155 min, (ESI) <i>m/z</i> . [M+H] ⁺ 432.2 C ₂₃ H ₂₂ FN ₇ O
11	¹ H NMR (400MHz, DMSO- <i>d</i> ₆) Shift 8.52	12	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) Shift

	- 8.40 (m, 1H), 8.29 - 8.18 (m, 2H), 7.92 - 7.73 (m, 1H), 7.55 - 7.40 (m, 1H), 7.36 - 7.25 (m, 3H), 7.25 - 7.13 (m, 1H), 6.90 - 6.79 (m, 1H), 4.37 (d, J=10.8 Hz, 3H), 4.05 - 3.47 (m, 5H), 2.43 - 2.07 (m, 2H). LC-MS: Rt =2.206 min, (ESI) m/z. [M+H] ⁺ 430.2; C ₂₃ H ₂₀ FN ₇ O		8.45-8.61 (m, 2H), 8.17-8.29 (m, 1H), 7.90 (br s, 1H), 7.53 (d, J=9.03 Hz, 1H), 7.33 (d, J=11.80 Hz, 1H), 7.21-7.30 (m, 3H), 6.90 (t, J=6.65 Hz, 1H), 4.51-5.00 (m, 2H), 4.09-4.44 (m, 3H), 3.47-3.73 (m, 4H), 3.09-3.32 (m, 3H). LC-MS: Rt =1.305 min, (ESI) m/z. [M+H] ⁺ 448.2; C ₂₃ H ₂₂ FN ₇ O ₂
13	¹ H NMR (400 MHz, DMSO-d ₆) Shift 8.54 (br s, 1H), 8.25 (br d, J=5.27 Hz, 2H), 7.86 (br s, 1H), 7.51 (br d, J=9.03 Hz, 1H), 7.14-7.41 (m, 4H), 6.89 (m, 1H), 3.90-5.15 (m, 5H), 1.50-2.28 (m, 7H). LC-MS: Rt =1.521 min, (ESI) m/z. [M+H] ⁺ 456.2; C ₂₅ H ₂₂ FN ₇ O	14	¹ H NMR (400 MHz, DMSO-d ₆) Shift 8.42-8.74 (m, 1H), 8.04-8.32 (m, 2H), 7.88 (s, 1H), 7.45-7.73 (m, 2H), 7.02-7.42 (m, 4H), 6.88 (t, J=6.65 Hz, 1H), 4.86-5.17 (m, 2H), 4.07-4.46 (m, 3H), 3.50-3.89 (m, 3H). LC-MS: Rt =1.228 min, (ESI) m/z. [M+H] ⁺ 470.2; C ₂₄ H ₂₀ FN ₉ O
15	¹ H NMR (400 MHz, DMSO-d ₆) Shift 8.41-8.58 (m, 2H), 8.35 (br s, 1H), 7.90 (br s, 1H), 7.44-7.68 (m, 3H), 7.16-7.28 (m, 1H), 6.74-6.93 (m, 3H), 5.19 (br s, 1H), 4.35 (s, 3H), 3.42 (br d, J=5.06 Hz, 1H), 3.16 (br dd, J=7.26, 13.64 Hz, 1H), 1.61 (br s, 3H), 1.07 (br s, 3H). LC-MS: Rt =1.395 min, (ESI) m/z. [M+H] ⁺ 414.2; C ₂₃ H ₂₃ N ₇ O	16	¹ H NMR (400 MHz, DMSO-d ₆) Shift 9.19 (s, 1H), 8.23 (s, 1H), 8.25-8.19 (m, 1H), 8.53-8.15 (m, 1H), 8.08 (s, 1H), 7.83-7.66 (m, 2H), 7.62 (br d, J = 7.6 Hz, 1H), 7.55-7.44 (m, 2H), 7.40-7.21 (m, 1H), 7.15 (s, 2H), 5.10 (s, 2H), 4.19 (s, 3H), 3.67 (br s, 3H). LC-MS: Rt = 2.362 min, (ESI) m/z. [M+H] ⁺ 520.2; C ₂₅ H ₂₀ F ₃ N ₉ O
17	¹ H NMR (400 MHz, DMSO-d ₆) Shift 9.19 (s, 1H), 8.36 (br d, J = 2.0 Hz, 1H), 8.24 (s, 1H), 8.00 (br s, 1H), 7.76 (d, J = 9.4 Hz, 1H), 7.60 (br s, 2H), 7.49 (dd, J = 1.8, 9.5 Hz, 1H), 7.16 (s, 2H), 5.12-4.99 (m, 1H), 4.93 (br s, 2H), 4.78 (br t, J = 6.8 Hz, 2H), 4.64-4.58 (m, 2H), 4.25 (br s, 3H). LC-MS: Rt = 2.329 min, (ESI) m/z. [M+H] ⁺ 496.2; C ₂₄ H ₂₀ F ₃ N ₇ O ₂	18	¹ H NMR (400 MHz, DMSO-d ₆) δ = 8.77 - 8.56 (m, 1H), 8.53 (d, J = 6.8 Hz, 1H), 8.23 (s, 1H), 7.97 (s, 1H), 7.66 (br s, 1H), 7.62 - 7.53 (m, 2H), 7.27 (br t, J = 7.1 Hz, 1H), 7.14 (br s, 2H), 6.91 (t, J = 6.7 Hz, 1H), 4.82 - 4.56 (m, 2H), 4.25 - 4.08 (m, 2H), 3.45 (q, J = 6.8 Hz, 3H), 1.15 (br t, J = 7.0 Hz, 3H) LC-MS: Rt = 1.964 min, (ESI) m/z. [M+H] ⁺ 400.2; C ₂₂ H ₂₁ N ₇ O
19	¹ H NMR (400 MHz, DMSO-d ₆) Shift 8.43-9.02 (m, 2H), 8.22 (br s, 1H), 7.99 (br s, 1H), 7.54 (br d, J=9.03 Hz, 1H), 7.11-7.38 (m, 4H), 6.89 (br t, J=6.53 Hz, 1H), 4.07-5.87 (m, 5H), 3.45-3.94 (m, 4H), 0.93 (br d, J=6.53 Hz, 3H). LC-MS: Rt =1.340 min, (ESI) m/z. [M+H] ⁺ 460.2; C ₂₄ H ₂₂ FN ₇ O ₂	20	¹ H NMR (400 MHz, DMSO-d ₆) Shift 9.22-9.44 (m, 1H), 8.43 (br d, J=7.26 Hz, 1H), 8.18-8.30 (m, 1H), 8.13 (br d, J=6.60 Hz, 1H), 7.92-8.05 (m, 1H), 7.69 (br d, J=8.80 Hz, 1H), 7.50 (br d, J=9.46 Hz, 1H), 7.17-7.38 (m, 3H), 4.49-4.94 (m, 2H), 4.17-4.40 (m, 3H), 3.42 (br s, 1H), 1.88-2.23 (m, 1H), 0.57-1.02 (m, 6H). LC-MS: Rt =1.546 min, (ESI) m/z. [M+H] ⁺ 471.2; C ₂₅ H ₂₃ FN ₈ O
21	¹ H NMR (400 MHz, DMSO-d ₆) Shift 8.42 (d, J=7.28 Hz, 2H), 8.20 (s, 1H), 7.80 (s, 1H), 7.51 (d, J=9.03 Hz, 1H), 7.29 (d, J=11.80 Hz, 1H), 7.19-7.26 (m, 3H), 6.85 (t, J=6.53 Hz, 1H), 4.90 (br d, J=5.77 Hz, 2H), 4.51 (s, 2H), 4.26 (br d, J=6.02 Hz, 2H), 4.21 (s, 3H), 4.16-4.23 (m, 1H), 1.54 (s, 3H). LC-MS: Rt =1.221 min, (ESI) m/z. [M+H] ⁺ 460.2; C ₂₄ H ₂₂ FN ₇ O ₂	22	¹ H NMR (400 MHz, DMSO-d ₆) Shift 8.34-8.67 (m, 1H), 8.08-8.32 (m, 2H), 7.62-7.90 (m, 1H), 7.51 (br s, 1H), 7.10-7.40 (m, 4H), 6.86 (br s, 1H), 4.29-5.10 (m, 5H), 3.61-4.11 (m, 5H), 2.14 (br d, J=6.02 Hz, 2H). LC-MS: Rt =1.242 min, (ESI) m/z. [M+H] ⁺ 460.2; C ₂₄ H ₂₂ FN ₇ O ₂
23	¹ H NMR (400 MHz, DMSO-d ₆) Shift 8.35-8.65 (m, 1H), 8.00-8.33 (m, 2H), 7.87 (br s, 1H), 7.52 (br d, J=9.03 Hz, 1H), 7.14-7.39 (m, 4H), 6.76-6.98 (m,	24	¹ H NMR (400 MHz, DMSO-d ₆) Shift 8.30-8.62 (m, 1H), 7.87-8.28 (m, 2H), 7.54 (br d, J=9.03 Hz, 1H), 7.06-7.39 (m, 5H), 6.66-6.98 (m, 1H), 4.21-4.91

	1H), 5.35-5.86 (m, 1H), 4.45-4.92 (m, 2H), 4.37 (s, 3H), 3.73-4.23 (m, 2H), 1.13-2.01 (m, 7H). LC-MS: Rt =1.366 min, (ESI) <i>m/z</i> . [M+H] ⁺ 474.2; C ₂₅ H ₂₄ FN ₇ O ₂		(m, 5H), 3.71 (br s, 1H), 3.41-3.61 (m, 2H), 1.82-2.07 (m, 1H), 1.43-1.79 (m, 4H), 0.79-1.40 (m, 3H). LC-MS: Rt =1.518 min, (ESI) <i>m/z</i> . [M+H] ⁺ 488.3; C ₂₆ H ₂₆ FN ₇ O ₂
25	1H NMR (400 MHz, DMSO-d ₆) Shift 8.52 (d, J=6.82 Hz, 1H), 8.45 (s, 1H), 8.40 (br s, 1H), 7.97 (s, 1H), 7.59-7.65 (m, 1H), 7.57 (d, J=9.02 Hz, 2H), 7.17-7.25 (m, 1H), 6.81-6.90 (m, 2H), 5.24 (s, 1H), 4.66 (br s, 1H), 4.34 (s, 4H), 3.61-3.89 (m, 3H), 0.97 (d, J=6.82 Hz, 3H). LC-MS: Rt =1.305 min, (ESI) <i>m/z</i> . [M+H] ⁺ 442.2; C ₂₄ H ₂₃ N ₇ O ₂	26	1H NMR (400 MHz, DMSO-d ₆) Shift 8.52 (br dd, J=6.90, 15.94 Hz, 2H), 8.23 (s, 1H), 7.89 (s, 1H), 7.55 (d, J=9.03 Hz, 1H), 7.18-7.42 (m, 4H), 6.79-6.98 (m, 1H), 6.11-6.54 (m, 1H), 4.56-5.05 (m, 2H), 4.13-4.44 (m, 3H), 3.90 (br s, 2H). LC-MS: Rt =1.409 min, (ESI) <i>m/z</i> . [M+H] ⁺ 454.2; C ₂₂ H ₁₈ F ₃ N ₇ O
27	1H NMR (400 MHz, DMSO-d ₆) Shift 8.50 (br dd, J=7.15, 14.68 Hz, 2H), 8.22 (s, 1H), 7.87 (s, 1H), 7.55 (d, J=9.03 Hz, 1H), 7.17-7.40 (m, 4H), 6.81-6.95 (m, 1H), 4.64 (br s, 2H), 4.23 (s, 3H), 3.57-4.12 (m, 2H), 1.74 (br t, J=19.20 Hz, 3H). LC-MS: Rt =1.468 min, (ESI) <i>m/z</i> . [M+H] ⁺ 468.2; C ₂₃ H ₂₀ F ₃ N ₇ O	28	1H NMR (400 MHz, DMSO-d ₆) Shift 8.01-8.73 (m, 3H), 7.65 (br s, 1H), 7.48 (br d, J=8.03 Hz, 1H), 7.13-7.37 (m, 4H), 6.78 (br s, 1H), 4.97-5.69 (m, 1H), 3.79-4.88 (m, 4H), 1.46 (br s, 3H). LC-MS: Rt =1.535 min, (ESI) <i>m/z</i> . [M+H] ⁺ 486.2; C ₂₃ H ₁₉ F ₄ N ₇ O
29	1H NMR (400 MHz, DMSO-d ₆) Shift 8.52 (br d, J=6.82 Hz, 1H), 8.03-8.50 (m, 2H), 7.93 (s, 1H), 7.39-7.71 (m, 3H), 7.24 (br t, J=7.26 Hz, 1H), 6.76-6.98 (m, 3H), 4.51-4.89 (m, 2H), 4.35 (s, 3H), 3.40-3.54 (m, 2H), 1.14 (br t, J=6.82 Hz, 3H). LC-MS: Rt =1.337 min, (ESI) <i>m/z</i> . [M+H] ⁺ 400.2; C ₂₂ H ₂₁ N ₇ O	30	1H NMR (400 MHz, DMSO-d ₆) Shift 8.63 (d, J=7.53 Hz, 1H), 8.10-8.33 (m, 2H), 7.49-7.64 (m, 1H), 7.15-7.42 (m, 4H), 6.82-7.02 (m, 1H), 4.88 (br s, 1H), 4.55 (s, 1H), 4.20-4.44 (m, 3H), 3.43-3.57 (m, 1H), 3.26 (br d, J=7.28 Hz, 1H), 2.55 (s, 1H), 2.26 (s, 2H), 0.98-1.18 (m, 3H). LC-MS: Rt =1.407 min, (ESI) <i>m/z</i> . [M+H] ⁺ 432.2; C ₂₃ H ₂₂ FN ₇ O
31	1H NMR (400 MHz, DMSO-d ₆) Shift 8.62-8.88 (m, 1H), 8.51 (d, J=6.60 Hz, 1H), 8.23 (br s, 1H), 8.13 (br s, 1H), 7.91 (br s, 1H), 7.56 (br s, 1H), 7.32 (br d, J=11.88 Hz, 1H), 7.25 (br s, 3H), 6.89 (br s, 1H), 5.29 (br s, 1H), 4.38 (br s, 3H), 1.78 (br d, J=1.54 Hz, 10H), 1.14-1.29 (m, 1H). LC-MS: Rt =1.259 min, (ESI) <i>m/z</i> . [M+H] ⁺ 470.2; C ₂₆ H ₂₄ FN ₇ O	32	1H NMR (400MHz, DMSO-d ₆) Shift = 8.47 (br d, J=6.5 Hz, 1H), 8.03 - 7.80 (m, 3H), 7.79 - 7.56 (m, 2H), 7.54 - 7.29 (m, 3H), 7.26 - 7.13 (m, 1H), 7.03 (br s, 1H), 6.85 (dt, J=1.0, 6.8 Hz, 1H), 6.55 - 6.39 (m, 2H), 5.24 (br s, 1H), 4.84 (br s, 1H), 4.34 - 4.04 (m, 1H), 2.22 - 2.17 (m, 3H), 1.60 (d, J=7.0 Hz, 3H). LC-MS: Rt = 1.656 min, (ESI) <i>m/z</i> . [M+H] ⁺ 455.2; C ₂₆ H ₂₃ FN ₆ O
33	1H NMR (400 MHz, DMSO-d ₆) δ ppm 8.51 (d, J=6.75 Hz, 1 H) 7.82 - 7.98 (m, 2 H) 7.68 (br s, 1 H) 7.58 (d, J=8.63 Hz, 2 H) 7.21 - 7.28 (m, 1 H) 6.89 (t, J=6.75 Hz, 1 H) 6.57 (s, 2 H) 5.36 - 5.45 (m, 2 H) 5.29 (br s, 1 H) 5.22 (br d, J=13.76 Hz, 1 H) 3.10 - 3.24 (m, 2 H) 1.59 (br s, 3 H) 1.40 (t, J=6.00 Hz, 3 H) 1.05 (br s, 3 H) LC-MS: Rt = 2.295 min, (ESI) <i>m/z</i> = 416.2 [M+H] ⁺ ; C ₂₄ H ₂₅ N ₅ O ₂	34	1H NMR (400 MHz, DMSO-d ₆) Shift 9.12-9.33 (m, 1H), 8.40 (d, J=7.26 Hz, 1H), 8.19-8.28 (m, 1H), 7.97-8.17 (m, 1H), 7.75 (br d, J=9.24 Hz, 1H), 7.15-7.46 (m, 4H), 4.50-4.96 (m, 2H), 4.16-4.39 (m, 3H), 3.10-3.36 (m, 2H), 1.85-2.21 (m, 1H), 0.59-1.03 (m, 6H). LC-MS: Rt =1.937 min, (ESI) <i>m/z</i> . [M+H] ⁺ 564.2; C ₂₆ H ₂₃ F ₆ N ₇ O
35	1H NMR (400 MHz, DMSO-d ₆) Shift 8.49 (d, J=7.48 Hz, 1H), 8.09-8.33 (m, 2H), 7.69-7.84 (m, 1H), 7.45 (d, J=9.68 Hz, 1H),	36	1H NMR (400 MHz, DMSO-d ₆) Shift 9.08-9.34 (m, 1H), 8.11-8.49 (m, 2H), 7.91-8.10 (m, 1H), 7.69-7.77 (m, 1H),

	7.18-7.36 (m, 3H), 7.07 (dd, J=2.20, 9.68 Hz, 1H), 4.43-4.86 (m, 2H), 4.22-4.40 (m, 3H), 4.00-4.12 (m, 2H), 3.63-3.73 (m, 2H), 3.32 (s, 5H), 1.90-2.24 (m, 1H), 0.60-1.00 (m, 6H). LC-MS: Rt =1.564 min, (ESI) m/z. [M+H] ⁺ 520.3; C ₂₇ H ₃₀ FN ₇ O ₃		7.47 (d, J=9.46 Hz, 1H), 7.32 (d, J=11.66 Hz, 1H), 7.13-7.30 (m, 2H), 4.50-4.93 (m, 2H), 4.20-4.38 (m, 3H), 3.02-3.37 (m, 2H), 1.92-2.18 (m, 1H), 0.57-1.02 (m, 6H). LC-MS: Rt =1.777 min, (ESI) m/z. [M+H] ⁺ 514.2; C ₂₅ H ₂₃ F ₄ N ₇ O
37	¹ H NMR (400 MHz, DMSO-d ₆) Shift 8.53 (m, 1.7H), 8.14-8.29 (m, 1.3H), 7.90 (s, 1H), 7.53 (d, J=9.24 Hz, 1H), 7.13-7.40 (m, 4H), 6.90 (t, J=6.38 Hz, 1H), 4.47-4.88 (m, 2H), 4.19-4.44 (m, 3H). LC-MS: Rt =1.231 min. (ESI) m/z. [M+H] ⁺ 407.2; C ₂₁ H ₁₅ D ₃ FN ₇ O	38	¹ H NMR (400 MHz, DMSO-d ₆) δ = 8.75 (d, J = 4.8 Hz, 2H), 8.44 (br s, 1H), 7.75 - 7.61 (m, 3H), 7.41 (br d, J = 9.2 Hz, 1H), 7.34 (t, J = 4.9 Hz, 1H), 7.21 - 7.09 (m, 2H), 6.81 (t, J = 6.5 Hz, 1H), 6.28 (br s, 2H), 5.76 - 4.73 (m, 2H), 4.69 - 4.35 (m, 1H), 2.20 (s, 3H), 1.66 (br d, J = 6.8 Hz, 3H) LC-MS: Rt = 2.219 min, (ESI) m/z. [M+H] ⁺ 456.2; C ₂₅ H ₂₂ FN ₇ O
39	¹ H NMR (400 MHz, DMSO-d ₆) δ = 9.30 - 9.09 (m, 1H), 8.87 - 8.71 (m, 2H), 8.01 - 7.82 (m, 1H), 7.79 - 7.49 (m, 3H), 7.46 - 7.35 (m, 2H), 7.23 - 6.95 (m, 1H), 6.74 - 6.42 (m, 2H), 5.74 - 4.89 (m, 2H), 4.79 - 4.28 (m, 1H), 2.19 (s, 2H), 1.72 - 1.55 (m, 3H) LC-MS: Rt = 2.585 min, (ESI) m/z. [M+H] ⁺ 524.2; C ₂₆ H ₂₁ F ₄ N ₇ O	40	¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 8.45 - 8.56 (m, 1 H) 7.60 - 7.98 (m, 3 H) 7.49 - 7.58 (m, 1 H) 7.14 - 7.27 (m, 2 H) 6.83 - 6.91 (m, 1 H) 6.58 (br s, 2 H) 4.77 - 5.97 (m, 1 H) 3.52 (dq, J=13.57, 6.82 Hz, 1 H) 3.08 - 3.18 (m, 1 H) 2.19 (s, 3 H) 1.53 - 1.70 (m, 3 H) 0.63 - 1.14 (m, 3 H) LC-MS: Rt = 2.357 min, (ESI) m/z = 392.2 [M+H] ⁺ ; C ₂₅ H ₂₄ F ₃ N ₇ O
41	¹ H NMR (400 MHz, DMSO-d ₆) δ = 9.23 (s, 1H), 8.15 - 7.59 (m, 4H), 7.47 - 7.47 (m, 1H), 7.58 - 7.43 (m, 1H), 6.59 (s, 2H), 5.49 - 5.12 (m, 3H), 4.92 - 4.62 (m, 2H), 3.56 (br s, 4H), 3.29 - 3.07 (m, 3H), 1.39 (br d, J = 5.7 Hz, 3H) LC-MS: Rt = 2.585 min, (ESI) m/z = 500.1 [M+H] ⁺ ; C ₂₅ H ₂₄ F ₃ N ₅ O ₃	42	¹ H NMR (400MHz, DMSO-d ₆) δ 9.19 (s, 1H), 8.04 (s, 1H), 7.74 (br d, J=9.4 Hz, 1H), 7.58 (br s, 2H), 7.47 (br dd, J=1.2, 9.4 Hz, 2H), 7.43 - 7.11 (m, 2H), 6.61 (s, 2H), 5.45 - 5.35 (m, 1H), 5.28 - 5.20 (m, 1H), 5.18 - 5.11 (m, 1H), 5.05 (s, 2H), 3.67 (br s, 2H), 1.39 (d, J=6.1 Hz, 3H) ; LC-MS: Rt = 1.714 min, (ESI) m/z. [M+H] ⁺ 522.1; C ₂₆ H ₂₂ F ₃ N ₇ O ₂
43	¹ H NMR (400 MHz, DMSO-d ₆) δ = 9.21 (s, 1H), 8.03 (s, 1H), 7.74 (d, J = 9.4 Hz, 1H), 7.66 (br s, 1H), 7.54 (br s, 2H), 7.47 (br d, J = 9.4 Hz, 1H), 6.59 (s, 2H), 5.39 (br d, J = 4.3 Hz, 1H), 5.32 - 5.04 (m, 2H), 4.71 (br s, 2H), 2.29 (br s, 1H), 1.88 (br s, 6H), 1.39 (br d, J = 6.1 Hz, 3H) LC-MS: Rt = 2.758 min, (ESI) m/z. [M+H] ⁺ 508.1; C ₂₇ H ₂₄ F ₃ N ₅ O ₂	44	¹ H NMR (400 MHz, DMSO-d ₆) δ = 9.21 (br s, 1H), 8.04 (br s, 1H), 7.91 - 7.38 (m, 5H), 6.58 (br s, 2H), 5.58 - 4.98 (m, 3H), 4.85 - 4.52 (m, 2H), 4.46 - 4.05 (m, 1H), 3.69 - 3.39 (m, 2H), 3.25 - 2.98 (m, 3H), 1.40 (br s, 3H), 1.13 (br s, 3H) LC-MS: Rt = 2.600 min, (ESI) m/z. [M+H] ⁺ 514.3; C ₂₆ H ₂₆ F ₃ N ₅ O ₃
45	¹ H NMR (400 MHz, DMSO-d ₆) Shift 8.09-8.63 (m, 3H), 7.75-7.87 (m, 1H), 7.45-7.57 (m, 1H), 7.09-7.40 (m, 4H), 6.74-6.97 (m, 1H), 4.49-5.01 (m, 2H), 3.83-4.47 (m, 4H), 3.55-3.80 (m, 1H), 2.93-3.16 (m, 3H), 2.540-2.62 (m, 1.5H), 1.92-2.43 (m, 2.5H). LC-MS: Rt =1.342 min, (ESI) m/z. [M+H] ⁺ 474.2; C ₂₅ H ₂₄ FN ₇ O ₂	46	¹ H NMR (400 MHz, DMSO-d ₆) δ = 8.53 (d, J = 6.8 Hz, 1H), 7.92 (s, 2H), 7.72 - 7.51 (m, 3H), 7.31 - 7.19 (m, 1H), 6.90 (t, J = 6.6 Hz, 1H), 6.65 - 6.52 (m, 2H), 5.41 (br s, 1H), 5.34 - 5.10 (m, 2H), 4.80 - 4.51 (m, 2H), 3.45 (br d, J = 4.6 Hz, 2H), 1.39 (br d, J = 5.9 Hz, 3H), 1.12 (t, J = 7.1 Hz, 3H) LC-MS: Rt = 1.405 min, (ESI) m/z. [M+H] ⁺ 402.2; C ₂₃ H ₂₃ N ₅ O ₂
47	¹ H NMR (400 MHz, DMSO-d ₆) δ = 8.53 (d, J = 6.8 Hz, 1H), 7.92 (s, 2H), 7.62 - 7.43 (m, 3H), 7.24 (br d, J = 6.8 Hz, 1H), 6.90 (t, J = 6.9 Hz, 1H), 6.57 (s, 2H), 5.40 (br d, J = 5.3 Hz, 1H), 5.35 - 5.05 (m, 2H), 4.87 -	48	¹ H NMR (400MHz, DMSO-d ₆) δ 9.18 (s, 1H), 8.03 (s, 1H), 7.73 (d, J=9.5 Hz, 1H), 7.58 (br s, 2H), 7.46 (dd, J=1.5, 9.5 Hz, 2H), 7.42 - 7.07 (m, 2H), 6.59 (s, 2H), 5.44 - 5.34 (m, 1H), 5.27 - 5.18

	4.49 (m, 2H), 3.45 (br s, 2H), 1.39 (br d, J = 6.0 Hz, 3H), 1.12 (t, J = 7.0 Hz, 3H) LC-MS: Rt = 1.409 min, (ESI) m/z. [M+H] ⁺ 402.2; C ₂₃ H ₂₃ N ₅ O ₂		(m, 1H), 5.17 - 5.08 (m, 1H), 5.05 (s, 2H), 3.66 (br s, 3H), 1.39 (d, J=6.3 Hz, 3H) ; LC-MS: Rt = 1.739 min, (ESI) m/z. [M+H] ⁺ 522.2; C ₂₆ H ₂₂ F ₃ N ₇ O ₂
49	¹ H NMR (400MHz, DMSO-d ₆) δ 9.18 (s, 1H), 8.03 (s, 1H), 7.73 (d, J=9.4 Hz, 1H), 7.58 (br s, 2H), 7.46 (br dd, J=1.4, 9.5 Hz, 2H), 7.42 - 7.00 (m, 2H), 6.59 (s, 2H), 5.43 - 5.34 (m, 1H), 5.28 - 5.19 (m, 1H), 5.17 - 5.11 (m, 1H), 5.05 (s, 2H), 3.66 (br s, 3H), 1.39 (d, J=6.1 Hz, 3H) ; LC-MS: Rt = 1.738 min, (ESI) m/z. [M+H] ⁺ 522.0; C ₂₆ H ₂₂ F ₃ N ₇ O ₂	50	¹ H NMR (400 MHz, DMSO-d ₆) δ = 9.22 (s, 1H), 8.10 - 7.92 (m, 2H), 7.77 (br d, J = 8.3 Hz, 1H), 7.67 (br s, 1H), 7.57 - 7.54 (m, 1H), 7.49 (br d, J = 8.0 Hz, 1H), 6.58 (s, 2H), 5.41 (br s, 1H), 5.23 (br dd, J = 1.8, 19.9 Hz, 2H), 4.81 - 4.61 (m, 2H), 1.39 (br d, J = 6.1 Hz, 3H) LC-MS: Rt = 2.457 min, (ESI) m/z. [M+H] ⁺ 459.2; C ₂₃ H ₁₇ D ₃ F ₃ N ₅ O ₂
51	¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 9.23 (s, 1 H) 8.06 (s, 1 H) 7.27 - 7.96 (m, 5 H) 6.59 (s, 2 H) 5.42 (br s, 1 H) 5.26 (br s, 2 H) 4.57 - 4.85 (m, 2 H) 3.39 - 3.46 (m, 2 H) 1.40 (br d, J=6.13 Hz, 3 H) 1.13 (t, J=7.00 Hz, 3 H) LC-MS: Rt = 2.562 min , (ESI) m/z = 470.2 [M+H] ⁺ ; C ₂₄ H ₂₂ F ₃ N ₅ O	52	¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 9.21 (br s, 1 H) 7.87 - 8.02 (m, 1 H) 7.77 (d, J=9.38 Hz, 1 H) 7.64 (br s, 1 H) 7.43 - 7.61 (m, 3 H) 6.58 (br s, 2 H) 5.41 (br s, 1 H) 5.24 (br d, J=17.76 Hz, 2 H) 4.55 - 4.87 (m, 2 H) 3.27 (br s, 2 H) 1.90 - 2.20 (m, 1 H) 1.40 (br d, J=5.88 Hz, 3 H) 0.65 - 0.94 (m, 6 H) LC-MS: Rt = 2.769 min , (ESI) m/z = 498.2 [M+H] ⁺ ; C ₂₆ H ₂₆ F ₃ N ₅ O ₂
53	¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 8.52 (br d, J=6.38 Hz, 1 H) 7.77 - 8.01 (m, 2 H) 7.67 (br s, 1 H) 7.55 (br d, J=9.13 Hz, 2 H) 7.25 (br t, J=7.75 Hz, 1 H) 6.89 (td, J=6.75, 1.13 Hz, 1 H) 6.57 (br s, 2 H) 5.13 - 5.47 (m, 3 H) 4.52 - 4.81 (m, 2 H) 3.30 (br d, J=3.50 Hz, 2 H) 2.10 (br d, J=11.63 Hz, 1 H) 1.40 (br d, J=6.00 Hz, 3 H) 0.60 - 0.97 (m, 6 H) LC-MS: Rt = 2.428 min , (ESI) m/z = 430.2 [M+H] ⁺ ; C ₂₅ H ₂₇ N ₅ O ₂	54	¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 8.52 (br d, J=6.38 Hz, 1 H) 7.72 - 8.09 (m, 2 H) 7.45 - 7.71 (m, 3 H) 7.25 (br t, J=7.75 Hz, 1 H) 6.84 - 6.93 (m, 1 H) 6.57 (br s, 2 H) 5.12 - 5.48 (m, 3 H) 4.51 - 4.81 (m, 2 H) 3.14 - 3.31 (m, 2 H) 2.07 (br s, 1 H) 1.40 (br d, J=5.88 Hz, 3 H) 0.58 - 0.97 (m, 6 H) LC-MS: Rt = 2.429 min, (ESI) m/z = 430.2 [M+H] ⁺ ; C ₂₅ H ₂₇ N ₅ O ₂
55	¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 8.52 (br d, J=6.38 Hz, 1 H) 7.80 - 8.04 (m, 2 H) 7.42 - 7.73 (m, 3 H) 7.25 (br t, J=7.82 Hz, 1 H) 6.89 (td, J=6.75, 1.00 Hz, 1 H) 6.57 (br s, 2 H) 5.11 - 5.47 (m, 3 H) 4.50 - 4.84 (m, 2 H) 3.28 (br s, 2 H) 2.08 (br s, 1 H) 1.40 (br d, J=5.88 Hz, 3 H) 0.63 - 0.98 (m, 6 H) LC-MS: Rt = 2.430 min, (ESI) m/z = 430.2 [M+H] ⁺ ; C ₂₅ H ₂₇ N ₅ O ₂	56	¹ H NMR (400 MHz, DMSO-d ₆) δ = 8.53 (d, J = 6.8 Hz, 1H), 7.88 (s, 1H), 7.70 (br s, 1H), 7.60 - 7.51 (m, 3H), 7.26 - 7.20 (m, 1H), 6.89 (dt, J = 0.9, 6.8 Hz, 1H), 6.57 (s, 2H), 5.41 (br dd, J = 4.4, 8.6 Hz, 1H), 5.26 - 5.09 (m, 2H), 4.67 (br s, 2H), 2.30 (br s, 1H), 1.91 (br s, 6H), 1.39 (d, J = 6.1 Hz, 3H) LC-MS: Rt = 1.649 min, (ESI) m/z. [M+H] ⁺ 440.2; C ₂₆ H ₂₅ N ₅ O ₂
57	¹ H NMR (400 MHz, DMSO-d ₆) δ = 8.49 (d, J = 6.9 Hz, 1H), 8.14 (s, 1H), 7.88 (s, 1H), 7.73 - 7.36 (m, 4H), 7.35 - 6.99 (m, 2H), 6.87 (dt, J = 1.0, 6.8 Hz, 1H), 6.60 (s, 2H), 5.39 (ddd, J = 1.6, 4.0, 5.9 Hz, 1H), 5.27 - 5.18 (m, 1H), 5.17 - 5.08 (m, 1H), 5.00 (s, 2H), 3.66 (br s, 3H), 1.38 (d, J = 6.1 Hz, 3H) LC-MS: Rt = 2.044 min, (ESI) m/z. [M+H] ⁺ 454.2; C ₂₅ H ₂₃ N ₇ O ₂	58	¹ H NMR (400MHz, DMSO-d ₆) Shift 8.53 - 7.97 (m, 3H), 7.53 (br d, J=9.1 Hz, 1H), 7.38 - 7.17 (m, 4H), 7.10 - 6.87 (m, 1H), 4.94 - 4.47 (m, 2H), 4.39 - 4.20 (m, 3H), 3.35 - 3.31 (m, 2H), 2.26 - 1.94 (m, 1H), 1.06 - 0.62 (m, 6H). LC-MS: RT =2.439 min, (ESI) m/z. [M+H] ⁺ 464.2; C ₂₄ H ₂₃ F ₂ N ₇ O
59	¹ H NMR (400 MHz, DMSO-d ₆) Shift 8.11-8.58 (m, 3H), 7.85 (s, 1H), 7.51 (d,	60	¹ H NMR (400 MHz, DMSO-d ₆) Shift 8.40-8.85 (m, 1.7 H), 8.19-8.29 (m,

	J=9.02 Hz, 1H), 7.18-7.39 (m, 4H), 6.81-6.95 (m, 1H), 3.85-5.07 (m, 5H), 1.85-2.49 (m, 6H). 19F NMR (376.5 MHz, DMSO-d ₆) Shift -116.31, -116.95, -166.45, -170.46. LC-MS: RT =2.690 min, (ESI) <i>m/z</i> . [M+H] ⁺ 474.2; C ₂₅ H ₂₁ F ₂ N ₇ O		1.3H), 7.79-8.05 (m, 1H), 7.54 (d, J=9.02 Hz, 1H), 7.08-7.46 (m, 4H), 6.89 (t, J=6.60 Hz, 1H), 5.75-5.86 (m, 0.15H), 5.01-5.12 (m, 0.85H), 4.27-4.47 (m, 3H), 2.77-3.46 (m, 7H), 1.43-1.76 (m, 3H). 19F NMR (376.5 MHz, DMSO-d ₆) Shift -110.40, -112.23, -111.62. LC-MS: RT =1.372 min, (ESI) <i>m/z</i> . [M+H] ⁺ 462.2; C ₂₄ H ₂₄ FN ₇ O ₂
61	1H NMR (400 MHz, DMSO-d ₆) Shift 8.13-8.58 (m, 3H), 7.84 (s, 1H), 7.51 (d, J=9.02 Hz, 1H), 7.17-7.41 (m, 4H), 6.89 (t, J=6.60 Hz, 1H), 3.95-5.01 (m, 5H), 2.52-2.71 (m, 3H), 1.97-2.46 (m, 3H). 19F NMR (376.5 MHz, DMSO-d ₆) Shift -116.32, -117.13. LC-MS: RT =2.442 min, (ESI) <i>m/z</i> . [M+H] ⁺ 481.2; C ₂₆ H ₂₁ FN ₈ O	62	1H NMR (400 MHz, DMSO-d ₆) Shift 8.04-8.64 (m, 3H), 7.87 (s, 1H), 7.52 (d, J=9.24 Hz, 1H), 7.08-7.45 (m, 4H), 6.81-6.96 (m, 1H), 3.79-5.12 (m, 5H), 1.76-2.47 (m, 6H). 19F NMR (376.5 MHz, DMSO-d ₆) Shift -64.86, -111.54, -112.23. LC-MS: Rt =1.697 min, (ESI) <i>m/z</i> . [M+H] ⁺ 524.2; C ₂₆ H ₂₁ F ₄ N ₇ O
63	1H NMR (400 MHz, DMSO-d ₆) Shift 8.59 (br s, 1H), 8.51 (d, J=6.82 Hz, 1H), 8.22 (s, 1H), 8.00 (s, 1H), 7.65-7.73 (m, 1H), 7.59 (d, J=8.36 Hz, 1H), 7.54 (d, J=9.02 Hz, 1H), 7.20-7.27 (m, 1H), 7.09 (br s, 2H), 6.88 (t, J=6.82 Hz, 1H), 5.01-5.36 (m, 1H), 4.51-4.68 (m, 1H), 4.35-4.52 (m, 1H), 4.26 (s, 3H), 3.80 (dd, J=3.74, 11.88 Hz, 1H), 3.58-3.74 (m, 2H), 0.95 (d, J=7.04 Hz, 3H). LC-MS: Rt =1.284 min, (ESI) <i>m/z</i> . [M+H] ⁺ 442.2; C ₂₄ H ₂₃ N ₇ O ₂	64	1H NMR (400 MHz, DMSO-d ₆) Shift 8.45-8.59 (m, 1H), 7.95 (s, 1H), 7.81-7.99 (m, 1H), 7.66-7.74 (m, 1H), 7.49-7.59 (m, 2H), 7.19-7.25 (m, 1H), 6.84-6.90 (t, J=6.71 Hz, 1H), 6.55 (s, 2H), 4.82-5.58 (m, 4H), 4.51-4.72 (m, 1H), 4.10-4.46 (m, 1H), 3.76-3.83 (m, 1H), 3.62-3.71 (m, 2H), 1.21-1.40 (m, 3H), 0.87-0.99 (m, 3H). LC-MS: Rt =1.337 min, (ESI) <i>m/z</i> . [M+H] ⁺ 444.3; C ₂₅ H ₂₅ N ₅ O ₃
65	1H NMR (400 MHz, DMSO-d ₆) δ = 8.41 (t, J = 5.9 Hz, 1H), 7.73 - 7.63 (m, 2H), 7.55 (s, 2H), 7.49 (d, J = 9.2 Hz, 1H), 7.23 - 7.18 (m, 1H), 6.83 (t, J = 6.7 Hz, 1H), 6.31 (s, 2H), 5.46 - 5.37 (m, 1H), 5.28 - 5.02 (m, 3H), 4.91 - 4.82 (m, 1H), 4.59 (br d, J = 16.6 Hz, 1H), 1.49 (br d, J = 6.4 Hz, 3H), 1.41 (dd, J = 4.1, 6.1 Hz, 3H) LC-MS: Rt = 1.660 min, (ESI) <i>m/z</i> . [M+H] ⁺ 470.1; C ₂₄ H ₂₂ F ₃ N ₅ O ₂	66	1H NMR (400 MHz, DMSO-d ₆) δ = 8.53 (d, J = 6.8 Hz, 1H), 8.07 (br s, 1H), 7.91 (s, 1H), 7.77 - 7.64 (m, 1H), 7.60 - 7.54 (m, 2H), 7.27 (br t, J = 7.8 Hz, 1H), 6.91 (t, J = 6.3 Hz, 1H), 6.61 (s, 2H), 6.49 - 6.13 (m, 1H), 5.45 - 5.37 (m, 1H), 5.32 - 5.13 (m, 2H), 4.70 (br s, 2H), 3.85 (br d, J = 3.8 Hz, 2H), 1.39 (d, J = 6.1 Hz, 3H) LC-MS: Rt = 2.340 min, (ESI) <i>m/z</i> . [M+H] ⁺ 438.2; C ₂₃ H ₂₁ F ₂ N ₅ O ₂
67	1H NMR (400 MHz, DMSO-d ₆) Shift 9.19 (s, 1H), 8.10 (s, 1H), 7.79-8.04 (m, 1H), 7.77 (dd, J=4.39, 9.41 Hz, 1H), 7.65-7.73 (m, 1H), 7.55 (d, J=8.28 Hz, 1H), 7.44-7.50 (m, 1H), 6.57 (s, 2H), 5.06-5.54 (m, 4H), 4.01-4.82 (m, 2H), 3.78-3.92 (m, 1H), 3.57-3.77 (m, 2H), 1.33-1.42 (m, 3H), 0.87-0.93 (m, 3H). 19F NMR (376.5 MHz, DMSO-d ₆) Shift -60.43. LC-MS: Rt =1.653 min, (ESI) <i>m/z</i> . [M+H] ⁺ 512.2; C ₂₆ H ₂₄ F ₃ N ₅ O ₃	68	1H NMR (400 MHz, DMSO-d ₆) δ = 9.12 (s, 1H), 8.01 (s, 1H), 7.70 (d, J = 9.4 Hz, 1H), 7.62 (s, 2H), 7.56 - 7.49 (m, 1H), 7.48 - 7.37 (m, 2H), 7.22 (s, 1H), 6.40 (s, 2H), 5.21 (t, J = 3.1 Hz, 2H), 5.06 (s, 2H), 5.01 (t, J = 3.0 Hz, 2H), 3.67 (s, 3H) LC-MS: Rt = 2.381 min, (ESI) <i>m/z</i> . [M+H] ⁺ 508.2; C ₂₅ H ₂₀ F ₃ N ₇ O ₂
69	1H NMR (400 MHz, DMSO-d ₆) Shift 8.65 (d, J=6.16 Hz, 1H), 8.49 (br d, J=6.60 Hz, 1H), 8.30 (s, 1H), 7.84-7.93 (m, 2H), 7.58 (br d, J=17.83 Hz, 2H),	70	1H NMR (400 MHz, DMSO-d ₆) Shift 9.23 (br s, 1H), 8.66 (br s, 1H), 8.45 (br s, 1H), 7.97-8.15 (m, 2H), 7.84-7.88 (m, 1H), 7.70 (br d, J=14.30 Hz, 2H),

	7.47-7.53 (m, 1H), 7.20-7.26 (m, 1H), 6.88 (q, J=7.41 Hz, 1H), 4.78 (br d, J=6.16 Hz, 2H), 3.46-3.62 (m, 2H), 2.88-3.00 (m, 3H), 1.15-1.25 (m, 3H) LC-MS: Rt =1.640 min, (ESI) <i>m/z</i> . [M+H] ⁺ 401.2; C ₂₁ H ₂₀ N ₈ O		7.57 (br s, 2H), 7.45 (br s, 1H), 7.11 (br s, 1H), 5.05-5.30 (m, 2H), 3.56-3.88 (m, 3H), 2.91 (s, 3H). LC-MS: Rt =1.484 min, (ESI) <i>m/z</i> . [M+H] ⁺ 521.3; C ₂₄ H ₁₉ F ₃ N ₁₀ O
71	¹ H NMR (400 MHz, DMSO-d ₆) δ = 8.78 (s, 1H), 7.70 (br d, J = 9.7 Hz, 1H), 7.60 (s, 2H), 7.52 - 7.47 (m, 1H), 7.45 - 7.39 (m, 2H), 7.20 (s, 1H), 6.31 (s, 2H), 5.42 (ddd, J = 1.7, 4.1, 6.0 Hz, 1H), 5.29 - 5.21 (m, 1H), 5.17 - 5.11 (m, 1H), 5.08 (s, 2H), 3.67 (s, 3H), 1.42 (d, J = 6.2 Hz, 3H) LC-MS: Rt = 2.486 min, (ESI) <i>m/z</i> = 540.2 [M+H] ⁺ ; C ₂₆ H ₂₁ F ₄ N ₇ O ₂	72	¹ H NMR (400MHz, DMSO-d ₆) δ 7.98 - 7.64 (m, 3H), 7.64 - 7.45 (m, 3H), 7.45 - 7.04 (m, 3H), 6.61 (s, 2H), 5.44 - 5.35 (m, 1H), 5.27 - 5.18 (m, 1H), 5.18 - 5.11 (m, 1H), 5.08 (s, 2H), 3.67 (br s, 3H), 1.41 - 1.36 (m, 3H) ; LC-MS: Rt = 1.826 min, (ESI) <i>m/z</i> . [M+H] ⁺ 522.2; C ₂₆ H ₂₂ F ₃ N ₇ O ₂
73	¹ H NMR (400MHz, DMSO-d ₆) δ 7.97 - 7.66 (m, 3H), 7.65 - 7.45 (m, 3H), 7.44 - 6.99 (m, 3H), 6.60 (s, 2H), 5.43 - 5.34 (m, 1H), 5.27 - 5.17 (m, 1H), 5.17 - 5.09 (m, 1H), 5.07 (s, 2H), 3.73 - 3.54 (m, 3H), 1.38 (d, J=6.1 Hz, 3H) ; LC-MS: Rt = 1.828 min, (ESI) <i>m/z</i> . [M+H] ⁺ 522.2; C ₂₆ H ₂₂ F ₃ N ₇ O	74	¹ H NMR (400 MHz, DMSO-d ₆) δ = 8.04 - 7.81 (m, 3H), 7.69 - 7.31 (m, 6H), 6.62 (s, 2H), 5.43 - 5.35 (m, 1H), 5.26 - 5.11 (m, 2H), 5.08 (s, 2H), 3.66 (br s, 3H), 1.38 (d, J = 6.1 Hz, 3H) LC-MS: Rt = 2.352 min, (ESI) <i>m/z</i> . [M+H] ⁺ 522.2; C ₂₆ H ₂₂ F ₃ N ₇ O ₂
75	¹ H NMR (400 MHz, DMSO-d ₆) δ = 8.60 (s, 1H), 8.36 - 7.99 (m, 4H), 7.95 (d, J = 9.1 Hz, 2H), 7.65 (br d, J = 9.3 Hz, 2H), 6.01 - 5.93 (m, 1H), 5.89 (br s, 2H), 5.83 (br d, J = 14.1 Hz, 1H), 5.74 - 5.67 (m, 1H), 5.58 (br s, 2H), 4.20 (br s, 3H), 2.84 (s, 3H), 2.00 (d, J = 6.3 Hz, 3H) LC-MS: Rt = 2.165 min, (ESI) <i>m/z</i> . [M+H] ⁺ 468.2; C ₂₆ H ₂₅ N ₇ O ₂	76	¹ H NMR (400MHz, DMSO-d ₆) Shift 9.18 (s, 1H), 8.47 (br s, 1H), 8.33 - 8.14 (m, 1H), 8.08 (s, 1H), 7.87 - 7.68 (m, 5H), 7.47 (br d, J=8.4 Hz, 1H), 5.09 (s, 2H), 3.68 (br s, 3H), 2.71 (s, 3H). ¹⁹ F NMR (376MHz, DMSO-d ₆) Shift -60.427. LC-MS: Rt =3.535 min, (ESI) <i>m/z</i> . [M+H] ⁺ 521.3; C ₂₄ H ₁₉ F ₃ N ₁₀ O
77	(400MHz, DMSO-d ₆) Shift 8.77 - 8.46 (m, 3H), 7.98 (s, 1H), 7.88 - 7.65 (m, 3H), 7.55 (br d, J=9.0 Hz, 1H), 7.28 (br s, 1H), 6.91 (br t, J=6.5 Hz, 1H), 4.63 (br s, 2H), 3.73 - 3.51 (m, 2H), 3.03 - 2.62 (m, 3H), 1.25 - 1.06 (m, 3H). LC-MS: Rt =2.973 min, (ESI) <i>m/z</i> . [M+H] ⁺ 401.2; C ₂₁ H ₂₀ N ₈ O	78	¹ H NMR (400 MHz, DMSO-d ₆) δ = 8.86 (s, 1H), 8.01 (s, 1H), 7.73 - 7.31 (m, 6H), 7.28 - 6.93 (m, 2H), 6.60 (s, 2H), 5.46 - 5.35 (m, 1H), 5.27 - 5.19 (m, 1H), 5.18 - 5.10 (m, 1H), 5.03 (s, 2H), 3.66 (br s, 3H), 1.38 (d, J = 6.1 Hz, 3H) LC-MS: Rt = 2.254 min, (ESI) <i>m/z</i> = 504.0 [M+H] ⁺ ; C ₂₆ H ₂₃ F ₂ N ₇ O ₂
79	¹ H NMR (400MHz, DMSO-d ₆) Shift = 8.36 (s, 1H), 7.78 (s, 1H), 7.55 (s, 1H), 7.29 - 6.91 (m, 1H), 6.69 - 6.51 (m, 1H), 5.75 (s, 1H), 5.40 (s, 1H), 4.45 (s, 1H), 4.15 (s, 1H), 3.86 (br s, 2H), 3.16 (br d, J=4.4 Hz, 2H), 2.03 (s, 2H), 1.62 (s, 2H), 1.39 (br s, 3H), 1.11 (s, 3H). LC-MS: Rt = 1.702 min, (ESI) <i>m/z</i> . [M+H] ⁺ 502.2; C ₂₈ H ₃₁ N ₅ O ₄	80	¹ H NMR (400MHz, DMSO-d ₆) Shift 9.28 - 9.12 (m, 1H), 8.16 - 7.86 (m, 1H), 7.78 - 7.50 (m, 3H), 7.46 (br d, J=9.7 Hz, 1H), 7.38 - 7.02 (m, 2H), 6.81 (br s, 2H), 5.16 (br d, J=2.2 Hz, 2H), 5.10 - 4.88 (m, 4H), 3.79 (s, 3H). ¹⁹ F NMR (376MHz, DMSO-d ₆) Shift -60.408, -60.457; -113.851, -115.468. LC-MS: Rt =4.112 (ESI) <i>m/z</i> . [M+H] ⁺ 526.3
81	¹ H NMR (400 MHz, DMSO-d ₆) Shift 8.51 (br s, 1H), 7.82-8.05 (m, 1H), 7.44-7.75 (m, 1H), 7.15-7.39 (m, 2H), 6.68-6.94 (m, 3H), 5.24-5.73 (m, 2H), 4.97 (br s, 3H), 4.37-4.80 (m, 2H), 3.49-3.91	82	¹ H NMR (400MHz, DMSO-d ₆) Shift 8.59 - 8.41 (m, 1H), 8.15 - 7.81 (m, 1H), 7.81 - 7.44 (m, 3H), 7.36 - 7.01 (m, 3H), 6.93 - 6.63 (m, 3H), 5.13 (td, J=1.5, 3.0 Hz, 2H), 5.06 - 4.85 (m, 4H),

	(m, 4H), 0.93 (br s, 3H). 19F NMR (376 MHz, DMSO-d6) Shift -116.33 (br s, 1F). LC-MS: Rt =1.395 min, (ESI) m/z . [M+H] ⁺ 448.2; C ₂₄ H ₂₂ FN ₅ O ₃		3.85 - 3.50 (m, 3H). 19F NMR (376MHz, DMSO-d6) Shift -113.938, -115.488. LC-MS: Rt =3.269 min, (ESI) m/z . [M+H] ⁺ 458.2; C ₂₄ H ₂₀ FN ₇ O ₂
83	1H NMR (400MHz, DMSO-d6) Shift 8.32 - 7.93 (m, 1H), 7.68 - 7.43 (m, 3H), 7.39 - 7.17 (m, 1H), 7.16 - 6.93 (m, 3H), 6.82 (br s, 2H), 5.28 (br s, 2H), 5.09 - 4.93 (m, 4H), 3.86 - 3.52 (m, 3H). 19F NMR (376MHz, DMSO-d6) Shift -113.863, -114.252, -115.681, -115.827; -158.023. LC-MS: Rt =0.809 min, (ESI) m/z . [M+H] ⁺ 476.3; C ₂₄ H ₁₉ F ₂ N ₇ O ₂	84	1H NMR (400MHz, DMSO-d6) Shift 9.00 - 8.77 (m, 1H), 7.72 (br d, J=9.5 Hz, 1H), 7.65 - 7.53 (m, 1H), 7.47 (br d, J=9.9 Hz, 2H), 7.38 - 7.01 (m, 2H), 6.79 (br s, 2H), 5.33 - 5.20 (m, 2H), 5.14 - 4.86 (m, 4H), 3.82 - 3.53 (m, 3H). 19F NMR (376MHz, DMSO-d6) Shift -60.560, -61.047, -61.162; -113.827, -115.669; -154.764. LC-MS: Rt =4.270 min, (ESI) m/z . [M+H] ⁺ 544.2; C ₂₅ H ₁₈ F ₅ N ₇ O ₂
85	1H NMR (400 MHz, DMSO-d6) Shift 9.13-9.35 (m, 1H), 7.87-8.20 (m, 1H), 7.68-7.84 (m, 1H), 7.43-7.58 (m, 1H), 7.30 (dd, J=11.88, 18.51 Hz, 1H), 6.81 (br d, J=11.63 Hz, 1H), 5.04-5.42 (m, 2H), 4.44-5.04 (m, 4H), 3.74 (s, 1H), 3.51 (br s, 2H), 3.03 (s, 1H), 1.00-1.19 (m, 3H). 19F NMR (376 MHz, DMSO-d6) Shift -60.54--60.31 (m, 3F), -115.78 (br d, J=15.71 Hz, 1F). LC-MS: Rt =1.659 min, (ESI) m/z . [M+H] ⁺ 474.2; C ₂₃ H ₁₉ F ₄ N ₅ O ₂	86	1H NMR (400 MHz, DMSO-d6) Shift 8.46 - 8.57 (m, 1 H) 7.84 - 7.91 (m, 1 H) 7.47 - 7.81 (m, 2 H) 7.19 - 7.35 (m, 2 H) 6.78 (br s, 3 H) 5.14 - 5.37 (m, 2 H) 4.74 - 5.03 (m, 3 H) 4.47 (s, 1 H) 3.51 (br d, J=6.38 Hz, 2 H) 1.01 - 1.16 (m, 3 H). 19F NMR (376 MHz, DMSO-d6) Shift -115.78 (br d, J=11.45 Hz, 1 F). LC-MS: Rt =0.721 min, (ESI) m/z . [M+H] ⁺ 406.2; C ₂₂ H ₂₀ FN ₅ O ₂
87	1H NMR (400 MHz, DMSO-d6) Shift 7.96 - 8.37 (m, 2 H) 7.70 - 7.81 (m, 1 H) 7.48 - 7.69 (m, 2 H) 7.27 - 7.46 (m, 1 H) 6.99 - 7.13 (m, 2 H) 6.70 - 6.89 (m, 2 H) 5.06 - 5.37 (m, 2 H) 4.81 - 5.04 (m, 4 H) 3.51 - 3.82 (m, 3 H) 2.17 - 2.29 (m, 3 H). 19F NMR (376 MHz, DMSO-d6) Shift -116.26 - -113.01 (m, 1 F). LC-MS: Rt =0.754 min, (ESI) m/z . [M+H] ⁺ 472.4; C ₂₅ H ₂₂ FN ₇ O ₂	88	1H NMR (400 MHz, DMSO-d6) Shift 9.20 (br s, 1H), 7.09-8.20 (m, 6H), 6.89 (br s, 2H), 5.19 (br s, 4H), 4.97 (br s, 2H), 3.98 (br s, 3H). 19F NMR (376 MHz, DMSO-d6) Shift -60.46 (br s, 1F), -114.10 (br s, 1F). LC-MS: Rt =1.655 min, (ESI) m/z . [M+H] ⁺ 527.2; C ₂₄ H ₁₈ F ₄ N ₈ O ₂
89	1H NMR (400 MHz, DMSO-d6) Shift 9.22 (s, 1H), 8.06 (br s, 1H), 7.72 (br d, J=9.46 Hz, 1H), 7.60 (s, 1H), 7.23-7.57 (m, 4H), 6.72 (s, 2H), 5.20 (br s, 2H), 4.99 (br d, J=2.86 Hz, 4H), 3.60 (s, 3H), 1.65 (br s, 3H). 19F NMR (376 MHz, DMSO-d6) Shift -60.41 (br s, 1F). LC-MS: Rt =0.781 min, (ESI) m/z . [M+H] ⁺ 522.3; C ₂₆ H ₂₂ F ₃ N ₇ O ₂	90	1H NMR (400 MHz, DMSO-d6) Shift 9.22 (s, 1H), 8.06 (br s, 1H), 7.72 (br d, J=9.24 Hz, 1H), 7.60 (s, 1H), 7.13-7.55 (m, 4H), 6.63 (s, 2H), 5.39 (br d, J=4.84 Hz, 1H), 5.07-5.31 (m, 2H), 5.00 (br s, 2H), 3.60 (s, 3H), 1.67 (br s, 3H), 1.39 (d, J=6.16 Hz, 3H). 19F NMR (376 MHz, DMSO-d6) Shift -60.41 (br s, 1F). LC-MS: Rt =0.802 min, (ESI) m/z . [M+H] ⁺ 536.3; C ₂₇ H ₂₄ F ₃ N ₇ O ₂
91	1H NMR (400 MHz, DMSO-d6) Shift 8.88 (s, 1H), 8.17 (s, 1H), 6.96-7.83 (m, 7H), 6.70 (s, 2H), 5.22 (s, 2H), 5.06 (s, 2H), 4.98 (s, 2H), 3.65 (s, 3H). 19F NMR (376.5 MHz, DMSO-d6) Shift -60.57, -155.01. LC-MS: Rt =1.545 min, (ESI) m/z . [M+H] ⁺ 526.3; C ₂₅ H ₁₉ F ₄ N ₇ O ₂	92	1H NMR (400 MHz, DMSO-d6) Shift 8.25 (d, J=6.82 Hz, 1H), 7.31-7.89 (m, 5H), 7.02-7.30 (m, 2H), 6.98 (t, J=6.71 Hz, 1H), 6.69 (s, 2H), 5.18-5.27 (m, 2H), 5.03 (s, 2H), 4.98 (m, 2H), 3.66 (s, 3H). 19F NMR (376.5 MHz, DMSO-d6) Shift -158.28. LC-MS: Rt =1.300 min, (ESI) m/z . [M+H] ⁺ 458.3; C ₂₄ H ₂₀ FN ₇ O ₂

93	¹H NMR (400 MHz, DMSO-d₆) Shift 8.90 (s, 1H), 7.71 (br d, J=9.38 Hz, 1H), 7.61 (s, 1H), 7.30-7.49 (m, 4H), 6.71 (s, 2H), 5.19 (br s, 2H), 4.93-5.06 (m, 4H), 3.61 (s, 3H), 1.66 (br s, 3H). ¹⁹F NMR (376 MHz, DMSO-d₆) Shift -60.91--60.37 (m, 3F), -154.84 (br s, 1F). LC-MS: Rt =1.570 min, (ESI) <i>m/z</i>. [M+H]⁺ 540.4; C₂₆H₂₁F₄N₇O₂	94	¹H NMR (400 MHz, DMSO-d₆) Shift 8.92-9.41 (m, 1H), 7.11-8.15 (m, 5H), 6.68-6.99 (m, 2H), 4.27-5.42 (m, 7H), 3.42-4.06 (m, 4H), 2.08 (br d, J=7.26 Hz, 2H). ¹⁹F NMR (376 MHz, DMSO-d₆) Shift -64.04--58.45, -116.36. LC-MS: Rt =0.928 MIN, 1.033 min, (ESI) <i>m/z</i>. [M+H]⁺ 516.2; C₂₅H₂₁F₄N₅O₃
95	¹H NMR (400 MHz, DMSO-d₆) Shift 9.21 (br s, 1H), 8.05 (br s, 1H), 7.71 (br d, J=9.24 Hz, 1H), 7.63 (s, 1H), 7.30-7.54 (m, 4H), 6.71 (br s, 2H), 5.18 (br s, 2H), 4.90-5.08 (m, 4H), 3.87 (q, J=6.68 Hz, 2H), 1.64 (br s, 3H), 1.16 (br t, J=6.49 Hz, 3H). ¹⁹F NMR (376 MHz, DMSO-d₆) Shift -60.42. LC-MS: Rt =0.942 min, (ESI) <i>m/z</i>. [M+H]⁺ 536.2; C₂₇H₂₄F₃N₇O₂	96	¹H NMR (400 MHz, DMSO-d₆) 8.25 (d, J=6.88 Hz, 1H), 7.62 (s, 1H), 7.32-7.55 (m, 4H), 7.19-7.27 (m, 1H), 6.98 (t, J=6.73 Hz, 1H), 6.70 (s, 2H), 5.20 (br s, 2H), 4.98 (br s, 4H), 3.61 (s, 3H), 1.64 (br s, 3H). ¹⁹F NMR (376 MHz, DMSO-d₆) -158.13 (br s, 1F). LC-MS: Rt =0.801 min, (ESI) <i>m/z</i>. [M+H]⁺ 472.1; C₂₅H₂₂FN₇O₂
97	¹H NMR (400 MHz, DMSO-d₆) Shift 9.22 (s, 1H), 8.06 (br s, 1H), 7.72 (br d, J=9.46 Hz, 1H), 7.62 (s, 1H), 7.30-7.57 (m, 4H), 6.73 (s, 2H), 4.68-5.36 (m, 6H), 3.63 (s, 3H), 2.00 (br s, 2H), 0.73 (br s, 3H). ¹⁹F NMR (376 MHz, DMSO-d₆) Shift -60.41 (br s, 1F). LC-MS: Rt =1.003 min, (ESI) <i>m/z</i>. [M+H]⁺ 536.3; C₂₇H₂₄F₃N₇O	98	¹H NMR (400 MHz, DMSO-d₆) Shift 9.21 (s, 1H), 8.17 (s, 1H), 8.06 (br s, 1H), 7.74 (br d, J=9.46 Hz, 1H), 7.21-7.67 (m, 4H), 6.80 (br s, 2H), 6.06 (s, 1H), 4.70-5.40 (m, 6H), 3.20 (br s, 3H), 2.03 (s, 3H). ¹⁹F NMR (376 MHz, DMSO-d₆) Shift -60.46 (br s, 1F). LC-MS: Rt =0.949 min, (ESI) <i>m/z</i>. [M+H]⁺ 522.3; C₂₆H₂₂F₃N₇O₂
99	¹H NMR (400 MHz, DMSO-d₆) Shift 9.21 (br s, 1H), 8.21-8.59 (m, 1H), 8.10 (s, 1H), 7.69-7.88 (m, 2H), 6.99-7.66 (m, 5H), 6.73 (br s, 2H), 4.77-5.50 (m, 6H), 1.97-2.42 (m, 3H). ¹⁹F NMR (376 MHz, DMSO-d₆) Shift -60.45 (br s, 1F). LC-MS: Rt =0.786 min, (ESI) <i>m/z</i>. [M+H]⁺ 519.3; C₂₇H₂₁F₃N₆O₂	100	¹H NMR (400 MHz, DMSO-d₆) Shift 9.22 (br s, 1H), 8.25 (br s, 1H), 7.94-8.18 (m, 1H), 7.69-7.91 (m, 2H), 7.13-7.66 (m, 5H), 6.65 (br s, 2H), 4.72-5.49 (m, 5H), 1.73-2.40 (m, 4H), 1.36 (br s, 3H). ¹⁹F NMR (376 MHz, DMSO-d₆) Shift -60.44 (br s, 1F). LC-MS: Rt =0.801 min, (ESI) <i>m/z</i>. [M+H]⁺ 533.3; C₂₈H₂₃F₃N₆O₂
101	¹H NMR (400 MHz, DMSO-d₆) Shift 8.90 (s, 1H), 7.71 (br d, J=9.38 Hz, 1H), 7.63 (s, 1H), 7.43-7.52 (m, 2H), 7.29-7.43 (m, 2H), 6.71 (s, 2H), 5.18 (br s, 2H), 4.90-5.08 (m, 4H), 3.88 (q, J=7.13 Hz, 2H), 1.65 (br s, 3H), 1.16 (br t, J=7.07 Hz, 3H). ¹⁹F NMR (376 MHz, DMSO-d₆) Shift -61.06--60.17 (m, 3F), -154.91 (br s, 1F). LC-MS: Rt =1.62 min, (ESI) <i>m/z</i>. [M+H]⁺ 554.3; C₂₇H₂₃F₄N₇O₂	102	¹H NMR (400 MHz, DMSO-d₆) Shift 9.20 (br s, 1H), 8.05 (br s, 1H), 7.38-7.75 (m, 4H), 6.61 (br s, 2H), 5.13-5.49 (m, 2H), 4.92-5.13 (m, 2H), 3.41-3.97 (m, 7H), 1.07-1.74 (m, 7H). ¹⁹F NMR (376 MHz, DMSO-d₆) Shift -60.42. LC-MS: Rt =2.666 min, (ESI) <i>m/z</i>. [M+H]⁺ 550.2; C₂₈H₂₆F₃N₇O₂
103	¹H NMR (400 MHz, DMSO-d₆) Shift 9.22 (s, 1H), 8.06 (br s, 1H), 7.59-7.78 (m, 3H), 7.58 (s, 1H), 7.18-7.50 (m, 3H), 6.49 (s, 2H), 4.99 (br s, 2H), 3.58 (s, 3H), 2.18 (s, 3H), 1.68 (br s, 3H). LC-MS: Rt =0.802 min, (ESI) <i>m/z</i>. [M+H]⁺ 494.4; C₂₅H₂₂F₃N₇O	104	¹H NMR (400 MHz, DMSO-d₆) δ 9.25 (s, 1H), 8.22 (s, 1H), 8.01-8.13 (m, 2H), 7.72 (d, J=9.68 Hz, 1H), 7.62 (s, 1H), 7.46 (br d, J=9.46 Hz, 1H), 7.28 (br s, 2H), 7.14 (d, J=12.10 Hz, 1H), 5.04 (br s, 2H), 4.28 (s, 3H), 3.52 (s, 3H), 1.77 (s, 3H) LC-MS: (ESI)<i>m/z</i>=552.3 [M+1]⁺, RT=0.764 min C₂₆H₂₁F₄N₉O

105	1H NMR (400 MHz, DMSO-d6) δ 9.22 (s, 1H), 8.39 (s, 1H), 8.07 (br s, 2H), 7.72 (br d, J=9.46 Hz, 1H), 7.63 (s, 1H), 7.45 (dd, J=1.43, 9.57 Hz, 1H), 7.36 (br d, J=6.60 Hz, 2H), 6.88 (s, 2H), 5.01 (br s, 2H), 4.33 (s, 3H), 3.56 (s, 3H), 1.67 (br s, 3H). LC-MS: (ESI) m/z =534.3 [M+1] ⁺ , RT= 0.762 min. C ₂₆ H ₂₂ F ₃ N ₇ O	106	1H NMR (400 MHz, DMSO-d6) δ 9.20 (s, 1H), 8.05 (br s, 1H), 7.73 (br d, J=9.24 Hz, 1H), 7.34-7.65 (m, 4H), 7.30 (d, J=1.76 Hz, 1H), 6.70 (s, 2H), 6.20 (d, J=1.76 Hz, 1H), 5.32-5.46 (m, 1H), 4.97-5.31 (m, 4H), 3.33 (s, 3H), 1.37 (d, J=6.16 Hz, 3H). LC-MS: Rt =0.836 min, (ESI) m/z . [M+H] ⁺ 522.3; C ₂₆ H ₂₂ F ₃ N ₇ O ₂
107	1H NMR (400 MHz, DMSO-d6) δ 9.20 (s, 1H), 8.05 (br s, 1H), 7.73 (br d, J=9.24 Hz, 1H), 7.46 (br d, J=9.46 Hz, 4H), 7.30 (d, J=1.32 Hz, 1H), 6.79 (s, 2H), 6.20 (d, J=1.76 Hz, 1H), 5.05-5.22 (m, 4H), 4.97 (br s, 2H), 3.34 (s, 3H). LC-MS: Rt =0.799 min, (ESI) m/z . [M+H] ⁺ 508.4; C ₂₅ H ₂₀ F ₃ N ₇ O ₂	108	1H NMR (400 MHz, DMSO-d6) δ 10.17-10.63 (m, 1H), 9.21 (s, 1H), 7.93-8.12 (m, 1H), 7.60-7.82 (m, 2H), 7.51-7.59 (m, 1H), 7.42-7.50 (m, 1H), 7.22 (d, J=1.88 Hz, 1H), 5.41-5.67 (m, 2H), 4.81-5.04 (m, 2H), 3.55-3.71 (m, 3H), 1.96-2.07 (m, 3H), 1.82-1.95 (m, 3H). 19F NMR (376 MHz, DMSO-d6) δ 60.416. LC-MS: Rt =2.320 min, (ESI) m/z . [M+H] ⁺ 487.2; C ₂₂ H ₂₁ F ₃ N ₈ O ₂
109	1H NMR (400 MHz, DMSO-d6) Shift 9.21 (s, 1H), 8.06 (br s, 1H), 7.71 (d, J=9.46 Hz, 1H), 7.67 (br s, 1H), 7.58 (s, 1H), 7.44 (dd, J=1.43, 9.57 Hz, 1H), 7.36 (br s, 1H), 7.25 (br d, J=8.80 Hz, 1H), 6.48 (s, 2H), 4.97 (br s, 2H), 4.78 (br t, J=9.02 Hz, 2H), 3.58 (s, 3H), 3.09 (br t, J=9.13 Hz, 2H), 1.67 (br s, 3H). 19F NMR (376 MHz, DMSO-d6) Shift -60.99--60.11 (m, 3F). LC-MS: Rt =2.54 min, (ESI) m/z . [M+H] ⁺ 522.2; C ₂₆ H ₂₂ F ₃ N ₇ O ₂	110	1H NMR (400 MHz, DMSO-d6) δ 9.18 (s, 1H), 7.88 (s, 1H), 7.67 (d, J=9.54 Hz, 1H), 7.45-7.56 (m, 2H), 7.36-7.43 (m, 2H), 7.32 (s, 1H), 6.32 (s, 2H), 5.35-5.47 (m, 1H), 5.26-5.35 (m, 1H), 5.15-5.26 (m, 1H), 4.12 (d, J=6.53 Hz, 4H), 3.56 (s, 3H), 2.11 (s, 3H), 1.39 (d, J=6.02 Hz, 3H). LC-MS: Rt =0.840 min, (ESI) m/z . [M+H] ⁺ 522.3; C ₂₇ H ₂₆ F ₃ N ₇ O
111	1H NMR (400 MHz, DMSO-d6) δ 9.24 (br s, 1H), 8.22 (s, 1H), 7.95-8.16 (m, 2H), 7.74 (br d, J=9.02 Hz, 1H), 7.47 (br d, J=9.90 Hz, 1H), 6.92-7.38 (m, 4H), 6.19 (br s, 1H), 5.14 (br s, 2H), 4.29 (br s, 3H), 3.48 (br s, 3H). LC-MS: Rt =0.786 min, (ESI) m/z . [M+H] ⁺ 538.3; C ₂₅ H ₁₉ F ₄ N ₉ O	112	1H NMR (400 MHz, DMSO-d6) Shift 9.21 (s, 1H), 7.97-8.28 (m, 1H), 7.54-7.84 (m, 2H), 7.15-7.48 (m, 4H), 6.57 (s, 2H), 6.17 (d, J=1.88 Hz, 1H), 5.08 (br s, 2H), 4.78 (t, J=9.07 Hz, 2H), 3.09 (br t, J=9.07 Hz, 2H). 19F NMR (376 MHz, DMSO-d6) Shift -60.46 (s, 3F). LC-MS: Rt =0.755 min, (ESI) m/z . [M+H] ⁺ 508.4; C ₂₅ H ₂₀ F ₃ N ₇ O ₂
113	1H NMR (400 MHz, DMSO-d6) Shift 9.18 (s, 1H), 8.05 (s, 1H), 7.72 (br d, J=9.26 Hz, 3H), 7.45 (dd, J=1.75, 9.51 Hz, 2H), 7.03-7.36 (m, 2H), 6.50 (s, 2H), 5.05 (s, 2H), 4.78 (br t, J=9.07 Hz, 2H), 3.54-3.82 (m, 3H), 3.10 (t, J=9.07 Hz, 2H). 19F NMR (376 MHz, DMSO-d6) Shift -60.44 (s, 1F). LC-MS: Rt =0.807 min, (ESI) m/z . [M+H] ⁺ 508.2; C ₂₅ H ₂₀ F ₃ N ₇ O ₂	114	1H NMR (400 MHz, DMSO-d6) δ 10.49-11.14 (m, 1H), 8.52 (br d, J=5.94 Hz, 1H), 7.79-8.13 (m, 2H), 7.45-7.65 (m, 2H), 7.15-7.33 (m, 1H), 6.83-6.97 (m, 1H), 5.55-5.71 (m, 2H), 5.26-5.50 (m, 1H), 4.53-4.88 (m, 1H), 3.92-4.36 (m, 1H), 3.71-3.87 (m, 1H), 3.67 (br d, J=17.39 Hz, 2H), 1.97-2.07 (m, 3H), 0.78-1.11 (m, 3H). LC-MS: Rt =1.628 min, (ESI) m/z . [M+H] ⁺ 395.3; C ₂₀ H ₂₂ N ₆ O ₃
115	1H NMR (400 MHz, DMSO-d6) Shift 9.25 (s, 1H), 8.24 (s, 1H), 8.11 (s, 2H), 7.73 (d, J=9.38 Hz, 1H), 7.42-7.65 (m, 3H), 7.36 (d, J=4.25 Hz, 1H), 7.26 (s, 2H), 4.99-5.24 (m, 2H), 4.27 (s, 3H), 3.53-3.62 (m, 3H). 19F NMR (376 MHz,	116	¹ H NMR (400 MHz, MeOD) δ 8.75 (s, 2H), 8.40 (s, 2H), 7.87 – 7.61 (m, 2H), 7.55 (d, J = 8.8 Hz, 1H), 7.32 (s, 1H), 7.18 (s, 1H), 6.83 (s, 1H), 6.51 (s, 1H), 5.68 (s, 1H), 5.40 (s, 1H), 4.73 – 4.53 (m, 2H), 3.24 (s, 2H), 2.94 (s, 2H),

	DMSO-d ₆) Shift -60.47 (s, 1F), -174.46 (br s, 1F). LC-MS: RT =0.786 min, (ESI) <i>m/z</i> . [M+H] ⁺ 538.3; C ₂₅ H ₁₉ N ₉ O ₄		2.41 – 2.13 (m, 2H), 1.84 – 1.65 (m, 3H). LC-MS: Rt =0.981 min, (ESI) <i>m/z</i> . 464.2 [M+H] ⁺ . C ₂₇ H ₂₅ N ₇ O
117	¹ H NMR (400MHz, DMSO-d ₆) Shift 8.68 (d, J=6.8 Hz, 1H), 8.54 (s, 1H), 8.26 (br s, 1H), 7.65 (d, J=9.0 Hz, 1H), 7.63 - 7.60 (m, 1H), 7.63 - 7.60 (m, 1H), 7.57 - 7.55 (m, 1H), 7.54 (br s, 1H), 7.28 - 7.15 (m, 1H), 6.93 - 6.82 (m, 3H), 6.58 (br s, 1H), 5.26 (br s, 1H), 4.36 (s, 3H), 3.55 - 3.43 (m, 1H), 3.21 - 3.09 (m, 1H), 1.67 (br s, 3H), 1.08 (br s, 2H). LC-MS: Rt =2.296 min, (ESI) <i>m/z</i> . [M+H] ⁺ 413.9; C ₂₃ H ₂₃ N ₇ O	118	¹ H NMR (400 MHz, DMSO-d ₆) Shift 8.67 (br d, J=6.50 Hz, 1H), 8.02-8.62 (m, 2H), 7.66 (d, J=8.88 Hz, 1H), 7.58 (br s, 2H), 7.15-7.28 (m, 1H), 6.76-6.94 (m, 3H), 6.60 (br s, 1H), 4.57-4.98 (m, 2H), 4.36 (s, 3H), 3.37-3.61 (m, 2H), 1.15 (br s, 3H). LC-MS: Rt =1.324 min, (ESI) <i>m/z</i> . [M+H] ⁺ 400.1; C ₂₂ H ₂₁ N ₇ O
119	¹ H NMR (400 MHz, DMSO-d ₆) δ = 8.67 (d, J = 7.0 Hz, 1H), 7.74 - 7.53 (m, 4H), 7.26 - 7.15 (m, 1H), 6.92 - 6.83 (m, 1H), 6.67 (s, 2H), 6.57 (br s, 1H), 5.46 - 5.19 (m, 3H), 5.00 (br s, 2H), 3.31 - 3.25 (m, 1H), 3.14 (dd, J = 7.0, 14.1 Hz, 1H), 1.63 (br d, J = 3.2 Hz, 3H), 1.20 - 0.90 (m, 3H) LC-MS: Rt = 2.426 min, (ESI) <i>m/z</i> . [M+H] ⁺ 402.1; C ₂₃ H ₂₃ N ₅ O ₂	120	¹ H NMR (400 MHz, DMSO-d ₆) δ = 8.80 (d, J = 4.9 Hz, 2H), 8.62 - 8.50 (m, 1H), 7.79 (s, 2H), 7.66 - 7.54 (m, 2H), 7.52 - 7.42 (m, 1H), 7.39 (br t, J = 4.8 Hz, 1H), 7.17 (br s, 1H), 6.81 (br s, 1H), 6.61 - 6.41 (m, 3H), 5.38 (br d, J = 6.8 Hz, 1H), 5.02 - 4.88 (m, 1H), 4.54 - 4.21 (m, 1H), 2.21 (s, 3H), 1.63 (d, J = 7.1 Hz, 3H) LC-MS: Rt = 2.341 min, (ESI) <i>m/z</i> . [M+H] ⁺ 438.2; C ₂₅ H ₂₃ N ₇ O
121	¹ H NMR (400 MHz, DMSO-d ₆) δ = 8.66 (br d, J = 6.3 Hz, 1H), 7.84 - 7.44 (m, 4H), 7.22 (br t, J = 7.6 Hz, 1H), 6.93 - 6.82 (m, 1H), 6.58 (br s, 3H), 5.51 - 5.02 (m, 3H), 4.93 - 4.57 (m, 2H), 3.60 - 3.34 (m, 2H), 1.39 (br d, J = 5.8 Hz, 3H), 1.12 (br s, 3H) LC-MS: Rt = 2.385 min, (ESI) <i>m/z</i> . [M+H] ⁺ 402.1; C ₂₃ H ₂₃ N ₅ O ₂	122	¹ H NMR (400 MHz, DMSO-d ₆) δ = 8.56 (br d, J = 7.2 Hz, 1H), 7.93 (q, J = 8.1 Hz, 1H), 7.85 - 7.70 (m, 2H), 7.62 - 7.54 (m, 2H), 7.51 - 7.24 (m, 2H), 7.20 - 7.13 (m, 1H), 7.09 - 6.96 (m, 1H), 6.81 (dt, J = 1.3, 6.8 Hz, 1H), 6.46 (br s, 3H), 5.24 (br d, J = 3.8 Hz, 1H), 4.98 - 4.14 (m, 2H), 2.20 (s, 3H), 1.58 (d, J = 7.0 Hz, 3H) LC-MS: Rt = 2.623 min, (ESI) <i>m/z</i> . [M+H] ⁺ 455.1; C ₂₆ H ₂₃ FN ₆ O
123	¹ H NMR (500 MHz, DMSO-d ₆) Shift 8.65 (br s, 1H), 8.27-8.61 (m, 1H), 8.23 (s, 1H), 7.65 (d, J=8.54 Hz, 1H), 7.27-7.49 (m, 1H), 7.27 (br s, 2H), 7.14-7.22 (m, 1H), 6.83-6.90 (m, 1H), 6.66 (br s, 1H), 4.07-5.97 (m, 6H), 3.51-4.00 (m, 3H), 0.75-1.05 (m, 3H). ¹⁹ F NMR (376.5 MHz, DMSO-d ₆) Shift -114.28, -116.70. LC-MS: Rt =1.553 min, (ESI) <i>m/z</i> . [M+H] ⁺ 460.2; C ₂₄ H ₂₂ FN ₇ O ₂	124	¹ H NMR (400 MHz, DMSO-d ₆) Shift 8.25-8.80 (m, 1H), 7.64 (br d, J=8.53 Hz, 2H), 7.06-7.47 (m, 2H), 6.68-6.92 (m, 3H), 6.51-6.67 (m, 1H), 5.35 (br s, 1H), 4.35-5.13 (m, 3H), 3.43-3.98 (m, 6H), 0.88 (br d, J=7.03 Hz, 3H). ¹⁹ F NMR (376 MHz, DMSO-d ₆) Shift -116.47 (br s, 1F). LC-MS: Rt =1.539 min, (ESI) <i>m/z</i> . [M+H] ⁺ 448.3; C ₂₄ H ₂₂ FN ₅ O ₃
125	¹ H NMR (400 MHz, DMSO) Shift 9.27 (s, 1H), 7.86 (d, J=9.24 Hz, 1H), 7.62 (s, 1H), 7.29-7.56 (m, 4H), 6.61-6.88 (m, 3H), 5.20 (br s, 2H), 5.06 (br s, 2H), 4.97 (br s, 2H), 3.59 (s, 3H), 1.64 (br s, 3H). LC-MS: Rt =1.109 min, (ESI) <i>m/z</i> . [M+H] ⁺ 522.1; C ₂₆ H ₂₂ F ₃ N ₇ O ₂	126	
127	¹ H NMR (400 MHz, DMSO-d ₆) δ 11.84 (s, 1H), 7.80-7.68 (m, 2H), 7.59 - 7.51 (m, 2H), 7.46 (s, 1H), 7.18 - 7.13 (m,	128	¹ H NMR (400 MHz, dmsO-d ₆) δ 8.90 - 8.71 (m, 1H), 8.53 (s, 3H), 8.00 - 7.76 (m, 1H), 7.59 - 7.43 (m, 3H), 7.23 (s, 2H),

	2H), 6.45 (s, 2H), 4.98 (s, 2H), 4.46 – 4.33 (m, 2H), 3.70 – 3.62 (m, 2H), 3.48–3.38 (m, 2H), 3.09 (s, 3H), 2.21 (s, 3H), 1.05–0.99 (m, 1H), 0.57 – 0.33 (m, 2H), 0.31 – 0.11 (m, 2H). LC-MS: Rt = 0.90 min, (ESI) <i>m/z</i> . [M+H] ⁺ 430.2 ; C ₂₅ H ₂₇ N ₅ O ₂		5.64 - 5.45 (m, 1H), 5.30 – 5.09 (m, 1H), 5.06 – 4.99 (m, 1H), 4.95 – 4.89 (m, 1H), 3.29 – 3.18 (m, 2H), 3.00 – 2.77 (m, 2H), 2.31 (s, 1H), 2.03 (s, 1H), 1.79 – 1.20 (m, 3H). LC-MS: Rt = 0.918 min, (ESI) <i>m/z</i> . [M+H] ⁺ , 464.2. C ₂₇ H ₂₅ N ₇ O
129	¹ H NMR (400 MHz, MeOD) δ 8.49 (s, 3H), 8.01 (s, 1H), 7.75 (d, <i>J</i> = 7.2 Hz, 1H), 7.68 – 7.57 (m, 3H), 7.24 (dd, <i>J</i> = 5.2, 2.8 Hz, 2H), 5.49 (s, 1H), 5.21 – 5.08 (m, 4H), 3.66 (d, <i>J</i> = 8.0 Hz, 2H), 3.49 (d, <i>J</i> = 8.4 Hz, 2H), 3.18 (s, 3H), 2.97 (s, 2H), 2.34 (s, 2H), 1.37 (d, <i>J</i> = 6.4 Hz, 1H), 1.00 (s, 1H), 0.53 (s, 2H), 0.29 (s, 1H). LC-MS: Rt = 1.000 min, (ESI) <i>m/z</i> . [M+H] ⁺ 456.3; C ₂₇ H ₂₉ N ₅ O ₂	130	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 12.10 – 12.08 (m, 1H), 7.76 – 7.72 (m, 1H), 7.56 – 7.54 (m, 4H), 7.16 – 7.14 (m, 2H), 6.44 – 6.43 (m, 2H), 4.74 – 4.69 (m, 2H), 3.15 – 3.10 (m, 1H), 2.85 – 2.80 (m, 2H), 2.13 – 2.05 (m, 2H), 1.26 – 1.20 (m, 2H), 1.20 – 1.16 (m, 6H). LC-MS: Rt = 0.905 min, (ESI) <i>m/z</i> . [M+H] ⁺ 401.2. C ₂₄ H ₂₅ N ₅ O
131	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ = 12.77 (br s, 1H), 8.13 (s, 1H), 8.05 – 7.83 (m, 1H), 7.82 – 7.66 (m, 1H), 7.82 – 7.45 (m, 3H), 6.70 (br s, 2H), 5.51 – 5.22 (m, 1H), 5.19 – 5.04 (m, 1H), 5.03 – 4.84 (m, 3H), 4.78 (br d, <i>J</i> = 7.1 Hz, 1H), 3.42 (br s, 2H), 2.17 – 1.85 (m, 1H), 1.08 – 0.57 (m, 6H) LC-MS: Rt = 2.023 min, (ESI) <i>m/z</i> . [M+H] ⁺ 484.2; C ₂₅ H ₂₄ F ₃ N ₅ O ₂	132	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ = 13.16 – 12.43 (m, 1H), 8.52 – 8.29 (m, 1H), 8.28 – 8.18 (m, 1H), 8.17 – 8.11 (m, 1H), 8.07 – 7.84 (m, 1H), 7.83 – 7.65 (m, 1H), 7.65 – 7.55 (m, 2H), 7.55 – 7.42 (m, 1H), 7.26 – 7.01 (m, 2H), 5.09 – 4.69 (m, 2H), 4.42 – 4.02 (m, 3H), 3.33 – 3.32 (m, 2H), 2.17 – 1.91 (m, 1H), 1.05 – 0.47 (m, 6H) LC-MS: Rt = 2.130 min, (ESI) <i>m/z</i> . [M+H] ⁺ 496.1; C ₂₅ H ₂₄ F ₃ N ₇ O
133	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) Shift 12.85 (br s, 1H), 8.20–8.29 (m, 1H), 8.17 (s, 2H), 7.63–7.82 (m, 2H), 7.60 (br s, 1H), 7.26–7.37 (m, 2H), 7.22 (br s, 1H), 5.00 (br s, 1H), 4.73 (br s, 1H), 4.38 (s, 1H), 3.91–4.11 (m, 2H), 3.33 (s, 3H), 3.17–3.26 (m, 1H), 2.05–2.20 (m, 1H), 1.90–2.05 (m, 1H), 0.96 (br d, <i>J</i> = 6.50 Hz, 4H), 0.88 (br d, <i>J</i> = 6.63 Hz, 1H), 0.69 (br d, <i>J</i> = 6.25 Hz, 2H). LC-MS: Rt = 1.761 min, (ESI) <i>m/z</i> . [M+H] ⁺ 572.1; C ₂₄ H ₂₃ F ₆ N ₇ OS	134	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ = 12.77 (br dd, <i>J</i> = 2.4, 5.9 Hz, 1H), 7.93 (br s, 1H), 7.82 – 7.42 (m, 5H), 6.60 (br s, 2H), 5.40 (br s, 3H), 4.95 – 4.63 (m, 2H), 3.48 (br s, 2H), 1.38 (br d, <i>J</i> = 3.9 Hz, 3H), 1.14 (br t, <i>J</i> = 6.8 Hz, 3H) LC-MS: Rt = 2.601 min, (ESI) <i>m/z</i> = 470.2 [M+H] ⁺ ; C ₂₄ H ₂₂ F ₃ N ₅ O ₂
135	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 12.35 (br s, 1 H) 7.41 – 7.90 (m, 5 H) 7.19 (br s, 2 H) 6.60 (br s, 2 H) 4.67 – 5.48 (m, 5 H) 3.48 (br s, 2 H) 1.39 (br d, <i>J</i> = 4.50 Hz, 3 H) 1.14 (br t, <i>J</i> = 6.63 Hz, 3 H) LC-MS: Rt = 2.254 min, (ESI) <i>m/z</i> = 402.2 [M+H] ⁺ ; C ₂₃ H ₂₃ N ₅ O ₂	136	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ = 12.44 – 11.68 (m, 1H), 7.67 (s, 1H), 7.62 – 7.47 (m, 4H), 7.17 (dd, <i>J</i> = 3.2, 6.0 Hz, 2H), 6.28 (s, 2H), 5.48 – 5.36 (m, 1H), 5.29 – 5.06 (m, 2H), 4.78 (s, 2H), 3.34 (br d, <i>J</i> = 7.4 Hz, 2H), 2.05 (td, <i>J</i> = 6.8, 13.8 Hz, 1H), 1.42 (d, <i>J</i> = 6.1 Hz, 3H), 0.83 (br d, <i>J</i> = 6.3 Hz, 6H) LC-MS: Rt = 2.453 min, (ESI) <i>m/z</i> = 430.2 [M+H] ⁺ ; C ₂₅ H ₂₇ N ₅ O ₂
137	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ = 8.99 – 8.68 (m, 1H), 8.27 – 8.08 (m, 1H), 8.00 – 7.40 (m, 4H), 7.18 – 7.09 (m, 1H), 7.07 – 6.94 (m, 2H), 4.99 – 4.71 (m, 2H), 2.62 (s, 1H), 2.58 (s, 1H), 2.50 (br s, 3H), 0.95 (d, <i>J</i> = 6.5 Hz, 3H), 0.88 – 0.80 (m, 1H), 0.69 (d, <i>J</i> = 6.5 Hz, 3H) LC-MS: Rt = 1.617 min, (ESI) <i>m/z</i> . [M+H] ⁺ 514.3; C ₂₅ H ₂₃ F ₄ N ₇ O	138	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ = 12.73 – 12.43 (m, 1H), 8.02 (br d, <i>J</i> = 6.4 Hz, 1H), 7.90 – 7.82 (m, 1H), 7.78 (br s, 1H), 7.73 – 7.64 (m, 1H), 7.47 (br d, <i>J</i> = 8.5 Hz, 1H), 7.20 (d, <i>J</i> = 10.9 Hz, 1H), 7.17 (br s, 2H), 4.95 – 4.69 (m, 2H), 3.46 – 3.22 (m, 2H), 2.91 – 2.57 (m, 3H), 2.16 – 2.03 (m, 1H), 0.99 – 0.78 (m, 6H) LC-MS: Rt = 2.498 min,

			(ESI) m/z . [M+H] ⁺ 514.2; C ₂₅ H ₂₃ F ₄ N ₇ O
139	1H NMR (400 MHz, DMSO-d ₆) Shift 9.01 (s, 0.7H), 8.66 (s, 0.3H), 8.53 (d, J=6.60 Hz, 0.7H), 8.31 (d, J=6.60 Hz, 0.3H), 8.04-8.20 (m, 1H), 7.35-7.86 (m, 2H), 7.08-7.26 (m, 2H), 6.91-7.08 (m, 2H), 6.71-6.91 (m, 1H), 4.19-5.11 (m, 3H), 2.75-2.86 (m, 1H), 2.63-2.70 (m, 1H), 2.56-2.63 (m, 3H), 2.34-2.46 (m, 1H), 2.15-2.27 (m, 3H), 1.92-2.15 (m, 2H). 19F NMR (376.5 MHz, DMSO-d ₆) Shift -118.93, -119.11, -119.89. LC-MS: Rt =1.824 min, (ESI) m/z . [M+H] ⁺ 572.3; C ₂₄ H ₂₃ F ₆ N ₇ OS	140	1H NMR (400 MHz, DMSO-d ₆) Shift 7.35 - 8.50 (m, 7 H) 6.96 - 7.35 (m, 1 H) 4.53 - 5.22 (m, 2 H) 2.60 - 2.98 (m, 3 H) 1.05 - 1.27 (m, 3 H). 19F NMR (376 MHz, DMSO-d ₆) Shift -58.95 - -58.53 (m, 1 F) -120.17 - -118.91 (m, 1 F). LC-MS: Rt =1.613 min, (ESI) m/z . [M+H] ⁺ 486.2; C ₂₃ H ₁₉ F ₄ N ₇ O
141	1H NMR (400 MHz, DMSO-d ₆) Shift 12.20-12.38 (m, 1H), 8.75-8.97 (m, 1H), 8.14-8.65 (m, 1H), 7.56-7.67 (m, 2H), 7.35-7.54 (m, 1H), 7.12-7.22 (m, 2H), 7.03 (br s, 2H), 6.95 (d, J=11.04 Hz, 1H), 4.82-5.13 (m, 2H), 3.51-3.70 (m, 3H), 2.59-2.70 (m, 3H), 1.75-2.06 (m, 3H). 19F NMR (376.5 MHz, DMSO-d ₆) Shift -116.39, -118.62 LC-MS: Rt =0.790 min, (ESI) m/z . [M+H] ⁺ 484.1; C ₂₅ H ₂₂ FN ₉ O	142	1H NMR (400 MHz, DMSO-d ₆) δ 12.99 (br s, 1H), 7.87-8.05 (m, 2H), 7.69-7.84 (m, 2H), 7.48-7.60 (m, 3H), 7.22 (br s, 1H), 6.97-7.13 (m, 1H), 6.22 (br s, 1H), 5.25 (br s, 2H), 3.54-3.66 (m, 3H), 2.87 (br s, 3H). LC-MS: Rt =0.774 min, (ESI) m/z . [M+H] ⁺ 538.2; C ₂₅ H ₁₉ F ₄ N ₉ O
143	1H NMR (400 MHz, DMSO-d ₆) Shift 9.25 - 9.27 (m, 1 H) 9.26 (s, 1 H) 9.14 - 9.19 (m, 1 H) 8.87 - 9.01 (m, 1 H) 8.06 (s, 1 H) 6.96 - 7.21 (m, 3 H) 4.62 - 4.95 (m, 2 H) 3.47 - 3.60 (m, 2 H) 2.58 - 2.63 (m, 3 H) 1.05 - 1.20 (m, 3 H). 19F NMR (376 MHz, DMSO-d ₆) Shift -65.75 - -65.59 (m, 1 F) -119.33 - -119.19 (m, 1 F). LC-MS: Rt =1.520 min, (ESI) m/z . [M+H] ⁺ 487.3; C ₂₂ H ₁₈ F ₄ N ₈ O	144	1H NMR (400 MHz, DMSO-d ₆) δ = 9.05 - 8.85 (m, 1H), 8.44 - 8.25 (m, 1H), 8.21 - 8.13 (m, 1H), 7.82 - 7.67 (m, 1H), 7.44 (d, J = 9.8 Hz, 1H), 7.16 (t, J = 11.3 Hz, 1H), 7.01 (br dd, J = 2.3, 9.8 Hz, 3H), 4.76 (s, 1H), 4.49 (s, 1H), 3.76 (d, J = 14.4 Hz, 3H), 3.51 (br d, J = 6.6 Hz, 1H), 3.30 (br s, 1H), 2.61 (d, J = 3.9 Hz, 3H), 1.19 - 1.03 (m, 3H) LC-MS: Rt = 2.228 min, (ESI) m/z . [M+H] ⁺ 448.2; C ₂₃ H ₂₂ FN ₇ O ₂
145	1H NMR (400 MHz, DMSO-d ₆) Shift 8.02-8.43 (m, 2H), 7.62-8.02 (m, 3H), 7.19-7.62 (m, 4H), 6.83-7.19 (m, 2H), 4.75-5.19 (m, 1H), 4.75-5.19 (m, 1H), 3.51-3.83 (m, 6H), 2.68-2.97 (m, 3H) LC-MS: Rt =1.319 min, (ESI) m/z . [M+H] ⁺ 500.3 C ₂₅ H ₂₂ FN ₉ O ₂	146	LC-MS: Rt =1.056 min, (ESI) m/z . 447.2 [M+H] ⁺ . C ₂₅ H ₂₆ N ₄ O ₂ S require 446.57. HPLC Purity: 99.72% (214 nm), 99.84% (254 nm).
147	¹ H NMR (400 MHz, DMSO-d ₆) δ 8.09 - 8.07 (m, 2H), 7.97 - 7.95 (m, 1H), 7.70 (s, 1H), 7.52 - 7.48 (m, 3H), 7.43 - 7.40 (m, 1H), 6.47 (s, 2H), 5.11 (s, 2H), 3.75 - 3.70 (m, 1H), 3.18 (s, 3H), 3.12 (s, 2H), 2.84 - 2.81 (m, 2H), 2.19 - 2.17 (m, 2H), 2.03 - 1.98 (m, 1H), 1.23 (s, 2H), 0.50 - 0.47 (m, 1H), 0.36 - 0.34 (m, 1H), 0.12 - 0.07 (m, 2H). LC-MS: Rt =1.156 min, (ESI) m/z . 473.2 [M+H] ⁺ . C ₂₇ H ₂₈ N ₄ O ₂ S	148	¹ H NMR (400 MHz, DMSO-d ₆) δ 8.12 (d, J = 4.0 Hz, 1H), 7.99 (d, J = 8.0 Hz, 1H), 7.82 (s, 1H), 7.69 (m, 1H), 7.55 - 7.43 (m, 4H), 6.50 (s, 2H), 5.07 (s, 2H), 2.25 (s, 1H), 2.22 (s, 3H), 1.78 (s, 6H). LC-MS: Rt = 1.079 min, (ESI) m/z . [M+H] ⁺ , 415.2. C ₂₄ H ₂₂ N ₄ OS
149	¹ H NMR (400 MHz, DMSO-d ₆) δ 7.98 -	150	¹ H NMR (400 MHz, DMSO-d ₆) δ 8.37

	7.96 (m, 2H), 7.79 (m, 1H), 7.67 (s, 1H), 7.49 – 7.46 (m, 3H), 6.45 (s, 2H), 4.92 – 4.80 (m, 2H), 3.62 – 3.56 (m, 1H), 3.40 (s, 2H), 3.12 (s, 3H), 2.79 (s, 3H), 2.21 (s, 2H), 1.02 – 0.96 (m, 1H), 0.45 (s, 1H), 0.32 – 0.27 (m, 1H), 0.04 (s, 2H). LC-MS: Rt = 1.156 min, (ESI) m/z. 473.2 [M+H] ⁺ . C ₂₆ H ₂₈ N ₄ O ₂ S		– 8.31 (m, 2H), 7.79 – 7.67 (m, 3H), 7.41 (s, 2H), 6.49 (s, 2H), 5.16 (s, 2H), 3.70 – 3.46 (m, 3H), 3.17 (s, 3H), 2.22 (s, 3H), 1.15 – 1.09 (m, 1H), 0.45 – 0.34 (m, 2H), 0.32 – 0.14 (m, 2H). LC-MS: Rt = 1.133 min, (ESI) m/z. [M+H] ⁺ 515.1. C ₂₆ H ₂₅ F ₃ N ₄ O ₂ S
151	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) 1H NMR (400 MHz, DMSO) δ 8.19 (s, 1H), 8.07 (d, <i>J</i> = 8.4 Hz, 1H), 7.78 (s, 1H), 7.68 (s, 1H), 7.59 (dd, <i>J</i> = 8.4, 2.0 Hz, 1H), 7.46 (s, 2H), 6.52 (s, 2H), 5.12 (s, 2H), 3.69 (t, <i>J</i> = 9.6 Hz, 1H), 3.46 (d, <i>J</i> = 7.6 Hz, 1H), 3.26 (s, 1H), 3.16 (s, 3H), 2.21 (s, 3H), 1.15 – 1.03 (m, 1H), 0.48 (s, 1H), 0.37 – 0.29 (m, 1H), 0.07 (s, 2H). LC-MS: Rt = 1.156 min, (ESI) m/z. [M+H] ⁺ 526.1; [M+2+H] ⁺ 528.1. C ₂₅ H ₂₅ BrN ₄ O ₂ S	152	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.66 (s, 1H), 8.94 – 8.61 (m, 3H), 8.07 – 7.89 (m, 2H), 7.87 – 7.54 (m, 2H), 7.47 – 7.22 (m, 2H), 7.21 – 6.96 (m, 1H), 5.28 (s, 1H), 5.04 – 4.86 (m, 1H), 4.76 (m, 1H), 4.48 (d, <i>J</i> = 16.0 Hz, 1H), 3.57 (d, <i>J</i> = 8.0 Hz, 2H), 3.45 – 3.37 (m, 1H), 3.29 (s, 1H), 3.20 – 3.07 (m, 2H), 3.02 – 2.03 (m, 5H), 2.40 – 2.13 (m, 4H), 1.99 (d, <i>J</i> = 16.0 Hz, 2H), 1.59 (s, 3H). LC-MS: Rt = 0.926 min, (ESI) m/z. 578.4 [M+H] ⁺ . C ₃₃ H ₃₅ N ₇ O ₅
153	¹ H NMR (400 MHz, MeOD) δ 8.77 (s, 2H), 8.39 (s, 1H), 8.24 – 8.12 (m, 2H), 8.10 – 7.94 (m, 1H), 7.92 – 7.78 (m, 1H), 7.70 – 7.66 (m, 1H), 7.42 – 7.28 (m, 1H), 5.55 – 5.40 (m, 0.5H), 5.35 – 5.20 (m, 0.5H), 5.17 – 5.02 (m, 1H), 4.67 – 4.47 (m, 1H), 3.06 – 2.88 (m, 2H), 2.42 – 2.22 (m, 2H), 1.77 (s, 3H), 1.41 – 1.24 (m, 2H). ¹⁹ F NMR (376 MHz, MeOD) δ - 63.20, 74.02, 75.91. LC-MS: Rt = 1.277 min, (ESI) m/z. [M+H] ⁺ 549.2. C ₂₈ H ₂₃ F ₃ N ₆ O ₅	154	¹ H NMR (400 MHz, CD ₃ OD) δ 8.32 – 8.11 (m, 2H), 7.92 (s, 1H), 7.75 – 7.55 (m, 3H), 5.36 – 5.18 (m, 2H), 3.85–3.73 (m, 1H), 3.58 (d, <i>J</i> = 8.0 Hz, 1H), 3.44 – 3.35 (s, 1H), 3.26 (s, 3H), 3.00 – 2.90 (m, 2H), 2.40 – 2.20 (m, 2H), 1.40 – 1.25 (m, 2H), 1.11 (s, 1H), 0.95 – 0.85 (m, 1H), 0.63 – 0.53 (m, 1H), 0.45 – 0.33 (m, 1H), 0.13 – 0.08 (m, 1H). LC-MS: Rt = 0.859 min, (ESI) m/z. [M+H] ⁺ 541.2. C ₂₈ H ₂₇ F ₃ N ₄ O ₂ S
155	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.90 (s, 1H), 8.80 (d, <i>J</i> = 4.0 Hz, 2H), 7.95 – 7.60 (m, 3H), 7.55 – 7.30 (m, 3H), 7.18 (s, 1H), 6.45 (s, 2H), 5.70 – 5.30 (m, 1H), 5.20 – 4.50 (m, 2H), 3.05 – 2.60 (m, 5H), 2.25 – 1.95 (m, 2H), 1.66 (s, 3H). LC-MS: Rt = 0.942 min, (ESI) m/z. [M+H] ⁺ 465.2, C ₂₆ H ₂₄ N ₈ O	156	¹ H NMR (400 MHz, CD ₃ OD) δ 8.76 (s, 1H), 8.75 (s, 1H), 7.99 (s, 1H), 7.40 – 7.35 (m, 2H), 7.34 (s, 1H), 6.01 (s, 1H), 5.53 – 5.40 (m, 2H), 4.49 (s, 2H), 4.58 – 4.50 (m, 2H), 4.06 – 4.01 (m, 3H), 3.31 – 3.18 (m, 2H), 3.15 – 2.93 (m, 2H), 2.36 – 2.29 (m, 2H), 1.76 – 1.65 (m, 3H). LC-MS: Rt = 0.911 min, (ESI) m/z. [M+H] ⁺ 470.2; C ₂₆ H ₂₇ N ₇ O ₂
157	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.79 (d, <i>J</i> = 4.0 Hz, 2H), 8.06 – 7.69 (m, 1H), 7.59 – 7.53 (m, 1H), 7.49 (s, 1H), 7.39 (s, 1H), 7.12 – 6.85 (m, 1H), 6.47 (s, 2H), 5.34 – 5.16 (m, 1H), 4.79 – 4.40 (m, 4H), 3.96 (s, 5H), 3.02 (d, <i>J</i> = 8.0 Hz, 2H), 2.81 (t, <i>J</i> = 8.0 Hz, 2H), 2.25 – 2.08 (m, 2H), 1.63 (d, <i>J</i> = 8.0 Hz, 3H). LC-MS: Rt = 0.671 min, (ESI) m/z. [M+H] ⁺ 470.2,	158	NT
159	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) Shift 8.66 (d, <i>J</i> = 6.88 Hz, 1H), 8.12 (s, 1H), 7.78 (s, 1H), 7.66 (d, <i>J</i> = 8.88 Hz, 1H), 7.47 (s, 2H), 7.30 (br s, 2H), 7.17–7.25 (m, 1H), 6.89 (br t, <i>J</i> = 6.69 Hz, 1H), 6.59 (s, 1H), 4.77 (br s, 2H), 3.41–3.57 (m, 2H), 2.54–3.11 (m, 3H), 1.17 (t, <i>J</i> = 7.00	162	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) Shift 9.26 (s, 1H), 8.53 (d, <i>J</i> = 5.3 Hz, 1H), 8.20 (d, <i>J</i> = 5.3 Hz, 1H), 8.07 (br s, 1H), 7.81 (br s, 1H), 7.47 (br s, 1H), 7.44 – 7.39 (m, 1H), 7.34 (br s, 2H), 5.13 (s, 2H), 3.41 (br d, <i>J</i> = 7.3 Hz, 2H), 3.33 (br s, 1H), 2.92 (br s, 2H), 2.13 – 1.91 (m,

	Hz, 3H). LC-MS: Rt =1.262 min, (ESI) m/z . [M+H] ⁺ 400.1; C ₂₂ H ₂₁ N ₇ O		1H), 0.76 (br s, 6H). LC-MS: Rt =0.723 min, (ESI) m/z . [M+H] ⁺ 446.3; C ₂₃ H ₂₃ N ₇ O ₅
163	¹ H NMR (400 MHz, DMSO-d ₆) Shift 8.50 (br d, J=6.60 Hz, 2H), 7.91 (br s, 1H), 7.79 (s, 1H), 7.53 (d, J=8.80 Hz, 1H), 7.41 (s, 2H), 7.23-7.30 (m, 2H), 6.89 (t, J=6.71 Hz, 1H), 5.03 (br d, J=6.82 Hz, 1H), 3.45-3.53 (m, 2H), 2.93 (s, 3H), 1.58 (br d, J=6.82 Hz, 3H), 0.72-1.15 (m, 3H). LC-MS: Rt =3.743 min, (ESI) m/z . [M+H] ⁺ 432.3;	164	¹ H NMR (400MHz, DMSO-d ₆) Shift 9.10 - 8.60 (m, 3H), 8.52 - 8.27 (m, 1H), 8.13 (s, 1H), 8.05 - 7.88 (m, 2H), 7.65 (br s, 2H), 7.52 (br s, 1H), 5.10 - 4.72 (m, 2H), 3.45 - 3.18 (m, 2H), 3.14 - 2.84 (m, 3H), 2.68 (s, 3H), 2.16 - 1.88 (m, 1H), 1.08 - 0.62 (m, 6H). LC-MS: Rt =1.623 min, (ESI) m/z . [M+H] ⁺ 442.2; C ₂₅ H ₂₇ N ₇ O
165	¹ H NMR (400 MHz, DMSO-d ₆) Shift 8.45-8.60 (m, 1H), 7.82-8.31 (m, 2H), 7.42-7.82 (m, 5H), 7.13-7.31 (m, 1H), 6.83-6.92 (m, 1H), 4.30-5.09 (m, 2H), 3.11-3.33 (m, 2H), 2.55 (br s, 3H), 1.87-2.23 (m, 1H), 0.59-1.04 (m, 6H). LC-MS: Rt =1.568 min, (ESI) m/z . [M+H] ⁺ 429.2; C ₂₃ H ₂₄ N ₈ O	166	¹ H NMR (400MHz, DMSO-d ₆) Shift 9.10 - 8.60 (m, 3H), 8.52 - 8.27 (m, 1H), 8.13 (s, 1H), 8.05 - 7.88 (m, 2H), 7.65 (br s, 2H), 7.52 (br s, 1H), 5.10 - 4.72 (m, 2H), 3.45 - 3.18 (m, 2H), 3.14 - 2.84 (m, 3H), 2.68 (s, 3H), 2.16 - 1.88 (m, 1H), 1.08 - 0.62 (m, 6H). LC-MS: Rt =1.623 min, (ESI) m/z . [M+H] ⁺ 442.2; C ₂₅ H ₂₇ N ₇ O
167	¹ H NMR (400 MHz, DMSO-d ₆) Shift 9.00 (s, 1H), 8.49 (s, 1H), 8.01-8.11 (m, 1H), 7.39-7.52 (m, 3H), 7.28-7.39 (m, 2H), 6.76 (br s, 2H), 5.49-6.49 (m, 1H), 4.61-4.80 (m, 2H), 2.87-2.95 (m, 3H), 2.64-2.70 (m, 3H), 2.58 (s, 3H). ¹⁹ F NMR (376 MHz, DMSO-d ₆) Shift -59.29 (s, 3F). LC-MS: Rt =1.840 min, (ESI) m/z . [M+H] ⁺ 522.2; C ₂₆ H ₂₂ F ₃ N ₇ O ₂	168	¹ H NMR (400 MHz, DMSO-d ₆) Shift 8.42-8.65 (m, 1H), 7.93-8.31 (m, 1H), 7.85-7.93 (m, 1H), 7.69-7.85 (m, 1H), 7.35-7.62 (m, 3H), 7.11-7.34 (m, 2H), 6.88 (t, J=6.71 Hz, 1H), 4.50-4.93 (m, 2H), 3.44-3.68 (m, 4H), 3.10-3.32 (m, 3H), 2.73-2.97 (m, 3H). ¹⁹ F NMR (376.5 MHz, DMSO-d ₆) Shift -119.21, -119.78. LC-MS: Rt =1.289 min, (ESI) m/z . [M+H] ⁺ 448.3; C ₂₃ H ₂₂ FN ₇ O ₂
169	¹ H NMR (400 MHz, DMSO-d ₆) Shift 8.41 - 8.63 (m, 1 H), 7.92 - 8.15 (m, 1 H), 7.71 - 7.91 (m, 2 H), 7.33 - 7.56 (m, 3 H), 7.14 - 7.27 (m, 2 H), 6.88 (t, J=6.75 Hz, 1 H), 4.34 - 5.02 (m, 2 H), 2.82 - 3.18 (m, 2 H), 2.52 - 2.81 (m, 2 H), 1.93 - 2.26 (m, 3 H), 1.56 - 1.87 (m, 3 H). LC-MS: Rt =1.462 min, (ESI) m/z . [M+H] ⁺ 456.2; C ₂₅ H ₂₂ FN ₇ O	170	¹ H NMR (400 MHz, DMSO-d ₆) Shift 8.97 (s, 1H), 8.44-8.55 (m, 2H), 7.96 (s, 1H), 7.51-7.60 (m, 2H), 7.38 (d, J=8.14 Hz, 1H), 7.16-7.26 (m, 1H), 6.88 (t, J=6.27 Hz, 1H), 6.82 (br s, 2H), 5.01-5.39 (m, 1H), 4.53-4.71 (m, 1H), 4.11-4.48 (m, 1H), 3.84 (dd, J=3.85, 11.77 Hz, 1H), 3.62-3.77 (m, 2H), 2.61 (s, 3H), 0.94 (d, J=7.04 Hz, 3H). LC-MS: Rt =2.003 min, (ESI) m/z . [M+H] ⁺ 442.2; C ₂₄ H ₂₃ N ₇ O ₂
171	¹ H NMR (400 MHz, DMSO-d ₆) Shift 8.47-8.58 (m, 1H), 7.85-8.46 (m, 2H), 7.75-7.85 (s, 1H), 7.50-7.58 (m, 1H), 7.43 (br s, 2H), 7.20-7.32 (m, 2H), 6.89 (t, J=6.71 Hz, 1H), 4.85-5.92 (m, 1H), 3.39-3.62 (m, 3H), 3.20 (s, 3H), 3.05-3.28 (m, 1H) 2.92 (s, 3H), 1.50-1.75 (m, 3H). ¹⁹ F NMR (376.5 MHz, DMSO-d ₆) Shift -118.53, -119.65, -120.69. LC-MS: Rt =1.383 min, (ESI) m/z . [M+H] ⁺ 462.3; C ₂₄ H ₂₄ FN ₇ O ₂	172	¹ H NMR (400 MHz, DMSO-d ₆) Shift 9.10-9.39 (m, 1H), 9.00 (s, 1H), 8.16-8.74 (m, 1H), 8.06 (s, 1H), 7.80 (d, J=7.53 Hz, 1H), 7.48 (d, J=9.54 Hz, 1H), 6.74-7.36 (m, 3H), 4.16-5.89 (m, 2H), 3.49-3.96 (m, 4H), 2.55-2.68 (m, 3H), 0.92 (d, J=6.53 Hz, 3H). ¹⁹ F NMR (376.5 MHz, DMSO-d ₆) Shift -60.43, -118.60, -119.72. LC-MS: Rt =1.583 min, (ESI) m/z . [M+H] ⁺ 528.2; C ₂₅ H ₂₁ F ₄ N ₇ O ₂

173	1H NMR (400 MHz, DMSO-d6) Shift 9.17-9.31 (m, 1H), 7.94-8.30 (m, 2H), 7.77-7.87 (m, 1H), 7.69-7.76 (m, 1H), 7.38-7.56 (m, 3H), 7.23 (d, J=11.00 Hz, 1H), 4.54-4.89 (m, 2H), 2.78-2.98 (m, 3H). 19F NMR (376.5 MHz, DMSO-d6) Shift -60.38, -60.44, -118.63, -119.29. LC-MS: Rt =1.503 min, (ESI) <i>m/z</i> . [M+H] ⁺ 475.2; C ₂₂ H ₁₄ D ₃ F ₄ N ₇ O	174	1H NMR (400 MHz, DMSO-d6) Shift 8.22-8.61 (m, 2H), 7.87-8.07 (m, 1H), 7.78 (s, 1H), 7.47-7.55 (m, 1H), 7.41 (br s, 2H), 7.11-7.30 (m, 2H), 6.88 (t, J=6.65 Hz, 1H), 4.12-5.23 (m, 2H), 3.51-3.92 (m, 3H), 2.92 (s, 3H), 0.88 (d, J=6.78 Hz, 3H). 19F NMR (376.5 MHz, DMSO-d6) Shift -119.26, -120.20. LC-MS: Rt =2.304 min, (ESI) <i>m/z</i> . [M+H] ⁺ 460.2; C ₂₄ H ₂₂ FN ₇ O ₂
175	1H NMR (400 MHz, DMSO-d6) Shift 8.40-8.64 (m, 1H), 7.95-8.32 (m, 1H), 7.69-7.94 (m, 2H), 7.40-7.61 (m, 3H), 7.15-7.36 (m, 2H), 6.89 (t, J=6.60 Hz, 1H), 6.11-6.50 (m, 1H), 4.53-5.04 (m, 2H), 3.63-4.10 (m, 2H), 2.72-2.98 (m, 3H). 19F NMR (376.5 MHz, DMSO-d6) Shift -119.26, -119.63, -120.56, -121.90. LC-MS: Rt =1.400 min, (ESI) <i>m/z</i> . [M+H] ⁺ 452.2; C ₂₂ H ₁₈ F ₃ N ₇ O	176	1H NMR (400 MHz, DMSO-d6) Shift 8.86-9.15 (m, 1H), 8.17-8.80 (m, 2H), 7.92 (br s, 1H), 7.57 (d, J=7.78 Hz, 1H), 6.72-7.34 (m, 5H), 5.41-5.85 (m, 0.2H), 4.28-5.16 (m, 1.8H), 3.53-3.92 (m, 4H), 2.60 (s, 3H), 0.94 (d, J=6.53 Hz, 3H). 19F NMR (376.5 MHz, DMSO-d6) Shift -119.70, -120.05. LC-MS: Rt =2.166 min, (ESI) <i>m/z</i> . [M+H] ⁺ 460.2; C ₂₄ H ₂₂ FN ₇ O ₂
177	1H NMR (400 MHz, DMSO-d6) Shift 8.41-8.58 (m, 1H), 8.21 (s, 0.21H, HCOOH), 7.91-8.15 (m, 1H), 7.65-7.90 (m, 2H), 7.33-7.59 (m, 3H), 7.13-7.32 (m, 2H), 6.87 (t, J=6.53 Hz, 1H), 4.57-4.98 (m, 2H), 4.05-4.57 (m, 1H), 3.71-4.01 (m, 1H), 3.44-3.52 (m, 3H), 2.91-3.16 (m, 3.9H), 2.58-2.65 (m, 0.6H), 1.91-2.03 (m, 2.5H). 19F NMR (376.5 MHz, DMSO-d6) Shift -119.18, -119.36, -119.98. LC-MS: Rt =1.349 min, (ESI) <i>m/z</i> . [M+H] ⁺ 474.3; C ₂₄ H ₂₃ F ₆ N ₇ OS	178	1H NMR (400 MHz, DMSO-d6) Shift 8.22-8.61 (m, 2H), 7.87-8.07 (m, 1H), 7.78 (s, 1H), 7.47-7.55 (m, 1H), 7.41 (br s, 2H), 7.11-7.30 (m, 2H), 6.88 (t, J=6.65 Hz, 1H), 4.12-5.23 (m, 2H), 3.51-3.92 (m, 3H), 2.92 (s, 3H), 0.88 (d, J=6.78 Hz, 3H). 19F NMR (376.5 MHz, DMSO-d6) Shift -119.26, -120.20. LC-MS: Rt =2.304 min, (ESI) <i>m/z</i> . [M+H] ⁺ 460.2; C ₂₄ H ₂₂ FN ₇ O ₂
179	1H NMR (400 MHz, DMSO-d6) Shift 8.41-8.61 (m, 1H), 7.93-8.13 (m, 1H), 7.69-7.89 (m, 2H), 7.34-7.58 (m, 3H), 7.12-7.31 (m, 2H), 6.87 (t, J=6.71 Hz, 1H), 4.11-5.02 (m, 3H), 2.57-3.02 (m, 3H), 1.78-2.31 (m, 4H), 1.30-1.70 (m, 2H). 19F NMR (376.5 MHz, DMSO-d6) Shift -119.35, -119.94. LC-MS: Rt =1.452 min, (ESI) <i>m/z</i> . [M+H] ⁺ 444.3; C ₂₄ H ₂₂ FN ₇ O	180	1H NMR (400 MHz, DMSO-d6) Shift 9.15-9.31 (m, 1H), 7.94-8.28 (m, 2H), 7.66-7.88 (m, 2H), 7.34-7.55 (m, 3H), 7.16-7.29 (m, 1H), 4.52-4.91 (m, 2H), 3.43-3.52 (m, 2H), 2.78-3.00 (m, 3H), 1.03-1.19 (m, 3H). 19F NMR (376.5 MHz, DMSO-d6) Shift -60.37, -60.44, -119.21, -119.92. LC-MS: Rt =1.580 min, (ESI) <i>m/z</i> . [M+H] ⁺ 486.3; C ₂₃ H ₁₉ F ₄ N ₇ O
181	1H NMR (400 MHz, DMSO-d6) Shift 9.13 - 9.28 (m, 1 H) 7.98 (br s, 2 H) 7.54 - 7.88 (m, 3 H) 7.36 - 7.53 (m, 3 H) 7.12 - 7.32 (m, 1 H) 7.02 (br d, J=10.88 Hz, 1 H) 4.90 - 5.20 (m, 2 H) 3.54 - 3.82 (m, 3 H) 2.73 - 2.94 (m, 3 H). 19F NMR (376 MHz, DMSO-d6) Shift -60.66 (s, 1 F) - 119.61 - -117.01 (m, 1 F). LC-MS: Rt =1.496 min, (ESI) <i>m/z</i> . [M+H] ⁺ 538.2; C ₂₅ H ₁₉ F ₄ N ₉ O	182	1H NMR (400 MHz, DMSO-d6) Shift 8.40-8.61 (m, 1H), 7.97-8.28 (m, 1H), 7.69-7.92 (m, 2H), 7.40-7.62 (m, 3H), 7.19-7.34 (m, 2H), 6.88 (t, J=6.49 Hz, 1H), 4.59-5.05 (m, 2H), 4.10-4.59 (m, 2H), 2.71-2.96 (m, 3H). 19F NMR (376.5 MHz, DMSO-d6) Shift -68.10, -68.99, -119.46, -120.09. LC-MS: Rt =1.337 min, (ESI) <i>m/z</i> . [M+H] ⁺ 444.3; C ₂₂ H ₁₇ F ₄ N ₇ O
183	1H NMR (400 MHz, DMSO-d6) Shift 9.13 - 9.28 (m, 1 H) 7.98 (br s, 2 H) 7.54 - 7.88 (m, 3 H) 7.36 - 7.53 (m, 3 H) 7.12 - 7.32 (m, 1 H) 7.02 (br d, J=10.88 Hz, 1	184	1H NMR (400 MHz, DMSO-d6) Shift 9.12-9.33 (m, 1H), 8.05-8.17 (m, 1H), 7.90-8.02 (m, 1H), 7.67-7.88 (m, 2H), 7.36-7.49 (m, 3H), 7.23 (d, J=10.78

	H) 4.90 - 5.20 (m, 2 H) 3.54 - 3.82 (m, 3 H) 2.73 - 2.94 (m, 3 H). 19F NMR (376 MHz, DMSO-d6) Shift -60.66 (s, 1 F) - 119.61 - -117.01 (m, 1 F). LC-MS: Rt =1.496 min, (ESI) <i>m/z</i> . [M+H] ⁺ 538.2; C ₂₅ H ₁₉ F ₄ N ₉ O		Hz, 1H), 4.47-4.96 (m, 2H), 3.40 (br s, 2H), 2.71-2.96 (m, 3H), 1.90-2.20 (m, 1H), 0.66-0.99 (m, 6H). 19F NMR (376 MHz, DMSO-d6) Shift -84.67--83.60 (m, 3F), -113.70--112.30 (m, 2F), -120.55--118.62 (m, 1F). LC-MS: Rt =1.887 min, (ESI) <i>m/z</i> . [M+H] ⁺ 564.3; C ₂₆ H ₂₃ F ₆ N ₇ O
185	1H NMR (400 MHz, DMSO-d6) Shift 8.37-8.66 (m, 1H), 7.93-8.18 (m, 1H), 7.67-7.89 (m, 2H), 7.33-7.59 (m, 3H), 7.06-7.31 (m, 2H), 6.77-6.95 (m, 1H), 3.77-4.89 (m, 4H), 2.99-3.23 (m, 3H), 2.68-2.99 (m, 3H), 1.18-2.05 (m, 6H). 19F NMR (376.5 MHz, DMSO-d6) Shift -119.06, -119.59, -120.35. LC-MS: Rt =1.454 min, (ESI) <i>m/z</i> . [M+H] ⁺ 488.3; C ₂₆ H ₂₆ FN ₇ O ₂	186	1H NMR (400 MHz, DMSO-d6) Shift 8.41-8.61 (m, 1H), 7.93-8.34 (m, 1H), 7.85-7.93 (m, 1H), 7.71-7.85 (m, 1H), 7.32-7.71 (m, 3H), 7.13-7.32 (m, 2H), 6.88 (t, J=6.63 Hz, 1H), 4.39-4.89 (m, 2H), 3.38-3.58 (m, 2H), 2.75-3.04 (m, 3H), 1.01-1.21 (m, 3H). 19F NMR (376.5 MHz, DMSO-d6) Shift -119.31, -119.99. LC-MS: Rt =1.329 min, (ESI) <i>m/z</i> . [M+H] ⁺ 418.2; C ₂₂ H ₂₀ FN ₇ O
187	1H NMR (400 MHz, DMSO-d6) Shift 8.43-8.63 (m, 1H), 7.98-8.29 (m, 1H), 7.85-7.94 (m, 1H), 7.74-7.84 (m, 1H), 7.35-7.62 (m, 3H), 7.15-7.32 (m, 2H), 6.89 (t, J=6.65 Hz, 1H), 4.55-4.94 (m, 2H), 3.57-3.85 (m, 2H), 2.70-2.97 (m, 5H). 19F NMR (376.5 MHz, DMSO-d6) Shift -119.41. LC-MS: Rt =1.241 min, (ESI) <i>m/z</i> . [M+H] ⁺ 443.2; C ₂₃ H ₁₉ FN ₈ O	188	(400MHz, DMSO-d6) Shift 8.77 - 8.46 (m, 3H), 7.98 (s, 1H), 7.88 - 7.65 (m, 3H), 7.55 (br d, J=9.0 Hz, 1H), 7.28 (br s, 1H), 6.91 (br t, J=6.5 Hz, 1H), 4.63 (br s, 2H), 3.73 - 3.51 (m, 2H), 3.03 - 2.62 (m, 3H), 1.25 - 1.06 (m, 3H). LC-MS: Rt =2.973 min, (ESI) <i>m/z</i> . [M+H] ⁺ 401.2; C ₂₁ H ₂₀ N ₈ O
189	1H NMR (400 MHz, DMSO-d6) Shift 9.01 (s, 0.7H), 8.66 (s, 0.3H), 8.53 (d, J=6.60 Hz, 0.7H), 8.31 (d, J=6.60 Hz, 0.3H), 8.04-8.20 (m, 1H), 7.35-7.86 (m, 2H), 7.08-7.26 (m, 2H), 6.91-7.08 (m, 2H), 6.71-6.91 (m, 1H), 4.19-5.11 (m, 3H), 2.75-2.86 (m, 1H), 2.63-2.70 (m, 1H), 2.56-2.63 (m, 3H), 2.34-2.46 (m, 1H), 2.15-2.27 (m, 3H), 1.92-2.15 (m, 2H). 19F NMR (376.5 MHz, DMSO-d6) Shift -118.93, -119.11, -119.89. LC-MS: Rt =1.824 min, (ESI) <i>m/z</i> . [M+H] ⁺ 572.3; C ₂₄ H ₂₃ F ₆ N ₇ OS	190	1H NMR (400MHz, DMSO-d6) Shift 8.37 - 7.75 (m, 2H), 8.39 - 7.73 (m, 1H), 7.58 - 7.39 (m, 3H), 7.33 - 7.19 (m, 2H), 7.07 - 6.93 (m, 1H), 6.95 - 6.42 (m, 1H), 4.90 - 4.47 (m, 2H), 3.27 - 3.03 (m, 1H), 3.33 - 3.03 (m, 1H), 2.89 (s, 3H), 2.23 - 1.95 (m, 1H), 1.00 - 0.66 (m, 6H). 19F NMR (376MHz, DMSO-d6) Shift -119.073, -120.192; 158.442, -159.220. LC-MS: Rt =1.97 min, (ESI) <i>m/z</i> . [M+H] ⁺ 464.1; C ₂₄ H ₂₃ F ₂ N ₇ O
191	1H NMR (400 MHz, DMSO-d6) Shift 8.65 (d, J=6.16 Hz, 1H), 8.49 (br d, J=6.60 Hz, 1H), 8.30 (s, 1H), 7.84-7.93 (m, 2H), 7.58 (br d, J=17.83 Hz, 2H), 7.47-7.53 (m, 1H), 7.20-7.26 (m, 1H), 6.88 (q, J=7.41 Hz, 1H), 4.78 (br d, J=6.16 Hz, 2H), 3.46-3.62 (m, 2H), 2.88-3.00 (m, 3H), 1.15-1.25 (m, 3H) LC-MS: Rt =1.640 min, (ESI) <i>m/z</i> . [M+H] ⁺ 401.2; C ₂₁ H ₂₀ N ₈ O	192	1H NMR (400 MHz, CHLOROFORM-d) Shift 8.28-8.68 (m, 1H), 7.57-8.19 (m, 3H), 7.07-7.57 (m, 5H), 6.75-6.98 (m, 1H), 5.49-5.86 (m, 1H), 4.44-5.01 (m, 2H), 3.74-4.41 (m, 2H), 2.93 (s, 3H), 1.18-1.96 (m, 6H). 19F NMR (376.5 MHz, DMSO-d6) Shift -118.56, -120.12. LC-MS: Rt =1.365 min, (ESI) <i>m/z</i> . [M+H] ⁺ 474.3; C ₂₅ H ₂₄ FN ₇ O ₂
193	1H NMR (400MHz, DMSO-d6) Shift 9.18 (s, 1H), 8.47 (br s, 1H), 8.33 - 8.14 (m, 1H), 8.08 (s, 1H), 7.87 - 7.68 (m, 5H), 7.47 (br d, J=8.4 Hz, 1H), 5.09 (s,	194	1H NMR (400 MHz, DMSO-d6) Shift 8.43-8.60 (m, 1H), 7.93-8.23 (m, 1H), 7.84-7.93 (m, 1H), 7.75-7.84 (m, 1H), 7.35-7.56 (m, 4H), 7.18-7.29 (m, 1H),

	2H), 3.68 (br s, 3H), 2.71 (s, 3H). 19F NMR (376MHz, DMSO-d6) Shift -60.427. LC-MS: Rt =3.535 min, (ESI) <i>m/z</i> . [M+H] ⁺ 521.3; C ₂₄ H ₁₉ F ₃ N ₁₀ O		6.82-6.92 (m, 1H), 3.84-5.07 (m, 2H), 3.01-3.32 (m, 2H), 2.78-2.96 (m, 3H), 1.00-1.23 (m, 3H). LC-MS: Rt =1.390 min, (ESI) <i>m/z</i> . [M+H] ⁺ 434.2; C ₂₂ H ₂₀ ClN ₇ O
195	1H NMR (400 MHz, DMSO-d6) Shift 8.82 (br d, J=5.72 Hz, 1H), 8.06 (br s, 1H), 7.97 (br d, J=5.72 Hz, 1H), 7.65-7.84 (m, 3H), 7.47 (br s, 2H), 7.25 (br s, 1H), 7.04 (br d, J=5.94 Hz, 2H), 5.10 (br s, 2H), 3.60 (br s, 3H), 2.78-3.06 (m, 3H). LC-MS: Rt =1.453 min, (ESI) <i>m/z</i> . [M+H] ⁺ 538.2; C ₂₅ H ₁₉ F ₄ N ₉ O	196	1H NMR (400MHz, DMSO-d6) Shift 8.37 - 7.75 (m, 2H), 8.39 - 7.73 (m, 1H), 7.58 - 7.39 (m, 3H), 7.33 - 7.19 (m, 2H), 7.07 - 6.93 (m, 1H), 6.95 - 6.42 (m, 1H), 4.90 - 4.47 (m, 2H), 3.27 - 3.03 (m, 1H), 3.33 - 3.03 (m, 1H), 2.89 (s, 3H), 2.23 - 1.95 (m, 1H), 1.00 - 0.66 (m, 6H). 19F NMR (376MHz, DMSO-d6) Shift -119.073, -120.192; 158.442, -159.220. LC-MS: Rt =1.97 min, (ESI) <i>m/z</i> . [M+H] ⁺ 464.1; C ₂₄ H ₂₃ F ₂ N ₇ O
197	1H NMR (400 MHz, DMSO-d6) Shift 8.33-8.61 (m, 1H), 8.20 (s, 0.6H, HCOOH), 7.63-8.05 (m, 3H), 7.33-7.61 (m, 3H), 7.09-7.30 (m, 2H), 6.72-6.96 (m, 1H), 4.34-5.03 (m, 3H), 2.63-3.02 (m, 6H), 1.92-2.35 (m, 6H). 19F NMR (376.5 MHz, DMSO-d6) Shift -119.22, -122.68. LC-MS: Rt =1.344 min, (ESI) <i>m/z</i> . [M+H] ⁺ 473.3; C ₂₅ H ₂₅ FN ₈ O	198	1H NMR (400 MHz, DMSO-d6) Shift 9.33 (br s, 1H), 7.88-8.42 (m, 2H), 7.55-7.85 (m, 3H), 7.37-7.55 (m, 3H), 6.91-7.36 (m, 2H), 4.92-5.14 (m, 2H), 3.48-3.85 (m, 3H), 2.74-2.93 (m, 3H). 19F NMR (376 MHz, DMSO-d6) Shift -120.51--115.64 (m, 1F). LC-MS: Rt =1.204 min, (ESI) <i>m/z</i> . [M+H] ⁺ 495.3; C ₂₅ H ₁₉ FN ₁₀ O
199	1H NMR (400 MHz, DMSO-d6) Shift 8.41 - 8.56 (m, 2 H) 8.21 - 8.32 (m, 1 H) 7.99 - 8.14 (m, 1 H) 7.87 - 7.95 (m, 1 H) 7.76 - 7.86 (m, 2 H) 7.44 - 7.56 (m, 3 H) 7.16 (s, 2 H) 6.81 - 7.03 (m, 2 H) 5.15 - 5.26 (m, 2 H) 2.88 (s, 3 H). 19F NMR (376 MHz, DMSO-d6) Shift -117.24 - -115.16 (m, 1 F). LC-MS: Rt =1.271 min, (ESI) <i>m/z</i> . [M+H] ⁺ 467.2; C ₂₅ H ₁₉ FN ₈ O	200	1H NMR (400 MHz, DMSO-d6) Shift 9.23 (br s, 1H), 8.66 (br s, 1H), 8.45 (br s, 1H), 7.97-8.15 (m, 2H), 7.84-7.88 (m, 1H), 7.70 (br d, J=14.30 Hz, 2H), 7.57 (br s, 2H), 7.45 (br s, 1H), 7.11 (br s, 1H), 5.05-5.30 (m, 2H), 3.56-3.88 (m, 3H), 2.91 (s, 3H). LC-MS: Rt =1.484 min, (ESI) <i>m/z</i> . [M+H] ⁺ 521.3; C ₂₄ H ₁₉ F ₃ N ₁₀ O
201	1H NMR (400MHz, DMSO-d6) Shift 8.53 - 8.36 (m, 1H), 8.28 - 7.92 (m, 1H), 7.88 - 7.75 (m, 2H), 7.55 - 7.37 (m, 3H), 7.29 - 7.16 (m, 2H), 4.87 - 4.43 (m, 2H), 3.58 (br t, J=4.2 Hz, 4H), 3.52 - 3.36 (m, 4H), 3.00 - 2.76 (m, 3H), 2.45 - 2.29 (m, 4H), 1.19 - 1.05 (m, 3H). 19F NMR (376MHz, DMSO-d6) Shift -119.304, -120.046. LC-MS: Rt =3.633 min, (ESI) <i>m/z</i> . [M+H] ⁺ 517.3 C ₂₇ H ₂₉ FN ₈ O ₂	202	1H NMR (400 MHz, DMSO-d6) Shift 8.02-8.43 (m, 2H), 7.62-8.02 (m, 3H), 7.19-7.62 (m, 4H), 6.83-7.19 (m, 2H), 4.75-5.19 (m, 1H), 4.75-5.19 (m, 1H), 3.51-3.83 (m, 6H), 2.68-2.97 (m, 3H) LC-MS: Rt =1.319 min, (ESI) <i>m/z</i> . [M+H] ⁺ 500.3 C ₂₅ H ₂₂ FN ₉ O ₂
203	1H NMR (400 MHz, DMSO-d6) Shift 8.55-8.69 (m, 1H), 8.17 (br s, 1H), 7.79 (s, 1H), 7.64 (d, J=8.80 Hz, 1H), 7.44 (br s, 2H), 7.10-7.31 (m, 2H), 6.86 (t, J=6.60 Hz, 1H) 124, 6.61 (br s, 1H), 4.61-5.85 (m, 2H), 3.50-4.04 (m, 3H), 3.28-3.36 (m, 1H), 2.68-3.06 (m, 3H), 0.80-1.01 (m, 3H). 19F NMR (376.5 MHz, DMSO-d6) Shift -119.63 LC-MS: Rt =1.479 min, (ESI) <i>m/z</i> . [M+H] ⁺ 460.3;	204	1H NMR (400 MHz, DMSO-d6) Shift 8.31-8.45 (m, 1H), 7.92-8.17 (m, 1H), 7.72-7.85 (m, 2H), 7.58-7.69 (m, 1H), 7.44 (br s, 3H), 7.14-7.32 (m, 2H), 7.02 (br d, J=11.13 Hz, 1H), 4.83-5.08 (m, 2H), 3.53-3.86 (m, 3H), 3.39-3.48 (m, 2H), 2.64-2.95 (m, 3H), 2.16 (br s, 6H). 19F NMR (376 MHz, DMSO-d6) Shift -120.02--116.80 (m, 1F).LC-MS: Rt =1.342 (ESI) <i>m/z</i> . [M+H] ⁺ 527.4; C ₂₇ H ₂₇ FN ₁₀ O

	<chem>C24H22FN7O2</chem>		
205	¹H NMR (400MHz, DMSO-d₆) Shift 9.06 - 8.84 (m, 1H), 8.31 (d, J=6.6 Hz, 1H), 8.24 - 8.11 (m, 1H), 7.52 (br t, J=7.5 Hz, 1H), 7.33 - 6.89 (m, 5H), 4.94 - 4.45 (m, 2H), 3.60 (br s, 2H), 2.61 (d, J=2.4 Hz, 3H), 1.22 - 1.07 (m, 3H). ¹⁹F NMR (376MHz, DMSO-d₆) Shift -119.164, -119.681; -157.688, -158.649. C-MS: Rt =3.824 (ESI) <i>m/z</i>. [M+H]⁺ 436.3 <chem>C22H19F2N7O</chem>	206	¹H NMR (400 MHz, DMSO-d₆) Shift 8.14-8.38 (m, 2H), 7.75-8.01 (m, 1H), 7.35-7.55 (m, 3H), 7.18-7.31 (m, 2H), 6.85 (br d, J=7.04 Hz, 1H), 5.53-5.67 (m, 1H), 4.45-4.94 (m, 2H), 3.44 (br s, 2H), 2.77-2.97 (m, 3H), 1.48-1.70 (m, 6H), 0.98-1.26 (m, 3H). ¹⁹F NMR (376 MHz, DMSO-d₆) Shift -121.18--118.30 (m, 1F). LC-MS: Rt =1.370 min, (ESI) <i>m/z</i>. [M+H]⁺ 476.3; <chem>C25H26FN7O2</chem>
207	¹H NMR (400 MHz, DMSO-d₆) Shift 9.25 - 9.27 (m, 1 H) 9.26 (s, 1 H) 9.14 - 9.19 (m, 1 H) 8.87 - 9.01 (m, 1 H) 8.06 (s, 1 H) 6.96 - 7.21 (m, 3 H) 4.62 - 4.95 (m, 2 H) 3.47 - 3.60 (m, 2 H) 2.58 - 2.63 (m, 3 H) 1.05 - 1.20 (m, 3 H). ¹⁹F NMR (376 MHz, DMSO-d₆) Shift -65.75 - -65.59 (m, 1 F) -119.33 - -119.19 (m, 1 F). LC-MS: Rt =1.520 min, (ESI) <i>m/z</i>. [M+H]⁺ 487.3; <chem>C22H18F2N8O</chem>	208	¹H NMR (400 MHz, DMSO-d₆) Shift 8.14-8.38 (m, 2H), 7.75-8.01 (m, 1H), 7.35-7.55 (m, 3H), 7.18-7.31 (m, 2H), 6.85 (br d, J=7.04 Hz, 1H), 5.53-5.67 (m, 1H), 4.45-4.94 (m, 2H), 3.44 (br s, 2H), 2.77-2.97 (m, 3H), 1.48-1.70 (m, 6H), 0.98-1.26 (m, 3H). ¹⁹F NMR (376 MHz, DMSO-d₆) Shift -121.18--118.30 (m, 1F). LC-MS: Rt =1.370 min, (ESI) <i>m/z</i>. [M+H]⁺ 476.3; <chem>C25H26FN7O2</chem>
209	¹H NMR (400 MHz, DMSO-d₆) Shift 12.55-12.90 (m, 1H), 8.89-9.00 (m, 1H), 8.12-8.30 (m, 1H), 7.95-8.10 (m, 1H), 7.76-7.90 (m, 1H), 7.52-7.73 (m, 2H), 7.46 (s, 2H), 7.16-7.37 (m, 1H), 6.97-7.10 (m, 1H), 5.10-5.25 (s, 2H), 2.60-2.98 (m, 3H). ¹⁹F NMR (376.5 MHz, DMSO-d₆) Shift -60.70, -60.82, -117.24, -119.11. LC-MS: Rt =1.490 min, (ESI) <i>m/z</i>. [M+H]⁺ 485.3; <chem>C22H16F4N8O</chem>	210	¹H NMR (400MHz, DMSO-d₆) Shift 8.50 - 8.26 (m, 1H), 8.21 - 7.93 (m, 1H), 7.81 (br d, J=5.9 Hz, 2H), 7.63 (br s, 1H), 7.44 (s, 3H), 7.35 - 7.13 (m, 2H), 7.02 (br d, J=10.3 Hz, 1H), 5.12 - 4.86 (m, 2H), 3.86 - 3.46 (m, 9H), 2.96 - 2.69 (m, 3H), 2.44 - 2.30 (m, 4H). ¹⁹F NMR (376MHz, DMSO-d₆) Shift -117.195, -119.505. LC-MS: Rt =1.673 min, (ESI) <i>m/z</i>. [M+H]⁺ 569.2; <chem>C29H29FN10O2</chem>
211	¹H NMR (400 MHz, DMSO-d₆) Shift 8.50 (br s, 1H), 7.74-8.27 (m, 2H), 7.62 (br s, 1H), 7.29-7.52 (m, 3H), 6.91-7.29 (m, 2H), 4.74-5.27 (m, 6H), 3.59 (br s, 3H), 2.62-2.98 (m, 3H). LC-MS: Rt =1.982 min, (ESI) <i>m/z</i>. [M+H]⁺ 473.3; <chem>C24H21FN8O2</chem>	212	¹H NMR (400 MHz, DMSO-d₆) Shift 9.15-9.31 (m, 1H), 8.33 (s, 1H), 8.07-8.16 (m, 1H), 7.92-8.03 (m, 1H), 7.76-7.86 (m, 1H), 7.58-7.75 (m, 2H), 7.41-7.55 (m, 3H), 7.18-7.33 (m, 1H), 4.71-5.17 (m, 2H), 3.53-3.83 (m, 3H), 2.80-2.97 (m, 3H). LC-MS: Rt =1.544 min, (ESI) <i>m/z</i>. [M+H]⁺ 554.2; <chem>C25H19ClF3N9O</chem>
213	¹H NMR (400 MHz, DMSO-d₆) Shift 8.83 - 9.07 (m, 1 H) 8.34 - 8.50 (m, 2 H) 8.15 - 8.29 (m, 1 H) 7.62 - 7.72 (m, 1 H) 7.09 - 7.24 (m, 1 H) 6.96 - 7.07 (m, 2 H) 4.61 - 4.95 (m, 2 H) 3.51 - 3.61 (m, 2 H) 2.58 - 2.64 (m, 3 H) 1.05 - 1.19 (m, 3 H). ¹⁹F NMR (376 MHz, DMSO-d₆) Shift -65.19 - -64.80 (m, 1 F) -119.50 (br d, J=20.60 Hz, 1 F). LC-MS: Rt =1.633 min, (ESI) <i>m/z</i>. [M+H]⁺ 487.3; <chem>C22H18F4N8O</chem>	214	¹H NMR (400 MHz, DMSO-d₆) Shift 7.35 - 8.50 (m, 7 H) 6.96 - 7.35 (m, 1 H) 4.53 - 5.22 (m, 2 H) 2.60 - 2.98 (m, 3 H) 1.05 - 1.27 (m, 3 H). ¹⁹F NMR (376 MHz, DMSO-d₆) Shift -58.95 - -58.53 (m, 1 F) -120.17 - -118.91 (m, 1 F). LC-MS: Rt =1.613 min, (ESI) <i>m/z</i>. [M+H]⁺ 486.2; <chem>C23H19F4N7O</chem>
215	¹H NMR (400 MHz, DMSO-d₆) Shift 8.99 (s, 1H), 8.06-8.47 (m, 1H), 7.57 (br d, J=7.75 Hz, 1H), 7.33 (br d, J=7.63 Hz, 1H), 7.24 (s, 1H), 7.18 (br d, J=10.76 Hz, 1H), 7.05 (br s, 2H), 5.49-6.15 (m,	216	¹H NMR (400 MHz, DMSO-d₆) Shift 8.15 (s, 0.16H, HCOOH), 7.76-7.99 (m, 2H), 7.35-7.52 (m, 2H), 6.85-7.27 (m, 3H), 6.62-6.78 (m, 1H), 4.30-4.74 (m, 4H), 3.01-3.21 (m, 4H), 2.71-2.96

	1H), 4.50-5.06 (m, 2H), 3.17 (br dd, J=7.75, 14.88 Hz, 2H), 2.63 (s, 3H), 0.83-1.04 (m, 3H) LC-MS: Rt =0.78 min, (ESI) <i>m/z</i> . [M+H] ⁺ 474.3; C ₂₃ H ₁₉ F ₄ N ₅ O ₂		(m, 3H), 0.93-1.21 (m, 3H). 19F NMR (376.5 MHz, DMSO-d ₆) Shift -119.74, -119.89. LC-MS: Rt =1.623 min, (ESI) <i>m/z</i> . [M+H] ⁺ 420.3; C ₂₃ H ₂₂ FN ₅ O ₂
217	1H NMR (400 MHz, DMSO-d ₆) Shift 8.75-9.25 (m, 1H), 8.14-8.49 (m, 2H), 7.64-7.86 (m, 1H), 7.46 (br d, J=7.82 Hz, 1H), 7.12-7.24 (m, 2H), 7.02 (br s, 2H), 4.31-4.93 (m, 2H), 3.49-3.65 (m, 4H), 3.00-3.32 (m, 3H), 2.54-2.77 (m, 6H), 2.43 (br s, 4H), 1.04-1.18 (m, 3H), ~90% of purity. LC-MS: Rt =0.774 min, (ESI) <i>m/z</i> . [M+H] ⁺ 531.3; C ₂₈ H ₃₁ FN ₈ O ₂	218	1H NMR (400 MHz, DMSO-d ₆) Shift 8.15 (s, 0.16H, HCOOH), 7.76-7.99 (m, 2H), 7.35-7.52 (m, 2H), 6.85-7.27 (m, 3H), 6.62-6.78 (m, 1H), 4.30-4.74 (m, 4H), 3.01-3.21 (m, 4H), 2.71-2.96 (m, 3H), 0.93-1.21 (m, 3H). 19F NMR (376.5 MHz, DMSO-d ₆) Shift -119.74, -119.89. LC-MS: Rt =1.623 min, (ESI) <i>m/z</i> . [M+H] ⁺ 420.3; C ₂₃ H ₂₂ FN ₅ O ₂
219	1H NMR (400 MHz, DMSO-d ₆) Shift 7.88-8.15 (m, 1H), 7.81 (s, 1H), 7.41-7.60 (m, 3H), 7.14-7.28 (m, 1H), 6.84-7.13 (m, 3H), 6.62-6.77 (m, 1H), 4.87 (s, 2H), 4.38-4.61 (m, 2H), 3.51-3.91 (m, 3H), 3.00-3.22 (m, 2H), 2.64-2.97 (m, 3H). 19F NMR (376.5 MHz, DMSO-d ₆) Shift -117.53, -119.22. LC-MS: Rt =1.720 min, (ESI) <i>m/z</i> . [M+H] ⁺ 472.1; C ₂₅ H ₂₂ FN ₇ O ₂	220	1H NMR (400 MHz, DMSO-d ₆) Shift 9.13-9.40 (m, 1H), 8.86-9.09 (m, 1H), 8.11-8.31 (m, 1H), 7.71-7.98 (m, 1H), 7.42 (br dd, J=9.35, 19.50 Hz, 1H), 7.16 (br dd, J=10.94, 19.62 Hz, 1H), 7.01 (br d, J=8.93 Hz, 2H), 6.56-6.83 (m, 1H), 4.54-5.07 (m, 2H), 3.53 (br d, J=5.38 Hz, 1H), 3.29 (br s, 1H), 2.61 (br d, J=9.54 Hz, 3H), 1.02-1.19 (m, 3H). LC-MS: Rt =0.899 min, (ESI) <i>m/z</i> . [M+H] ⁺ 486.3; C ₂₃ H ₁₉ F ₄ N ₇ O
221	1H NMR (400 MHz, DMSO-d ₆) Shift 8.93 (s, 1H), 8.13 (br d, J=6.16 Hz, 1H), 7.47 (br d, J=7.26 Hz, 1H), 7.29 (s, 1H), 7.22 (t, J=7.70 Hz, 1H), 6.86-7.13 (m, 4H), 6.81 (s, 1H), 6.72 (d, J=7.92 Hz, 1H), 6.56 (br d, J=6.16 Hz, 1H), 4.77 (br t, J=9.35 Hz, 1H), 4.49 (br dd, J=3.30, 10.34 Hz, 1H), 2.60 (s, 3H). 19F NMR (376 MHz, DMSO-d ₆) Shift -117.76 (br s, 1F). LC-MS: Rt =0.802 min, (ESI) <i>m/z</i> . [M+H] ⁺ 458.3; C ₂₄ H ₂₀ FN ₇ O ₂	222	1H NMR (400 MHz, DMSO-d ₆) Shift 8.81-9.21 (m, 1H), 8.33-8.63 (m, 1H), 7.74-8.31 (m, 3H), 7.40-7.68 (m, 1H), 6.91-7.28 (m, 3H), 5.37-5.90 (m, 1H), 4.71-5.05 (m, 1H), 4.38-4.70 (m, 1H), 3.80-3.93 (m, 3H), 3.22 (br d, J=6.75 Hz, 2H), 2.61 (s, 3H), 0.69-1.12 (m, 3H). LC-MS: Rt =2.220 min, (ESI) <i>m/z</i> . [M+H] ⁺ 487.3; C ₂₅ H ₂₃ FN ₈ O ₂
223	1H NMR (400 MHz, DMSO-d ₆) Shift 9.00 (s, 1H), 8.89 (br d, J=16.51 Hz, 1H), 8.57 (br d, J=3.67 Hz, 1H), 8.15-8.48 (m, 1H), 7.95-8.15 (m, 1H), 7.41-7.66 (m, 2H), 6.83-7.41 (m, 5H), 5.45-6.29 (m, 1H), 4.61 (br d, J=10.15 Hz, 2H), 3.15-3.29 (m, 2H), 2.63 (s, 3H), 0.78-1.12 (m, 3H). LC-MS: Rt =0.807 min, (ESI) <i>m/z</i> . [M+H] ⁺ 483.3; C ₂₇ H ₂₃ FN ₆ O ₂	224	1H NMR (400 MHz, DMSO-d ₆) Shift 7.92-8.19 (m, 1H), 7.83 (s, 1H), 7.57 (br s, 1H), 7.47 (s, 2H), 7.31 (br d, J=7.83 Hz, 1H), 7.13-7.28 (m, 2H), 5.48-6.23 (m, 1H), 4.49-5.02 (m, 2H), 3.18 (br d, J=8.44 Hz, 2H), 2.96 (br s, 3H), 0.81-1.11 (m, 3H). LC-MS: Rt =0.78 min, (ESI) <i>m/z</i> . [M+H] ⁺ 474.3; C ₂₃ H ₁₉ F ₄ N ₅ O ₂
225	1H NMR (400 MHz, DMSO-d ₆) Shift 8.93 (s, 1H), 8.13 (br d, J=6.16 Hz, 1H), 7.47 (br d, J=7.26 Hz, 1H), 7.29 (s, 1H), 7.22 (t, J=7.70 Hz, 1H), 6.86-7.13 (m, 4H), 6.81 (s, 1H), 6.72 (d, J=7.92 Hz, 1H), 6.56 (br d, J=6.16 Hz, 1H), 4.77 (br t, J=9.35 Hz, 1H), 4.49 (br dd, J=3.30, 10.34 Hz, 1H), 2.60 (s, 3H). 19F NMR (376 MHz, DMSO-d ₆) Shift -117.76 (br	226	1H NMR (400 MHz, DMSO-d ₆) Shift 9.00 (s, 1H), 8.25 (br d, J=6.38 Hz, 1H), 7.14-7.51 (m, 3H), 6.85-7.13 (m, 4H), 5.40-6.21 (m, 1H), 4.36-4.88 (m, 2H), 2.99-3.20 (m, 1H), 3.07 (br d, J=6.82 Hz, 1H), 2.63 (s, 3H), 0.55-1.09 (m, 3H). 19F NMR (376 MHz, DMSO-d ₆) Shift -119.88 (br d, J=16.02 Hz,

	s, 1F). LC-MS: Rt =0.802 min, (ESI) <i>m/z</i> . [M+H] ⁺ 458.3; C ₂₄ H ₂₀ FN ₇ O ₂		1F). LC-MS: Rt =0.842 min, (ESI) <i>m/z</i> . [M+H] ⁺ 406.2; C ₂₂ H ₂₀ FN ₅ O ₂
227	¹ H NMR (400 MHz, DMSO-d ₆) Shift 8.60 (d, J=7.04 Hz, 1H), 7.89 (d, J=6.38 Hz, 1H), 7.81 (s, 1H), 7.57-7.72 (m, 2H), 7.48 (s, 2H), 7.15-7.34 (m, 1H), 7.07 (d, J=11.22 Hz, 1H), 6.85 (t, J=6.71 Hz, 1H), 6.58 (s, 1H), 5.07 (s, 2H), 3.54 (s, 3H), 2.85 (s, 3H), 1.77 (s, 3H). ¹⁹ F NMR (376 MHz, DMSO-d ₆) Shift -117.27 (br s, 1F). LC-MS: Rt =0.719 min, (ESI) <i>m/z</i> . [M+H] ⁺ 484.4; C ₂₅ H ₂₂ FN ₉ O	228	¹ H NMR (400 MHz, DMSO-d ₆) Shift 9.00 (s, 1H), 8.06-8.52 (m, 2H), 7.86 (d, J=7.95 Hz, 1H), 6.83-7.48 (m, 6H), 5.14-6.64 (m, 1H), 4.39-4.93 (m, 2H), 3.85 (d, J=5.01 Hz, 3H), 2.56-2.70 (m, 6H). LC-MS: Rt =0.761 min, (ESI) <i>m/z</i> . [M+H] ⁺ 472.2; C ₂₅ H ₂₂ FN ₇ O ₂
229	¹ H NMR (400 MHz, DMSO-d ₆) 8.52 (br s, 1H), 8.03 (br s, 2H), 7.91 (br s, 1H), 7.82 (br s, 1H), 7.75 (br s, 1H), 7.49 (br s, 3H), 7.22 (br s, 1H), 6.97 (br s, 1H), 6.87 (br s, 1H), 6.68 (br s, 1H), 5.17 (br s, 2H), 3.63-3.82 (m, 3H), 2.92 (br s, 3H). ¹⁹ F NMR (376 MHz, DMSO-d ₆) -116.39 (s, 1F) LC-MS: Rt =0.800 min, (ESI) <i>m/z</i> . [M+H] ⁺ 497.1; C ₂₆ H ₂₁ FN ₈ O ₂	230	¹ H NMR (400 MHz, DMSO-d ₆) Shift 8.99 (s, 1H), 8.08-8.54 (m, 2H), 7.62 (d, J=1.63 Hz, 1H), 7.16 (d, J=10.88 Hz, 1H), 7.04 (br s, 2H), 5.42-5.78 (m, 1H), 4.75-5.07 (m, 1H), 4.54-4.75 (m, 1H), 3.28 (br d, J=7.38 Hz, 1H), 3.18 (br d, J=7.50 Hz, 1H), 2.61 (d, J=3.13 Hz, 3H), 0.87-1.04 (m, 3H). ¹⁹ F NMR (376 MHz, DMSO-d ₆) Shift -120.15-118.26 (m, 1F). LC-MS: Rt =0.847 min, (ESI) <i>m/z</i> . [M+H] ⁺ 485.4; C ₂₁ H ₁₈ BrFN ₆ O ₂
231	¹ H NMR (400 MHz, DMSO-d ₆) Shift 8.50 (br d, J=3.38 Hz, 1H), 8.18 (s, 1H), 8.08 (d, J=8.63 Hz, 1H), 7.90 (d, J=6.38 Hz, 1H), 7.79 (s, 1H), 7.65 (s, 1H), 7.46 (s, 2H), 7.22 (dd, J=4.44, 9.19 Hz, 1H), 7.05 (d, J=11.13 Hz, 1H), 5.04 (br s, 2H), 3.47-3.71 (m, 3H), 2.85 (s, 3H), 1.79 (s, 3H). ¹⁹ F NMR (376 MHz, DMSO-d ₆) Shift -120.22--116.68 (m, 1F). LC-MS: Rt =1.24 min, (ESI) <i>m/z</i> . [M+H] ⁺ 485.3; C ₂₄ H ₂₁ FN ₁₀ O	232	¹ H NMR (400 MHz, DMSO-d ₆) Shift 8.87-9.41 (m, 1H), 7.64-8.23 (m, 4H), 7.35-7.59 (m, 3H), 7.07-7.32 (m, 1H), 4.36-5.16 (m, 3H), 3.47-4.08 (m, 4H), 2.60-3.08 (m, 3H), 1.97-2.30 (m, 2H). ¹⁹ F NMR (376 MHz, DMSO-d ₆) Shift -60.42 (br d, J=43.49 Hz, 3F), -122.45--117.86 (m, 1F). LC-MS: Rt =1.009 min, (ESI) <i>m/z</i> . [M+H] ⁺ 528.3; C ₂₅ H ₂₁ F ₄ N ₇ O ₂
233	¹ H NMR (400 MHz, DMSO-d ₆) Shift 9.25 (s, 1H), 8.97 (s, 1H), 8.15 (d, J=6.38 Hz, 1H), 8.04 (s, 1H), 7.73 (d, J=9.46 Hz, 1H), 7.57 (s, 1H), 7.47 (dd, J=1.54, 9.46 Hz, 1H), 6.63-7.24 (m, 3H), 5.01 (s, 2H), 3.52 (s, 3H), 2.60 (s, 3H), 1.79 (s, 3H). ¹⁹ F NMR (376 MHz, DMSO-d ₆) Shift -60.40 (br s, 3F), -116.73 (br s, 1F). LC-MS: Rt =0.994 min, (ESI) <i>m/z</i> . [M+H] ⁺ 522.3; C ₂₆ H ₂₁ F ₄ N ₉ O	234	¹ H NMR (400 MHz, DMSO-d ₆) Shift 8.60 (br s, 1H), 8.23 (s, 1H), 7.70-8.10 (m, 2H), 7.38-7.70 (m, 3H), 7.04-7.38 (m, 2H), 6.84 (br s, 1H), 6.27-6.60 (m, 1H), 4.36-5.18 (m, 3H), 3.79-4.04 (m, 2H), 3.45 (br s, 2H), 2.97 (br s, 2H), 2.38-2.50 (m, 1H), 2.11 (br s, 2H). LC-MS: Rt =1.081 min, (ESI) <i>m/z</i> . [M+H] ⁺ 460.4; C ₂₄ H ₂₂ FN ₇ O ₂
235	¹ H NMR (400 MHz, DMSO) Shift 9.10 (s, 1H), 8.88 (s, 1H), 8.09 (d, J=6.38 Hz, 1H), 7.82 (d, J=9.24 Hz, 1H), 7.57 (s, 1H), 7.38 (d, J=9.24 Hz, 1H), 6.94 (d, J=10.78 Hz, 1H), 6.65-6.88 (m, 3H), 5.03 (br s, 2H), 3.46 (s, 3H), 2.56 (s, 3H), 1.73 (s, 3H). LC-MS: Rt =1.113 min, (ESI) <i>m/z</i> . [M+H] ⁺ 552.1; C ₂₆ H ₂₁ F ₄ N ₉ O	236	¹ H NMR (400 MHz, DMSO-d ₆) Shift 9.25 (s, 1H), 8.04 (s, 1H), 7.88 (br d, J=6.38 Hz, 1H), 7.81 (s, 1H), 7.73 (d, J=9.46 Hz, 1H), 7.62 (s, 1H), 7.37-7.56 (m, 3H), 7.07 (d, J=11.22 Hz, 1H), 5.04 (br s, 2H), 3.55 (s, 3H), 2.84 (s, 3H), 1.79 (s, 3H). ¹⁹ F NMR (376 MHz, DMSO-d ₆) Shift -60.40, -117.07. LC-MS: Rt =1.017 min, (ESI) <i>m/z</i> . [M+H] ⁺ 522.3;

			$C_{26}H_{21}F_4N_9O$
237	1H NMR (400 MHz, DMSO-d_6) Shift 12.20-12.38 (m, 1H), 8.75-8.97 (m, 1H), 8.14-8.65 (m, 1H), 7.56-7.67 (m, 2H), 7.35-7.54 (m, 1H), 7.12-7.22 (m, 2H), 7.03 (br s, 2H), 6.95 (d, $J=11.04$ Hz, 1H), 4.82-5.13 (m, 2H), 3.51-3.70 (m, 3H), 2.59-2.70 (m, 3H), 1.75-2.06 (m, 3H). ^{19}F NMR (376.5 MHz, DMSO-d_6) Shift -116.39, -118.62 LC-MS: $R_t = 0.790$ min, (ESI) m/z. $[M+H]^+$ 484.1; $C_{25}H_{22}FN_9O$	238	1H NMR (400 MHz, DMSO) Shift 9.26 (s, 1H), 7.84-7.96 (m, 2H), 7.80 (s, 1H), 7.64 (s, 1H), 7.48 (s, 2H), 7.42 (dd, $J=1.21, 9.35$ Hz, 1H), 7.06 (d, $J=11.22$ Hz, 1H), 6.78 (s, 1H), 5.10 (s, 2H), 3.53 (s, 3H), 2.84 (s, 3H), 1.77 (s, 3H). LC-MS: $R_t = 1.113$ min, (ESI) m/z. $[M+H]^+$ 552.1; $C_{26}H_{21}F_4N_9O$
239	1H NMR (400 MHz, DMSO-d_6) δ 9.23 (br s, 1H), 7.87-8.56 (m, 2H), 7.68-7.84 (m, 2H), 7.43-7.55 (m, 3H), 7.01-7.37 (m, 2H), 6.17 (br s, 1H), 4.84-5.28 (m, 2H), 3.45-3.83 (m, 3H), 2.86 (br s, 3H). LC-MS: $R_t = 0.811$ min, (ESI) m/z. $[M+H]^+$ 538.3; $C_{25}H_{19}F_4N_9O$	240	1H NMR (400 MHz, DMSO-d_6) 8.91 (br s, 1H), 8.23 (br d, $J=8.13$ Hz, 1H), 7.97 (br d, $J=6.75$ Hz, 1H), 7.89 (br s, 1H), 7.81 (s, 1H), 7.34 (br s, 2H), 7.13 (br d, $J=11.26$ Hz, 1H), 6.50 (s, 1H), 5.17 (br s, 2H), 3.23-3.28 (m, 3H), 2.87 (s, 3H), 1.96 (br s, 3H) ^{19}F NMR (376 MHz, DMSO-d_6) -60.85 (s, 3F), -118.24 (br s, 1F). LC-MS: $R_t = 0.759$ min, (ESI) m/z. $[M+H]^+$ 513.3; $C_{24}H_{20}F_4N_8O$
241	1H NMR (400 MHz, DMSO-d_6) 9.28 (br s, 1H), 8.10 (br s, 1H), 7.92 (br s, 1H), 7.82 (s, 1H), 7.73 (d, $J=9.76$ Hz, 1H), 7.55 (s, 2H), 7.47 (br d, $J=8.63$ Hz, 1H), 7.29 (br s, 1H), 7.11 (br d, $J=10.38$ Hz, 1H), 5.19 (br s, 1H), 5.04-5.14 (m, 1H), 3.59 (s, 3H), 2.86 (br s, 3H). ^{19}F NMR (376 MHz, DMSO-d_6) -60.47 (s, 3F), -118.15 (s, 1F), -173.54 (s, 1F). LC-MS: $R_t = 1.961$ min, (ESI) m/z. $[M+H]^+$ 556.1; $C_{25}H_{18}F_5N_9O$	242	1H NMR (400 MHz, DMSO-d_6) δ 9.24 (br s, 1H), 8.22 (s, 1H), 7.95-8.16 (m, 2H), 7.74 (br d, $J=9.02$ Hz, 1H), 7.47 (br d, $J=9.90$ Hz, 1H), 6.92-7.38 (m, 4H), 6.19 (br s, 1H), 5.14 (br s, 2H), 4.29 (br s, 3H), 3.48 (br s, 3H). LC-MS: $R_t = 0.786$ min, (ESI) m/z. $[M+H]^+$ 538.3; $C_{25}H_{19}F_4N_9O$
243	1H NMR (400 MHz, DMSO-d_6) δ 8.43 (br s, 1H), 7.76-7.97 (m, 1H), 7.72-8.01 (m, 2H), 7.39-7.66 (m, 3H), 7.03-7.36 (m, 3H), 6.17 (br s, 1H), 4.77-5.16 (m, 2H), 3.57 (br t, $J=4.29$ Hz, 4H), 3.37-3.50 (m, 6H), 2.86 (br s, 2H), 2.31-2.39 (m, 4H). LC-MS: $R_t = 0.614$ min, (ESI) m/z. $[M+H]^+$ 569.4; $C_{29}H_{29}FN_{10}O_2$	244	1H NMR (400 MHz, DMSO-d_6) δ 9.23 (br s, 1H), 7.86-8.62 (m, 2H), 7.71-7.84 (m, 2H), 7.40-7.64 (m, 3H), 7.28 (br s, 1H), 7.09 (br d, $J=10.38$ Hz, 1H), 6.27 (br s, 1H), 4.76-5.34 (m, 2H), 3.47-4.17 (m, 2H), 2.85 (br s, 3H), 0.90-1.26 (m, 3H). LC-MS: $R_t = 0.801$ min, (ESI) m/z. $[M+H]^+$ 552.3; $C_{26}H_{21}F_4N_9O$
245	1H NMR (400 MHz, DMSO-d_6) δ 12.99 (br s, 1H), 7.87-8.05 (m, 2H), 7.69-7.84 (m, 2H), 7.48-7.60 (m, 3H), 7.22 (br s, 1H), 6.97-7.13 (m, 1H), 6.22 (br s, 1H), 5.25 (br s, 2H), 3.54-3.66 (m, 3H), 2.87 (br s, 3H). LC-MS: $R_t = 0.774$ min, (ESI) m/z. $[M+H]^+$ 538.2; $C_{25}H_{19}F_4N_9O$	246	1H NMR (400 MHz, DMSO-d_6) Shift 8.52 (br d, $J=4.63$ Hz, 1H), 7.62-8.03 (m, 3H), 7.44-7.59 (m, 3H), 7.02-7.39 (m, 3H), 6.72-6.99 (m, 1H), 6.18 (br s, 1H), 4.67-5.25 (m, 2H), 3.44-3.79 (m, 3H), 2.87 (br s, 3H). ^{19}F NMR (376 MHz, DMSO-d_6) Shift -120.00--116.92 (m, 1F). LC-MS: $R_t = 0.645$ min, (ESI) m/z. $[M+H]^+$ 470.3; $C_{24}H_{20}FN_9O$
247	1H NMR (400 MHz, DMSO-d_6) Shift 8.84-8.73 (m, 1H), 8.33-8.10 (m, 2H), 8.00-7.86 (m, 1H), 7.84-7.74 (m, 2H), 7.58-7.48 (m,	248	1H NMR (400 MHz, DMSO-d_6) δ 9.15-9.28 (m, 1H), 8.05 (br s, 2H), 7.68-7.89 (m, 3H), 7.37-7.62 (m, 4H),

	2H), 7.48-7.38 (m, 2H), 7.29-7.17 (m, 1H), 4.87-4.49 (m, 2H), 3.89 (s, 3H), 3.58-3.35 (m, 2H), 2.99-2.85 (m, 3H), 1.18-1.07 (m, 3H). LC-MS: Rt = 2.109 min, (ESI) <i>m/z</i> . [M+H] ⁺ 498.1; C ₂₆ H ₂₄ FN ₉ O		7.05 (br s, 1H), 6.42 (br s, 1H), 4.92-5.33 (m, 2H), 2.90 (br s, 3H). LC-MS: Rt = 0.814 min, (ESI) <i>m/z</i> . [M+H] ⁺ 574.3; C ₂₅ H ₁₇ F ₆ N ₉ O
249	1H NMR (400 MHz, DMSO-d ₆) δ = 9.04 - 8.82 (m, 1H), 8.55 - 8.15 (m, 2H), 7.94 - 7.74 (m, 1H), 7.53 (br t, J = 9.5 Hz, 1H), 7.32 - 7.11 (m, 2H), 7.02 (br s, 2H), 4.80 (s, 1H), 4.52 (s, 1H), 3.75 - 3.38 (m, 8H), 2.70 - 2.51 (m, 7H), 1.20 - 1.03 (m, 3H) LC-MS: Rt = 2.142 min, (ESI) <i>m/z</i> . [M+H] ⁺ 517.3; C ₂₇ H ₂₉ FN ₈ O ₂	250	1H NMR (400 MHz, DMSO-d ₆) Shift 9.58-9.37 (m, 1H), 9.35-9.17 (m, 2H), 9.00-8.73 (m, 2H), 8.73-8.53 (m, 1H), 8.52-8.33 (m, 1H), 8.12-7.73 (m, 2H), 7.48 (br d, J = 9.7 Hz, 1H), 5.13-4.75 (m, 2H), 3.43 (br d, J = 2.4 Hz, 2H), 3.40 (br s, 1H), 3.13-2.98 (m, 4H), 2.73 (s, 3H), 2.12-1.95 (m, 4H), 1.16 (br s, 3H). LC-MS: Rt = 1.343 min, (ESI) <i>m/z</i> . [M+H] ⁺ 501.3; C ₂₇ H ₃₀ ClFN ₈ O
251	1H NMR (400 MHz, DMSO-d ₆) δ = 9.07 - 8.88 (m, 1H), 8.55 - 8.40 (m, 2H), 7.90 - 7.77 (m, 1H), 7.48 - 7.39 (m, 1H), 7.35 - 7.26 (m, 1H), 7.16 (t, J = 10.7 Hz, 1H), 7.00 (br s, 2H), 5.22 - 5.18 (m, 1H), 4.78 (s, 1H), 4.50 (s, 1H), 3.74 (s, 1H), 3.51 (br d, J = 5.8 Hz, 1H), 2.61 (d, J = 4.9 Hz, 3H), 1.46 (t, J = 5.7 Hz, 6H), 1.16 - 1.04 (m, 3H) LC-MS: Rt = 2.138 min, (ESI) <i>m/z</i> . [M+H] ⁺ 476.2; C ₂₅ H ₂₆ FN ₇ O ₂	252	1H NMR (400 MHz, DMSO-d ₆) δ ppm 8.56 (d, J=7.00 Hz, 2 H) 7.98 (d, J=6.38 Hz, 1 H) 7.81 (s, 1 H) 7.62 (br d, J=8.88 Hz, 1 H) 7.13 - 7.26 (m, 4 H) 6.77 - 6.90 (m, 1 H) 6.51 (br s, 1 H) 4.76 (br s, 2 H) 3.48 (br s, 2 H) 2.67 - 2.93 (m, 3 H) 1.15 (br s, 3 H) LC-MS: Rt = 2.357 min, (ESI) <i>m/z</i> = 418.2 [M+H] ⁺ ; C ₂₂ H ₂₀ FN ₇ O
253	1H NMR (400 MHz, DMSO-d ₆) δ = 9.35 - 9.22 (m, 1H), 8.99 - 8.81 (m, 1H), 8.22 - 8.10 (m, 1H), 8.01 - 7.84 (m, 1H), 7.73 - 7.66 (m, 1H), 7.58 (s, 1H), 7.50 (br dd, J = 1.2, 9.3 Hz, 1H), 7.17 (s, 1H), 7.01 (br s, 2H), 6.94 (br d, J = 10.9 Hz, 1H), 5.08 (s, 2H), 3.58 (s, 3H), 2.60 (s, 3H) LC-MS: Rt = 2.092 min, (ESI) <i>m/z</i> . [M+H] ⁺ 495.2; C ₂₅ H ₁₉ FN ₁₀ O	254	1H NMR (400 MHz, DMSO-d ₆) δ = 8.63 - 8.43 (m, 1H), 8.39 - 8.07 (m, 1H), 7.95 - 7.68 (m, 2H), 7.59 - 7.36 (m, 3H), 7.33 - 7.18 (m, 2H), 6.90 (t, J = 6.6 Hz, 1H), 6.49 - 6.15 (m, 1H), 4.64 (br s, 2H), 3.89 (br s, 2H), 2.95 - 2.73 (m, 3H) LC-MS: Rt = 2.178 min, (ESI) <i>m/z</i> . [M+H] ⁺ 454.1; C ₂₂ H ₁₈ F ₃ N ₇ O
255	1H NMR (400 MHz, DMSO-d ₆) δ = 8.96 (s, 1H), 8.53 (d, J = 6.8 Hz, 1H), 8.15 (d, J = 6.5 Hz, 1H), 7.87 (s, 1H), 7.50 (d, J = 9.0 Hz, 1H), 7.26 - 7.17 (m, 2H), 7.03 - 6.84 (m, 4H), 4.97 (s, 2H), 3.44 (s, 3H), 2.59 (s, 3H), 1.85 (s, 3H) LC-MS: Rt = 2.088 min, (ESI) <i>m/z</i> . [M+H] ⁺ 484.2; C ₂₅ H ₂₂ FN ₉ O	256	1H NMR (400 MHz, DMSO-d ₆) δ = 9.04 - 8.80 (m, 1H), 8.46 - 8.31 (m, 1H), 8.23 - 8.09 (m, 1H), 7.83 (s, 1H), 7.70 - 7.55 (m, 1H), 7.47 (br d, J = 9.1 Hz, 1H), 7.25 - 7.12 (m, 2H), 7.08 - 6.89 (m, 3H), 5.06 - 4.93 (m, 2H), 3.58 (br s, 9H), 2.60 (s, 3H), 2.39 (br s, 4H) LC-MS: Rt = 2.046 min, (ESI) <i>m/z</i> . [M+H] ⁺ 569.3; C ₂₉ H ₂₉ FN ₁₀ O ₂
257	1H NMR (400 MHz, DMSO-d ₆) δ = 9.04 - 8.78 (m, 1H), 8.62 - 8.40 (m, 1H), 8.26 - 8.07 (m, 1H), 7.91 - 7.74 (m, 1H), 7.71 - 7.56 (m, 1H), 7.51 (br d, J = 8.5 Hz, 1H), 7.29 - 7.12 (m, 2H), 7.11 - 6.78 (m, 4H), 5.14 - 4.93 (m, 2H), 3.85 - 3.53 (m, 3H), 2.60 (br s, 3H) LC-MS: Rt = 2.060 min, (ESI) <i>m/z</i> . [M+H] ⁺ 470.2; C ₂₄ H ₂₀ FN ₉ O	258	1H NMR (400 MHz, DMSO-d ₆) δ = 9.03 - 8.87 (m, 1H), 8.52 - 8.14 (m, 1H), 7.70 (br d, J = 5.5 Hz, 1H), 7.56 (s, 1H), 7.39 - 7.26 (m, 1H), 7.20 - 7.05 (m, 2H), 7.05 - 6.94 (m, 2H), 5.46 - 5.07 (m, 1H), 4.74 (s, 1H), 4.61 - 4.37 (m, 2H), 3.57 - 3.39 (m, 2H), 2.85 (br dd, J = 4.8, 19.3 Hz, 2H), 2.61 (br d, J = 2.3 Hz, 3H), 1.23 - 1.15 (m, 6H), 1.14 - 1.04 (m, 3H) LC-MS: Rt = 2.119 min, (ESI) <i>m/z</i> . [M+H] ⁺ 505.2; C ₂₆ H ₂₉ FN ₈ O ₂
259	1H NMR (400 MHz, DMSO-d ₆) δ = 9.29 (br s, 2H), 8.81 - 8.32 (m, 3H), 8.30	260	H NMR (400 MHz, DMSO-d ₆) Shift 9.15-8.91 (m, 1H), 8.90-8.72 (m, 1H),

	- 8.08 (m, 1H), 7.84 (br d, J = 4.5 Hz, 1H), 7.73 - 7.52 (m, 2H), 7.43 - 7.12 (m, 2H), 5.13 (br s, 2H), 3.64 (br s, 3H), 2.70 (s, 3H) LC-MS: Rt = 1.695 min, (ESI) <i>m/z</i> . [M+H] ⁺ 538.2; C ₂₅ H ₁₉ F ₄ N ₉ O		8.55-8.23 (m, 1H), 8.20 (d, J = 11.0 Hz, 1H), 7.97-7.74 (m, 2H), 7.66-7.58 (m, 1H), 7.56-7.50 (m, 1H), 7.23 (dd, J = 10.9, 13.2 Hz, 1H), 7.06 (br s, 2H), 4.93-4.51 (m, 2H), 3.94 (d, J = 3.9 Hz, 3H), 3.41 (br s, 2H), 2.67 (d, J = 8.4 Hz, 3H), 1.30-1.03 (m, 3H). LC-MS: Rt = 2.166 min, (ESI) <i>m/z</i> . [M+H] ⁺ 498.2; C ₂₆ H ₂₄ FN ₉ O
261	¹ H NMR (400 MHz, DMSO-d ₆) δ = 9.08 - 8.71 (m, 1H), 8.59 - 8.39 (m, 1H), 8.29 - 8.09 (m, 1H), 7.85 - 7.66 (m, 1H), 7.58 - 7.39 (m, 1H), 7.30 - 7.14 (m, 2H), 7.12 - 6.94 (m, 2H), 6.91 - 6.78 (m, 1H), 5.53 - 5.30 (m, 1H), 4.90 - 4.79 (m, 1H), 4.67 - 4.38 (m, 1H), 4.30 - 4.15 (m, 1H), 3.89 (br dd, J = 1.9, 3.7 Hz, 1H), 2.64 - 2.57 (m, 3H), 1.90 - 1.78 (m, 1H), 1.70 - 1.40 (m, 2H), 1.28 - 1.12 (m, 1H) LC-MS: Rt = 1.996 min, (ESI) <i>m/z</i> . [M+H] ⁺ 460.1; C ₂₄ H ₂₂ FN ₇ O ₂	262	¹ H NMR (400 MHz, DMSO-d ₆) δ = 9.07 - 8.85 (m, 1H), 8.48 - 8.14 (m, 1H), 8.12 - 7.95 (m, 1H), 7.80 - 7.59 (m, 1H), 7.44 (br d, J = 9.6 Hz, 1H), 7.24 (br d, J = 9.1 Hz, 1H), 7.16 (dt, J = 3.1, 10.7 Hz, 1H), 7.00 (br s, 2H), 4.80 - 4.44 (m, 2H), 3.57 - 3.41 (m, 2H), 3.18 (br d, J = 3.3 Hz, 4H), 3.09 - 2.90 (m, 4H), 2.61 (br s, 6H), 1.18 - 1.03 (m, 3H) LC-MS: Rt = 2.158 min, (ESI) <i>m/z</i> . [M+H] ⁺ 516.3; C ₂₇ H ₃₀ FN ₉ O
263	¹ H NMR (400 MHz, DMSO-d ₆) δ = 9.05 - 8.85 (m, 1H), 8.44 - 8.25 (m, 1H), 8.21 - 8.13 (m, 1H), 7.82 - 7.67 (m, 1H), 7.44 (d, J = 9.8 Hz, 1H), 7.16 (t, J = 11.3 Hz, 1H), 7.01 (br dd, J = 2.3, 9.8 Hz, 3H), 4.76 (s, 1H), 4.49 (s, 1H), 3.76 (d, J = 14.4 Hz, 3H), 3.51 (br d, J = 6.6 Hz, 1H), 3.30 (br s, 1H), 2.61 (d, J = 3.9 Hz, 3H), 1.19 - 1.03 (m, 3H) LC-MS: Rt = 2.228 min, (ESI) <i>m/z</i> . [M+H] ⁺ 448.2; C ₂₃ H ₂₂ FN ₇ O ₂	264	¹ H NMR (400 MHz, DMSO-d ₆) δ = 9.13 - 8.79 (m, 1H), 8.60 - 8.21 (m, 2H), 7.79 (br s, 1H), 7.59 - 7.16 (m, 2H), 7.15 - 6.92 (m, 3H), 6.85 (br t, J = 6.7 Hz, 1H), 5.17 (s, 2H), 4.11 - 3.84 (m, 3H), 2.60 (s, 3H) LC-MS: Rt = 2.170 min, (ESI) <i>m/z</i> . [M+H] ⁺ 471.2; C ₂₃ H ₁₉ FN ₁₀ O
265	¹ H NMR (400 MHz, DMSO-d ₆) δ = 9.07 - 8.82 (m, 1H), 8.52 - 8.46 (m, 1H), 8.36 (br d, J = 6.6 Hz, 1H), 8.26 - 8.17 (m, 1H), 8.14 - 8.05 (m, 2H), 7.26 - 7.15 (m, 2H), 7.00 (br d, J = 6.4 Hz, 1H), 4.91 - 4.50 (m, 2H), 3.54 (br d, J = 5.9 Hz, 2H), 2.61 (d, J = 6.3 Hz, 3H), 1.17 - 1.06 (m, 3H) LC-MS: Rt = 2.131 min, (ESI) <i>m/z</i> . [M+H] ⁺ 419.2; C ₂₁ H ₁₉ FN ₈ O	266	¹ H NMR (400 MHz, DMSO-d ₆) δ = 9.00 - 8.80 (m, 1H), 8.62 - 8.12 (m, 2H), 7.97 - 7.73 (m, 1H), 7.54 (br d, J = 9.0 Hz, 1H), 7.28 - 7.14 (m, 2H), 7.03 (br s, 2H), 6.93 - 6.82 (m, 1H), 4.92 - 4.57 (m, 2H), 3.81 - 3.62 (m, 2H), 2.93 - 2.84 (m, 2H), 2.61 (s, 3H) LC-MS: Rt = 1.308 min, (ESI) <i>m/z</i> . [M+H] ⁺ 443.2; C ₂₃ H ₁₉ FN ₈ O
267	¹ H NMR (400 MHz, DMSO-d ₆) δ = 9.06 - 8.85 (m, 1H), 8.81 - 8.66 (m, 1H), 8.41 - 8.16 (m, 1H), 7.93 - 7.75 (m, 1H), 7.67 - 7.55 (m, 1H), 7.37 - 7.28 (m, 1H), 7.16 (dd, J = 10.9, 14.9 Hz, 1H), 7.01 (br d, J = 1.1 Hz, 2H), 4.79 (s, 1H), 4.52 (s, 1H), 3.52 (br d, J = 6.1 Hz, 2H), 2.61 (d, J = 4.6 Hz, 3H), 1.20 - 1.03 (m, 3H) LC-MS: Rt = 2.244 min, (ESI) <i>m/z</i> . [M+H] ⁺ 436.2; C ₂₂ H ₁₉ F ₂ N ₇ O	268	¹ H NMR (400MHz, DMSO-d ₆) Shift = 9.19 (s, 1H), 8.16 (br s, 1H), 8.05 (s, 1H), 7.73 (d, J=9.5 Hz, 2H), 7.57 - 7.40 (m, 3H), 7.35 (s, 1H), 7.29 (br s, 2H), 7.31 - 7.09 (m, 1H), 5.09 (s, 2H), 3.66 (br s, 3H), 2.72 - 2.58 (m, 3H). LC-MS: Rt = 1.711 min, (ESI) <i>m/z</i> . [M+H] ⁺ 520.1; C ₂₅ H ₂₀ F ₃ N ₉ O
269	¹ H NMR (400 MHz, DMSO-d ₆) δ = 8.99 - 8.68 (m, 1H), 8.27 - 8.08 (m, 1H), 8.00 - 7.40 (m, 4H), 7.18 - 7.09 (m, 1H), 7.07 - 6.94 (m, 2H), 4.99 - 4.71 (m, 2H), 2.62 (s, 1H), 2.58 (s, 1H), 2.50 (br s, 3H), 0.95 (d, J = 6.5 Hz, 3H), 0.88 - 0.80 (m, 1H), 0.69 (d, J = 6.5 Hz, 3H) LC-	270	¹ H NMR (400 MHz, DMSO-d ₆) δ = 8.47 (br d, J = 5.0 Hz, 1H), 8.03 - 7.94 (m, 1H), 7.84 (br s, 1H), 7.77 (s, 1H), 7.48 (br d, J = 8.9 Hz, 1H), 7.33 (s, 1H), 7.28 - 7.19 (m, 1H), 6.98 (br s, 2H), 6.87 (t, J = 7.1 Hz, 1H), 4.77 - 4.28 (m, 2H), 3.63 - 3.34 (m, 2H), 2.83

	MS: Rt = 1.617 min, (ESI) m/z . $[M+H]^+$ 514.3; C ₂₅ H ₂₃ F ₄ N ₇ O		(br s, 3H), 2.32 (s, 3H), 1.22 - 1.11 (m, 3H) LC-MS: Rt = 2.057 min, (ESI) m/z . $[M+H]^+$ 414.2; C ₂₃ H ₂₃ N ₇ O
271	¹ H NMR (400 MHz, DMSO-d ₆) Shift 9.04 (s, 1H), 9.10-8.76 (m, 1H), 8.61-8.39 (m, 1H), 8.31-8.14 (m, 1H), 8.34-8.11 (m, 1H), 7.91-7.72 (m, 1H), 7.53-7.45 (m, 1H), 7.56-7.42 (m, 1H), 7.24-7.06 (m, 2H), 7.05-6.90 (m, 2H), 6.89-6.76 (m, 1H), 4.83-4.52 (m, 2H), 4.00-3.58 (m, 1H), 3.52-3.42 (m, 1H), 3.27-3.05 (m, 4H), 2.64-2.57 (m, 3H), 1.23-1.13 (m, 3H). LC-MS: Rt = 1.104 min, (ESI) m/z . $[M+H]^+$ 462.3; C ₂₄ H ₂₄ FN ₇ O ₂	272	¹ H NMR (400MHz, DMSO-d ₆) δ 9.06 - 8.86 (m, 2H), 8.56 - 8.50 (m, 1H), 8.48 - 8.18 (m, 1H), 7.89 - 7.73 (m, 1H), 7.26 - 7.11 (m, 1H), 7.10 - 6.95 (m, 3H), 4.87 - 4.54 (m, 2H), 3.62 - 3.34 (m, 2H), 2.62 (d, J=6.5 Hz, 3H), 1.21 - 1.06 (m, 3H) ; LC-MS: Rt = 1.889 min, (ESI) m/z . $[M+H]^+$ 419.1; C ₂₁ H ₁₉ FN ₈ O
273	¹ H NMR (400 MHz, DMSO-d ₆) δ = 9.05 - 8.75 (m, 1H), 8.53 (br d, J = 7.4 Hz, 1H), 8.16 (br d, J = 6.9 Hz, 1H), 7.82 - 7.69 (m, 1H), 7.53 (br d, J = 9.4 Hz, 1H), 7.26 - 7.14 (m, 2H), 7.04 (br d, J = 1.9 Hz, 2H), 6.88 (s, 1H), 4.83 (br s, 2H), 3.89 (br dd, J = 3.8, 8.3 Hz, 1H), 3.41 - 3.35 (m, 1H), 3.21 - 2.87 (m, 4H), 2.65 - 2.56 (m, 4H), 2.18 - 1.97 (m, 2H) LC-MS: Rt = 2.127 min, (ESI) m/z . $[M+H]^+$ 474.2; C ₂₅ H ₂₄ FN ₇ O ₂	274	¹ H NMR (400 MHz, DMSO-d ₆) δ = 9.04 - 8.85 (m, 1H), 8.52 - 8.18 (m, 1H), 7.81 - 7.59 (m, 1H), 7.54 - 7.41 (m, 1H), 7.34 - 7.14 (m, 2H), 7.04 (br s, 2H), 6.89 - 6.73 (m, 1H), 4.85 (s, 1H), 4.54 (s, 1H), 3.53 (br dd, J = 1.9, 14.5 Hz, 2H), 2.64 - 2.53 (m, 6H), 1.24 - 1.05 (m, 3H) LC-MS: Rt = 2.265 min, (ESI) m/z . $[M+H]^+$ 432.2; C ₂₃ H ₂₂ FN ₇ O
275	¹ H NMR (400 MHz, DMSO-d ₆) δ = 9.10 (s, 1H), 8.84 (s, 1H), 8.23 (s, 1H), 7.90 (br s, 1H), 7.71 (d, J = 9.5 Hz, 1H), 7.44 - 7.41 (m, 1H), 7.40 - 7.36 (m, 2H), 6.55 (br s, 2H), 4.93 (br s, 2H), 4.62 (br s, 1H), 3.54 (s, 2H), 2.64 (s, 3H), 1.19 (br s, 6H) LC-MS: Rt = 2.316 min, (ESI) m/z . $[M+H]^+$ 512.2; C ₂₅ H ₂₄ F ₃ N ₇ O ₂	276	¹ H NMR (400 MHz, DMSO-d ₆) δ = 9.04 - 8.87 (m, 1H), 8.60 - 8.46 (m, 1H), 8.45 - 8.17 (m, 1H), 7.94 - 7.79 (m, 1H), 7.57 - 7.49 (m, 1H), 7.30 - 7.11 (m, 2H), 7.02 (br s, 2H), 6.95 - 6.84 (m, 1H), 4.82 - 4.51 (m, 2H), 3.57 - 3.35 (m, 2H), 2.64 - 2.59 (m, 3H), 1.17 - 1.05 (m, 3H) LC-MS: Rt = 1.051 min, (ESI) m/z . $[M+H]^+$ 518.2; C ₂₂ H ₂₀ FN ₇ O
277	¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 8.75 - 8.99 (m, 1 H) 8.15 - 8.56 (m, 2 H) 7.74 (br s, 1 H) 7.50 (br d, J=9.06 Hz, 1 H) 7.09 - 7.26 (m, 2 H) 6.84 (br s, 1 H) 6.73 (br s, 2 H) 4.31 - 4.94 (m, 2 H) 3.37 (br s, 2 H) 2.63 (s, 3 H) 2.15 (br s, 1 H) 0.84 - 0.85 (m, 1 H) 0.61 - 1.06 (m, 5 H) LC-MS: Rt = 2.387 min, (ESI) m/z = 446.2 $[M+H]^+$; C ₂₄ H ₂₄ FN ₇ O	278	¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.73 - 12.43 (m, 1H), 8.02 (br d, J = 6.4 Hz, 1H), 7.90 - 7.82 (m, 1H), 7.78 (br s, 1H), 7.73 - 7.64 (m, 1H), 7.47 (br d, J = 8.5 Hz, 1H), 7.20 (d, J = 10.9 Hz, 1H), 7.17 (br s, 2H), 4.95 - 4.69 (m, 2H), 3.46 - 3.22 (m, 2H), 2.91 - 2.57 (m, 3H), 2.16 - 2.03 (m, 1H), 0.99 - 0.78 (m, 6H) LC-MS: Rt = 2.498 min, (ESI) m/z . $[M+H]^+$ 514.2; C ₂₅ H ₂₃ F ₄ N ₇ O
279	¹ H NMR (400MHz, DMSO-d ₆) Shift = 8.52 (br d, J=6.6 Hz, 1H), 8.46 - 8.11 (m, 1H), 7.95 (s, 1H), 7.66 - 7.46 (m, 3H), 7.40 - 7.12 (m, 4H), 6.90 (br t, J=6.6 Hz, 1H), 4.62 (br s, 2H), 3.45 (br d, J=6.4 Hz, 2H), 2.98 - 2.55 (m, 3H), 1.15 (br t, J=6.9 Hz, 3H). LC-MS: Rt = 1.454 min, (ESI) m/z . $[M+H]^+$ 400.2; C ₂₂ H ₂₁ N ₇ O	280	¹ H NMR (400 MHz, DMSO-d ₆) δ = 8.97 - 8.71 (m, 1H), 8.54 - 8.39 (m, 1H), 8.15 (br s, 1H), 7.79 (br s, 1H), 7.47 (br d, J = 9.1 Hz, 1H), 7.25 - 7.06 (m, 2H), 6.83 (br t, J = 6.4 Hz, 1H), 6.72 (br s, 2H), 4.80 - 4.52 (m, 2H), 4.26 - 3.82 (m, 2H), 3.13 (br s, 3H), 2.63 (s, 3H), 1.87 - 1.81 (m, 2H), 1.73 - 1.33 (m, 4H) LC-MS: Rt = 2.317 min, (ESI) m/z . $[M+H]^+$ 488.2; C ₂₆ H ₂₆ FN ₇ O ₂
281	¹ H NMR (400 MHz, DMSO-d ₆) δ = 9.09 - 8.94 (m, 1H), 8.72 (br dd, J = 2.3, 3.5	282	¹ H NMR (400 MHz, DMSO-d ₆) δ = 9.32 - 9.07 (m, 1H), 9.00 - 8.73 (m,

	Hz, 1H), 8.09 (d, $J = 6.4$ Hz, 1H), 7.83 - 7.60 (m, 2H), 7.45 - 7.31 (m, 1H), 7.11 (d, $J = 11.1$ Hz, 1H), 6.71 (br s, 2H), 4.80 (br s, 2H), 4.49 (d, $J = 2.1$ Hz, 1H), 3.60 (br s, 2H), 2.62 (s, 3H), 1.40 - 1.13 (m, 6H) LC-MS: Rt = 2.356 min, (ESI) m/z . $[M+H]^+$ 530.2; C ₂₅ H ₂₃ F ₄ N ₇ O ₂		1H), 8.15 (br s, 1H), 8.02 - 7.82 (m, 1H), 7.78 - 7.63 (m, 1H), 7.50 - 7.39 (m, 1H), 7.19 (d, $J = 10.8$ Hz, 1H), 7.09 - 6.93 (m, 2H), 5.40 - 5.26 (m, 1H), 4.98 - 4.55 (m, 2H), 4.29 - 4.12 (m, 1H), 4.00 - 3.82 (m, 1H), 2.63 (s, 3H), 1.90 - 1.79 (m, 1H), 1.69 - 1.52 (m, 2H), 1.28 - 1.11 (m, 1H) LC-MS: Rt = 2.344 min, (ESI) m/z . $[M+H]^+$ 527.1; C ₂₅ H ₂₁ F ₄ N ₇ O ₂
283	¹ H NMR (400 MHz, DMSO-d ₆) δ = 9.30 - 9.13 (m, 1H), 9.04 - 8.86 (m, 1H), 8.36 - 8.16 (m, 1H), 8.07 - 7.89 (m, 1H), 7.74 (t, $J = 8.8$ Hz, 1H), 7.51 - 7.43 (m, 1H), 7.17 (dd, $J = 10.9, 17.5$ Hz, 1H), 7.05 - 6.96 (m, 2H), 4.87 - 4.56 (m, 2H), 3.40 - 3.33 (m, 2H), 2.64 - 2.60 (m, 3H), 1.20 - 1.06 (m, 3H) LC-MS: Rt = 2.497 min, (ESI) m/z . $[M+H]^+$ 486.2; C ₂₃ H ₁₉ F ₄ N ₇ O	284	¹ H NMR (400 MHz, DMSO-d ₆) δ = 9.32 - 9.09 (m, 1H), 9.05 - 8.85 (m, 1H), 8.31 - 8.13 (m, 1H), 8.11 - 7.83 (m, 1H), 7.81 - 7.67 (m, 1H), 7.55 - 7.40 (m, 1H), 7.21 - 7.11 (m, 1H), 7.09 - 6.87 (m, 2H), 4.57 (s, 2H), 3.29 - 3.11 (m, 2H), 2.64 - 2.60 (m, 3H), 2.18 - 1.97 (m, 1H), 0.97 - 0.69 (m, 6H) LC-MS: Rt = 1.965 min, (ESI) m/z . $[M+H]^+$ 514.2; C ₂₅ H ₂₃ F ₄ N ₇ O
285	¹ H NMR (400MHz, DMSO-d ₆) Shift = 9.29 - 8.54 (m, 2H), 8.18 - 7.78 (m, 2H), 7.66 (br s, 1H), 7.38 (br d, $J = 7.9$ Hz, 1H), 7.13 (br s, 1H), 6.72 (br s, 2H), 4.95 - 4.39 (m, 2H), 4.22 - 3.82 (m, 1H), 3.52 (br s, 2H), 3.31 - 3.10 (m, 3H), 2.63 (s, 3H), 1.21 (br s, 3H). LC-MS: Rt = 2.517 min, (ESI) m/z . $[M+H]^+$ 530.2; C ₂₅ H ₂₃ F ₄ N ₇ O ₂	286	¹ H NMR (400 MHz, DMSO-d ₆) δ = 9.33 - 9.07 (m, 1H), 9.05 - 8.75 (m, 1H), 8.22 - 8.09 (m, 1H), 8.05 - 7.92 (m, 1H), 7.88 - 7.70 (m, 1H), 7.69 - 7.27 (m, 2H), 7.25 - 7.08 (m, 2H), 4.92 - 4.60 (m, 2H), 4.32 - 3.91 (m, 2H), 3.18 - 2.96 (m, 3H), 2.64 - 2.58 (m, 3H), 2.14 - 1.69 (m, 3H), 1.51 - 1.14 (m, 1H) LC-MS: Rt = 1.843 min, (ESI) m/z . $[M+H]^+$ 542.2; C ₂₆ H ₂₃ F ₄ N ₇ O ₂
287	¹ H NMR (400 MHz, DMSO-d ₆) δ = 9.15 (s, 1H), 8.82 (s, 1H), 8.19 (d, $J = 1.5$ Hz, 1H), 8.01 (s, 1H), 7.73 (d, $J = 9.3$ Hz, 1H), 7.45 (dd, $J = 1.8, 9.5$ Hz, 1H), 7.37 - 7.24 (m, 2H), 6.79 (br s, 2H), 4.70 (s, 2H), 3.71 (s, 2H), 3.32 (s, 3H), 2.58 (s, 3H), 1.45 (s, 6H) LC-MS: Rt = 2.611 min, (ESI) m/z . $[M+H]^+$ 526.2; C ₂₆ H ₂₆ F ₃ N ₇ O ₂	288	¹ H NMR (400 MHz, DMSO-d ₆) δ = 9.22 (br s, 1H), 9.01 - 8.75 (m, 1H), 8.22 (br d, $J = 2.0$ Hz, 1H), 8.00 (br s, 1H), 7.73 (d, $J = 9.4$ Hz, 1H), 7.46 (dd, $J = 1.6, 9.5$ Hz, 1H), 7.42 - 7.27 (m, 2H), 6.89 (br s, 2H), 4.85 (br d, $J = 3.9$ Hz, 2H), 4.12 (br dd, $J = 1.4, 7.7$ Hz, 2H), 3.06 (s, 3H), 2.62 (s, 3H), 1.98 - 1.66 (m, 3H), 1.38 - 1.08 (m, 1H) LC-MS: Rt = 2.518 min, (ESI) m/z . $[M+H]^+$ 524.2; C ₂₆ H ₂₄ F ₃ N ₇ O ₂
289	¹ H NMR (400 MHz, DMSO-d ₆) Shift 9.23-9.10 (m, 1H), 8.97 (s, 1H), 8.46-8.14 (m, 1H), 8.05-7.84 (m, 1H), 7.75 (d, $J = 9.5$ Hz, 1H), 7.48 (dd, $J = 1.8, 9.5$ Hz, 1H), 7.44 (br s, 2H), 6.90 (br s, 2H), 5.15 - 4.81 (m, 3H), 4.77 (br s, 2H), 4.60 (br t, $J = 6.8$ Hz, 2H), 2.63 (s, 3H). LC-MS: Rt = 2.285 min, (ESI) m/z . $[M+H]^+$ 496.2; C ₂₄ H ₂₀ F ₃ N ₇ O ₂	290	¹ H NMR (400 MHz, DMSO-d ₆) δ = 9.28 - 8.80 (m, 2H), 8.39 - 7.94 (m, 2H), 7.73 (br d, $J = 9.3$ Hz, 1H), 7.54 - 7.26 (m, 3H), 6.85 (br s, 2H), 4.87 - 4.57 (m, 2H), 4.16 (br d, $J = 1.4$ Hz, 1H), 3.50 (br s, 1H), 3.31 - 3.02 (m, 4H), 2.67 - 2.56 (m, 3H), 1.16 (br s, 3H) LC-MS: Rt = 2.461 min, (ESI) m/z . $[M+H]^+$ 512.2; C ₂₅ H ₂₄ F ₃ N ₇ O ₂
291	¹ H NMR (400 MHz, DMSO-d ₆) δ = 9.13 - 8.80 (m, 1H), 8.65 (br d, $J = 6.6$ Hz, 1H), 8.41 - 8.12 (m, 1H), 7.65 (d, $J = 8.9$ Hz, 1H), 7.39 (br s, 2H), 7.24 - 7.17 (m, 1H), 6.92 - 6.78 (m, 3H), 6.59 (br s, 1H), 4.98 - 4.52 (m, 2H), 3.56 -	292	¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 9.18 (br s, 1 H) 8.07 - 8.25 (m, 1 H) 7.81 - 8.06 (m, 2 H) 7.74 (br d, $J = 8.13$ Hz, 1 H) 7.28 - 7.65 (m, 3 H) 6.97 (br s, 2 H) 4.50 - 4.99 (m, 2 H) 3.30 (br s, 2 H) 2.50 (br s, 3 H) 1.91 - 2.19 (m, 1

	3.40 (m, 2H), 2.62 (s, 3H), 1.13 (br s, 3H) LC-MS: Rt = 2.283 min , (ESI) m/z = 400.2 [M+H] ⁺ ; C ₂₂ H ₂₁ N ₇ O		H) 0.64 - 1.00 (m, 1 H) 0.64 - 1.00 (m, 5 H) LC-MS: Rt = 2.838 min , (ESI) m/z = 496.2 [M+H] ⁺ ; C ₂₅ H ₂₄ F ₃ N ₇ O
293	¹ H NMR (400 MHz, DMSO-d ₆) Shift 9.24 (br d, J = 17.9 Hz, 2H), 9.09-8.57 (m, 2H), 8.35 (br s, 1H), 8.08 (br d, J = 10.5 Hz, 1H), 7.79 (br d, J = 9.4 Hz, 1H), 7.62 (br s, 1H), 7.55 (br d, J = 7.4 Hz, 1H), 7.51-7.30 (m, 2H), 7.18 (br s, 1H), 5.09 (br s, 2H), 3.62 (br s, 3H), 2.71-2.68 (m, 3H). LC-MS: Rt = 1.707 min, (ESI) m/z . [M+H] ⁺ 520.1; C ₂₅ H ₂₀ F ₃ N ₉ O	294	¹ H NMR (400 MHz, DMSO-d ₆) δ = 9.15 (s, 1H), 8.93 (s, 1H), 8.10 (br d, J = 1.6 Hz, 1H), 7.99 (s, 1H), 7.78 (d, J = 9.5 Hz, 1H), 7.47 (dd, J = 1.6, 9.5 Hz, 1H), 7.40 (s, 1H), 7.29 - 7.14 (m, 2H), 6.98 (s, 1H), 6.84 (br s, 2H), 6.27 - 6.05 (m, 1H), 3.56 (s, 3H), 2.61 (s, 3H), 1.51 (d, J = 7.0 Hz, 3H) LC-MS: Rt = 2.371 min, (ESI) m/z . [M+H] ⁺ 534.2; C ₂₆ H ₂₂ F ₃ N ₉ O
295	¹ H NMR (400 MHz, DMSO-d ₆) δ = 8.65 (d, J = 6.9 Hz, 1H), 8.33 - 8.04 (m, 1H), 7.93 (br s, 1H), 7.66 (d, J = 8.8 Hz, 1H), 7.57 - 7.40 (m, 2H), 7.29 - 7.16 (m, 1H), 7.09 - 6.78 (m, 3H), 6.57 (s, 1H), 4.91 - 4.60 (m, 2H), 3.61 - 3.33 (m, 2H), 2.53 - 2.51 (m, 3H), 1.29 (d, J = 12.2 Hz, 1H), 1.14 (br t, J = 6.3 Hz, 3H) LC-MS: Rt = 2.468 min , (ESI) m/z = 400.1 [M+H] ⁺ ; C ₂₂ H ₂₁ N ₇ O	296	¹ H NMR (400 MHz, DMSO-d ₆) δ = 9.22 (br s, 1H), 8.95 (br s, 1H), 8.21 (br d, J = 5.0 Hz, 1H), 8.05 (s, 1H), 7.73 (d, J = 9.4 Hz, 1H), 7.53 - 7.31 (m, 3H), 6.87 (br s, 2H), 4.71 (br s, 2H), 4.19 - 4.06 (m, 1H), 4.04 - 3.84 (m, 1H), 3.11 (s, 3H), 2.62 (s, 3H), 2.00 - 1.72 (m, 3H), 1.68 - 1.22 (m, 3H) LC-MS: Rt = 2.581 min, (ESI) m/z . [M+H] ⁺ 538.2; C ₂₇ H ₂₆ F ₃ N ₇ O ₂
297	¹ H NMR (400 MHz, DMSO-d ₆) Shift 8.99 (br s, 1H), 8.61-8.42 (m, 2H), 7.88 (br s, 1H), 8.00-7.79 (m, 1H), 7.61-7.48 (m, 2H), 7.39 (br d, J = 7.9 Hz, 1H), 7.25 (br t, J = 7.7 Hz, 1H), 6.89 (dt, J = 0.9, 6.8 Hz, 1H), 6.85 (br s, 2H), 4.62 (br s, 2H), 3.30-3.18 (m, 2H), 2.63 (s, 3H), 2.14-1.93 (m, 1H), 0.99-0.61 (m, 6H). LC-MS: Rt = 2.316 min, (ESI) m/z . [M+H] ⁺ 428.3; C ₂₄ H ₂₅ N ₇ O	298	¹ H NMR (400 MHz, DMSO-d ₆) δ = 9.16 (br s, 1H), 9.07 (s, 1H), 8.36 (br s, 1H), 7.97 (br s, 1H), 7.77 (d, J = 9.5 Hz, 1H), 7.59 - 7.39 (m, 3H), 6.85 (br s, 2H), 5.24 (br d, J = 4.4 Hz, 1H), 3.26 (dd, J = 7.2, 13.6 Hz, 1H), 2.91 - 2.75 (m, 1H), 2.63 (s, 3H), 2.07 - 1.87 (m, 1H), 1.64 (br s, 3H), 1.01 - 0.55 (m, 6H) LC-MS: Rt = 2.726 min , (ESI) m/z = 510.2 [M+H] ⁺ ; C ₂₆ H ₂₆ F ₃ N ₇ O
299	¹ H NMR (400 MHz, DMSO-d ₆) Shift 9.18 (br s, 1H), 9.13-9.03 (m, 1H), 8.47 (br s, 1H), 8.21-8.11 (m, 1H), 7.98 (br s, 1H), 7.77 (br d, J = 9.4 Hz, 1H), 7.56-7.42 (m, 4H), 4.85-4.64 (m, 3H), 3.27-3.15 (m, 2H), 2.65 (s, 3H), 2.15-2.02 (m, 1H), 0.93 (br s, 4H), 0.70 (br s, 2H). LC-MS: Rt = 2.642 min, (ESI) m/z . [M+H] ⁺ 496.3; C ₂₅ H ₂₄ F ₃ N ₇ O	300	¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 9.02 (br s, 1 H) 8.39 - 8.53 (m, 2 H) 7.91 (br s, 1 H) 7.49 - 7.62 (m, 2 H) 7.41 (d, J =8.25 Hz, 1 H) 7.21 - 7.28 (m, 1 H) 6.74 - 7.01 (m, 3 H) 5.18 (br s, 1 H) 3.02 - 3.28 (m, 2 H) 2.62 (s, 3 H) 1.61 (br s, 3 H) 0.84 - 1.20 (m, 3 H) LC-MS: Rt = 2.178 min , (ESI) m/z = 414.2 [M+H] ⁺ ; C ₂₃ H ₂₃ N ₇ O
301	¹ H NMR (400 MHz, DMSO-d ₆) δ 9.39 (br s, 1H), 9.16 (s, 1H), 8.24-8.43 (m, 1H), 7.78-7.99 (m, 2H), 7.55 (s, 2H), 7.31 (br s, 1H), 7.10 (br d, J =11.29 Hz, 1H), 5.08-5.39 (m, 2H), 3.61 (s, 3H), 2.85 (br s, 3H). LC-MS: (ESI) m/z =557.3 [M+1] ⁺ , RT= 0.749 min	302	¹ H NMR (400 MHz, DMSO-d ₆) 9.24 (s, 1H), 8.09 (s, 1H), 7.99 (br s, 1H), 7.80 (s, 1H), 7.72 (br d, J =9.38 Hz, 1H), 7.33-7.50 (m, 6H), 5.03-5.19 (m, 2H), 3.55 (s, 3H), 2.84 (s, 3H) ¹⁹ F NMR (376 MHz, DMSO-d ₆) -60.48 (s, 1F), -174.29 (br s, 1F) LC-MS: (ESI) m/z =538.1 [M+1] ⁺ ; RT=2.897 min
303	¹ H NMR (400 MHz, DMSO-d ₆) Shift 8.93 (br s, 1H), 8.00-8.15 (m, 1H), 7.92 (br d, J =4.88 Hz, 1H), 7.81 (s, 1H), 7.65 (d, J =9.38 Hz, 1H), 7.54 (s, 2H), 7.37 (br	304	¹ H NMR (400 MHz, DMSO-d ₆) δ 9.26 - 9.11 (m, 1H), 8.81 (d, J = 4.9 Hz, 2H), 8.49 (br d, J = 1.1 Hz, 1H), 8.13 (br d, J = 5.1 Hz, 1H), 7.74 - 7.57 (m, 3H),

d, J=9.51 Hz, 1H), 6.90-7.32 (m, 3H), 4.94-5.30 (m, 2H), 3.57 (s, 3H), 2.86 (br s, 3H), 2.08 (s, 1H) 19F NMR (376 MHz, DMSO-d6) Shift - 109.29 (br s, 1F), -118.19 (br s, 1F), -173.53 (br s, 1F) LC-MS: (ESI) m/z= 538.3 [M+1] ⁺ , RT=0.723 min	7.42 (t, J= 4.9 Hz, 1H), 6.73 (br s, 2H), 5.50 - 5.09 (m, 4H), 5.00 (br s, 2H), 4.96 - 4.87 (m, 1H), 1.68 (br d, J= 7.0 Hz, 3H); LC-MS, [MH] ⁺ 484.2
--	---

生物测试例1 PRMT5体外抑制活性实验

实验材料

PRMT5(Active Motif , 目录号 31921) , [3H]-SAM(PerkinElmer , 目录号 NET155V001MC), SAM(Sigma, 目录号A7007), MTA (Sigma, 目录号D5011), SAH (Sigma, 目录号A9384), 384孔板 (Perkin Elmer, 目录号6007299), Echo 550(生产厂家: Labcyte, 型号: Echo 550), 384-well Flashplate (生产厂家: Perkin Elmer, 型号: SMP410A001PK)

实验方法

- 10
1. 酶反应过程
- (1)配置1x assay buffer(modified Tris Buffer)。
- (2)稀释化合物: 化合物溶解在100% DMSO中, 使用Echo 550将化合物溶液加入384孔板中。
- (3)配置酶溶液: 将PRMT5加入1x assay buffer配置酶溶液1; 将PRMT5和 MTA加入1x assay buffer配置酶溶液2。
- 15
- (4)配置底物溶液: 将肽段和[3H]-SAM加入1x assay buffer。
- (5)将15 μL酶溶液加入384孔板, 阴性对照孔加入15 μL 1x assay buffer, 室温孵育30分钟。
- (6)每孔加入15 μL底物溶液, 室温孵育90分钟。
- 20
- (7)配置终止反应液: 将预冷的SAM加入1x assay buffer。
- (8)每孔加入10μL终止反应液终止反应。
- (9)将25 μL/孔的混合溶液转移至Flashplate, 室温孵育1小时。
- (10)用dH2O + 0.1% Tween-20溶液清洗Flashplate三次。
- (11)用Microbeta读取放射值。.
- 25
2. 数据分析
- (1)根据公式1将原始数据换算成% inhibition:
- 公式1: % inhibition = (Max-Signal)/ (Max-Min) *100
- (2)将% inhibition数据带入XL-Fit公式2, 获得IC50值:
- 公式2: Y=Bottom + (Top-Bottom)/(1+(IC50/X)*HillSlope)
- 30
- 其中, Y是% inhibition, X是化合物浓度。

经实验方法测得部分化合物生物活性, 见表3

表3

实施例编号.	酶活抑制率PRMT5 MTA (2.0 um) IC50(nm)
1	5.1
2	3.0

4	1.7
127	3.7
132	4.4
146	2.5
147	2.9
148	2.6

生物测试例2 HCT116、HCT116-MTAP-KO细胞体外抑制增殖实验

实验材料

HCT116细胞系购自中国科学院细胞库，利用CRISPR/Cas9技术敲除MTAP基因，

5 获得HCT116-MTAP-KO细胞株。

McCoy'5A培养基(Gibco, 目录号16600082), 胎牛血清(Gibco, 目录号 10099141C), 盘尼西林-链霉素双抗(Gibco, 目录号 15140122), 胰酶(Gibco, 目录号25200056), CellTiter-Glo检测试剂盒(Promega, 目录号G7572), 384 孔透明平底黑壁细胞培养板(Corning, 目录号3764), 超微量加样仪(Tecan, 目录号 D300e), 多功能酶标仪(Biotek,

10 目录号SynergyHTX)

实验方法

1. 细胞培养: HCT116和HCT116-MTAP-KO细胞培养条件为McCoy'5A培养基+10%胎牛血清+1%盘尼西林-链霉素双抗; 保证其始终处于对数生长期, 细胞活率大于95%。
- 15 2. 化合物浓度梯度配制: 待测化合物通过超微量加样仪加入384孔板中, 从30 μM(HCT116细胞)或3 μM(HCT116-MTAP-KO细胞)开始, 用DMSO进行3倍稀释, 共9个浓度, 设置三复孔。
3. 化合物处理细胞: 将胰酶消化的HCT116或HCT116-MTAP-KO细胞悬液加入点好待测化合物的384 孔板中, 每孔40 μL, 即每孔含100个细胞, DMSO终浓度为0.4%。
- 20 将细胞培养板置于37摄氏度, 5%二氧化碳培养箱中培养6天。
4. 检测: 向细胞培养板中加入每孔20 μL的CellTiter-Glo试剂, 室温振荡孵育30分钟。使用多功能酶标仪检测578 nm的发光信号。
5. 数据分析:
- GraphPad Prism 8.0软件使用四参数抑制剂-反应的模型对数据进行拟合, 得到测
- 25 试化合物的IC₅₀值(半数抑制浓度)。

经实验方法测得部分化合物生物活性, “A”表示 IC₅₀(nm)<100, “B”表示 100<IC₅₀(nm)<1000, “C”表示 1000<IC₅₀(nm)<10000, 见表4, 其中, 第一列为细胞增殖抑制率HCT116 MTAP WT IC₅₀(nm), 第二列为细胞增殖抑制率HCT116-MTAP null

30 IC₅₀(nm):

表4

	细胞增殖抑制率 HCT116 MTAP WT IC ₅₀ (nm)	细胞增殖抑制率 HCT116- MTAP null IC ₅₀ (nm)		细胞增殖抑制率HCT116 MTAP WT IC ₅₀ (nm)	细胞增殖抑制率 HCT116- MTAP null IC ₅₀ (nm)
--	---	--	--	---	--

1	C	A	2	C	A
3	C	A	4	C	A
5	C	A	6	C	A
7	C	A	8	C	A
9	C	B	10	C	A
11	C	A	12	B	A
13	B	A	14	C	A
15	C	B	16	C	B
19	B	A	18	C	A
23	C	A	20	B	A
25	C	B	22	C	B
27	C	A	24	C	A
29	C	B	26	C	A
31	C	A	28	C	A
33	C	B	30	C	A
35	C	A	32	C	A
37	C	A	34	A	A
39	C	A	36	B	A
41	C	A	38	C	A
43	C	A	40	C	A
45	C	A	42	C	A
47	C	A	44	C	A
49	C	A	50	C	B
51	C	B	52	C	A
53	C	A	54	C	B
55	C	A	56	C	B
57	C	B	58	B	A
59	C	A	60	C	A
61	C	A	62	C	A
63	C	A	64	C	B
65	C	B	66	C	B
67	C	B	68	C	A
69	C	B	74	C	B
71	C	A	78	C	A
73	C	A	80	C	A
75	C	A	82	C	A
81	C	A	84	C	A
83	B	A	86	C	A
85	C	A	88	C	A
87	C	A	90	B	A
89	C	A	92	C	A
91	C	A	94	C	B
93	C	A	96	C	A
95	C	A	98	C	A
97	C	A	100	C	A
99	C	A	102	C	A
101	C	A	104	B	A
103	C	B	106	C	A
105	C	A	108	C	A
107	C	A	110	C	B

109	C	A	112	B	A
111	A	A	116	C	A
113	C	B	118	C	B
115	B	A	120	C	A
117	C	B	122	C	A
119	C	A	124	C	A
121	C	B	126	C	A
123	B	A	128	B	B
125	C	A	130	C	A
127	C	A	132	C	A
129	C	A	134	C	A
131	C	B	136	C	B
133	B	A	138	C	B
135	C	B	140	C	B
137	C	B	142	C	B
139	C	A	144	C	B
141	C	B	146	C	B
143	C	A	150	C	B
147	C	B	154	C	B
151	C	B	156	C	B
153	C	B	158	C	B
155	C	B	160	C	B
157	C	B	162	C	B
159	C	B	166	B	A
163	C	B	168	C	B
167	C	B	170	B	A
169	B	A	172	B	A
171	C	B	174	A	B
173	C	B	176	C	B
175	C	B	178	C	B
177	C	B	180	C	B
179	C	A	182	B	A
181	C	B	184	C	B
183	C	A	188	C	A
185	C	A	190	C	B
189	C	A	192	C	B
195	C	B	194	C	A
199	C	B	210	C	B
203	C	A	212	C	B
205	C	A	214	C	B
207	C	A	216	C	B
209	C	A	218	C	A
211	C	B	222	C	A
213	C	B	224	C	B
215	C	A	226	C	B
217	C	B	228	C	B
219	C	B	230	C	B
221	C	A	232	C	B
223	C	B	234	C	A
225	C	A	236	C	A

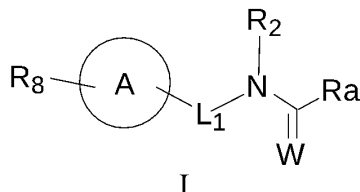
227	C	A	238	C	B
229	C	A	240	C	A
231	C	B	242	B	A
233	C	A	244	C	A
235	A	A	246	C	A
237	C	B	250	C	A
239	C	A	252	C	B
241	B	A	254	C	B
243	C	B	258	C	B
245	C	A	262	C	A
247	C	B	264	C	B
249	C	B	268	C	B
253	C	B	272	C	B
255	C	B	274	C	B
257	C	B	276	C	B
259	C	A	278	C	A
261	C	B	280	C	B
263	C	B	282	C	A
267	C	A	284	B	A
269	C	B	286	C	A
271	C	A	288	C	A
273	C	A	290	C	A
277	C	A	292	C	B
279	C	B	294	C	A
283	C	A	296	C	B
285	B	A	298	C	B
293	C	B	300	C	A
297	C	A	302	B	A
299	C	A	304	B	A
303	B	A			

在本发明提及的所有文献都在本申请中引用作为参考，就如同每一篇文献被单独引用作为参考那样。此外应理解，在阅读了本发明的上述讲授内容之后，本领域技术人员可以对本发明作各种改动或修改，这些等价形式同样落于本申请所附权利要求书所限定的范围。

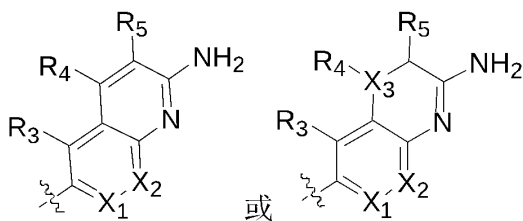
5

权 利 要 求 书

1、一种如下式I所示的化合物，或其药学上可接受的立体异构体、盐或氘代产物：



其中，



Ra选自下组：

W为O或S；

X₁、X₂各自独立地选自下组：CR、N；X₃为N；

10 所述的L₁选自下组：化学键、-O-、-CHR-、-C(R)R-；

A环选自下组：取代或未取代的8-12元的稠合二环杂环基(包括碳环或杂环，优选为五并六环)、取代或未取代的7-10元的稠合二环杂芳基(优选为五并六环)；

R₈选自下组：H、氘、卤素、氰基、氨基、硝基、羟基、巯基、醛基、羧基、C₂-C₆炔基、SF₅、取代或未取代或卤代的C₁-C₆烷基、未取代或卤代的C₁-C₆烷氧基、或R₈

15 为 ；

所述的L₃选自下组：化学键、-O-、-CHR-、-C(R)R-、羰基、S、-NH-；

B环选自下组：取代或未取代的苯环、取代或未取代的5-6元的杂芳环、取代或未取代的C₃-C₆碳环(包括饱和或部分不饱和的情况)、取代或未取代的3-7元的杂环(包括饱和或部分不饱和的情况)；

20 R₂选自下组：R₇、-L₂R₇；其中，所述的L₂选自下组：-O-、-CHR-、-C(R)R-、羰基；

其中R₇选自下组：氢或无、取代或未取代的C₁-C₆烷基、取代或未取代的C₆₋₁₀的芳环、取代或未取代的5-12元(优选为5-6元或8-10元)的杂芳环、取代或未取代的C₃-C₁₀碳环(包括饱和或部分不饱和的情况，包括单环、稠环、螺环或桥环)、取代或未取代的3-10元的杂环(包括饱和或部分不饱和的情况，包括单环、稠环、螺环或桥环)；

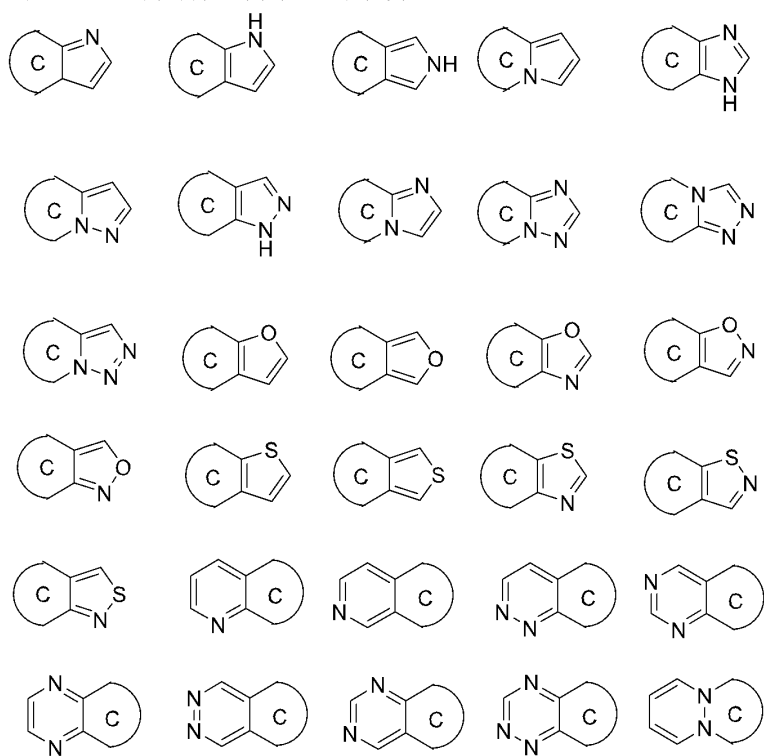
25 R₃选自下组：H、氘、卤素、氰基、取代或未取代的C₁-C₆烷基；

R₄和R₅各自独立地选自下组：H、卤素、氰基、取代或未取代的C₁-C₆烷基、取代或未取代的C₁-C₆烷氧基、取代或未取代的C₃-C₆碳环(包括饱和或部分不饱和的情况)、取代或未取代的3-6元的杂环；或R₄和R₅与相连的环原子共同形成5-12元饱和或不饱和环，且所述的环可以是取代或未取代的；

30 R为H、氘、卤素、取代或未取代的C₁-C₄烷基，取代或未取代的C₁-C₄烷氧基、取代或未取代C₃-C₆环烷基；

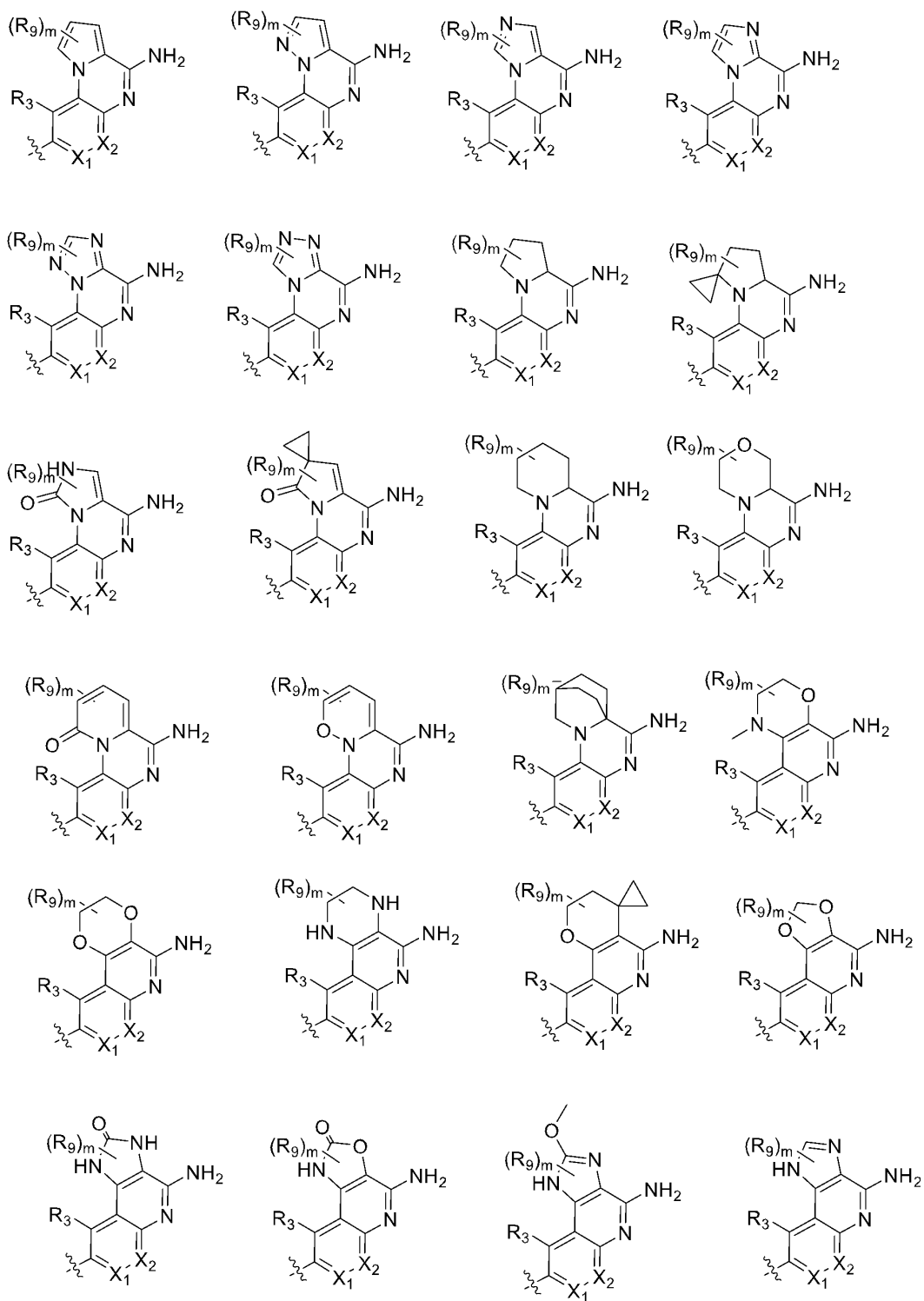
- 除非特别说明,上述各式中,所述的取代指对应基团上的氢原子被一个或多个选自下组的取代基所取代:氘、氚、卤素、羟基、羧基、巯基、苄基、C₁-C₁₂烷氧基羰基、C₁-C₆醛基、氨基、C₁-C₆酰胺基、硝基、氰基、未取代或卤代的C₁-C₆烷基、未取代或卤代的C₃-C₈环烷基、C₂-C₁₀烯基、C₁-C₆烷氧基、C₁-C₆烷基-胺基、C₆-C₁₀芳基、
- 5 五元或六元杂芳基、五元或六元非芳香性杂环基、-O-(C₆-C₁₀芳基)、-O-(五元或六元杂芳基)、C₁-C₁₂烷氨基羰基、未取代或卤代的C₂-C₁₀酰基、磺酰基(-SO₂-OH)、磷酰基(-PO₃-OH)、未取代或卤代的C₁-C₄烷基-S(O)₂-、未取代或卤代C₁-C₄烷基-SO-、-SF₅。

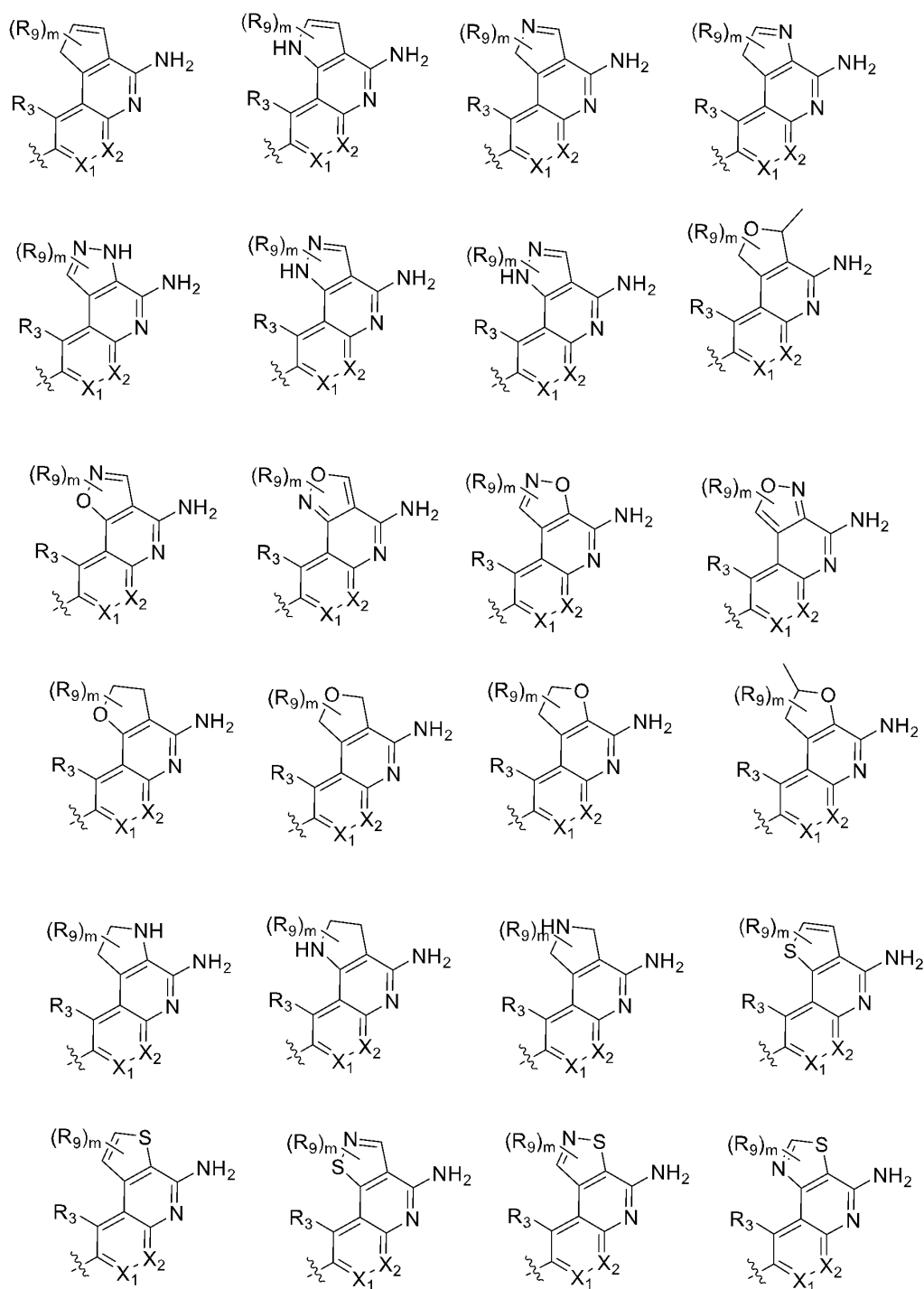
2、如权利要求1所述的化合物,或其药学上可接受的立体异构体、盐或氘代产物,其特征在于,A环具有选自下组的结构:



10

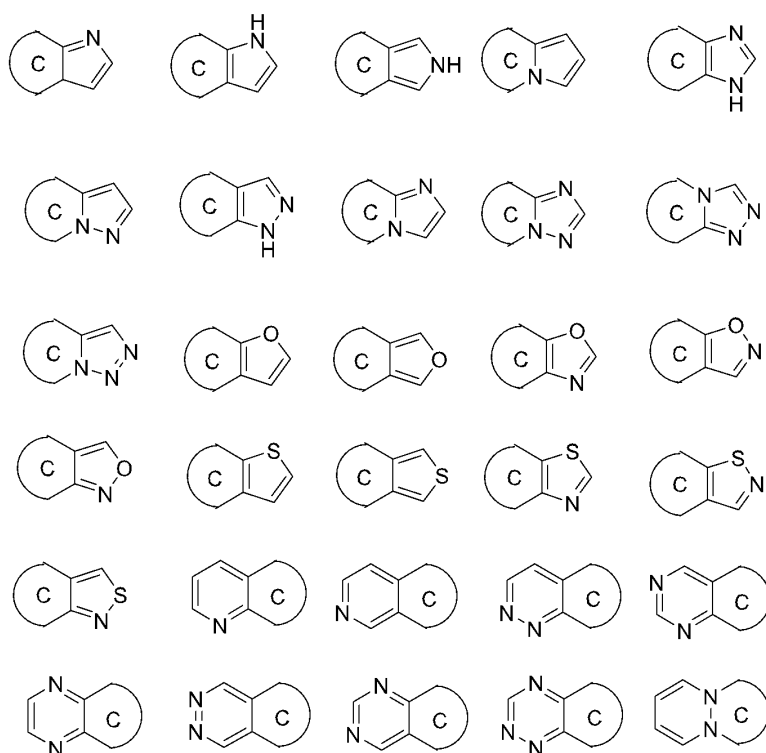
3、如权利要求1所述的化合物,或其药学上可接受的盐或氘代产物,其特征在于,Ra选自下组:





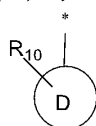
其中, 所述的 R_9 选自下组: 氕、氘、卤素、羟基、羧基、未取代或卤代的 C_1 - C_6 烷基、未取代或卤代的 C_1 - C_6 烷氧基、未取代或取代的 C_1 - C_6 烷基-OH、-NH(未取代或卤代的 C_1 - C_6 烷基)、-N(未取代或卤代的 C_1 - C_6 烷基)₂; m选自0、1、2或3。

- 5 4、如权利要求1所述的化合物, 或其药学上可接受的盐或氘代产物, 其特征在于, 所述的 L_1 为- CH_2 -、- $CH(CH_3)$ -; A环选自下组:



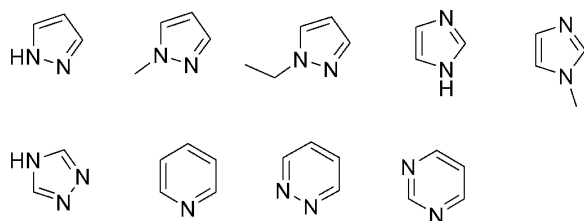
其中，C环选自下组：取代或未取代的苯环、取代或未取代的5-6元的杂芳环、取代或未取代的C₃-C₆碳环(包括饱和或部分不饱和的情况)、取代或未取代的3-6元的杂环(包括饱和或部分不饱和的情况)。

- 5、如权利要求1所述的化合物，或其药学上可接受的立体异构体、盐或氘代产物，其特征在于，所述的R₂为邻位取代的5元或6元杂芳环，如下式：



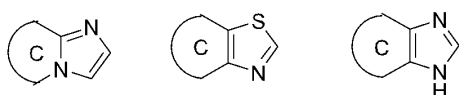
其中，R₁₀为位于连接位点邻位的取代基，其选自下组：氢、氘、卤素、未取代或卤代的C₁-C₃烷基，未取代或卤代的C₁-C₃烷氧基；

- 10 较佳地，所述的D环选自下组：取代或未取代的苯环、取代或未取代的5-6元的杂芳环，更佳地，D环选自下组：



且A环选自下组：取代或未取代的8-12元的稠合二环杂环基(包括碳环或杂环，优选为五并六环)、取代或未取代的7-10元的稠合二环杂芳基(优选为五并六环)；较佳地，A环选自下组：

15



其中，C环选自下组：取代或未取代的苯环、取代或未取代的5-6元的杂芳环；所述的 R_8 为 CF_3 。

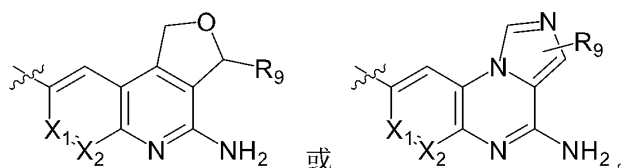
- 6、如权利要求1所述的化合物，或其药学上可接受的立体异构体、盐或氘代产物，
5 其特征在于，所述的 R_2 选自下组： R_7 、 $-L_2R_7$ ；其中，所述的 L_2 选自下组： $-O-$ 、 $-CHR-$ 、羰基、 S 、 $-NH-$ ；其中 R_7 选自下组：取代或未取代的 C_1 - C_6 烷基、取代或未取代的 C_6 - 10 的芳环、取代或未取代的5-12元的杂芳环。

- 7、如权利要求1所述的化合物，或其药学上可接受的立体异构体、盐或氘代产物，
10 其特征在于，所述的 R_7 选自下组：取代或未取代的 C_1 - C_6 烷基、取代或未取代的苯环、取代或未取代的5-7元的杂芳环。

8、如权利要求1所述的化合物，或其药学上可接受的立体异构体、盐或氘代产物，
其特征在于， R_2 选自下组： R_7 、 $-(CHR)R_7$ ；其中 R_7 选自下组：取代或未取代的 C_6 - 10 的芳环、取代或未取代的5-12元的杂芳环。

- 9、如权利要求1所述的化合物，或其药学上可接受的立体异构体、盐或氘代产物，
15 其特征在于，所述的 R_2 为取代或未取代的5-7元杂芳环；且所述的A环选自下组：取代或未取代的7-10元的稠合二环杂芳基；所述的 R_8 为 CF_3 。

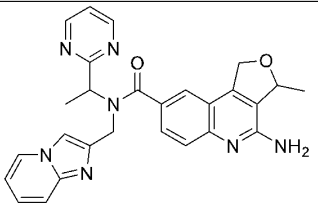
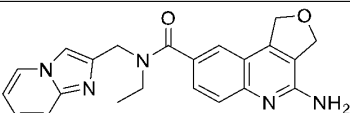
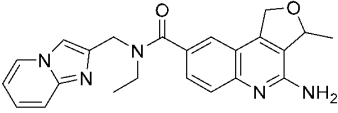
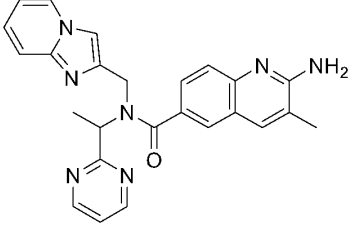
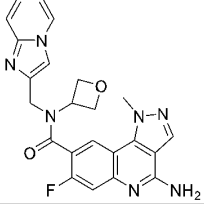
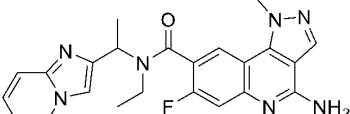
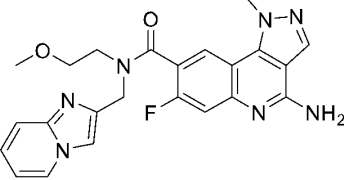
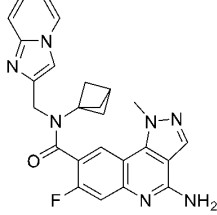
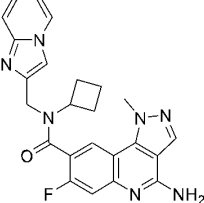
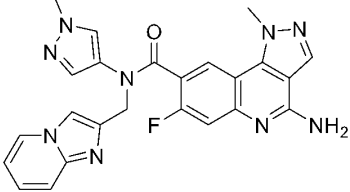
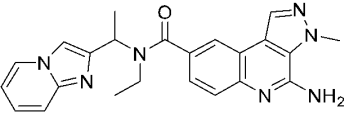
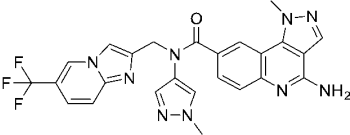
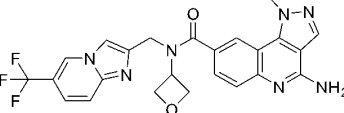
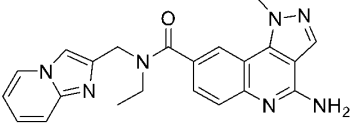
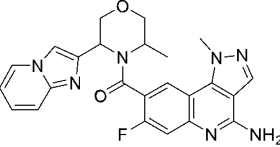
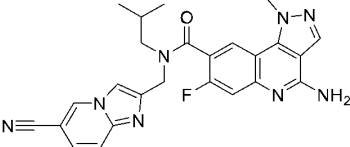
10、如权利要求1所述的化合物，或其药学上可接受的立体异构体、盐或氘代产物，
其特征在于，所述的 R_a 具有如下式所示的结构：



- 20 11、如权利要求1-10任一所述的化合物，或其药学上可接受的立体异构体、盐或氘代产物，其特征在于，所述的化合物具有选自下表的结构：

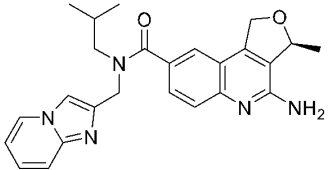
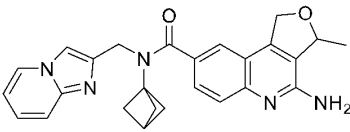
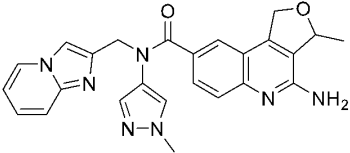
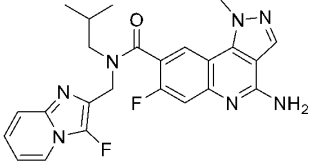
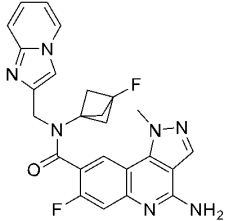
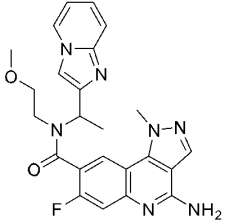
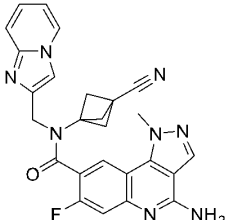
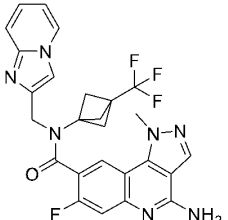
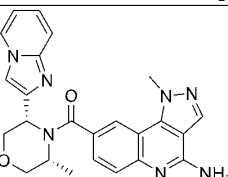
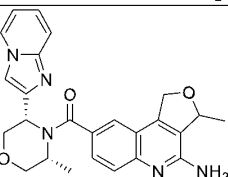
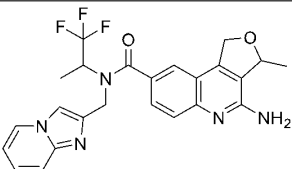
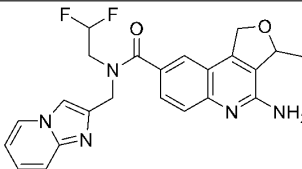
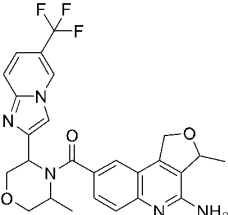
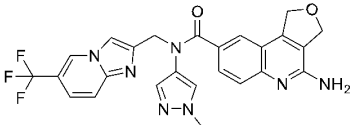
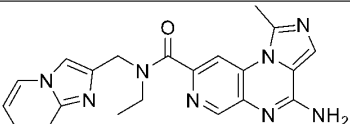
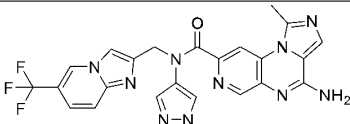
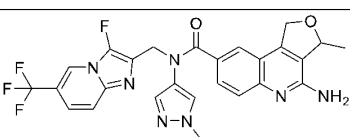
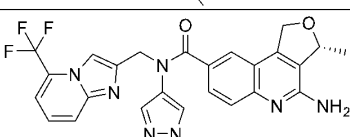
表1

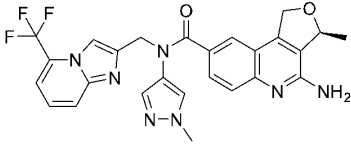
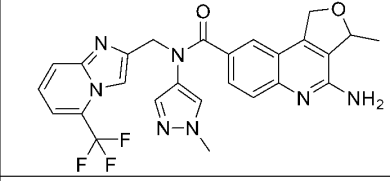
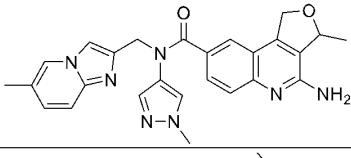
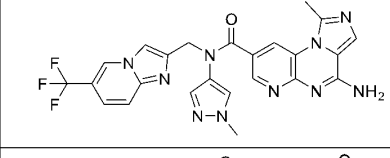
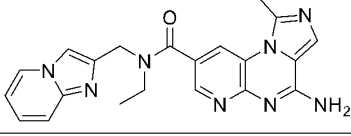
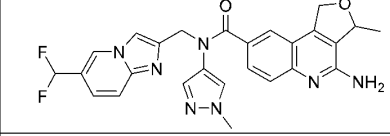
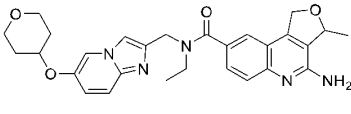
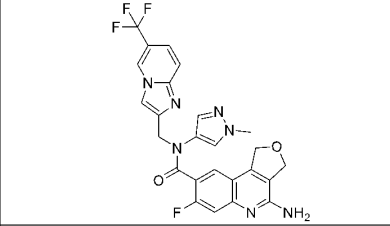
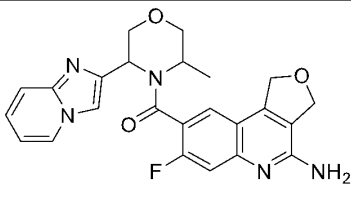
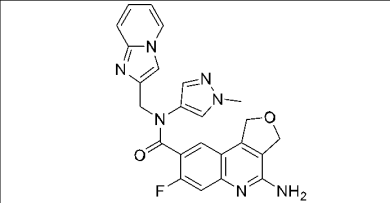
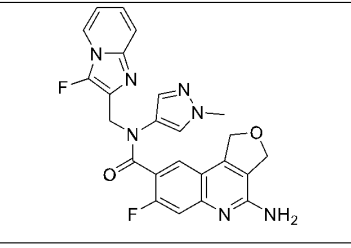
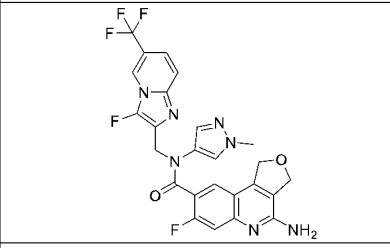
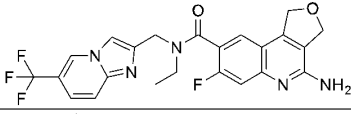
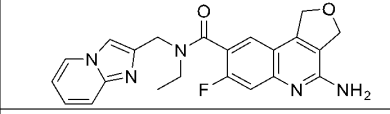
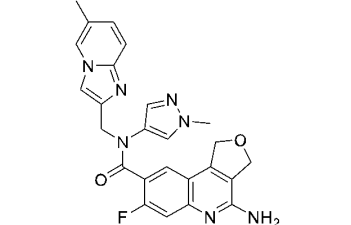
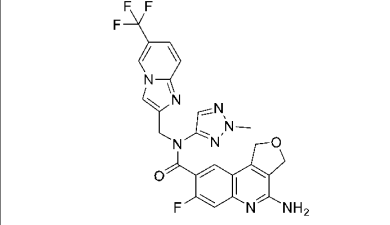
NO.	结构	NO.	结构
1		2	
3		4	

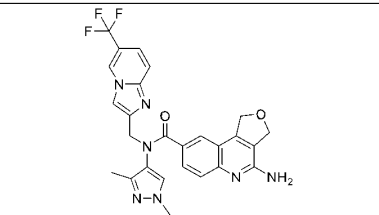
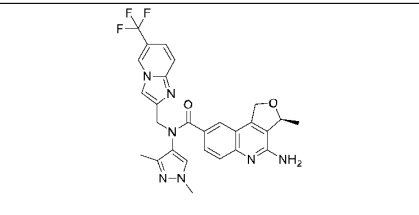
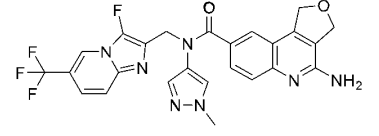
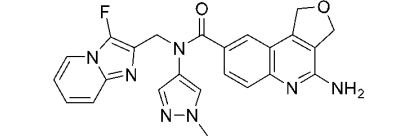
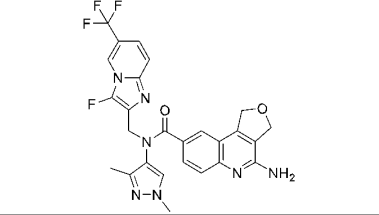
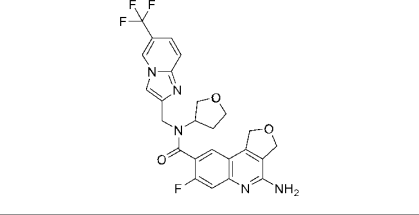
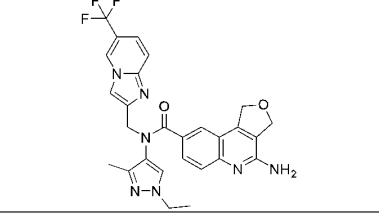
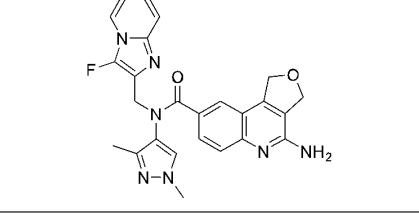
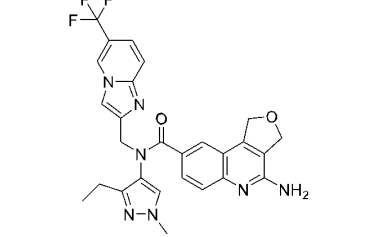
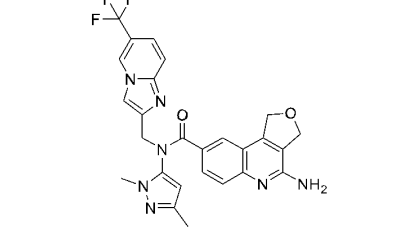
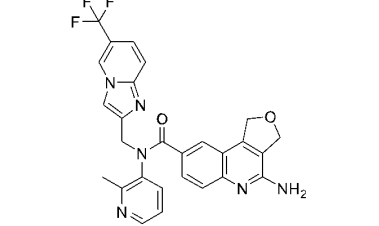
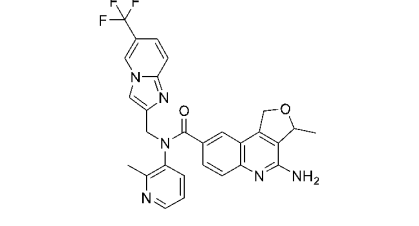
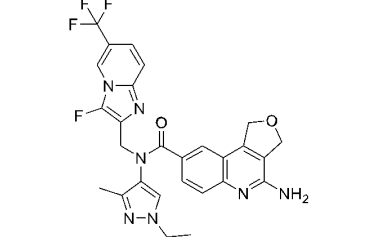
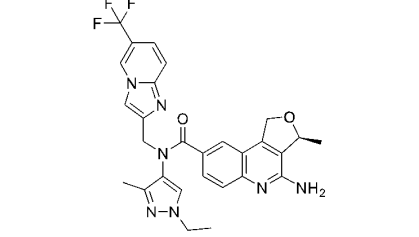
5		6	
7		8	
9		10	
11		12	
13		14	
15		16	
17		18	
19		20	

21		22	
23		24	
25		26	
27		28	
29		30	
31		32	
33		34	
35		36	

37		38	
39		40	
41		42	
43		44	
45		46	
47		48	
49		50	
51		52	
53		54	

55		56	
57		58	
59		60	
61		62	
63		64	
65		66	
67		68	
69		70	
71		72	

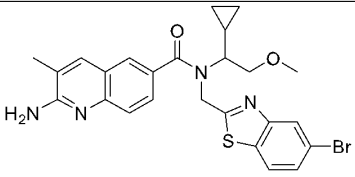
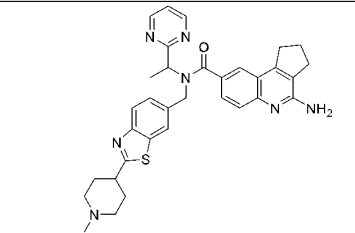
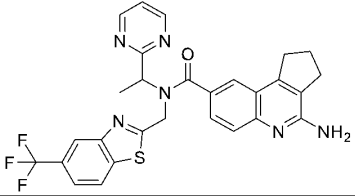
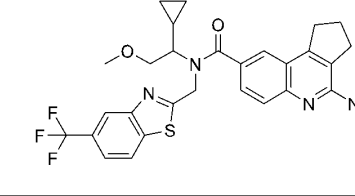
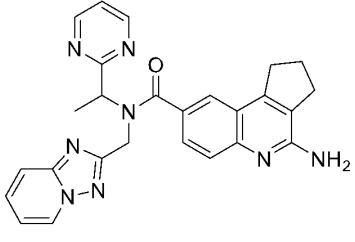
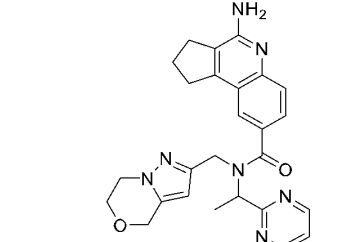
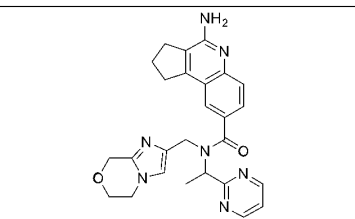
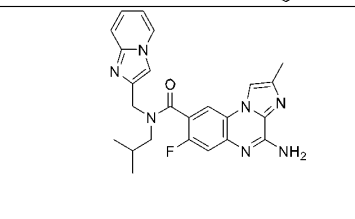
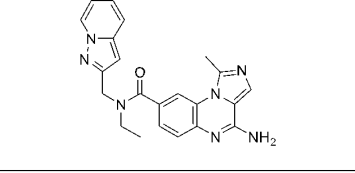
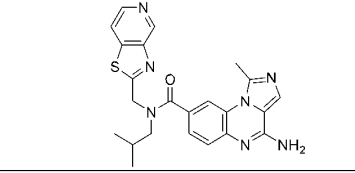
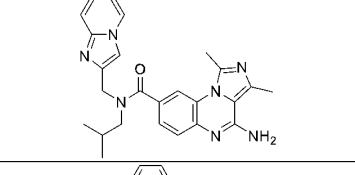
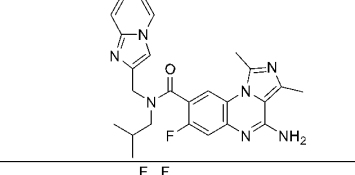
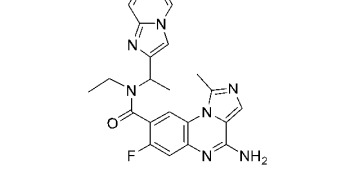
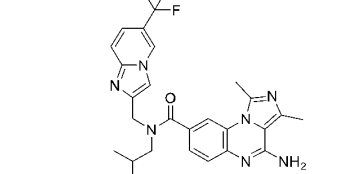
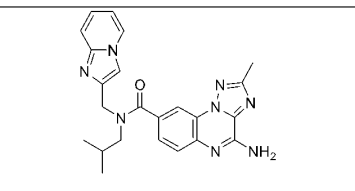
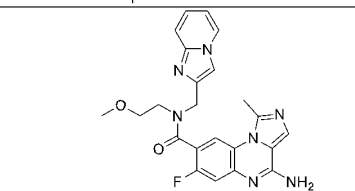
73		74	
75		76	
77		78	
79		80	
81		82	
83		84	
85		86	
87		88	

89		90	
91		92	
93		94	
95		96	
97		98	
99		100	
101		102	

103		104	
105		106	
107		108	
109		110	
111		112	
113		114	
115		116	

117		118	
119		120	
121		122	
123		124	
125		126	
127		128	
129		130	
131		132	

133		134	
135		136	
137		138	
139		140	
141		142	
143		144	
145		146	
147		148	
149		150	

151		152	
153		154	
155		156	
157		158	
159		160	
161		162	
163		164	
165		166	

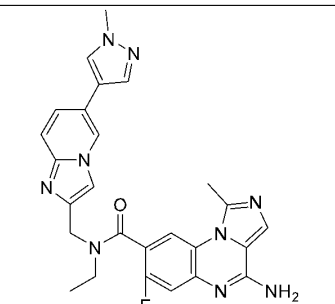
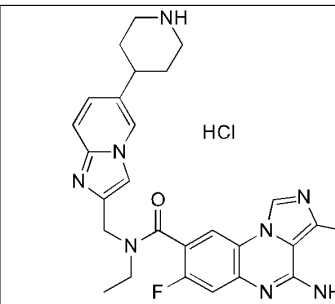
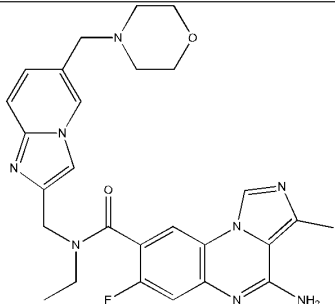
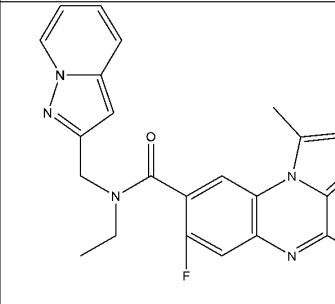
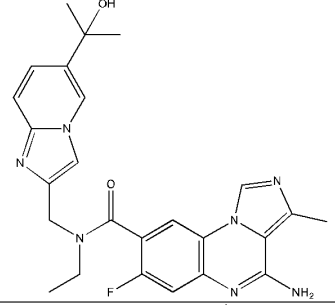
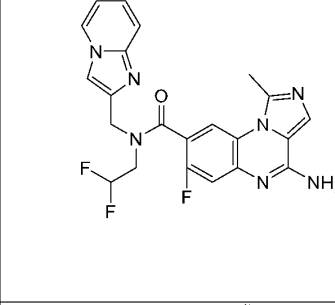
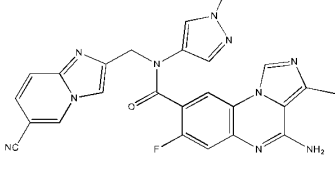
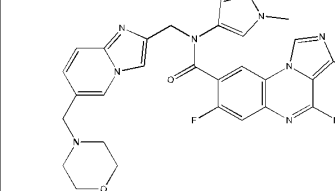
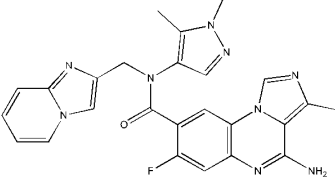
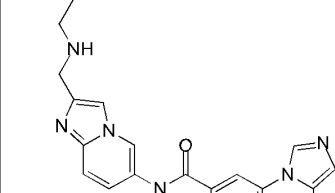
167		168	
169		170	
171		172	
173		174	
175		176	
177		178	
179		180	
181		182	

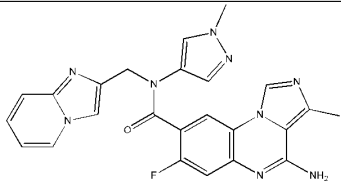
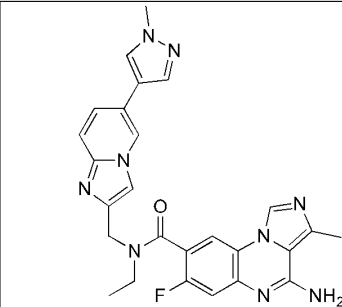
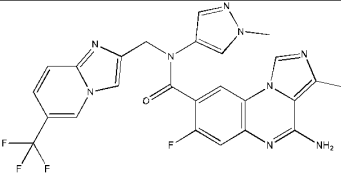
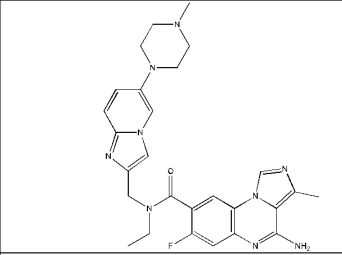
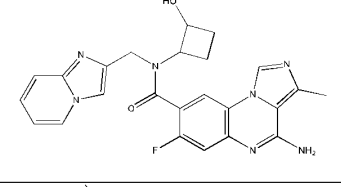
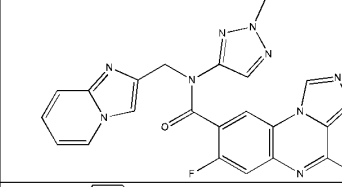
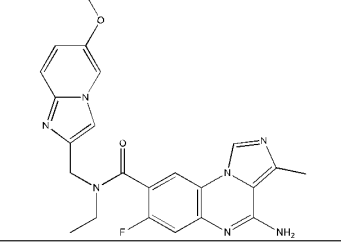
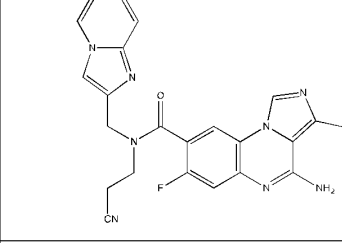
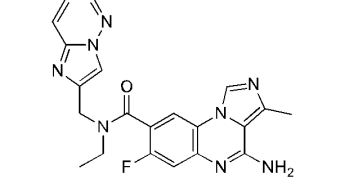
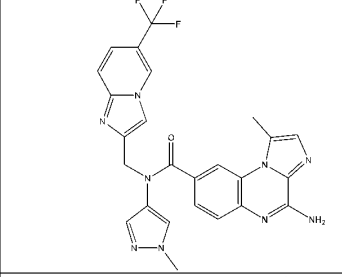
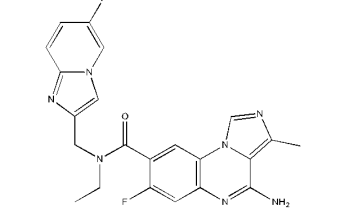
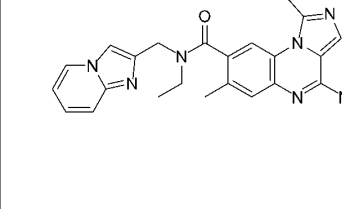
183		184	
185		186	
187		188	
189		190	
191		192	
193		194	
195		196	
197		198	

199		200	
201		202	
203		204	
205		206	
207		208	
209		210	
211		212	
213		214	

215		216	
217		218	
219		220	
221		222	
223		224	
225		226	
227		228	
229		230	

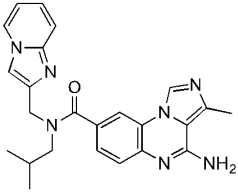
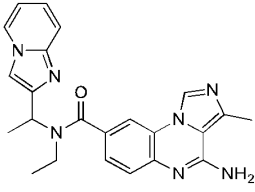
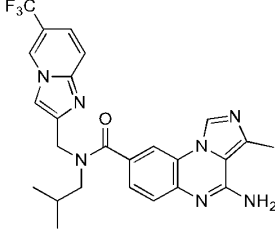
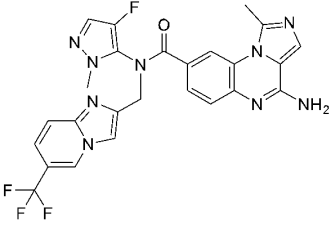
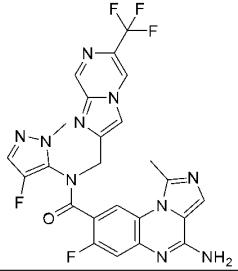
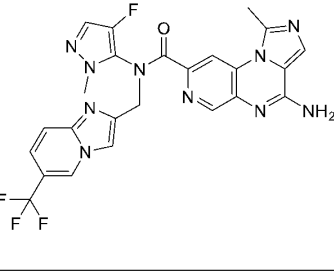
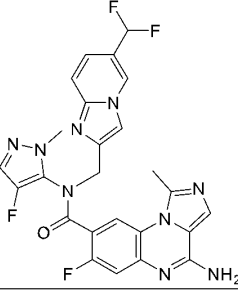
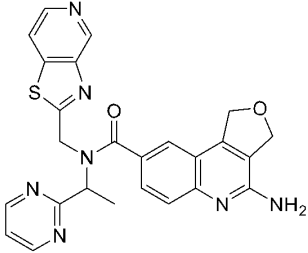
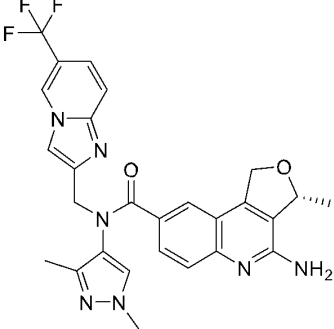
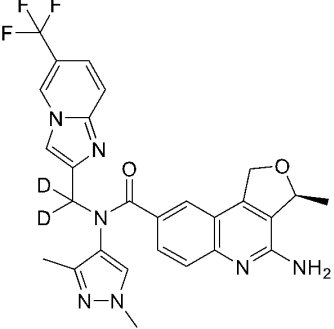
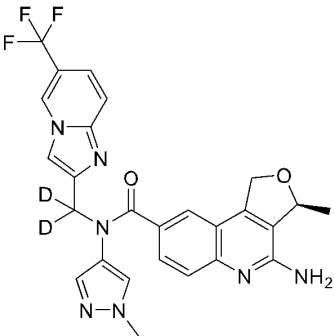
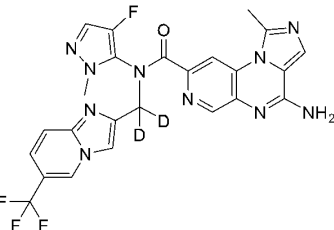
231		232	
233		234	
235		236	
237		238	
239		240	
241		242	
243		244	
245		246	

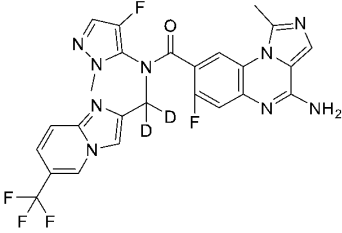
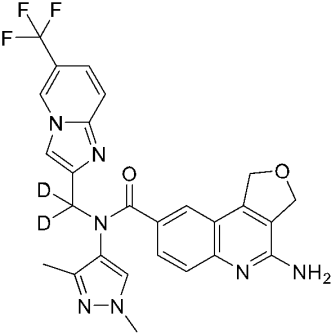
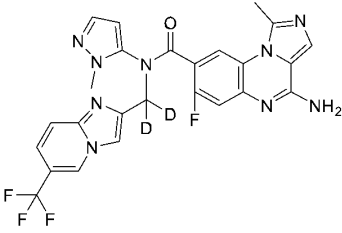
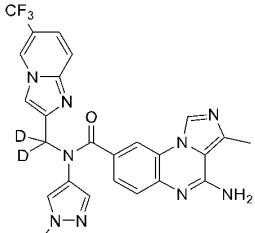
247		248	
249		250	
251		252	
253		254	
255		256	

257		258	
259		260	
261		262	
263		264	
265		266	
267		268	

269		270	
271		272	
273		274	
275		276	
277		278	
279		280	
281		282	

283		284	
285		286	
287		288	
289		290	
291		292	
293		294	
295		296	

297		298	
299		300	
301		302	
303		304	
305		306	
307		308	

309		310	
311		312	

。

- 12、一种药物组合物，其特征在于，所述的药物组合物含有治疗有效量的如权利要求1-11任一所述的化合物、其可药用的盐、外消旋体、光学异构体、立体异构体或互变异构体中的一种或多种，以及一种或多种可药用的载体、赋形剂、佐剂、辅料和/或稀释剂。

13、如权利要求1-11任一所述的化合物、其外消旋体、立体异构体或可药用盐在制备治疗或预防与PRMT5的基因水平异常或表达异常(如对应的核酸突变、缺失，或MTAP基因水平异常，或所述的甲基转移酶产生异位或融合或过高表达)相关的疾病的药物中的用途。

- 14、如权利要求13所述的用途，其特征在于，所述的疾病选自下组：所述疾病或病症卵巢癌、食管癌、肺癌、淋巴瘤、胶质母细胞瘤、结肠癌、黑色素瘤、胃癌、胰腺癌或膀胱癌。